

Copper Hydride-Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes

Liela Bayeh, Stephen L. Buchwald

Submitted date: 23/07/2019 • Posted date: 24/07/2019

Licence: CC BY-NC-ND 4.0

Citation information: Bayeh, Liela; Buchwald, Stephen L. (2019): Copper Hydride-Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes. ChemRxiv. Preprint.

The general enantioselective synthesis of axially chiral disubstituted allenenes from prochiral starting materials remains a long-standing challenge in organic synthesis. Here, we report an efficient enantio- and chemoselective copper hydride-catalyzed semi-reduction of conjugated enynes to furnish 1,3-disubstituted allenenes using water as the proton source. This protocol is sufficiently mild to accommodate an assortment of functional groups including keto, ester, amino, halo, and hydroxyl groups. Additionally, applications of this method for the selective synthesis of mono-deuterated allenenes and chiral 2,5-dihydropyrroles are described.

File list (4)

Manuscript-Final.pdf (546.42 KiB)	view on ChemRxiv • download file
Supporting Information.pdf (597.99 KiB)	view on ChemRxiv • download file
NMR Spectra.pdf (4.66 MiB)	view on ChemRxiv • download file
SFC GC and HPLC Traces.pdf (1.82 MiB)	view on ChemRxiv • download file

Copper Hydride-Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes

Liela Bayeh-Romero and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

ABSTRACT: The general enantioselective synthesis of axially chiral disubstituted allenenes from prochiral starting materials remains a long-standing challenge in organic synthesis. Here, we report an efficient enantio- and chemoselective copper hydride-catalyzed semi-reduction of conjugated enynes to furnish 1,3-disubstituted allenenes using water as the proton source. This protocol is sufficiently mild to accommodate an assortment of functional groups including keto, ester, amino, halo, and hydroxyl groups. Additionally, applications of this method for the selective synthesis of mono-deuterated allenenes and chiral 2,5-dihydropyrroles are described.

Allenenes form a distinctive class of compounds capable of exhibiting axial chirality. They are represented in over 2,900 natural metabolites and synthetic compounds, and have been studied with regard to biological activity for over forty years.¹ The introduction of allenenes into steroids, prostaglandins, carbacyclins, and unnatural amino acids and nucleosides has been shown to increase the metabolic stability, bioavailability, and potency of these bioactive compounds.² Additionally, these cumulated dienes have found use in molecular materials and as synthetic intermediates in complex chemical syntheses as substrates due to their substituent-loading capability and enhanced reactivity under mild reaction conditions. Their transformation often takes advantage of axial-to-central chirality transfer to generate one or more new stereogenic centers.³ Finally, chiral allenenes have also been explored in asymmetric autocatalysis and as ligands for the development of enantioselective transformations.⁴⁻⁶

While the utility of chiral allenenes has been widely explored, the selective synthesis of these valuable materials still remains a challenge in organic synthesis.^{3a, 7} Traditional approaches to access enantioenriched allenenes most commonly start from chiral, enantioenriched precursors wherein the allene product is generated through nucleophilic displacement, rearrangement or elimination with central-to-axial chirality transfer (Figure 1) or through resolution of racemic allenenes. More recently, several methods have employed achiral or racemic starting materials in catalytic asymmetric versions of these reactions to access the desired product using catalysts bearing chiral ligands. However, the majority of these reports target the synthesis of tri- or tetrasubstituted allenenes.⁸

The direct catalytic conversion of prochiral 1,3-enynes to enantioenriched allenenes has become a practical synthetic strategy in recent years, owing to the accessibility of these substrates.⁹ Early reports by Hayashi describe the direct catalytic and enantioselective conversion of 1,3-enynes to boryl-, silyl-, or aryl allenenes via palladium or rhodium catalysis.^{8a-d} Since then, methods detailing the stereoselective transformations of enynes, including reports by Loh, Feng, Tang, Sun and Malcolmson, have provided novel routes to enantioenriched allenenes containing esters, lactones or amines.^{8g, i, n, p, 10}

The LCuH-catalyzed hydrofunctionalization of 1,3-enynes to access enantioenriched allenenes was first reported by the Hoveyda group wherein trisubstituted allenyl boronate derivatives are generated in high yield and enantioselectivity (Scheme 1a).¹¹ Shortly thereafter, the Ge and Engle groups independently disclosed their own reports of enyne hydroboration, followed by Ge's report of the catalytic asymmetric hydroarylation of enynes to provide access to quinoline-substituted allenenes.¹²⁻¹⁴

Despite these recent advances, fewer reports describe the catalytic synthesis of enantioenriched 1,3-disubstituted allenenes from prochiral or racemic precursors.^{10, 15-20} While these

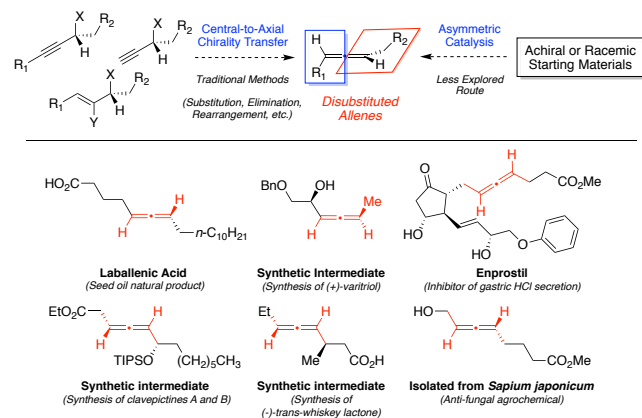
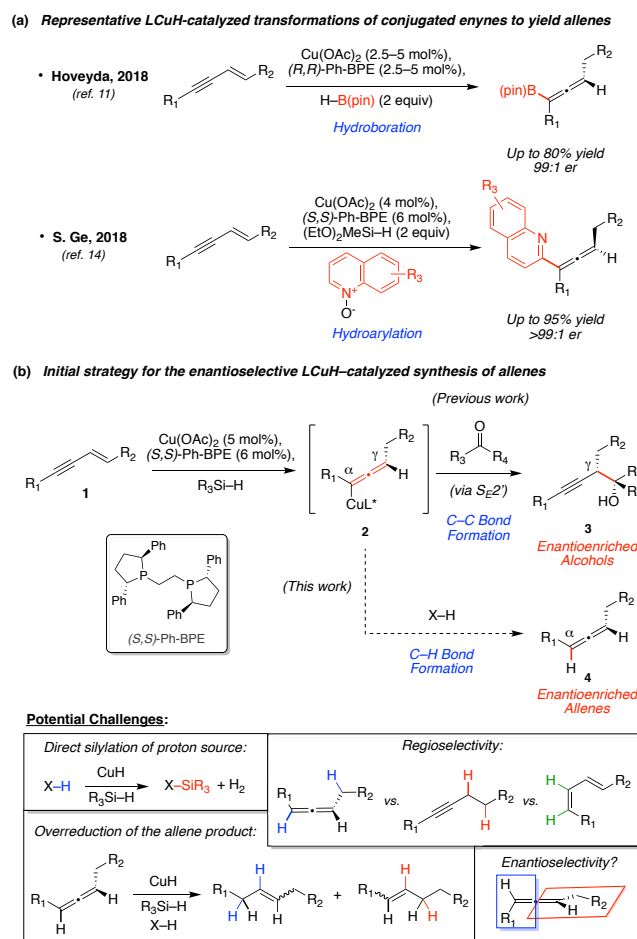


Figure 1. Synthetic strategies for the construction of enantiioenriched allenenes and representative examples of valuable 1,3-disubstituted allenenes

methods have offered elegant and innovative routes to this class of allenes, the vast majority of them provide access to a limited scope of products including allenyl esters,^{16, 18} alcohols,¹⁹ and amines.^{10, 16, 20} This modest scope is perhaps due to difficulty in controlling the stereochemical outcome of a three-carbon axis of chirality possessing two hydrogen substituents without an additional functional group handle. Consequently, there persists an unmet need for a general strategy to access a broad range of 1,3-disubstituted axially chiral allenes.

Scheme 1. Precedent for the Proposed Asymmetric LCuH-Catalyzed Semi-Reduction of 1,3-Enynes

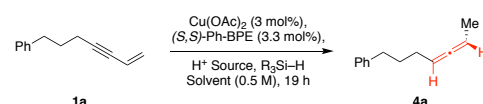


In the course of our ongoing studies on the hydroalkylation of 1,3-enynes with imines, we serendipitously discovered an alternative strategy for the synthesis of 1,3-disubstituted allenes (Scheme 1b). Analogous to our previous report on the hydroalkylation of conjugated enynes with ketones,²¹ enantioenriched allenyl copper intermediates **2** are generated *via* hydrocupration of an achiral 1,3-enyne starting material (**1**). However, trapping of the allenyl copper species **2** directly with a proton, instead of a ketone (which favors the alternative S_E2' reaction pathway to yield γ -adduct **3**), would provide access to axially chiral 1,3-disubstituted allenes (**4**). Potential challenges in developing this reaction include avoiding the unproductive silylation of the protonating reagent,²² the regioselectivity²³ and enantioselectivity of the process, and preventing further reduction of the allene product in the presence of the copper hydride catalyst. To date, the semi-reduction of 1,3-enynes to enantioenriched disubstituted allenes has only been demonstrated with the stoichiometric use of chiral metal reducing

agents.²⁴ Herein, we report the asymmetric catalytic semi-reduction of 1,3-enynes to furnish axially chiral allenes enabled by CuH-catalysis.

We began our studies utilizing 1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane [(*S,S*)-Ph-BPE] in combination with Cu(OAc)₂ and dimethoxy(methyl)silane (DMMS) to generate a chiral LCuH complex previously shown to engage 1,3-enyne **1a** (Table 1).²¹ At room temperature with *t*-BuOH as the proton source, the complete consumption of **1a** occurred yielding a complex mixture consisting primarily of products from the unselective hydrogenation of the desired product, allene **4a** (entry 1). Decreasing the reaction temperature to -10 °C slowed the over-reduction and provided **4a** in 34% yield and 60:40 enantiomeric ratio (er) (entry 2). A subsequent screen of several ethereal solvents indicated that both chemo- and enantioselectivity were enhanced by replacing THF with 1,2-dimethoxyethane (DME) (entries 3–5).

Table 1. Reaction Optimization^a



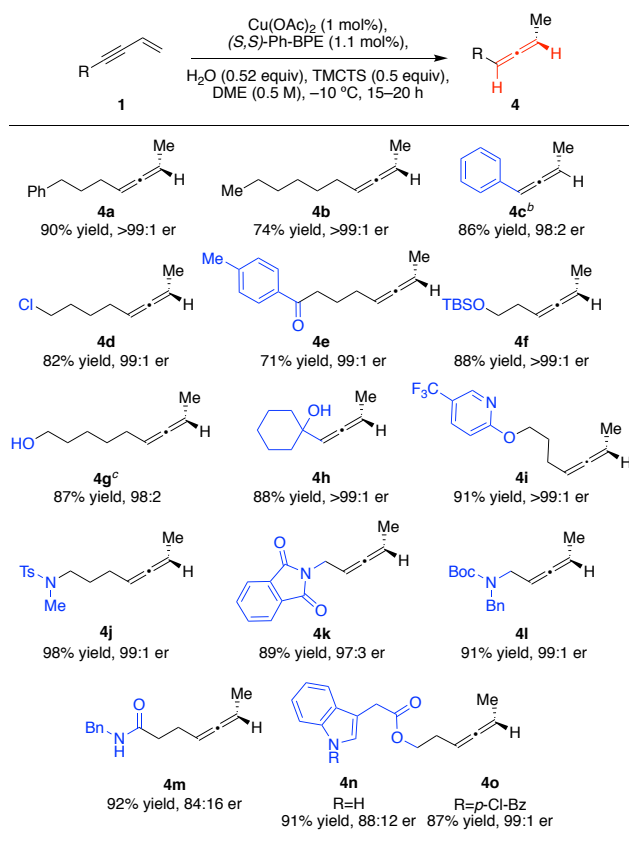
Entry	T (°C)	Solvent	Proton Source	Silane	% Conv.	% Yield ^b	er ^c
1	23	THF	<i>t</i> -BuOH (1.5 equiv)	DMMS	100	0	–
2	–10	THF	<i>t</i> -BuOH (1.5 equiv)	DMMS	100	34	60:40
3	–10	MTBE ^d	<i>t</i> -BuOH (1.5 equiv)	DMMS	64	36	87:13
4	–10	1,4-Dioxane	<i>t</i> -BuOH (1.5 equiv)	DMMS	67	26	92:8
5	–10	DME	<i>t</i> -BuOH (1.5 equiv)	DMMS	50	36	96:4
6	–10	DME	<i>i</i> -PrOH (1.5 equiv)	DMMS	100	68	99:1
7	–10	DME	<i>i</i> -PrOH (1.1 equiv)	DMMS	100	90	99:1
8	–10	DME	H ₂ O (0.55 equiv)	DMMS	100	90	>99:1
9 ^e	–10	DME	H ₂ O (0.52 equiv)	TMCTS	100	90 ^f	>99:1

^a Conditions: Reactions were carried out under N₂ atmosphere. 0.2 mmol enyne (1 equiv), copper(II) acetate (3 mol%), (*S,S*)-Ph-BPE (3.3 mol%), silane (4 equiv) in solvent (0.4 mL). ^b Yield was determined by ¹H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. ^c Enantiomeric ratio was determined by GC analysis, and the absolute configuration of **4a** was determined by analogy to desilylated **4f** (see the Supporting Information for more details). ^d MTBE = methyl *tert*-butyl ether. ^e Reaction was run with 1 mol% copper(II) acetate and 1.1 mol% (*S,S*)-Ph-BPE over 16.5 h instead. ^f Reported as an average of two isolated yields.

The use of a sterically less hindered proton source, *i*-PrOH, provided improved conversion and enantiomeric ratio of product **4a**. Moreover, we found that by decreasing the quantity of *i*-PrOH to 1.1 equivalents minimized the amount of overreduction that was observed (entries 6–7). As the use of a less hin-

dered proton source proved beneficial for both yield and er, we next examined the use of H₂O (0.55 equiv) which resulted in the efficient delivery of both protons in the enyne semi-reduction (entry 8). Further, we found that substituting DMMS with 0.5 equiv of 2,4,6,8-tetramethylcyclotetrasiloxane (TMCTS) and decreasing the catalyst loading to 1 mol% provided improved reaction conditions for the enantioselective semi-reduction of 1,3-enyne **1a** affording the desired product (*R*)-**4a** in 90% isolated yield and >99:1 er (entry 9).

Table 2. Substrate Scope of the LCuH-Catalyzed Asymmetric Semi-Reduction of 1,3-Enynes to Allenes^a



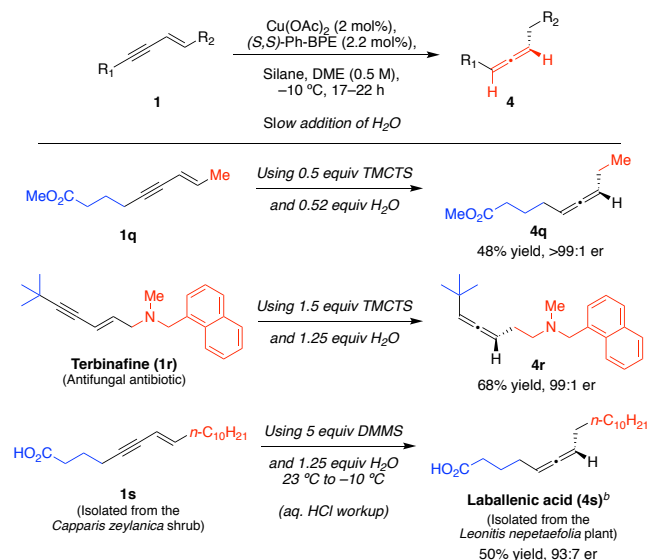
^a Reactions were carried out under N₂ atmosphere at -10 °C. Isolated yields and enantiomeric ratios are reported as an average of two independent runs. ^b Yield was determined by ¹H NMR spectroscopy using mesitylene as an internal standard due to the volatility of the product. ^c With 0.25 equiv H₂O instead. ^d Yield and diastereomeric ratio reported for a single run.

Next, we surveyed the generality of the LCuH-catalyzed asymmetric semi-reduction of an assortment of terminal 1,3-enynes (Table 2). Unfunctionalized substrates are efficiently converted to the corresponding allenes with good yield and exceptional er (4a–c). Enynes bearing a variety of functional groups are tolerated under the reaction conditions including potentially reducible groups such as alkyl chlorides (4d) and ketones (4e) as well as ethers (4f, 4i), amines (4j, 4l), and var-

ious heterocycles (4i, 4k, 4n, 4o). Substrates containing unprotected alcohols are not only tolerated, but the unhindered primary alcohol of enyne **1g**, itself, serves as a proton source in the reduction, permitting the use of only 0.25 equivalents of H₂O additive to furnish allene **4g**. The reactivity of and selectivity in the semi-reduction of sterically more encumbered enyne **1h**, bearing an unprotected propargylic alcohol, were unaffected, providing allenyl alcohol **4h** with 88% yield and >99:1 er. While substrates containing free N–H bonds react with high yield, the allene products are produced with a diminished er (4m, n). In the case of **1n** it was demonstrated that the use of the protected variant, **1o**, provided significantly improved results (4o). Finally, this protocol exhibits excellent catalyst control in the semi-reduction of chiral enyne **1p** to furnish either diastereomer of allene **4p** depending on the enantiomer of ligand used.

Our initial efforts to effect the asymmetric semi-reduction of internal 1,3-enyne substrates proved considerably more challenging. This difficulty was presumably due, in part, to an increased energetic barrier to hydrocupration, resulting in unproductive silylation of the proton source and, in some cases, competitive overreduction of the initially-formed allene products. To ameliorate these issues, we found that the utilization of a protocol with the slow addition of water was essential (Table 3). The reaction of ester-containing enyne **1q** occurred in moderate yield, largely due to competitive overreduction of the desired product, **4q**. The antifungal antibiotic Terbinafine (**1r**) was cleanly transformed to **4r** in 68% yield and 99:1 er, although it necessitated an increase in H₂O and TMCTS loading.²⁵ The direct conversion of fatty acid natural product **1s** to laballenenic acid (**4s**), a seed oil natural product isolated from the *Leonitis nepetaefolia* plant could also be accomplished^{26–29} The *in situ* protection of carboxylic acid **1s** with DMMS (to furnish the corresponding silyl ester) at room temperature was carried out, followed by slow addition of water at -10 °C to deliver laballenenic acid in 50% yield and 93:7 er.

Table 3. Select Examples of the LCuH-Catalyzed Asymmetric Semi-Reduction of Internal Enynes to Allenes^a



^a Reactions were carried out under N₂ atmosphere at -10 °C, H₂O was added over a 16 hour time period. Isolated yields and enantiomeric ratios are reported as an average of two independent

runs. ^b Reaction required a 1 hour pre-stir at room temperature prior to addition of water at -10°C

Based on previous mechanistic studies and DFT calculations,^{11, 21} we propose the following mechanism detailed in Figure 2. After generation of the chiral LCuH complex **I**, enantioselective hydrocupration of enyne **II** affords a chiral propargylic copper species (**III**). This undergoes a stereospecific 1,3-isomerization to yield allenyl copper intermediate **V**. Next intermediate **V** is protonated to furnish the final product, allene **VI**. σ -Bond metathesis between **VII** and silane (**VIII**) results in the formation of silanol **IX** and regeneration of **I**. As less than a full equivalent of water is utilized in this process, we propose that silanol **IX** can also facilitate proto-demetalation, producing siloxane **X**.

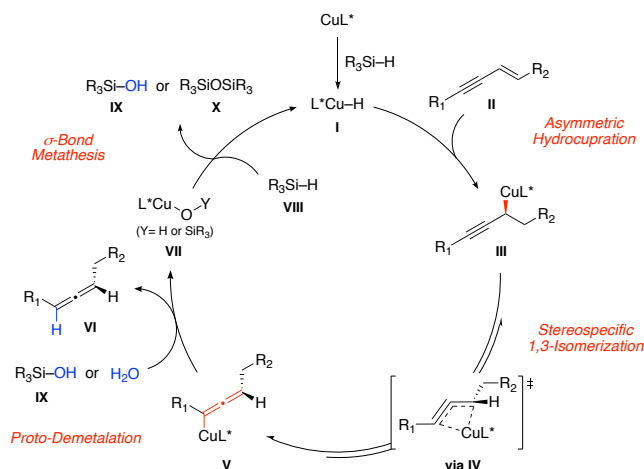
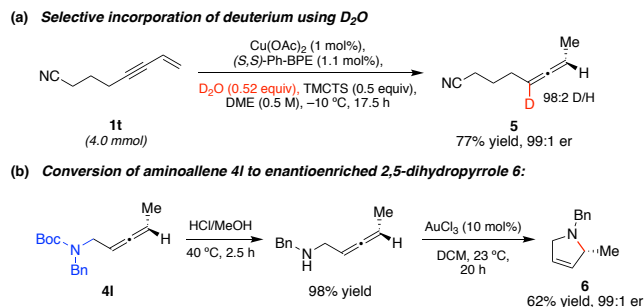


Figure 2. Proposed catalytic cycle for the LCuH-catalyzed conversion of 1,3-enynes to allenes

Two examples demonstrating further applications of this methodology are depicted in Scheme 2. The incorporation of deuterium into molecular scaffolds is pervasive not only in the pharmaceutical industry, due to the enhanced metabolic stability and safety imparted by corresponding deuterio-analogs, but also in mechanistic studies and protein crystallography.³⁰ Substitution of H_2O for D_2O selectively delivers enantioenriched mono-deuterated products, as exhibited in the conversion of enyne **1t** to allene **5** with 98:2 D/H incorporation (Scheme 2a). This protocol represents a new strategy for the deuterium labeling of allenes, employing an affordable, easy to handle and abundant deuterium source.

Scheme 2. Applications of the LCuH-Catalyzed Asymmetric Reduction for Deuterium Incorporation and Heterocycle Synthesis



Additionally, enantioenriched allenyl alcohols and amines are known to serve as valuable synthetic intermediates toward the production of chiral heterocycles including dihydrofurans and dihydropyrroles.^{3h, 31, 32} Taking advantage of the highly selective nature of gold-catalyzed cycloisomerization chemistry, α -aminoallene **4l** furnished 2,5-dihydropyrrole **6** with complete axial-to-point chirality transfer (Scheme 2b).^{33, 34}

In summary, we have developed a LCuH-catalyzed asymmetric semi-reduction of 1,3-enynes to supply highly enantioenriched 1,3-disubstituted allenes in up to 98% yield and >99:1 er. This chemistry benefits from the functional group tolerance afforded by the mild reducing nature of LCuH catalysts and employs only 1–2 mol% catalyst loading. Moreover, the utilization of substoichiometric quantities of H_2O as the proton source and TMCTS as the hydride source provides an efficient protocol for the hydrogenation of terminal 1,3-enynes. The reduction of internal conjugated enynes is enabled via slow addition of water and has been demonstrated through the late-stage derivatization of antibiotic Terbinafine and the synthesis of the seed oil natural product, laballenic acid. Furthermore, this protocol provides an efficient synthetic route for the construction of deuterio-allenes as well as aza-heterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General procedural information and characterization data (PDF)
NMR Spectra (PDF)
SFC, GC and HPLC Traces (PDF)

AUTHOR INFORMATION

Corresponding Author

* sbuchwal@mit.edu

Funding Sources

The Arnold and Mabel Beckman Foundation
The National Institutes of Health (R35-GM122483)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Research reported in this publication was supported by the Arnold and Mabel Beckman Foundation (LBR) and the National Institutes of Health (R35-GM122483). The authors would like to thank Nippon Chemical Industrial Co., Ltd., Solvias AG, and Takasago International Corporation for donations of ligands used in this project. We thank Dr. M. Kumar for his assistance with HRMS analysis and R. Liu, Dr. A. Thomas and Dr. S. McCann for their counsel in the preparation of this manuscript. We are grateful to E. Tsai and Drs. S. Guo and Y. Yang for supplying some of the starting materials used in this project and the National Institutes of Health for a supplemental grant for the purchase of supercritical fluid chromatography (SFC) equipment (GM058160-17S1). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

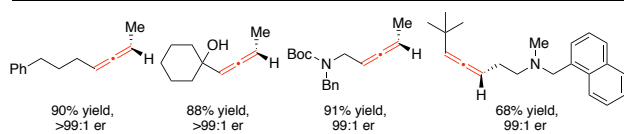
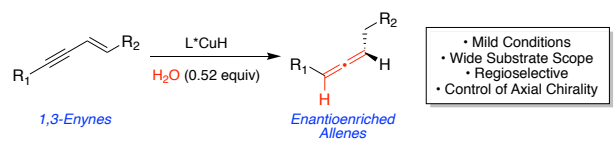
- (1) For selected reviews on allenes, see: (a) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH, 2004. (b) Hoffmann-Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216. (c) Dembitsky, V. M.; Maoka, T. Allenic and cumulenilic lipids. *Prog. Lipid Res.* **2007**, *46*, 328–375. (d) Kim, H.; Williams, L. Recent developments in allene-based synthetic methods. *Curr. Opin. Drug Discov. Devel.* **2008**, *11*, 870–894.
- (2) For selected references on bioactive allenes, see: (a) Krause, N.; Hoffmann-Röder, A., Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*, 2004. (b) Ban, H. S.; Onagi, S.; Uno, M.; Nabeyama, W.; Nakamura, H. Allene as an Alternative Functional Group for Drug Design: Effect of C–C Multiple Bonds Conjugated with Quinazolines on the Inhibition of EGFR Tyrosine Kinase. *ChemMedChem* **2008**, *3*, 1094–1103. (c) Ching, C. K.; Lam, S. K., A comparison of two prostaglandin analogues (enprostil vs misoprostol) in the treatment of acute duodenal ulcer disease. *J. Gastroenterol.* **1995**, *30*, 607–614.
- (3) For selected reviews and references on the synthetic utility of allenes, see: (a) Hoffmann-Röder, A.; Krause, N. Enantioselective Synthesis of and with Allenes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933–2935. (b) Brummond, K. M.; Chen, H., Allenes in Natural Product Synthesis. In *Modern Allene Chemistry*, 2004. (c) Hashmi, A. S. K., New and Selective Transition Metal Catalyzed Reactions of Allenes. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590–3593. (d) Rivera-Fuentes, P.; Diederich, F., Allenes in Molecular Materials. *Angew. Chem. Int. Ed.* **2012**, *51*, 2818–2828. (e) Yu, S.; Ma, S., Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074–3112. (f) Ma, S., Electrophilic Addition and Cyclization Reactions of Allenes. *Acc. Chem. Res.* **2009**, *42*, 1679–1688. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C., Exploiting [2+2] cycloaddition chemistry: achievements with allenes. *Chem. Soc. Rev.* **2010**, *39*, 783–816. (h) Krause, N.; Winter, C., Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chemical Reviews* **2011**, *111*, 1994–2009. (i) Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M., The conversion of allenes to strained three-membered heterocycles. *Chem. Soc. Rev.* **2014**, *43*, 3136–3163. (j) Alonso, J. M.; Quirós, M. T.; Muñoz, M. P., Chirality transfer in metal-catalyzed intermolecular addition reactions involving allenes. *Org. Chem. Front.* **2016**, *3*, 1186–1204. (k) Sutherland, D. R.; Kinsman, L.; Angiolini, S. M.; Rosair, G. M.; Lee, A.-L., Gold(I)-Catalyzed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer. *Chem. Eur. J.* **2018**, *24*, 7002–7009.
- (4) Sato, I.; Matsueda, Y.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Soai, K., Highly Enantioselective Asymmetric Autocatalysis of Pyrimidin-5-yl Alkanol Induced by Chiral 1,3-Disubstituted Hydrocarbon Allenes. *Helv. Chim. Acta* **2002**, *85*, 3383–3387.
- (5) Cai, F.; Pu, X.; Qi, X.; Lynch, V.; Radha, A.; Ready, J. M., Chiral Allene-Containing Phosphines in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2011**, *133*, 18066–18069.
- (6) Vanitcha, A.; Damelin-court, C.; Gontard, G.; Vanthuyne, N.; Mouriès-Mansuy, V.; Fensterbank, L., Bis-phosphine allene ligand: coordination chemistry and preliminary applications in catalysis. *Chem. Comm.* **2016**, *52*, 6785–6788.
- (7) For selected reviews on the asymmetric synthesis of allenes, see: (a) Krause, N.; Hoffmann-Röder, A., Synthesis of allenes with organometallic reagents. *Tetrahedron* **2004**, *60*, 11671–11694. (b) Brummond, K. M.; DeForrest, J. E., Synthesizing Allenes Today (1982–2006). *Synthesis* **2007**, *2007*, 795–818. (c) Yu, S.; Ma, S., How easy are the syntheses of allenes? *Chem. Comm.* **2011**, *47*, 5384–5418. (d) Ye, J.; Ma, S., Conquering three-carbon axial chirality of allenes. *Org. Chem. Front.* **2014**, *1*, 1210–1224. (e) Shirakawa, S.; Liu, S.; Kaneko, S., Organocatalyzed Asymmetric Synthesis of Axially, Planar, and Helical Chiral Compounds. *Chem. Asian J.* **2016**, *11*, 330–341. (f) Chu, W.-D.; Zhang, Y.; Wang, J., Recent advances in catalytic asymmetric synthesis of allenes. *Cat. Sci. Tech.* **2017**, *7*, 4570–4579.
- (8) For references concerning the catalytic asymmetric synthesis of chiral tri- or tetrasubstituted allenes, see: (a) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T., Axially chiral allenylboranes: catalytic asymmetric synthesis by palladium-catalyzed hydroboration of but-1-en-3-yne and their reaction with an aldehyde. *J. Chem. Soc., Chem. Comm.* **1993**, 1468–1469. (b) Han, J. W.; Tokunaga, N.; Hayashi, T., Palladium-Catalyzed Asymmetric Hydrosilylation of 4-Substituted 1-Buten-3-yne. Catalytic Asymmetric Synthesis of Axially Chiral Allenylsilanes. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916. (c) Hayashi, T.; Tokunaga, N.; Inoue, K., Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryltitanates to Enynones Giving Axially Chiral Allenes. *Org. Lett.* **2004**, *6*, 305–307. (d) Ogasawara, M.; Ito, A.; Yoshida, K.; Hayashi, T., Synthesis of 2,5-Bis(binaphthyl)phospholes and Phosphametalloocene Derivatives and Their Application in Palladium-Catalyzed Asymmetric Hydrosilylation. *Organomet.* **2006**, *25*, 2715–2718. (e) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X., Iron Porphyrin-Catalyzed Olefination of Ketenes with Diazoacetate for the Enantioselective Synthesis of Allenes. *J. Am. Chem. Soc.* **2007**, *129*, 1494–1495. (f) Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y., Palladium-Catalyzed Asymmetric Allylic Alkylation of 2,3-Allenyl Acetates Using a Chiral Diaminophosphine Oxide. *Adv. Synth. Catal.* **2009**, *351*, 1773–1778. (g) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W., Enantioselective Bromolactonization of Conjugated (Z)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665. (h) Li, H.; Müller, D.; Guénée, L.; Alexakis, A., Copper-Catalyzed Enantioselective Synthesis of Axially Chiral Allenes. *Org. Lett.* **2012**, *14*, 5880–5883. (i) Inokuma, T.; Furukawa, M.; Suzuki, Y.; Kimachi, T.; Kobayashi, Y.; Takemoto, Y., Organocatalyzed Isomerization of α -Substituted Alkynoates into Trisubstituted Allenates by Dynamic Kinetic Resolution. *ChemCatChem* **2012**, *4*, 983–985. (j) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K., Phase-transfer-catalyzed asymmetric synthesis of tetrasubstituted allenes. *Nat. Chem.* **2013**, *5*, 240. (k) Wang, Y.; Zhang, W.; Ma, S., A Room-Temperature Catalytic Asymmetric Synthesis of Allenes with ECNU-Phos. *J. Am. Chem. Soc.* **2013**, *135*, 11517–11520. (l) Qian, H.; Yu, X.; Zhang, J.; Sun, J., Organocatalytic Enantioselective Synthesis of 2,3-Allenates by Intermolecular Addition of Nitroalkanes to Activated Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 18020–18023. (m) Tap, A.; Blond, A.; Wakchaure, V. N.; List, B., Chiral Allenes via Alkynylogous Mukaiyama Aldol Reaction. *Angew. Chem. Int. Ed.* **2016**, *55*, 8962–8965. (n) Wang, M.; Liu, Z.-L.; Zhang, X.; Tian, P.-P.; Xu, Y.-H.; Loh, T.-P., Synthesis of Highly Substituted Racemic and Enantioenriched Allenylsilanes via Copper-Catalyzed Hydrosilylation of (Z)-2-Alken-4-ynoates with Silylboronate. *J. Am. Chem. Soc.* **2015**, *137*, 14830–14833. (o) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X., Direct Synthesis of Chiral Allenates from the Asymmetric C–H Insertion of α -Diazoesters into Terminal Alkynes. *Angew. Chem. Int. Ed.* **2015**, *54*, 9512–9516. (p) Yao, Q.; Liao, Y.; Lin, L.; Lin, X.; Ji, J.; Liu, X.; Feng, X., Efficient Synthesis of Chiral Trisubstituted 1,2-Allenyl Ketones by Catalytic Asymmetric Conjugate Addition of Malonic Esters to Enynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 1859–1863. (q) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J., Enantioselective Synthesis of Trisubstituted Allenes via Cu(I)-Catalyzed Coupling of Diazoalkanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 14558–14561. (r) Poulsen, P. H.; Li, Y.; Lauridsen, V. H.; Jørgensen, D. K. B.; Palazzo, T. A.; Meazza, M.; Jørgensen, K. A., Organocatalytic Formation of Chiral Trisubstituted Allenes and Chiral Furan Derivatives. *Angew. Chem. Int. Ed.* **2018**, *57*, 10661–10665. (s) Zhang, Y.; Yu, B.; Gao, B.; Zhang, T.; Huang, H., Triple-Bond Insertion Triggers Highly Regioselective 1,4-Aminomethylamination of 1,3-Enynes with Aminals Enabled by Pd-Catalyzed C–N Bond Activation. *Org. Lett.* **2019**, *21*, 535–539.
- (9) For selected reviews on the synthesis of 1,3-enynes, see: (a) Zhou, Y.; Zhang, Y.; Wang, J., Recent advances in transition-metal-catalyzed synthesis of conjugated enynes. *Org. Bio. Chem.* **2016**, *14*, 6638–6650. (b) Trost, B. M.; Masters, J. T., Transition metal-catalyzed couplings of alkynes to 1,3-enynes: modern methods and synthetic applications. *Chem. Soc. Rev.* **2016**, *45*, 2212–2238.

- (10) Adamson, N. J.; Jeddi, H.; Malcolmson, S. J., Preparation of Chiral Allenes through Pd-Catalyzed Intermolecular Hydroamination of Conjugated Enynes: Enantioselective Synthesis Enabled by Catalyst Design. *J. Am. Chem. Soc.* **2019**, *141*, 8574–8583.
- (11) Huang, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H., Enantioselective Synthesis of Trisubstituted Allenyl-B(pin) Compounds by Phosphine-Cu-Catalyzed 1,3-Enyne Hydroboration. Insights Regarding Stereochemical Integrity of Cu-Allenyl Intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 2643–2655.
- (12) Sang, H. L.; Yu, S.; Ge, S., Copper-catalyzed asymmetric hydroboration of 1,3-enynes with pinacolborane to access chiral allenylboronates. *Org. Chem. Front.* **2018**, *5*, 1284–1287.
- (13) Gao, D.-W.; Xiao, Y.; Liu, M.; Liu, Z.; Karunananda, M. K.; Chen, J. S.; Engle, K. M., Catalytic, Enantioselective Synthesis of Allenyl Boronates. *ACS Cat.* **2018**, *8*, 3650–3654.
- (14) Yu, S.; Sang, H. L.; Zhang, S.-Q.; Hong, X.; Ge, S., Catalytic asymmetric synthesis of chiral trisubstituted heteroaromatic allenenes from 1,3-enynes. *Commun. Chem.* **2018**, *1*, 64.
- (15) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T., Catalytic Synthesis of Allenes via Isomerization of Alkynes under Phase-Transfer Catalyzed Conditions. *Synlett* **2000**, 493–494.
- (16) Trost, B. M.; Fandrick, D. R.; Dinh, D. C., Dynamic Kinetic Asymmetric Allylic Alkylations of Allenes. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.
- (17) Wei, X.-F.; Wakaki, T.; Itoh, T.; Li, H.-L.; Yoshimura, T.; Miyazaki, A.; Oisaki, K.; Hatanaka, M.; Shimizu, Y.; Kanai, M., Catalytic Regio- and Enantioselective Proton Migration from Skipped Enynes to Allenes. *Chem* **2019**, *5*, 585–599.
- (18) For examples of catalytic asymmetric allenyl ester synthesis, see: (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T., Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes: A Synergistic Effect of Dibenzalacetone on High Enantioselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090. (b) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I., Palladium-Catalyzed Asymmetric Alkylation of 2,3-Alkadienyl Phosphates. Synthesis of Optically Active 2-(2,3-Alkadienyl)malonates. *Chem. Lett.* **2002**, *31*, 140–141. (c) Ogasawara, M.; Nagano, T.; Hayashi, T., A New Route to Methyl (R,E)-(-)-Tetradeca-2,4,5-trienoate (Pheromone of *Acanthoscelides obtectus*) Utilizing a Palladium-Catalyzed Asymmetric Allene Formation Reaction. *J. Org. Chem.* **2005**, *70*, 5764–5767. (d) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H., Enantioselective Synthesis of Chiral Allenates by Guanidine-Catalyzed Isomerization of 3-Alkynoates. *J. Am. Chem. Soc.* **2009**, *131*, 7212–7213. (e) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y., Bifunctional Hydrogen-Bond Donors That Bear a Quinazoline or Benzothiadiazine Skeleton for Asymmetric Organocatalysis. *Chem. Eur. J.* **2011**, *17*, 10470–10477. (f) Crouch, I. T.; Neff, R. K.; Frantz, D. E., Pd-Catalyzed Asymmetric β -Hydride Elimination en Route to Chiral Allenes. *J. Am. Chem. Soc.* **2013**, *135*, 4970–4973. (g) Song, S.; Zhou, J.; Fu, C.; Ma, S., Catalytic enantioselective construction of axial chirality in 1,3-disubstituted allenenes. *Nat. Comm.* **2019**, *10*, 507.
- (19) For examples of catalytic asymmetric allenyl alcohol synthesis, see: (a) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S., Catalytic Asymmetric Synthesis of Optically Active Allenes from Terminal Alkynes. *Org. Lett.* **2012**, *14*, 1346–1349. (b) Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E., Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions. *J. Am. Chem. Soc.* **2017**, *139*, 1998–2005.
- (20) For examples of catalytic asymmetric allenyl amine synthesis, see: (a) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.-I.; Naota, T., Palladium-Catalyzed Asymmetric Amination and Imidation of 2,3-Allenyl Phosphates. *Org. Lett.* **2005**, *7*, 5837–5839. (b) Imada, Y.; Nishida, M.; Naota, T., Sequential asymmetric homoallenylation of primary amines with a palladium catalyst. *Tetrahedron Lett.* **2008**, *49*, 4915–4917. (c) Boutier, A.; Kammerer-Pentier, C.; Krause, N.; Prestat, G.; Poli, G., Pd-Catalyzed Asymmetric Synthesis of N-Allenyl Amides and Their Au-Catalyzed Cycloisomerization Hydroalkylation: A New Route Toward Enantioenriched Pyrrolidones. *Chem. Eur. J.* **2012**, *18*, 3840–3844. (d) Wan, B.; Ma, S., Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines. *Angew. Chem. Int. Ed.* **2013**, *52*, 441–445. (e) Wu, Z.; Berhal, F.; Zhao, M.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V., Palladium-Catalyzed Efficient Enantioselective Synthesis of Chiral Allenes: Steric and Electronic Effects of Ligands. *ACS Cat.* **2014**, *4*, 44–48. (f) Poh, J.-S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V., Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow-Generated Diazo Compounds and Propargylated Amines. *Angew. Chem. Int. Ed.* **2017**, *56*, 1864–1868.
- (21) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L., Copper-catalyzed asymmetric addition of olefin-derived nucleophiles to ketones. *Science* **2016**, *353*, 144.
- (22) For selected references on copper-catalyzed alcohol silylation with hydrosilanes, see: (a) Schubert, U.; Lorenz, C., Conversion of Hydrosilanes to Silanols and Silyl Esters Catalyzed by [Ph₃PCuH]₆. *Inorg. Chem.* **1997**, *36*, 1258–1259. (b) Ito, H. W., Akiko and; Sawamura, M., Versatile Dehydrogenative Alcohol Silylation Catalyzed by Cu(I)-Phosphine Complex. *Org. Lett.* **2005**, *7*, 1869–1871. (c) Jeon, M.; Han, J.; Park, J., Catalytic Synthesis of Silanols from Hydrosilanes and Applications. *ACS Cat.* **2012**, *2*, 1539–1549.
- (23) For an example of the selective reduction of a 1,3 enyne to a 1,3-diene, see: Whittaker, A. M.; Lalic, G., Monophasic Catalytic System for the Selective Semireduction of Alkynes. *Org. Lett.* **2013**, *15*, 1112–1115.
- (24) For examples of chiral aluminum hydride reagents used for the semi-reduction of 1,3-enynes, see: (a) Evans, R. J. D.; Landor, S. R.; Regan, J. P., The asymmetric synthesis and absolute configuration of allenic alcohols. *Chem. Comm.* **1965**, 397–398. (b) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R., The asymmetric reduction of alkenynols with the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene- α -D-glucofuran complex and the determination of the absolute configuration of naturally occurring allenenes. *Chem. Comm.* **1966**, 585–586. (c) Cowie, J. S.; Landor, P. D.; Landor, S. R.; Punja, N., Allenes. Part XXII. The synthesis and absolute configuration of laballenic and lamallenic acids. *J. Chem. Soc., Perkin Trans.1* **1972**, 2197–2201. (d) Evans, R. J. D.; Landor, S. R.; Regan, J. P., Asymmetric syntheses. Part VII. Asymmetric reduction of ketones and alk-2-en-4-yn-1-ols with a lithium bismethylaluminum hydride complex; determination of the absolute configurations of allenic alcohols. *J. Chem. Soc., Perkin Trans.1* **1974**, 552–556. (e) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R., Asymmetric syntheses. Part VIII. Asymmetric synthesis of β -allenic alcohols with the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene- α -D-glucofuranose complex; determination of the absolute configuration of marasin (nona-3,4-diene-6,8-diyn-1-ol) and 9-methylmarasin (deca-3,4-diene-6,8-diyn-1-ol). *J. Chem. Soc., Perkin Trans.1* **1974**, 557–561.
- (25) McClellan, K. J.; Wiseman, L. R.; Markham, A., Terbinafine. An update of its use in superficial mycoses. *Drugs* **1999**, *58*, 179–202.
- (26) Tlili, N.; Elfalleh, W.; Saadaoui, E.; Khaldi, A.; Triki, S.; Nasri, N., The caper (*Capparis L.*): Ethnopharmacology, phytochemical and pharmacological properties. *Fitoterapia* **2011**, *82*, 93–101.
- (27) Bagby, M. O.; Smith, C. R.; Wolff, I. A., Laballenic Acid. A New Allenic Acid from *Leonotis nepetaefolia* Seed Oil. *J. Org. Chem.* **1965**, *30*, 4227–4229.
- (28) Tang, X.; Huang, X.; Cao, T.; Han, Y.; Jiang, X.; Lin, W.; Tang, Y.; Zhang, J.; Yu, Q.; Fu, C.; Ma, S., CuBr₂-catalyzed enantioselective routes to highly functionalized and naturally occurring allenenes. *Org. Chem. Front.* **2015**, *2*, 688–691.
- (29) Yu, Q.; Ma, S., An Enantioselective Synthesis of (R)-5,6-Octadecadienoic Acid. *Eur. J. Org. Chem.* **2015**, *2015*, 1596–1601.
- (30) Gant, T. G., Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem.* **2014**, *57*, 3595–3611.
- (31) Ma, S., Transition Metal-Catalyzed/Mediated Reaction of Allenes with a Nucleophilic Functionality Connected to the α -Carbon Atom. *Acc. Chem. Res.* **2003**, *36*, 701–712.
- (32) Alcaide, B.; Almendros, P., Novel Cyclization Reactions of Aminoallenenes. *Adv. Synth. Cat.* **2011**, *353*, 2561–2576.

