Transition-Metal and Brønsted Acid co-Catalysed Tandem Transformations

Dissertation

der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard Karls Universität Tübingen
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)

vorgelegt von
M. Sc. Prasad Mahesh Kathe
aus Mumbai/Indien

Tübingen
2021

Gedruckt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Eberhard Karls Universität Tübingen.

Tag der mündlichen Qualifikation:	31.03.2021
Stellvertretender Dekan:	Prof. Dr. József Fortágh
1. Berichterstatter:	Jun.-Prof. Dr. Ivana Fleischer
2. Berichterstatter:	Prof. Dr. Thomas Ziegler

Transition-Metal and Brønsted Acid co-Catalysed Tandem Transformations

Prasad Mahesh Kathe

Printed and published with the support of the German Academic Exchange Service (DAAD)

I. Preface

The following cumulative thesis comprises mainly three projects based on olefin isomerization and concomitant functionalization. An introduction describing the state of the art in tandem catalytic processes, a summary of both published and unpublished results and published scientific articles along-with the respective supporting information have been included.

This work has been carried out at the Institute of Organic Chemistry of Eberhard Karls Universität Tübingen, Germany, in the period from October 2017 to November 2020 under the supervision of Prof. Dr. Ivana Fleischer. The German Academic Exchange Service (DAAD) has funded the doctoral stay.

II. Acknowledgements:

At the very beginning, I would like to thank my advisor Prof. Ivana Fleischer. Thank you for your valuable insights, patience and most importantly, for your relentless efforts in helping me tackle problems that I encountered both inside and outside the lab. You fostered an invigorating atmosphere in the research group built on trust and high levels of scientific integrity. Also, I will be forever indebted to you for the opportunity to be the co-'wordsmith' for our Perspective article. I consider myself lucky to have regularly been given opportunities to attend several scientific events, even in the early stages of my doctoral studies.

Dr. Paul Gehrtz: Thanks for introducing me to the chemistry of unique odours. Moreover, I would like to thank you for proof-reading and critically assessing my first manuscript (and this thesis!). You incited me to challenge my own assumptions and address potential confirmation bias. You also gave me an interesting glimpse into the German culture through uncanny examples. Finally, thanks for giving me the opportunity to contribute and present some results on nickel catalysis in Konstanz! There is no doubt in my mind that you will perform exceedingly well at Merck!

M.Sc Tanno Schmidt: You have been an inspiration mainly owing to your unreal (almost insane) work-ethic, discipline, and an innate ability to pay attention to details. I learned a great deal about the chemistry of dtbpx from the impressively large body of data that you managed to generate in a short period of time. Thanks for letting me contribute a tiny bit to the chemistry you developed.

M.Sc Valentin Geiger/M.Sc Regina Oechsner: Firstly, a big thank you for all the cool scientific/non-scientific discussions and for putting up with my 'different' sense of humour at times. Valentin, thanks for reminding me the importance of not losing touch with basic OrgChem (especially when it comes to quenching deadly carcinogens!). Regina, thanks for reminding me that inorganic synthesis can be fun as well and that there is always an opportunity to avoid column chromatography! Thank you both for the consistent and timely maintenance of laboratory equipment!

I would like to thank other current/past members of the research group. Alexandru Caciuleanu (thanks a lot for the heterocycles collab, for tolerating Borat level humor and for teaching me basic Romanian), Anne Haupt, Johannes Walz, Dr. Marlene Böldl, Dr. Vera Hirschbeck.

To my family and friends back home and in the States: Firstly, thank you mom and dad for the sacrifices you made and for the constant support and encouragement that you provided. I would

not have been able to step out of my comfort zone otherwise. I would like to thank my cousins for their timely advice and helpful conversations. Lastly, a big thank you to all my friends and former classmates (Ruia/ICT) back home. The skype calls that went on for hours were refreshing and often helped me unwind after a stressful week. Special thanks to Sayali, Harshad and Sanika. Thank you for hearing me out and helping me maintain my sanity in these long and arduous years abroad.

III. Summary

Transition metal catalyzed remote functionalization provides unique entry to generate molecular complexity. Exploiting transition metal hydrides as highly reactive catalytic intermediates in olefin isomerization has enabled functionalization at an inert reaction site. While tandem catalytic processes have significantly contributed to the synthetic arsenal, developing new reactivity for C-heteroatom bond formation, and employing non-precious transition metals has a great potential to expand this research domain.

Compounds possessing the C-S bond have demonstrably found several applications not only in the agrochemical and pharmaceutical industry, but also as bioconjugates. The first project of the doctoral thesis established a palladium catalyzed tandem process for synthesizing benzylic thioethers from allylarenes and thiols. The methodology comprising the isomerization of a terminal double bond and subsequent hydrothiolation was based on the *in situ* generation of a palladium hydride intermediate in presence of a Brønsted acid. The optimized catalyst system includes palladium acetate, 1,2-bis[(di-*tert*-butyl)phosphinomethyl]benzene and triflic acid. Preliminary mechanistic studies included NMR, MS analysis as well as a study of reaction kinetics and deuteration experiments. These investigations helped probe the nature of intermediates in the catalytic cycle. The substrate scope was examined under the optimized reaction conditions. Moreover, a remote functionalization was accomplished by switching the catalyst precursor to bis(benzonitrile)palladium(II)chloride.

The construction of indole fused ring systems is a synthetically valuable endeavour. Thus, efforts have been directed to using modern synthetic tools such as organocatalysis and cooperative catalysis in development of efficient transformations. In the past decade, research in transition metal catalyzed oxa-Pictet-Spengler cyclization has gained momentum. The methodology exploits the strategically placed heterocyclic tether as a nucleophile to attack an oxacarbenium ion generated by the transition metal and Brønsted acid. The aim of the second project was to devise alternative catalytic method relying on non-precious transition metal catalyst. $Ni[P(OMe)_3]_4H^+$ was one of the first nickel hydrides studied in isomerization chemistry. Interestingly, the synthetic utility of tetrakistrialkylphosphine nickel hydrides was never investigated other than in activating small molecules like H_2. Hence, a synthetic methodology that uses a simple nickel hydride was developed for the synthesis of oxacyclic scaffolds. After screening a few nickel catalysts, $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ was chosen owing to its high activity at a catalyst loading of 1 mol%. Triflic acid was used as the Brønsted acid for oxacarbenium ion generation and subsequent cyclization. The catalytic experiments for oxa-Pictet-Spengler cyclization were accomplished with

turnover numbers of as high as 1198 h^{-1}. A catalyst loading of 0.075 mol% at a preparative scale highlights the robustness of the catalytic system. The scope of the substrates could be extended to synthesize cyclic hemiaminals. Moreover, the catalyst enabled selective single bond migration of olefins and rapid conjugative migration of allyl arenes.

The goal of the final project was to explore the reactivity of $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ in an olefin isomerization/hydrolysis sequence in the deprotection of for allylethers. The complex $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ can serve as a potential replacement for classical precious metal based catalytic systems such as $Pd(PPh_3)_4$/barbituric acid. Similar to the previous project, a sequential addition of the nickel catalyst and Brønsted acid was necessary to perform the deprotection. Stoichiometric amount of p-toluenesulfonic acid was used along-with the nickel catalyst. Several functional groups including pinacol-borane and sulfone were tolerated. Moreover, the presence of heterocyclic rings such as oxazoles did not hinder the deprotection. Furthermore, deallylation of *N*-allylamides was also possible. Preliminary studies were conducted to demonstrate orthogonality in deprotection by employing benzyl and TBDPS protecting groups.

The aforementioned synthetic transformations featuring metal-hydride based olefin isomerization form a central part of this doctoral thesis. A more detailed summary and publications are presented in chapter 1, 2, 3 and 4 of this thesis respectively.

IV. Zusammenfassung

Übergangsmetall-katalysierte Fernfunktionalisierung bietet eine einzigartige Möglichkeit die molekulare Komplexität zu generieren. Die Verwendung von Übergangsmetallhydriden als hochreaktiven katalytischen Zwischenstufen in der Olefinisomerisierung ermöglicht die Funktionalisierung an einer inerten Reaktionsstelle in sogenannten Tandemreaktionen. Obwohl bereits zahlreiche Transformationen und Katalysatoren entwickelt worden sind, gibt es auf diesem Gebiet ein großes Potenzial, diesen Forschungsbereich zu erweitern, zum Beispiel durch die Entwicklung neuer Methoden für die C-Heteroatom-Bindungsknüpfung oder durch die Verwendung von Nichtedelmetallen als Katalysatoren.

Schwefelhaltige Verbindungen haben viele Anwendungen nicht nur in der agrochemischen und pharmazeutischen Industrie gefunden, sondern auch als Biokonjugate. Das erste Projekt im Rahmen der Doktorabeit etablierte eine Palladium-katalysierte Tandemreaktion zur Synthese benzylischer Thioether aus Allylaromaten und Thiolen. Die angewandte Methode, die die Isomerisierung der terminalen Doppelbindung mit einer Hydrothiolierung kombinierte, basierte auf der *in situ* Erzeugung eines Palladiumhydridkomplexes in der Gegenwart einer Brønsted Säure. Das optimierte Katalysatorsystem beinhaltete Palladiumacetat, 1,2-Bis[(di-*tert*-butyl)phosphinomethyl]benzol und Trifluormethansulfonsäure. Vorläufige mechanistische Studien umfassten NMR- und MS-Analyse, sowie eine Reaktionskinetikuntersuchung und Deuterierungsexperimente. Diese Studien halfen, die Zwischenprodukte im katalytischen Zyklus zu untersuchen. Die Substratbandbreite wurde unter den optimierten Reaktionsbedingungen untersucht. Darüber hinaus konnte eine Fernfunktionalisierung durch den Einsatz von Bis(benzonitril)palladium(II)chlorid als Katalysatorvorläufer erreicht werden.

Der Aufbau von Indol-fusionierten Ringsystemen stellt ein synthetisch wertvolles Unterfangen dar. So wurden moderne synthetische Werkzeuge wie Organokatalyse oder kooperative Katalyse wurde bei der Entwicklung neuer Transformationen zur deren Synthese eingesetzt. Ein Beispiel für eine effiziente Methode ist die Übergangsmetall-katalysierte Oxa-Pictet-Spengler Cyclisierung, die in den letzten zehn Jahren erforscht wurde. Sie nutzt einen strategisch platzierten heterozyklischen Teil des Moleküls als Nucleophil, um ein Oxacarbeniumion, welches durch das Übergangsmetall und die Brønsted Säure generiert wurde, intramolekular anzugreifen. Das Ziel des zweiten Projekts war es, alternative katalytische Verfahren zu entwickeln, die auf Nichtedelmetallkatalysatoren basieren. Einer der ersten Nickelhydride, die in der Isomerisierungschemie untersucht wurden, war $Ni[P(OMe)_3]_4H^+$. Interessanterweise wurde der synthetische Nutzen von Tetrakistrialkylphosphin-Nickelhydriden nie untersucht, außer bei der Aktivierung kleiner Moleküle wie H_2. Daher wurde im Rahmen dieser Doktorarbeit eine Methode

zur Synthese fusionierter Ringsysteme entwickelt, die Nickelhydrid verwendet und die Isomerisierung von Allylethern, Protonierung und Reaktion mit einem Nukleophil kombiniert. Nach dem Screening einiger Nickelkatalysatoren wurde $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ aufgrund seiner hohen Aktivität bei einer Katalysatorladung von 1 mol% ausgewählt. Trifluormethansulfonsäure wurde als Brønsted Säure für die Erzeugung der Oxacarbeniumionen und die anschließende Cyclisierung gewählt. In den katalytischen Experimenten zur Oxa-Pictet-Spengler Cyclisierung wurden Umsatzfrequenzen von bis zu 1198 h^{-1} erreicht. Die verwendete Katalysatorbelastung von nur 0,075 mol% im größeren präparativen Massstab unterstreicht die Robustheit des Katalysatorsystems. Die Bandbreite der Substrate konnte auf die Synthese zyklischer Hemiaminale erweitert werden. Darüber hinaus wurde gezeigt, dass sich der Katalysator für selektive Doppelbindungsmigrationen um eine Position und die schnelle konjugative Migration von Allylarenen eignet.

Das Ziel des letzten Projekts war es, die Reaktivität von $[Ni(PMe_3)_4H](SO_2CF_3)_2N$ in der Entschützung von Allylethern basierend auf der sequenziellen Olefinisomerisierung und Hydrolyse zu erforschen. Dabei kann $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ als möglicher Ersatz für etablierte Edelmetall-basierte katalytische Systeme wie $Pd(PPh_3)_4$/Barbitursäure dienen. Ähnlich wie beim vorherigen Projekt war eine sequenzielle Zugabe des Nickelkatalysators und der Brønsted Säure erforderlich, um die Deallylierung durchzuführen. Stöichiometrische Menge an p-Toluolsulfonsäure wurde zusammen mit dem Nickelkatalysator verwendet. Mehrere funktionelle Gruppen, darunter Pinacolboran oder Sulfon wurden toleriert. Auch die Anwesenheit von heterozyklischen Ringen wie Oxazolen behinderte die Entschützung nicht. Darüber hinaus war auch eine Deallylierung von *N*-Allylamiden möglich. Die ersten Studien zur Demonstration der Orthogonalität durch den Einsatz von Benzyl- und TBDPS-Schutzgruppen wurden durchgeführt.
Die oben aufgelisteten synthetischen Transformationen, die auf der Metallhydrid-katalysierten Olefinisomerisierung basieren, bilden d zentralen Teil dieser Doktorarbeit. Eine ausführlichere Zusammenfassung und Veröffentlichungen sind in Kapiteln 1, 2,3 and 4 dargestellt.

V. Publications

Publications incorporated into this thesis

Paper I: Palladium-Catalyzed Tandem Isomerization/Hydrothiolation of Allylarenes.
P. M. Kathe, I. Fleischer
Org. Lett. **2019**, *21*, 2213-2217
https://pubs.acs.org/doi/10.1021/acs.orglett.9b00504

Paper II: Tandem Olefin Isomerization/Cyclization catalyzed by Complex Nickel Hydride and Brønsted acid
P. M. Kathe, A. Caciuleanu, A. Berkefeld, I. Fleischer
J. Org. Chem. **2020**, *85*, 15183-15196
https://pubs.acs.org/doi/10.1021/acs.joc.0c02033

Paper III: Nickel Hydride-Catalyzed Cleavage of Allyl Ethers Induced by Isomerization
P. M. Kathe, A. Berkefeld, I. Fleischer
Synlett. 2021 DOI: 10.1055/s-0040-1706683

Publications with minor contributions:

Paper IV: Nickel-Catalyzed Coupling of Arylzinc Halides with Thioesters
P. Gehrtz, P. Kathe, I. Fleischer
Chem. Eur. J. **2018**, *24*, 8774 –8778.
https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/chem.201801887

Paper V: Tandem Acid/Pd-Catalyzed Reductive Rearrangement of Glycol Derivatives
T. Schmidt, B. Ciszek, P. Kathe, I. Fleischer
Chem. Eur. J. **2020**, *26*, 3641 –3646.
https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/chem.202000251

Poster Presentations:

Poster I: Nickel hydride/Brønsted acid co-Catalyzed synthesis of Oxacyclic scaffolds
P. M. Kathe, A. Caciuleanu, A. Berkefeld, I. Fleischer
53. Jahrestreffen Deutscher Katalytiker, Weimar 2020 (Cancelled due to COVID-19)

Poster II: Palladium catalyzed tandem isomerization/hydrothiolation of Allyl arenes

P. M. Kathe, I. Fleischer
European Symposium on Organic Chemistry, Vienna 2019

Poster III: Palladium catalyzed tandem isomerization/hydrothiolation of Allyl arenes
P. M. Kathe, I. Fleischer
Hochschule trifft Industrie, Darmstadt 2019

Poster IV: Palladium Catalyzed Tandem Isomerization/Hydrothiolation of Allyl Arenes
P. M. Kathe, I. Fleischer
ORCHEM: Lecture Conference of the German Chemical Society (GDCh), Berlin **2018**

Poster V: Insights into the Nickel Catalyzed Fukuyama Cross-coupling Reaction
P. M. Kathe, P. Gehrtz, I. Fleischer
Jung Chemiker Forum: Frühjahrssymposium, Konstanz **2018**

VI. Abstract

Transition metal catalysed tandem transformations based on double-bond migration have enabled distal functionalization by merging multiple reaction steps. This methodology stands out as a step-economical approach in rapidly assembling molecular complexity. In the presented doctoral thesis, it provided an impetus not only to discover new tandem transformations but also to develop non-precious transition metal-based alternatives for existing transformations.

The project comprises three parts. First, the reactivity of palladium hydride complex in a novel C-S bond formation methodology was explored. Branched benzylic thioethers were synthesized from corresponding allyl arenes in a double bond migration/hydrothiolation sequence. This was accompanied by reaction kinetics, isotope labelling and NMR investigation. Also, a remote C-S bond formation strategy was disclosed for the first time.

In the second part, a structurally simple nickel-hydride was used along with a Brønsted acid to append a pyran ring onto heterocyclic scaffolds. The driving force behind this transformation is the generation of ‘inium’-cation by the synergistic action of a metal-hydride and Brønsted acid. Several classes of heterocycles such as tetrahydropyran-indoles, oxazine-indoles, isochromans and cyclic hemiaminals could be targeted. The double bond migration/cyclization could be carried out with catalyst loading as low as 0.075 mol%.

Finally, to further explore the synthetic potential of nickel-hydride, a strategy for O-allyl deprotection was developed. Several O-allylated phenols with varying electronic bias as well as O-allylated aliphatic alcohols and amides displayed compatibility with the optimized reaction conditions.

VII. Abstract (German)

Übergangsmetall-katalysierte Tandemtransformationen, die auf der Migration einer Doppelbindung basieren, ermöglichen die distale Funktionalisierung durch die Kombination mehrerer Reaktionsschritte. Diese Methodik zeichnet sich durch einen schrittsparenden Ansatz zum schnellen Aufbau der molekularen Komplexität aus. Das Ziel dieser Doktorarbeit war nicht nur die Entwicklung neuer Tandemtransformationen, sondern auch die Etablierung günstigerer Alternativen zu Übergangsmetall-basierten Katalysatoren für bekannte Transformationen.

Das Projekt besteht aus drei Teilen. Zunächst wurde die Reaktivität eines Palladiumhydridkomplexes in einer neuartigen Methode zur C-S-Bindungknüpfung untersucht. Verzweigte Benzylthioether wurden aus entsprechenden Allylarenen in einer Sequenz bestehend aus Doppelbindungsmigration und Hydrothiolierung synthetisiert. Diese Transformation wurde mittels Reaktionskinetik, Isotopenmarkierung und NMR untersucht. Außerdem wurde zum ersten Mal eine Strategie zur Bildung entfernter C-S-Bindungen entwickelt.

Im zweiten Teil wurde ein strukturell einfaches komplexes Nickelhydrid zusammen mit einer Brønsted Säure verwendet, um einen Pyranring an heterocyclische Gerüste anzubringen. Die treibende Kraft hinter dieser Cyclisierung ist die Erzeugung von ‚Inium'-Kationen durch die synergistische Wirkung des Metallhydrids und der Brønsted Säure. Verschiedene Klassen von Heterocyclen wie Tetrahydropyran-Indol, Oxazin-Indol, Isochroman und cyclische Hemi-Aminale wurden synthetisiert. Die Isomerisierung/Cyclisierung konnte mit einer Katalysatorladung von nur 0,075 mol-% durchgeführt werden.

Um das Synthesepotential des Nickelhydrids weiter zu untersuchen, wurde schließlich eine Strategie zur Entschützung von Allylethern entwickelt. Mehrere O-allylierte Phenole mit unterschiedlichen elektronischen Eigenschaften, sowie O-allylierte aliphatische Alkohole und Amide zeigten Kompatibilität mit den optimierten Reaktionsbedingungen.

VIII. Personal Contribution

Paper I:

I designed the experiments and optimized the reaction conditions for the catalysis. Also, I synthesized the substrates, performed the catalytic reactions, and collected analytical data for the supporting information of the manuscript. The analytical data includes the one obtained from $^{1}H/^{2}D/^{19}F/^{13}C$ NMR spectroscopy. Furthermore, I compiled the results and drafted the manuscript.
The HRMS analysis was performed by the analytical department of the University of Tübingen.

Paper II:

The catalysts $[Ni(PMe_3)_4H](SO_2CF_3)_2$, $Ni(PMe_3)_4$, $Ni(PPh_3)_4$, were provided by Dr. Andreas Berkefeld. Using the provided catalysts, I designed the experiments and optimized the reaction conditions for the catalysis. Alexandru Caciuleanu and I synthesized the substrates. I performed the catalytic reactions and collected analytical data for the supporting information of the manuscript. The analytical data includes the one obtained from $^{1}H/^{19}F/^{13}C$ NMR spectroscopy. I compiled the results and drafted the manuscript.
The HRMS analysis was performed by the analytical department of the University of Tübingen.

Paper III:

The catalysts $[Ni(PMe_3)_4H](SO_2CF_3)_2$, $Ni(PMe_3)_4$, $Ni(PPh_3)_4$, were provided by Dr. Andreas Berkefeld. Using the provided catalysts, I optimized the reaction conditions for the catalysis, synthesized the substrates, performed the catalytic reactions, and collected analytical data for the supporting information of the manuscript. The analytical data includes the one obtained from $^{1}H/^{19}F/^{13}C$ NMR spectroscopy. I compiled the results and drafted the manuscript.
The HRMS analysis was performed by the analytical department of the University of Tübingen.

IX. Objective

The aim of the doctoral study is the development of synthetic methodologies for tandem catalysis involving double isomerization using transition metal hydrides and Brønsted acids.

Chapter 1 includes a detailed account on the state of art in transition metal catalyzed olefin isomerization, remote functionalization processes. A short summary of the use of deuteration experiments in remote functionalization has been provided

Chapter 2 includes the summary of the main results as excerpts taken from the following publications

- Palladium Catalyzed Tandem Isomerization/Hydrothiolation of Allyl Arenes.
- Tandem Olefin Isomerization/Cyclization Catalyzed by Complex Nickel Hydride and Brønsted Acid
- Nickel hydride Catalysed Deallylation Induced by Olefin Isomerization

Chapter 3 summarizes unpublished results of this doctoral study

Chapter 4 is a compilation of published articles

Table of Contents

Dedicated To

My Grandfather,

Nilkanth Ganpat Warik

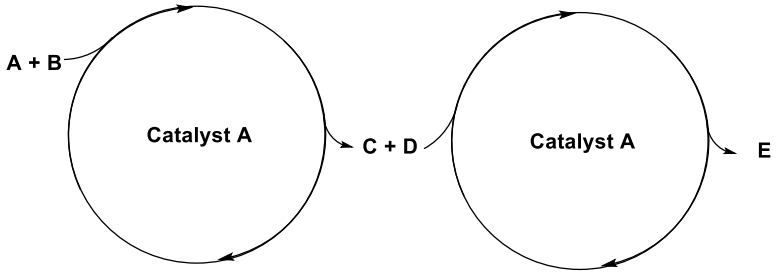
CHAPTER 1

INTRODUCTION

1 Introduction

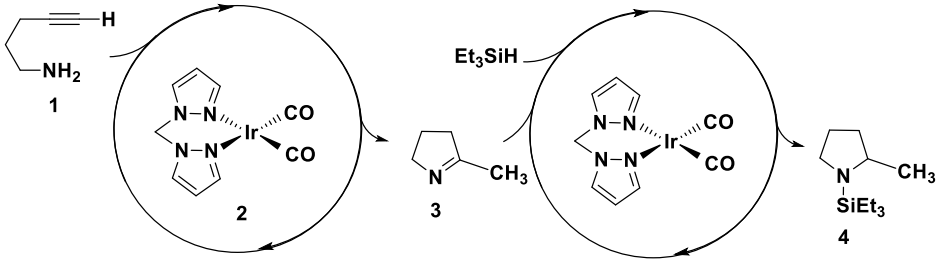
1.1 Concurrent Tandem Catalysis

The concept of sequential metal catalysis was conceived through the diligent design of polymer-supported enzymatic and homogeneous catalysts.[1] Such catalytic approaches derive their inspiration from nature that is a playground for a complex array of biochemical pathways acting in sequence.[2] Nature has the ability to merge several processes through the action of enzymes and co-factors. In the 1970s, Mosbach laid the foundation for sequential catalytic processes in which the product of the first reaction acted as the substrate for the next reaction.[3] Hexokinase and glucose isomerase were immobilized on polystyrene, which catalyzed phosphorylation of glucose to give glucose-1-phosphate, followed by glucose 1,6-diphosphate. This spurred the growth of sequential processes.



Scheme 1.1: Simplified representation of tandem catalysis process involving single catalyst[4]

One of the earliest of them being the cycloisomerization/hydroformylation sequence of 1,4-butadiene towards the synthesis of cyclohexene propanal derivatives.[1] Some of the most common tandem catalytic processes employ the same catalyst for merging two transformations as shown in Scheme 1.1. At the beginning, the emphasis on developing a tandem process relied on a suitable 'template'. Especially in the case of radical cyclizations for synthesis of fused carbocycles.[5] An example of a strategically placed tether is the iridium catalyzed tandem hydroamination/reductive silylation of alkynylamine derivatives to give a disubstituted pyrrolidine (Scheme 1.2).[6a, 6b]

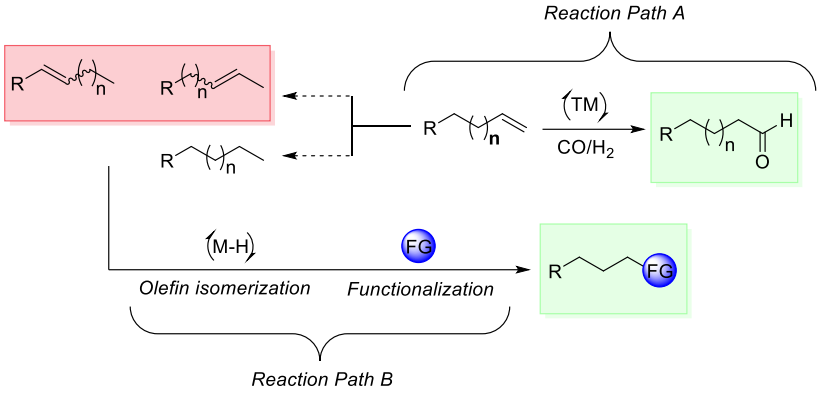


Scheme 1.2: Iridium catalyzed tandem hydroamination/silylation[6b]

Tandem approaches based on strategically placed unsaturated side-chains are atom-economical, a term (atom-economy) coined in the late 1990s by Trost.[7] Another example is the ene-yne cycloisomerization cascade catalyzed by palladium.[8] Interestingly, this was one of the first examples of a cascade process wherein the catalytic cycle of palladium did not initiate with the classical oxidative addition pathway, but rather through the formation of palladium hydride species generated in the presence of acetic acid. Initial carbopalladation of the palladium triggered the ene-yne cascade.[9] The exponential rise of catalytic tandem processes necessitated a systematic classification. A review by Baker and co-workers has described the classification of 'concurrent tandem catalysis' cycles based on the number of catalysts involved and the number of reaction steps.[4]

Alongside the development of cross-coupling chemistry, efforts were directed to optimizing industrially relevant homogeneous catalytic processes such as hydroformylation and hydrogenation in terms of catalyst/ligand design. Catalytic hydroformylation, a process for producing aldehydes carried out annually at > 10^7 ton scale is accompanied by a number of side reactions such as olefin hydrogenation, phosphine degradation and olefin isomerization. The catalyst systems in the case of hydroformylation are normally $[HM(CO)_xL_y]$ that is, metal carbonyl hydrides. Hydrogenation and isomerization occur due to the presence of catalytically active metal hydride species.[10a, 10b] Suppressing these side reactions entails not only ligand design but also shifting the equilibrium and development of a thermodynamically feasible termination step for regeneration of the catalyst.

Transition-metal hydrides, formally represented as organometallic species possessing a metal-hydrogen bond are the catalytic intermediates responsible for olefin isomerization. Initially regarded as a side reaction responsible for yield depletion in hydroformylation, exploiting the transposition and follow-up functionalization of double bonds as a tandem process has garnered increasing attention (Scheme 1.3). One of the most intensely studied processes is the isomerization/hydroformylation sequence.[11] The isolation and purification of thermodynamically unstable intermediates in homogeneous catalytic processes that are conducted at a large scale is normally avoided. Apart from ensuring high atom-economy, a reduction in process cost is desirable.

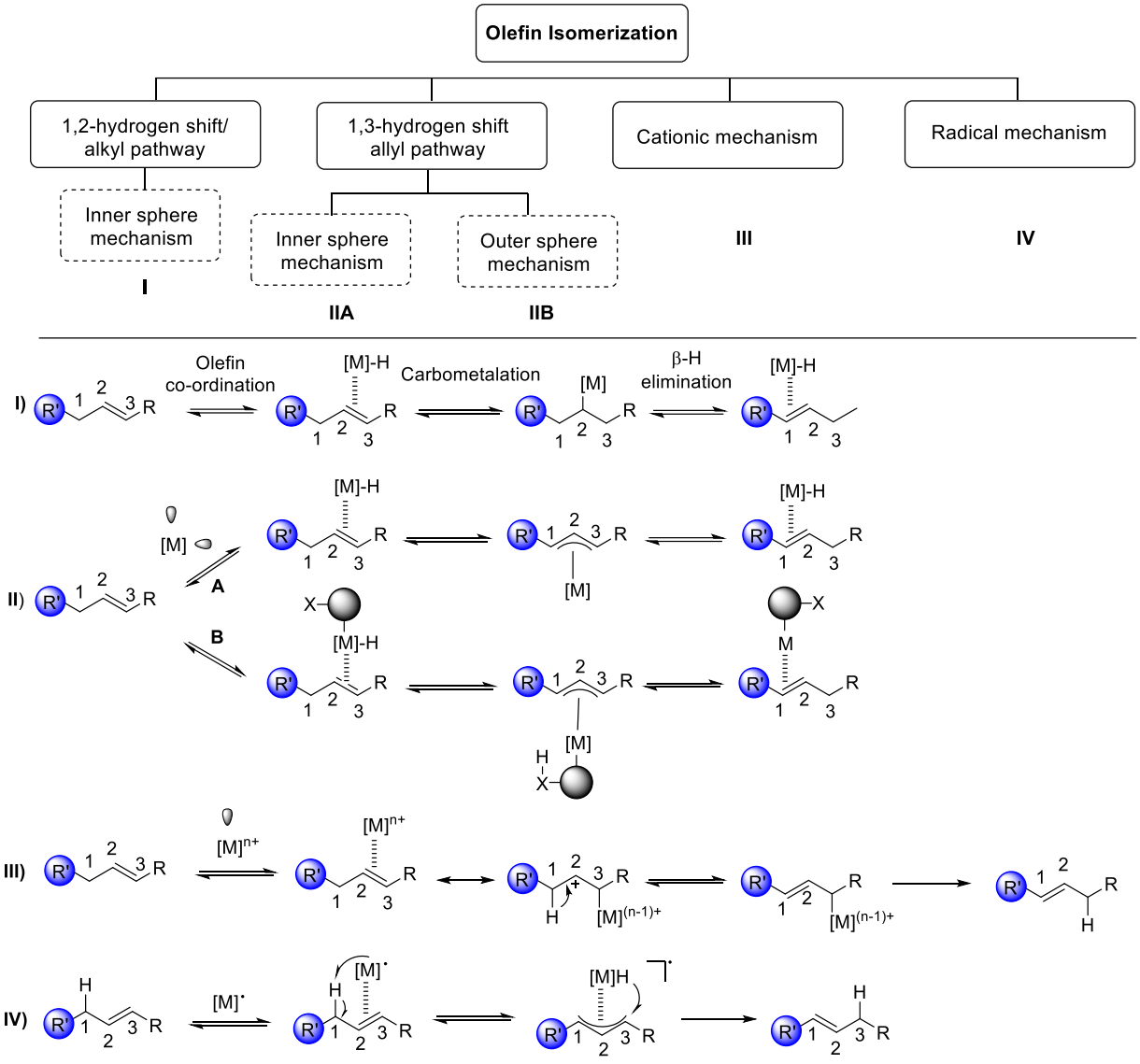


Scheme 1.3: Pathways leading to hydroformylation and olefin isomerization/hydrofunctionalization

1.2 Mechanisms of Transition Metal Catalyzed Olefin Isomerization

Before delving into olefin isomerization in tandem catalytic reactions, it is important to understand the fundamental mechanisms proposed for the double bond isomerization.[12a, 12b, 12c, 12d] There have been mainly two mechanisms proposed for this process. One of them involves a double bond undergoing insertion into the metal hydride followed by β-hydride elimination. The other one is based on the activation of allylic hydrogen upon olefin coordination to form a π-allyl type system that subsequently undergoes re-protonation on the other terminus of allyl complex leading to an overall change in the position of the double bond. A more detailed illustration for mechanisms of olefin isomerization is shown below (Scheme 1.4). Moreover, the π-allyl type mechanism can follow two routes depending on whether the hydrogen is abstracted in the inner or the outer sphere. The π-allyl type inner-sphere mechanism (Scheme 1.4: **IIA**) demands the presence of free coordination sites on the metal. One of the orbitals is responsible for coordination to the olefin whereas the other abstracts a proton. In absence of two vacant coordination sites, the outer sphere mechanism (Scheme 1.4: **IIB**) is possible wherein a ligand also acts as a base and hence abstracts the proton leading to the π-allyl intermediate.

There is yet another third type (**III**) of 1,3-allyl shift mechanism that is encountered with electrophilic metal salts. A carbonium ion, generated after protonation of the olefin, eventually forms the cationic species. The in-situ generated proton formed by the generation of the olefin cleaves the M-C bond to re-generate the catalyst. Lastly, radical pathway involving abstraction of 'H' atom, subsequent isomerization and eventually hydrogen atom transfer by the metal on allylic position gives the final product (**IV**).



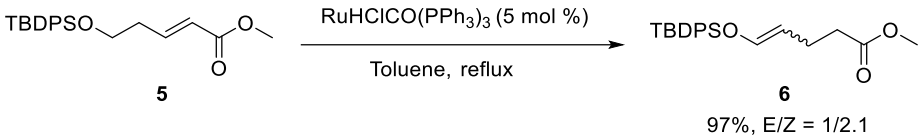
Scheme 1.4: General Mechanisms for transition metal catalyzed olefin isomerization

1.3 Catalysts for Long Chain Olefin Isomerization

Before discussing the variety of functionalizations that have been employed for tandem isomerization/functionalization of olefin, the different types of catalyst systems that have enabled isomerization over a long chain shall be discussed. This section shall serve as a foundation for understanding the mechanistic underpinnings of olefin isomerization processes. Processes involving isomerization over 1-2 bonds are not discussed here (except for one ruthenium catalyzed isomerization). It should be noted that a selection of reported methods is presented in the following sections.

1.3.1 Ruthenium

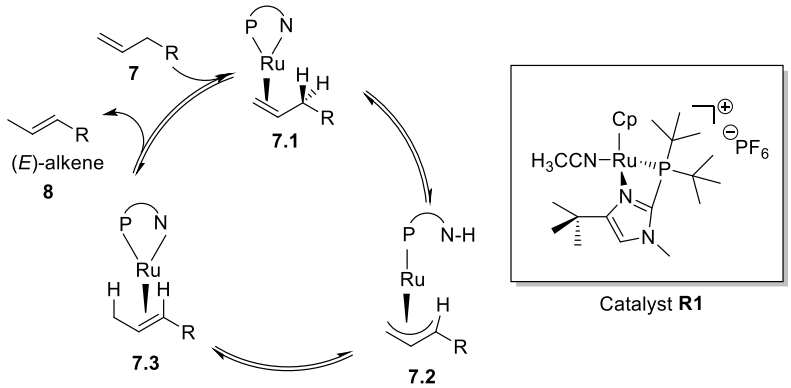
In 2000, Mori and co-workers reported a deconjugative isomerization based on a ruthenium hydride catalyst $RuHCl(CO)(PPh_3)_3$ (Scheme 1.5).[13] The authors showed that double bonds conjugated with a carbonyl group at one position in a molecule could be shifted over multiple bonds for conjugation with either another double bond or a protected hydroxy group. Although no mechanism for this transformation has been suggested, it is likely that the ruthenium hydride undergoes 1,2-alkyl shift (chain-walking).



Scheme 1.5: $RuHClCO(PPh_3)_3$ catalyzed olefin isomerization[13]

In 2007, Grotjahn and co-workers reported a highly active ruthenium based catalyst for isomerization over more than 30 carbons (Scheme 1.6).[14] A cationic ruthenium complex (**R1**) enabled long-chain isomerization and generated pure (*E*)-isomers employing a low catalyst loading. The authors propose that the imidazole ligand serves not only as a hemilabile ligand but also as an internal base assisting in forming the Ru(allyl) complex.

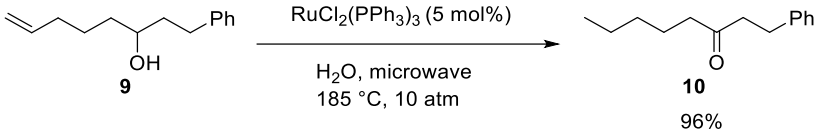
Redox isomerization (i.e the olefin isomerization concomitantly resulting in an oxidation or reduction) leading to an aldehyde from the corresponding alcohol even over longer chains was possible with this catalyst system. Normally, for substrates containing a non-polar functionality, isomerization at room temperature was possible, however, substrates containing polar functionality such as amide or aldehyde demanded a higher temperature (70 °C) for isomerization.



Scheme 1.6: Mechanism for Ruthenium catalyzed long chain olefin isomerization[14]

Another Ru(II) based catalyst system for converting an alkenol to an ketone was reported by Matsubara (Scheme 1.7).[15] A $RuCl_2(PPh_3)_3$ catalyst brought about the isomerization with

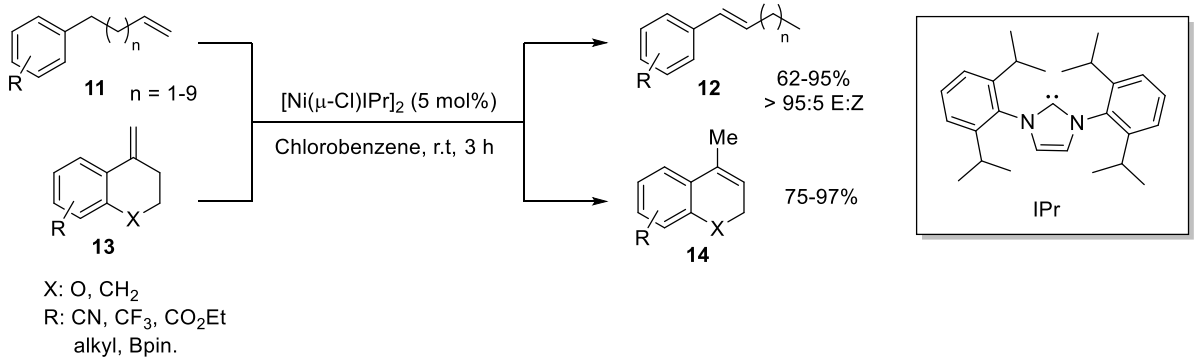
water as a solvent under microwave irradiation at 185 °C and catalytic amounts of methanol. Methanol was deemed necessary for converting the alkenyl ether to the corresponding ketone. The presence of water was crucial for the transformation to occur since it enabled the formation of active catalytic species $RuH(OH)L_n$.



Scheme 1.7: Ruthenium catalyzed long-chain redox isomerization[15]

1.3.2 Nickel

A mechanistically distinct isomerization of terminal olefins catalyzed by Ni(I) dimer was reported by Schoenebeck and co-workers in 2019 (Scheme 1.8).[16] They postulated the generation of an open shell Ni(I) radical species. This species was responsible for a 1,3-hydrogen atom transfer through radical relocation. The lack of deuterium scrambling along-with EPR evidence pointed towards a mechanism that exclusively involves the 1, 3 hydride shift pathway. Isomerization leading to a tri-substituted double bond and over 9 carbons was possible. Remarkably, this is one of the few examples in olefin isomerization chemistry where exclusively the 1,3-hydride shift pathway is proven to be functional.

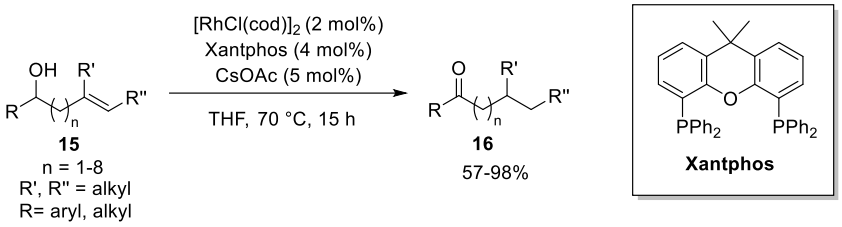


Scheme 1.8: Ni(I) catalyzed olefin isomerization through a metalloradical intermediate[16]

1.3.3 Rhodium

The development of an efficient tandem olefin isomerization/hydroformylation process relies on the ability of rhodium complexes to effectively isomerize double bonds. While a rigorous investigation of the tandem process has been conducted for its industrial utility, there are very few reports on the selective long-chain isomerization.

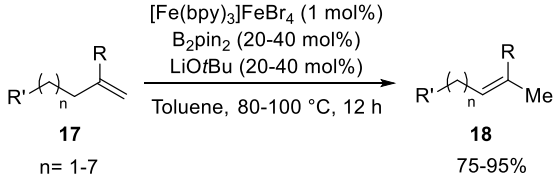
A [RhCl(cod)]$_2$/Xantphos system was used for a long-chain isomerization of alkenyl alcohols terminating in the formation of ketones (Scheme 1.9).[17] In this case, the coordination of oxygen of the alcohol to the Rhodium center followed by β-hydride elimination was proposed to generate the Rhodium hydride. The wide bite-angle rigid diphosphine Xantphos could effectively stabilize the generated Rh-H. The Rh-H then engages in a migratory insertion with the terminal alkene and triggers a 'chain-walking' process. The isomerization of allylic alcohol to the corresponding ketone regenerates the Rh-H that reenters the catalytic cycle. Interestingly, the authors demonstrated convergent reactivity by employing an isomeric mixture of olefins that gave the corresponding ketone in 85% yield.

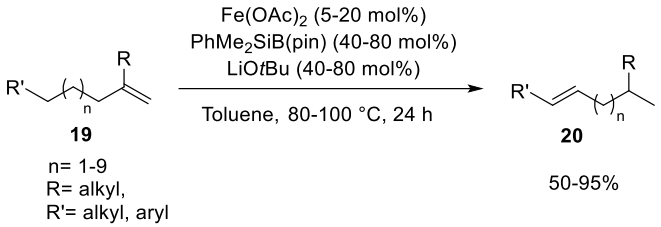


Scheme 1.9: Rhodium catalyzed long-chain olefin isomerization of alkenols[17]

1.3.4 Iron

Iron is an attractive choice as a catalyst owing to its abundance in the earth's crust.[18] Koh and co-workers disclosed a unique regioselective, tunable iron-catalyzed isomerization that converts cheap olefin feedstocks into value-added chemicals.[19] The catalytic design derived its inspiration from the iron catalyzed hydroboration of olefins using bis(pinacolato)diboron.[20] The authors envisioned that in the absence of a protodemetalation event (which leads to the hydroboration product), β-hydride elimination would give rise to Fe-H species. This was indeed the case as mono-isomerization could be observed when $[Fe(bpy)_3]^{2+}[FeBr_4]^{2-}$ was used along-with bis(pinacolato)diboron and lithium *t*-butoxide (*t*-BuOLi) as a base (Scheme 1.10). Modulation of the reactivity was possible by switching the iron precatalyst to a sterically less encumbered $Fe(OAc)_2$. In this case, (dimethylphenylsilyl)boronic acid pinacol ester was used along-with *t*-BuOLi. The formation of a thermodynamically favored conjugative migration occurred.



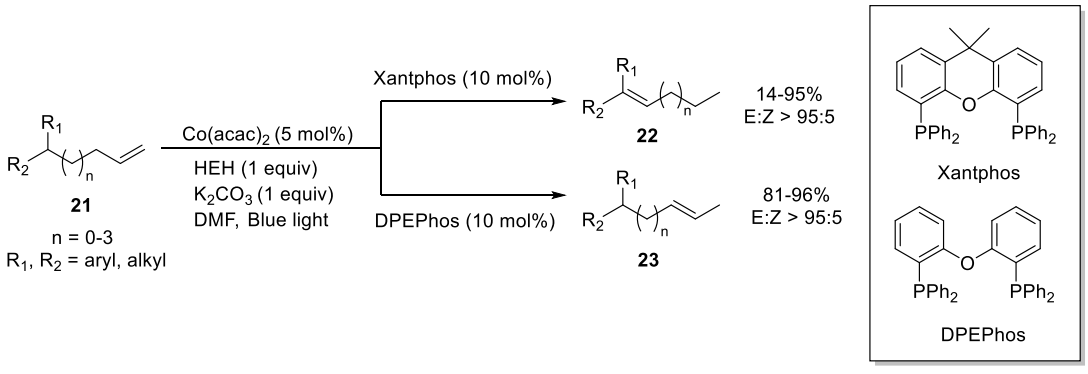


Scheme 1.10: Iron catalyzed switchable olefin isomerization[20]

Owing to the three stable redox states of iron being Fe(I/II/III), a mechanism that involves a single electron transfer (metal hydrogen atom transfer) is possible. To probe the presence of any radical species, the authors performed classical experiments with radical scavengers. However, the outcome of the reaction was unaffected. The presence of deuterium on the benzylic position under the reaction conditions led to its scrambling all over the alkyl chain. Moreover, in a 'cross-over' experiment that uses both deuterated and non-deuterated reactants, a transfer of deuterium is indicative of the fact that the Fe-H intermediate dissociates. This evidence links to the likelihood of the classical 'chain-walking' process. Using the developed catalyst system, a migration over 9 carbons was possible. Moreover, divergent reactivity relying on differing iron pre-catalyst was demonstrated.

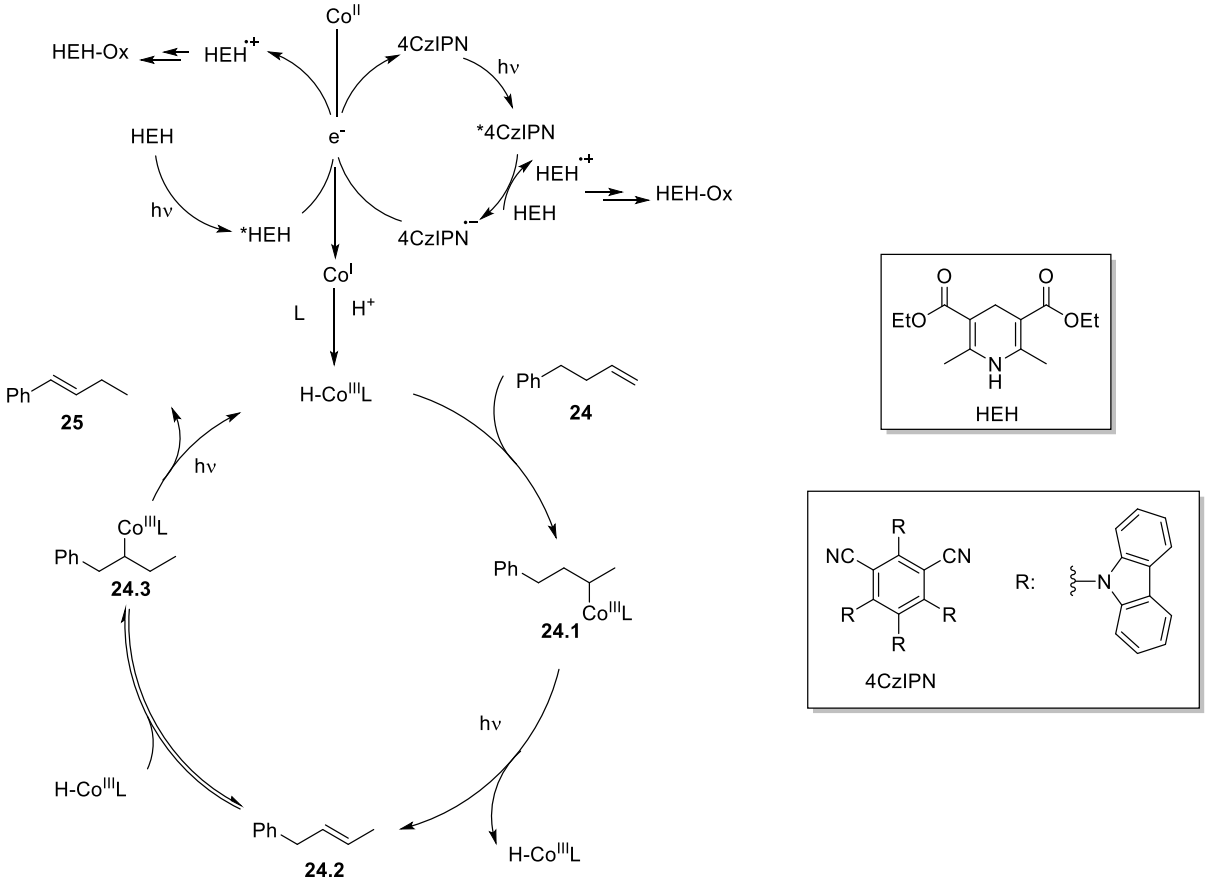
1.3.5 Cobalt

The E to Z isomerization of olefin has been accomplished through photosensitized triplet energy transfer.[21] Up until recently, there have been no reports on positional isomerization over multiple bonds using a photocatalyst. König and co-workers developed a double bond isomerization catalyzed by cobalt in presence of visible light and Hanztsch ester as the reductant (Scheme 1.11).[22] The catalyst system is comprised of $Co(acac)_2$ and Xantphos as the ligand. The isomerization was proposed to occur through the classical metal-hydride insertion/elimination pathway. Analogous to the influence of the nature of phosphine on nickel catalyzed isomerizations as described in the previous sections, the authors tested the transformation with different phosphines. The use of DPEPhos enabled a selective single bond isomerization. Isomerization involving multiple bonds needed a thermodynamic driving force (e.g a phenyl ring), while Xantphos was used as a ligand.



Scheme 1.11: Cobalt catalyzed photocatalytic long-chain olefin isomerization

In the proposed mechanism, the authors suggest Co(II) to Co(I) reduction brought about by the photocatalyst and an electron transfer agent such as the Hanztsch ester (Scheme 1.12). The donor-acceptor dye (4CzIPN) in its excited state accepts an electron from the Hanztsch ester to form the radical anion and ultimately transfers the electron to Co(II) bringing about its reduction to Co(I). The coordination of the phosphine generates Co(III)-H from Co(I).



Scheme 1.12: Mechanism of cobalt catalyzed long chain isomerization in presence of a photocatalyst[22]

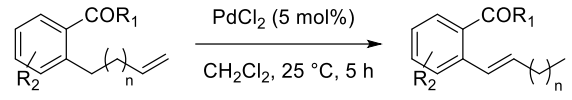
The Co-H thus adds to the double bond in a Markovnikov manner to give **24.1**. Remarkably, the β-hydride elimination is proposed to occur photochemically. The Co-H finally dissociates from the carbon chain after the β-hydride elimination and a conjugated system is formed.

1.3.6 Palladium

Double bond transposition catalyzed by Palladium is by far the most extensively studied process among long-chain isomerizations. This is on one hand owing to the ability of palladium to effectively switch redox states during a catalytic cycle in presence of suitable ligand without undergoing deactivation. On the other hand, a plethora of methods for generation of hydride complexes of palladium are available.[23] One of the earliest examples of double bond

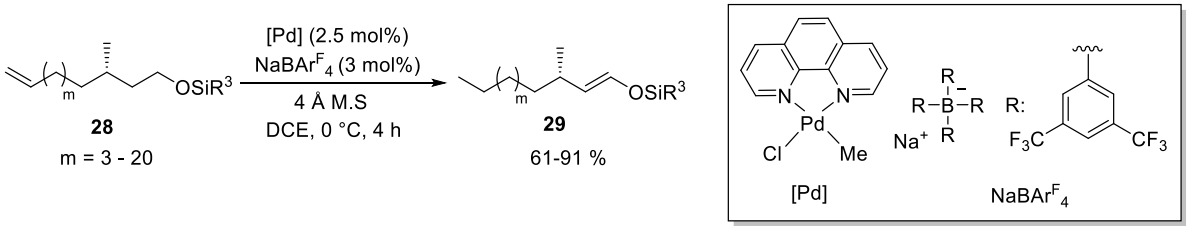
isomerization with palladium was presented by Davies and co-workers. $PdCl_2(CH_3CN)_2$ was used for a conjugative migration of 4-phenyl-1-butene. The mechanism of single bond isomerization catalyzed by this Pd(II) complex was not investigated until the 1980s. Sen and co-workers proposed a cationic Pd(II) complex to be an intermediate responsible for isomerization. This was in contrast to the mechanism involving abstraction of allylic hydrogen and formation of Pd(IV) that was proposed to operate in earlier reports.[12b]

On the similar lines, a long-chain olefin isomerization catalyzed by $PdCl_2$ was reported by Hou and co-workers (Scheme 1.13).[24] The authors discovered Pd(0) as the catalytically active species. The in-situ generated Pd(0) was analyzed by XRD, SEM analysis. Moreover, upon monitoring the reaction, an induction period of 30 mins was observed. The palladium nanoparticles could be recycled and used multiple times in the catalytic experiment. Interestingly, this procedure was amenable to substrates possessing a functional group ortho to the ω-alkenyl chain. Some examples of functional groups used are carboxylic acid, cyano, and amide. Isomerization over 6 carbon atoms was possible without any considerable loss in the catalyst activity.



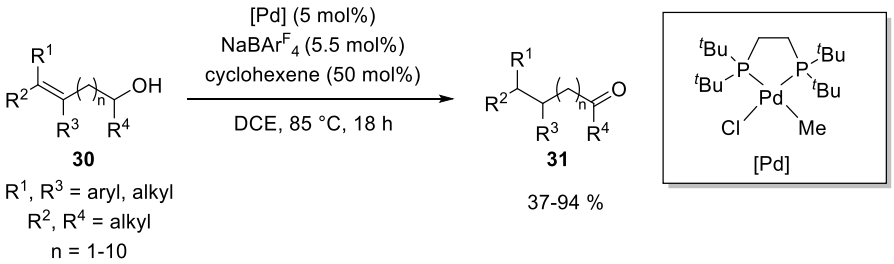
Scheme 1.13: Conjugative isomerization catalyzed by palladium nanoparticles[24]

During an investigation of palladium catalyzed hydrosilylation reactions, Brookhart and co-workers discovered the ability of a palladium complex (BPhen)Pd(Me)Cl to undergo insertion into olefin and subsequent β-H elimination.[25] They developed a chain-walking isomerization for synthesizing silyl enol ethers. The complex [Pd] is proposed to form a cationic palladium species *in-situ* that is stabilized by the $BAr^F{}_4^-$ counterion and to undergo the carbopalladation/β-H elimination sequence in a repeated manner. Only one example of migration over 5 bonds was reported with a poor E/Z ratio. Kochi and co-workers used the same catalyst systems and extended the scope of substrates that could be employed in the isomerization (Scheme 1.14).[26] They postulated a non-dissociative mechanism of olefin isomerization. As the name suggests, the olefin does not decoordinate from the palladium catalyst. Advantageously, olefin isomerization occurring through this mechanism is unlikely to have competitive product interference through olefin coordination. The terminal alkene is more likely to coordinate. A synthetically intriguing aspect of the non-dissociative mechanism is the retention of stereochemical fidelity.



Scheme 1.14: Palladium catalyzed non-dissociative long-chain isomerization[26]

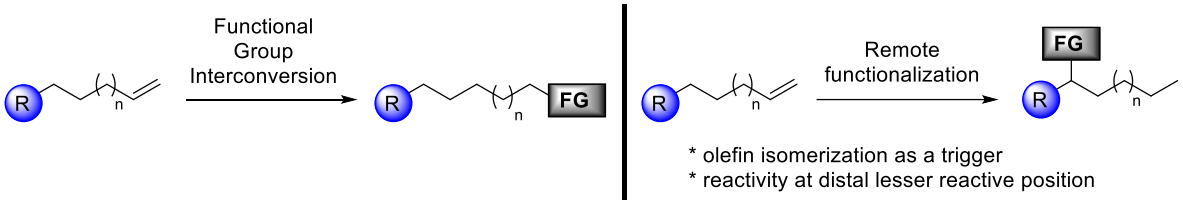
The versatility of complexes of the type Pd(L^L)MeCl was exploited by Mazet and co-workers in their report on long-chain migration that results in loss of conjugation with an arene to give ketones (Scheme 1.15).[27] Ligands with unique donor abilities and properties to modulate the hydricity of palladium hydride were chosen for investigation. The complex (X) turned out to be the most efficient in the catalysis. Tri-substituted alkenols bearing a variety of functional groups could be converted to the corresponding ketones. Internal di-substituted alkenes could be isomerized over 10 carbons. Studies of deuterium incorporation pointed toward an irreversible addition of the metal hydride across the double bond for initiating the isomerization. Crossover experiments involving the use of deuterated and non-deuterated substrate were performed. These studies indicated a non-dissociative mechanism under operation for allyl alcohols as substrates. However, studies on long-chain isomerization leading to the corresponding aldehyde led to the conclusion that dissociation of the catalyst occurs. This was confirmed by subjecting an enantio-pure starting material possessing methyl group in the center to catalytic conditions. The erosion of enantiomeric excess was observed. Interestingly, this observation is in strong contrast to the one observed by Kochi and co-workers as described in the previous paragraph. This echoes the multifaceted effects of the nature of ligand on the metal center. Mazet and co-workers systematically investigated the bi-directional nature of the long-chain isomerization in a recent work.[28] Additionally, the report features the first example of enantioselective deconjugative migration. Using a chiral biphosphine (*S*)-Binapine, *ee* of over 85% was achieved owing to stereoselective metal-hydride addition to the double bond.



Scheme 1.15: Palladium catalyzed long-range deconjugative migration of olefins[27]

1.4 The concept of 'Remote Functionalization'

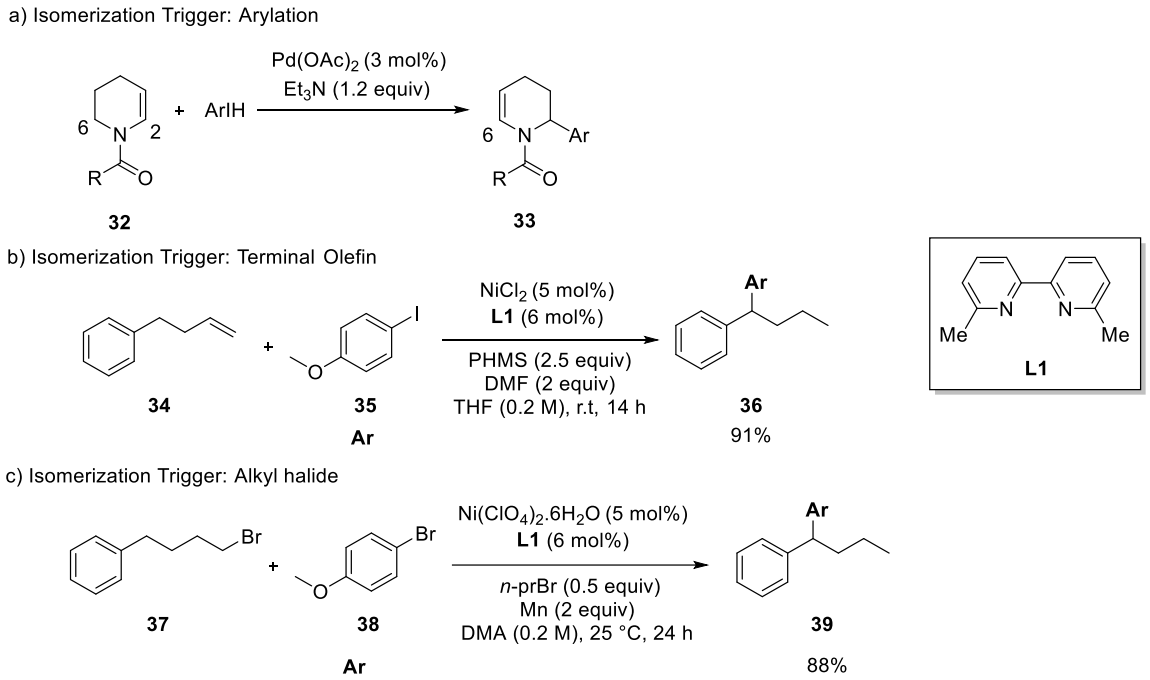
It is important to note that the olefin isomerization pathways are in equilibrium in the absence of a thermodynamic sink or a suitable termination step to regenerate the catalyst. The concept of 'remote functionalization' relies on enabling reactivity of the substrate at a lesser reactive site that is often 'remote' to the original reacting center (Scheme 1.16).[29] Olefin isomerization is an ideal tool to trigger bond movement from a relatively more reactive site to a less reactive site and driving force may be a thermodynamically favored termination step. The goal is to use a mixture of isomers and react them in a convergent manner to give a single product.



Scheme 1.16: The concept of remote functionalization

From its inception in the 1970s by the pioneering work of Breslow that displayed a biomimetic approach, the field of distal functionalization of relatively unreactive C-C and C-H bonds has advanced significantly.[30a, 30b] To establish a distal reactivity selectively, the inherent property of the substrate is exploited. This may be the presence of a carbonyl group leading to the formation of a Michael acceptor or the presence of a phenyl ring or even generation of stable tri/tetra-substituted olefin. An example is the palladium-catalyzed tandem arylation/isomerization.[31]

As displayed in Scheme 1.17, there are three ways of triggering metal catalyzed double bond isomerization. The isomerization of double bond followed by arylation was reported by Zhu and co-workers and is one of the first examples of nickel catalyzed remote functionalization (Scheme 1.17b).[32] Isomerization can also be initiated by arylation and follow-up β-hydride elimination. (Scheme 1.17a). Finally, isomerization can also be triggered by the use of alkyl bromides wherein the catalyst inserts in the C-halogen bond and engages in a β-hydride elimination generating an alkene, which eventually undergoes isomerization in presence of the metal hydride (Scheme 1.17c).[33]

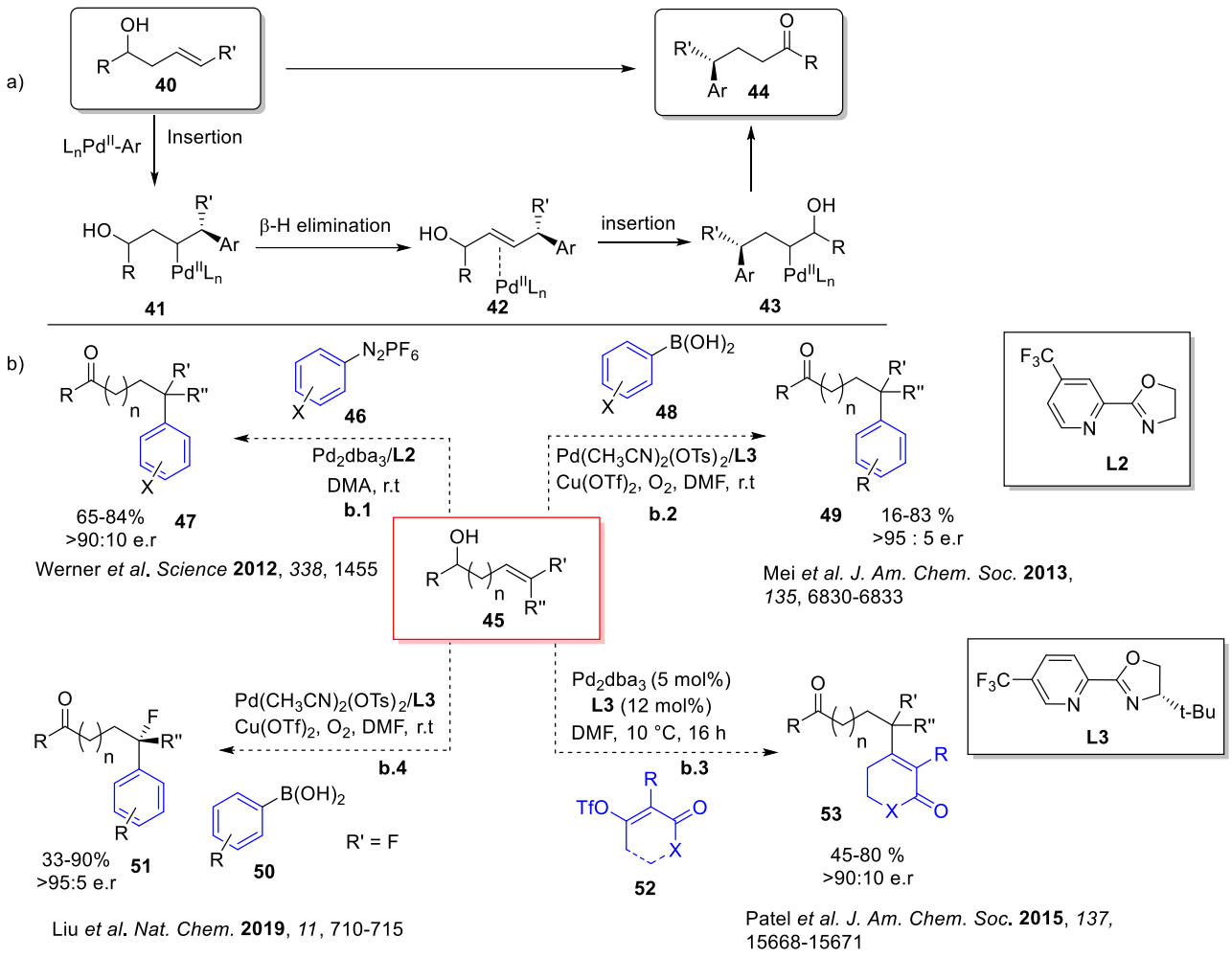


Scheme 1.17: Types of possible 'triggers' for metal catalyzed olefin isomerization

1.4.1 Palladium-catalyzed Remote Functionalization

1.4.1.1 Redox-relay Heck arylation

Recently, Bonfield *et al.* reviewed remote functionalization in context of redox-relay stereoselective Heck arylation methodologies that have mainly been developed by the Sigman group.[34] The development of a redox-relay transformation entails a regioselective addition of Pd-Ar along the double bond followed by its isomerization. In the following section, a series of articles published by the Sigman group are discussed collectively. An overview of this chemistry can be obtained by considering the different group functional groups added that result in the formation of the 'remote' stereo-center. One of the first reports of this methodology was through the use of arene diazonium salts (Scheme 1.18 **b.1**) .[35] The authors decided to employ the PyRox family of ligands given their low Lewis basicity that enabled compatibility with the arene diazonium salts. Although only two examples were shown featuring migration over >2 carbons, high selectivity for the carbopalladation on the electronically non-biased alkene is reported.



Scheme 1.18: a) General mechanism for remote Heck-arylation triggered by olefin isomerization. b) Selected examples based on remote Heck-arylation for functionalization[35, 36a, 36b, 36c]

Building on the previous report with aryl-diazoniums, the Sigman group developed an oxidative transformation using boronic acid as the aryl equivalent (Scheme 1.18 **b.2**).[36a] The oxidative variant involved a $Pd(CH_3CN)_2Cl_2$ catalyst along-with $Cu(OTf)_2$ in an O_2 atmosphere. The question on site selectivity posed in the previously described article was answered in this work. The authors discovered that the electronic nature of boronic acid was the key in determining site selectivity. Quantifying the observed site selectivity through a Hammett plot indeed pointed toward a strong electronic influence on the formation of Pd-Ar species. Under the catalytic conditions, several heteroaromatic boronic acids could be successfully coupled. However, the enantioselectivity was independent of the nature of substrates. A non-dissociative nature of olefin migration is suspected in this case leading to high enantioselectivity of product.

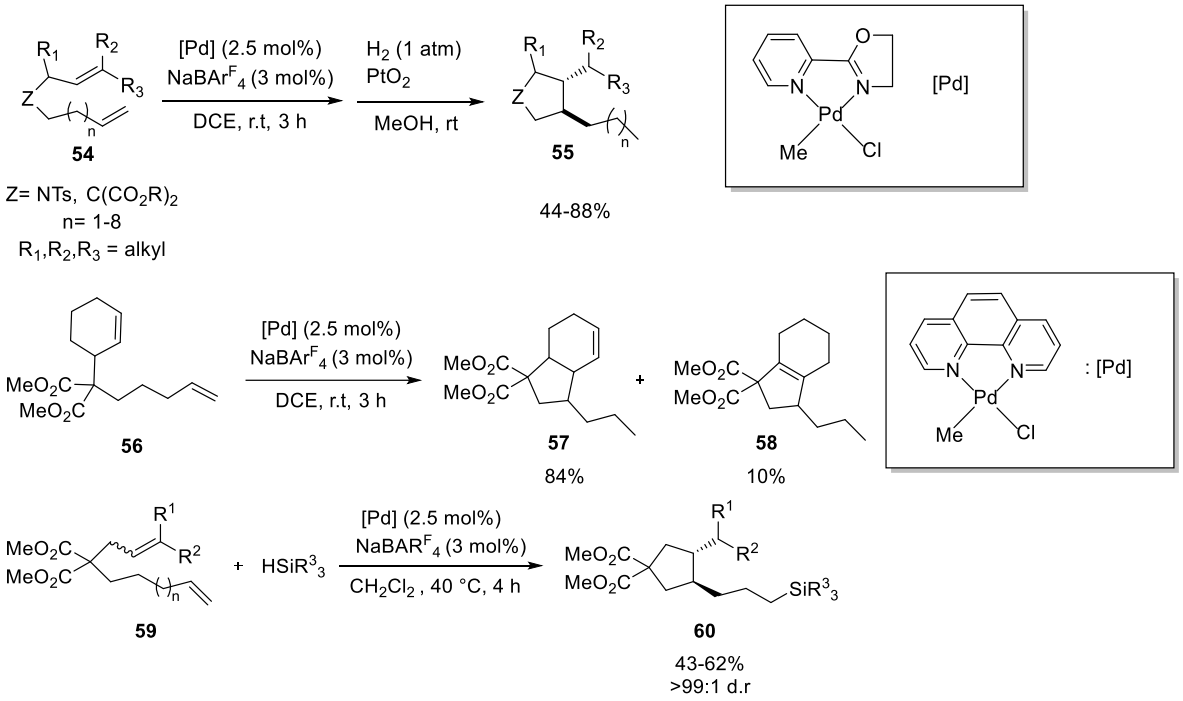
The potential of the catalyst system developed in the above oxidative transformation was expanded through the construction of remote quaternary stereocenter (Scheme 1.18).[37] The evaluation of substrates under the optimized conditions revealed that the site selectivity of formation of Pd-Ar species was not dependent on the nature of boronic acids, but instead on the electronic character of the olefin. A mechanistic experiment involving the use of enantioenriched substrate impressively showed retention of stereochemistry. Hence, the catalyst remains bound to the carbon chain selectively on a single face.

Further extensions of the redox-relay strategy were achieved by applying triflates as substrates (Scheme 1.18 **b.3**).[36b, 38a, 38b]. In a collaborative effort with the Toste group, Sigman and co-workers reported a redox-relay strategy for enantioselective heck arylation of alkenyl fluorides with boronic acids as coupling partners (Scheme 1.18 **b.4**) .[36c] Fluorine can impart characteristic properties to a molecule, mainly in terms of electronic influence, as a chemical isostere, and also stability toward degradation (in case of fluorinated arenes). The main difficulty associated with the development of this transformation was the possibility of β-fluoride elimination. The classical system for a non-fluorinated substrate proved to be effective also in this case. The product featuring tertiary C-F bond was obtained in 90% yield using $Pd(dba)_2$ as catalyst and **L3** as the ligand. Oxidative conditions were necessary due to the use of boronic acid. Experiments on reaction kinetics with fluorinated, corresponding methylated, non-fluorinated analog showed that the olefin coordination to the palladium center is the rate-determining step. The electron-poor alkenyl fluoride reacts much slower than the non-fluorinated analog. The migratory insertion was shown to be dependent on the steric demand as tri-substituted alkene did not react at all in the presence of an alkenyl fluoride. Migration over 6 carbons was possible under the optimized conditions. Lastly, an expeditious access to β-amino alcohols was provided by Sigman and co-workers through their aza-Wacker type reaction on tri-substituted alkenyl alcohol.[39]

1.4.1.2 Formation/Cleavage of Carbocycles

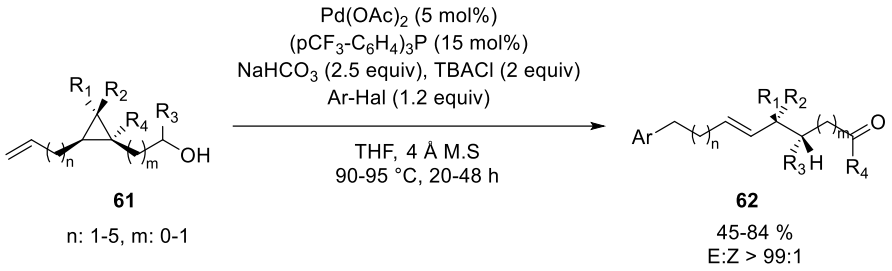
In 2012, Kochi and co-workers reported a tandem olefin isomerization/cyclization catalyzed by palladium(II) catalyst precursors with bidentate N,N-ligands (Scheme 1.19).[40] In this case, BAR^F_4 was employed as a counterion to stabilize the cationic palladium complex. The product generated after cyclization still possessed a double bond and hence was susceptible to undergo isomerization. The methodology could be modified for the development of a remote silylation/cyclization process. The same catalyst system with triethylsilane, in the absence of the sacrificial alkene, delivered the silylated cyclized product **60**. The authors proposed the initial formation of $Pd\text{-}SiEt_3$ species that undergoes addition to the double bond such that the palladium is bound on the more substituted end. A chain walking process ensues leading to cyclization,

mediated by the coordination of palladium to the double bond in the ring. Preliminary investigation using deuterated alkene showed a scrambling over the deuterium chain.



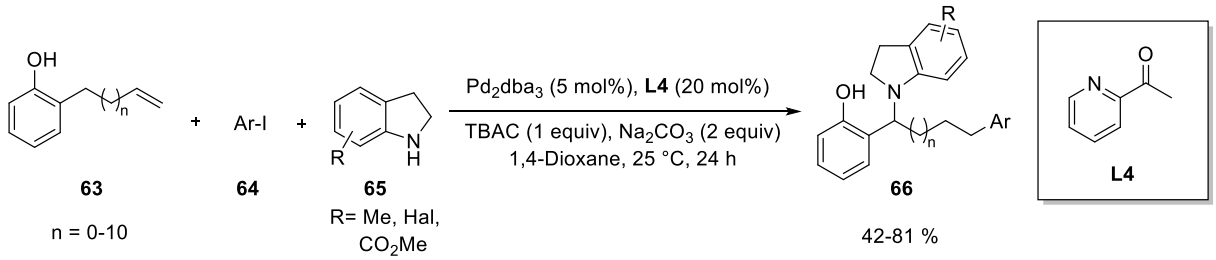
Scheme 1.19: Palladium catalyzed tandem olefin isomerization/cycloisomerization for the synthesis of fused ring systems[40, 41]

The strategic placement of a cyclopropane ring remote to a double bond was exploited to develop a Heck arylation based on a redox-relay strategy. Marek and co-workers used a system comprising $Pd(OAc)_2$, phosphine, and an inorganic base that could generate product **62** from **61** in a highly stereoselective manner (Scheme 1.20).[42] Isomerization of double bond was possible over 5 carbons. The stereochemistry of the beta position of cyclopropane was inconsequential to the resultant stereochemistry of the quaternary center. The authors demonstrated a broad substrate scope and synthesized several aldehydes and ketones featuring the quaternary center. Based on deuterium labelling experiments, the classical insertion, elimination mechanism of the isomerization mechanism was proposed. Interestingly, the deuterium in the alpha position of the cyclopropane ring did not result in any scrambling. The presence in beta position, however, led to the loss of deuterium in the corresponding product. The authors reasoned this loss by invoking a keto-enol tautomerization of the adjacent carbonyl. Accordingly, increasing the chain length by a single carbon preserved the stereochemical integrity.



Scheme 1.20: Palladium catalyzed tandem arylation/ring opening functionalization through olefin isomerization[42]

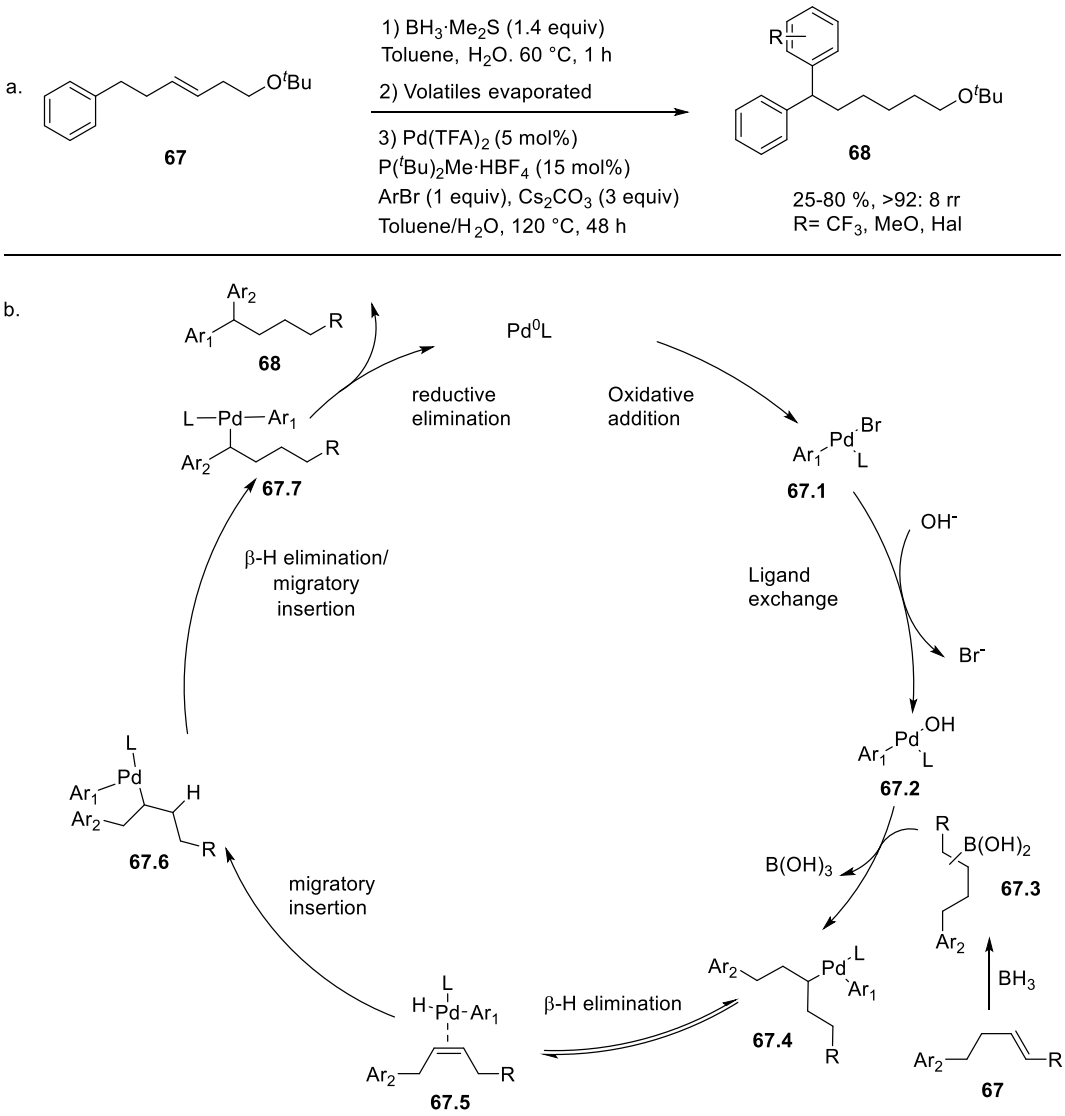
The following set of transformations that will be discussed take advantage of presence of phenyl ring to have directionality in olefin isomerization. Yao and co-workers utilized Heck arylation as a trigger for olefin isomerization (Scheme 1.21).[43] In this case, instead of termination of the isomerization process upon reductive elimination to generate a double bond in conjugation with phenyl ring, addition of aryl amine resulted in benzylic functionalization. Thus, a [1,n] type functionalization was achieved. 2 or 4-allyl ortho-phenols were used in the catalysis as the authors proposed the formation of quinone-methide intermediate before the attack of arylamine. Only Heck product was observed when reactant lacking the appropriately placed hydroxy group was used. The hydroxy group played an important role in the olefin isomerization since the quinone methide intermediate is thought to act as a thermodynamic driving force for the isomerization. Migration over 10 carbons was accomplished by this catalyst system.



Scheme 1.21: Palladium catalyzed tandem conjugative isomerization and functionalization of O-alkenyl phenols with aryl amines[43]

Very recently, Baudoin and co-workers reported a migratory Suzuki-Miyaura cross coupling using $Pd(TFA)_2$ and $P(t\text{-}Bu)_2Me{\cdot}BF_4$ as catalyst system (Scheme 1.22).[44] Borane was used to generate the intermediate boronate **67.3**. Transmetalation eventually led to the carbopalladated species bearing the aryl group **67.4** that performed the olefin migration and arylation. The authors encountered site selectivity issues associated with competing for direct arylation. These could be reduced with a bulky *t*-butyl group at the end of the olefin. The presence of this group directed the carbopalladation on the distal end of the olefin and resulted in an impressive selectivity of >99:1 (branched: linear). The performance of the reaction was

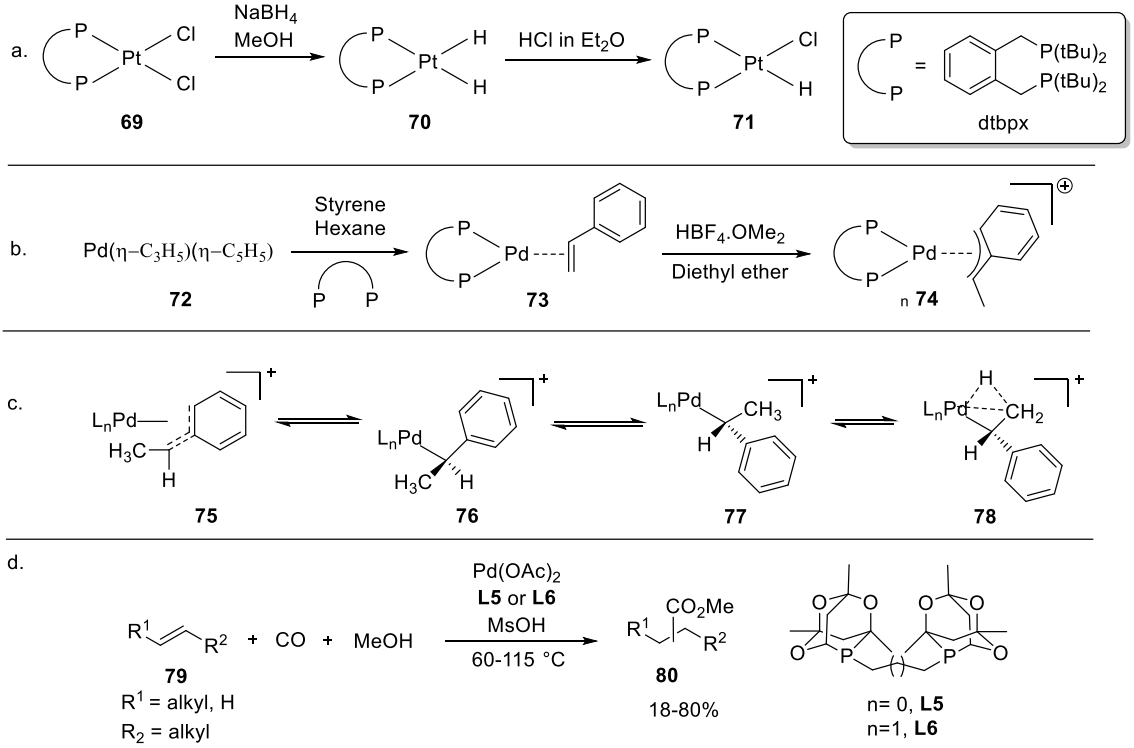
independent of the electronic nature of coupling partners. This result was corroborated through deuteration experiments.



Scheme 1.22: Palladium catalyzed conjugative migratory Suzuki-Miyaura cross-coupling[44]

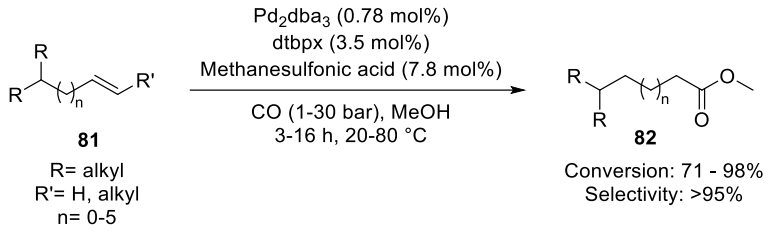
Alkoxycarbonylation provides access to valuable linear esters that are obtained from internal alkenes through a tandem isomerization sequence. The development of this transformation is based on investigations of the alkoxycarbonylation of ethene, where a special class of diphosphines with a wide bite angle gave highly active palladium-based catalysts.[45]. These bulky diphosphines could stabilize a metal hydride species as demonstrated by Shaw and co-workers in their synthesis of PtH_2(dtbpx).[46] This complex features the first metal (di)-hydride stabilized by dtbpx. A detailed study on the fluxional behaviour of η^3-Pd and -Pt(dtbpx) complexes of styrene

highlighted the ability of this ligand class in the stabilizing a metal hydride (Scheme 1.23). Pringle and co-workers systematically studied the effect of various phosphines on the tandem isomerization/alkoxycarbonylation of C11/C12 alkenes.[47] The isomerization step was found to be rate-limiting and using dtbpx gave the linear product in 80% selectivity. The catalytically active palladium hydride species was generated by the combination of Pd_2dba_3, dtbpx and methanesulfonic acid.



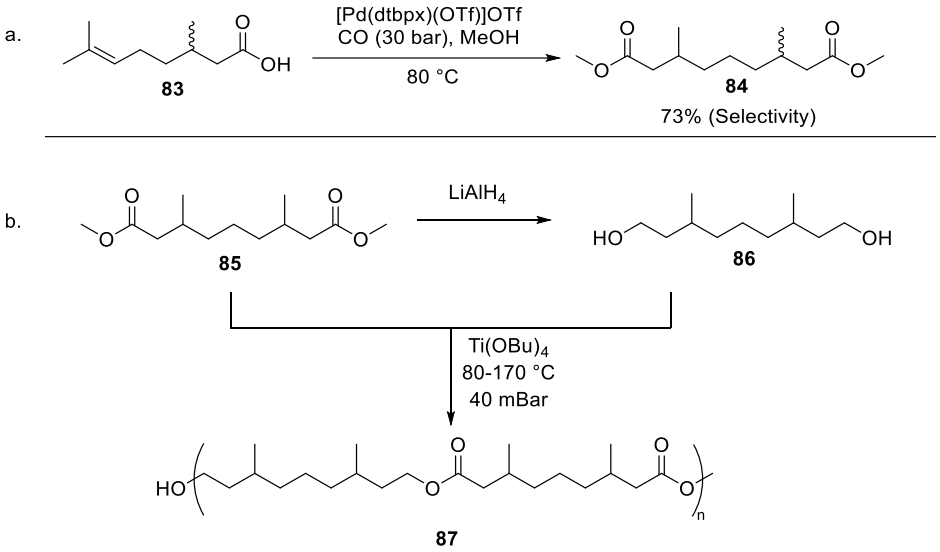
Scheme 1.23: a) Synthesis of mononuclear platinum hydride with dtbpx as ligand. b) Cationic η3-benzyl palladium complex with dtbpx as ligand. c) Fluxional character of η3-benzyl palladium complex.[45, 46, 47, 48]

Eastham and co-workers significantly optimized this system and reported a procedure that resulted in a much high linear selectivity (>99%) for methoxy esters (Scheme 7.24).[49] It is noteworthy that methoxycarbonylation could be carried out at atmospheric pressure of CO. Moreover, regardless of the double bond placement in the olefin, the high linear selectivity was maintained. The synthesis of α-ω saturated diesters was accomplished through a tandem olefin isomerization/methoxycarbonylation of oleochemicals (methyl linoleate) using the same catalytic system albeit under harsher reaction conditions.[50] The diesters are a valuable feedstock for their use in lubricants and plasticizers. Moreover, they serve as raw materials for polymer synthesis.



Scheme 1.24: Palladium catalyzed tandem isomerization-methoxycarbonylation[50]

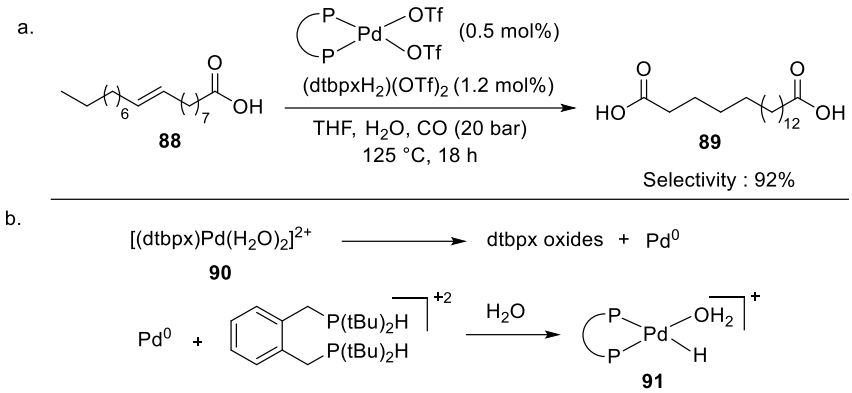
Building upon the optimized system for isomerizing methoxycarbonylation and previous literature reports with catalyst systems involving dtbpx, Mecking and co-workers reported the methoxycarbonylation of citronellic acid using [(dtbpx)Pd(OTf)](OTf) as the catalyst (Scheme 1.25).[51] The uniqueness of the catalyst system is evident by the isomerization of a hindered alkene occurring at room temperature. With a CO pressure of 40 bar and temperature of 90 °C, the desired methoxy ester was obtained in 75% selectivity compared to the other products arising from unselective methoxycarbonylation. Polymerization of the diester along-with the corresponding diol resulted in a novel polymer, highlighting the synthetic potential of such diesters.



Scheme 1-25: a) Palladium catalyzed methoxycarbonylation of citronellic acid. b) Titanium catalyzed polymerization of diester with diol.[51]

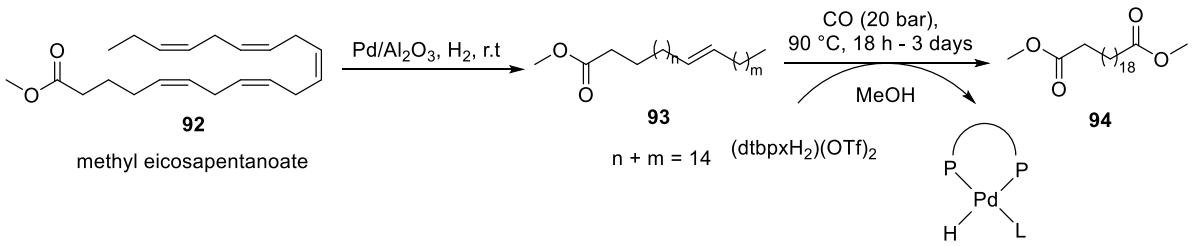
A catalyst system comprising of $Pd(OTf)_2$(dtbpx) and (dtbpxH_2)$(OTf)_2$ was used to achieve isomerizing hydroxycarbonylation of oleic acid (Scheme 1.26).[52] The use of water as a nucleophile complicated the optimization for a suitable reaction system due to solubility issues. The authors could successfully use a mixture of THF and water (ratio 10:1) for achieving complete conversion and TON of 122. Moreover, the role of H_2O was not just limited to that of a nucleophile. It was also responsible for the generation of catalytic palladium hydride. A variety of

fatty acids and derivatives such as erucic acid and high oleic sunflower oil were employed in this transformation. NMR experiments pointed to the generation of $PdH(H_2O)(dtbpx)$ that was accompanied by reduction in $Pd(H_2O)_2(dtbpx)$. Moreover, the concentration of $(dtbpxH_2)(OTf)_2$ decreased with increasing concentration of the hydride clearly indicating of involvement of protonated ligand in hydride generation.



Scheme 1.26: a) Pd(OTf)(dtbpx) catalyzed tandem isomerization/hydroxycarbonylation of long-chain fatty acids. b) Role of protonated phosphine in the generation of palladium hydride[52]

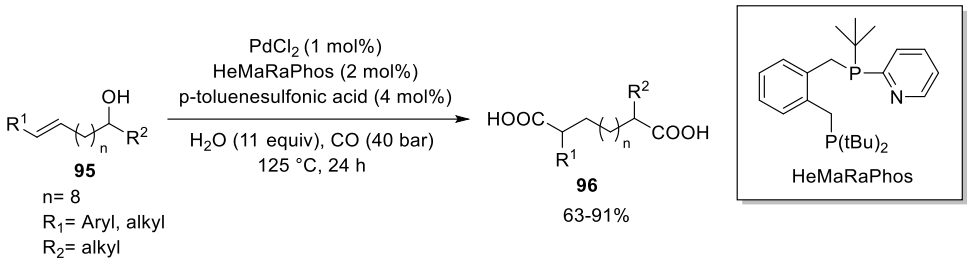
Kroth, Mecking and co-workers reported a novel dual-catalysis approach employing heterogeneous palladium along-with a homogeneous palladium hydride generated upon addition of $(dtbpxH_2)(OTf)_2$ (Scheme 1.27).[53] This approach allowed the selective functionalization of mixture of polyunsaturated fatty acids. Palladium supported on alumina was responsible for partial hydrogenation of the polyunsaturated substrate to give **93**. A methanolic solution of the protonated phosphine resulted in generation of palladium hydride and hence a homogeneous intermediate for catalysis. The optimized catalyst system could be employed also to give diester of tall acid, a byproduct of the pulp and paper industry. The average selectivity of the catalytic system for the formation of di-ester was >80%.



Scheme 1.27: Tandem reductive olefin isomerization/methoxycarbonylation using heterogeneous palladium catalyst[53]

A very recent report by Beller describes the synthesis of dicarboxylic acids by palladium catalyzed carbonylation of allylic alcohols (Scheme 1.28).[54] The optimized catalyst system consists of a palladium(II) salt, a pyridine-substituted ligand HeMaRaPhos and a Brønsted acid.

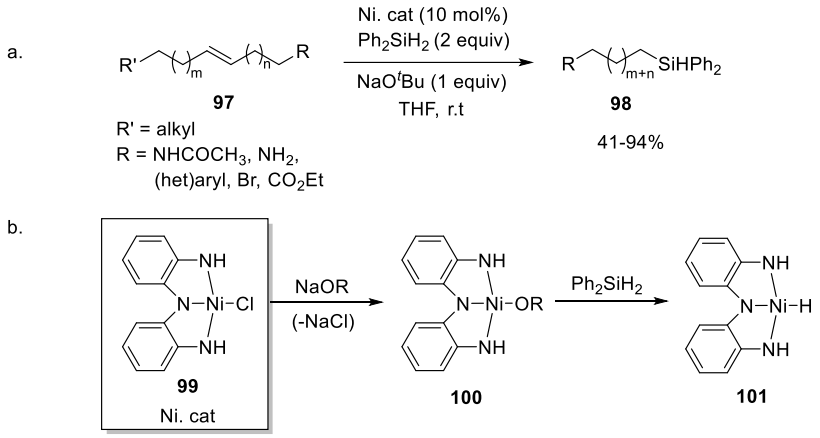
An experiment on 1 mole scale employing 3-pentene-2-ol as a substrate resulted in the formation of the corresponding dicarboxylic acid with very high selectivity for the linear product. Double bond isomerization over 8 bonds was possible giving the dicarboxylic acid as product albeit with a slightly lower selectivity. Interestingly, the pyridine ring serves multiple purposes in the reaction. Firstly, it assists in the formation of the active palladium hydride. Secondly, it acts as a hemilabile ligand and hence can play an active role in the stabilization of the active catalyst. Most importantly, a regioisomeric mixture of C6 alcohols could give a single dicarboxylic acid in a convergent manner.



Scheme 1.28: Palladium catalyzed isomerization/carbonylation of allylic alcohols[54]

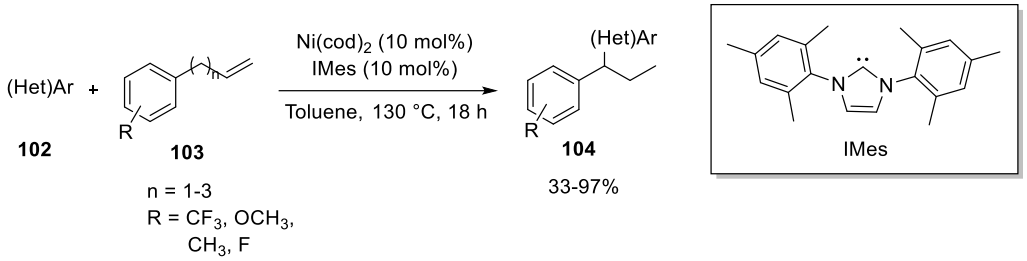
1.4.2 Nickel catalyzed Remote Functionalization

In the following section, selected methodologies involving nickel catalysed long-chain olefin isomerization, functionalization have been discussed. While Chirik and co-workers reported an olefin isomerization/anti-Markovnikov selective hydrosilylation using di-imino iron(0) dinitrogen complex, the high sensitivity of this catalyst towards air and moisture combined with the lack of ease of preparation hinder the overall applicability of this protocol. Xile Hu and co-workers reported a well-defined bis(amino) amide nickel pincer complex for catalysing a tandem isomerization/hydrosilylation (Scheme 1.29).[55] *In-situ* activation of the catalyst using NaOiPr furnished the nickel(II) hydride. Impressively, the authors demonstrated high TON's (10000) and TOF's (83000 h^{-1}). This indicates that the catalyst is one of the most active hydrosilylation catalysts reported. Substrates possessing the valuable nitrogen-based functions such as carbamates, sulfonylamides, Boc-protected amines could be applied under catalytic conditions.



Scheme 1-29: a) Nickel catalyzed tandem olefin isomerization/hydrosilylation. b) In-situ generation of nickel hydride[55]

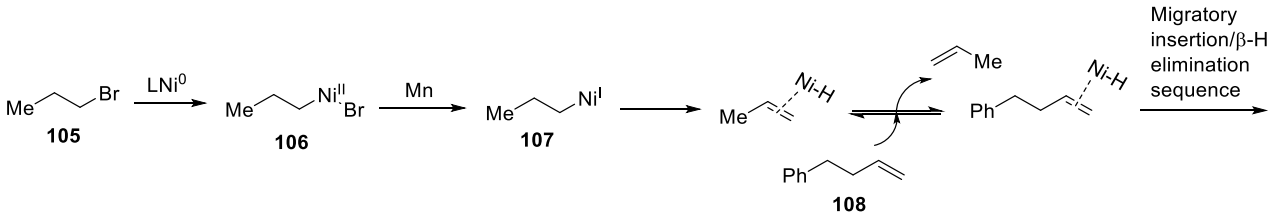
To expand the scope of the above hydrosilylation for tertiary silanes, Hu and co-workers used a heterogeneous catalyst $Ni(OtBu)_2 \cdot xKCl$ that was generated by the action of KOtBu on the nickel(II)chloride-TMEDA complex.[56] Interestingly, the heterogeneous catalyst was highly active for hydrosilylation using tertiary silanes. The authors also characterized the nanoparticles and conducted a poisoning test using Hg that impaired the catalytic performance. Using a mixture of isomers of octene, the hydrosilylation protocol was successful in synthesizing triethoxy(octyl)silane in a convergent manner. Triethoxy(octyl) silane is an important ingredient for coatings industry and is produced in ton scale annually. Unsaturated fatty acids could also be employed as substrates. In this case, the isomerization over 8 carbons was possible and product was obtained with high terminal selectivity (>10:1).



Scheme 1.30: Nickel catalyzed tandem olefin isomerization/hydroheteroarylation of allyl arenes[57]

In 2013, Ong and co-workers developed the first nickel catalyzed tandem olefin isomerization/hydroheteroarylation using $Ni(cod)_2$ and IMes as a ligand (Scheme 1.30).[57] The carbon on a benzimidazole skeleton possessing the most acidic hydrogen was the reaction site. Interestingly, a switch in selectivity from branched to linear was possible by using $AlMe_3$ in catalytic amounts. A η^3-nickel hydride intermediate was proposed to be involved in the isomerization pathway. Isomerization over 3 bonds and the reactivity of internal double bonds was demonstrated.

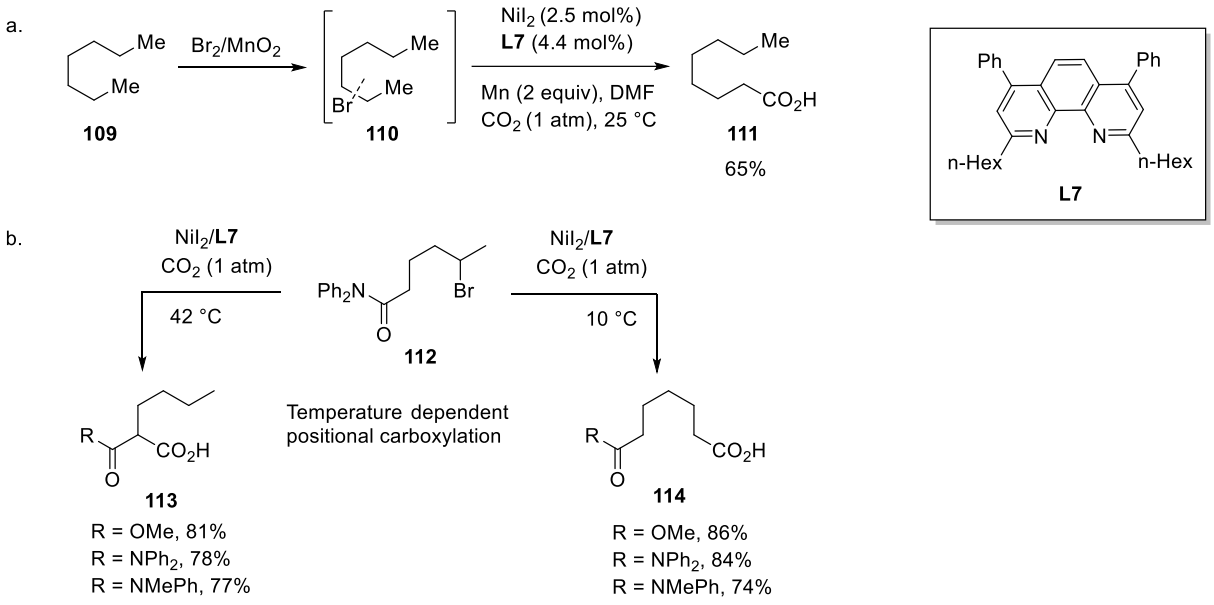
The past decade saw the advent of nickel catalyzed remote functionalization processes that use abundantly available petrochemical feedstock (technical grade olefin mixtures) by a convergent reactivity. The transformations discussed in the following section have a common ground in the catalyst system employed. Bipyridine based ligands have been used for stabilization of the nickel hydride. *n*-propyl bromide was used as a sacrificial alkyl halide for the generation (partial) of nickel hydride. Manganese or zinc was employed as a reductant for reducing Ni(II) to Ni(I). In certain cases, polymethylhydrosiloxane (PMHS) was employed as a hydride source. (Scheme 1.31)



Scheme 1.31: Mechanism of generation of nickel hydride in presence of sacrificial alkyl halide, reductant and a ligand

Martin and co-workers developed an expeditious one-pot procedure for direct conversion of isomeric mixture of olefins to corresponding fatty acids (Scheme 1.32).[58a, 58b] The first step involves the bromination of the hydrocarbon feedstock. The mixture of alkyl bromides does not need purification and could be carried on for the nickel catalyzed carboxylation. The catalyst system is simple and comprises low loadings of both NiI_2 and **L7** as the ligand and manganese as reductant. The transformation proceeding at room temperature highlights the mildness of the reaction conditions. The catalyst system had to be chosen to favor the β-hydride elimination of

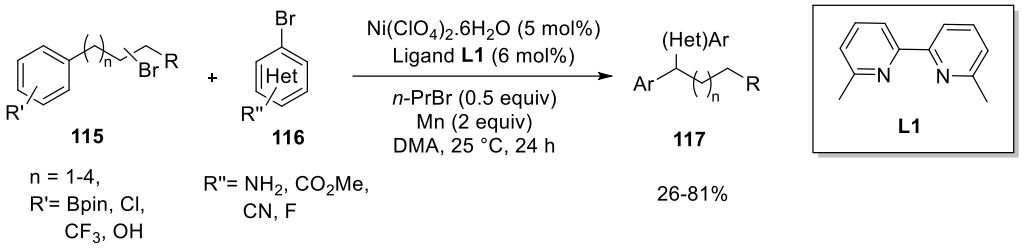
carbonickelated species over carboxylation. In this manner, the formation of a terminal C-Ni bond would be favored. The optimized reaction displayed an impressive chemoselectivity profile with acetals, heterocycles, nitriles, sulfonamides being tolerated. Interestingly, the authors discovered an unusual temperature-dependent site selectivity. For example, the carboxylation of the amide precursor **112** at 50 °C under standard conditions resulted in the formation of branched isomer whereas lowering the temperature to 25 °C led to the formation of linear isomer with high selectivity. A non-dissociative pathway for isomerization was proposed since stereochemical erosion did not occur. This methodology forms the basis of utilization of hydrocarbon feedstock in a convergent manner to obtain value added products.



Scheme 1.32: a) Nickel catalyzed remote carboxylation of olefins b) Temperature dependent site-selectivity of carboxylation[58a]

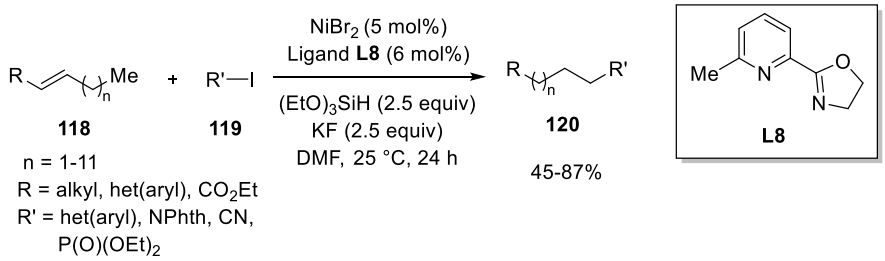
The first remote cross-electrophile coupling between alkyl and (hetero)aryl bromides was developed in 2017 (Scheme 1.33).[33] The synthetic design relied on enabling greater reactivity of alkyl bromides with Ni(0) compared to aryl bromides. The oxidative addition into the alkyl bromide led to the formation of nickel hydride that resulted in the conjugative migration of the double bond. Considering the complexity of the reaction design, remarkably mild conditions have been employed. Apart from the compatibility with various functional groups such as nitrile, silane, boronic acid pinacol ester, and phosphate ester, a transformation of primary and secondary alkyl bromides in a regio-convergent manner was also displayed. The role of the sacrificial alkyl bromide was elucidated using deuterated *n*-propyl bromide. Deuterium was detected all over the hydrocarbon chain of the substrate alkyl bromide. The nickel hydride isomerized the

in situ generated olefin in a dissociative manner. This was confirmed by performing an experiment in which an alkene and alkyl bromide were present in equal amounts. Equal amounts of coupling products were generated, hence confirming this hypothesis. The authors presented a mechanistic proposal in which a migratory insertion/β-hydride elimination sequence was responsible for conjugative migration. Finally, upon the of Ni(I) benzyl species (at the site of functionalization) was generated and reacted in the oxidative addition with a (hetero)aryl bromide to give a Ni(III) species that subsequently underwent reductive elimination to furnish the 1,1-diarylalkane product.



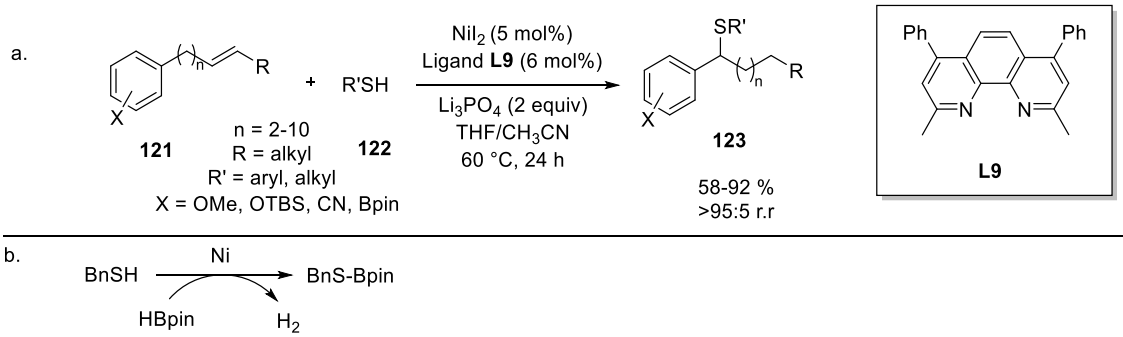
Scheme 1.33: Nickel catalyzed cross-electrophile coupling between alkyl and (hetero)aryl bromides[33]

To obtain linear selectivity in a hydroalkylation process, Zhu and co-workers envisioned a catalytic approach that draws heavily from the previously described remote functionalization (Scheme 1.34).[59] The catalytic system was optimized to enable a thermodynamically undesirable isomerization to terminal olefin and a follow-up hydroalkylation. As opposed to the remote cross-electrophile coupling, in this case, triethoxysilane was used to generate the nickel hydride. Additionally, mild reaction conditions enabled regioconvergent reactivity of petroleum feedstock to give a single product with high linear selectivity. The versatility of this catalytic system was highlighted through a remote hydroarylation of boron-containing alkenes.[60] Alkyl aryl boronates are valuable building blocks in organic synthesis. Beta alkenyl boronate could undergo isomerization using the in-situ generated nickel hydride and finally react with the aryl iodide. The only addition/change to the catalyst system, in this case, was the use of KF along-with ligand **L8**. The transformation was, however, not regiospecific. Upon employing an alkene possessing both Bpin and phenyl functional groups, the two possible products of hydroarylation were formed in almost the same amount. Impressively, the transformation was employed for late-stage functionalization of pharmaceutically relevant compounds.



Scheme 1.34: Nickel catalyzed remote terminal selective hydroalkylation[59]

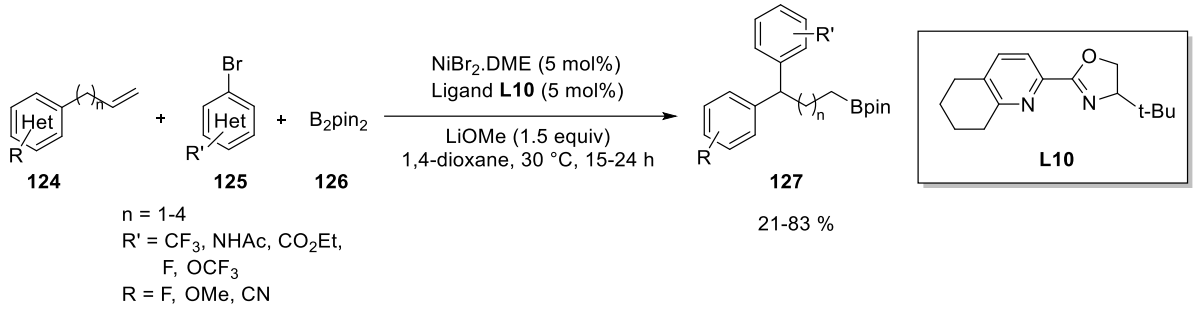
Zhu and co-workers reported a nickel catalysed remote hydrothiolation employing aromatic and aliphatic thiols as nucleophiles (Scheme 1.35).[61] While the catalyst system is similar to that in the previously illustrated transformations, stoichiometric amounts of pinacol borane and Li_3PO_4 were necessary for the reaction. Interestingly, using an external hydride source such as dimethoxy(methyl)silane with DMSO as solvent switched the regioselectivity and gave the terminal thioether exclusively. Initially, the authors proposed the presence of the disulfide BnS-SBn as the putative intermediate. To prove its existence, a series of NMR experiments were performed. It was observed that the formation of Bpin-SBn is preceded by the formation of the disulfide. To confirm this assertion, separate stoichiometric experiments with Bpin-SBn were performed. These experiments gave the product thioether in comparable yield. Deuteration experiments further reinforced this assertion. The use of deuterated thiol did not lead to the scrambling of deuterium over the alkyl chain, whereas scrambling was observed upon the use of DBpin. The lack of deuterium incorporation on the benzylic position explains why the reaction progress is independent of the electronic character of the phenyl ring. Furthermore, the presence of beta hydrogens on the ethereal solvent proved to be vital for a successful reaction. A variety of functional groups were tolerated in this transformation including nitriles, carboxylic acids, acetylated amine, and cysteine could be employed in the catalytic reaction.



Scheme 1.35: a) Nickel catalyzed tandem conjugative olefin isomerization/hydrothiolation. b) Formation of BnS-Bpin as the putative intermediate for hydrothiolation

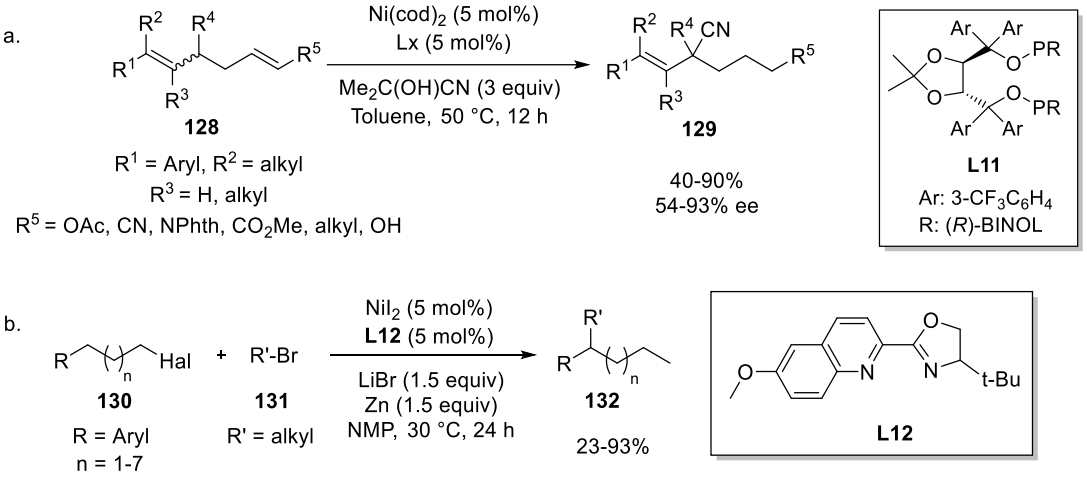
An example of conjugative migration with difunctionalization is the 1,n-arylboration of allyl benzene type systems.[62] When allyl benzene is used along-with aryl halide and a boronate precursor, selectivity issues may arise from competitive Heck-type products and branched aryl boronated products. A catalyst system comprising $NiCl_2DME$, ligand **L10** and LiOMe was successfully employed selectively giving 1,1-diaryl alkanes (Scheme 1.36). The products of arylboration were also functionalized for the synthesis of fenpiprane, prozapine, fendiline. Similarly, Zhu and co-workers reported a nickel catalysed variant of migratory remote arylation

using aryl boronates.[63] The oxidative addition of alcohol is responsible for generating a nickel hydride that displaces the double bond in a conjugative manner. Unlike the remote cross electrophile coupling that involved oxidative addition of aryl halide on carbonickelated species at benzylic position, the placement of the aryl group occurs through early transmetalation in the catalytic cycle. Hence, a two-electron redox catalytic cycle is proposed to occur. Moreover, the nickel hydride generated in this catalytic system enables a non-dissociative chain-walking. Interestingly, the nickel (II) aryl hydride is vital for the isomerization to occur. This was identified by carrying out the reaction with a nickel (0) precursor and hydride source without the aryl boronic acid. It did not lead to isomerization.



Scheme 1.36: Nickel catalyzed remote 1,n-type difunctionlization of allyl arenes using bromoarenes and pinacolboranes[62]

Yin and co-workers delineated an approach for remote cross-electrophile alkylation of alkyl bromides (Scheme 1.37).[64] The catalyst system comprises a NiI_2, a bulky ligand **L12**, LiBr and Zn as the reductant. This is the first example of a remote formation of C_{sp3}-C_{sp3} bond with nickel catalysis. Deuteration experiments showed that the 'chain-walking' event occurred on both the alkyl bromides. The trigger for isomerization is oxidative addition in the C-halogen bond and eventual generation of a double bond. However, using allyl benzene did not yield any product arising from the remote coupling. The switching of redox states can be readily accomplished by electrochemical means in a nickel catalysed cross-coupling reaction. In 2020, Fang and co-workers reported the first nickel catalysed migratory hydrocyanation of non-conjugated dienes.[65] The experimental design relied on 'trapping' one of the olefins with a directing group (such as phenyl ring) so that the other olefin can be engaged in the catalytic cycle. Acetone cyanohydrin was used as the nitrile source along with $Ni(cod)_2$. The transformation displayed a remarkably broad substrate scope with various nitrogen-containing functions and heterocyclic motifs being tolerated. Although the double bond migration was possible only over 3 bonds, a quaternary centre was generated with an enantiomeric excess of 82%. An iterative olefin insertion/beta-hydride elimination pathway was proposed. A mixture of 3 regioisomers could be reacted in a convergent manner to give a single product.



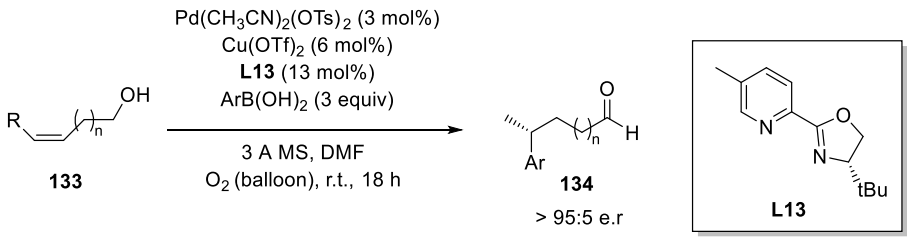
Scheme 1-37: Remote cross-electrophile alkylation of activated and un-activated alkyl bromides[64, 65]

1.5 Deuterium Labelling Experiments in Remote Functionalization

The site-selective deuteration of an organic scaffold or catalyst precursor provides valuable insight into the catalytic cycle. Unique features of mechanistic experiments that rely on deuterium incorporation are the ease of spectroscopic analysis (NMR/IR/MS), traceability, and reactivity differences arising from differing bond strengths. The difference in the zero-point energy of carbon-deuterium to carbon-hydrogen bond leads to differing free energies. The bond undergoing the reaction is usually weakened in the activated complex. Since the C-D bond has a lower zero-point energy (greater stability), it results in a higher barrier for activation. It is important to know that other bonds in the compound are considered non-reactive and hence, un-affected during the reaction.[66] Using isotopically labelled compounds can be helpful in several non-kinetic aspects of the reaction as well. Not only ^{2}H but also ^{35}S, ^{32}P, ^{37}Cl, ^{131}I have seen applications in obtaining mechanistic insight. There are a few key factors to be addressed in labelling experiments, such as the site-selective incorporation of the isotope and the extent of enrichment. Perhaps of a greater importance is the analysis of product(s) from the isotopically labelled reactants and determining isotopic distribution. Isotope labelling can also be applied as a tool to decipher metabolic pathways.

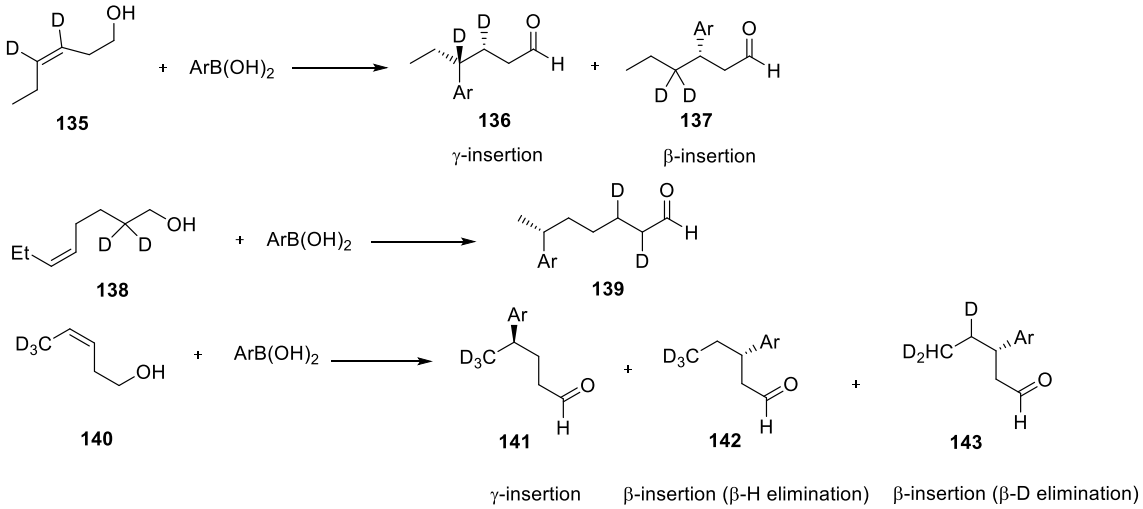
The following section gives a compilation of key results obtained from deuteration experiments in the context of remote functionalization reactions. The comparison of initial rates of catalytic experiments in which deuterated and non-deuterated counterparts are used gives . Apart from knowing the magnitude of kinetic isotope effect (KIE), deuterium labelling has been extensively used in organometallic chemistry to trace a reaction path. Specific examples include palladium catalyzed cycloisomerization, allylic substitution, ruthenium catalyzed ene-yne metathesis.[67] The aim of the following examples is to give the reader an overview of experimental design for deuterium labelling and the conclusions that can be drawn from the same.

Example 1: Heck Arylation/Isomerization: As mentioned in Section 1.4.1.1, the remote functionalization triggered by Heck arylation has been extensively investigated.[68] The deuterium labelling experiments were performed to understand the preferential site of carbopalladation, the directionality and reversibility of chain-walking process.



Scheme 1.38: Palladium catalyzed redox-relay arylation using aryl boronic acids[68]

Deuteration Experiments: Substrate **135** with deuterated olefinic protons was chosen for the initial analysis. The deuterium was intact on both the positions when the arylation occurred on the γ-position. When the arylation occurred on β-position, the γ-position was found to be doubly deuterated. No scrambling of deuterium was observed on the other end of the chain. Double deuteration in substrate **138** on one of the central carbons was done. Substrate **140** with deuteration on terminal methyl group was subjected to remote Heck-arylation with arenes possessing donating/withdrawing groups. Upon reaction, the presence of deuterium solely on the site α to the carbon was the major product(s). **141** and **142**

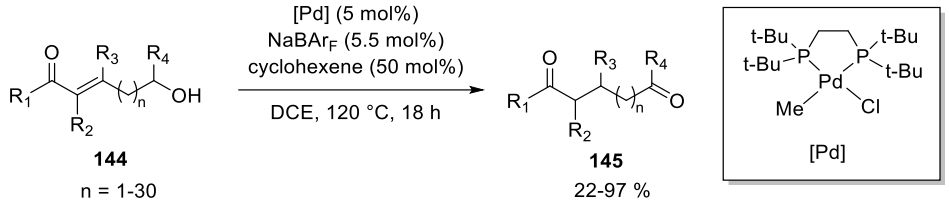


Scheme 1.39: Deuteration experiments

Analysis/Mechanistic Proposal: The absence of deuterium on the carbons α, δ and ϵ in **136** and **137** indicates that the chain-walking process is irreversible and is directed toward the alcohol. As γ-insertion occurs in Substrate **138**, the palladium preferentially moves toward the alcohol. Upon β insertion of the arene, there are two pathways for the palladium, one involving β-H elimination from the benzylic position and the other involving β-H elimination. Interestingly the products from both these pathways were isolated. This confirms the fact that although reversibility in this catalytic system is possible, the formation of product aldehyde is favoured in the end. Finally, the product arising from substrate **138** shows deuterium on a position adjacent to that in the substrate which arises of-course due to the β-H elimination. In this case, the lack of deuterium on any of the positions α, β and γ in major products **141** and **142** confirms that directionality and irreversibility of the isomerization process prevails.

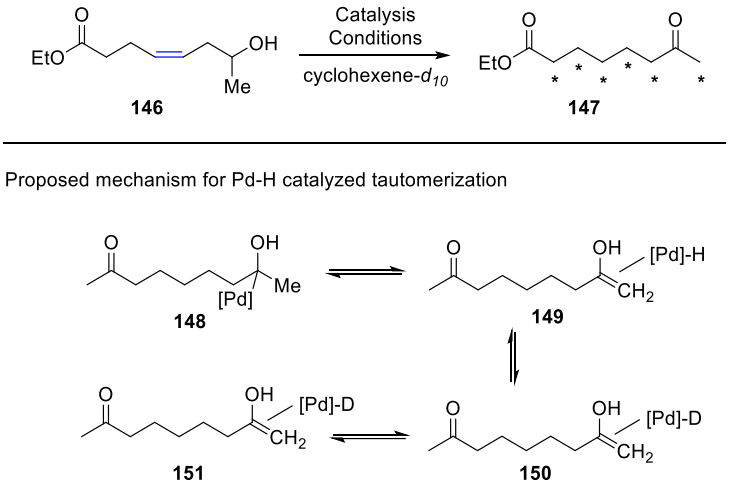
These experiments serve as a roadmap to gauge the reversibility and directionality of the process. The key is to design experiments with deuterium incorporated on the olefin, at the distal end of the carbon chain and in the mid-point which the putative palladium hydride is thought to traverse.

Example 2: **Long Chain De-conjugative migration:** Mazet and co-workers studied a de-conjugative isomerization of α,β-unsaturated compounds with the termination occurring through formation of ketone.[28] As in the previous example, the deuterium labelling experiments were carried out to probe the directionality of isomerization.



Scheme 1.40: Palladium catalyzed long-chain deconjugative migration[28]

Deuteration Experiments: The catalytic system uses cyclohexene as a sacrificial alkene for the palladium hydride generation. Therefore, fully deuterated cyclohexene was used. Substrate **146** was subjected to the catalysis conditions. Deuterium was detected all over the carbon chain. Moreover, a trace of deuterium was found on the methyl group.

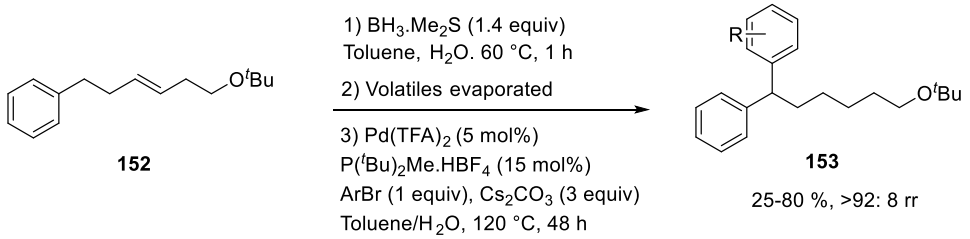


Scheme 1.41: Deuteration Experiments

Analysis/Mechanistic Proposal: The presence of deuterium all over the carbon chain indicates no preferential directionality in the isomerization. Moreover, the fact that the product ketone is formed indicates the reversibility (dissociative nature of Pd-H) of the isomerization. Scrambling

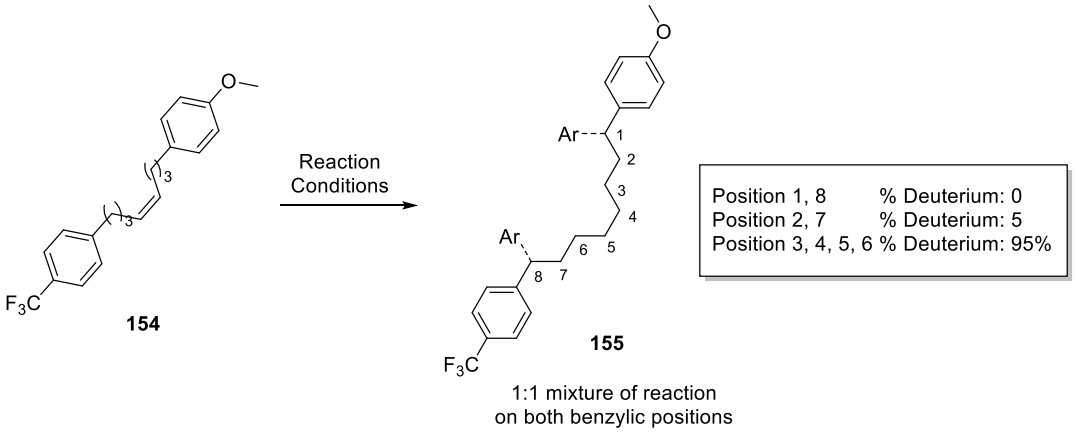
of Pd-H with Pd-D (**149** to **150**) also occurred because of tautomerization, which explains the incorporation of deuterium on the methyl group, albeit in traces.

Example 3:Remote Migratory Suzuki-Miyaura: Baudoin and co-workers reported a palladium catalysed remote migratory Suzuki-Miyaura cross coupling reaction.[44]



Scheme 1.42: Palladium catalyzed remote migratory Suzuki-Miyaura cross coupling[44]

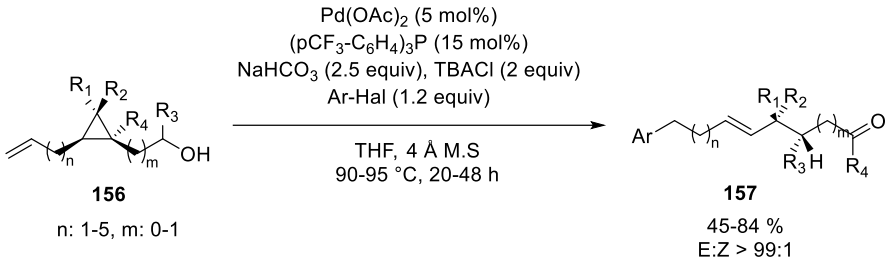
Deuteration Experiments: In the catalytic system, the generation of palladium hydride occurs on the substrate itself. For this reason, deuterated alkene **154** with two electronically different arenes at the end of the chain was chosen as a substrate for investigation. Deuterium scrambling was observed on position 2 and 3. But there was no deuterium detection on position 1, which is the benzylic position and a mixture of 1:1 of product **155** was isolated.



Scheme 1.43: Deuteration Experiments

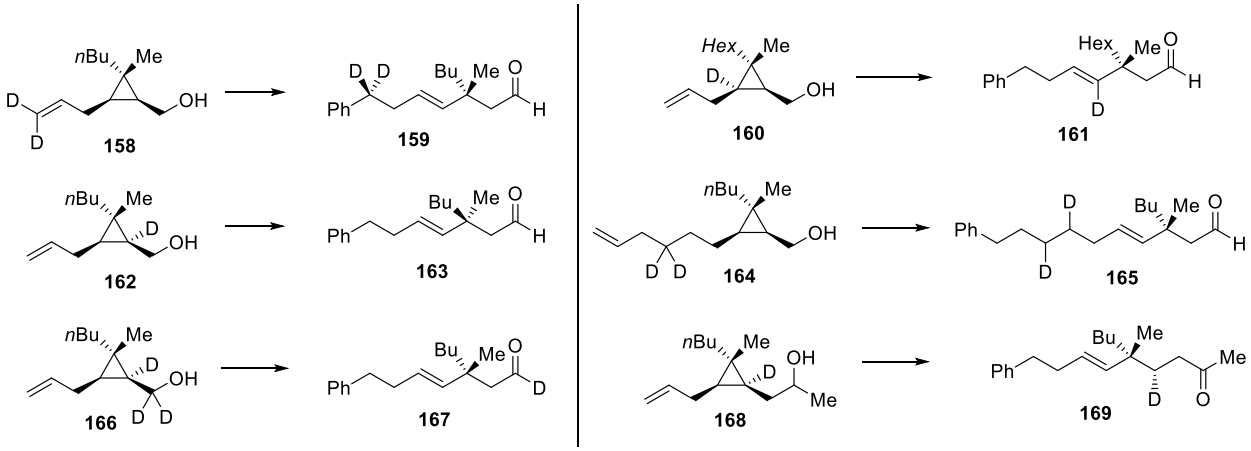
Analysis/Mechanistic Proposal: Although there is no electronic preference of the character of aryl boronic acid, a scrambling of deuterium in the manner shown in Scheme 1.43 points to lack of directionality in isomerization. Moreover, the absence of deuterium on benzylic position clarifies the fact that the transformation is independent of the electronic predisposition of benzylic position. The extent of deuterium incorporation often gives a hint on the nature of isomerization. In this case, a mere 5% incorporation in homobenzylic position indicates that isomerization occurs irreversibly and that the benzyl palladium intermediate acts as a thermodynamic sink.

Example 4: **Redox-relay Heck arylation/cyclopropane ring opening:** In 2017, a unique remote arylation and concomitant generation of quaternary center through cyclopropane ring opening and the isomerization of alcohol to the corresponding carbonyl was reported by Marek.[42] Owing to three different functionalization events occurring, deuterium labelling experiments were conducted to understand this reactivity separately.



Scheme 1.44: Palladium catalyzed long-chain isomerization triggered by arylation[42]

Deuteration Experiments: Several deuterated substrates were synthesized. Subjecting substrate 5 possessing deuterium on the alkene led to retention of deuterium. Presence of deuterium on homoallylic position led to 1,2-placement of deuterium in the product of catalysis. Then, substrates containing deuterium on both ends of cyclopropane ring were synthesized. Interestingly, the loss of deuterium was observed in substrate **162**. Placement of deuterium on the hydroxy-substituted C-atom led to its incorporation in the aldehyde product.



Scheme 1.45: Deuteration experiments

Analysis/Mechanistic Proposal: The first two experiments with deuterium on the olefin and at homoallylic position (**158** and **160**) point to the classical 1,2-hydrogen shift mechanism of olefin isomerization. As there is no further scrambling of deuterium, a uni-directional process is proposed to occur. The presence of deuterium on the product olefin indicated that the opening of cyclopropane ring is faster than generation of an alkylidene cyclopropane intermediate since that

would have led to deuterium scrambling. The authors accounted for the loss of deuterium in product by proposing the occurrence of a rapid keto-enol tautomerization. This explanation would also account for erosion of stereochemistry in product **163**. Moreover, similar deuterium labelling in the presence of a secondary alcohol **168** led to retention of deuterium. Expectedly, product **167** was obtained with deuterium attached to the carbonyl carbon atom. As a summary, deuteration on various sites of the compound is essential especially at sites where functionalization is predicted to occur.

1.6 References

[1] C. U. Pittman Jr, L. R. Smith, *J. Am. Chem. Soc.* **1975**, *97*, 1749-1754.
[2] M. P. Plesniak, H.-M. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 0077.
[3] K. Mosbach, *Scientific American* **1971**, *26*, 225.
[4] J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020.
[5] M. Malacria, *Chem. Rev.* **1996**, *96*, 289-306.
[6] a)P. A. Zoretic, X. Weng, M. L. Caspar, D. G. Davis, *Tetrahedron Lett.* **1991**, *32*, 4819-4822; b)L. D. Field, B. A. Messerle, S. L. Wren, *Organometallics* **2003**, *22*, 4393-4395.
[7] B. M. Trost, *Science* **1991**, *254*, 1471.
[8] B. M. Trost, D. C. Lee, F. Rise, *Tetrahedron Lett.* **1989**, *30*, 651-654.
[9] B. M. Trost, Y. Shi, *J. Am. Chem. Soc.* **1993**, *115*, 12491-12509.
[10] a)H.-W. Bohnen, B. Cornils, in *Advances in Catalysis, Vol. 47*, Academic Press, **2002**, pp. 1-64; b)K. A. Ostrowski, T. A. Faßbach, D. Vogelsang, A. J. Vorholt, *ChemCatChem* **2015**, *7*, 2607-2613.
[11] M. Vilches-Herrera, L. Domke, A. Börner, *ACS Catal.* **2014**, *4*, 1706-1724.
[12] a)S. Biswas, *Comments on Inorganic Chemistry* **2015**, *35*, 300-330; b)A. Sen, T. W. Lai, *Inorg.* **1984**, *23*, 3257-3258; c)H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* **2018**, *4*, 153-165; d)E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816-9826.
[13] H. Wakamatsu, M. Nishida, N. Adachi, M. Mori, *J. Org. Chem.* **2000**, *65*, 3966-3970.
[14] D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592-9593.
[15] K. Ishibashi, M. Takahashi, Y. Yokota, K. Oshima, S. Matsubara, *Chem. Lett.* **2005**, *34*, 664-665.
[16] A. Kapat, T. Sperger, S. Guven, F. Schoenebeck, *Science* **2019**, *363*, 391-396.
[17] W. Dong, H. Yang, W. Yang, W. Zhao, *Org. Lett.* **2020**, *22*, 1265-1269.
[18] A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778-789.
[19] X. Yu, H. Zhao, P. Li, M. J. Koh, *J. Am. Chem. Soc.* **2020**, *142*, 18223-18230.
[20] Y. Liu, Y. Zhou, H. Wang, J. Qu, *RSC Adv.* **2015**, *5*, 73705-73713.
[21] J. J. Molloy, J. B. Metternich, C. G. Daniliuc, A. J. B. Watson, R. Gilmour, *Angew. Chem. Int. Ed* **2018**, *57*, 3168-3172.
[22] Q.-Y. Meng, T. E. Schirmer, K. Katou, B. König, *Angew. Chem. Int. Ed* **2019**, *58*, 5723-5728.
[23] V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011-2034.

[24] L. T. N. Chuc, C.-S. Chen, W.-S. Lo, P.-C. Shen, Y.-C. Hsuan, H.-H. G. Tsai, F.-K. Shieh, D.-R. Hou, *ACS Omega* **2017**, *2*, 698-711.
[25] A. M. LaPointe, F. C. Rix, M. Brookhart, *J. Am. Chem. Soc.* **1997**, *119*, 906-917.
[26] Y. Yamasaki, T. Kumagai, S. Kanno, F. Kakiuchi, T. Kochi, *J. Org. Chem.* **2018**, *83*, 9322-9333.
[27] E. Larionov, L. Lin, L. Guénée, C. Mazet, *J. Am. Chem. Soc.* **2014**, *136*, 16882-16894.
[28] L. Lin, C. Romano, C. m. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 10344-10350.
[29] D. Fiorito, S. Scaringi, C. Mazet, *Chem. Soc. Rev.* **2021**.
[30] a)R. Breslow, *Acc. Chem. Res.* **1980**, *13*, 170-177; b)R. Breslow, *Chem. Soc. Rev.* **1972**, *1*, 553-580.
[31] K. Nilsson, A. Hallberg, *J. Org. Chem.* **1990**, *55*, 2464-2470.
[32] Y. He, Y. Cai, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 1061-1064.
[33] F. Chen, K. Chen, Y. Zhang, Y. He, Y.-M. Wang, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 13929-13935.
[34] H. E. Bonfield, D. Valette, D. M. Lindsay, M. Reid, *Chem. Eur. J.* **2020**.
[35] E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455.
[36] a)T.-S. Mei, E. W. Werner, A. J. Burckle, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 6830-6833; b)H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 3462-3465; c)J. Liu, Q. Yuan, F. D. Toste, M. S. Sigman, *Nat. Chem* **2019**, *11*, 710-715.
[37] T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340-344.
[38] a)H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 14226-14229; b)H. H. Patel, M. B. Prater, S. O. Squire, M. S. Sigman, *J. Am. Chem. Soc.* **2018**, *140*, 5895-5898.
[39] A. Bahamonde, B. Al Rifaie, V. Martín-Heras, J. R. Allen, M. S. Sigman, *J. Am. Chem. Soc.* **2019**, *141*, 8708-8711.
[40] T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, *J. Am. Chem. Soc.* **2012**, *134*, 16544-16547.
[41] T. Kochi, K. Ichinose, M. Shigekane, T. Hamasaki, F. Kakiuchi, *Angew. Chem. Int. Ed* **2019**, *58*, 5261-5265.
[42] S. Singh, J. Bruffaerts, A. Vasseur, I. Marek, *Nat. Commun.* **2017**, *8*, 14200.
[43] C. Han, Z. Fu, S. Guo, X. Fang, A. Lin, H. Yao, *ACS Catal.* **2019**, *9*, 4196-4202.
[44] Y. Baumgartner, O. Baudoin, *ACS Catal.* **2020**, *10*, 10508-10515.
[45] W. Clegg, M. R. J. Elsegood, G. R. Eastham, R. P. Tooze, X. Lan Wang, K. Whiston, *Chem. Commun.* **1999**, 1877-1878.
[46] C. J. Moulton, B. L. Shaw, *J. Chem. Soc. Chem. Commun* **1976**, 365-366.
[47] R. I. Pugh, E. Drent, P. G. Pringle, *Chem. Commun.* **2001**, 1476-1477.
[48] L. E. Crascall, J. L. Spencer, *J. Chem. Soc. Dalton. Trans* **1992**, 3445-3452.
[49] C. Jimenez Rodriguez, D. F. Foster, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2004**, 1720-1721.
[50] C. Jiménez-Rodriguez, G. R. Eastham, D. J. Cole-Hamilton, *Inorg. Chem. Commun* **2005**, *8*, 878-881.
[51] H. Busch, F. Stempfle, S. Heß, E. Grau, S. Mecking, *Green Chem.* **2014**, *16*, 4541-4545.
[52] V. Goldbach, L. Falivene, L. Caporaso, L. Cavallo, S. Mecking, *ACS Catal.* **2016**, *6*, 8229-8238.
[53] S. K. Hess, N. S. Schunck, V. Goldbach, D. Ewe, P. G. Kroth, S. Mecking, *J. Am. Chem. Soc.* **2017**, *139*, 13487-13491.
[54] J. Yang, J. Liu, Y. Ge, W. Huang, H. Neumann, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed* **2020**, *59*, 20394-20398.
[55] I. Buslov, J. Becouse, S. Mazza, M. Montandon-Clerc, X. Hu, *Angew. Chem. Int. Ed* **2015**, *54*, 14523-14526.
[56] I. Buslov, F. Song, X. Hu, *Angew. Chem. Int. Ed* **2016**, *55*, 12295-12299.
[57] W.-C. Lee, C.-H. Wang, Y.-H. Lin, W.-C. Shih, T.-G. Ong, *Org. Lett.* **2013**, *15*, 5358-5361.
[58] a)F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* **2017**, *545*, 84-88; b)M. Gaydou, T. Moragas, F. Juliá-Hernández, R. Martin, *J. Am. Chem. Soc.* **2017**, *139*, 12161-12164.

[59] F. Zhou, J. Zhu, Y. Zhang, S. Zhu, *Angew. Chem. Int. Ed* **2018**, *57*, 4058-4062.
[60] Y. Zhang, B. Han, S. Zhu, *Angew. Chem. Int. Ed* **2019**, *58*, 13860-13864.
[61] Y. Zhang, X. Xu, S. Zhu, *Nat. Commun.* **2019**, *10*, 1752.
[62] W. Wang, C. Ding, Y. Li, Z. Li, Y. Li, L. Peng, G. Yin, *Angew. Chem. Int. Ed* **2019**, *58*, 4612-4616.
[63] Y. He, C. Liu, L. Yu, S. Zhu, *Angew. Chem. Int. Ed* **2020**, *59*, 9186-9191.
[64] Y. Li, Y. Li, L. Peng, D. Wu, L. Zhu, G. Yin, *Chem. Sci.* **2020**, *11*, 10461-10464.
[65] R. Yu, S. Rajasekar, X. Fang, *Angew. Chem. Int. Ed* **2020**, *59*, 21436-21441.
[66] K. B. Wiberg, *Chem. Rev.* **1955**, *55*, 713-743.
[67] G. C. Lloyd-Jones, M. P. Muñoz, *J. Labelled. Comp. Radiopharm* **2007**, *50*, 1072-1087.
[68] M. J. Hilton, L.-P. Xu, P.-O. Norrby, Y.-D. Wu, O. Wiest, M. S. Sigman, *J. Org. Chem.* **2014**, *79*, 11841-11850.

CHAPTER 2

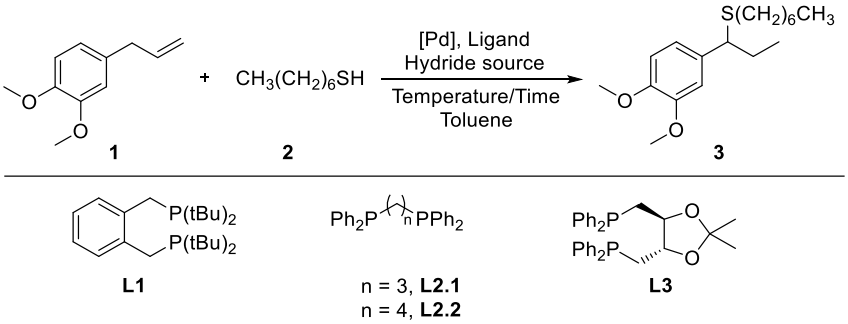
SUMMARY OF PUBLISHED RESULTS

2 Summary of the Published Results

2.1 Palladium-Catalyzed Tandem Isomerization/Hydrothiolation of Allylarenes

The aim of the project was the development of a tandem catalytic process for a novel C-S bond formation based on the combination of isomerization and hydrothiolation of allylarenes. The success of the transformation relied on the stability of the *in situ* generated palladium hydride in the presence of highly coordinating thiols. For this purpose, the catalyst system including a palladium precatalyst, ligand and Brønsted acid as the hydride source was optimized for the reaction of allylarene **1** and heptane-1-thiol (Table 2.1). Palladium salts were chosen for optimization purposes owing to their known ability to catalyse double-bond transposition. Furthermore, a series of bidentate ligands were evaluated for effectively stabilizing the catalytically active species. The catalyst system for the tandem process had to be optimized in a manner that there would be a minimum deviation in reaction conditions for olefin isomerization and hydrothiolation.

Table 2.1. Optimization of the reaction conditions.



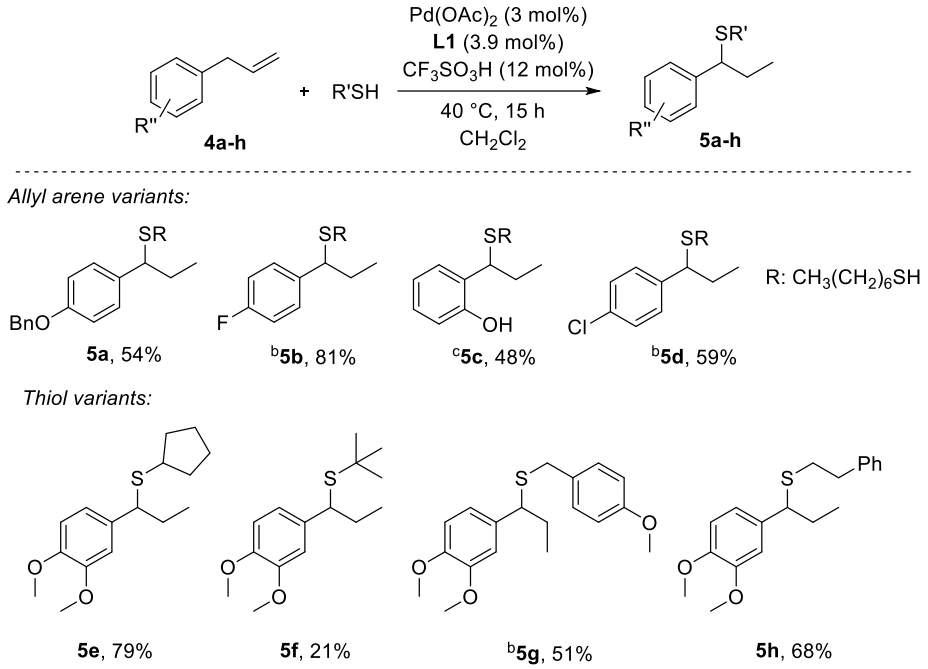
Entry	Pd. Salt (mol%)	Ligand (mol%)	Hydride source (mol%)	Yield (%)[a]
1	$Pd(OAc)_2$ (3)	**L3** (6)	CF_3SO_3H (12)	50
2	$Pd(OAc)_2$ (3)	**L1** (5.4)	CF_3SO_3H (12)	94
3	$Pd(OAc)_2$ (3)	**L2.1** (6)	CF_3SO_3H (12)	0
4	$Pd(OAc)_2$ (3)	**L2.2** (6)	CF_3SO_3H (12)	74
5[c]	$Pd(OAc)_2$ (3)	**L2.2** (5)	$(EtO)_2MeSiH$ (5)	0
6[d]	$Pd(OAc)_2$ (3)	**L1** (3.9)	CF_3SO_3H (12)	97
7[b]	$Pd(CH_3CN)_2Cl_2$ (3)	**L1** (5.4)	CF_3SO_3H (12)	0
8[b]	$Pd(PhCN)_2Cl_2$ (3)	**L1** (5.4)	CF_3SO_3H (12)	0
9[b]	Pd(dppp)(OTf)	None	None	0

*Reaction Conditions: **1** (0.5 mmol), heptane-1-thiol (0.55 mmol), toluene (0.5 M), 50 °C, 18 h. [a]Determined by quantitative GC-FID analysis using n-pentadecane as the standard. [b]4-methoxy allylbenzene (0.5 mmol). [c]4-Methoxy allyl benzene at room temperature. [d]DCM (0.5 M), 40 °C, 15 h.*

Complexes $Pd(CH_3CN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ were chosen for optimization following literature precedent on olefin isomerization.[1a, 1b, 1c] Given the spontaneous generation of

$Pd(0)L_n$ from palladium acetate, this Pd(II) salt was used in the screening as well.[2] Strongly donating bidentate ligands featuring a wide-bite angle have shown promising results in long-chain olefin isomerization.[3a, 3b, 3c] To this end, we screened bidentate ligands. Through ligand screening, clearly flexible steric bulk proved to be beneficial as **L3** gave 50% yield (Table 2.1, Entry 2). Multiple batches of **L1** with varying amount of dioxide impurity were tested. Notably, the performance of the catalytic system was found to be independent of the presence of oxide (in amounts less than 25%). Finally, a few hydride sources to generate the catalytically active palladium hydride were screened. This included $(EtO)_2MeSiH$. The ligand (**L1**) gave the highest yield in the tandem process when used along with triflic acid and palladium acetate. The other Pd(II) salts that were screened did not yield any thioether product.(Table 2.1, Entry 4 & 5) Ligands that could be successfully employed in the catalysis, albeit in lesser yield, resulted in minor amount of thioether (Table 2.1, Entry 8 & 9). The triflate counterion can effectively stabilize the palladium hydride. In the absence of heptane-1-thiol, acid catalyzed dimerization of the intermediate styrene occurred. It was important to have minimum time lapse between addition of thiol and the acid to minimize dimerization. Control experiments were performed in the absence of $Pd(OAc)_2$ and **L1** and in the absence of acid and led to partial isomerization. Moreover, the possibility of a hidden Brønsted acid catalysis from metal triflate was eliminated through the reaction with $Pd(dppp)(OTf)_2$ (Table 2.1, Entry 1). Due to the tendency of beta methyl styrene to undergo acid-catalyzed dimerization, relatively lower reaction temperatures were employed. At this temperature, the catalyst and ligand loadings of 3 and 3.9 mol% were necessary for a very good yield of the thioether (Table 2.1, Entry 7).

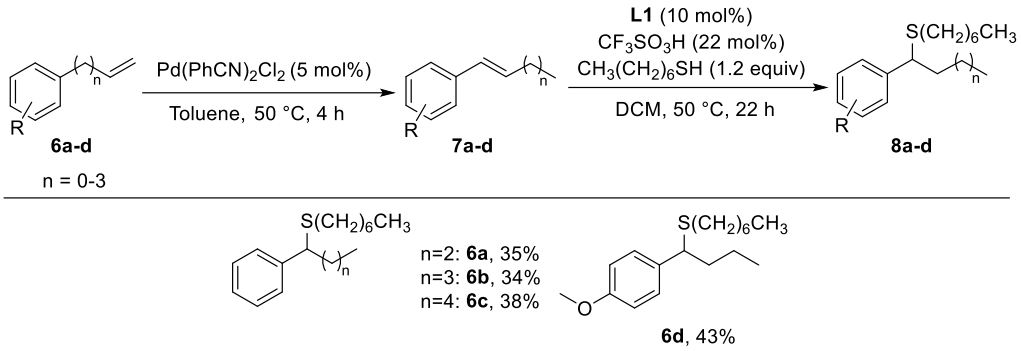
The scope of the optimized reaction conditions was tested for synthesizing a variety of benzylic thioethers from allyl arenes and aliphatic thiols. Electron rich arenes in general exhibited higher reactivity. Substrates bearing benzyloxy, fluorine, chlorine, hydroxy substituents were tolerated under the reaction conditions and gave yields ranging from 48-81%. Bromo-substituted allylarene did not undergo any reaction. A possible explanation could be oxidative addition of Pd(0), however, more experimentation would be necessary to confirm this assertion. Allyl arenes bearing strongly electron withdrawing substituents only led to conjugative migration (either partial or complete) and no benzylic thioether could be spectroscopically detected (GC-MS). Only aliphatic thiols gave the corresponding thioethers in isolable yields. Based on the substrates that were tested, a trend in reactivity depending on the nucleophilicity and steric properties of the thiol was observed. Aromatic thiols, typically prone to oxidative dimerization, did not undergo any reaction.



*Scheme 2.1: Selected examples of benzylic thioethers synthesized by tandem olefin isomerization/hydrothiolation. Reaction Conditions: Allyl arene (0.5 mmol), heptane-1-thiol (0.55 mmol), $Pd(OAc)_2$ (3 mol%), L1 (3.9 mol%), CF_3SO_3H (12 mol%), DCM (1 mL), 40 °C, 15 h. [b] Allyl arene (0.25 mmol), heptane-1-thiol (0.27 mmol), $Pd(OAc)_2$ (6 mol%), **L1** (12 mol%), CF_3SO_3H (16 mol%), DCM (1 mL), 50 °C, 64 h. [c]Toluene (1 mL), 24 h, 50 °C*

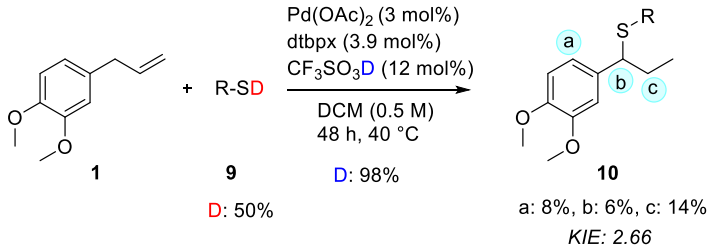
Allylarene possessing internal double bond underwent no reaction. To enable a distal functionalization, $PdCl_2(PhCN)_2$ was used (Scheme 2.2). While new modular ligand systems have enabled olefin migration over 30 carbons,[4] $PdCl_2(PhCN)_2$ was chosen as it is readily available and air-stable. While designing experiments for a distal functionalization, it was observed that adding all the reaction components at the onset terminated the reaction after isomerization over one position. However, upon sequential addition of catalyst followed by the ligand, the desired thioethers could be obtained. Competing olefin dimerization and presence of equilibrium mixture of olefins contributed to yield loss. Thus, the strategy mainly relied on

initial conjugative migration to benzylic position followed by addition of ligand, thiol and the Brønsted acid. Remote migratory hydrothiolation over 4 carbons was accomplished.



