Organic Syntheses

Rhodium-Catalyzed Atroposelective Azide-Alkyne Cycloaddition

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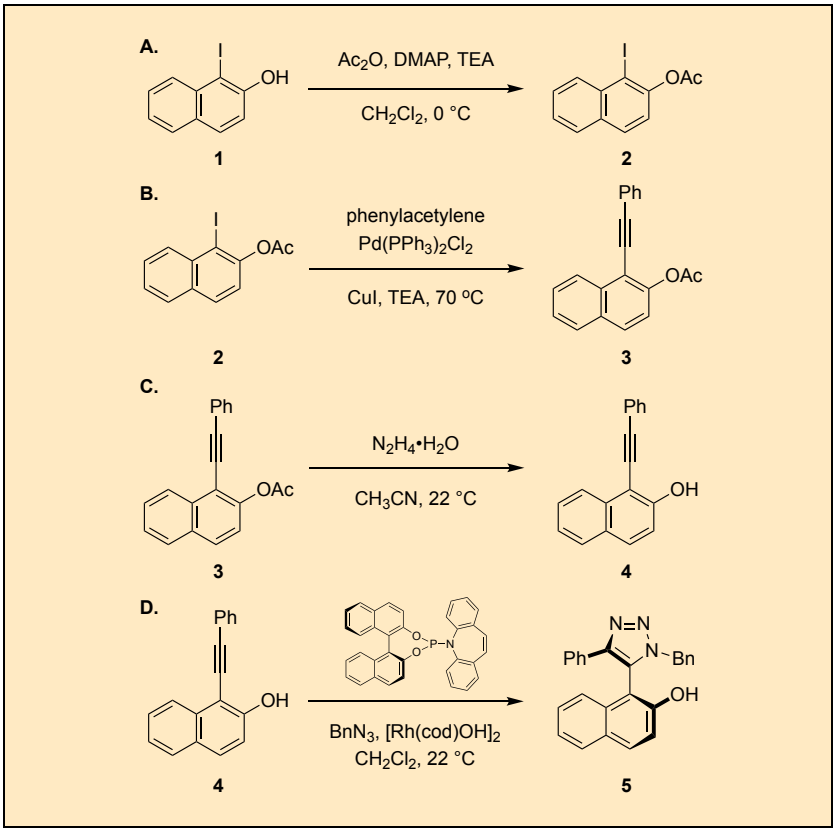

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Procedure (Note 1)

A. *1-Iodonaphthalen-2-yl acetate (***2***).* A 100-mL, single-necked (24/40), round-bottom flask equipped with a 3-cm Teflon-coated magnetic stirring bar is charged with 1-iodo-2-naphthol (**1**, 4.50 g, 16.66 mmol, 1.00 equiv) (Note 2), and 4-dimethylaminopyridine (DMAP) (102 mg, 0.83 mmol, 4.99 mol%)(Note 3), using a polypropylene anti-static weighing funnel (Figure 1A). The flask is capped with a rubber septum connected to a nitrogen line, then dichloromethane (DCM) (30 mL) (Note 4) is added through the rubber septum using a 50 mL high-density polyethylene (HDPE) syringe with a 5" 16-gauge needle. The flask is cooled to 0 °C in an ice bath (Figure 1B), and triethylamine (TEA) (5.0 mL, 35.87 mmol, 2.15 equiv) (Note 5) is added via a 6 mL HDPE syringe with a 3" 18-gauge needle (Figure 1C). Then acetic anhydride (1.9 mL, 20.23 mmol, 1.21 equiv) (Note 6) is slowly added using a 3 mL HDPE syringe with a 3" 18-gauge needle over 2 min to obtain a brown solution (Figure 1D). After the addition of acetic anhydride, the reaction is stirred at 0 °C for 30 min, and an aliquot of the reaction mixture by thin-layer chromatography (TLC) indicates complete consumption of 1-iodo-2-naphthol and a new product formation (Note 7) (Figure 1E). The reaction mixture is a brown solution (Figure 1F). The stirring bar is removed, and the reaction mixture is transferred to a 250-mL separatory funnel rinsing the round-bottom flask with DCM (10 mL). Aqueous 2N HCl (50 mL) (Note 8) is added, the separatory funnel is gently swirled (Note 9), and then the contents were allowed to settle to afford two liquid phases (Figure 1G). The bottom organic layer and top aqueous layers were separated, and the top aqueous layer is further extracted with DCM (2 x 30 mL). The combined DCM layers are returned into the separatory funnel, washed with 2N HCl (100 mL), washed with brine (Note 10) (100 mL), and then dried over anhydrous Na_2SO_4 (16 g) (Note 11) (Figure 1H). The solution was vacuum filtered through a 110 mL disposable 10 μm polyethylene fritted funnel (Note 12) into a 250-mL round-bottom flask and the solid is washed with additional DCM (20 mL) (Figure 1I). The filtrate is concentrated under vacuum using a rotary evaporator (40 °C/50 mbar) (Figure 1J). The crude residue is transferred to a 100-mL flask with a glass pipette using DCM (4 × 5 mL), concentrated and dried under high vacuum (10 mbar) to obtain a brown oil (Run 1: 5.30 g; Run 2: 5.36 g) (Figure 1K). The TLC analysis shows the major product and an impurity (Note 13) (Figure 1L). The crude brown oil is used directly in the next step without further purification (Note 14, and 15).

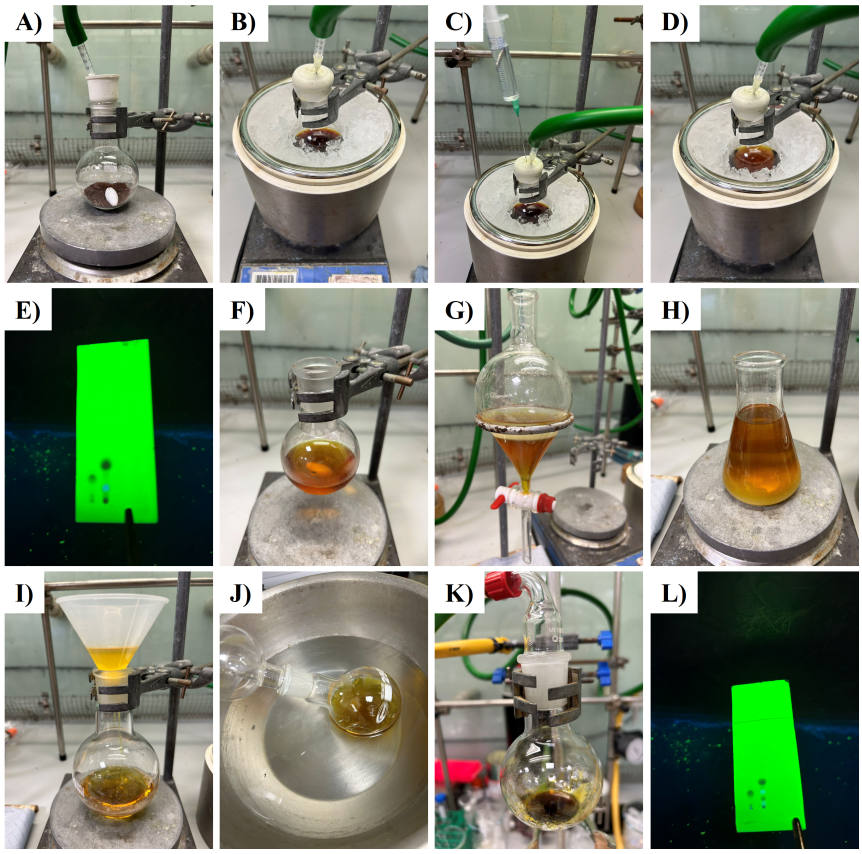


Figure 1. Acylation of 1-iodo-2-naphthol; A. A single-necked flask charged with 1-iodo-2-naphthol and DMAP; B. DCM is added and cooled to 0 °C in an ice bath; C. TEA is added by a syringe; D. Reaction mixture after adding Ac_2O; E. TLC analysis (PE: EtOAc = 8:1) of the reaction, Left lane: 1-iodo-2-naphthol, right lane: reaction sample; F. Reaction mixture after completion; G. Extracting the reaction with DCM and wash with 2N HCl to remove TEA, and DMAP; H. Organic layers are combined and dried over anhydrous Na_2SO_4; I. Filtering Na_2SO_4 through a plug of cotton; J. Concentrating the filtrate under vacuum using a rotary evaporator; K. Drying the crude product under high vacuum to obtain a brown oil; L. TLC analysis (PE: EtOAc = 8:1) of the crude brown oil, Left lane: 1-iodo-2-naphthol, right lane: obtained oil

B. *1-(Phenylethynyl)naphthalen-2-yl acetate (**3**).* To the flask containing crude **2** is added $Pd(PPh_3)_2Cl_2$ (240 mg, 0.34 mmol, 2.05 mol%) (Note 16), and CuI (162 mg, 0.85 mmol, 5.10 mol%) (Note 17), using a polypropylene anti-static weighing funnel. The flask is a capped with a rubber septum connected to a nitrogen line. Then, TEA (30 mL) (Note 5) is added via a 50 mL HDPE syringe with a 5″ 16-gauge needle. The septum was equipped with an outlet needle and the solution is bubbled with nitrogen for 15 min (Figure 2A). The outlet needle is removed and the flask is transferred to a preheated heating block (Note 18) at 70 °C (external temperature) and stirred using an IKA stirrer plate (Figure 2B). Then, phenylacetylene (2.2 mL, 20.03 mmol, 1.20 equiv) (Note 19) is added by a 3 mL HDPE syringe with a 3″ 18-gauge needle to obtain a black solution (Figure 2C). After stirring for 1.5 h, TLC analysis shows the completion of the reaction (Note 20) (Figure 2D). The reaction is cooled to ambient temperature (21 – 22 °C) (Figure 2E) and EtOAc (30 mL) (Note 21) is added via a 50 mL HDPE syringe with a 5″ 16-gauge needle (Figure 2F). The mixture is sonicated and then vacuum-filtered over a 250-mL sintered funnel (10 – 20 μm) prepacked with layer of Celite® S (10 g, 1.0 cm) (Note 22) into a 250 mL round bottom-flask. The filtered solid is washed with additional EtOAc (3 × 30 mL) (Figure 2G). The brown filtrate was concentrated under vacuum using a rotary evaporator (50 °C/59 mbar) to obtain a brown oil. The crude brown oil is further dried under vacuum (10 mbar) for 30 min (Run 1: 6.03 g; Run 2: 6.35 g) (Figure 2H), and used directly in the next step without further purification (Note 23, and 24).

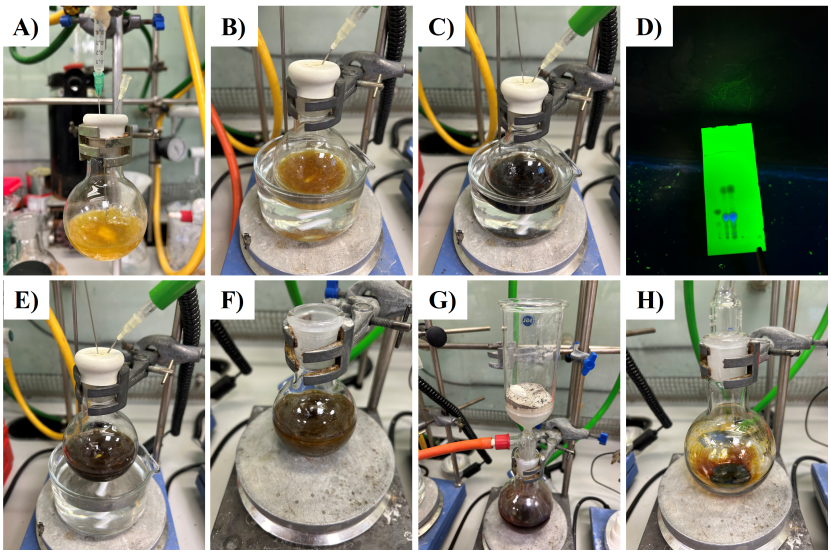


Figure 2. Sonogashira coupling: A. The mixture is bubbled with nitrogen; B. The reaction is heated to 70 °C; C. Phenylacetylene is added by a syringe; D. TLC analysis (PE: EtOAc = 8:1) of the reaction, left lane: Crude 2 from step A, right lane: reaction sample; E. Reaction mixture after completion; F. EtOAc is added to dilute the mixture; G. The mixture is filtered through Celite; H) The filtrate is concentrated to obtain the crude product as a brown oil

C. *1-(Phenylethynyl)naphthalen-2-ol (**4**)*. To the flask containing crude product **3** is added acetonitrile (60 mL) via a 100-mL graduated cylinder (Note 25) (Figure 3A). Hydrazine hydrate (2.3 mL, 36.92 mmol, 2.21 equiv) (Note 26) is added using a 3 mL HDPE syringe with a 3″ 18-gauge needle. The solution is stirred at ambient temperature (21 – 22 °C) for 10 min to obtain an orange suspension (Figure 3B). TLC analysis indicates the completion of the reaction (Note 27) (Figure 3C). The reaction is quenched by adding 1N HCl (50 mL) via a 100-mL graduated cylinder. Water (50 mL) is added, and the mixture is transferred to a 500 mL separatory funnel rinsing the round-bottom flask with EtOAc (50 mL) (Figure 3D). The top organic and bottom aqueous layer are separated, and the bottom aqueous layer is further extracted with EtOAc (3 × 50 mL). The combined organic layers are washed with brine (150 mL), dried over anhydrous Na_2SO_4 (25 g), and vacuum filtered through a 110-mL disposable 10 μm polyethylene fritted funnel (Note 12) into a 500-mL round-bottom flask. The filtered solid is washed with

additional EtOAc (3 × 20 mL) to obtain a red solution (Figure 3E). The solution is concentrated under vacuum using a rotary evaporator (40 °C/150 mbar) to obtain a brown oil.

