Development of Copper(I) Hydride-Catalyzed Asymmetric Olefin Hydrofunctionalization Reactions

by

Sheng Feng

B.S. Material Chemistry
Peking University, 2017

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN CHEMISTRY
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

May 2022

Signature of Author: _____
Department of Chemistry
May 11, 2022

Certified by: _____
Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Accepted by: _____
Adam Willard
Associate Professor
Graduate Officer

This doctoral thesis has been examined by a committee of the
Department of Chemistry as follows:

Professor Timothy F. Jamison: _____
Thesis Committee Chair
Robert R. Taylor Professor of Chemistry

Professor Stephen L. Buchwald: _____
Thesis Supervisor
Camille Dreyfus Professor of Chemistry

Professor Mohammad Movassaghi: _____
Thesis Committee
Professor of Chemistry

Development of Copper(I) Hydride-Catalyzed Asymmetric Olefin Hydrofunctionalization Reactions

by

Sheng Feng

Submitted to the Department of Chemistry
on May 13, 2022 in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy in
Chemistry

ABSTRACT

The work described in this dissertation focuses on developing copper(I) hydride (CuH)-catalyzed enantioselective hydrofunctionalization reactions of olefins. The first chapter highlights a method on CuH-catalyzed asymmetric hydroamination of strained trisubstituted alkenes, including cyclobutenes and cyclopropenes. The second chapter presents an approach for accessing enantioenriched α-quaternary carboxylic acids, through CuH-catalyzed hydrocarboxylation of allenes. The third chapter demonstrates the enantioselective hydrocarbamoylation of alkenes enable by dual CuH and Pd catalysis.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgements

Despite my eagerness to graduate and move on to the next stage of life, a small part of me feel sad about having to leave MIT soon, where there are so many people whom I am blessed to have met.

First of all, I would like to thank Prof. Steve Buchwald. Steve has always been very supportive, both in my research and career development. I am grateful that he has imparted his wisdom to me, but at the same time given me plenty of freedom to explore chemistry on my own. Steve also sets an example for me as a scientist. His firm belief in trying to make our chemistry useful to others, has greatly influenced my perspectives towards research. I also want to thank my thesis committee chair Prof. Tim Jamison and committee member Prof. Mo Movassaghi, for all their valuable inputs and advices on my projects and career development.

I am grateful to my undergraduate supervisor, Prof. Jianbo Wang. He welcomed me into his lab when I was just an ignorant freshman, and later on gave me the opportunity to work on my own projects. In his lab, I was able to pursuit projects out of curiosity, and the welcoming environment there always made me feel at home. I also want to thank my undergraduate mentor, Ying Xia, who guided me into the field of organic chemistry and taught me all the experimental skills.

I would not have survived grad school without the support from my friends in the Buchwald group. I've known Yujing Zhou since I was a freshman in Prof. Jianbo Wang's lab. Although we've had some ups and downs, our friendship was able to last till today. We've been through a lot together and can talk about everything. I know that I can always trust her and that she'd have my back when I need it. I am also grateful to Sheng Guo, who've been like a big brother to me and helped me tremendously both in research and in life. I was lucky to know Yuyang Dong, my desk neighbor for the past year, who is a truly brilliant and efficient chemist. His curiosity and passion about chemistry constantly reminds me of what it should be like to do research. His storytelling and jokes have also brightened my days. I also want to thank Yuxuan Ye, who used to work next to my hood, for helping me become familiar with the field of CuH and get started in the lab when I was new to the group. Further, I really want to thank Alex Schuppe for always being willing to help, especially during my postdoctoral application process and when I was writing my manuscripts.

I want to extend my gratitude to all my labmates, with whom I had the privilege to work over these years. Special thanks to Richard Liu, Veronika Kottisch, and Simon Rössler for helping to edit my manuscripts. Many thanks to Yang Yang, Yik Ki Au, Dennis Kutateladze, Heemal Dhanjee, Megan Greaves, Seoungtae Kim, Mahesh Parsutkar, Mike Strauss, Elaine Reichert, Levi Knippel, Jacob Rodriguez, Azin Saebi, Jessica Xu, Mycah Uehling, Joey Dennis, Scott McCann, Liela Bayeh, Jeff Yang, Frieda Zhang, Mike Gribble, Hojoon Park, Saki Ichikawa, and Anthony Rojas. I'd also like to thank my mentors during my visit to Steve's lab as an undergraduate summer intern, Spencer Shinabery, Tim Senter, and Kashif Khan. I am especially grateful to our lab manager Christine Nguyen for help keeping the lab running and editing my manuscripts. I also want to thank my collaborators at University of Pittsburgh, Prof. Peng Liu

and Dr. Hua Hao. I've gained lots of insights on my project through our computational collaboration.

Outside the lab, I am grateful for my friendship with Wencong Wang. We shared many stories with each other, and being around her always makes me feel relaxed, even when we are not chatting. She genuinely cares about me and has offered me numerous emotional support during my difficult times. My appreciation also goes to my fellow graduate students, Gen Li and Shaoxiong Luo, who supported me throughout grad school. Special thanks to my friends from high school, Fanying Chen, Ho Tat Lam, and Changnan Peng. It was great to be reunited in Boston, and I had a lot of fun hanging out with you guys.

Finally, I want to express my deepest appreciation to my parents. Thank you for your unconditional love, for celebrating my success, and for always being there for me no matter what happened. It gives me a peace of mind when I face all the challenges in my life knowing that you always got my back.

Preface

Parts of this dissertation have been adapted from the following articles co-written by the author.

1. Feng, S.; Hao, H.; Liu, P.; Buchwald, S. L. Diastereo- and Enantioselective CuH-Catalyzed Hydroamination of Strained Trisubstituted Alkenes. *ACS Catal*. **2020**, *10*, 282−291.

Reprinted with permission from the American Chemical Society.

2. Feng, S.; Buchwald, S. L. CuH-Catalyzed Regio- and Enantioselective Hydrocarboxylation of Allenes: Toward Carboxylic Acids with Acyclic Quaternary Centers. *J. Am. Chem. Soc*. **2021**, *143*, 4935−4941.

Reprinted with permission from the American Chemical Society.

3. Feng, S.; Dong, Y.; Buchwald, S. L. Enantioselective CO-Free Hydrocarbamoylation of Alkenes. *Submitted*.

Respective Contributions

This thesis contains work that is the result of collaborative efforts between the author and other colleagues at MIT. The specific contributions of the author are detailed below.

The author performed all the experimental work described in Chapter 1. Dr. Hua Hao and Prof. Peng Liu at University of Pittsburgh conducted the calculations.

The author performed all the experimental work described in Chapter 2.

The author performed all the experimental work described in Chapter 3. Dr. Yuyang Dong carried out the X-ray crystallographic analysis.

Table of Contents

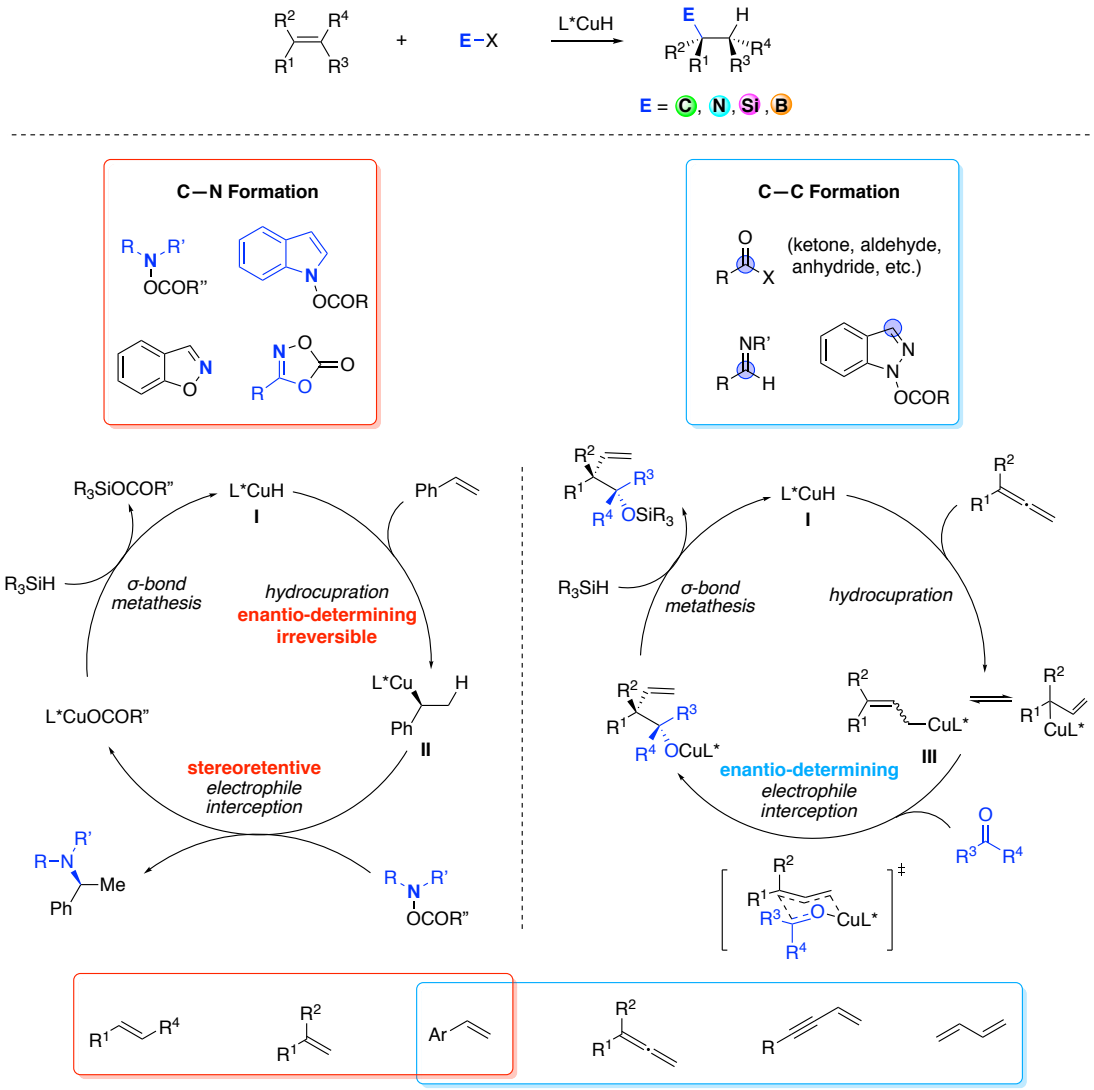
Introduction

The asymmetric hydrofunctionalization of alkenes represents a straightforward synthetic strategy to enable the net addition of H–X (X = e.g., N, C, Si, B, O, S) across the C–C double bond of prochiral olefins.[1] Since the discovery of copper hydride (CuH)-catalyzed hydroamination in 2013, independently, by the Buchwald and Miura groups,[2] L*CuH (**I**) catalysis has been used for the development of a number of methods for the enantioselective hydrofunctionalization of alkenes (Scheme 1).[3] Reaction of **I** with an olefin, results in the production of L*Cu(alkyl) intermediate **II**, which can react with a range of electrophiles ultimately resulting in the formation of new products with the creation of C–C and C–X bonds. In this way, stable and readily available olefins can serve as simple precursors to intermediate **II** that can act as surrogates for traditional alkyl metals, RMX (R = Zn, Mg; X = Br, Cl, I) and participate in a variety of reactions. Additionally, these L*CuH-catalyzed transformations can be rendered enantioselective if a chiral ligand is employed.

One type of L*CuH-catalyzed hydrofunctionalization is hydroamination where **II** engages an electrophilic aminating reagent. Following the initial development of L*CuH-catalyzed asymmetric hydroamination of vinyl arenes to furnish α-chiral tertiary amines,[2] the scope of both the olefinic pronucleophile and the nitrogen-containing electrophile has been greatly expanded. Besides activated olefins such as vinyl arenes,[2] vinyl silanes,[4] and vinyl boronates,[5] unactivated alkenes, including terminal,[2a] 1,1-disubstituted,[6] and internal ones,[7] also served as substrates in the hydroamination chemistry. The successful transformation of unactivated olefins, which have a higher barrier for hydrocupration than e.g., styrene, was made possible by employing a sterically demanding bidentate phosphine ligand (DTBM-SEGPHOS, Scheme 2) that promoted hydrocupration owing to the enhanced attractive ligand-substrate

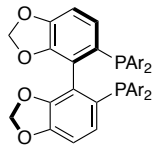
dispersion interaction.[8] By further designing different electrophilic aminating reagents, a broad range of enantioenriched tertiary,[2] secondary,[9] and primary amines,[10] as well as indoles[11] and amides,[12] could be accessed through similar C–N bond-forming hydrofunctionalization approaches. In most cases examined to date, the regio- and enantioselectivity of the hydroamination reaction is dictated by the hydrocupration step.[13]

Scheme 1. Background of CuH-catalyzed asymmetric hydrofunctionalization reactions

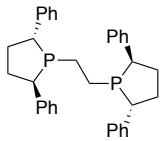


A side reaction in some L*CuH-catalyzed asymmetric hydrofunctionalization reactions is the competitive reduction of the electrophile by **I**.[14] This undesirable process became particularly pronounced during initial attempts to apply the hydrofunctionalization strategy to C–C bond formation via reaction of *in situ*-formed **II** to aldehydes, ketones, or imines. The discovery that Ph-BPE ligated CuH (Scheme 2) resulted in decreased rate of reduction of ketones led to the development of CuH-catalyzed enantio- and diastereoselective addition of enyne-derived nucleophiles to ketones.[15] Other C–C bond forming transformations were subsequently achieved utilizing different electrophiles that contain carbonyl or imine components, such as aldehydes,[16] anhydrides,[17] *in-situ* formed ketene intermediates,[18] CO_2,[19] imines,[20] and pyridines.[21] Hydrocupration of allenes[22] or conjugated olefins such as dienes,[16a,23] and enynes[15] results in the formation of allyl copper-type intermediates (**III**). The subsequent carbonyl addition step usually proceeds via a stereo-determining chair-like transition state comprised of the carbonyl compound and **III** (Scheme 1). Even reactions with certain vinyl arenes have been found to go through such six-membered transition states via a dearomative process.[16b,21] Unlike in the case of hydroamination, unactivated alkenes have not yet been shown to participate in these carbonyl addition processes. Aside from carbonyl addition, enantioselective allylation[24] and intramolecular alkylation of alkenes[25] have also been achieved.

Scheme 2. Commonly employed ligands in CuH-catalyzed hydrofunctionalization reactions



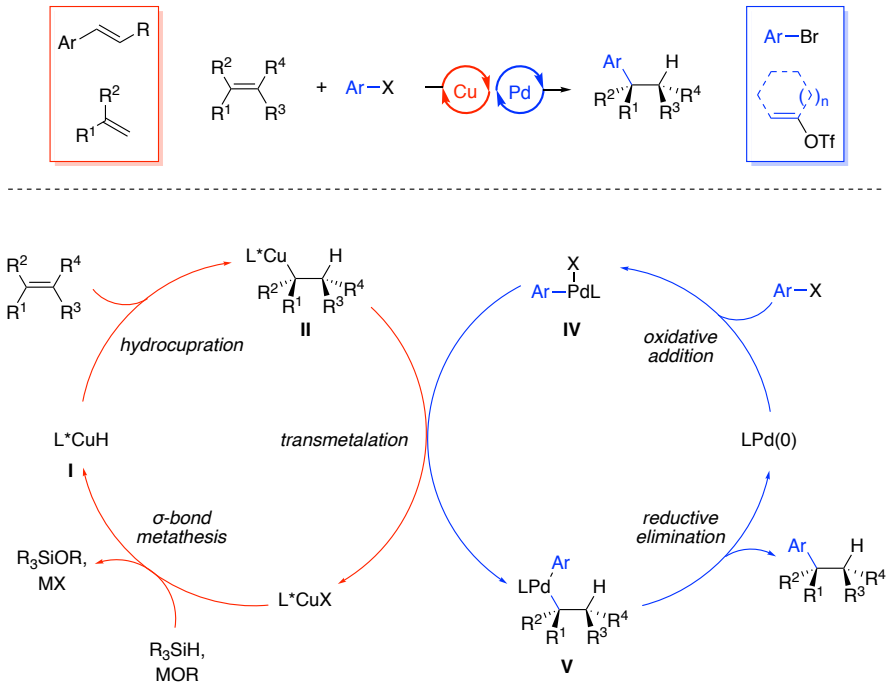
Ar = 3,5-^{t}Bu-4-MeO-C_6H_2
(*R*)-DTBM-SEGPHOS



(*R*,*R*)-Ph-BPE

Besides directly engaging an electrophile, the stereodefined intermediate **II** can also be incorporated into a Pd-catalyzed cross-coupling process (Scheme 3). Specifically, the oxidative addition of ArX with LPd(0) would form the oxidative addition complex **IV**, which then undergoes stereospecific transmetalation with intermediate **II**. The resulting alkyl Pd(II) species **V** undergoes reductive elimination to provide the cross-coupling product. Prototypical cross-coupling partners such as aryl halides and enol sulfonates have been utilized in dual CuH and Pd catalysis to achieve asymmetric hydroarylation[26] and hydrovinylation[27] of alkenes, respectively. Additionally, the Riant group has employed CuH/Pd dual catalytic processes for 1,4-reduction and allylic alkylation of α,β-unsaturated carbonyl compound.[28]

Scheme 3. Asymmetric hydrofunctionalization reactions enabled by dual CuH and Pd catalysis



This dissertation focuses on further developing CuH-catalyzed asymmetric hydrofunctionalization of alkenes. Chapter 1 describes an approach to synthesize

enantioenriched cyclopropenes and cyclobutenes, through hydroamination of the corresponding trisubstituted strained alkenes. Chapter 2 and 3 detail the development of asymmetric hydrocarboxylation and hydrocarbamoylation reactions with the use of readily available carboxylation and carbamoylation reagents, respectively. In chapter 2, a commercially available fluoroformate is employed in the hydrocarboxylation of allenes to provide enantioenriched α-quaternary carboxylic acids. In chapter 3, we leveraged dual CuH/Pd catalysis to achieve the asymmetric hydrocarbamoylation of alkenes using carbamoyl chlorides.

References

(1) (a) Chen, J.; Lu, Z. *Org. Chem. Front*. **2018**, *5*, 260−272. (b) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev*. **2016**, *116*, 8912−9000. (c) Coombs, J. R.; Morken, J. P. *Angew. Chem., Int. Ed*. **2016**, *55*, 2636−2649. (d) Blieck, R.; Taillefer, M.; Monnier, F. *Chem. Rev*. **2020**, *120*, 13545−13598. e) Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev*. **2018**, *118*, 6026−6052. f) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, aah5133.

(2) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc*. **2013**, *135*, 15746−15749. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, Masahiro. *Angew. Chem., Int. Ed*. **2013**, *52*, 10830−10834.

(3) (a) Liu, R. Y.; Buchwald, S. L. *Acc. Chem. Res*. **2020**, *53*, 1229−1243. (b) Pirnot, M. T.; Wang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 48−57.

(4) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2015**, *54*, 1638−1641.

(5) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc*. **2015**, *137*, 15620−15623.

(6) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2014**, *136*, 15913−15916.

(7) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62−66.

(8) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc*. **2017**, *139*, 16548−16555.

(9) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 9716−9721.

(10) Guo, S.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 15976−15984.

(11) Ye, Y.; Kim, S.; Jeong, J.; Baik, M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 3901−3909.

(12) Zhou, Y.; Engl, O. D.; Bandar, J. S.; Chant, E. D.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2018**, *57*, 6672−6675.

(13) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 14812−14818.

(14) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc*. **2003**, *125*, 8779−8789.

(15) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144–150.

(16) (a) Li, C.; Shin, K.; Liu, R. Y.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2019**, *58*, 17074−17080. (b) Dong, Y.; Schuppe, A. W.; Mai, B. K.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2022**, *144*, 5985−5995.

(17) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 5821−5824.

(18) (a) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2017**, *139*, 8126−8129. (b) Link, A.; Zhou, Y.; Buchwald, S. L. *Org. Lett*. **2020**, *22*, 5666−5670.

(19) (a) Gui, Y.; Hu, N.; Chen, X.; Liao, L.; Ju, T.; Ye, J.; Zhang, Z.; Li, J.; Yu, D. *J. Am. Chem. Soc*. **2017**, *139*, 17011−17014. (b) Chen, X.; Zhu, L.; Gui, Y.; Jing, K.; Jiang, Y.; Bo, Z.; Lan, Y.; Li, J.; Yu, D. *J. Am. Chem. Soc*. **2019**, *141*, 18825−18835. (c) Qiu, J.; Gao, S.; Li, C.; Zhang, L.; Wang, Z.; Wang, X.; Ding, K. *Chem. Eur. J*. **2019**, *25*, 13874−13878. (d) Wang, M.; Jin, X.;

Wang, X.; Xia, S.; Wang, Y.; Huang, S.; Li, Y.; He, L.; Ma, X. *Angew. Chem., Int. Ed.* **2021**, *60*, 3984−3988.

(20) (a) Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 4666−4669. (b) Yang, Y. Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 9787−9790. (c) Liu, R. Y.; Yang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 14077−14080. (d) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc*. **2018**, *140*, 7083−7087. (e) Zhou, P.; Shao, X.; Malcolmson, S. J. *J. Am. Chem. Soc*. **2021**, *143*, 13999−14008.

(21) Gribble, M. W.; Guo, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 5057−5060.

(22) (a) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 2007−2011. (b) Liu, R. Y.; Zhou, Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 2251−2256. (c) Ye, Y.; Kevlishvili, I.; Feng, S.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2020**, *142*, 10550−10556.

(23) (a) Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 5062−5070. (b) Knippel, J. L.; Ye, Y.; Buchwald, S. L. *Org. Lett.* **2021**, *23*, 2153−2157.

(24) (a) Wang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 5024−5027. (b) Sommer, H.; Marek, I. *Chem. Sci*. **2018**, *9*, 6503−6508. (c) Xu-Xu, Q.; Zhang, X.; You, S. *Org. Lett.* **2020**, *22*, 1530−1534.

(25) Wang, Y.; Bruno, N. C.; Placeres, Á. L.; Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 10524−10527.

(26) (a) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 6275−6279. (b) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 8372−8375. (c) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L.

Angew. Chem. Int. Ed. **2017**, *56*, 7242−7246. (d) Schuppe, A. W.; Borrajo-Calleja, G. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 18668−18672. (e) Lu, Z.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2020**, *59*, 16128−16132.

(27) (a) Schuppe, A. W.; Knippel, J. L.; Borrajo-Calleja, G. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2021**, *143*, 5330−5335. (b) Hou, C.; Schuppe, A. W.; Knippel, J. L.; Ni, A. Z.; Buchwald, S. L. *Org. Lett.* **2021**, *23*, 8816−8821.

(28) (a) Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem. Int. Ed*. **2013**, *52*, 3208−3212. (b) Nahra, F.; Macé, Y.; Boreux, A.; Billard, F.; Riant, O. *Chem. Eur. J*. **2014**, *20*, 10970−10981.

Chapter 1. Diastereo- and Enantioselective CuH-Catalyzed Hydroamination of Strained Trisubstituted Alkenes

1.1 Introduction

Cyclobutylamine and cyclopropylamine substructures are found in a variety of bioactive molecules and pharmaceutical compounds (Figure 1a).[1] Moreover, the stereoisomers of these compounds can exhibit remarkable differences in bioactivity.[2] Thus, considerable effort has been expended to developing methods for the stereoselective construction of these structural units. Currently, most synthetic approaches to enantioenriched cyclobutylamines are based on [2+2] cycloadditions[3] and the Amadori−Heyns rearrangement.[4] Among these methods, few are catalytic and effective in an intermolecular context.[3f–h,4] In contrast, for the catalytic, enantioselective synthesis of cyclopropylamines, a number of elegant methods have been developed.[5] The most well-known processes include intramolecular C−H activation of prochiral aminocyclopropanes,[6] cyclopropanation of vinylcarbamates,[7] carboamination of cyclopropenes,[8] and rare-earth-metal-catalyzed hydroamination of cyclopropenes.[9] Despite these advances, the development of a unified synthetic strategy that allows for the stereoselective formation of multiple types of polysubstituted cyclobutyl- and cyclopropylamines would be desirable. We proposed that a general, enantioselective hydroamination of cyclic alkenes could address this challenge.

Our group and others have reported copper-hydride(CuH)-catalyzed enantioselective hydrofunctionalization reactions of various unsaturated substrates.[10,11] In particular, CuH-catalyzed hydroamination has been applied on a broad range of olefins,[12] such as styrene derivatives,[12a-e] 1,1-disubstituted alkenes,[12d-f] and unactivated *trans*-1,2-disubstituted alkenes[12g]. These reactions proceed through enantioselective hydrocupration of the alkene to form a chiral alkylcopper species, which is then trapped by an electrophile such as a hydroxylamine ester.[13] We postulated that the CuH-catalyzed stereoselective hydroamination of 1-substituted

cyclobutenes and cyclopropenes could potentially furnish cyclobutyl- and cyclopropylamines bearing various types of substituents and with adjacent stereocenters (Figure 1b).

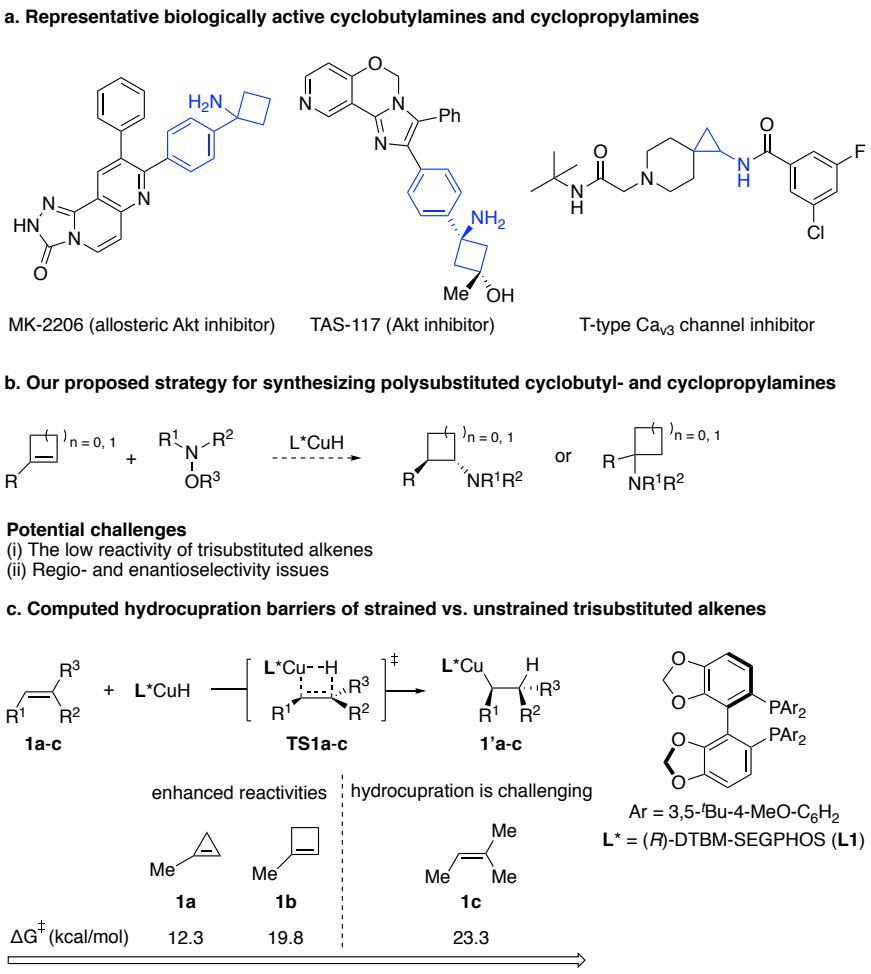


Figure 1. Proposed CuH-catalyzed hydroamination of 1-substituted cyclobutenes and cyclopropenes. (a) Representative biologically active cyclobutylamines and cyclopropylamines. (b) Proposed catalytic strategy. (c) DFT-computed activation barriers of the hydrocupration of **1a-1c**. Geometries were optimized at the B3LYP/SDD−6-31G(d) level of theory. Single point energies were calculated at the M06/SDD−6-311+G(d,p)/SMD(THF) level.

Despite the generality and broad utility of published CuH-catalyzed approaches, a common obstacle has been the unwanted CuH-catalyzed reduction of the electrophile, a side reaction that depletes the electrophilic reagent.[11b,12c,14] For unactivated substrates with high barriers for reaction with CuH (hydrocupration), the reduction of the electrophile is a significant side reaction, resulting in greatly diminished yields or even no product formation. For instance, CuH-catalyzed hydrofunctionalization of unactivated trisubstituted alkenes has been extremely challenging in general. However, the hydroamination of certain activated trisubstituted alkenes such as allylic alcohol derivatives[12a,15] and β,β-disubstituted styrenes[12a] have been achieved. Activation of olefins through ring strain is a strategy that has long been utilized by organic chemists to achieve new strain-enabled reactivities.[16] Thus, we wondered whether the partial release of the ring strain energy of 1-substituted cyclobutenes and cyclopropenes in the hydrocupration step would help lower their hydrocupration barriers, and thereby allow the hydroamination of these strained trisubstituted alkenes to proceed faster than competing reduction of the electrophile.

At the outset, it was unclear to us whether these strained trisubstituted alkenes[17] would be reactive enough to undergo CuH-catalyzed hydroamination reactions. Thus, we performed DFT calculations on the hydrocupration barriers of strained and unstrained trisubstituted alkenes (Figure 1c). The DTBM-SEGPHOS(**L1**)-based CuH catalyst system has been shown to exhibit high levels of enantioselectivity as well as enhanced reactivity in hydroamination reactions[12,18] and was therefore chosen in our calculations. Our results indicated that the hydrocupration barriers of 1-methylcyclobutene (**1b**) and 1-methylcyclopropene (**1a**) are 3.5 and 11.0 kcal/mol lower, respectively, than that of the acyclic trisubstituted olefin 2-methylbut-2-ene (**1c**). Based

on these promising results, we proceeded to experimentally investigate the CuH-catalyzed hydroamination of 1-substituted cyclobutenes and cyclopropenes.

1.2 Results and Discussion

1.2.1 Hydroamination of 1-Substituted Cyclobutenes

We initiated our study by examining the CuH-catalyzed hydroamination reaction of 1,3-diphenyl-3-methylcyclobut-1-ene (**2a**) using Bn_2NOBz (**3a**). In previous CuH-catalyzed hydroamination reactions, simple styrene derivatives were generally converted selectively to the Markovnikov isomers of products[12a-b] (Figure 2a). However, when α-methyl-styrene[12f] was employed, the anti-Markovnikov isomer was instead favored by a 7:1 ratio (Figure 2b), indicating that tertiary alkyl copper species are perhaps hard to form by hydrocupration or react slowly with the electrophile. In contrast to this observation, we found that, using $Cu(OAc)_2$ as the precatalyst and DTBM-SEGPHOS (**L1**) as the ligand, the reaction of phenylcyclobutene (**2a**) with Bn_2NOBz (**3a**) afforded the Markovnikov product exclusively in 85% yield (Figure 2c). The reaction not only generated a fully substituted carbon center on the cyclobutane ring, but also formed the 1,1,3,3-tetrasubstituted aminocyclobutane product with a 13:1 *cis*/*trans* ratio. 3-Substituted 1-arylcyclobutylamine subunits, though found in a number of interesting molecules,[1b,19] have been difficult to prepare through the diastereoselective installation of 3-substituents,[20] and highly stereoselective approaches to directly access these structures are rare.[21] Our CuH-catalyzed hydroamination approach on 3,3-disubstituted 1-arylcyclobutenes can provide a method to rapidly construct a diverse range of 3,3-disubstituted 1-aryl-1-aminocyclobutanes in good stereoselectivities.

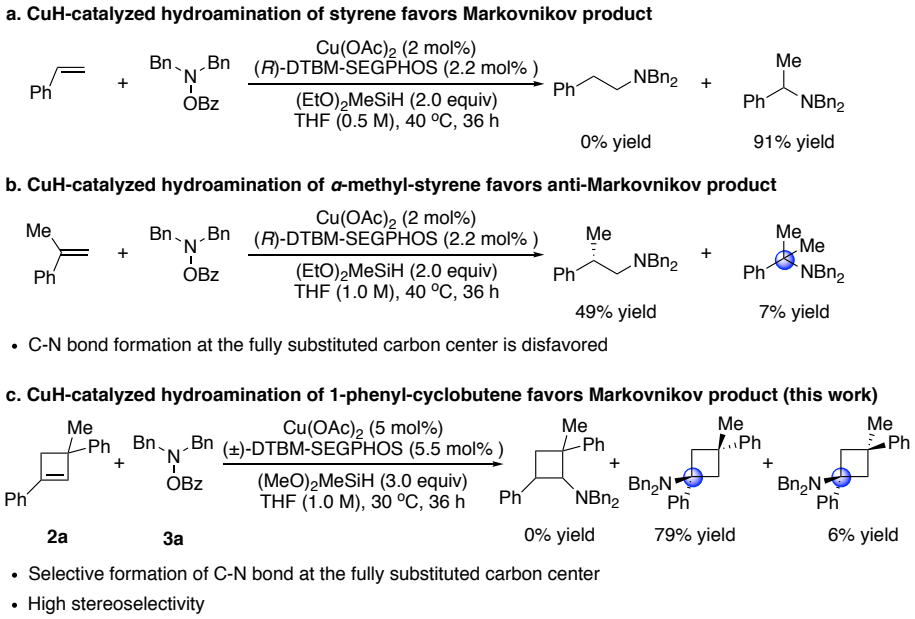
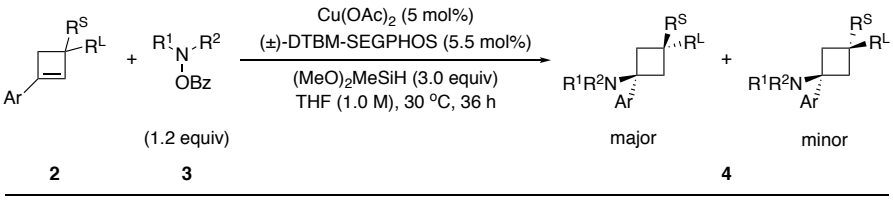


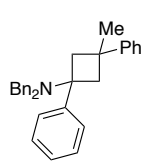
Figure 2. Regioselectivity of the CuH-catalyzed hydroamination using different phenyl-substituted alkenes.

After identifying the optimal reaction conditions (shown in Figure 2c),[22] we investigated the substrate scope for the hydroamination of 1-arylcyclobutenes (Table 1). In all cases, the Markovnikov products were formed exclusively. We found that 1-arylcyclobutenes bearing *para*- (**4b**, **4h**), *meta*- (**4c**), and *ortho*- (**4d**) substituents were all suitable for the hydroamination reaction. An electron-withdrawing group on the arene (**4c**) greatly improved the stereoselectivity of the reaction, while electron-donating substituent (**4b**) led to a slightly diminished yield and diastereomer ratio. A 1-pyridyl cyclobutene was also well tolerated (**4e**). Moreover, arylcyclobutenes without any substituents at the 3-position were also able to undergo the hydroamination reaction to selectively form the Markovnikov products (**4d**, **4e**) in good yields, suggesting that the regioselectivity was not a result of the steric repulsion from the 3-

substituents. A 1-phenylcyclobutene with a spiro-fused cyclohexyl group at the 3-position also reacted efficiently (**4f**).

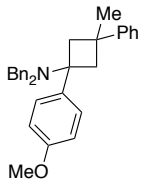
Table 1. Substrate Scope for the CuH-Catalyzed Hydroamination of 1-Arylcyclobutenes[a]





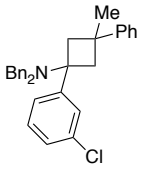
4a

85% yield, 13:1[b]



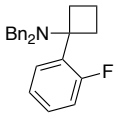
4b

65% yield, 5:1[b]



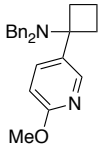
4c

79% yield, 29:1[b]



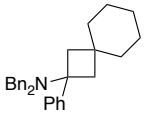
4d

71% yield[c, d]



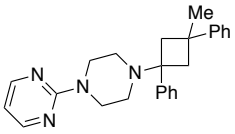
4e

75% yield [c, d]



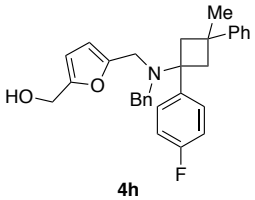
4f

90% yield[d]



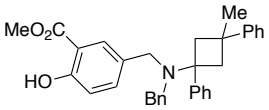
4g

66% yield, 13:1[b]



4h

78% yield, 11:1[b, e]



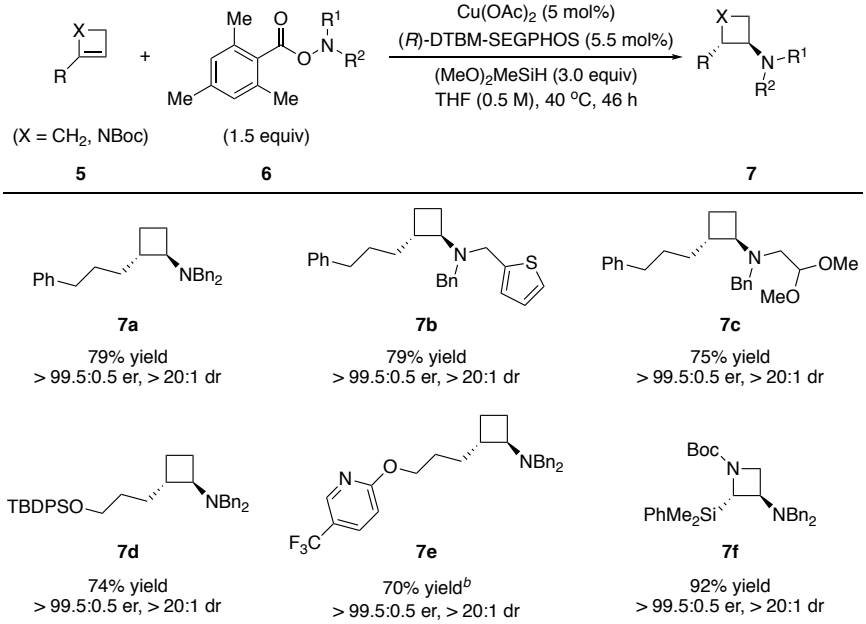
4i

77% yield, 13:1[b, e]

[a]Isolated yields on 0.5 mmol scale (average of two runs). [b]Ratio refers to the ratio of major and minor stereoisomers. [c]Reaction was carried out with 1.2 equiv of Bn_2NOPiv, THF (0.5 M) at 40 °C. [d]Reaction was carried out with (*R*)-DTBM-SEGPHOS instead. [e]4 equiv of $(MeO)_2MeSiH$ was used.

We next evaluated a range of hydroxylamine esters in this reaction. It was found that a number of functional groups such as an alcohol (**4h**), an ester (**4i**), and a phenol (**4i**) were tolerated under the hydroamination reaction conditions. Moreover, heterocycles such as pyrimidine (**4g**) and furan (**4h**) were shown to be compatible in the reaction.

Table 2. Substrate Scope for the CuH-Catalyzed Hydroamination of 1-Alkylcyclobutenes[a]



[a]Isolated yields on 0.5 mmol scale (average of two runs). [b]Reaction was carried out with 1.2 equiv of $Bn_2NOC(O)Mes$.

We also examined the hydroamination of 1-alkylcyclobutenes, which lack the activating influence of an aryl substituent on the alkene. We chose (3-(cyclobut-1-en-1-yl)propyl)benzene (**5a**) as our model substrate, for which a series of amination reagents were evaluated.[22] We found that the use of the mesitoyl hydroxylamine ester **6a** gave the highest yield. Under the optimal reaction conditions, hydroamination of **5a** provided the 1,2-disubstituted aminocyclobutane

product **7a** in 79% yield with >99.5:0.5 er and >20:1 dr (Table 2). That the regioselectivity is totally opposite of that observed with the aryl-substituted cyclobutene substrates is consistent with what we observed in, e.g., a comparison of the hydroamination of styrene and 1-dodecene.[12a]

A range of functional groups and heterocycles were found to be compatible with the reaction conditions (Table 2). For example, amination reagents containing a thiophene (**7b**) and an acetal (**7c**) as well as 1-alkylcyclobutenes bearing a silyl ether (**7d**) and a pyridine (**7e**) were all suitable coupling partners in this hydroamination reaction, each providing the corresponding product in good yield with >99.5:0.5 er and >20:1 dr (Table 2).

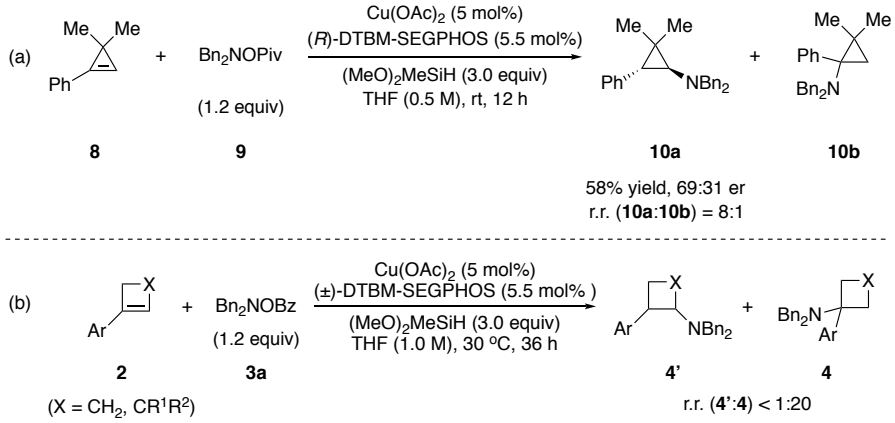
To demonstrate that our hydroamination method is also applicable to 1-silyl substituted four-membered cycloalkenes, we carried out the hydroamination reaction of 1-silyl-4-azacyclobutene (**5d**) with the amination reagent (**6a**), which resulted in the formation of an aminoazetidine product (**7f**) in excellent yield, enantio- and diastereoselectivity (Table 2).

1.2.2 Hydroamination of 1-Substituted Cyclopropenes

We were also interested in applying the hydroamination chemistry to other strained trisubstituted olefins, and thus we turned our attention to the hydroamination of 1-substituted cyclopropenes. While exploring different types of cyclopropenes, we had two interesting observations regarding the selectivity of these reactions. First, in contrast to the regioselectivity observed with 1-arylcyclobutenes (**2**) (Scheme 1b), the formation of the anti-Markovnikov hydroamination product was found to be preferred when using 1-phenylcyclopropene derivative **8** as the substrate (Scheme 1a). Second, while the hydroamination of 1-alkylcyclobutenes were able to proceed with excellent enantioselectivity (Scheme 2b), the reaction with 1-

alkylcyclopropene **11** provided the hydroamination product **12** with only 55.5:44.5 er (Scheme 2a).

Scheme 1. Comparison of the regioselectivity in CuH-catalyzed hydroamination of 1-phenylcyclopropene and 1-arylcyclobutenes



Scheme 2. Comparison of the enantioselectivity in the CuH-catalyzed hydroamination of 1-alkylcyclopropene and 1-alkylcyclobutene

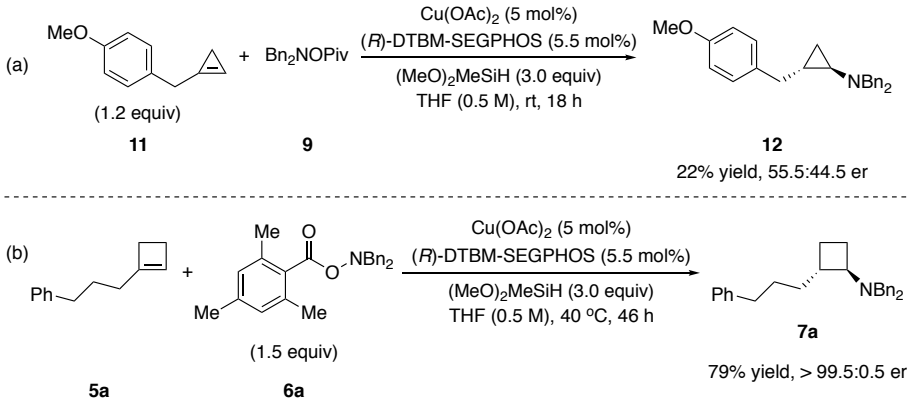
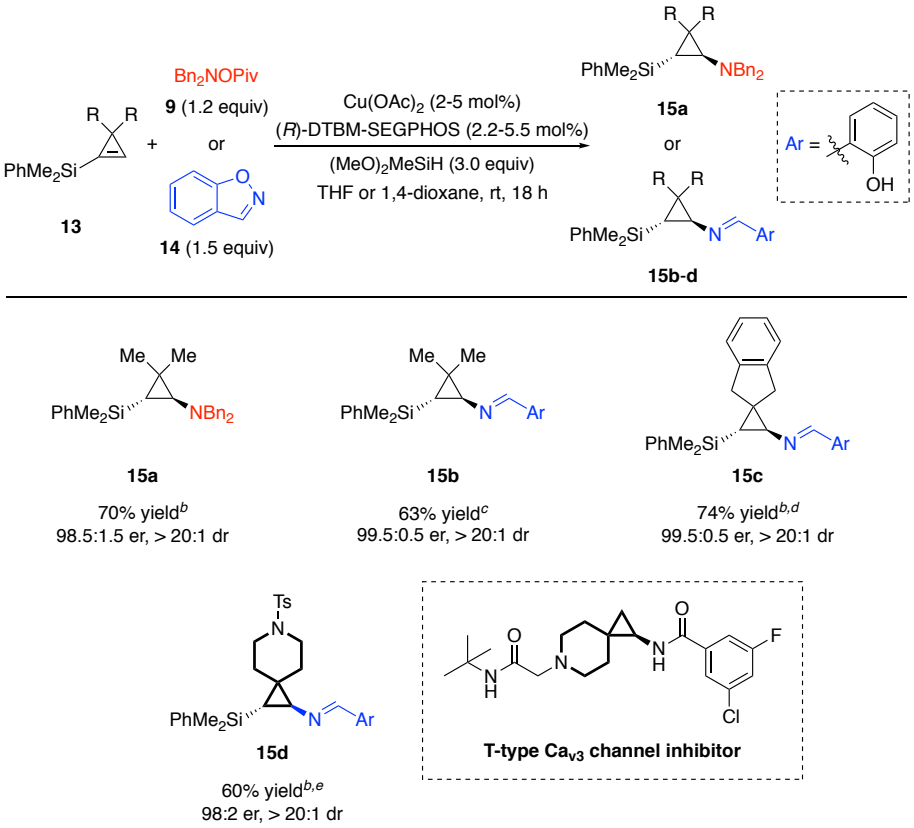


Table 3. Substrate Scope for the CuH-Catalyzed Hydroamination of 1-Silylcyclopropenes[a]



[a]Isolated yields on 0.5 mmol scale (average of two runs). [b]$Cu(OAc)_2$ (5 mol%), (*R*)-DTBM-SEGPHOS (5.5 mol%), 1,4-dioxane (0.5 M). [c]$Cu(OAc)_2$ (2 mol%), (*R*)-DTBM-SEGPHOS (2.2 mol%), THF (1.0 M). [d]**14** was added *via* syringe pump over 2 h. [e]**14** was added *via* syringe pump over 2.5 h.

We reasoned that installation of a bulky group at the 1-position of the cyclopropene may help restore the enantioselectivity due to increased ligand-substrate repulsion in the disfavored hydrocupration transition state. Thus we investigated the hydroamination of 1-silyl cyclopropenes. First, we examined the hydroamination reaction with 1-silyl-3,3-dimethylcyclopropene (**13a**) and Bn_2NOPiv (**9**) (Table 3), finding that the reaction proceeded smoothly to give the 1,2-disubstituted aminocyclopropane product (**15a**) in 70% yield, with

98.5:1.5 er and >20:1 dr. As previously shown by our DFT calculations, cyclopropenes hydrocuprate much faster than cyclobutenes. As a result, we discovered that 1-silylcyclopropene (**13a**) was even able to react with 1,2-benzisoxazole (**14**), an electrophile that is highly susceptible to competing Kemp elimination in the presence of CuH and therefore couples only with the most activated olefins.[12e,30] The protected primary amine product **15b** was obtained in 63% yield with excellent enantio- and diastereoselectivity. Moreover, 1-silylcyclopropenes bearing 3-spirocycloalkyl substituents were also capable of reacting with 1,2-benzisoxazole (**14**) to give the corresponding hydroamination products (**15c**, **15d**) in moderate or good yields and with high stereoselectivities. The latter is related to a key intermediate for the synthesis of a T-type Ca_{V3} channel inhibitor (Table 3).[1e]

1.3 Computational Studies

Our experimental results not only demonstrated the generality of the CuH-catalyzed hydroamination of cyclopropenes and cyclobutenes, but also led to several interesting mechanistic questions regarding reactivity and selectivity. First, what is the origin of the enhanced reactivities of 1-substituted cyclobutenes and cyclopropenes as compared to acyclic trisubstituted alkenes? Second, why do the hydroamination reactions with 1-phenylcyclobutene (**2a**) and 1-phenylcyclopropene (**8**) form opposite regioisomers? Lastly, why is the hydroamination with 1-alkylcyclobutene (**5a**) highly enantioselective, while the reaction with 1-alkylcyclopropene (**11**) occurs with low enantioselectivity? To address these questions, we performed density-functional theory (DFT) calculations to reveal factors that control reactivity, regio-, and enantioselectivity in the CuH-catalyzed hydroamination of strained cyclic alkenes. We surmised that the angular strain,[23] the ease to distort the alkenyl carbon to a pyramidalized

transition state geometry,[24] and the diminished steric repulsions with the DTBM-SEGPHOS ligand may all affect the reactivity and selectivity of cyclopropenes and cyclobutenes. Therefore, we employed the distortion/interaction model[25] to analyze the effects of catalyst/substrate distortion and the interaction energies between the CuH catalyst and the alkene in the hydrocupration transition state.

1.3.1 Computational Details

Geometries were optimized in the gas phase using the B3LYP[26] functional and a mixed basis set of SDD for Cu and 6-31G(d) for other atoms. Single point energies were calculated with the M06[27] functional and a mixed basis set of SDD for Cu and 6-311+G(d,p) for other atoms. Solvation energy corrections were considered in tetrahydrofuran (THF) solvent using the SMD[28] solvation model. All geometry optimizations and single-point energy calculations were performed using Gaussian 09.[29]

A modified version[18] of the distortion/interaction model (or activation strain model),[25] namely the ligand-substrate interaction model, was employed to decompose the activation energy ($\Delta E^{\ddagger}$) using Eq. 1.

$$\Delta E^{\ddagger} = \Delta E_{\text{sub-dist}} + \Delta E_{\text{cat-dist}} + \Delta E_{\text{int-space}} + \Delta E_{\text{int-bond}} \qquad \text{(Eq. 1)}$$

where $\Delta E^{\ddagger}$ is the gas-phase electronic energy of the hydrocupration transition state with respect to the separated alkene substrate and the L*CuH catalyst; $\Delta E_{\text{sub-dist}}$ and $\Delta E_{\text{cat-dist}}$ are the energies to distort the alkene substrate and the catalyst into the transition state geometries, respectively; $\Delta E_{\text{int-space}}$ is the through-space interaction energy between the (*R*)-DTBM-SEGPHOS ligand and the substrate calculated from the interaction energy of a supramolecular complex of the ligand and the substrate at the transition state geometry in the absence of the CuH moiety; $\Delta E_{\text{int-bond}}$ is

the through-bond interaction energy between the catalyst and the substrate calculated from $\Delta E_{\text{int-bond}} = \Delta E^{\ddagger} - \Delta E_{\text{sub-dist}} - \Delta E_{\text{cat-dist}} - \Delta E_{\text{int-space}}$. The overall distortion energy of the catalyst and the substrate (ΔE_{dist}) is calculated from $\Delta E_{\text{dist}} = \Delta E_{\text{sub-dist}} + \Delta E_{\text{cat-dist}}$.

1.3.2 Origin of the Enhanced Reactivity of Strained Trisubstituted Alkenes

We performed the ligand-substrate interaction model analysis to investigate the origin of the enhanced reactivities of 1-methylcyclopropene (**1a**) and 1-methylcyclobutene (**1b**) in the hydrocupration as compared to the acyclic trisubstituted alkene, 2-methylbut-2-ene (**1c**) (Figure 3). Using this approach, the computed activation energy ($\Delta E^{\ddagger}$) is dissected to distortion energies of the substrate and the catalyst ($\Delta E_{\text{sub-dist}}$ and $\Delta E_{\text{cat-dist}}$), and the through-space and through-bond interaction energies between the L*CuH catalyst and the substrate ($\Delta E_{\text{int-space}}$ and $\Delta E_{\text{int-bond}}$) (Figure 3b). Among the four different energy components, the main factor that promotes the hydrocupration of 1-methylcyclopropene (**1a**) is the highly favorable through-bond interaction energy ($\Delta E_{\text{int-bond}} = -33.9$ kcal/mol). The strong catalyst-substrate interaction in **TS-1a** is due to the prominent pyramidalization of both sp^2 carbons of **1a** as evidenced by the out-of-plane dihedral angles of the C1-Me and C2-H groups (α_{Me} and α_{H}, Figure 3a). Frontier molecular orbital (FMO) theory analysis indicates the pyramidalization of 1-methylcyclopropene decreases its LUMO energy, and thus promotes the FMO interactions between the alkene π^* orbital and the HOMO of CuH ($\sigma_{\text{Cu-H}}$, see section 1.5 for details). Interestingly, although the pyramidalization of **1a** in **TS-1a** is much more significant than that of **1b** and **1c** in **TS-1b** and **TS-1c**, the energies to distort these substrates are comparable ($\Delta E_{\text{sub-dist}}$ = 22.4, 22.2, and 23.0 kcal/mol, respectively). This observation is consistent with previous reports that indicated easier distortion of cyclopropene as compared to cyclobutene and acyclic alkenes.[24] Because the sp^2 carbons of

cyclopropene have significant angular strain,[23] pyramidalization of cyclopropene is promoted by strain release. The propensity of out-of-plane distortion of 1-methylcyclopropene **1a** is further demonstrated in Figure 3c, where the distortion energies of three alkenes (**1a**, **1b**, and **1c**) are plotted against the out-of-plane dihedral angle of the alkenyl Me and H groups. In the transition state region (α = 120~140°), 1-methylcyclopropene (**1a**) requires much smaller distortion energy than 1-methylcyclobutene (**1b**) and 2-methylbut-2-ene (**1c**). The ligand-substrate interaction model analysis also revealed the impact of catalyst distortion energy ($\Delta E_{\text{cat-dist}}$) on the reactivity. **TS-1a** and **TS-1b** both have smaller catalyst distortion energies than **TS-1c**. This indicates the smaller sizes of the strained cyclic alkenes as compared to 2-methylbut-2-ene (**1c**) also contribute to the reactivities of these substrates through decreasing steric repulsions with the L*CuH catalyst.

Taken together, the above analysis indicates the greater reactivities of 1-methylcyclopropene (**1a**) and 1-methylcyclobutene (**1b**) in hydrocupration are due to the combination of two effects. First, the ease to distortion of strained cyclic alkenes leads to greater pyramidalization of the alkenyl carbons in 1-methylcyclopropene, which in turn promotes the bonding interactions with the CuH catalyst. Second, the smaller sizes of cyclopropene and cyclobutene than the acyclic analogues decrease the catalyst-substrate steric repulsions in the hydrocupration transition state.

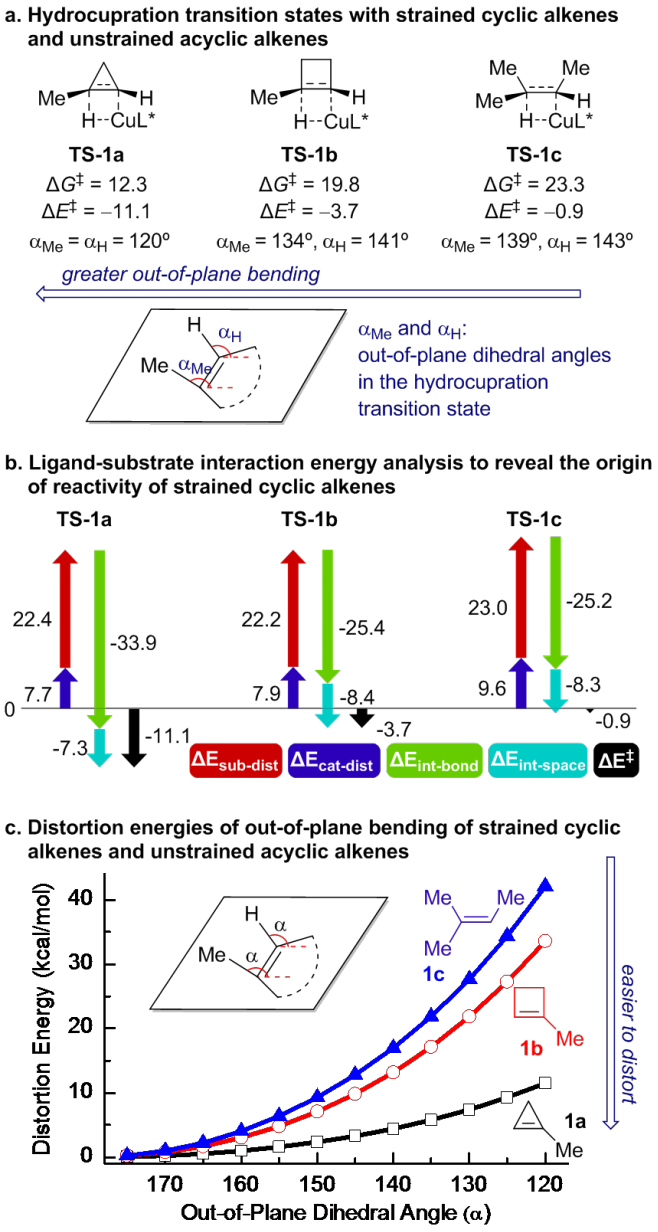


Figure 3. Origin of enhanced hydrocupration reactivity of strained cyclic alkenes **1a** and **1b**. All energies are in kcal/mol.

1.3.3 Origin of the Regioselectivity Reversal in the Hydroamination Reactions with 1-Phenylcyclobutene and 1-Phenylcyclopropene Derivatives

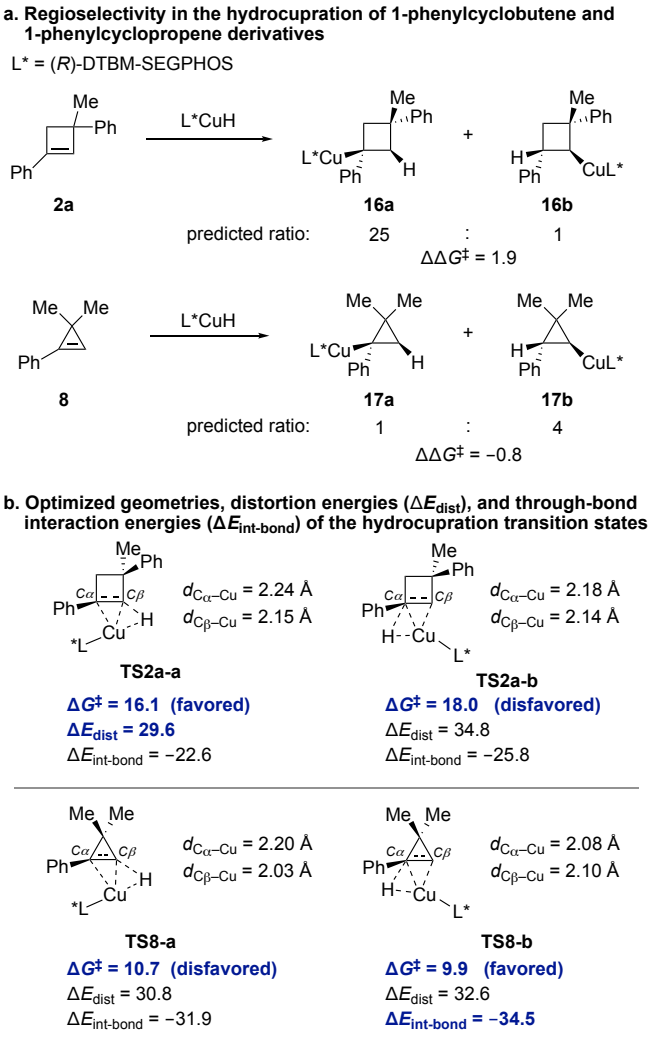


Figure 4. Origin of the reversed regioselectivities of the hydroamination of 1-phenylcyclobutene derivative (**2a**) and 1-phenylcyclopropene derivative (**5**). All energies are in kcal/mol.

Next, we computed the regioisomeric hydrocupration transition states with 1-phenylcyclobutene and 1-phenylcyclopropene derivatives 2a and 8 (Figure 4). These substrates were chosen in the computational study because their hydroamination reactions lead to opposite regioisomers (Table 1 and Scheme 1). Our DFT calculations indicated that the hydrocupration of 2a favors the formation of the tertiary benzylic copper intermediate 16a by 1.9 kcal/mol. By contrast, in the reaction with 8, hydrocupration to form the secondary alkylcopper intermediate

17b is favored by 0.8 kcal/mol. These computed regioselectivities of hydrocupration are consistent with the experimentally observed hydroamination regioselectivities with these substrates. Although we have not yet computationally confirmed the regioselectivity-determining step in the catalytic cycle, the exergonicity of the hydrocupration of strained cyclic alkenes 2a and 8 (−13.9 and −29.5 kcal/mol, respectively, see section 1.5 for details) suggests that the hydrocupration is most likely irreversible and thus regioselectivity-determining.

The origin of the regioselectivity reversal was analyzed using the ligand-substrate interaction model, as shown in Figure 4b. In the hydrocupration of 1-phenylcyclopropene derivative **8**, regioisomer **TS8-b** is more favorable because of the strongly stabilizing through-bond interactions between the L*CuH catalyst and the substrate ($\Delta E_{\text{int-bond}}$ = −34.5 kcal/mol). At first glance, these results are counterintuitive because **TS8-b** forms a secondary alkyl-copper bond which is expected to be less electronically favorable than the formation of the benzylic copper bond via **TS8-a**. Closer examination of the four-membered cyclic hydrocupration transition states (**TS8-a** and **TS8-b**) revealed an unusual rhombus-shaped geometry, in which the diagonal Cu−C bond is shorter than the forming Cu-C bond. Therefore, **TS8-b** is stabilized by the favorable bonding interaction between the Cu center and the benzylic carbon due to the short Cu−Cα distance (2.08 Å). By contrast, **TS8-a** has a much longer distance between Cu and the benzylic carbon (2.20 Å) that leads to a less favorable through-bond interaction energy. In the hydrocupration with 1-phenylcyclobutene derivative **2a**, the through-bond interactions in both regioisomeric transition states are weaker than those in the transition states with 1-phenylcyclopropene derivative **5** because of smaller degrees of pyramidalization of **2a** (*vide supra*). Nonetheless, **TS2a-b** still has more favorable through-bond interactions than **TS2a-a** ($\Delta\Delta E_{\text{int-bond}}$ = −3.2 kcal/mol) because of the shorter Cu−Cα distance (2.18 and 2.24 Å in **TS2a-b**

and **TS2a-a**, respectively). However, **TS2a-b** requires a much higher energy (ΔE_{dist} = 34.8 kcal/mol) to distort the cyclobutene derivative **2a** to facilitate the through-bond interactions with CuH. Therefore, the regioselectivity in the reaction with **2a** is distortion-energy controlled ($\Delta\Delta E_{dist}$ = 5.2 kcal/mol) and favors the formation of the benzylic copper intermediate (**16a**) via **TS2a-a**.

1.3.4 Enantioselectivity of the Hydroamination Reactions with 1-Alkylcyclobutene and 1-Alkylcyclopropene

Finally, we investigated the origin of the notably different enantioselectivities in the hydroamination of 1-alkylcyclobutene and 1-alkylcyclopropene (Table 2 and Scheme 2). We computed the hydrocupration transition states with the two different π faces of 1-methylcyclobutene **1b** and 1-methylcyclopropene **1a** (Figure 5). In the reaction with **1b**, DFT calculations predicted strong preference for **TS-1b** that leads to the experimentally observed (*1R*,*2R*)-aminocyclobutane. The computed enantioselectivity ($\Delta\Delta G^{\ddagger}$ = 2.7 kcal/mol) is comparable to the difference between the distortion energies of the hydrocupration transition states ($\Delta\Delta E_{dist}$ = 2.6 kcal/mol), indicating the enantioselectivity is controlled by steric effects that lead to distortions of the catalyst and the substrate. Indeed, the less favorable transition state **TS-1b'** is destabilized due to steric repulsions between the cyclobutene moiety and the *P*-aryl group in the more-occupied quadrant (quadrant II). The ligand-substrate steric repulsions in **TS-1b'** are evidenced by the short C…H distance of 2.52 Å between the *P*-aryl group and the methylene group on cyclobutene. The C…H distance between the *P*-aryl group and the 1-methyl substituent is much longer (2.79 Å in **TS-1b'**), indicating that the steric repulsions with the cyclobutene moiety, rather than the 1-substituent, dictate the enantioselectivity.

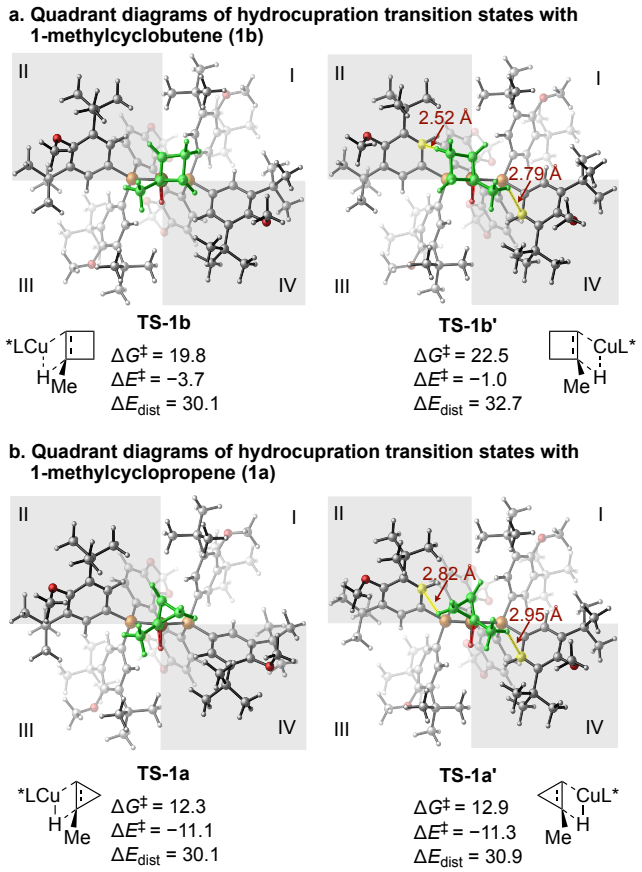


Figure 5. Origin of enantioselectivities in the hydroamination of 1-alkylcyclobutene and 1-alkylcyclopropene. All energies are in kcal/mol.

In the hydrocupration of 1-methylcyclopropene (**1a**), the two enantiomeric transition states **TS-1a** and **TS-1a'** have comparable activation energies. This is consistent with the low *e.r.* observed in the hydroamination of 1-alkylcyclopropene **11**. Their similar distortion energies (30.1 and 30.9 kcal/mol for **TS-1a** and **TS-1a'**, respectively) indicate that the ineffective stereoinduction is due to comparable ligand-substrate steric repulsions in both enantiomeric transition states. The transition state quadrant diagrams in Figure 5b show that due to the smaller size of the cyclopropene moiety compared to the cyclobutene, steric repulsions with the *P*-aryl

group in quadrant II of **TS-1a'** are diminished. This is evidenced by the much longer C…H distance (2.82 Å) between the *P*-aryl group and the methylene on the cyclopropene in **TS-1a'**.

1.4 Conclusion

In summary, we have developed the diastereo- and enantioselective CuH-catalyzed hydroamination reactions of 1-substituted cyclobutenes and cyclopropenes. DFT studies showed that strained trisubstituted olefins exhibit enhanced rates of hydrocupration compared to unstrained trisubstituted analogues, which allows for the effective hydroamination reactions of these substrates. For 1-arylcyclobutenes, Markovnikov products were selectively formed in the hydroamination reactions and a tetrasubstituted carbon center was generated in the cyclobutane product. By contrast, the opposite regioselectivity was observed for the hydroamination of 1-phenylcyclopropene derivatives. DFT studies revealed the Markovnikov-selectivity with 1-arylcyclobutenes is due to a smaller distortion energy in the hydrocupration transition state to form the benzylic copper intermediate, while the *anti*-Markovnikov-selectivity with 1-arylcyclopropenes is controlled by catalyst-substrate through-bond interactions. Moreover, the hydroamination reactions of 1-alkylcyclobutenes as well as 1-silyl substituted three- and four-membered cycloalkenes were shown to produce a variety of aminocyclobutanes and aminocyclopropanes bearing contiguous stereocenters in excellent enantio- and diastereoselectivity. We also showed that the small size of the cyclopropene moiety in 1-alkylcyclopropenes leads to insufficient ligand-substrate steric interactions for the chiral induction in hydrocupration. Accordingly, the hydroamination of 1-alkylcyclobutenes proceeds with considerably higher levels of enantioselectivity compared to 1-alkylcyclopropenes. We anticipate that our studies on the scope, regio-, and enantioselectivity of CuH-catalyzed

hydroamination using various types of strained trisubstituted alkenes can facilitate further developments in asymmetric hydrofuctionalization of strained alkenes.

1.5 Experimental

1.5.1 General Information

Computational Details: Additional information pertaining to the computational work in this Chapter (performed by Hua Hao and Peng Liu), including methods, supplementary figures, further discussion, and Cartesian coordinates of key structures can be found in the published report (Feng, S.; Hao, H.; Liu, P.; Buchwald, S. L. *ACS Catal*. **2020**, *10*, 281–291) and are not reproduced here.

General Analytical Information: All new compounds were characterized by NMR spectroscopy, IR spectroscopy, elemental analysis or high resolution mass spectrometry, optical rotation (if chiral and non-racemic) and melting point analysis (if solids). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker 400 or 500 MHz spectrometer. Chemical shifts for ^{1}H NMR are reported as follows: chemical shift in reference to residual $CHCl_3$ at 7.26 ppm (δ ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sex = sextet, sep = septet, dd = double of doublets, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. Chemical shifts for ^{13}C NMR are reported in terms of chemical shift in reference to the $CDCl_3$ solvent signal (77.16 ppm). Chemical shifts for ^{19}F NMR are reported in ppm relative to $CFCl_3$ (0.00 ppm). IR spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points were measured on a Mel-Temp capillary melting point apparatus. Optical rotations were measured using a Jasco P-1010 digital polarimeter. Elemental

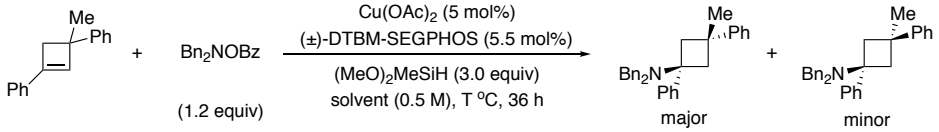
analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system. Enantiomeric excesses (ee's) were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument; specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. Thin-layer chromatography (TLC) was performed on silica gel 60Å F_{254} plates (SiliaPlate from Silicycle) and visualized with UV light, iodine or potassium permanganate stain. Preparatory thin-layer chromatography (Prep-TLC) was performed on silica gel GF with UV 254 (20 x 20 cm, 1000 microns, catalog # TLG-R10011B-341 from Silicycle) and visualized with UV light. Isolated yields reported reflect the average values from two independent runs.

General Reagent Information: All reactions were performed under a nitrogen atmosphere using the indicated method in the general procedures. Tetrahydrofuran (THF) was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and purified by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide. Anhydrous 1,4-dioxane was purchased from Aldrich Chemical Company in a Sure-Seal™ bottle and used as received. Copper(II) acetate was purchased from Strem and was 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. DTBM-SEGPHOS was purchased from Takasago International Co. and used as received. Diethoxymethylsilane was purchased from TCI America. Dimethoxy(methyl)silane (DMMS) was purchased from Tokyo Chemical Industry Co. (TCI). Both silanes were stored in a nitrogen-filled glove box at −20 °C for long-term storage. (***Caution****: Dimethoxy(methyl)silane (DMMS, CAS#16881-77-9) is listed by several vendors (TCI, Alfa Aesar) SDS or MSDS as a H318, a*

category 1 Causes Serious Eye Damage. Other vendors (Sigma-Aldrich, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precaution as outlined for the handling of hazardous materials in prudent practices in the laboratory[31]*. At the end of the reaction either ammonium fluoride in methanol, aqueous sodium hydroxide (1 M) or aqueous hydrochloric acid (1 M) should be carefully added to the reaction mixture. This should be allowed to stir for at least 30 min or the time indicated in the detailed reaction procedure*). 1,2-Benzisoxazole was purchased from Tokyo Chemical Industry Co. (TCI) and stored in a refrigerator at 4 °C. All other solvents and commercial reagents were used as received from Sigma Aldrich, Alfa Aesar, Acros Organics, TCI and Combi-Blocks, unless otherwise noted. Flash column chromatography was performed using 40-63 μm silica gel (SiliaFlash® F60 from Silicycle), or with the aid of a Biotage Isolera Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g). Organic solutions were concentrated *in vacuo* using a Buchi rotary evaporator.

1.5.2 Optimization and General Procedures for Hydroamination Reactions

Table S1. Effect of Solvent and Temperature on Hydroamination of 1-Arylcyclobutenes [a]

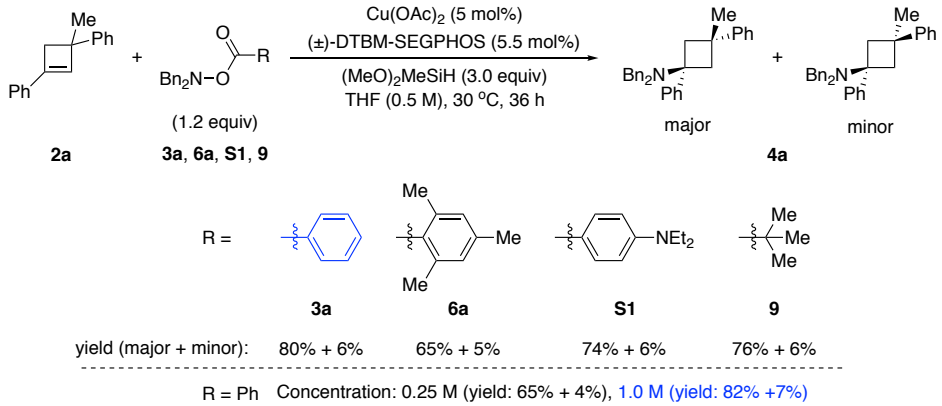


2a **3a** **4a**

solvent	T (°C)	yield (major + minor)
MTBE	40	70% + 10%
dioxane	40	70% + 8%
CyH	40	63% + 10%
toluene	40	68% + 9%
THF	40	80% + 8%
THF	50	80% + 8%
THF	30	80% +6%
THF	rt	61% + 5%
THF	0	<10%

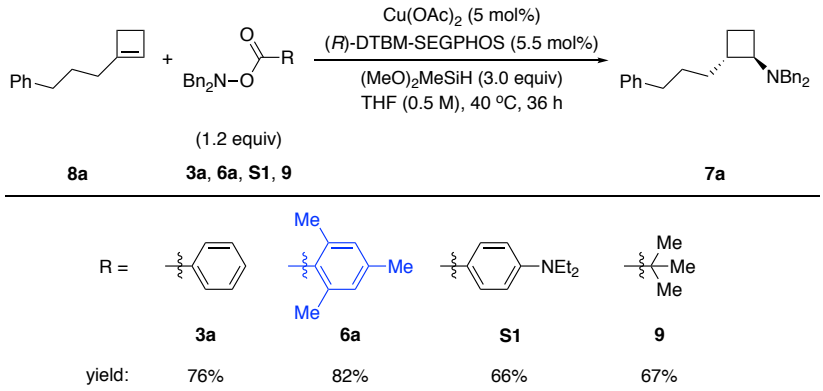
[a]Reactions were conducted on 0.1 mmol scale. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard.

Table S2. Evaluation of Different Amination Reagents and Concentrations in the Hydroamination of 1-Arylcyclobutenes [a]



[a]Reactions were conducted on 0.1 mmol scale. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard.

Table S3. Evaluation of Different Amination Reagents in the Hydroamination of 1-Alkylcyclobutenes[a]



[a]Reactions were conducted on 0.1 mmol scale. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard.

General Procedures for CuH-Catalyzed Hydroamination Reactions[32]

General Procedure A

An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.9 mg, 0.033 mmol), (*R*)-DTBM-SEGPHOS (21.1 mg, 0.018 mmol), and (*S*)-DTBM-SEGPHOS (21.1 mg, 0.018 mmol). The reaction tube was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous THF (0.65 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at rt. Then dimethoxymethylsilane (DMMS) (0.24 mL, 1.95 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 10 min at rt to prepare an orange CuH stock solution.

A separate oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was loosely capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. The alkene (0.5 mmol, 1.0 equiv) and the amine electrophile (0.6 mmol, 1.2 equiv) were added to the reaction tube. Then the CuH stock solution (0.68 mL) was added via a 1 mL syringe to the reaction tube in one portion. The reaction tube was capped and then removed from the glove box. The reaction mixture was allowed to stir at 30 $^{\circ}$C for 36 h.

General Procedure B

An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol). The reaction tube was loosely capped (cap:

Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous THF (1.20 mL) was added to the tube via syringe. The tube was capped and the mixture was stirred for 15 min at rt. Then DMMS (0.22 mL, 1.80 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 10 min at rt to prepare an orange CuH stock solution.

A separate oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was loosely capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. The alkene (0.5 mmol, 1.0 equiv) and the amine electrophile (0.6 mmol or 0.75 mmol, as indicated for each substrate) were added to the reaction tube. Then the CuH stock solution (1.18 mL) was added via syringe to the reaction tube in one portion. The reaction tube was capped and then removed from the glove box. The reaction mixture was allowed to stir at 40 $^{\circ}$C for 36 or 46 h as indicated for each substrate.

General Procedure C

An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol). The reaction tube was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous 1,4-dioxane (0.60 mL) was added to the tube with a 1 mL syringe. The tube was capped and the mixture was stirred for 10 min at rt. Then DMMS (0.22 mL, 1.80 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 15 min at rt to prepare a dark red CuH stock solution.

A separate oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was loosely capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. The alkene (0.5 mmol, 1.0 equiv), the amine electrophile (0.6 mmol, 1.2 equiv), and anhydrous 1,4-dioxane (0.50 mL) were added to the reaction tube. Then the CuH stock solution (0.68 mL) was added via a 1 mL syringe to the reaction tube in one portion. The reaction tube was capped and then taken out of the glove box. The reaction mixture was allowed to stir at rt for 18 h.

General Procedure D

An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol). The reaction tube was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous 1,4-dioxane (0.60 mL) was added to the tube with a 1 mL syringe. The tube was capped and the mixture was stirred for 10 min at rt. Then DMMS (0.22 mL, 1.80 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 15 min at rt to prepare a dark red CuH stock solution.

A second oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into the glovebox. 1,2-Benzisoxazole (92 μL) and anhydrous 1,4-dioxane (0.35 mL) were added to the tube to prepare the 1,2-benzisoxazole stock solution. The tube was capped and then gently swirled to mix the solution.

A third oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was loosely capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. The alkene (0.5 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (0.50 mL) were added to the reaction tube. Then the CuH stock solution (0.68 mL) was added via a 1 mL syringe to the reaction tube in one portion. (Note: The CuH solution should be added directly into the alkene solution instead of along the wall of the reaction tube, otherwise the remaining CuH solution on the wall of the reaction tube may cause decomposition of the 1,2-benzisoxazole that was subsequently added slowly along the wall of the reaction tube.) The reaction mixture was stirred at rt for 30 s. Then while the reaction mixture was stirred at rt, 1,2-benzisoxazole (10 μL) was added over 1 min via microsyringe. The reaction tube was capped and the septum was punctured with a long needle attached to a 1 mL syringe containing the 1,2-benzisoxazole stock solution (0.32 mL). The reaction tube was then taken out of the glove box. While the reaction mixture was stirred at rt, the 1,2-benzisoxazole solution was added slowly via syringe pump at a rate of 0.13 or 0.16 mL/h (as indicated for each substrate). (Note: The tip of the needle should touch the wall of the reaction tube during the slow addition of 1,2-benzisoxazole.) The reaction mixture was allowed to stir at rt for 18 h.

Workup A

After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. NH_4F in MeOH (1 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 30 min and transferred to a 100 mL round bottom flask with the aid of EtOAc. A small aliquot of

the solution was transferred to a 20 mL scintillation vial, concentrated *in vacuo*, analyzed by ^{1}H NMR in $CDCl_3$ to determine the diastereomeric ratio (dr), and then the NMR sample was transferred backed to the 100 mL round bottom flask. The combined solution was concentrated *in vacuo*. The resulting mixture was dissolved in EtOAc, filtered through a short plug of Celite, and washed with additional EtOAc. The collected EtOAc solution was concentrated *in vacuo*, and the crude material was immediately purified by silica gel column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm).

Workup B

After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. NH_4F in MeOH (1 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 30 min, and then transferred to a 20 mL scintillation vial. The reaction tube was rinsed four times with additional EtOAc (5-10 mL in total). The combined EtOAc solution was concentrated *in vacuo*, and the crude material was immediately purified by silica gel column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm).

Workup C

After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred vigorously at rt, sat. LiOH in MeOH (2.5 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 1 h, transferred to a 100 mL round bottom flask with the aid of EtOAc, and concentrated *in vacuo*. The resulting mixture was dissolved in EtOAc, sonicated for 5 min,

filtered through a pad of Celite, and washed with additional EtOAc. The collected EtOAc solution was concentrated *in vacuo*, and the crude material was immediately purified by silica gel column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm).

Workup D

After the reaction was completed, the cap of the reaction tube was removed, and the reaction mixture was diluted with EtOAc (1.5 mL). While the reaction mixture was stirred at 0 $^{\circ}$C, sat. aq. $NaHCO_3$ (2 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at 0 $^{\circ}$C for 5 min, and then at rt for 30 min. The mixture was transferred with the aid of EtOAc to a 125 mL separatory funnel containing brine (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10-15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was transferred to a 20 mL scintillation vial with the aid of EtOAc, and then concentrated *in vacuo*. The crude material was immediately purified by silica gel column chromatography (~ 30 g silica gel, diameter of the column was ~ 2 cm, length of the packed column was ~ 18 cm).

1.5.3 Structural Determination of the Hydroamination Products

Single Crystal X-ray Diffraction Data for Compound 7b (P19056): A crystal of **7b** was obtained by slowly evaporating the EtOH solution of **7b** at 0 $^{\circ}$C (in air). The absolute configuration of **7b** was determined by X-ray crystallographic analysis. The absolute configuration of **10a**, **7a-e**, **12**, and **15a-d** was assigned by analogy to **7b**.

CCDC 1945177 contains the supplementary crystallographic data for **7b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

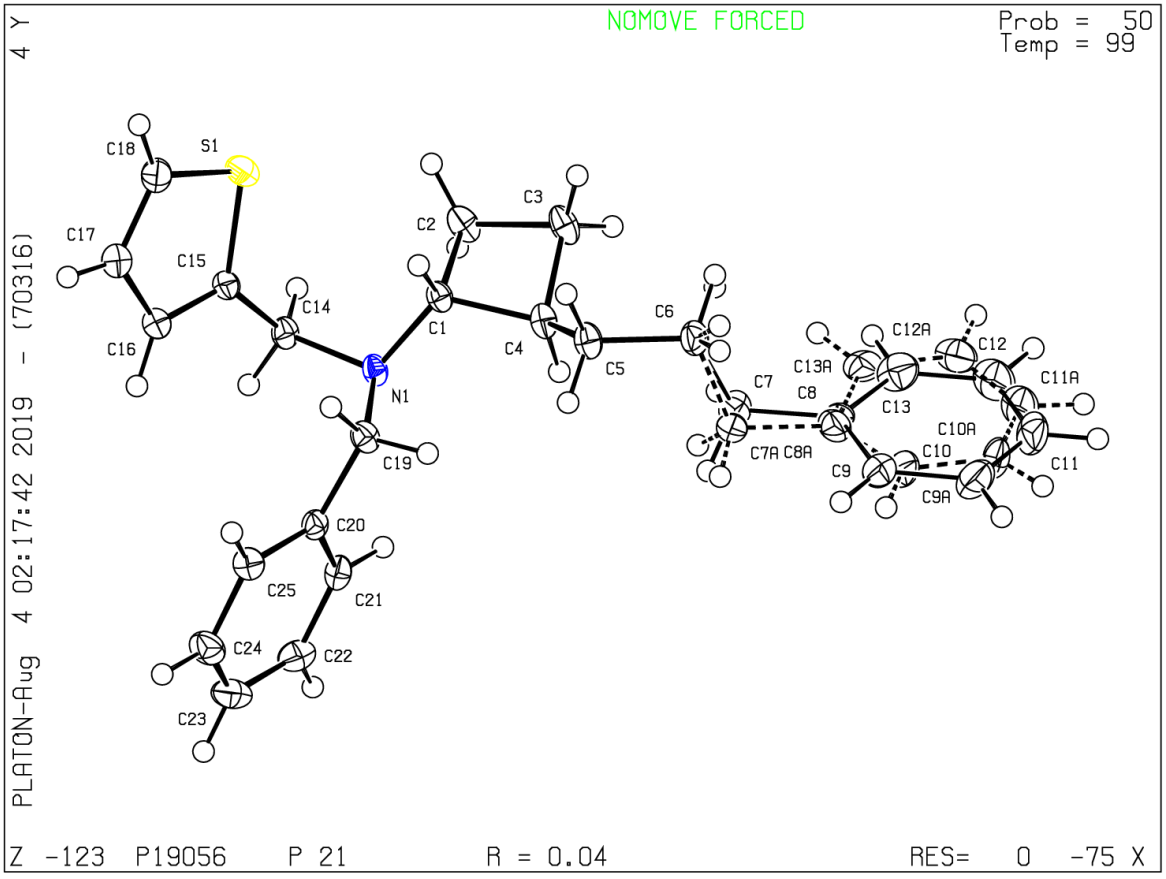


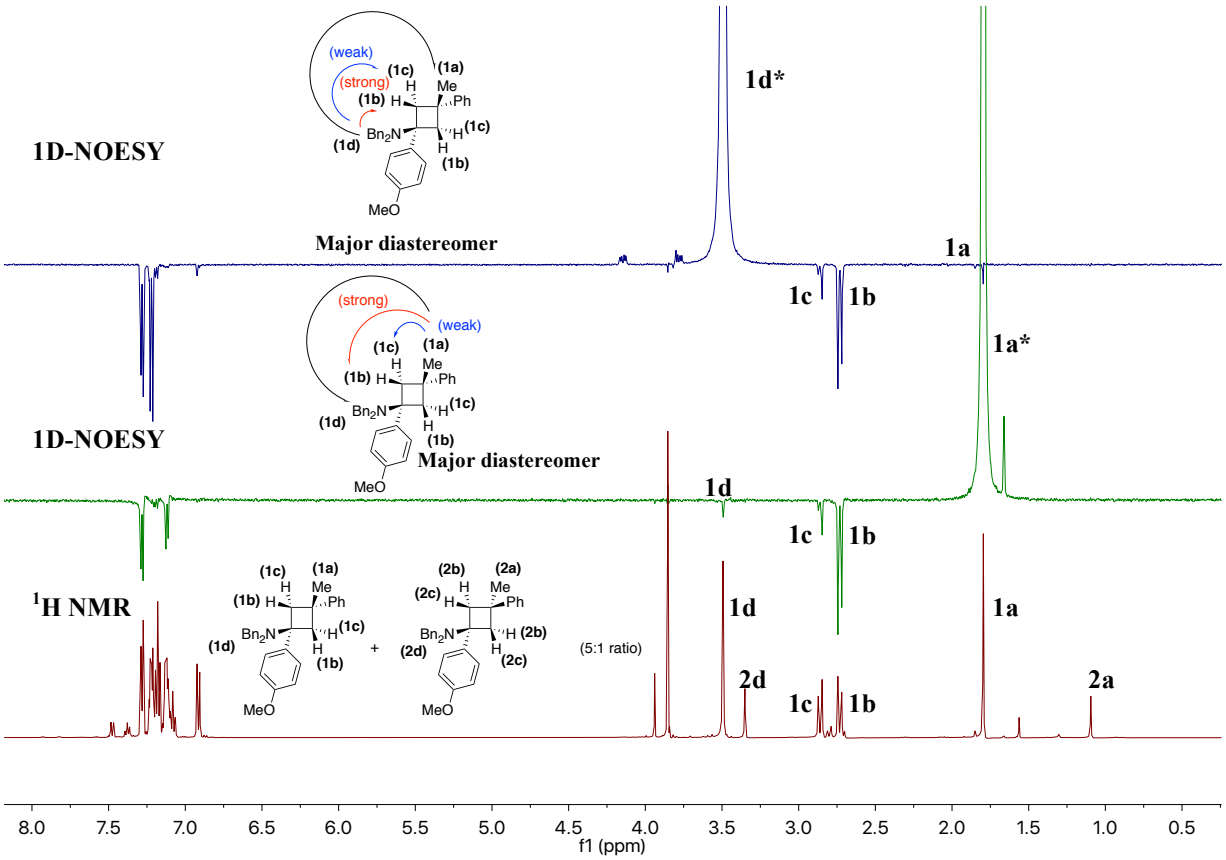
Table S4. Crystal data and structure refinement for 7b (P19056)

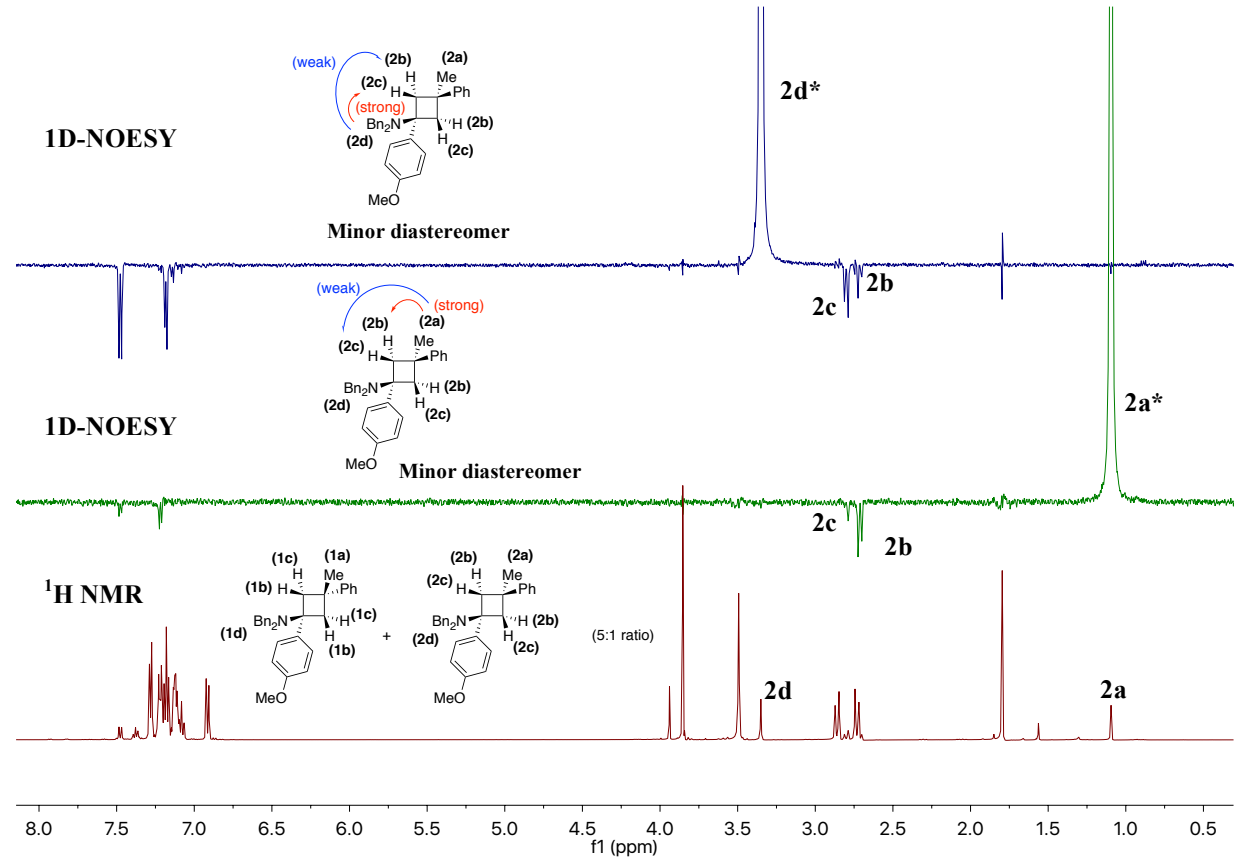
Identification code	P19056
Empirical formula	C25 H29 N S
Formula weight	375.55
Temperature	99(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	$P2_1$	
Unit cell dimensions	a = 13.0414(11) Å	a= 90°.
	b = 5.7208(4) Å	b= 93.997(4)°.
	c = 14.1145(12) Å	g = 90°.
Volume	1050.48(15) $Å^3$	
Z	2	
Density (calculated)	1.187 Mg/m^3	
Absorption coefficient	0.163 mm^{-1}	
F(000)	404	
Crystal size	0.570 x 0.165 x 0.160 mm^3	
Theta range for data collection	1.446 to 30.541°.	
Index ranges	-18<=h<=18, -8<=k<=8, -20<=l<=20	
Reflections collected	89778	
Independent reflections	6421 [R(int) = 0.0653]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6421 / 366 / 309	
Goodness-of-fit on F^2	1.125	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1092	
R indices (all data)	R1 = 0.0454, wR2 = 0.1098	
Absolute structure parameter	0.04(2)	
Extinction coefficient	0.192(12)	

Largest diff. peak and hole 0.365 and -0.438 e.Å^{-3}

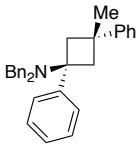
1D-NOESY Analysis of 4b (a 5:1 mixture of major and minor diastereomers): The configuration of the major and minor diastereomers in **4b** was determined by 1D-NOESY analysis of **4b** (a 5:1 mixture of major and minor diastereomers). The configuration of the major diastereomers in **4a**, **4c**, **4g-i** was assigned by analogy to **4b**.





1.5.4 Characterization Data for the Hydroamination Products

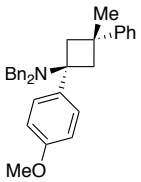
(1*r*,3*r*)-*N*,*N*-dibenzyl-3-methyl-1,3-diphenylcyclobutan-1-amine (4a)



Following general procedure **A**, (3-methylcyclobut-1-ene-1,3-diyl)dibenzene (110 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOBz (190 mg, 0.60 mmol, 1.2 equiv) were used. After Workup **A** and purification by column chromatography [hexanes (80 mL) followed by hexanes/EtOAc = 100:1], the title compound was obtained as a white solid (1st run: 181 mg, 87% yield, 13:1 dr; 2nd run: 174 mg, 83% yield, 13:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 13:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.19-6.94 (m, 18H), 3.39 (s, 4H), 2.77 (d, J = 12.6 Hz, 2H), 2.64 (d, J = 12.7 Hz, 2H), 1.70 (s, 3H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 152.22, 141.73,

141.14, 128.93, 128.01, 127.79, 127.48, 127.36, 126.37, 126.28, 125.12, 125.02, 62.72, 55.02, 44.97, 36.07, 33.25. **m.p.** 128.0-129.7 °C. **IR** (thin film): 3063, 3024, 2842, 1600, 1491, 1454, 1272, 1029, 908, 692 cm^{-1}. **EA** Calcd. for $C_{31}H_{31}N$: C, 89.16; H, 7.48. Found: C, 88.96; H, 7.45.

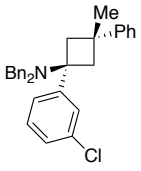
(1*r*,3*r*)-*N*,*N*-dibenzyl-1-(4-methoxyphenyl)-3-methyl-3-phenylcyclobutan-1-amine (4b)



Following general procedure **A**, 1-methoxy-4-(3-methyl-3-phenylcyclobut-1-en-1-yl)benzene (125 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOBz (190 mg, 0.60 mmol, 1.2 equiv) were used. After the reaction was completed, the reaction mixture was transferred to a 100 mL round bottom flask, and the reaction tube was rinsed with additional EtOAc. Then HCl in MeOH (1.25 M, 15 mL) was added to the flask to quench the reaction mixture and acidify the mixture. The flask was swirled gently to mix the components, allowed to sit for 30 min, and then the resulting mixture was concentrated *in* vacuo. Hexanes (~ 20 mL) was added. The precipitate was broken into small pieces using a spatula, and the resulting suspension was sonicated for 5-10 min. The suspension was filtered through a Buchner funnel (porosity: fine) under reduced pressure. The 100 mL flask was rinsed with hexane (~20 mL) and the suspension was poured into the funnel. The solid in the funnel was washed with additional hexanes (~10 mL). Then the solid in the above 100 mL round bottom flask and Buchner funnel was dissolved with 1 M NaOH (~ 50 mL in total) and CH_2Cl_2 (~50 mL in total). The resulting mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was collected in a 500 mL round bottom flask. A small aliquot of the solution was transferred to a 20 mL scintillation vial, concentrated *in vacuo*, analyzed by ^1H NMR in $CDCl_3$ to determine the diastereomeric ratio (dr), and then the NMR sample was

transferred backed to the 500 mL round bottom flask. The combined solution was concentrated *in vacuo*, and immediately purified by column chromatography (~ 30 g silica gel) with a gradient of hexanes (100 mL) → hexanes/Et_2O = [30:1 (90 mL) → 20:1 (160 mL)]. The title compound was obtained as a white solid (1st run: 140 mg, 62% yield, 5:1 dr; 2nd run: 150 mg, 67% yield, 5:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 5:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 4H), 7.25-7.07 (m, 13H), 6.94-6.90 (m, 2H), 3.86 (s, 3H), 3.50 (s, 4H), 2.87 (d, *J* = 12.6 Hz, 2H), 2.74 (d, *J* = 12.7 Hz, 2H), 1.80 (s, 3H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 157.91, 152.16, 141.23, 134.16, 128.92, 128.62, 127.98, 127.78, 126.34, 125.13, 124.99, 112.66, 62.21, 55.25, 55.02, 45.26, 35.87, 33.27. **m.p.** 134.5-136.8 °C. **IR** (thin film): 3059, 3025, 2931, 2834, 1605, 1511, 1247, 1179, 1028, 698 cm^{-1}. **HRMS** Calcd. m/z for $C_{32}H_{34}NO^+$ $[M+H]^+$: 448.2635; found 448.2655.

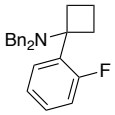
(1*r*,3*r*)-*N*,*N*-dibenzyl-1-(3-chlorophenyl)-3-methyl-3-phenylcyclobutan-1-amine (4c)



Following general procedure **A**, 1-chloro-3-(3-methyl-3-phenylcyclobut-1-en-1-yl)benzene (127 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOBz (190 mg, 0.60 mmol, 1.2 equiv) were used. After Workup **A** and purification by column chromatography [hexanes (200 mL) followed by hexanes/EtOAc = 100:1], the title compound was obtained as a white solid (1st run: 180 mg, 80% yield, 29:1 dr; 2nd run: 178 mg, 78% yield, 29:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 29:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 7.34-7.09 (m, 19H), 3.50 (s, 4H), 2.88-2.85 (m, 2H), 2.78-2.74 (m, 2H), 1.80 (s, 3H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 151.75, 143.88, 140.75, 133.60, 128.92, 128.70, 128.09, 127.90, 127.63, 126.54, 126.52, 125.64, 125.19, 125.10, 62.61, 54.91, 44.95, 36.12, 33.27. **m.p.** 142.6-144.0 °C. **IR** (thin film): 3061, 3025, 2933, 2838, 1592, 1494,

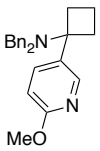
1262, 1172, 1027, 695 cm^{-1}. **HRMS** Calcd. m/z for $C_{31}H_{31}NCl^{+}$ $[M+H]^{+}$: 452.2140; found 452.2143.

***N,N*-dibenzyl-1-(2-fluorophenyl)cyclobutan-1-amine (4d)**



Following general procedure **B**, 1-(cyclobut-1-en-1-yl)-2-fluorobenzene (74 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOPiv (178 mg, 0.60 mmol, 1.2 equiv) were used. The reaction was run at 40 °C for 36 h. After Workup **B** and purification by column chromatography with a gradient of hexanes (150 mL) → hexanes/Et_2O = [100:1 (100 mL) → 80:1 (240 mL) → 60:1 (60 mL)], the title compound was obtained as a colorless oil (1st run: 124 mg, 72% yield; 2nd run: 123 mg, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.21 (m, 8H), 7.19-7.15 (m, 4H), 7.13-7.08 (m, 2H), 3.57 (s, 4H), 2.47-2.44 (m, 4H), 2.28-2.18 (m, 1H), 1.80-1.71 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.36 (d, J = 246.4 Hz), 141.51, 130.24 (d, J = 5.8 Hz), 129.04 (d, J = 14.6 Hz), 128.61, 128.53, 127.69, 126.22, 123.26 (d, J = 3.5 Hz), 116.28 (d, J = 24.6 Hz), 67.34 (d, J = 2.4 Hz), 54.76 (d, J = 2.9 Hz), 33.23 (d, J = 1.5 Hz), 16.30. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.85. **IR** (thin film): 3062, 3027, 2943, 2839, 1483, 1446, 1212, 1141, 1028, 695 cm^{-1}. **EA** Calcd. for $C_{24}H_{24}NF$: C, 83.44; H, 7.00. Found: C, 83.31; H, 7.14.

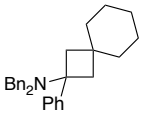
***N,N*-dibenzyl-1-(6-methoxypyridin-3-yl)cyclobutan-1-amine (4e)**



Following general procedure **B**, 5-(cyclobut-1-en-1-yl)-2-methoxypyridine (81 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOPiv (178 mg, 0.60 mmol, 1.2 equiv) were used. The reaction was run at 40 °C for 36 h. After Workup **B** and purification by column chromatography with a gradient of hexanes (100 mL) → hexanes/Et_2O = [50:1 (100 mL) → 40:1 (40 mL) → 30:1 (90 mL) → 20:1 (100 mL) → 15:1 (90 mL) → 10:1 (100 mL)], the title

compound was obtained as a colorless oil (1st run: 134 mg, 75% yield; 2nd run: 136 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.34-7.28 (m, 4H), 7.25-7.22 (m, 4H), 7.18-7.14 (m, 2H), 6.88 (dd, *J* = 8.6, 0.7 Hz, 1H), 4.04 (s, 3H), 3.42 (s, 4H), 2.35 (qd, *J* = 9.3, 2.4 Hz, 2H), 2.22 (tt, *J* = 8.4, 2.9 Hz, 2H), 1.86-1.78 (m, 1H), 1.60-1.49 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.13, 146.23, 141.02, 138.71, 129.58, 128.82, 128.03, 126.67, 110.07, 66.31, 53.91, 53.56, 33.25, 14.80. **IR** (thin film): 3024, 2943, 2840, 1599, 1488, 1368, 1285, 1132, 1023, 696 cm^{-1}. **EA** Calcd. for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31. Found: C, 80.71; H, 7.08.

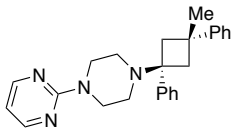
***N*,*N*-dibenzyl-2-phenylspiro[3.5]nonan-2-amine (4f)**



Following general procedure **A**, instead of using (*R*)-DTBM-SEGPHOS (21.1 mg) and (*S*)-DTBM-SEGPHOS (21.1 mg) to prepare the CuH stock solution, (*R*)-DTBM-SEGPHOS (42.2 mg) was used. 2-Phenylspiro[3.5]non-1-ene (99 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOBz (190 mg, 0.60 mmol, 1.2 equiv) were also used. After Workup **A** and purification by column chromatography with a gradient of hexanes (150 mL) → hexanes/Et_2O = [100:1 (100 mL) → 80:1 (240 mL) → 60:1 (60 mL)], the title compound was obtained as a white solid (1st run: 177 mg, 89% yield; 2nd run: 179 mg, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.42-7.40 (m, 2H), 7.35 (tt, *J* = 6.5, 1.4 Hz, 1H), 7.24-7.22 (m, 4H), 7.17-7.13 (m, 4H), 7.11-7.07 (m, 2H), 3.39 (s, 4H), 2.30 (d, *J* = 12.4 Hz, 2H), 2.22 (d, *J* = 12.4 Hz, 2H), 1.72-1.70 (m, 2H), 1.43 (p, *J* = 5.7 Hz, 2H), 1.33-1.28 (m, 4H), 1.18-1.15 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.49, 141.36, 128.96, 127.92, 127.78, 127.59, 126.33, 62.86, 54.65, 44.26, 40.60, 38.66, 31.81, 26.10, 22.95, 22.85. **m.p.** 81.8-82.5 °C. **IR** (thin film): 3060, 3025,

2920, 2847, 1493, 1444, 1296, 1171, 1028, 693 cm^{-1}. **HRMS** Calcd. m/z for $C_{29}H_{34}N^+$ $[M+H]^+$: 396.2686; found 396.2690.

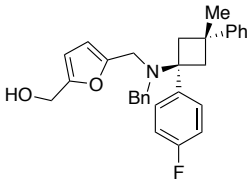
2-(4-((1*r*,3*r*)-3-methyl-1,3-diphenylcyclobutyl)piperazin-1-yl)pyrimidine (4g)



Following general procedure **A**, (3-methylcyclobut-1-ene-1,3-diyl)dibenzene (110 mg, 0.50 mmol, 1.0 equiv) and 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (171 mg, 0.60 mmol, 1.2 equiv) were used. After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. NH_4F in MeOH (1 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 30 min and transferred to a 100 mL round bottom flask with the aid of CH_2Cl_2. A small aliquot of the solution was transferred to a 20 mL scintillation vial, concentrated *in vacuo*, analyzed by ^1H NMR in $CDCl_3$ to determine the diastereomeric ratio (dr), and then the NMR sample was transferred backed to the 100 mL round bottom flask. The combined solution was concentrated *in vacuo*. The resulting mixture was dissolved in CH_2Cl_2, filtered through a cotton ball that was stuck in a pipette, and washed with additional CH_2Cl_2. The CH_2Cl_2 solution was collected in a 20 mL scintillation vial, concentrated *in vacuo*, and the crude material and immediately purified by column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm) with a gradient of hexanes/EtOAc = [20:1 (60 mL) → 15:1 (150 mL) → 12:1 (60 mL) → 10:1 (200 mL) → 8:1 (80 mL) → 5:1 (100 mL) → 4:1 (100 mL) (the above volumes refer to the volume of hexanes used)]. The resulting material was redissolved in CH_2Cl_2 (3 mL), filtered through a short plug of basic activated alumina, and washed with additional EtOAc. The collected EtOAc solution was concentrated *in vacuo* to afford the pure product as a white solid

(1st run: 128 mg, 66% yield, 13:1 dr; 2nd run: 128 mg, 66% yield, 13:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 13:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.7 Hz, 2H), 7.28-7.24 (m, 4H), 7.19-7.10 (m, 4H), 7.06-7.04 (m, 2H), 6.43 (t, *J* = 4.8 Hz, 1H), 3.88 (br, 4H), 2.81 (d, *J* = 11.4 Hz, 2H), 2.77 (d, *J* = 11.5 Hz, 2H), 2.42 (br, 4H), 1.77 (s, 3H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 151.75, 143.88, 140.75, 133.60, 128.92, 128.70, 128.09, 127.90, 127.63, 126.54, 126.52, 125.64, 125.19, 125.10, 62.61, 54.91, 44.95, 36.12, 33.27. **m.p.** 197.0-198.9 °C. **IR** (thin film): 3021, 2932, 2853, 1584, 1493, 1357, 1261, 1181, 1012, 700 cm^{-1}. **HRMS** Calcd. m/z for $C_{25}H_{29}N_4^+$ $[M+H]^+$: 385.2387; found 385.2396.

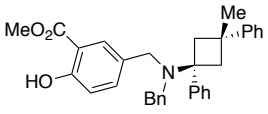
(5-((benzyl((1*r*,3*r*)-1-(4-fluorophenyl)-3-methyl-3-phenylcyclobutyl)amino)methyl)furan-2-yl)methanol (4h)



General procedure **A** was followed, except DMMS (0.32 mL, 2.60 mmol) (Note: An extra equivalence of DMMS was used in order to silylate the alcohol in the amination reagent.) was used to prepare the CuH stock solution. The stock CuH solution (0.74 mL) was added to the reaction tube containing 1-fluoro-4-(3-methyl-3-phenylcyclobut-1-en-1-yl)benzene (119 mg, 0.50 mmol, 1.0 equiv) and (5-(((benzoyloxy)(benzyl)amino)methyl)furan-2-yl)methanol (202 mg, 0.60 mmol, 1.2 equiv). After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. NH_4F in MeOH (5 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 1 h and transferred to a 100 mL round bottom flask with the aid of CH_2Cl_2. A small aliquot of the solution was transferred to a 20 mL scintillation vial, concentrated *in vacuo*, analyzed by ^{1}H

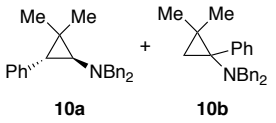
NMR in $CDCl_3$ to determine the diastereomeric ratio (dr), and then transferred backed to the 100 mL round bottom flask. The combined solution was concentrated *in vacuo*. The resulting mixture was dissolved in CH_2Cl_2, filtered through a cotton ball that was stuck in a pipette, and washed with additional CH_2Cl_2. The CH_2Cl_2 solution was collected in a 20 mL scintillation vial, concentrated *in vacuo*, and the crude material was immediately purified by column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm) with a gradient of hexanes/EtOAc = [20:1 (60 mL) → 15:1 (150 mL) → 12:1 (60 mL) → 10:1 (200 mL) → 8:1 (80 mL) → 5:1 (100 mL) → 4:1 (100 mL) (the above volumes refer to the volume of hexanes used)]. The resulting material was redissolved in CH_2Cl_2 (3 mL), filtered through a short plug of basic activated alumina, and washed with additional EtOAc. The collected EtOAc solution was concentrated *in vacuo* to afford the pure product as a white solid (1st run: 173 mg, 76% yield, 11:1 dr; 2nd run: 182 mg, 80% yield, 11:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 11:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.28-7.10 (m, 10H), 7.06-7.00 (m, 2H), 5.96 (d, J = 3.1 Hz, 1H), 5.78 (d, J = 3.1 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.54 (s, 2H), 3.49 (s, 2H), 2.92-2.88 (m, 2H), 2.82-2.78 (m, 2H), 1.84 (s, 3H), 1.43 (t, J = 6.0 Hz, 1H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 161.33 (d, J = 245.2 Hz), 153.72, 152.58, 151.96, 140.79, 137.56 (d, J = 3.1 Hz), 128.68, 128.60, 128.27, 128.11, 127.77, 126.28, 125.17, 125.07, 114.28 (d, J = 21.0 Hz), 108.49 (d, J = 19.7 Hz), 61.82, 57.55, 54.73, 46.93, 44.80, 35.81, 32.99. **^{19}F NMR** (major diastereomer, 376 MHz, $CDCl_3$) δ -116.55. **m.p.** 124.3-125.9 °C. **IR** (thin film): 3359, 3025, 2932, 2866, 1601, 1508, 1224, 1157, 1010, 699 cm^{-1}. **EA** Calcd. for $C_{30}H_{30}FNO_2$: C, 79.09; H, 6.64. Found: C, 79.01; H, 6.62.

methyl 5-((benzyl((1*r*,3*r*)-3-methyl-1,3-diphenylcyclobutyl)amino)methyl)-2-hydroxybenzoate (4i)



General procedure **A** was followed, except DMMS (0.32 mL, 2.60 mmol) was used to prepare the CuH stock solution. The stock CuH solution (0.74 mL) was added to the reaction tube containing (3-methylcyclobut-1-ene-1,3-diyl)dibenzene (110 mg, 0.50 mmol, 1.0 equiv) and methyl 5-(((benzoyloxy)(benzyl)amino)methyl)-2-hydroxybenzoate (235 mg, 0.60 mmol, 1.2 equiv). After Workup **A** (5 mL sat. NH_4F in MeOH was used to quench the reaction mixture) and purification by column chromatography with a gradient of hexanes (200 mL) → hexanes/Et_2O = [50:1 (100 mL) → 30:1 (180 mL) → 20:1 (100 mL)], the title compound was obtained as a white solid (1st run: 190 mg, 77% yield, 13:1 dr; 2nd run: 190 mg, 77% yield, 13:1 dr). ^{1}H NMR analysis of the crude reaction mixture indicated 13:1 dr. **^{1}H NMR** (major diastereomer, 400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.57 (d, *J* = 2.2 Hz, 1H), 7.40-7.34 (m, 2H), 7.28-7.06 (m, 14H), 6.76 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.50 (s, 2H), 3.45 (s, 2H), 2.96-2.92 (m, 2H), 2.82-2.78 (m, 2H), 1.85 (s, 3H). **^{13}C NMR** (major diastereomer, 101 MHz, $CDCl_3$) δ 170.64, 160.21, 152.26, 141.79, 141.05, 136.61, 131.76, 130.15, 128.94, 128.18, 127.85, 127.53, 127.40, 126.47, 126.38, 125.22, 117.04, 111.32, 62.77, 55.25, 54.47, 52.26, 45.13, 36.12, 33.35. **m.p.** 111.7-112.4 °C. **IR** (thin film): 3023, 2951, 2836, 1674, 1441, 1207, 1087, 908, 731, 696 cm^{-1}. **EA** Calcd. for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77. Found: C, 80.47; H, 6.84.

(1*S*,3*R*)-*N*,*N*-dibenzyl-2,2-dimethyl-3-phenylcyclopropan-1-amine (10a) + *N*,*N*-dibenzyl-2,2-dimethyl-1-phenylcyclopropan-1-amine (10b)



10a **10b**

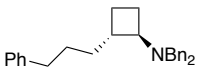
Following general procedure **C**, 1,4-dioxane was replaced with an equal volume of THF, and (3,3-dimethylcycloprop-1-en-1-yl)benzene (72 mg, 0.50 mmol, 1.0 equiv, freshly prepared) and Bn_2NOPiv (178 mg, 0.60 mmol, 1.2 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexanes (150 mL) → hexanes/Et_2O = [120:1 (180 mL) → 100:1 (150 mL) → 80:1 (80 mL)] (the product on TLC was visualized with I_2), a 8:1 mixture of the title compound (a mixture of **10a** and **10b**, 8:1 ratio**)** was obtained as a colorless oil (1st run: 101 mg, 59% yield, 69:31 er for **10a**; 2nd run: 98 mg, 57% yield, 69:31 er for **10a**). **EA** Calcd. for $C_{25}H_{27}N$: C, 87.93; H, 7.97. Found: C, 88.34; H, 7.96. ^{1}H NMR analysis of the crude reaction mixture indicated an 8:1 ratio of **10a** and **10b**. To separately obtain characterization data and confirm the structure of **10a** and **10b**, a small aliquot of the title compound was purified with preparative thin-layer chromatography (20 x 20 cm, 250 microns, catalog # TLG-R10014B-323 from Silicycle) eluting with hexane/EtOAc = 80:1 to give pure **10a** and **10b**.

Major regioisomer **10a**: White solid. **m.p.** 48.0-49.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 8H), 7.29-7.25 (m, 4H), 7.19-7.16 (m, 1H), 7.13-7.11 (m, 2H), 3.77 (d, *J* = 13.6 Hz, 2H), 3.68 (d, *J* = 13.6 Hz, 2H), 2.20 (d, *J* = 4.6 Hz, 1H), 1.76 (d, *J* = 4.6 Hz, 1H), 1.19 (s, 3H), 0.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.52, 138.72, 129.68, 128.66, 128.14, 127.93, 126.97, 125.58, 58.41, 53.80, 36.76, 27.80, 21.41, 20.58. **DEPT-135 NMR** (101 MHz, $CDCl_3$) δ 129.66, 128.64, 128.12, 127.92, 126.96, 125.57, 58.41 (CH_2), 53.80, 36.76, 21.40, 20.57. **SFC** analysis: OJ-H (5:95 IPA: $scCO_2$ to 30:70 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.96 min (minor), 4.84 min (major), 69:31 er. **Specific rotation** $[\alpha]_D^{23}$: +13.8 (c =

1.0, $CHCl_3$). **IR** (thin film): 3061, 3026, 2919, 1602, 1494, 1454, 1373, 1029, 745, 697 cm^{-1}. **EA** Calcd. for $C_{25}H_{27}N$: C, 87.93; H, 7.97. Found: C, 87.64; H, 8.04.

Minor regioisomer **10b**: White solid. **m.p.** 88.4-90.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.17 (m, 15H), 4.13 (br, 1H), 3.43-3.40 (m, 3H), 1.61 (s, 3H), 0.85 (s, 3H), 0.53-0.50 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.31, 132.14, 129.22, 128.00, 127.63, 126.87, 126.63, 70.74, 56.33, 27.84, 25.25, 22.80, 21.43. **DEPT-135 NMR** (101 MHz, $CDCl_3$) δ 132.15, 129.22, 128.04, 127.63, 126.87, 126.57, 70.74 (CH_2), 27.85(CH_2), 25.25, 21.43. **IR** (thin film): 3026, 2925, 2865, 1494, 1454, 1377, 1122, 1027, 740, 697 cm^{-1}. **HRMS** Calcd. m/z for $C_{25}H_{28}N^+$ $[M+H]^+$: 342.2216; found 342.2228.

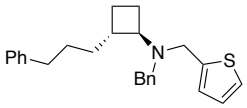
(1*R*,2*R*)-*N*,*N*-dibenzyl-2-(3-phenylpropyl)cyclobutan-1-amine (7a)



Following general procedure **B**, (3-(cyclobut-1-en-1-yl)propyl)benzene (86 mg, 0.50 mmol, 1.0 equiv) and $Bn_2NOC(O)Mes$ (270 mg, 0.75 mmol, 1.5 equiv) were used. The reaction was run at 40 °C for 46 h. After Workup **C** and purification by column chromatography with a gradient of hexanes (80 mL) → hexanes/Et_2O = [100:1 (100 mL) → 80:1 (until the majority of the product is eluted) → 40:1 (40 mL)] (the product on TLC was visualized with I_2), the title compound was obtained as a colorless oil (1st run: 145 mg, 78% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 147 mg, 80% yield, > 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.16 (m, 15H), 3.64 (d, *J* = 13.9 Hz, 2H), 3.54 (d, *J* = 14.0 Hz, 2H), 2.93 (q, *J* = 7.9 Hz, 1H), 2.61-2.48 (m, 2H), 2.35-2.26 (m, 1H), 1.92-1.75 (m, 3H), 1.60-1.46 (m, 3H), 1.36-1.26 (m, 1H), 1.19-1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.91, 140.13, 128.91, 128.49, 128.35, 128.18, 126.76, 125.70, 63.46, 54.88, 41.10, 36.10, 35.66, 29.22, 23.04, 21.16.

SFC analysis: OJ-H (5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 2 min hold time, 2.50 mL/min), 5.27 min (major), 7.14 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: -37.1 (c = 1.0, $CHCl_3$). **IR** (thin film): 3060, 3025, 2929, 2854, 1602, 1493, 1452, 1143, 1028, 744 cm^{-1}. **EA** Calcd. for $C_{27}H_{31}N$: C, 87.75; H, 8.46. Found: C, 87.49; H, 8.48.

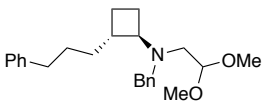
(1*R*,2*R*)-*N*-benzyl-2-(3-phenylpropyl)-*N*-(thiophen-2-ylmethyl)cyclobutan-1-amine (7b)



Following general procedure **B**, (3-(cyclobut-1-en-1-yl)propyl)benzene (86 mg, 0.50 mmol, 1.0 equiv) and *N*-benzyl-*N*-(thiophen-2-ylmethyl)-*O*-(2,4,6-trimethylbenzoyl)hydroxylamine (274 mg, 0.75 mmol, 1.5 equiv) were used. The reaction was run at 40 °C for 46 h. After the reaction was completed, the reaction mixture was filtered through a short plug of silica gel, and washed with additional EtOAc. The EtOAc solution was collected in a 20 mL scintillation vial, and then solvent was carefully removed under high vacuum by fitting a red septum onto the vial, inserting a needle into the septum, connecting the needle to a liquid N_2 trap, connecting the first liquid N_2 trap to a second liquid N_2 trap, and then connecting the second trap to the vacuum line on a Schlenk dual-manifold (Note: The liquid N_2 traps are necessary to insure that DMMS is completely trapped. After the evaporation process, the traps were maintained inside a fumehood. After their contents were thawed, the traps were washed thoroughly with acetone and the waste was poured into a container designated for organic liquid waste). The crude material was immediately purified by column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm) with a gradient of hexanes (100 mL) → hexanes/Et_2O = [50:1 (100 mL) → 40:1 (40 mL) → 30:1 (150 mL) → 20:1 (80 mL) → 15:1 (60 mL) → 10:1 (200 mL) (the above volumes refer to the volume of hexanes

used)] (the product on TLC was visualized with I_2). The title compound was obtained as a white solid (1st run: 146 mg, 78% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 151 mg, 80% yield, > 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.37-7.19 (m, 9H), 6.98 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.88 (dd, *J* = 3.4, 1.0 Hz, 1H), 3.85 (d, *J* = 14.8 Hz, 1H), 3.79 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 14.0 Hz, 1H), 3.58 (d, *J* = 14.0 Hz, 1H), 2.99 (q, *J* = 7.8 Hz, 1H), 2.65-2.52 (m, 2H), 2.37-2.28 (m, 1H), 2.00-1.77 (m, 3H), 1.67-1.52 (m, 3H), 1.41-1.33 (m, 1H), 1.26-1.16 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.03, 142.86, 139.73, 128.95, 128.50, 128.35, 128.25, 126.88, 126.41, 125.74, 125.70, 124.65, 62.95, 54.20, 48.71, 41.33, 36.09, 35.73, 29.16, 23.32, 21.08. **m.p.** 50.6-51.3 °C. **SFC** analysis: CEL-1 (1:99 MeOH: $scCO_2$ to 3:97 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 5.18 min (minor), 5.46 min (major), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: -39.9 (c = 1.0, $CHCl_3$). **IR** (thin film): 3025, 2927, 2852, 1602, 1494, 1452, 1335, 1142, 1028, 694 cm^{-1}. **EA** Calcd. for $C_{25}H_{29}NS$: C, 79.95; H, 7.78. Found: C, 79.67; H, 7.79.

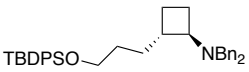
(1*R*,2*R*)-*N*-benzyl-*N*-(2,2-dimethoxyethyl)-2-(3-phenylpropyl)cyclobutan-1-amine (7c)



Following general procedure **B**, (3-(cyclobut-1-en-1-yl)propyl)benzene (86 mg, 0.50 mmol, 1.0 equiv) and *N*-benzyl-*N*-(2,2-dimethoxyethyl)-*O*-(2,4,6-trimethylbenzoyl)hydroxylamine (268 mg, 0.75 mmol, 1.5 equiv) were used. The reaction was run at 40 °C for 46 h. After Workup **C** and purification by column chromatography with a gradient of hexanes (100 mL) → hexanes/Et_2O = [50:1 (100 mL) → 40:1 (40 mL) → 30:1 (90 mL) → 20:1 (100 mL) → 15:1 (150 mL) → 10:1 (until the product is completely eluted)] (the product on TLC was visualized with I_2), the title compound was obtained as a colorless oil (1st run: 140 mg, 76% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 135 mg, 74% yield, > 99.5:0.5 er, >

20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 7H), 7.22-7.18 (m, 3H), 4.30 (t, *J* = 5.2 Hz, 1H), 3.73 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 14.0 Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.94 (q, *J* = 7.8 Hz, 1H), 2.70-2.53 (m, 4H), 2.27 (pd, *J* = 8.7, 3.8 Hz, 1H), 1.95 (q, *J* = 9.4, 8.7 Hz, 1H), 1.90-1.74 (m, 2H), 1.69-1.53 (m, 3H), 1.40-1.32 (m, 1H), 1.18 (p, *J* = 8.9, 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.87, 140.24, 128.99, 128.47, 128.34, 128.18, 126.82, 125.70, 104.06, 64.56, 56.35, 53.84, 53.78, 53.17, 41.42, 36.08, 35.61, 29.18, 23.68, 20.89. **SFC** analysis: OJ-H (5:95 IPA (0.15% DEA): scCO2 to 15:85 IPA (0.15% DEA): scCO2 linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.36 min (major), 4.81 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: -50.5 (c = 1.0, $CHCl_3$). **IR** (thin film): 3025, 2930, 2828, 1495, 1452, 1368, 1191, 1123, 1073, 735 cm^{-1}. **EA** Calcd. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05. Found: C, 78.23; H, 9.16.

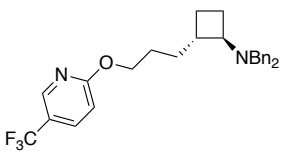
(1*R*,2*S*)-*N*,*N*-dibenzyl-2-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)cyclobutan-1-amine (7d)



Following general procedure **B**, *tert*-butyl(3-(cyclobut-1-en-1-yl)propoxy)diphenylsilane (175 mg, 0.50 mmol, 1.0 equiv) and $Bn_2NOC(O)Mes$ (270 mg, 0.75 mmol, 1.5 equiv) were used. The reaction was run at 40 °C for 46 h. After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. aq. $NaHCO_3$ (1 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at rt for 30 min. The mixture was transferred with the aid of EtOAc to a 125 mL separatory funnel containing brine (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10-15 mL). The combined organic layers were concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through a short plug of Na_2SO_4, washed

with additional EtOAc, and concentrated *in vacuo*. The crude material was immediately purified by column chromatography (~ 30 g silica gel, diameter of the column ~ 2 cm, length of the packed column ~ 18 cm) with a gradient of hexanes (100 mL) → hexanes/Et_2O = [60:1 (120 mL) → 50:1 (150 mL) → 40:1 (80 mL)] (the product on TLC was visualized with I_2), the title compound was obtained as a colorless oil (1st run: 205 mg, 75% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 199 mg, 73% yield, > 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H), 7.46-7.37 (m, 10H), 7.33-7.29 (m, 4H), 7.26-7.22 (m, 2H), 3.65-3.60 (m, 4H), 3.56 (d, *J* = 14.0 Hz, 2H), 2.94 (q, *J* = 8.1 Hz, 1H), 2.32-2.22 (m, 1H), 1.92-1.84 (m, 1H), 1.82-1.75 (m, 2H), 1.65-1.57 (m, 1H), 1.56-1.46 (m, 2H), 1.35-1.29 (m, 1H), 1.17-1.13 (m, 1H), 1.09 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.18, 135.72, 134.31, 129.62, 128.89, 128.17, 127.71, 126.75, 64.18, 63.52, 54.93, 41.04, 32.16, 30.49, 27.04, 23.06, 21.18, 19.38. **SFC** analysis: CEL-1 (1:99 MeOH (0.1% DEA): $scCO_2$, 2.50 mL/min), 12.57 min (major), 13.68 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{27}$: -61.7 (c = 1.0, $CHCl_3$). **IR** (thin film): 3027, 2929, 2856, 1493, 1427, 1360, 1110, 1028, 823, 698 cm^{-1}. **HRMS** Calcd. m/z for $C_{37}H_{46}NOSi^+$ $[M+H]^+$: 548.3343; found 548.3369.

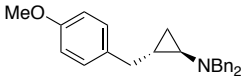
(1*R*,2*S*)-*N*,*N*-dibenzyl-2-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)propyl)cyclobutan-1-amine (7e)



Following general procedure **B**, 2-(3-(cyclobut-1-en-1-yl)propoxy)-5-(trifluoromethyl)pyridine (129 mg, 0.50 mmol, 1.0 equiv) and $Bn_2NOC(O)Mes$ (216 mg, 0.60 mmol, 1.2 equiv) were used. The reaction was run at 40 °C for 46 h. After Workup **B** and purification by column chromatography with a gradient of hexanes (100 mL) → hexanes/Et_2O = [50:1 (100 mL) → 30:1 (90 mL) → 20:1

(160 mL) → 15:1 (120 mL) → 10:1 (80 mL) → 8:1 (80 mL) (the above volumes refer to the volume of hexanes used)] (the product on TLC was visualized with I_2), the title compound was obtained as a colorless oil (1st run: 157 mg, 69% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 161 mg, 71% yield, > 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.38-7.36 (m, 4H), 7.25-7.21 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 4H), 6.80 (d, *J* = 8.7 Hz, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 3.66 (d, *J* = 14.0 Hz, 2H), 3.55 (d, *J* = 14.0 Hz, 2H), 2.97 (q, *J* = 8.1 Hz, 1H), 2.38-2.29 (m, 1H), 1.96-1.80 (m, 3H), 1.79-1.62 (m, 3H), 1.46-1.36 (m, 1H), 1.23-1.12 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.15, 145.06 (q, *J* = 4.5 Hz), 140.08, 135.62 (q, *J* = 3.1 Hz), 128.88, 128.20, 126.81, 124.23 (q, *J* = 271.2 Hz), 119.81 (q, *J* = 32.9 Hz), 111.34, 66.90, 63.52, 54.94, 40.92, 32.21, 26.80, 22.92, 21.16. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.47. **SFC** analysis: AD-H (8:92 IPA (0.15% DEA): $scCO_2$, 2.50 mL/min), 5.19 min (major), 5.81 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{27}$: -31.5 (c = 1.0, $CHCl_3$). **IR** (thin film): 3028, 2938, 2798, 1613, 1500, 1315, 1291, 1122, 1077, 698 cm^{-1}. **EA** Calcd. for $C_{27}H_{29}F_3N_2O$: C, 71.35; H, 6.43. Found: C, 71.35; H, 6.37.

(1*R*,2*R*)-*N*,*N*-dibenzyl-2-(4-methoxybenzyl)cyclopropan-1-amine (12)



An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol). The reaction tube was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous THF (0.60 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at rt. Then

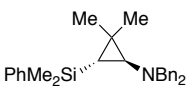
DMMS (0.22 mL, 1.80 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 10 min at rt to prepare a dark red CuH stock solution.

A separate oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into the glovebox. 1-(Cycloprop-1-en-1-ylmethyl)-4-methoxybenzene (53 mg, 73% purity[33], 0.24 mmol, 1.2 equiv, freshly prepared), Bn_2NOPiv (60 mg, 0.2 mmol, 1.0 equiv), and anhydrous THF (0.20 mL) were added to the reaction tube. Then the CuH stock solution (0.27 mL) was added via a 1 mL syringe to the reaction tube in one portion. The reaction tube was capped and then removed from the glove box. The reaction mixture was allowed to stir at rt for 18 h.

After the reaction was completed, the cap of the reaction tube was removed. While the reaction mixture was stirred at rt, sat. NH_4F in MeOH (0.4 mL) was added slowly to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred at rt for 30 min, and then transferred to a 20 mL scintillation vial with EtOAc. The solution was concentrated *in vacuo*, redissolved in hexane/EtOAc=2:1, and then passed through a short plug of silica gel eluting with hexane/EA=2:1. The resulting solution was collected in another 20 mL scintillation vial, concentrated *in vacuo*, and then $CDCl_3$ and 1,1,2,2-tetrachloroethane (16.8 mg, 0.1 mmol) were added. ^1H NMR analysis of the crude reaction mixture was carried out to determine the NMR yield. Then the solution in the NMR tube was transferred backed to the 20 mL vial with CH_2Cl_2. The solution was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (20 x 20 cm, 1000 microns, catalog # TLG-R10011B-341 from Silicycle) eluting with hexane/EtOAc = 20:1, followed by another purification with preparative thin layer chromatography (20 x 20 cm, 250 microns, catalog # TLG-R10014B-323 from Silicycle) eluting

with hexane/EtOAc = 15:1 to give the product. The title compound was obtained as a light yellow oil (1st run: 15.7 mg, 22% yield, 55.5:44.5 er, > 20:1 dr; 2nd run: 15.6 mg, 22% yield, 55.5:44.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 10H), 7.06-7.04 (m, 2H), 6.84-6.81 (m, 2H), 3.81 (s, 3H), 3.71 (d, *J* = 13.5 Hz, 2H), 3.60 (d, *J* = 13.5 Hz, 2H), 2.50 (dd, *J* = 14.5, 5.9 Hz, 1H), 2.22 (dd, *J* = 14.5, 8.1 Hz, 1H), 1.73 (dt, *J* = 6.7, 3.4 Hz, 1H), 0.97-0.92 (m, 1H), 0.60 (dt, *J* = 8.6, 4.2 Hz, 1H), 0.41 (q, *J* = 5.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.88, 139.07, 133.84, 129.51, 129.37, 128.10, 126.89, 113.77, 58.51, 55.36, 43.56, 37.59, 23.51, 14.67. **SFC** analysis: CEL-1 (1:99 MeOH: $scCO_2$ to 2:98 MeOH: $scCO_2$ linear gradient over 16 min with 1 min hold time, 2.50 mL/min), 7.67 min (major), 10.17 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: -6.8 (c = 1.0, $CHCl_3$). **IR** (thin film): 3027, 2914, 2832, 1611, 1510, 1452, 1244, 1175, 1036, 747 cm^{-1}. **HRMS** Calcd. m/z for $C_{25}H_{28}NO^+$ $[M+H]^+$: 358.2165; found 358.2177.

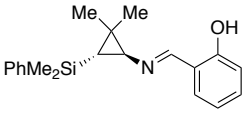
(1*R*,3*R*)-*N*,*N*-dibenzyl-3-(dimethyl(phenyl)silyl)-2,2-dimethylcyclopropan-1-amine (15a)



Following general procedure **C**, (3,3-dimethylcycloprop-1-en-1-yl)dimethyl(phenyl)silane (101 mg, 0.50 mmol, 1.0 equiv) and Bn_2NOPiv (178 mg, 0.60 mmol, 1.2 equiv) were used. After Workup **D** and purification by column chromatography with a gradient of hexanes (100 mL) → hexanes/Et_2O = [100:1 (100 mL) → 80:1 (240 mL) → 60:1 (60 mL)] (the product on TLC was visualized with I_2), the title compound was obtained as a white solid (1st run: 139 mg, 70% yield, 98.5:1.5 er, > 20:1 dr; 2nd run: 139 mg, 70% yield, 98.5:1.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.38-7.24 (m, 13H), 3.71 (d, *J* = 13.6 Hz, 2H), 3.54 (d, *J* = 13.6 Hz, 2H), 1.82 (d, *J* = 6.0 Hz, 1H), 1.04 (s, 3H), 0.91 (s, 3H), 0.28 (s, 3H), 0.26 (s, 3H), -0.22 (d, *J* = 6.0 Hz, 1H). **^{13}C NMR** (101

MHz, $CDCl_3$) δ 140.21, 139.16, 133.89, 129.52, 128.82, 128.10, 127.81, 126.90, 58.88, 54.76, 25.87, 23.77, 22.87, 19.43, -0.92, -1.20. **m.p.** 57.5-58.3 °C. **SFC** analysis: AD-H (5:95 IPA: $scCO_2$ to 20:80 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 2.68 min (major), 2.88 min (minor), 98.5:1.5 er. **Specific rotation** $[\alpha]_D^{23}$: +6.6 (c = 1.0, $CHCl_3$). **IR** (thin film): 3063, 3027, 2947, 1453, 1369, 1247, 1113, 1072, 812, 728 cm^{-1}. **EA** Calcd. for $C_{27}H_{33}NSi$: C, 81.14; H, 8.32. Found: C, 81.18; H, 8.31.

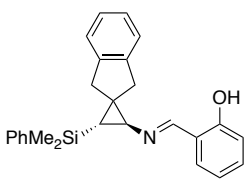
2-((*E*)-(((1*R*,3*R*)-3-(dimethyl(phenyl)silyl)-2,2-dimethylcyclopropyl)imino)methyl)phenol (15b)



An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (2.2 mg, 0.012 mmol) and (*R*)-DTBM-SEGPHOS (15.6 mg, 0.013 mmol). The reaction tube was loosely capped (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. Anhydrous THF (0.60 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at rt. Then DMMS (0.22 mL, 1.80 mmol) was added in one portion via a 1 mL syringe and the stirring was continued for another 10 min at rt to prepare an orange CuH stock solution. A second oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was loosely capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. To the second reaction tube, (3,3-Dimethylcycloprop-1-en-1-yl)dimethyl(phenyl)silane (101 mg, 0.5 mmol, 1.0 equiv) was added, and then the CuH stock solution (0.68 mL) was added via a 1 mL syringe in one portion. The reaction mixture was stirred at rt for 0.5 min, and then 1,2-benzisoxazole (76

μL) was added slowly over 2 min via microsyringe while the reaction mixture was stirred at rt. The reaction tube was capped and then removed from the glove box. The reaction mixture was allowed to stir at rt for 18 h. After Workup **D** and purification by column chromatography (silica gel was pretreated with hexanes containing 1% NEt_3) with a gradient of hexanes (contain 0.1% NEt_3) (100 mL) → hexanes (contain 0.1% NEt_3)/Et_2O = [150:1 (75 mL) → 100:1 (100 mL) → 70:1 (70 mL) → 60:1 (60 mL) → 50:1 (100 mL)], the title compound was obtained as a yellow oil (1st run: 103 mg, 63% yield, 99.5:0.5 er, > 20:1 dr; 2nd run: 100 mg, 62% yield, 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.09 (s, 1H), 8.49 (s, 1H), 7.58-7.55 (m, 2H), 7.42-7.39 (m, 3H), 7.33-7.26 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 2.84 (d, *J* = 5.3 Hz, 1H), 1.39 (s, 3H), 1.14 (s, 3H), 0.46 (d, *J* = 5.3 Hz, 1H), 0.40 (s, 3H), 0.39 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.97, 160.57, 139.34, 133.86, 131.62, 130.62, 129.13, 127.99, 119.48, 118.80, 116.88, 57.25, 26.74, 24.36, 23.74, 23.62, -1.10, -1.18. **SFC** analysis: OJ-H (2:98 MeOH (0.1% DEA): scCO2 to 7:93 MeOH (0.1% DEA): scCO2 linear gradient over 10 min with 1 min hold time, 2.50 mL/min), 4.89 min (major), 7.50 min (minor), 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: -107.2 (c = 1.0, $CHCl_3$). **IR** (thin film): 2948, 1620, 1495, 1414, 1277, 1200, 1113, 955, 905, 698 cm^{-1}. **EA** Calcd. for $C_{20}H_{25}NOSi$: C, 74.25; H, 7.79. Found: C, 74.42; H, 7.98.

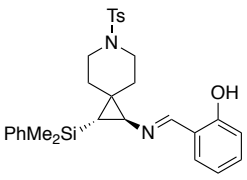
2-((*E*)-(((2*R*,3*R*)-2-(dimethyl(phenyl)silyl)-1',3'-dihydrospiro[cyclopropane-1,2'-inden]-3-yl)imino)methyl)phenol (15c)



Following general procedure **D**, (1',3'-dihydrospiro[cyclopropane-1,2'-inden]-2-en-2-yl)dimethyl(phenyl)silane (138 mg, 0.50 mmol, 1.0 equiv) was used, and the 1,2-benzisoxazole solution was added slowly via syringe

pump at a rate of 0.16 mL/h. After Workup **D** and purification by column chromatography (silica gel was pretreated with hexanes containing 1% NEt_3) with a gradient of hexanes (contain 0.1% NEt_3) (100 mL) → hexanes (contain 0.1% NEt_3)/Et_2O = [80:1 (80 mL) → 60:1 (60 mL) → 40:1 (80 mL) → 30:1 (60 mL) → 20:1 (40 mL) → 15:1 (60 mL) → 10:1 (40 mL)], the title compound was obtained as a yellow solid (1st run: 145 mg, 73% yield, 99.5:0.5 er, > 20:1 dr; 2nd run: 149 mg, 75% yield, 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.96 (s, 1H), 8.48 (s, 1H), 7.60-7.58 (m, 2H), 7.40-7.36 (m, 3H), 7.34-7.30 (m, 1H), 7.26-7.24 (m, 2H), 7.20-7.16 (m, 3H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H), 3.40 (d, *J* = 16.7 Hz, 1H), 3.29-3.21 (m, 2H), 3.05 (d, *J* = 5.5 Hz, 1H), 2.77 (d, *J* = 16.2 Hz, 1H), 0.84 (d, *J* = 5.5 Hz, 1H), 0.43 (s, 3H), 0.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.24, 160.55, 142.44, 142.31, 138.66, 133.86, 131.88, 130.81, 129.32, 128.10, 126.50, 126.33, 124.55, 124.24, 119.32, 118.94, 116.90, 56.75, 40.72, 38.66, 35.31, 22.02, -1.46, -1.75. **m.p.** 123.4-124.1 °C. **SFC** analysis: AD-H (5:95 MeOH (0.1% DEA): scCO2 to 20:80 MeOH (0.1% DEA): scCO2 linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.34 min (major), 4.65 min (minor), 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: +67.8 (c = 1.0, $CHCl_3$). **IR** (thin film): 3066, 3019, 2951, 2891, 2836, 1619, 1426, 1277, 1113, 733 cm^{-1}. **EA** Calcd. for $C_{26}H_{27}NOSi$: C, 78.54; H, 6.85. Found: C, 78.28; H, 6.70.

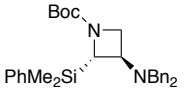
2-((*E*)-(((1*R*,2*R*)-2-(dimethyl(phenyl)silyl)-6-tosyl-6-azaspiro[2.5]octan-1-yl)imino)methyl)phenol (15d)



Following general procedure **D**, 1-(dimethyl(phenyl)silyl)-6-tosyl-6-azaspiro[2.5]oct-1-ene (199 mg, 0.50 mmol, 1.0 equiv) was used, and the 1,2-benzisoxazole solution was added slowly via syringe pump at a rate of

0.13 mL/h. After Workup **D** and purification by column chromatography (silica gel was pretreated with hexanes containing 1% NEt_3) with a gradient of hexanes (contain 0.1% NEt_3)/CH_2Cl_2 = 50:1 (100 mL) → hexanes (contain 0.1% NEt_3)/EtOAc = [30:1 (60 mL) → 25:1 (50 mL) → 20:1 (40 mL) → 15:1 (60 mL) → 12:1 (60 mL) → 10:1 (80 mL) → 8:1 (80 mL) → 7:1 (140 mL) → 6:1 (60 mL) → 5:1 (100 mL) → 4:1 (40 mL) (the above volumes refer to the volume of hexanes used)], the title compound was obtained as a yellow solid (1st run: 163 mg, 63% yield, 98:2 er, > 20:1 dr; 2nd run: 147 mg, 57% yield, 98:2 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.48-7.46 (m, 2H), 7.40-7.28 (m, 6H), 7.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H), 3.35 (dt, *J* = 9.8, 4.1 Hz, 1H), 3.23 (dt, *J* = 9.7, 4.0 Hz, 1H), 2.82 (d, *J* = 5.4 Hz, 1H), 2.71-2.63 (m, 2H), 2.43 (s, 3H), 2.04 (ddd, *J* = 13.5, 9.5, 3.9 Hz, 1H), 1.83 (dt, *J* = 13.8, 3.7 Hz, 1H), 1.76 (ddd, *J* = 13.4, 9.5, 3.9 Hz, 1H), 1.33 (dt, *J* = 13.4, 3.7 Hz, 1H), 0.43 (d, *J* = 5.4 Hz, 1H), 0.33 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.95, 160.38, 143.42, 138.28, 133.70, 133.61, 132.05, 130.82, 129.77, 129.42, 128.12, 127.68, 119.16, 119.00, 116.92, 55.55, 46.15, 45.80, 32.66, 32.62, 31.02, 23.21, 21.65, -1.24, -1.36. **m.p.** 60.1-62.8 °C. **SFC** analysis: AD-H (20:80 MeOH (0.1% DEA): scCO2, 2.50 mL/min), 4.60 min (major), 5.80 min (minor), 98:2 er. **Specific rotation** $[\alpha]_D^{23}$: +13.8 (c = 1.0, $CHCl_3$). **IR** (thin film): 2953, 2844, 1619, 1427, 1334, 1276, 1163, 1090, 908, 722 cm^{-1}. **EA** Calcd. for $C_{29}H_{34}N_2O_3SSi$: C, 67.15; H, 6.61. Found: C, 67.54; H, 6.65.

***tert*-butyl (2*S*,3*R*)-3-(dibenzylamino)-2-(dimethyl(phenyl)silyl)azetidine-1-carboxylate (7f)**

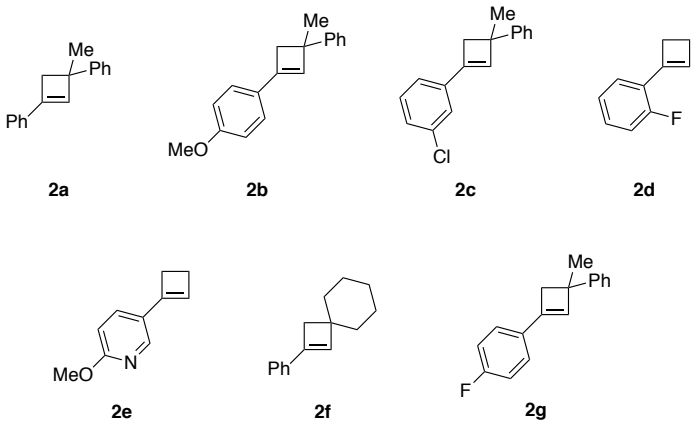


Following general procedure **B**, *tert*-butyl 4-(dimethyl(phenyl)silyl)azete-1(2*H*)-carboxylate (145 mg, 0.50 mmol, 1.0 equiv) and $Bn_2NOC(O)Mes$ (270 mg, 0.75

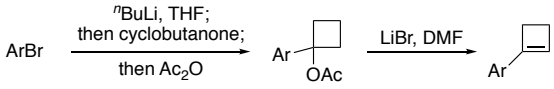
mmol, 1.5 equiv) were used. The reaction was run at 40 °C for 46 h. After Workup **D** and purification by column chromatography with a gradient of hexanes (100 mL) → hexanes/acetone = [80:1 (80 mL) → 70:1 (70 mL) → 50:1 (100 mL) → 30:1 (180 mL)] (the product on TLC was visualized with I_2), the title compound was obtained as a colorless oil (1st run: 223 mg, 92% yield, > 99.5:0.5 er, > 20:1 dr; 2nd run: 223 mg, 92% yield, > 99.5:0.5 er, > 20:1 dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 3H), 7.36-7.20 (m, 12H), 4.16 (d, *J* = 5.7 Hz, 1H), 3.94-3.92 (m, 1H), 3.63-3.45 (m, 6H), 1.43 (s, 9H), 0.40 (s, 3H), 0.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.64, 138.99, 136.27, 134.30, 129.42, 128.76, 128.33, 127.90, 127.09, 79.38, 57.41, 53.94, 52.87, 52.61, 28.56, -4.15, -4.68. **SFC** analysis: OJ-H (5:95 IPA: $scCO_2$ to 20:80 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 2.87 min (major), 3.17 min (minor), > 99.5:0.5 er. **Specific rotation** $[\alpha]_D^{23}$: +11.1 (c = 1.0, $CHCl_3$). **IR** (thin film): 2973, 1691, 1408, 1364, 1248, 1154, 1111, 1028, 832, 696 cm^{-1}. **EA** Calcd. for $C_{30}H_{38}N_2O_2Si$: C, 74.03; H, 7.87. Found: C, 73.75; H, 8.04.

1.5.5 Preparation of Alkene Substrates and Amination Reagents

Synthesis of 1-Arylcyclobutenes: All the 1-arylcyclobutenes used in this chapter are listed below. **2a-c**[35], **2f-g**[35] are known compounds and were prepared by following previously reported procedures.



Synthesis of **2d**, **2e**.



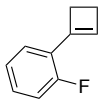
General Procedure E[36]

A 250 mL round bottom flask containing a magnetic stir bar was charged with the corresponding aryl bromide (21.0 mmol, 1.05 equiv) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (63 mL) was added, and then the mixture was cooled to -78 °C. ^{n}BuLi (2.5 M in hexane, 1.1 equiv, 8.8 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 15 min, and then cyclobutanone (20.0 mmol, 1.0 equiv, 1.40 g) in anhydrous THF (20 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 30 min, and was allowed to warm to rt and stirred for an additional 30 min. Then the reaction mixture was cooled to -78 °C, and Ac_2O (40.0 mmol, 2.0 equiv, 4.08 g) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The septum was removed, and the reaction mixture was concentrated *in vacuo*.

Et_2O and aq. $NaHCO_3$ were added. The layers were separated, and the organic layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and then purified by column chromatography on silica gel to afford the corresponding 1-arylcyclobutyl acetate.

A 50 mL round bottom flask containing a magnetic stir bar was charged with the corresponding 1-arylcyclobutyl acetate (1.0 equiv) and LiBr (10.0 equiv), and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous DMF (13 mL) was added, and then the reaction mixture was stirred at 100 °C for 1 h or overnight (as indicated for each substrate). The mixture was allowed to cool to rt, and was immediately quenched with water. Et_2O and aq. $NaHCO_3$ were added. The layers were separated, and the organic layer was extract with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and then purified by column chromatography on silica gel to afford the corresponding 1-arylcyclobutene (Note: **2d** and **2e** are very air-sensitive, and therefore need to be immediately stored under nitrogen in the glovebox freezer at -30 °C once prepared).

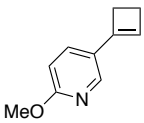
1-(cyclobut-1-en-1-yl)-2-fluorobenzene (2d)



Following general procedure **E**, 1-(2-fluorophenyl)cyclobutyl acetate (6.29 mmmol, 1.31 g) was used. The title compound was obtained as a colorless oil (0.47 g, 36% yield over two steps) after purification by column chromatography on silica gel (eluting with pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.19 (m, 2H), 7.14-7.03 (m, 2H), 6.42-6.40 (m, 1H), 2.91-2.89 (m, 2H), 2.64-2.63 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.25 (d, J = 251.3 Hz), 140.96, 133.13 (d, J = 7.3 Hz), 128.66 (d, J = 8.4 Hz), 127.01 (d, J = 4.4 Hz), 123.97 (d, J =

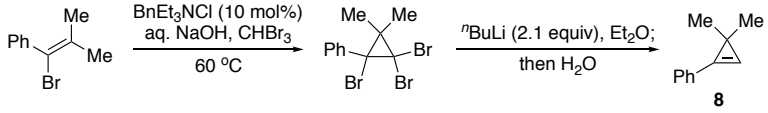
3.5 Hz), 123.04 (d, J = 14.3 Hz), 115.61 (d, J = 21.0 Hz), 30.00, 27.96. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.94. **IR** (thin film): 3070, 2918, 2834, 1490, 1446, 1237, 1214, 1176, 1031, 747 cm^{-1}. **HRMS** Calcd. m/z for $C_{10}H_{10}F^+$ $[M+H]^+$: 149.0761; found 149.0757.

5-(cyclobut-1-en-1-yl)-2-methoxypyridine (2e)



Following general procedure **E**, 1-(6-methoxypyridin-3-yl)cyclobutyl acetate (6.60 mmmol, 1.46 g) was used. The title compound was obtained as a white solid (0.26 g, 18% yield over two steps) after purification by column chromatography on silica gel (eluting with pentane ~ pentane/Et_2O = 30:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, J = 2.3 Hz, 1H), 7.57 (dd, J = 8.6, 2.4 Hz, 1H), 6.68 (dd, J = 8.6, 0.7 Hz, 1H), 6.20 (t, J = 1.2 Hz, 1H), 3.93 (s, 3H), 2.80-2.78 (m, 2H), 2.56-2.54 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.50, 143.39, 143.12, 134.78, 126.64, 124.65, 110.69, 77.48, 77.16, 76.84, 53.60, 28.90, 26.91. **m.p.** 46.7-48.0 °C. **IR** (thin film): 2948, 2840, 1723, 1681, 1601, 1492, 1372, 1288, 1020, 832 cm^{-1}. **HRMS** Calcd. m/z for $C_{10}H_{12}NO^+$ $[M+H]^+$: 162.0913; found 162.0905.