Scheme 2.2: Distal functionalization in tandem olefin isomerization/hydrothiolation. Reaction Conditions: 1. $PdCl_2(PhCN)_2$ (5 mol%), toluene (0.3 mL), alkene (0.5 mmol), 4 h, 60 °C 2. L1 (10 mol%), CF_3SO_3H (22 mol%), heptane-1-thiol (0.55 mmol), DCM (1 mL), 50 °C, 22 h

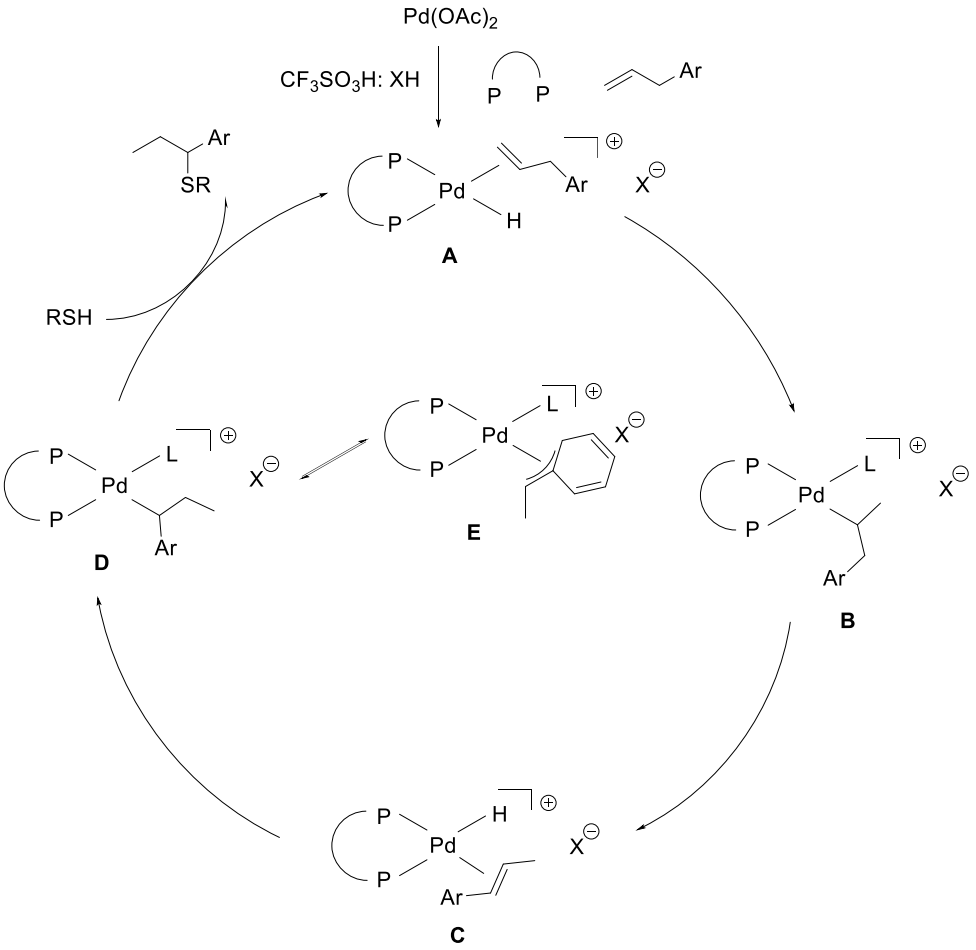
The use of Brønsted acid for generating catalytically active palladium hydride points to the classical chain-walking mechanism (one involving iterative olefin insertion/β-H elimination sequence). However, understanding the role of thiol in the catalytic process was essential to develop a mechanistic (preliminary) outline. Heptane-1-thiol used previously in the reaction optimization was partially (50%) deuterated by treatment with methanol-d_4. Furthermore, deuterated triflic acid was used for this transformation.



Scheme 2.3: Kinetic isotope effect and labelling experiments

Upon comparing the initial rates of hydrothiolation of deuterated and non-deuterated reagents, a kinetic isotope effect of 2.66 was observed (Scheme 2.3). Possibly, multiple steps in which cleavage and formation of C-H, S-H and Pd-H are a part of the catalytic cycle (Scheme 4). Hence, further experimentation/calculations are deemed necessary to unambiguously determine the rate determining step in the catalytic cycle. Interestingly, the presence of deuterium on the *ortho*-position of the phenyl ring was confirmed by ^{2}H NMR. Integral analysis of ^{1}H NMR's of both non-deuterated and deuterated thioether indicated incorporation of deuterium over the allyl chain albeit in a relatively small amount. To test if a η^3-benzyl palladium intermediate **E** is a pre-condition for the hydrothiolation, 2-allyl-1,3-dimethoxybenzene was subjected to the reaction conditions. The corresponding thioether was obtained, albeit in a low yield. The competing dimerization of the intermediate β-methyl styrene

consumed a considerable amount of the reactant. Thus, η^3-benzylpalladium **E** is proposed to behave as an intermediate that is in equilibrium with the key intermediate **D**, which is the carbopalladated complex, upon availability of the ortho proton(s). Two pathways may be responsible for regeneration of palladium hydride depending on the interaction of the thiol with the metal center. One of them involves thiol coordination to the palladium center and subsequent reductive elimination. Another plausible pathway is the direct outer sphere attack of thiol on carbopalladated complex **D.**



Scheme 2.4: Simplified proposed reaction mechanism for tandem olefin isomerization/hydrothiolation.

In conclusion, a transition metal catalyzed tandem process for C-S bond formation was developed and studied for the first time. The reaction design displayed the stability of palladium hydride in presence of co-ordinating thiols. Moreover, efforts were directed to probe the role of the thiol in catalytic cycle. Based on preliminary mechanistic experiments, the possibility of thiol regenerating the palladium hydride was highlighted. This transformation not only extends

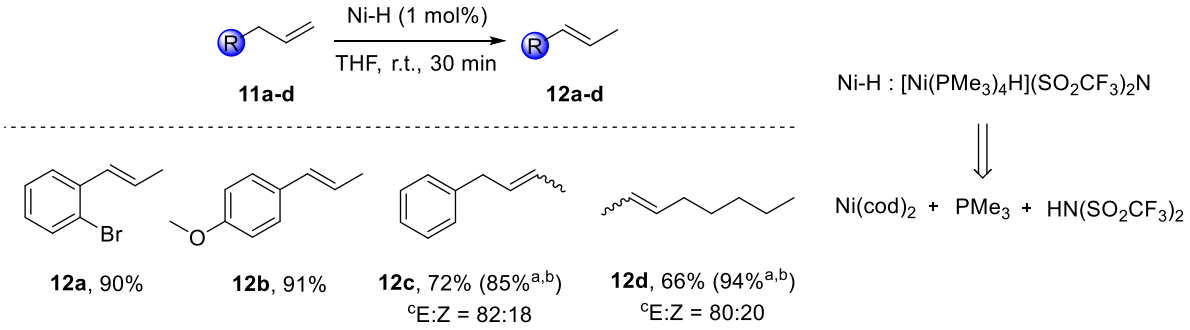
the scope of the current palladium-hydride based reactions, but also demonstrates the potential of structurally simple palladium salts in remote functionalization.

P. M. Kathe, I. Fleischer
Palladium Catalyzed Tandem Olefin Isomerization/Hydrothiolation of Allylarenes
Org. Lett. **2019**, *7*, 2213–2217.

2.2 Tandem Olefin Isomerization/Cyclization Catalyzed by Complex Nickel Hydride and Brønsted Acid

The aim of the project was to develop a catalytic system for synthesizing indole-based oxacyclic scaffolds using non-precious transition metal hydrides. This strategy is based on metal hydride mediated olefin isomerization and subsequent acid-catalyzed cyclization. In the last few decades, the structural properties of mono-nuclear nickel hydrides bearing a bulky non-coordinating counterion (of the form $[Ni(PX_3)_4H]Y$) were studied and their ability to activate CO_2 and H_2 was investigated.[5a, 5b, 5c]

Analogous to one of the first nickel hydrides $[Ni(P(OMe_3)_4)H]Cl$ studied in isomerization of but-1-ene, we decided to study complexes such as $[Ni(PPh_3)_4H]N(SO_2CF_3)_2$, $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ for tandem cyclization.[6] $[Ni(PMe_3)_4H]N(SO_2CF_3)_2N$ was synthesized by our collaborator Dr. Andreas Berkefeld from $Ni(cod)_2$, PMe_3 and bis-triflimide $(SO_2CF_3)_2NH$ as the hydride source and counterion. Investigation on isomerization of allyl arenes by $[Ni(PMe_3)_4H](SO_2CF_3)_2N$ (Ni-H) revealed the complex to be highly active giving the corresponding β-methyl styrene in 30 minutes at room temperature (Scheme 2.5). The isomerization efficiency was found to be independent on the electronic character of allyl arene.

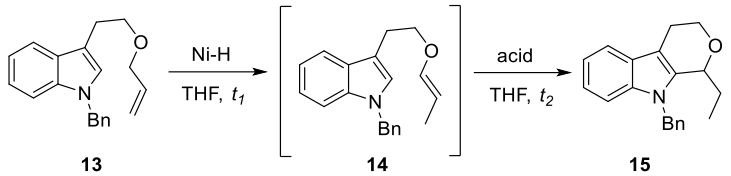


Scheme 2.5: Ni-H catalyzed olefin isomerization. Reaction Conditions: ***11*** *(0.25 mmol), [a]Determined by quantitative GC-FID analysis using n-pentadecane as an internal standard, [b]DCM (0.1 M), [c]ratio determined after 15 h by GC-FID analysis*

The single double bond isomerization was observed in 1-octene and 4-phenyl-but-1-ene and the E-isomer was obtained predominantly (E:Z >80:20). While a chain-walking mechanism is most likely operating in this case, the mechanism for the E/Z isomerization is unclear and needs further investigation. Internal and terminal di-substituted double bonds did not undergo isomerization with Ni-H.

After investigating double bond isomerization, the synthesis of two types of fused-indole ring systems, such as tetrahydropyran-indole and oxazino-indole was targeted. The corresponding precursors featuring the O-allyl tether at the C-3 position of N-substituted indoles were synthesized.

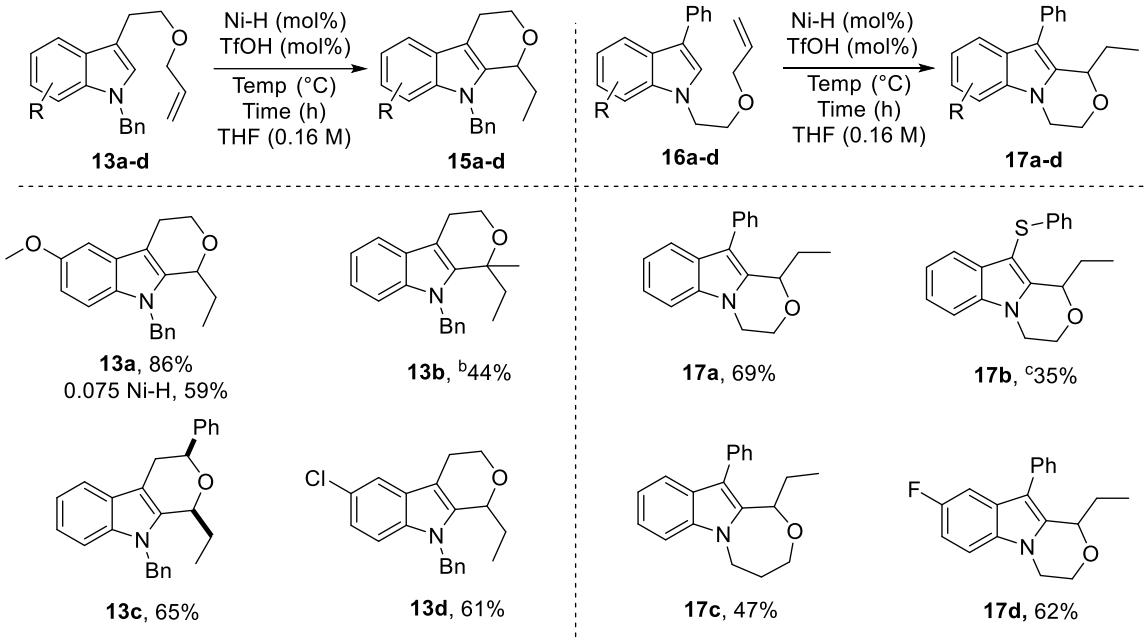
Table 2.2 Optimization of Reaction Conditions.



Entry	Ni-H (mol%)	Brønsted acid (mol%)	Temperature(°C)/Time (t_1,t_2 /h)	Time (t_1,t_2/h)	Yield (%)
1	5	$Bi(OTf)_3$ (5)	r.t/	4,4	62
2	5	TfOH (5)	r.t	0.5,0.5	80
[b]3	5	TfOH (5)	r.t	0.5,0.5	30:40:30
4	1	TfOH (4)	r.t	0.3,0.3	81
[c]5	5	-	130	0.3,18	41

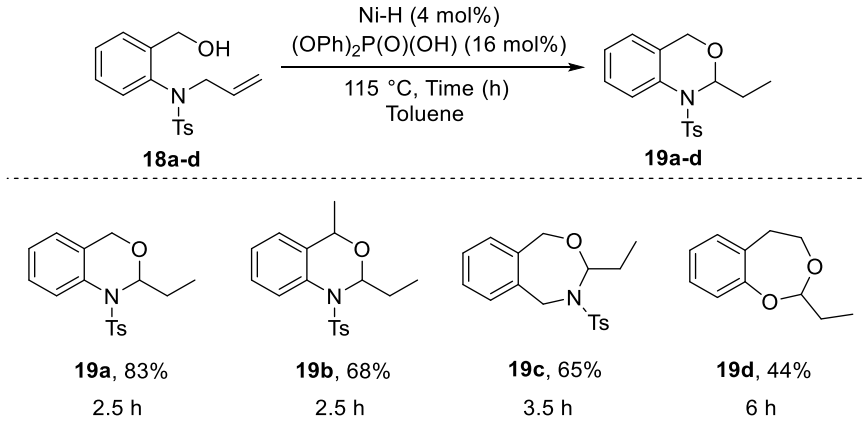
*Reaction Conditions: **13** (0.25 mmol), THF (0.16 M) [b]All components added at the beginning (Ratio of **13**:**14**:**15** determined by GC-FID) [c]Xylene*

While Ni-H isomerized terminal double bonds, an acid was necessary to generate the oxocarbenium cation. Metal triflates are known for releasing triflic acid and acting as catalysts in hydrofunctionalization reactions. Accordingly, using $Bi(OTf)_3$ proved useful and gave the product THP-Indole **15** in 62% yield (Table 2.2, Entry 1). Unfortunately, large deviations in the yield with the same reaction conditions were seen in presence of $Bi(OTf)_3$. Strong Brønsted acid such as triflic acid resulted in formation of product **15** in 80% yield (Table 2.2, Entry 2). Sequential addition of the catalysts was vital for complete conversion of **13**. Addition of all the components at the onset led to mixture of **13**, **14** and **15** (Table 2.2, Entry 3). Attempts to drive the isomerization of O-allyl ether to completion failed. After screening several parameters with Ni-H as the catalyst, a maximum isomerization of 43% was achieved. The partial isomerization was however, inconsequential, as the subsequent addition of acid gave the cyclization product. Ni-H loading of 1 mol% and 4 mol% Brønsted acid furnished product **15** in 81% yield (Table 2.2, Entry 4). In absence of the Brønsted acid, only 41% of the product was formed under much harsher reaction conditions. Precursors for fused indoles possessing functional groups such as halogens, thioarene, and thiocyanate were synthesized by a sequence involving Fischer indole synthesis, Apple reaction and nucleophilic substitution with allyl alcohol. Whereas the oxazinoindole precursors were obtained by Fischer indole synthesis followed by N- and O-alkylation. A selection of successfully converted allylethers is depicted in Scheme 2.6. High diastereoselectivity was observed in the synthesis of **13c** in which the pyran ring possessed a phenyl group. Moreover, THP-indole **13b** featuring quaternary center was synthesized albeit with relatively harsher reaction conditions and higher catalyst loading.



Scheme 2.6: Selected examples of pyran fused indoles synthesized by tandem olefin isomerization/cyclization Reaction Conditions: substrate (0.25 mmol), Ni-H (1 mol%), CF_3SO_3H (4 mol%), THF (1.5 mL), r.t, 40 min. [b]Ni-H (4 mol%), CH_3SO_3H (16 mol%), 60 °C, 1 h. [c]Ni-H (2 mol%), CH_3SO_3H (8 mol%), 60 °C, 1 h

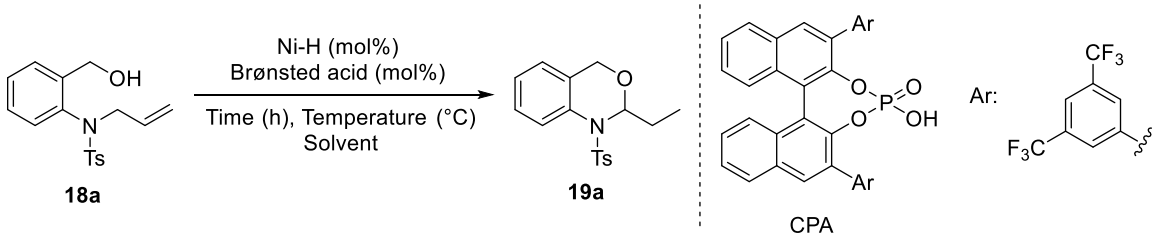
Thiocyanate substitution on C-3 position of the precursor for oxazine-indole was not tolerated. Either the strong co-ordination ability or electron withdrawing character of thiocyanate may have led to no reactivity. Only olefin isomerization on the O-allyl tether was observed in this case. Attempts to induce enantioselectivity in the synthesis of THP-indoles failed when CPA (Chiral Phosphoric Acid) was used and <5% enantiomeric excess was obtained. In this case, a higher temperature (80 °C) was necessary to obtain isolable yields. when using a relatively weaker Brønsted acid might have hampered the enantiomeric excess. Also, the absence of functionalities that promote non-covalent interactions and hence induce ee may explain the negative outcome. Importantly, THP indole **13a** was obtained in 59% yield with catalyst loading of 0.075 mol%. An analogous transformation for synthesizing O,O/O,N-acetals was possible by switching nucleophile from the electron rich arene to a heteroatom (in this case oxygen). The overall reaction design was similar to the partial isomerization by Ni-H followed by cyclization in presence of a Brønsted acid. The use of strong acid would have not only led to product formation but also hydrolysis. For this reason, a much weaker Brønsted acid such as diphenyl phosphate (p*Ka* = 3.88 in DMSO) was used for optimization. The product mixed acetal was obtained in 83% yield with Ni-H loading of 4 mol% and 15 mol% Brønsted acid. Sterics of the nucleophilic arm influenced the reactivity. The presence of methyl group decreased the yield to 63%, whereas two methyl groups almost shut down the reactivity giving traces of mixed acetal. 7-Membered O,O- (**19d**) and O,N-acetals (**19c**) could be synthesized in yields of 44 and 65% respectively.



Scheme 2.7: Selected examples of cyclic acetals synthesized by tandem isomerization/cyclization. Reaction Conditions: ***18*** *(0.25 mmol), Ni-H (4 mol%), $(PhO)_2(O)P(OH)$ (15 mol%), toluene (0.16 M), 115 °C*

Efforts were also directed to induce chirality, as this scaffold presents possibilities for non-covalent interactions. A chiral phosphoric acid (CPA) of higher strength (p*Ka* = 2.63 in DMSO) was tested. While the reaction could be carried out at 40 °C, a period of 6 days was necessary to obtain the product O, N acetal in isolable yield. HPLC analysis revealed a modest e.r of 65:35. The e.r was found to be solvent independent. A stronger chiral phosphoric acid may have the potential to improve the e.r.

Table 2.3: Screening for enantioselective transformation



Entry	Ni-H (mol %)	Acid (mol %)	Time (days)	**18a**: **19a** (%)	e.r
1[c]	4	DPP (15)	4	75:25	50:50
2[d]	4	CPA (15)	4.5	72:28	65:35
3[d]	4	CPA (15)	6	74:26	65:35
4[e]	4	CPA (15)	4.5	60:40	62:38

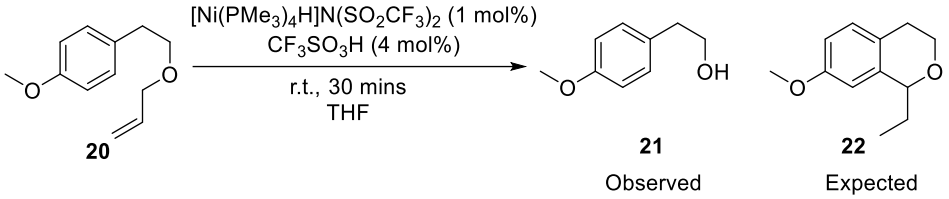
Reaction Conditions: ***18a*** *(0.1 mmol), [a] Ratio determined by NMR spectroscopy. [b] Determined by HPLC analysis [c] Isolated yield, temperature: 50 °C, toluene (0.16 M), [d]Temperature: 40 °C, toluene (0.16 M), [e] Temperature: 40 °C, toluene (0.16 M).*

Evidently, the potential of Ni-H in synthesizing different classes of heterocycles with high TON's is displayed in this project. This sheds light on the synthetically underexplored Ni(II) hydrides and may incite future studies for potential synthetic applications.

P. M. Kathe, A. Caciuleanu, A. Berkefeld, I. Fleischer
Tandem Olefin Isomerization/Cyclization Catalyzed by Complex Nickel Hydride and Brønsted Acid
J. Org. Chem. **2020**, *23*, 15183–15196.

2.3 Nickel-Hydride Catalyzed Cleavage of Allyl Ethers Induced by Isomerization

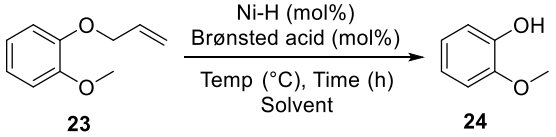
The focus of the final project was on developing a nickel hydride catalyzed deallylation methodology. Similar to the synthesis of oxa-cyclic scaffolds, deallylation strategies for O-allyl/allyloxycarbonyl protecting groups have primarily relied on using precious transition metal catalysts. We sought to investigate the deallylation of allylaryl- as well as allylalkylethers. In the previous project, upon treating the precursor **20** of an isochroman derivative with NiH and triflic acid, the product alcohol was formed predominantly whereas only traces of the isochroman **22** was observed. This served as a starting point of the investigation.



Scheme 2.8: De-allylation product obtained from attempted olefin isomerization/cyclization

The optimization was performed using ether **23**. Based on the experience from the second project, the sequential addition strategy was employed. While Ni-H was used for isomerization, a few Brønsted acids were screened. Importantly, high reaction temperatures (>50 °C in this case) were avoided while using triflic acid to prevent product degradation (Table 2.4, Entry 1). Using catalytic amounts of weaker Brønsted acid such as $(PhO)_2P(O)(OH)$

Table 2.4. Optimization of reaction conditions for de-allylation.

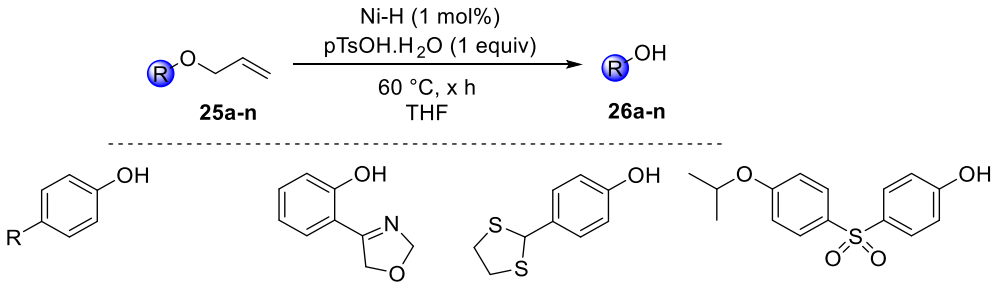


Entry	Ni-H (mol%)	Acid (mol%)	Time (h)	Temp (°C)	Yield (%)
[b]1	2	F_3CSO_3H (10)	15	r.t	38
2	1	$(PhO)_2P(O)OH$ (8)	1	60	-
3	0.5	$TsOH·H_2O$ (100)	1	60	84
4	1	CSA (100)	5	60	1:4[c]
[d]5	0.5	$TsOH·H_2O$ (10)	5	60	Traces
[e]6	1	$TsOH·H_2O$ (100)	1	60	73

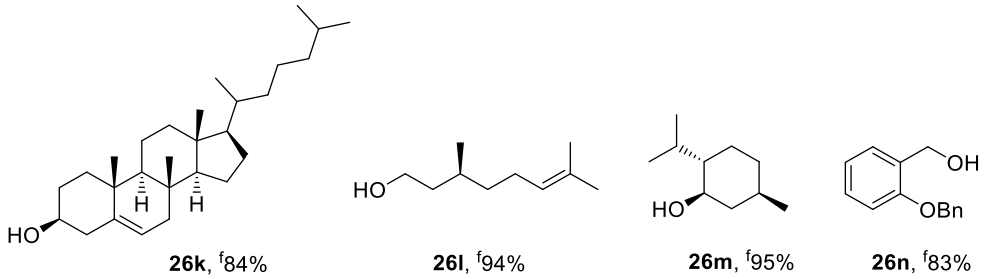
*Reaction Conditions: **23** (0.25 mmol), $[Ni(PMe_3)_4H](SO_2CF_3)_2N$, Brønsted acid, THF (0.16 M), 30 min r.t. with Ni-H, then 60 °C for time (h). [b]r.t. with F_3CSO_3H for 15 h. [c]ratio determined by ^1H NMR analysis [d]H_2O (1 equiv) [e]reaction at 4.2 mmol.*

(p*Ka* = 2.4 in H_2O) did not lead to hydrolysis and a mixture of terminal and internal isomer of **23** was isolated (Table 2.4, Entry 2). The phenol that resulted from the de-allylation was accompanied by the formation of propanal. The deallylation hence is an outcome of isomerization followed by acid hydrolysis of the O-alkenyl ether. Using stoichiometric amount of strong acid such as p-toluenesulfonic acid (p*Ka* = -2.8 in H_2O) successfully led to complete hydrolysis over a period of 60 minutes in refluxing THF (Table 2.4, Entry 3). The phenol was obtained in 84% yield without the need for column purification. A minimum Ni-H loading of 0.5 mol% was necessary to obtain an isolable yield. Longer reaction times were necessary when camphorsulfonic acid (CSA, p*Ka* = 1.5 in H_2O) was used (Table 2.4, Entry 4). The hydrolysis could not be affected by using equimolar amount of water (Table 2.4, Entry 5). The optimized reaction conditions could be employed for deallylation at a relatively higher scale of 4.2 mmol. (Table 2.4, Entry 6)

Under the optimized reaction conditions, *O*-allylated phenol derivatives bearing electron donating substituents such as t-butyl and methylsulfanyl delivered the product phenols in good to excellent yields (**26c** and **26g**). The presence of strongly electron withdrawing groups such as CF_3 or NO_2 however, shut down the reactivity and the corresponding reactant along with its isomers were obtained. Nevertheless, functional groups such as OH, Bpin and Cl were tolerated and gave the corresponding phenols in yields ranging from 50 to 80% (**26a**, **26b** and **26e**). O-Allyl ether bearing arylsulfonyl linkage on the para position was successfully employed in the deprotection furnishing 41% of phenol **26j**. Longer reaction times were necessary to achieve isolable yields. Unfortunately, complete conversion of the O-allyl ether in the case of substrates bearing electron withdrawing groups could not be achieved. This could be partly owing to the isomerization taking place to a lesser extent (in the range of 20-30%). The presence of a formyl group in the para position led to formation of **26f** in 17%. 1,3-Dithiane protection of the formyl increased the yield to 52%. Amine was not tolerated under the reaction conditions owing to instantaneous salt formation upon addition of the strong acid. However, nitrogen heterocycle at the ortho position of O-allylated arene resulted in 62% yield of **26h**.



[b]R= Cl, **26a**, 56% [b]R= OH, **26e**, 89% **26h**, [d]62% **26i**, [e]52% **26j**, [b]41%
[b]R= Bpin, **26b**, 73% [b]R= CHO, **26f**, 17%
[a]R= tBu, **26c**, 93% [a]R= SCH_3, **26g**, 95%
[c]R= OTBDPS, **26d**, 33%



26k, [f]84% **26l**, [f]94% **26m**, [f]95% **26n**, [f]83%

Scheme 2.9: Selected examples of Ni-H catalyzed de-allylation. Reaction conditions: ***25*** *(0.25 mmol), $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$, Brønsted acid, THF (0.16 M), 30 min r.t. with Ni-H, then 60 °C for time (x) h. [a]6 h, [b]15 h [c]22 h, camphorsulfonic acid (1 equiv), [d]$TsOH{\cdot}H_2O$ (2 equiv), [e]10 h, [f]1.5 h*

Furthermore, allylethers derived from aliphatic alcohols gave an excellent yield mainly since no column purification was necessary in this case. No racemisation of chiral centres in compounds **26k**, **26l** and **26m** was observed. The deallylation of N-allyl amide successfully delivered N-methyl benzamide in a moderate yield. An attempt to deallylate N-allylated caprolactam however, led to complex, unidentifiable product mixture. It was also of interest to display orthogonality with the deallylation methodology since the presence of multiple hydroxy groups in a compound can complicate the task of selective protection/deprotection. To this end, benzyl and TBDPS protected allylethers were synthesized. Upon subjecting them to the reaction conditions, the product phenols **26n** and **26d** was obtained in 83 and 33% yields, respectively. While TBDPS has a relatively higher acid stability (250 times higher than TBS with a half-life of 225 min in 1% HCl-MeOH at room temperature), it may undergo hydrolysis in p-toluenesulfonic acid at 60 °C.[7] Accordingly, camphorsulfonic acid was chosen and an alternative. Incomplete conversion, partly due to the use of a weaker acid, led to low yield of 33%.

In summary, the structurally simple Ni-H was used to trigger olefin isomerization ultimately leading to deallylation. This work displays the potential of Ni-H in replacing the classical $Pd(PPh_3)_4$/barbituric acid system for deallylation.

P. M. Kathe, A. Berkefeld, I. Fleischer
Nickel Hydride Catalyzed Cleavage of Allyl Ethers Induced by Isomerization
Synlett. **2021** DOI: 10.1055/s-0040-1706683

2.4 References

[1] a)A. Sen, T. W. Lai, *Inorg.* **1984**, *23*, 3257-3258; b)N. R. Davies, A. D. DiMichiel, V. A. Pickles, *Aust. J. Chem.* **1968**, *21*, 385-395; c)M. B. Sparke, L. Turner, A. J. M. Wenham, *J. Catal.* **1965**, *4*, 332-340.

[2] W. A. Carole, T. J. Colacot, *Chem. Eur. J* **2016**, *22*, 7686-7695.

[3] a)J. T. Christl, P. Roesle, F. Stempfle, P. Wucher, I. Göttker-Schnetmann, G. Müller, S. Mecking, *Chem. Eur. J* **2013**, *19*, 17131-17140; b)P. Roesle, L. Caporaso, M. Schnitte, V. Goldbach, L. Cavallo, S. Mecking, *J. Am. Chem. Soc.* **2014**, *136*, 16871-16881; c)V. Goldbach, L. Falivene, L. Caporaso, L. Cavallo, S. Mecking, *ACS Catal.* **2016**, *6*, 8229-8238.

[4] L. Lin, C. Romano, C. m. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 10344-10350.

[5] a)A. J. M. Miller, J. A. Labinger, J. E. Bercaw, *Organometallics* **2011**, *30*, 4308-4314; b)S. A. Burgess, A. J. Kendall, D. R. Tyler, J. C. Linehan, A. M. Appel, *ACS Catal.* **2017**, *7*, 3089-3096; c)C. J. Curtis, A. Miedaner, W. W. Ellis, D. L. DuBois, *J. Am. Chem. Soc.* **2002**, *124*, 1918-1925.

[6] C. A. Tolman, *J. Am. Chem. Soc.* **1972**, *94*, 2994-2999.

[7] J. S. Davies, C. L. Higginbotham, E. J. Tremeer, C. Brown, R. C. Treadgold, *J. Chem. Soc., Perkin Trans. 1* **1992**, 3043-3048.

CHAPTER 3

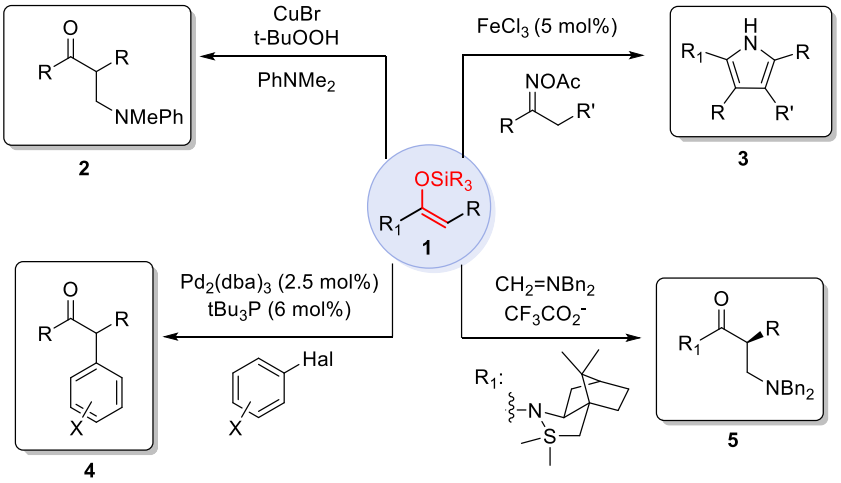
UNPUBLISHED RESULTS

3 Unpublished Results

3.1 Synthesis of β-amino ketones from Protected Homoallylic Alcohols

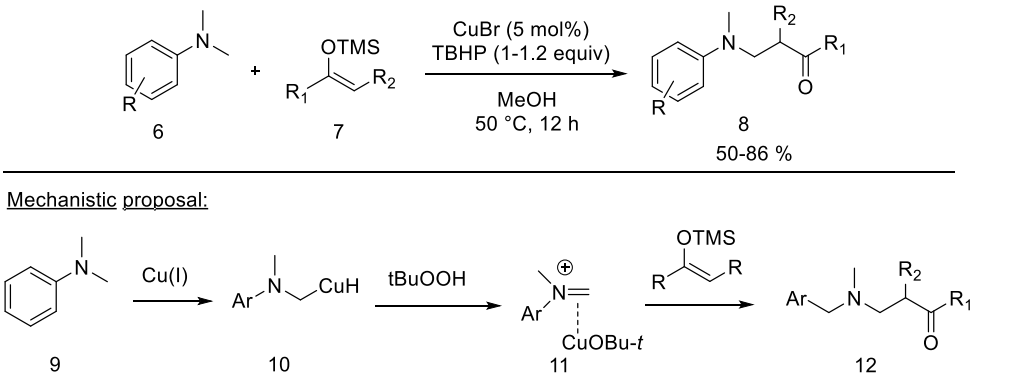
3.1.1 Introduction

Silyl enol ethers have been traditionally used as substituted carbonyl equivalents in the Mukaiyama aldol reaction giving ketones.[1] Modern synthetic methods including transition metal catalysis have enabled their application in α-arylation, synthesis of heterocycles and aminomethylation (Scheme 3.1).[2a, 2b, 2c, 2d] The following section will discuss the latest advances in aminomethylation in terms of reaction design and mechanistic investigations.



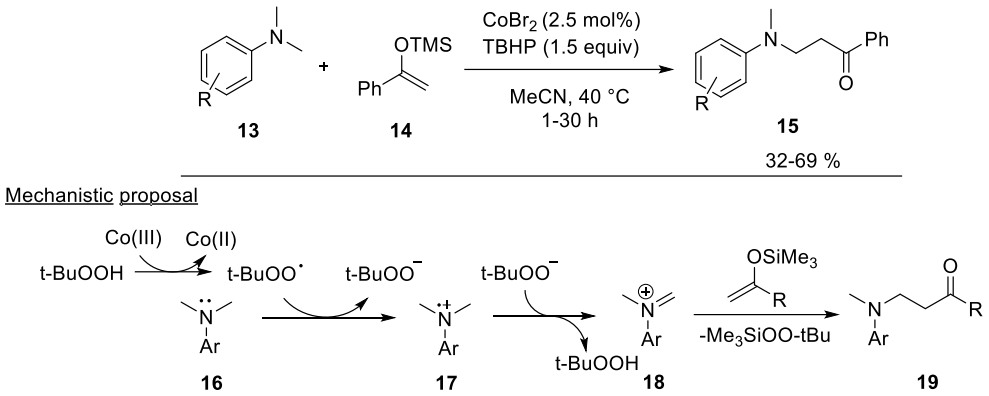
Scheme 3.1: Modern methods of silyl enol ether functionalization

A copper catalyzed coupling of *N*,*N*-dimethylanilines with silyl enol ethers using TBHP (*t*-butyl hydroperoxide) as an oxidant was reported.[2b] The proposed reaction mechanism involved activation of C_{sp3}-H bond of amine by copper and subsequent generation of iminium cation. This simplified mechanism however does not account for the significant drop in yield observed when BHT (butylated hydroxyl toluene) was used as a radical scavenger.



Scheme 3.2: Copper catalyzed amino-methylation of silyl enol ethers with anilines[2b]

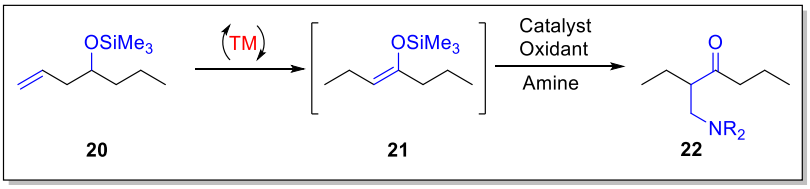
Similar conditions were used in aminomethylation using $CoBr_2$.[3] Based on the mechanistic investigation by Doyle and co-workers, which show that *t*-butylperoxy radical is the thermodynamically favoured oxidant,[4] the authors proposed a mechanism involving two single electron transfers leading to generation of an iminium cation. The *t*-butylperoxy anion is formed because of these SET events.



Scheme 3.3: Cobalt catalyzed aminomethylation of silyl enol ethers[3]

Silyl-enol ethers have shown promise as a synthetically versatile motif. Its reactivity not only with iminium cations but also aryl halides and O-acetylated oximes exemplifies its potential in organic synthesis. Quite surprisingly, a tandem/one-pot transformation, which takes advantage of an *in situ* generated silyl-enol ether has received no attention. The synthesis of silyl protected homoallylic alcohols is straightforward either through Barbier type allylation or the Sakurai reaction and subsequent protection of carbonyl compounds.[5] These reactions in classical organic synthesis have been optimized over the years with the goal of enhancing the scope. The readily available robust methods for synthesis of protected homoallylic alcohols make them a valuable precursor for functionalization. Silyl protected homoallylic alcohol can serve as a latent silyl enol ether and thus be used as a diversification strategy especially in cases when isolation and purification of the enol ether is not desirable. The following preliminary results highlight the potential of a one pot generation of silyl enol ethers from protected homo-allylic alcohols and follow-up aminomethylation.

AIM



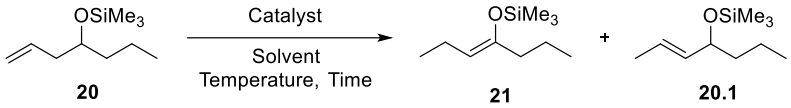
Scheme 3.4: One-pot catalytic synthesis of beta-amino ketones from protected silyl enol-ethers

3.1.2 Preliminary Results and Discussion

The homoallylic alcohol was synthesized by the reaction of butyraldehyde with allyl bromide. This was followed by TMS protection using HMDS. The one-pot reaction of the synthesized substrate **20** consists of two parts. The first is the metal catalyzed isomerization of homoallylic ether to silyl enol ether **21**. The second is the metal catalyzed oxidative functionalization of the latter.

Although there are several metal catalysts known to affect the isomerization (1), the catalyst system needs to be compatible with a follow-up oxidative functionalization. For this purpose, a handful of transition metal catalysts were screened (Table 3.1). The Pd(II) salt $PdCl_2(CH_3CN)_2$ gave the best result with 85% yield of the silyl enol ether after just 2 hours (Table 3.1, Entry 7).

Table 3.1. Optimization of reaction conditions for the isomerization of **20**.



Entry	Catalyst	Solvent	Temperature (°C)	Yield:X (%)[b]
1	$RuHCl(PPh_3)_3$	Toluene	100	9
2	$PdCl_2(PhCN)_2$	DCM	r.t	4
3	$[Ni(PMe_3)_4H]N(SO_2CF_3)_2$	THF	50	-
4	$RuCOH_2(PPh_3)_3$	Toluene	r.t	-
5	Pd(dppp)OTf	Toluene	50	-
6	$RuH_2(PPh_3)_4$	DCM	r.t	-
7	$PdCl_2(CH_3CN)_2$	Toluene	50	85[c]

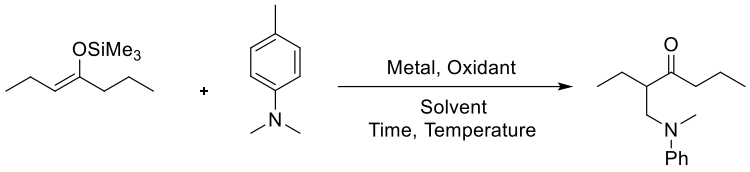
*Reaction Conditions: **20** (0.5 mmol), Catalyst (5 mol%), Solvent (0.5 M), 18 h. [b]Determined by quantitative GC-FID analysis using pentadecane as an internal standard. [c]2 h*

Having a straightforward catalytic process for isomerization, the next task was to combine it with follow-up reaction. The optimization of the follow-up oxidative amination entailed screening the metal catalysts, oxidants, solvents, and the amines as potential coupling partners (Table 3.2). Following the mechanistic precedent set by Sakai et al, we chose to rely on an oxidant and cobalt catalyst to enable two single electron transfer processes and hence generate the iminium cation.[3]

The ability of Co(II/III) redox couple to engage in multiple single electron transfers mediated by an oxidant shall ultimately determine the extent of formation of iminium cation. Nucleophilic attack on this cation shall furnish the product. Upon screening a few cobalt and copper salts, a combination of $CoBr_2$ along-with TBHP as an oxidant in acetonitrile was found to give the highest yield of 62% after 18 h (Table 3.2, Entry 3). Switching the copper salt to CuBr led to an identical outcome and gave **23** in 61% (Table 3.2, Entry 2). Unfortunately,

screening other oxidants resulted in poor to moderate yield of the product **23**. Having these conditions in hand, the next task was to merge the two optimized processes.

Table 2. Optimization of reaction conditions for aminomethylation of silyl-enol ether Y.

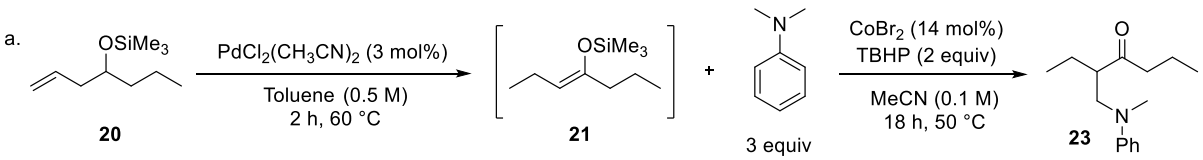


21 22 23

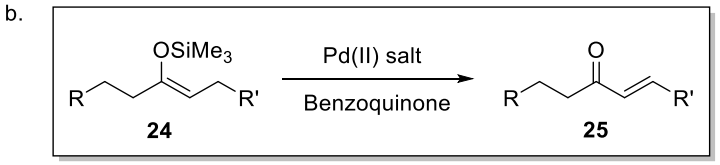
Entry	Catalyst	Oxidant	Solvent	Yield[a]
1	CuCN	TBHP	MeCN	55
2	CuBr	TBHP	MeCN	61
3	$CoBr_2$	TBHP	MeCN	62
4	$CoBr_2$	DTBP	MeCN	47
5	$CoBr_2$	H_2O_2	MeCN	50
6	$CoBr_2$	mCPBA	MeCN	39
7	$CoBr_2$	TBHP	MeOH	17[b]
8	$CoBr_2$	DTBP	MeOH	27[b]
9	$CoBr_2$	DTBP	MeOH[c]	26[b]
10	$CoBr_2$	DTBP	MeOH[d]	32[b]

Reaction Conditions: ***21*** *(0.25 mmol),* ***22*** *(0.75 mmol), Catalyst (14 mol%), Solvent (0.1 M), Oxidant (0.5 mmol), 50 °C, 18 h. [a]Determined by quantitative GC-FID analysis using mesitylene as an internal standard. [b]2 h. [c]Solvent (0.16 M). [d]Solvent (0.5 M).*

Merging the two optimized processes indeed resulted in product **23**, albeit in low yield of 31%. A side reaction led to the consumption of much of the silyl enol ether resulting in diminished yields. To investigate the process further, we decided to probe the compatibility of Pd(II) catalyst with the reactants in the second step to decipher if a side reaction would be triggered. A possible side reaction could be the Saegusa-Ito oxidation which is the oxidative formation of α,β-unsaturated ketone from silyl enol ether in the presence of Pd(II) (Scheme 3.5). NMR investigations of crude reaction mixture did not show presence of hept-2-ene-4-one, however 4-heptanone was formed. This can be simply a result of oxidation of silyl enol ether by TBHP.

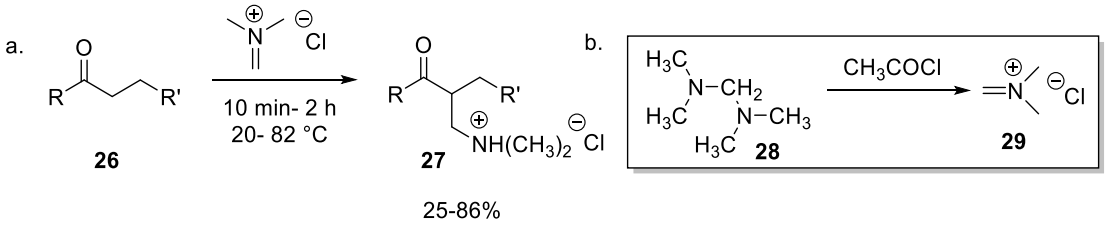


20 21 23



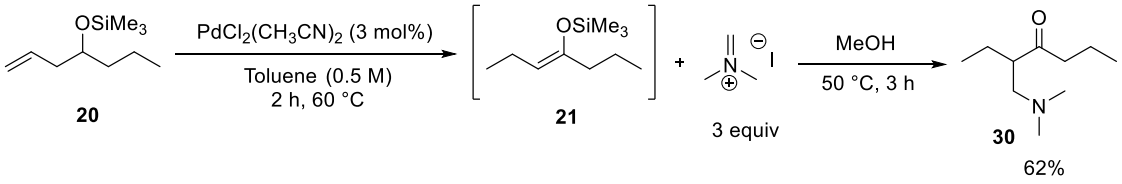
Scheme 3.5: a. Palladium catalyzed one-pot olefin isomerization and oxidative amino-methylation. b. The Saegusa-Ito Oxidation

Further optimization of the one-pot process led to little improvement in the yield and most of the silyl-enol ether was still consumed by the oxidant. The use of DEAD for the generation of iminium cation as reported in the literature and follow-up reaction with silyl enol ether did not yield in any β-aminoketone.[6] In 1970's, Tietze reported a Mannich reaction variant for aminomethylation of aldehydes and ketones.[7] The iminium cation **29** is generated by a simple reaction that uses the aminal **28** and acetyl chloride as illustrated in Figure 4.



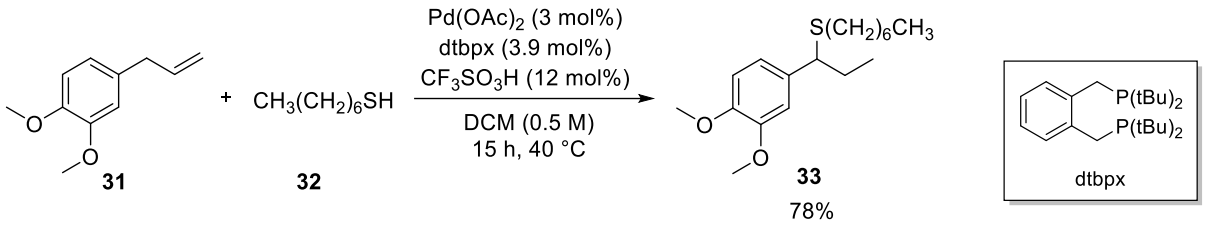
Scheme 3.6: a. Aminomethylation of carbonyl compounds using iminium cations. b. Synthesis of iminium cation[7]

As pointed out in the previous paragraphs, the iminium cation plays an important role in this type of reactivity. A Co(II/III) redox cycle and corresponding electron transfers generate initially an iminium radical cation and eventually the iminium cation. Examining the optimized reaction system for the 'one-pot' transformation and considering past literature reports, the use of Eschenmoser's salt **29** as a bench-stable iminium component for the reaction was envisioned. For the one-pot transformation, Eschenmoser's salt was added to the silyl enol ether generated from isomerization in methanol as the solvent. In this case, the product of aminomethylation **30** was obtained in 62% yield without chromatographic purification. Although the current results are limited to an aliphatic substrate, the one-pot aminomethylation methodology has potential to be extended to aromatic ones. Furthermore, owing to its operational simplicity, this methodology could be employed in late-stage diversification of biologically relevant compounds. Increasing the efficiency of olefin isomerization and developing other iminium ion equivalents for the reaction could pave the way for further development of this transformation.



Scheme 3.7: Palladium catalyzed one pot olefin isomerization/amino-methylation of protected homo-allylic alcohols

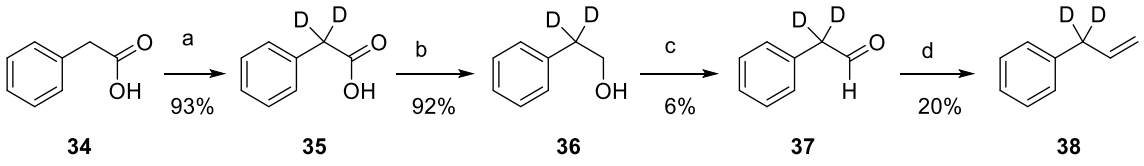
3.2 Palladium Catalysed Tandem Isomerization/Hydrothiolation of Allylarenes



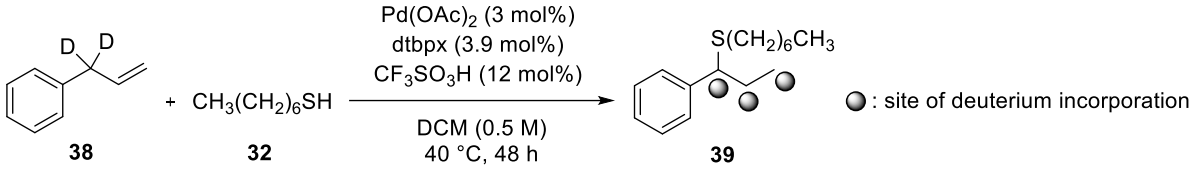
Scheme 3.8: Synthesis of benzylic thioethers from allyl arenes and thiols by tandem olefin isomerization/hydrothiolation[8]

The synthesis of benzylic thioethers in a tandem catalytic isomerization/hydrothiolation reaction has been accomplished and is disclosed in Kathe *et al*.[8] The catalyst system involves $Pd(OAc)_2$, dtbpx, and CF_3SO_3H as the hydride source. The following section includes a summary of results that have not been included in the published articles. To get information about the operating mechanism of the tandem reaction, deuteration and NMR studies were performed. The substrate **38** was obtained after deuteration on benzylic position. The synthesis of deuterated substrate was performed according to literature report and is illustrated in the Scheme 3.9.[9]

Phenyl acetic acid was refluxed with deuterated sodium hydroxide, hence installing the deuterium in the first step. The deuterated acid was reduced with LAH, oxidized with DMP and finally a Wittig reaction gave the deuterated allyl benzene as the product. The deuterated substrate was subjected to reaction conditions with non-deuterated thiol and acid (Scheme 3.10). Although the yield of the thioether **39** was remarkably low, ^2H NMR showed a scrambling of deuterium over the carbon chain. This observation does not necessary rule out a π-allyl mechanism involving intermolecular deuterium transfer. Given the fact that an in-situ palladium hydride is the active catalytic species, the likelihood of a mechanism involving an iterative olefin insertion/β-H elimination (chain-walking) pathway is high.



Scheme 3.9: Reaction sequence for the synthesis of deuterated allyl benzene. Reaction Conditions: a) 40 wt% NaOD in D_2O (2.35 equiv), 100 °C, 18 h; b) Lithium aluminium hydride (1.2 equiv) , 0 °C- r.t., 18 h, THF; c) Dess-Martin periodinane, DCM, 1 h, r.t.; d) methyl triphenylphosphonium bromide (3.8 equiv), n-BuLi (1.6 M in n-hexane), (4.6 equiv), THF, 0 °C - r.t., 15 h.

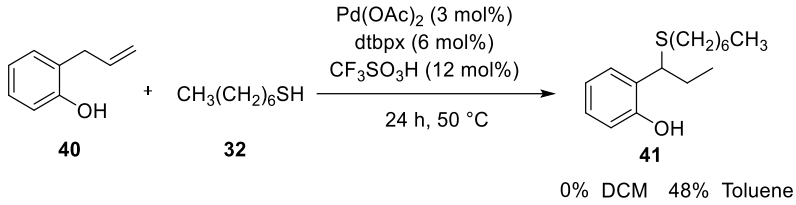


Scheme 3.10: Tandem isomerization/hydrothiolation of allyl arenes

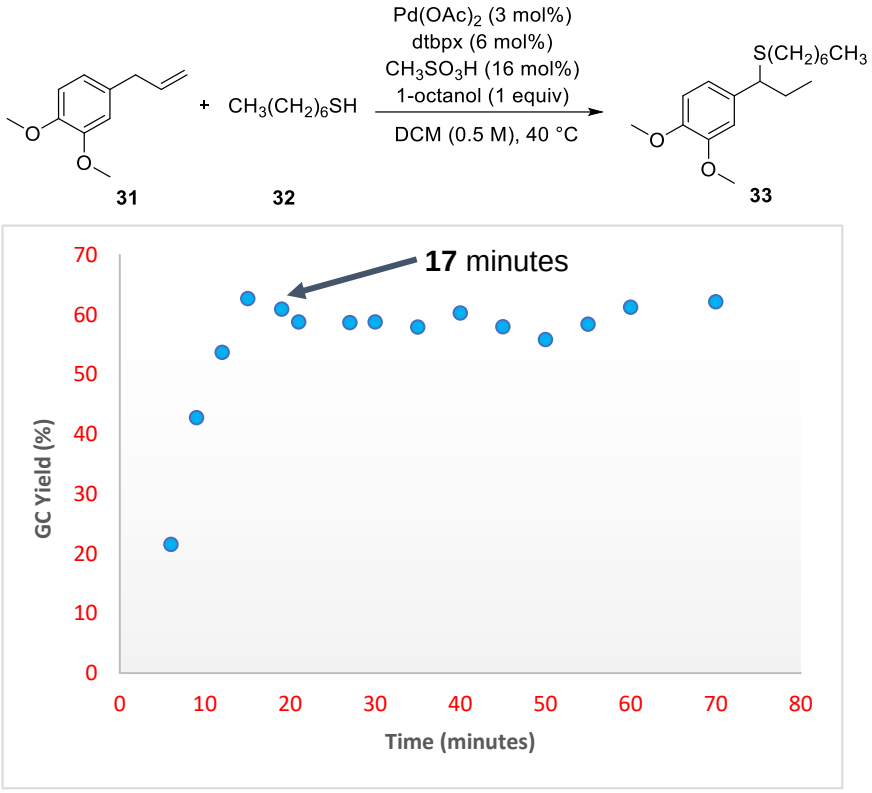
The putative palladium hydride intermediate could not be detected directly through ^{1}H-NMR spectroscopy under the reaction conditions. It is hence an elusive, thermodynamically unstable intermediate. To obtain an indirect evidence of the presence of palladium hydride, the following experiments were performed. In presence of $CDCl_3$ as the reaction solvent, the palladium hydride may result in an irreversible protodehalogenation to generate $CDHCl_2$ that can be spectroscopically detected. This is analogous to the other late-transition metal hydrides that have been reported to catalyse protodehalogenation.[10]

The reactions were performed under an inert atmosphere inside a Schlenk tube and aliquots were transferred to a NMR tube under an inert atmosphere. A solution of the catalyst precursor $Pd(OAc)_2$ along-with dtbpx in $CDCl_3$ was stirred for 1 h at r.t. This was followed by addition of heptan-1-thiol, upon which the reaction mixture initially turned light green followed by dark orange. Upon maintaining this reaction mixture for 1 h at 40 °C, a sample was withdrawn for spectroscopic analysis. A triplet with equal intensity seen at 5.24 ppm represents the 'H' atom in $CDHCl_2$. The addition of triflic acid to the reaction mixture and the subsequent NMR shows that the triplet remains unchanged in ^{1}H NMR. The results of these NMR experiments corroborate the fact that the thiol can play an active role in regeneration of palladium hydride. (NMR data in the next section)

During the investigations on the substrate scope for this transformation, a marked difference in the reactivity of substrates possessing a hydroxy group was observed. A competition experiment was performed wherein 1-octanol was added to a reaction set up under the optimized conditions. 1-octanol suppressed the reaction and no formation of benzylic thioether was observed. Upon switching the solvent to toluene, however, both O/S-benzylic functionalized products were formed albeit with poor yields. This unusual observation led to a kinetic study that confirmed that 1-octanol acted as a 'poison' (Scheme 3.12). While a plausible explanation could be the coordination/β-hydride elimination to give strongly coordinating carbonyl ligand, further studies are necessary to confirm this assertion. Furthermore, the formation of benzylic thioether from 2-hydroxy-allylbenzene was found to be solvent dependent as well. In this case, the reactivity difference was drastic since the reaction carried out in toluene yielded 48% of **41** while that in DCM gives no detectable product.



Scheme 3.11: Solvent dependence on tandem isomerization/hydrothiolation



Scheme 3.12: Kinetic profile of tandem isomerization/hydrothiolation upon adding 1-octanol

3.3 Experimental Details

Solvents and Reagents: All reactions were carried out in flame-dried glassware using Schlenk techniques with argon. Solvents were purchased dry and under septa or dried and degassed using usual techniques. Chemicals were purchased from Sigma Aldrich, Merck, Fluka Chemicals, Acros Organics, ABCR, Chem Pur, Alfa Aesar and TCI Chemicals.

Chromatography: For the column chromatography silica gel (60 Å) was used as a stationary phase. Thin layer chromatography was performed with aluminium plates coated with silica gel 60 F254 (layer thickness: 0.2 mm) and analysed under UV-light (254 nm) or stained with a potassium permanganate solution.

Nuclear magnetic resonance spectroscopy (NMR) All NMR spectra were recorded on a Bruker AVII+400 spectrometer at room temperature. The ^{13}C-NMR-spectra were recorded at

100.6 MHz -Broadband decoupling. The chemical shift (δ) of the ^{1}H- and ^{13}C-NMR-spectra are indicated in ppm.

Residual signals of deuterated solvents:

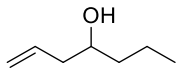
$CDCl_3$, $\delta_{H/C}$ = 7.26/77.0 THF-d_8, $\delta_{H/C}$ = 3.58/67.6

Coupling constants J are measured in Hertz [Hz]. For the description for the shape and the multiplicity of the peaks in the ^{1}H-NMR are used following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet.

Gas Chromatography (GC) GC-FID (flame ionization detection) analysis was carried out on an Agilent 7820A system with injector 7683B using dry hydrogen as a carrier gas. The temperature program 50-280 M 15 was used for GC measurement. (50 °C to 280 °C within 15 minutes). For GC sample preparation, QuadraSil®MP was added as a metal scavenger to the reaction mixture. This was followed by addition of suitable amount of an internal standard (n-Pentadecane or Mesitylene). After passing the crude reaction mixture through Celite filled in a Pasteur pipette plugged with cotton, GC analysis was performed. The internal standard method was used for quantitative GC-FID for yield determination. Therefore, calibration was conducted by variation of mass ratio of substrate and standard and analysing the different samples by GC-FID. From the obtained data the peak area ratio of standard to product as plotted against the mass ratio of product to standard. Linear regression led to the determination of the slope (response factor). Gas chromatography−mass spectrometry (GC-MS) was performed on an Agilent 7820A GC system in combination with an Agilent 5977 B using an EI source and a quadrupole analyzer.

Synthesis of protected homoallylic alcohol:

hepta-1-en-4-ol (34)



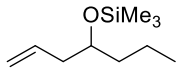
34

To a 250 mL three neck flask fitted with a reflux condenser was added 60 mL of a sat. NH_4Cl and 9 mL THF. To this solution butyraldehyde (5.4 mL, 60 mmol, 1 equiv) was added along-with (4.7 g, 72 mmol, 1.2 equiv) zinc powder. Finally, allyl bromide (6.2 mL, 72 mmol, 1.2 equiv) was added dropwise to this solution. The reaction mixture was heated to reflux and stirred for one hour, following which, it was quenched with 55 mL 10% aq. HCl. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product obtained in this manner was used for the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.76 (m, 1H), 5.18 – 5.08 (m, 2H), 3.71 – 3.60 (m, 1H), 2.35 – 2.24 (m, 1H), 2.19 – 2.07 (m, 1H), 1.55 – 1.31 (m, 4H), 0.97 – 0.88 (m, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.9, 118.4, 70.4, 41.9, 38.9, 18.8, 14.0.

(hept-1-en-4-yloxy)trimethylsilane (20)



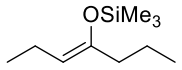
20

In a 100 mL Schlenk round-bottom flask fitted with condenser was added hepta-1-en-4-ol (9.57 g, 11.5 mL, 84 mmol, 1 equiv), hexamethyldisilazane (13.8 mL, 67 mmol, 0.79 equiv) and N-bromosuccinimide (0.75 g, 4.2 mmol). The mixture was then stirred for one and a half hours at 50 °C. After cooling down to room temperature the reaction mixture was passed through a silica plug (20 g) and washed with 200 mL of *n*-pentane. The eluent was then concentrated under reduced pressure to obtain the product as a colorless oil (11.2 g, 60.4 mmol, 72 %). Spectral data matches with the one reported in the literature.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.73 (m, 1H), 5.09 – 4.99 (m, 2H), 3.73 – 3.61 (m, 1H), 2.24 – 2.15 (m, 2H), 1.47 – 1.21 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.11 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.0, 116.2, 71.6, 41.8, 38.8, 18.5, 13.7, 0.0 (Si**C**H$_3$).

(E/Z)-(hept-3-en-4-yloxy)trimethylsilane (21)



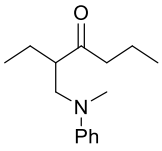
21

In a flame dried 100 mL Schlenk round-bottom flask with stir bar was added 25 mL THF and Diisopropylamine (3.5 mL, 25 mmol, 1.25 equiv). To this solution is added *n*-butyllithium (2.5 M in n-hexane, 10 mL, 25 mmol, 1.25 equiv) at 0 °C. The resulting solution was stirred for 15 minutes at 0° C. Following this, the reaction mixture was cooled down to -78° C. To the solution 4-heptanon (2.8 mL, 20 mmol, 1 equiv) was added in a dropwise manner. After stirring for 30 minutes, TMSCl (3.2 mL, 25 mmol, 1.25 equiv) was added dropwise to the reaction mixture. The solution was allowed to reach room temperature and stirred for further 30 min. Then 60 mL sat. $NaHCO_3$ is added and the combined reaction mixture was extracted with n-pentane (3 × 55 mL). The organic phase was dried over $MgSO_4$ and was concentrated under reduced pressure. The product was purified by Kugel-rohr distillation (50 mbar, 150° C). The product was obtained as a colorless oil (1.62 g, 8.7 mmol, 43 %). Spectral data matches the one reported in the literature.[12]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (t, *J* = 7.0 Hz, 1H), 4.43 (t, *J* = 7.0 Hz, 1H), 2.06 – 1.89 (m, 4H), 1.47 (h, *J* = 7.4 Hz, 2H), 0.97 – 0.86 (m, 6H), 0.18 (s, 9H) ($Si(CH_3)_3$ from the *Z*-isomer) , 0.17 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.4, **149.0**, **110.0**, 109.3, **38.2**, 32.7, 19.9, **19.8**, 19.7, 18.2, 15.0, **14.1**, 13.3, **13.3**, 0.2, **0.0**. (Peaks of minor isomer marked in bold)

3-((methyl(p-tolyl)amino)methyl)heptan-4-one (23)



23

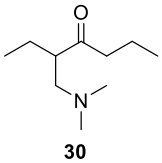
In a tube with stirrer was added 5 mL of acetonitrile (degassed), followed by *N, N*-dimethyl-*p*-toluidine (202.8 mg, 215 µL, 1.5 mmol, 3 equiv), (Z)-(hept-3-en-4-yloxy)trimethylsilane (93 mg, 0.5 mmol, 1 equiv) and copper(I) chloride (7.5 mg, 0.07 mmol). To this solution 0.1 mL (1 mmol) of *tert*-butyl hydroperoxide as a 10 M solution in n-hexane (0.1 mL, 1 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at 50 °C for 18 hours. The reaction was quenched with 5 mL water and 5 mL ethyl acetate. The reaction mixture was transferred to a separating funnel and the aqueous layer was extracted with ethyl acetate (3 × 8 mL). The combined organic layers where dry over $MgSO_4$ and the solvent was removed with reduced pressure. The crude product was purified by a column chromatography (97:3, *n*-hexane : Et_2O). The product was obtained as a light orange oil (70.1 mg, 0.3 mmol, 61 %).

R_f : 0.79 (*n*-hexane/Et_2O: 95/5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 3.51 (dd, *J* = 14.5, 9.2 Hz, 1H), 3.31 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.85 (s, 3H), 2.35 (td, *J* = 7.1, 3.3 Hz, 2H), 2.27 (s, 3H), 1.71 – 1.40 (m, 4H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 214.6, 147.0, 125.8, 112.6, 55.7, 51.5, 46.8, 39.5, 23.4, 20.2, 16.6, 13.7, 11.8.

3-((dimethylamino)methyl)heptan-4-one (30)



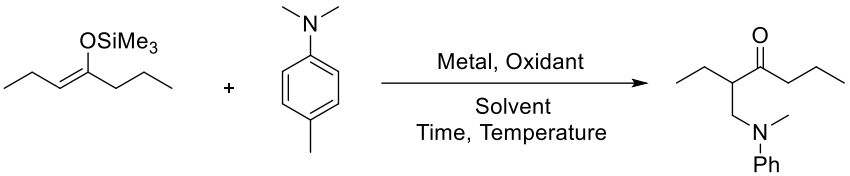
30

A flame-dried Schlenk tube with stir-bar was charged with bis(acetonitrile)palladium(II)chloride (6.5 mg, 25 µmol), (hept-1-en-4-yloxy)trimethylsilane (93 mg, 0.5 mmol, 1 equiv) and toluene (0.5 M). The mixture is heated for two hours at 50 °C ensuring complete isomerization. Following this, 4 mL of methanol and dimethyl (methylidene)ammonium iodide (236 mg, 1.28 mmol, 2.5 equiv) was added to the solution. The tube was stirred for three hours at 50 °C. The reaction mixture was then quenched with 3 mL of water. The aqueous phase was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was distilled under reduced pressure. The product was obtained as a dark yellow oil (53.4 mg, 0.31 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (dd, *J* = 12.8, 8.9 Hz, 1H), 3.46 – 3.35 (m, 1H), 3.14 – 3.05 (m, 1H), 2.80 (s, 6H), 2.69 – 2.51 (m, 2H), 1.92 – 1.78 (m, 1H), 1.73 – 1.54 (m, 3H), 0.90 (t, *J* = 7.7 Hz, 6H).

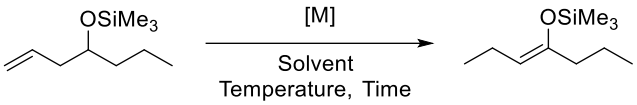
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 210.4, 57.0, 48.2, 44.4, 43.7, 24.1, 16.8, 13.6, 10.5.

General Procedure for Catalysis Experiments (oxidative aminomethylation):



To a reaction vessel with stir bar was added 2.5 mL CH_3CN or MeOH. Followed by that, N,N-dimethyl p-toluidine (0.11 mL, 0.75 mmol), enol ether (46.5 mg, 0.25 mmol) and metal salt (14 mol%) was added. To this mixture an oxidant (0.5 mmol, 2 equiv) was added dropwise. The tube was heated up to 50 °C and stirred for 18 h. After cooling down to room temperature, 50 µL of Mesitylene was added as an internal standard and the yield of the product was determined by quantitative GC-FID analysis.

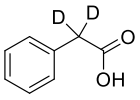
General Procedure for Catalysis Experiments (Olefin Isomerization):



A flame-dried 15 mL Schlenk tube with stir-bar was charged with the catalyst (5 mol%). This was followed by adding 1 mL DCM or Toluene. Followed by that 2 (93 mg, 0.5 mmol) and the resulting mixture was stirred for 18 hours at room temperature or 50/100 °C. To the reaction mixture was added QuadraSil ®MP as metal scavenger and n-pentadecane as an internal standard. The yield was analysed by quantitative GC-FID analysis.

Synthesis of deuterated substrate:

2-phenylacetic-2,2-d_2 acid(35)



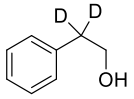
35

In a Schlenk round bottom flask, 5.5 g of phenyl acetic acid (40.4 mmol) was dissolved in 10 mL of 40 wt. % NaOD in D_2O (94 mmol). The mixture was heated to 110 °C. Extra D_2O was added till the complete dissolution of the solid. The reaction was stirred for 15 h at 110 °C. After cooling to room temperature, the solution was acidified with 6 M hydrochloric acid. The organic layer was extracted with CH_2Cl_2 (3 × 20 mL), dried over anhydrous $MgSO_4$ and concentrated to yield deuterated acid as a white solid (5.18 g, 37.5 mmol, 93 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 15H), 3.64 (s, **0.1**H).

0.1 integral indicates 96% deuteration on the benzylic position

2-phenylethan-2,2-d_2-1-ol (36)



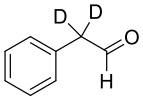
36

A solution of d_2-phenyl acetic acid (5.2 g, 37.68 mmol, 1 equiv) in 35 mL of THF was degassed by bubbling argon for one hour. To an ice-cooled suspension of LAH (1.716 g, 45.21 mmol, 1.2 equiv) in 40 mL THF, the degassed solution was added dropwise via cannula. The ice bath was removed after the addition was completed. After 18 hours of stirring, the reaction was quenched with an excess amount of 1 M HCl till clear solution was obtained. The solution was diluted with additional ethyl acetate. The organic layer was washed with H_2O (1 × 30 mL) and brine (1 × 30 mL). The combined aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated to yield the product as a white solid. (4.3 g, 34.7 mmol, 92.4%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.16 (m, 3H), 3.80 (s, 2H), 1.59 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.4, 129.0, 128.5, 126.4, 63.5.

2-phenylacetaldehyde-2,2-d_2 (37)

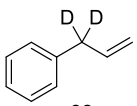


37

To a solution of 4 g 2-phenyl-2-d_2-ethanol (4 g, 32.2 mmol, 1 equiv) in 150 mL of dry DCM in a 250 mL Schlenk round bottom flask, 8 g $NaHCO_3$ and DMP (20.5 g, 48.3 mmol, 1.5 equiv) was added in sequence. The reaction was stirred for one hour at r.t. After no more reactant was observed (TLC), the reaction mixture was diluted with 150 mL of Et_2O and quenched by the adding 100 mL aq. $Na_2S_2O_3$ solution. The organic layer was washed with water and brine. The resulting aqueous was extracted with Et_2O (3 × 20 mL) and the combined organic layer was dried over $MgSO_4$. While concentrating the organic phase under reduced pressure, a solid precipitated. After filtration of the solid, the concentration of resultant organic phase resulted in a similar outcome. Finally, the volume was reduced to approx. 4 to 5 ml. The mixture including the insoluble solid was then subjected to bulb-to-bulb distillation. The product was obtained as a colorless oil (250 mg, 2 mmol, 6 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 1.6 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.26 – 7.11 (m, 3H).

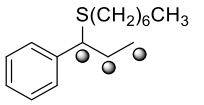
(allyl-1,1-d_2)benzene (38)



38

To an ice-cooled suspension of CH_3PPh_3Br (2.342 g, 6.557 mmol, 3.8 equiv) in 10 mL THF, 3.0 mL of *n*-BuLi (2.5 M in *n*-hexane) was added via syringe pump over ten minutes. The solution was stirred at 0 °C for additional 30 minutes. A solution of phenylacetaldehyde (200 mg, 1.639 mmol, 1 equiv) in 5 mL THF degassed by bubbling Argon for a period of 30 minutes, was added dropwise. After the addition was complete, the reaction was allowed to attain room temperature and stirred for 15 hours. The reaction was quenched with 10 mL of a sat. NH_4Cl and diluted with 15 mL of Et_2O. The organic layer was washed with water (2 × 15 mL) and brine (15 mL). The aqueous phase was extracted 15 mL of Et_2O (3 × 15 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The product 5 after purification by column chromatography on Silica gel (n-hexane as the eluent) was obtained as a colorless oil. (40 mg, 0.33 mmol, 20 %).

heptyl(1-phenylpropyl)sulfane (39)



: site of deuterium incorporation

39

A flame dried 25 mL Schlenk tube with stir bar was charged with 1,2-bis[(di-tert.-butylphosphino)methyl]benzene (10 mol%, 0.035 mmol, 14.2 mg) inside a glove box. The tube was taken outside the box and was charged with $Pd(OAc)_2$ (5 mol%, 4.03 mg, 0.017 mmol). After evacuating and backfilling the Schlenk tube, 0.8 mL DCM and the deuterated allyl benzene (43 mg, 0.36 mmol, 1 equiv) was added. After stirring for a couple of minutes, CF_3SO_3H (22 mol%, 0.06 mmol, 7 µL) or was added, which was followed by addition of the heptane-1-thiol (62.09 µL, 0.39 mmol, 1.1 equiv) respectively. The Schlenk tube was transferred to a preheated oil bath at 50 °C and the contents were for 62 h. After completion of the reaction, the reaction mixture was diluted with 5 mL DCM. The organic phase was washed with water. The combined aqueous phases were back extracted with DCM three times. The combined organic phases were dried over anhydrous $MgSO_4$. Rotary evaporation was employed to remove DCM. Preparative TLC separation with n-hexane as the mobile phase was attempted to purify the crude product. Considerable amount of product may have been lost in the separation. It was finally obtained as a light orange oil (9 mg, 0.03 mmol, 9%).

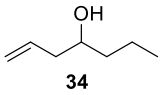
Note: It is suspected that the 1H NMR obtained still contains heptane-1-thiol however due to overlapping signals it is difficult to distinguish from the thioether. Nevertheless, it is clear that thioether is present in the product. The sites of deuteration have been assigned based on ^2H NMR that clearly indicates a scrambling on the propyl chain.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 5H), 2.36 – 2.14 (m, 1H), 2.00 – 1.76 (m, 1H), 1.62 – 1.52 (m, 2H), 1.51 – 1.36 (m, 2H), 1.33 – 1.17 (m, 8H), 0.94 – 0.82 (m, 6H).

3.4 NMR Spectra

hepta-1-en-4-ol (34)

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



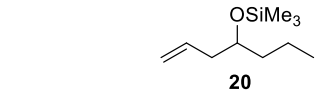
34

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

34

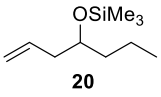
(hept-1-en-4-yloxy)trimethylsilane (20)

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

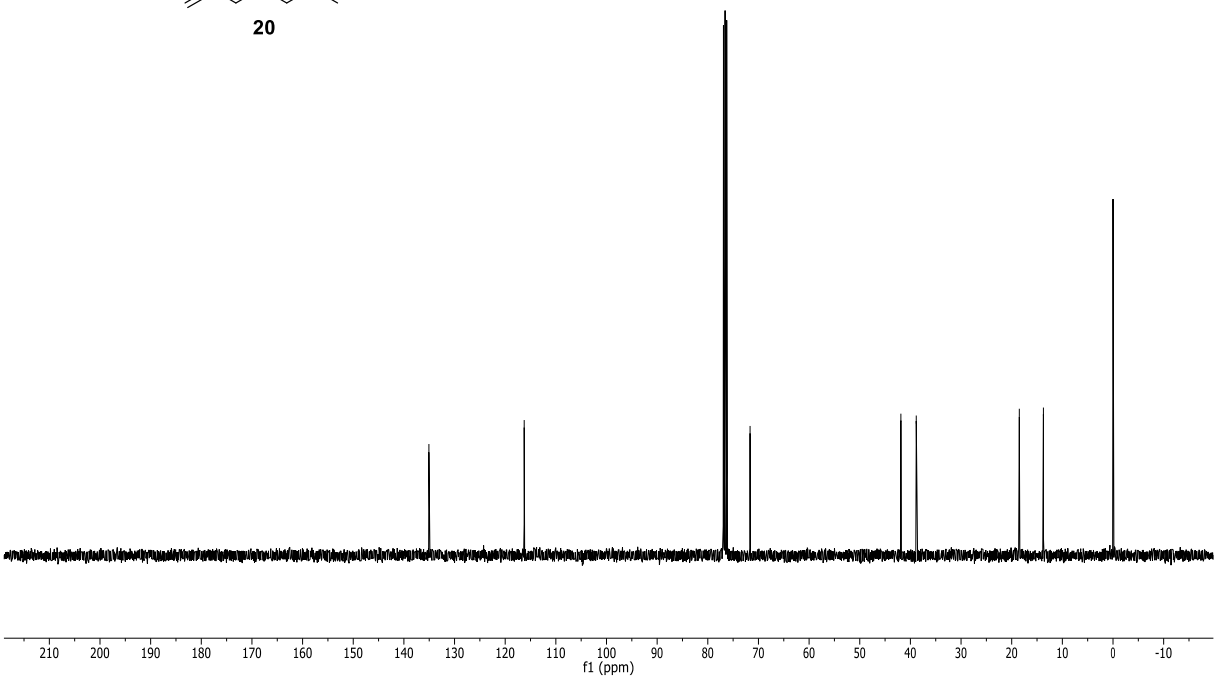


20

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

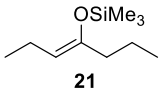


20



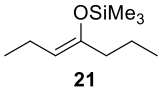
(E/Z)-(hept-3-en-4-yloxy)trimethylsilane (21)

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



21

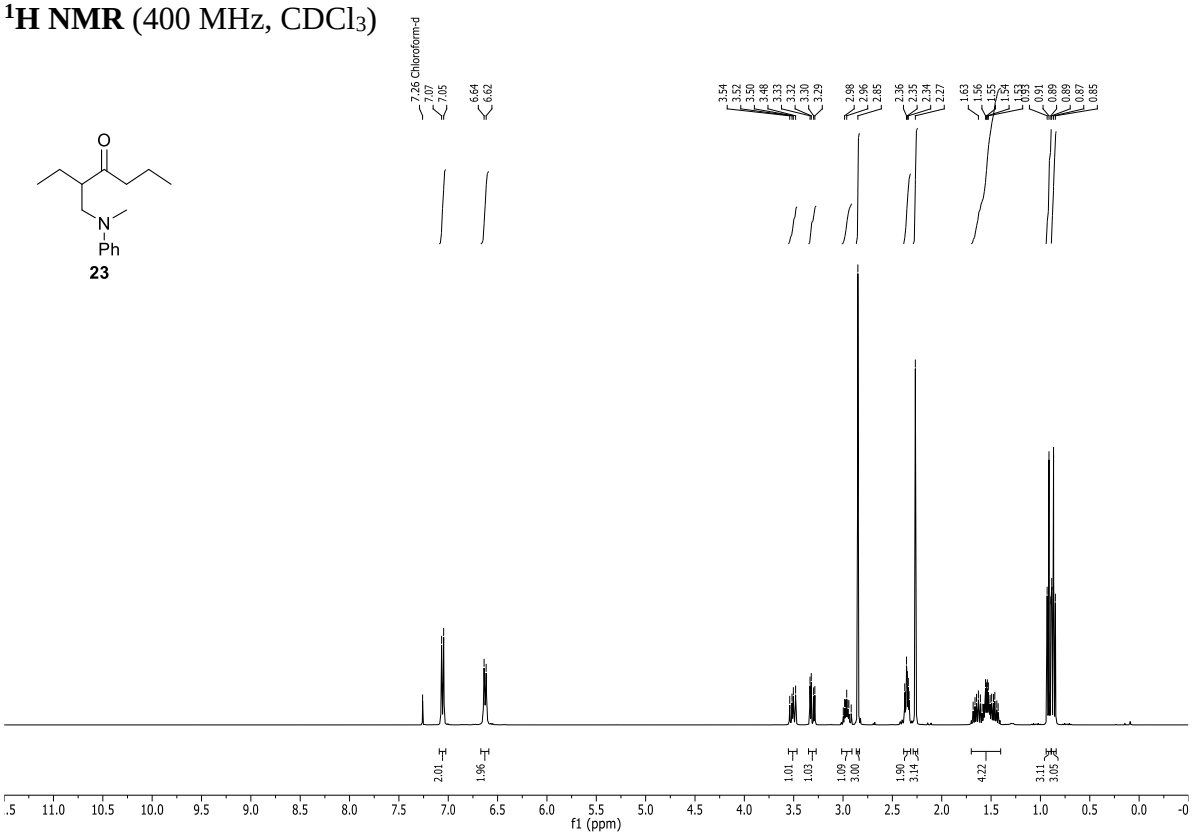
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



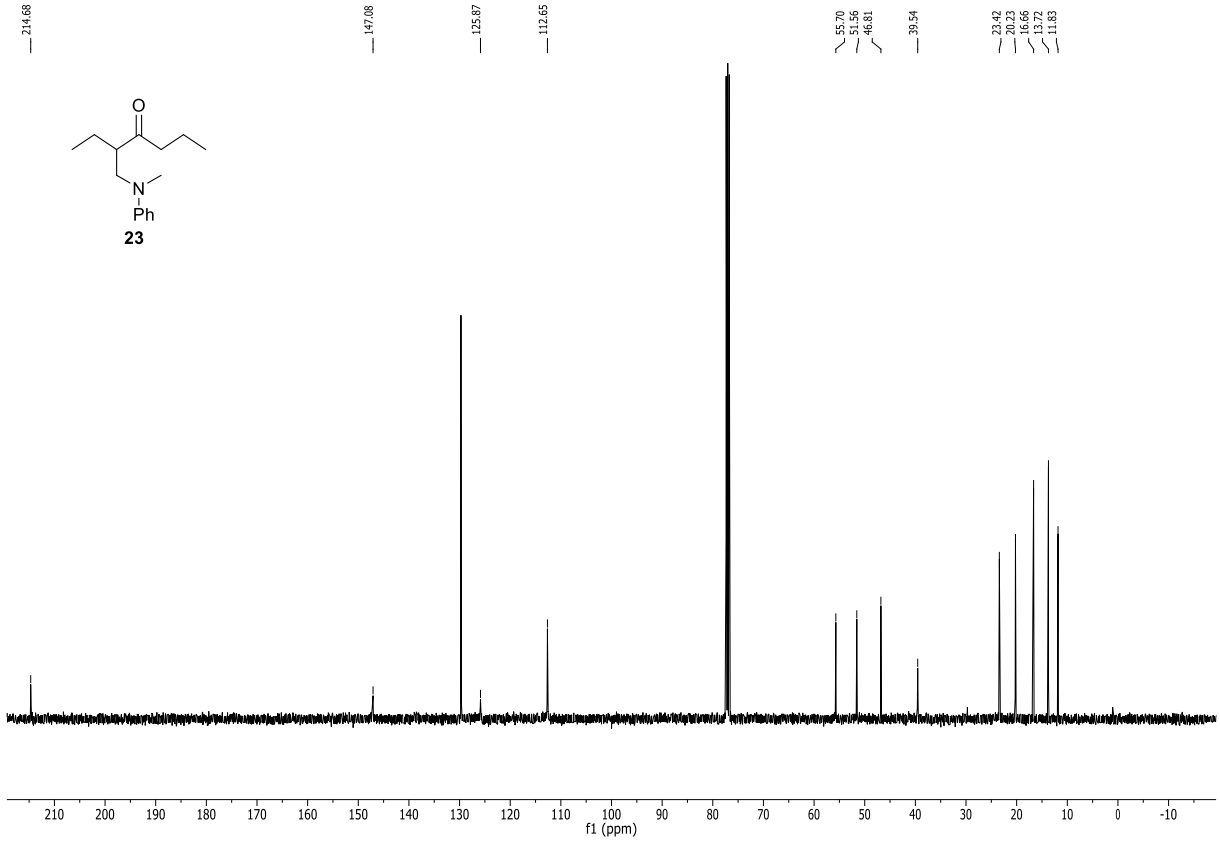
21

3-((methyl(p-tolyl)amino)methyl)heptan-4-one (23)

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

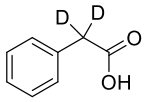


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



2-phenylacetic-2,2-d_2 acid (35)

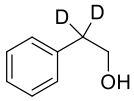
^{1}H NMR (400 MHz, $CDCl_3$)



35

2-phenylethan-2,2-d_2-1-ol (36)

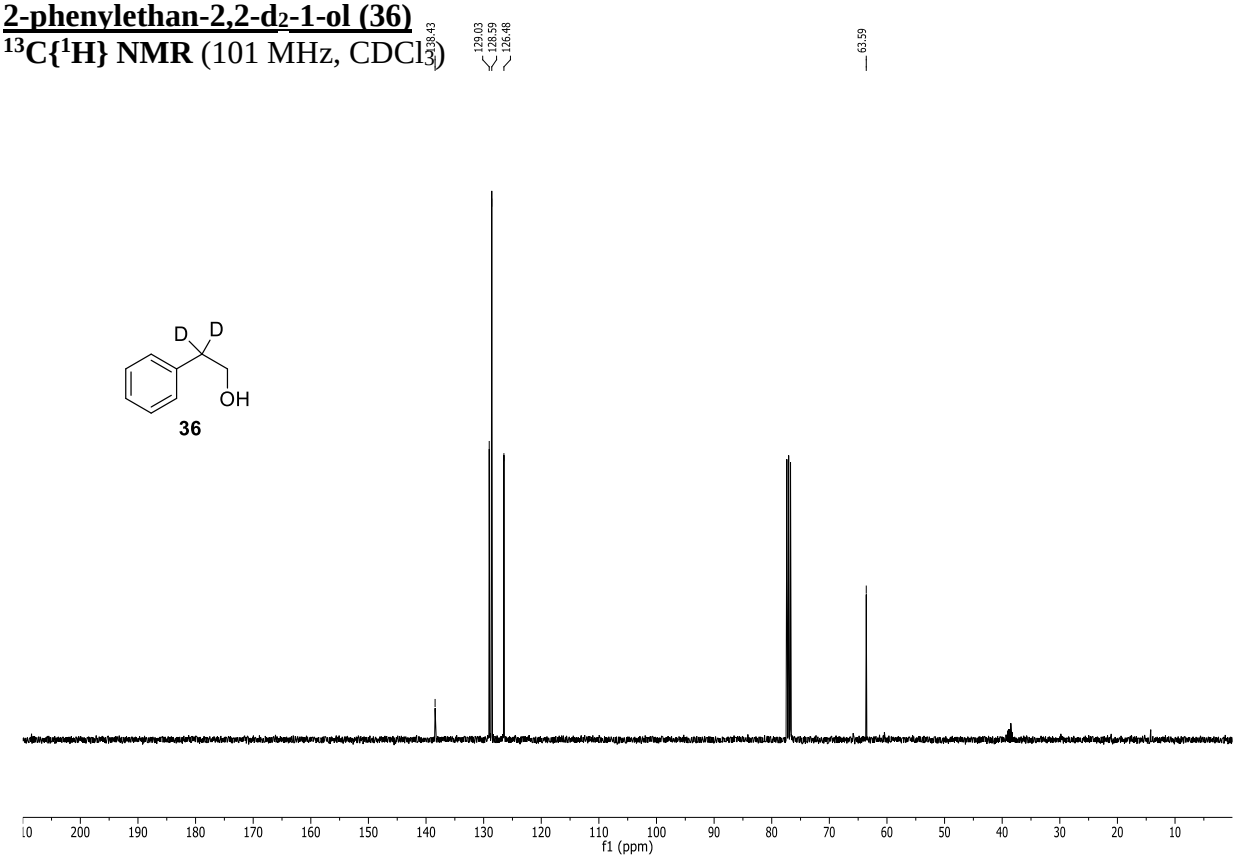
^{1}H NMR (400 MHz, $CDCl_3$)



36

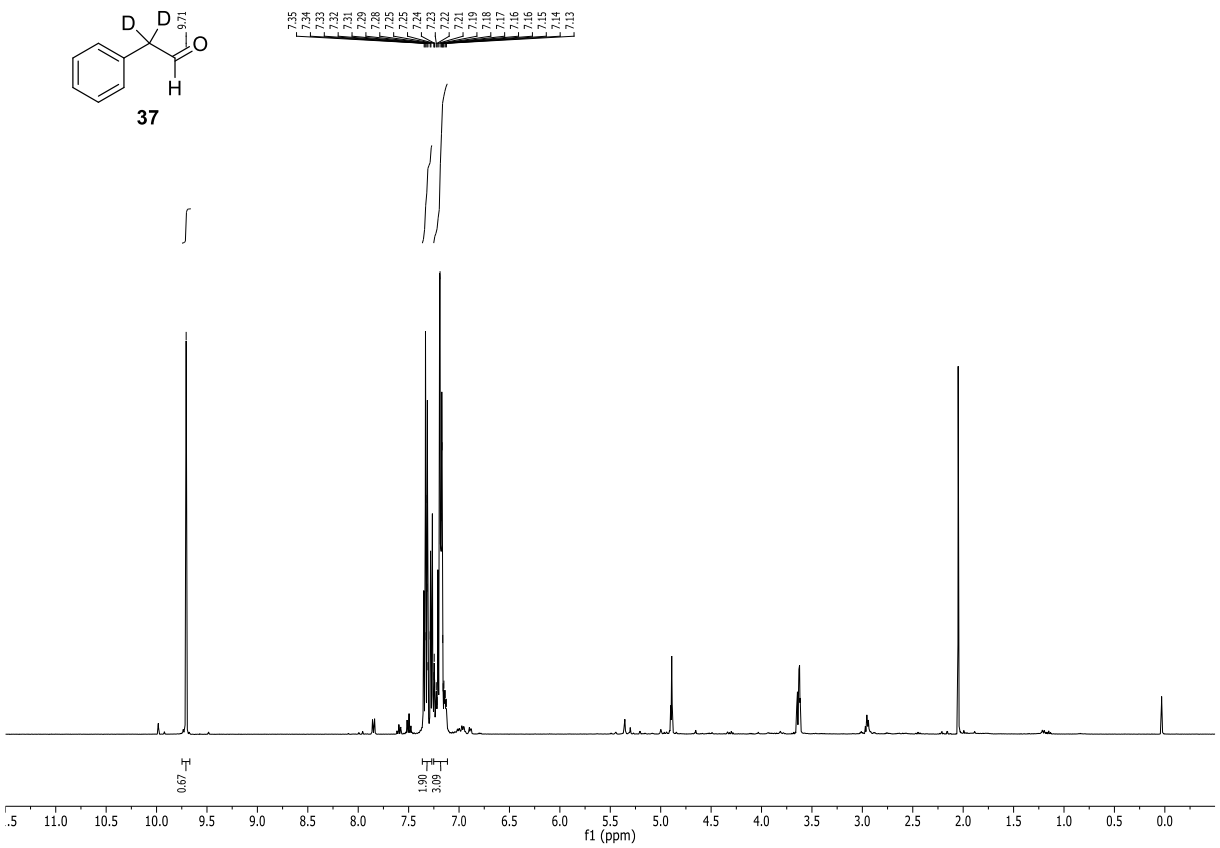
2-phenylethan-2,2-d_2-1-ol (36)

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



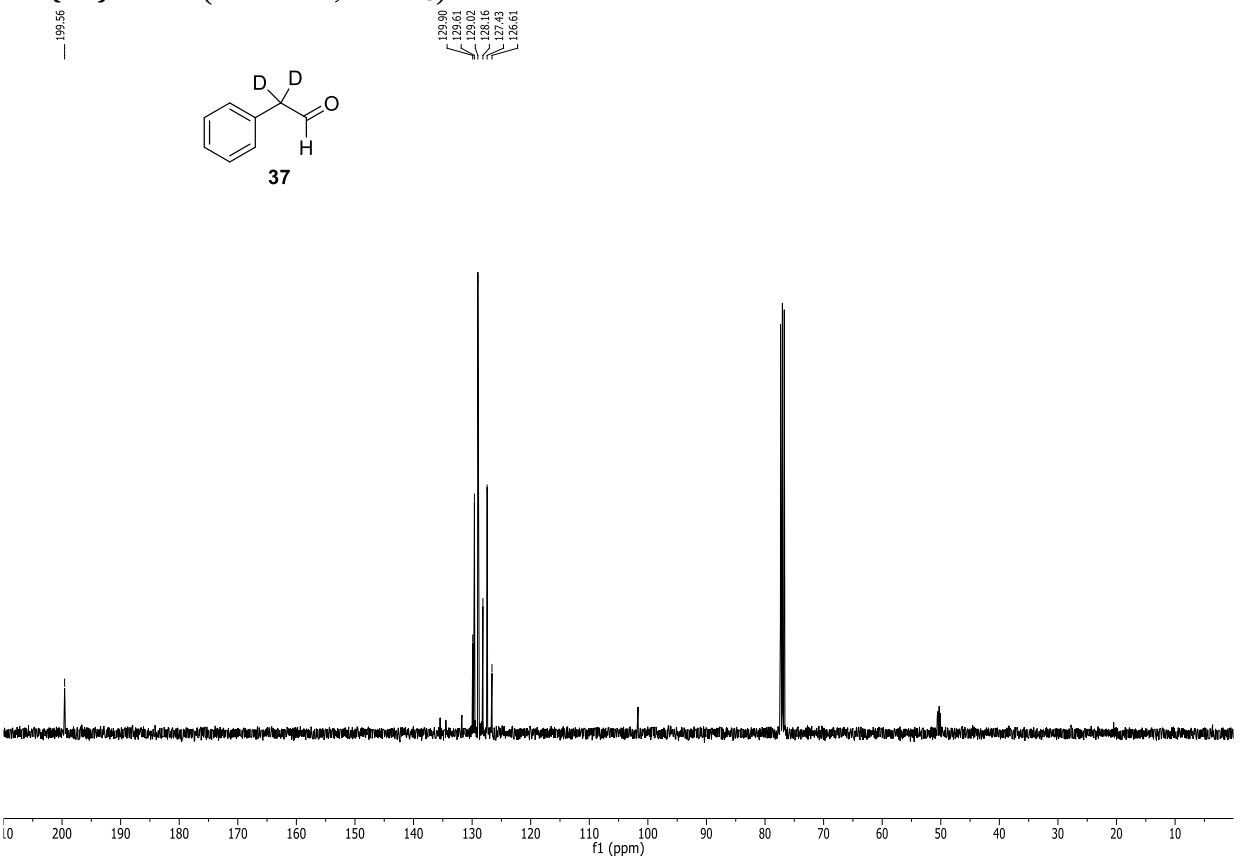
2-phenylacetaldehyde-2,2-d_2 (37)

^1H NMR (400 MHz, $CDCl_3$)



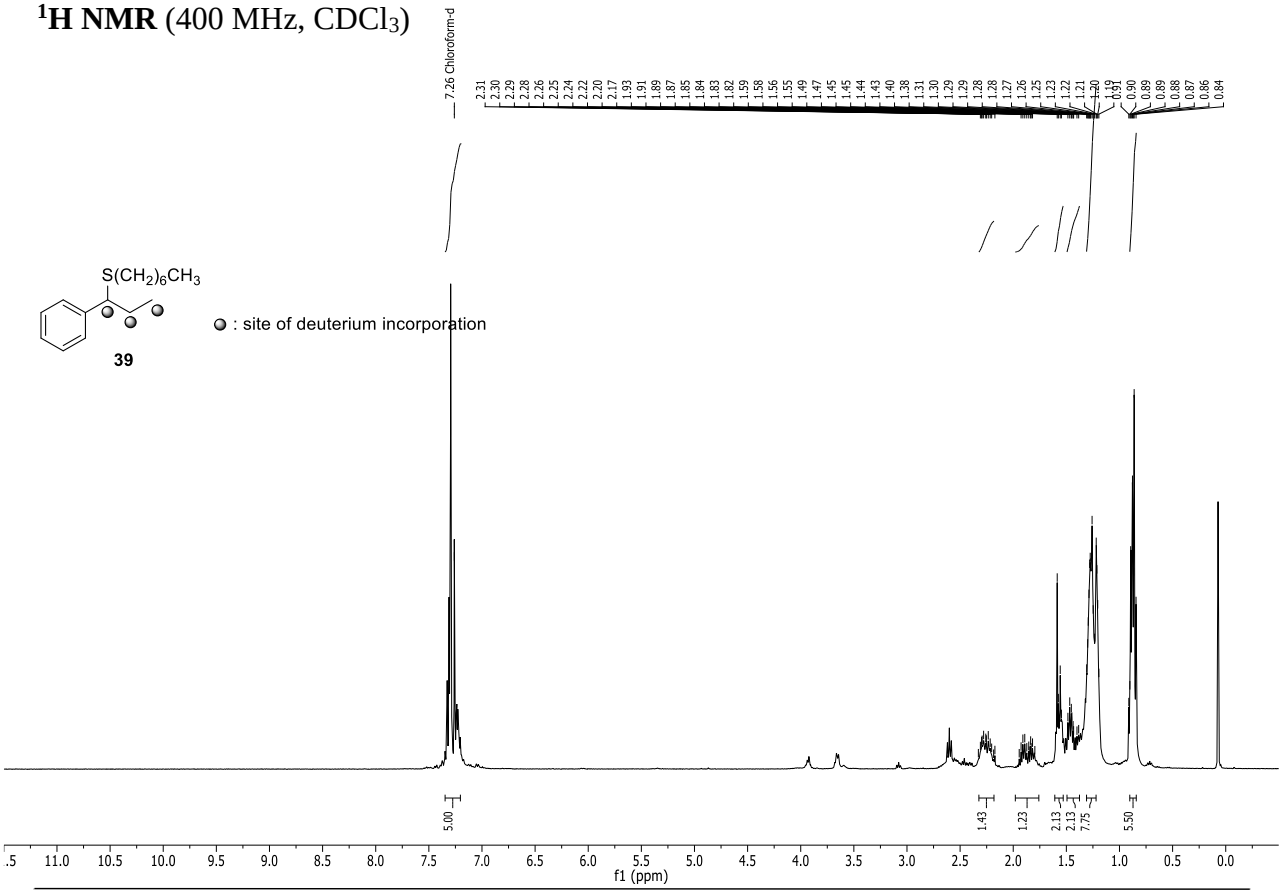
2-phenylacetaldehyde-2,2-d_2 (37)

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

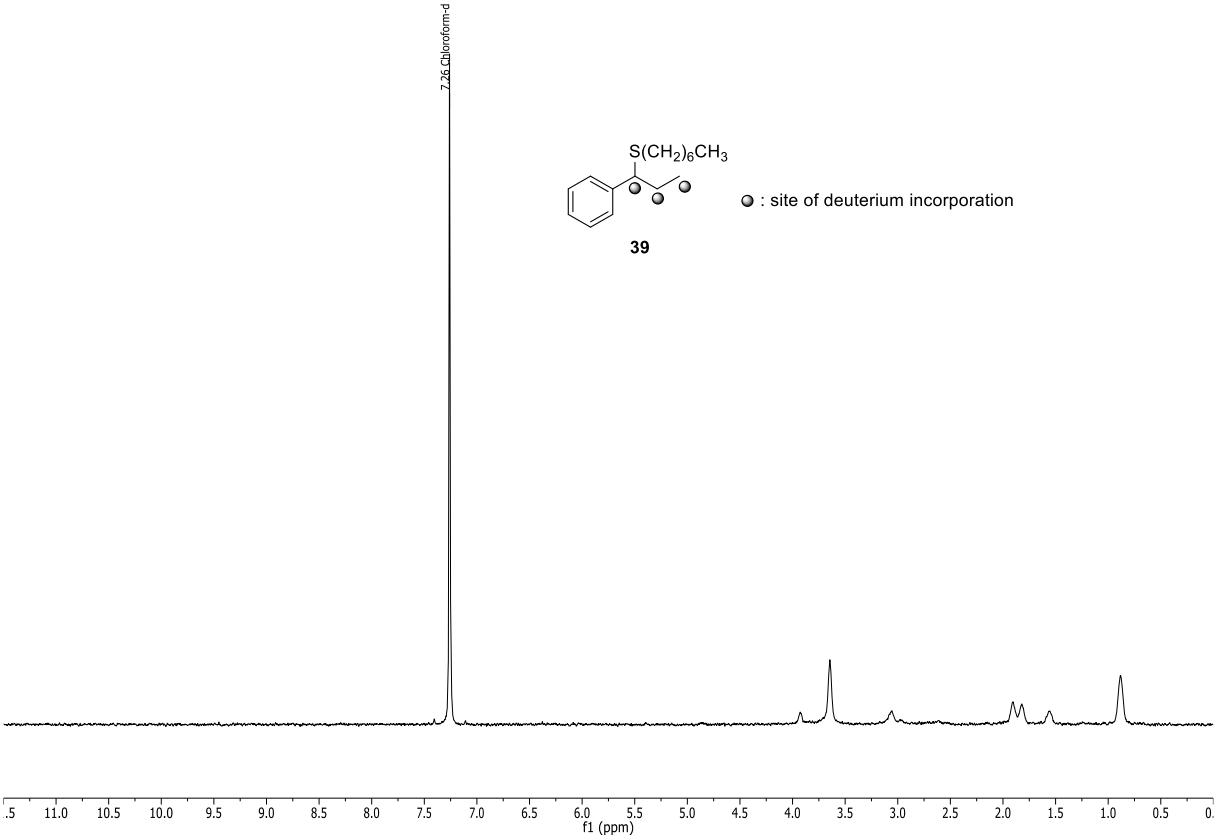


heptyl(1-phenylpropyl)sulfane (39)

^1H NMR (400 MHz, $CDCl_3$)

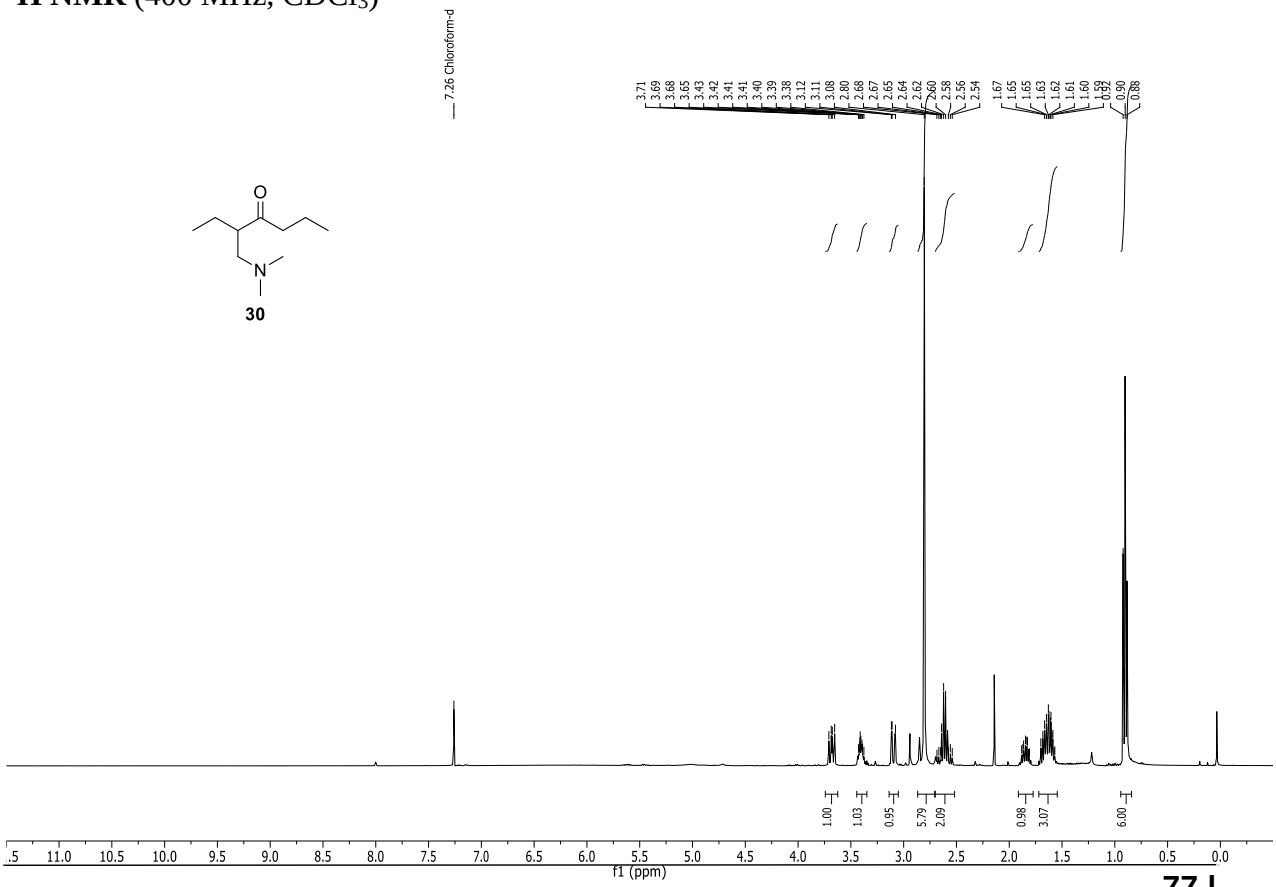


heptyl(1-phenylpropyl)sulfane (39)



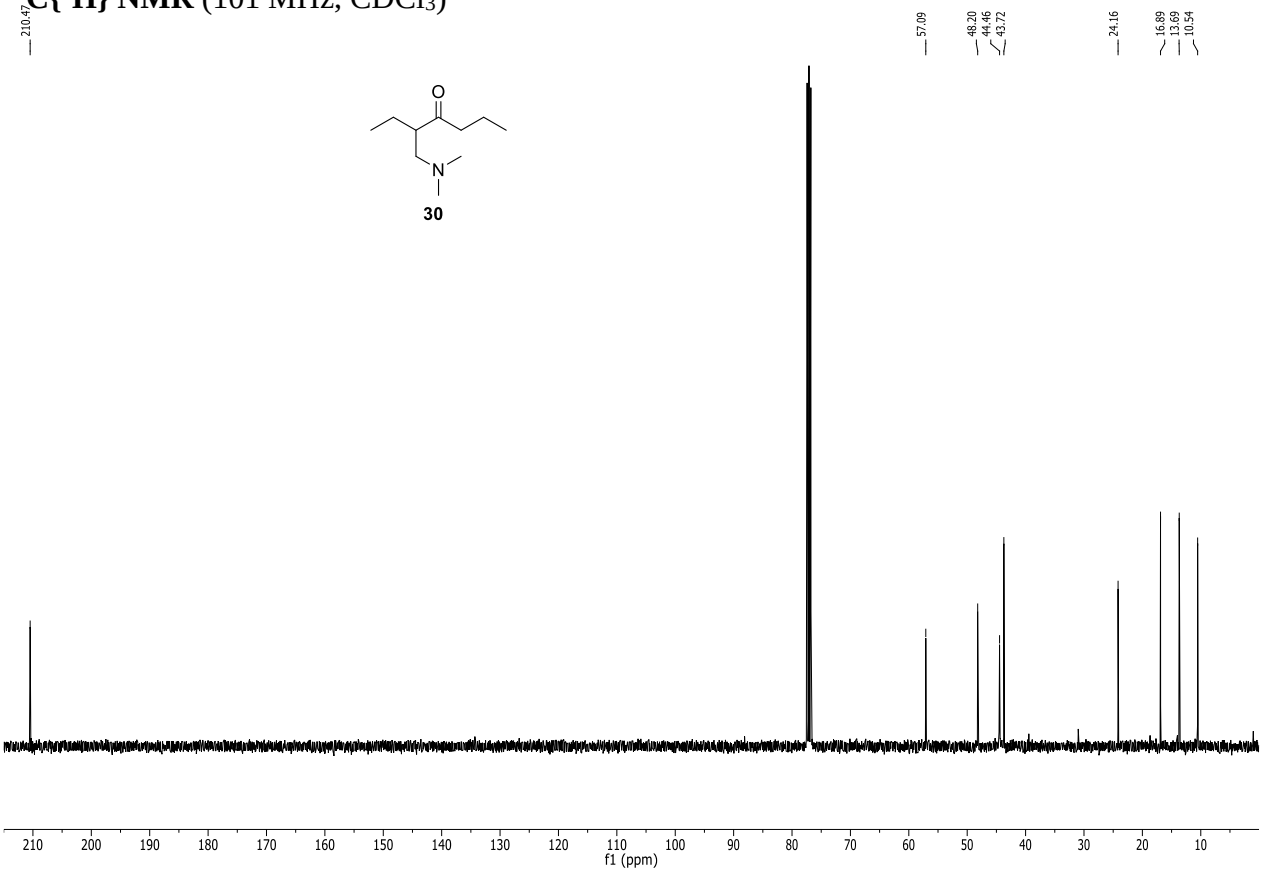
3-((dimethylamino)methyl)heptan-4-one (30)

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



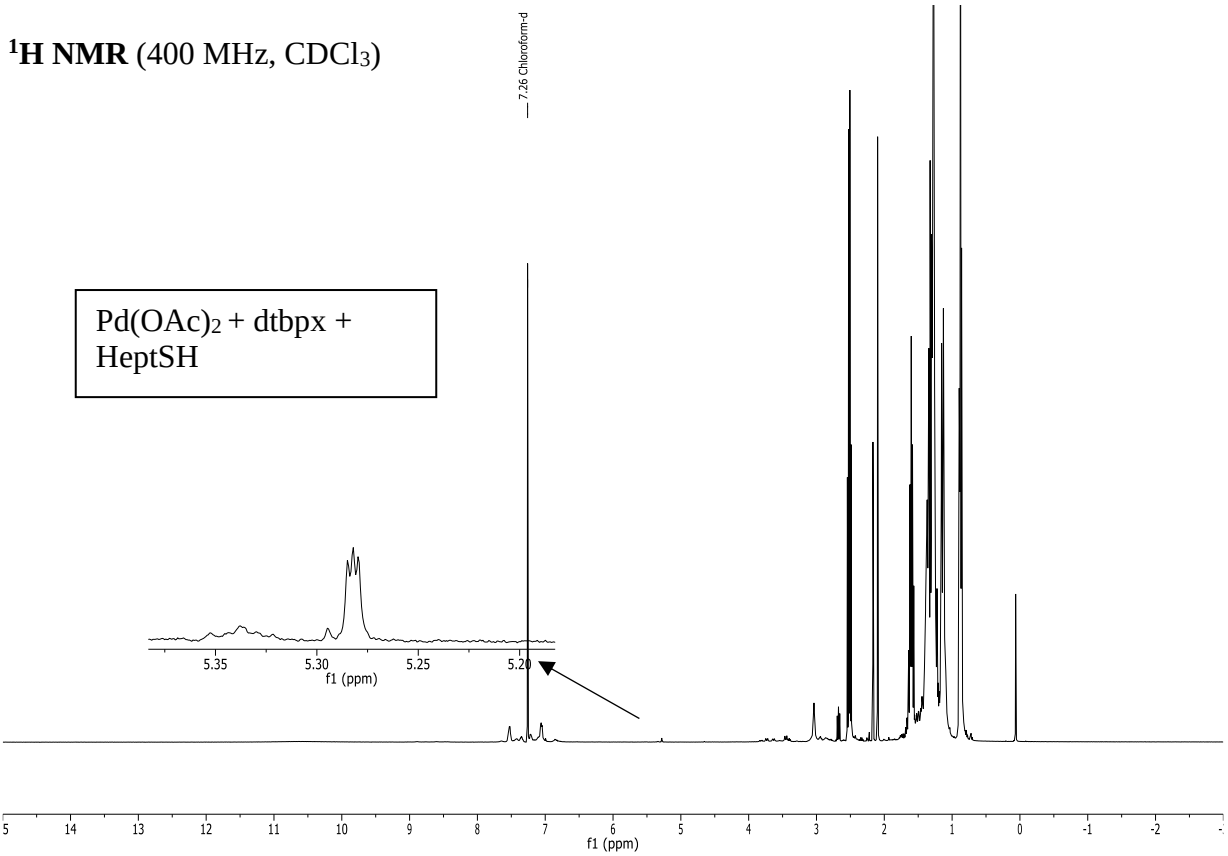
3-((dimethylamino)methyl)heptan-4-one (30)

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



In a flame dried Schlenk tube was added 1,2-bis[(di-tert.-butylphosphino)methyl]benzene (dtbpx) (4.5 mol%, 17.3 mg, 0.043 mmol) inside a glove box. The tube was taken outside the box and $Pd(OAc)_2$ (3 mol%, 6.72 mg, was added. A yellow colored solution is formed. The solution was stirred for 1.5 h at r.t. Followed by this, heptane thiol (38.8 µL, 0.32 mmol) was added to the solution and the solution was stirred for another hour at 40 °C. An orange colored solution was observed at the end of this stirring period. The NMR spectrum recorded at that point is shown below

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



3.5 References

[1] T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011-1014.

[2] a)T. Iwama, V. H. Rawal, *Org. Lett.* **2006**, *8*, 5725-5728; b)L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2009**, *11*, 3730-3733; c)R. Moumné, M. Larregola, Y. Boutadla, S. Lavielle, P. Karoyan, *Tetrahedron Lett.* **2008**, *49*, 4704-4707; d)H. B. Yang, N. Selander, *Chem. Eur. J.* **2017**, *23*, 1779-1783.

[3] N. Sakai, T. Muraoka, S. Matsumoto, A. Mutsuro, Y. Ogiwara, *Synlett* **2017**, *28*, 343-346.

[4] M. O. Ratnikov, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 1549-1557.

[5] A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *17*, 1295-1298.

[6] T. Suga, S. Iizuka, T. Akiyama, *Org. Chem. Front.* **2016**, *3*, 1259-1264.

[7] G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed* **1976**, *15*, 239-240.

[8] P. M. Kathe, I. Fleischer, *Org. Lett.* **2019**.

[9] Q. Wu, L. Wang, R. Jin, C. Kang, Z. Bian, Z. Du, X. Ma, H. Guo, L. Gao, *Eur. J. Org. Chem.* **2016**, *2016*, 5415-5422.

[10] M. A. Esteruelas, J. Herrero, M. Oliván, *Organometallics* **2004**, *23*, 3891-3897.

[11] R. W. Hoffmann, M. Bewersdorf, *Liebigs. Ann. Chem.* **1992**, *1992*, 643-653.

[12] F. A. Davis, B. Yang, *J. Am. Chem. Soc.* **2005**, *127*, 8398-8407.

CHAPTER 4

PUBLICATIONS

OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 2213–2217

pubs.acs.org/OrgLett

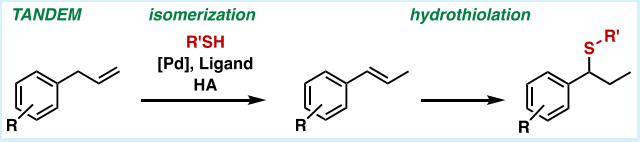
Palladium-Catalyzed Tandem Isomerization/Hydrothiolation of Allylarenes

Prasad M. Kathe and Ivana Fleischer*

Institute of Organic Chemistry, Faculty of Mathematics and Natural Sciences, Eberhard-Karls University Tuebingen, Auf der Morgenstelle 18, 72076 Tuebingen, Germany

Supporting Information

ABSTRACT: Herein we report a tandem olefin migration/hydrothiolation of allyl benzenes facilitated by an *in situ* generated palladium hydride. A catalyst system composed of palladium acetate and bidentate ligand dtbpx (1,2-bis(di-*tert*-butylphosphinomethyl)benzene in the presence of catalytic amounts of triflic acid led to the tandem transformation, which furnished benzylic thioethers. The reaction exhibits high regioselectivity and can be conducted under mild conditions. The robustness of the catalyst is displayed through reactions with coordinating thiols.



The conjugative migration of a double bond of allyl benzenes (migration over one carbon atom) is a well-understood and extensively investigated process.[1] In general, transition metal hydrides have enabled the use of mild reaction conditions in alkene isomerizations.[2] A large portion of work in this field was essentially intended toward developing additional reactivity in a tandem process, which is often referred to as remote functionalization.[3] Allylic isomerization was combined with various functionalizations of the benzylic position, which enabled formation of new C−C[4] or C−heteroatom[5] bonds from easily available precursors. To the best of our knowledge, this strategy was not applied in the formation of new C−S bonds.

The ubiquity of branched thioethers in a range of biologically relevant compounds (Figure 1) has triggered

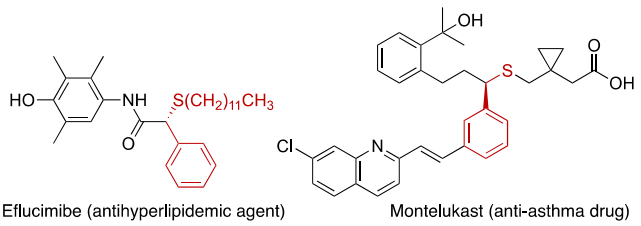


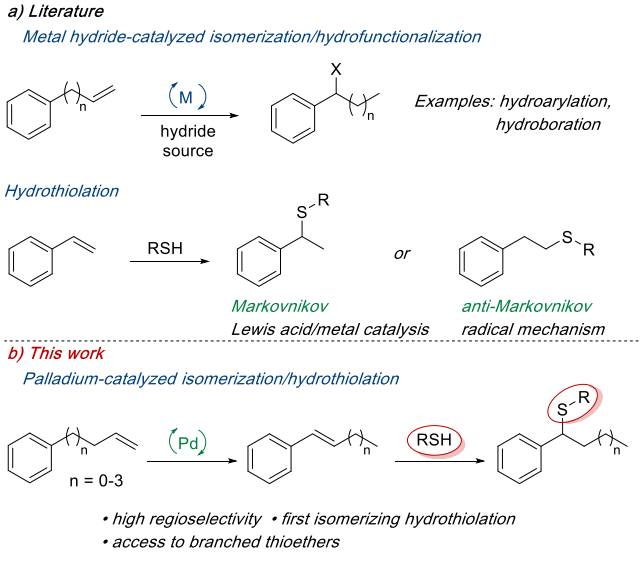
Figure 1. Thioether moiety in biologically relevant compounds.

efforts directed toward catalytic C−S bond formation through hydrothiolation of olefins.[6] This method complements other strategies for catalytic C−S bond construction,[7] such as couplings[8] or carbonylations.[9] Barring some exceptions,[10] a radical pathway is proposed to give rise to an anti-Markovnikov product.[11] This, also called a thiol−ene "click" reaction, has been exploited as a synthetic tool mostly in materials chemistry.[12] In contrast, an acid- or metal-catalyzed cationic pathway usually provides the Markovnikov product.[13]

Palladium-catalyzed alkene hydrothiolations are rare,[14] probably due to catalyst poisoning by formation of strong M−S bonds.[15] However, based on our experience with Pd-catalyzed transformations of thiols,[9e] we envisaged a process that would enable a tandem conjugative migration−hydrothiolation using a palladium hydride precursor (Scheme 1b). This would stand out as an atom and step economic transformation furnishing benzylic thioethers.

We started our investigation by employing 4-allyl-1,2-dimethoxybenzene (**1a**) and heptane-1-thiol (**2a**) as reaction

Scheme 1. (a) Prior Work in Hydrothiolation and Conjugative Migration/Hydrofunctionalization; (b) This Work

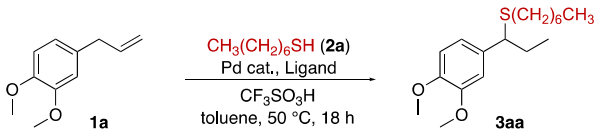


Received: February 7, 2019
Published: March 14, 2019

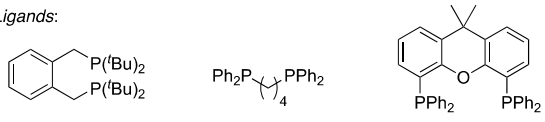
DOI: 10.1021/acs.orglett.9b00504
Org. Lett. 2019, 21, 2213−2217

partners (Table 1). The initial choice of the catalyst system depended on its activity in the isomerization. We confirmed

Table 1. Optimization of Reaction Conditions[a]



Ligands:



L1 L2 L3

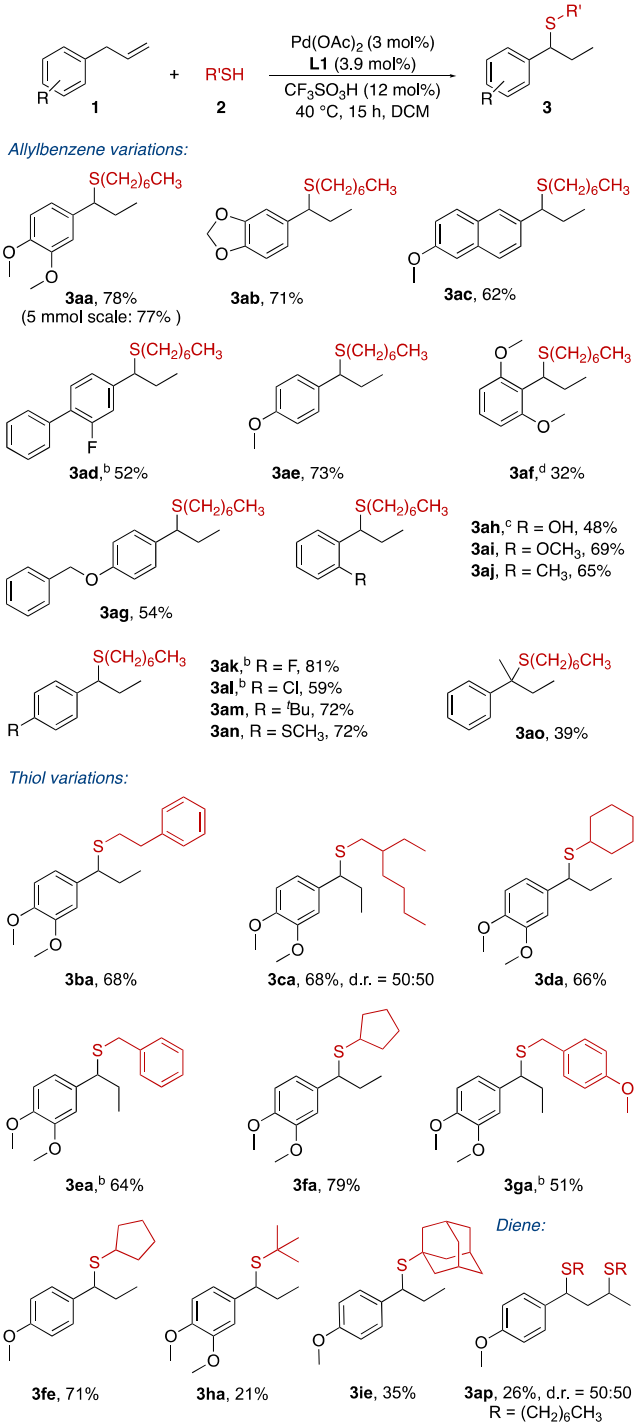
entry	Pd cat. (mol %)	ligand (mol %)	conv (%)[b]	yield (%)[b]
1	$Pd(OAc)_2$ (5)	**L1** (9.4)	100	94
2	$Pd(OAc)_2$ (3)	**L1** (5.4)	100	93
3	$Pd(OAc)_2$ (2)	**L1** (3.4)	100	51
4	$Pd(OAc)_2$ (3)	**L2** (3.9)	85	74
5	$Pd(acac)_2$ (5)	**L1** (9.4)	–	–
6	$Pd(OAc)_2$ (3)	**L3** (6)	–	–
7[c]	$Pd(OAc)_2$ (3)	**L1** (3.9)	100	94
8[d]	$Pd(OAc)_2$ (3)	**L1** (3.9)	99	97

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), CF_3SO_3H (12 mol %), toluene (1 mL), 50 °C, 18 h. [b]Determined by GC-FID analysis using pentadecane as the internal standard. [c]Solvent: DCM. [d]Solvent: DCM, CF_3SO_3H (12 mol %), 40 °C, 15 h.

that palladium acetate in combination with a strong acid as a hydride source and **L1** as a ligand resulted in rapid conjugative migration, which was known to occur during carbonylations.[16] Employing the standard isomerization conditions to hydrothiolation, we were delighted to observe conversion to the product arising from Markovnikov hydrothiolation of the isomerized double bond (entry 1). Only a small amount (<5%) of anti-Markovnikov regioisomer was detected. This was avoided by the use of freshly distilled heptanethiol (stored under argon). The amount of catalyst could be reduced to 3 mol %, while diminished activity was observed using 2 mol % of catalyst (entries 2, 3). Further optimization including use of other palladium salts as catalyst precursors led to little or no conversion (entry 5, only 1 example shown). Ligand **L1** displayed superior reactivity when compared to other bidentate ligands such as **L2** (entry 4). The strong ligand effects point to the significance of stability of the catalytic metal hydride in this transformation.[16] Use of bulky and rigid phosphine such as **L3** resulted in no yield (entry 6). Solvent screening revealed that polar, chlorinated solvents offer high yields. In the presence of DCM, the reaction could be carried out under much milder conditions and relatively lower loadings of catalyst and ligand (entries 7, 8 and Supporting Information for more details). Another important aspect was the use of a partially oxidized ligand in different purchased samples. Fortunately, the use of pure ligand also led to complete conversion and comparable yields to the batch with partially oxidized phosphine. Hence, there appears to be no influence of the oxide on the reactivity.

The scope of this transformation was investigated by employing a variety of substituted allyl benzenes (Scheme 2). Substrates with alkoxy substituents such as **3aa**, **3ab**, **3ae** gave good yields in the range 71−78%. The model reaction of **1a** with **2a** was also tested at a 5 mmol scale. Product isolation and purification by column chromatography provided 1.2 g,

Scheme 2. Tandem Isomerization−Hydrothiolation of Various Allylbenzenes and Thiols[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), Pd (3 mol %), **L1** (3.9 mol %), CF_3SO_3H (12 mol %), DCM (1 mL), 40 °C, 15 h. [b]**1** (0.25 mmol), **2** (0.27 mmol), Pd (6 mol %), **L1** (12 mol %), CF_3SO_3H (16 mol %), 50 °C, 64 h. [c]Toluene (1 mL), **L1** (6 mol %), 24 h, 50 °C. [d]CF_3SO_3H (16 mol %).

77% of **3a**. Substrates with −Cl and −F required higher catalyst loadings and slightly elevated temperature and time to achieve full conversion. Such products can be used in downstream chemistry.

1-Allylnaphthalene showed no reactivity possibly due to steric effects. However, the use of 2-allyl-6-methoxy naph-

DOI: 10.1021/acs.orglett.9b00504
Org. Lett. 2019, 21, 2213−2217

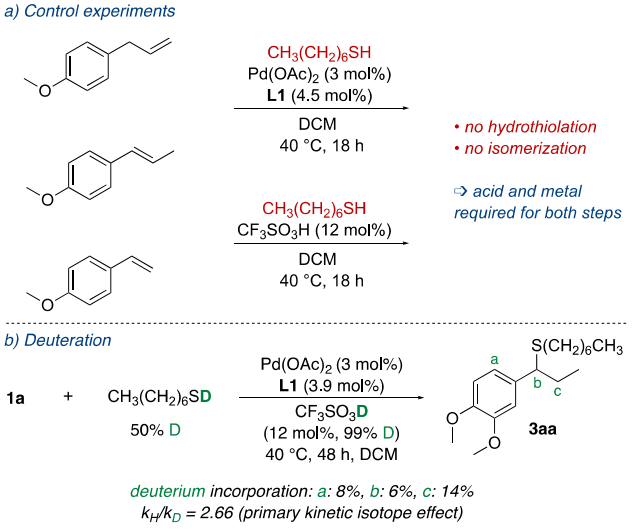
thalene resulted in complete conversion and afforded the corresponding thioether **3ac** in 62% yield. A striking influence of solvent was observed in the case of **3ah**, wherein the reaction with DCM resulted in no conversion; however, under the same reaction conditions, switching the solvent to toluene led to a 49% yield of **3ah**. Substrates with amino functionality showed very poor reactivity to give corresponding thiothers, although conjugative migration did take place. An obvious reason is the formation of an ammonium cation, hence deactivating the aromatic system. Similar behavior was observed for electron-poor allylbenzenes containing CF_3, CN functionalities. Notably, also *o*-substituted alkenes furnished the corresponding products (**3ai**, **3aj**) in good yields. The presence of a methyl substituent in the benzylic position still allowed for the tandem transformation; however, the product **3ao** was obtained in lower yield. Interestingly, the use of (buta-1,3-dien-1-yl)-4-methoxybenzene led to dihydrothiolation and resulted in formation of **3ap** in 26% yield.

Furthermore, aliphatic thiols with differing steric and electronic attributes were tested in the hydrothiolation of **1a**. It became clear that more nucleophilic thiols are the most effective in catalysis. Under identical reaction conditions, the similar reactivity of primary and secondary thiols was noted, with products **3ca**, **3da**, and **3fa** obtained in yields of 68%, 66%, and 74%, respectively. Thiols with higher acidity (benzyl mercaptan with a pK_a in the range 8−9) displayed poorer reactivity. Thus, **3ea** and **3ga** were synthesized from corresponding benzyl mercaptan derivatives in 64% and 51% yields under more forcing reaction conditions. Thiols possessing high steric bulk resulted in rather low yields albeit with complete conversion of starting material. Dimerization of the isomerized internal olefin was confirmed by MS.

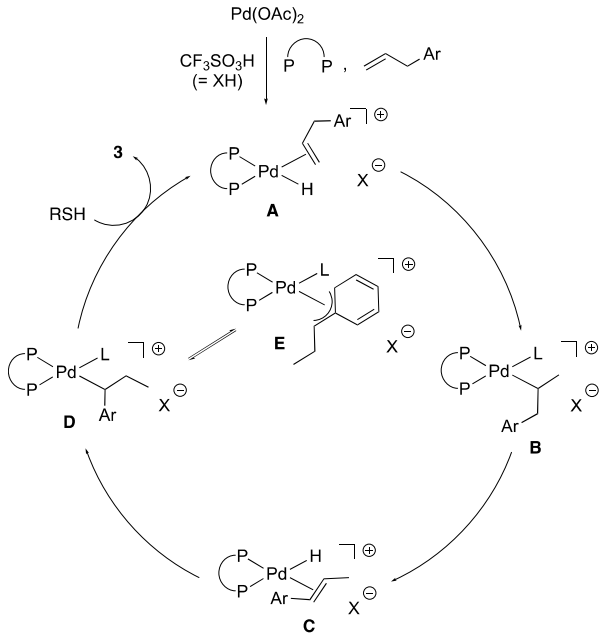
Control experiments were conducted in the absence of triflic acid or catalyst precursor and ligand using 4-allylanisole as the substrate (Scheme 3a). In both cases, no product was formed. Similar experiments carried out with *trans*-anethole and 4-methoxystyrene resulted in the same outcome. This shows that neither the isomerization nor the following hydrothiolation are acid- or purely metal-catalyzed.

Moreover, preliminary mechanistic investigations were performed through deuteration experiments, which were conducted using partially deuterated heptane-1-thiol and deuterated triflic acid (Scheme 3b). Varying amounts of deuterium incorporation were found on all three carbon atoms of the propyl group (b, c and CH_3 group, which could not be quantified due to overlap; see SI). This suggests a reversible insertion of alkene into the Pd−H bond and isomerization. Interestingly, deuterium was also found in the *ortho*-position (a) on benzene. This observation hints toward the existence of a π-benzylic Pd-intermediate (**F**, Scheme 4). However, when

Scheme 3. Isomerizing Hydrothiolation: (a) Control Experiments Catalyst Components; (b) Deuteration



Scheme 4. Proposed Catalytic Cycle



2,6-dimethoxy-1-allylbenzene was subjected to the same reaction conditions, we observed the formation of Markovnikov product **3af** albeit in lower yield. This indicates that the presence of the benzylic intermediate is not a precondition for the hydrothiolation to take place.

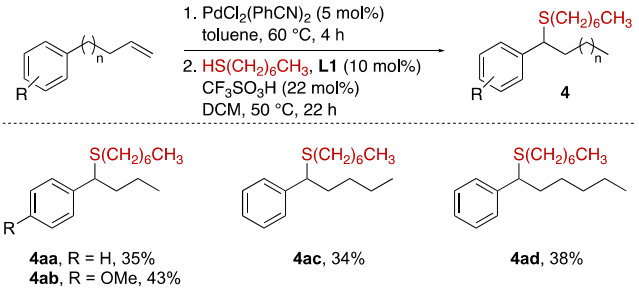
In addition, a comparison of kinetic profiles of reaction with deuterated and nondeuterated acid and thiol showed a significant primary kinetic isotope effect. However, cleavage of X−H and M−H bonds may be involved in many steps of the catalytic cycle. In accordance to the above experiments and accepted mechanism for related reactions,[16] we propose a catalytic cycle based on the formation of palladium hydride **A** from triflic acid. Insertion of olefin into the Pd−H bond results in the alkyl complex **B**, which undergoes β-hydride elimination to furnish the complex **C** with a conjugated aromatic system. The repeated insertion leads to complex **D**, which can be stabilized by the η^3-coordination mode in **E**. The incorporation of deuterium in the alkyl chain is indicative of a chain walking mechanism of isomerization. The reaction of **D** with the thiol leads to the formation of **3** and the regeneration of the palladium hydride. It is unclear if this proceeds via coordination of thiol, which can also occur earlier in the cycle, or direct substitution.

To extend the scope of this reactivity, we directed our efforts toward increasing the chain length of the olefin. Under the conditions developed for allylbenzenes, no isomerization of 1-phenyl-4-butene was observed. $PdCl_2(PhCN)_2$ has been established as an efficient precatalyst for double bond migration in similar systems.[17] Thus, we envisioned a simple

DOI: 10.1021/acs.orglett.9b00504
Org. Lett. 2019, 21, 2213−2217

approach to accomplish the desired reactivity for longer chain substrates (Scheme 5). $PdCl_2(PhCN)_2$ was employed for

Scheme 5. One-Pot Isomerization−Hydrothiolation of Longer Chain Olefins[a]



[a]Reaction Conditions: (1) $PdCl_2(PhCN)_2$ (5 mol %), toluene (0.3 mL), alkene (0.5 mmol), 4 h, 60 °C; (2) **L1** (10 mol %), CF_3SO_3H (22 mol %), heptane-1-thiol (0.55 mmol), DCM (0.7 mL), 50 °C, 22 h.

double bond migration to generate β-substituted styrenes. In this case, the isomerization occurs without the need of an external hydride source. This was followed by the sequential addition of the ligand **L1**, acid, and thiol. Indeed, this one-pot approach proved to be suitable for the conversion of terminal alkenes with varying chain lengths and furnished the corresponding benzylic thioethers **4** in moderate yields.

In conclusion, we have developed a methodology for efficient Pd-catalyzed tandem isomerization/hydrothiolation of allylbenzenes. The catalyst system consisting of a Pd(II) precursor, bidentate phosphine ligand, and strong Brønsted acid was able to convert a variety of 3-arylpropenes and thiols to branched benzylic thioethers in a highly regioselective manner. The stability and activity of palladium hydride in the presence of highly coordinating thiols was demonstrated. Overall this transformation serves as a convenient strategy in achieving benzylic functionalization starting from allylated aromatic precursors. Further efforts to render this transformation asymmetric are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00504.

Experimental procedures, analytical data, and mechanistic discussion (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ivana.fleischer@uni-tuebingen.de.

ORCID

Ivana Fleischer: 0000-0002-2609-6536

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from DAAD (Deutscher Akademischer Austauschdienst, fellowship P.K.) and the University of Tübingen (Institutional Strategy: Deutsche Forschungsgemeinschaft ZUK 63) is gratefully acknowledged.

■ REFERENCES

(1) (a) Tolman, C. A. Chemistry of tetrakis(triethyl phosphite) nickel hydride, $HNi[P(OEt)_3]_4^+$. IV. Mechanism of olefin isomerization. *J. Am. Chem. Soc.* **1972**, *94*, 2994−2999. (b) McGrath, D. V.; Grubbs, R. H. The mechanism of aqueous ruthenium(II)-catalyzed olefin isomerization. *Organometallics* **1994**, *13*, 224−235. (c) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 7998−8009. (d) Spallek, M. J.; Stockinger, S.; Goddard, R.; Trapp, O. Modular Palladium Bipyrazoles for the Isomerization of Allylbenzenes − Mechanistic Considerations and Insights into Catalyst Design and Activity, Role of Solvent, and Additive Effects. *Adv. Synth. Catal.* **2012**, *354*, 1466−1480. (e) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. Tandem Isomerization and C−H Activation: Regioselective Hydroheteroarylation of Allylarenes. *Org. Lett.* **2013**, *15*, 5358−5361. (f) Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo, W. A. L. Isomerization of Allylbenzenes. *Chem. Rev.* **2015**, *115*, 5462−5569. (g) Chuc, L. T. N.; Chen, C.-S.; Lo, W.-S.; Shen, P.-C.; Hsuan, Y.-C.; Tsai, H.-H. G.; Shieh, F.-K.; Hou, D.-R. Long-Range Olefin Isomerization Catalyzed by Palladium(0) Nanoparticles. *ACS Omega* **2017**, *2*, 698−711. (h) Kapat, A.; Sperger, T.; Guven, S.; Schoenebeck, F. *E*-Olefins through intramolecular radical relocation. *Science* **2019**, *363*, 391−396.

(2) Larionov, E.; Li, H.; Mazet, C. Well-defined transition metal hydrides in catalytic isomerizations. *Chem. Commun.* **2014**, *50*, 9816−9826.

(3) (a) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* **2016**, *8*, 209. (b) Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153−165.

(4) (a) Yamakawa, T.; Yoshikai, N. Alkene Isomerization−Hydroarylation Tandem Catalysis: Indole C2-Alkylation with Aryl-Substituted Alkenes Leading to 1,1-Diarylalkanes. *Chem. - Asian J.* **2014**, *9*, 1242−1246. (b) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C−H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1061−1064. (c) Peng, L.; Li, Y.; Li, Y.; Wang, W.; Pang, H.; Yin, G. Ligand-Controlled Nickel-Catalyzed Reductive Relay Cross-Coupling of Alkyl Bromides and Aryl Bromides. *ACS Catal.* **2018**, *8*, 310−313.

(5) (a) Scheuermann, M. L.; Johnson, E. J.; Chirik, P. J. Alkene Isomerization−Hydroboration Promoted by Phosphine-Ligated Cobalt Catalysts. *Org. Lett.* **2015**, *17*, 2716−2719. (b) Huang, J.; Yan, W.; Tan, C.; Wu, W.; Jiang, H. Palladium-catalyzed regioselective hydroboration of aryl alkenes with B_2pin_2. *Chem. Commun.* **2018**, *54*, 1770−1773.

(6) (a) Yang, Y.; Rioux, R. M. Highly stereoselective anti-Markovnikov hydrothiolation of alkynes and electron-deficient alkenes by a supported Cu-NHC complex. *Green Chem.* **2014**, *16*, 3916−3925. (b) Kuciński, K.; Pawluć, P.; Marciniec, B.; Hreczycho, G. Highly Selective Hydrothiolation of Unsaturated Organosilicon Compounds Catalyzed by Scandium(III) Triflate. *Chem. - Eur. J.* **2015**, *21*, 4940−4943. (c) Kennemur, J. L.; Kortman, G. D.; Hull, K. L. Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines. *J. Am. Chem. Soc.* **2016**, *138*, 11914−11919. (d) Mosaferi, E.; Ripsman, D.; Stephan, D. W. The air-stable carbocation salt $[(MeOC_6H_4)CPh_2][BF_4]$ in Lewis acid catalyzed hydrothiolation of alkenes. *Chem. Commun.* **2016**, *52*, 8291−8293. (e) Yang, X.-H.; Davison, R. T.; Dong, V. M. Catalytic Hydrothiolation: Regio- and Enantioselective Coupling of Thiols and Dienes. *J. Am. Chem. Soc.* **2018**, *140*, 10443−10446.

(7) Lee, C.-F.; Basha, R. S.; Badsara, S. S. Engineered C−S Bond Construction. *Top. Curr. Chem.* **2018**, *376*, 25.

DOI: 10.1021/acs.orglett.9b00504
Org. Lett. 2019, 21, 2213−2217

(8) (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-i.; Kato, Y.; Kosugi, M. The Palladium Catalyzed Nucleophilic Substitution of Aryl Halides by Thiolate Anions. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385−1389. (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols. *J. Am. Chem. Soc.* **2006**, *128*, 2180−2181. (c) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols With Aryl and Heteroaryl Iodides via Thiyl Radicals. *J. Am. Chem. Soc.* **2016**, *138*, 1760−1763. (d) Ichiishi, N.; Malapit, C. A.; Woźniak, Ł.; Sanford, M. S. Palladium- and Nickel-Catalyzed Decarbonylative C−S Coupling to Convert Thioesters to Thioethers. *Org. Lett.* **2018**, *20*, 44−47. (e) Jones, K. D.; Power, D. J.; Bierer, D.; Gericke, K. M.; Stewart, S. G. Nickel Phosphite/Phosphine-Catalyzed C−S Cross-Coupling of Aryl Chlorides and Thiols. *Org. Lett.* **2018**, *20*, 208−211. (f) Liu, C.; Szostak, M. Decarbonylative thioetherification by nickel catalysis using air- and moisture-stable nickel precatalysts. *Chem. Commun.* **2018**, *54*, 2130−2133. (g) Gehrtz, P. H.; Geiger, V.; Schmidt, T.; Sršan, L.; Fleischer, I. Cross-Coupling of Chloro(hetero)arenes with Thiolates Employing a Ni(0)-Precatalyst. *Org. Lett.* **2019**, *21*, 50−55.

(9) (a) Xiao, W.-J.; Vasapollo, G.; Alper, H. Highly Regioselective Thiocarbonylation of Conjugated Dienes via Palladium-Catalyzed Three-Component Coupling Reactions. *J. Org. Chem.* **2000**, *65*, 4138−4144. (b) Xiao, W.-J.; Alper, H. Highly Stereoselective Palladium-Catalyzed Dithiocarbonylation of Propargylic Mesylates with Thiols and Carbon Monoxide. *J. Org. Chem.* **2005**, *70*, 1802−1807. (c) Burhardt, M. N.; Taaning, R. H.; Skrydstrup, T. Pd-Catalyzed thiocarbonylation with stoichiometric carbon monoxide: Scope and applications. *Org. Lett.* **2013**, *15*, 948−951. (d) Burhardt, M. N.; Ahlburg, A.; Skrydstrup, T. Palladium-Catalyzed Thiocarbonylation of Aryl, Vinyl, and Benzyl Bromides. *J. Org. Chem.* **2014**, *79*, 11830−11840. (e) Hirschbeck, V.; Gehrtz, P. H.; Fleischer, I. Regioselective Thiocarbonylation of Vinyl Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 16794−16799.

(10) (a) Weïwer, M.; Coulombel, L.; Duñach, E. Regioselective indium(iii) trifluoromethanesulfonate-catalyzed hydrothiolation of non-activated olefins. *Chem. Commun.* **2006**, 332−334. (b) Kuciński, K.; Pawluć, P.; Hreczycho, G. Scandium(III) Triflate-Catalyzed anti-Markovnikov Hydrothiolation of Functionalized Olefins. *Adv. Synth. Catal.* **2015**, *357*, 3936−3942. (c) Kristensen, S. K.; Laursen, S. L. R.; Taarning, E.; Skrydstrup, T. Ex Situ Formation of Methanethiol: Application in the Gold(I)-Promoted Anti-Markovnikov Hydrothiolation of Olefins. *Angew. Chem., Int. Ed.* **2018**, *57*, 13887−13891. (d) Tamai, T.; Fujiwara, K.; Higashimae, S.; Nomoto, A.; Ogawa, A. Gold-Catalyzed Anti-Markovnikov Selective Hydrothiolation of Unactivated Alkenes. *Org. Lett.* **2016**, *18*, 2114−2117.

(11) (a) Griesbaum, K. Problems and Possibilities of the Free-Radical Addition of Thiols to Unsaturated Compounds. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273−287. (b) Biermann, U.; Metzger, J. O. Regioselectivity of Radical Addition of Thiols to 1-Alkenes. *Eur. J. Org. Chem.* **2018**, *2018*, 730−734. (c) Sinha, A. K.; Equbal, D. Thiol−Ene Reaction: Synthetic Aspects and Mechanistic Studies of an Anti-Markovnikov-Selective Hydrothiolation of Olefins. *Asian J. Org. Chem.* **2019**, *8*, 32−47.

(12) (a) Hoyle, C. E.; Bowman, C. N. Thiol-Ene Click Chemistry. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540−1573. (b) Dondoni, A.; Marra, A. Recent applications of thiol-ene coupling as a click process for glycoconjugation. *Chem. Soc. Rev.* **2012**, *41*, 573−586. (c) Lowe, A. B. Thiol-ene "click" reactions and recent applications in polymer and materials synthesis: a first update. *Polym. Chem.* **2014**, *5*, 4820−4870.

(13) (a) Cabrero-Antonino, J. R.; Leyva-Pérez, A.; Corma, A. Iron-Catalysed Markovnikov Hydrothiolation of Styrenes. *Adv. Synth. Catal.* **2012**, *354*, 678−687. (b) Savolainen, M. A.; Wu, J. Markovnikov-Selective Hydrothiolation of Styrenes: Application to the Synthesis of Stereodefined Trisubstituted Olefins. *Org. Lett.* **2013**, *15*, 3802−3804. (c) Ma, H.; Ren, X.; Zhou, X.; Ma, C.; He, Y.; Huang, G. Palladium and copper co-catalyzed Markovnikov hydrothiolation of terminal olefins and alkynes. *Tetrahedron Lett.* **2015**, *56*, 6022−6029.

(14) Tamai, T.; Ogawa, A. Regioselective Hydrothiolation of Alkenes Bearing Heteroatoms with Thiols Catalyzed by Palladium Diacetate. *J. Org. Chem.* **2014**, *79*, 5028−5035.

(15) DuBois, M. R. Catalytic applications of transition-metal complexes with sulfide ligands. *Chem. Rev.* **1989**, *89*, 1−9.

(16) (a) Jimenez Rodriguez, C.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. Highly selective formation of linear esters from terminal and internal alkenes catalysed by palladium complexes of bis-(di-tert-butylphosphinomethyl)benzene. *Chem. Commun.* **2004**, 1720−1721. (b) Roesle, P.; Dürr, C. J.; Möller, H. M.; Cavallo, L.; Caporaso, L.; Mecking, S. Mechanistic Features of Isomerizing Alkoxycarbonylation of Methyl Oleate. *J. Am. Chem. Soc.* **2012**, *134*, 17696−17703.

(17) (a) Harrod, J. F.; Chalk, A. J. Homogeneous Catalysis. I. Double Bond Migration in n-Olefins, Catalyzed by Group VIII Metal Complexes. *J. Am. Chem. Soc.* **1964**, *86*, 1776−1779. (b) Sparke, M. B.; Turner, L.; Wenham, A. J. M. The isomerization of olefins by palladium complexes. *J. Catal.* **1965**, *4*, 332−340. (c) Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M. $[(RCN)_2PdCl_2]$-Catalyzed E/Z Isomerization of Alkenes: A Non-Hydride Binuclear Addition−Elimination Pathway. *Angew. Chem., Int. Ed.* **2011**, *50*, 9602−9606.

DOI: 10.1021/acs.orglett.9b00504
Org. Lett. 2019, 21, 2213−2217

SUPPORTING INFORMATION

Palladium-Catalyzed Tandem Isomerization/Hydrothiolation of Allylarenes

Prasad Kathe, Ivana Fleischer*

Eberhard Karls Universität Tübingen, Faculty of Science,

Institute of Organic Chemistry

* ivana.fleischer@uni-tuebingen.de

Table of Contents:

1. General Procedures/Analytical Techniques

Solvents and Reagents:

All solvents were distilled before use (or purchased from the respective supplier as dry solvents). Reactions with oxygen- or moisture-sensitive reagents were carried out under Argon using standard Schlenk techniques. Starting materials were used without further purification, except for 1-heptanethiol, which was distilled and stored under argon as well as 4-allyl-1,2-dimethoxybenzene, which was purified prior to use by Kugelrohr distillation.

The ligand dtpbx (1,2-bis[(di-tert.-butylphosphino)methyl]benzene) was obtained commercially from ABCR or Strem. Other chemicals were purchased from Acros Organics, Chem Pur, Sigma-Aldrich, ABCR, TCI Chemicals, Fluka Chemicals, Alfa Aesar and were used as such without any further purification. Some allylated substrates were synthesized by a Grignard reaction on the corresponding aryl bromides (see general procedure B).

Chromatography:

Column chromatography was carried out using silica gel (60 Å) as stationary phase, either using gravity flow conditions under isocratic elution or flash column chromatography under gradient elution: Gradients were set up depending on the solvent ratios found ideal via thin layer chromatography (TLC).

TLC was performed with aluminum plates coated with silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution

Analytical Techniques:

NMR spectra were recorded using a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz). All measurements were performed at ambient temperature. Coupling constants J are given in Hertz [Hz]. ^{1}H NMR splitting patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet.

Gas Chromatography

Gas Chromatography (GC-FID) analysis was carried out on a HP6890 GC-System with injector 7683B and Agilent 7820A system. Dry hydrogen was used as the carrier gas, for the measurements the following method was used: Heating from 50 °C to 280 °C within 15 minutes. Pentadecane was added as the internal standard. For the calibration, samples with different amounts of substrate and standard (pentadecane) were measured with GC-FID and the obtained data were used to plot A(standard)/A(substrate) against m(standard)/m(substrate). The resulting slope, after linear regression, is equivalent to the response factor R, which can be used to quantify unknown samples by using equation 1.

$$\frac{A_{PD}}{A_{reactant}} = R \cdot \frac{m_{PD}}{m_{reactant}} . \qquad (1)$$

Gas Chromatography-Mass Spectrometry was performed on an Agilent 7820A GC system in combination with an Agilent 5977 B using an EI source and a quadrupole analyzer. Samples were diluted in organic solvent and passed through aluminum oxide prior to GC-MS analysis. Crude samples were additionally stirred with QuadraSil scavengers for several minutes beforehand. For all analyses the following method was used: Heating from 50 °C to 280 °C within 15 minutes.

Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR system. Absorption bands are given in wave numbers $\tilde{\nu}$ (cm^{-1})

General Procedure for Isomerizing Hydrothiolation: (A)

A flame dried 25 mL Schlenk tube with stir bar was charged with 1,2-bis[(di-tert.-butylphosphino)methyl]benzene (3.9 mol%, 0.027 mmol, 10.9 mg) inside a glove box. The tube was taken outside the box and was charged with $Pd(OAc)_2$ (3 mol%, 3.36 mg, 0.015 mmol). After evacuating and backfilling the Schlenk tube, 1 mL DCM and the allyl-substituted arene (0.50 mmol) was added. After stirring for a couple of minutes, CF_3SO_3H (12 mol%, 0.06 mmol 5.3 µL) or CH_3SO_3H (16 mol%, 0.08 mmol, 5.5 µL) was added, which was immediately followed by addition of the thiol (0.55 mmol). The Schlenk tube was transferred to a preheated oil bath at 38 °C and the contents were stirred at 500 r.p.m for 15 h. After completion of the reaction, the reaction mixture was diluted with 5 mL DCM. The organic phase was washed with water. The combined aqueous phases were back extracted with DCM three times. The combined organic phases were dried over anhydrous $MgSO_4$. Rotary evaporation was employed to remove DCM. The crude reaction mixture was adsorbed to silica gel and subjected to column chromatography with mixtures of hexane and diethylether.

General Procedure for Allylation: (B)

A flame-dried 50 mL round-bottom flask was charged with Mg turnings (272 mg, 11.2 mmol) and LiCl (509 mg, 12.0 mmol) under argon. The round bottom flask was heated under reduced pressure to take off residual moisture from LiCl. The flask was allowed to cool to RT and this was followed by addition of 16 mL THF. Then, the substituted bromobenzene (9.6 mmol, 1.2 equiv.) was added. The contents of the reaction vessel were stirred vigorously at room temperature under argon for 2 hours and cooled down to 0 °C using an ice bath. In a separate pre-heated round bottom flask, a solution of $Fe(acac)_3$ (169 mg, 5 mol%) in dry THF (8 mL) was prepared. This solution was transferred to the main reaction vessel under Ar atmosphere. The solution was stirred for 5 minutes. After that, allyl acetate (863 µL, 8.0 mmol, 1 equiv.) was added and the solution was stirred for 45 min at 0°C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) at 0 °C under Ar atmosphere. Following that, the reaction mixture was diluted with 10 mL EtOAc. The inorganic solids were filtered off. The liquid contents were then transferred to a separating funnel for phase separation. The aqueous phase was extracted with EtOAc (3 ×7-8 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was adsorbed to silica and subjected to column chromatography.

General Procedure for Isomerizing Hydrothiolation (for long chains): (C)

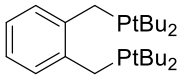
A flame dried 25 mL Schlenk tube with stir bar was charged with $PdCl_2(PhCN)_2$ (5 mol%, 0.025 mmol, inside a glove box. 1,2-bis[(di-tert.-butylphosphino)methyl]benzene (dtbpx) (10 mol%, 0.05 mmol, 10.9 mg) was weighed separately in a scintillation vial. The tube was taken outside the box followed by evacuation and backfilling with Argon, 0.3 mL dry Toluene was added to the tube along with 0.5 mmol of the long chain terminal olefin. The tube was then transferred to a pre-heated oil bath at 60 °C. The contents of the reaction vessel were stirred for 2 hours. The schlenk tube was then taken out of the oil bath. The contents were allowed to cool to ambient temperature. This was followed by addition of 0.7 mL DCM and the 1,2-bis[(di-tert.-butylphosphino)methyl]benzene from the scintillation vial. The reaction mixture was stirred. Later, CF_3SO_3H and 0.55 mmol Heptane thiol were added under Argon and the reaction mixture was heated to 50 °C. After completion of the reaction, the reaction mixture was allowed to attain ambient temperature, then diluted with 5 mL DCM. The organic phase was washed with water. The combined aqueous phases were back extracted with DCM (3x). The combined organic phases were dried over anhydrous $MgSO_4$. Rotary evaporation was employed to remove DCM. The crude reaction mixture was subjected to preparative TLC using varying amounts of hexane and Diethylether as the mobile phase.

2. ^{31}P NMR analysis of phosphine ligand L1

The ligand batches purchased from the supplier were found to be partially oxidized. Hence, the actual content of non-oxidized ligand introduced in the reaction was calculated based on the molar ratio obtained from integrals of ^{31}P NMR spectra.

One of the batches (**spectrum A**) showed presence of oxide in 75:25 molar ratio. Another batch (**spectrum B**) showed presence of oxide in 70:30 molar ratio. Based on this, the amount of oxide introduced under standard reaction conditions was calculated (1.3 mol%) for 3.9 mol% of ligand used. Finally, one of the batches was found to be completely clean without any trace of oxide.