A flash column (4.5 cm diameter x 49 cm height) is packed with a slurry of silica gel (100 g) (Note 28) in petroleum ether (PE) (Note 29). The crude residue was diluted with DCM (2 mL) and transferred to the top of the silica, with subsequent rinses of the round-bottom flask using DCM (1.5 mL x 2). Once adsorbed, sea sand is added to protect the silica layer (Figure 3F). The purification is performed using 550 mL of petroleum ether (PE) followed by 1470 mL of 4.8% EtOAc-PE (20:1 PE:EtOAc). After 850 mL of solvent is passed through the column, during which no product was detected, 25 fractions were subsequently collected using 50-mL test tubes (Figure 3G). The fractions are analyzed by TLC (Note 30), and the desired product is obtained in fractions 4-17 (Figure 3H). The fractions containing product are combined in a 1-L round-bottom flask and concentrated by rotary evaporation (40 °C/150 mbar). The resulting oil is transferred to a 100-mL flask with a glass pipette using DCM (4 × 5 mL), and concentrated by rotary evaporation (40 °C/33 mbar) to obtain an off-white solid (Run 1: 3.33 g; Run 2: 3.65 g) (Figure 3I). DCM (0.5 mL) and pentane (20 mL) are added to the flask containing the solid (Note 31). The suspension is sonicated for 2 min, stirred vigorously for 10 min, and vacuum-filtered through a 60-mL sintered funnel (10 - 15 μm) (Figure 3J). The solid is washed with cold pentane (10 mL), to give an off-white solid (Run 1: 2.63 g, 10.76 mmol, 64.6% yield; Run 2: 2.58 g, 10.56 mmol, 63.4% yield) which was used in the next step (Note 32 and 33) (Figure 3K). TLC analysis confirms the improved purity (Note 34) (Figure 3L). The filtrate is concentrated to give a brown solid that contains impurities (Run 1: 701 mg; Run 2: 745 mg) (Note 35).

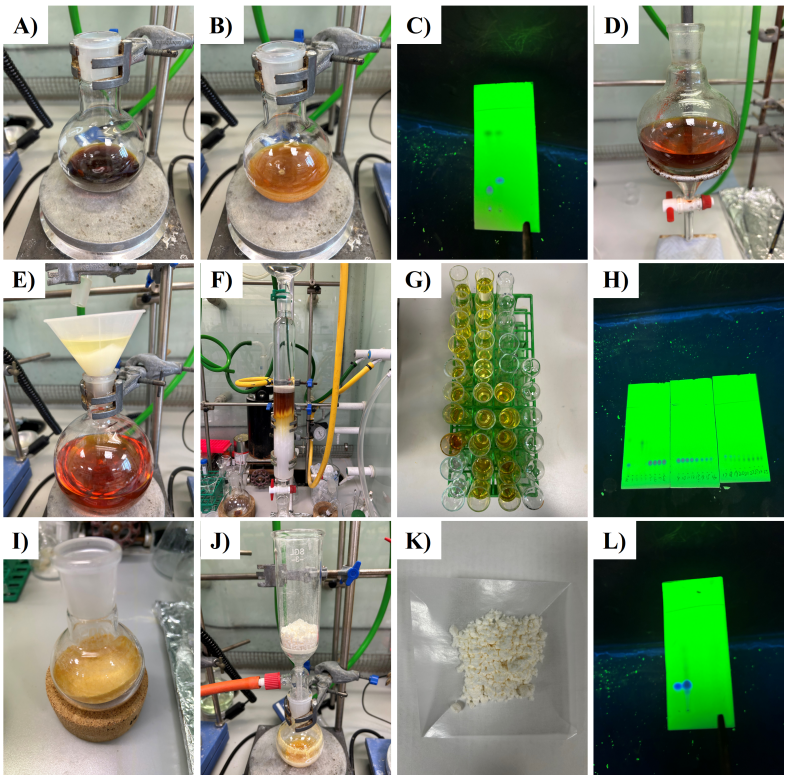


Figure 3. Deacylation: A. Crude product 3 from step B is dissolved in acetonitrile; B. Hydrazine hydrate is added and stirred for 10 min; C. TLC analysis (PE: DCM = 4:1) of the reaction, Left lane: step B crude mixture, right lane: step C reaction sample; D. The reaction is extracted with EtOAc; E. The organic layers are combined, dried over Na_2SO_4 and filtered through a plug of cotton; F. The mixture is concentrated and loaded onto a silica gel column; G. Fractions are collected; H. TLC analysis (PE: EtOAc = 8:1) of the fractions; I. The fractions containing product are concentrated to obtain a beige solid; J. The residue is washed with DCM/pentane and filtered; K. 1-(phenylethynyl)naphthalen-2-ol is obtained as a white solid; L. TLC analysis (PE: EtOAc = 8:1) of the solid and filtrate, Left lane: solid, right lane: filtrate

D. *(S)-1-(1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)naphthalen-2-ol* (**5**). A 250-mL, single-necked, round-bottom flask equipped with a 5 x 2 cm Teflon-coated magnetic stirring bar is charged with 1-(phenylethynyl)naphthalen-2-

ol (**4**, 2.01 g, 8.23 mmol, 1.00 equiv), $[Rh(cod)(OH)]_2$ (38 mg, 0.08 mmol, 1.00 mol%) (Note 36), and (*S*)-(+)-*N*-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)-dibenzo[*b*,*f*]azepine (85 mg, 0.17 mmol, 2.03 mol%) (Note 37) using a polypropylene anti-static weighing funnel (Figure 4A). DCM (64 mL) is added using a 100-mL glass graduated cylinder. Subsequently, a solution of benzyl azide in DCM (18.1 mL, 9.05 mmol, 1.10 equiv) (Note 38, 39, and 40) is added immediately via a 24-mL HDPE syringe with a 3″ 18-gauge needle to obtain a yellow solution (Note 41) (Figure 4B). The reaction is stirred at ambient temperature (21 - 22 °C) for 14 h (Note 42) (Figure 4C), after which TLC analysis indicates the total consumption of starting material (**4**) (Note 43) (Figure 4D). The mixture is concentrated to obtain a yellow solid (Figure 4E). DCM (4 mL) is added using a 6 mL HDPE syringe with a 3″ 18-gauge needle, the resulting mixture is sonicated, and the suspension is filtered through a 60-mL sintered funnel (10 - 15 μm). The round-bottom flask is further rinsed with DCM (8 mL), transferred to the 60-mL sintered funnel containing the bulk solids, and filtered to obtain yellow-grey solid. The solid is carefully washed with DCM (8 mL), dried under vacuum to give an off white solid (Run 1: 2.52 g, 81.1 % yield, >99% ee; Run 2: 2.51 g, 80.8 % yield, >99% ee) (Note 44, 45, and 46) (Figure 4F and 4G). The filtrate is concentrated to obtain a light brown oil (Note 47). TLC analysis demonstrates the good purity of the solid, with impurities remaining in the filtrate (Note 48) (Figure 4H).

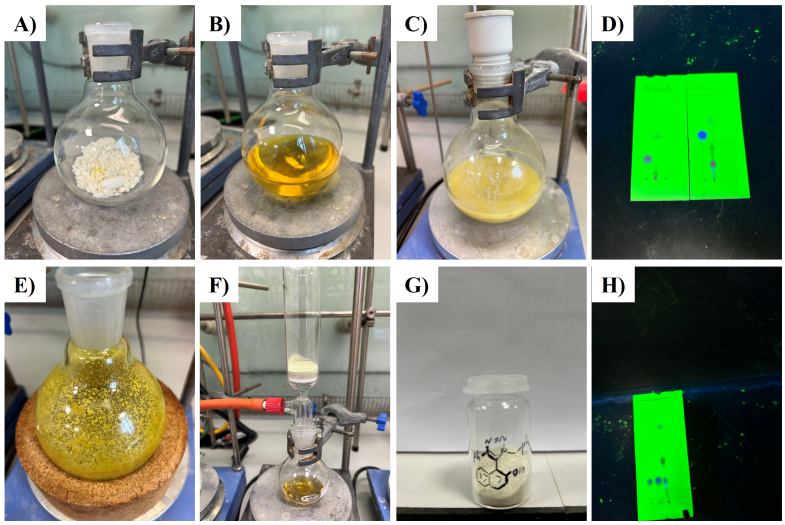


Figure 4. Rhodium-catalyzed atroposelective azide-alkyne cycloaddition; A. The flask is charged with 1-(phenylethynyl)naphthalen-2-ol, $[Rh(cod)(OH)]_2$ and (*S*)-ligand; B. DCM and benzyl azide are added immediately; C. Reaction mixture after completion; D. TLC analysis of the reaction; E. The reaction is concentrated to obtain yellow solid; F. The solid is washed with DCM and filtered to give the solid; G. Compound (5) is obtained as a light grey solid; H. TLC analysis (PE: EtOAc = 2:1) of the solid and the filtrate

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 2-iodo-1-naphthol, triethylamine, 4-dimethylaminopyridine, acetic anhydride, dichloromethane, NaCl, Na_2SO_4, HCl solution, phenylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, hydrazine hydrate, acetonitrile, silica gel, petroleum ether, ethyl acetate, pentane, benzyl azide, $[Rh(cod)OH]_2$, and 1,3,5-trimethoxybenzene.

2. Submitting authors: 1-Iodo-2-naphthol was obtained from Fluorochem, Inc. and used as received. TLC analysis showed an impurity. The purity of **1** was determined to be 95.7 wt% by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, 99%) as the internal standard. Checking authors: 1-Iodo-2-naphthol (97%) was purchased from Oakwood Chemical and used as received. The purity of **1** was determined to be 97.1 wt% by qNMR using 1,3,5- trimethoxybenzene (Sigma-Aldrich, ≥99%) as the internal standard.
3. Submitting authors: 4-Dimethylaminopyridine (DMAP, 95%) was obtained from Fluorochem, Inc. and used as received. Checking authors: 4-(Dimethylamino)pyridine (purum, ≥98%) was purchased from Sigma Aldrich and used as received.
4. Dichloromethane (Analytical grade) was obtained from Fisher, and used as received.
5. Triethylamine (99%) was obtained from Thermo Scientific, and used as received.
6. Submitting authors: Acetic anhydride (97%) was obtained from Acros Organics, and used as received. Checking authors: Acetic anhydride (99.5%) was purchased from Sigma Aldrich and used as received.
7. The reaction solution was directly used for TLC monitoring, and reaction progress was determined by TLC analysis on silica gel using 1:8 EtOAc: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.30).
8. 2 M HCl solution was prepared by slowly adding concentrated HCl (100 mL) to 500 mL water. Care should be taken with exothermic dilution of HCl. Concentrated HCl (37 wt%) was obtained from Fisher, and used as received.
9. Gas evolution and pressure build-up observed upon swirling of separatory funnel.

10. Checking authors: Sodium chloride (Bioreagent, ≥99%) was purchased from Sigma Aldrich.
11. Anhydrous Na_2SO_4 (99%) was obtained from Fisher and used as received.
12. The submitting authors gravity filtered the solution through a plug of cotton.
13. The crude TLC analysis was performed on silica gel using 1:8 EtOAc: petroleum ether as eluent and visualization under 254 nm UV.
14. Submitting authors: A 1 mmol scale reaction was conducted, and the pure (**2**) (287 mg, 92% yield) was isolated by silica gel column chromatography, eluting with 1:10 EtOAc: petroleum ether. Checking authors: A small portion of the crude material was purified using the author's purification procedure to obtain (**2**) as a yellow viscous oil with 99.8% purity as determined by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, ≥99%) as an internal standard.
15. 1-Iodonaphthalen-2-yl acetate (**2**): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.81 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.60 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 2.45 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 150.2, 135.4, 132.3, 132.2, 130.3, 128.5, 128.4, 126.6, 121.5, 94.7, 21.5 ; HRMS (ESI+) calc. for $C_{12}H_9IO_2$ [M+H]+ 312.9720, found 312.9721.
16. $Pd(PPh_3)_2Cl_2$ (98%) was obtained from Sigma-Aldrich, and used as received.
17. CuI (99%) was purchased from Sigma-Aldrich, and used as received.
18. The submitting authors used a preheated oil bath.
19. Phenylacetylene (98%) was obtained from Sigma-Aldrich, and used as received.
20. The reaction solution was directly used for TLC monitoring, and reaction progress was determined by TLC analysis on silica gel using 1:8 EtOAc: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.23).
21. Submitting authors: Ethyl acetate (Analytical Grade) was obtained from Fisher and used as received. Checking authors: Ethyl acetate (HPLC Grade) was purchased from Sigma Aldrich and used as received.
22. Checking authors: Celite® S (filter aid, dried, untreated) was obtained from Sigma Aldrich.
23. Submitting authors: A 0.8 mmol scale reaction was conducted to afford pure (**3**) (195 mg, 85% yield) after purification by silica gel column chromatography eluting with 1:10 EtOAc/petroleum ether, followed by

trituration with petroleum ether and filtration. Checking authors: A small portion of the crude material was purified using author's purification procedure to obtain (**3**) as a light-yellow solid with 98.6% purity as determined by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, ≥99%) as an internal standard.