Synthesis of 1-Arylcyclopropene:



(3,3-dimethylcycloprop-1-en-1-yl)benzene (8)

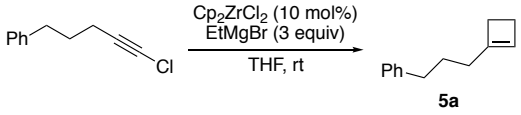
A 25 mL round bottom flask containing a magnetic stir bar was charged with (1-bromo-2-methylprop-1-en-1-yl)benzene[37] (5.05 mmol, 1.0 equiv, 1.07 g), $BnEt_3NCl$ (0.505 mmol, 0.1 equiv, 115 mg), and bromoform (40.4 mmol, 8.0 equiv, 3.5 mL). While the

reaction mixture was stirred vigorously at rt, NaOH (40.4 mmol, 8.0 equiv, 1.62 g) in water (1.6 mL) was added dropwise. Then the flask was capped with a septum and attached to a balloon filled with air. The reaction mixture was stirred vigorously at 60 °C for 36 h. The reaction mixture was allowed to cool to rt, and diluted with CH_2Cl_2 (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were filtered through a short plug of silica gel and washed with Et_2O. The resulting solution was concentrated *in vacuo*, and then purified by column chromatography on silica gel eluting with hexanes to give (1,2,2-tribromo-3,3-dimethylcyclopropyl)benzene.

A 25 mL round bottom flask containing a magnetic stir bar was charged with (1,2,2-tribromo-3,3-dimethylcyclopropyl)benzene (2.0 mmol, 1.0 equiv, 766 mg) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous Et_2O (4 mL) was added, and then the mixture was cooled to -78 °C. *n*BuLi (2.5 M in hexane, 2.1 equiv, 1.68 mL) was added dropwise at -78 °C. The reaction mixture was allowed to slowly warmed to rt over 2 h while being stirred. Then the reaction mixture was cooled to 0 °C, and water (0.2 mL) was added dropwise. The reaction mixture was allowed to warm to rt and was stirred at rt for 10 min. Then saturated aqueous NH_4Cl (2 mL) was added dropwise, and the reaction mixture was stirred at rt for 5 min. The septum on the flask was removed. The reaction mixture was diluted with pentane (50 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with pentane (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel (eluting with pentane) to give the title compound as a colorless oil (0.25 g, 53% yield over two steps) (Note: **8** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). **^{1}H NMR** (400 MHz,

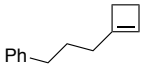
$CDCl_3$) δ 7.52-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.34-7.30 (m, 2H), 1.35 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.23, 129.58, 128.87, 128.73, 128.52, 115.19, 27.02, 19.41. **IR** (thin film): 2924, 2861, 1675, 1598, 1493, 1444, 1371, 1308, 1024, 700 cm^{-1}. **HRMS** Calcd. m/z for $C_{11}H_{13}^+$ $[M+H]^+$: 145.1012; found 145.1022.

Synthesis of 1-Alkylcyclobutenes:[38,39]



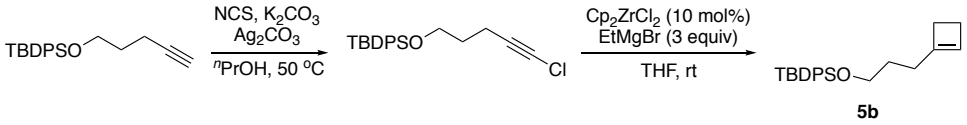
5a

(3-(cyclobut-1-en-1-yl)propyl)benzene (5a)

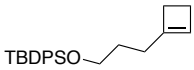


A 100 mL round bottom flask containing a magnetic stir bar was transferred into a nitrogen-filled glovebox. Cp_2ZrCl_2 (1.2 mmol, 0.1 equiv, 351 mg) was added to the flask. The flask was capped with a septum, removed from the glovebox, and then attached to a balloon filled with argon. Anhydrous THF (24 mL) was added. While the reaction mixture was stirred at rt, EtMgBr (1 M in THF, 36 mmol, 3.0 equiv, 36 mL) was added dropwise. Then (5-chloropent-4-yn-1-yl)benzene[40] (12 mmol, 1.0 equiv, 2.14 g) was added dropwise at rt. The reaction mixture was stirred at rt for 48 h. The reaction mixture was cooled to 0 °C in an ice bath, and water was added slowly to quench the reaction mixture. The mixture was diluted with water (50 mL) and pentane (50 mL). The layers were separated and the aqueous layer was extracted with pentane (50 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with pentane (Note: (5-chloropent-4-yn-1-yl)benzene was not fully consumed in the reaction, and it could poison the CuH catalyst in the subsequent hydroamination reactions.

Therefore, the last few product-containing fractions from the column chromatography were analyzed by GC to determine whether they contained (5-chloropent-4-yn-1-yl)benzene, and only the clean fractions were collected.) to afford the title compound as a colorless oil (0.58 g, 28% yield) (Note: **5a** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.21-7.18 (m, 3H), 5.71 (br, 1H), 2.67-2.63 (m, 2H), 2.44-2.42 (m, 2H), 2.37-2.35 (m, 2H), 2.06-2.03 (m, 2H), 1.81-1.74 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.47, 142.65, 128.61, 128.41, 127.15, 125.82, 35.76, 31.31, 30.80, 28.72, 26.71. **IR** (thin film): 3028, 2922, 2842, 1630, 1604, 1496, 1453, 1171, 1030, 698 cm^{-1}. **HRMS** Calcd. m/z for $C_{13}H_{17}^+$ $[M+H]^+$: 173.1325; found 173.1315.



***tert*-butyl(3-(cyclobut-1-en-1-yl)propoxy)diphenylsilane (5b)**



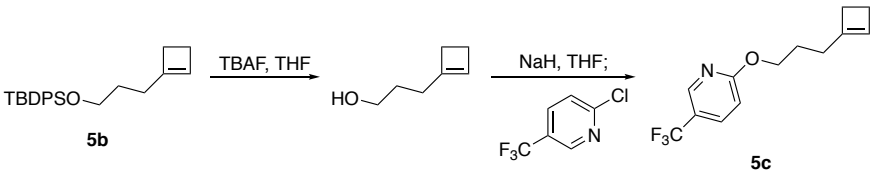
A 100 mL round bottom flask containing a magnetic stir bar was charged with NCS (22.0 mmol, 2.0 equiv, 2.95 g), K_2CO_3 (5.5 mmol, 0.5 equiv, 0.76 g), and Ag_2CO_3 (0.11 mmol, 0.1 equiv, 0.30 g) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous ^{n}PrOH (22 mL) was added. Then *tert*-butyl(pent-4-yn-1-yloxy)diphenylsilane[41] (11.0 mmol, 1.0 equiv, 3.55 g) was added dropwise at rt. The reaction mixture was stirred at 50 °C for 48 h. Then the reaction mixture was cooled to 0 °C, and brine was added. The resulting mixture was extracted with Et_2O, and the combined organic layers were washed with water (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The residue was purified by column chromatography on silica gel to give *tert*-butyl((5-chloropent-4-yn-1-yl)oxy)diphenylsilane.

A 100 mL round bottom flask containing a magnetic stir bar was transferred into a nitrogen-filled glovebox. Cp_2ZrCl_2 (1.2 mmol, 0.1 equiv, 351 mg) was added to the flask. The flask was capped with a septum, removed from the glovebox, and then attached to a balloon filled with argon. Anhydrous THF (24 mL) was added. While the reaction mixture was stirred at rt, EtMgBr (1 M in THF, 36 mmol, 3.0 equiv, 36 mL) was added dropwise. Then *tert*-butyl((5-chloropent-4-yn-1-yl)oxy)diphenylsilane (12 mmol, 1.0 equiv, 4.28 g) was added dropwise at rt. The reaction mixture was stirred at rt for 72 h. The reaction mixture was cooled to 0 $^{\circ}$C in an ice bath, and water was added slowly to quench the reaction mixture. The mixture was diluted with water (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with 0-2% EtOAc in hexanes to give a mixture of the title compound and the 1-chloroalkyne starting material. The isolated material contains 24% (w/w) *tert*-butyl((5-chloropent-4-yn-1-yl)oxy)diphenylsilane impurity, which was removed by carrying out a further transformation.

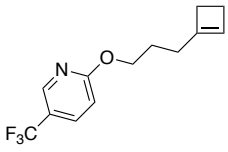
A 25 mL round bottom flask containing a magnetic stir bar was charged with the material isolated from the previous step (1.69 g material, contains 1.14 mmol of *tert*-butyl((5-chloropent-4-yn-1-yl)oxy)diphenylsilane, 1.0 equiv) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (5.7 mL) was added, and then the mixture was cooled to -78 $^{\circ}$C. ^{n}BuLi (2.5 M in hexane, 2.28 mmol, 2.0 equiv, 0.91 mL) was

added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, and then anhydrous PhCHO (4.56 mmol, 4.0 equiv, 484 mg) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 30 min, and was allowed to warm to rt and stirred for 30 min. Water was slowly added to quench the reaction mixture. The resulting mixture was extracted with hexane (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 0-2% EtOAc in hexanes to give the title compound as a colorless oil (1.21 g, 13% overall yield) (Note: **8b** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.45-7.36 (m, 6H), 5.63 (tt, *J* = 1.7, 0.9 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.39-2.37 (m, 2H), 2.32-2.29 (m, 2H), 2.11-2.07 (m, 2H), 1.74-1.67 (m, 2H), 1.05 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.39, 135.74, 134.25, 129.65, 127.73, 126.99, 63.70, 31.31, 29.90, 27.55, 27.03, 26.61, 19.40. **IR** (thin film): 3071, 2929, 2856, 1472, 1427, 1105, 953, 822, 737, 699 cm^{-1}. **EA** Calcd. for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63. Found: C, 78.91; H, 8.63.



5b **5c**

2-(3-(cyclobut-1-en-1-yl)propoxy)-5-(trifluoromethyl)pyridine (5c)

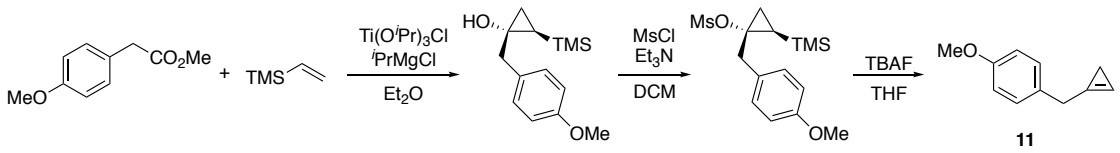


A 25 mL round bottom flask containing a magnetic stir bar was charged with **5b** (2.4 mmol, 1.0 equiv, 843 mg) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (4.8 mL) was added, and then the mixture was cooled to 0 °C. TBAF (1 M in THF, 2.0 equiv, 4.8 mL) was

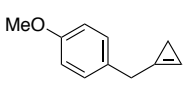
added dropwise at 0 °C. The reaction mixture was allowed to warm to rt and was stirred at rt for 3 h. Then the reaction mixture was diluted with saturated aqueous NH_4Cl and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-40% Et_2O in pentane) to afford 3-(cyclobut-1-en-1-yl)propan-1-ol. A 25 mL round bottom flask containing a magnetic stir bar was charged with 3-(cyclobut-1-en-1-yl)propan-1-ol (2.24 mmol, 1.12 equiv, 251 mg) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (4.5 mL) was added, and then the mixture was cooled to 0 °C. NaH (2.7 mmol, 1.35 equiv, 65 mg) was added in several portions at 0 °C. The mixture was allowed to warm to rt and was stirred at rt for 15 min. Then 2-chloro-5-(trifluoromethyl)pyridine (2.0 mmol, 1.0 equiv, 364 mg) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-3% EtOAc in hexanes) to give the title compound as a colorless oil (0.50 g, 93% yield over two steps) (Note: **5c** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44-8.41 (m, 1H), 7.75 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.72 (br, 1H), 4.37 (t, *J* = 6.6 Hz, 2H), 2.44 (ddd, *J* = 4.2, 2.7, 1.1 Hz, 2H), 2.36-2.33 (m, 2H), 2.16 (dt, *J* = 7.7, 3.7 Hz, 2H), 1.93 (tt, *J* = 7.2, 6.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.13, 149.53, 145.07 (q, *J* = 4.4 Hz), 135.69 (q, *J* = 3.2 Hz), 127.60, 124.21 (q, *J* = 271.0 Hz), 119.91 (q, *J* = 33.0 Hz), 111.37, 66.50, 31.29, 27.65, 26.68, 26.25. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -

61.52. **IR** (thin film): 2924, 2844, 1614, 1501, 1315, 1160, 1123, 1078, 1011, 834 cm^{-1}. **EA** Calcd. for $C_{13}H_{14}F_3NO$: C, 60.70; H, 5.49. Found: C, 60.72; H, 5.66.

Synthesis of 1-Alkylcyclopropene:[42]



1-(cycloprop-1-en-1-ylmethyl)-4-methoxybenzene (11)

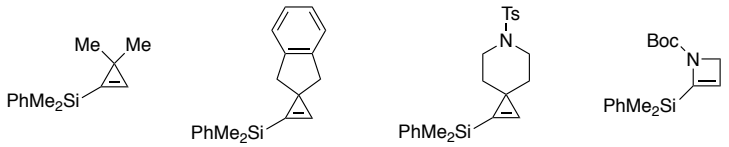


A 250 mL round bottom flask containing a magnetic stir bar was capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous Et_2O (53 mL) and $Ti(O^iPr)_3Cl$ (7.50 mmol, 1.5 equiv, 1.95 g) were added, and then the mixture was cooled to -60 °C. ^{i}PrMgCl (2.0 M in Et_2O, 2.9 equiv, 7.25 mL) was added dropwise at -60 °C. The reaction mixture was stirred at -60 °C for 10 min, and then a mixture of methyl 2-(4-methoxyphenyl)acetate (5.0 mmol, 1.0 equiv, 0.90 g) and trimethyl(vinyl)silane (7.5 mmol, 1.5 equiv, 0.75 g) in anhydrous Et_2O (0.27 mL) was added dropwise. The reaction mixture was allowed to warm to -25 °C over 30 min, stirred at -25 ~ -20 °C for 1 h, and then was warmed to 0 °C and stirred for 2 h. Water (2.5 mL) in THF (10 mL) was added slowly, and then the reaction mixture was allowed to warm to rt and stirred for 30 min. The reaction mixture was passed through a short plug of Celite, washed with Et_2O, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (pretreated with 1% Et_3N in hexanes) and eluted with a gradient of hexanes/Et_2O = 8:1~3:1 to afford 1-(4-methoxybenzyl)-2-(trimethylsilyl)cyclopropan-1-ol.

A 25 mL round bottom flask containing a magnetic stir bar was charged with 1-(4-methoxybenzyl)-2-(trimethylsilyl)cyclopropan-1-ol (1.8 mmol, 1.0 equiv, 0.45 g), and then CH_2Cl_2 (10 mL) and Et_3N (7.2 mmol, 4.0 equiv, 0.73 g) were added. The mixture was cooled to 0 $^{\circ}$C, and MsCl (3.6 mmol, 2.0 equiv, 0.41 g) was added dropwise. The reaction mixture was stirred at 0 $^{\circ}$C for 1 h. Then the reaction mixture was allowed to warm to rt, and saturated aqueous $NaHCO_3$ (10 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and used in the next step without further purification.

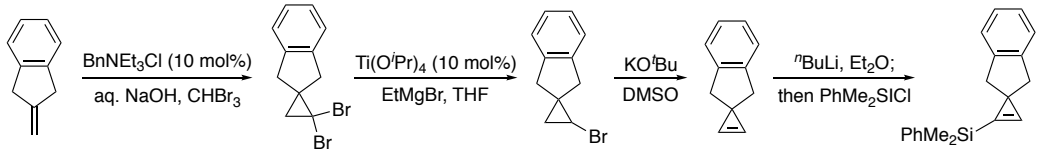
A 100 mL round bottom flask containing a magnetic stir bar was charged with the crude material from the last step. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (10 mL) was added, and then TBAF (1 M in THF, 9.9 mL) was added dropwise at rt. The reaction mixture was stirred at rt for 2 h, and then saturated aqueous NH_4Cl (10 mL) and Et_2O (30 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and immediately purified by column chromatography on silica gel (eluting with pentane and then pentane/Et_2O = 60:1) to give the title compound as a colorless oil (0.23 g, 73% purity[33], 21% yield over 3 steps) (Note: **11** was stored under nitrogen in the glovebox freezer at -30 $^{\circ}$C once prepared). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20-7.17 (m, 2H), 6.88-6.86 (m, 2H), 6.57 (m, 1H), 3.81 (s, 3H), 3.79 (s, 2H), 1.01 (d, J = 1.8 Hz, 2H). **IR** (thin film): 2955, 2876, 2834, 1610, 1511, 1301, 1244, 1174, 1035, 840 cm^{-1}. **HRMS** Calcd. m/z for $C_{11}H_{13}O^+$ $[M+H]^+$: 161.0961; found 161.0972.

Synthesis of 1-Silyl Substituted Three- and Four-Membered Cycloalkenes:



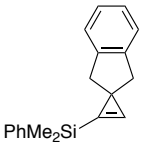
13a **13b** **13c** **5d**

All the 1-silyl substituted three- and four-membered cycloalkenes used in this chapter are listed above. **13a**[43] is a known compound and was prepared by following previously reported procedures.



13b

(1',3'-dihydrospiro[cyclopropane-1,2'-inden]-2-en-2-yl)dimethyl(phenyl)silane (13b)



A 50 mL round bottom flask containing a magnetic stir bar was charged with 2-methylene-2,3-dihydro-1*H*-indene (19.0 mmol, 1.0 equiv, 2.51 g), $BnEt_3NCl$ (1.9 mmol, 0.1 equiv, 439 mg), and bromoform (76.0 mmol, 4.0 equiv, 6.7 mL). While the reaction mixture was stirred vigorously at rt, NaOH (76.0 mmol, 4.0 equiv, 3.1 g) in water (3.1 mL) was added dropwise. Then the flask was capped with a septum and attached to a balloon filled with air. The reaction mixture was stirred vigorously at 60 °C for 24 h. The reaction mixture was allowed to cool to rt, and diluted with CH_2Cl_2 (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and then

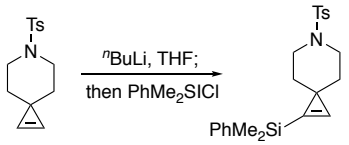
purified by column chromatography on silica gel eluting with hexanes/ CH_2Cl_2 = 100:1 to give 2,2-dibromo-1',3'-dihydrospiro[cyclopropane-1,2'-indene].

A 100 mL round bottom flask containing a magnetic stir bar was charged with 2,2-dibromo-1',3'-dihydrospiro[cyclopropane-1,2'-indene] (13.5 mmol, 1.0 equiv) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (27 mL) and $Ti(O^iPr)_4$ (0.13 mmol, 0.1 equiv, 0.40 mL) were added. While the reaction mixture was stirred at rt, EtMgBr (3 M in Et_2O, 1.3 equiv, 5.8 mL) was added over 1 h via syringe pump. The reaction mixture was stirred at rt for 4 h. Then the reaction mixture was cooled to 0 $^\circ$C, and 10% aq. H_2SO_4 (10 mL) was added dropwise to quench the reaction mixture. The mixture was diluted with H_2O (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with E_2O (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-2% Et_2O in pentane) to give 2-bromo-1',3'-dihydrospiro[cyclopropane-1,2'-indene].

A 100 mL round bottom flask containing a magnetic stir bar was charged with 2-bromo-1',3'-dihydrospiro[cyclopropane-1,2'-indene] (6.0 mmol, 1.0 equiv, 1.34 g) and then capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous DMSO (13 mL) was added. While the reaction mixture was stirred at rt, KO^tBu (9.0 mmol, 1.5 equiv, 1.01 g) in anhydrous DMSO (3.3 mL) was added dropwise. The reaction mixture was stirred at rt overnight. Then the reaction mixture was cooled to 0 $^\circ$C, and water (100 mL) was slowly added to quench the reaction mixture. Et_2O (75 mL) was added. The layers were separated and the

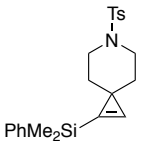
aqueous layer was extract with Et_2O (100 mL). The combine organic layers were washed with water (3 x 75 mL), then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with pentane) to give 1',3'-dihydrospiro[cyclopropane-1,2'-inden]-2-ene.

A 10 mL round bottom flask with a magnetic stir bar was charged with 1',3'-dihydrospiro[cyclopropane-1,2'-inden]-2-ene (1.35 mmol, 1.0 equiv, 192 mg) and anhydrous Et_2O (1.4 mL) under nitrogen. The mixture was cooled to -78 $^{\circ}$C, and ^{n}BuLi (2.5 M in hexane, 1.05 equiv, 0.57 mL) was added dropwise. The reaction mixture was stirred at -78 $^{\circ}$C for 1 h, and then at -10 $^{\circ}$C for 1 h. The resulting solution was added over 20 min to another 25 mL round bottom flask containing $PhMe_2SiCl$ (1.48 mmol, 1.1 equiv, 263 mg) and anhydrous Et_2O (2.8 mL) at -40 $^{\circ}$C under nitrogen. The reaction mixture was stirred at -40 $^{\circ}$C for 1 h and at rt for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL). Then water (20 mL) and Et_2O (60 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (60 mL). The combined organic layers were dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluted with 0-2% CH_2Cl_2 in hexanes) to afford the title compound as a colorless oil (0.29 g, 20% yield over 4 steps) (Note: **13b** was stored under nitrogen in the glovebox freezer at -30 $^{\circ}$C once prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96-7.95 (m, 1H), 7.56-7.53 (m, 2H), 7.41-7.32 (m, 3H), 7.16 (s, 4H), 2.87 (d, J = 17.0 Hz, 2H), 2.71 (d, J = 17.2 Hz, 2H), 0.43 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.63, 137.40, 133.81, 131.79, 129.44, 127.99, 126.85, 125.97, 124.27, 44.30, 26.60, -1.94. **IR** (thin film): 3068, 2957, 2880, 2825, 1676, 1482, 1427, 1248, 1113, 733 cm^{-1}. **EA** Calcd. for $C_{19}H_{20}Si$: C, 82.55; H, 7.29. Found: C, 82.74; H, 7.45.



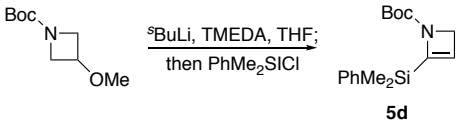
13c

1-(dimethyl(phenyl)silyl)-6-tosyl-6-azaspiro[2.5]oct-1-ene (13c)



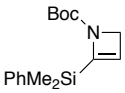
A 25 mL round bottom flask with a magnetic stir bar was charged with 6-tosyl-6-azaspiro[2.5]oct-1-ene[44] (3.0 mmol, 1.0 equiv, 790 mg) and anhydrous THF (8.7 mL) under nitrogen. The mixture was cooled to -78 °C, and *n*BuLi (2.5 M in hexane, 1.02 equiv, 1.23 mL) was added dropwise (Note: The addition process of *n*BuLi needs to be terminated once the reaction mixture turns from colorless to slightly pinkish. Otherwise, disilylated byproduct, which is difficult to seperate from the product, is formed). Then the reaction mixture was stirred at -10 °C for 1 h. The resulting suspension was added over 30 min to another 50 mL round bottom flask containing $PhMe_2SiCl$ (3.3 mmol, 1.1 equiv, 563 mg) and anhydrous THF (6.0 mL) at -40 °C under nitrogen. The reaction mixture was stirred at -40 °C for 1 h and at rt for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL). Then water (30 mL) and CH_2Cl_2 (60 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (60 mL). The combined organic layers were dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluted with hexanes/EtOAc/ CH_2Cl_2 = 30:1:2) to afford the title compound as a white solid (0.90 g, 76% yield) (Note: **13c** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.64-7.62 (m, 2H), 7.41-7.39 (m, 2H), 7.37-7.27 (m, 5H), 3.11 (ddd, *J* = 10.8, 6.6, 3.9 Hz, 2H), 2.81 (ddd, *J* = 11.5, 8.5, 3.6 Hz, 2H), 2.47 (s, 3H), 1.61 (td, *J* = 8.6, 4.2 Hz, 2H), 1.41-1.35 (m, 2H), 0.32 (s, 6H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 143.29, 136.99, 136.86, 133.65, 133.51, 131.87, 129.62, 129.55, 127.99,

127.87, 47.20, 38.17, 22.52, 21.69, -2.25. **m.p.** 65.6-66.2 °C. **IR** (thin film): 2937, 2903, 2837, 1667, 1428, 1351, 1247, 1162, 1112, 722 cm^{-1}. **EA** Calcd. for $C_{22}H_{27}NO_2SSi$: C, 66.46; H, 6.84. Found: C, 66.33; H, 6.61.



5d

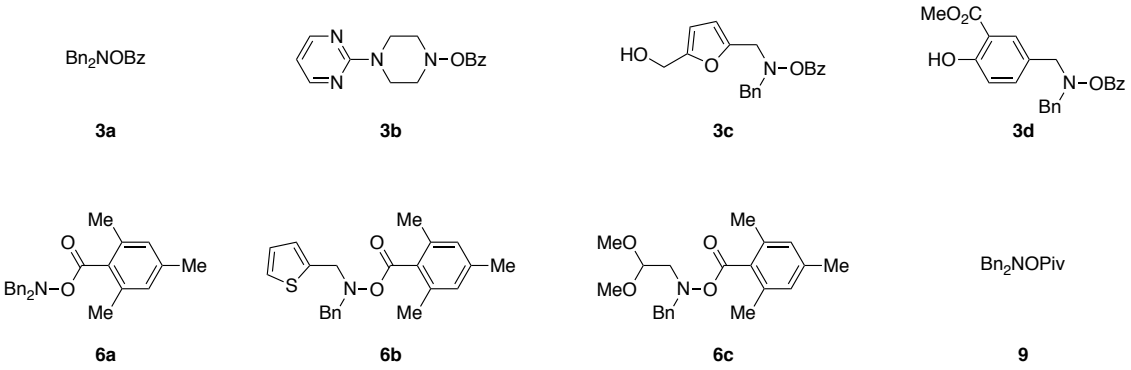
***tert*-butyl 4-(dimethyl(phenyl)silyl)azete-1(2*H*)-carboxylate[45] (5d)**



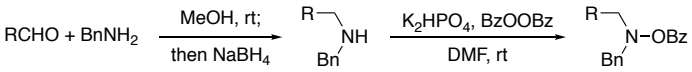
A 100 mL round bottom flask containing a magnetic stir bar was capped with a septum. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Then *tert*-butyl 3-methoxyazetidine-1-carboxylate (4.0 mmol, 1.0 equiv, 749 mg) and anhydrous THF (25 mL) were added, and the mixture was cooled to -78 °C. TMEDA (10.0 mmol, 2.5 equiv, 1.16 g) was added. Then ^{s}BuLi (1.3 M in cyclohexane, 2.5 equiv, 7.7 mL) was added dropwise over 10 min while the reaction mixture was stirred at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, and then $PhMe_2SiCl$ (10.0 mmol, 2.5 equiv, 1.71 g) was added. The reaction mixture was stirred at -78 °C for 1 h, and then at rt for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL). Then Et_2O (100 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluted with 0-9% Et_2O in hexanes). The resulting material was redissolved in Et_2O (3 mL), filtered through a short plug of basic activated alumina, and washed with additional Et_2O. The collected Et_2O solution was concentrated *in vacuo* to afford the pure product as a

colorless oil (0.47 g, 40% yield) (Note: **5d** was stored under nitrogen in the glovebox freezer at -30 °C once prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.40-7.33 (m, 3H), 5.89 (s, 1H), 4.55 (s, 2H), 1.33 (s, 9H), 0.47 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.48, 152.00, 136.47, 134.23, 129.46, 127.85, 126.31, 80.34, 59.78, 28.48, -3.07. **IR** (thin film): 2977, 1695, 1390, 1366, 1247, 1164, 1139, 1113, 1020, 814 cm^{-1}. **HRMS** Calcd. m/z for $C_{16}H_{24}NO_2Si^+$ $[M+H]^+$: 290.1571; found 290.1575.

Synthesis of Amination Reagents: All the amination reagents used in this chapter are listed below. **3a**[46], **3b**[47], **6a**[48], **9**[49] are known compounds and were prepared by following previously reported procedures.



Synthesis of **3c**, **3d**.



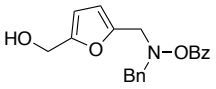
General Procedure F

A 100 mL round bottom flask containing a magnetic stir bar was charged with the corresponding aldehyde (1.0 equiv), $BnNH_2$ (1.0 equiv), and MeOH (2.0 M). The reaction mixture was stirred at rt for 6 h. Then $NaBH_4$ (2.0 equiv) was added in several portions at rt. The

reaction mixture was stirred at rt overnight, and then quenched with 5 M aq. NaOH. The resulting mixture was concentrated *in vacuo*, and then diluted with CH_2Cl_2 and water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and used in the next step without further purification.

A 100 mL round bottom flask containing a magnetic stir bar was charged with the crude material from the first step, and then DMF and K_2HPO_4 were added. BzOOBz was then added in one portion at rt. The reaction mixture was stirred at rt until BzOOBz was completely consumed (as indicated by TLC analysis), and then diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and then purified by column chromatography on silica gel to give the corresponding amination reagent.

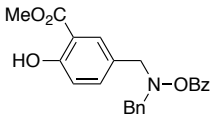
(5-(((benzoyloxy)(benzyl)amino)methyl)furan-2-yl)methanol (3c)



Following general procedure **F**, 5-(hydroxymethyl)furan-2-carbaldehyde (40 mmol, 5.0 g) and $BnNH_2$ (40 mmol, 4.4 mL) were used in the first step, and BzOOBz (contains 25% water, 40 mmol, 12.9 g), K_2HPO_4 (80 mmol, 13.9 g), and DMF (50 mL) were used in the second step. The title compound was obtained as a white solid (2.83 g, 21% yield over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.54 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.47-7.39 (m, 4H), 7.35-7.26 (m, 3H), 6.28 (d, *J* = 3.1 Hz, 1H), 6.23 (d, *J* = 3.1 Hz, 1H), 4.56 (s, 2H), 4.24 (s, 2H), 4.23 (s, 2H), 2.06 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.87, 154.34, 149.61, 135.46, 133.10, 129.68, 129.48, 129.25, 128.51, 128.47, 127.91, 111.05, 108.70, 62.08, 57.62, 54.12. **m.p.** 80.5-82.3 °C. **IR** (thin film): 3419, 3031, 2864, 1733, 1450, 1242,

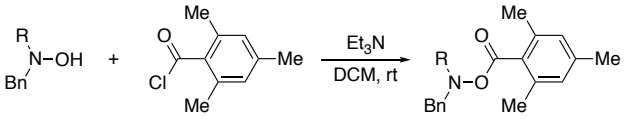
1083, 1062, 1015, 698 cm^{-1}. **EA** Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68. Found: C, 71.48; H, 5.74.

methyl 5-(((benzoyloxy)(benzyl)amino)methyl)-2-hydroxybenzoate (3d)

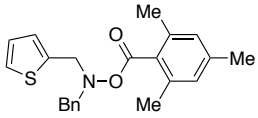


Following general procedure **F**, methyl 5-formyl-2-hydroxybenzoate (20 mmol, 3.6 g) and $BnNH_2$ (20 mmol, 2.2 mL) were used in the first step, and BzOOBz (contains 25% water, 22 mmol, 7.1 g), K_2HPO_4 (40 mmol, 7.0 g), and DMF (25 mL) were used in the second step. The title compound was obtained as a white solid (3.31 g, 42% yield over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.87-7.83 (m, 3H), 7.56 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.51 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.44-7.42 (m, 2H), 7.39-7.24 (m, 5H), 6.93 (d, *J* = 8.5 Hz, 1H), 4.20 (s, 2H), 4.12 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.52, 164.88, 161.27, 137.26, 135.81, 133.02, 131.01, 129.57, 129.41, 129.31, 128.50, 128.44, 127.85, 126.77, 117.78, 112.16, 62.17, 61.36, 52.39. **m.p.** 111.7-112.4 °C. **IR** (thin film): 3032, 2953, 1739, 1674, 1595, 1489, 1441, 1241, 1086, 707 cm^{-1}. **EA** Calcd. for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41. Found: C, 70.33; H, 5.53.

Synthesis of **6b**, **6c**.



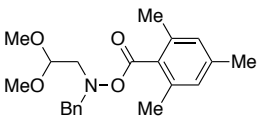
_N_-benzyl-_N_-(thiophen-2-ylmethyl)-_O_-(2,4,6-trimethylbenzoyl)hydroxylamine (6b)



A 100 mL round bottom flask containing a magnetic stir bar was charged with *N*-benzyl-*N*-(thiophen-2-ylmethyl)hydroxylamine[48] (10.0 mmol, 1.0

equiv, 2.19 g), CH_2Cl_2 (25 mL), and Et_3N (14.4 mmol, 1.44 equiv, 2.0 mL). The mixture was cooled to 0 °C, and 2,4,6-trimethylbenzoyl chloride (12.0 mmol, 1.2 equiv, 2.19 g) in CH_2Cl_2 (5 mL) was added dropwise. Then the reaction mixture was stirred at rt overnight. The reaction mixture was passed through a short plug of basic alumina, and washed with additional EtOAc. The resulting solution was concentrated *in vacuo*, and then purified by column chromatography on silica gel to give the title compound as a white solid (1.51 g, 41% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.36-7.27 (m, 4H), 7.06-7.05 (m, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.76 (s, 2H), 4.43 (s, 2H), 4.16 (s, 2H), 2.25 (s, 3H), 1.95 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.30, 139.43, 138.16, 136.23, 135.28, 129.73, 129.41, 128.53, 128.26, 127.87, 127.51, 126.67, 126.05, 61.64, 56.74, 21.24, 19.11, 19.10. **m.p.** 84.3-85.4 °C. **IR** (thin film): 3029, 2921, 1747, 1611, 1431, 1235, 1160, 1053, 851, 696 cm^{-1}. **EA** Calcd. for $C_{22}H_{23}NO_2S$: C, 72.30; H, 6.34. Found: C, 72.21; H, 6.34.

_N_-benzyl-_N_-(2,2-dimethoxyethyl)-_O_-(2,4,6-trimethylbenzoyl)hydroxylamine (6c)



A 100 mL round bottom flask containing a magnetic stir bar was charged with *N*-benzyl-*N*-(2,2-dimethoxyethyl)hydroxylamine[48] (8.0 mmol, 1.0 equiv, 1.69 g), CH_2Cl_2 (20 mL), and Et_3N (11.5 mmol, 1.15 equiv, 1.6 mL). The mixture was cooled to 0 °C, and 2,4,6-trimethylbenzoyl chloride (8.0 mmol, 1.0 equiv, 1.82 g) in CH_2Cl_2 (4 mL) was added dropwise. Then the reaction mixture was stirred at rt overnight. The reaction mixture was passed through a short plug of basic alumina, and washed with additional EtOAc. The resulting solution was concentrated *in vacuo*, and then purified by column chromatography on silica gel to give the title compound as a colorless oil (1.43 g, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.34-7.24 (m, 3H), 6.78 (s, 2H), 4.77 (t, J = 5.1 Hz, 1H), 4.21

(s, 2H), 3.40 (s, 6H), 3.24 (d, J = 5.1 Hz, 2H), 2.25 (s, 3H), 2.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.43, 139.54, 136.30, 135.31, 129.66, 129.49, 128.50, 128.38, 127.85, 102.05, 63.58, 60.33, 53.96, 21.24, 19.41. **IR** (thin film): 2921, 2833, 1748, 1612, 1454, 1238, 1127, 1054, 851, 698 cm^{-1}. **EA** Calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61. Found: C, 70.43; H, 7.49.

1.6 References and Notes

(1) (a) Hirai, H.; Sootome, H.; Nakatsuru, Y.; Miyama, K.; Taguchi, S.; Tsujioka, K.; Ueno, Y.; Hatch, H.; Majumder, P. K.; Pan, B.; Kotani, H. *Mol. Cancer. Ther*. **2010**, *9*, 1956−1967. (b) Mimura, N.; Hideshima, T.; Shimomura, T.; Suzuki, R.; Ohguchi, H.; Rizq, O.; Kikuchi, S.; Yoshida, Y.; Cottini, F.; Jakubikova, J.; Cirstea, D.; Gorgun, G.; Minami, J.; Tai, Y.; Richardson, P. G.; Utsugi, T.; Iwama, A.; Anderson, K. C. *Cancer. Res*. **2014**, *74*, 4458−4469. (c) Bisacchi, G. S.; Singh, J.; Godfrey, J. D.; Kissick, T. P.; Mitt, T.; Malley, M. F.; Marco, J. D. D.; Gougoutas, J. Z.; Mueller, R. H.; Zahler, R. *J. Org. Chem*. **1995**, *60*, 2902−2905. (d) Ho, G. D.; Tulshian, D.; Heap, C. R. PCT Int. Appl. WO 2012047703, 2012. (e) Xie, X.; Kayser, F. PCT Int. Appl. WO 2017083867, 2017.

(2) Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci*. **2006**, *2*, 85−100.

(3) For selected examples of [2+2] reactions for synthesizing entioenriched cyclobutylamine derivatives, see: (a) Ghosez, L.; Mahuteau-Betzer, F.; Genicot, C.; Vallribera, A.; Cordier, J. *Chem. Eur. J*. **2002**, *8*, 3411−3422. (b) Coote, S. C.; Bach, T. *J. Am. Chem. Soc*. **2013**, *135*, 14948−14951. (c) Brimioulle, R.; Bach, T. *Science* **2013**, *342*, 840−843. (d) Coote, S. C.; Pöthig, A.; Bach, T. *Chem. Eur. J*. **2015**, *21*, 6906−6912. (e) Niemeyer, Z. L.; Pindi, S.; Khrakovsky, D. A.; Kuzniewski, C. N.; Hong, C. M.; Joyce, L. A.; Sigman, M. S.; Toste, F. D. *J. Am. Chem. Soc*. **2017**, *139*, 12943−12946. (f) Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc*. **2016**, *138*, 7808−7811. (g) Zheng, W.; Sun, G.; Chen, L.; Kang, Q. *Adv. Synth. Catal*. **2018**, *360*, 1790−1794. (h) Zhong, X.; Tang, Q.; Zhou, P.; Zhong, Z.; Dong, S.; Liu, X.; Feng, X. *Chem. Commun*. **2018**, *54*, 10511−10514.

(4) For synthesis of chiral cyclobutylamine derivatives via Amadori-Heyns rearrangements, see: (a) Aitken, D. J.; Caboni, P.; Eijsberg, H.; Frongia, A.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci,

F. *Adv. Synth. Catal*. **2014**, *356*, 941−945. (b) Melis, N.; Ghisu, L.; Guillot, R.; Caboni, P.; Secci, F.; Aitken, D. J.; Frongia, A. *Eur. J. Org. Chem*. **2015**, 4358−4366.

(5) Dian, L.; Marek, I. *Chem. Rev*. **2018**, *118*, 8415−8434.

(6) (a) Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem. Sci.* **2015**, *6*, 5164−5171. (b) Pedroni, J.; Cramer, N. *Angew. Chem., Int. Ed*. **2015**, *54*, 11826−11829.

(7) For selected examples, see: (a) Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org. Lett*. **2013**, *15*, 772−775. (b) Chanthamath, S.; Ozaki, S.; Shibatomi, K.; Iwasa, S. *Org. Lett*. **2014**, *16*, 3012−3015. (c) Xie, M.; Zhou, P.; Niu, H.; Qu, G.; Guo, H. *Org. Lett*. **2016**, *18*, 4344−4347. (d) Xu, H.; Li, Y.; Cai, Y.; Wang, G.; Zhu, S.; Zhou, Q. *J. Am. Chem. Soc*. **2017**, *139*, 7697−7700.

(8) (a) Simaan, M.; Marek, I. *Angew. Chem., Int. Ed*. **2018**, *57*, 1543−1546. (b) Li, Z.; Zhang, M.; Zhang, Y.; Liu, S.; Zhao, J.; Zhang, Q. *Org. Lett.* **2019**, *21*, 5432−5437.

(9) (a) Teng, H.; Luo, Y.; Wang, B.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed*. **2016**, *55*, 15406−15410. (b) Teng, H.; Luo, Y.; Nishiura, M.; Hou, Z. *J. Am. Chem. Soc*. **2017**, *139*, 16506−16509.

(10) For a review on CuH-catalyzed enantioselective C−N bond formation reactions, see: Pirnot, M. T.; Wang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 48−57.

(11) For selected examples of CuH-catalyzed enantioselective C−C bond formation reactions, see: (a) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144−150. (b) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 9787−9790. (c) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 5821−5824. (d) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 8372−8375. (e) Wang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 5024−5027.

(12) For selected examples of CuH-catalyzed enantioselective hydroamination reactions, see: (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc*. **2013**, *135*, 15746−15749. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, Masahiro. *Angew. Chem., Int. Ed*. **2013**, *52*, 10830−10834. (c) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 9716−9721. (d) Ichikawa, S.; Zhu, S.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2018**, *57*, 8714−8718. (e) Guo, S.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 15976−15984. (f) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2014**, *136*, 15913−15916. (g) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62−66. (h) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc*. **2015**, *137*, 15620−15623. (i) Takata, T.; Hirano, K.; Miura, M. *Org. Lett*. **2019**, *21*, 4284−4288. (j) Takata, T.; Nishikawa, D.; Hirano, K.; Miura, M. *Chem. Eur. J*. **2018**, *24*, 10975–10978. (k) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2014**, *16*, 1498−1501.

(13) (a) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 14812−14818. (b) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 12758−12772. (c) Ye, Y.; Kim, S.; Jeong, J.; Baik, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2019**, *141*, 3901−3909. (d) Tobisch, S. *Chem. Sci*. **2017**, *8*, 4410−4423.

(14) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc*. **2003**, *125*, 8779−8789.

(15) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *Nat. Chem.* **2016**, *8*, 144−150. (b) Shi, S.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353−356.

(16) (a) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 312−322. (b) Luef, W.; Keese, R. *Top. Stereochem*. **1991**, *20*, 231−318. (c) Wilson, M. R.; Taylor, R. E. *Angew. Chem., Int. Ed*. **2013**, *52*, 4078−4087.

(17) Sommer, H.; Marek, I. *Chem. Sci.* **2018**, *9*, 6503−6508.

(18) (a) Lu, G. Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc*. **2017**, *139*, 16548−16555. (b) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018,** *140*, 13976-13984.

(19) (a) Furuyama, H.; Goto, Y.; Kawanishi, N.; Mita, T.; Naya, A.; Ogino, Y.; Onozaki, Y.; Sakamoto, T.; Wang, J. PCT Int. Appl. WO 2009148916, 2009. (b) Fan, W.; Kawanishi, N.; Lee, S.; Liu, H.; Moore, J. A. I.; Ogino, Y.; Onozaki, Y.; Pandi, B.; Sakamoto, T.; Siu, T. PCT Int. Appl. WO 2010104933, 2010. (c) Liang, P.; Mitsuya, M.; Ogino, Y.; Qi, C.; Takahashi, H.; Tempest, P.; Wang, J.; Wang, Z.; Zhang, S.; Zhou, N.; Zhu, J. PCT Int. Appl. WO 2011133733, 2011. (d) Shiers, J. J.; Watts, J. P.; Onions, S. T.; Quddus, M. A.; Wriggles, W. J. W.; Sambrook, C. P.; Naylor, A.; Londesbrough, D. PCT Int. Appl. WO 2016102672, 2016.

(20) Grongsaard, P.; Bulger, P. G.; Wallace, D. J.; Tan, L.; Chen, Q.; Dolman, S. J.; Nyrop, J.; Hoerrner, R. S.; Weisel, M.; Arredondo, J.; Itoh, T.; Xie, C.; Wen, X.; Zhao, D.; Muzzio, D. J.; Bassan, E. M.; Shultz, C. S. *Org. Process Res. Dev*. **2012**, *16*, 1069−1081.

(21) Shao, P. P.; Ye, F. *Tetrahedron Lett.* **2008**, *49*, 3554−3557.

(22) See section 1.5 for details.

(23) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444–4452.

(24) (a) Liu, F.; Paton, R. S.; Kim, S.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 15642–15649. (b) Lopez, S. A.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1778−1783.

(25) Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem., Int. Ed.* **2017**, *56*, 10070−10086.

(26) (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(27) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(28) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

(29) *Gaussian 09, Revision D.01*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

(30) CuH-catalyzed hydroamination of 1-alkylcyclobutene **5a** using 1,2-benzisoxazole (**14**) was not successful.

(31) "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of Chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update."; Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.

(32) The cyclobutene and cyclopropene substrates are air-sensitive, and therefore have to be stored in the glovebox. For this reason, the hydroamination reactions are set up in the glovebox.

(33) Cyclopropenes bearing 3-hydrogen polymerize through ene-reaction when in their liquid phase.[34] For this reason, characterization data of compound **12** by ^{13}C NMR was not provided.

The purity of **12** was determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as the internal standard.

(34) Lin, H.; Tsai, R.; Wu, H.; Lee, H.; Lee, G. *Tetrahedron* **2016**, *72*,184−191.

(35) Homs, A.; Obradors, C.; Lebœuf. D.; Echavarren, A. M. *Adv. Synth. Catal*. **2014**, *356*, 221−228.

(36) Juteau, H.; Gareau, Y. *Synthetic Communications*. **1998**, *28*, 3795−3805.

(37) Lauriers, A. J.; Legault, C. Y. *Org. Lett*. **2016**, *18*, 108−111.

(38) Shi, D.; Liu, Z.; Zhang, Z.; Shi, W.; Chen, H. *ChemCatChem* **2015**, *7*, 1424−1426.

(39) Kasai, K.; Liu, Y.; Hara, R.; Takahashi, T. *Chem. Commun*. **1998**, 1989−1990.

(40) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem*. **2011**, *76*, 7195−7203.

(41) Clausen, D. J.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 5178−5181.

(42) Mizojiri, R.; Urabe, H.; Sato, F. *J. Org. Chem*. **2000**, *65*, 6217−6222.

(43) Basheer, A.; Mishima, M.; Marek, I. *Org. Lett*. **2011**, *13*, 4076−4079.

(44) Ernouf, G.; Brayer, J.; Folléas, B.; Demoute, J.; Meyer, C.; Cossy, J. *Org. Lett*. **2015**, *17*, 3786−3789.

(45) Hodgson, D. M.; Pearson, C. I.; Kazmi, M. *Org. Lett*. **2014**, *16*, 856−859.

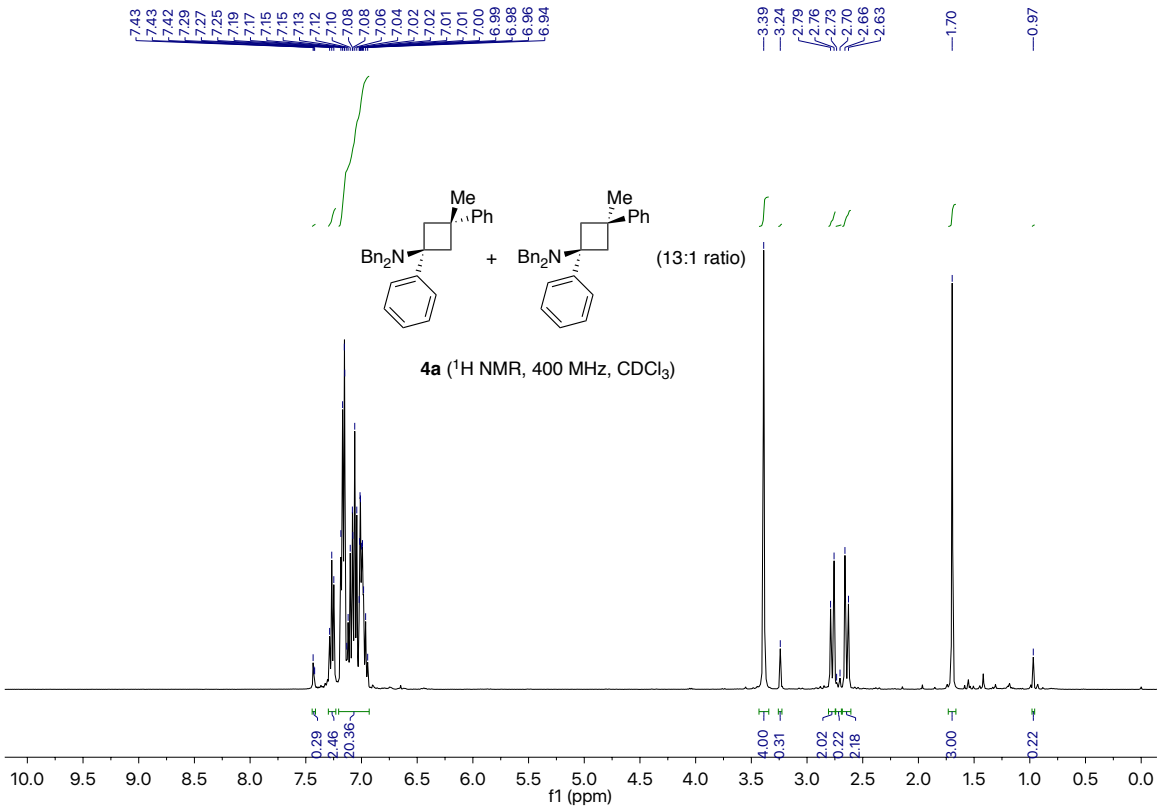
(46) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 13976−13984.

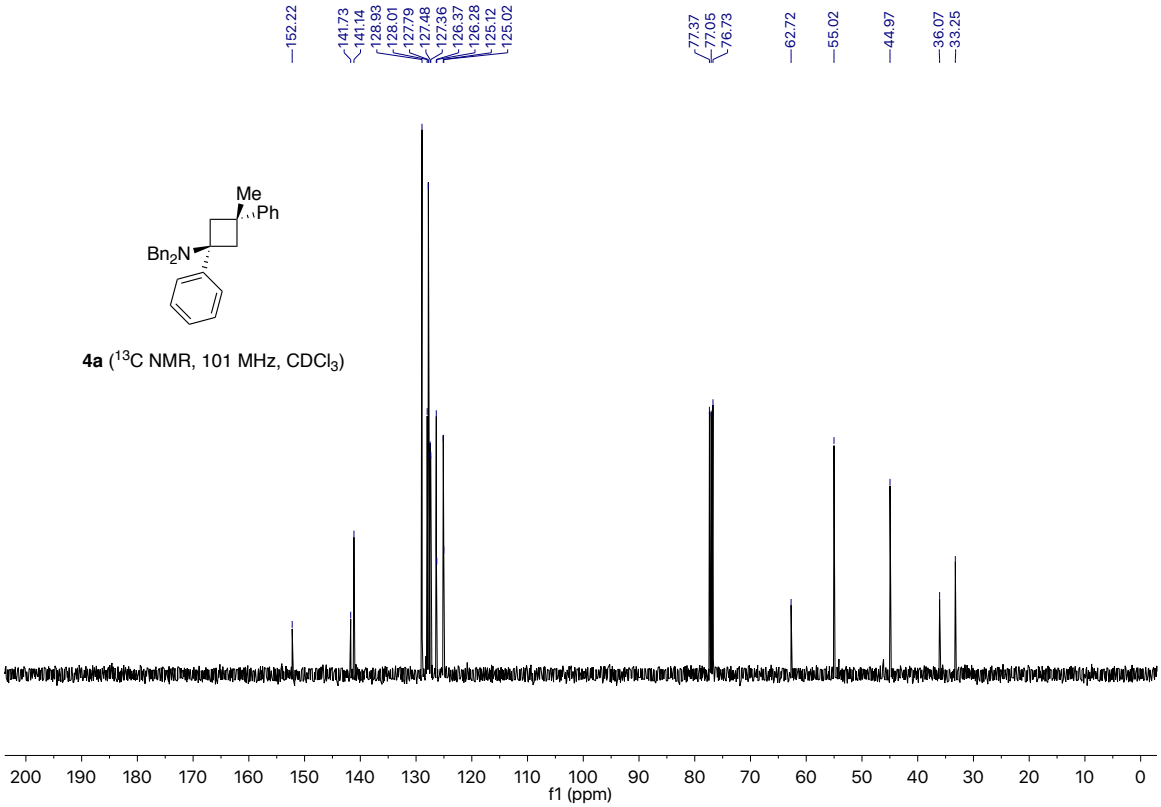
(47) Shi, S.; Buchwald, S. L. *Nat. Chem*. **2015**, *7*, 38−44.

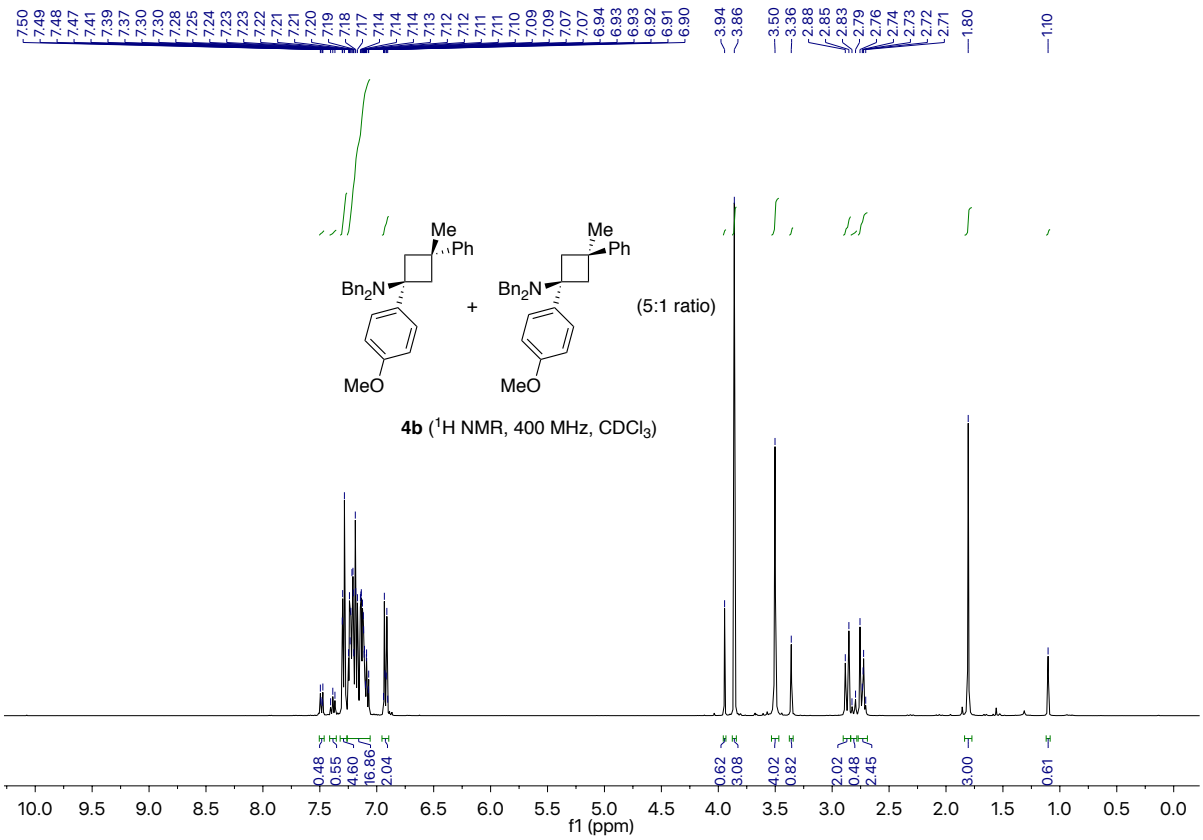
(48) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62−66.

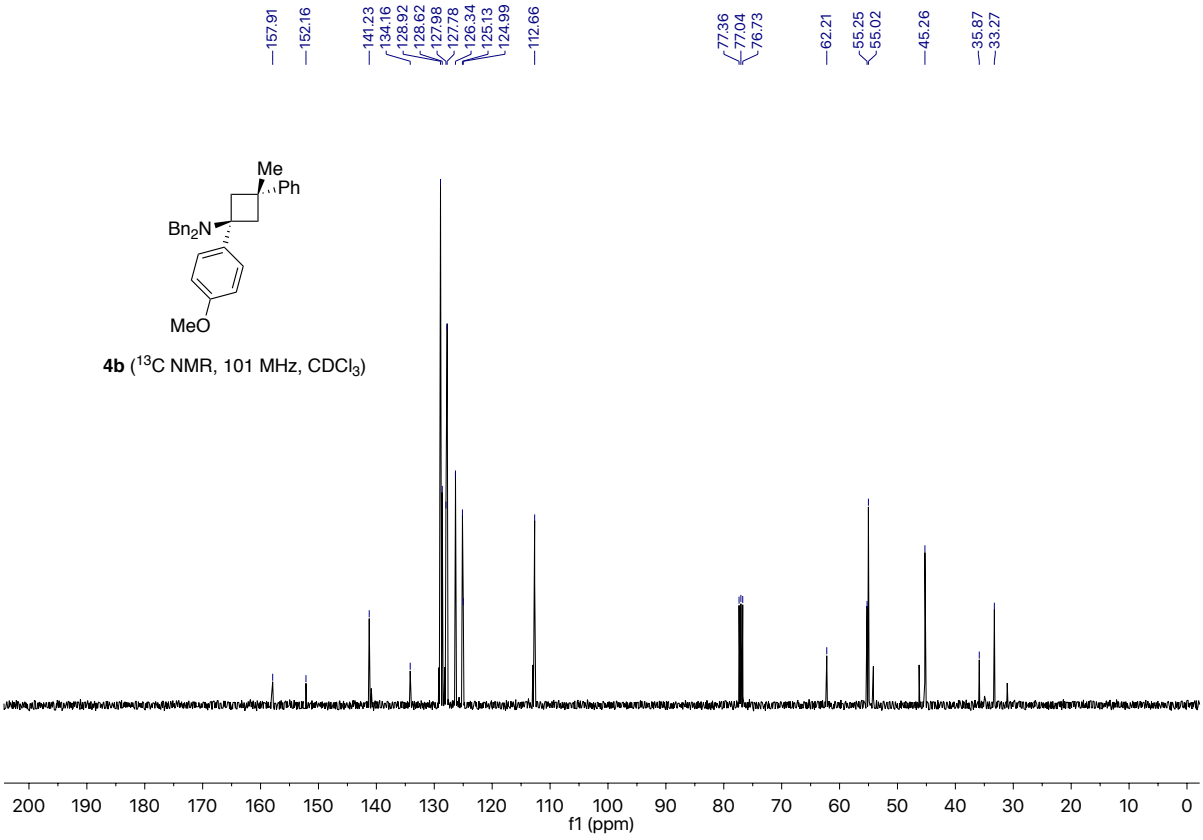
(49) Liu, R. Y.; Buchwald, S. L. *Org. Synth*. **2018**, *95*, 80−96.

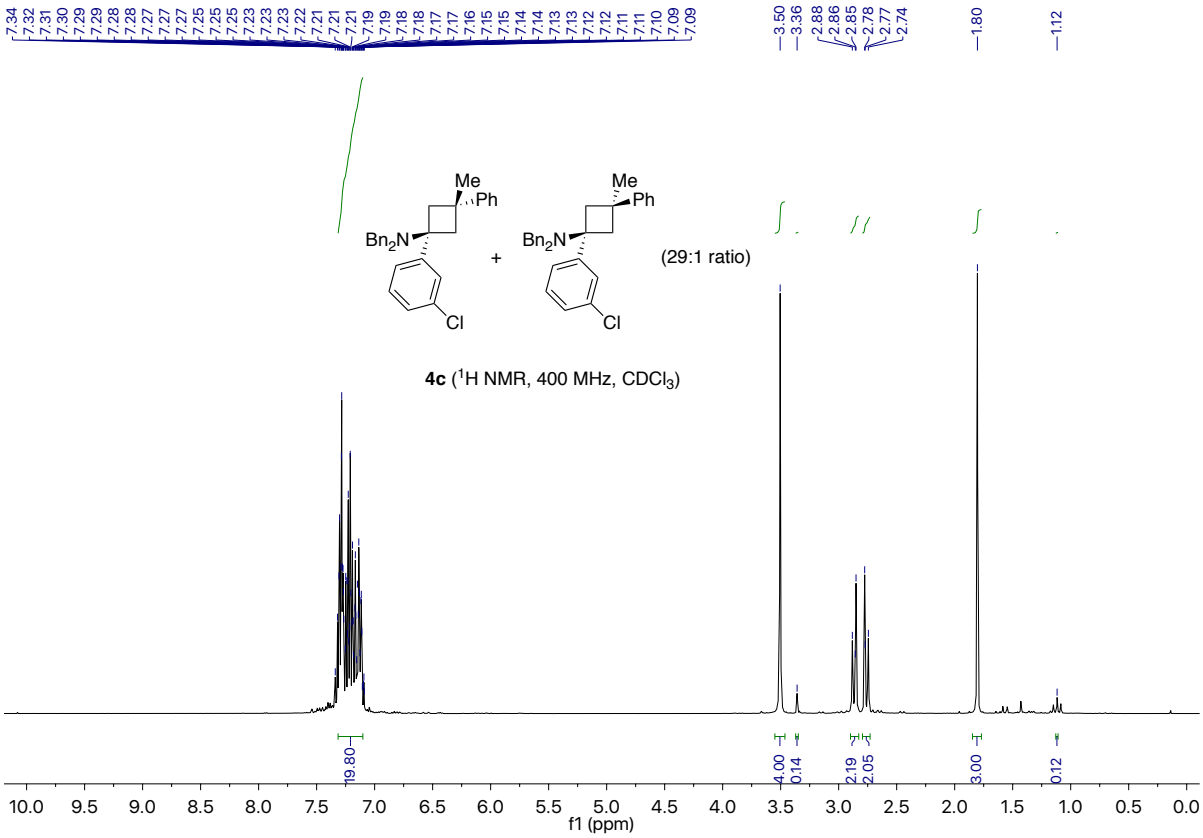
1.7 Spectra and Chromatograms

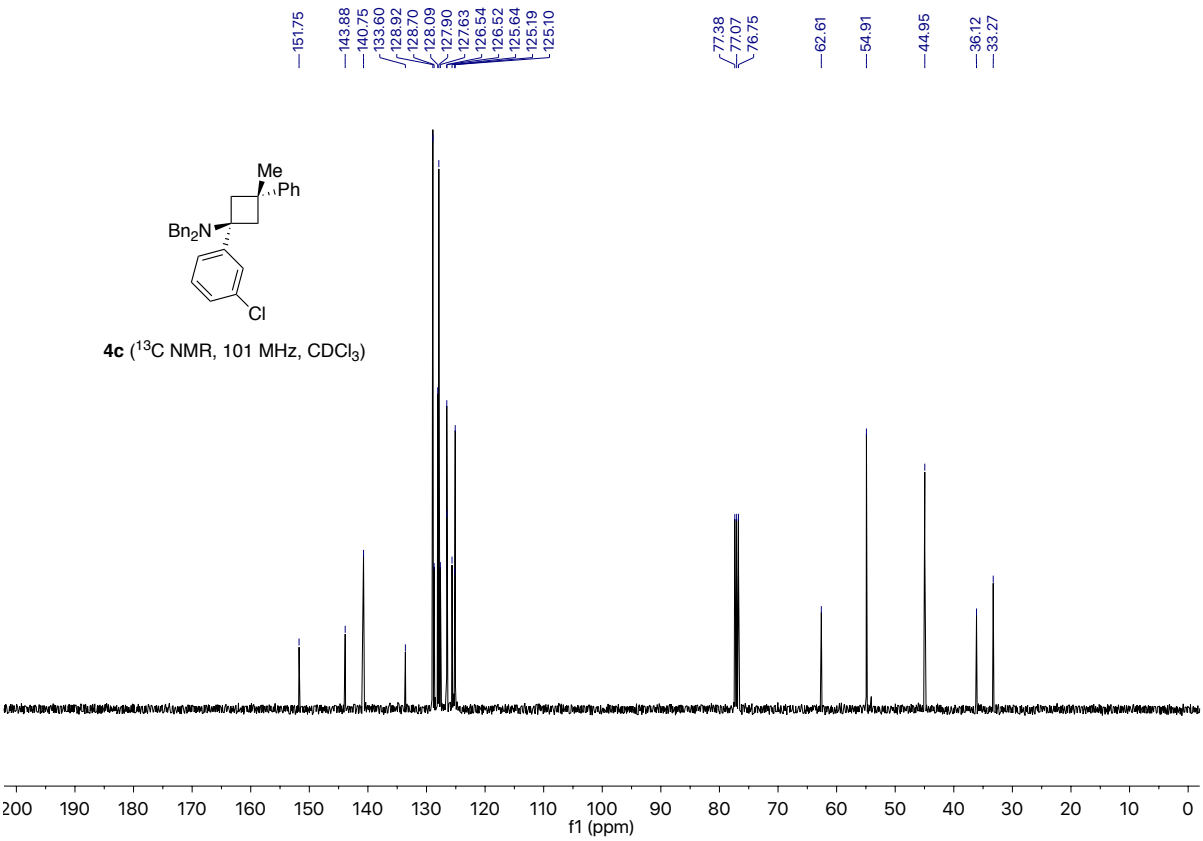


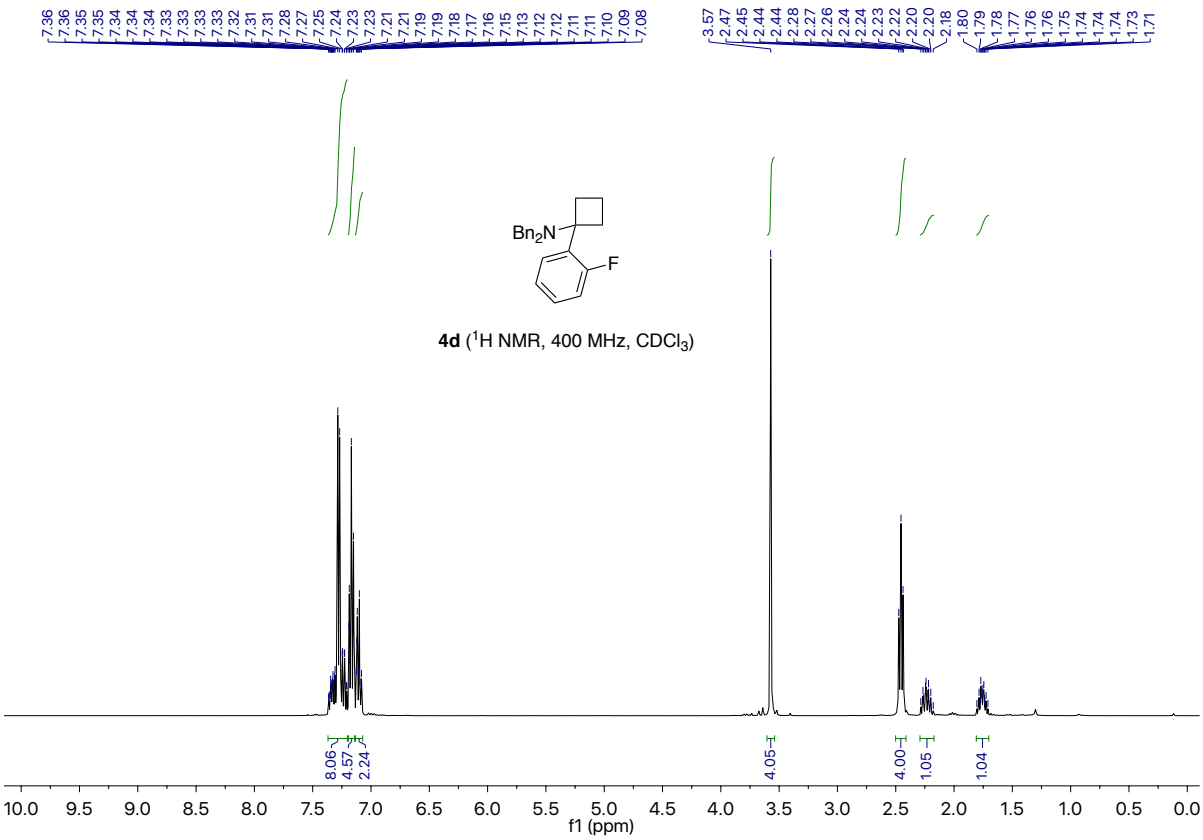



Me
Ph
Bn2N
MeO
+
Me
Ph
Bn2N
MeO
(5:1 ratio)
4b (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

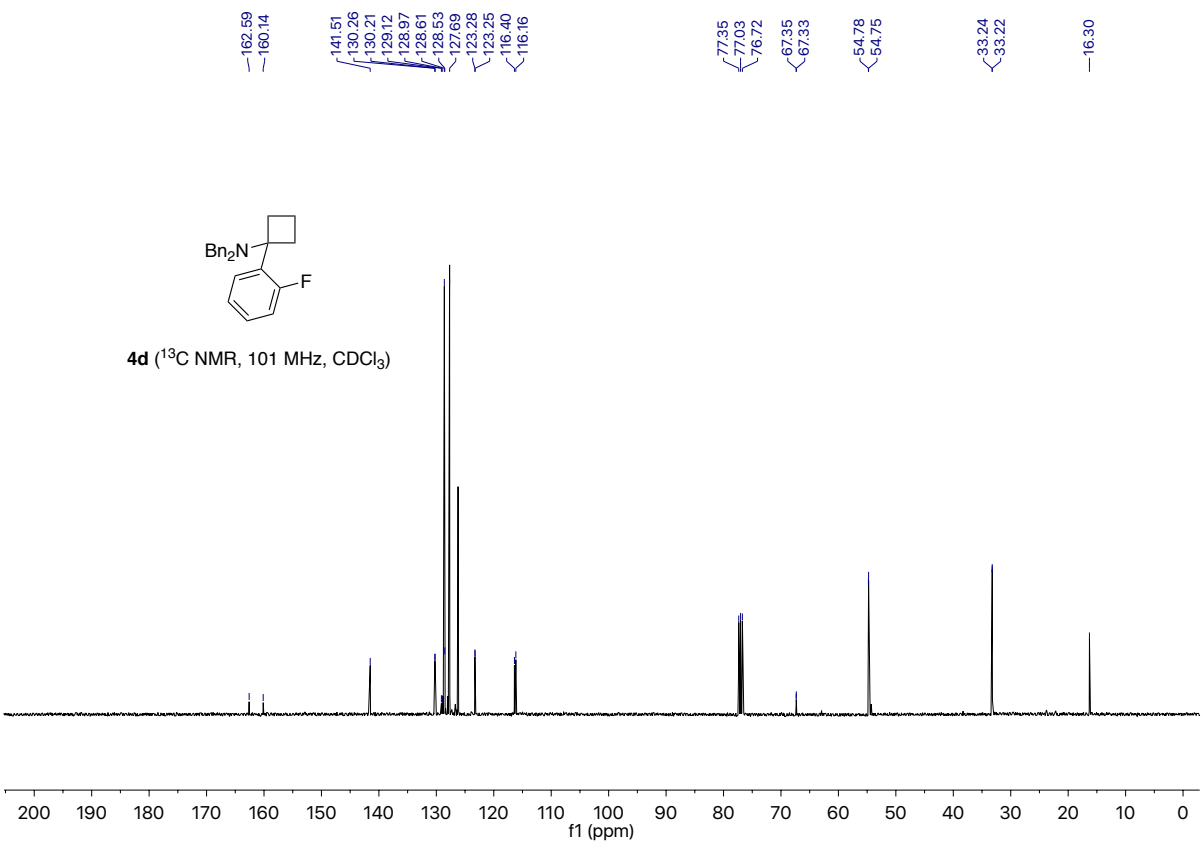

Me
Ph
Bn2N
MeO
4b (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


Me
Ph
Bn2N
Cl
+
(29:1 ratio)
4c (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

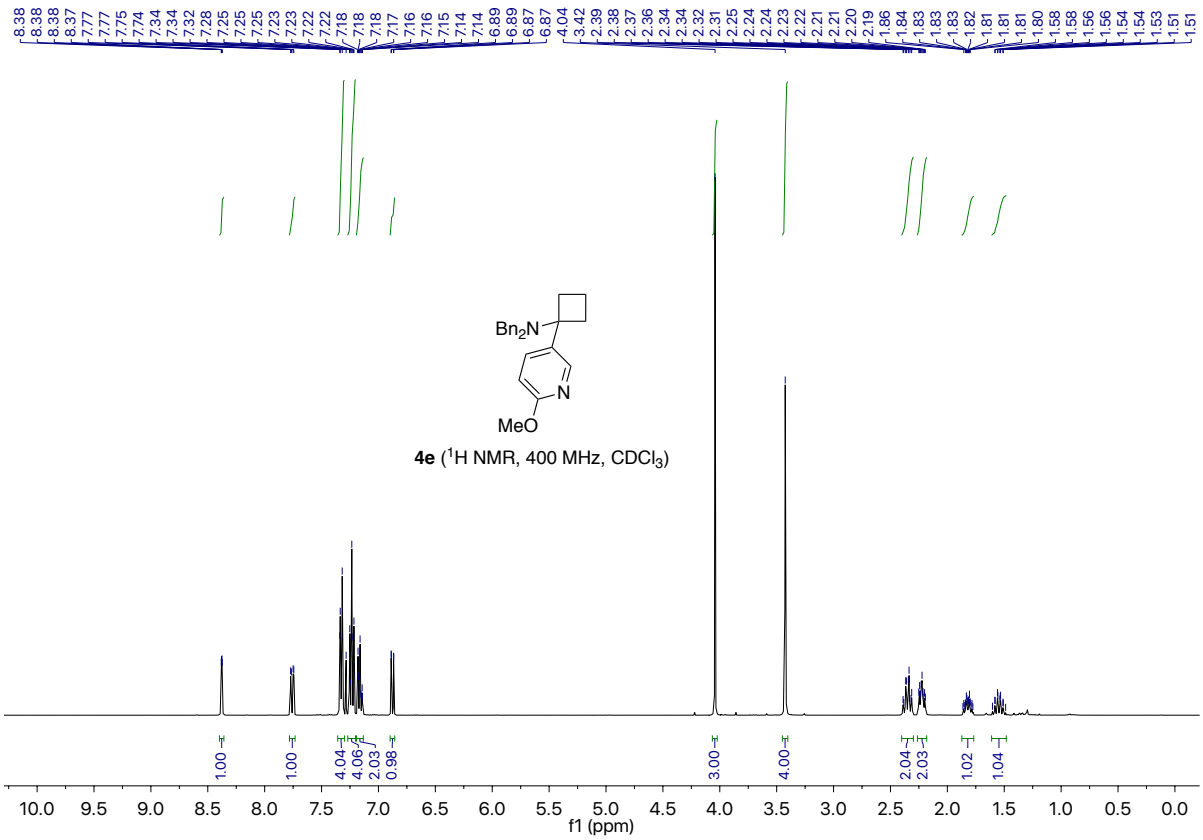

Me
Ph
Bn2N
Cl
4c (13C NMR, 101 MHz, CDCl3)
f1 (ppm)



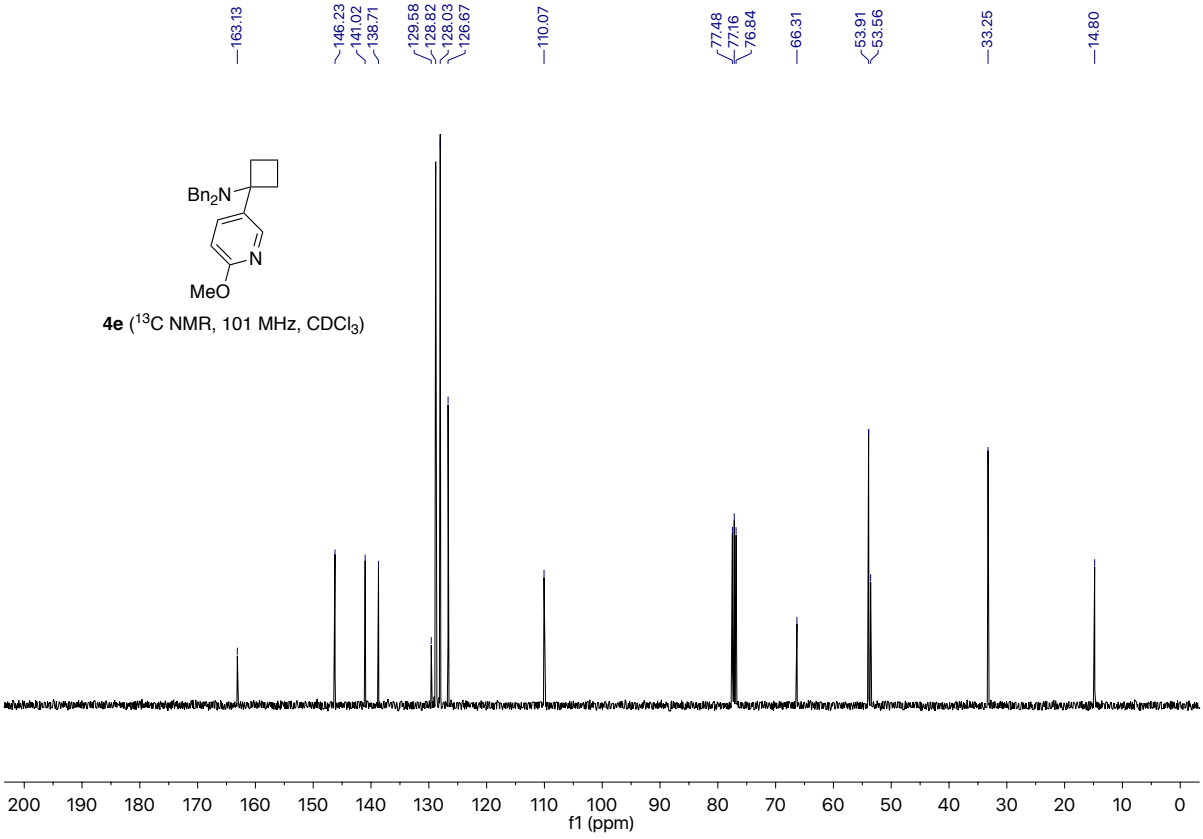
4d (^{1}H NMR, 400 MHz, $CDCl_3$)



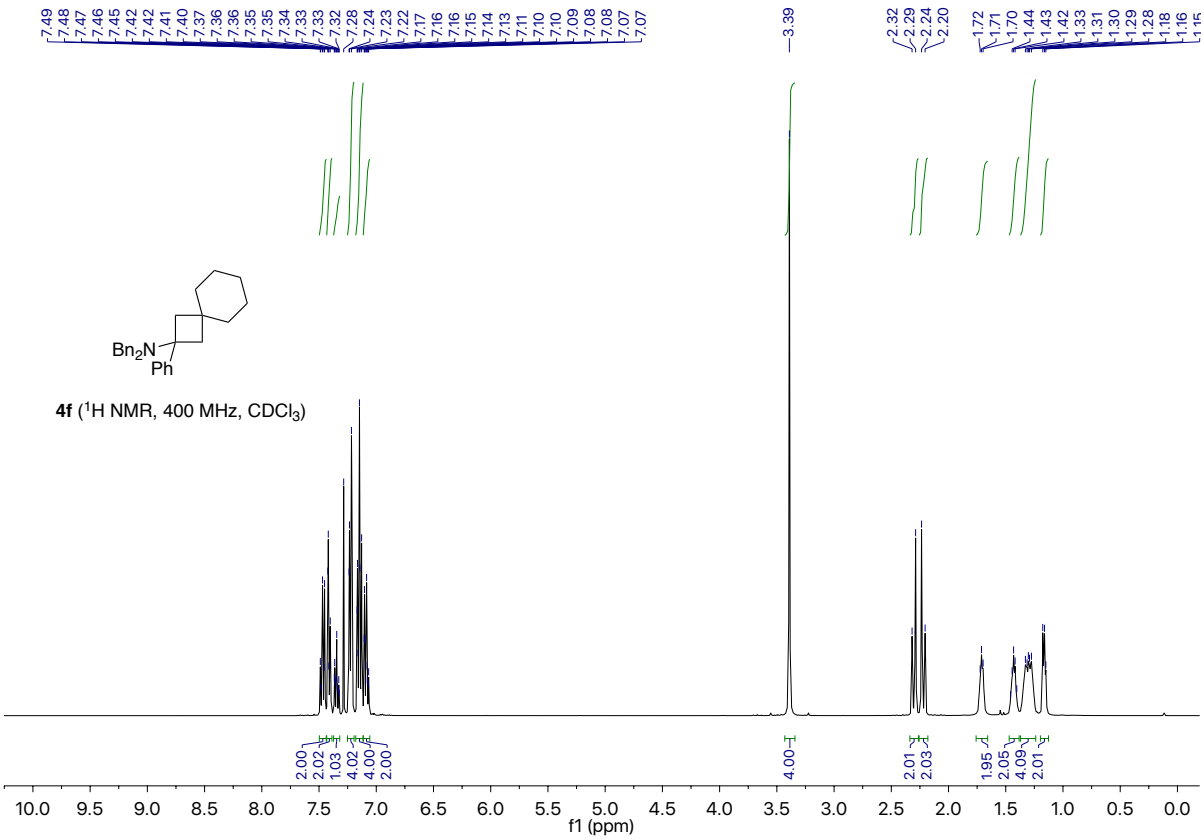
4d (^{13}C NMR, 101 MHz, $CDCl_3$)



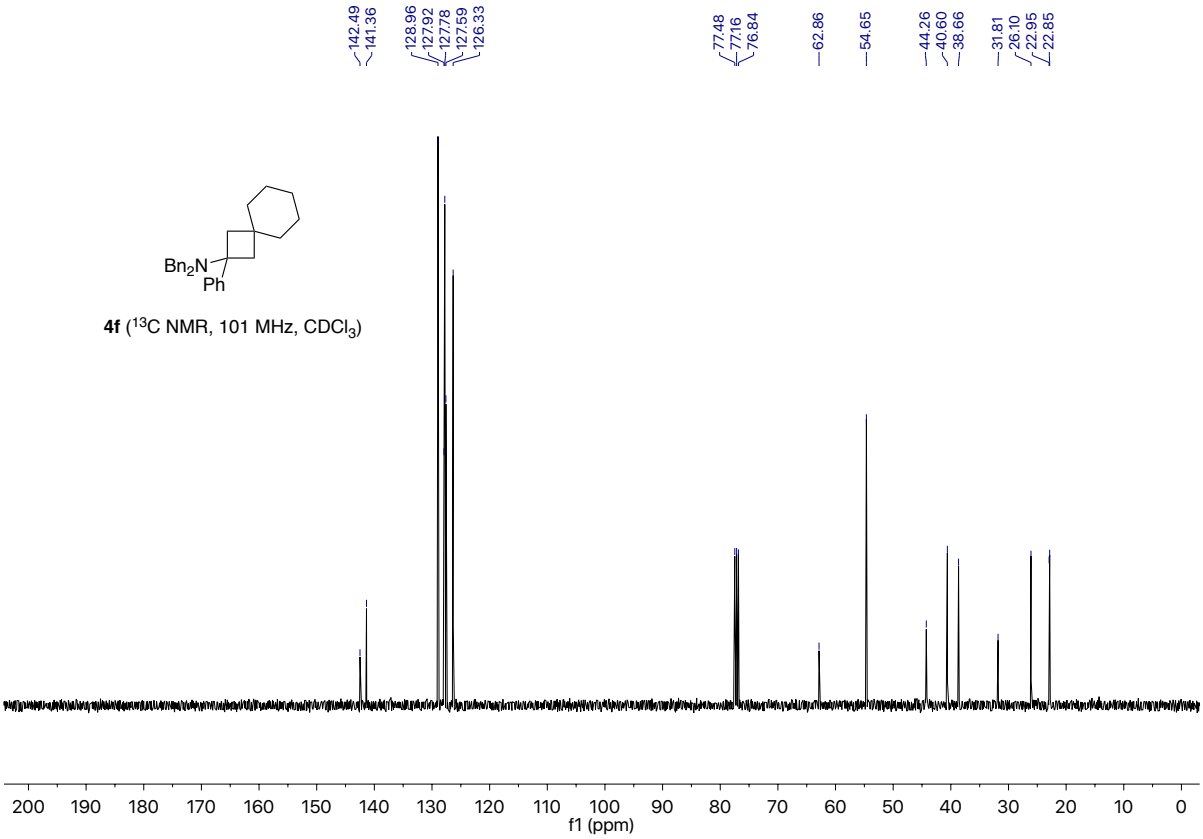
4e (^{1}H NMR, 400 MHz, $CDCl_3$)



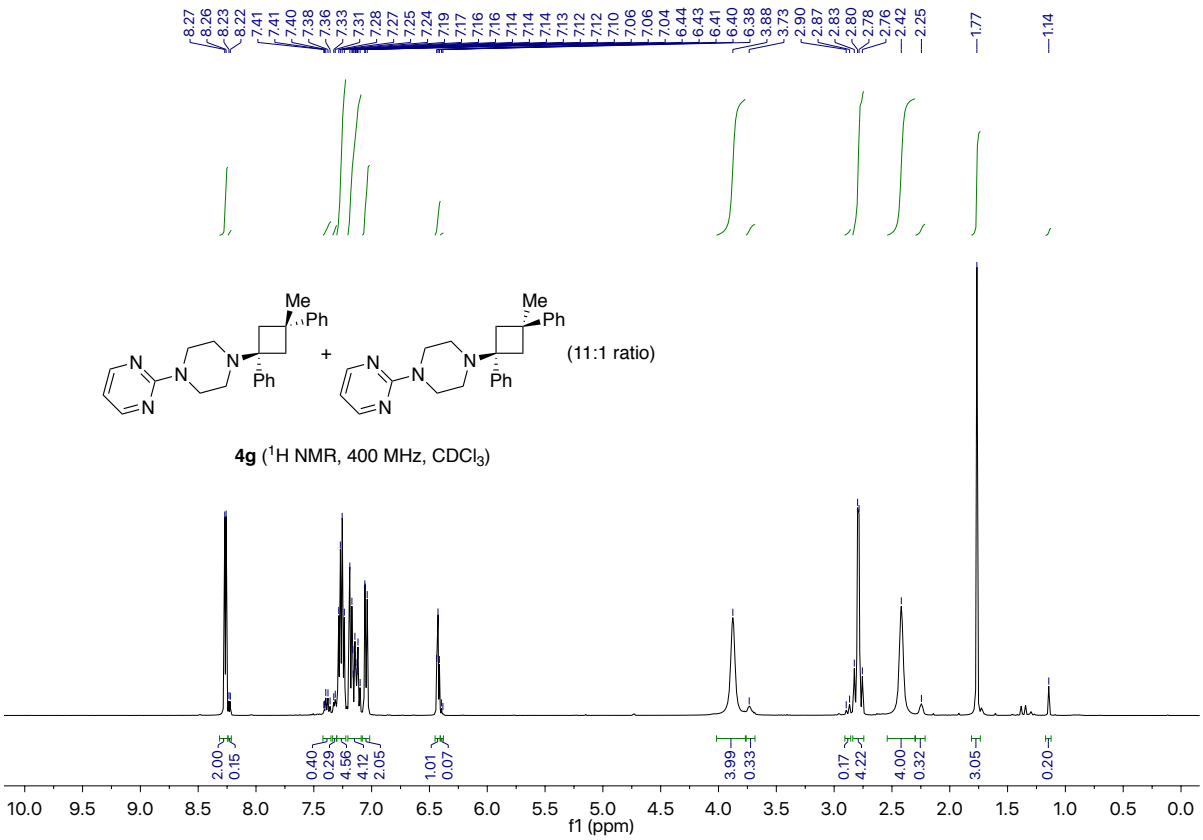
4e (^{13}C NMR, 101 MHz, $CDCl_3$)

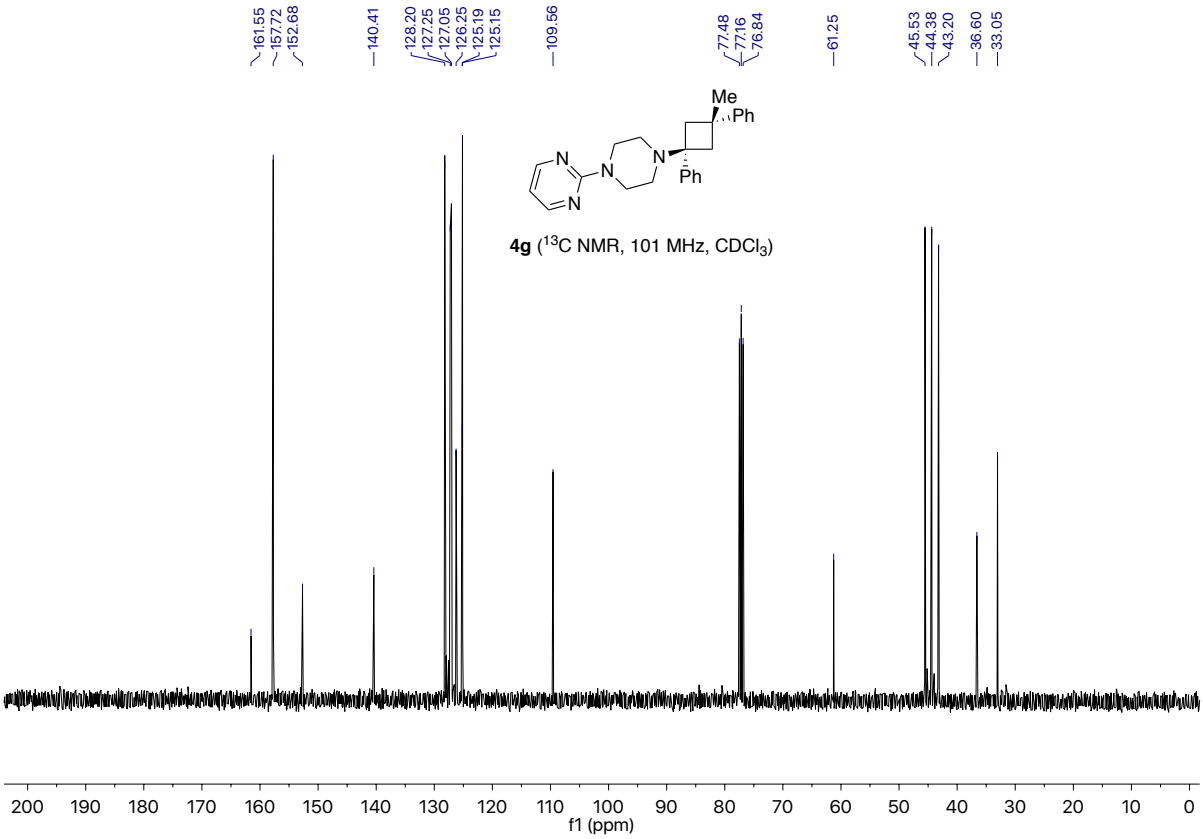


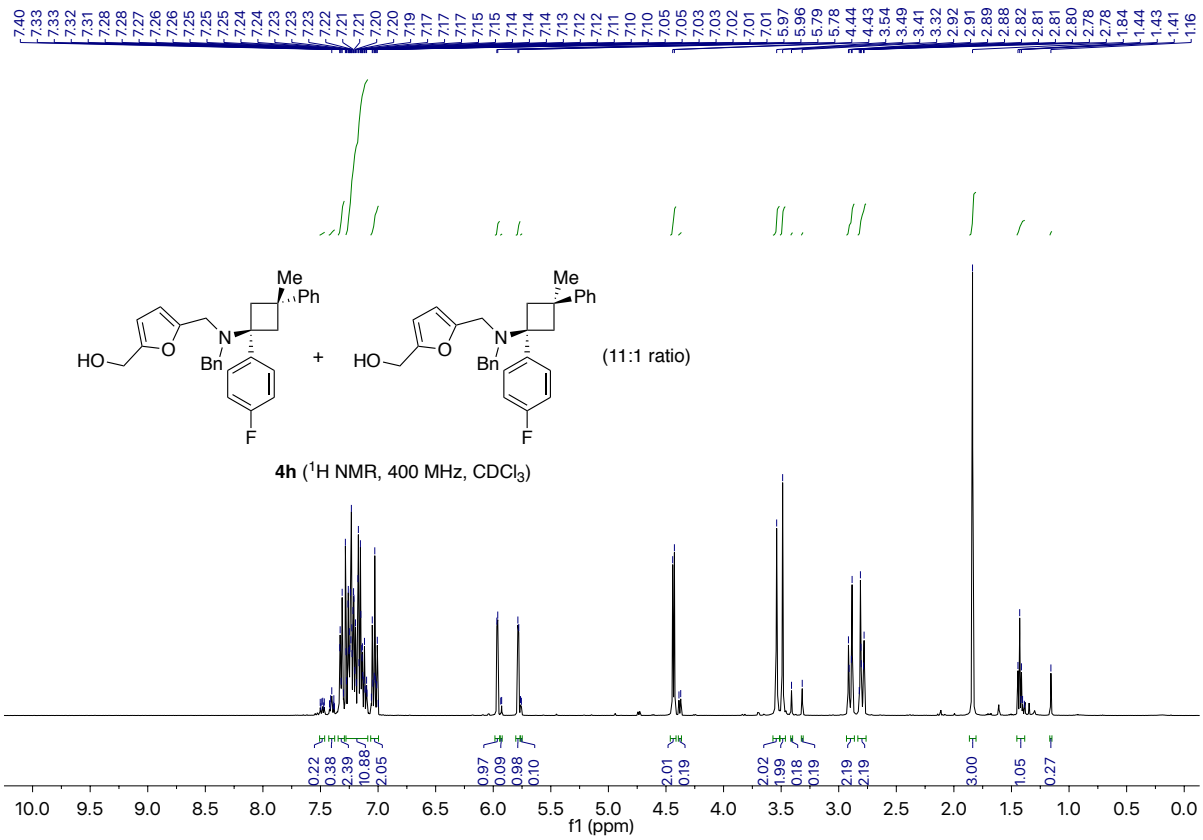
4f (^{1}H NMR, 400 MHz, $CDCl_3$)



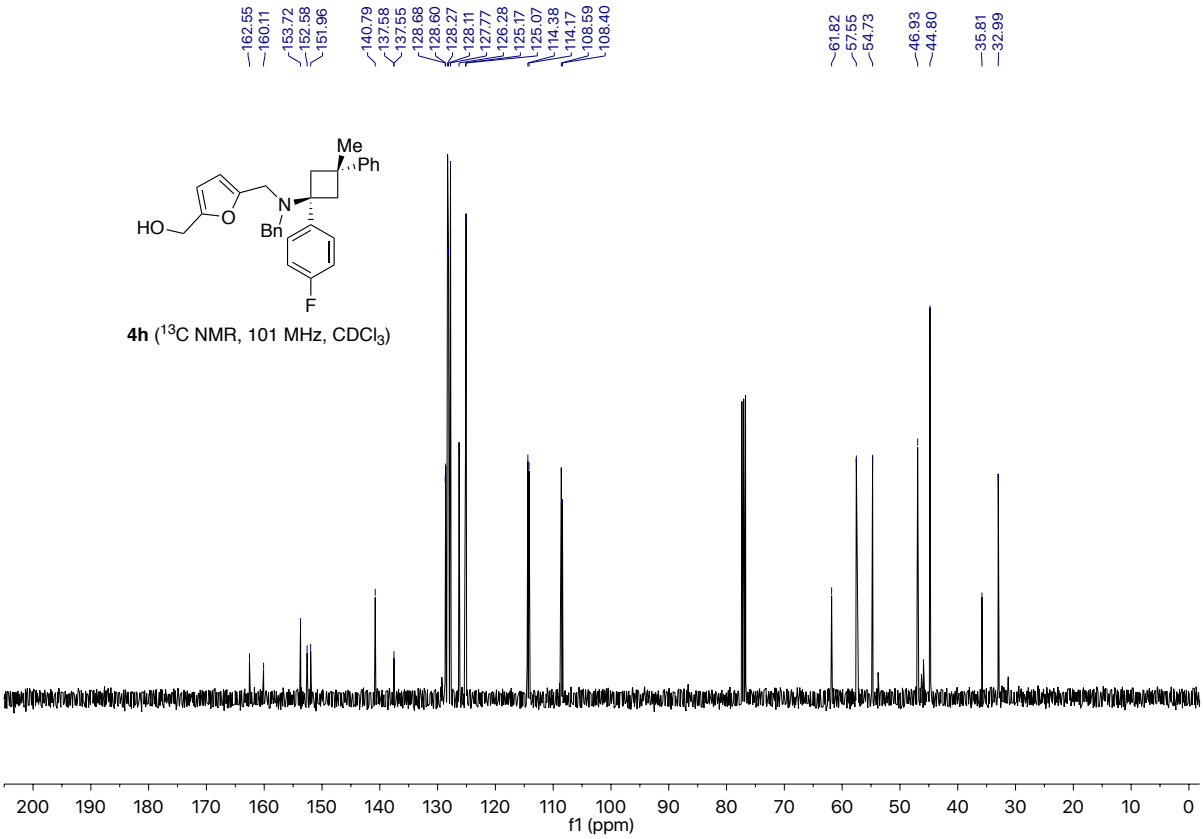
4f (^{13}C NMR, 101 MHz, $CDCl_3$)


8.27
8.26
8.23
8.22
7.41
7.41
7.40
7.38
7.36
7.33
7.31
7.28
7.27
7.25
7.24
7.19
7.17
7.16
7.16
7.14
7.14
7.14
7.13
7.12
7.12
7.10
7.06
7.06
7.04
6.44
6.43
6.41
6.40
6.38
3.88
3.73
2.90
2.87
2.83
2.80
2.78
2.76
2.42
2.25
1.77
1.14
Me
Ph
Ph
+
Me
Ph
Ph
(11:1 ratio)
4g (1H NMR, 400 MHz, CDCl3)
2.00
0.15
0.40
0.29
4.56
4.12
2.05
1.01
0.07
3.99
0.33
0.17
4.22
4.00
0.32
3.05
0.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

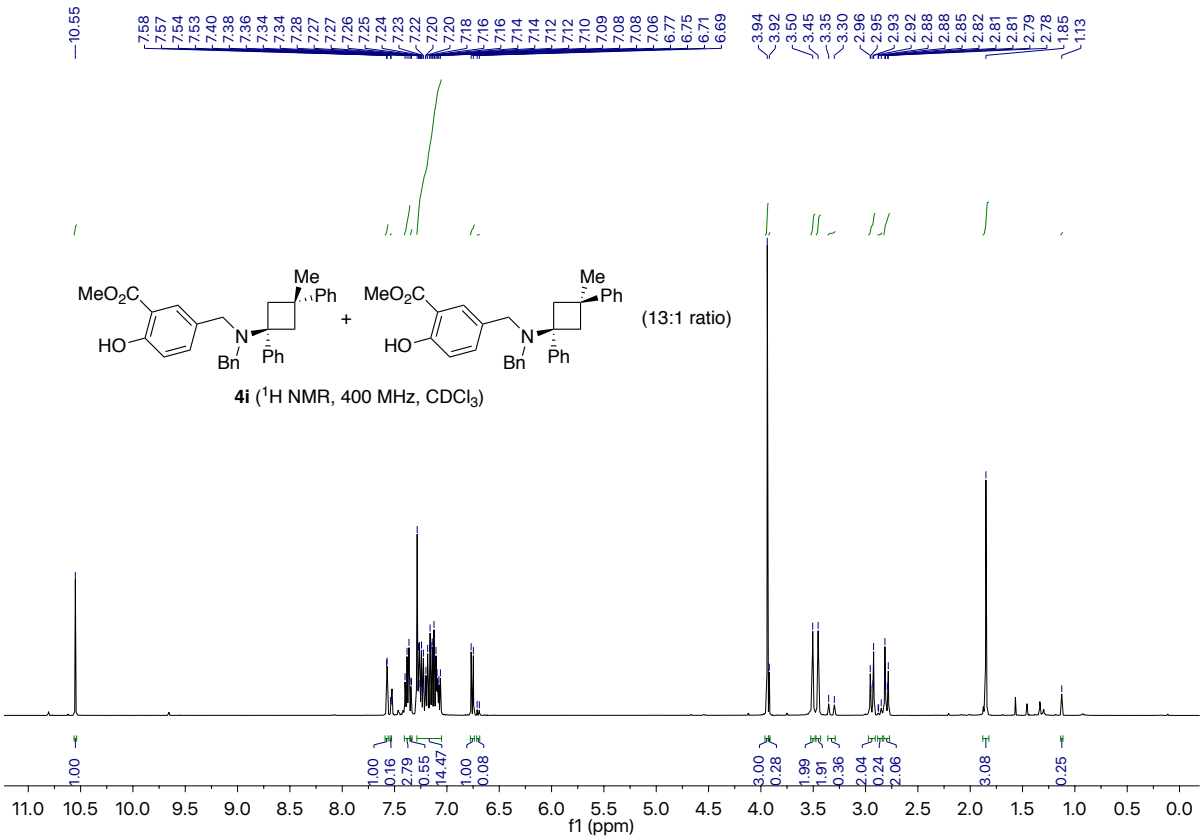

161.55
157.72
152.68
140.41
128.20
127.25
127.05
126.25
125.19
125.15
109.56
77.48
77.16
76.84
61.25
45.53
44.38
43.20
36.60
33.05
Me
Ph
Ph
4g (13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

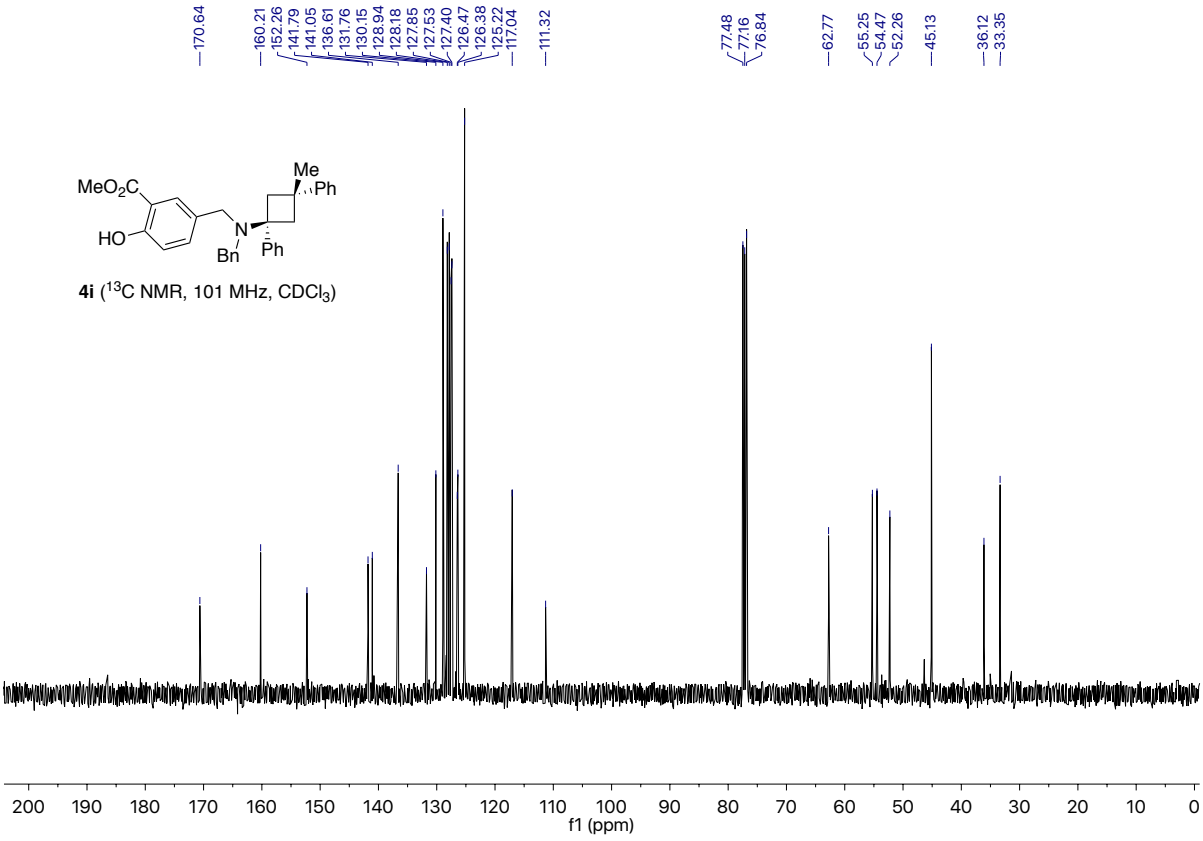


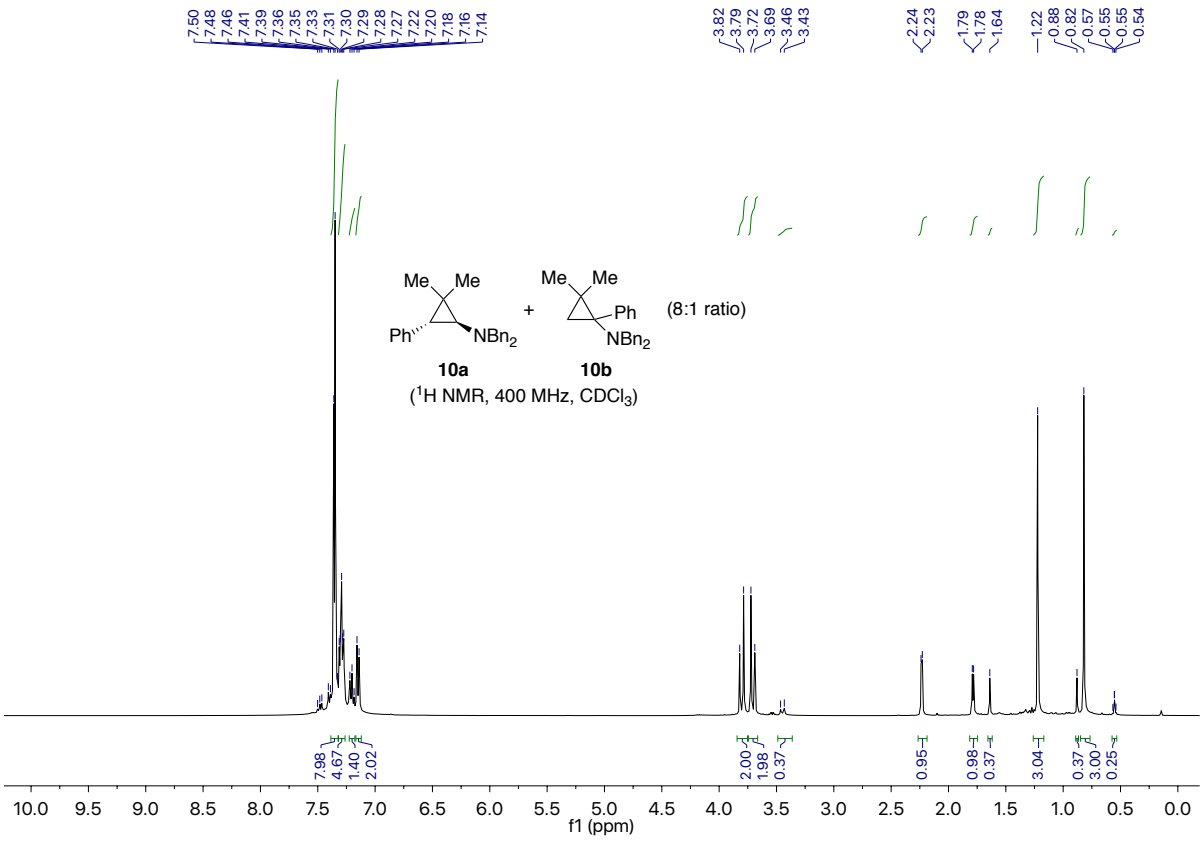
4h (^{1}H NMR, 400 MHz, $CDCl_3$)

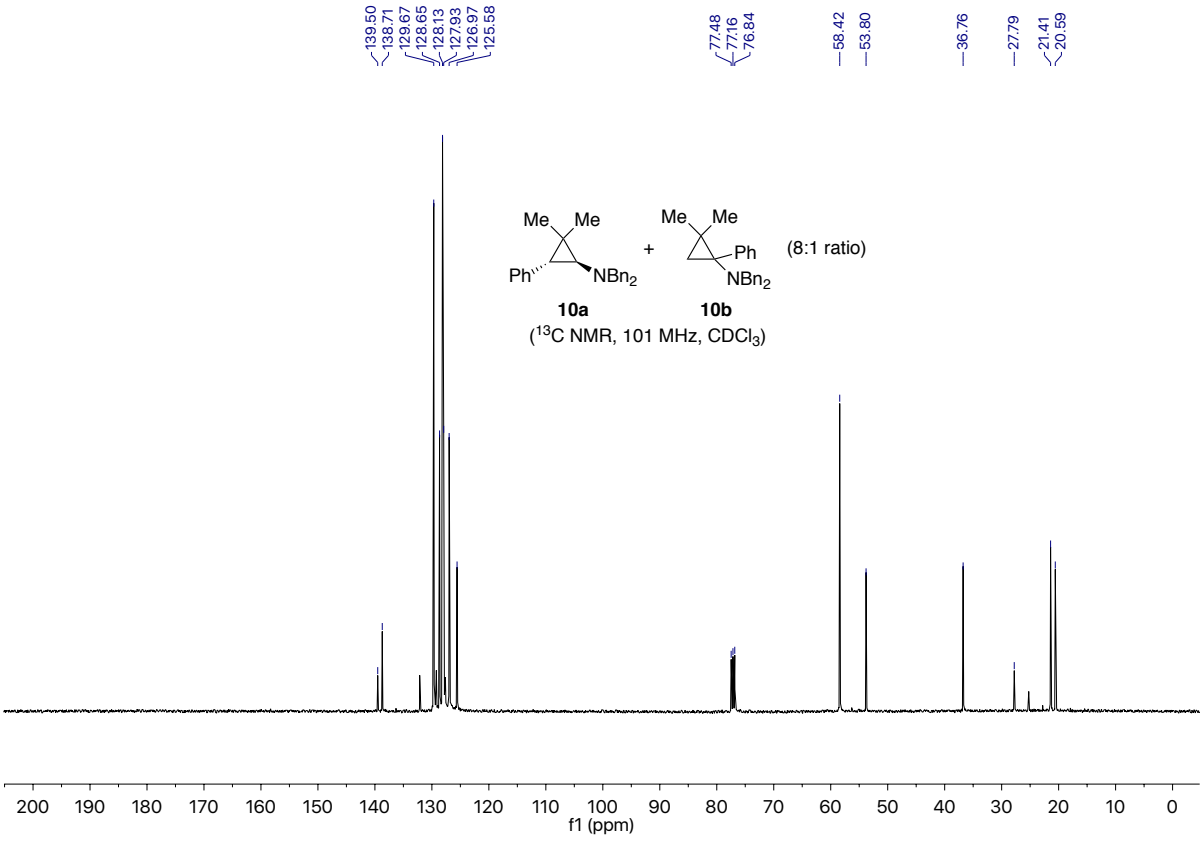


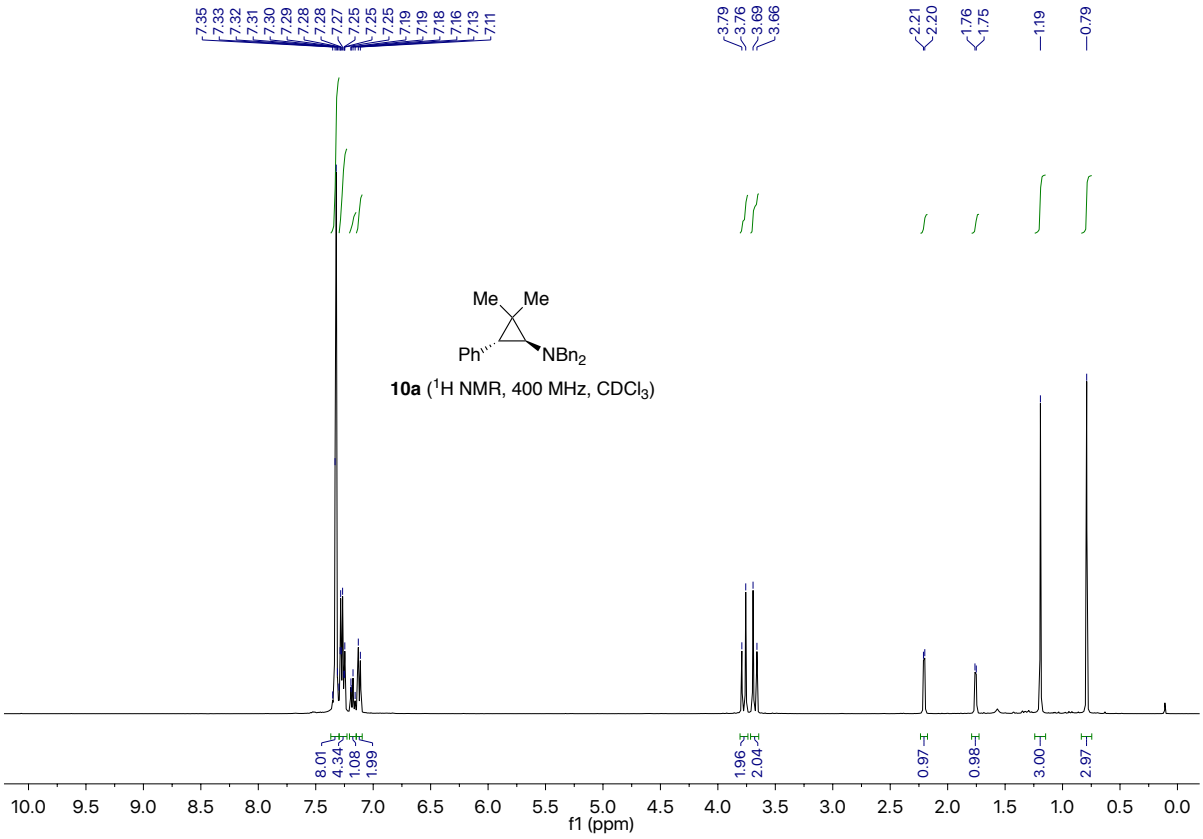
4h (^{13}C NMR, 101 MHz, $CDCl_3$)


MeO2C
HO
Me
Ph
N
Bn
Ph
+
MeO2C
HO
Me
Ph
N
Bn
Ph
(13:1 ratio)
4i (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

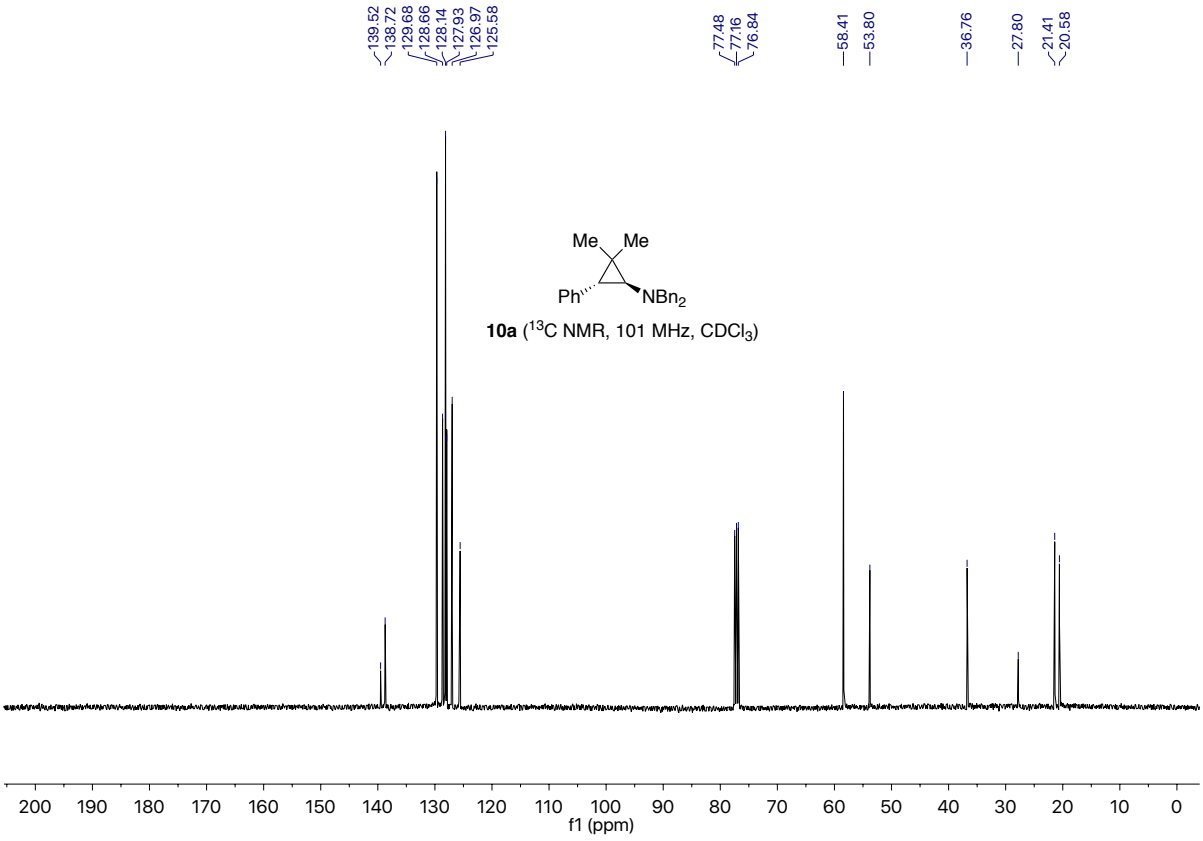

MeO2C
HO
Me
Ph
N
Bn
Ph
4i (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


7.50 7.48 7.46 7.41 7.39 7.36 7.35 7.33 7.31 7.30 7.29 7.28 7.27 7.22 7.20 7.18 7.16 7.14
3.82 3.79 3.72 3.69 3.46 3.43
2.24 2.23
1.79 1.78 1.64
1.22
0.88 0.82 0.57 0.55 0.55 0.54
Me Me
Ph
NBn2
+
Me Me
Ph
NBn2
(8:1 ratio)
10a
10b
(1H NMR, 400 MHz, CDCl3)
7.98 4.67 1.40 2.02
2.00 1.98 0.37
0.95
0.98 0.37
3.04
0.37 3.00 0.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

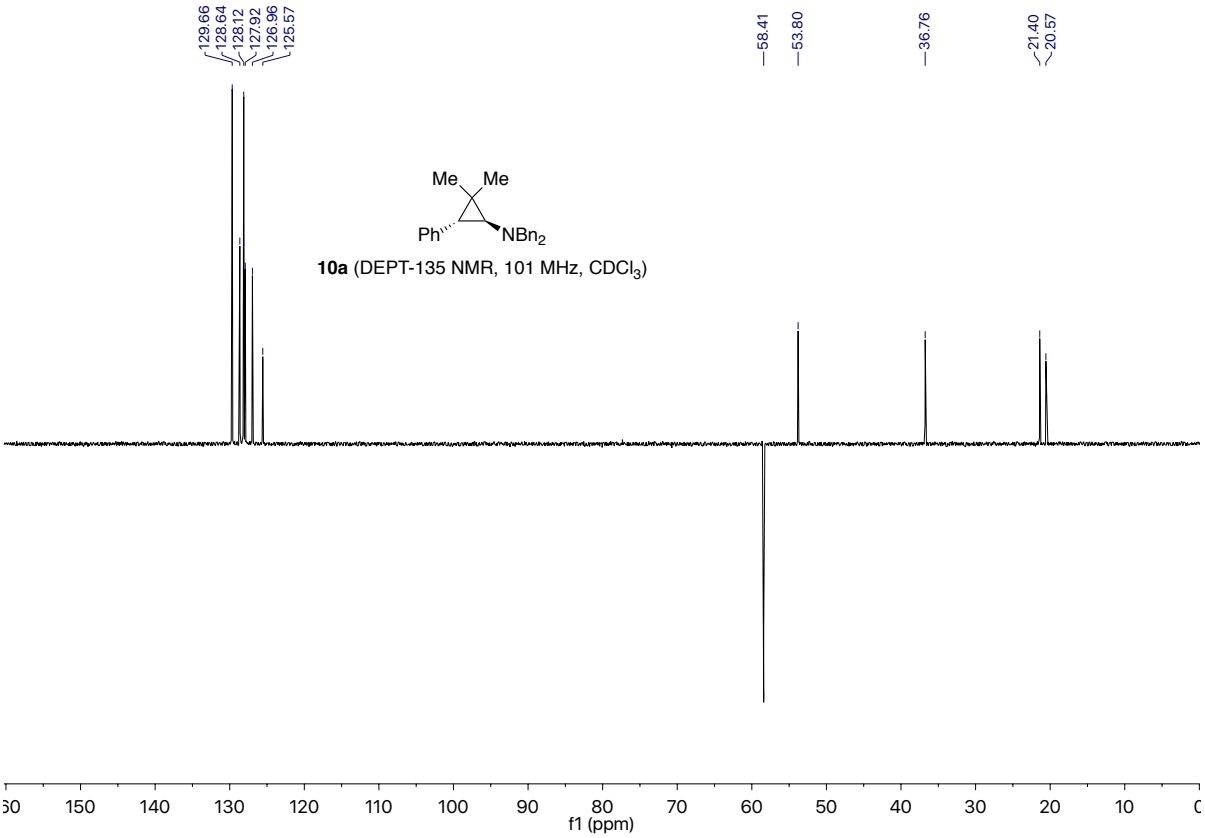

139.50 138.71 129.67 128.65 128.13 127.93 126.97 125.58
77.48 77.16 76.84
58.42
53.80
36.76
27.79
21.41 20.59
Me Me
Ph
NBn2
+
Me Me
Ph
NBn2
(8:1 ratio)
10a
10b
(13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



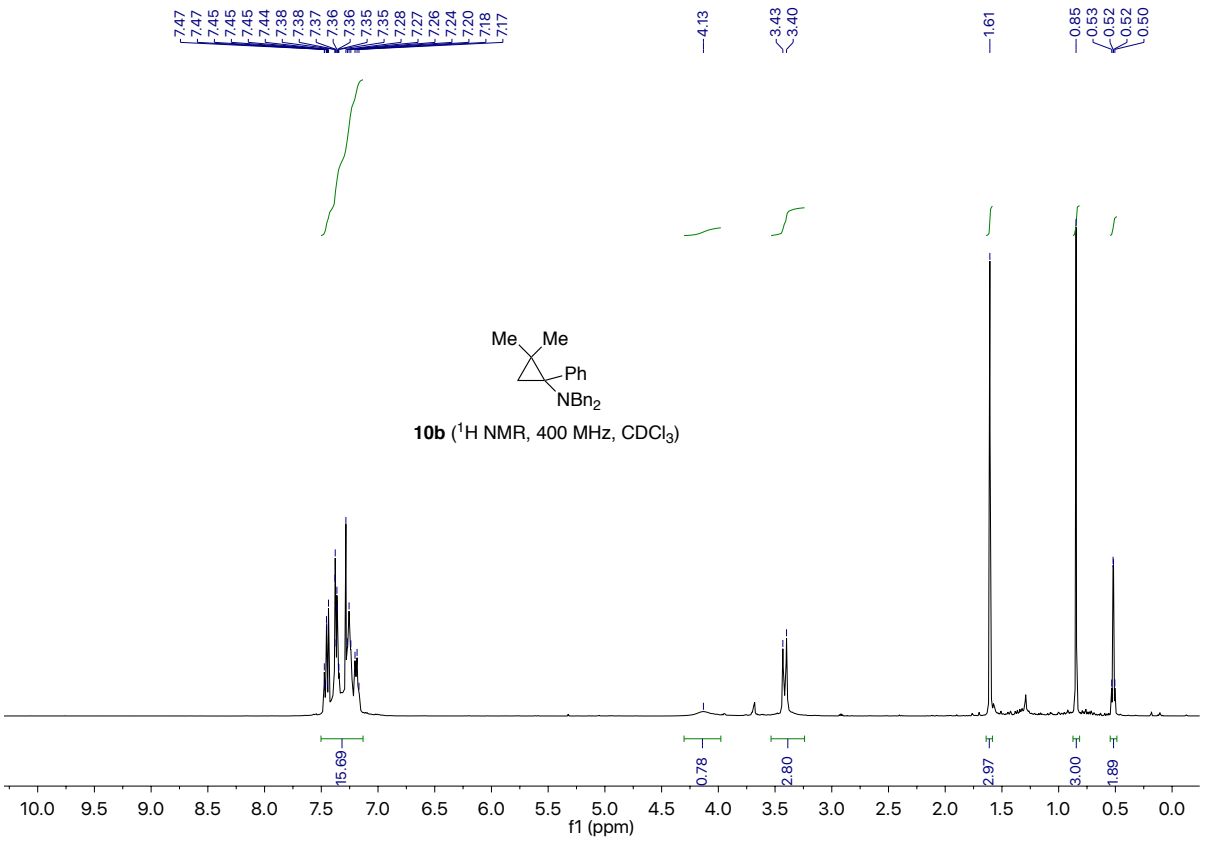
10a (^{1}H NMR, 400 MHz, $CDCl_3$)



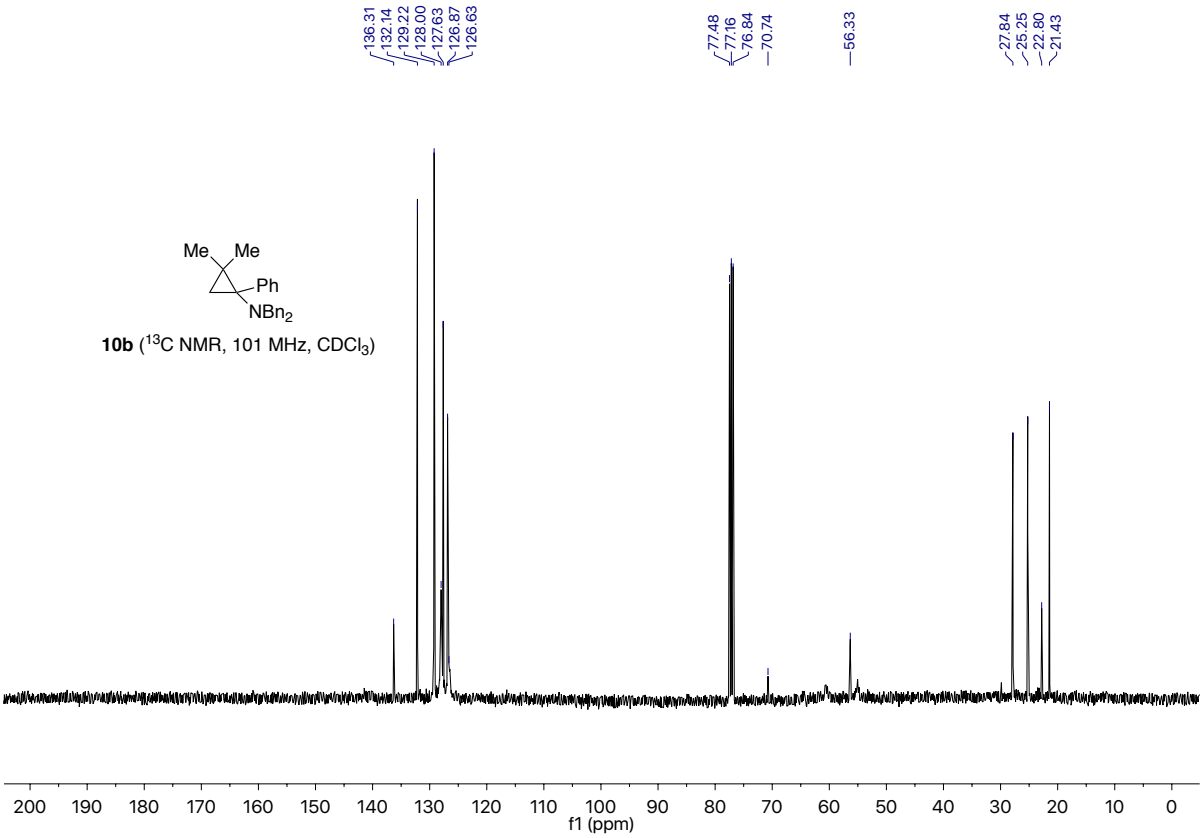
10a (^{13}C NMR, 101 MHz, $CDCl_3$)

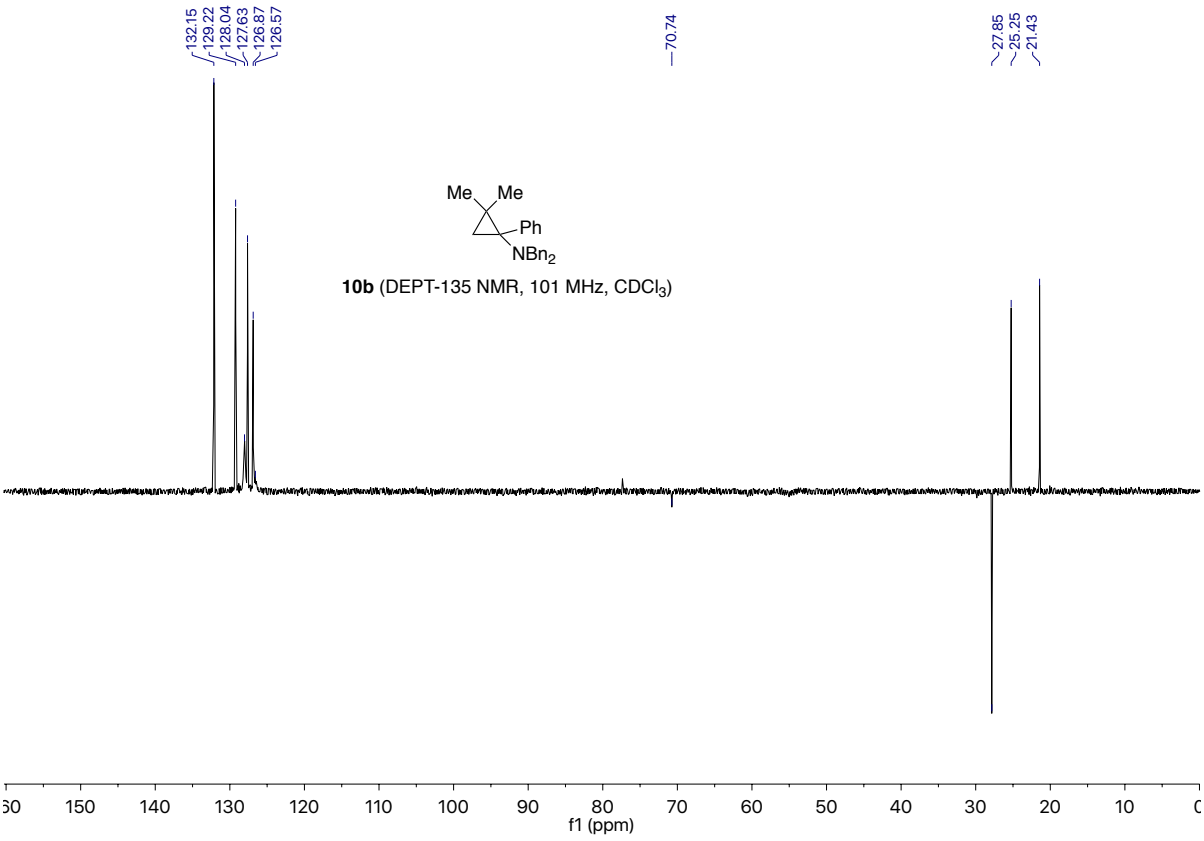


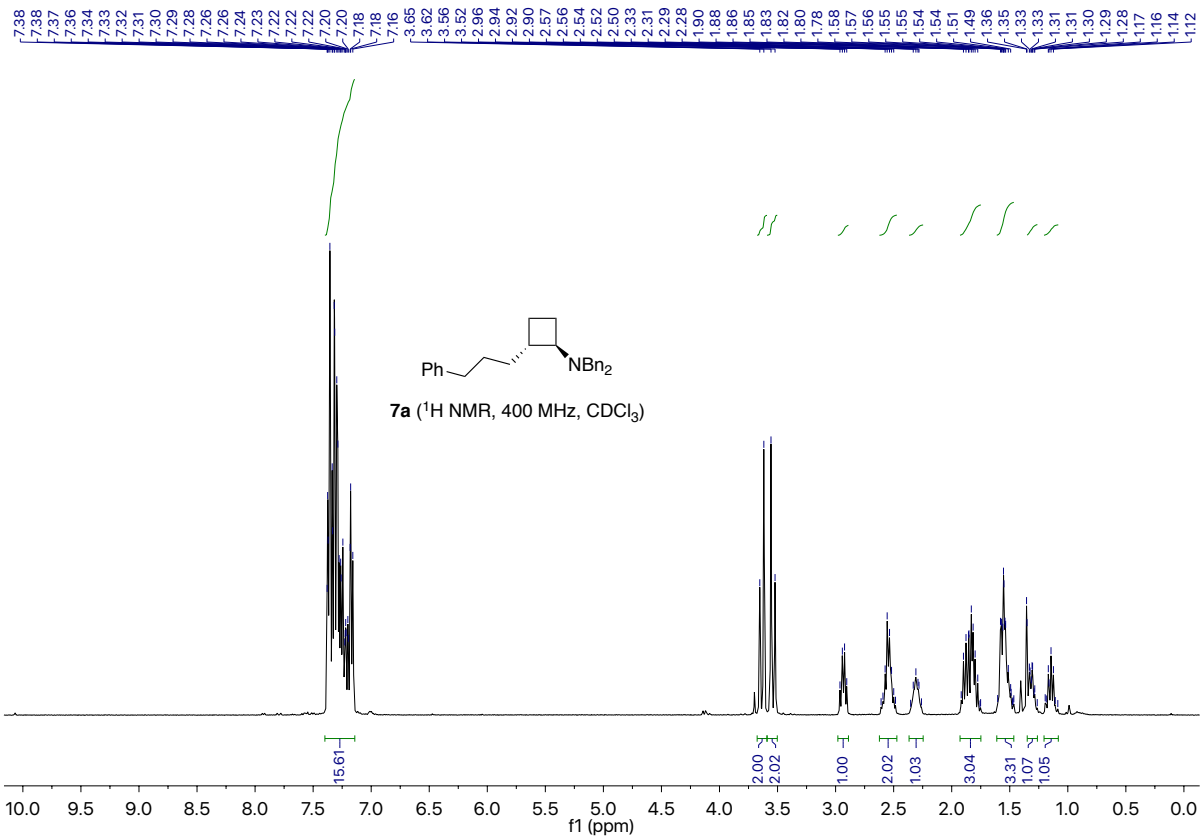
10a (DEPT-135 NMR, 101 MHz, $CDCl_3$)

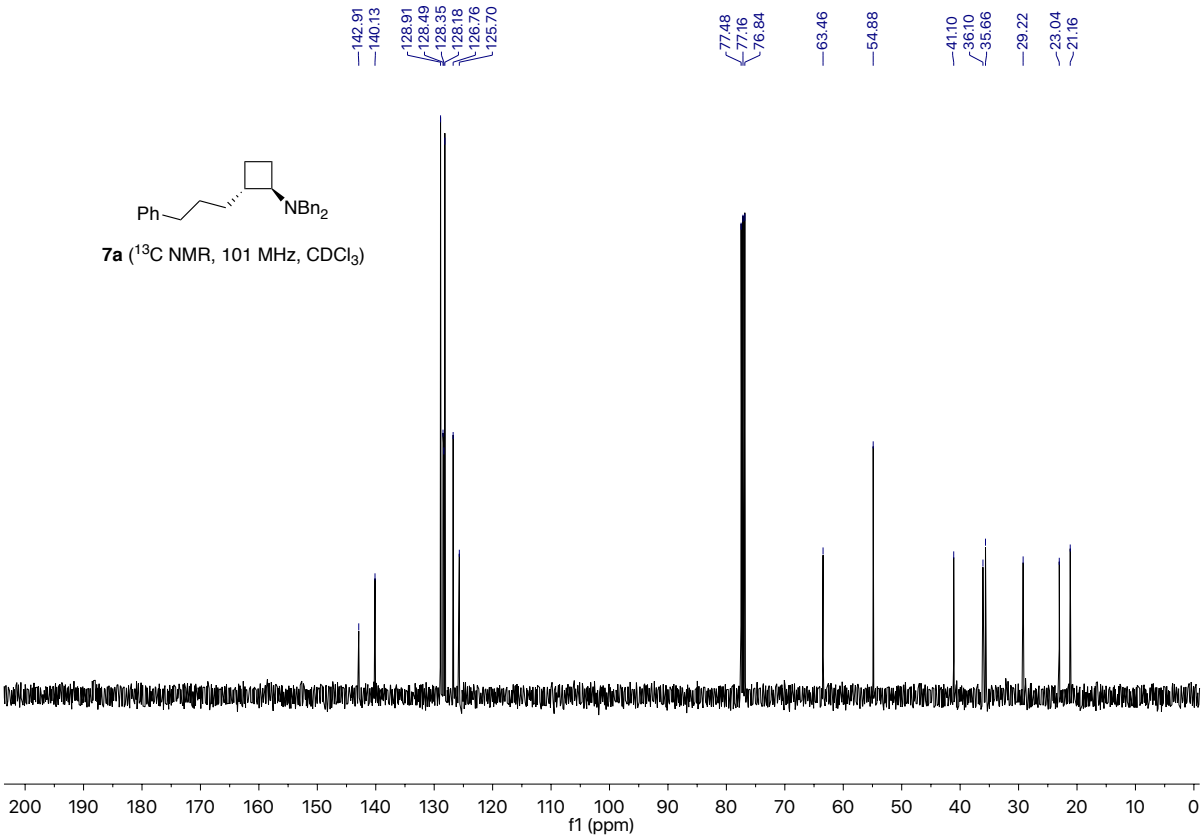


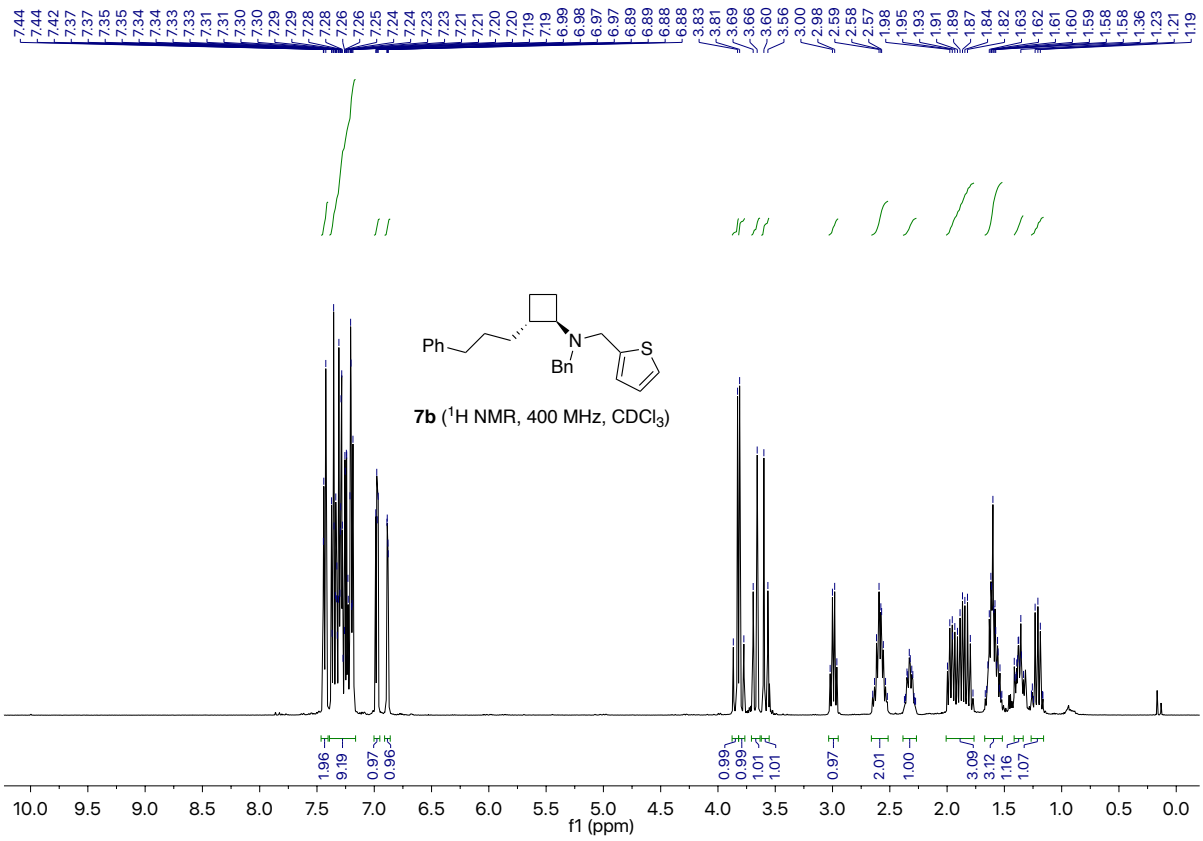
10b (^{1}H NMR, 400 MHz, $CDCl_3$)

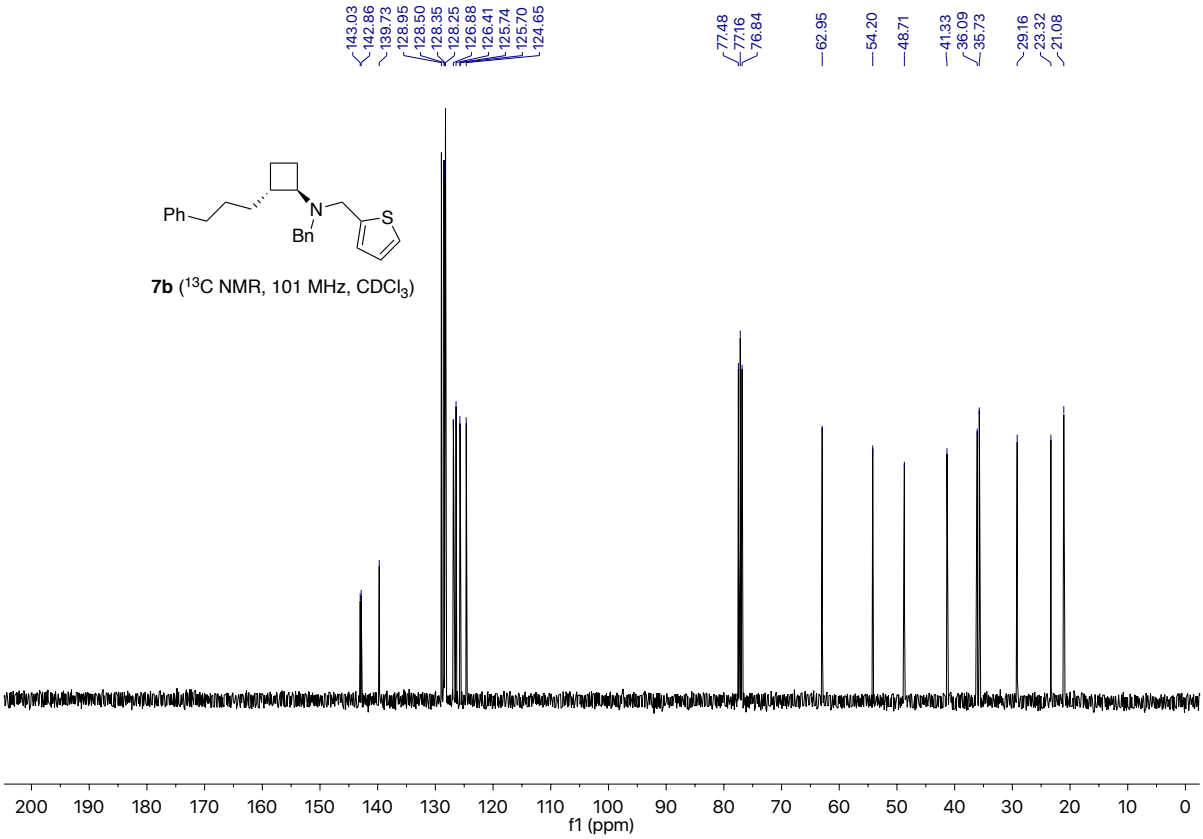

136.31
132.14
129.22
128.00
127.63
126.87
126.63
77.48
77.16
76.84
70.74
56.33
27.84
25.25
22.80
21.43
Me
Me
Ph
NBn2
10b (13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

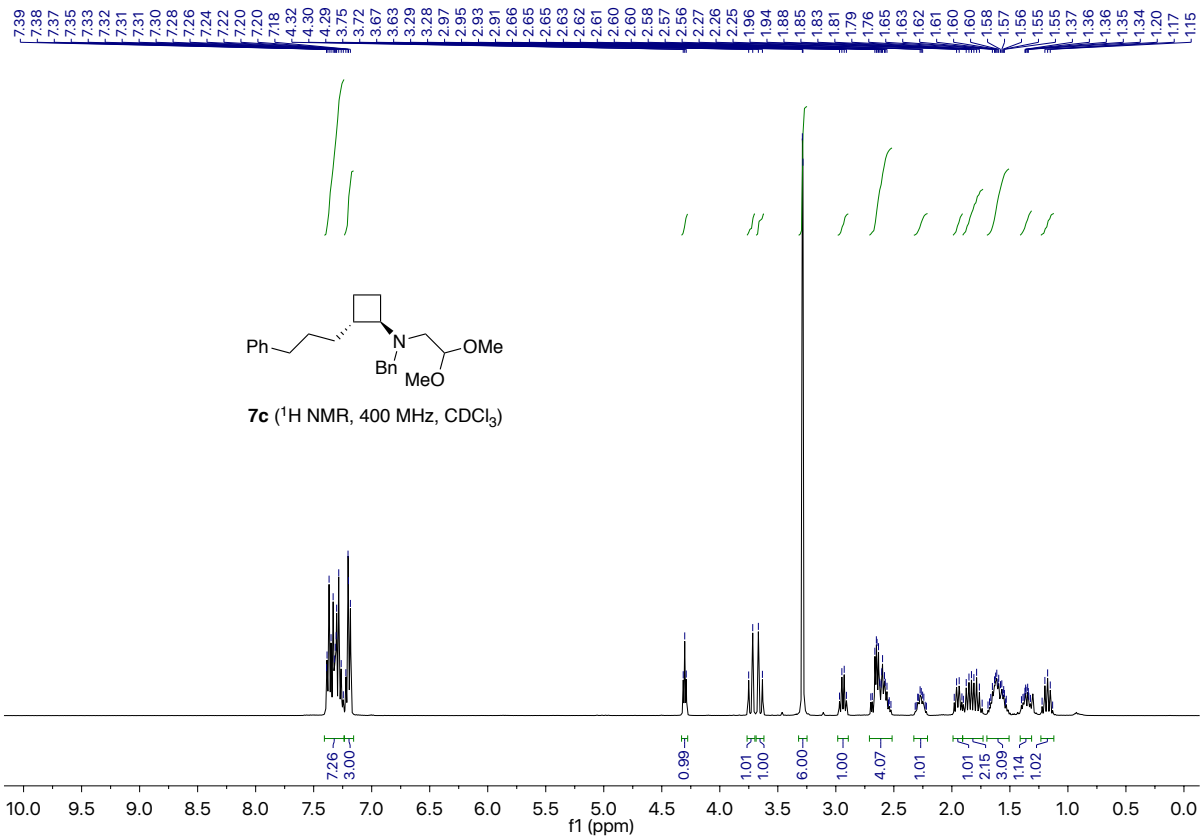

132.15
129.22
128.04
127.63
126.87
126.57
70.74
27.85
25.25
21.43
Me
Me
Ph
NBn2
10b (DEPT-135 NMR, 101 MHz, CDCl3)
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Ph
NBn2
7a (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

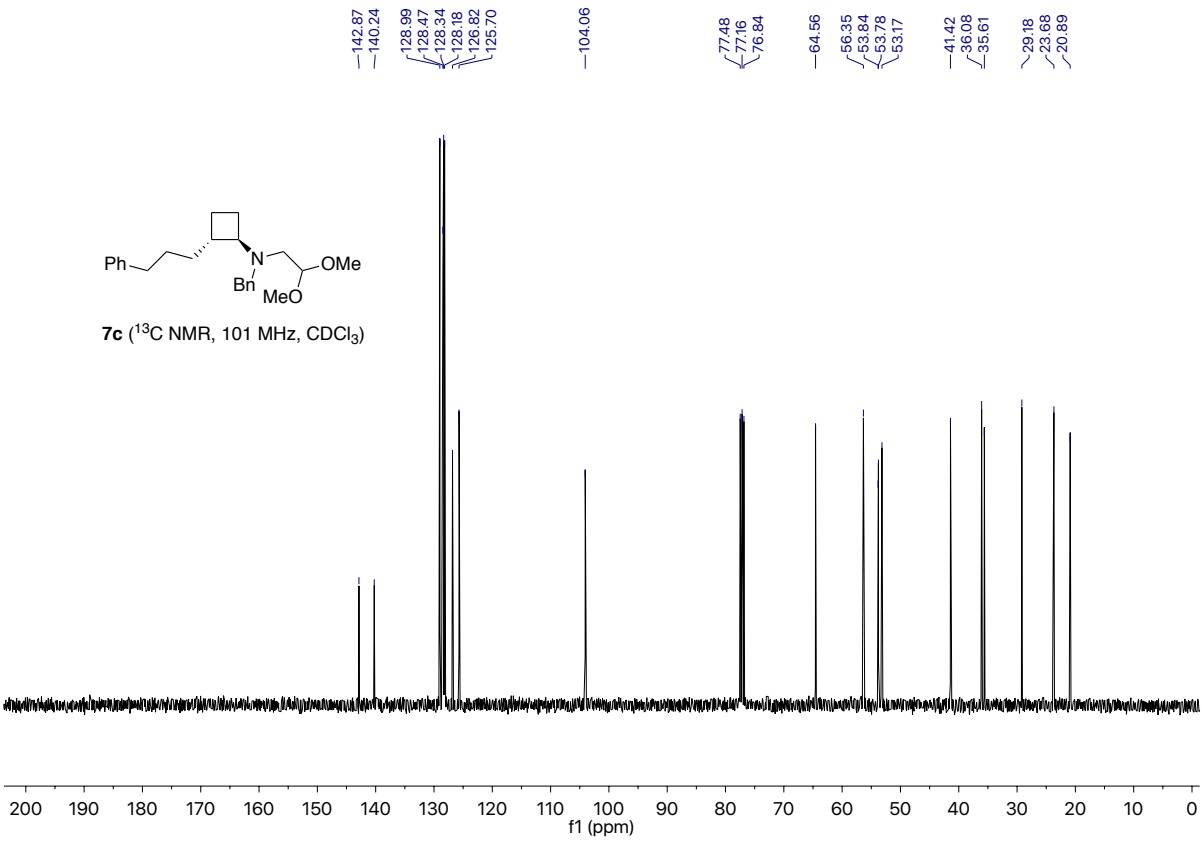

Ph
NBn2
7a (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


Ph
N
Bn
S
7b (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

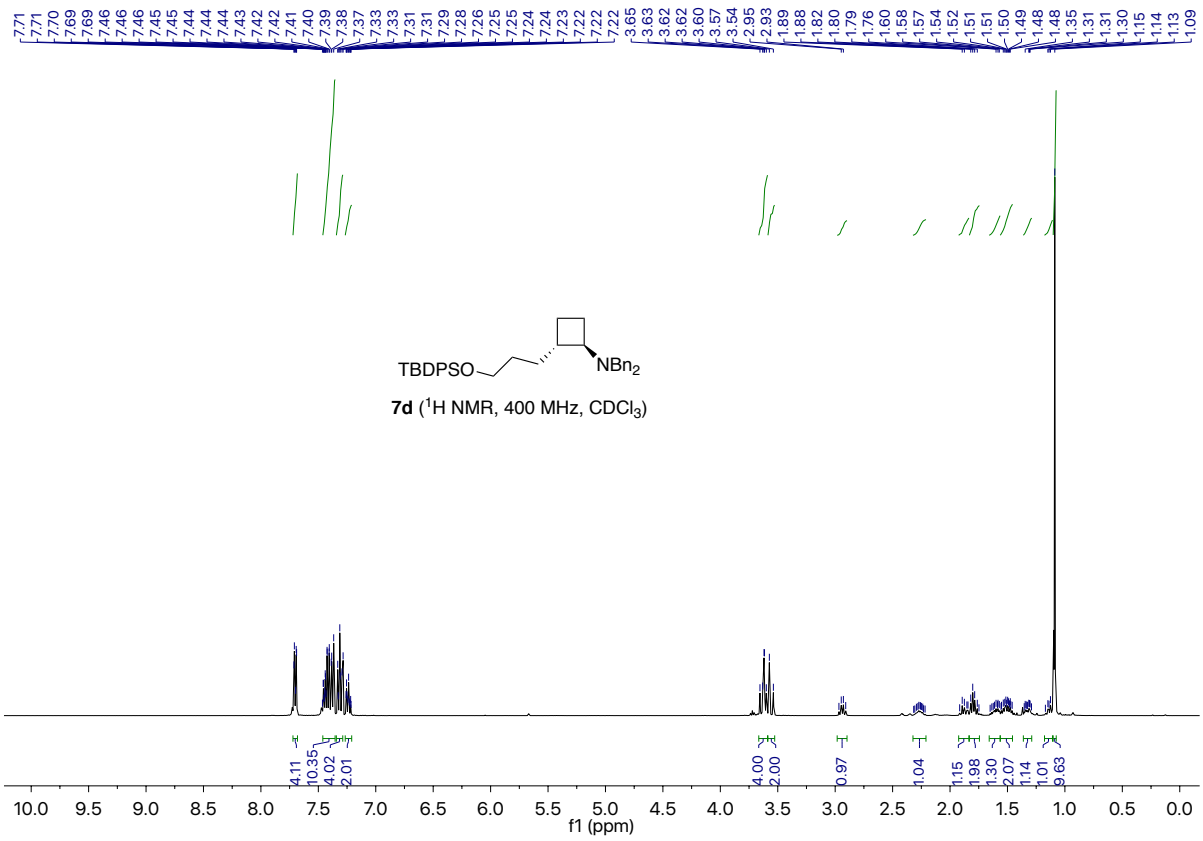

Ph
N
Bn
S
7b (13C NMR, 101 MHz, CDCl3)
f1 (ppm)