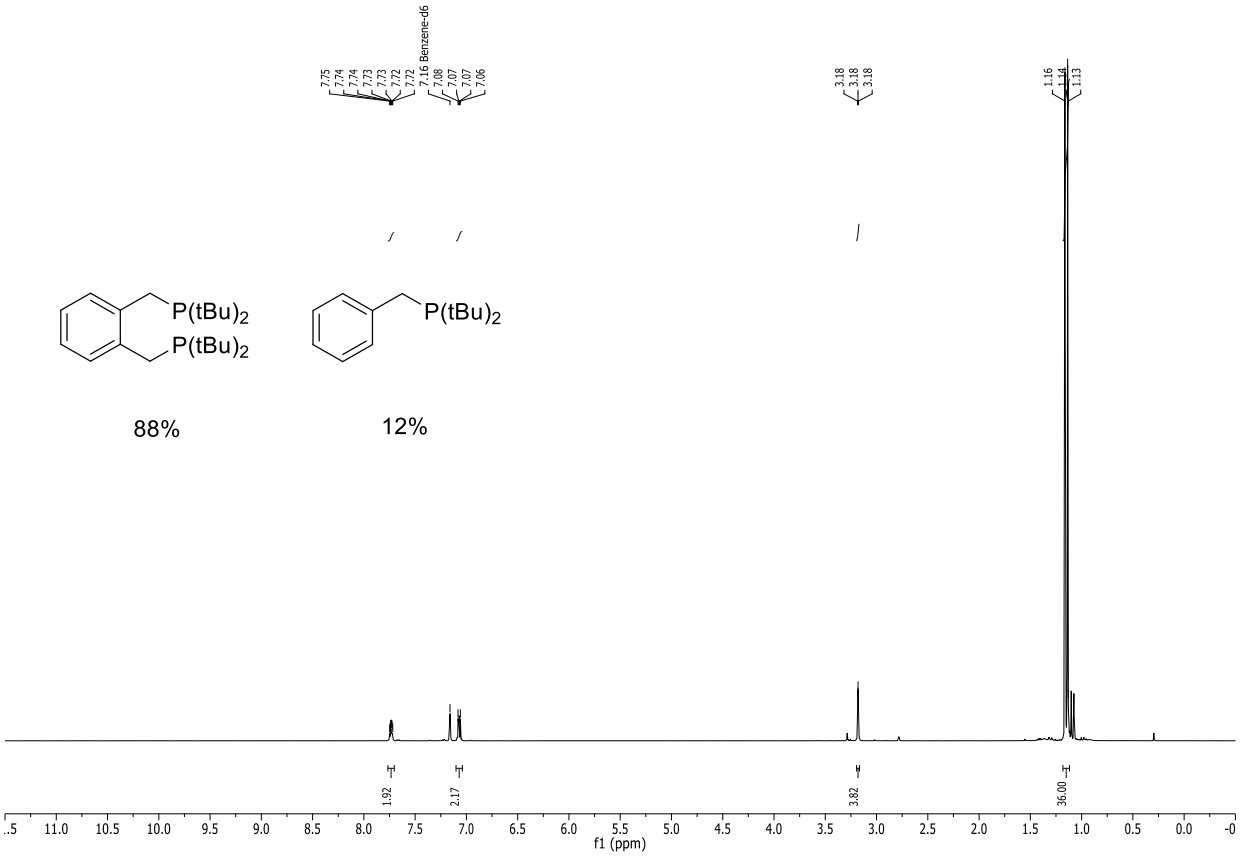
The ligand was also synthesized independently (following procedure reported in literature).[1] We observed no phosphine oxide however an unreacted mono-substituted phosphine impurity was observed in 88:12 molar ratio. For the hydrothiolation on 5 mmol scale, this ligand mixture was employed. (**L1.1**). The analytical data conforms to the literature report.[2]

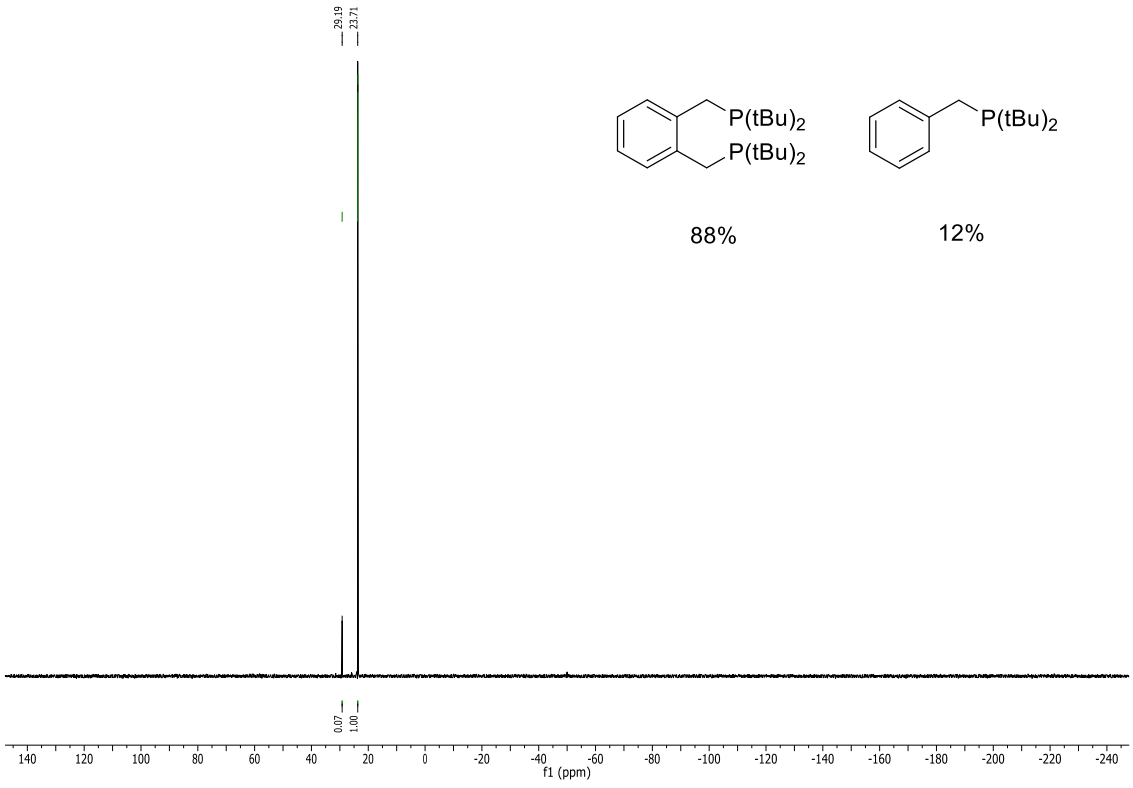


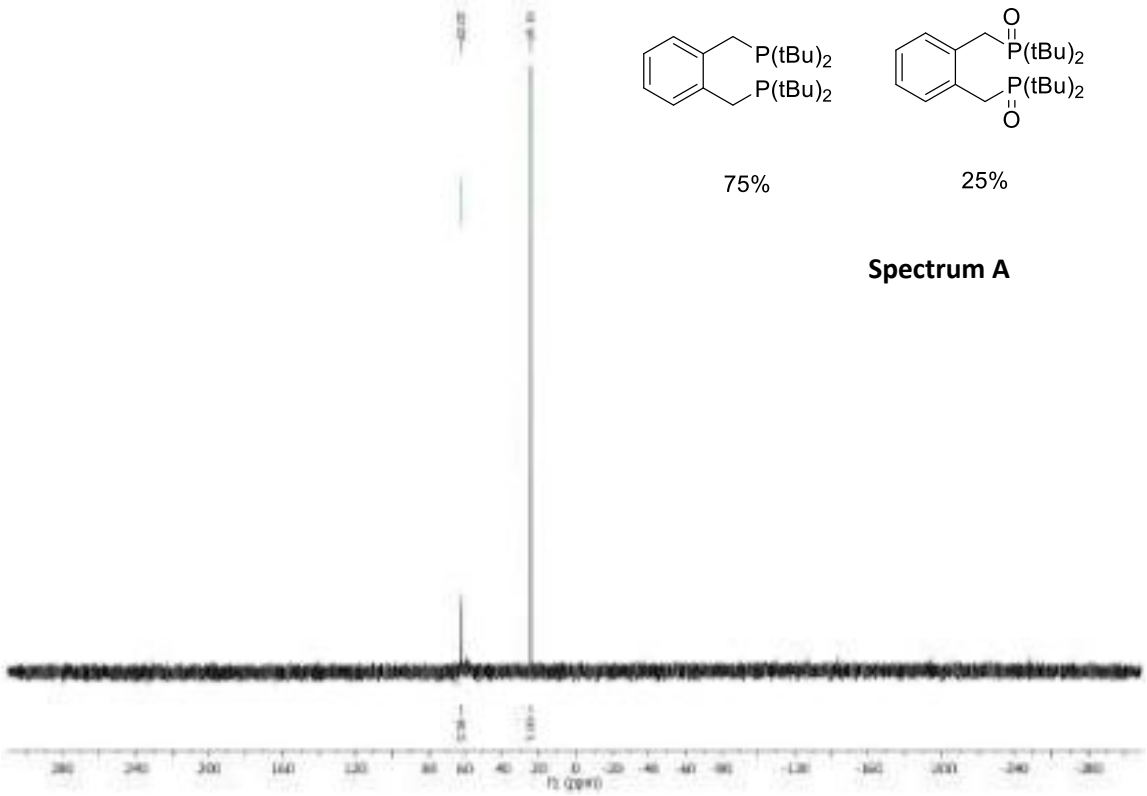
L1.1

^{1}H NMR (400 MHz, Benzene-d6) δ 7.75-7.71 (m, 2H), 7.10 – 7.02 (m, 2H), 3.20 – 3.16 (m, 4H), 1.15 (d, *J* = 10.6 Hz, 36H).

^{31}P NMR (162 MHz, C_6D_6) δ 23.71.


7.75
7.74
7.74
7.73
7.73
7.72
7.72
7.72
7.16 Benzene-d6
7.08
7.07
7.07
7.06
3.18
3.18
3.18
1.16
1.14
1.13
P(tBu)2
P(tBu)2
P(tBu)2
88%
12%
1.92
2.17
3.82
36.00
f1 (ppm)

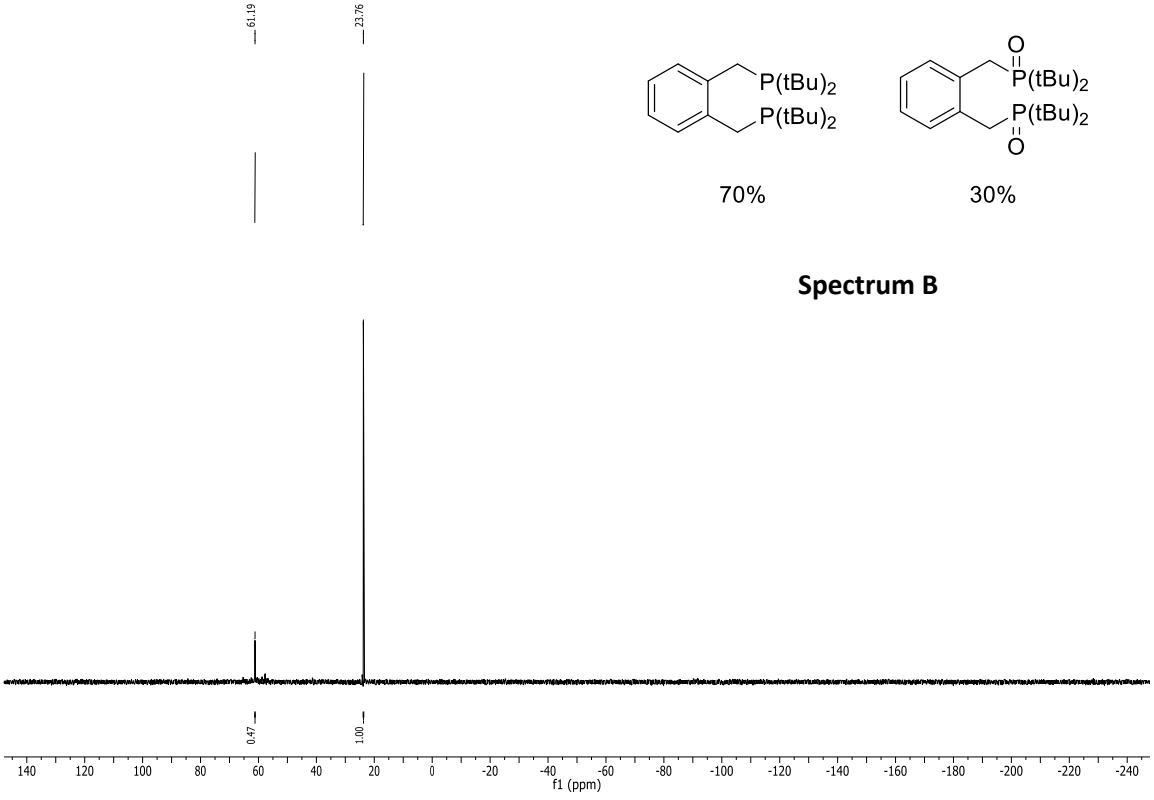

29.19
23.71
P(tBu)2
P(tBu)2
P(tBu)2
88%
12%
0.07
1.00
f1 (ppm)



75%

25%

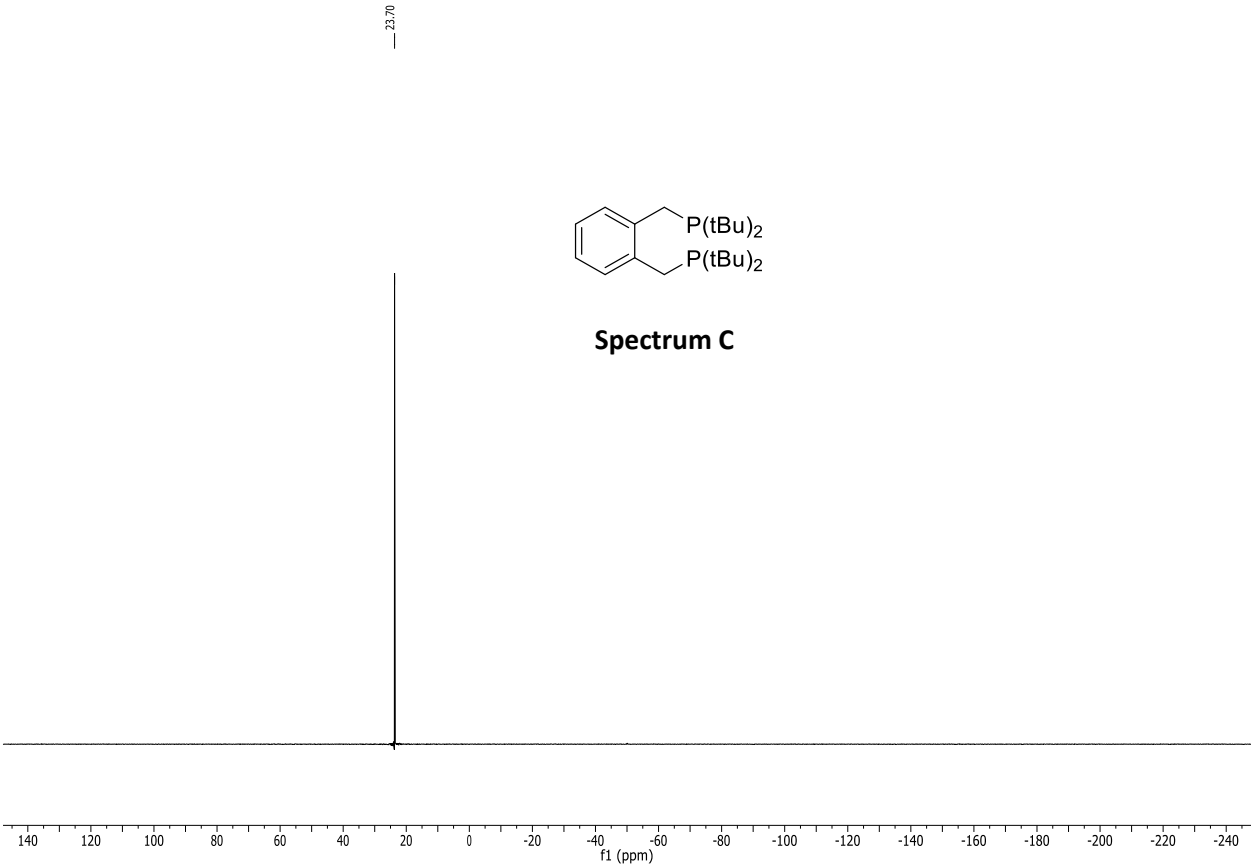
Spectrum A



70%

30%

Spectrum B



Spectrum C

3. Optimization of reaction conditions

Screening of catalyst precursors and ligands

The optimization of reaction conditions was carried out using the General Procedure **(A)**. The catalyst precursors, ligands and their amounts were varied to obtain the optimal conditions for the reaction. The use of $Pd(OAc)_2$ was found to give optimal yield. **L5** furnished 61% yield (Entry 10) whereas the other derivatives of BINAP **L6** and **L7** surprisingly resulted in no yield (Entries 12 and 13). Small bite angle **L2** resulted in good yield (Entry 7). Hydride sources other than triflic acid led to conversion to the internal isomer of 4-allyl 1,2-dimethoxy benzene and not the follow-up hydrothiolation.

Scheme S1. Tandem Isomerization/Hydrothiolation

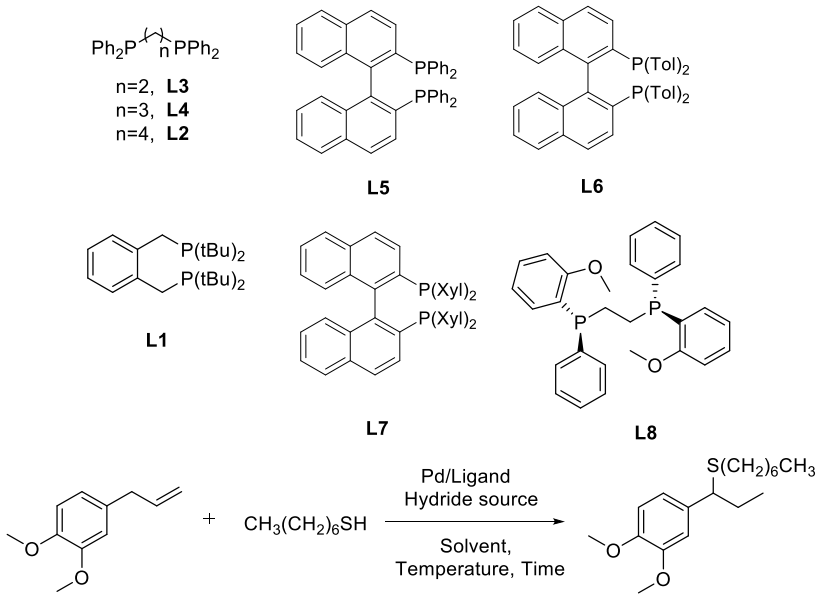


Table S1. Optimization of pre-catalyst and ligands.

Entry[a]	[Pd] source	Acid	Ligand	% Conversion[b]	% Yield[b]
1	$Pd(dppp)(OTf)_2$	-	-	0	0
2	$Pd(CH_3CN)_2Cl_2$	CF_3SO_3H	**L2**	0	0
4	$Pd(acac)_2$	CF_3SO_3H	**L2**	0	0
5	$Pd(OAc)_2$	HCOOH	**L2**	72	0
6	$Pd(OAc)_2$	CF_3SO_3H	**L1**	100	94
7	$Pd(OAc)_2$	CF_3SO_3H	**L2**	85	74
8	$Pd(OAc)_2$	CF_3SO_3H	**L3**	63	61
9	$Pd(OAc)_2$	CF_3SO_3H	**L4**	65	10
10	$Pd(OAc)_2$	CF_3SO_3H	**L5**	61	57
11	$Pd(OAc)_2$	CF_3SO_3H	**L6**	0	0
12	$Pd(OAc)_2$	CF_3SO_3H	**L7**	0	0
13	$Pd(OAc)_2$	CF_3SO_3H	**L8**	0	0

[a]General Reaction Conditions: 4-allyl-1,2-dimethoxy benzene (0.50 mmol), heptane-1-thiol (0.55 mmol), Pd source (3 mol%), Ligand (6 mol%), acid (14 mol%), toluene (1 mL), 24 h, 50 °C, [b]determined by quantitative GC-FID using pentadecane as an internal standard.

After screening for the optimal catalyst system, the catalyst loading, time and temperature were optimized before proceeding to substrate screening. It was found out that Pd/Phosphine ligand ratio could be decreased to as low as 3 : 3.9 instead of the standard 1 : 2. There wasn't any significant decrease in the conversion and yield even after the temperature was lowered to 40 °C.

Table S2. Optimization of catalyst loading, time and temperature

[a]Entry	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Time (h)	Temperature (°C)	[b]%Conversion	[b]% Yield
1	5	9.4	24	50	100	94
2	3	5.4	24	50	100	94
3	2	3.4	24	50	100	51
4	3	3.9	24	50	100	92
5[c]	3	3.9	18	40	100	99
6[c]	3	3.9	15	40	100	97

[a]General Reaction Conditions: 4-allyl 1,2-dimethoxy benzene (0.50 mmol), heptane-1-thiol (0.55 mmol), $Pd(OAc)_2$, **L1** (30% oxidized), CF_3SO_3H (12 mol%), Toluene (1 mL), [b]calculated by quantitative GC-FID using pentadecane as an internal standard.

4. Deuteration Experiments

Synthesis of deuterated heptane-1-thiol

A frame dried 25 mL Schlenk tube with stirring bar was charged with heptanethiol (0.75 mL, 4.8 mmol, 1.0 equiv), which was dissolved in deuterated methanol (d4) (0.8 mL, 19.2 mmol, 4.0 equiv) and stirred for 48 hours at room temperature. The solvent was removed under reduced pressure and the product was used without further purification. The product was obtained as a colorless liquid (0.586 g, 4.4 mmol, 92% yield, 52.5 % deuterated). The extent of deuteration was determined through GC-MS by a method described below.

Determination of extent of deuteration:

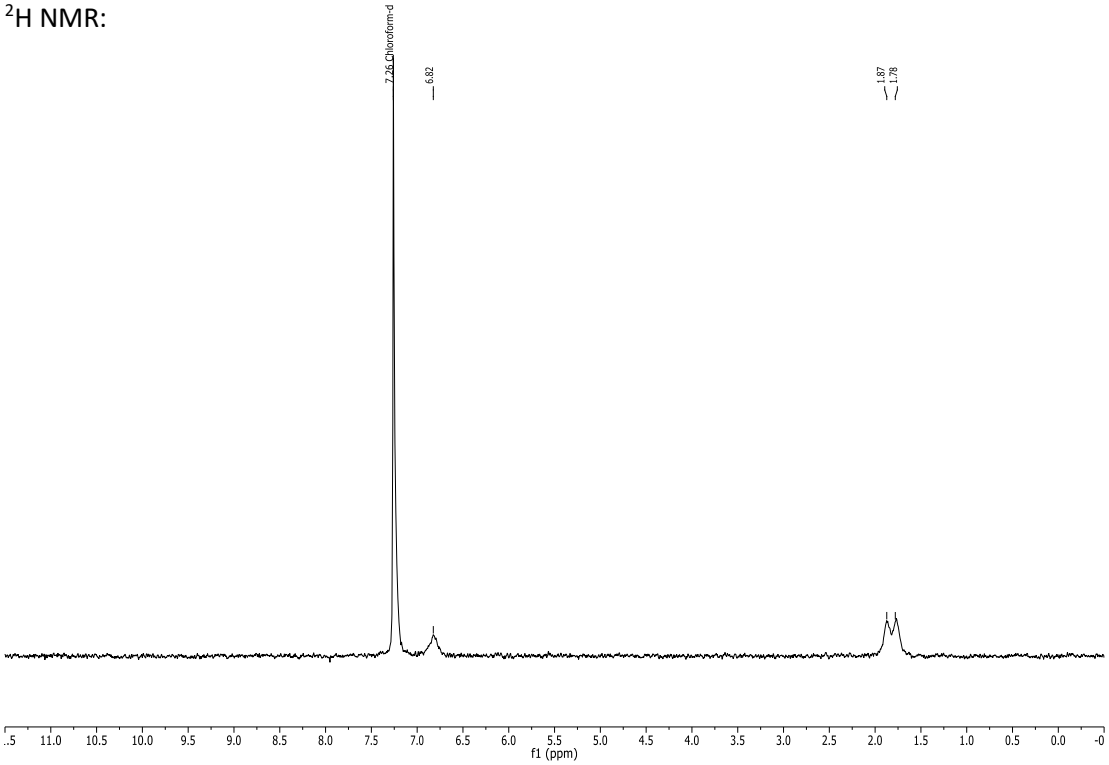
The intensities of peaks corresponding to deuterated and non-deuterated heptane-1-thiol were obtained by GC-MS. The deuterium incorporation was found to be 52.5%. [3a]

Deuteration Experiment:

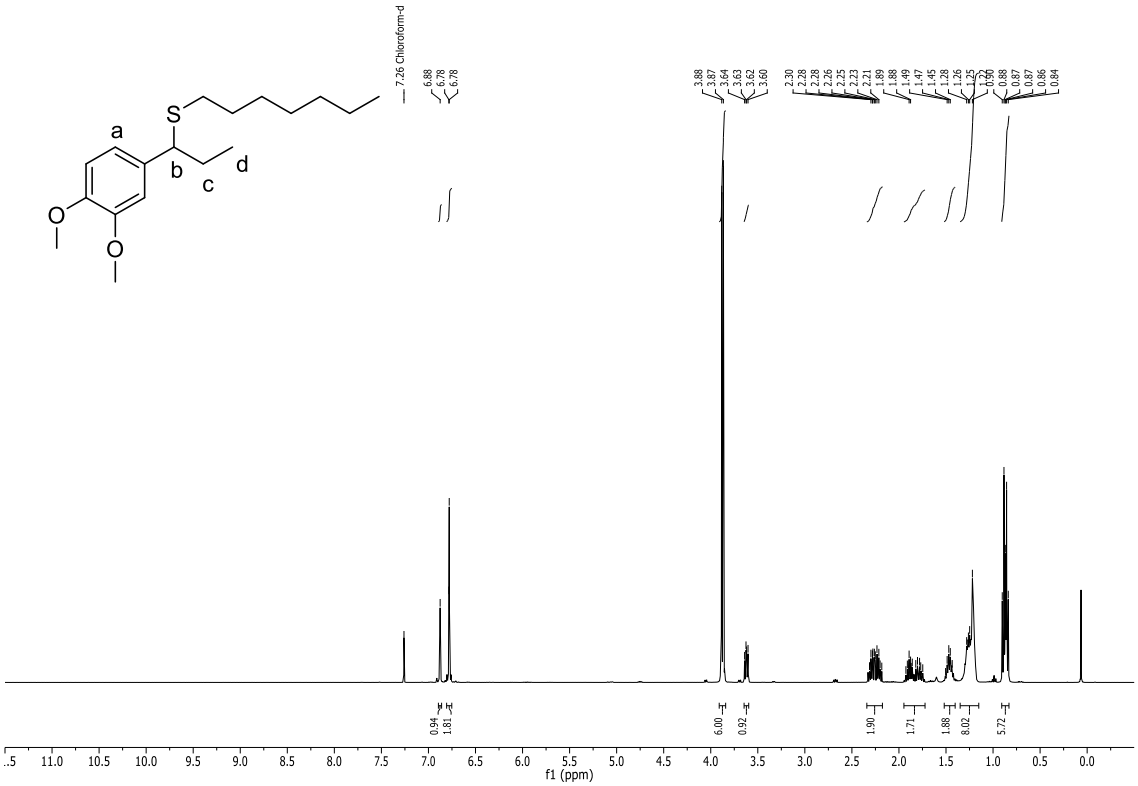
A flame dried 25 mL Schlenk tube with stirring bar was charged with ligand **L1** (3.9 mol%, 0.027 mmol, 10.9 mg) inside the glove box. Outside the box, the tube was evacuated and backfilled three times with Argon and $Pd(OAc)_2$ (3 mol%, 0.015 mmol, 3.36 mg) was charged under Argon counterflow, followed by 1 ml dry DCM, 4-allyl-1,2-dimethoxy benzene (89 mg, 0.50 mmol,1 equiv), CF_3SO_3D (12 mol%, 0.06 mmol, 5.3 µL) and finally deuterated heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv). The reaction was stirred for 48 h at 40 °C. The product was isolated in 49 % yield (75.9 mg, 0.24 mmol) following the standard workup procedure elucidated in General Procedure **A**.

The integrals obtained from ^1H NMR from the deuterated and non-deuterated product were compared and accordingly the extent of deuteration was determined. ^2H NMR was also recorded and the spectrum is given below.

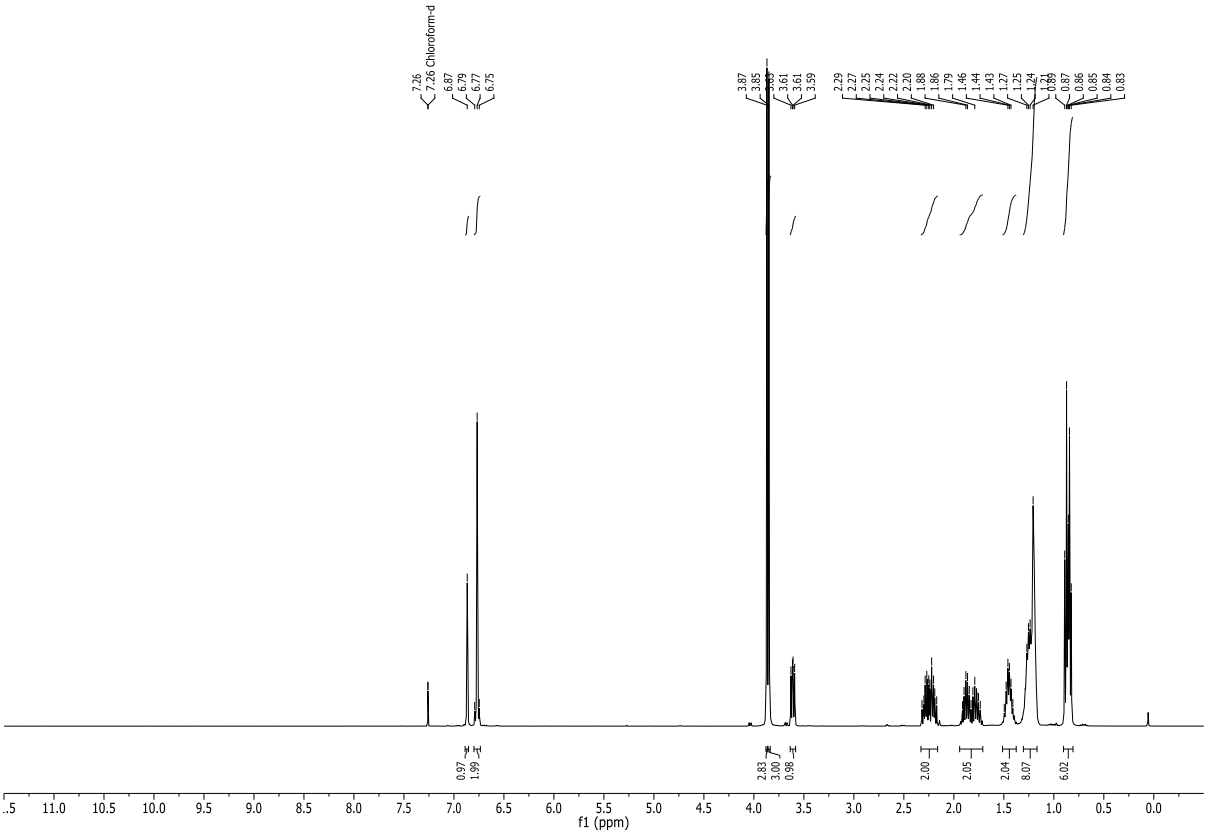
^{2}H NMR:



^{1}H NMR with deuterated heptane-1-thiol:



Extent of deuteration obtained through the above spectrum a: 8 %, b: 6 %, c: 14 %



Comparison of integrals of deuterated and non-deuterated products:

1H-NMR (Non-deuterated): Integral 6.78 ppm: 1.96

1H-NMR (deuterated): Integral 6.78 ppm: 1.81 (Percentage incorporation = 8%)

1H-NMR (Non-deuterated): Integral 3.62 ppm: 0.98

1H-NMR (deuterated): Integral 3.62 ppm: 0.92 (Percentage incorporation = 6%)

1H-NMR (Non-deuterated): Integral 1.72-1.95 ppm: 1.99

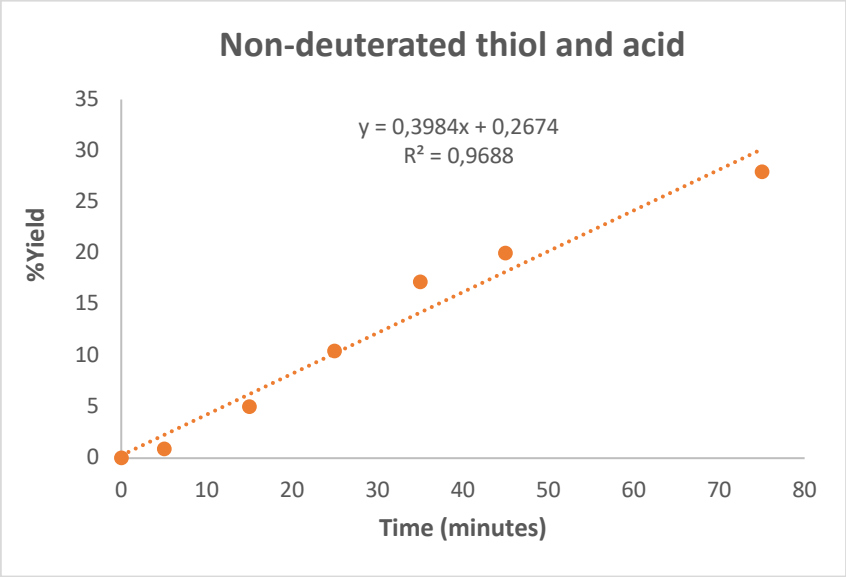
1H-NMR (deuterated): Integral 1.72-1.95 ppm: 1.71 (Percentage incorporation = 14%)

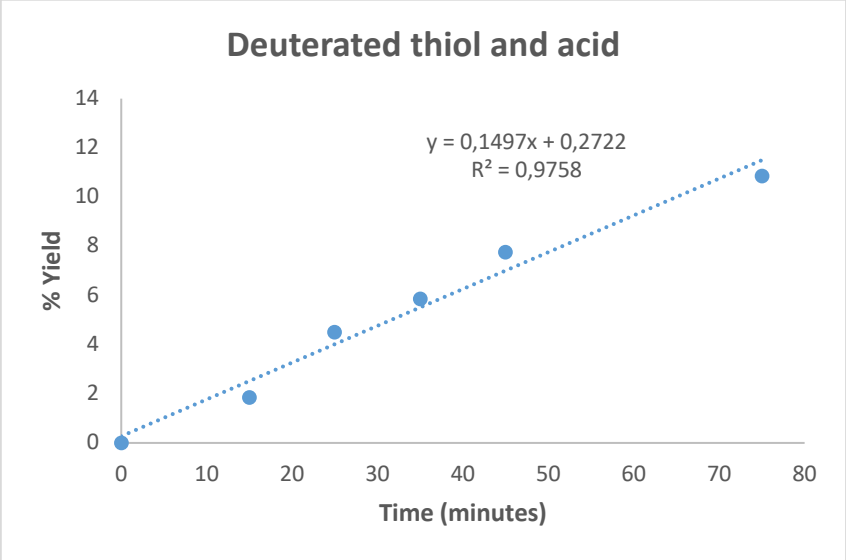
Initial Rate Analysis for comparison of rate constants of deuterated and non-deuterated reactions:

Procedure for monitoring reaction kinetics: (Determination of Kinetic Isotope Effect)

The reaction was set-up according to General Procedure (A). The only difference was the use of a lower concentration (0.14 M) instead of 0.5 M. 3.5 mL dry DCM was used as the solvent for both the reactions involving deuterated and non-deuterated substrates instead of the standard volume of 1 mL. The samples (100 µL each) were drawn at set time intervals. Quadrasil was added to these samples, followed by filtration through glass pipettes filled with aluminiumoxide. The samples were analyzed using quantitative GC-FID with pentadecane as an internal standard.

The yield obtained through GC analysis was plotted against time to obtain the initial kinetic profile of the reaction.





The yields were recorded at the initial stages assuming that first order reaction kinetics was followed. The rate equation for such a kinetic profile can be represented as follows:

$$Rate = -\frac{dx}{dt}.k[A]^1$$

Owing to the fact that the kinetic analysis was done in the very initial stages of the reaction,[3b] the concentration of limiting reactant [A] was assumed to be constant and equal to the initial concentration $[A]_0$. The rate equation thus changes to the following

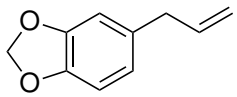
$$Rate = -\frac{dx}{dt}.k[A]_0{}^1$$

The slope from both the plots represents the value of k_H[A] and k_D[A] respectively.

The ratio of the slopes is $k_H[A]_o / k_D[A]_o = 2.66$ and hence indicates a primary kinetic isotope effect.

5. Spectra and Analytical Data

5-allylbenzo[d][1,3]dioxole (**1b**)



1b

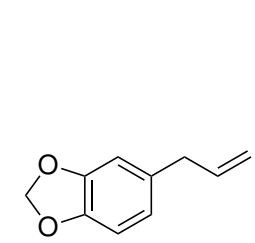
The compound **1b** was synthesized from 5-bromobenzo[d][1,3]dioxole (1.92 g, 9.6 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using *n*-hexane as the mobile phase isolated as a colorless oil (310 mg, 1.91 mmol, 14%). Conforms to reported analytical data.[7]

$C_{10}H_{12}O$ (162.18 g/mol)

R_f : 0.6 (hexane : Et_2O 99:1)

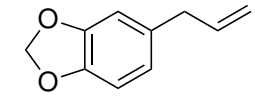
^{1}H NMR (400 MHz, Chloroform-d): δ 6.75 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.64 (dd *J* = 7.9, 1.6, 0.7 Hz, 1H), 6.00 – 5.88 (m, 3H), 5.11 – 5.03 (m, 2H), 3.31 (dt, *J* = 6.8, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 145.8, 137.6, 133.8, 121.3, 115.6, 109.1, 108.1, 100.8, 39.9.



1b

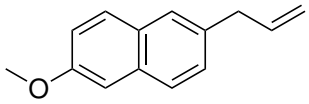
147.63
145.82
137.60
133.87
121.30
115.68
109.10
108.17
100.80
39.92
f1 (ppm)



1b

7.26 Chloroform-d
6.76
6.74
6.69
6.65
6.63
5.97
5.95
5.94
5.93
5.90
5.88
5.10
5.09
5.09
5.07
5.07
5.05
5.05
5.05
3.32
3.30
0.98
0.93
0.98
3.20
1.99
2.00
f1 (ppm)

2-allyl-6-methoxynaphthalene (**1c**)



1c

The compound **1c** was synthesized from 6-methoxy-2-bromonapthalene (2.27 g, 9.6 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using *n*-hexane as the mobile phase and isolated as a white crystalline solid (647.1 mg, 3.26 mmol, 34%). Conforms to reported analytical data.[6]

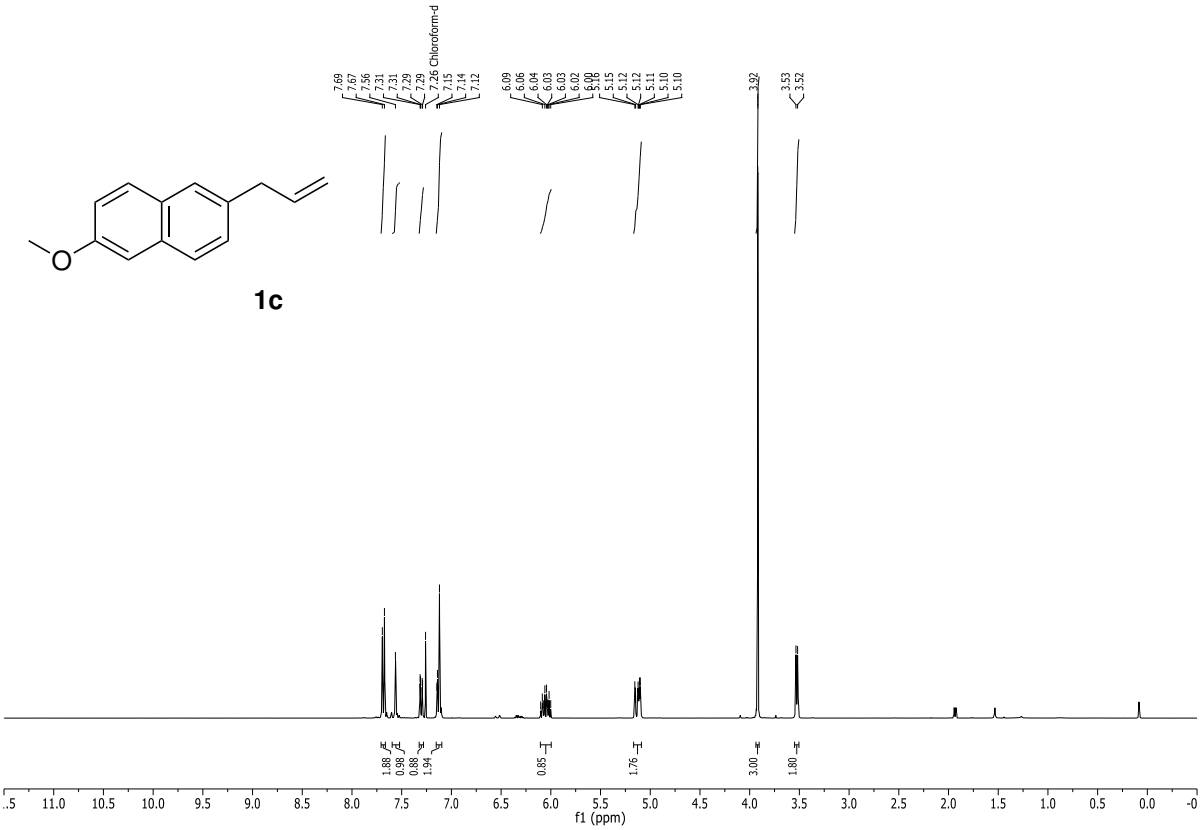
$C_{14}H_{14}O$ (198.26 g/mol)

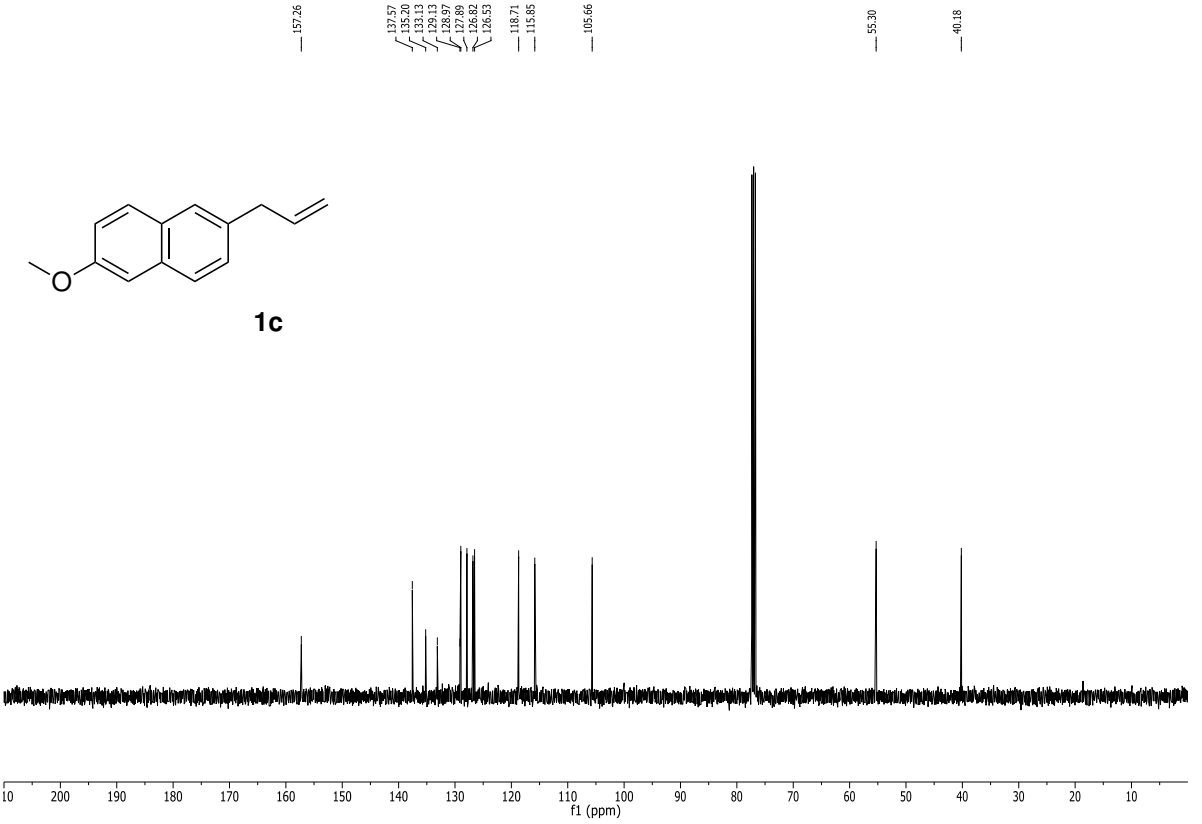
R_f : 0.37 (hexane: Et_2O 99:1)

m.p: 53-55 °C

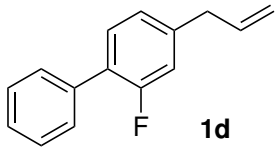
^{1}H NMR (400 MHz, Chloroform-d) δ 7.72 – 7.66 (m, 2H), 7.56 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.05 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.17 – 5.09 (m, 2H), 3.92 (s, 3H), 3.55 – 3.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 137.5, 135.2, 133.1, 129.1, 128.9, 127.8, 126.8, 126.5, 118.7, 115.8, 105.6, 55.3, 40.2.


7.69
7.67
7.56
7.31
7.31
7.29
7.26 Chloroform-d
7.15
7.14
7.12
6.09
6.06
6.04
6.03
6.03
6.02
5.15
5.12
5.12
5.11
5.10
5.10
3.52
3.53
3.52
O
1c
1.88
0.98
0.88
1.94
0.85
1.76
3.00
1.80
f1 (ppm)


157.26
137.57
135.20
133.13
129.13
128.97
127.89
126.82
126.53
118.71
115.85
105.66
55.30
40.18
O
1c
f1 (ppm)

4-allyl-2-fluoro-1,1'-biphenyl (**1d**)



1d

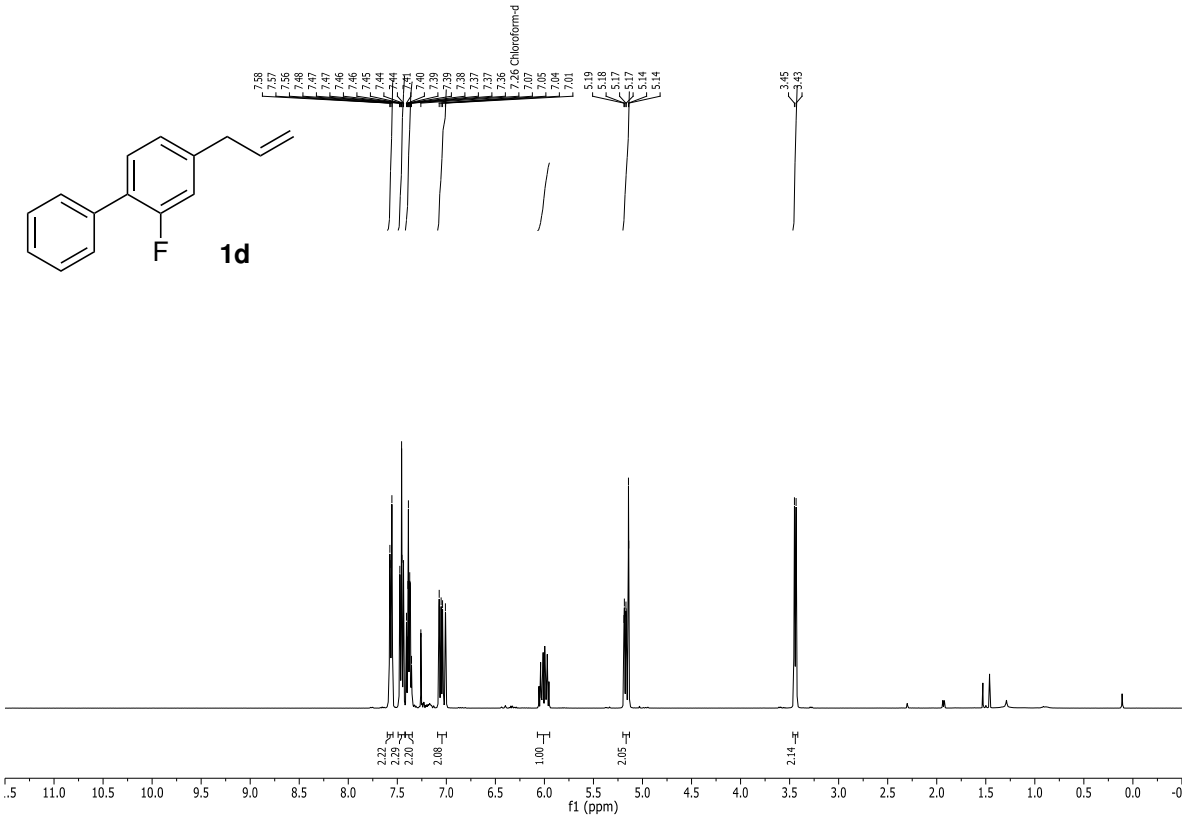
The compound **1d** was synthesized from 4-bromo-2-fluoro-1,1'-biphenyl (2.41 g, 9.60 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using n-hexane as the mobile phase and isolated as a colorless oil (520 mg, 2.44 mmol, 26%). Conforms to reported analytical data.[5]

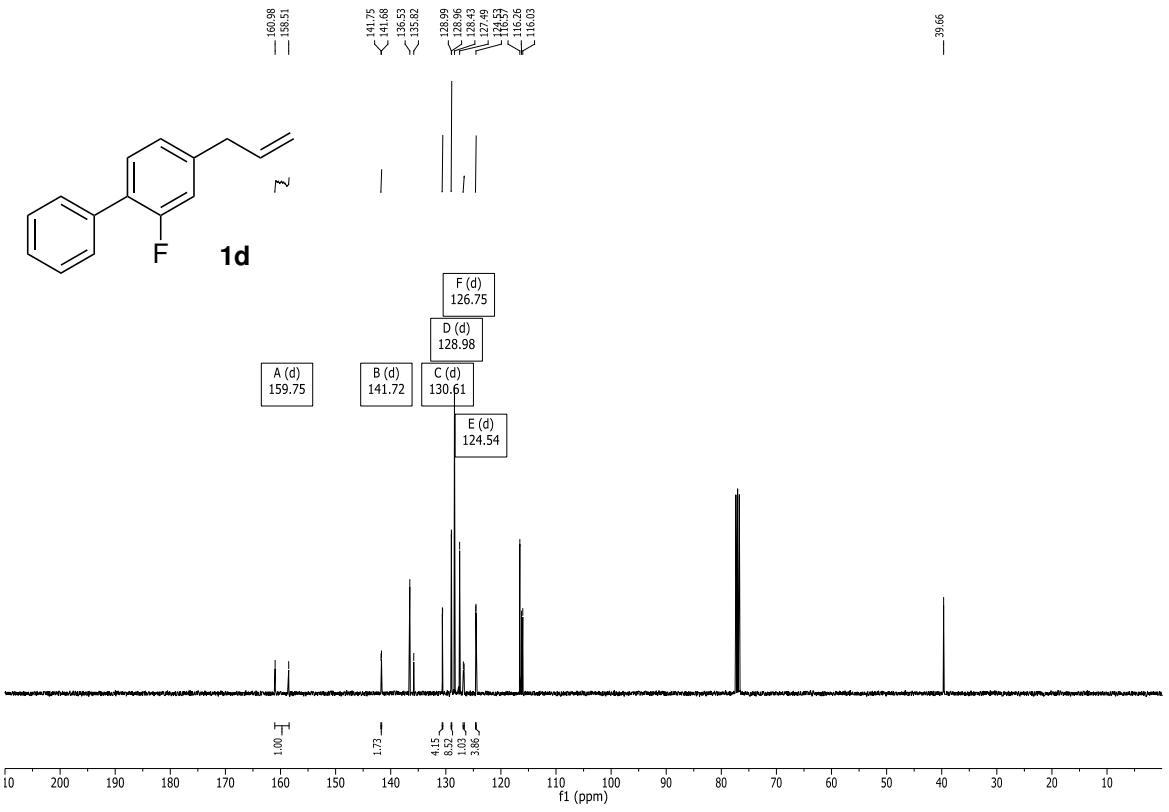
$C_{15}H_{13}F$ (212.26 g/mol)

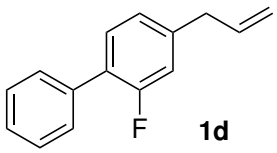
R_f: 0.57 (hexane 100)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 – 7.53 (m, 2H), δ 7.49 – 7.42 (m, 1H), 7.43 – 7.34 (m, 1H)7.10 – 6.99 (m, 2H), 6.00 (ddt, *J* = 16.9, 10.2, 6.8 Hz, 1H), 5.21 – 5.11 (m, 2H), 3.48 – 3.41 (m, 2H).
^{13}C NMR (101 MHz, Chloroform-d) δ 159.75 (d, *J* = 247.9 Hz), 141.72 (d, *J* = 7.6 Hz), 136, 135, 130.61 (d, *J* = 4.0 Hz), 128.98 (d, *J* = 2.9 Hz), 128.43, 127.49, 126.75 (d, *J* = 13.6 Hz), 124.54 (d, *J* = 3.2 Hz), 116.57, 116.26, 116.03, 39.66.

^{19}F NMR (376 MHz, Chloroform-d) δ -118.44


1d
F
Chloroform-d
f1 (ppm)

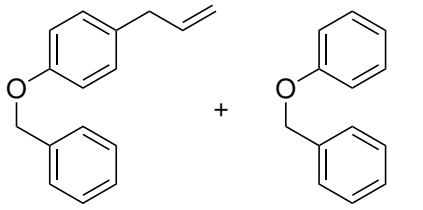

1d
F
A (d) 159.75
B (d) 141.72
C (d) 130.61
D (d) 128.98
E (d) 124.54
F (d) 126.75
f1 (ppm)


F

1d

-118.44
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

1-allyl-4-(benzyloxy)benzene (**1g**)



1g **1g'**

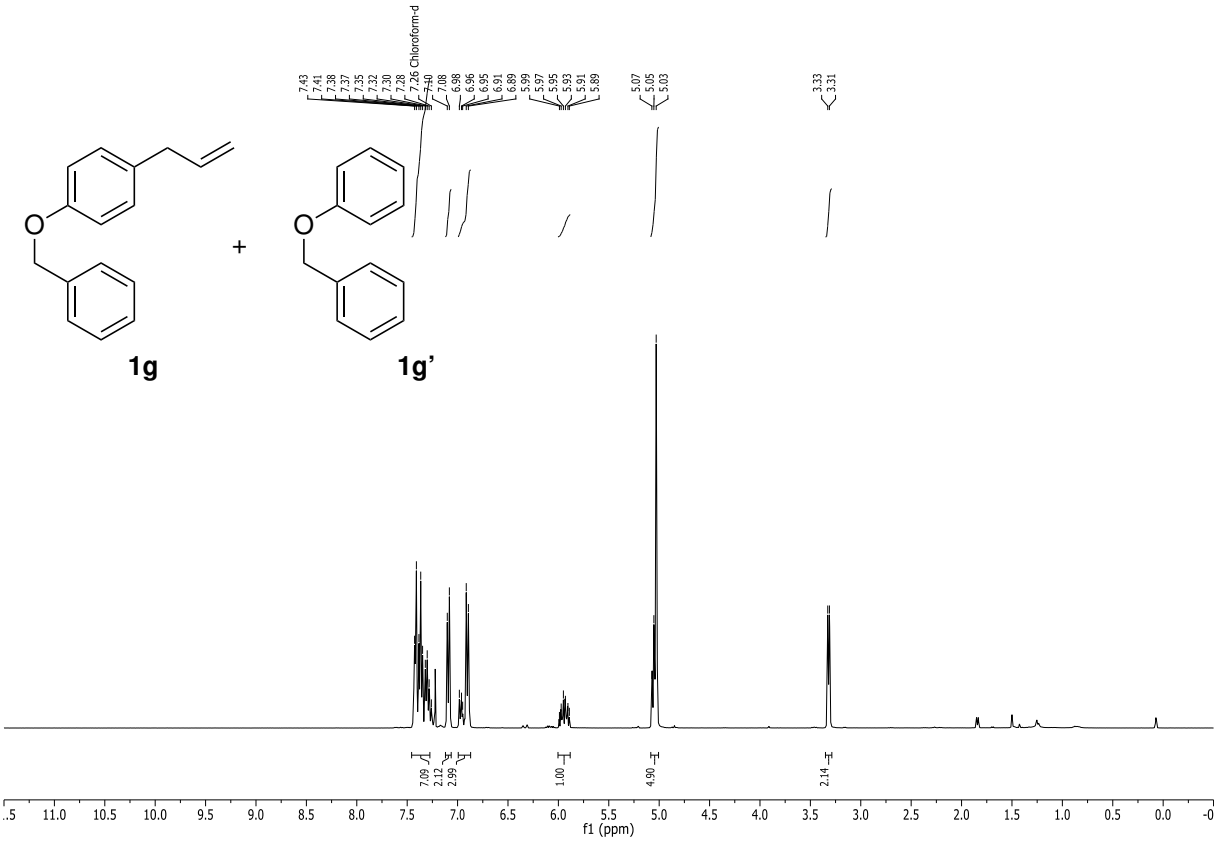
The compound **1e** was synthesized according to general procedure (B) from 1-(benzyloxy)-4-bromobenzene (2.52 g, 9.6 mmol, 1 equiv) and allyl acetate (1.241 mL, 12 mmol, 1.25). It was purified by column chromatography using n-hexane as the mobile phase isolated as a colorless oil as mixture of **1g** and **1g'** in ratio of 75:25 determined by GC-FID analysis. (278 mg, 1.23 mmol).

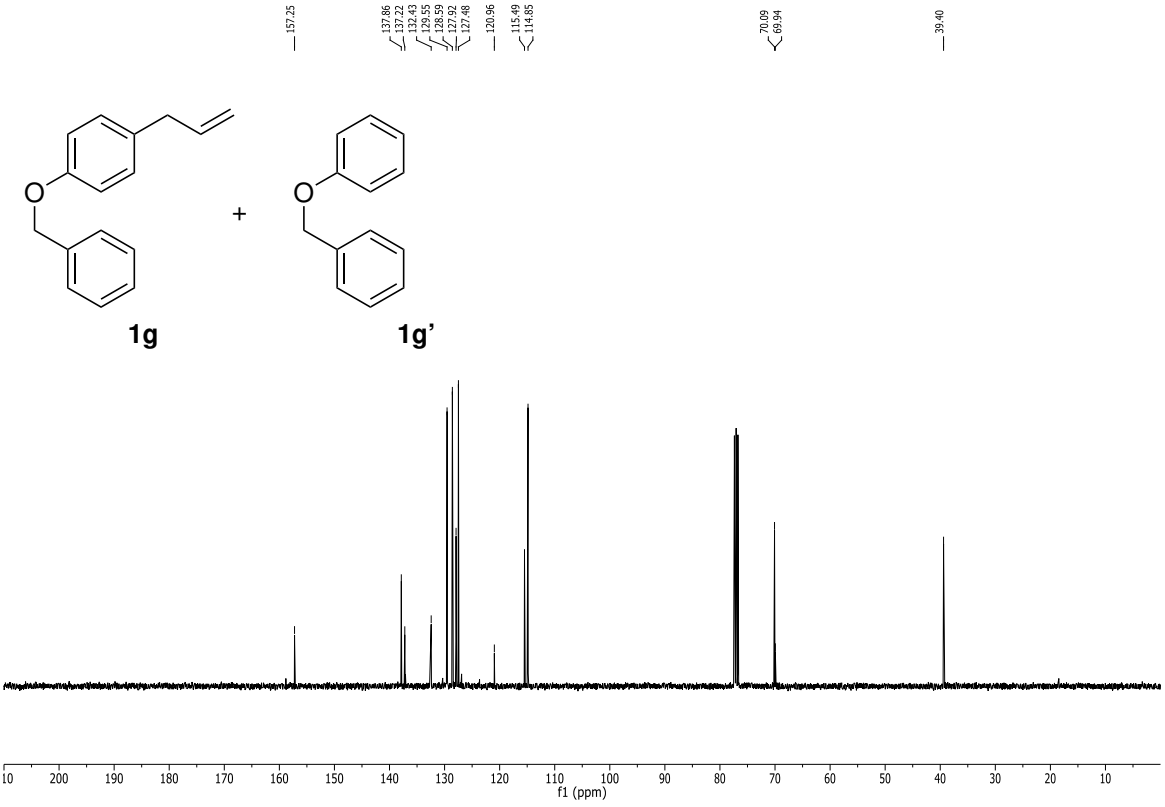
$C_{10}H_{12}O$ (224.30 g/mol)

R_f : 0.4 (hexane : Et_2O 97.5: 2.5)

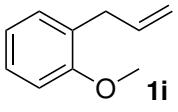
^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 (m, 7H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.01 – 6.86 (m, 3H), δ 6.00 – 5.88 (m, 1H), 5.09 – 5.01 (m, 5H), 3.36 – 3.29 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 137.8, 137.2, 132.4, 129.5, 128.5, 127.9, 127.4, 120.9, 115.4, 114.8, 70.0, 69.9, 39.4.


7.43
7.41
7.38
7.37
7.35
7.32
7.30
7.28
7.26 Chloroform-d
7.10
7.08
6.98
6.96
6.95
6.91
6.89
5.99
5.97
5.95
5.93
5.91
5.89
5.07
5.05
5.03
3.33
3.31
O
+
O
1g
1g'
7.09
2.12
2.99
1.00
4.90
2.14
f1 (ppm)


157.25
137.86
137.22
132.43
129.55
128.59
127.92
127.48
120.96
115.49
114.85
70.09
69.94
39.40
O
+
O
1g
1g'
f1 (ppm)

1-allyl-2-methoxybenzene (**1i**)



1i

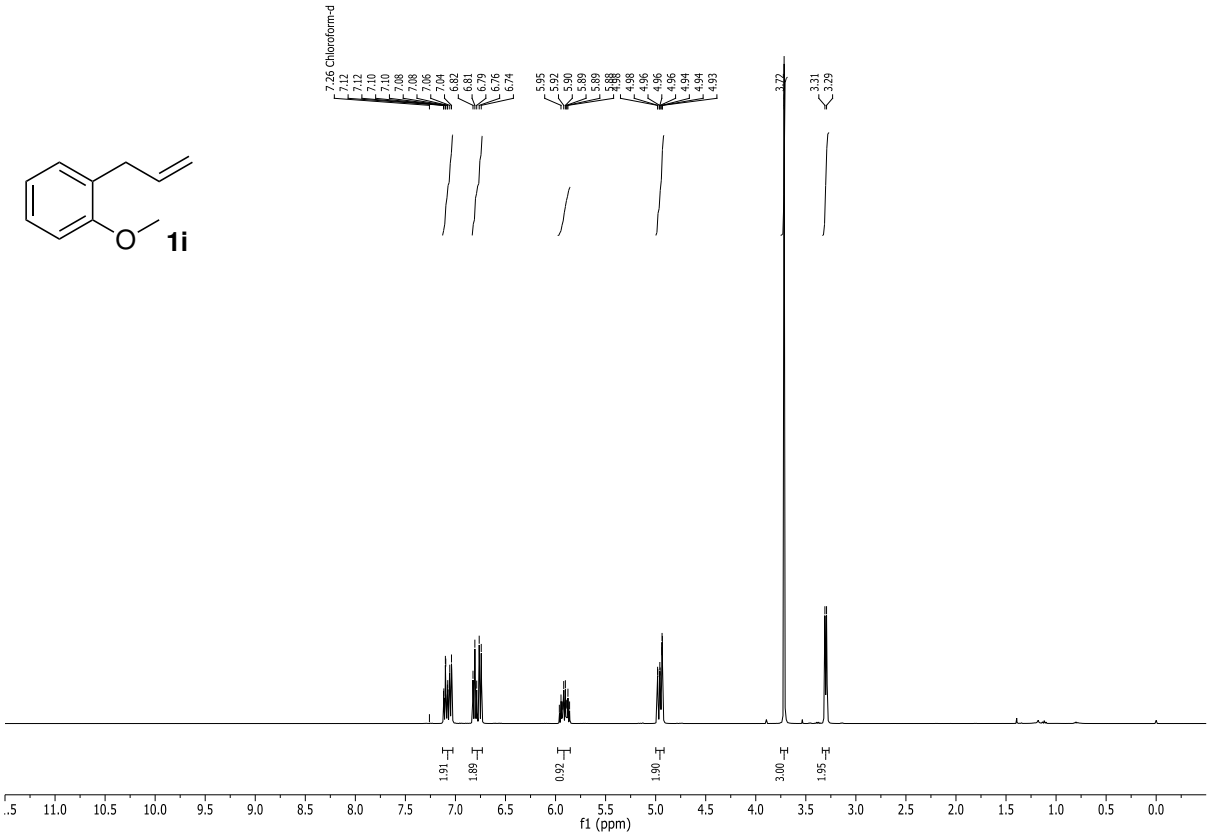
The compound **1i** was synthesized from 2-bromoanisole (1.795 g, 9.60 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using n-hexane as the mobile phase isolated as a colorless oil (545 mg, 3.68 mmol, 38%). Conforms to reported analytical data.[6]

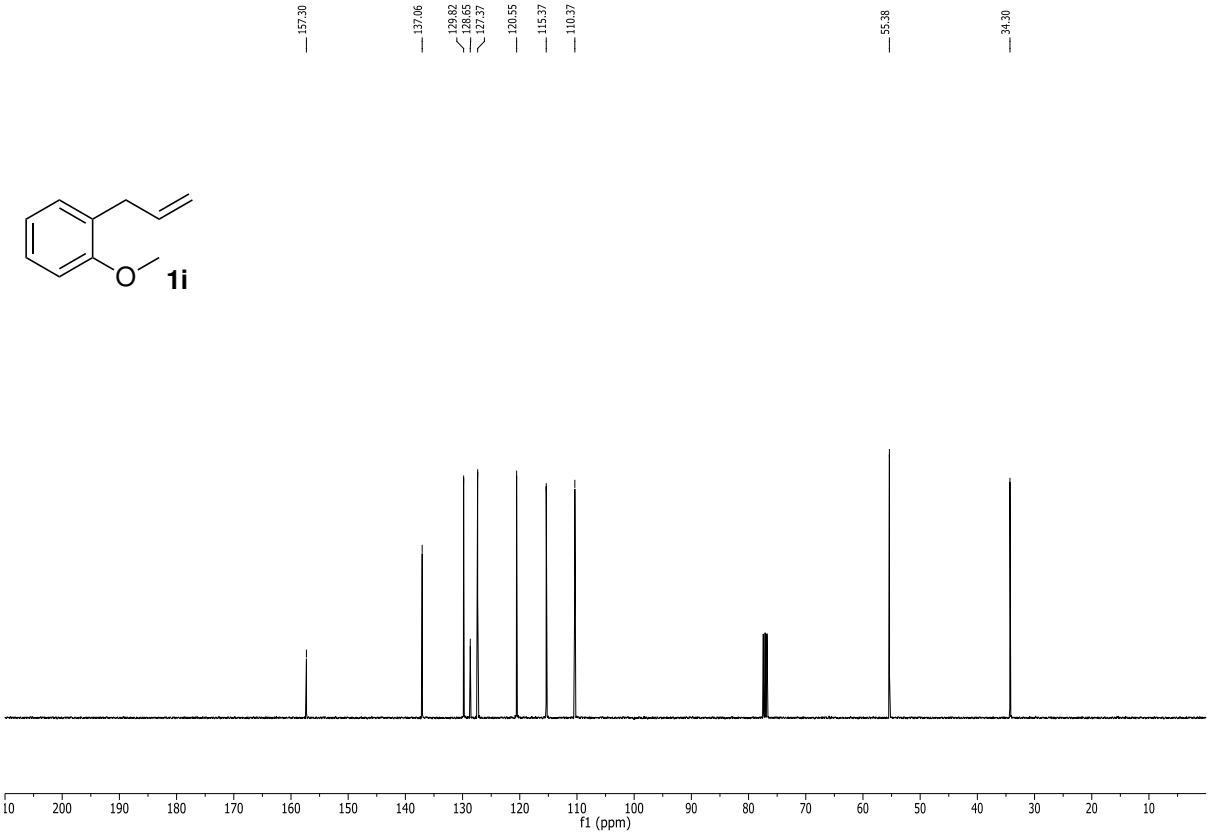
$C_{10}H_{12}O$ (148.20 g/mol)

R_f: 0.45 (hexane: Et_2O 99:1)

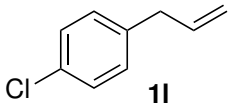
^{1}H NMR (400 MHz, Chloroform-d) δ 7.13 – 7.02 (m, 2H), 6.84 – 6.73 (m, 2H), δ 5.99 – 5.83 (m, 1H), 5.00 – 4.91 (m, 2H), 3.72 (s, 3H), 3.30 (d, *J* = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 137.0, 129.8, 128.6, 127.3, 120.5, 115.3, 110.3, 55.3, 34.3.


7.26 Chloroform-d
7.12
7.10
7.08
7.06
7.04
6.82
6.81
6.79
6.76
6.74
5.95
5.92
5.90
5.89
5.88
4.98
4.96
4.96
4.96
4.94
4.94
4.93
3.72
3.31
3.29
1i
1.91
1.89
0.92
1.90
3.00
1.95
f1 (ppm)


157.30
137.06
129.82
128.65
127.37
120.55
115.37
110.37
55.38
34.30
1i
f1 (ppm)

1-allyl-4-chlorobenzene (**1l**)



1l

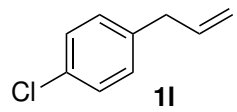
The compound **1l** was synthesized from 1-bromo-4-chlorobenzene (1.83 g, 9.6 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using *n-hexane* as mobile phase and isolated as a colorless oil (424 mg, 2.72 mmol, 29%). Conforms to reported analytical data.[5]

C_9H_9Cl (152.62 g/mol)

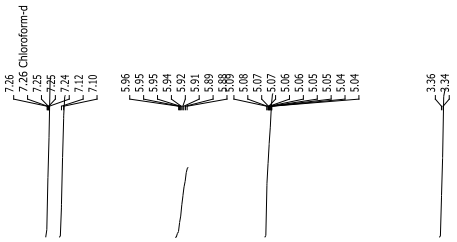
R_f : 0.71 (Pentane 100)

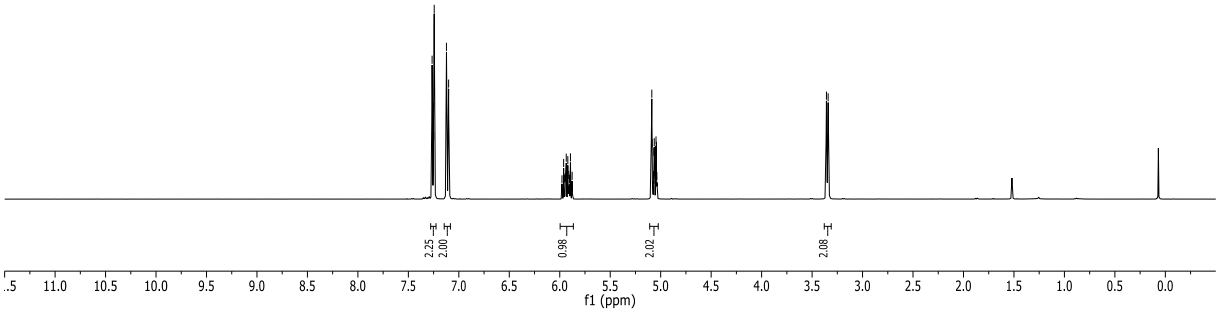
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29-7.22 (m, 2H), 7.14 – 7.08 (d, *J* = 8.3 Hz, 2H), 5.99 – 5.87 (m, 1H), 5.11 – 5.03 (m, 2H), 3.35 (d, *J* = 6.7, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 136.8, 131.8, 129.9, 128.4, 116.2, 39.5.

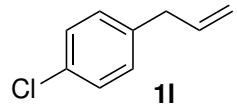

Cl

1l

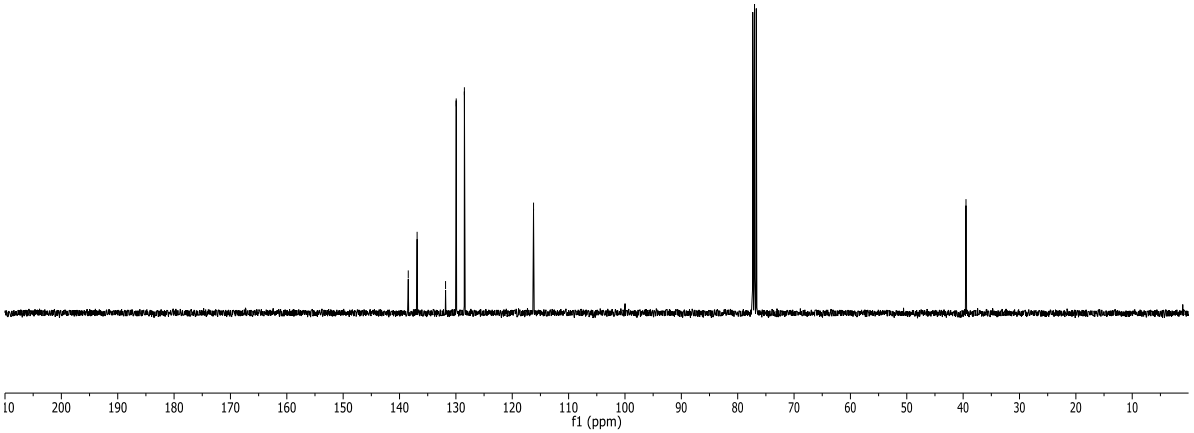

7.26 Chloroform-d
7.26
7.25
7.25
7.24
7.12
7.10
5.96
5.95
5.95
5.94
5.92
5.91
5.89
5.08
5.07
5.07
5.06
5.06
5.05
5.05
5.04
5.04
3.36
3.34


2.25
2.00
0.98
2.02
2.08
f1 (ppm)

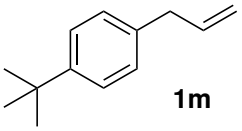

138.45
136.88
131.83
129.94
128.49
116.22
39.50


Cl

1l


f1 (ppm)

1-allyl-4-(tert-butyl)benzene (**1m**)



1m

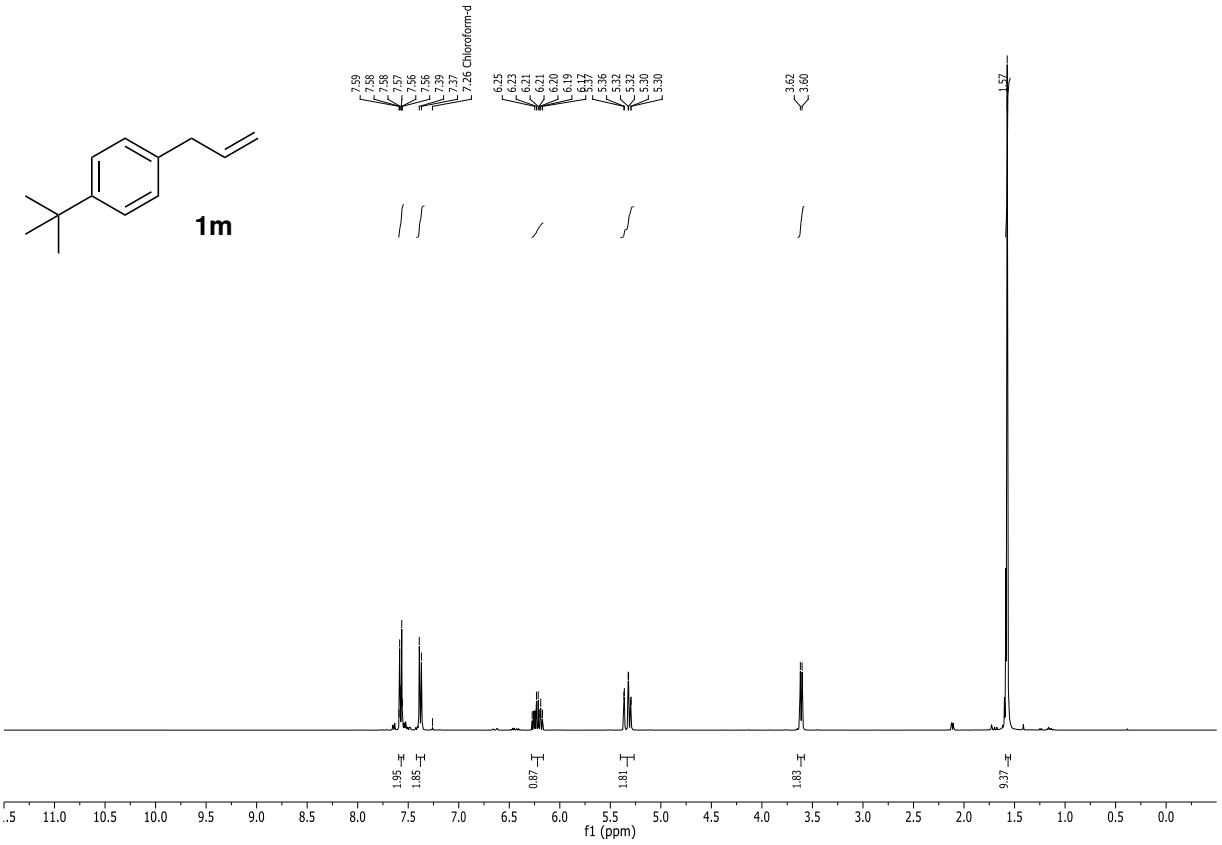
The compound **1m** was synthesized from 4-*tert*-butyl-1-bromobenzene (2.04 g, 9.6 mmol, 1 equiv) and allyl acetate (1.201 g, 12.0 mmol, 1.25 equiv) according to general procedure (B). It was purified by column chromatography using n-hexane as the eluent and isolated as a colorless oil (101 mg, 0.58 mmol, 5%). Conforms to reported analytical data.[5]

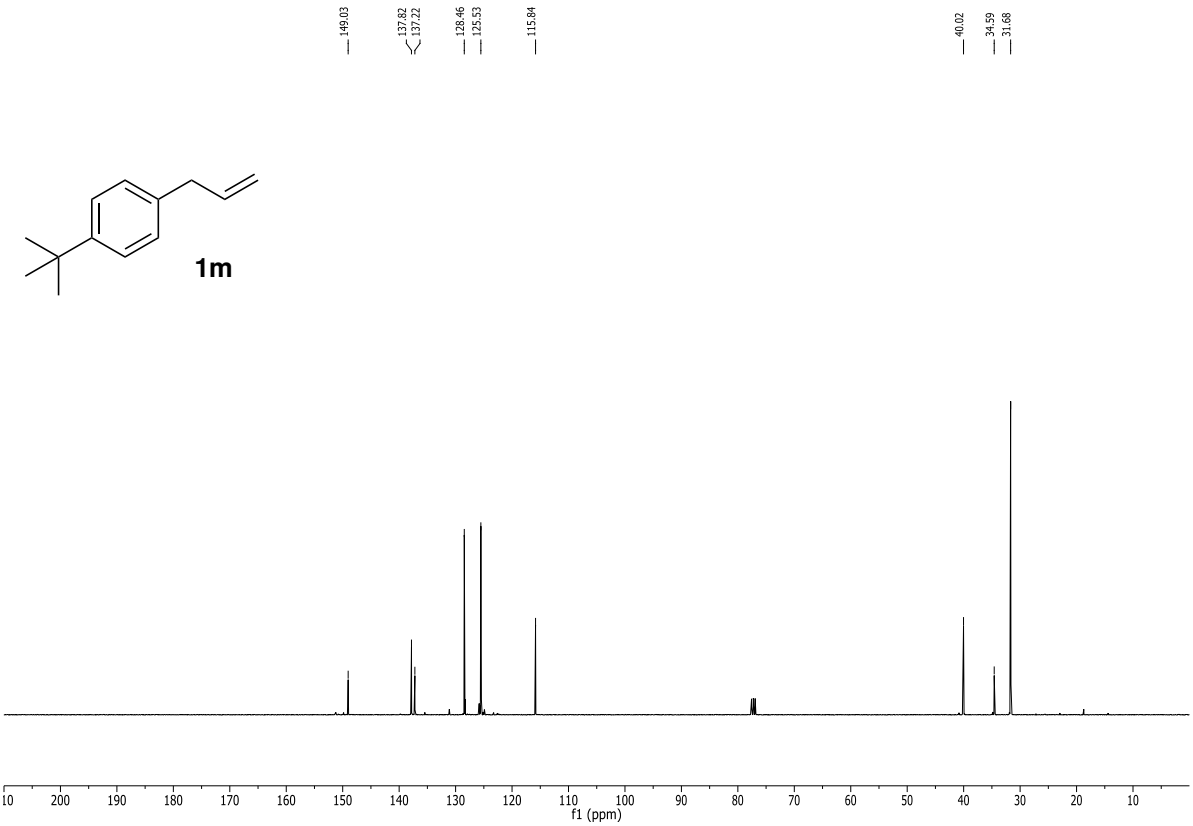
$C_{13}H_{18}$ (174.28 g/mol)

R_f : 0.78 (hexane 100)

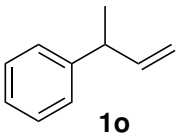
^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 7.3 Hz, 2H), 6.22 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.38 – 5.28 (m, 2H), 3.61 (dt, *J* = 6.9, 1.4 Hz, 2H), 1.57 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 137.8, 137.2, 128.4, 125.5, 115.8, 40.0, 34.5, 31.6.


7.59
7.58
7.58
7.57
7.56
7.56
7.39
7.37
7.26 Chloroform-d
6.25
6.23
6.21
6.20
6.19
5.37
5.36
5.32
5.32
5.30
5.30
3.62
3.60
1.57
1m
1.95
1.85
0.87
1.81
1.83
9.37
f1 (ppm)


149.03
137.82
137.22
128.46
125.53
115.84
40.02
34.59
31.68
1m
f1 (ppm)

but-3-en-2-ylbenzene (**1o**)



1o

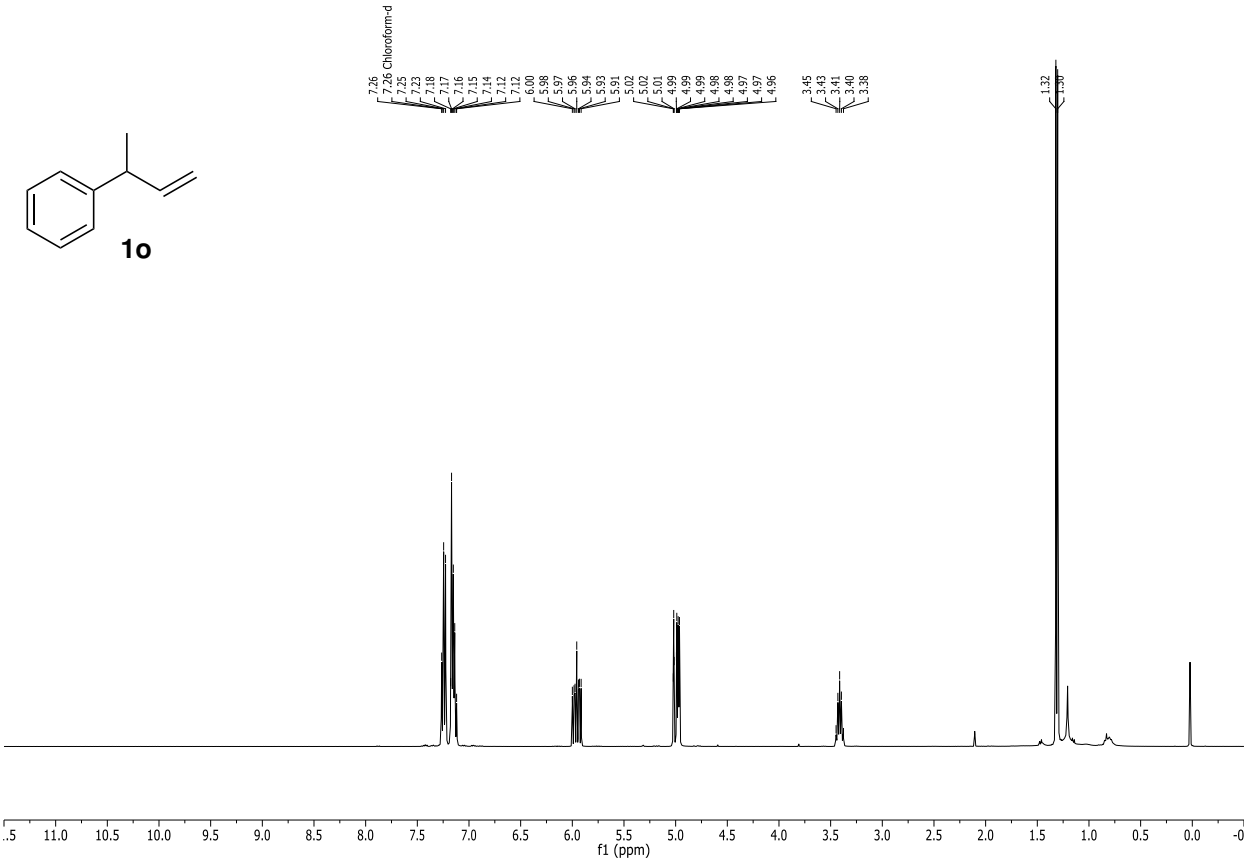
Methyl triphenylphosphonium bromide (2.42 g, 7.8 mmol, 1.3 equiv) was added to a flame dried 100 mL Schlenk round bottom flask. The flask was heated under high vacuum at 100 °C for 30 minutes. In a 25 mL Schlenk round bottom flask was added (797 µL, 6 mmol, 1 equiv) of 2-phenyl propanal, which was then dissolved in 10 mL of dry THF. The wittig salt was allowed to cool and 13 mL of dry THF was added. The flask was cooled to -20 °C. This was followed by dropwise addition of n-butyllithium (3.12 mL, 7.8 mmol, 1.3 equiv; 2.5 M in n-hexane). After the addition was finished, the contents of the reaction vessel were stirred for 30 minutes at -20 °C. This was followed by dropwise addition of the THF solution of 2-phenyl propanal at -20 °C. The reaction mixture was then allowed to attain room temperature and stirred for a period of 16 hours. The reaction was quenched by adding 15 mL NH_4Cl. This was followed by dilution with 20 mL diethyl ether. The mixture was transferred to a separating funnel and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and finally washed with brine. The combined organic layers were dried over $MgSO_4$. Rotary evaporation of the solvent gave the crude product. This was filtered through silica gel using n-hexane as the mobile phase (120 mL). The rotary evaporation of the eluted n-hexane gave the product **1o** as a colorless oil (95 mg, 0.71 mmol, 12 %). The spectra obtained conform to those reported in the literature.[8]

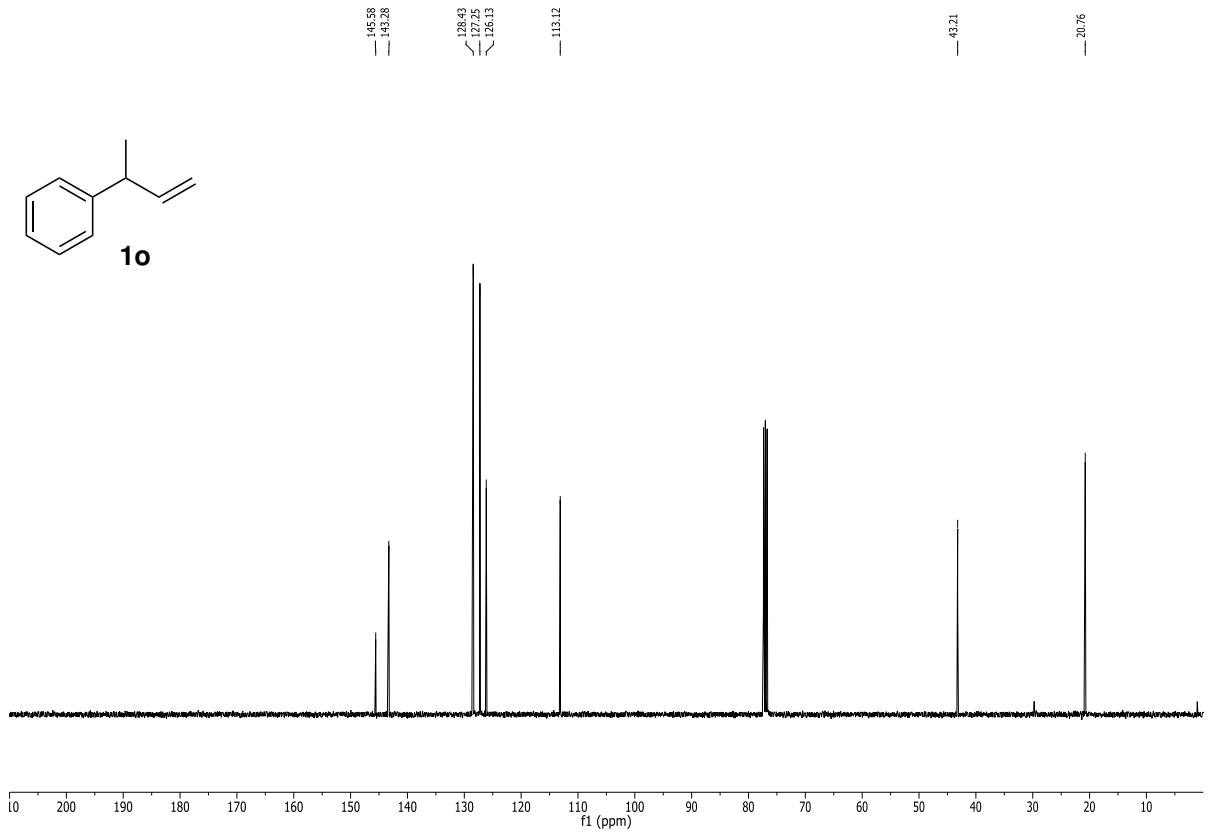
$C_{10}H_{12}$ (132,21 g/mol)

R_f : 0.52 (Hexane 100)

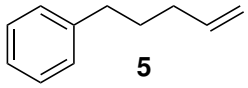
^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.30 (m, 2H), 7.28 – 7.19 (m, 3H), 6.04 (ddd, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.11 – 5.03 (m, 2H), 3.53 – 3.45 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 143.2, 128.4, 127.2, 126.1, 113.1, 43.2, 20.7.


7.26 Chloroform-d
7.26
7.25
7.23
7.18
7.17
7.16
7.15
7.14
7.12
7.12
6.00
5.98
5.97
5.96
5.94
5.93
5.91
5.02
5.02
5.01
4.99
4.99
4.99
4.98
4.98
4.97
4.97
4.96
3.45
3.43
3.41
3.40
3.38
1.32
1.30
1o
f1 (ppm)


145.58
143.28
128.43
127.25
126.13
113.12
43.21
20.76
1o
f1 (ppm)

pent-4-en-1-ylbenzene (**5**)



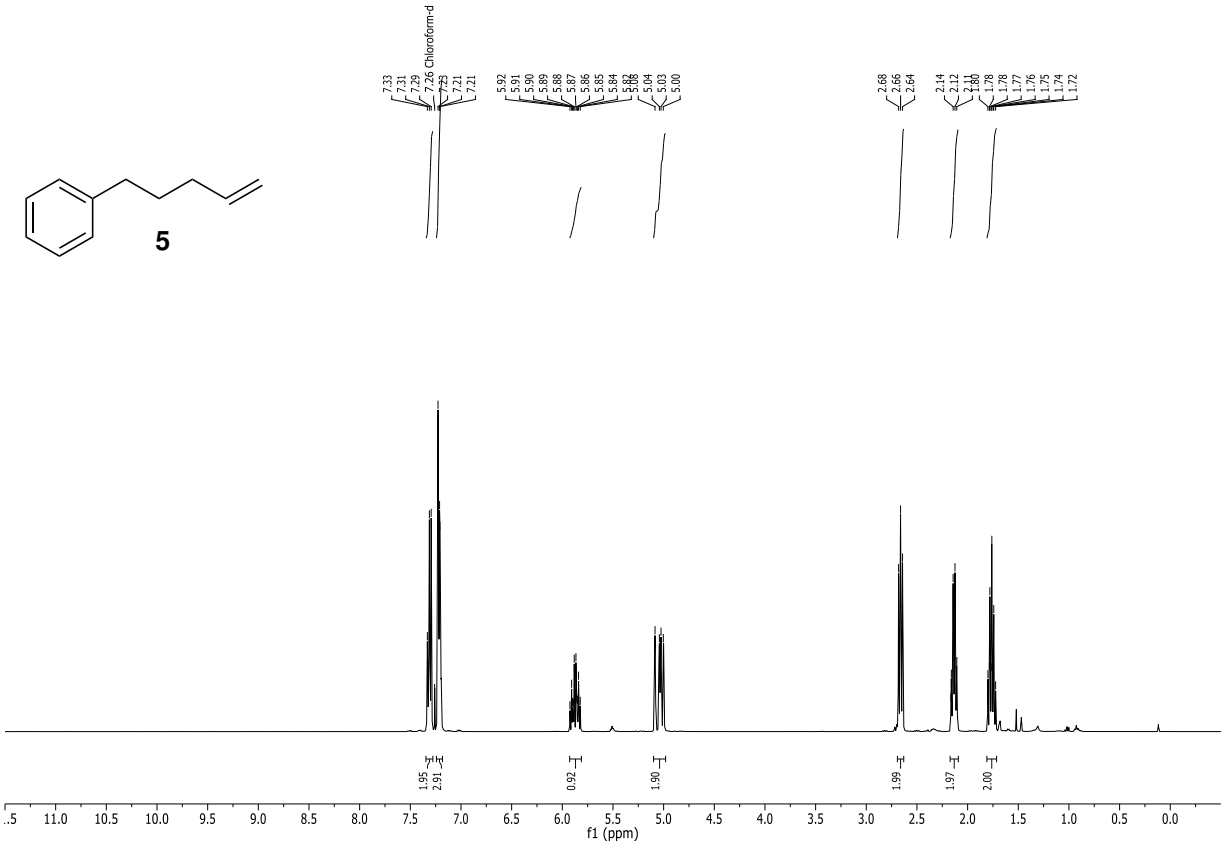
5

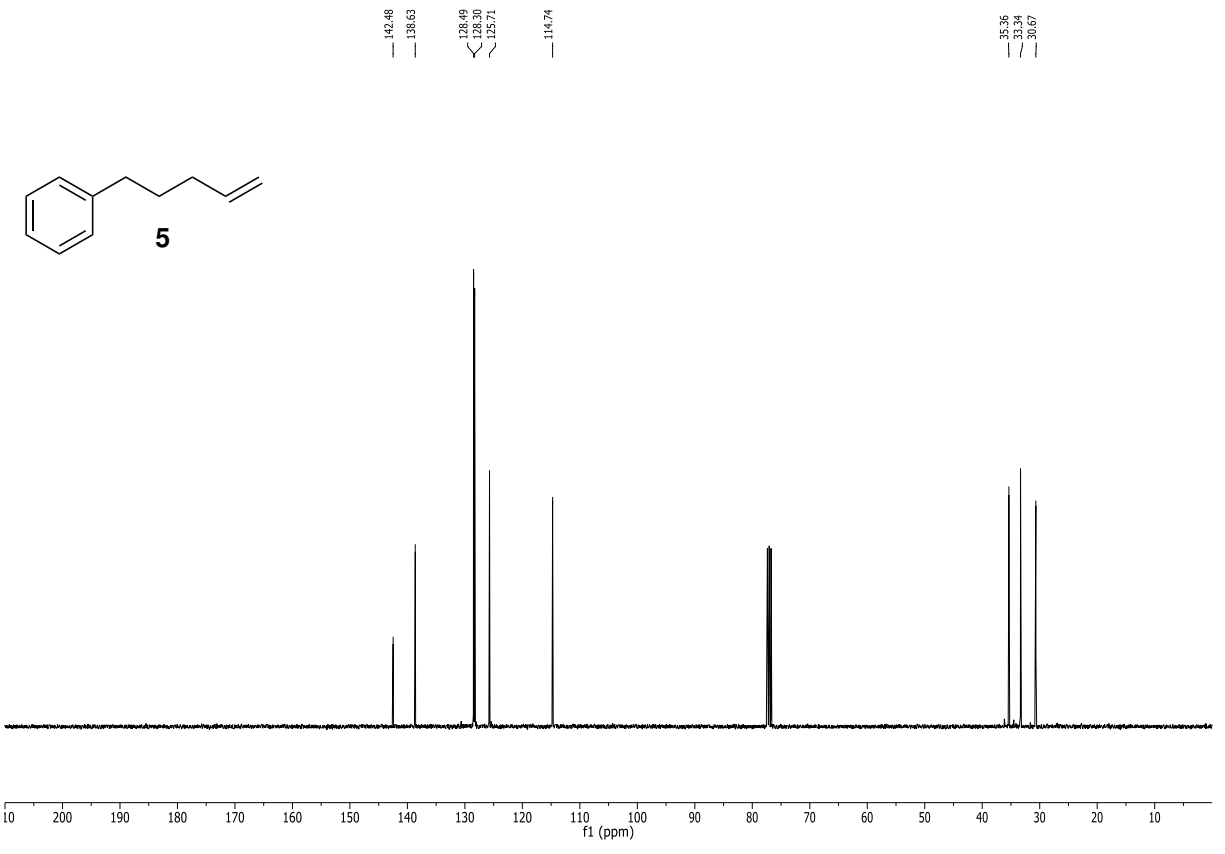
The compound **5** was synthesized from benzyl magnesium chloride (2 M solution in Et_2O) (4.12 mL, 8.25 mmol, 1 equiv) and 4-bromobut-1-ene (1.06 mL, 10.5 mmol, 1.27 equiv) using the synthetic procedure from Chirik et al.[4a] Column chromatography using n-hexane as an eluent furnished the pure product (760 mg, 5.2 mmol, 63%). The analytical data is in accordance with the previous literature report.[4c]

R_f = 0.62 (hexane 100)

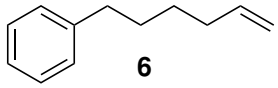
^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 5.95 – 5.80 (m, 1H), 5.11 – 4.98 (m, 2H), 2.69 – 2.63 (m, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.76 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 138.6, 128.4, 128.3, 125.7, 114.7, 35.3, 33.3, 30.6.


Chloroform-d
7.33
7.31
7.29
7.26
7.25
7.21
7.21
5.92
5.91
5.90
5.89
5.88
5.87
5.86
5.85
5.84
5.04
5.03
5.00
2.68
2.66
2.64
2.14
2.12
2.11
2.08
1.78
1.78
1.77
1.76
1.75
1.74
1.72
5
1.95
2.91
0.92
1.90
1.99
1.97
2.00
f1 (ppm)


142.48
138.63
128.49
128.30
125.71
114.74
35.36
33.34
30.67
5
f1 (ppm)

hex-5-en-1-ylbenzene (**6**)



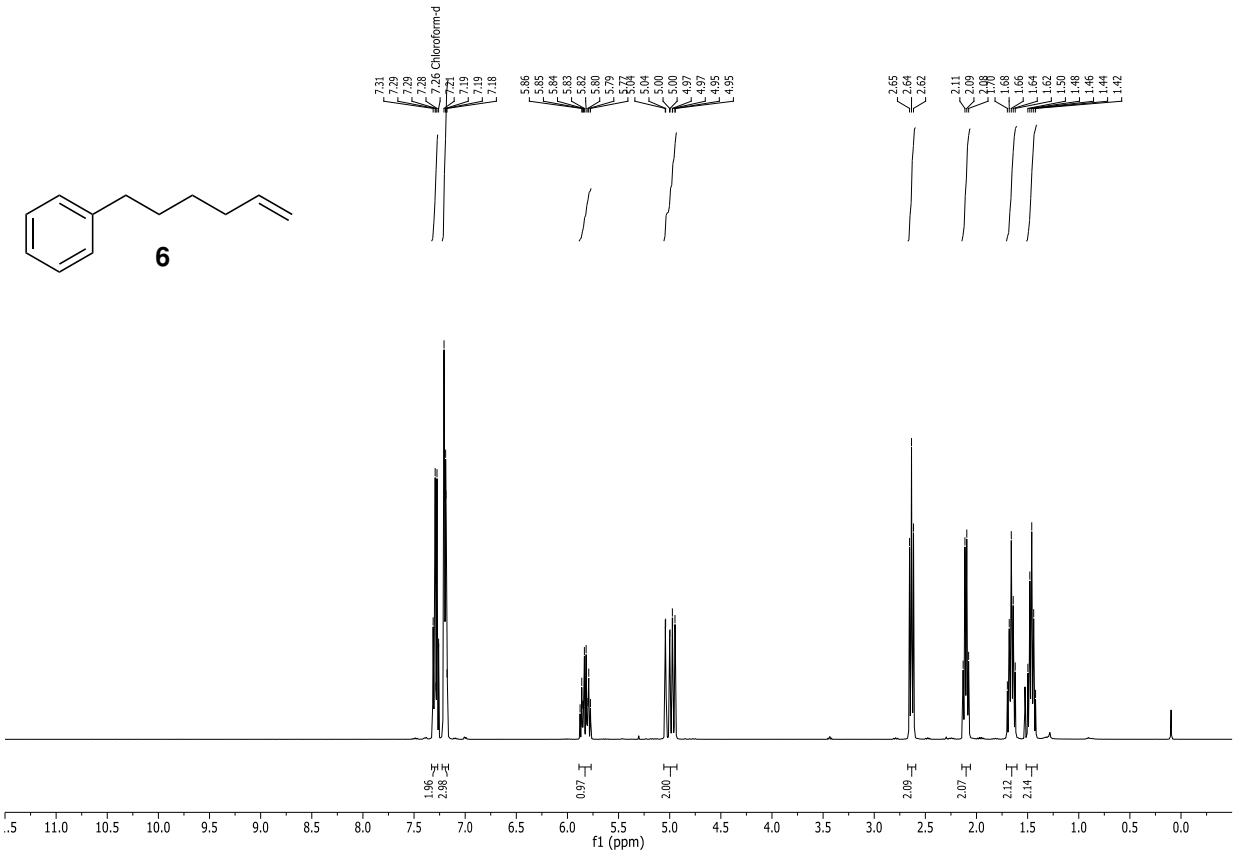
6

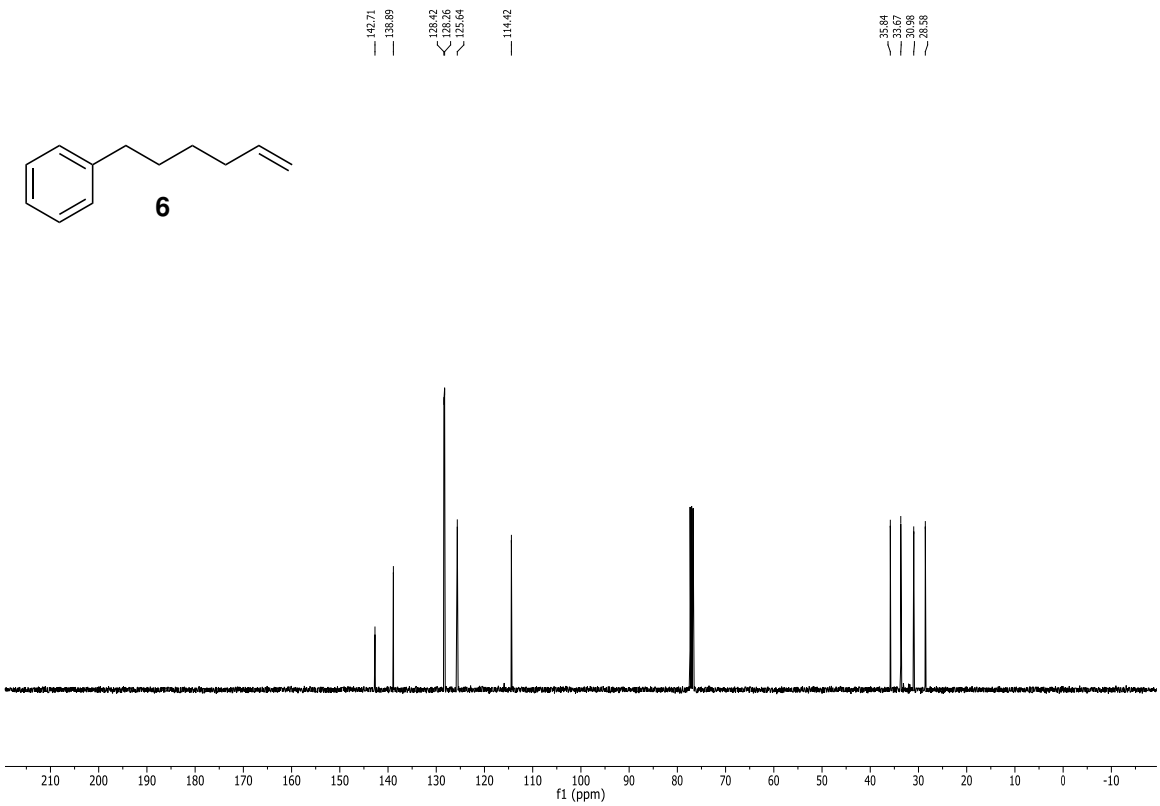
The compound **6** was synthesized from benzyl magnesium chloride (2 M solution in Et_2O) (8.25 mmol, 4.12 mL, 1 equiv) and 5-bromopent-1-ene (10.5 mmol, 4.12 mL, 1.27 equiv) using the synthetic procedure from Chirik et al.[4] Column chromatography using n-hexane as an eluent furnished the pure product (621 mg, 3.88 mmol, 47%). The analytical data is in accordance with the previous literature report.[4b]

R_f = 0.58 (hexane 100)

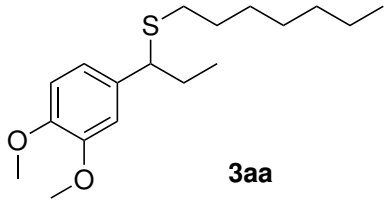
^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 5.90 – 5.76 (m, 1H), 5.06 – 4.92 (m, 2H), 2.67 – 2.59 (m, 2H), 2.10 (q, *J* = 7.2 Hz, 2H), 1.72 - 1.60 (m, 2H), 1.53 – 1.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 138.8, 128.2, 125.6, 114.4, 35.8, 33.6, 30.9, 28.5.


Chloroform-d
7.31
7.29
7.29
7.28
7.26
7.21
7.19
7.19
7.18
5.86
5.85
5.84
5.83
5.82
5.80
5.79
5.77
5.04
5.00
5.00
4.97
4.97
4.95
4.95
2.65
2.64
2.62
2.11
2.09
2.08
1.70
1.68
1.66
1.64
1.62
1.50
1.48
1.46
1.44
1.42
6
1.96
2.98
0.97
2.00
2.09
2.07
2.12
2.14
f1 (ppm)


142.71
138.89
128.42
128.26
125.64
114.42
35.84
33.67
30.98
28.58
6
f1 (ppm)

(1-(3,4-dimethoxyphenyl)propyl)(heptyl)sulfane (**3aa**)



3aa

The compound **3aa** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) and purified by flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes then 2. hexane/diethylether 92:8). The product was isolated as a yellow oil (120.9 mg, 0.39 mmol, 78% yield).

Procedure at 5 mmol scale:

In a 25 mL pressure tube was added 1,2-bis[(di-*tert*-butylphosphino)methyl]benzene (3.9 mol%, 0.21 mmol, 84.5 mg) inside a glove box. The tube was taken outside the box and was charged with $Pd(OAc)_2$ (3 mol%, 33.6 mg, 0.15 mmol). After evacuating and backfilling the Schlenk tube, 10 ml DCM and 4-allyl-1,2-dimethoxybenzene (5.00 mmol, 891 mg, 859 µL, 1 equiv) were added. After stirring for 5 minutes, CF_3SO_3H (12 mol%, 0.60 mmol, 90 mg, 53 µL) was added immediately followed by addition of heptane-1-thiol (5.50 mmol, 727 mg, 860 µL, 1.1 equiv). The reaction vessel was transferred to a pre-heated oil bath at 40 °C and stirred at 1000 r.p.m for 15 h. After the completion of the reaction, the reaction mixture was diluted with 20 ml DCM. The contents were washed with water (2×10ml). The aqueous phase was back-extracted with DCM (3×10ml). The combined organic phases were passed through a cotton plugged glass funnel containing aluminum oxide and magnesium sulfate and the solvent was removed on rotary evaporator. The crude product was subjected to column chromatography (dry load) with gradient elution: 1. 100% hexane till remaining heptane-1-thiol is eluted; 2. hexane/Et_2O: 92:8. The product was obtained as a yellow oil (1.225 g, 3.95 mmol, 77 %).

$C_{18}H_{30}O_2S$ (310.49 g/mol)

R_f : 0.16 (hexane/diethylether 90:10)

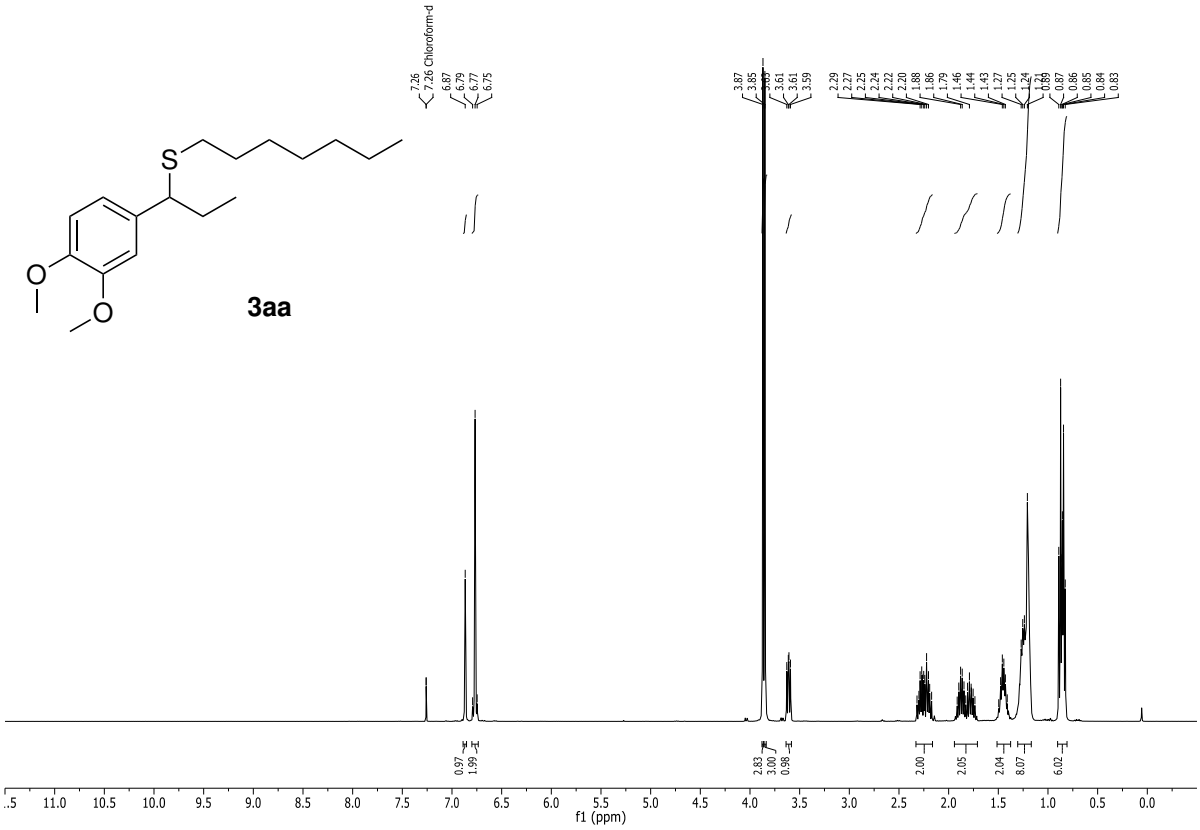
m.p : ambient temperature

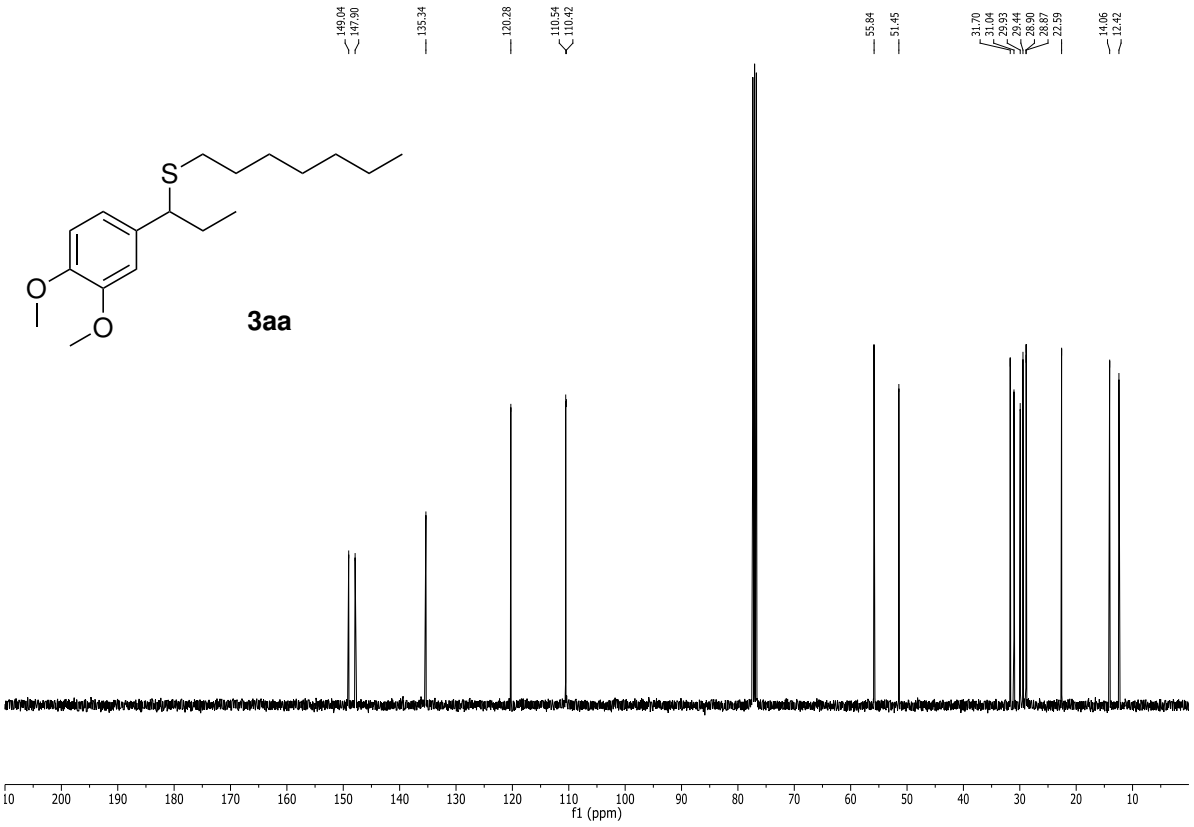
^{1}H NMR (400 MHz, Chloroform-d) δ 6.87 (s, 1H), 6.74-6.68 (m, 2H), 3.81 (s 3H), 3.79 (s, 3H), 3.62 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.34 – 2.16 (m, 2H), 1.95 – 1.72 (m, 2H), 1.45-1.34 (m 2H), 1.35 – 1.16 (m, 8H), 0.86-0.74 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.9, 135.3, 120.2, 110.5, 110.4, 55.8, 51.4, 31.7, 31.0, 29.9, 29.4, 28.9, 28.8, 22.6, 14.0, 12.4.

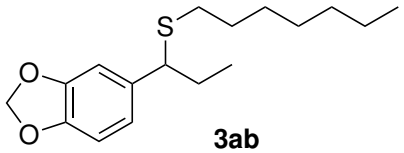
IR: (ν) (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 2855, 1588, 1513, 1461, 1260, 1230, 1137, 1038, 801, 764.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z 333.18587, found 333.18589


7.26 Chloroform-d
3aa
f1 (ppm)


3aa
f1 (ppm)

5-(1-(heptylthio)propyl)benzo[d][1,3]dioxole (**3ab**)



3ab

The compound **3ab** was synthesized from 5-allylbenzo[d][1,3]dioxole (81 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (104.4 mg, 0.35 mmol, 71%). Preparative TLC was employed for separation and isolation using a mixture of hexane and diethylether as the mobile phase (hexane/diethylether 97.5:2.5).

$C_{17}H_{26}O_2S$ (294.45 g/mol)

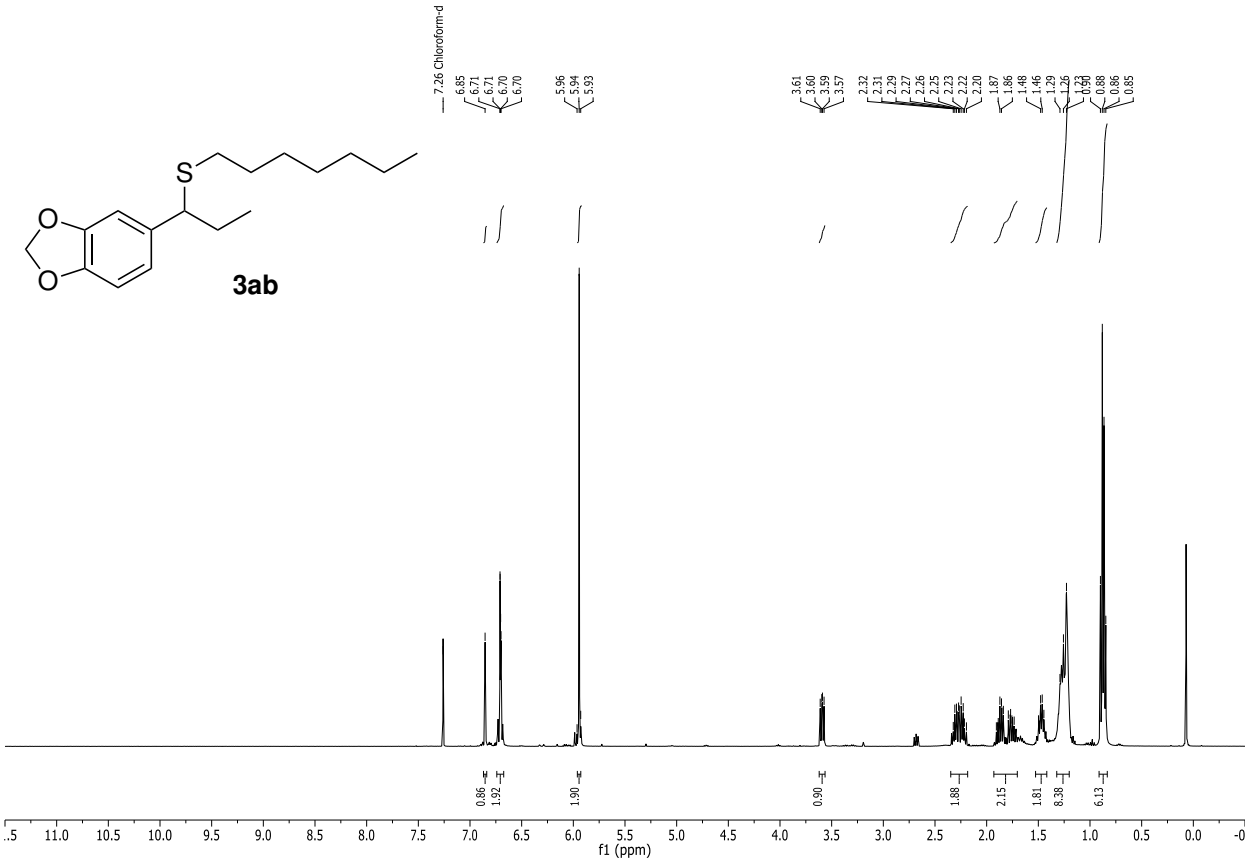
R_f : 0.47 (hexane/diethylether 95:5)

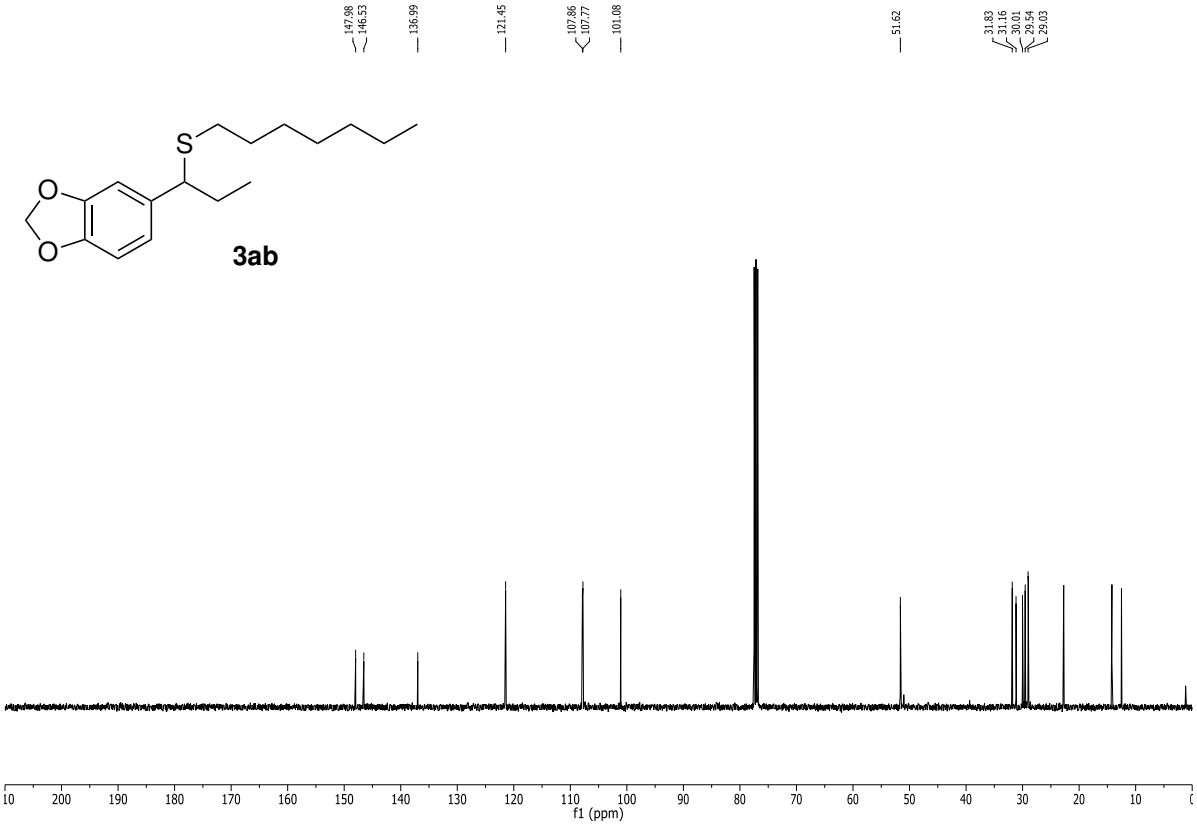
^{1}H NMR (400 MHz, Chloroform-d) δ 6.85 (d, *J* = 1.5 Hz, 1H), 6.73 – 6.67 (m, 2H), 5.94 (s, 2H), 3.59 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.36 – 2.18 (m, 2H), 1.92 – 1.69 (m, 2H), 1.53-1.40 (m, 2H), 1.33 – 1.18 (m, 8H), 0.92 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 146.5, 136.9, 121.4, 107.8, 107.7, 101.1, 77.1, 51.6, 31.8, 31.1, 30.01, 29.5, 29.1, 29.0, 22.7, 14.2, 12.5.

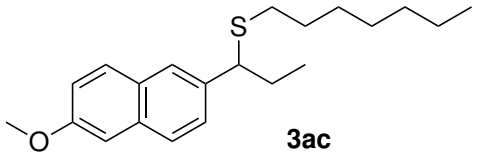
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3019, 2922, 2855, 1461, 1356, 1285, 1215, 1114, 1085, 842, 749.

HR-MS (EI): calculated (m/z): 294.16480, found: 294.16664.


7.26 Chloroform-d
6.85
6.71
6.71
6.70
6.70
5.96
5.94
5.93
3.61
3.60
3.59
3.57
2.32
2.31
2.29
2.27
2.26
2.25
2.23
2.22
2.20
1.87
1.86
1.48
1.46
1.29
1.26
0.88
0.86
0.85
S
O
O
3ab
0.86
1.92
1.90
0.90
1.88
2.15
1.81
8.38
6.13
f1 (ppm)


147.98
146.53
136.99
121.45
107.86
107.77
101.08
51.62
31.83
31.16
30.01
29.54
29.03
S
O
O
3ab
f1 (ppm)

heptyl(1-(6-methoxynaphthalen-2-yl)propyl)sulfane (**3ac**)



3ac

The compound **3ac** was synthesized following the General Procedure (A) from 2-allyl-6-methoxynaphthalene (99.1 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv). The crude product was purified by column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes then 2. hexane/diethylether 97.5:2.5) and isolated as a yellow oil (102.3 mg, 0.31 mmol, 62%).

$C_{21}H_{30}OS$ (330.53 g/mol)

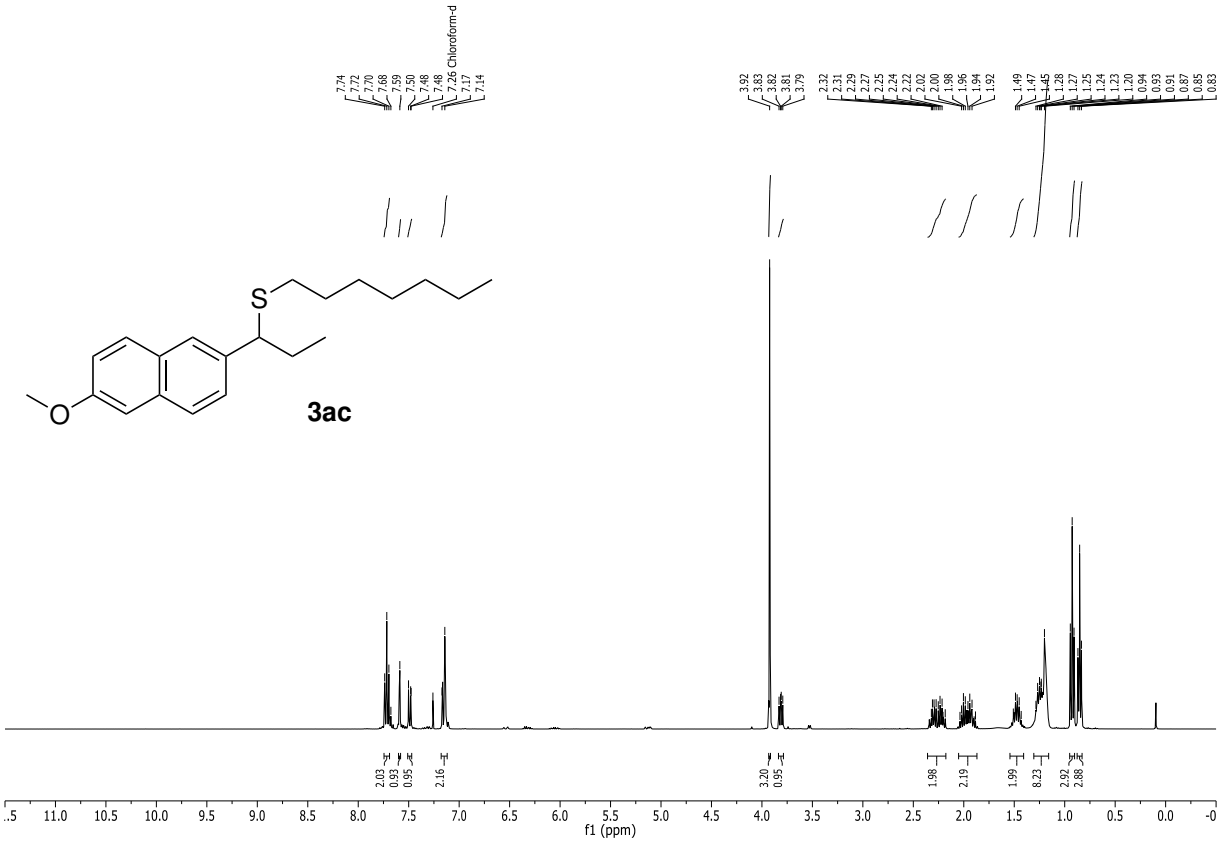
R_f : 0.31 (hexane/diethylether 97.5:2.5)

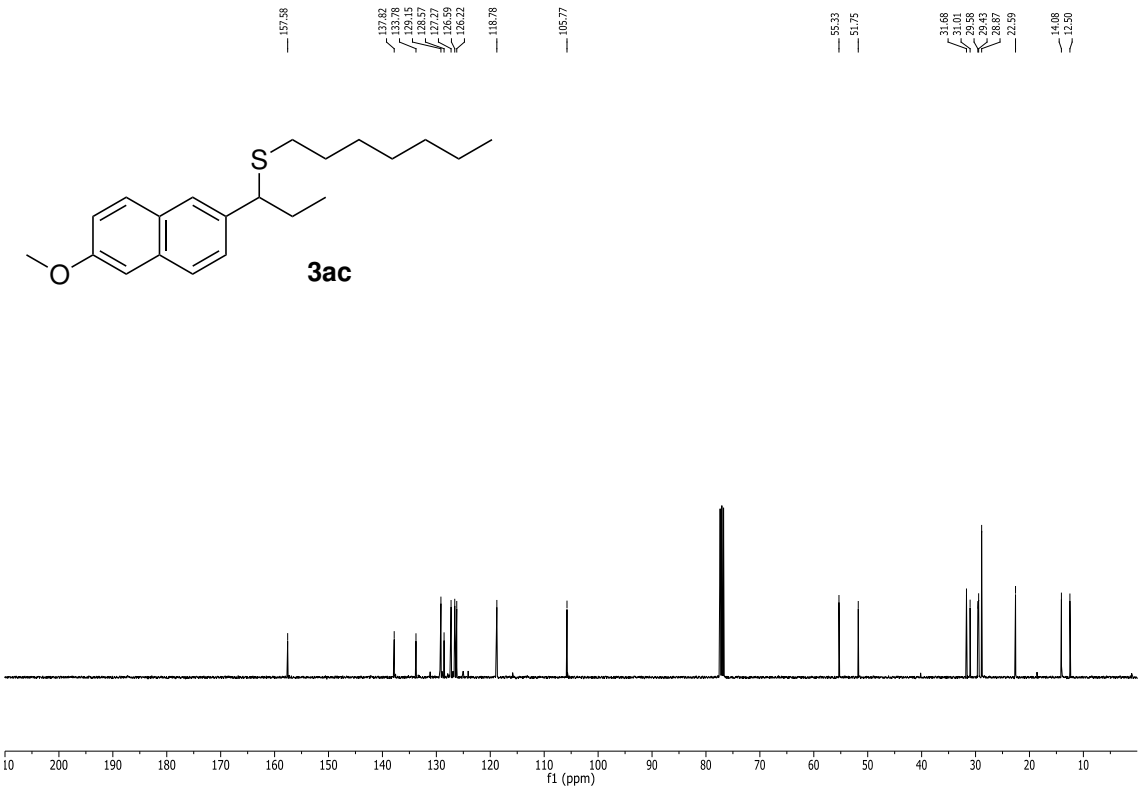
^{1}H NMR (400 MHz, Chloroform-d) δ 7.76 – 7.69 (m, 2H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.49 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.18 – 7.12 (m, 2H), 3.92 (s, *J* = 2.7 Hz, 3H), 3.81 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.35 – 2.17 (m, 2H), 2.05 – 1.86 (m, 2H), 1.55 – 1.40 (m, 2H), 1.32 – 1.15 (m, 8H) 0.93 (t, *J* = 7.3 Hz, 1H), 0.85 (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 137.8, 133.7, 129.1, 128.5, 127.2, 126.6, 126.2, 118.8, 105.7, 55.3, 51.7, 31.6, 31.0, 29.6, 29.4, 28.8, 22.6, 14.0, 12.5.

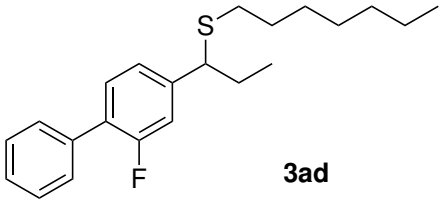
IR: **(ATR) $\tilde{\nu}$ (cm^{-1}):** 2955, 2922, 2851, 1632, 1602, 1461, 1390, 1263, 1196, 1032, 849, 808

HR-MS (ESI): calc. for [M+Na]+ m/z: 330.20118, found: 330.19939


7.74
7.72
7.70
7.68
7.59
7.50
7.48
7.48
7.26 Chloroform-d
7.17
7.14
3.92
3.83
3.82
3.81
3.79
2.32
2.31
2.29
2.27
2.25
2.24
2.22
2.02
2.00
1.98
1.96
1.94
1.92
1.49
1.47
1.45
1.28
1.27
1.25
1.24
1.23
1.20
0.94
0.93
0.91
0.87
0.85
0.83
S
O
3ac
2.03
0.93
0.95
2.16
3.20
0.95
1.98
2.19
1.99
8.23
2.92
2.88
f1 (ppm)


157.58
137.82
133.78
129.15
128.57
127.27
126.59
126.22
118.78
105.77
55.33
51.75
31.68
31.01
29.58
29.43
28.87
22.59
14.08
12.50
S
O
3ac
f1 (ppm)

(1-(2-fluoro-[1,1'-biphenyl]-4-yl)propyl)(heptyl)sulfane (**3ad**)



3ad

The compound **3ad** was synthesized following the General Procedure (A with the following changes) Palladium acetate (3.36 mg, 0.06 mmol) **L1** (18.08 mg, 0.12 mmol) CF_3SO_3H (4.2 µL, 0.16 mmol)) from 4-allyl-2-fluoro-1,1-biphenyl (53.1 mg, 0.25 mmol, 1 equiv) and heptane-1-thiol (35.6 mg, 0.27 mmol, 1.1 equiv) as a yellow oil (44.7 mg, 0.12 mmol, 52%). Preparative TLC was employed for separation and isolation using hexane as the mobile phase.

$C_{22}H_{29}FS$ (344.53 g/mol)

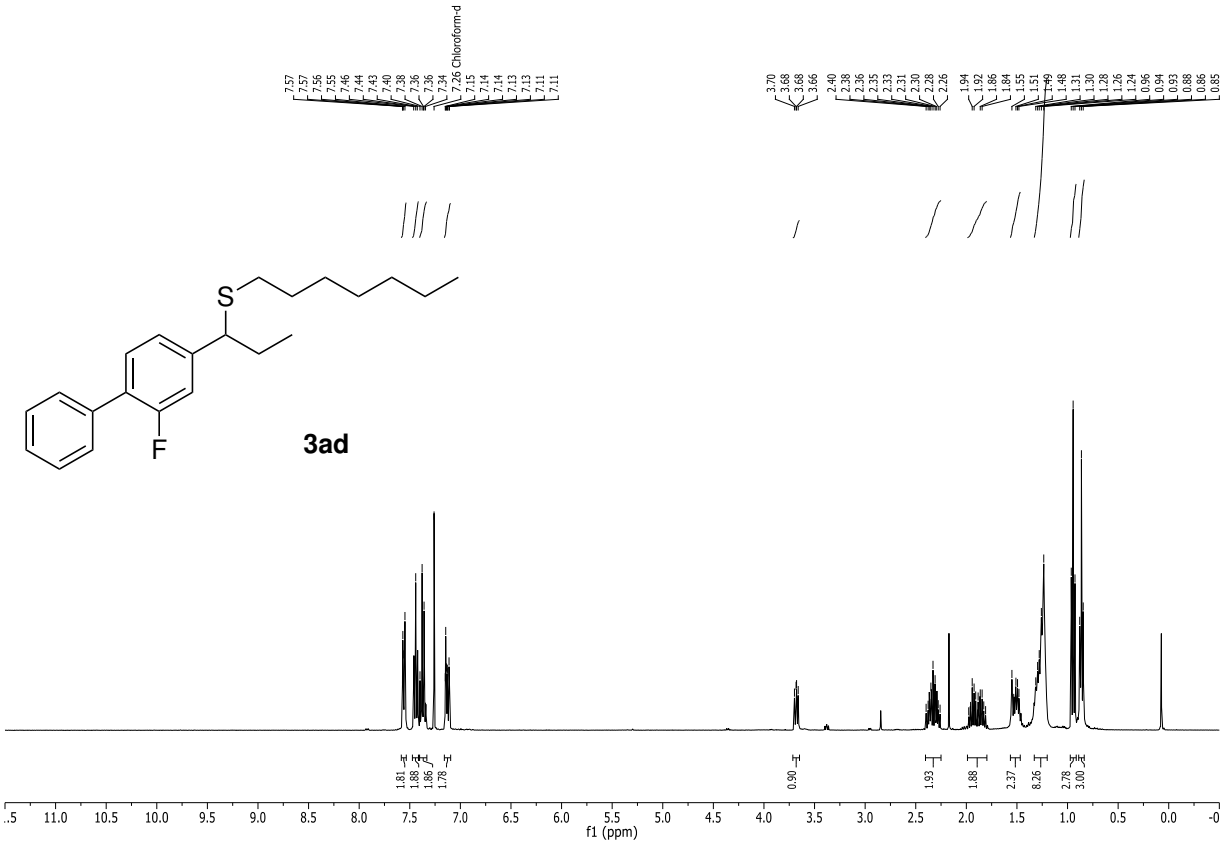
^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.48 – 7.41 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.16 – 7.09 (m, 2H), 3.68 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.42 – 2.23 (m, 2H), 2.00 – 1.78 (m, 2H), 1.58 – 1.44 (m, 2H), 1.35 – 1.19 (m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.89 – 0.84 (m, 3H).

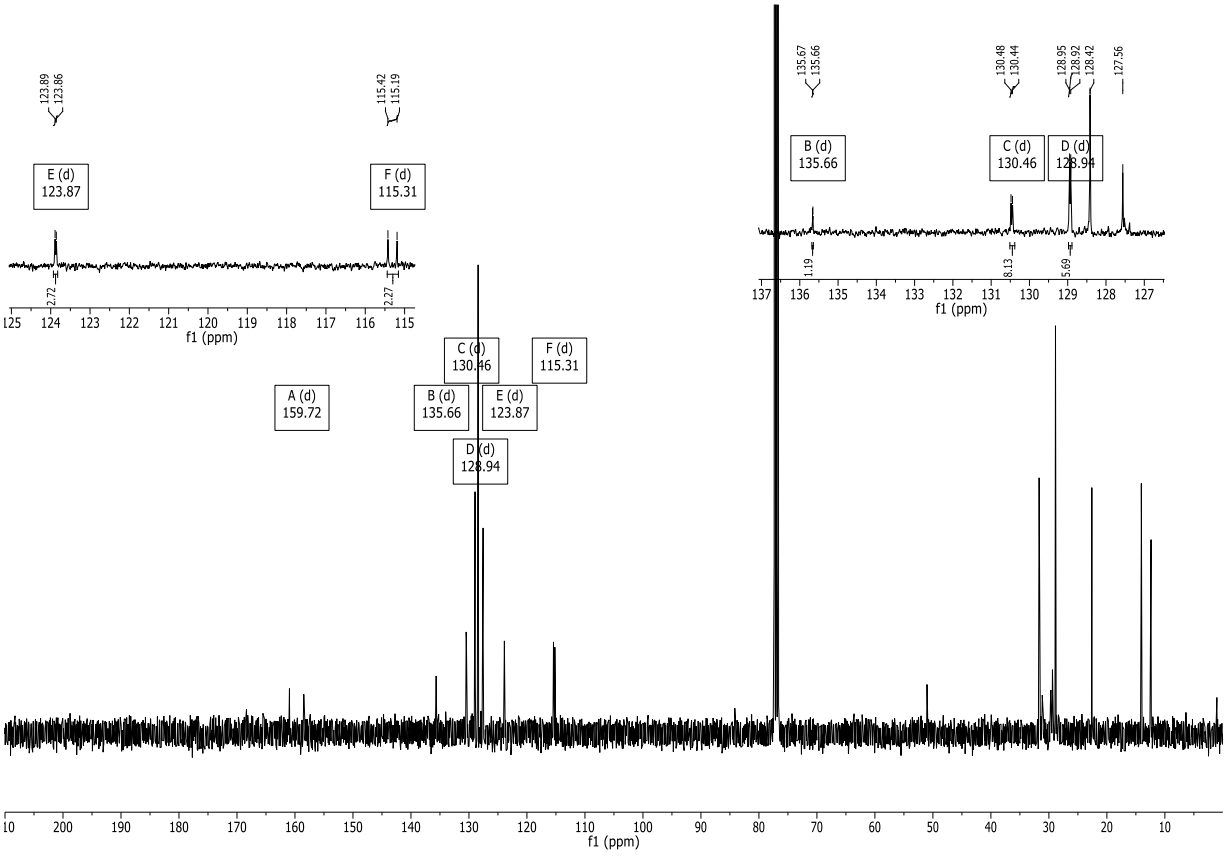
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, *J* = 248.2 Hz), 135.6 (d, *J* = 1.1 Hz), 130.4 (d, *J* = 4.0 Hz), 128.9 (d, *J* = 3.0 Hz), 128.4, 127.5, 123.8 (d, *J* = 3.2 Hz), 115.3 (d, *J* = 23.4 Hz),51.0, 31.6, 28.8, 22.5, 14.0, 12.3.

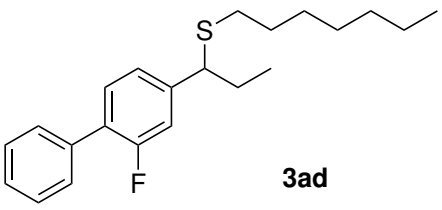
^{19}F NMR (376 MHz, Chloroform-d) δ -118.13.

IR: **(ATR) $\tilde{\nu}$ (cm^{-1})**: 3056, 2922, 2855, 1483, 1416, 1379, 1125, 950, 868, 764, 697

HR-MS (EI): calculated (m/z): 344.19685, measured: 344.19535


Chloroform-d
S
F
3ad
f1 (ppm)

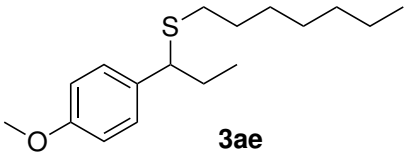

E (d)
123.87
F (d)
115.31
B (d)
135.66
C (d)
130.46
D (d)
128.94
A (d)
159.72
f1 (ppm)


S
F

3ad

-118.10
-118.12
-118.13
-118.15
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

Heptyl(1-(4-methoxyphenyl)propyl)sulfane (**3ae**)



3ae

The compound **3ae** was synthesized from 4-allylanisole (74 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (102 mg, 0.36 mmol, 73%). Preparative TLC was employed for separation and isolation using hexane as the mobile phase.

$C_{17}H_{28}OS$ (280.47 g/mol)

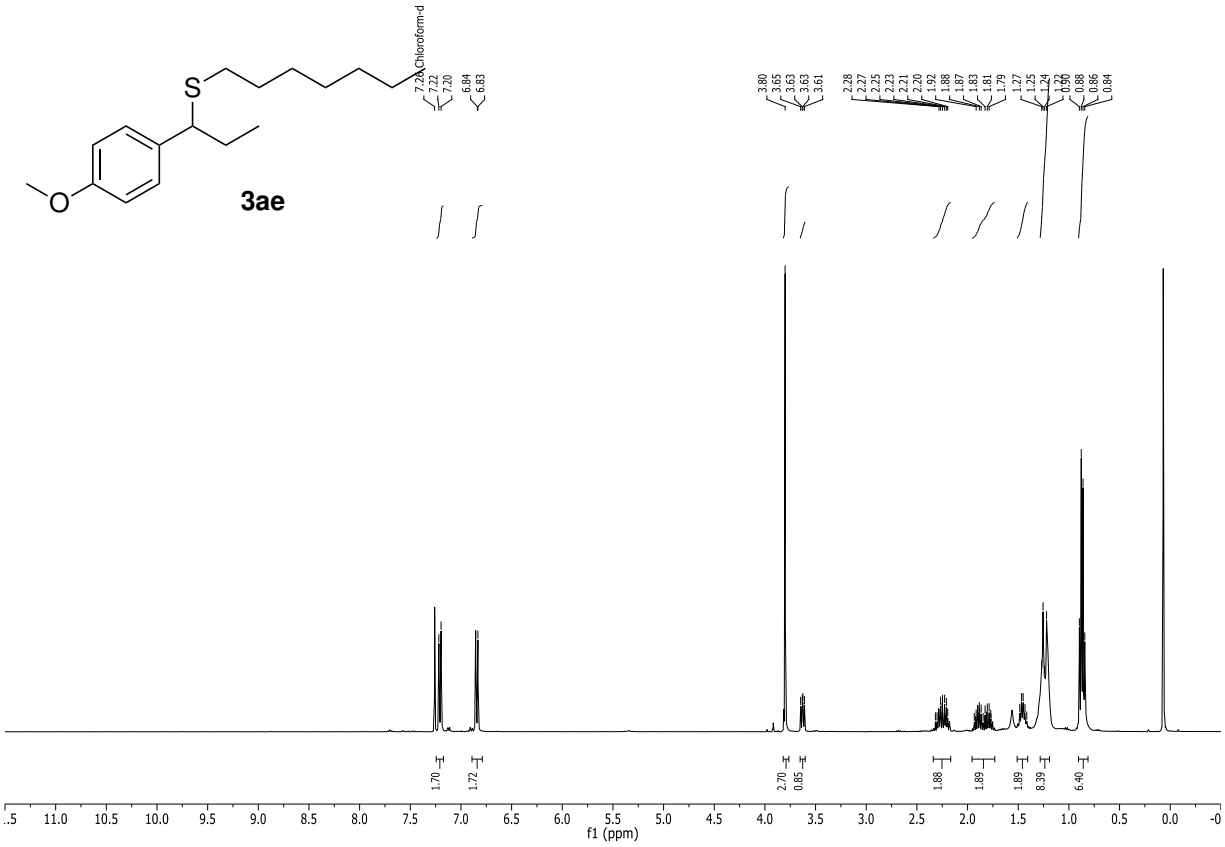
R_f: 0.34 (hexane/diethylether 97:03)

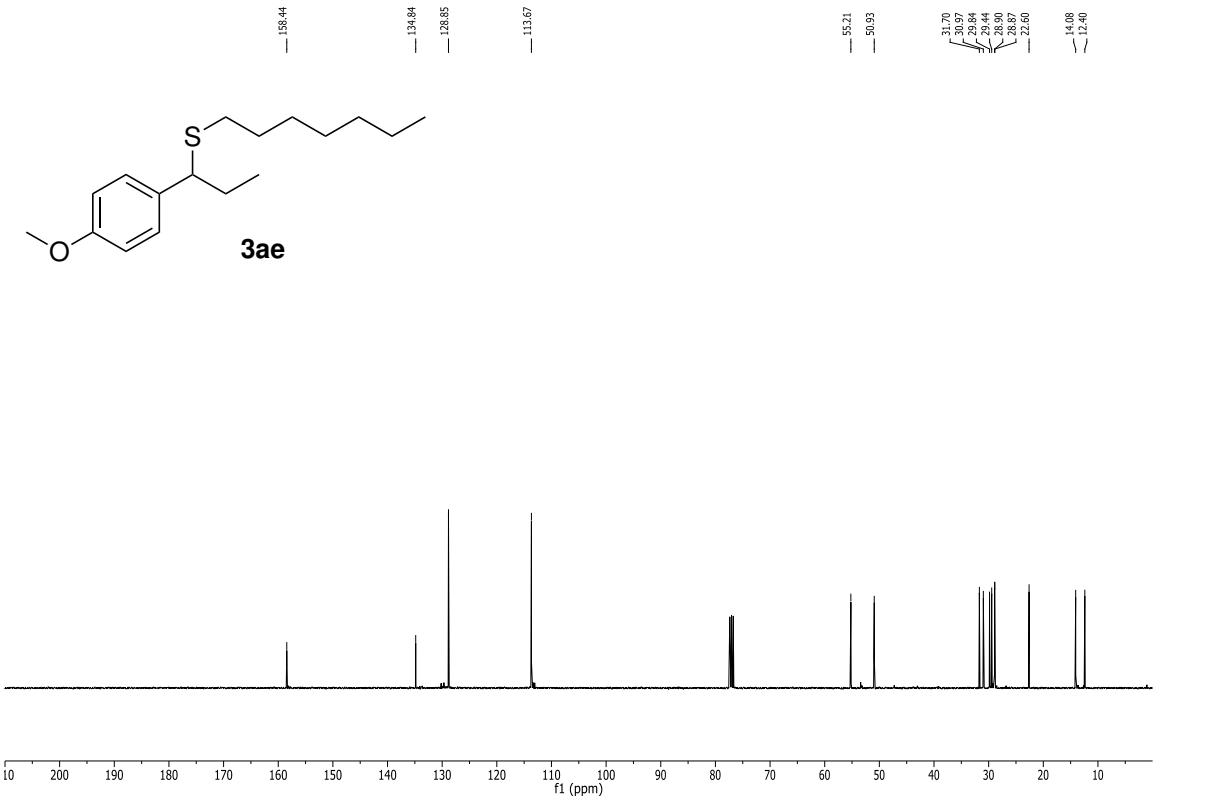
^{1}H NMR (400 MHz, Chloroform-d) δ 7.24 – 7.19 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.82 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.63 (dd, *J* = 8.7, 6.0 Hz, 1H), 2.34 – 2.15 (m, 2H), 1.98 – 1.71 (m, 2H), 1.53 – 1.40 (m, 2H), 1.35 – 1.17 (m, 8H), 0.91-0.84 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 134.8, 128.8, 113.6, 55.2, 50.9, 31.7, 30.9, 29.8, 29.4, 28.9, 28.8, 22.6, 14.0, 12.4.

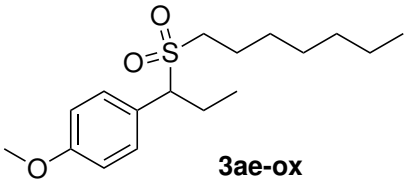
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2922, 2855, 1610, 1509, 1461, 1300, 1248, 1174, 1036, 827, 775, 689.

HR-MS (ESI): calculated for (m/z): 280.18553, found: 280.18867


S
O
3ae
Chloroform-d
7.26
7.22
7.20
6.84
6.83
3.80
3.65
3.63
3.63
3.61
2.28
2.27
2.25
2.23
2.21
2.20
1.92
1.88
1.87
1.83
1.81
1.79
1.27
1.25
1.24
0.90
0.88
0.86
0.84
1.70
1.72
2.70
0.85
1.88
1.89
1.89
8.39
6.40
f1 (ppm)


S
O
3ae
158.44
134.84
128.85
113.67
55.21
50.93
31.70
30.97
29.84
29.44
28.90
28.87
22.60
14.08
12.40
f1 (ppm)

1-(1-(heptylsulfonyl)propyl)-4-methoxybenzene (**3ae-ox**)



3ae-ox

The compound **3ae-ox** was synthesized from 4-allyl anisole (74 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The crude thioether was used without purification for follow-up oxidation. For this, the crude product was transferred in 25 mL round bottom flask and diluted with 3 mL DCM. The contents of the flask were cooled to 0 °C. To this was added 3 equiv of 70% *m*-chloroperbenzoic acid (369 mg, 1.5 mmol). The reaction mixture was stirred at 0 °C for 3 hours. After completion of the reaction, it was quenched using 5 mL aq. $NaHCO_3$. The layers were separated and the organic layer was dried over $MgSO_4$. After the removal of solvent by rotary evaporation, the product was adsorbed on silica and subjected to flash column chromatography (12g SiO_2, Gradient elution: 1. hexane/diethylether 90:10 for elution of relatively non polar impurities 2. hexane/diethylether 75:25 for elution of product) to give pure product as a white oil (74.4 mg, 48%, 0.23 mmol)

$C_{17}H_{28}O_3S$ (312.46 g/mol)

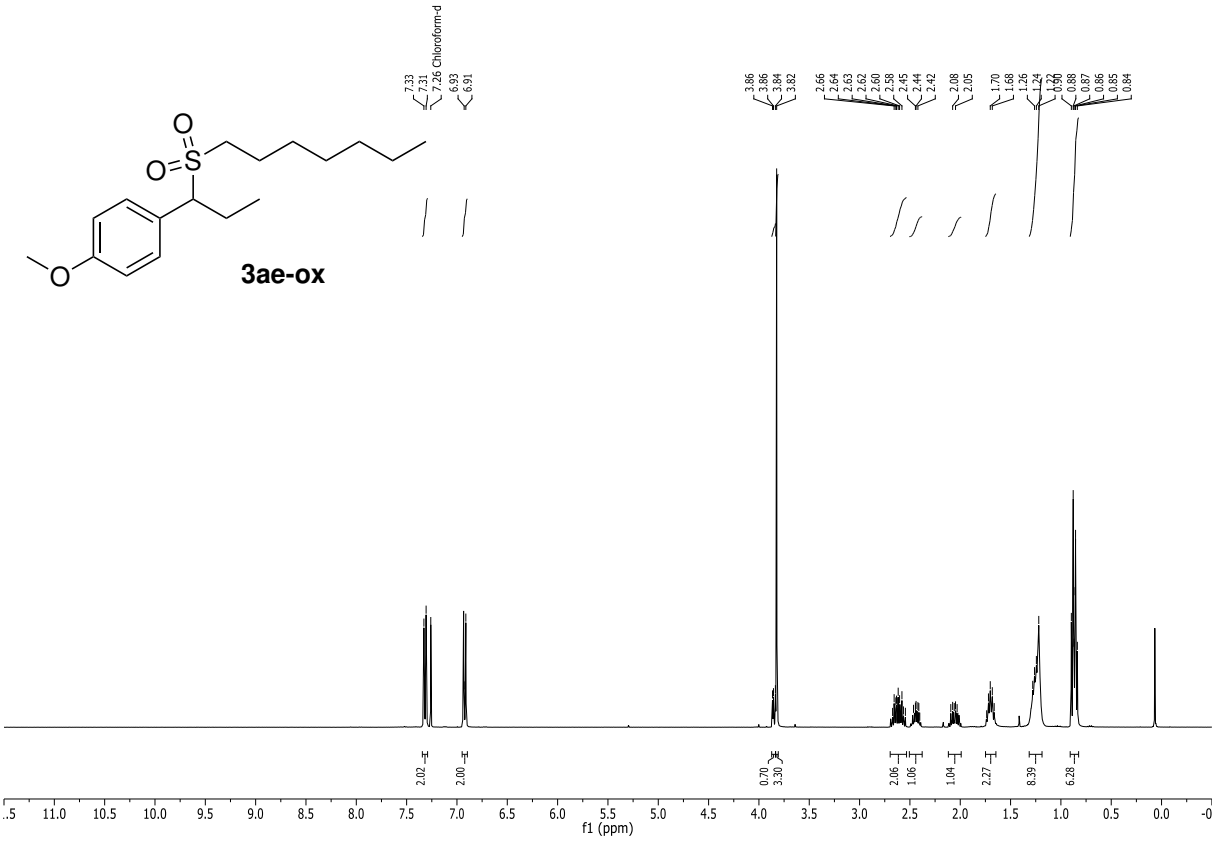
R_f : 0.3 (hexane/Et_2O 75:25)

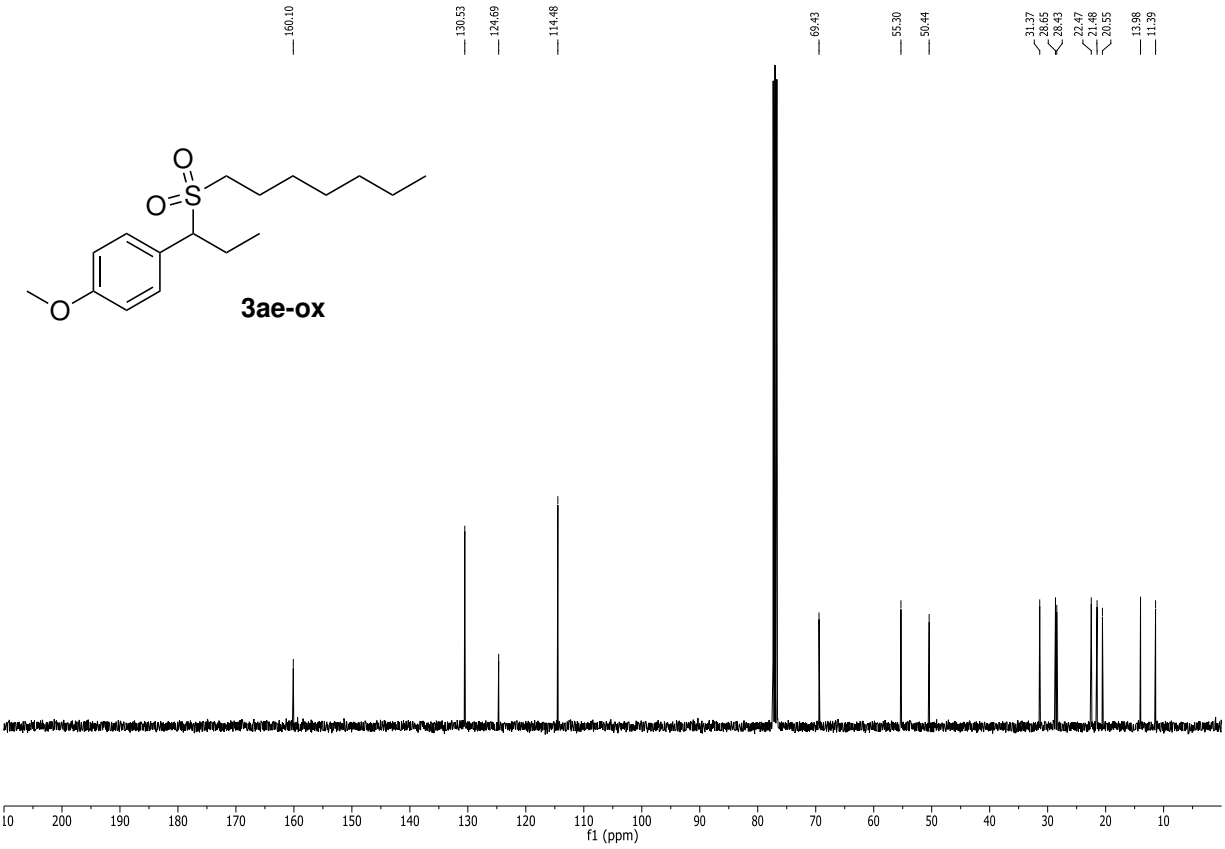
^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.29 (m, 2H), 6.96 – 6.88 (m, 2H), 3.86 (d, *J* = 3.7 Hz, 1H), 3.82 (s, 3H), 2.62 (qdd, *J* = 13.7, 8.7, 7.5 Hz, 2H), 2.44 (dtt, *J* = 13.6, 7.4, 3.7 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.75 – 1.65 (m, 2H), 1.32 – 1.17 (m, 8H), 0.87 (dt, *J* = 9.0, 7.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 130.5, 124.6, 114.4, 69.4, 55.3, 50.4, 31.3, 28.6, 28.4, 22.4, 21.4, 20.5, 13.9, 11.3.