24. 1-(Phenylethynyl)naphthalen-2-yl acetate (**3**): light yellow solid, .m.p. = 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.3 Hz, 1H), 7.86 (dd, *J* = 8.5, 3.3 Hz, 2H), 7.61 (ddd, *J* = 7.6, 5.2, 2.1 Hz, 3H), 7.53 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.46 – 7.34 (m, 3H), 7.28 (d, *J* = 8.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 150.5, 134.0, 131.8, 131.5, 129.9, 128.8, 128.6, 128.4, 127.5, 126.4, 126.4, 123.3, 121.3, 113.4, 99.6, 82.6, 21.1; HRMS (ESI+) calc. for $C_{20}H_{14}O_2$ [M+H]+ 287.10666, found 287.10665. The compound (3) is stable on the benchtop at room temperature under air atmosphere.
25. Submitting authors: Acetonitrile (Analytical Grade) was obtained from Fisher and used as received. Checking authors: Acetonitrile (HPLC Grade) was purchased from Sigma Aldrich and used as received.
26. Hydrazine hydrate (N_2H_4, 50-60%) was obtained from Sigma-Aldrich and used as received.
27. An aliquot of reaction was diluted with DCM and used for TLC monitoring. Reaction progress was determined by TLC analysis on silica gel using 1:4 DCM: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.30). The Rf of TLC analysis (1:8 EtOAc: petroleum ether) of compound (**4**) was the same as intermediate (**3**).
28. Submitting authors: Silica gel (0.040-0.063 mm, 230-400 mesh) was obtained from Sigma-Aldrich and used as received. Checking authors: Silica gel (high-purity grade, 70-230 mesh) was purchased from Sigma Aldrich and used as received.
29. Submitting authors: Petroleum Ether (40-60°C) (Analytical grade) was obtained from Fisher and used as received. Checking authors: Petroleum Ether (ACS grade) was purchased from Sigma Aldrich and used as received.
30. The fractions were determined by TLC analysis on silica gel using 1:8 EtOAc: petroleum ether as eluent and visualization under 254 nm UV.
31. Pentane (99%) was obtained from Fisher and used as received.
32. 1-(Phenylethynyl)naphthalen-2-ol (**4**): off white solid, m.p. = 91-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.79 (dd, *J* = 8.6, 5.1 Hz, 2H), 7.70 – 7.61 (m, 2H), 7.56 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.48 – 7.35 (m,

4H), 7.24 (d, J = 9.0 Hz, 1H), 6.20 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 133.7, 131.8, 130.9, 129.0, 128.7, 128.6, 128.5, 127.6, 125.0, 124.3, 122.8, 116.5, 103.0, 101.4, 81.7; HRMS (ESI+) calc. for $C_{18}H_{12}O$ [M+H]+ 245.0961, found 245.0961. The product (4) is stable on the benchtop at room temperature under air atmosphere.

33. The purity of (**4**) was determined to be 98.4 wt% for Run 1 and 99.3 wt% for Run 2 by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, ≥99%) as the internal standard.
34. The solid was evaluated by TLC analysis on silica gel using 1:8 EtOAc: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.24).
35. The filtrate could be further purified by silica gel column chromatography, if desired.
36. Hydroxy(cyclooctadiene)rhodium(I) dimer (95%) was obtained from Sigma-Aldrich and used as received. This catalyst should be a light-yellow powder. The submitting authors note that this chemical from some other suppliers is an orange solid, which did not perform well in this reaction.
37. Submitting authors: (*S*)-(+)-*N*-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-dibenzo[b,f]azepine (97%, 99% ee) was obtained from Bide Pharmatech Ltd, and used as received. The compound was not totally stable, changing color from white to yellow powder over a few days at ambient temperature. The purity of this ligand should be checked before use by simple TLC analysis or NMR. Checking authors: (*S*)-(+)-*N*-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-dibenzo[b,f]azepine (98%, 99% ee) was purchased from Ambeed and used as received.
38. Submitting authors: Benzyl azide (practical grade) was obtained from Fluorochem, Inc. and used after flushing the compound through a short column of silica gel with petroleum ether. Checking authors: Benzyl azide solution (~0.5 M in dichloromethane, ≥ 95%) was purchased from Sigma-Aldrich and used as received.
39. The submitting authors noted that without the additional purification of benzyl azide, the reaction provided compound **5** with reduced ee (78%).
40. The submitting authors previously carried out the reaction on a 10 mmol scale using freshly synthesized benzyl azide, and the reaction was completed within 3 h.

41. The four chemicals should be mixed together as soon as possible. Mixing the $[Rh(cod)OH]_2$ and ligand first, for 15 min, followed by the alkyne and azide gave a lower 85% ee.
42. Precipitate formation is observed if some solvent evaporation occurs. Without solvent loss, the reaction mixture remained clear. This has no noticeable impact on reaction outcome.
43. The reaction was evaluated by TLC analysis on silica gel using 1:2 EtOAc: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.19).
44. (*S*)-1-(1-Benzyl-4-phenyl-1*H*-1,2,3-triazol-5-yl)naphthalen-2-ol (**5**): off white solid, m.p. = 213-215 °C for Run 1 and 209-210 °C for Run 2; >99% ee, $[\alpha]_D^{20}$ = +72.1 for Run 1 and +71.6 for Run 2 (c = 1.0, DMSO); $[\alpha]_D^{20}$ = +24.6 for Run 1 and +27.2 for Run 2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.21 – 7.08 (m, 7H), 6.92 – 6.85 (m, 2H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 15.2 Hz, 1H), 5.18 (d, *J* = 15.2 Hz, 1H) ; ^{13}C NMR (126 MHz, DMSO-d_6) δ: 154.5, 144.2, 135.2, 132.7, 132.1, 131.3, 129.0, 128.5, 128.4, 128.2, 127.7, 127.7, 127.6, 127.5, 127.4, 125.2, 123.2, 122.5, 118.1, 105.7, 51.3.; HRMS (ESI+) calc. for $C_{25}H_{19}N_3O$ [M+H]+ 378.16009, found 378.16006. The product (**5**) is stable on the benchtop at room temperature under air atmosphere.
45. The purity of the title compound (**5**) was determined to be 99.2 wt% for both Run 1 and Run 2 by qNMR using 1,3,5-trimethoxybenzene (Sigma-Aldrich, ≥99%) as the internal standard.
46. Compound **5** was shown to have >99% ee for both Run 1 and Run 2. Racemic **5** was prepared by an identical procedure without including the chiral ligand. Chiral HPLC, Column: Chiralpak IC-3 (0.3 cm × 10 cm), Mobile phase： n-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, wavelength = 254 nm, column temperature = 30° C, t (major) = 2.5 min, t (minor) = 2.1 min. The reaction mixture of **5** showed a 94% ee.
47. The filtrate showed 70% ee for Run 1 and 72% ee for Run 2. Chiral HPLC, Column: Chiralpak IC-3 (0.3 cm × 10 cm), Mobile phase： n-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, wavelength = 254 nm, column temperature = 30° C, t (major) = 2.5 min, t (minor) = 2.1 min.
48. The solid and filtrate were evaluated by TLC analysis on silica gel using 1:2 EtOAc: petroleum ether as eluent and visualization under 254 nm UV (Rf = 0.19).

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.

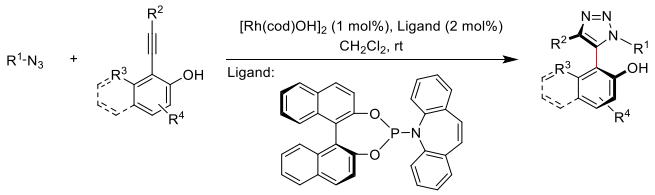
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

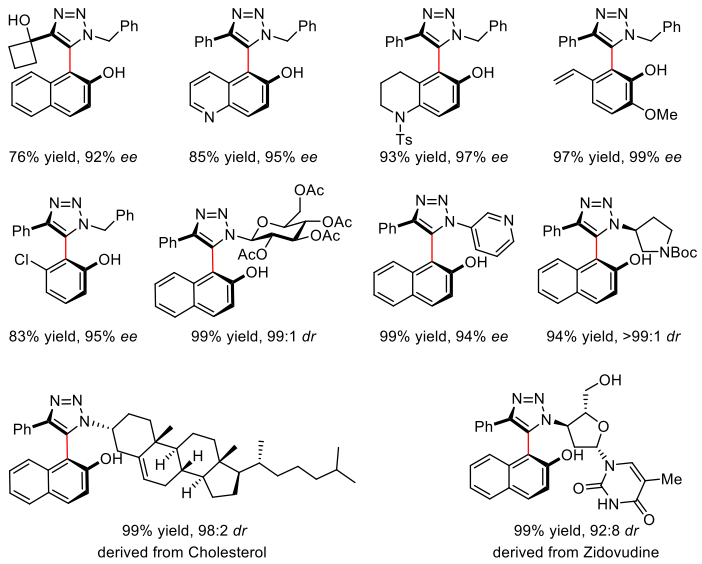
Discussion

As the flagship of click chemistry, azide-alkyne cycloaddition (AAC) has been widely applied in chemistry and biology.[3] A large number of efforts have been devoted to the development of chemo- and stereoselective AAC for accessing structurally diverse triazoles. For example, a variety of regioselective AAC reactions of terminal and internal alkynes have been well developed *via* metal-catalysis or strain release strategies.[4] However, as the classical AAC process itself does not generate stereogenic elements, its

application in enantioselective synthesis is inherently limited.. Current strategies of asymmetric AAC reactions mainly relied on (dynamic) kinetic resolution,[5] and desymmetrization of diynes[6] to convert achiral or racemic compounds into enantiomerically enriched products. In this context, building on our previous study on the regioselective cycloaddition of internal alkynes and azides,[7] we developed a rhodium-catalyzed atroposelective AAC between *ortho*-alkynyl phenols/naphthols and azides for the construction of a chiral axis through the click process (Scheme 1).[8] This methodology directly installs the chiral element *via* AAC, and demonstrates a very broad structural scope (Scheme 2), excellent functional group tolerance, high efficiency, and excellent enantioselectivity, providing a modular and rapid access to structurally diverse axially chiral molecules *via* click chemistry.

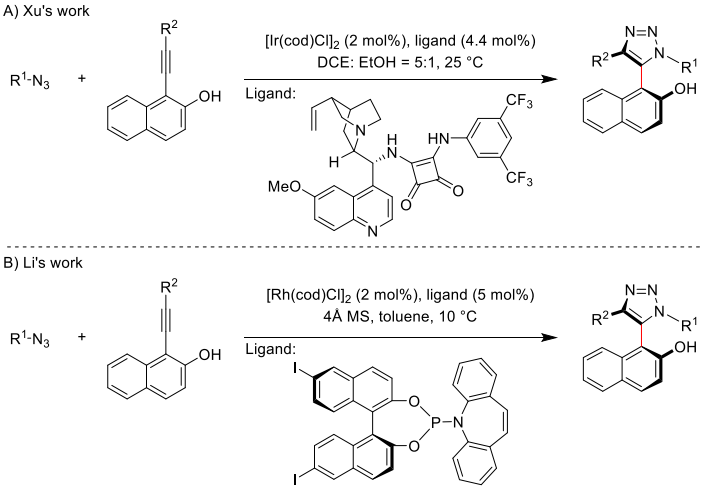


Scheme 1: Rhodium-catalyzed atroposelective AAC



Scheme 2: Selective substrate scope of the axially chiral triazoles

It is worth noting that Xu's group and Li's group reported similar chemistry between *ortho*-alkynylnaphthols and azides under iridium and rhodium catalysis slightly prior to our study (Scheme 3).[9] Moreover, Xu's group further developed a rhodium-catalyzed atroposelective AAC reaction between *N*-alkynylindoles and azides for the construction of chiral C-N axis, expanding the structural diversity of axially chiral triazoles.[10]



Scheme 3: Similar atroposelective AAC methodologies

These works have paved the way for click chemistry in axial chirality, and hold great promise for broad applications across atroposelective synthesis, medicinal chemistry, and chemical biology.

References

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Provincial Key R&D Program (2021C03082), Joint Funding Foundation of Zhejiang University-Huahai Pharmaceutical Co, Ltd., and Postdoctoral Science Foundation of China (2021M702891).