(33) Morita, N.; Krause, N., Gold Catalysis in Organic Synthesis: Efficient Cycloisomerization of α -Aminoallenes to 3-Pyrrolines. *Org. Lett.* **2004**, *6*, 4121-4123.

(34) Morita, N.; Krause, N., Gold-Catalyzed Cycloisomerization of α -Aminoallenes to 3-Pyrrolines– Optimization and Mechanistic Studies. *Eur. J. Org. Chem.* **2006**, *2006*, 4634-4641.

For Table of Contents Only:



Manuscript-Final.pdf (546.42 KiB)

[view on ChemRxiv](#) • [download file](#)

Supporting Information

Copper Hydride-Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes

Liela Bayeh-Romero and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts
02139, United States

*Correspondence to: sbuchwal@mit.edu

Contents

I.	Materials and Methods	S2
II.	General Procedures for the CuH-Catalyzed Enyne Semi-Reduction	S3
III.	Characterization Data for 1,3-disubstituted allenes	S4
IV.	Further Confirmation of Absolute Configuration.....	S16
V.	Deuterium Labeling Experiments	S17
VI.	Cycloisomerization of Allenamine 4l	S17
VII.	Preparation of 1,3-Enyne Substrates.....	S18
VIII.	References.....	S25

I. Materials and Methods

General procedural information. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring unless otherwise stated. Anhydrous tetrahydrofuran (THF), toluene and dichloromethane (CH_2Cl_2) were purchased from Sigma-Aldrich, stored in CYCLE-TAINER[®] solvent delivery kegs and dried by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide. Anhydrous 1,2-dimethoxyethane (DME, anhydrous, 99.5%, inhibitor free) was purchased from Sigma Aldrich and stored in a nitrogen-filled glovebox over activated 4Å molecular sieves. Liquids and solutions were transferred via syringe. Copper(II) acetate was purchased from Strem Chemicals Inc. and used as received. 1,2-Bis((2*S*,5*S*)2,5-diphenylphospholano)ethane, 1,2-Bis((2*R*,5*R*)2,5-diphenylphospholano)ethane (Ph-BPE) ligands were purchased from Namena Corp. and stored in a nitrogen-filled glove box. 2,4,6,8-Tetramethylcyclotetrasiloxane (TMCTS, moisture sensitive) was purchased from Oakwood Chemical and used as received. Deionized water was obtained directly from the in-house DI water line and used as is. All other commercially obtained materials were used as received. Flash chromatography purifications were conducted with the assistance of a Biotage Isolera Chromatography System unless otherwise indicated. Reusable SNAP cartridges (10–100g) were refilled with silica gel purchased from Silicycle (SilicaFlash[®] F60, 40–63 µm). Organic solutions were concentrated with the aid of a Buchi rotary evaporator. Isolated yields and enantiomeric ratios (er) reported in tables 2 and 3 of the manuscript reflect an average of two independent runs unless specified otherwise.

General analytical information. All reactions were monitored by thin-layer chromatography using Silicycle Siliaplate pre-coated plates (0.25 mm) and visualized with UV light and/or iodine stain. All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400, 500 or 600 MHz instrument. ¹H and ¹³C NMR spectra were recorded in CDCl_3 (unless otherwise noted) and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform in the deuterated solvent (7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C NMR), multiplicity, coupling constant (Hz) and integration. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and reported in terms of frequency of absorption (cm^{-1}). Melting points were obtained by use of a Mel-Temp capillary melting point apparatus. Elemental analysis (EA) was acquired by Atlantic Microlabs Inc., Norcross, GA. High resolution mass spectrometry (HRMS) analysis was performed on a JEOL AccuTOF LC-Plus 46 DART system or an Agilent Technologies 6545 Q-TOF LC/MS system. Low resolution mass spectrometry (LRMS) data were measured using an Agilent Technologies 6850 series gas chromatography (GC) system equipped with a 5975 series inert mass selective detector. Optical rotations were measured on a Jasco Model 1010 polarimeter ([α]_D values are reported in degrees and concentration in g/100 mL). GC analyses were performed on an Agilent Technologies 6850 series gas chromatograph with FID detector and high pressure liquid chromatography (HPLC) analyses were conducted on an Agilent Technologies 1200 series system. Enantiomeric ratios (er) of the allene products were determined by GC, HPLC, or Waters Acquity UPC2 SFC chiral stationary phase analysis as detailed for each product.

II. General Procedures for the Asymmetric Semi-Reduction of 1,3-Enynes

General procedure A: Synthesis of enantioenriched allenes from terminal 1,3-enynes

In a nitrogen-filled glovebox, a stock solution of catalyst was prepared as follows: an oven-dried screw-cap 1 dram vial (VWR cat.66010-243) equipped with a magnetic stir bar was charged with copper(II) acetate (5.5 mg, 30 μ M, 3 mol%) and ((+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane ((S,S)-Ph-BPE, 16.7 mg, 33 μ M, 3.3 mol%). The solids were dissolved in 1,2-dimethoxyethane (DME, 300 μ L), the vial was capped and the mixture was stirred for 30-40 min to yield a homogenous blue solution. At this point, the resulting catalyst solution should be used within 30 min.

Meanwhile, in a nitrogen-filled glovebox an oven-dried screw-cap reaction tube (16mm \times 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar was charged with 1,3-enyne substrate (1.00 mmol, 1 equiv) and DME (1.9 mL). Then the Cu(OAc)₂•(S,S)-Ph-BPE catalyst solution (100 μ L, 1 mol%) was added to the substrate and the reaction tube was capped with a Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part # 73804-15425) and removed from the glovebox. Water (9.4 μ L, 0.52 mmol, 0.52 equiv) was added to the reaction solution using a Hamilton gastight glass microsyringe, and the reaction tube was placed in cooling bath equipped with a Julabo FT902 immersion cooler set to -10 $^{\circ}$ C with stirring. 2,4,6,8-Tetramethylcyclotetrasiloxane (TMCTS, 121.5 μ L, 0.5 equiv, 0.5 mmol) was added slowly down the wall of the reaction tube. The reaction was stirred for 15 – 20 h as indicated below for each substrate. Subsequently, the reaction tube was removed from the cooling bath, uncapped and 2 mL of solvent (as indicated for each substrate) was added to the reaction solution. The solution was quickly passed through a plug of silica gel (ca. 0.5 g) before the reaction mixture could warm to rt, the silica was further rinsed with solvent to ensure the product was fully eluted. The resulting crude reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator and purified by column chromatography (see details for each substrate below) to afford the desired product. For reactions where traces of starting material remain or trace over-reduction of the allene product is observed, careful column chromatography followed by GC analysis of product-containing fractions was required to ensure high purity. Enantiopurity of the allene products was determined by GC, HPLC, or Waters Acquity UPC2 SFC chiral stationary phase analysis as described below for each substrate. The absolute stereochemistry was assigned by analogy to that of **S2**.

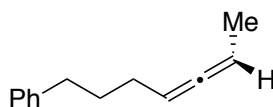
General procedure B: Synthesis of enantioenriched allenes from internal 1,3-enynes

In a nitrogen-filled glovebox, a stock solution of catalyst was prepared according to general procedure A using 150 μ L DME instead to yield a solution containing 1 mol% catalyst loading per 50 μ L DME.

Meanwhile, in a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube (16mm \times 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar was charged with 1,3-enyne substrate (0.50 mmol, 1 equiv) and DME (0.4 mL). Then, the catalyst Cu(OAc)₂•(S,S)-Ph-BPE solution (100 μ L, 2 mol%) was added to the substrate and the reaction tube was capped with a Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part #

73804-15425). A separate 1 dram vial was charged with DME (1.5 mL), capped with a Teflon-lined silicone septum screw cap and removed from the glovebox along with the reaction tube. The reaction tube was placed in a cooling bath equipped with a Julabo FT902 immersion cooler set to $-10\text{ }^{\circ}\text{C}$ with stirring. Water (amount indicated for each substrate) was added to the 1 dram vial containing DME using a Hamilton gastight glass microsyringe to yield a stock solution of water. Silane (amount indicated for each substrate) was added slowly down the wall of the reaction tube. Slow addition of one-third of the water/DME solution (taken into a 1 mL syringe with a needle) was immediately initiated with the aid of a Harvard Apparatus PHD Ultra syringe pump at a rate of $0.5\text{ }\mu\text{L}/\text{min}$. After stirring for a total of 17 – 22 h at $-10\text{ }^{\circ}\text{C}$, the reactions were worked up and purified according to general procedure A. The absolute stereochemistry was assigned by analogy to (R)-laballenic acid (**4s**).

III. Characterization Data for 1,3-Disubstituted Allenes



(R)-hepta-4,5-dien-1-ylbenzene (4a): Following general procedure A, hept-6-en-4-yn-1-ylbenzene (170 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with hexanes (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with hexanes. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 100% hexanes eluting at 60 mL/min and collecting 4 mL fractions in order to avoid significant contamination from adjacent impurities) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 158 mg, 92% yield, >99:1 er; Run 2: 1.00 mmol scale, 152 mg, 88% yield, >99:1 er).

^1H NMR (600 MHz, CDCl_3) δ 7.28 – 7.30 (m, 2H), 7.18 – 7.21 (m, 3H), 5.06 – 5.11 (m, 2H), 2.67 (dd, $J = 7.7\text{ Hz}$, 2H), 2.01 – 2.05 (m, 2H), 1.75 (p, $J = 7.5\text{ Hz}$, 2H), 1.68 (dd, $J = 4.9\text{ Hz}$, 3H).

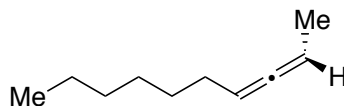
^{13}C NMR (151 MHz, CDCl_3) δ 205.01, 142.66, 128.63, 128.40, 125.80, 90.08, 85.87, 35.39, 30.98, 28.43, 14.77.

IR (neat): 2925, 1963, 1496, 871, 743, 697 cm^{-1}

HRMS (DART) Calcd. m/z for $\text{C}_{13}\text{H}_{17} [\text{M}+\text{H}]^+$: 173.1330. Found: 173.1326

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20B GC Column (30 m, 0.25 mm, 0.25 μm , 7 inch cage), 8 psi: $70\text{ }^{\circ}\text{C}$, hold for 50 min, $1\text{ }^{\circ}\text{C}/\text{min}$ to $100\text{ }^{\circ}\text{C}$, hold for 20 min, $2\text{ }^{\circ}\text{C}/\text{min}$ to $150\text{ }^{\circ}\text{C}$; $t_r = 121.3\text{ min}$ (major) and 121.6 min (minor).

Specific rotation $[\alpha]_{\text{D}}^{23}$: -51.09 ($c = 1.0$, CHCl_3)



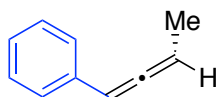
(R)-deca-2,3-diene (4b): Following general procedure A, dec-1-en-3-yne (136 mg, 1.00 mmol, 1 equiv) was used. After 16 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 100% pentane eluting at 60 mL/min) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 104 mg, 75% yield, >99:1 er; Run 2: 1.00 mmol scale, 100 mg, 72% yield, >99:1 er). The spectral data match those previously reported in the literature.¹

¹H NMR (400 MHz, CDCl₃) δ 5.10 – 4.97 (m, 2H), 2.04 – 1.92 (m, 2H), 1.65 (dd, J = 5.8, 4.4 Hz, 3H), 1.46 – 1.19 (m, 8H), 0.89 (t, J = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 204.85, 90.50, 85.48, 31.88, 29.30, 29.06, 28.90, 22.82, 14.77, 14.24.

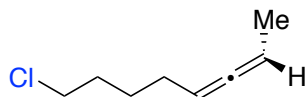
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20 β GC Column (30 m, 0.25 mm, 0.25 μ m, 7 inch cage), 8 psi: 70 °C isocratic; t_r = 24.1 min (major) and 24.9 min (minor).

Specific rotation $[\alpha]_D^{23}$: -44.92 (c = 1.0, CHCl₃).



(R)-buta-1,2-dien-1-ylbenzene (4c): Following general procedure A, but-3-en-1-yn-1-ylbenzene (128 mg, 1.00 mmol, 1 equiv) was used. After 17 h, the reaction was diluted with pentane (5.0 mL) and quickly passed through a short plug of silica gel atop a plug of basic alumina (ca. 0.5 g each) before the reaction solution could warm to rt, and the silica gel/basic alumina were washed with pentane. Due to the volatility of the desired product, the crude mixture was carefully concentrated with the aid of a rotary evaporator to approx. 0.5 mL, diluted with CDCl₃ and mesitylene (0.10 mmol) was added as an internal standard. This product is unstable when stored at rt on the bench and should therefore be stored diluted under argon at low temperature. (Run 1: 1.00 mmol scale, 86% ¹H-NMR yield, 98.5:1.5 er; Run 2: 1.00 mmol scale, 86% ¹H-NMR yield, 99:1 er). The spectral data match those previously reported in the literature.²

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20 β GC Column (30 m, 0.25 mm, 0.25 μ m, 7 inch cage), 8 psi: 70 °C for 50 min, then 1 °C/min to 150 °C; t_r = 70.4 min (major) and 71.1 min (minor).



(R)-8-chloroocta-2,3-diene (4d): Following general procedure A, 8-chlorooct-1-en-3-yne (143 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with pentane (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with pentane. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 100% pentane eluting at 60 mL/min and collecting 4 mL fractions in order to avoid significant contamination from adjacent impurities) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 118 mg, 82% yield, 99:1 er; Run 2: 1.00 mmol scale, 120 mg, 82% yield, 99:1 er). Due to product volatility and limitations of available HRMS equipment, LRMS data is reported for this compound.

¹H NMR (400 MHz, CDCl₃) δ 5.12 – 4.97 (m, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.01 (ddd, *J* = 13.7, 7.2, 3.2 Hz, 2H), 1.88 – 1.76 (m, 2H), 1.65 (dd, *J* = 6.8, 3.4 Hz, 3H), 1.55 (tt, *J* = 9.7, 6.4 Hz, 2H).

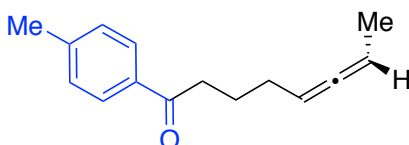
¹³C NMR (101 MHz, CDCl₃) δ 204.96, 89.75, 86.00, 45.07, 32.07, 28.16, 26.38, 14.69.

IR (neat): 2938, 1963, 1441, 1282, 871, 700 cm⁻¹

LRMS (GC-MS) Calcd. for C₈H₁₃Cl [M⁺]: 144.07. Found: 144.10.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20β GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 70 °C isocratic; t_r = 63.7 min (major) and 65.6 min (minor).

Specific rotation [α]_D²³: -39.99 (*c* = 10, CHCl₃).



(R)-1-(p-tolyl)octa-5,6-dien-1-one (4e): Following general procedure A, 1-(*p*-tolyl)oct-7-en-5-yn-1-one (106 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with CH₂Cl₂ (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with CH₂Cl₂. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-7% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 0.50 mmol scale, 69.8 mg, 65% yield, 99:1 er; Run 2: 1.00 mmol scale, 165 mg, 77% yield, 99:1 er).

¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.06 (h, *J* = 5.1 Hz, 2H), 3.02 – 2.94 (m, 2H), 2.41 (s, 3H), 2.08 (tt, *J* = 7.1, 4.8 Hz, 2H), 1.86 (p, *J* = 7.3 Hz, 2H), 1.67 – 1.61 (m, 3H).

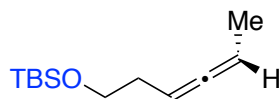
¹³C NMR (126 MHz, CDCl₃) δ 205.08, 200.13, 143.78, 134.77, 129.38, 128.32, 89.76, 86.06, 37.81, 28.54, 23.86, 21.76, 14.72.

IR (neat): 2857, 1965, 1680, 1606, 1229, 806 cm⁻¹

HRMS (DART) Calcd. m/z for $C_{15}H_{19}O$ $[M+H]^+$: 215.1430. Found: 215.1437.

Determination of enantiomeric ratio by SFC analysis: OJ-H column, 2.5 mL/min: 99:1 scCO₂/MeOH isocratic; t_r = 5.32 min (major) and 5.53 min (minor).

Specific rotation $[\alpha]_D^{23}$: -38.60 (c = 1.0, CHCl₃)



(R)-tert-butyl(hexa-3,4-dien-1-yloxy)dimethylsilane (4f): Following general procedure A, tert-butyl(hex-5-en-3-yn-1-yloxy)dimethylsilane (145 mg, 0.69 mmol, 1 equiv) was used. After 17 h, the reaction was diluted with pentane (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with pentane. The crude mixture was concentrated with the aid of a rotary evaporator and purified on silica gel eluting with 100% pentane to afford the title compound as a volatile colorless oil. (Run 1: 0.69 mmol scale, 126 mg, 86% yield, >99:1 er; Run 2: 1.00 mmol scale, 202 mg, 89% yield, >99:1 er).

¹H NMR (400 MHz, CDCl₃) δ 5.00 – 5.08 (m, 2H), 3.66 (t, J = 6.8 Hz, 2H), 2.17 – 2.23 (m, 2H), 1.64 (dd, J = 5.4, 4.7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

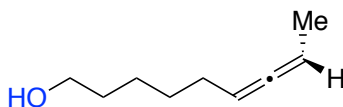
¹³C NMR (101 MHz, CDCl₃) δ 205.51, 86.99, 85.49, 63.16, 32.81, 26.09, 18.50, 14.64, -5.10.

IR (neat): 2954, 1966, 1254, 1100, 833, 774 cm⁻¹

HRMS (APCI) Calcd. m/z for $C_{12}H_{25}OSi$ $[M+H]^+$: 213.1675. Found: 213.1669

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20B GC Column (30 m, 0.25 mm, 0.25 μ m, 7 inch cage), 8 psi: 70 °C hold for 50 min, 0.1 °C/min to 75 °C; t_r = 96.6 min (major) and 97.8 min (minor).

Specific rotation $[\alpha]_D^{23}$: -27.45 (c = 1.0, CHCl₃)



(R)-nona-6,7-dien-1-ol (4g): Following general procedure A, non-8-en-6-yn-1-ol (138 mg, 1.00 mmol, 1 equiv) and water (4.51 μ L, 0.25 mmol, 0.25 equiv) was used. After 16.5 h, the reaction was directly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc (8 mL). The crude mixture was concentrated on a rotary evaporator. Subsequently, 1.25M HCl in MeOH (5 mL) was added to the resulting pale-yellow oil along with a small magnetic stir bar. The solution was stirred vigorously for 30 min at rt during which time a white precipitate formed. The solution was concentrated to yield a white residue which was suspended in EtOAc (ca. 10 mL), sonicated for 5 min and filtered through a plug of silica gel and the silica gel was washed with EtOAc. The filtrate was concentrated and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 125 mg, 89% yield, 97.5:2.5 er; Run 2: 1.00 mmol scale, 119 mg, 85% yield, 99:1 er).

¹H NMR (400 MHz, CDCl₃) δ 5.06 – 4.95 (m, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 2.03 (s, 1H), 2.01 – 1.90 (m, 2H), 1.61 (dd, *J* = 5.9, 4.3 Hz, 3H), 1.54 (p, *J* = 6.8 Hz, 2H), 1.44 – 1.31 (m, 4H).

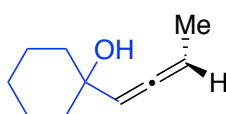
¹³C NMR (101 MHz, CDCl₃) δ 204.79, 90.18, 85.56, 62.88, 32.62, 28.96, 28.85, 25.22, 14.65.

IR (neat): 3324 (br), 2930, 2857, 1962, 1051, 871 cm⁻¹

HRMS (ESI) Calcd. *m/z* for C₉H₁₇O [M+H]⁺: 141.1272. Found: 141.1272.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20β GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 70 °C hold for 50 min, 1 °C/min to 100 °C, hold for 20 min, 2 °C/min to 150 °C; *t_r* = 109.9 min (major) and 110.4 min (minor).

Specific rotation [α]_D²³: -40.10 (*c* = 1.0, CHCl₃)



(R)-1-(buta-1,2-dien-1-yl)cyclohexan-1-ol (4h): Following general procedure A, 1-(but-3-en-1-yn-1-yl)cyclohexan-1-ol (150 mg, 1.00 mmol, 1 equiv) was used. After 17.5 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-45% EtOAc/Hexanes) to afford the title compound as a fragrant colorless oil. (Run 1: 1.00 mmol scale, 127 mg, 83% yield, >99:1 er; Run 2: 1.00 mmol scale, 145 mg, 92% yield, >99:1 er).

¹H NMR (500 MHz, CDCl₃) δ 5.27 (p, *J* = 7.0 Hz, 1H), 5.21 – 5.24 (m, 1H), 1.69 (dd, *J* = 7.0, 3.3 Hz, 3H), 1.67 – 1.51 (m, 6H), 1.52 – 1.41 (m, 3H), 1.39 – 1.30 (m, 1H)

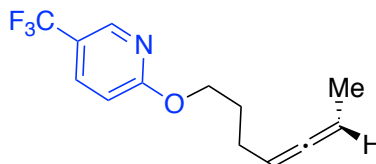
¹³C NMR (126 MHz, CDCl₃) δ 202.48, 99.82, 89.41, 70.91, 38.57, 38.51, 25.69, 22.80, 22.76, 14.57.

IR (neat): 3357 (br), 3928, 1965, 1445, 956, 869 cm⁻¹

HRMS (ESI) Calcd. *m/z* for C₁₀H₁₇O [M+H]⁺: 153.1274. Found: 153.1276.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20β GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 70 °C hold for 50 min, 1 °C/min to 100 °C, hold for 20 min, 2 °C/min to 150 °C; *t_r* = 108.4 min (major) and 110.3 min (minor).

Specific rotation [α]_D²³: -30.50 (*c* = 1.0, CHCl₃)



(R)-2-(hepta-4,5-dien-1-yloxy)-5-(trifluoromethyl)pyridine (4i): Following general procedure A, 2-(hept-6-en-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (255 mg, 1.00 mmol, 1 equiv) was used. After 18 h, the reaction was diluted with hexanes (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with 1:9 CH₂Cl₂/hexanes. The crude mixture was concentrated with the aid of a rotary

evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 2-7% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 235 mg, 92% yield, >99:1 er; Run 2: 1.00 mmol scale, 229 mg, 89% yield, >99:1 er).

¹H NMR (500 MHz, CDCl₃) δ 8.42 (s, 1H), 7.74 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.39 (t, *J* = 6.6 Hz, 2H), 2.17 – 2.09 (m, 2H), 1.90 (p, *J* = 6.9 Hz, 2H), 1.63 (dd, *J* = 6.7, 3.5 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 205.01, 166.17, 145.08 (q, *J*_{C-F} = 4.6 Hz), 135.61 (q, *J*_{C-F} = 3.2 Hz), 124.23 (q, *J*_{C-F} = 271.0 Hz), 119.89 (q, *J*_{C-F} = 33.2 Hz), 111.33, 89.49, 86.32, 66.17, 28.35, 25.30, 14.59.

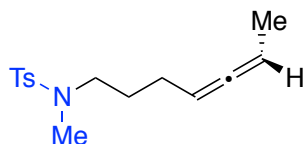
¹⁹F NMR (565 MHz, CDCl₃) δ -61.60.

IR (neat): 1962, 1613, 1501, 1313, 1120, 834 cm⁻¹

HRMS (ESI) Calcd. *m/z* for C₁₃H₁₅F₃NO [M+H]⁺: 258.1100. Found: 258.1102.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20B GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 70 °C hold for 50 min, 1 °C/min to 100 °C, hold for 20 min, 0.5 °C/min to 150 °C; *t*_r = 156.4 min (major) and 157.0 min (minor).

Specific rotation [α]_D²³: -32.25 (c = 1.0, CHCl₃)



(R)-N-(hepta-4,5-dien-1-yl)-N,4-dimethylbenzenesulfonamide (4j): Following general procedure A, N-(hepta-6-en-4-yn-1-yl)-N,4-dimethylbenzenesulfonamide (277 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 269 mg, 96% yield, 99:1 er; Run 2: 1.00 mmol scale, 278 mg, 99% yield, 99:1 er).

¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 5.04 (ddq, *J* = 10.0, 5.3, 2.8, 2.3 Hz, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 2.40 (s, 3H), 2.05 – 1.94 (m, 2H), 1.68 – 1.56 (m, 5H).

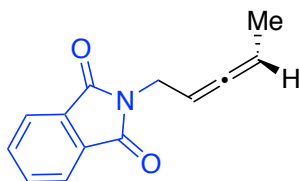
¹³C NMR (151 MHz, CDCl₃) δ 204.81, 143.27, 134.62, 129.68, 127.44, 89.33, 86.30, 49.65, 34.83, 26.97, 25.66, 21.54, 14.57.

IR (neat): 2930, 2853, 1962, 1338, 1158, 715 cm⁻¹

Elemental Analysis Calcd. for C₁₅H₂₁NO₂S: C, 64.48; H, 7.58. Found: C, 64.78; H, 7.60

Determination of enantiomeric ratio by HPLC analysis: OJ-H column, 1 mL/min: 100% hexanes for 80 min then gradient to 97:3 hexanes/iPrOH over 20 min, hold for 10 min, gradient to 100% hexanes over 5 min; *t*_r = 105.2 min (major) and 110.9 min (minor) λ = 230 nm.

Specific rotation [α]_D²³: -30.50 (c = 1.0, CHCl₃)



(R)-2-(penta-2,3-dien-1-yl)isoindoline-1,3-dione (4k): Following general procedure A, 2-(pent-4-en-2-yn-1-yl)isoindoline-1,3-dione (106 mg, 0.50 mmol, 1 equiv) was used. After 16 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 0-30% EtOAc/Hexanes) to afford the title compound as a white solid. (Run 1: 0.50 mmol scale, 93.3 mg, 88% yield, 97:3 er; Run 2: 0.50 mmol scale, 96.0 mg, 90% yield, 97:3 er). The spectral data match those previously reported in the literature.³

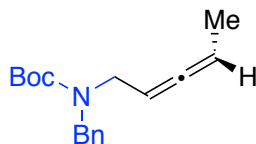
¹H NMR (500 MHz, CDCl₃) δ 7.85 (dd, J = 5.4, 3.0 Hz, 2H), 7.71 (dd, J = 5.4, 3.1 Hz, 2H), 5.20 – 5.11 (m, 2H), 4.27 (dd, J = 4.9, 3.6 Hz, 2H), 1.56 (dd, J = 5.7, 4.5 Hz, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 204.90, 167.95, 134.02, 132.32, 123.39, 123.35, 89.17, 86.19, 36.90, 14.03.

Determination of enantiomeric ratio by SFC analysis: OD-H column, 2.5 mL/min: 95:5 to 80:20 scCO₂/MeOH over 7 min; t_r = 3.7 min (minor) and 3.9 min (major).

Specific rotation $[\alpha]_D^{23}$: -39.01 (c = 1.0, CHCl₃). [lit.³ (S)-isomer: $[\alpha]_D^{19}$: +38.9 (c = 0.98 in CHCl₃)]

MP: 50 – 51 °C



Tert-butyl (R)-benzyl(penta-2,3-dien-1-yl)carbamate (4l): Following general procedure A, tert-butyl benzyl(pent-4-en-2-yn-1-yl)carbamate (271 mg, 1.00 mmol, 1 equiv) was used. After 15.5 h, the reaction was diluted with CH₂Cl₂ (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, and the silica gel was washed with CH₂Cl₂. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-12% EtOAc/hexanes) to afford a mixture of two rotamers of the title compound as a viscous colorless oil (Run 1: 1.00 mmol scale, 252 mg, 92% yield, Run 2: 0.50 mmol scale, 123 mg, 90% yield). The enantiomeric ratio was determined to be 99:1 for both runs after deprotecting **4l** to yield **S3** (see experimental procedure for **S3**).

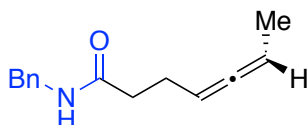
¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.20 (m, 3H), 5.21 – 4.94 (m, 2H), 4.44 (bs, 2H), 3.96 – 3.63 (m, 2H), 1.66 (dd, J = 7.0, 3.2 Hz, 3H), 1.47 (bs, 9H).

¹³C NMR (151 MHz, CDCl₃) δ (205.68 and 205.33), (155.81 and 155.47), (138.51 and 138.33), 128.47, 128.05, 127.51, 127.16, (87.14 and 86.91), (79.82 and 79.76), (49.60 and 49.21), 45.42, 28.49, 14.38.

IR (neat): 2973, 1962, 1691, 1234, 1162, 872 cm^{-1}

Elemental Analysis Calcd. for $\text{C}_{17}\text{H}_{23}\text{O}_2$: C, 74.69; H, 8.48. Found: C, 74.67; H, 8.63

Specific rotation $[\alpha]_{\text{D}}^{23}$: -28.42 ($c=1.0$, CHCl_3)



(R)-N-benzylhepta-4,5-dienamide (4m): Following general procedure A, N-benzylhept-6-en-4-ynamide (107 mg, 0.50 mmol, 1 equiv) was used. After 18 h, the reaction was quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 10-40% EtOAc/Hexanes) to afford the title compound as a white solid. (Run 1: 0.50 mmol scale, 99.1 mg, 92% yield, 80:20 er; Run 2: 0.50 mmol scale, 98.8 mg, 92% yield, 88:12 er).

^1H NMR (600 MHz, CDCl_3) δ 7.34 – 7.31 (m, 2H), 7.28 – 7.26 (m, 3H), 6.25 (bs, 1H), 5.13 – 5.04 (m, 2H), 4.41 (dq, $J=14.7, 5.8$ Hz, 2H), 2.32 (m, 4H), 1.61 (dd, $J=7.0, 3.3$ Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 204.61, 172.41, 138.46, 128.66, 127.79, 127.43, 89.33, 86.95, 43.55, 35.58, 24.58, 14.50.

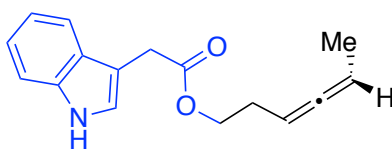
IR (CHCl_3): 3284, 1962, 1642, 1543, 872, 696 cm^{-1}

HRMS (ESI) Calcd. m/z for $\text{C}_{14}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 216.1383. Found: 216.1384.

Determination of enantiomeric ratio by SFC analysis: AD-H column, 2.5 mL/min: 97:3 to 90:10 $\text{scCO}_2/\text{MeOH}$ over 25 min; $t_{\text{r}} = 21.3$ min (major) and 22.6 min (minor).

Specific rotation $[\alpha]_{\text{D}}^{23}$: -36.70 ($c=1.0$, CHCl_3)

MP: 38 – 39 $^{\circ}\text{C}$



(R)-hexa-3,4-dien-1-yl 2-(1H-indol-3-yl)acetate (4n): Following general procedure A, hex-5-en-3-yn-1-yl 2-(1H-indol-3-yl)acetate (127 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 2-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 0.50 mmol scale, 115 mg, 90% yield, 87:13 er; Run 2: 0.75 mmol scale, 174 mg, 91% yield, 88.5:11.5 er).

^1H NMR (400 MHz, CDCl_3) δ 8.08 (bs, 1H), 7.63 (d, $J=7.9$ Hz, 1H), 7.36 (d, $J=8.0$ Hz, 1H), 7.24 – 7.11 (m, 3H), 5.14 – 4.96 (m, 2H), 4.17 (t, $J=6.8$ Hz, 2H), 3.79 (s, 2H), 2.31 (qd, $J=6.7, 3.0$ Hz, 2H), 1.63 (dd, $J=6.9, 3.3$ Hz, 3H).

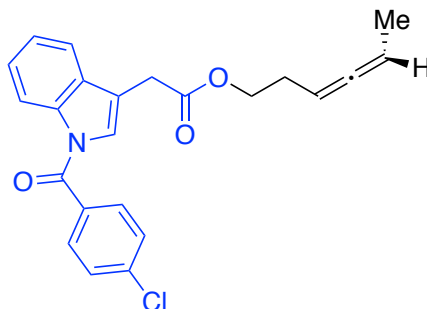
^{13}C NMR (101 MHz, CDCl_3) δ 205.48, 172.37, 136.18, 127.24, 123.32, 122.12, 119.61, 118.87, 111.34, 108.19, 86.48, 86.09, 64.18, 31.41, 28.31, 14.44.

IR (neat): 3404, 1962, 1723, 1451, 1157, 740 cm^{-1}

HRMS (ESI) calcd. m/z for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 256.1332. Found: 256.1333.

Determination of enantiomeric ratio by HPLC analysis: AD-H column, 0.7 mL/min: 99:1 hexanes/*i*PrOH for 30 min, gradient to 97:3 hexanes/*i*PrOH over 30 min, hold at 97:3 hexanes/*i*PrOH; t_r = 113.0 min (minor) and 115.5 min (major), λ = 210 nm.

Specific rotation $[\alpha]_D^{23}$: -21.90 (c = 1.0, CHCl_3)



(R)-hexa-3,4-dien-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (4o): Following general procedure A, hex-5-en-3-yn-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (196 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, and the silica gel was washed with EtOAc. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-8% EtOAc/hexanes) to afford the title compound as a viscous colorless oil. (Run 1: 0.50 mmol scale, 174 mg, 88% yield, 99:1 er; Run 2: 0.50 mmol scale, 170 mg, 86% yield, 98:2 er).

^1H NMR (600 MHz, CDCl_3) δ 8.38 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.29 (s, 1H), 5.10 – 5.04 (m, 1H), 5.03 – 4.97 (m, 1H), 4.18 (t, J = 6.8 Hz, 2H), 3.71 (d, J = 1.2 Hz, 2H), 2.30 (qd, J = 6.7, 2.9 Hz, 2H), 1.62 (dd, J = 7.0, 3.2 Hz, 3H).

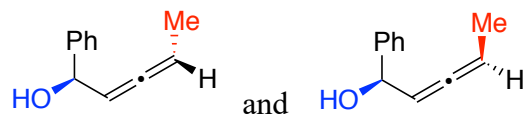
^{13}C NMR (151 MHz, CDCl_3) δ 205.50, 170.71, 167.40, 138.40, 136.23, 132.98, 130.68, 130.55, 129.08, 125.72, 125.52, 124.19, 119.18, 116.60, 115.05, 86.60, 85.93, 64.45, 31.03, 28.27, 14.46.

IR (neat): 2853, 1965, 1734, 1682, 1451, 1358 cm^{-1}

HRMS (ESI) Calcd. for $\text{C}_{23}\text{H}_{21}\text{ClNO}_3$ $[\text{M}+\text{Na}]^+$: 416.1024. Found: 416.1027.

Determination of enantiomeric ratio by SFC analysis: Cel-1 column, 2.5 mL/min: 95:5 to 80:20 scCO_2 /MeOH over 6 min; t_r = 2.6 min (minor) and 2.7 min (major).

Specific Rotation $[\alpha]_D^{23}$: -17.33 (c = 1.0, CHCl_3)



(1R,3R)- and (1R,3S)-1-phenylpenta-2,3-dien-1-ol (4p): Following general procedure **A**, (S)-1-phenylpent-4-en-2-yn-1-ol (79.1 mg, 0.50 mmol, 1 equiv) and either (S,S)-Ph-BPE (to yield **(1R,3R)-4p**) or (R,R)-Ph-BPE (to yield **(1R,3S)-4p**) was used. After 17 h, the reaction was diluted with EtOAc (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and subsequently diluted with THF (3.0 mL) and taken into a rubber septum sealed oven-dried 10 mL round-bottom flask equipped with a magnetic stir bar under an atmosphere of nitrogen. After the solution was cooled to 0 °C, tetrabutylammonium fluoride (1.0 mL, 1M THF, 2 equiv) was added dropwise to the stirring solution. After stirring for 1 h, the reaction was complete as indicated by TLC analysis and quenched by adding brine (25 mL). The resulting solution was extracted with CH₂Cl₂ (3 x 20 mL) and the combined extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* with the aid of a rotary evaporator. The crude material was purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 0-15% EtOAc/hexanes) to afford the title compound as a pale-yellow oil. (With (S,S)-Ph-BPE: 0.50 mmol scale, 70.0 mg, 87% yield, >15:1 dr; With (R,R)-Ph-BPE: 0.50 mmol scale, 68.4 mg, 85% yield, 1:>15 dr).

(1R,3R)-1-phenylpenta-2,3-dien-1-ol

¹H NMR (600 MHz, CDCl₃) δ 7.42 – 7.38 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 5.42 – 5.30 (m, 2H), 5.26 – 5.20 (m, 1H), 2.13 (bs, 1H), 1.73 (dd, J = 7.0, 3.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.07, 143.23, 128.61, 127.84, 126.27, 95.71, 89.94, 72.29, 14.52.

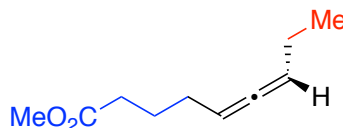
IR (neat): 3348 (br), 1966, 1270, 1118, 870, 697 cm⁻¹

HRMS (ESI) Calcd. for C₁₁H₁₃O [M+H]⁺: 161.0961. Found: 161.0962.

(1R,3S)-1-phenylpenta-2,3-dien-1-ol

¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 5.42 – 5.31 (m, 2H), 5.27 – 5.22 (m, 1H), 2.17 (s, 1H), 1.71 (dd, J = 7.0, 3.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 203.18, 143.28, 128.58, 127.80, 126.22, 95.68, 89.79, 72.37, 14.38.



Methyl (R)-nona-5,6-dienoate (4q): Following general procedure **B**, methyl (E)-non-7-en-5-ynoate (166 mg, 1.0 mmol, 1 equiv), and TMCTS (121.5 μL, 0.5 equiv, 0.5 mmol) was used. The stock solution of water was prepared using 28.11 μL (1.56 mmol, 1.56 equiv). After 17 h, the reaction was diluted with CH₂Cl₂ (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, and the silica gel was washed with CH₂Cl₂. The crude mixture was concentrated with the aid of a rotary evaporator and purified

with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-9% EtOAc/hexanes) to afford the title compound as a volatile colorless oil. (Run 1: 0.50 mmol scale, 83.6 mg, 50% yield, >99:1 er; Run 2: 0.50 mmol scale, 75.8 mg, 45% yield, >99:1 er).

¹H NMR (400 MHz, CDCl₃) δ 5.15 (qt, *J* = 6.1, 3.0 Hz, 1H), 5.08 (qt, *J* = 6.5, 3.3 Hz, 1H), 3.66 (s, 3H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.08 – 1.93 (m, 4H), 1.74 (p, *J* = 7.7 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

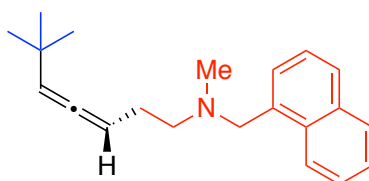
¹³C NMR (101 MHz, CDCl₃) δ 203.82, 174.25, 93.33, 90.65, 51.63, 33.52, 28.51, 24.46, 22.12, 13.58.

IR (neat): 2965, 1959, 1737 (s), 1436, 1153, 878 cm⁻¹

HRMS (ESI) Calcd. for C₁₀H₁₇O₂ [M+H]⁺: 169.1223. Found: 169.1222

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20B GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 70 °C hold for 50 min, 1 °C/min to 100 °C, hold for 20 min, 2 °C/min to 150 °C; *t_r* = 96.2 min (major) and 97.9 min (minor).

Specific rotation [α]_D²³: -54.56 (*c* = 1.0, CHCl₃)



(R)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hepta-3,4-dien-1-amine (4r): Following general procedure B, terbinafine (146 mg, 0.50 mmol, 1 equiv), and TMCTS (182 μL, 1.5 equiv, 0.75 mmol) was used. The stock solution of water was prepared using 33.9 μL (1.88 mmol, 3.75 equiv). After 20 h, the reaction was diluted with CH₂Cl₂ (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, and the silica gel was washed with CH₂Cl₂. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-5% EtOAc/hexanes) to afford the title compound as a viscous colorless oil. (Run 1: 0.50 mmol scale, 98.5 mg, 67% yield, 99:1 er; Run 2: 0.50 mmol scale, 99.3 mg, 68% yield, 99:1 er).

¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.37 (m, 4H), 5.22 (q, *J* = 6.5 Hz, 1H), 5.17 – 5.09 (m, 1H), 4.02 – 3.85 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.37 – 2.21 (m, 5H), 1.06 (s, 9H).

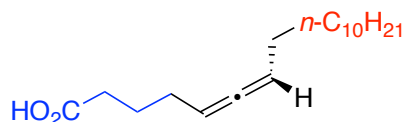
¹³C NMR (151 MHz, CDCl₃) δ 201.44, 135.16, 134.00, 132.66, 128.50, 127.96, 127.47, 125.91, 125.68, 125.25, 124.86, 103.34, 90.82, 60.84, 57.87, 42.38, 31.78, 30.35, 27.29.

IR (neat): 2957, 2787, 1959, 1360, 790, 773 cm⁻¹

Elemental Analysis Calcd. for C₂₁H₂₇N: C, 85.96; H, 9.27. Found: C, 84.06; H, 9.40.