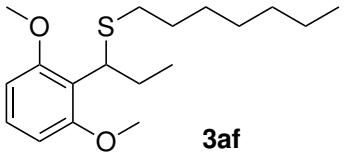
IR (ATR) $\tilde{\nu}$ (cm-1): 2929, 2855, 1714, 1610, 1513, 1461, 1290, 1252, 1178, 1129, 1033, 913, 830, 731.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 335.16514 found 335.16570


7.33
7.31
7.26 Chloroform-d
6.93
6.91
3.86
3.86
3.84
3.82
2.66
2.64
2.63
2.62
2.60
2.58
2.45
2.44
2.42
2.08
2.05
1.70
1.68
1.26
1.24
0.90
0.88
0.87
0.86
0.85
0.84
3ae-ox
2.02
2.00
0.70
3.30
2.06
1.06
1.04
2.27
8.39
6.28
f1 (ppm)


160.10
130.53
124.69
114.48
69.43
55.30
50.44
31.37
28.65
28.43
22.47
21.48
20.55
13.98
11.39
3ae-ox
f1 (ppm)

(1-(2,6-dimethoxyphenyl)propyl)(heptyl)sulfane (**3af**)



3af

The compound **3af** was synthesized from 2-allyl-1,3-dimethoxybenzene (0.5 mmol, 1 equiv, 89 mg) and heptane-1-thiol (0.55 mmol, 1.1 equiv, 72.6 mg) following General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes) then 2. hexane/diethylether 94:6) and obtained as a colorless oil (49.6 mg, 0.16 mmol, 32%).

$C_{18}H_{30}O_2S$ (310.50 g/mol)

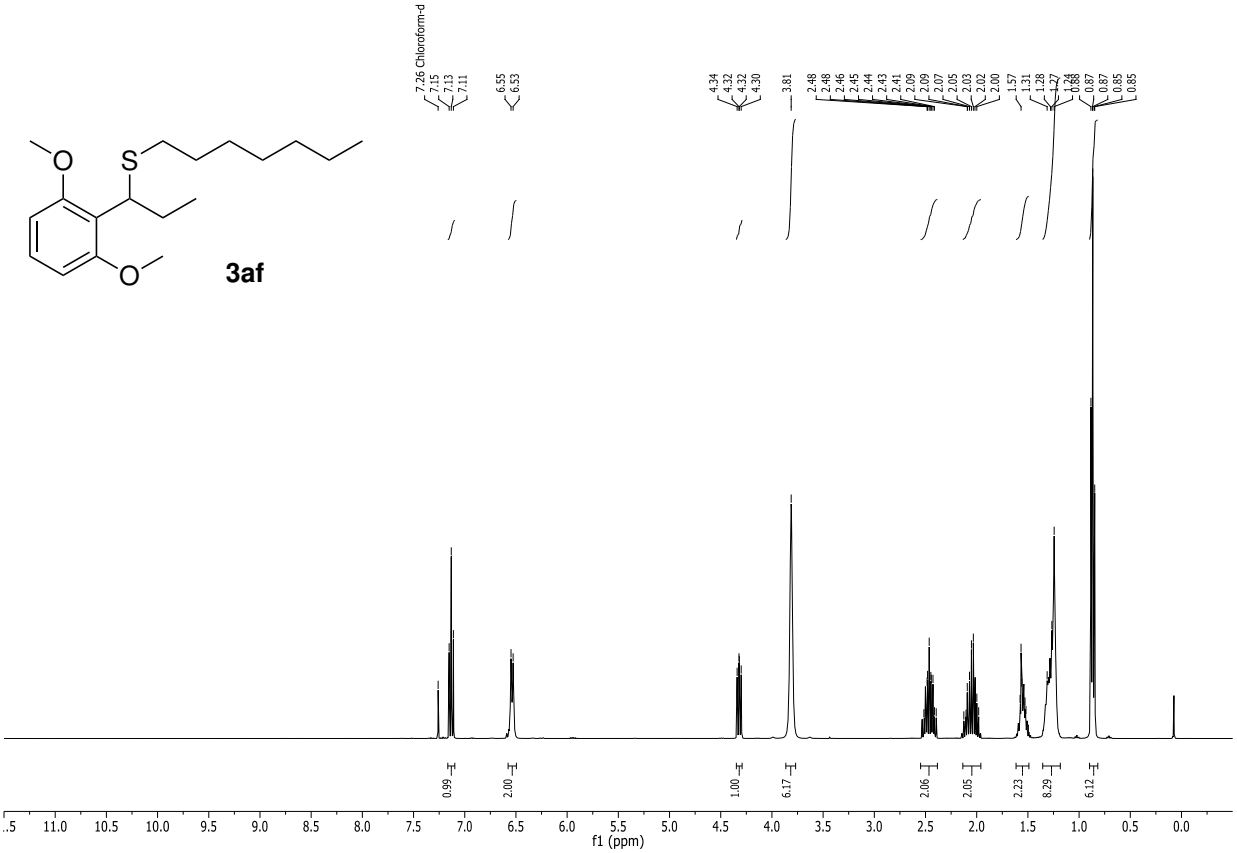
R_f : 0.35 (hexane/Et_2O 90:10)

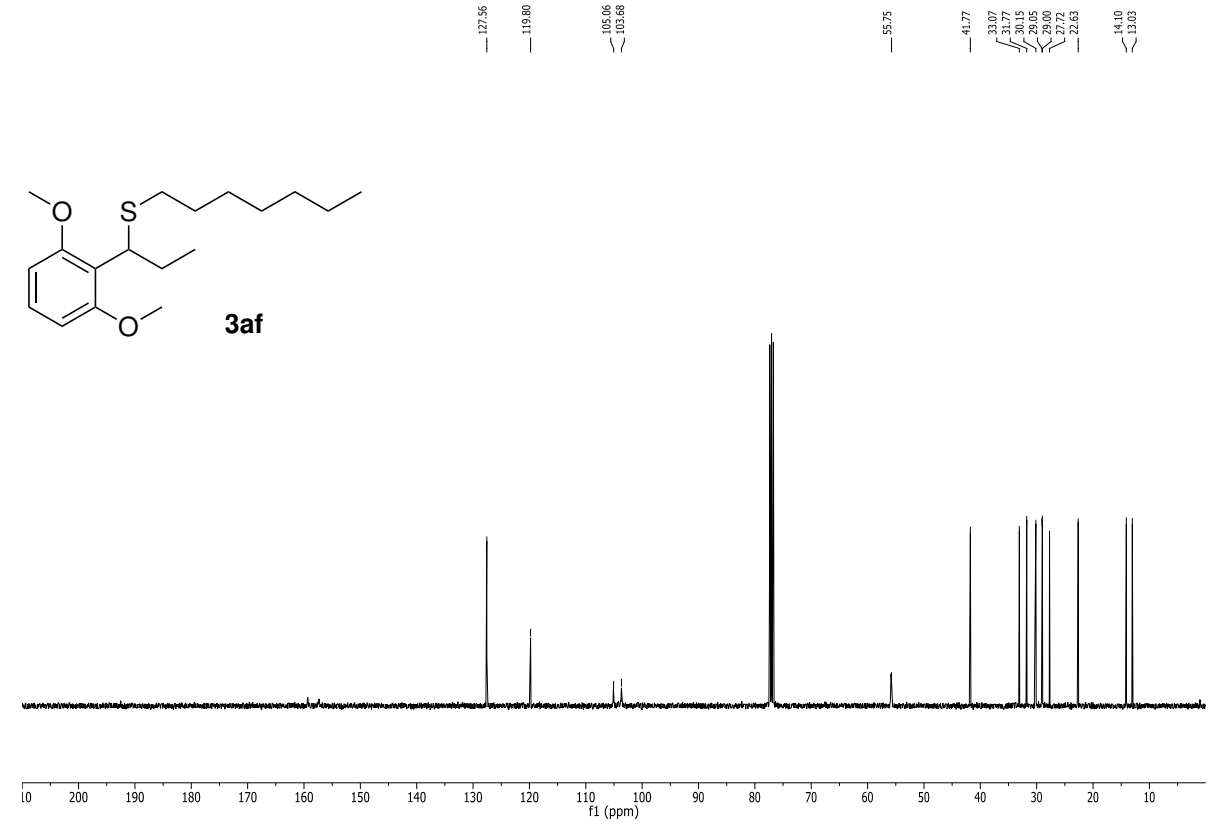
^{1}H NMR (400 MHz, Chloroform-d): δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 2H), 4.32 (dd, *J* = 8.6, 7.2 Hz, 1H), 3.81 (s, 6H), 2.55 – 2.37 (m, 2H), 2.16 – 1.92 (m, 2H), 1.61 – 1.48 (m, 2H), 1.35 – 1.20 (m, 8H), 0.90 – 0.82 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.5, 119.8, 105.0, 103.6, 55.7, 41.7, 33.0, 31.7, 30.1, 29.0, 29.0, 27.7, 22.6, 14.1, 13.0.

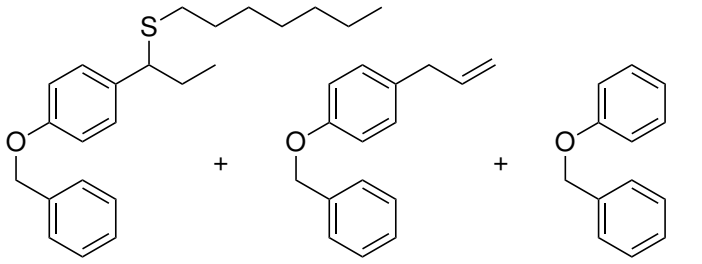
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2855, 2955, 2922, 1591, 1472, 1259, 1110, 1036, 1077, 881, 834, 779.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 333.18587 found 333.18615


7.26 Chloroform-d
7.15
7.13
7.11
6.55
6.53
4.34
4.32
4.32
4.30
3.81
2.48
2.48
2.46
2.45
2.44
2.43
2.41
2.09
2.09
2.07
2.05
2.03
2.02
2.00
1.57
1.31
1.28
1.27
1.24
0.88
0.87
0.87
0.85
0.85
O
S
O
3af
0.99
2.00
1.00
6.17
2.06
2.05
2.23
8.29
6.12
f1 (ppm)


127.56
119.80
105.06
103.68
55.75
41.77
33.07
31.77
30.15
29.05
29.00
27.72
22.63
14.10
13.03
O
S
O
3af
f1 (ppm)

(1-(4-(benzyloxy)phenyl)propyl)(heptyl)sulfane (**3ag**)



3ag **1g** **1g'**

The compound **3ag** was synthesized from 1-allyl-4-(benzyloxy)benzene (0.50 mmol, 112.1 mg, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A with the following changes) Palladium acetate **L1** (11.5 mg, 0.045 mmol) CF_3SO_3H (4.2 µL, 0.16 mmol)) from as a yellow oil. (96.27 mg, 0.26 mmol, 54%) and was isolated as a mixture along with 2g2 and 2g3. Purification was attempted using Preparative TLC using hexane as the mobile phase. (Due to presence of reactants after attempts to purify the compound, the NMR contains additional signals corresponding to 2g2 and 2g3. The exact signals for the compound were not assigned as it is unclear with the multiple overlaps observed in the spectrum).

$C_{23}H_{32}OS$ (356.56 g/mol)

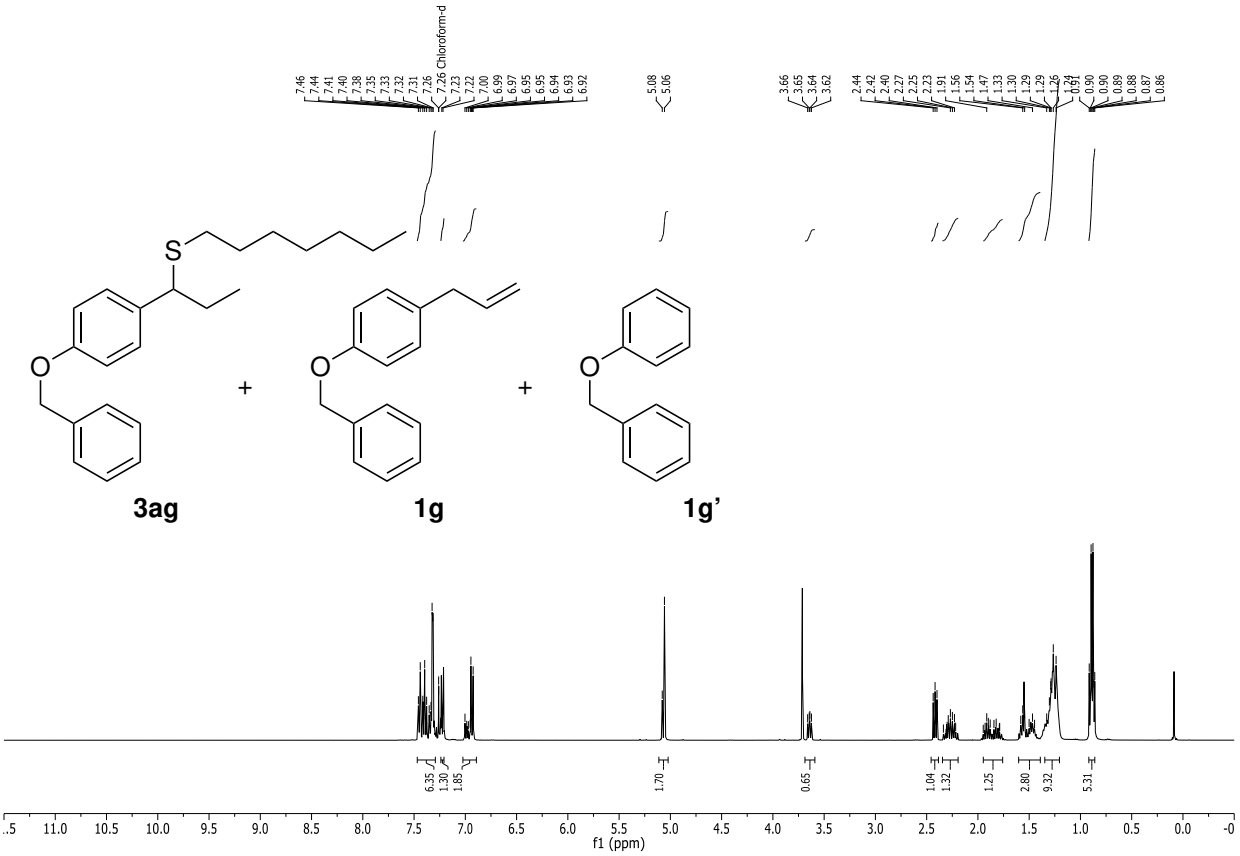
R_f: 0.42 (hexane: Et_2O 97.5:2.5)

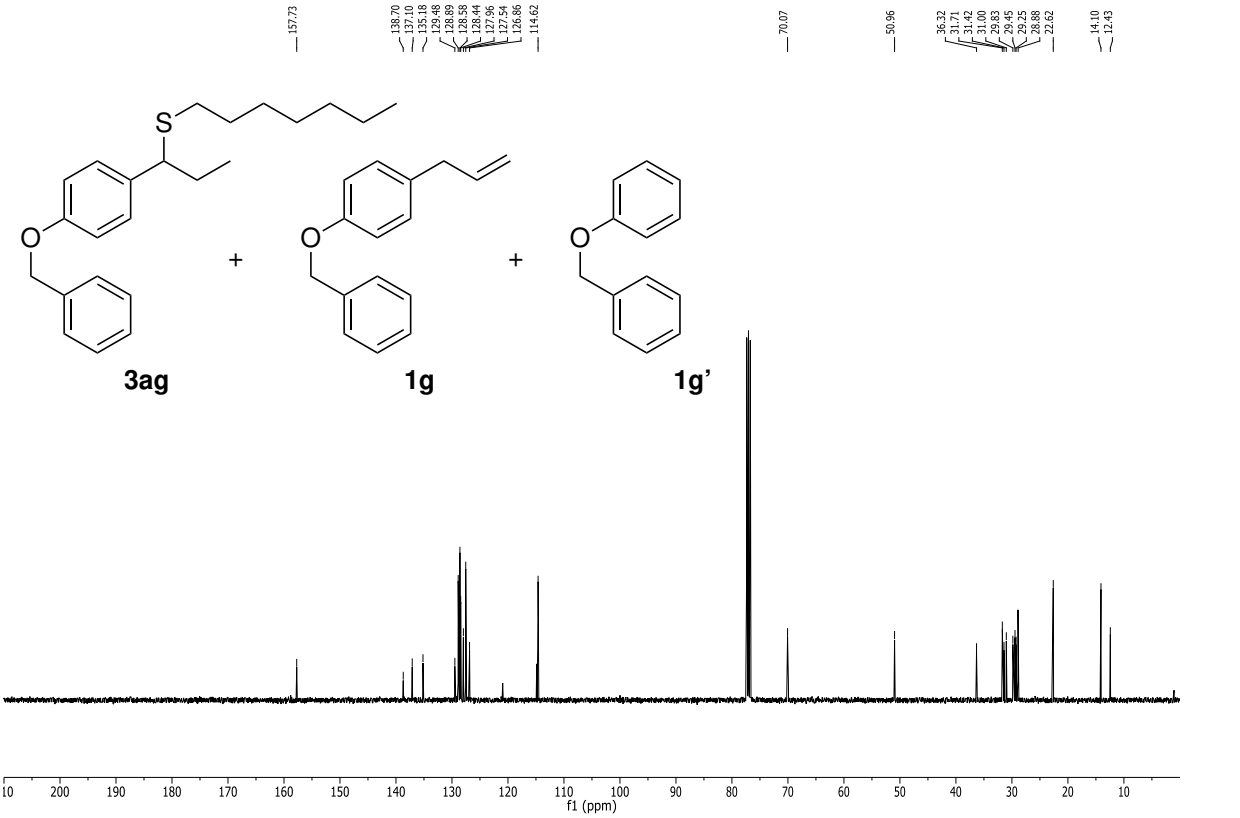
^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 – 7.30 (m, 6H), 7.24 – 7.12 (m, 2H), 6.98 – 6.84 (m, 2H), 5.02 (d, *J* = 8.6 Hz, 2H), 3.66 (s, 1H), 3.59 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.37 (d, *J* = 7.3 Hz, 1H), 2.28 – 2.11 (m, 1H), 1.90 – 1.68 (m, 1H), 1.58 – 1.41 (m, 3H), 1.33 – 1.11 (m, 10H), 0.89 – 0.77 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 138.7, 137.1, 135.1, 129.4, 128.8, 128.5, 128.4, 127.9, 127.5, 126.8, 114.6, 70.0, 50.9, 36.3, 31.7, 31.4, 31.0, 29.8, 29.4, 29.2, 28.8, 22.6, 14.1, 12.4.

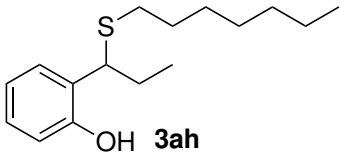
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 3030, 2899, 1610, 1505, 1453, 1237, 1174, 913, 805, 857, 730

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 379.20661 found: 379.20709


Chloroform-d
3ag
1g
1g'
f1 (ppm)


3ag
1g
1g'
f1 (ppm)

2-(1-(heptylthio)propyl)phenol (**3ah**)



3ah

The compound **3ah** was synthesized from 2-allylphenol (67.08 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes) then 2. hexane/diethylether 95:5) as a yellow oil (63.8 mg, 0.24 mmol, 48%). The reaction was carried out for 24 hours at 50 °C.

$C_{16}H_{26}OS$ (266.44 g/mol)

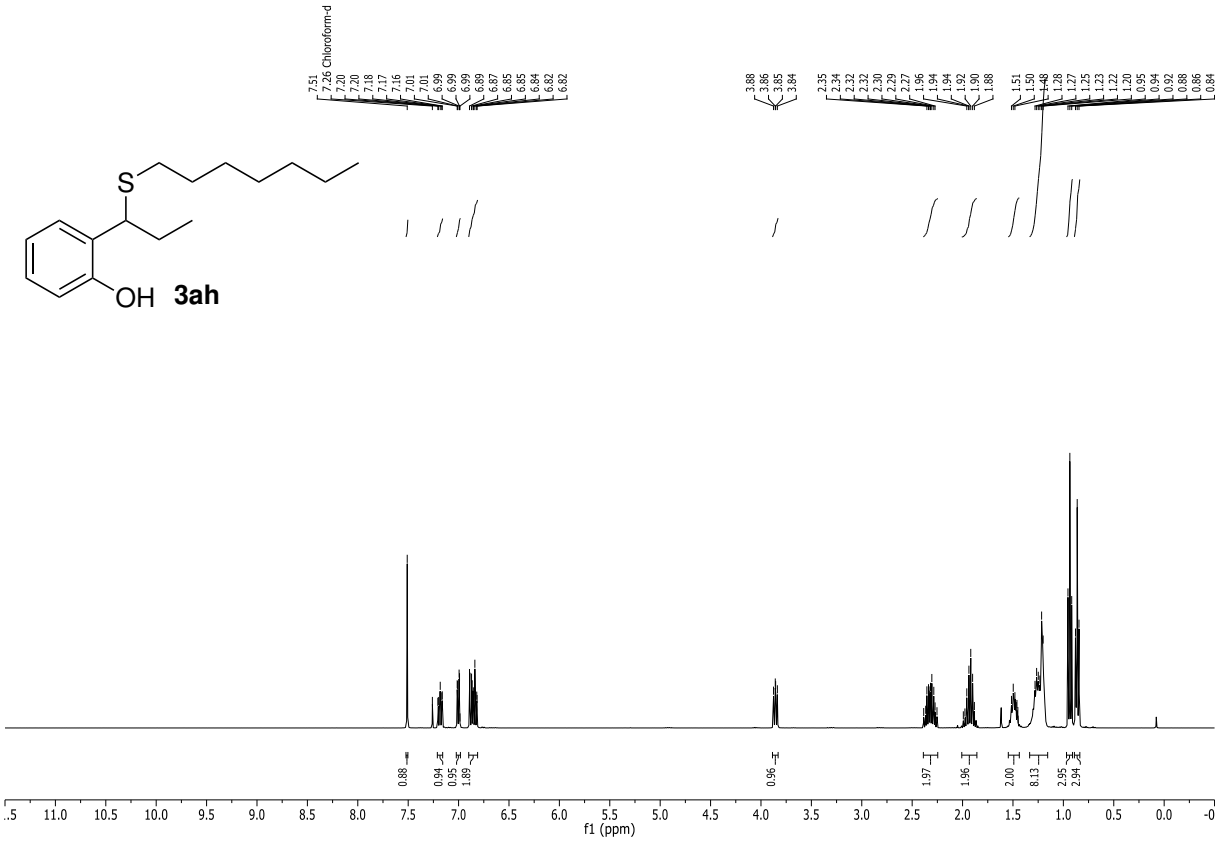
R_f : 0.47 (hexane/diethylether 90:10)

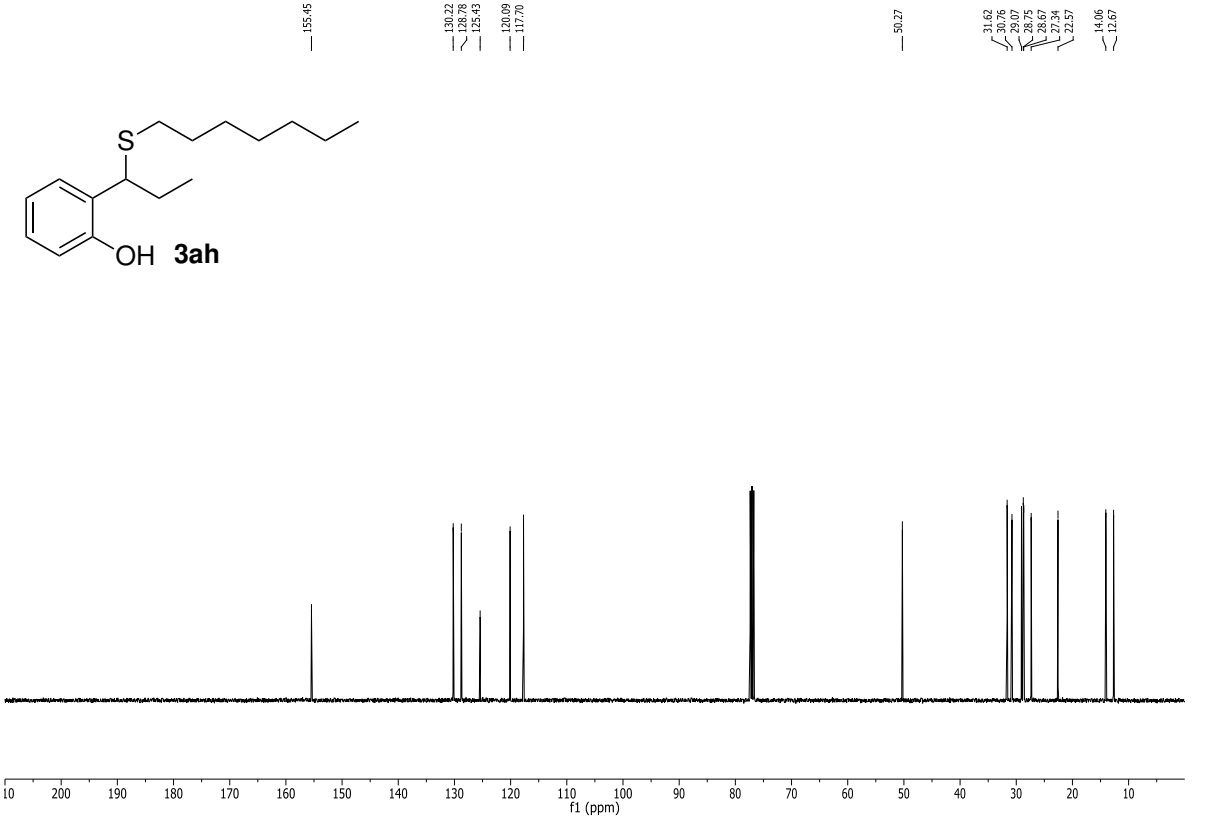
^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 (s, 1H), 7.18 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.90 – 6.81 (m, 2H), 3.86 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.39- 2.34 (m2H), 2.00 – 1.86 (m, 2H), 1.54-1.44 (m, 2H), 1.34 – 1.17 (m, 8H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 130.2, 128.8, 125.4, 120.1, 117.7, 50.3, 31.6, 30.7, 29.1, 28.7, 28.7, 27.3, 22.5, 14.0, 12.6.

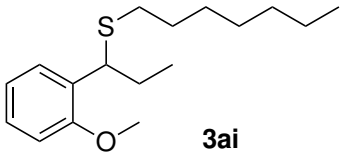
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3272, 2955, 2922, 2855, 1580, 1483, 1453, 1356, 1259, 1107, 1039, 752, 864

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 289.15966, found: 289.15978


Chloroform-d
S
OH
3ah
f1 (ppm)


S
OH
3ah
f1 (ppm)

heptyl(1-(2-methoxyphenyl)propyl)sulfane (**3ai**)



3ai

The compound **3ai** was synthesized from 2-methoxy-1-allylbenzene (74 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The crude product was purified by column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes then 2. hexane/diethylether 98:2) and isolated as a yellow oil (96.6 mg, 0.34 mmol, 69%).

$C_{17}H_{28}OS$ (280.47 g/mol)

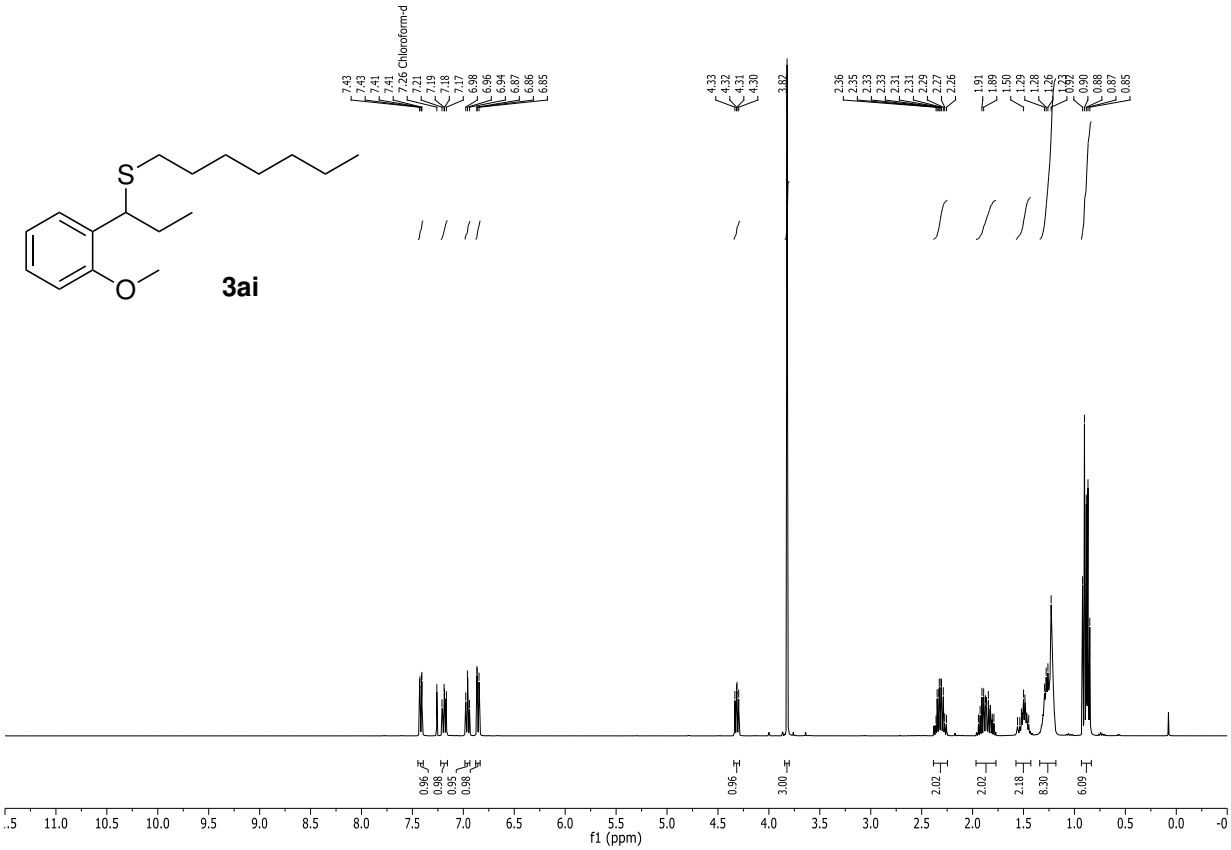
R_f: 0.14 (hexane/diethylether 99:1)

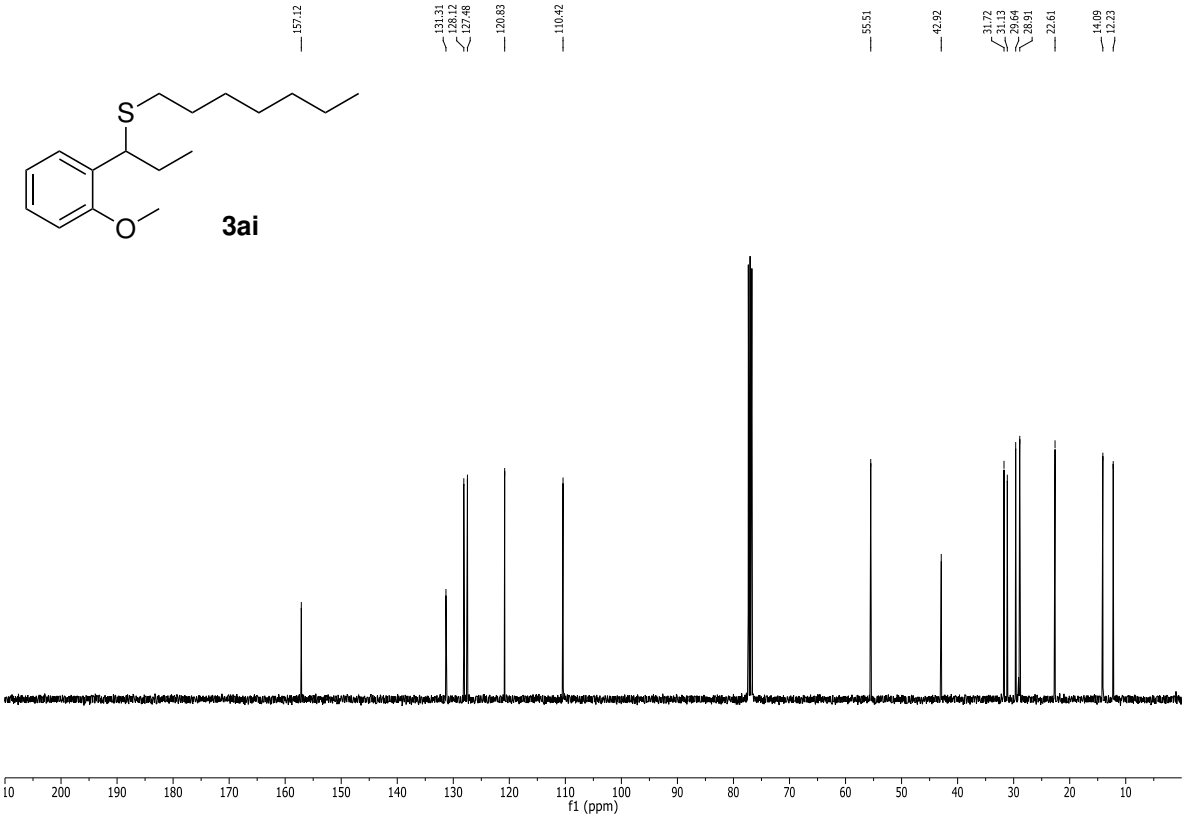
^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.32 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.82 (s, 3H), 2.38 – 2.24 (m, 2H), 1.96 – 1.77 (m, 2H), 1.57 – 1.43 (m, 2H), 1.32 – 1.17 (m, 8H), 0.94 – 0.84 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 131.3, 128.1, 127.4, 120.8, 110.4, 55.5, 42.9, 31.7, 31.1, 29.6, 28.9, 22.6, 14.2, 12.2.

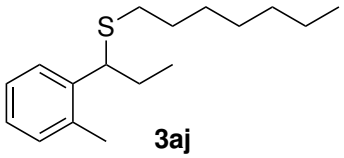
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2922, 1599, 1461, 1487, 1237, 1285, 1145, 1028, 886, 749

HR-MS (ESI): calc. for $[M+Na]^+$ m/z 303.17531, found 303.17550


Chloroform-d
3ai
f1 (ppm)


3ai
f1 (ppm)

heptyl(1-(o-tolyl)propyl)sulfane (**3aj**)



3aj

The compound **3aj** was synthesized from 2-allyl toluene (66.1 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (87.2 mg, 0.33 mmol, 65%). Preparative TLC was employed for separation and isolation using n-hexane as the mobile phase.

$C_{17}H_{28}S$ (264.47 g/mol)

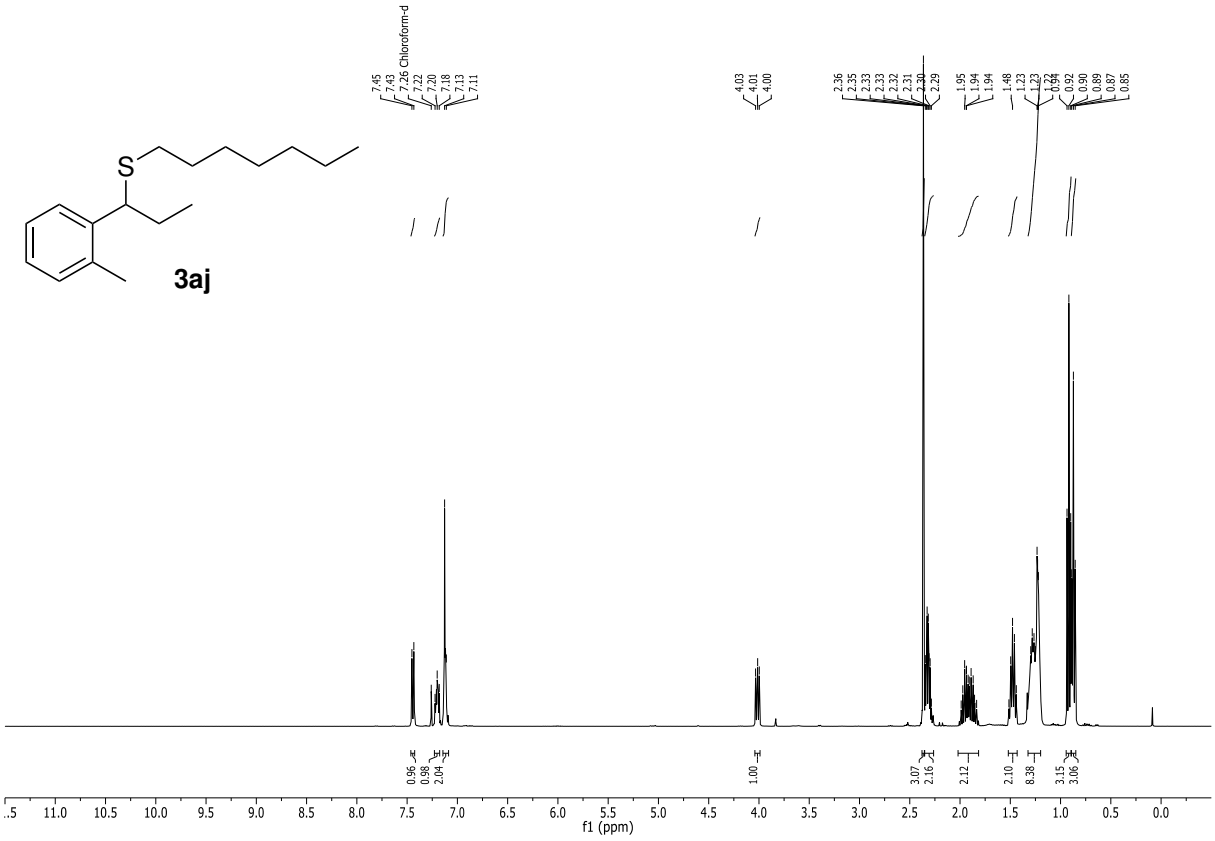
R_f: 0.72 (hexane 100).

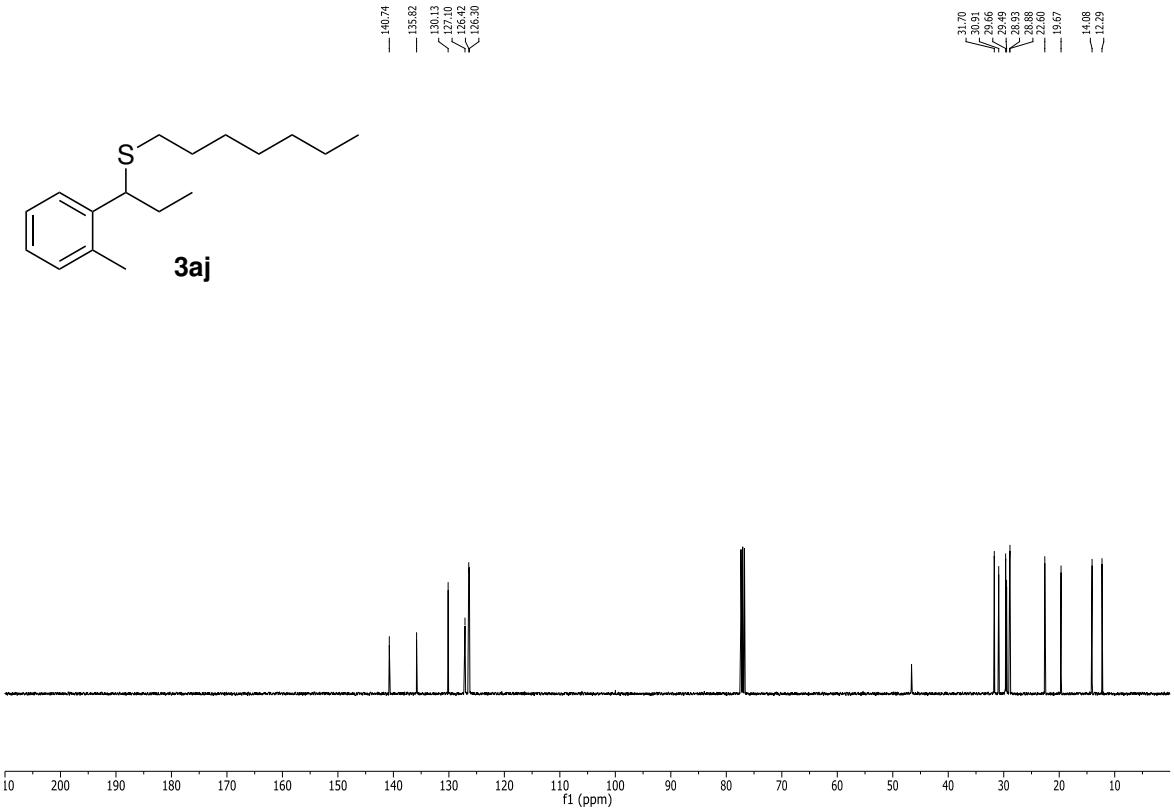
^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 – 7.09 (m, 2H), 4.02 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.36 (s, 3H), 2.35 – 2.26 (m, 2H), 2.00 – 1.82 (m, 2H), 1.52 – 1.43 (m, 2H), 1.34 – 1.19 (m, 8H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 135.8, 130.1, 127.1, 126.4, 126.3, 31.7, 30.9, 29.6, 29.4, 28.9, 28.8, 22.6, 19.6, 14.0, 12.2.

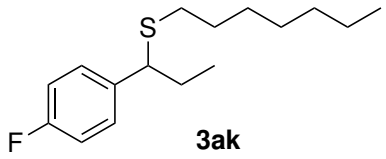
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3019, 2922, 2855, 1461, 1285, 1114, 1285, 1356, 1215, 1084, 842, 749.

HR-MS (EI) calculated for (m/z) : 264.19062, found: 264.18969


7.45
7.43
7.26 Chloroform-d
7.22
7.20
7.18
7.13
7.11
4.03
4.01
4.00
2.36
2.35
2.33
2.33
2.32
2.31
2.30
2.29
1.95
1.94
1.94
1.48
1.23
1.23
0.92
0.90
0.89
0.87
0.85
S
3aj
0.96
0.98
2.04
1.00
3.07
2.16
2.12
2.10
8.38
3.15
3.06
f1 (ppm)


140.74
135.82
130.13
127.10
126.42
126.30
31.70
30.91
29.46
29.49
28.93
28.88
22.60
19.67
14.08
12.29
S
3aj
f1 (ppm)

(1-(4-fluorophenyl)propyl)(heptyl)sulfane (**3ak**)



3ak

The compound **3ak** was synthesized from 4-allyl fluorobenzene (34.1 mg, 0.25 mmol, 1 equiv) and heptane-1-thiol (36.3 mg, 0.27 mmol, 1.1 equiv) following the General Procedure (A with the following changes) Palladium acetate (3.36 mg, 0.06 mmol) **L1** (18.08 mg, 0.12 mmol) CF_3SO_3H (4.2 µL, 0.16 mmol). The product was purified using preparative TLC as a yellow oil (54 mg, 0.2 mmol, 81%). The reaction was carried out for 64 hours at 50 °C.

$C_{16}H_{25}FS$ (268.43 g/mol)

R_f : 0.33 (hexane 100)

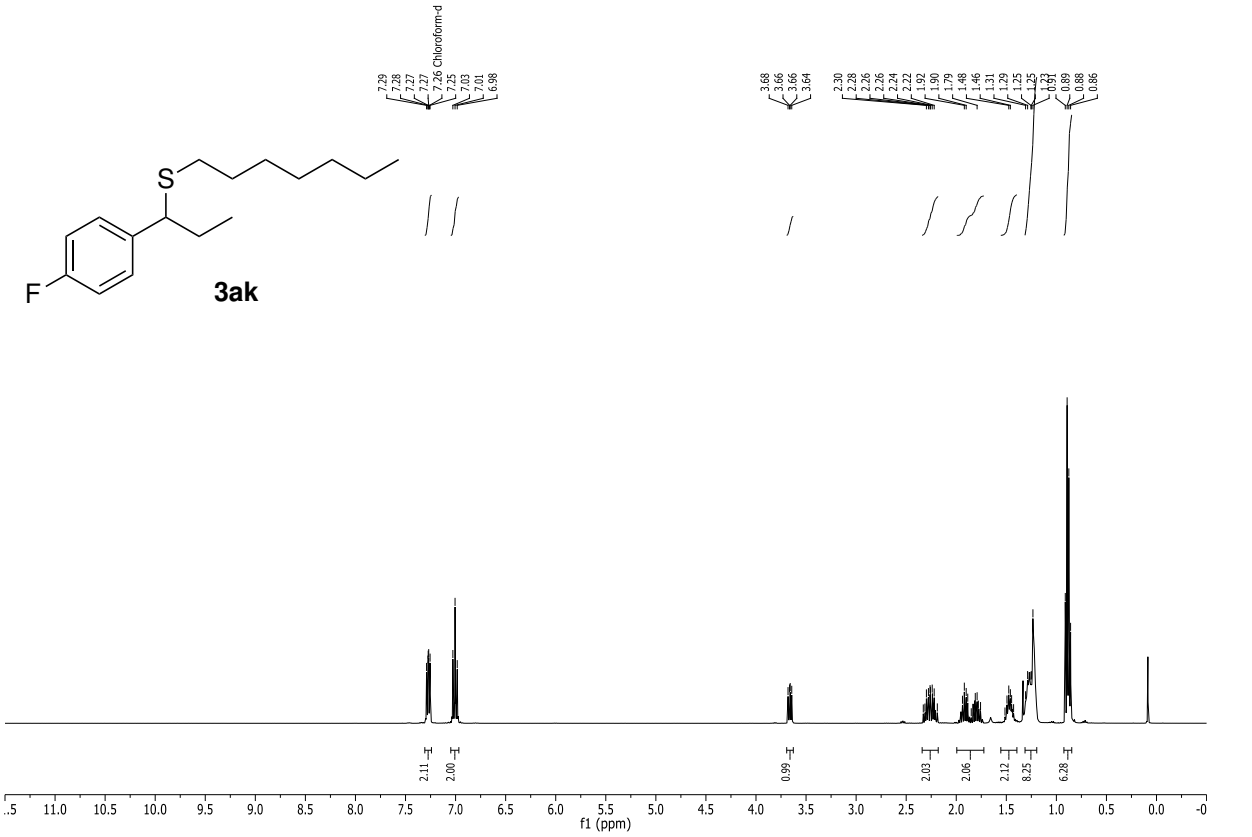
^{1}H NMR (400 MHz, Chloroform-d) δ 7.30-7.22 (m, 2H), 7.03 – 6.95 (m, 2H), 3.65 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.34 – 2.15 (m, 2H), 1.97 – 1.70 (m, 2H), 1.52 – 1.40 (m, 2H), 1.31 – 1.15 (m, 8H), 0.93 – 0.81 (m, 6H).

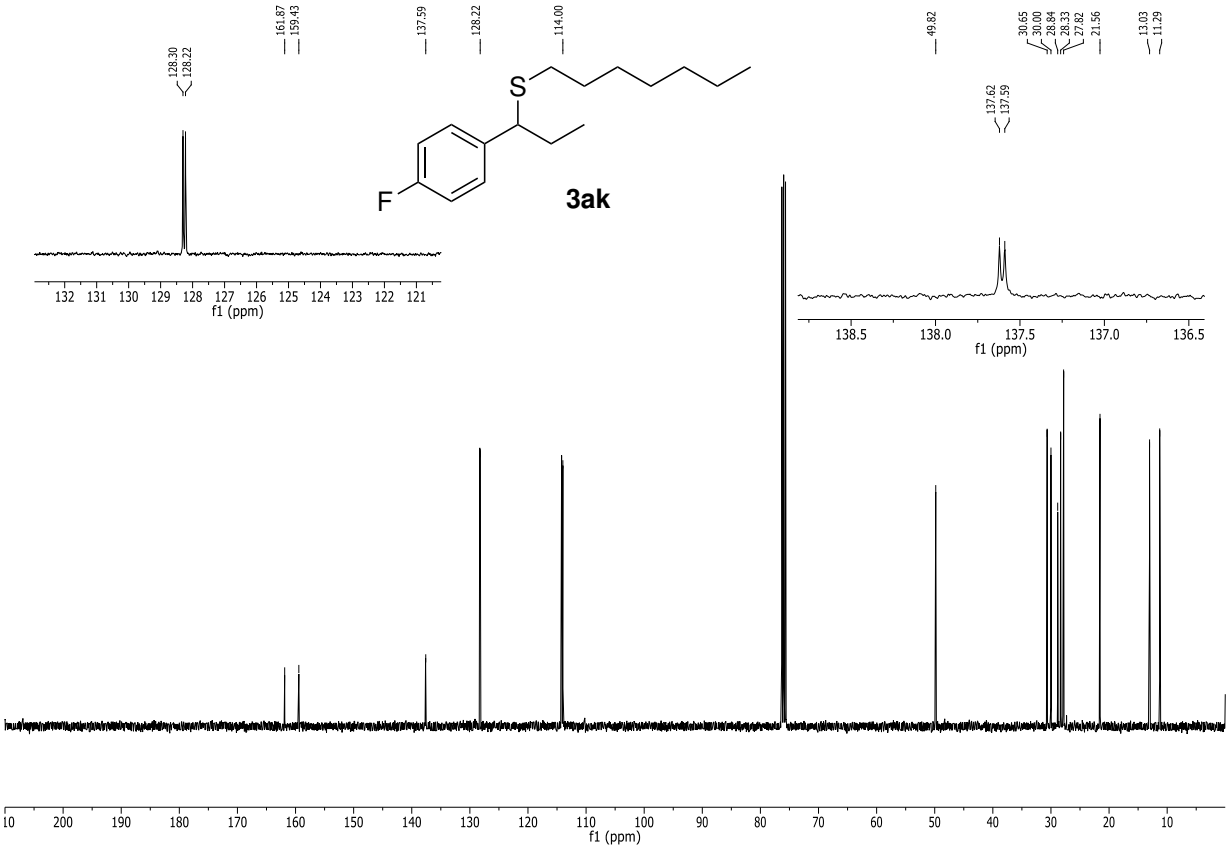
^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, Chloroform-d) δ 160.6 (d, *J* = 244.9 Hz), 137.6 (d, *J* = 3.2 Hz), 128.2 (d, *J* = 7.9 Hz), 114.1 (d, *J* = 21.3 Hz), 49.8, 30.6, 30.0, 28.8, 28.3, 27.8, 21.5, 13.0, 11.2.

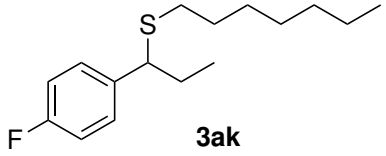
^{19}F NMR (376 MHz, Chloroform-d) δ -115.97 (tt, *J* = 8.7, 5.4 Hz).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3037, 2922, 2855, 1505, 1461, 1222, 1155, 775, 827.5, 723

HR-MS (EI): calculated (m/z): 268.16551, found: 268.16621


7.29
7.28
7.27
7.27
7.26 Chloroform-d
7.25
7.03
7.01
6.98
3.68
3.66
3.66
3.64
2.30
2.28
2.26
2.26
2.24
2.22
1.92
1.90
1.79
1.48
1.46
1.31
1.29
1.25
1.23
0.91
0.89
0.88
0.86
S
F
3ak
2.11
2.00
0.99
2.03
2.06
2.12
8.25
6.28
f1 (ppm)

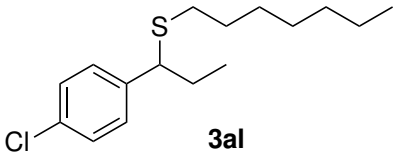

161.87
159.43
137.59
128.22
114.00
128.30
128.22
49.82
30.65
30.00
28.84
28.33
27.82
21.56
13.03
11.29
137.62
137.59
S
F
3ak
f1 (ppm)
f1 (ppm)
f1 (ppm)


S
F

3ak

-115.97
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

(1-(4-chlorophenyl)propyl)(heptyl)sulfane (**3al**)



3al

The compound **3al** was synthesized from 4-allyl-1-chlorobenzene (38.1 mg, 0.25 mmol, 1 equiv) and heptane-1-thiol (36.3 mg, 0.27 mmol, 1.1 equiv) following the General Procedure (A with the following changes) Palladium acetate (3.36 mg, 0.06 mmol) **L1** (18.08 mg, 0.12 mmol) CF_3SO_3H (4.2 µL, 0.16 mmol)). The product was purified using preparative TLC with hexane as the mobile phase and isolated as a yellow oil (42.0 mg, 0.29 mmol, 59% yield). The reaction was carried out for 64 hours at 50 °C

$C_{16}H_{25}ClS$ (284.88 g/mol)

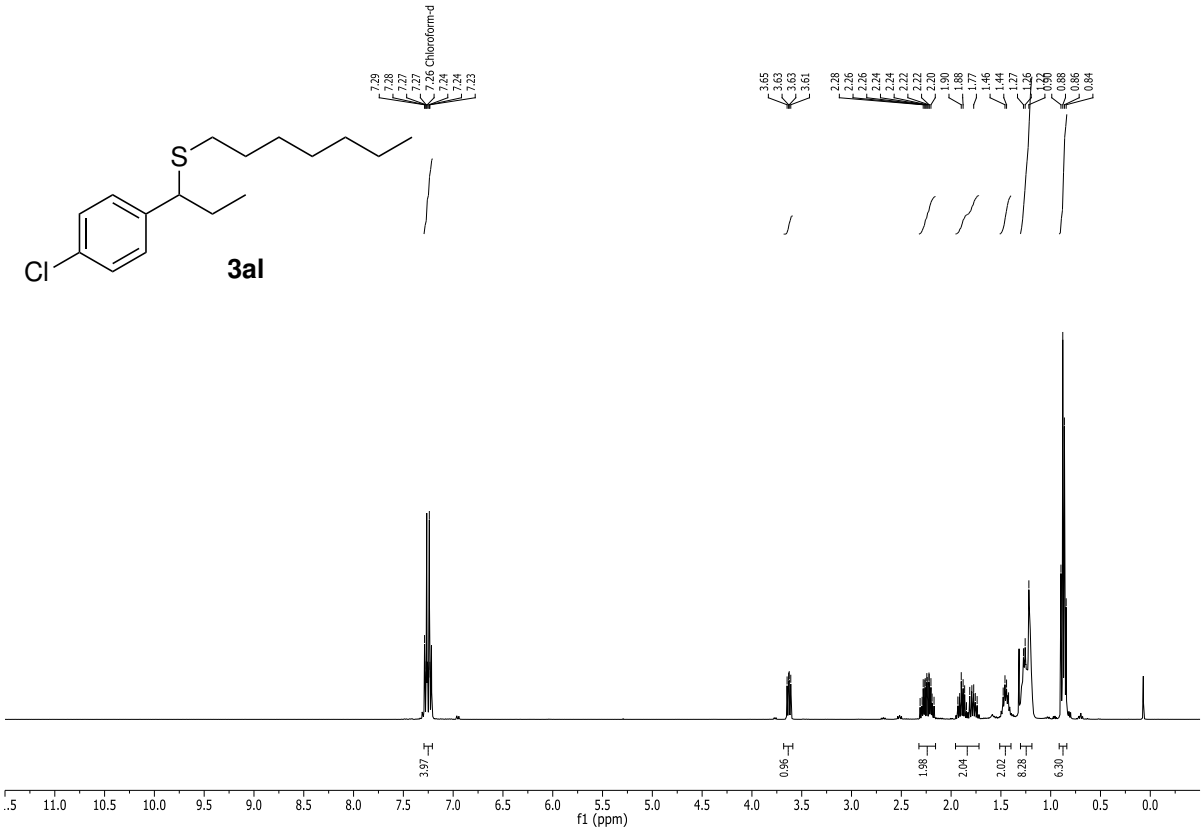
R_f : 0.41 (hexane 100)

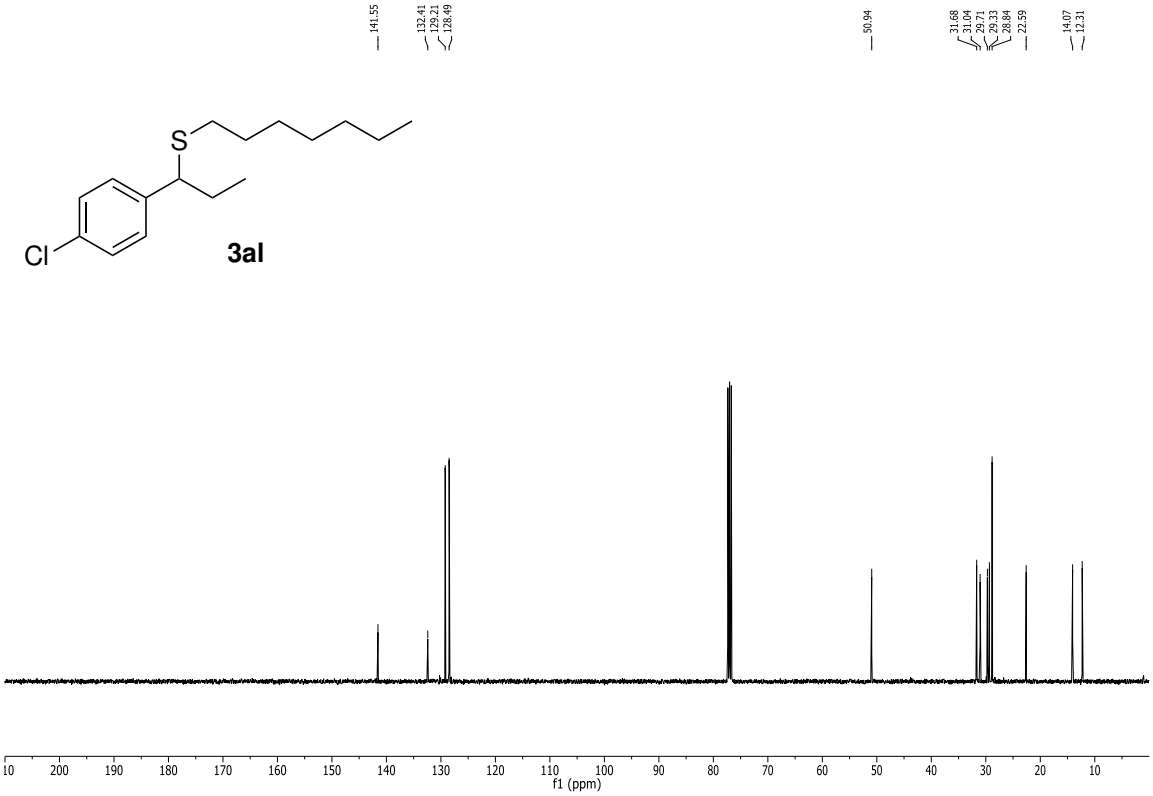
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29-7.21 (m, 4H), 3.63 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.33 – 2.15 (m, 2H), 1.96 – 1.70 (m, 2H), 1.51 – 1.39 (m, 2H), 1.31 – 1.15 (m, 8H), 0.92 - 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 132.4, 129.2, 128.4, 50.9, 31.7, 31.0, 29.7, 29.3, 28.8, 22.6, 14.1, 12.3.

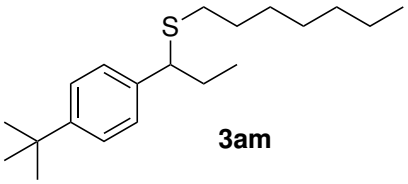
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 2855, 1490, 1457, 1405, 1088, 1013, 846, 816, 752

HR-MS (EI): calculated (m/z): 284.13600, found: 284.13309


7.29
7.28
7.27
7.27
7.26 Chloroform-d
7.24
7.24
7.23
3.65
3.63
3.63
3.61
2.28
2.26
2.24
2.24
2.22
2.22
2.20
1.90
1.88
1.77
1.46
1.44
1.27
1.26
1.22
0.90
0.88
0.86
0.84
S
Cl
3al
3.97
0.96
1.98
2.04
2.02
8.28
6.30
f1 (ppm)


141.55
132.41
129.21
128.49
50.94
31.68
31.04
29.71
29.33
28.84
22.59
14.07
12.31
S
Cl
3al
f1 (ppm)

(1-(4-(*tert*-butyl)phenyl)propyl)(heptyl)sulfane (**3am**)



3am

The compound **3am** was synthesized from 4-tert-butyl allyl benzene (87.1 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (110 mg, 0.36 mmol, 72% yield). Preparative TLC was employed for separation and isolation using hexane as the mobile phase (hexane: 100)

$C_{20}H_{34}S$ (306.55 g/mol)

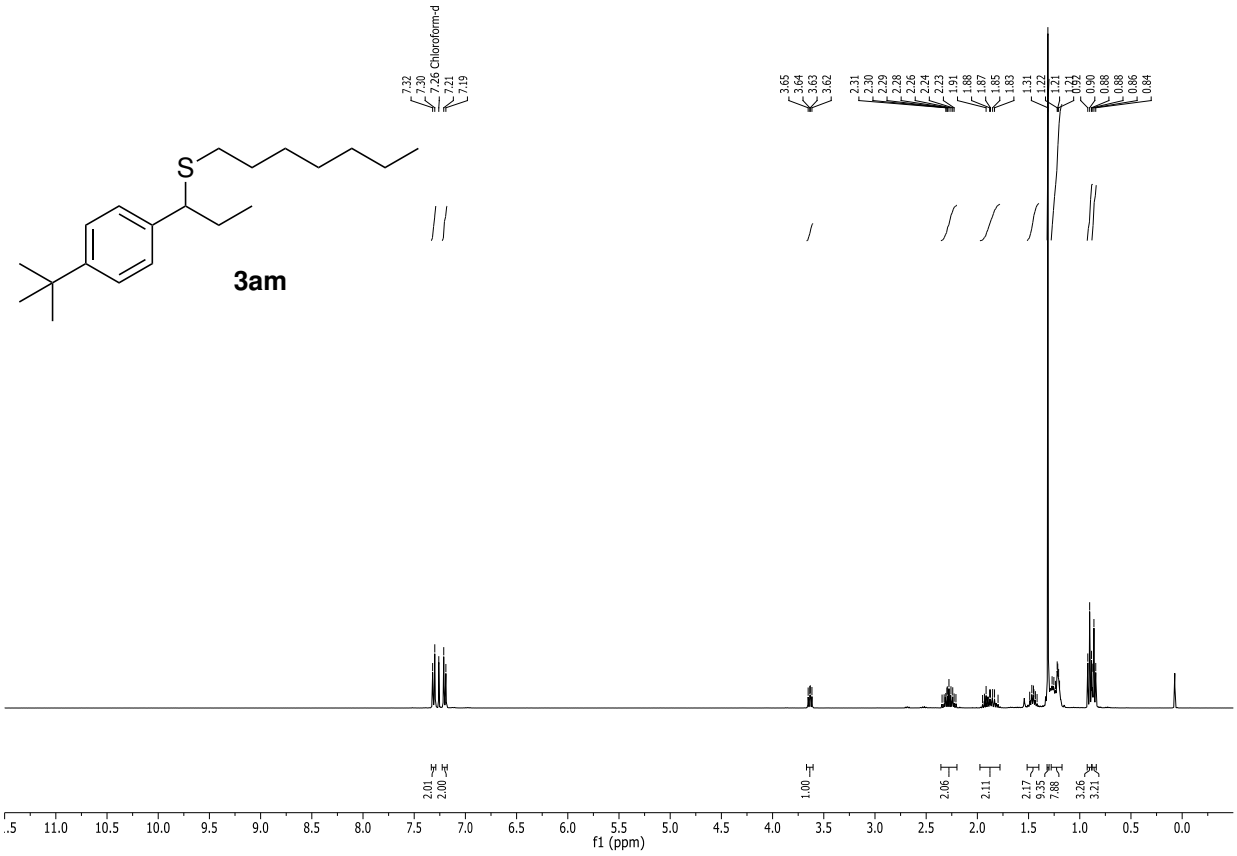
R_f : 0.52 (hexane/diethylether 99:01)

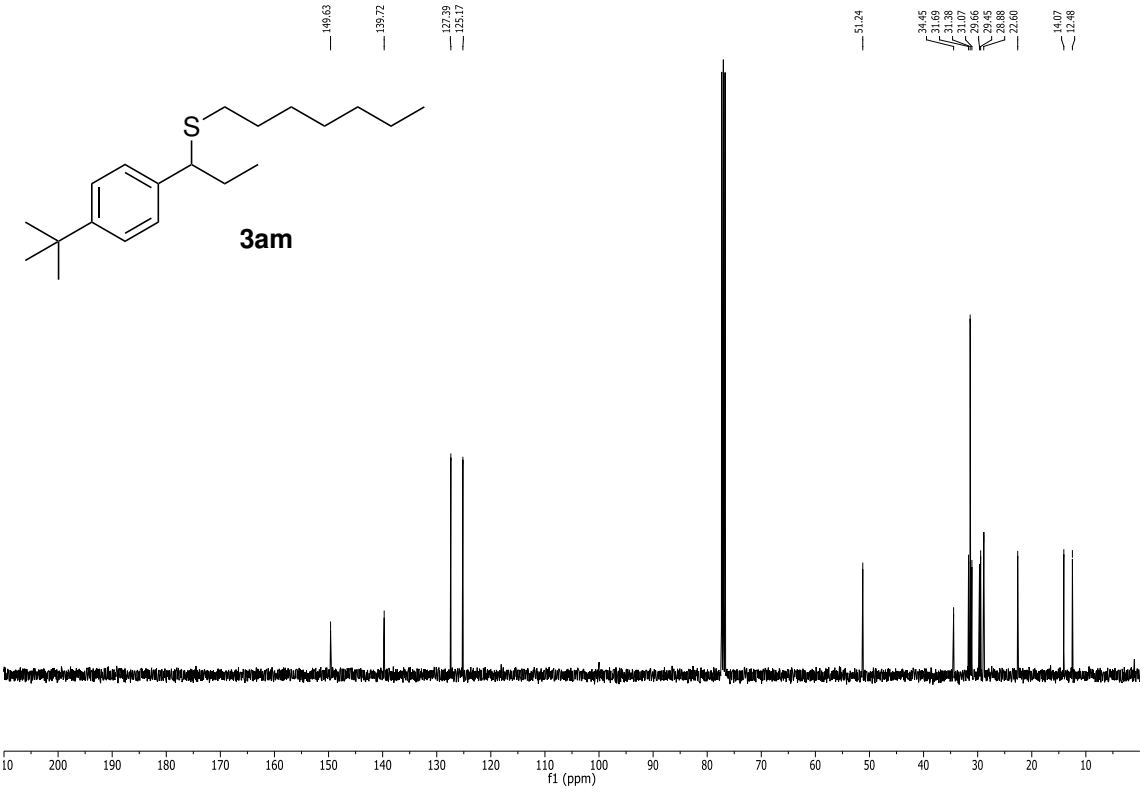
^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 – 7.29 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.18 (d, *J* = 8.4 Hz, 2H), 3.63 (dd, *J* = 8.4, 6.3 Hz, 1H), 2.36 – 2.19 (m, 2H), 1.97 – 1.79 (m, 2H), 1.46 (dtd, *J* = 7.8, 6.3, 1.5 Hz, 2H), 1.31 (s, 9H), 1.29 – 1.17 (m, 8H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 139.7, 127.4, 125.1, 51.2, 34.4, 31.7, 31.4, 31.0, 29.6, 29.4, 28.9, 22.6, 14.0, 12.5.

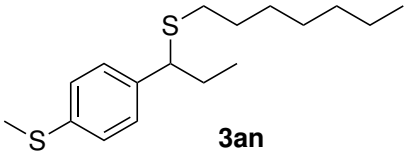
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2922, 2855, 1506, 1461, 1413, 1364, 1267, 1111, 1018, 820.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z 329.22734, found 329.22738


7.32
7.30
7.26 Chloroform-d
7.21
7.19
3.65
3.64
3.63
3.62
2.31
2.30
2.29
2.28
2.26
2.24
2.23
1.91
1.88
1.87
1.85
1.83
1.31
1.22
1.21
0.92
0.90
0.88
0.88
0.86
0.84
S
3am
2.01
2.00
1.00
2.06
2.11
2.17
9.35
7.88
3.26
3.21
f1 (ppm)


149.63
139.72
127.39
125.17
51.24
34.45
31.69
31.38
31.07
29.66
29.45
28.88
22.60
14.07
12.48
S
3am
f1 (ppm)

heptyl(1-(4-(methylthio)phenyl)propyl)sulfane (**3an**)



3an

The compound **3an** was synthesized following the General Procedure (A) from 1-(methylthio)-4-(2-propen-1-yl)-benzene (82.13 mg, 0.50 mmol, 1 equiv) and heptane-1-thiol (72.6 mg, 0.55 mmol, 1.1 equiv). The crude product was purified by flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the heptane-1-thiol elutes then 2. hexane/diethylether 98:2) and isolated as a yellow oil (106.6 mg, 0.36 mmol, 72%)

$C_{17}H_{28}S_2$ (296.53 g/mol)

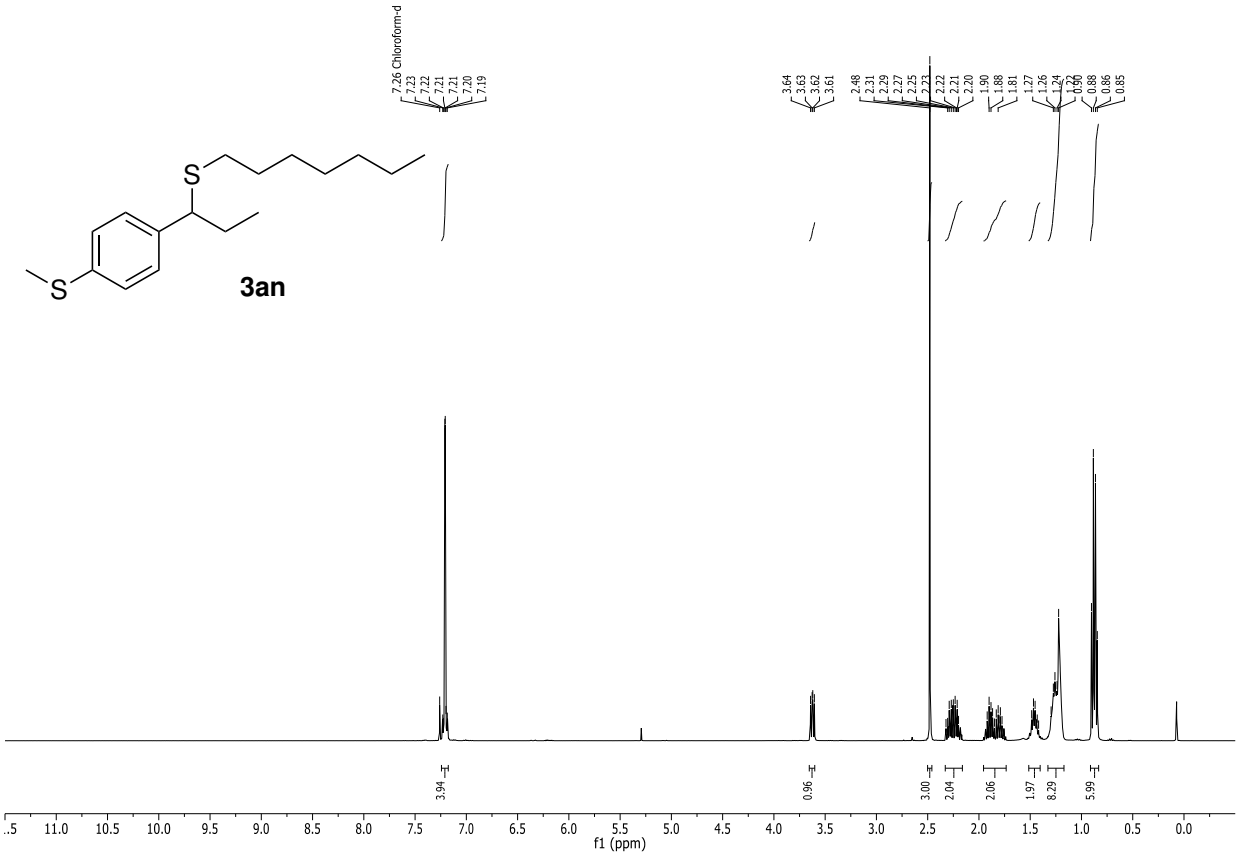
R_f : 0.26 (hexane/diethylether 99:1)

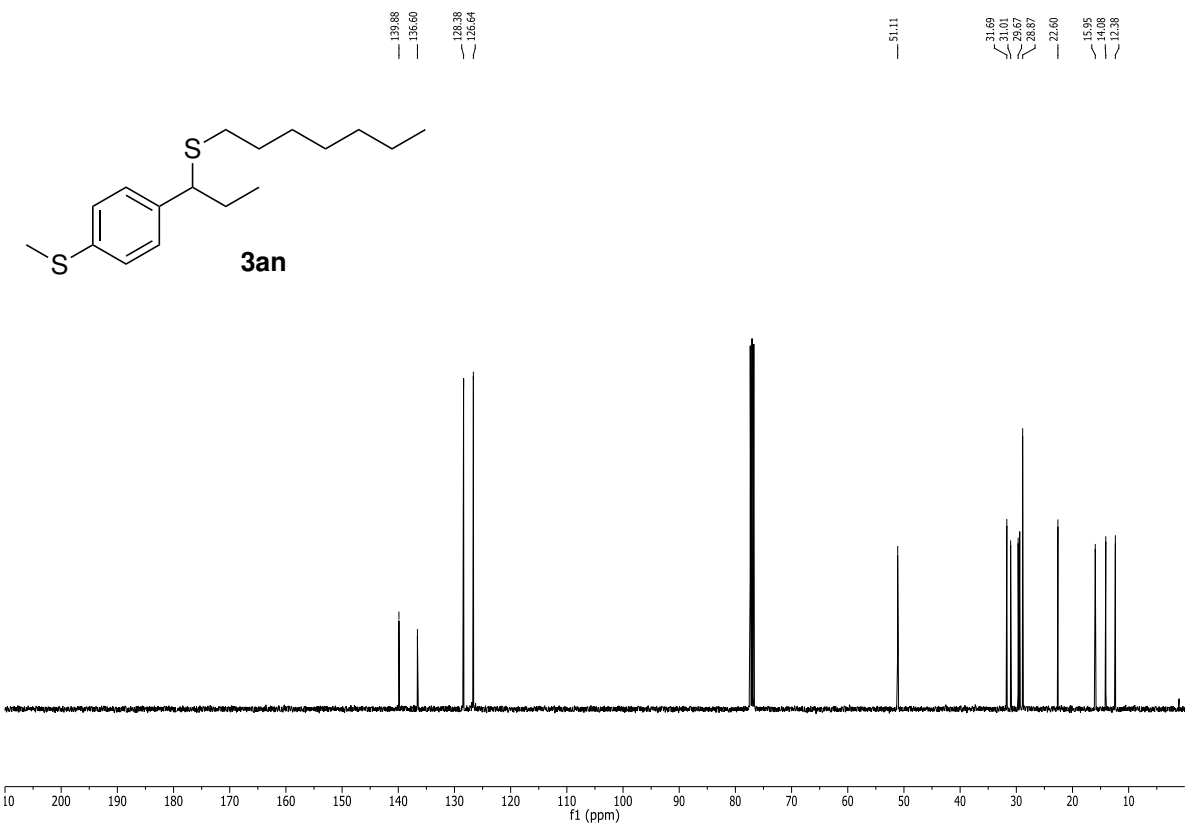
^{1}H NMR (400 MHz, Chloroform-d) δ 7.24 – 7.17 (m, 4H), 3.62 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.48 (s, 3H), 2.33 – 2.14 (m, 2H), 1.98 – 1.69 (m, 2H), 1.55 – 1.38 (m, 2H), 1.29 – 1.15 (m, 8H), 0.93 - 0.82 (m, , 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 136.6, 128.3, 126.6, 51.1, 31.6, 31.2, 29.6, 28.8, 22.6, 15.9, 14.1, 12.3.

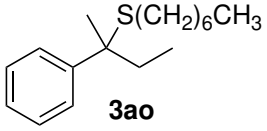
IR: (ATR) $\tilde{\nu}$ (cm^{-1}) 3019, 2955, 2855, 2922, 1595, 1457, 1490, 1375, 1092, 965, 842, 812, 752.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 319.15246, found: 319.15262


7.26 Chloroform-d
7.23
7.22
7.21
7.21
7.20
7.19
3.64
3.63
3.62
3.61
2.48
2.31
2.29
2.27
2.25
2.23
2.22
2.21
2.20
1.90
1.88
1.81
1.27
1.26
1.24
0.90
0.88
0.86
0.85
S
S
3an
3.94
0.96
3.00
2.04
2.06
1.97
8.29
5.99
f1 (ppm)


139.88
136.60
128.38
126.64
51.11
31.69
31.01
29.67
28.87
22.60
15.95
14.08
12.38
S
S
3an
f1 (ppm)

heptyl(2-phenylbutan-2-yl)sulfane (**3ao**):



3ao

The compound **3ao** was synthesized from but-3-en-2-ylbenzene (0.50 mmol, 1 equiv, 75 µL) and heptane-1-thiol (0.55 mmol, 1.1 equiv, 86 µL) following General Procedure (A). The following changes were made in the procedure: 5 mol% of $Pd(OAc)_2$ (0.025 mmol, 5.6 mg) was employed along with 10 mol% of **L1** (0.05 mmol, 23.7 mg) and 19 mol% of CF_3SO_3H (0.096 mmol, 8.5 µL). The reaction mixture was heated at 50 °C for 48 h. The compound was isolated using preparative TLC (Hexane 100%) and obtained as a yellow oil (51.4 mg, 0.19 mmol, 39%).

$C_{17}H_{28}S$ (264.47 g/mol)

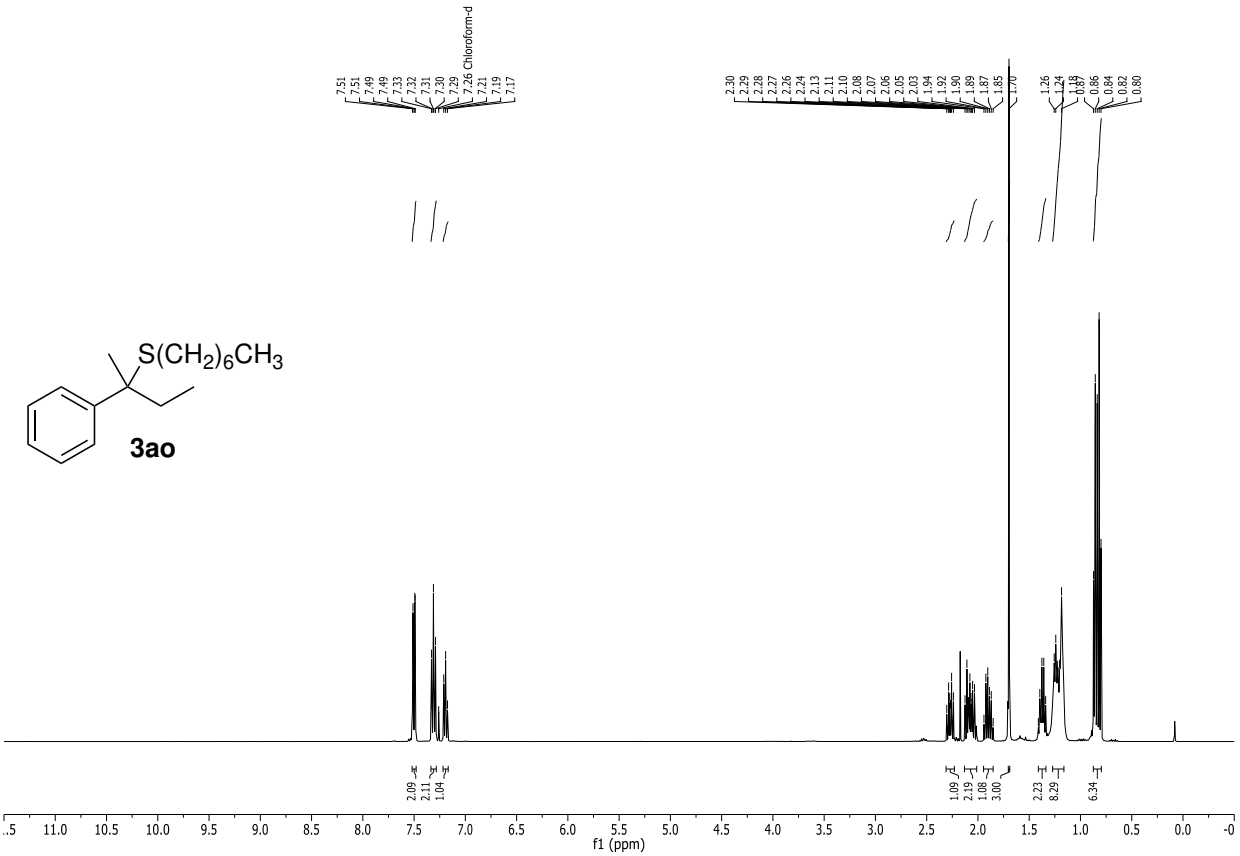
R_f : 0.6 (Hexane 100)

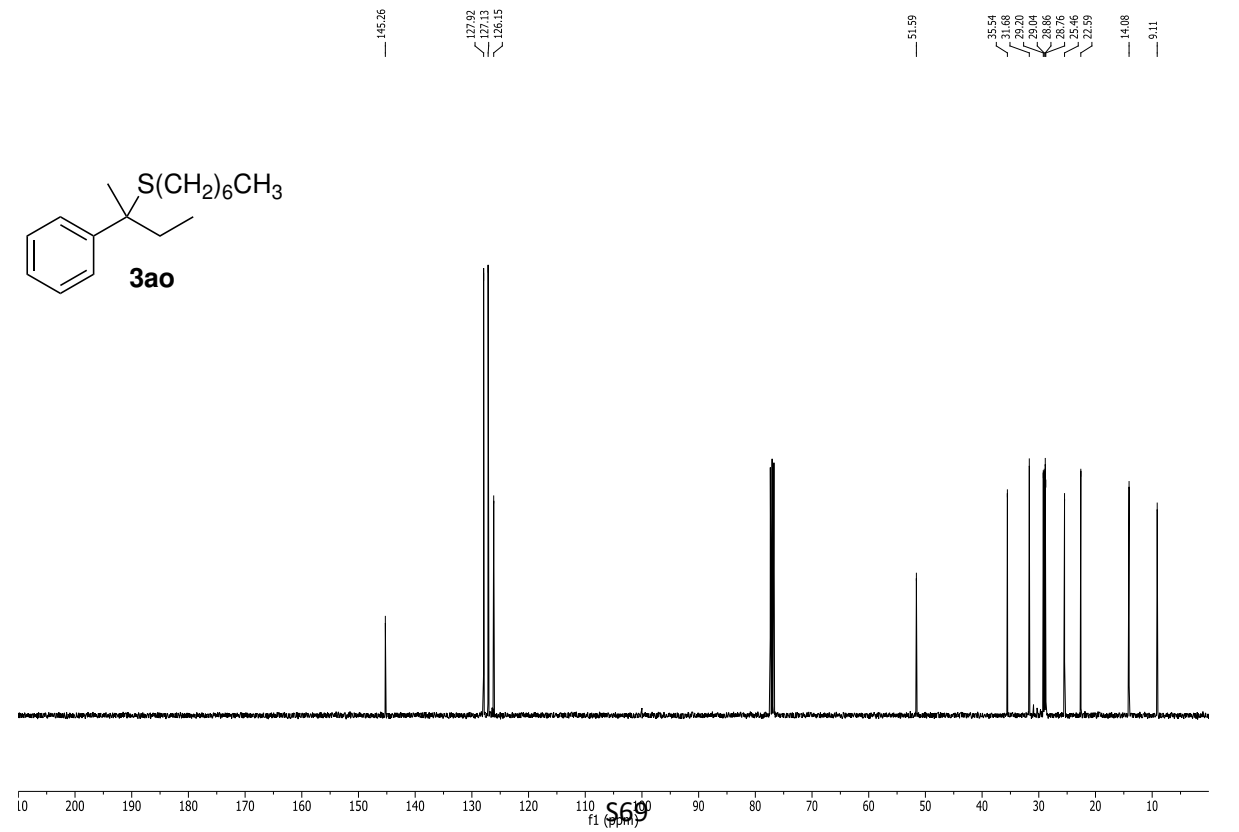
^{1}H NMR (400 MHz, Chloroform-d) δ 7.52 – 7.48 (m, 2H), 7.35 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 2.33 – 2.23 (m, 1H), 2.13 – 2.01 (m, 2H), 1.97 – 1.85 (m, 1H), 1.70 (s, 3H), 1.42 – 1.33 (m, 2H), 1.28 – 1.14 (m, 8H), 0.88 – 0.79 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 127.9, 127.1, 126.1, 51.5, 35.5, 31.6, 29.2, 29.0, 28.8, 28.7, 25.4, 22.5, 14.0, 9.1.

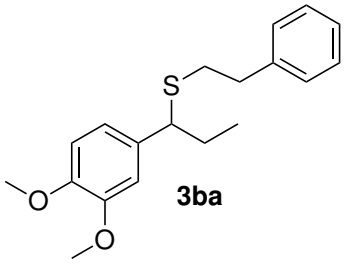
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2922, 2855, 1490, 1457, 1375, 1092, 1028, 745, 697.

HR-MS (ESI): calc. for $[M]^+$ m/z: 364.19062, found: 364.18837


7.51
7.51
7.49
7.49
7.33
7.32
7.31
7.30
7.29
7.26 Chloroform-d
7.21
7.19
7.17
2.30
2.29
2.28
2.27
2.26
2.24
2.13
2.11
2.10
2.08
2.07
2.06
2.05
2.03
1.94
1.92
1.90
1.89
1.87
1.85
1.70
1.26
1.24
0.88
0.86
0.84
0.82
0.80
S(CH2)6CH3
3ao
2.09
2.11
1.04
1.09
2.19
1.08
3.00
2.23
8.29
6.34
f1 (ppm)


145.26
127.92
127.13
126.15
51.59
35.54
31.68
29.20
29.04
28.86
28.76
25.46
22.59
14.08
9.11
S(CH2)6CH3
3ao
f1 (ppm)

(1-(3,4-dimethoxyphenyl)propyl)(phenethyl)sulfane (**3ba**)



3ba

The compound **3ba** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and 2-phenylethane thiol (76.0 mg, 0.55, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane : 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 90:10) and obtained as a yellow oil (107.6 mg, 0.34 mmol, 68% yield).

$C_{19}H_{24}O_2S$ (316.45 g/mol)

R_f : 0.3 (hexane : diethylether 90 : 10)

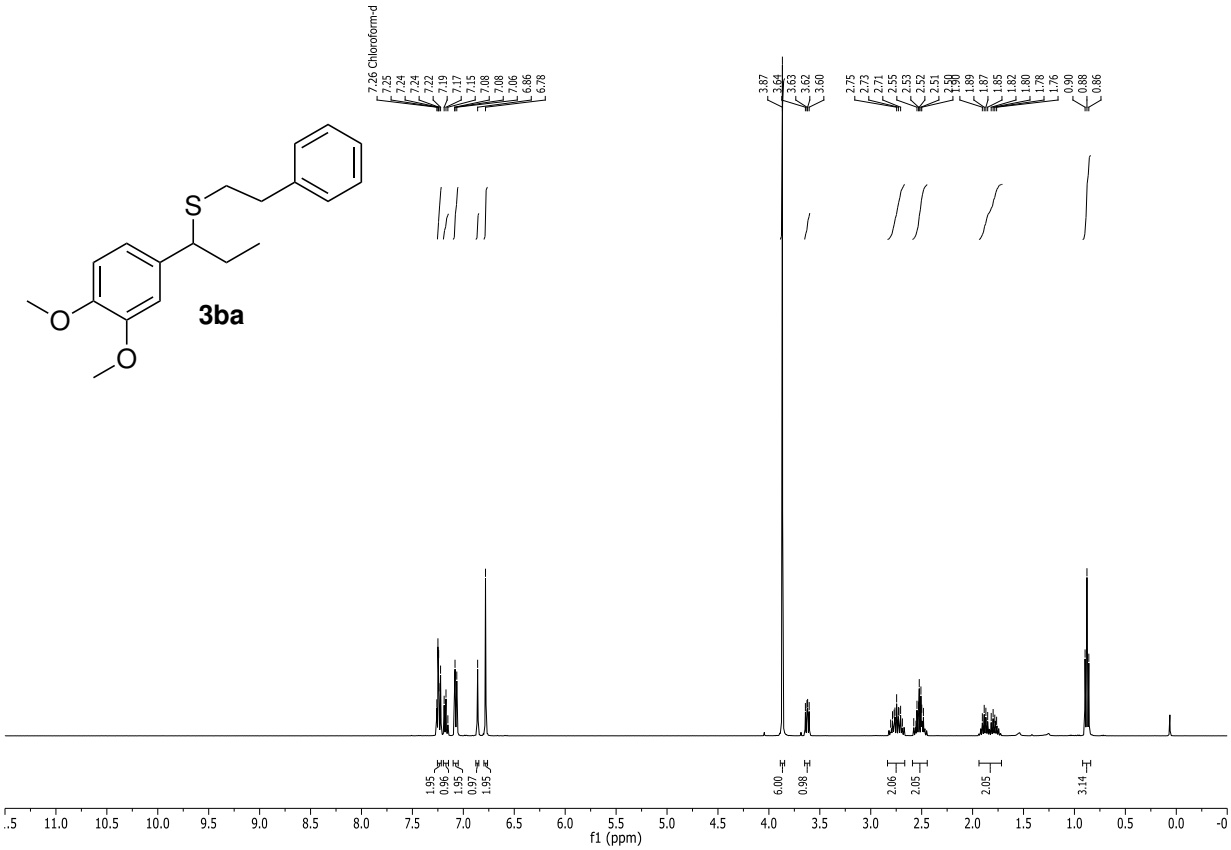
^{1}H NMR (400 MHz, Chloroform-d): δ 7.25 – 7.22 (m, 1H), 7.21 – 7.16 (m, 1H), 7.11 – 7.04 (m, 2H), 6.86 (d, *J* = 1.4 Hz, 1H), 6.78 (d, *J* = 1.1 Hz, 2H), 3.87 (s, 6H), 3.62 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.84 – 2.65 (m, 2H), 2.60 – 2.44 (m, 2H), 1.95 – 1.71 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

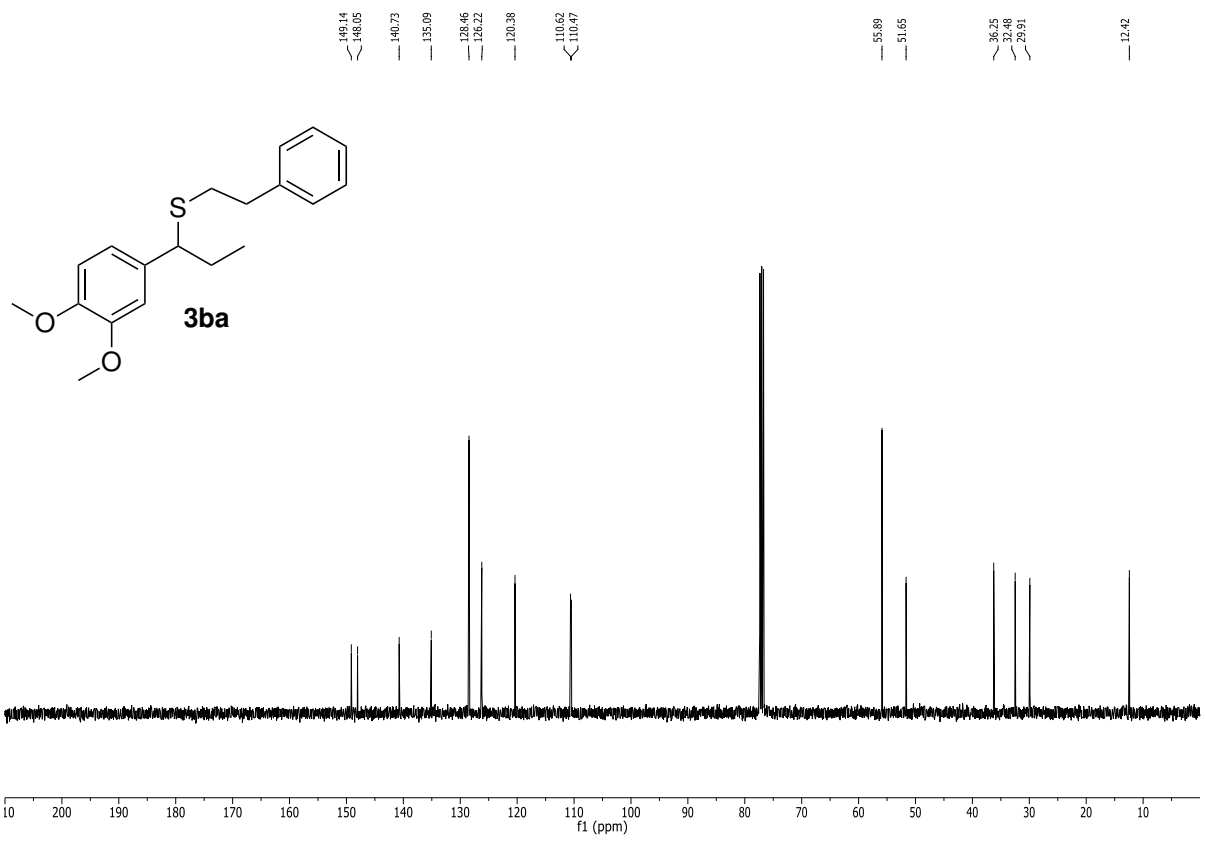
(Note: In the ^{1}H NMR spectrum, the signals corresponding to two non-equivalent methoxy groups have coalesced into one signal which integrates to 6 protons. It is not seen as two singlets)

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 148.1, 140.7, 135.1, 128.4, 126.2, 120.3, 110.6, 110.4, 55.8, 51.6, 36.2, 32.4, 29.9, 12.4.

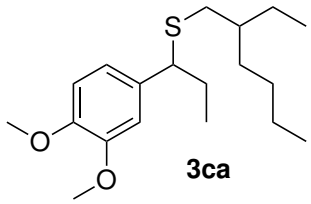
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2926, 1588, 1513, 1454, 1260, 1228, 1137, 1029, 909, 805, 731, 697.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 339.13892, found: 339.13907


7.26 Chloroform-d
7.25
7.24
7.24
7.22
7.19
7.17
7.15
7.08
7.08
7.06
6.86
6.78
3.87
3.64
3.63
3.62
3.60
2.75
2.73
2.71
2.55
2.53
2.52
2.51
1.89
1.87
1.85
1.82
1.80
1.78
1.76
0.90
0.88
0.86
S
O
O
3ba
1.95
0.96
1.95
0.97
1.95
6.00
0.98
2.06
2.05
2.05
3.14
f1 (ppm)


149.14
148.05
140.73
135.09
128.46
126.22
120.38
110.62
110.47
55.89
51.65
36.25
32.48
29.91
12.42
S
O
O
3ba
f1 (ppm)

(1-(3,4-dimethoxyphenyl)propyl)(2-ethylhexyl)sulfane (**3ca**)



3ca

The compound **3ca** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and 2-ethyl-1-hexanethiol (80.4 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 95:5) and obtained as a colorless oil (110.3 mg, 0.33 mmol, 68%, d.r. = 50:50).

$C_{19}H_{32}O_2S$ (324.52 g/mol)

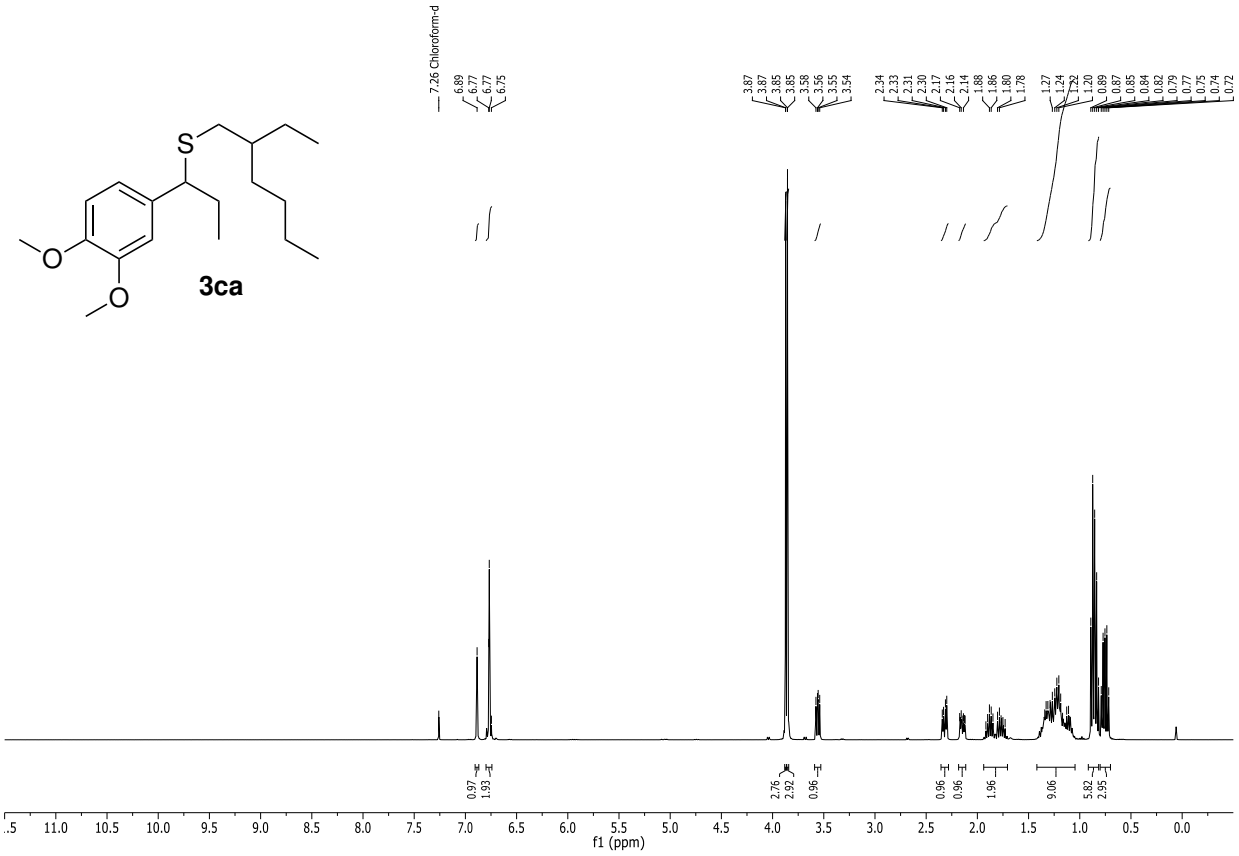
R_f : 0.33 (hexane/Et_2O 90:10)

^{1}H NMR (400 MHz, Chloroform-d) δ 6.89 (d, *J* = 1.6 Hz, 1H), 6.80 – 6.73 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H) 3.56 (dd, *J* = 8.7, 6.0 Hz, 1H), 2.32 (dd, *J* = 12.4, 4.9 Hz, 1H), 2.15 (ddd, *J* = 12.5, 6.3, 2.6 Hz, 1H), 1.96 – 1.69 (m, 2H), 1.43 – 1.02 (m, 9H), 0.95 – 0.65 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 147.9, 135.5, 120.4, 110.4, 55.8, 52.1 and 51.9 (2 diastereomers), 39.2 and 39.1 (2 diastereomers), 35.2, 32.5 and 32.4 (2 diastereomers), 30.1, 25.8, 25.5, 22.9, 14.1, 14.0, 12.4, 10.9, 10.7.

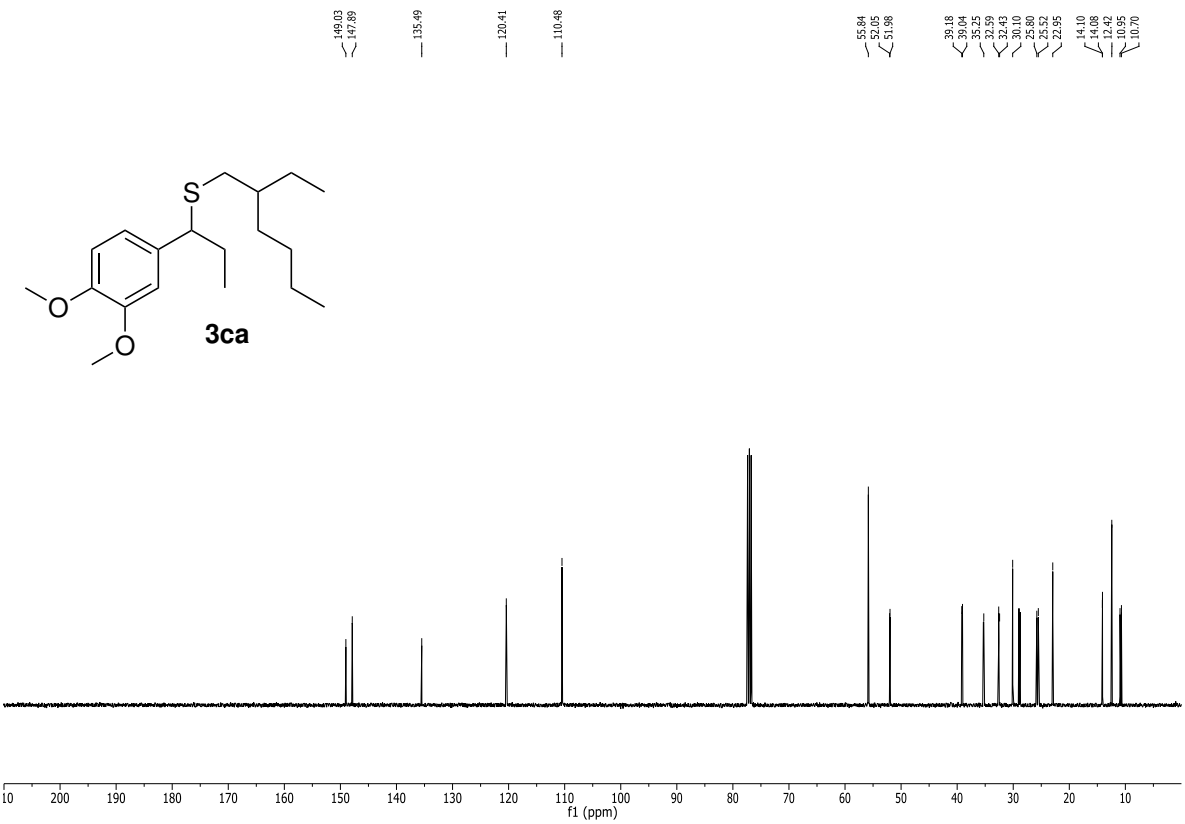
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2870, 2926, 1587, 1513, 1461, 1259, 1230, 1140, 1028, 801, 764,

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 347.20152 found: 347.20203


7.26 Chloroform-d
6.89
6.77
6.77
6.75
3.87
3.87
3.85
3.85
3.58
3.56
3.55
3.54
2.34
2.33
2.31
2.30
2.17
2.16
2.14
1.88
1.86
1.80
1.78
1.27
1.24
1.22
1.20
0.89
0.87
0.85
0.84
0.82
0.79
0.77
0.75
0.74
0.72
0.97
1.93
2.76
2.92
0.96
0.96
0.96
1.96
9.06
5.82
2.95
f1 (ppm)

S
O
O

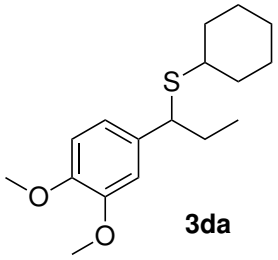
3ca


149.03
147.89
135.49
120.41
110.48
55.84
52.05
51.98
39.18
39.04
35.25
32.39
32.43
30.10
25.80
25.52
22.95
14.10
14.08
12.42
10.95
10.70
f1 (ppm)

S
O
O

3ca

cyclohexyl(1-(3,4-dimethoxyphenyl)propyl)sulfane (**3da**)



3da

The compound xx was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg , 0.5 mmol, 1 equiv) and cyclohexanethiol (63.9 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified by flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the cyclohexanethiol elutes); 2. hexane/diethylether 90:10). The compound was isolated as a yellow oil (98.6 mg, 0.335 mmol, 66 % yield)

$C_{17}H_{26}O_2S$ (294,45 g/mol)

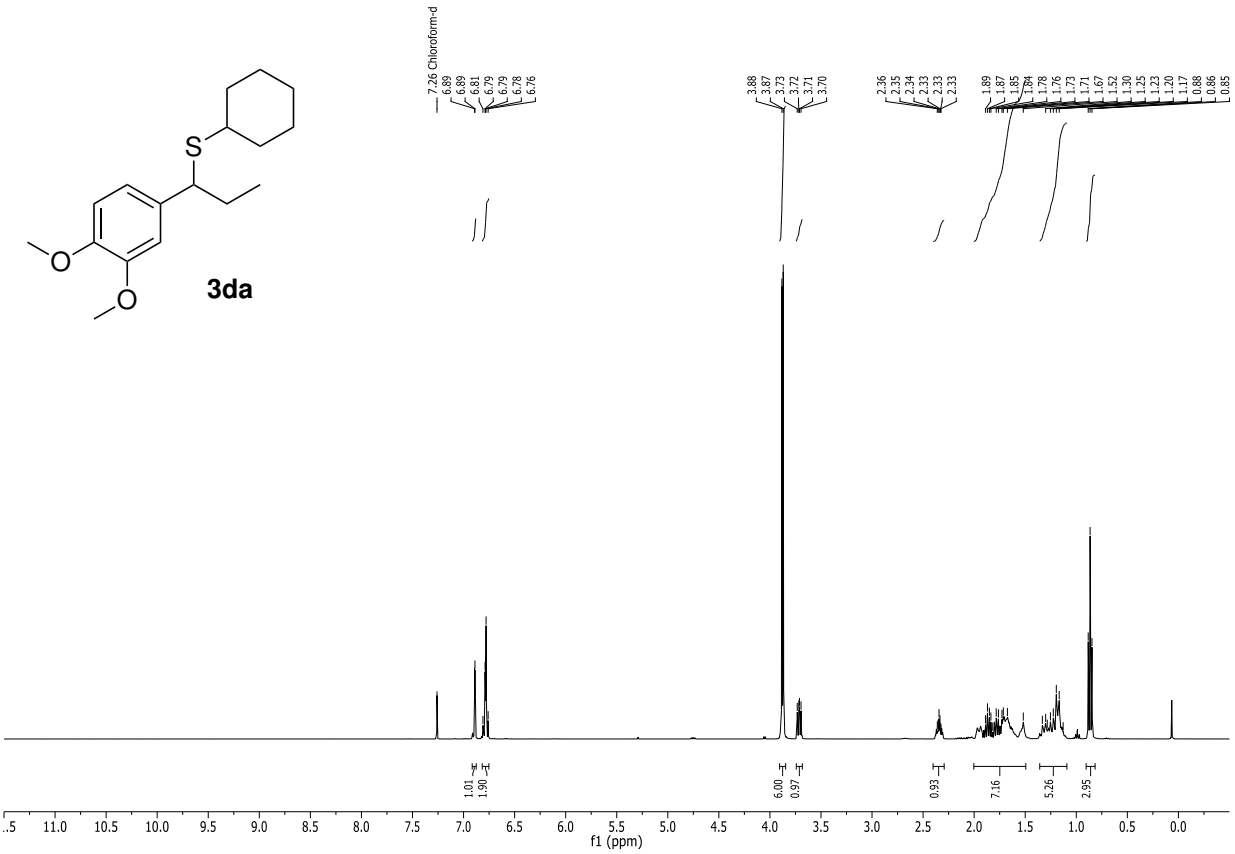
R_f: 0.27 (hexane : diethyl ether 90:10).

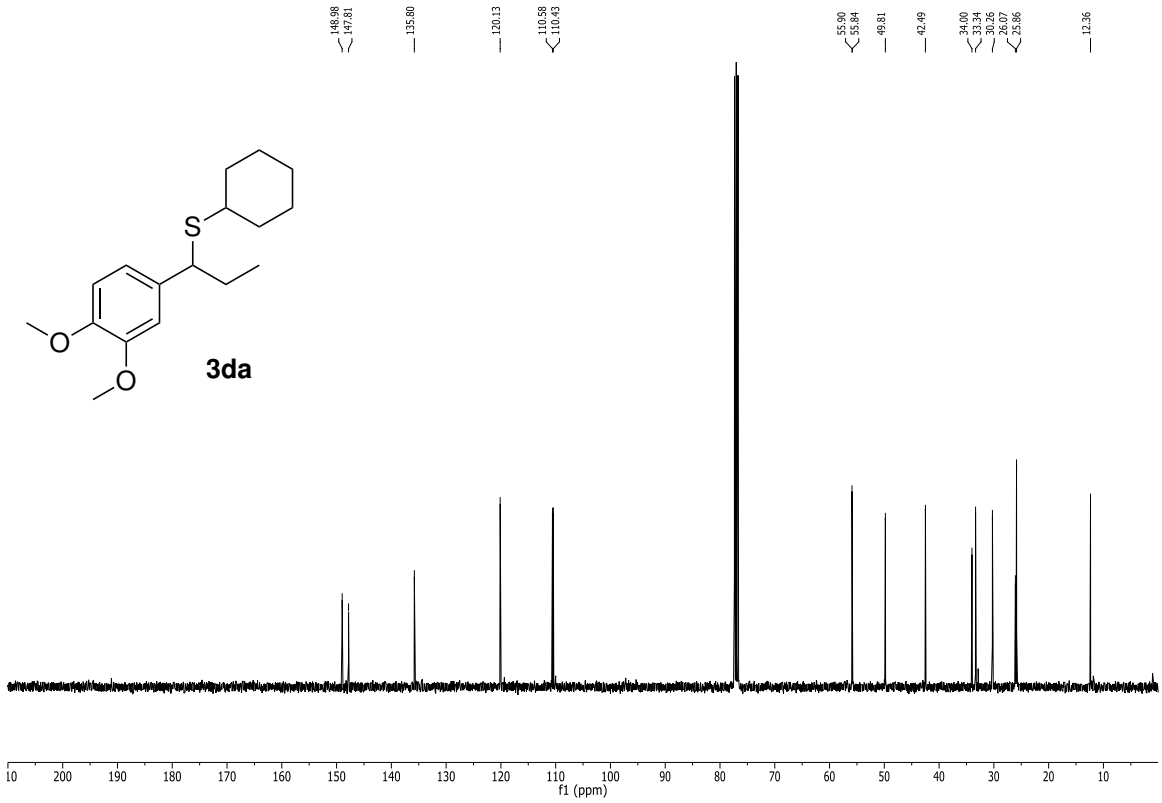
^{1}H-NMR (400 MHz, Chloroform-d) δ: 6.89 (d, *J* = 1.7 Hz, 1H), 6.85 – 6.70 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.52 – 2.16 (m, 1H), 2.05 – 1.45 (m, 7H), 1.42 – 1.08 (m, 5H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 148.9 , 147.8 , 135.8 , 120.1 , 110.5 , 110.4 , 55.9, 55.8, 49.8 , 42.4 , 34.0 , 33.3 , 30.2 , 26.0 , 25.8, 25.8, 12.3.

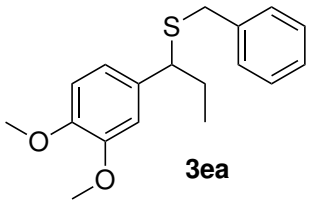
FT-IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 2851, 1590, 1513, 1446, 1260, 1229, 1137, 1029, 913, 854, 805, 764, 731.

HR-MS: m/z = [M+Na$^+$] calc. for $C_{17}H_{26}O_2S$ 317.15457, found 317.15475


7.26 Chloroform-d
6.89
6.89
6.81
6.79
6.79
6.78
6.76
3.88
3.87
3.73
3.72
3.71
3.70
2.36
2.35
2.34
2.33
2.33
2.33
1.89
1.87
1.85
1.84
1.78
1.76
1.73
1.71
1.67
1.52
1.30
1.25
1.23
1.20
1.17
0.88
0.86
0.85
S
O
O
3da
1.01
1.90
6.00
0.97
0.93
7.16
5.26
2.95
f1 (ppm)


148.98
147.81
135.80
120.13
110.58
110.43
55.90
55.84
49.81
42.49
34.00
33.34
30.26
26.07
25.86
12.36
S
O
O
3da
f1 (ppm)

benzyl(1-(3,4-dimethoxyphenyl)propyl)sulfane (**3ea**)



3ea

The compound **3ea** was synthesized from 4-allyl-1,2-dimethoxybenzene (44.5 mg, 0.25 mmol, 1 equiv) and benzyl mercaptan (34.1 mg, 0.27 mmol, 1.1 equiv) following the General Procedure (A with the following changes, Palladium acetate (3.36 mg, 0.06 mmol), **L1** (18.08 mg, 0.12 mmol), CF_3SO_3H (4.2 µL, 0.16 mmol)). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 95:5) and obtained as a colorless oil as a yellow oil (48.38 mg, 0.15 mmol, 64%).

$C_{18}H_{22}O_2S$ (302. 43 g/mol)

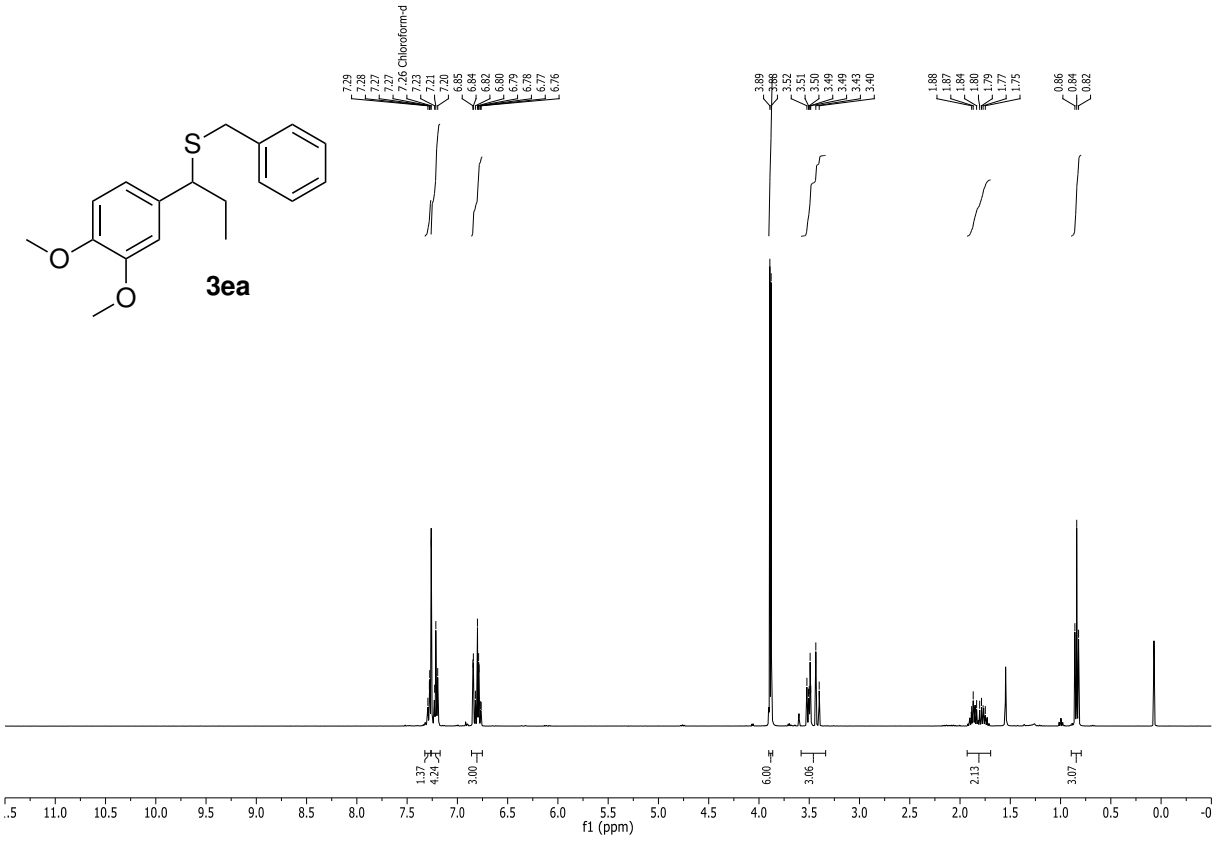
R_f : 0.16 (hexane: Et_2O 90:10)

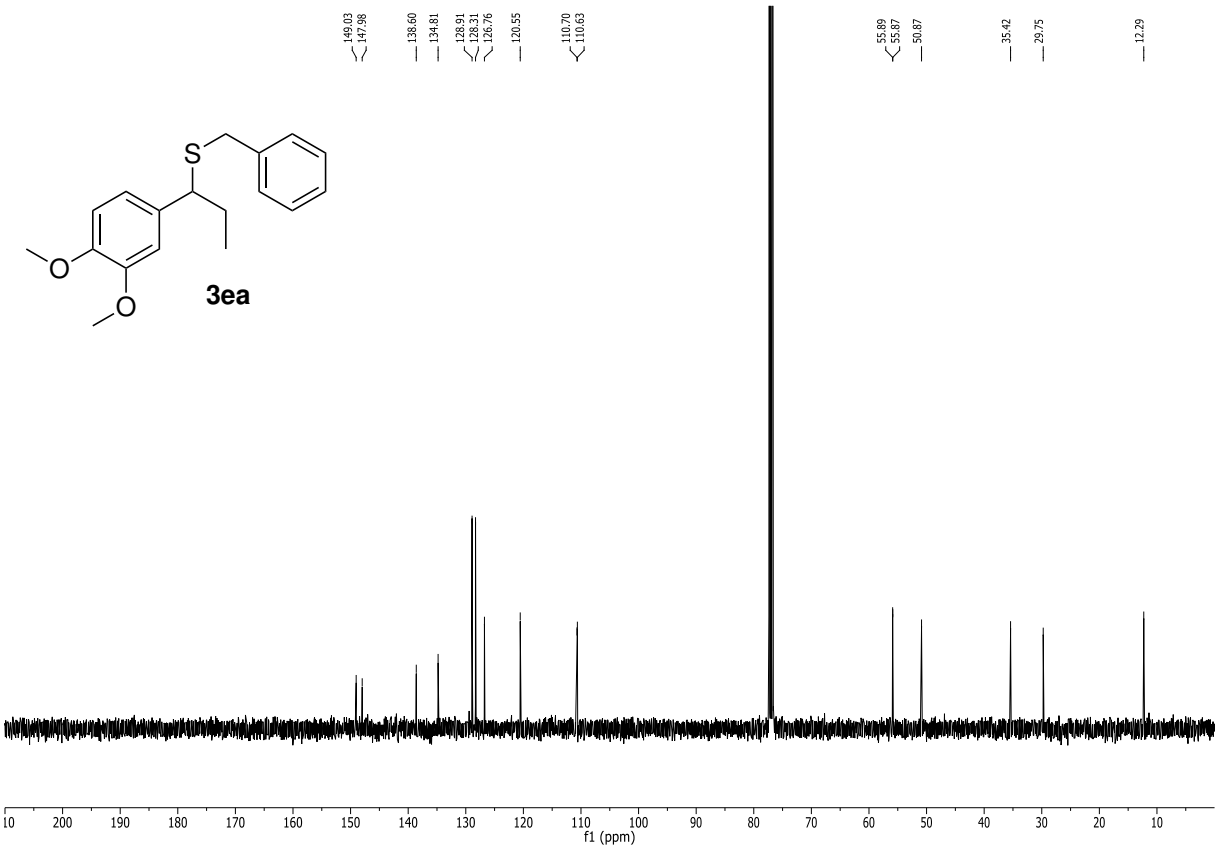
^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.21 (m, 4H), 6.86 – 6.76 (m, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.56 – 3.39 (m, 3H), 1.93 – 1.71 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.9, 138.6, 134.8, 128.9, 128.3, 126.7, 120.5, 110.7, 110.6, 55.8, 55.8, 50.8, 35.4, 29.7, 12.3.

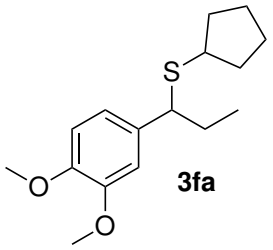
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3026, 2959, 2929, 2832, 1513, 1453, 1259, 1453, 1230, 1136, 764, 730

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 325.12327, found: 325.12359


7.29
7.28
7.27
7.27
7.26 Chloroform-d
7.23
7.21
7.20
6.85
6.84
6.82
6.80
6.79
6.78
6.77
6.76
3.89
3.88
3.52
3.51
3.50
3.49
3.49
3.43
3.40
1.88
1.87
1.84
1.80
1.79
1.77
1.75
0.86
0.84
0.82
S
O
O
3ea
1.37
4.24
3.00
6.00
3.06
2.13
3.07
f1 (ppm)


149.03
147.98
138.60
134.81
128.91
128.31
126.76
120.55
110.70
110.63
55.89
55.87
50.87
35.42
29.75
12.29
S
O
O
3ea
f1 (ppm)

cyclopentyl(1-(3,4-dimethoxyphenyl)propyl)sulfane (**3fa**)



3fa

The compound **3fa** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and cyclopentane thiol (56.2 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane : 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 99:1) and obtained as a yellow oil (124.8 mg, 0.39 mmol, 79%).

$C_{19}H_{24}O_2S$ (316.45 g/mol)

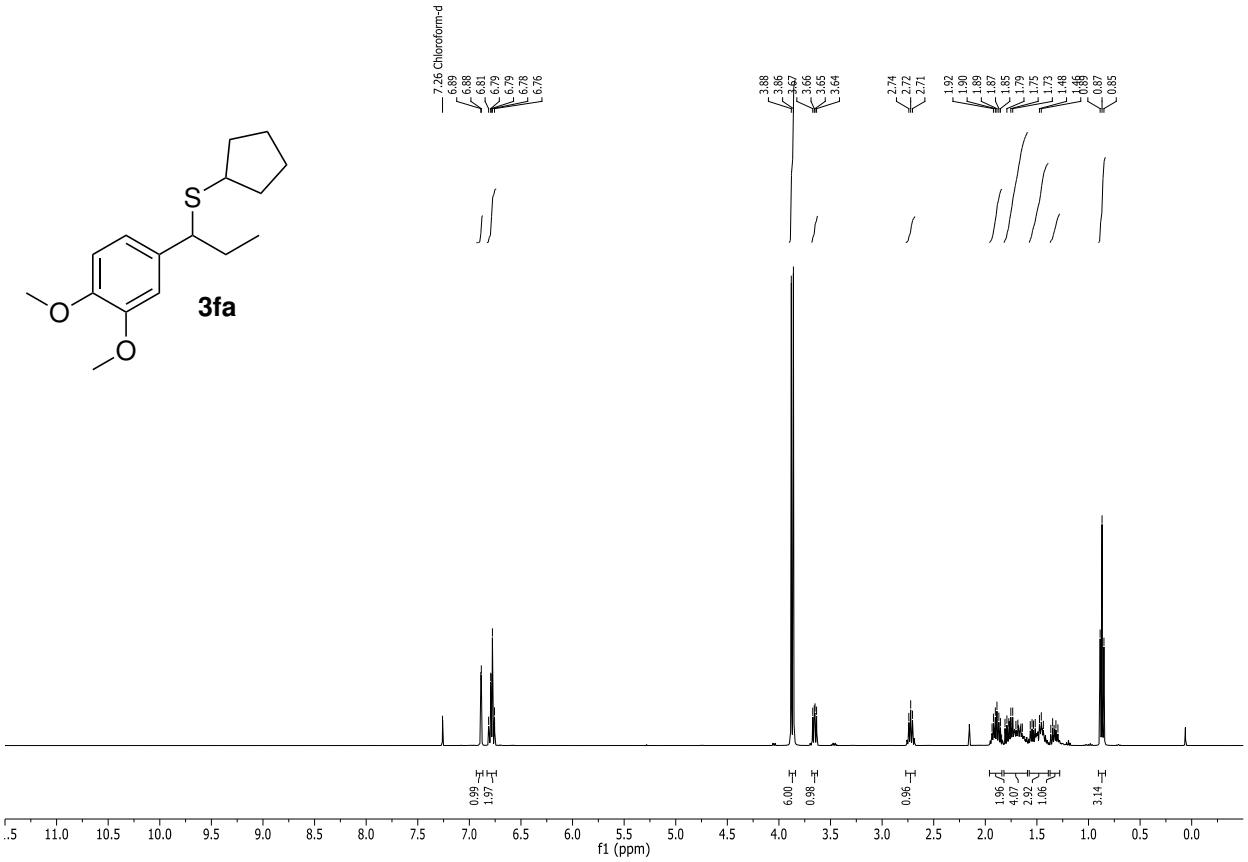
R_f : 0.41 (hexane : diethylether 90 : 10)

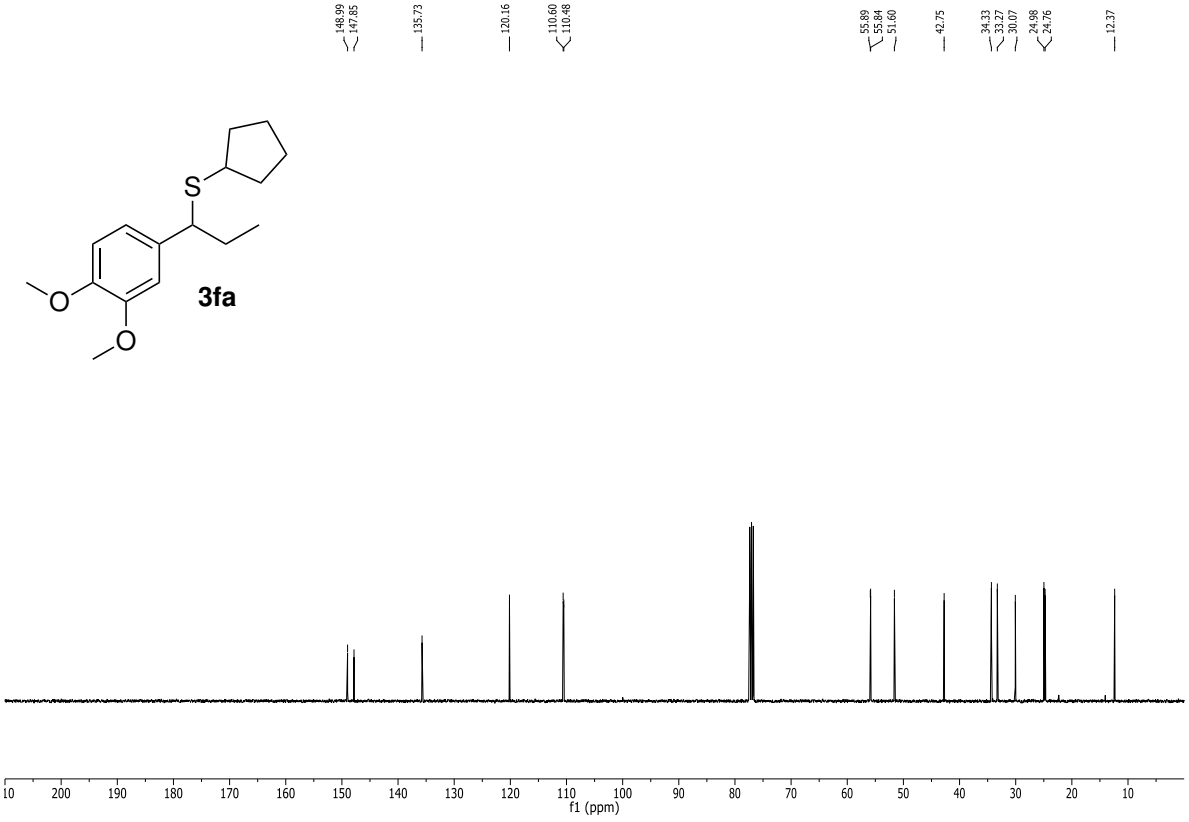
^{1}H NMR (400 MHz, Chloroform-d) δ 6.89 (d, *J* = 1.8 Hz, 1H), 6.82 – 6.74 (m, 2H) , δ 3.88 (s, 3H), 3.86 (s, 3H) 3.65 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.72 (p, *J* = 7.2 Hz, 1H), 1.96 – 1.84 (m, 2H), 1.81 – 1.58 (m, 4H), 1.55 – 1.40 (m, 3H), 1.37 – 1.23 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.8, 135.7, 120.1, 110.6, 110.4, 55.8, 55.8, 51.6, 42.7, 34.3, 33.2, 30.1, 24.9, 24.7, 12.3.

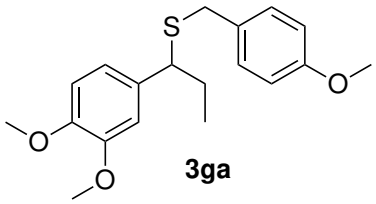
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2866, 1588, 1513, 1450, 1260, 1230, 1137, 1029, 854, 805, 764, 731.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 303.13892, found: 303.13926


7.26 Chloroform-d
6.89
6.88
6.81
6.79
6.79
6.78
6.76
3.88
3.86
3.67
3.66
3.65
3.64
2.74
2.72
2.71
1.92
1.90
1.89
1.87
1.85
1.79
1.75
1.73
1.48
0.87
0.85
S
O
O
3fa
0.99
1.97
6.00
0.98
0.96
1.96
4.07
2.92
1.06
3.14
f1 (ppm)


148.99
147.85
135.73
120.16
110.60
110.48
55.89
55.84
51.60
42.75
34.33
33.27
30.07
24.98
24.76
12.37
S
O
O
3fa
f1 (ppm)

(1-(3,4-dimethoxyphenyl)propyl)(4-methoxybenzyl)sulfane (**3ga**)



3ga

The compound **3ga** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and (4-methoxyphenyl)methanethiol (77 mg, 0.55 mmol, 1.1) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane: 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 95:5 and obtained as a colorless oil as a yellow oil (81.19 mg, 0.25 mmol, 51%).

$C_{18}H_{22}O_3S$ (318.43 g/mol)

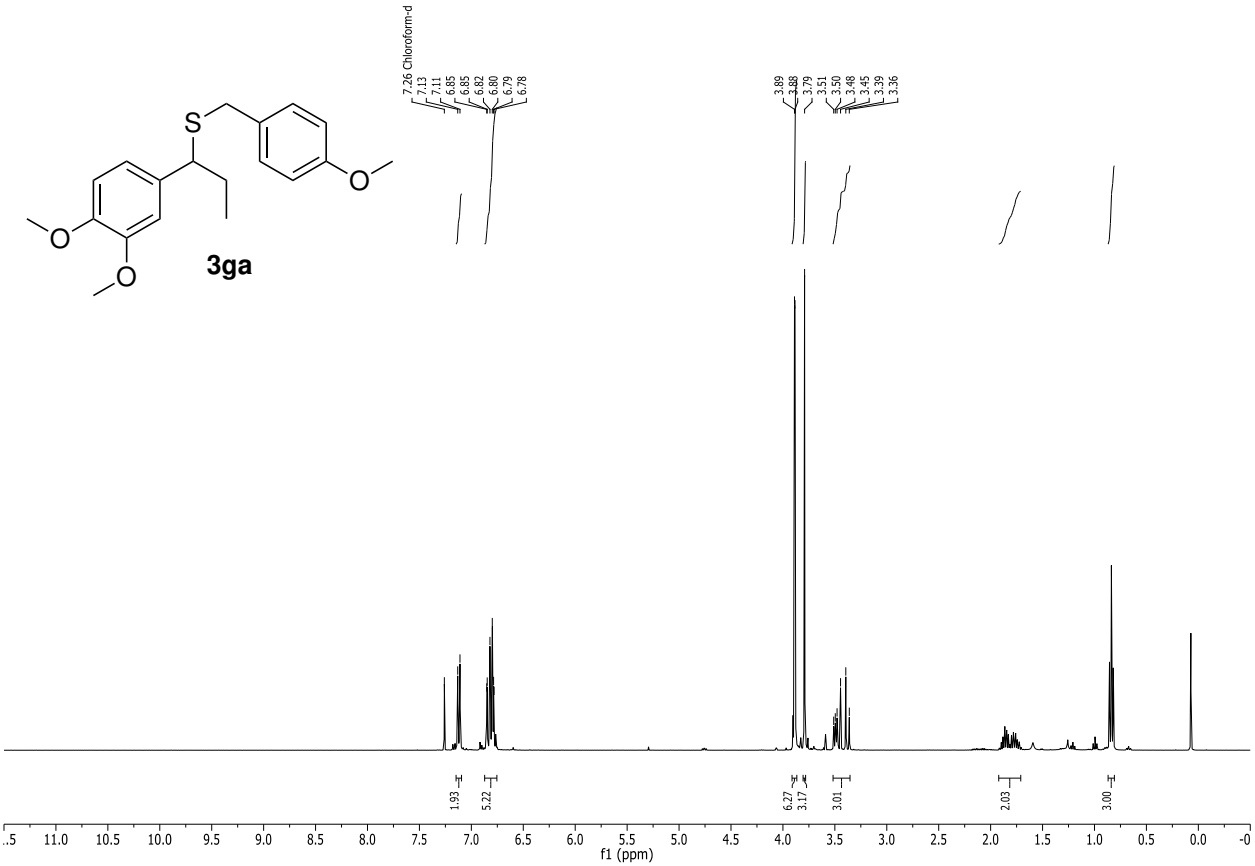
R_f: 0.3 (hexane: Et_2O 85:15)

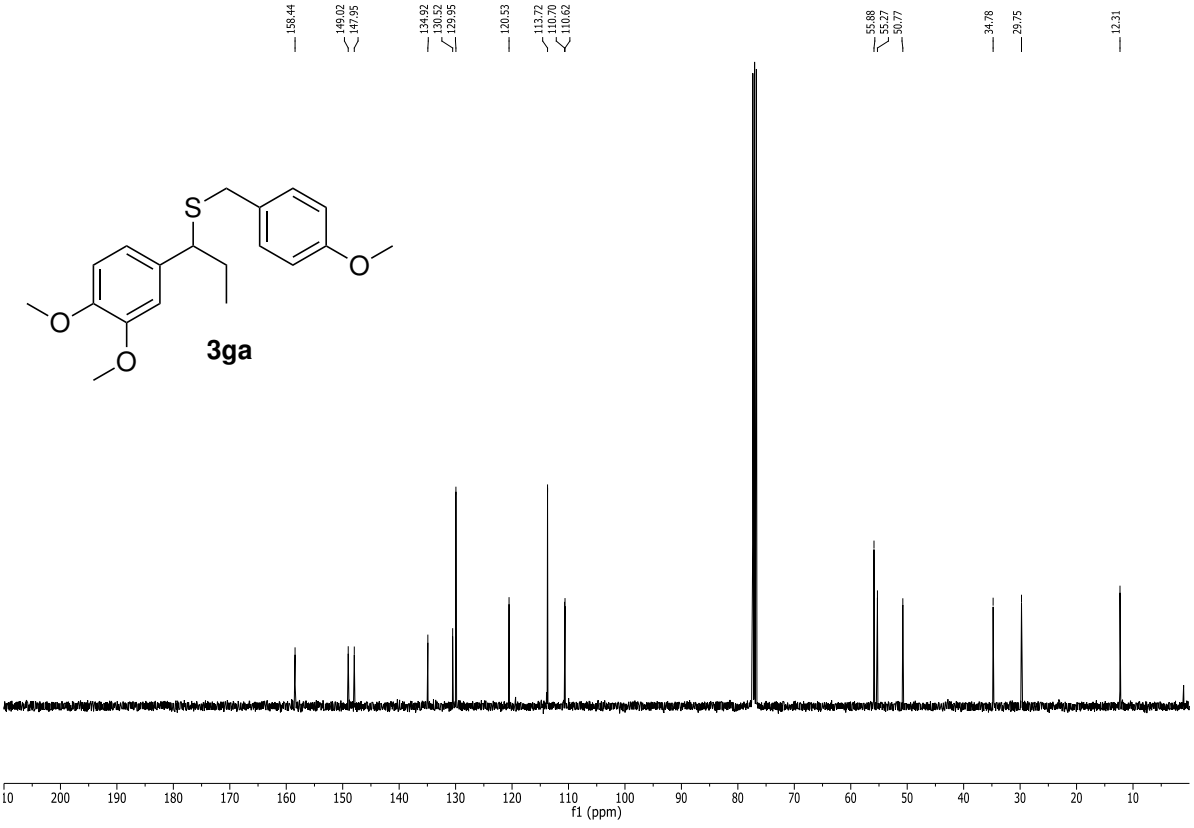
^{1}H NMR (400 MHz, Chloroform-d) δ 7.15 – 7.09 (m, 2H), 6.89 – 6.74 (m, 5H), 3.89 (d, *J* = 2.0 Hz, 6H), 3.79 (s, 3H), 3.54 – 3.34 (m, 3H), 1.93 – 1.69 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 149.0, 147.9, 134.9, 130.5, 129.9, 120.5, 113.7, 110.7, 110.6, 55.8, 55.2, 50.7, 34.7, 29.7, 12.3.

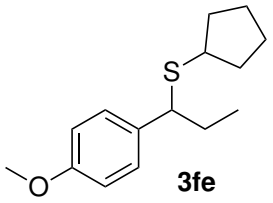
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 2996, 2832, 1606, 1461, 1509, 1230, 1174, 1025 805, 760, 754

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 355.13384 found: 355.13441


7.26 Chloroform-d
7.13
7.11
6.85
6.85
6.82
6.80
6.79
6.78
3.89
3.88
3.79
3.51
3.50
3.48
3.45
3.39
3.36
S
O
O
O
3ga
1.93
5.22
6.27
3.17
3.01
2.03
3.00
f1 (ppm)


158.44
149.02
147.95
134.92
130.52
129.95
120.53
113.72
110.70
110.62
55.88
55.27
50.77
34.78
29.75
12.31
S
O
O
O
3ga
f1 (ppm)

cyclopentyl(1-(4-methoxyphenyl)propyl)sulfane (**3fe**)



3fe

The compound **3fe** was synthesized from 4-allylanisole (74 mg, 0.50 mmol, 1 equiv) and cyclopentane thiol (56.2 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A) The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane : 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 99:1) as a yellow oil in (88 mg, 0.35 mmol, 71%).

$C_{15}H_{22}OS$ (250.40 g/mol)

R_f : 0.42 (hexane/diethylether 97.5:2.5)

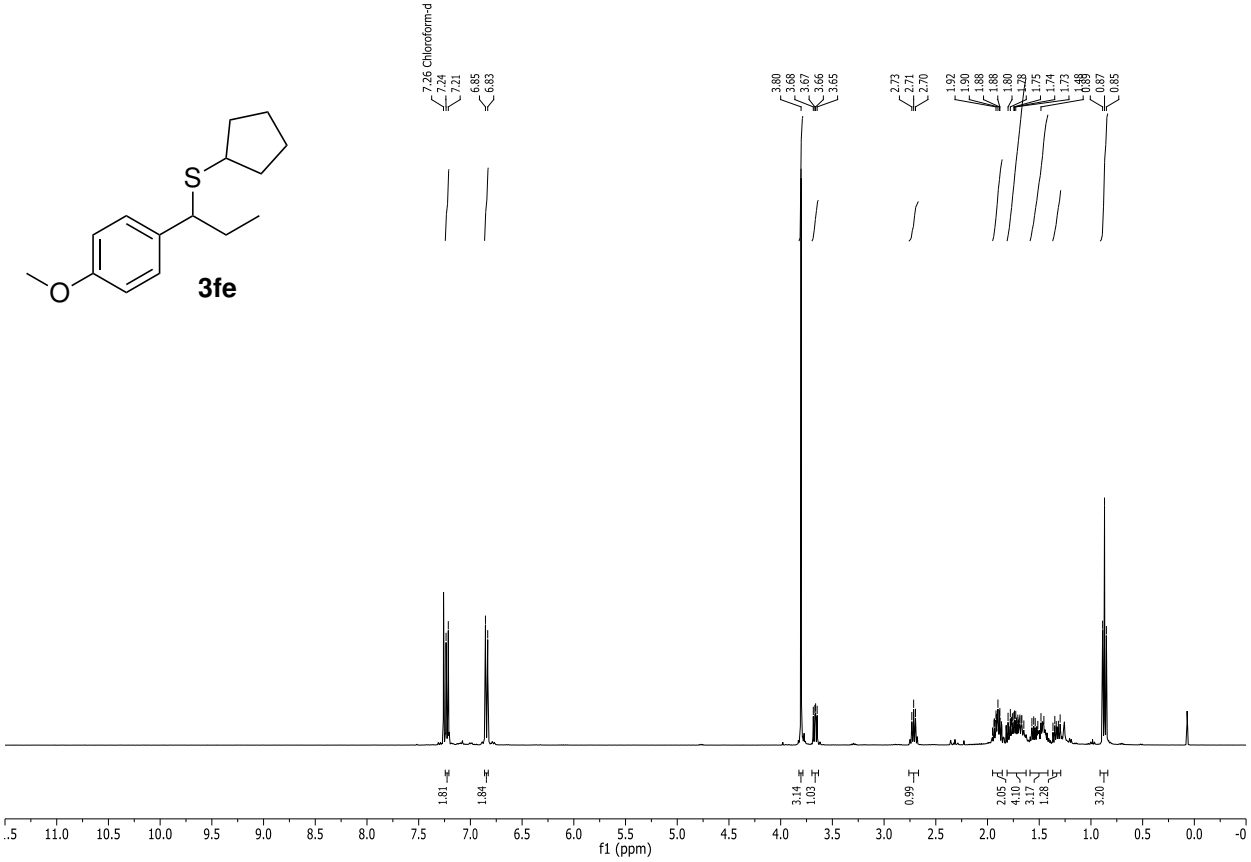
^{1}H NMR (400 MHz, Chloroform-d)

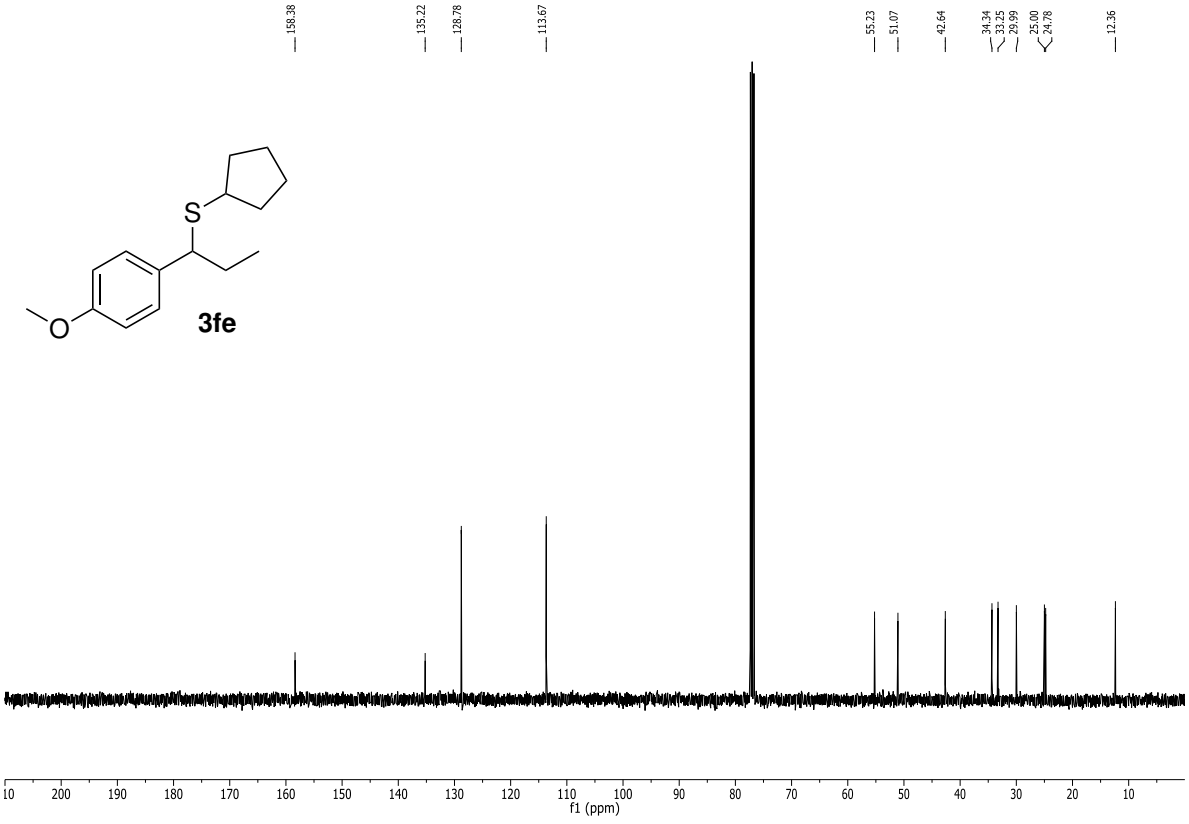
^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.67 (dd, *J* = 8.9, 6.0 Hz, 1H), 2.75 – 2.67 (m, 1H), 1.96 – 1.85 (m, 2H), 1.83 – 1.63 (m, 4H), 1.59 – 1.42 (m, 3H), 1.37 – 1.24 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 135.2, 128.7, 113.6, 55.2, 51.1, 42.6, 34.3, 33.2, 29.9, 25.0, 24.7, 12.3.

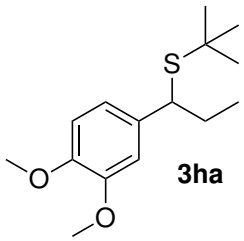
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2866, 1610.2, 1509.6, 1457.4, 1300.8, 1244.9, 1174.1, 1110.7, 1036.2, 775

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 273.12836, found 273.12849


7.26 Chloroform-d
7.24
7.21
6.85
6.83
3.80
3.68
3.67
3.66
3.65
2.73
2.71
2.70
1.92
1.90
1.88
1.88
1.80
1.28
1.75
1.74
1.73
0.88
0.87
0.85
1.81
1.84
3.14
1.03
0.99
2.05
4.10
3.17
1.28
3.20
f1 (ppm)
3fe


158.38
135.22
128.78
113.67
55.23
51.07
42.64
34.34
33.25
29.99
25.00
24.78
12.36
f1 (ppm)
3fe

tert-butyl(1-(3,4-dimethoxyphenyl)propyl)sulfane (**3ha**)



3ha

The compound **3ha** was synthesized from 4-allyl-1,2-dimethoxybenzene (89 mg, 0.50 mmol, 1 equiv) and 2-methyl-2-propanethiol (49.6 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane : 100 (till the cyclopentane thiol elutes) then 2. hexane/diethylether 95:5) and obtained as a colorless oil (28.2 mg, 0.1 mmol, 21%).

$C_{15}H_{24}O_2S$ (268.41 g/mol)

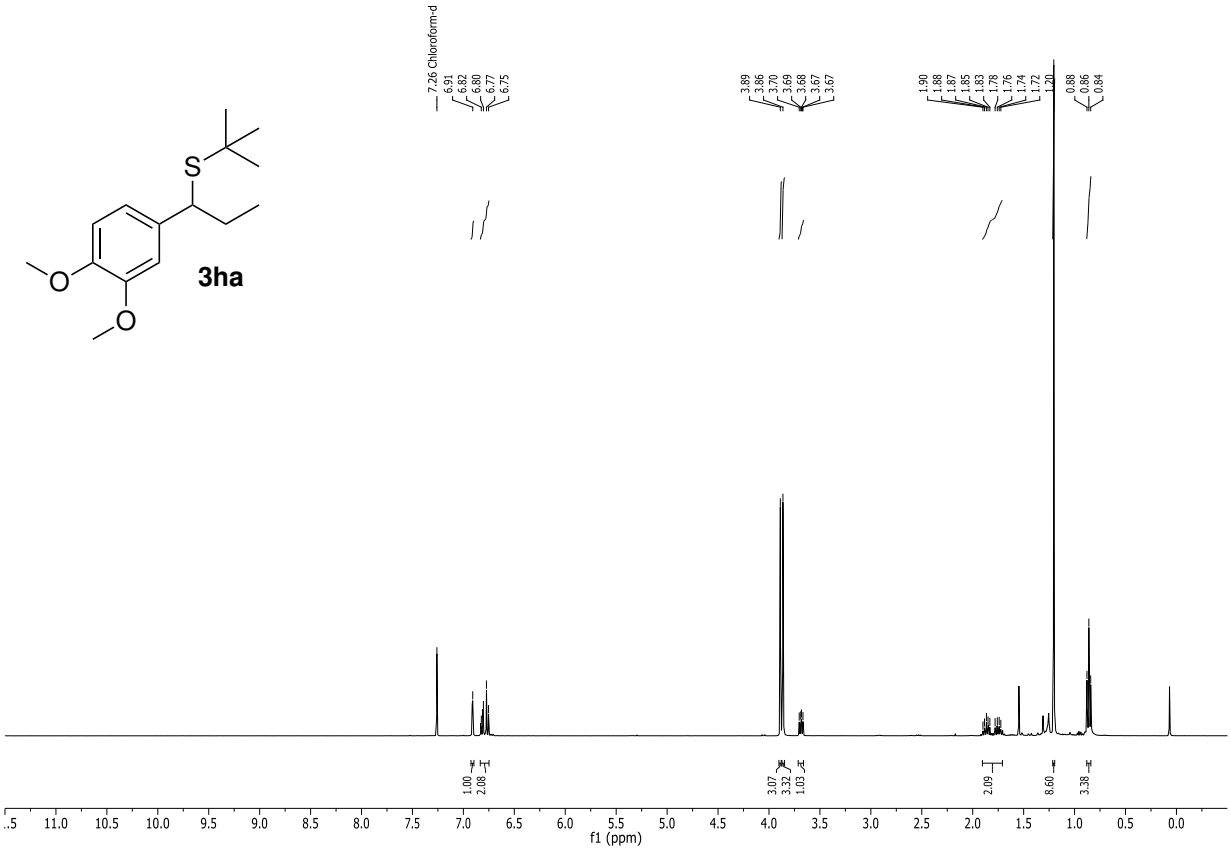
R_f : 0.16 (hexane : Et_2O 90 : 10)

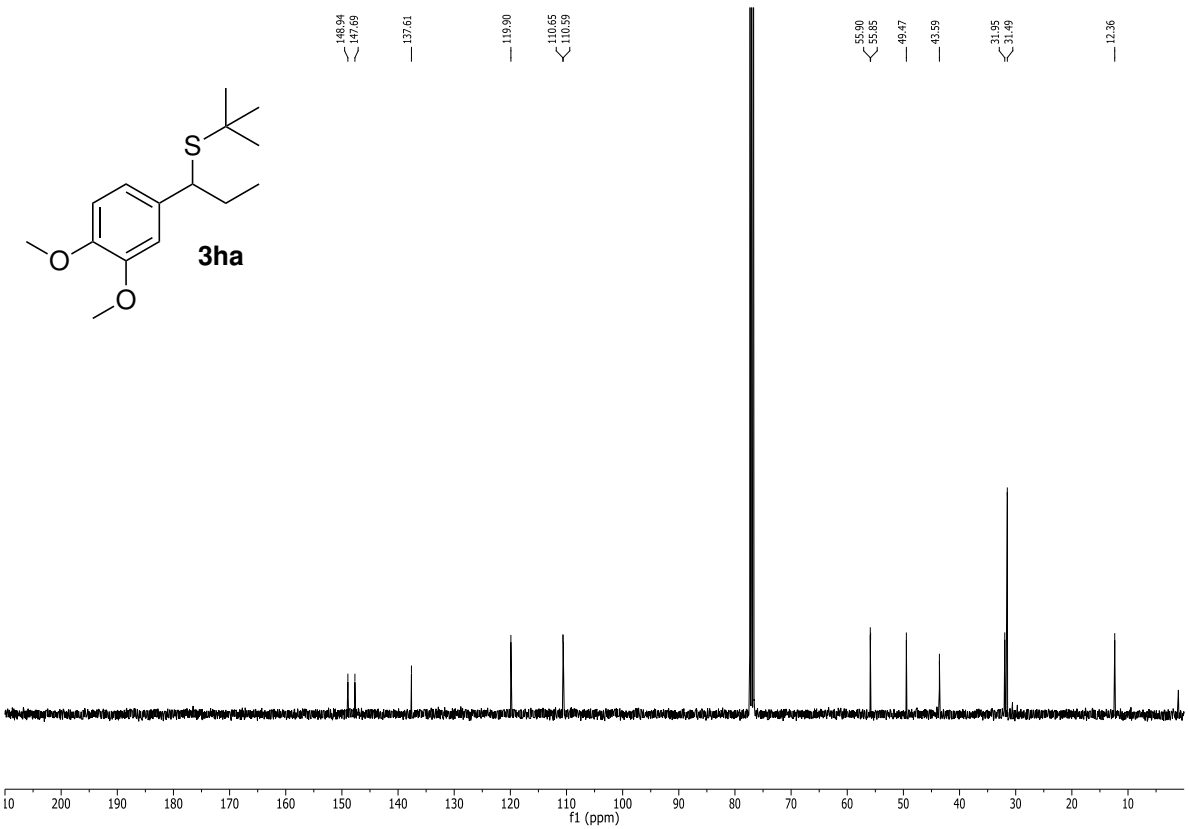
^{1}H NMR (400 MHz, Chloroform-d) δ 6.91 (d, *J* = 2.0 Hz, 1H), 6.84 – 6.74 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.68 (dd, *J* = 8.8, 6.0 Hz, 1H), 1.92 – 1.68 (m, 2H), 1.20 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.6, 137.6, 119.9, 110.6, 110.5, 55.9, 55.8, 49.4, 43.5, 31.9, 31.4, 12.3.

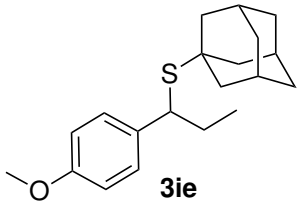
IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 2926, 1587, 1513, 1457, 1259, 1230, 1135, 1028, 853, 764, 803

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 291.13892, found 291.13936


7.26 Chloroform-d
6.91
6.82
6.80
6.77
6.75
3.89
3.86
3.70
3.69
3.68
3.67
3.67
1.90
1.88
1.87
1.85
1.83
1.78
1.76
1.74
1.72
1.20
0.88
0.86
0.84
1.00
2.08
3.07
3.32
1.03
2.09
8.60
3.38
f1 (ppm)
3ha


148.94
147.69
137.61
119.90
110.65
110.59
55.90
55.85
49.47
43.59
31.95
31.49
12.36
f1 (ppm)
3ha

Adamantan-1-yl(1-(4-methoxyphenyl)propyl)sulfane (**3ie**)



3ie

The compound **3ie** was synthesized from 4-allylanisole (74 mg, 0.50 mmol, 1 equiv) and adamantanethiol (92.4 mg, 0.55 mmol, 1.1 equiv) following the General Procedure (A). The product was purified using flash column chromatography (12 g SiO_2, Gradient elution: 1. hexane : 100 (till the adamantane thiol elutes) then 2. hexane/diethylether 95:5) and obtained as a white oil (60.6 mg, 0.17 mmol, 35%).

$C_{21}H_{30}O_2S$ (316.50 g/mol)

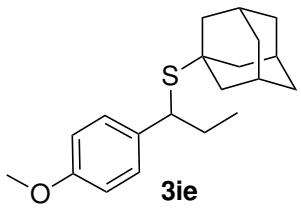
R_f: (hexane : diethylether 90 : 10) 0.72

^{1}H NMR (400 MHz, Chloroform-d) δ ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.75 (dd, *J* = 6.2 Hz, 1H), 1.96 – 1.59 (m, 17H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 136.6, 127.5, 112.5, 54.2, 45.3, 44.9, 43.1, 35.3, 31.3, 28.7, 11.3.

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2900, 2848, 1610, 1510, 1450, 1297, 1245, 1174, 1036, 909, 824, 731, 686.