2. Experimental verification ("checking") was performed by Moshood O. Ganiu under the supervision of *Organic Syntheses* Editor Nathan D. Ide, nathan.ide@abbvie.com, https://orcid.org/0000-0002-7738-0094 and with financial support from Organic Syntheses, Inc.
3. For reviews, see: (a) Fairbanks, B. D.; Macdougall, L. J.; Mavila, S.; Sinha, J.; Kirkpatrick, B. E.; Anseth, K. S.; Bowman, C. N. Photoclick Chemistry: A Bright Idea. *Chem. Rev.* **2021**, *121*, 6915-6990. DOI: 10.1021/acs.chemrev.0c01212. (b) Fantoni, N. Z.; El-Sagheer, A. H.; Brown, T. A Hitchhiker's Guide to Click-Chemistry with Nucleic Acids. *Chem. Rev.* **2021**, *121*, 7122-7154. DOI: 10.1021/acs.chemrev.0c00928. (c) Kaur, J.; Saxena, M.; Rishi, N. An Overview of Recent Advances in Biomedical Applications of Click Chemistry. *Bioconjug. Chem.* **2021**, *32*, 1455-1471. DOI: 10.1021/acs.bioconjchem.1c00247. (d) Kolb, H. C.; Sharpless, K. B. The Growing Impact of Click Chemistry on Drug Discovery. *Drug Discov. Today* **2003**, *8*, 1128-1137. DOI: 10.1016/s1359-6446(03)02933-7. (e) Kumar, G. S.; Lin, Q. Light-Triggered Click Chemistry. *Chem. Rev.* **2021**, *121*, 6991-7031. DOI: 10.1021/acs.chemrev.0c00799. (f) Suazo, K. F.; Park, K. Y.; Distefano, M. D. A Not-So-Ancient Grease History: Click Chemistry and Protein Lipid Modifications. *Chem. Rev.* **2021**, *121*, 7178-7248. DOI: 10.1021/acs.chemrev.0c01108. (g) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical-Biology Applications. *Chem. Rev.* **2013**, *113*, 4905-4979. DOI: 10.1021/cr200409f.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

1-Iodo-2-naphthol; (2033-42-3)
DMAP: 4-Dimethylaminopyridine; (1122-58-3)
TEA: Triethylamine; (121-44-8)
Ac_2O: Acetic anhydride; (108-24-7)
$Pd(PPh_3)_2Cl_2$: Bis(triphenylphosphine)palladium(II) dichloride; (13965-03-2)
CuI: Copper(I) iodide; (7681-65-4)
Phenylacetylene; (536-74-3)
Hydrazine hydrate; (10217-52-4)
Benzyl azide; (622-79-7)
$[Rh(cod)OH]_2$: Hydroxy(cyclooctadiene)rhodium(I) dimer; (73468-85-6)
(*S*)-(+)-*N*-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)-dibenzo[b,*f*]azepine; (942939-38-0)

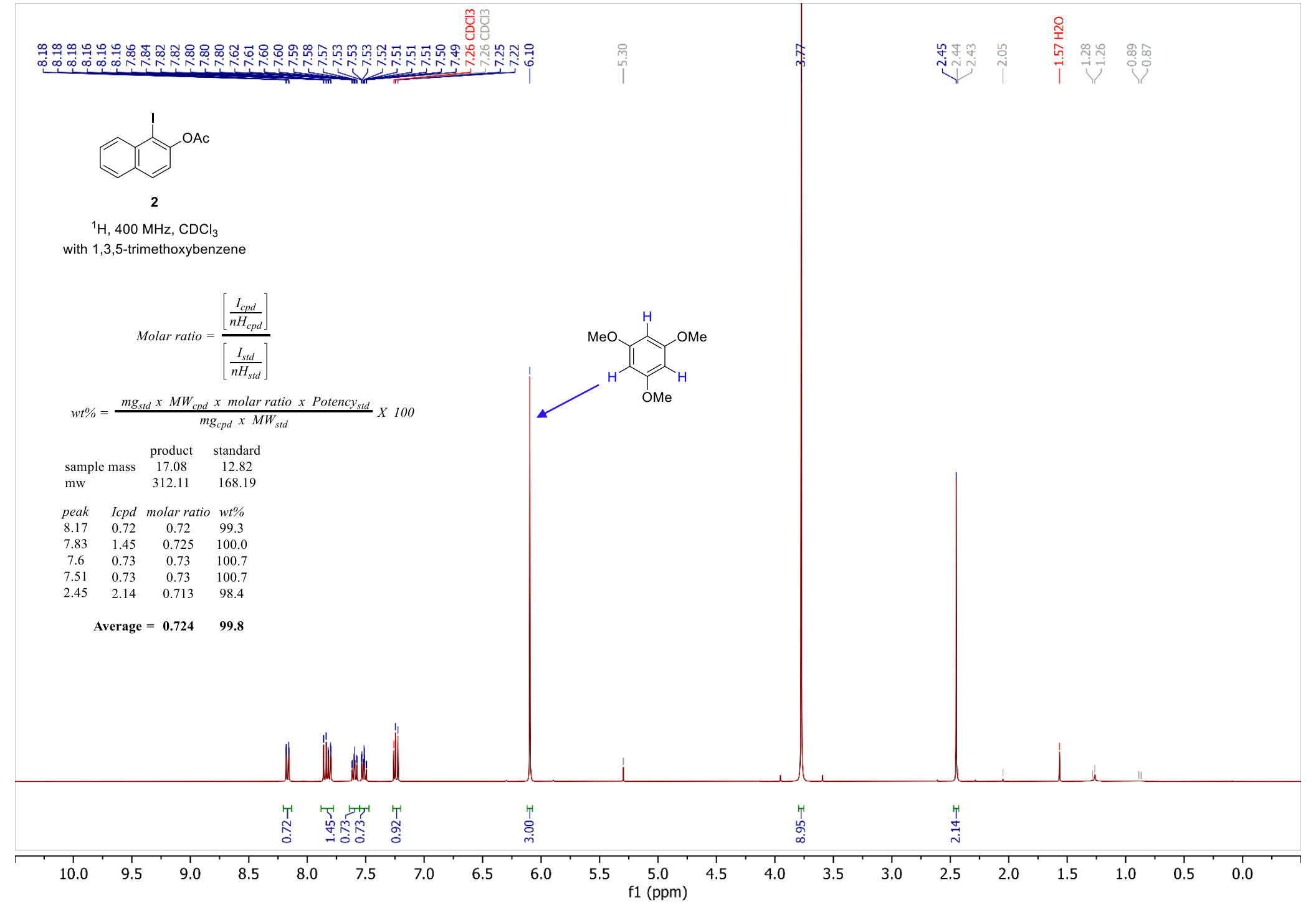
Linwei Zeng was born in Zhejiang, China. He received his B.Eng. (2012) from Zhejiang University of Technology, followed by an M.Pharm. (2015) and Ph.D. (2021) from Zhejiang University, where he conducted his doctoral research under the supervision of Professor Sunliang Cui. He completed his postdoctoral research (2021-2023) under Professors Fengzhi Zhang and Sunliang Cui, and then continued his postdoctoral work at the University of Cambridge. His research spans synthetic chemistry and interdisciplinary fields, including drug discovery and chemical biology.

Jiaming Li was born in Zhejiang, China. He received his B.Eng. (2019) from East China University of Science and Technology. He obtained his Ph.D. (2024) from Zhejiang University under the supervision of Professor Sunliang Cui, focusing on the development of multicomponent reactions and their applications in drug discovery. He is currently continuing his postdoctoral research on synthetic chemistry and medicinal chemistry within the same group.

Sunliang Cui received his B.Sc. (2003) and Ph.D. (2008) from Zhejiang University under the supervision of Prof. Yanguang Wang. He then completed postdoctoral training at Colorado State University (2008–2010) and the University of South Florida (2010–2012). In 2012, he began his independent academic career at Zhejiang University, where he is currently a full professor. The research interests of his group range from organic synthesis to multidisciplinary fields, with a particular focus on medicinal chemistry and drug discovery.

Moshood O. Ganiu received his undergraduate degree from Lagos State University, where he pursued undergraduate research with Prof. M. S. Owolabi. He obtained his Ph.D. from Louisiana State University working under the guidance of Prof. Rendy Kartika. Following his graduate studies, Moshood joined the Discovery Scale-Up group at Amgen. In 2024, Moshood joined the Process Chemistry group at AbbVie where he is currently a Senior Scientist.