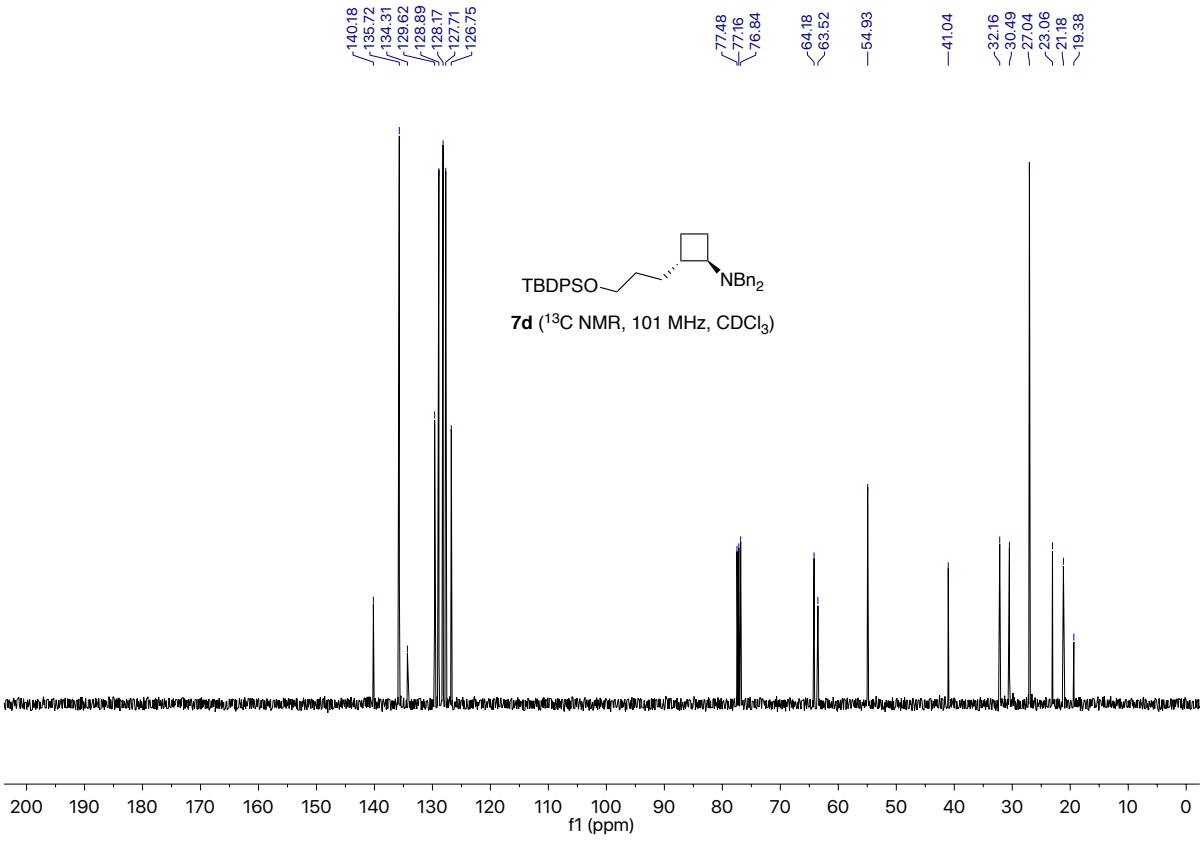


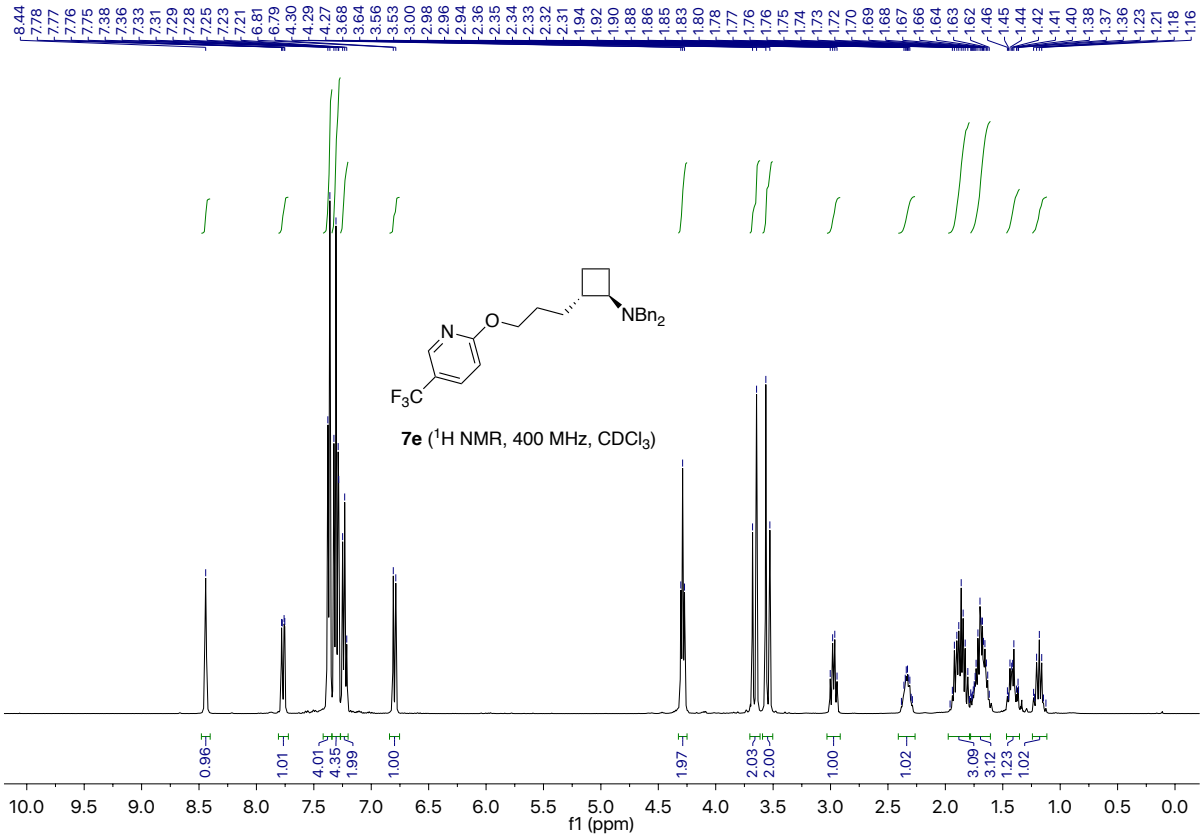
7c (^{1}H NMR, 400 MHz, $CDCl_3$)

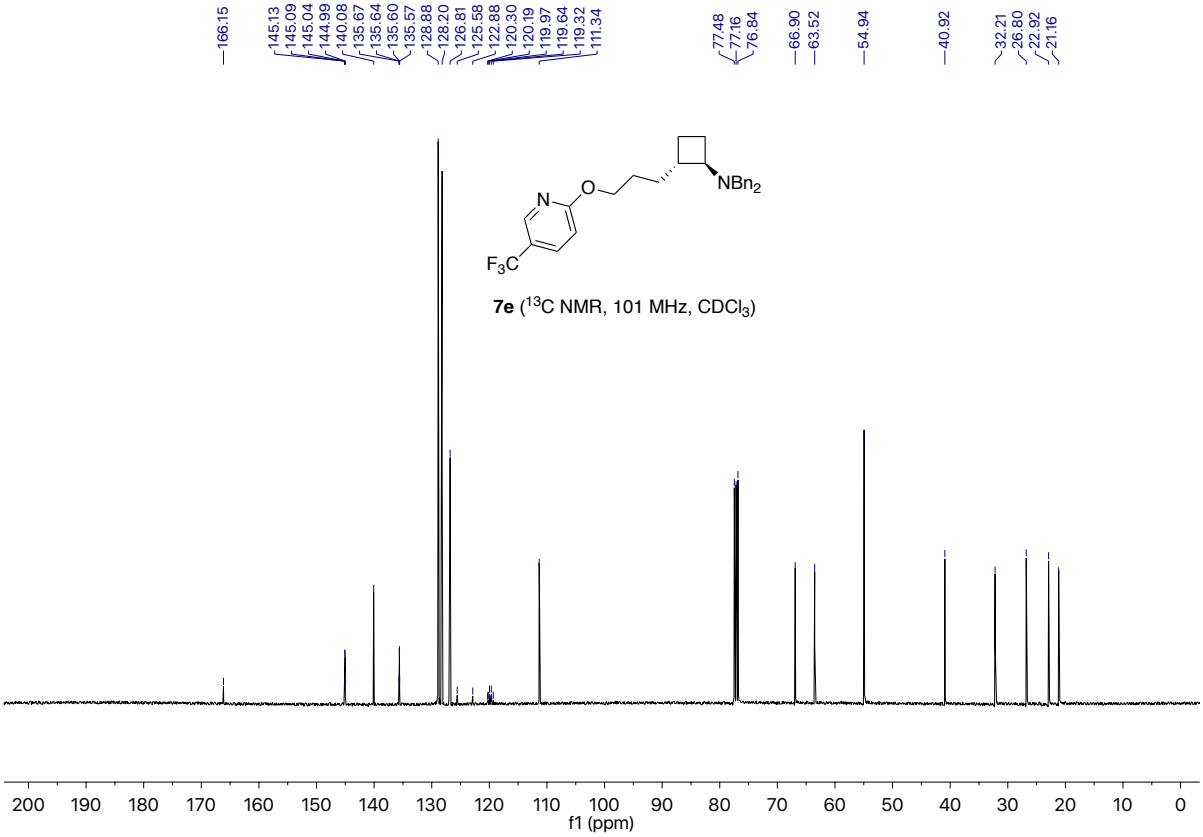


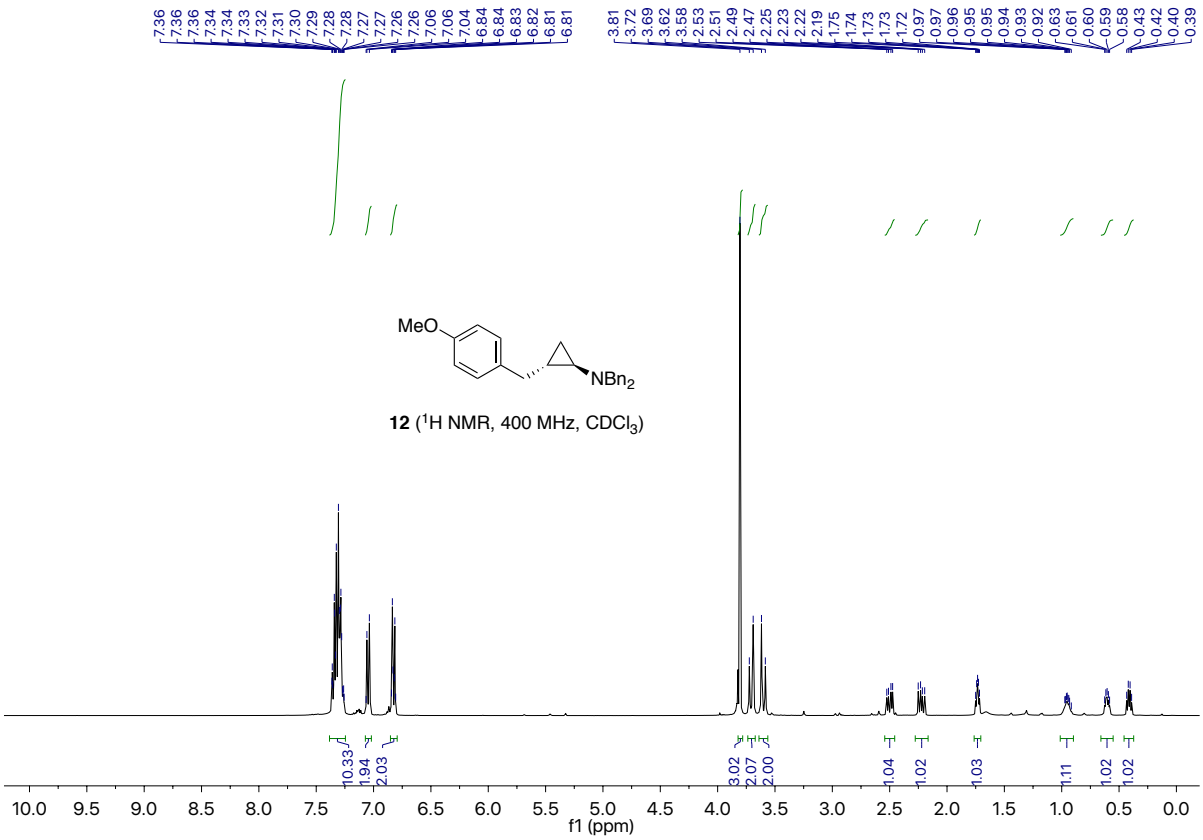
7c (^{13}C NMR, 101 MHz, $CDCl_3$)

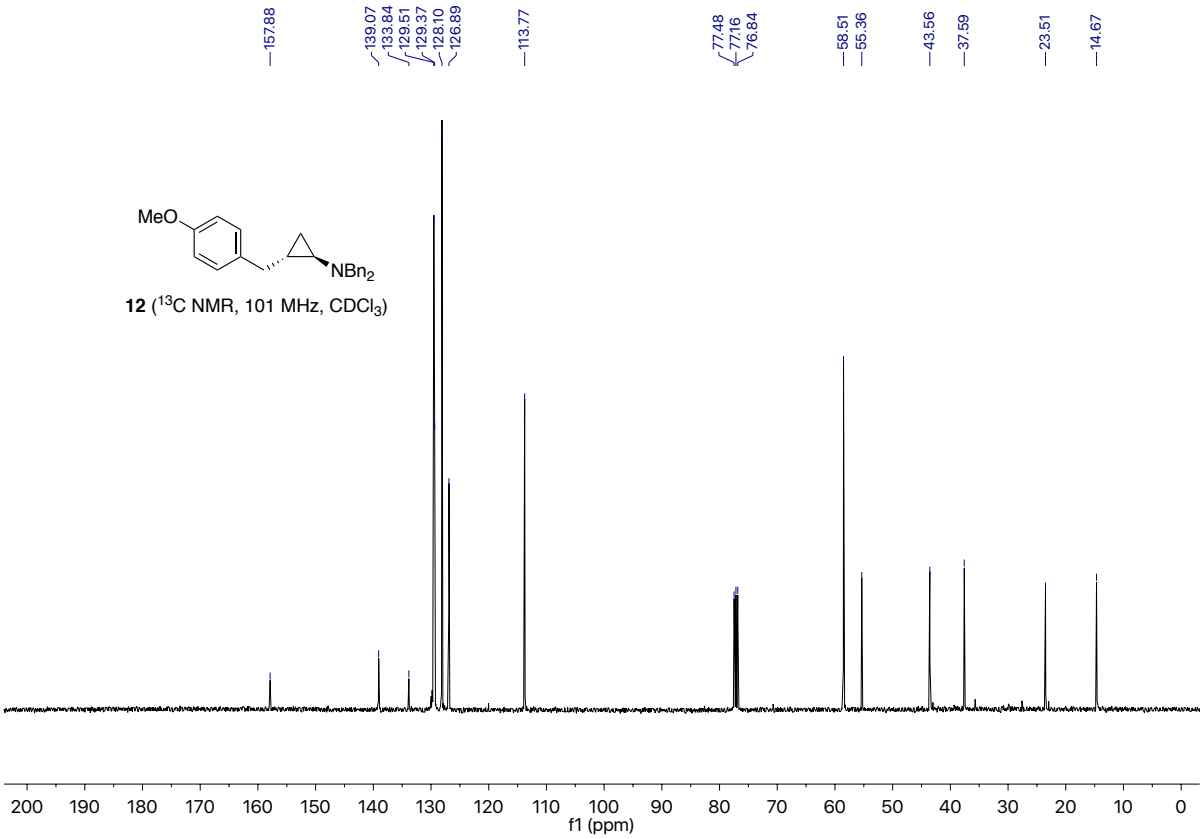

TBDPSO
NBn2
7d (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

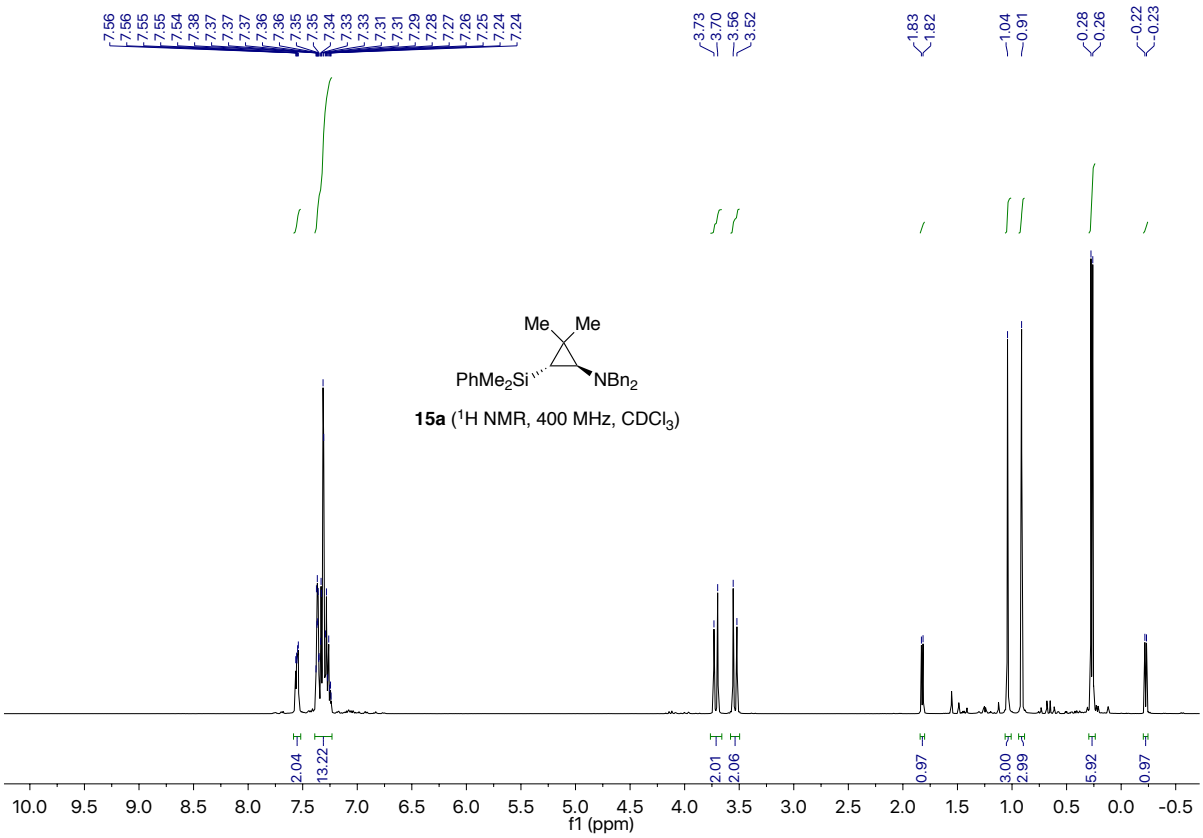

TBDPSO
NBn2
7d (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


NBn2
N
O
F3C
7e (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

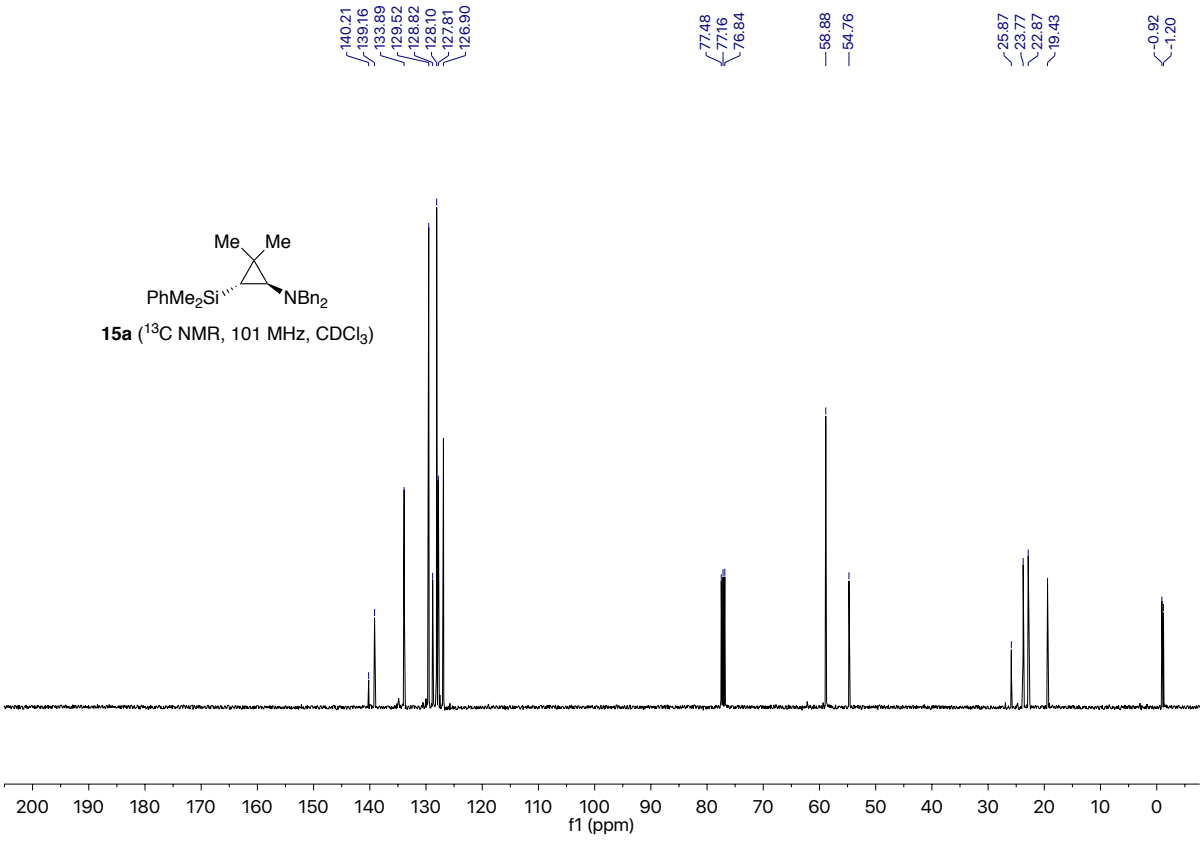

NBn2
N
O
F3C
7e (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


MeO
NBn2
12 (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

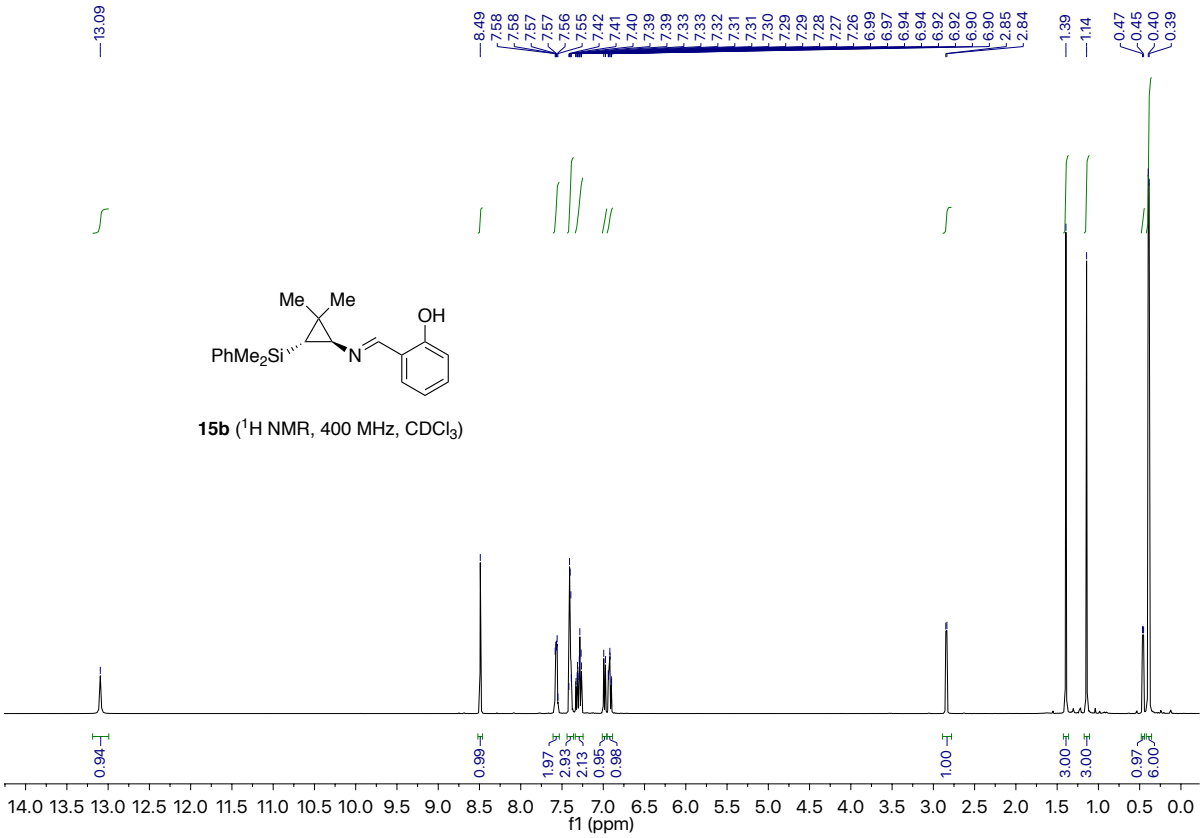

MeO
NBn2
12 (13C NMR, 101 MHz, CDCl3)
f1 (ppm)



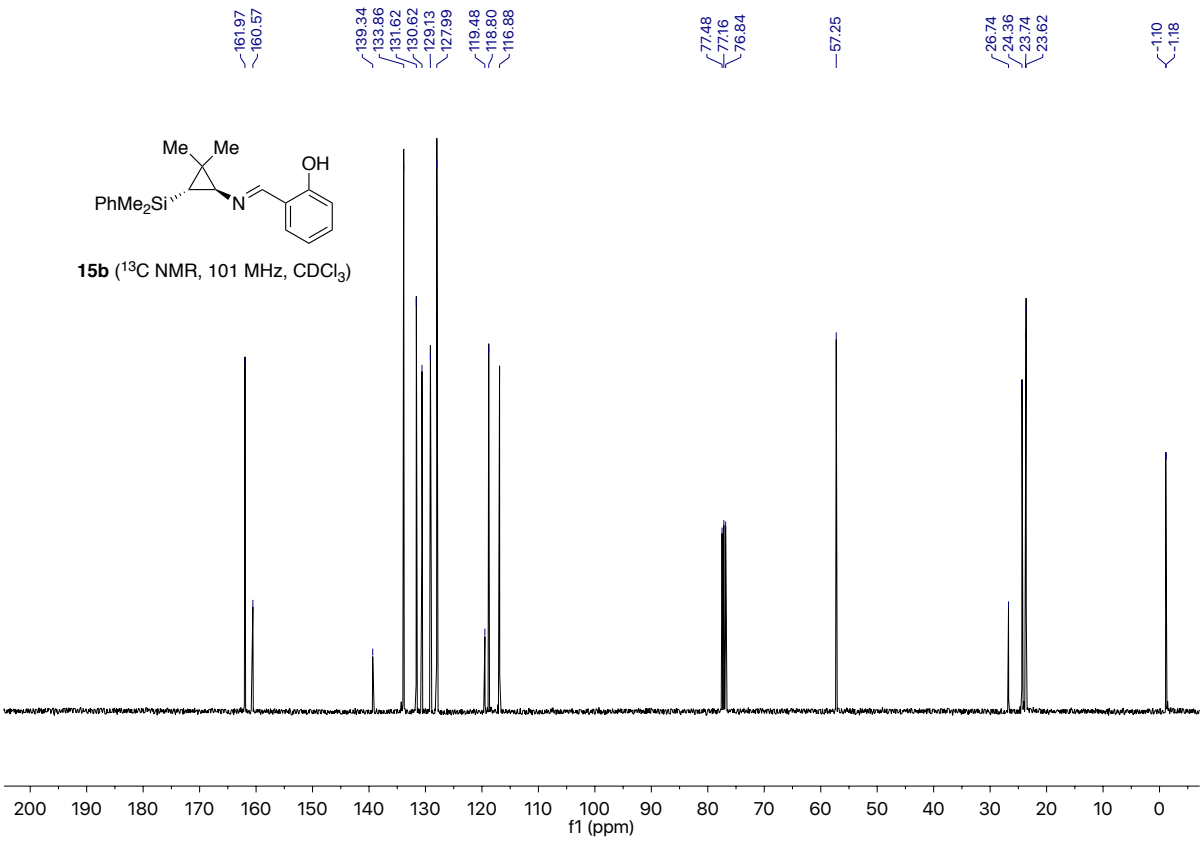
15a (^{1}H NMR, 400 MHz, $CDCl_3$)



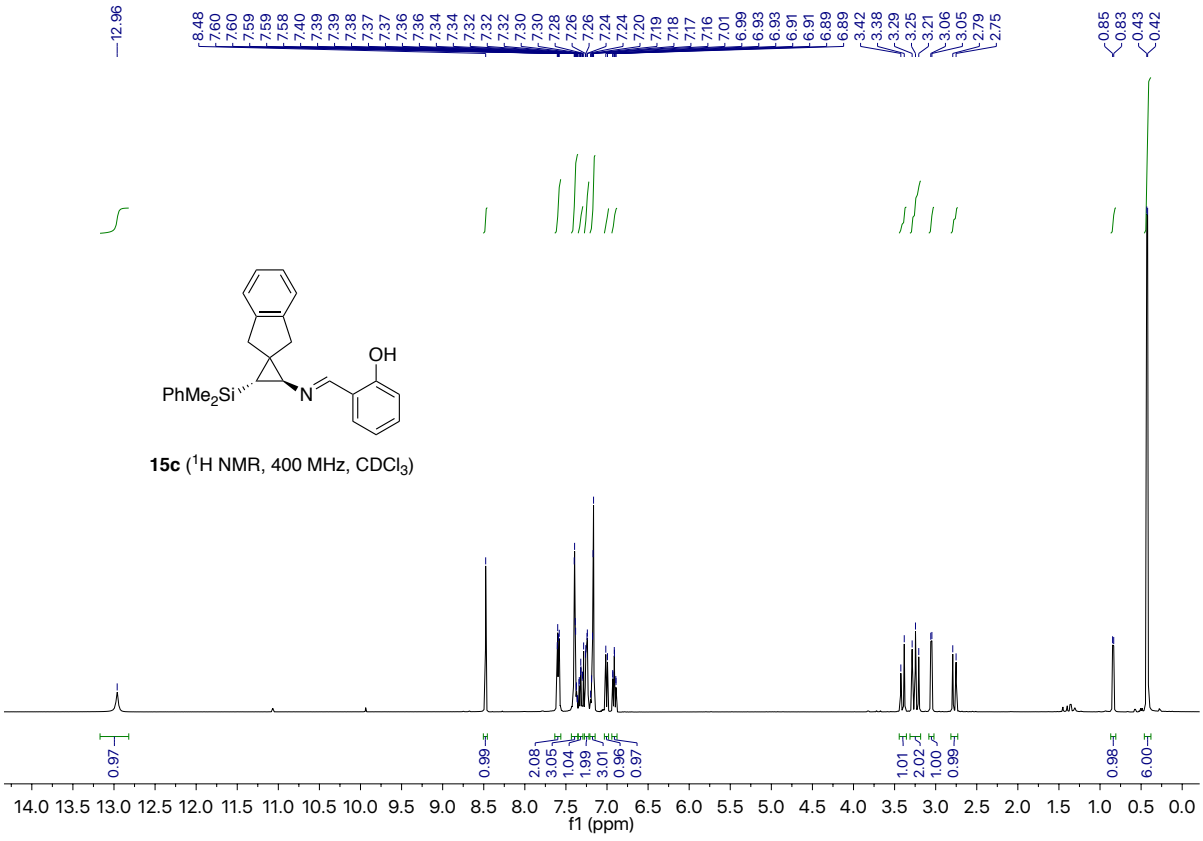
15a (^{13}C NMR, 101 MHz, $CDCl_3$)



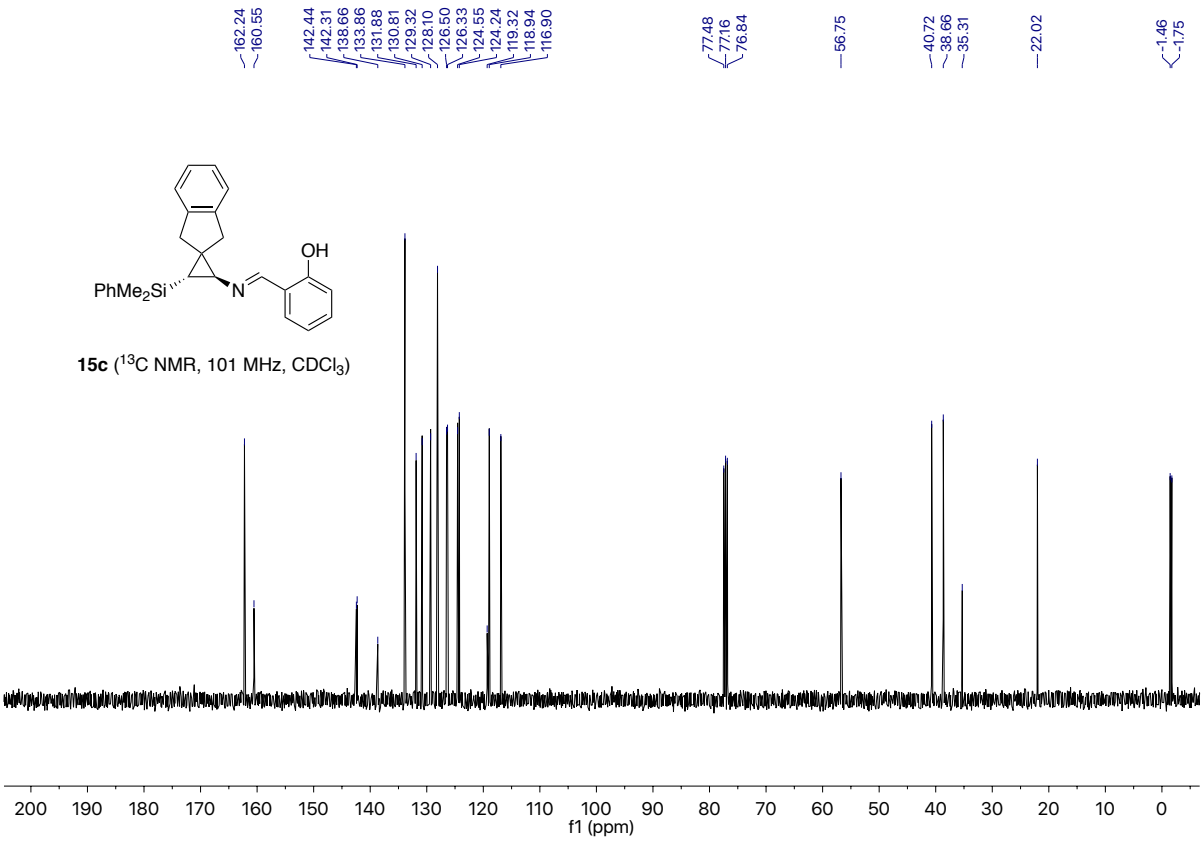
15b (^{1}H NMR, 400 MHz, $CDCl_3$)



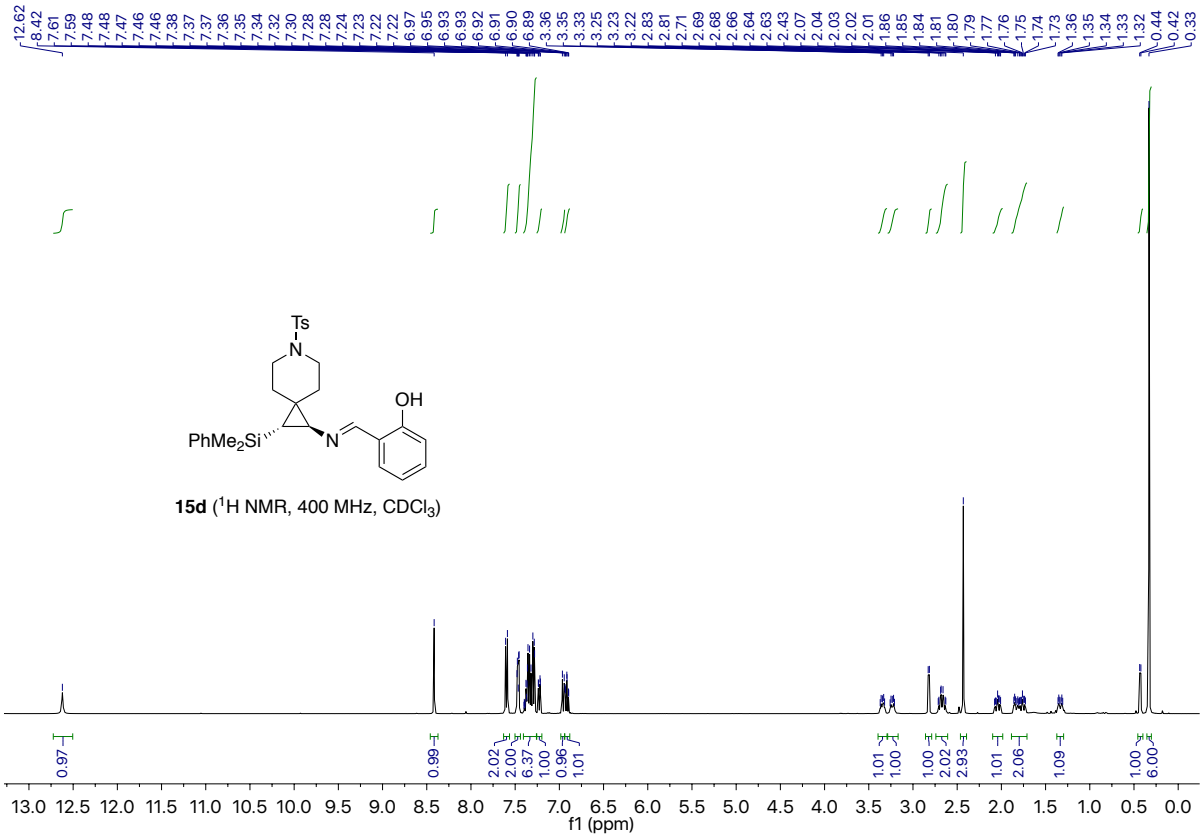
15b (^{13}C NMR, 101 MHz, $CDCl_3$)



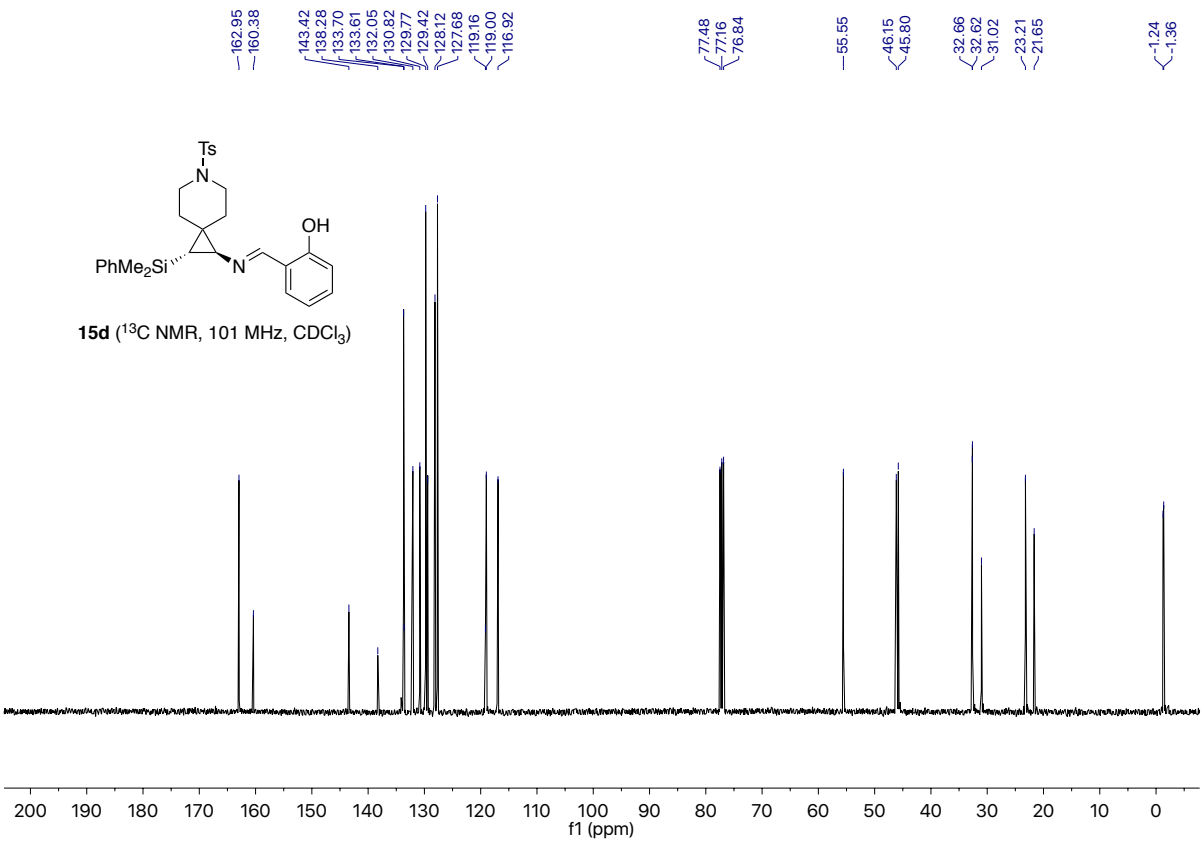
15c (^{1}H NMR, 400 MHz, $CDCl_3$)



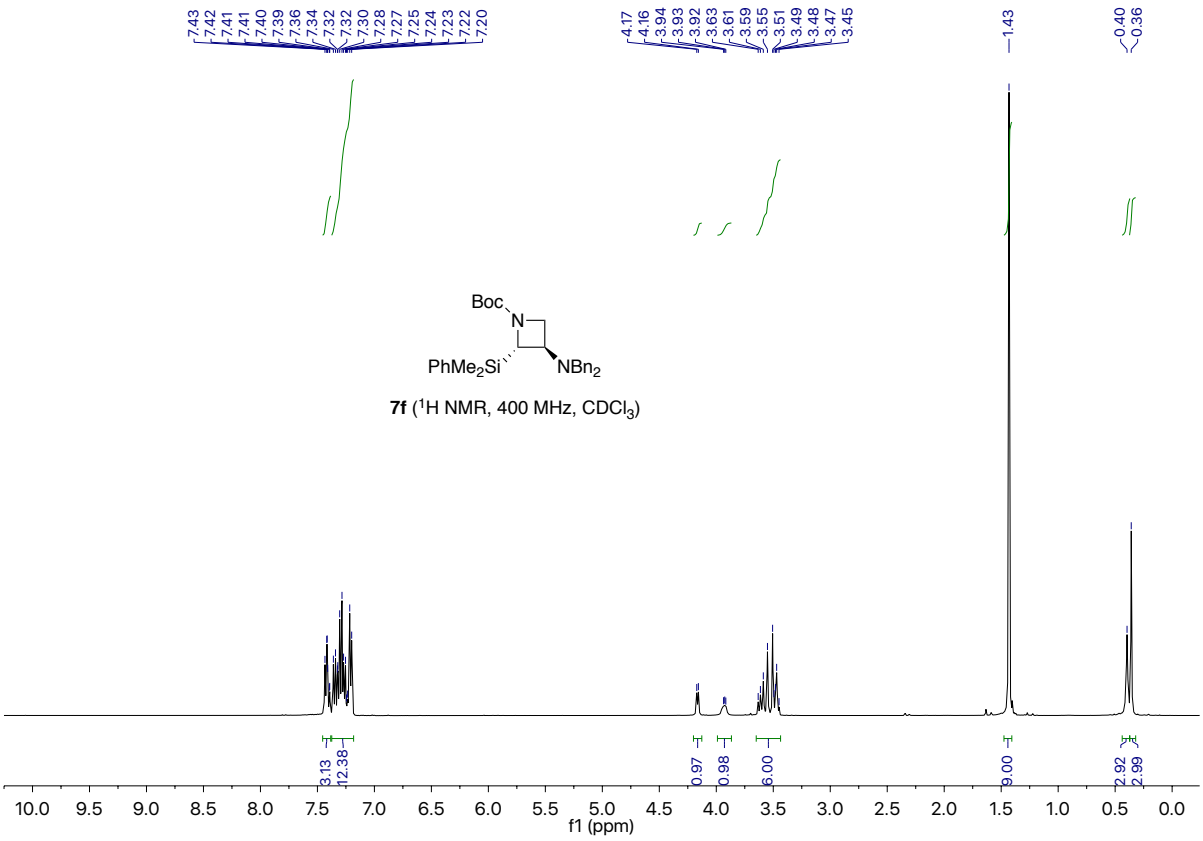
15c (^{13}C NMR, 101 MHz, $CDCl_3$)



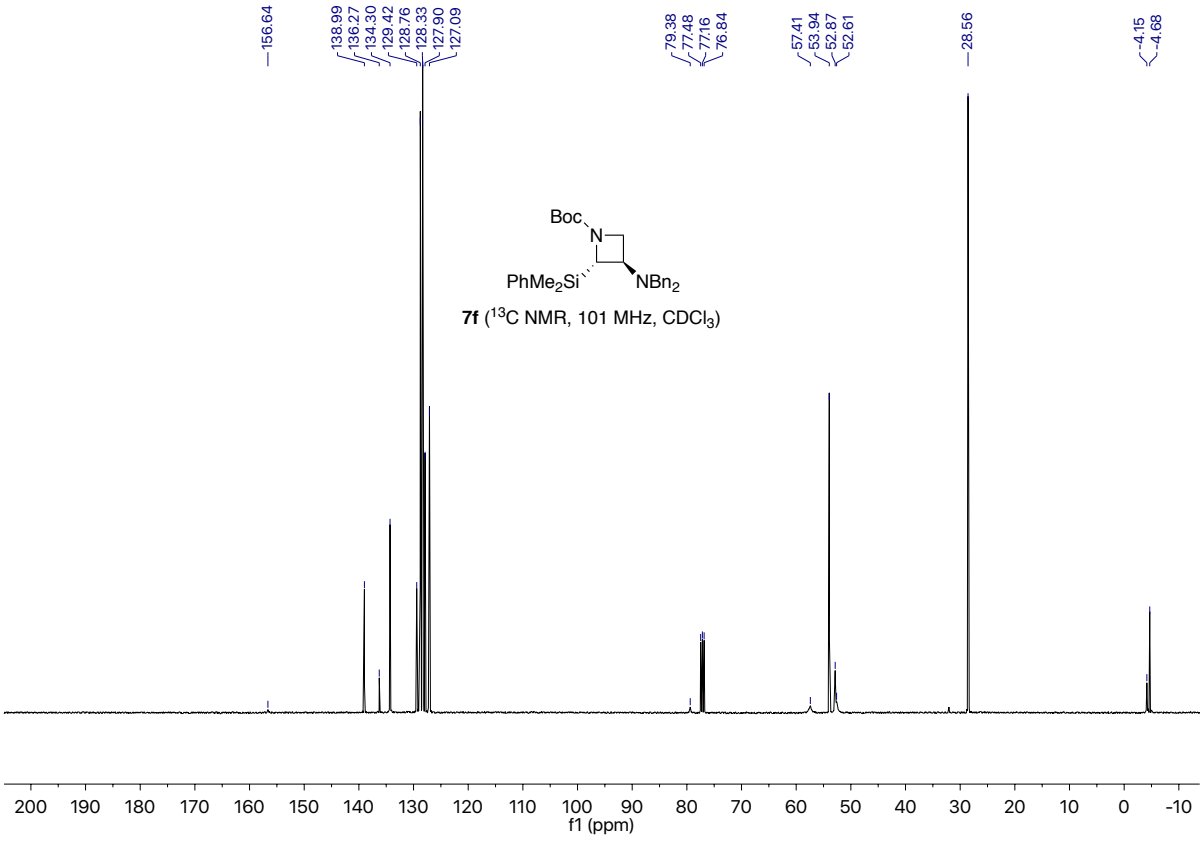
15d (^{1}H NMR, 400 MHz, $CDCl_3$)



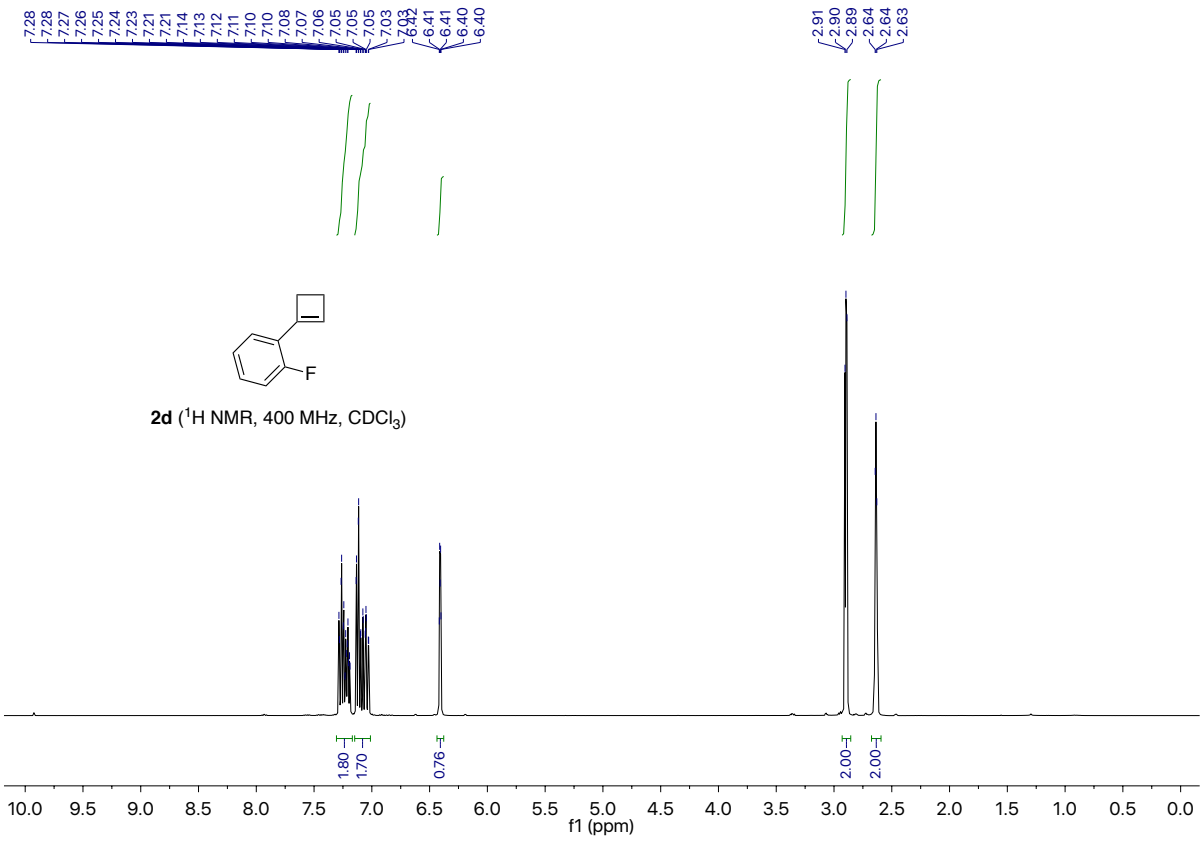
15d (^{13}C NMR, 101 MHz, $CDCl_3$)



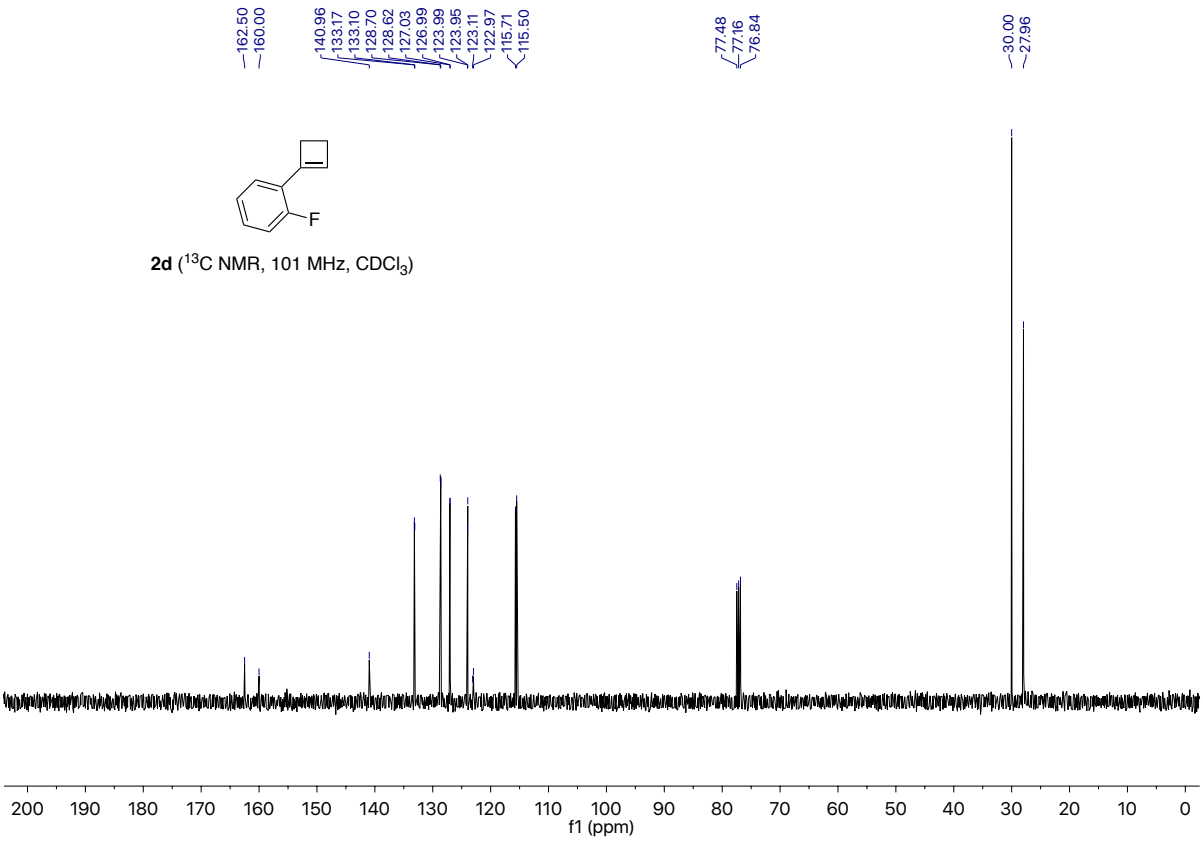
7f (^{1}H NMR, 400 MHz, $CDCl_3$)



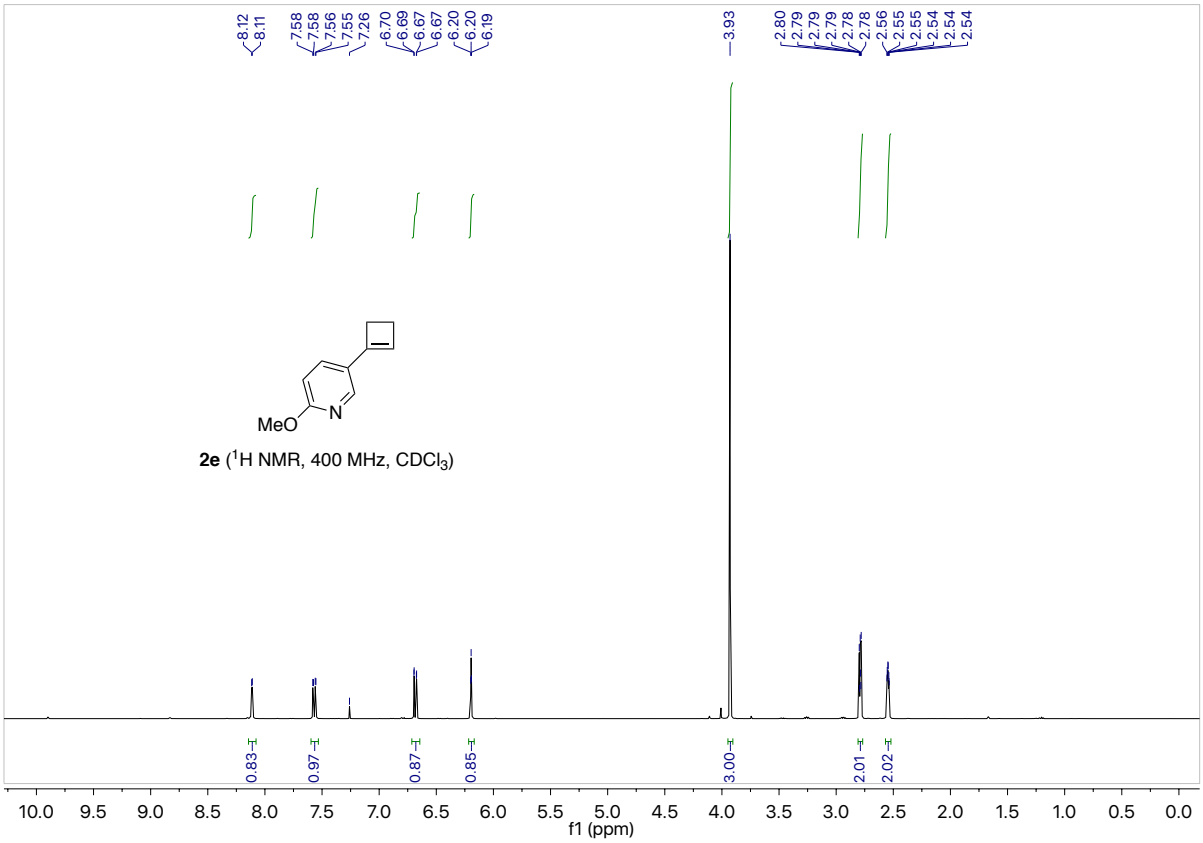
7f (^{13}C NMR, 101 MHz, $CDCl_3$)



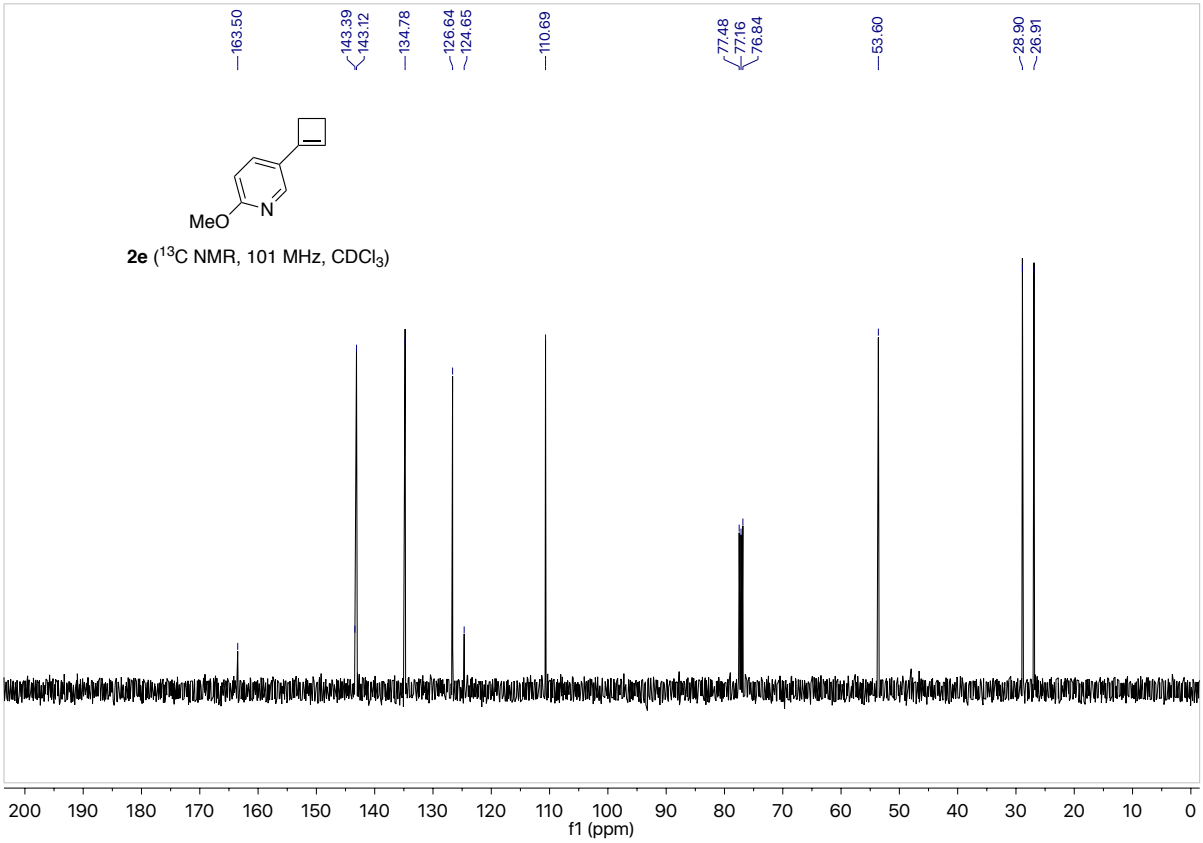
2d (^{1}H NMR, 400 MHz, $CDCl_3$)



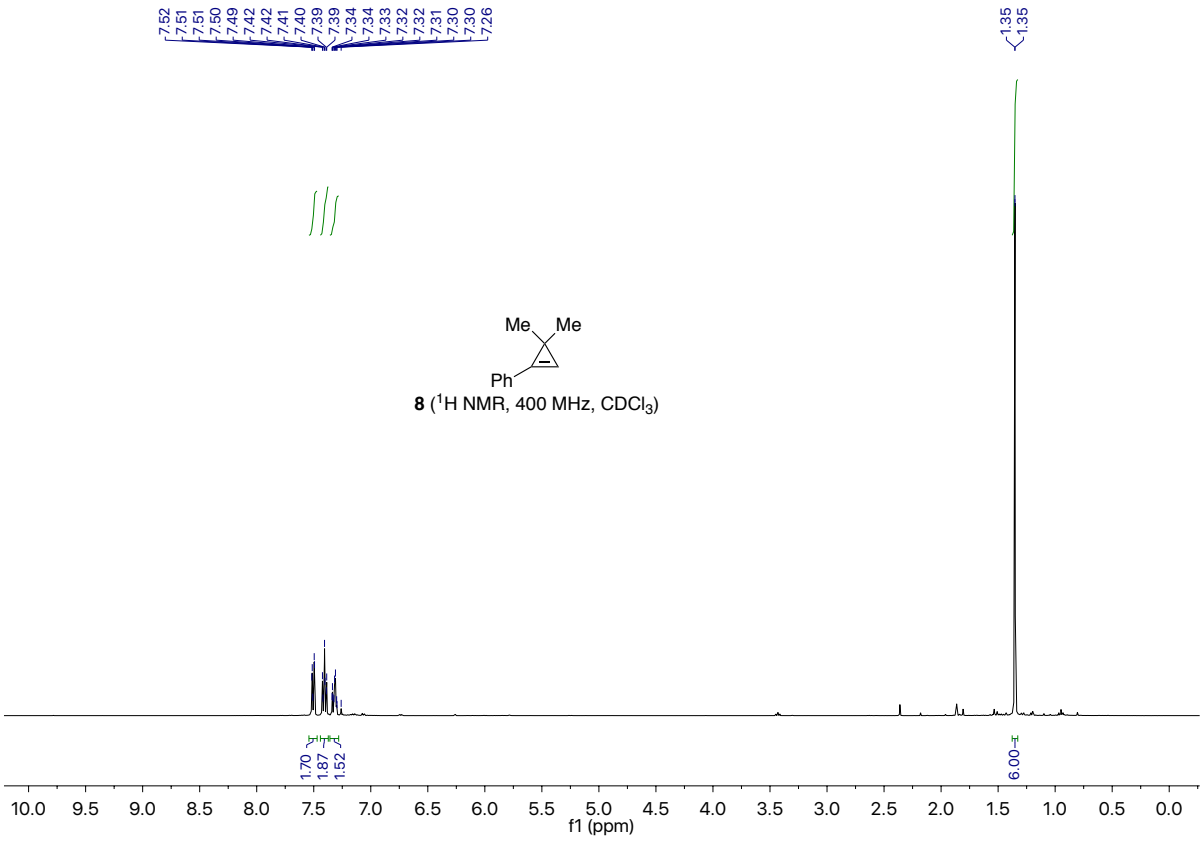
2d (^{13}C NMR, 101 MHz, $CDCl_3$)



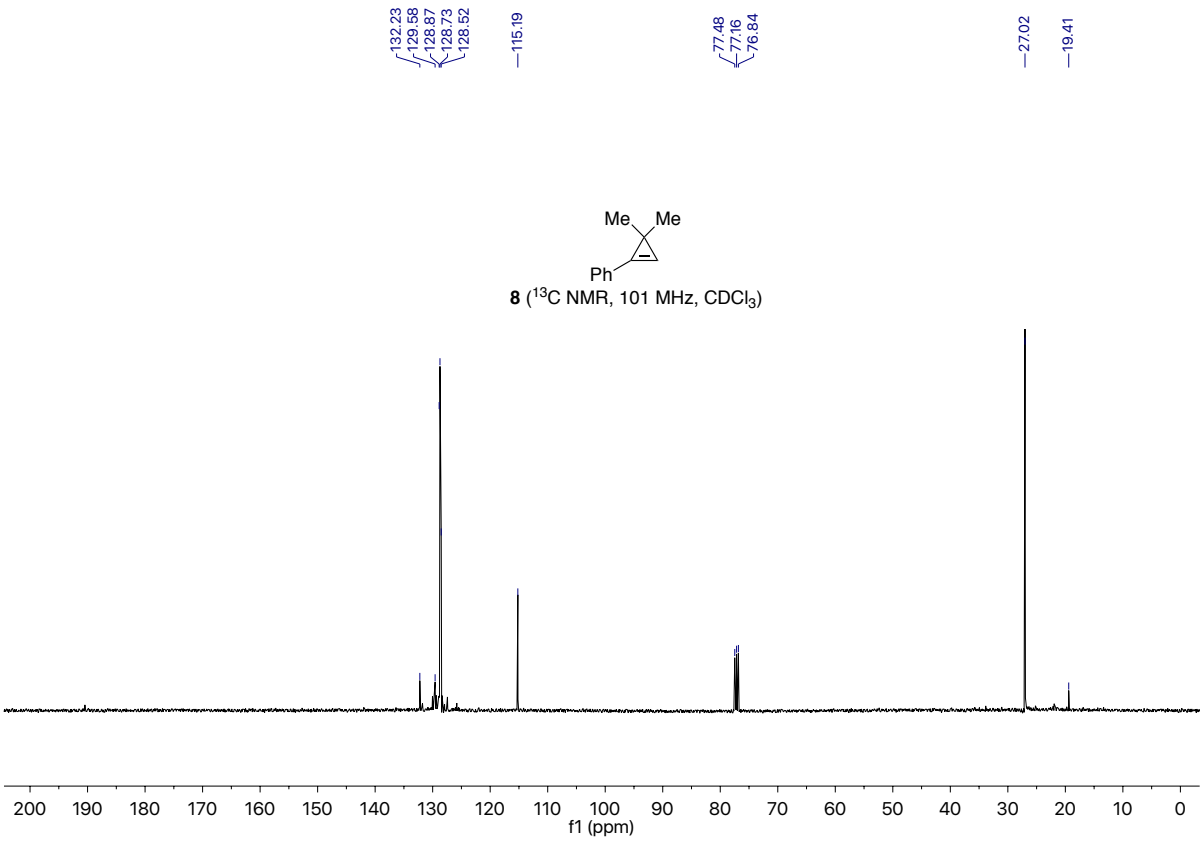
2e (^{1}H NMR, 400 MHz, $CDCl_3$)



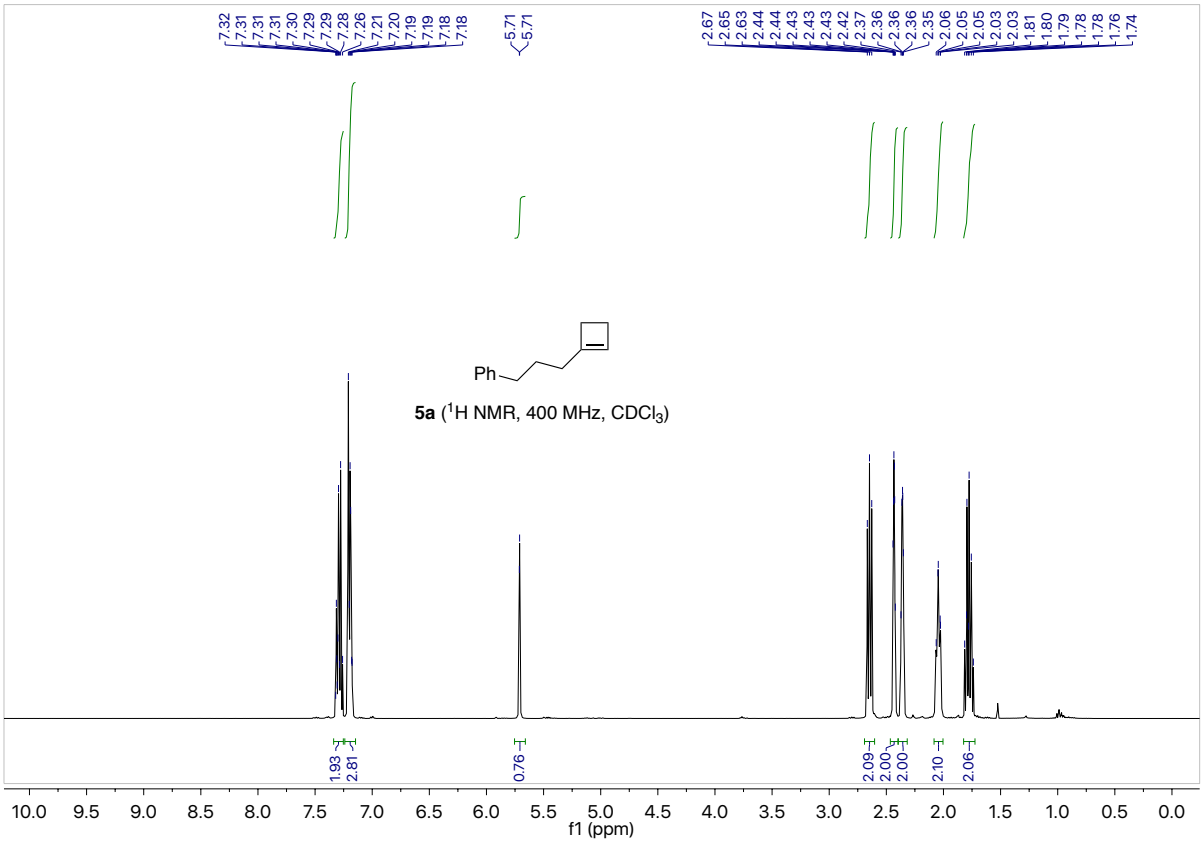
2e (^{13}C NMR, 101 MHz, $CDCl_3$)

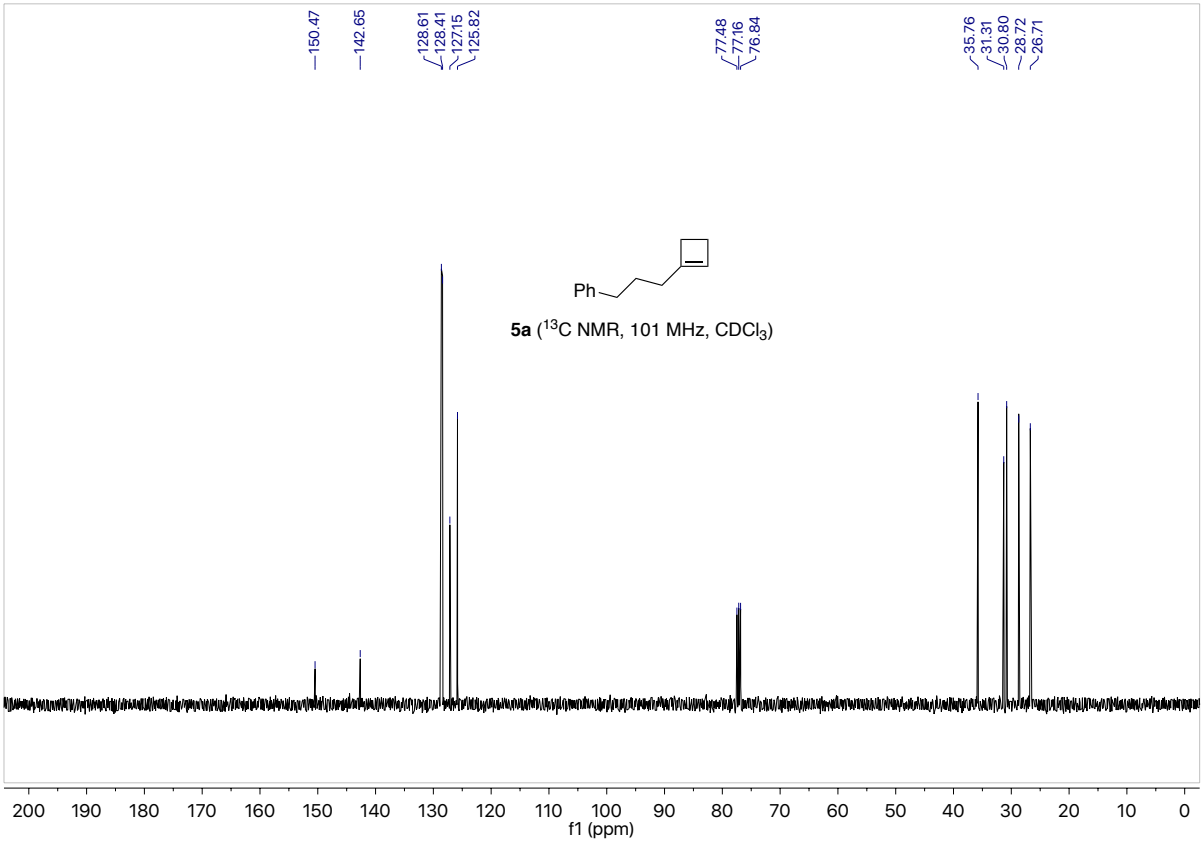


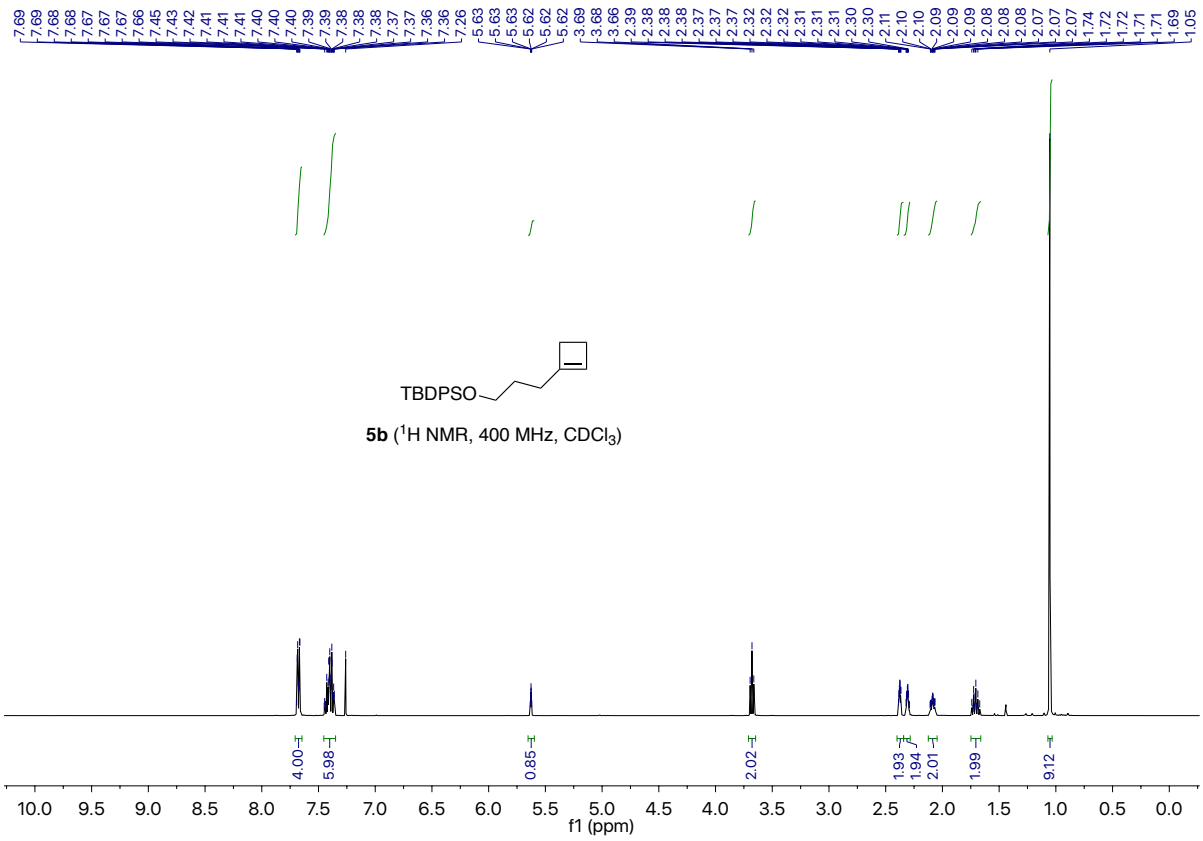
8 (^{1}H NMR, 400 MHz, $CDCl_3$)



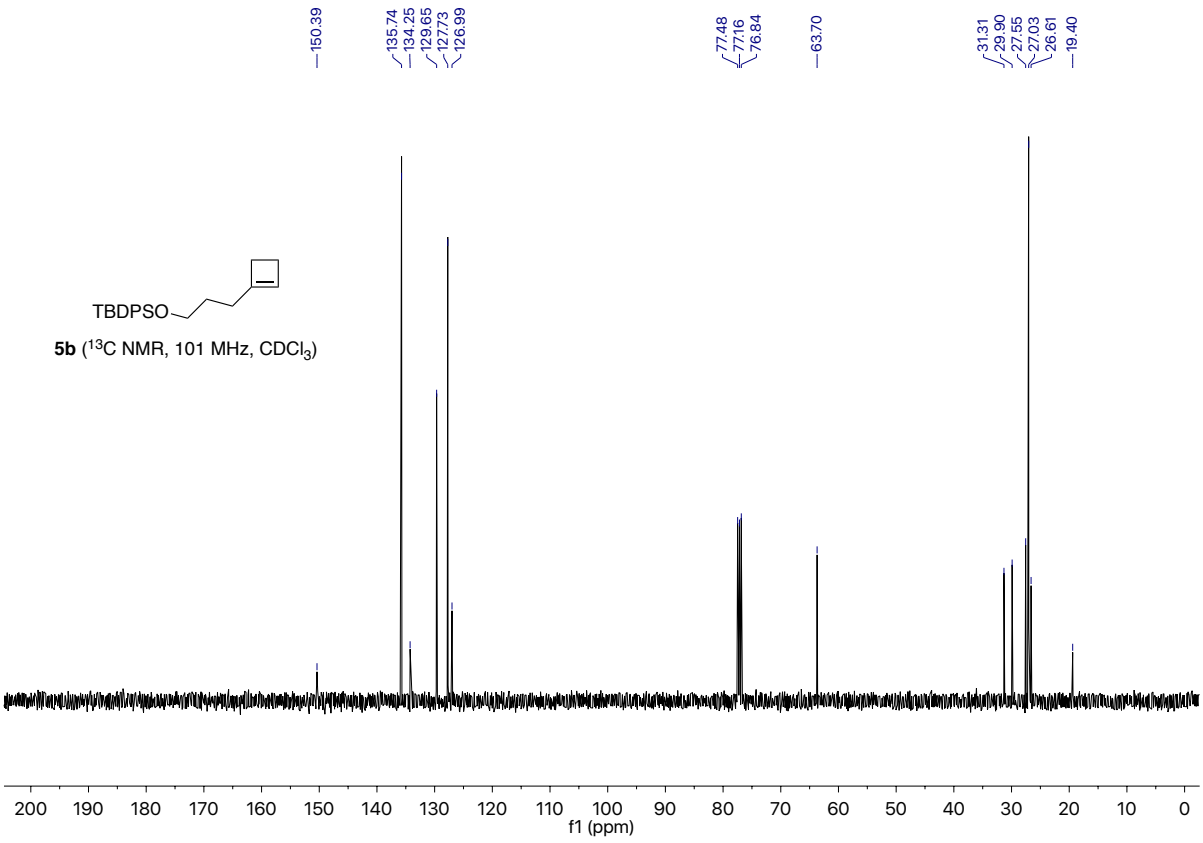
8 (^{13}C NMR, 101 MHz, $CDCl_3$)


7.32
7.31
7.31
7.31
7.30
7.29
7.29
7.28
7.26
7.21
7.20
7.19
7.19
7.18
7.18
5.71
5.71
2.67
2.65
2.63
2.44
2.44
2.43
2.43
2.42
2.37
2.36
2.36
2.35
2.06
2.05
2.05
2.03
2.03
1.81
1.80
1.79
1.78
1.78
1.76
1.74
Ph
5a (1H NMR, 400 MHz, CDCl3)
1.93
2.81
0.76
2.09
2.00
2.00
2.10
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

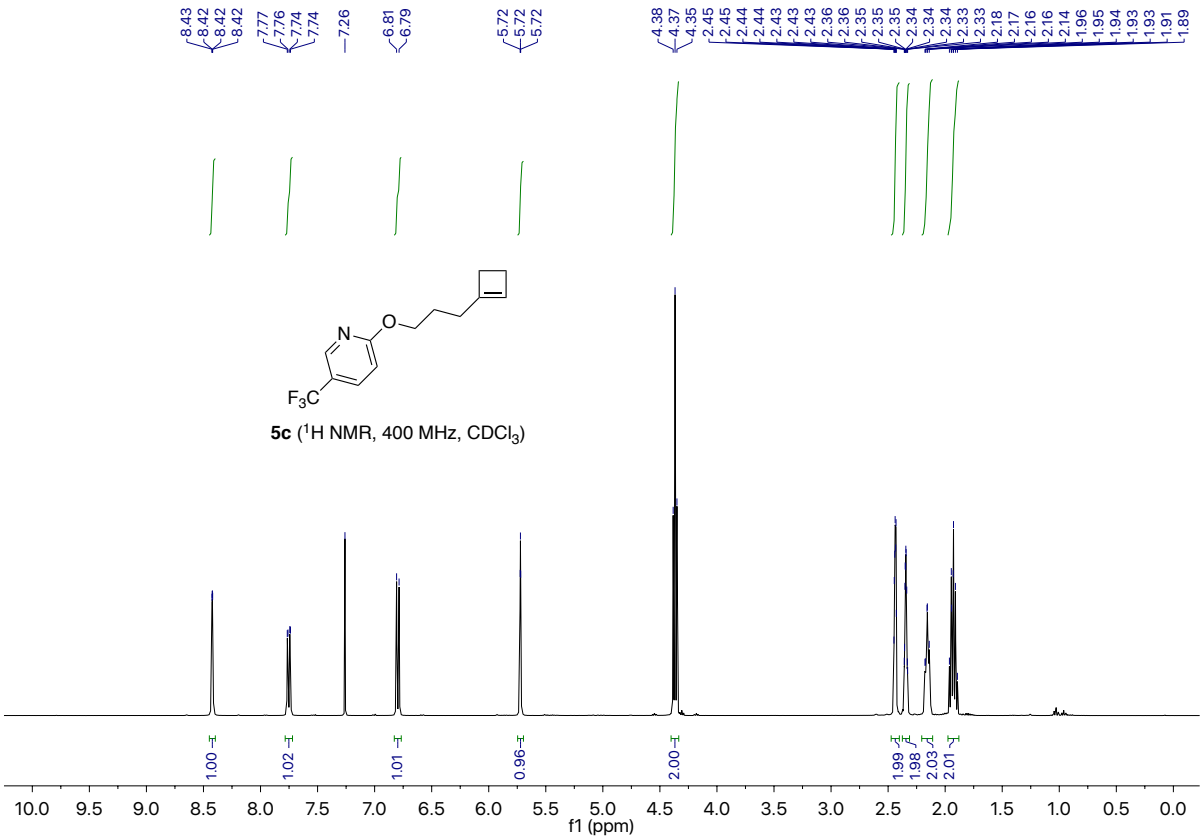

150.47
142.65
128.61
128.41
127.15
125.82
77.48
77.16
76.84
35.76
31.31
30.80
28.72
26.71
Ph
5a (13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



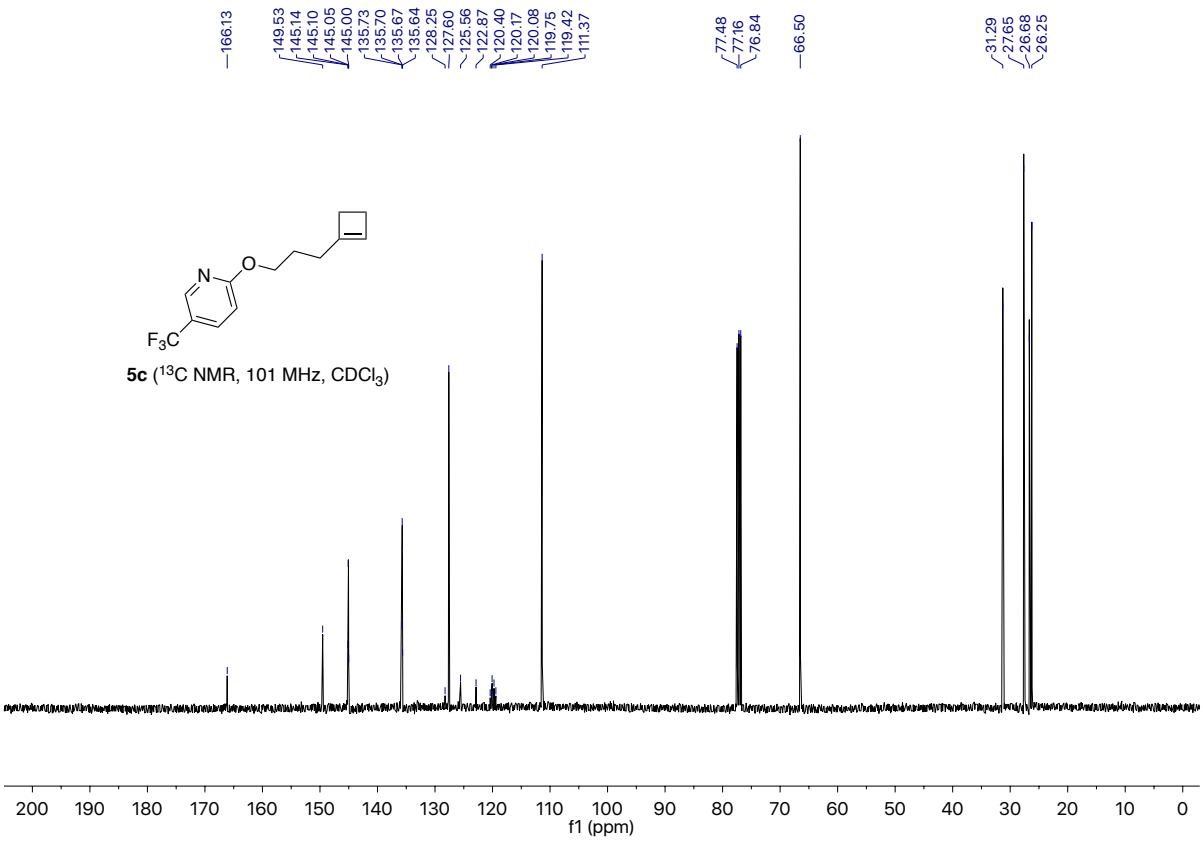
5b (^{1}H NMR, 400 MHz, $CDCl_3$)



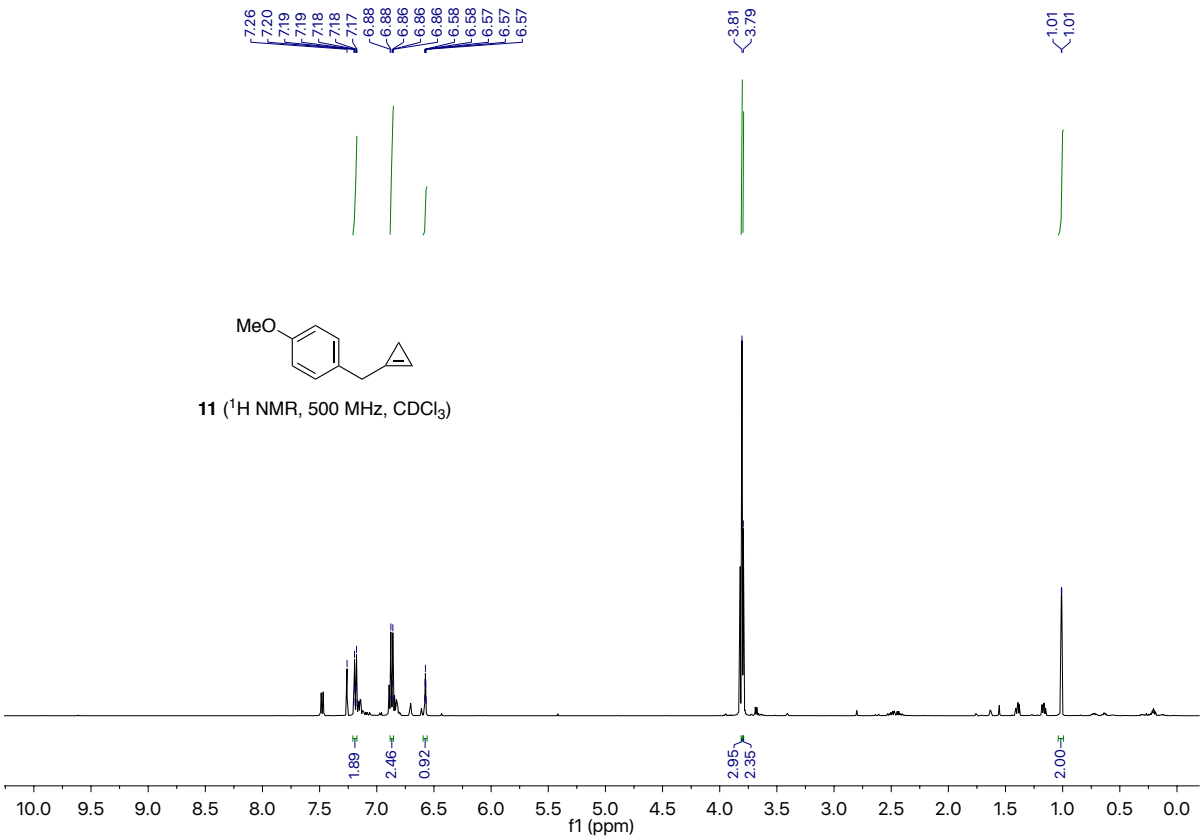
5b (^{13}C NMR, 101 MHz, $CDCl_3$)



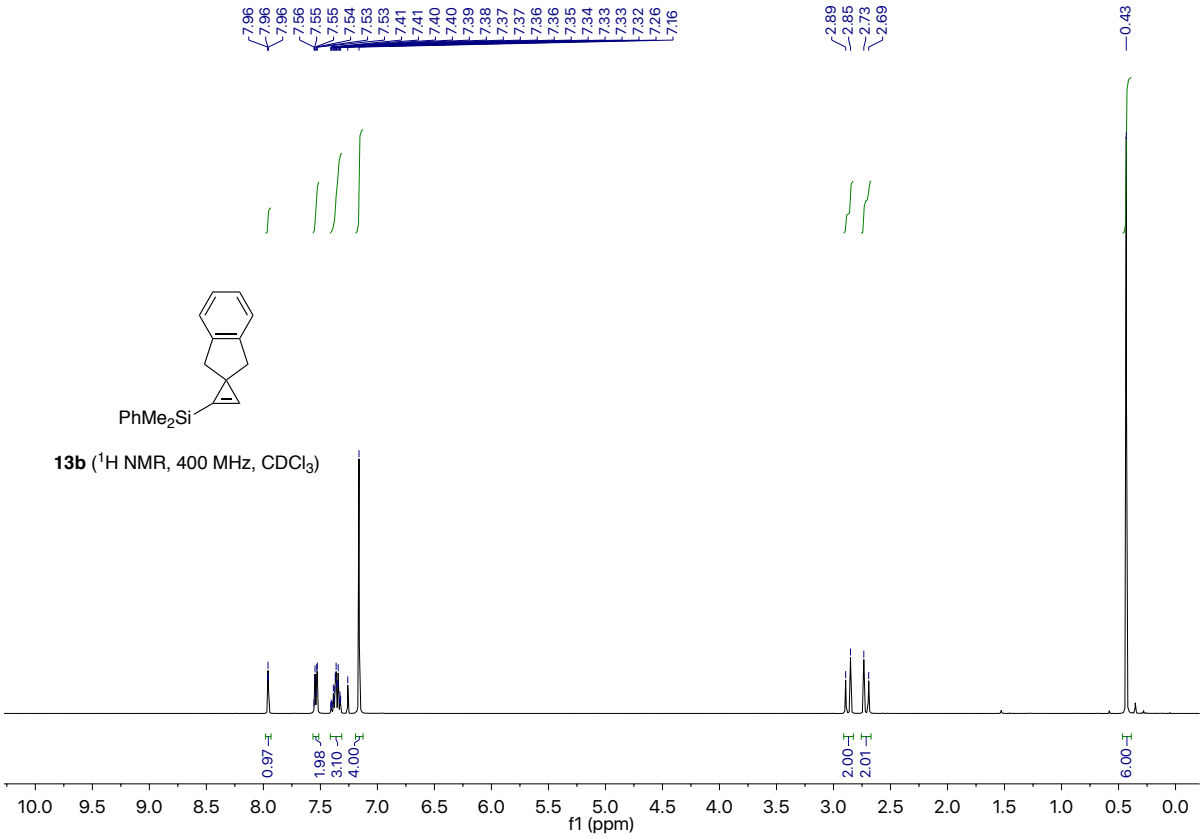
5c (^{1}H NMR, 400 MHz, $CDCl_3$)



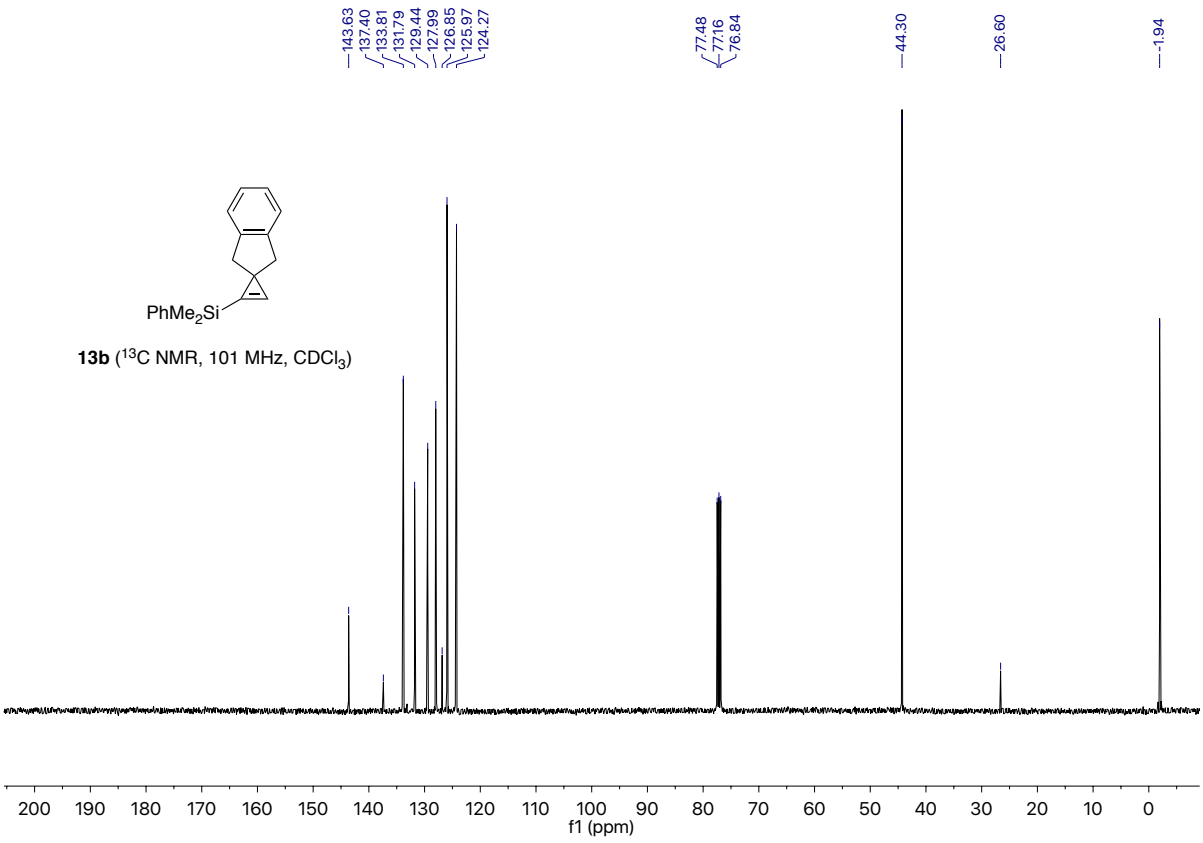
5c (^{13}C NMR, 101 MHz, $CDCl_3$)



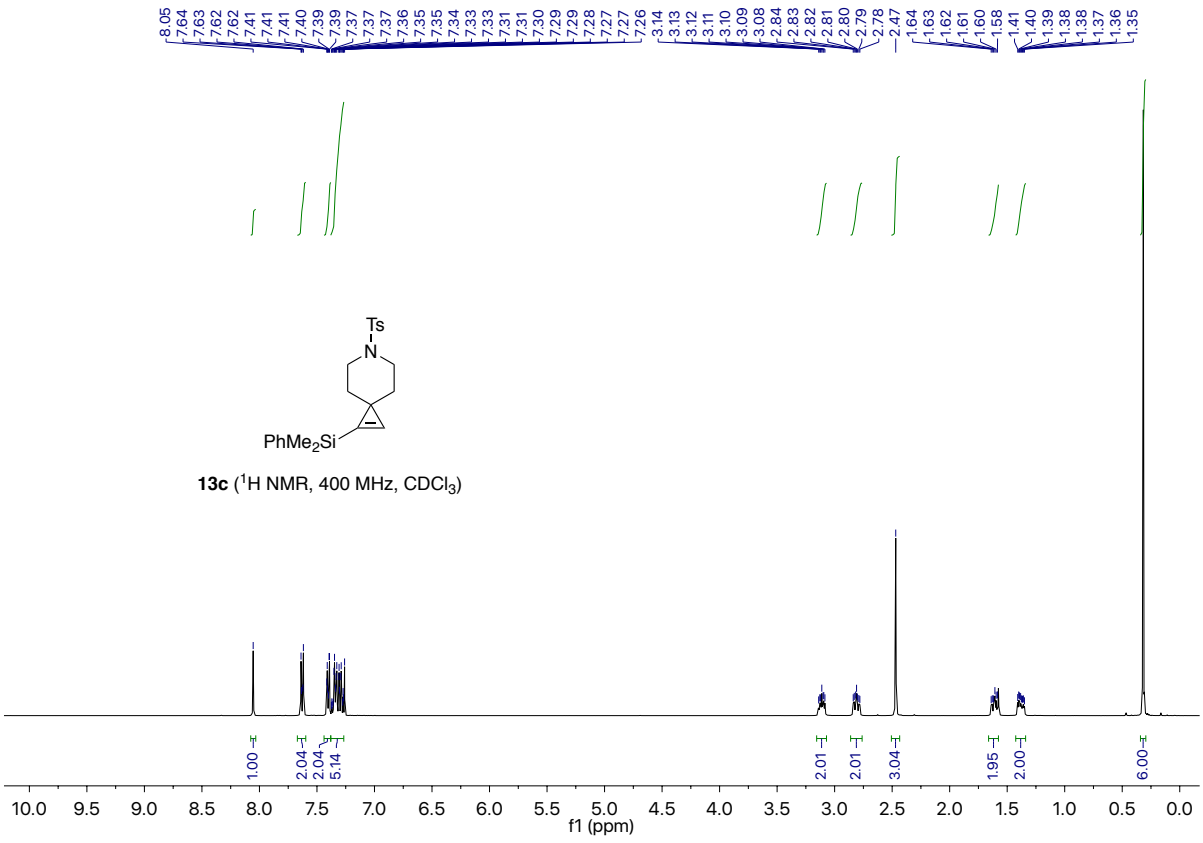
11 (^{1}H NMR, 500 MHz, $CDCl_3$)



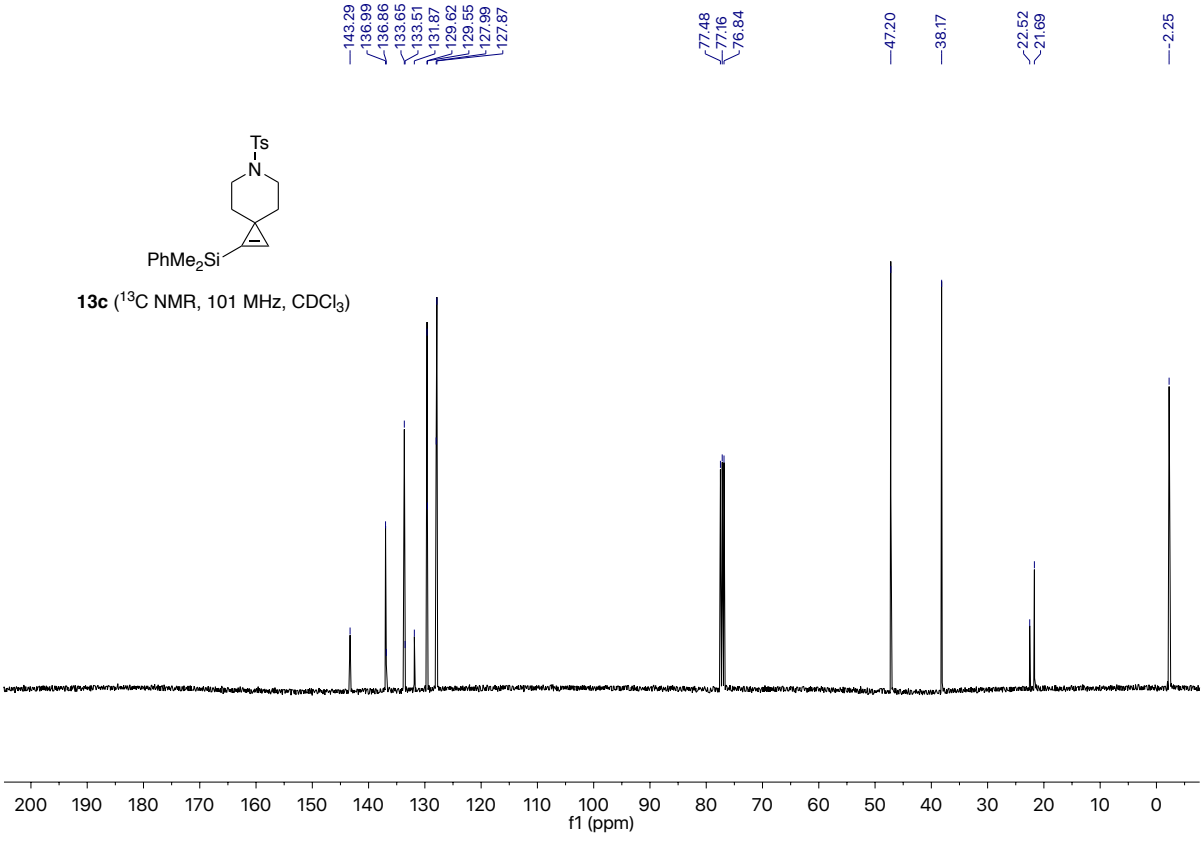
13b (^{1}H NMR, 400 MHz, $CDCl_3$)



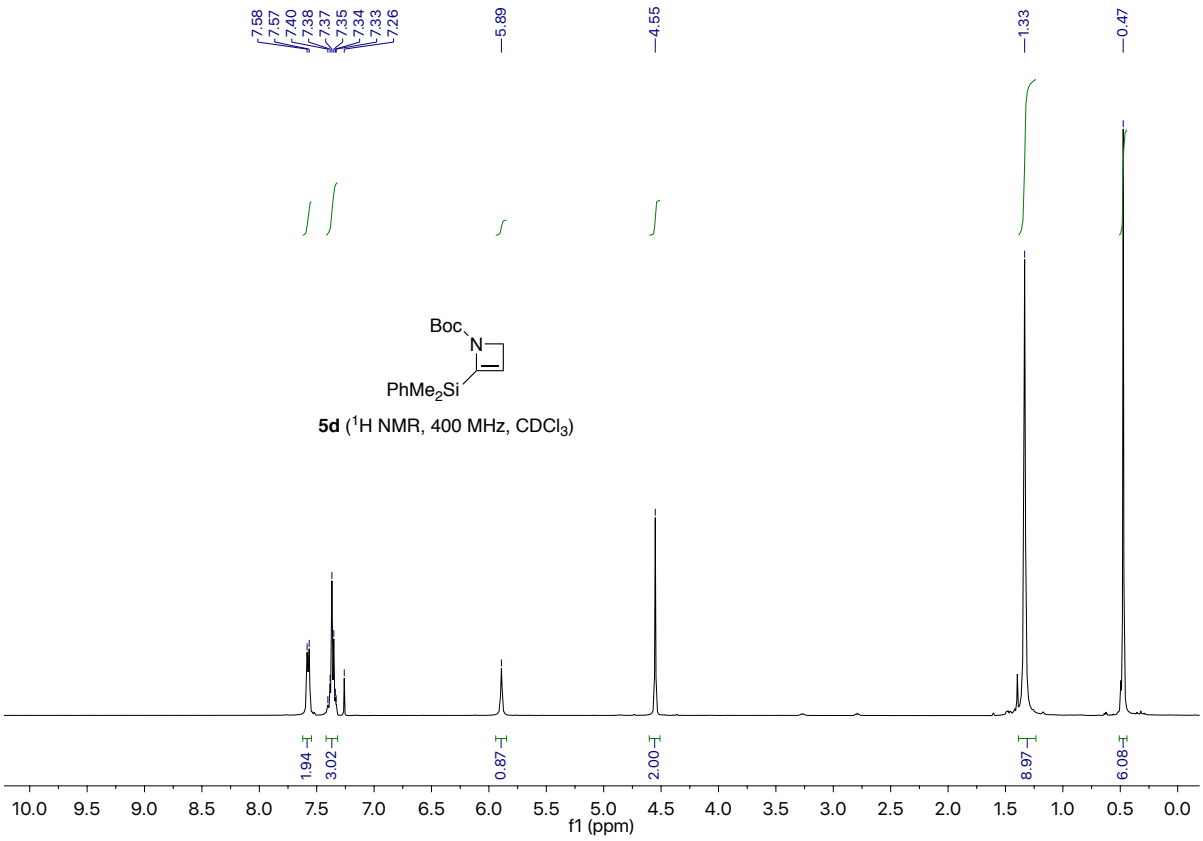
13b (^{13}C NMR, 101 MHz, $CDCl_3$)



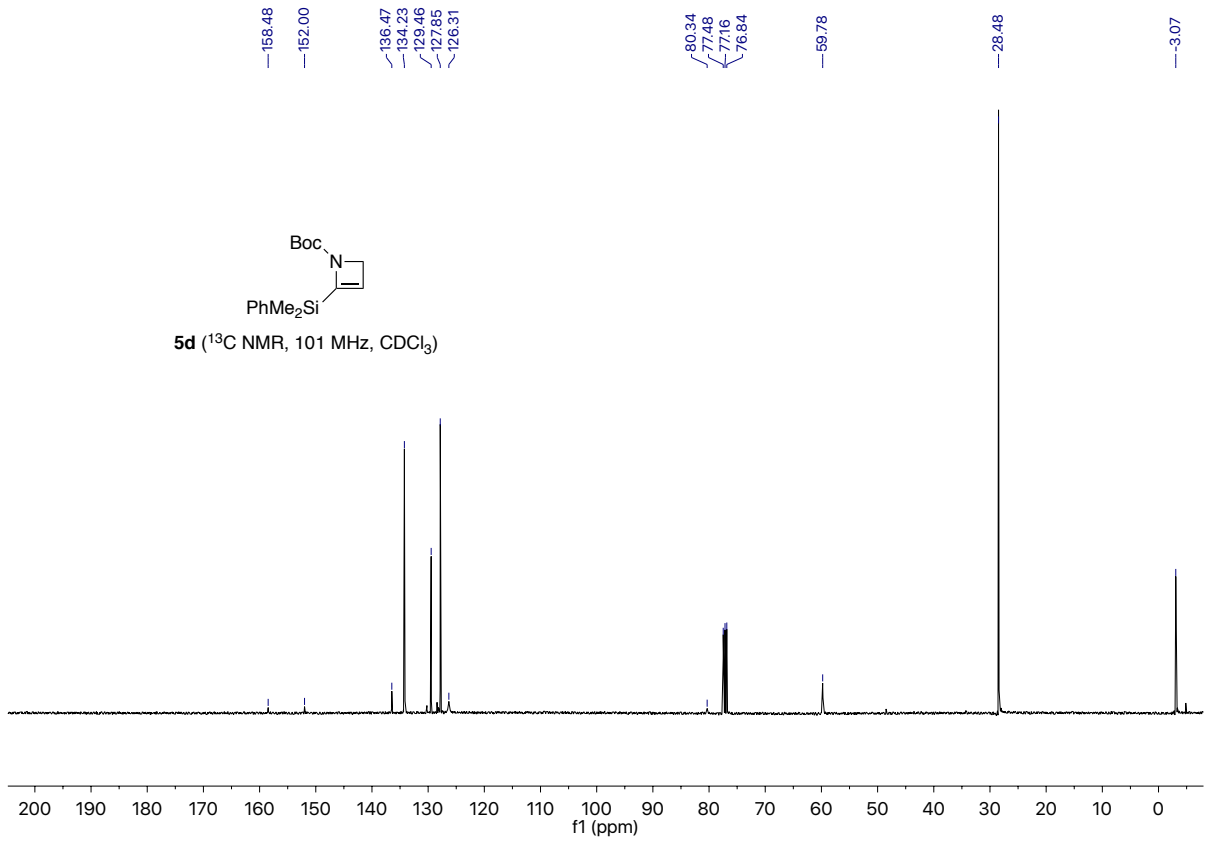
13c (^{1}H NMR, 400 MHz, $CDCl_3$)



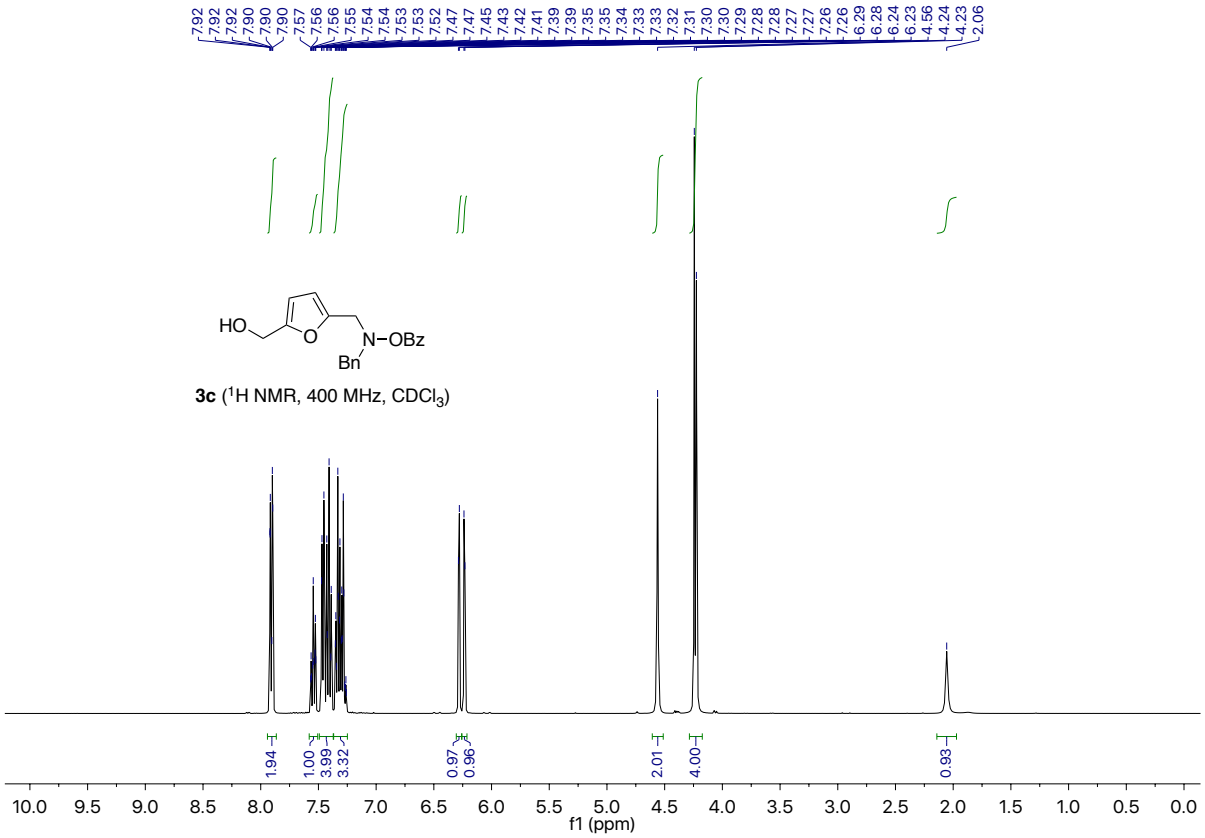
13c (^{13}C NMR, 101 MHz, $CDCl_3$)

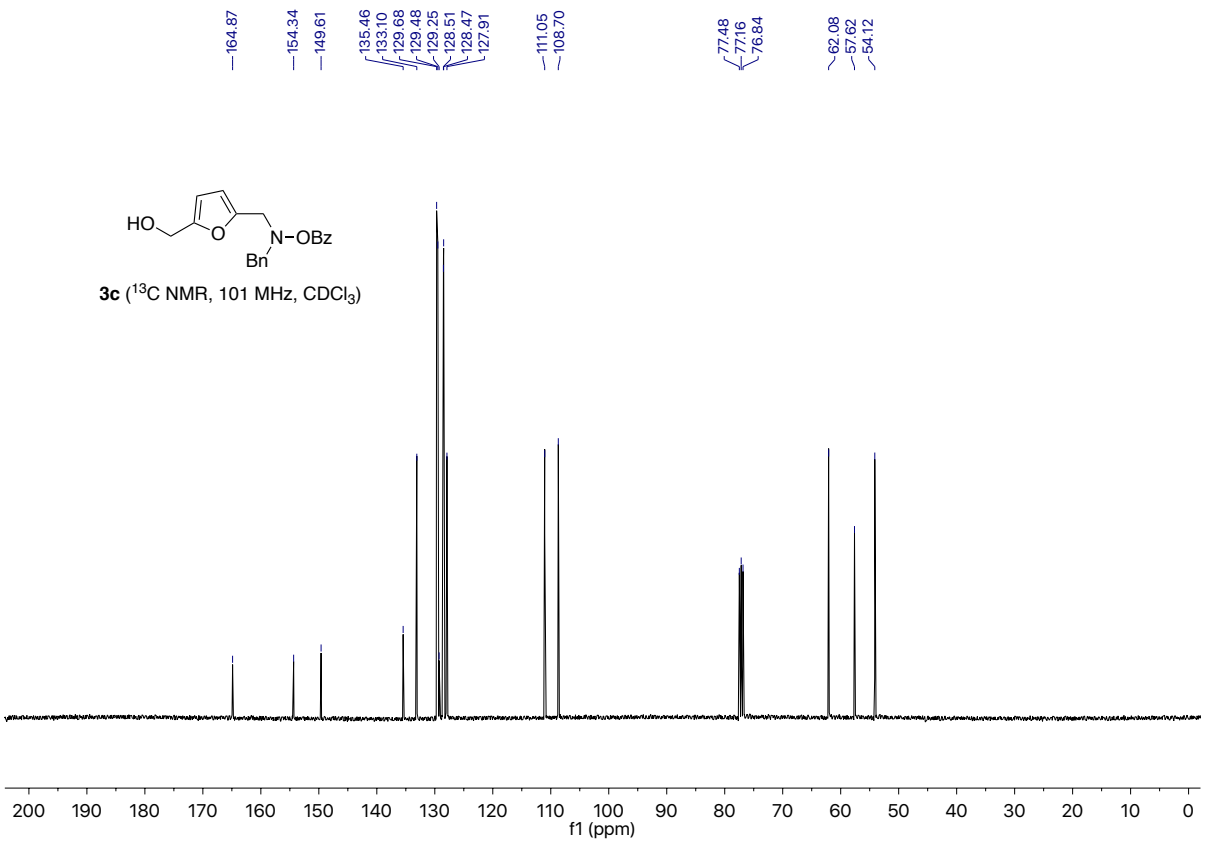


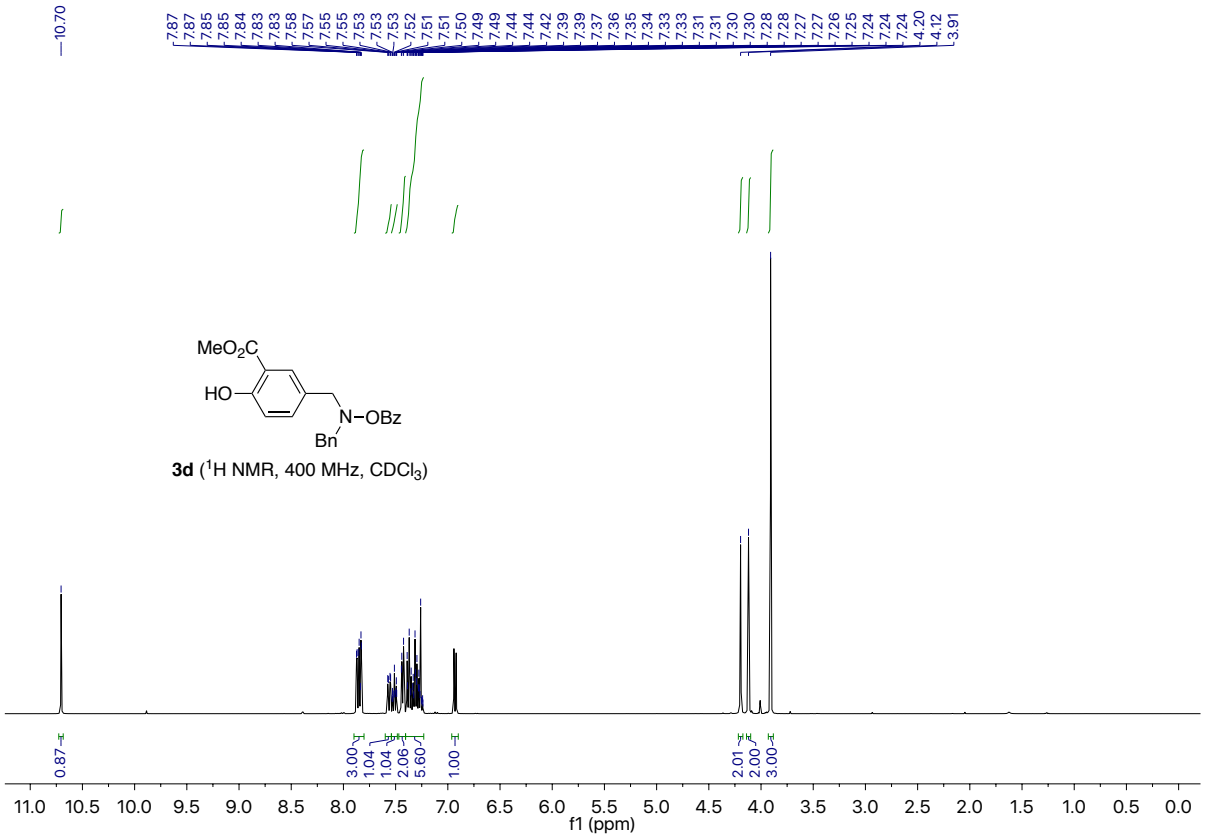
5d (^{1}H NMR, 400 MHz, $CDCl_3$)



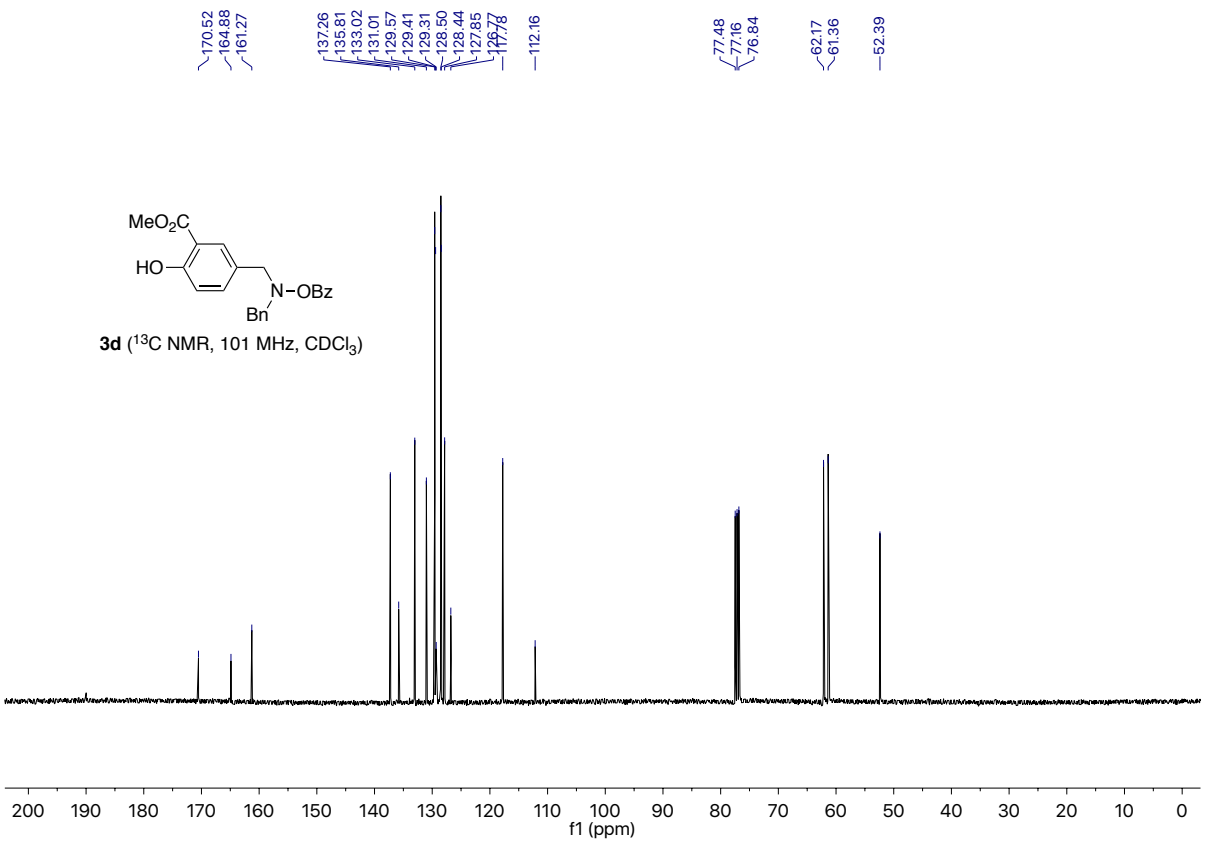
5d (^{13}C NMR, 101 MHz, $CDCl_3$)


HO
O
N–OBz
Bn
3c (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

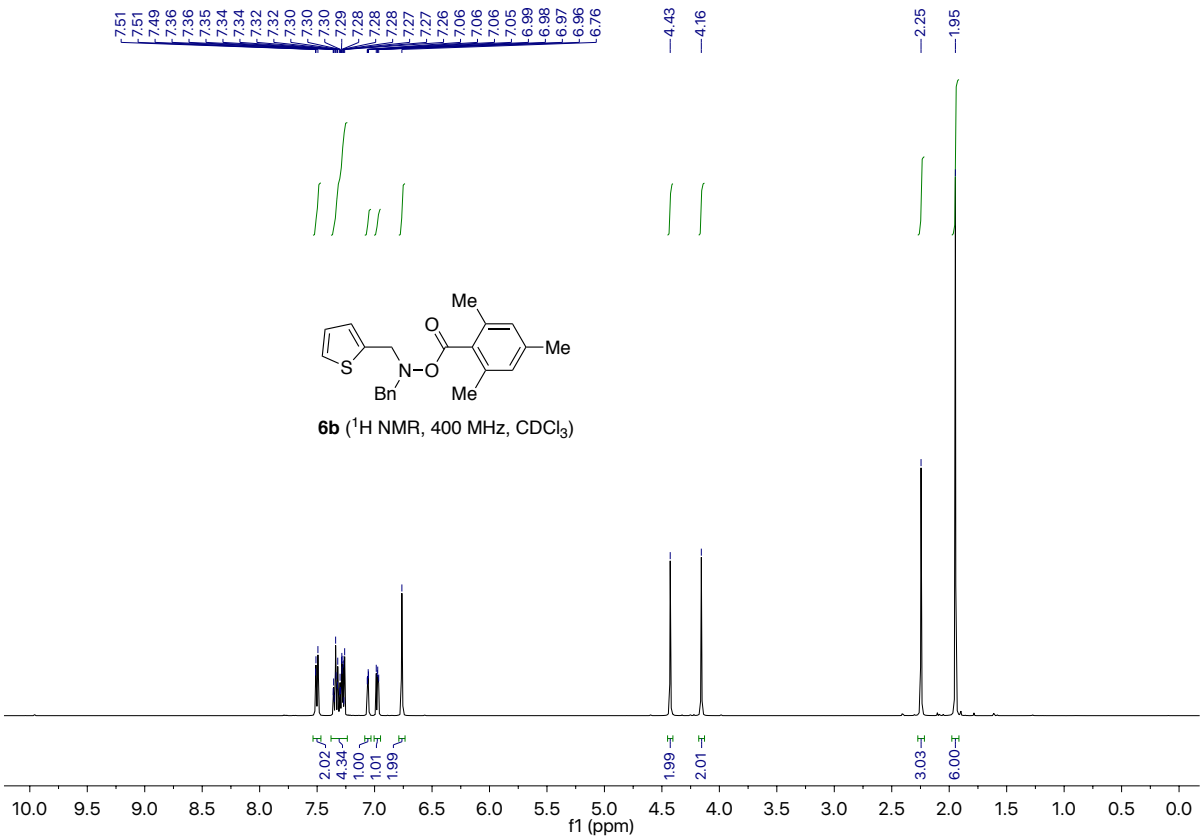

HO
O
N–OBz
Bn
3c (13C NMR, 101 MHz, CDCl3)
f1 (ppm)



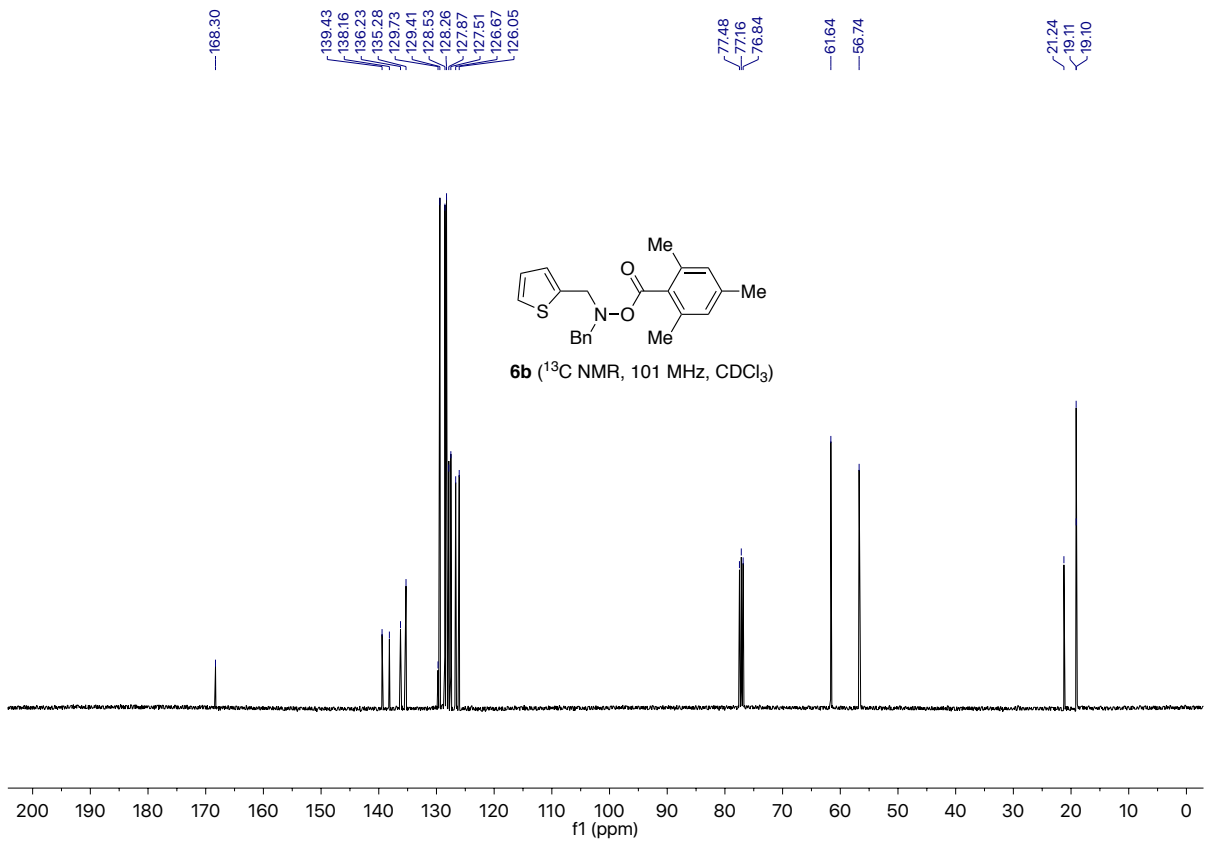
3d (^{1}H NMR, 400 MHz, $CDCl_3$)



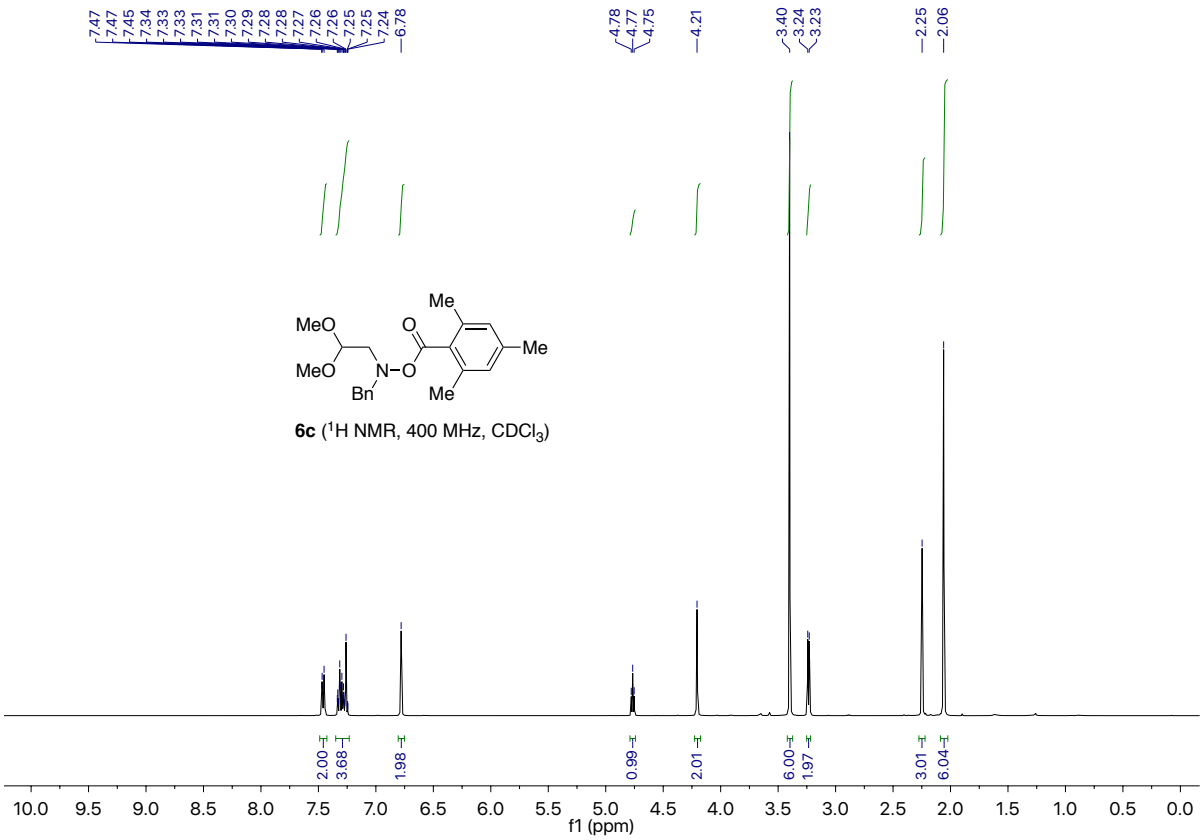
3d (^{13}C NMR, 101 MHz, $CDCl_3$)



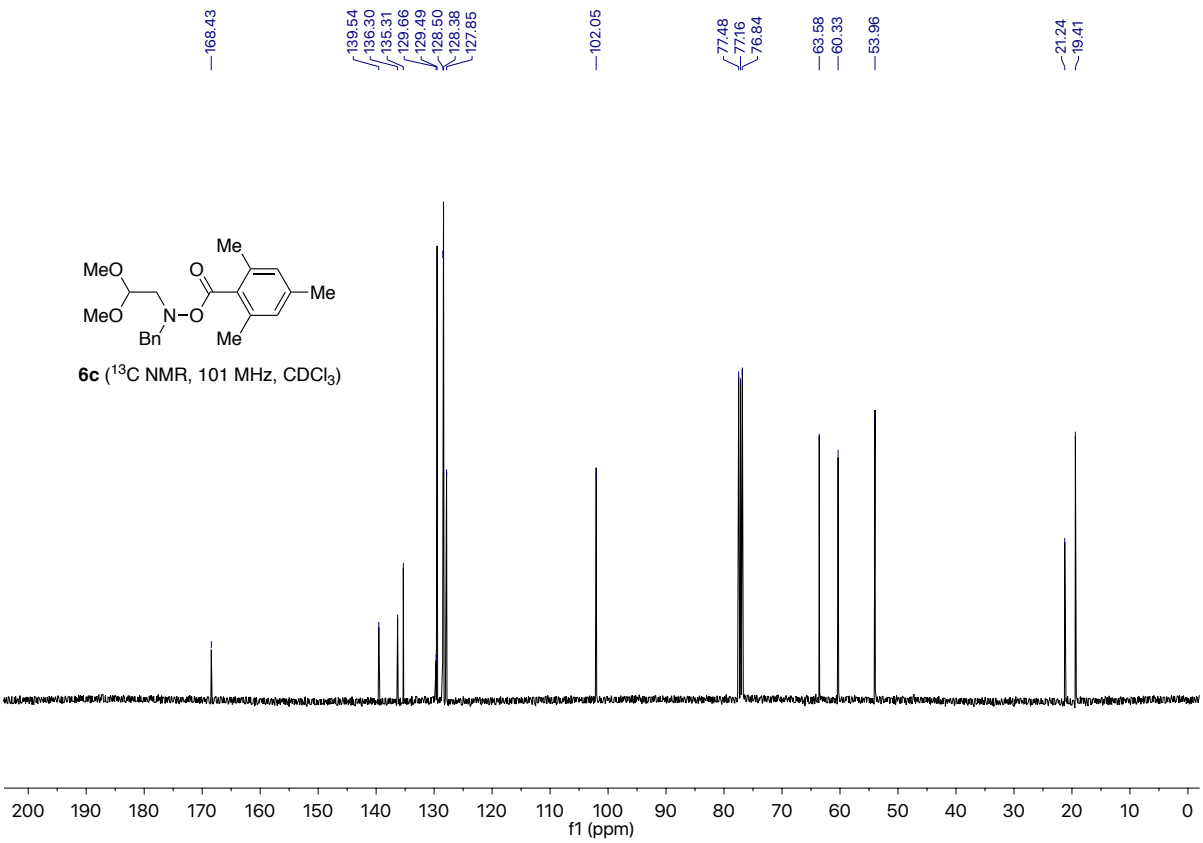
6b (^{1}H NMR, 400 MHz, $CDCl_3$)



6b (^{13}C NMR, 101 MHz, $CDCl_3$)

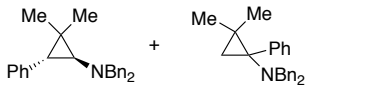


6c (^{1}H NMR, 400 MHz, $CDCl_3$)



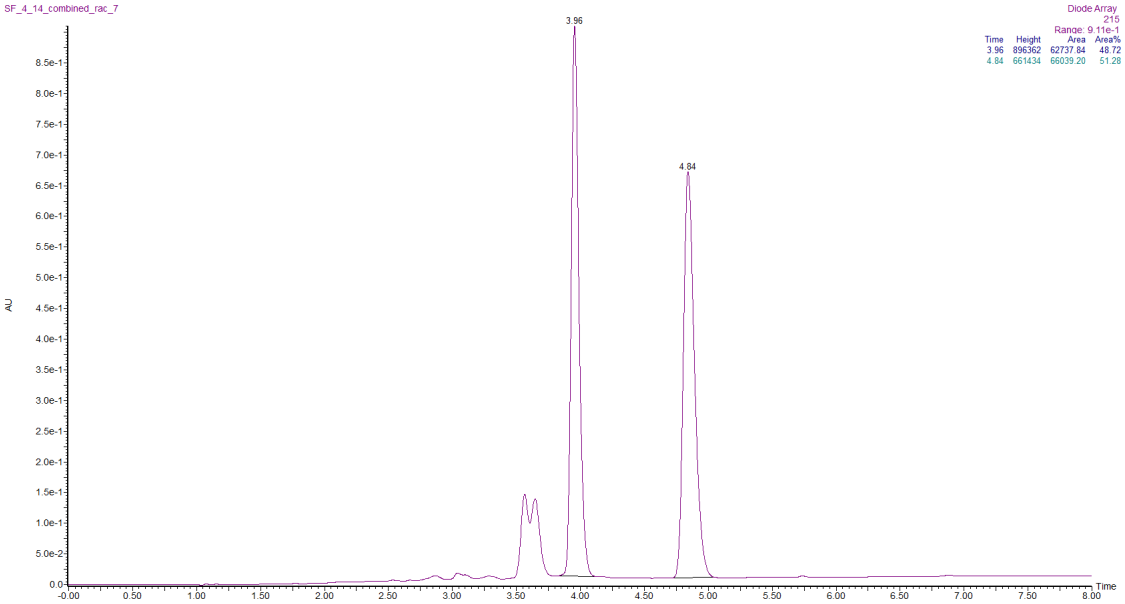
6c (^{13}C NMR, 101 MHz, $CDCl_3$)

(1*S*,3*R*)-*N*,*N*-dibenzyl-2,2-dimethyl-3-phenylcyclopropan-1-amine (10a) + *N*,*N*-dibenzyl-2,2-dimethyl-1-phenylcyclopropan-1-amine (10b)

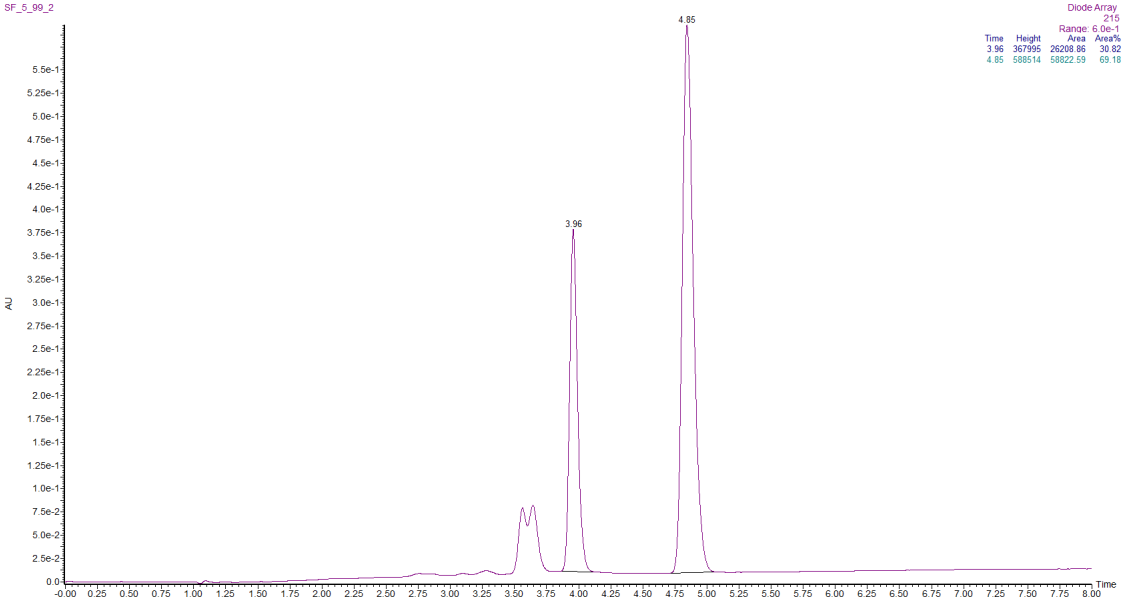


10a **10b** (8:1 ratio)

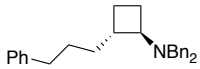
Racemic:



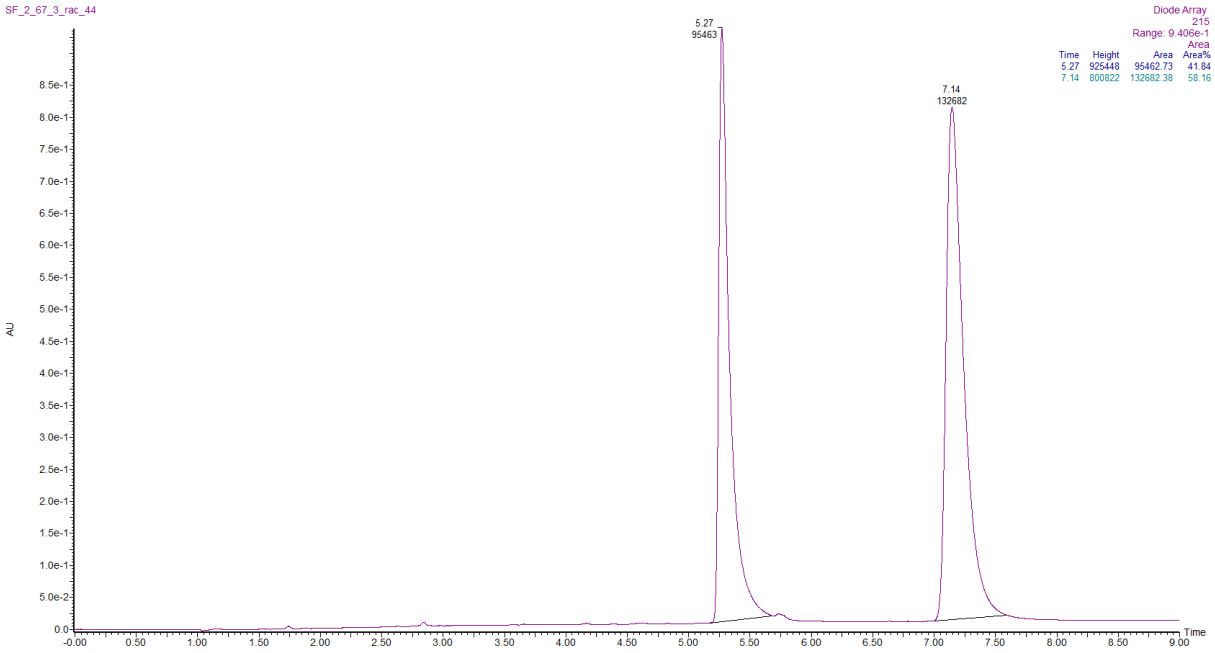
Enantioenriched:



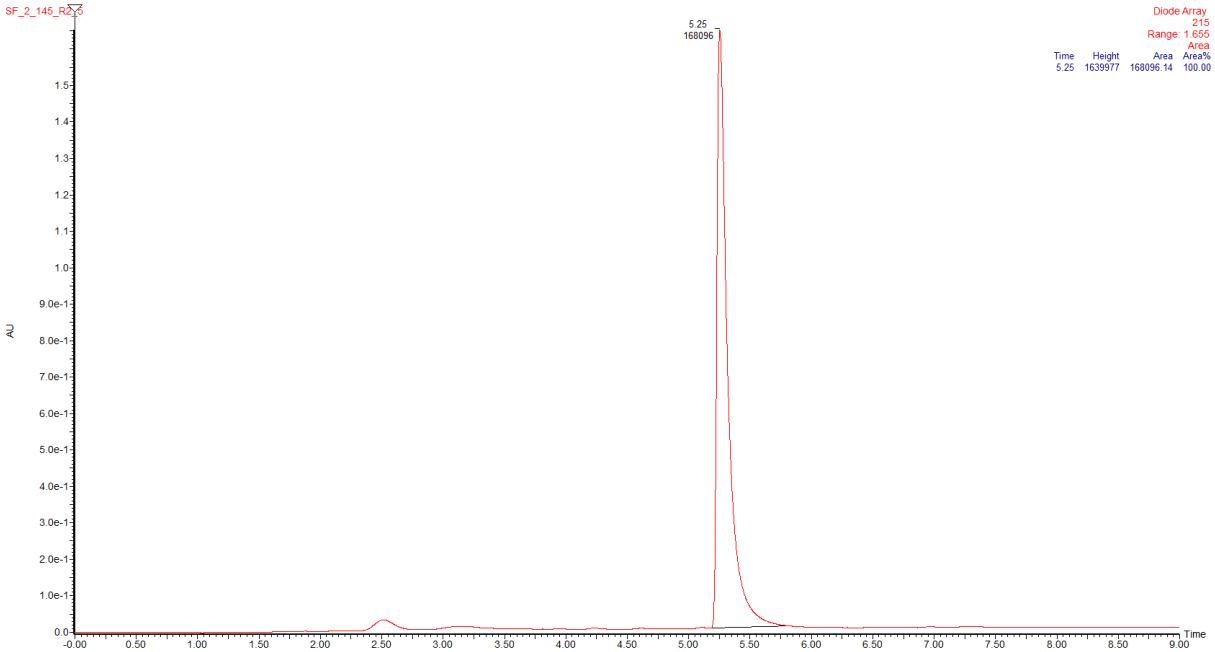
(1*R*,2*R*)-*N*,*N*-dibenzyl-2-(3-phenylpropyl)cyclobutan-1-amine (7a)



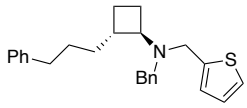
Racemic:



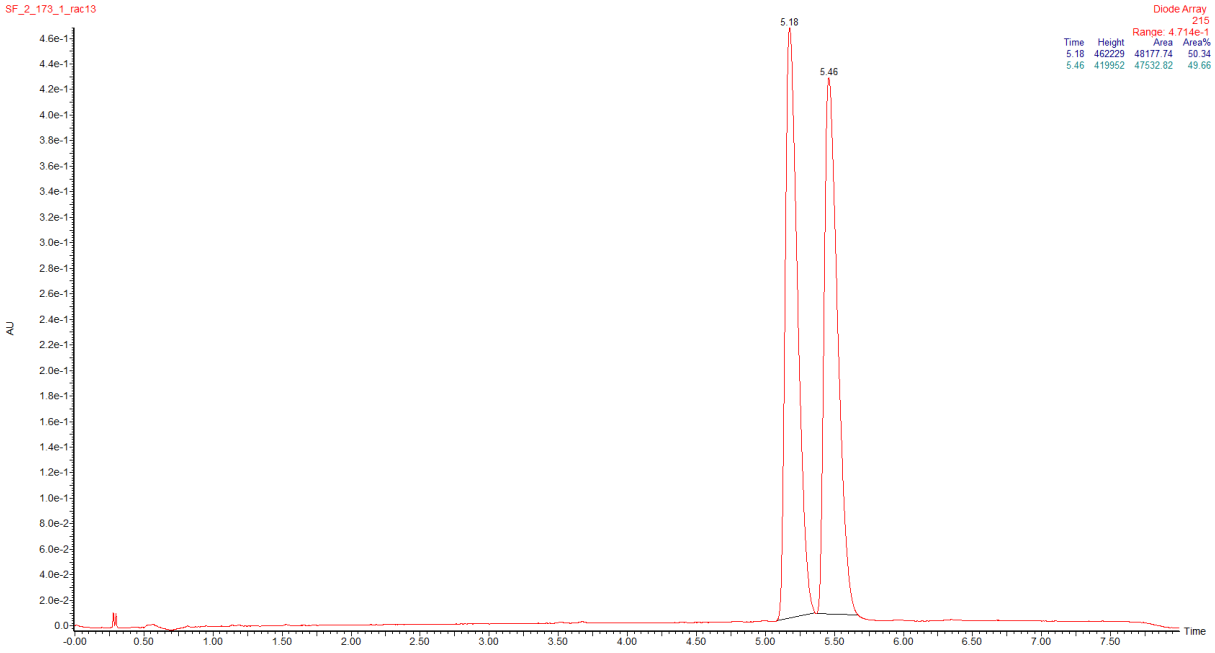
Enantioenriched:



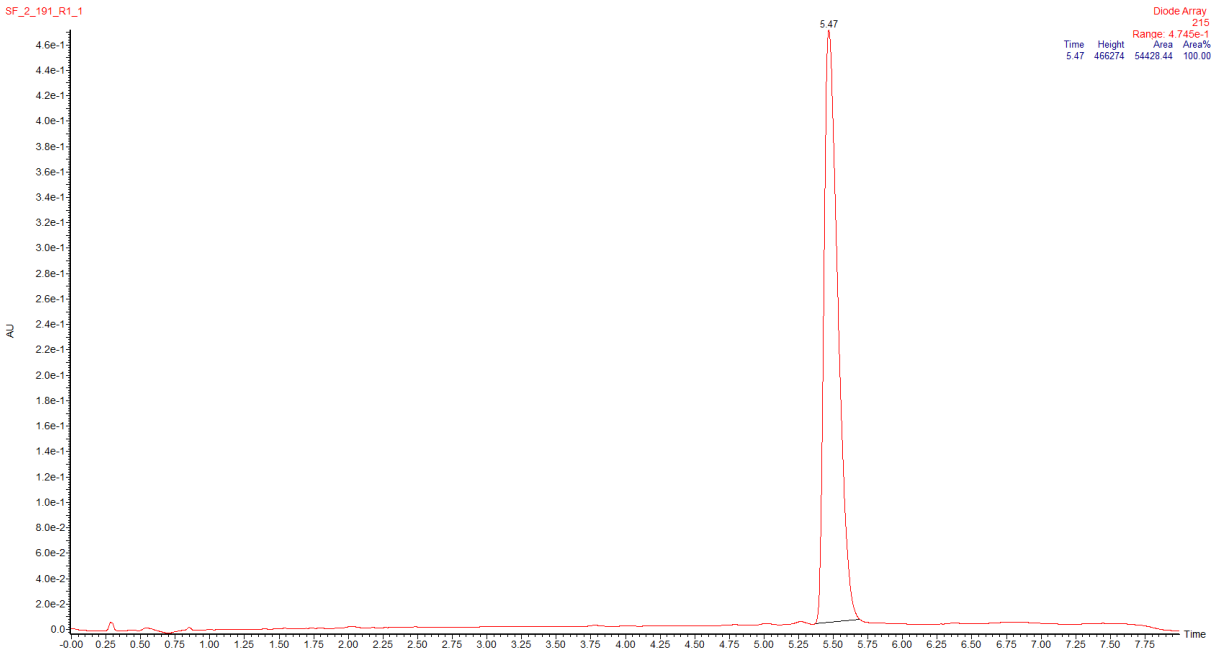
(1*R*,2*R*)-*N*-benzyl-2-(3-phenylpropyl)-*N*-(thiophen-2-ylmethyl)cyclobutan-1-amine (7b)