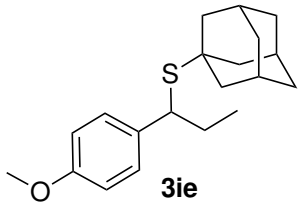
HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 339.17561, found: 339.17531


S
O

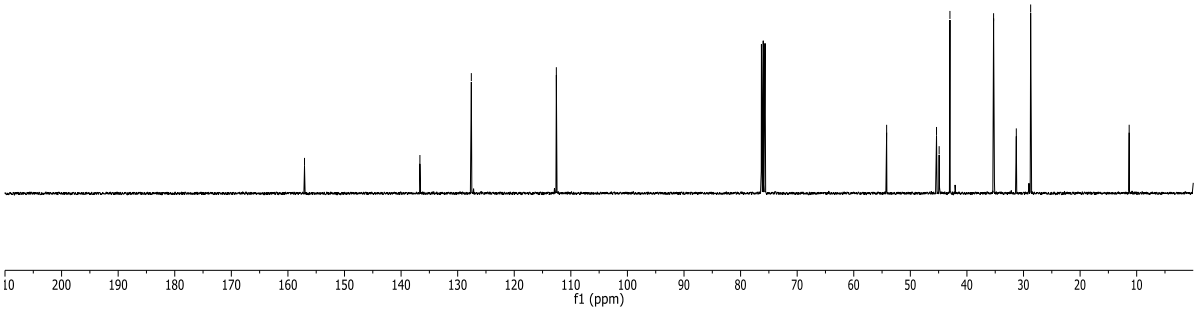
3ie

7.26 Chloroform-d
7.24
7.22
6.83
6.81
3.79
3.76
3.76
1.95
1.86
1.84
1.79
1.78
1.74
1.71
1.66
1.63
0.86
0.84
0.83
2.00
2.03
3.18
1.06
17.41
3.13
f1 (ppm)

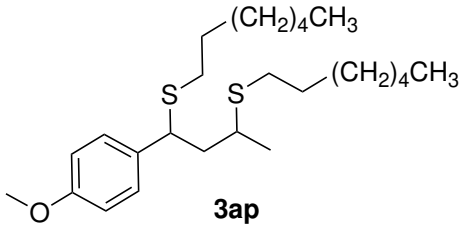

157.07
136.67
127.59
112.56
54.19
45.37
44.91
43.00
35.29
31.27
28.74
11.33


S
O

3ie


f1 (ppm)

(1-(4-methoxyphenyl)butane-1,3-diyl)bis(heptylsulfane) (**3ap**)



3ap

The compound **3ap** was synthesized from (*E*)-1-(buta-1,3-dien-1-yl)-4-methoxybenzene (80.1 mg, 0.50 mmol, 1eq) and heptane-1-thiol (86 µL, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (56 mg, 0.13 mmol, 26 %, d.r. = 50:50). Preparative TLC was used for purification using hexane as the mobile phase

$C_{25}H_{44}OS_2$ (424.78 g/mol)

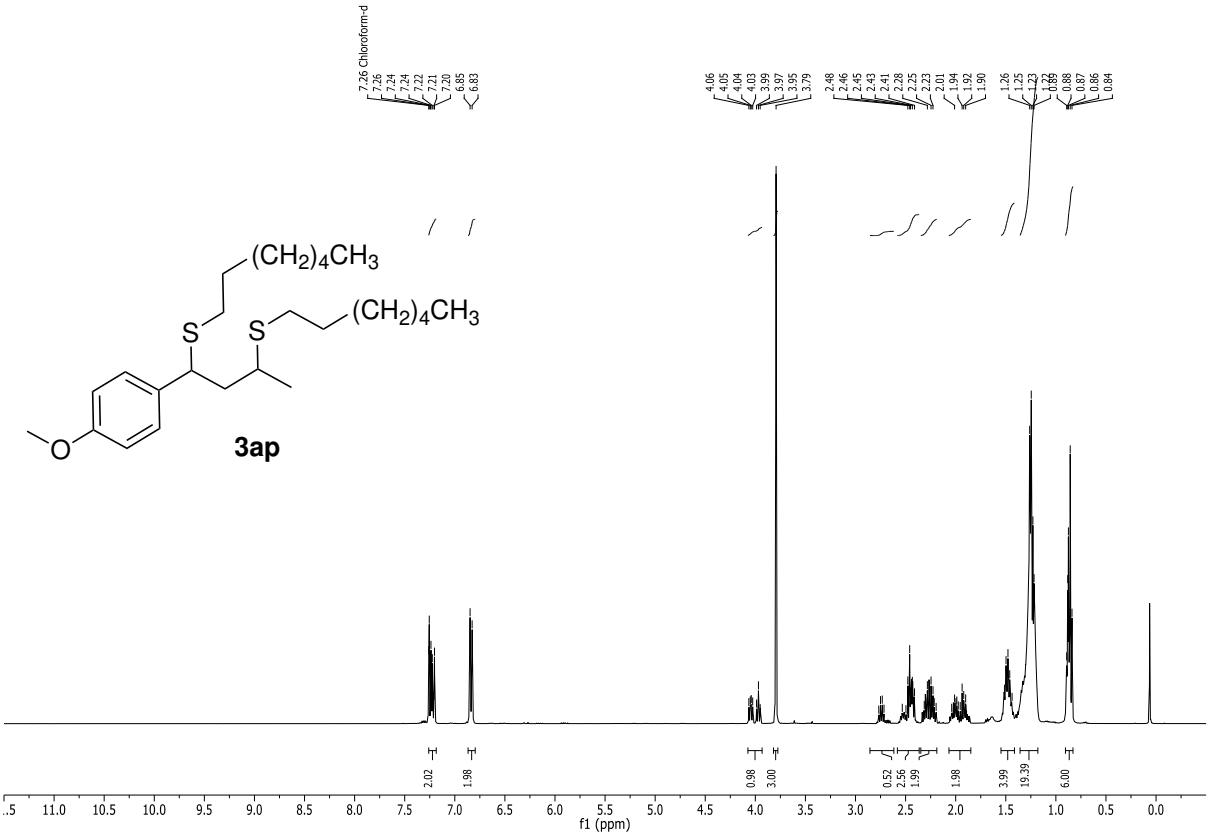
R_f : 0.26 (hexane/Et_2O 97.5:2.5)

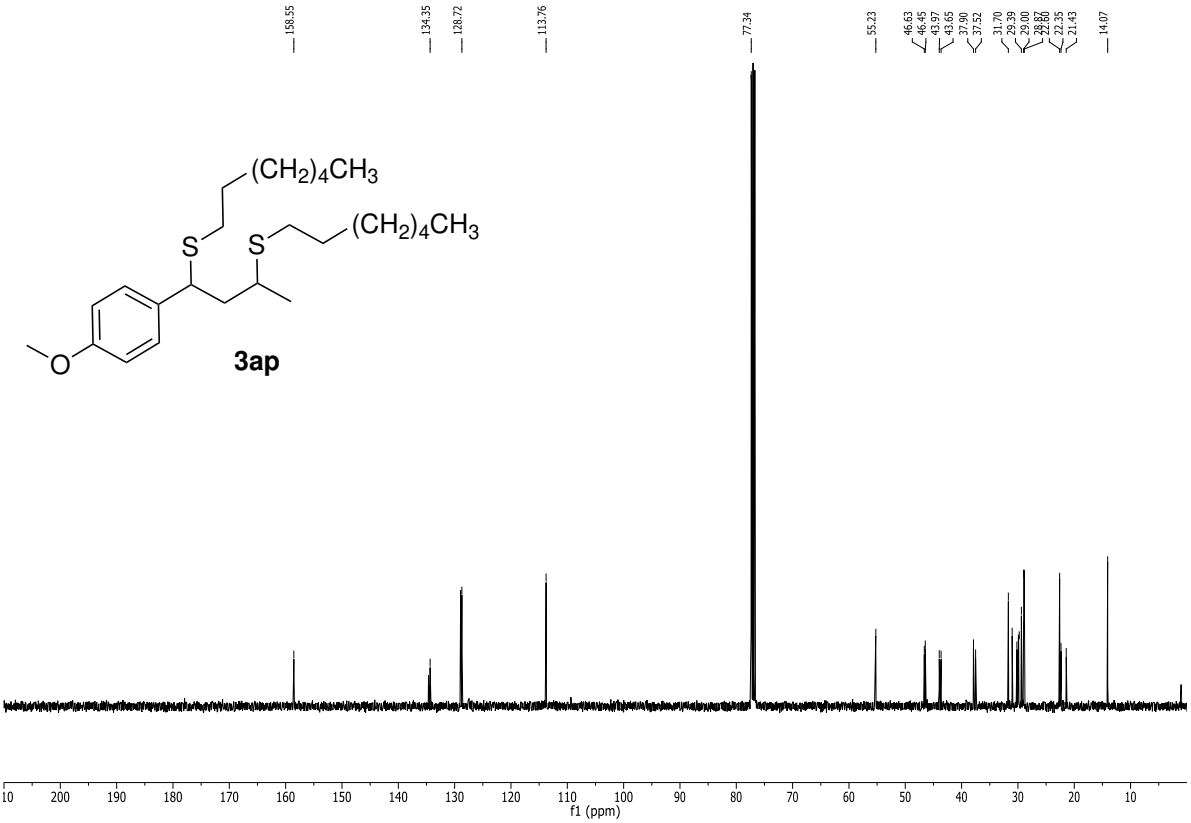
^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 (m, 2H), 6.84 (d, *J* = 7.7 Hz, 2H), 4.09 – 3.93 (m, 1H), 3.79 (s, 3H), 2.81 – 2.64 (m, 1H), 2.58 – 2.39 (m, 3H), 2.35 – 2.18 (m, 2H), 2.09 – 1.85 (m, 2H), 1.56 – 1.42 (m, 4H), 1.39 – 1.16 (m, 19H), 0.93 – 0.81 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 134.3, 128.7, 113.7, 55.2, 46.6 and 46.4 (2 diastereomers), 43.9, 43.6, 37.9, 37.5, 31.7, 31.0, 30.1, 29.9, 29.7, 29.3, 29.0, 28.8, 22.6, 22.3, 21.4, 14.0.

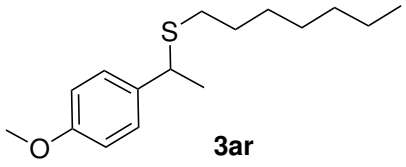
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 2855, 1610, 1174, 1509, 1461, 1248, 1300, 1036, 909, 834, 730

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 447.27258 found 447.27220


7.26 Chloroform-d
7.26
7.24
7.24
7.22
7.21
7.20
6.85
6.83
4.06
4.05
4.04
4.03
3.99
3.97
3.95
3.79
2.48
2.46
2.45
2.43
2.41
2.28
2.25
2.23
2.01
1.94
1.92
1.90
1.26
1.25
1.23
0.89
0.88
0.87
0.86
0.84
(CH2)4CH3
S
S
(CH2)4CH3
O
3ap
2.02
1.98
0.98
3.00
0.52
2.56
1.99
1.98
3.99
19.39
6.00
f1 (ppm)


158.55
134.35
128.72
113.76
77.34
55.23
46.63
46.45
43.97
43.65
37.90
37.52
31.70
29.39
29.00
22.35
21.43
14.07
(CH2)4CH3
S
S
(CH2)4CH3
O
3ap
f1 (ppm)

heptyl(1-(4-methoxyphenyl)ethyl)sulfane (**3ar**)



3ar

The compound **3ar** was synthesized from 4-methoxystyrene (67 µL, 0.50 mmol, 1 equiv) and heptane-1-thiol (86 µL, 0.55 mmol, 1.1 equiv) following the General Procedure (A) as a yellow oil (89.2mg, 0.33 mmol, 67%). Preparative TLC was used for purification using hexane as the mobile phase.

$C_{16}H_{26}OS$ (266.44 g/mol)

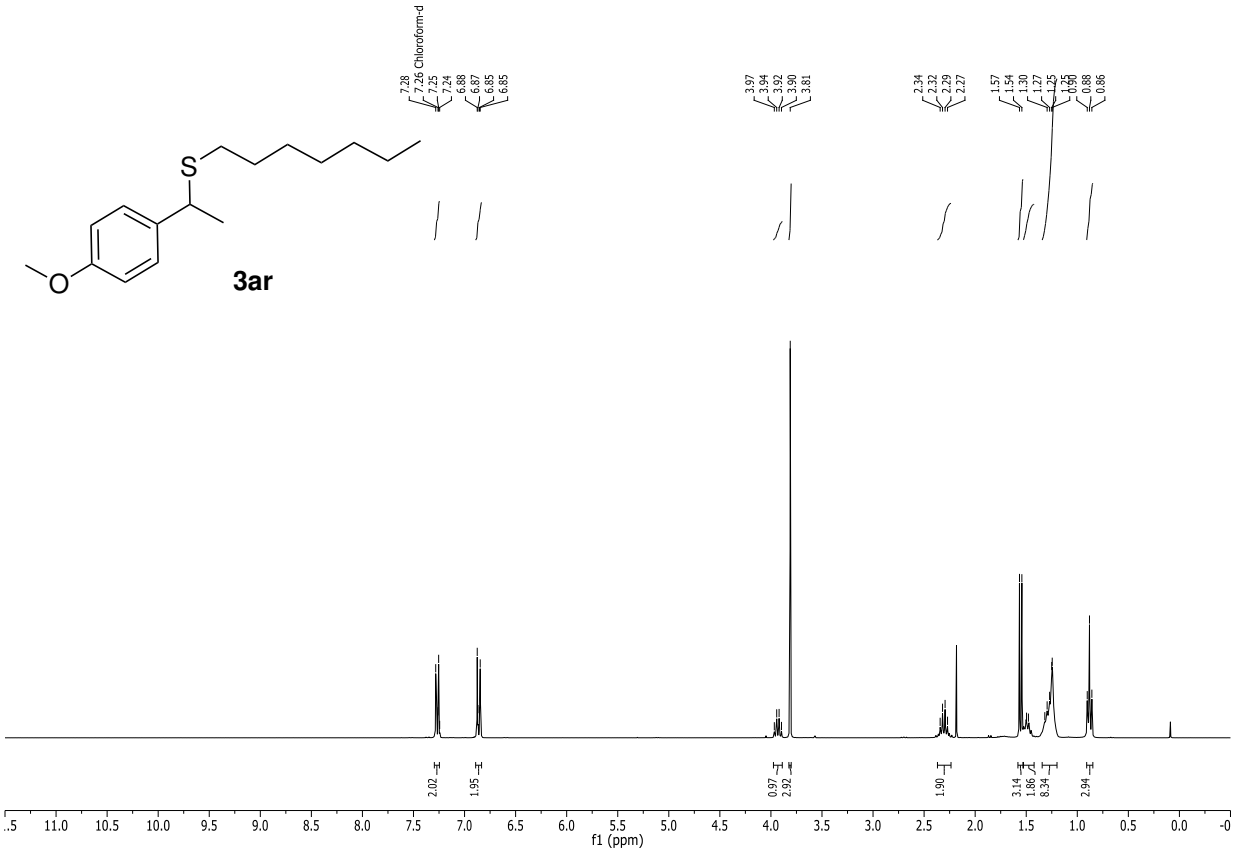
R_f: 0.33 (hexane 100)

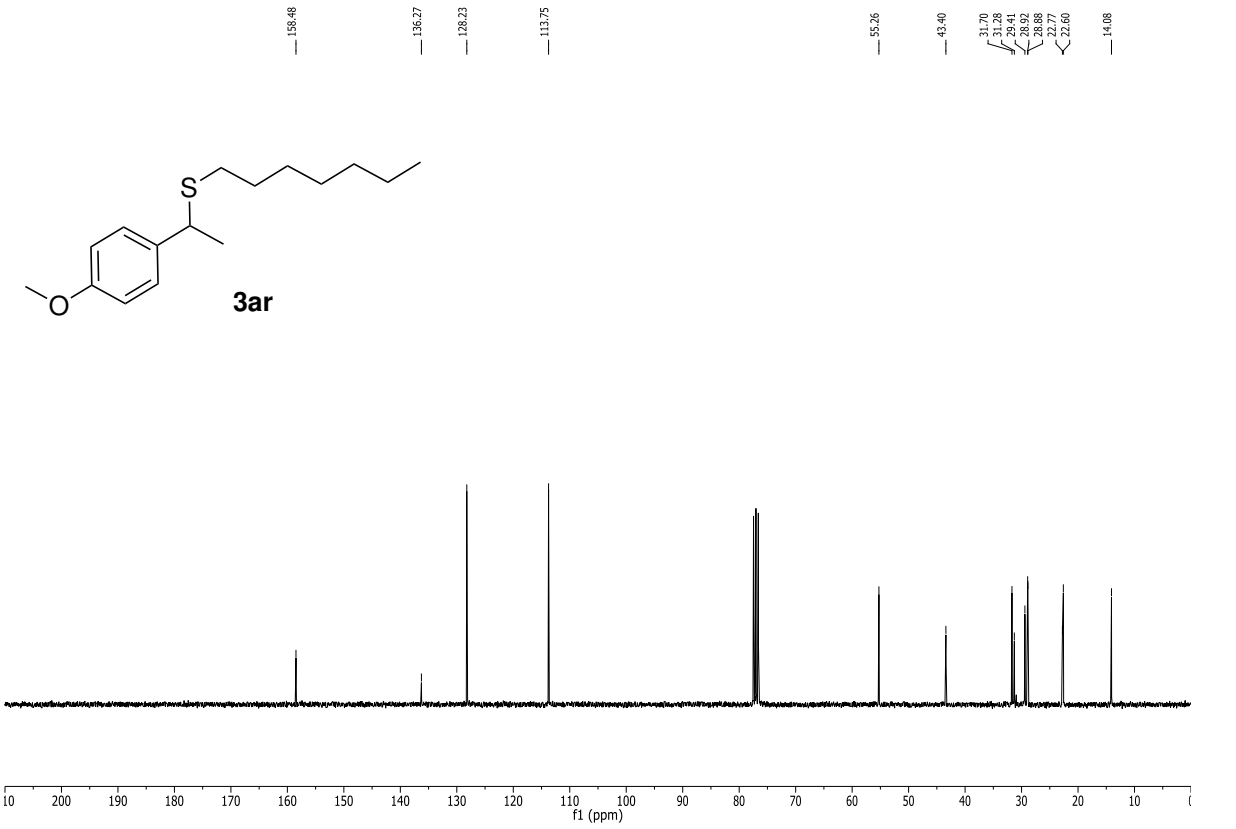
^{1}H NMR (300 MHz, Chloroform-d) δ 7.26 (s, 2H), 6.91 – 6.82 (m, 2H), 3.93 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.31 (q, *J* = 7.2 Hz, 2H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.52- 1.43 (m, 2H), 1.36 – 1.19 (m, 8H), 0.92 – 0.85 (t, *J* = 6.5 Hz 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 136.2, 128.2, 113.7, 55.2, 43.4, 31.7, 31.2, 29.4, 28.9, 28.8, 22.7, 22.6, 14.0.

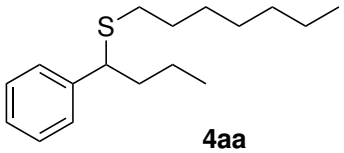
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2922, 2855, 1610, 1509, 1300, 1244, 1174, 1110, 1032, 782.

HR-MS (ESI): calc. for $[M+Na]^+$ m/z: 289.15966 found: 289.15958


7.28 Chloroform-d
7.26
7.25
7.24
6.88
6.87
6.85
6.85
3.97
3.94
3.92
3.90
3.81
2.34
2.32
2.29
2.27
1.57
1.54
1.30
1.27
1.25
0.90
0.88
0.86
S
O
3ar
2.02
1.95
0.97
2.92
1.90
3.14
1.86
8.34
2.94
f1 (ppm)


158.48
136.27
128.23
113.75
55.26
43.40
31.70
31.28
29.41
28.92
28.88
22.77
22.60
14.08
S
O
3ar
f1 (ppm)

Heptyl(1-phenylbutyl)sulfane (**4aa**)



4aa

The compound **4aa** was synthesized from 4-phenyl-but-1-ene (0.5 mmol, 1 equiv, 66.1 mg) and heptane thiol (0.55 mmol, 1.1 equiv, 72.6 mg) according to the General Procedure C. 22 mol% of CF_3SO_3H (9.7 µL) was used. The crude compound was purified by preparative TLC using hexane as the mobile phase. The compound was isolated as a yellow oil (46.2 mg, 0.17 mmol, 35 %)

$C_{17}H_{28}S$ (264.47 g/mol)

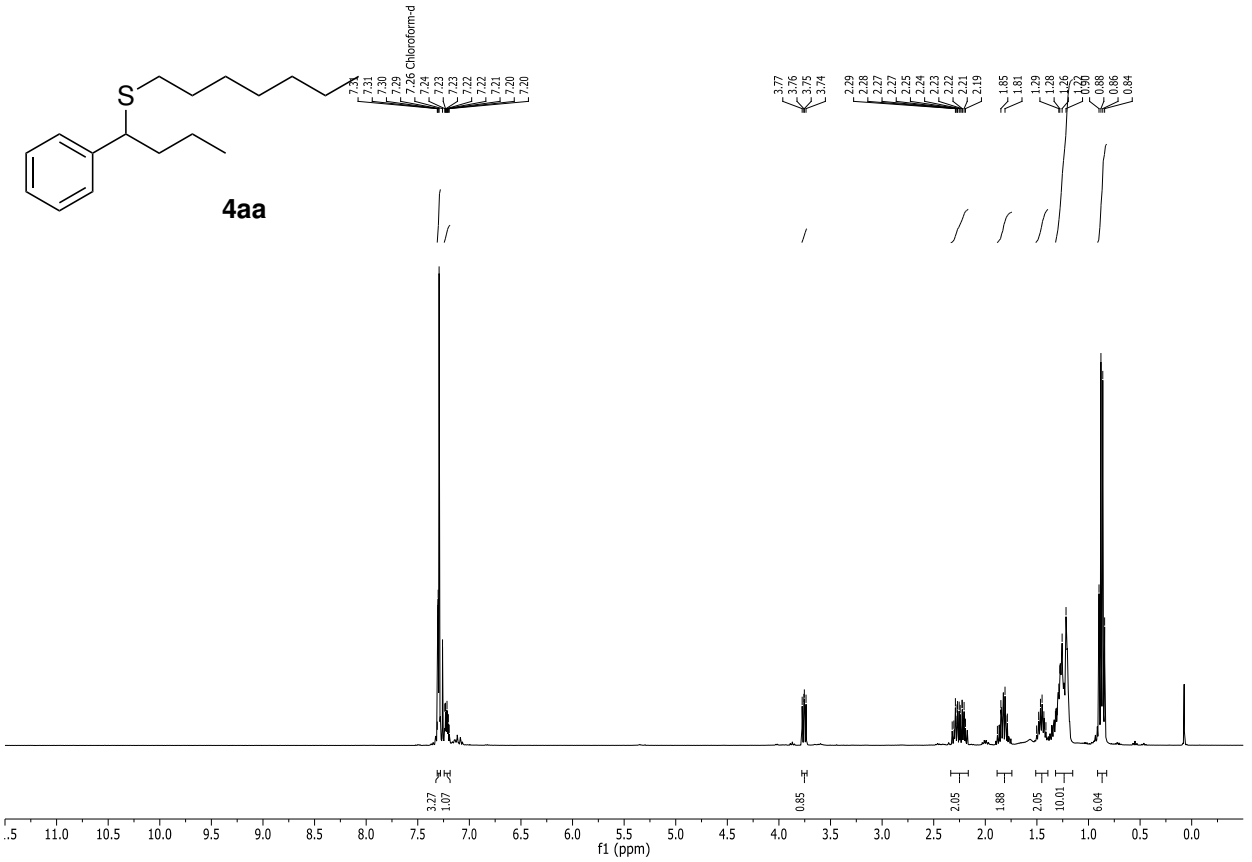
R_f = 0.5 (hexane 100)

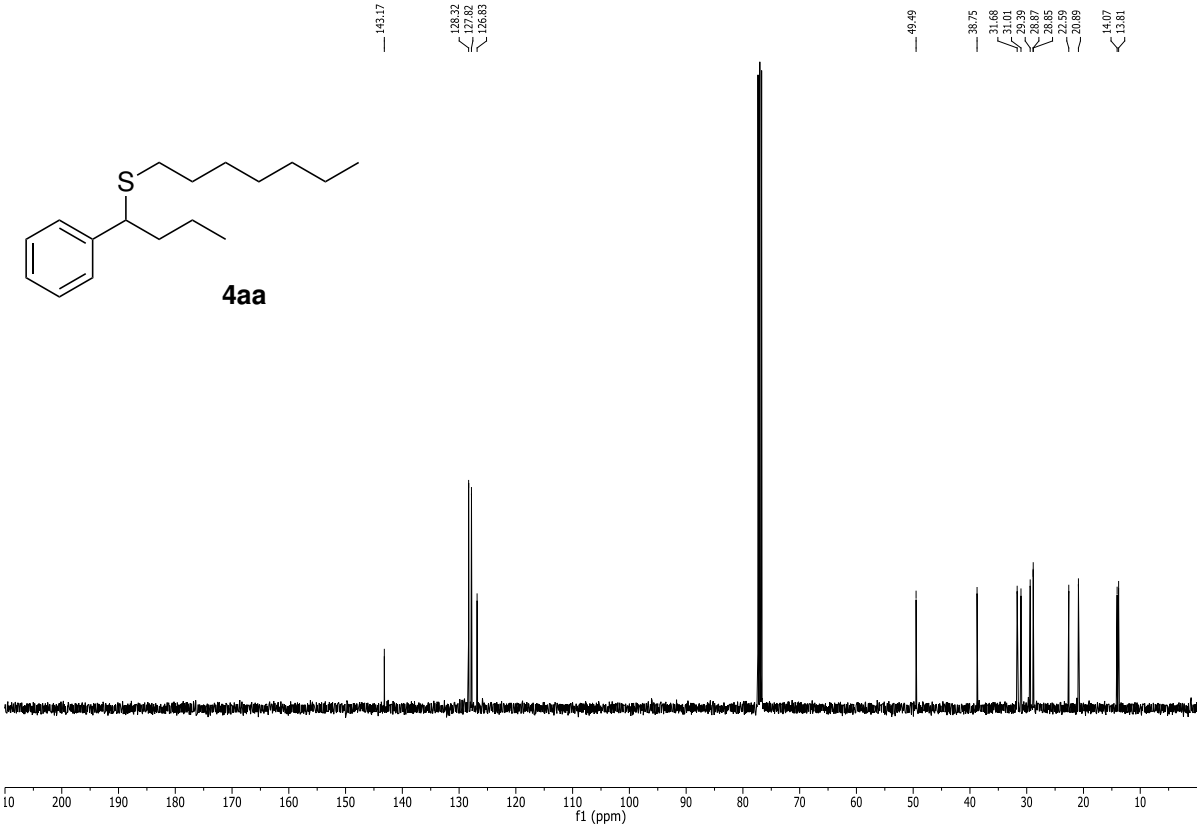
^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 (d, *J* = 3.5 Hz, 4H), 7.25 – 7.19 (m, 1H), 3.76 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.33 – 2.15 (m, 2H), 1.91 – 1.73 (m, 2H), 1.51 – 1.40 (m, 2H), 1.34 – 1.17 (m, 10H), 0.92 - 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 128.3, 127.8, 126.8, 49.4, 38.7, 31.6, 31.0, 29.3, 28.8, 28.8, 22.5, 20.8, 14.0, 13.8.

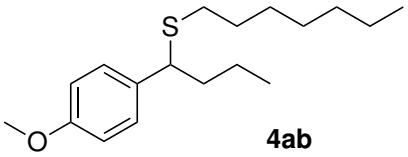
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 2955, 2922, 2855, 1490, 1453, 1379, 1390, 723, 697

HR-MS: (EI with CI source)**:** calculated m/z: 264.190623, found m/z: 264. 19199


Chloroform-d
7.34
7.31
7.30
7.29
7.26
7.24
7.23
7.23
7.22
7.22
7.21
7.20
7.20
3.77
3.76
3.75
3.74
2.29
2.28
2.27
2.27
2.25
2.24
2.23
2.22
2.21
2.19
1.85
1.81
1.29
1.28
1.26
0.92
0.88
0.86
0.84
S
4aa
3.27
1.07
0.85
2.05
1.88
2.05
10.01
6.04
f1 (ppm)


143.17
128.32
127.82
126.83
49.49
38.75
31.68
31.01
29.39
28.87
28.85
22.59
20.89
14.07
13.81
S
4aa
f1 (ppm)

Heptyl(1-(4-methoxyphenyl)butyl)sulfane (**4ab**)



4ab

The compound **4ab** was synthesized from 4-phenyl-but-1-ene (0.5 mmol, 1 equiv, 81.1 mg) and heptane-1-thiol (0.55 mmol, 1.1 equiv, 86 µL) according to the General Procedure C. 22 mol% of CF_3SO_3H (9.7 µL) was used. The crude compound was purified by preparative TLC using hexane:EtOAc mixture (98:2) as the mobile phase. The compound was obtained as a colorless oil (62 mg, 0.21 mmol, 43%).

$C_{18}H_{30}OS$ (294.50 g/mol)

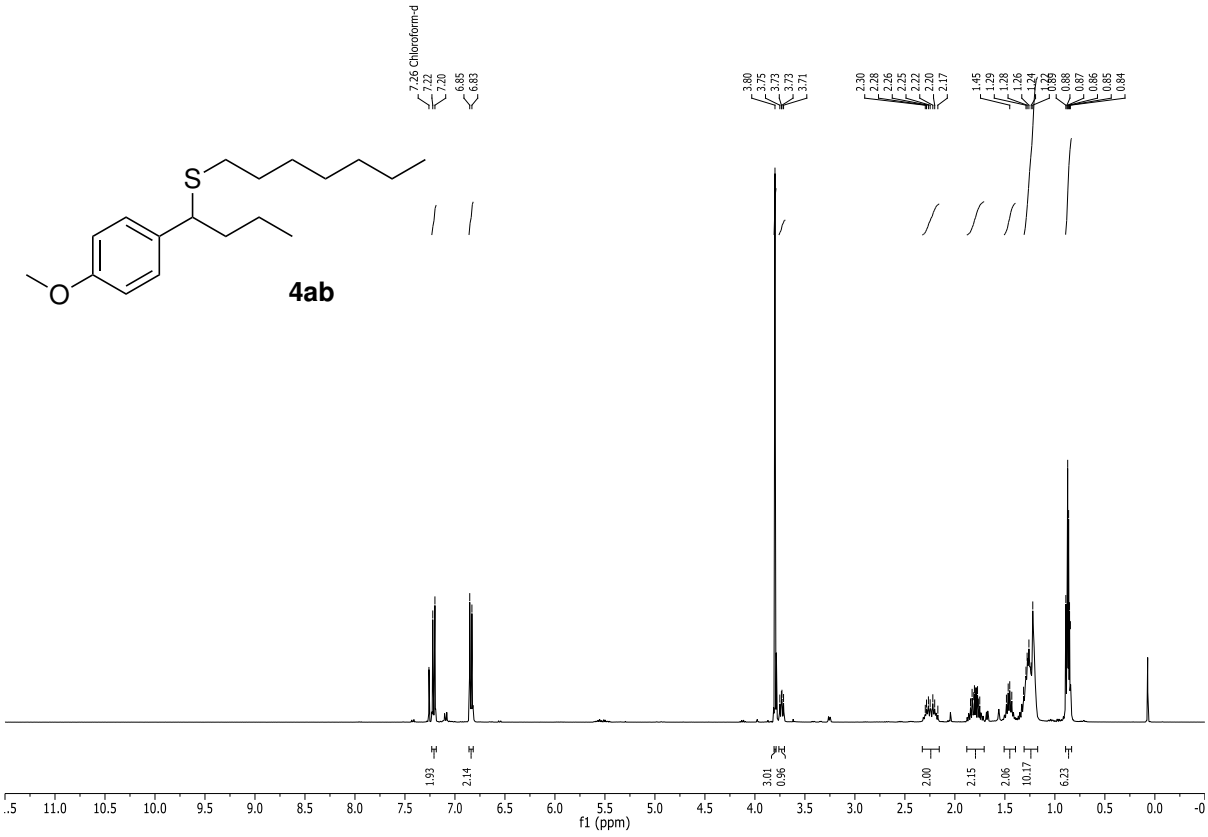
R_f : 0.30 (hexane/Et_2O 97.5:2.5)

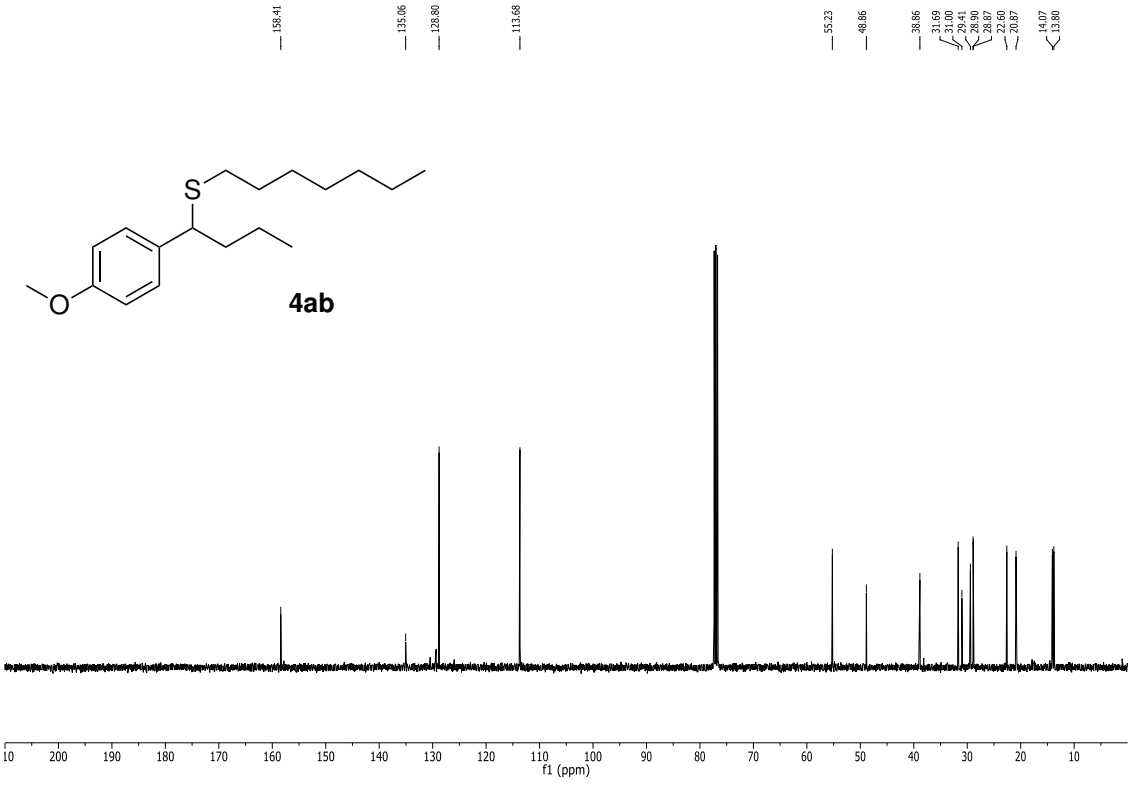
^{1}H NMR (400 MHz, Chloroform-d): δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.73 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.33 – 2.16 (m, 2H), 1.88 – 1.70 (m, 2H), 1.51 – 1.41 (m, 2H), 1.33 – 1.17 (m, 10H), 0.91 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 135.0, 128.8, 113.6, 55.2, 48.8, 38.8, 31.6, 31.0, 29.4, 28.9, 28.8, 22.6, 20.8, 14.0, 13.8.

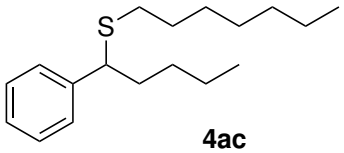
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2922, 2855, 1610, 1509, 1411, 1300, 1244, 1174, 1110, 1030, 831, 735

HR-MS (EI with CI source) calculated m/z: 294.190623, found m/z: 294. 19199


7.26 Chloroform-d
7.22
7.20
6.85
6.83
3.80
3.75
3.73
3.73
3.71
2.30
2.28
2.26
2.25
2.22
2.20
2.17
1.45
1.29
1.28
1.26
1.24
0.89
0.88
0.87
0.86
0.85
0.84
S
O
4ab
1.93
2.14
3.01
0.96
2.00
2.15
2.06
10.17
6.23
f1 (ppm)


158.41
135.06
128.80
113.68
55.23
48.86
38.86
31.69
31.00
29.41
29.00
28.87
22.60
20.67
14.07
13.80
S
O
4ab
f1 (ppm)

heptyl(1-phenylpentyl)sulfane (**4ac**)



4ac

The compound **4ac** was synthesized from 5-phenyl-pent-1-ene (0.5 mmol, 1 equiv, 73 mg) and heptane thiol (0.55 mmol, 1.1 equiv, 86 µL) according to the General Procedure C. 22 mol% of CF_3SO_3H (9.7 µL) was used. The crude compound was purified by preparative TLC using n-hexane as the mobile phase. (The compound could not be entirely purified by chromatographic separation and showed presence of an unidentifiable impurity, which is possibly one of the many positional isomers of the olefin). The compound was obtained as a yellow oil (47.2 mg, 0.16 mmol, 34 %).

$C_{18}H_{30}S$ (278.50 g/mol)

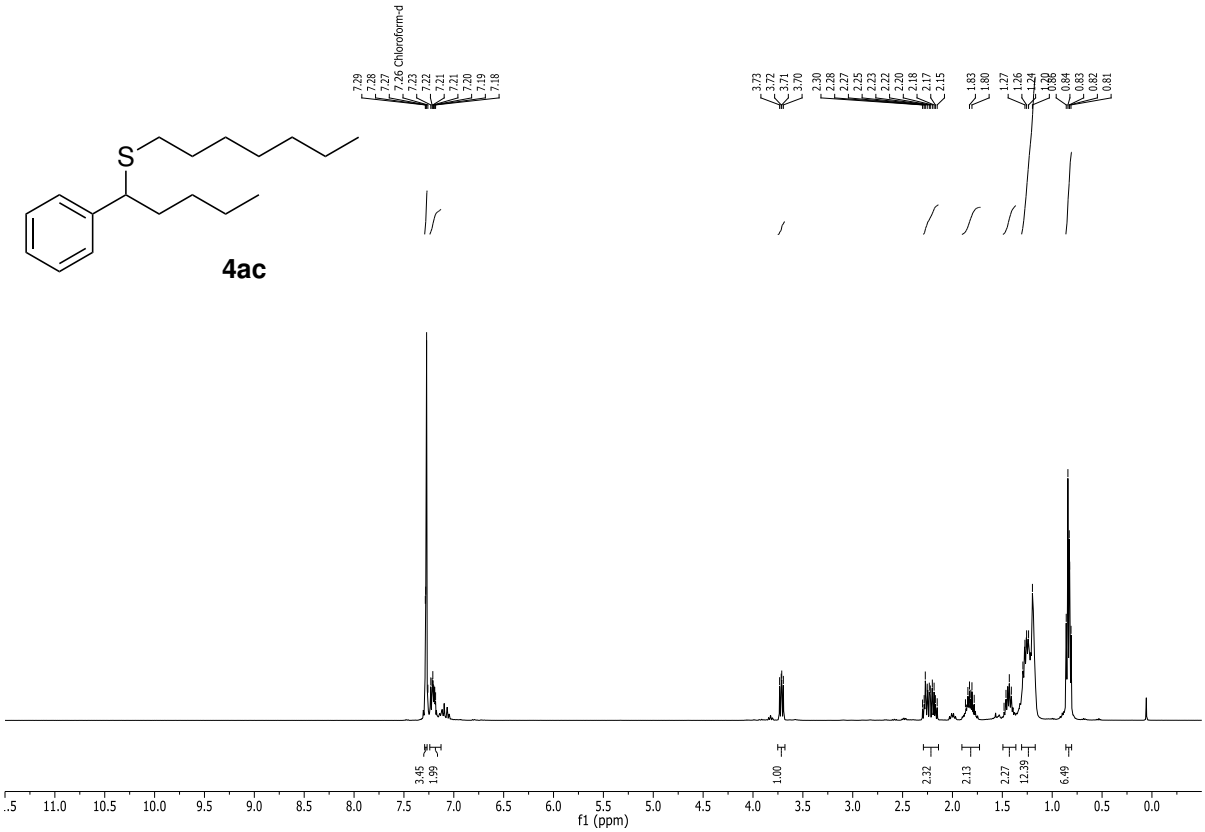
R_f = 0.55 (hexane 100)

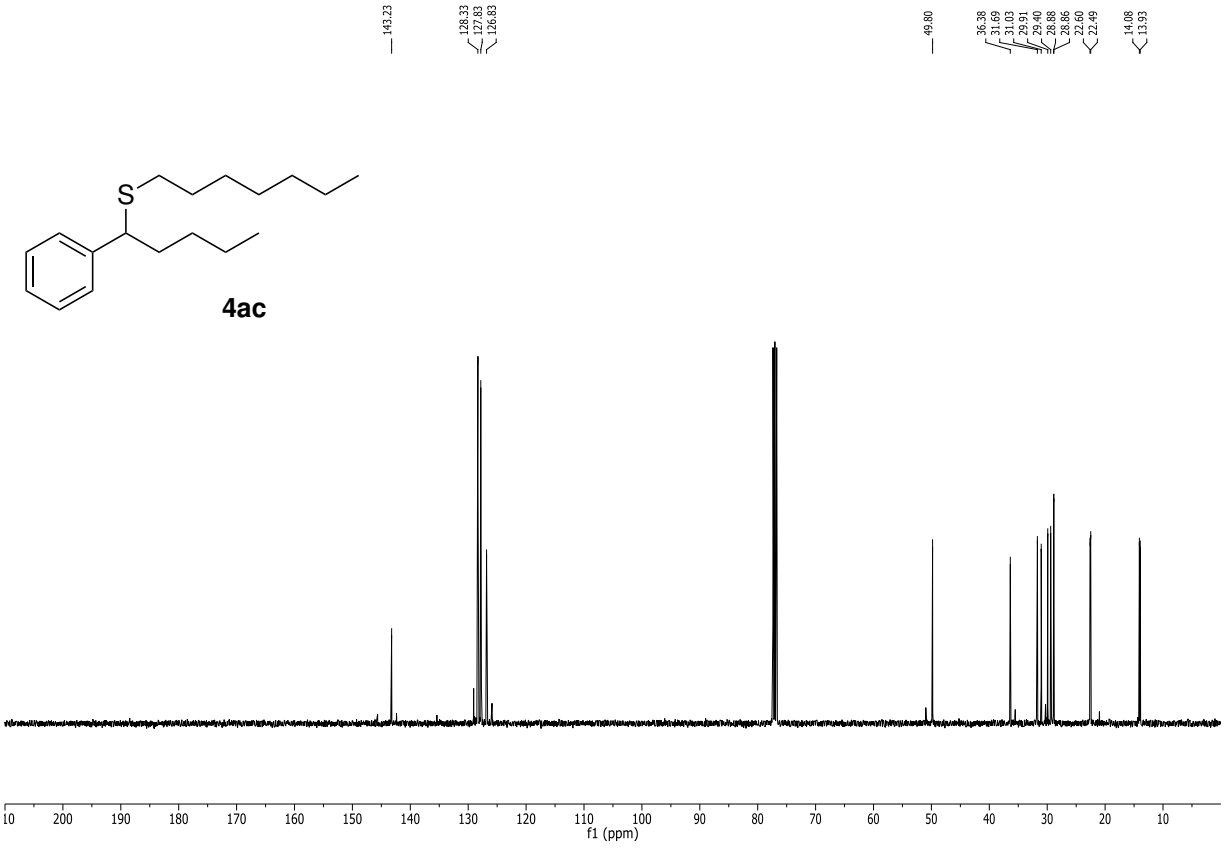
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.26 (m, 3H), 7.24 – 7.15 (m, 2H), 3.71 (dd, *J* = 8.5, 6.4 Hz, 1H), 2.33 – 2.14 (m, 2H), 1.91 – 1.74 (m, 2H), 1.51 – 1.36 (m, 2H), 1.32 – 1.15 (m, 12H), 0.88 – 0.79 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.2, 128.3, 127.8, 126.8, 49.8, 36.3, 31.6, 31.0, 29.9, 29.4, 28.88, 28.86, 22.6, 22.4, 14.0, 13.9

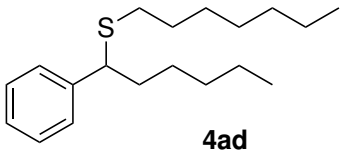
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 2955, 2922, 2855, 1490, 1453, 1379, 1390, 723, 697.

HR-MS (EI with CI source) calculated m/z: 278.206273, found 278.20739


7.29
7.28
7.27
7.26 Chloroform-d
7.23
7.22
7.21
7.21
7.20
7.19
7.18
3.73
3.72
3.71
3.70
2.30
2.28
2.27
2.25
2.23
2.22
2.20
2.18
2.17
2.15
1.83
1.80
1.27
1.26
1.24
0.88
0.84
0.83
0.82
0.81
S
4ac
3.45
1.99
1.00
2.32
2.13
2.27
12.39
6.49
f1 (ppm)


143.23
128.33
127.83
126.83
49.80
36.38
31.69
31.03
29.91
29.40
28.88
28.86
22.60
22.49
14.08
13.93
S
4ac
f1 (ppm)

heptyl(1-phenylhexyl)sulfane (**4ad**)



4ad

The compound **4ad** was synthesized from 6-phenyl-Hex-1-ene (80.13 mg, 0.5 mmol, 1 equiv) and heptane thiol (86 µL, 0.55 mmol, 1.1 equiv) according to the General Procedure C. 22 mol% of CF_3SO_3H (9.7 µL) was used. The crude compound was purified by preparative TLC using hexane as the mobile phase. (The compound could not be entirely purified by chromatographic separation and showed presence of an unidentifiable impurity which is possibly one of the many positional isomers of the olefin). The compound was obtained as a yellow oil (55.48 mg, 0.19 mmol, 38%).

$C_{19}H_{32}S$ (292.53 g/mol)

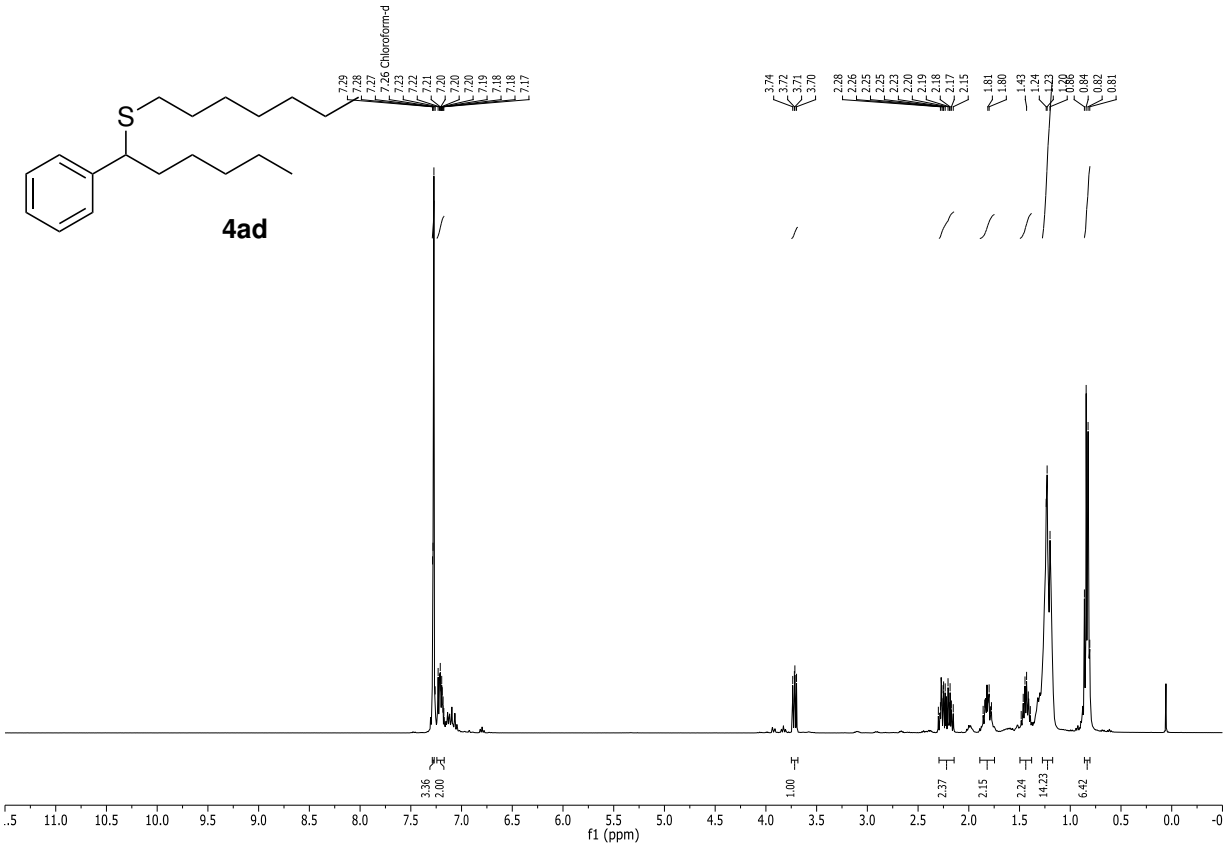
R_f = 0.6 (hexane 100)

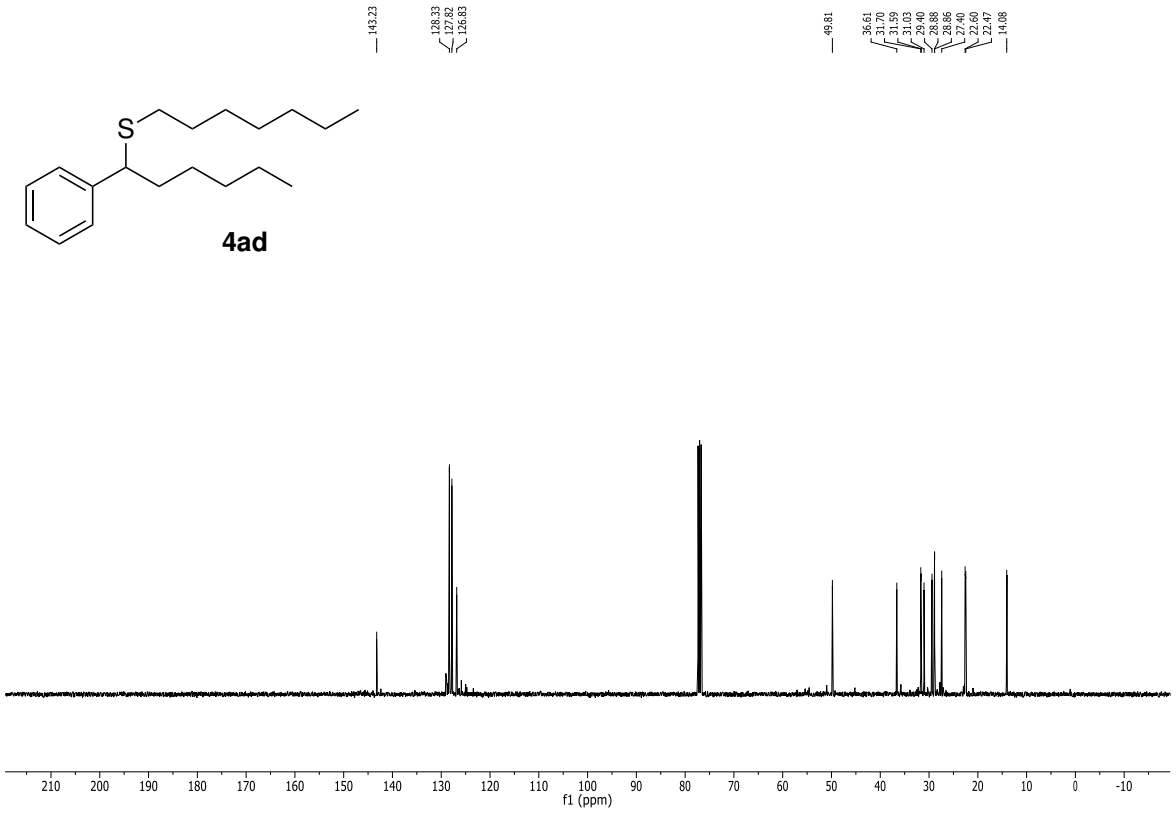
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.27 (m, 2H), 7.25 – 7.16 (m, 1H), 3.72 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.31 – 2.14 (m, 2H), 1.88 – 1.76 (m, 2H), 1.50 – 1.37 (m, 2H), 1.29 – 1.16 (m, 14H), 0.90 – 0.78 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.2, 128.3, 127.8, 126.8, 49.8, 36.6, 31.7, 31.5, 31.0, 29.4, 28.88, 28.86, 27.4, 22.6, 22.4, 14.0

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 2922, 2855, 1490, 1379, 1453, 1069, 1028, 752, 723

HR-MS (EI with CI source) calculated m/z: 292.221923, found 292.22249


Chloroform-d
4ad
f1 (ppm)


4ad
f1 (ppm)

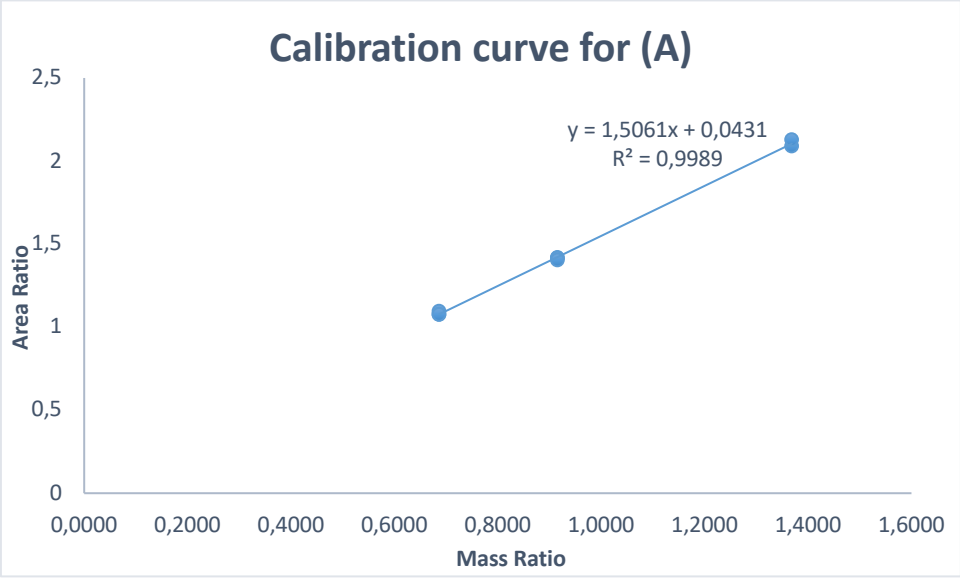
6. GC-FID Analysis Calibration Data

(1-[3,4-dimethoxyphenylpropyl]heptyl)sulfane (A)

For the purpose of quantitative analysis through GC-FID, stock solutions of (A) and the internal standard (pentadecane) were prepared in 10 mL calibrated volumetric flask. 0.24 mmol (of both the compounds) were taken in separate volumetric flasks. These were then diluted using 10 mL of DCM. To get different ratios of (A) and standard, a volume of 200, 300 and 400 µL of stock solution of (A) was taken in GC vials. Each volume measurement was performed in triplicates. A constant volume of 400 µL (of the standard) was added to the each of the nine GC vials. From the volume used and the dilution factor, the absolute weight of the compound taken in the GC vial was determined and it is given in the table below.

Calibration for (1-[3,4-dimethoxyphenylpropyl]heptyl)sulfane (A)

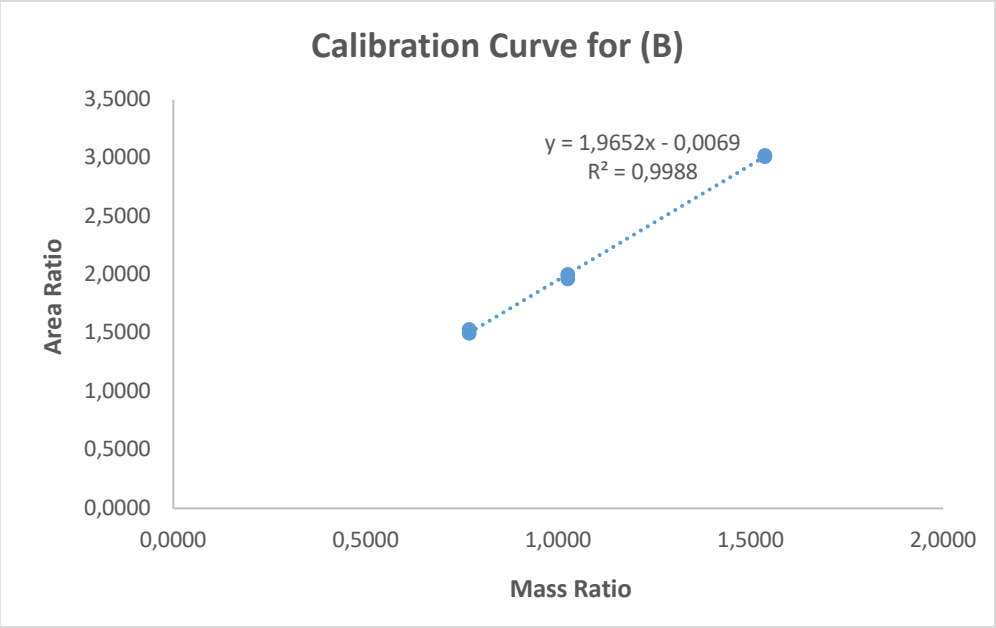
Entry	Mass (A) (mg)	Area (A)	Mass (Pentadecane) (mg)	Area (Pentadecane)
1	1.544	2179.1	2.12	4551.6
2	1.544	2322.9	2.12	4944.4
3	2.316	3386	2.12	4806.3
4	2.316	3307.1	2.12	4682.3
5	2.316	3343.1	2.12	4708.5
6	3.088	4551.7	2.12	4980.8
7	3.088	4657.6	2.12	5018.1
8	3.088	4401.7	2.12	4737.6



Calibration for 2-(1-(3,4-dimethoxyphenyl)propyl)-1,3-dimethoxybenzene (B)

For the purpose of quantitative analysis through GC-FID, stock solutions of **(B)** and the internal standard (Pentadecane) were prepared in 10 mL calibrated volumetric flask. 0.16 mmol (of both the compounds) were taken in separate volumetric flasks. These were then diluted using 10 mL of DCM. To get different ratios of (A) and standard, a volume of 200, 300 and 400 µL of stock solution of (A) was taken in GC vials. Each volume measurement was performed in duplicates. A constant volume of 400 µL (of the standard) was added to the each of the nine GC vials. From the volume used and the dilution factor, the absolute weight of the compound taken in the GC vial was determined and it is given in the table below

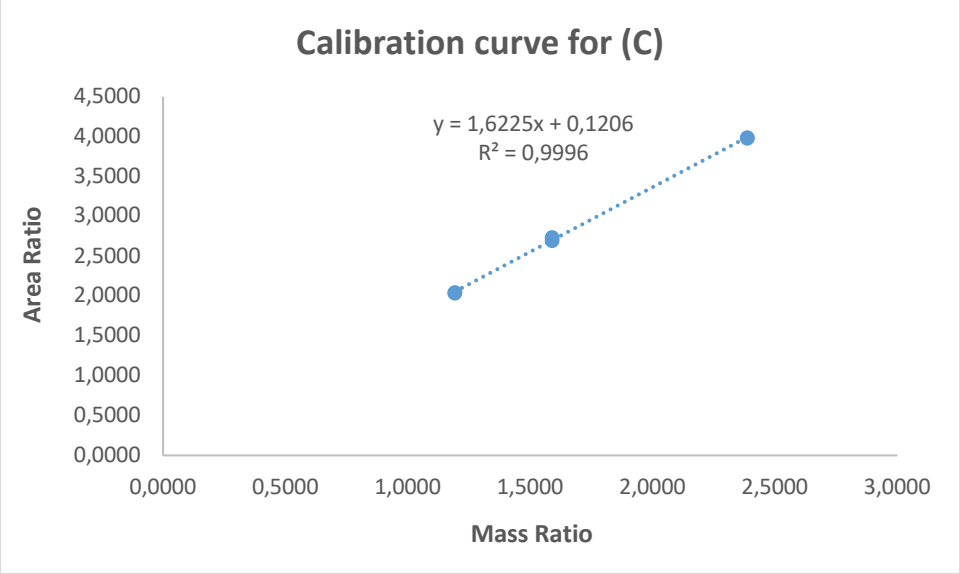
Entry	Mass (B) (mg)	Area (B)	Mass (Pentadecane) (mg)	Area (Pentadecane)
1	1.011	1097	1.359	3304
2	1.011	1142	1.359	3457
3	1.516	1675	1.359	3356
4	1.516	1786	1.359	3510
5	2.022	2276	1.359	3416
6	2.022	2337	1.359	3583



Calibration for 4-allyl-1,2-dimethoxybenzene (C)

For the purpose of quantitative analysis through GC-FID, stock solutions of **(C)** and the internal standard (pentadecane) were prepared in 10 mL calibrated volumetric flask. 0.2 mmol (of both the compounds) were taken in separate volumetric flasks. These were then diluted using 10 mL of DCM. To get different ratios of (A) and standard, a volume of 200, 300 and 400 µL of stock solution of (A) was taken in GC vials. Each volume measurement was performed in triplicates. A constant volume of 400 µL (of the standard) was added to the each of the nine GC vials. From the volume used and the dilution factor, the absolute weight of the compound taken in the GC vial was determined and it is given in the table below

Entry	Mass (C) mg	Area (C)	Mass (Pentadecane) (mg)	Area (Pentadecane)
1	0.712	1558.3	1.699	6218.2
2	0.712	1588.3	1.699	6324.6
3	1.069	2214.6	1.699	6057.2
4	1.069	2212	1.699	5970
5	1.425	3308	1.699	6741
6	1.425	3184	1.699	6522



7. References

1. Newman, P. D.; Campbell, R. A.; Tooze, R. P.; Eastham, G. R.; Thorpe, J. M.; Edwards, P. G. **2002**, *U.S. Patent No. 6,376,715*. Washington, DC: U.S. Patent and Trademark Office.
2. Goldbach, V.; Falivene, L.; Caporaso, L.; Cavallo, L.; Mecking, S., Single-Step Access to Long-Chain α,ω-Dicarboxylic Acids by Isomerizing Hydroxycarbonylation of Unsaturated Fatty Acids. *ACS Catal*. **2016**, *6*, 8229-8238.
3. (a) Hesse, M.;, H, Meier.; Zeeh, B. *Spectroscopic Methods in Organic Chemistry*; Thieme, 2nd edition **2007**, pp 280-281. (b) Anslyn, E.V. and Dougherty, D.A., 2006. *Modern physical organic chemistry* **2006**, University science books.
4. (a) Scheuermann, M. L.; Johnson, E. J.; Chirik, P. J., Alkene Isomerization–Hydroboration Promoted by Phosphine-Ligated Cobalt Catalysts. *Org. Lett.* **2015**, *17*, 2716-2719. (b) Yang, C.T.; Zhang, Z.Q.; Liu, Y.C; Liu, L., Copper-Catalyzed Cross-Coupling Reaction of Organoboron Compounds with Primary Alkyl Halides and Pseudohalides. *Angew. Chem. Int. Ed*. **2011**, *50*, 3904 –3907. (c) Movassaghi, M.; Ahmad, O.K., A Stereospecific Palladium-Catalyzed Route to Monoalkyl Diazenes for Mild Allylic Reduction. *Angew. Chem. Int. Ed*. **2008**, *47*, 8909-8912.
5. Mayer, M.; Czaplik,W. M.; Jacobi von Wangelin, A., Practical Iron-Catalyzed Allylations of Aryl Grignard Reagents. *Adv. Synth. Catal*. **2010,** *352*, 2147-2152.
6. Denmark, S. E.; Werner, N. S., Cross-Coupling of Aromatic Bromides with Allylic Silanolate Salts. *J. Am. Chem. Soc.* **2008,** *130*, 16382-16393.
7. Mohottalage, S.; Tabacchi, R.; Guerin, P. M., Components from Sri Lankan *Piper betle* L. leaf oil and their analogues showing toxicity against the housefly, *Musca domestica*. *Flavour Frag. J.* **2007,** *22*, 130-138.
8. López-Pérez, A.; Adrio, J.; Carretero, J. C. Palladium-catalyzed cross-coupling reaction of secondary benzylic bromides with Grignard reagents. *Org. Lett.* **2009,** *11*, 5514-5517.

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

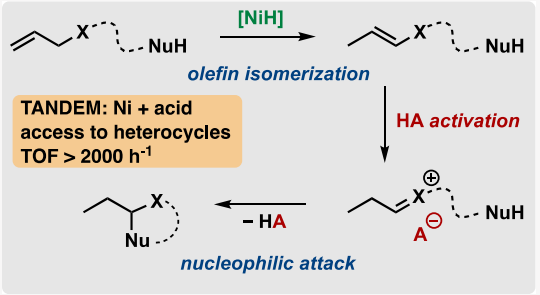
Tandem Olefin Isomerization/Cyclization Catalyzed by Complex Nickel Hydride and Brønsted Acid

Prasad M. Kathe, Alexandru Caciuleanu, Andreas Berkefeld,* and Ivana Fleischer*

Cite This: J. Org. Chem. 2020, 85, 15183−15196 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We disclose a nickel/Brønsted acid-catalyzed tandem process consisting of double bond isomerization of allyl ethers and amines and subsequent intramolecular reaction with nucleophiles. The process is accomplished by $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ in the presence of triflic acid. The methodology provides rapid access to tetrahydropyran-fused indoles and other oxacyclic scaffolds under very low catalyst loadings.



INTRODUCTION

The metal-catalyzed positional isomerization of a double bond is an emerging synthetic transformation[1] that can be combined with follow-up reactions in tandem processes.[2] Such reaction sequences allow for an efficient construction of complex structures in a simple manner from a diverse range of readily available starting materials. The combination of these two (or more) reactions enables functionalization of an otherwise unreactive carbon atom.

Allyl ethers and amines are excellent and straightforward to synthetize substrates for tandem isomerizations. In their seminal work, Terada and co-workers reported the use of complex ruthenium hydride in conjunction with a Brønsted acid for the sequential generation of enamines by isomerization of allyl amines and subsequent acid-catalyzed generation of iminium intermediates and Friedel−Crafts alkylation of electron-rich arenes.[3] The intramolecular version of this reaction provides an efficient route toward synthetically valuable and structurally diverse heterocyclic compounds (Scheme 1a).[4] This was further explored by Scheidt and co-workers[5] in transformation of indole-containing allyl ethers *via* isomerization/oxa-Pictet-Spengler cyclization.[6] They employed a catalyst system comprising an *in situ* generated complex iridium hydride and bismuth triflate to give a range of tetrahydropyran-fused indoles. Further extension was reported by groups of Nielsen and Saa who developed a ruthenium-catalyzed synthesis of acetals.[7]

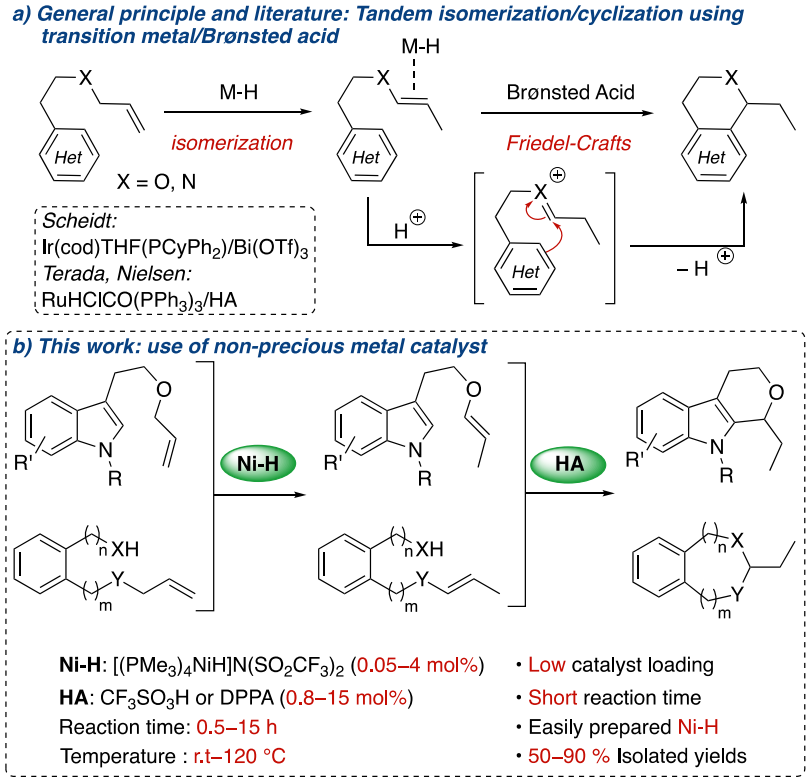
While a great variety of catalysts has been reported for the cyclization step, including enantioselective versions,[8] the isomerization so far has relied only on precious metals such as Ru and Ir. A mechanistically distinct radical cyclo-isomerization[9] of related substrates using a cobalt catalyst was reported by Shenvi and co-workers.[9d] The lack of strategies based on base metal catalysts and our experience with isomerizing transformations[10] and nickel catalysis[11] gave us an impetus to address this shortcoming. The application of a homogeneous nickel catalyst in this chemistry complements the portfolio of nickel catalyzed isomerizations[12] and corresponding tandem processes,[13] providing robust and economical synthetic routes toward libraries of versatile N- and O-containing heterocyclic building blocks. The disadvantage of some of the tandem isomerization nickel catalysts is the need to employ stoichiometric amounts of additives and activators. A relatively simple isomerization catalyst was reported by Tolman in 1972[14] who explored the generation of complex nickel hydrides from readily available phosphine stabilized zero-valent nickel precursors such as $((EtO)_3P)_4Ni$ and Brønsted acid. The *in situ* generated nickel hydride catalyzes the isomerization of simple alkenes such as 1-butene. Mechanistic studies pointed to a migratory insertion, β-hydride elimination pathway for the isomerization which requires the presence of free coordination sites on a metal center. Further insights by Maschmeyer *et al.* revealed $[L_3NiH]^+$ as the catalytically active species.[15]

Notwithstanding the ready availability of reactive complex nickel hydrides, no practical applications of related Ni(0) complexes or corresponding hydrides have been reported. Herein, we disclose the use of the complex $[(Me_3P)_4NiH]N(SO_2CF_3)_2$[16] (**Ni−H**), easily synthesized

Received: August 23, 2020
Published: November 11, 2020

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

Scheme 1. Tandem Isomerization/Cyclization of Allyl Ethers and Amines



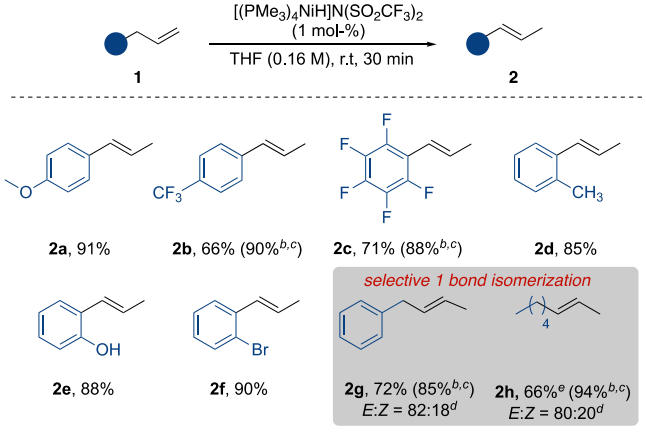
DPPA = dkiphenylphosphoric acid.

from $Ni(PMe_3)_4$ and $HN(SO_2CF_3)_2$, as an efficient isomerization precatalyst. Moreover, this acidic nickel hydride could also work synergistically with a strong Brønsted acid to result in tandem isomerizing cyclizations of allyl ethers and amines (Scheme 1b).

RESULTS AND DISCUSSION

Following the mentioned reports, we sought to investigate the capability of **Ni−H** to catalyze olefin isomerization in allyl benzenes. As depicted in Scheme 2, the allyl benzenes **1a−f** underwent rapid olefin isomerization at room temperature regardless of the electronic nature of functional group, giving the corresponding β-methylstyrenes exclusively as the *E*-isomers. Notably, the double bond in 4-phenyl-1-butene (**1g**) migrated selectively over a single carbon atom, since only traces of the regioisomer were found. Both geometrical isomers were initially present with E/Z = 51:49, but conversion of (*Z*) into (*E*) isomer occurred on prolonged reaction times, typically overnight. A selective one bond isomerization was also observed with 1-octene. Substrates with an internal double bond or a terminal disubstituted double bond did not undergo positional isomerization, but the reaction of (*Z*)-2-octene with 1 mol % of catalyst led to 79:21 mixture of *E*- and *Z*-isomers after 22 h. Possibly, the reason is kinetic control of the reaction.

Scheme 2. Olefin Isomerization Catalyzed by Ni−H[a]

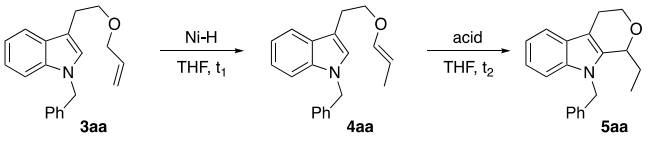


[a]Reaction conditions: alkene (0.25 mmol), **Ni−H** (1 mol %), THF (0.16 M), isolated yield; [b]GC yield using pentadecane as an internal standard; [c]CH_2Cl_2 (0.16 M); [d]E/Z ratio after 15 h; [e]**Ni-H** (0.17 mol %), isolated yield.

With the established isomerization procedure in hand, we proceeded to investigate the follow-up cyclization of indole-substituted allylether **3aa**. We chose to use $Bi(OTf)_3$ as a cocatalyst and a source of triflic acid owing to its superior activity in Friedel−Crafts type reactions as compared to other triflates.[17] Unlike the initially investigated alkenes, it was observed that incomplete isomerization of **3aa** to **4aa** occured (57:43 after 2 h), providing an equilibrium mixture eventually. Addition of a fresh aliquot of **Ni−H** neither led to any further isomerization nor to any cyclization. The addition of equimolar amounts of $Bi(OTf)_3$ after 4 h resulted in formation of **5aa** in 30−60% yield (Table 1, entries 1−2). Since the addition of all reaction components at the onset of reaction appears to result in incomplete conversion to product, a sequential addition was tested, in which the reactant was stirred with **Ni−H** for the given amount of time (t_1) followed by addition of the acid and prolonged stirring (t_2). Still, the use of $Bi(OTf)_3$ did not give

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

Table 1. Optimization of Reaction Conditions for Tandem Olefin Isomerization/Oxa-Pictet Spengler Cyclization[a]



entry	Ni−H (mol %)	acid (mol %)	time (t_1;t_2/h)	T (°C)	yield (%)[e]
1[b]	5	$Bi(OTf)_3$ (5)	4/4	r.t	31
2	5	$Bi(OTf)_3$ (5)	4/4	r.t	62
3	5	TfOH (5)	0.5/0.5	r.t	80
4	5	TfOH (15)	0.3/0.3	r.t	12
5	1	TfOH (4)	0.3/0.3	r.t	80
6[c]	5	None	18	130	41
7[d]	1	$(PhO)_2P(O)OH$ (4)	0.5/18	120	78

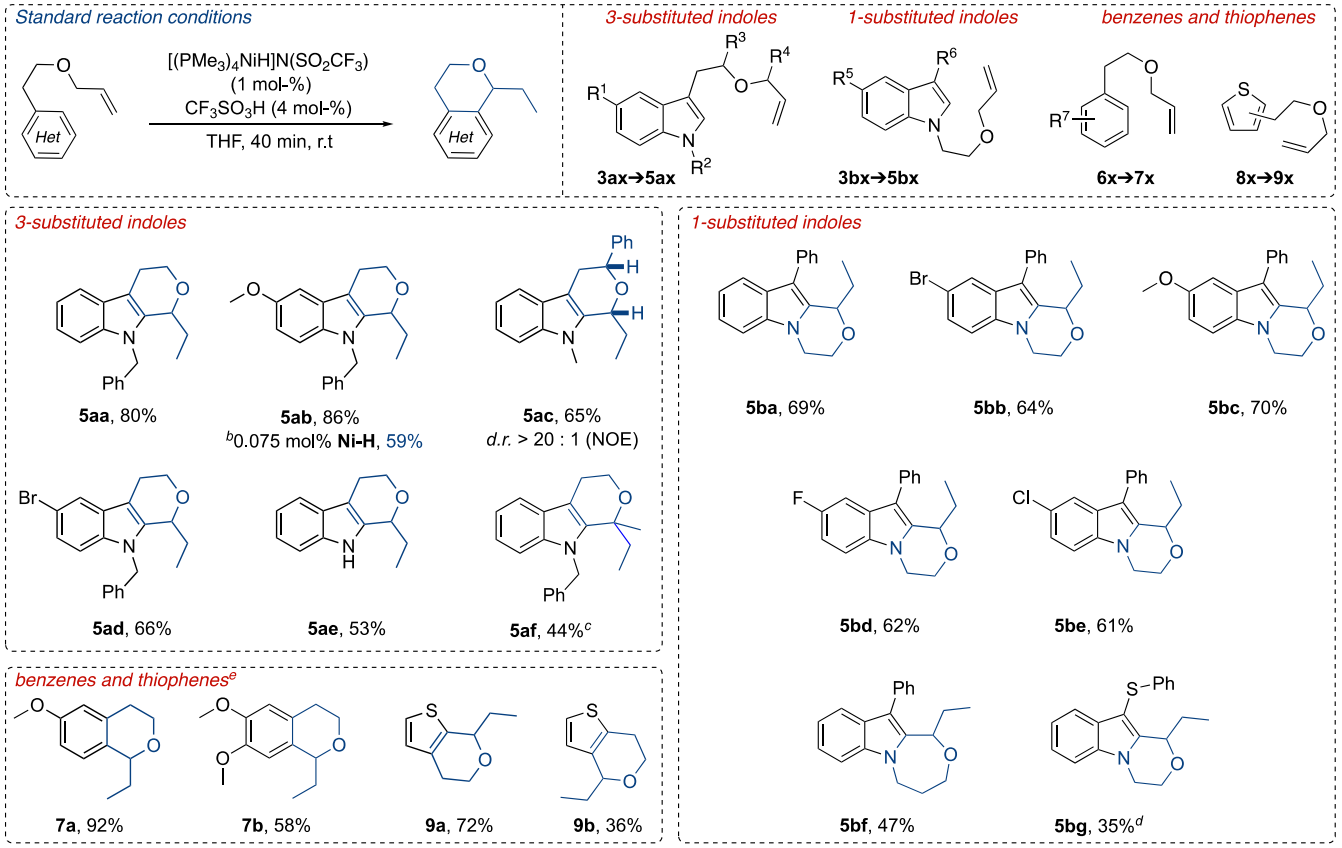
[a]Reaction conditions: **3aa** (0.25 mmol), **Ni−H**, acid, THF (0.16 M). [b]Solvent: CH_2Cl_2. [c]Solvent: xylene, 130 °C, determined by quantitative GC-FID analysis. [d]Solvent: toluene. [e]Isolated yield.

reproducible results, and triflic acid (TfOH) was used instead. We were pleased to find that with 5 mol % **Ni−H** and 5 mol % TfOH, product **5aa** was formed in 80% yield (entry 3). While a high excess of acid (15 mol %) was detrimental, the reaction time could be shortened to overall 40 min with concurrent lowering of catalyst loading to 1 mol % without any loss of yield (entries 4, 5). At room temperature, no reaction occurred in the absence of either **Ni−H** precatalyst or the Brønsted acid. Notably, using only **Ni−H** under forcing reaction conditions afforded product **5aa** in 41% yield (entry 6).

We tested the scope of the developed methodology by subjecting a number of O-allylated indole derivatives to isomerization/cyclization (Scheme 3). The C-3 substituted indoles with methoxy and bromo substituents smoothly underwent cyclization to give products **5ab** and **5ad** in yields of 86% and 66%, respectively. In an effort to display the robustness of this catalytic system at a preparative scale, the loading of **Ni−H** could be lowered to 0.075 mol % and the TfOH to 1.5 mol % for the synthesis of **5ab** at a 4 mmol scale in 59% yield (>98% purity, see Supporting Information) and hence without a major loss in catalytic activity (TOF = 1190 h^{-1}).

C-3 substituted unprotected indoles could also undergo cyclization albeit giving a moderate 53% yield (**5ae**). A substrate possessing a phenyl ring adjacent to the *O*-allyl tether was tested and the product **5ac** could be isolated with a high d.r. of 20:1 in 65% yield. Incomplete conversion was observed when the optimized conditions were used for synthesis of **5af** with a methyl group on the allyl chain. For the purpose of enabling complete conversion, higher loadings of precatalysts and elevated temperatures were employed to give **5af** in 44% yield. We went on to test selected N-substituted indoles in catalysis. Substrates without a substituent in the 3-position

Scheme 3. Isomerizing Friedel−Crafts Cyclization for Synthesis of Various Pyran-Fused Heterocycles[a]



[a]Reaction conditions: substrate (0.25 mmol), **Ni−H** (1 mol %), CF_3SO_3H (4 mol %), THF (1.5 mL), r.t., 40 min; [b]**3ab** (4.0 mmol), **Ni−H** (0.075 mol %) CF_3SO_3H (1.5 mol %) [c]**Ni-H** (4 mol %), CH_3SO_3H (16 mol %), THF (1.5 mL), 60 °C, 60 min; [d]**Ni-H** (2 mol %), CH_3SO_3H (8 mol %), THF (1.5 mL), 40 °C, 60 min; [e]**Ni-H** (0.05 mol %), CF_3SO_3H (1 mol %).

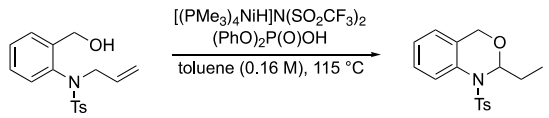
https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

resulted in the formation of oligomers under acid catalysis. Also in this case, various 5-substituted indoles reacted to the corresponding products **5ba–be** in good yields. N-substituted indole with an extra carbon in the N–O bridge resulted in product **5bf** in 47% yield. Furthermore, we tested two polar substituents on the C-3 position. The presence of a thioether function was tolerated but resulted in a lower yield. The presence of thiocyanate function on C-3 position failed to afford any cyclized product but isomerization of the double bond was observed.

The optimized reaction conditions were further put to test for synthesis of oxacyclic scaffolds based on electron rich phenyl and thiophenyl rings using a low **Ni–H** loading of 0.05 mol %. The reaction of 2-(3-methoxyphenyl)ethylallylether afforded isochroman derivative **7a** in 92% yield. However, substitution at the 4-position resulted mainly in deallylation. A lower yield was obtained for the dimethoxy substituted substrate. Substitutions on the thiophene ring at 2- and 3-positions were also tolerated to furnish the products **9a** and **9b** in 72 and 36% yield, respectively, and a remarkable TOF of 2170 h^{-1} for **9a**.

In order to extend the scope of the methodology and to broaden the variability of oxacylic scaffolds, we aimed at the intramolecular cyclization of *in situ* generated electrophiles with pendant nucleophilic heteroatoms. First, we tested the synthesis of 1,3-oxazines as cyclic hemiaminal ethers.[7a] The alternative synthetic strategy toward related structures through Mannich condensation of phenols can be limited by the competitive formation of dimers.[18] Considering the lack of examples of 3d-metal catalyzed transformations using this particular class of substrates, we capitalized on the ability of **Ni–H** to engage in tandem processes to achieve the desired outcome using **10a** as the substrate. The instability of the reaction product (Table 2) necessitates the use of a weaker Brønsted acid but harsher reaction conditions (115 °C) and a higher amount of precatalyst (4 mol %) were required.

Table 2. Optimization of Reaction Conditions for the Synthesis of Mixed Acetals[a]



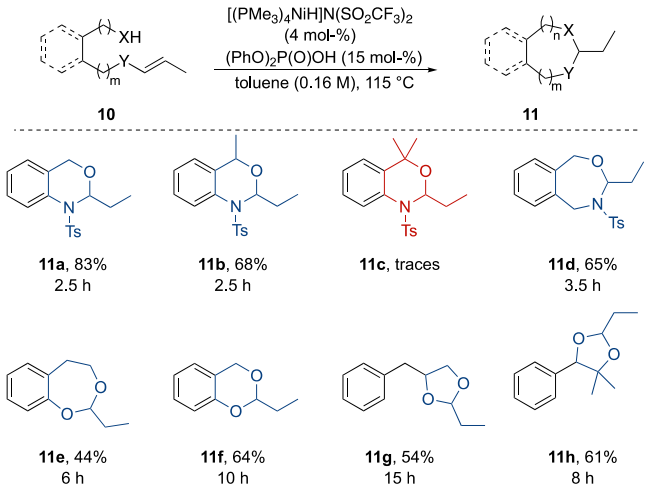
10a 11a

	Ni–H (mol %)	acid (mol %)	time (h)	yield (%)[b]
1	1	8	15	42
2	2	15	2.5	55
3	4	15	2.5	83
4	4	20	2.5	81

[a]Conditions: **10a** (0.25 mmol), **Ni–H**, $(PhO)_2P(O)OH$, toluene (1.5 mL), 115 °C. [b]Isolated yield.

Upon optimizing the reaction conditions for the synthesis of *O,N*-acetals, we turned our attention to evaluate the generality and robustness of these conditions (Scheme 4). Another 6-membered *O,N*-acetal with a single substituent on the benzylic position (**11b**) could be obtained in 68% yield. However, the presence of two methyl groups was detrimental for the transformation and did not lead to complete conversion (**11c**). Acetal formation may be kinetically challenged owing to the steric hindrance by the methyl groups, and formal deallylation was observed instead. Contrary to **11c**, the synthesis of the 7-membered analogue **11d** and the corresponding *O,O*-acetals **11e–f** was accomplished in good yields. Moreover, two 1,3-dioxolane derivates **11g–h** were obtained in 54% and 61% yields, respectively.

Scheme 4. Synthesis of Cyclic Acetals[a]



[a]Conditions: **10** (0.25 mmol), **Ni–H** (4 mol %), $(PhO)_2P(O)OH$ (15 mol %), toluene (1.5 mL), 115 °C.

CONCLUSIONS

This report describes a methodology, which exploits readily available complex nickel hydride working in tandem with a Brønsted acid to enable the synthesis of O-containing heterocycles by a isomerization/cyclization strategy. The employed nickel precatalyst performs selectively in migrating a double bond in allyl arenes and other terminal olefins over one bond. This reactivity serves as a platform to open new avenues in nickel hydride/Brønsted acid co-catalyzed tandem transformations. Our methodology has advantages over state-of-the art catalyst systems that require either refluxing conditions and high catalyst loadings (Ru) or a preactivation and catalyst addition (Ir) in portions. Moreover, we report unusually low catalyst loadings for nickel in general.

EXPERIMENTAL SECTION

General Experimental Information. Solvents and Reagents. All solvents were distilled and dried before use or purchased from the respective supplier as dry solvents. Reactions with oxygen- or moisture-sensitive reagents were carried out under argon using standard Schlenk techniques. Other chemicals were purchased from Acros Organics, Chem-Pur, Sigma-Aldrich, ABCR, TCI Chemicals, Fluka Chemicals, Alfa Aesar and were used as received. Used abbreviations of reagents: THF (tetrahydrofuran). The complexes $[(Me_3P)_4NiH]N(SO_2CF_3)_2$, $Ni(PMe_3)_4$, and $Ni(PPh_3)_4$ were synthesized according to the procedure reported in the literature.[16b,19] Column chromatography was carried out using silica gel (60 Å) as the stationary phase, either using gravity flow conditions under isocratic elution or flash column chromatography under gradient elution. Gradients were set up depending on the solvent ratios found ideal *via* thin layer chromatography (TLC). TLC was performed with aluminum plates coated with silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution. Gas Chromatography (GC-FID) analysis was carried out on a HP6890 GC-System with injector 7683B and Agilent 7820A system. Dry hydrogen was used as the carrier gas, and for the measurements, the following method was used: Heating from 50 to 280 °C within 15 min. Pentadecane was added as the

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183–15196

internal standard. For the calibration, samples with different amounts of substrate and standard (pentadecane) were measured with GC-FID, and the obtained data were used to plot A(standard)/A(substrate) against m(standard)/m(substrate). The resulting slope computed from linear regression is equivalent to the response factor R, which can be used to quantify unknown samples. Gas chromatography−mass spectrometry was performed on an Agilent 7820A GC system in combination with an Agilent 5977 B using an EI source and a quadrupole analyzer. Samples were diluted in an organic solvent and passed through aluminum oxide prior to GC−MS analysis. Crude samples were additionally stirred with QuadraSil scavengers for several minutes prior to analysis. For all analyses, the following method was used: Heating from 50 to 280 °C within 15 min. "Synkam S1121" chiral HPLC was used for determination of enantiomeric ratios. Reprosil Chiral-OM (5 μm) was used as a column (125 × 4 mm) with a 206 PHD UV detector from Linear. NMR spectra were recorded using a Bruker AVANCE 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker AVANCE 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz). All ^{13}C NMR spectra were recorded with proton decoupling. All measurements were done at ambient temperature. Chemical shifts δ are reported in parts per million relative to the residual ^{1}H and natural abundance ^{13}C NMR resonances of the solvents: $CDCl_3$, $\delta_{H/C}$ = 7.26/77.0; THF-d_8, $\delta_{H/C}$ = 3.58/67.6. Coupling constants J are given in Hertz [Hz]. ^{1}H NMR splitting patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; and m = multiplet. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR system. Absorption bands are given in wave numbers $\tilde{\nu}$ (cm^{-1}). HRMS (ESI, APCI, EI) analysis was carried out by the mass spectrometry department of the Institute of Organic Chemistry, University of Tübingen.

General Procedure (A). Tandem Olefin Isomerization/Oxa-Pictet Spengler Cyclization and Synthesis of Oxacyclic Scaffolds. To a flame-dried 20 mL Schlenk tube inside a glove box was added $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.05−1 mol %). Outside the box, dry THF (0.16 M) was added under Ar counterflow, and a yellow colored solution formed. After the addition of the substrate (0.25 mmol), the reaction mixture was stirred for 20 min at room temperature. This was followed by the addition of triflic acid (0.8−4 mol %), and the reaction mixture was stirred further for 20 min. The reaction mixture was then diluted with 5 mL ethyl acetate and washed with water and brine (2 × 5 mL). The aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic phases were dried over magnesium sulfate. Organic solvents were removed by rotary evaporation. This was followed by column chromatography using dry loading.

General Procedure (B). Synthesis of O,O/O,N-Acetals. To a flame-dried 20 mL Schlenk tube inside a glove box was added $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (4 mol %). Outside the box, dry toluene (0.16 M) was added under Ar counterflow affording a yellow solution. After the addition of the substrate (0.25 mmol), the reaction mixture was stirred for 30 min at room temperature. This was followed by addition of diphenyl phosphate (8−16 mol %), and the reaction mixture was heated (oil bath) further for the time specified for every substrate. The reaction mixture was then diluted with 5 mL EtOAc and washed with water and sat. NaCl (2 × 5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over magnesium sulfate. Organic solvents were removed by rotary evaporation. This was followed by column chromatography using dry loading.

General Procedure (C). Olefin Isomerization by [Ni-(PMe$_3$)$_4$H]Tf$_2$N. For a typical experiment to test olefin isomerization, the pre-catalyst $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1 mol %) was added to a Schlenk tube in a glove box. The Schlenk tube was taken outside the glove box, evacuated, and backfilled with argon. This was followed by addition of dry CH_2Cl_2 (0.16 M), affording a yellow colored solution to which the substrate was added. The progress of alkene isomerization was monitored by GC-FID. For the purpose of isolation of the isomerized product, the reaction mixture was passed through a Pasteur pipette with cotton plug and aluminum oxide. The Schlenk tube was washed with 2 mL CH_2Cl_2, and the solvent was again passed through the Pasteur pipette. Careful rotary evaporation of the solvent (owing to the volatility of the products) was done followed by recording NMR spectra of the reaction mixture.

General Procedure (AA). Synthesis of Substrates 6a, 6b, 8a, and 8b by O-Allylation. In a flame-dried 3-neck round bottom flask fitted with reflux condenser, NaH (60% dispersion in mineral oil, 1.5 equiv) was added. This was followed by addition of dry THF (0.1 M). The corresponding alcohol (1 equiv) was then added, and the mixture was heated to 50 °C (oil bath) for 1 h. The mixture was then cooled to 0 °C before the addition of allyl bromide (2 equiv). The reaction mixture was stirred at ambient temperature overnight and then quenched with 50 mL of sat. NH_4Cl solution. The aqueous phase was extracted with EtOAc (2 × 40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (mixture of *n*-hexane and ethyl acetate).

General Procedure (AB). Synthesis of Indole Derivatives 3aa−3af. 1. Fischer indole synthesis of tryptophol: Phenylhydrazine·HCl (1 equiv) was dissolved in a 1:1 mixture of 4% aqueous H_2SO_4 solution (0.69 M) and dimethylacetamide (0.69 M). Past heating it to 100 °C (oil bath), 2,3-dihydrofuran (1 equiv) was added drop-wise. After 2 h, the reaction mixture was cooled to ambient temperature and extracted with ethyl acetate. The organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation at 12 mmHg and 50 °C. The crude tryptophol was purified by column chromatography (*n*-hexane/ethyl acetate 1:1) and used as such for the Appel reaction. **2. Appel reaction**: In a dry 3-neck round-bottom flask, tryptophol was dissolved in dry CH_2Cl_2 and cooled to 0 °C. After that, triphenylphosphine (1.1 equiv), imidazole (2.2 equiv), and iodine (1.1 equiv) were added in that order. The mixture was stirred at ambient temperature till completion. The reaction was diluted with CH_2Cl_2 and washed with water, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography. **3. O-Allylation of the iodide**: The product of Apple reaction (1 equiv) and freshly distilled allyl alcohol (30 equiv) were heated to 90 °C (oil bath). Cesium carbonate (2 equiv) was added, and the yellow mixture was heated further for 2 h at 100 °C (oil bath). The mixture was then cooled to ambient temperature and quenched with 10 mL of sat. NH_4Cl solution. The aqueous phase was extracted with dichloromethane. The organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was obtained as red oil. **4. *N*-Substitution with benzyl group**: The substrate was dissolved in *N*,*N*-dimethyl formamide and cooled to 0 °C. Freshly crushed KOH (3 equiv) was added, and the reaction mixture was warmed to ambient temperature. After 1 h, the mixture was cooled to 0 °C before adding benzyl chloride (1.5 equiv) dropwise. The reaction was then warmed to ambient temperature and allowed to stir till reaction completion before quenching with H_2O. This was followed by extraction with ethyl acetate. The organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography.

General Procedure (AC). Synthesis of 3-Phenyl Substituted Indoles. 1. Fischer-indole synthesis of 3-substituted indole. In a three neck flask was added *N*,*N*-dimethylurea and L-(+)-tartaric acid. The mixture was heated at 70 °C (oil bath) till no solid was present and a "melt" was formed. To this melt was added the corresponding phenyl hydrazine hydrochloride followed by the aldehyde. The mixture was stirred until consumption of the reactants. While still hot, water was added to the mixture. This was followed by extraction with ethyl acetate (3 × 25 mL). The excess solvent was taken off by rotary evaporation. The compound was then purified by column chromatography (*n*-hexane and ethyl acetate). **2. *N*-Alkylation of indole**. The purified indole was then added to a Schlenk tube followed by dry N,*N*-dimethyl formamide (1 M). The reaction mixture was cooled to 0 °C, and crushed KOH (3 equiv) was added. The reaction mixture was allowed to attain room temperature and stirred for 1 h. The reaction mixture was then again cooled to 0 °C

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

followed by dropwise addition of freshly distilled 2-bromoethanol (1.5 equiv). The reaction was stirred at room temperature until completion. The reaction was quenched by addition of sat. NH_4Cl followed by extractive work-up with ethyl acetate. The crude product obtained after rotary evaporation was then taken to the next step without purification. **3. O-Allylation of −OH**. The crude alcohol was added to a Schlenk tube under Ar and dissolved in 1 M dry *N,N*-dimethyl formamide. The reaction mixture was cooled to 0 °C followed by addition of NaH (60% dispersion in mineral oil) (3 equiv). This was followed by addition of freshly distilled allyl bromide (1.5 equiv). The reaction mixture was allowed to attain room temperature and stirred till completion.

General Procedure for Optimization of Reaction Conditions. To a flame-dried 20 mL Schlenk tube inside a glove box was added $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.05−1 mol %). Outside the box, dry THF (0.16 M) was added under Ar counterflow affording a yellow colored solution. After the addition of the substrate (0.25 mmol), the reaction mixture was stirred for *X* h (please see Supporting Information) at room temperature. This was followed by addition of acid, and the reaction mixture was stirred further for *Y* h (please see Supporting Information) at the indicated temperature. Following this, the standard pentadecane was added (100 μL). To monitor the reaction, 0.1 mL was taken from the reaction mixture, and the sample was diluted with 1 mL of ethyl acetate, passed through a Pasteur pipette fitted with cotton containing basic aluminum oxide, and transferred into a GC vial. Through GC calibration (shown in following sections), the quantity of analyte was determined. Please see Supporting Information for table of optimization.

(*E*)-1-Methoxy-4-(prop-1-en-1-yl)benzene (2a). Compound **2a** was synthesized from 1-allyl-4-methoxybenzene (37.05 mg, 0.25 mmol) and $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: 91%, 33.7 mg, 0.22 mmol. The spectral data matches with the one reported in the literature.[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21−7.15 (m, 2H), 6.79−6.73 (m, 2H), 6.27 (dd, *J* = 15.8, 1.7 Hz, 1H), 6.08−5.95 (m, 1H), 3.72 (s, 3H), 1.78 (dd, *J* = 6.6, 1.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 158.5, 130.8, 130.3, 126.8, 123.5, 113.8, 55.2, 18.4.

(E)-1-(Prop-1-en-1-yl)-4-(trifluoromethyl)benzene (2b). Compound **2b** was synthesized from 1-allyl-4-(trifluoromethyl)-benzene (46.5 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: 30.69 mg, 0.16 mmol, 66%. The spectral data matches with the one reported in literature.[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 6.49−6.29 (m, 2H), 1.92 (dd, *J* = 6.2, 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 141.3, 129.9, 128.5 (d, $^2J_{C-F}$ = 32.3 Hz), 125.9, 125.4 (q, $^3J_{C-F}$ = 3.8 Hz), 124.3 (d, $^1J_{C-F}$ = 271.7 Hz), 18.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.39. Note: Owing to the lack of enhancement by NOE, the peaks corresponding to quaternary carbons in the ^{13}C NMR spectrum do not have a good signal to noise ratio.

(*E*)-1,2,3,4,5-Pentafluoro-6-(prop-1-en-1-yl)benzene (2c). Compound **2c** was synthesized from allylpentafluorobenzene (52.0 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: 45.7 mg, 0.22 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67−6.48 (m, 1H), 6.28 (dq, *J* = 16.2, 1.7 Hz, 1H), 2.01−1.91 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 135.9 (td, $^3J_{C-F,}$ = 7.5 Hz, $^4J_{C-F}$ = 2.3 Hz), 115.2, 19.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −144.1, −158.1, −163.6. Note: Solvent peak of residual CH_2Cl_2 detected at 5.3 ppm in ^{1}H NMR. Owing to the lack of enhancement by NOE, the peaks corresponding to quaternary and F-substituted carbons in the ^{13}C NMR spectrum do not have a good signal to noise ratio.

(*E*)-1-Methyl-2-(prop-1-en-1-yl)benzene (2d). Compound **2d** was synthesized from 2-allylphenol (33.5 mg, 0.25 mmol) and $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil (28 mg, 0.21 mmol, 85%). The spectral data matches with the one reported in the literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.1 Hz, 1H), 7.20−7.08 (m, 3H), 6.60 (dd, *J* = 15.7, 1.8 Hz, 1H), 6.19−6.04 (m, 1H), 2.33 (s, 4H), 1.91 (dd, *J* = 6.6, 1.8 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 137.0, 134.7, 130.1, 128.8, 126.9, 126.7, 126.0, 125.3, 19.8, 18.8.

(*E*)-2-(Prop-1-en-1-yl)phenol (2e). Compound **2e** was synthesized from 2-allylphenol (33.5 mg, 0.25 mmol) and $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: (88%, 29.4 mg, 0.22 mmol). The spectral data matches with the one reported in the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.14−7.06 (m, 1H), 6.95−6.85 (m, 1H), 6.83−6.75 (m, 1H), 6.66−6.54 (m, 1H), 6.28−6.15 (m, 1H), 1.92 (dd, *J* = 6.6, 1.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 152.3, 128.3, 127.9, 127.4, 125.2, 125.0, 120.9, 115.6, 18.9.

(*E*)-1-Bromo-2-(prop-1-en-1-yl)benzene (2f). Compound **2f** was synthesized from 2-allylbromobenzene (48 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: 43.2 mg, 0.22 mmol, 90%. The spectral data matches with the one reported in the literature.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58−7.43 (m, 2H), 7.28−7.20 (m, 1H), 7.10−7.02 (m, 1H), 6.74 (dd, *J* = 15.7, 1.8 Hz, 1H), 6.19 (dq, *J* = 15.6, 6.7 Hz, 1H), 1.93 (dd, *J* = 6.6, 1.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 137.7, 132.8, 129.9, 128.8, 128.0, 127.3, 126.8, 123.0, 18.7.

But-2-en-1-ylbenzene (2g). Compound **2g** was synthesized from but-3-en-1-ylbenzene (33 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) in CH_2Cl_2 (0.16 M) following the procedure **C** outlined for olefin isomerization. The compound was obtained as colorless oil: 23.7 mg, 0.18 mmol, 72%, *E*/*Z*: 80:20. This value of *E*/*Z* ratio is in agreement with the one obtained from quantitative GC-FID analysis: 82:18, traces of other regioisomers were detected. The spectral data matches with the one reported in the literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 3H), 7.24−7.16 (m, 4H), 5.70−5.46 (m, 2H), 3.43 (d, *J* = 5.3 Hz, 1H), **3.34** (d, *J* = 5.5 Hz, **1H**), **1.79−1.70** (m, **1H**), 1.71 (dd, *J* = 4.8, 1.2 Hz, 3H). Note: Protons corresponding to the minor (Z) isomer are displayed in bold where possible. Due to close overlap of peaks in aromatic region, the exact assignment of peaks to major/minor isomers was not done.; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 141.0, 130.0, **129.0**, 128.48 (corresponds to two ^{13}C nuclei), 128.41, 128.3 (corresponds to two ^{13}C nuclei), 126.3, **125.87**, 125.82, 124.8, 39.0, **33.1**, 17.9, **12.8**. Note: ^{13}C nuclei corresponding to the minor (*Z*) isomer are displayed in bold where possible. Close overlap complicates the spectral assignment.

2-Octene (2h). Compound **2h** was synthesized from 1-octene (559.4 mg, 4.99 mmol) and $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (5.46 mg, 9.17 μmol) in THF (8.3 M) following the procedure **C** outlined for olefin isomerization. The product was obtained as colorless oil: 369 mg, 3.29 mmol, 66%, *E*/*Z* = 80:20. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.50−5.33 (m, 2H), 2.09−1.89 (m, 2H), 1.69−1.56 (m, 3H), 1.41−1.21 (m, 6H), 0.89 (td, *J* = 7.0, 2.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 131.6, 124.5, 32.5, 31.4, 29.3, 22.5, 17.9, 14.0.

3-(2-(Allyloxy)ethyl)-1-benzyl-1*H*-indole (3aa). Compound **3aa** was synthesized from 3-(2-(allyloxy)ethyl)-1H-indole (1.3 g, 9.6 mmol, 1 equiv) following the general procedure **AB** for *N*-benzylation. The crude mixture was purified by column chromatography (*n*-hexane/ethyl acetate 93:7) and obtained as colorless oil: 821.4 mg, 2.8 mmol, 62% over two steps. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 4.7 Hz, 1H), 7.35−7.22 (m, 4H), 7.21−7.06 (m, 4H), 6.97 (s, 1H), 6.00−5.85 (m, 1H), 5.30−5.21 (m, 3H), 5.20−5.11 (m, 1H), 4.07−4.00 (m, 2H), 3.82−3.68 (m, 2H), 3.12−3.01 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 137.7, 136.5,

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

134.9, 128.7, 128.2, 127.5, 126.8, 126.1, 121.7, 119.0, 118.9, 116.8, 112.1, 109.6, 71.9, 70.7, 49.9, 25.8.

3-(2-(Allyloxy)ethyl)-1-benzyl-5-methoxy-1*H*-indole (3ab). Compound **3ab** was synthesized from 3-(2-(allyloxy)ethyl)-5-methoxy-1*H*-indole (1.91 g, 8.3 mmol, 1 equiv) following the general procedure **AB** followed for N-benzylation. The crude mixture was purified by column chromatography (*n*-hexane/ethyl acetate 90:10) and obtained as yellow oil: 1.97 g, 6.10 mmol, 74%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26−7.15 (m, 3H), 7.04−6.98 (m, 4H), 6.89 (s, 1H), 6.78−6.72 (m, 1H), 5.96−5.79 (m, 1H), 5.25−5.06 (m, 4H), 3.96 (dt, J = 5.7, 1.4 Hz, 2H), 3.78 (s, 3H), 3.65 (t, J = 7.3 Hz, 2H), 2.96 (t, J = 7.4, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 153.8, 137.8, 134.9, 131.8, 128.7, 128.5, 127.5, 126.8, 126.7, 116.8, 111.8, 111.6, 110.4, 100.9, 71.9, 70.7, 55.9, 50.1, 25.8.

3-(2-(Allyloxy)-2-phenylethyl)-1-methyl-1*H*-indole (3ac). Compound **3ac** was synthesized from 2-(1-methyl-1*H*-indol-3-yl)-1-phenylethan-1-ol (1.1 g, 4.3 mmol, 1 equiv) and allyl bromide (557 μL, 779 mg, 6.45 mmol, 2 equiv) using the procedure reported by Scheidt *et al.*[9] The compound was purified by column chromatography (*n*-hexane/ethyl acetate 9:1) and obtained as yellow oil: 910 mg, 3.12 mmol, 73%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57−7.50 (m, 1H), 7.36−7.27 (m, 6H), 7.23−7.17 (m, 1H), 7.11−7.04 (m, 1H), 6.72 (s, 1H), 5.96−5.79 (m, 1H), 5.27−5.08 (m, 2H), 4.61−4.53 (m, 1H), 3.99−3.89 (m, 1H), 3.84−3.74 (m, 1H), 3.70 (s, 3H), 3.29 (dd, J = 14.6, 7.3 Hz, 1H), 3.06 (dd, J = 14.6, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 142.5, 136.7, 135.0, 128.2, 127.6, 127.4, 126.8, 121.2, 119.0, 118.5, 116.5, 111.1, 109.0, 99.9, 82.0, 69.7, 34.3, 32.5.

3-(2-(Allyloxy)ethyl)-1-benzyl-5-bromo-1*H*-indole (3ad). Compound **3ad** was synthesized from 3-(2-(allyloxy)ethyl)-5-bromo-1*H*-indole (610 mg, 2.17 mmol) following the general procedure **AB** for *N*-benzylation. The crude mixture was purified by column chromatography (12 g SiO_2, stepwise elution: 1. *n*-hexane/ethyl acetate 93:7 for 5 CV followed by *n*-hexane/ethyl acetate 9:1) and obtained as colorless oil: 452 mg, 1.22 mmol, 56%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, THF-d_8): δ = 7.75 (s, 1H), 7.27−7.18 (m, 4H), 7.17−7.12 (m, 3H), 7.11−7.04 (m, 2H), 5.96−5.82 (m, 1H), 5.30 (s, 2H), 5.23 (d, J = 17.3 Hz, 1H), 5.07 (d, J = 10.5 Hz, 1H), 4.02−3.92 (m, 2H), 3.64 (t, J = 7.0 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, THF-d_8): δ = 138.0, 135.5, 135.3, 130.2, 128.3, 127.8, 127.1, 126.5, 123.8, 121.4, 114.9, 112.5, 111.1, 71.3, 70.4, 49.4, 25.5.

3-(2-(Allyloxy)ethyl)-1*H*-indole (3ae). Compound **3ae** was synthesized from 3-(2-iodoethyl)-1*H*-indole (500 mg, 1.84 mmol, 1 equiv) following the general procedure **AB** for O-allylation. The crude mixture was purified by column chromatography (*n*-hexane/ethyl acetate 90:10) and obtained as yellow oil: 210 mg, 1.04 mmol, 57%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.68−7.58 (m, 1H), 7.40−7.31 (m, 1H), 7.26−7.07 (m, 2H), 7.06 (d, J = 2.2 Hz, 1H), 6.06−5.86 (m, 1H), 5.37−5.14 (m, 2H), 4.10−4.00 (m, 2H), 3.77 (t, J = 7.3 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 136.1, 134.9, 127.5, 121.9, 119.2, 118.8, 116.8, 113.0, 111.0, 71.9, 70.6, 25.8.

1-Benzyl-3-(2-(but-3-en-2-yloxy)ethyl)-1*H*-indole (3af). Compound **3af** was prepared from 3-(2-(but-3-en-2-yloxy)ethyl)-1*H*-indole (370 mg, 1.71 mmol) and following general procedure **AB** for N-benzylation. The compound was isolated as yellow oil after purification by flash column chromatography (12 g SiO_2, stepwise elution, *n*-hexane/ethyl acetate 97.5:2.5 followed by *n*-hexane/ethyl acetate 95:5). The product was obtained as colorless oil (260 mg, 0.85 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (m, 1H), 7.33−7.24 (m, 4H), 7.23−7.05 (m, 1H), 6.98 (s, 1H), 5.85−5.67 (m, 1H), 5.28 (s, 2H), 5.23−5.05 (m, 2H), 3.95−3.79 (m, 1H), 3.83−3.68 (m, 1H), 3.68−3.53 (m, 1H), 3.10−2.99 (m, 2H), 1.26 (dd, J = 6.4, 1.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 140.5, 137.7, 136.5, 128.7, 128.3, 127.5, 126.8, 126.1, 121.6, 119.1, 118.9, 115.6, 112.3, 109.6, 68.6, 49.8, 26.0, 21.3; IR: $\tilde{\nu}$ = 3056, 2974, 2926, 2855, 1464, 1330, 1174, 1088, 924, 734, 697; HRMS (ESI) m/z [M + H]$^+$: calcd for $C_{21}H_{24}NO$, 306.1856; found, 306.1853.

1-(2-(Allyloxy)ethyl)-3-phenyl-1*H*-indole (3ba). Compound **3ba** was synthesized from 2-(3-phenyl-1*H*-indol-1-yl)ethan-1-ol (300 mg, 1.26 mmol, 1 equiv) and allyl bromide (162 μL, 1.89 mmol, 1.5 equiv) following general procedure **AC** for O-allylation. The crude compound was purified by column chromatography (*n*-hexane/ethyl acetate 95:5) and obtained as colorless oil: 200 mg, 0.72 mmol, 56%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02−7.88 (m, 1H), 7.74−7.61 (m, 2H), 7.52−7.32 (m, 4H), 7.33−7.13 (m, 3H), 5.93−5.73 (m, 1H), 5.29−5.08 (m, 2H), 4.34 (t, J = 5.7 Hz, 2H), 3.99−3.89 (m, 2H), 3.79 (t, J = 5.7 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 136.9, 135.6, 134.3, 128.7, 127.3, 126.3, 126.2, 125.7, 121.9, 119.9, 117.2, 116.9, 109.6, 72.2, 68.9, 46.3.

1-(2-(Allyloxy)ethyl)-5-bromo-3-phenyl-1*H*-indole (3bb). Compound **3bb** was synthesized from 2-(5-bromo-3-phenyl-1*H*-indol-1-yl)ethan-1-ol (1.3 g, 4.11 mmol, 1 equiv) and allyl bromide (545 μL, 6.16 mmol, 1.5 equiv) following general procedure **AC** for O-allylation. The crude compound purified by column chromatography (*n*-hexane/ethyl acetate 95:5) and obtained as yellow oil: 420 mg, 1.17 mmol, 29%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, J = 2.6 Hz, 1H), 7.58−7.48 (m, 2H), 7.43−7.31 (m, 2H), 7.31−7.14 (m, 4H), 5.83−5.64 (m, 1H), 5.19−5.01 (m, 2H), 4.23 (t, J = 5.5 Hz, 2H), 3.90−3.81 (m, 2H), 3.70 (t, J = 5.5 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 135.6, 134.9, 134.1, 128.8, 127.9, 127.3, 127.2, 126.1, 124.7, 122.4, 117.2, 116.7, 113.4, 111.2, 72.2, 68.9, 46.6.

1-(2-(Allyloxy)ethyl)-5-methoxy-3-phenyl-1*H*-indole (3bc). Compound **3bc** was synthesized from 2-(5-methoxy-3-phenyl-1*H*-indol-1-yl)ethan-1-ol (710 mg, 2.65 mmol, 1 equiv) and allyl bromide (352 μL, 3.97 mmol, 1.5 equiv) following general procedure AC for O-allylation. The crude compound purified by column chromatography (*n*-hexane/ethyl acetate 90:10) and obtained as colorless oil: 350 mg, 1.13 mmol, 43%. The spectral data matches with the one reported in literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70−7.61 (m, 2H), 7.51−7.41 (m, 2H), 7.44−7.37 (m, 1H), 7.36−7.26 (m, 3H), 6.99−6.90 (m, 1H), 5.93−5.77 (m, 1H), 5.28−5.12 (m, 2H), 4.32 (t, J = 5.6 Hz, 2H), 3.99−3.91 (m, 2H), 3.89 (s, 3H), 3.79 (t, J = 5.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 154.5, 135.8, 134.3, 132.2, 128.8, 127.2, 126.8, 126.5, 125.6, 117.2, 116.5, 112.1, 110.4, 101.7, 72.2, 69.0, 56.0, 46.5.

1-(2-(Allyloxy)ethyl)-5-fluoro-3-phenyl-1*H*-indole (3bd). Compound **3bd** was synthesized from 2-(6-fluoro-3-phenyl-1*H*-indol-1-yl)ethan-1-ol (620 mg, 2.43 mmol, 1 equiv) and allyl bromide (323 μL, 3.64 mmol, 1.5 equiv) following general procedure AC for O-allylation. The compound was purified by column chromatography (*n*-hexane/ethyl acetate 9:1) and isolated as colorless oil: 314 mg, 1.06 mmol, 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65−7.55 (m, 3H), 7.48−7.37 (m, 3H), 7.33−7.24 (m, 2H), 7.00 (td, J = 9.0, 2.5 Hz, 1H), 5.82 (ddt, J = 17.1, 10.3, 5.5 Hz, 1H), 5.24−5.11 (m, 2H), 4.33 (t, J = 5.5 Hz, 2H), 3.94 (dt, J = 5.5, 1.5 Hz, 2H), 3.79 (t, J = 5.5 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.3 (d, $^1J_{C-F}$ = 234.5 Hz), 135.2, 134.2, 133.5, 128.8, 127.7, 127.1, 126.5 (d, $^3J_{C-F}$ = 9.8 Hz), 125.9, 117.2, 116.9 (d, $^4J_{C-F}$ = 4.7 Hz), 110.4 (d, $^4J_{C-F}$ = 2.0 Hz), 110.1, 104.9 (d, $^2J_{C-F}$ = 24.0 Hz), 72.2, 68.9, 46.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −124.55; IR: $\tilde{\nu}$ = 3075, 2933, 2978, 2858, 1602, 1543, 1438, 1345, 1110, 991, 857, 793, 760; HRMS (ESI) m/z [M + Na]$^+$: calcd for $C_{19}H_{18}FNONa$, 318.1265; found, 318.1266.

1-(2-(Allyloxy)ethyl)-5-chloro-3-phenyl-1*H*-indole (3be). Compound **3be** was synthesized from 2-(5-chloro-3-phenyl-1*H*-indol-1-yl)ethan-1-ol (583 mg, 2.15 mmol, 1 equiv) and allyl bromide (283 μL, 396 mg, 3.19 mmol 1.5 equiv) following general procedure AC for O-allylation.[23] The compound was purified by column chromatography (*n*-hexane/ethyl acetate 93:7) and obtained as yellow oil: 278 mg, 0.89 mmol, 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 2.0 Hz, 1H), 7.54−7.49 (m, 2H), 7.35 (dd, J = 8.4, 7.0 Hz, 2H), 7.25 (s, 1H), 7.22−7.17 (m, 1H), 7.15−7.08 (m, 2H), 5.79−5.65 (m, 1H), 5.15−5.01 (m, 2H), 4.20 (t, J = 5.5 Hz, 2H), 3.83 (dt, J = 5.5, 1.5 Hz, 2H), 3.66 (t, J = 5.5 Hz, 2H); ^{13}C{^{1}H} NMR

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

(101 MHz, $CDCl_3$): δ = 135.3, 134.9, 134.2, 128.8, 127.4, 127.3, 127.2, 126.0, 125.8, 122.2, 119.4, 117.3, 116.7, 110.7, 72.2, 68.9, 46.6; IR: $\tilde{\nu}$ = 2903, 2862, 2981, 1602, 1546, 1438, 1371, 1237, 1043, 1095, 797, 760; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{19}H_{18}ClNONa$, 334.0969; found, 334.0971.

1-(3-(Allyloxy)propyl)-3-phenyl-1*H*-indole (3bf). Compound **3bf** was synthesized from 3-(3-phenyl-1*H*-indol-1-yl)propan-1-ol (778.4 mg, 3.1 mmol, 1 equiv) and allyl bromide (400 μL, 4.6 mmol, 1.5 equiv) following the general procedure **AB** for O-allylation, purified by column chromatography *n*-hexane/ethyl acetate 9:1 and isolated as yellow oil: 274.2 mg, 0.94 mmol, 30%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (dd, J = 8.4, 1.4 Hz, 1H), 7.71−7.61 (m, 2H), 7.49−7.36 (m, 3H), 7.30−7.12 (m, 4H), 6.03−5.82 (m, 1H), 5.38−5.14 (m, 2H), 4.30 (t, J = 6.7 Hz, 2H), 3.98−3.89 (m, 2H), 3.37 (t, J = 5.8 Hz, 2H), 2.19−2.06 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 137.0, 135.8, 134.8, 128.9, 127.4, 126.3, 126.0, 125.8, 122.0, 120.1, 120.0, 117.2, 116.9, 109.9, 72.1, 66.7, 43.1, 30.4.

1-(2-(Allyloxy)ethyl)-3-(phenylthio)-1*H*-indole (3bg). Compound **3bg** was synthesized from 2-(3-(phenylthio)-1*H*-indol-1-yl)ethan-1-ol (680.1 mg, 2.5 mmol, 1 equiv) and allyl bromide (328 μL, 3.79 mmol, 1.5 equiv) following the general procedure AB for O-allylation, purified by column chromatography *n*-hexane/ethyl acetate 9:1 and isolated as yellow oil: 539.3 mg, 1.74 mmol, 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.26 (s, 1H), 7.21−7.11 (m, 3H), 7.14−7.07 (m, 2H), 7.09−7.00 (m, 1H), 5.89−5.75 (m, 1H), 5.25−5.10 (m, 2H), 4.36 (t, J = 5.5 Hz, 2H), 3.99−3.91 (m, 2H), 3.80 (t, J = 5.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 139.6, 136.9, 134.9, 134.1, 129.9, 128.6, 125.7, 124.6, 122.5, 120.5, 119.8, 117.3, 109.8, 100.8, 72.2, 68.6, 46.6; IR $\tilde{\nu}$ (cm^{-1}): $\tilde{\nu}$ = 3052, 2933, 2855, 1580, 1505, 1457, 1349, 1244, 1207, 1155, 1103, 991, 924, 734, 689; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{19}H_{19}NOSNa$, 332.1080; found, 332.1079.

9-Benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (5aa). The compound **5aa** was synthesized from 3-(2-(allyloxy)-ethyl)-1-benzyl-1*H*-indole (72 mg, 0.25 mmol, 1 equiv) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) and THF (1.5 mL) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 95:5) and obtained as colorless oil: 57.6 mg, 0.19 mmol, 80%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (dd, J = 5.7, 2.9 Hz, 1H), 7.28−7.17 (m, 3H), 7.14−7.06 (m, 3H), 6.98−6.92 (m, 2H), 5.33−5.09 (m, 2H), 4.74−4.65 (m, 1H), 4.14−4.02 (m, 1H), 3.92−3.78 (m, 1H), 2.92−2.78 (m, 2H), 1.91−1.64 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 137.5, 137.2, 136.3, 128.8, 127.4, 126.9, 125.9, 121.6, 119.4, 118.1, 109.7, 108.1, 72.8, 61.3, 47.3, 27.1, 22.5, 9.8.

9-Benzyl-1-ethyl-6-methoxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (5ab). Compound **5ab** was synthesized from 3-(2-(allyloxy)ethyl)-1-benzyl-5-methoxy-1*H*-indole (1.29 g, 4.0 mmol), $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.9 mg, 3.0 μmol), triflic acid (5 μL, 0.06 mmol) in THF (0.16 M) using general procedure **A** for catalysis. The crude product obtained after work-up was purified by recrystallization with *n*-hexane/ethyl acetate (20:3). The final product was obtained as an off-white solid: 763 mg, 2.37 mmol, 59%, with >98% purity as determined by ^{1}H NMR spectroscopy. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.14 (m, 4H), 6.96−6.86 (m, 4H), 6.70 (dd, J = 8.8, 2.5 Hz, 1H), 5.13 (q, J = 17.2 Hz, 2H), 4.65−4.59 (m, 1H), 4.08−3.97 (m, 1H), 3.79 (s, 3H), 2.85−2.67 (m, 2H), 1.85−1.57 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 154.1, 137.5, 137.0, 132.3, 128.7, 127.3, 127.2, 125.9, 111.2, 110.2, 107.6, 100.4, 72.8, 61.3, 55.9, 47.4, 27.1, 22.5, 9.8.

1-Ethyl-9-methyl-3-phenyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (5ac). The compound **5ac** was synthesized from 3-(2-(allyloxy)-2-phenylethyl)-1-methyl-1*H*-indole (0.25 mmol, 72.7 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 95:5) and obtained as colorless oil: 45 mg, 0.15 mmol, 62%, d.r. > 20:1 (computed from ^{1}H−^{1}H NOESY data). The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47−7.39 (m, 3H), 7.36−7.29 (m, 2H), 7.28−7.21 (m, 2H), 7.18−7.11 (m, 1H), 7.08−7.00 (m, 1H), 5.10 (dd, J = 5.8, 2.7 Hz, 1H), **4.87** (dd, J = 10.7, 2.8 Hz, **2H**), 4.62 (dd, J = 10.5, 3.0 Hz, 1H), 3.63 (s, 3H), 3.04−2.92 (m, 1H), 2.90−2.77 (m, 1H), 2.22−2.06 (m, 1H), 1.99−1.86 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H). **Note**: The chemical shift displayed in bold above refers to the minor diastereomer; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 142.8, 137.7, 135.6, 128.3, 127.4, 126.3, 125.9, 121.3, 119.2, 118.0, 109.3, 108.8, 76.6, 74.0, 31.0, 30.8, 28.1, 8.6.

9-Benzyl-6-bromo-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole (5ad). The compound **5ad** was synthesized from 3-(2-(allyloxy)ethyl)-1-benzyl-5-bromo-1*H*-indole (0.25 mmol, 92.5 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 95:5) and obtained as yellow oil: 61 mg, 0.16 mmol, 66%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 1.9 Hz, 1H), 7.30−7.14 (m, 4H), 7.01−6.88 (m, 3H), 5.29−5.10 (m, 2H), 4.73−4.64 (m, 1H), 4.15−4.01 (m, 1H), 3.91−3.79 (m, 1H), 2.86−2.73 (m, 1H), 1.88−1.61 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 137.6, 136.9, 135.8, 128.8, 128.6, 127.5, 125.8, 124.2, 120.8, 112.7, 111.1, 107.7, 72.6, 61.1, 47.4, 27.0, 22.3, 9.8.

1-Ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (5ae). The compound **5ae** was synthesized from 3-(2-(allyloxy)ethyl)-1*H*-indole (0.25 mmol, 50 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol) and TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 85:15) and obtained as yellow oil: 27 mg, 0.13 mmol, 53%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1H), 7.48−7.37 (m, 1H), 7.29−7.20 (m, 1H), 7.13−6.98 (m, 2H), 4.79−4.64 (m, 1H), 4.26−4.13 (m, 1H), 3.82−3.67 (m, 1H), 2.96−2.78 (m, 1H), 2.70−2.56 (m, 1H), 1.95−1.65 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 135.8, 134.7, 127.2, 121.6, 119.6, 118.1, 110.8, 108.3, 73.8, 64.5, 27.5, 22.40, 9.3.

9-Benzyl-1-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole (5af). The compound **5af** was synthesized from 1-benzyl-3-(2-(but-3-en-2-yloxy)ethyl)-1*H*-indole (0.25 mmol, 76.3 mg) using the general procedure **A** for catalysis. Following changes were made to the standard procedure. $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (5 mol %, 0.0125 mmol, 8.0 mg), CH_3SO_3H (20 mol %, 3.2 μL, 0.049 mmol), THF (0.16 M). Following the initial 30 min of room temperature stirring with the precatalyst, the reaction mixture was heated to 60 °C (oil bath) for additional 30 min. The crude product was purified by flash column chromatography on silica gel (12 g SiO_2, stepwise elution *n*-hexane/ethyl acetate 97:3 for 5 CV (column volume) and then 95:5) and obtained as colorless oil: 34 mg, 0.11 mmol, 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.44 (m, 1H), 7.22−7.10 (m, 3H), 7.07−6.94 (m, 3H), 6.84 (d, J = 9.1 Hz, 2H), 5.32 (s, 2H), 4.01−3.82 (m, 2H), 2.88−2.69 (m, 2H), 1.90 (dq, J = 14.7, 7.4 Hz, 1H), 1.69 (dq, J = 14.6, 7.3 Hz, 1H), 1.39 (s, 3H), 0.70 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.9, 137.8, 137.0, 128.6, 127.1, 126.6, 125.6, 121.6, 119.4, 118.1, 110.0, 108.7, 75.2, 59.9, 48.0, 32.9, 25.2, 22.8, 7.9. IR: 2967, 2862, 2929, 1464, 1345, 1308, 1151, 1080, 907, 726, 697; HRMS (ESI) m/z $[M]^+$: calcd for $C_{21}H_{23}NO$, 305.1774; found, 305.1775.

1-Ethyl-10-phenyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]-indole (5ba). This compound **5ba** was synthesized from 1-(2-(allyloxy)ethyl)-3-phenyl-1*H*-indole (69.4 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) following general procedure **A**

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

for catalysis. Purification by flash column chromatography (12 g SiO_2, static elution. *n*-hexane/ethyl acetate 95:5) gave the compound as a white solid: 47.9 mg, 0.17 mmol, 69%. The spectral data matches with the one reported in the literature.[5] mp = 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.0 Hz, 1H), 7.45−7.38 (d, 4H), 7.28−7.18 (m, 2H), 7.16 (d, J = 5.8 Hz, 1H), 7.07 (d, J = 6.9 Hz, 1H), 5.22 (dd, J = 7.5, 3.3 Hz, 1H), 4.29−4.19 (m, 1H), 4.14−3.98 (m, 2H), 3.99−3.88 (m, 1H), 1.69−1.48 (m, 2H), 0.72 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 135.5, 135.4, 132.2, 129.5, 128.5, 127.4, 126.1, 121.4, 120.3, 119.0, 111.6, 108.5, 75.1, 62.1, 41.9, 26.3, 9.3.

8-Bromo-1-ethyl-10-phenyl-3,4-dihydro-1*H*-[1,4]oxazino-[4,3-*a*]indole (5bb). This compound **5bb** was synthesized from 1-(2-(allyloxy)ethyl)-5-bromo-3-phenyl-1*H*-indole (89 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) by following general procedure **A** for catalysis. Purification by flash column chromatography (12 g SiO_2, static elution. *n*-hexane/ethyl acetate 90:10) gave the compound asyellow oil: 57 mg, 0.16 mmol, 64%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73−7.70 (m, 1H), 7.49−7.37 (m, 4H), 7.35−7.28 (m, 2H), 7.19 (d, J = 8.6 Hz, 1H), 5.27 (dd, J = 7.5, 3.3 Hz, 1H), 4.33 (dt, J = 11.5, 3.8 Hz, 1H), 4.19−3.98 (m, 3H), 1.74−1.55 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 134.7, 134.0, 133.4, 129.4, 129.0, 128.7, 126.5, 124.2, 121.5, 113.6, 111.3, 109.9, 75.0, 61.9, 41.9, 26.2, 9.2.

1-Ethyl-8-methoxy-10-phenyl-3,4-dihydro-1*H*-[1,4]oxazino-[4,3-*a*]indole (5bc). This compound **5bc** was synthesized from 1-(2-(allyloxy)ethyl)-5-methoxy-3-phenyl-1*H*-indole (76 mg, 0.25 mmol) using $[(Me_3P)_4NiH]$ $N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) by general procedure **A** for catalysis. Purification by flash column chromatography (12 g SiO_2, static elution. *n*-hexane/ethyl acetate 95:5) gave the compound as colorless oil: 53.9 mg, 0.175 mmol, 70%. The spectral data matches with the one reported in the literature.[5] ^{1}H NMR (400 MHz, chloroform-*d*): δ = 7.42 (d, J = 4.4 Hz, 4H), 7.32−7.26 (m, 1H), 7.19 (dd, J = 8.8, 0.6 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 5.25 (dd, J = 7.5, 3.3 Hz, 1H), 4.27 (dt, J = 11.4, 3.8 Hz, 1H), 4.15−3.94 (m, 3H), 3.78 (s, 3H), 1.74−1.53 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 154.9, 135.7, 132.9, 130.7, 129.4, 128.6, 127.6, 126.1, 111.6, 111.3, 109.2, 100.8, 75.0, 62.0, 56.0, 41.9, 26.3, 9.3.

1-Ethyl-8-fluoro-10-phenyl-3,4-dihydro-1*H*-[1,4]oxazino-[4,3-*a*]indole (5bd). Compound **5bd** was synthesized from 1-(2-(allyloxy)ethyl)-5-fluoro-3-phenyl-1*H*-indole (73.8 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) following general procedure **A** for catalysis. The compound was purified by flash column chromatography (12 g SiO_2 static elution, *n*-hexane/ethyl acetate 95:5) and obtained as a white solid: 46 mg, 0.15 mmol, 62%. mp: 104−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.29 (m, 4H), 7.27−7.11 (m, 3H), 6.89 (m, 1H), 5.20 (dd, J = 7.4, 3.5 Hz, 1H), 4.24 (dt, J = 11.3, 3.7 Hz, 1H), 4.14−3.88 (m, 3H), 1.74−1.46 (m, 2H), 0.72 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.6 (d, $^1J_{C-F}$ = 234.9 Hz), 135.0, 133.9, 132.0, 129.3, 128.6, 127.7 (d, $^3J_{C-F}$ = 9.8 Hz), 126.3, 111.7 (d, $^4J_{C-F}$ = 4.8 Hz), 109.7 (d, $^2J_{C-F}$ = 26.5 Hz), 109.1 (d, $^3J_{C-F}$ = 9.7 Hz), 104.0 (d, $^2J_{C-F}$ = 24.1 Hz), 75.0, 62.0, 41.9, 26.2, 9.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.8; HRMS (ESI) m/z [M]$^+$: calcd for $C_{19}H_{18}FNO$, 295.1367; found, 295.1369.

8-Chloro-1-ethyl-10-phenyl-3,4-dihydro-1*H*-[1,4]oxazino-[4,3-*a*]indole (5be). Compound 5be was synthesized from 1-(2-(allyloxy)ethyl)-5-chloro-3-phenyl-1*H*-indole (0.32 mmol, 100 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (2.06 mg, 2.48 μmol), TfOH (1.9 mg, 1.12 μL, 0.012 mmol) in THF (0.16 M) by general procedure A for catalysis. The product was purified by flash column chromatography (12 g SiO_2, stepwise elution *n*-hexane/ethyl acetate 9:1) isolated as colorless oil: 60 mg, 0.19 mmol, 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.44 (m, 1H), 7.40−7.27 (m, 4H), 7.27−7.18 (m, 1H), 7.18−7.04 (m, 2H), 5.24−5.14 (m, 1H), 4.23 (dt, J = 11.5, 4.0 Hz, 1H), 4.11−3.88 (m, 3H), 1.70−1.46 (m, 2H), 0.71 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 134.8, 133.8, 133.6, 129.4, 128.7, 128.4, 126.5, 126.0, 121.6, 118.5, 111.43, 109.5, 75.0, 62.0, 41.9, 26.2, 9.2; IR: $\tilde{\nu}$ = 2967, 2873, 2933, 1602, 1453, 1341, 1062, 1088, 965, 730, 790; HRMS (ESI) m/z [M]$^+$: calcd for $C_{19}H_{18}ClNO$, 311.1071; found, 311.1070.

1-Ethyl-11-phenyl-4,5-dihydro-1*H*,3*H*-[1,4]oxazepino[4,3-*a*]indole (5bf). Compound **5bf** was synthesized from 1-(3-(allyloxy)propyl)-3-phenyl-1*H*-indole (72.8 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol), TfOH (1.5 mg, 0.88 μL, 0.01 mmol) in THF (0.16 M) following the general procedure **A** for catalysis. The crude product was purified by flash column chromatography on silica gel (12 g SiO_2, stepwise elution *n*-hexane/ethyl acetate 97:3 for 5 CV (column volume) and then 95:5) and obtained as yellow oil: 34.5 mg, 0.118 mmol, 47%. The spectral data matches with the one reported in literature.[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, J = 7.9 Hz, 1H), 7.44−7.37 (m, 4H), 7.35−7.27 (m, 2H), 7.25−7.18 (m, 1H), 7.12−7.00 (m, 1H), 4.98 (dd, J = 8.9, 5.3 Hz, 1H), 4.53−4.28 (m, 2H), 4.14−3.99 (m, 1H), 3.85−3.71 (m, 1H), 2.12−1.86 (m, 3H), 1.84−1.67 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 137.2, 136.1, 135.1, 130.3, 128.4, 127.4, 126.3, 122.0, 119.6, 119.5, 116.1, 108.6, 76.1, 65.0, 42.3, 30.6, 27.1, 10.5.

1-Ethyl-10-(phenylthio)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]-indole (5bg). Compound **5bg** was synthesized from 1-(2-(allyloxy)-ethyl)-3-(phenylthio)-1*H*-indole (0.25 mmol, 77.3 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (3.2 mg, 4.96 μmol), $MeSO_3H$ (1.9 mg, 1.12 μL, 0.012 mmol) in THF (0.16 M) following the general procedure **A** for catalysis. The compound was purified by column chromatography (*n*-hexane/ethyl acetate 95:5) and obtained as yellow oil: 0.087 mmol, 27.05 mg, 35%. The isomerization was carried out for 30 min, and the cyclization with acid was carried out at 40 °C (oil bath) for 30 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64−7.55 (m, 1H), 7.42−7.33 (m, 1H), 7.32−7.24 (m, 1H), 7.22−7.11 (m, 3H), 7.04 (d, J = 7.0 Hz, 3H), 5.06 (dd, J = 8.5, 3.3 Hz, 1H), 4.37−4.26 (m, 1H), 4.23−4.08 (m, 2H), 4.05−3.92 (m, 1H), 2.30−2.02 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 141.1, 139.0, 136.1, 128.7, 125.3, 124.5, 122.0, 121.1, 119.1, 108.9, 94.8, 74.6, 61.0, 42.0, 26.7, 9.5; HRMS (APCI) m/z [M + H]$^+$: calcd for $C_{19}H_{20}NOS$, 310.1260; found, 310.1267; IR $\tilde{\nu}$ = 3053, 2967, 2929, 2874, 1737, 1580, 1472, 1364, 1312, 1237, 1114, 1081, 734, 689.

1-(2-(Allyloxy)ethyl)-3-methoxybenzene (6a). Following the general procedure **AA**, the reaction of 2-(3-methoxyphenyl)ethan-1-ol (593.0 mg, 3.9 mmol, 1 equiv), NaH (60% dispersion in mineral oil, 312.0 mg, 7.8 mmol, 2 equiv), and allyl bromide (0.7 mL, 7.8 mmol, 2 equiv) gave after 24 h and purification by chromatography (*n*-hexane/ethyl acetate 98:2) the product as colorless oil: 227 mg, 1.2 mmol, 30%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, J = 7.4 Hz, 1H), 6.85−6.74 (m, 3H), 5.99−5.86 (m, 1H), 5.24 (dd, J = 15.5, 1.7 Hz, 1H), 5.16 (dd, J = 10.3, 1.8 Hz, 1H), 4.01 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 3.66 (t, J = 7.4 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.7, 140.6, 134.9, 129.4, 121.4, 117.0, 114.7, 111.6, 72.0, 71.2, 55.2, 36.5.

4-(2-(Allyloxy)ethyl)-1,2-dimethoxybenzene (6b). Following the general procedure **AA**, the reaction of 2-(3,4-dimethoxyphenyl)-ethan-1-ol (500.0 mg, 2.74 mmol, 1 equiv), NaH (60% dispersion in mineral oil, 220 mg, 5.5 mmol, 2 equiv), and allyl bromide (0.47 mL, 5.5 mmol, 2 equiv) gave after 36 h and purification by chromatography (*n*-hexane/ethyl acetate 9:1) the product as colorless oil: 227.0 mg, 1.2 mmol, 30%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82−6.73 (m, 3H), 6.01−5.81 (m, 1H), 5.31−5.13 (m, 2H), 3.99 (dt, J = 5.6, 1.4 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.63 (t, J = 7.1 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 148.7, 147.4, 134.8, 131.6, 120.7, 116.8, 112.2, 111.2, 71.8, 71.4, 55.9, 35.9.

1-Ethyl-6-methoxyisochromane (7a). The compound **7a** was synthesized from 1-(2-(allyloxy)ethyl)-3-methoxybenzene (0.25 mmol, 48 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.08 mg, 1.24

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

μmol) and TfOH (0.22 μL, 2.5 μmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography ($^{-4}$ μmol) and TfOH (0.22 μL, 2.5 × 10^{-3} mmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, 12 g SiO_2, static elution, *n*-hexane/ethyl acetate 98:2) and obtained as colorless oil: 44 mg, 0.22 mmol, 92%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04−6.95 (m, 1H), 6.76 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.69−6.61 (m, 1H), 4.72−4.61 (m, 1H), 4.20−4.07 (m, 1H), 3.79 (s, 3H), 3.78−3.72 (m, 1H), 3.07−2.89 (m, 1H), 2.72−2.59 (m, 1H), 2.06−1.70 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 157.7, 135.4, 130.5, 125.8, 113.3, 112.3, 76.7, 63.1, 55.2, 29.5, 28.7, 9.5.

1-Ethyl-6,7-dimethoxyisochromane (7b). The compound **7b** was synthesized from 4-(2-(allyloxy)ethyl)-1,2-dimethoxybenzene (0.25 mmol, 48 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.08 mg, 1.24 μ^{-4} mmol), TfOH (0.22 μL, 2.5 μmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 93:7) and obtained as colorless oil: 32 mg, 0.14 mmol, 58%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.59 (s, 1H), 6.55 (s, 1H) 4.63 (dd, *J* = 7.9, 2.7 Hz, 1H), 4.17−4.06 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78−3.66 (m, 1H), 2.97−2.82 (m, 1H), 2.59 (dt, *J* = 15.9, 3.6 Hz, 2H), 2.03−1.86 (m, 1H), 1.76 (dd, *J* = 14.6, 7.5 Hz, 1H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 147.4, 130.1, 126.2, 111.4, 107.9, 76.5, 63.2, 56.0, 55.8, 28.8, 28.7, 9.5.

3-(2-(Allyloxy)ethyl)thiophene (8a). Following the general procedure **AA**, the reaction of 2-(thiophen-3-yl)ethan-1-ol (1.32 mL, 11.7 mmol, 1 equiv), NaH (60% dispersion in mineral oil, 0.94 g, 23.4 mmol, 2 equiv), and allyl bromide (2.0 mL, 23.4 mmol, 2 equiv) gave after 24 h and purification by column chromatography (*n*-hexane/ethyl acetate 98:2) the product as colorless oil: 1.0 g, 6.1 mmol, 52%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26−7.24 (m, 1H), 7.04−7.02 (m, 1H), 6.98 (d, *J* = 4.9 Hz, 1H), 5.98−5.87 (m, 1H), 5.29 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.16 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.0 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 139.3, 134.9, 128.6, 125.3, 121.1, 117.0, 72.0, 70.5, 30.8.

2-(2-(Allyloxy)ethyl)thiophene (8b). Following the general procedure **AA**, the reaction of 2-(thiophen-2-yl)ethan-1-ol (900 mg, 7.02 mmol, 1 equiv), NaH (60% dispersion in mineral oil, 220 mg, 14.0 mmol, 2 equiv), and allyl bromide (0.47 mL, 14.04 mmol, 2 equiv) gave after 24 h and purification by chromatography (*n*-hexane/ethyl acetate 98:2) the product as colorless oil. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.89−6.83 (m, 1H), 6.01−5.86 (m, 1H), 5.35−5.24 (m, 1H), 5.23−5.15 (m, 1H), 4.02 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.12 (t, *J* = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 141.2, 134.7, 126.6, 125.1, 123.6, 117.0, 71.9, 70.8, 30.5.

7-Ethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran (9a). The compound **9a** was synthesized from 3-(2-(allyloxy)ethyl)thiophene (0.25 mmol, 42.3 mg) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.08 mg, 1.24 × 10^{-4} mmol), TfOH (0.22 μL, 2.5 μmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 95:5) and obtained as colorless oil: 30 mg, 0.18 mmol, 72%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 5.0, 0.9 Hz, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 4.76−4.66 (m, 1H), 4.21 (ddd, *J* = 11.4, 5.7, 2.1 Hz, 1H), 3.75 (ddd, *J* = 11.3, 10.6, 3.8 Hz, 1H), 2.96−2.79 (m, 1H), 2.64−2.53 (m, 1H), 1.98−1.71 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 137.5, 133.4, 127.1, 122.4, 76.2, 64.4, 30.2, 26.3, 9.5.

4-Ethyl-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran (9b). The compound **9b** was synthesized from 2-(2-(allyloxy)ethyl)thiophene (0.50 mmol, 84.1 mg, 1 equiv) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.16 mg, 0.25 μmol), TfOH (0.57 μL, 6.5 μmol) in THF (0.16 M) by general procedure **A** for catalysis. The crude product was purified by column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 98:2) and obtained as colorless oil (30 mg, 0.17 mmol, 36%). The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 4.5 Hz, 1H), 6.76 (d, *J* = 5.2 Hz, 1H), 4.62 (m, 1H), 4.21 (m, 1H), 3.77 (m, 1H), 3.07−2.91 (m, 1H), 2.79−2.68 (m, 1H), 2.01−1.87 (m, 1H), 1.80−1.67 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 137.3, 133.0, 123.9, 122.3, 76.7, 63.7, 28.3, 25.7, 9.5.

***N*-Allyl-*N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (10a).** Compound **10a** was synthesized from *N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (2 g, 7.2 mmol, 1 equiv) and allyl benzene (0.858 mL, 10 mmol, 1.38 equiv) as per the reported procedure.[7a] The final product was obtained as a brown flaky solid (1.5 g, 4.71 mmol, 66%). Some of the product could be recrystallized from boiling *n*-hexane (oil bath) to give a white crystalline solid; however, the recovery of the product was poor (<500 mg). The crude product was purified by column chromatography (*n*-hexane/ethyl acetate 7:3) and obtained as a white solid (445 mg, 1.40 mmol, 20%). mp = 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64−7.50 (m, 3H), 7.38−7.24 (m, 3H), 7.13 (td, J = 7.7, 1.6 Hz, 1H), 6.44 (dd, J = 8.0, 1.2 Hz, 1H), 5.71 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.06−4.90 (m, 3H), 4.50 (dd, J = 13.0, 5.8 Hz, 2H), 3.73 (dd, J = 13.9, 8.2 Hz, 1H), 2.88 (br s, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.0, 142.3, 137.0, 134.6, 131.8, 131.1, 129.6, 129.0, 128.3, 128.1, 127.5, 120.0, 61.2, 55.1, 21.6; IR: $\tilde{\nu}$ = 3507, 2955, 2888, 1453, 1593, 1334, 1401, 1058, 1289, 1115, 1010, 872, 820, 663; HRMS (ESI) *m*/*z* [M + Na]$^+$: calcd for $C_{17}H_{19}NO_3SNa$, 340.0978; found, 340.0981.

***N*-Allyl-*N*-(2-(1-hydroxyethyl)phenyl)-4-methylbenzenesulfonamide (10b).** Compound **10b** was synthesized as per the reported procedure.[7a] *N*-(2-acetylphenyl)-*N*-allyl-4-methylbenzenesulfonamide (2 g, 6.07 mmol, 1 equiv) was dissolved in 100 mL methanol, and the solution was then cooled at 0 °C and $NaBH_4$ (689 mg, 18.21 mmol, 3 equiv) was added in portions. After the complete addition, the solution was warmed at room temperature, and the mixture was stirred for 4 h. The reaction was then quenched by the addition of 40 mL of acetone, and the solvents were evaporated under reduced pressure. The crude product was dissolved in ethyl acetate and washed three times with water and brine (3 × 30 mL). The organic phase was dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography (*n*-hexane/ethyl acetate 4:1) as a yellow solid: 1.21 g, 3.65 mmol, 60%. **mp** = 106−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69−7.57 (m, 1H), 7.55−7.48 (m, 2H), 7.40−7.27 (m, 4H), 7.18−7.03 (m, 1H), 6.46 (ddd, *J* = 8.1, 1.3 Hz, 1H), 5.77−5.65 (m, 1H), 5.47 (q, *J* = 6.7 Hz, 1H), 5.06−4.94 (m, 1H), 4.53 (ddt, *J* = 13.8, 5.5, 1.4 Hz, 1H), 3.71 (ddt, *J* = 13.9, 8.3, 0.8 Hz, 1H), 2.46 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.8, 143.9, 141.9, 136.6, 135.1, 132.4, 131.2, 129.6, 129.3, 128.7, 128.3, 128.1, 120.1, 54.6, 30.4, 21.7; HRMS (ESI) *m*/*z* [M + Na]$^+$: calcd for $C_{18}H_{21}NO_3SNa$, 354.1134; found, 354.1136; IR $\tilde{\nu}$ = 3533, 2974, 2929, 1595, 1490, 1449, 1397, 1330, 1282, 1155, 1088, 1039, 995, 931, 894, 857, 812, 749, 704.

***N*-Allyl-*N*-(2-(hydroxymethyl)benzyl)-4-methylbenzenesulfonamide (10d).** The compound **10d** was synthesized according to the reported procedure.[7a] *N*-(2-(hydroxymethyl)benzyl)-4-methylbenzenesulfonamide (1.17 g, 4.0 mmol, 1 equiv), allyl bromide (960 mg, 8 mmol, 2 equiv) and potassium carbonate (1.105 g, 8.0 mmol, 2 equiv) were dissolved in *N*,*N*-dimethyl formamide and stirred for 16 h at 75 °C (oil bath). Then, ethyl acetate (30 mL) and water (30 mL) were added to the mixture, and the aq phase was extracted five times with ethyl acetate (5 × 20 mL). The combined organic phases were washed with water and brine (3 × 30 mL), dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The desired product was isolated from the crude mixture by column chromatography (*n*-hexane/ethyl acetate 7:3) as a yellow solid: 0.341 g, 1.02 mmol, 26%. mp = 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79−7.72 (m, 2H), 7.38−7.28 (m, 4H), 7.28−7.24 (m, 3H), 5.39

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

(ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.02−4.86 (m, 2H), 4.78 (s, 2H), 4.45 (s, 2H), 3.72 (dt, J = 6.7, 1.3 Hz, 2H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.8, 139.6, 136.6, 133.8, 132.2, 130.3, 130.2, 129.9, 129.4, 128.4, 128.1, 127.6, 127.5, 119.5, 63.2, 50.1, 48.8, 21.7; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{18}H_{21}NO_3SNa$, 354.1134; found, 354.1138; IR $\tilde{\nu}$ = 3511, 3063, 2922, 2870, 1595, 1490, 1453, 1334, 1215, 1155, 1088, 1036, 902, 892, 812, 734.

2-(2-(Allyloxy)phenyl)ethan-1-ol (10e). The compound **10e** was synthesized according to the reported procedure.[7b] In a flame-dried round-bottom flask 2-(2-hydroxyethyl)phenol (2 g, 14.5 mmol, 1 equiv) was dissolved under Ar in 20 mL of dry THF. The solution was cooled to 0 °C, NaH (60% dispersion in oil) (0.36 g, 15.2 mmol, 1.05 equiv) was added in portions, and the mixture was stirred for 10 min at 0 °C. Then, allyl bromide (1.03 mL, 14.5 mmol, 1 equiv) was added, and the reaction mixture was stirred at room temperature. After 5 h, the reaction was quenched by the slow addition of 30 mL of saturated NH_4Cl aq solution and 50 mL of water at 0 °C and the mixture was stirred for another 30 min at r.t. The aqueous phase was extracted three times with ethyl acetate (3 × 40 mL), and the combined organic phases were washed three times with water and brine (3 × 25 mL), dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The desired compound was isolated by flash chromatography (12g silica, gradient elution: 1. *n*-hexane/ethyl acetate 95:5 for elution of relatively non polar impurities 2. *n*-hexane/ethyl acetate 70:30 for elution of product). The product was isolated as colorless oil: 0.78 g, 4 mmol, 28%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.16 (m, 2H), 6.94−6.84 (m, 2H) 6.12−6.01 (ddt, J = 17.3, 10.4, 5.1 Hz, 1H), 5.45−5.39 (m, 1H), 5.31−5.26 (m, 1H) 4.56 (dt, J = 5.2, 1.6 Hz, 2H), 3.91−3.80 (m, 2H), 1.62−1.58 (m, 1H). **Note**: Water signal overlaps with the −OH signal in the above compound, giving rise to an integral of 2H; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.6, 133.2 131.0, 127.8, 127.3, 120.9, 117.4, 111.7, 68.8, 62.9, 34.2; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{11}H_{14}O_2Na$, 201.0880; found, 201.0888; IR $\tilde{\nu}$ = 3336, 2926, 2873, 1599, 1490, 1453, 1423, 1289, 1237, 1189, 1017, 924, 749.

(2-(Allyloxy)phenyl)methanol (10f). Compound **10f** was synthesized according to the reported procedure.[7b] In a round bottom flask fitted with condenser was added 2-hydroxy benzylalcohol (1g, 8.05 mmol, 1 equiv). This was dissolved in 16 mL of acetone. To this solution was added K_2CO_3 (2.8 g, 20 mmol, 2.48 equiv) and freshly distilled allyl bromide (0.842 mL, 9.8 mmol, 1.2 equiv). The reaction mixture was refluxed (oil bath) overnight. After the completion of the reaction the contents in the flask were allowed to cool down. The reaction mixture was diluted with 20 mL ethyl acetate and 20 mL water. This was followed by separation of phases. The aqueous phase was extracted thrice with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The desired product was purified by column chromatography over silica gel (*n*-hexane/ethyl acetate 85:15) and obtained as colorless oil: 803 mg, 4.89 mmol, 61%. The spectral data matches with the one reported in literature.[7b] ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.25 (m, 1H), 7.26−7.22 (m, 1H), 7.00−6.84 (m, 1H), 6.17−5.97 (m, 1H), 5.49−5.35 (m, 1H), 5.36−5.25 (m, 1H), 4.72 (s, 2H), 4.60 (dt, J = 5.2, 1.6 Hz, 2H), 2.26 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 156.4, 133.0, 129.3, 128.7, 120.8, 117.6, 111.4, 68.7, 62.1.

1-(Allyloxy)-3-phenylpropan-2-ol (10g). The compound **10g** was synthesized according to the reported procedure.[7b] Freshly cut Na (77 mg, 3.3 mmol, 0.3 equiv) was dissolved in 8 mL allylalcohol. Then, 2-benzyloxirane (1.5 g, 11 mmol, 1 equiv) was added dropwise, and the reaction was stirred at reflux (oil bath) until full conversion. The reaction was then cooled to 0 °C and the reaction was quenched by the addition of 30 mL of saturated NH_4Cl aq solution and 20 mL of water. The aq phase was extracted with diethyl ether (3 × 25 mL), and the combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The desired compound was isolated by column chromatography (*n*-hexane/ethyl acetate 4:1) as colorless oil: 1.73 g, 9 mmol, 80%. The spectral data matches with the one reported in the literature.[7b] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.28 (m, 2H), 7.25−7.21 (m, 3H), 6.02−5.79 (m, 1H), 5.39−5.11 (m, 2H), 4.08−4.00 (m, 3H), 3.47 (dd, J = 9.5, 3.4 Hz, 1H), 3.35 (dd, J = 9.5, 7.1 Hz, 1H), 2.81 (dd, J = 6.7, 2.8 Hz, 2H), 2.07 (br s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.1, 134.6, 129.5, 129.4, 128.7, 128.6, 126.6, 117.4, 73.6, 72.4, 71.5, 40.0.

1-(Allyloxy)-2-methyl-1-phenylpropan-2-ol (10h). The compound **10h** was synthesized according to the reported procedure.[7b] In a flame-dried round-bottom flask NaH (60% dispersion in oil) (0.149 g, 6.22 mmol, 1.15 equiv) was dissolved in 10 mL dry THF and the solution was cooled at 0 °C. A 2-methyl-1-phenylpropane-1,2-diol (0.9 g, 5.4 mmol, 1 equiv) solution in THF (10 mL) was added dropwise, and the resulting mixture was stirred for 15 min at 0 °C. Then, allyl bromide (0.52 mL, 5.95 mmol, 1.1 equiv) was added dropwise to the mixture, and the reaction was heated to room temperature and stirred for 6 h. After this period, the reaction was quenched by the addition of 10 mL of saturated NH_4Cl aq solution and 20 mL of water. The aq phase was extracted three times with ethyl acetate (3 × 30 mL), and the combined organic phases were washed three times with brine (3 × 30 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The desired product was separated by column chromatography (*n*-hexane/ethyl acetate 5:1) as colorless oil: 0.212 g, 1.02 mmol, 19%. Spectral data conforms to the literature report.[7b] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.26 (m, 5H), 5.96−5.85 (m, 1H), 5.29−5.11 (m, 2H), 4.17 (s, 1H), 4.01−3.95 (m, 1H), 3.82−3.74 (m, 1H), 2.56 (br s, 1H), 1.17 (s, 3H), 1.10 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.3, 134.8, 128.4, 128.3, 128.2, 128.1, 128.0, 116.9, 88.1, 73.0, 70.1, 26.2, 24.4.

2-Ethyl-1-tosyl-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazine (11a). Compound **11a** was synthesized from *N*-(2-(hydroxymethyl)-phenyl)-4 methylbenzenesulfonamide (79.2 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) following general procedure B for catalysis; however, following changes were made. Reaction time after addition of diphenyl phosphate: 2.5 h. The compound was purified by flash column chromatography (12 g SiO_2 static elution, *n*-hexane/ethyl acetate 95:5) and obtained as a white solid: 65 mg, 0.2 mmol, 83%. mp = 83−85 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (dd, J = 8.1, 1.2 Hz, 1H), 7.39−7.30 (m, 2H), 7.26−7.13 (m, 1H), 7.09−6.97 (m, 3H), 6.78−6.71 (m, 1H), 5.64−5.60 (m, J = 7.1 Hz, 1H), 4.51 (d, J = 15.6 Hz, 1H), 4.03 (d, J = 15.6 Hz, 1H), 2.27 (s, 3H), 1.69−1.52 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 143.5, 135.6, 132.5, 129.0, 127.7, 127.2, 127.1, 126.0, 124.2, 85.2, 60.8, 24.6, 21.5, 9.4; IR $\tilde{\nu}$ = 2967, 2877, 1595, 1490, 1457, 1375, 1047, 991, 1207, 1162, 760, 793, 823, 685; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{17}H_{19}NO_3SNa$, 340.0978; found, 340.9791.

2-Ethyl-4-methyl-1-tosyl-1,4-dihydro-2*H*-benzo[*d*][1,3]-oxazine (11b). Compound **11b** was synthesized from *N*-allyl-*N*-(2-(1-hydroxyethyl)phenyl)-4-methylbenzenesulfonamide (84.5 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) by the general procedure **B** for catalysis; however, following changes were made. Reaction time after addition of diphenyl phosphate: 3 h. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 92:8) isolated as colorless oil: 57.4 mg, 0.17 mmol, 68%. **Note**: A mixture of diastereomers was isolated in ratio 2:1. The resonances for major isomer are reported below. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, J = 8.1, 1.3 Hz, 1H), 7.38−7.33 (m, 1H), 7.32−7.24 (m, 2H), 7.05 (dd, J = 8.1, 4.8 Hz, 2H), 6.91 (dt, J = 7.8, 1.3 Hz, 1H), 5.44 (t, J = 6.1 Hz, 1H), 3.52 (q, J = 6.6 Hz, 1H), 2.28 (s, 3H), 1.71−1.53 (m, 3H), 1.23 (d, J = 6.6 Hz, 3H), 0.88 (dt, J = 14.7, 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.6, 136.4, 133.2, 131.9, 129.2, 128.2, 127.8, 127.5, 127.3, 126.5, 124.70, 123.6, 86.5, 68.3, 29.2, 21.5, 20.5, 9.2; IR $\tilde{\nu}$ = 2933, 2967, 2873, 1595, 1487, 1453, 1080, 1371, 1162, 816, 682; HRMS (ESI) m/z $[M + Na]^+$: calcd for $C_{18}H_{21}NO_3SNa$, 354.1134; found, 354.1137.

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

3-Ethyl-4-tosyl-1,3,4,5-tetrahydrobenzo[*e*][1,3]oxazepine (11d). Compound **11d** was synthesized from *N*-allyl-*N*-(2-(hydroxymethyl)benzyl)-4-methylbenzenesulfonamide (82.7 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) by the general procedure **B** for catalysis. Reaction time after addition of diphenyl phosphate: 3 h. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 93:7) isolated as a white solid: 52 mg, 0.17 mmol, 65%. mp: 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.29 (m, 2H), 7.19−7.13 (m, 2H), 7.08−7.02 (m, 1H), 6.94 (dd, J = 8.3, 1.0 Hz, 2H), 6.63 (d, J = 7.5 Hz, 1H), 5.07−4.98 (m, 1H), 4.79−4.60 (m, 3H), 3.91 (dt, J = 15.4 Hz, 1.2 Hz, 1H), 2.27 (s, 3H), 1.96−1.67 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 142.8, 137.0, 136.8, 135.2, 128.8, 128.1, 127.0, 126.9, 125.7, 91.1, 71.5, 45.6, 27.8, 21.4, 9.6; HRMS (ESI) m/z [M + Na]$^+$: calcd for $C_{18}H_{21}NO_3SNa$, 354.1134; found, 354.1136; IR $\tilde{\nu}$ = 2978, 2862, 1449, 1494, 1379, 1293, 1174, 1098, 1043, 916, 834, 749, 887, 808.