Determination of enantiomeric ratio by HPLC analysis: IC column, 0.4 mL/min: 100% hexanes with 0.15% DEA; *t_r* = 12.5 min (minor) and 12.8 min (major), λ = 254 nm.

Specific rotation [α]_D²³: -40.08 (*c* = 1.0, CHCl₃)



(R)-Laballenic Acid (4s): General procedure **B** was modified as follows: After adding catalyst solution to (E)-octadec-7-en-5-ynoic acid (139 mg, 0.50 mmol, 1 equiv) in DME (0.4 mL), in the glovebox, dimethoxy(methyl)silane (DMMS) (309 μ L, 5 equiv, 2.5 mmol) was added to the uncapped reaction tube. The solution was left to stir vigorously for 20 min until gas evolution subsided and the solution became a strong yellow color, at which point the reaction tube was capped and removed from the glovebox to continue stirring at rt for an additional 1 h. H₂O (33.9 μ L, 1.88 mmol, 3.75 equiv) was added to the 1 dram vial containing DME (1.5 mL) using a Hamilton gastight glass microsyringe to yield a stock solution of water. After cooling the reaction solution to -10 °C, one-third of the water/DME mixture was taken into a 1 mL syringe with needle and inserted into the reaction tube. Slow addition of the water solution was initiated with the aid of a Harvard Apparatus PHD Ultra syringe pump at a rate of 0.5 μ L/min. After 21 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt, the silica gel was washed with EtOAc.

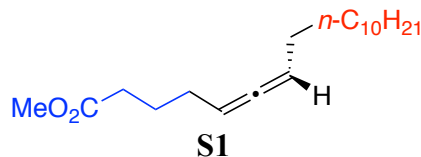
1N aqueous HCl (15 mL) was added to the yellow solution which immediately became colorless. The mixture was stirred vigorously for 3 h to ensure complete deprotection of the carboxylic acid followed by extraction of the aqueous with EtOAc (3x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The crude reaction material was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-10-40% EtOAc/hexanes) to afford the title compound as a pale-yellow oil. The enantiomeric ratio was determined after conversion of the free acid to the methyl ester (**S1**) using Ma's previously reported conditions.⁴ (Run 1: 0.50 mmol scale, 74.5 mg, 53% yield, 93:7 er; Run 2: 0.250 mmol scale, 32.3 mg, 46% yield, 93.5:6.5 er). The spectral data match those previously reported in the literature.⁴

¹H NMR (600 MHz, CDCl₃) δ 5.10 (ddt, J = 6.4, 3.0, 3.0 Hz, 1H), 5.05 (ddt, J = 6.3, 3.0, 3.0 Hz, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.04 (qd, J = 7.2, 2.9 Hz, 2H), 1.97 (qd, J = 7.0, 3.0 Hz, 2H), 1.76 (p, J = 7.4 Hz, 2H), 1.43 – 1.18 (m, 18H), 0.88 (t, J = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 204.21, 179.48, 91.79, 89.80, 33.35, 32.08, 29.83, 29.79, 29.63, 29.51, 29.38, 29.35, 29.28, 29.09, 28.36, 24.15, 22.84, 14.27.

IR (neat): 2923, 2853, 1959, 1709, 1455, 1078 cm⁻¹

Specific rotation [α]_D²³: -38.07 (c = 0.96, CHCl₃). [lit.⁴ [α]_D²⁹: -42.7 (c = 0.96 in CHCl₃)]



Alternative workup to yield methyl ester S1 directly: After following the procedure detailed for the synthesis of **4s** (0.5 mmol scale), a methanolic HCl solution (8 mL, 1.25 N, 20 equiv) was

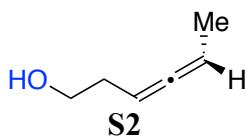
used in place of the aforementioned aqueous HCl solution. After stirring for 1 h at rt, the solution was transferred into a separatory funnel with saturated ammonium chloride (20 mL) and extracted with CH₂Cl₂ (3x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (25g SNAP cartridge, 0-8% EtOAc/Hexanes) to yield the methyl ester derivative **S1** (68.2 mg, 46% yield, 98:2 er). The spectral data match those previously reported in the literature.⁴

¹H NMR (400 MHz, CDCl₃) δ 5.12–5.01 (m, 2H), 3.67 (s, 3H), 2.35 (t, J = 7.6 Hz, 2H), 1.98 (dtd, J = 19.8, 7.0, 3.1 Hz, 4H), 1.74 (p, J = 7.5 Hz, 2H), 1.45 – 1.17 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 204.19, 174.24, 91.67, 89.92, 51.62, 33.52, 32.08, 29.83, 29.80, 29.64, 29.51, 29.38, 29.28, 29.10, 28.51, 24.48, 22.84, 14.27.

Determination of enantiomeric ratio by HPLC analysis: Chiralcel OD-H column, 0.5 ml/min: 100% hexanes; t_R = 20.4 min (minor) and 21.5 min (major) [Lit.⁴: t_R = 21.7 min (minor) and 22.8 min (major), λ = 214 nm]

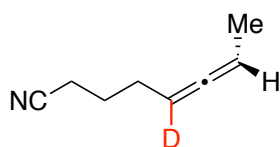
IV. Further Confirmation of Absolute Configuration



(R)-hexa-3,4-dien-1-ol (S2): To an oven-dried 10 mL round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum under an atmosphere of nitrogen were added THF (1.57 mL) and allene **4f** (100 mg, 0.47 mmol, 1 equiv) sequentially. Tetrabutylammonium fluoride (1.04 mL, 1M THF, 2.2 equiv) was added dropwise to the stirring solution. After stirring for 4 h, the reaction was complete as indicated by TLC analysis and quenched by adding deionized water (3 mL). The resulting solution was extracted with Et₂O (3 x 5 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* with the aid of a rotary evaporator. The crude material was purified on silica gel (0–50% pentane/Et₂O) to afford the title compound as a colorless oil (19.2 mg, 41% yield). The spectral data match those previously reported in the literature.³

Specific rotation $[\alpha]_D^{23}$: -62.4 (c = 0.9, CHCl₃) [lit.³ $[\alpha]_D^{20}$: -33.6 (c = 0.66, CHCl₃)]

V. Deuterium Labeling Experiments



(R)-octa-5,6-dienitrile-5-d (5): Following general procedure A, oct-7-en-5-ynenitrile (477 mg, 4.0 mmol, 1 equiv) and D₂O (0.52 equiv, 20.0 mg, 37.5 μ L) was used. After 17.5 h, the reaction was diluted with CH₂Cl₂ (4.0 mL) and quickly passed through a short plug of silica gel (ca. 2 g) before the reaction solution could warm to rt, the silica gel was washed with CH₂Cl₂. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-15% EtOAc/hexanes) to afford the title compound as a volatile colorless oil. Percent deuterium incorporation was determined by ²H NMR analysis with methanol-d₄ as an internal standard in addition to comparison of the ¹H NMR spectra with those of the non-deutero isomer obtained from the use of H₂O instead (Run 1: 4.0 mmol scale, 390 mg, 80% yield, 99:1 er, 98:2 D/H incorporation; Run 2: 1.8 mmol scale, 160 mg, 73% yield, 99:1 er, 98:2 D/H incorporation).

¹H NMR (400 MHz, CDCl₃) δ 5.12 (qt, *J* = 6.8, 3.6 Hz, 1H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.12 (td, *J* = 7.1, 2.8 Hz, 2H), 1.77 (p, *J* = 7.2 Hz, 2H), 1.65 (d, *J* = 7.0 Hz, 3H).

²H NMR (77 MHz, CH₂Cl₂) δ 5.06

¹³C NMR (126 MHz, CDCl₃) δ 205.15, 119.75, 87.97 (t, *J* = 25 Hz), 86.93, 27.42, 24.66, 16.40, 14.52.

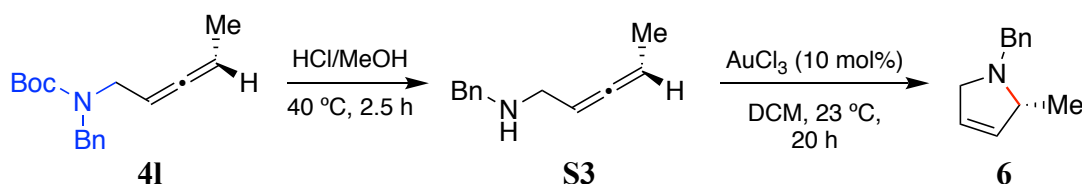
IR (neat): 2939, 2247, 1959, 1441, 798, 553 cm⁻¹

HRMS (ESI) Calcd. for C₈H₁₁DN [M+H]⁺: 123.1027. Found: 123.1036.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20 β GC Column (30 m, 0.25 mm, 0.25 μ m, 7 inch cage), 8 psi: 70 $^{\circ}$ C for 50 min, then 1 $^{\circ}$ C/min to 100 $^{\circ}$ C, hold for 5 min; *t_R* = 79.6 min (major) and 80.4 min (minor)

Specific Rotation [α]_D²³: -62.84 (*c* = 1.0, CHCl₃)

VI. Cycloisomerization of Alleneamine 4l



(R)-N-benzylpenta-2,3-dien-1-amine (S3): Allene **4l** (137 mg, 0.5 mmol, 1 equiv) was taken into an oven-dried screw-cap reaction tube (16mm \times 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar and diluted in methanolic HCl (2.0 mL, 1.25 N, 2.5 mmol, 5 equiv). The

reaction tube was capped with a Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part # 73804-15425) and transferred to an oil bath pre-heated to 40 °C. The reaction solution was stirred vigorously at 40 °C until complete conversion was indicated by TLC analysis (ca. 2.5 h). Concentration of the crude reaction solution with the aid of a rotary evaporator furnished a white salt which was dissolved in saturated aqueous NaHCO₃ (80 mL) and taken into a separatory funnel. CH₂Cl₂ (30 mL) was added and the solution was shaken vigorously. The organics were collected and the aqueous was re-extracted with CH₂Cl₂ (2x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. The crude oil was purified with the aid of a Biotage Isolera (10 g SNAP cartridge, 0-50% EtOAc/hexanes) to afford **S3** as a pale-yellow oil (85.0 mg, 88% yield, 99:1 er). The spectral data match those previously reported.⁵

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20β GC Column (30 m, 0.25 mm, 0.25 μm, 7 inch cage), 8 psi: 100 °C for 60 min, then 0.25 °C/min to 150 °C; t_r = 148.0 min (major) and 149.1 min (minor).

(R)-1-benzyl-2-methyl-2,5-dihydro-1H-pyrrole (6): To an oven-dried 1 dram vial containing a magnetic stir bar and gold(III) chloride under nitrogen atmosphere was added a solution of **S3** (30.0 mg, 0.17 mmol, 1 equiv) in anhydrous CH₂Cl₂ (0.5 mL). After the reaction mixture was stirred vigorously at rt for 20 h, the vial was uncapped and the solution was filtered through a plug of celite atop a plug of silica gel (ca. 0.3 g each), and the silica gel and celite were washed with Et₂O. The crude reaction solution was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (10g SNAP cartridge, 0-80% EtOAc/Hexanes) to afford the title compound as a pale-yellow oil (18.5 mg, 62% yield, 99:1 er).

¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.33 (m, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.24 (td, J = 7.2, 3.5 Hz, 1H), 5.76 – 5.70 (m, 1H), 5.70 – 5.64 (m, 1H), 4.03 (d, J = 13.1 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.56 (d, J = 13.1 Hz, 1H), 3.26 – 3.17 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 133.52, 128.91, 128.40, 126.96, 126.64, 65.48, 60.13, 58.43, 20.45.

IR (neat): 3059, 2916, 2870, 2782, 1491, 695 cm⁻¹

HRMS (ESI) Calcd. for C₁₂H₁₆N [M+H]⁺: 174.1277. Found: 174.1283.

Determination of enantiomeric ratio by GC analysis: Hydrodex β-3P column (25 m, 0.25 mm), 7.5 PSI: 110 °C for 20 min, then 10 °C/min to 220 °C, hold for 5 min; t_r = 27.0 min (minor) and 27.1 min (major).

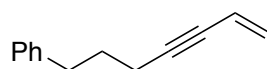
Specific Rotation [α]_D²³: -138.0 (c = 0.8, CHCl₃)

VII. Preparation of 1,3-Enyne Substrates

The following substrates were prepared according to literature reports: **1b**,⁶ **1c**,⁷ **1d**,⁸ **1f**,⁹ **1g**,⁸ **1h**,¹⁰ **1j**,⁸ **1m**,⁸ and **1t**.¹¹ Terbinafine was purchased as the HCl salt from Combi Blocks Inc.

General procedure C: Sonogashira coupling for the synthesis of 1,3-enynes

In a nitrogen-filled glovebox, an oven-dried 50 mL three-neck flask containing a magnetic stir-bar was charged with bis(triphenylphosphine)palladium(II) chloride (281 mg, 0.40 mmol, 3 mol%) and copper(I) iodide (114 mg, 0.60 mmol, 4 mol%). The reaction flask was sealed with a rubber septum and removed from the glovebox. Under an atmosphere of nitrogen, triethylamine (11.2 mL, 80.0 mmol, 4.0 equiv) was added *via* syringe and the suspension was cooled to 0 °C in an ice/water bath. Alkyne starting material (20.0 mmol, 1 equiv) was added slowly at 0 °C and the solution was allowed to stir for approximately 10-20 min. Vinyl halide starting material (40.0 mmol, 2.0 equiv) was slowly added to the reaction mixture at 0 °C. After stirring for 10 min, the reaction solution was allowed to warm to rt. After vigorously stirring for an additional 16 h at rt, or upon the complete consumption of alkyne starting material as indicated by GC analysis, the flask was uncapped and the crude reaction mixture was quenched by adding deionized water (400 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL) and the combined extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator. All crude reaction mixtures were purified on silica gel to afford the desired 1,3-enyne products.



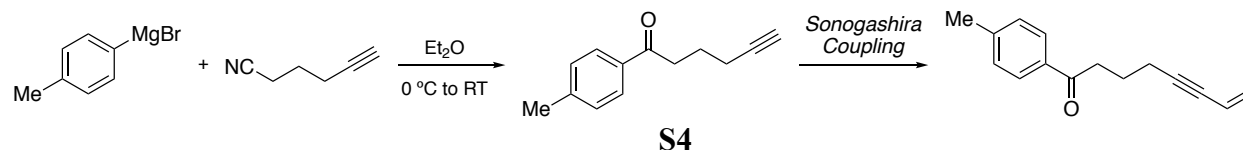
Hept-6-en-4-yn-1-ylbenzene (1a): Following general procedure C, copper(I) iodide (114 mg, 0.60 mmol, 3 mol%), bis(triphenylphosphine)palladium(II) chloride (281 mg, 0.40 mmol, 2 mol%), triethylamine (13.3 mL, 96.0 mmol, 4.8 equiv), pent-4-yn-1-ylbenzene (3.04 mL, 20.0 mmol, 1 equiv) and bromoethane (34.0 mL, 1M in THF, 34.0 mmol, 1.7 equiv) was used. After stirring for 16.5 h at rt, the crude reaction solution was diluted with hexanes (30 mL) and filtered through a plug of silica gel and concentrated on a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 100% hexanes) to afford the title compound as a colorless oil (2.64 g, 78% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 3H), 5.85 (ddt, *J* = 17.6, 11.1, 2.2 Hz, 1H), 5.62 (dd, *J* = 17.5, 2.2 Hz, 1H), 5.43 (dd, *J* = 11.1, 2.2 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.36 (td, *J* = 7.1, 2.1 Hz, 2H), 1.90 (p, *J* = 7.3 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 141.64, 128.58, 128.41, 125.96, 125.67, 117.67, 90.66, 79.93, 34.87, 30.28, 18.82.

IR (neat): 2942, 2225, 1206, 1496, 973, 698 cm⁻¹

HRMS (ESI) Calcd. *m/z* for C₁₃H₁₅ [M + H]⁺: 171.1174. Found: 171.1168.



1-(p-tolyl)hex-5-yn-1-one (S4): An oven-dried 500 mL round bottom flask was equipped with a magnetic stir bar and sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (this process was repeated a total of three times). Anhydrous diethyl ether (45 mL) was added via syringe followed by p-tolylmagnesium bromide (0.5 M in Et₂O, 66 mL, 33 mmol, 2.2 equiv). The solution was cooled to ca. 0 °C using an ice-water bath. Hex-5-ynenitrile (1.4 g, 15 mmol, 1 equiv) was added to the Grignard solution dropwise over a period of 10 min with vigorous stirring, eventually yielding an opaque white suspension. The reaction mixture was left to slowly warm to rt while stirring. After 15.5 h, the reaction mixture was cooled to 0 °C using an ice-water bath and carefully quenched by addition of water (20 mL) over 2 h with the aid of a Harvard Apparatus PHD Ultra syringe pump. After further dilution with water (40 mL), the crude mixture was poured into a separatory funnel and extracted with EtOAc (3x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator to yield a yellow oil. Subsequent purification with the aid of a Biotage Isolera (100 g SNAP cartridge, 025% EtOAc/Hexanes) provided the title compound as a yellow oil (2.38 g, 85% yield). The spectral data match those previously reported in the literature.¹²

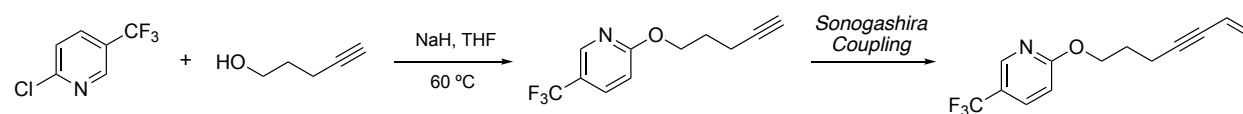
1-(p-tolyl)oct-7-en-5-yn-1-one (1e): Following general procedure C, 1-(p-tolyl)hex-5-yn-1-one (S4) (3.04 mL, 20.0 mmol, 1 equiv) was used. After stirring for 16 h at rt, the crude reaction solution was diluted with hexanes (20 mL) and filtered through a plug of silica gel and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-7% EtOAc/hexanes) to afford the title compound as a yellow oil (2.01 g, 82% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.78 (ddt, *J* = 17.6, 11.0, 2.2 Hz, 1H), 5.55 (dd, *J* = 17.5, 2.3 Hz, 1H), 5.39 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.48 – 2.38 (m, 5H), 1.98 (p, *J* = 7.0 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 199.45, 143.90, 134.63, 129.38, 128.30, 125.93, 117.60, 90.30, 80.27, 37.25, 23.26, 21.76, 19.01.

IR (neat): 2936, 2224, 1679 (s), 1606, 1232, 806 cm⁻¹

HRMS (DART) Calcd. for C₁₅H₁₇O [M+H]⁺: 213.1274. Found: 213.1281.



2-(hept-6-en-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (1i): In a nitrogen-filled glovebox, an oven-dried round bottom flask with magnetic stir bar was charged with sodium hydride (432 mg, 18.0 mmol, 1.2 equiv) and the flask was sealed with a rubber septum and removed from the glovebox. Under an atmosphere of nitrogen, anhydrous THF (20 mL) was added followed by careful addition of 2-chloro-5-(trifluoromethyl)pyridine (2.72 g, 15.0 mmol, 1 equiv) in THF (4

mL) while stirring (caution: gas evolution was observed). After stirring for 20 min at rt, the reaction solution was heated to 60 °C and stirred for 17.5 h. The reaction mixture was allowed to cool to rt and quenched by addition of water (5 mL). The orange-red solution was poured into a separatory funnel containing 15 mL water and extracted with CH₂Cl₂ (3x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. Purification with the aid of a Biotage Isolera (50g SNAP cartridge, 2-20% EtOAc/Hexanes) afforded the desired alkyne intermediate, 2-(pent-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine. The isolated material was taken directly on to the Sonogashira coupling.

Compound **4i** was prepared following general procedure **C**, with 2-(pent-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (1.60 g, 7.0 mmol, 1 equiv), bis(triphenylphosphine)palladium(II) chloride (195 mg, 0.28 mmol, 4 mol%), and copper(I) iodide (63.5 mg, 0.33 mmol, 5 mol%). The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 2-10% EtOAc/hexanes) to afford the title compound as colorless oil (1.0 g, 58% yield).

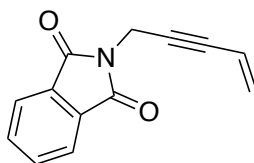
¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 7.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.76 (ddt, *J* = 17.5, 11.0, 2.1 Hz, 1H), 5.55 (dd, *J* = 17.5, 2.2 Hz, 1H), 5.38 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.45 (t, *J* = 6.2 Hz, 2H), 2.50 (dt, *J* = 7.1, 2.2 Hz, 2H), 2.02 (p, *J* = 6.6 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 165.95, 145.03 (q, *J* = 4.5 Hz), 135.60 (q, *J* = 3.2 Hz), 125.84, 124.17 (q, *J* = 271.1 Hz), 120.00 (q, *J* = 33.0 Hz), 117.56, 111.29, 89.67, 80.06, 65.35, 28.13, 16.20.

¹⁹F NMR (565 MHz, CDCl₃) δ -61.70.

IR (neat): 2957, 2229, 1613, 1120, 1290, 659 cm⁻¹

HRMS (ESI) Calcd. for C₁₃H₁₃F₃NO [M+H]⁺: 256.0944. Found: 256.0948.



2-(pent-4-en-2-yn-1-yl)isoindoline-1,3-dione (1k): Following general procedure **C**, 2-(prop-2-yn-1-yl)isoindoline-1,3-dione (1.10 g, 5.9 mmol, 1 equiv) was used, and the reaction was stirred for 20 h at rt. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 10-100% EtOAc/hexanes) to afford the title compound as an off-white solid (512 mg, 41% yield).

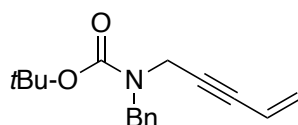
¹H NMR (600 MHz, CDCl₃) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.74 (ddt, *J* = 17.6, 11.0, 2.0 Hz, 1H), 5.63 (dd, *J* = 17.6, 2.2 Hz, 1H), 5.47 (dd, *J* = 11.1, 2.2 Hz, 1H), 4.57 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 167.24, 134.30, 132.21, 128.16, 123.68, 116.58, 83.35, 81.80, 27.85.

IR (neat): 1766, 1704, 1389, 1317, 1109, 721 cm⁻¹

HRMS (ESI) Calcd. for C₁₃H₁₀NO₂ [M+H]⁺: 212.0706. Found: 212.0710.

MP: 114–115 °C



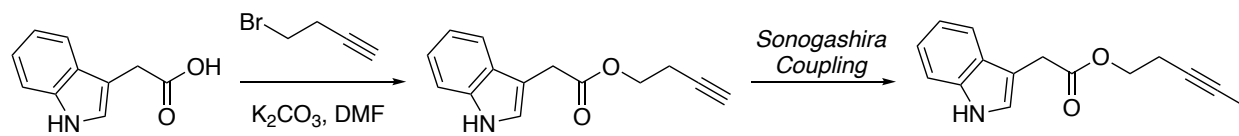
Tert-butyl benzyl(pent-4-en-2-yn-1-yl)carbamate (1l): Following general procedure C, tert-butyl benzyl(prop-2-yn-1-yl)carbamate (prepared according to literature report,¹³ 4.66 g, 19.0 mmol, 1 equiv) was used. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-20% EtOAc/hexanes) to afford the title compound as a yellow oil consisting of a rotameric mixture (3.45 g, 67% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 17.6, 11.0, 2.0 Hz, 1H), 5.62 (dd, *J* = 17.6, 2.2 Hz, 1H), 5.48 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.57 (s, 2H), 4.29 – 3.95 (m, 2H), 1.50 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 155.27, 137.81, (128.62 and 128.15), 127.74, 127.44, 127.25, 116.97, 85.63, (82.51 and 82.23), 80.58, (49.47 and 49.24), (36.30 and 36.04), 28.52.

IR (neat): 2976, 2926, 1694 (s), 1406, 1159, 698 cm⁻¹

HRMS (ESI) Calcd. for C₁₇H₂₂NO₂: 272.1645. Found: 272.1646.



Hex-5-en-3-yn-1-yl 2-(1H-indol-3-yl)acetate (1n): An oven-dried 50 mL round bottom flask with magnetic stir bar was charged with potassium carbonate (3.87 g, 28.0 mmol, 2 equiv) and 2-(1H-indol-3-yl)acetic acid (2.45 g, 14.0 mmol, 1 equiv) and the vessel was subsequently sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (this process was repeated a total of three times). DMF (28 mL) was added to the solids via syringe and the suspension was heated to 50 °C with vigorous stirring for 15 min prior to the addition of 4-bromobut-1-yne (3.72 g, 28.0 mmol, 2 equiv) via syringe. After stirring for 4.5 h, the reaction solution was allowed to cool to rt and then filtered through a plug of celite. The filtrate was concentrated with the aid of a rotary evaporator and the crude reaction material was purified with the aid of a Biotage Isolera (100g SNAP cartridge, 20-80% EtOAc/Hexanes) to afford but-3-yn-1-yl 2-(1H-indol-3-yl)acetate as a yellow oil (1.15 g, 36% yield). The isolated material was taken directly on to the Sonogashira coupling.

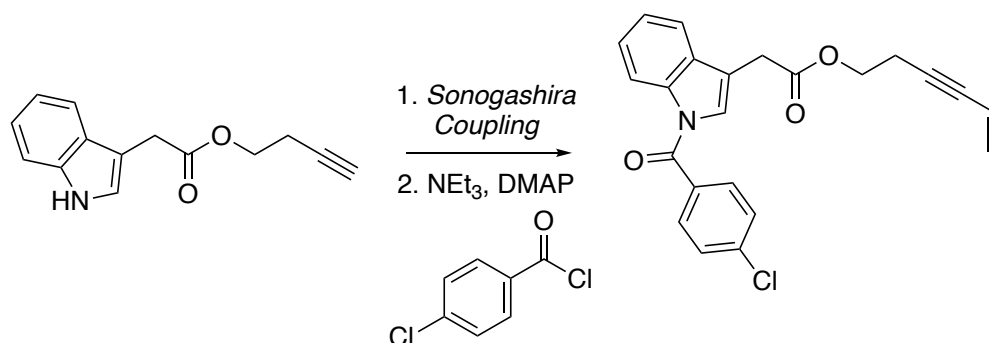
Compound **1n** was prepared following general procedure C, with but-3-yn-1-yl 2-(1H-indol-3-yl)acetate (1.14 g, 5.0 mmol, 1 equiv). The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a yellow oil (540 mg, 43% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.13 (m, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 5.79 (ddt, *J* = 17.5, 11.0, 2.0 Hz, 1H), 5.61 (dd, *J* = 17.6, 2.3 Hz, 1H), 5.46 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 2H), 2.68 (td, *J* = 6.8, 2.1 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.06, 136.17, 127.23, 126.64, 123.34, 122.22, 119.73, 118.90, 117.24, 111.33, 108.13, 86.38, 80.86, 62.73, 31.32, 19.90.

IR (neat): 3404, 1727, 1458, 1156, 911, 740 cm^{-1}

HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 254.1176. Found: 254.1180.



Hex-5-en-3-yn-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (1o**):** Compound **1o** was prepared following the Sonogashira protocol (10.8 mmol scale) outlined for **1n**, followed by benzoylation of the indole as follows: the crude reaction mixture was taken into an oven-dried 100 mL round bottom flask with magnetic stir bar and DMAP (132 mg, 1.08 mmol, 10 mol%) was added. The flask was sealed with a rubber septum and evacuated and backfilled with nitrogen. Anhydrous CH_2Cl_2 (33 mL) was syringed in to the flask and the solution cooled to 0 °C in an ice-water bath followed by addition of triethylamine (4.5 mL, 32.3 mmol, 3 equiv). After stirring for 30 min, 4-chlorobenzoyl chloride (2.08 mL, 16.2 mmol, 1.5 equiv) was added by syringe and the solution was allowed to warm to rt. After stirring for 23 h, the reaction mixture was poured onto saturated aqueous ammonium chloride (60 mL) and extracted with CH_2Cl_2 (2x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. Purification with the aid of a Biotage Isolera (100g SNAP cartridge, 0-20% EtOAc/Hexanes) afforded the title compound as an off-white solid (1.30 g, 32% 2-step yield).

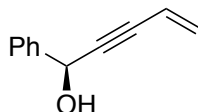
^1H NMR (400 MHz, CDCl_3) δ 8.37 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.29 (s, 1H), 5.72 (dd, J = 17.5, 11.0 Hz, 1H), 5.55 (d, J = 16.0 Hz, 1H), 5.42 (d, J = 11.0 Hz, 1H), 4.23 (t, J = 6.7 Hz, 2H), 3.74 (s, 2H), 2.64 (t, J = 6.3 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 170.54, 167.41, 138.44, 136.26, 132.96, 130.71, 130.51, 129.10, 126.75, 125.82, 125.55, 124.24, 119.22, 117.15, 116.61, 114.86, 86.07, 80.92, 63.00, 30.97, 19.92.

IR (neat): 3072, 2956, 1736, 1674, 1451, 749 cm^{-1}

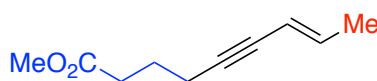
HRMS (ESI) Calcd. for $\text{C}_{23}\text{H}_{19}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$: 392.1048. Found: 392.1056.

MP: 71–72 °C



(S)-1-phenylpent-4-en-2-yn-1-ol (1p): Following general procedure C, (R)-1-phenylprop-2-yn-1-ol (1.98 g, 15.0 mmol, 1 equiv) was used, and the solution was stirred for 49 h at rt. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0–15% EtOAc/hexanes) to afford the title compound as an off-white solid (1.10 g, 46% yield,). The spectral data match those previously reported in the literature.¹⁴

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20B GC Column (30 m, 0.25 mm, 0.25 μ m, 7 inch cage), 8 psi: 90 °C for 50 min then 0.5 °C/min to 150 °C; t_r = 158.0 min (major) and 160.6 min (minor).



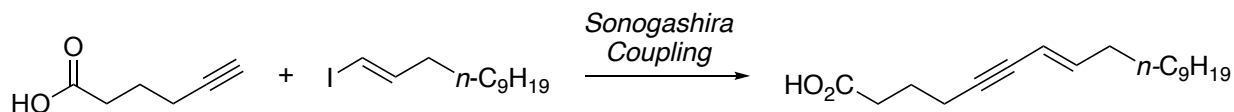
Methyl (E)-non-7-en-5-ynoate (1q): Following general procedure C, methyl hex-5-ynoate (2.60 g, 20.0 mmol, 1 equiv) and 1-bromoprop-1-ene (4.84 g, 40.0 mmol, 2 equiv, mixture of E/Z isomers) was used. After stirring for 20 h at rt, the reaction solution was diluted with hexanes (20 mL) and filtered through a plug of silica gel and concentrated on a rotary evaporator. The crude reaction mixture was carefully purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0–7% EtOAc/hexanes, 70 mL/min). The product was collected in two fractions in order to separate some of the E-isomer from the Z-isomer. The title compound was isolated as a colorless oil (920 mg of >20:1 E/Z and 1.88 g of a 4:1 E/Z mixture, 70% total yield).

¹H NMR (400 MHz, CDCl₃) δ 6.05 (dq, J = 15.7, 6.7 Hz, 1H), 5.45 (dq, J = 15.7, 1.9 Hz, 1H), 3.67 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H), 2.35 (td, J = 6.9, 2.1 Hz, 2H), 1.83 (p, J = 7.1 Hz, 2H), 1.74 (dd, J = 6.7, 1.8 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 173.81, 138.58, 110.98, 87.04, 80.18, 51.70, 33.02, 24.12, 18.93, 18.59.

IR (neat): 2953, 1736 (s), 1436, 1212, 1155, 953 cm⁻¹

HRMS (ESI) Calcd. for C₁₀H₁₅O₂ [M+H]⁺: 167.0167. Found: 167.1068.



(E)-octadec-7-en-5-ynoic acid (1s): Following general procedure C, hex-5-ynoic acid (1.02 g, 9.1 mmol, 1 equiv) and (E)-1-iodododec-1-ene (4.00 g, 3.6 mmol, 1.5 equiv, prepared according to literature report¹⁵) was used. After stirring for 12 h at rt, the crude reaction solution was taken into 1N aqueous HCl (50 mL) and extracted with CH₂Cl₂ (3x 40 mL). The combined organic extracts were washed with brine (1x 30 mL), dried over magnesium sulfate, filtered and concentrated. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g

SNAP cartridge, 0–25% EtOAc/hexanes). The title compound was isolated as an off-white solid (854 mg, 34% yield). The spectral data match those previously reported in the literature.¹⁶

References:

1. Ng, S.-S.; Jamison, T. F., Enantioselective and regioselective nickel-catalyzed multicomponent coupling of chiral allenes, aromatic aldehydes, and silanes. *Tetrahedron* **2005**, *61* (48), 11405-11417.
2. Khrakovsky, D. A.; Tao, C.; Johnson, M. W.; Thornbury, R. T.; Shevick, S. L.; Toste, F. D., Enantioselective, Stereodivergent Hydroazidation and Hydroamination of Allenes Catalyzed by Acyclic Diaminocarbene (ADC) Gold(I) Complexes. *Angewandte Chemie International Edition* **2016**, *55* (20), 6079-6083.
3. Webster, S.; Sutherland, D. R.; Lee, A.-L., Chirality Transfer in Gold(I)-Catalysed Hydroalkoxylation of 1,3-Disubstituted Allenes. *Chemistry – A European Journal* **2016**, *22* (51), 18593-18600.
4. Yu, Q.; Ma, S., An Enantioselective Synthesis of (R)-5,6-Octadecadienoic Acid. *European Journal of Organic Chemistry* **2015**, *2015* (7), 1596-1601.
5. Boutier, A.; Kammerer-Pentier, C.; Krause, N.; Prestat, G.; Poli, G., Pd-Catalyzed Asymmetric Synthesis of N-Allenyl Amides and Their Au-Catalyzed Cycloisomerizative Hydroalkylation: A New Route Toward Enantioenriched Pyrrolidones. *Chemistry – A European Journal* **2012**, *18* (13), 3840-3844.
6. Miller, K. M.; Luanphaisarnont, T.; Molinaro, C.; Jamison, T. F., Alkene-Directed, Nickel-Catalyzed Alkyne Coupling Reactions. *Journal of the American Chemical Society* **2004**, *126* (13), 4130-4131.
7. Brooks, J. L.; Huang, Y.-W.; Frontier*, A. J., Preparation of 5-Hydroxycyclopentenones Via Conjugate Addition-Initiated Nazarov Cyclization. *Organic Syntheses* **2014**, 93-105.
8. Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L., Copper-catalyzed asymmetric addition of olefin-derived nucleophiles to ketones. *Science* **2016**, *353* (6295), 144.
9. Rotsides, C. Z.; Hu, C.; Woerpel, K. A., Diastereoselective Synthesis of Eight-Membered-Ring Allenes from Propargylic Epoxides and Aldehydes by Silylene Insertion into Carbon–Oxygen Bonds. *Angewandte Chemie International Edition* **2013**, *52* (49), 13033-13036.
10. Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P., Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions. *The Journal of Organic Chemistry* **2011**, *76* (22), 9320-9328.
11. Xie, L.-G.; Shaaban, S.; Chen, X.; Maulide, N., Metal-Free Synthesis of Highly Substituted Pyridines by Formal [2+2+2] Cycloaddition under Mild Conditions. *Angewandte Chemie International Edition* **2016**, *55* (41), 12864-12867.
12. Ito, K.; Nakanishi, S.; Otsuji, Y., 1-Trimethylsiloxyallylic Iron Complexes as a β -Acylcarbanion Equivalent. *Chemistry Letters* **1987**, *16* (10), 2103-2106.
13. Honzawa, S.; Uchida, M.; Tashiro, T.; Sugihara, T., Alpha-Oxidation of Amine Derivatives by bis(2,2,2-Trichloroethyl) Azodicarboxylate and Application of Its Products as Iminium Ion Equivalents. *Heterocycles* **2017**, *95* (2), 994-1029.
14. Pünner, F.; Hilt, G., Regioselective solvent-dependent benzannulation of conjugated enynes. *Chemical Communications* **2012**, *48* (30), 3617-3619.

15. Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruett, S. T.; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, G. P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C., Discovery of a Fluorinated Enigmol Analog with Enhanced in Vivo Pharmacokinetic and Anti-Tumor Properties. *ACS Medicinal Chemistry Letters* **2016**, 7 (5), 537-542.
16. Tlili, N.; Elfalleh, W.; Saadaoui, E.; Khaldi, A.; Triki, S.; Nasri, N., The caper (*Capparis L.*): Ethnopharmacology, phytochemical and pharmacological properties. *Fitoterapia* **2011**, 82 (2), 93-101.