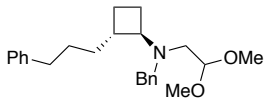
Racemic:



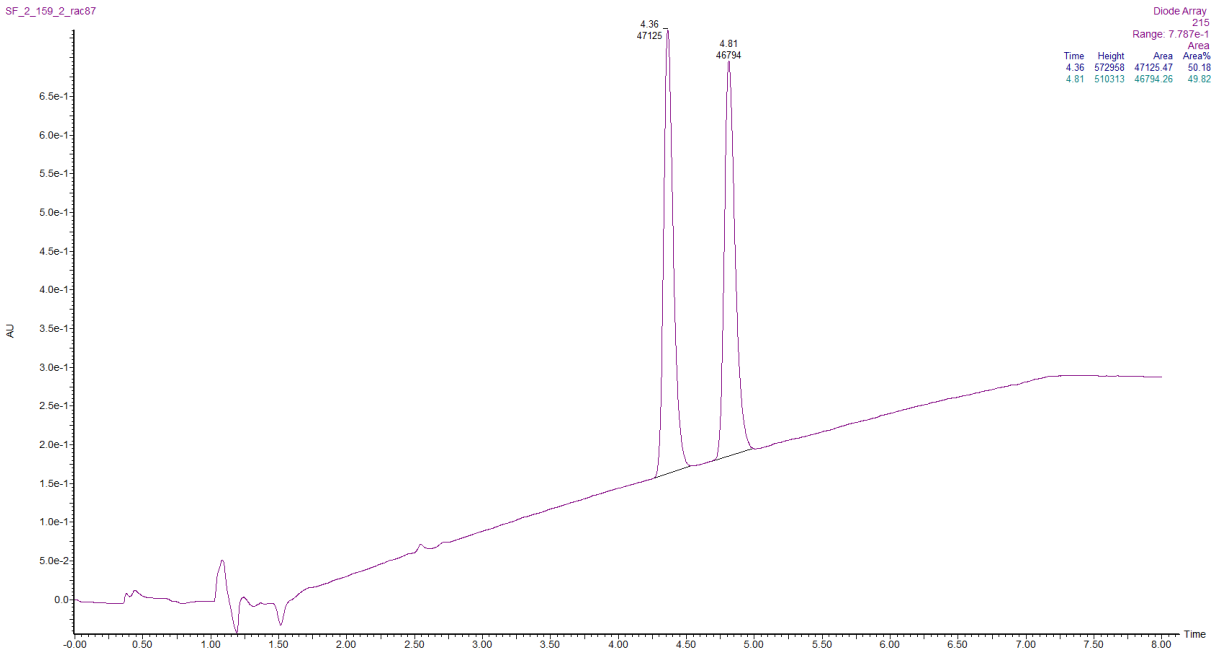
Enantioenriched:



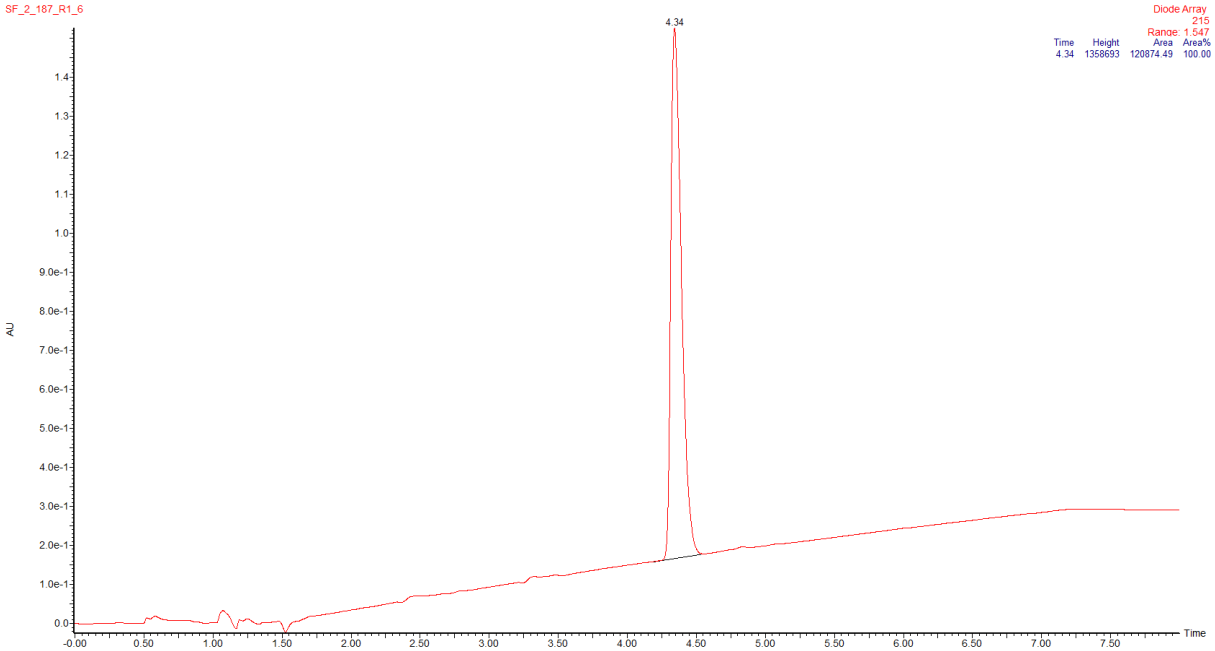
(1*R*,2*R*)-*N*-benzyl-*N*-(2,2-dimethoxyethyl)-2-(3-phenylpropyl)cyclobutan-1-amine (7c)



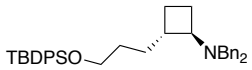
Racemic:



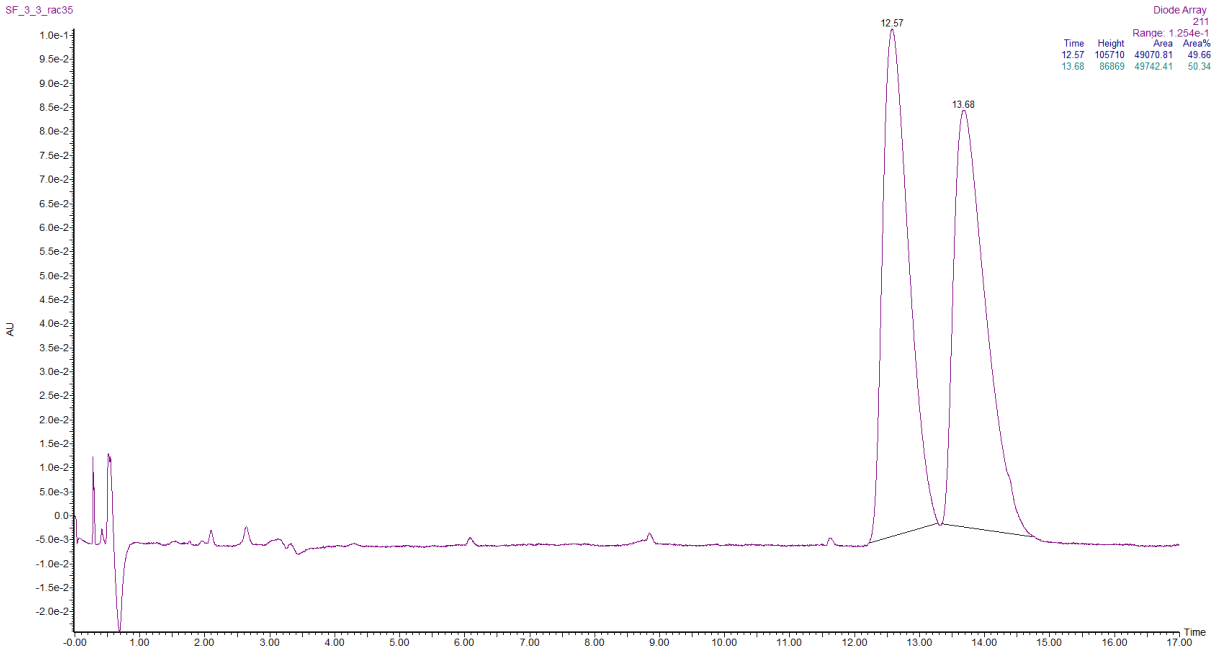
Enantioenriched:



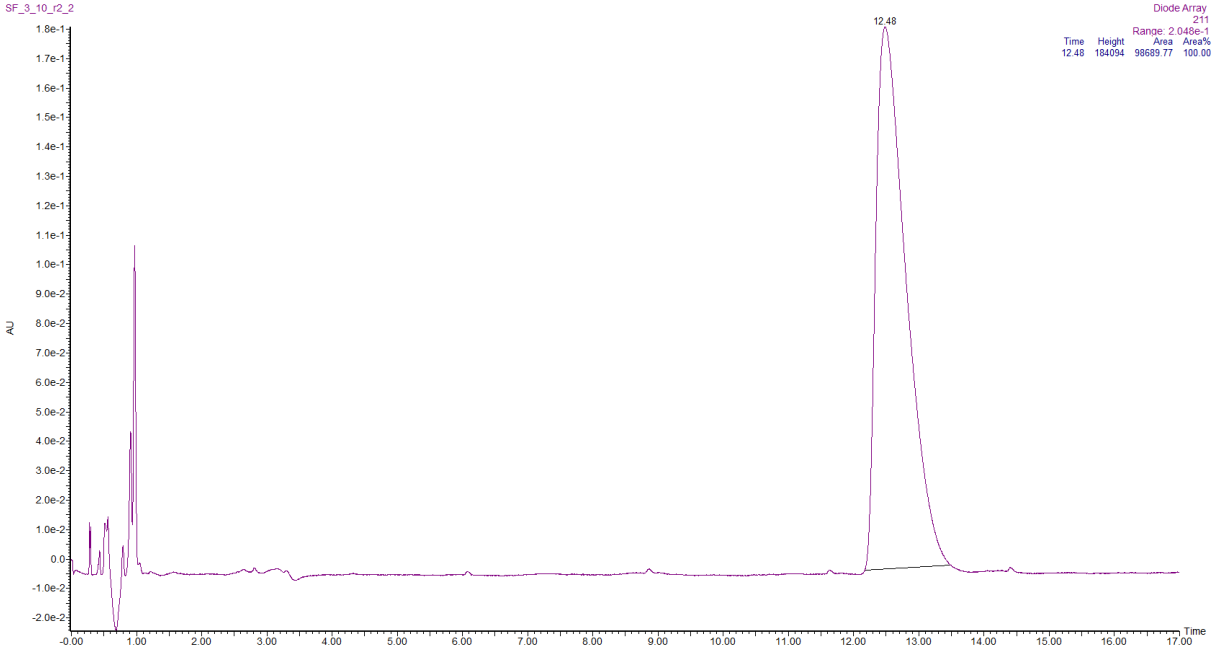
(1*R*,2*S*)-*N*,*N*-dibenzyl-2-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)cyclobutan-1-amine (7d)



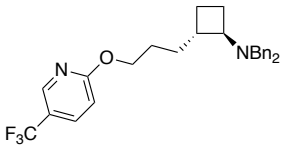
Racemic:



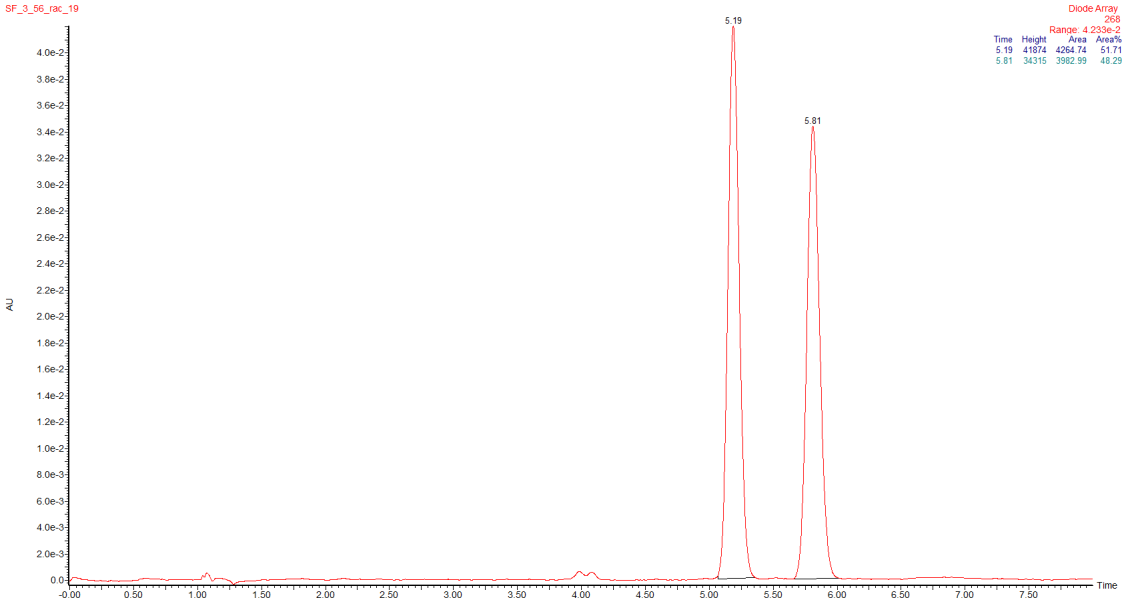
Enantioenriched:



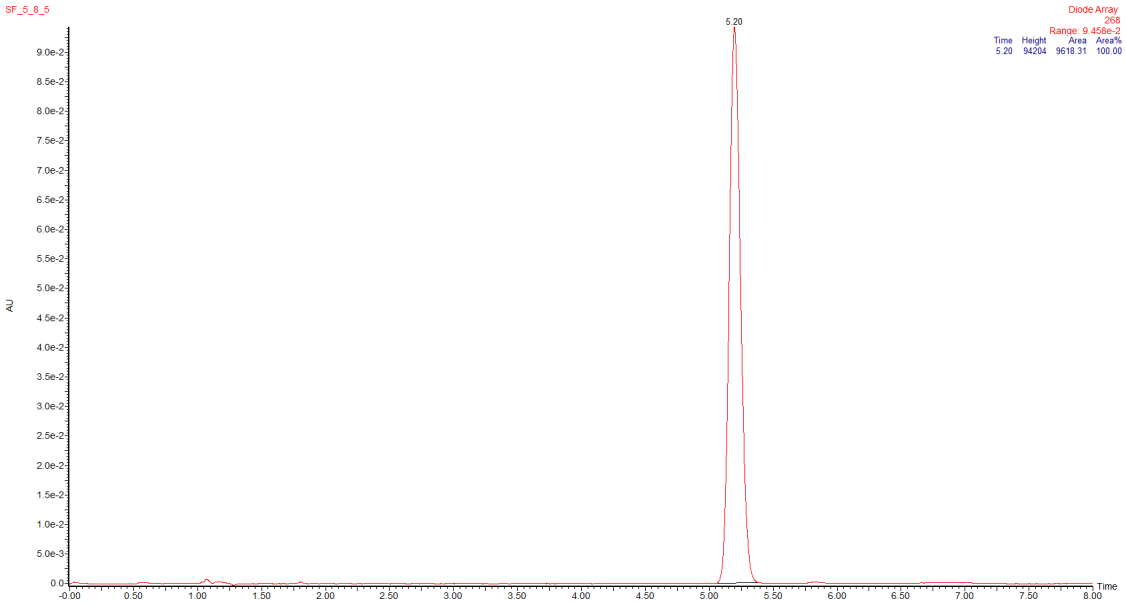
(1*R*,2*S*)-*N*,*N*-dibenzyl-2-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)propyl)cyclobutan-1-amine (7e)



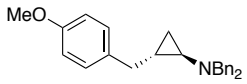
Racemic:



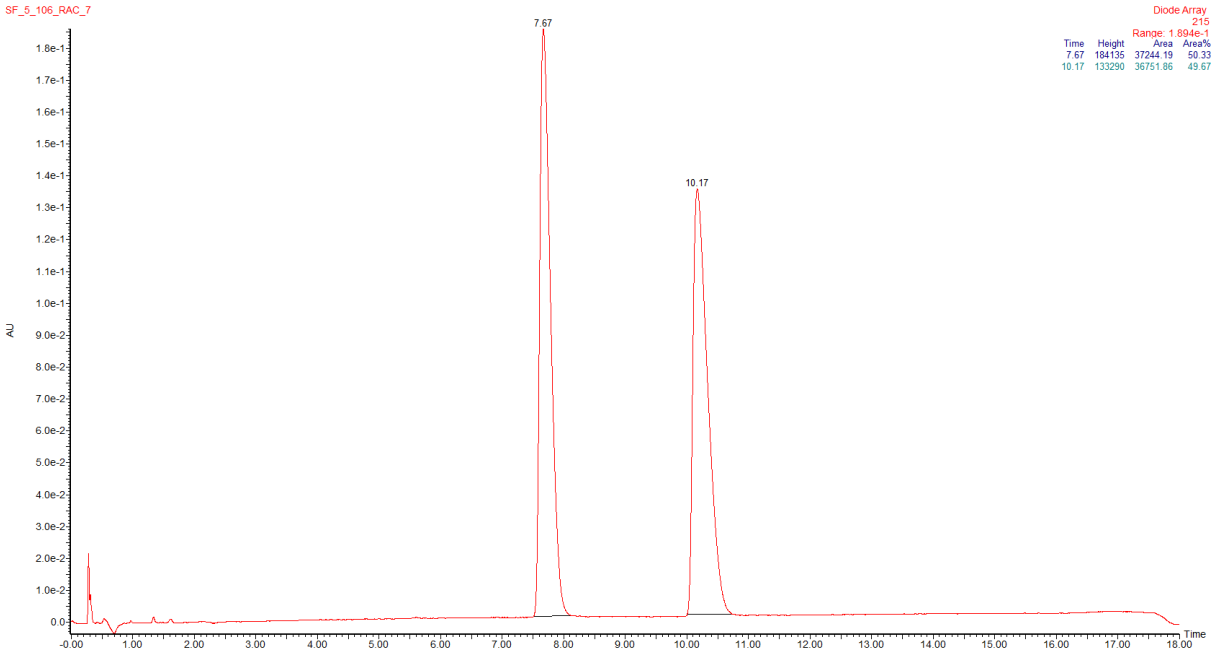
Enantioenriched:



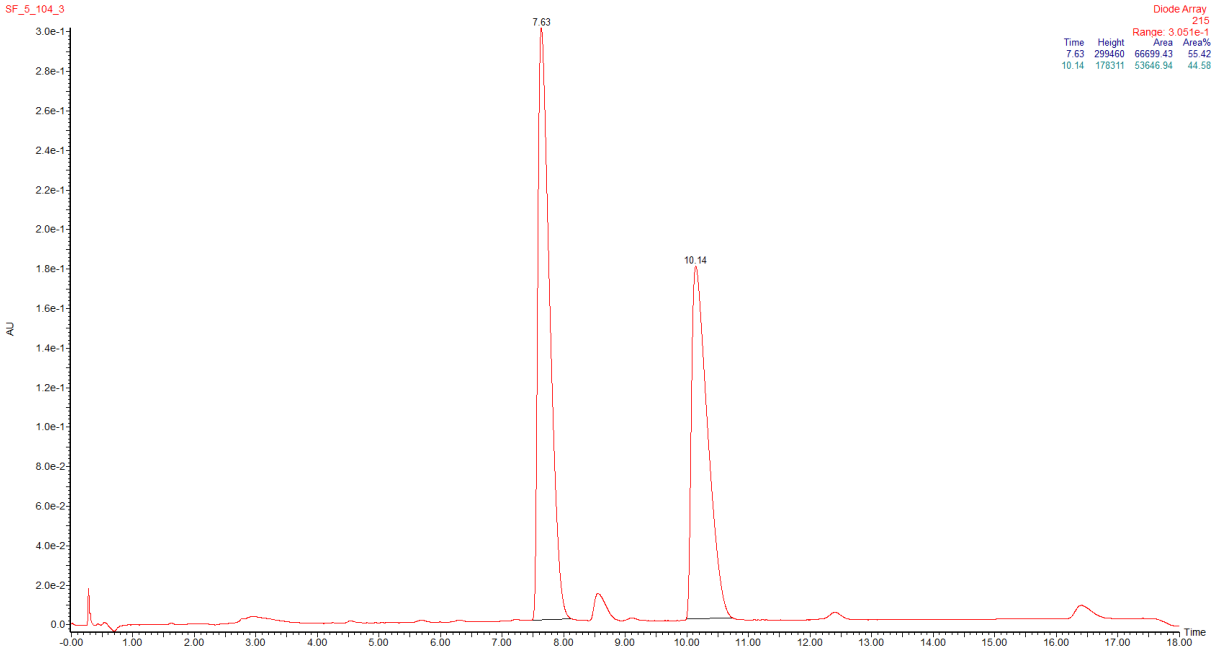
(1*R*,2*R*)-*N*,*N*-dibenzyl-2-(4-methoxybenzyl)cyclopropan-1-amine (12)



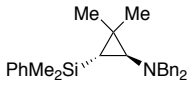
Racemic:



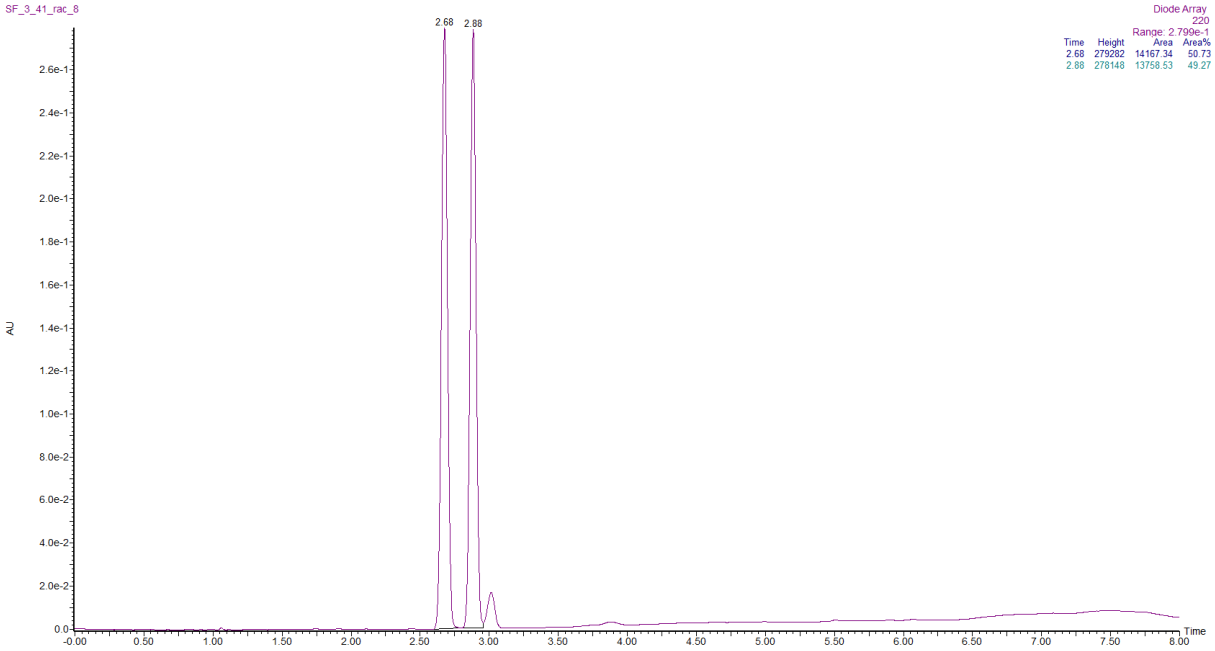
Enantioenriched:



(1*R*,3*R*)-*N*,*N*-dibenzyl-3-(dimethyl(phenyl)silyl)-2,2-dimethylcyclopropan-1-amine (15a)

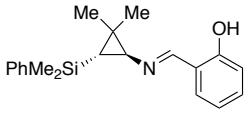


Racemic:

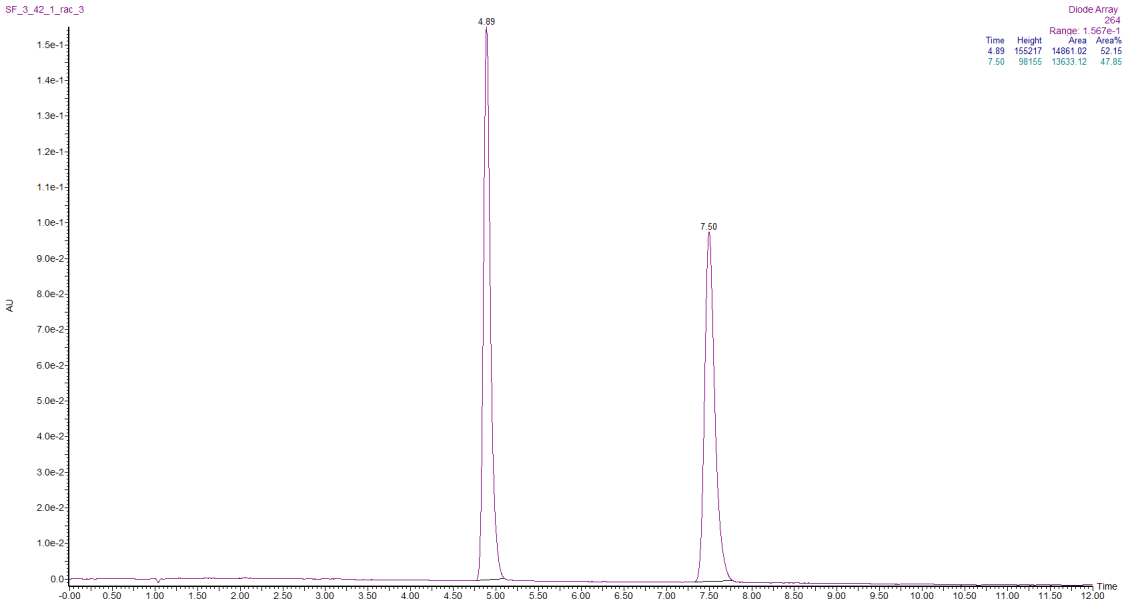


Enantioenriched:

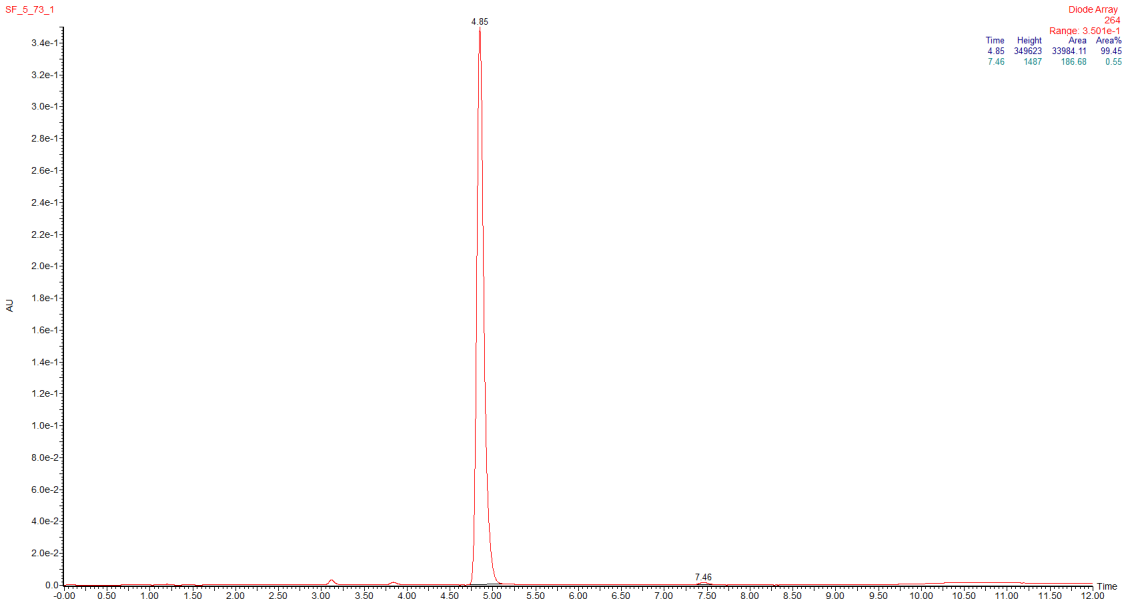
2-((*E*)-(((1*R*,3*R*)-3-(dimethyl(phenyl)silyl)-2,2-dimethylcyclopropyl)imino)methyl)phenol (15b)



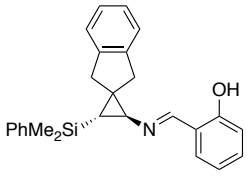
Racemic:



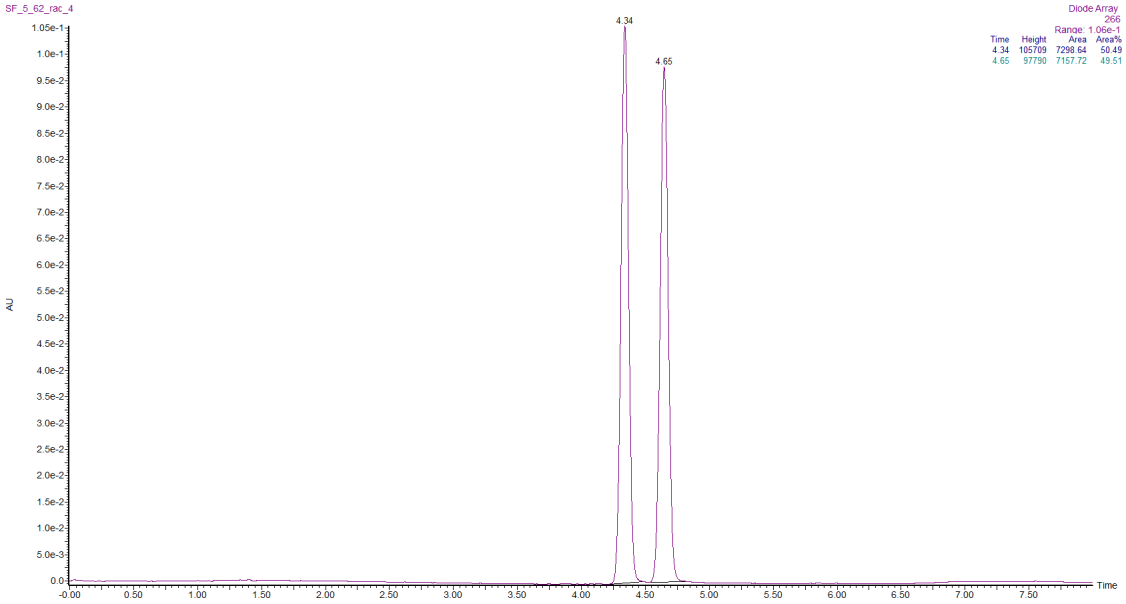
Enantioenriched:



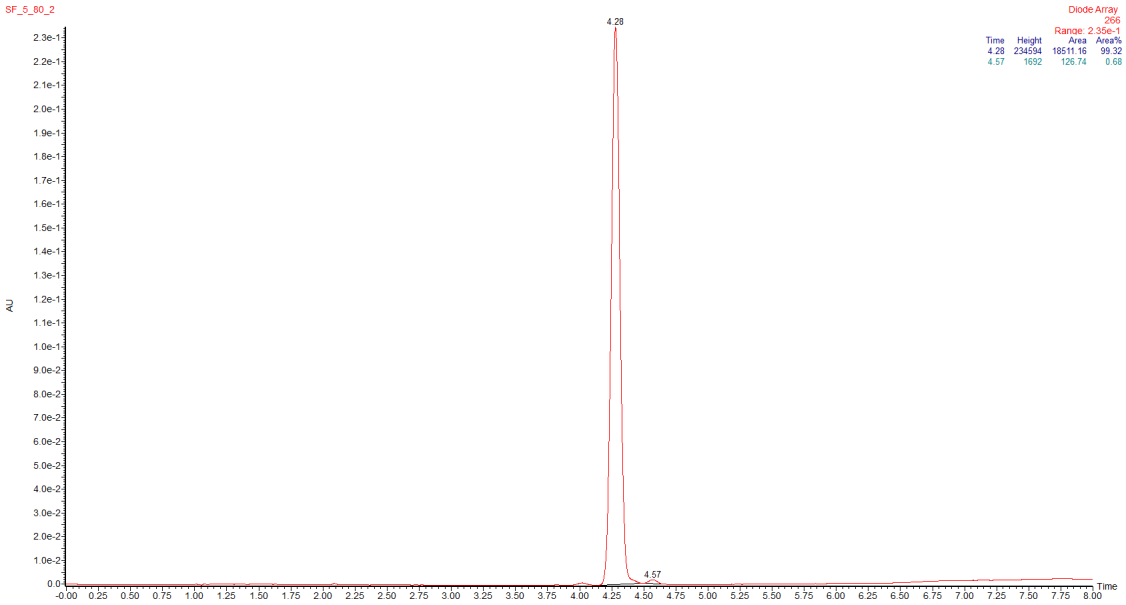
2-((*E*)-(((2*R*,3*R*)-2-(dimethyl(phenyl)silyl)-1',3'-dihydrospiro[cyclopropane-1,2'-inden]-3-yl)imino)methyl)phenol (15c)



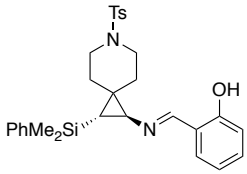
Racemic:



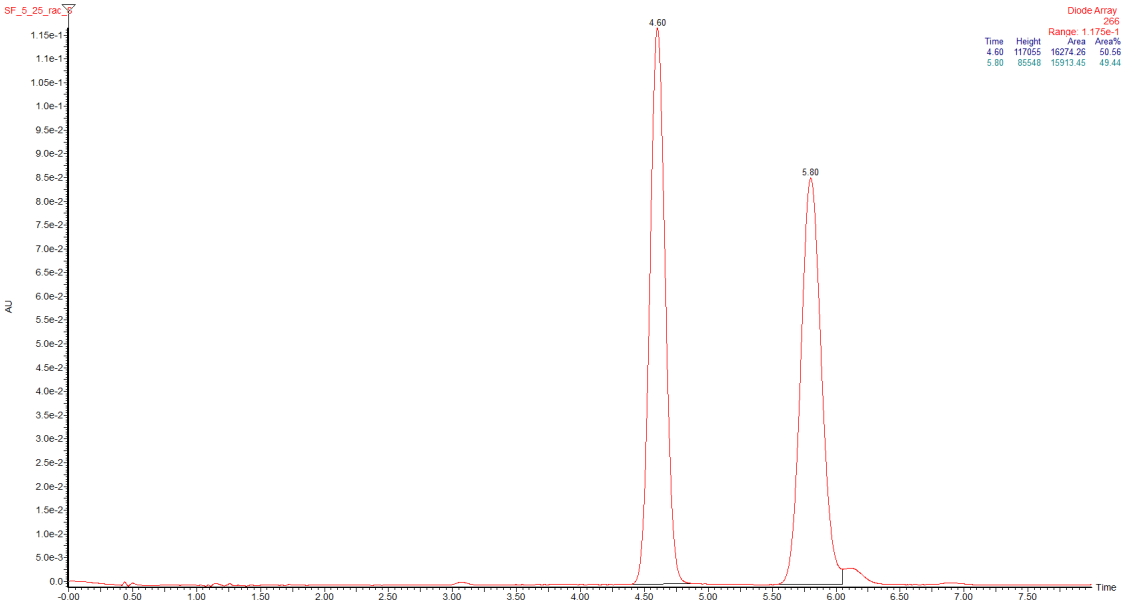
Enantioenriched:



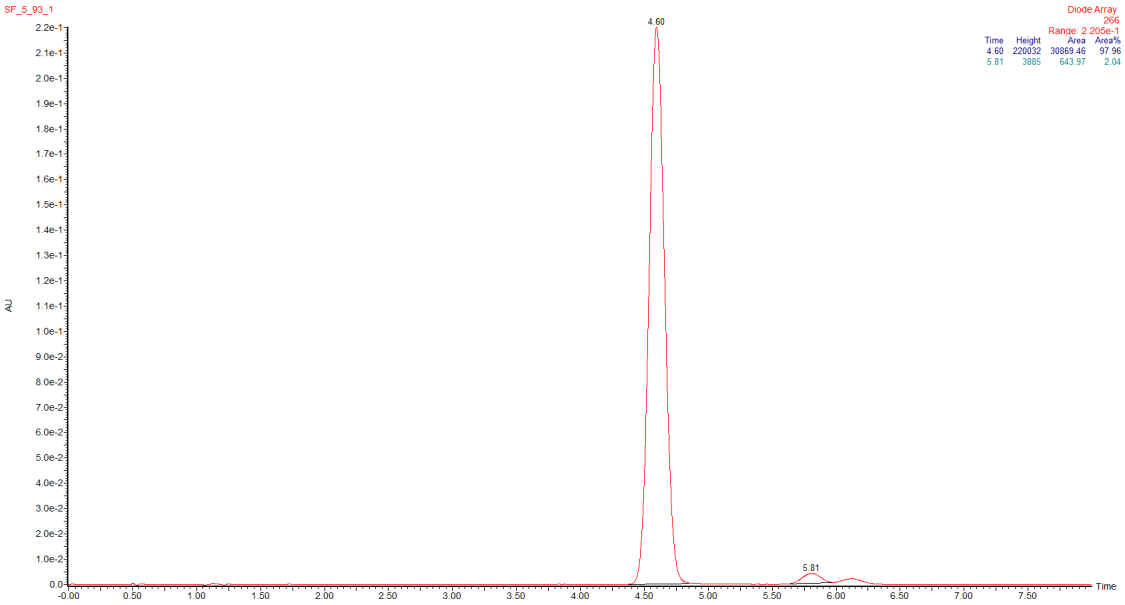
2-((*E*)-(((1*R*,2*R*)-2-(dimethyl(phenyl)silyl)-6-tosyl-6-azaspiro[2.5]octan-1-yl)imino)methyl)phenol (15d)



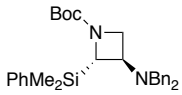
Racemic:



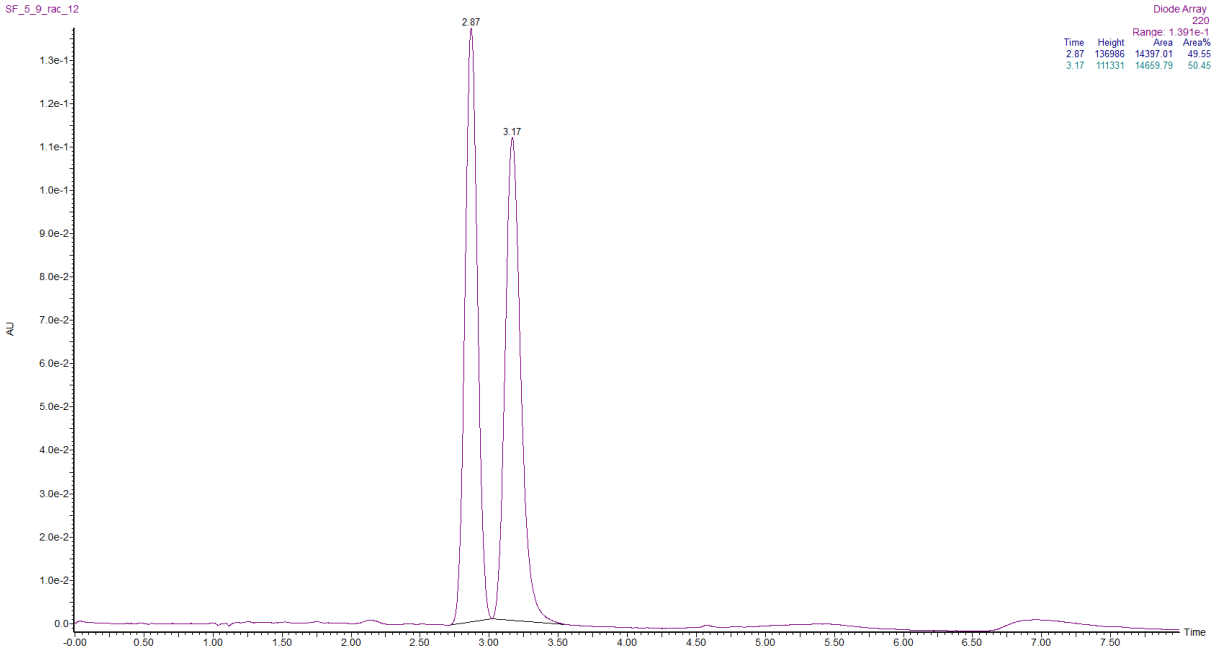
Enantioenriched:



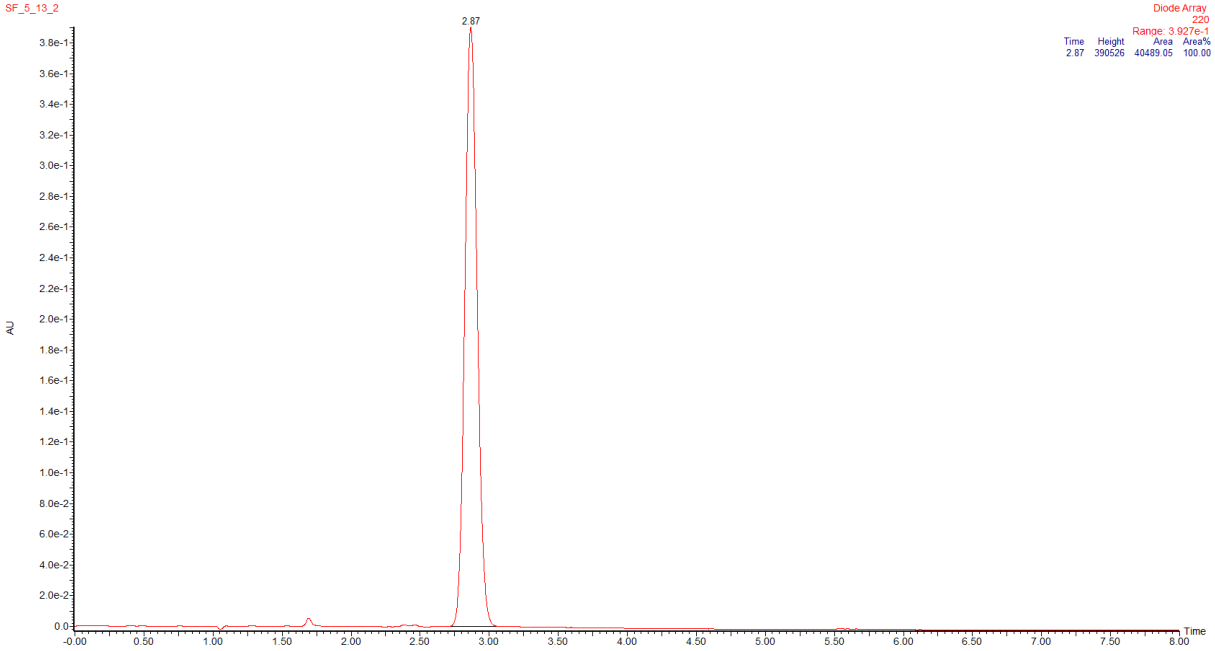
tert-butyl (2_S_,3_R_)-3-(dibenzylamino)-2-(dimethyl(phenyl)silyl)azetidine-1-carboxylate (7f)



Racemic:



Enantioenriched:



Chapter 2. CuH-Catalyzed Regio- and Enantioselective Hydrocarboxylation of Allenes: Toward Carboxylic Acids with Acyclic Quaternary Centers

2.1 Introduction

All-carbon quaternary stereocenters, a structural feature that can impart significant chemical and biological impact to a molecule, are critical to many synthetic and medicinal applications.[1–4] Consequently, catalytic and enantioselective approaches for constructing all-carbon quaternary centers, especially functionalized stereocenters, are highly desirable.[5–8] Carboxylic acids, a chemically versatile functional group, that can bear an α-stereogenic center often serve as useful synthetic intermediates.[9–13] More importantly, α-chiral carboxylic acid derivatives themselves constitute an essential class of compounds in pharmaceutical, agrochemical, and natural product arenas (Figure 1A).[14–16] Methods for generating enantioenriched α-chiral carboxylic acids have long been sought after.[17] Prominent synthetic strategies targeting α-chiral carboxylic acids or esters via asymmetric catalysis include hydrogenation of α,β-unsaturated carboxylic acids,[18] carbene-induced C−H insertion with diazoacetates,[19–21] enantioselective protonation[22,23] or hydrogen atom transfer[24] processes, and α-functionalization of carboxylic acid derivatives.[25–50] Nonetheless, catalytic access[51] to enantioenriched acyclic carboxylic acids or esters featuring an all-carbon α-quaternary stereocenter remains challenging.[5,6] In this regard, common synthetic methods include allylic alkylation of geometrically pure alkenes,[52–55] often with superstoichiometric organometallic reagents, and α-functionalization of carboxylic acid derivatives,[35–44,50] which typically necessitates a β-directing group or electron-withdrawing group (Figure 1B).

As an alternative, the hydrocarboxylation[56–67] of prochiral unsaturated substrates represents a straightforward approach for preparing carboxylic acids. Asymmetric hydrocarboxylation has typically[68,69] been achieved through palladium-catalyzed hydroxy- and alkoxycarbonylation processes using CO gas or a carbon monoxide surrogate.[70–77] Despite

significant advances in this area, the vast majority of the methods can only synthesize α-tertiary acids or esters from vinyl arenes, and a highly enantioselective technique for the assembly of α-quaternary carboxylic acids through a hydrocarboxylation or hydroesterification of unsaturated substrates is still unknown.[68]

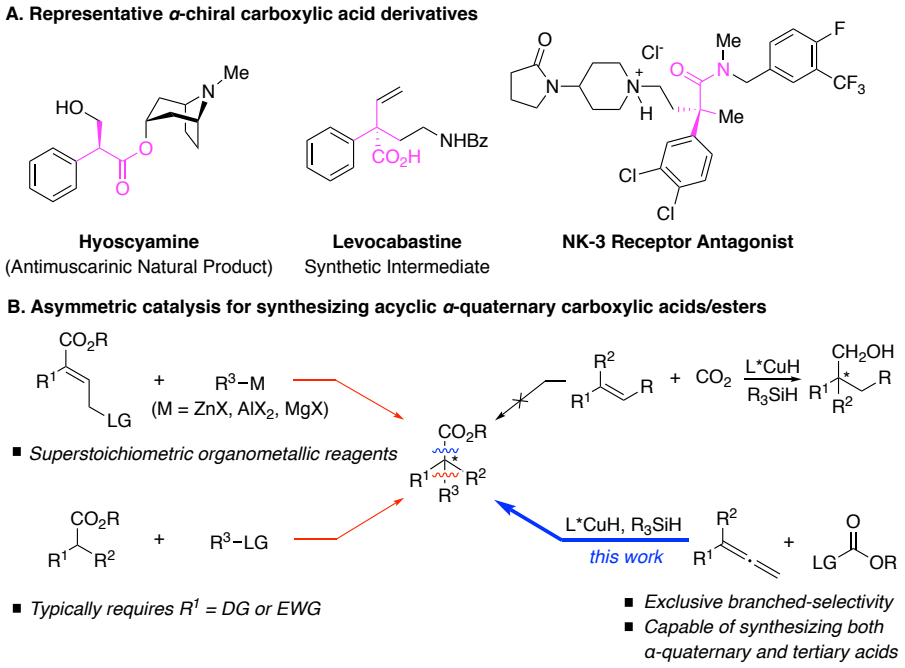


Figure 1. (A) Overview of bioactive α-chiral carboxylic acid derivatives. (B) Previous strategies and our approach to synthesize acyclic α-quaternary carboxylic acid derivatives.

Based upon our research program in copper hydride (CuH)- catalyzed asymmetric hydrofunctionalization of unsaturated substrates,[78–91] we sought to develop a hydrocarboxylation method for constructing enantioenriched carboxylic acids, especially α-quaternary acids. Specifically, we envisioned that a chiral organocopper species, generated in situ from the hydrocupration of an unsaturated substrate, could engage a suitable carboxylation reagent to

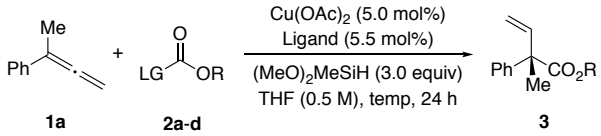
afford enantioenriched carboxylic acids. Previously, when CO_2 was used as an electrophile in CuH-catalyzed olefin hydrofunctionalization reactions, the initially-formed silylated carboxylic acid intermediates underwent facile reduction and led to the formation of hydroxymethylene products.[92–96] To circumvent this reduction pathway, we targeted the CuH-catalyzed hydroesterification, as the products are unreactive under the reaction conditions and can be readily hydrolyzed to give the corresponding carboxylic acids. An ester directly attached to a leaving group is proposed as the electrophile for realizing the hydrocarboxylation process (Figure 1B). In order to obtain α-quaternary esters and acids, we sought to perform a regioselective hydrocarboxylation of allenes as the unsaturated substrate. Herein, we report a highly enantioselective CuH-catalyzed hydrocarboxylation to furnish both *α*-quaternary and tertiary carboxylic acid derivatives.

2.2 Results and Discussion

We chose 1-phenyl-1-methylallene (**1a**) as our model substrate since the branched selective hydrocarboxylation of 1-aryl-1-alkylallenes would produce valuable acyclic quaternary *α*-vinyl-*α*-aryl carboxylic acids that have been used as intermediates in the preparation of (+)-epilaurene[13] and several pharmaceutical ingredients.[10,52] We began our investigation with diphenyl carbonate (**2a**) as the reagent for carboxylate introduction. A series of chiral bisphosphine ligands were evaluated in the hydrocarboxylation of **1a** with diphenyl carbonate (Table S1), and the highest level of enantioselectivity was obtained with (*R*,*R*)-Ph-BPE (**L1**). Under these conditions, the ester product was formed in 42% yield (90:10 er) exclusively as the branched isomer (Table 1, entry 1). In addition to the moderate level of enantioselectivity that was observed, the use of **2a** appeared to result in a sluggish reaction rate. We next attempted to

improve the activity of electrophile by replacing **2a** with Boc_2O (**2b**) or methyl chloroformate (**2c**), which resulted in no desired hydroesterification product being formed (Table 1, entries 2−3). With **2c**, we needed an alkoxide base to regenerate LCuH from a LCuCl intermediate,[97] and we ascribed the low yield to the incompatibility between the base and methyl chloroformate. Since LCuH regeneration from LCuF complexes can proceed in the absence of a base additives,[98] we investigated the use of fluoroformates[99,100] as potential carboxylation reagents. When commercially available 1-adamantyl fluoroformate (**2d**) was employed, product **3** was obtained in 83% yield (Table 1, entry 4). Upon reexamining the suitability of different ligands in reactions with **2d** (Table 1, entry 5−6, and Table S2), we found that when (*R*)-DTBM-SEGPHOS (**L2**) was used (Table 1, entry 5), the branched product was obtained as a single regioisomer in 92% yield and 99:1 er.

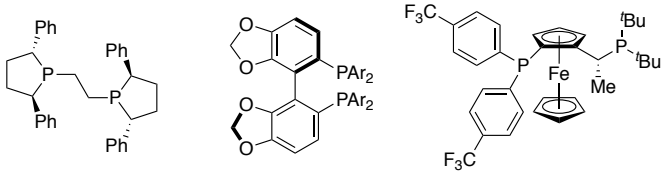
Table 1. Evaluation of Reaction Conditions for the CuH-Catalyzed Hydrocarboxylation of Allene[a]



Entry	Ligand	Electrophile	Temp (°C)	Yield[b] (%)	er[c]
1	**L1**	**2a**	40	42	10:90
2	**L1**	**2b**	40	<5	-
3[d]	**L1**	**2c**	25	<5	-
4	**L1**	**2d**	25	83	13:87

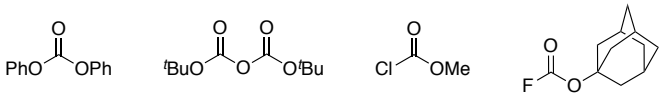
5[e]	**L2**	**2d**	25	92	99:1
6[f]	**L3**	**2d**	25	77	96:4

Ligand:



(*R*,*R*)-Ph-BPE (**L1**) Ar = 3,5-^{t}Bu-4-MeO-C_6H_2 (*R*)-DTBM-SEGPHOS (**L2**) SL-J011-1 (**L3**)

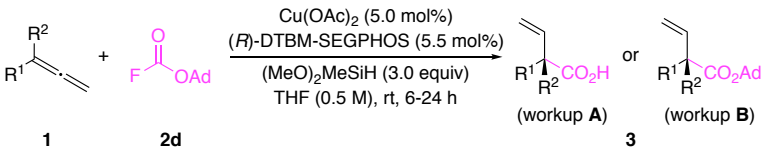
Electrophile:



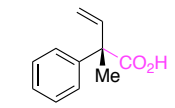
2a **2b** **2c** **2d**

[a]Conditions: 0.10 mmol **2** (1.0 equiv), **1a** (2.0 equiv), copper (II) acetate (5.0 mol%), ligand (5.5 mol%), dimethoxy(methyl)silane (3.0 equiv) in THF (0.5 M). [b]Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. [c]Enantiomeric ratio was determined by SFC analysis. [d]Either LiOMe (1.1 equiv) or CsOBz (1.1 equiv) was used as an additive; **1a** (1.5 equiv) was used. [e]**1a** (1.2 equiv) was used. [f]**1a** (1.0 equiv) and **2** (1.2 equiv) were used.

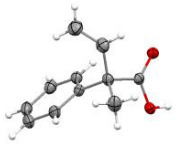
Table 2. Substrate Scope for the CuH-Catalyzed Hydrocarboxylation of Allenes[a]



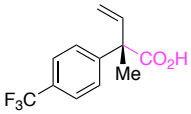
1 **2d** **3**



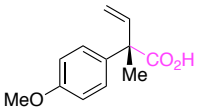
3a
89% yield
99:1 er



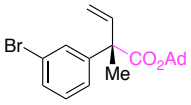
Crystal Structure of **3a**



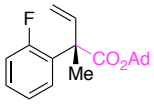
3b
93% yield
96:4 er



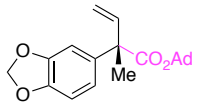
3c
55% yield
97.5:2.5 er[b]



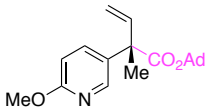
3d
70% yield
99:1 er[c]



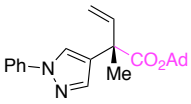
3e
74% yield
96:4 er[b]



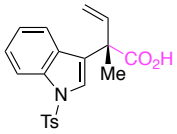
3f
77% yield
98:2 er[b]



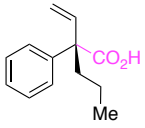
3g
88% yield
98.5:1.5 er



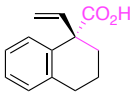
3h
70% yield
96.5:3.5 er



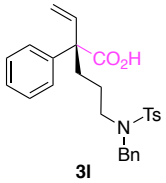
3i
76% yield
97.5:2.5 er[d]



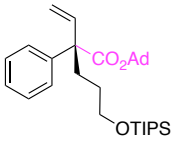
3j
87% yield
98:2 er[b]



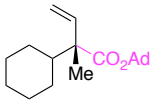
3k
59% yield
99:1 er[b]



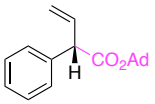
3l
78% yield
99:1 er[b,e]



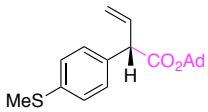
3m
75% yield
98.5:1.5 er[b]



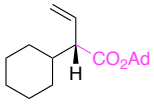
3n
70% yield
94.5:5.5 er[d]



3o
70% yield
93:7 er[d,f]



3p
72% yield
93:7 er[d,f]



3q
80% yield
93:7 er[d,f]

[a]Conditions: 0.50 mmol **2d** (1.0 equiv), **1** (1.2 equiv), copper (II) acetate (5.0 mol%), **L2** (5.5 mol%), dimethoxy(methyl)silane (3.0 equiv) in THF (0.5 M); workup **A**: NH_4F/MeOH workup followed by hydrolysis using TFA; workup **B**: NH_4F/MeOH workup; yields refer to average isolated yields of two runs; see section 2.4 for details. [b]Reaction was carried out at 40 °C. [c]Reaction was carried out at 30 °C. [d]**L3** was used as the ligand instead. [e]**1** (1.1 equiv) was used. [f]Reaction was carried out at 0 °C in 1,2-dimethoxyethane (DME, 1.0 mL).

With the optimal reaction conditions identified, we first examined the substrate scope using 1,1-disubstituted allenes (Table 2). We found that a broad range of 1,1-disubstituted allenes in combination with **2d** were transformed to the desired products in good yields and with excellent enantioselectivity. Moreover, the ester products could be easily hydrolyzed to carboxylic acids in the presence of trifluoroacetic acid (TFA) in near-quantitative yields. To demonstrate the feasibility of this in situ hydrolysis protocol, half of the ester products in Table 2 were isolated as carboxylic acids (**3a**−**c**, **3i**−**l**) without any purification of the intermediate esters.[101] 1-Aryl-1-alkylallenes bearing an electron-withdrawing (**3b**) and -donating group (**3c**) on the arenes were both compatible. Additionally, reactions of arenes substituted with *para*- (**3b**, **3c**), *meta*- (**3d**), and *ortho*- (**3e**) groups resulted in the formation of the products in high yields and enantioselectivity. Functional groups such as an acetal (**3f**), a sulfonamide (**3l**), and a siloxy group (**3m**) were also well tolerated. Allenes containing heterocycles, including a pyridine (**3g**) and pyrazole (**3h**), were suitable substrates for the hydrocarboxylation reaction. However, when an allene substituted with an indole (**3i**) was utilized, better results were found if ligand **L3** was used in place of **L2**. We speculate that this is due to the sterically demanding environment of the substrate that requires the use of a less bulky ligand. Allenes containing functionalized primary alkyl groups (**3j**, **3l**−**m**) as well as an exocyclic allene (**3k**) were also accommodated in this

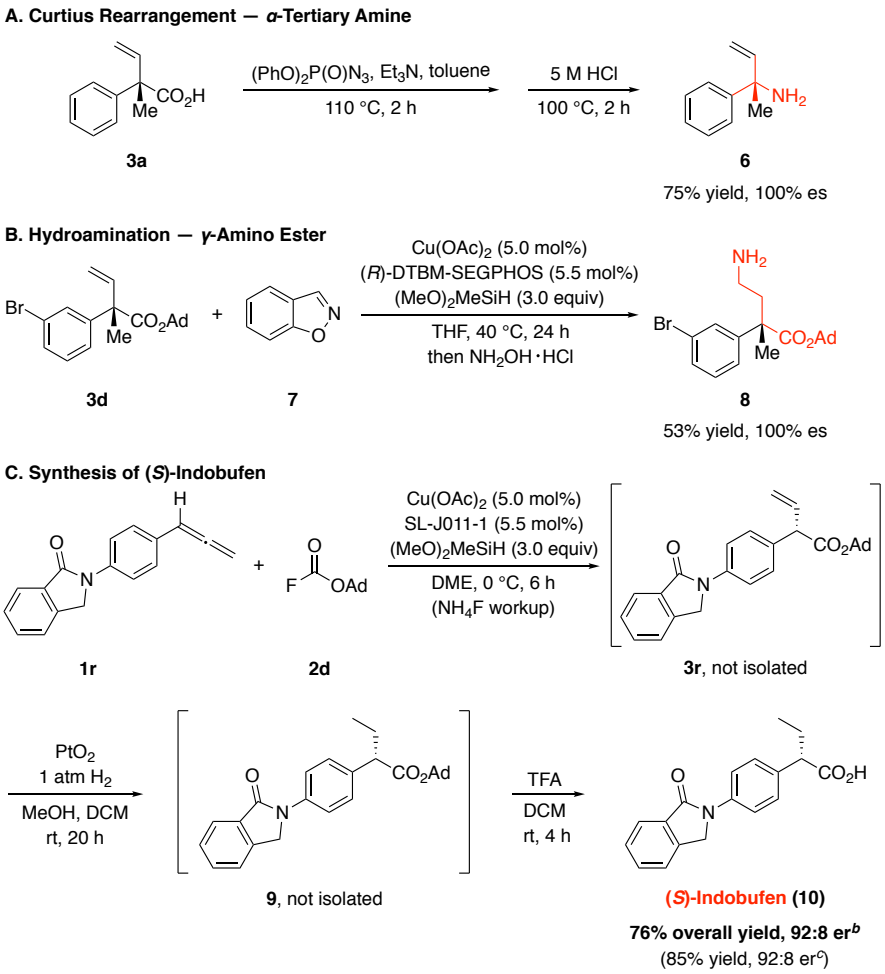
protocol. Furthermore, 1-cyclohexyl-1-methylallene (**3n**) was efficiently transformed to the hydroxycarboxylation product when ligand **L3** was employed.

We were also interested in expanding this method toward the synthesis of α-tertiary esters, which under many conditions are difficult to access in high enantioselectivity due to the easily epimerizable stereogenic center. Thus, we next examined the reaction of a monosubstituted allene, phenylallene (**1o**), under our standard reaction conditions. However, the product ester was formed with a poor level of enantioselectivity, 69.5:30.5 er (Table S4). After reevaluating the reaction parameters, the carboxylation product **3o** could be isolated in 70% yield and 93:7 er using **L3** as ligand (Table 2). A thioether-containing 1-aryl allene (**1p**) and cyclohexylallene (**1q**) were also converted to the corresponding α-tertiary esters in good yields and high enantioselectivity.

To further demonstrate the synthetic utility of our method, we examined the transformation of the hydrocarboxylation products into compounds of interest (Scheme 1). For example, chiral α-tertiary amines are found in a variety of natural products and biologically active compounds, and are difficult to access in an enantioenriched form by standard hydroamination reactions.[102−104] By employing a Curtius rearrangement, we were able to convert α-quaternary carboxylic acid **3a** to α-tertiary amine **6** in a stereoretentive fashion (Scheme 1a). Additionally, we sought to apply our hydrocarboxylation products to the synthesis of enantioenriched γ-amino acid derivatives, which play an important role as γ-aminobutyric acid transaminase inhibitors and in peptide chemistry.[105] By derivatization of the resulting vinyl group in **3d**, an α-quaternary γ-amino ester **8** could be accomplished using a CuH-catalyzed hydroamination reaction[106] (Scheme 1b). We also utilized the method for the preparation of the pharmaceutical indobufen, a platelet aggregation inhibitor marketed under brand name

Ibustrin.[107] (*S*)-Indobufen, previously prepared by the separation of the racemic mixture,[108] was found to be far more potent than the (*R*)-enantiomer in terms of its antiplatelet and anti-inflammatory activities,[108–110] and thus an enantioselective synthetic route to (*S*)-indobufen would be of interest. In our approach, CuH-catalyzed hydrocarboxylation of allene **1r** gave ester **3r**, which underwent subsequent hydrogenation and hydrolysis to furnish (*S*)-Indobufen (**10**) in 76% overall yield and 92:8 er, without the need for any chromatographic purification.

Scheme 1. Applications of the CuH-Catalyzed Hydrocarboxylation Reactions[a]



[a]See section 2.4 for experimental details. [b]**1r** (1.0 equiv) and **2d** (1.2 equiv) were used. [c]**2d** (1.0 equiv) and **1r** (1.2 equiv) were used.

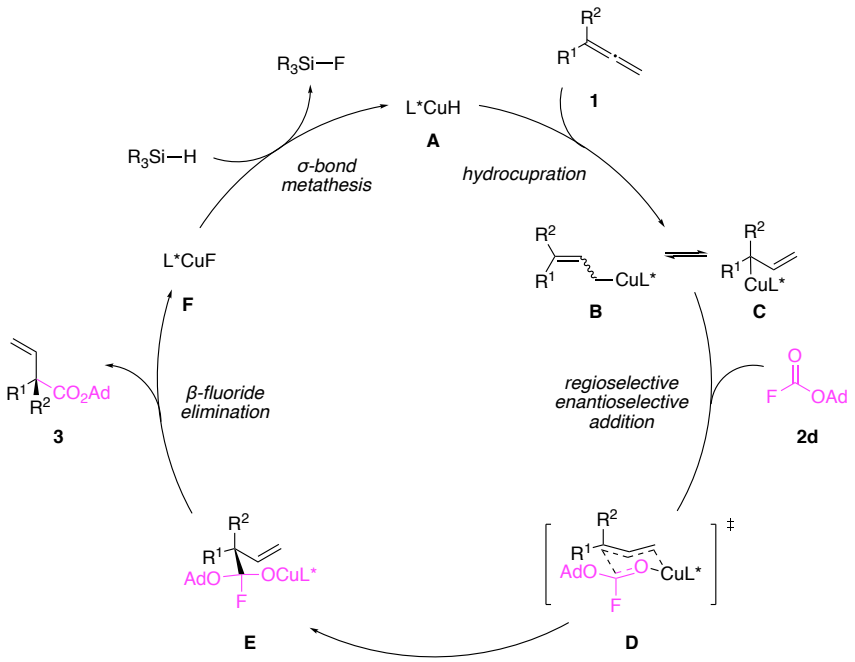


Figure 2. Proposed mechanism for the CuH-catalyzed hydrocarboxylation of allenes.

Based on previous DFT calculations on CuH-catalyzed reactions involving allenes,[111,112] a plausible mechanism can be proposed for this transformation, as depicted in Figure 2. An allene (**1**) first undergoes hydrocupration with a CuH catalyst to generate a rapidly equilibrating mixture of allylcopper species (**B** and **C**). The less hindered terminal allylic copper (**B**) reacts preferentially with fluoroformate **2d** through an enantio-determining six-membered transition state (**D**), to form intermediate **E**. Subsequent collapse of the tetrahedral intermediate by *β*-fluoride elimination leads to the branched carboxylation product **3** and CuF. A *σ*-bond metathesis reaction between CuF and the silane regenerates the CuH catalyst. It is worth noting that the

presence of the fluorine atom in **2d** may lead to unusual energetic preferences in transition state **D** due to dipole minimization or stereoelectronic effects. Although we can propose a plausible sequence of elementary steps by analogy to related reactions,[111,112] at this point we cannot definitively pinpoint stereochemical details of the enantio-determining transition state **D** and explain the subtle substituent effects on enantioselectivity.

2.3 Conclusion

In conclusion, we have developed a highly enantioselective CuH-catalyzed hydrocarboxylation to synthesize α-chiral carboxylic acids and esters, in particular α-quaternary ones. A commercially available fluoroformate was used as the carboxylation reagent to react with allenes in exclusive branched selectivity. The reaction proceeded under mild conditions and could tolerate a variety of important functional groups and heterocycles. Further derivatization of the carboxylation products provided other pharmaceutically and synthetically useful scaffolds. We anticipate that this carboxylation strategy using a fluoroformate may be extended to the discovery of other types of important asymmetric carboxylation processes.

2.4 Experimental

2.4.1 General Information

General Analytical Information: All new compounds were characterized by NMR spectroscopy, IR spectroscopy, elemental analysis or high-resolution mass spectrometry, optical rotation (if chiral and non-racemic) and melting point analysis (if solids). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer. Chemical shifts for ^{1}H NMR are reported as follows: chemical shift in reference to residual $CHCl_3$ at 7.26 ppm (δ ppm),

multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sex = sextet, sep = septet, dd = double of doublets, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. Chemical shifts for ^{13}C NMR are reported in terms of chemical shift in reference to the $CDCl_3$ solvent signal (77.16 ppm). Chemical shifts for ^{19}F NMR are reported in ppm relative to $CFCl_3$ (0.00 ppm). IR spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points were measured on a Mel-Temp capillary melting point apparatus. Optical rotations were measured using a Jasco P-1010 digital polarimeter. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system. Enantiomeric ratios (er's) were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument; specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. High-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series chromatographs using a Chiralpak® columns (25 cm) as noted for each. Thin-layer chromatography (TLC) was performed on silica gel 60Å F_{254} plates (SiliaPlate from Silicycle) and visualized with UV light, iodine or potassium permanganate stain. Preparatory thin-layer chromatography (Prep-TLC) was performed on silica gel GF with UV 254 (20 x 20 cm, 1000 microns, catalog # TLG-R10011B-341 from Silicycle) and visualized with UV light. Isolated yields reported reflect the average values from two independent runs.

General Reagent Information: All reactions were performed under a nitrogen or argon atmosphere using the indicated method in the general procedures. Tetrahydrofuran (THF) was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and purified by passage

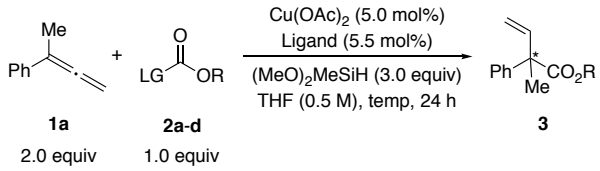
under argon pressure through two packed columns of neutral alumina and copper(II) oxide. Anhydrous 1,2-dimethoxyethane (DME) was purchased from Millipore-Sigma in a Sure-Seal™ bottle and used as received. Copper(II) acetate was purchased from Strem and was used as received. 1,2-Bis((2*S*,5*S*)2,5-diphenylphospholano)ethane, 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 glovebox. DTBM-SEGPHOS was purchased from Takasago International Co. and used as received. Josiphos ligand (*R*)-1-{(S_P)-2-[Bis[4-(trifluoromethyl)-phenyl]phosphino]ferrocenyl}ethyldi-tert-butylphosphine (Josiphos SL-J011-1) was a generous gift from Solvias and stored in a nitrogen-filled glovebox. Dimethoxy(methyl)silane (DMMS) was purchased from Tokyo Chemical Industry Co. (TCI). Both silanes were stored in a nitrogen-filled glovebox at −30 °C for long-term storage. (***Caution****: Dimethoxy(methyl)silane (DMMS, CAS#16881-77-9) is listed by several vendors (TCI, Alfa Aesar) SDS or MSDS as a H318, a category 1 Causes Serious Eye Damage. Other vendors (Sigma-Aldrich, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precaution as outlined for the handling of hazardous materials in prudent practices in the laboratory*[113]*. At the end of the reaction either ammonium fluoride in methanol, aqueous sodium hydroxide (1 M) or aqueous hydrochloric acid (1 M) should be carefully added to the reaction mixture. This should be allowed to stir for at least 30 min or the time indicated in the detailed reaction procedure*). All reactions should be (and were) carried out in a well-ventilated hood or in a glovebox. 1-Adamantyl fluoroformate was purchased from Millipore-Sigma and used as received (for batch no. 05601mh) or after recrystallization[2] (for batch no. 0000028781). All other solvents and commercial reagents were used as received from Millipore-Sigma, Alfa Aesar, Acros Organics, TCI and Combi-Blocks, unless otherwise noted. Flash column chromatography

was performed using 40-63 μm silica gel (SiliaFlash® F60 from Silicycle), or with the aid of a Biotage Isolera Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g). Organic solutions were concentrated *in vacuo* with the aid of a Buchi rotary evaporator.

2.4.2 Optimization and General Procedures for Hydrocarboxylation Reactions

2.4.2.1 Optimization of CuH-Catalyzed Hydrocarboxylation of 1,1-disubstituted Allenes

Table S1. Evaluation of Different Electrophiles[a]

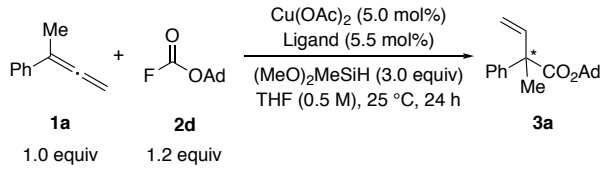


Entry	Ligand	LG, OR	Temp (°C)	Yield[b] (%)	er[c]
1	(*R*,*R*)-Ph-BPE	PhO, OPh (2a)	40	42	90:10
2	(*R*)-DTBM-SEGPHOS	PhO, OPh (2a)	40	<5	-
3	SL-J011-1	PhO, OPh (2a)	40	8	-
4	(*S*,*S*)-BenzP*	PhO, OPh (2a)	40	<5	-
5	(*R*,*R*)-QuinoxP*	PhO, OPh (2a)	40	<5	-
6	(*S*)-3H-QuinoxP*	PhO, OPh (2a)	40	53	80:20
7	(*R*,*R*)-BiphenylP*	PhO, OPh (2a)	40	<5	-
8	(*R*,*R*)-Ph-BPE	BocO, O^{t}Bu (2b)	40	<5	-
9	(*R*)-DTBM-SEGPHOS	BocO, O^{t}Bu (2b)	40	<5	-
10[d]	(*R*,*R*)-Ph-BPE	Cl, OMe (2c)	25	<5	-

11[e]	(*R*,*R*)-Ph-BPE	Cl, OMe (2c)	25	<5	-
12[d]	(*R*)-DTBM-SEGPHOS	Cl, OMe (2c)	25	<5	-
13[e]	(*R*)-DTBM-SEGPHOS	Cl, OMe (2c)	25	<5	-
14	**(*R*,*R*)-Ph-BPE**	**F, OAd (2d)**	**25**	**83**	**87:13**

[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. [c]Enantiomeric ratio was determined by SFC analysis on commercial chiral columns. [d]LiOMe (1.1 equiv) was used as an additive; allene (1.5 equiv) was used. [e]CsOBz (1.1 equiv) was used as an additive; allene (1.5 equiv) was used.

Table S2. Evaluation of Different Ligands in Reactions with Electrophile 2d[a]

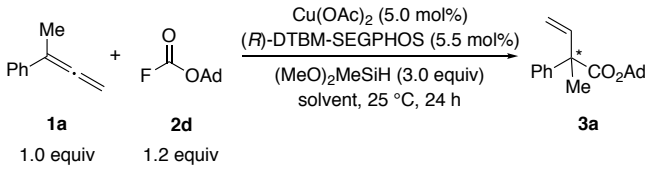


Entry	Ligand	Yield[b] (%)	er[c]
1	**(*R*)-DTBM-SEGPHOS**	**77**	**99:1**
2	(*R*,*R*)-QuinoxP*	23	83:17
3	(*S*)-3H-QuinoxP*	66	77.5:22.5
4	(*S*,*S*)-BenzP*	47	84.5:15.5
5	SL-J011-1	77	96:4

[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard.

[c]Enantiomeric ratio was determined by SFC analysis on commercial chiral columns (specified in the experimental section for each compound).

Table S3. Evaluation of Other Reaction Parameters[a]

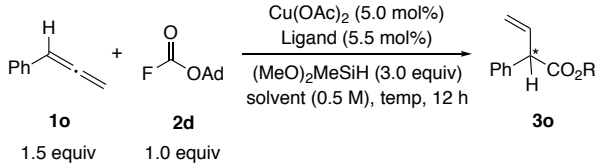


Entry	Solvent	Yield[b] (%)	er[c]
1	1,4-Dioxane (0.5 M)	64	99:1
2	MTBE (0.5 M)	43	99.5:0.5
3	CyH (0.5 M)	55	99.5:0.5
4	Toluene (0.5 M)	68	99:1
5	THF (0.5 M)	77	99:1
6	THF (1.0 M)	76	99:1
7	THF (0.25 M)	75	99:1
8[d]	THF (0.5 M)	51	n.d.
9[e]	**THF (0.5 M)**	**92**	**99:1**

[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. [c]Enantiomeric ratio was determined by SFC analysis on commercial chiral columns (specified in the experimental section for each compound). [d]$Cu(OAc)_2$ (2.0 mol%) and (*R*)-DTBM-SEGPHOS (2.2 mol%) were used. [e]**1a** (1.2 equiv) and **2d** (1.0 equiv) were used.

2.4.2.2 Optimization of CuH-Catalyzed Hydrocarboxylation of 1-Substituted Allenes

Table S4. Optimization Table for Phenylallene[a]



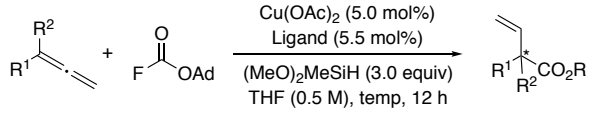
Entry	Ligand	solvent	Temp (°C)	Yield[b] (%)	er[c]
1	(*R*,*R*)-Ph-BPE	THF	rt	72	79:21
2[d]	(*R*)-DTBM-SEGPHOS	THF	rt	83	69.5:30.5
3	SL-J011-1	THF	rt	85	88.5:11.5
4	SL-J011-1	1,4-dioxane	rt	89	89.5:10.5
5	SL-J011-1	MTBE	rt	85	90:10
6	SL-J011-1	CyH	rt	85	87:13
7	SL-J011-1	toluene	rt	84	88.5:11.5
8	SL-J011-1	CPME	rt	83	88.5:11.5
9	SL-J011-1	DME	rt	85	90:10
10	**SL-J011-1**	**DME**	**0[e]**	**93**	**93.5:6.5**

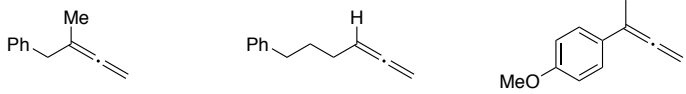
[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. [c]Enantiomeric ratio was determined by SFC analysis on commercial chiral columns (specified in the experimental section for each compound). [d]Allene (2.0 equiv) was used. [e]Cooled to 0 °C using an ice/water bath.

2.4.2.3 Examination of Allenes with Different Substitution Patterns

In addition to the examples shown in Table 2 and 3, we have examined allenes bearing less or more bulky substituents. The results are summarized in Table S5.

Table S5. Reactivity and Enantioselectivity in Reactions Using Different Types of Allenes[a]





temp	rt	rt	40 °C
(*R*)-DTBM-SEGPHOS	55% yield, 73:27 er[b]	83% yield, 77.5:22.5 er[c]	no reaction[b]
SL-J011-1	90% yield, 70.5:29.5 er[b]	87% yield, 67.5:32.5 er[d]	
(*R*,*R*)-Ph-BPE	80% yield, 67.5:32.5 er[b]	78% yield, 61.5:38.5 er[d]	

[a]Reactions were conducted on 0.1 mmol scale. FCO_2Ad (1.0 equiv) was used. Yields were determined by ^1H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. Enantiomeric ratio was determined by SFC analysis on commercial chiral columns (specified in the experimental section for each compound). [b]Allene (1.2 equiv) was used. [c]Allene (2.0 equiv) was used. [d]Allene (1.5 equiv) was used.

2.4.2.4 General Procedures for CuH-Catalyzed Hydrocarboxylation Reactions[114]

General Procedure A

An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed and anhydrous

THF (0.60 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at room temperature. Next, the cap was removed and dimethoxymethylsilane (DMMS) (0.22 mL, 1.8 mmol) was added in one portion via a 1 mL syringe. The tube was recapped, and the mixture was stirred for another 10 min at room temperature to prepare an orange-colored CuH stock solution.

A separate oven-dried screw-cap reaction tube (Fisherbrand, 20*125 mm, part no. 1495937A) containing a magnetic stir bar was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18), and then transferred into the glovebox. The cap was removed, and allene (0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (0.50 mmol, 99 mg, 1.0 equiv. Note: Weighed out as a solid. Low melting point ~30 °C. Hold the bottle using an iron clamp to prevent melting the solids) were added. Anhydrous THF (0.50 mL) was added to the reaction tube via a 1 mL syringe while rinsing the walls of the tube. Next, the CuH stock solution (0.68 mL) was added via a 1 mL syringe to the reaction tube in one portion. The reaction tube was capped and removed from the glovebox. The reaction mixture was allowed to stir at the temperature and time as indicated for each substrate.

General Procedure B

An oven-dried screw-cap reaction tube (Fisherbrand, 20*125 mm, part no. 1495937A) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 0.050 equiv). The reaction tube was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18), and then transferred into a nitrogen-filled glovebox. The cap was removed and SL-J011-1 (18.7

mg, 0.0275 mmol, 0.055 equiv) was added to the tube. Anhydrous 1,2-dimethoxyethane (DME, 0.50 mL) was added via a 1 mL syringe. The tube was capped and the mixture was stirred for 10 min at room temperature. The cap was removed and allene (0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (0.50 mmol, 99 mg, 1.0 equiv. Note: Weighed out as a solid. Low melting point ~30 °C. Hold the bottle using an iron clamp to prevent melting the solids) were added. Anhydrous DME (0.50 mL) was added via a 1 mL syringe while rinsing the walls of the tube. The reaction tube was capped, removed from the glovebox, and then submerged in an ice/water bath. The reaction mixture was stirred at 0 °C for 5 min, and then DMMS (0.18 mL, 1.50 mmol) was added in one portion via a 1 mL syringe by piercing the septum of the cap. The reaction mixture was stirred at 0 °C for 6−7 h (as indicated for each substrate).

Workup A (the products are isolated as carboxylic acids)

After the reaction mixture had stirred for the amount of time as indicated for each substrate, the reaction mixture was allowed to warm (or cool) to room temperature (if applicable), and the cap of the reaction tube was removed. While the reaction mixture was stirred at room temperature, sat. NH_4F in MeOH (10 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at room temperature for 1 h, and then transferred to a 100 mL round bottom flask. The reaction tube was rinsed with EtOAc, and the mixture was concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in 50% hexane/EtOAc (1 mL), and was filtered through a short plug of basic activated alumina (2.5-3 g) eluting with 50% hexane/EtOAc (~10 mL). The resulting solution was collected in a 20 mL scintillation vial, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was again dissolved in 50% hexane/EtOAc, and then

filtered through a short plug (using a plugged pipette) of silica gel (~1.5 g) eluting with 50% hexane/EtOAc (~10 mL). The resulting solution was collected in a 20 mL scintillation vial and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was diluted with CH_2Cl_2 and transferred to a reaction tube (Fisherbrand, 16*125 mm, part no.1495935A). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator. Afterwards, the reaction tube was left under high vacuum for 20 min. CH_2Cl_2 (1.0 mL) and a magnetic stir bar were added to the tube. While the solution was stirred at room temperature, trifluoroacetic acid (0.38 mL, 5.0 mmol, 10 equiv) was added dropwise via a 1 mL syringe. The tube was capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and the mixture was stirred at room temperature for 3−14 h (as indicated for each substrate). The resulting mixture was then transferred to a 125 mL separatory funnel with CH_2Cl_2 (25 mL) and extracted with 1 M aq. NaOH (50 mL) (Note: The aqueous layer contains the sodium salt of the product. In cases where the phases were difficult to separate, a 9" pipette was used to stir the biphasic mixture in the separatory funnel to help the phases separate). The aqueous layer was washed with CH_2Cl_2 (2 x 25 mL), and the organic layers were discarded. Then 6 M aq. HCl (10 mL) was added to the aqueous layer, and the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in CH_2Cl_2 and filtered through a short plug of silica gel (~0.3 g) eluting with 5:1 CH_2Cl_2/MeOH, and the resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the products as carboxylic acids.

Workup B (the products were isolated as esters)

After the reaction mixture had stirred for the amount of time as indicated for each substrate, the reaction mixture was allowed to warm (or cool) to room temperature (if applicable), and the cap of the reaction tube was removed. While the reaction mixture was stirred at room temperature, sat. NH_4F in MeOH (10 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred with the tube uncapped at room temperature for 30 min, then the mixture was transferred to a 100 mL round bottom flask. The tube was rinsed with EtOAc, and the mixture was concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in EtOAc (1 mL), then filtered through a short plug of basic activated alumina (~2.5 g) eluting with EtOAc (~10 mL). The resulting solution was collected in a 20 mL scintillation vial, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was immediately purified by silica gel column chromatography (~30 g silica gel, diameter of the column ~2 cm, length of the packed column ~18 cm) to give the products as esters.

2.4.2.5 Determination of the absolute configuration of the hydrocarboxylation product

Single Crystal X-ray Diffraction Data for Compound 3a (P20120): A crystal of **3a** was obtained by slowly evaporating a solution of **3a** the $CDCl_3$ at 0 °C (in air). The absolute configuration of **3a** was determined by X-ray crystallographic analysis. The absolute configuration of **3b-q** and **10** was assigned by analogy to **3a** (Note: Reactions with **L2** and **L3** as the ligand give the same major enantiomer).

CCDC 2050451 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

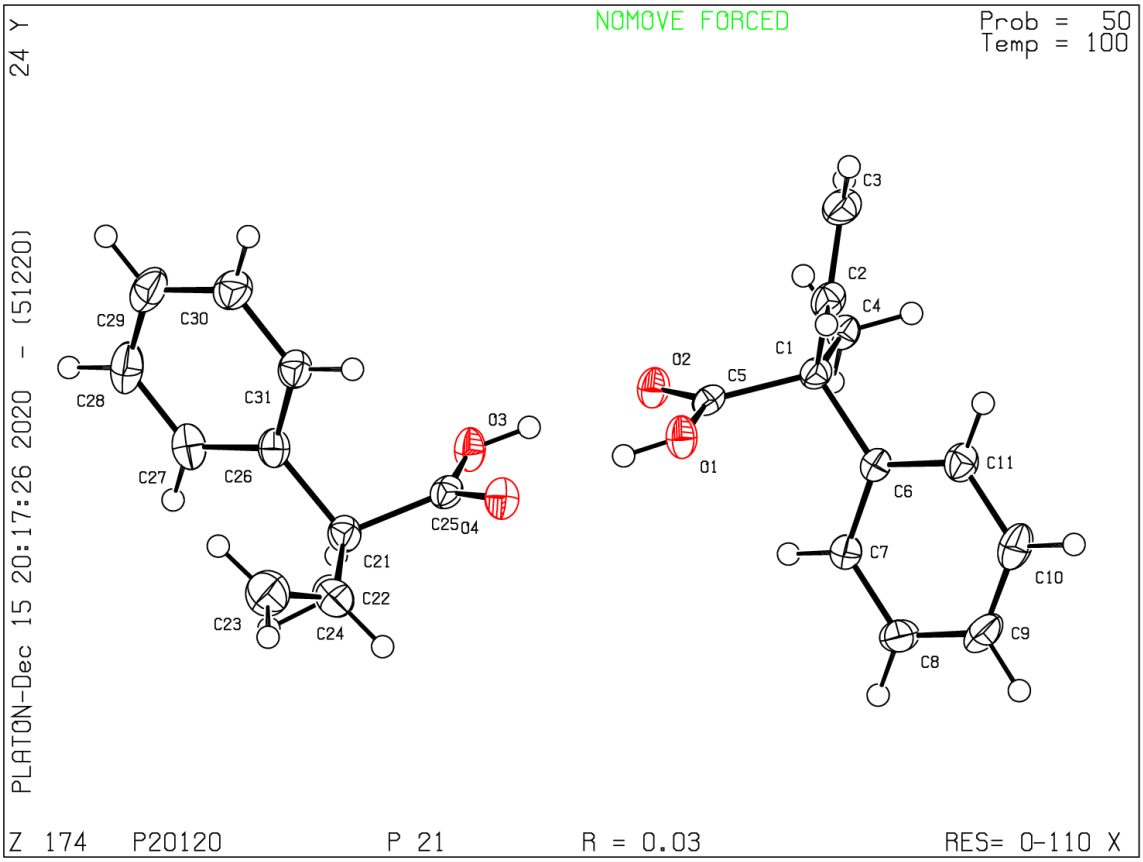


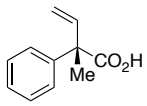
Table S6. Crystal data and structure refinement for P20120

Identification code	P20120	
Empirical formula	C11 H12 O2	
Formula weight	176.21	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.9503(3) Å	a= 90°.
	b = 6.14990(10) Å	b= 91.8740(11)°.

	c = 13.0888(3) Å g = 90°.
Volume	961.42(4) $Å^3$
Z	4
Density (calculated)	1.217 Mg/m^3
Absorption coefficient	0.668 mm^{-1}
F(000)	376
Crystal size	0.315 x 0.040 x 0.035 mm^3
Theta range for data collection	3.378 to 74.620°.
Index ranges	-14<=h<=14, -7<=k<=7, -16<=l<=16
Reflections collected	26117
Independent reflections	3918 [R(int) = 0.0461]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3918 / 3 / 243
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0292, wR2 = 0.0748
R indices (all data)	R1 = 0.0303, wR2 = 0.0757
Absolute structure parameter	0.11(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.151 and -0.206 $e.Å^{-3}$

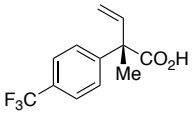
2.4.3 Characterization Data for the Hydrocarboxylation Products

(*S*)-2-methyl-2-phenylbut-3-enoic acid (3a)



Following general procedure **A**, buta-2,3-dien-2-ylbenzene (78 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at room temperature for 24 h. After Workup **A** (the hydrolysis reaction using trifluoroacetic acid was run at room temperature for 3 h), the title compound was obtained as a white solid (1st run: 78 mg, 89% yield, 99:1 er; 2nd run: 78 mg, 89% yield, 99:1 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 4H), 7.33-7.28 (m, 1H), 6.44 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.36 (d, *J* = 10.7 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H), 1.70 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.30, 142.75, 140.60, 128.62, 127.28, 126.71, 115.63, 53.74, 23.29. The spectral data match those previously reported in the literature.[115a] **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH: $scCO_2$ to 15:85 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.31 min (major), 3.53 min (minor), 99:1 er. **Specific rotation** $[\alpha]_D^{23}$: −5.7 (c = 1.0, $CHCl_3$).

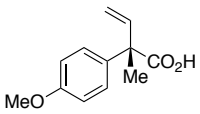
(*S*)-2-methyl-2-(4-(trifluoromethyl)phenyl)but-3-enoic acid (3b)



Following general procedure **A**, 1-(buta-2,3-dien-2-yl)-4-(trifluoromethyl)benzene (119 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at room temperature for 18 h. After Workup **A** (the hydrolysis reaction using trifluoroacetic acid was run at room temperature for 3 h), the title compound was obtained as a colorless liquid (1st run: 113 mg, 93% yield, 96:4 er; 2nd run: 114 mg, 93% yield, 96:4 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 6.38 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.38 (d, *J* = 10.7 Hz, 1H), 5.22 (d, *J* = 17.5 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.62, 146.61,

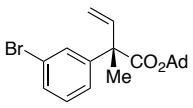
139.72, 129.66 (q, J = 32.5 Hz), 127.29, 125.60 (q, J = 3.9 Hz), 124.17 (q, J = 272.2 Hz), 116.58, 53.82, 23.30. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −62.61. The spectral data match those previously reported in the literature.[115b] **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 2:98 MeOH: $scCO_2$ to 8:92 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 1.50 mL/min), 5.10 min (major), 5.52 min (minor), 96:4 er. **Specific rotation** $[\alpha]_D^{23}$: −3.9 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

(*S*)-2-(4-methoxyphenyl)-2-methylbut-3-enoic acid (3c)



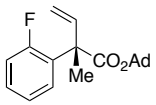
Following general procedure **A**, 1-(buta-2,3-dien-2-yl)-4-methoxybenzene (96 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 24 h. After Workup **A** (**Note**: ~10 mL EtOAc was used as the eluent instead during the filtration of the crude mixture through a plug of basic activated alumina. The hydrolysis reaction using trifluoroacetic acid was run at room temperature for 14 h), the title compound was obtained as a white solid (1st run: 55 mg, 53% yield, 97.5:2.5 er; 2nd run: 58 mg, 56% yield, 97.5:2.5 er). **m.p.** 57.9-58.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.92-6.88 (m, 2H), 6.41 (dd, J = 17.5, 10.7 Hz, 1H), 5.32 (dd, J = 10.6, 0.8 Hz, 1H), 5.19 (dd, J = 17.5, 0.8 Hz, 1H), 3.83 (s, 3H), 1.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.29, 158.70, 140.91, 134.75, 127.89, 115.31, 113.94, 55.40, 52.97, 23.37. **IR** (thin film): 2985, 2836, 1698, 1510, 1463, 1248, 1180, 827 cm^{-1}. **EA** Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.63; H, 6.80. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH: $scCO_2$ to 15:85 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.55 min (major), 4.83 min (minor), 97.5:2.5 er. **Specific rotation** $[\alpha]_D^{23}$: −7.9 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

adamantan-1-yl (*S*)-2-(3-bromophenyl)-2-methylbut-3-enoate (3d)



Following general procedure **A**, 1-bromo-3-(buta-2,3-dien-2-yl)benzene (126 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 30 °C for 24 h. After Workup **B** and purification by column chromatography with a gradient of hexane (200 mL) → hexane/EtOAc = [100:1 (200 mL) → 80:1 (80 mL) → 60:1 (120 mL) → 50:1 (100 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a white solid (1st run: 138 mg, 71% yield, 99:1 er; 2nd run: 135 mg, 69% yield, 99:1 er). **m.p.** 51.5-52.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 1.6 Hz, 1H), 7.36 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.22-7.15 (m, 2H), 6.31 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.27 (d, *J* = 10.7 Hz, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 2.15 (br, 3H), 2.06 (d, *J* = 3.0 Hz, 6H), 1.64 (t, *J* = 3.1 Hz, 6H), 1.55 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.98, 146.66, 140.97, 129.87, 129.81, 125.40, 122.48, 115.19, 81.58, 54.39, 41.21, 36.27, 30.95, 23.53. **IR** (thin film): 2910, 2851, 1723, 1564, 1238, 1122, 1052, 782 cm^{-1}. **EA** Calcd. for $C_{21}H_{25}BrO_2$: C, 64.79; H, 6.47. Found: C, 64.89; H, 6.72. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 3:97 IPA: $scCO_2$, 2.50 mL/min), 4.45 min (major), 4.85 min (minor), 99:1 er. **Specific rotation** $[\alpha]_D^{24}$: −11.5 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

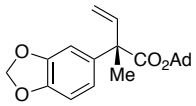
adamantan-1-yl (*S*)-2-(2-fluorophenyl)-2-methylbut-3-enoate (3e)



Following general procedure **A**, 1-(buta-2,3-dien-2-yl)-2-fluorobenzene (89 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 20 h. After Workup **B** and purification by column chromatography with a gradient of hexane (150 mL) → hexane/Et_2O = [100:1 (100 mL)

→ 80:1 (80 mL) → 70:1 (210 mL) → 60:1 (60 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 119 mg, 72% yield, 96:4 er; 2nd run: 125 mg, 76% yield, 96:4 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H), 7.11 (td, *J* = 7.6, 1.3 Hz, 1H), 7.04 (ddd, *J* = 11.4, 8.2, 1.1 Hz, 1H), 6.35 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.14 (d, *J* = 17.5 Hz, 1H), 2.15 (br, 3H), 2.08 (d, *J* = 2.8 Hz, 6H), 1.66 (br, 6H), 1.61 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.19, 160.60 (d, *J* = 246.9 Hz), 140.32, 132.01 (d, *J* = 13.4 Hz), 128.52 (d, *J* = 8.6 Hz), 128.01 (d, *J* = 4.5 Hz), 123.90 (d, *J* = 3.1 Hz), 115.60 (d, *J* = 22.3 Hz), 115.26, 81.12, 51.91, 41.09, 36.34, 30.95, 22.40. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −112.00. **IR** (thin film): 2909, 2851, 1728, 1489, 1451, 1239, 1055, 754 cm^{-1}. **HRMS** Calcd. m/z for $C_{21}H_{26}O_2F^+$ $[M+H]^+$: 329.1911; found 329.1913. **HPLC** analysis: OD-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; Hex/IPA = 98/2, 0.3 mL/min, 210 nm, 23°C), 19.20 min (major), 20.16 min (minor), 96:4 er. **Specific rotation** $[\alpha]_D^{24}$: −17.8 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

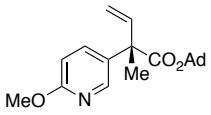
adamantan-1-yl (*S*)-2-(benzo[d][1,3]dioxol-5-yl)-2-methylbut-3-enoate (3f)



Following general procedure **A**, 5-(buta-2,3-dien-2-yl)benzo[d][1,3]dioxole (104 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 12 h. After Workup **B** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/Et_2O = [60:1 (240 mL) → 50:1 (250 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a white solid (1st run: 138 mg, 78% yield, 98:2 er; 2nd run: 134 mg, 76% yield, 98:2 er). **m.p.** 87.8-89.0 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.79 (t, *J* = 1.1 Hz, 1H), 6.74 (d, *J* = 1.1 Hz, 2H), 6.32 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.94 (s, 2H), 5.22 (dd, *J* = 10.7,

0.9 Hz, 1H), 5.12 (dd, *J* = 17.5, 0.9 Hz, 1H), 2.14 (br, 3H), 2.07 (d, *J* = 3.0 Hz, 6H), 1.64 (br, 6H), 1.53 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.58, 147.61, 146.21, 141.84, 138.30, 119.69, 114.39, 108.00, 107.52, 101.09, 81.23, 54.16, 41.22, 36.30, 30.95, 23.75. **IR** (thin film): 2909, 2852, 1721, 1486, 1237, 1122, 1040, 921 cm^{-1}. **EA** Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.66; H, 7.52. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 20:80 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.26 min (major), 3.49 min (minor), 98:2 er. **Specific rotation** $[\alpha]_D^{24}$: −8.3 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

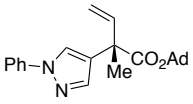
adamantan-1-yl (*S*)-2-(6-methoxypyridin-3-yl)-2-methylbut-3-enoate (3g)



Following general procedure **A**, 5-(buta-2,3-dien-2-yl)-2-methoxypyridine (97 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at room temperature for 24 h. After Workup **B** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/Et_2O = [40:1 (80 mL) → 30:1 (150 mL) → 25:1 (150 mL) → 20:1 (80 mL) → 15:1 (90 mL) → 10:1 (100 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 152 mg, 89% yield, 98.5:1.5 er; 2nd run: 151 mg, 88% yield, 98.5:1.5 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 6.29 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.23 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 17.5 Hz, 1H), 3.92 (s, 3H), 2.13 (br, 3H), 2.05 (d, *J* = 2.9 Hz, 6H), 1.63-1.62 (m, 6H), 1.56 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.11, 163.00, 144.88, 141.23, 137.73, 132.34, 114.89, 110.38, 81.57, 53.50, 52.32, 41.22, 36.25, 30.93, 23.50. **IR** (thin film): 2909, 2852, 1723, 1604, 1492, 1288, 1242, 1054 cm^{-1}. **EA** Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97.

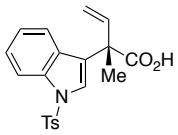
Found: C, 73.92; H, 7.79. **HPLC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; Hex/IPA = 99.5/0.5, 0.3 mL/min, 230 nm, 23°C), 25.53 min (minor), 27.05 min (major), 98.5:1.5 er. **Specific rotation** $[\alpha]_D^{24}$: −6.4 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

adamantan-1-yl (*S*)-2-methyl-2-(1-phenyl-1H-pyrazol-4-yl)but-3-enoate (3h)



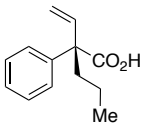
Following general procedure **A**, 4-(buta-2,3-dien-2-yl)-1-phenyl-1H-pyrazole (118 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at room temperature for 18 h. After Workup **B** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/Et_2O = [40:1 (80 mL) → 30:1 (90 mL) → 25:1 (100 mL) → 20:1 (140 mL) → 15:1 (90 mL) → 10:1 (100 mL) → 8:1 (160 mL)], the title compound was obtained as a white solid (1st run: 123 mg, 65% yield, 96.5:3.5 er; 2nd run: 140 mg, 74% yield, 96.5:3.5 er). **m.p.** 48.4-49.2 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.68-7.66 (m, 3H), 7.45-7.41 (m, 2H), 7.28-7.24 (m, 1H), 6.29 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.18-5.11 (m, 2H), 2.16 (br, 3H), 2.11 (d, *J* = 2.9 Hz, 6H), 1.65 (br, 6H), 1.64 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.03, 141.75, 140.29, 140.16, 129.51, 126.69, 126.39, 124.99, 119.01, 113.77, 81.54, 48.02, 41.28, 36.28, 30.96, 23.48. **IR** (thin film): 2909, 2851, 1721, 1600, 1502, 1242, 1052, 754 cm^{-1}. **EA** Calcd. for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50. Found: C, 76.73; H, 7.59. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH: $scCO_2$, 1.50 mL/min), 17.13 min (major), 18.22 min (minor), 96.5:3.5 er. **Specific rotation** $[\alpha]_D^{24}$: 9.0 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

(*S*)-2-methyl-2-(1-tosyl-1H-indol-3-yl)but-3-enoic acid (3i)



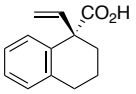
General procedure **B** was followed, except THF was used as solvent and the reaction was carried out at room temperature for 24 h. 3-(Buta-2,3-dien-2-yl)-1-tosyl-1H-indole (194 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. After Workup **A** [**Note**: During the filtration of the crude mixture through a plug of basic activated alumina and then a plug of silica gel prior to the hydrolysis reaction, EtOAc (~10 mL for each filtration) was used as the eluent instead of 50% hexane/EtOAc. The hydrolysis reaction using trifluoroacetic acid was run at room temperature for 8 h], the title compound was obtained as a white solid (1st run: 148 mg, 80% yield, 97.5:2.5 er; 2nd run: 134 mg, 72% yield, 97.5:2.5 er). **m.p.** 75.3-76.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.49 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.40 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 5.03 (d, *J* = 17.4 Hz, 1H), 2.33 (s, 3H), 1.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.75, 145.13, 138.80, 135.65, 135.27, 130.06, 128.99, 126.94, 124.77, 124.10, 124.02, 123.20, 121.36, 116.23, 113.85, 48.68, 23.32, 21.71. **IR** (thin film): 2987, 1703, 1447, 1369, 1280, 1172, 1133, 909 cm^{-1}. **EA** Calcd. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18. Found: C, 64.87; H, 4.99. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 4:96 MeOH: $scCO_2$, 2.50 mL/min), 21.35 min (minor), 22.17 min (major), 97.5:2.5 er. **Specific rotation** $[\alpha]_D^{24}$: −10.2 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

(*S*)-2-phenyl-2-vinylpentanoic acid (3j)



Following general procedure **A**, hexa-1,2-dien-3-ylbenzene (95 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 24 h. After Workup **A** (the hydrolysis reaction using trifluoroacetic acid was run at room temperature for 3 h), the title compound was obtained as a colorless liquid (1st run: 89 mg, 87% yield, 98:2 er; 2nd run: 88 mg, 86% yield, 98:2 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.31-7.27 (m, 1H), 6.40 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.36 (d, *J* = 10.9 Hz, 1H), 5.11 (d, *J* = 17.6 Hz, 1H), 2.17 (ddd, *J* = 13.4, 10.9, 5.8 Hz, 1H), 2.08 (ddd, *J* = 13.5, 11.0, 5.7 Hz, 1H), 1.36-1.22 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.79, 141.50, 139.55, 128.41, 127.57, 127.17, 116.67, 57.66, 38.92, 18.26, 14.70. **IR** (thin film): 2960, 2872, 1697, 1466, 1399, 1269, 924, 697 cm^{-1}. **EA** Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.67; H, 7.79. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 30:70 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.34 min (major), 3.61 min (minor), 98:2 er. **Specific rotation** $[\alpha]_D^{23}$: 13.2 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

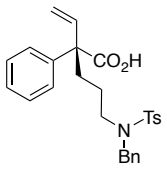
(*S*)-1-vinyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (3k)



Following general procedure **A**, 1-vinylidene-1,2,3,4-tetrahydronaphthalene (94 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 24 h. After Workup **A** (the hydrolysis reaction using trifluoroacetic acid was run at room temperature for 3 h), the title compound was obtained as a pale yellow solid (1st run: 55 mg, 54% yield, 99:1 er; 2nd run: 65 mg, 64% yield, 99:1 er). **m.p.** 57.3-57.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22-7.11 (m, 4H), 6.20 (dd, *J* =

17.4, 10.6 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 4.72 (d, J = 17.4 Hz, 1H), 2.88-2.74 (m, 2H), 2.37 (ddd, J = 12.9, 9.1, 3.8 Hz, 1H), 1.94 (ddd, J = 13.0, 6.6, 3.6 Hz, 1H), 1.88-1.74 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.58, 142.02, 137.48, 134.57, 130.59, 129.42, 127.29, 125.71, 116.85, 54.44, 33.61, 29.64, 18.98. **IR** (thin film): 2935, 2638, 1695, 1448, 1405, 1265, 923, 733 cm^{-1}. **EA** Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.04; H, 6.86. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH: $scCO_2$ to 15:85 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.78 min (minor), 4.33 min (major), 99:1 er. **Specific rotation** $[\alpha]_D^{23}$: 40.5 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

(*S*)-5-((*N*-benzyl-4-methylphenyl)sulfonamido)-2-phenyl-2-vinylpentanoic acid (3l)

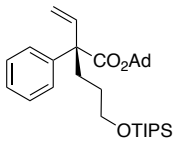


Following general procedure **A**, *N*-benzyl-4-methyl-*N*-(4-phenylhexa-4,5-dien-1-yl)benzenesulfonamide (230 mg, 0.55 mmol, 1.1 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 21 h. Then the reaction mixture was allowed to cool to room temperature, and the cap of the reaction tube was removed. While the reaction mixture was stirred at room temperature, sat. NH_4F in MeOH (10 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred with the tube uncapped at room temperature for 30 min, then the mixture was transferred to a 100 mL round bottom flask, the tube was rinsed with EtOAc, and then the mixture was concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in EtOAc, and then was filtered through a short plug of basic activated alumina (~2.5 g) eluting with EtOAc (~10 mL). The resulting solution was collected in a 20 mL scintillation vial, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue

was immediately purified by silica gel column chromatography eluting with 0-6% acetone/hexane. Product-containing fractions were combined and then concentrated *in* vacuo with the aid of a rotary evaporator. The residue was diluted with CH_2Cl_2 and transferred to a reaction tube (Fisherbrand, 16*125 mm, part no.1495935A). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator and the reaction tube was left under high vacuum for 20 min. CH_2Cl_2 (1.0 mL) and a magnetic stir bar were added to the tube. While the solution was stirred at room temperature, trifluoroacetic acid (0.38 mL, 5.0 mmol, 10 equiv) was added dropwise via a 1 mL syringe. The tube was capped (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15) and the mixture was stirred at room temperature for 3 h. The mixture was concentrated *in vacuo* with the aid of a rotary evaporator, and then purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0-2.5% MeOH/CH_2Cl_2). The title compound was obtained as a pale yellow liquid (1st run: 180 mg, 78% yield, 99:1 er; 2nd run: 180 mg, 78% yield, 99:1 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.34-7.25 (m, 8H), 7.20-7.15 (m, 4H), 6.17 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.29 (d, *J* = 10.9 Hz, 1H), 4.99 (d, *J* = 17.7 Hz, 1H), 4.25 (s, 2H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.94-1.79 (m, 2H), 1.32-1.20 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.71, 143.31, 140.89, 138.69, 137.11, 136.26, 129.83, 128.67, 128.54, 128.49, 127.88, 127.34, 127.31, 127.28, 117.08, 57.10, 51.83, 48.01, 33.42, 23.33, 21.65. **IR** (thin film): 3026, 2923, 1733, 1699, 1495, 1333, 1154, 928 cm^{-1}. **HRMS** Calcd. m/z for $C_{27}H_{30}NO_4S^+$ $[M+H]^+$: 464.1890; found 464.1887. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 15:85 MeOH: $scCO_2$ to 40:60 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 5.46 min (minor), 5.64 min

(major), 99:1 er. **Specific rotation** $[\alpha]_D^{24}$: −3.7 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

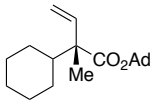
adamantan-1-yl (*S*)-2-phenyl-5-((triisopropylsilyl)oxy)-2-vinylpentanoate (3m)



Following general procedure **A**, triisopropyl((4-phenylhexa-4,5-dien-1-yl)oxy)silane (198 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 40 °C for 20 h. Then the reaction mixture was allowed to cool to room temperature, and the cap of the reaction tube was removed. The reaction mixture was diluted with EtOAc (2 mL). While the reaction mixture was stirred at room temperature, aq. sat. $NaHCO_3$ (5 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was transferred to a 125 mL separatory funnel containing brine (30 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in EtOAc, and then was filtered through a short plug of basic activated alumina (~2.5 g) eluting with EtOAc (~10 mL). The resulting solution was collected in a 20 mL scintillation vial, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was immediately purified by silica gel column chromatography (~30 g silica gel, diameter of the column ~2 cm, length of the packed column ~18 cm, the sample was loaded onto silica gel as a solution in hexane) with a gradient of hexane (200 mL) → hexane/Et_2O = [200:1 (200 mL) → 150:1 (450 mL) → 70:1 (140 mL)] (the product on TLC was visualized with $KMnO_4$ stain). The title compound was obtained as a colorless liquid (1st run: 192 mg, 75% yield, 98.5:1.5 er; 2nd run: 193 mg, 76% yield, 98.5:1.5 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H), 7.26-7.21

(m, 1H), 6.39 (dd, J = 17.7, 10.9 Hz, 1H), 5.27 (dd, J = 10.9, 0.9 Hz, 1H), 5.05 (dd, J = 17.7, 0.9 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 2.26-2.12 (m, 5H), 2.08 (d, J = 2.8 Hz, 6H), 1.65 (br, 6H), 1.55-1.46 (m, 2H), 1.13-1.07 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.29, 142.89, 140.56, 128.15, 127.40, 126.55, 115.59, 81.06, 63.83, 57.86, 41.24, 36.33, 32.99, 30.94, 28.59, 18.20, 12.14. **IR** (thin film): 2940, 2911, 2864, 1723, 1458, 1234, 1102, 882 cm^{-1}. **EA** Calcd. for $C_{32}H_{50}O_3Si$: C, 75.24; H, 9.87. Found: C, 75.30; H, 10.03. **SFC** analysis: OD-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 2:98 IPA: $scCO_2$ to 7:93 IPA: $scCO_2$ linear gradient over 18 min with 1 min hold time, 2.50 mL/min), 13.75 min (minor), 14.61 min (major), 98.5:1.5 er. **Specific rotation** $[\alpha]_D^{24}$: 1.9 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

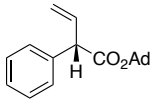
adamantan-1-yl (*S*)-2-cyclohexyl-2-methylbut-3-enoate (3n)



General procedure **B** was followed, except THF was used as solvent and the reaction was carried out at room temperature for 24 h. Buta-2,3-dien-2-ylcyclohexane (82 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. After Workup **B** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/EtOAc = [80:1 (160 mL) → 60:1 (120 mL) → 40:1 (120 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 115 mg, 73% yield, 94.5:5.5 er; 2nd run: 107 mg, 68% yield, 94.5:5.5 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.97 (dd, J = 17.6, 10.8 Hz, 1H), 5.08 (dd, J = 10.8, 1.1 Hz, 1H), 5.02 (dd, J = 17.6, 1.1 Hz, 1H), 2.15 (br, 3H), 2.09 (d, J = 2.9 Hz, 6H), 1.76-1.69 (m, 3H), 1.66-1.51 (m, 9H), 1.29-1.15 (m, 2H), 1.14-0.98 (m, 5H), 0.91 (qd, J = 12.5, 3.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.91, 142.06, 113.78, 80.33, 53.02, 45.45, 41.43, 36.39,

30.96, 28.19, 27.58, 27.06, 27.02, 26.74, 15.14. **IR** (thin film): 2909, 2851, 1718, 1450, 1228, 1102, 1056, 912 cm^{-1}. **EA** Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.92; H, 10.31. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 20:80 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.47 min (minor), 3.59 min (major), 94.5:5.5 er. **Specific rotation** $[\alpha]_D^{24}$: −26.9 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

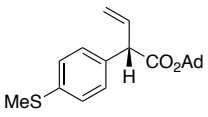
adamantan-1-yl (*S*)-2-phenylbut-3-enoate (3o)



Following general procedure **B**, propa-1,2-dien-1-ylbenzene (70 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 0 °C for 7 h. After Workup **B** and purification by column chromatography with a gradient of hexane (200 mL) → hexane/Et_2O = [100:1 (100 mL) → 80:1 (80 mL) → 70:1 (350 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 101 mg, 68% yield, 93:7 er; 2nd run: 107 mg, 72% yield, 92.5:7.5 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.30-7.25 (m, 1H), 6.20 (ddd, *J* = 17.2, 10.2, 8.1 Hz, 1H), 5.20 (dt, *J* = 10.2, 1.0 Hz, 1H), 5.16 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.22 (d, *J* = 8.1 Hz, 1H), 2.17 (br, 3H), 2.11 (d, *J* = 2.8 Hz, 6H), 1.67 (br, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.43, 138.85, 136.50, 128.67, 128.06, 127.17, 117.04, 81.34, 57.05, 41.31, 36.29, 30.96. **IR** (thin film): 3028, 2909, 2851, 1725, 1453, 1154, 1053, 696 cm^{-1}. **EA** Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.10; H, 8.30. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 15:85 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.73 min (minor), 5.11 min (major),

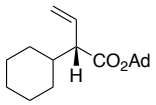
93:7 er. **Specific rotation** $[\alpha]_D^{24}$: 26.0 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

adamantan-1-yl (*S*)-2-methyl-2-(4-(methylthio)phenyl)but-3-enoate (3p)



Following general procedure **B**, methyl(4-(propa-1,2-dien-1-yl)phenyl)sulfane (97 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 0 °C for 6 h. After Workup **B** and purification by column chromatography with a gradient of hexane (200 mL) → hexane/Et_2O = [100:1 (100 mL) → 80:1 (80 mL) → 70:1 (70 mL) → 60:1 (120 mL) → 50:1 (200 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 127 mg, 74% yield, 93.5:6.5 er; 2nd run: 118 mg, 69% yield, 93:7 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (s, 4H), 6.14 (ddd, *J* = 17.2, 10.2, 8.0 Hz, 1H), 5.17 (dt, *J* = 10.2, 1.1 Hz, 1H), 5.12 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.15 (dt, *J* = 8.0, 0.9 Hz, 1H), 2.47 (s, 3H), 2.14 (br, 3H), 2.07 (d, *J* = 2.9 Hz, 6H), 1.64 (br, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.33, 137.20, 136.34, 135.74, 128.57, 126.94, 117.12, 81.44, 56.47, 41.31, 36.28, 30.96, 16.05. **IR** (thin film): 2909, 2851, 1723, 1493, 1296, 1160, 1053, 921 cm^{-1}. **EA** Calcd. for $C_{22}H_{28}O_2S$: C, 73.64; H, 7.65. Found: C, 73.79; H, 7.70. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.85 min (minor), 5.36 min (major), 93:7 er. **Specific rotation** $[\alpha]_D^{24}$: 35.5 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

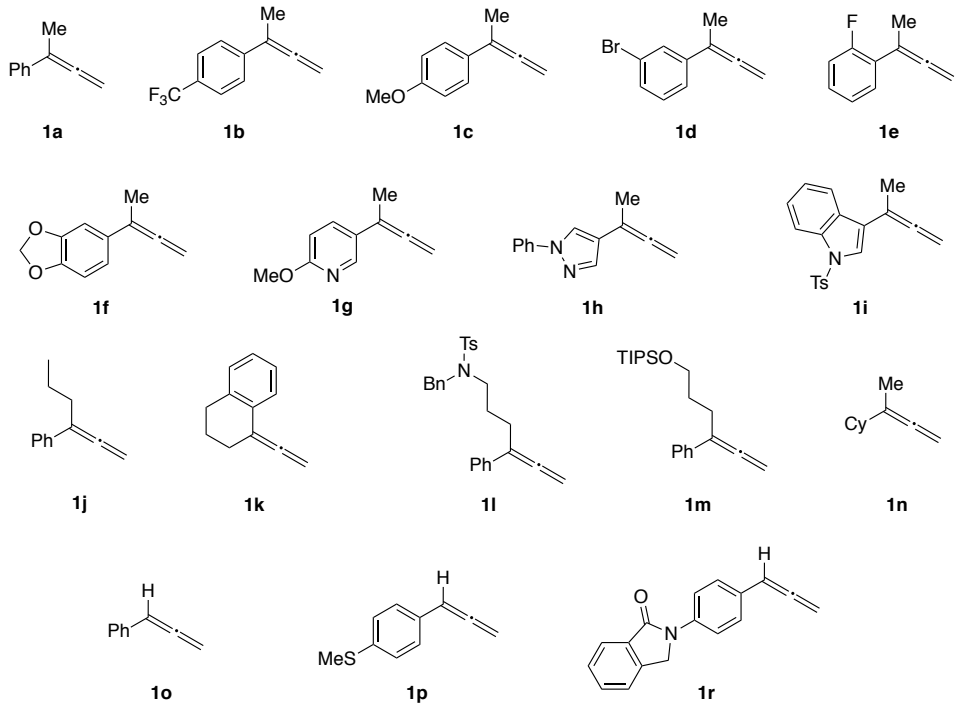
adamantan-1-yl (*S*)-2-cyclohexylbut-3-enoate (3q)



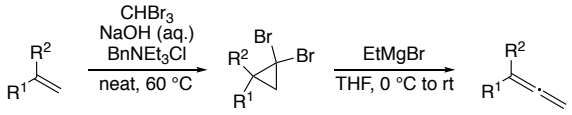
Following general procedure **B**, propa-1,2-dien-1-ylcyclohexane (73 mg, 0.60 mmol, 1.2 equiv) and 1-adamantyl fluoroformate (99 mg, 0.50 mmol, 1.0 equiv) were used. The reaction was run at 0 °C for 6 h. After Workup **B** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/EtOAc = [80:1 (160 mL) → 60:1 (120 mL) → 40:1 (120 mL)] (the product on TLC was visualized with $KMnO_4$ stain), the title compound was obtained as a colorless liquid (1st run: 116 mg, 77% yield, 93:7 er; 2nd run: 126 mg, 83% yield, 93:7 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 17.1, 9.9 Hz, 1H), 5.10-5.03 (m, 2H), 2.60 (t, *J* = 9.0 Hz, 1H), 2.15 (br, 3H), 2.10 (d, *J* = 2.7 Hz, 6H), 1.73-1.56 (m, 12H), 1.30-0.97 (m, 4H), 0.90-0.80 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.08, 136.07, 117.41, 80.53, 58.62, 41.50, 40.11, 36.37, 31.19, 30.97, 30.28, 26.48, 26.30, 26.27. **IR** (thin film): 2910, 2850, 1724, 1449, 1241, 1164, 1055, 914 cm^{-1}. **EA** Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.49; H, 10.00. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 15:85 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.33 min (minor), 4.72 min (major), 93:7 er. **Specific rotation** $[\alpha]_D^{24}$: −39.6 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

2.4.4 Preparation of Allene Substrates

All of the allenes used in this chapter are listed below. **1a-c**[116], **1d-e**[117], **1f**[116], **1g**[118], **1j**[119], **1k**[117], **1m**[120], **1n**[116], **1o**[120] are known compounds and were prepared by following previously reported procedures.



General Procedure D[121]



Preparation of 1,1-dibromocyclopropanes:

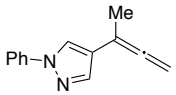
A 50 mL round bottom flask containing a magnetic stir bar was charged with the alkene. Then, $BnNEt_3Cl$ and bromoform were added. While the mixture was vigorously stirred, 25 M aq. NaOH was added dropwise. Then the flask was sealed with a rubber septum, attached to a balloon filled with air by piercing the rubber septum with a needle attached to the balloon, and submerged in an oil bath preheated to 60 °C. The reaction mixture was stirred vigorously at 60 °C for 24 h. The reaction mixture was then allowed to cool to room temperature, the septum was removed, and the contents of the flask were transferred to a separatory funnel containing CH_2Cl_2

(100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel to give the corresponding 1,1-dibromocyclopropane.

Preparation of allenes:

A 50 mL round bottom flask containing a magnetic stir bar was charged with 1,1-dibromocyclopropane, sealed with a rubber septum, and connected to a Schlenk line by piercing the septum with a needle attached to a rubber hose. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times). The argon inlet was replaced with a balloon filled with argon. Anhydrous THF was added via syringe. The flask was cooled to 0 °C with the aid of an ice/water bath. Once cool, EtMgBr (3 M in Et_2O) was added dropwise at 0 °C via syringe. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 1 h. After the reaction mixture had stirred for 1 h, the rubber septum was removed. The flask was cooled to 0 °C with the aid of an ice/water bath, and the reaction mixture was quenched with sat. aq. NH_4Cl (10 mL). Next, the contents of the flask were transferred to a separatory funnel containing water (40 mL) and Et_2O (40 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel to give the corresponding allene (Note: Once prepared, the allenes were stored in the glovebox freezer at −30 °C).

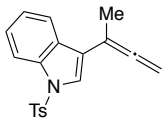
4-(buta-2,3-dien-2-yl)-1-phenyl-1H-pyrazole (1h)



A 250 mL round bottom flask containing a magnetic stir bar was sealed with a rubber septum and connected to a Schlenk line by piercing the septum with a needle attached to a rubber hose. The flask was evacuated and backfilled with argon (this process was repeated a total of three times. The argon inlet was replaced with a balloon filled with argon. Anhydrous THF (50 mL) was added via syringe. The septum was removed and Ph_3PCH_3Br (30.0 mmol, 1.2 equiv, 10.7 g) was added quickly at once. Then the flask was immediately sealed with the septum, purged with argon for 1 min, and submerged in an ice/water bath. While the reaction mixture was stirred at 0 °C, the septum was removed and KO^{t}Bu (30.0 mmol, 1.2 equiv, 3.37 g) was added in one portion. The flask was immediately sealed with the septum. The reaction mixture was stirred at 0 °C for 30 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 30 min. Next, the reaction mixture was cooled to 0 °C with the aid of an ice/water bath, and 1-(1-phenyl-1H-pyrazol-4-yl)ethan-1-one (25.0 mmol, 1.0 equiv, 4.66 g) was added portionwise by temporarily removing, then replacing the septum. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and then stirred at room temperature overnight. The septum was removed, the reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator, and then Et_2O (50 mL) was added. The resulting mixture was filtered through a plug of silica gel (~15 g) using a fritted funnel and washed with additional Et_2O (~150 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator, and then purified by column chromatography on silica gel (eluted with Et_2O/pentane = 0-7%) to give 1-phenyl-4-(prop-1-en-2-yl)-1H-pyrazole as a colorless liquid (4.55 g, 99% yield).

Following general procedure **D**, 1-phenyl-4-(prop-1-en-2-yl)-1H-pyrazole (3.68 g, 1.0 equiv, 20.0 mmol), bromoform (5.2 mL, 3.0 equiv, 60.0 mmol), $BnNEt_3Cl$ (91 mg, 0.02 equiv, 0.4 mmol), and 25 M NaOH (3.2 mL) were used to prepare 4-(2,2-dibromo-1-methylcyclopropyl)-1-phenyl-1H-pyrazole (2.86 g, 40% yield). Then 4-(2,2-dibromo-1-methylcyclopropyl)-1-phenyl-1H-pyrazole (1.42 g, 1.0 equiv, 4.0 mmol), EtMgBr (3 M in Et_2O, 1.3 equiv, 1.7 mL), and THF (8 mL) were used in the next step. After purification by column chromatography on silica gel (eluting with Et_2O/pentane = 0-10%), the title compound was obtained as a yellow liquid (0.74 g, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69-7.67 (m, 3H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 5.00 (q, *J* = 3.1 Hz, 2H), 2.05 (t, *J* = 3.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.90, 140.25, 139.24, 129.54, 126.45, 123.25, 121.81, 119.01, 92.05, 76.80, 17.57. **IR** (thin film): 3049, 2972, 1945, 1600, 1503, 1409, 1270, 952 cm^{-1}. **HRMS** Calcd. m/z for $C_{13}H_{13}N_2^+$ $[M+H]^+$: 197.1073; found 197.1074.

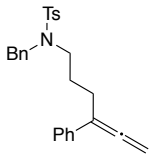
3-(buta-2,3-dien-2-yl)-1-tosyl-1H-indole (1i)



Following general procedure **D**, 3-(prop-1-en-2-yl)-1-tosyl-1H-indole[10] (6.23 g, 1.0 equiv, 20.0 mmol), bromoform (10.5 mL, 6.0 equiv, 120.0 mmol), $BnNEt_3Cl$ (137 mg, 0.03 equiv, 0.6 mmol), and 25 M NaOH (3.2 mL) were used to prepare 3-(2,2-dibromo-1-methylcyclopropyl)-1-tosyl-1H-indole (7.17 g, 74% yield). Then 3-(2,2-dibromo-1-methylcyclopropyl)-1-tosyl-1H-indole (2.90 g, 1.0 equiv, 6.0 mmol), EtMgBr (3 M in Et_2O, 1.5 equiv, 3.0 mL), and THF (12 mL) were used in the next step (Note: CH_2Cl_2 was used in the extraction steps instead of Et_2O). After purification by column chromatography on silica gel (eluting with hexane/CH_2Cl_2 = 3:1 → 2.5:1), the title compound was obtained as a white solid (1.07 g, 55% yield). **m.p.** 122.5-123.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz,

1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.44 (s, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.23-7.19 (m, 3H), 5.13 (q, *J* = 2.4 Hz, 2H), 2.33 (s, 3H), 2.13 (t, *J* = 2.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.27, 145.07, 135.72, 135.27, 130.01, 129.15, 126.93, 125.01, 123.36, 122.50, 121.40, 119.05, 113.67, 93.62, 77.54, 21.71, 18.67. **IR** (thin film): 2922, 1943, 1596, 1447, 1370, 1173, 1134, 714 cm^{-1}. **HRMS** Calcd. m/z for $C_{19}H_{18}NO_2S^+$ $[M+H]^+$: 324.1053; found 324.1052.

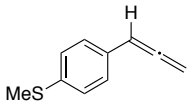
***N*-benzyl-4-methyl-*N*-(4-phenylhexa-4,5-dien-1-yl)benzenesulfonamide (1l)**



A 50 mL round bottom flask containing a magnetic stir bar was charged with PPh_3 (918 mg, 1.0 equiv, 3.5 mmol) and BnNHTs (1.10 g, 1.2 equiv, 4.2 mmol), sealed with a septum and connected to a Schlenk line by piercing the septum with a needle attached to a rubber hose. The flask was evacuated and backfilled with argon (this process was repeated for a total of three times), and then attached to a balloon filled with argon. Anhydrous THF (10 mL) and 4-phenylhexa-4,5-dien-1-ol[120] (610 mg, 1.0 equiv, 3.5 mmol) were added via syringe. While the reaction mixture was stirred at 0 °C, diisopropyl azodicarboxylate (849 mg, 1.2 equiv, 4.2 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. Then the septum was removed, and aq. NH_4Cl and water (30 mL) were added. The contents were transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc = 10:1~9:1~6:1) to give the title compound as a white solid. **m.p.** 74.2-74.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2

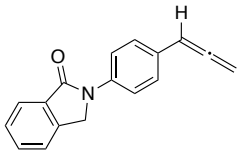
Hz, 2H), 7.33-7.20 (m, 12H), 4.98 (t, *J* = 3.4 Hz, 2H), 4.35 (s, 2H), 3.24-3.20 (m, 2H), 2.45 (s, 3H), 2.23 (tt, *J* = 7.2, 3.4 Hz, 2H), 1.62 (p, *J* = 7.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.22, 143.29, 137.24, 136.58, 136.06, 129.83, 128.69, 128.48, 128.44, 127.86, 127.32, 126.80, 125.99, 104.14, 78.88, 52.04, 47.74, 26.57, 26.06, 21.67. **IR** (thin film): 3030, 2922, 1940, 1597, 1494, 1453, 1337, 1157, 695 cm^{-1}. **EA** Calcd. for $C_{26}H_{27}NO_2S$: C, 74.79; H, 6.52. Found: C, 74.49; H, 6.45.

methyl(4-(propa-1,2-dien-1-yl)phenyl)sulfane (1p)



Following general procedure **D**, methyl(4-vinylphenyl)sulfane[123] (4.51 g, 1.0 equiv, 30.0 mmol), bromoform (7.9 mL, 3.0 equiv, 90.0 mmol), $BnNEt_3Cl$ (137 mg, 0.02 equiv, 0.6 mmol), and 25 M NaOH (4.8 mL) were used to prepare (4-(2,2-dibromocyclopropyl)phenyl)(methyl)sulfane (1.06 g, 11% yield). Then (4-(2,2-dibromocyclopropyl)phenyl)(methyl)sulfane (1.06 g, 1.0 equiv, 3.3 mmol), EtMgBr (3 M in Et_2O, 1.3 equiv, 1.4 mL), and THF (7 mL) were used in the next step. After purification by column chromatography on silica gel (eluting with Et_2O/pentane = 0-0.5%), the title compound was obtained as a pale yellow liquid (495 mg, 92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 4H), 6.13 (t, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 2H), 2.48 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.88, 136.98, 130.98, 127.21, 127.09, 93.62, 79.13, 16.20. **IR** (thin film): 2978, 2918, 1940, 1595, 1492, 1433, 1097, 853 cm^{-1}. **EA** Calcd. for $C_{10}H_{10}S$: C, 74.03; H, 6.21. Found: C, 73.84; H, 6.13.

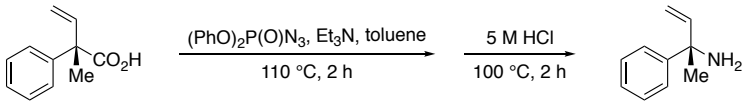
2-(4-(propa-1,2-dien-1-yl)phenyl)isoindolin-1-one (1r)



Following general procedure **D**, 2-(4-vinylphenyl)isoindolin-1-one[124] (1.67 g, 1.0 equiv, 7.1 mmol), bromoform (3.7 mL, 6.0 equiv, 42.6 mmol), $BnNEt_3Cl$ (48 mg, 0.03 equiv, 0.2 mmol), and 25 M NaOH (1.1 mL) were used to prepare 2-(4-(2,2-dibromocyclopropyl)phenyl)isoindolin-1-one (1.63 g, 56% yield). Then 2-(4-(2,2-dibromocyclopropyl)phenyl)isoindolin-1-one (1.63 g, 1.0 equiv, 4.0 mmol), EtMgBr (3 M in Et_2O, 1.3 equiv, 1.7 mL), and THF (8 mL) were used in the next step (Note: CH_2Cl_2 was used in the extraction steps instead of Et_2O). After purification by column chromatography on silica gel (eluting with hexane/CH_2Cl_2/EtOAc = 7:2:1), the title compound was obtained as a pale brown solid (493 mg, 50% yield). **m.p.** 159.0-160.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93-7.91 (m, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.61-7.57 (m, 1H), 7.52-7.48 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.17 (t, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 6.8 Hz, 2H), 4.85 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.00, 167.56, 140.16, 138.43, 133.39, 132.21, 130.10, 128.55, 127.50, 124.27, 122.73, 119.64, 93.54, 79.14, 50.85. **IR** (thin film): 3041, 1938, 1682, 1606, 1515, 1392, 1153, 730 cm^{-1}. **HRMS** Calcd. m/z for $C_{17}H_{14}NO^+$ $[M+H]^+$: 248.1070; found 248.1066.

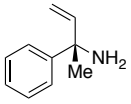
2.4.5 Product Derivatization

2.4.5.1 Curtius Rearrangement



3a **6**

(*S*)-2-phenylbut-3-en-2-amine (6)

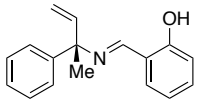


An oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no.1495935A) containing a magnetic stir bar was charged with **3a** (53 mg, 0.30

mmol, 1.0 equiv). The reaction tube was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into a nitrogen-filled glovebox. The cap was removed, and anhydrous toluene (2.7 mL) and triethylamine (63 μL, 0.45 mmol, 1.5 equiv) were added to the tube via syringe. While the solution was stirred at room temperature, diphenyl phosphorazidate (124 mg, 0.45 mmol, 1.5 equiv) was added dropwise. The tube was capped, attached to a balloon (N_2), and then removed from the glovebox. The tube was submerged in an oil bath preheated to 110 °C. The reaction mixture was stirred at 110 °C for 2 h. The reaction mixture was then allowed to cool to room temperature and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was transferred to a separatory funnel containing Et_2O (30 mL) and water (30 mL), and then the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was filtered through a short plug of silica gel eluting with hexane/EtOAc = 10:1 (~10 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator, transferred to a reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C), and concentrated again. Afterwards, 5 M HCl (0.18 mL) was added via syringe. The tube was capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), attached to a balloon (air), and submerged in an oil bath preheated to 100 °C. The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was allowed to cool to room temperature and transferred to a separatory funnel. 1 M NaOH (5 mL) and brine (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel

(~15 g) [50mL CH_2Cl_2 initially; then CH_2Cl_2/(2 M NH_3 in MeOH) = 25:1, 100mL; then CH_2Cl_2/(2 M NH_3 in MeOH) = 10:1, 100mL]. The title compound was obtained as a pale yellow liquid (1st run: 34 mg, 77% yield, 99:1 er, 100% es; 2nd run: 32 mg, 73% yield, 99:1 er, 100% es). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.25-7.21 (m, 1H), 6.13 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.21 (dd, *J* = 17.3, 0.9 Hz, 1H), 5.10 (dd, *J* = 10.5, 0.8 Hz, 1H), 1.86 (br, 2H), 1.57 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.59, 147.17, 128.36, 126.71, 125.70, 111.10, 56.87, 29.87. The spectral data match those previously reported in the literature.[125] **Specific rotation** $[\alpha]_D^{23}$: −25.2 (c = 1.0, $CHCl_3$).

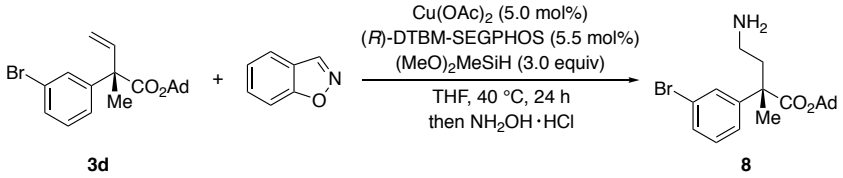
(*S*,*E*)-2-(((2-phenylbut-3-en-2-yl)imino)methyl)phenol (6')



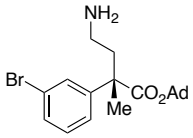
In order to determine the enantiomeric ratio of **6**, the title compound was prepared. A reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with **6** (15 mg, 0.10 mmol, 1.0 equiv) and 2-hydroxybenzaldehyde (21 μL, 0.20 mmol, 2.0 equiv). Isopropanol (0.2 mL) was added via syringe. The tube was capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60) and submerged in an oil bath preheated to 60 °C. The reaction mixture was stirred at 60 °C overnight. The reaction mixture was allowed to cool to room temperature and directly purified by preparative thin layer chromatography (hexane/EtOAc/Et_3N = 100:3:1). The title compound was obtained as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.89 (br, 1H), 8.27 (s, 1H), 7.43-7.27 (m, 6H), 7.23 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.04-7.02 (m, 1H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H), 6.11 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.39 (dd, *J* = 10.6, 0.8 Hz, 1H), 5.29 (dd, *J* = 17.4, 0.8 Hz, 1H), 1.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.58, 161.58, 142.92, 132.83, 132.05, 128.63, 127.37, 126.93, 118.75, 117.34, 115.49, 67.85,

27.65. **IR** (thin film): 3058, 2980, 2932, 1624, 1579, 1493, 1280, 928 cm^{-1}. **HRMS** Calcd. m/z for $C_{17}H_{18}NO^+$ $[M+H]^+$: 252.1383; found 252.1386. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 2:98 MeOH (0.1% DEA): $scCO_2$ to 7:93 MeOH (0.1% DEA): $scCO_2$ linear gradient over 10 min with 1 min hold time, 2.50 mL/min), 5.51 min (major), 6.13 min (minor), 99:1 er. **Specific rotation** $[\alpha]_D^{24}$: −49.1 (c = 1.0, $CHCl_3$).

2.4.5.2 Hydroamination



adamantan-1-yl (*S*)-4-amino-2-(3-bromophenyl)-2-methylbutanoate (8)



An oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (3.6 mg, 0.020 mmol) and (*R*)-DTBM-SEGPHOS (25.9 mg, 0.022 mmol). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed, and anhydrous THF (0.40 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at room temperature. Then the cap was removed and DMMS (0.15 mL, 1.2 mmol) was added in one portion via a 1 mL syringe. The mixture was stirred for another 10 min at room temperature to prepare the CuH stock solution.

A second oven-dried screw-cap reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and transferred into the glovebox. The cap was removed,

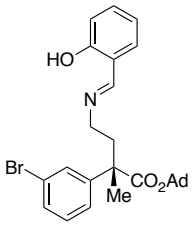
and 1,2-Benzisoxazole (78 μL) and anhydrous THF (0.30 mL) were added to the tube via syringe to prepare the 1,2-benzisoxazole stock solution. The tube was capped and then gently swirled to mix the solution.

A third oven-dried screw-cap reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) containing a magnetic stir bar was charged with alkene **3d** (117 mg, 0.3 mmol, 1.0 equiv), loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and then transferred into the glovebox. The cap was removed, and the CuH stock solution (0.41 mL) was added via a 1 mL syringe to the reaction tube in one portion. While the reaction mixture was stirred at room temperature, 1,2-benzisoxazole (6 μL, 0.06 mmol) was added over 1 min via microsyringe. The reaction tube was capped and the septum was punctured with a 4" needle attached to a 1 mL syringe containing the 1,2-benzisoxazole stock solution (0.19 mL, contains 0.39 mmol 1,2-benzisoxazole). The reaction tube was then taken out of the glove box. While the reaction mixture was stirred at 40 °C, the 1,2-benzisoxazole solution was added slowly via syringe pump at a rate of 19 μL/h (Note: The tip of the needle should touch the wall of the reaction tube during the slow addition of 1,2-benzisoxazole). The reaction mixture was allowed to stir at 40 °C for a total of 24 h.

Next, the reaction mixture was cooled to 0 °C, the cap was removed, and $NH_2OH{\cdot}HCl$ (0.5 M in MeOH, 1.2 mL) was added dropwise to the tube (Caution: gas evolution observed). The mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* with the aid of a rotary evaporator. 0.5 M aq. NaOH (10 mL) was added and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a

rotary evaporator. The residue was purified by column chromatography on silica gel (~15 g) [eluting with CH_2Cl_2 100mL; CH_2Cl_2/(2 M NH_3 in MeOH) = 15:1, 150 mL; 10:1, 150 mL]. Product-containing fractions were collected, concentrated and redissolved in CH_2Cl_2/(2 M NH_3 in MeOH) = 6:1 (2 mL). The resulting solution was filtered through a short plug of basic alumina (~1.5 g) eluting with ~10 mL 6:1 CH_2Cl_2/(2 M NH_3 in MeOH). The resulting solution was concentrated to give the title compound as a colorless liquid (1st run: 60 mg, 49% yield, 99:1 er, 100% es; 2nd run: 70 mg, 57% yield, 99:1 er, 100% es). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (t, *J* = 1.8 Hz, 1H), 7.37-7.34 (m, 1H), 7.26-7.23 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 2.66 (br, 2H), 2.17-2.10 (m, 4H), 2.04-1.97 (m, 7H), 1.73 (br, 2H), 1.63 (t, *J* = 2.8 Hz, 6H), 1.48 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.28, 146.77, 129.95, 129.80, 129.27, 124.80, 122.64, 81.31, 49.95, 42.98, 41.22, 38.46, 36.27, 30.93, 23.21. **IR** (thin film): 2910, 2852, 1719, 1564, 1457, 1243, 1053, 872 cm^{-1}. **HRMS** Calcd. m/z for $C_{21}H_{29}NO_2Br^+$ $[M+H]^+$: 406.1376; found 406.1384. **Specific rotation** $[\alpha]_D^{24}$: 14.8 (c = 1.0, $CHCl_3$).

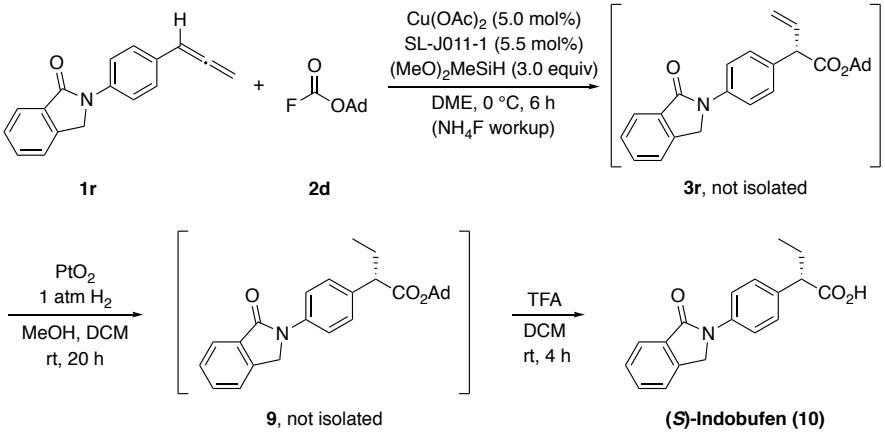
adamantan-1-yl (*S*)-2-(3-bromophenyl)-4-(((*E*)-2-hydroxybenzylidene)amino)-2-methylbutanoate (8')



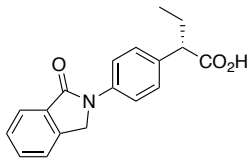
In order to determine the enantiomeric ratio of **8**, the title compound was prepared. A reaction tube (Fisherbrand, 13*100 mm, part no. 1495935C) containing a magnetic stir bar was charged with **8** (20 mg, 0.05 mmol, 1.0 equiv) and 2-hydroxybenzaldehyde (10 μL, 0.10 mmol, 2.0 equiv). Isopropanol (0.1 mL) was added via syringe. The tube was capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60) and submerged in an oil bath preheated to 60 °C. The reaction mixture was stirred at 60 °C overnight. The reaction

mixture was allowed to cool to room temperature and directly purified by preparative thin layer chromatography (hexane/EtOAc/Et_3N = 100:10:0.5). The title compound was obtained as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.29 (br, 1H), 8.28 (s, 1H), 7.48 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.22-7.18 (m, 2H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 3.53 (tq, *J* = 11.0, 6.2 Hz, 2H), 2.38-2.31 (m, 1H), 2.29-2.21 (m, 1H), 2.15 (br, 3H), 2.06 (br, 6H), 1.64 (br, 6H), 1.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.00, 165.23, 161.21, 146.25, 132.31, 131.28, 130.05, 129.98, 129.34, 124.88, 122.74, 118.91, 118.67, 117.12, 81.55, 56.14, 50.09, 41.26, 40.42, 36.26, 30.94, 23.36. **IR** (thin film): 2910, 2852, 1720, 1632, 1458, 1279, 1053, 755 cm^{-1}. **HRMS** Calcd. m/z for $C_{28}H_{33}NO_3Br^+$ $[M+H]^+$: 510.1638; found 510.1642. **SFC** analysis: OJ-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 20:80 MeOH (0.1% DEA): $scCO_2$ to 40:60 MeOH (0.1% DEA): $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.38 min (minor), 4.76 min (major), 99:1 er. **Specific rotation** $[\alpha]_D^{24}$: 24.7 (c = 1.0, $CHCl_3$).

2.4.5.3 Synthesis of (*S*)-Indobufen



(*S*)-Indobufen (10)



An oven-dried screw-cap reaction tube (Fisherbrand, 20*125 mm, part no. 1495937A) containing a magnetic stir bar was charged with $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 0.050 equiv). The reaction tube was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18), and then transferred into a nitrogen-filled glovebox. The cap was removed and SL-J011-1 (18.7 mg, 0.0275 mmol, 0.055 equiv), 2-(4-(propa-1,2-dien-1-yl)phenyl)isoindolin-1-one **1r** (124 mg, 0.50 mmol, 1.0 equiv), and 1-adamantyl fluoroformate **2d** (119 mg, 0.60 mmol, 1.2 equiv) were added to the tube. Anhydrous 1,2-dimethoxyethane (DME, 1.0 mL) was added via a 1 mL syringe. The tube was capped and the mixture was stirred for 10 min at room temperature. The reaction tube was removed from the glovebox, and then placed in an ice bath. Anhydrous DME (0.5 mL) was added via a 1 mL syringe to rinse the wall of the tube. The reaction mixture was stirred at 0 °C for 5 min, and then DMMS (0.18 mL, 1.50 mmol, 3.0 equiv) was added in one portion via a 1 mL syringe. The reaction mixture was stirred at 0 °C. After the reaction mixture had stirred at 0 °C for 6 h, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature, and the cap of the reaction tube was removed. While the reaction mixture was stirred at room temperature, sat. NH_4F in MeOH (10 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred with the tube uncapped in a well-ventilated hood at room temperature for 30 min, then transferred to a 100 mL round bottom flask with the aid of CH_2Cl_2, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in CH_2Cl_2, and then was filtered through a short plug of basic activated alumina (~2.5 g) eluting with 1:1 EtOAc/CH_2Cl_2 (~7 mL). The resulting solution was collected

in a reaction tube (Fisherbrand, 20*150 mm, part no. 1495937C), concentrated *in vacuo* with the aid of a rotary evaporator, and left under high vacuum overnight to give a crude mixture containing intermediate **3r**.

A magnetic stir bar was added to the reaction tube containing **3r**. The tube was capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18) and connected to a Schlenk line by piercing the septum with a needle attached to a rubber hose. The tube was evacuated and backfilled with argon (this process was repeated for a total of three times). PtO_2 (4.5 mg, 0.05 mmol) was added into the tube by temporarily removing the cap and then the tube was immediately recapped. Anhydrous CH_2Cl_2 (3.0 mL) and anhydrous MeOH (4.0 mL) were added via syringe. While the reaction mixture was stirred, the reaction tube was briefly evacuated using a needle connected to a Schlenk line until the solvent began to bubble. The Schlenk line was closed to vacuum, and the tube was then carefully backfilled with hydrogen by piercing the septum with a needle connected to a hydrogen-filled balloon. This evacuation-refill cycle was repeated a total of three times. The filled balloon was left attached to the tube at the end of the third cycle. The reaction mixture was then stirred at room temperature for 20 h. Then, the balloon was removed and an empty needle was inserted into the septum. Using a gentle stream of argon directed into the reaction mixture, the hydrogen in the headspace and reaction mixture was displaced. (*Caution: to ensure that hydrogen is fully removed, the solution should be carefully sparged with argon to reduce the risk of fire during the subsequent filtration*). After 5 min, the cap was removed. The mixture was poured onto a layer (in a fritted funnel) of Celite (a layer of sand was placed on top of Celite) and filtered to remove PtO_2. The Celite pad was washed with additional 1:1 EtOAc/CH_2Cl_2 (ca. 10 mL). (*Caution: during the filtration, solvent should be continuously added so that the Celite pad*

and other solids do not fully dry. PtO_2 at the top of the filter cake may ignite if not continuously covered with solvent. After the filtration was complete, the wet filter cake should be carefully transferred to a properly labeled waste bottle containing water.). After the filtration is complete, the resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator. The residue was transferred to a reaction tube (Fisherbrand, 16*125 mm, part no. 1495935A) with CH_2Cl_2, concentrated *in vacuo* with the aid of a rotary evaporator, and left under high vacuum for 20 min to give a crude mixture containing intermediate **9**.

CH_2Cl_2 (1.0 mL) and a magnetic stir bar were added to the reaction tube containing **9**. While the solution was stirred at room temperature, trifluoroacetic acid (0.38 mL, 5.0 mmol, 10 equiv) was added dropwise via syringe. The tube was capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-15425; Septum: Thermo Scientific B7995-15), and the mixture was stirred at room temperature for 4 h. The reaction mixture was then transferred to a 125 mL separatory funnel with CH_2Cl_2 (25 mL) and extracted with 1 M aq. NaOH (50 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 25 mL) and the organic layers were discarded. Next, 6 M aq. HCl (10 mL) was added to the aqueous layer, and the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved in CH_2Cl_2 and filtered through a short plug of silica gel (~0.3 g) eluting with 5:1 CH_2Cl_2/MeOH, and the resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a white solid (1st run: 115 mg, 78% yield, 92:8 er; 2nd run: 110 mg, 74% yield, 93:7 er). Duplicate experiments using fluoroformate **2d** as the limiting reagent was carried out following the same procedure except **1r** (148 mg, 0.60 mmol, 1.2 equiv) and **2d** (99 mg, 0.50 mmol, 1.0 equiv) were used in the first step. In the duplicate experiments,

the title compound was obtained as a white solid (1st run: 122 mg, 82% yield, 92:8 er; 2nd run: 131 mg, 89% yield, 92.5:7.5 er). **m.p.** 184.0-185.2 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.61-7.57 (m, 1H), 7.51-7.47 (m, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.83 (s, 2H), 3.48 (t, *J* = 7.7 Hz, 1H), 2.12 (dp, *J* = 14.8, 7.4 Hz, 1H), 1.83 (dp, *J* = 14.9, 7.4 Hz, 1H), 0.93 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.50, 167.73, 140.22, 138.75, 134.73, 133.20, 132.27, 128.98, 128.55, 124.34, 122.76, 119.84, 52.82, 50.91, 26.43, 12.23. **IR** (thin film): 2964, 2875, 1695, 1514, 1384, 1305, 1160, 732 cm^{-1}. **HRMS** Calcd. m/z for $C_{18}H_{18}NO_3^+$ $[M+H]^+$: 296.1281; found 296.1280. **SFC** analysis: OD-H (Chiralcel®, 4.6 x 250 mm, 5 μM particle size; 25:75 MeOH: $scCO_2$ to 30:70 MeOH: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.66 min (minor), 5.00 min (major), 92:8 er. **Specific rotation** $[\alpha]_D^{23}$: 44.3 (c = 1.0, $CHCl_3$). The absolute stereochemistry was assigned as (*S*) by analogy.

2.5 References and Notes

(1) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. *Nature* **2019**, *569*, 703−707.

(2) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729−6777.

(3) Li, C.; Ragab, S. S.; Liu, G.; Tang, W. *Nat. Prod. Rep.* **2020**, *37*, 276−292.

(4) Christoffers, J.; Baro, A. Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; Wiley-VCH, 2005.

(5) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev*. **2017**, *117*, 12564−12580.

(6) Das, J. P.; Marek, I. *Chem. Commun*. **2011***, 47*, 4593−4623.

(7) Quasdorf, K.; Overman, L. E. *Nature* **2014**, *516*, 181−191.

(8) Zeng, X.; Cao, Z.; Wang, Y.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330−7396.

(9) Hoyle, J. The Synthetic Uses of Carboxylic Acids and Their Derivatives. In *The Chemistry of Acid Derivatives*; Wiley: 1992. Vol. 2.

(10) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. International Patent WO 209243 (A1), Nov. 15, 2018.

(11) Hanessian, S.; Jennequin, T.; Boyer, N.; Babonneau, V.; Soma, U.; Mannoury la Cour, C.; Millan, M. J.; De Nanteuil, G. *ACS Med. Chem. Lett*. **2014**, *5*, 550−555.

(12) Knust, H.; Nettekoven, M.; Ratni, H.; Vifian, W.; Wu, X. International Patent WO 033995 (A1), Mar. 19, 2009.

(13) Fadel, A.; Canet, J.-L.; Salaün, J. *Tetrahedron: Asymmetry* **1993**, *4*, 27−30.

(14) *Bioactive Carboxylic Compound Classes: Pharmaceuticals and Agrochemicals*; Lamberth, C.; Dinges, J., Eds.; Wiley-VCH: 2016.

(15) Ramadan, M.; Goeters, S.; Watzer, B.; Krause, E.; Lohmann, K.; Bauer, R.; Hempel, B.; Imming, P. *J. Nat. Prod.* **2006**, *69*, 1041−1045.

(16) Gülcan, H. O.; Ünlü, S.; Dimoglo, A.; Şahin, Y.; Esiringu, I.; Erçetin, T.; Öz, D.; Şahin, M. F. *Arch. Pharm.* **2015**, *348*, 55−61.

(17) Corey, E. J.; Kürti, L. *Enantioselective Chemical Synthesis: Methods, Logic and Practice*; Direct Book Publishing, 2010.

(18) Zhu, S.; Zhou, Q. *Acc. Chem. Res*. **2017**, *50*, 988−1001.

(19) Zhang, X. P.; Cui, X. Asymmetric C−H Functionalization by Transition Metal-Catalyzed Carbene Transfer Reactions. In *Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: 2014; Vol 7, pp 86−120.

(20) Davies, H. M. L.; Liao, K. *Nat. Rev. Chem*. **2019**, *3*, 347−360.

(21) Qiu, H.; Li, M.; Jiang, L.; Lv, F.; Zan, L.; Zhai, C.; Doyle, M. P.; Hu, W. *Nat. Chem*. **2012**, *4*, 733−738.

(22) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359−369.

(23) Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.; Chi, Y. R. *J. Am. Chem. Soc*. **2016**, *138*, 7212−7215.

(24) Sandoval, B. A.; Meichan, A. J.; Hyster, T. K. *J. Am. Chem. Soc*. **2017**, *139*, 11313−11316.

(25) Cheng, Q.; Tu, H.; Zheng, C.; Qu, J.; Helmchen, G.; You, S. *Chem. Rev.* **2019**, *119*, 1855−1969.

(26) Schwarz, K. J.; Amos, J. L.; Klein, C.; Do, D. T.; Snaddon, T. N. *J. Am. Chem. Soc*. **2016**, *138*, 5214−5217.

(27) Jiang, X.; Beiger, J. J.; Hartwig, J. F. *J. Am. Chem. Soc*. **2017**, *139*, 87−90.

(28) Kotani, S.; Yoshiwara, Y.; Ogasawara, M.; Sugiura, M.; Nakajima, M. *Angew. Chem., Int. Ed*. **2018**, *57*, 15877−15881.