2-Ethyl-4,5-dihydrobenzo[*d*][1,3]dioxepine (11e). Compound **11e** was synthesized from 2-(2-(allyloxy)phenyl)ethan-1-ol (44.5 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) by general procedure B for catalysis. Reaction time after addition of diphenyl phosphate: 15 h. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 98:2) isolated as colorless oil: 21 mg, 0.11 mmol, 44%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23−7.08 (m, 2H), 7.05−6.96 (m, 2H), 4.48 (dd, J = 6.0, 4.8 Hz, 1H), 4.27−4.14 (m, 1H), 3.59−3.44 (m, 1H), 3.39−3.22 (m, 2H), 2.75−2.62 (m, 1H), 2.02−1.73 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 158.7, 132.8, 130.3, 127.6, 123.6, 121.0, 108.1, 68.5, 37.3, 29.1, 9.0; IR $\tilde{\nu}$ = 1487, 1353, 1453, 1379, 1237, 1118, 936, 1036, 760, 670; HRMS (EI) m/z [M]$^+$: calcd for $C_{11}H_{14}O_2$, 178.0988; found, 178.0996.

2-Ethyl-4*H*-benzo[*d*][1,3]dioxine (11f). Compound **11f** was synthesized from (2-(allyloxy)phenyl)methanol (41.05 mg, 0.25 mmol) $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (2.4 μmol, 1.6 mg) and diphenyl phosphate (0.02 mmol, 5 mg) in toluene (0.16 M) by general procedure B for catalysis. Reaction time after addition of diphenyl phosphate: 10 h. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 98:2) isolated as colorless oil: 25.4 mg, 0.16 mmol, 64%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21−7.12 (m, 1H), 7.02−6.82 (m, 3H), 5.06−4.94 (m, 2H), 4.85 (d, J = 14.6 Hz, 1H), 1.95−1.79 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 153.0, 127.9, 124.8, 120.9, 120.9, 116.6, 100.7, 66.5, 27.6, 7.9; IR $\tilde{\nu}$ = 2933, 2970, 2851, 1461, 1487, 1401, 1244, 1051, 1107, 939, 992, 749; HRMS (EI) m/z [M]$^+$: calcd for $C_{10}H_{12}O_2$, 164.0832; found, 164.0851.

4-Benzyl-2-ethyl-1,3-dioxolane (11g). Compound **11g** was synthesized from 1-(allyloxy)-3-phenylpropan-2-ol (48 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) following the general procedure B for catalysis and the following changes apply. Reaction time after addition of diphenyl phosphate: 12 h reaction temperature. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexaneethyl acetate 98:2) isolated as colorless oil: 26 mg, 0.13 mmol, 54%. The spectral data matches with the one reported in the literature.[10] Note: The product was isolated as a mixture of diastereomers (d.r. 2:1). The resonances for the major diastereomer are mentioned below. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 2H), 7.28−7.14 (m, 3H), 4.89 (t, J = 4.6 Hz, 1H), 4.39−4.22 (m, 1H), 3.92−3.82 (m, 1H), 3.70−3.54 (m, 1H), 3.04 (ddd, J = 13.7, 6.4, 2.7 Hz, 1H), 2.85−2.71 (m, 1H), 1.79−1.60 (m, 2H), 0.97 (q, J = 7.7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 137.5, 129.1, 128.5, 126.5, 105.7, 77.1, 69.2, 40.1, 39.5, 27.3, 27.2, 7.9.

2-Ethyl-4,4-dimethyl-5-phenyl-1,3-dioxolane (11h). Compound **11h** was synthesized from 1-(allyloxy)-2-methyl-1-phenylpropan-2-ol (51.5 mg, 0.25 mmol) using $[(Me_3P)_4NiH]N(SO_2CF_3)_2$ (0.01 mmol, 6.6 mg) and diphenyl phosphate (0.04 mmol, 9.35 mg) in toluene (0.16 M) by general procedure B for catalysis, and the following changes apply. Reaction time after addition of diphenyl phosphate: 8 h. The product was purified by flash column chromatography (12 g SiO_2, static elution, *n*-hexane/ethyl acetate 98:2) isolated as colorless oil: 31 mg, 0.15 mmol, 61%. The spectral data matches with the one reported in the literature.[7b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.28 (m, 5H), 5.05 (t, J = 4.5 Hz, 1H), 4.64 (s, 1H), 1.83−1.67 (m, 2H), 1.36 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H), 0.71 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.1, 127.7, 126.0, 102.9, 86.7, 80.7, 27.5, 26.0, 24.8, 8.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02033.

Experimental details and characterization data for the synthetized compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Andreas Berkefeld − *Faculty of Science and Mathematics, Eberhard Karls University Tübingen, 72076 Tübingen, Germany;* orcid.org/0000-0002-2757-7841; Email: andreas.berkefeld@uni-tuebingen.de

Ivana Fleischer − *Faculty of Science and Mathematics, Eberhard Karls University Tübingen, 72076 Tübingen, Germany;* orcid.org/0000-0002-2609-6536; Email: ivana.fleischer@uni-tuebingen.de

Authors

Prasad M. Kathe − *Faculty of Science and Mathematics, Eberhard Karls University Tübingen, 72076 Tübingen, Germany*

Alexandru Caciuleanu − *Faculty of Science and Mathematics, Eberhard Karls University Tübingen, 72076 Tübingen, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02033

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from DAAD (Deutscher Akademischer Austauschdienst, fellowship P. K.) and the University of Tübingen is gratefully acknowledged.

■ REFERENCES

(1) For recent reviews on isomerization, see: (a) Massad, I.; Marek, I. Alkene Isomerization through Allylmetals as a Strategic Tool in Stereoselective Synthesis. *ACS Catal.* **2020**, *10*, 5793−5804. (b) Molloy, J. J.; Morack, T.; Gilmour, R. Positional and Geometrical Isomerisation of Alkenes: The Pinnacle of Atom Economy. *Angew. Chem., Int. Ed.* **2019**, *58*, 13654−13664. (c) Liu, Q.; Liu, X.; Li, B. Base-Metal-Catalyzed Olefin Isomerization Reactions. *Synthesis* **2019**, *51*, 1293−1310. (d) Larionov, E.; Li, H.; Mazet, C. Well-defined transition metal hydrides in catalytic isomerizations. *Chem. Commun.* **2014**, *50*, 9816−9826.

(2) For recent reviews on isomerization-based tandem reactions, see: (a) Kathe, P.; Fleischer, I. Cooperative Use of Brønsted Acids and

Metal Catalysts in Tandem Isomerization Reactions of Olefins. *ChemCatChem* **2019**, *11*, 3343−3354. (b) Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153−165. (c) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* **2016**, *8*, 209. (d) Goldbach, V.; Roesle, P.; Mecking, S. Catalytic Isomerizing ω-Functionalization of Fatty Acids. *ACS Catal.* **2015**, *5*, 5951−5972.

(3) Sorimachi, K.; Terada, M. Relay Catalysis by a Metal-Complex/Bronsted Acid Binary System in a Tandem Isomerization/Carbon-Carbon Bond Forming Sequence. *J. Am. Chem. Soc.* **2008**, *130*, 14452−14453.

(4) (a) Ishoey, M.; Nielsen, T. E. Synthesis of Heterocycles through Transition-Metal-Catalyzed Isomerization Reactions. *Chem.—Eur. J.* **2014**, *20*, 8832−8840. (b) Toda, Y.; Terada, M. Relay Catalysis by a Ruthenium Complex−Chiral Brønsted Acid Binary Sytem for Ternary Reaction Sequence Involving Enantioselective Pictet−Spengler-Type Cyclization as the Key Step. *Synlett* **2013**, *24*, 752−756. (c) Hansen, C. L.; Clausen, J. W.; Ohm, R. G.; Ascic, E.; Le Quement, S. T.; Tanner, D.; Nielsen, T. E. Ruthenium Hydride/Brønsted Acid-Catalyzed Tandem Isomerization/N-Acyliminium Cyclization Sequence for the Synthesis of Tetrahydro-β-carbolines. *J. Org. Chem.* **2013**, *78*, 12545−12565.

(5) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. A Tandem Isomerization/Prins Strategy: Iridium (III)/Brønsted Acid Cooperative Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 12910−12914.

(6) (a) Cox, E. D.; Cook, J. M. The Pictet-Spengler condensation: a new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 1797−1842. (b) Pictet, A.; Spengler, T. Über die Bildung von Isochinolinderivaten durch Einwirkung von Methylal auf Phenyl-äthylamin, Phenyl-alanin und Tyrosin. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030−2036.

(7) (a) Bernárdez, R.; Suárez, J.; Fañanás-Mastral, M.; Varela, J. A.; Saá, C. Tandem Long Distance Chain-Walking/Cyclization via $RuH_2(CO)(PPh_3)_3$/Bronsted Acid Catalysis: Entry to Aromatic Oxazaheterocycles. *Org. Lett.* **2016**, *18*, 642−645. (b) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. Synthesis of Oxacyclic Scaffolds via Dual Ruthenium Hydride/Brønsted Acid-Catalyzed Isomerization/Cyclization of Allylic Ethers. *Chem.—Eur. J.* **2014**, *20*, 3297−3300.

(8) For recent selected reports on Pictet-Spengler-type cyclizations, see: (a) Maskeri, M. A.; O'Connor, M. J.; Jaworski, A. A.; Davies, A. V.; Scheidt, K. A. A Cooperative Hydrogen Bond Donor−Brønsted Acid System for the Enantioselective Synthesis of Tetrahydropyrans. *Angew. Chem., Int. Ed.* **2018**, *57*, 17225−17229. (b) Zheng, C.; Xia, Z.-L.; You, S.-L. Unified Mechanistic Understandings of Pictet-Spengler Reactions. *Chem* **2018**, *4*, 1952−1966. (c) Fan, W.-T.; Li, N.-K.; Xu, L.; Qiao, C.; Wang, X.-W. Organo-Catalyzed Asymmetric Michael−Hemiketalization−Oxa-Pictet−Spengler Cyclization for Bridged and Spiro Heterocyclic Skeletons: Oxocarbenium Ion as a Key Intermediate. *Org. Lett.* **2017**, *19*, 6626−6629. (d) Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B. Nitrated Confined Imidodiphosphates Enable a Catalytic Asymmetric Oxa-Pictet−Spengler Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 9429−9432. (e) Larghi, E. L.; Kaufman, T. S. Synthesis of Oxacycles Employing the Oxa-Pictet−Spengler Reaction: Recent Developments and New Prospects. *Eur. J. Org. Chem.* **2011**, 5195−5231. (f) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. Chiral Lewis Acid-Mediated Enantioselective Pictet−Spengler Reaction of Nb-Hydroxytryptamine with Aldehydes. *J. Org. Chem.* **1998**, *63*, 6348−6354.

(9) For selected reports on cycloisomerization, see: (a) Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. Simple, Chemoselective, Catalytic Olefin Isomerization. *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791. (b) Li, G.; Kuo, J. L.; Han, A.; Abuyuan, J. M.; Young, L. C.; Norton, J. R.; Palmer, J. H. Radical Isomerization and Cycloisomerization Initiated by H• Transfer. *J. Am. Chem. Soc.* **2016**, *138*, 7698−7704. (c) Lorenc, C.; Vibbert, H. B.; Yao, C.; Norton, J. R.; Rauch, M. H· Transfer-Initiated Synthesis of γ-Lactams: Interpretation of Cyclo-isomerization and Hydrogenation Ratios. *ACS Catal.* **2019**, *9*, 10294−10298. (d) Matos, J. L. M.; Green, S. A.; Chun, Y.; Dang, V. Q.; Dushin, R. G.; Richardson, P.; Chen, J. S.; Piotrowski, D. W.; Paegel, B. M.; Shenvi, R. A. Cycloisomerization of Olefins in Water. *Angew. Chem., Int. Ed.* **2020**, *59*, 12998−13003.

(10) Kathe, P. M.; Fleischer, I. Palladium-Catalyzed Tandem Isomerization/Hydrothiolation of Allylarenes. *Org. Lett.* **2019**, *21*, 2213.

(11) (a) Gehrtz, P. H.; Geiger, V.; Schmidt, T.; Sršan, L.; Fleischer, I. Cross-Coupling of Chloro(hetero)arenes with Thiolates Employing a Ni(0)-Precatalyst. *Org. Lett.* **2019**, *21*, 50−55. (b) Gehrtz, P. H.; Kathe, P.; Fleischer, I. Nickel-Catalyzed Coupling of Arylzinc Halides with Thioesters. *Chem.—Eur. J.* **2018**, *24*, 8774−8778.

(12) For recent examples of Ni-catalyzed isomerization, see: (a) Kapat, A.; Sperger, T.; Guven, S.; Schoenebeck, F. E-Olefins through intramolecular radical relocation. *Science* **2019**, *363*, 391−396. (b) Weber, F.; Schmidt, A.; Röse, P.; Fischer, M.; Burghaus, O.; Hilt, G. Double-Bond Isomerization: Highly Reactive Nickel Catalyst Applied in the Synthesis of the Pheromone (9Z,12Z)-Tetradeca-9,12-dienyl Acetate. *Org. Lett.* **2015**, *17*, 2952−2955. (c) Wang, L.; Liu, C.; Bai, R.; Pan, Y.; Lei, A. Easy access to enamides: a mild nickel-catalysed alkene isomerization of allylamides. *Chem. Commun.* **2013**, *49*, 7923−7925. (d) Wille, A.; Tomm, S.; Frauenrath, H. A Highly Z-Selective Isomerization (Double-Bond Migration) Procedure for Allyl Acetals and Allyl Ethers Mediated by Nickel Complexes. *Synthesis* **1998**, 305−308.

(13) For Ni-catalyzed isomerizing tandem reactions, see: (a) Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R. Tackling Remote sp_3 C−H Functionalization via Ni-Catalyzed "chain-walking" Reactions. *Isr. J. Chem.* **2020**, *60*, 195−206. (b) Zhang, Y.; Xu, X.; Zhu, S. Nickel-catalysed selective migratory hydrothiolation of alkenes and alkynes with thiols. *Nat. Commun.* **2019**, *10*, 1752. (c) He, J.; Song, P.; Xu, X.; Zhu, S.; Wang, Y. Migratory Reductive Acylation between Alkyl Halides or Alkenes and Alkyl Carboxylic Acids by Nickel Catalysis. *ACS Catal.* **2019**, *9*, 3253−3259. (d) Gaydou, M.; Moragas, T.; Juliá-Hernández, F.; Martin, R. Site-Selective Catalytic Carboxylation of Unsaturated Hydrocarbons with CO2 and Water. *J. Am. Chem. Soc.* **2017**, *139*, 12161−12164. (e) Weber, F.; Ballmann, M.; Kohlmeyer, C.; Hilt, G. Nickel-Catalyzed Double Bond Transposition of Alkenyl Boronates for in Situ syn-Selective Allylboration Reactions. *Org. Lett.* **2016**, *18*, 548−551. (f) Buslov, I.; Song, F.; Hu, X. An Easily Accessed Nickel Nanoparticle Catalyst for Alkene Hydrosilylation with Tertiary Silanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 12295−12299. (g) Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. Linear-Selective Hydroarylation of Unactivated Terminal and Internal Olefins with Trifluoromethyl-Substituted Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 13098−13101. (h) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. Tandem Isomerization and C−H Activation: Regioselective Hydroheteroarylation of Allylarenes. *Org. Lett.* **2013**, *15*, 5358−5361. (i) Richmond, E.; Khan, I. U.; Moran, J. Enantioselective and Regiodivergent Functionalization of N-Allylcarbamates by Mechanistically Divergent Multicatalysis. *Chem.—Eur. J.* **2016**, *22*, 12274−12277.

(14) (a) Tolman, C. A. Chemistry of tetrakis(triethyl phosphite)-nickel hydride, $HNi[P(OEt)_3]_4^+$. IV. Mechanism of olefin isomerization. *J. Am. Chem. Soc.* **1972**, *94*, 2994−2999. (b) Tolman, C. A. Chemistry of tetrakis(triethyl phosphite) nickel hydride, $HNi[P(OEt)_3]_4^+$. I. Nickel hydride formation and decay. *J. Am. Chem. Soc.* **1970**, *92*, 4217−4222.

(15) Bartlett, S. A.; Badiola, K. A.; Arandiyan, H.; Masters, A. F.; Maschmeyer, T. The Autocatalytic Isomerization of Allylbenzene by Nickel(0) Tetrakis(triethylphosphite). *Eur. J. Inorg. Chem.* **2018**, 3384−3387.

(16) (a) Neary, M. C.; Quinlivan, P. J.; Parkin, G. Zerovalent Nickel Compounds Supported by 1,2-Bis(diphenylphosphino)benzene: Synthesis, Structures, and Catalytic Properties. *Inorg. Chem.* **2018**, *57*, 374−391. (b) Koch, F.; Berkefeld, A. Reactant or reagent? Oxidation of H_2 at electronically distinct nickel-thiolate sites $[Ni_2(\mu\text{-}SR)_2]^+$ and

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

[Ni−SR]$^+$. *Dalton Trans.* **2018**, *47*, 10561−10568. (c) Tolman, C. A. Electronic effects of phosphorus ligands on the protonation of NiL_4 complexes. *Inorg. Chem.* **1972**, *11*, 3128−3129.
(17) Bouguerne, B.; Hoffmann, P.; Lherbet, C. Bismuth Triflate as a Safe and Readily Handled Source of Triflic Acid: Application to the Oxa−Pictet−Spengler Reaction. *Synth. Commun.* **2010**, *40*, 915−926.
(18) (a) Botla, V.; Pilli, N.; Koude, D.; Misra, S.; Malapaka, C. Molecular Engineering of Tetracyclic 2,3-Dihydro-1H-benzo[2,3]-benzofuro[4,5-e][1,3]oxazine Derivatives: Evaluation for Potential Anticancer Agents. *Arch. Pharm.* **2017**, *350*, 1700169. (b) Higham, C. S.; Dowling, D. P.; Shaw, J. L.; Cetin, A.; Ziegler, C. J.; Farrell, J. R. Multidentate aminophenol ligands prepared with Mannich condensations. *Tetrahedron Lett.* **2006**, *47*, 4419−4423. (c) Issa, S.; Walchshofer, N.; Kassab, I.; Termoss, H.; Chamat, S.; Geahchan, A.; Bouaziz, Z. Synthesis and antiproliferative activity of oxazinocarbazole and N,N-bis(carbazolylmethyl)amine derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 2567−2577.
(19) Schunn, R. A.; Ashby, E. C.; Dilts, J. Tetrakis-(triphenylphosphine)nickel(0). *Inorg. Synth.* **1972**, *13*, 124−126.
(20) Kumar, R.; Sharma, A.; Sharma, N.; Kumar, V.; Sinha, A. K. Neutral Ionic Liquid [hmim]Br as a Green Reagent and Solvent for the Mild and Efficient Dehydration of Benzyl Alcohols into (E)-Arylalkenes Under Microwave Irradiation. *Eur. J. Org. Chem.* **2008**, 5577−5582.
(21) Rauf, W.; Brown, J. M. Catalytic Amide-Mediated Methyl Transfer from Silanes to Alkenes in Fujiwara−Moritani Oxidative Coupling. *Angew. Chem., Int. Ed.* **2008**, *47*, 4228−4230.
(22) Tiecco, M.; Tingoli, M. Regiochemistry and Stereochemistry of Nickel-Promoted, Carbon-Carbon Bond-Forming Reactions of Cyclic Sulfur Compounds. *J. Org. Chem.* **1985**, *50*, 3828−3831.
(23) Gregg, Z. R.; Griffiths, J. R.; Diver, S. T. Conformational Control of Initiation Rate in Hoveyda−Grubbs Precatalysts. *Organometallics* **2018**, *37*, 1526−1533.
(24) Albright, H.; Vonesh, H. L.; Schindler, C. S. Superelectrophilic Fe(III)−Ion Pairs as Stronger Lewis Acid Catalysts for (E)-Selective Intermolecular Carbonyl−Olefin Metathesis. *Org. Lett.* **2020**, *22*, 3155−3160.
(25) Lamb, J. R.; Hubbell, A. K.; MacMillan, S. N.; Coates, G. W. Carbonylative, Catalytic Deoxygenation of 2,3-Disubstituted Epoxides with Inversion of Stereochemistry: An Alternative AlkeneIsomerization Method. *J. Am. Chem. Soc.* **2020**, *142*, 8029−8035.

https://dx.doi.org/10.1021/acs.joc.0c02033
J. Org. Chem. 2020, 85, 15183−15196

SUPPORTING INFORMATION

Tandem Olefin Isomerization/Cyclization Catalyzed by Complex Nickel Hydride and Brønsted Acid

Prasad M. Kathe, Alexandru Caciuleanu, Andreas Berkefeld,* Ivana Fleischer*

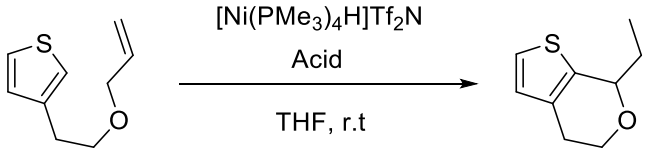
Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

*ivana.fleischer@uni-tuebingen.de
*andreas.berkefeld@uni-tuebingen.de

Table of Contents:

1. Optimization of Reaction Conditions

Table S1. Optimization of Reaction Conditions with thiophene-based substrate:



sr. no	**Ni-H** (mol-%)	acid (mol-%)	Time X+Y (h)	Yield (%)[a]
1	5	TfOH (20 mol%)	3+3	87
2	5	TfOH (20 mol%)	2.5+2.5	77
3	5	TfOH (20 mol%)	2+2	77
4	5	TfOH (20 mol%)	1.5+1.5	>99
5	3	TfOH (12 mol%)	1.5+1.5	>99
7	1.25	TfOH (5 mol%)	25+25 min	>99
8	1	TfOH (4 mol%)	20+20 min	>99
9	0.5	TfOH (2 mol%)	20+20 min	>98
10	0.25	TfOH (1 mol%)	30+30 min	>98
12	-	TfOH (5 mol%)	1.5+1.5	-
13	1	$FeCl_3$(4 mol%)	0.5+15	33
14[b]	1	MSA (4 mol%)	0.5+17	>99
15[c]	1	DPP (4 mol%)	0.5+24	97
16[b]	1	CSA (4 mol%)	0.5+24	27
17	1	$Bi(OTf)_3$ (4 mol%)	15+15 min	>99

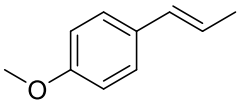
[a]Yield determined by quantitative GC-FID analysis. [b]Reaction performed at 60 °C. [c] Reaction performed at 115 °C, solvent = toluene.

Note: Time (X+Y) indicates that the reaction mixture comprised of reactant, **Ni-H** and solvent was stirred for X h, followed by addition of the acid and further stirring for Y h.

2. Olefin Isomerization Experiments: Spectral Data for Products 2a-2h

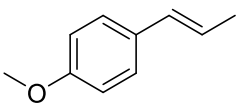
(*E*)-1-Methoxy-4-(prop-1-en-1-yl)benzene (**2a)**

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

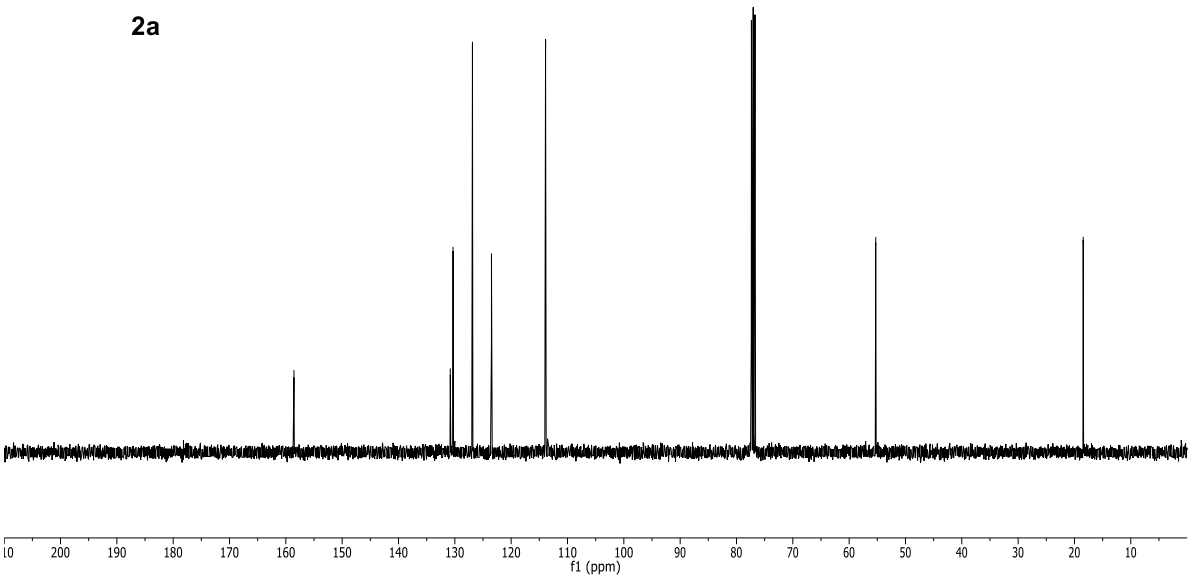


2a

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

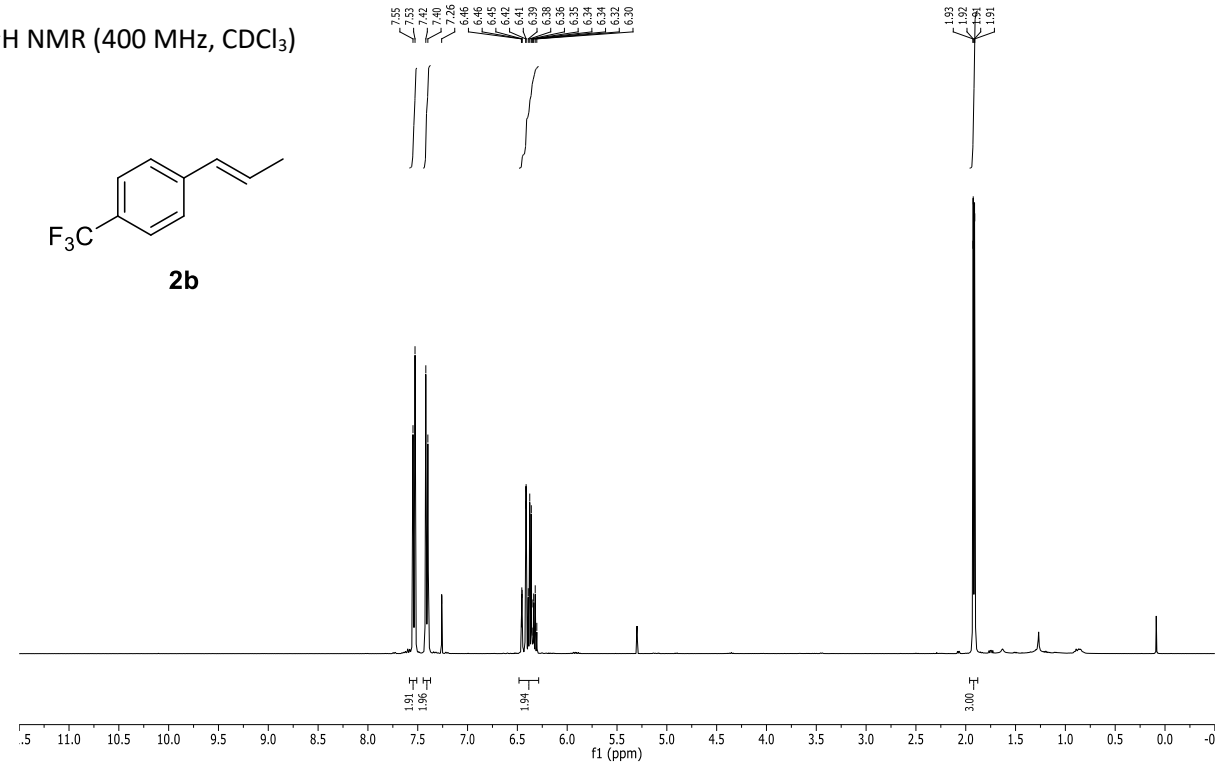


2a

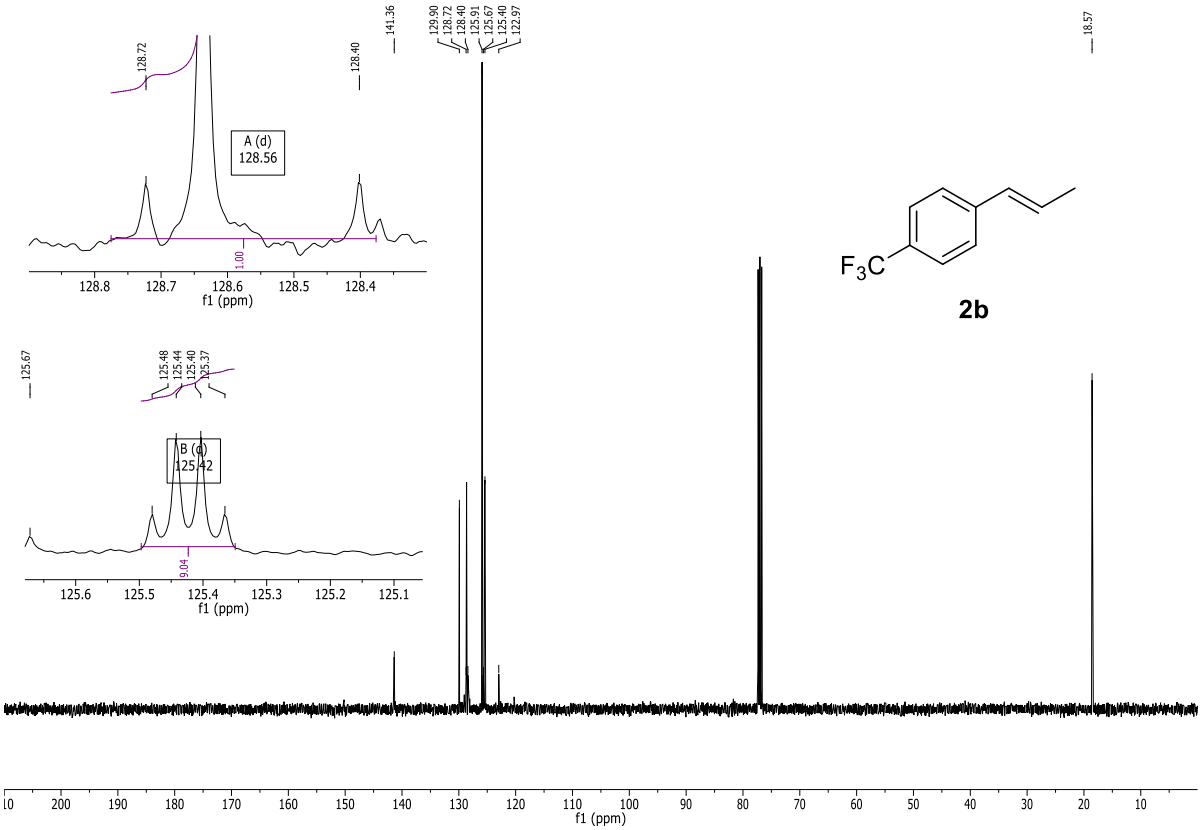


(*E*)-1-(Prop-1-en-1-yl)-4-(trifluoromethyl)benzene (**2b)**

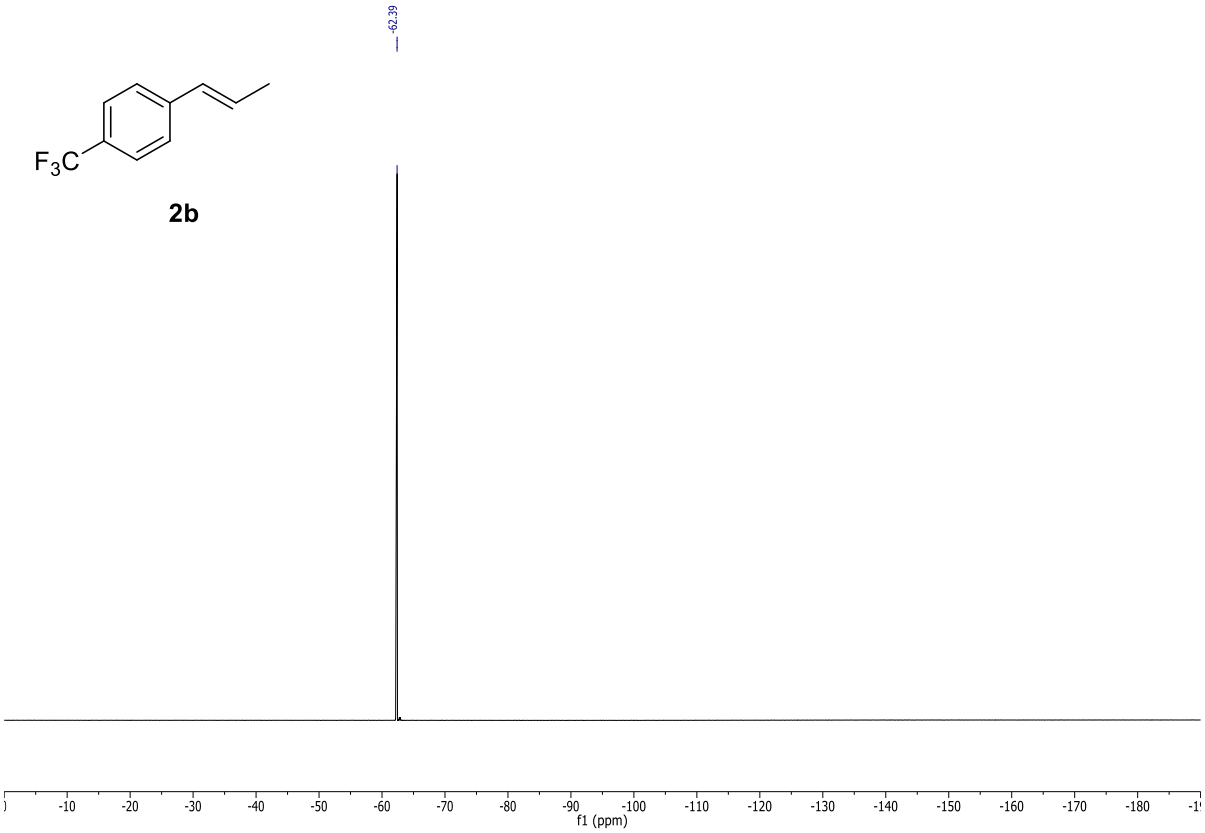
^{1}H NMR (400 MHz, $CDCl_3$)



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



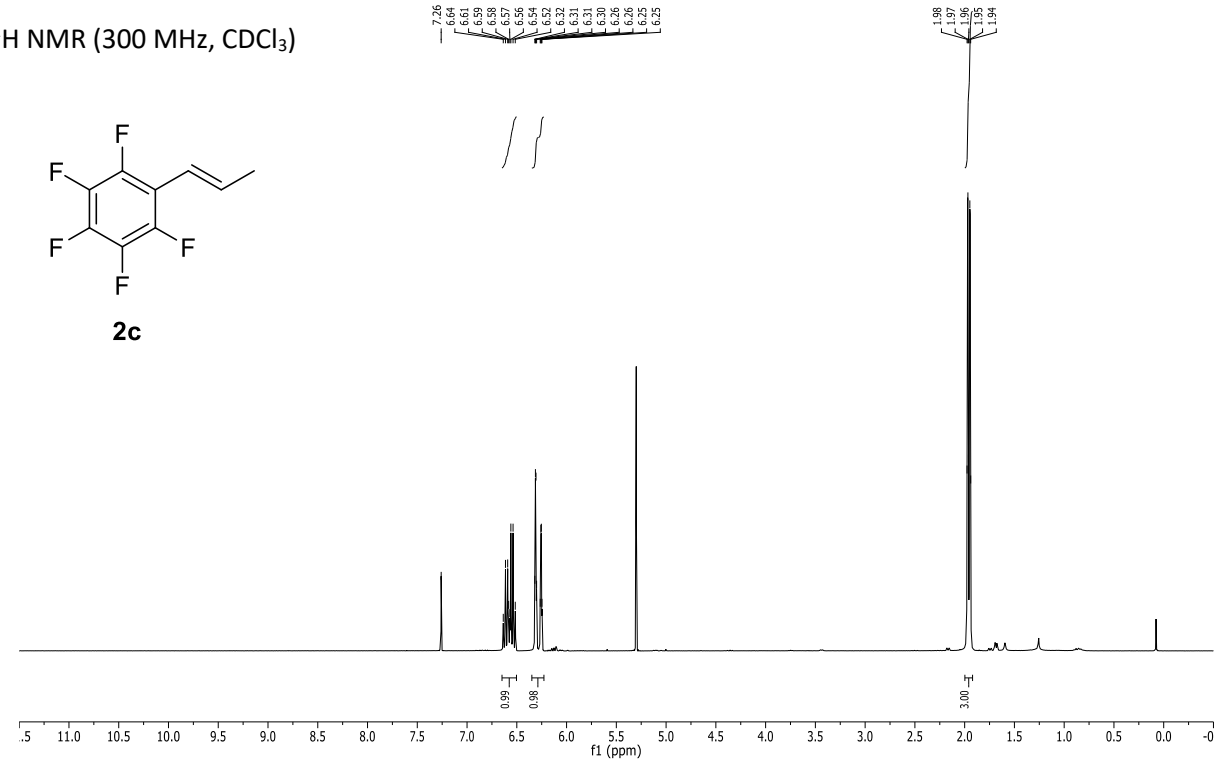
^{19}F NMR (282 MHz, $CDCl_3$)



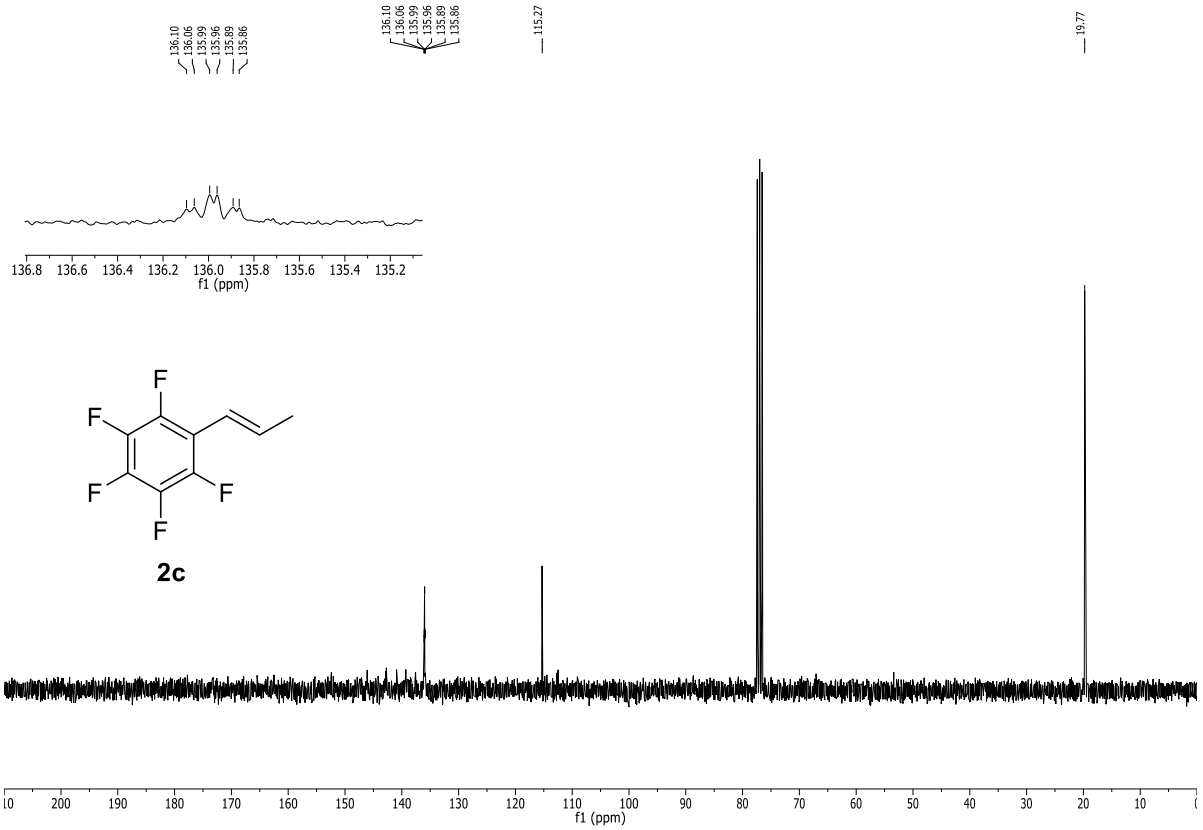
2b

(*E*)-1,2,3,4,5-Pentafluoro-6-(prop-1-en-1-yl)benzene (**2c**)

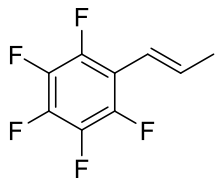
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



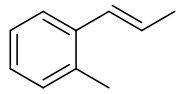
^{19}F NMR (376 MHz, $CDCl_3$)



2c

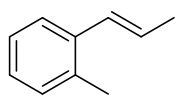
(E)-1-Methyl-2-(prop-1-en-1-yl)benzene (**2d**)

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



2d

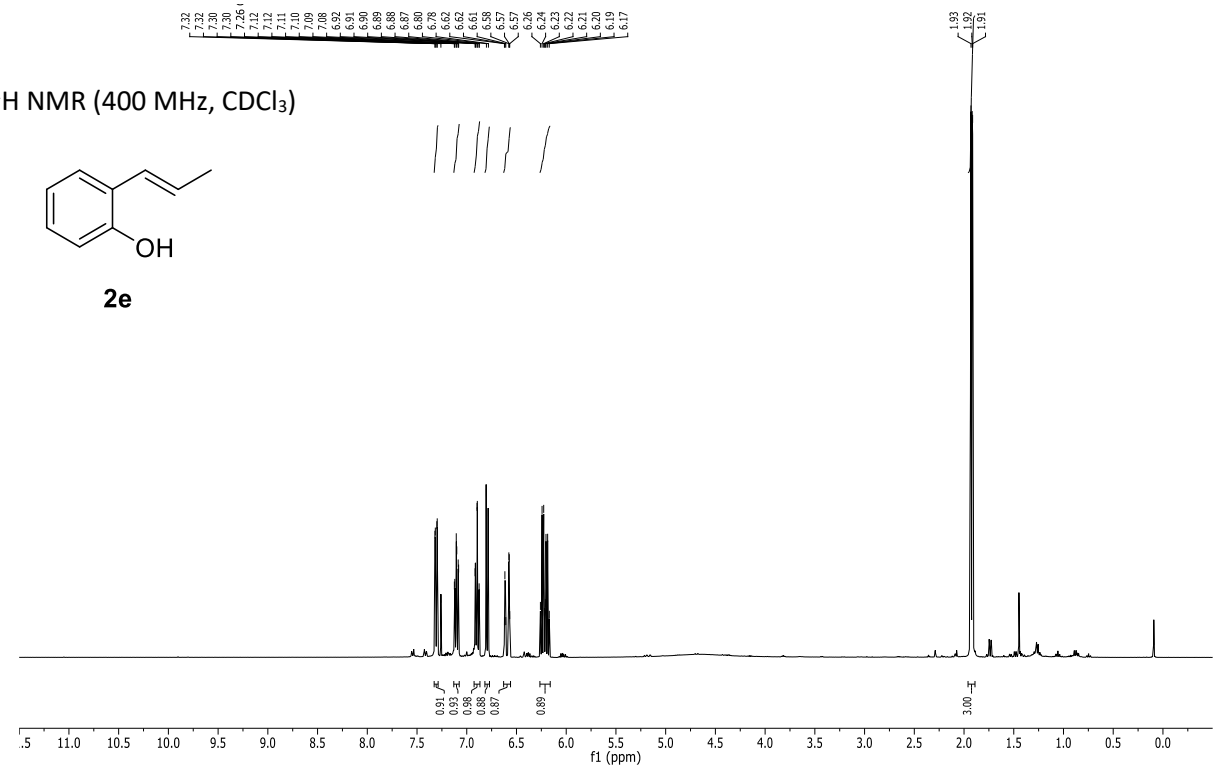
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



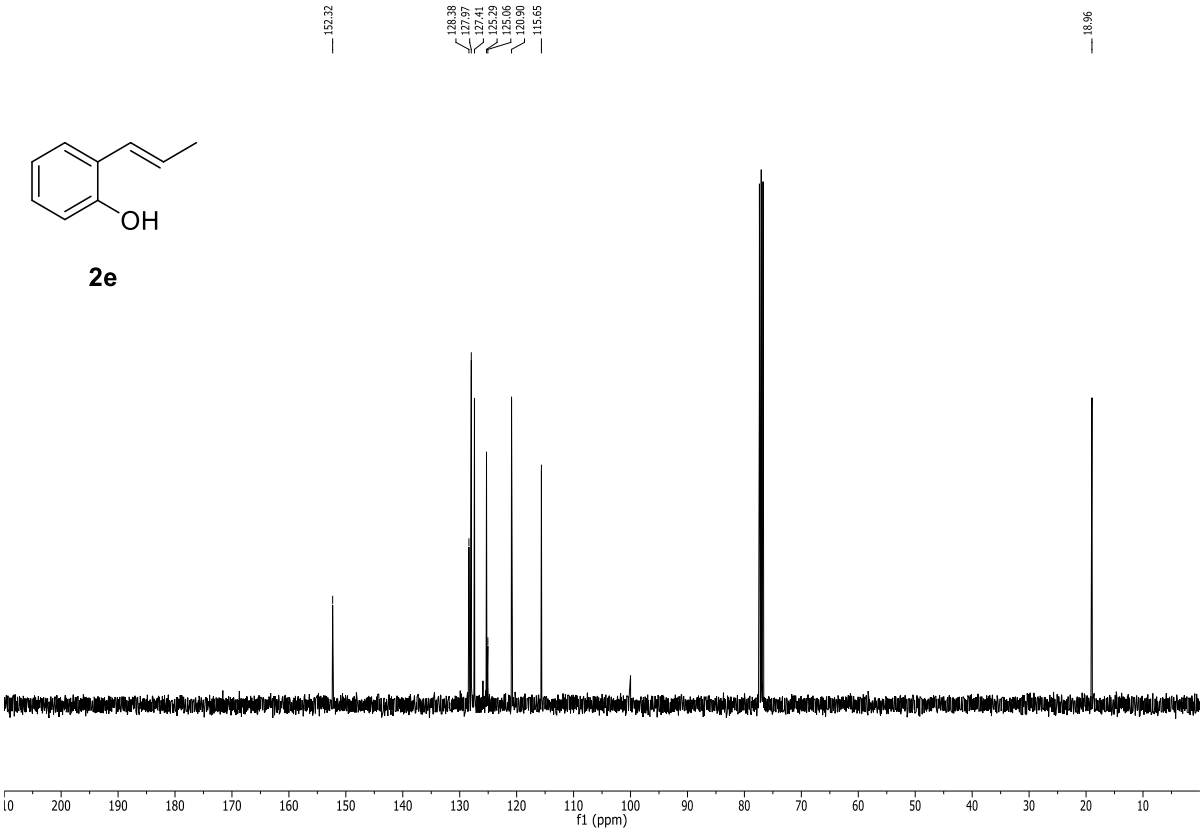
2d

(*E*)-2-(Prop-1-en-1-yl)phenol (**2e**)

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

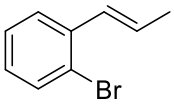


$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



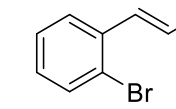
(*E*)-1-Bromo-2-(prop-1-en-1-yl)benzene (**2f**)

^{1}H NMR (300 MHz, $CDCl_3$)



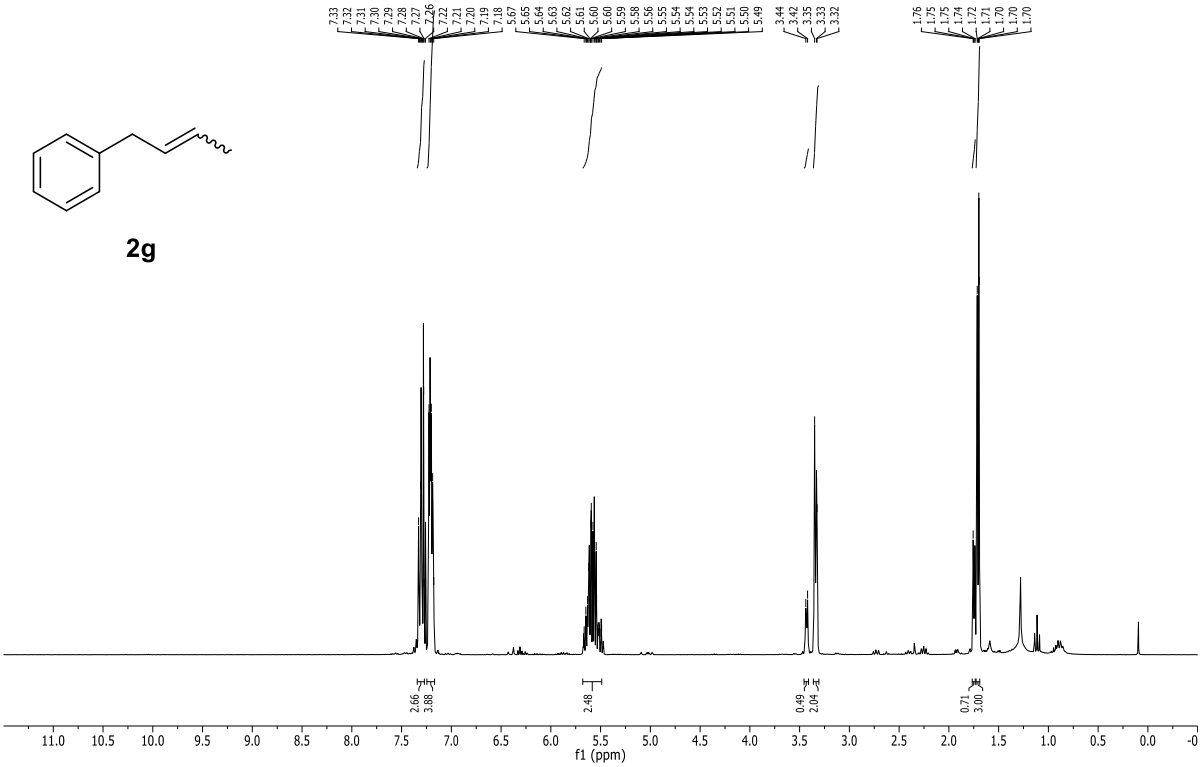
2f

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)

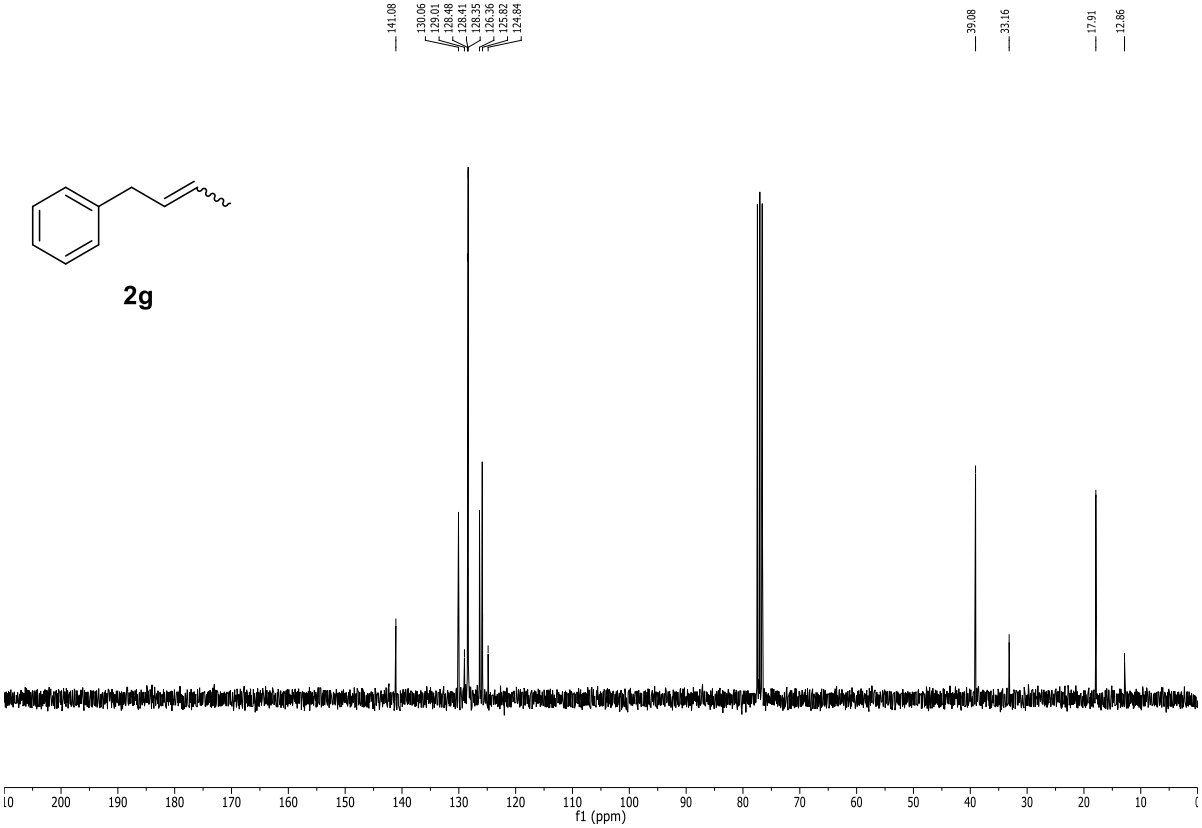


2f

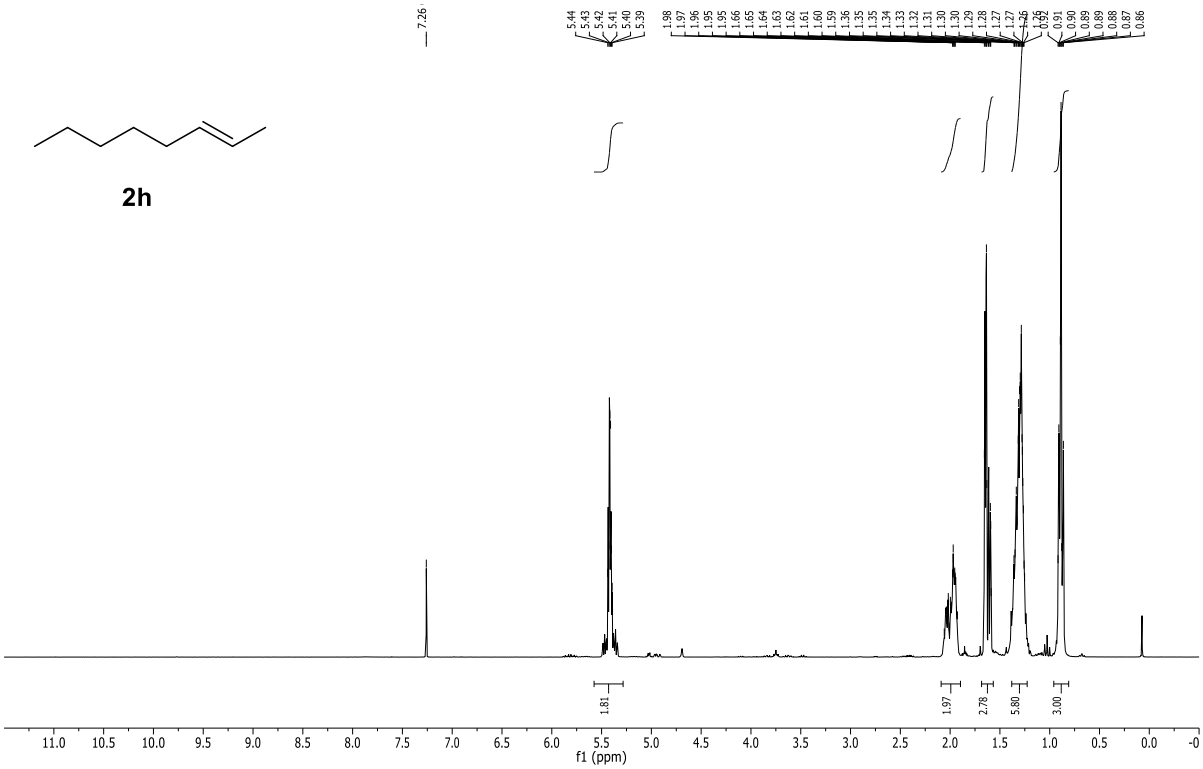
But-2-en-1-ylbenzene (**2g**) ^{1}H NMR (300 MHz, $CDCl_3$)



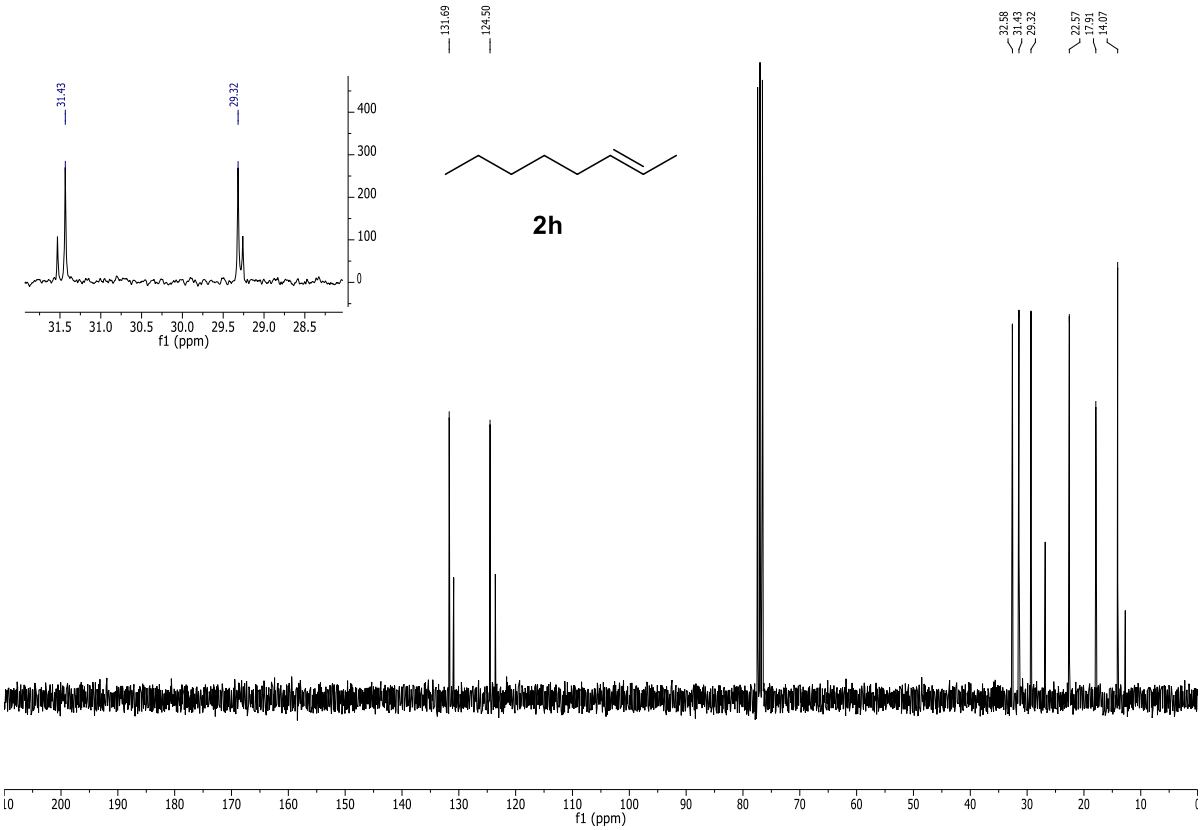
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$)



2-Octene (**2h**) ^{1}H NMR (300 MHz, $CDCl_3$)



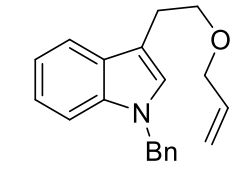
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$)



3. Spectral Data for Indole Based Substrates 3aa-3af, 3ba-3bg

3-(2-(Allyloxy)ethyl)-1-benzyl-1H-indole (**3aa**)

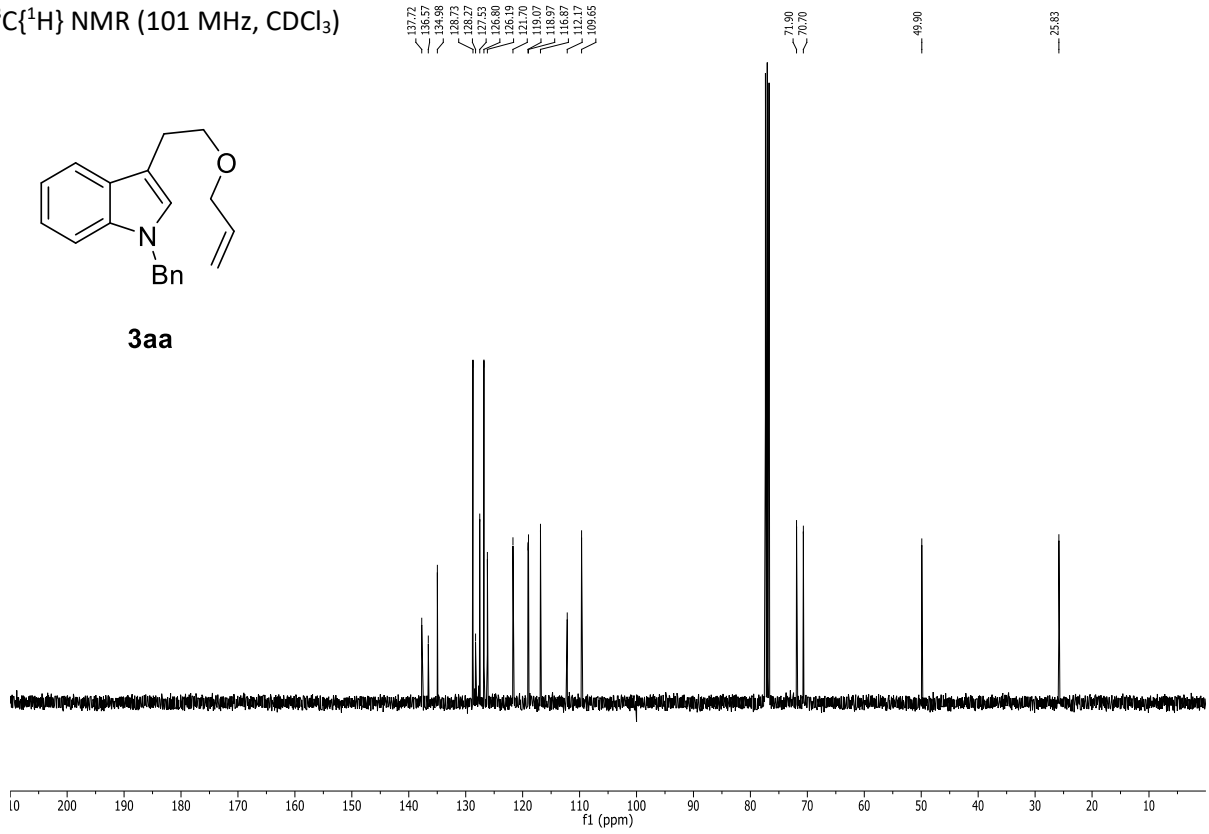
^{1}H NMR (400 MHz, $CDCl_3$)



3aa

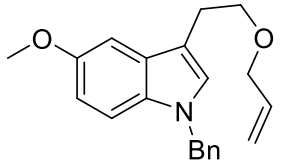
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

3aa



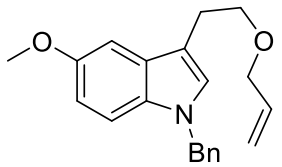
3-(2-(Allyloxy)ethyl)-1-benzyl-5-methoxy-1H-indole (**3ab**)

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



3ab

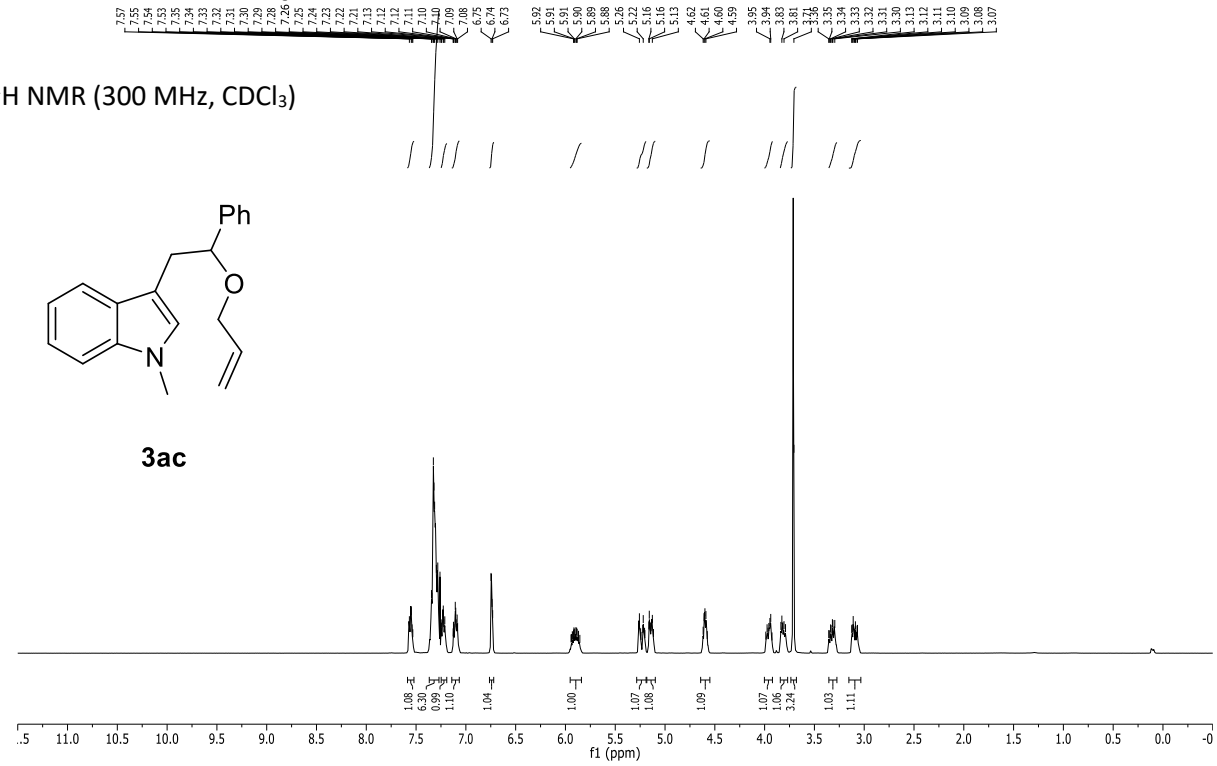
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



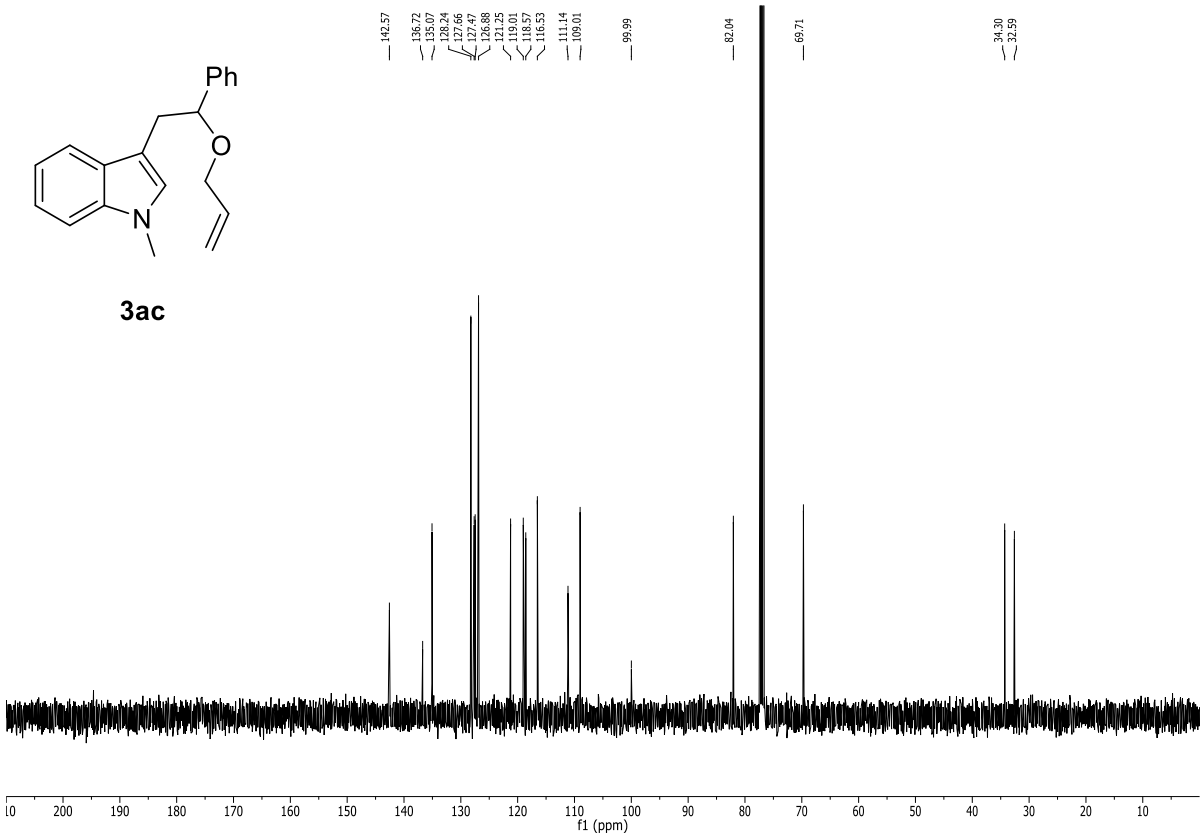
3ab

3-(2-(Allyloxy)-2-phenylethyl)-1-methyl-1H-indole (**3ac**)

^{1}H NMR (300 MHz, $CDCl_3$)

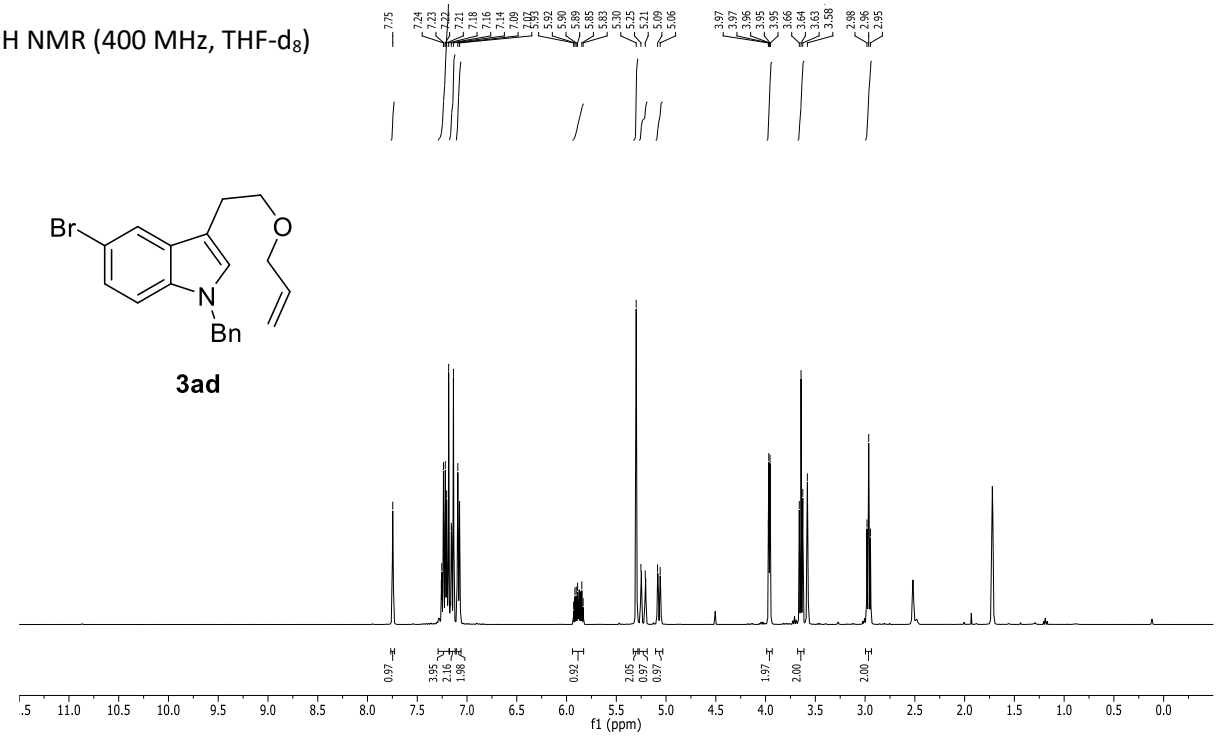


$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)

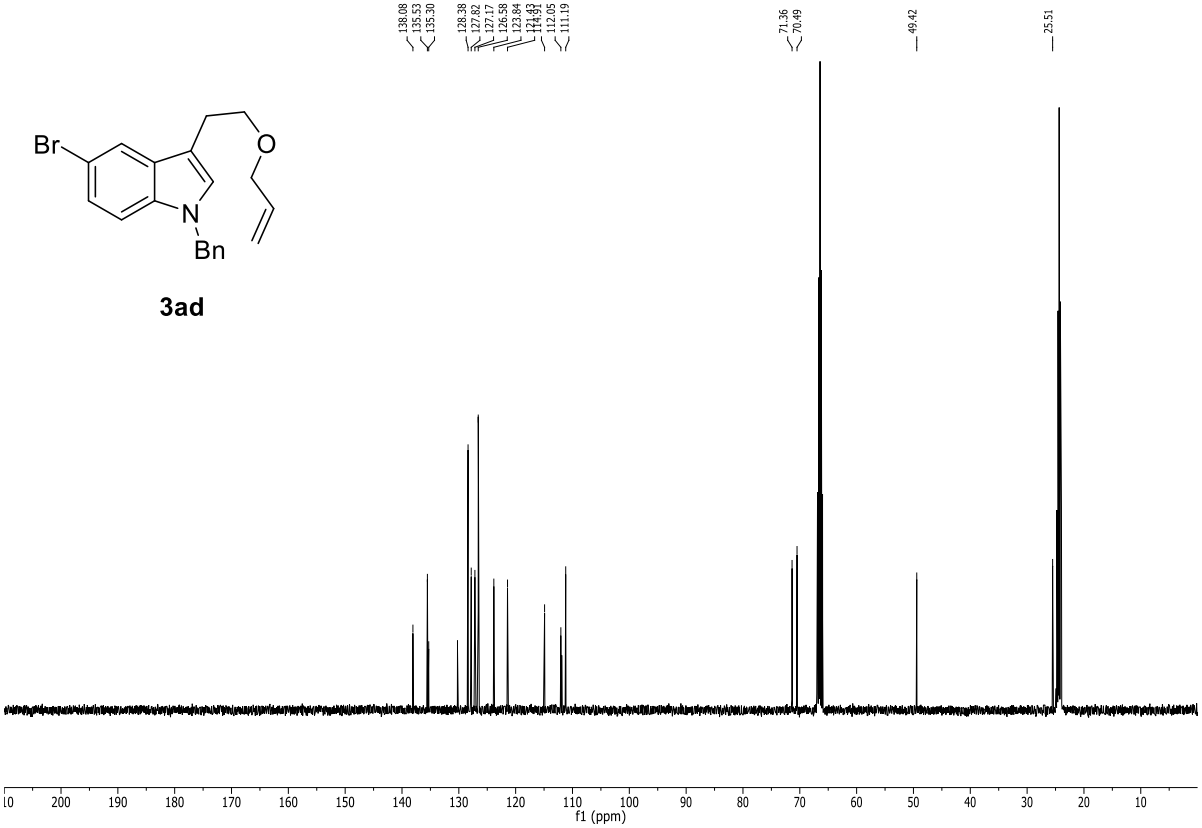


3-(2-(Allyloxy)ethyl)-1-benzyl-5-bromo-1H-indole (**3ad)**

^{1}H NMR (400 MHz, THF-d_8)

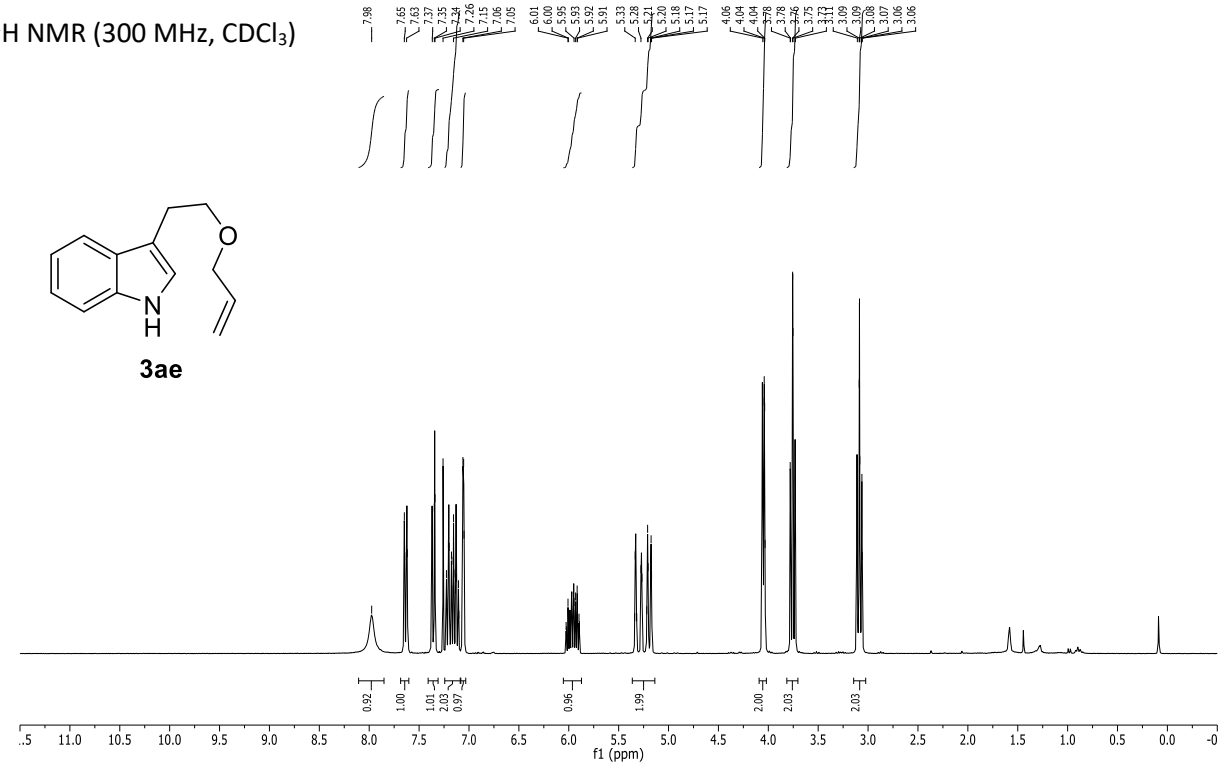


^{13}C{^{1}H} NMR (101 MHz, THF-d_8)



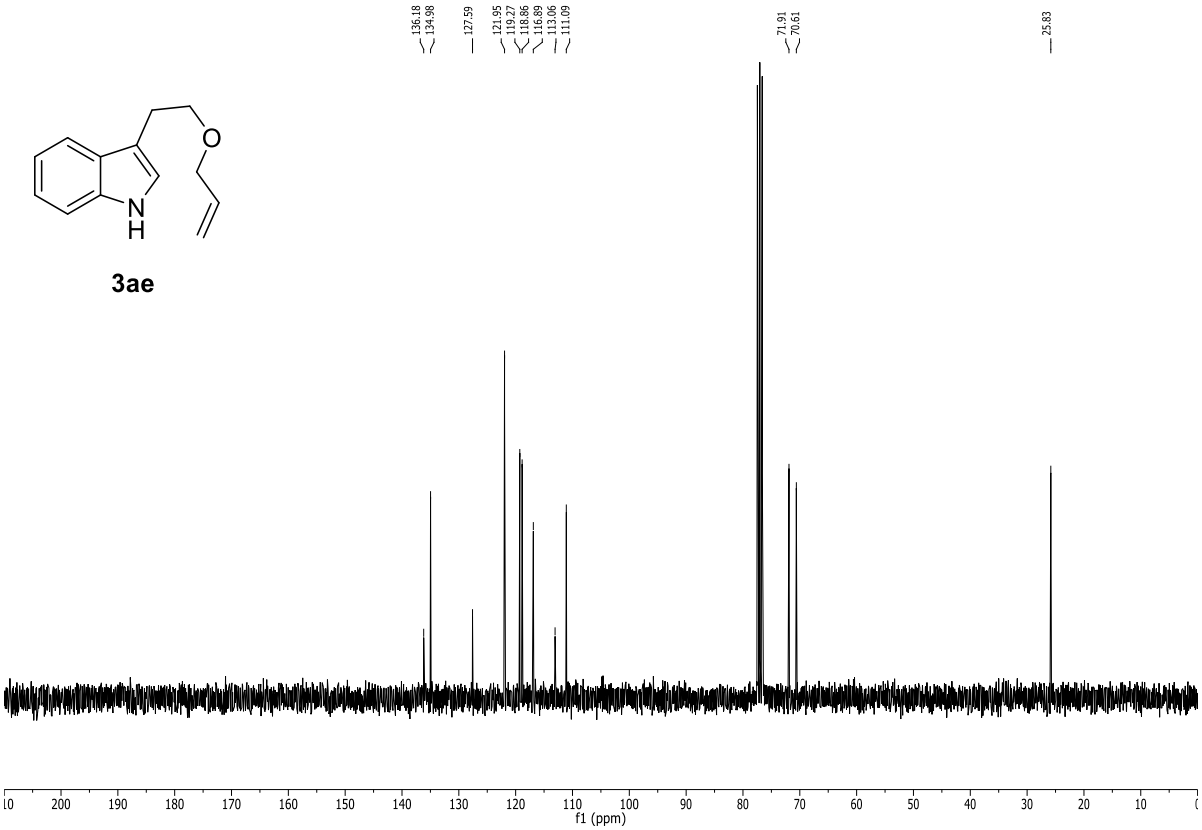
3-(2-(Allyloxy)ethyl)-1H-indole (**3ae)**

^{1}H NMR (300 MHz, $CDCl_3$)



3ae

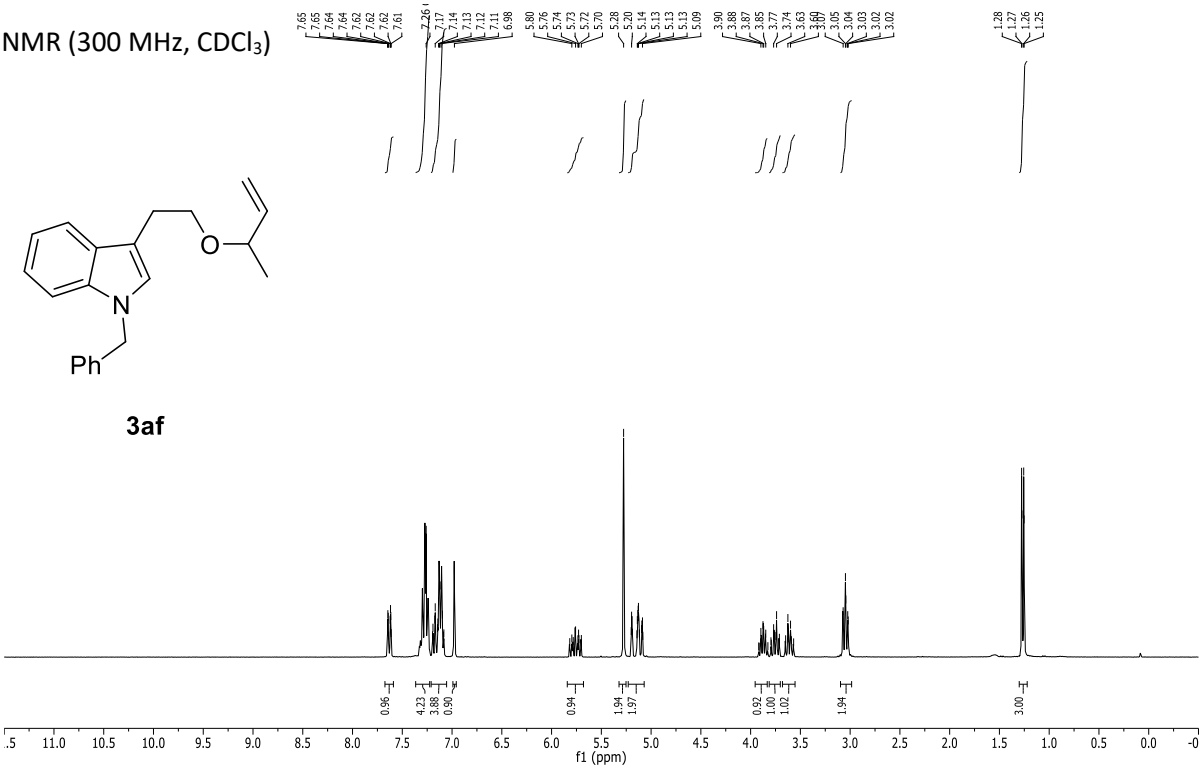
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



3ae

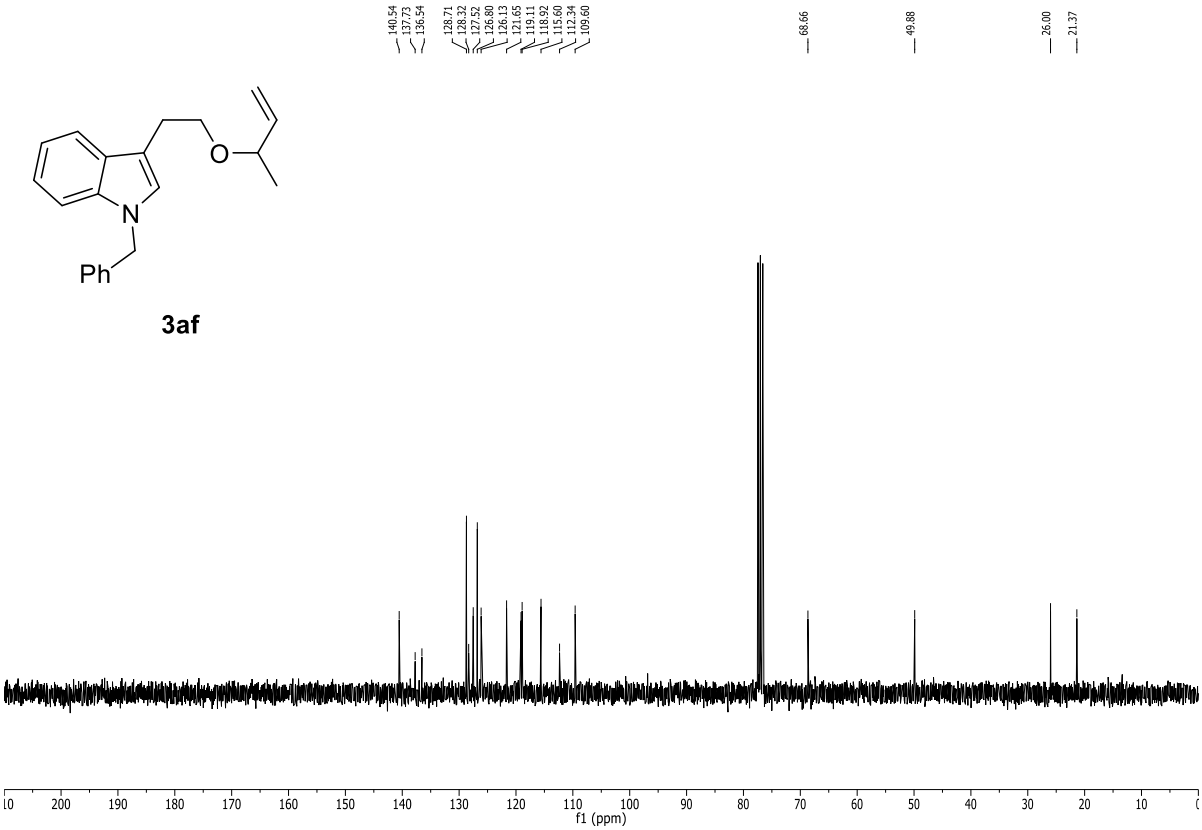
1-Benzyl-3-(2-(but-3-en-2-yloxy)ethyl)-1H-indole (**3af**)

^{1}H NMR (300 MHz, $CDCl_3$)



3af

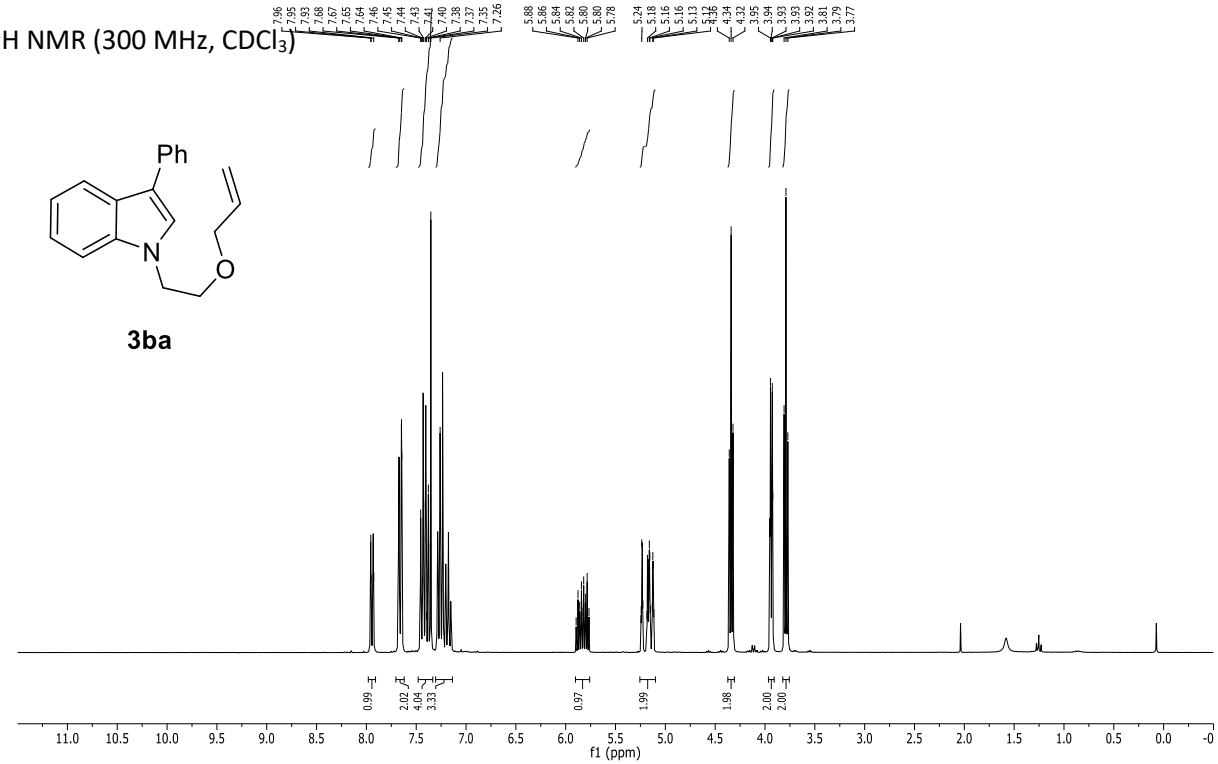
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



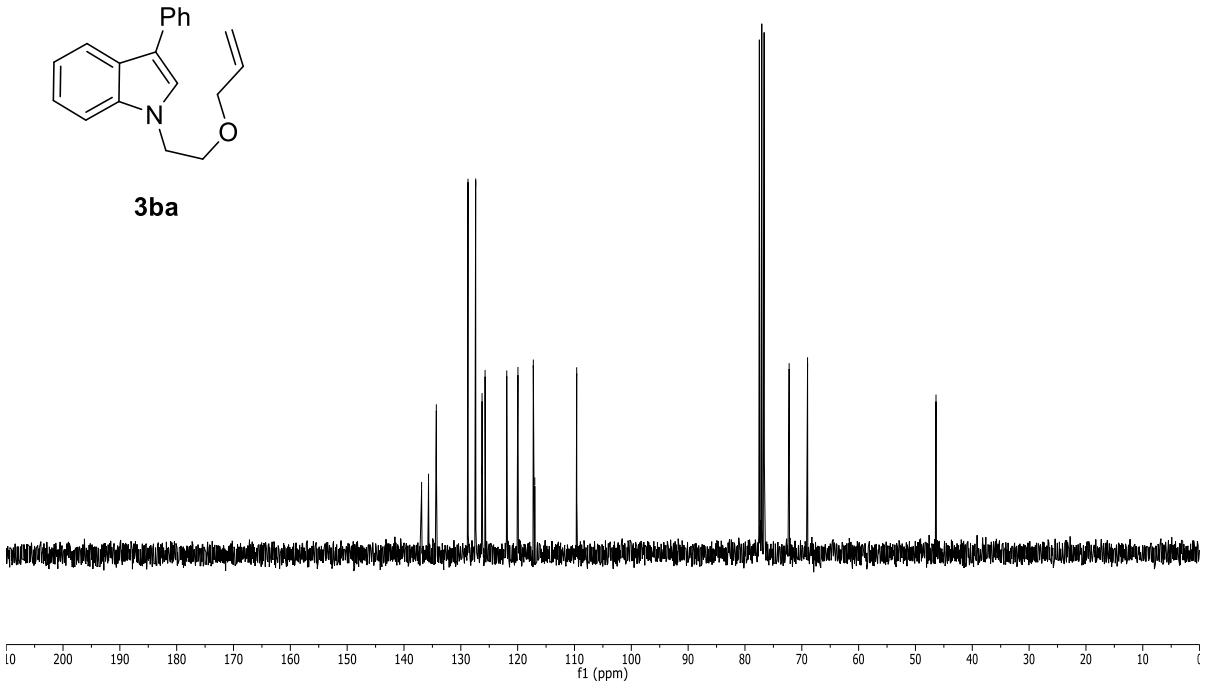
3af

1-(2-(Allyloxy)ethyl)-3-phenyl-1H-indole (**3ba**)

^{1}H NMR (300 MHz, $CDCl_3$)

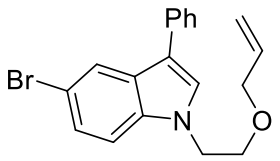


$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)



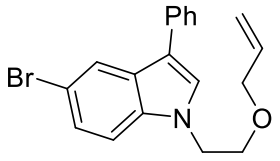
1-(2-(Allyloxy)ethyl)-5-bromo-3-phenyl-1H-indole (**3bb**)

^{1}H NMR (300 MHz, $CDCl_3$)



3bb

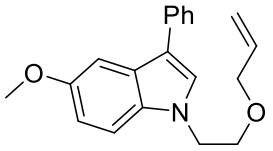
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



3bb

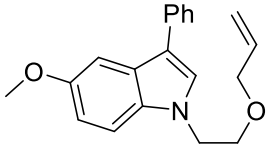
1-(2-(Allyloxy)ethyl)-5-methoxy-3-phenyl-1H-indole (**3bc**)

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



3bc

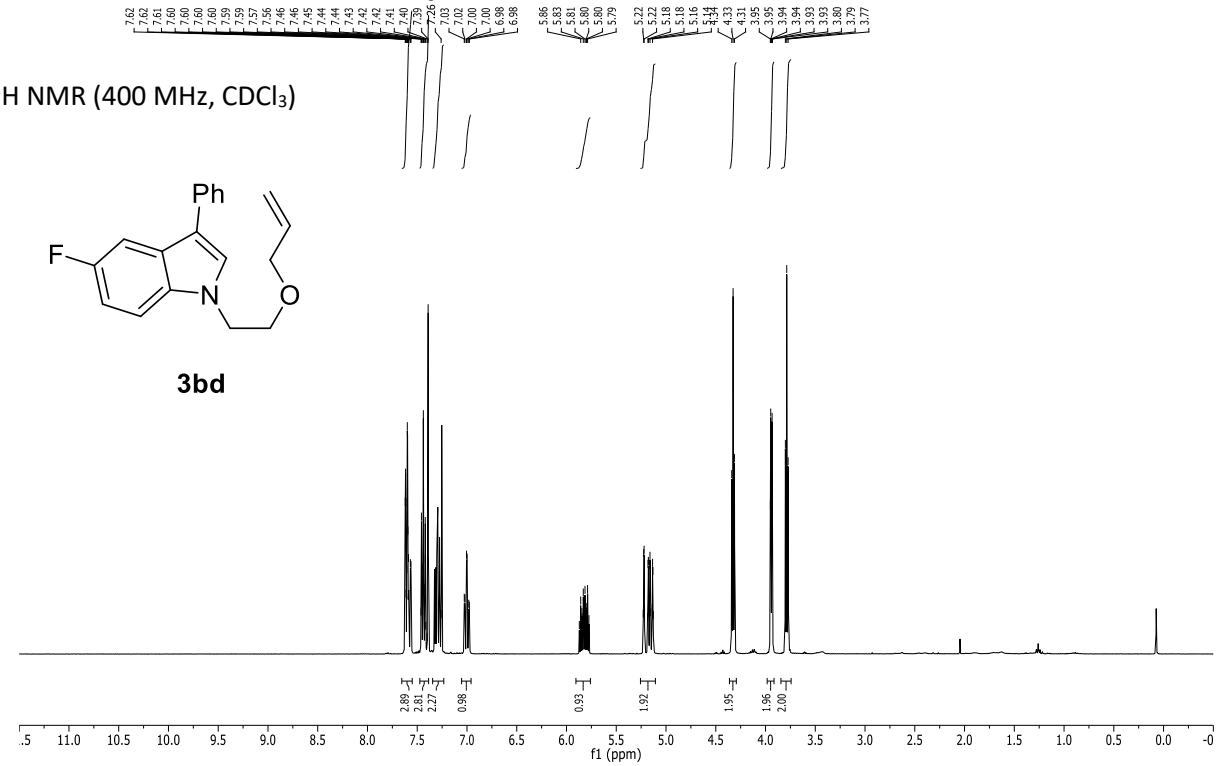
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



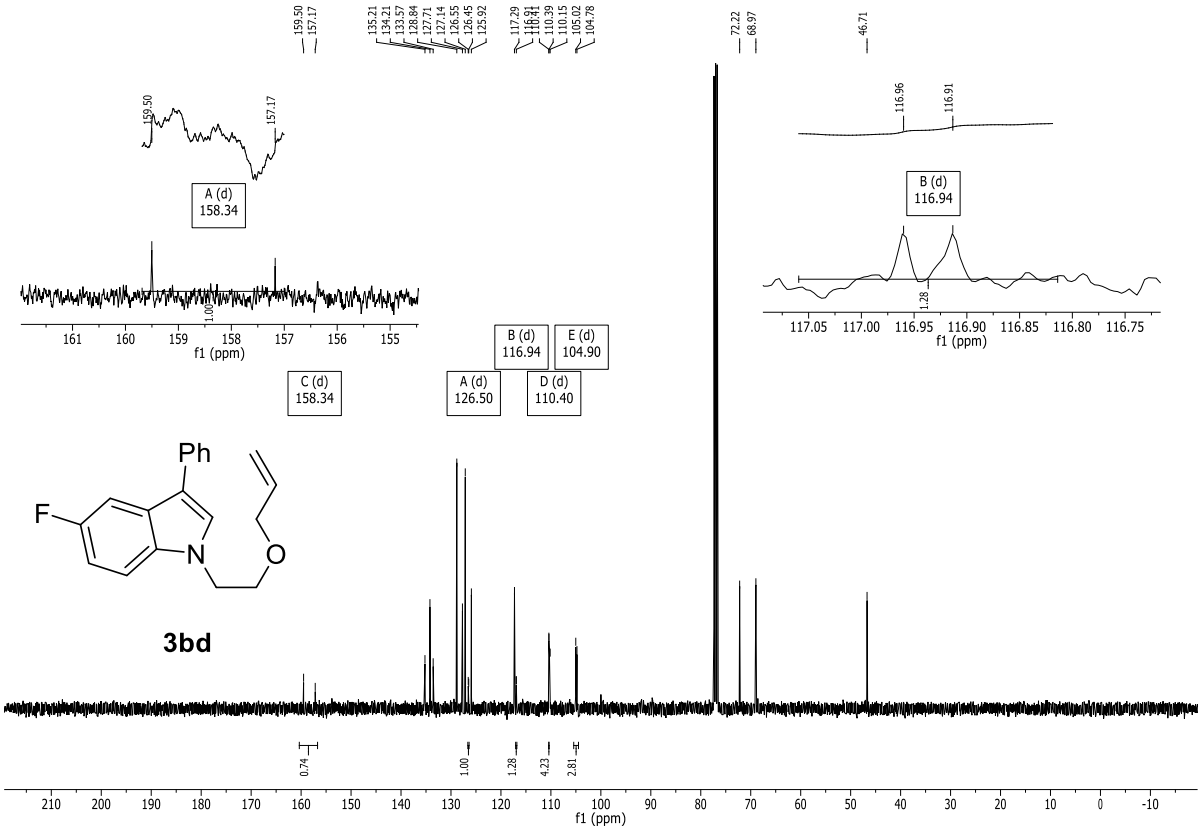
3bc

1-(2-(Allyloxy)ethyl)-5-fluoro-3-phenyl-1H-indole (**3bd**)

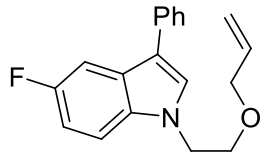
^{1}H NMR (400 MHz, $CDCl_3$)



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



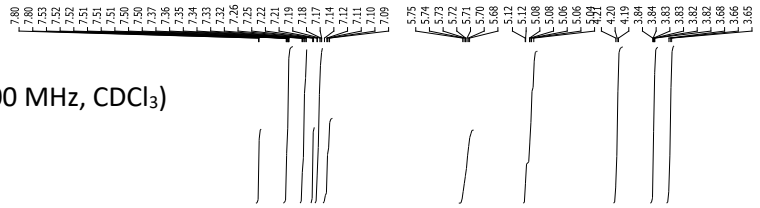
^{19}F NMR (376 MHz, $CDCl_3$)

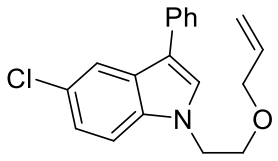


3bd

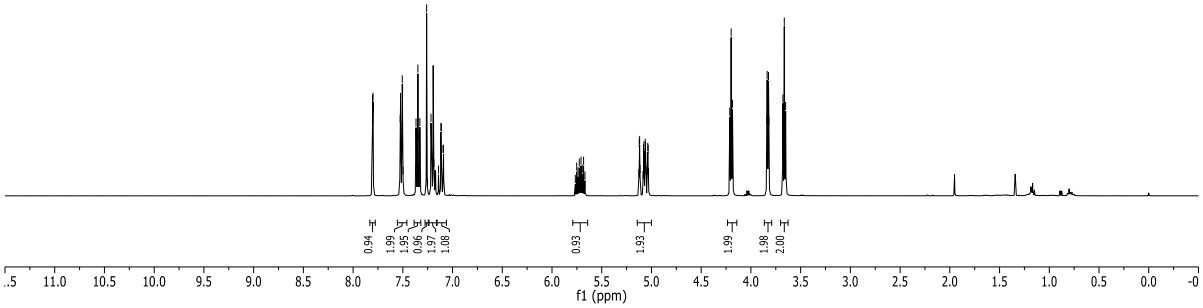
1-(2-(Allyloxy)ethyl)-5-chloro-3-phenyl-1H-indole (**3be**)

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

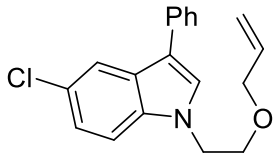




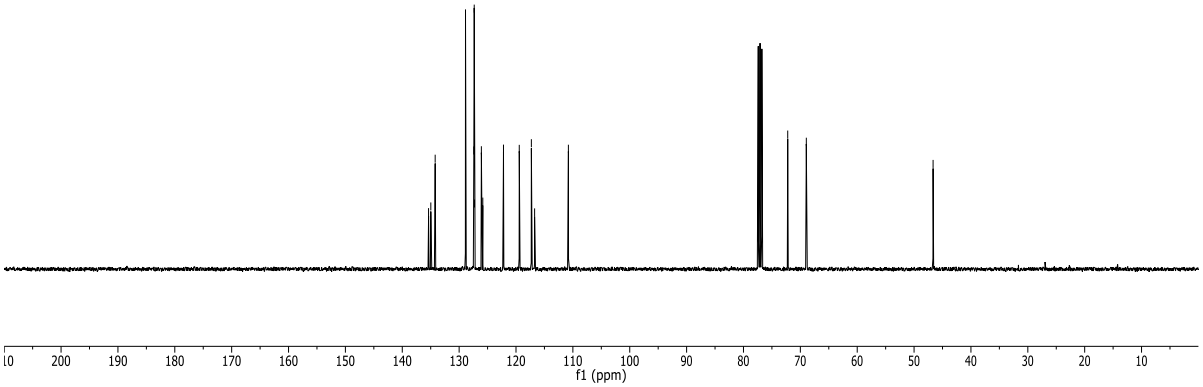
3be



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

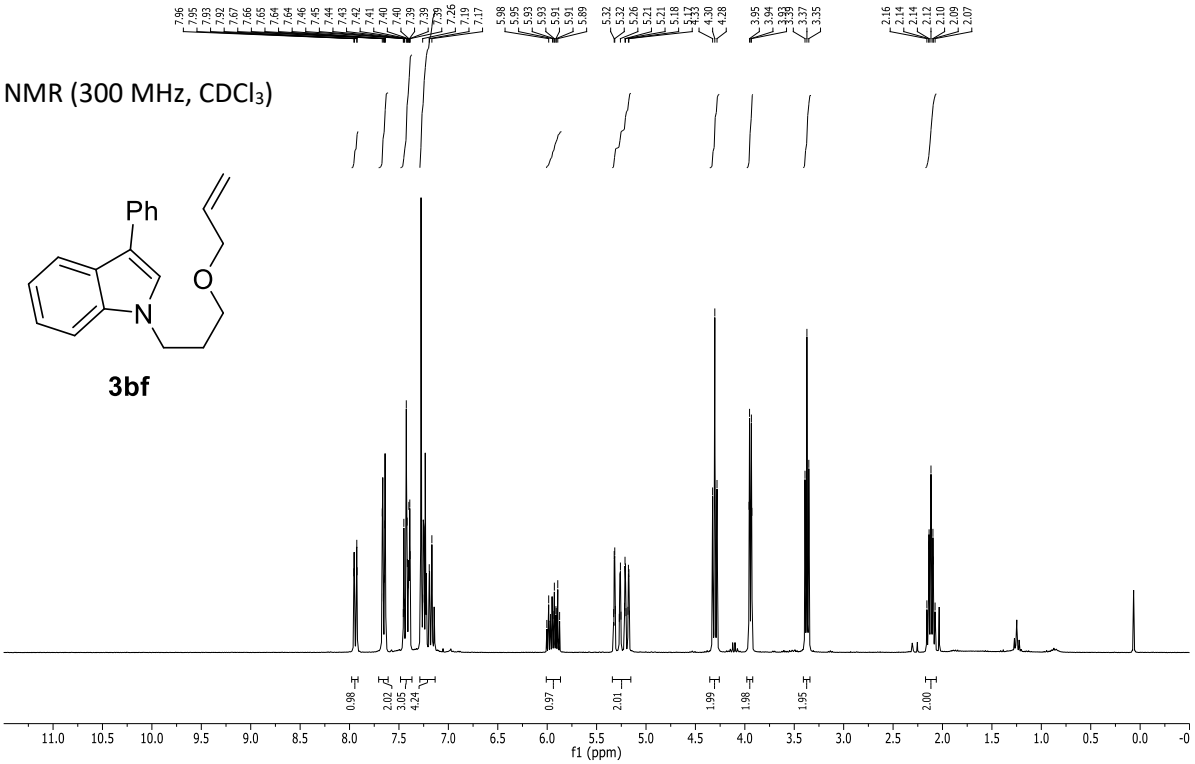


3be

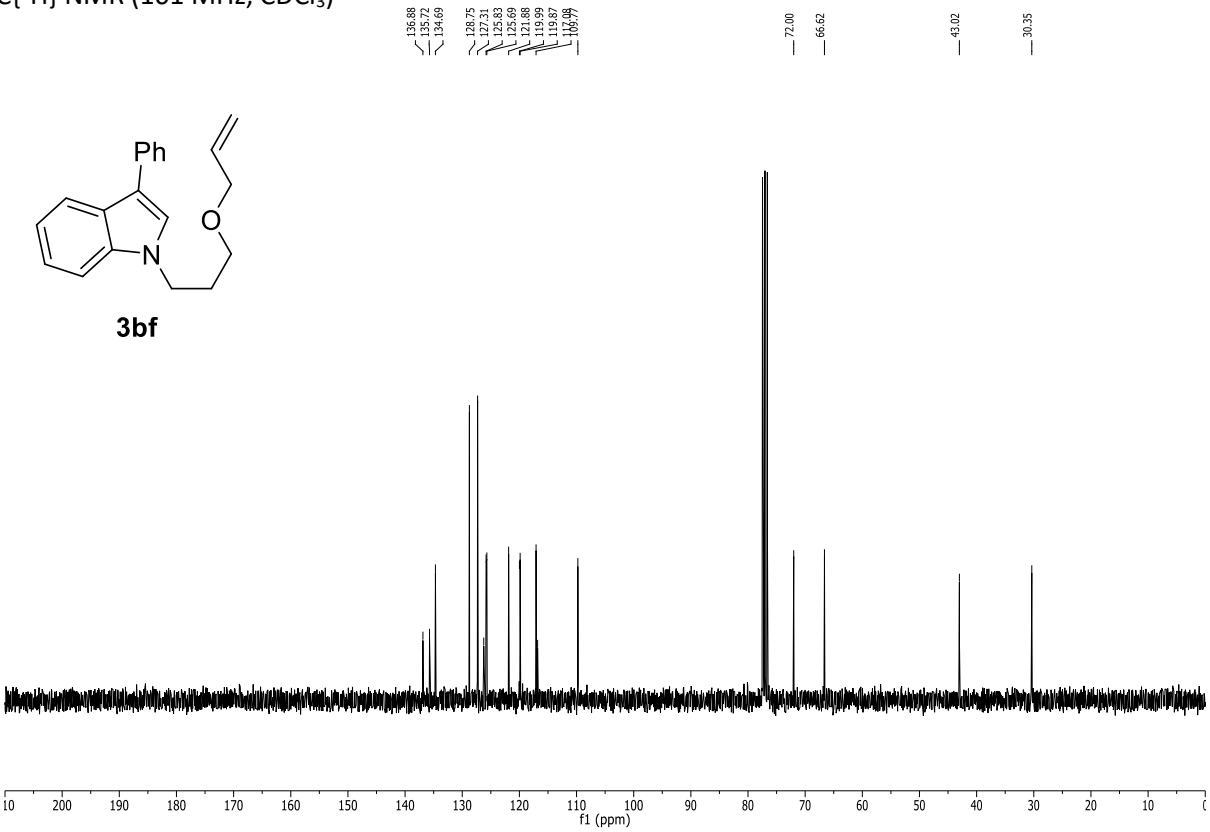


1-(3-(Allyloxy)propyl)-3-phenyl-1H-indole (**3bf**)

^{1}H NMR (300 MHz, $CDCl_3$)

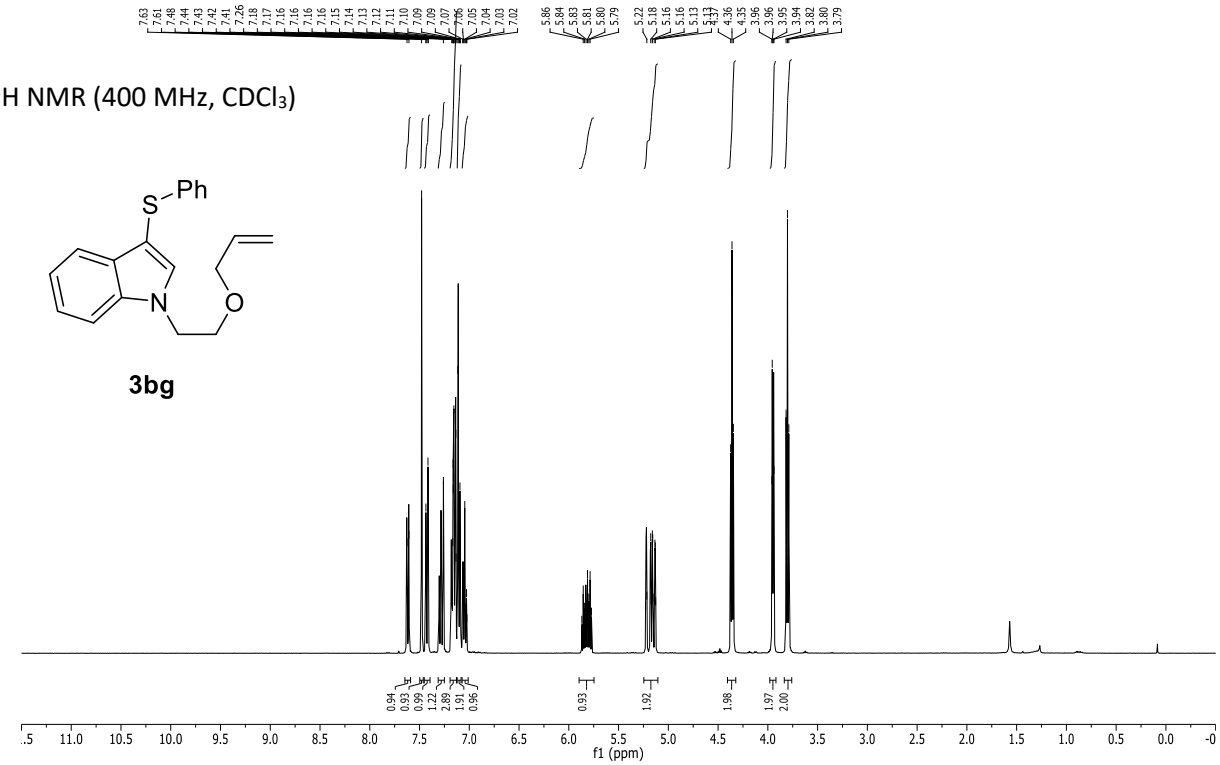


$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)

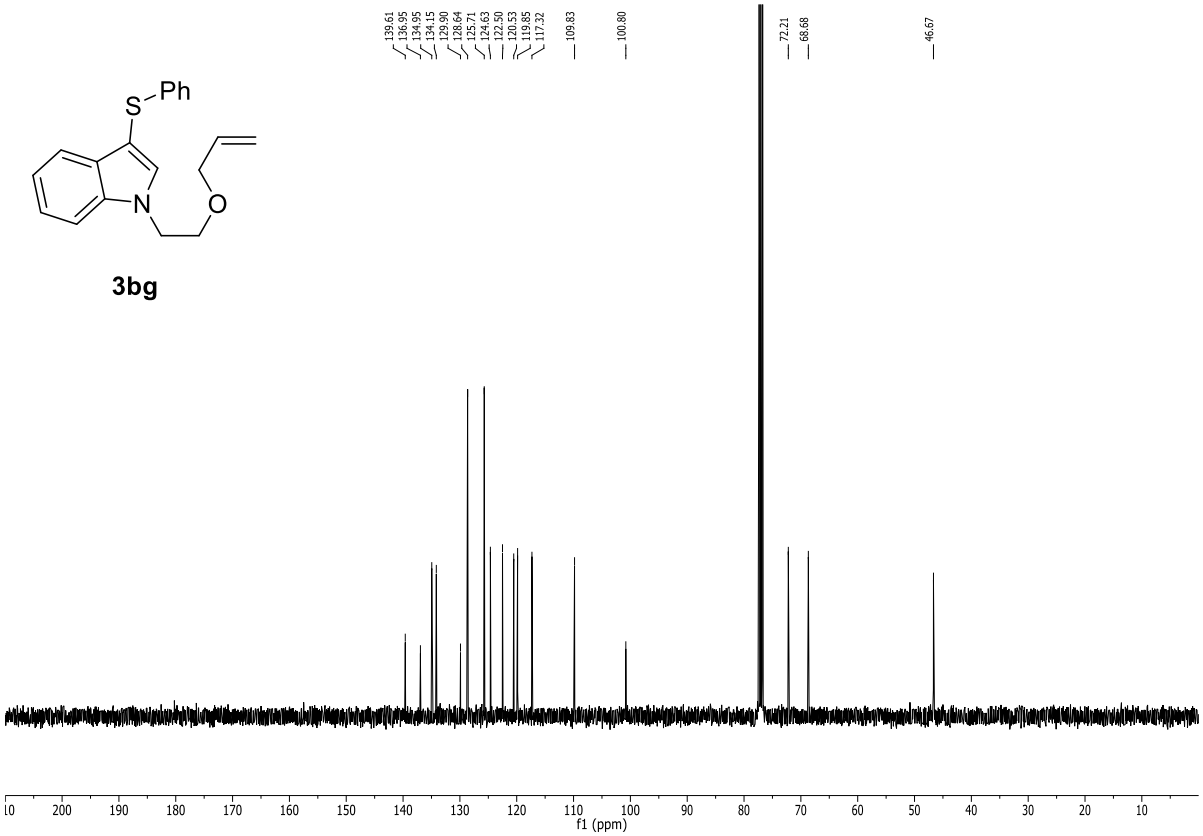


1-(2-(Allyloxy)ethyl)-3-(phenylthio)-1H-indole (**3bg**)

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



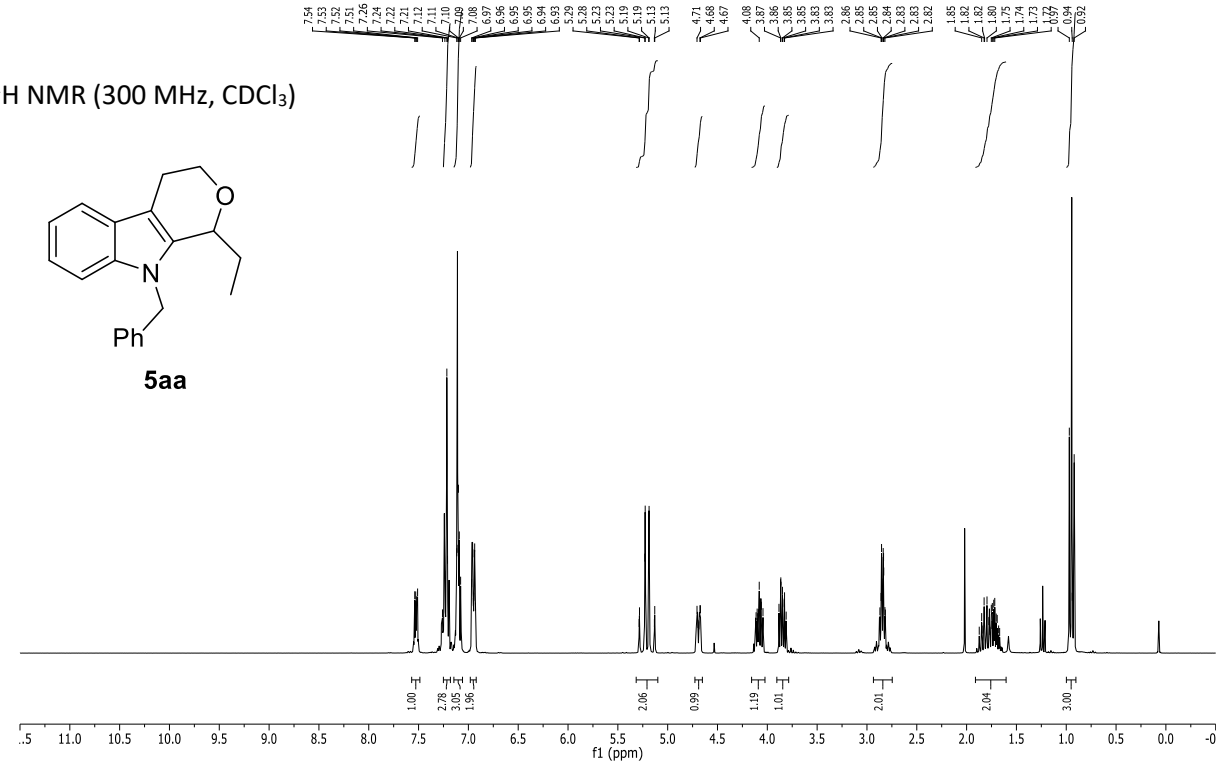
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



4. Spectral Data for Indole Based Cyclization Products 5aa-5af, 5ba-5bg

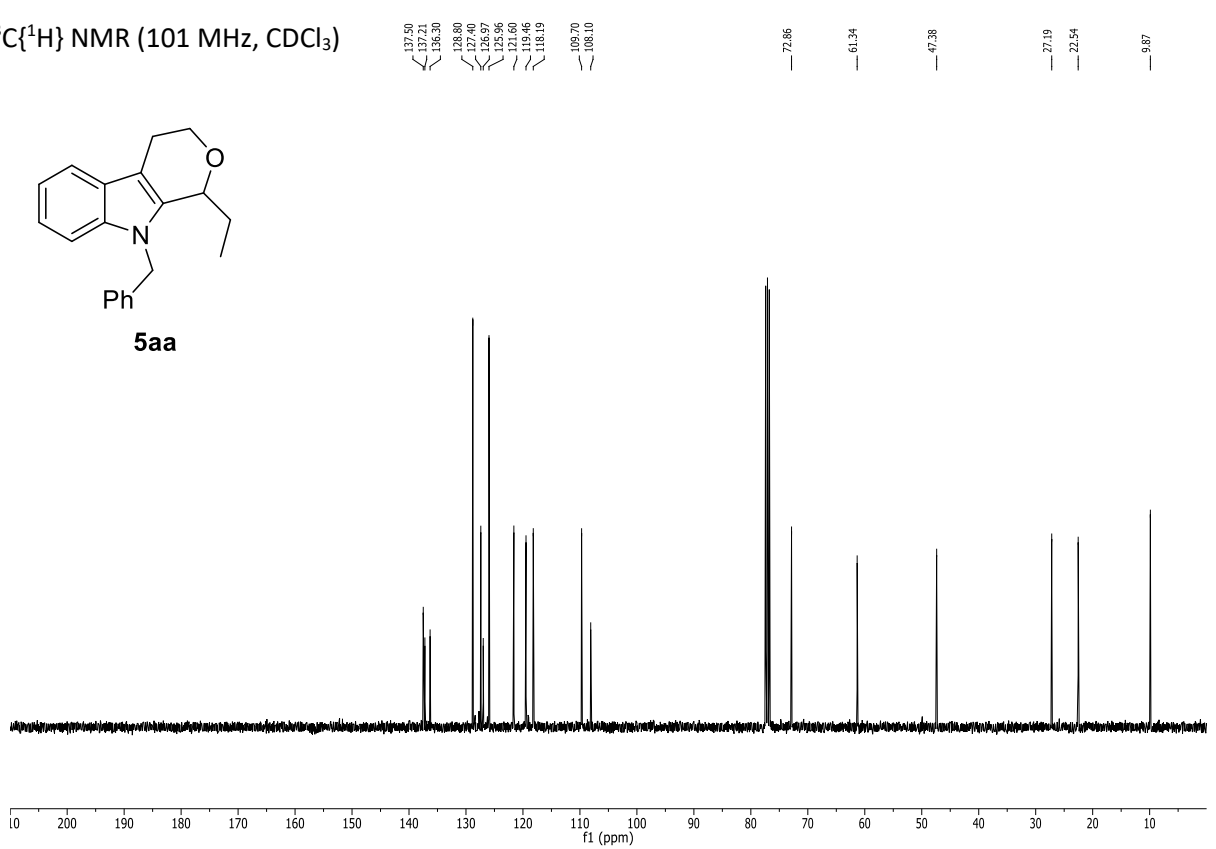
9-Benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5aa**)

^{1}H NMR (300 MHz, $CDCl_3$)



5aa

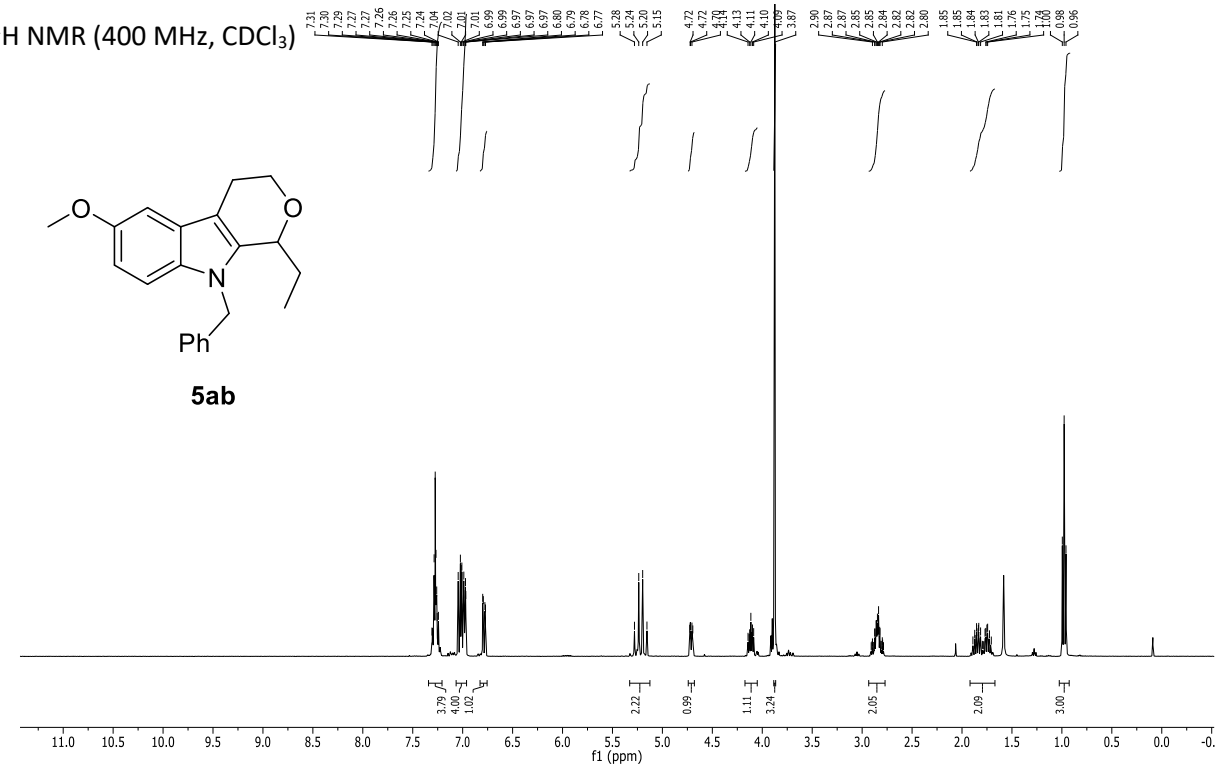
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



5aa

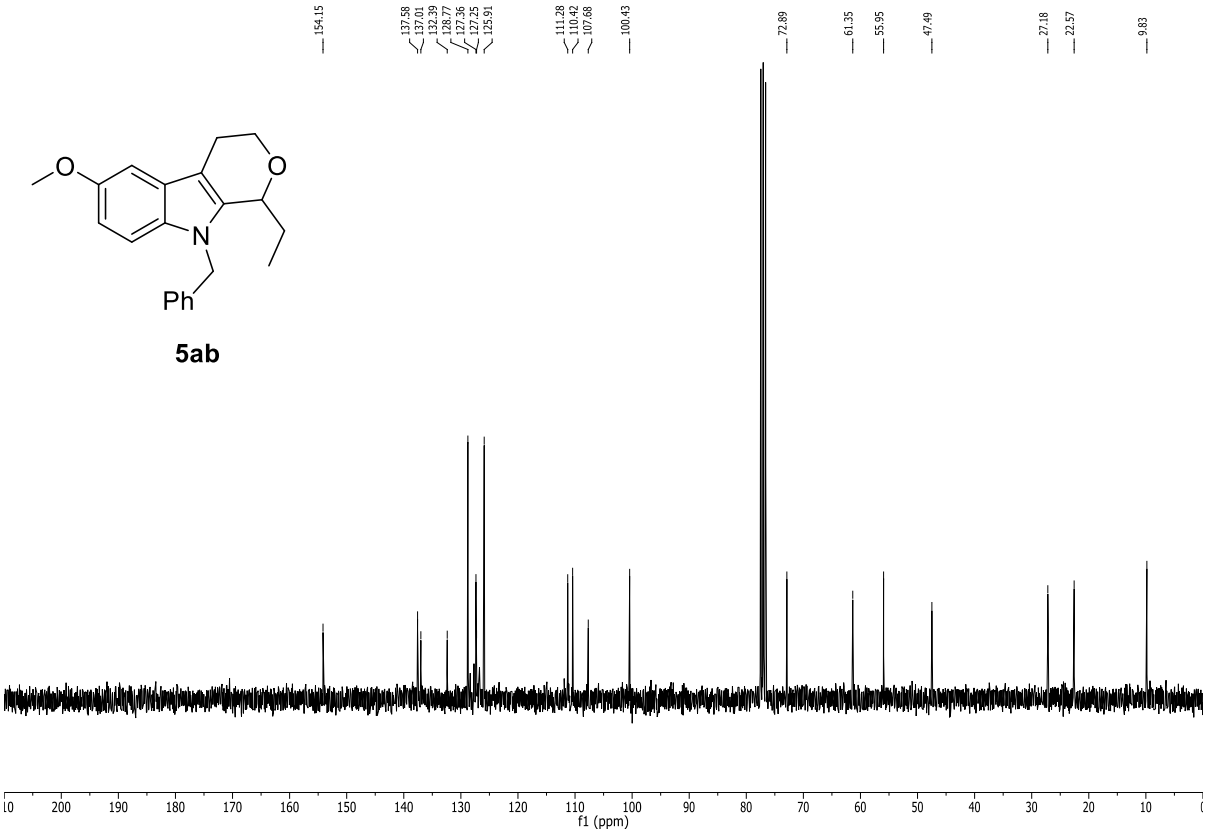
9-Benzyl-1-ethyl-6-methoxy-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5ab**) (4 mmol scale)

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



5ab

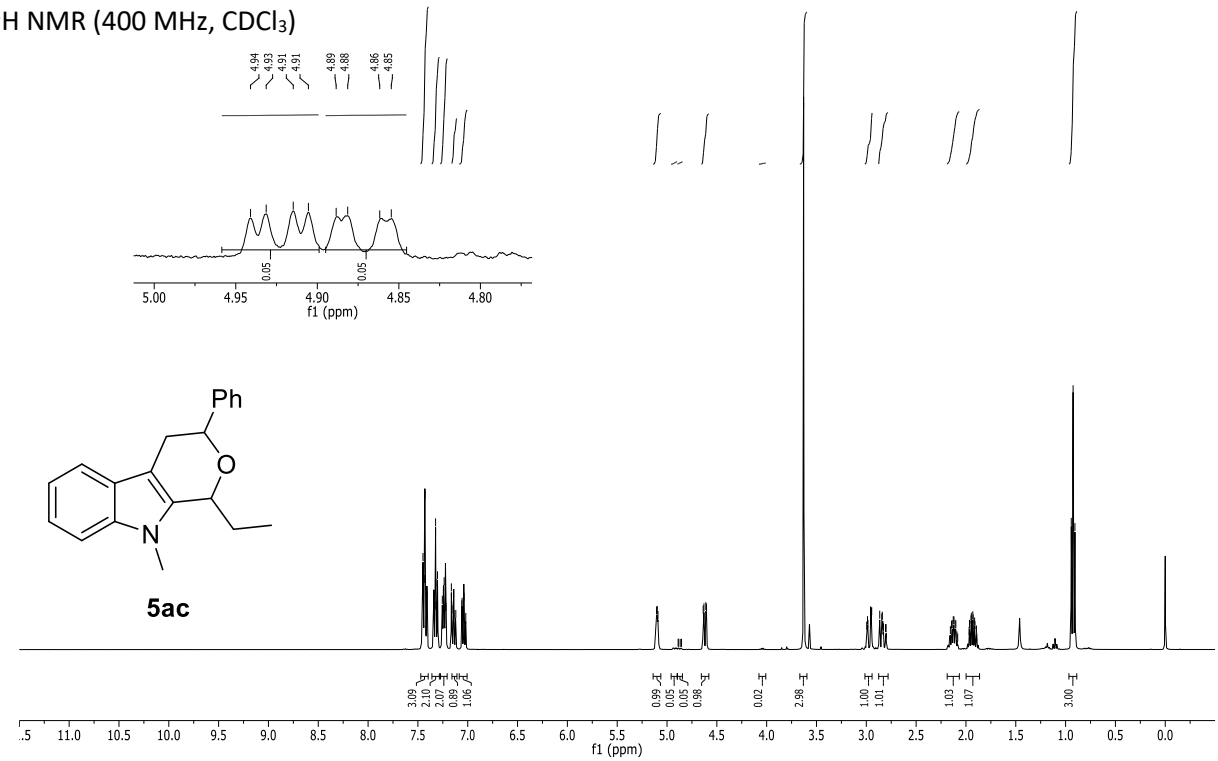
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



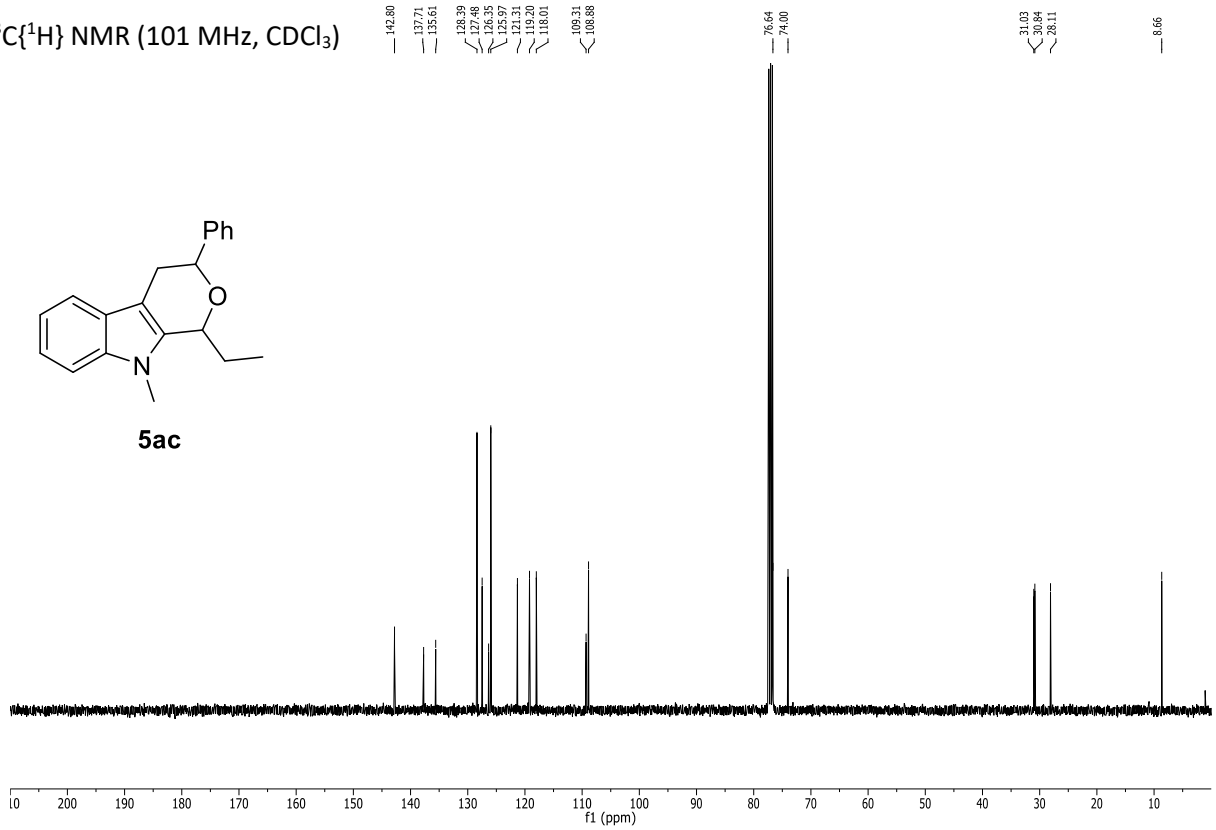
5ab

1-Ethyl-9-methyl-3-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5ac)**

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

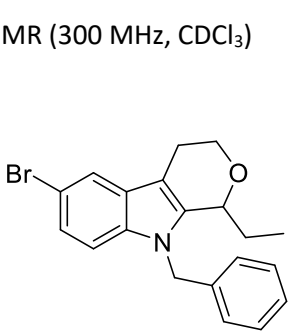


$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



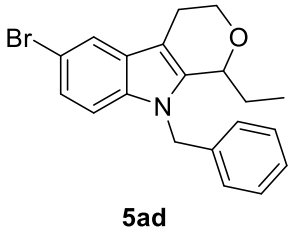
9-Benzyl-6-bromo-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5ad**)

^{1}H NMR (300 MHz, $CDCl_3$)



5ad

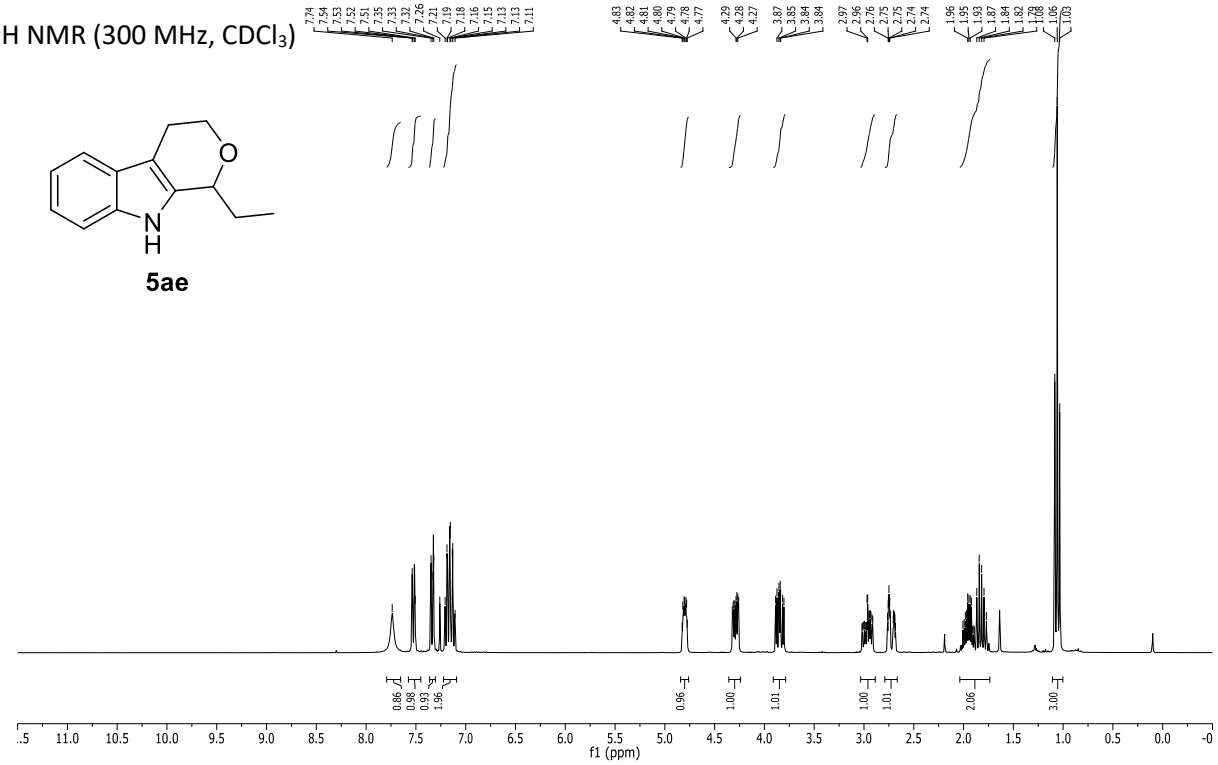
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



5ad

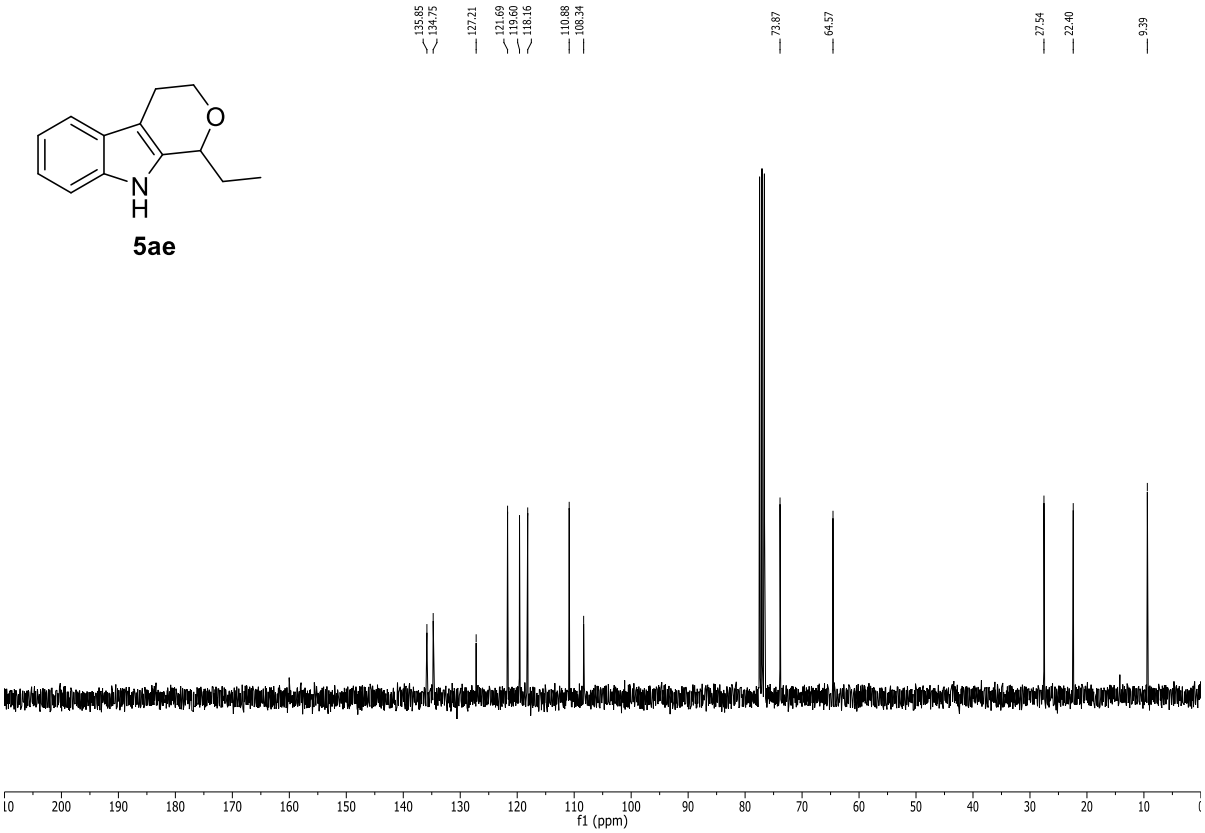
1-Ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5ae**)

^{1}H NMR (300 MHz, $CDCl_3$)



5ae

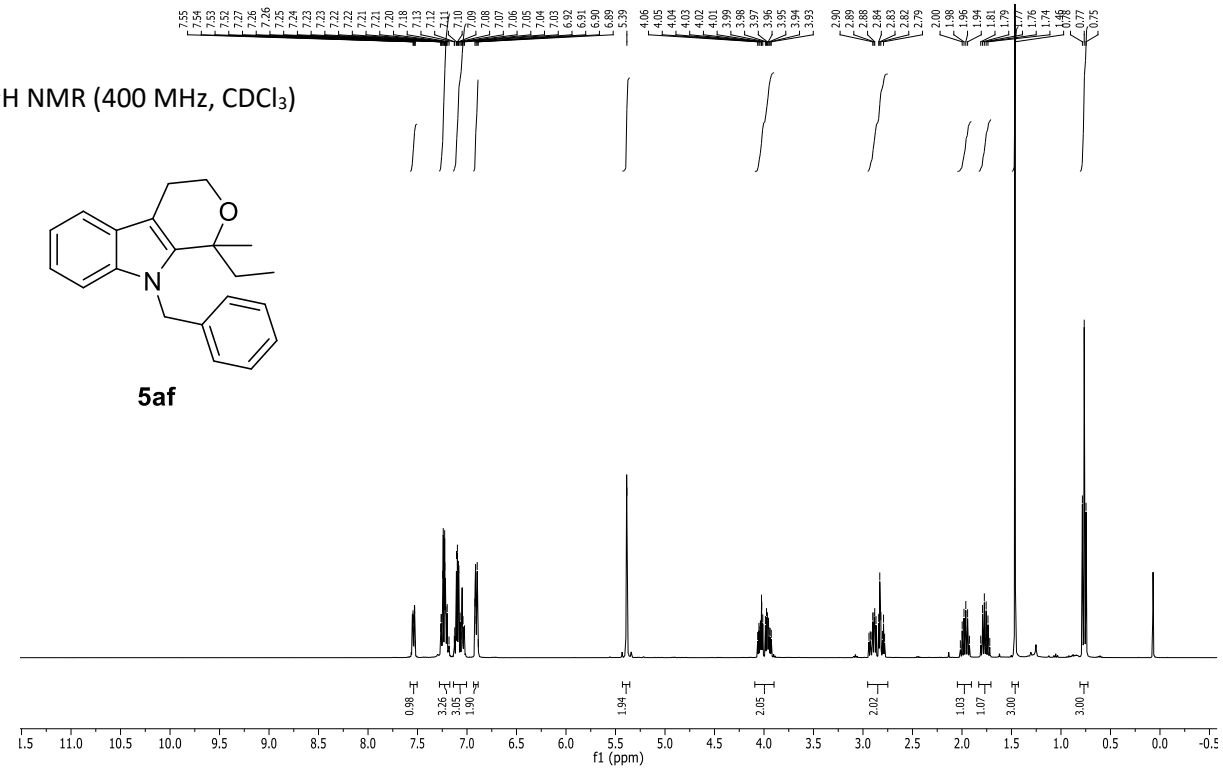
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



5ae

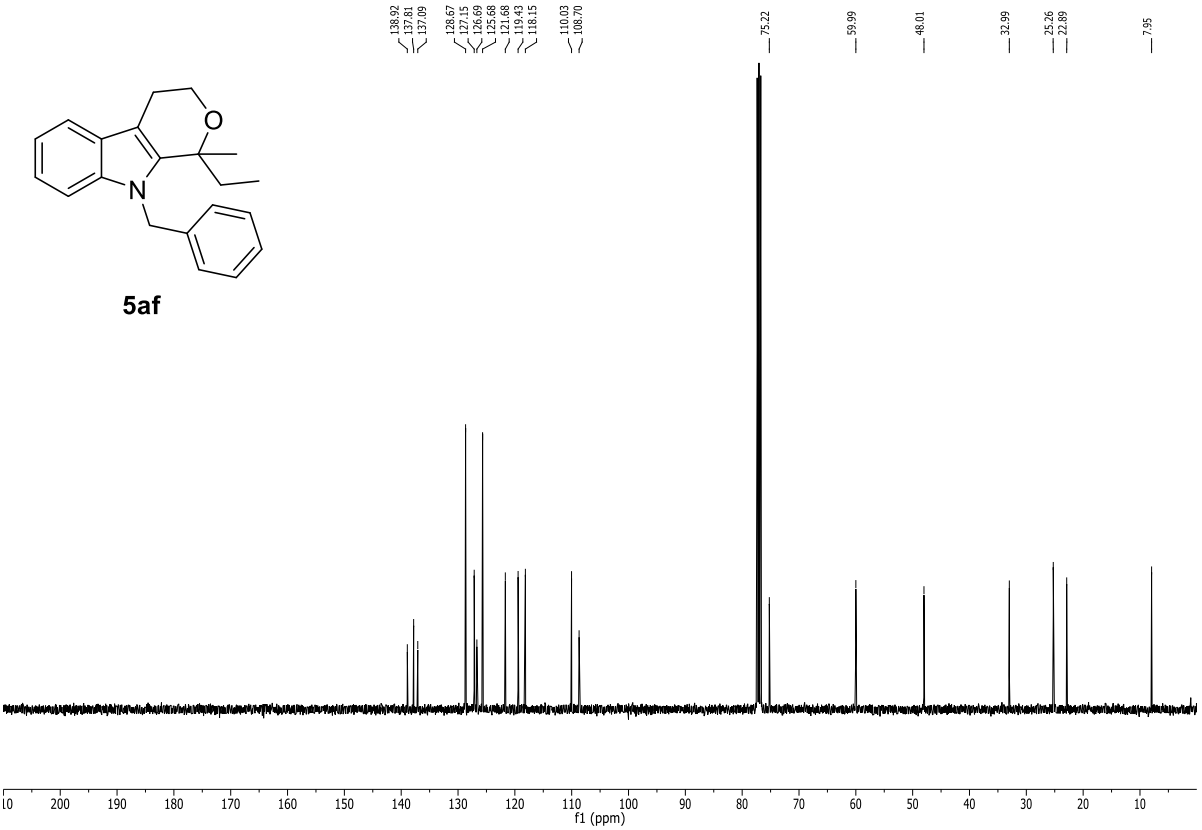
9-Benzyl-1-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**5af**)

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



5af

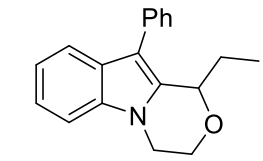
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



5af

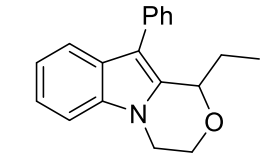
1-Ethyl-10-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5ba**)

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



5ba

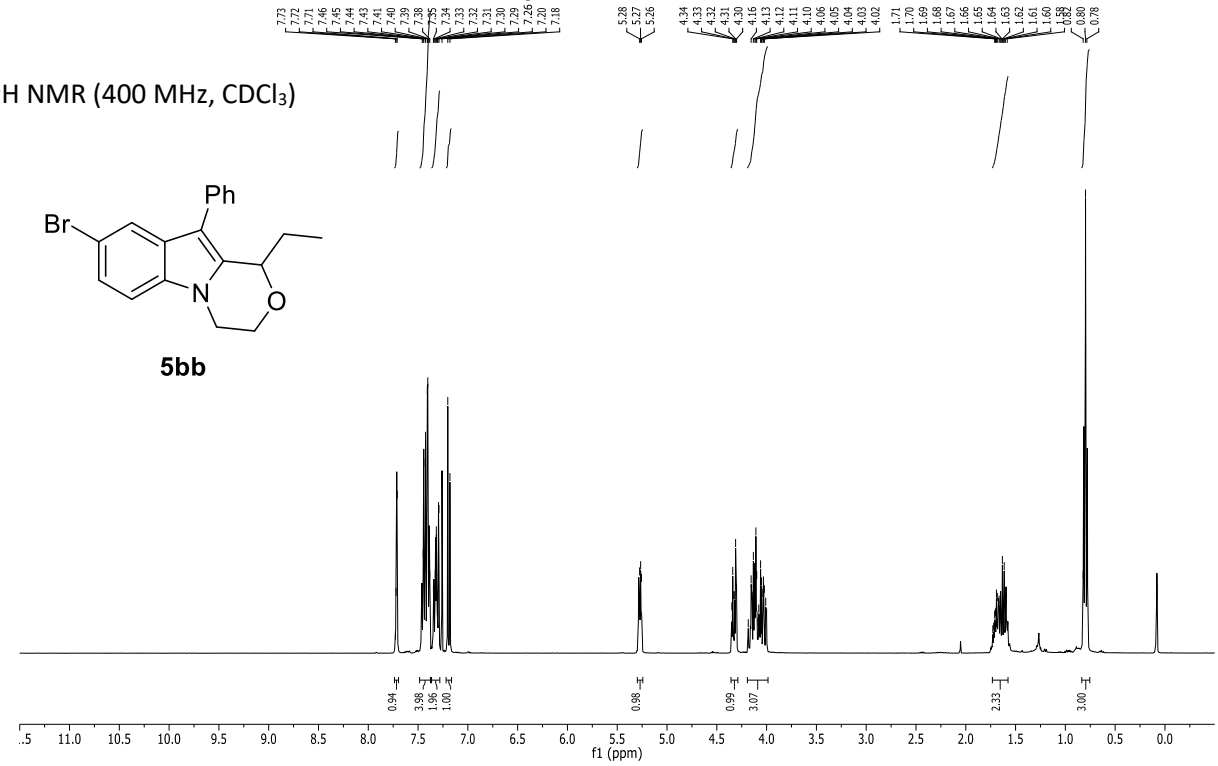
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



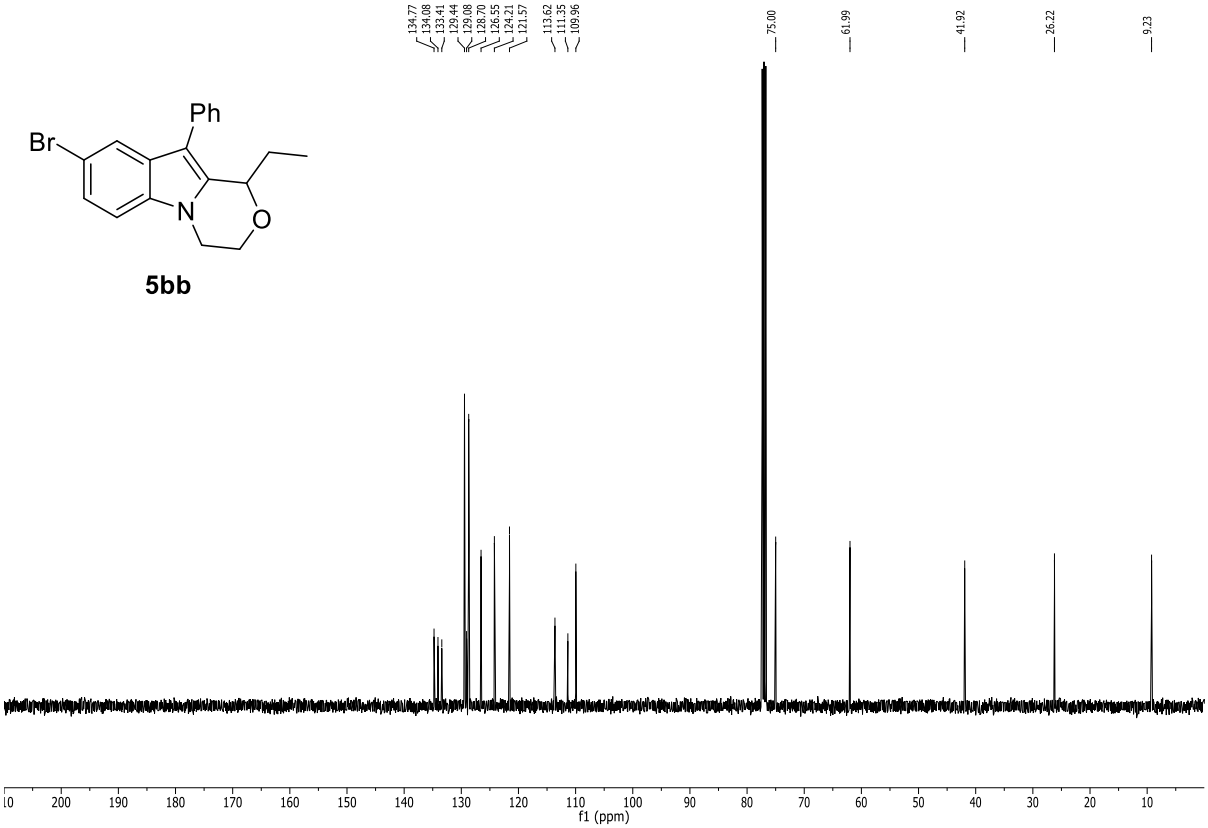
5ba

8-Bromo-1-ethyl-10-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5bb**)