Nathan D. Ide received his undergraduate degree from Hope College, where he pursued undergraduate research with Prof. Stephen K. Taylor. He obtained a Ph.D. from the University of Illinois at Urbana-Champaign, working under the guidance of Prof. David Y. Gin. He currently serves as the Head of Process Chemistry at AbbVie.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mw 312.11 168.19
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7.51 0.73 0.73 100.7
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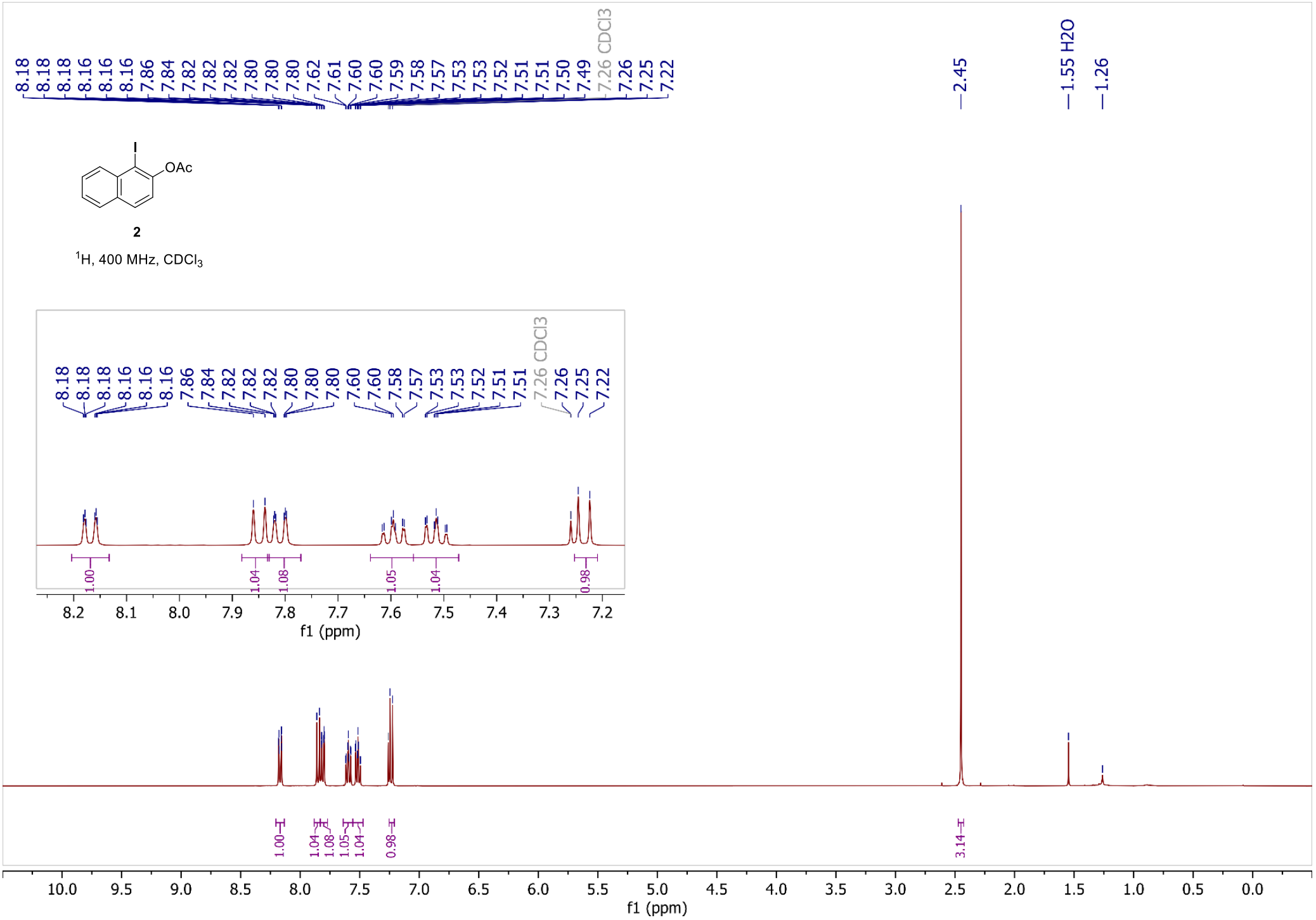
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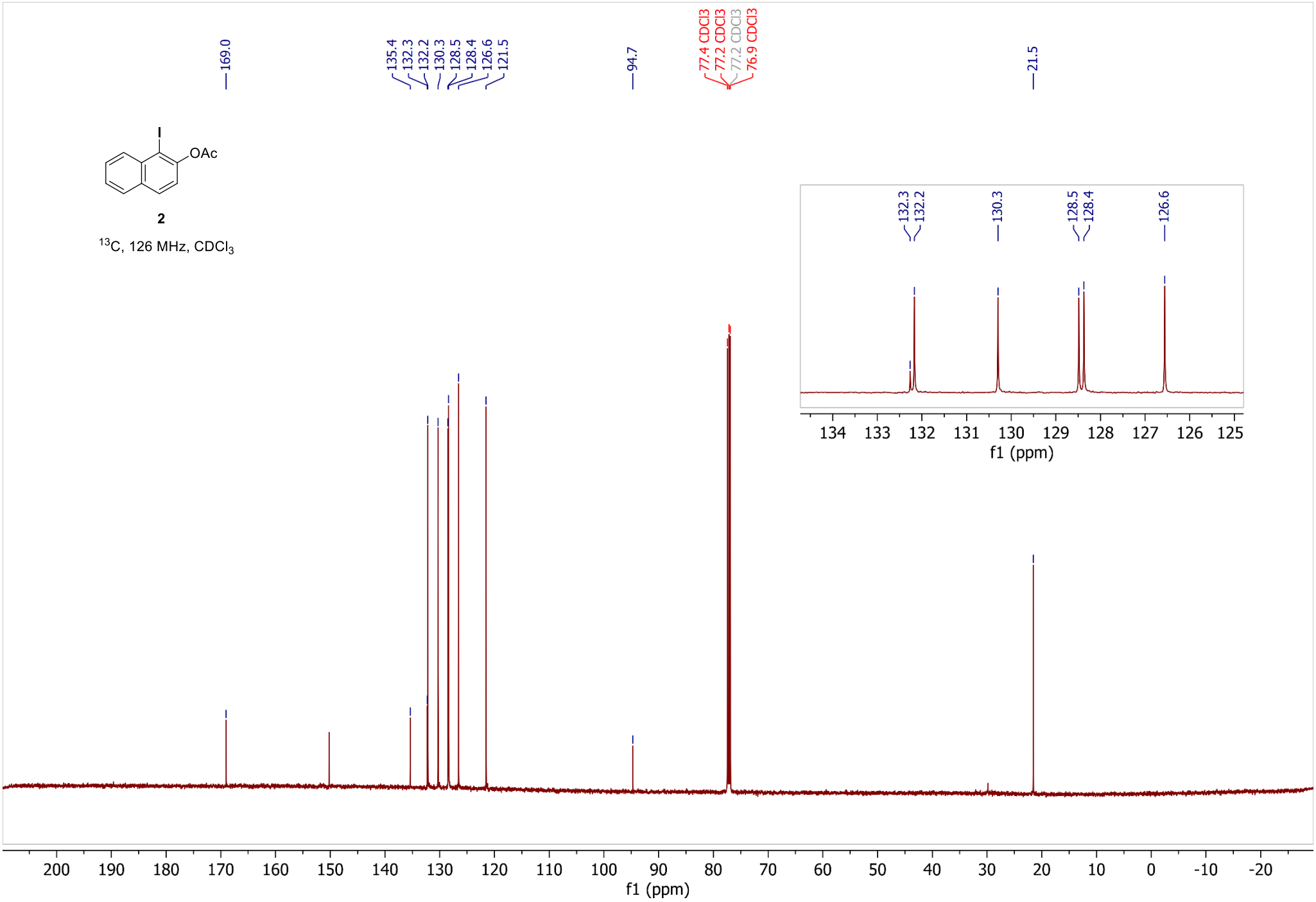