Supporting Information.pdf (597.99 KiB)

[view on ChemRxiv](#) • [download file](#)

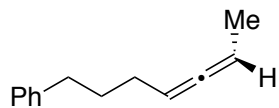
Compiled NMR Spectra

**Copper Hydride-Catalyzed Enantioselective Synthesis of Axially
Chiral 1,3-Disubstituted Allenes**

Liela Bayeh-Romero and Stephen L. Buchwald*

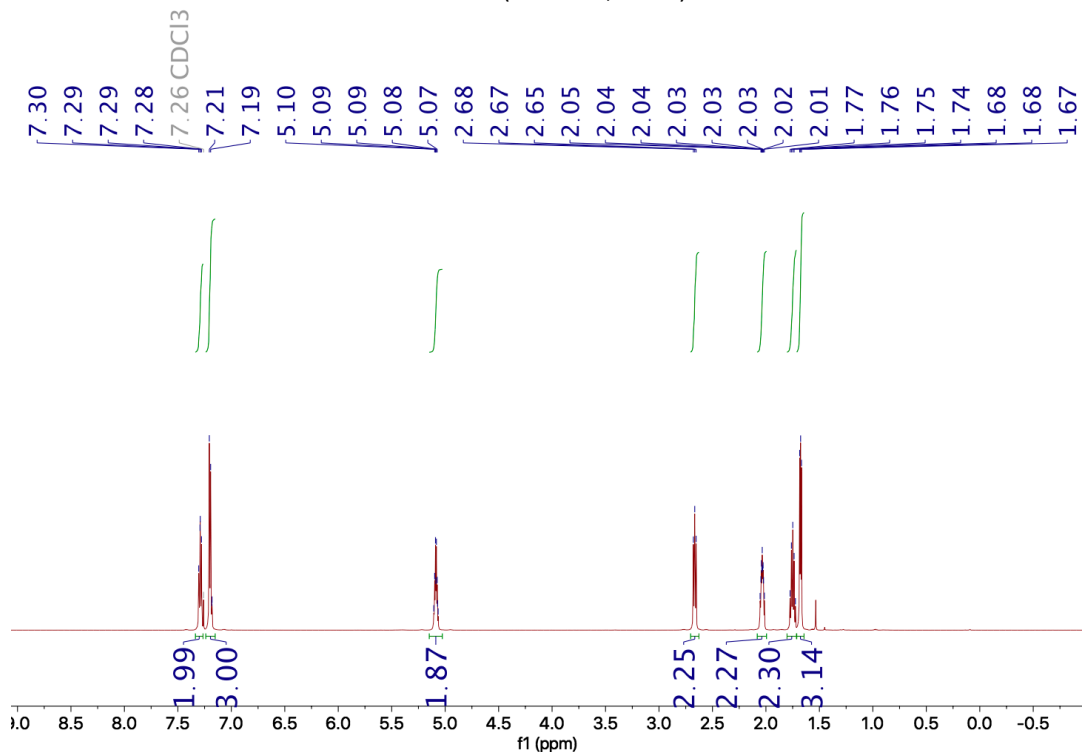
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts
02139, United States

*Correspondence to: sbuchwal@mit.edu

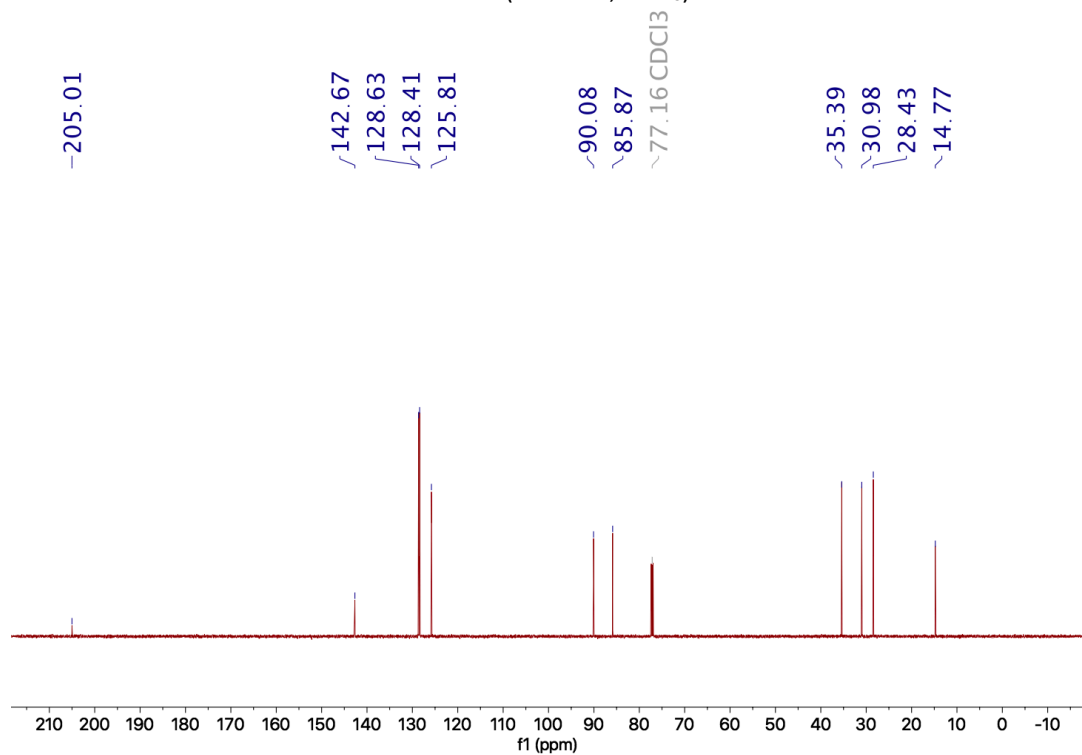


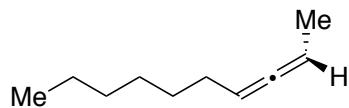
4a

^1H NMR (500 MHz, CDCl_3)



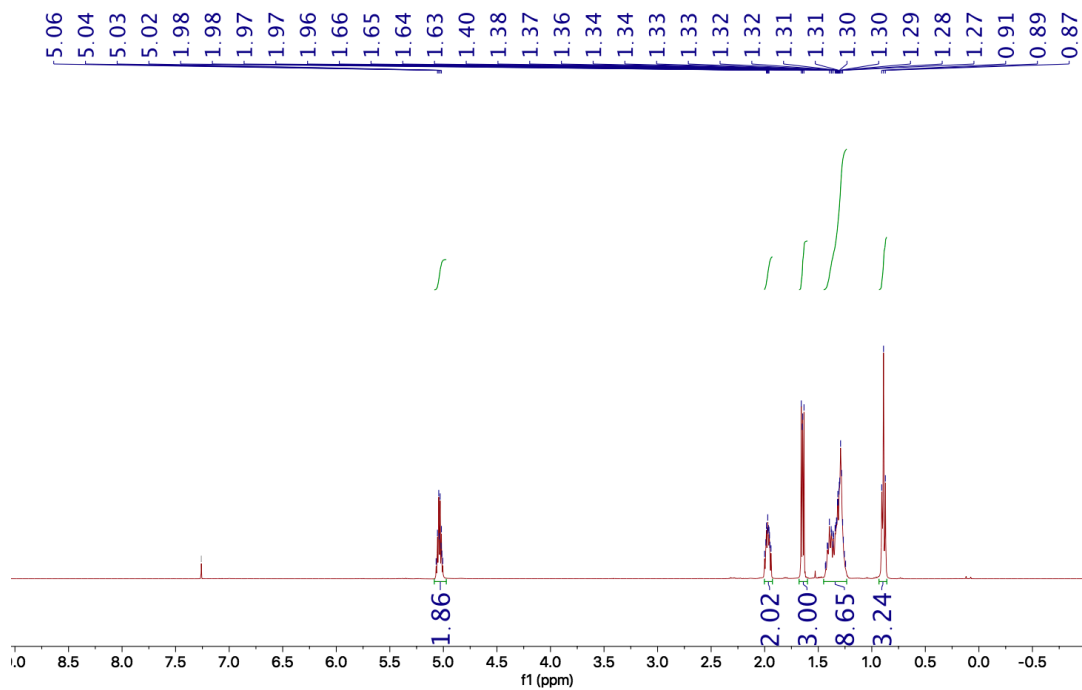
^{13}C NMR (151 MHz, CDCl_3)



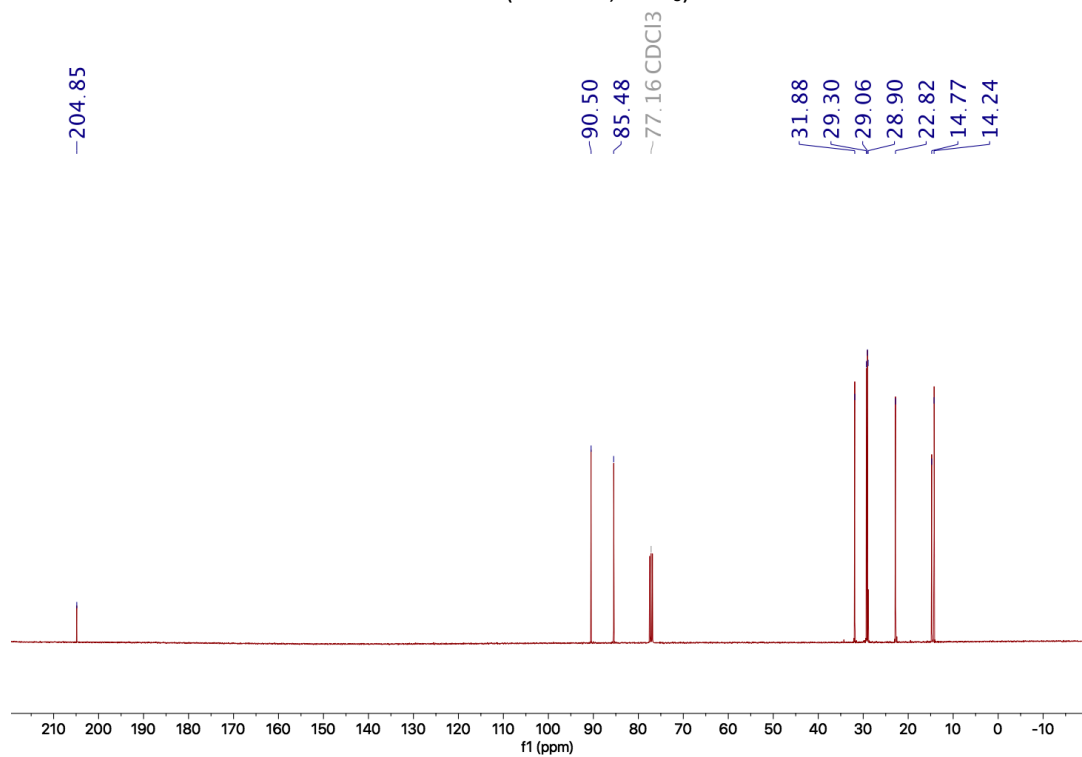


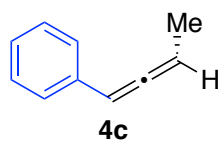
4b

^1H NMR (400 MHz, CDCl_3)

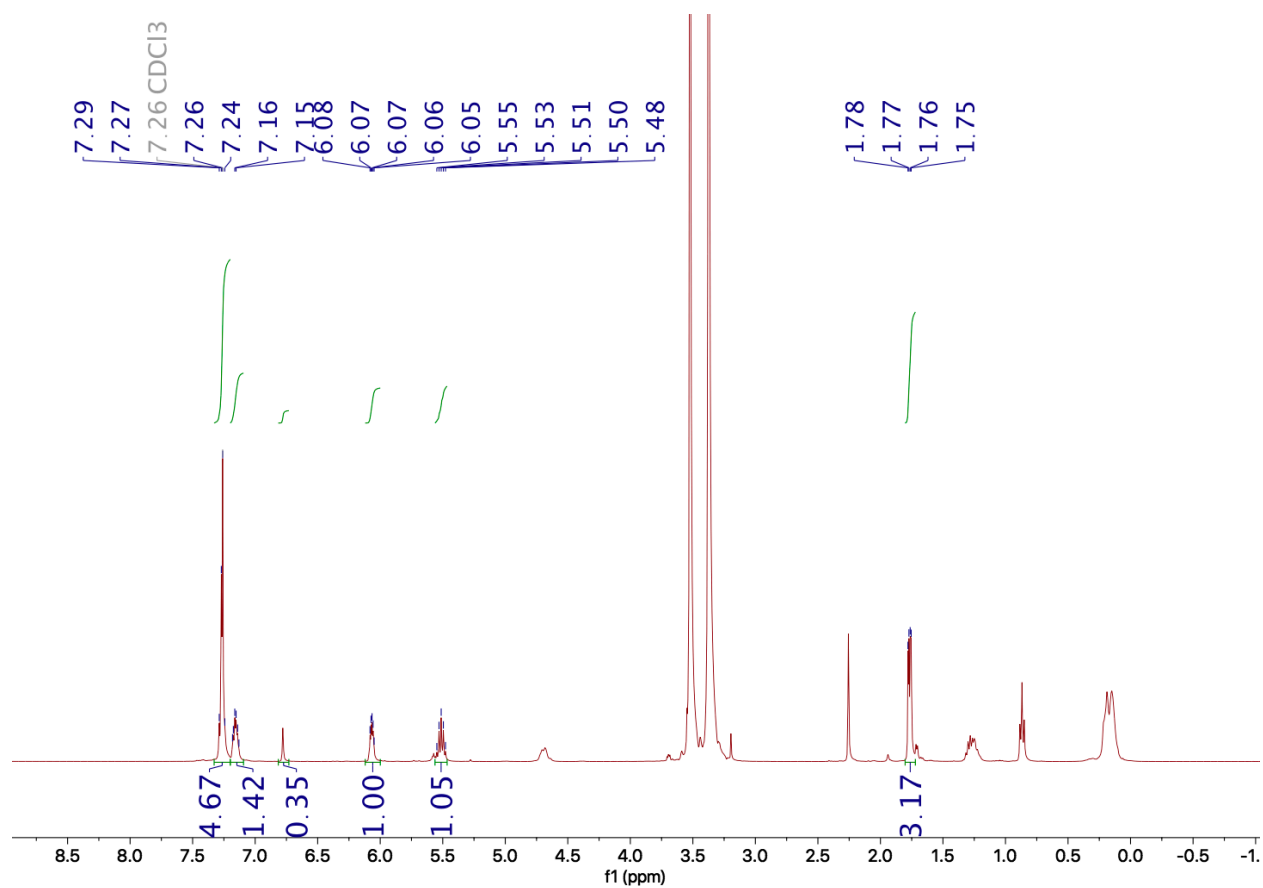


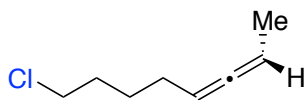
^{13}C NMR (101 MHz, CDCl_3)





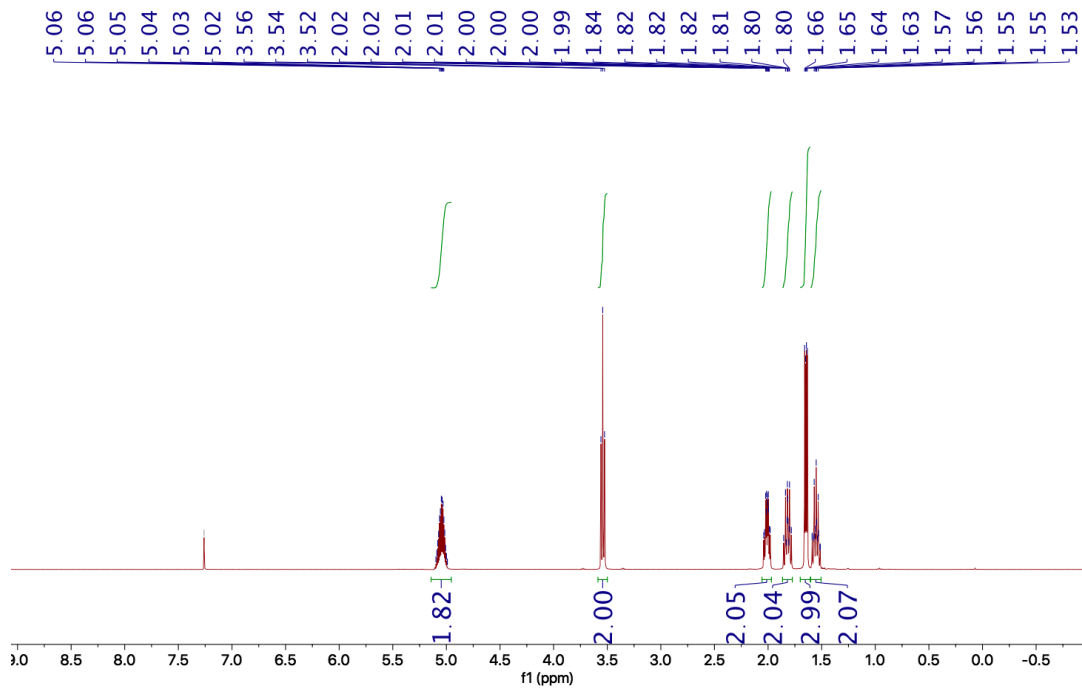
^1H NMR (400 MHz, CDCl_3) of crude reaction mixture containing 0.10 mmol mesitylene internal standard



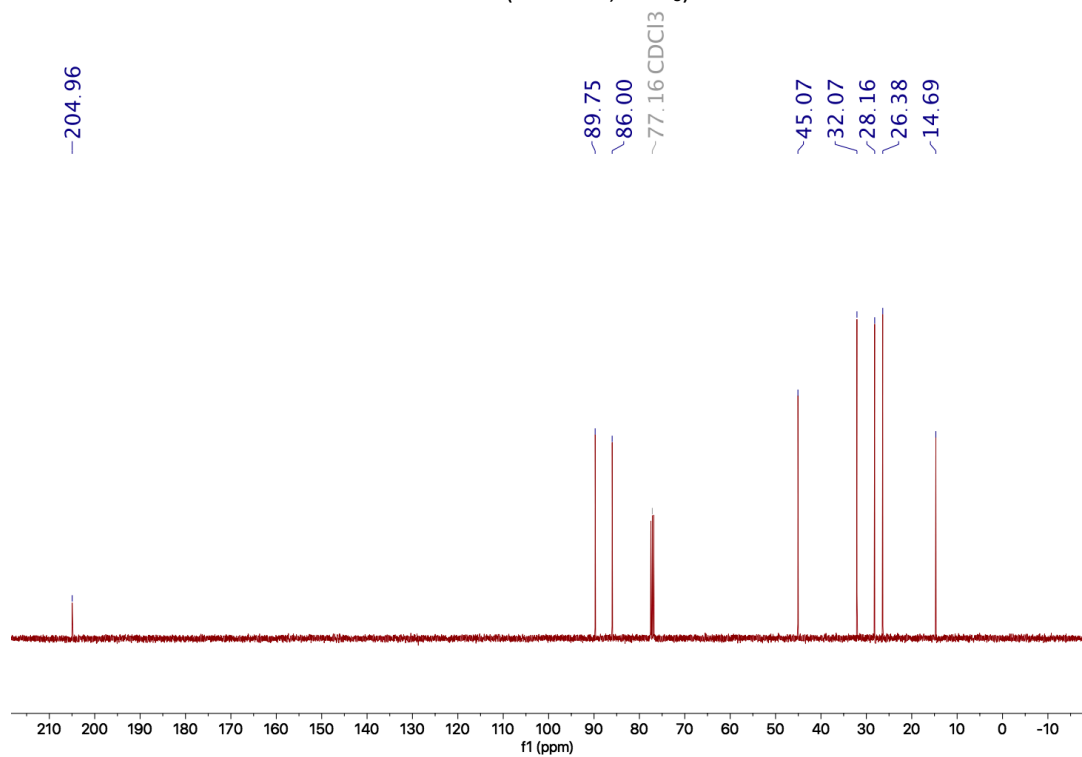


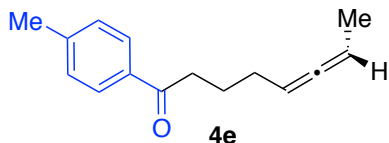
4d

¹H NMR (400 MHz, CDCl₃)

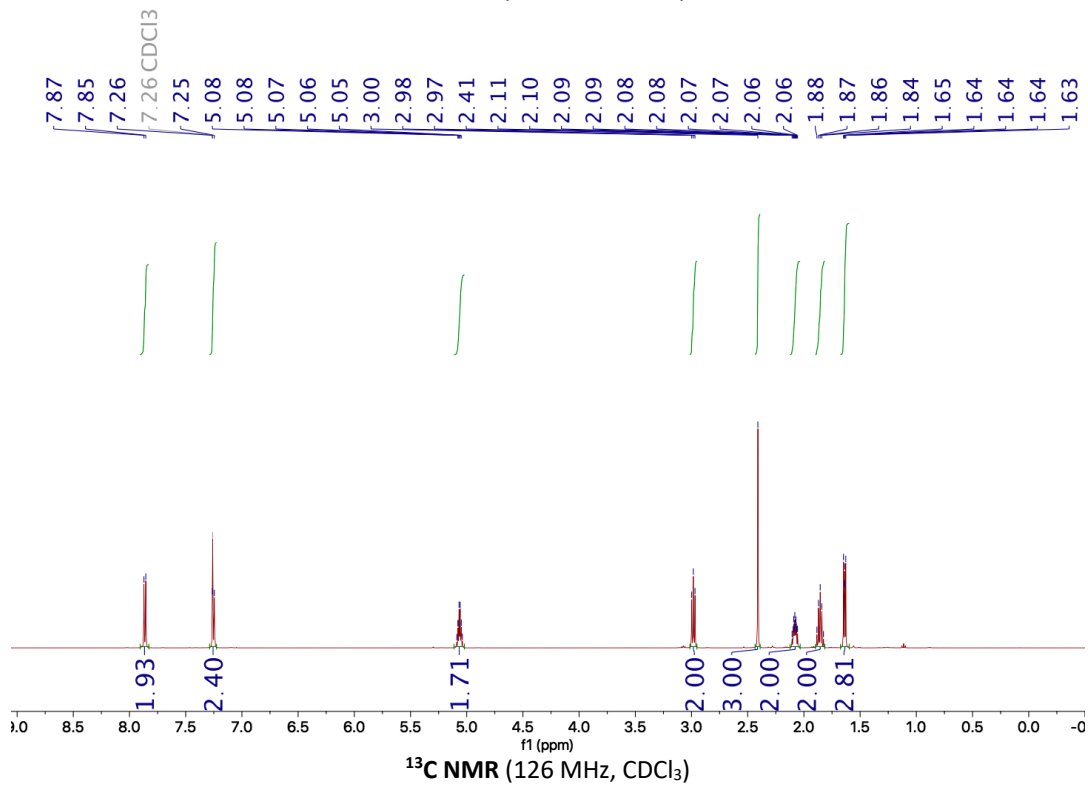


¹³C NMR (101 MHz, CDCl₃)

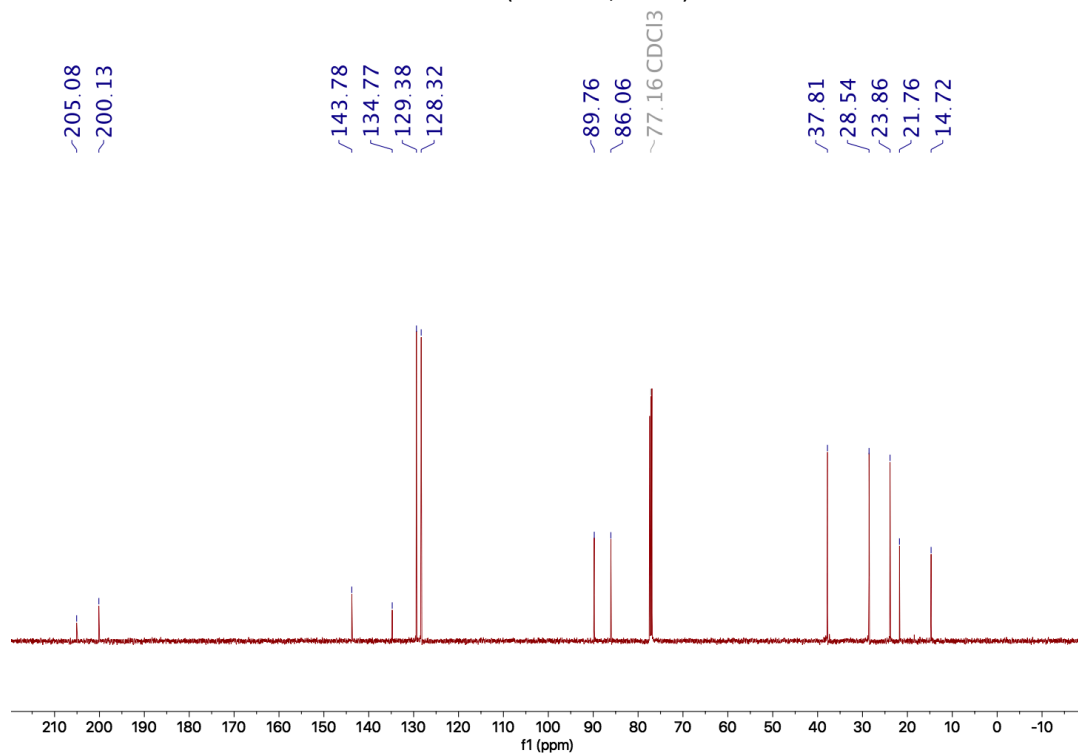


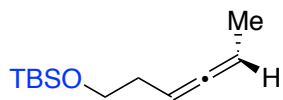


^1H NMR (500 MHz, CDCl_3)



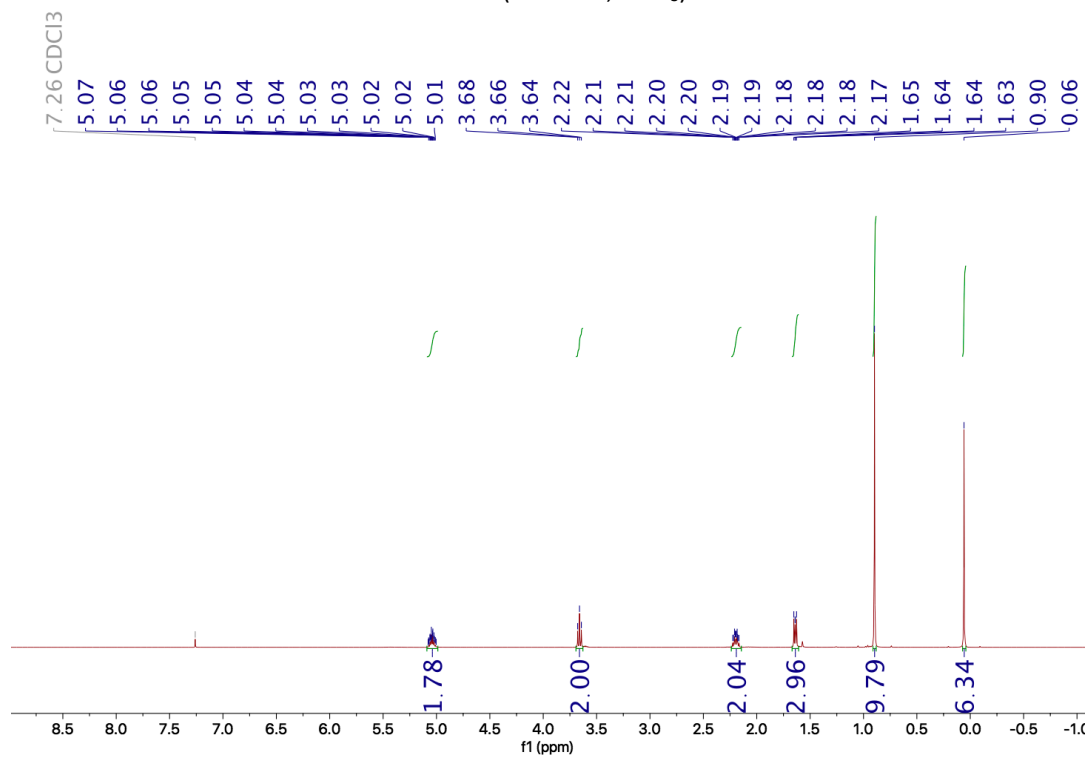
^{13}C NMR (126 MHz, CDCl_3)



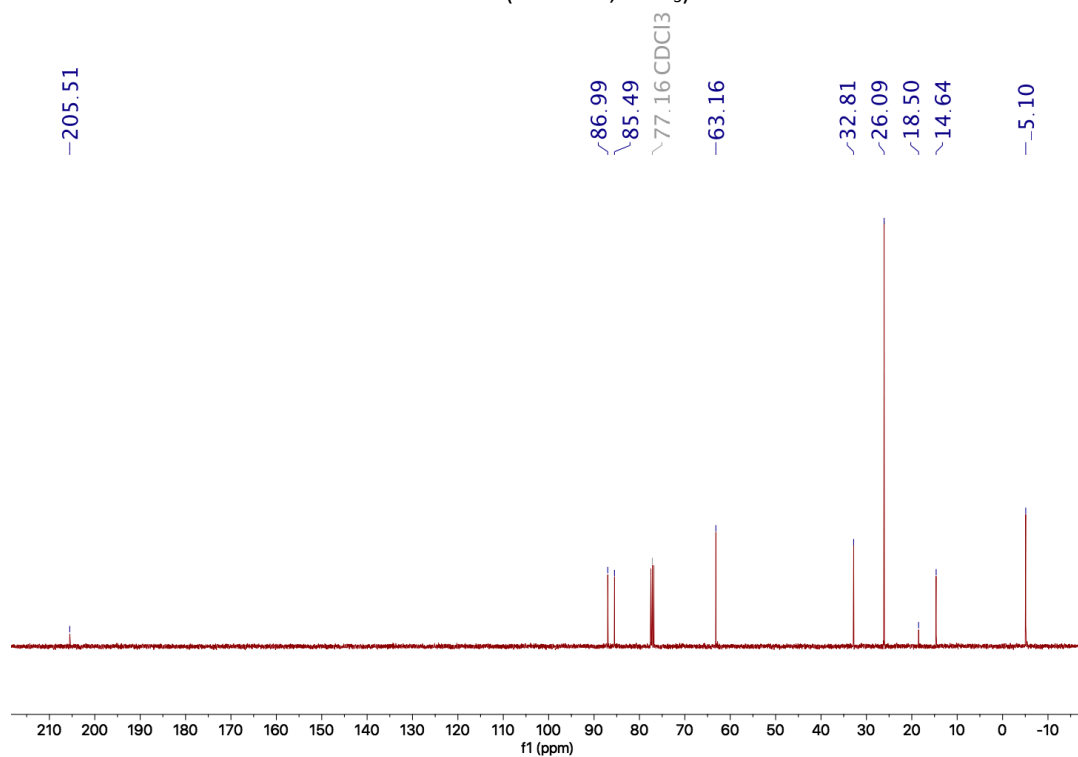


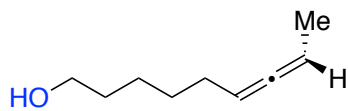
4f

^1H NMR (400 MHz, CDCl_3)



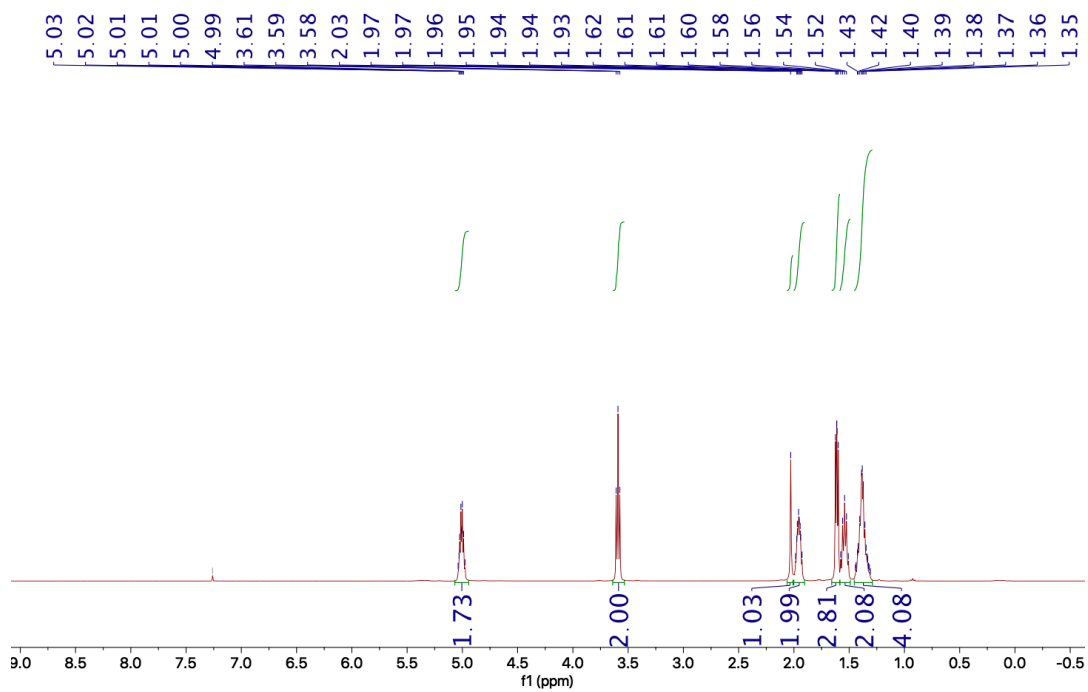
^{13}C NMR (101 MHz, CDCl_3)



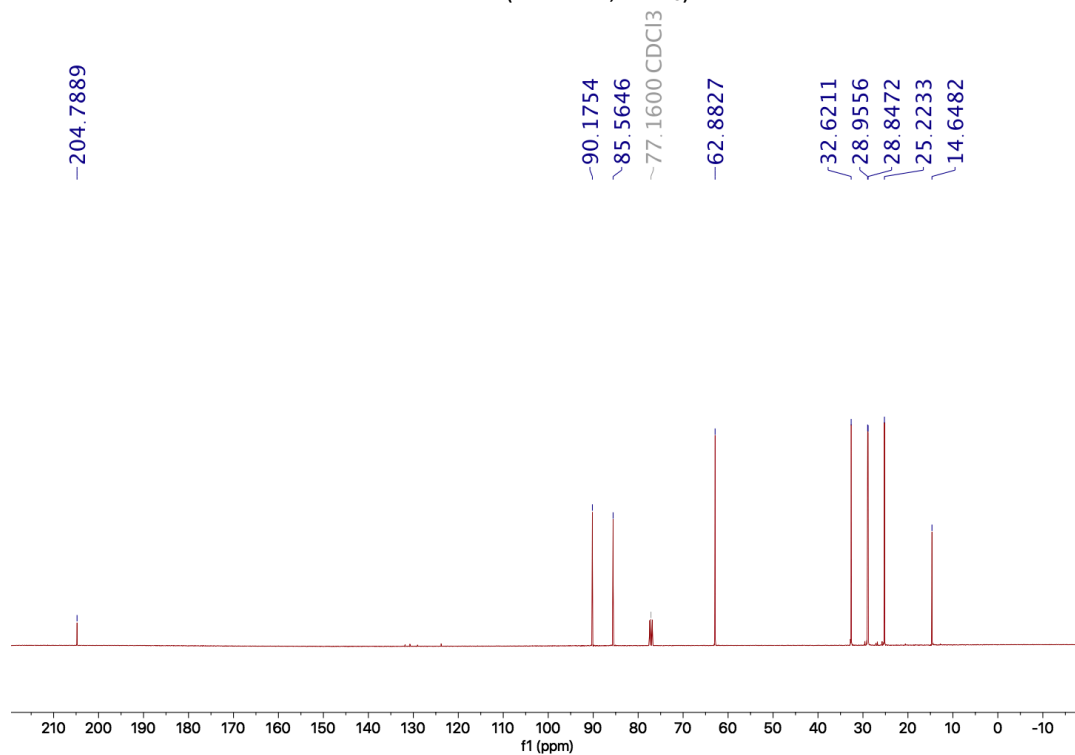


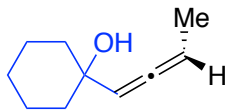
4g

¹H NMR (400 MHz, CDCl₃)



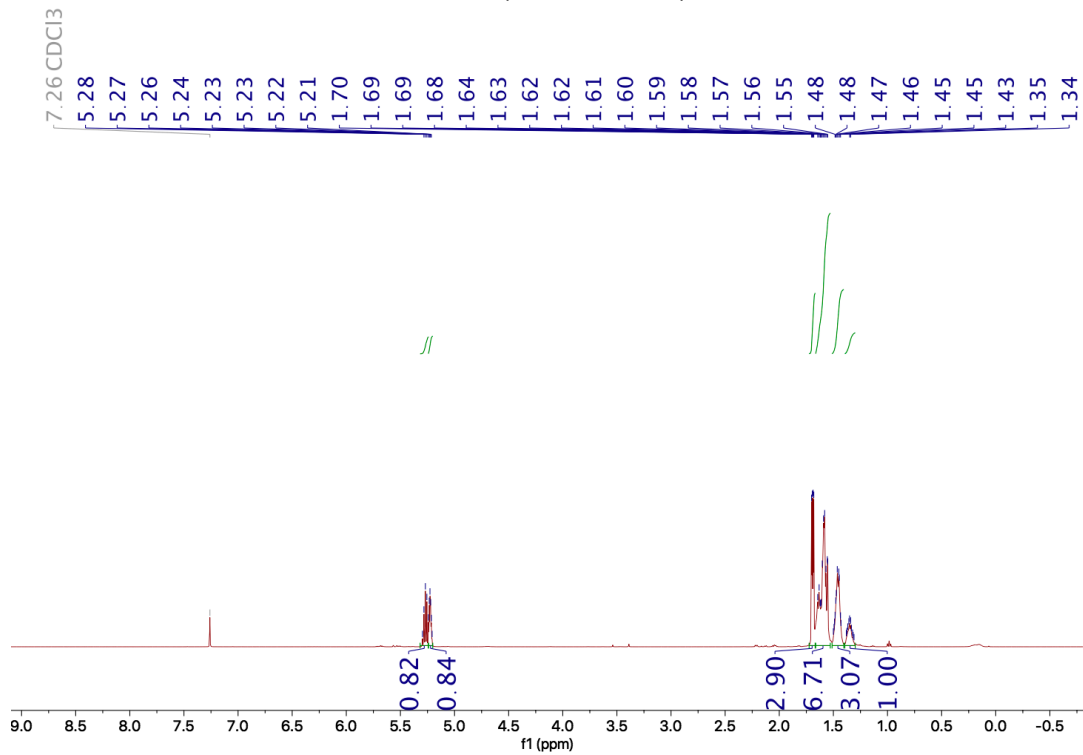
¹³C NMR (101 MHz, CDCl₃)



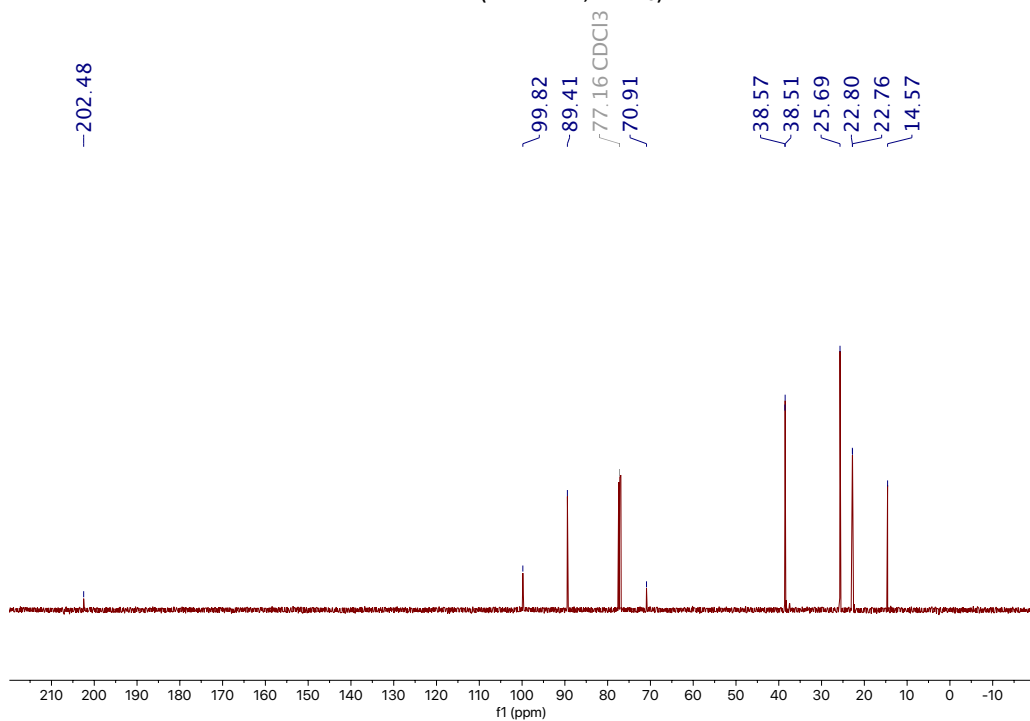


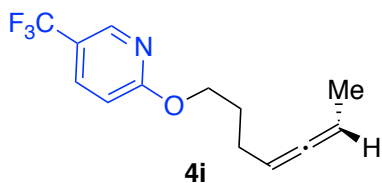
4h

^1H NMR (500 MHz, CDCl_3)



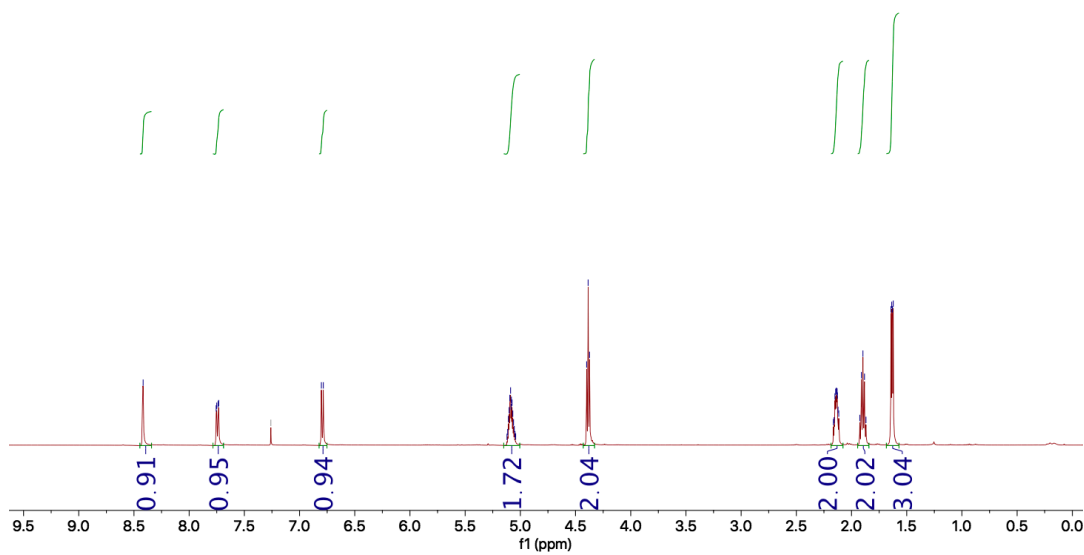
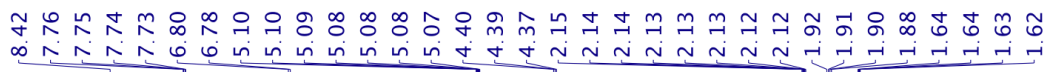
^{13}C NMR (126 MHz, CDCl_3)



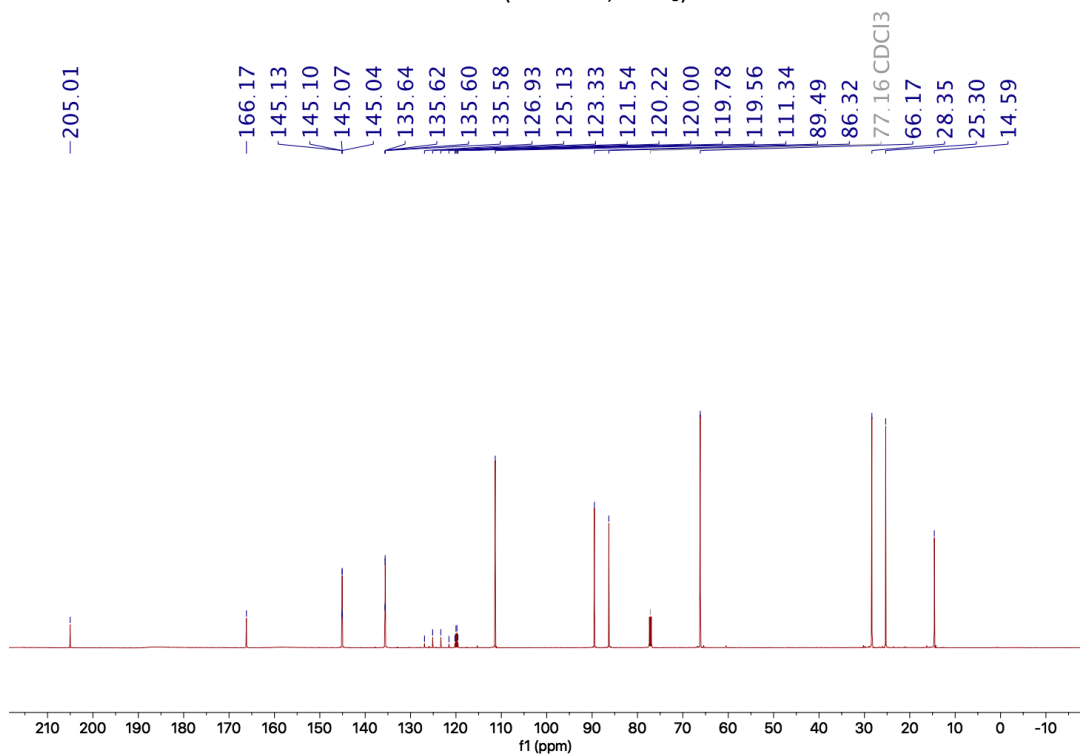


4i

^1H NMR (500 MHz, CDCl_3)

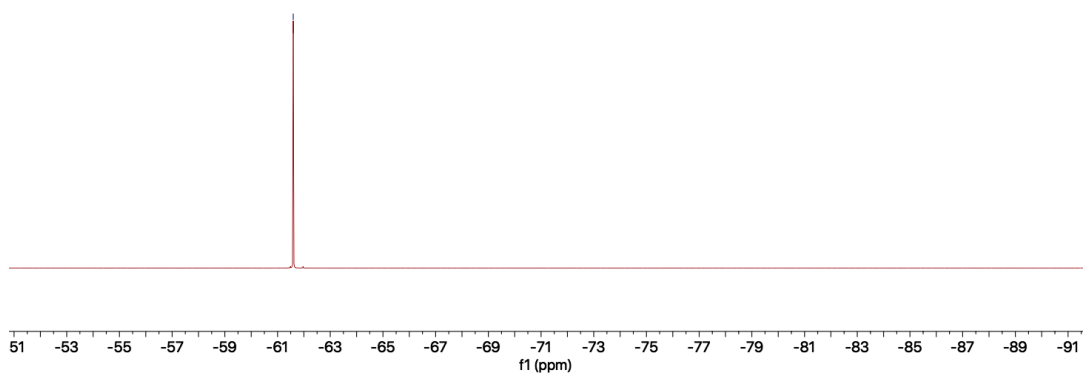


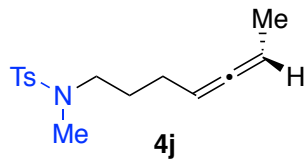
^{13}C NMR (151 MHz, CDCl_3)