(29) Schwarz, K. J.; Yang, C.; Fyfe, J. W. B.; Snaddon, T. N. *Angew. Chem., Int. Ed*. **2018**, *57*, 12102−12105.

(30) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 3500−3501.

(31) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 5604−5607.

(32) Huang, Z.; Liu, Z.; Zhou, J. *J. Am. Chem. Soc*. **2011**, *133*, 15882−15885.

(33) Jette, C. I.; Tong, Z. J.; Hadt, R. G.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2020**, *59*, 2033−2038.

(34) Kim, B.; Kim, Y.; Lee, S. Y. *J. Am. Chem. Soc*. **2021**, *143*, 73−79.

(35) Fujita, T.; Yamamoto, T.; Morita, Y.; Chen, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc*. **2018**, *140*, 5899−5903.

(36) He, Z.; Jiang, X.; Hartwig, J. F. *J. Am. Chem. Soc*. **2019**, *141*, 13066−13073.

(37) Zhu, Y.; Zhang, L.; Luo, S. *J. Am. Chem. Soc*. **2014**, *136*, 14642−14645.

(38) Wang, D.; Zhang, L.; Luo, S. *Org. Lett*. **2017**, *19*, 4924−4927.

(39) Wang, Y.; Chai, J.; You, C.; Zhang, J.; Mi, X.; Zhang, L.; Luo, S. *J. Am. Chem. Soc*. **2020**, *142*, 3184−3195.

(40) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc*. **2006**, *128*, 16050−16051.

(41) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc*. **2013**, *135*, 17298−17301.

(42) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3309−3310.

(43) Asad, S. A.; Ulicki, J.; Shevyrev, M.; Uddin, N.; Alberch, E.; Hossain, M. M. *Eur. J. Org. Chem*. **2014**, 5695−5699.

(44) Hashimoto, T.; Sakata, K.; Maruoka, K. *Angew. Chem., Int. Ed*. **2009**, *48*, 5014−5017.

(45) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 3302−3303.

(46) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc*. **2014**, *136*, 17662−17668.

(47) Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc*. **2015**, *137*, 7128−7134.

(48) Guan, H.; Zhang, Q.; Walsh, P. J.; Mao, J. *Angew. Chem., Int. Ed*. **2020**, *59*, 5172−5177.

(49) Wang, Z.; Yin, H.; Fu, G. C. *Nature* **2018**, *563*, 379−383.

(50) Wang, Z.; Yang, Z.; Fu, G. C. *Nat. Chem*. **2021**, *13*, 236−242.

(51) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc*. **2017**, *139*, 527−533.

(52) Murphy, K. E.; Hoveyda, A. H. *Org. Lett*. **2005**, *7*, 1255−1258.

(53) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604−15605.

(54) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2010**, *49*, 8370−8374.

(55) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2017**, *56*, 11545−11548.

(56) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc*. **2008**, *130*, 15254−15255.

(57) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc*. **2008**, *130*, 14936−14937.

(58) Gaydou, M.; Moragas, T.; Juliá-Hernández, F.; Martin, R. *J. Am. Chem. Soc.* **2017**, *139*, 12161−12164.

(59) Seo, H.; Liu, A.; Jamison, T. F. *J. Am. Chem. Soc*. **2017**, *139*, 13969−13972.

(60) Meng, Q.; Wang, S.; Huff, G. S.; König, B. *J. Am. Chem. Soc.* **2018**, *140*, 3198−3201.

(61) Alkayal, A.; Tabas, V.; Montanaro, S.; Wright, I. A.; Malkov, A. V.; Buckley, B. R. *J. Am. Chem. Soc.* **2020**, *142*, 1780−1785.

(62) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed*. **2011**, *50*, 523−527.

(63) Tani, Y.; Kuga, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Commun.* **2015**, *51*, 13020−13023.

(64) Li, H.; Dong, K.; Jiao, H.; Neumann, H.; Jackstell, R.; Beller, M. *Nat. Chem*. **2016**, *8*, 1159−1166.

(65) Dong, K.; Fang, X.; Gülak, S.; Franke, R.; Spannenberg, A.; Neumann, H.; Jackstell, R.; Beller, M. *Nat. Commun*. **2017**, *8*, 1−7.

(66) Yang, J.; Liu, J.; Neumann, H.; Franke, R.; Jackstell, R.; Beller, M. *Science* **2019**, *366*, 1514−1517.

(67) Sang, R.; Kucmierczyk, P.; Dühren, R.; Razzaq, R.; Dong, K.; Liu, J.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed*. **2019**, *58*, 14365−14373.

(68) Kawashima, S.; Aikawa, K.; Mikami, K. *Eur. J. Org. Chem*. **2016**, 3166−3170.

(69) Yuan, Y.; Wu, F.; Schünemann, C.; Holz, J.; Kamer, P. C. J.; Wu, X. *Angew. Chem., Int. Ed*. **2020**, *59*, 22441−22445.

(70) Godard, C.; Muñoz, B. K.; Ruiz, A.; Claver, C. *Dalton Trans*. **2008**, 853.

(71) Cometti, G.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *236*, C31−C32.

(72) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803−2804.

(73) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708−7709.

(74) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9197−9200.

(75) Li, J.; Chang, W.; Ren, W.; Dai, J.; Shi, Y. *Org. Lett*. **2016**, *18*, 5456−5459.

(76) Li, J.; Ren, W.; Dai, J. Shi, Y. *Org. Chem. Front*. **2018**, *5*, 75−79.

(77) Tian, D.; Xu, R.; Zhu, J.; Huang, J.; Dong, W.; Claverie, J.; Tang, W. *Angew. Chem., Int. Ed.* **2021**, *60*, 6305−6309.

(78) Pirnot, M. T.; Wang, Y.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2016**, *55*, 48−57.

(79) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, aah5133.

(80) Liu, R. Y.; Buchwald, S. L. *Acc. Chem. Res.* **2020**, *53*, 1229−1243.

(81) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144–150.

(82) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 9787−9790.

(83) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 5821−5824.

(84) Yuan, Y.; Zhang, X.; Qian, H.; Ma, S. *Chem. Sci*. **2020**, *11*, 9115−9121.

(85) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc*. **2012**, *134*, 8428−8431.

(86) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 2007−2011.

(87) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. *J. Am. Chem. Soc*. **2018**, *140*, 598−601.

(88) Jang, W. J.; Yun, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 12116−12120.

(89) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 7083−7087.

(90) Liu, R. Y.; Zhou, Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 2251−2256.

(91) Tan, Y.; Tang, X.; Liu, P.; Kong, D.; Chen, Y.; Tian, P.; Lin, G. *Org. Lett.* **2018**, *20*, 248−251.

(92) Gui, Y.; Hu, N.; Chen, X.; Liao, L.; Ju, T.; Ye, J.; Zhang, Z.; Li, J.; Yu, D. *J. Am. Chem. Soc.* **2017**, *139*, 17011−17014.

(93) Chen, X.; Zhu, L.; Gui, Y.; Jing, K.; Jiang, Y.; Bo, Z.; Lan, Y.; Li, J.; Yu, D. *J. Am. Chem. Soc.* **2019**, *141*, 18825−18835.

(94) Qiu, J.; Gao, S.; Li, C.; Zhang, L.; Wang, Z.; Wang, X.; Ding, K. *Chem. Eur. J.* **2019**, *25*, 13874−13878.

(95) Li, W.; Chen, L.; Lin, Z.; Man, S.; Qin, X.; Lyu, Y.; Li, C.; Leng, G. *Inorg. Chem.* **2020**, *59*, 9667−9682.

(96) Wang, M.; Jin, X.; Wang, X.; Xia, S.; Wang, Y.; Huang, S.; Li, Y.; He, L.; Ma, X. *Angew. Chem., Int. Ed.* **2021**, *60*, 3984−3988.

(97) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474.

(98) Suess, A. M.; Uehling, M. R.; Kaminsky, W.; Lalic, G. *J. Am. Chem. Soc.* **2015**, *137*, 7747−7753.

(99) Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. *ACS Catal.* **2017**, *7*, 8200−8204.

(100) Han, J.; Zhou, W.; Zhang, P.; Wang, H.; Zhang, R.; Wu, H.; Zhang, J. *ACS Catal.* **2019**, *9*, 6890−6895.

(101) The only exception was the hydrolysis to give carboxylic acid **3l**, which was carried out after first isolating the corresponding ester in order to facilitate its purification.

(102) Pascaud, X.; Honde C.; Le Gallou, B.; Chanoine, F.; Roman, F.; Bueno, L.; Junien, J. L. *J. Pharm. Pharmacol*. **1990**, *42*, 546−552.

(103) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. *Nat. Prod. Rep.* **2016**, *33*, 491−522.

(104) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem*. **2014**, *3*, 1234−1260.

(105) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3−99.

(106) Guo, S.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 15976−15984.

(107) Cattaneo, M.; Bevilacqua, C.; Lecchi ,A.; Mannucci, P. M. *Haemostasis* **1987**, *17*, 293−300.

(108) Yao, Y. CN 101270072 (A), Sep. 24, 2008.

(109) Cerletti, C.; Manarini, S.; Colombo, M.; Tavani, A. *J. Pharm. Pharmacol.* **1990**, *42*, 885−887.

(110) Patrignani, P.; Volpi, D.; Ferrario, R.; Romanzini, L.; Somma, M. D.; Patrono, C. *Eur. J. Pharmacol.* **1990**, *191*, 83−88.

(111) Ye, Y.; Kevlishvili, I.; Feng, S.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2020**, *142*, 10550−10556.

(112) Liu, R. Y.; Yang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 14077−14080.

(113) "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of Chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update." Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.

(114) Inside a nitrogen-filled glovebox, 1-adamantyl fluoroformate (3.09 g, batch no. 0000028781) was dissolved in minimum amount of anhydrous pentane (~11 mL), and the resulting solution was filtered with the aid of a syringe filter (13mm w/ 0.2 μm PTFE membrane, VWR, Cat. No. 28145-491). The flask was rinsed with pentane (2 x 1 mL) and the resulting solution was filtered through the same syringe filter. The combined filtrate was collected in a 50 mL flask, capped with a septum, and kept in the glovebox freezer (−30 °C) overnight. The resulting suspension was quickly poured into a fritted funnel connected to the vacuum system. The solid in the funnel was then quickly washed with ~5 mL cold pentane (−30 °C). Crystalline 1-adamantyl fluoroformate (1.58 g) was recovered.

(115) (a) Gao, M.; Wang, D.; Zheng, Q.; Huang, Z.; Wang, M. *J. Org. Chem*. **2007**, *72*, 6060−6066. (b) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2017**, *56*, 11545−11548.

(116) Oda, S.; Sam, B.; Kriche, M. J. *Angew. Chem., Int. Ed*. **2015**, *54*, 8525−8528.

(117) Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett*. **2014**, *16*, 4658−4661.

(118) Schwartz, L. A.; Holmes, M.; Brito, G. A.; Gonçalves, T. P.; Richardson, J.; Ruble, J. C.; Huang, K.-W.; Krische, M. J. *J. Am. Chem. Soc*. **2019**, *141*, 2087−2096.

(119) Frey, H.; Kaupp, G. *Synthesis* **1990**, *10*, 931−934.

(120) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864−3867.

(121) Ye, Y.; Kevlishvili, I.; Feng, S.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 10550−10556.

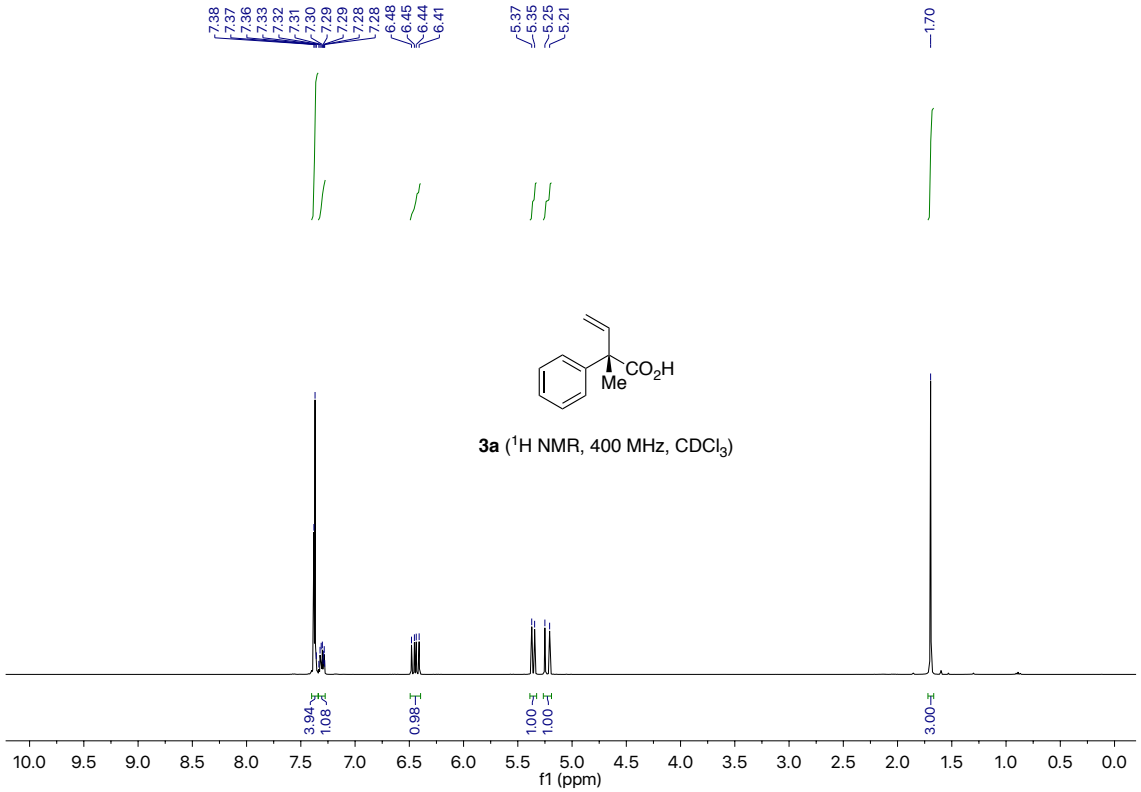
(122) Yang, B.; Ren, X.; Shen, X.; Li, T.; Lu, Z. *Chin. J. Chem.* **2018**, *36*, 1017−1023.

(123) Seferos, D. S.; Banach, D. A.; Alcantar, N. A.; Israelachvili, J. N.; Bazan, G. C. *J. Org. Chem*. **2004**, *69*, 1110−1119.

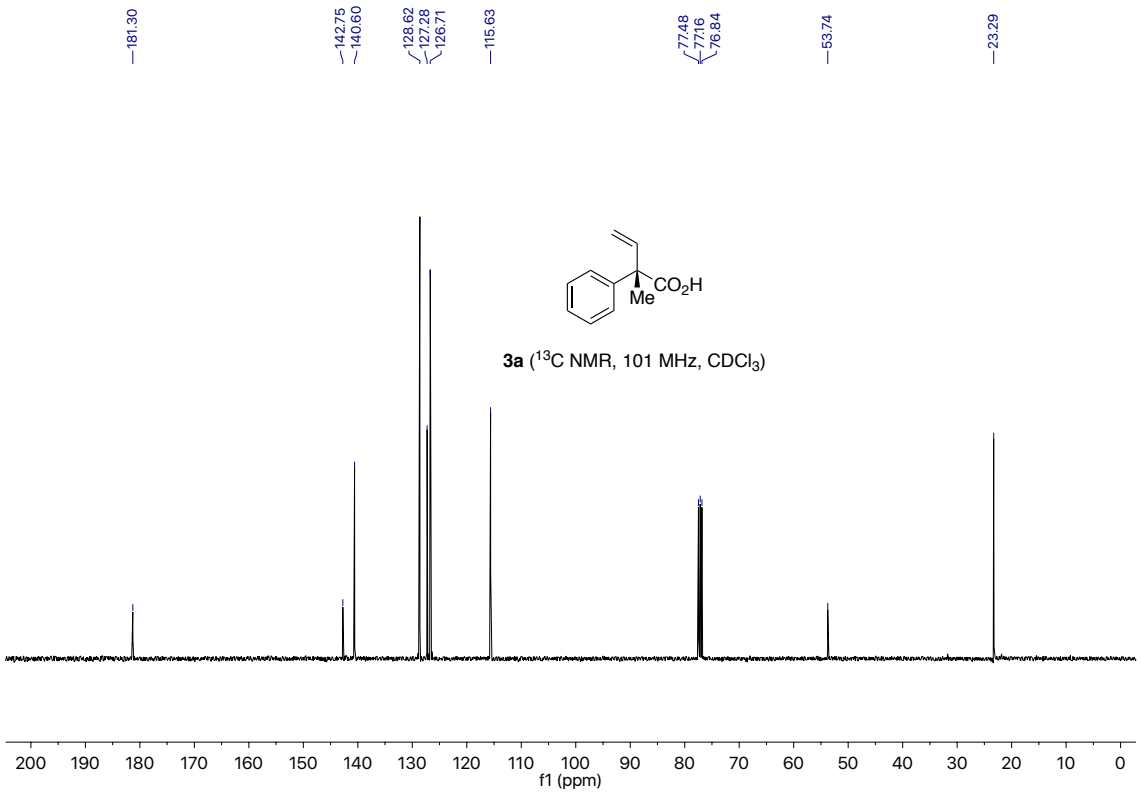
(124) Ogiwara, Y.; Uchiyama, T.; Sakai, N. *Angew. Chem., Int. Ed*. **2016**, *55*, 1864−1867.

(125) Hennum, M.; Odden, H. H.; Gundersen, L. *Eur. J. Org. Chem*. **2017**, 846−860.

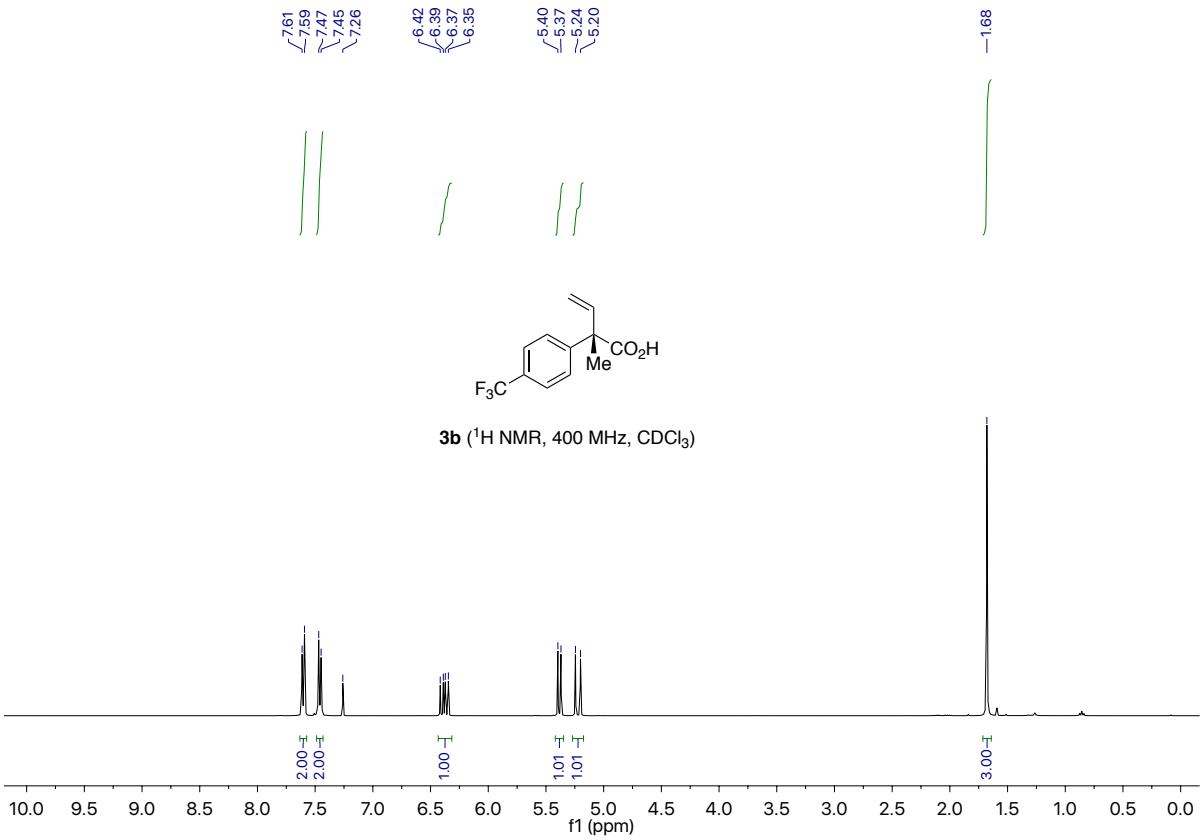
2.6 Spectra and Chromatograms



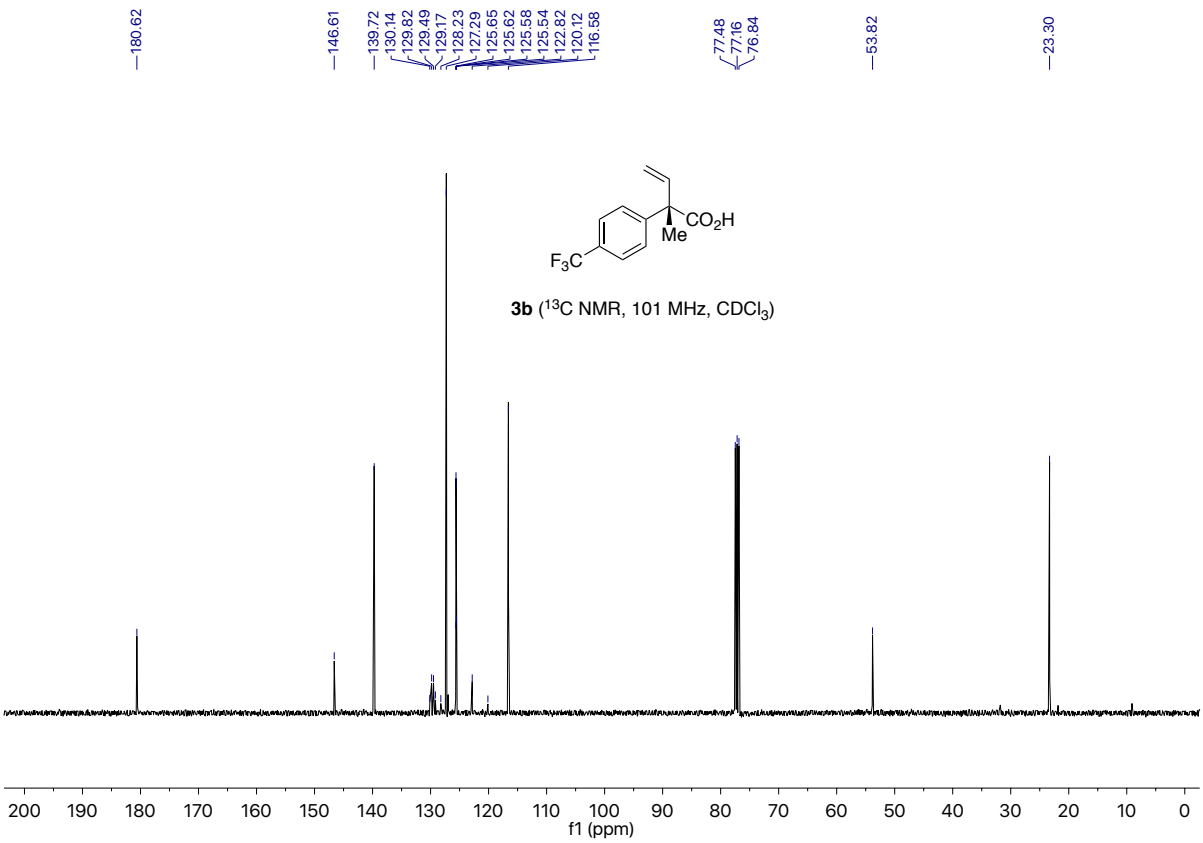
3a (^{1}H NMR, 400 MHz, $CDCl_3$)



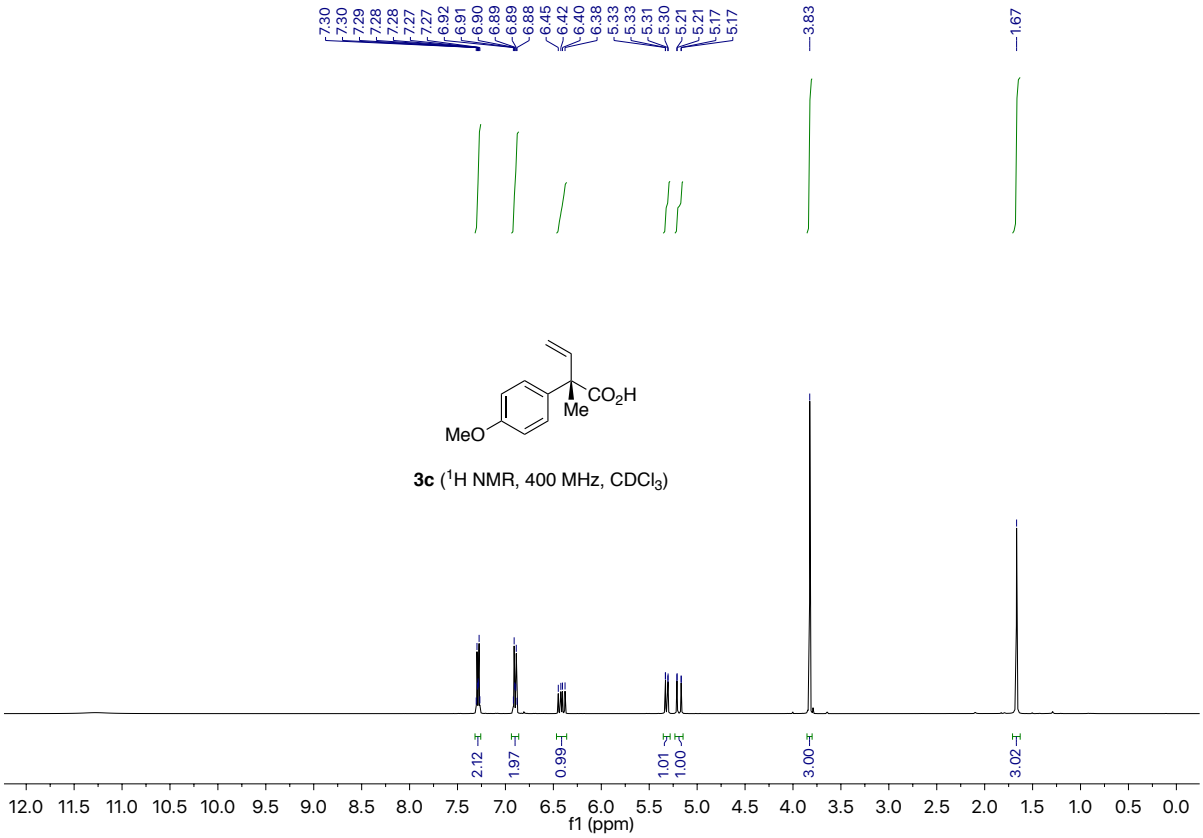
3a (^{13}C NMR, 101 MHz, $CDCl_3$)



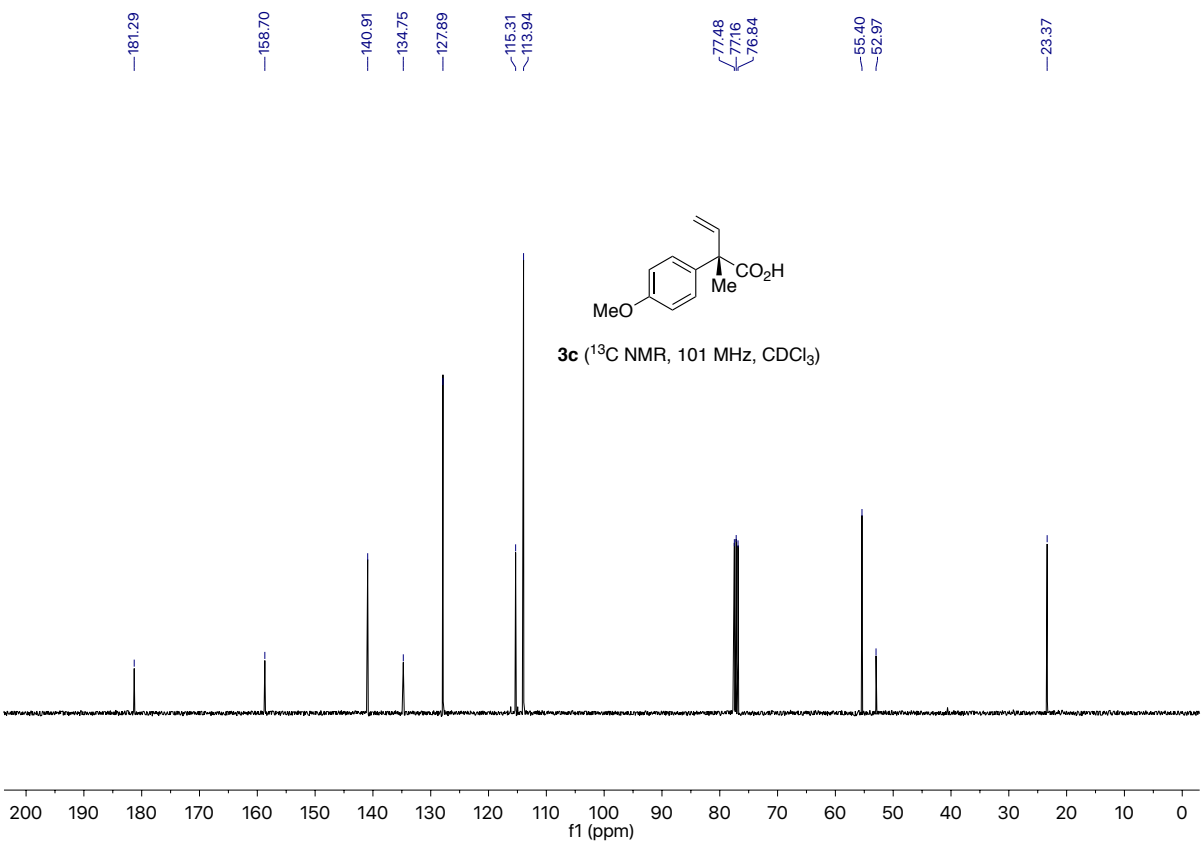
3b (^{1}H NMR, 400 MHz, $CDCl_3$)



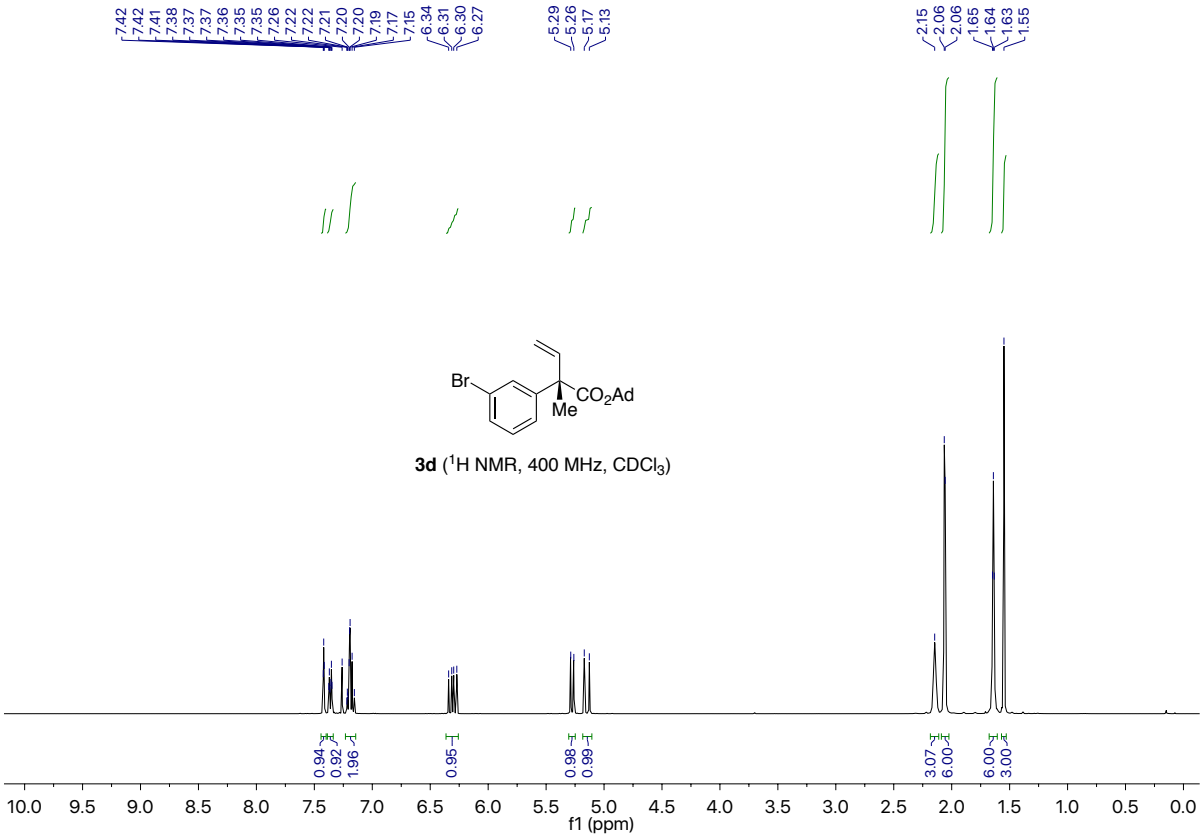
3b (^{13}C NMR, 101 MHz, $CDCl_3$)



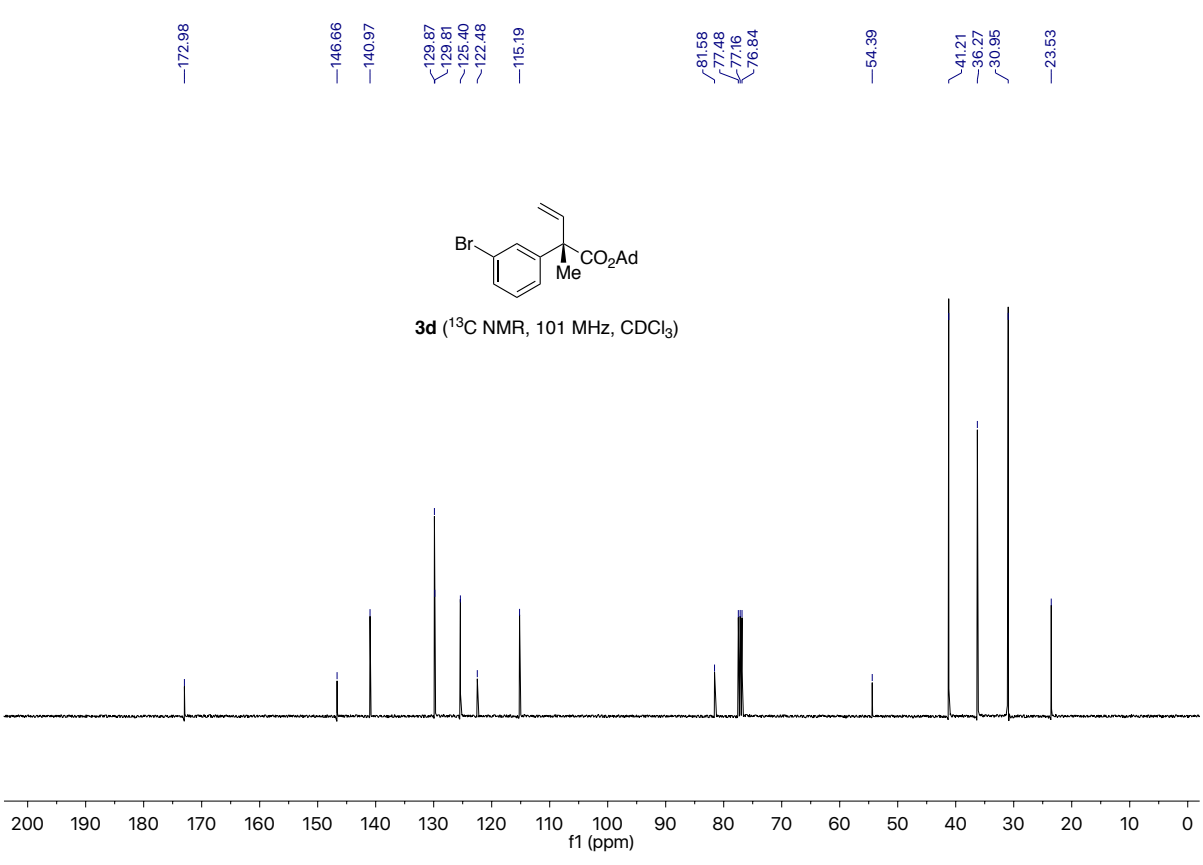
3c (^{1}H NMR, 400 MHz, $CDCl_3$)



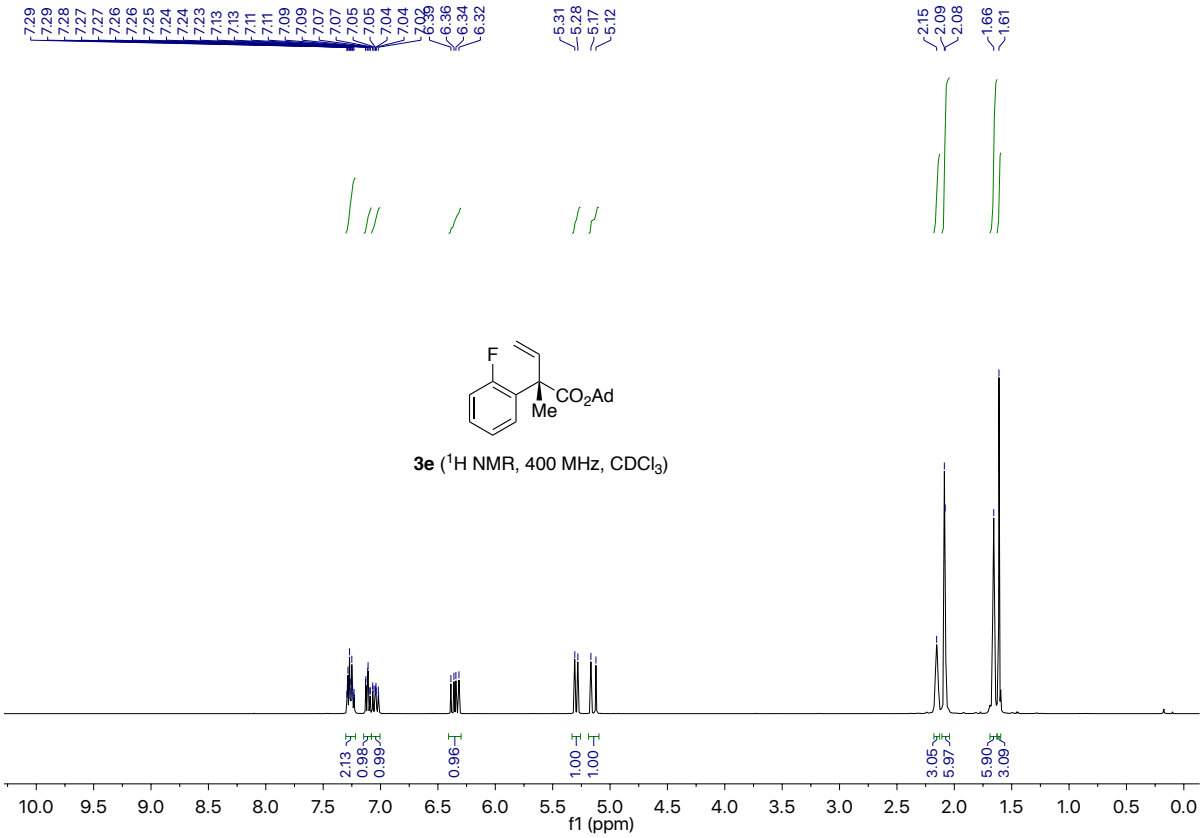
3c (^{13}C NMR, 101 MHz, $CDCl_3$)



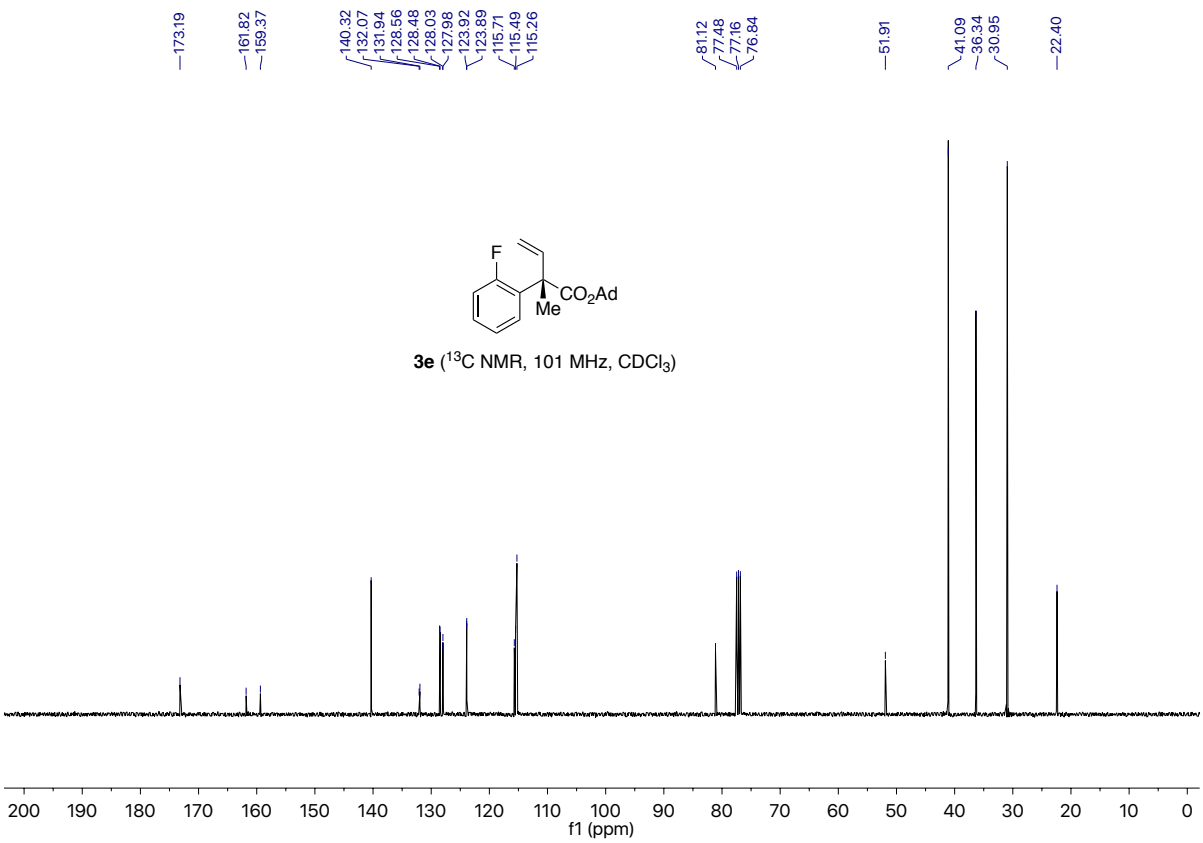
3d (^{1}H NMR, 400 MHz, $CDCl_3$)



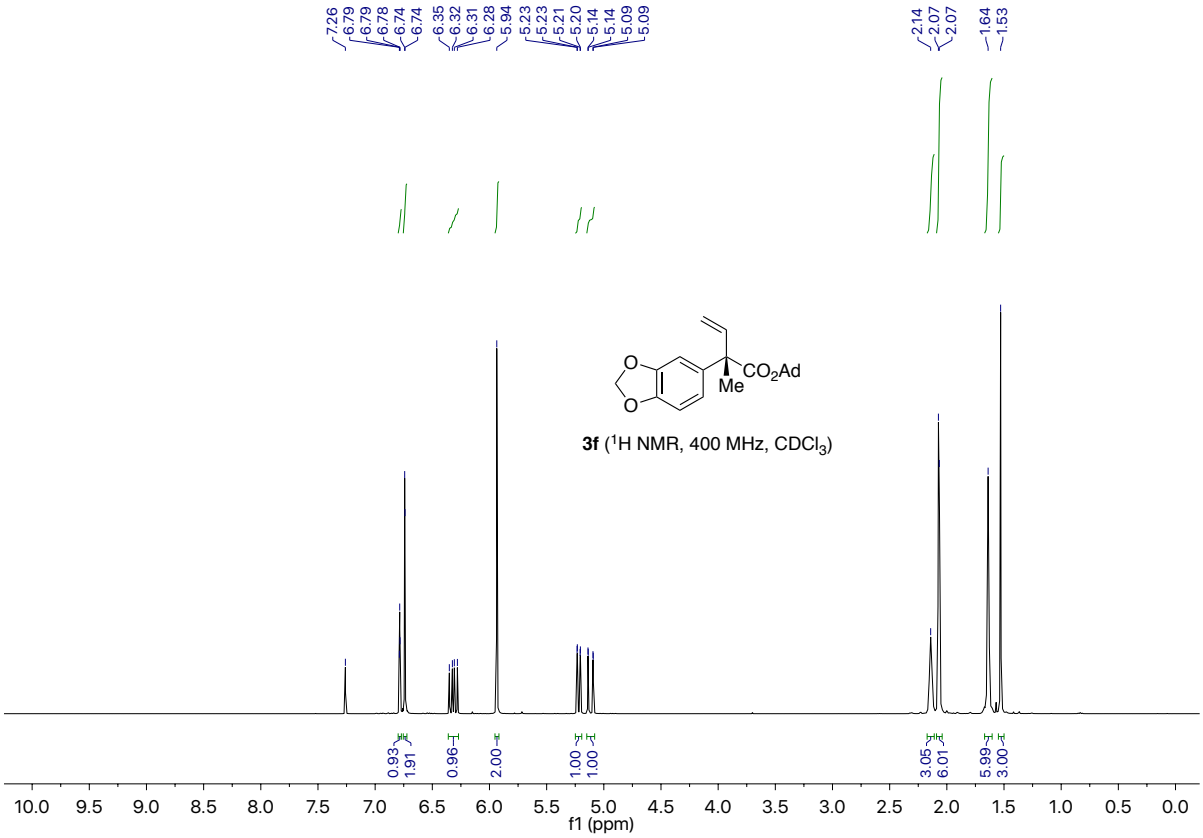
3d (^{13}C NMR, 101 MHz, $CDCl_3$)



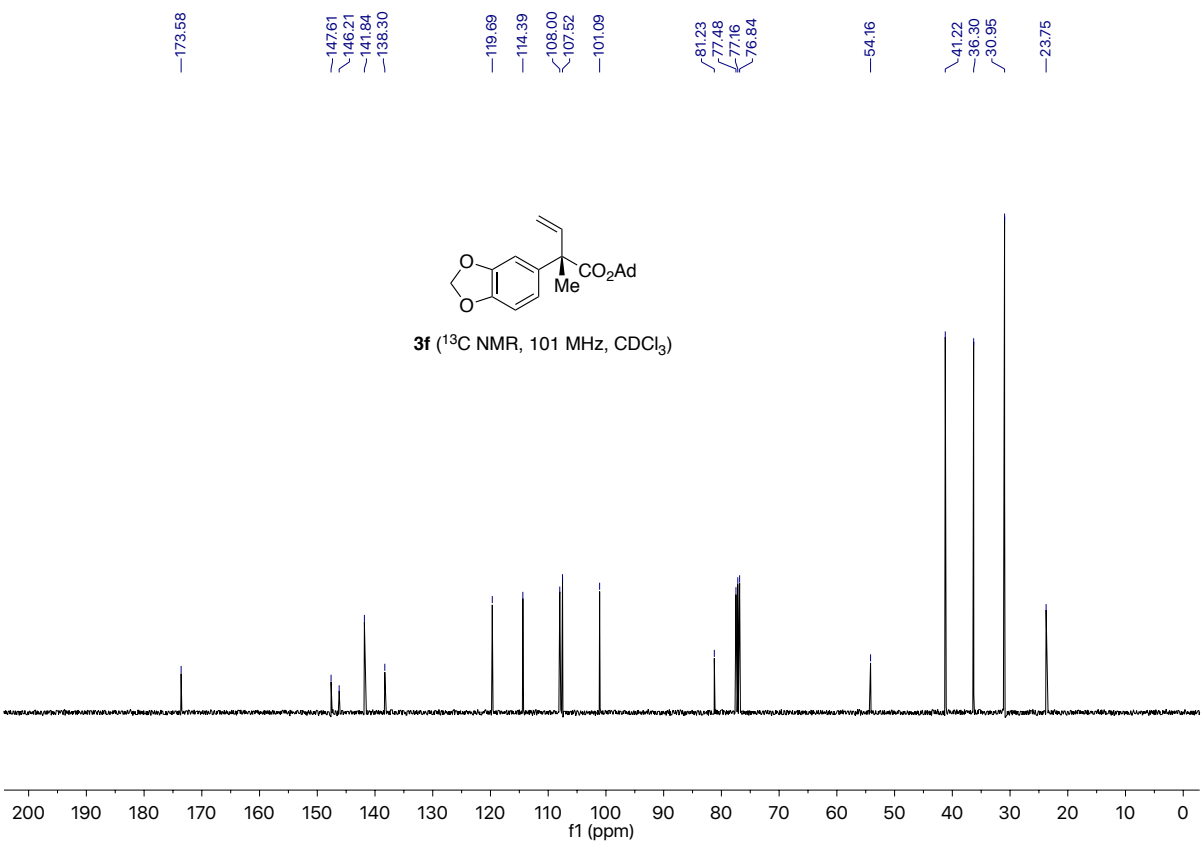
3e (^{1}H NMR, 400 MHz, $CDCl_3$)



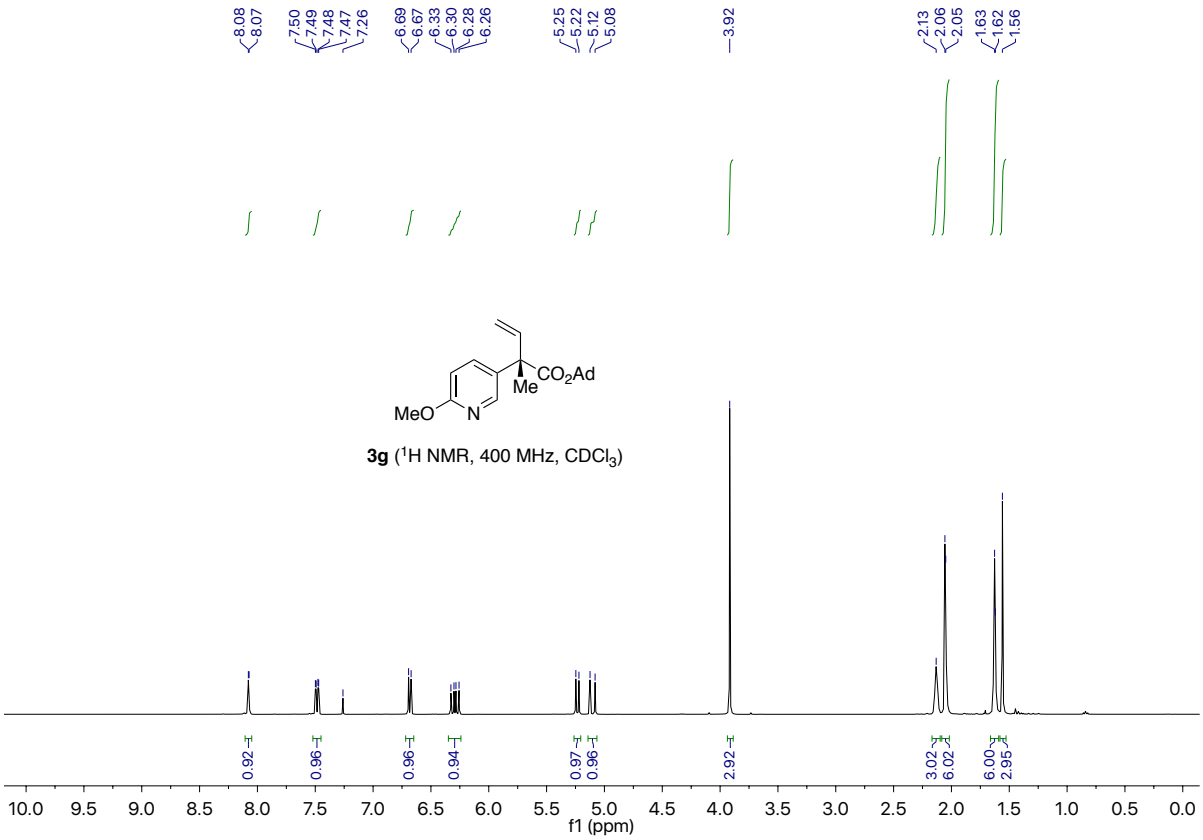
3e (^{13}C NMR, 101 MHz, $CDCl_3$)



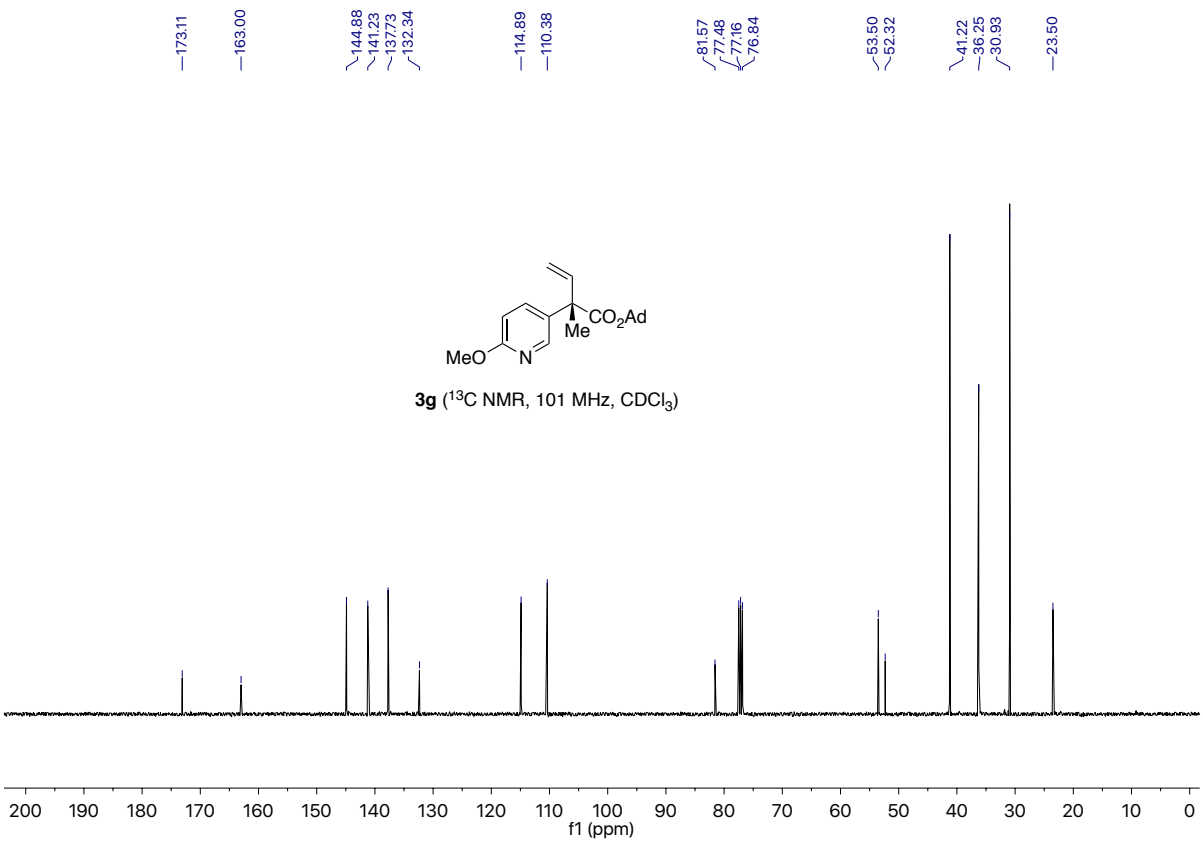
3f (^{1}H NMR, 400 MHz, $CDCl_3$)



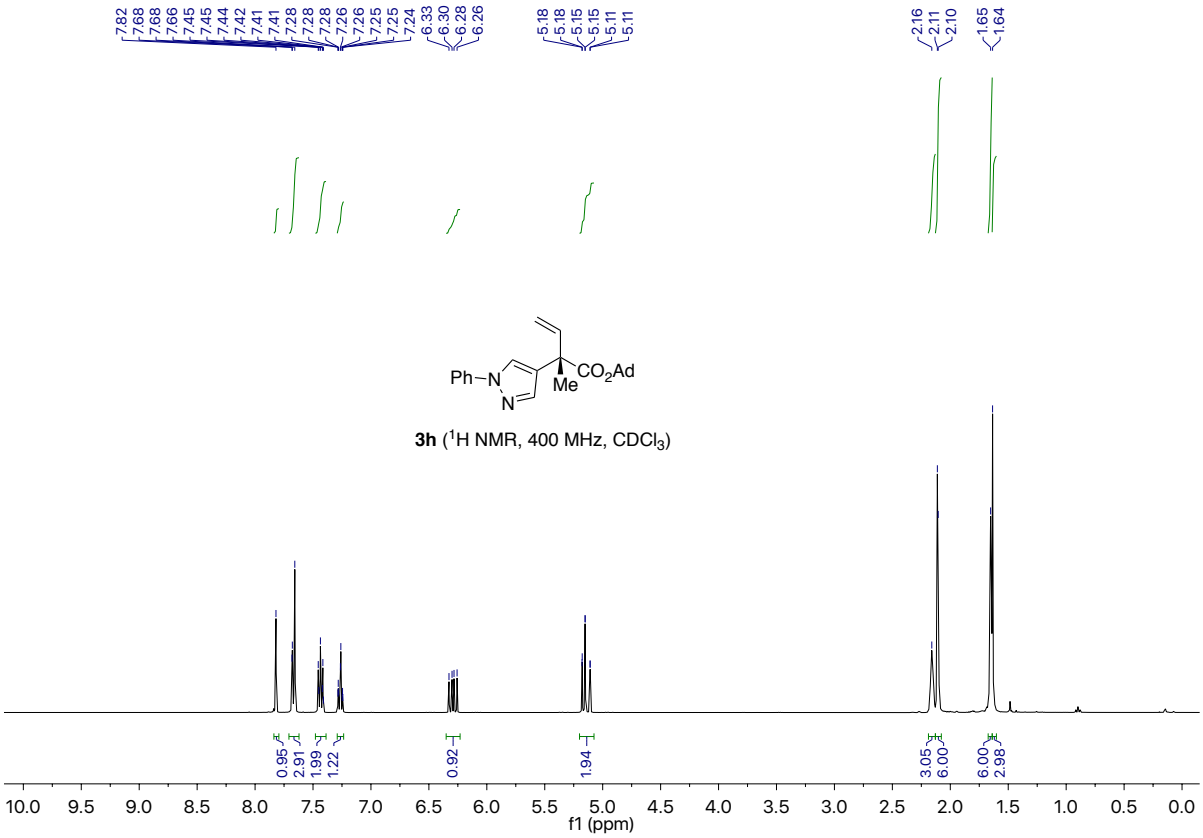
3f (^{13}C NMR, 101 MHz, $CDCl_3$)



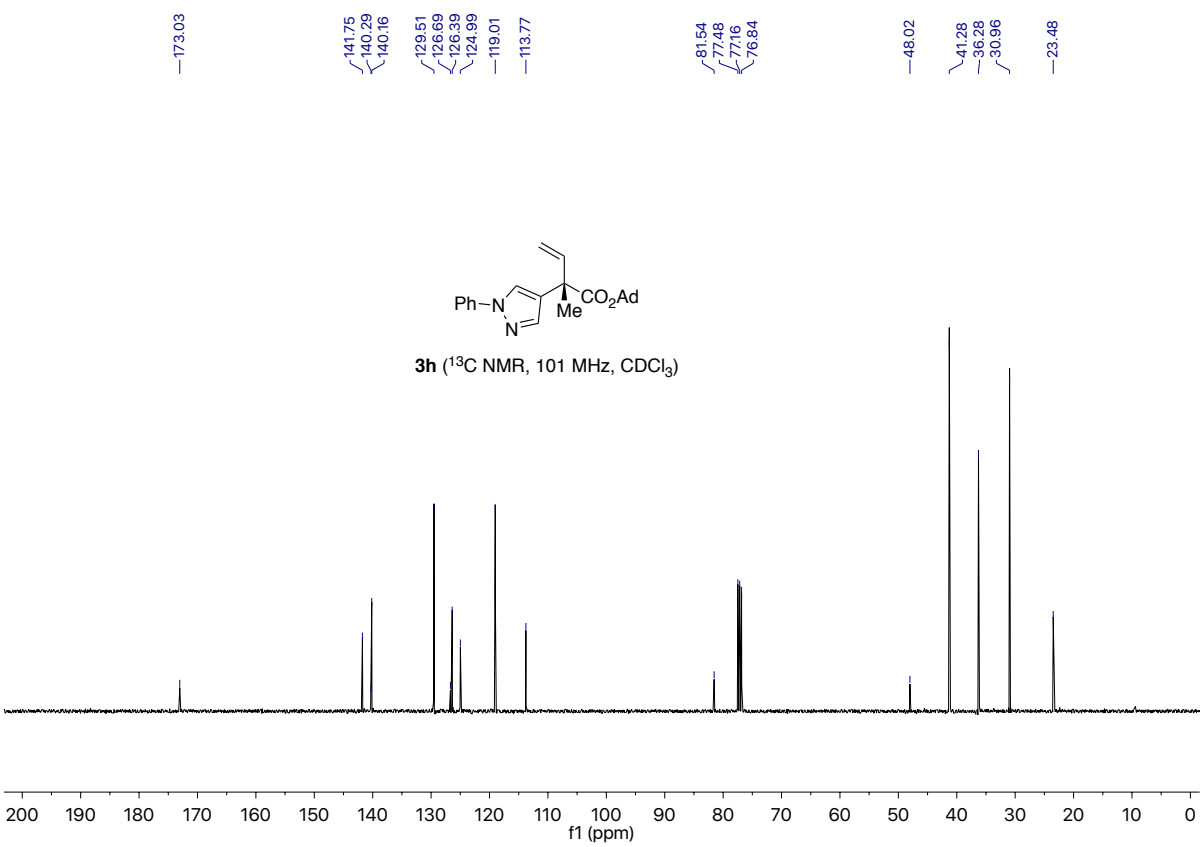
3g (^{1}H NMR, 400 MHz, $CDCl_3$)



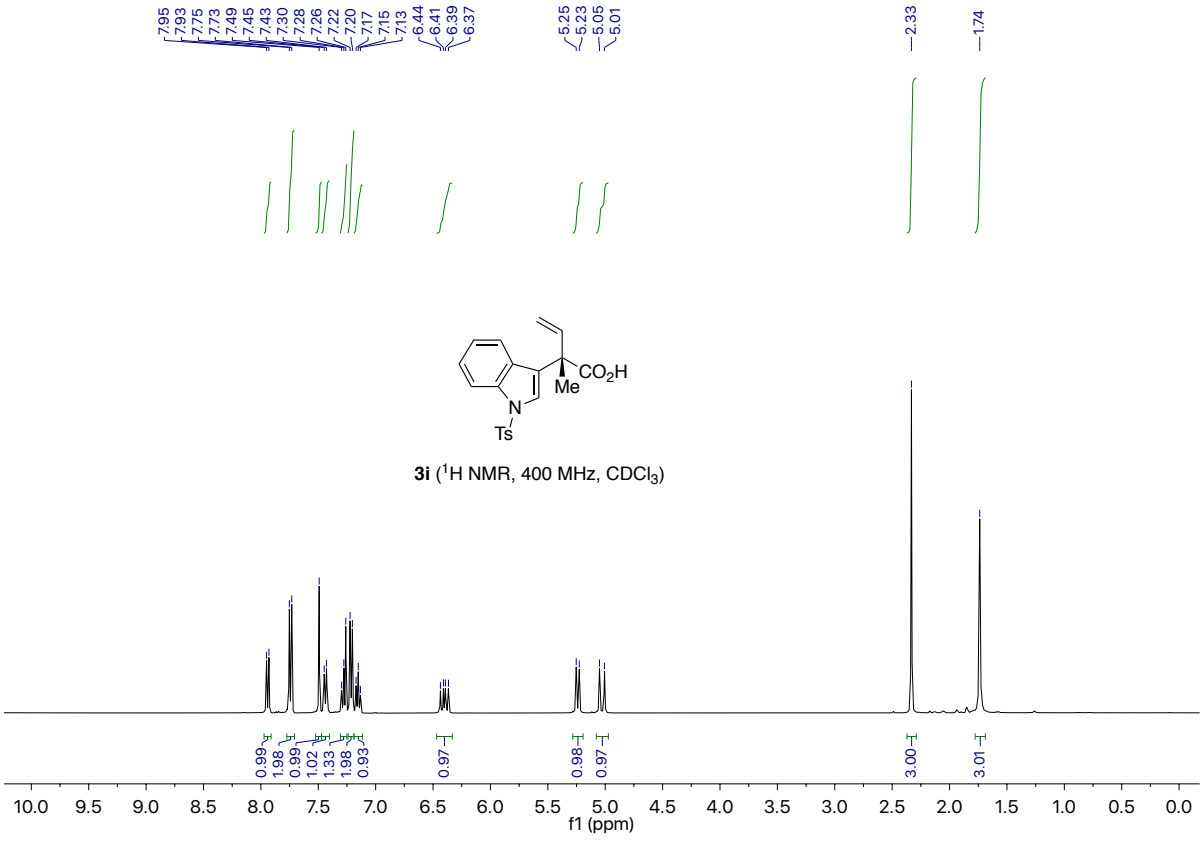
3g (^{13}C NMR, 101 MHz, $CDCl_3$)



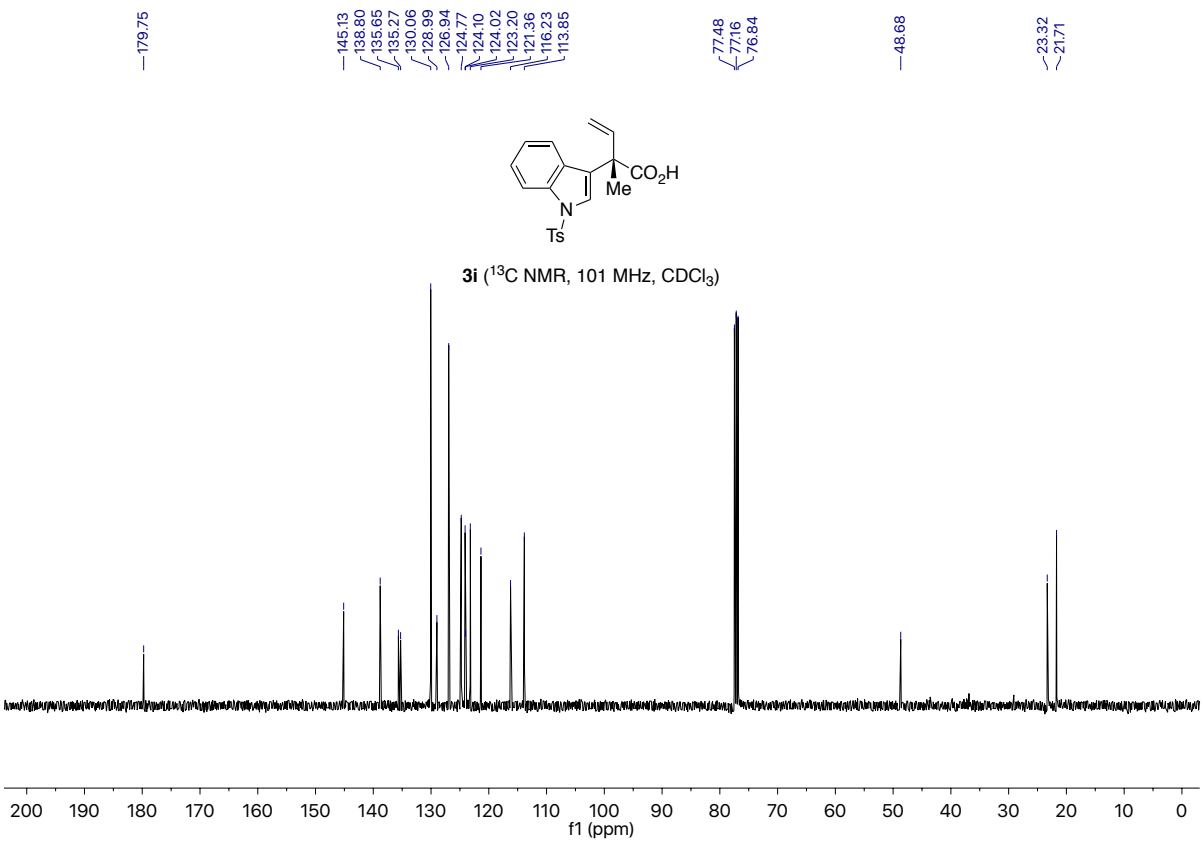
3h (^{1}H NMR, 400 MHz, $CDCl_3$)



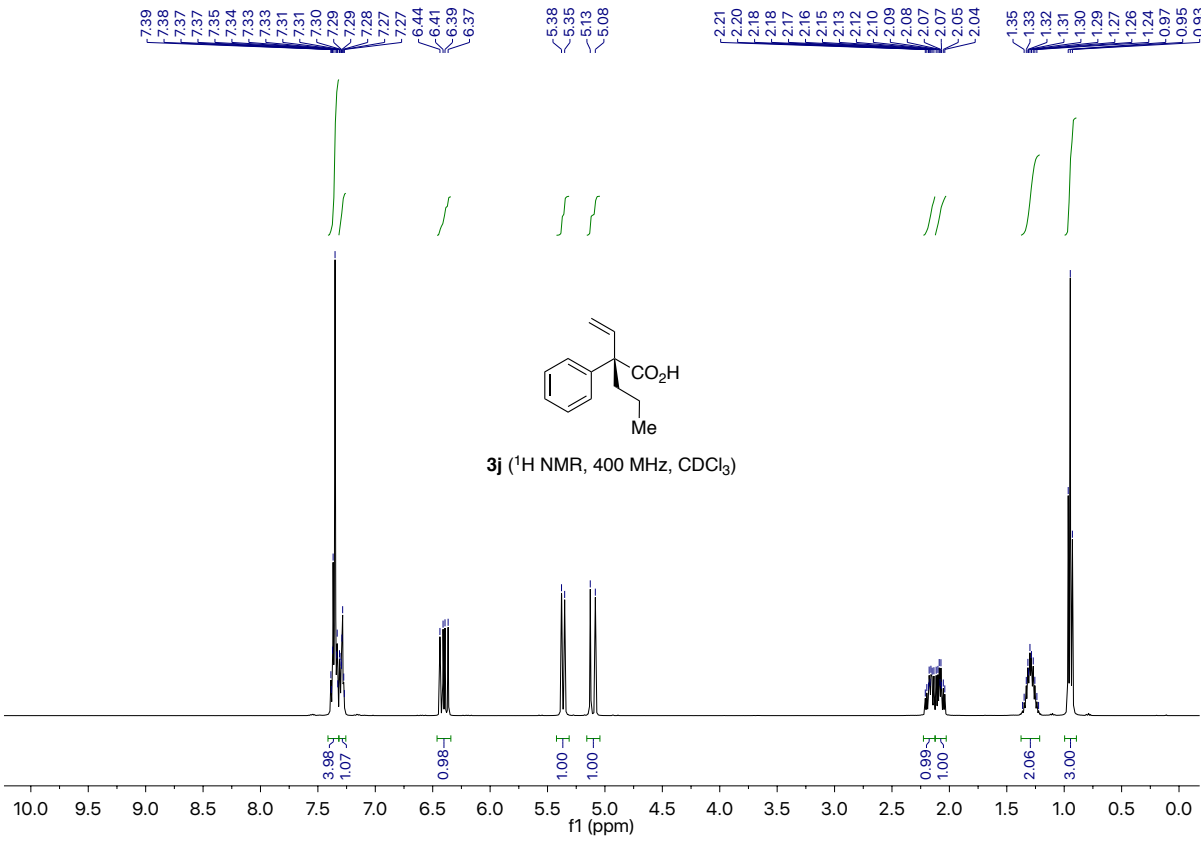
3h (^{13}C NMR, 101 MHz, $CDCl_3$)



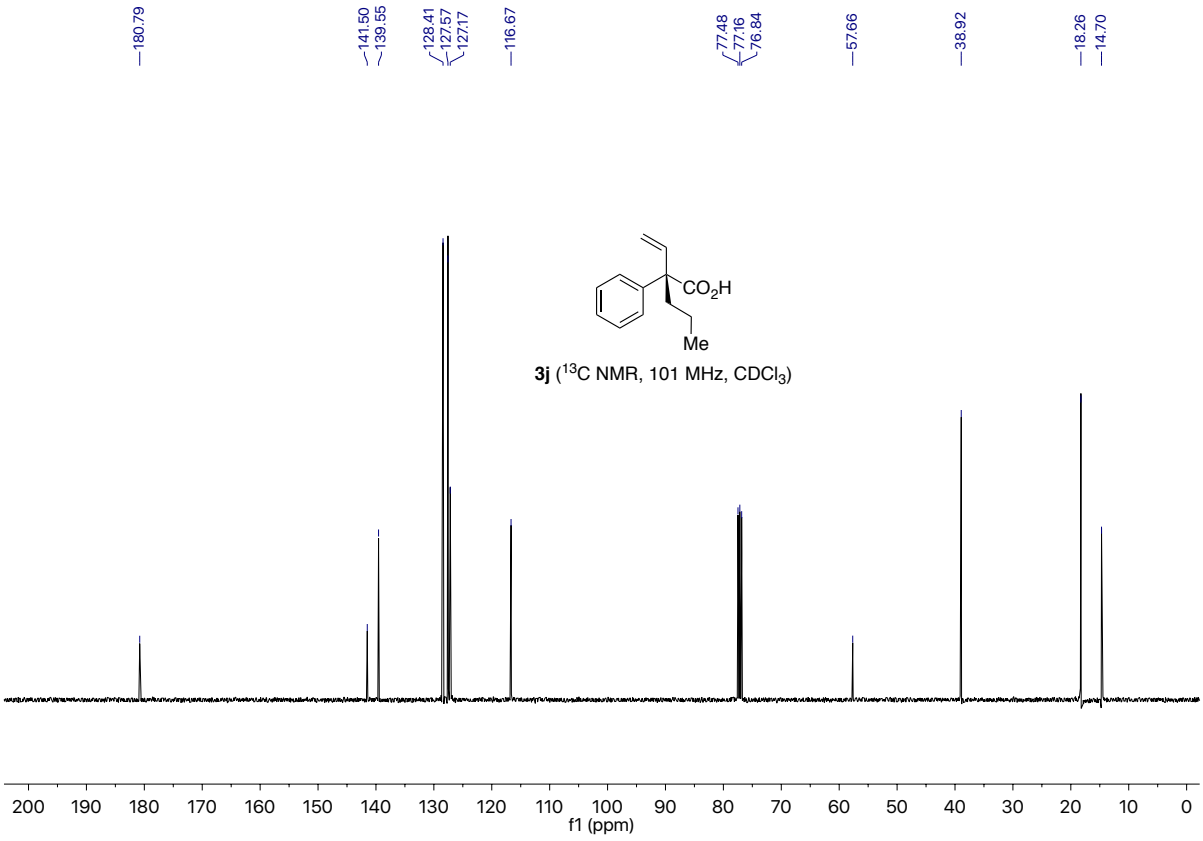
3i (^{1}H NMR, 400 MHz, $CDCl_3$)



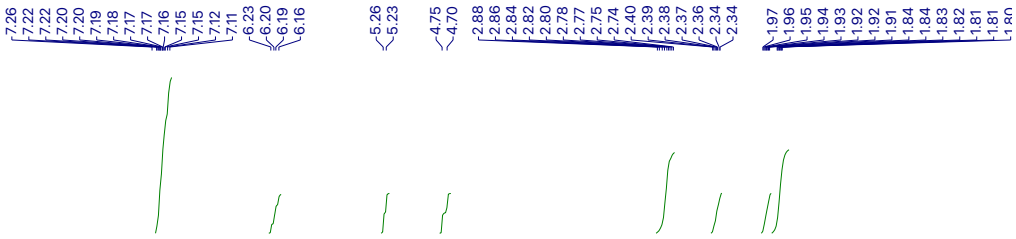
3i (^{13}C NMR, 101 MHz, $CDCl_3$)

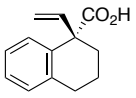


3j (^{1}H NMR, 400 MHz, $CDCl_3$)

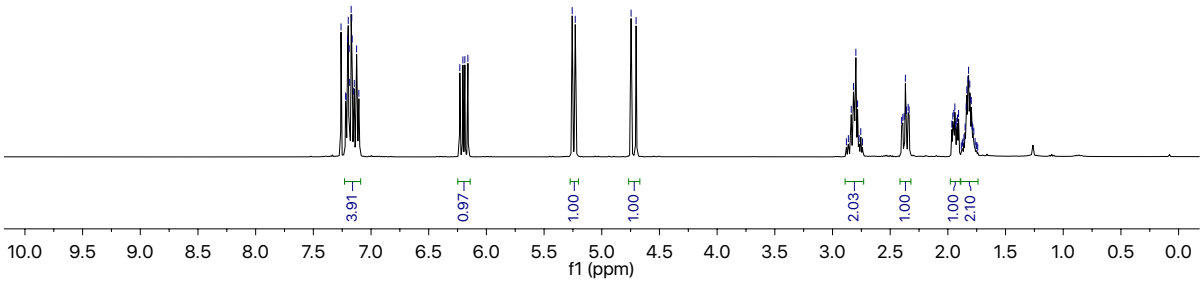


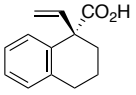
3j (^{13}C NMR, 101 MHz, $CDCl_3$)



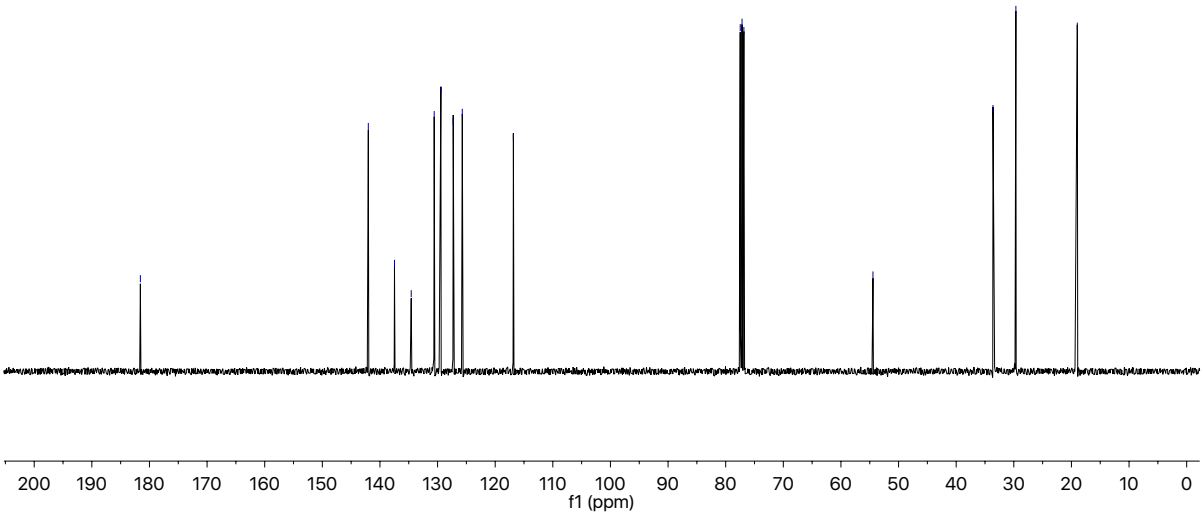


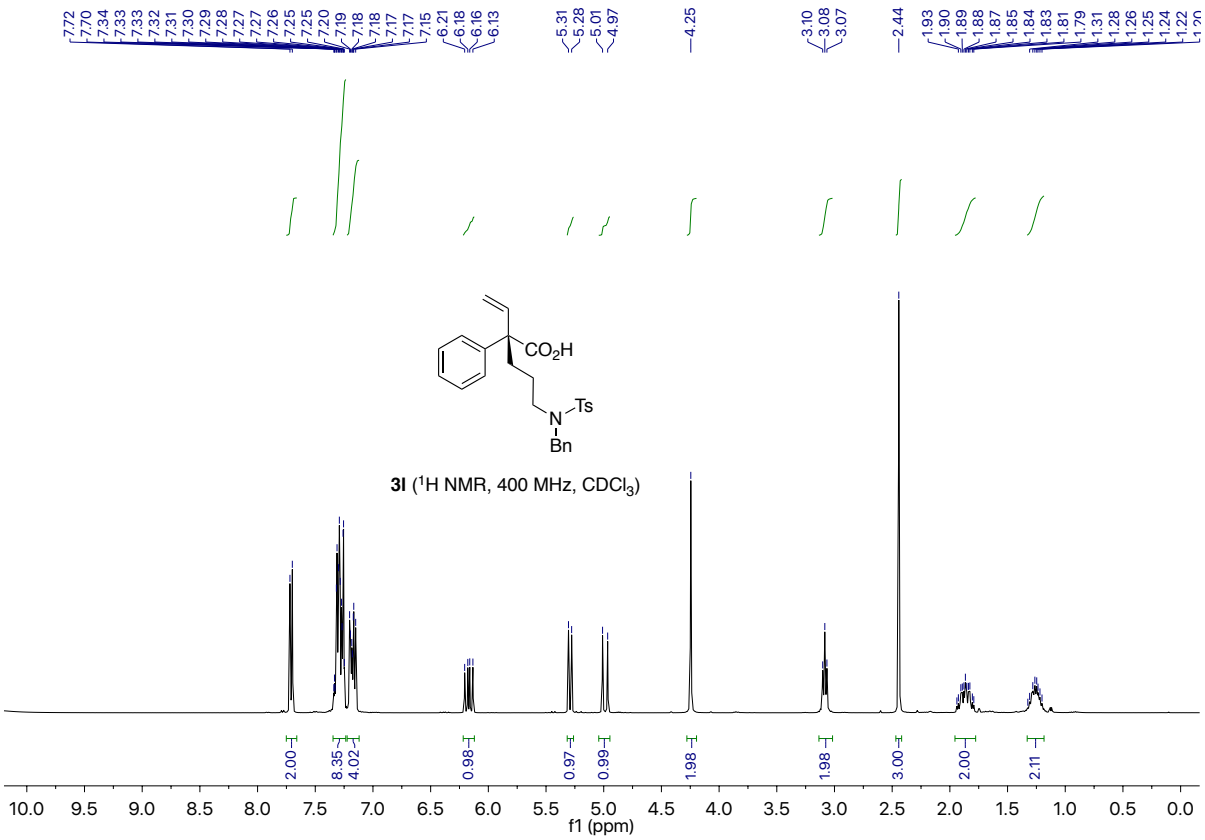
3k (^{1}H NMR, 400 MHz, $CDCl_3$)

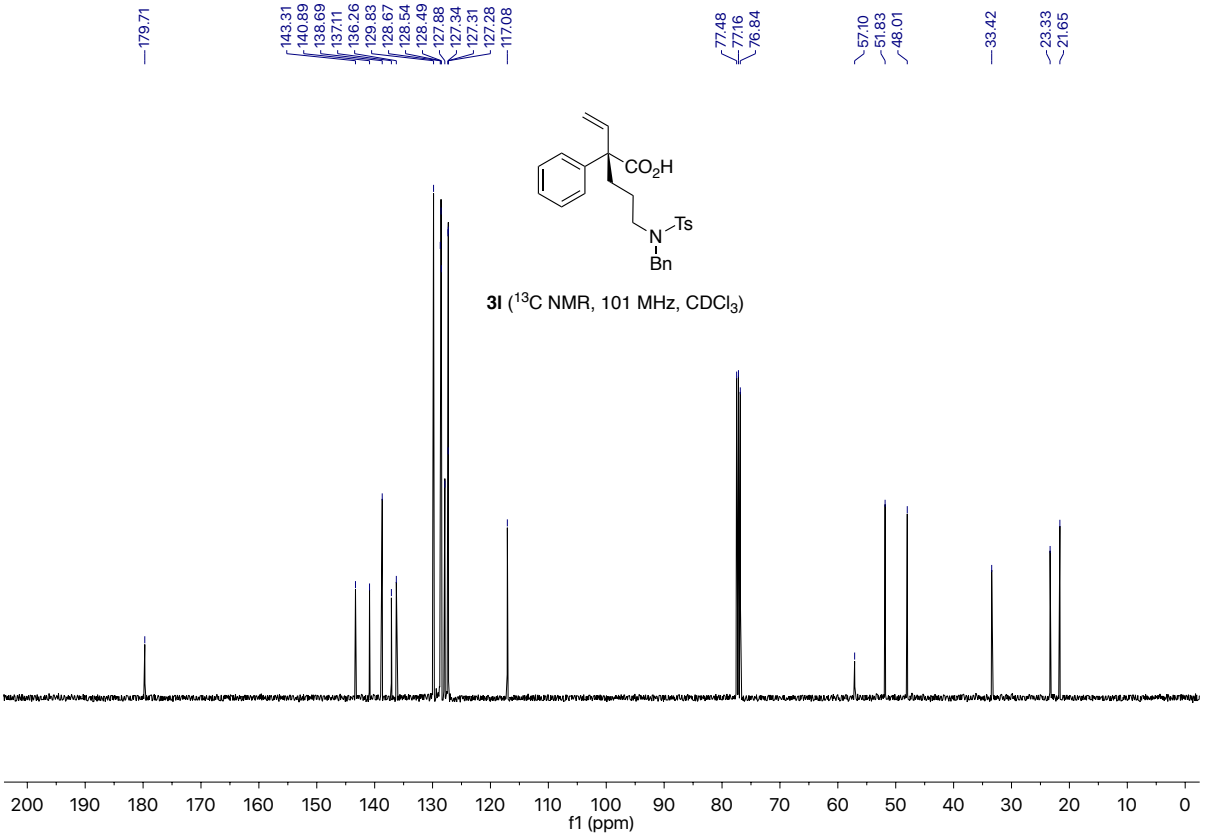


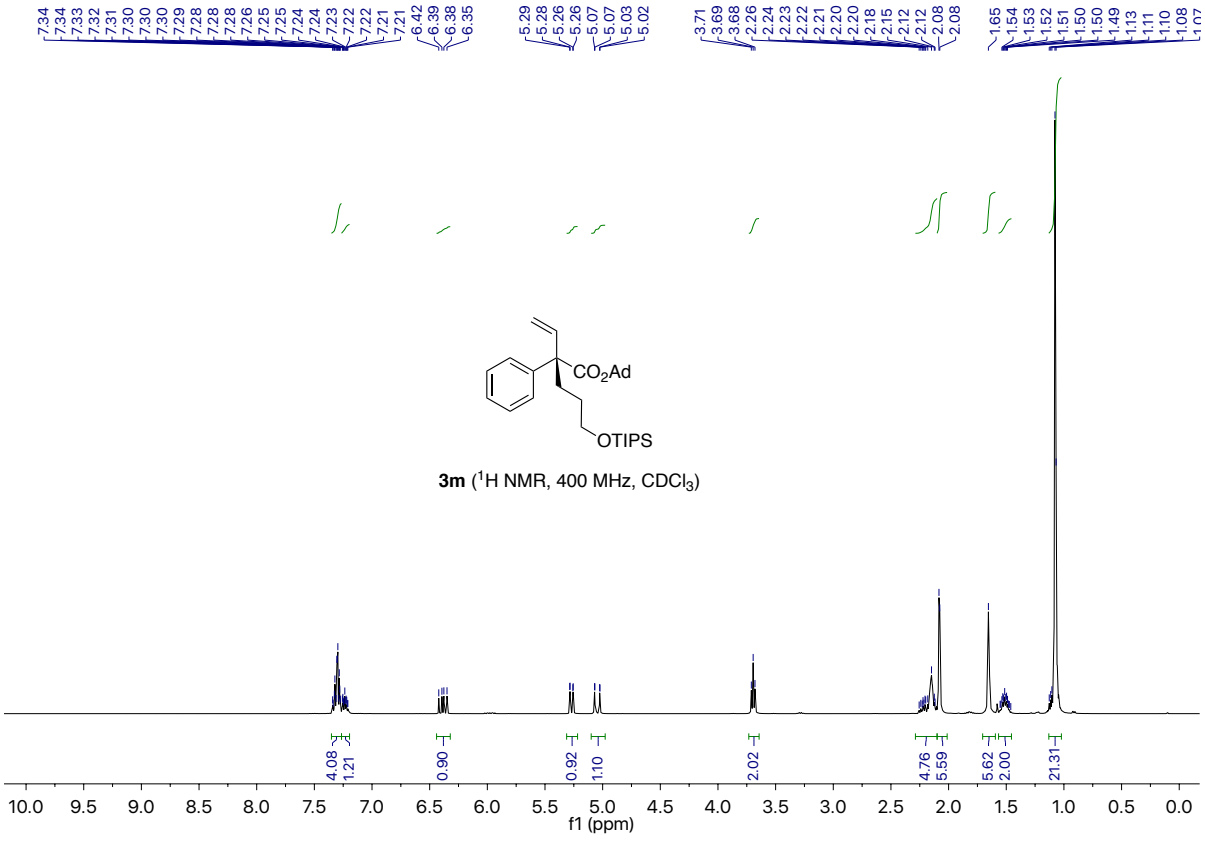


3k (^{13}C NMR, 101 MHz, $CDCl_3$)

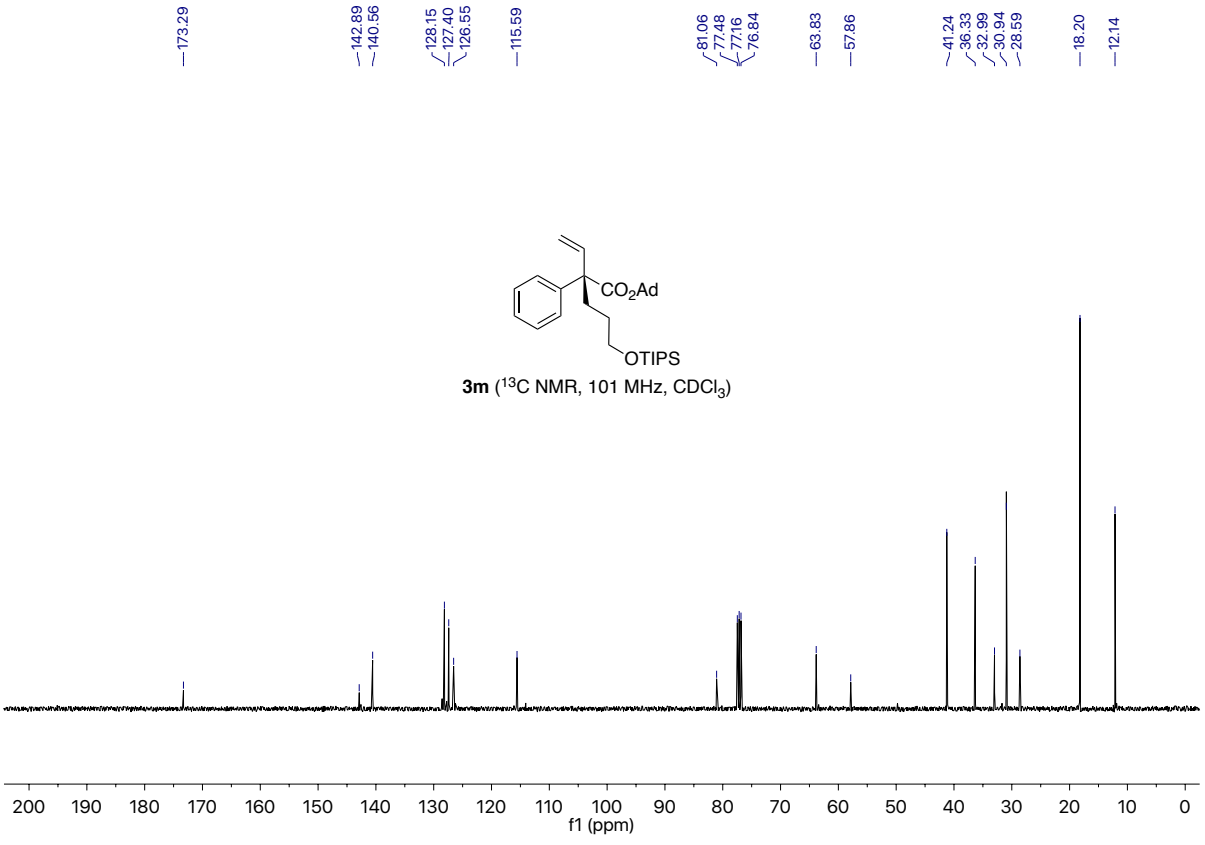



CO2H
N
Ts
Bn
3l (1H NMR, 400 MHz, CDCl3)
f1 (ppm)

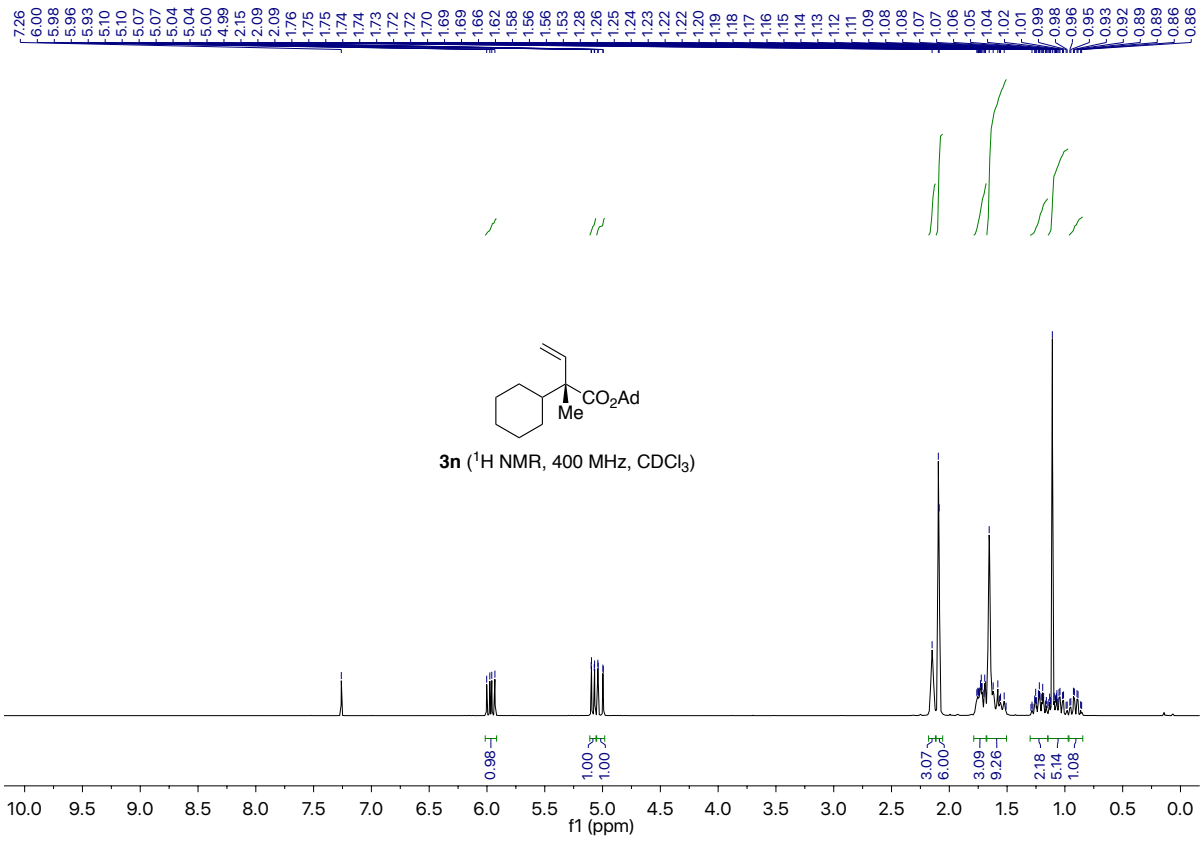

CO2H
N
Ts
Bn
3l (13C NMR, 101 MHz, CDCl3)
f1 (ppm)



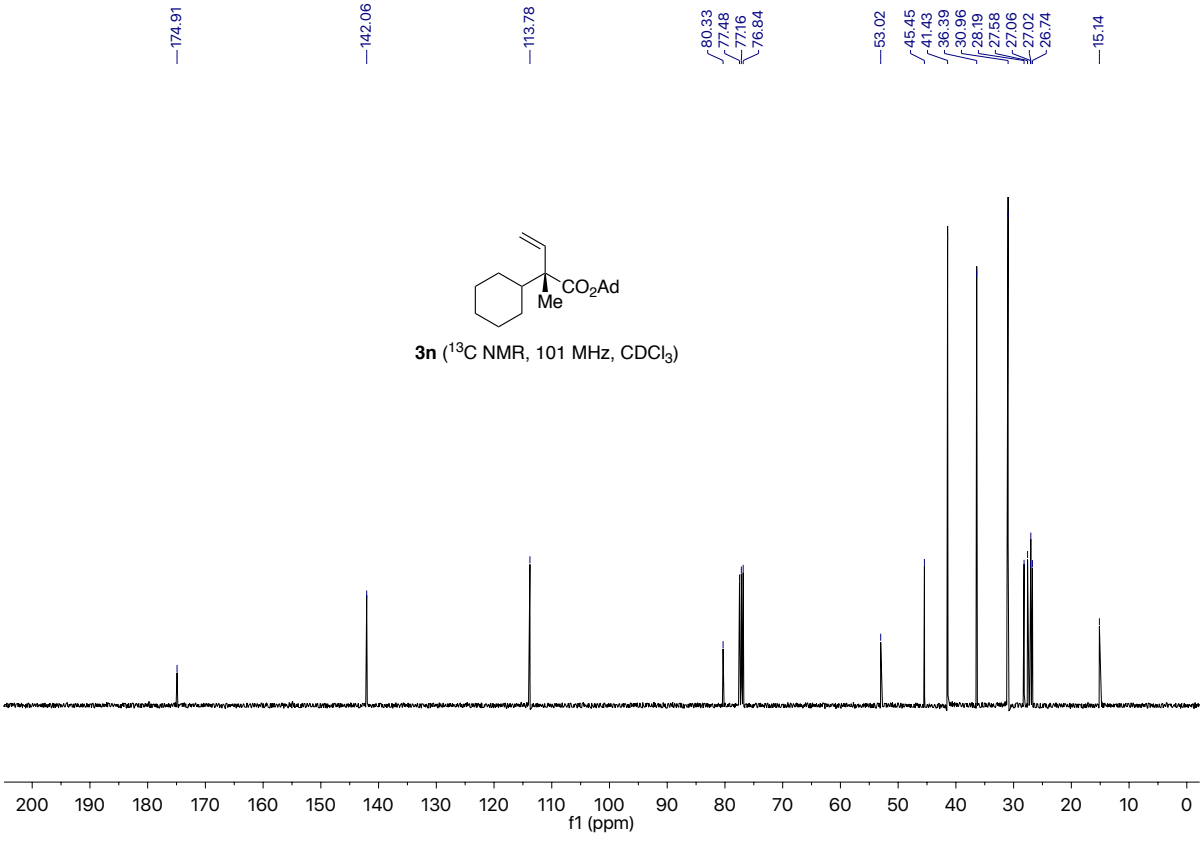
3m (^{1}H NMR, 400 MHz, $CDCl_3$)



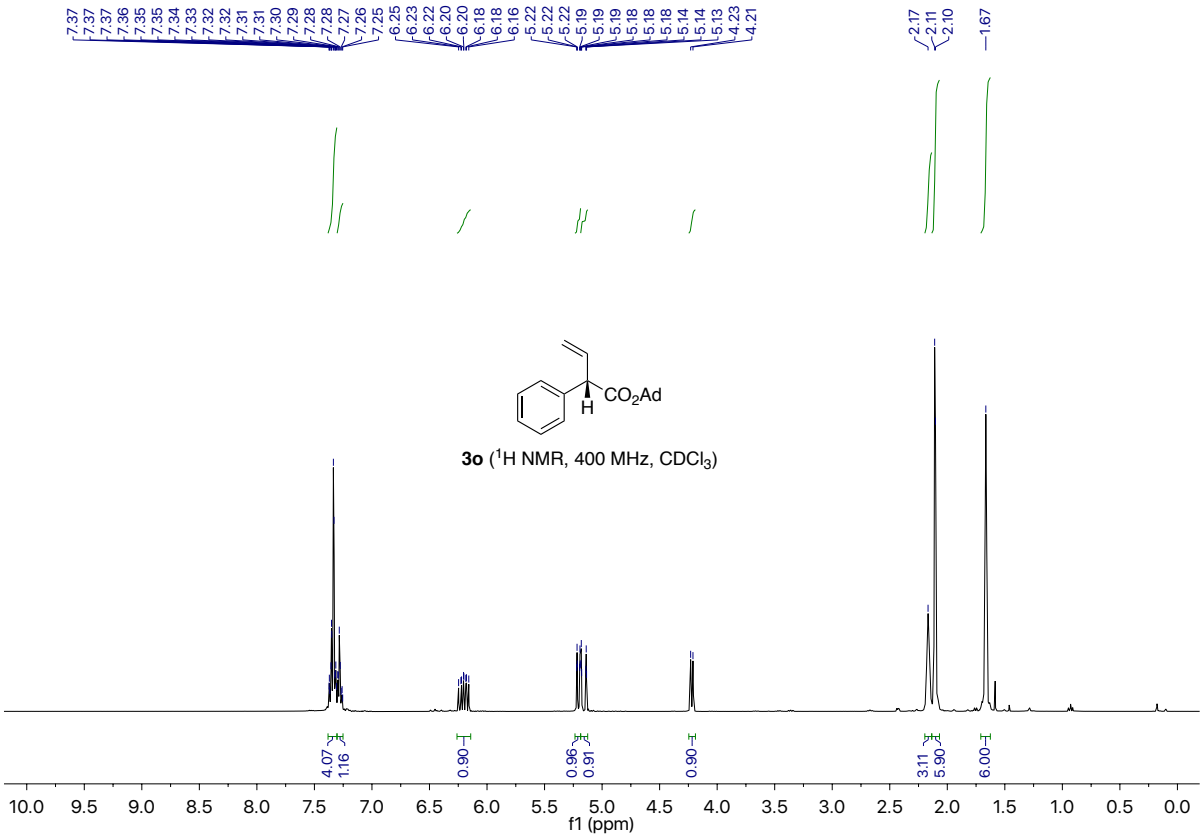
3m (^{13}C NMR, 101 MHz, $CDCl_3$)



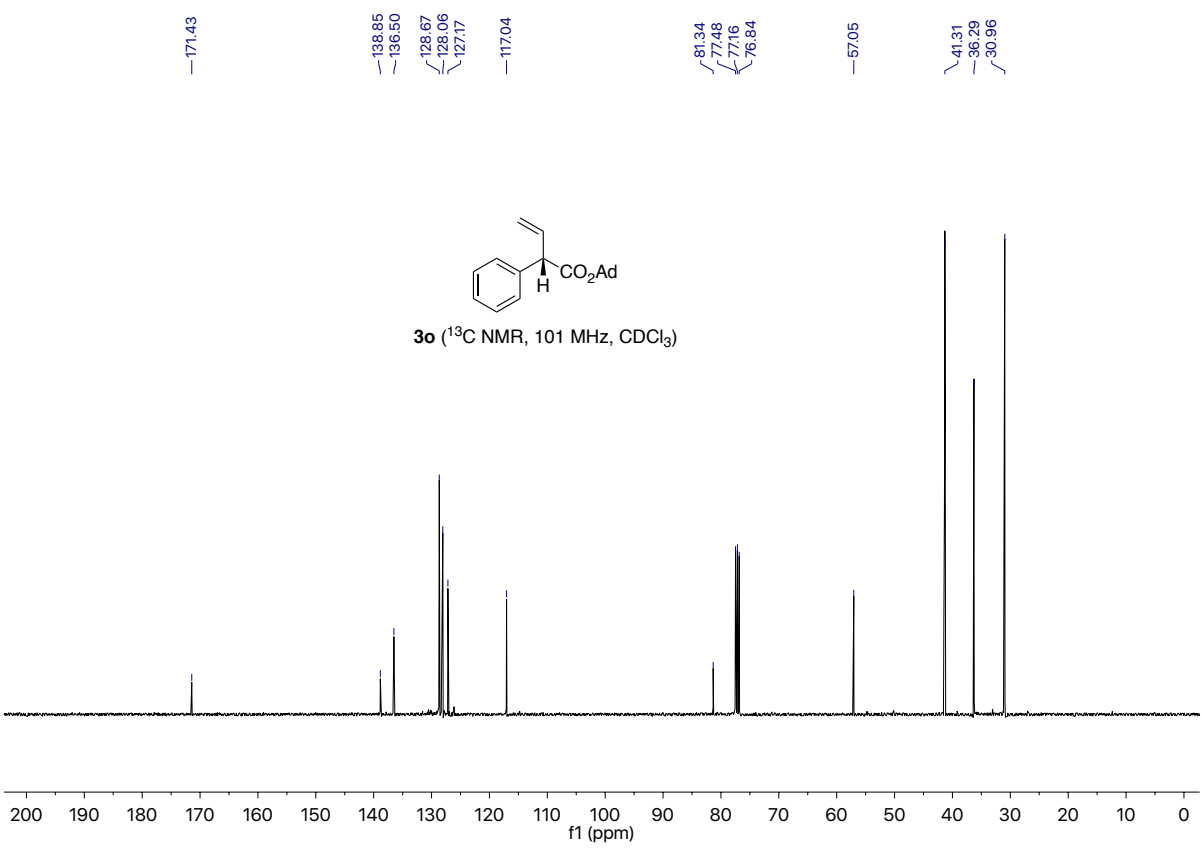
3n (^{1}H NMR, 400 MHz, $CDCl_3$)



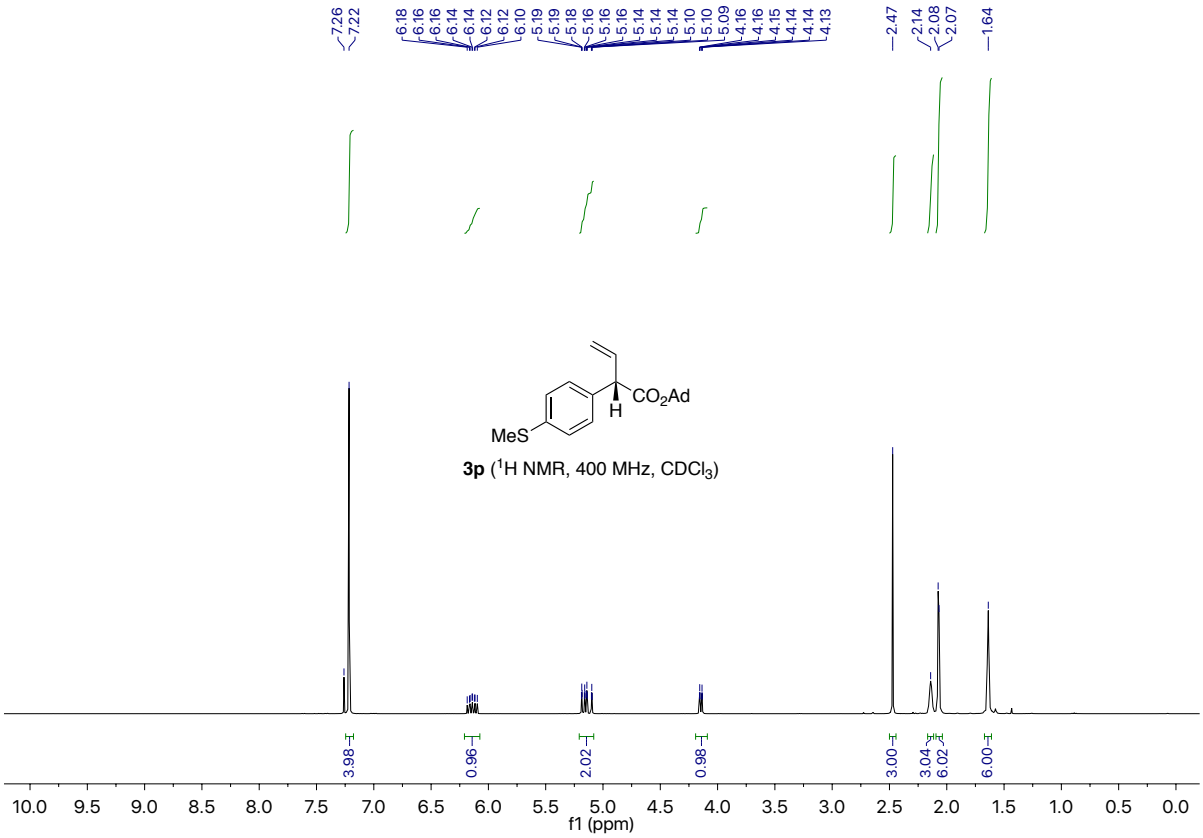
3n (^{13}C NMR, 101 MHz, $CDCl_3$)



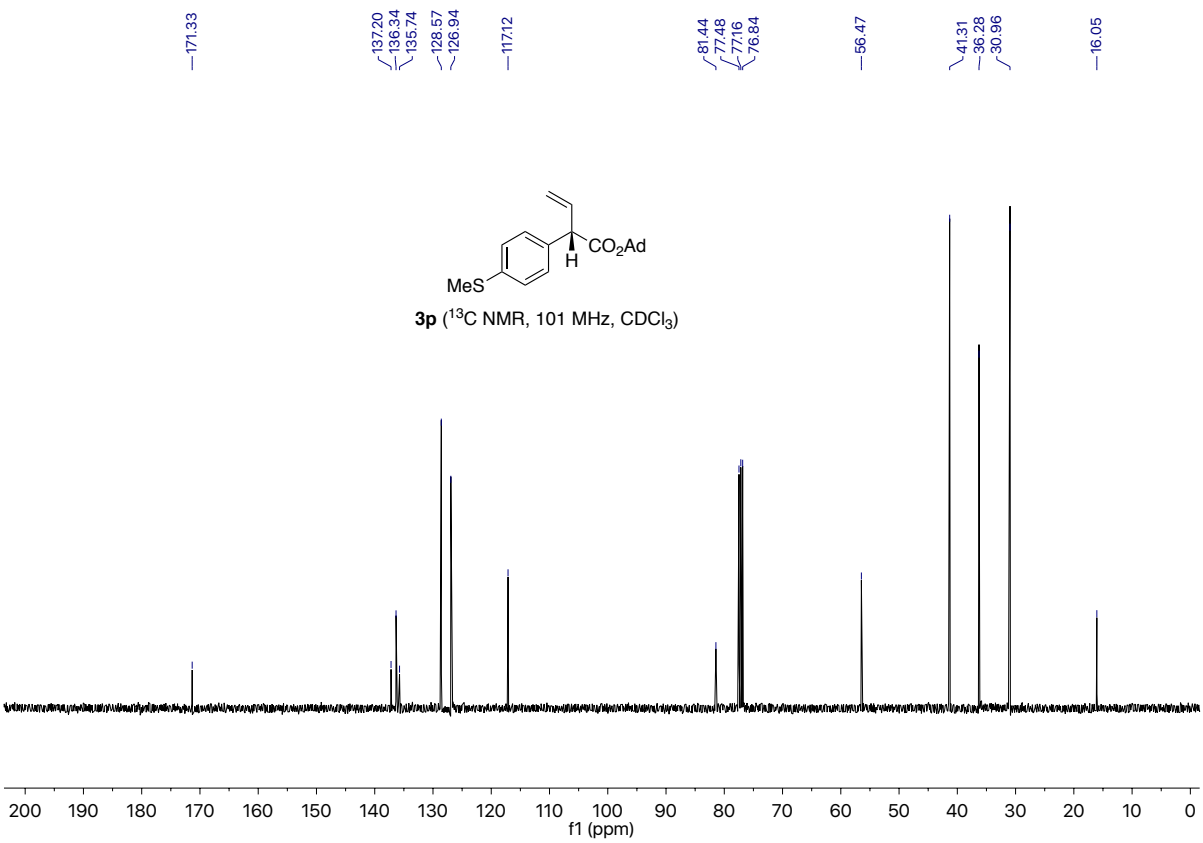
3o (^{1}H NMR, 400 MHz, $CDCl_3$)



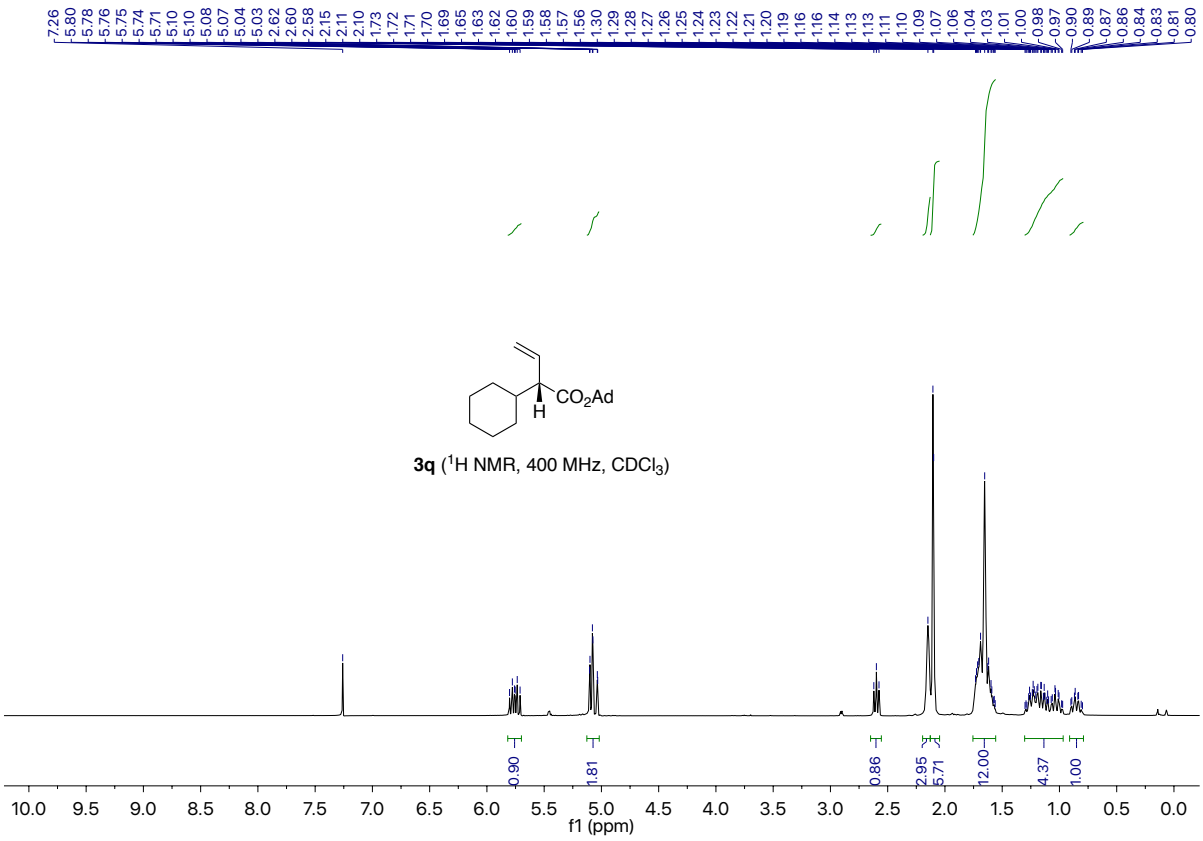
3o (^{13}C NMR, 101 MHz, $CDCl_3$)



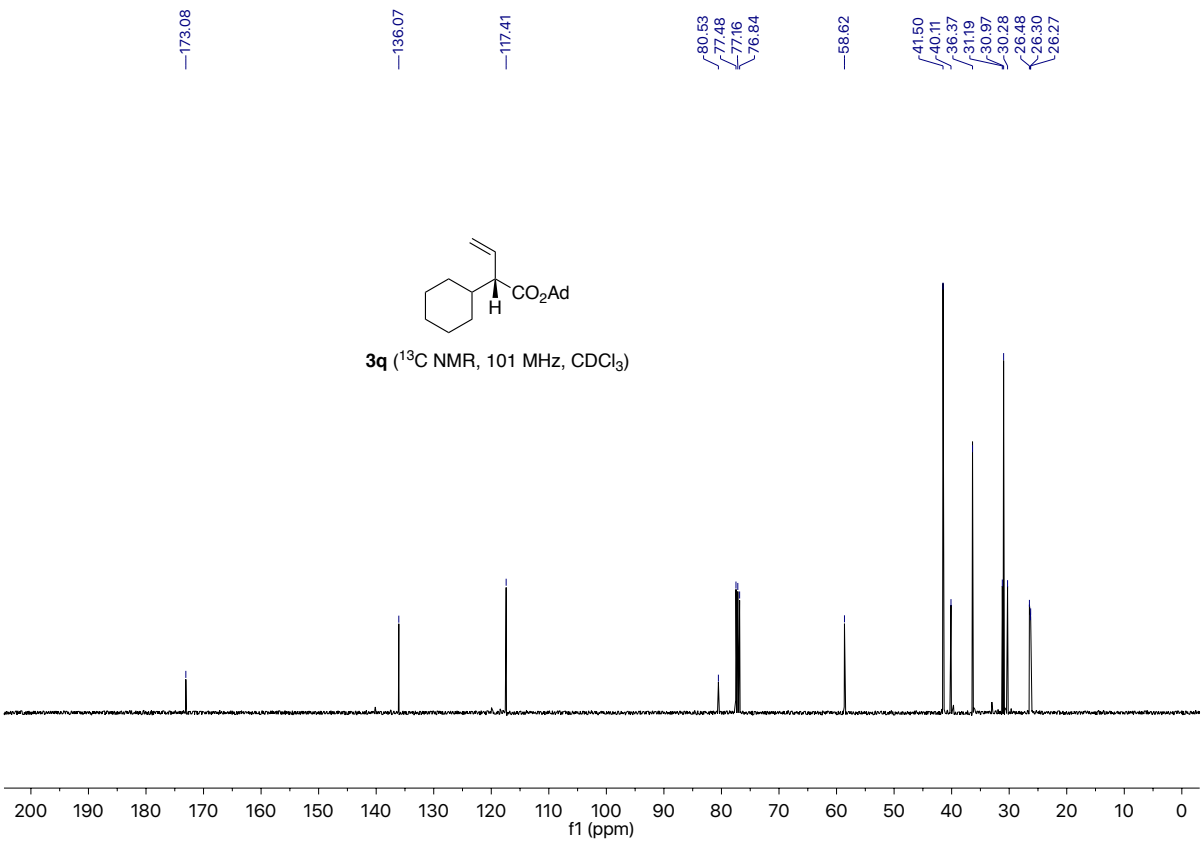
3p (^{1}H NMR, 400 MHz, $CDCl_3$)



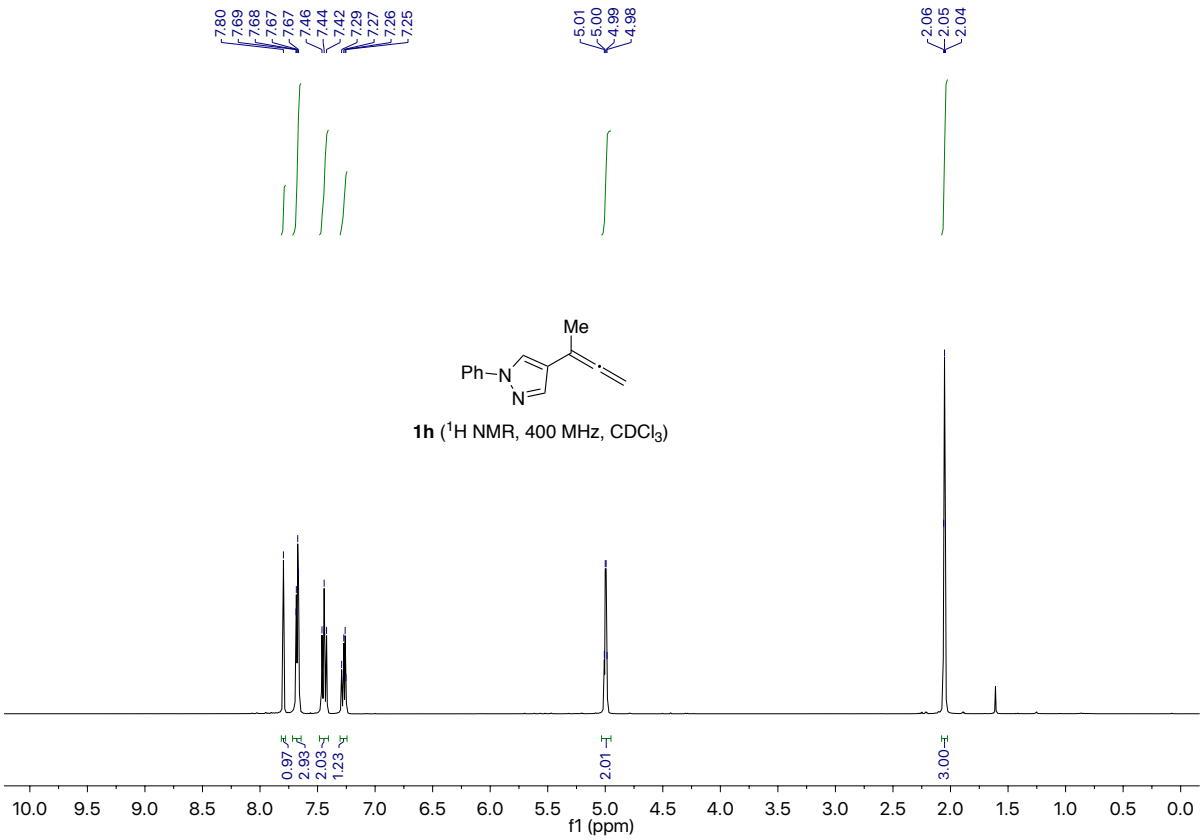
3p (^{13}C NMR, 101 MHz, $CDCl_3$)



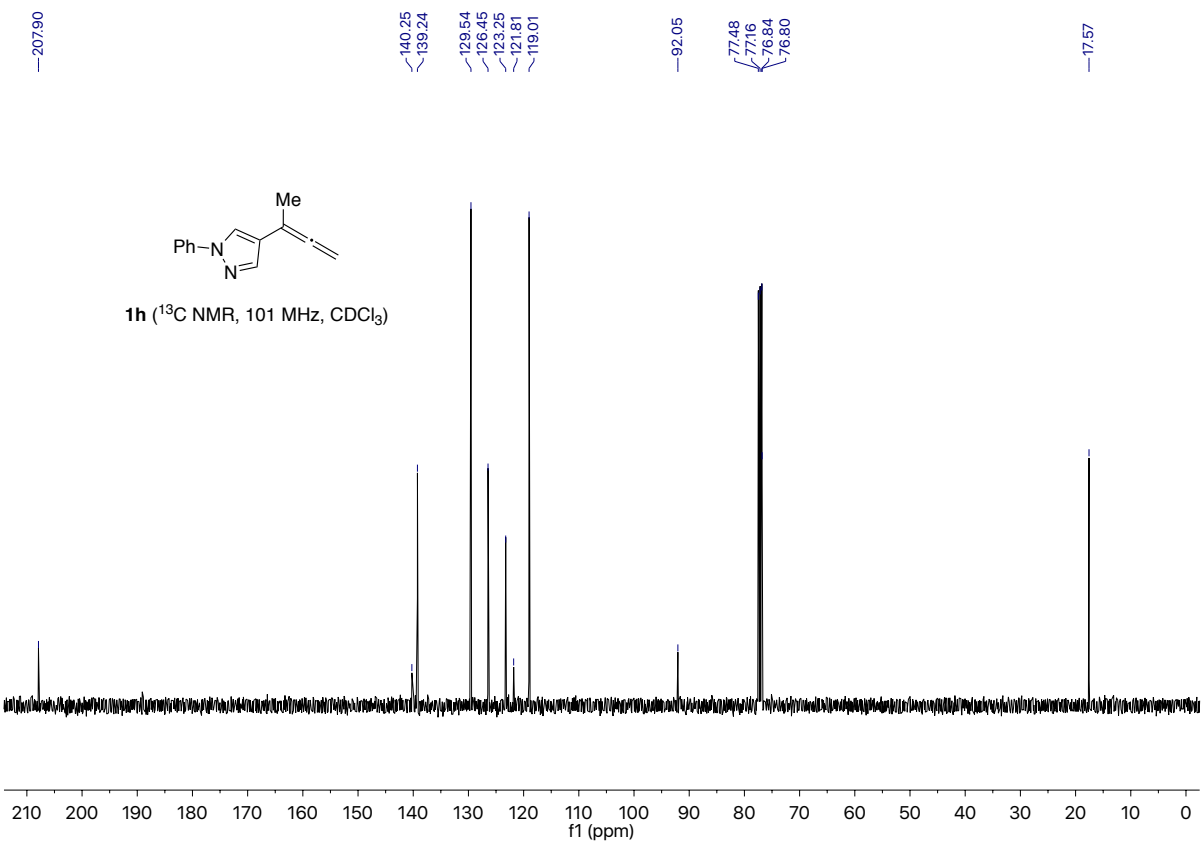
3q (^{1}H NMR, 400 MHz, $CDCl_3$)



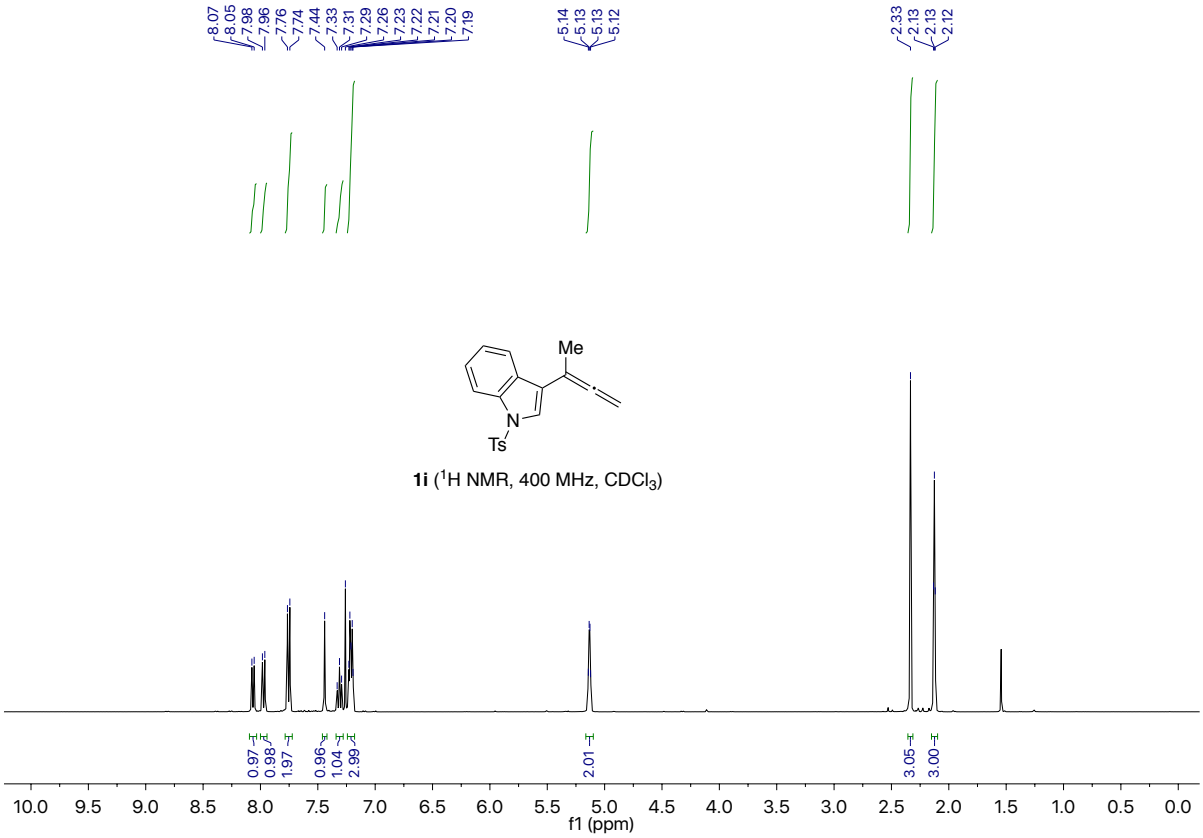
3q (^{13}C NMR, 101 MHz, $CDCl_3$)



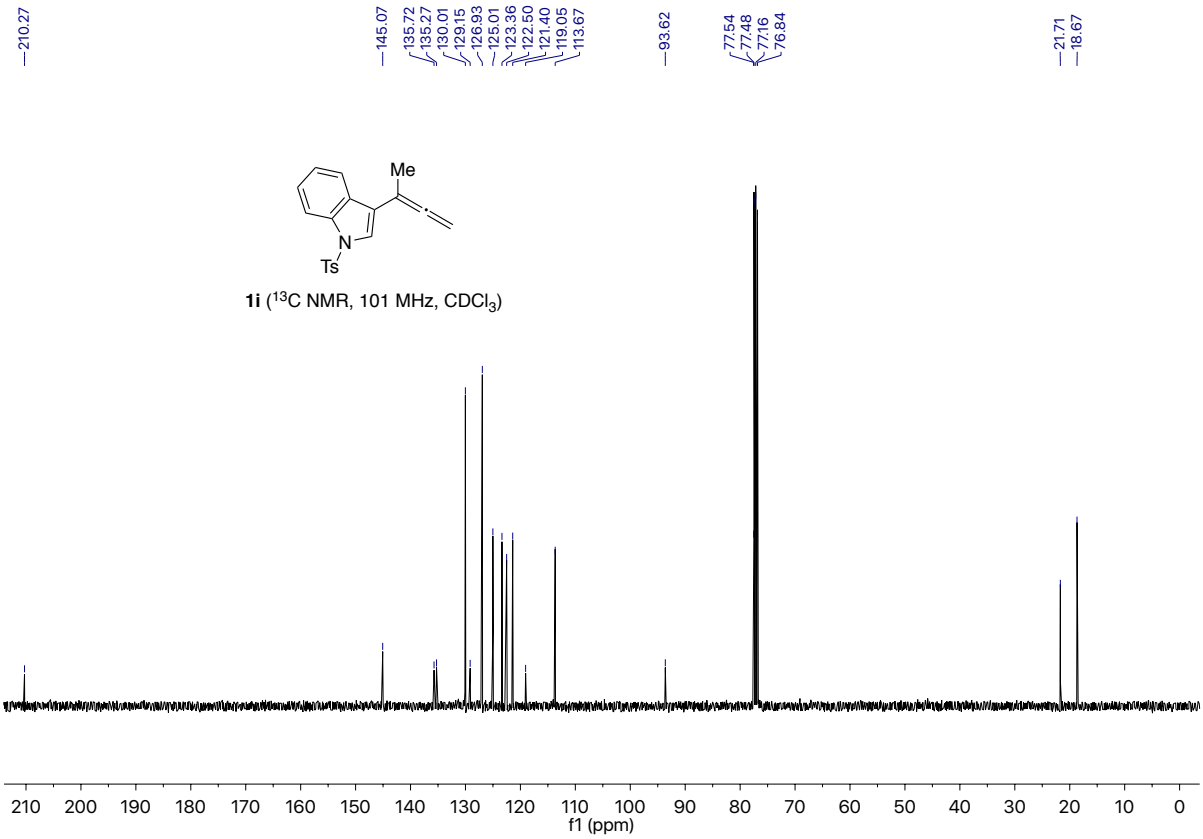
1h (^{1}H NMR, 400 MHz, $CDCl_3$)



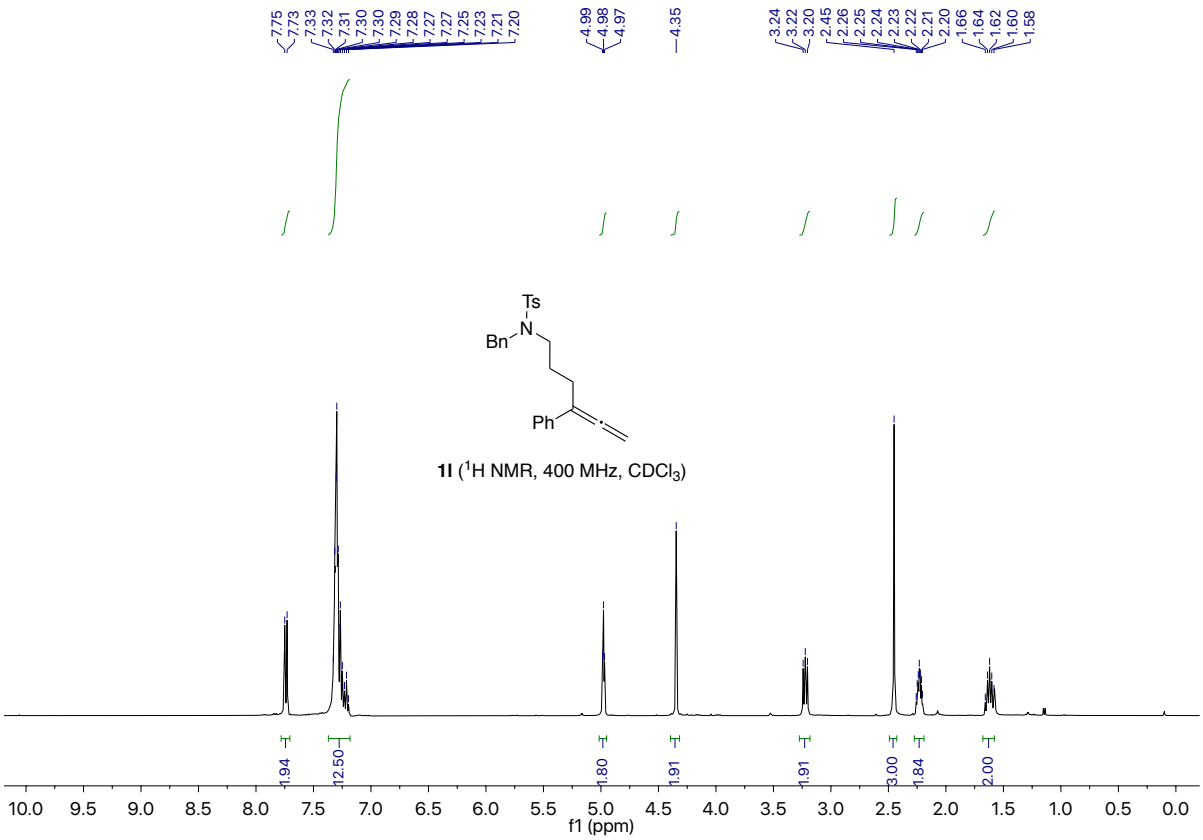
1h (^{13}C NMR, 101 MHz, $CDCl_3$)



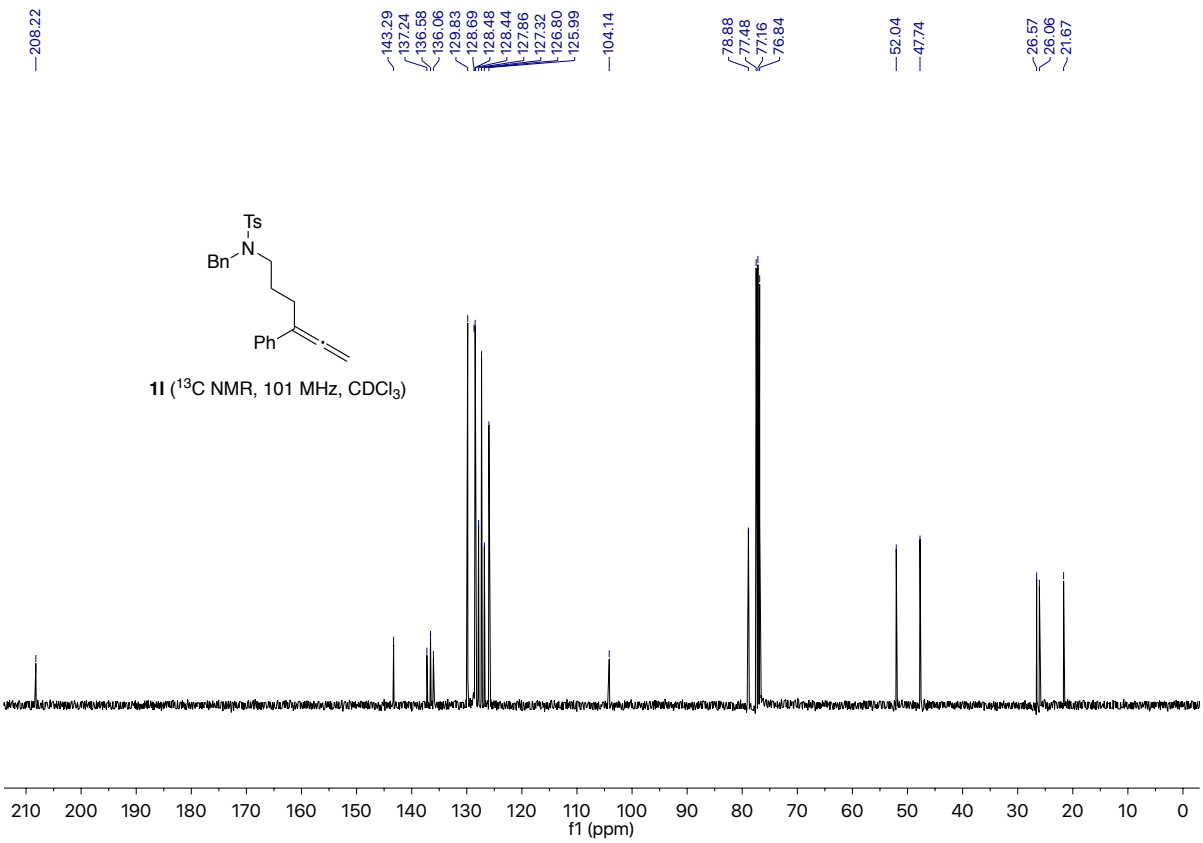
1i (^{1}H NMR, 400 MHz, $CDCl_3$)



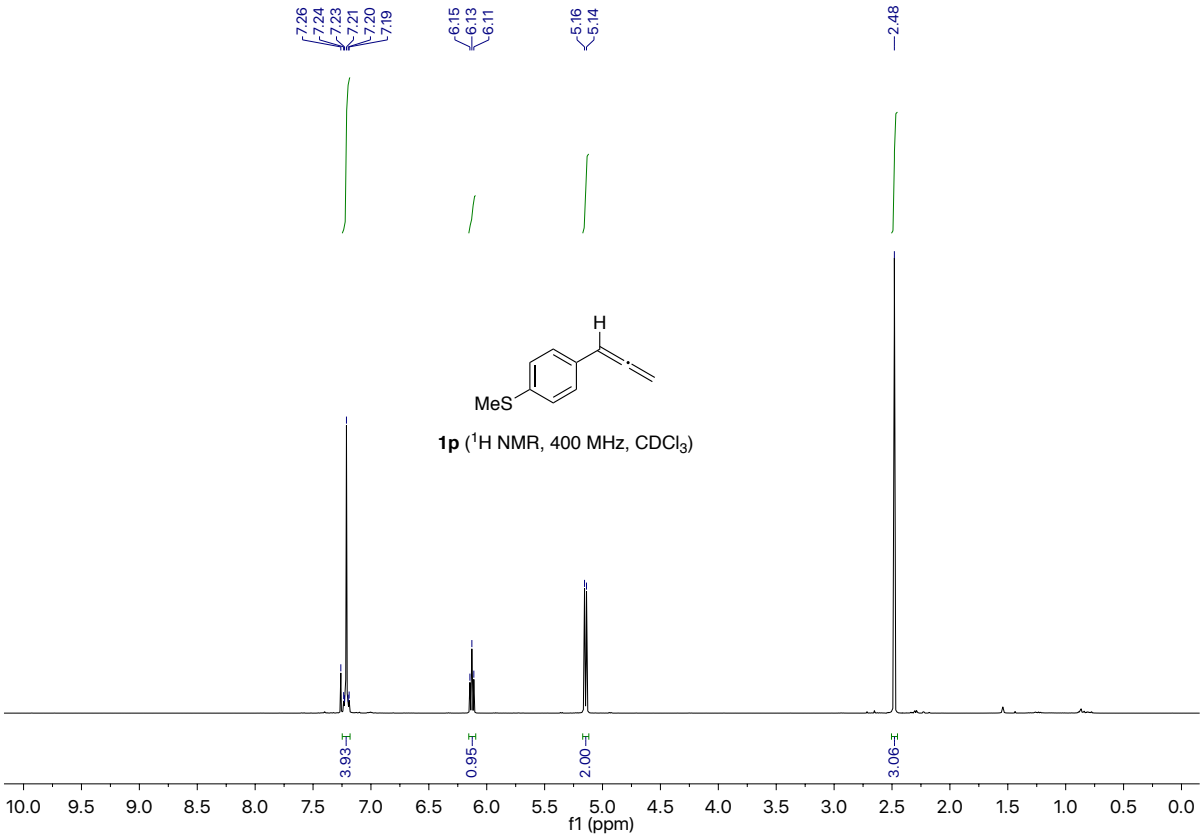
1i (^{13}C NMR, 101 MHz, $CDCl_3$)



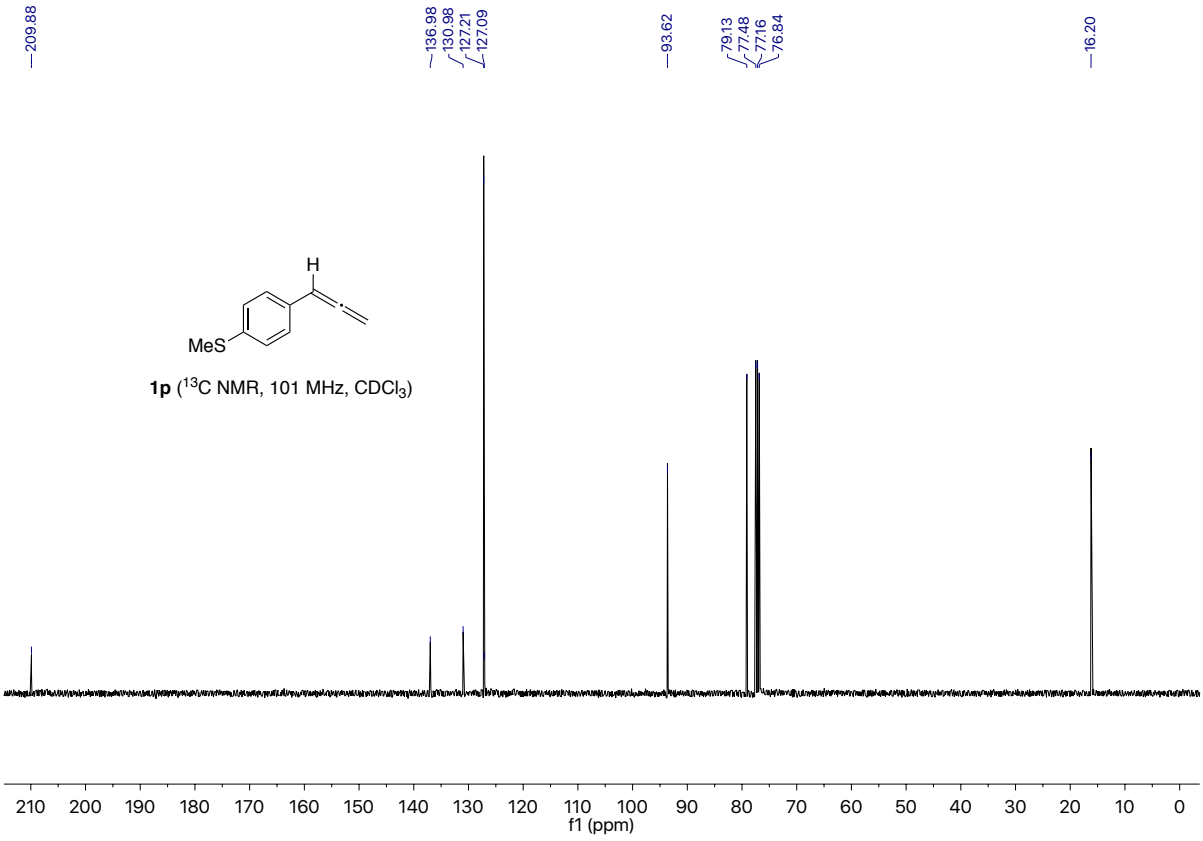
1l (^{1}H NMR, 400 MHz, $CDCl_3$)



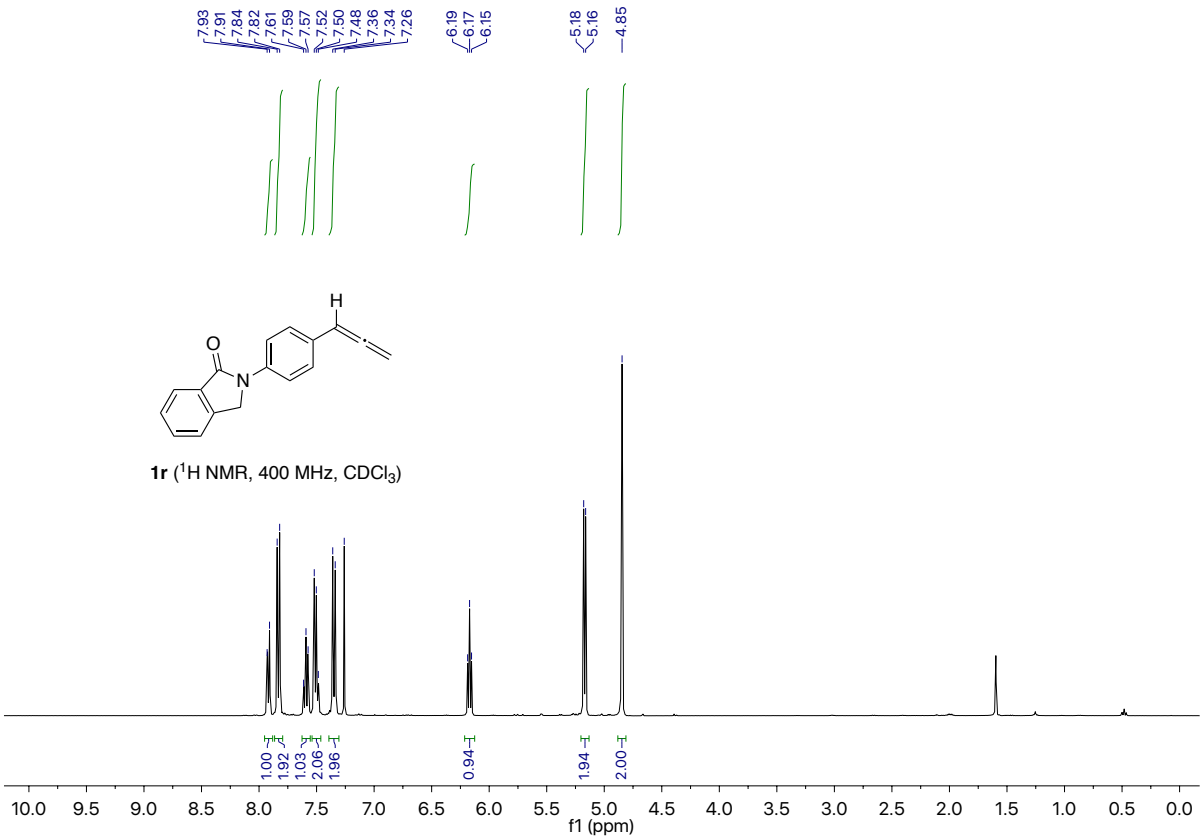
1l (^{13}C NMR, 101 MHz, $CDCl_3$)



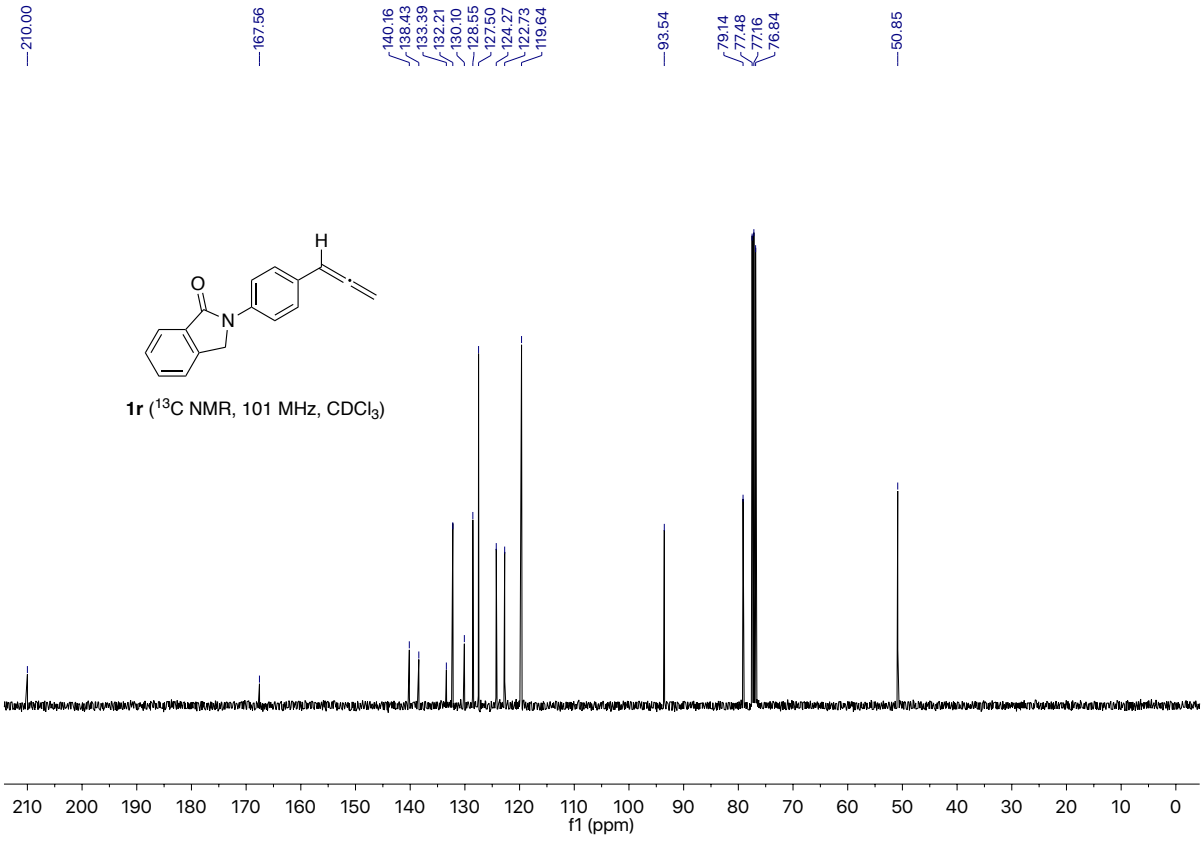
1p (^{1}H NMR, 400 MHz, $CDCl_3$)



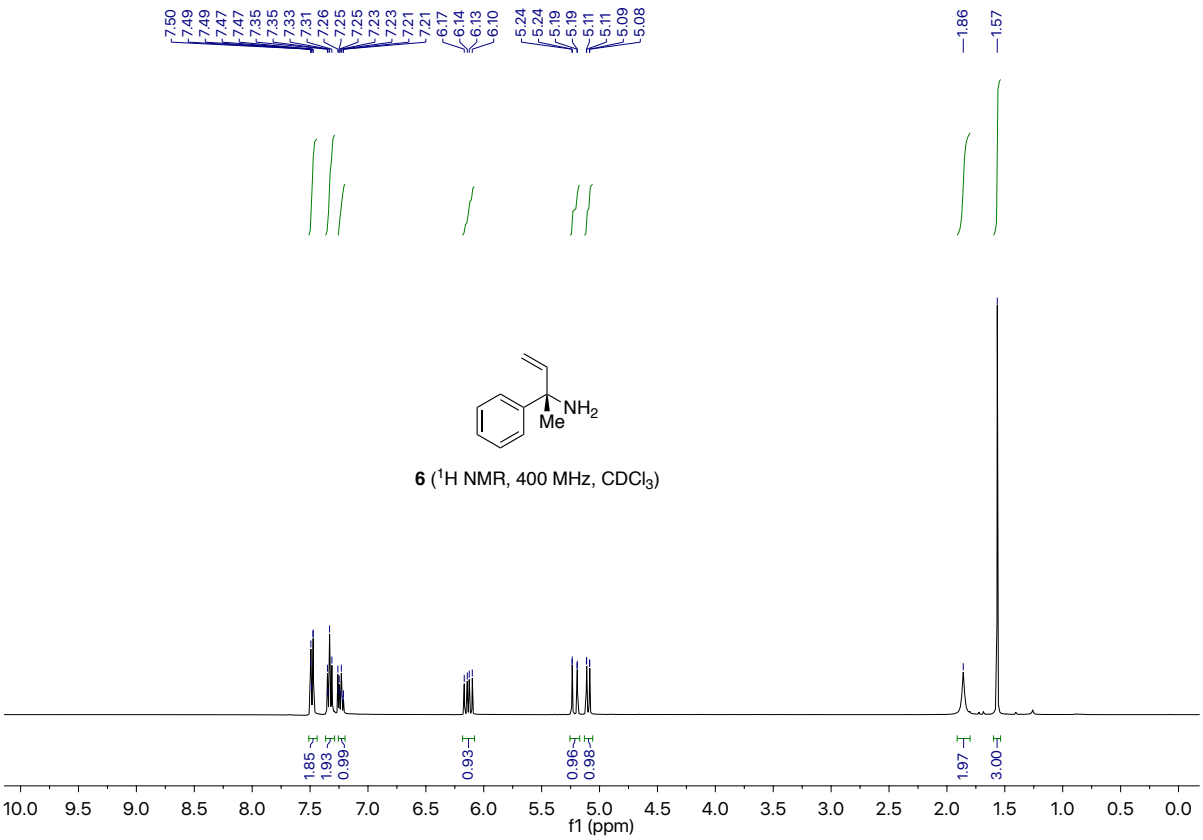
1p (^{13}C NMR, 101 MHz, $CDCl_3$)