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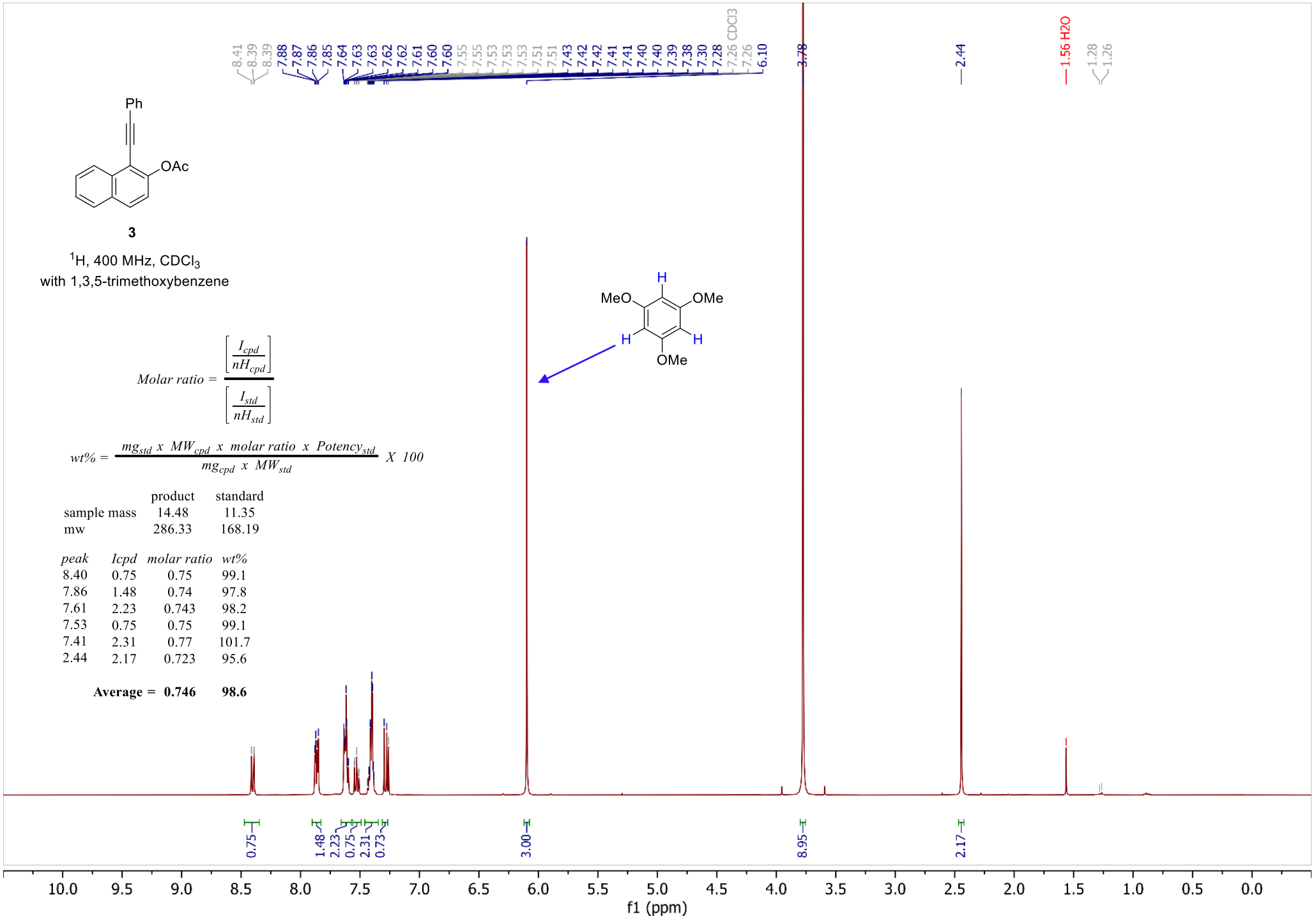
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OAc
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OMe
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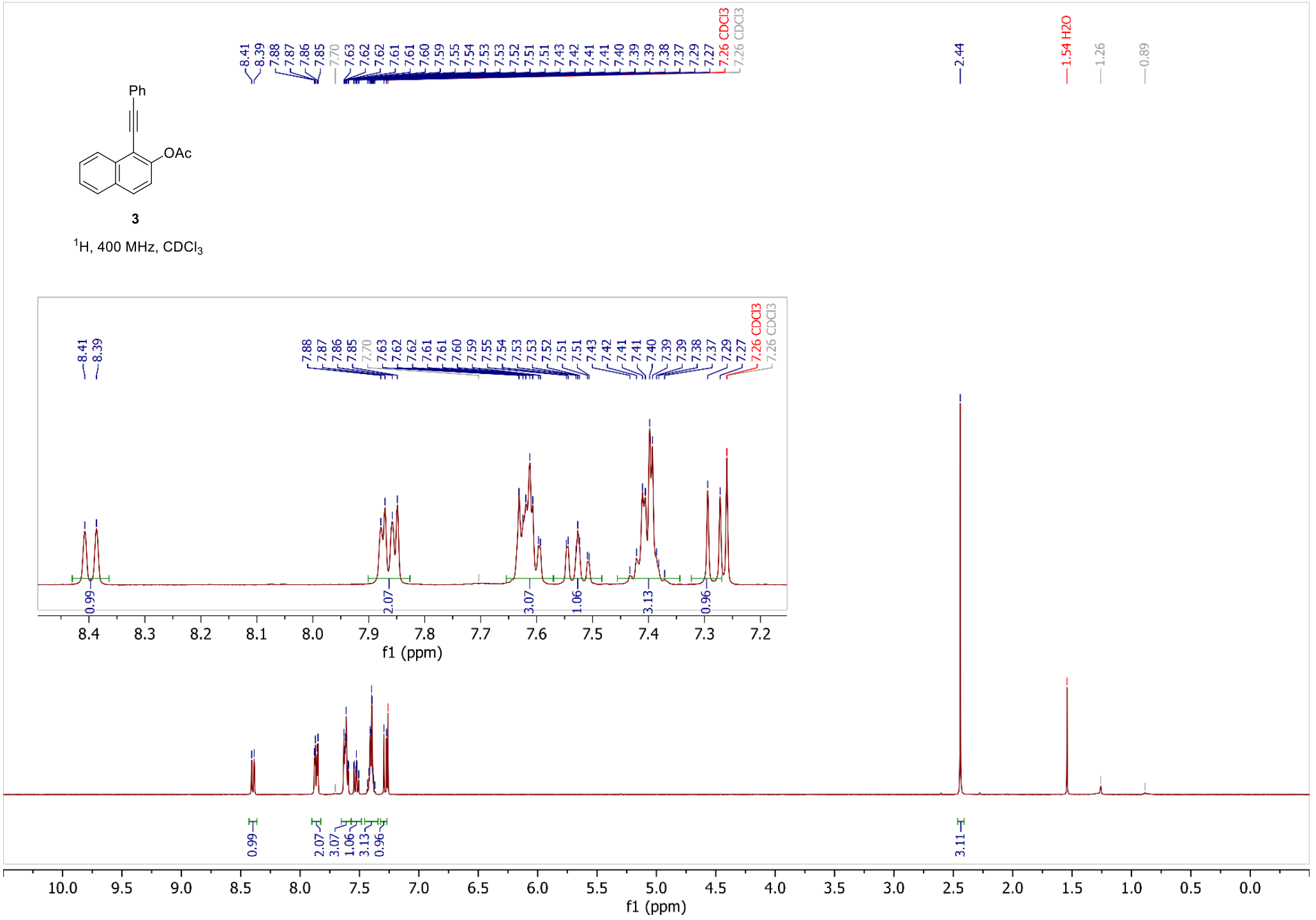
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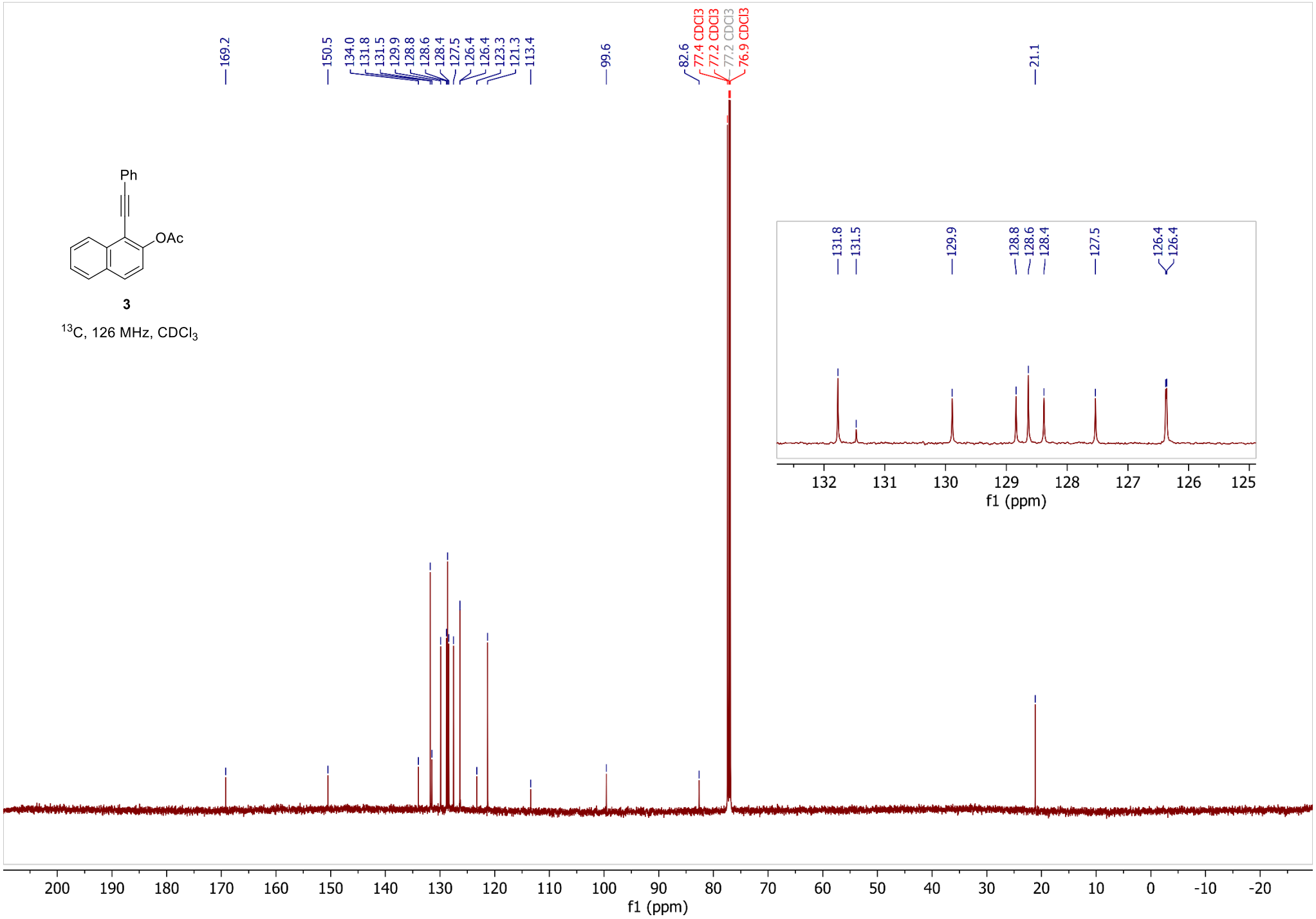
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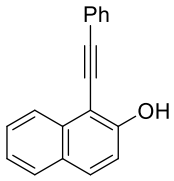
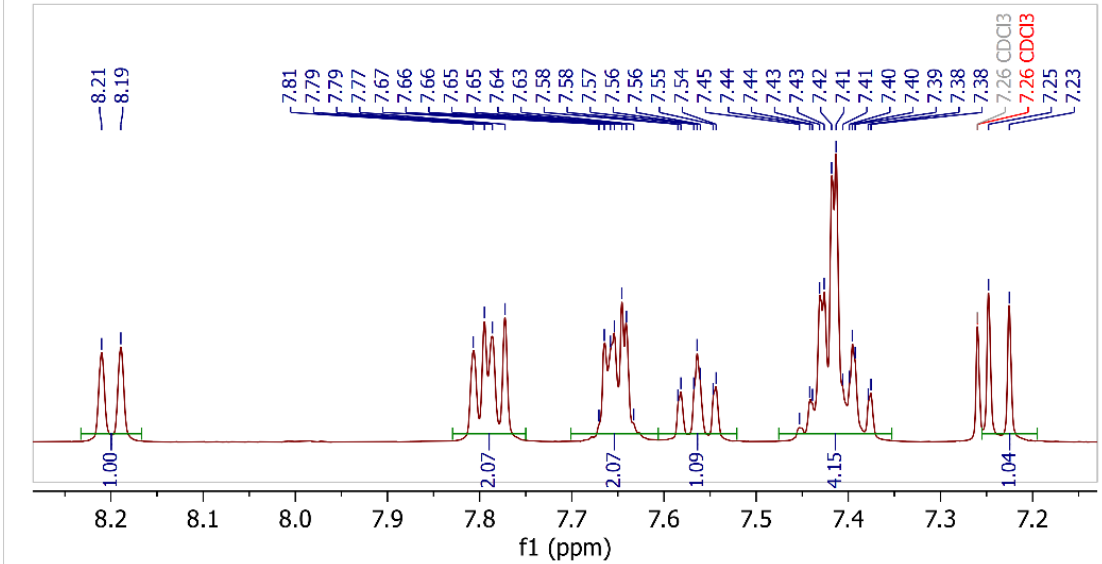
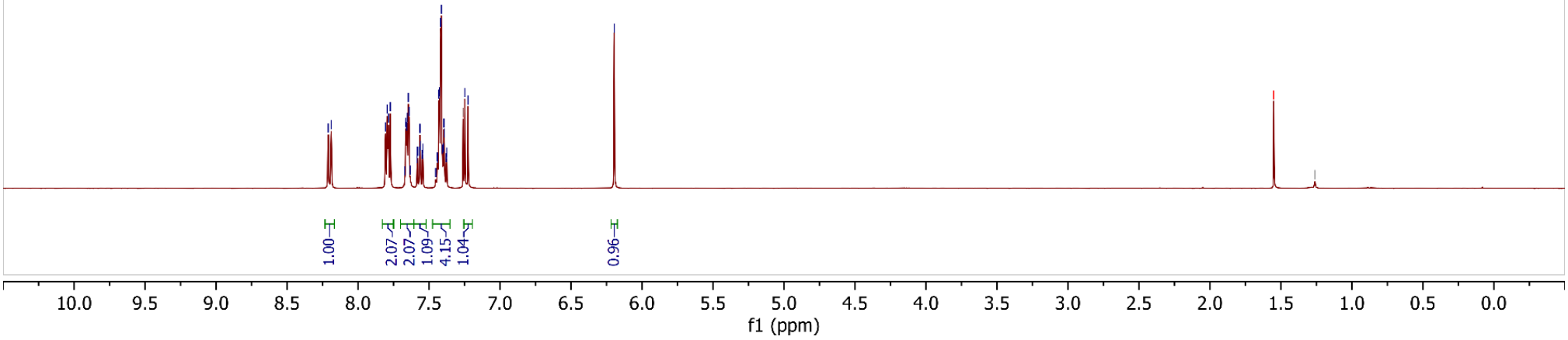
-20
f1 (ppm)