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

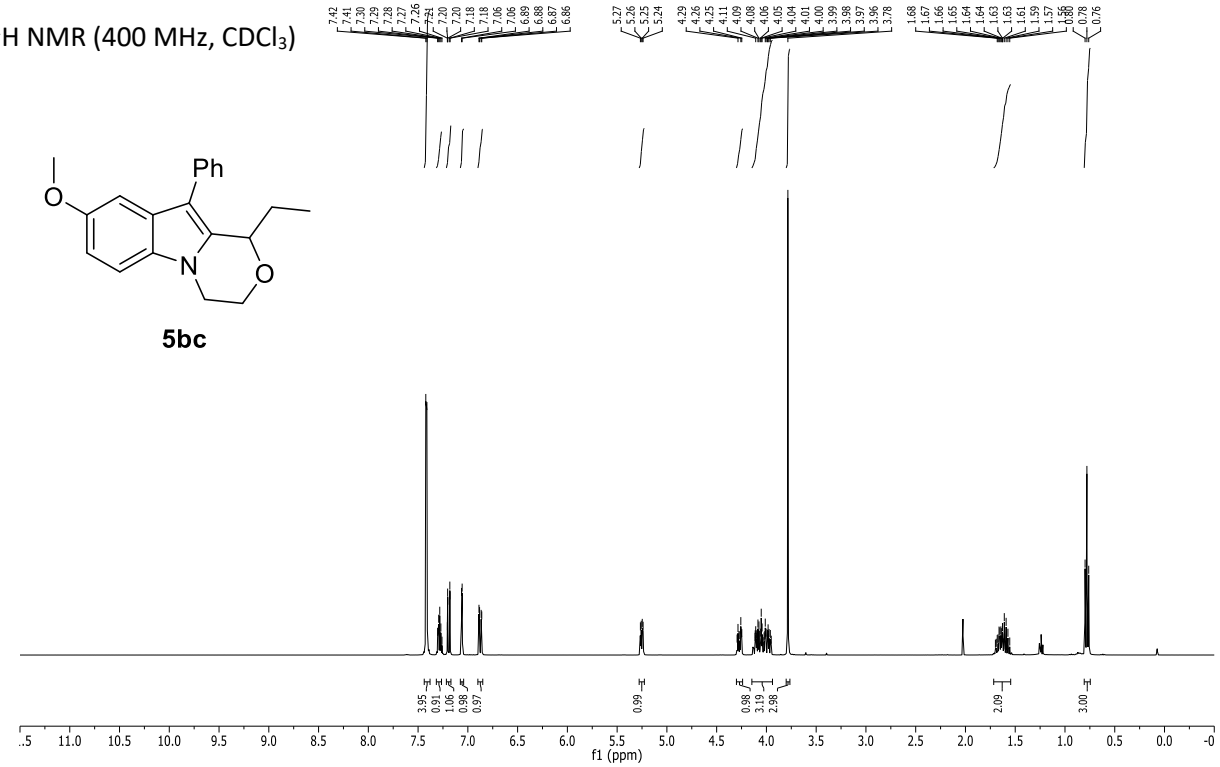


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)

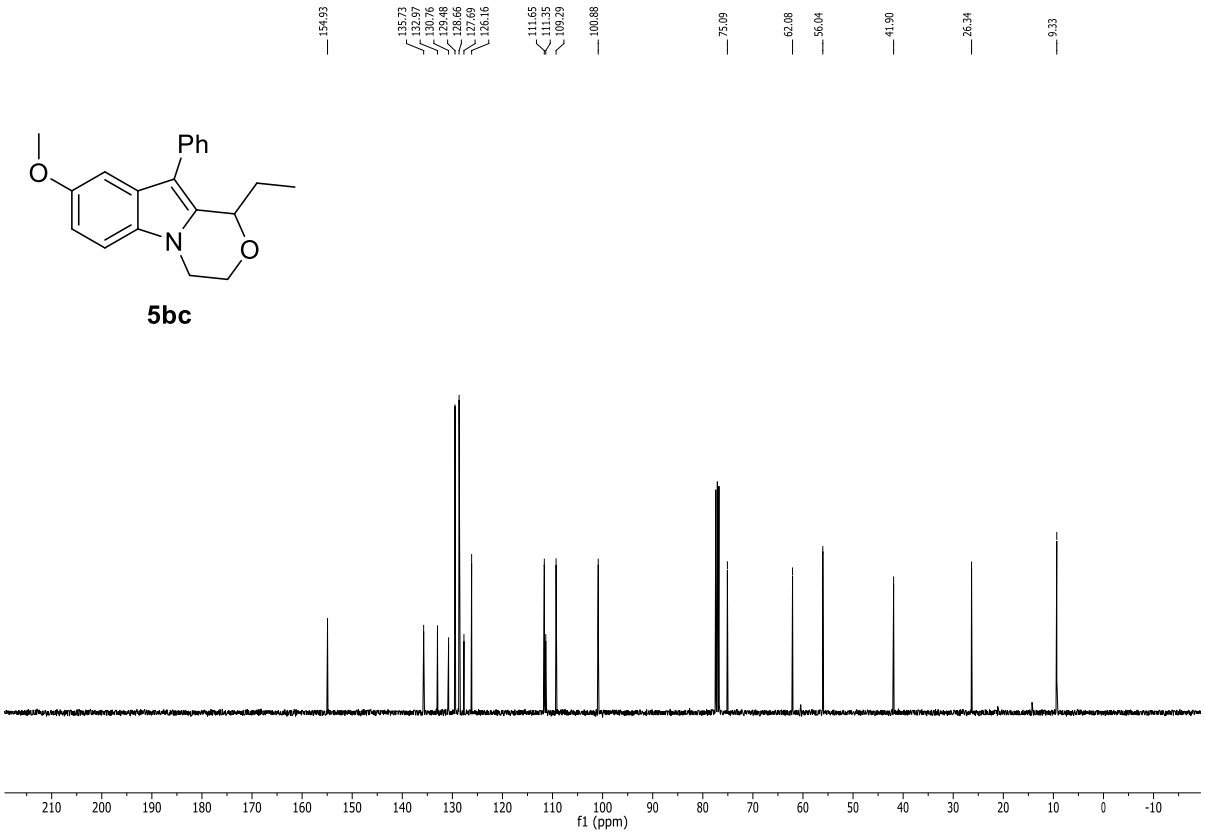


1-Ethyl-8-methoxy-10-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5bc**)

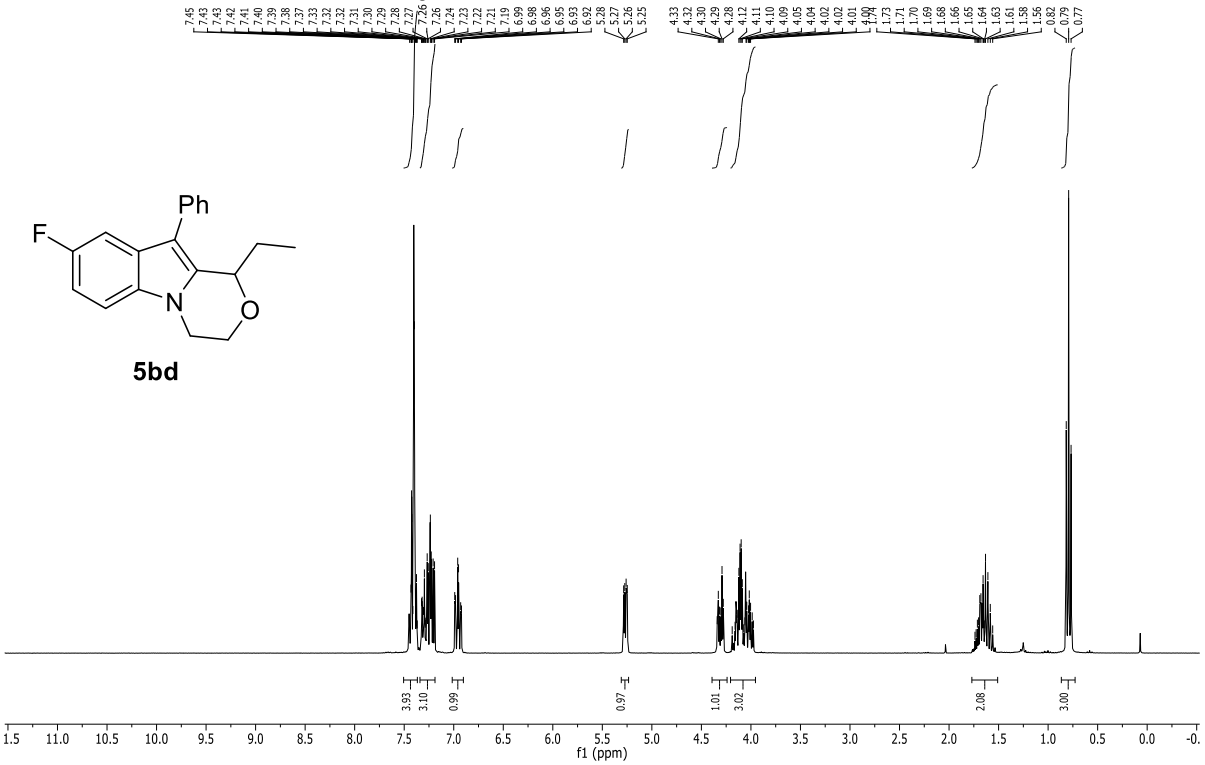
^{1}H NMR (400 MHz, $CDCl_3$)



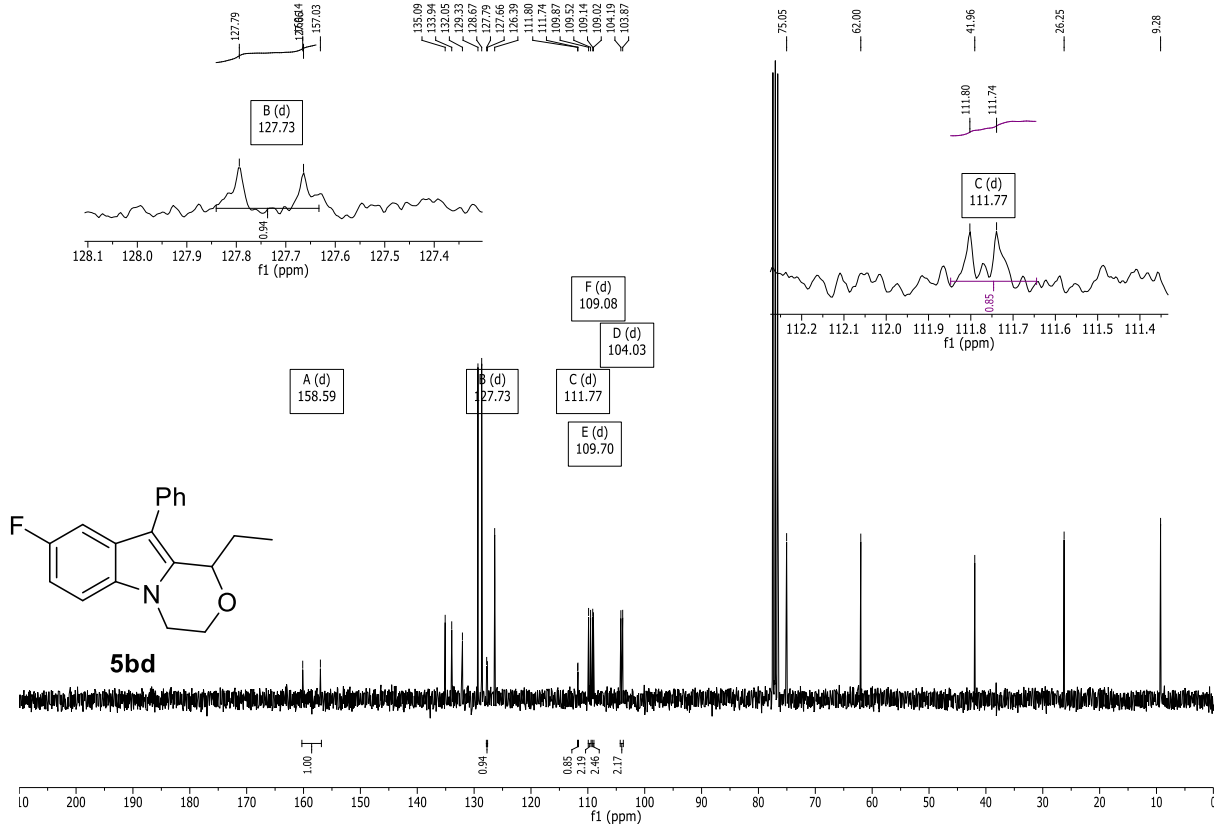
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)__



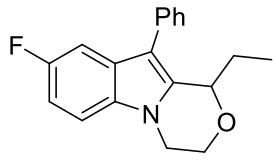
1-Ethyl-8-fluoro-10-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5bd)** ^{1}H NMR (300 MHz, $CDCl_3$)



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



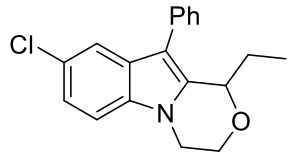
^{19}F NMR (282 MHz, $CDCl_3$)



5bd

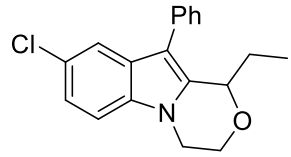
8-Chloro-1-ethyl-10-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5be**)

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



5be

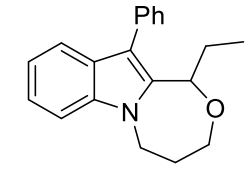
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)



5be

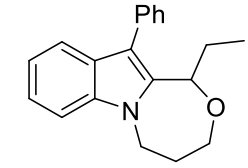
1-Ethyl-11-phenyl-4,5-dihydro-1H,3H-[1,4]oxazepino[4,3-a]indole (**5bf**)

^{1}H NMR (300 MHz, $CDCl_3$)



5bf

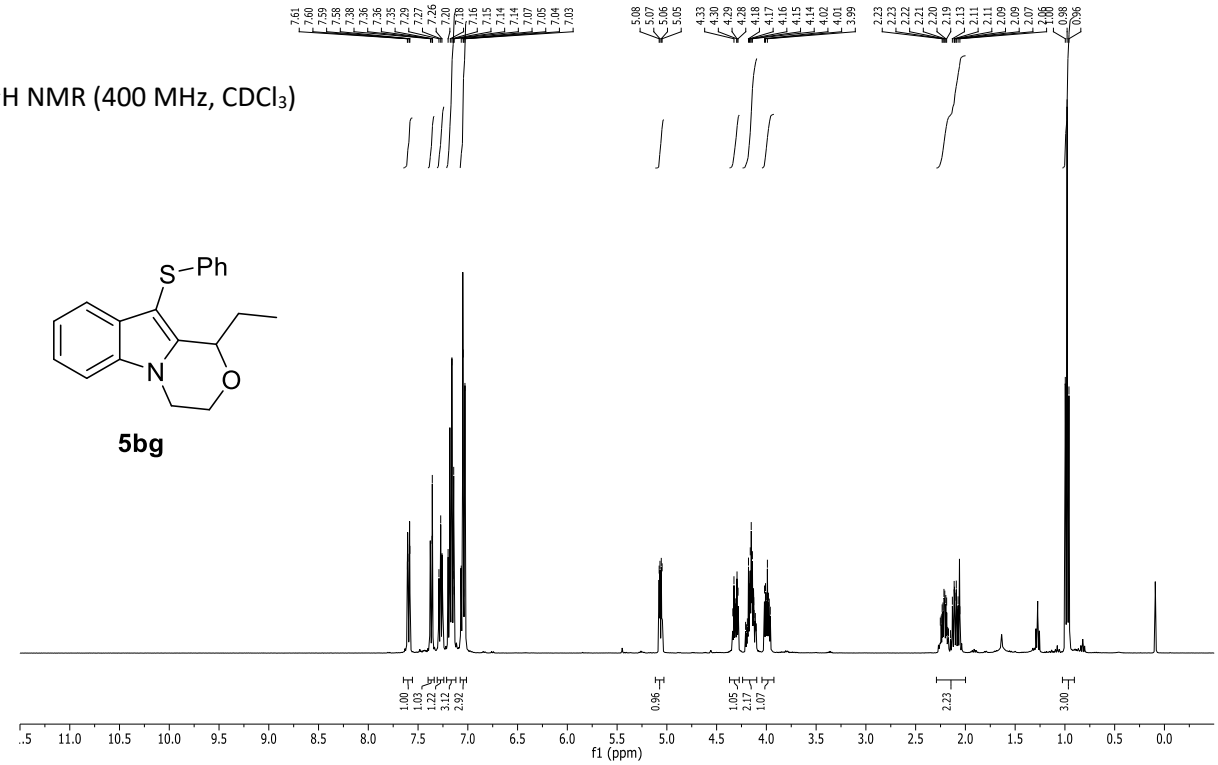
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



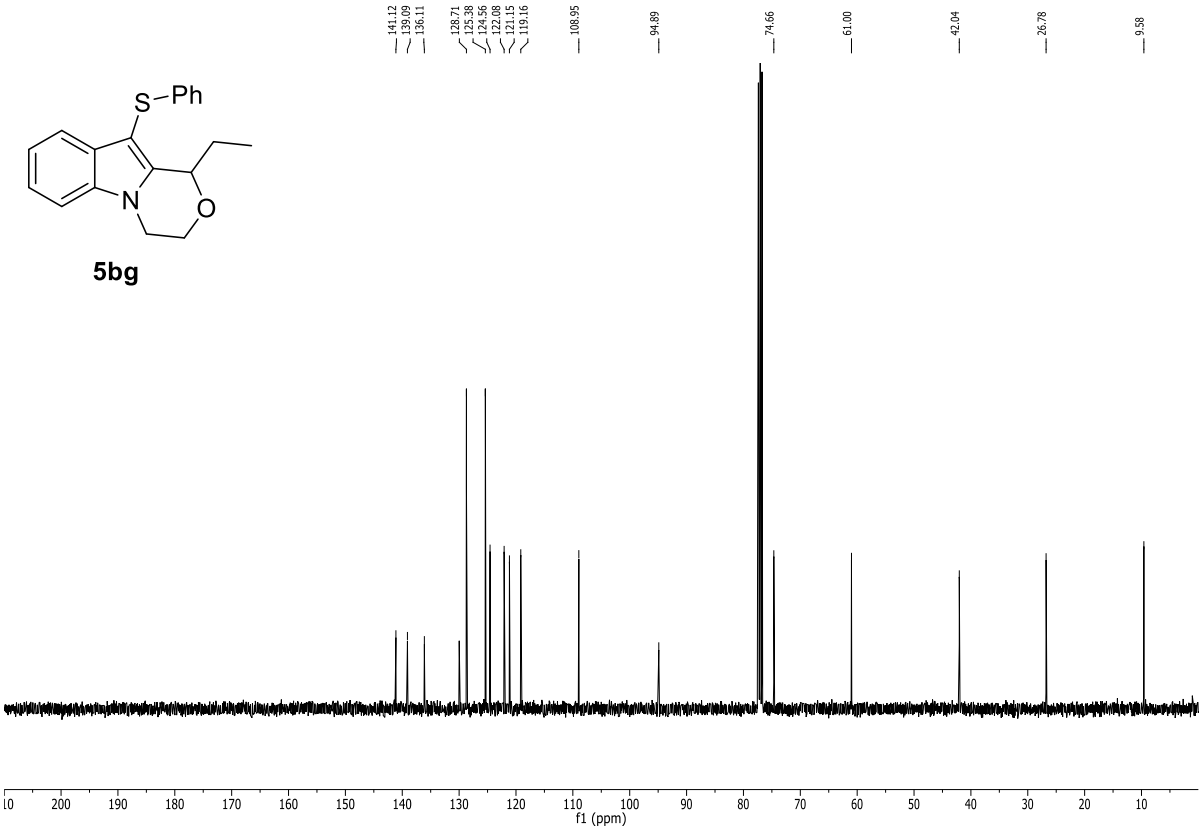
5bf

1-Ethyl-10-(phenylthio)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**5bg**)

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



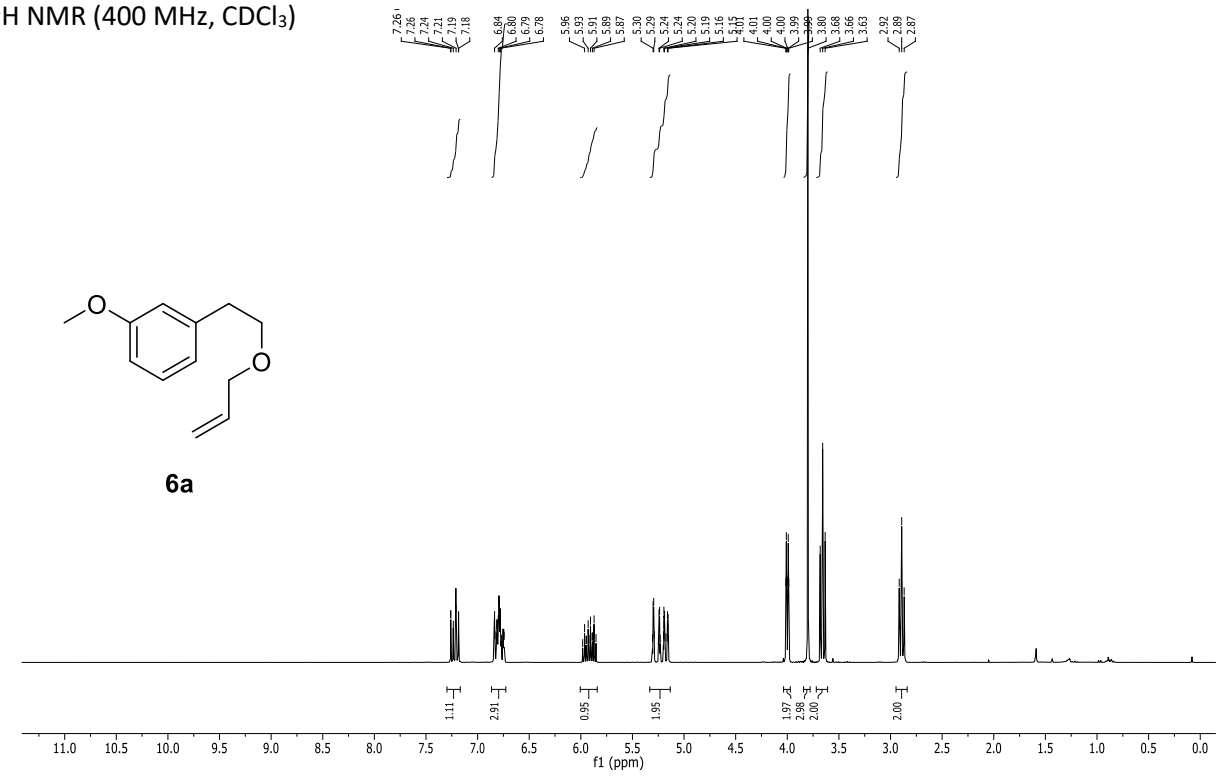
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



5. Spectral Data for O-Allylated Substrates 6a-b, 8a-b and Products 7a-b, 9a-b

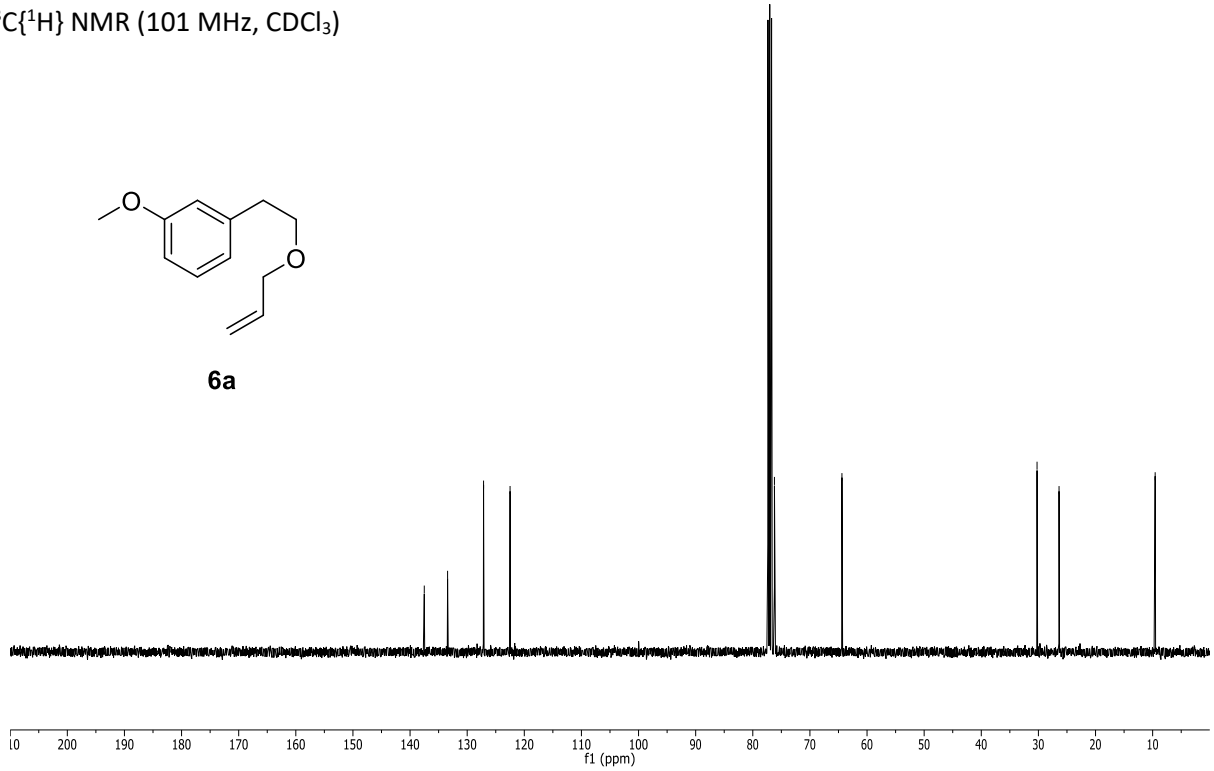
1-(2-(Allyloxy)ethyl)-3-methoxybenzene (**6a**)

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



6a

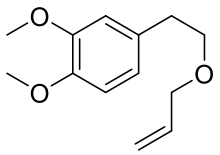
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



6a

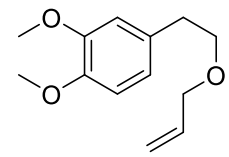
4-(2-(Allyloxy)ethyl)-1,2-dimethoxybenzene (**6b**)

^{1}H NMR (300 MHz, $CDCl_3$)



6b

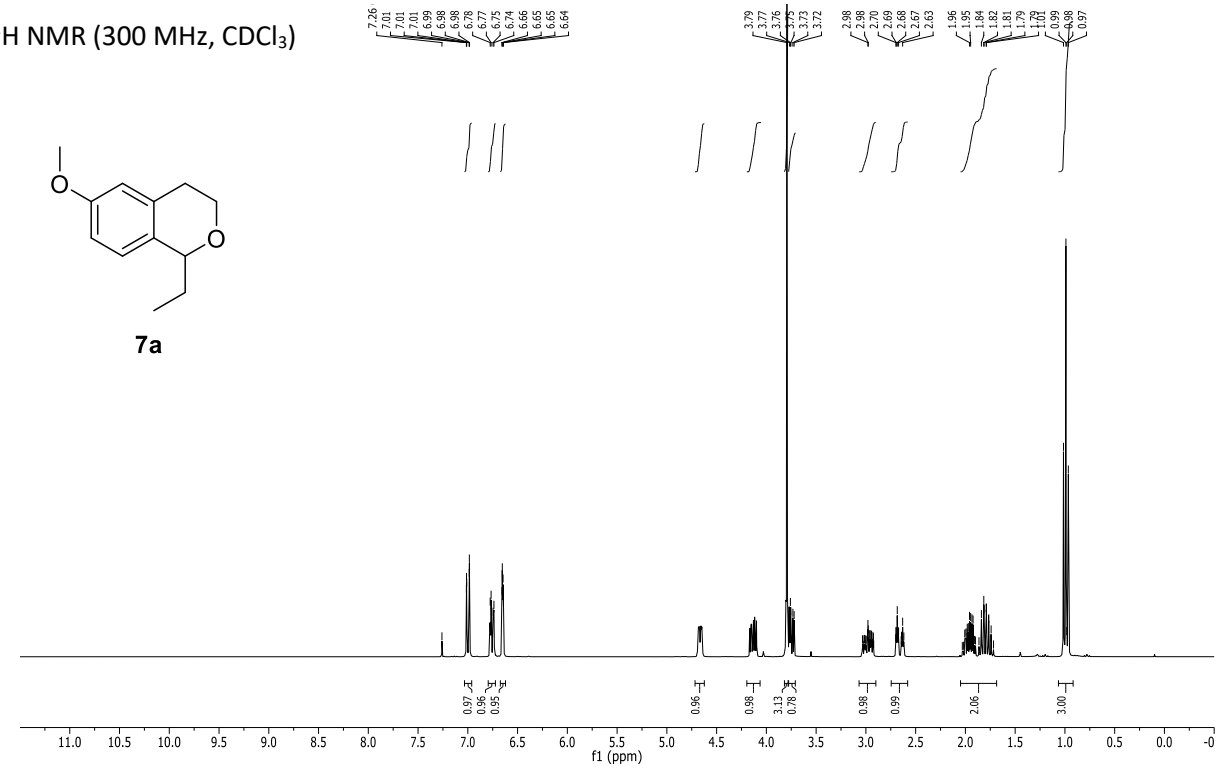
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



6b

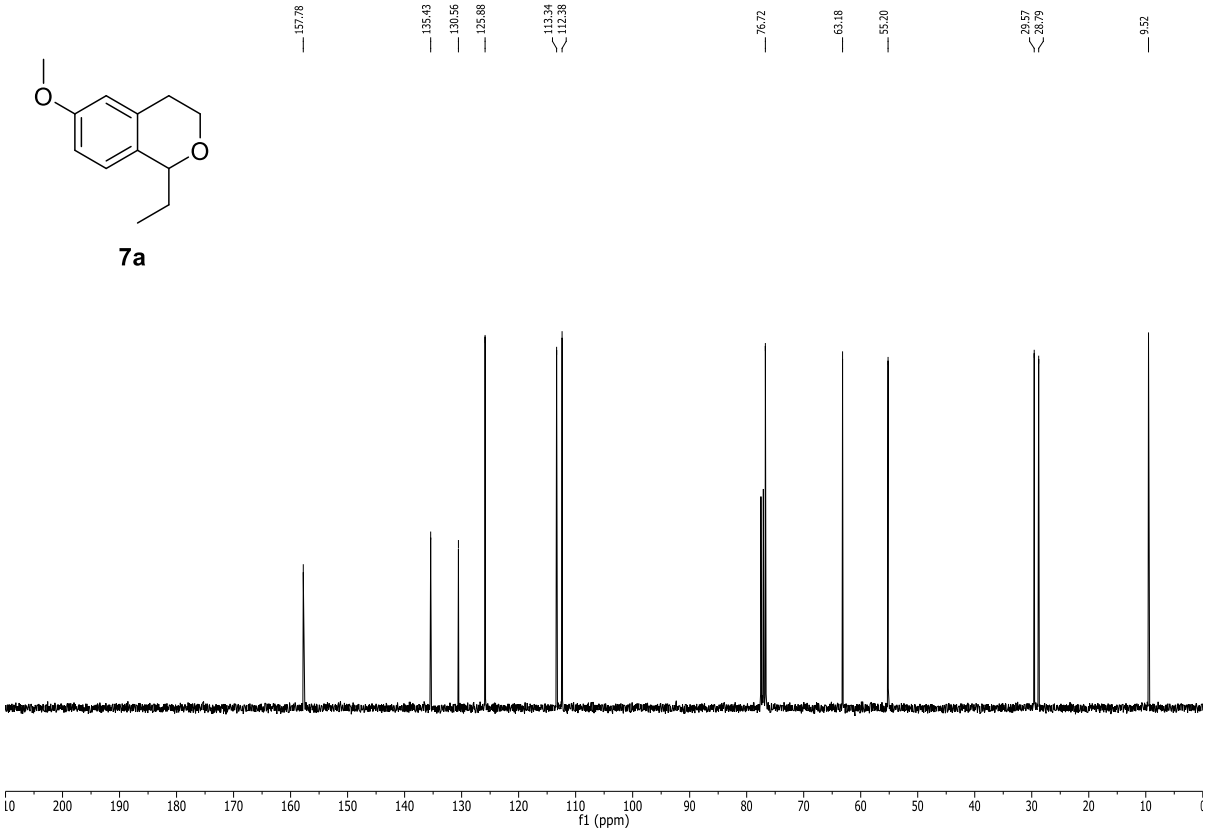
1-Ethyl-6-methoxyisochromane (**7a**)

^{1}H NMR (300 MHz, $CDCl_3$)



7a

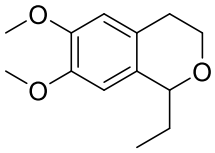
$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)



7a

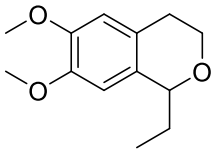
1-ethyl-6,7-dimethoxyisochromane**(7b)**

^{1}H NMR (300 MHz, $CDCl_3$)



7b

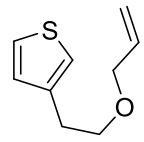
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



7b

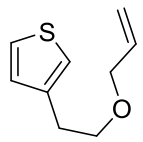
3-(2-(Allyloxy)ethyl)thiophene (**8a**)

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



8a

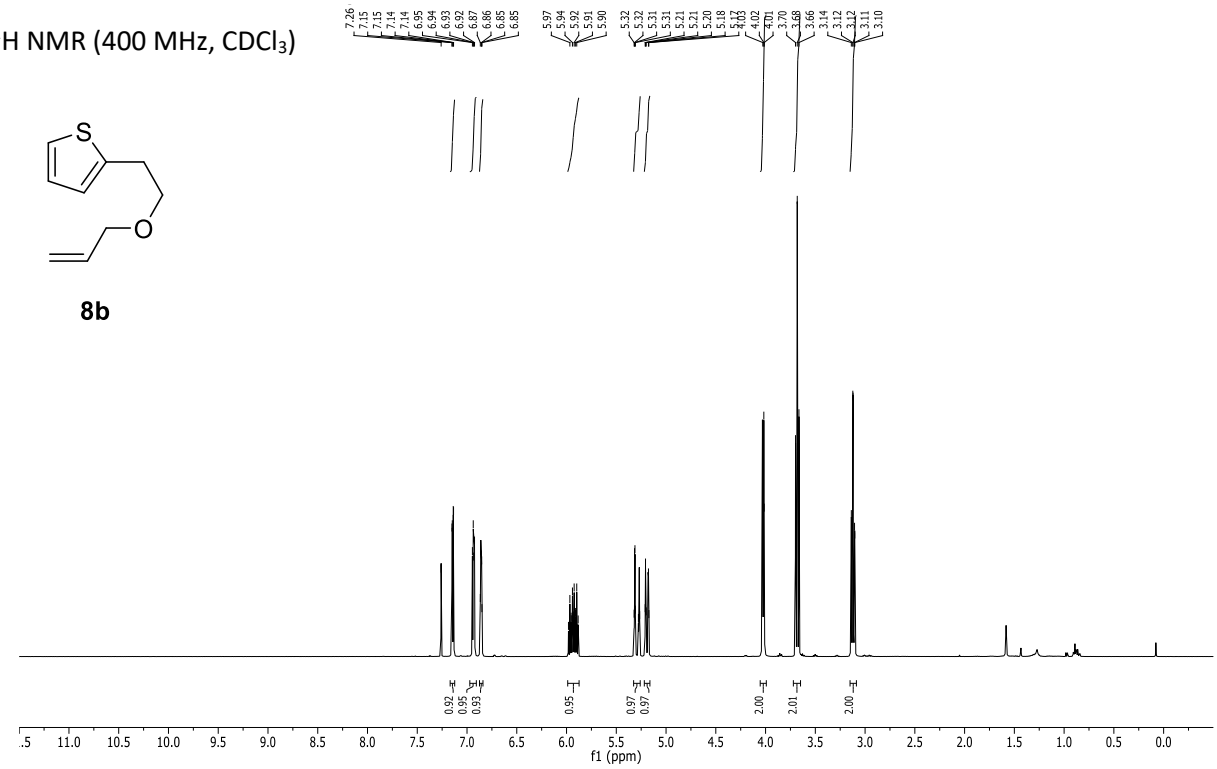
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



8a

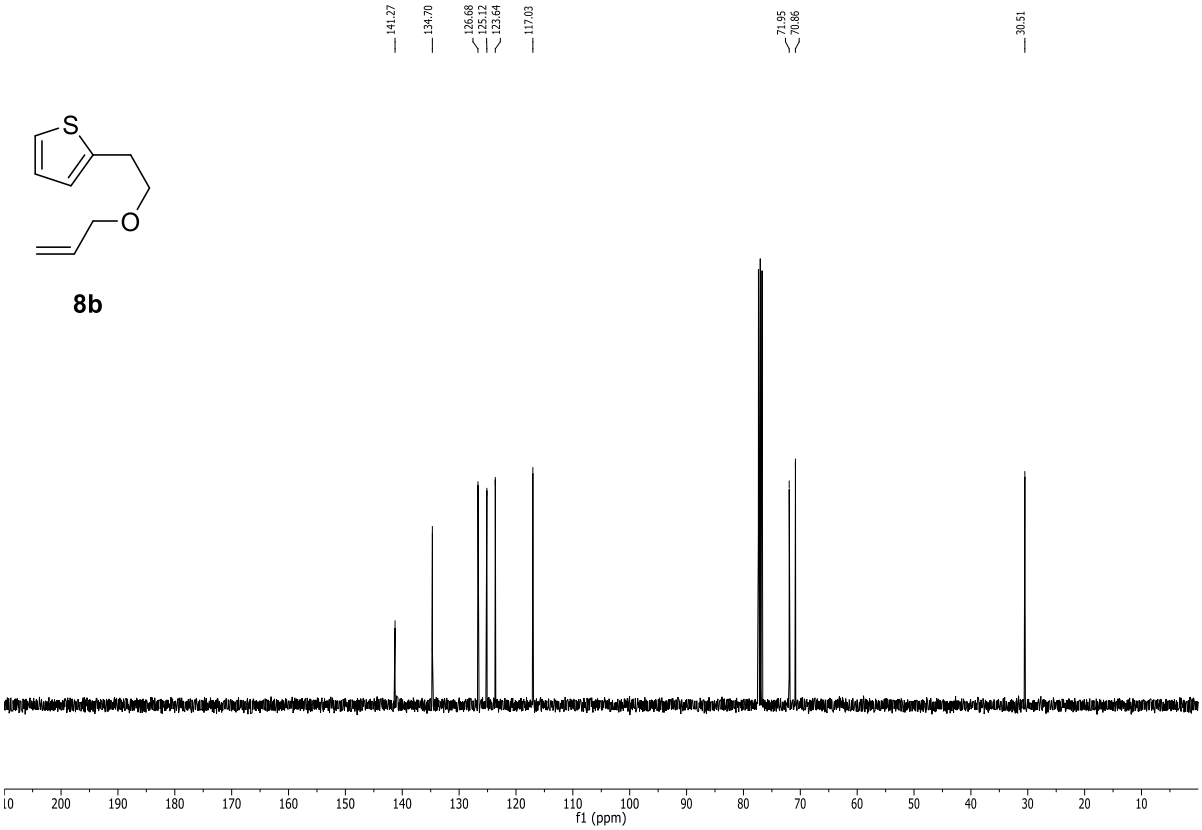
2-(2-(Allyloxy)ethyl)thiophene (**8b**)

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



8b

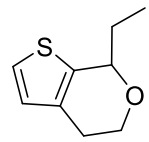
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



8b

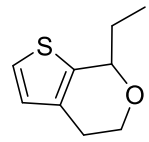
7-Ethyl-4,7-dihydro-5H-thieno[2,3-c]pyran (**9a**)

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



9a

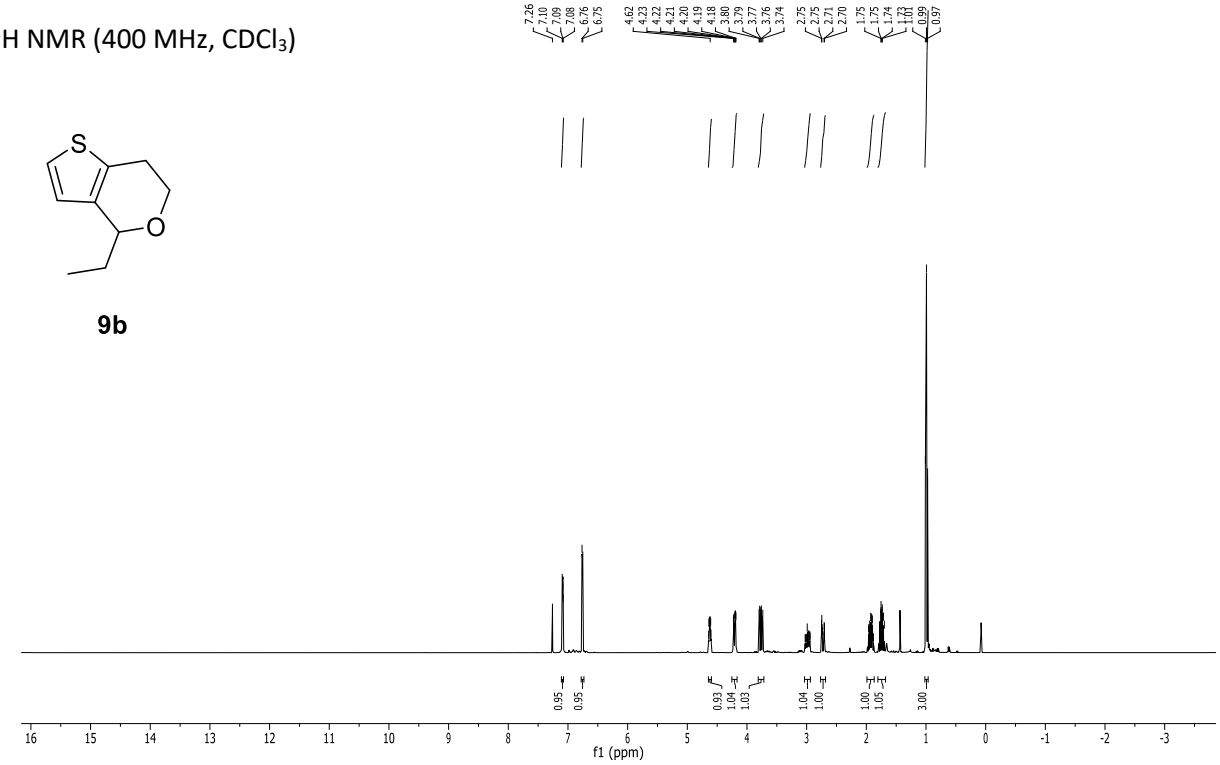
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



9a

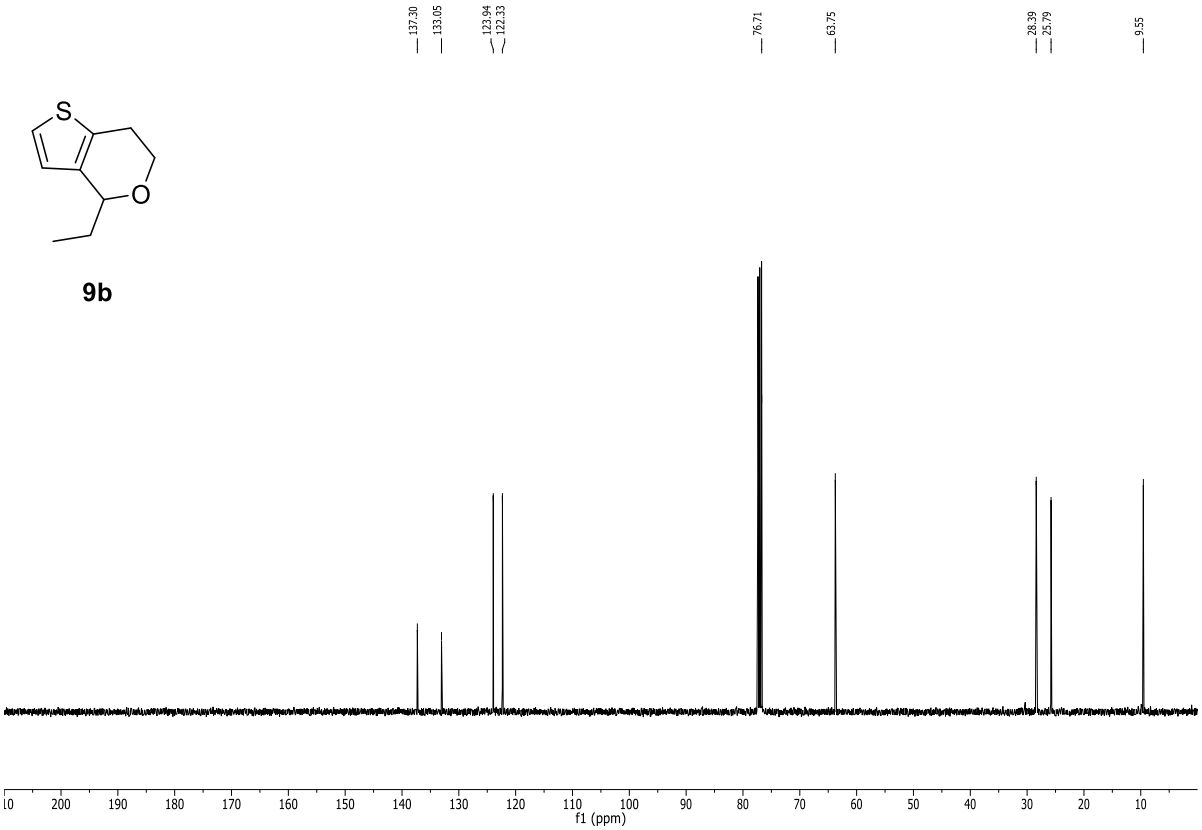
4-Ethyl-6,7-dihydro-4H-thieno[3,2-c]pyran (**9b**)

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



9b

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

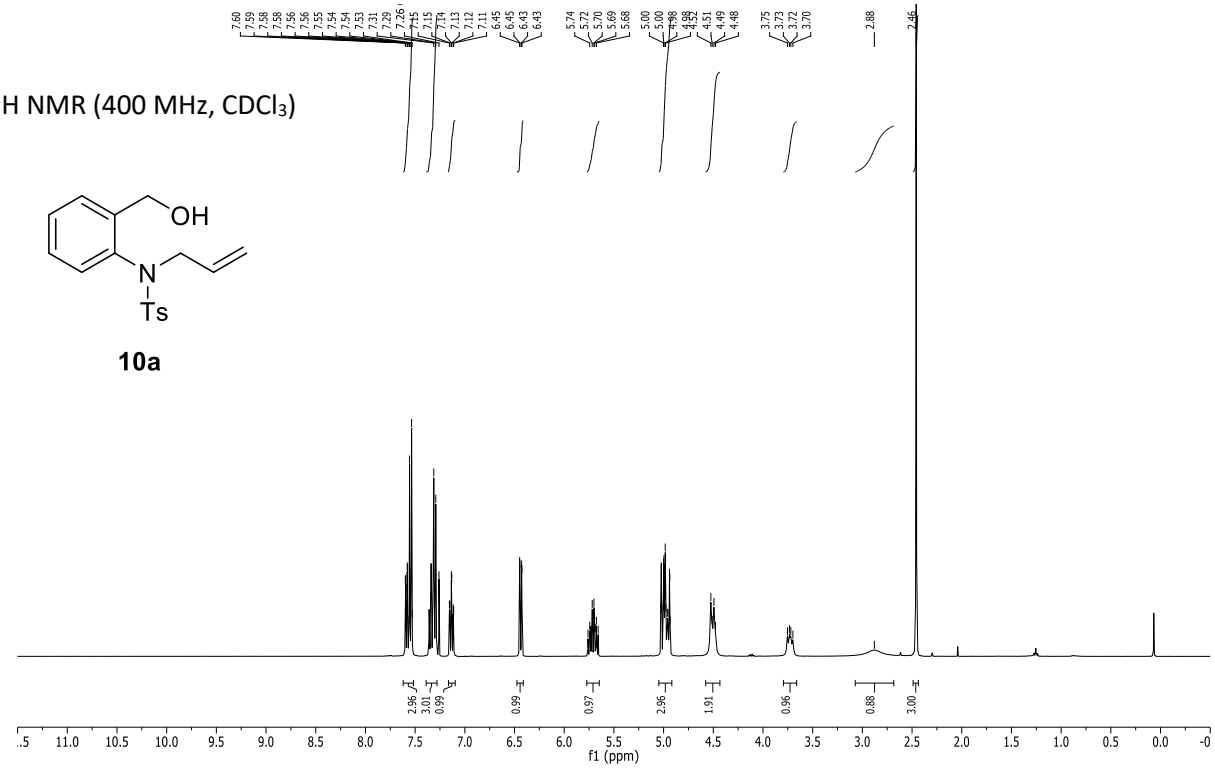


9b

6. Spectral Data for Substrates for Acetalization 10a-10h, and Products 11a-11h

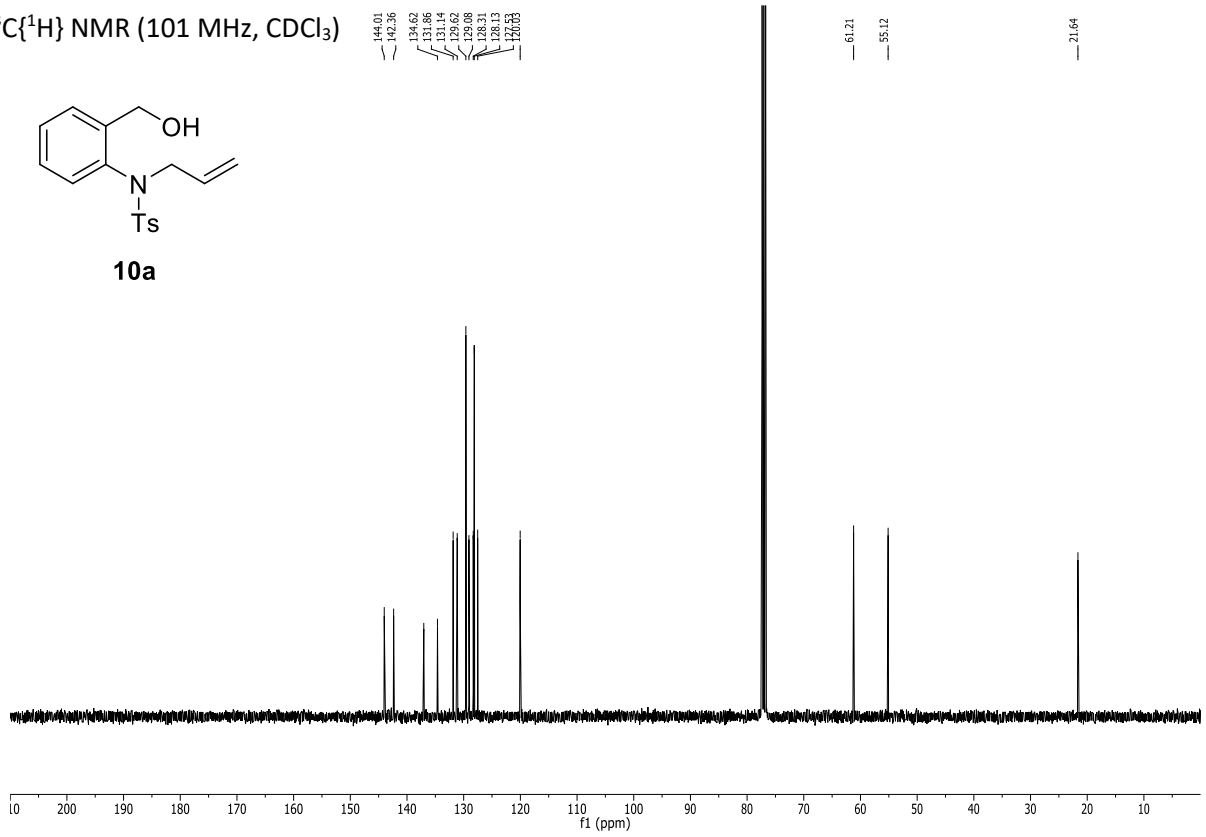
N-Allyl-*N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide **(10a)**

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



10a

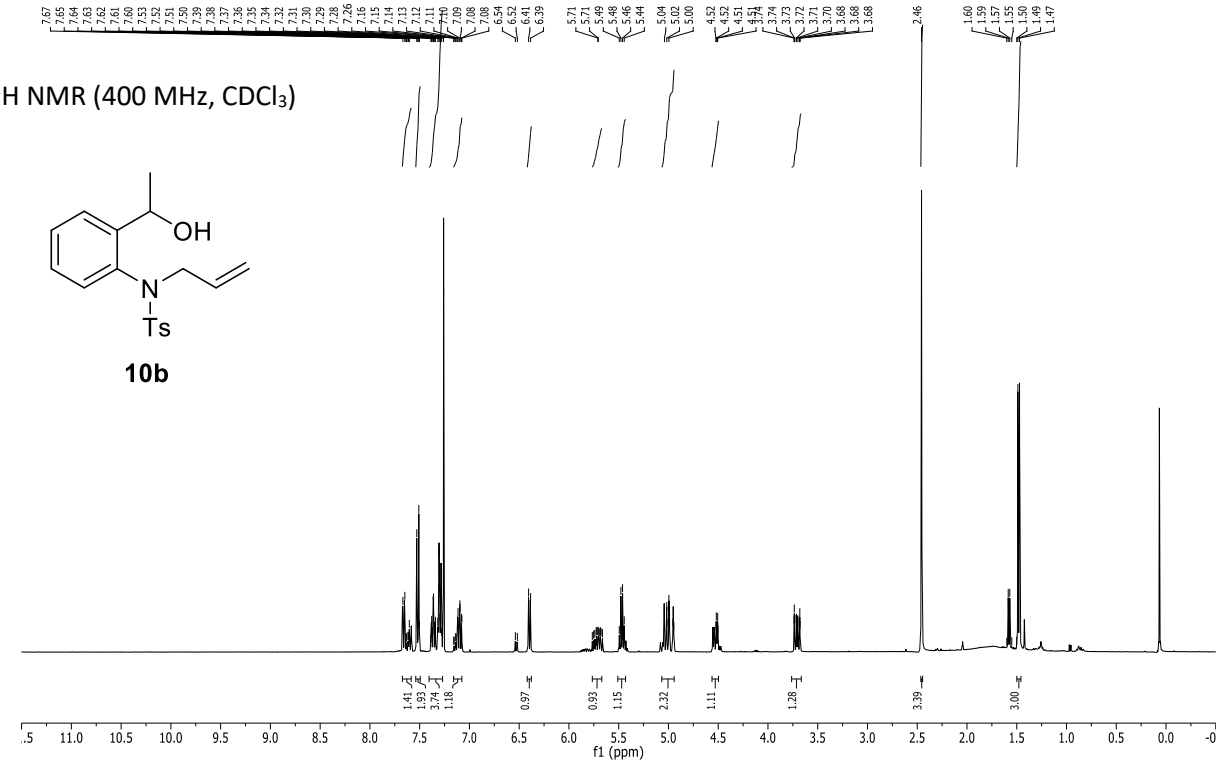
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



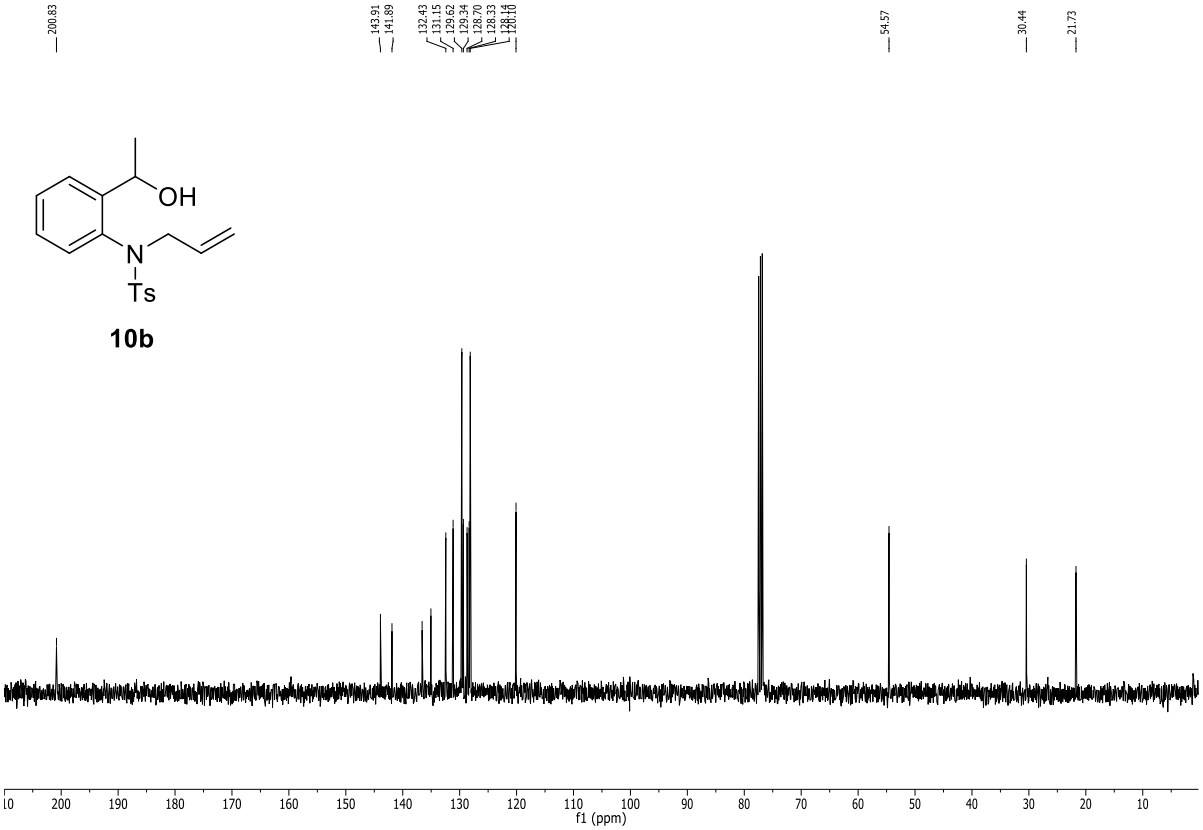
10a

N-Allyl-N-(2-(1-hydroxyethyl)phenyl)-4-methylbenzenesulfonamide (**10b)**

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

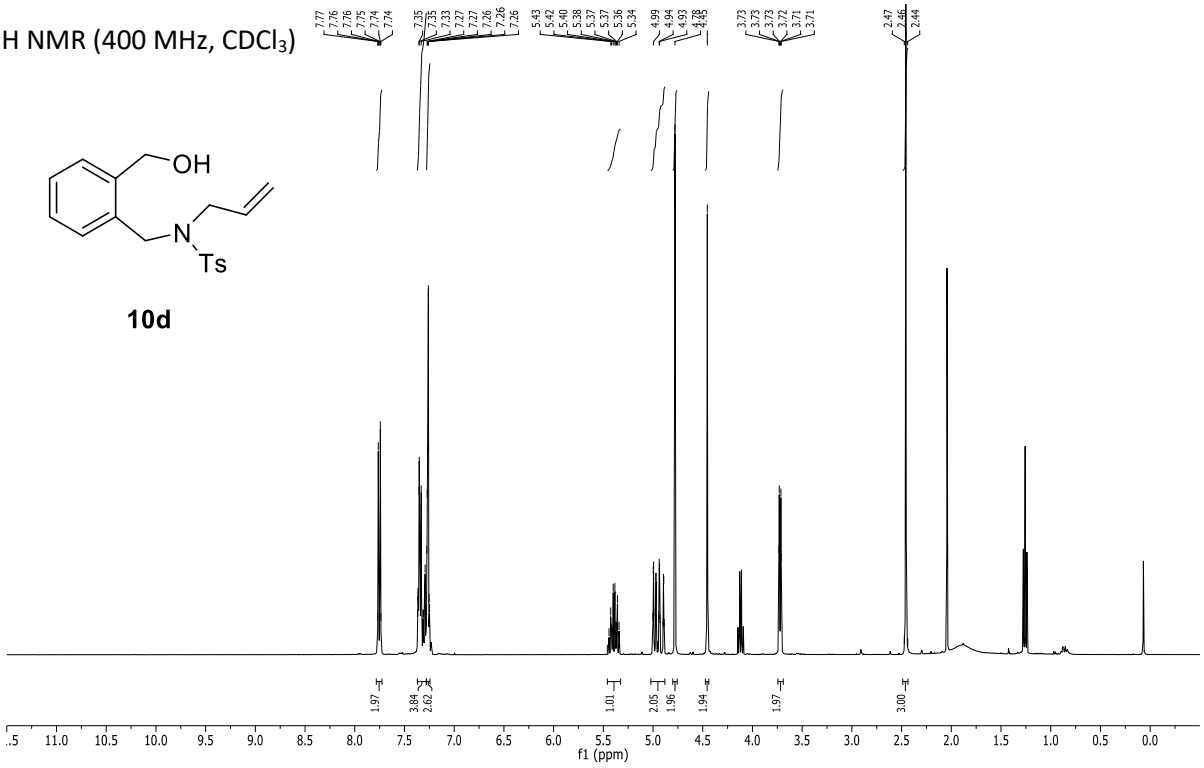


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



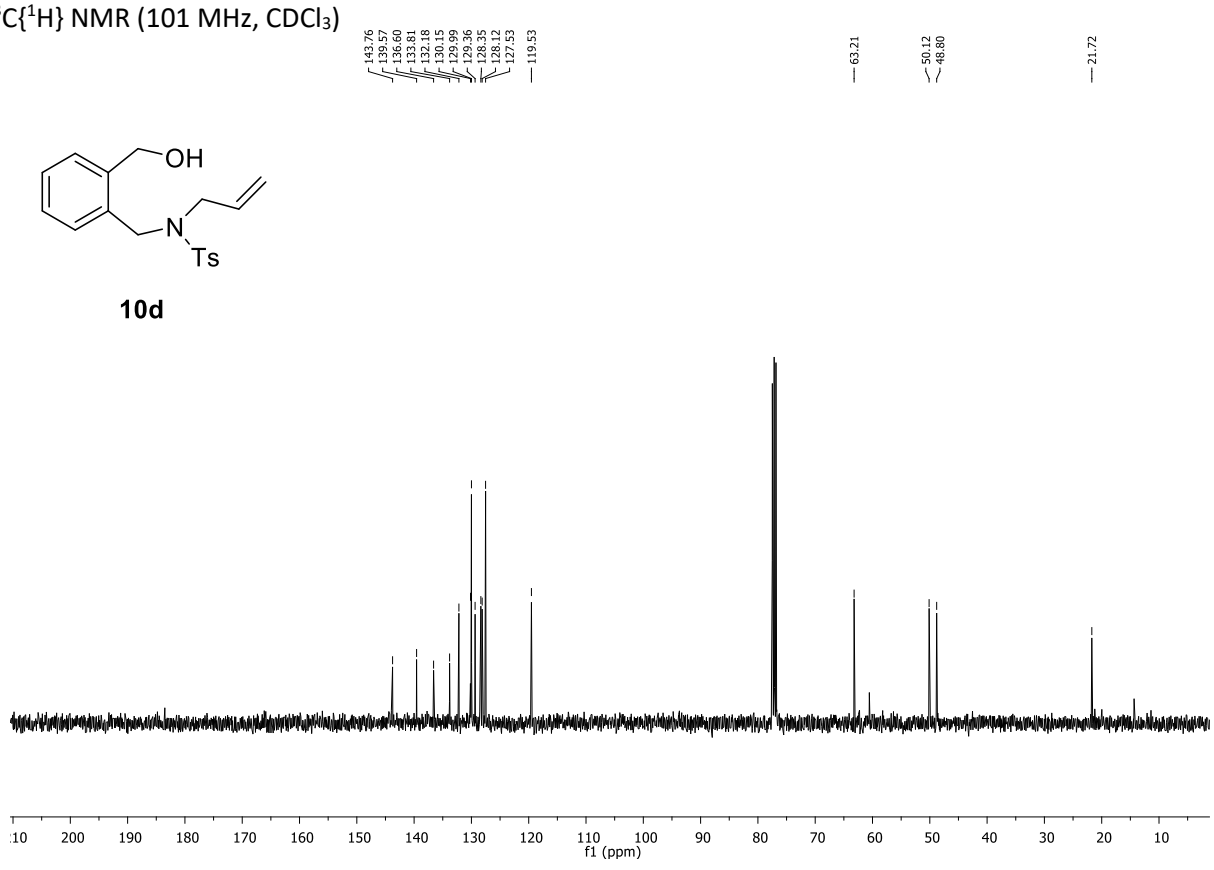
N-Allyl-N-(2-(hydroxymethyl)benzyl)-4-methylbenzenesulfonamide (**10d**)

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



10d

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

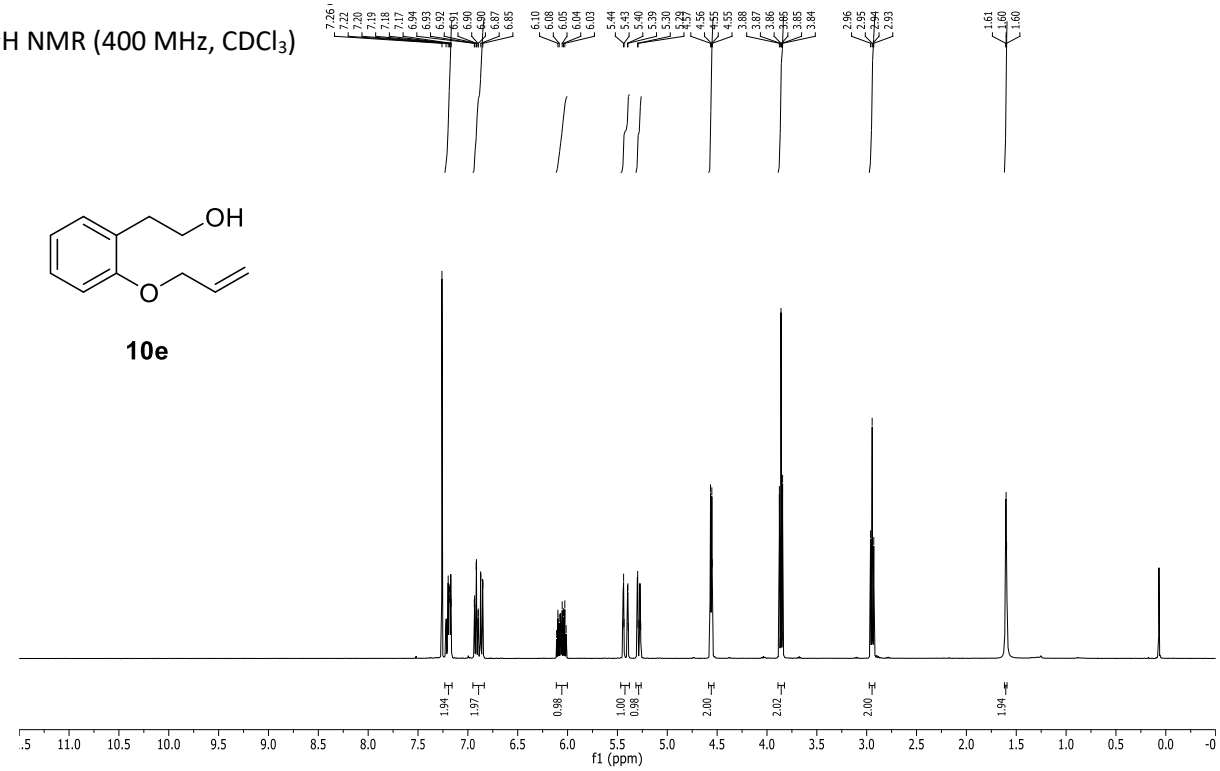


OH
N
Ts

10d

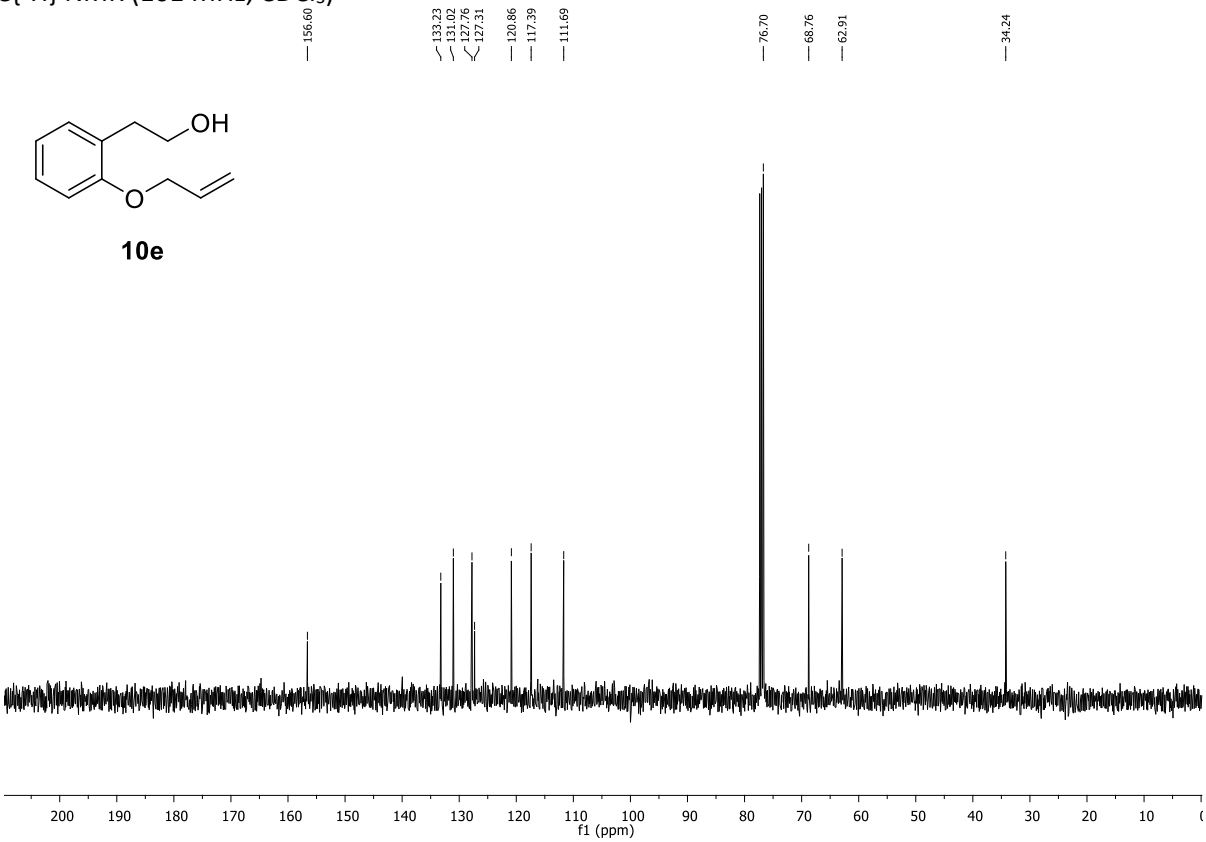
2-(2-(Allyloxy)phenyl)ethan-1-o**l** (**10e**)

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



10e

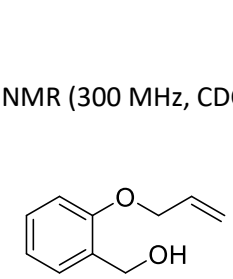
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



10e

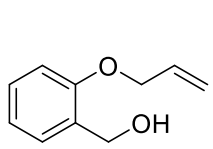
(2-(Allyloxy)phenyl)methanol (**10f**)

^{1}H NMR (300 MHz, $CDCl_3$)



10f

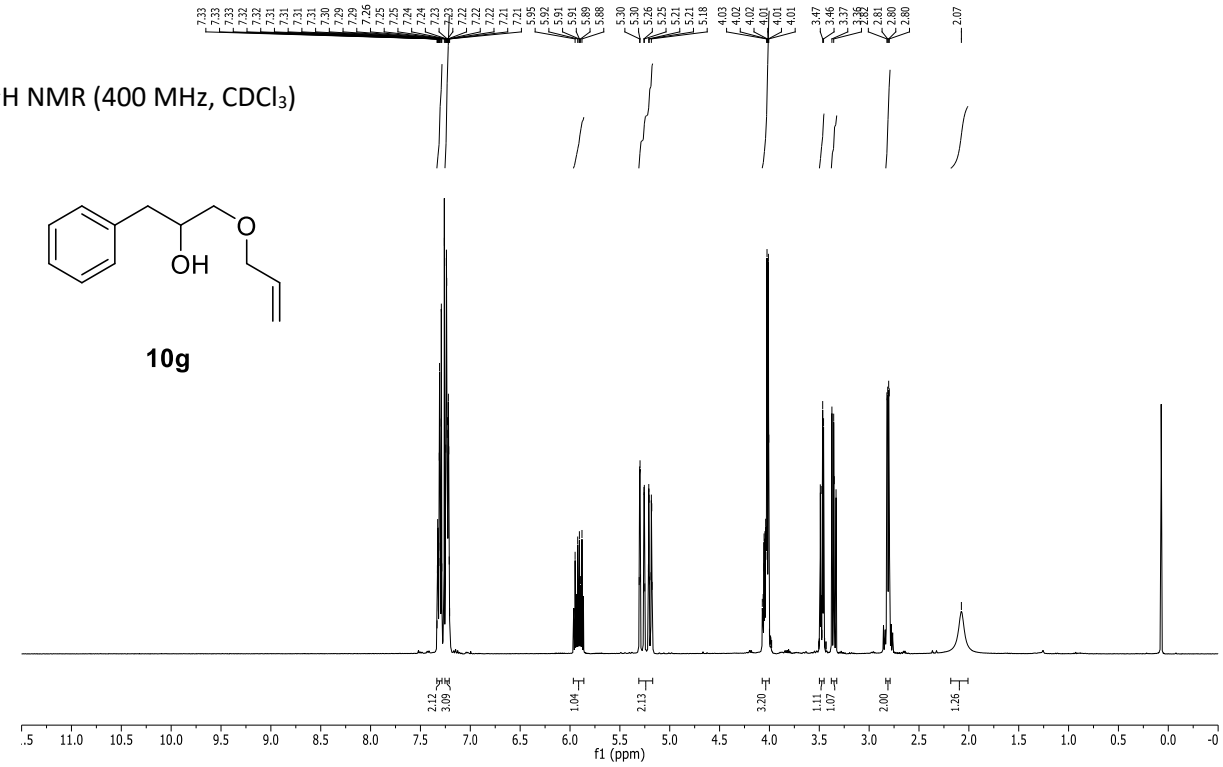
$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)



10f

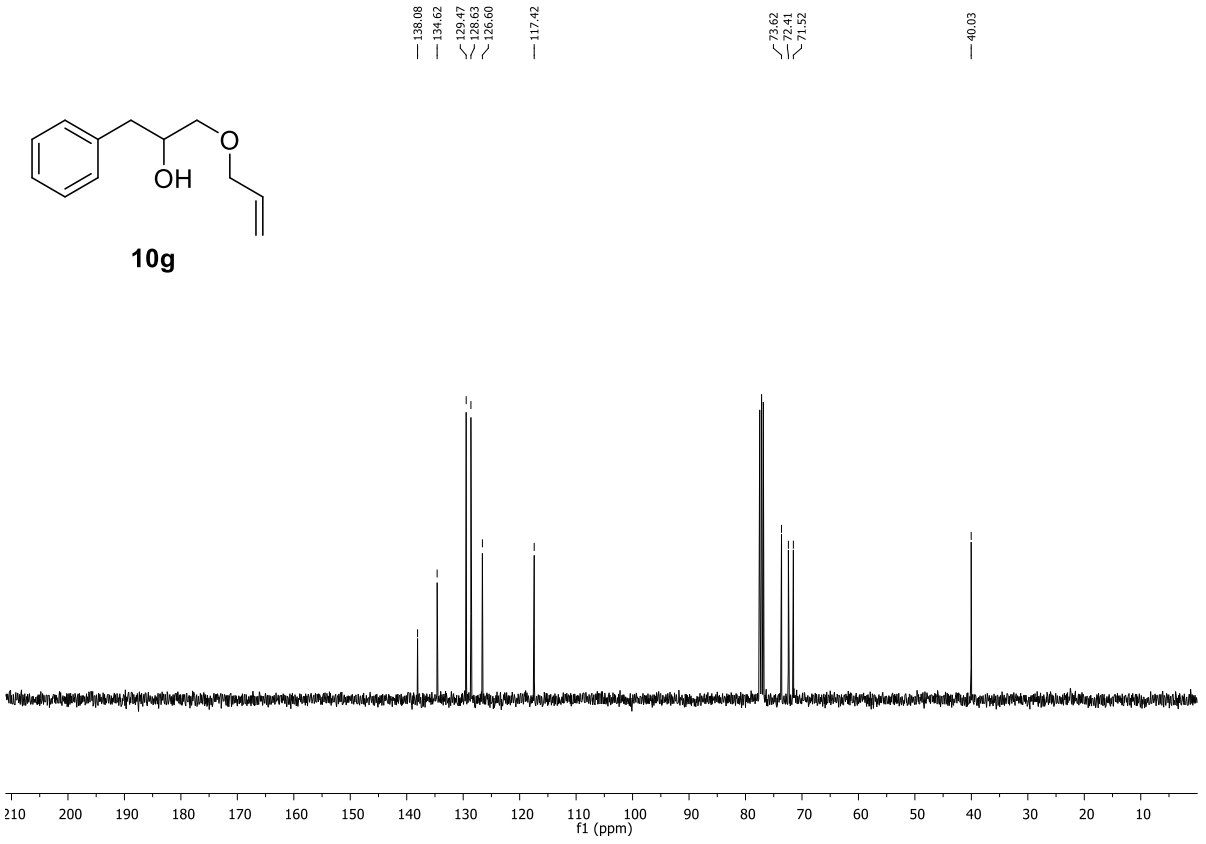
1-(Allyloxy)-3-phenylpropan-2-ol (**10g**)

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



10g

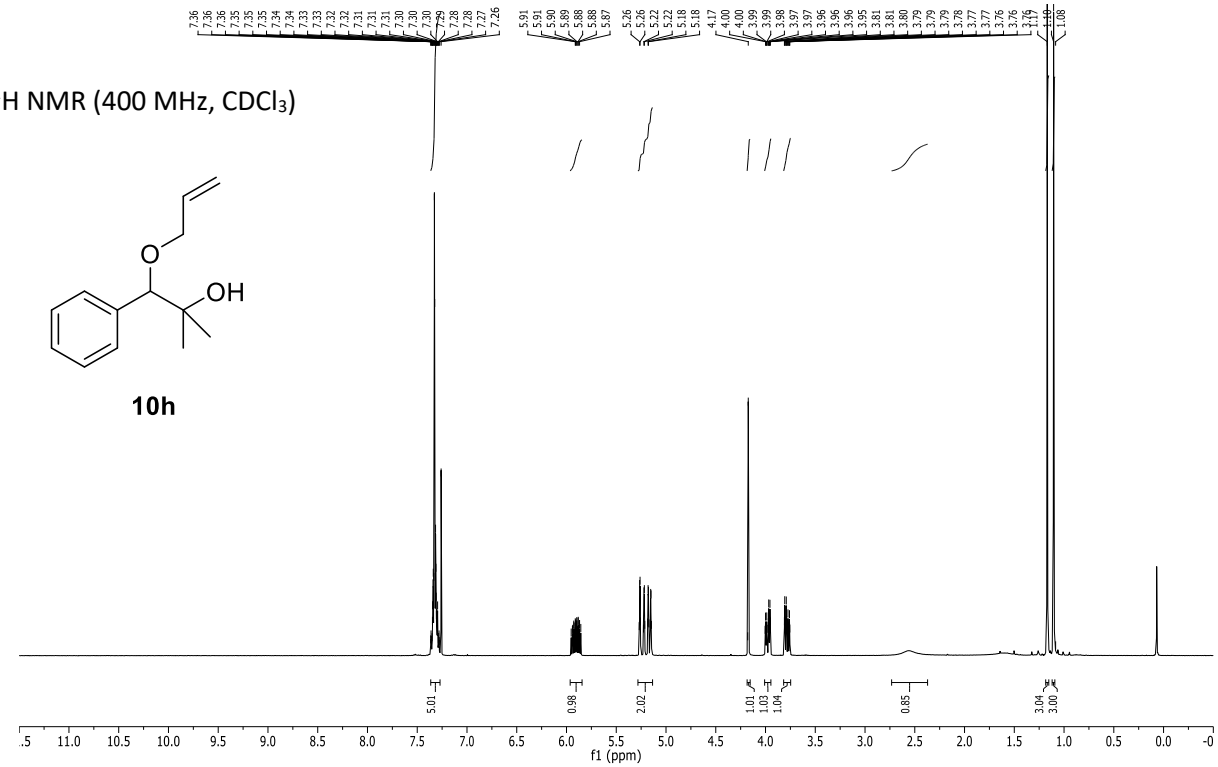
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



10g

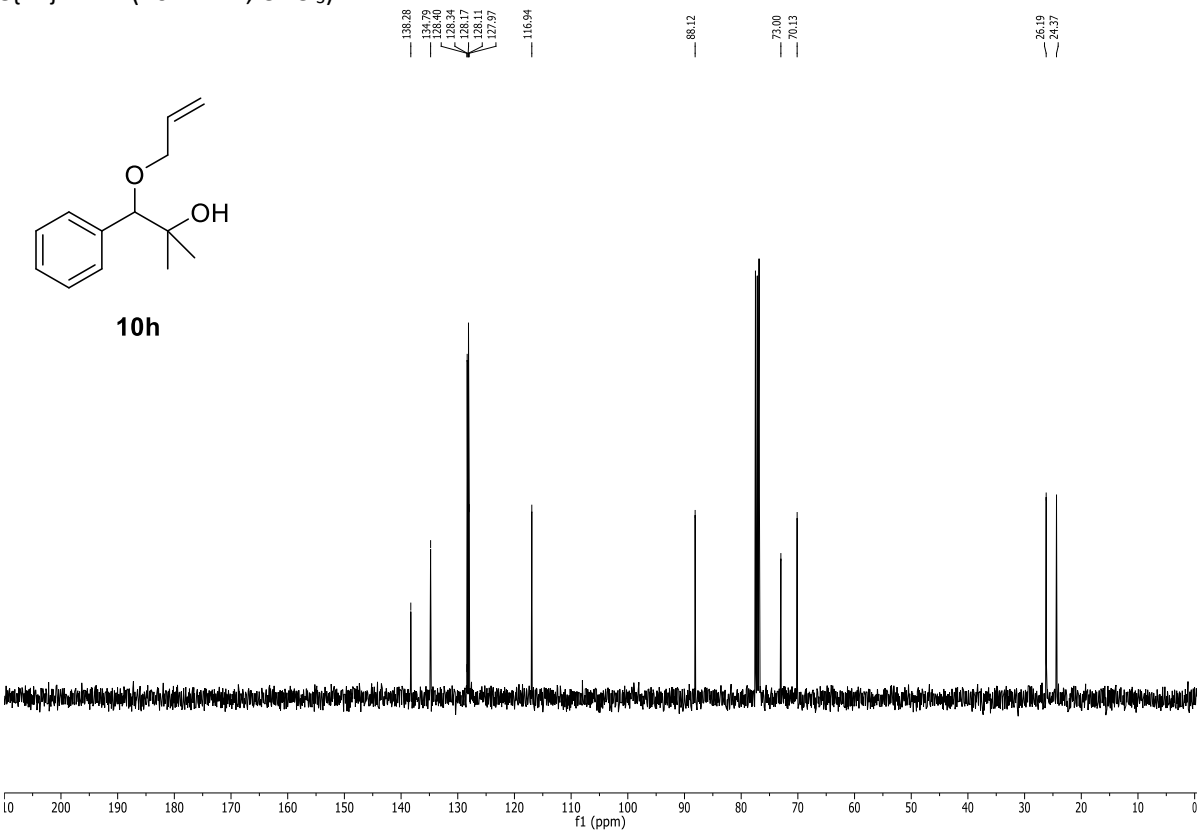
1-(Allyloxy)-2-methyl-1-phenylpropan-2-ol (**10h**)

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



10h

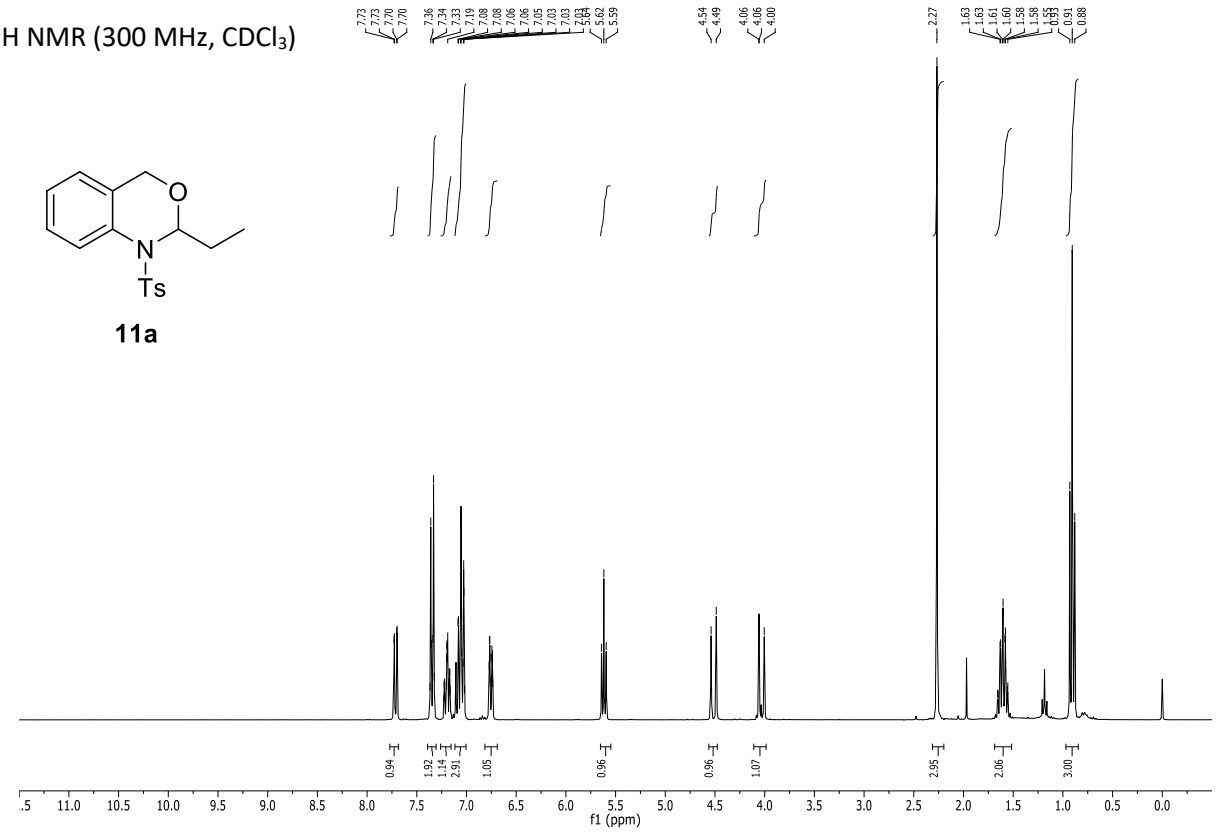
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



10h

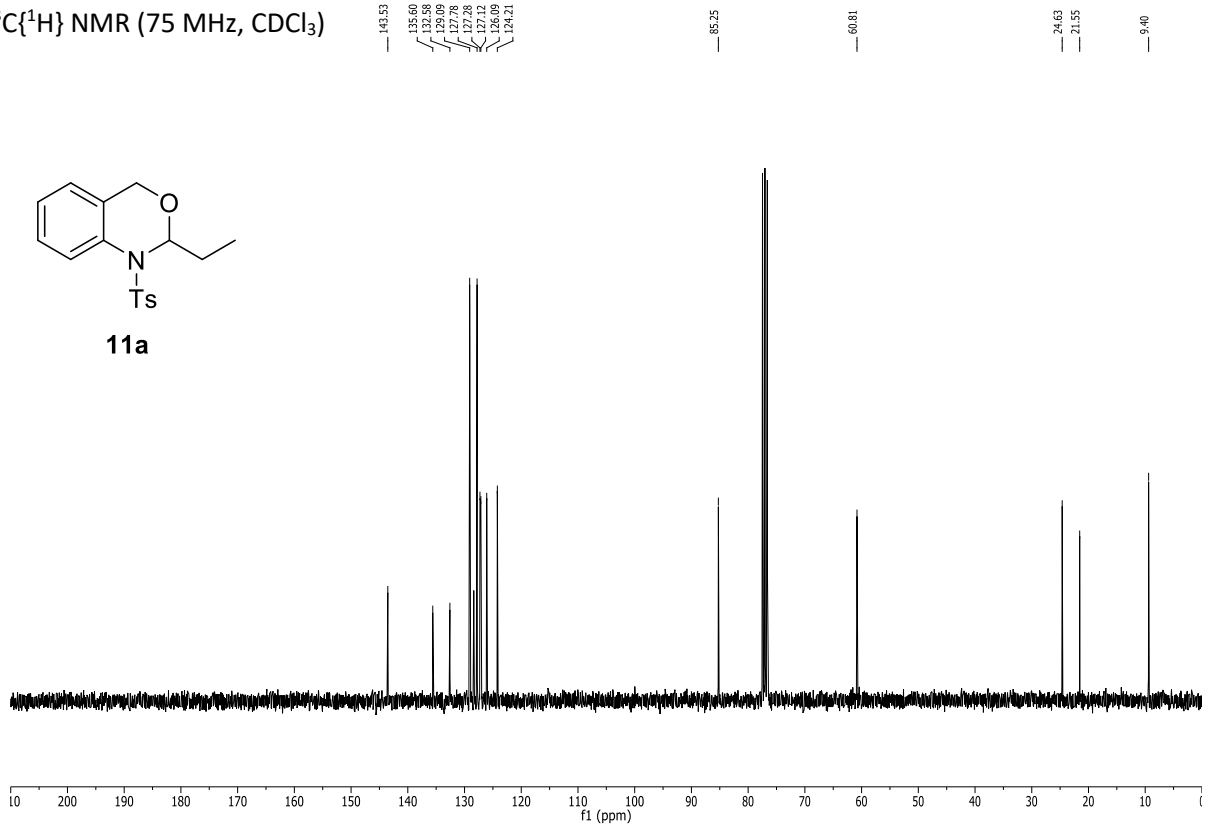
2-Ethyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**11a**)

^{1}H NMR (300 MHz, $CDCl_3$)



11a

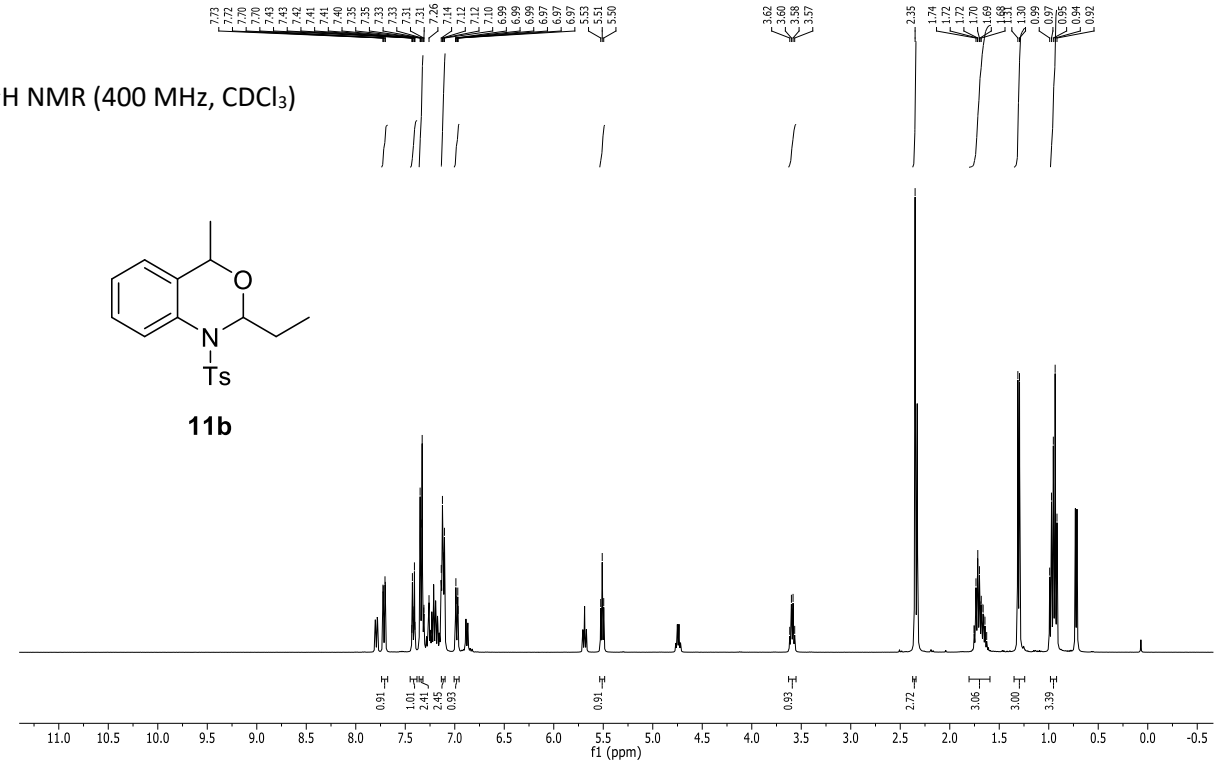
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



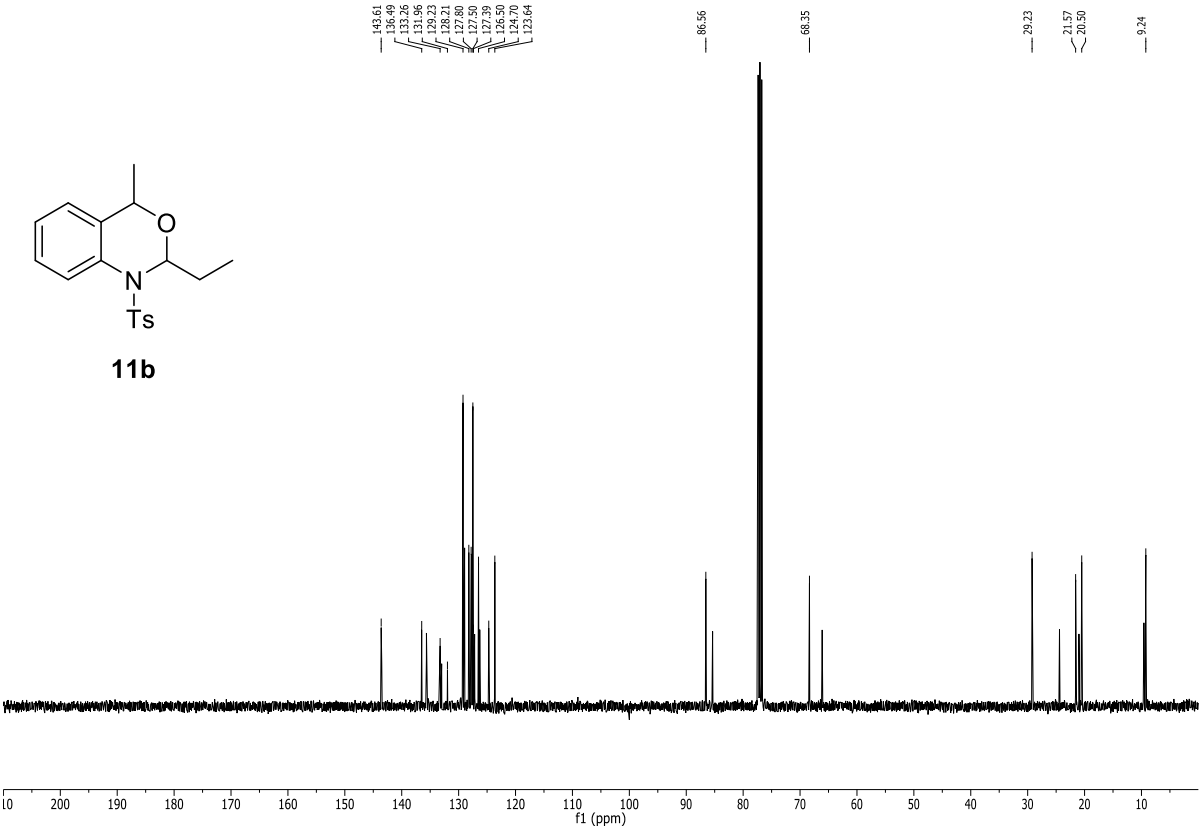
11a

2-Ethyl-4-methyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**11b**)

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

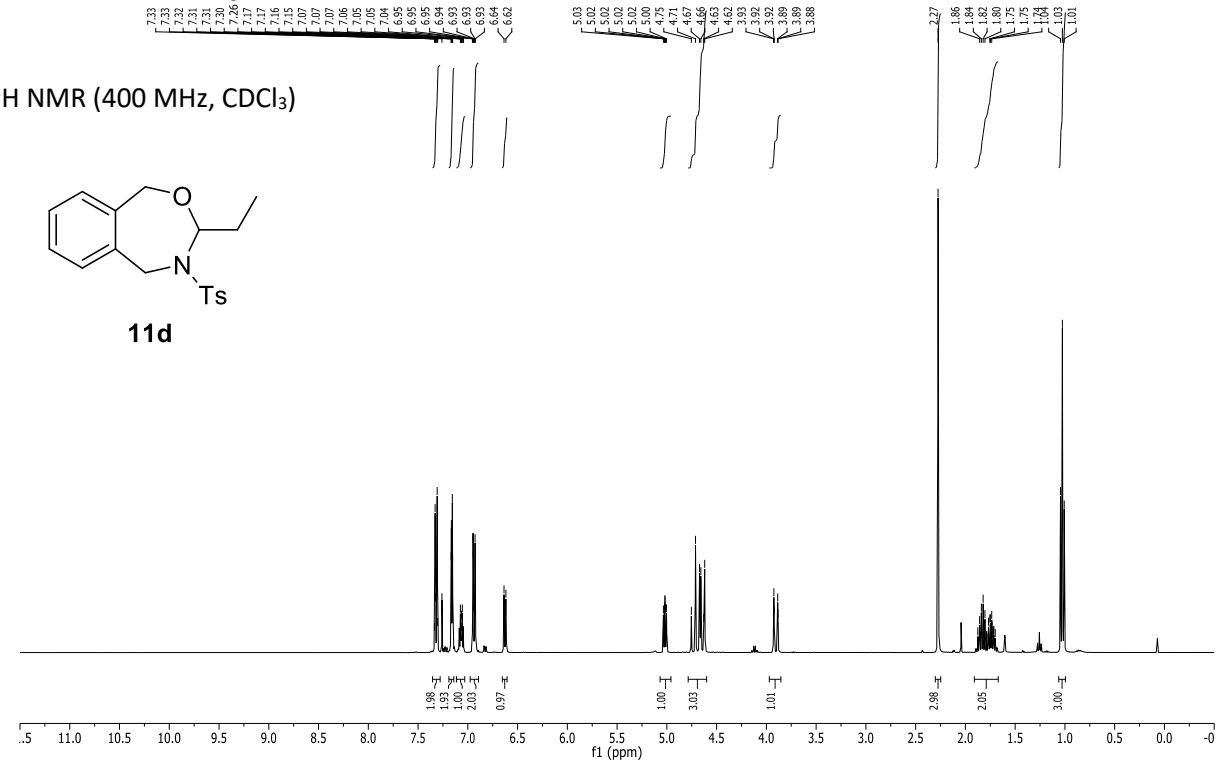


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

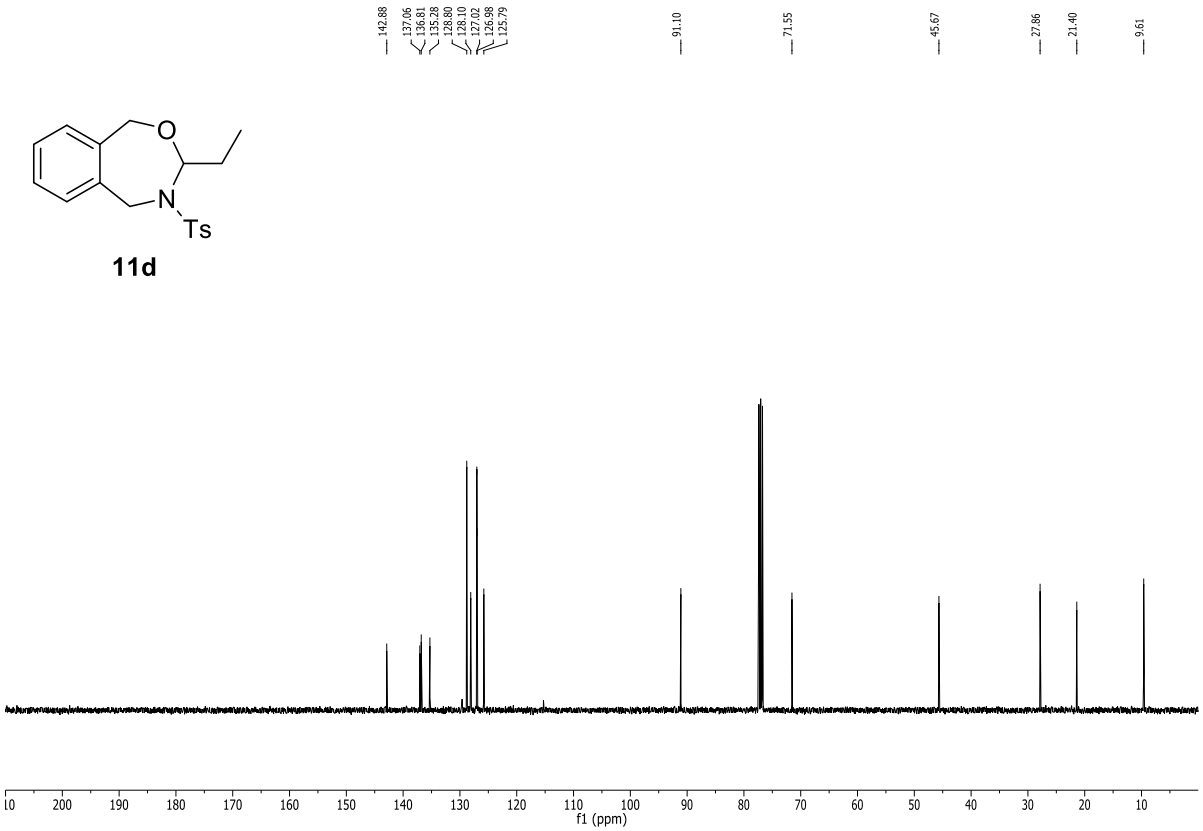


3-Ethyl-4-tosyl-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepine (**11d)**

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

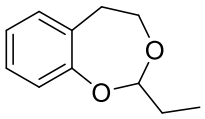


$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)



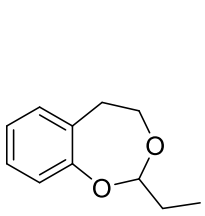
2-Ethyl-4,5-dihydrobenzo[d][1,3]dioxepine (**11e**)

^{1}H NMR (300 MHz, $CDCl_3$)



11e

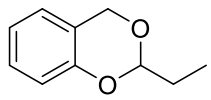
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



11e

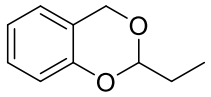
2-Ethyl-4H-benzo[d][1,3]dioxine (**11f**)

^{1}H NMR (300 MHz, $CDCl_3$)



11f

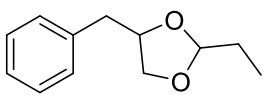
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



11f

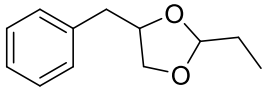
4-Benzyl-2-ethyl-1,3-dioxolane (**11g**)

^{1}H NMR (300 MHz, $CDCl_3$)



11g

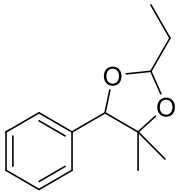
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



11g

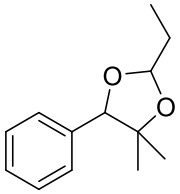
2-Ethyl-4,4-dimethyl-5-phenyl-1,3-dioxolane (**11h**)

^{1}H NMR (300 MHz, $CDCl_3$)



11h

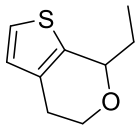
^{13}C NMR (75 MHz, $CDCl_3$)



11h

7. GC-FID Analysis Calibration Data

Calibration Data for Gas Chromatography:

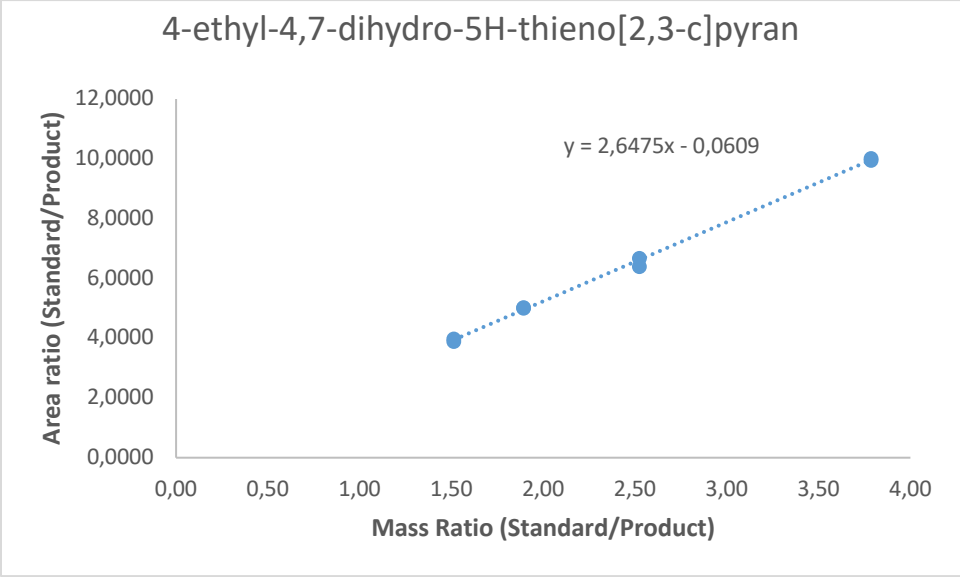


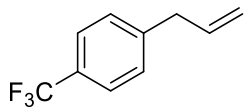
9a

For the purpose of obtaining a calibration curve a stock solution of compound **9a** was prepared as described in the following paragraph

Compound **9a** was weighed into a 10 mL standard flask (42.06 mg, 0.25 mmol) anddissolved in CH_2Cl_2. From this stock solution, four sets of dilutions were prepared in GC vials: 100 µL, 150 µL, 200 µL, 250 µL, two each. A similar procedure was followed for pentadecane, the internal standard (0.25 mmol, 53.1 mg). However, this time 300 µL was added to every GC vial containing the previously prepared dilutions. Upon diluting the mixtures with CH_2Cl_2, they were subjected to GC analysis.

area (product)	area (pentadecane)	mass (product)	mass (pentadecane)
537	5344	0.42	1.59
528	5288	0.42	1.59
777	4982	0.63	1.59
821	5488	0.63	1.59
1043	5225	0.84	1.59
1010	5073	0.84	1.59
1269	4944	1.05	1.59
1499	5954	1.05	1.59



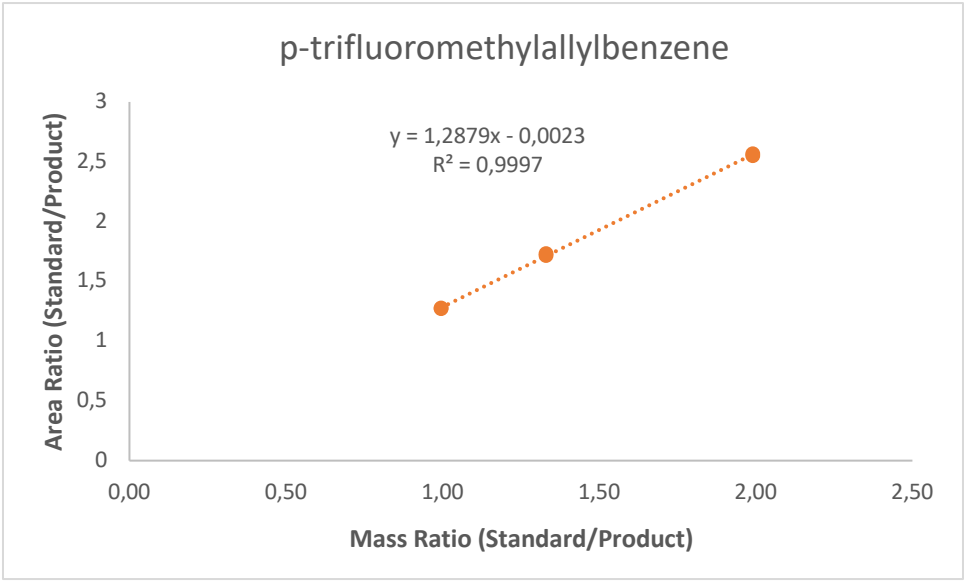


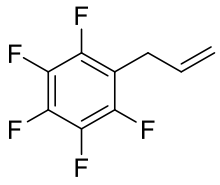
1b

For the purpose of obtaining a calibration curve a stock solution of compound **1b** was prepared as described in the following paragraph.

1-allyl-4-(trifluoromethyl)benzene was weighed into a 10 mL standard flask (46.54 mg, 0.25 mmol) anddissolved in ethyl acetate. From this stock solution, three sets of dilutions were prepared in GC vials: 300 µL, 200 µL, 400 µL, two each. A similar procedure was followed for pentadecane, the internal standard (0.25 mmol, 53.1 mg). However, this time 350 µL was added to every GC vial containing the previously prepared dilutions. Upon diluting the mixtures with ethyl acetate, they were subjected to GC analysis.

area (product)	area (pentadecane)	mass (product)	mass (pentadecane)
3833.3	6628.8	1.39	1.85
3634.9	6226.4	1.39	1.85
2338.7	5994.2	0.93	1.85
2615.4	6669.4	0.93	1.85
5340.5	6811.7	1.86	1.85
5122	6503	1.86	1.85



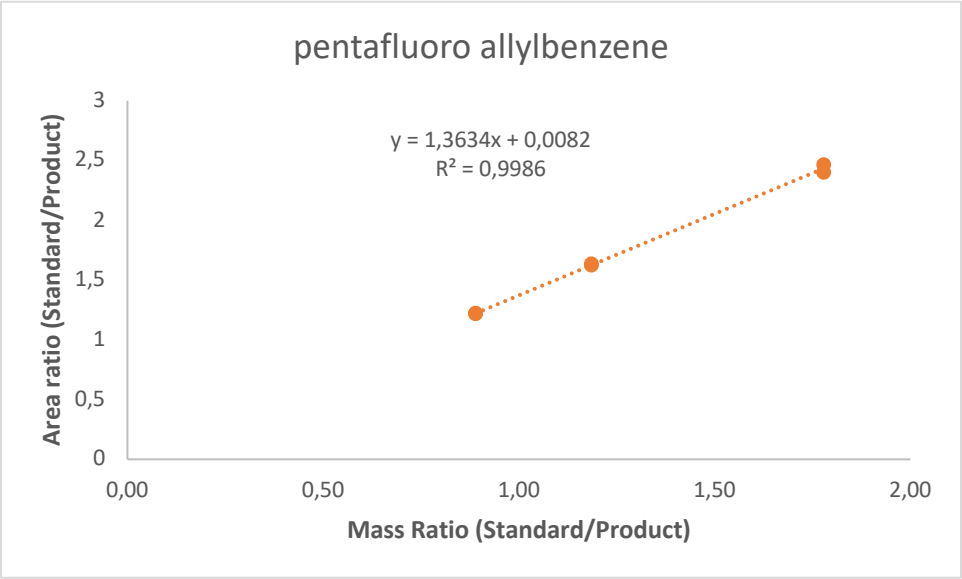


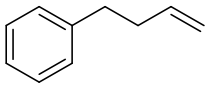
1c

For the purpose of obtaining a calibration curve a stock solution of compound **1c** was prepared as described in the following paragraph.

Compound **1c** was weighed into a 10 mL standard flask (52.03 mg, 0.25 mmol) and dissolvedin ethyl acetate. From this stock solution, three sets of dilutions were prepared in GC vials 300 µL, 200 µL, 400 µL, two each. A similar procedure was followed for pentadecane, the internal standard (0.25 mmol, 53.1 mg). However, this time 350 µL was added to every GC vial containing the previously prepared dilutions. After dilution of the mixtures with ethyl acetate, samples were subjected to GC analysis.

area (product)	area (pentadecane)	mass (product)	mass (pentadecane)
3664.5	5953.2	1.56	1.85
4059.9	6629.5	1.56	1.85
2639.2	6333.5	1.04	1.85
2576.5	6349.7	1.04	1.85
4845.4	5888.4	2.08	1.85
4817.6	5888.7	2.08	1.85



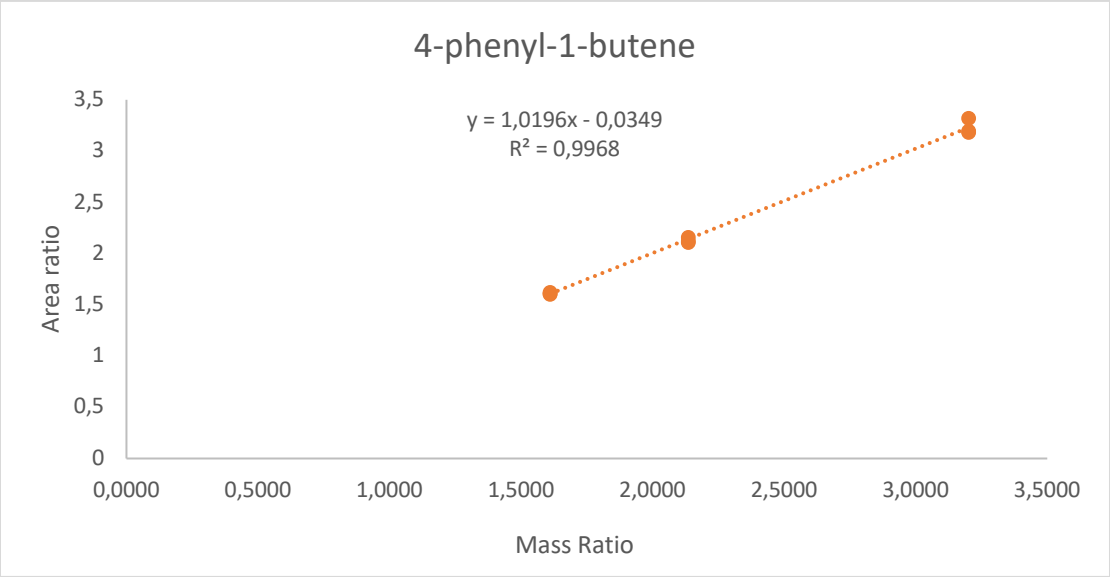


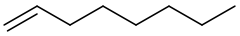
1g

For the purpose of obtaining a calibration curve a stock solution of **1g** was prepared as described in the following paragraph

Compound **1g** was weighed into a 10 mL standard flask (0.25 mmol, 33.0 mg) and dissolved in ethyl acetate. From this stock solution, three sets of dilutions were prepared in GC vials: 300 µL, 200 µL, 400 µL, three each. A similar procedure was followed for pentadecane, the internal standard (0.25 mmol, 53.1 mg). However, this time 400 µL was added to every GC vial containing the previously prepared dilutions. After diluting the mixtures with ethyl acetate, samples were subjected to GC analysis.

area (product)	area (pentadecane)	mass (product)	mass (pentadecane)
1492	4951.1	0.634	2.03
1589	5064	0.634	2.03
1575	5032	0.634	2.03
2403	5191	0.951	2.03
2320	4926	0.951	2.03
2324	4897	0.951	2.03
3131	5051	1.26	2.03
3041	4944	1.26	2.03
3186	5120	1.26	2.03



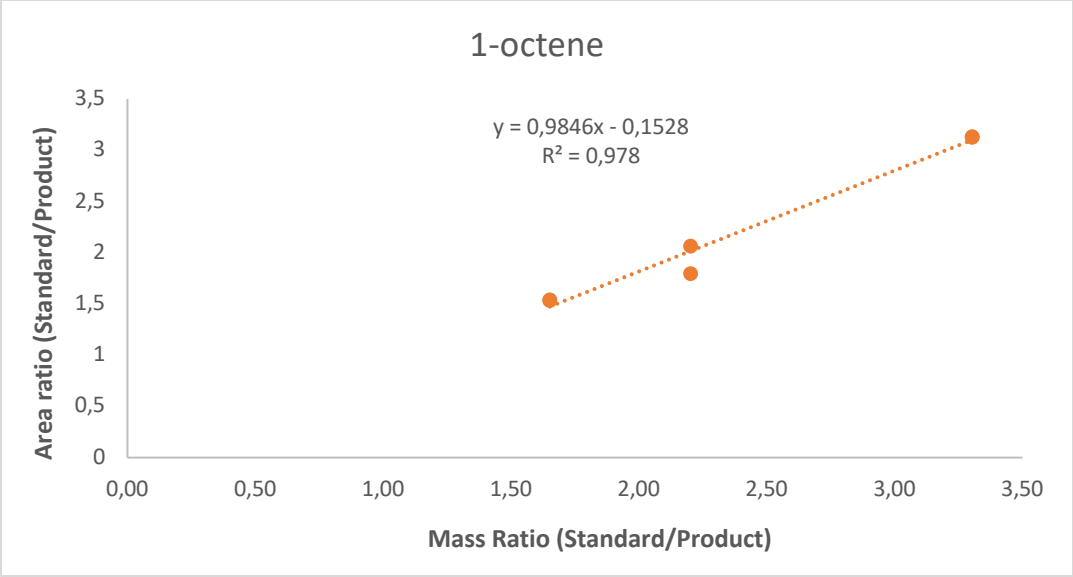


1h

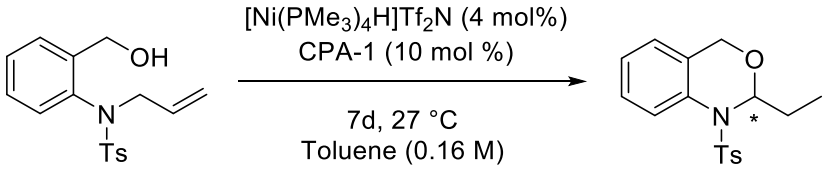
For the purpose of obtaining a calibration curve a stock solution of compound **1h** was prepared as described in the following paragraph

1-octene was weighed into a 10 mL standard flask (28.05 mg, 0.25 mmol) and dissolvedin ethyl acetate. From this stock solution, three sets of dilutions were prepared in GC vials: 300 µL, 200 µL, 400 µL, two each. A similar procedure was followed for pentadecane, the internal standard (0.25 mmol, 53.1 mg). However, this time 350 µL was added to every GC vial containing the previously prepared dilutions. After diluting the mixtures with ethyl acetate, samples were subjected to GC analysis.

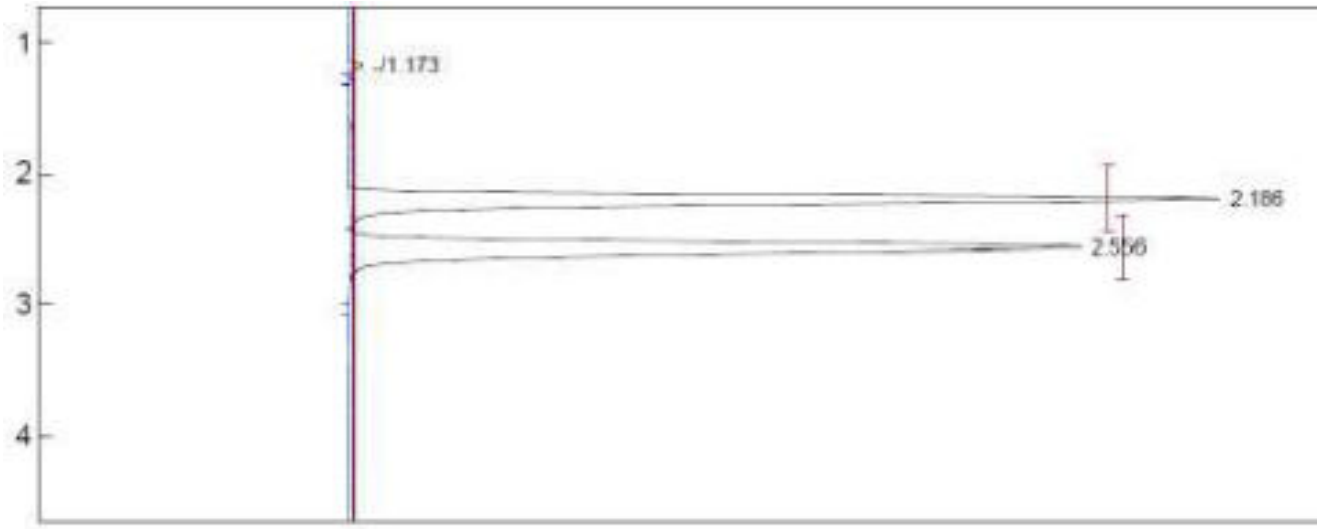
area (product)	area (pentadecane)	mass (product)	mass (pentadecane)
3541.2	6341.3	0.84	1.85
3149.2	6491.4	0.84	1.85
2022.5	6336.7	0.56	1.85
1902.2	5947.6	0.56	1.85
4307.7	6614.1	1.12	1.85
3724.3	5702.6	1.12	1.85



8. HPLC Data: Enantioselective Isomerization/Acetalization

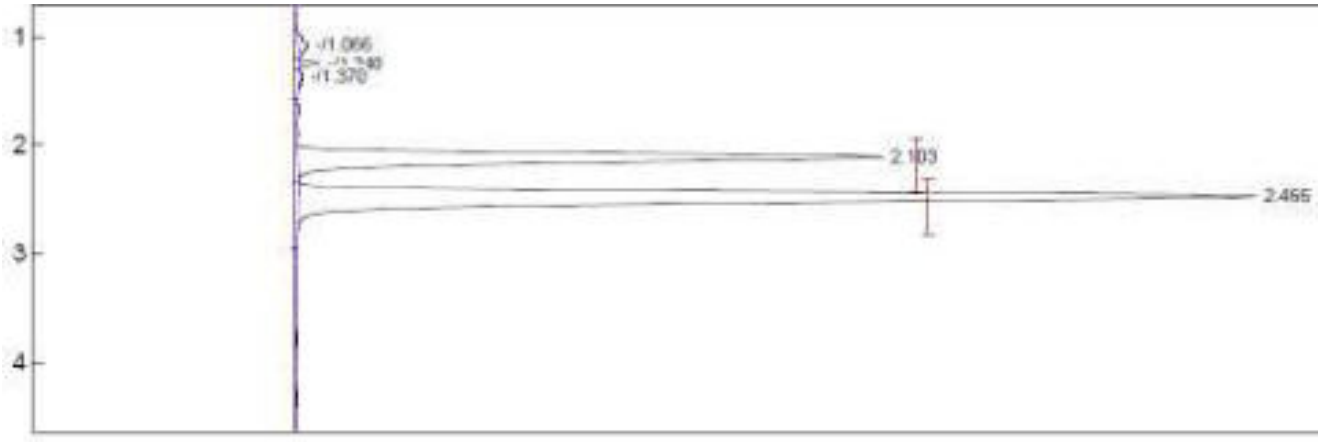


10a **11a**



Component	Retention	Area	Internal	Units	NormPotency%
	2.186	4501.5268	0.0000		0.0000
	2.556	4522.3844	0.0000		0.0000

Column: Reprosil Chiral OM Wavelength- 254 nm
Eluent: hexane:*i*-propanol 93:7 (static elution), run time: 25 mins
Temperature: r.t.



Component	Retention	Area	Internal	Units	NormPotency%
	2.103	2081.0530	0.0000		0.0000
	2.466	3978.6920	0.0000		0.0000

Column- Reprosil Chiral OM Wavelength- 254 nm
Eluent: hexane:*i*-propanol : 93 : 7 (static elution), run time: 25 mins.
Temperature: r.t.

Comparison of areas of peak at 2.103 and 2.466 indicate a ratio of **66:34**.

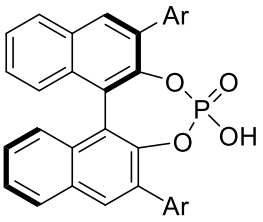
Similarly, other enantiomeric ratios were determined.

The reactions for evaluating the enantiomeric excess were carried out as per general catalysis procedure A. The crude product was analyzed by HPLC.

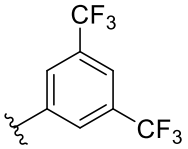
Table S2. Reaction trials with chiral phosphoric acid.

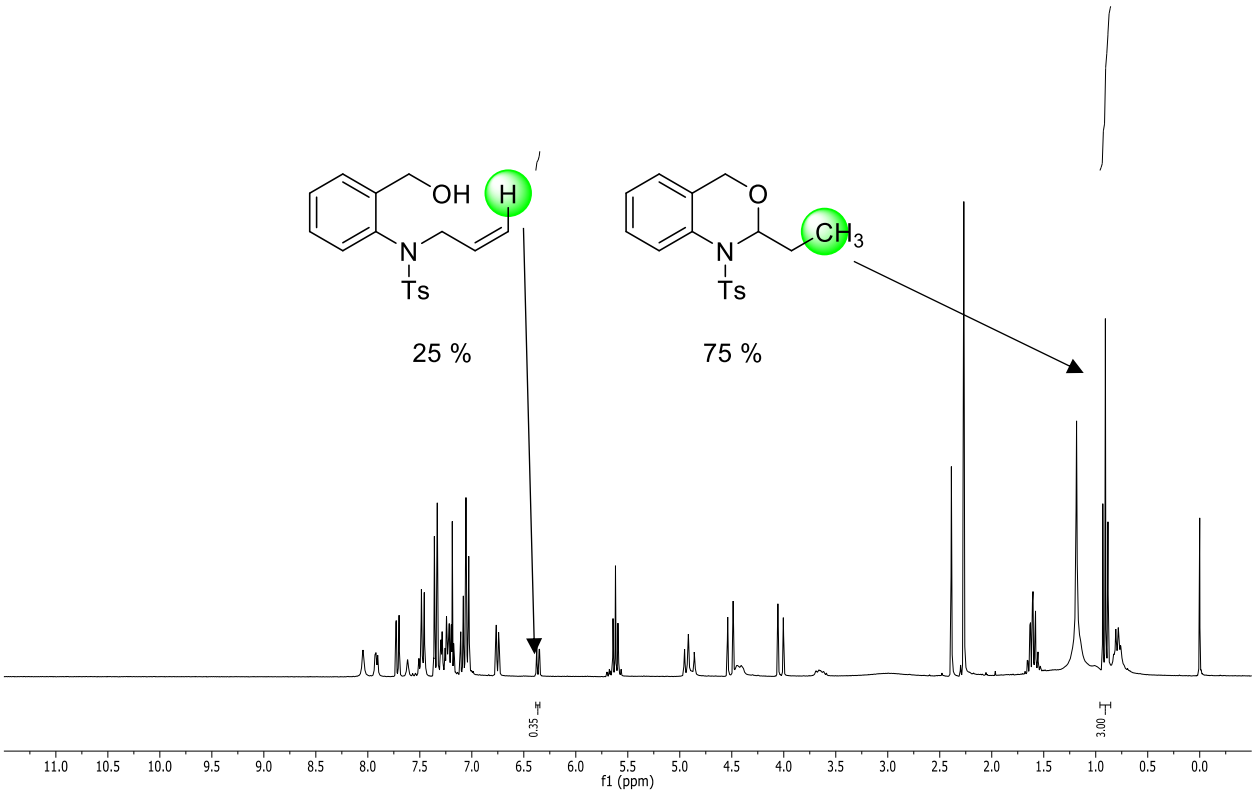
sr. no	**Ni-H** (mol-%)	Acid (mol-%)	Time (days)	**11a:10a (%)**[a]	**e.r.**[b]
[c]1	4	DPP (15)	4	75 : 25	racemic
[d]2	4	CPA-1 (15)	4.5	72 : 28	65 : 35
[e]3	4	CPA-1 (15)	6	74 : 26	65 : 35
[f]4	4	CPA-1 (15)	4.5	60 : 40	62 : 38

General reaction conditions: **1** (0.1 mmol). [a] Ratio determined by NMR spectroscopy. [b] Determined by HPLC analysis. [c] Isolated yield, temperature: 50 °C, solvent = toluene. [d] Temperature: 40 °C, solvent = toluene, [e] Temperature: 40 °C, solvent = toluene. [f] Temperature: 40 °C, solvent = THF.



CPA-1

Ar: 


OH
H
N
Ts
25 %
O
CH3
N
Ts
75 %
0.35
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

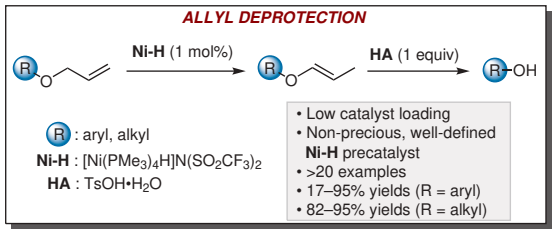
Synlett P. M. Kathe et al. Cluster

Nickel Hydride Catalyzed Cleavage of Allyl Ethers Induced by Isomerization

Prasad M. Kathe[a]
Andreas Berkefeld*[b]
Ivana Fleischer*[a]

[a] Institute of Organic Chemistry, Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
ivana.fleischer@uni-tuebingen.de
[b] Institute of Inorganic Chemistry, Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
andreas.berkefeld@uni-tuebingen.de

Published as part of the Cluster
Modern Nickel-Catalyzed Reactions



Received: 04.11.2020
Accepted: 27.12.2020
Published online: 22.01.2021
DOI: 10.1055/s-0040-1706683; Art ID: st-2020-k0584-c

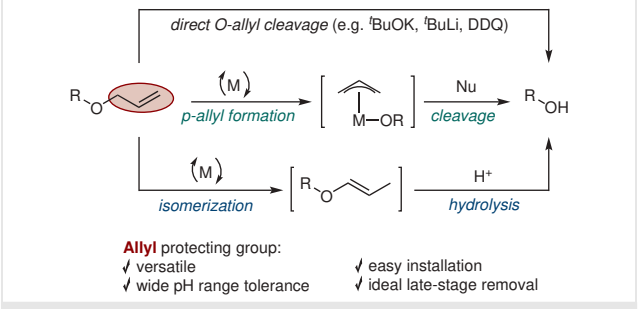
Crowd-Reviewed

Abstract This report discloses the deallylation of *O*- and *N*-allyl functional groups by using a combination of a Ni-H precatalyst and excess Brønsted acid. Key steps are the isomerization of the *O*- or *N*-allyl group through Ni-catalyzed double-bond migration followed by Brønsted acid induced O/N–C bond hydrolysis. A variety of functional groups are tolerated in this protocol, highlighting its synthetic value.

Key words nickel catalysis, deprotection, allylic ethers, isomerization, selectivity

The use of protecting groups undoubtedly permits the development of synthetic routes toward desired organic scaffolds. Depending on the requirements in a synthesis, numerous protecting groups for acidic functional groups can be used. The ideal protecting group is complementary to the requisite conditions in the relevant synthetic steps, such as a certain pH range or reagents, and it should not affect the overall desired reactivity. In turn, the protection and deprotection steps should be selective for the particular functionality. Owing to their ubiquitous nature and reactivity in target molecules and intermediates, the presence of hydroxy groups often requires the employment of protecting groups. To address the many needs, a wide range of acetal-, ether- and ester-based protecting groups for hydroxy functionality have been developed.[1]

A particularly attractive O-protecting group is allyl, thanks to several factors such as its ease of installation, use of inexpensive and readily available reagents, and stability under various reaction conditions (Scheme 1).[2] Beside the methods reported for the direct cleavage of allyl groups by using nucleophiles or oxidants,[3] those using homogeneous metal catalysts stand out due to their mild reaction conditions and often high selectivity. This has been impressively demonstrated in several total syntheses of natural compounds.[4] These reactions usually follow two main mechanisms. The first is based on the formation of a metal allyl intermediate by oxidative addition in the presence of a nucleophile or reducing agent.[5] The underlying principle in other cases is an initial olefin isomerization (single-bond transposition) to an enol ether, followed by hydrolysis.[6] Although the isomerization of allylic alcohols, ethers, and related substrates has been studied extensively,[7] its application or suggested involvement in the deallylation is much less well investigated. Furthermore, the use of nonprecious metals in allyl deprotection methods is rare but clearly desirable.



Scheme 1 General principle and deallylation methodologies

An important feature in deprotection chemistry is the concept of orthogonality, based on the selective removal of a protecting group through differential reactivity and stability.[8] Recently, Yamada and co-workers reported an elegant method for orthogonal oxidative deprotection of *p*-methylbenzyl ethers in the presence of a *p*-methoxybenzyl group, and vice-versa.[9] In this context, the chemoselective removal of an allyl group in the presence of a benzyl protecting group is of interest.

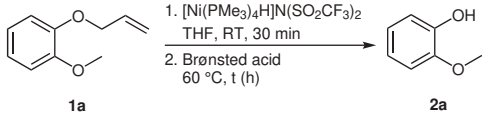
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

During our investigations of nickel hydride/ Brønsted acid catalyzed tandem reactions of allyl ethers for the generation of oxacyclic scaffolds, we observed an unexpected loss of an allyl group under the reaction conditions in some cases.[10] A plausible explanation was an initial isomerization to form an alkenyl ether, as later proven by independent experiments, and subsequent acidic hydrolysis owing to the presence of water in the acid.

Having obtained this result and based on our interest in isomerization reactions[11] and nickel catalysis,[12] we envisaged developing a general catalytic process for O-deallylation of ethers. To investigate this further, we chose the O-allylated phenol **1a** as a substrate and the complex nickel hydride $[Ni(PMe_3)_40]N(SO_2CF_3)_2$ from our original study as a precatalyst, due to its structural simplicity (Table 1). The precatalyst can by synthesized in two steps from bis(cycloocta-1,5-dienyl)nickel(0), the appropriate ligand, and bistriflimidic acid on a gram scale, and can be stored under argon on the bench.[13] In line with our previous investigations, partial isomerization to the corresponding enol ether occurred. This was followed by subsequent addition of a Brønsted acid in an attempt to obtain 2-methoxyphenol (**2a**). Initial experiments using catalytic amounts of diphenylphosphoric and triflic acid gave only a mixture of the starting material and its isomer (Table 1, entries 1 and 2). Increasing the amount of precatalyst and the use of a weaker acid gave only traces of **2a** (entries 3 and 4). The use of triflic acid (10 mol%) with a prolonged reaction time led to formation of **2a** in a moderate yield of 38% (entry 5).

Upon screening of additional Brønsted acids, we found that a stoichiometric amount of *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) gave complete conversion into the phenol (isolated yield 73%) within 30 minutes (Table 1, entry 6). $TsOH{\cdot}H_2O$ is an attractive option owing to its bench stability, its ease of handling, and its straightforward removal through aqueous workup, after which the product **2a** was determined to be spectroscopically pure without the need for column chromatographic purification. This reaction was also demonstrated at 5 mmol scale (entry 6). A control experiment with $TsOH{\cdot}H_2O$ in the absence of the catalyst led to complete recovery of unreacted **1a** (entry 7). The precatalyst loading could be decreased to 0.5 mol% without any loss in activity (entry 8). Unfortunately, longer reaction times were deemed necessary to achieve complete conversion when 0.5 equiv of $TsOH.H_2O$ were used (entry 9), and only traces of product were detected when using 1 mol% of acid (entry 10). In addition, we examined whether a catalytic amount of acid could be used in the presence of water to promote the hydrolysis, but we found this not to be the case (entry 11). Addition of all components at the onset of the reaction resulted in 1:1 mixture of **1a** and **2a** (entry 12). Furthermore, the use of slightly weaker camphorsulfonic acid (CSA) required longer reaction times for complete conversion (entry 13).

Table 1 Optimization of the Reaction Conditions for the Ni-Catalyzed Deallylation[a]



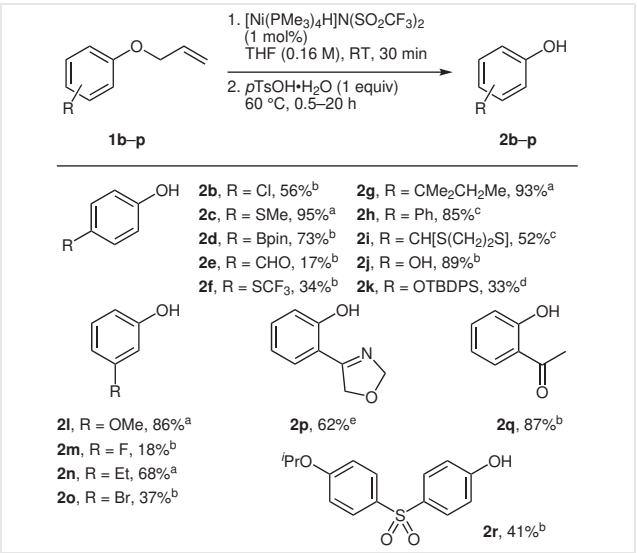
1a **2a**

Entry	Ni-H (mol%)	Acid (mol%)	Time (h)	Yield[b] (%) of **2a**
1	1	$(PhO)_2P(O)OH$ (8)	1	–[c]
2	1	$MeSO_3H$ (8)	1	–[c]
3	5	$(PhO)_2P(O)OH$ (120)	0.5	traces
4	5	$(PhO)_2P(O)OH$ (200)	0.5	traces
5[d]	2	F_3CSO_3H (10)	15	38
6	1	$TsOH{\cdot}H_2O$ (100)	0.5	73 (79)[e]
7	–	$TsOH{\cdot}H_2O$ (100)	1	-[f]
8	0.5	$TsOH{\cdot}H_2O$ (100)	1	84
9	0.5	$TsOH{\cdot}H_2O$ (50)	15	75
10	1	$TsOH{\cdot}H_2O$ (1)	1	traces
11[g]	0.5	$TsOH{\cdot}H_2O$ (10)	5	traces
12[h]	0.5	$TsOH{\cdot}H_2O$ (100)	1	(1:1)[i]
13	1	CSA (100)	5	(1:4)[i]

[a] Reaction conditions: **1a** (0.25 mmol), $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$, Brønsted acid, THF (0.16 M), 30 min, RT with Ni-H, then 60 °C for the indicated time with acid.
[b] Isolated yield.
[c] Mixture of olefin isomers (unreacted **1a** along with enol ethers).
[d] 30 min at RT with Ni-H then 15 h at RT with F_3CSO_3H.
[e] Yield at 5 mmol scale.
[f] **1a** was recovered.
[g] With H_2O (1 equiv).
[h] All reaction components were added at the start.
[i] Ratio **1a**/**2a** determined by ^1H NMR analysis.

Therefore, a system consisting of 1 mol% of Ni-H and 1 equivalent of $TsOH{\cdot}H_2O$ was chosen for further study of the transformation. With an operationally simple and straightforward protocol in hand, we proceeded to evaluate its generality through deprotection of a variety of substituted O-allylated compounds, starting with aryl allyl ethers **1b–p** (Scheme 2). First, the influence of substituents in the 3- and 4-positions of the phenyl ring was evaluated. Compounds containing electron-donating groups performed much better under the catalytic conditions than those with electron-withdrawing substituents. Ethers **1c**, **1g**, **1h**, **1l**, and **1n** were smoothly deallylated to the corresponding phenols in yields of 68–95%. Note that no column chromatographic purification was necessary to obtain phenols **2c** and **2g** in adequate purity (>95%). The boronate ester **1d** was converted in a satisfactory 73% yield, albeit with a longer reaction time of 20 hours. The 4-trifluoromethylsulfanyl ether **1f** underwent deallylation to give **2f** in 34% yield. Upon testing the halide-substituted ethers **1b**, **1m**, and **1o**, we obtained the corresponding phenols in low to moderate yields of 56,

18, and 37%, respectively. A competing dehalogenation was not observed; low yields are therefore attributable to lower reactivity in both steps. Note that the isomerization to an enol ether was more closely investigated in our previous work; although it was never complete (usually 50%), it did not impact the overall yield if both reactions were successful.

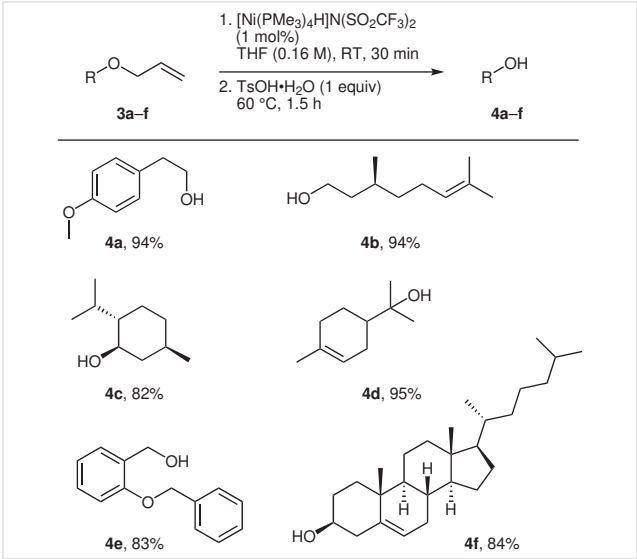


Scheme 2 Substrate scope of Ni-catalyzed deprotection of aryl allyl ethers. Reaction time for the second step: [a] 6 h, [b] 15 h, [c] 10 h, [d] 22 h [camphersulfonic acid (1 equiv)], [e] 15 h [TsOH·H_2O (2 equiv)].

Although the aldehyde **1e** displayed poor reactivity and gave **2e** in only 17% yield, its protected derivative **1i** underwent deallylation to give a 52% yield of **2i**. The allyl group could be successfully removed from the monoprotected hydroquinone **1j**. A selective allyl deprotection was observed in the presence of a *tert*-butyl(diphenyl)silyl group by using a weaker acid (CSA); however, the reaction was slow, and only a 33% yield of **2k** was obtained.

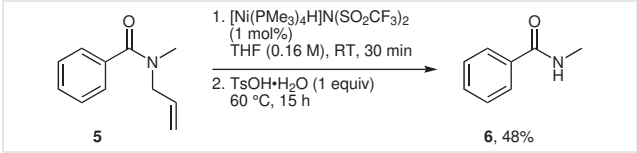
In the presence of an oxazole motif, deallylation to the phenol **2p** occurred in 62% yield; an additional equivalent of TsOH·H_2O was used in this case. In contrast to other substrates with electron-withdrawing groups, the 2-acetyl-substituted ether **1q** was converted into the product in good yield (87%). Moreover, it was found that a sulfone functionality, which is often found in biologically active compounds, can be present in the molecule, as **2r** was obtained in 41% yield.

Primary, secondary and tertiary alkyl allyl ethers **3** also underwent facile C–O bond cleavage (Scheme 3). The homobenzylic alcohol **4a**, citronellol (**4b**), (–)-menthol (**4c**), and α-terpenol (**4d**) were obtained from the corresponding allyl ethers in appreciable yields of 82–95%. Note that the allyl protecting group was removed selectively in the presence of a benzyl group in the case of **4e**. Moreover, the protected cholesterol derivative **3f** gave cholesterol (**4f**) without any racemization in 84% yield. The internal double bonds in substrates **3b**, **4d**, and **4f** did not isomerize during the transformation. It is noteworthy that, apart from **4e**, all aliphatic compounds were obtained in high yields without the need for chromatographic purification.



Scheme 3 Deallylation of alkyl allyl ethers: substrate scope

In addition, we also examined the feasibility of deallylation of amides, which has received less attention in the literature[14] despite its potential in, for example, the synthesis of immobilized DNA oligomers, where allyl groups are used to protect the nucleotide bases.[15] Employing our *O*-deallylation method, the deprotection of *N*-allylated benzamide **5** was possible and gave the corresponding product **6** in 48% yield (Scheme 4). To the best of our knowledge, there are no previous reports on the deallylation of amides by employing a nickel catalyst.



Scheme 4 Deprotection of amide **5**

In summary, we have developed a rapid and straightforward protocol for a nickel hydride catalyzed, Brønsted acid promoted deprotection of allyl ethers.[16] The transformation occurs through an initial nickel-catalyzed isomerization of the terminal double bond to the enol ether, which, in turn, is hydrolytically cleaved by the Brønsted acid. The deprotection of the allyl ether moiety occurs chemoselectively in the presence of internal double bonds and other protecting groups, such as the widely used benzyl group. The low catalyst loading along with the generality of the substrate

scope, point to the robustness of the protocol, which is suitable for both aryl and alkyl ethers. Moreover, a deprotection of an *N*-allylamide has been achieved.

Funding Information

Financial support from the German Academic Exchange Service New Delhi, the Deutscher Akademischer Austauschdienst (fellowship for P.K.), and the University of Tübingen is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706683.

References and Notes

(1) (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis, 4th ed*; Wiley-Interscience: Hoboken, **2006**, 16. (b) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833.
(2) Guibé, F. *Tetrahedron* **1997**, *53*, 13509.
(3) (a) Kitov, P. I.; Bundle, D. R. *Org. Lett.* **2001**, *3*, 2835. (b) Bailey, W. F.; England, M. D.; Mealy, M. J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* **2000**, *2*, 489. (c) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603. (d) Atienza, B. J. P.; Truong, N.; Williams, F. J. *Org. Lett.* **2018**, *20*, 6332.
(4) (a) Walia, M.; Teijaro, C. N.; Gardner, A.; Tran, T.; Kang, J.; Zhao, S.; O'Connor, S. E.; Courdavault, V.; Andrade, R. B. *J. Nat. Prod.* **2020**, *83*, 2425. (b) Liu, Z.; Meng, Y.; Yuan, P.; Wang, Z.; Gao, J.-M.; Zheng, H. *Org. Lett.* **2020**, *22*, 520. (c) Praveen Kumar, V.; Kishi, Y. *J. Am. Chem. Soc.* **2020**, *142*, 14743.
(5) (a) Gärtner, D.; Konnerth, H.; von Wangelin, A. J. *Catal. Sci. Technol.* **2013**, *3*, 2541. (b) Tanaka, S.; Suzuki, Y.; Saburi, H.; Kitamura, M. *Tetrahedron* **2015**, *71*, 6559. (c) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, *68*, 1146. (d) Taniguchi, T.; Ogasawara, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 1136. (e) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932. (f) Mao, Y.; Liu, Y.; Hu, Y.; Wang, L.; Zhang, S.; Wang, W. *ACS Catal.* **2018**, *8*, 3016. (g) Hemming, D. S.; Talbot, E. P.; Steel, P. G. *Tetrahedron Lett.* **2017**, *58*, 17. (h) Chouhan, M.; Kumar, K.; Sharma, R.; Grover, V.; Nair, V. A. *Tetrahedron Lett.* **2013**, *54*, 4540. (i) Giedyk, M.; Turkowska, J.; Lepak, S.; Marculewicz, M.; ó Proinsias, K.; Gryko, D. *Org. Lett.* **2017**, *19*, 2670. (j) Meng, C.; Niu, H.; Ning, J.; Wu, W.; Yi, J. *Molecules* **2020**, *25*, 602.
(6) (a) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (c) Varela-Álvarez, A.; Sordo, J. A.; Piedra, E.; Nebra, N.; Cadierno, V.; Gimeno, J. *Chem. Eur. J.* **2011**, *17*, 10583.
(7) (a) Huang, G.; Ke, M.; Tao, Y.; Chen, F. *J. Org. Chem.* **2020**, *85*, 5321; corrigendum: J. Org. Chem.; 2020, 85, 6830. (b) Gao, W.; Zhang, X.; Xie, X.; Ding, S. *Chem. Commun.* **2020**, *56*, 2012. (c) Trost, B. M.; Cregg, J. J.; Quach, N. *J. Am. Chem. Soc.* **2017**, *139*, 5133. (d) Bolyog-Nagy, E.; Udvardy, A.; Barczáné-Bertók, A.; Joó, F.; Kathó, A. *Inorg. Chim. Acta* **2017**, *455*, 514. (e) Li, H.; Mazet, C. *J. Am. Chem. Soc.* **2015**, *137*, 10720. (f) Erbing, E.; Vázquez-Romero, A.; Bermejo Gómez, A.; Platero-Prats, A. E.; Carson, F.; Zou, X.; Tolstoy, P.; Martín-Matute, B. *Chem. Eur. J.* **2016**, *22*, 15659.
(8) Ghosh, B.; Kulkarni, S. S. *Chem. Asian J.* **2020**, *15*, 450.
(9) Ikeuchi, K.; Murasawa, K.; Ohara, K.; Yamada, H. *Org. Lett.* **2019**, *21*, 6638.
(10) Kathe, P. M.; Caciuleanu, A.; Berkefeld, A.; Fleischer, I. *J. Org. Chem.* **2020**, *85*, 15183.
(11) Kathe, P. M.; Fleischer, I. *Org. Lett.* **2019**, *21*, 2213.
(12) (a) Gehrtz, P. H.; Geiger, V.; Schmidt, T.; Sršan, L.; Fleischer, I. *Org. Lett.* **2019**, *21*, 50. (b) Gehrtz, P. H.; Kathe, P.; Fleischer, I. *Chem. Eur. J.* **2018**, *24*, 8774.
(13) (a) Neary, M. C.; Quinlivan, P. J.; Parkin, G. *Inorg. Chem.* **2018**, *57*, 374. (b) Koch, F.; Berkefeld, A. *Dalton Trans.* **2018**, *47*, 10561. (c) Tolman, C. A. *Inorg. Chem.* **1972**, *11*, 3128.
(14) (a) Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem.* **2008**, *2008*, 5042. (b) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298. (c) Kamijo, S.; Huo, Z.; Jin, T.; Kanazawa, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 6389. (d) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.
(15) Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691.
(16) **2-Methoxyphenol (2a): Typical Procedure**
In a glove box, a flame-dried 15 mL Schlenk tube was charged with $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ (1.6 mg, 2.48 μmol, 1 mol%). The Schlenk tube was removed from the glove box and anhyd THF (1.5 mL, 0.16 M) was added. 1-(Allyloxy)-2-methoxybenzene (**1a**; 41.1 mg, 0.250 mmol, 1 equiv) was then added under an argon counterflow and the mixture was stirred at RT for 30 min. $TsOH{\cdot}H_2O$ (1 equiv) was added, and the mixture was refluxed for 1 h. The reaction was quenched by addition of EtOAc (2 mL) and H_2O (2 mL), and the mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were dried ($MgSO_4$). Rotary evaporation gave pure **2a**, without any chromatographic purification, as a light-brown oil; yield: 26.1 mg (0.21 mmol, 84%). The NMR spectral data matched those reported in the literature.[17] **Note:** The glove box setup for the reaction is not necessary: the catalyst can be stored on the bench under an inert atmosphere.
(17) Song, L. X.; Wang, H. M.; Yang, Y.; Xu, P. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2185.

Synlett

Accounts and Rapid Communications in Chemical Synthesis

Supporting Information

for DOI: 10.1055/s-0040-1706683

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Thieme

SUPPORTING INFORMATION

Nickel Hydride-Catalyzed Cleavage of Allyl Ethers Induced by Isomerization

P. M. Kathe, A. Berkefeld*, I. Fleischer*

Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

* ivana.fleischer@uni-tuebingen.de
* andreas.berkefeld@uni-tuebingen.de

Contents

1. GENERAL INFORMATION

1.1. Chemicals/Solvents

Both phenols and alcohols were obtained from ABCR, Alfa Aesar, Acros Organics, Sigma Aldrich, ChemPur and used without further purification. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF) and dichloromethane (DCM) were purchased as dry septum sealed flasks from Acros Organics and used as received. p-Toluenesulfonic acid monohydrate was obtained from Sigma Aldrich. The complex $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ was synthesized according to procedure reported in the literature.[1]

1.2. Chromatography

Column chromatography was carried out using silica gel (60 Å) as stationary phase, either using gravity flow conditions under isocratic elution or flash column chromatography under gradient elution. Gradients were set up depending on the solvent ratios found ideal via thin layer chromatography (TLC). CV stands for column volume in this case (25 mL).

TLC was performed with aluminum plates coated with silica gel 60 F254 (layer thickness: 0.2 mm) and analyzed under UV-light (254 nm) or stained with a potassium permanganate solution.

Gas Chromatography (GC-FID) analysis was carried out on a HP6890 GC-System with injector 7683B and Agilent 7820A system. Dry hydrogen was used as the carrier gas, for the measurements the following method was used: Heating from 50 °C to 280 °C within 15 minutes.

Gas Chromatography-Mass Spectrometry was performed on an Agilent 7820A GC system in combination with an Agilent 5977 B using an EI source and a quadrupole analyzer. Samples were diluted in organic solvent and passed through aluminum oxide prior to GC-MS analysis. For all analyses, the following method was used: Heating from 50 °C to 280 °C within 15 minutes.

1.3. Analytical Techniques

NMR spectra were recorded using a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometers at ambient temperature. Chemical shifts are reported in parts per million relative to the residual ^{1}H and natural abundance ^{13}C NMR resonances of deuterated solvents. ^{1}H/^{13}C{^{1}H} NMR resonances of the solvents: $CDCl_3$, $\delta_{H/C}$=7.26/77.0; THF-d_8, $\delta_{H/C}$=3.58,1.78/67.6. Coupling constants J are given in Hertz [Hz]. ^{1}H NMR multiplet patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet.

Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer, equipped with an ATR system. Absorption bands are given in wave numbers $\tilde{\nu}$ (cm^{-1}).

HR-MS (ESI, APCI, EI) analysis was carried out by the mass spectrometry department (Instrument: Agilent MSD 5977) of the Institute of Organic Chemistry, University of Tübingen.

1.4. General Procedures

Procedure A: Synthesis of O-allylated substrates from phenols

The respective phenol (1 equiv) was added to a round bottom flask equipped with a stir bar and a reflux condenser. This was followed by addition of acetone (0.2 M) to dissolve the phenol and addition of K_2CO_3 (4 equiv) and allyl bromide (2 equiv) in a single portion. The reaction mixture was heated to reflux until completion as monitored by TLC. After cooling to room temperature, ethyl acetate and H_2O were added to the reaction mixture to dissolve any precipitate, and the reaction mixture transferred to a separating funnel. The aqueous phase was extracted with ethyl acetate (3×). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give the crude O-allylated substrate. Purification by column chromatography gave the product.

Procedure B: Synthesis of O-allylated substrates from alcohols

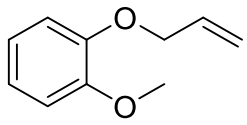
The aliphatic alcohol (1 equiv) was added to a flame-dried round bottom Schlenk flask equipped with a stir bar and dissolved in dry DMF (0.75 M). The reaction mixture was cooled to 0 °C in an ice-bath, followed by portion-wise addition of sodium hydride (3 equiv, 60% oil dispersion) after which the reaction mixture was stirred for 10 minutes. Then, allyl bromide (1.5 equiv) was added dropwise to the reaction mixture that was allowed to warm room temperature and stirred until completion. The reaction was finally quenched by the slow addition of aq. NH_4Cl, diluted with water and ethyl acetate and then transferred to a separating funnel. The aqueous phase was extracted with ethyl acetate (3×), the combined organic phases dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product. Purification by column chromatography or bulb-to-bulb distillation afforded the product.

Procedure C: Catalysis

Inside a glovebox, a flame-dried 15 mL Schlenk tube was charged with $[Ni(PMe_3)_4H](SO_2CF_3)_2N$ (1.6 mg, 2.48 µmol, 1 mol-%), and dry THF was added (0.16 M, 1.5 mL) using a Schlenk line. The O-allyl ether (0.25 mmol, 1 equiv) was then added under argon counter-flow. The reaction mixture was allowed to stir at room temperature for 30 minutes. This was followed by addition of *p*TsOH·H_2O (1 equiv) and the reaction mixture was then heated to reflux for the time specified. The reaction was quenched by addition of ethyl acetate and water followed by transfer to a separating funnel. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were then dried over $MgSO_4$ and dried by rotary evaporation to give the crude alcohol, which was finally purified by column chromatography on silica gel.

2. ANALYTICAL DATA: REACTANTS

1-(Allyloxy)-2-methoxybenzene (**1a**)



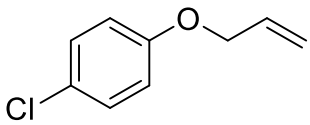
Compound **1a** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 95/5), affording a colorless oil (1.98 g, 12.1 mmol, 85%). The spectral data match those reported in the literature .[2]

R_f: n-hexane/EtOAc (95/5) = 0.3

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.86 (m, 4H), 6.16 – 6.02 (m, 1H), 5.41 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.28 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.62 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.88 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.4, 148.0, 133.4, 121.2, 120.7, 117.9, 113.5, 111.7, 69.8, 55.8.

1-(Allyloxy)-4-chlorobenzene (**1b**)



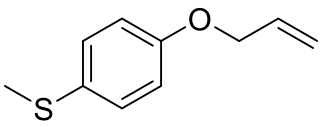
Compound **1b** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (539 mg, 3.20 mmol, 80%). The spectral data match those reported in the literature.[3]

R_f: n-hexane/EtOAc (99/1) = 0.55

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 2H), 6.88 – 6.80 (m, 2H), 6.10 – 5.97 (m, 1H), 5.45 – 5.37 (m, 1H), 5.33 – 5.27 (m, 1H), 4.51 (dt, *J* = 5.3, 1.5 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 132.9, 129.3, 125.6, 117.9, 116.0, 69.0.

(4-(Allyloxy)phenyl)(methyl)sulfane (**1c**)



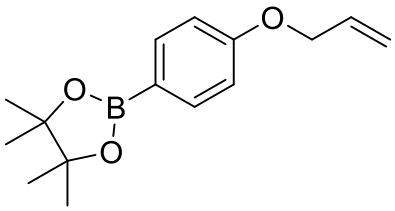
Compound **1c** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (738 mg, 4.10 mmol, 82%).