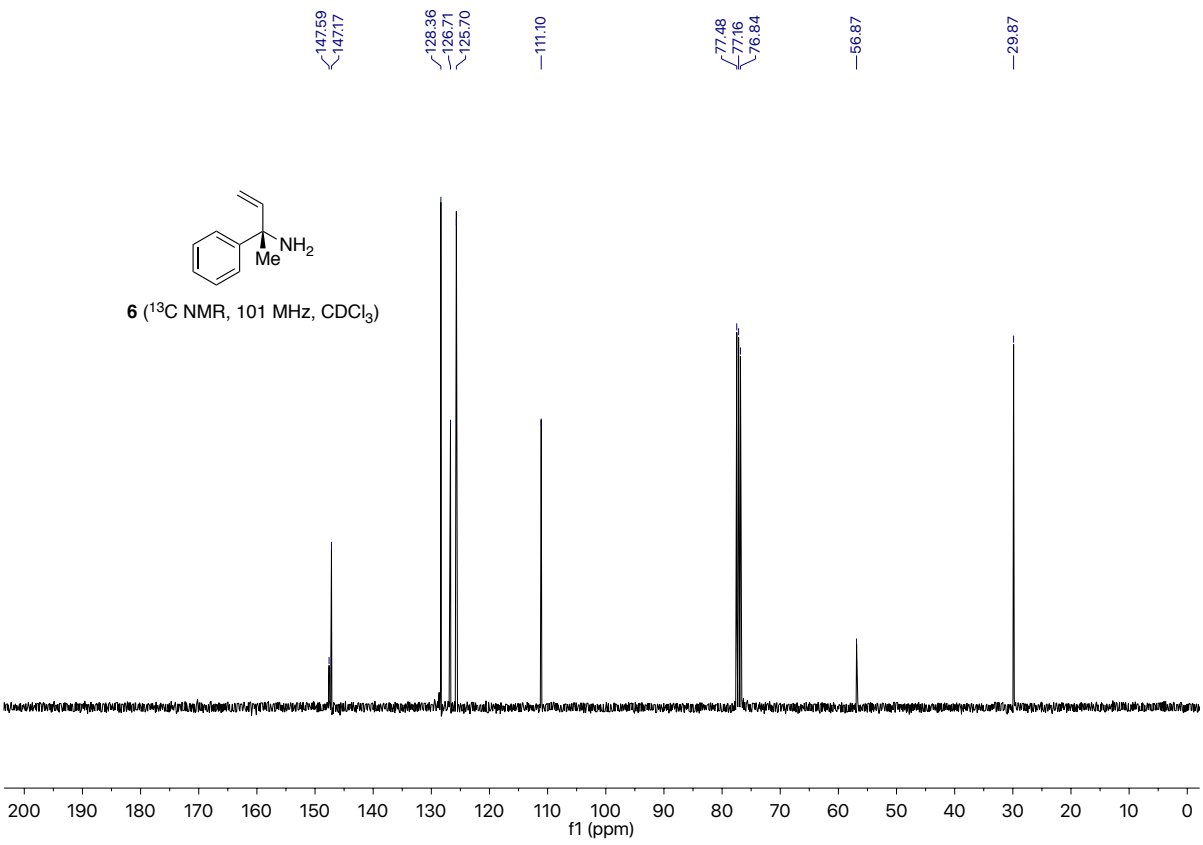
1r (^{1}H NMR, 400 MHz, $CDCl_3$)



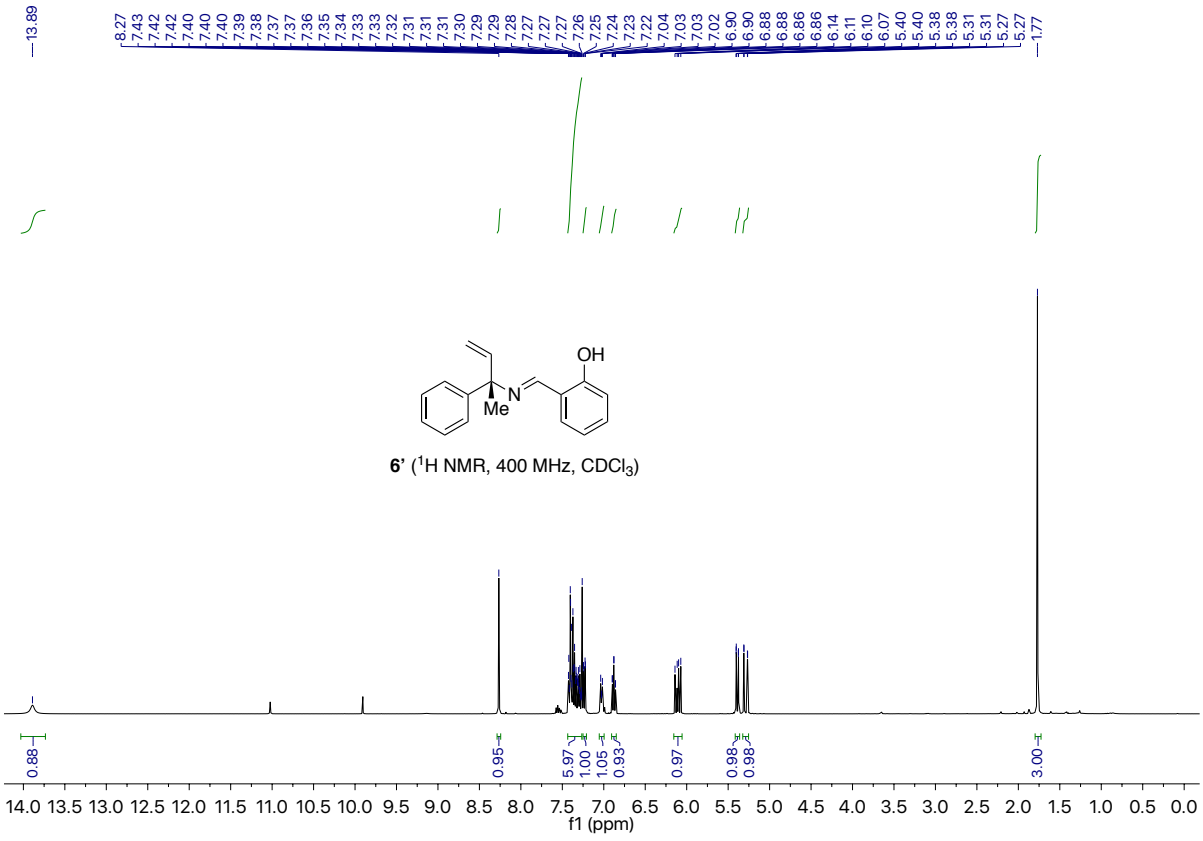
1r (^{13}C NMR, 101 MHz, $CDCl_3$)



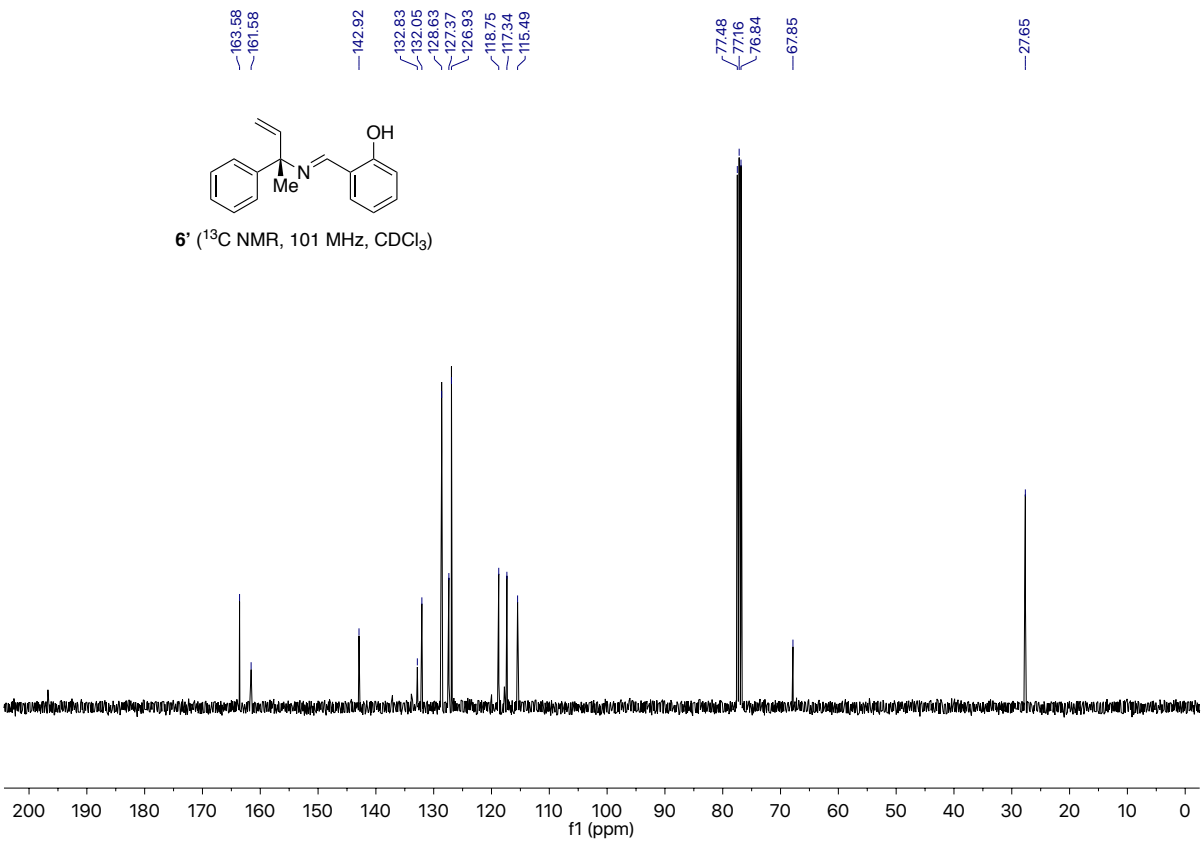
6 (^{1}H NMR, 400 MHz, $CDCl_3$)



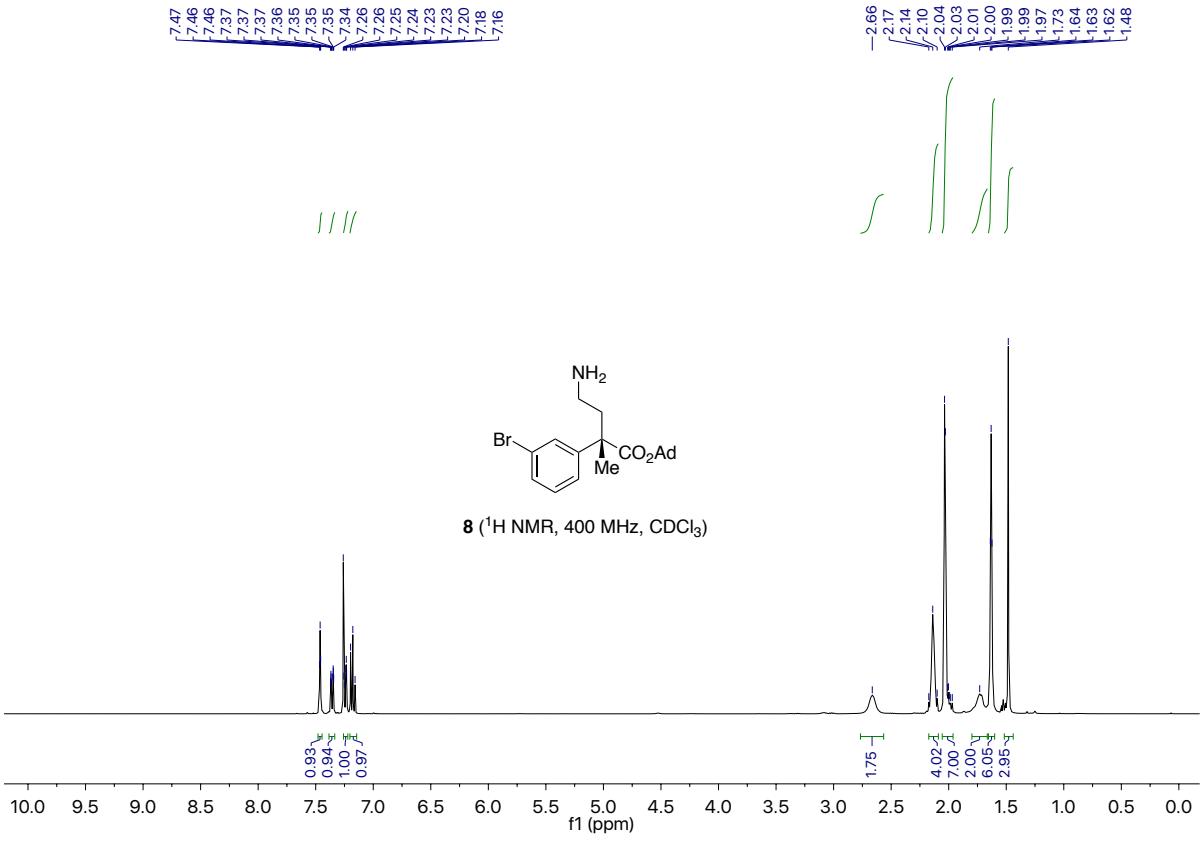
6 (^{13}C NMR, 101 MHz, $CDCl_3$)



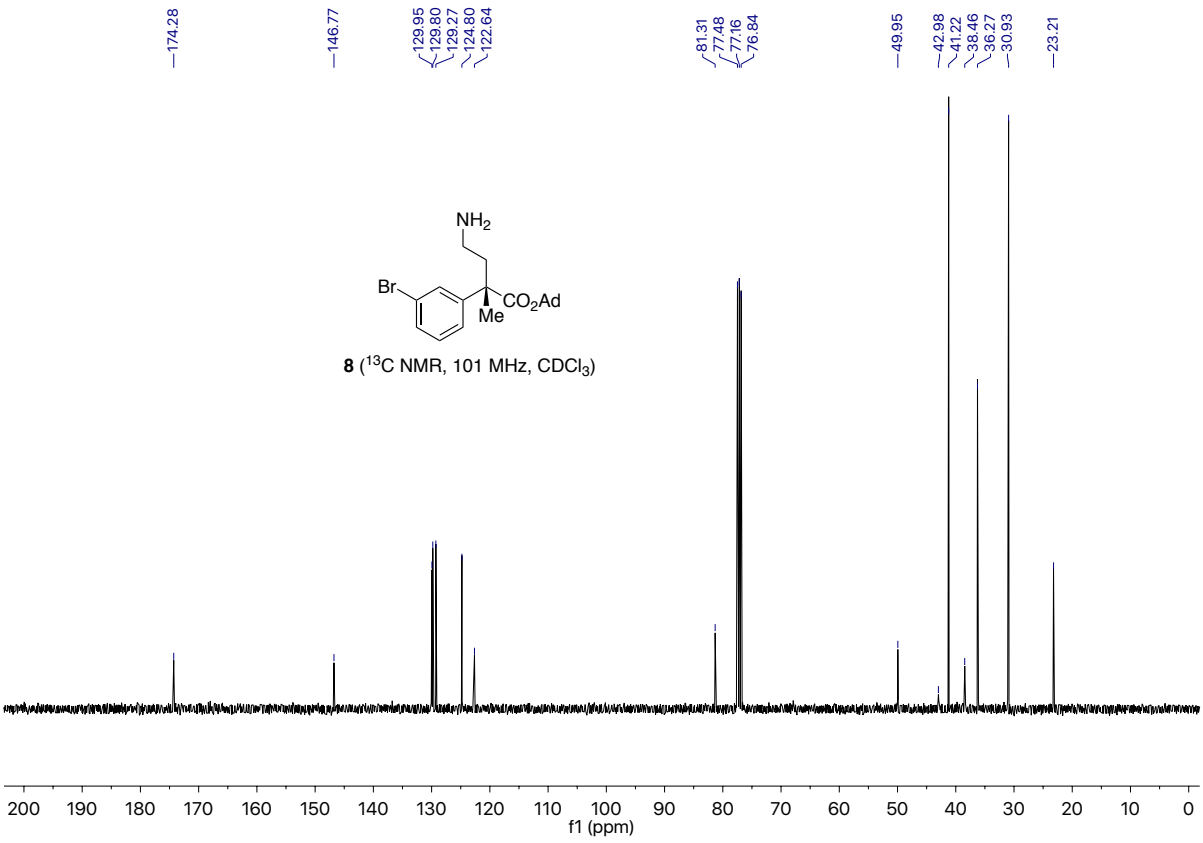
6' (^{1}H NMR, 400 MHz, $CDCl_3$)



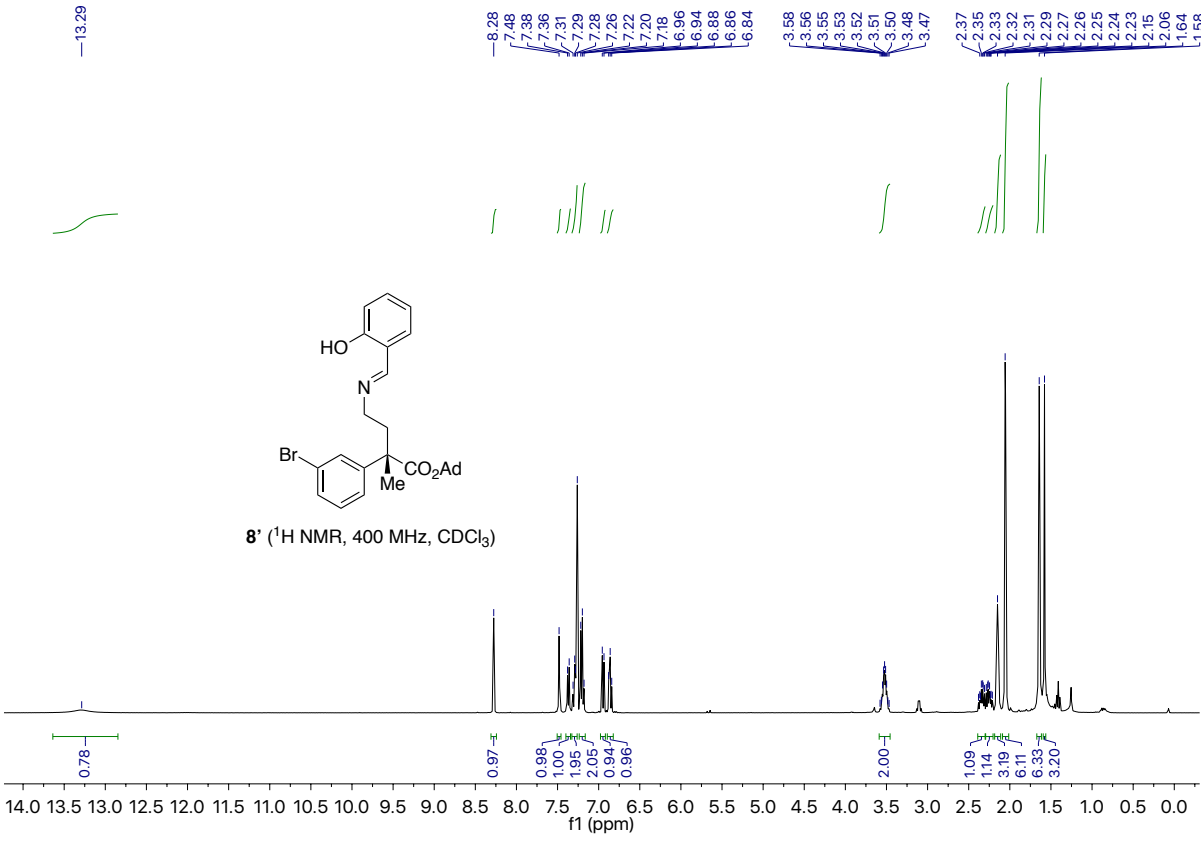
6' (^{13}C NMR, 101 MHz, $CDCl_3$)



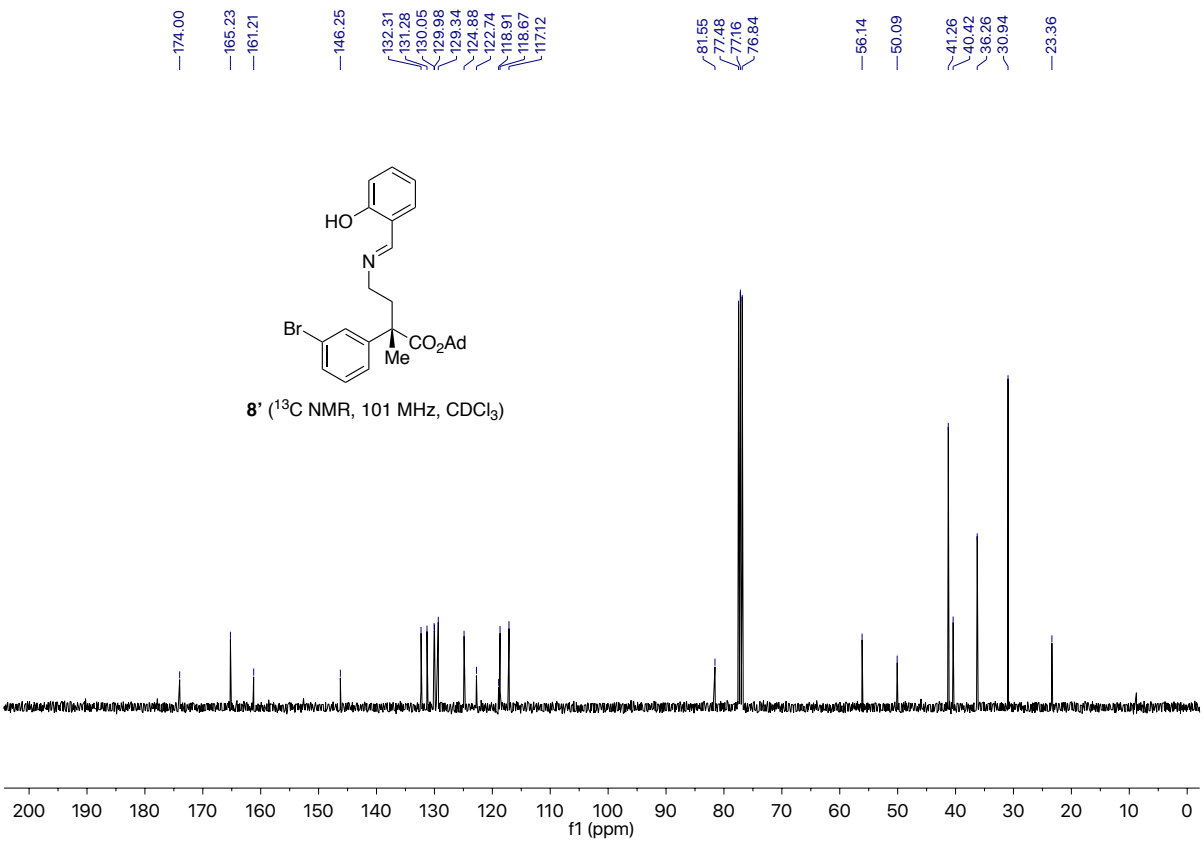
8 (^{1}H NMR, 400 MHz, $CDCl_3$)



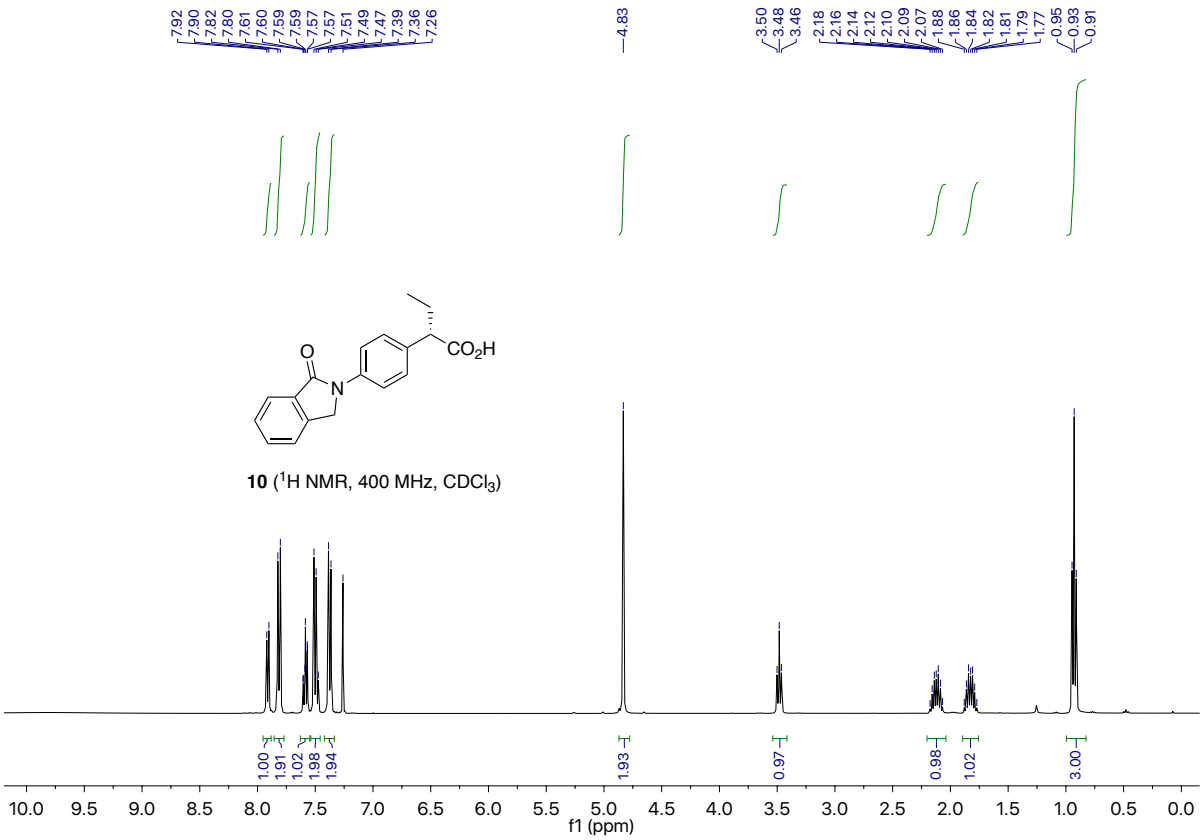
8 (^{13}C NMR, 101 MHz, $CDCl_3$)



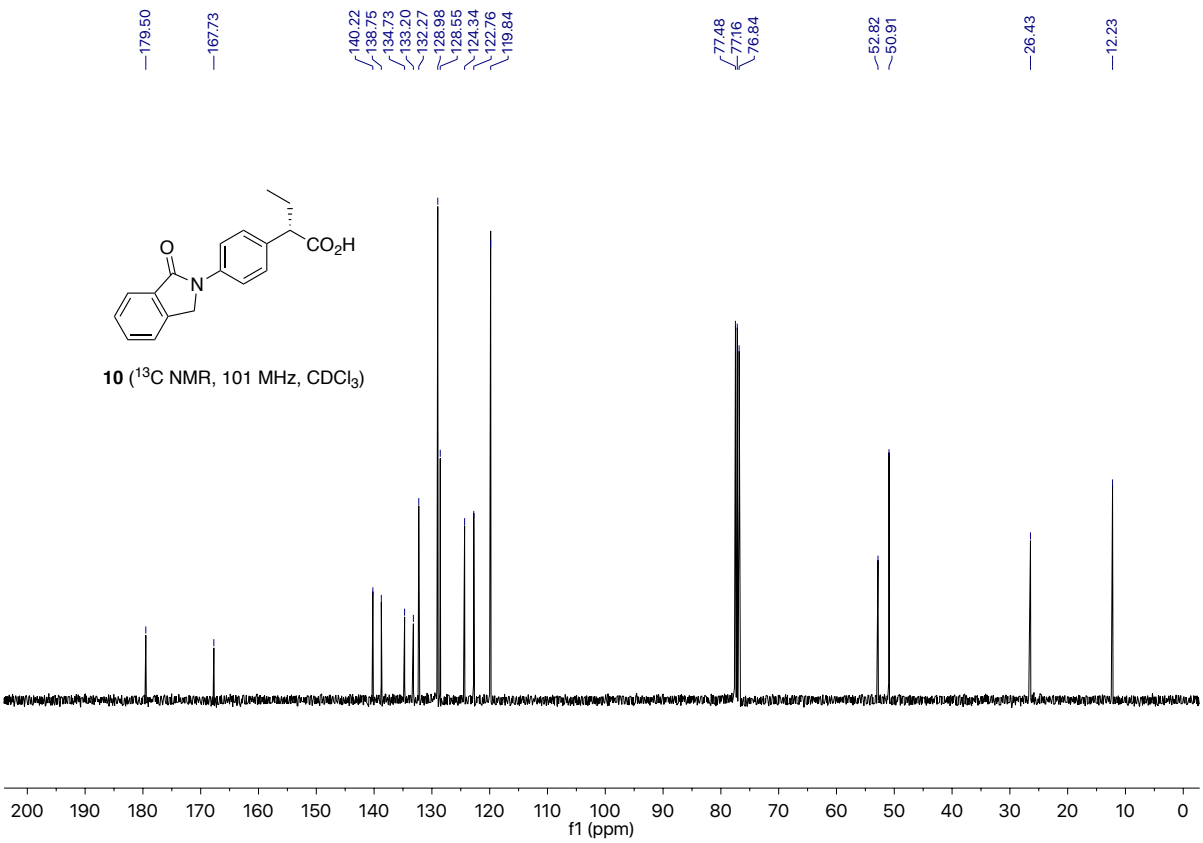
8' (^{1}H NMR, 400 MHz, $CDCl_3$)



8' (^{13}C NMR, 101 MHz, $CDCl_3$)

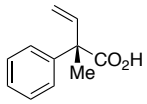


10 (^{1}H NMR, 400 MHz, $CDCl_3$)

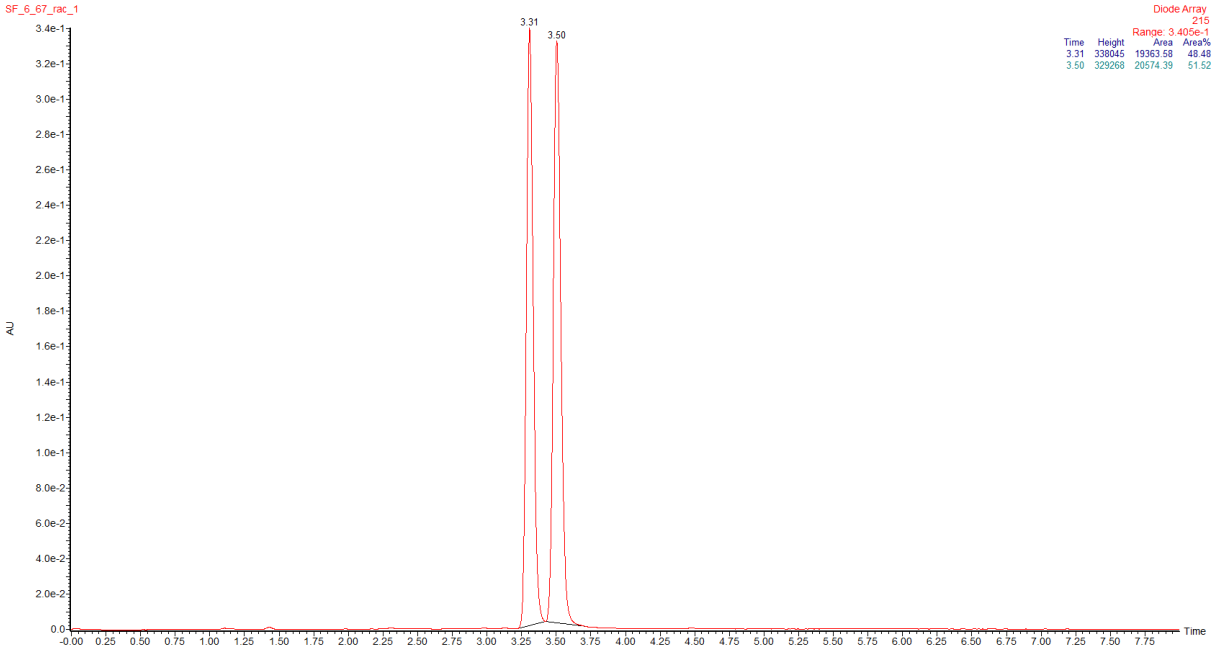


10 (^{13}C NMR, 101 MHz, $CDCl_3$)

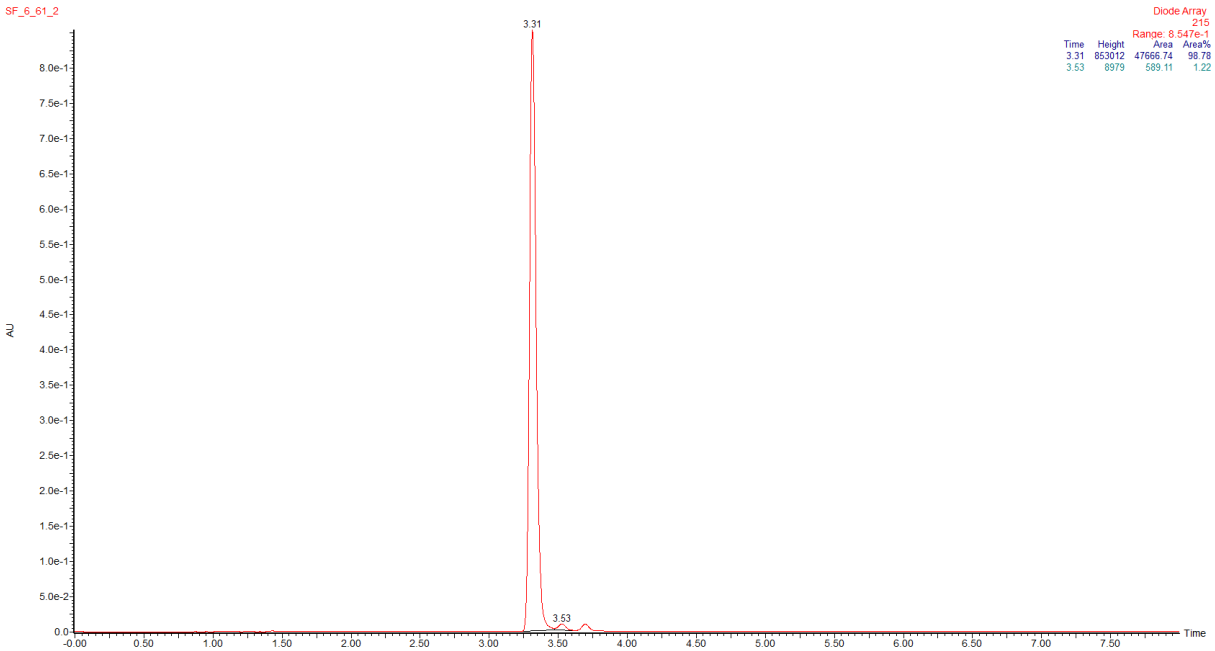
(*S*)-2-methyl-2-phenylbut-3-enoic acid (3a)



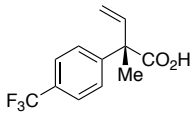
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



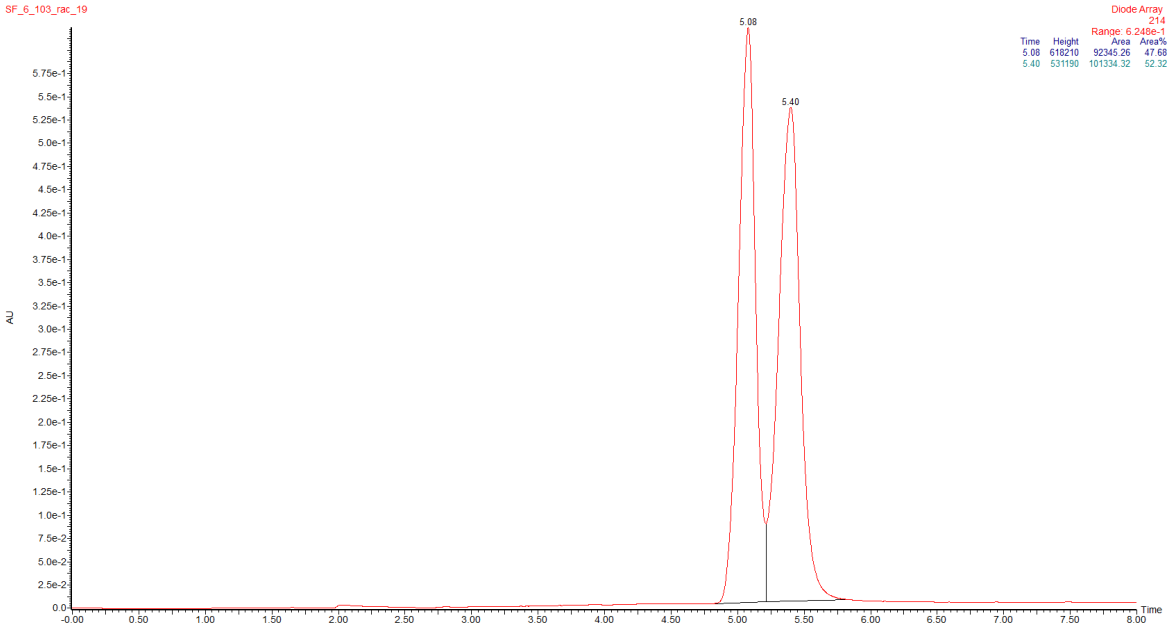
Enantioenriched(AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



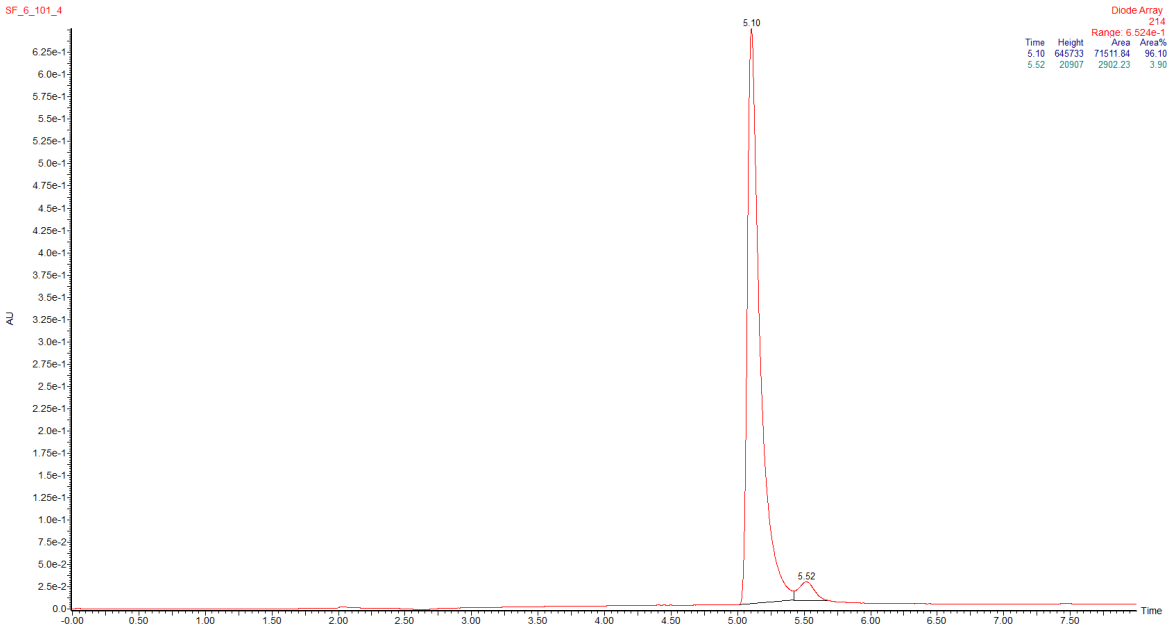
(*S*)-2-methyl-2-(4-(trifluoromethyl)phenyl)but-3-enoic acid (3b)



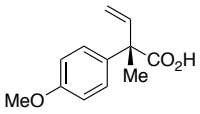
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



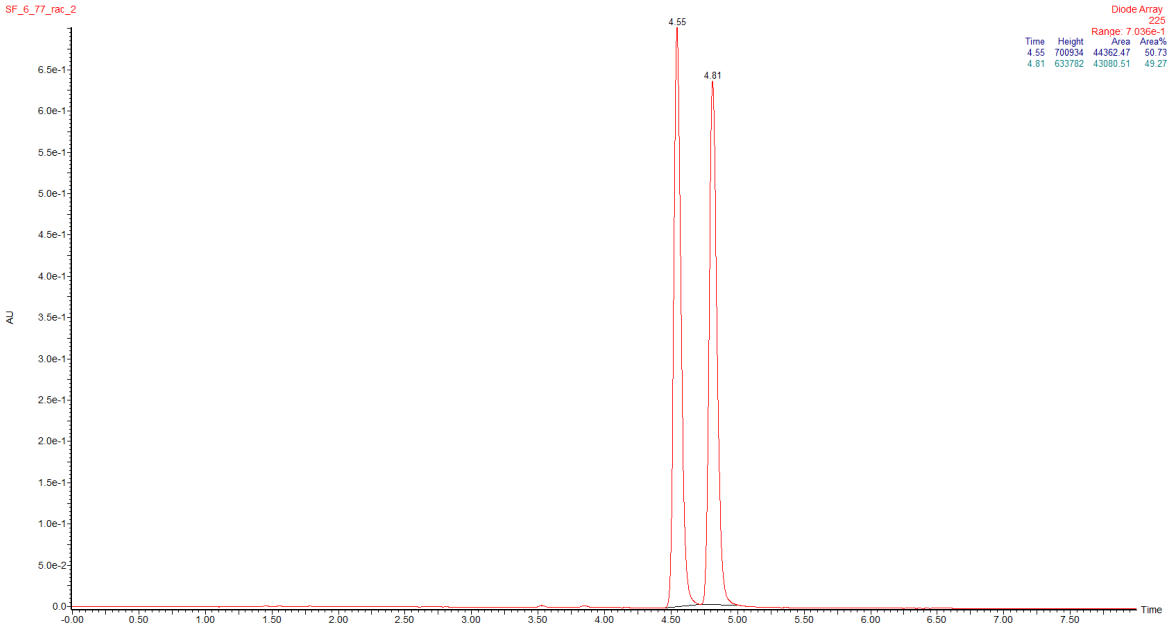
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



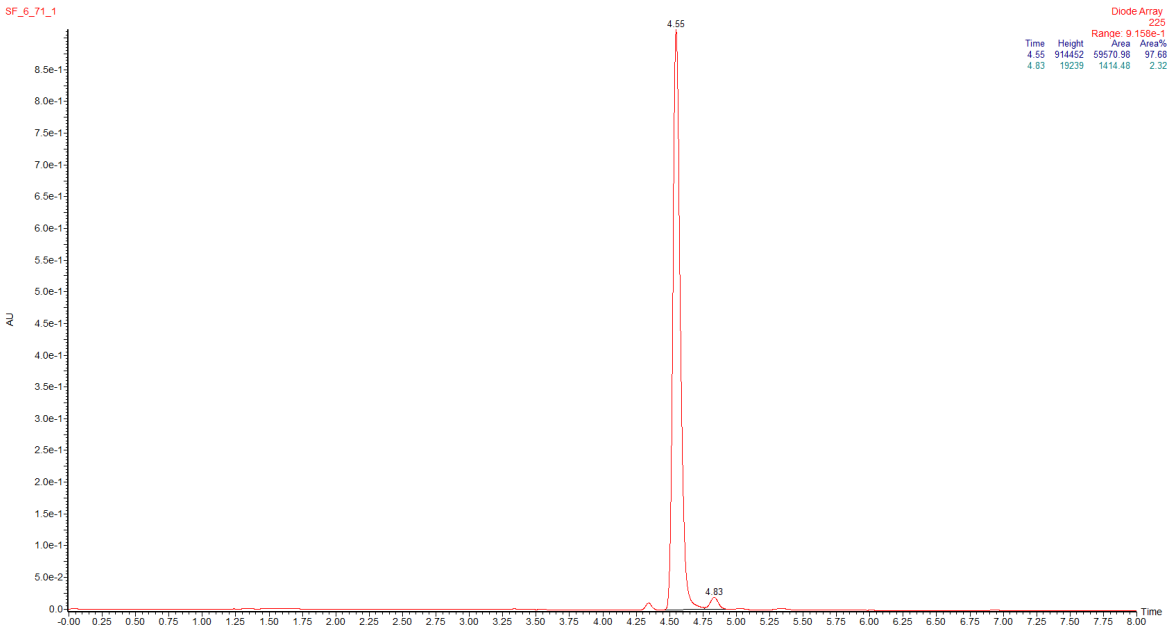
(*S*)-2-(4-methoxyphenyl)-2-methylbut-3-enoic acid (3c)



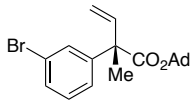
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



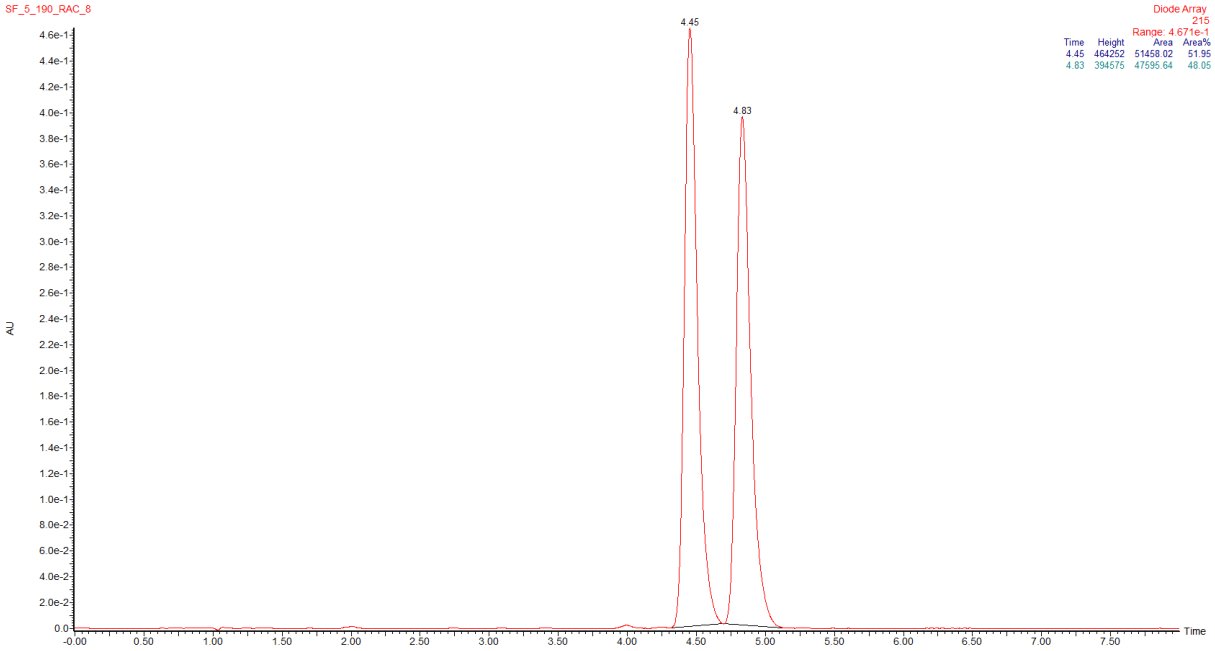
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



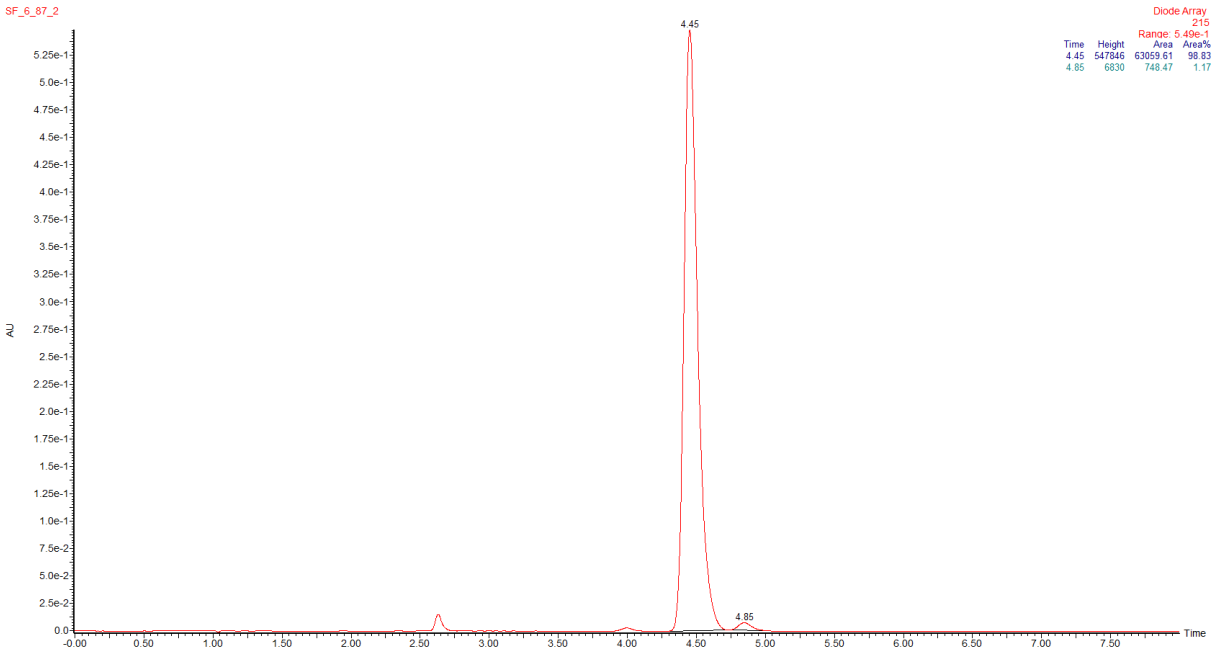
adamantan-1-yl (*S*)-2-(3-bromophenyl)-2-methylbut-3-enoate (3d)



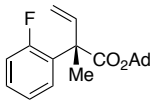
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



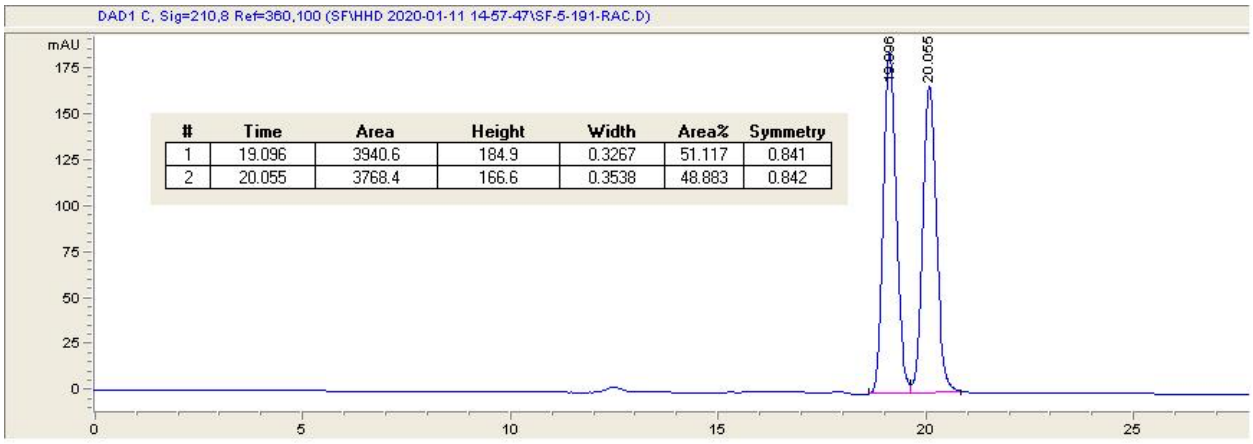
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



adamantan-1-yl (*S*)-2-(2-fluorophenyl)-2-methylbut-3-enoate (3e)

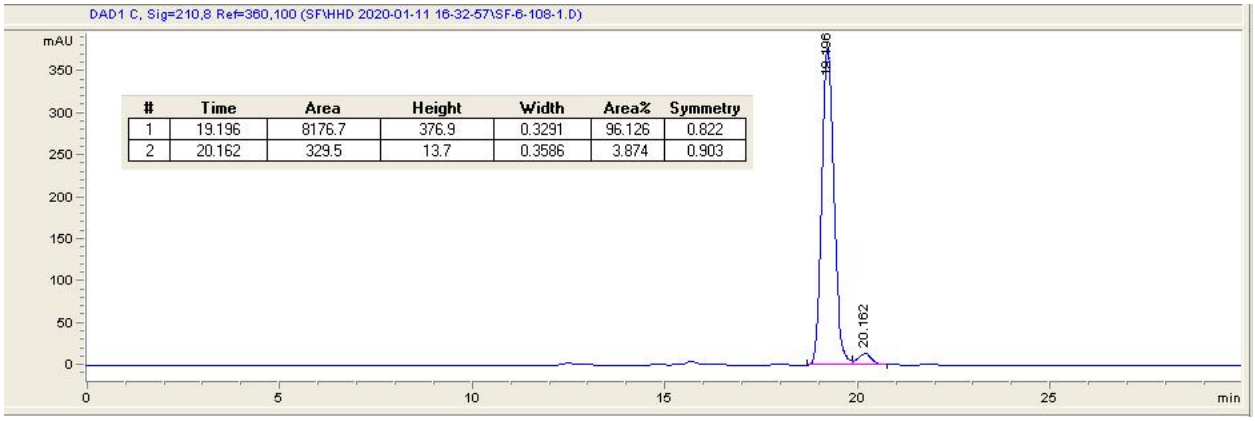


Recemic (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



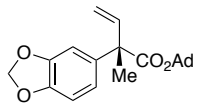
#	Time	Area	Height	Width	Area%	Symmetry
1	19.096	3940.6	184.9	0.3267	51.117	0.841
2	20.055	3768.4	166.6	0.3538	48.883	0.842

Enantioenriched (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):

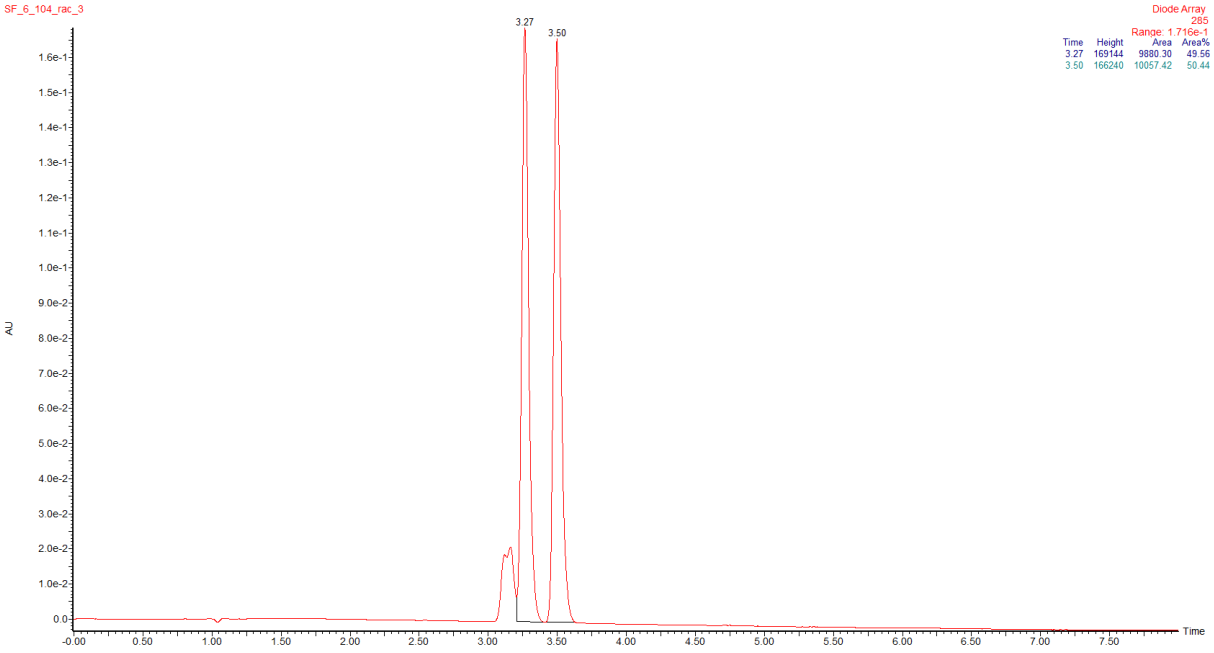


#	Time	Area	Height	Width	Area%	Symmetry
1	19.196	8176.7	376.9	0.3291	96.126	0.822
2	20.162	329.5	13.7	0.3586	3.874	0.903

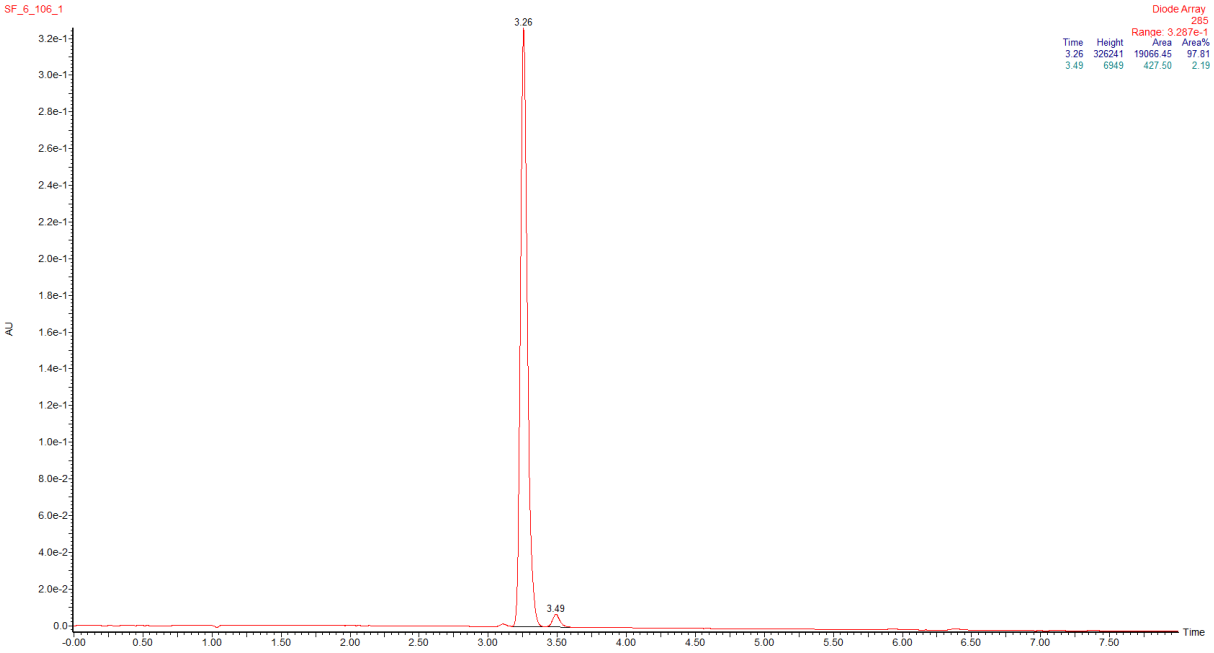
adamantan-1-yl (*S*)-2-(benzo[d][1,3]dioxol-5-yl)-2-methylbut-3-enoate (3f)



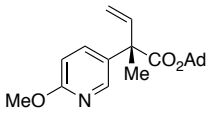
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



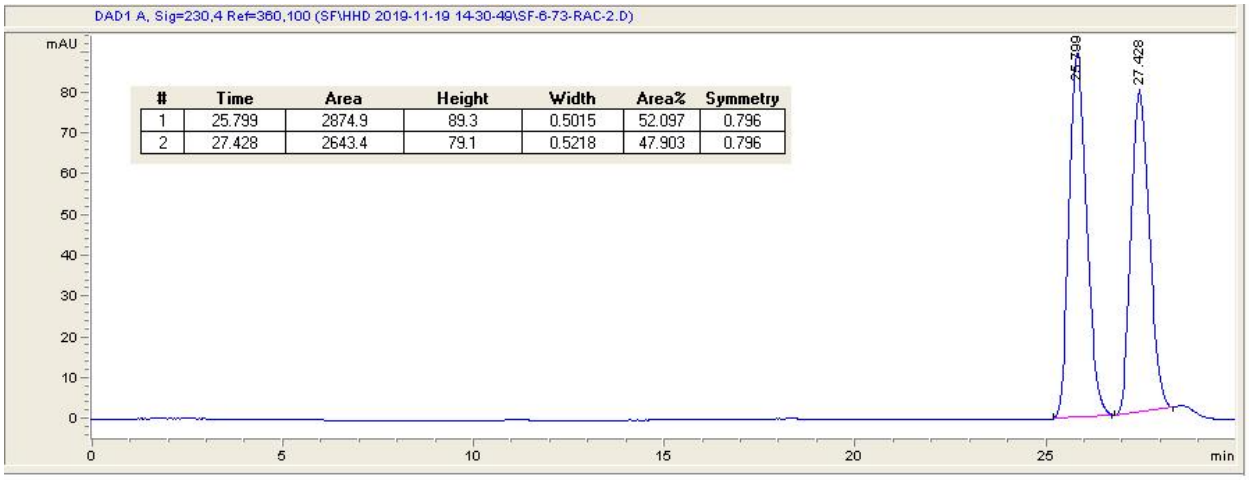
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



adamantan-1-yl (*S*)-2-(6-methoxypyridin-3-yl)-2-methylbut-3-enoate (3g)

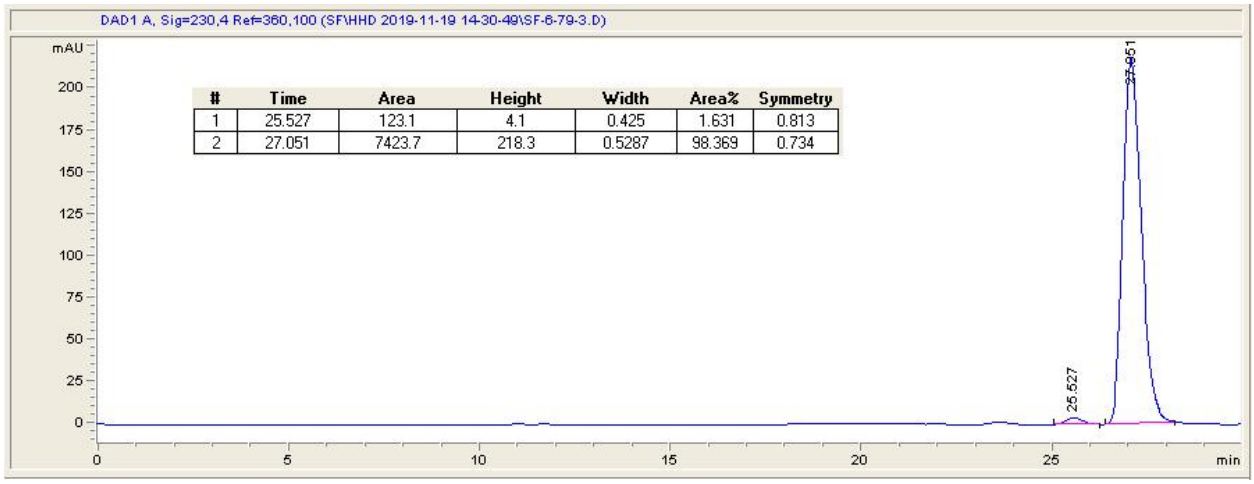


Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



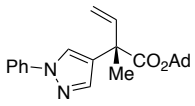
#	Time	Area	Height	Width	Area%	Symmetry
1	25.799	2874.9	89.3	0.5015	52.097	0.796
2	27.428	2643.4	79.1	0.5218	47.903	0.796

Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

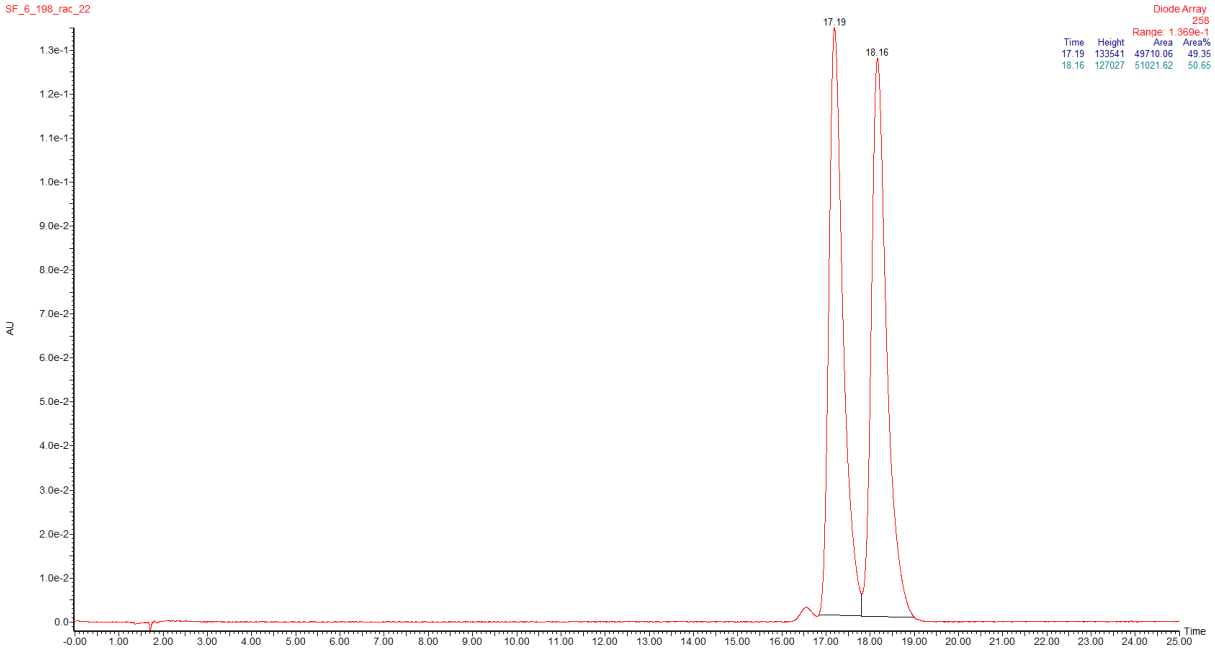


#	Time	Area	Height	Width	Area%	Symmetry
1	25.527	123.1	4.1	0.425	1.631	0.813
2	27.051	7423.7	218.3	0.5287	98.369	0.734

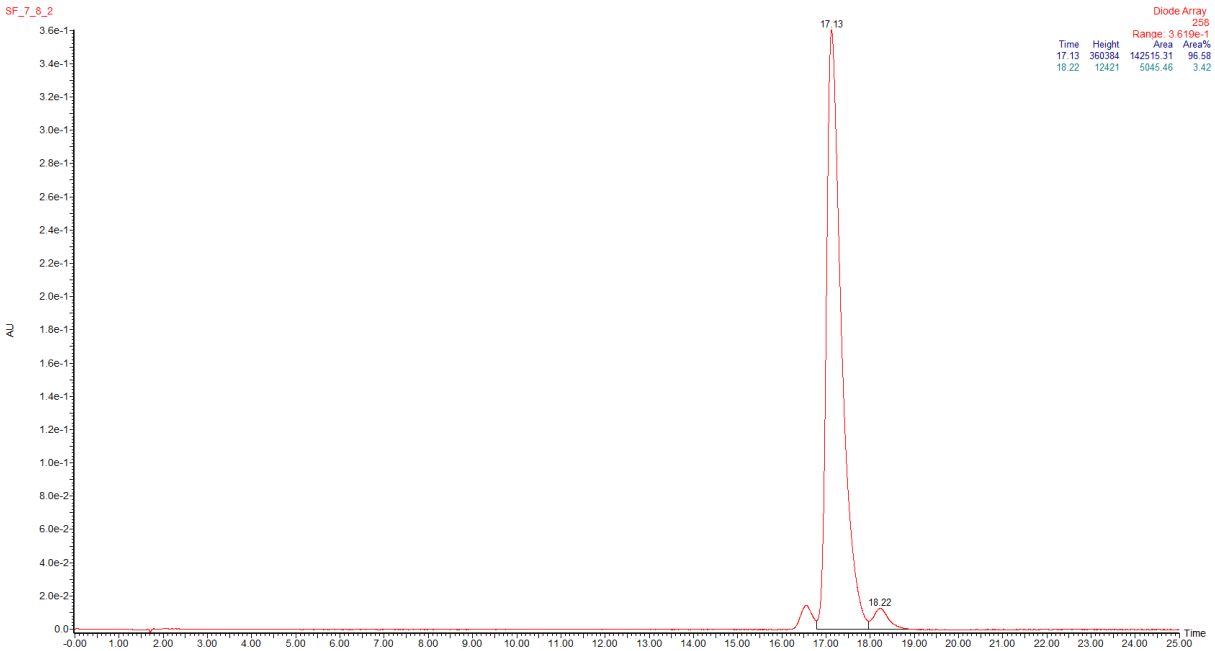
adamantan-1-yl (*S*)-2-methyl-2-(1-phenyl-1H-pyrazol-4-yl)but-3-enoate (3h)



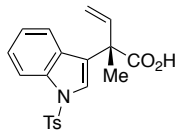
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



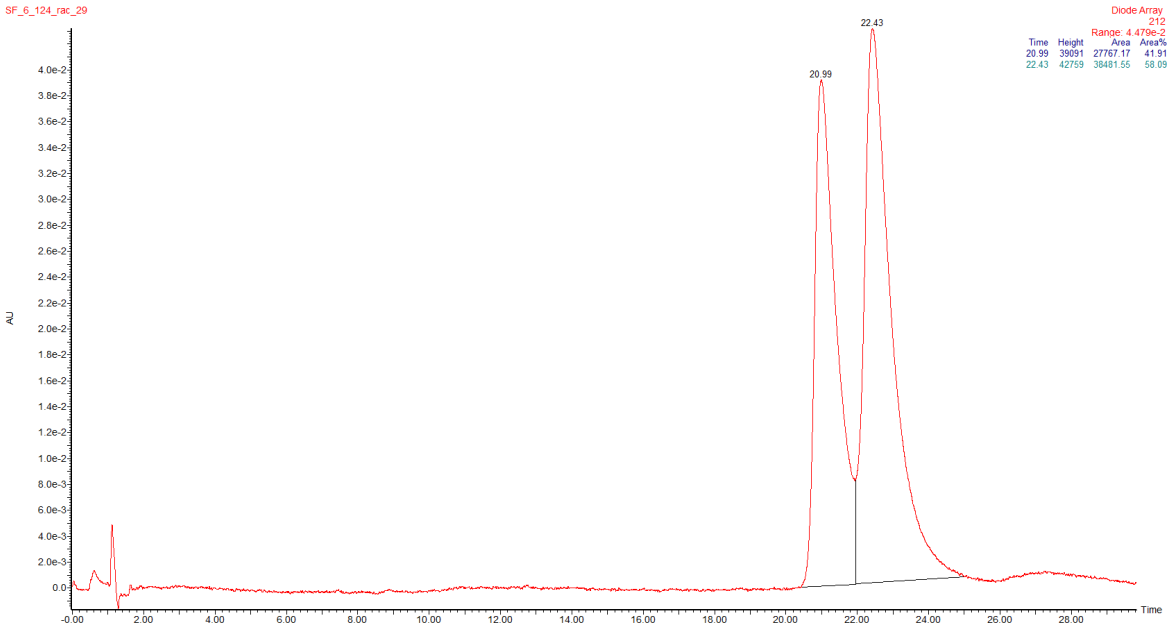
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



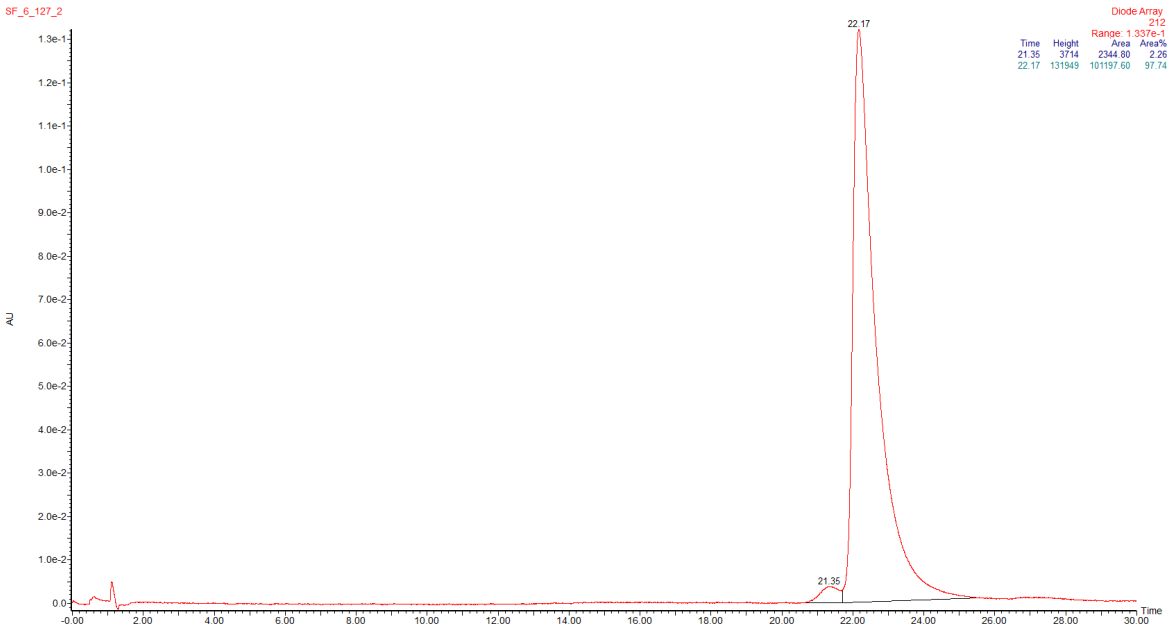
(*S*)-2-methyl-2-(1-tosyl-1H-indol-3-yl)but-3-enoic acid (3i)



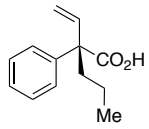
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



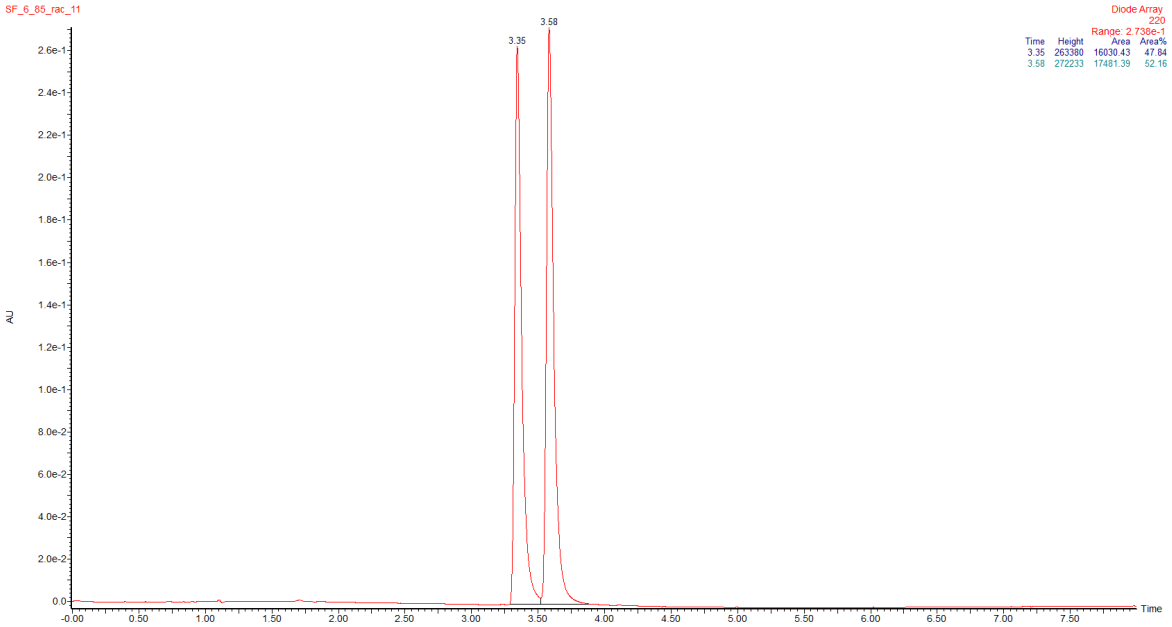
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



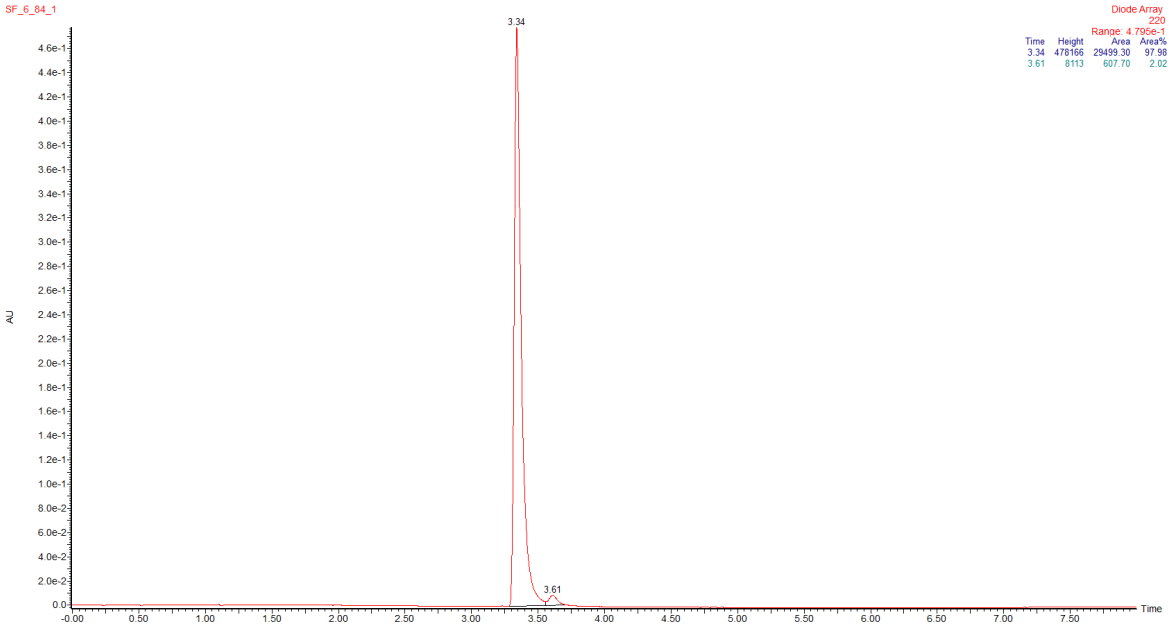
(*S*)-2-phenyl-2-vinylpentanoic acid (3j)



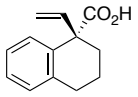
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



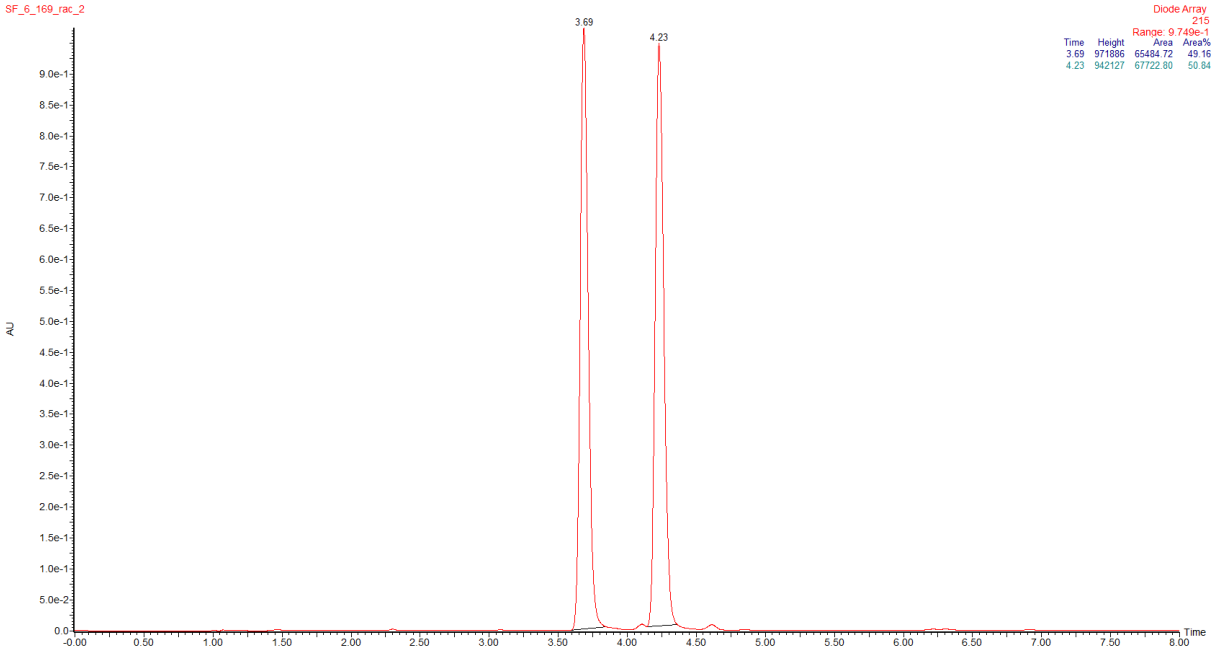
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



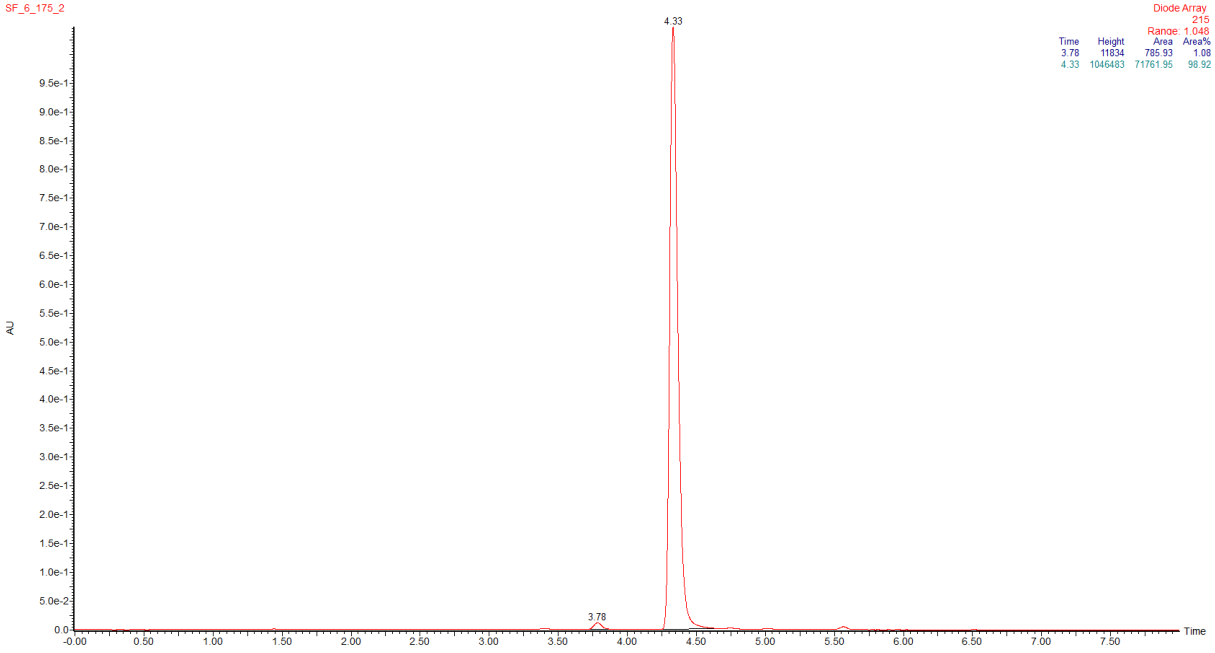
(*S*)-1-vinyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (3k)



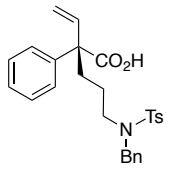
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



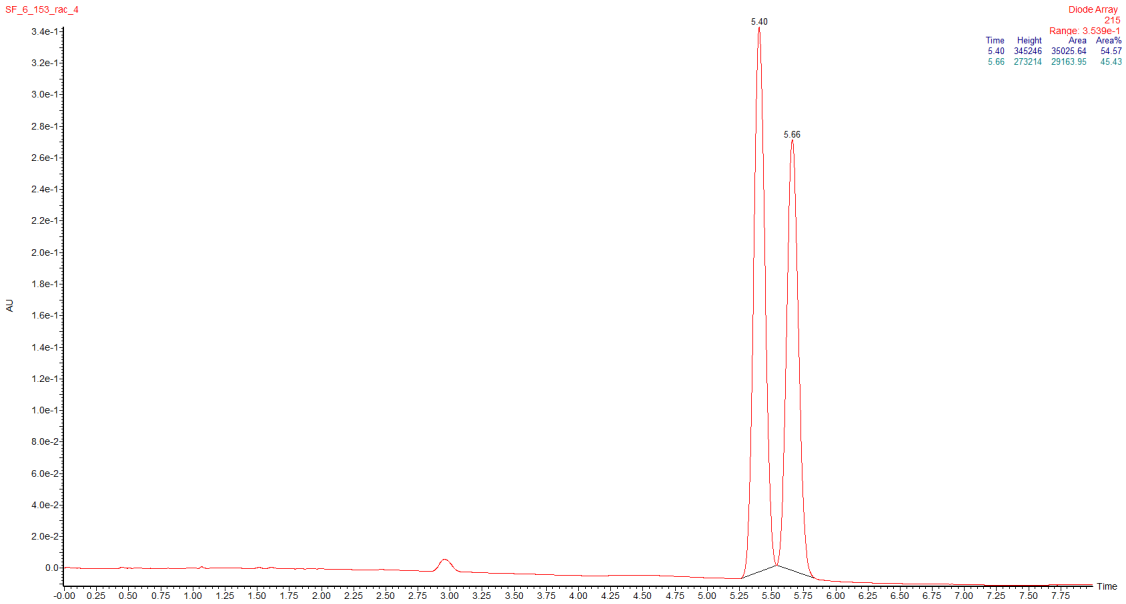
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



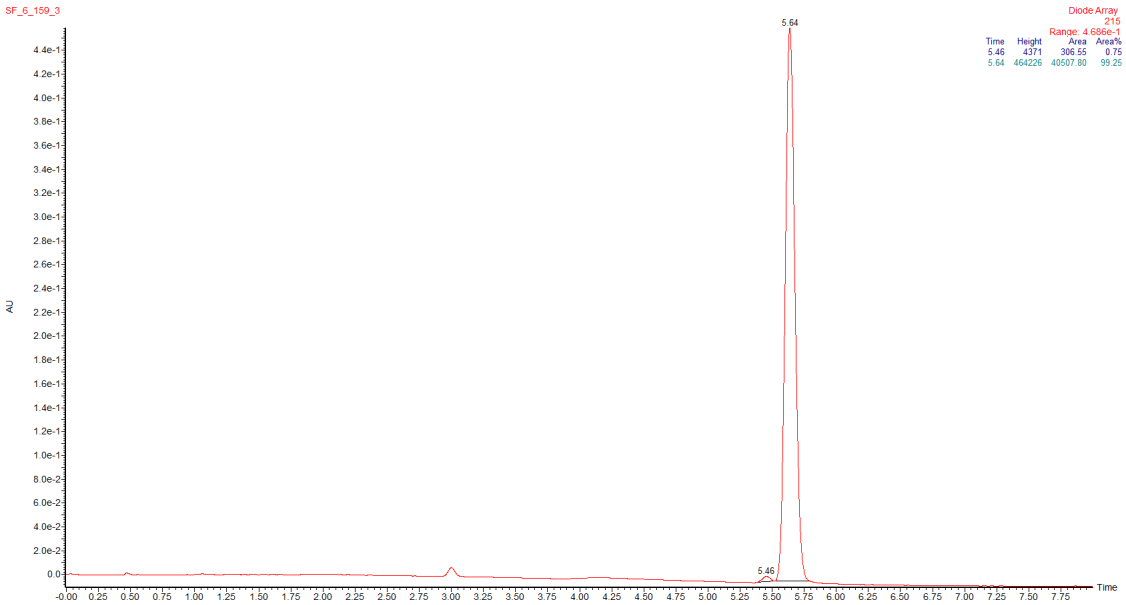
(*S*)-5-((*N*-benzyl-4-methylphenyl)sulfonamido)-2-phenyl-2-vinylpentanoic acid (3l)



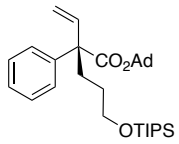
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



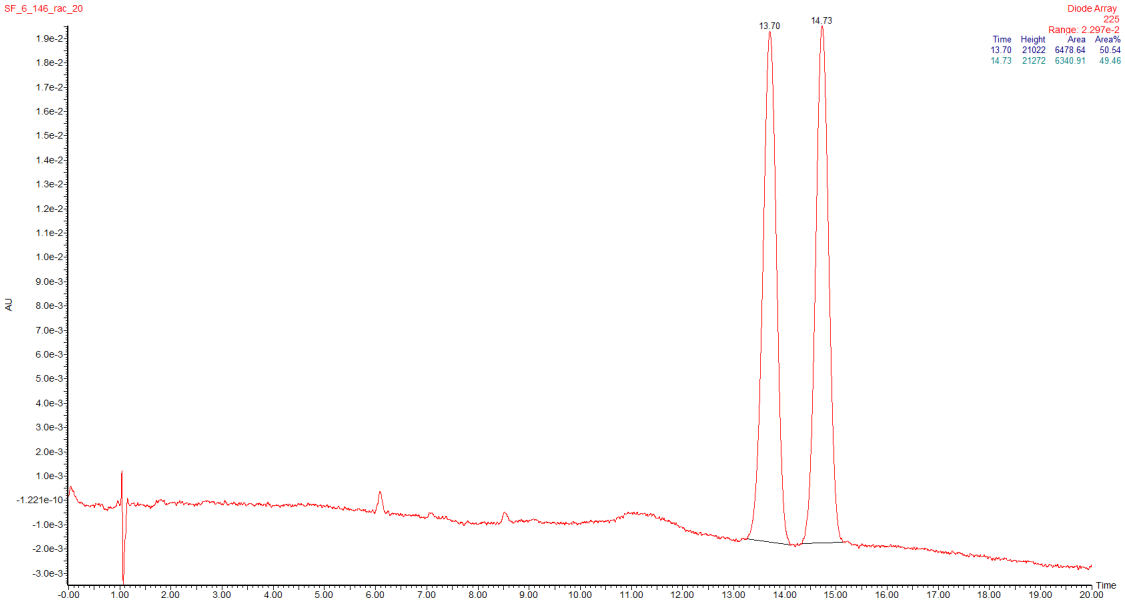
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



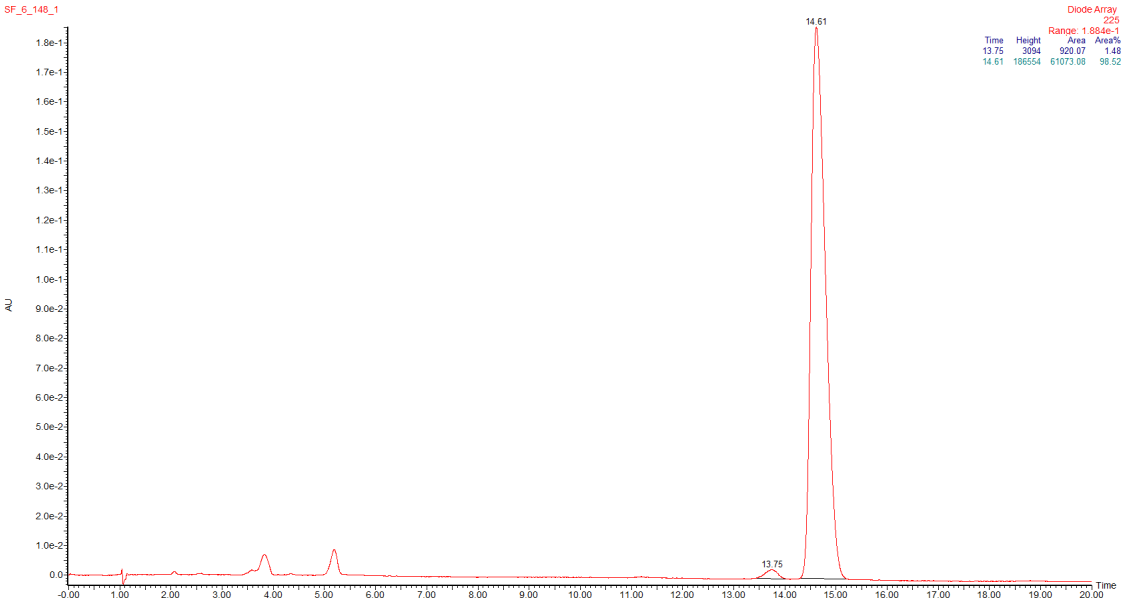
adamantan-1-yl (*S*)-2-phenyl-5-((triisopropylsilyl)oxy)-2-vinylpentanoate (3m)



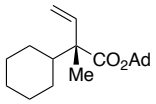
Racemic (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



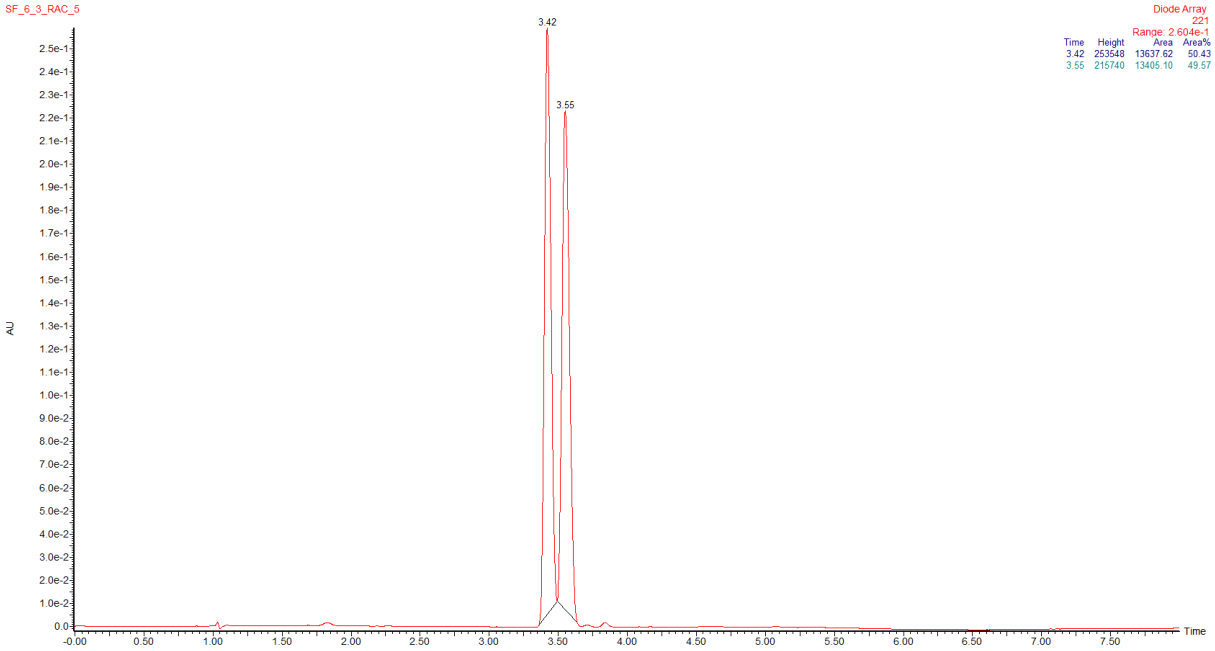
Enantioenriched (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



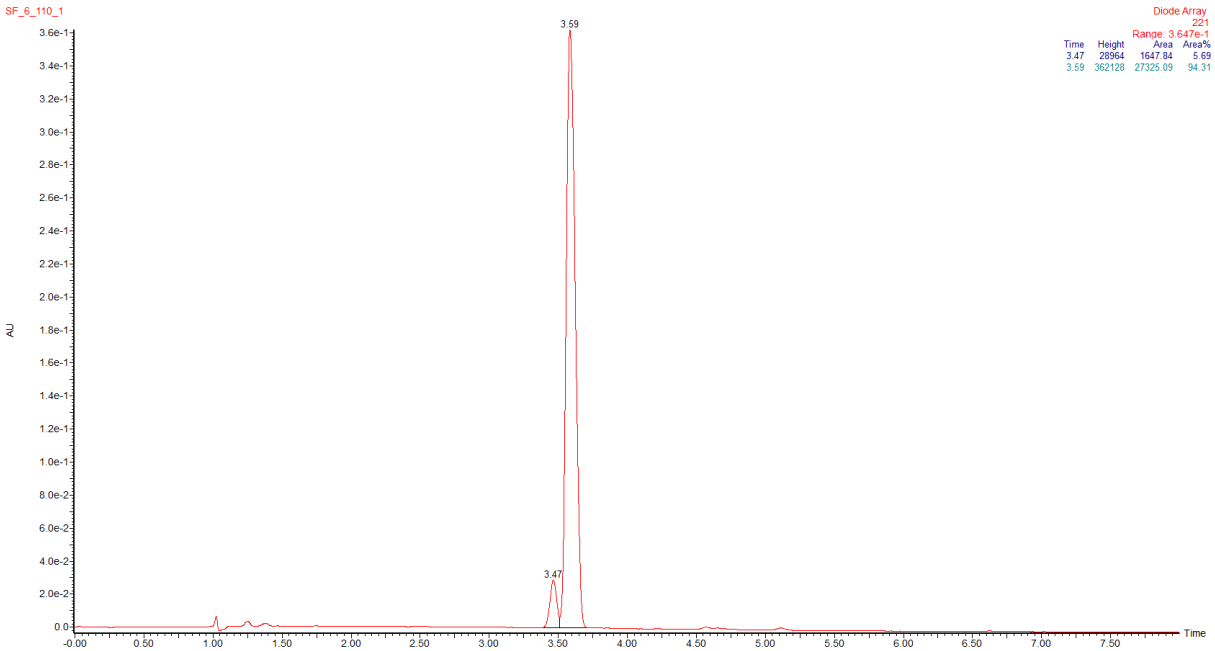
adamantan-1-yl (*S*)-2-cyclohexyl-2-methylbut-3-enoate (3n)



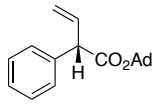
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



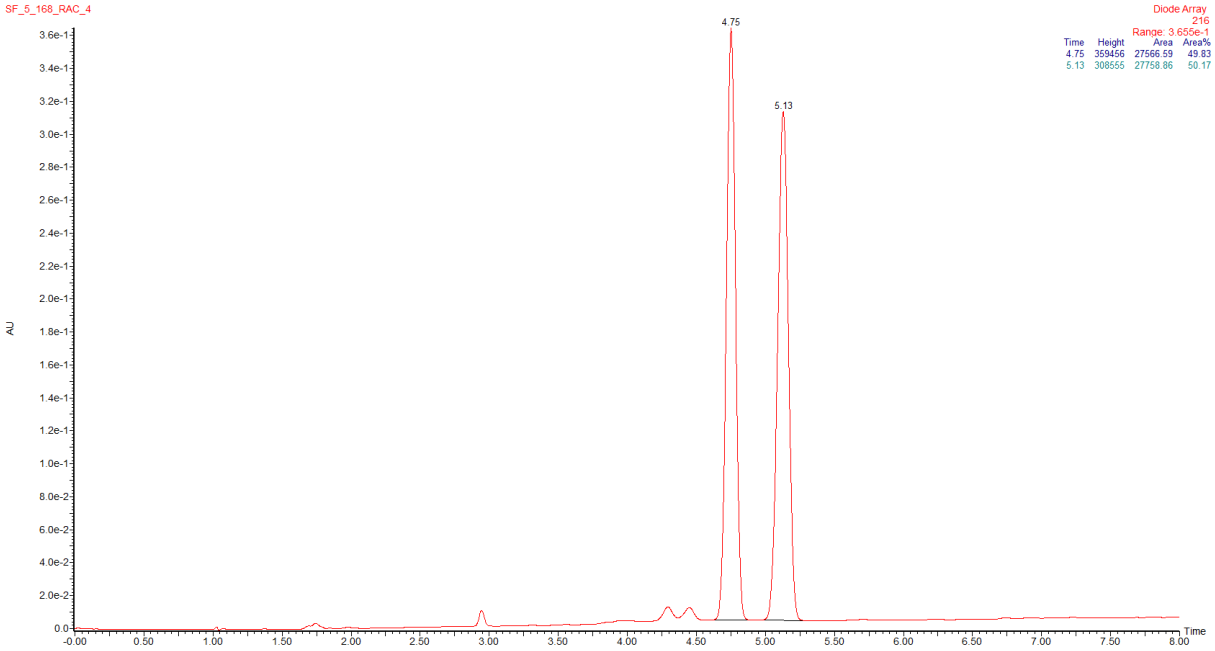
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



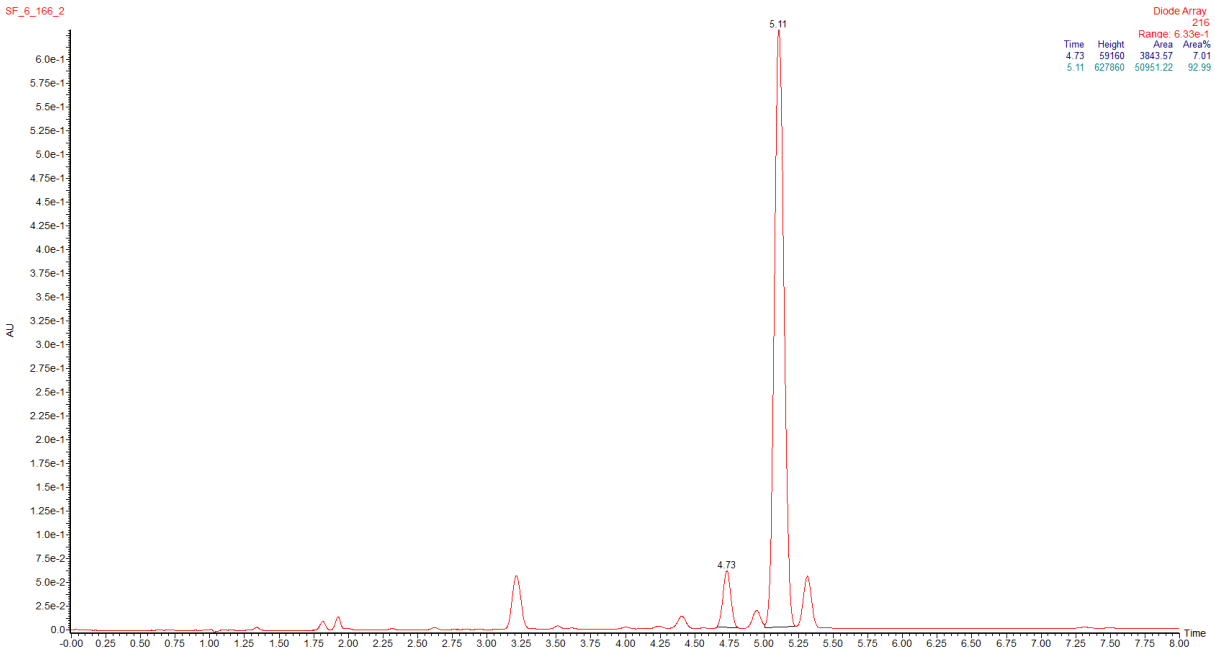
adamantan-1-yl (*S*)-2-phenylbut-3-enoate (3o)



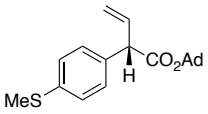
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



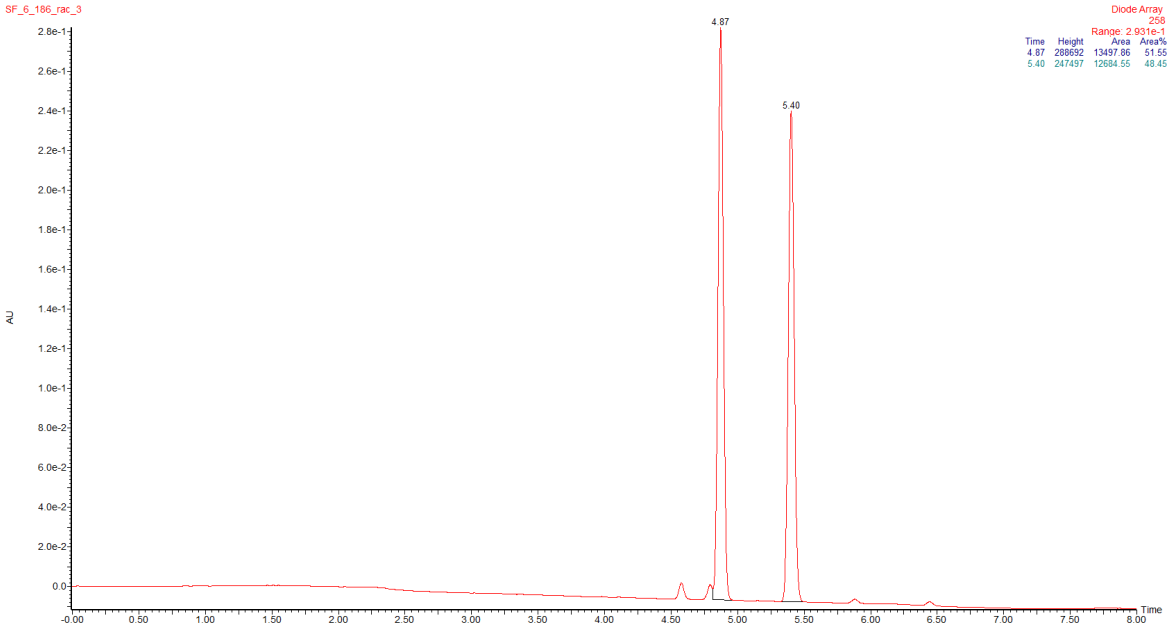
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



adamantan-1-yl (*S*)-2-methyl-2-(4-(methylthio)phenyl)but-3-enoate (3p)

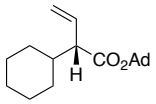


Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

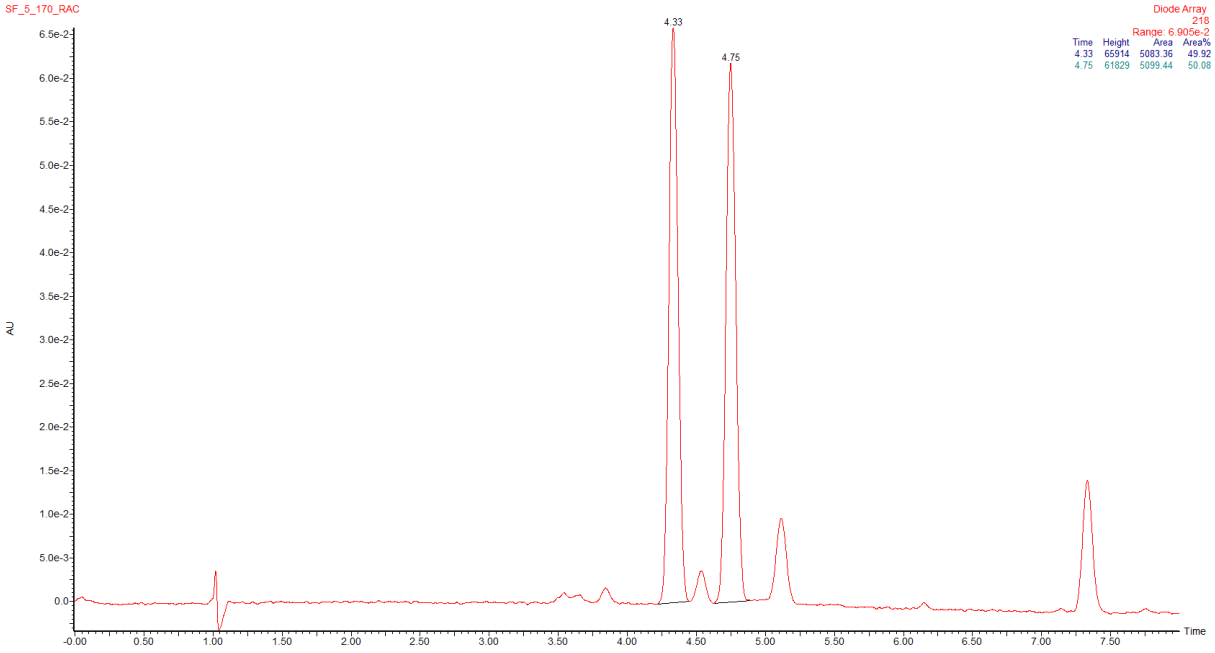


Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

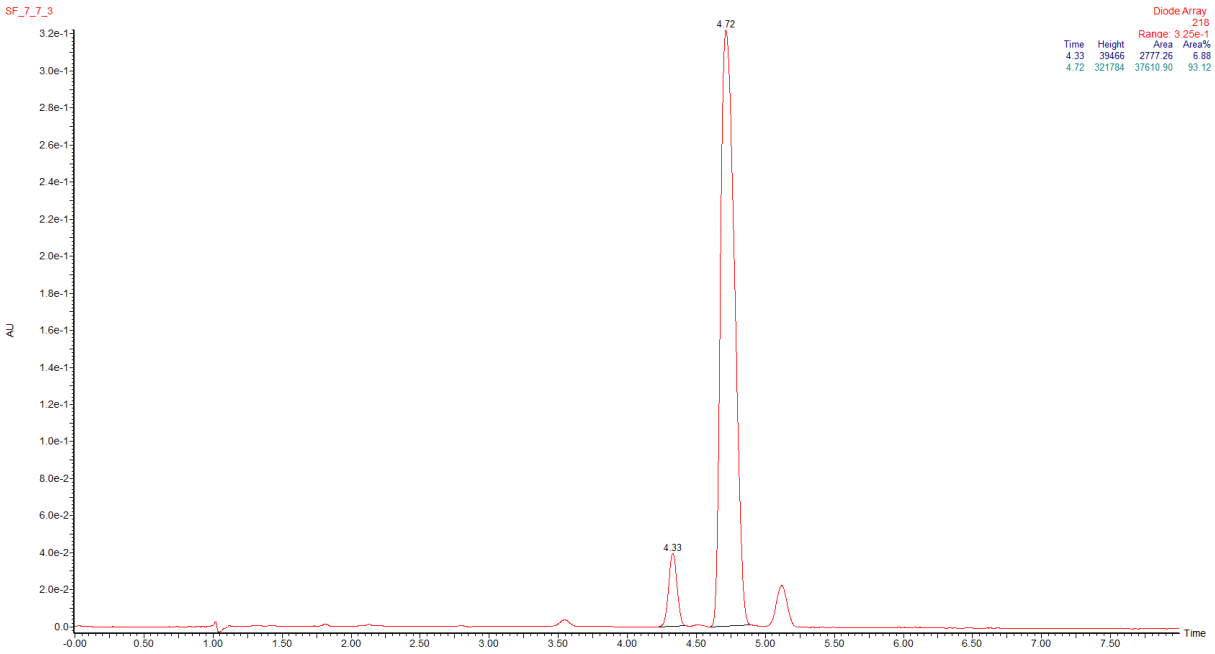
adamantan-1-yl (*S*)-2-cyclohexylbut-3-enoate (3q)



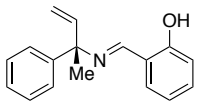
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



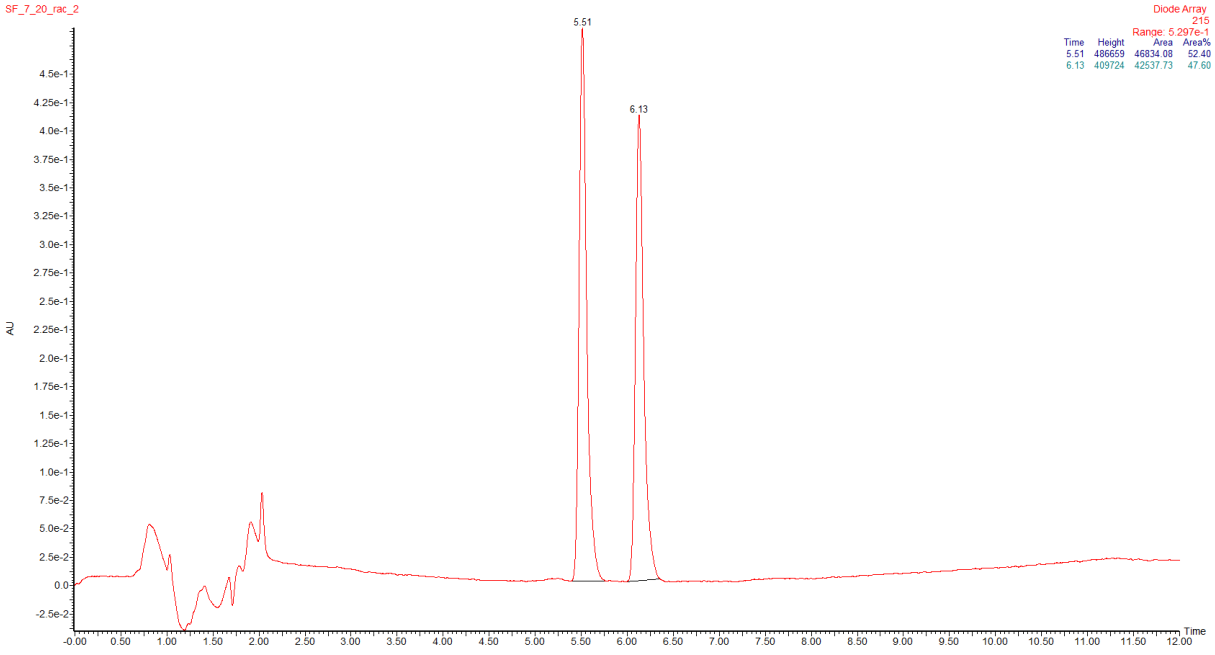
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



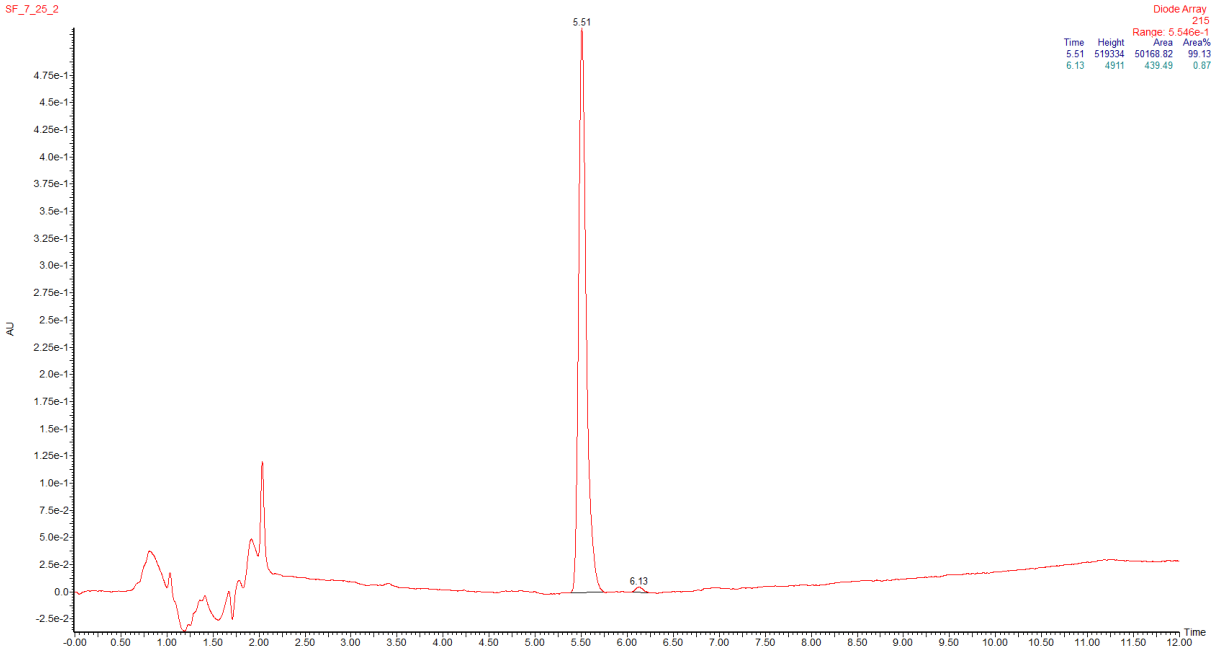
(*S*,*E*)-2-(((2-phenylbut-3-en-2-yl)imino)methyl)phenol (6')



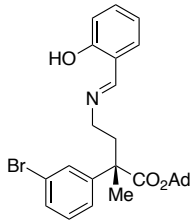
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



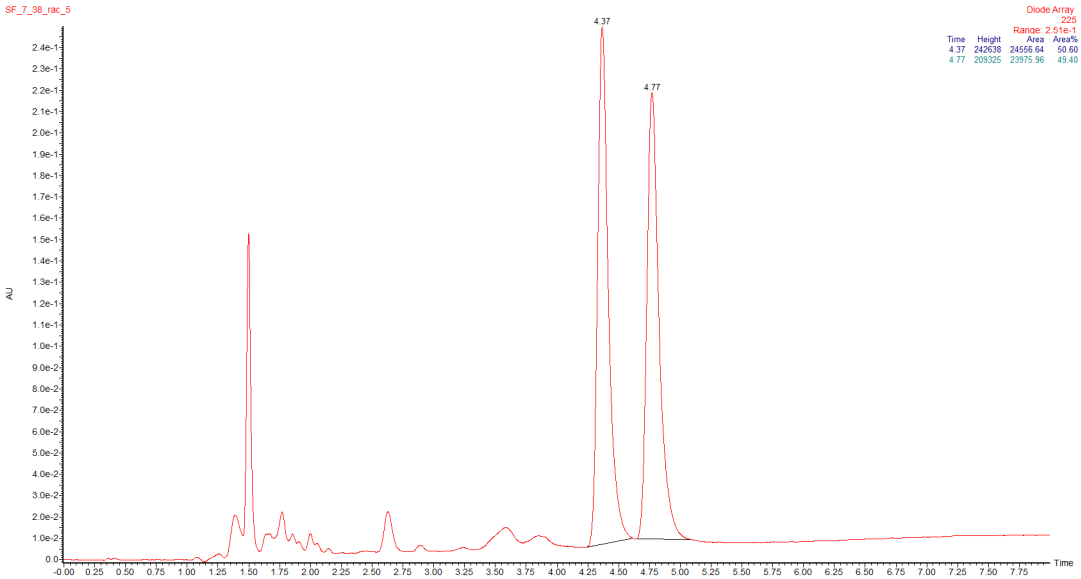
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



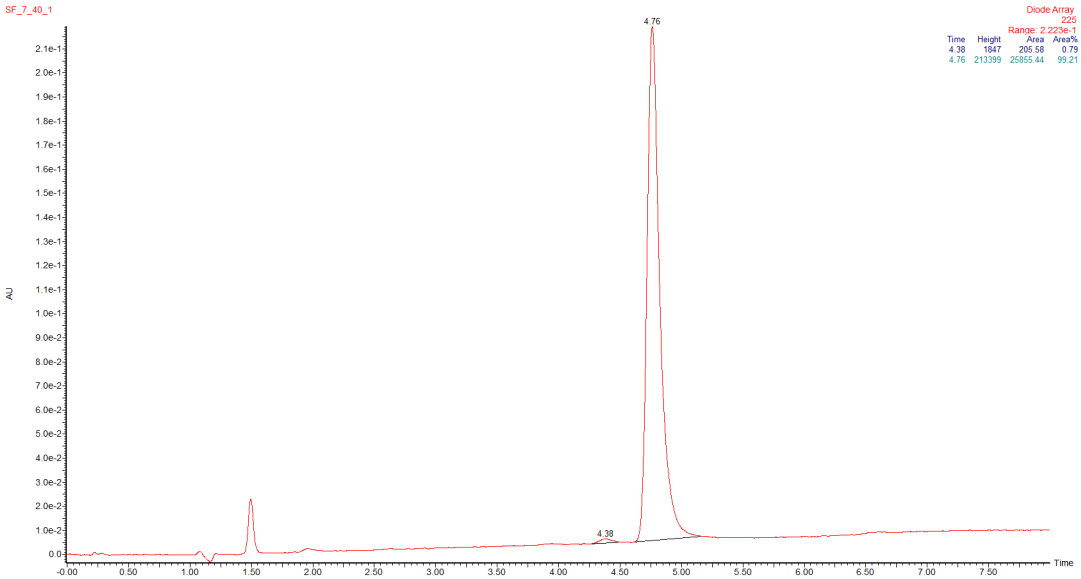
adamantan-1-yl (*S*)-2-(3-bromophenyl)-4-(((*E*)-2-hydroxybenzylidene)amino)-2-methylbutanoate (8')



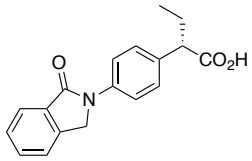
Racemic (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



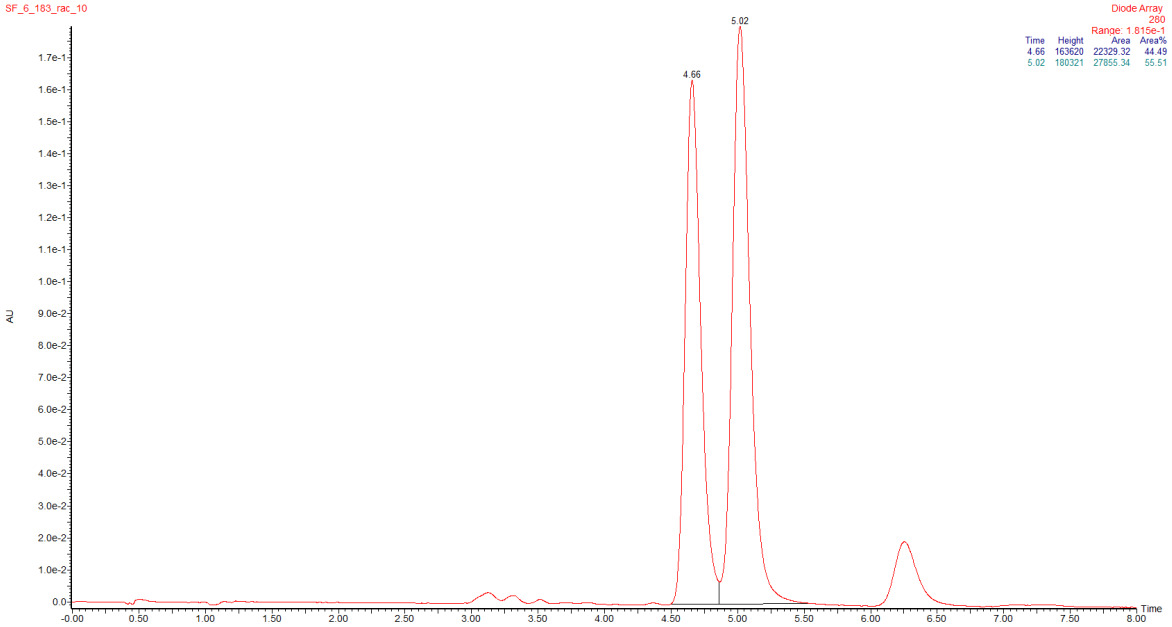
Enantioenriched (OJ-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



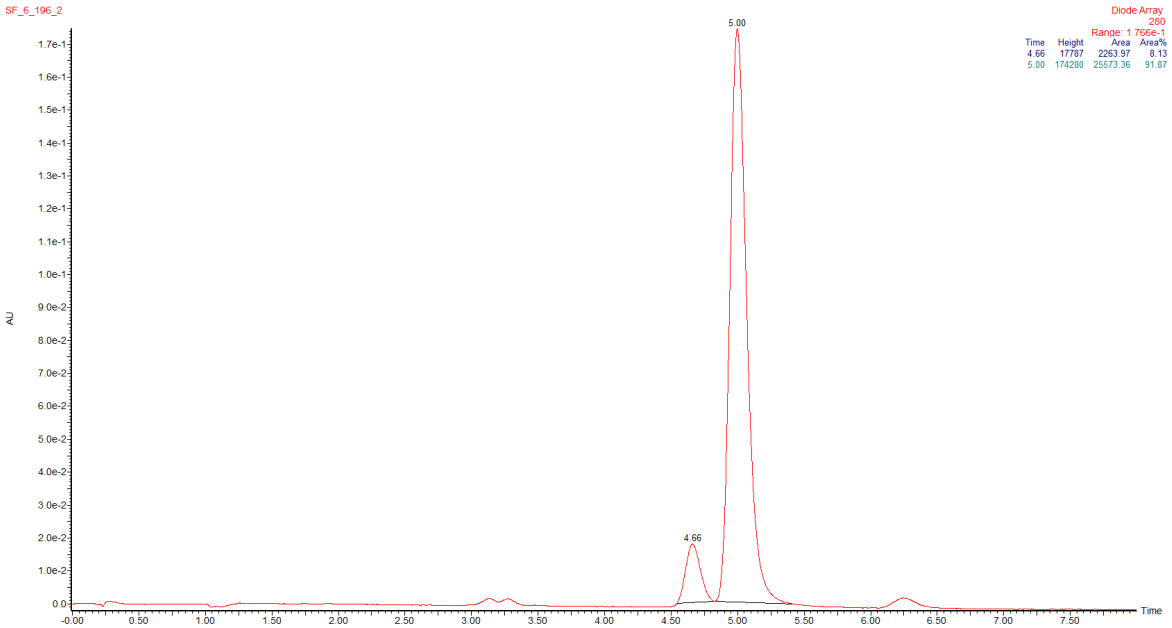
(*S*)-Indobufen (10)



Racemic (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



Enantioenriched (OD-H, Chiralcel®, 4.6 x 250 mm, 5 μM particle size):



Chapter 3. Enantioselective Hydrocarbamoylation of Alkenes

3.1 Introduction

Chiral amides are ubiquitous structural elements in pharmaceuticals, natural products, and biomolecules (Figure 1A).[1] For example, an amide substructure was present in 70% of the top 50 selling small molecule pharmaceuticals in 2020.[2] Owing to their importance, various catalytic methods for the asymmetric synthesis of amides have been developed, including the conjugate addition[3] or reduction[4] of α,β-unsaturated amides, and α-functionalization of amides.[5] These techniques typically require the use of a pre-existing racemic or prochiral amide. Alternatively, asymmetric hydroaminocarbonylation of alkenes[6] constitutes a straightforward route to access enantioenriched amides as it allows an amide group to be directly installed onto a readily available olefin precursor. Although direct or formal intramolecular asymmetric alkene hydrocarbamoylation has been demonstrated,[7] the analogous intermolecular enantioselective hydrocarbamoylation of alkenes is less developed. Employing a high pressure of CO, Wu recently reported a Cu-catalyzed asymmetric hydroaminocarbonylation of styrene derivatives.[8a-b] An analogous Pd-catalyzed transformation was developed by Guan, although high levels of regio- and enantioselectivity were limited to styrenes.[8c] Despite these recent advances, the development of a general enantioselective hydrocarbamoylation strategy that is CO-free[9] and compatible with various types of alkenes, including vinyl arenes, vinyl heterocycles, and challenging unactivated olefins, is of considerable interest.

Our group and others have demonstrated that copper hydride (CuH) catalysis can enable asymmetric hydrofunctionalization of alkenes.[10] This process leverages a stereodefined organocopper intermediate, formed by enantioselective hydrocupration of alkene, to intercept various electrophiles. Based upon this precedent, we felt that widely available carbamoyl chlorides, either commercially available or prepared from the corresponding amine in one step,

might obviate the need for CO in the asymmetric hydrocarbamoylation of alkenes. However, our preliminary experiments on the CuH-catalyzed alkene hydrocarbamoylation, utilizing styrene and *N*-methyl-*N*-phenylcarbamoyl chloride as substrates, failed to provide the corresponding enantioenriched amide product (Scheme S1).[11]

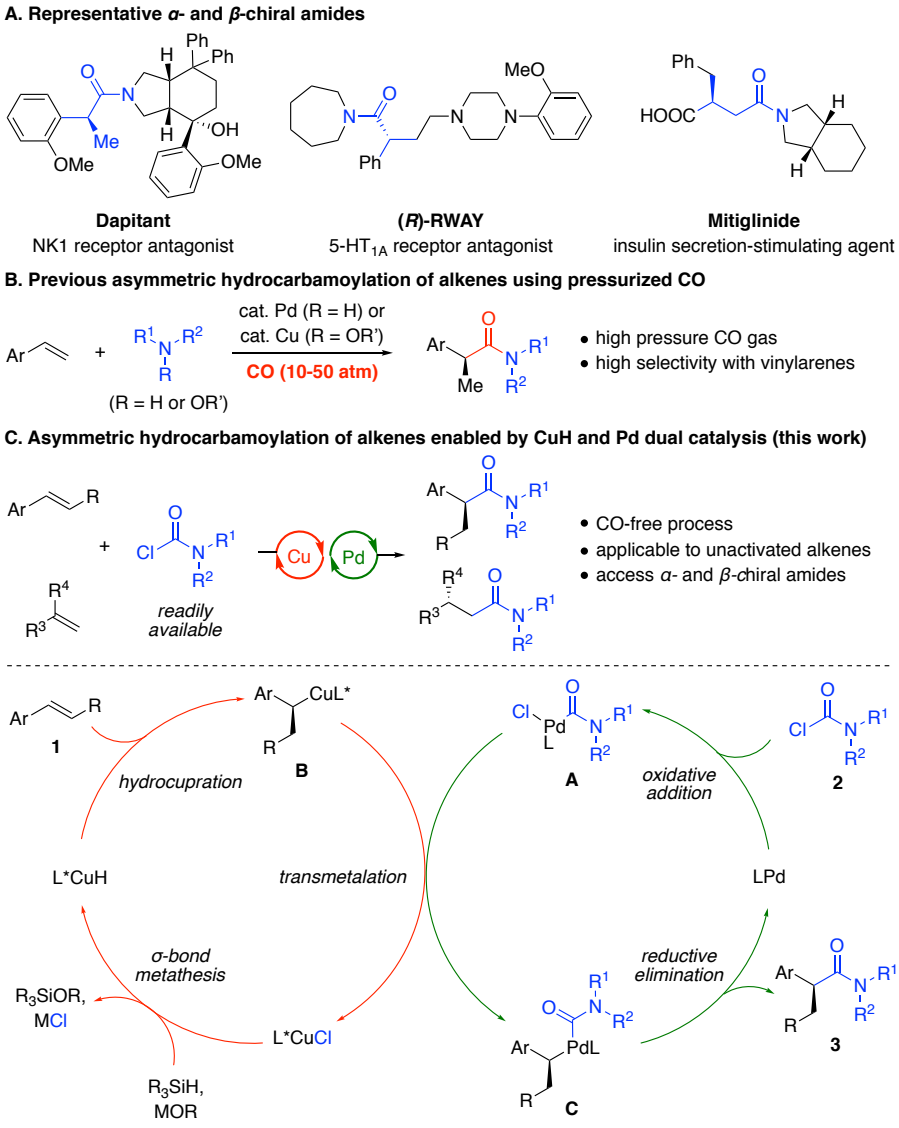


Figure 1. (A) Representative biologically active molecules with chiral amide substructures. (B) Previous intermolecular asymmetric hydrocarbamoylation of alkenes using a high pressure of

CO. (C) Our approach for enantioselective hydrocarbamoylation of alkenes utilizing dual CuH and Pd catalysis.

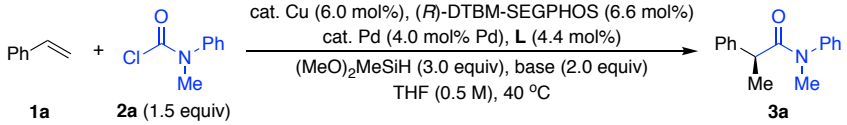
As an alternative, we envisioned that a dual CuH and Pd-catalyzed approach might enable the asymmetric hydrocarbamoylation of alkenes, in which the enantioenriched alkyl copper intermediate could undergo transmetallation with a carbamoyl Pd(II) oxidative addition complex.[12] To date, only "prototypical" cross coupling processes, such as arylation and vinylation, have been successfully enabled by dual CuH and Pd catalysis.[13,14] In this case, initial oxidative addition of carbamoyl chloride **2** with a Pd(0) catalyst and concomitant enantioselective hydrocupration of alkene **1** would result in oxidative addition complex **A** and alkyl copper **B**. Stereospecific transmetallation would form alkyl Pd(II) complex **C**. Intermediate **C** would undergo reductive elimination to form amide **3** and reform LPd, and the accompanying L*CuCl intermediate would react with a base and silane to regenerate the L*CuH catalyst. We felt that selection of the base would be crucial, as the use of a highly nucleophilic base might react with the carbamoyl chloride, whereas with a less nucleophilic one, regeneration of the CuH catalyst might be slowed. Moreover, the rates of the two catalytic cycles need to be well aligned to minimize undesired processes, such as racemization of **B**, reduction of carbamoyl chloride by CuH or decomposition of **A**.

3.2 Results and Discussion

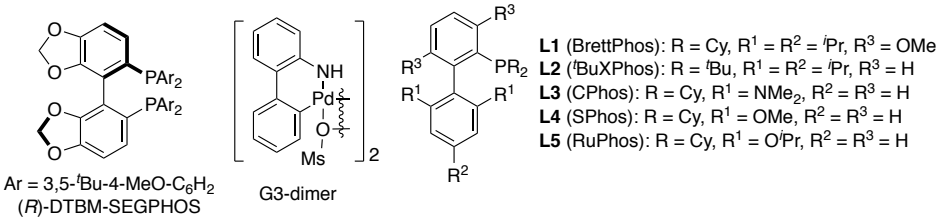
We were able to identify suitable reaction conditions with styrene (**1a**) and *N*-methyl-*N*-phenylcarbamoyl chloride (**2a**) as the model substrate combination (Table 1). We first examined the use of several weak bases (Table 1, entry 1-4), since a base such as NaOTMS, which has

been previously employed in CuH/Pd dual catalysis protocols,[13] would likely consume the carbamoyl chloride coupling partner. The use of KOBz, in conjunction with $Cu(OAc)_2$, (*R*)-DTBM-SEGPHOS, BrettPhos Pd G3, and $(MeO)_2MeSiH$, provided the desired hydrocarbamoylation product (**3a**) in good yield and enantioselectivity. Further evaluation of different copper and palladium sources showed that the yield and enantioselectivity were slightly improved using the combination of $Cu(OAc)_2$ and $[Pd(cinnamyl)Cl]_2$ (Table 1, entry 5-7). A series of biarylphosphine ligands were then examined (Table 1, entry 7-11), revealing SPhos (**L4**) as the ideal Pd ancillary ligand. Under the optimized conditions (Table 1, entry 10), amide **3a** was obtained in 95% yield and 97:3 er. However, when we attempted the same reaction between **1a** and diethylcarbamoyl chloride (**2b**) under the identical conditions, both the yield and enantioselectivity were considerably lower (66% yield, 78:22 er). Since compared to **2a**, the more electron rich **2b** might undergo oxidative addition with the LPd(0) intermediate at a reduced rate. Subsequent transmetallation with intermediate **B** would also be slower, which could lead to an increased level of racemization and decomposition of **B**. After minor modifications to the reaction conditions including the base, Cu, and Pd source (Table S1), [11] the corresponding amide was formed in 80% yield and 91:9 er. This observation also underlines the importance of matching the rates of the Cu and Pd catalytic cycles by tuning the reaction conditions.

Table 1. Optimization of the Enantioselective Hydrocarbamoylation of Styrene



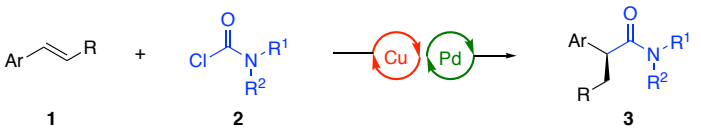
entry	base	cat. Cu	cat. Pd	L	yield[a]	er[b]
1	KOAc	CuOAc	G3-dimer	**L1**	86%	93:7
2	KOPiv	CuOAc	G3-dimer	**L1**	12%	–
3	KOBz	CuOAc	G3-dimer	**L1**	91%	94:6
4	NaOBz	CuOAc	G3-dimer	**L1**	72%	95:5
5	KOBz	CuOAc	$Pd(OAc)_2$	**L1**	87%	95:5
6	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	**L1**	90%	94.5:5.5
7	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L1**	93%	94.5:5.5
8	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L2**	67%	91.5:8.5
9	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L3**	77%	95.5:4.5
10	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L4**	95%	97:3
11	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L5**	87%	96.5:3.5

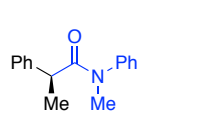


[a]Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. [b]Enantiomeric ratio was determined by SFC analysis.

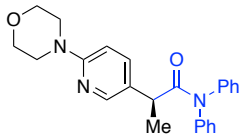
Having established the reaction conditions for the asymmetric hydrocarbamoylation of vinyl arenes, we next examined the scope of the reaction (Table 2). A number of vinyl heteroarenes, both electron rich and deficient, including pyridine (**3b**), carbazole (**3c**), indole (**3e**), pyrimidine (**3h**), and pyrazole (**3i**), efficiently underwent the hydrocarbamoylation reaction to provide the corresponding amide products in good yield and excellent enantioselectivity. *β*-Substituted styrenes (**3d**, **3j**, **3k**) were also successful substrates in this transformation, although the reaction conditions were modified slightly for those bearing basic *β*-amino substituents (**3j**, **3k**) due to the moderate enantioselectivity observed under the original conditions (74:26 er for **3j**, 82:18 er for **3k**). The protocol accommodated different substituents on the nitrogen atom of carbamoyl chlorides, including methylaryl (**3a**, **3d–f**, **3h–i**), dialkyl (**3c**, **3g**, **3k**, **3j**), and diphenyl (**3b**) substructure. To demonstrate the synthetic utility of this method, we prepared (*R*)-RWAY (**3j**), a 5-HT_{1A} receptor antagonist,[15] in one step from the corresponding arylalkene in excellent yield and enantioselectivity. We were also able to obtain the enantioenriched amide derivative of Cinnarizine (**3k**), an antihistamine drug. Additionally, the absolute configuration of a ferrocene derivative **3g** was confirmed by X-ray crystallography. The observed stereoselectivity of the reaction suggests a stereoretentive Cu-to-Pd transmetallation which is in accord with our previous observations (Figure 1C).[13]

Table 2. Substrate Scope for the Hydrocarbamoylation of Arylalkenes

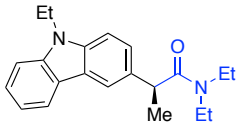




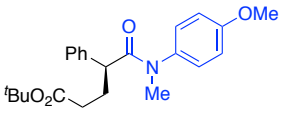
3a
77% yield
96:4 er[a]



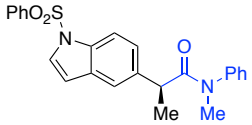
3b
65% yield
96:4 er[a]



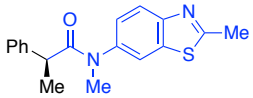
3c
66% yield
99:1 er[b]



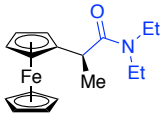
3d
91% yield
99:1 er[a]



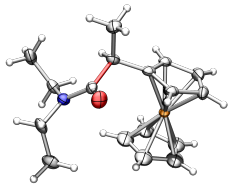
3e
73% yield
97:3 er[a]



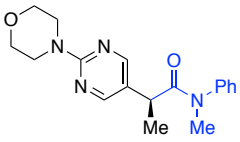
3f
84% yield
97:3 er[a]



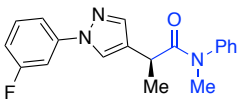
3g
66% yield
99:1 er[b]



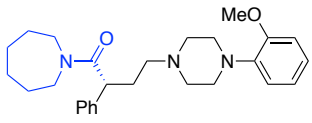
X-ray structure for **3g**



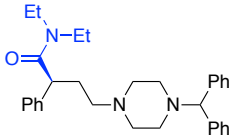
3h
56% yield
93:7 er[a]



3i
66% yield
98:2 er[a]
(65% yield, 98:2 er)[c]



3j
87% yield
97:3 er[d,e]
(R)-RWAY



3k
95% yield
93:7 er[d]
from Cinnarizine

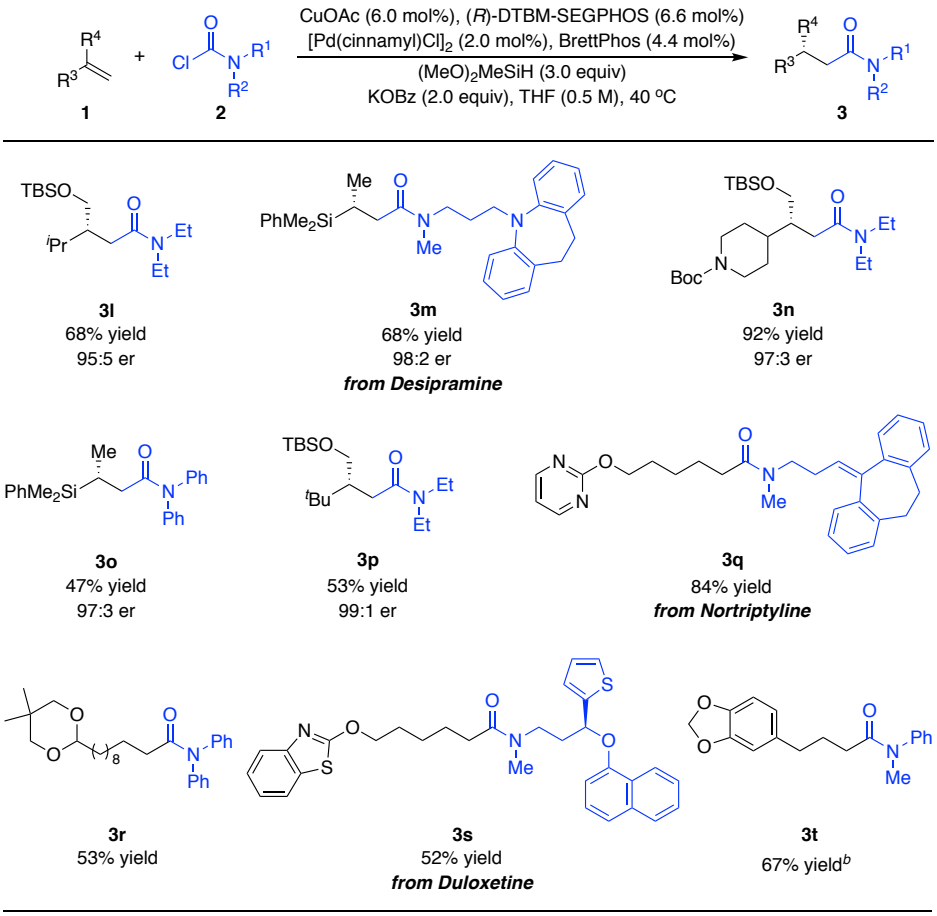
[a]Condition A: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), $Cu(OAc)_2$ (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), $[Pd(cinnamyl)Cl]_2$ (2.0 mol%), **L4** (4.4 mol%), KOBz (2 equiv), $(MeO)_2MeSiH$ (3 equiv), THF (0.5 M), 40 °C. [b]Condition B: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), CuOAc (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), G3-dimer (2.0 mol%), **L1** (4.4 mol%), NaOPiv (2 equiv), $(MeO)_2MeSiH$ (3 equiv), THF (0.5 M), 40 °C. [c]Isolated yields on a

1.0 mmol scale under Condition A (average of two runs). [d]Condition B, except NaOBz was used. [e]Condition B, except (*S*)-DTBM-MeO-BIPHEP was used.

We were also interested in applying our strategy to unactivated alkenes, including 1,1-disubstituted alkenes and terminal alkenes, to access *β*-chiral and linear amides, respectively, via anti-Markovnikov[13c,13e] hydrocarbamoylation. 1,1-disubstituted alkenes represent a challenging class of substrates in aminocarbonylation reactions due to their attenuated binding affinity towards metal hydride intermediates,[7e] and a general protocol for the intermolecular asymmetric hydroaminocarbonylation of 1,1-disubstituted alkenes remains elusive. Even for unactivated terminal olefins, only a few hydroaminocarbonylation reaction protocols are available that don't require the use of CO gas at elevated pressure.[16] In order to expand our hydrocarbamoylation protocol to unactivated alkenes, for which the hydrocupration step is more challenging compared to vinylarenes,[17] the reaction conditions were modified by manipulating the copper source and the Pd ancillary ligand (Table S2).[11] Using the optimized conditions, 1,1-disubstituted alkenes were coupled with different carbamoyl chlorides to provide the corresponding *β*-chiral amides (**3l–3p**) in moderate to good yields and excellent enantioselectivity (Table 3). As the difference in steric demand between the geminal substituents on the olefin increases, the enantioselectivity of the reaction also improves (**3l**, **3n**, **3p**, sequentially). Additionally, amides containing a silicon-substituted *β*-stereogenic center (**3m**, **3o**) could be obtained by employing an alkenyl silane as substrate. The protocol is also applicable to various readily available terminal alkenes, allowing them to react efficiently with dialkyl (**3q**, **3s**), diphenyl (**3r**), and *N*-methyl-*N*-phenyl carbamoyl chlorides (**3t**). Overall, the hydrocarbamoylation reaction of unactivated alkenes was able to tolerate a broad range of heterocycles, including azepane (**3m**), piperidine (**3n**),

pyrimidine (**3q**), benzothiazole (**3s**), and thiophene (**3s**). Functional groups such as acetal (**3r**, **3t**) and siloxyl (**3l**, **3n**, **3p**) were also compatible with the reaction conditions. Moreover, carbamoyl chlorides that are easily derived from several amine-containing pharmaceuticals, including Desipramine (**3m**), Nortriptyline (**3q**), and Duloxetine (**3s**), were successfully coupled with different unactivated alkenes, further demonstrating the synthetic utilities of our approach.

Table 3. Substrate Scope for the Hydrocarbamoylation of Unactivated Olefins[a]



[a]Condition C: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), CuOAc (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), [Pd(cinnamyl)Cl]$_2$ (2.0 mol%), **L1** (4.4 mol%), KOBz (2 equiv), (MeO)$_2$MeSiH (3 equiv), THF (0.5 M), 40 °C. [b]Condition C, except Pd(OAc)$_2$ (4.0 mol%), XPhos (4.4 mol%), and KOAc (2 equiv) were used instead.

3.3 Conclusion

In summary, we have developed a highly enantioselective hydrocarbamoylation reaction of olefins utilizing readily available carbamoyl chlorides as a practical carbamoylating reagent that obviates the need for CO gas. Under mild CuH and Pd dual catalysis conditions, a broad range of alkenes, including arylalkenes, 1,1-disubstituted alkenes, and terminal olefins, were able to undergo the reaction smoothly to furnish α- and β-chiral amides bearing diverse heterocycles and functional groups. In addition, we anticipate that the use of a non-traditional carbonyl cross-coupling partner, carbamoyl chlorides, in CuH/Pd cooperative catalysis may stimulate further developments in merging CuH catalysis with other types of carbonylative cross-coupling processes.

3.4 Experimental

3.4.1 General Information

General Analytical Information: All new compounds were characterized by NMR spectroscopy, IR spectroscopy, elemental analysis or high-resolution mass spectrometry, optical rotation (if chiral and non-racemic) and melting point analysis (if solids). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer. Chemical shifts for ^{1}H NMR are reported as follows: chemical shift in reference to residual $CHCl_3$ at 7.26 ppm (δ ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sex = sextet, sep = septet, dd = double of doublets, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. Chemical shifts for ^{13}C NMR are reported in terms of chemical shift in reference to the $CDCl_3$ solvent signal (77.16 ppm). Chemical shifts for ^{19}F NMR are reported in ppm relative to $CFCl_3$ (0.00 ppm). IR spectra were recorded on a Thermo Scientific Nicolet iS5

spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points were measured on a Mel-Temp capillary melting point apparatus and are uncorrected. Optical rotations were measured using a Jasco P-1010 digital polarimeter. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system. Enantiomeric ratios (er's) were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument; specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. High-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series chromatographs using a Chiralpak® columns (25 cm) as noted for each. Thin-layer chromatography (TLC) was performed on silica gel 60Å F_{254} plates (SiliaPlate from Silicycle) and visualized with UV light, iodine or potassium permanganate stain. Preparatory thin-layer chromatography (Prep-TLC) was performed on silica gel GF with UV 254 (20 x 20 cm, 1000 microns, catalog # TLG-R10011B-341 from Silicycle) and visualized with UV light. Isolated yields reported reflect the average values from two independent runs.

General Reagent Information: All reactions were performed under a nitrogen or argon atmosphere using the indicated method in the general procedures. Tetrahydrofuran (THF) was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and purified by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide. Copper(II) acetate and copper(I) acetate were purchased from Strem and used as received. DTBM-SEGPHOS was purchased from Takasago International Co. and used as received. (*S*)-DTBM-MeO-BIPHEP and biarylphosphine ligands were generous gifts from Solvias and Millipore-Sigma, respectively. Dimethoxy(methyl)silane (DMMS) was purchased from Tokyo

Chemical Industry Co. (TCI) and stored in a nitrogen-filled glovebox for long-term storage. (***Caution****: Dimethoxy(methyl)silane (DMMS, CAS#16881-77-9) is listed by several vendors (TCI, Alfa Aesar) SDS or MSDS as a H318, a category 1 Causes Serious Eye Damage. Other vendors (Sigma-Aldrich, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precaution as outlined for the handling of hazardous materials in prudent practices in the laboratory*[18]*. At the end of the reaction either ammonium fluoride in methanol, saturated aqueous sodium carbonate, aqueous sodium hydroxide (1 M) or aqueous hydrochloric acid (1 M) should be carefully added to the reaction mixture. This should be allowed to stir for at least 30 min or the time indicated in the detailed reaction procedure*). All reactions should be (and were) carried out in a well-ventilated hood or in a glovebox. Potassium benzoate and sodium benzoate were dried under high vacuum at 80 °C with stirring for 36 h. Potassium acetate and sodium pivalate were dried under high vacuum at 100 °C with stirring for 36 h. All other solvents and commercial reagents were used as received from Millipore-Sigma, Alfa Aesar, Acros Organics, TCI and Combi-Blocks, unless otherwise noted. Flash column chromatography was performed using 40-63 μm silica gel (SiliaFlash® F60 from Silicycle), or with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g). Reversed-phase column chromatography was performed with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System using prepacked SNAP C18 cartridges (43 g). Organic solutions were concentrated *in vacuo* with the aid of a Buchi rotary evaporator.