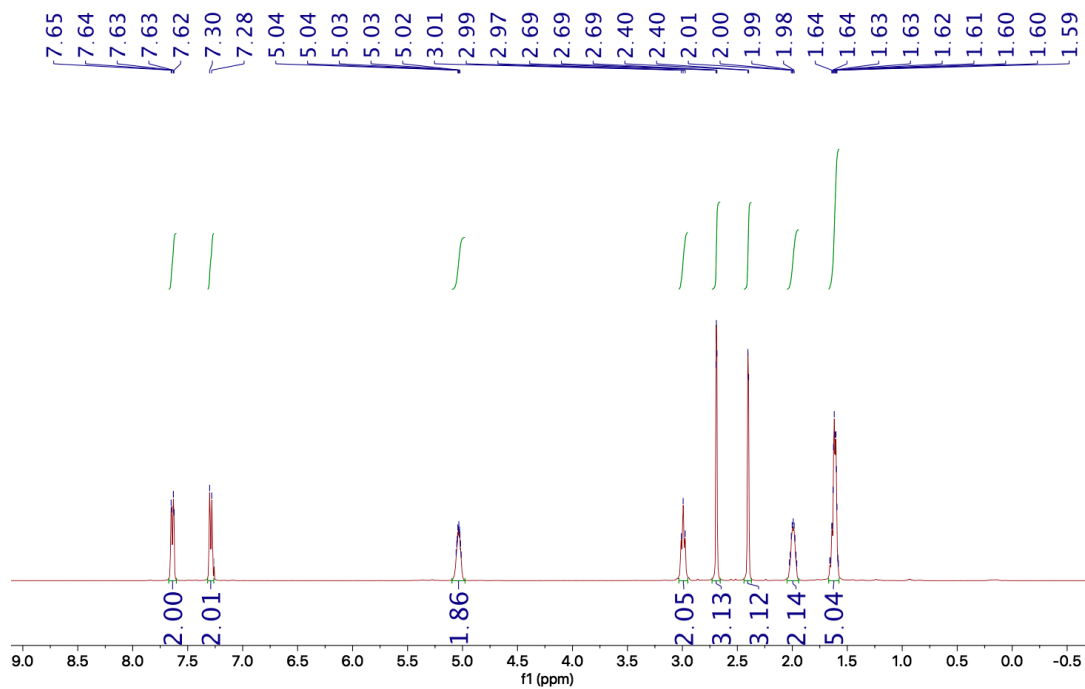
^{19}F NMR (565 MHz, CDCl_3)

-61.5957

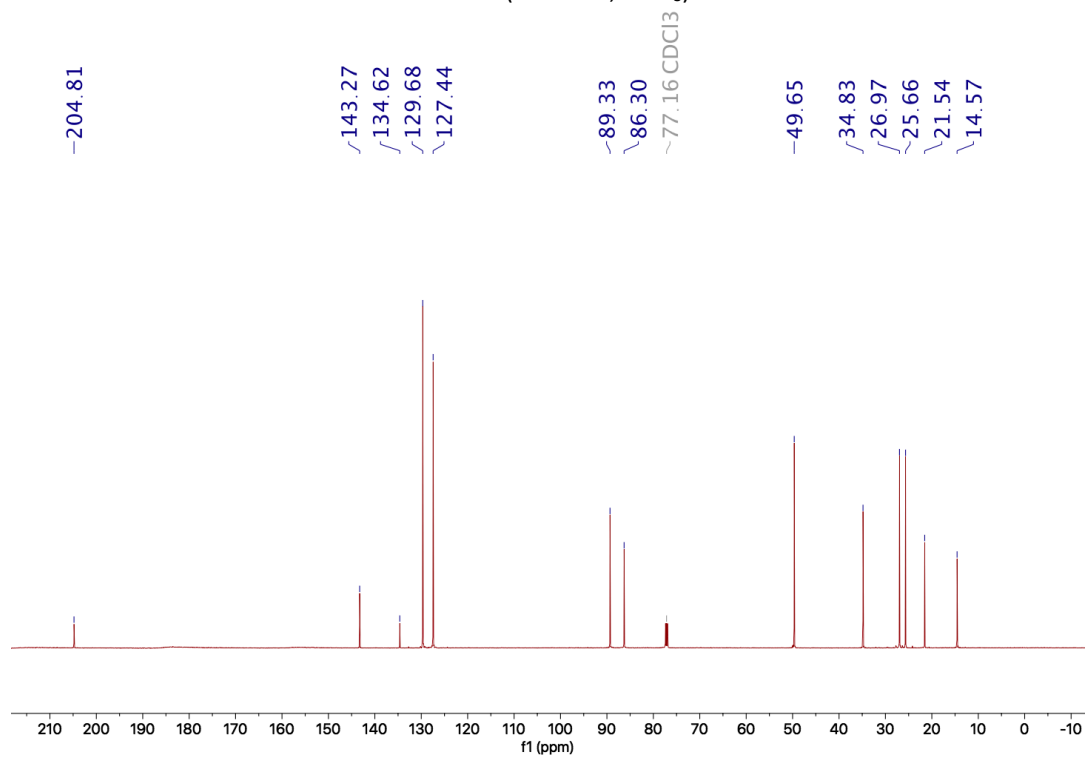


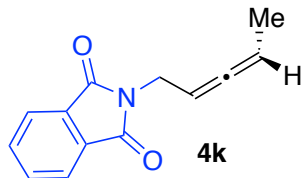


¹H NMR (400 MHz, CDCl₃)

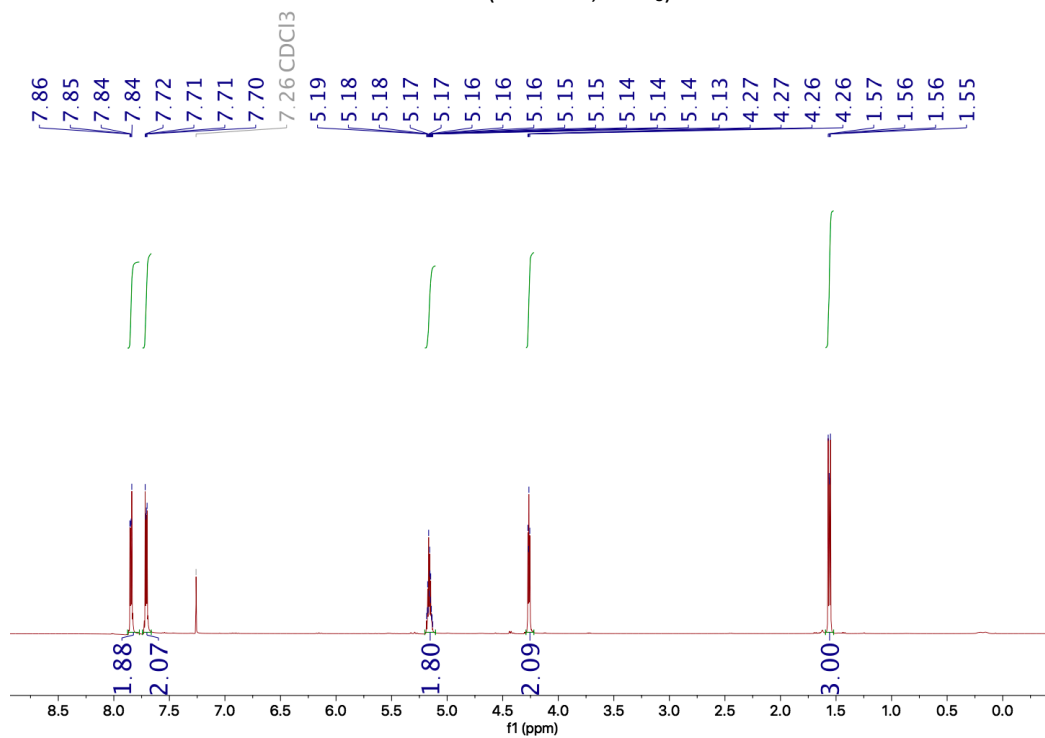


¹³C NMR (151 MHz, CDCl₃)

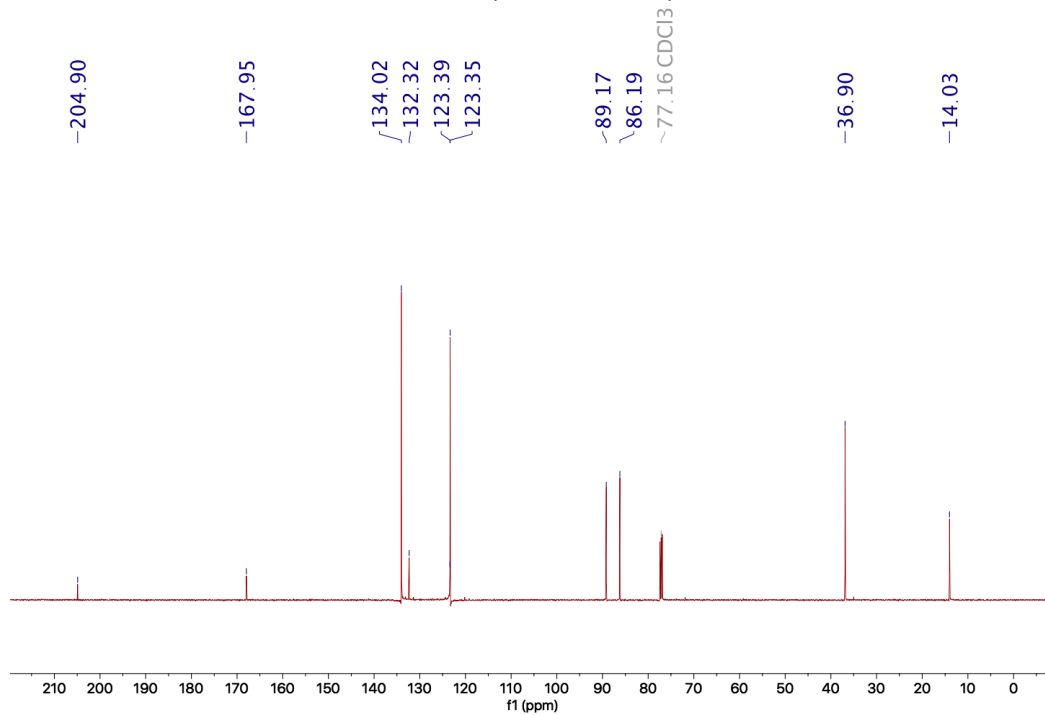


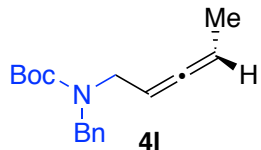


^1H NMR (500 MHz, CDCl_3)

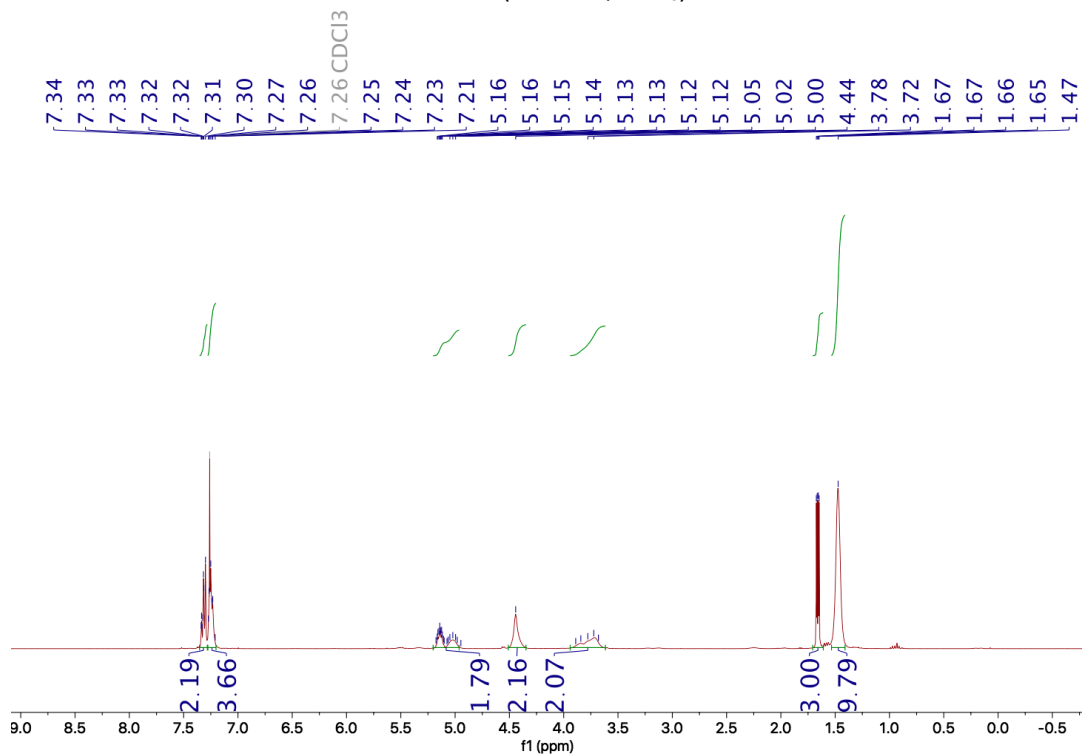


^{13}C NMR (126 MHz, CDCl_3)

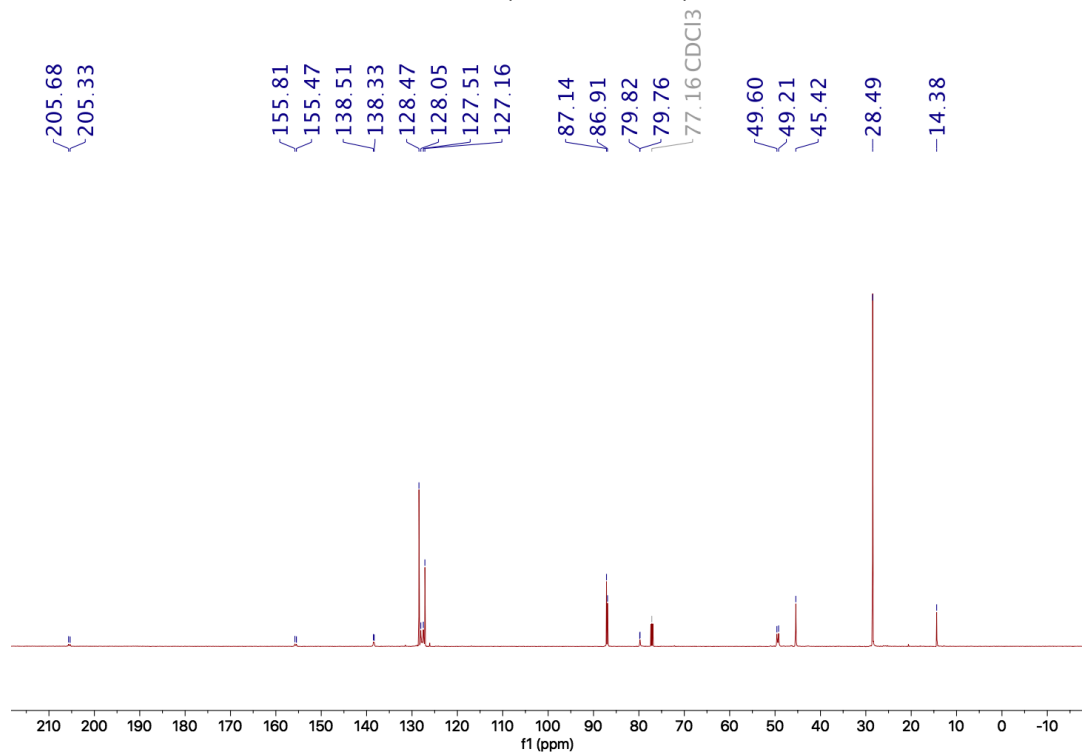


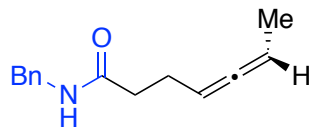


^1H NMR (400 MHz, CDCl_3)



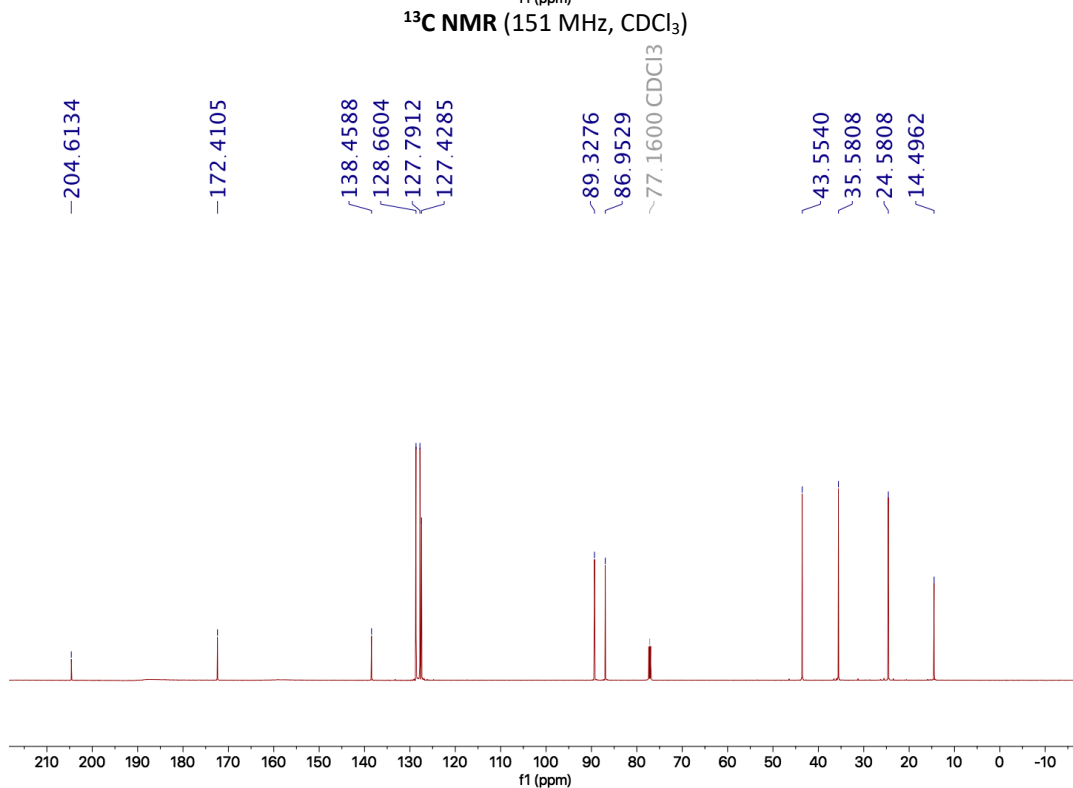
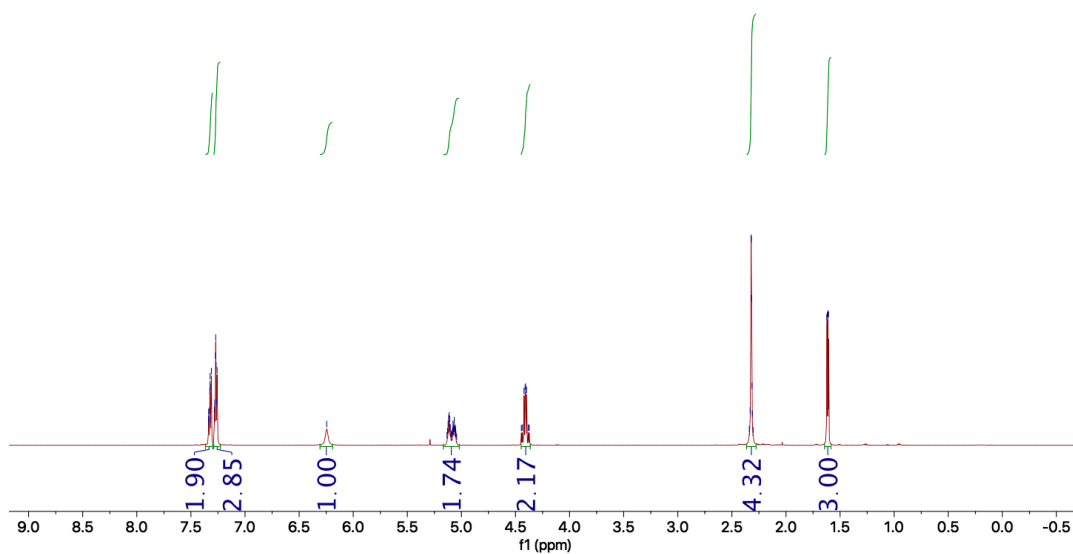
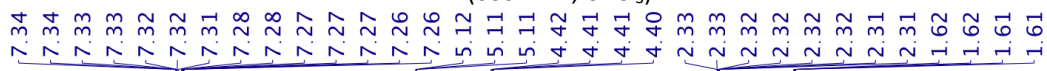
^{13}C NMR (151 MHz, CDCl_3)

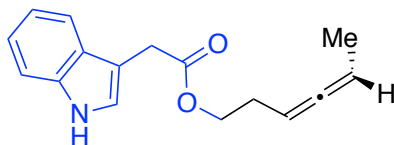




4m

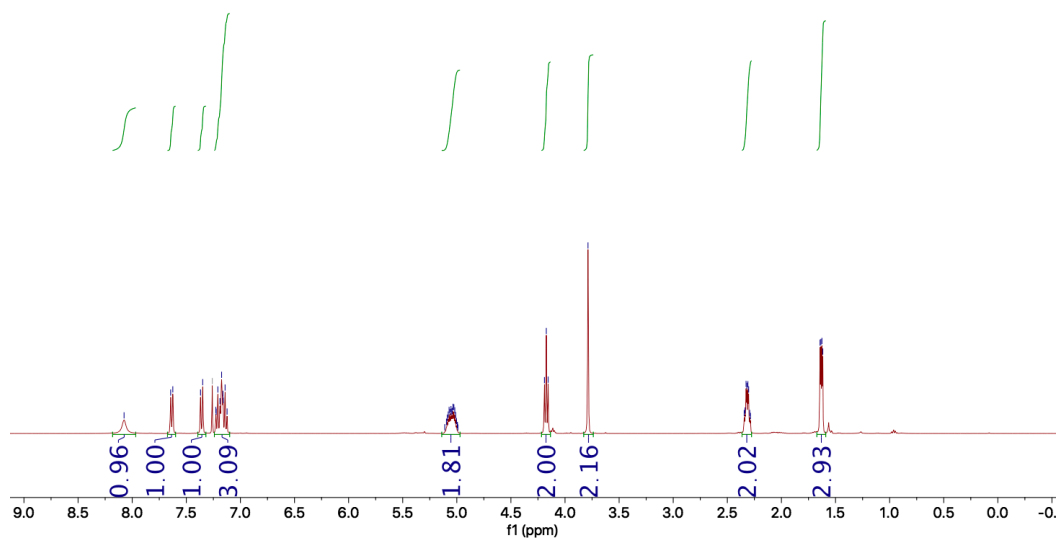
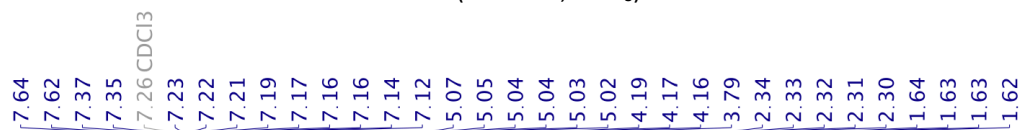
^1H NMR (600 MHz, CDCl_3)



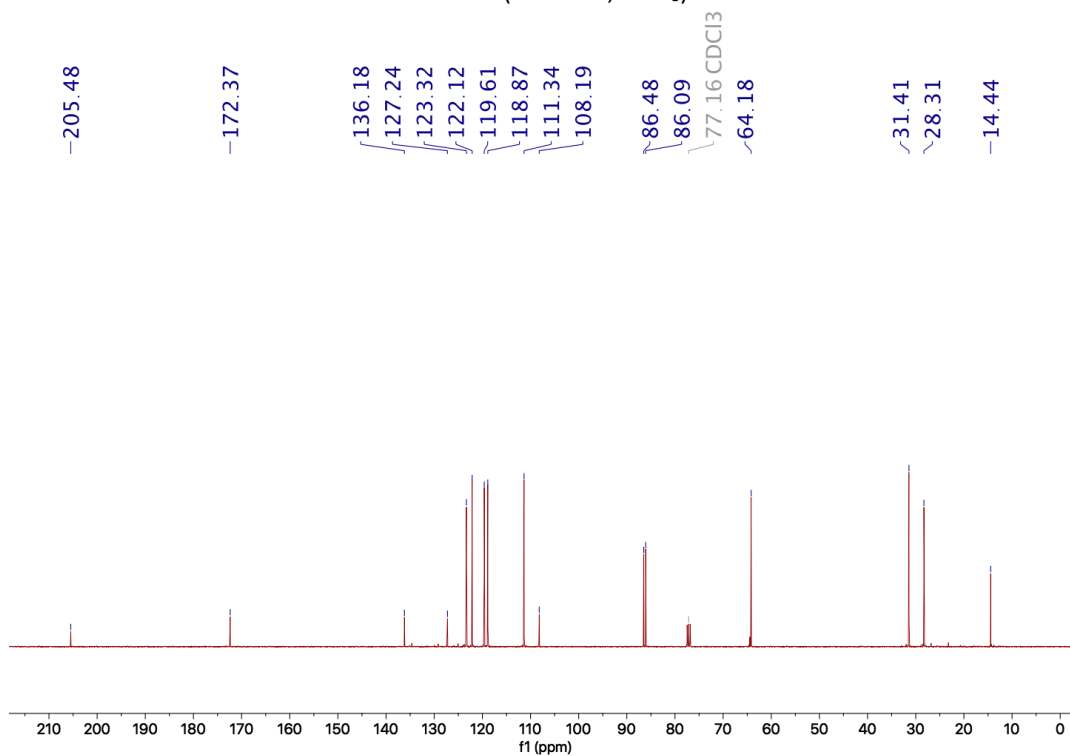


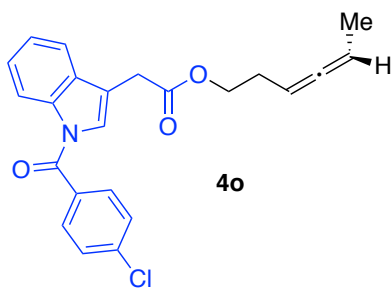
4n

^1H NMR (400 MHz, CDCl_3)

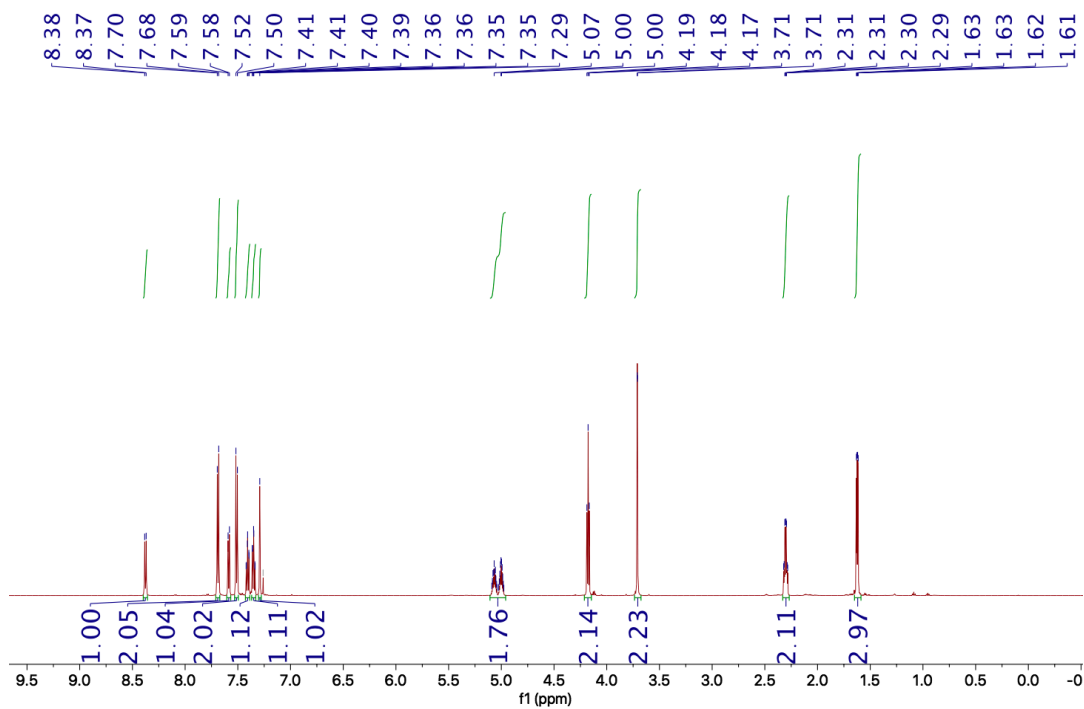


^{13}C NMR (101 MHz, CDCl_3)

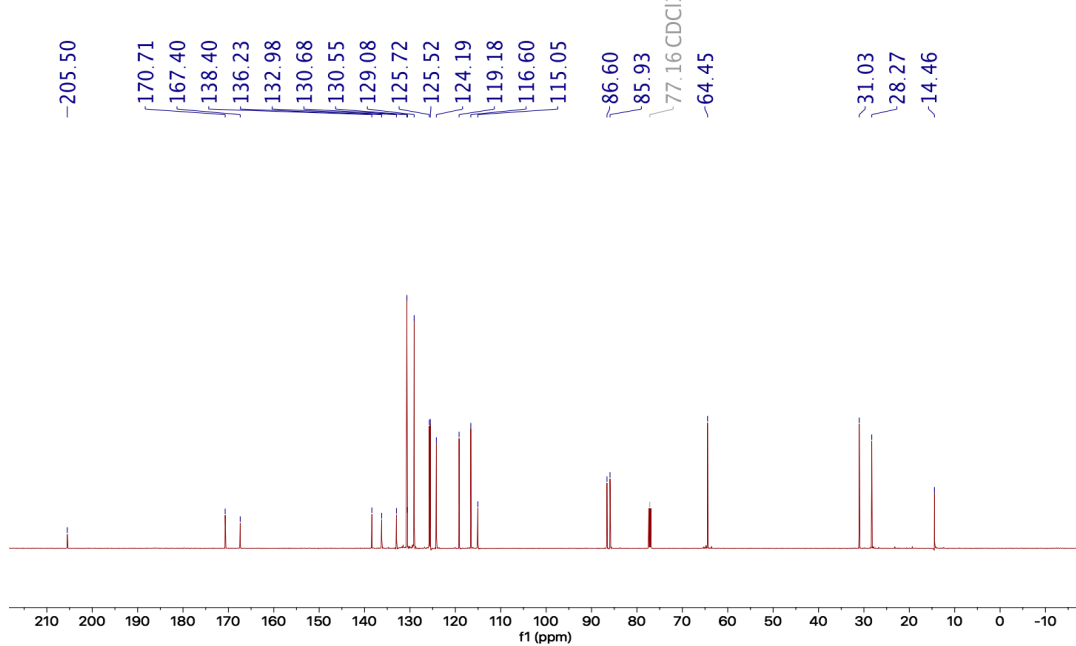


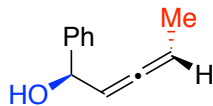


¹H NMR (600 MHz, CDCl₃)



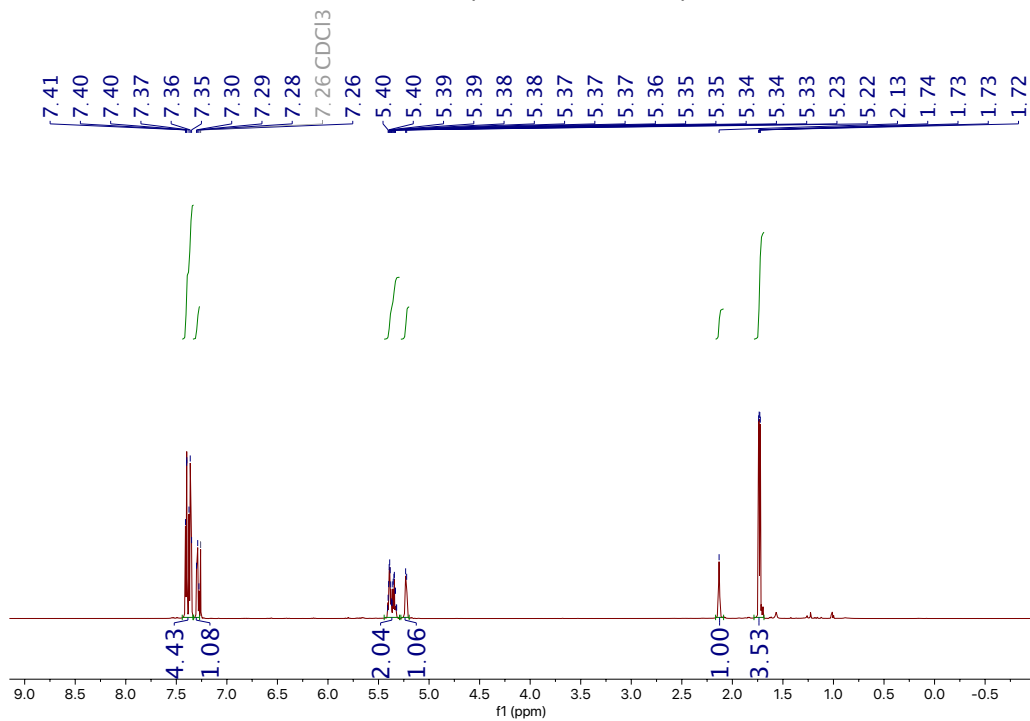
¹³C NMR (151 MHz, CDCl₃)



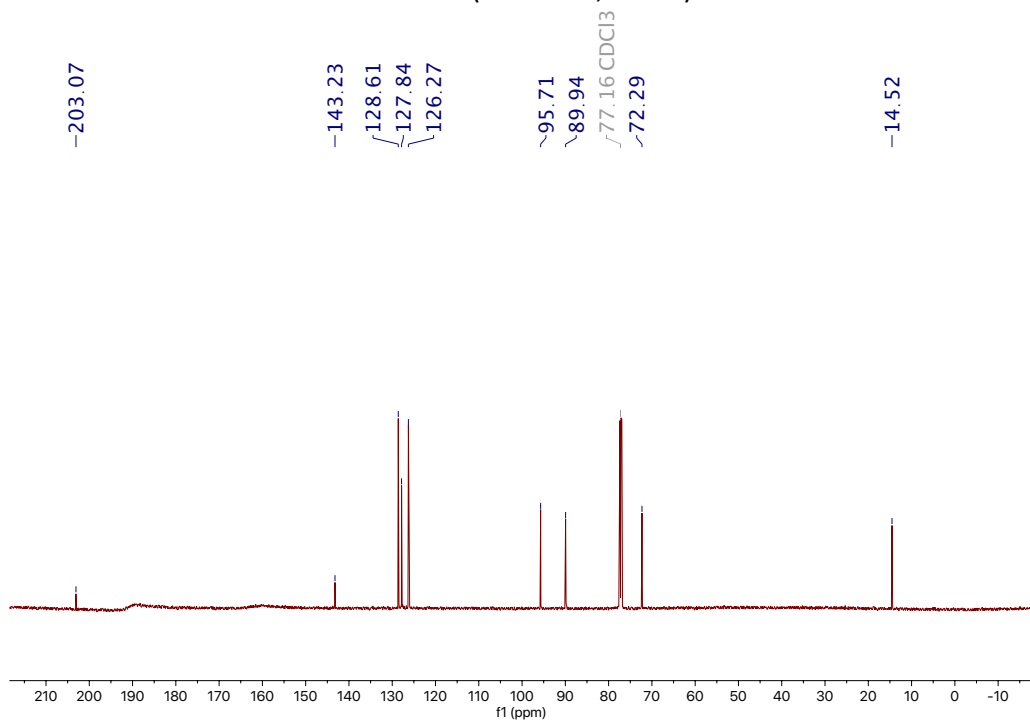


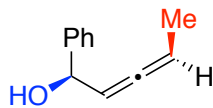
(R,R)-4p

^1H NMR (600 MHz, CDCl_3)



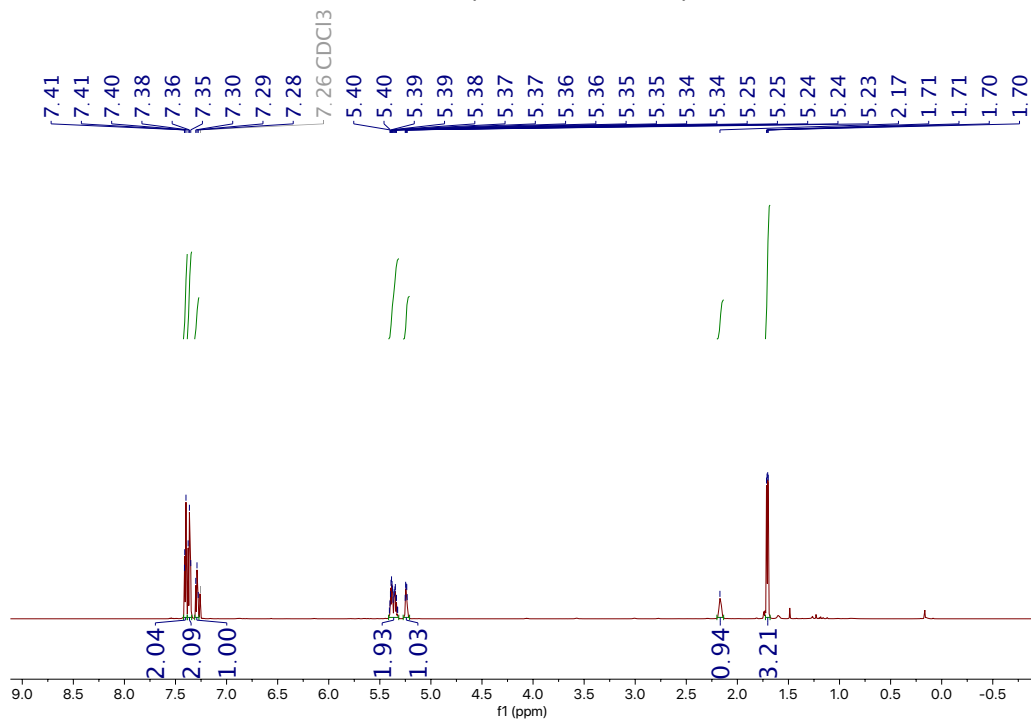
^{13}C NMR (151 MHz, CDCl_3)



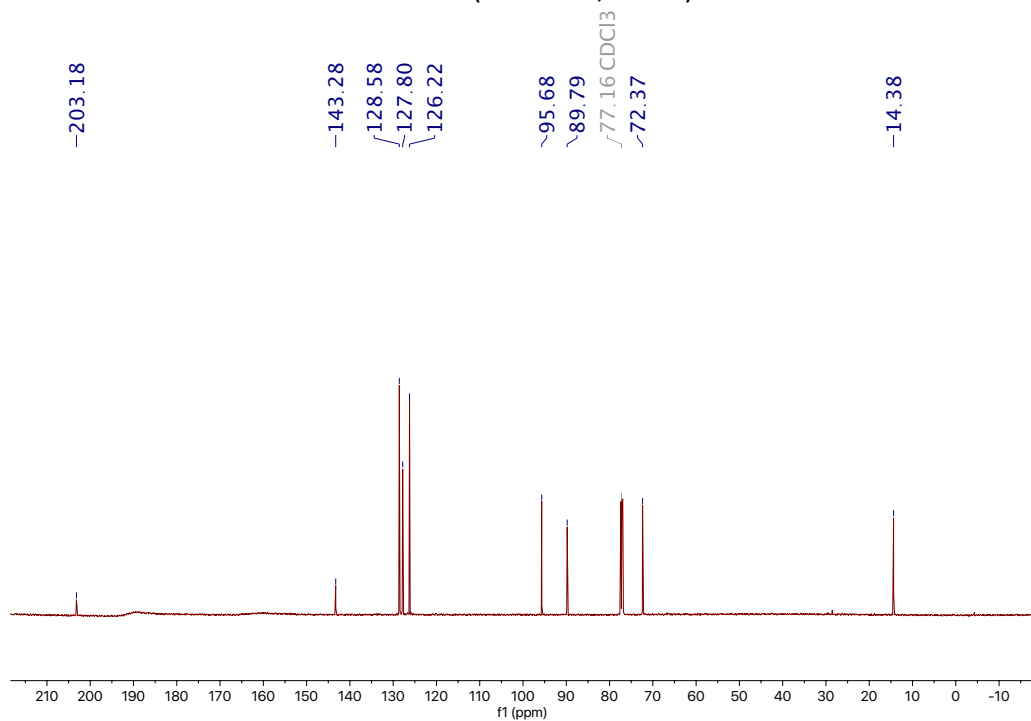


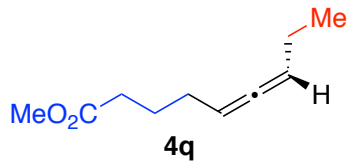
(R,S)-4p

^1H NMR (600 MHz, CDCl_3)

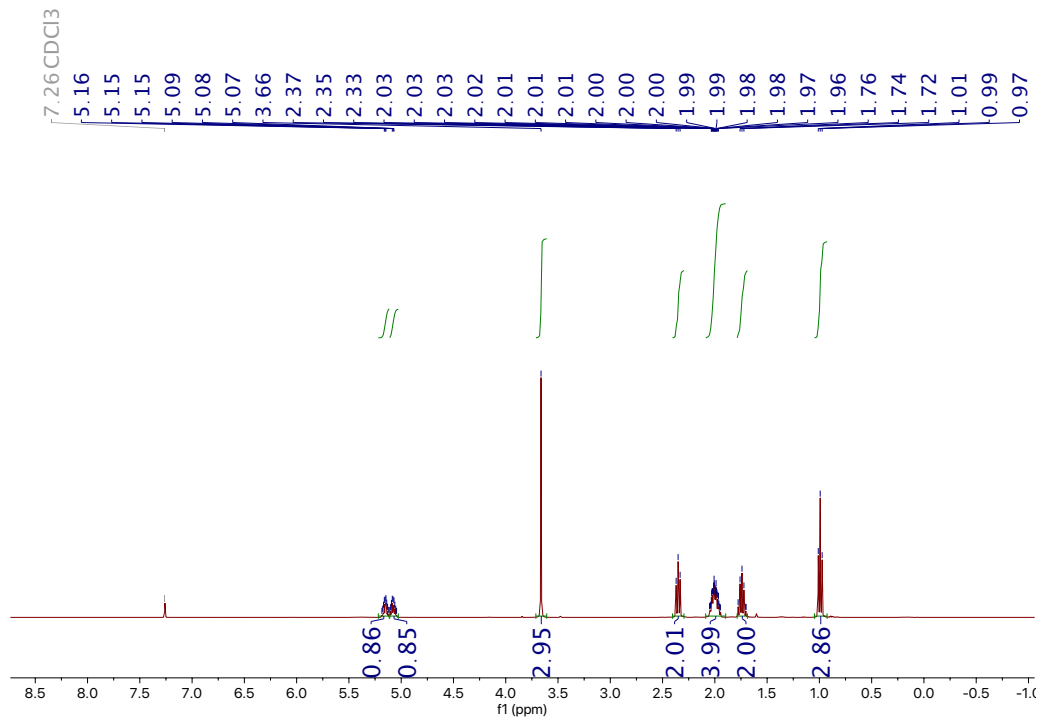


^{13}C NMR (151 MHz, CDCl_3)