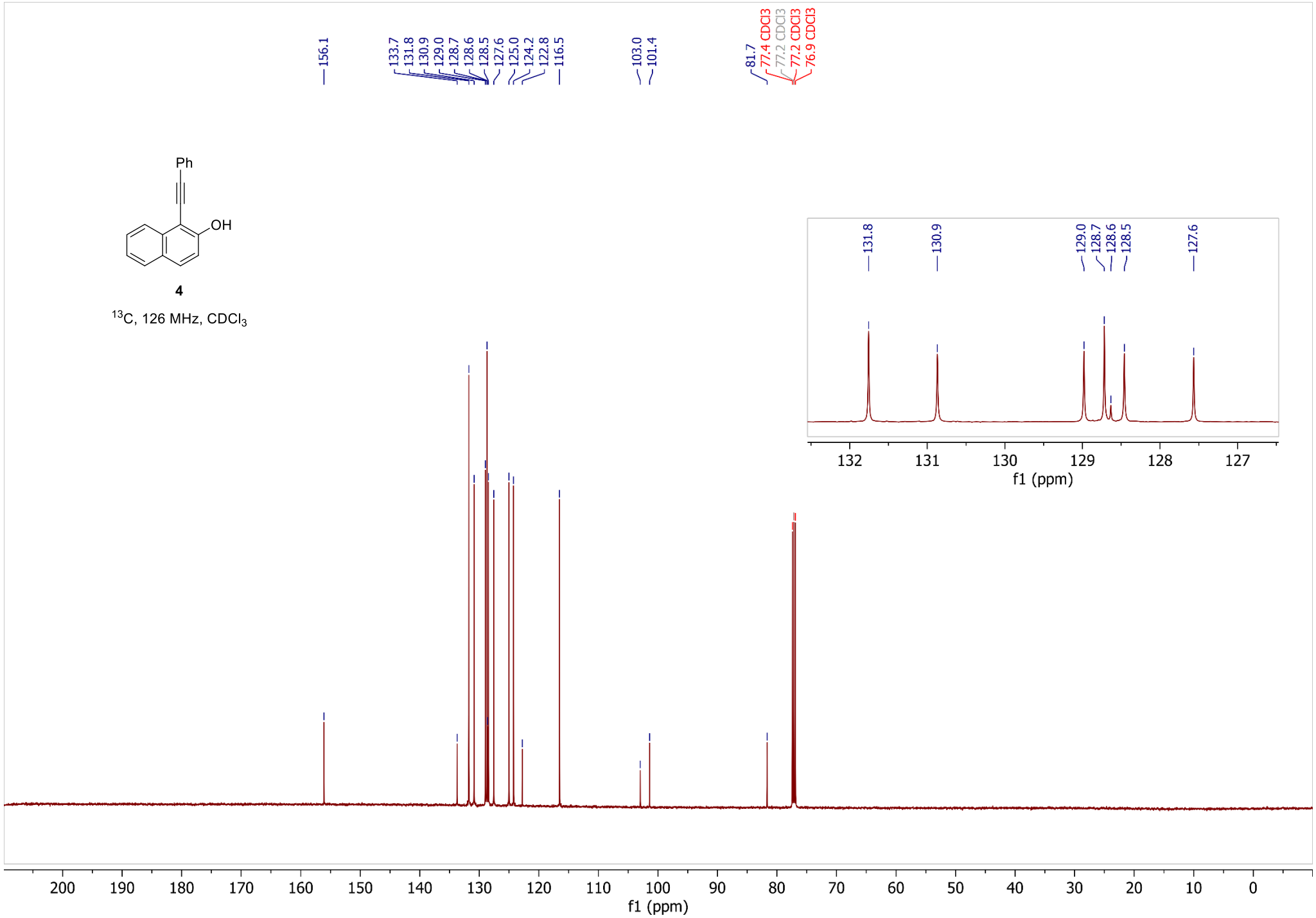


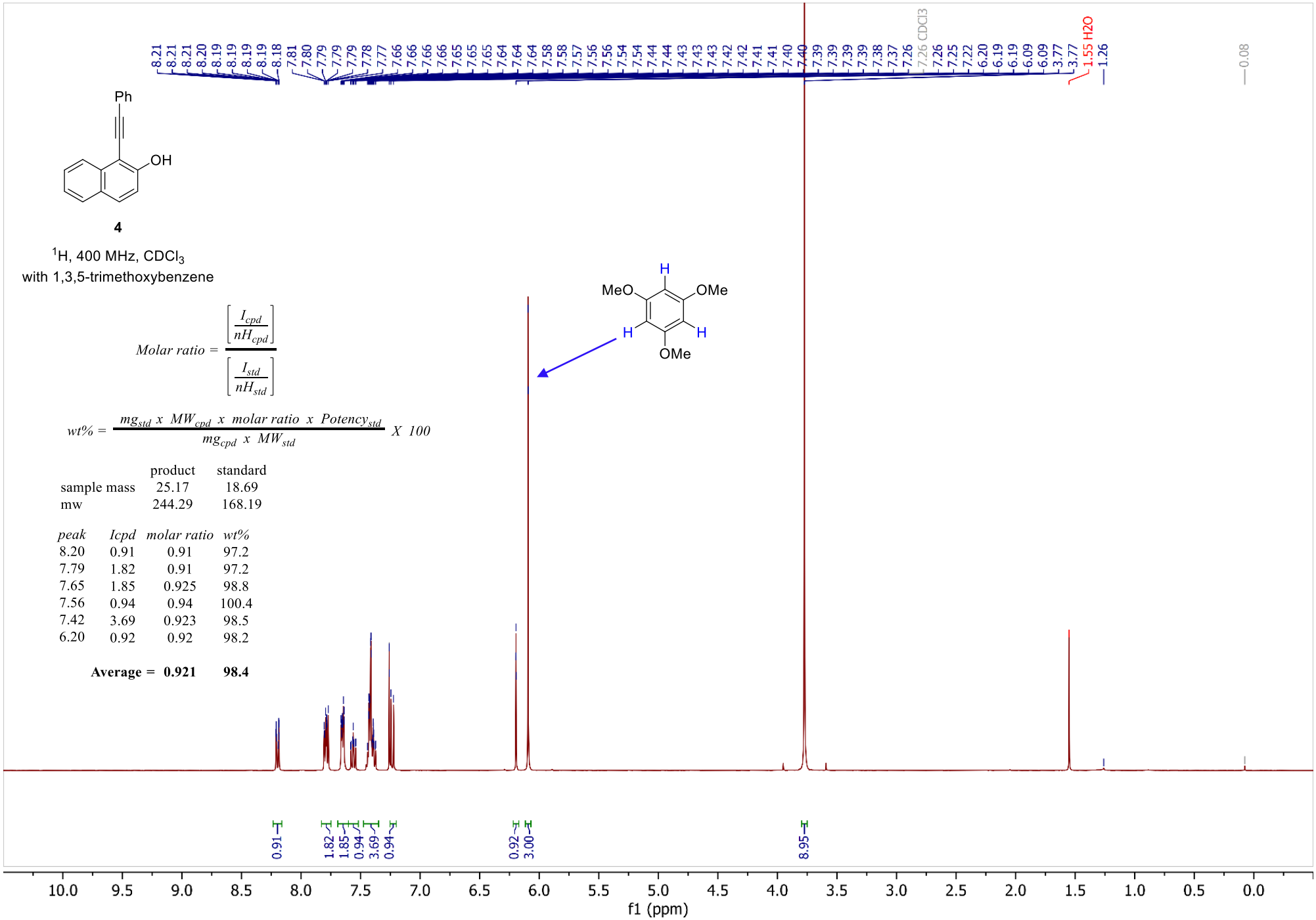
4

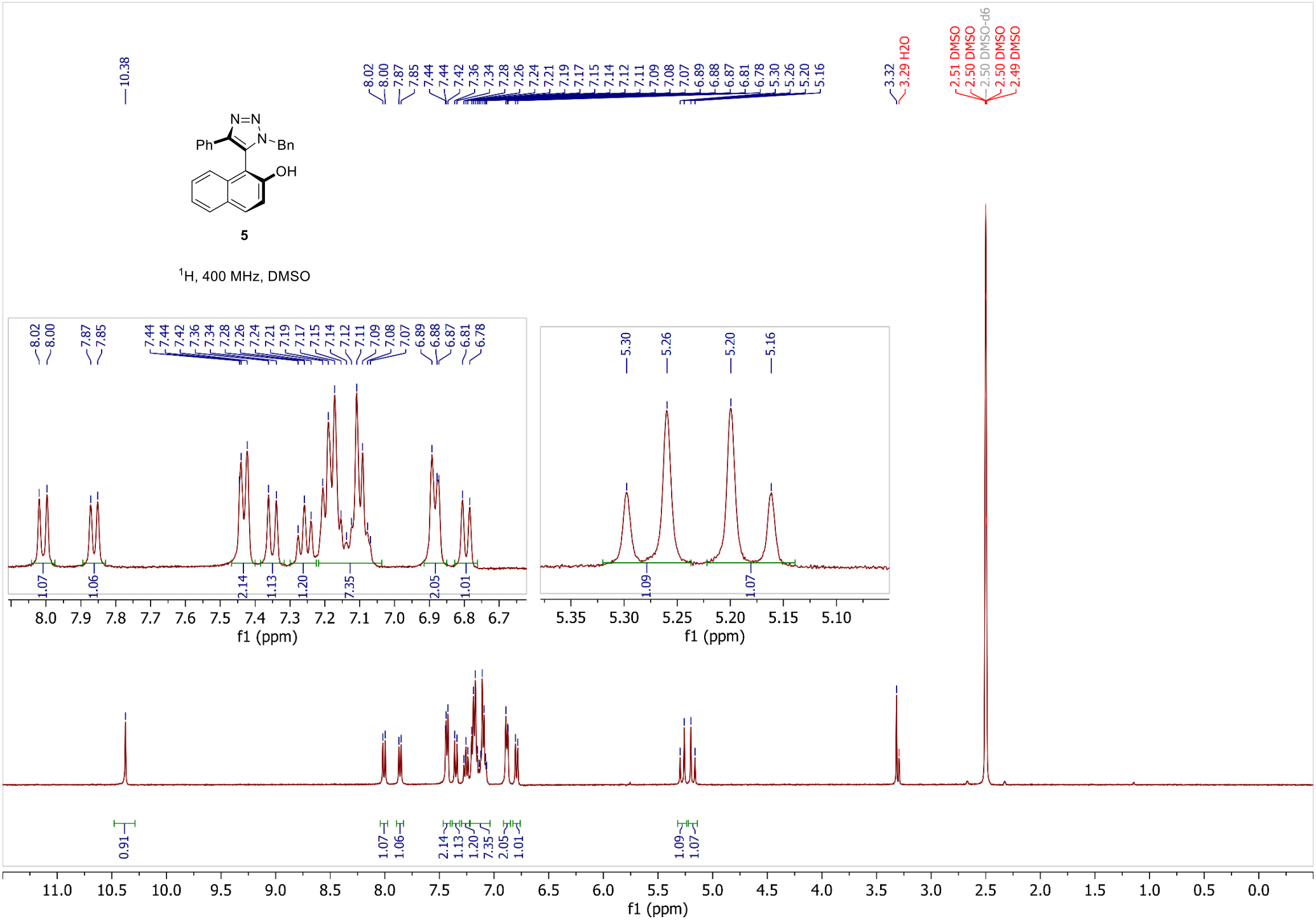
^{1}H, 400 MHz, $CDCl_3$

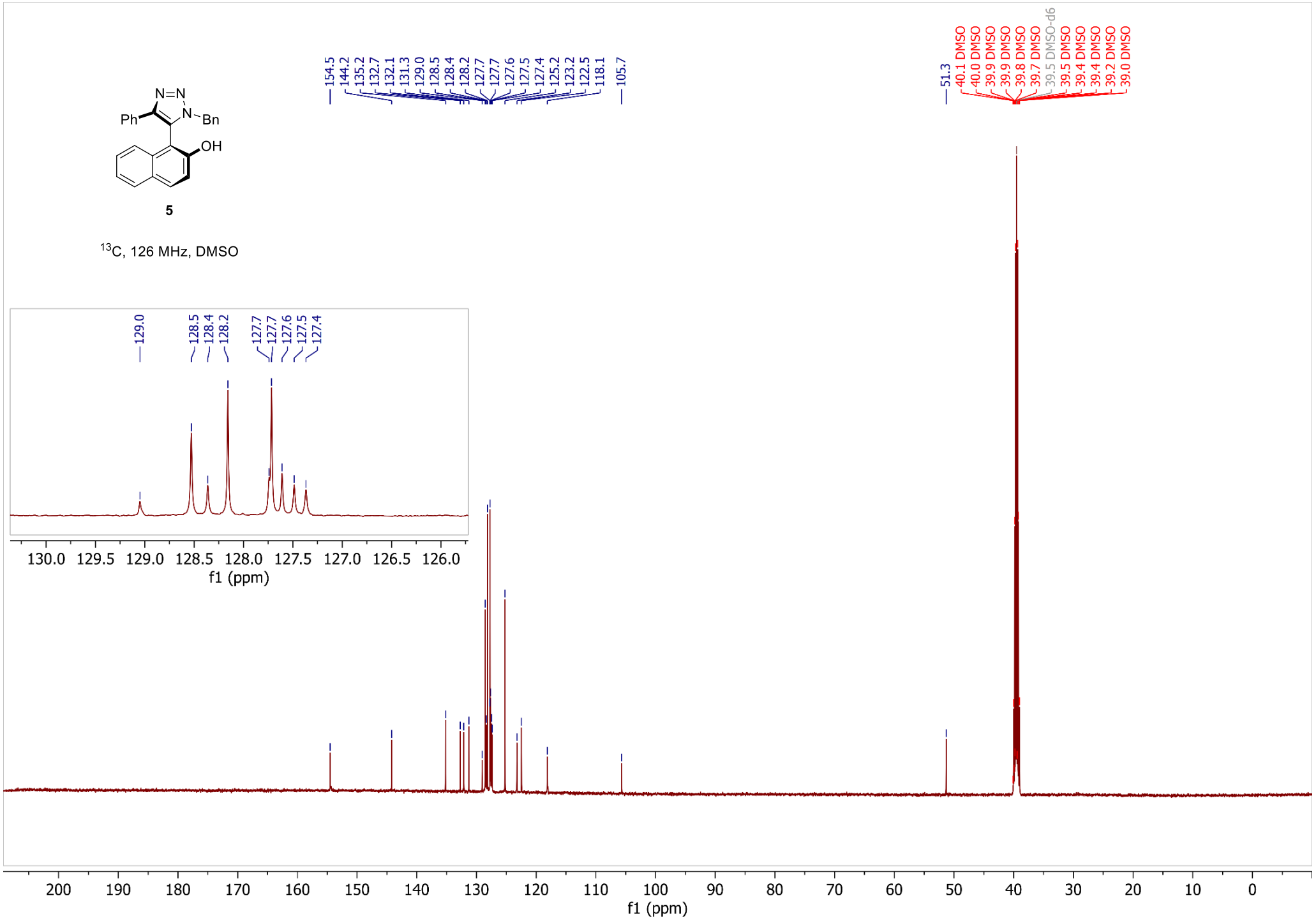


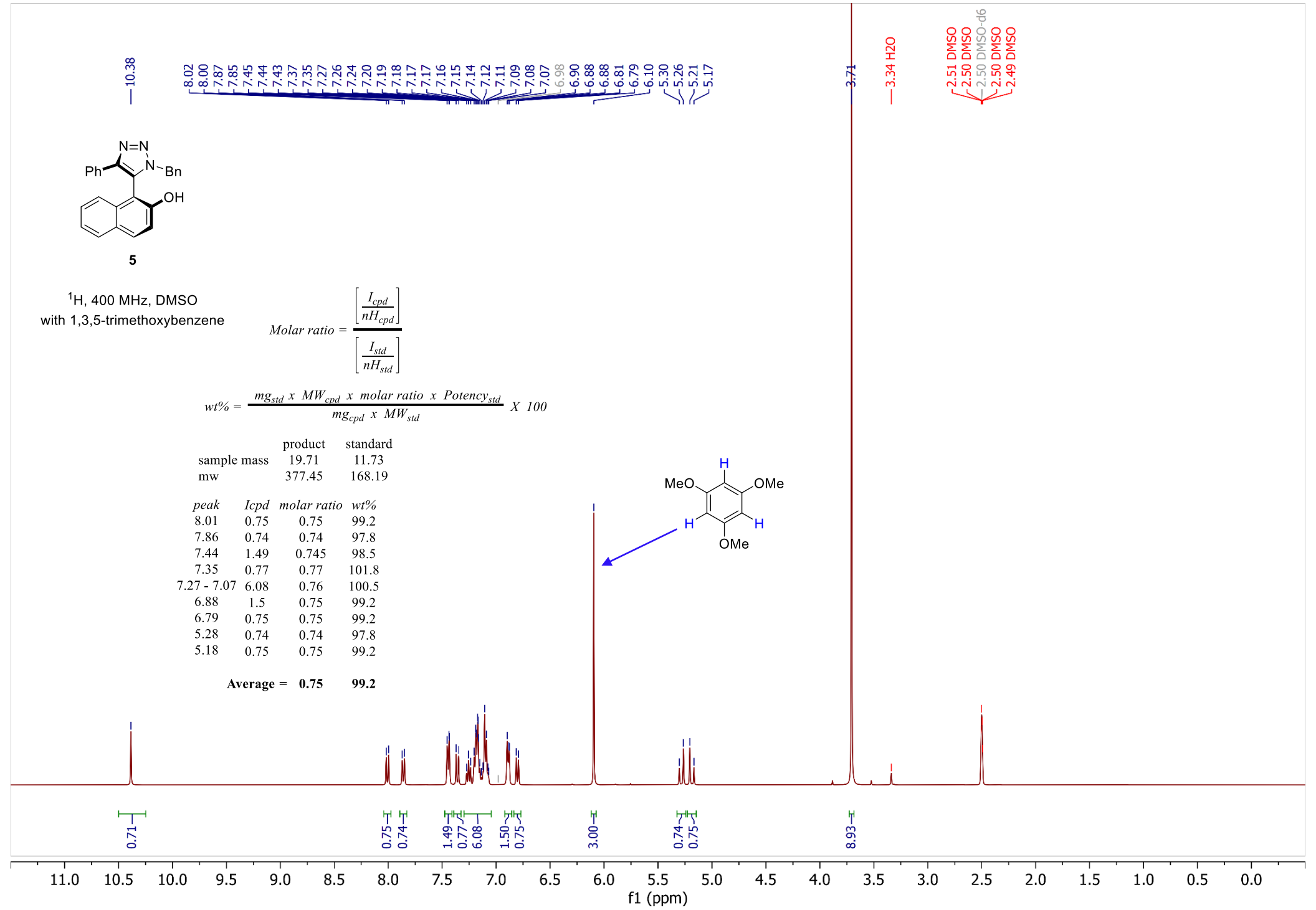



156.1
133.7
131.8
130.9
129.0
128.7
128.6
128.5
127.6
125.0
124.2
122.8
116.5
103.0
101.4
81.7
77.4 CDCl3
77.2 CDCl3
77.2 CDCl3
76.9 CDCl3
Ph
OH
4
13C, 126 MHz, CDCl3
131.8
130.9
129.0
128.7
128.6
128.5
127.6
132
131
130
129
128
127
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.21 8.21 8.21 8.20 8.19 8.19 8.19 8.19 8.18 7.81 7.80 7.79 7.79 7.79 7.78 7.77 7.66 7.66 7.66 7.65 7.65 7.65 7.64 7.64 7.64 7.58 7.58 7.57 7.56 7.56 7.54 7.54 7.44 7.44 7.43 7.43 7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.39 7.39 7.38 7.37 7.26 7.26 CDCl3 7.26 7.25 7.22 6.20 6.19 6.19 6.09 6.09 3.77 1.55 H2O 1.26 0.08
Ph
OH
4
1H, 400 MHz, CDCl3
with 1,3,5-trimethoxybenzene
H
MeO
OMe
H
H
OMe
Molar ratio = [Icpd / nHcpd] / [Istd / nHstd]
wt% = mgstd x MWcpd x molar ratio x Potencystd / mgcpd x MWstd X 100
product standard
sample mass 25.17 18.69
mw 244.29 168.19
peak Icpd molar ratio wt%
8.20 0.91 0.91 97.2
7.79 1.82 0.91 97.2
7.65 1.85 0.925 98.8
7.56 0.94 0.94 100.4
7.42 3.69 0.923 98.5
6.20 0.92 0.92 98.2
Average = 0.921 98.4
0.91 1.82 1.85 0.94 3.69 0.94 0.92 3.00 8.95
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
f1 (ppm)