3.4.2 Optimization and General Procedures for Hydrocarbamoylation Reactions

3.4.2.1 Optimization of the Hydrocarbamoylation Reactions

Scheme S1. Initial Experiment on CuH-Catalyzed Hydrocarbamoylation of Styrene

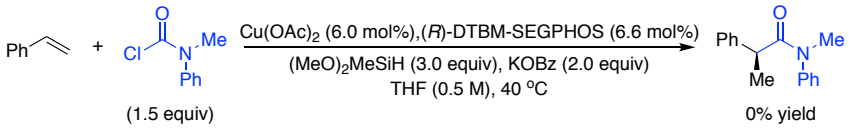
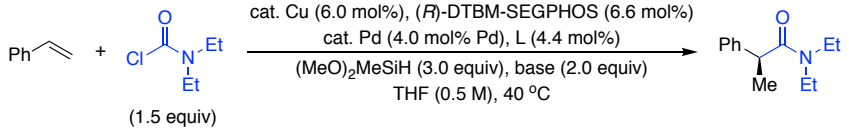


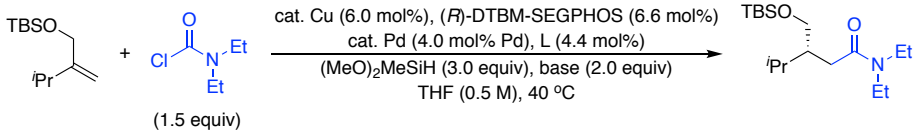
Table S1. Optimization of Hydrocarbamoylation of Styrene with Dialkylcarbamoyl Chloride Enabled by Dual CuH and Pd Catalysis [a]



Entry	base	cat. Cu	cat. Pd	L	yield[b] (%)	er[c]
1	KOBz	CuOAc	BrettPhos G4	-	56	79:21
2	KOAc	CuOAc	BrettPhos G4	-	67	95:5
3	NaOAc	CuOAc	BrettPhos G4	-	40	89:11
4	CsOAc	CuOAc	BrettPhos G4	-	54	93:7
5	KOAc	$Cu(OAc)_2$	BrettPhos G4	-	41	87.5:12.5
6	KOAc	CuOAc	$Pd(OAc)_2$	BrettPhos	64	86:14
7	KOAc	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	68	91:9
8	KOAc	CuOAc	G3-dimer	BrettPhos	78	91:9
9	KOAc	CuOAc	G3-dimer	^{t}BuBrettPhos	55	91:9
10	KOAc	CuOAc	G3-dimer	SPhos	62	79:21
11	**NaOPiv**	**CuOAc**	**G3-dimer**	**BrettPhos**	**80**	**91:9**

[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. [c]Enantiomeric ratio was determined by SFC analysis on commercial chiral columns

Table S2. Optimization of Hydrocarbamoylation of Unactivated Alkene [a]



Entry	base	cat. Cu	cat. Pd	L	yield[b] (%)
1	KOAc	CuOAc	$Pd(OAc)_2$	BrettPhos	54
2	KOAc	CuOAc	BrettPhos G4	-	57
3	KOAc	CuOAc	G3-dimer	BrettPhos	52
4	KOAc	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	62
5	**KOBz**	**CuOAc**	**$[Pd(cinnamyl)Cl]_2$**	**BrettPhos**	**75**
6	KOPiv	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	75
7	NaOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	47
8	NaOPiv	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	71
9	NaOAc	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	52
10	CsOPiv	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	63
11	CsOAc	CuOAc	$[Pd(cinnamyl)Cl]_2$	BrettPhos	65
12	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	XPhos	64
13	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	RuPhos	56

14	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	SPhos	60
15	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	DavePhos	57
16	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	CPhos	58
17	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	^{t}BuBrettPhos	58
18	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	BrettPhos	72

[a]Reactions were conducted on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard.

3.4.2.2 General Procedures for the Hydrocarbamoylation Reactions

General Procedure A

An oven-dried screw-cap reaction tube (tube **A**, Fisherbrand, 13*100 mm, part no. 1495935C) containing an oven-dried magnetic stir bar was charged with $Cu(OAc)_2$ (5.4 mg, 0.030 mmol) and (*R*)-DTBM-SEGPHOS (38.9 mg, 0.033 mmol) (Note: accurate weights of copper and ligand are critical for the reaction). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed and anhydrous THF (0.50 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at room temperature. Next, the cap was removed and dimethoxymethylsilane (DMMS) (0.18 mL, 1.5 mmol) was added in one portion via a 1 mL syringe. The tube was recapped, and the mixture was stirred for another 10 min at room temperature to prepare an orange-colored CuH solution. (If CuH solution was black instead of orange after adding DMMS and stirring for 10 min, it was discarded and a new batch was prepared. The solution may become black if too much $Cu(OAc)_2$ was added).

Another oven-dried screw-cap reaction tube (tube **B**, Fisherbrand, 13*100 mm, part no. 1495935C) containing an oven-dried magnetic stir bar was charged with $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol) and SPhos (9.0 mg, 0.022 mmol) (Note: accurate weights of palladium and ligand are critical for the reaction). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed and anhydrous THF (0.50 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 15 min at room temperature.

A third oven-dried screw-cap reaction tube (tube **C**, Fisherbrand, 20*125 mm, part no. 1495937A) containing an oven-dried magnetic stir bar (VWR, octagon 12.7*8 mm, catalog no. 58948-116) was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18), and then transferred into the nitrogen-filled glovebox. The cap was removed, and alkene (0.50 mmol, 1.0 equiv), carbamoyl chloride (0.75 mmol, 1.5 equiv), and potassium benzoate (160 mg, 2.0 equiv) were added. The entire CuH solution from tube **A** was added to tube **C** in one portion using a 9" glass pipette along the walls of tube **C** to rinse off residual starting materials on the walls. Tube **C** was capped, and the reaction mixture was stirred at rt for 1 min. Then tube **C** was uncapped, and the entire solution from tube **B** was added directly to the bottom of tube **C** in one portion using a 9" glass pipette while the reaction mixture was stirred. Tube **C** was capped, and then removed from the glovebox. The reaction mixture was stirred vigorously at 40 °C for 40 h (Note: Since the reaction is heterogeneous, it was important to ensure that the stir bar is centered to avoid splashing and stirred vigorously at ~550 rpm).

General Procedure B

An oven-dried screw-cap reaction tube (tube **A**, Fisherbrand, 13*100 mm, part no. 1495935C) containing an oven-dried magnetic stir bar was charged with CuOAc (8.8 mg, 0.072 mmol) and (*R*)-DTBM-SEGPHOS (93.4 mg, 0.079 mmol) (Note: accurate weights of copper and ligand are critical for the reaction). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed and anhydrous THF (1.2 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 10 min at room temperature. Next, the cap was removed and dimethoxymethylsilane (DMMS) (0.44 mL, 3.6 mmol) was added in one portion via a 1 mL syringe. The tube was recapped, and the mixture was stirred for another 10 min at room temperature to prepare an orange-colored CuH solution (which was enough for setting up two hydrocarbamoylation reactions in parallel).

Another oven-dried screw-cap reaction tube (tube **B**, Fisherbrand, 13*100 mm, part no. 1495935C) containing an oven-dried magnetic stir bar was charged with the palladium catalyst and biaryl phosphine ligand (as indicated for each substrate) (Note: accurate weights of palladium and ligand are critical for the reaction). The reaction tube was loosely capped with a septum-containing cap (cap: Thermo Scientific C4015-66; Septum: Thermo Scientific C4015-60), and then transferred into a nitrogen-filled glovebox. The cap was removed and anhydrous THF (0.50 mL) was added to the tube via a 1 mL syringe. The tube was capped and the mixture was stirred for 20 min at room temperature.

A third oven-dried screw-cap reaction tube (tube **C**, Fisherbrand, 20*125 mm, part no. 1495937A) containing an oven-dried magnetic stir bar (VWR, octagon 12.7*8 mm, catalog no.

58948-116) was loosely capped with a septum-containing cap (cap: Kimble Chase Open Top S/T Closure catalog no. 73804-18400; Septum: Thermo Scientific B7995-18), and then transferred into the nitrogen-filled glovebox. The cap was removed, and alkene (0.50 mmol, 1.0 equiv), carbamoyl chloride (0.75 mmol, 1.5 equiv), and base (2.0 equiv) were added. CuH solution (0.68 mL) from tube **A** was added to tube **C** in one portion using a 1 mL syringe along the walls of tube **C** to rinse off residual starting materials on the walls. Tube **C** was capped, and the reaction mixture was stirred at rt for 1 min. Then tube **C** was uncapped, and the entire solution from tube **B** was added directly to the bottom of tube **C** in one portion using a 9" glass pipette while the reaction mixture was stirred. Tube **C** was capped, and then removed from the glovebox. The reaction mixture was stirred vigorously at 40 °C for 40 h (Note: Since the reaction is heterogeneous, it was important to ensure that the stir bar is centered to avoid splashing and stirred vigorously at ~550 rpm).

Workup A

After the reaction mixture had stirred at 40 °C for 40 h, the reaction mixture was allowed to cool to room temperature, the cap of the reaction tube was removed, and the mixture was diluted with CH_2Cl_2 (2 mL). While the reaction mixture was stirred at room temperature, sat. aq. Na_2CO_3 (2 mL) was slowly added to quench the reaction mixture (*Caution: gas evolution observed*). The mixture was stirred uncapped at room temperature for 30 min, and then transferred to a 125 mL separatory funnel with CH_2Cl_2 (4 x 5 mL to rinse the tube). CH_2Cl_2 (20 mL), brine (30 mL), and H_2O (10 mL) were added to the separatory funnel. The layers were separated and then the aqueous layer was extracted with CH_2Cl_2 (40 mL*3) (Note: Phase separation was sometimes difficult during the first 1-2 extractions, in that case the mixture was

stirred with a 9" glass pipette to facilitate phase separation). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was immediately purified by silica gel column chromatography (~30 g silica gel, diameter of the column ~2 cm, length of the packed column ~18 cm. Product-containing fractions were repeatedly spotted on the TLC plate for ~10 times each for visualization with UV lamp, and then collected while rinsing each test tubes several times with EtOAc) or purified by reversed-phase chromatography (see workup **B**).

Workup B (purification by reversed-phase chromatography)

The crude residue from workup **A** was dissolved in DMSO (ca. 1.5 mL) by first using ~0.5 mL DMSO to dissolve the crude material, then ~1 mL in total to rinse the vial and syringe for 3-4 times, and then loaded onto a 43 g C18 column. After the chromatography was completed, fractions containing the product (as determined by LC-MS) were combined into a 1000 mL round-bottom flask and each test tube was rinsed with acetone (ca. 2 mL). The mixture was concentrated *in vacuo* with the aid of a rotary evaporator. Once only the aqueous phase remained, the mixture was diluted with CH_2Cl_2 (40 mL) and transferred to a separatory funnel containing sat. aq. Na_2CO_3 (50 mL) (Note: aq. Na_2CO_3 was used only if the chromatography was performed using water that contained 0.1% TFA). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator to give the corresponding amide product.

3.4.2.3 Determination of the absolute configuration of the hydrocarbamoylation product

Single Crystal X-ray Diffraction Data for Compound 3g

A crystal of **3g** was obtained by slowly evaporating a solution of **3g** in tetramethylsilane at 0 °C (in air). The absolute configuration of **3g** was determined by X-ray crystallographic analysis. The absolute configuration of **3a-f** and **3h-k** was assigned by analogy to **3g**.

CCDC 2157585 contains the supplementary crystallographic data for **3g**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

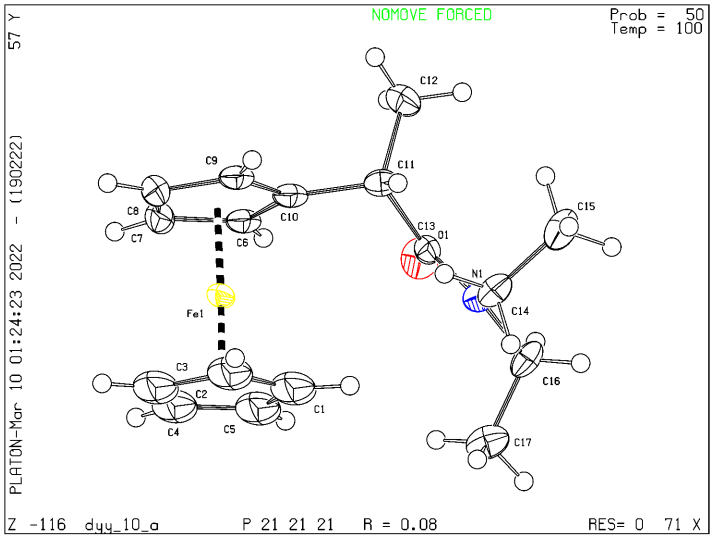


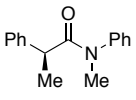
Table S3. Crystal Data and Structure Refinement for dyy_10_a

Identification code	dyy_10_a
Empirical formula	C17 H23 Fe N O
Formula weight	313.21
Temperature	100 K
Wavelength	1.54178 Å
Crystal system	Orthorhombic

Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.2955(3) Å	a= 90°.
	b = 7.9425(3) Å	b= 90°.
	c = 30.8662(12) Å	g = 90°.
Volume	1543.37(11) $Å^3$	
Z	4	
Density (calculated)	1.348 g/cm^3	
Absorption coefficient	7.780 mm^{-1}	
F(000)	664.0	
Crystal size	0.160 x 0.100 x 0.040 mm^3	
Theta range for data collection	2.863 to 66.584°.	
Index ranges	-6<=h<=7, -9<=k<=9, -36<=l<=36	
Reflections collected	36592	
Independent reflections	2712 [R(int) = 0.1056]	
Completeness to theta = 67.679°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2712 / 0 / 148	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0817, wR2 = 0.1948	
R indices (all data)	R1 = 0.0916, wR2 = 0.2036	
Absolute structure parameter	0.002(8)	

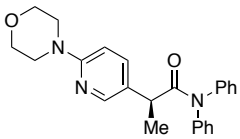
3.4.3 Characterization Data for the Hydrocarboxylation Products

(*S*)-*N*-methyl-*N*,2-diphenylpropanamide (3a)



Following general procedure **A**, styrene (52 mg, 0.50 mmol, 1.0 equiv) and methyl(phenyl)carbamic chloride (127 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/EtOAc = [30:1 (120 mL) → 25:1 (100 mL) → 20:1 (200 mL) → 15:1 (450 mL) → 12:1 (120 mL) → 10:1 (200 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 88 mg, 73% yield, 96:4 er; 2nd run: 96 mg, 80% yield, 96:4 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 3H), 7.22-7.15 (m, 3H), 7.03-7.00 (m, 4H), 3.64 (q, *J* = 6.9 Hz, 1H), 3.24 (s, 3H), 1.39 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.15, 143.95, 142.08, 129.65, 128.47, 127.95, 127.66, 126.72, 43.22, 37.84, 20.43. The spectral data match those previously reported in the literature.[19] **SFC** analysis: OJ-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 2.81 min (major), 3.84 min (minor), 96:4 er. **Specific rotation** $[\alpha]_D^{20}$: −40.1 (c = 1.0, $CHCl_3$).

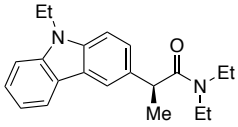
(*S*)-2-(6-morpholinopyridin-3-yl)-*N*,*N*-diphenylpropanamide (3b)



Following general procedure **A**, 4-(5-vinylpyridin-2-yl)morpholine (95 mg, 0.50 mmol, 1.0 equiv) and diphenylcarbamic chloride (174 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **A** and purification by column chromatography (the crude material was dissolved in CH_2Cl_2 and loaded onto the column with the aid of CH_2Cl_2) with a gradient of hexane (100 mL) → hexane/EtOAc = [10:1 (100 mL) → 5:1 (100 mL) → 4:1 (100 mL) → 3:1 (210 mL) → 2.5:1 (100 mL) → 2:1 (400 mL)] (Note: Volumes refer to the volume of

hexane that was used. Product-containing fractions were repeatedly spotted on the TLC plate for 8~10 times each for visualization with UV lamp), the title compound was obtained as a light yellow solid (1st run: 128 mg, 66% yield, 96:4 er; 2nd run: 125 mg, 64% yield, 96:4 er) (Note: $CDCl_3$ for the NMR analysis was passed through a short plug of basic alumina before using, and the NMR analysis was carried out within 30 min after the sample was prepared). **m.p.** 51.4-53.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.2 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.36-7.31 (m, 5H), 7.16-7.14 (m, 5H), 6.61 (d, *J* = 8.8 Hz, 1H), 3.83-3.81 (m, 4H), 3.75 (q, *J* = 6.9 Hz, 1H), 3.51-3.42 (m, 4H), 1.43 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.31, 158.95, 147.09, 142.76, 136.86, 129.82, 129.01, 128.15, 127.03, 126.45, 126.20, 107.25, 66.88, 45.92, 40.56, 20.31. **IR** (thin film): 2967, 2851, 1667, 1602, 1489, 1237, 1119, 943 cm^{-1}. **EA** Calcd. for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50. Found: C, 74.15; H, 6.55. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 20:80 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.97 min (major), 5.70 min (minor), 96:4 er. **Specific rotation** $[\alpha]_D^{20}$: 9.4 (c = 1.0, $CHCl_3$).

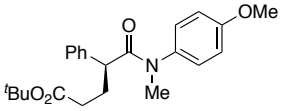
(*S*)-*N*,*N*-diethyl-2-(9-ethyl-9*H*-carbazol-3-yl)propanamide (3c)



Following general procedure **B**, 9-ethyl-3-vinyl-9*H*-carbazole (111 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), G3-dimer (7.4 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and sodium pivalate (124 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 15% 0.5 CV, 15-30% 8.5 CV, 30-50% 9.5 CV, 50-57% 2 CV, 57% 14.5 CV, 57-100% 3 CV, 100% 3 CV, 80% 1 CV), the title compound was obtained as a white solid (1st run: 108 mg, 67% yield, 99:1 er; 2nd run: 106 mg,

65% yield, 99:1 er). **m.p.** 122.5-124.2 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 1.3 Hz, 1H), 7.48-7.44 (m, 1H), 7.42-7.34 (m, 3H), 7.22 (t, *J* = 7.0 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.01 (q, *J* = 6.8 Hz, 1H), 3.56 (dq, *J* = 14.0, 7.1 Hz, 1H), 3.42 (dq, *J* = 14.3, 7.1 Hz, 1H), 3.26 (dq, *J* = 13.9, 7.0 Hz, 1H), 3.11 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.51, 140.35, 139.01, 133.17, 125.78, 125.18, 123.32, 122.85, 120.60, 119.01, 118.85, 108.80, 108.56, 43.32, 41.73, 40.36, 37.68, 21.82, 14.39, 13.97, 12.97. **IR** (thin film): 2971, 2930, 1635, 1461, 1329, 1232, 1081, 747 cm^{-1}. **EA** Calcd. for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13. Found: C, 77.96; H, 8.27. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 5.33 min (minor), 5.74 min (major), 99:1 er. **Specific rotation** $[\alpha]_D^{20}$: 80.3 (c = 1.0, $CHCl_3$).

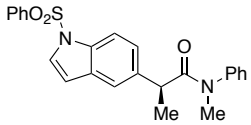
***tert*-butyl (*S*)-5-((4-methoxyphenyl)(methyl)amino)-5-oxo-4-phenylpentanoate (3d)**



Following general procedure **A**, *tert*-butyl (*E*)-4-phenylbut-3-enoate (109 mg, 0.50 mmol, 1.0 equiv) and (4-methoxyphenyl)(methyl)carbamic chloride (150 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography [(0.1% TFA in water)/MeCN 10% 0.5 CV, 10-52% 12 CV, 52% 2 CV, 52-67% 4 CV, 67%, 4 CV, 67-100% 9 CV, 100% 5 CV, 80% 1CV], the resulting material was dissolved in EtOAc and filtered through a short plug of silica gel (~1.2 g) eluting with EtOAc. The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a light yellow oil (1st run: 169 mg, 88% yield, 99:1 er; 2nd run: 179 mg, 93% yield, 99:1 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.16 (m, 3H), 7.02-

7.00 (m, 2H), 6.83 (br, 4H), 3.82 (s, 3H), 3.50 (t, J = 7.5 Hz, 1H), 3.19 (s, 3H), 2.33-2.25 (m, 1H), 2.17-2.02 (m, 2H), 1.98-1.89 (m, 1H), 1.38 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.11, 172.53, 159.06, 139.89, 136.44, 129.16, 128.49, 128.23, 126.96, 114.69, 80.20, 55.63, 48.15, 37.95, 33.69, 30.38, 28.21. **IR** (thin film): 2976, 2935, 1725, 1652, 1511, 1247, 1147, 1033, 838 cm^{-1}. **EA** Calcd. for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62. Found: C, 71.76; H, 7.66. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.70 min (major), 4.08 min (minor), 99:1 er. **Specific rotation** $[\alpha]_D^{20}$: -31.8 (c = 1.0, $CHCl_3$).

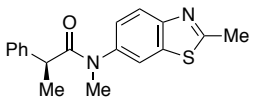
(*S*)-*N*-methyl-*N*-phenyl-2-(1-(phenylsulfonyl)-1*H*-indol-5-yl)propanamide (3e)



Following general procedure **A**, 1-(phenylsulfonyl)-5-vinyl-1*H*-indole (142 mg, 0.50 mmol, 1.0 equiv) and methyl(phenyl)carbamic chloride (127 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography [(0.1% TFA in water)/MeCN 10% 0.5 CV, 10-34% 6.5 CV, 34% 0.5 CV, 34-51% 5 CV, 51%, 3 CV, 51-65% 4 CV, 65% 6 CV, 65-75% 2.5 CV, 75-100% 2.5 CV, 100% 6 CV, 80% 1 CV], the title compound was obtained as a white solid (1st run: 153 mg, 73% yield, 97:3 er; 2nd run: 152 mg, 72% yield, 97:3 er). **m.p.** 51.8-53.4°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.80 (d, J = 8.6 Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.42 (m, 2H), 7.32-7.27 (m, 3H), 7.24 (br, 1H), 6.93-6.91 (m, 3H), 6.56 (d, J = 3.6 Hz, 1H), 3.70 (q, J = 6.9 Hz, 1H), 3.22 (s, 3H), 1.39 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.29, 143.84, 138.37, 137.30, 133.91, 133.82, 131.00, 129.64, 129.36, 127.98, 127.87, 126.91, 126.55, 124.73, 120.23, 113.37, 109.42, 42.85, 37.81, 20.62. **IR** (thin film): 2969, 2930, 1652, 1369, 1174, 1126, 995, 725 cm^{-1}. **EA** Calcd. for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30. Found: C,

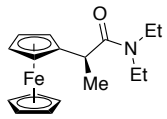
68.61; H, 5.39. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 6.25 min (major), 6.69 min (minor), 97:3 er. **Specific rotation** $[\alpha]_D^{20}$: -80.6 (c = 1.0, $CHCl_3$).

(*S*)-*N*-methyl-*N*-(2-methylbenzo[*d*]thiazol-6-yl)-2-phenylpropanamide (3f)



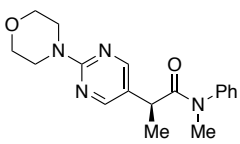
Following general procedure **A**, styrene (52 mg, 0.50 mmol, 1.0 equiv) and methyl(2-methylbenzo[*d*]thiazol-6-yl)carbamic chloride (181 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography [(0.1% TFA in water)/MeCN 10% 0.5 CV, 10-55% 12.5 CV, 55% 4 CV, 55-100% 12 CV, 100%, 5 CV, 80% 2CV], the resulting material was dissolved in 1:1 hexane/EtOAc and filtered through a short plug of silica gel (~1.2 g) eluting with 1:1 hexane/EtOAc. The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a light yellow oil (1st run: 126 mg, 81% yield, 97:3 er; 2nd run: 134 mg, 86% yield, 97:3 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.30 (br, 1H), 7.17-7.16 (m, 3H), 7.06 (br, 1H), 6.95-6.93 (m, 2H), 3.58 (q, *J* = 6.8 Hz, 1H), 3.27 (s, 3H), 2.85 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.18, 168.71, 152.74, 142.06, 140.53, 136.40, 128.54, 127.61, 126.84, 126.14, 123.17, 121.17, 43.70, 38.18, 20.55, 20.39. **IR** (thin film): 3028, 2970, 2928, 1655, 1454, 1375, 1168, 1055, 700 cm^{-1}. **EA** Calcd. for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.85. Found: C, 69.35; H, 5.86. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.42 min (major), 4.62 min (minor), 97:3 er. **Specific rotation** $[\alpha]_D^{20}$: -62.8 (c = 1.0, $CHCl_3$).

(*R*)-*N*,*N*-diethyl-2-ferrocenylpropanamide (3g)



Following general procedure **B**, vinylferrocene (106 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), G3-dimer (7.4 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and sodium pivalate (124 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 10% 0.5 CV, 10-100% 25 CV, 100% 5 CV, 50% 2 CV), the title compound was obtained as a red solid (1st run: 103 mg, 66% yield, 99:1 er; 2nd run: 102 mg, 65% yield, 99:1 er). **m.p.** 48.1-50.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.19-4.18 (m, 1H), 4.15 (s, 5H), 4.10-4.08 (m, 3H), 3.59-3.49 (m, 3H), 3.30-3.20 (m, 2H), 1.46 (d, J = 6.9 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.68, 90.37, 68.66, 67.58, 67.22, 67.16, 67.05, 42.30, 40.53, 35.41, 19.56, 15.10, 13.22. **IR** (thin film): 3094, 2971, 2931, 1637, 1427, 1251, 1105, 816 cm^{-1}. **HRMS** Calcd. m/z for $C_{17}H_{24}NOFe^+$ $[M+H]^+$: 314.1202; found 314.1196. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:40 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.34 min (major), 4.90 min (minor), 96:4 er. **Specific rotation** $[\alpha]_D^{20}$: 21.2 (c = 1.0, $CHCl_3$).

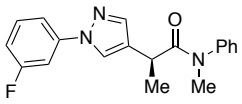
(*S*)-*N*-methyl-2-(2-morpholinopyrimidin-5-yl)-*N*-phenylpropanamide (3h)



Following general procedure **A**, 4-(5-vinylpyrimidin-2-yl)morpholine (96 mg, 0.50 mmol, 1.0 equiv) and methyl(phenyl)carbamic chloride (127 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **A** and purification by column chromatography (the crude material was dissolved in CH_2Cl_2 and loaded onto the column with the aid of CH_2Cl_2) with a gradient of hexane/EtOAc = [9:1 (90 mL) → 7:1 (70 mL) → 5:1 (100 mL) → 4:1 (160

mL) → 3:1 (150 mL) → 2:1 (140 mL) → 2:1 (140 mL) → 3:2 (150 mL) → 1:1 (200 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 90 mg, 55% yield, 93:7 er; 2nd run: 92 mg, 56% yield, 93:7 er) (Note: $CDCl_3$ for the NMR analysis was passed through a short plug of basic alumina before using, and the NMR analysis was carried out within 30 min after the sample was prepared). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.44-7.35 (m, 3H), 7.08 (d, *J* = 7.0 Hz, 2H), 3.74 (s, 8H), 3.47 (q, *J* = 6.9 Hz, 1H), 3.23 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.58, 161.21, 157.04, 143.77, 130.05, 128.37, 127.70, 123.40, 66.94, 44.46, 37.81, 37.74, 19.91. **IR** (thin film): 2969, 2853, 1657, 1599, 1495, 1358, 1255, 1117, 958 cm^{-1}. **HRMS** Calcd. m/z for $C_{18}H_{23}N_4O_2^+$ $[M+H]^+$: 327.1816; found 327.1826. **SFC** analysis: OJ-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.75 min (major), 4.25 min (minor), 93:7 er. **Specific rotation** $[\alpha]_D^{20}$: -148.0 (c = 1.0, $CHCl_3$).

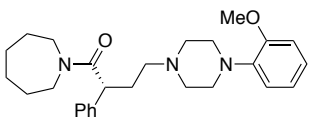
(*S*)-2-(1-(3-fluorophenyl)-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenylpropanamide (3i)



Following general procedure **A**, 1-(3-fluorophenyl)-4-vinyl-1*H*-pyrazole (94 mg, 0.50 mmol, 1.0 equiv) and methyl(phenyl)carbamic chloride (127 mg, 0.75 mmol, 1.5 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane (100 mL) → hexane/EtOAc = [15:1 (75 mL) → 12:1 (60 mL) → 10:1 (150 mL) → 8:1 (120 mL) → 6:1 (120 mL) → 5:1 (200 mL) → 4:1 (300 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 107 mg, 66% yield, 98:2 er; 2nd run: 107 mg, 66% yield, 98:2 er). Duplicate experiments were carried out on a 1.0 mmol scale following the same procedure except the

amounts for all the reagents were doubled, and the title compound was obtained as a light yellow oil (1st run: 214 mg, 66% yield, 98:2 er; 2nd run: 212 mg, 65% yield, 98:2 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.45-7.34 (m, 7H), 7.15 (d, *J* = 7.1 Hz, 2H), 6.94 (tt, *J* = 8.3, 1.9 Hz, 1H), 3.67 (q, *J* = 6.9 Hz, 1H), 3.27 (s, 3H), 1.39 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.25, 163.35 (d, *J* = 246.4 Hz), 143.96, 141.60 (d, *J* = 10.1 Hz), 140.52, 130.75 (d, *J* = 8.9 Hz), 129.98, 128.24, 127.58, 125.31, 124.71, 114.06 (d, *J* = 2.9 Hz), 113.02 (d, *J* = 21.5 Hz), 106.58 (d, *J* = 26.2 Hz), 37.80, 33.54, 20.71. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −111.09. **IR** (thin film): 3064, 2975, 2933, 1652, 1612, 1495, 1379, 1257, 864 cm^{-1}. **HRMS** Calcd. m/z for $C_{19}H_{19}N_3OF^+$ $[M+H]^+$: 324.1507; found 324.1509. **SFC** analysis: OJ-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.73 min (major), 4.13 min (minor), 98:2 er. **Specific rotation** $[\alpha]_D^{20}$: -147.1 (c = 1.0, $CHCl_3$).

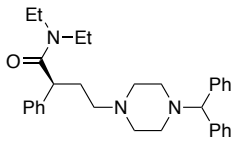
(*R*)-RWAY (3j)



General procedure **B** was followed, except (*S*)-DTBM-MeO-BIPHEP (91.0 mg, 0.079 mmol) was used when preparing the CuH stock solution. 1-Cinnamyl-4-(2-methoxyphenyl)piperazine (154 mg, 0.50 mmol, 1.0 equiv), azepane-1-carbonyl chloride (121 mg, 0.75 mmol, 1.5 equiv), G3-dimer (7.4 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and sodium benzoate (144 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography [(0.1% TFA in water)/MeCN 10% 0.5 CV, 10-34% 9.5 CV, 34% 2.5 CV, 34-45% 4 CV, 45%, 2 CV, 45-100% 5 CV, 100% 2 CV, 80% 1 CV], the title compound was obtained as a white solid (1st run: 194 mg, 89% yield, 97:3 er; 2nd run: 186 mg, 85% yield, 97:3 er). **m.p.** 74.1-75.2 °C. **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H), 7.24-7.20 (m, 1H), 7.01-6.89 (m, 3H), 6.85 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 3.72 (ddd, *J* = 12.8, 7.4, 5.0 Hz, 1H), 3.56 (dt, *J* = 14.4, 5.1 Hz, 1H), 3.34-3.22 (m, 2H), 3.09 (br, 4H), 2.64-2.61 (m, 4H), 2.40-2.32 (m, 3H), 1.93-1.83 (m, 1H), 1.80-1.59 (m, 3H), 1.57-1.40 (m, 4H), 1.37-1.29 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.49, 152.39, 141.56, 140.86, 128.77, 128.10, 126.88, 122.92, 121.07, 118.22, 111.35, 56.23, 55.47, 53.43, 50.86, 47.86, 46.50, 46.33, 32.44, 29.26, 27.61, 26.94, 26.73. The spectral data match those previously reported in the literature.[20] **SFC** analysis: CEL-1 (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH (0.1% DEA): $scCO_2$ to 15:85 MeOH (0.1% DEA): $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.34 min (major), 4.52 min (minor), 97:3 er. **Specific rotation** $[\alpha]_D^{20}$: -57.6 (c = 1.0, $CHCl_3$).

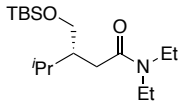
(*S*)-4-(4-benzhydrylpiperazin-1-yl)-*N*,*N*-diethyl-2-phenylbutanamide (3k)



Following general procedure **B**, 1-benzhydryl-4-cinnamylpiperazine (184 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), G3-dimer (7.4 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and sodium benzoate (144 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane (containing 0.5% Et_3N)/acetone = [5:1 (100 mL) → 4:1 (120 mL) → 3:1 (120 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a yellow oil (1st run: 225 mg, 95% yield, 94:6 er; 2nd run: 223 mg, 95% yield, 93:7 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.43 (m, 4H), 7.33-7.17 (m, 11H), 4.23 (s, 1H), 3.88 (t, *J* = 6.7 Hz, 1H), 3.51-3.42 (m, 1H), 3.41-3.13 (m, 3H), 2.45-2.25 (m, 11H), 1.89-1.80 (m, 1H), 1.10-1.04 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.12, 143.01, 140.92, 128.74, 128.57, 128.03, 126.99, 126.83, 76.49, 56.05,

53.40, 52.22, 46.25, 41.85, 40.59, 32.47, 14.52, 13.04. **IR** (thin film): 3059, 3024, 2963, 2934, 2806, 1637, 1451, 1140, 1008 cm^{-1}. **HRMS** Calcd. m/z for $C_{31}H_{40}N_3O^+$ $[M+H]^+$: 470.3166; found 470.3162. **SFC** analysis: OJ-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 MeOH (0.1% DEA): $scCO_2$ to 40:60 MeOH (0.1% DEA): $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.23 min (minor), 4.42 min (major), 93:7 er. **Specific rotation** $[\alpha]_D^{20}$: 52.1 (c = 1.0, $CHCl_3$).

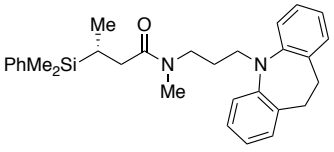
(*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-4-methylpentanamide (3l)



Following general procedure **B**, *tert*-butyldimethyl(3-methyl-2-methylenebutoxy)silane (107 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 50% 1.0 CV, 50-100% 14 CV, 100% 15 CV, 80% 1 CV), the resulting material was dissolved in EtOAc and filtered through a short plug of basic alumina (~2.1 g) eluting with EtOAc (~10 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a yellow oil (1^{st} run: 101 mg, 64% yield, 95:5 er; 2^{nd} run: 114 mg, 72% yield, 95:5 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.62-3.55 (m, 2H), 3.46-3.36 (m, 2H), 3.29 (m, 2H), 2.42 (dd, *J* = 15.1, 8.1 Hz, 1H), 2.18 (dd, *J* = 15.1, 5.3 Hz, 1H), 1.96-1.89 (m, 1H), 1.84 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 6H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.23, 63.08, 43.53, 42.18, 40.31, 31.68, 28.22, 26.05, 20.08, 19.99, 18.37, 14.57, 13.28, -5.36. **IR** (thin film): 2956, 2929, 2857, 1645, 1462, 1257, 1093, 836 cm^{-1}. **HRMS** Calcd. m/z for

$C_{17}H_{38}NO_2Si^+$ $[M+H]^+$: 316.2666; found 316.2665. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 1.88 min (major), 1.98 min (minor), 95:5 er. **Specific rotation** $[\alpha]_D^{20}$: 32.5 (c = 1.0, $CHCl_3$).

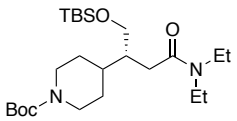
(*R*)-*N*-(3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)-3-(dimethyl(phenyl)silyl)-*N*-methylbutanamide (3m)



Following general procedure **B**, dimethyl(phenyl)(prop-1-en-2-yl)silane (88 mg, 0.50 mmol, 1.0 equiv), (3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)(methyl)carbamic chloride (247 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane (50 mL) → hexane/EtOAc = [15:1 (90 mL) → 12:1 (120 mL) → 10:1 (150 mL) → 8:1 (160 mL) → 6:1 (180 mL) → 5:1 (350 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 161 mg, 68% yield, 98:2 er; 2nd run: 162 mg, 68% yield, 98:2 er). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.50-7.48 (m, 2H), 7.34-7.33 (m, 3H), 7.16-7.09 (m, 5H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.93 (dt, *J* = 9.8, 7.2 Hz, 2H), 3.73 (t, *J* = 6.9 Hz, 1H), 3.69-3.58 (m, 1H), 3.38 (t, *J* = 7.1 Hz, 1H), 3.24-3.11 (m, 5H), 2.73 (2 × s, 3H, rotamers), 2.30-2.15 (m, 1H), 2.06-1.91 (m, 1H), 1.80-1.67 (m, 2H), 1.52-1.43 (m, 1H), 0.96 & 0.91 (2 × d, *J* = 7.3 Hz, 3H), 0.28-0.24 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 172.86, 172.78, 148.16, 147.90, 138.07, 137.86, 134.32, 134.28, 134.06, 130.14, 129.96, 129.12, 127.87, 126.62, 126.57, 123.01, 122.72, 120.14, 119.78, 48.37, 47.93, 47.64,

45.83, 35.55, 35.52, 34.98, 33.66, 32.29, 32.27, 26.76, 26.10, 16.33, 16.20, 14.99, 14.74, -4.54, -4.65, -5.13, -5.16. **IR** (thin film): 3066, 2951, 2866, 1643, 1487, 1248, 1110, 835 cm^{-1}. **EA** Calcd. for $C_{30}H_{38}N_2OSi$: C, 76.55; H, 8.14. Found: C, 76.52; H, 8.31. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 20:80 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 4.94 min (major), 5.31 min (minor), 98:2 er. **Specific rotation** $[\alpha]_D^{20}$: 6.7 (c = 1.0, $CHCl_3$).

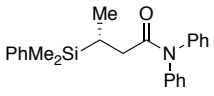
***tert*-butyl (*R*)-4-(1-((*tert*-butyldimethylsilyl)oxy)-4-(diethylamino)-4-oxobutan-2-yl)piperidine-1-carboxylate (3n)**



Following general procedure **B**, *tert*-butyl 4-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-2-yl)piperidine-1-carboxylate (178 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 50% 1.0 CV, 50-100% 14 CV, 100% 15 CV, 80% 1 CV), the resulting material was dissolved in EtOAc and filtered through a short plug of basic alumina (~2.1 g) eluting with EtOAc (~10 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a yellow oil (1st run: 209 mg, 91% yield, 97:3 er; 2nd run: 215 mg, 94% yield, 97:3 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (br, 2H), 3.62-3.55 (m, 2H), 3.46-3.21 (m, 4H), 2.63 (br, 2H), 2.44 (dd, *J* = 15.3, 8.2 Hz, 1H), 2.19 (dd, *J* = 15.3, 5.3 Hz, 1H), 1.99 (dp, *J* = 9.9, 4.9 Hz, 1H), 1.66-1.60 (m, 3H), 1.44 (s, 9H), 1.24-1.14 (m, 5H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.70, 154.98, 79.32, 62.68, 42.17, 42.02,

40.38, 37.04, 31.43, 29.71, 29.41, 28.60, 26.02, 18.34, 14.57, 13.27, -5.38. **IR** (thin film): 2929, 2856, 1693, 1642, 1422, 1250, 1171, 1090, 835, 775 cm^{-1}. **EA** Calcd. for $C_{24}H_{48}N_2O_4Si$: C, 76.55; H, 8.14. Found: C, 76.52; H, 8.31. **SFC** analysis: OD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 20:80 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.72 min (major), 3.89 min (minor), 97:3 er. **Specific rotation** $[\alpha]_D^{20}$: 24.5 (c = 1.0, $CHCl_3$).

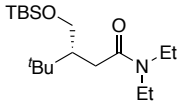
(*R*)-3-(dimethyl(phenyl)silyl)-*N*,*N*-diphenylbutanamide (3o)



Following general procedure **B**, dimethyl(phenyl)(prop-1-en-2-yl)silane (88 mg, 0.50 mmol, 1.0 equiv), diphenylcarbamic chloride (174 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 10% 0.5 CV, 10-28% 6 CV, 28% 1 CV, 28-50% 7.5 CV, 50% 1.5 CV, 50-60% 3 CV, 60% 6 CV, 60%-70% 3CV, 70% 1 CV, 70-77% 1.5 CV, 77% 10 CV), the resulting material was dissolved in Et_2O and filtered through a short plug of silica gel (~1.2 g) eluting with Et_2O (~10 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a yellow oil (1^{st} run: 94 mg, 50% yield, 97:3 er; 2^{nd} run: 82 mg, 44% yield, 97:3 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10 H), 7.20-7.18 (m, 5H), 2.39 (dd, *J* = 15.1, 4.2 Hz, 1H), 2.04 (dd, *J* = 15.1, 10.7 Hz, 1H), 1.57-1.48 (m, 1H), 1.03 (d, *J* = 7.4 Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.33, 143.15, 137.69, 133.99, 129.45, 129.03, 127.82, 126.57, 37.60, 16.63, 14.60, -4.78, -5.13. **IR** (thin film): 3066, 2954, 1671, 1490, 1249, 1112, 814, 700 cm^{-1}. **HRMS** Calcd. m/z for $C_{24}H_{28}NOSi^+$ $[M+H]^+$: 374.1935; found

374.1932. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 20:80 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$ linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 3.47 min (major), 4.34 min (minor), 97:3 er. **Specific rotation** $[\alpha]_D^{20}$: -5.1 (c = 1.0, $CHCl_3$).

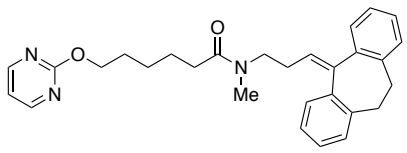
(*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-4,4-dimethylpentanamide (3p)



Following general procedure **B**, *tert*-butyl(3,3-dimethyl-2-methylenebutoxy)dimethylsilane (114 mg, 0.50 mmol, 1.0 equiv), diethylcarbamic chloride (102 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 50% 1.0 CV, 50-100% 11 CV, 100% 10 CV, 50% 1 CV), the resulting material was dissolved in EtOAc and filtered through a short plug of basic alumina (~2.1 g) eluting with EtOAc (~10 mL). The resulting solution was concentrated *in vacuo* with the aid of a rotary evaporator to give the title compound as a yellow oil (1st run: 82 mg, 50% yield, 99:1 er; 2nd run: 93 mg, 56% yield, 99:1 er). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.64 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.49-3.39 (m, 2H), 3.35-3.23 (m, 2H), 2.57 (dd, *J* = 15.5, 9.2 Hz, 1H), 2.17 (dd, *J* = 15.5, 3.6 Hz, 1H), 1.95 (dq, *J* = 7.7, 3.8 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.87 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.46, 62.75, 46.02, 42.20, 40.52, 32.79, 29.99, 28.66, 26.08, 18.31, 14.58, 13.29, -5.43, -5.48. **IR** (thin film): 2955, 2929, 2857, 1644, 1428, 1254, 1091, 831, 774 cm^{-1}. **EA** Calcd. for $C_{18}H_{39}NO_2Si$: C, 65.59; H, 11.93. Found: C, 65.68; H, 11.97. **SFC** analysis: AD-H (Chiralpak®, 4.6 x 250 mm, 5 μM particle size; 5:95 IPA: $scCO_2$ to 40:60 IPA: $scCO_2$

linear gradient over 6 min with 1 min hold time, 2.50 mL/min), 1.92 min (major), 2.01 min (minor), 99:1 er. **Specific rotation** $[\alpha]_D^{20}$: 24.5 (c = 1.0, $CHCl_3$).

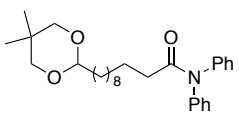
_N_-(3-(10,11-dihydro-5_H_-dibenzo[_a_,_d_][7]annulen-5-ylidene)propyl)-_N_-methyl-6-(pyrimidin-2-yloxy)hexanamide (3q)



Following general procedure **B**, 2-(pent-4-en-1-yloxy)pyrimidine (82 mg, 0.50 mmol, 1.0 equiv), (3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)(methyl)carbamic chloride (244 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane/EtOAc = [5:1 (100 mL) → 3:1 (120 mL) → 1:1 (100 mL) → 1:2 (70 mL) → 1:3 (200 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 195 mg, 85% yield; 2nd run: 190 mg, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.49 (dd, *J* = 4.6, 2.6 Hz, 2H), 7.27-7.07 (m, 7H), 7.04-7.00 (m, 1H), 6.90 (t, *J* = 4.7 Hz, 1H), 5.85-5.79 (m, 1H), 4.35-4.31 (m, 2H), 3.47-3.43 (m, 1H), 3.38-3.27 (m, 3H), 2.96 (br, 1H), 2.84-2.77 (m, 4H), 2.43-2.27 (m, 3H), 2.18-2.13 (m, 1H), 1.86-1.74 (m, 2H), 1.70-1.58 (m, 2H), 1.55-1.49 (m, 1H), 1.47-1.38 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 172.73, 172.68, 165.48, 159.33, 146.02, 144.41, 141.15, 140.67, 139.99, 139.67, 139.50, 139.42, 137.13, 137.06, 130.31, 130.06, 128.76, 128.47, 128.28, 128.24, 128.14, 127.97, 127.93, 127.60, 127.45, 127.22, 126.55, 126.21, 126.18, 126.04, 125.89, 114.89, 67.54, 49.60, 47.37, 35.39, 33.87, 33.61, 33.52, 32.79, 32.14, 32.01, 28.82, 28.70, 27.72, 25.95, 25.93, 25.20, 24.90. **IR** (thin film): 2928,

1641, 1578, 1562, 1425, 1322, 1021, 778 cm^{-1}. **EA** Calcd. for $C_{29}H_{33}N_3O_2$: C, 76.45; H, 7.30. Found: C, 76.19; H, 7.44.

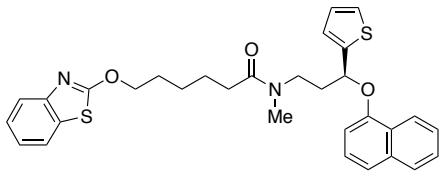
11-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*,*N*-diphenylundecanamide (3r)



Following general procedure **B**, 2-(dec-9-en-1-yl)-5,5-dimethyl-1,3-dioxane (127 mg, 0.50 mmol, 1.0 equiv), diphenylcarbamic chloride (174 mg, 0.75 mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane (50 mL) → hexane/EtOAc = [15:1 (150 mL) → 12:1 (120 mL) → 10:1 (150 mL) → 8:1 (440 mL)] (Note: Volumes refer to the volume of hexane that is being used), the title compound was obtained as a light yellow oil (1st run: 117 mg, 52% yield; 2nd run: 121 mg, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (br, 4H), 7.28-7.27 (m, 6H), 4.42 (t, *J* = 5.0 Hz, 1H), 3.62 (d, *J* = 11.1 Hz, 2H), 3.44 (d, *J* = 10.8 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.70-1.61 (m, 4H), 1.44-1.37 (m, 2H), 1.34-1.21 (m, 15H), 0.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.48, 143.17, 129.43, 102.45, 77.38, 35.41, 35.05, 30.30, 29.66, 29.65, 29.61, 29.55, 29.45, 29.36, 25.70, 24.12, 23.14, 22.00. **IR** (thin film): 2923, 2851, 1674, 1491, 1362, 1261, 1126, 1016, 755 cm^{-1}. **HRMS** Calcd. m/z for $C_{29}H_{42}NO_3^+$ $[M+H]^+$: 452.3159; found 452.3177.

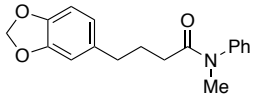
(*S*)-6-(benzo[*d*]thiazol-2-yloxy)-*N*-methyl-*N*-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)hexanamide (3s)

Following general procedure **B**, 2-(pent-4-en-1-yloxy)benzo[d]thiazole (110 mg, 0.50 mmol, 1.0 equiv), methyl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)carbamic chloride (270 mg, 0.75



mmol, 1.5 equiv), $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.010 mmol, 2.0 mol%), BrettPhos (11.8 mg, 0.022 mmol, 4.4 mol%), and potassium benzoate (160 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **A** and purification by column chromatography with a gradient of hexane/EtOAc = [8:1 (80 mL) → 6:1 (90 mL) → 4:1 (120 mL) → 3:1 (150 mL) → 2:1 (140 mL) → 3:2 (210 mL) → 1:1 (300 mL)] (Note: Volumes refer to the volume of hexane that was used), the title compound was obtained as a light yellow oil (1st run: 134 mg, 49% yield; 2nd run: 148 mg, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.37-8.30 (m, 1H), 7.79-7.76 (m, 1H), 7.70-7.62 (m, 2H), 7.53-7.45 (m, 2H), 7.42-7.33 (m, 2H), 7.29-7.18 (m, 3H), 7.08 (dd, *J* = 10.8, 3.3 Hz, 1H), 6.93 (ddd, *J* = 11.0, 5.1, 3.5 Hz, 1H), 6.82 (dd, *J* = 14.4, 7.6 Hz, 1H), 5.73-5.63 (m, 1H), 4.54 (t, *J* = 6.5 Hz, 1H), 4.41 (t, *J* = 6.6 Hz, 1H), 3.84-3.69 (m, 1H), 3.53-3.46 (m, 1H), 2.97 & 2.96 (2 × s, 3H), 2.54-2.10 (m, 4H), 1.87-1.80 (m, 1H), 1.68-1.41 (m, 4H), 1.23-1.04 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 173.12, 173.10, 172.99, 172.87, 153.18, 152.81, 149.59, 149.56, 144.94, 144.23, 134.76, 134.72, 131.95, 127.84, 127.66, 126.93, 126.73, 126.65, 126.45, 126.16, 126.07, 125.99, 125.88, 125.79, 125.63, 125.39, 125.19, 124.93, 124.91, 124.86, 123.52, 122.13, 121.73, 121.36, 121.20, 120.85, 120.81, 107.05, 106.92, 77.48, 77.16, 76.84, 74.69, 73.11, 72.02, 72.01, 46.15, 45.43, 37.82, 36.72, 36.05, 33.49, 33.36, 32.68, 28.84, 28.68, 25.76, 25.54, 24.98, 24.69. **IR** (thin film): 3063, 2944, 1645, 1535, 1442, 1250, 1218, 1094, 772 cm^{-1}. **EA** Calcd. for $C_{31}H_{32}N_2O_3S_2$: C, 68.35; H, 5.92. Found: C, 68.30; H, 5.78. **Specific rotation** $[\alpha]_D^{20}$: 47.7 (c = 1.0, $CHCl_3$).

4-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-*N*-phenylbutanamide (3t)

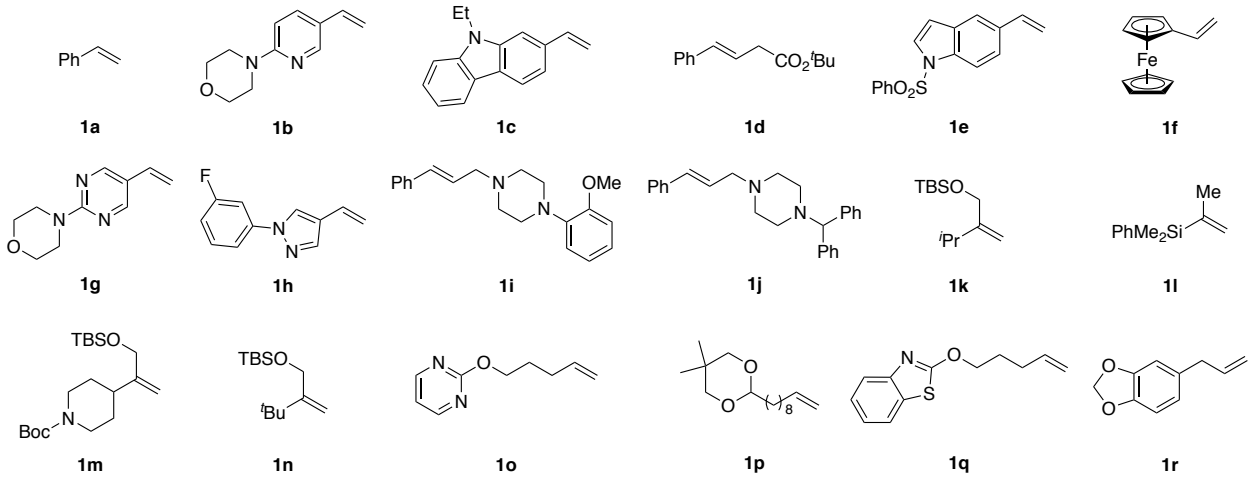


Following general procedure **B**, 5-allylbenzo[*d*][1,3]dioxole (81 mg, 0.50 mmol, 1.0 equiv), methyl(phenyl)carbamic chloride (127 mg, 0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 4.0 mol%), XPhos (10.5 mg, 0.022 mmol, 4.4 mol%), and potassium acetate (98 mg, 1.0 mmol, 2.0 equiv) were used. After Workup **B** and purification by reversed-phase column chromatography (water/MeCN 10% 0.5 CV, 10-26% 7 CV, 26% 2 CV, 26-33% 3 CV, 33% 4 CV, 33-47% 6.5 CV, 47% 9 CV, 47%-100% 8CV, 100% 6 CV, 80% 1 CV), the title compound was obtained as a colorless oil (1st run: 96 mg, 65% yield; 2nd run: 102 mg, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.57 (s, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 5.89 (s, 2H), 3.26 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.07 (t, *J* = 7.2 Hz, 2H), 1.84 (p, *J* = 7.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.93, 147.55, 145.65, 144.25, 135.74, 129.81, 127.81, 127.39, 121.21, 108.96, 108.11, 100.80, 37.41, 35.05, 33.41, 27.39. **IR** (thin film): 2929, 1652, 1595, 1488, 1441, 1242, 1119, 1037, 701 cm^{-1}. **EA** Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44. Found: C, 72.53; H, 6.58.

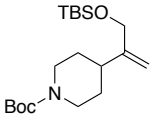
3.4.4 Preparation of Substrates

3.4.4.1 Preparation of alkenes

All of the alkenes used in this chapter are listed below. **1b**,[21] **1c**,[22] **1d**,[23] **1e**,[24] **1g**,[25] **1h**,[21] **1i**,[26] **1k**,[27] **1l**,[28] **1n**,[27] and **1o-1q**[29] are known compounds and were prepared by following previously reported procedures. **1a**, **1f**, **1j**, and **1r** are commercially available.



***tert*-butyl 4-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-2-yl)piperidine-1-carboxylate (1m)**

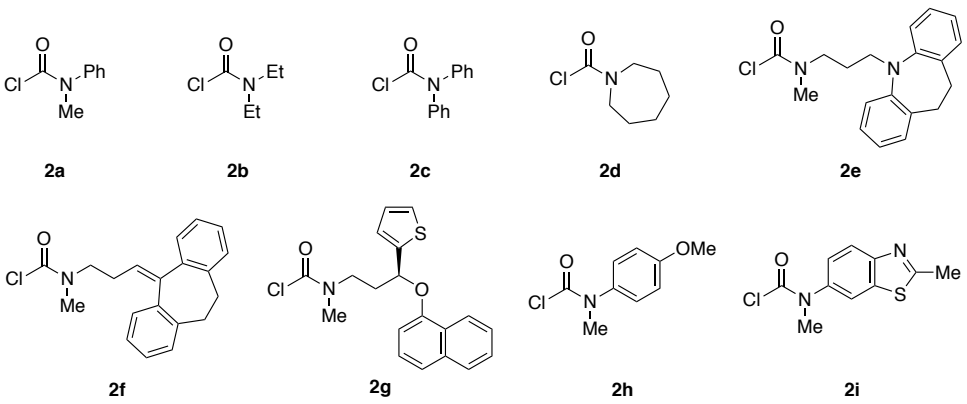


A 100 mL round bottom flask containing a magnetic stir bar was charged with *tert*-butyl 4-(3-hydroxyprop-1-en-2-yl)piperidine-1-carboxylate[30] (2.68 g, 1.0 equiv, 11.1 mmol), imidazole (1.51 g, 2.0 equiv, 22.2 mmol), and CH_2Cl_2 (30 mL). Then *tert*-butylchlorodimethylsilane (2.01 g, 1.2 equiv, 13.3 mmol) was added dropwise while the reaction mixture was stirred at room temperature. The flask was then capped with a septum and attached to a balloon filled with air, and the reaction mixture was stirred at room temperature overnight. Then the septum was removed, and water (50 mL) was added. The contents were transferred to a 125 mL separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel (eluting with 0-5% hexane/EtOAc) to give the title compound as a colorless oil (3.57 g, 10.0 mmol, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.05 (q, *J* = 1.7 Hz, 1H), 4.82 (t, *J* = 1.3 Hz, 1H), 4.18-4.12 (m, 4H), 2.68 (td, *J* = 13.0, 2.6 Hz, 2H), 2.05 (tt, *J* = 12.0, 3.5 Hz, 1H), 1.73-1.70 (m, 2H), 1.45 (s, 9H), 1.37 (qd, *J* = 12.7, 4.2 Hz, 2H), 0.91 (s, 9H),

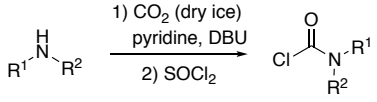
0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.96, 152.10, 107.98, 79.45, 77.48, 77.16, 76.84, 65.17, 44.44, 39.20, 31.41, 28.61, 26.05, 18.51, -5.24. **IR** (thin film): 2930, 2855, 1695, 1421, 1240, 1170, 1123, 836 cm^{-1}. **HRMS** Calcd. m/z for $C_{19}H_{38}NO_3Si^+$ $[M+H]^+$: 356.2616; found 356.2616.

3.4.4.2 Preparation of carbamoyl chlorides

All of the carbamoyl chlorides used in this chapter are listed below. **2h**[31] is a known compound and was prepared by following previously reported procedures. **2a-d** are commercially available.



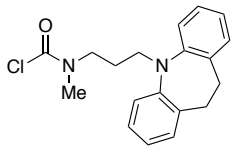
General Procedure C (Adapted from the literature procedure)[32]



A 100 mL round bottom flask (flask **A**) containing a magnetic stir bar was charged with the amine (1.0 equiv, 16 mmol), followed by addition of anhydrous toluene (13 mL), pyridine (1.4 mL, 1.1 equiv, 17 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.6 mL, 1.1 equiv, 17 mmol). The flask was placed in a NaCl-ice bath at -10 °C. Then a small chunk of dry ice (the surface of the dry ice was dried with a paper towel) was dropped into the flask. The flask was

capped with a septum and a needle was inserted into the septum. The mixture was stirred at -10 °C for 30 min. Meanwhile, additional chunks of dry ice were added when needed in order to maintain constant bubbling of the mixture. A second 250 mL flask (flask **B**) containing a magnetic stir bar was charged with $SOCl_2$ (1.4 mL, 1.2 equiv, 19 mmol), and anhydrous toluene (13 mL). The flask was capped with a septum, attached to a balloon under air, and then placed in a NaCl-ice bath at -10 °C. The mixture from flask **A** was quickly transferred to flask **B** via syringe while the mixture in flask **B** was stirred at -10 °C. Then the mixture in flask **B** was stirred at -10 °C for 1 h. Then, flask **B** was removed from the cooling bath, and the reaction mixture was poured into a separatory funnel containing 0.1 M HCl (50 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* with the aid of a rotary evaporator, and then purified by column chromatography on silica gel (0-10% hexane/EtOAc) to give the corresponding carbamoyl chloride **2**.

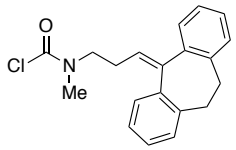
(3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)(methyl)carbamic chloride (2e)



Following general procedure **C**, 3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*-methylpropan-1-amine (4.3 g, 1.0 equiv, 16 mmol) was used. The title compound was obtained as a white solid (4.7 g, 90% yield). **m.p.** 50.5-52.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.17-7.07 (m, 6H), 6.97-6.93 (m, 2H), 3.81-3.76 (m, 2H), 3.51-3.48 (m, 1H), 3.46-3.42 (m, 1H), 3.18 (br, 4H), 2.96 & 2.88 (2 × s, 3H), 1.95-1.85 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.67, 149.30, 147.89, 147.82, 134.38, 130.14, 130.11, 126.66, 123.07, 123.01, 119.96, 119.80, 51.12, 49.58, 47.73, 47.44, 38.68, 36.86,

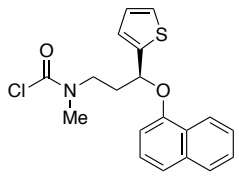
32.24, 26.22, 25.74. **IR** (thin film): 2921, 2841, 1729, 1486, 1384, 1230, 1099, 752 cm^{-1}. **HRMS** Calcd. m/z for $C_{19}H_{22}N_2OCl^+$ $[M+H]^+$: 329.1415; found 329.1413.

(3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)(methyl)carbamic chloride (2f)



Following general procedure **C**, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (4.2 g, 1.0 equiv, 16 mmol) was used. The title compound was obtained as a colorless oil (2.6 g, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.29-7.26 (m, 1H), 7.23-7.22 (m, 2H), 7.21-7.14 (m, 3H), 7.11-7.09 (m, 1H), 7.06-7.03 (m, 1H), 5.85-5.80 (m, 1H), 3.56-3.30 (m, 4H), 3.00-2.90 (m, 4H), 2.82-2.78 (m, 1H), 2.50-2.41 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.74, 149.32, 146.30, 145.79, 140.81, 140.68, 139.65, 139.58, 139.52, 137.20, 137.16, 130.32, 130.22, 128.67, 128.55, 128.30, 128.06, 127.98, 127.93, 127.85, 127.51, 127.46, 126.43, 126.24, 126.05, 126.00, 125.95, 52.63, 51.05, 38.42, 36.70, 33.87, 32.10, 32.03, 28.03, 27.45. **IR** (thin film): 3014, 2918, 1733, 1383, 1244, 1170, 1086, 756 cm^{-1}. **HRMS** Calcd. m/z for $C_{20}H_{21}NOCl^+$ $[M+H]^+$: 326.1306; found 326.1308.

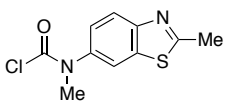
(*S*)-methyl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)carbamic chloride (2g)



Following general procedure **C**, *N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine (4.8 g, 1.0 equiv, 16 mmol) was used. The title compound was obtained as a light yellow oil (4.8 g, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.36-8.31 (m, 1H), 7.81-7.78 (m, 1H), 7.52-7.48 (m, 2H), 7.43-7.41 (m, 1H), 7.30-7.22 (m, 2H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.97-6.93 (m, 1H),

6.83 (d, J = 7.7 Hz, 1H), 5.72-5.69 (m, 1H), 3.84-3.60 (m, 2H), 3.11 & 3.04 (2 × s, 3H), 2.60-2.51 (m, 1H), 2.49-2.38 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.98, 152.92, 149.85, 149.41, 144.15, 143.94, 134.74, 127.77, 127.73, 126.93, 126.88, 126.61, 126.57, 126.11, 126.06, 125.79, 125.74, 125.62, 125.57, 125.29, 125.23, 125.14, 125.04, 121.99, 121.89, 121.23, 121.16, 107.11, 107.03, 74.08, 73.68, 49.88, 48.79, 39.25, 37.35, 37.29, 36.47. **IR** (thin film): 3053, 2954, 1729, 1578, 1395, 1235, 1094, 1064, 771 cm^{-1}. **HRMS** Calcd. m/z for $C_{19}H_{18}NO_2SClNa^+$ $[M+Na]^+$: 382.0639; found 382.0640.

methyl(2-methylbenzo[*d*]thiazol-6-yl)carbamic chloride (2i)



Following the literature procedure,[31] *N*,2-dimethylbenzo[*d*]thiazol-6-amine[33] (2.1 g, 1.0 equiv, 12 mmol) was used. The title compound was obtained as an orange solid (1.6 g, 57% yield). **m.p.** 79.0-81.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.96 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 3.51-3.41 (m, 3H), 2.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.12, 153.17, 140.02, 136.51, 125.68, 123.31, 120.76, 40.81, 20.37. **IR** (thin film): 2940, 1725, 1456, 1256, 1168, 1060, 842, 746 cm^{-1}. **HRMS** Calcd. m/z for $C_{10}H_{10}N_2OSCl^+$ $[M+H]^+$: 241.0197; found 241.0195.

3.5 References and Notes

(1) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Wiley-Interscience, New York, **2000**. (b) Pitzer, J.; Steiner, K. *J. Biotechnol*. **2016**, *235*, 32−46. (c) Theodosis-Nobelos, P.; Kourti, M.; Gavalas, A.; Rekka, E.A. *Bioorganic Med. Chem. Lett*. **2016**, *26*, 910−913. (d) Brown, D. G.; Boström, J. *J. Med. Chem*. **2016**, *59*, 4443−4458.

(2) For a freely accessible database on top selling pharmaceuticals, see: http://njardarson.lab.arizona.edu/contenpharmaceuticals-poster

(3) (a) Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvari, M. *Adv. Synth. Catal.* **2013**, *355*, 3037−3057. (b) Rodríguez-Fernández, M.; Yan, X.; Collados, J. F.; White, P. B.; Harutyunyan, S. R. *J. Am. Chem. Soc*. **2017**, *139*, 14224−14231. (c) Vargová, D.; Pérez, J. M.; Harutyunyan, S. R.; Šebesta, R. *Chem. Commun*. **2019**, *55*, 11766−11769.

(4) (a) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G.; *Chem. Rev*. **2014**, *114*, 2130−2169. (b) von Matt, P.; Pfaltz; A. *Tetrahedron: Asymmetry* **1991**, *2*, 691−700. (c) Yamada, T.; Ohsuka, Y.; Ikeno, T. *Chem. Lett*. **1998**, *11*, 1129−1130. (d) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 11253−11258. (e) Wen, J.; Jiang, J.; Zhang, X. *Org. Lett*. **2016**, *18*, 4451−4453. (f) Lang, Q.; Gu, G.; Cheng, Y.; Yin, Q.; Zhang, X. *ACS Catal*. **2018**, *8*, 4824−4828. (g) Link, A.; Zhou, Y.; Buchwald, S. L. *Org. Lett*. **2020**, *22*, 5666−5670.

(5) For selected examples on asymmetric α-functionalization of amides or α-halo amides, see: (a) Zhang, K.; Peng, Q.; Hou, X.; Wu, Y. *Angew. Chem. Int. Ed*. 2008, 47, 1741−1744. (b) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 9900−9901. (c) Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. *J. Am. Chem. Soc*. **2016**, *138*, 8997−9000. (d) Inukai, T.; Kano, T.; Maruoka, K. *Angew. Chem. Int. Ed*. **2020**, *59*,

2211−2214. (e) Jette, C. I.; Geibel, I.; Bachman, S.; Hayashi, M.; Sakurai, S.; Shimizu, H.; Morgan, J. B.; Stoltz, B. M. *Angew. Chem. Int. Ed*. **2019**, *58*, 4297−4301. (f) Yamashita, Y.; Noguchi, A.; Fushimi, S.; Hatanaka, M.; Kobayashi, S. *J. Am. Chem. Soc*. **2021**, *143*, 5598−5604. (g) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 4594−4595. (h) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc*. **2010**, *132*, 11027−11029. (i) Wang, Z.; Yin, H.; Fu, G. C. *Nature* **2018**, *563*, 379−383. (j) Li, B.; Li, T.; Aliyu, M. A.; Li, Z. H.; Tang, W. *Angew. Chem. Int. Ed*. **2019**, *58*, 11355−11359. (k) Devannah, V.; Sharma, R.; Watson, D. A. *J. Am. Chem. Soc*. **2019**, *141*, 8436−8440. (l) Mo, X.; Chen, B.; Zhang, G. *Angew. Chem. Int. Ed*. **2020**, *59*, 13998−14002. (m) Wang, Z.; Yang, Z.; Fu, G. C. *Nat. Chem*. **2021**, *13*, 236−242.

(6) For selected examples on racemic aminocarbonylation of olefins, see: (a) Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2013**, *52*, 14089−14093. (b) Dong, K.; Fang, X.; Jackstell, R.; Laurenczy, G.; Li, Y.; Beller, M. *J. Am. Chem. Soc*. **2015**, *137*, 6053−6058. (c) Liu, J.; Li, H.; Spannenberg, A.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2016**, *55*, 13544−13548. (d) Xu, T.; Sha, F.; Alper, H. *J. Am. Chem. Soc*. **2016**, *138*, 6629−6635. (e) Yang, H.; Yao, Y.; Chen, M.; Ren, Z.; Guan, Z. *J. Am. Chem. Soc*. **2021**, *143*, 7298−7305.

(7) For examples on intramolecular asymmetric hydrocarbamoylation of akenes, see: (a) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307−2309. (b) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 35−40. (c) Donets, P. A.; Cramer, N. *J. Am. Chem. Soc*. **2013**, *135*, 11772−11775. (d) Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X.; Zhang, X. *J. Am. Chem. Soc*. **2016**, *138*, 9017−9020. (e) You, C.; Li, S.; Li, X.; Lv, H.; Zhang, X. *ACS Catal*. **2019**, *9*, 8529−8533.

(8) (a) Yuan, Y.; Wu, F.; Schünemann, C.; Holz, J.; Kamer, P. C. J.; Wu, X. *Angew. Chem. Int. Ed*. **2020**, *59*, 22441−22445. (b) Yuan, Y.; Zhao, F.; Wu, X. *Chem. Sci.* **2021**, *12*,

12676−12681. (c) Yao, Y.; Yang, H.; Chen, M.; Wu, F.; Xu, X.; Guan, Z. *J. Am. Chem. Soc*. **2021**, *143*, 85−91.

(9) For selected reviews and examples on CO-free carbonylation reactions, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem. Int. Ed*. **2004**, *43*, 5580−5588. (b) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 6310−6320. (c) Fang, X.; Cacherat, B.; Morandi, B. *Nat. Chem*. **2017**, *9*, 1105−1109.

(10) For selected reviews, see: (a) Liu, R. Y.; Buchwald, S. L. *Acc. Chem. Res*. **2020**, *53*, 1229−1243. (b) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, aah5133.

(11) See section 3.4 for details.

(12) For a review on cross-coupling reactions of carbamoyl chlorides, see: Shrestha, M.; Wu, X.; Huang, W.; Qu, J.; Chen, Y. *Org. Chem. Front*. **2021**, *8*, 4024−4045.

(13) For examples on hydrofunctionalization of alkenes via CuH/Pd dual catalysis, see: (a) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. *Angew. Chem. Int. Ed*. **2016**, *55*, 6275−6279. (b) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 8372−8375. (c) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2017**, *56*, 7242−7246. (d) Schuppe, A. W.; Borrajo-Calleja, G. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2019**, *141*, 18668−18672. (e) Lu, Z.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2020**, *59*, 16128−16132. (f) Schuppe, A. W.; Knippel, J. L.; Borrajo-Calleja, G. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2021**, *143*, 5330−5335.

(14) Additionally, pioneering work by Riant have employed CuH/Pd dual catalytic processes for 1,4-reduction and allylic alkylation of *α*,*β*-unsaturated carbonyl compound: (a) Nahra, F.;

Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 3208−3212. (b) Nahra, F.; Macé, Y.; Boreux, A.; Billard, F.; Riant, O. *Chem. Eur. J.* **2014**, *20*, 10970−10981.

(15) McCarron, J. A.; Zoghbi, S. S.; Shetty, H. U.; Vermeulen, E. S.; Wikström, H. V.; Ichise, M.; Yasuno, F.; Halldin, C.; Innis, R. B.; Pike, V. W. *E. J. Nucl. Med. Mol. Imaging.* **2007**, *34*, 1670−1682.

(16) For examples on intermolecular hydrocarbamoylation of unactivated alkenes, see: (a) Ko, S.; Han, H.; Chang, S. *Org. Lett*. **2003**, *5*, 2687−2690. (b) Miyazaki, Y.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Chem. Lett*. **2012**, *41*, 298−300. For a one-pot formal hydrocarbamoylation of olefins through alkylborane intermediates, see: (c) Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem*. **2007**, *72*, 5898−5900.

(17) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc*. **2017**, *139*, 16548−16555.

(18) "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of Chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update." Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.

(19) Jia, Y.; Kündig, E. P. *Angew. Chem. Int. Ed*. **2009**, *48*, 1636−1639.

(20) Miró, R.; Cunillera, A.; Margalef, J.; Lutz, D.; Börner, A.; Pamiès, O.; Diéguez, M.; Godard, C. *Org. Lett*. **2020**, *22*, 9036−9040.

(21) Gribble, M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc*. **2017**, *139*, 2192−2195.

(22) Liu, L.; Guo, Q.; Li, J.; Yao, B.; Tian, W. *Chin. J. Chem*. **2013**, *31*, 456−464.

(23) He, M.; Yu, X.; Wang, Y.; Bao, M. *J. Org. Chem*. **2021**, *86*, 14720−12731.

(24) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 9716−9721.

(25) Pang, H.; Wang, Y.; Gallou, F.; Lipshutz, B. H. *J. Am. Chem. Soc*. **2019**, *141*, 17117−17124.

(26) Mokrosz, J. L.; Bojarski, A. J.; Charakchieva-Minol, S.; Duszynska, B.; Mokrosz, M. J.; Paluchowska, M. H. *Arch. Pharm*. **1995**, *328*, 604−608.

(27) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **2014**, *136*, 15913−15916.

(28) Murakami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem*. **2009**, *74*, 1415−1417.

(29) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2018**, *140*, 13976−13984.

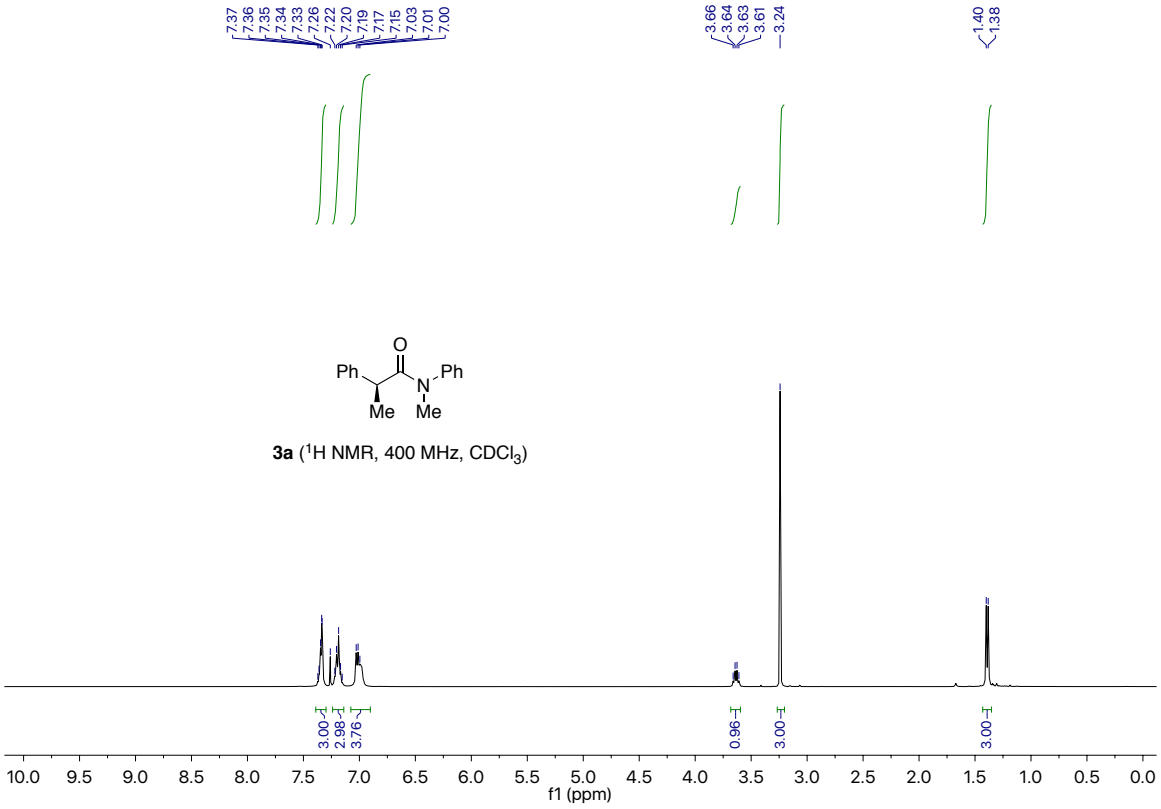
(30) Bös, M.; Canesso, R. *Heterocycles* **1994**, *38*, 1889−1896.

(31) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc*. **2010**, *132*, 9602−9603.

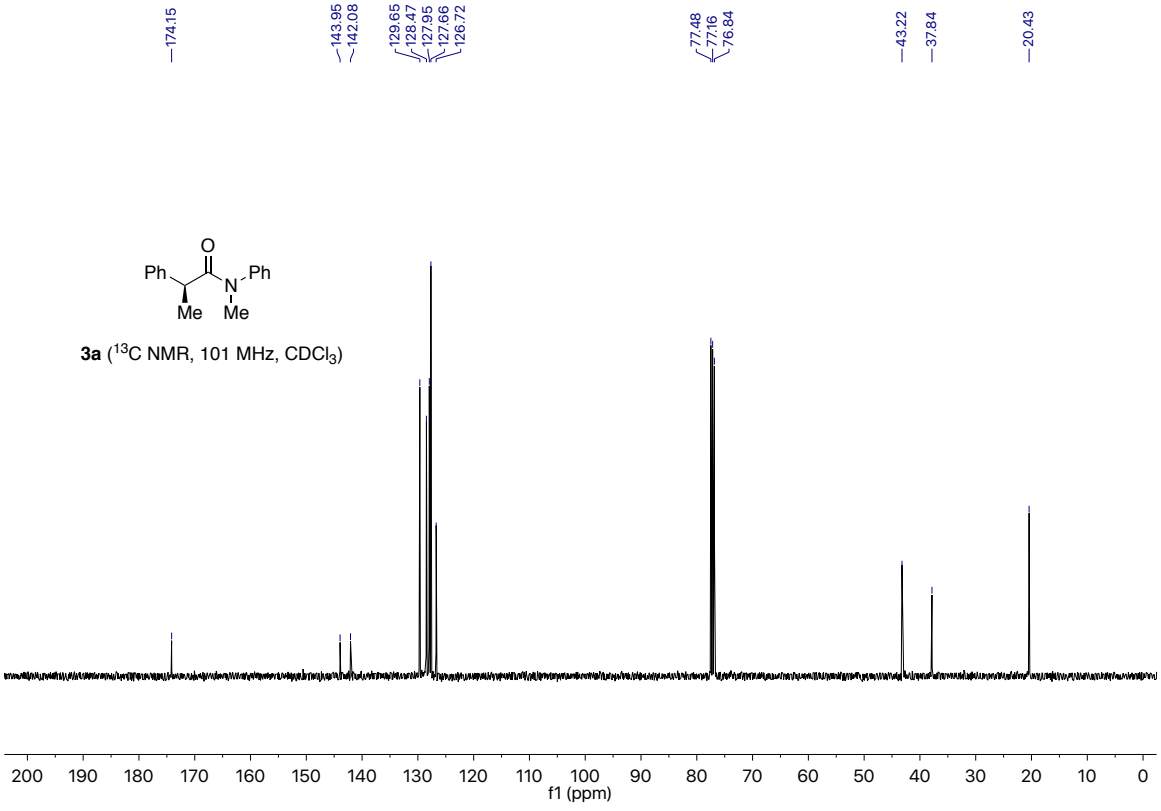
(32) McGhee, W. D.; Pan, Y.; Talley, J. J. *Tetrahedron Lett*. **1994**, *35*, 839−842.

(33) Levkoev, I. I.; Sveshnikov, N. N.; Barvyn, N. S.; Krasnova, T. V. *J. Gen. Chem. USSR*. **1960**, *30*, 311−319.

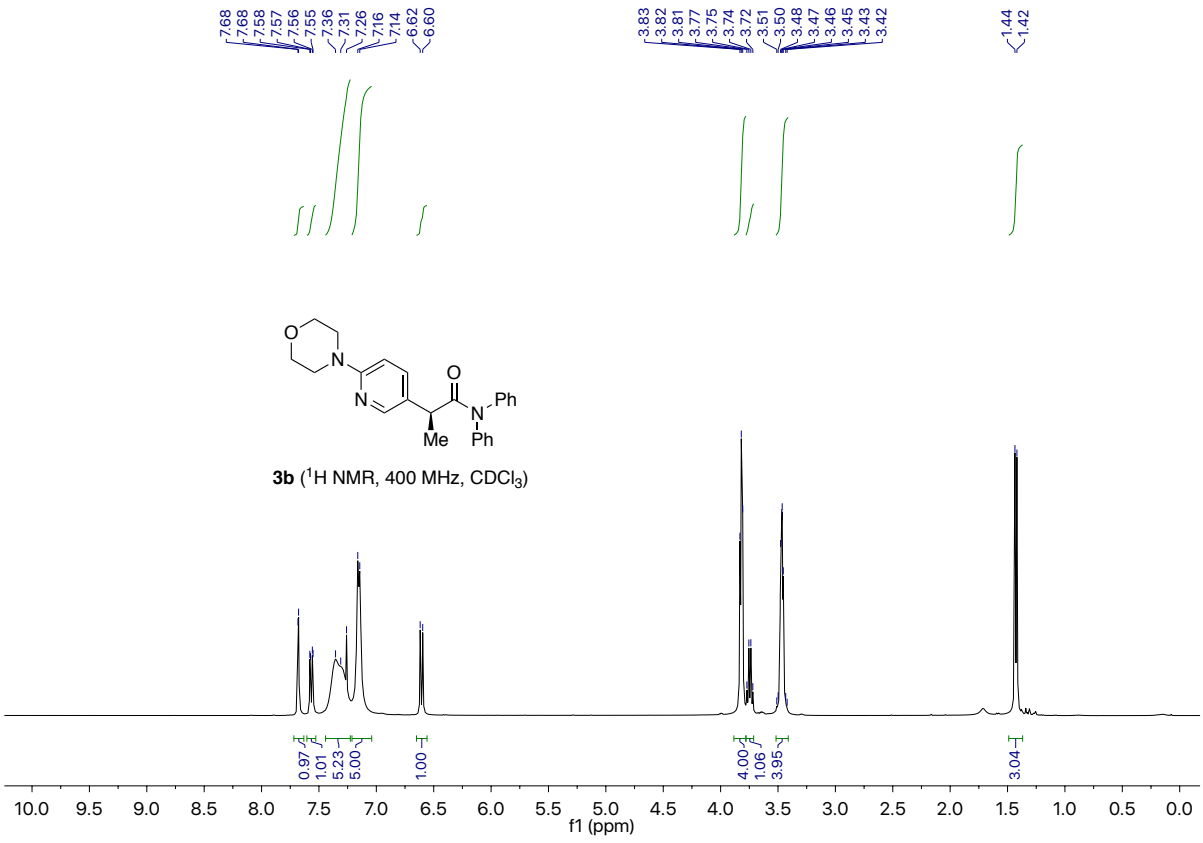
3.6 Spectra and Chromatograms



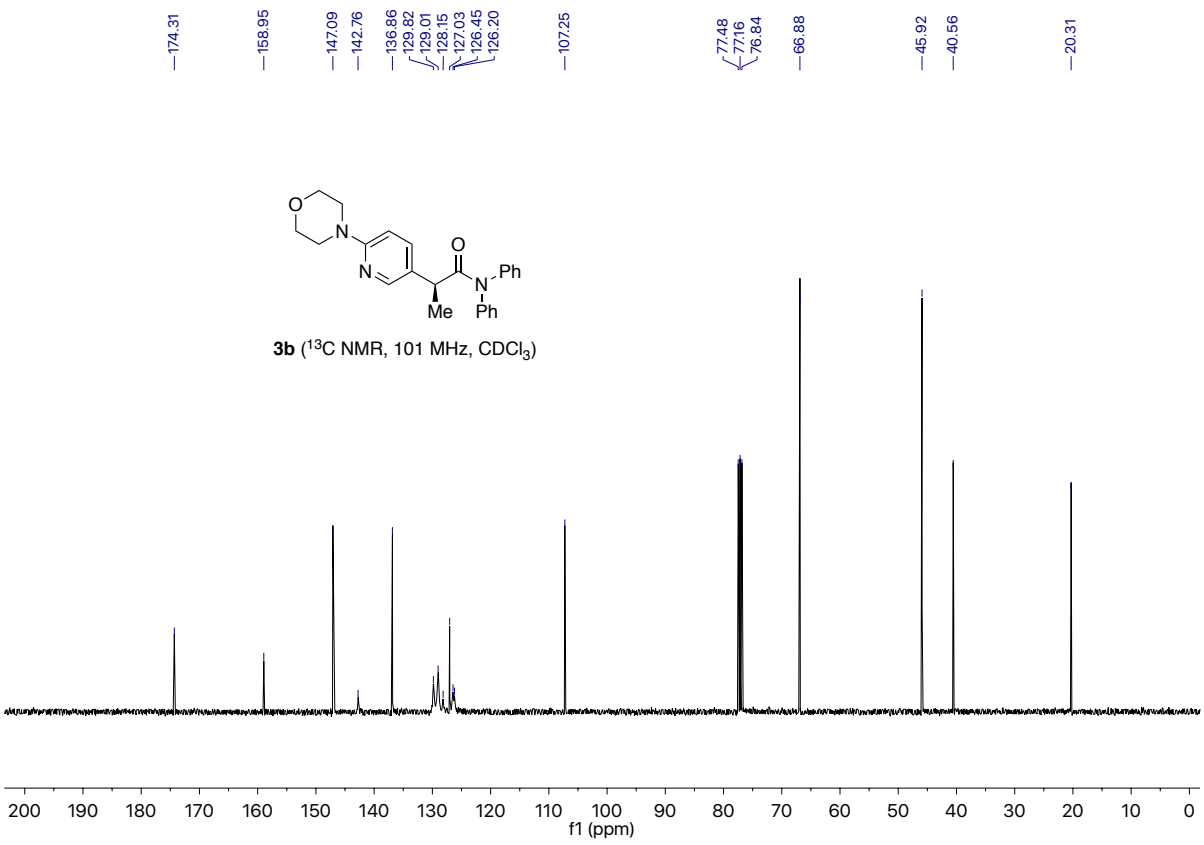
3a (^{1}H NMR, 400 MHz, $CDCl_3$)



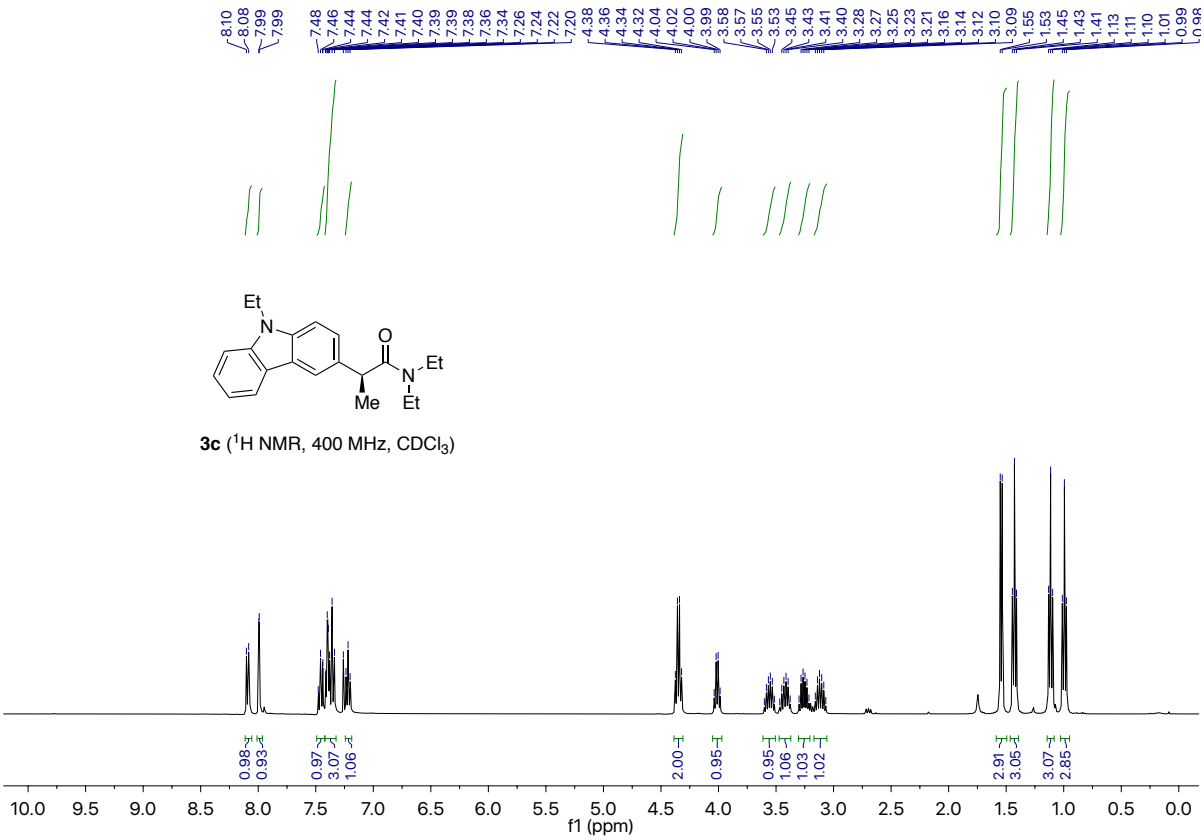
3a (^{13}C NMR, 101 MHz, $CDCl_3$)



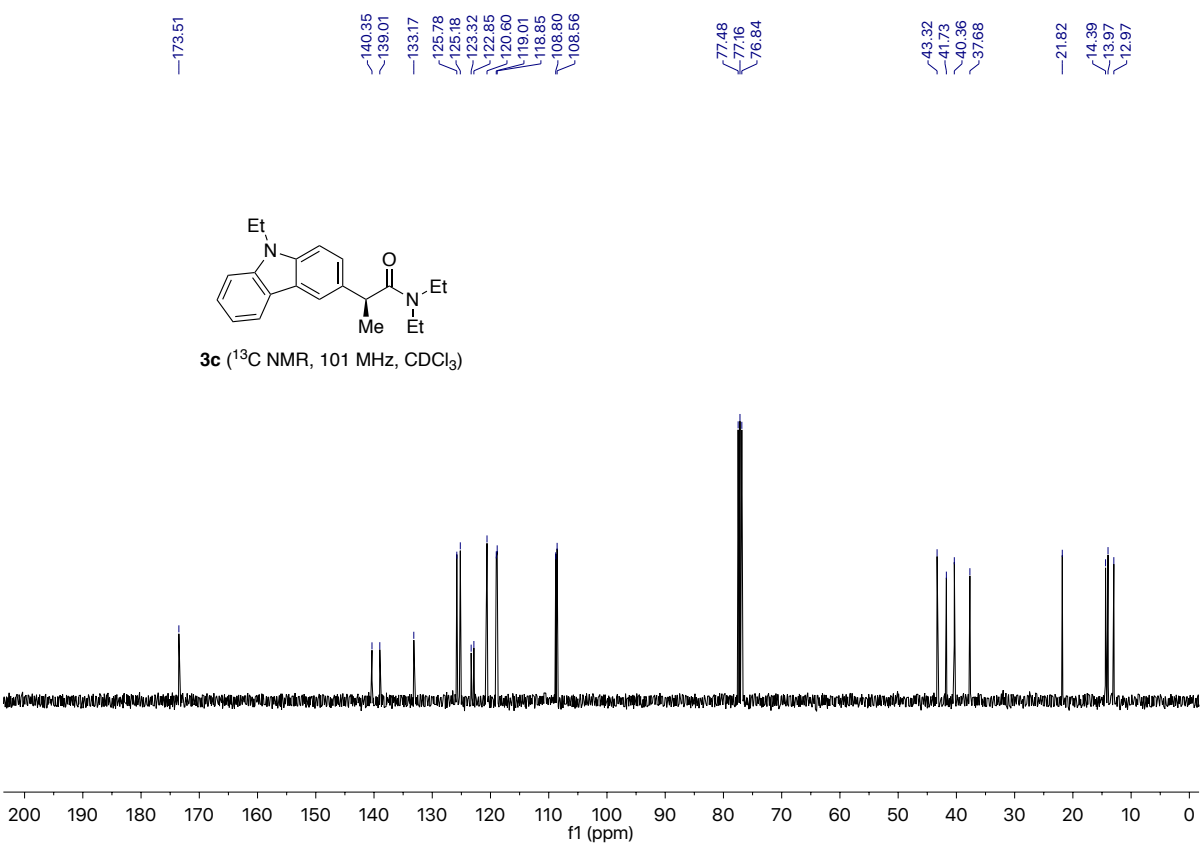
3b (^{1}H NMR, 400 MHz, $CDCl_3$)



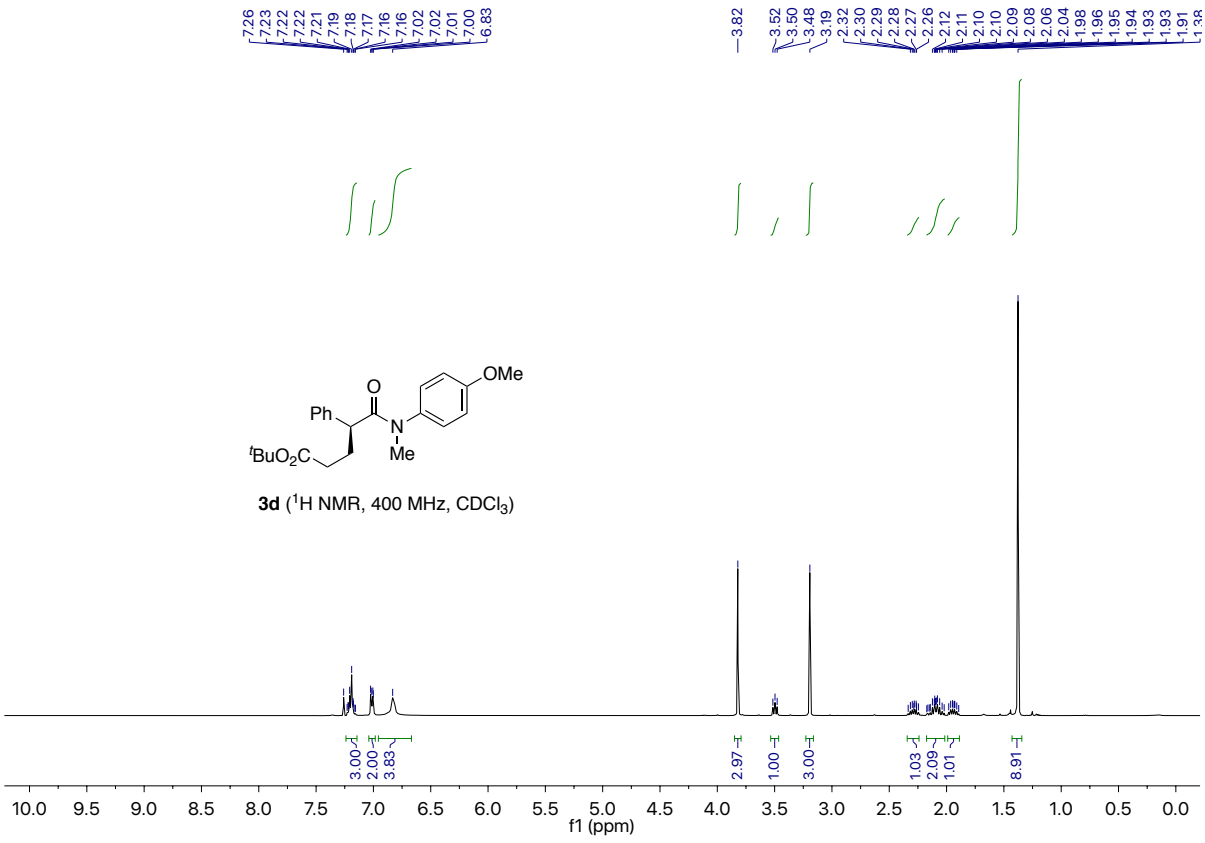
3b (^{13}C NMR, 101 MHz, $CDCl_3$)



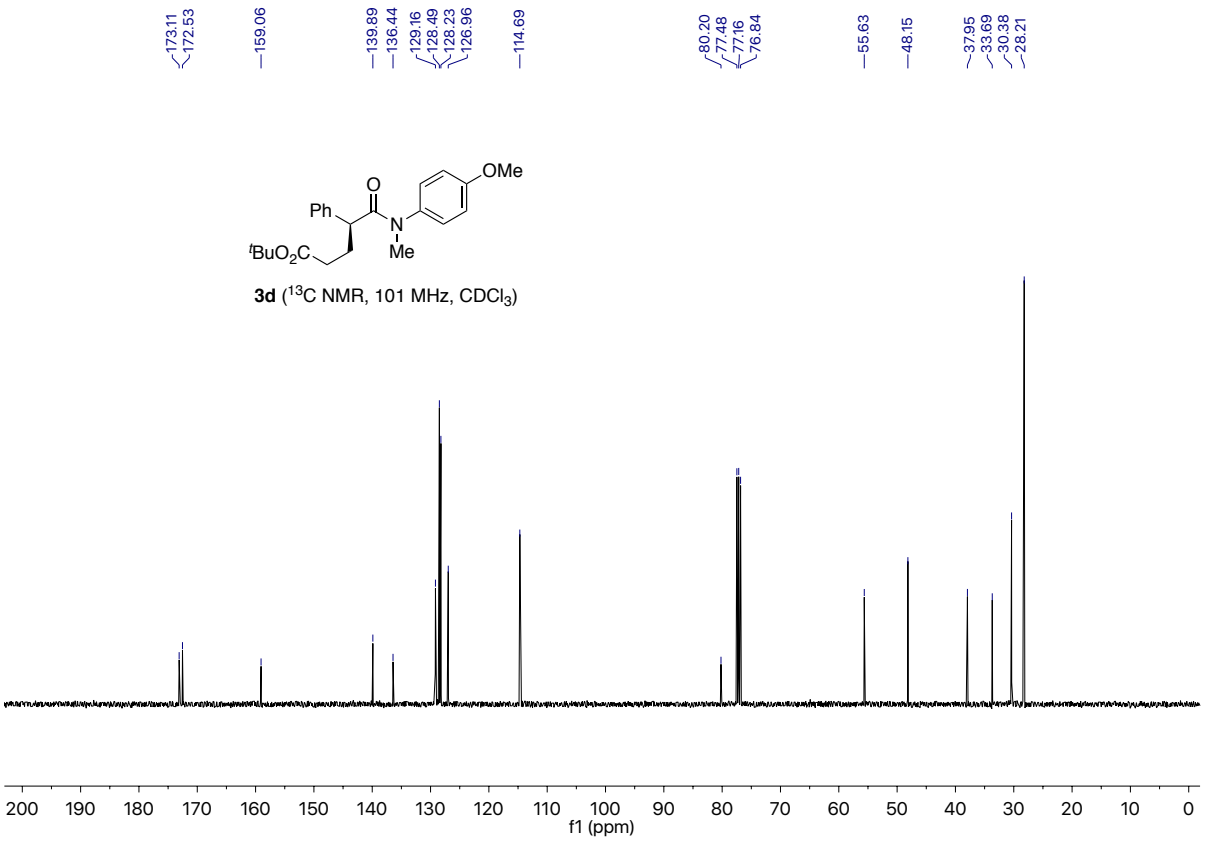
3c (^{1}H NMR, 400 MHz, $CDCl_3$)



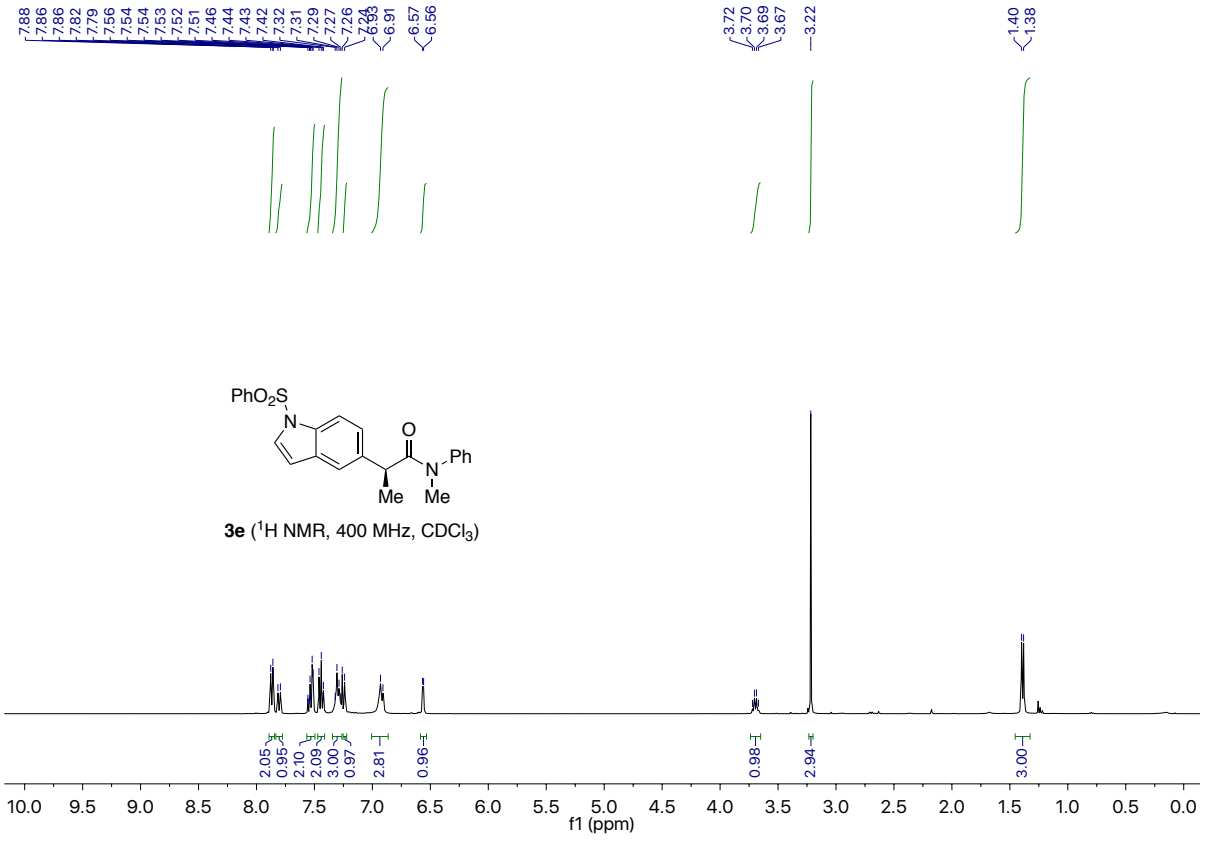
3c (^{13}C NMR, 101 MHz, $CDCl_3$)



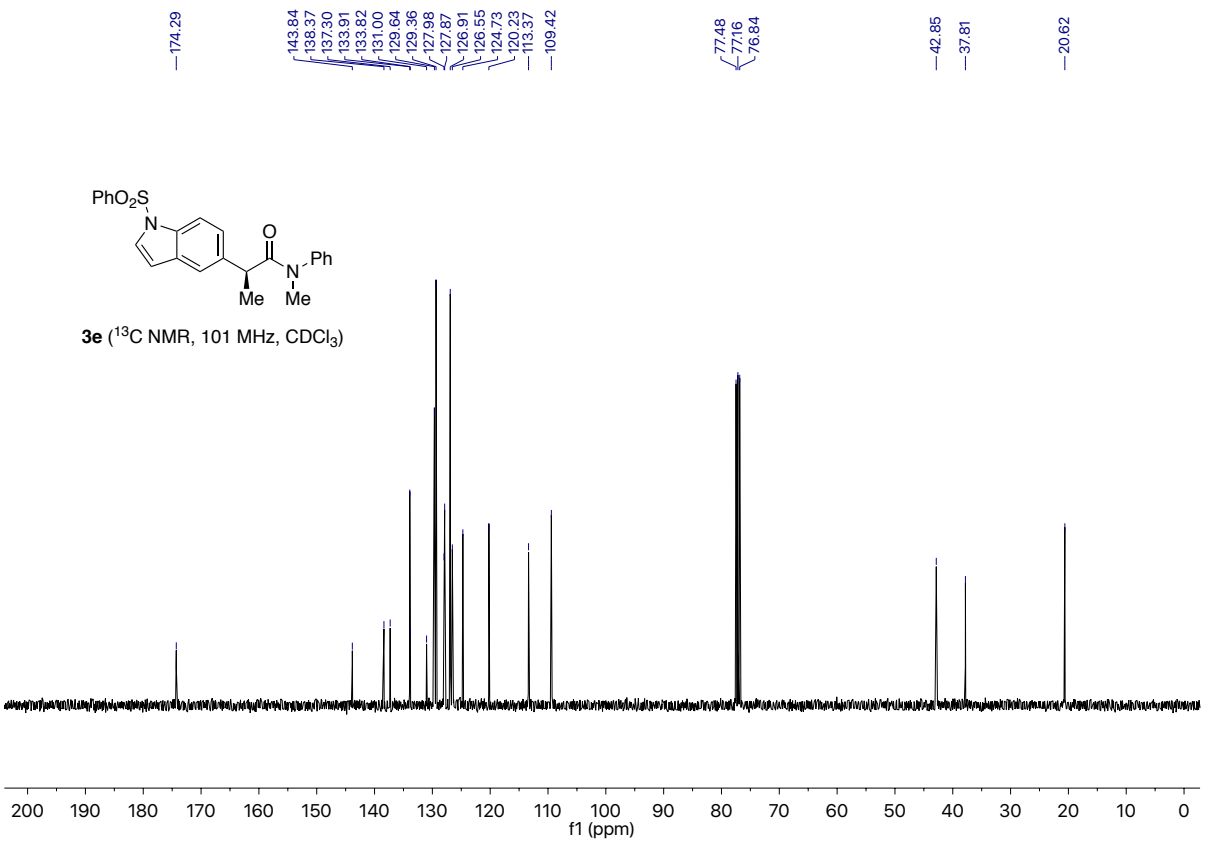
3d (^{1}H NMR, 400 MHz, $CDCl_3$)



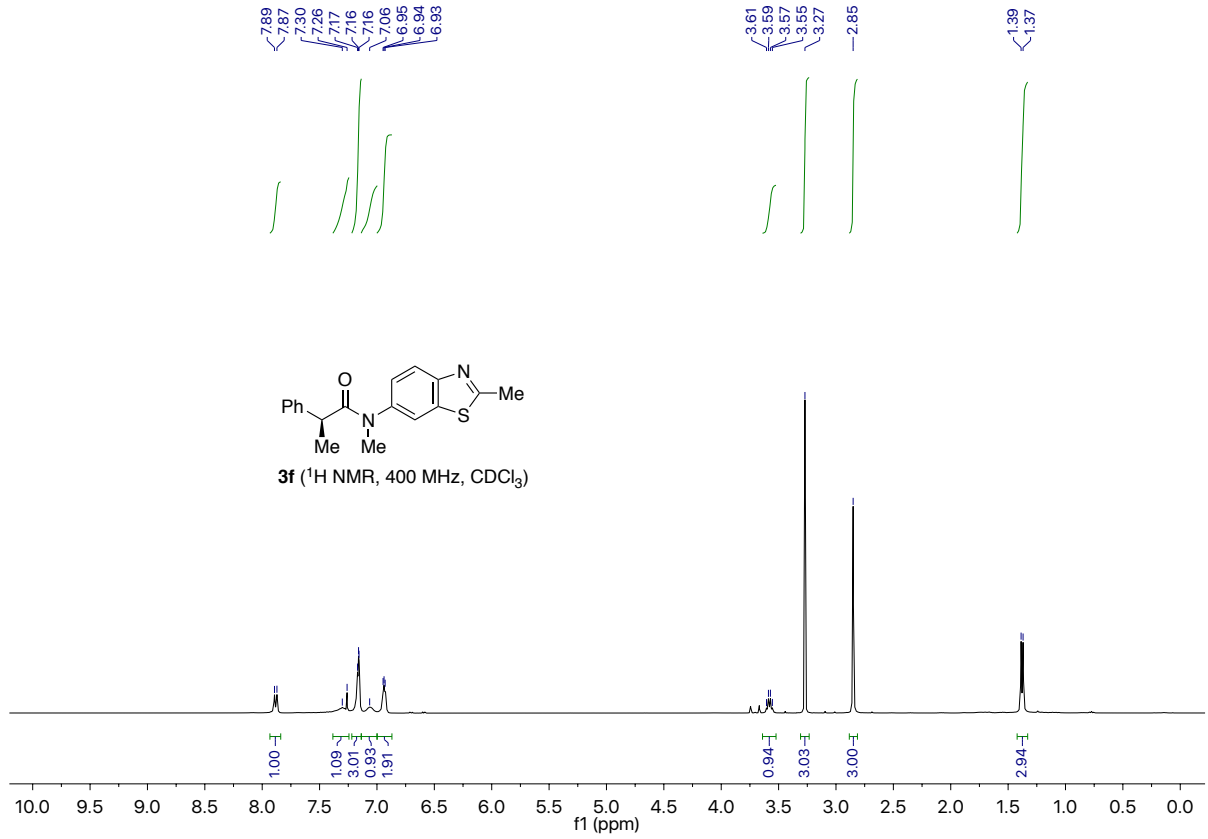
3d (^{13}C NMR, 101 MHz, $CDCl_3$)



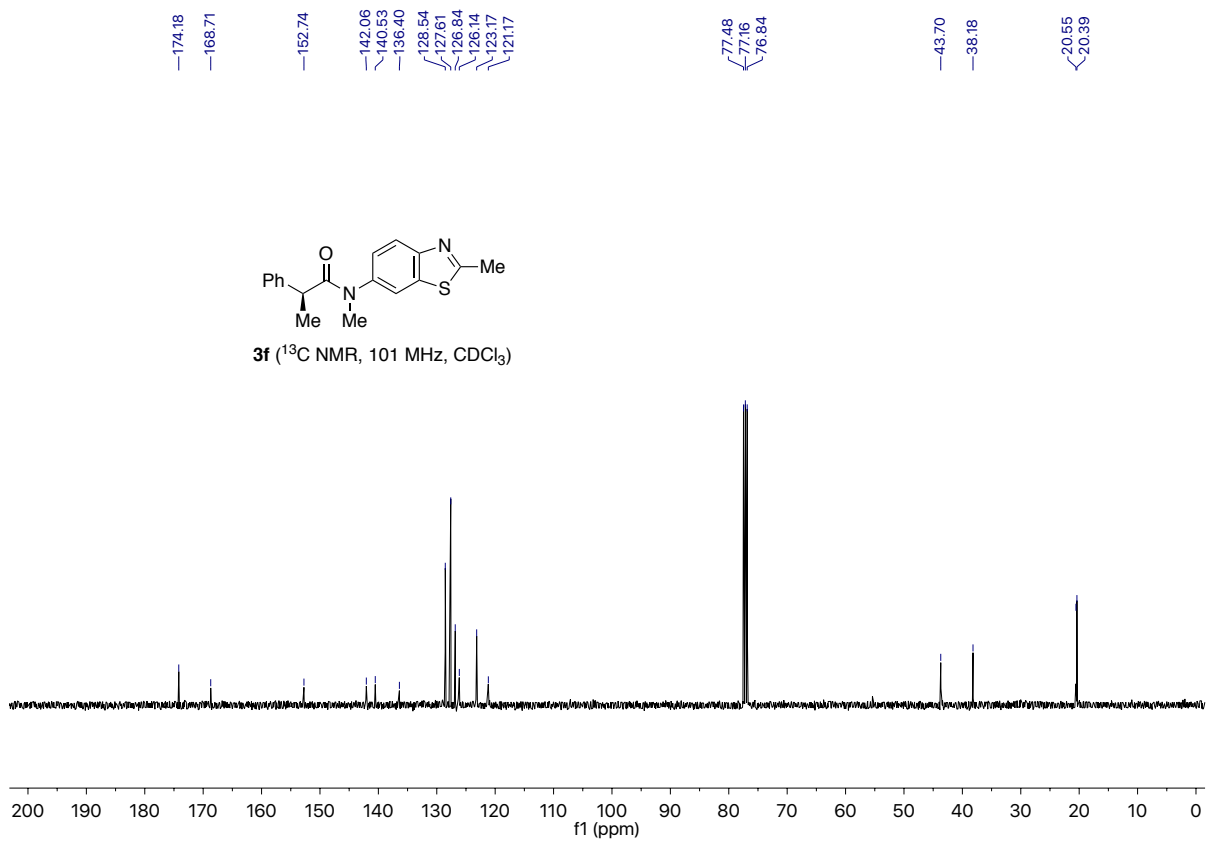
3e (^{1}H NMR, 400 MHz, $CDCl_3$)



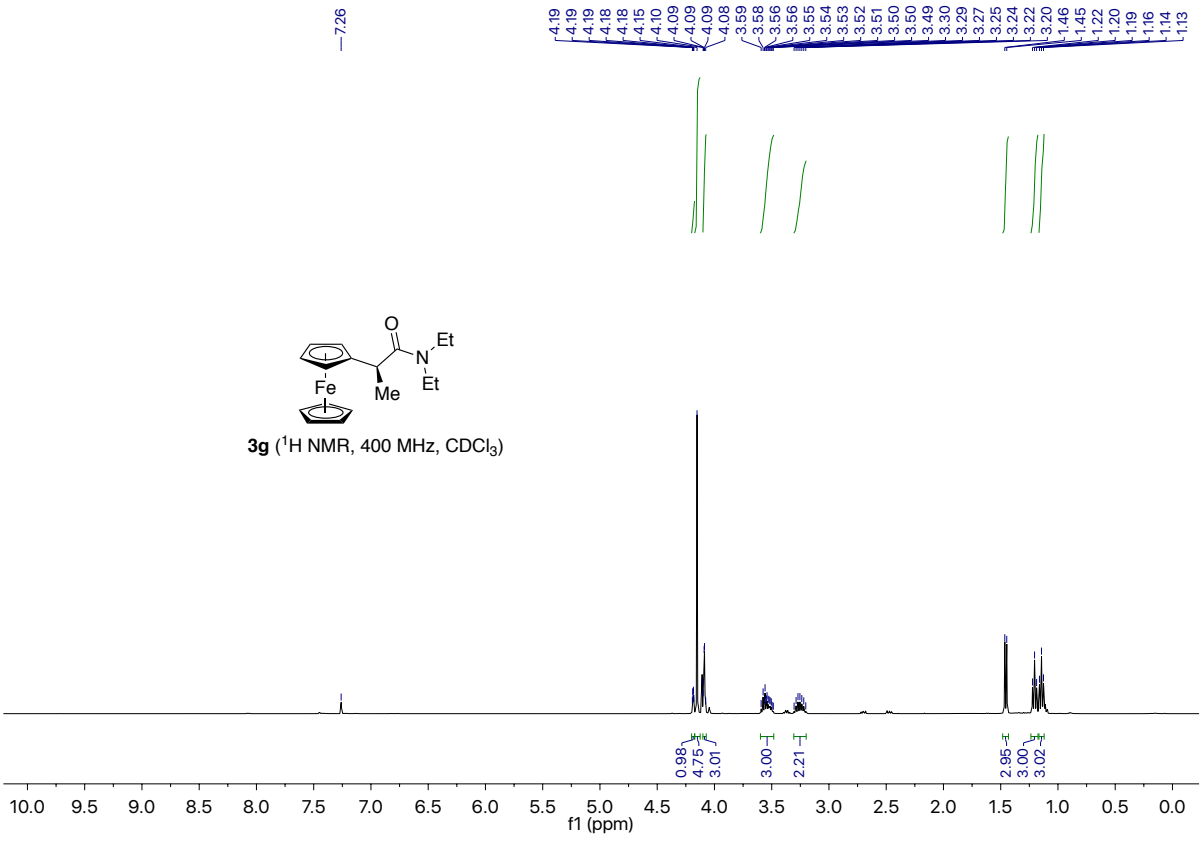
3e (^{13}C NMR, 101 MHz, $CDCl_3$)



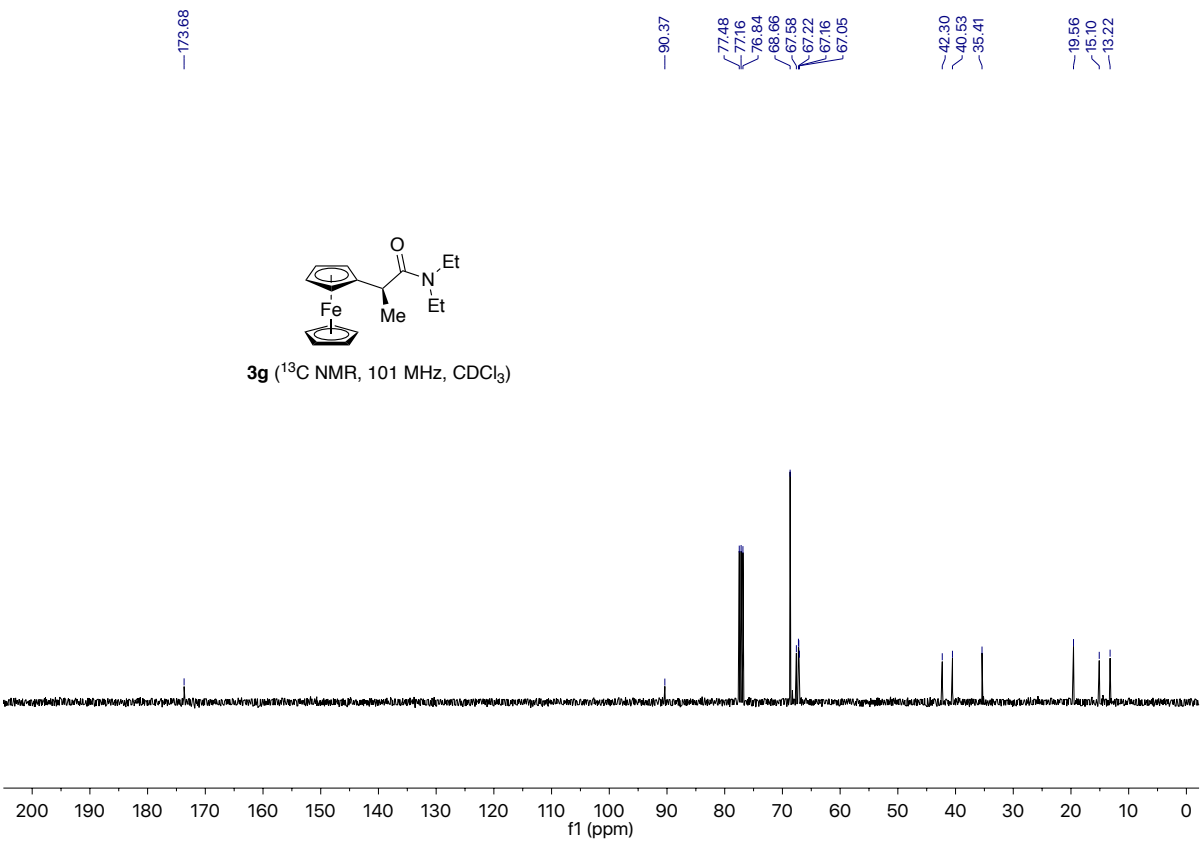
3f (^{1}H NMR, 400 MHz, $CDCl_3$)



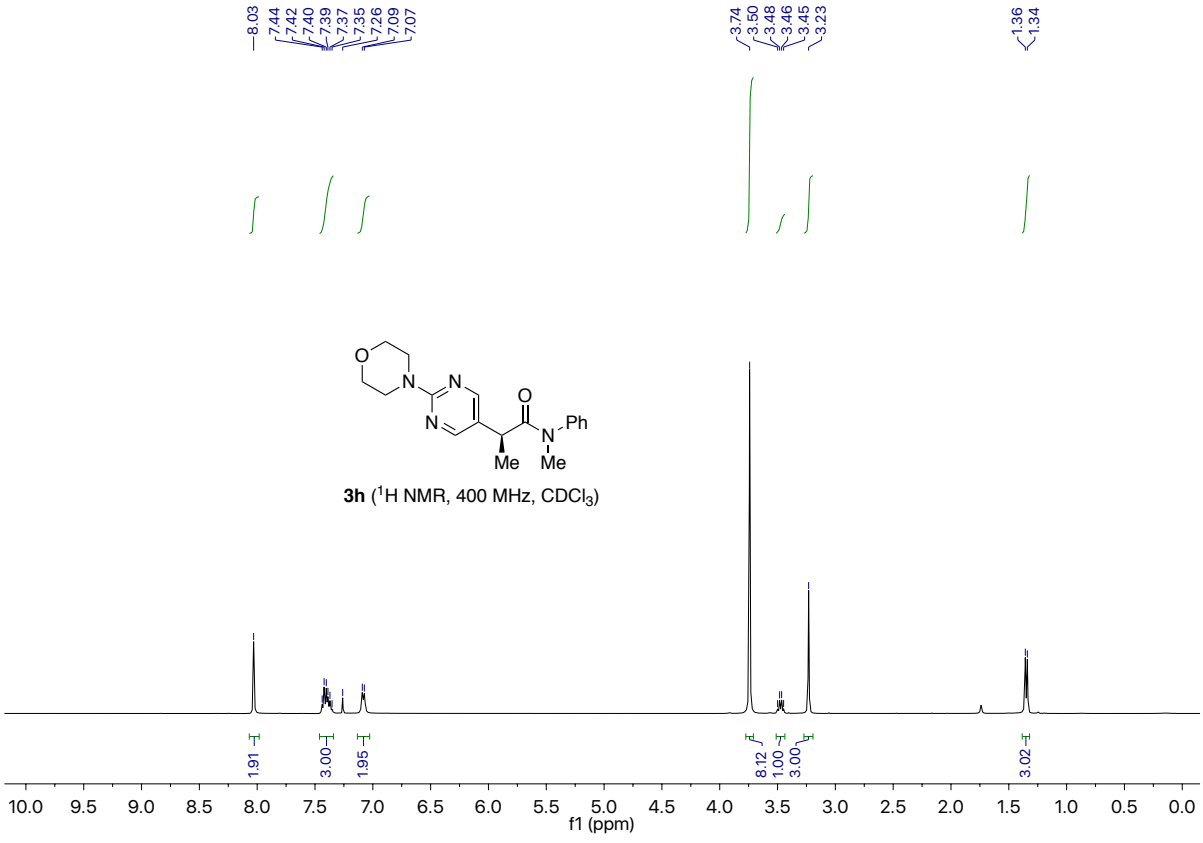
3f (^{13}C NMR, 101 MHz, $CDCl_3$)



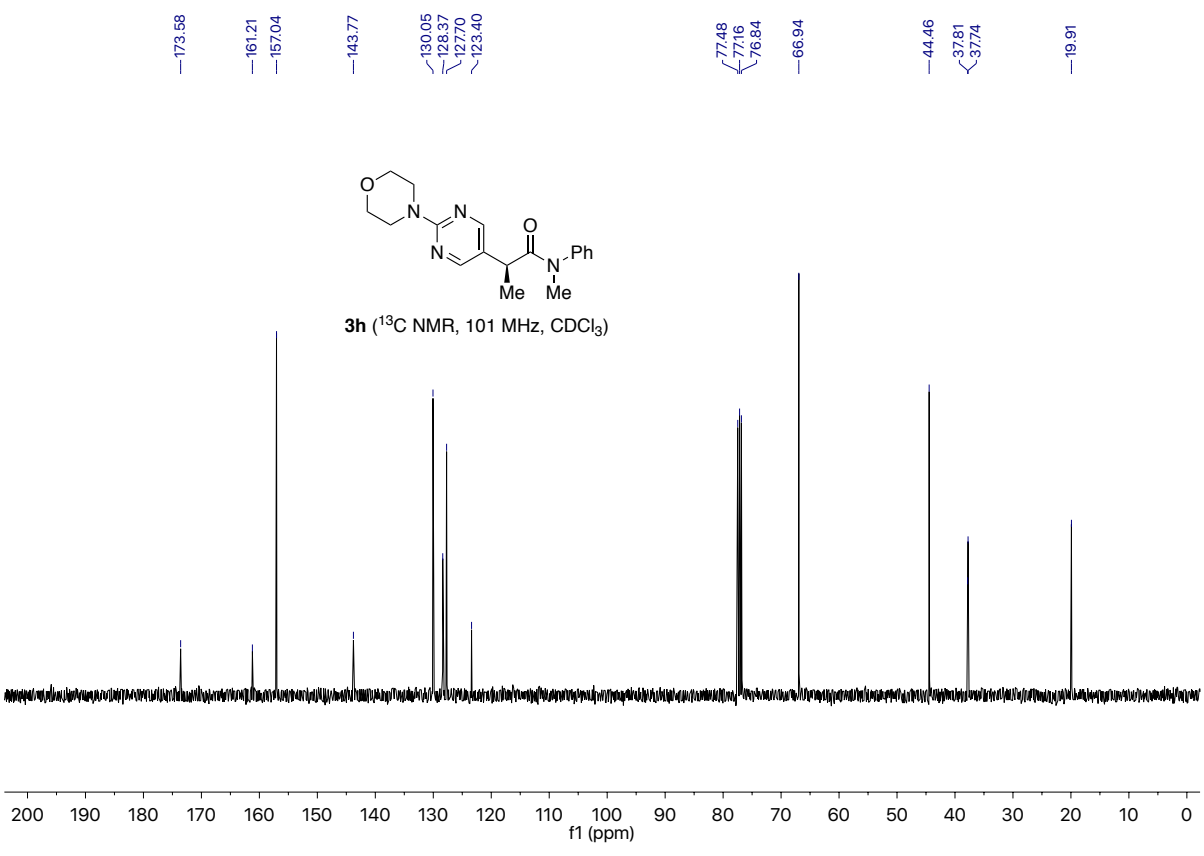
3g (^{1}H NMR, 400 MHz, $CDCl_3$)



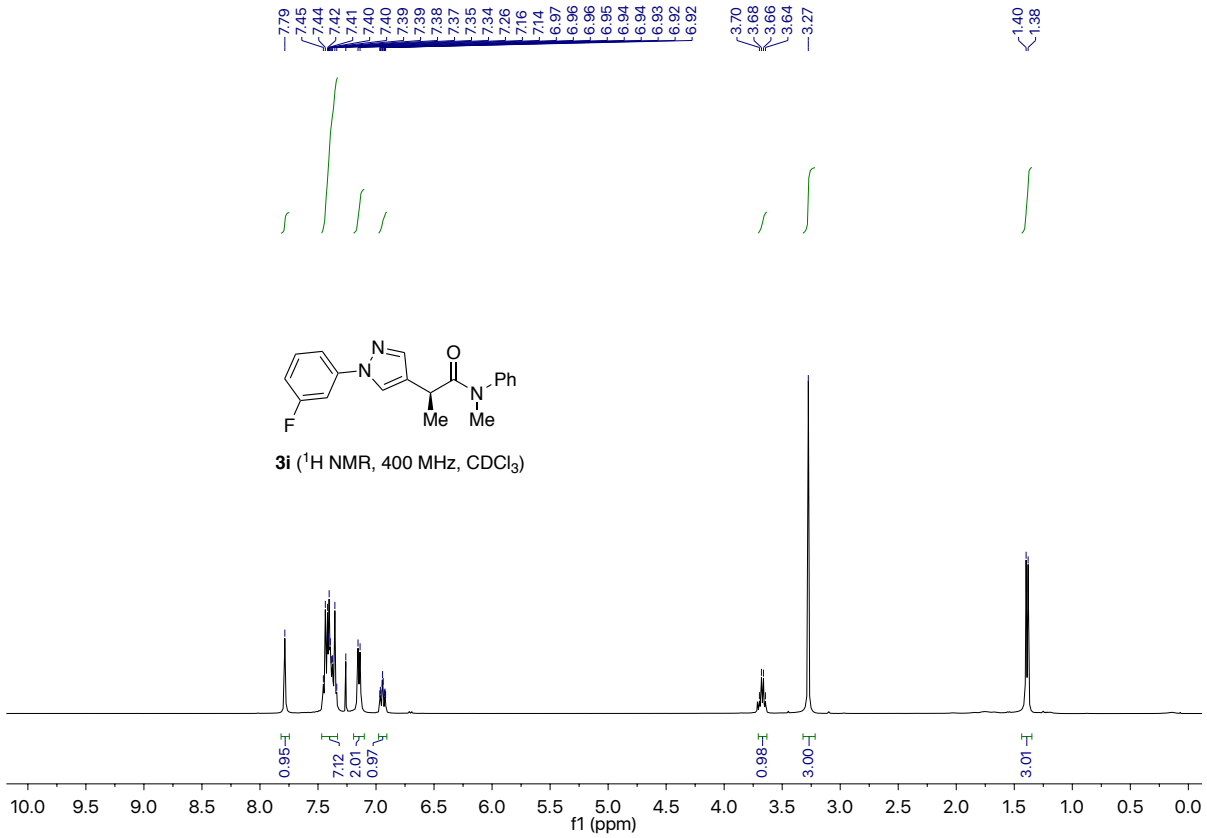
3g (^{13}C NMR, 101 MHz, $CDCl_3$)



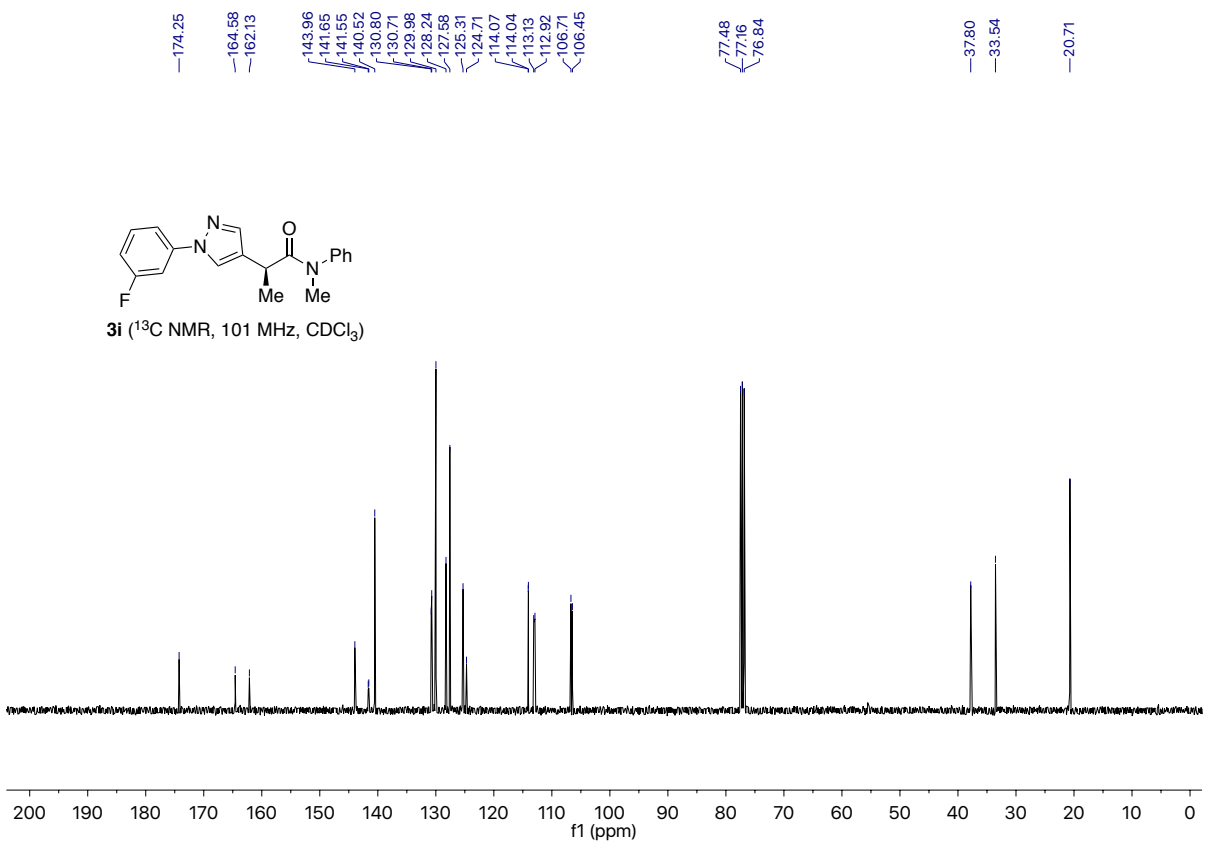
3h (^{1}H NMR, 400 MHz, $CDCl_3$)



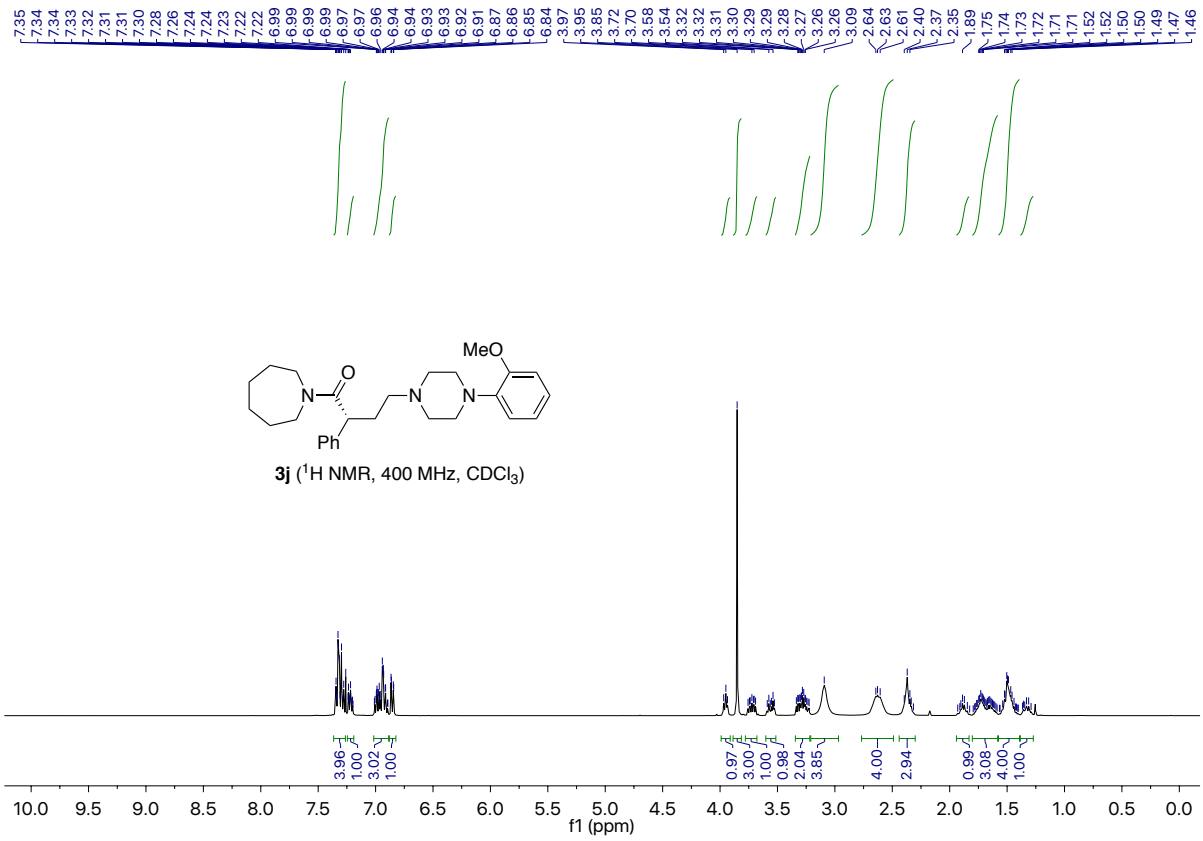
3h (^{13}C NMR, 101 MHz, $CDCl_3$)

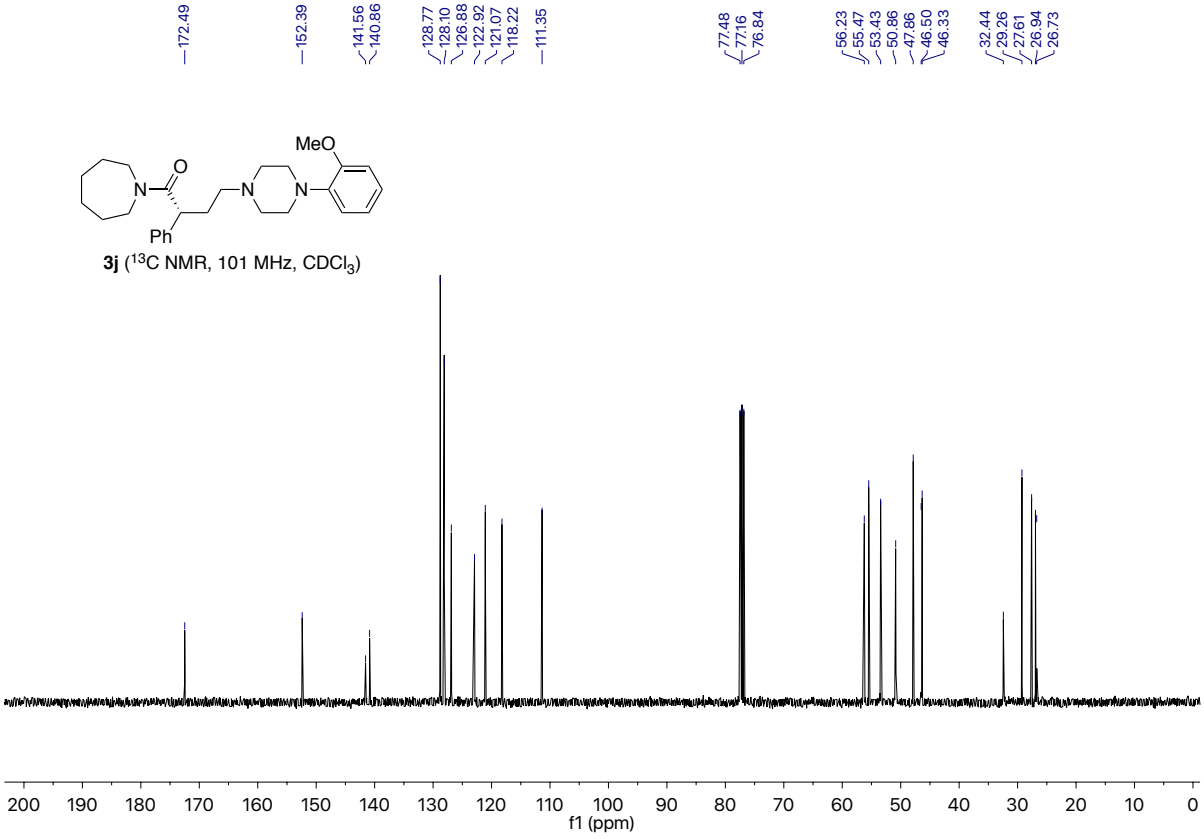


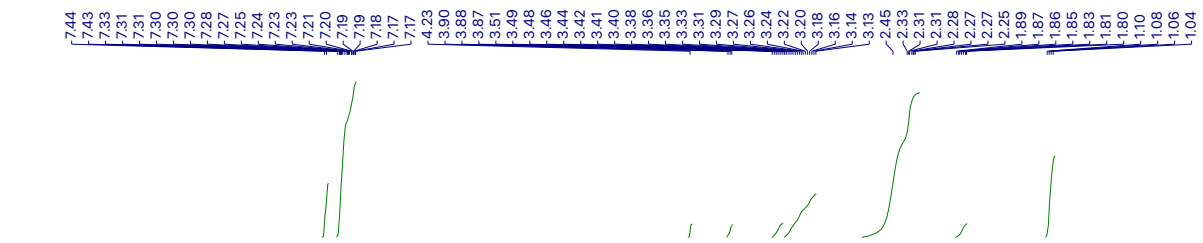
3i (^{1}H NMR, 400 MHz, $CDCl_3$)

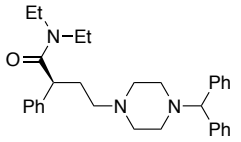


3i (^{13}C NMR, 101 MHz, $CDCl_3$)

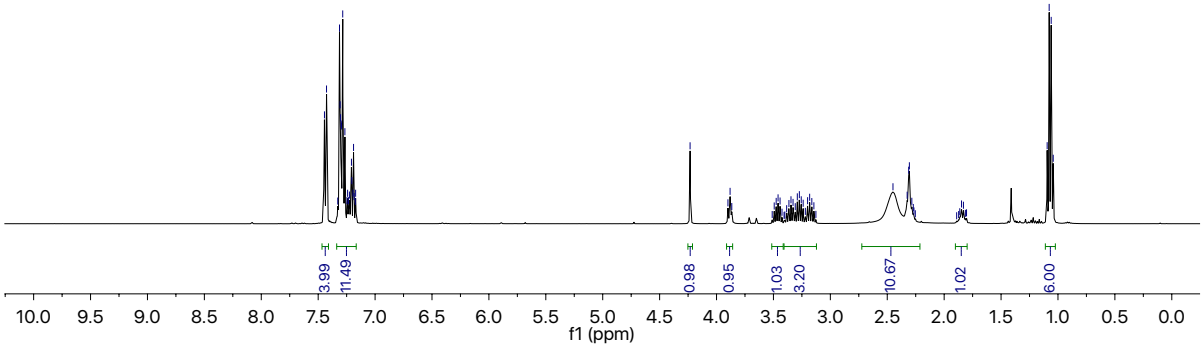

7.35 7.34 7.34 7.33 7.32 7.31 7.31 7.30 7.28 7.26 7.24 7.24 7.23 7.22 7.22 6.99 6.99 6.99 6.99 6.97 6.97 6.96 6.94 6.94 6.93 6.93 6.92 6.91 6.87 6.86 6.85 6.84
3.97 3.95 3.85 3.72 3.70 3.58 3.54 3.32 3.32 3.31 3.30 3.29 3.29 3.28 3.27 3.26 3.26 3.09 2.64 2.63 2.61 2.40 2.37 2.35 1.89 1.75 1.74 1.73 1.72 1.71 1.71 1.52 1.52 1.50 1.50 1.49 1.47 1.46
MeO
O
N
N
N
Ph
3j (1H NMR, 400 MHz, CDCl3)
3.96 1.00 3.02 1.00 0.97 3.00 1.00 0.98 2.04 3.85 4.00 2.94 0.99 3.08 4.00 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

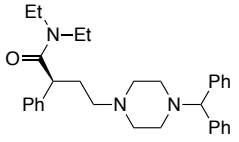

172.49 152.39 141.56 140.86 128.77 128.10 126.88 122.92 121.07 118.22 111.35
77.48 77.16 76.84
56.23 55.47 53.43 50.86 47.86 46.50 46.33
32.44 29.26 27.61 26.94 26.73
MeO
O
N
N
N
Ph
3j (13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



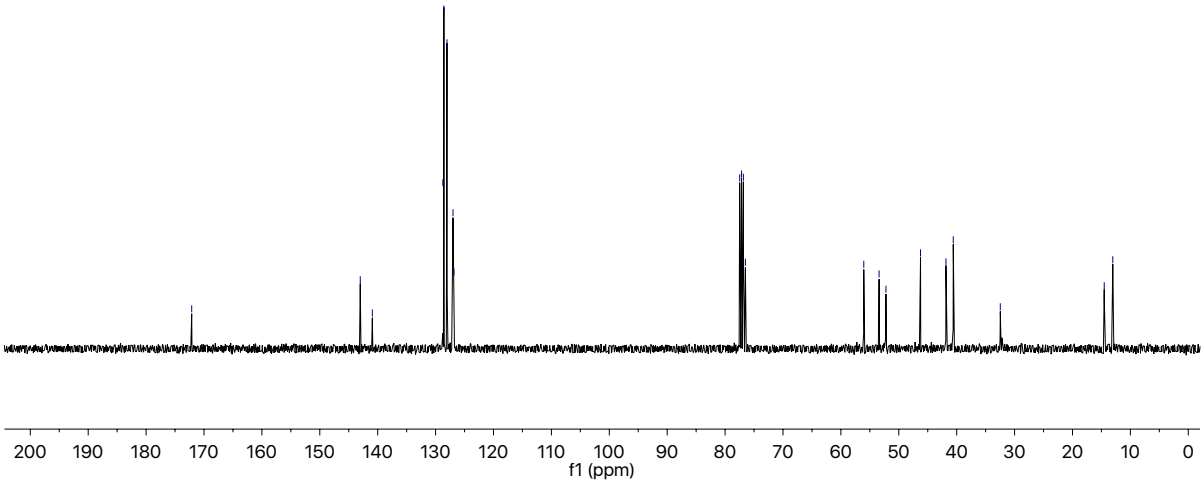


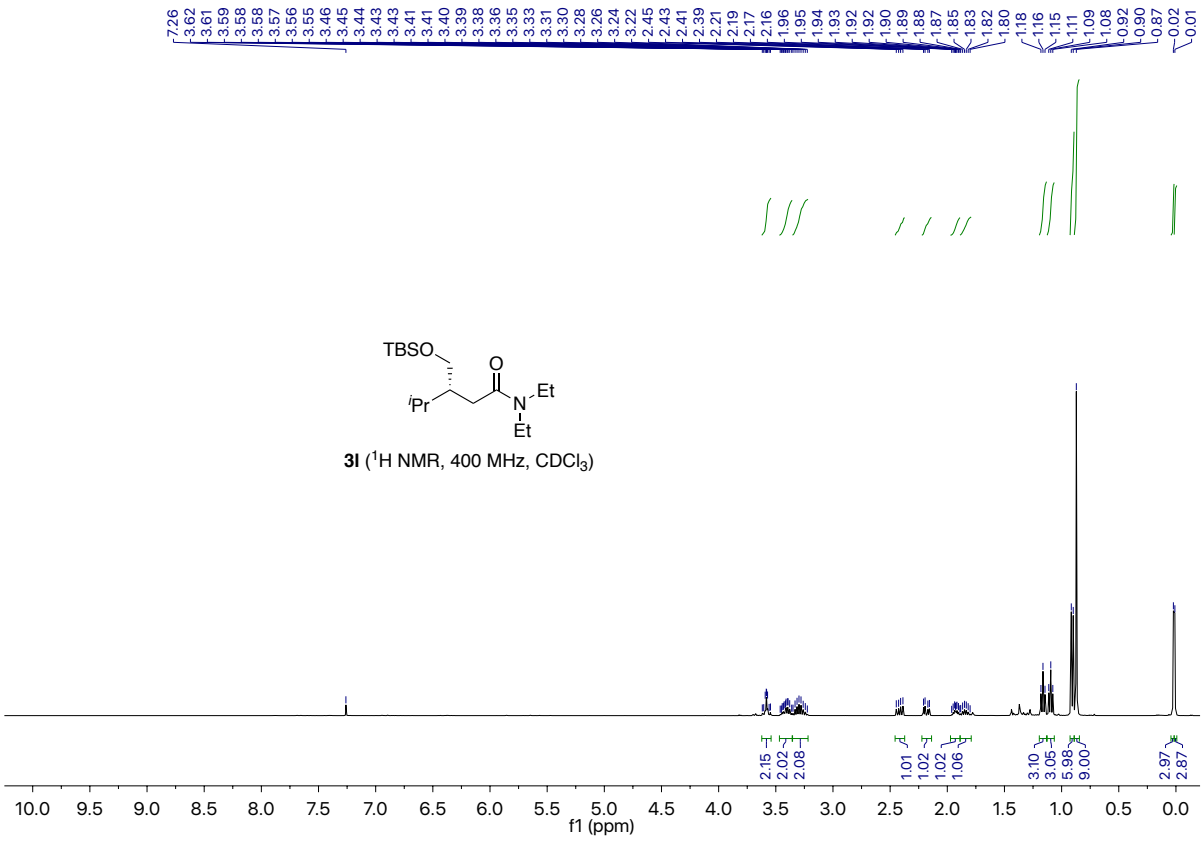
3k (^{1}H NMR, 400 MHz, $CDCl_3$)



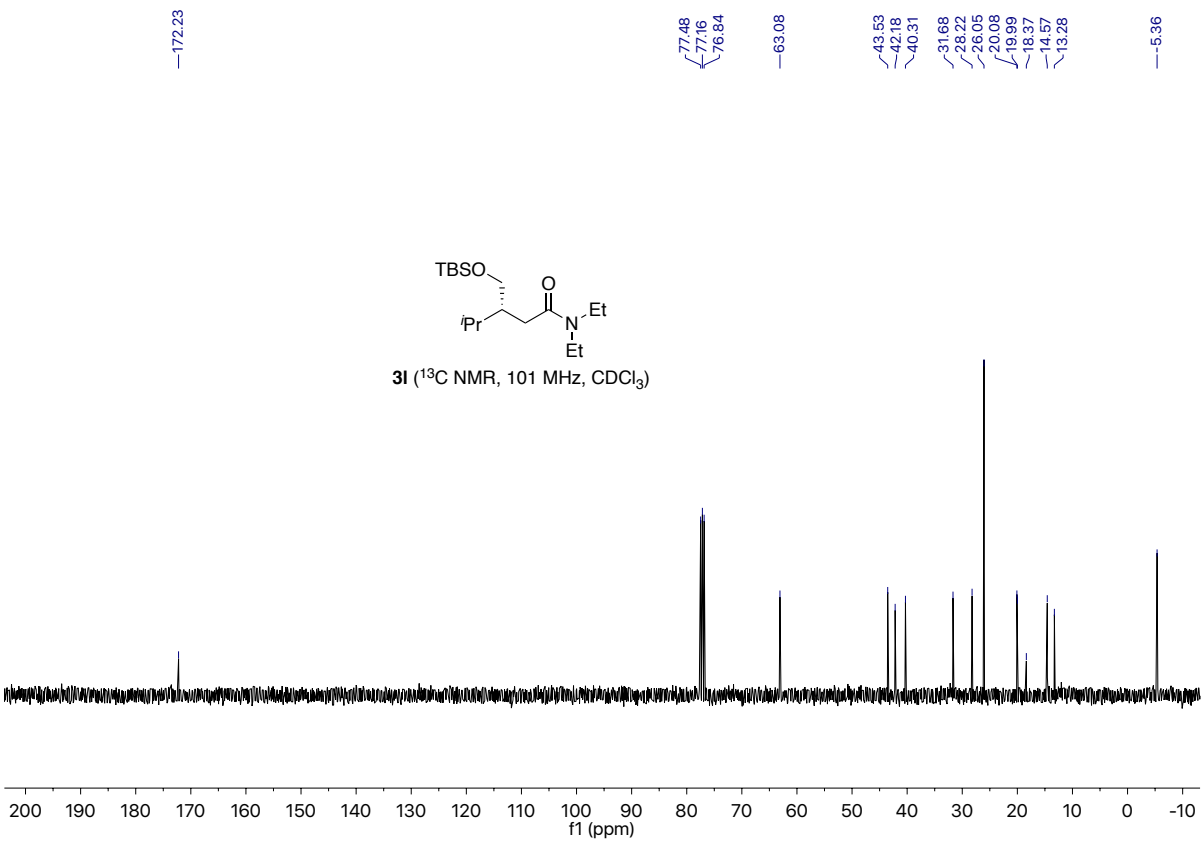


3k (^{13}C NMR, 101 MHz, $CDCl_3$)