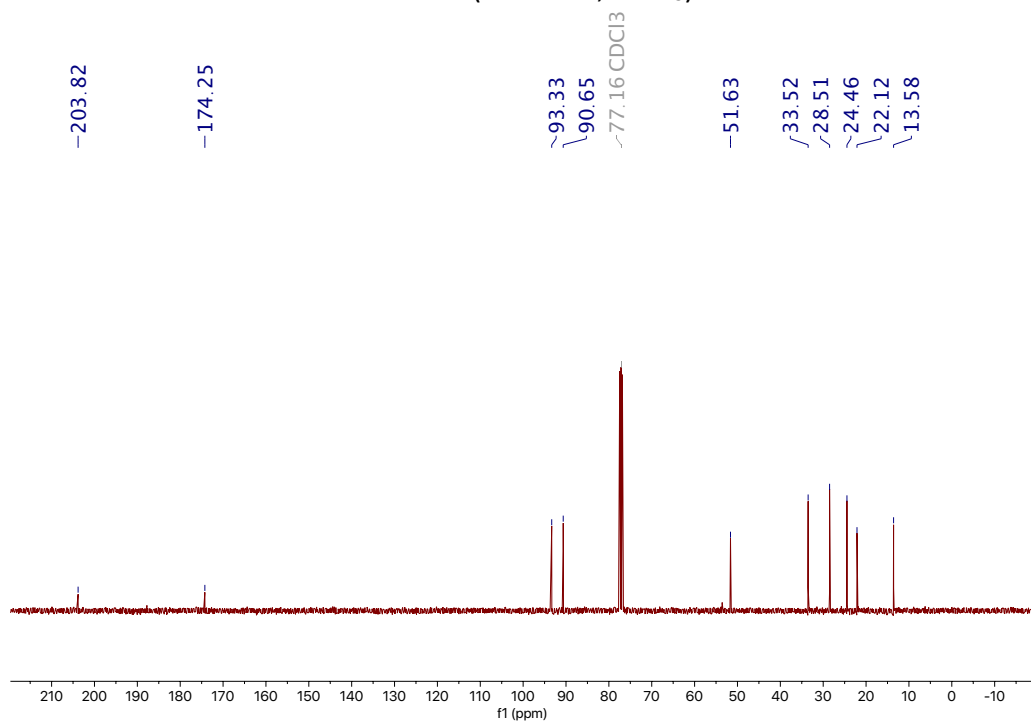


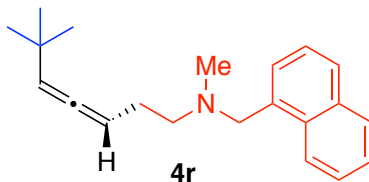


¹H NMR (400 MHz, CDCl₃)

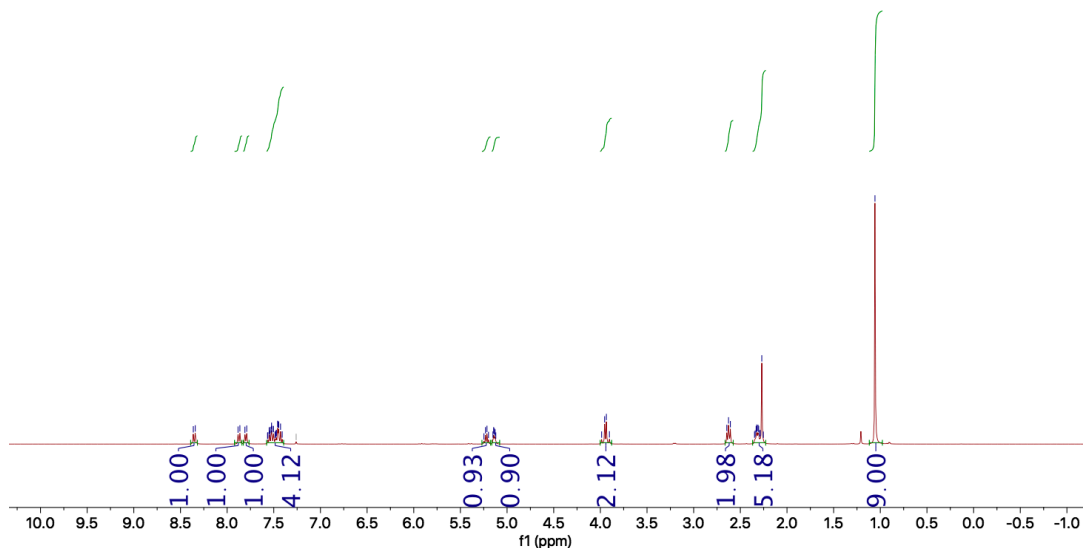


¹³C NMR (101 MHz, CDCl₃)

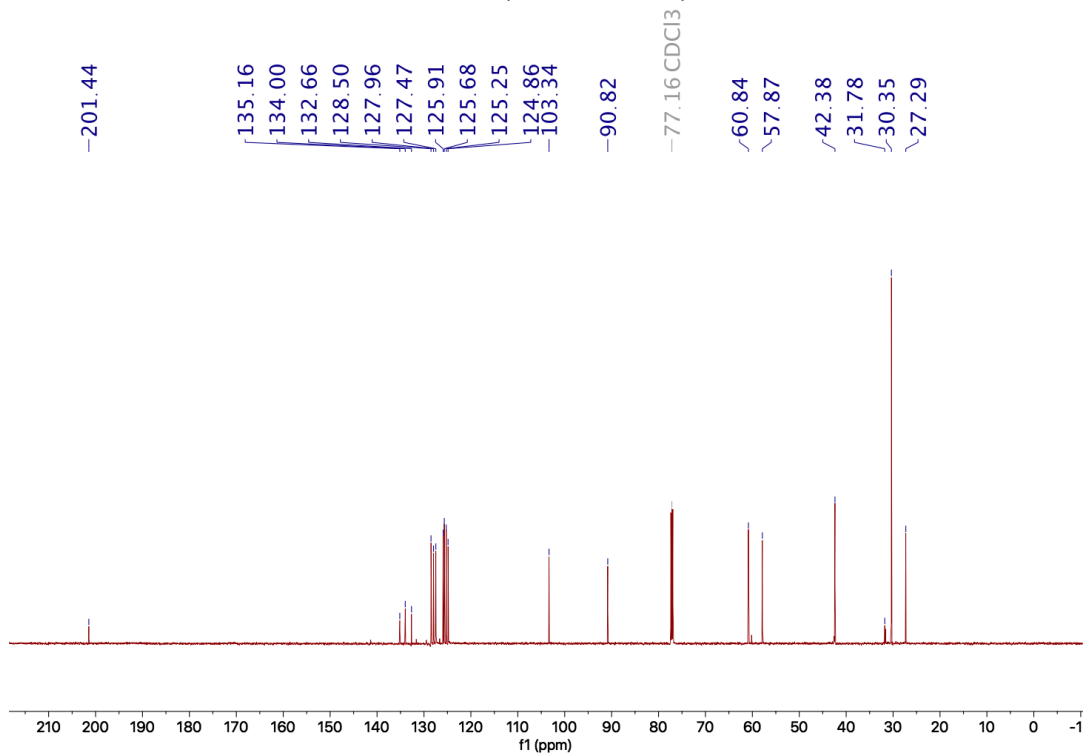


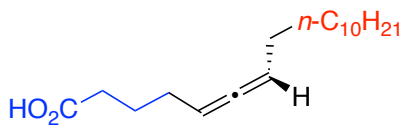


¹H NMR (400 MHz, CDCl₃)



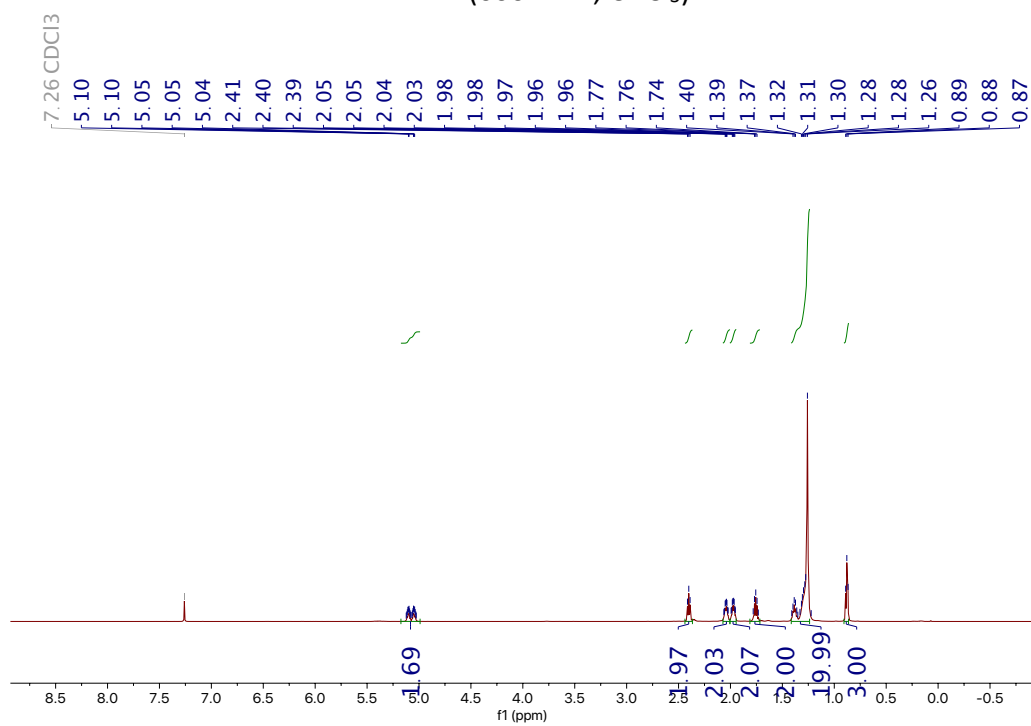
¹³C NMR (151 MHz, CDCl₃)



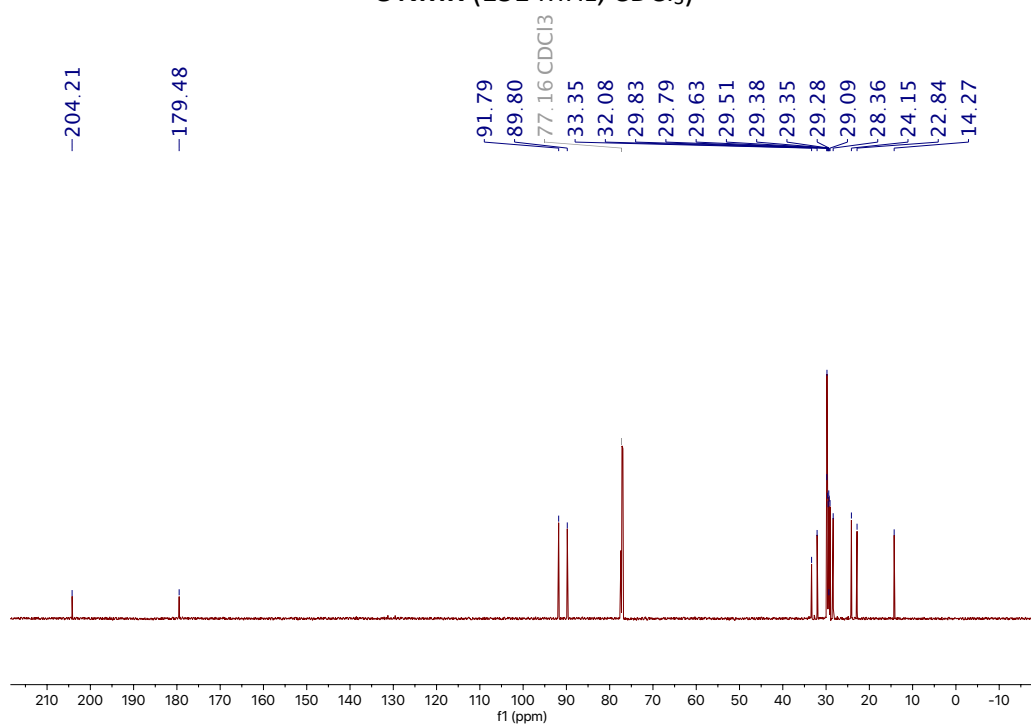


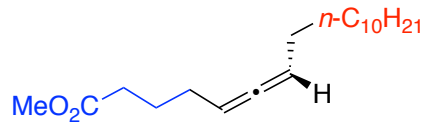
Laballenic acid (4s)

^1H NMR (600 MHz, CDCl_3)



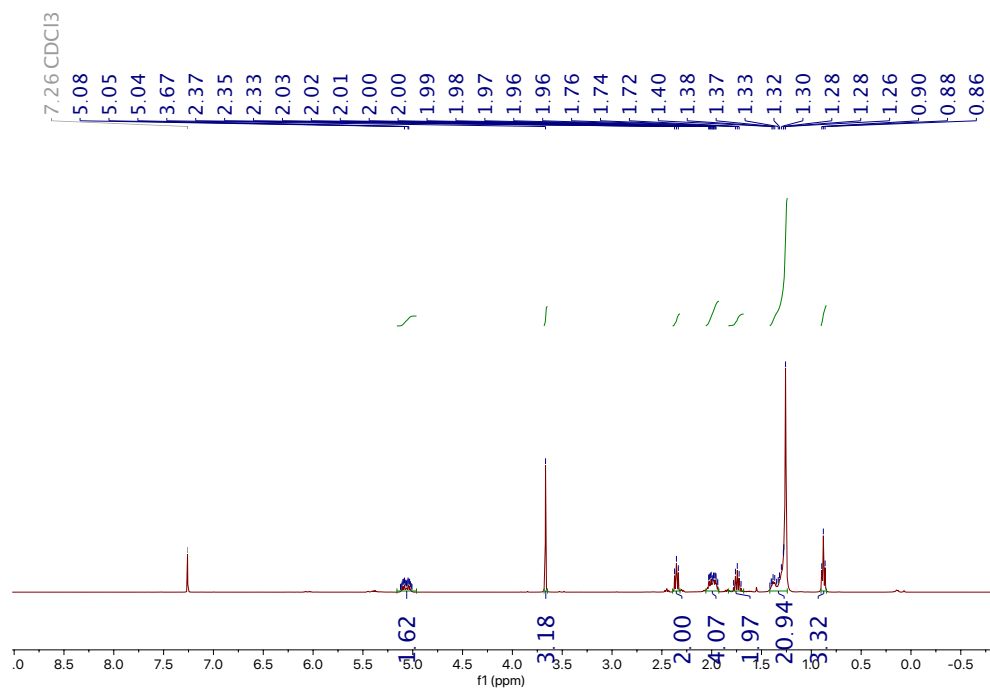
^{13}C NMR (151 MHz, CDCl_3)



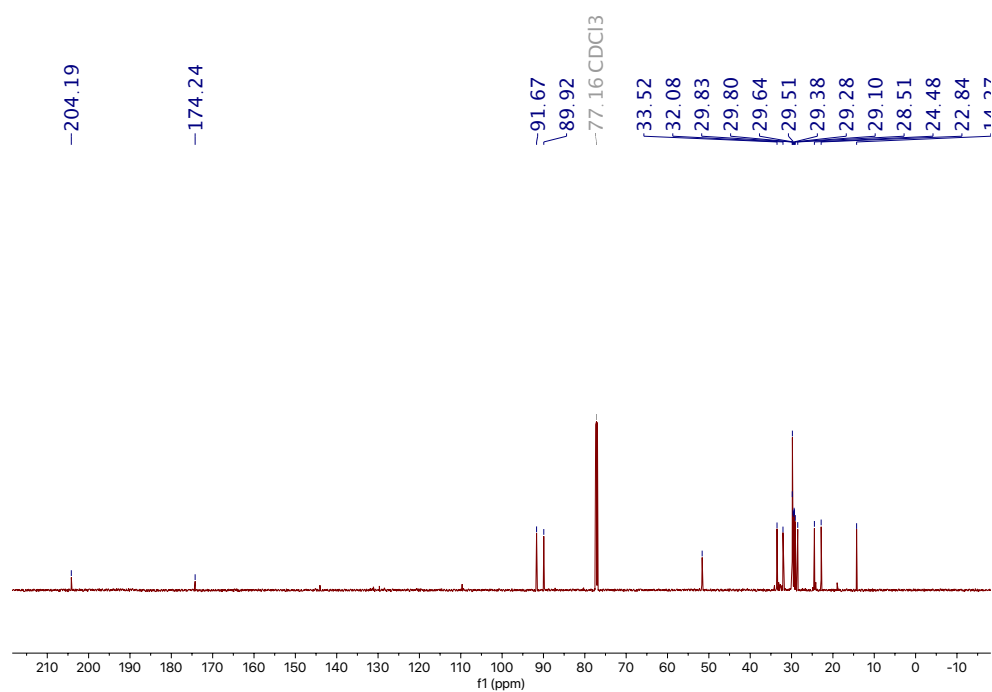


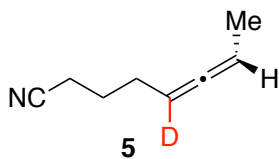
S1

¹H NMR (400 MHz, CDCl₃)

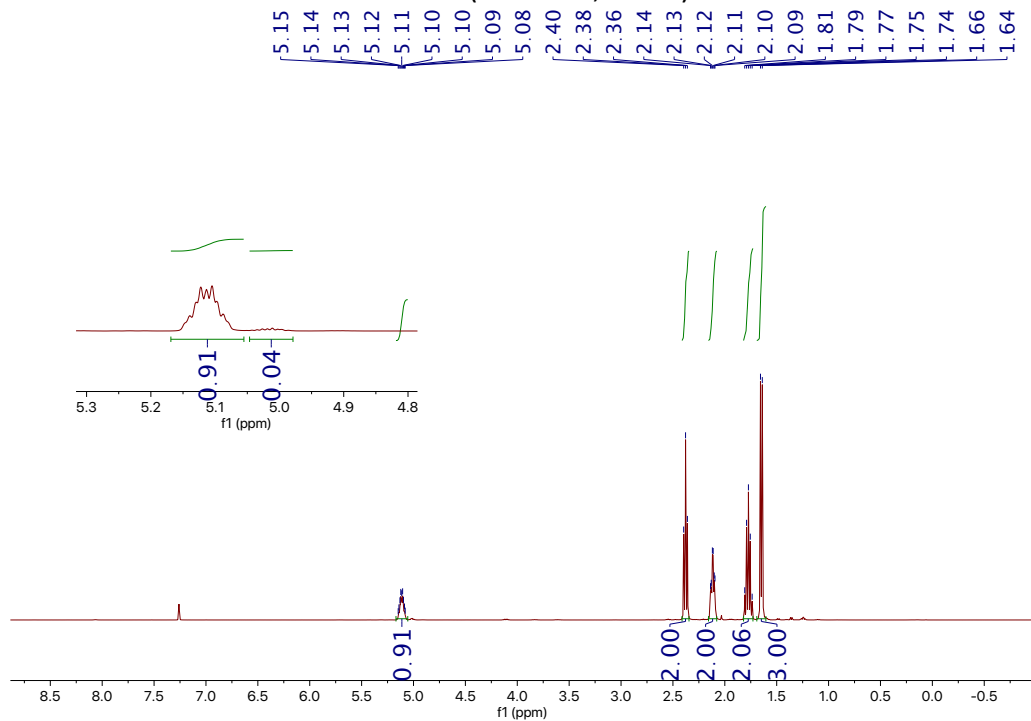


¹³C NMR (151 MHz, CDCl₃)

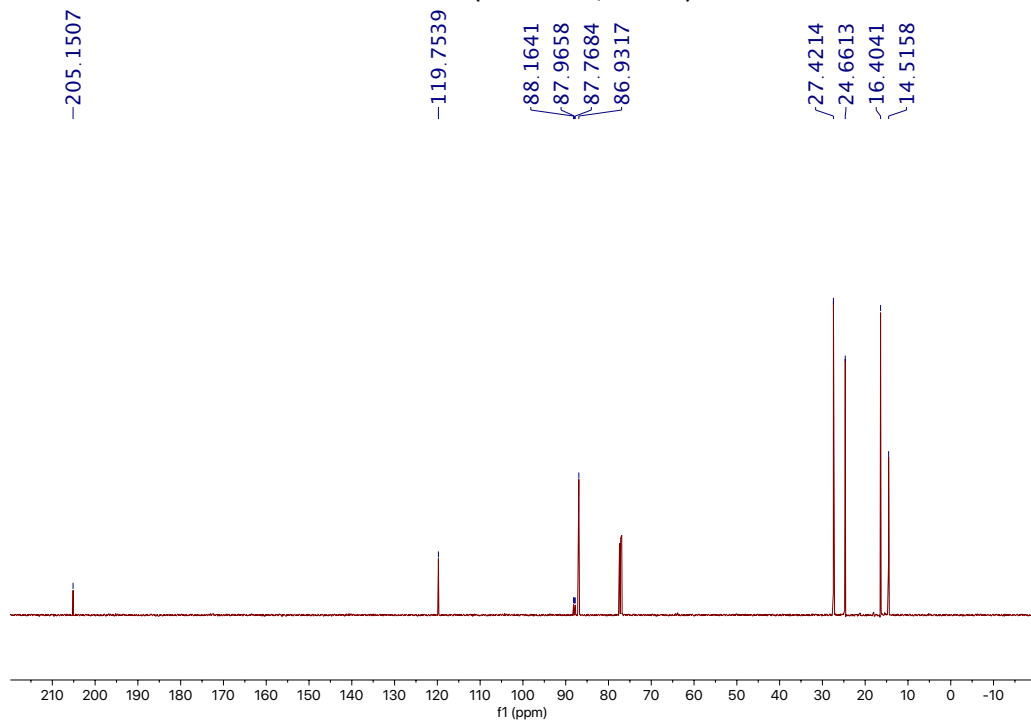




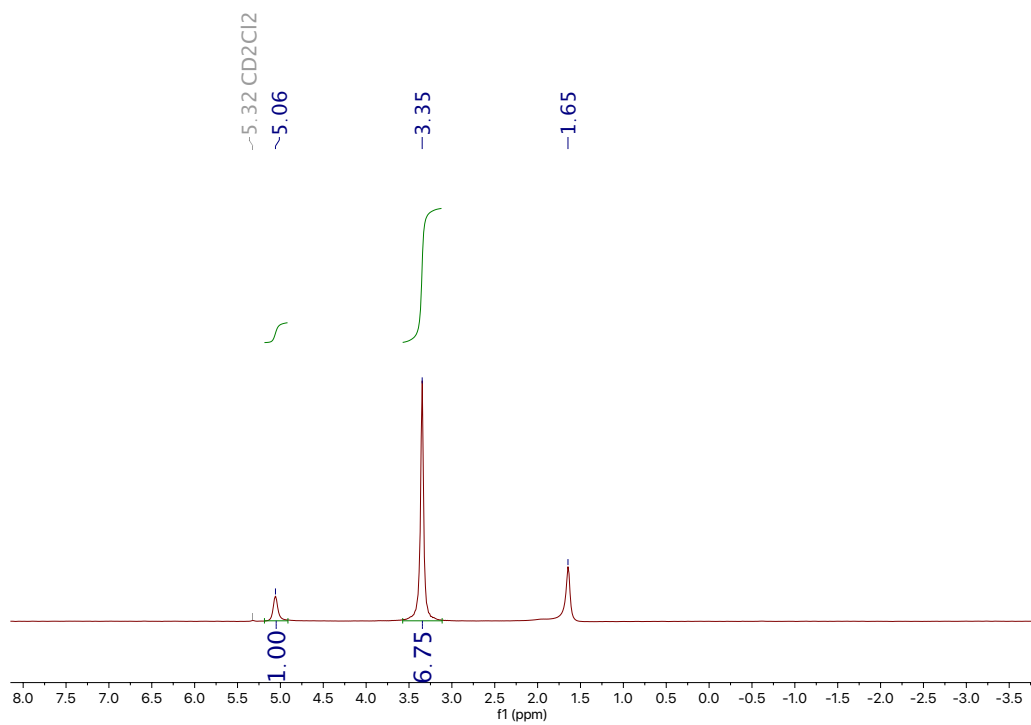
^1H NMR (400 MHz, CDCl_3)

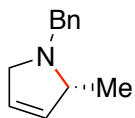


^{13}C NMR (126 MHz, CDCl_3)



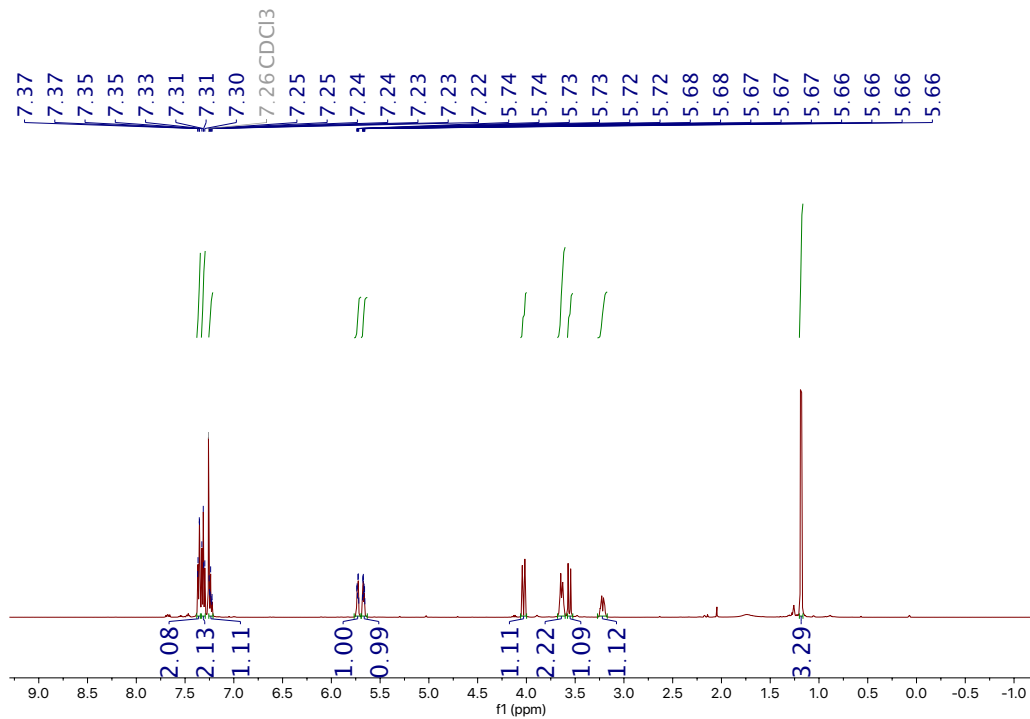
^2H NMR (77 MHz, CH_2Cl_2): 0.18 mmol **5** with 0.4 mmol methanol- d_4



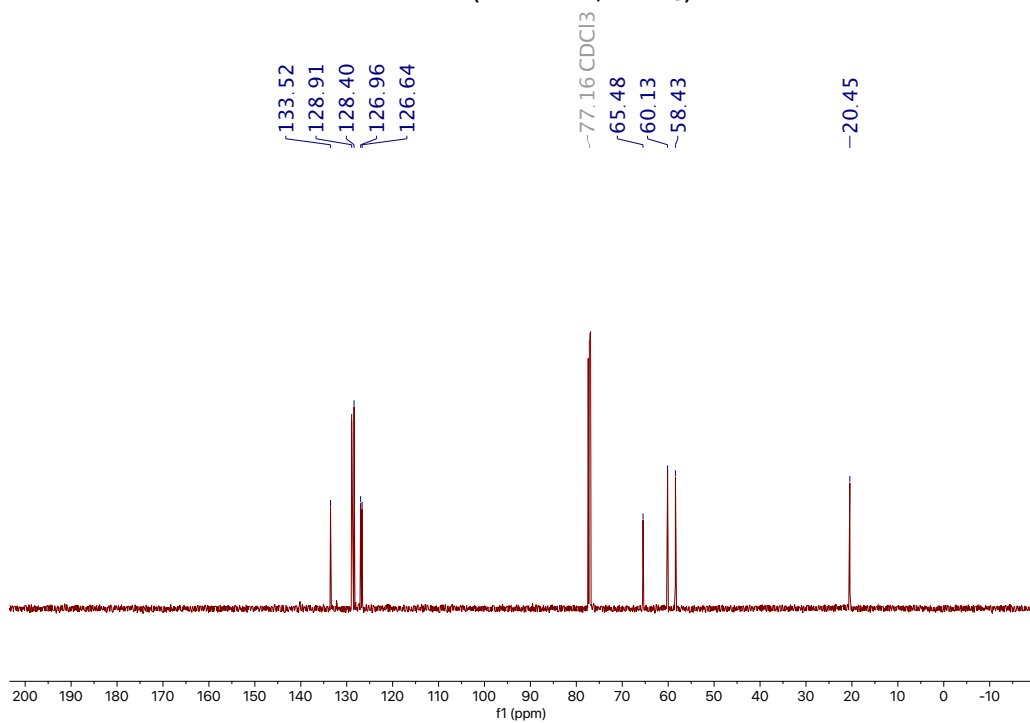


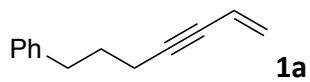
6

^1H NMR (500 MHz, CDCl_3)

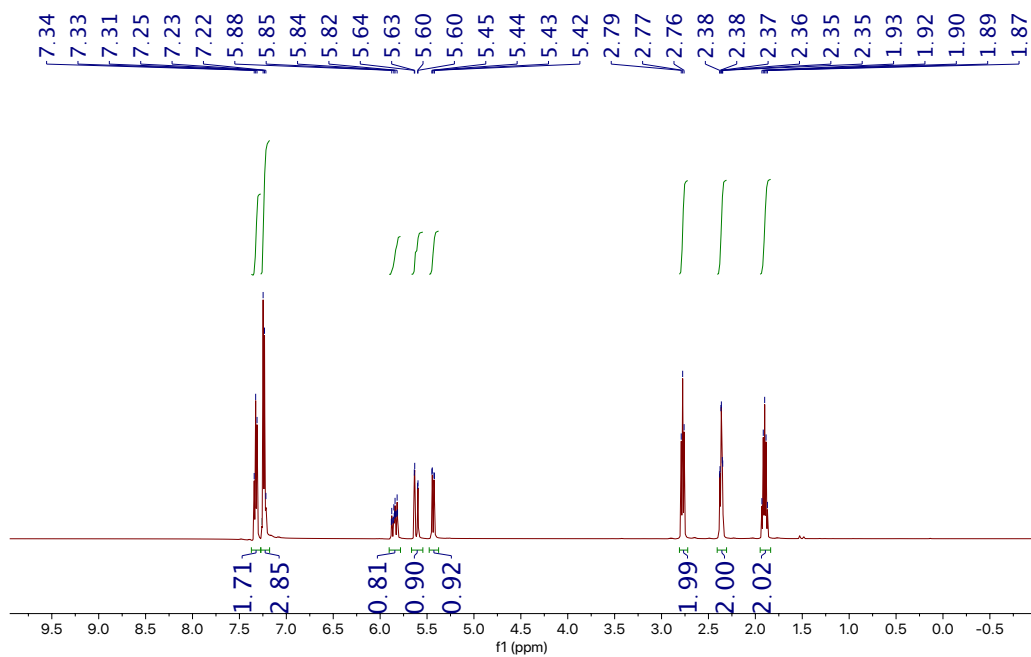


^{13}C NMR (126 MHz, CDCl_3)

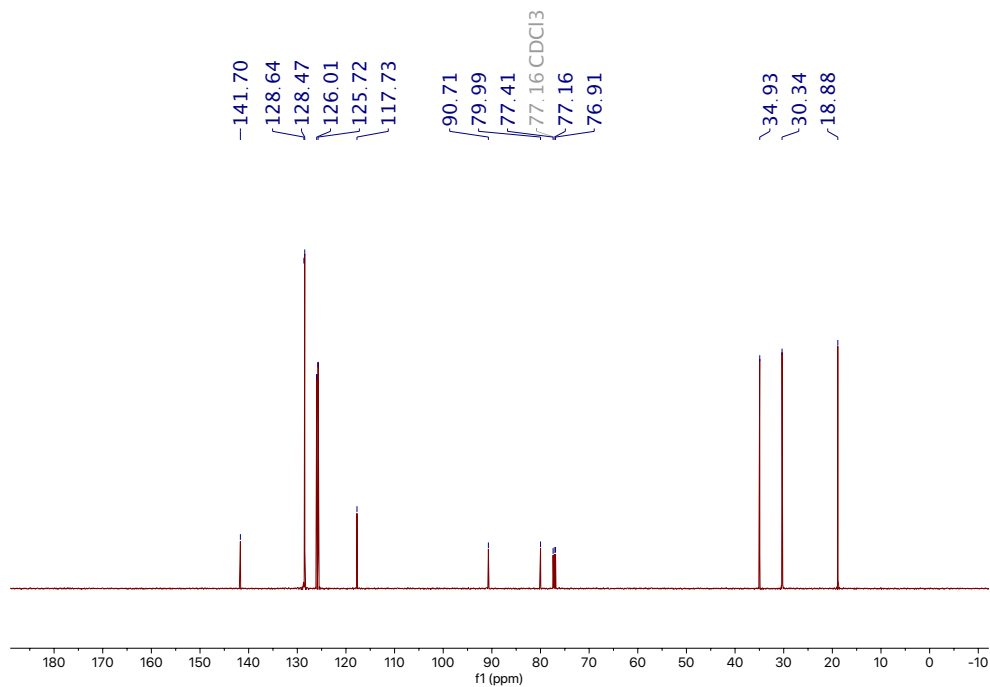


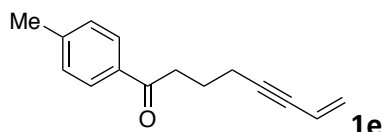


^1H NMR (500 MHz, CDCl_3)

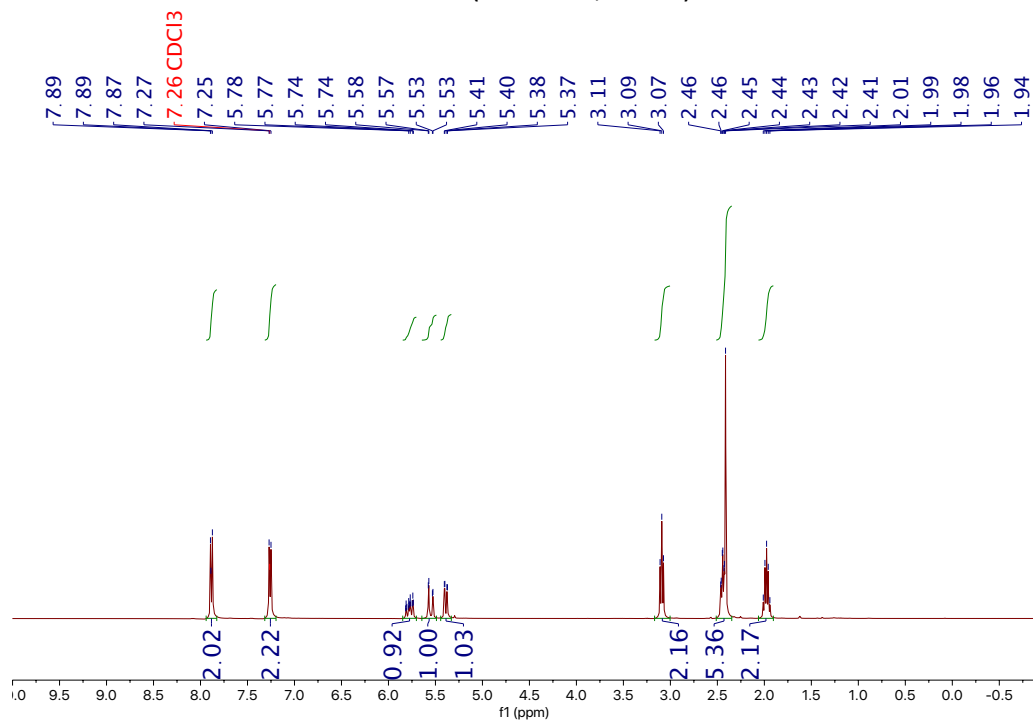


^{13}C NMR (126 MHz, CDCl_3)

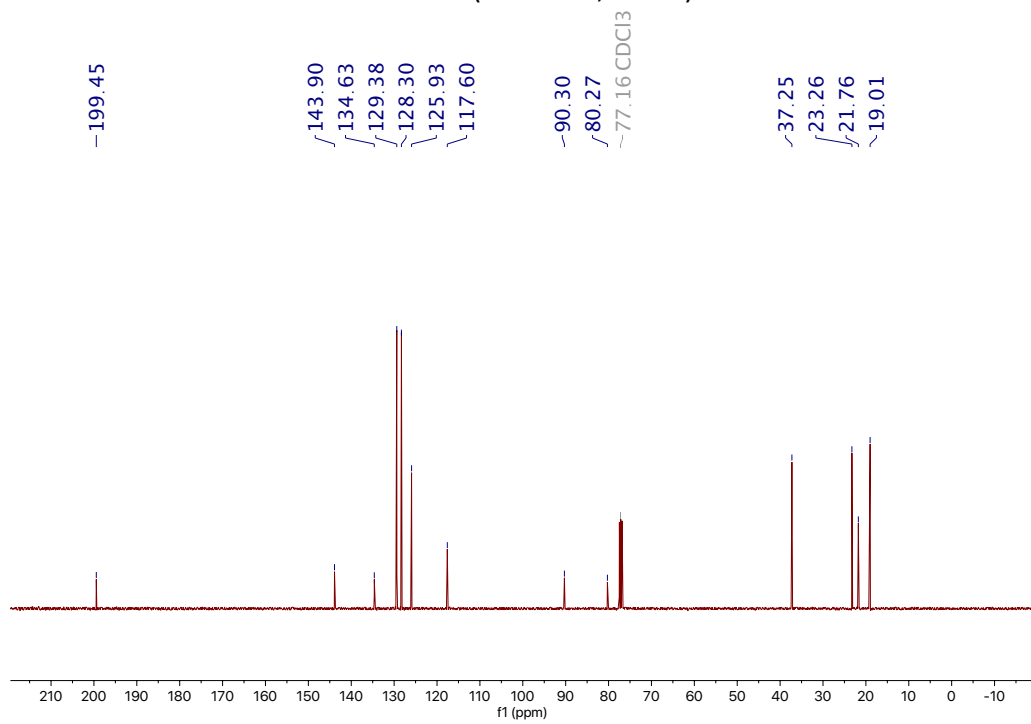


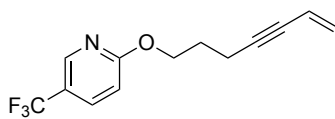


¹H NMR (400 MHz, CDCl₃)



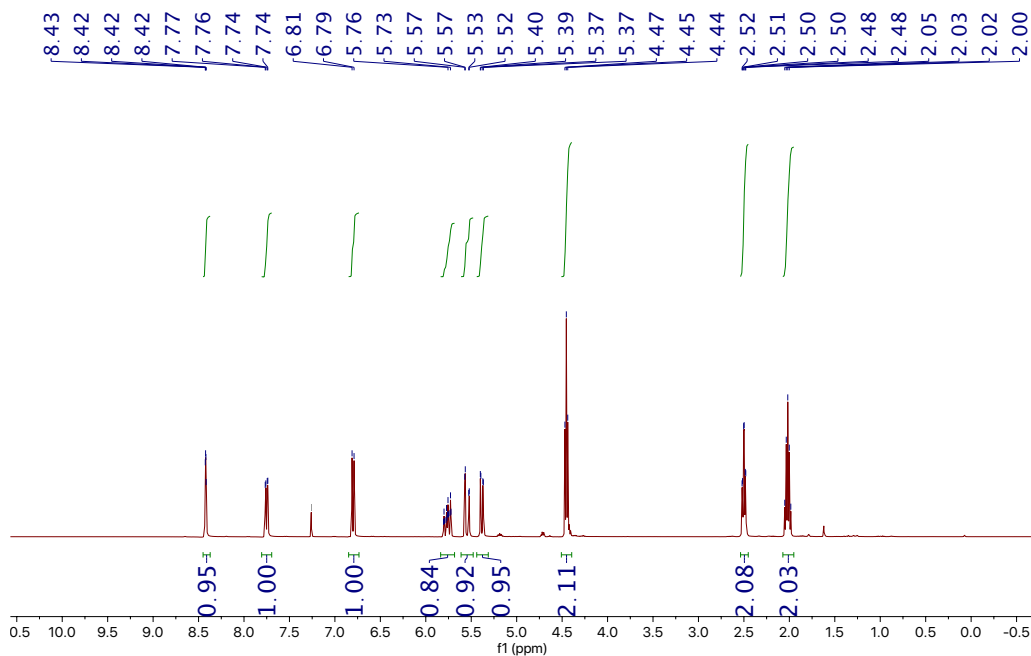
¹³C NMR (101 MHz, CDCl₃)