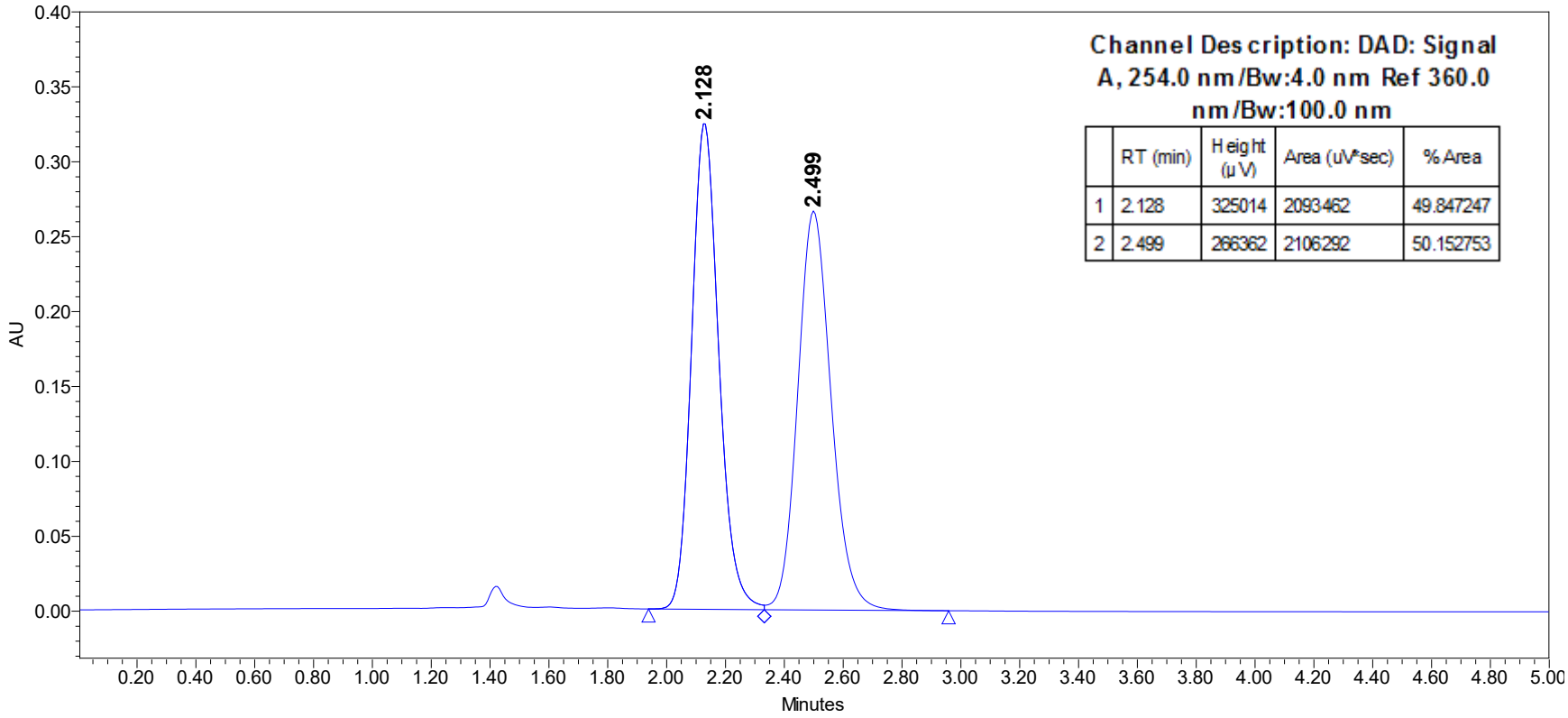

10.38
8.02
8.00
7.87
7.85
7.44
7.44
7.42
7.36
7.34
7.28
7.26
7.24
7.21
7.19
7.17
7.15
7.14
7.12
7.11
7.09
7.08
7.07
6.89
6.88
6.87
6.81
6.78
5.30
5.26
5.20
5.16
3.32
3.29 H2O
2.51 DMSO
2.50 DMSO
2.50 DMSO-d6
2.50 DMSO
2.49 DMSO
N=N
Ph
N
Bn
OH
5
1H, 400 MHz, DMSO
f1 (ppm)
f1 (ppm)
f1 (ppm)


N=N
Ph
N
Bn
OH
5
13C, 126 MHz, DMSO
154.5
144.2
135.2
132.7
132.1
131.3
129.0
128.5
128.4
128.2
127.7
127.7
127.6
127.5
127.4
125.2
123.2
122.5
118.1
105.7
51.3
40.1 DMSO
40.0 DMSO
39.9 DMSO
39.9 DMSO
39.8 DMSO
39.7 DMSO
39.5 DMSO-d6
39.5 DMSO
39.4 DMSO
39.4 DMSO
39.2 DMSO
39.0 DMSO
129.0
128.5
128.4
128.2
127.7
127.7
127.6
127.5
127.4
130.0 129.5 129.0 128.5 128.0 127.5 127.0 126.5 126.0
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


10.38
8.02
8.00
7.87
7.85
7.45
7.44
7.43
7.37
7.35
7.27
7.26
7.24
7.20
7.19
7.18
7.17
7.17
7.16
7.15
7.14
7.12
7.11
7.09
7.08
7.07
6.98
6.90
6.88
6.88
6.81
6.79
6.10
5.30
5.26
5.21
5.17
3.71
3.34 H2O
2.51 DMSO
2.50 DMSO
2.50 DMSO-d6
2.50 DMSO
2.49 DMSO
N=N
Ph
N
Bn
OH
5
1H, 400 MHz, DMSO
with 1,3,5-trimethoxybenzene
Molar ratio = [Icpd / nHcpd] / [Istd / nHstd]
wt% = mgstd x MWcpd x molar ratio x Potencystd / mgcpd x MWstd X 100
product standard
sample mass 19.71 11.73
mw 377.45 168.19
peak Icpd molar ratio wt%
8.01 0.75 0.75 99.2
7.86 0.74 0.74 97.8
7.44 1.49 0.745 98.5
7.35 0.77 0.77 101.8
7.27 - 7.07 6.08 0.76 100.5
6.88 1.5 0.75 99.2
6.79 0.75 0.75 99.2
5.28 0.74 0.74 97.8
5.18 0.75 0.75 99.2
Average = 0.75 99.2
H
MeO
OMe
H
H
OMe
0.71
0.75
0.74
1.49
0.77
6.08
1.50
0.75
3.00
0.74
0.75
8.93
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
f1 (ppm)

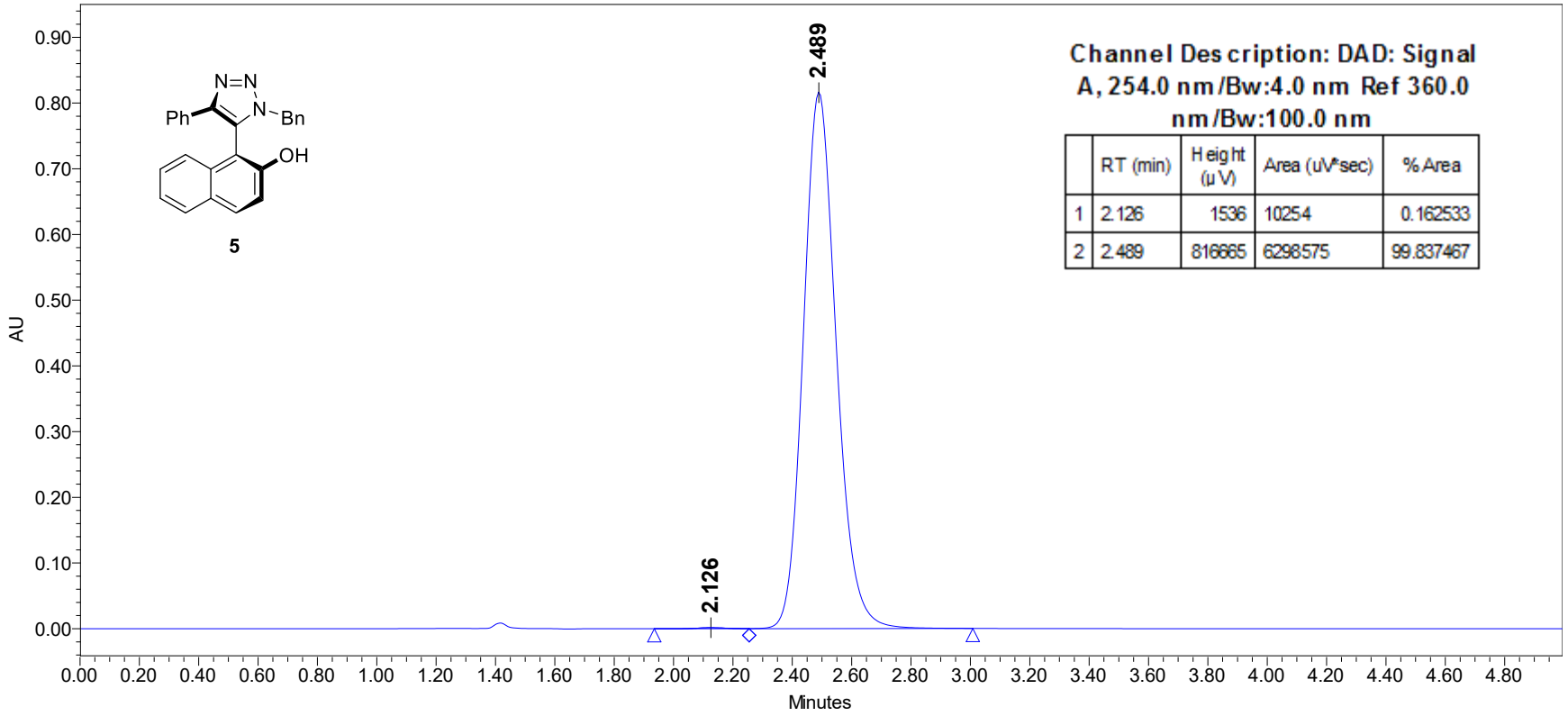
Chiral HPLC conditions: The chiral HPLC analysis was performed by isocratic elution using a 60:40 mixture of hexane (Sigma Aldrich, 98.5%): *i*-PrOH (Sigma Aldrich, HPLC grade) using a Chiralpak IC-3 (3 µm, 4.6 x 100 mm) Part Number 83523, Flowrate of 1 ml/min, monitoring at 254 nm at column temperature of 30 °C. t (major) = 2.5 min, t (minor) = 2.1 min.

Racemic mixture:



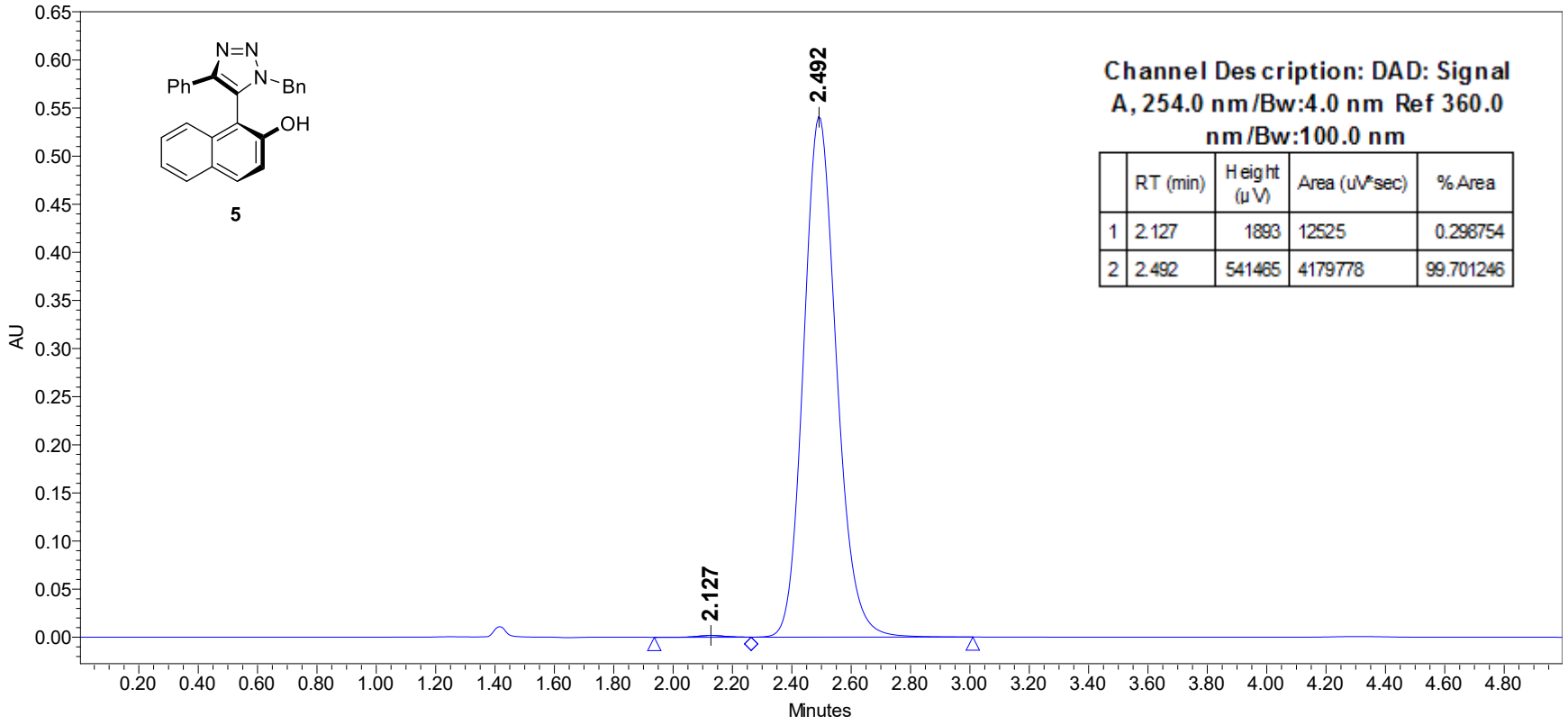
	RT (min)	Height (µV)	Area (uV*sec)	% Area
1	2.128	325014	2093462	49.847247
2	2.499	266362	2106292	50.152753

Run 1:



	RT (min)	Height (μV)	Area (uV*sec)	% Area
1	2.126	1536	10254	0.162533
2	2.489	816665	6298575	99.837467

Run 2:



	RT (min)	Height (µV)	Area (uV*sec)	% Area
1	2.127	1893	12525	0.298754
2	2.492	541465	4179778	99.701246