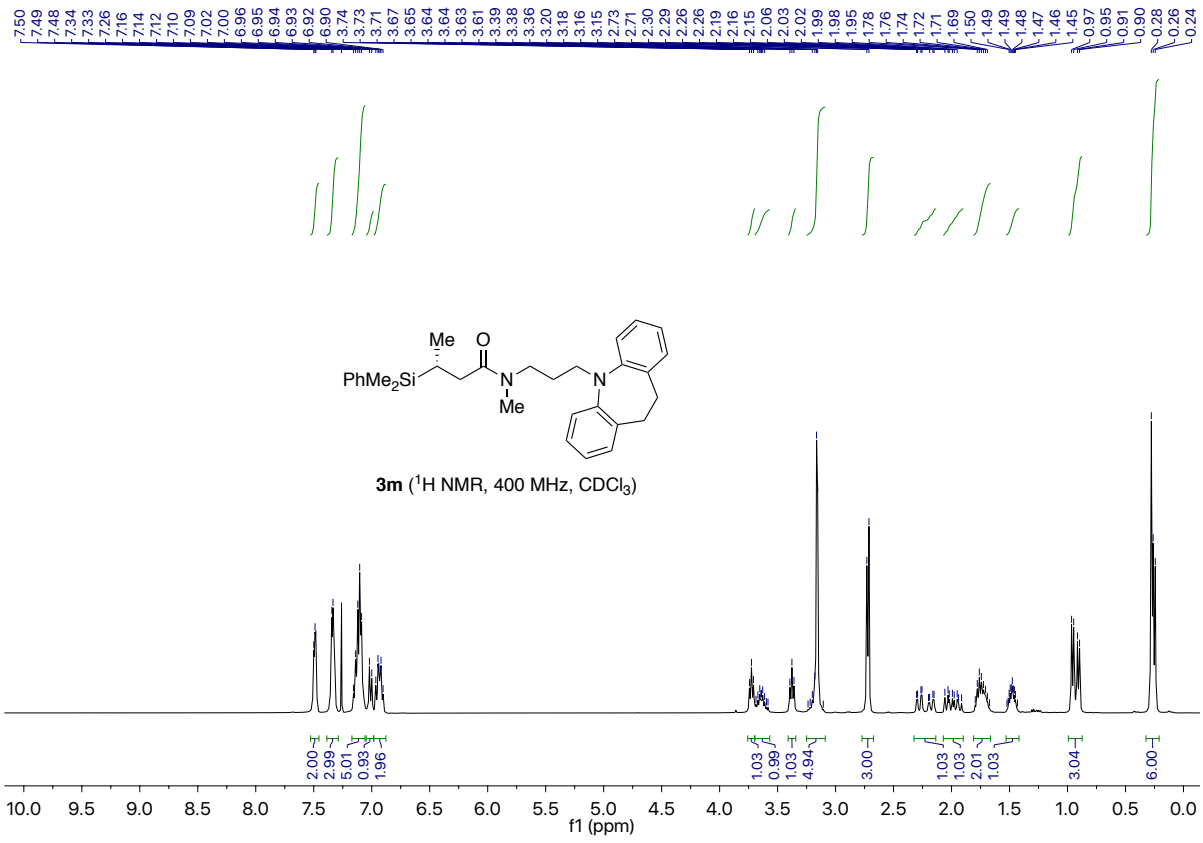




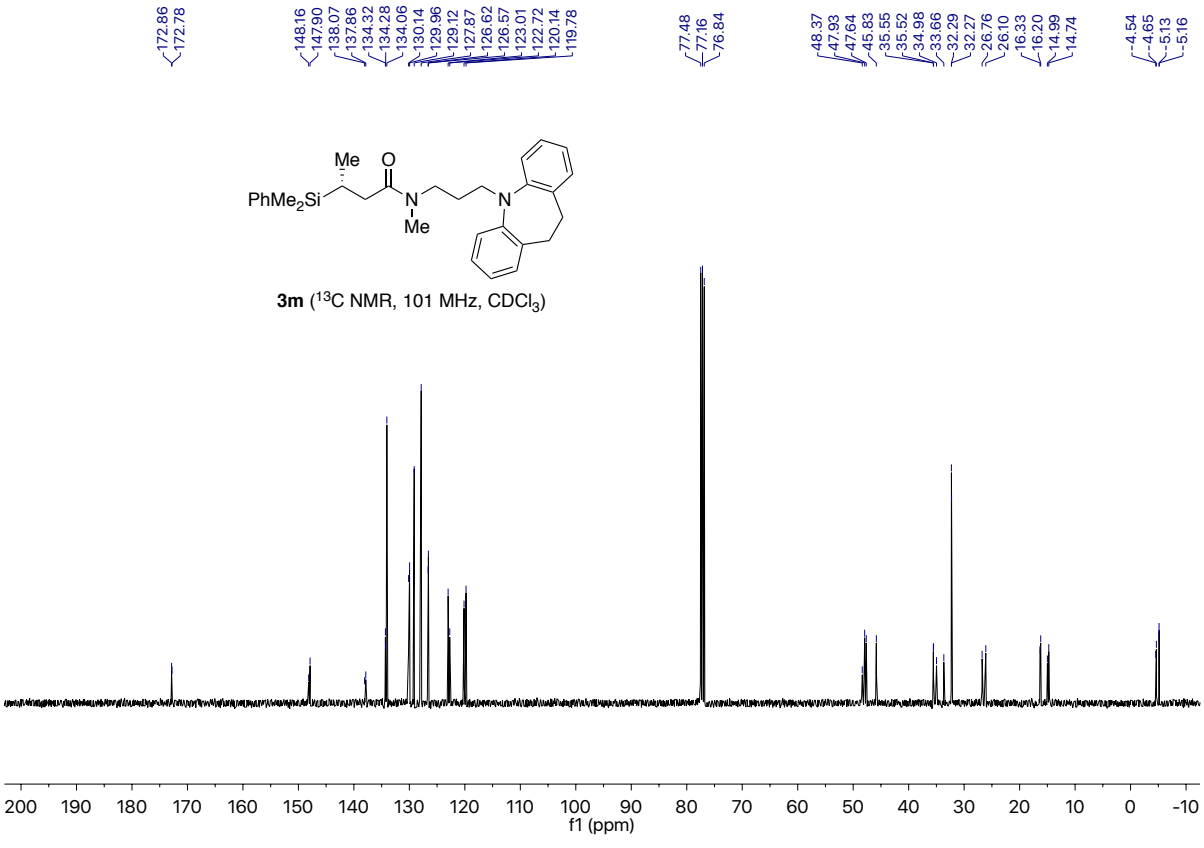
3l (^{1}H NMR, 400 MHz, $CDCl_3$)



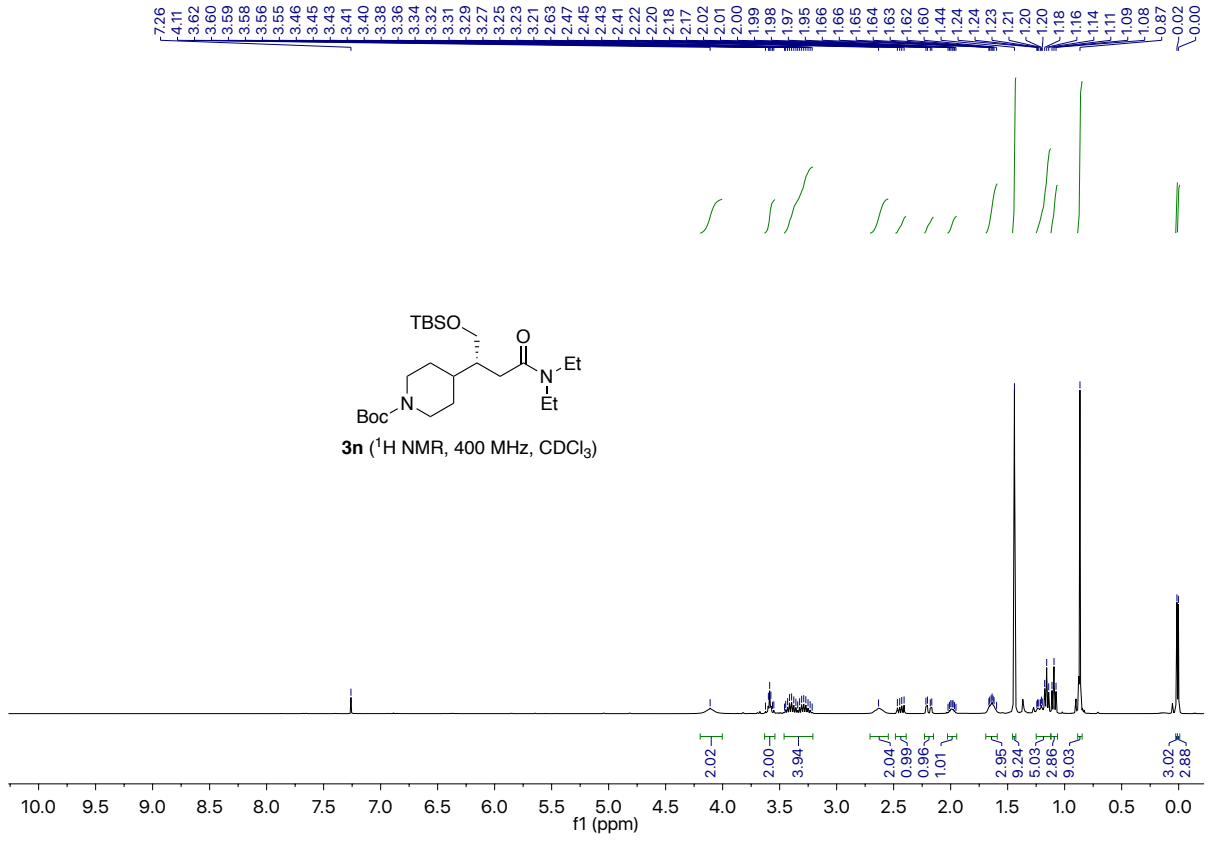
3l (^{13}C NMR, 101 MHz, $CDCl_3$)



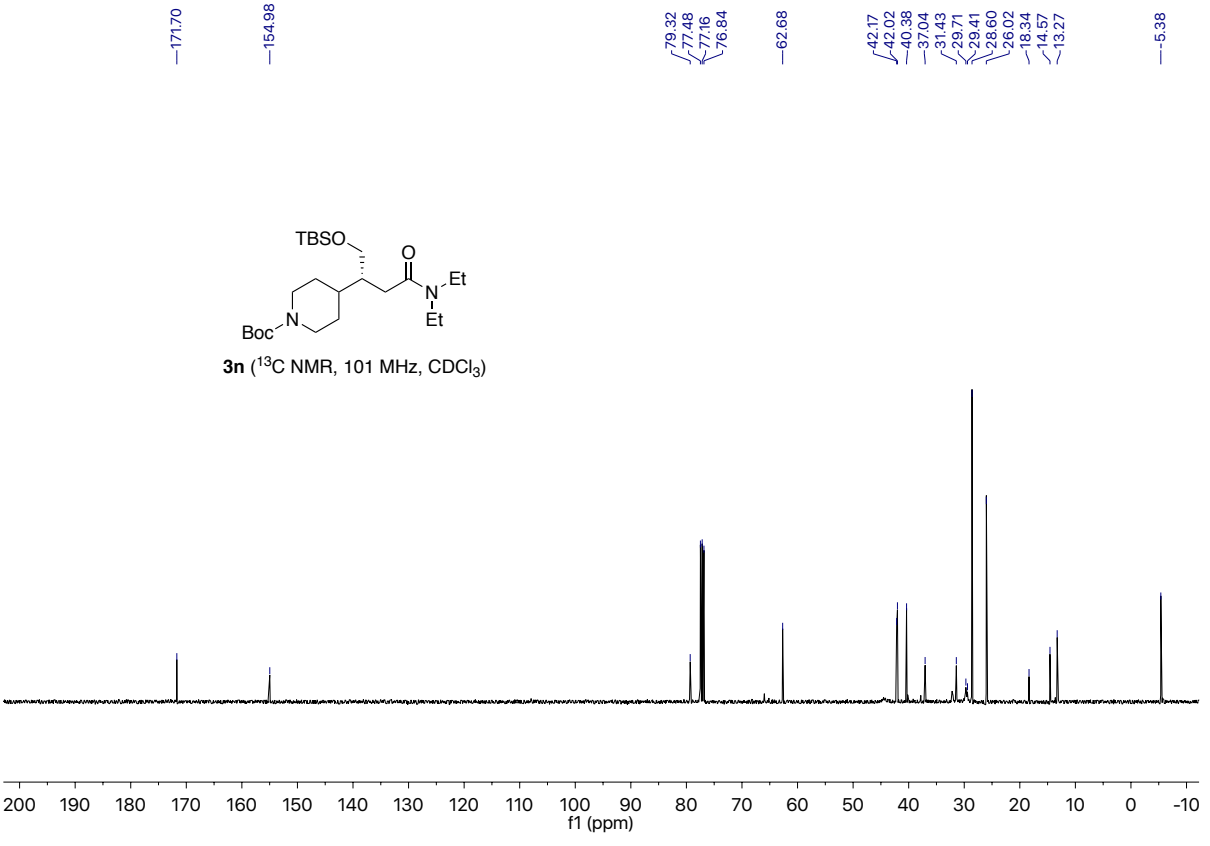
3m (^{1}H NMR, 400 MHz, $CDCl_3$)



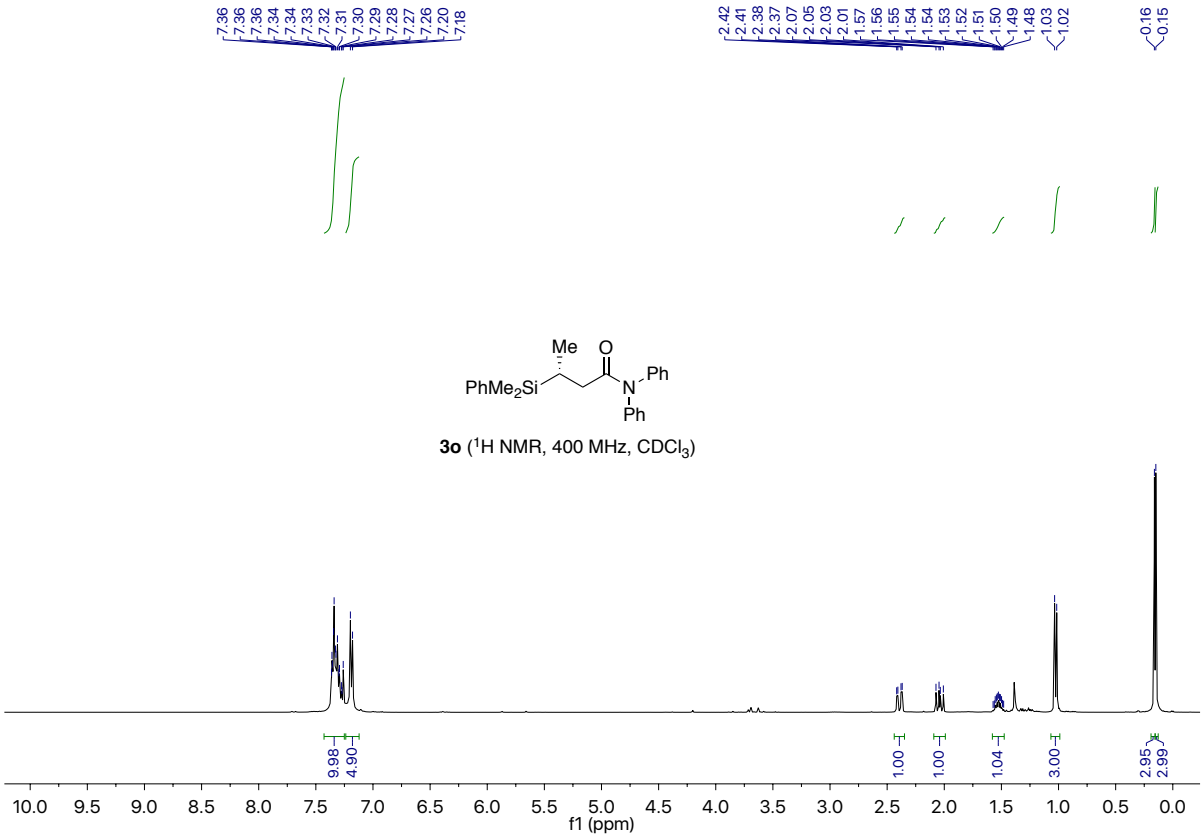
3m (^{13}C NMR, 101 MHz, $CDCl_3$)

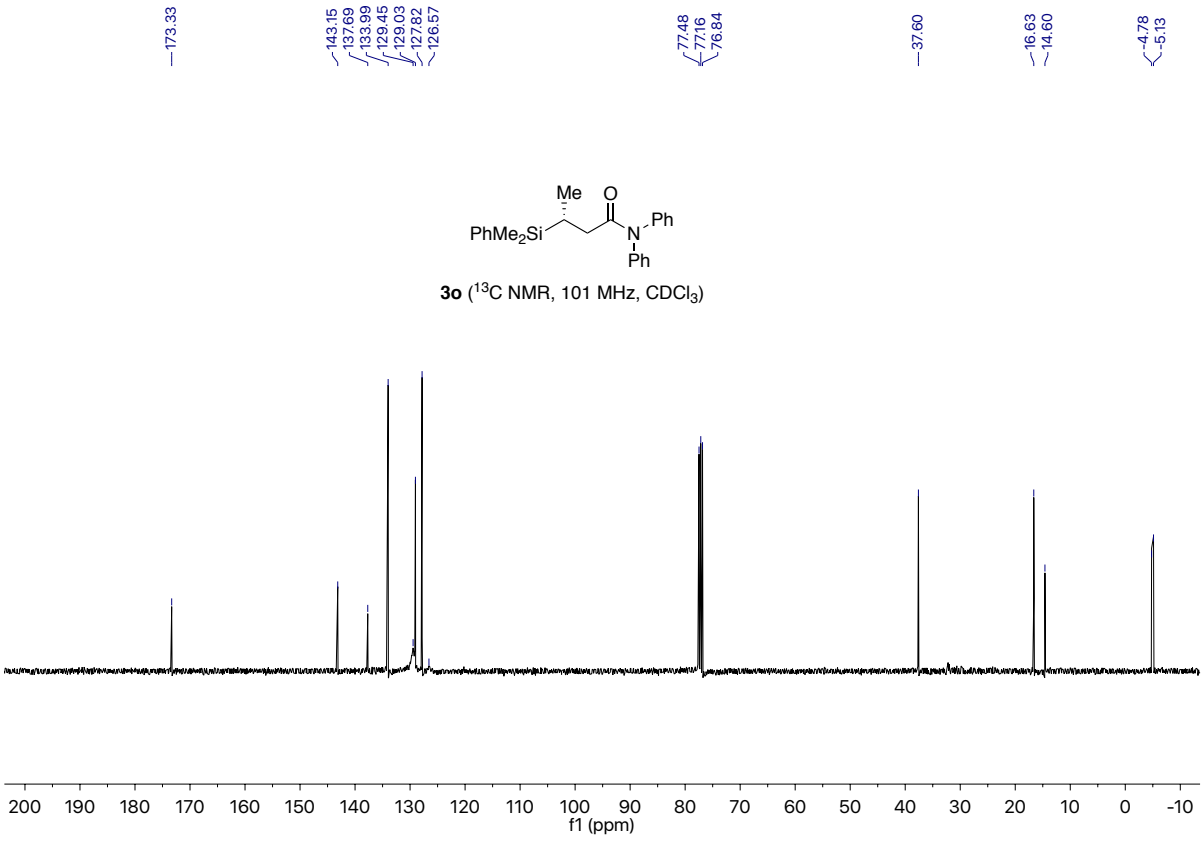


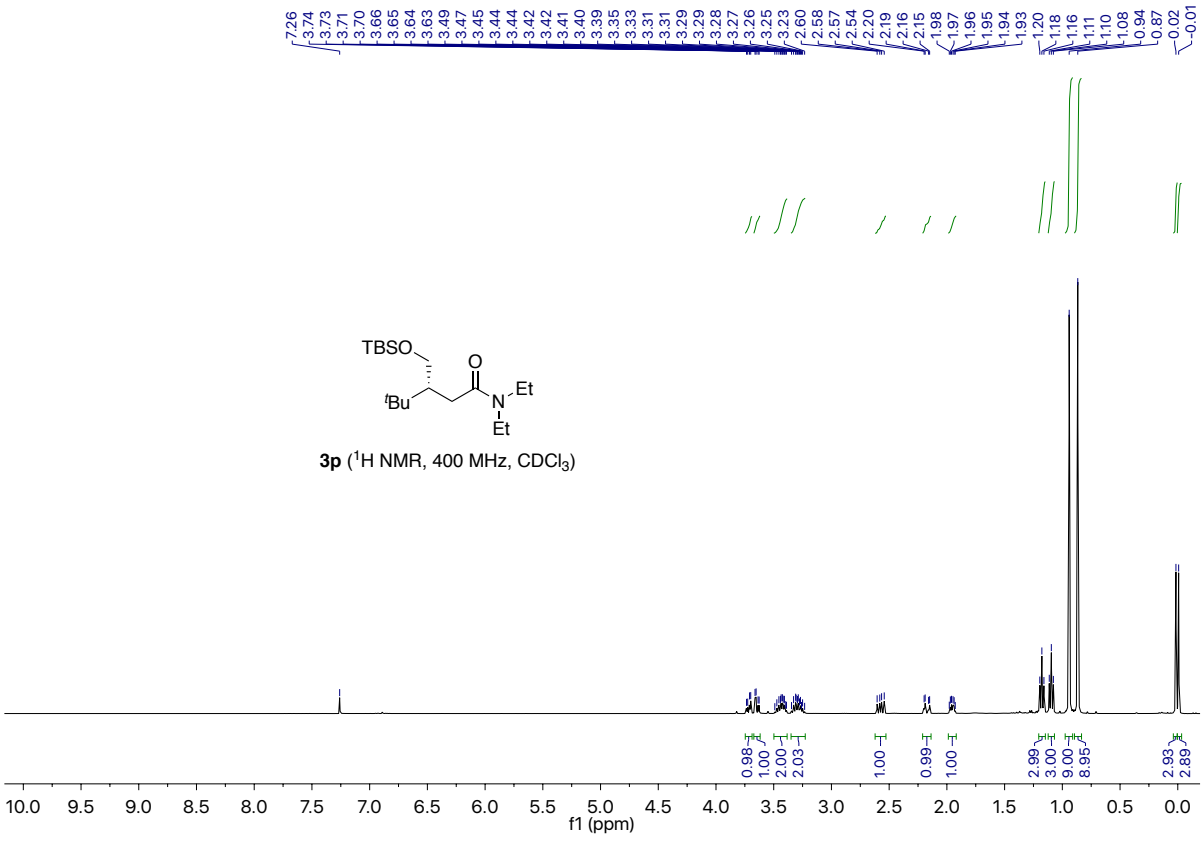
3n (^{1}H NMR, 400 MHz, $CDCl_3$)



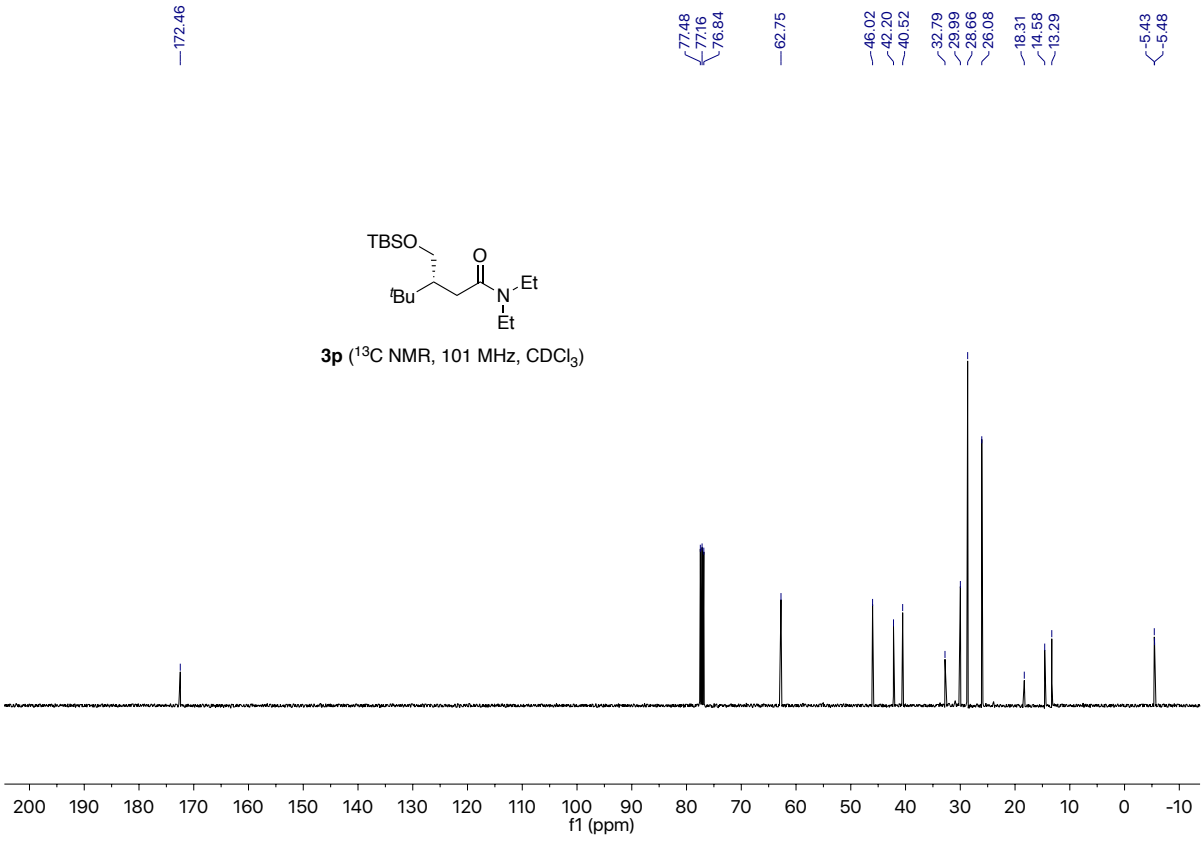
3n (^{13}C NMR, 101 MHz, $CDCl_3$)


7.36
7.36
7.36
7.34
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.20
7.18
2.42
2.41
2.38
2.37
2.07
2.05
2.03
2.01
1.57
1.56
1.55
1.54
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.03
1.02
0.16
0.15
Me
O
PhMe2Si
N
Ph
Ph
3o (1H NMR, 400 MHz, CDCl3)
9.98
4.90
1.00
1.00
1.04
3.00
2.95
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

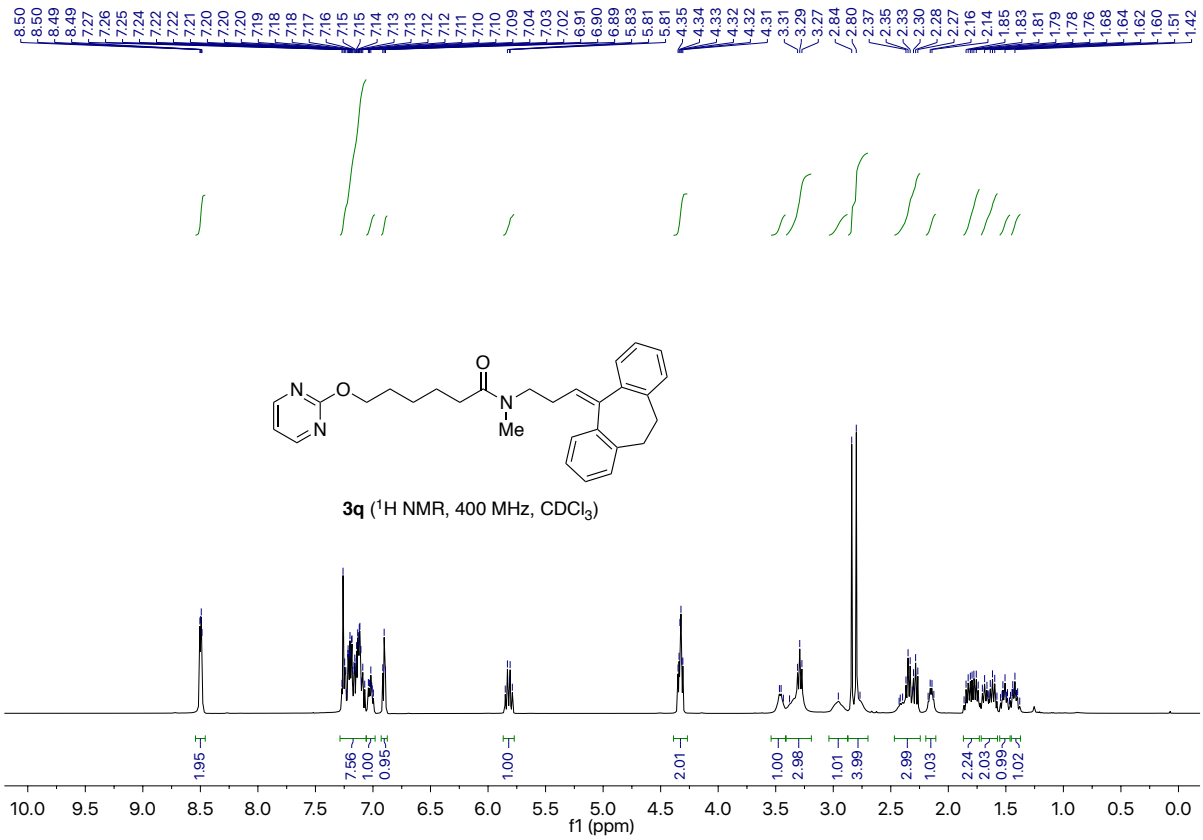

173.33
143.15
137.69
133.99
129.45
129.03
127.82
126.57
77.48
77.16
76.84
37.60
16.63
14.60
-4.78
-5.13
Me
O
PhMe2Si
N
Ph
Ph
3o (13C NMR, 101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



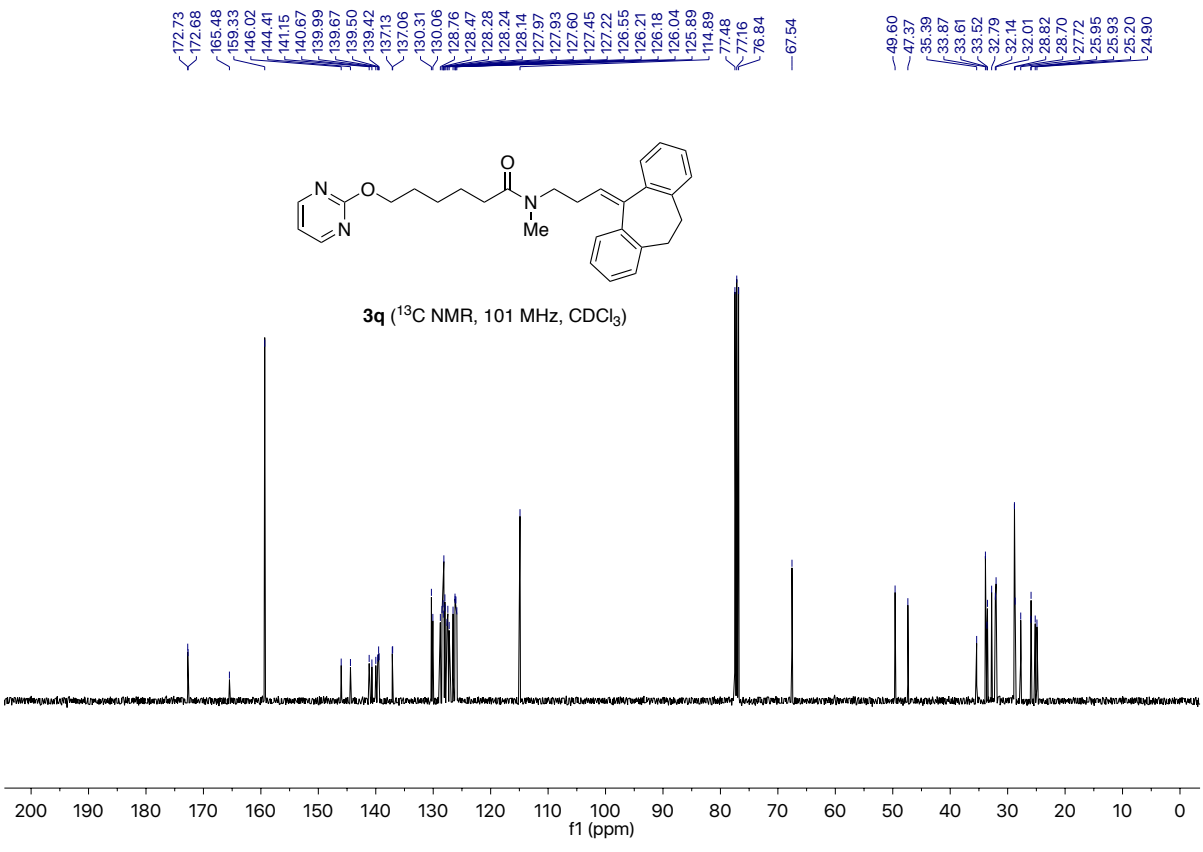
3p (^{1}H NMR, 400 MHz, $CDCl_3$)



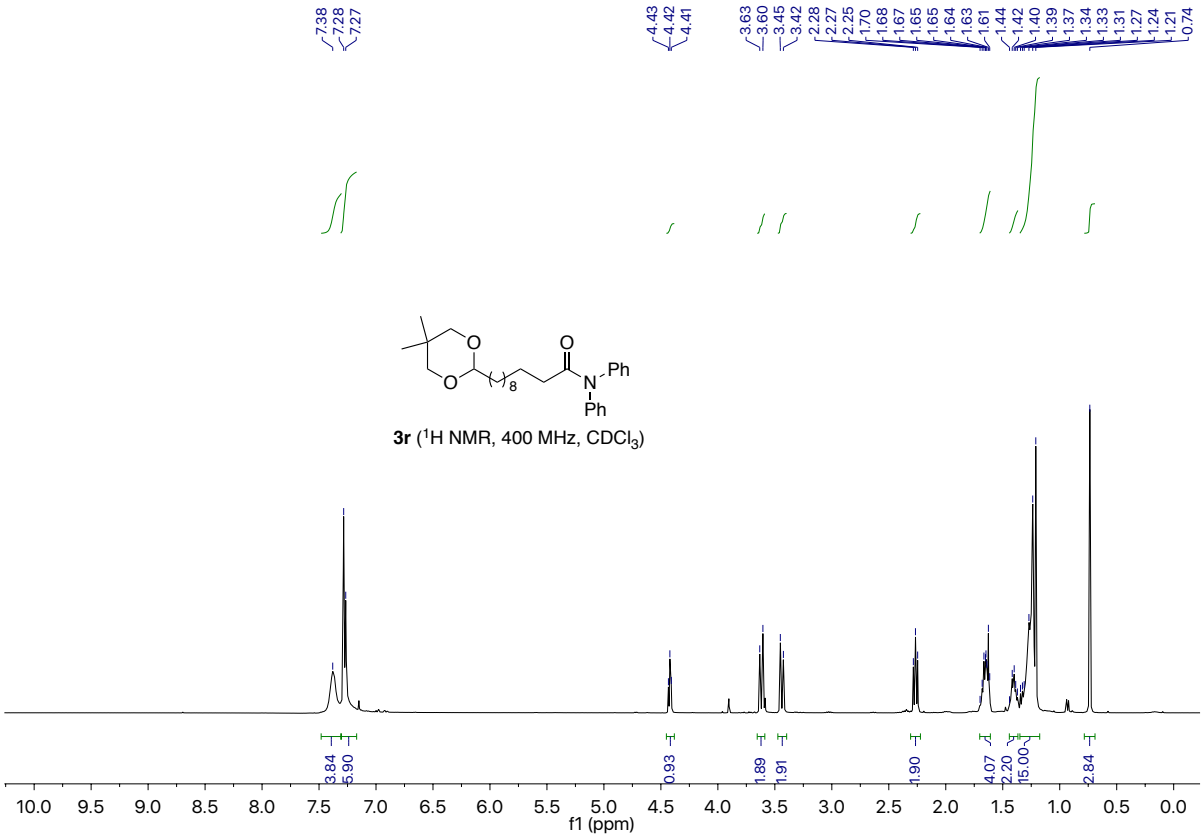
3p (^{13}C NMR, 101 MHz, $CDCl_3$)



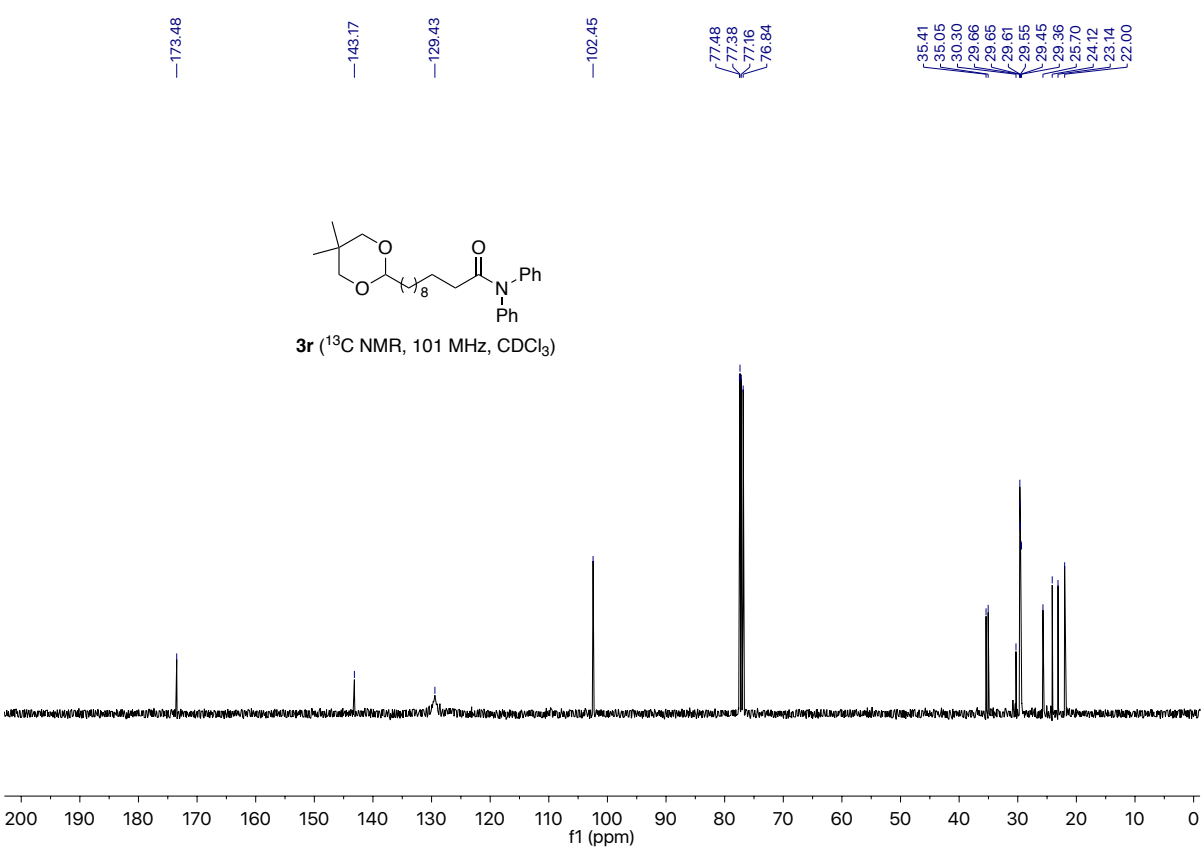
3q (^{1}H NMR, 400 MHz, $CDCl_3$)



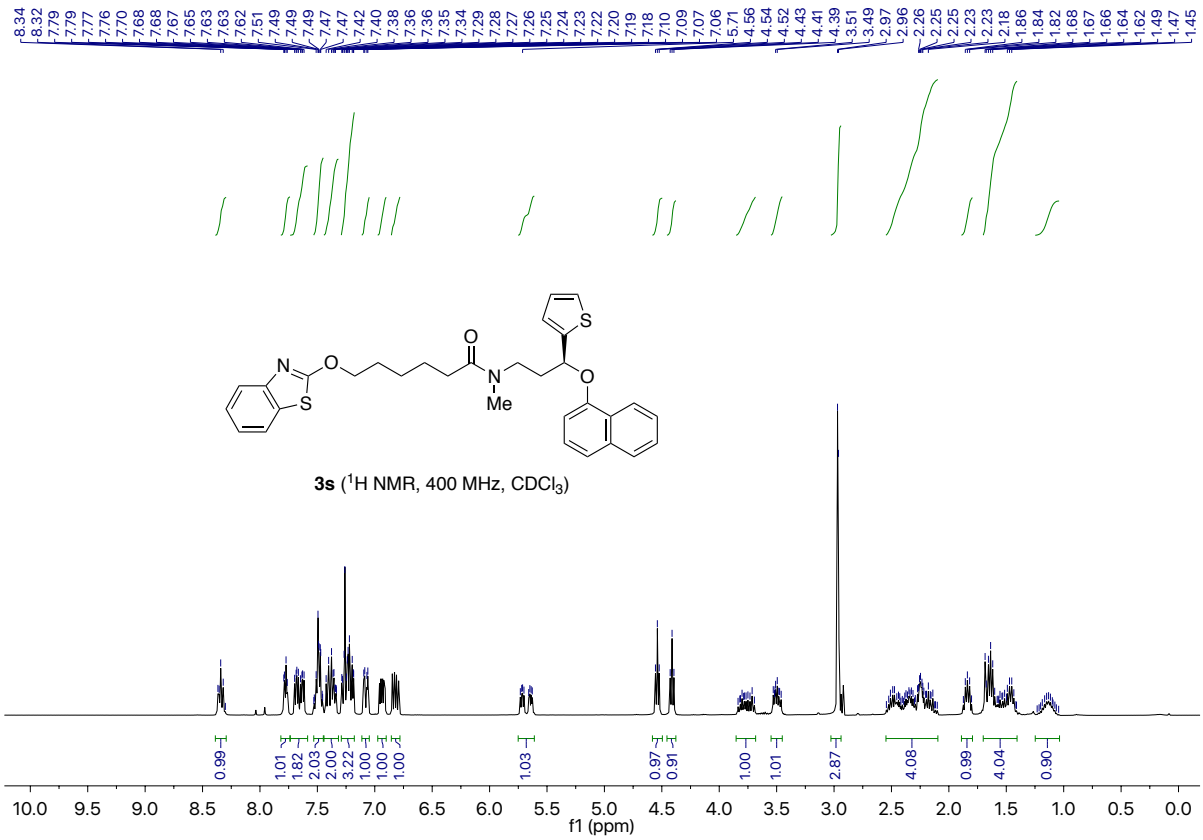
3q (^{13}C NMR, 101 MHz, $CDCl_3$)



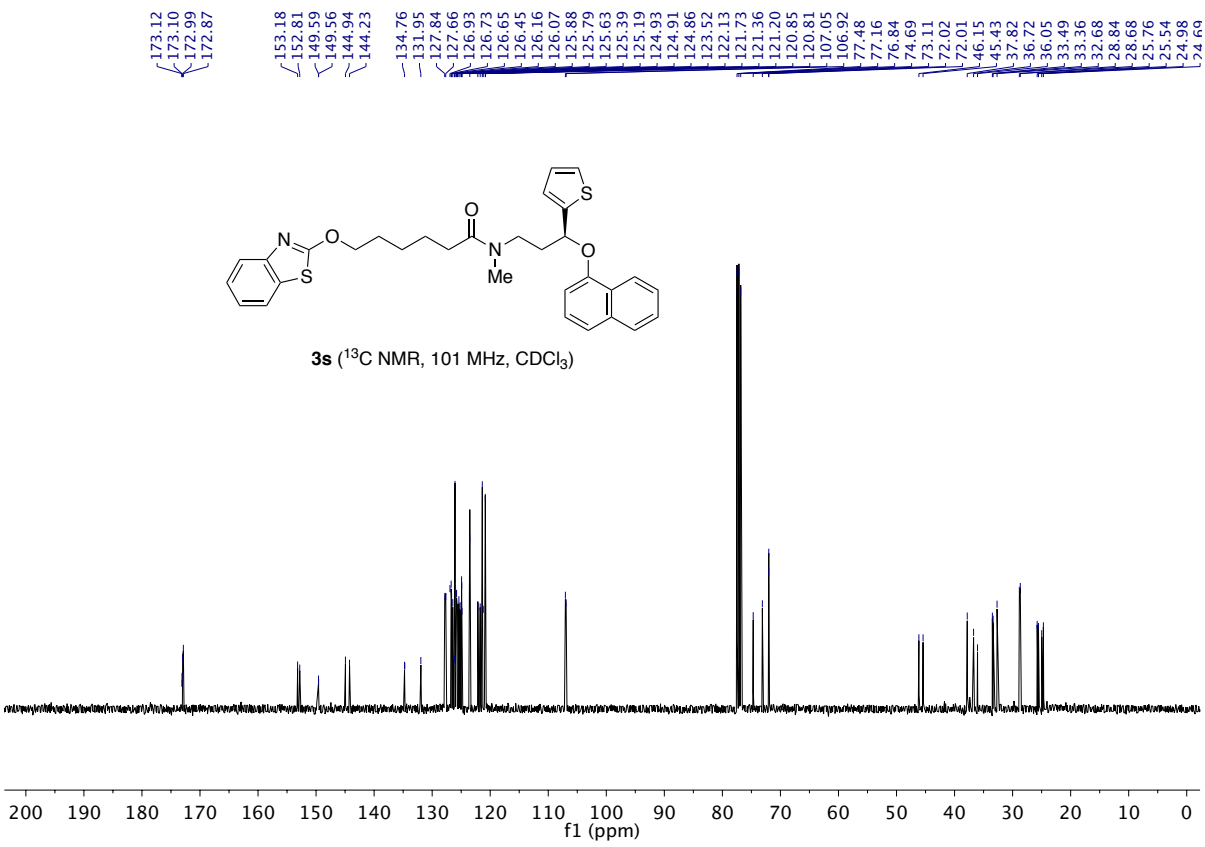
3r (^{1}H NMR, 400 MHz, $CDCl_3$)



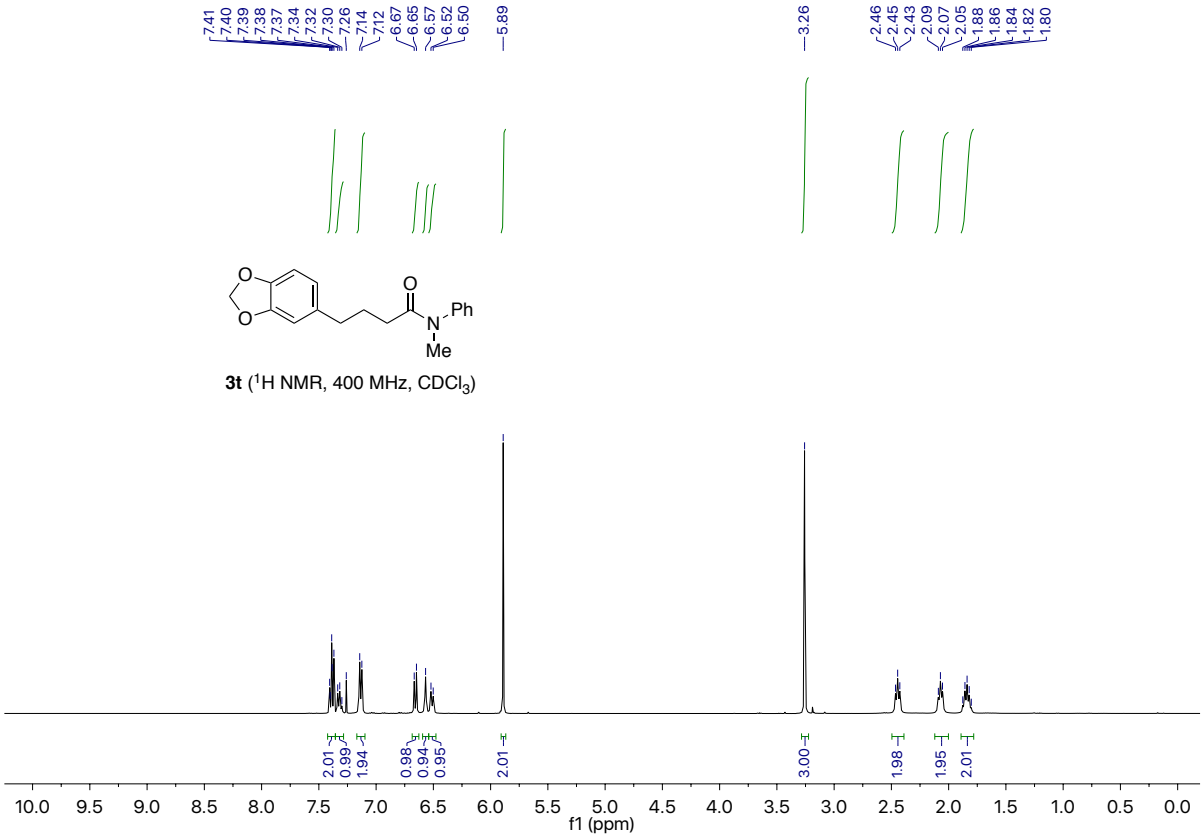
3r (^{13}C NMR, 101 MHz, $CDCl_3$)



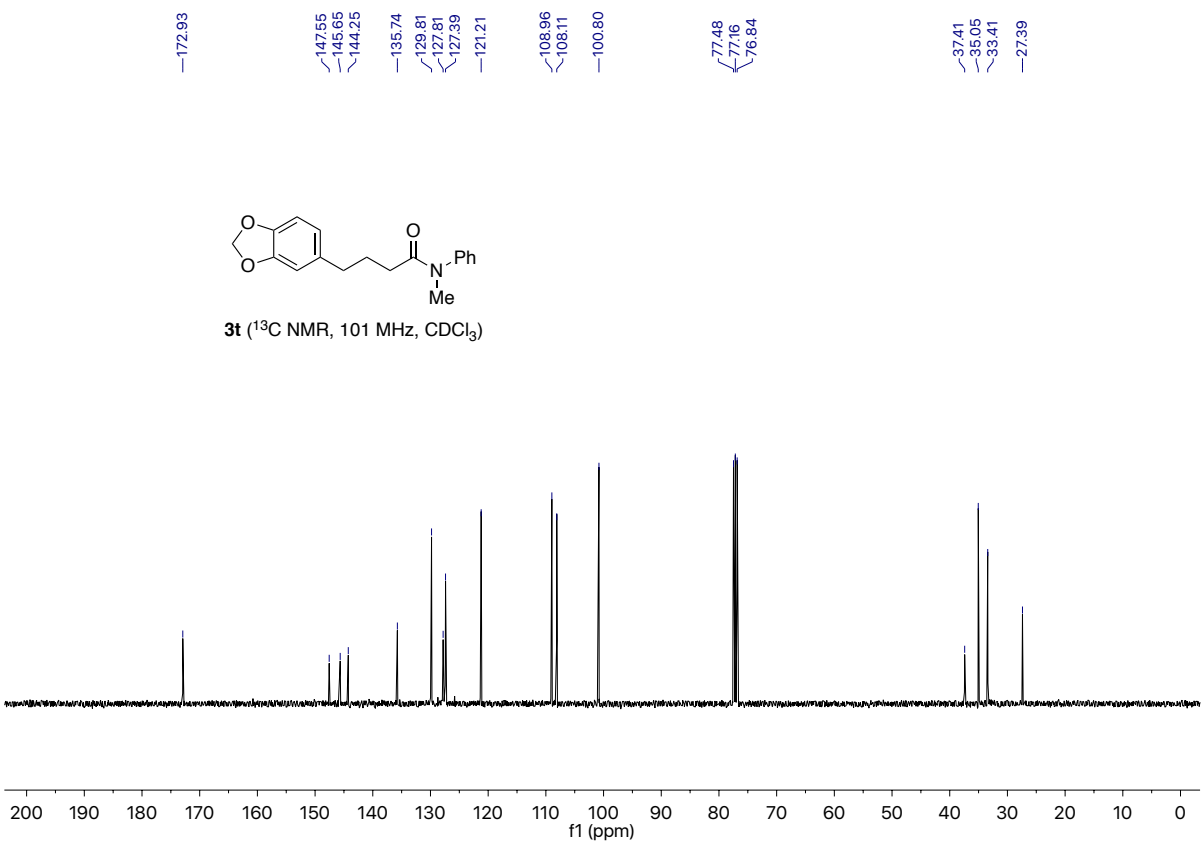
3s (^{1}H NMR, 400 MHz, $CDCl_3$)



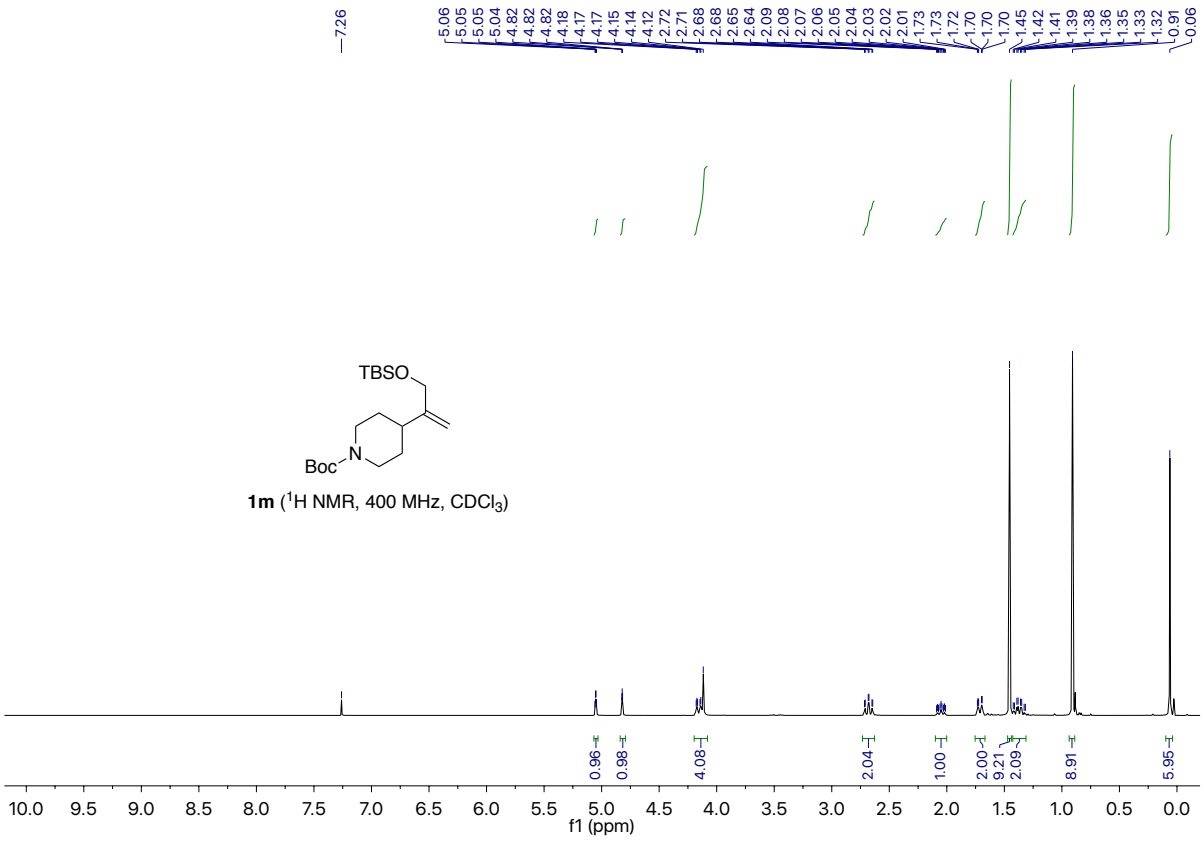
3s (^{13}C NMR, 101 MHz, $CDCl_3$)



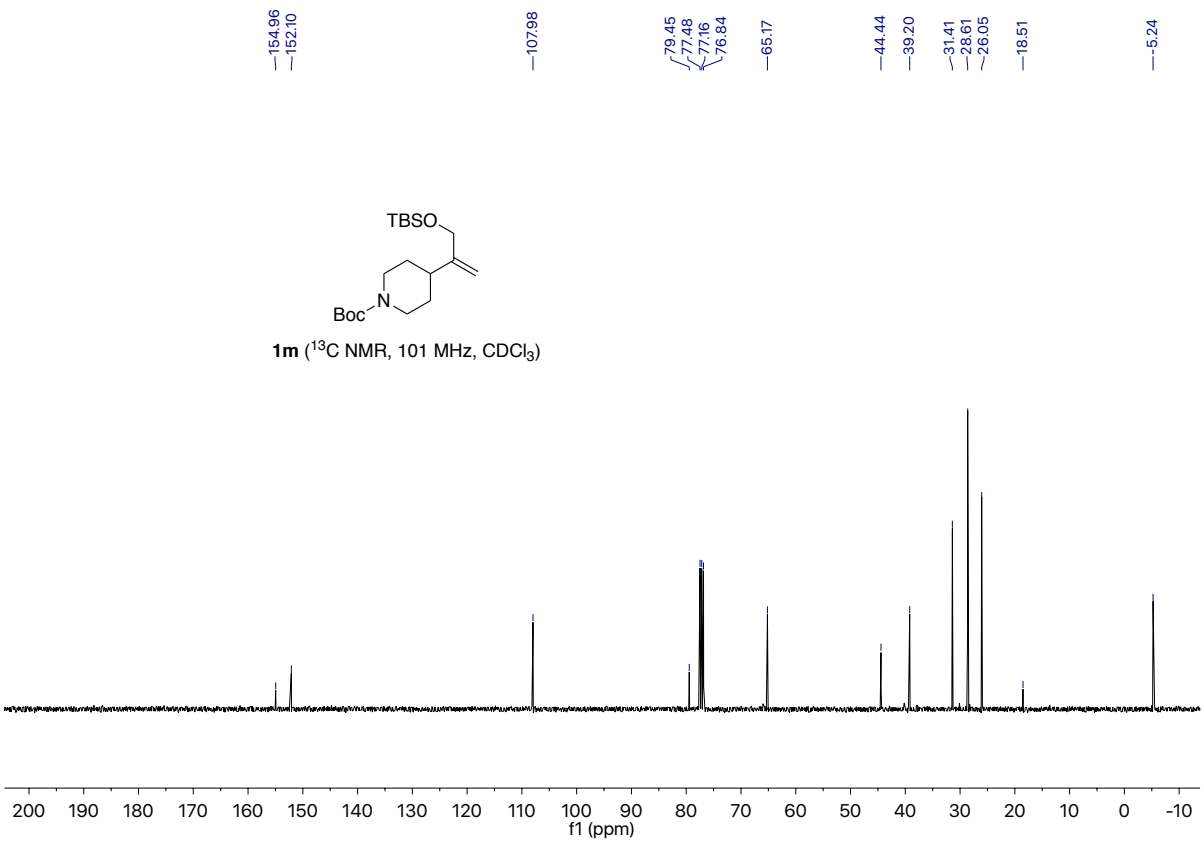
3t (^{1}H NMR, 400 MHz, $CDCl_3$)



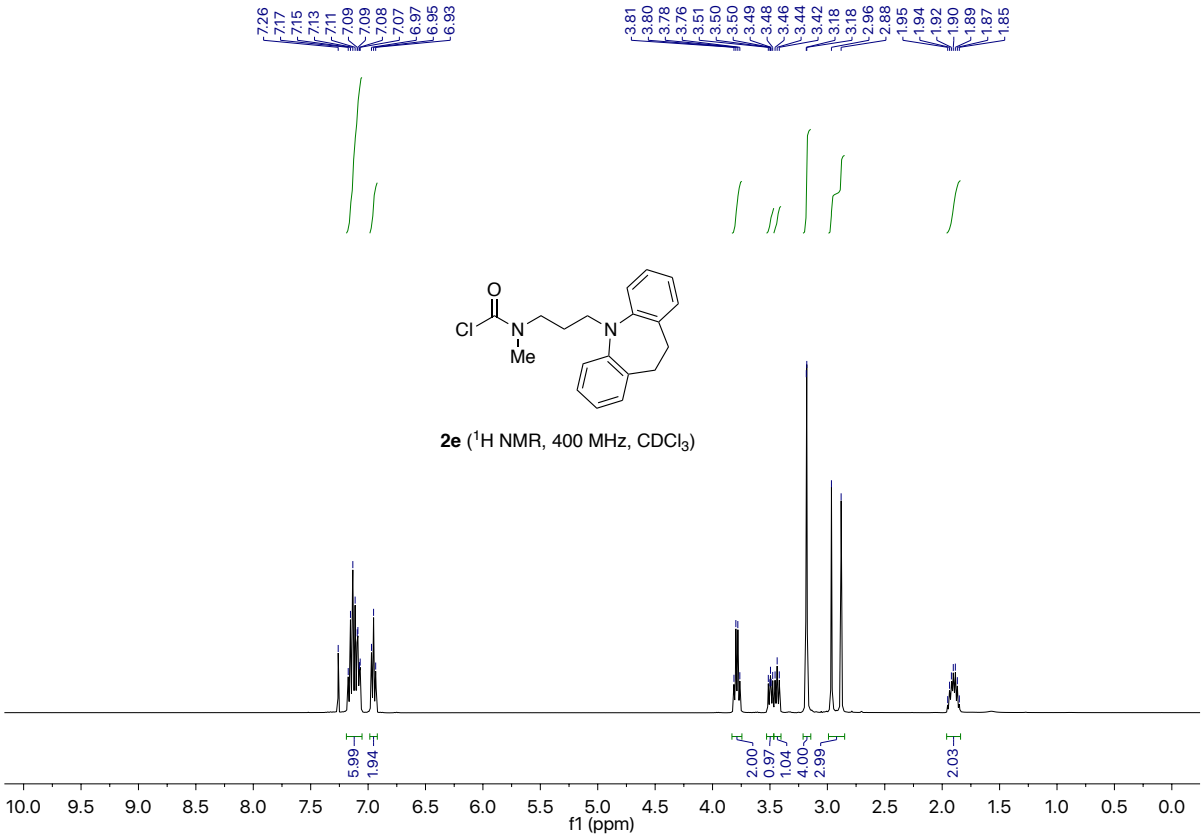
3t (^{13}C NMR, 101 MHz, $CDCl_3$)



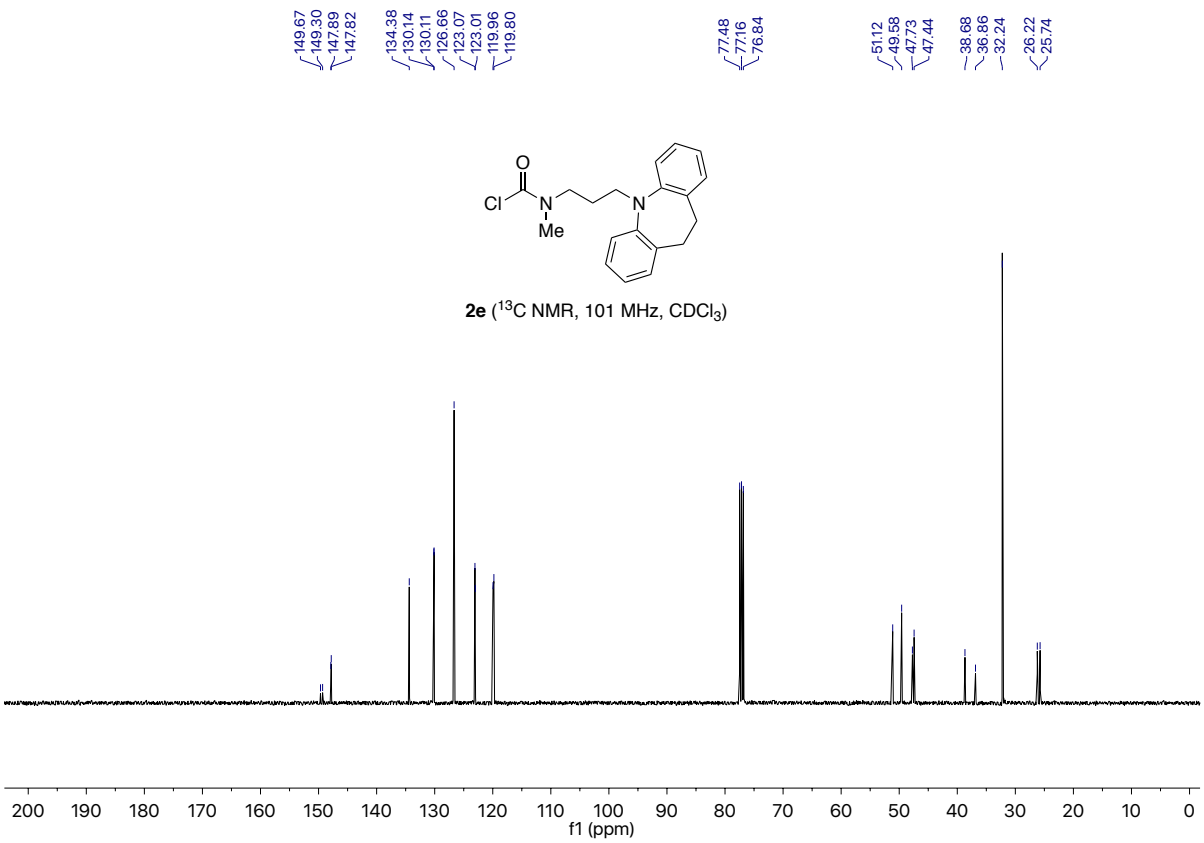
1m (^{1}H NMR, 400 MHz, $CDCl_3$)



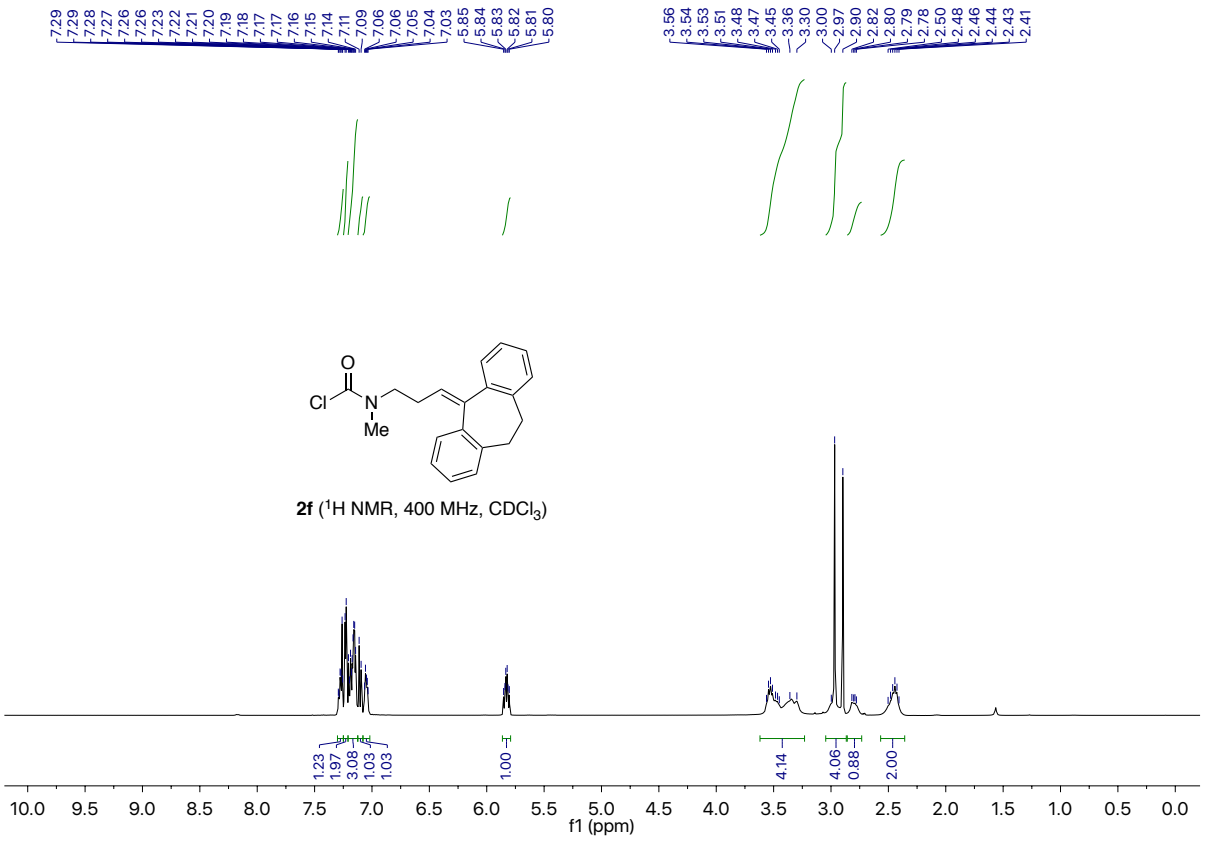
1m (^{13}C NMR, 101 MHz, $CDCl_3$)



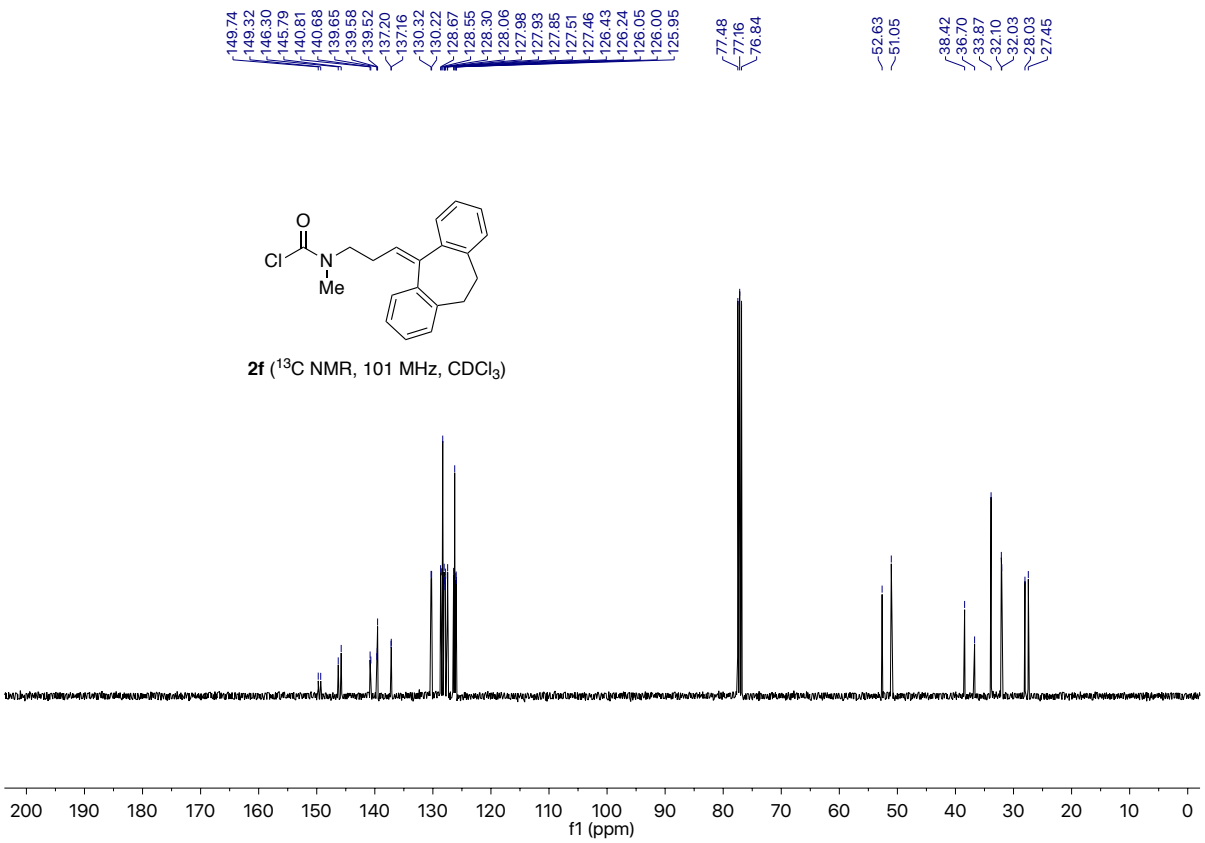
2e (^{1}H NMR, 400 MHz, $CDCl_3$)



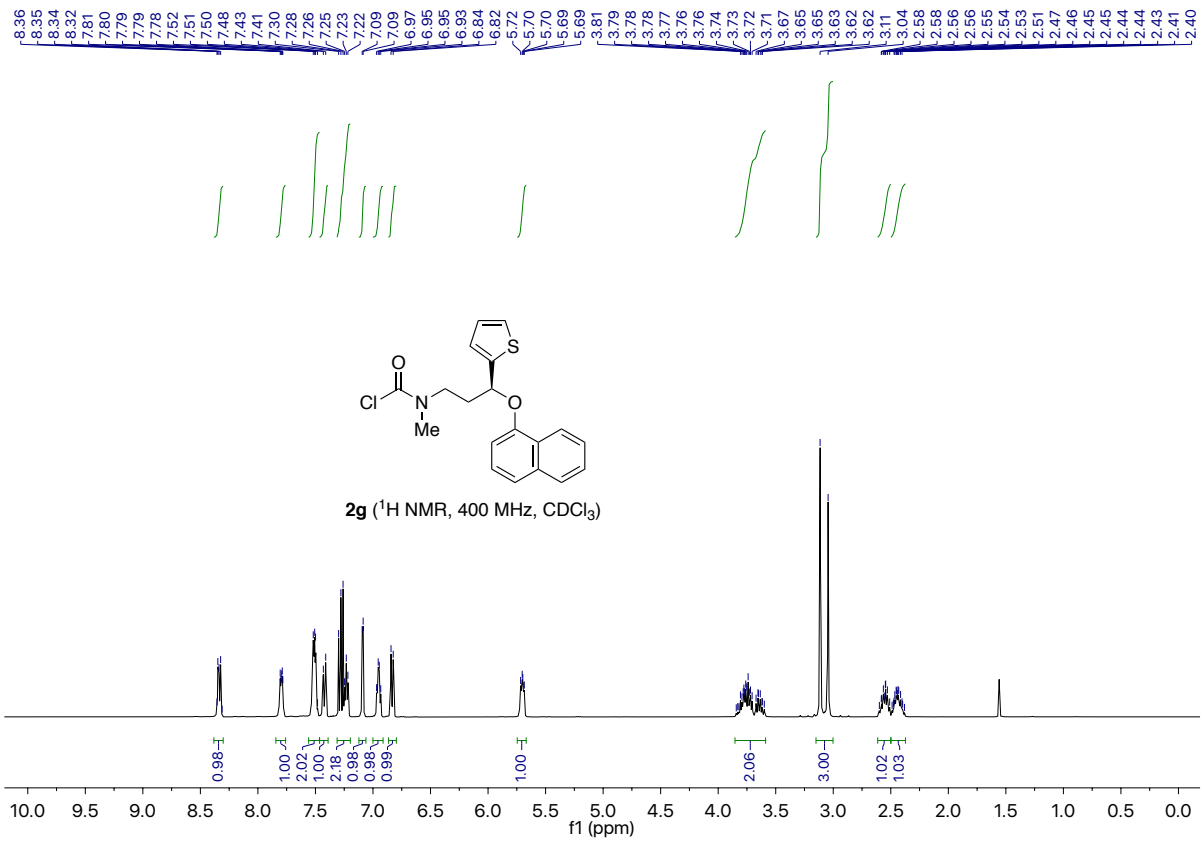
2e (^{13}C NMR, 101 MHz, $CDCl_3$)



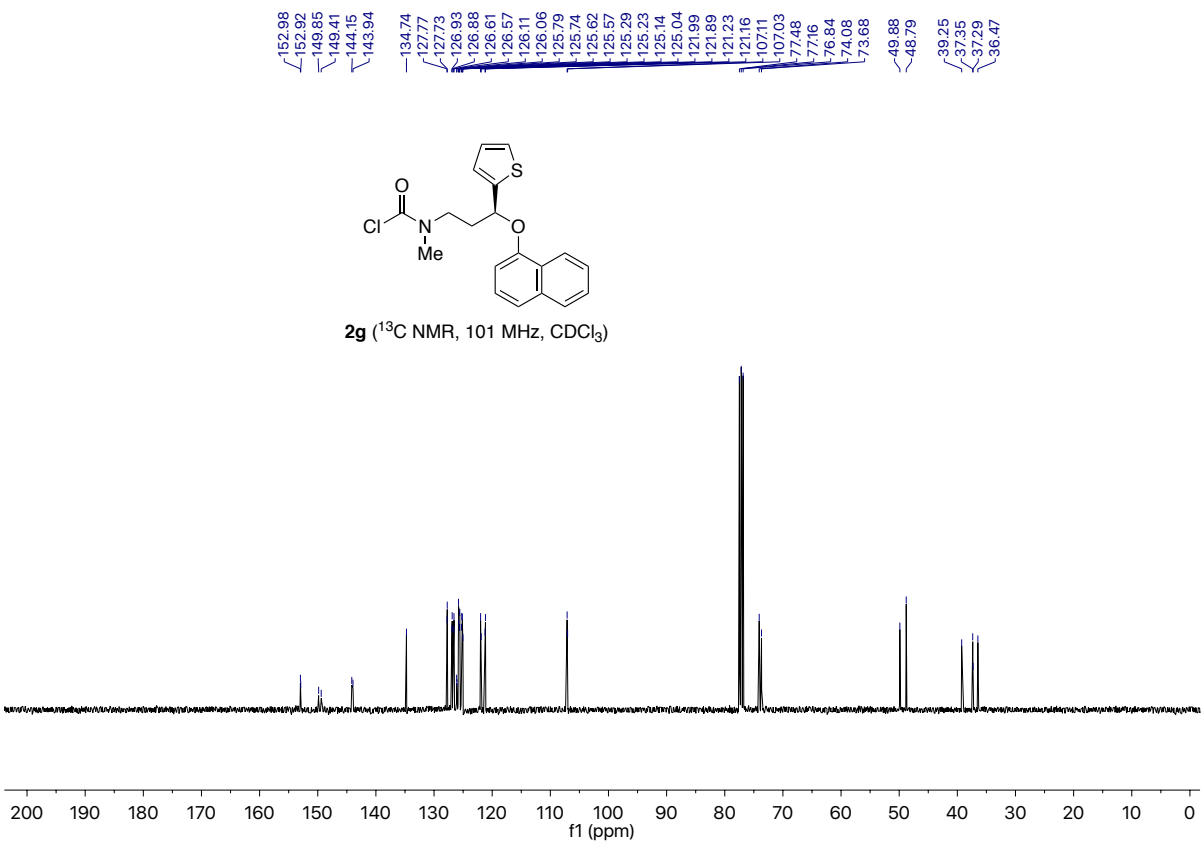
2f (^{1}H NMR, 400 MHz, $CDCl_3$)



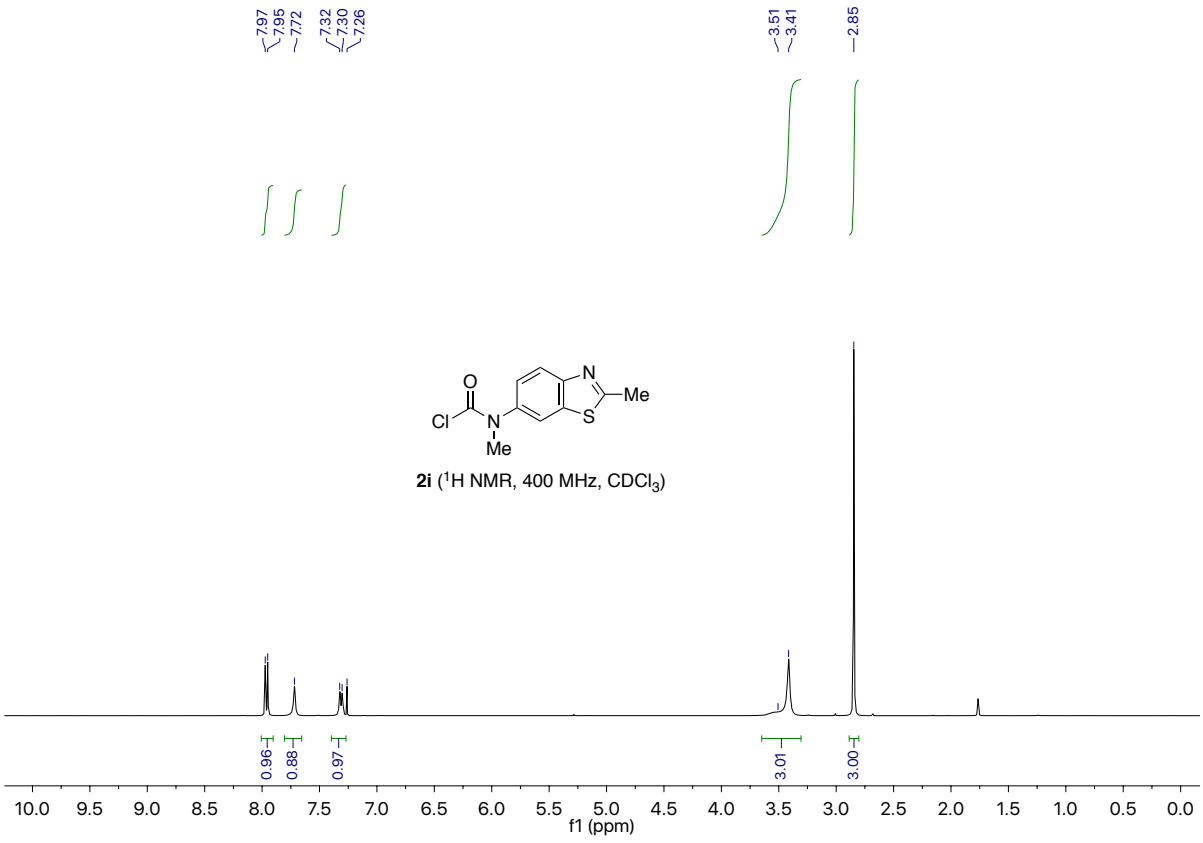
2f (^{13}C NMR, 101 MHz, $CDCl_3$)



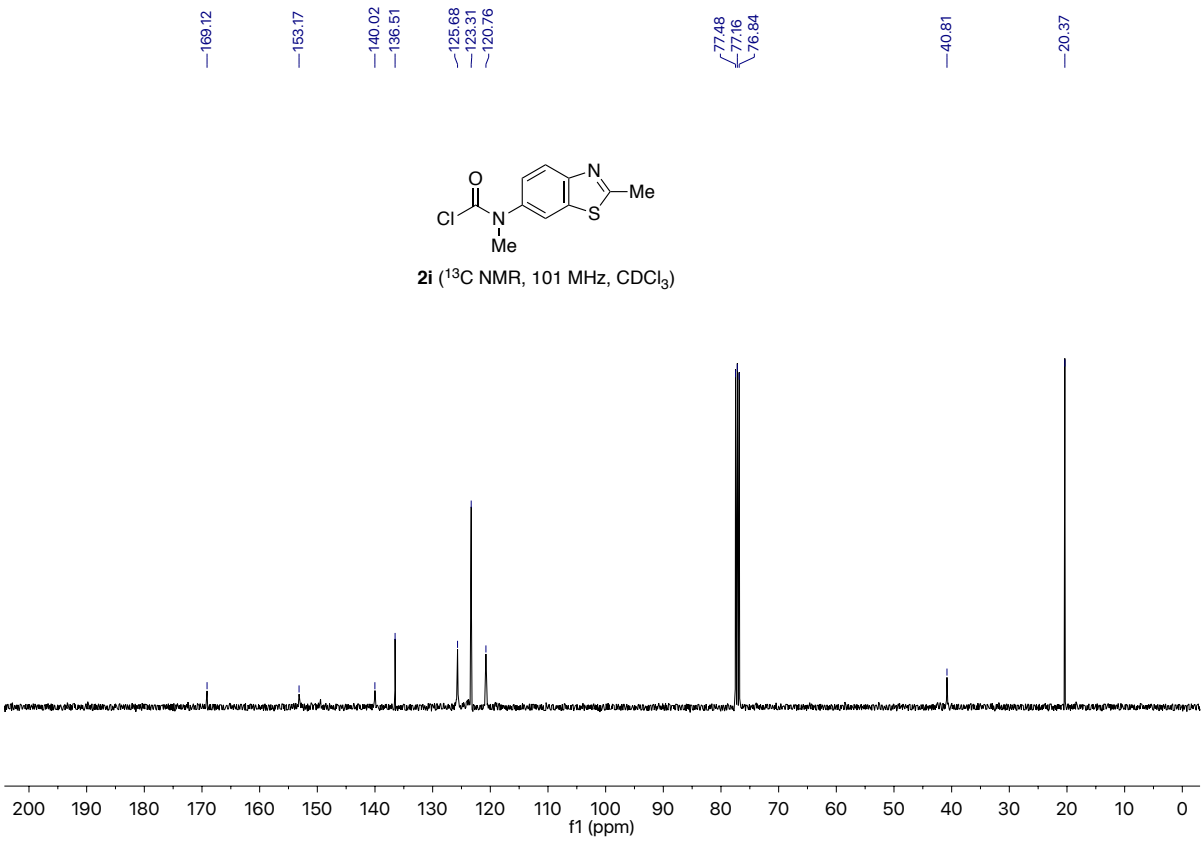
2g (^{1}H NMR, 400 MHz, $CDCl_3$)



2g (^{13}C NMR, 101 MHz, $CDCl_3$)

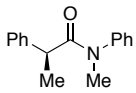


2i (^{1}H NMR, 400 MHz, $CDCl_3$)

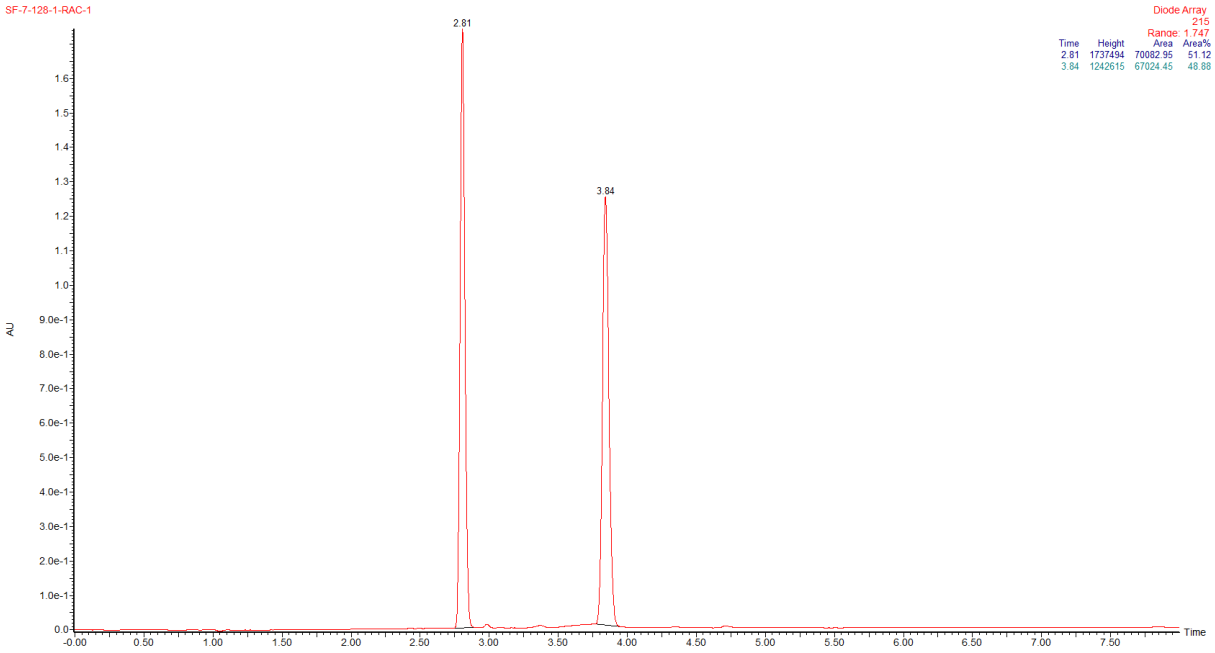


2i (^{13}C NMR, 101 MHz, $CDCl_3$)

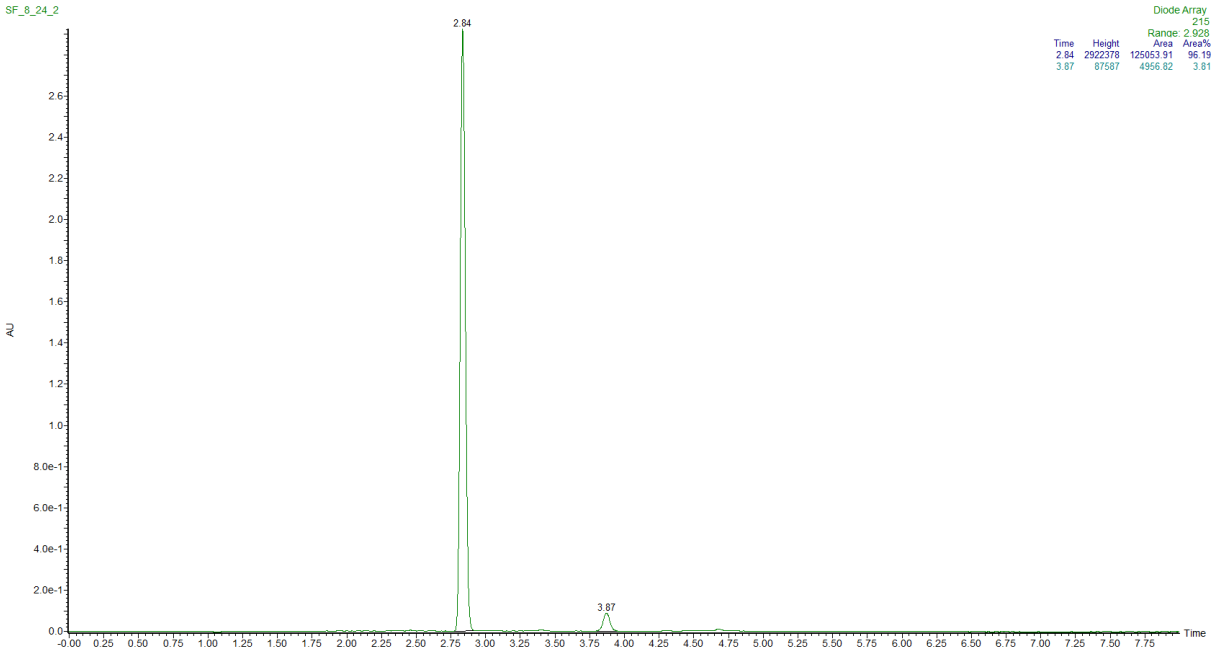
(*S*)-*N*-methyl-*N*,2-diphenylpropanamide (3a)



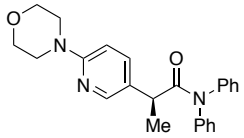
Racemic (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



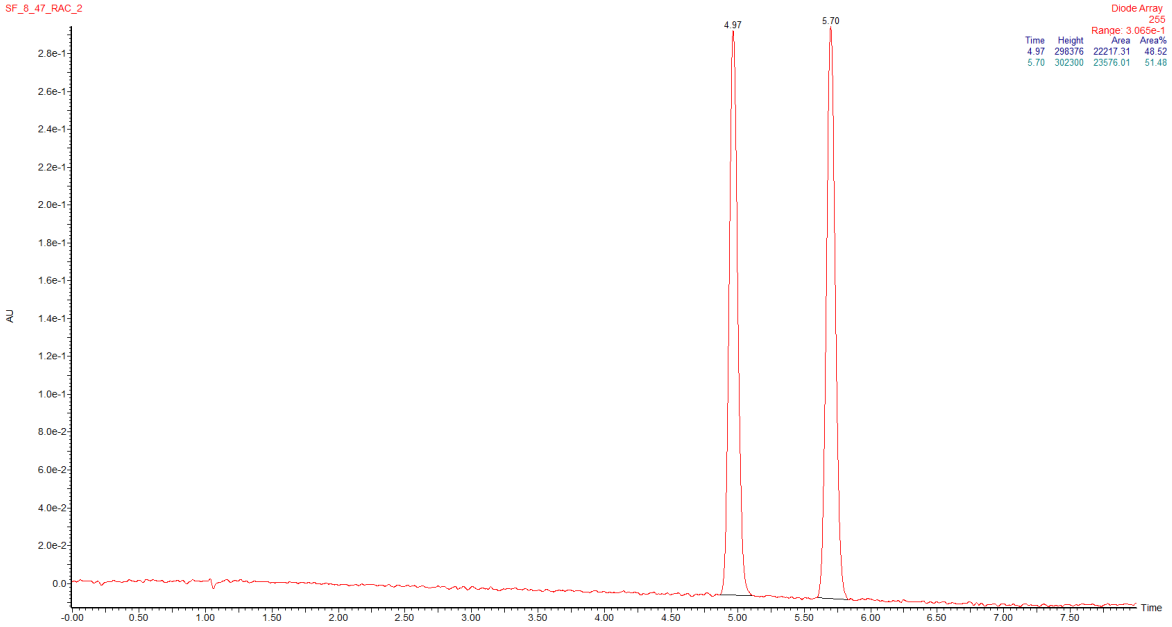
Enantioenriched (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



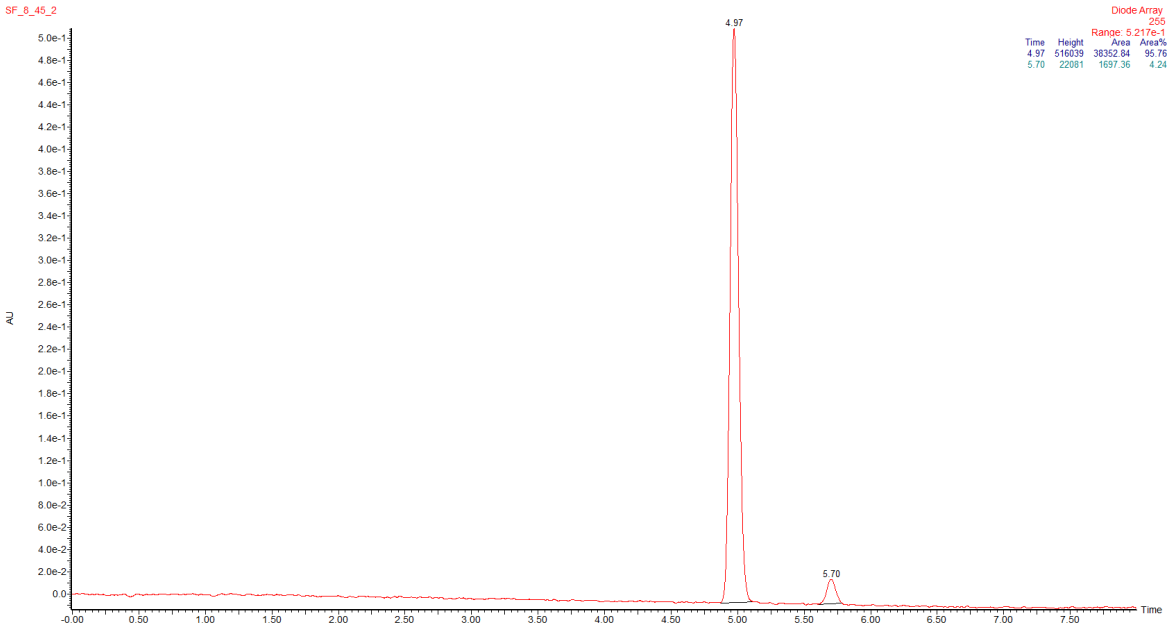
(*S*)-2-(6-morpholinopyridin-3-yl)-*N*,*N*-diphenylpropanamide (3b)



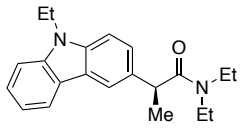
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



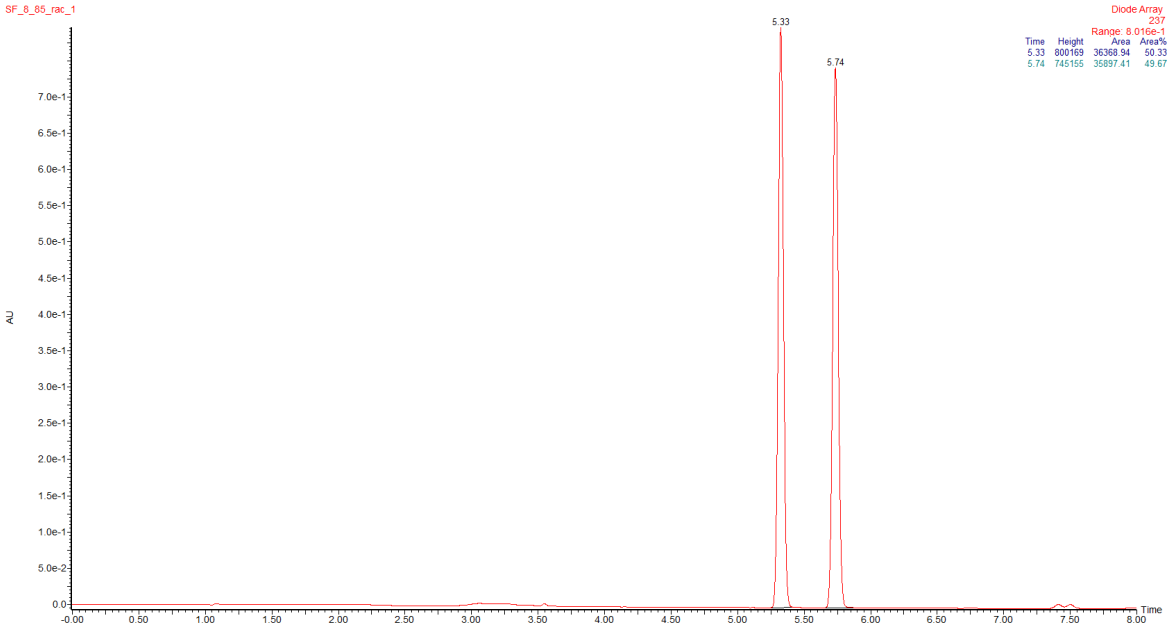
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



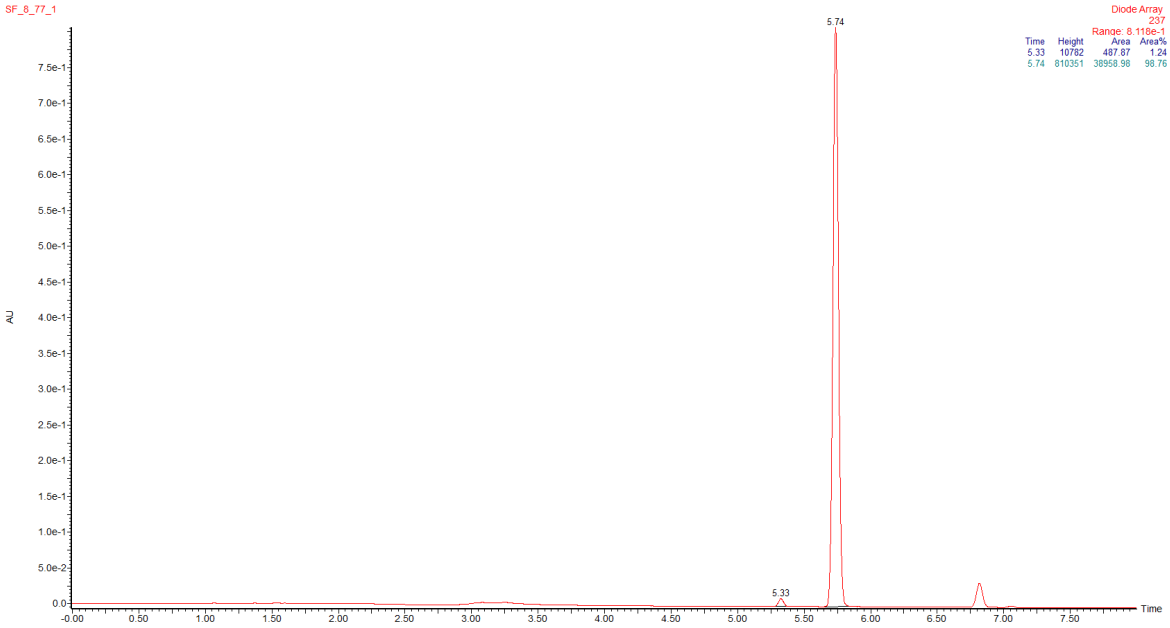
(*S*)-*N*,*N*-diethyl-2-(9-ethyl-9*H*-carbazol-3-yl)propanamide (3c)



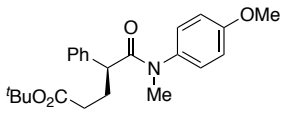
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



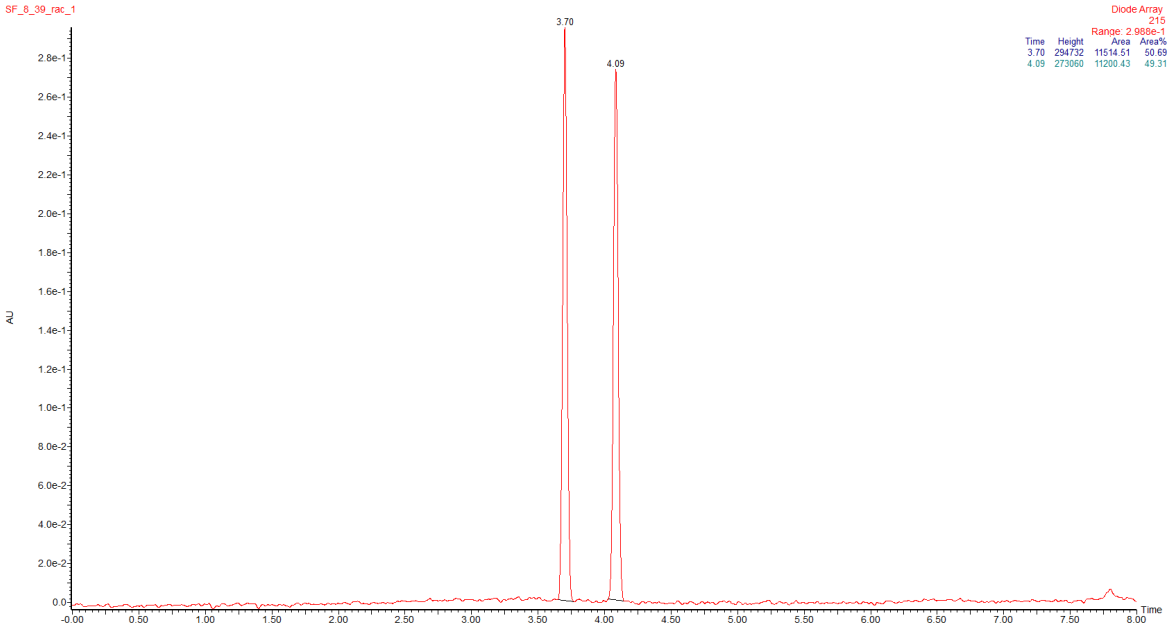
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



tert-butyl (_S_)-5-((4-methoxyphenyl)(methyl)amino)-5-oxo-4-phenylpentanoate (3d)

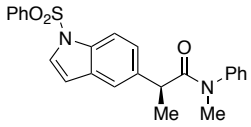


Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

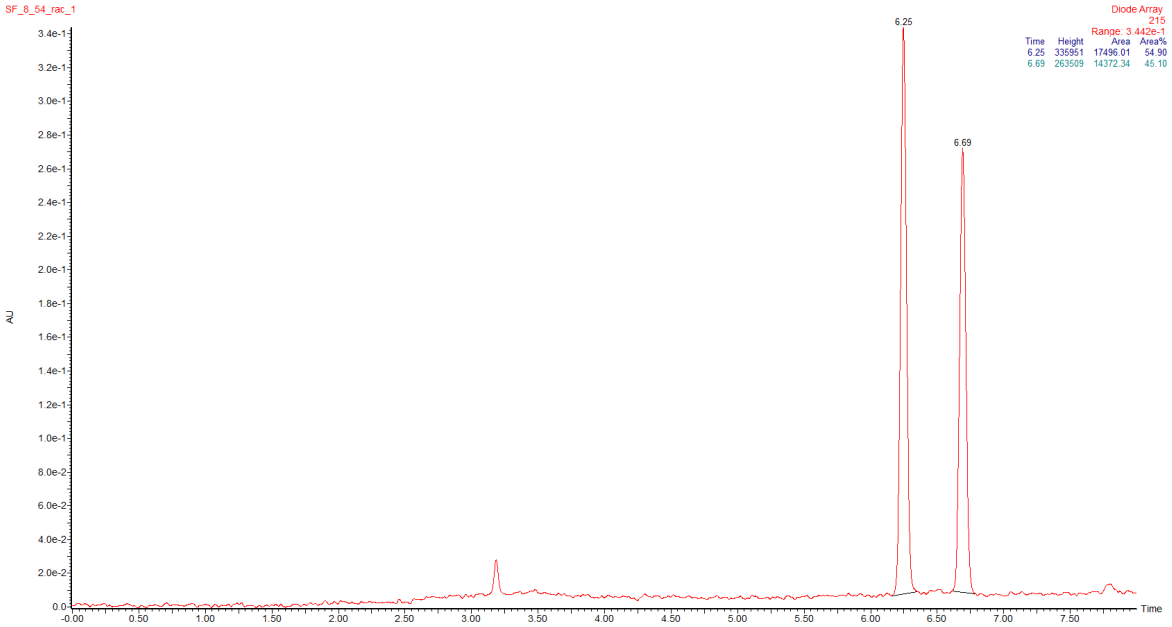


Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

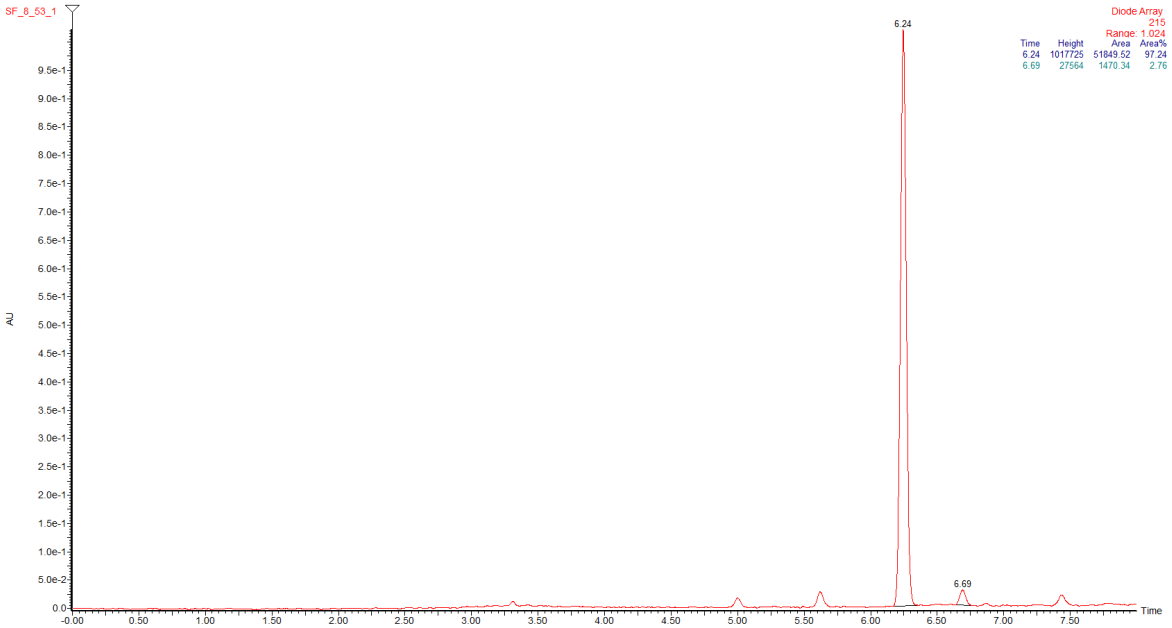
(*S*)-*N*-methyl-*N*-phenyl-2-(1-(phenylsulfonyl)-1*H*-indol-5-yl)propanamide (3e)



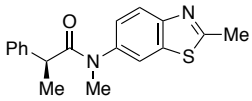
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



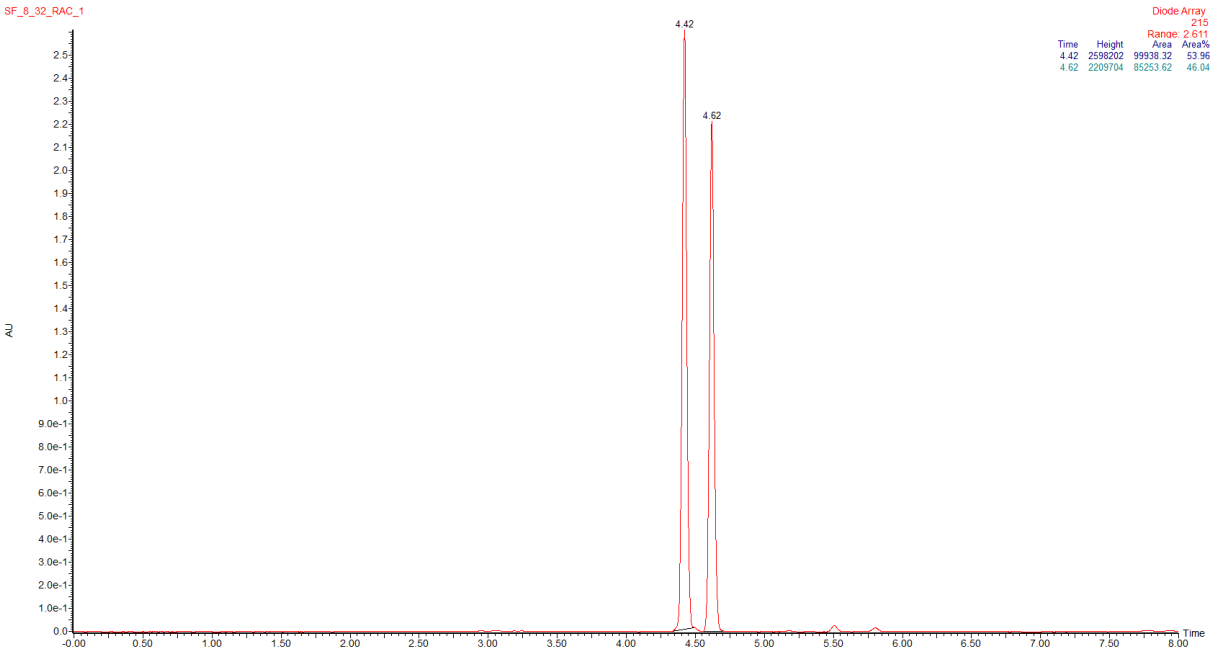
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



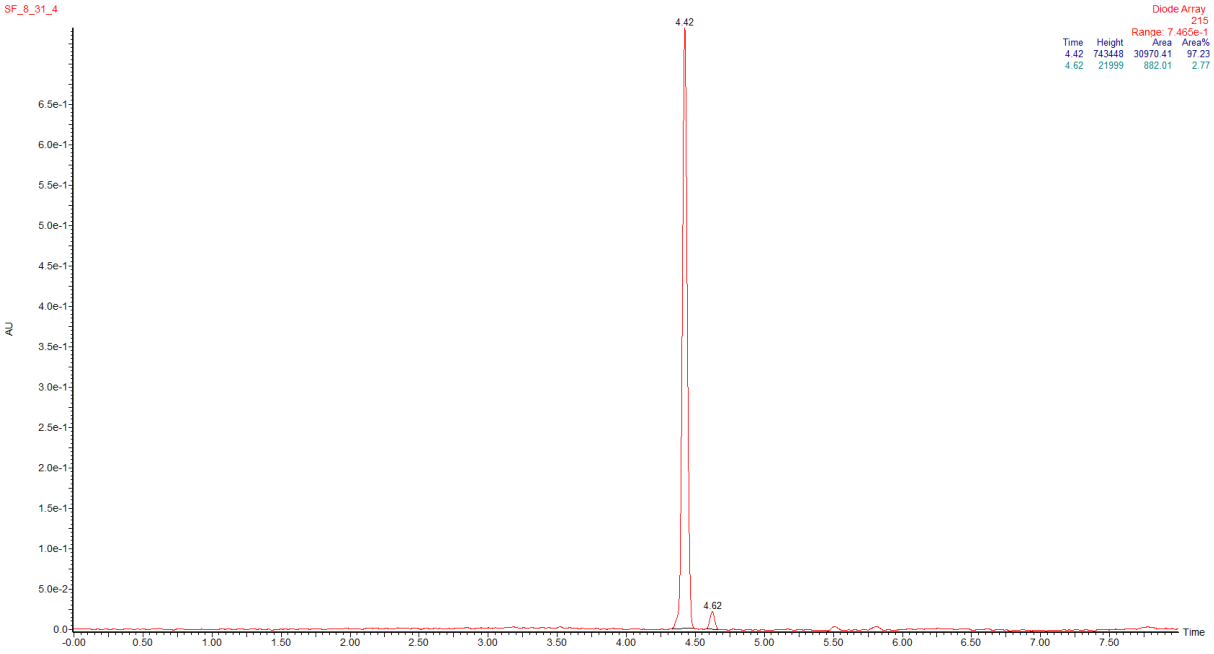
(*S*)-*N*-methyl-*N*-(2-methylbenzo[*d*]thiazol-6-yl)-2-phenylpropanamide (3f)



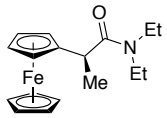
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



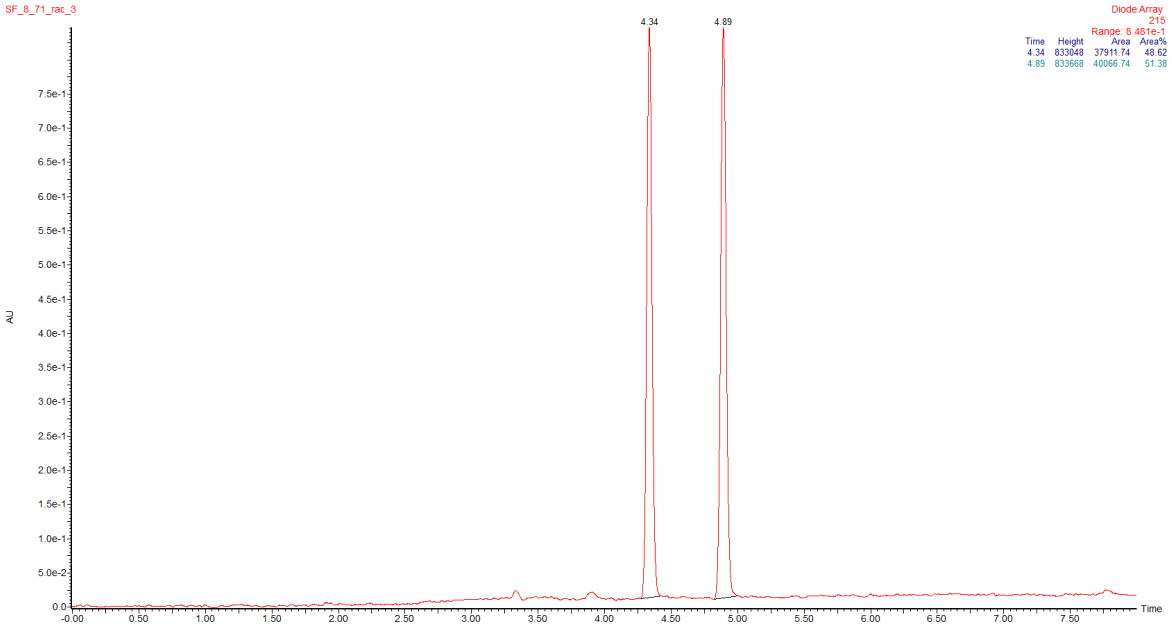
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



(*R*)-*N*,*N*-diethyl-2-ferrocenylpropanamide (3g)

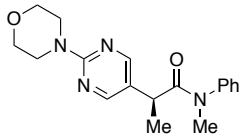


Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

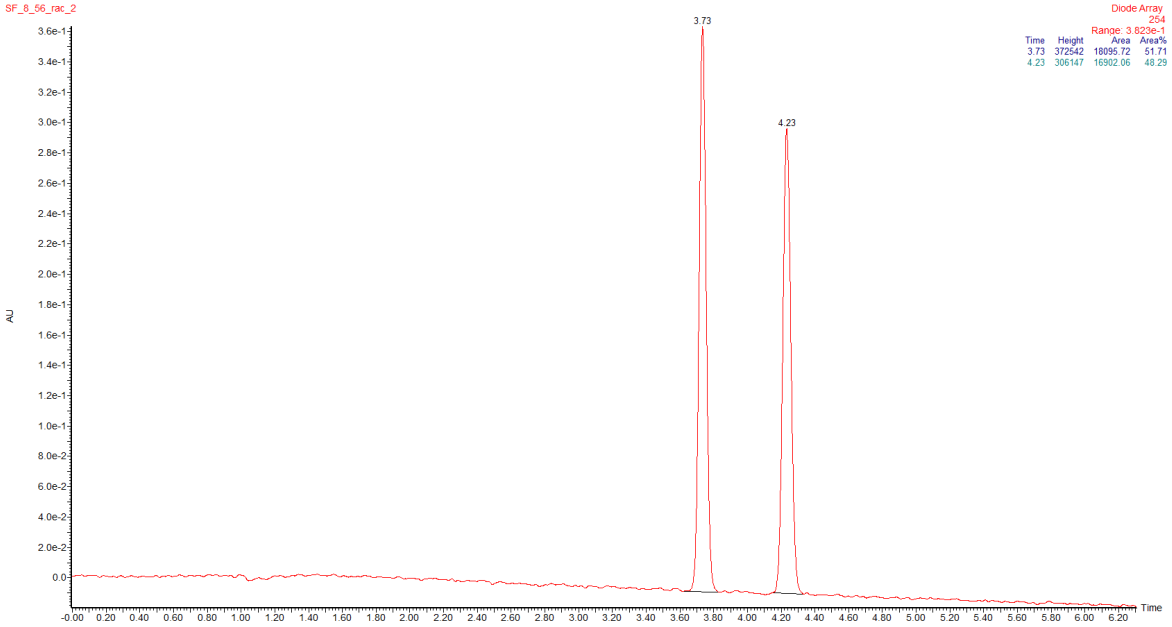


Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

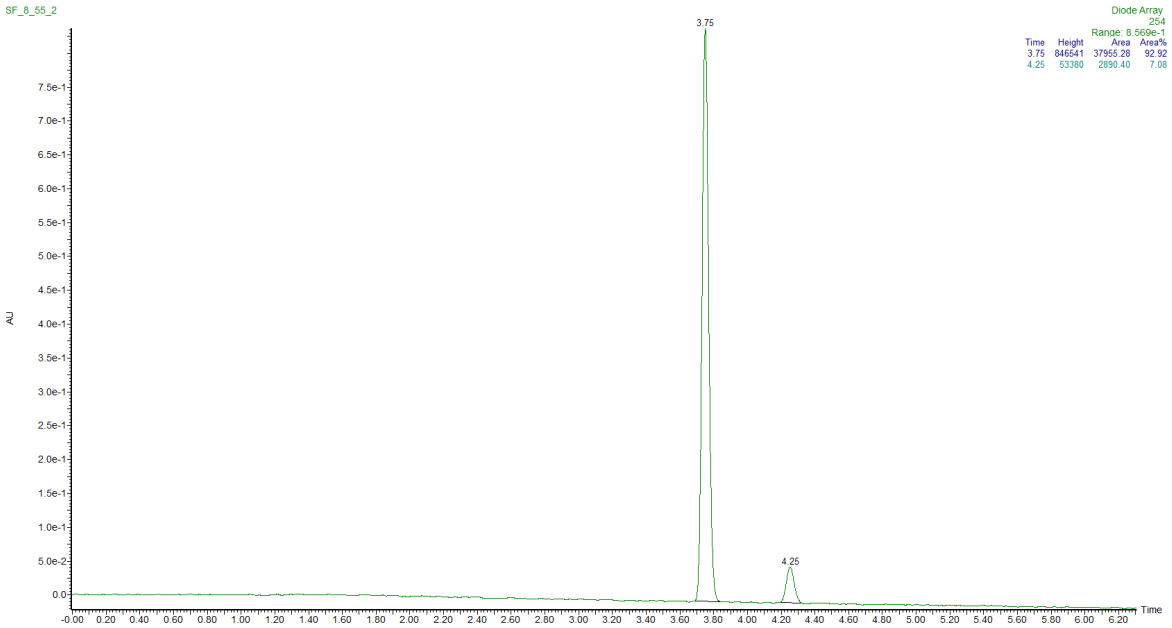
(*S*)-*N*-methyl-2-(2-morpholinopyrimidin-5-yl)-*N*-phenylpropanamide (3h)



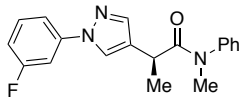
Racemic (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



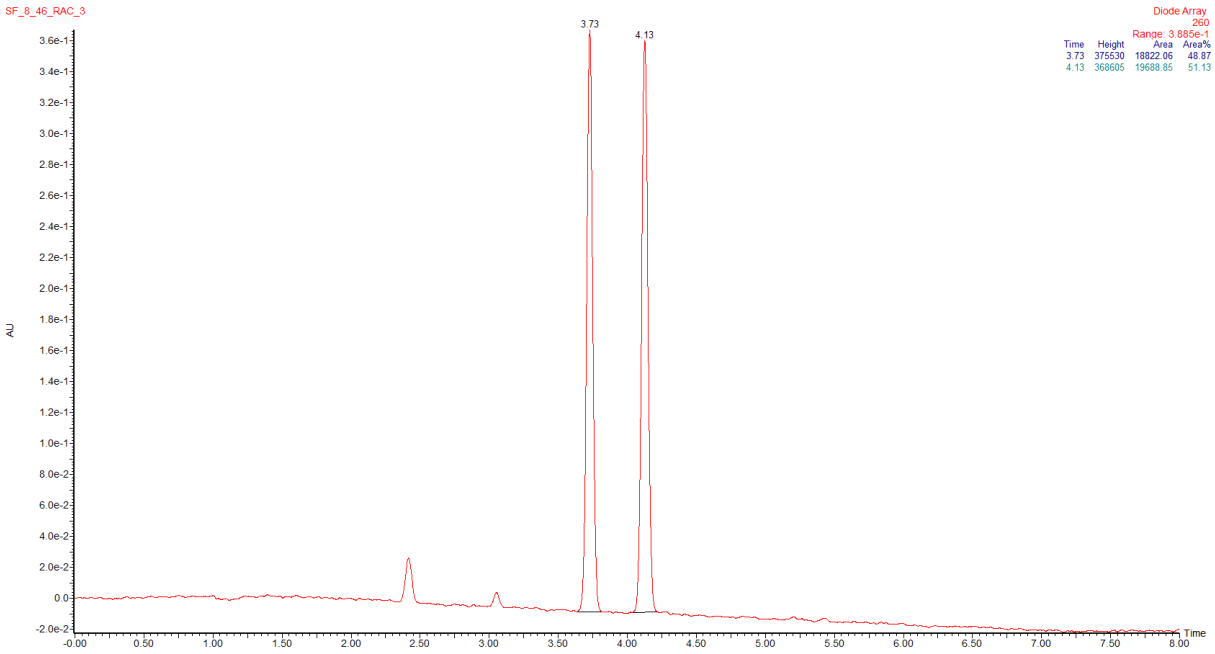
Enantioenriched (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



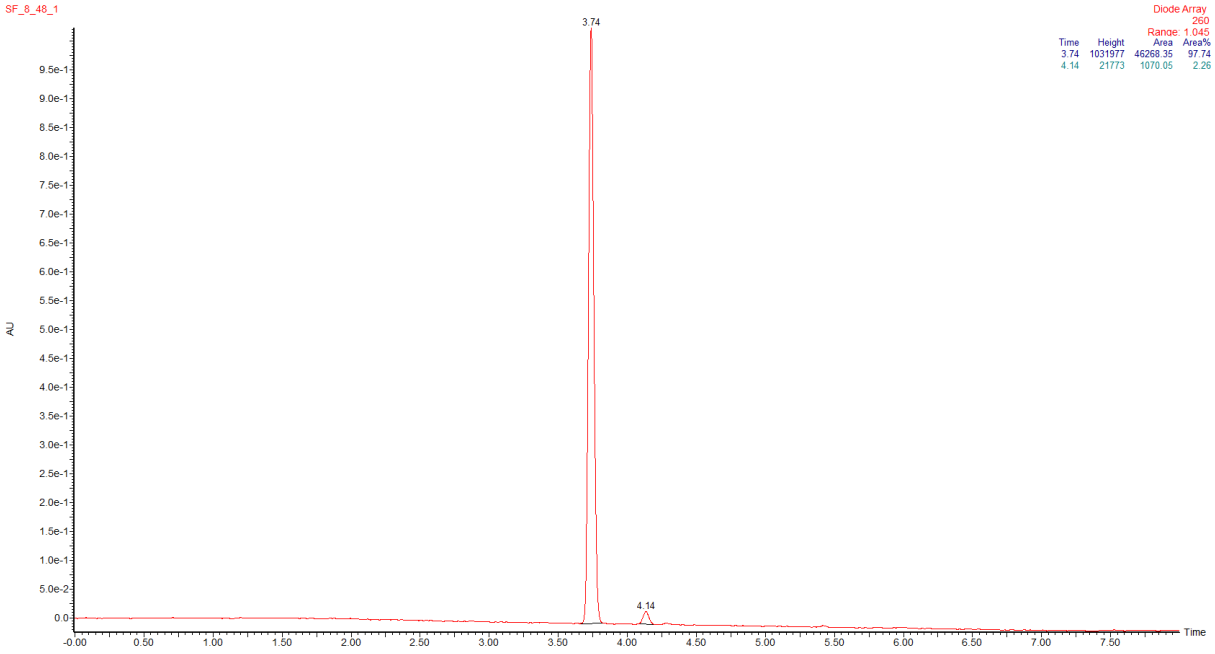
(*S*)-2-(1-(3-fluorophenyl)-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenylpropanamide (3i)



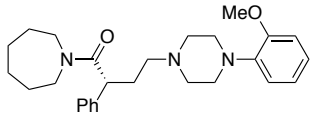
Racemic (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



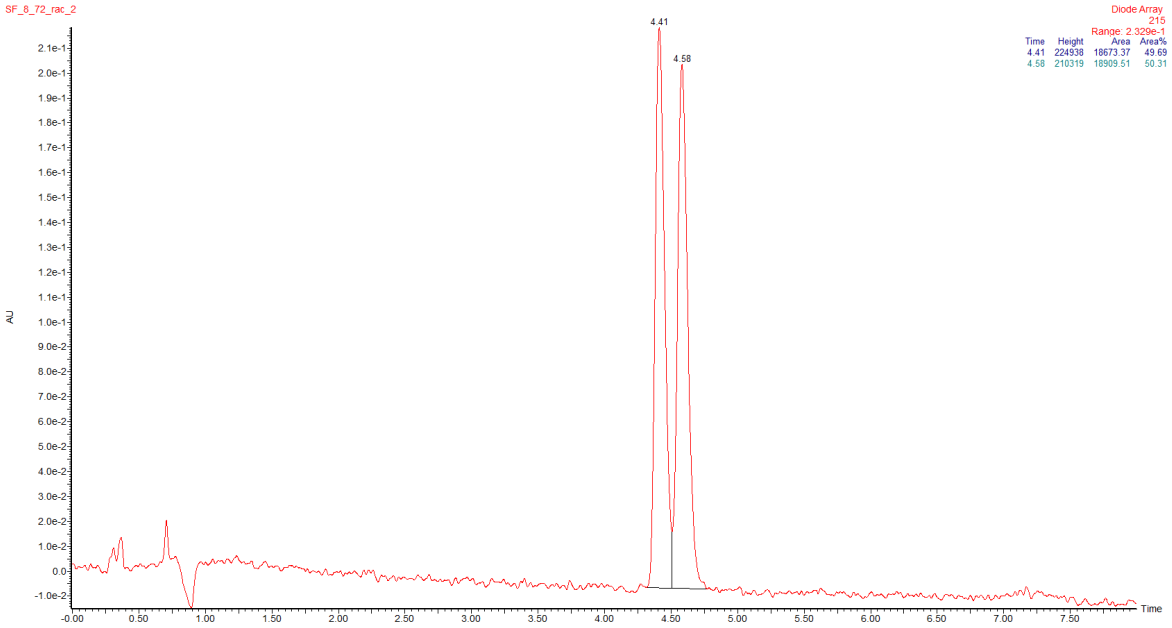
Enantioenriched (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



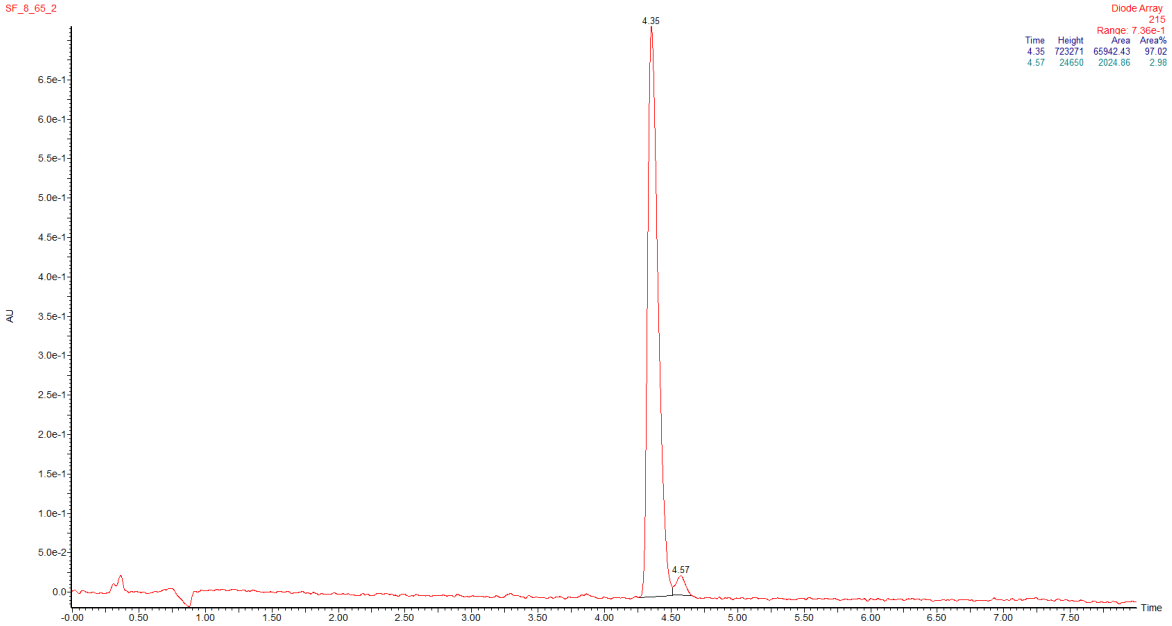
(*R*)-RWAY (3j)



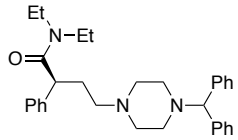
Racemic (CEL-1, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



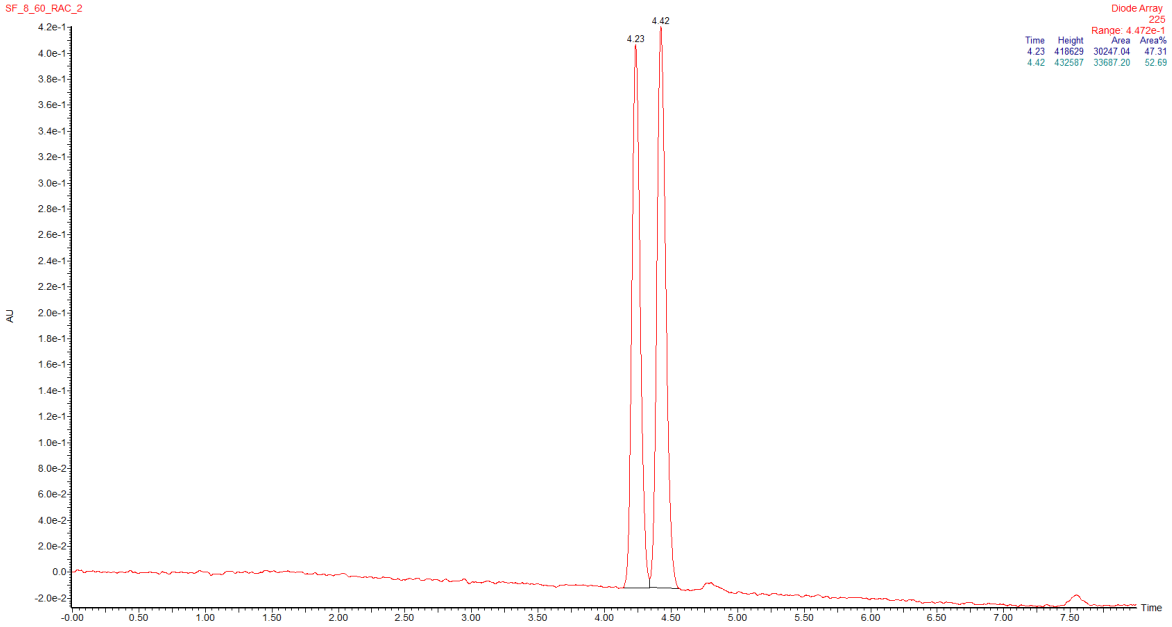
Enantioenriched (CEL-1, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



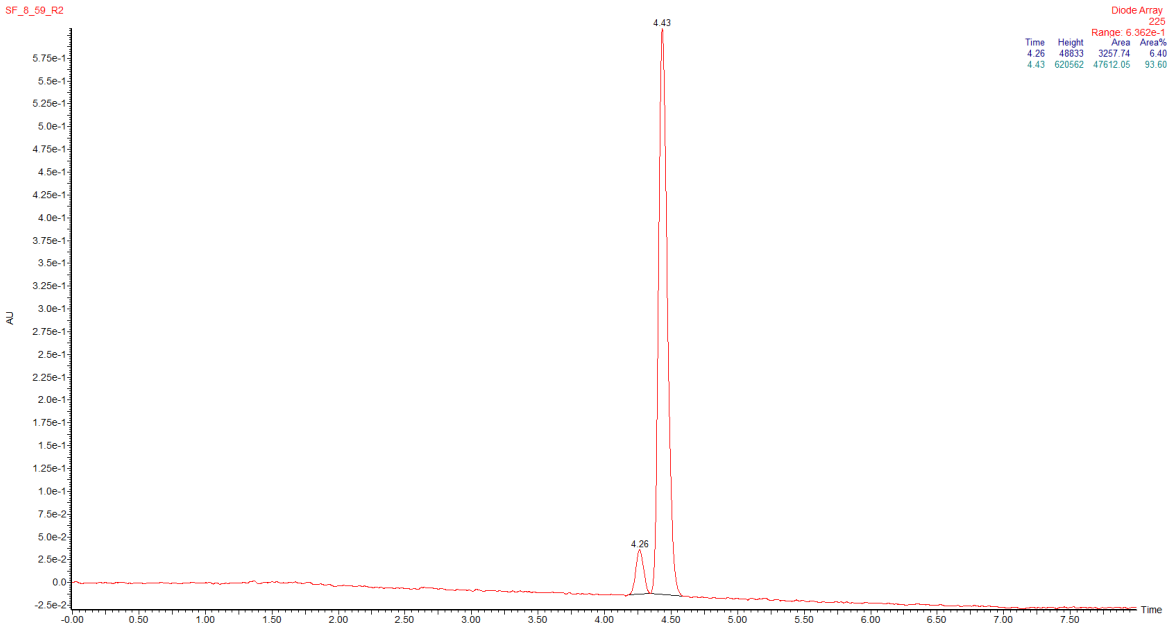
(*S*)-4-(4-benzhydrylpiperazin-1-yl)-*N*,*N*-diethyl-2-phenylbutanamide (3k)



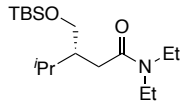
Racemic (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



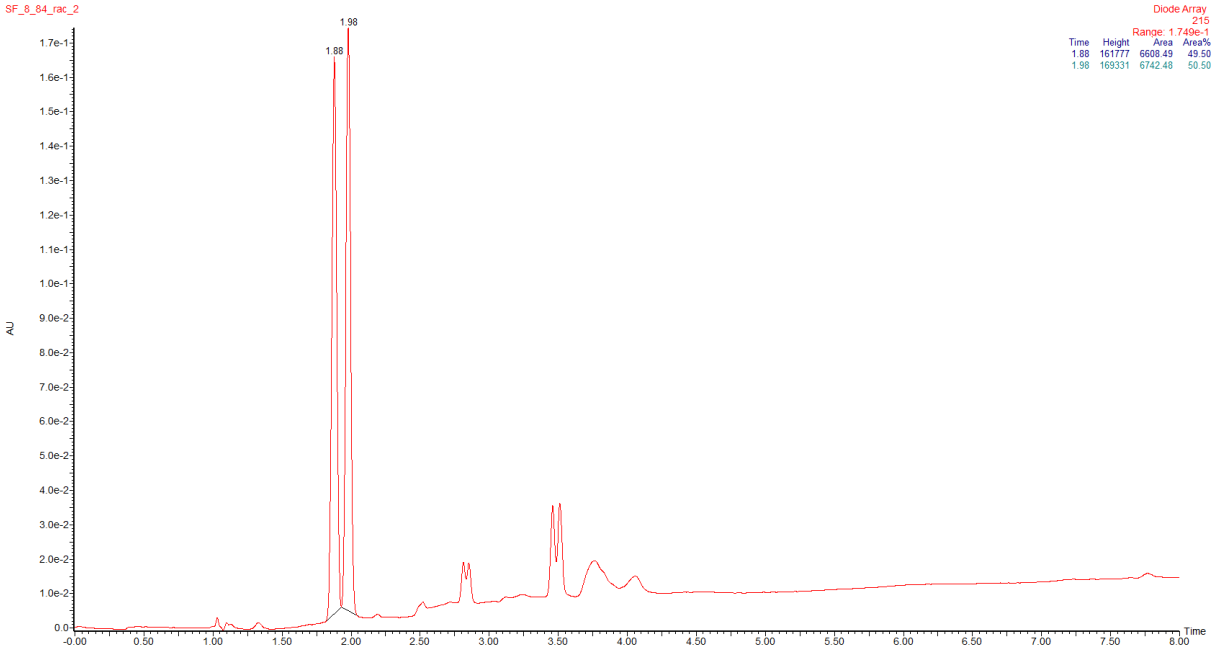
Enantioenriched (OJ-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



(*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-4-methylpentanamide (3l)

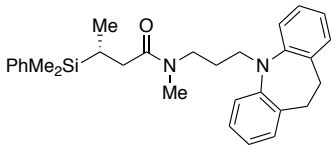


Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

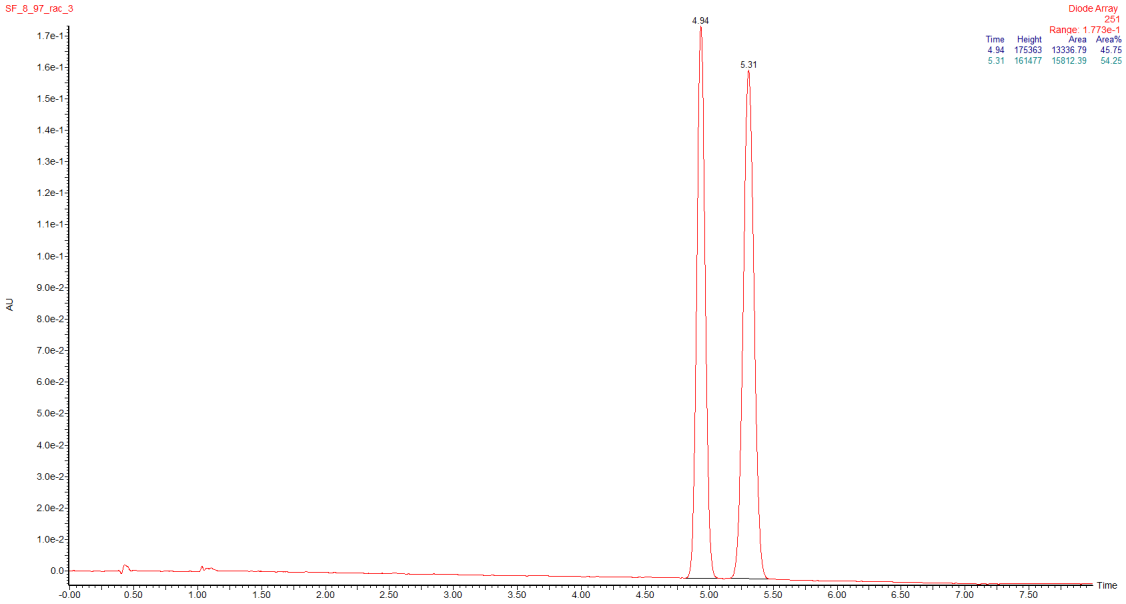


Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):

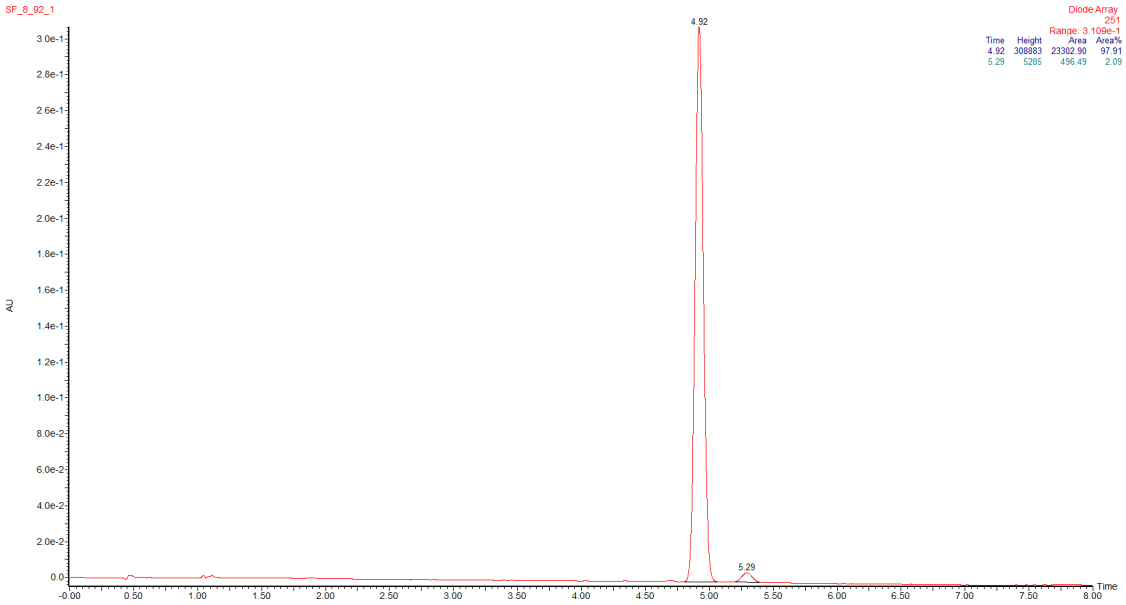
(*R*)-*N*-(3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)-3-(dimethyl(phenyl)silyl)-*N*-methylbutanamide (3m)



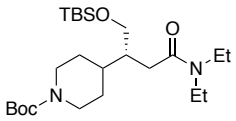
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



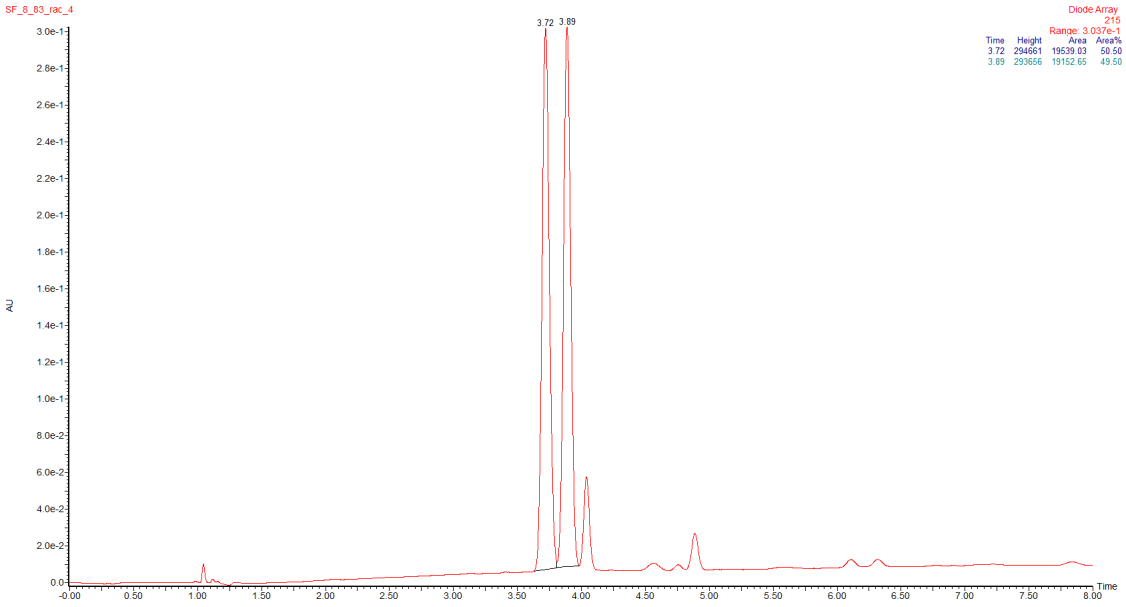
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



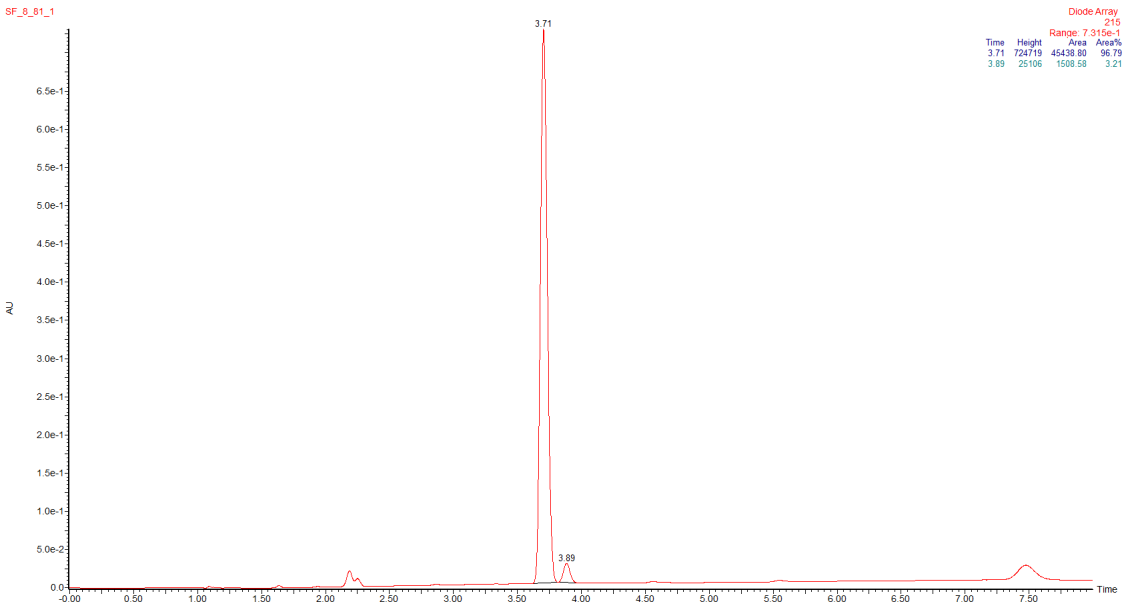
tert-butyl (_R_)-4-(1-((_tert_-butyldimethylsilyl)oxy)-4-(diethylamino)-4-oxobutan-2-yl)piperidine-1-carboxylate (3n)



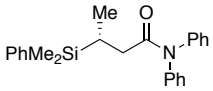
Racemic (OD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



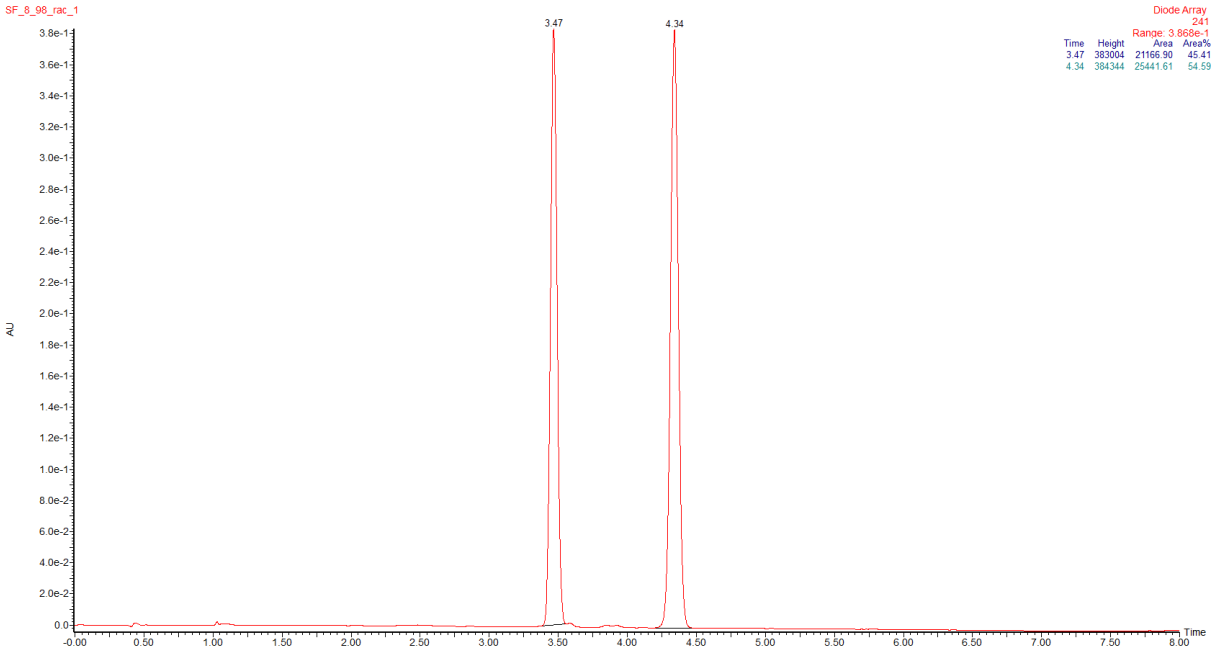
Enantioenriched (OD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



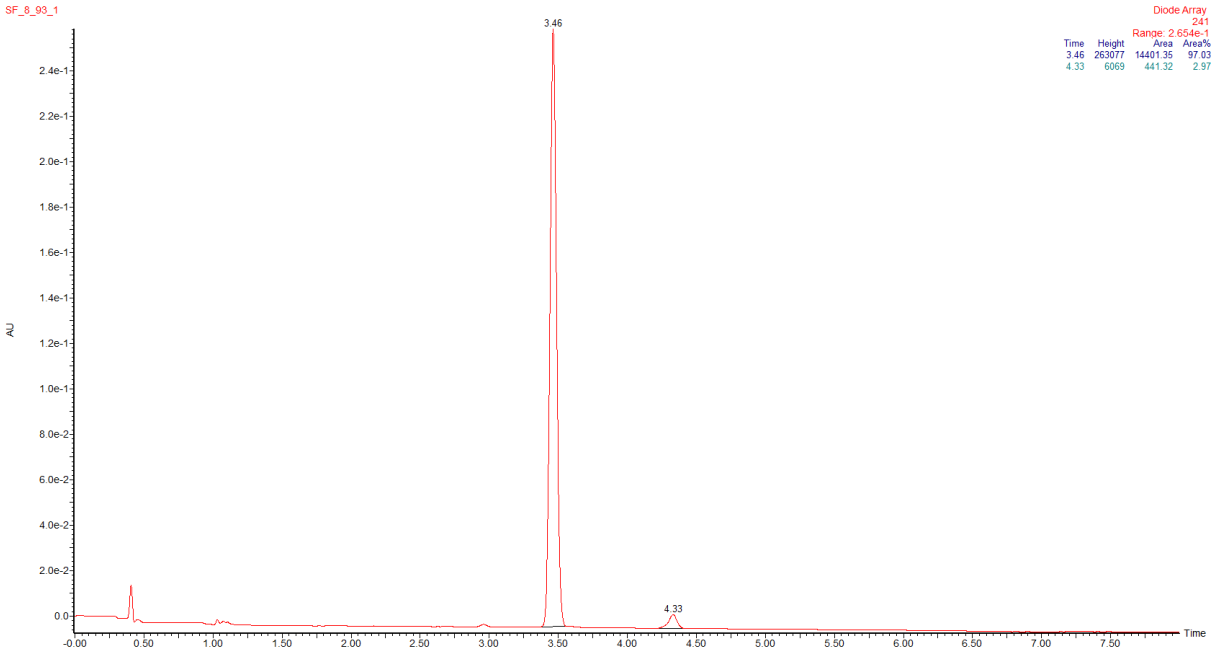
(*R*)-3-(dimethyl(phenyl)silyl)-*N*,*N*-diphenylbutanamide (3o)



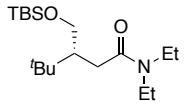
Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



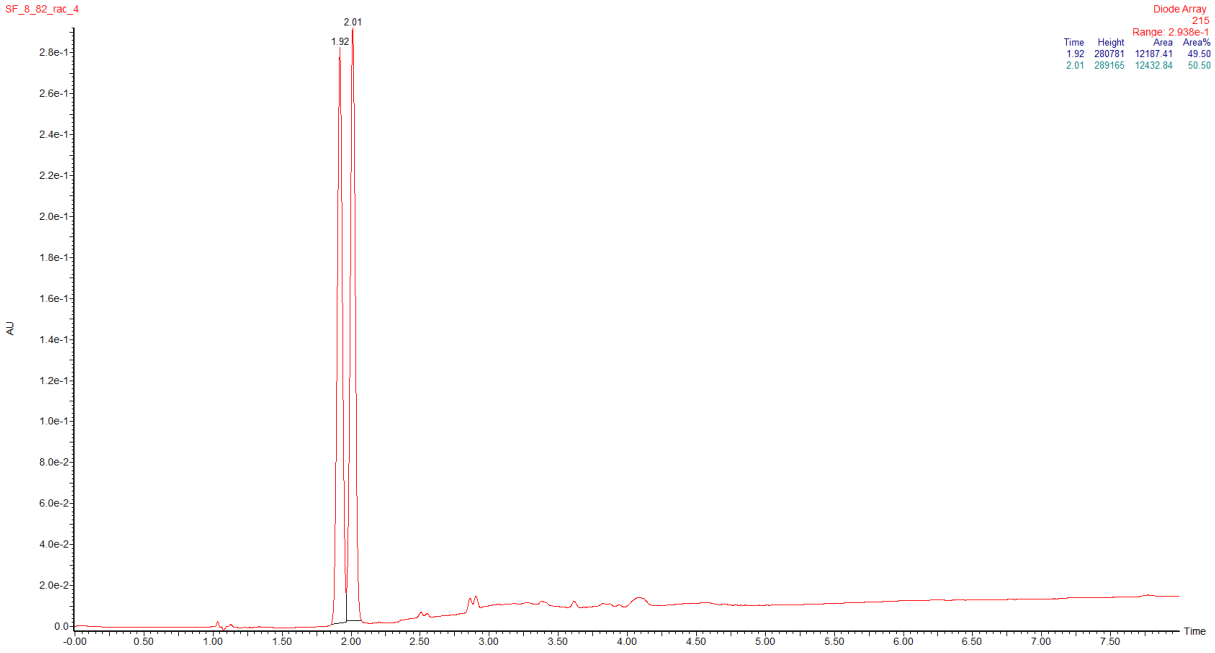
Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



(*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-4,4-dimethylpentanamide (3p)



Racemic (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):



Enantioenriched (AD-H, Chiralpak®, 4.6 x 250 mm, 5 μM particle size):