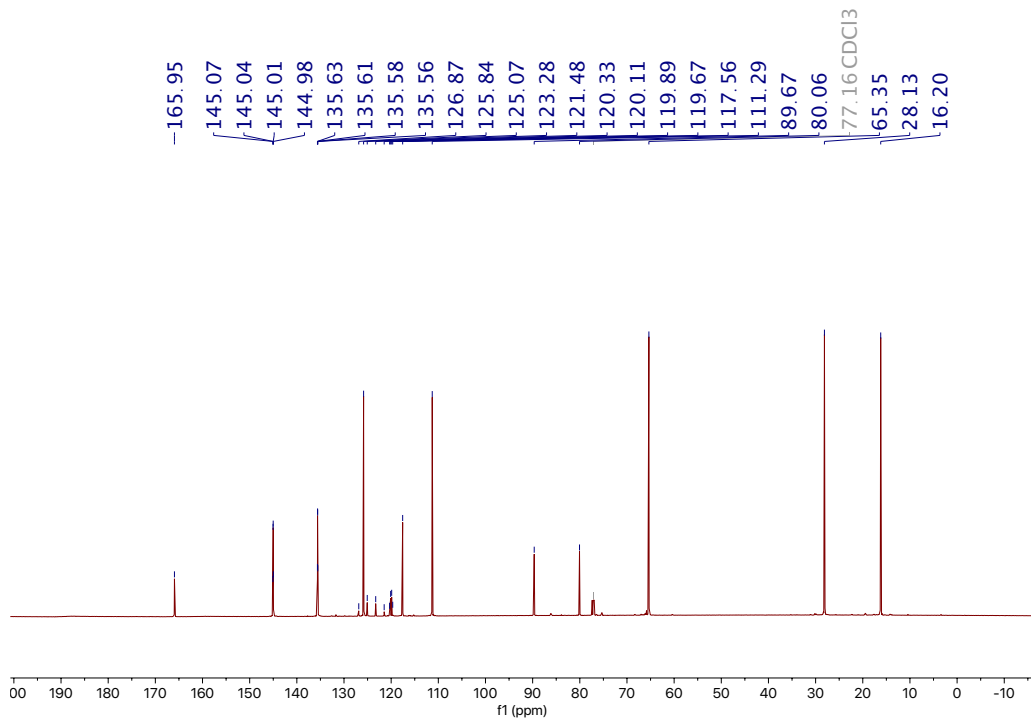


1i

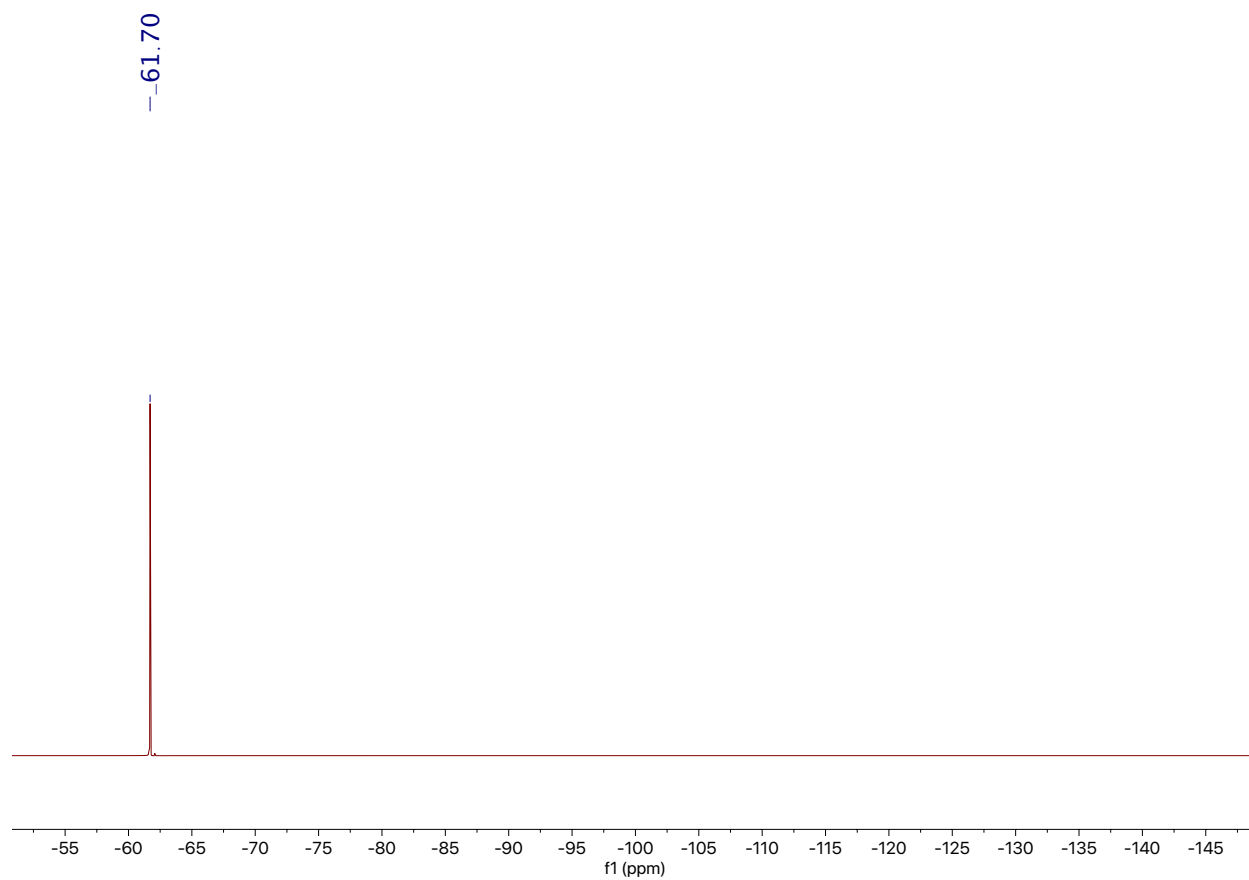
¹H NMR (400 MHz, CDCl₃)

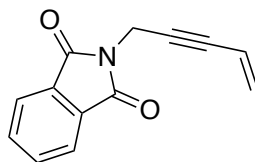


¹³C NMR (151 MHz, CDCl₃)



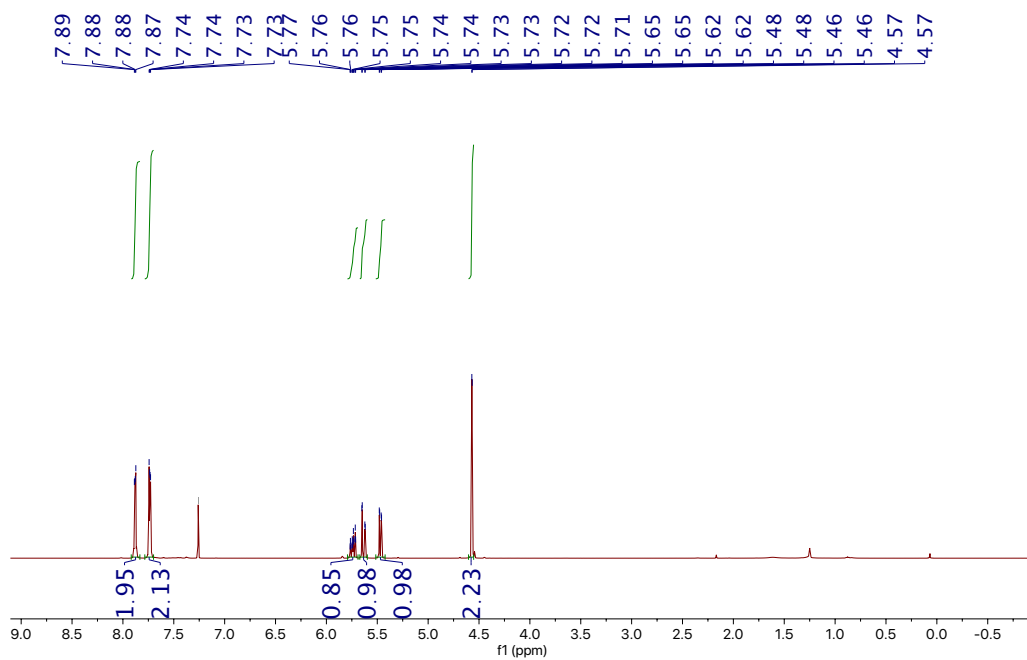
^{19}F NMR (565 MHz, CDCl_3)



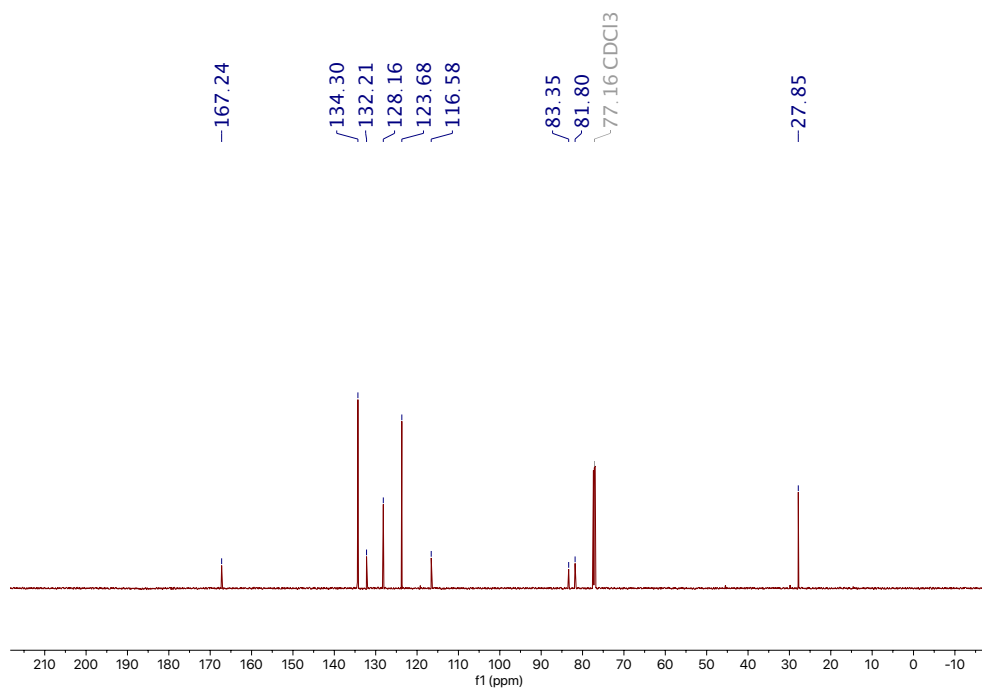


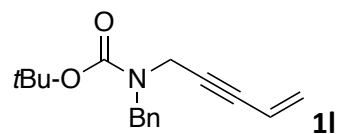
1k

^1H NMR (600 MHz, CDCl_3)

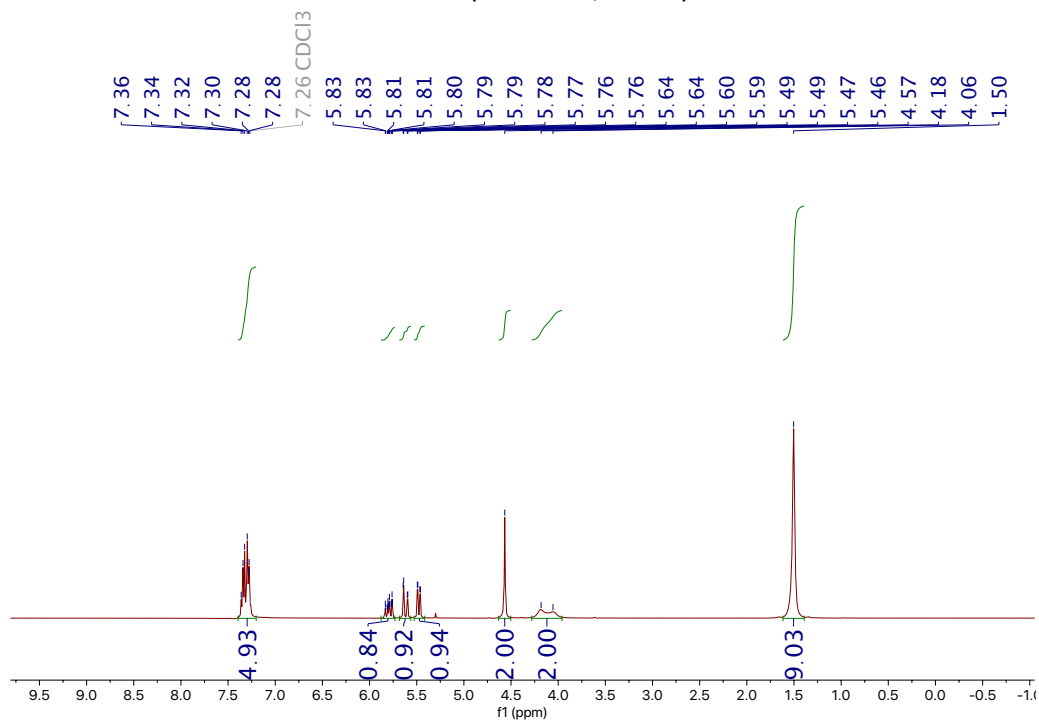


^{13}C NMR (151 MHz, CDCl_3)

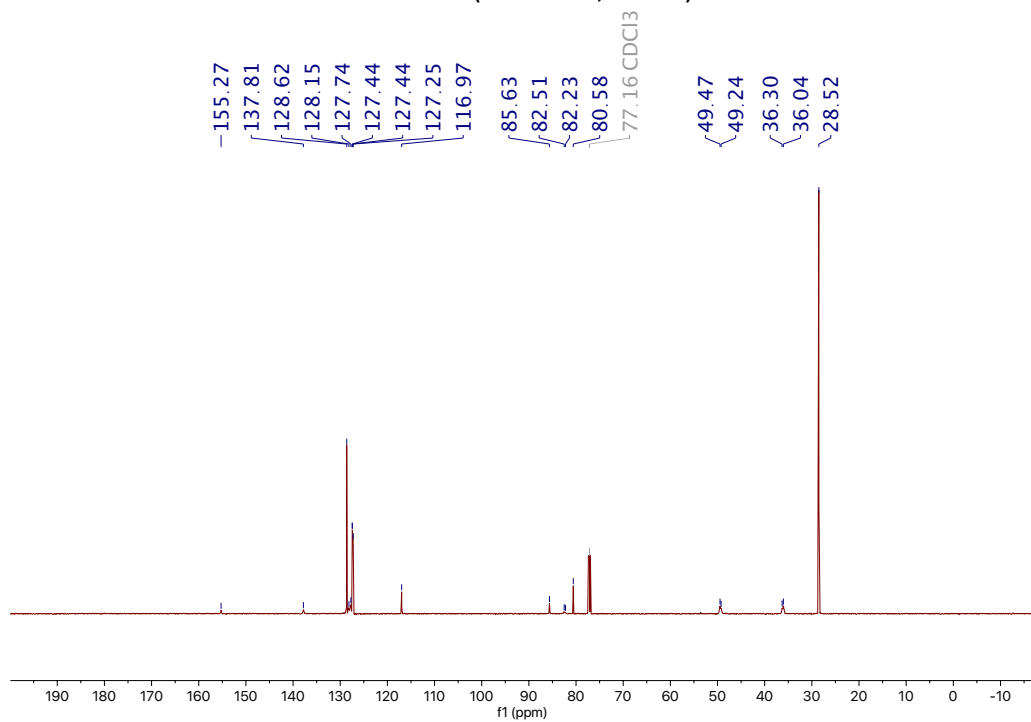


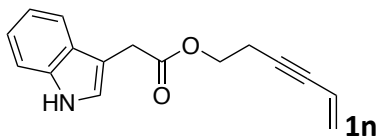


¹H NMR (400 MHz, CDCl₃)

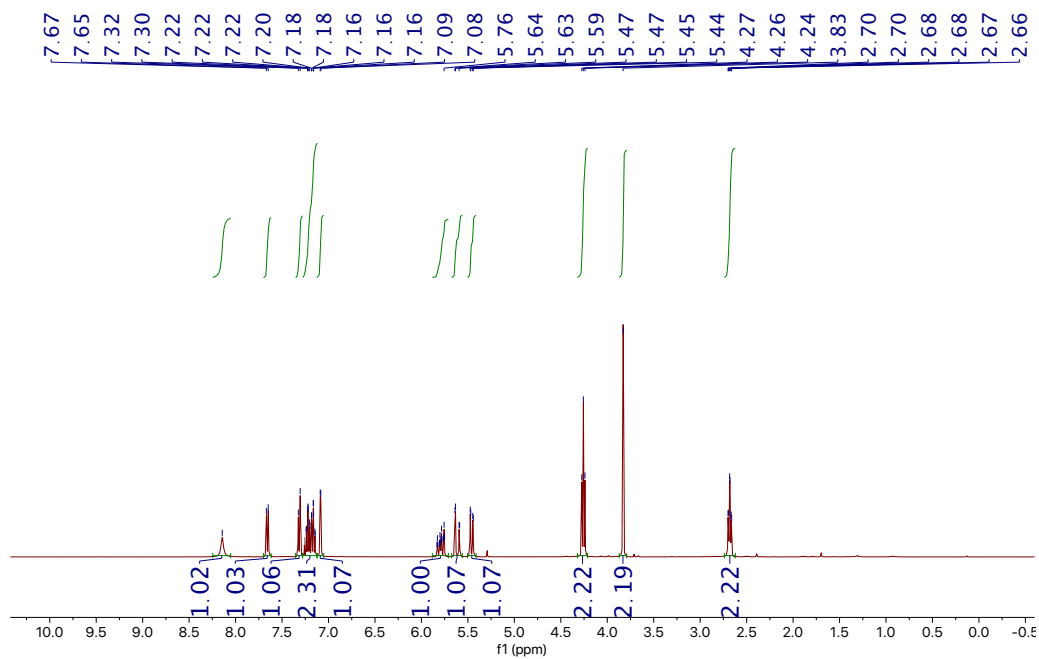


¹³C NMR (151 MHz, CDCl₃)

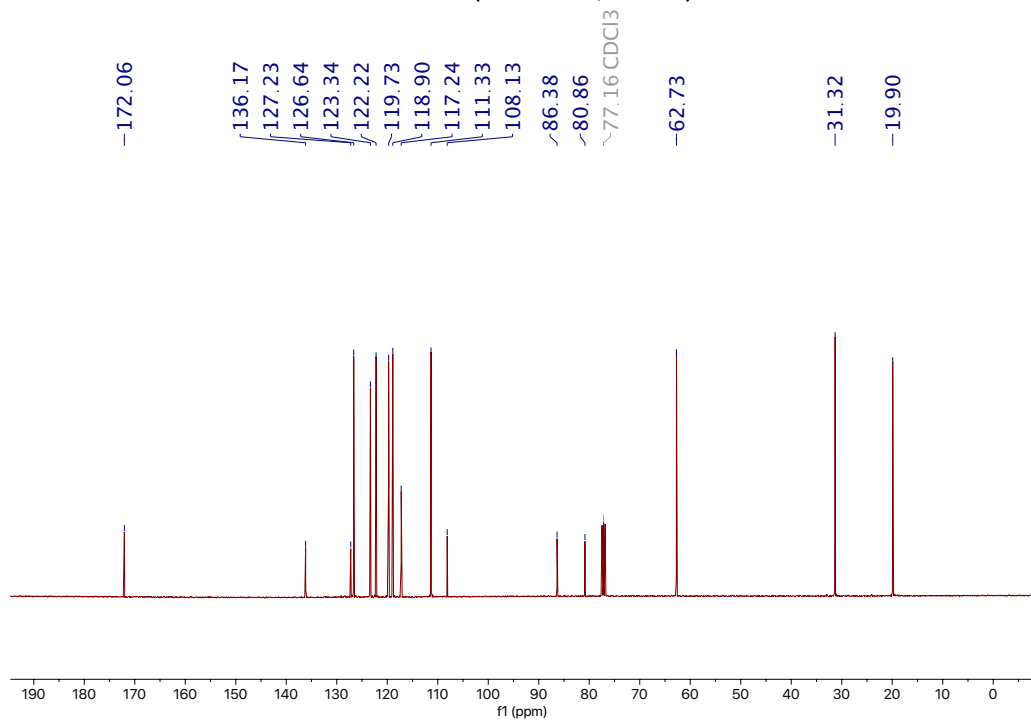


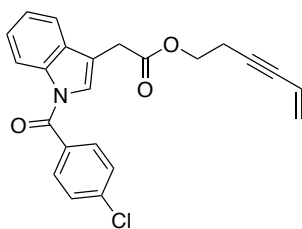


^1H NMR (400 MHz, CDCl_3)



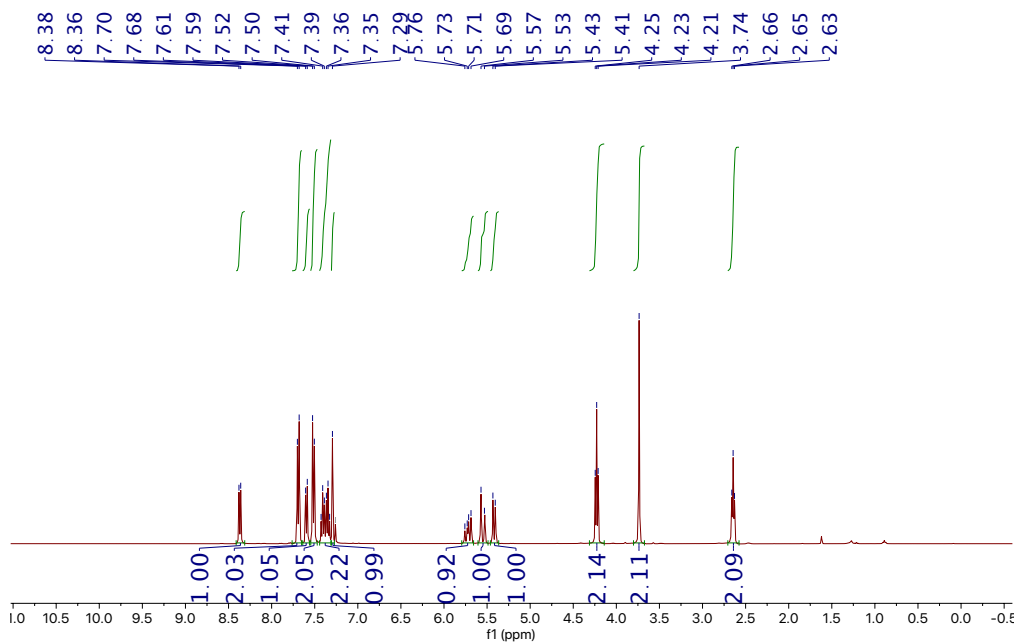
^{13}C NMR (101 MHz, CDCl_3)



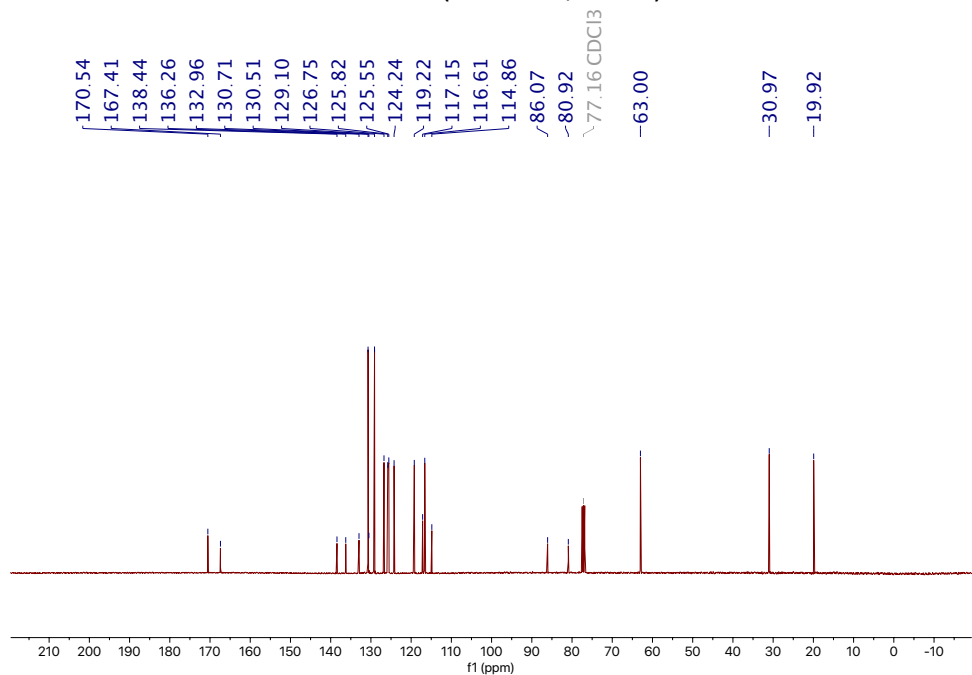


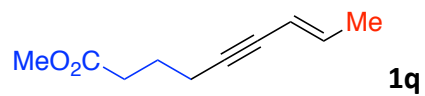
1o

¹H NMR (400 MHz, CDCl₃)

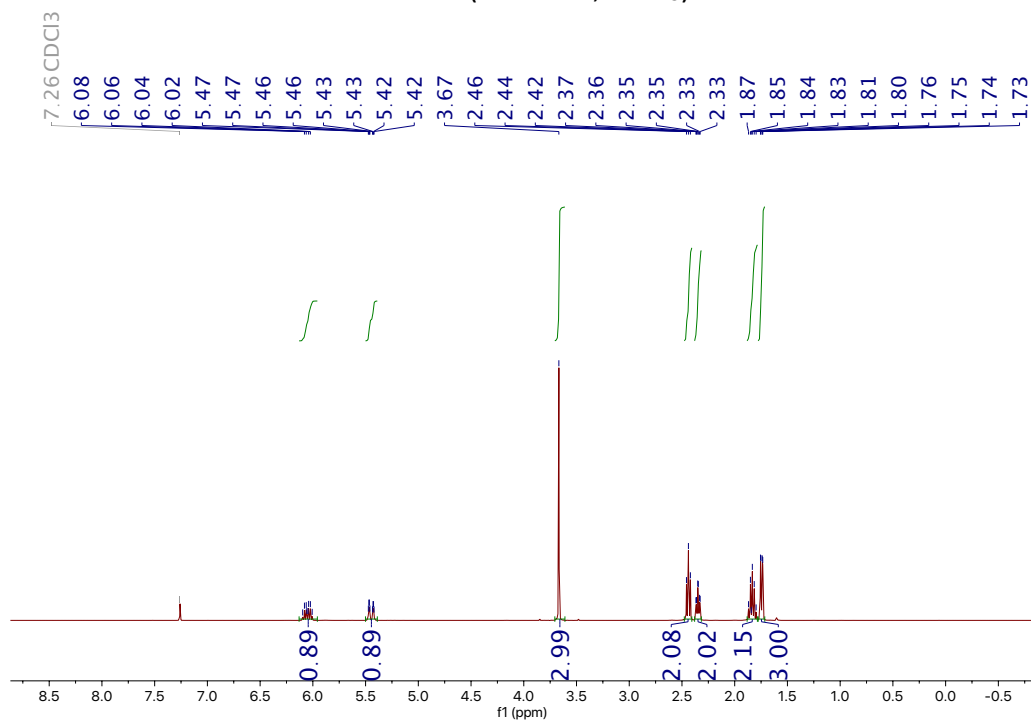


¹³C NMR (101 MHz, CDCl₃)

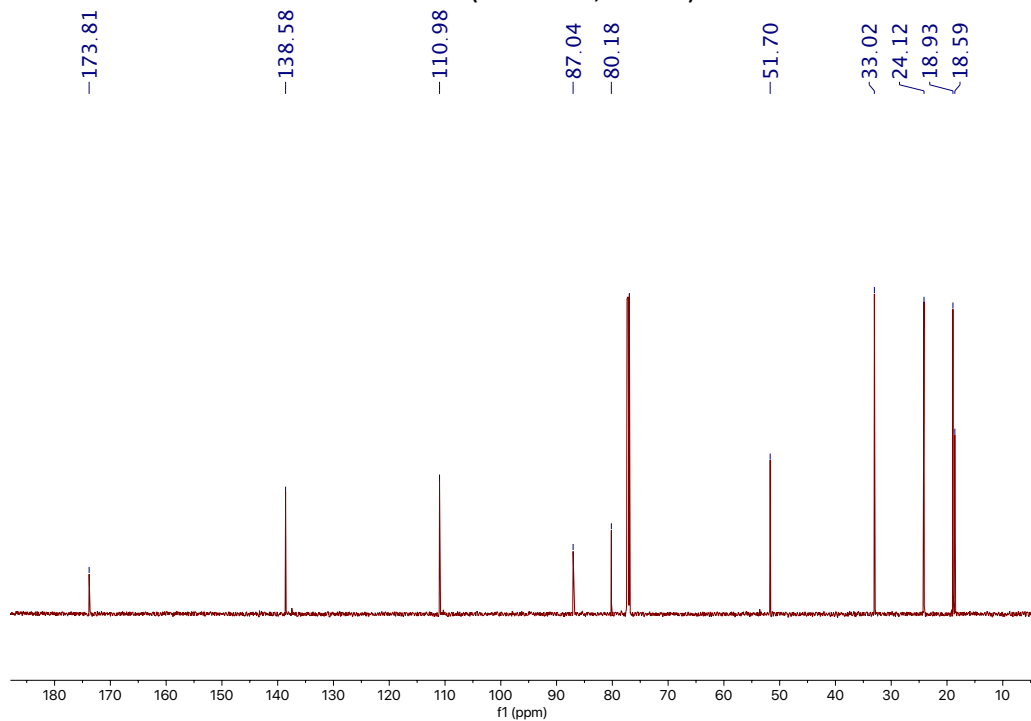


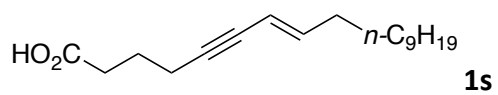


¹H NMR (400 MHz, CDCl₃)

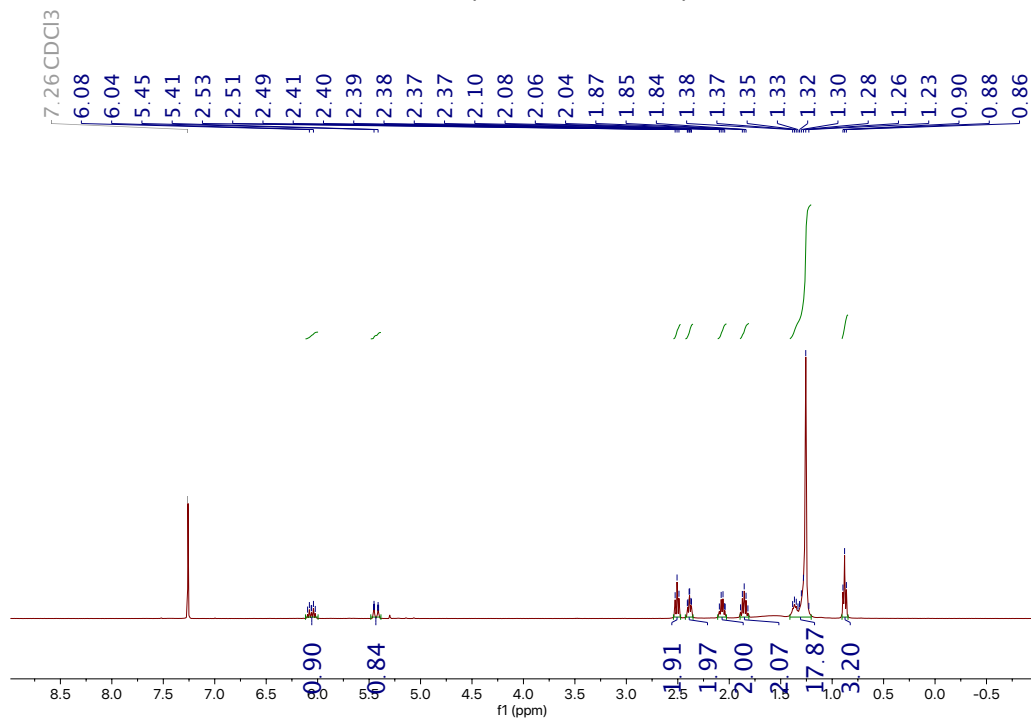


¹³C NMR (151 MHz, CDCl₃)





¹H NMR (400 MHz, CDCl₃)



NMR Spectra.pdf (4.66 MiB)

[view on ChemRxiv](#) • [download file](#)

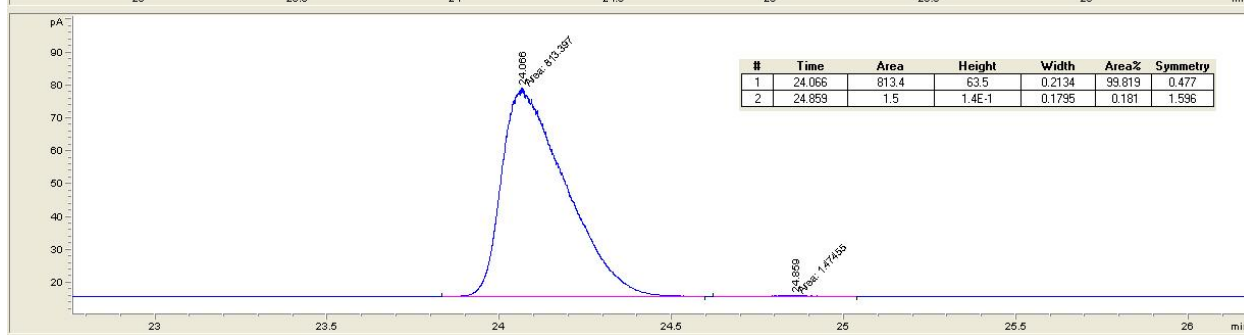
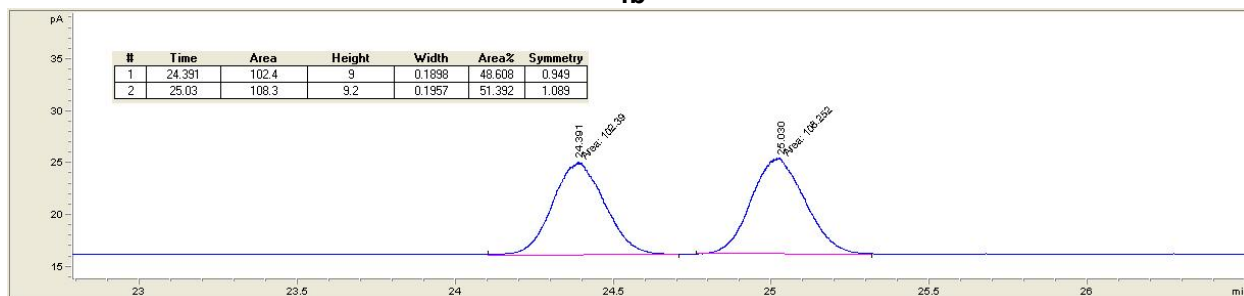
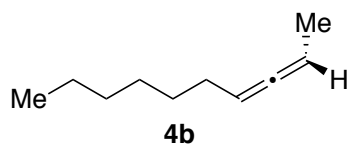
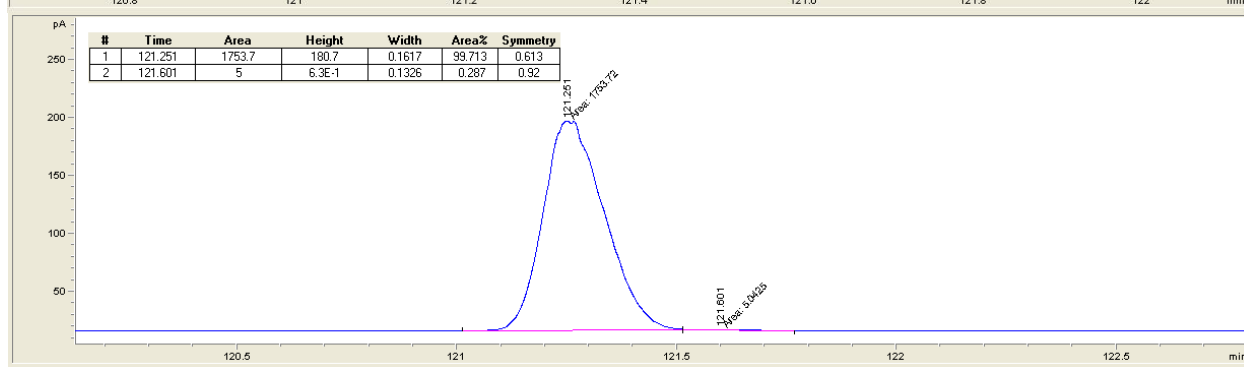
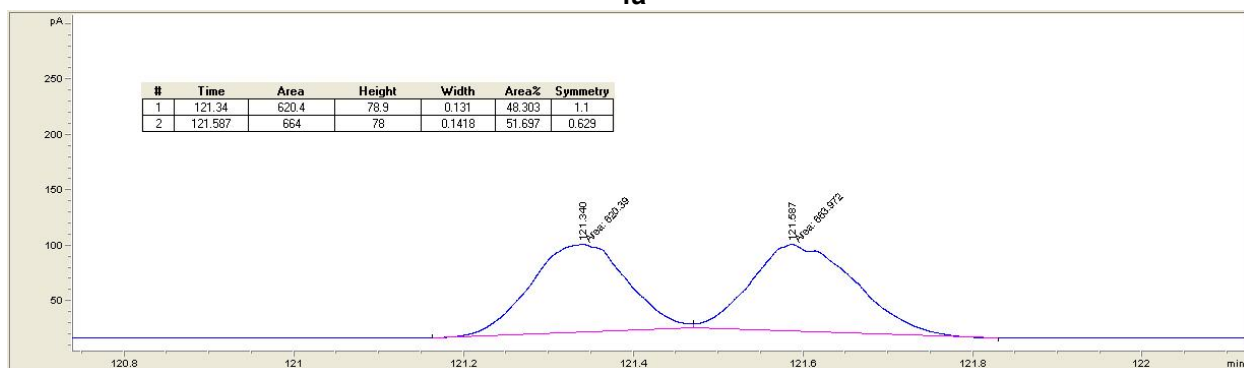
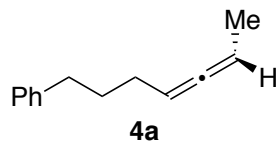
Compiled HPLC, SFC and GC Data

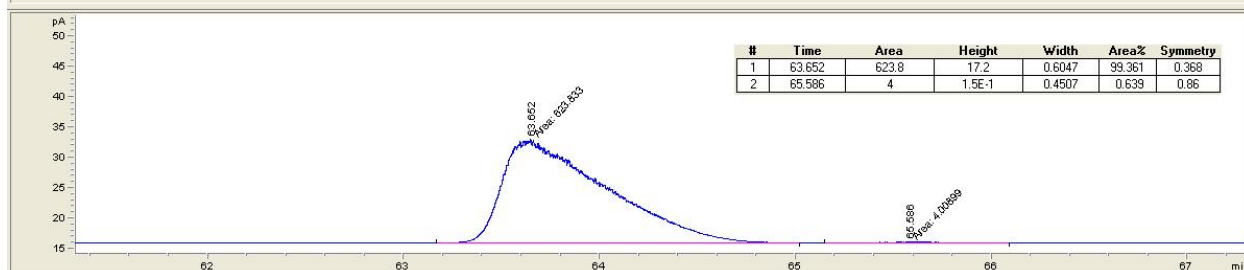
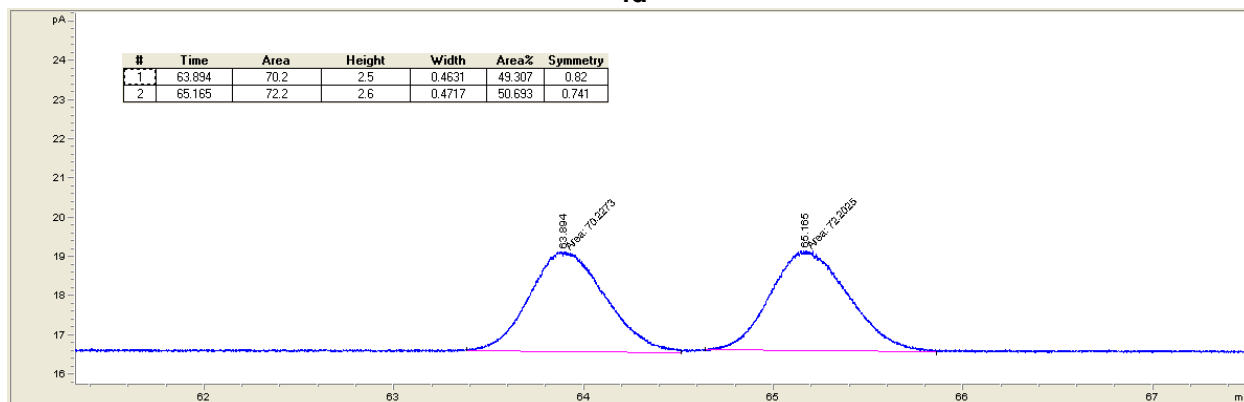
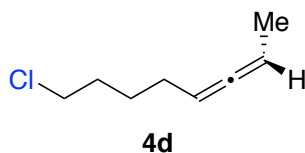
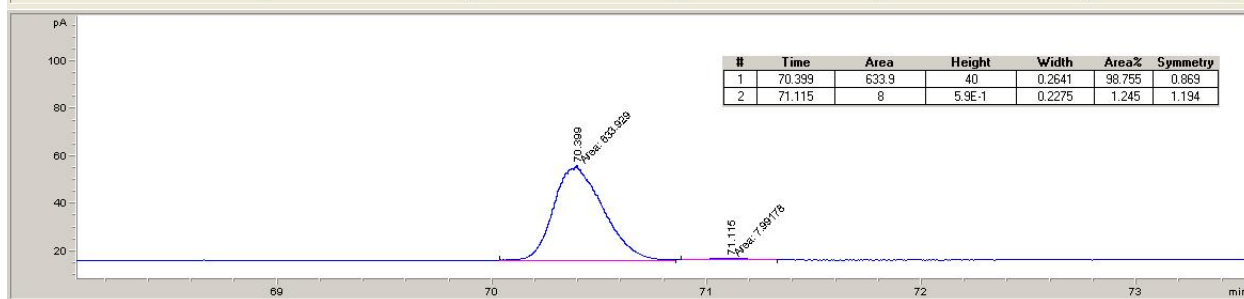
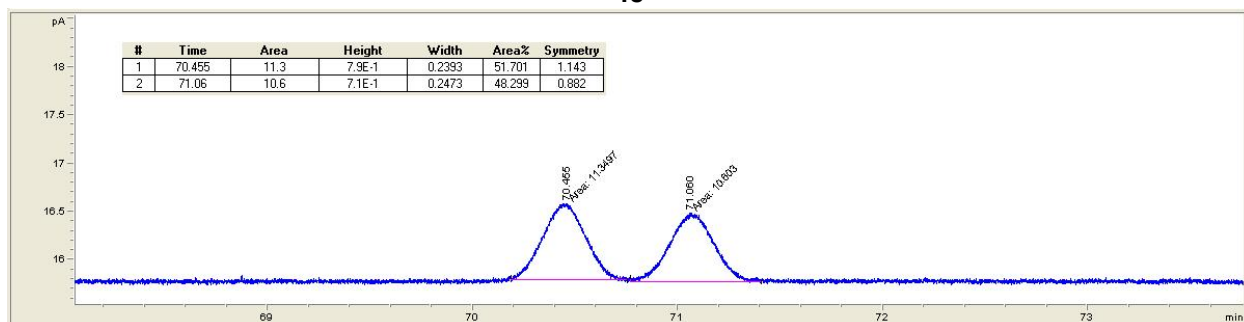
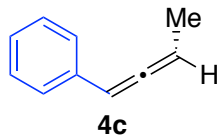
**Copper Hydride-Catalyzed Enantioselective Synthesis of Axially
Chiral 1,3-Disubstituted Allenes**

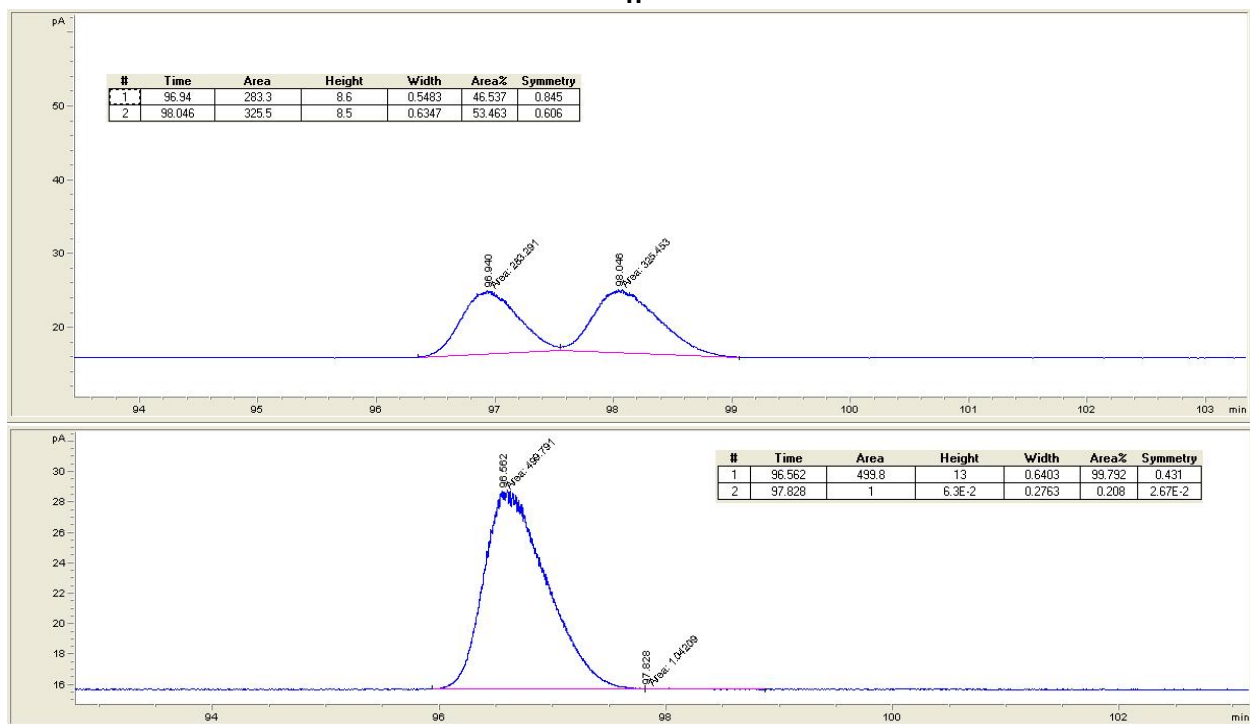
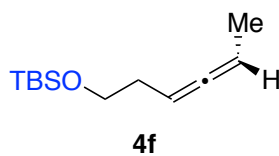
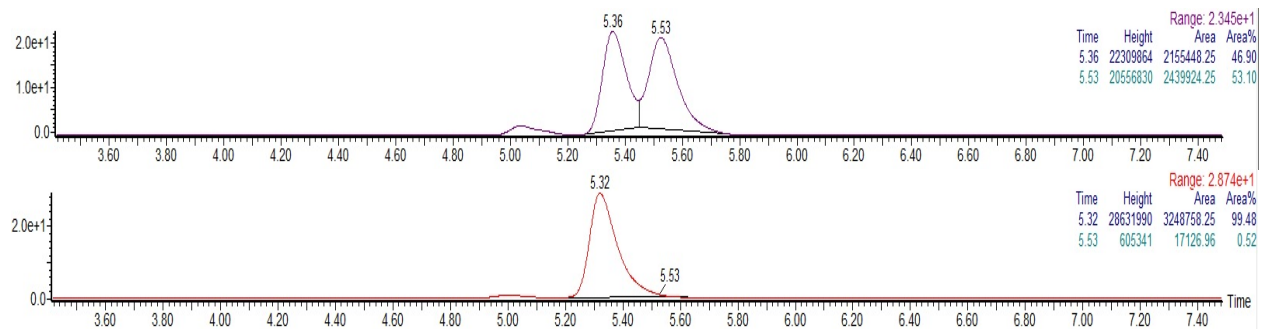
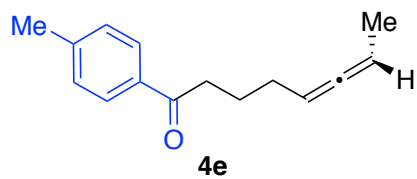
Liela Bayeh-Romero and Stephen L. Buchwald*

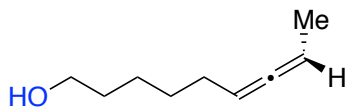
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts
02139, United States

*Correspondence to: sbuchwal@mit.edu

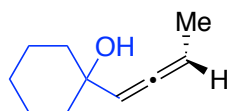
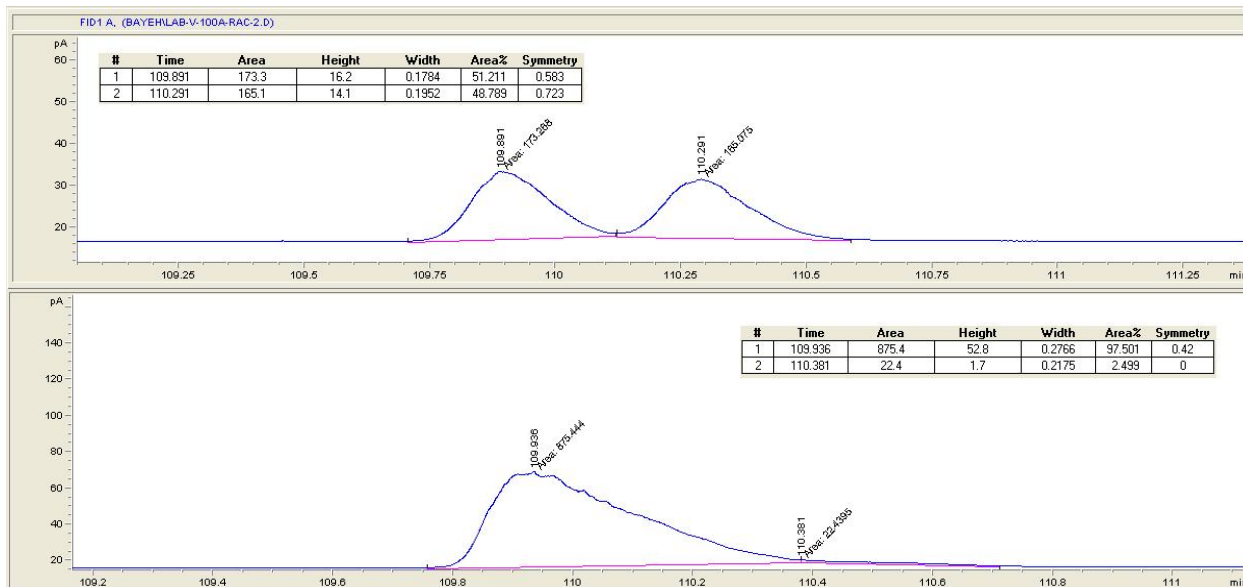




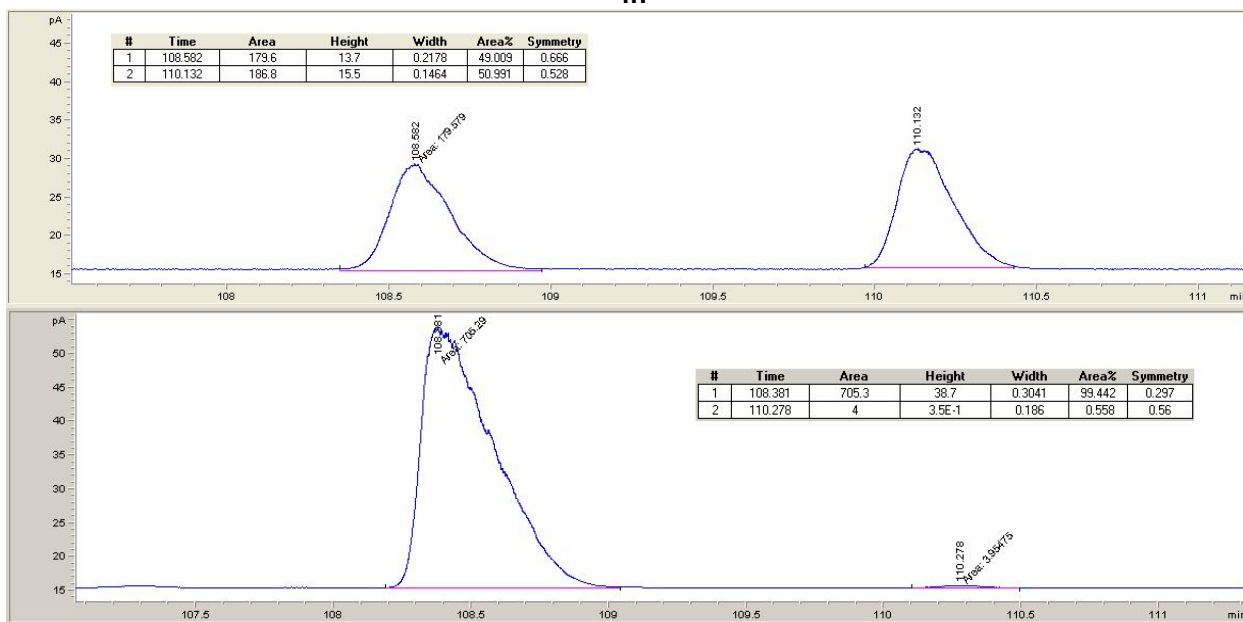


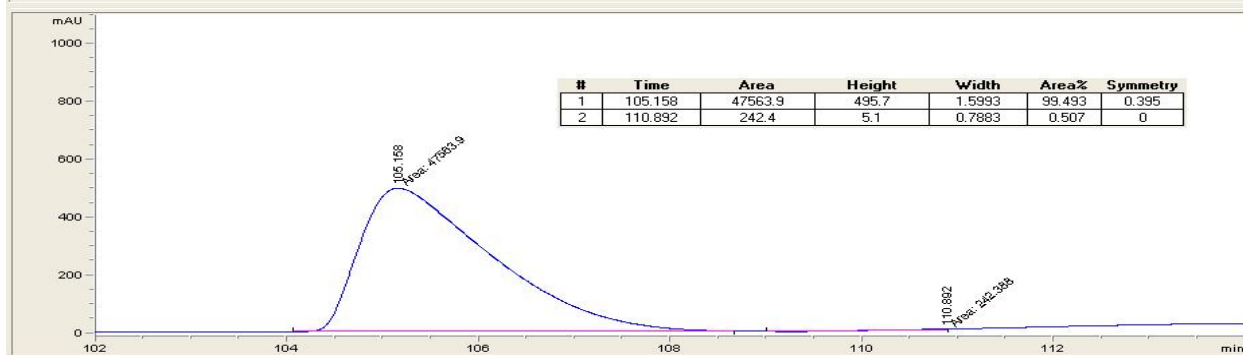
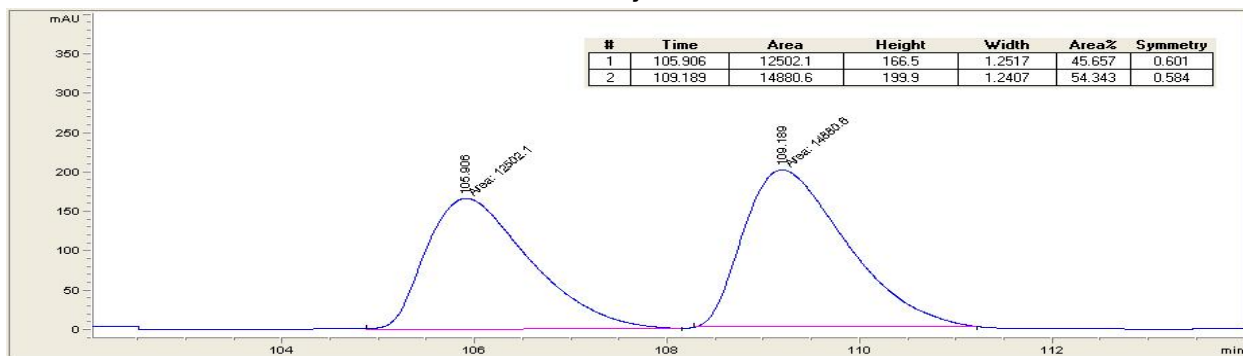
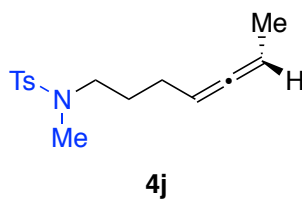
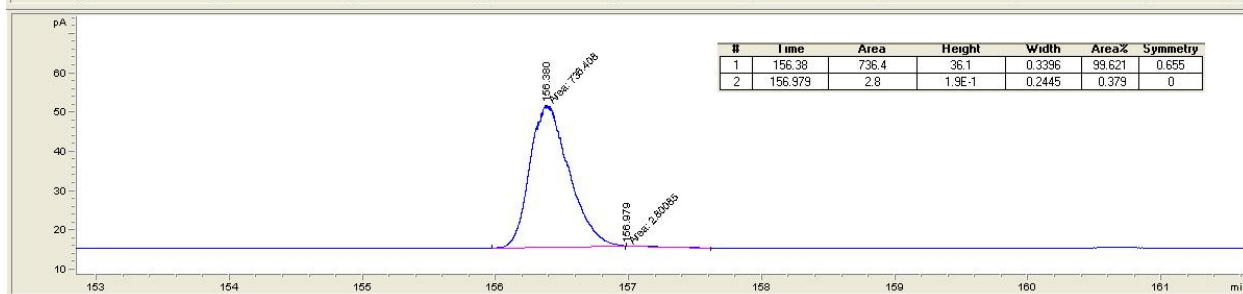
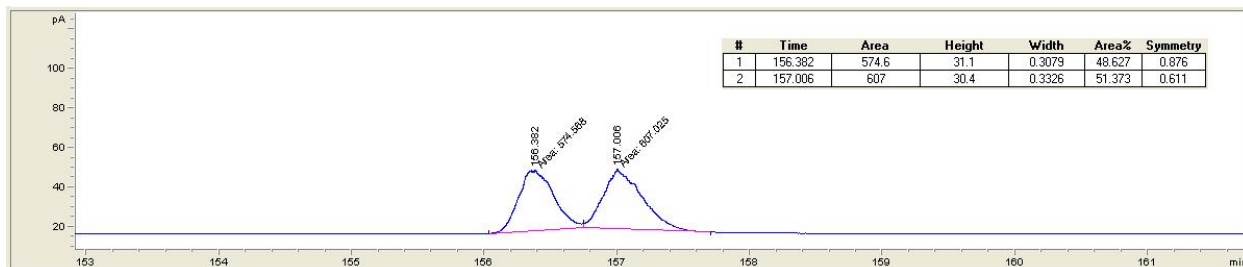
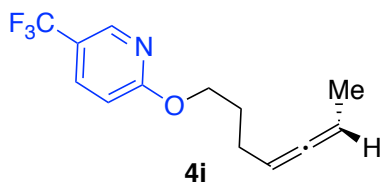


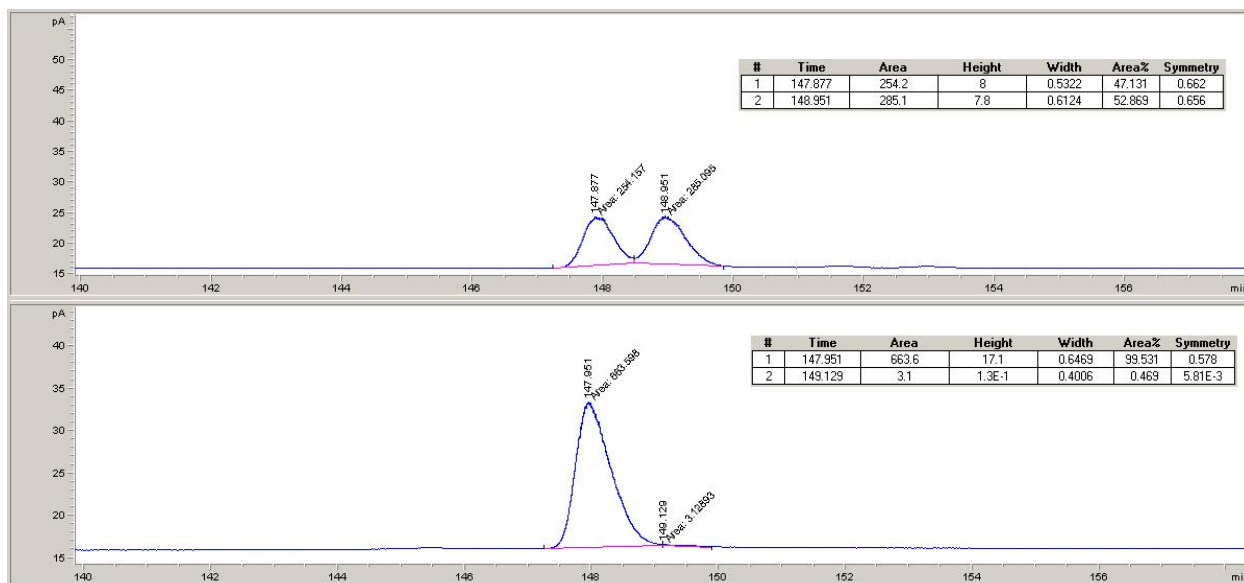
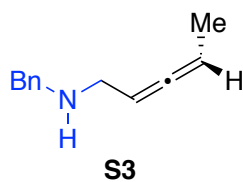
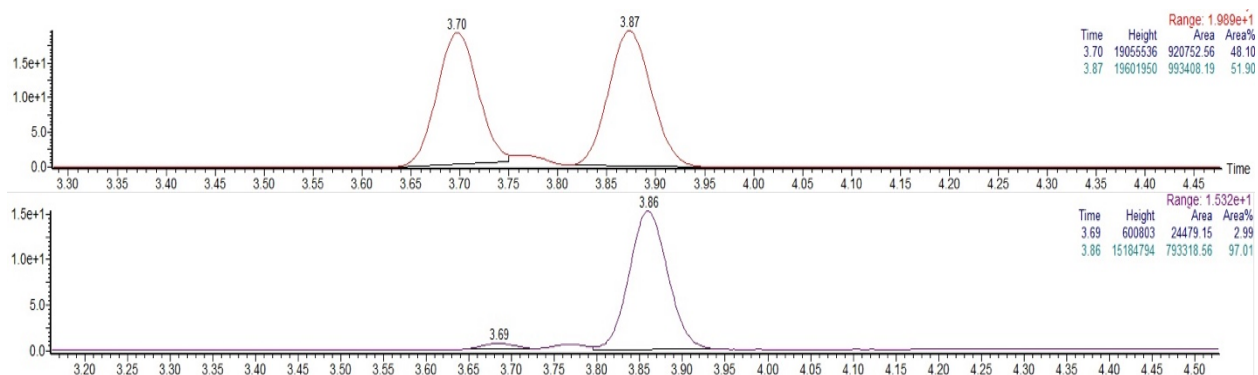
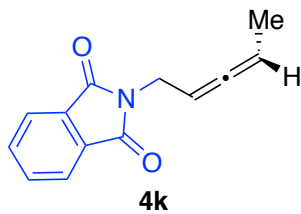
4g

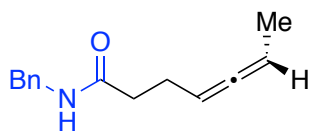


4h

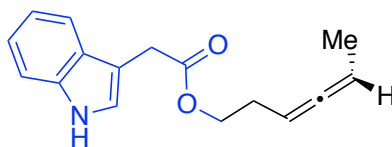
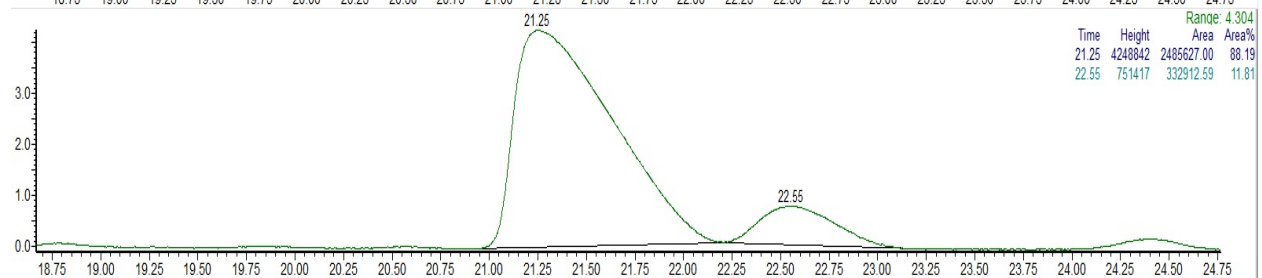
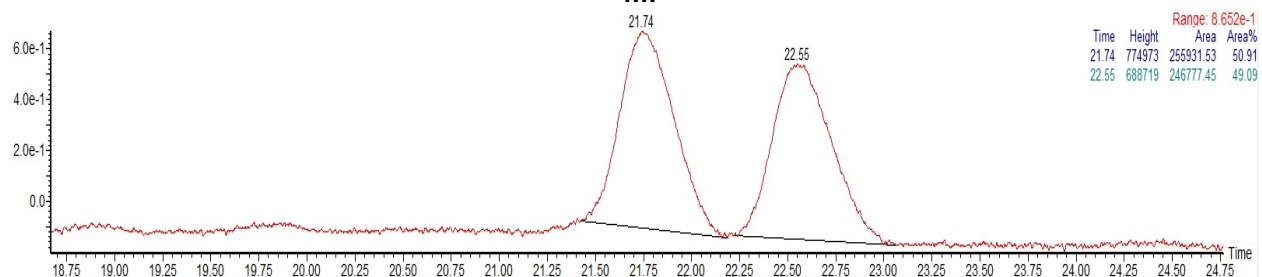




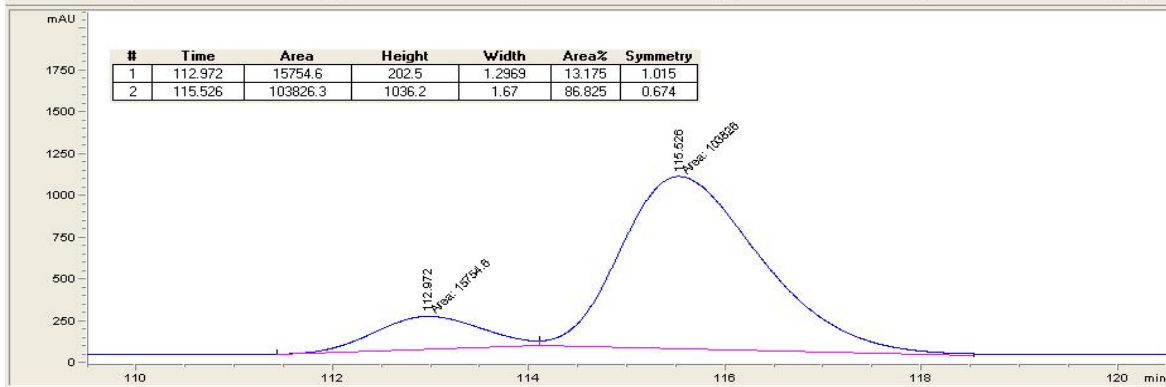
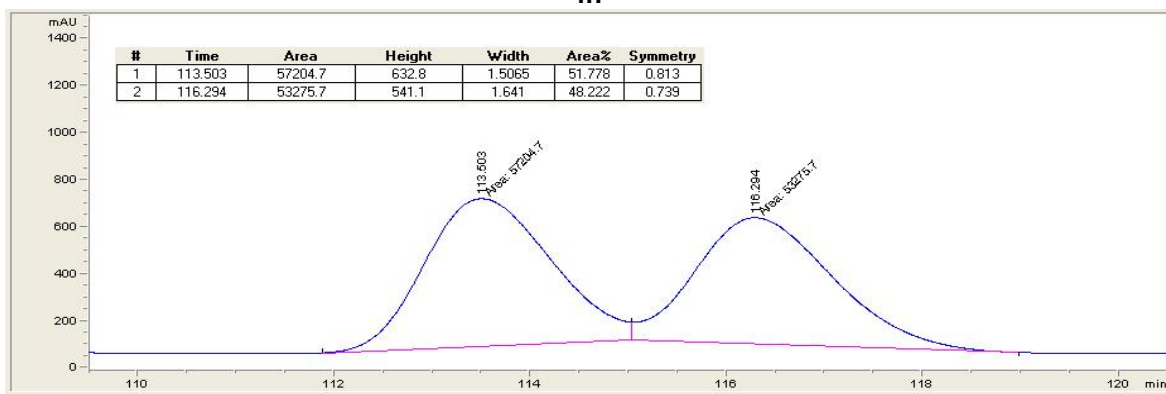


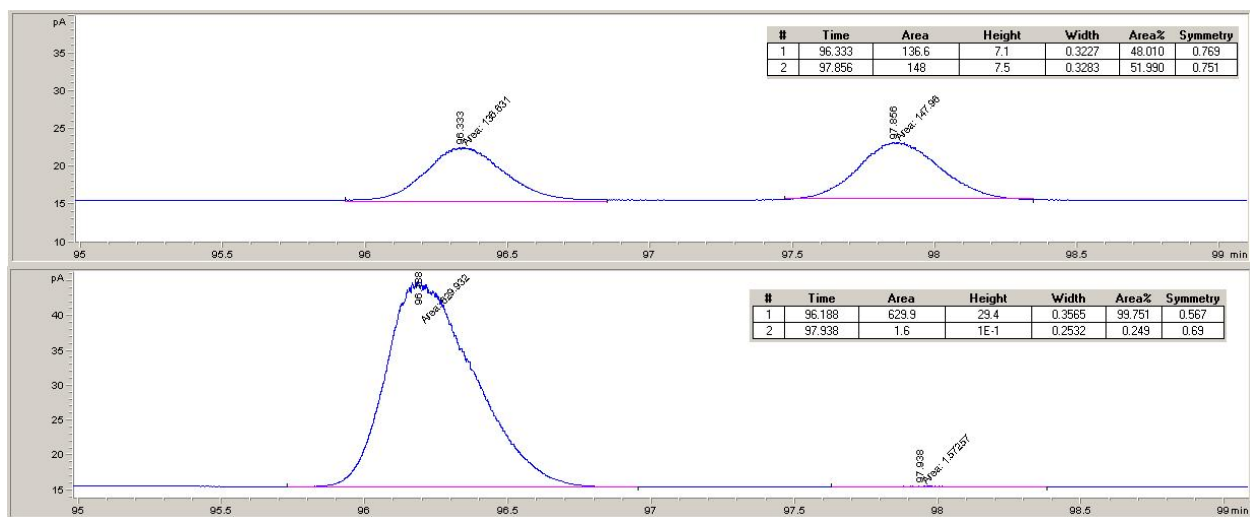
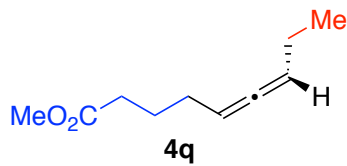
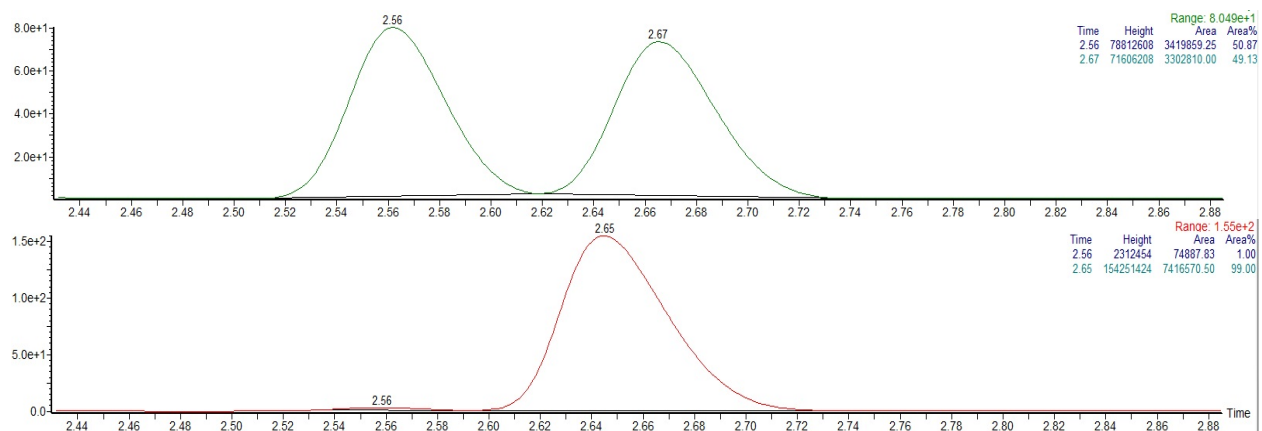
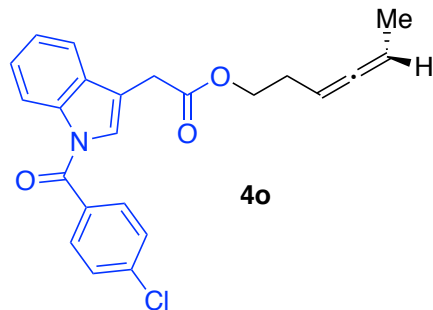


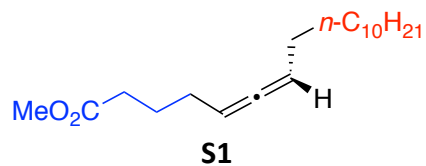
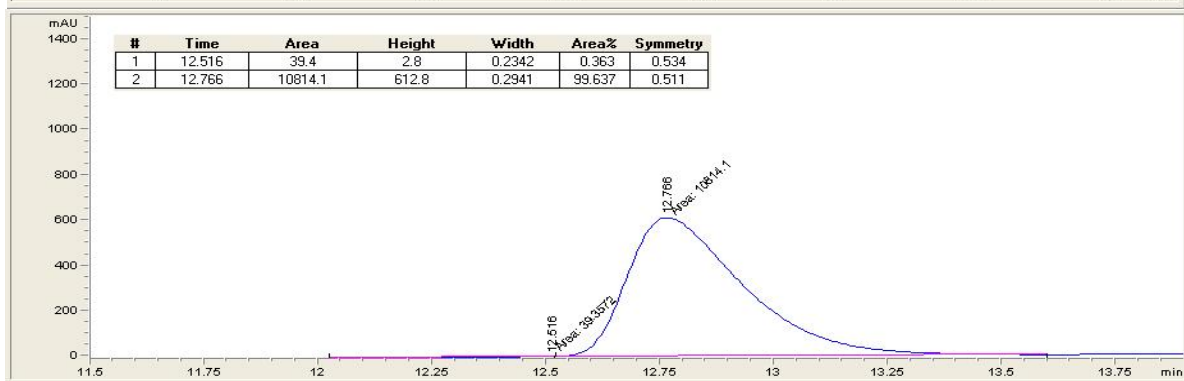
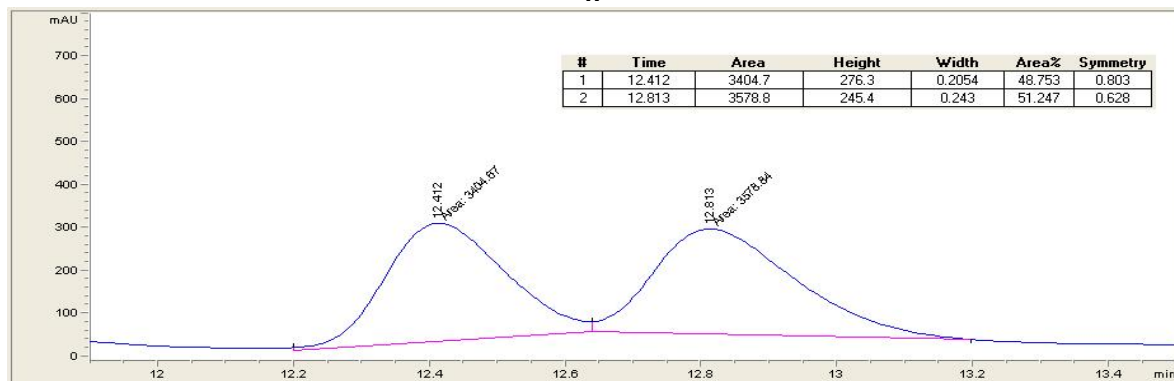
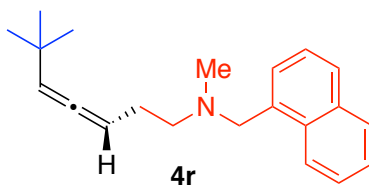
4m



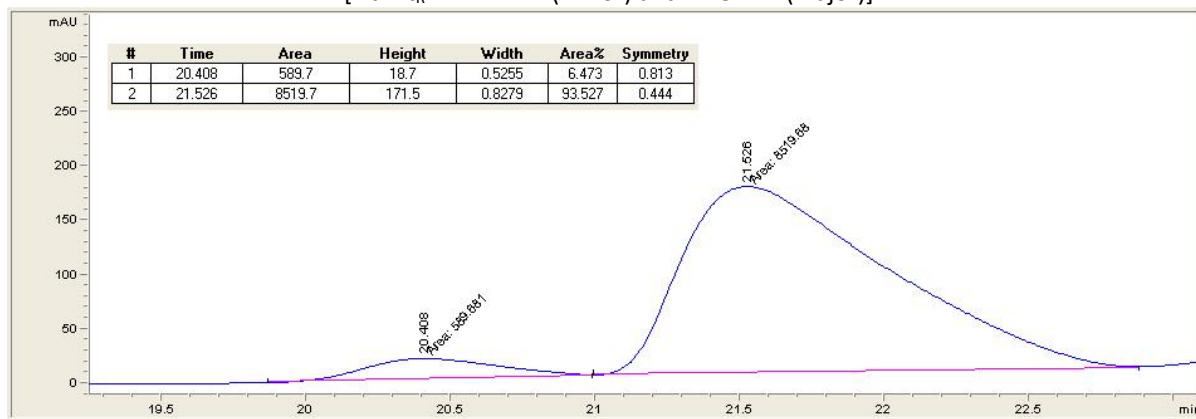
4n

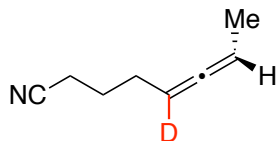




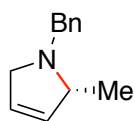
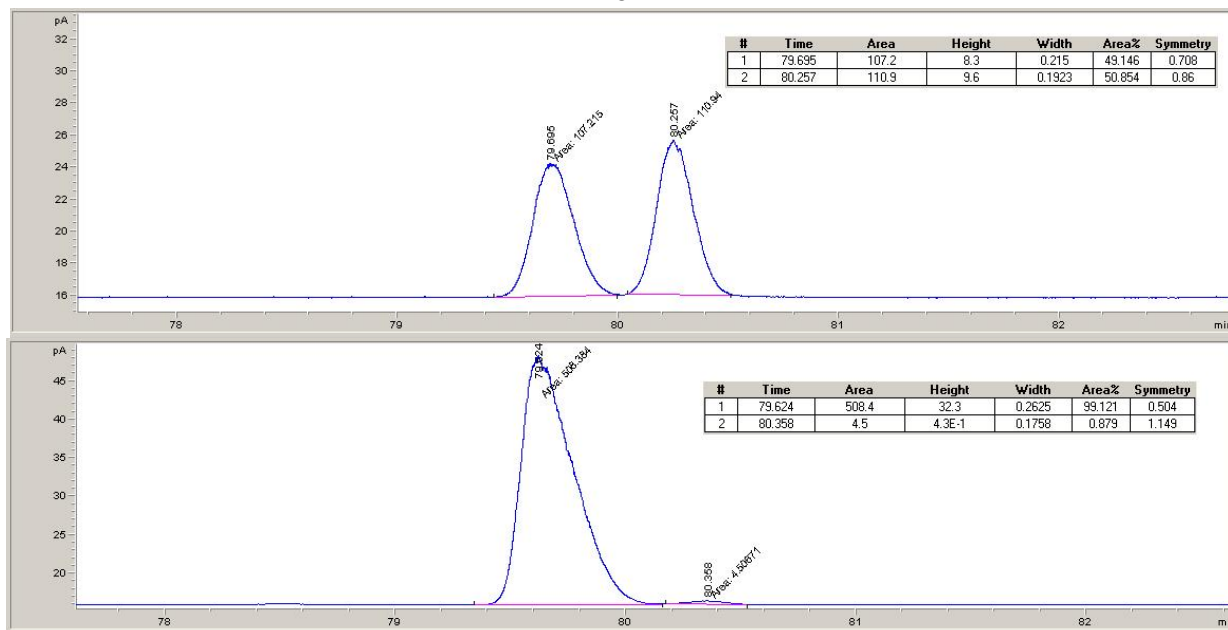


[Lit.¹: t_R = 21.7 min (minor) and 22.8 min (major)]

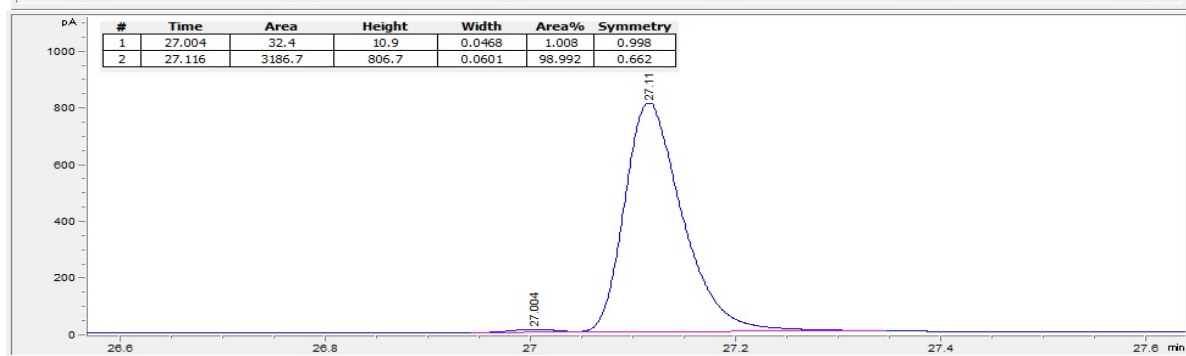
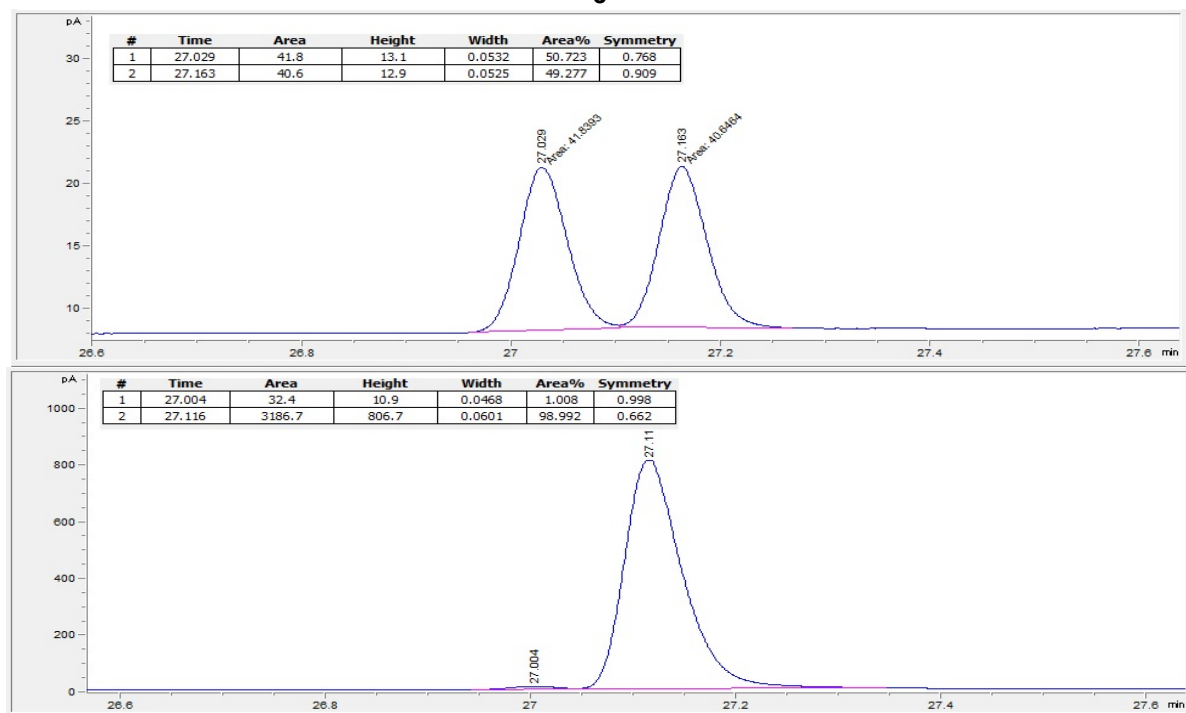


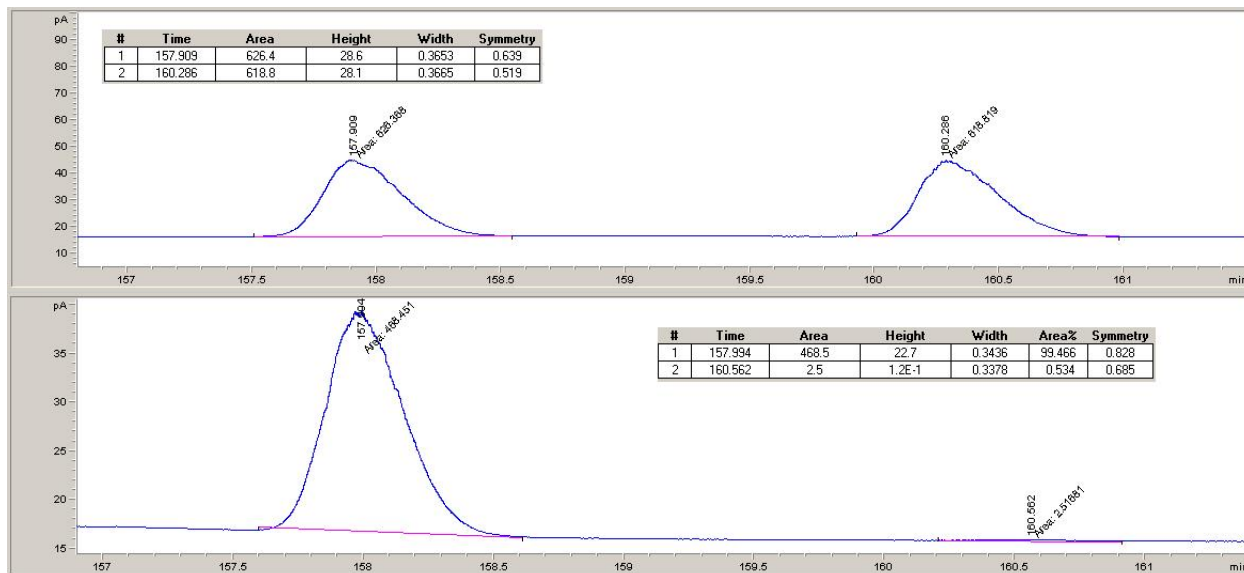
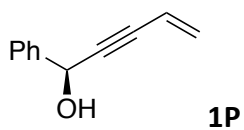


5



6





References:

1. Yu, Q.; Ma, S., An Enantioselective Synthesis of (R)-5,6-Octadecadienoic Acid. *European Journal of Organic Chemistry* **2015**, 2015 (7), 1596-1601.

SFC GC and HPLC Traces.pdf (1.82 MiB)

[view on ChemRxiv](#) • [download file](#)