R_f: n-hexane/EtOAc (99/1) = 0.3

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H), 6.91 – 6.81 (m, 2H), 6.12 – 5.97 (m, 1H), 5.46 – 5.36 (m, 1H), 5.33 – 5.25 (m, 1H), 4.52 (dt, *J* = 5.3, 1.5 Hz, 2H), 2.45 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 133.1, 130.0, 128.9, 117.7, 115.4, 68.9, 17.9.

2-(4-(Allyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1d**)



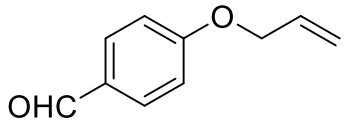
Compound **1d** was synthesized following general procedure B. It was obtained as a white solid (686.76 mg, 2.64 mmol, 88%) and is of sufficient purity for subsequent reactions. The spectral data match those reported in the literature.[4]

R_f: n-hexane/Et_2O (9/1) = 0.55

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H), 6.95 – 6.87 (m, 2H), 6.15 – 5.96 (m, 1H), 5.48 – 5.34 (m, 1H), 5.34 – 5.23 (m, 1H), 4.56 (dt, *J* = 5.3, 1.5 Hz, 2H), 1.33 (s, 12H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.1, 136.4, 133.0, 117.7, 114.0, 83.5, 68.5, 24.8.

4-(Allyloxy)benzaldehyde (**1e**)



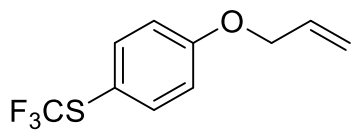
Compound **1e** was synthesized following general procedure A and was purified by column chromatography (n-hexane/EtOAc: 95/5), affording a colorless oil (689 mg, 4.25 mmol, 85%). The spectral data match those reported in the literature.[5]

R_f: n-hexane/Et_2O (90/10) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.86 – 7.79 (m, 2H), 7.05 – 6.95 (m, 2H), 6.14 – 5.97 (m, 1H), 5.50 – 5.37 (m, 1H), 5.37 – 5.29 (m, 1H), 4.62 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.8, 163.6, 132.2, 131.9, 130.0, 118.3, 115.0, 69.0.

(4-(Allyloxy)phenyl)(trifluoromethyl)sulfane (**1f**)



Compound **1f** was synthesized following general procedure A and was purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (655 mg, 2.8 mmol, 70%).

R_f: n-hexane/EtOAc (99/1) = 0.65

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H), 6.98 – 6.90 (m, 2H), 6.12 – 5.97 (m, 1H), 5.48 – 5.37 (m, 1H), 5.37 – 5.28 (m, 1H), 4.57 (dt, *J* = 5.3, 1.5 Hz, 2H).

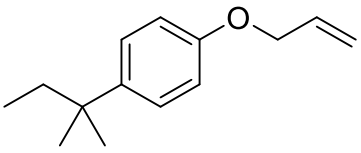
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.8, 138.2, 132.5, 129.6 (q, $^1J_{C\text{-}F}$ = 308.1 Hz), 118.2, 115.7, 114.9 (q, $^4J_{C\text{-}F}$ = 2.1 Hz), 68.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -43.89.

HR-MS (EI): calc. for $[M+H]^+$ m/z: 234.032071, found 234.03349.

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2988, 2937, 1591, 1490, 1289, 1248, 1107, 1017, 924, 827.

1-(Allyloxy)-4-(tert-pentyl)benzene (**1g**)



Compound **1g** was synthesized following general procedure A and was purified by column chromatography (n-hexane/EtOAc: 99.5/0.5), affording a colorless oil (743.6 mg, 3.63 mmol, 91%).

R_f: n-hexane/EtOAc (99.5/0.5) = 0.5

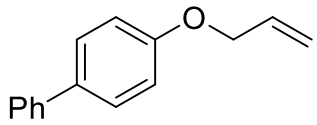
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 2H), 6.90 – 6.83 (m, 2H), 6.07 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.42 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.28 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.53 (dt, *J* = 5.3, 1.5 Hz, 2H), 1.62 (q, *J* = 7.4 Hz, 2H), 1.26 (s, 6H), 0.68 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 141.7, 133.6, 126.8, 117.5, 114.0, 68.8, 37.2, 36.9, 28.6, 9.1.

HR-MS (EI): calc. for $[M+H]^+$ m/z: 204.150866, found 204.15164.

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2963, 2873, 1610, 1509, 1461, 1289, 1244, 1185, 1118, 1025, 998, 924, 827, 778.

4-(Allyloxy)-1,1'-biphenyl (**1h**)



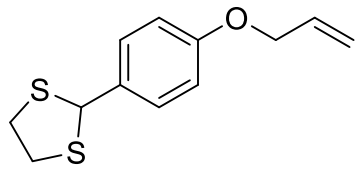
Compound **1h** was synthesized following general procedure A. and was obtained as a colorless oil after rotary evaporation of combined organic phases (681 mg, 3.24 mmol, 81%), requiring no additional purification. NMR spectral data match those reported in the literature.[6]

R_f: n-hexane/Et_2O (90/10) = 0.8

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 4H), 7.47 – 7.38 (m, 2H), 7.35 – 7.27 (m, 1H), 7.00 (d, *J* = 6.6 Hz, 2H), 6.17 – 6.02 (m, 1H), 5.51 – 5.40 (m, 1H), 5.37 – 5.27 (m, 1H), 4.63 – 4.56 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.1, 140.8, 133.9, 133.2, 128.7, 128.1, 126.7, 126.6, 117.7, 115.0, 68.9.

2-(4-(Allyloxy)phenyl)-1,3-dithiolane (**1i**)



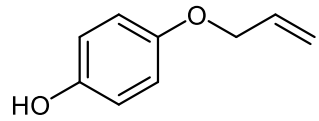
Compound **1i** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (743.6 mg, 3.12 mmol, 78%). NMR spectral data match those reported in the literature.[7]

R_f: n-hexane/Et_2O (97/3) = 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 6.90 – 6.82 (m, 2H), 6.12 – 5.97 (m, 1H), 5.63 (s, 1H), 5.46 – 5.36 (m, 1H), 5.33 – 5.25 (m, 1H), 4.56 – 4.49 (m, 2H), 3.56 – 3.44 (m, 2H), 3.41 – 3.29 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.4, 133.1, 131.9, 129.1, 117.7, 114.6, 68.8, 56.0, 40.2.

4-(allyloxy)phenol (**1j**)



Compound **1j** was synthesized from hydroquinone (2.00 g, 18.2 mmol, 4 equiv) and allyl bromide (394 µL, 4.56 mmol, 1 equiv) following the procedure reported in the literature.[8] Purification by column chromatography (n-hexane/EtOAc: 85/15) provided the compound as a light red solid. (455 mg, 3.0 mmol, 66 %). NMR spectral data match those reported in the literature.

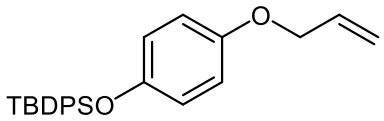
R_f: n-hexane/EtOAc: 85/15 = 0.22

m.p = 40-42 °C

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 6.85 – 6.73 (m, 4H), 6.12 – 5.97 (m, 1H), 5.45 – 5.35 (m, 1H), 5.32 – 5.23 (m, 1H), 4.48 (dt, *J* = 5.4, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 149.6, 133.5, 117.7, 116.09, 116.02, 69.7

(4-(allyloxy)phenoxy)(tert-butyl)diphenylsilane (**1k**)



Compound **1k** was synthesized from 4-(allyloxy)phenol (350 mg, 2.33 mmol, 1 equiv) and (tert-butyl)diphenylsilyl chloride (606 µL, 2.33 mmol, 1 equiv) following the procedure reported in the literature.[9] Purification by column chromatography (n-hexane/EtOAc: 97/3) provided the compound as a white solid. (653 mg, 1.68 mmol, 72%).

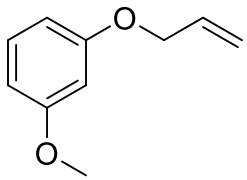
R_f: n-hexane/EtOAc (95/5) = 0.55

m.p = 84-86 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 4H), 7.48 – 7.32 (m, 6H), 6.72 – 6.61 (m, 4H), 6.09 – 5.93 (m, 1H), 5.36 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.24 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.41 (dt, *J* = 5.4, 1.5 Hz, 2H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 149.5, 135.5, 133.6, 133.1, 129.8, 127.7, 120.1, 117.4, 115.2, 69.3, 26.5, 19.4.

1-(Allyloxy)-3-methoxybenzene (**1l**)



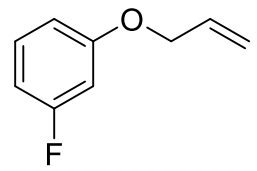
Compound **1l** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (554 mg, 3.36 mmol, 84%). NMR spectral data match those reported in the literature.[10]

R_f: n-hexane/EtOAc (90/10) = 0.71

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 1H), 6.56 – 6.48 (m, 3H), 6.13 – 6.00 (m, 1H), 5.47 – 5.38 (m, 1H), 5.32 – 5.26 (m, 1H), 4.55 – 4.49 (m, 2H), 3.79 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.8, 159.8, 133.2, 129.8, 117.7, 106.8, 106.4, 101.2, 68.8, 55.2.

1-(Allyloxy)-3-fluorobenzene (**1m**)



Compound **1m** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 95/5), affording a colorless oil (479 mg, 3.11 mmol, 74%).

R_f: n-hexane/EtOAc (99/1) = 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 1H), 6.74 – 6.60 (m, 3H), 6.11 – 5.98 (m, 1H), 5.46 – 5.37 (m, 1H), 5.35 – 5.28 (m, 1H), 4.56 – 4.49 (m, 2H).

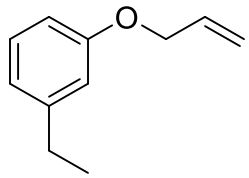
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 159.3 (d, $^3J_{C\text{-}F}$ = 10.8 Hz), 132.7 , 130.1 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 117.9 , 110.5 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 107.6 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 102.4 (d, $^2J_{C\text{-}F}$ = 24.9 Hz), 69.0.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -111.78.

GC-MS (EI) m/z: 152.0 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 2985, 2918, 2870, 1610, 1487, 1263, 1166, 1133, 1025, 831, 760, 678

1-(Allyloxy)-3-ethylbenzene (**1n**)



Compound **1n** was synthesized following general procedure A andpurified by column chromatography (n-hexane/EtOAc: 98/2), affording a colorless oil (460.7 mg, 2.84 mmol, 71%).

R_f: n-hexane/EtOAc (98/2) = 0.68

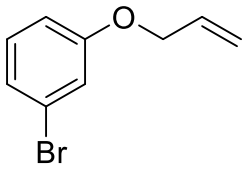
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.18 (m, 1H), 6.85 – 6.70 (m, 3H), 6.15 – 6.00 (m, 1H), 5.49 – 5.38 (m, 1H), 5.33 – 5.25 (m, 1H), 4.54 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.63 (q, *J* = 7.7 Hz, 2H), 1.24 (t, *J* = 7.7 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6, 145.9, 133.4, 129.2, 120.4, 117.5, 114.5, 111.6, 28.9, 15.5.

GC-MS (EI) m/z: 162.1 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3030, 2967, 2929, 2870, 1580, 1487, 1446, 1254, 1155, 1028, 924, 872, 773, 693.

1-(Allyloxy)-3-bromobenzene (**1o**)



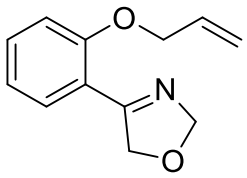
Compound **1o** was synthesized following general procedure A and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (799 mg, 3.75 mmol, 75%). NMR spectral data match those reported in the literature.[11]

R_f: n-hexane/EtOAc (99/1) = 0.4

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 – 7.05 (m, 3H), 6.90 – 6.82 (m, 1H), 6.13 – 5.94 (m, 1H), 5.47 – 5.37 (m, 1H), 5.35 – 5.27 (m, 1H), 4.56 – 4.48 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.3, 132.7, 130.5, 123.9, 122.7, 117.9, 113.7, 68.9.

4-(2-(Allyloxy)phenyl)-2,5-dihydrooxazol (**1p**)



Compound **1p** was synthesized following general procedure A and purified by column chromatography (n-hexane/Et_2O : 90/10), affording a colorless oil (792 mg, 3.89 mmol, 78%).

R_f: n-hexane/EtOAc (90/10) = 0.18

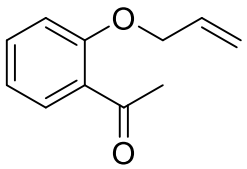
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 1.8 Hz, 1H), 8.00 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.08 (td, *J* = 7.6, 1.0 Hz, 1H), 7.03 – 6.96 (m, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.20 – 6.05 (m, 1H), 5.45 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.35 (dq, *J* = 17.3, 1.5 Hz, 1H), 4.68 (dt, *J* = 5.5, 1.4 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.3, 155.2, 150.9, 132.6, 131.1, 127.9, 121.0, 118.6, 116.5, 112.4, 102.8, 69.4.

GC-MS (EI) m/z: 201.1 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3172, 2981, 3078, 2822, 2870, 1606, 1464, 1494, 1278, 1244, 1129, 916, 797, 752, 678

1-(2-(Allyloxy)phenyl)ethan-1-one (**1q**)



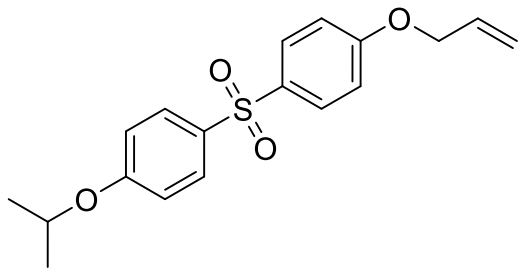
Compound **1q** was synthesized following general procedure A and purified by column chromatography (n-hexane/Et_2O : 90/10), affording a colorless oil (472.2 mg, 2.68 mmol, 67%). NMR spectral data match those reported in the literature.[12]

R_f: n-hexane/Et_2O (90/10) = 0.21

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.04 – 6.91 (m, 2H), 6.15 – 6.01 (m, 1H), 5.49 – 5.39 (m, 1H), 5.36 – 5.28 (m, 1H), 4.64 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.64 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.9, 157.9, 133.5, 132.6, 130.4, 128.6, 120.7, 118.2, 112.7, 69.3, 32.0.

1-(Allyloxy)-4-((4-isopropoxyphenyl)sulfonyl)benzene (**1r**)



Compound **1r** was synthesized following general procedure A and was obtained as a white solid after rotary evaporation of combined organic phase (722.9 mg, 2.17 mmol, 87%), requiring no additional purification.

m.p: 114-116 °C

R_f: n-hexane/EtOAc (75/25): 0.4

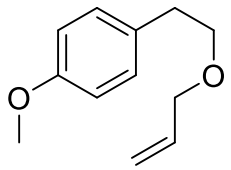
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 4H), 7.01 – 6.85 (m, 4H), 6.09 – 5.92 (m, 2H), 5.46 – 5.34 (m, 1H), 5.34 – 5.24 (m, 1H), 4.63 – 4.50 (m, 3H), 1.33 (d, *J* = 6.1 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0, 161.6, 134.1, 133.2, 132.1, 129.5, 118.4, 115.6, 115.0, 70.3, 69.0, 21.8.

HR-MS (ESI): calc. for $[M+H]^+$ m/z: 333.11551, found 333.11590.

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3093, 2933, 2978, 2873, 1587, 1490, 1252, 1140, 1293, 1103, 950, 991, 838, 723.

1-(2-(Allyloxy)ethyl)-4-methoxybenzene (**3a**)



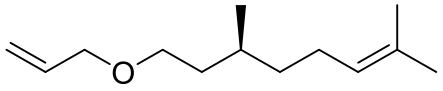
Compound **3a** was synthesized following general procedure B and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a colorless oil (634 mg, 3.26 mmol, 66%). NMR spectral data match those reported in the literature.[13]

R_f: n-hexane/Et_2O (90/10) = 0.35

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 6.5 Hz, 2H), 6.84 (d, *J* = 6.5 Hz, 2H), 5.99 – 5.84 (m, 1H), 5.31 – 5.22 (m, 1H), 5.20 – 5.14 (m, 1H), 4.03 – 3.95 (m, 2H), 3.79 (s, 3H), 3.62 (t, *J* = 7.3 Hz, 2H), 2.85 (t, *J* = 7.3 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.0, 134.8, 130.9, 129.8, 116.8, 113.7, 71.8, 71.5, 55.2, 35.4.

(S)-8-(Allyloxy)-2,6-dimethyloct-2-ene (**3b**)



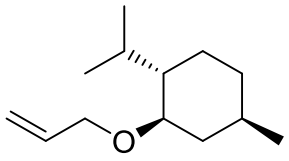
Compound **3b** was synthesized following general procedure B and purified by bulb-to-bulb distillation (*P* = 5 mbar, *T* = 125 °C), affording a colorless oil (845 mg, 4.3 mmol, 86%). NMR spectral data match those reported in the literature.[14]

R_f: n-hexane/EtOAc (99.5/0.5) = 0.2 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.85 (m, 1H), 5.32 – 5.06 (m, 3H), 4.01 – 3.92 (m, 2H), 3.51 – 3.39 (m, 2H), 2.07 – 1.89 (m, 2H), 1.67 (s, 3H), 1.66 – 1.62 (m, 1H), 1.60 (s, 3H), 1.58 – 1.52 (m, 1H), 1.45 – 1.28 (m, 2H), 1.20 – 1.11 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.1, 131.1, 124.8, 116.7, 71.8, 68.7, 37.2, 36.7, 29.5, 25.7, 25.4, 19.5, 17.6.

(1S,2R,4R)-2-(Allyloxy)-1-isopropyl-4-methylcyclohexane (**3c**)



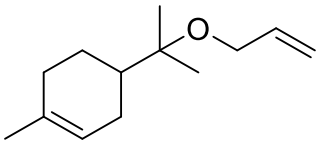
Compound **3c** was synthesized following general procedure B and was obtained as a colorless oil after rotary evaporation of combined organic phases (669 mg, 3.40 mmol, 85%), requiring no additional purification. NMR spectral data match those reported in the literature.[15]

R_f: n-hexane/EtOAc (99.5/0.5) = 0.2 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.85 (m, 1H), 5.32 – 5.22 (m, 1H), 5.18 – 5.09 (m, 1H), 4.19 – 4.07 (m, 1H), 3.96 – 3.81 (m, 1H), 3.08 (td, *J* = 10.6, 4.2 Hz, 1H), 2.31 – 2.18 (m, 1H), 2.09 (ddd, *J* = 12.2, 6.7, 2.9 Hz, 1H), 1.69 – 1.56 (m, 2H), 1.33 – 1.18 (m, 3H), 0.95 – 0.86 (m, 8H), 0.77 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.7, 116.3, 78.7, 69.5, 48.2, 40.5, 34.5, 31.5, 25.5, 23.3, 22.3, 21.0, 16.2.

4-(2-(Allyloxy)propan-2-yl)-1-methylcyclohex-1-ene (**3d**)



Compound **3d** was synthesized following general procedure B and purified by column chromatography (n-hexane/EtOAc: 99.5/0.5), affording and obtained as a colorless oil (718.9 mg, 3.7 mmol, 74%).

R_f: n-hexane/EtOAc (99.5/0.5) = 0.42 (stained with $KMnO_4$)

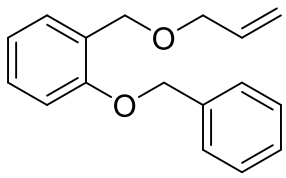
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 – 5.76 (m, 1H), 5.37 – 5.29 (m, 1H), 5.25 – 5.14 (m, 1H), 5.08 – 4.98 (m, 1H), 3.86 – 3.78 (m, 2H), 2.00 – 1.84 (m, 3H), 1.83 – 1.65 (m, 2H), 1.58 (s, 3H), 1.29 – 1.12 (m, 1H), 1.07 (s, 3H), 1.06 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.37, 134.0, 120.9, 115.2, 62.1, 42.0, 31.1, 26.8, 24.0, 23.3, 22.9, 22.5.

GC-MS (EI) m/z: 136.1 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 2967, 2922, 1438, 1379, 1244, 1140, 1066, 991, 916, 767.

1-((Allyloxy)methyl)-2-(benzyloxy)benzene (**3e**)



Compound **3e** was synthesized following general procedure B and purified by column chromatography (n-hexane/EtOAc: 97/3), affording a colorless oil (1.1 g, 4.3 mmol, 74.5%).

R_f: n-hexane/EtOAc (97/3) = 0.24

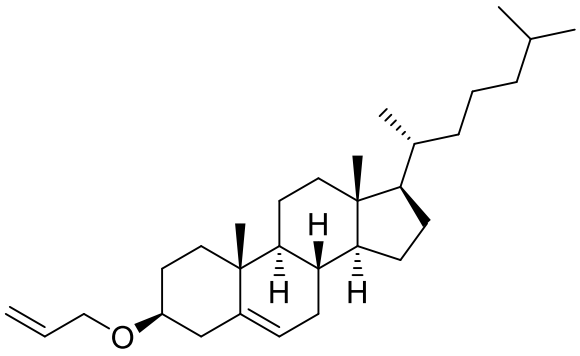
^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, Chloroform-d) δ 7.48 – 7.36 (m, 4H), 7.39 – 7.28 (m, 2H), 7.26 (s, 1H), 7.03 – 6.87 (m, 2H), 6.07 – 5.87 (m, 1H), 5.38 – 5.24 (m, 1H), 5.23 – 5.12 (m, 1H), 5.09 (s, 2H), 4.63 (s, 2H), 4.13 – 4.03 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.2, 137.2, 135.0, 128.9, 128.5, 128.5, 127.8, 127.3, 127.2, 120.8, 116.8, 111.7, 71.5, 70.0, 67.1.

GC-MS (EI) m/z: 254.1 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 3034, 2922, 2855, 1587, 1453, 1285, 1237, 1118, 1080, 920, 749, 693.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-(Allyloxy)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (**3f**)



Compound **3f** was synthesized following general procedure B and purified by column chromatography (DCM/MeOH: 99/1), affording a white solid (360 mg, 0.84 mmol, 65.4%). NMR spectral data match those reported in the literature.[13]

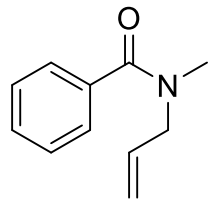
R_f: DCM/MeOH (99.5/0.5) = 0.55 ($KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 – 5.76 (m, 1H), 5.27 (q, *J* = 2.8, 2.0 Hz, 1H), 5.26 – 5.14 (m, 1H), 5.13 – 5.03 (m, 1H), 3.95 (dd, *J* = 5.6, 2.9 Hz, 2H), 3.22 – 3.04 (m, 1H), 2.37 – 2.24 (m, 1H), 2.23 – 2.07 (m, 1H),

2.01 – 1.68 (m, 5H), 1.56 – 1.32 (m, 7H), 1.30 – 1.12 (m, 7H), 1.13 – 0.97 (m, 6H), 0.93 (s, 5H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.79 (dd, *J* = 6.6, 1.3 Hz, 6H), 0.61 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 140.9, 135.4, 121.5, 116.4, 78.5, 69.0, 56.8, 56.1, 50.2, 42.3, 39.8, 39.5, 39.1, 37.2, 36.9, 36.2, 35.8, 31.9, 31.9, 28.4, 28.2, 28.0, 24.3, 23.8, 22.8, 21.0, 19.3, 18.7, 11.8.

N-Allyl-N-methylbenzamide (**5**)



Compound **5** was synthesized following general procedure B and was purified by column chromatography (n-hexane/EtOAc: 65/35), affording a colorless oil (723 mg, 4.12 mmol, 82.5%). NMR spectral data match those reported in the literature.[16] Note that the presence of rotamers of the unsymmetrical amide results in broad peaks with no defined splitting in ^{1}H NMR spectra at ambient temperature.

R_f: n-hexane/EtOAc (65/35) = 0.52

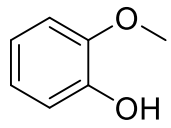
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 5H), 5.98 – 5.63 (m, 1H), 5.33 – 5.11 (m, 2H), 4.20 – 4.06 (m, 1H), 3.84 (s, 1H), 3.05 and 2.91 (2×s, 3H, rotamers).

GC-MS (EI) m/z: 175.1 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 2922, 1628, 1446, 1394, 1289, 1259, 1066, 790, 700, 603.

3. ANALYTICAL DATA: PRODUCTS

2-Methoxyphenol (**2a**)



Compound **2a** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min). The product was obtained as a light brown oil (26.1 mg, 0.21 mmol, 84 %) and was not further purified. NMR spectral data match those reported in the literature.[17]

Procedure at 4.9 mmol scale: Inside a glovebox, a flame-dried 100 mL Schlenk round bottom flask was charged with $[Ni(PMe_3)_4H]N(SO_2CF_3)_2$ (31 mg, 0.048 mmol, 1 mol-%), and dry THF was added (30 mL) using a Schlenk line. This was followed by addition of **1a (**800 mg, 4.87 mmol) under Ar counterflow. The reaction mixture was allowed to stir at room temperature for 30 min followed by addition of pTSA.H_2O

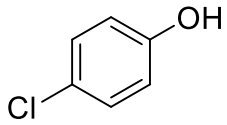
(842 mg, 4.87 mmol, 1 equiv). A reflux condenser was then attached to the reaction vessel and the temperature was raised to 60 °C and stirred for 1 h. The reaction progress was monitored by TLC. The reaction mixture was then allowed to cool down to room temperature, followed by addition of 20 mL of ethyl acetate and 20 mL of H_2O. The mixture was transferred to a separating funnel. The phases were separated and the organic phase was washed with 15 mL H_2O. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with 10 mL brine and dried over $MgSO_4$. Rotary evaporation of the solvent provided the product as a brown oil (474 mg, 3.82 mmol, 79%).

R_f: n-hexane/Et_2O (90/10) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 – 6.92 (m, 1H), 6.92 – 6.83 (m, 3H), 5.65 (s, 1H), 3.89 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.5, 145.6, 121.4, 120.1, 114.5, 110.7, 55.8.

4-Chlorophenol (**2b**)



Compound **2b** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 90/10), affording a white solid (18 mg, 0.14 mmol, 56 %). NMR spectral data match those reported in the literature.[18]

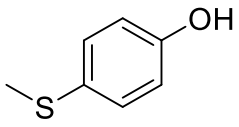
m.p = 39-41 °C

R_f: n-hexane/EtOAc (90/10) = 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 6.81 – 6.73 (m, 2H), 4.87 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.0, 129.5, 125.6, 116.6.

4-(Methylthio)phenol (**2c**)



Compound **2c** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 6 h) and isolated as a light brown solid (33.2 mg, 0.23 mmol, 95 %). NMR spectral data match those reported in the literature.[19]

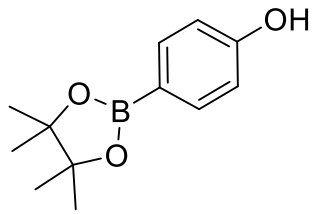
m.p = 82-84 °C

R_f: n-hexane/EtOAc (90/10) = 0.3

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 2H), 6.84 – 6.73 (m, 2H), 4.74 (s, 1H), 2.44 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.0, 130.4, 128.8, 116.1, 18.0.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**2d**)



Compound **2d** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by flash column chromatography (12 g SiO_2, static elution, n-hexane/EtOAc: 80/20), affording a white solid (40 mg, 0.18 mmol, 73 %). NMR spectral data match those reported in the literature.[20]

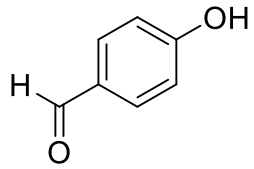
m.p = 104-106 °C

R_f: n-hexane/EtOAc (80/20) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 6.84- 6.80 (m, 2H), 1.34 (s, 12H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.4, 136.8, 114.8, 83.7, 24.8.

4-Hydroxybenzaldehyde (**2e**)



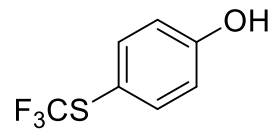
Compound **2e** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by flash column chromatography (12 g SiO_2, static elution, n-hexane/EtOAc: 65/35), affording a white solid (5 mg, 0.04 mmol, 17 %). NMR spectral data match those reported in the literature.[21]

R_f: n-hexane/EtOAc (65/35) = 0.2

^{1}H NMR (400 MHz, Chloroform-d) δ 9.78 (s, 1H), 9.25 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.7, 166.7, 135.2, 133.1, 119.1.

4-((trifluoromethyl)thio)phenol (**2f**)



Compound **2f** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by flash column chromatography (12 g SiO_2, static elution, 4 CV with n-hexane/EtOAc: 90/10 followed by n-hexane/EtOAc: 80/20), affording a light brown solid (16.5 mg, 0.08 mmol, 34 %). NMR spectral data match those reported in the literature.[22]

m.p = 57-59 °C

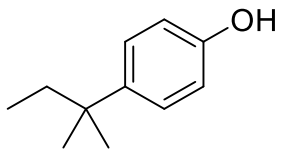
R_f: n-hexane/EtOAc (75/25) = 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 6.91 – 6.82 (m, 2H), 5.30 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.0, 138.5, 129.5 (q, $^1J_{C\text{-}F}$ = 308.0 Hz), 116.5, 115.1.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -43.93.

4-(*tert*-Pentyl)phenol (**2g**)



Compound **2g** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 6 h) and obtained as a white solid (38 mg, 0.23 mmol, 93 %). NMR spectral data match those reported in the literature.[23]

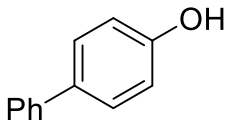
m.p =94-96 °C

R_f: n-hexane/EtOAc (75/25) = 0.5

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 6.82 – 6.73 (m, 2H), 4.52 (s, 1H), 1.61 (q, *J* = 7.4 Hz, 2H), 1.26 (s, 6H), 0.68 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.0, 141.8, 127.1, 114.7, 37.2, 36.9, 28.6, 9.1.

4-Phenylphenol (**2h**)



Compound **2h** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 10 h) and purified by column chromatography (n-hexane/EtOAc: 85/15), affording a white solid (36.16 mg, 0.21 mmol, 85 %). NMR spectral data match those reported in the literature.[24]

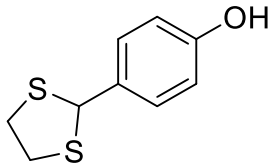
m.p = 160-162 °C

R_f: n-hexane/EtOAc (85/15) = 0.27

^{1}H NMR (300 MHz, THF-d8) δ 8.29 (s, 1H), 7.57 – 7.48 (m, 2H), 7.49 – 7.37 (m, 2H), 7.40 – 7.28 (m, 2H), 7.25 – 7.15 (m, 1H), 6.88 – 6.74 (m, 2H).

^{13}C{^{1}H} NMR (75 MHz, THF-d8) δ 157.3, 141.1, 132.1, 128.3, 127.6, 126.1, 125.9, 115.3.

4-(1,3-Dithiolan-2-yl)phenol (**2i**)



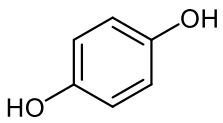
Compound **2i** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 10 h) and purified by flash column chromatography (12 g SiO_2, static elution, 3.5 CV with n-hexane/EtOAc: 95/5 then n-hexane/EtOAc: 87/13), affording a brown oil (26 mg, 0.13 mmol, 52 %). NMR spectral data match those reported in the literature.[7]

R_f: n-hexane/EtOAc (85/15) = 0.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 6.82 – 6.68 (m, 2H), 5.62 (s, 1H), 4.94 (s, 1H), 3.59 – 3.42 (m, 2H), 3.42 – 3.24 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.3, 132.0, 129.4, 115.3, 56.0, 40.2.

Hydroquinone (**2j**)



Compound **2j** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h). The compound was obtained as a red solid following work-up and required no additional purification (24 mg, 0.21 mmol, 89%). NMR spectral data match those reported in the literature.[25]

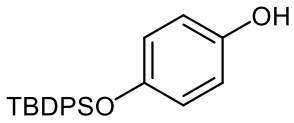
R_f: n-hexane/EtOAc (60/40) = 0.25

m.p = 170-172 °C

^{1}H NMR (400 MHz, THF-d8) δ 7.29 (s, 2H), 6.52 (s, 4H).

^{13}C{^{1}H} NMR (101 MHz, THF-d8) δ 150.3, 115.3

4-((tert-butyldiphenylsilyl)oxy)phenol (**2k**)



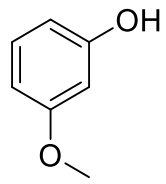
Compound **2k** was synthesized following general procedure C for catalysis (heating time with Camphorsulfonic acid = 22 h) and purified by flash column chromatography (12 g SiO_2, static elution, n-hexane/EtOAc: 93/7), affording a colorless oil (29 mg, 0.08 mmol, 33%). NMR spectral data match those reported in the literature.[26]

R_f: n-hexane/EtOAc (95/5) = 0.17

^{1}H NMR (400 MHz, THF-d8) δ 7.78 – 7.65 (m, 5H), 7.43 – 7.29 (m, 5H), 6.63 – 6.51 (m, 2H), 6.48 – 6.41 (m, 2H), 1.07 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, THF-d8) δ 151.8, 148.0, 135.4, 133.2, 129.6, 127.5, 119.6, 115.1, 26.0, 19.0.

3-Methoxyphenol (**2l**)



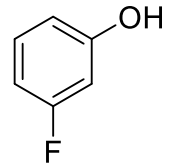
Compound **2l** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 6 h) and purified by column chromatography (n-hexane/EtOAc: 90/10), affording a brown oil (26 mg, 0.2 mmol, 86 %). NMR spectral data match those reported in the literature.[27]

R_f: n-hexane/Et_2O (90/10) = 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.09 (m, 1H), 6.55 – 6.47 (m, 1H), 6.47 – 6.40 (m, 2H), 5.07 (s, 1H), 3.78 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.8, 156.7, 130.2, 107.9, 106.5, 101.6, 55.3.

3-Fluorophenol (**2m**)



Compound **2m** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by flash column chromatography (12 g SiO_2, static elution, n-hexane/EtOAc: 90/10), affording a light brown oil (6 mg, 0.05 mmol, 18 %). NMR spectral data match those reported in the literature.[28]

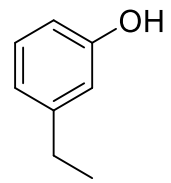
R_f: n-hexane/EtOAc (90/10) = 0.27

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.12 (m, 1H), 6.71 – 6.53 (m, 3H), 4.92 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C\text{-}F}$ = 245 Hz), 156.8 (d, $^3J_{C\text{-}F}$ = 11.2 Hz), 130.4 (d, $^3J_{C\text{-}F}$ = 10.0 Hz), 111.1 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 107.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 103.2 (d, $^2J_{C\text{-}F}$ = 24.6 Hz).

^{19}F{^{1}H} NMR NMR (376 MHz, $CDCl_3$) δ -111.6.

3-Ethylphenol (**2n**)



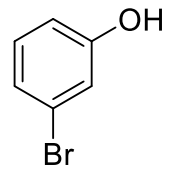
Compound **2n** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 6 h) and obtained as a colorless oil (20.7 mg, 0.16 mmol, 68 %). NMR spectral data match those reported in the literature.[29]

R_f: n-hexane/EtOAc (95/5) = 0.35

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.73 – 6.61 (m, 2H), 4.32 (s, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.4, 146.2, 129.5, 120.4, 114.8, 112.5, 28.7, 15.4.

3-Bromophenol (**2o**)



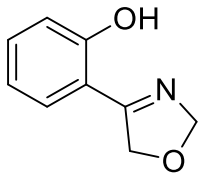
Compound **2o** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 90/10), affording a brown oil (16.0 mg, 0.09 mmol, 37 %). NMR spectral data match those reported in the literature.[30]

R_f: n-hexane/Et_2O (90/10) = 0.25

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 – 7.05 (m, 2H), 7.04 – 7.00 (m, 1H), 6.80 – 6.72 (m, 1H), 5.03 (s, 1H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.2, 130.8, 124.0, 122.8, 118.8, 114.2.

2-(2,5-Dihydrooxazol-4-yl)phenol (**2p**)



Compound **2p** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 75/25), affording a yellow solid (25 mg, 0.15 mmol, 62 %).

m.p: 178-180 °C

R_f: n-hexane/EtOAc (80/20) = 0.16

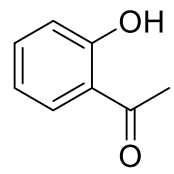
^{1}H NMR (400 MHz, THF-d8) δ 9.32 (s, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.28 – 7.18 (m, 1H), 7.00 – 6.88 (m, 2H), 6.85 (d, *J* = 1.8 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, THF-d8) δ 165.3, 154.5, 150.2, 130.5, 126.9, 119.5, 115.9, 114.8, 101.9.

GC-MS (EI) m/z: 161.0 (M^+).

IR: (ATR) $\tilde{\nu}$ (cm^{-1}): 3108, 2970, 2881, 2739, 1610, 1472, 1569, 1379, 1271, 1189, 1121, 924, 752, 715

2-Hydroxyacetophenone (**2q**)



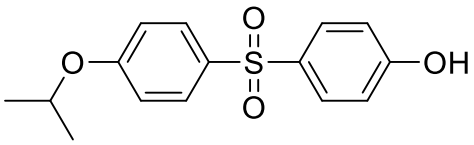
Compound **2q** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a light brown oil (29.6 mg, 0.21 mmol, 87 %). NMR spectral data match those reported in the literature.[31]

R_f: n-hexane/Et_2O (90/10) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.74 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.47 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.90 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 2.64 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.5, 162.3, 136.4, 130.7, 119.7, 118.9, 118.4, 26.6.

4-((4-Isopropoxyphenyl)sulfonyl)phenol (**2r**)



Compound **2r** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 99/1), affording a white solid (60 mg, 0.2 mmol, 41 %). NMR spectral data match those reported in the literature.[32]

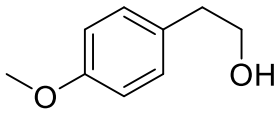
m.p: 125-127 °C

R_f: n-hexane/EtOAc (75/25) = 0.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.68 (m, 4H), 6.95 – 6.83 (m, 4H), 4.58 (p, *J* = 6.1 Hz, 1H),1.32 (d, *J* = 6 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 160.4, 132.9, 132.7, 129.6, 129.4, 116.1, 115.7, 70.4, 21.8.

2-(4-Methoxyphenyl)ethan-1-ol (**4a**)



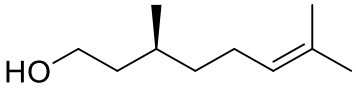
Compound **4a** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and obtained as a pale yellow oil (28.6 mg, 0.18 mmol, 94 %). NMR spectral data match those reported in the literature.[33]

R_f: n-hexane/EtOAc (90/10) = 0.14

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.83 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 2.82 (t, *J* = 6.5 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.2, 130.3, 129.9, 114.0, 63.8, 55.2, 38.2.

(*S*)-3,7-Dimethyloct-6-en-1-ol (**4b**)



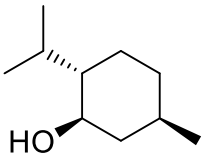
Compound **4b** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and obtained as a colorless oil (36.7 mg, 0.23 mmol, 94 %). NMR spectral data match those reported in the literature.[34]

R_f: n-hexane/EtOAc (99.5/0.5) = 0.2 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 – 5.04 (m, 1H), 3.75 – 3.60 (m, 2H), 2.05 – 1.90 (m, 3H), 1.71 – 1.65 (m, 3H), 1.63 – 1.51 (m, 5H), 1.43 – 1.28 (m, 2H), 1.24 – 1.10 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 131.2, 124.6, 61.2, 39.8, 37.2, 29.1, 25.7, 25.4, 19.5, 17.6.

(-)-Menthol (**4c**)



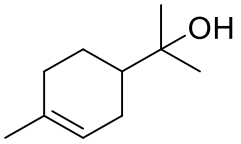
Compound **4c** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and obtained as a white solid (36.7 mg, 0.23 mmol, 94 %). NMR spectral data match those reported in the literature.[35]

R_f: n-hexane/EtOAc (99.5/0.5) = 0.4 (stained with $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 – 3.34 (m, 1H), 2.21 – 2.10 (m, 1H), 1.99 – 1.90 (m, 1H), 1.69 – 1.54 (m, 2H), 1.47 – 1.32 (m, 1H), 1.15 – 1.05 (m, 1H), 1.02 – 0.95 (m, 1H), 0.94 – 0.76 (m, 11H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 71.5, 50.1, 45.0, 34.5, 31.6, 25.8, 23.1, 22.2, 21.0, 16.0.

2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol (**4d**)



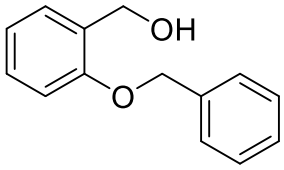
Compound **4d** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and obtained as a pale yellow oil (35 mg, 0.22 mmol, 95 %). NMR spectral data match those reported in the literature.[36]

R_f: n-hexane/EtOAc (99.5/0.5) = 0.4 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H), 2.11 – 1.96 (m, 3H), 1.93 – 1.73 (m, 2H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.56 – 1.43 (m, 1H), 1.41 – 1.24 (m, 2H), 1.19 (s, 3H), 1.17 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.0, 120.5, 72.7, 44.9, 31.0, 27.4, 26.8, 26.2, 23.9, 23.3.

(2-(Benzyloxy)phenyl)methanol (**4e**)



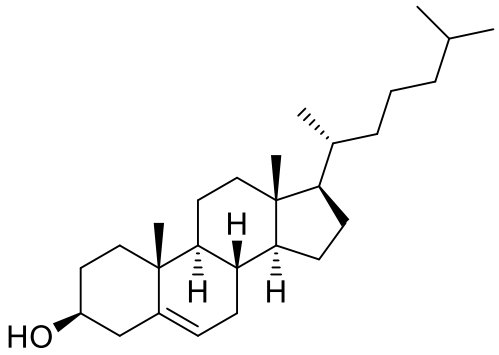
Compound **4e** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and purified by column chromatography (n-hexane/EtOAc: 85/15), affording a colorless oil (43 mg, 0.2 mmol, 81 %). NMR spectral data match those reported in the literature.[37]

R_f: n-hexane/EtOAc (90/10) = 0.11

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 3H), 7.38 – 7.27 (m, 3H), 7.33 - 7.27 (m, 1H), 6.96 (td, *J* = 8.3, 1.7 Hz, 2H), 5.11 (s, 2H), 4.73 (s, 2H), 2.32 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.5, 136.7, 129.4, 128.9, 128.8, 128.7, 128.1, 127.3, 121.0, 111.6, 70.0, 62.1.

Cholesterol (**4f**)



Compound **4f** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 90 min) and obtained as a white solid (65 mg, 0.16 mmol, 84 %). NMR spectral data match those reported in the literature.[38]

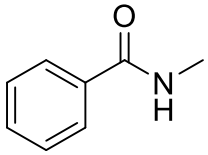
m.p: 147-149 °C

R_f: n-hexane/EtOAc (97/3) = 0.25 ($KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 – 5.30 (m, 1H), 3.62 – 3.42 (m, 1H), 2.39 – 2.15 (m, 2H), 1.99 (tt, *J* = 11.6, 3.1 Hz, 2H), 1.83 (ddd, *J* = 12.5, 6.4, 3.3 Hz, 3H), 1.70 (s, 1H), 1.61 – 1.42 (m, 5H), 1.37 – 1.22 (m, 6H), 1.18 – 1.06 (m, 6H), 1.00 (s, 4H), 0.97 – 0.82 (m, 12H), 0.68 (s, 3H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 140.7, 121.7, 71.8, 56.7, 56.1, 50.1, 42.3, 42.2, 39.8, 39.5, 37.2, 36.5, 36.2, 35.8, 31.9, 31.6, 28.2, 28.0, 24.3, 23.8, 22.8, 22.5, 21.1, 19.4, 18.7, 11.8.

N-Methylbenzamide (**6**)



Compound **6** was synthesized following general procedure C for catalysis (heating time with *p*TsOH·H_2O = 15 h) and purified by column chromatography (n-hexane/EtOAc: 65/35), affording a white crystalline solid (16 mg, 0.11 mmol, 47 %). NMR spectral data match those reported in the literature.[39]

m.p = 83-85 °C

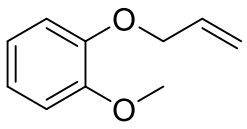
R_f: n-hexane/EtOAc (65/35) = 0.14

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.54 – 7.36 (m, 3H), 6.23 (s, 1H), 3.01 (d, *J* = 4.8 Hz, 3H).

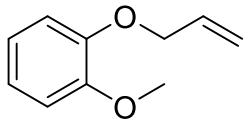
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.2, 134.6, 131.3, 128.5, 126.8, 26.8.

4. NMR SPECTRA: REACTANTS

1-(Allyloxy)-2-methoxybenzene (**1a**)

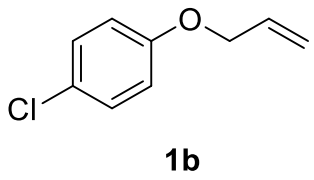


1a

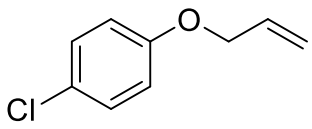


1a

1-(Allyloxy)-4-chlorobenzene (**1b**)

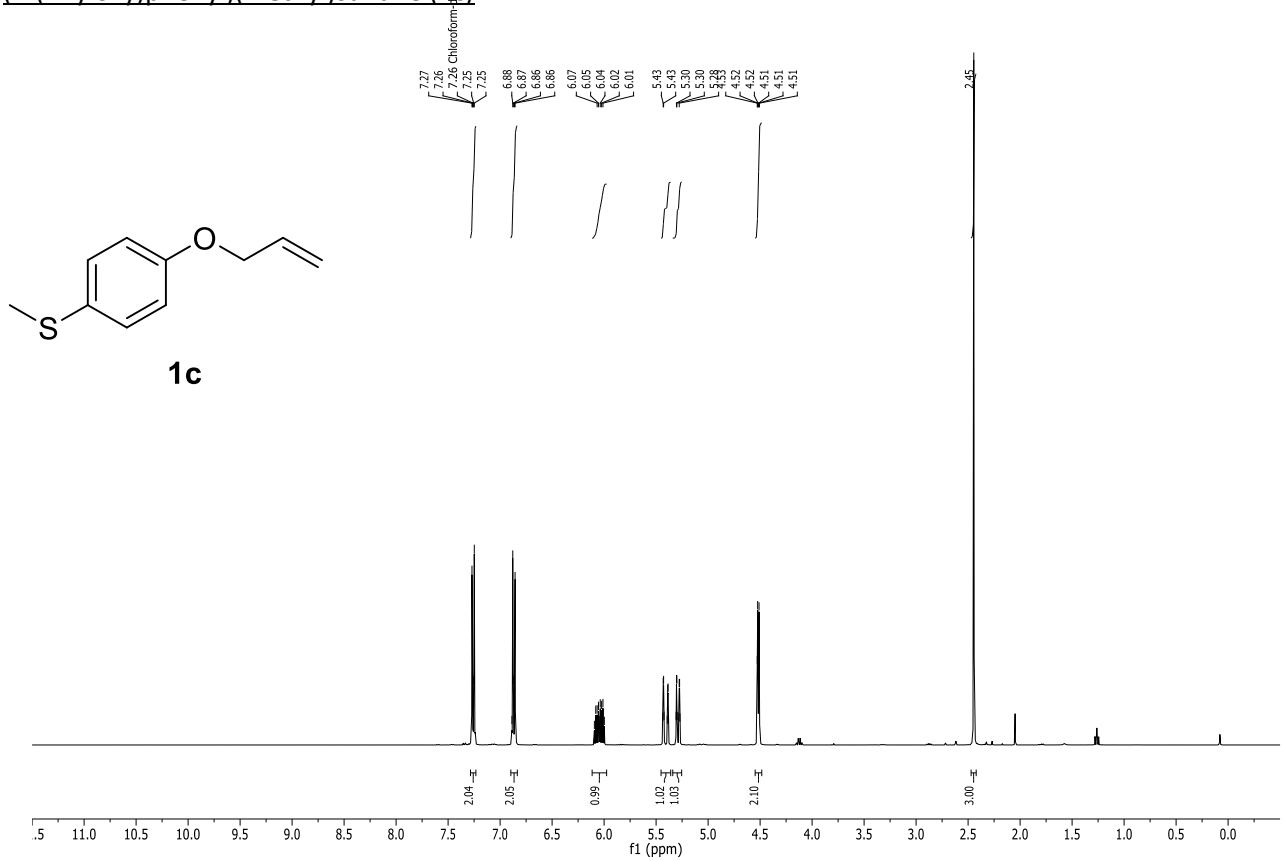


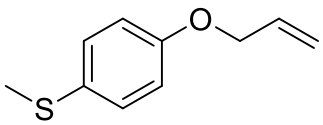
1b



1b

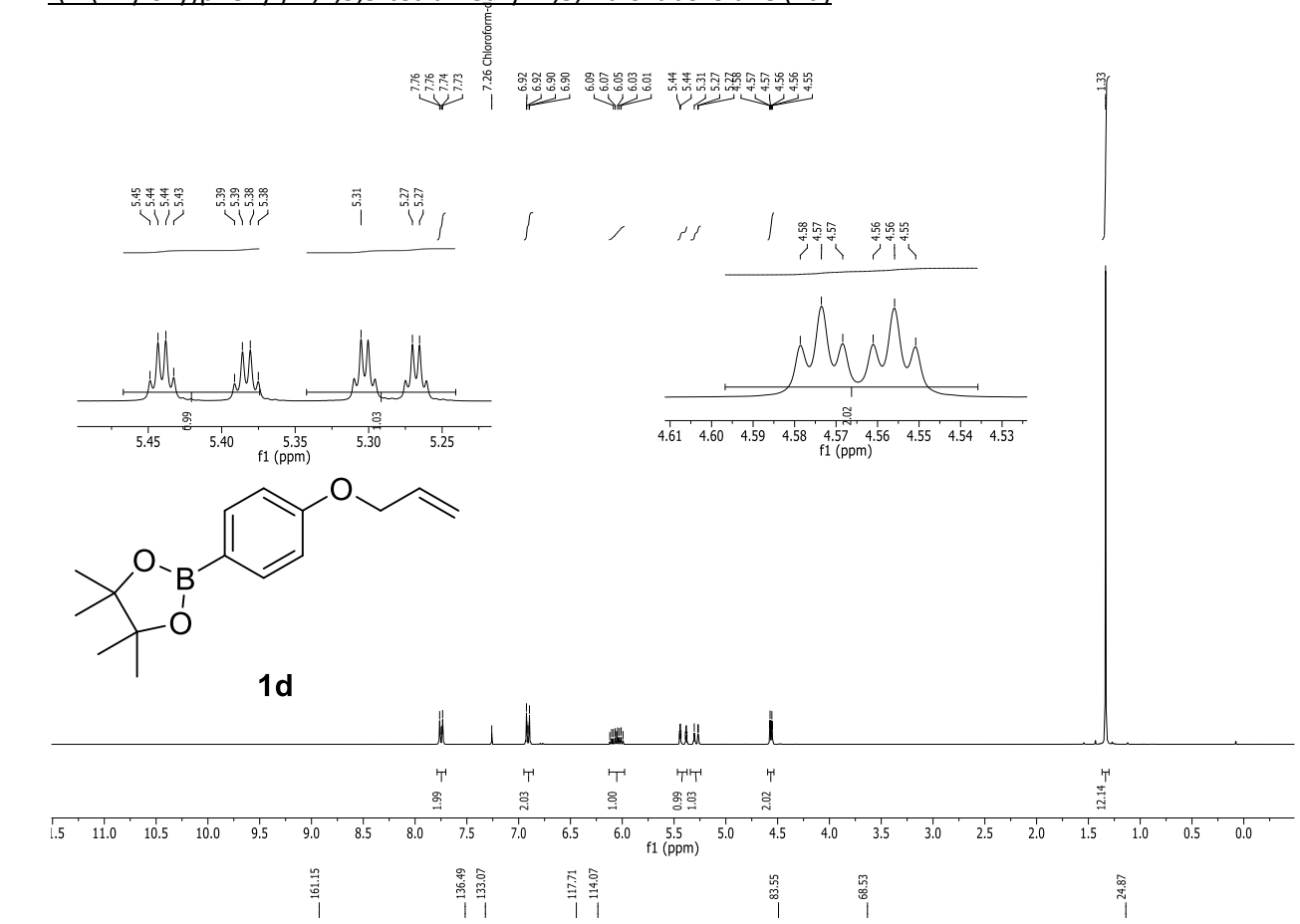
(4-(Allyloxy)phenyl)(methyl)sulfane (**1c**)

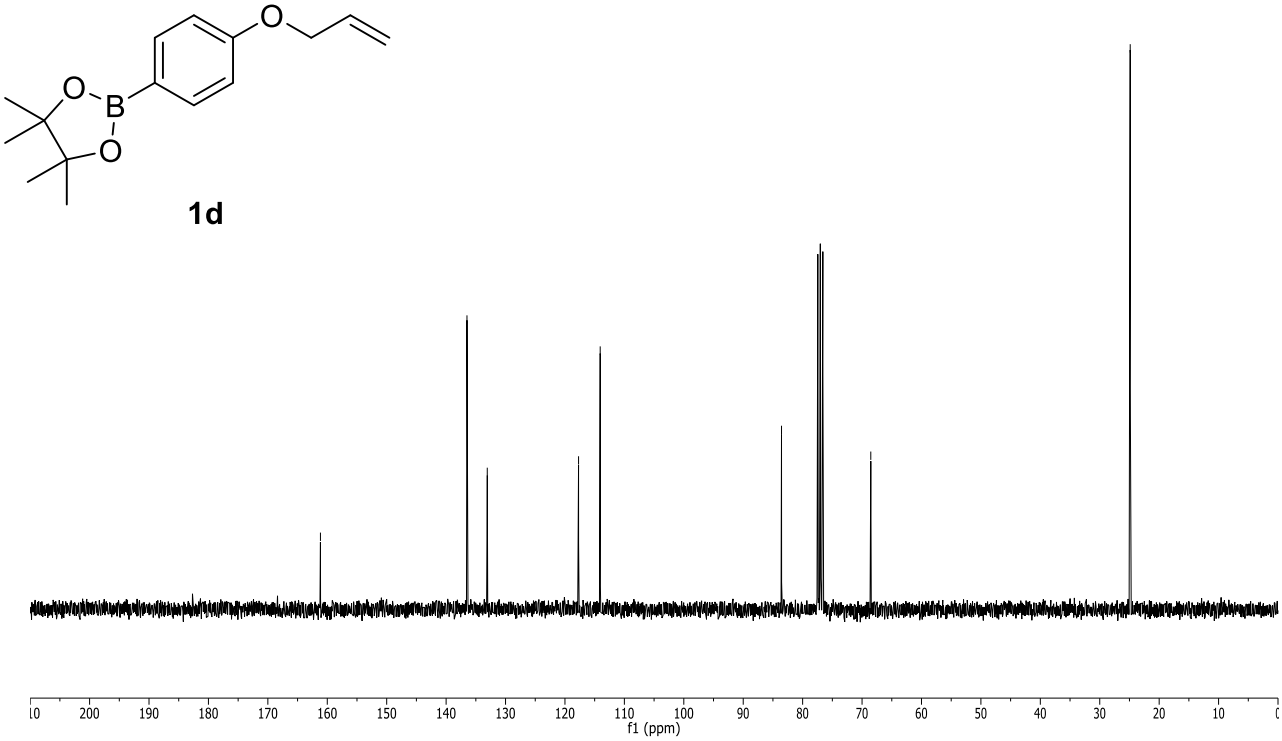




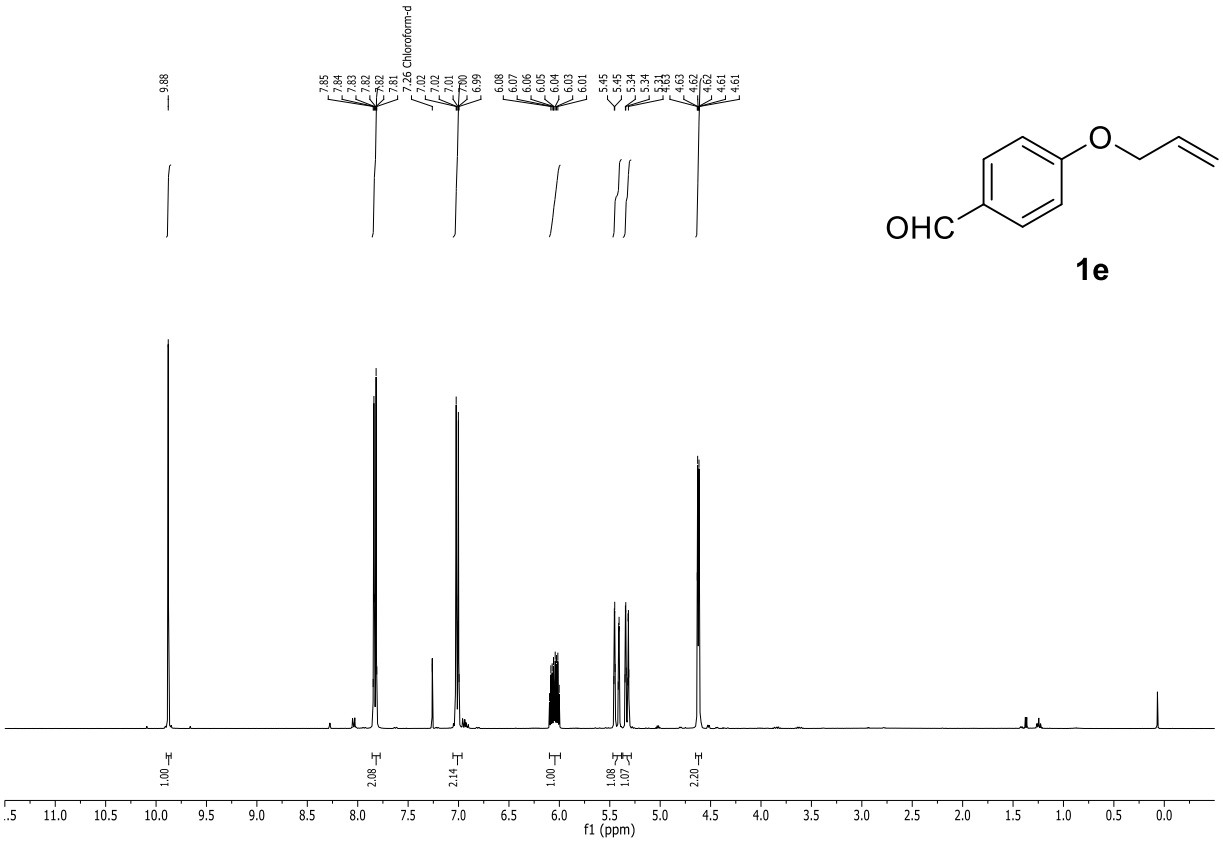
1c

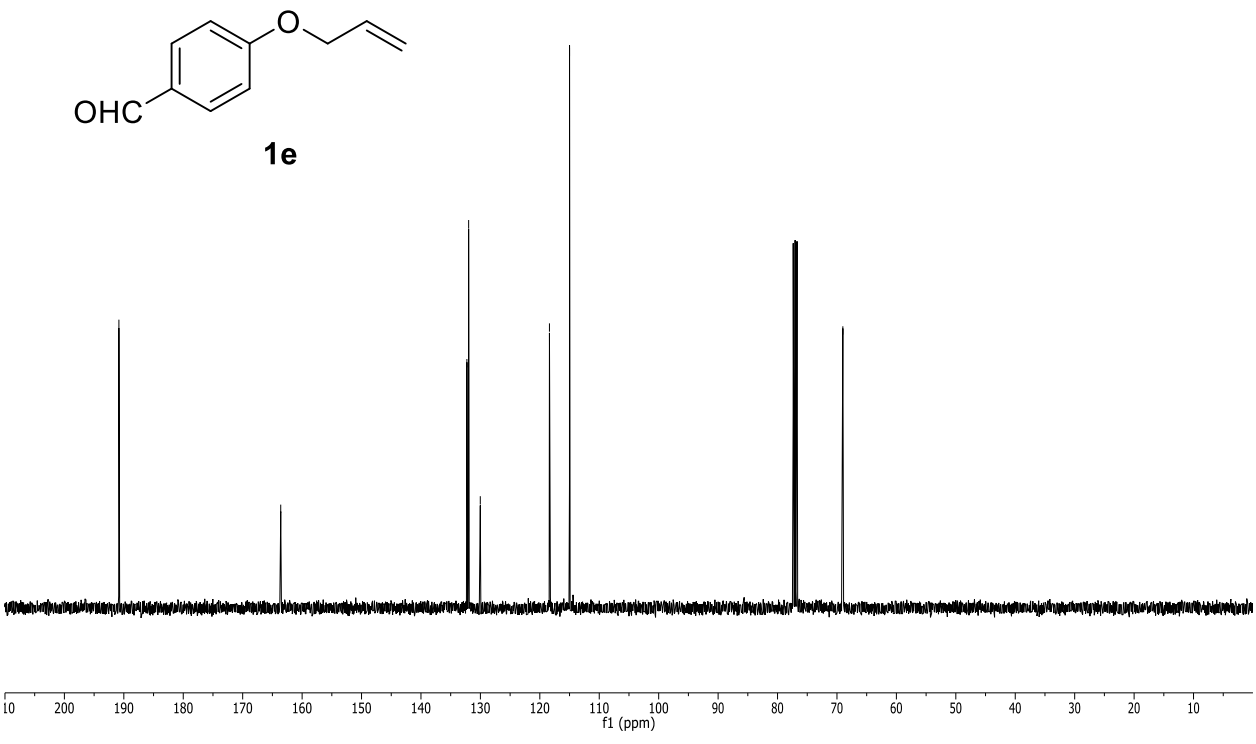
2-(4-(Allyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1d**)



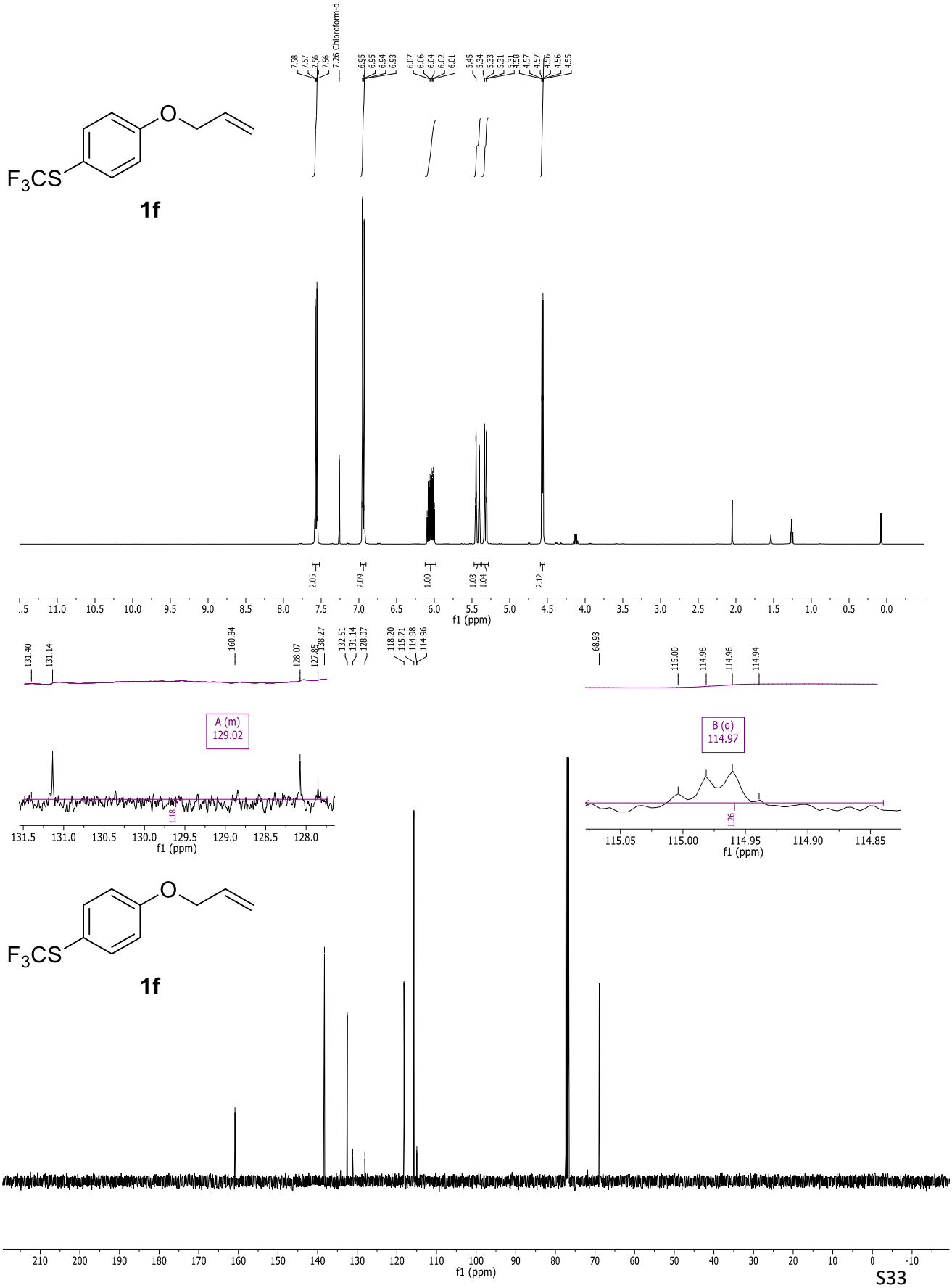


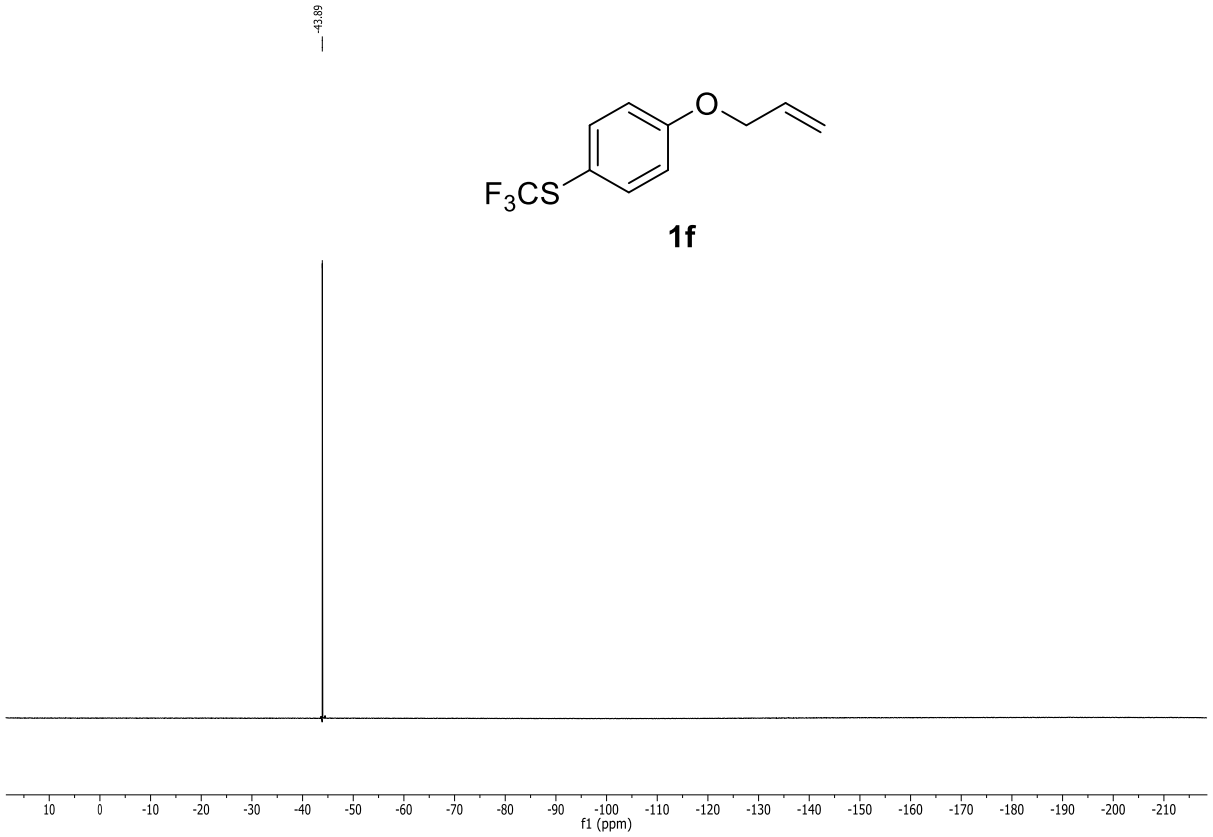
4-(Allyloxy)benzaldehyde (**1e**)





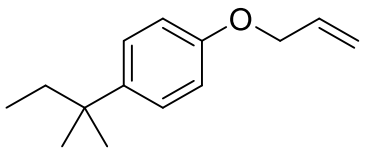
(4-(Allyloxy)phenyl)(trifluoromethyl)sulfane (**1f**)



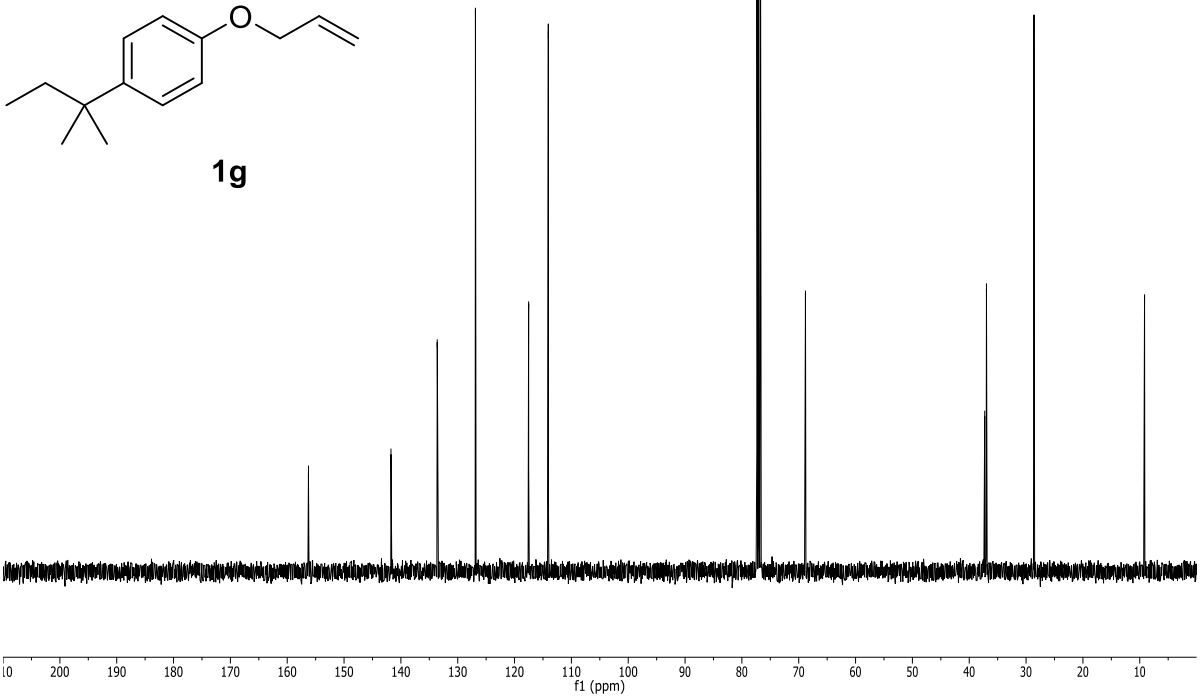

-43.89
O
F3CS
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

1f

1-(Allyloxy)-4-(tert-pentyl)benzene (**1g**)

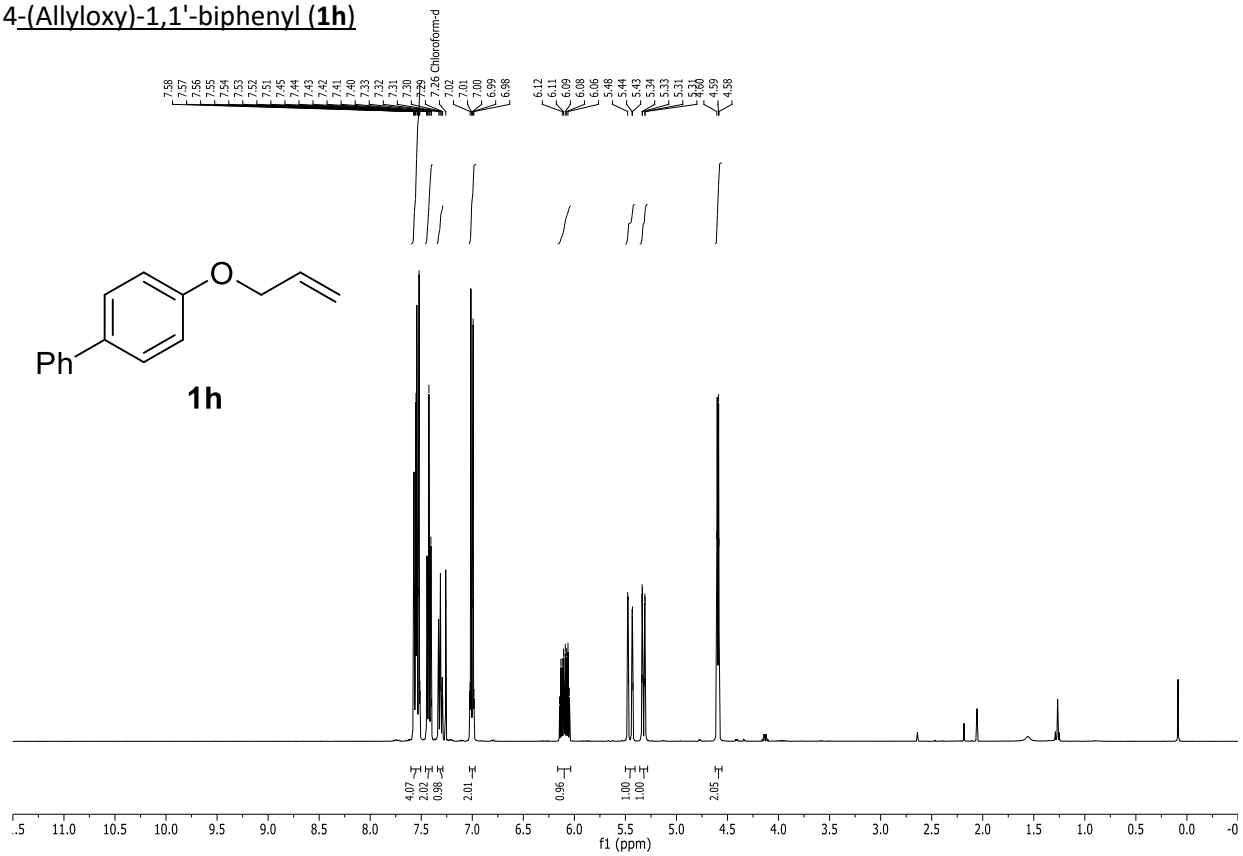


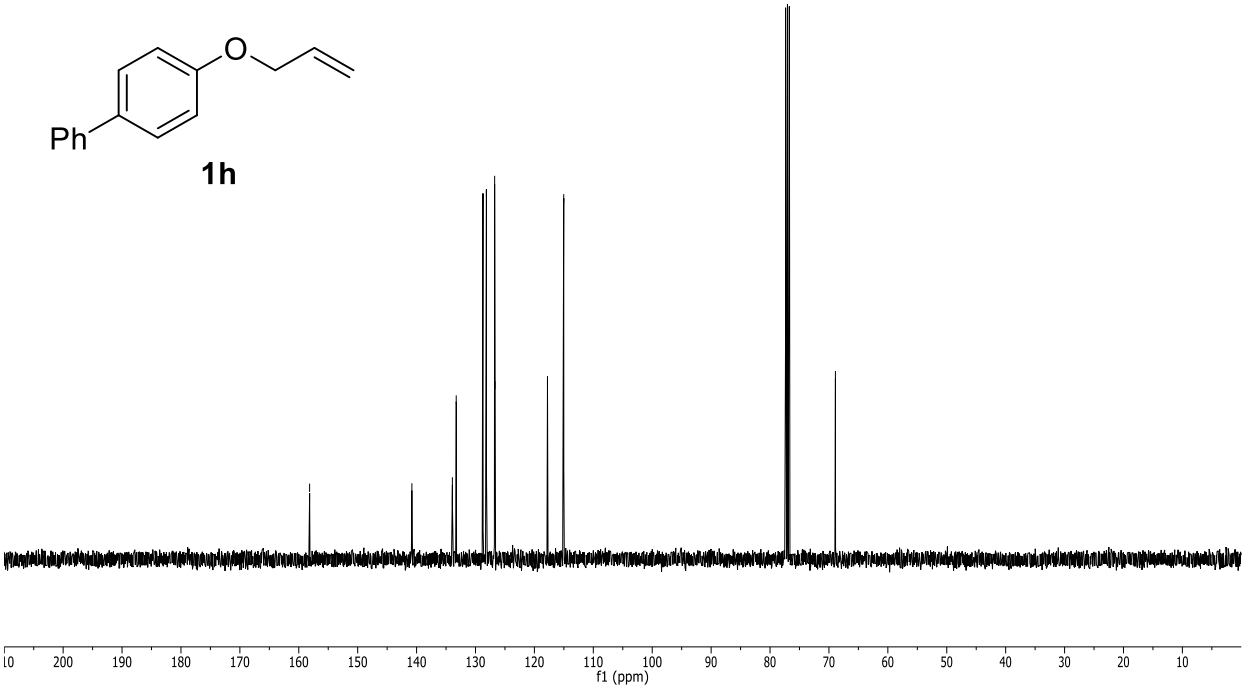
1g



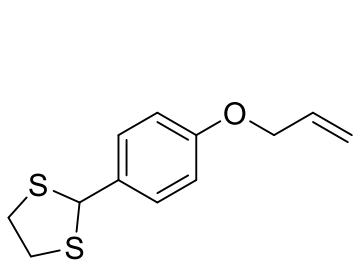
1g

4-(Allyloxy)-1,1'-biphenyl (**1h**)

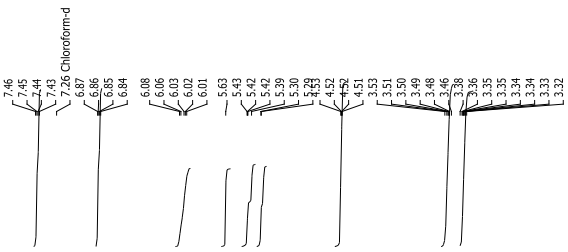


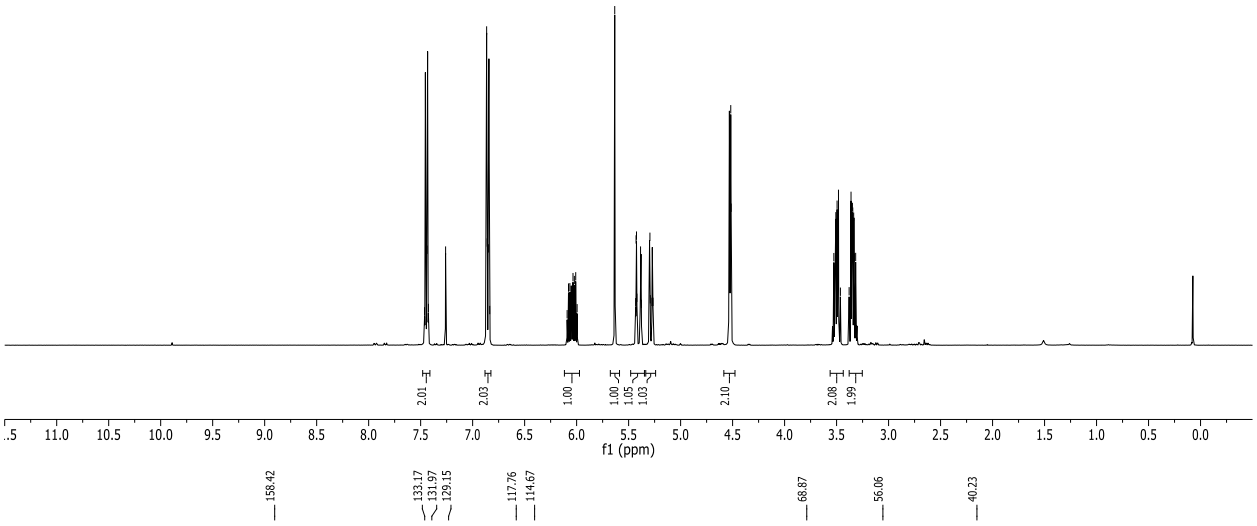


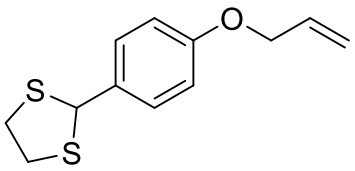
2-(4-(Allyloxy)phenyl)-1,3-dithiolane (**1i**)



1i

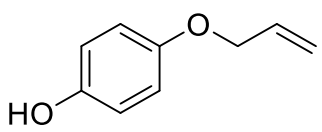




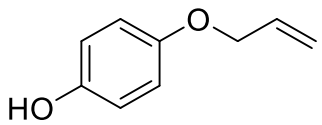


1i

4-(allyloxy)phenol (**1j**)

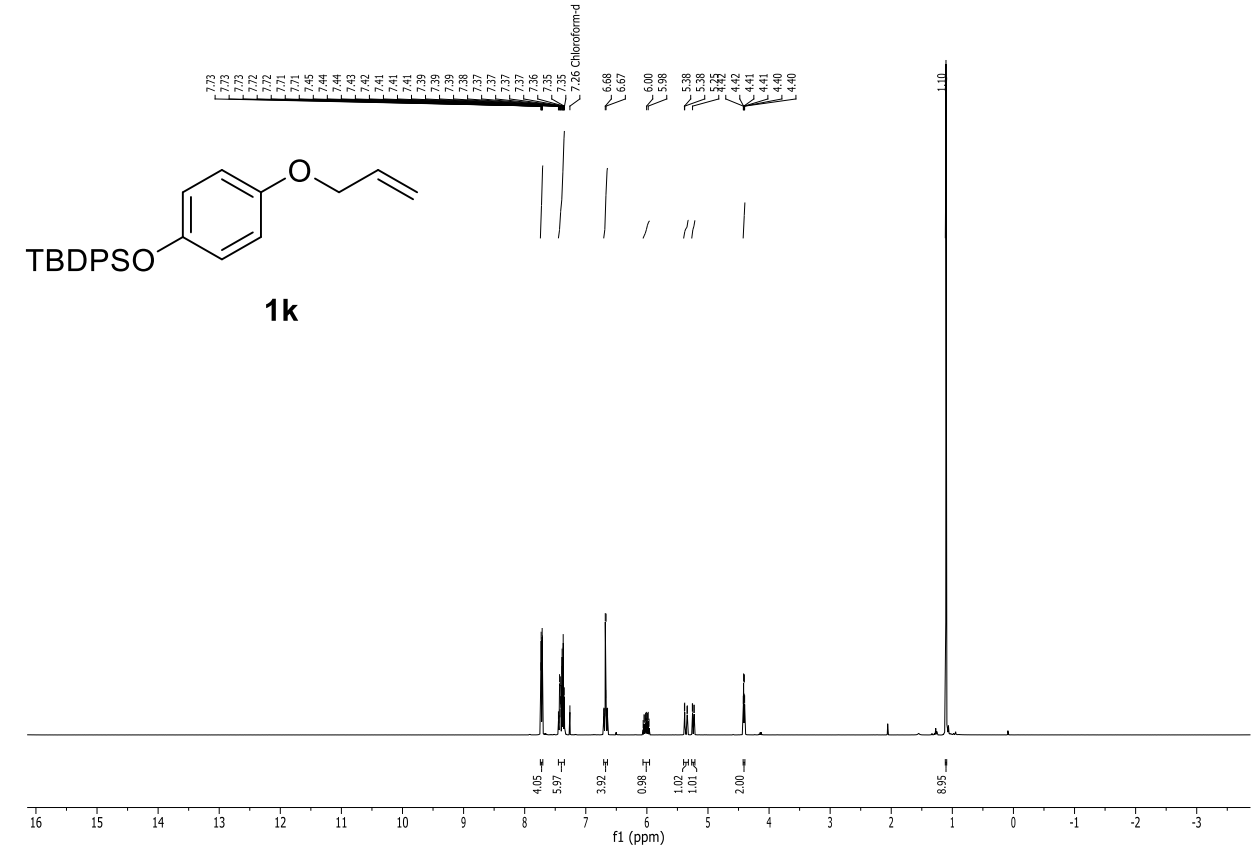


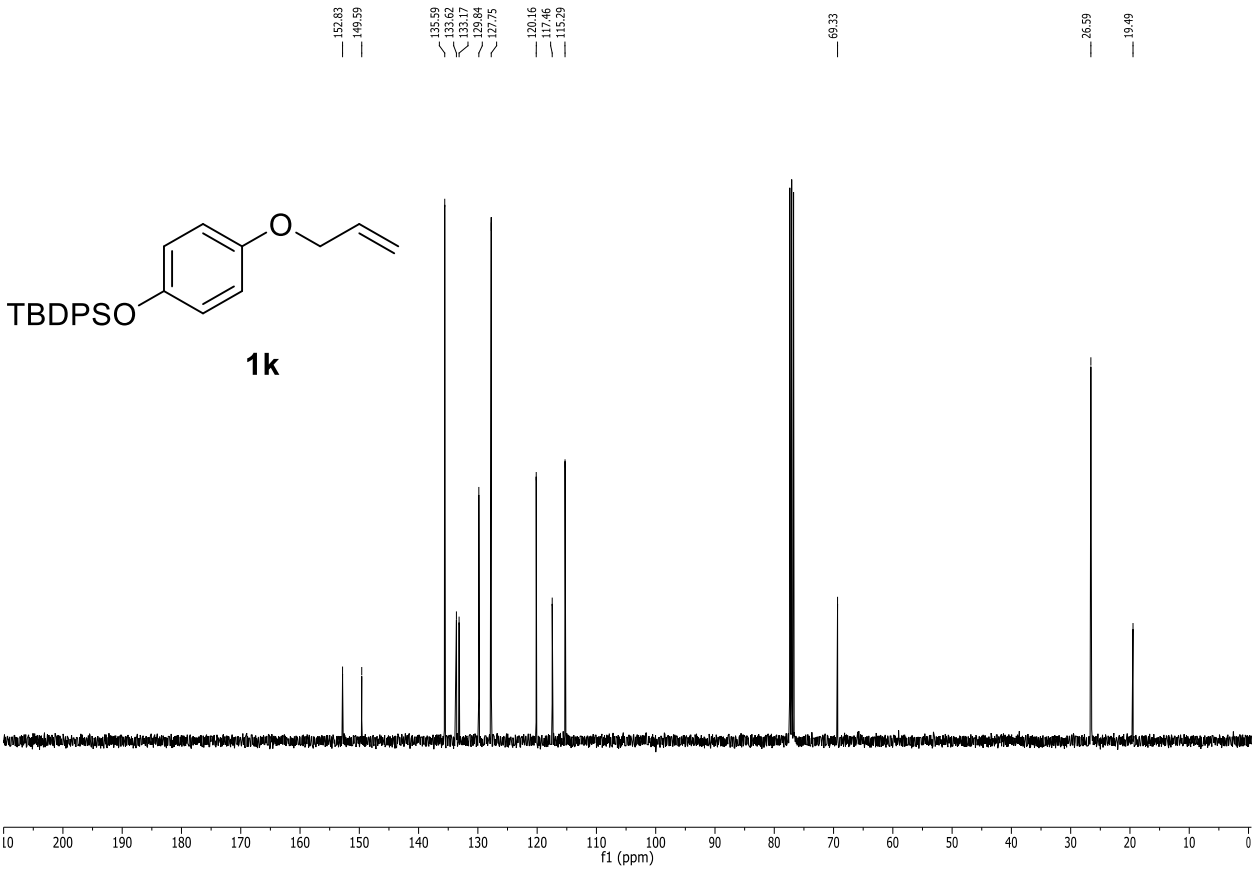
1j



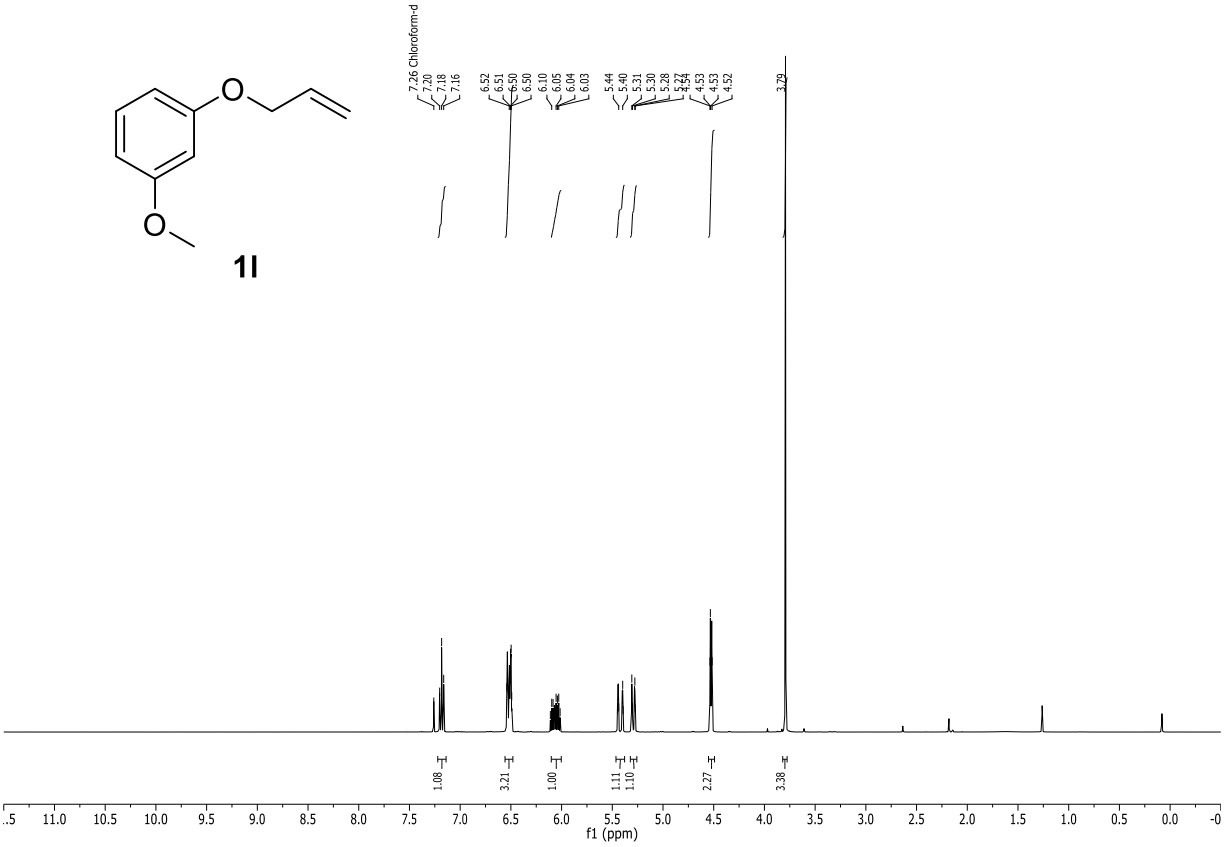
1j

(4-(allyloxy)phenoxy)(tert-butyl)diphenylsilane (**1k**)

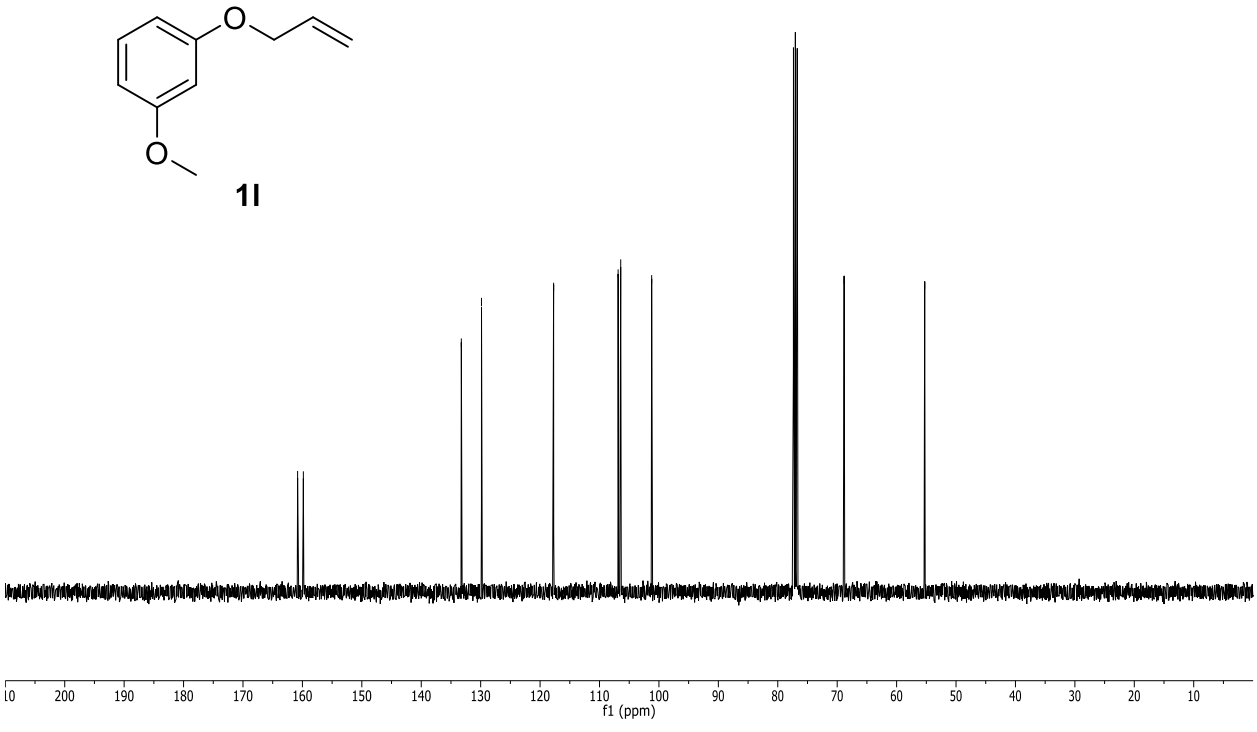




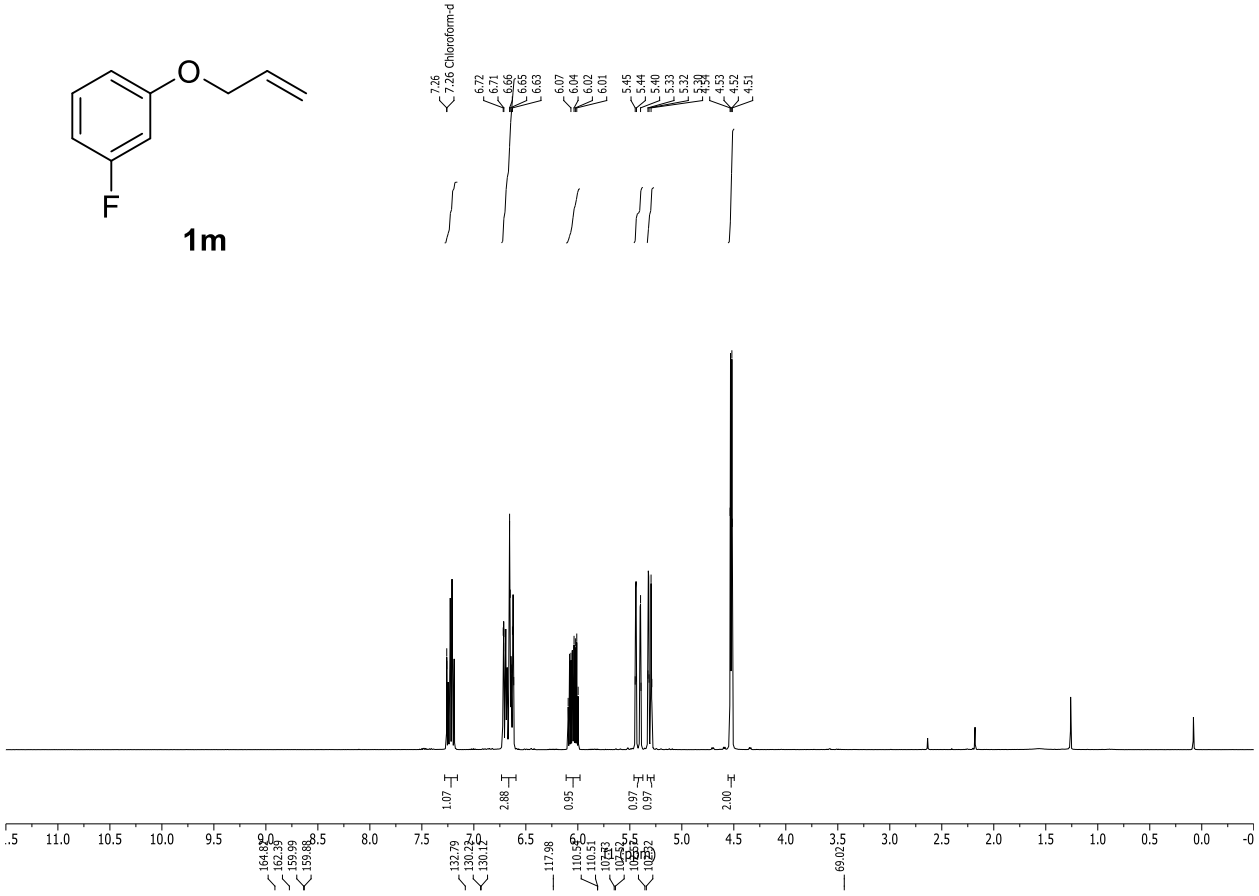
1-(Allyloxy)-3-methoxybenzene (**1l**)

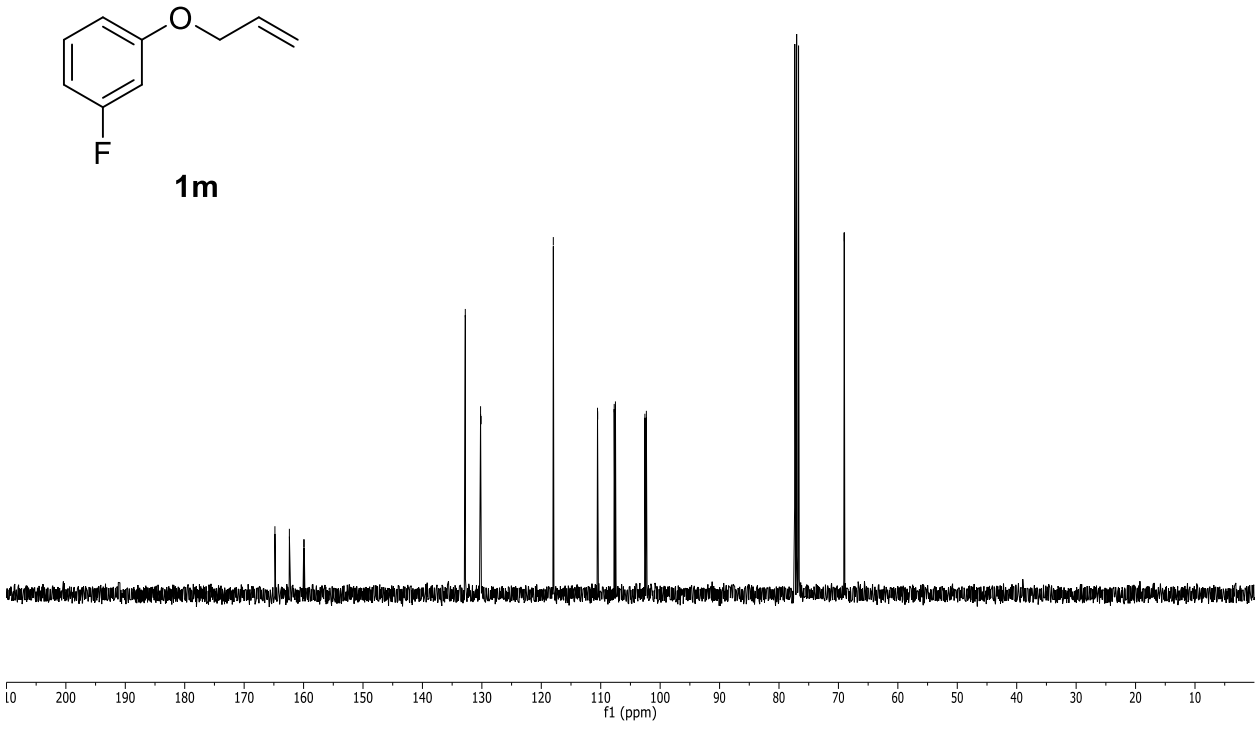


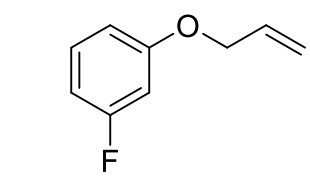
1l



1-(Allyloxy)-3-fluorobenzene (**1m**)



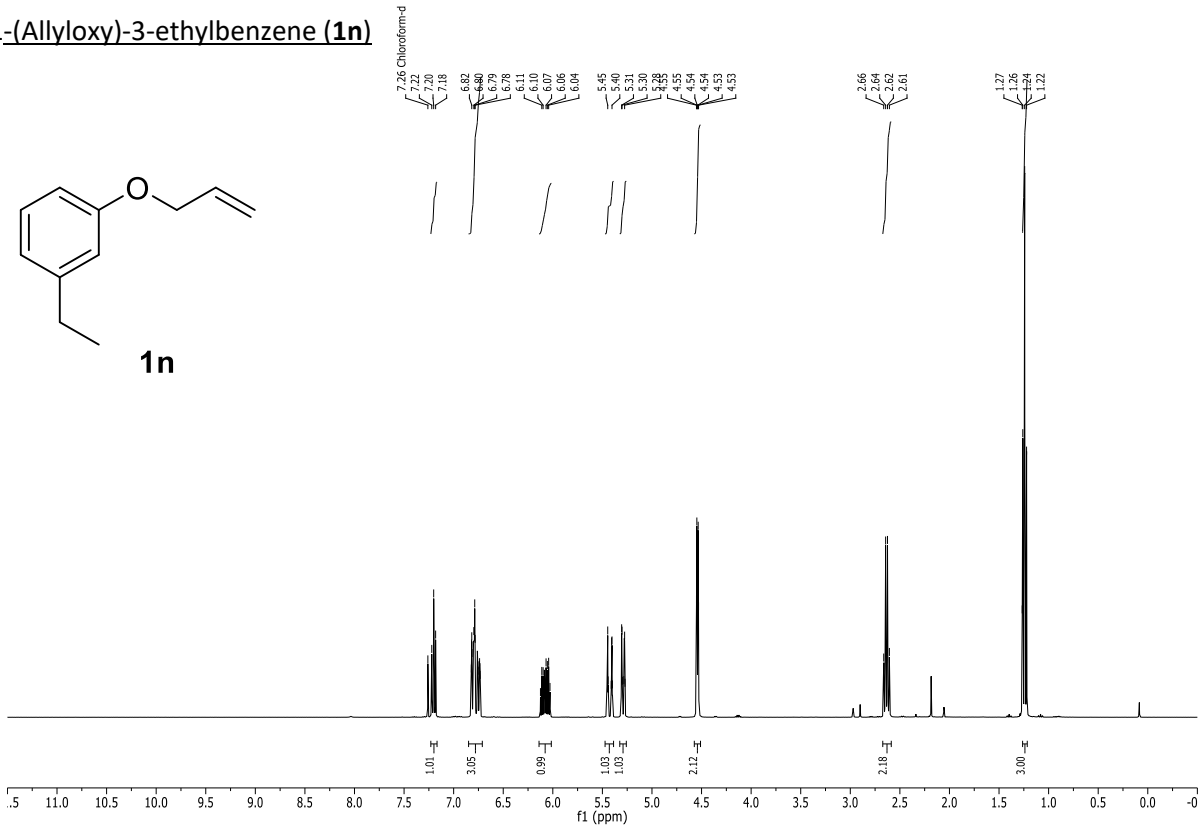


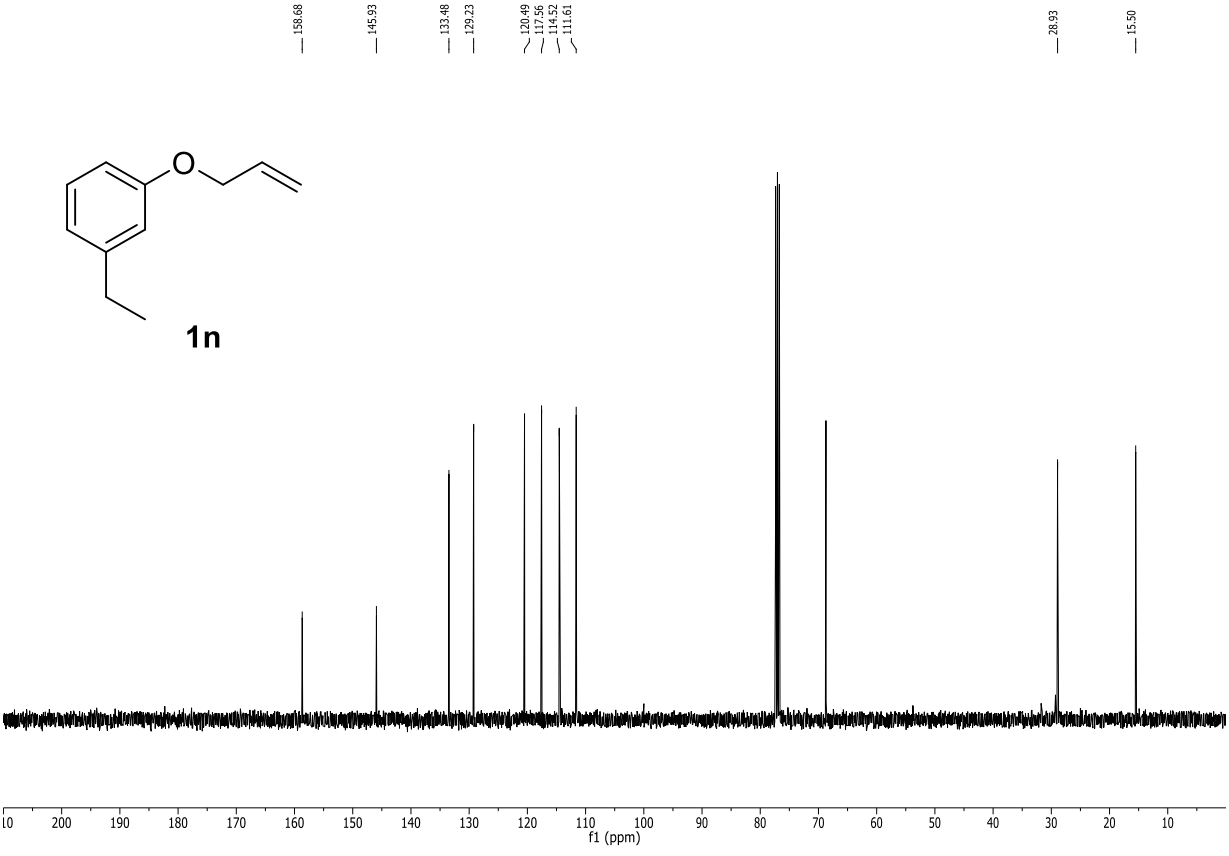

O
F

1m

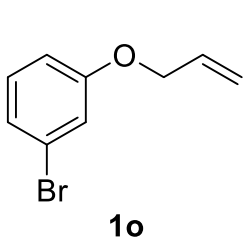
-111.78
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

1-(Allyloxy)-3-ethylbenzene (**1n**)

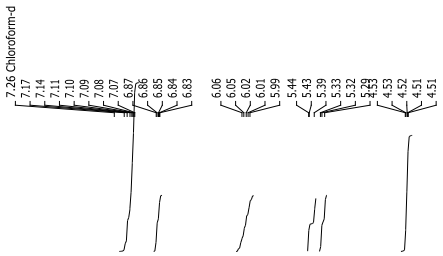


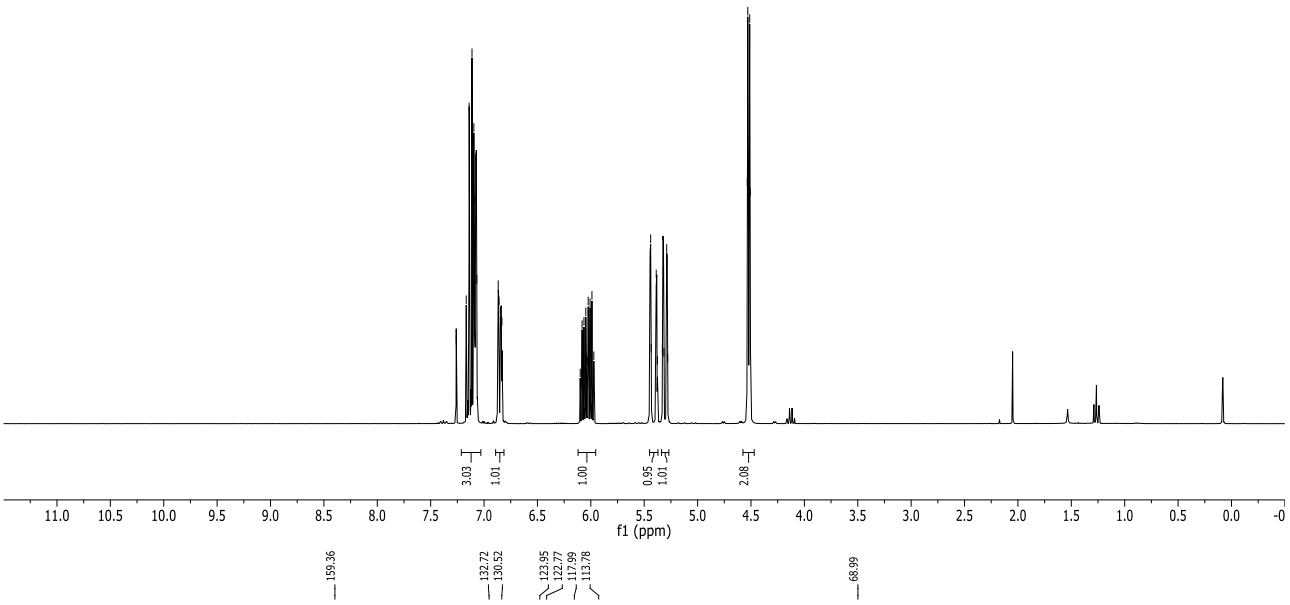


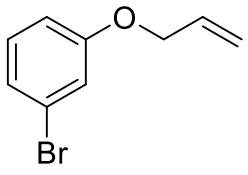
1-(Allyloxy)-3-bromobenzene (**1o**)



1o

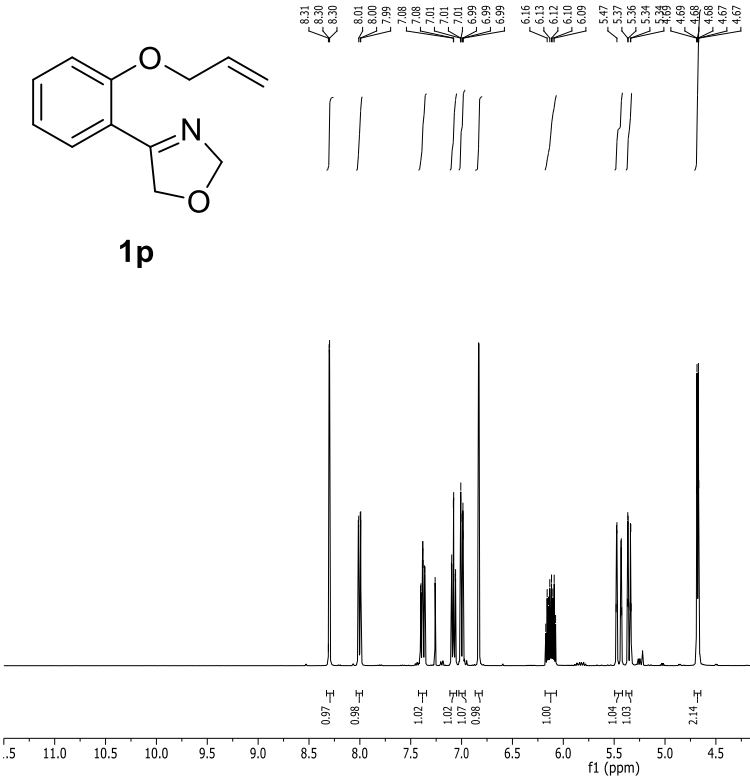


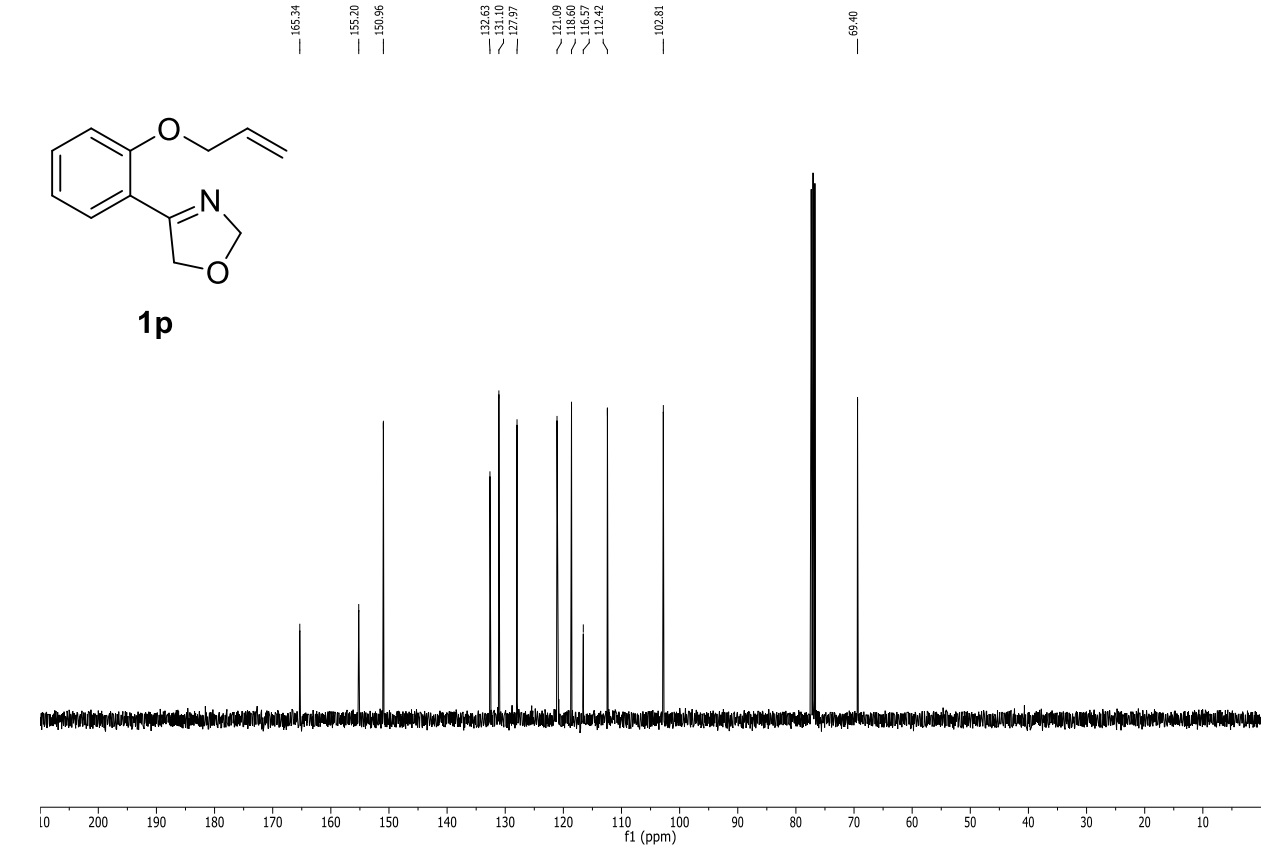




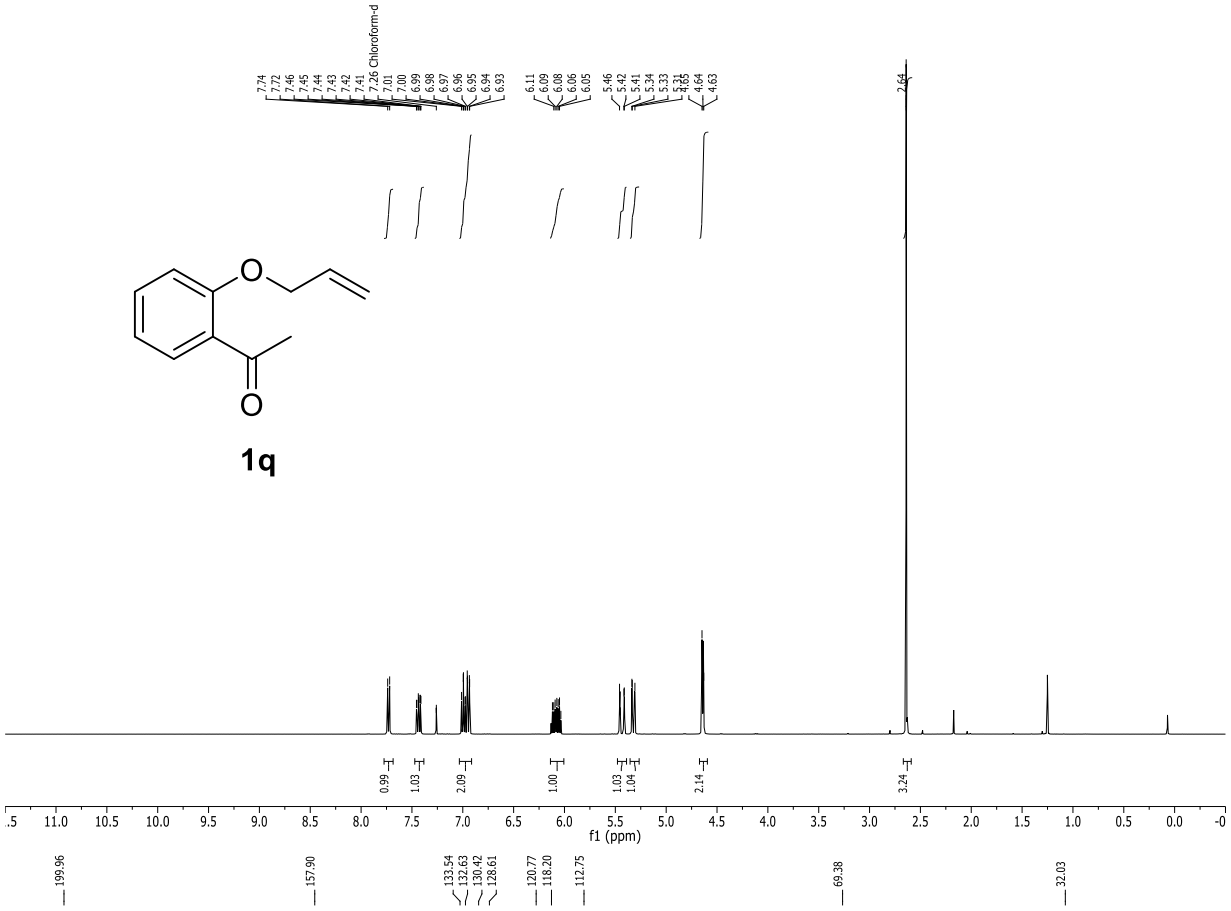
1o

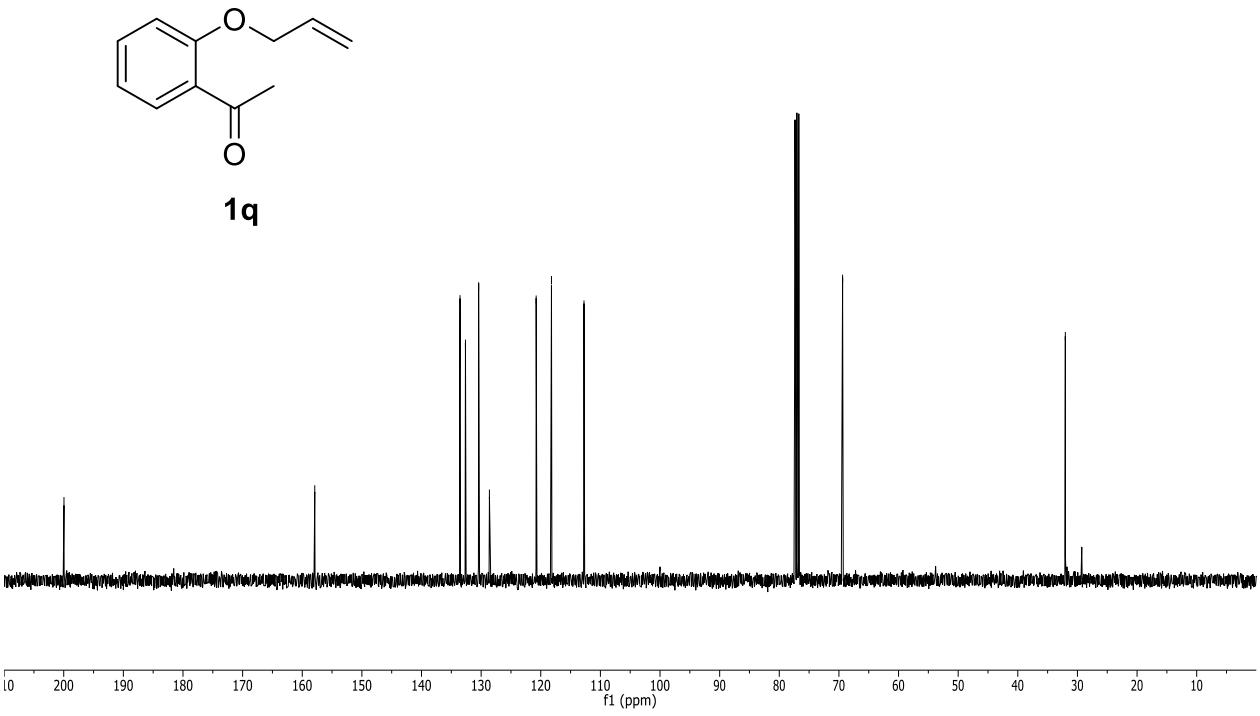
4-(2-(Allyloxy)phenyl)-2,5-dihydrooxazol (**1p**)



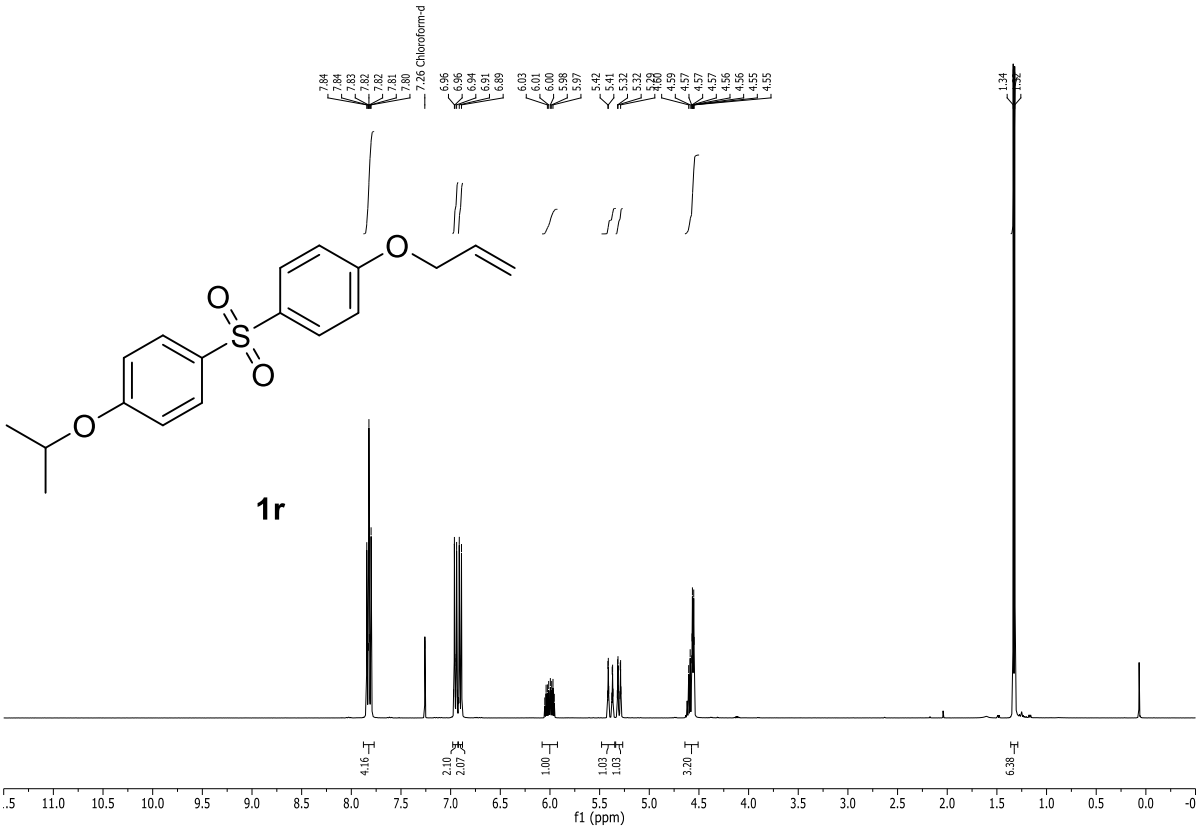


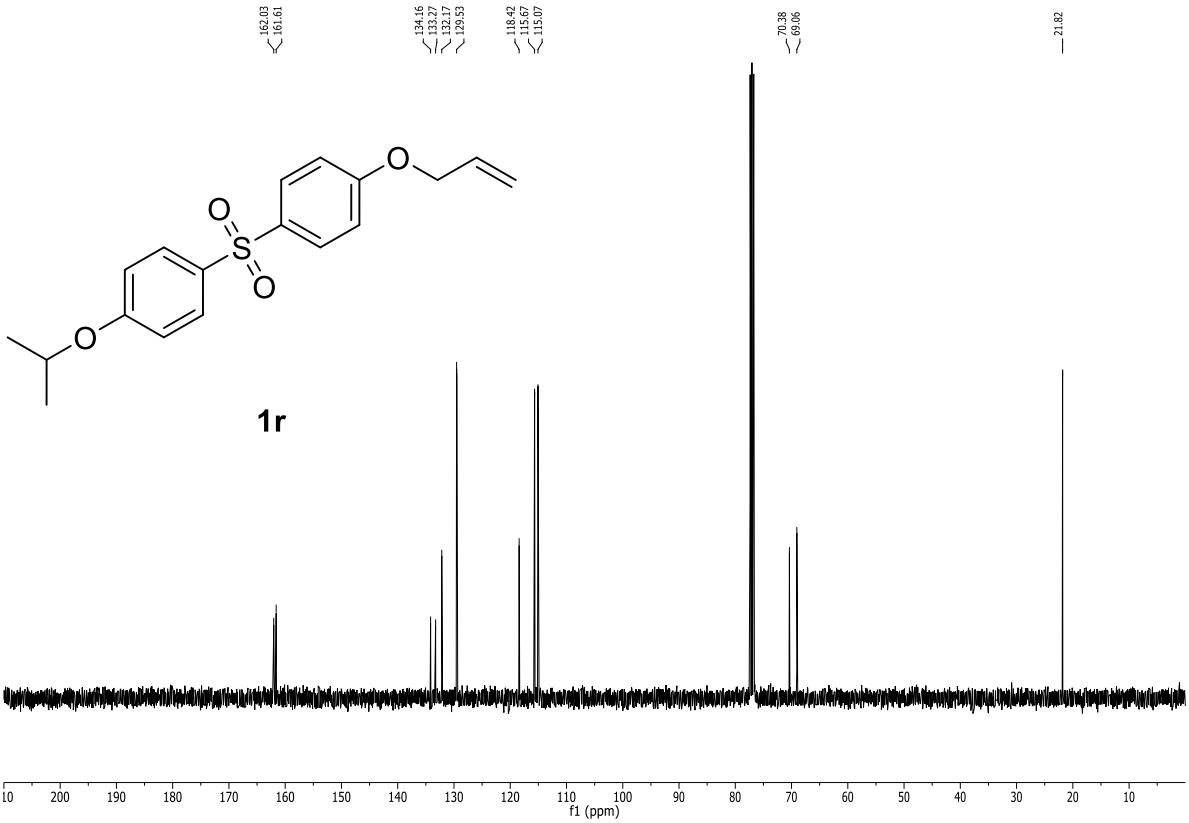
1-(2-(Allyloxy)phenyl)ethan-1-one (**1q**)



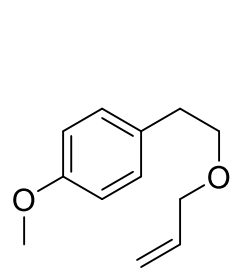


1-(Allyloxy)-4-((4-isopropoxyphenyl)sulfonyl)benzene (**1r**)

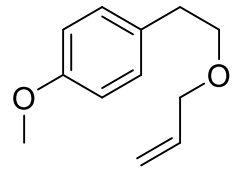




1-(2-(Allyloxy)ethyl)-4-methoxybenzene (**3a**)

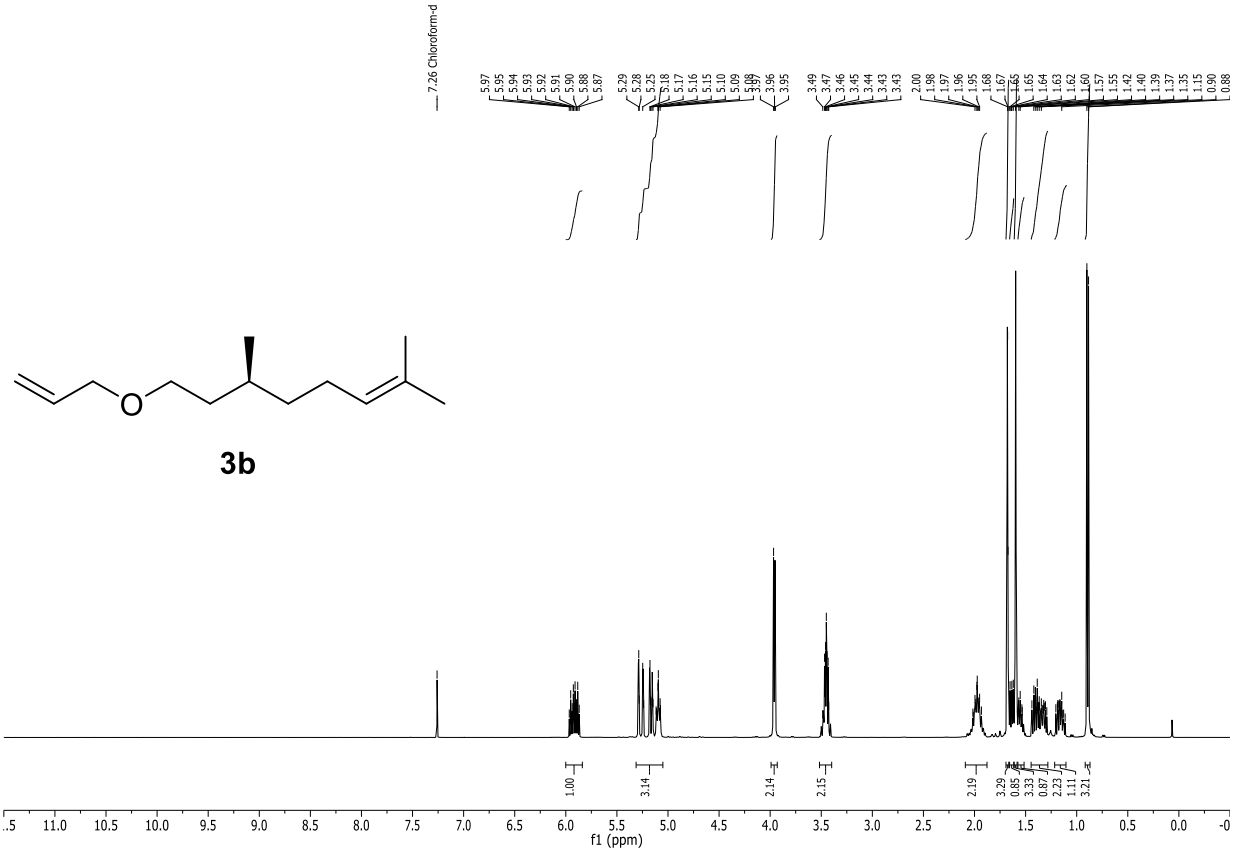


3a

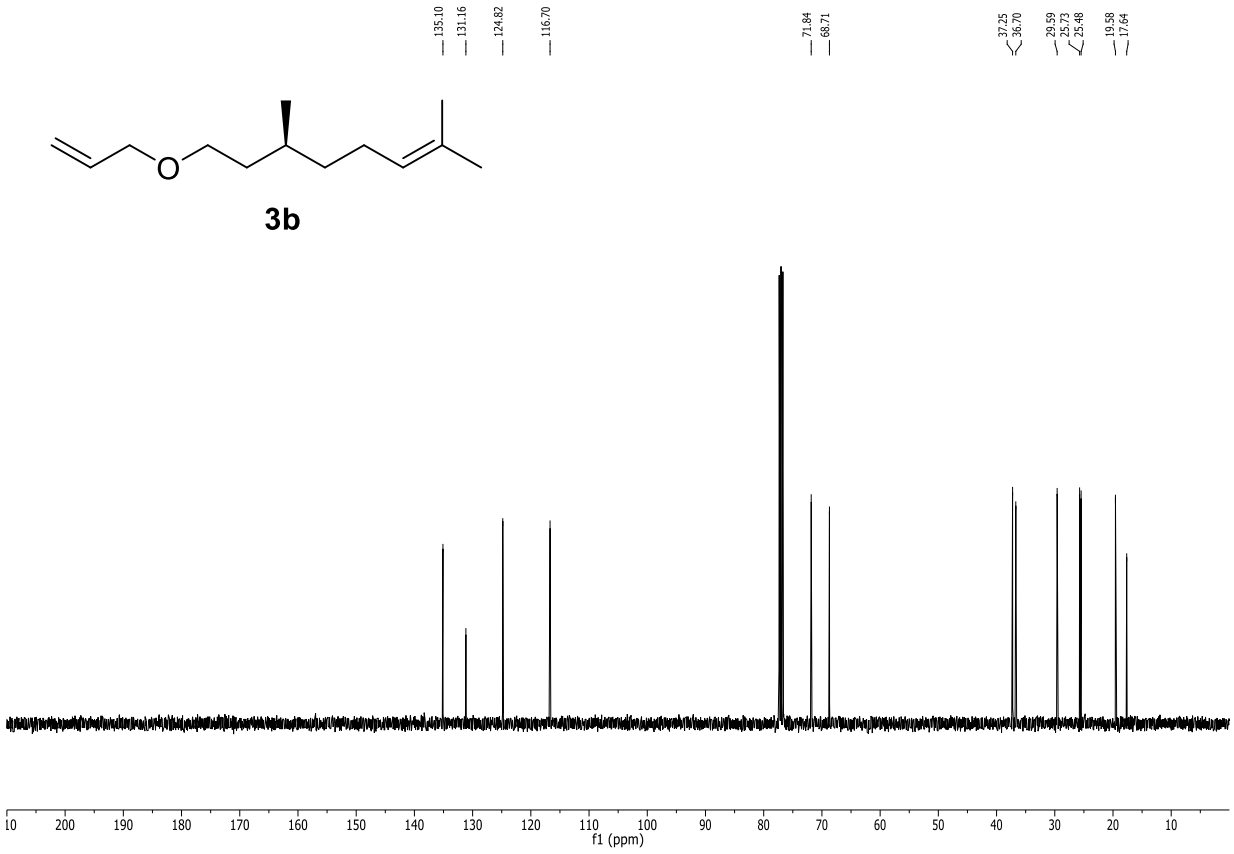


3a

(S)-8-(Allyloxy)-2,6-dimethyloct-2-ene (**3b**)

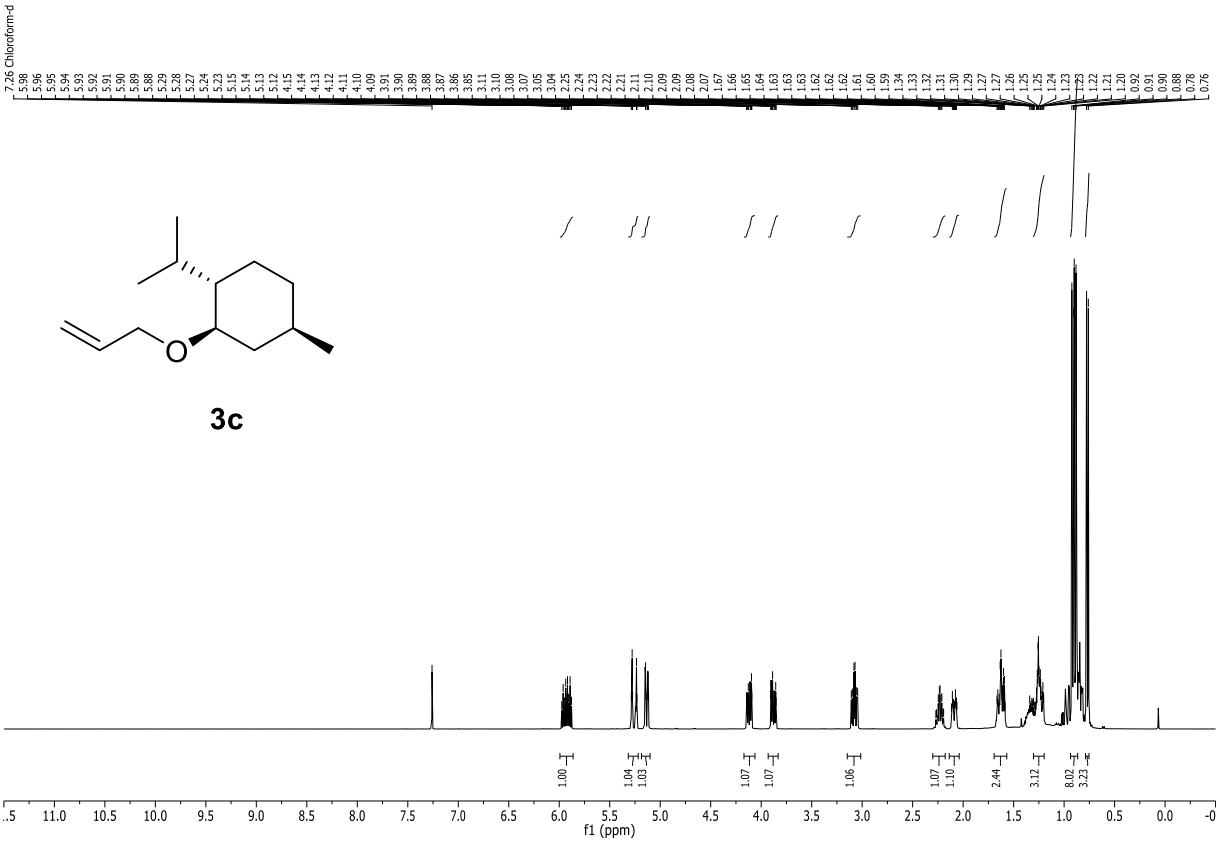


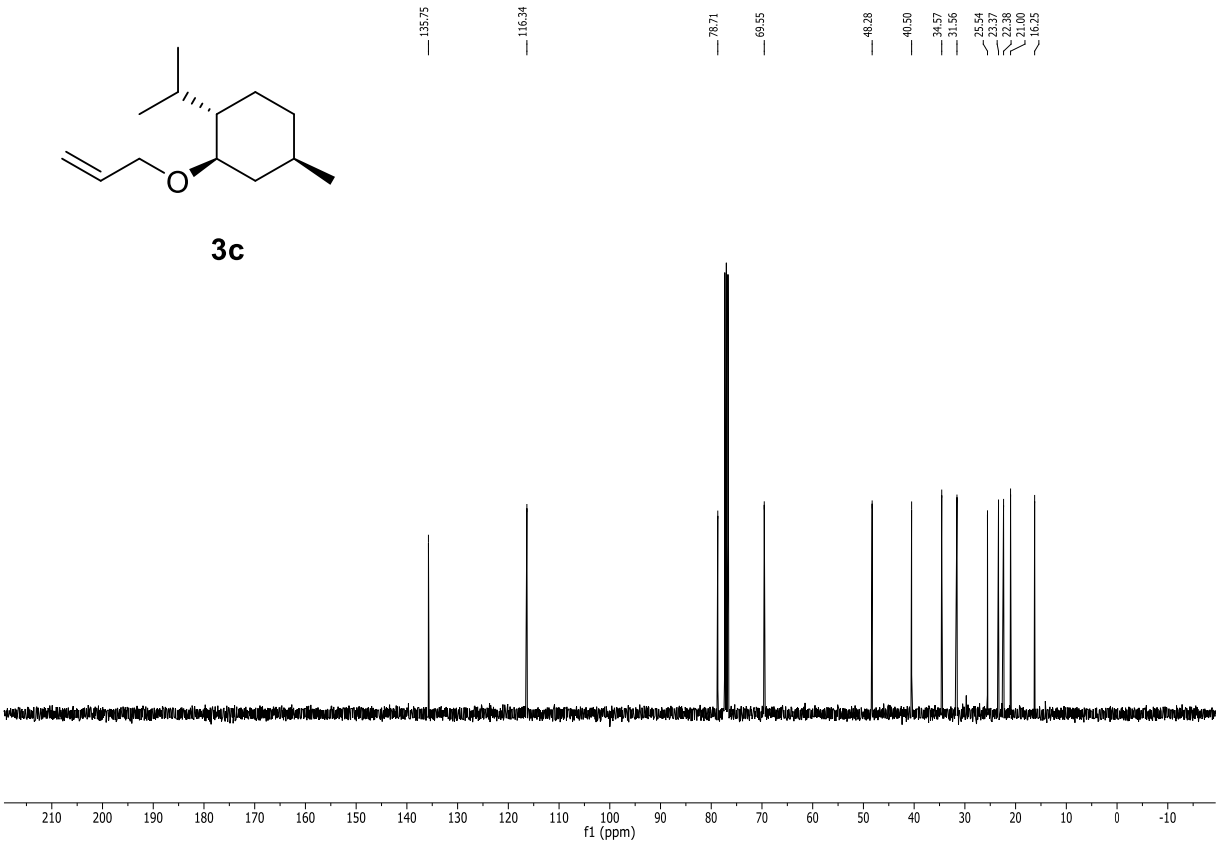
3b



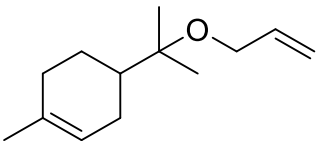
3b

(1S,2R,4R)-2-(Allyloxy)-1-isopropyl-4-methylcyclohexane(**3c**)

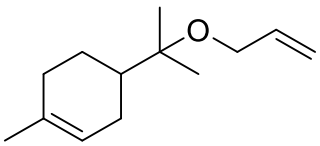




4-(2-(Allyloxy)propan-2-yl)-1-methylcyclohex-1-ene (**3d**)

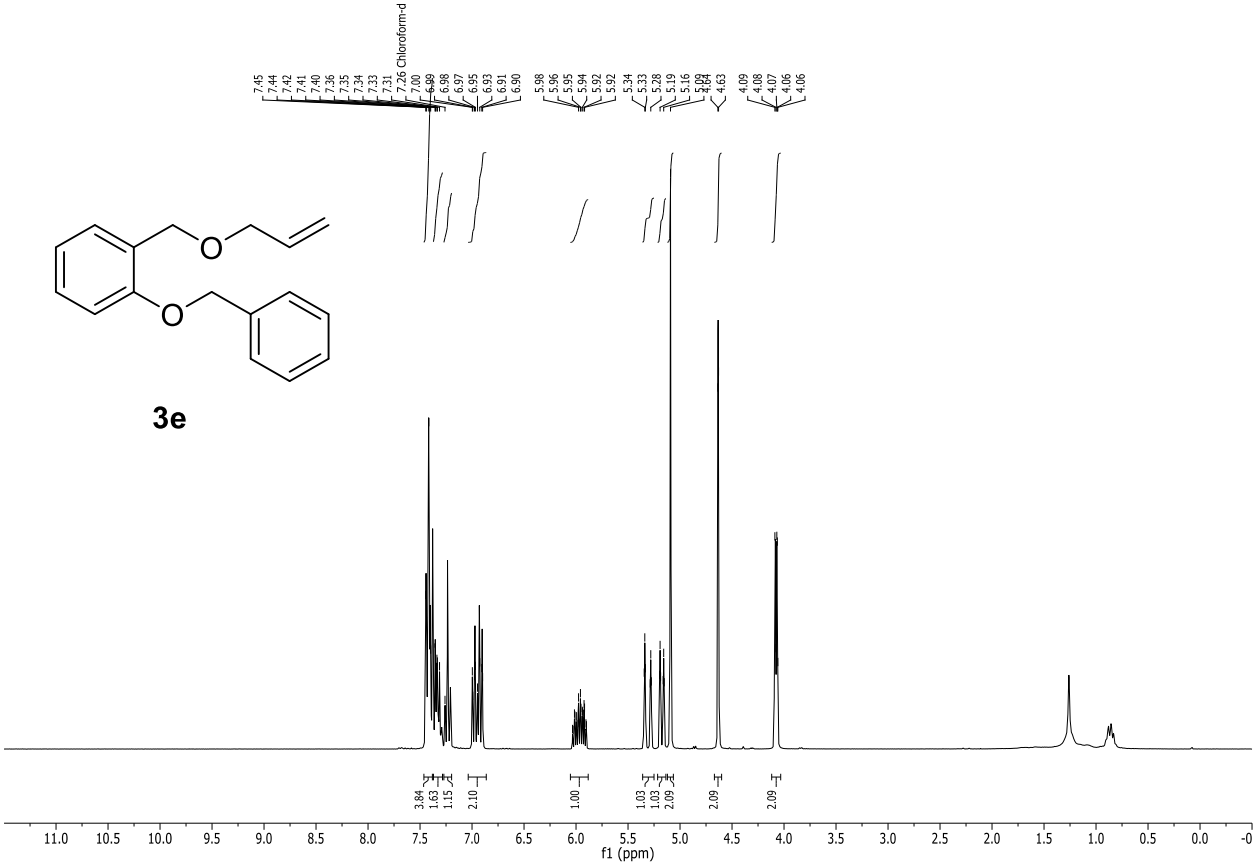


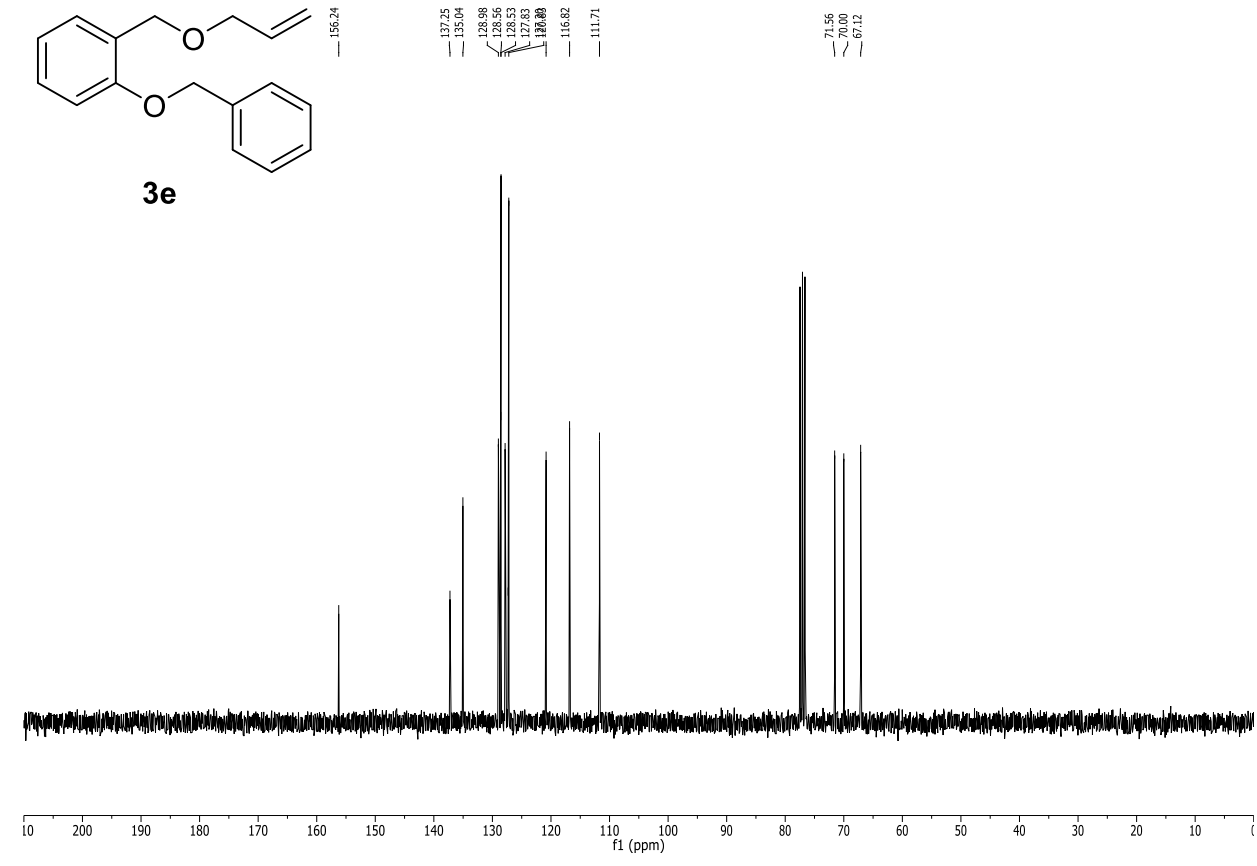
3d



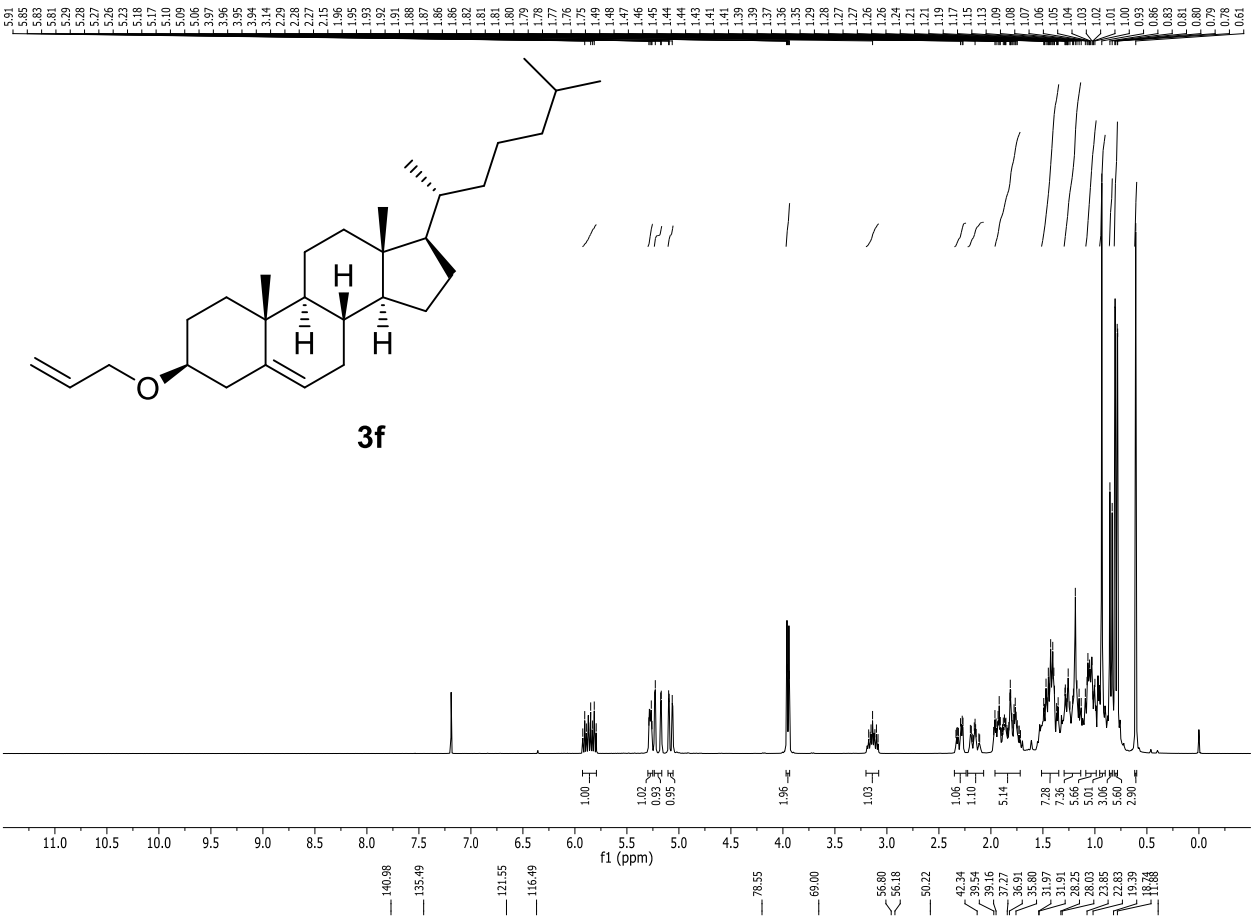
3d

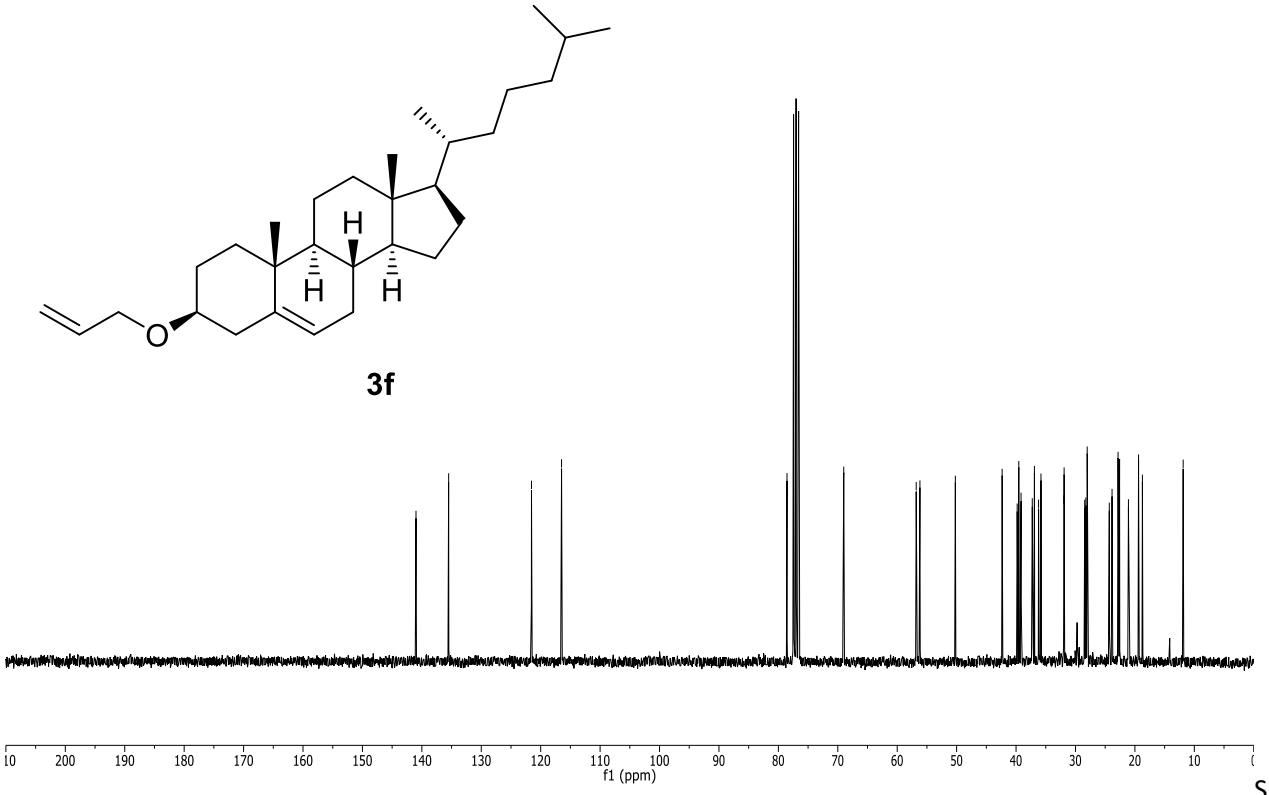
1-((Allyloxy)methyl)-2-(benzyloxy)benzene (**3e**)



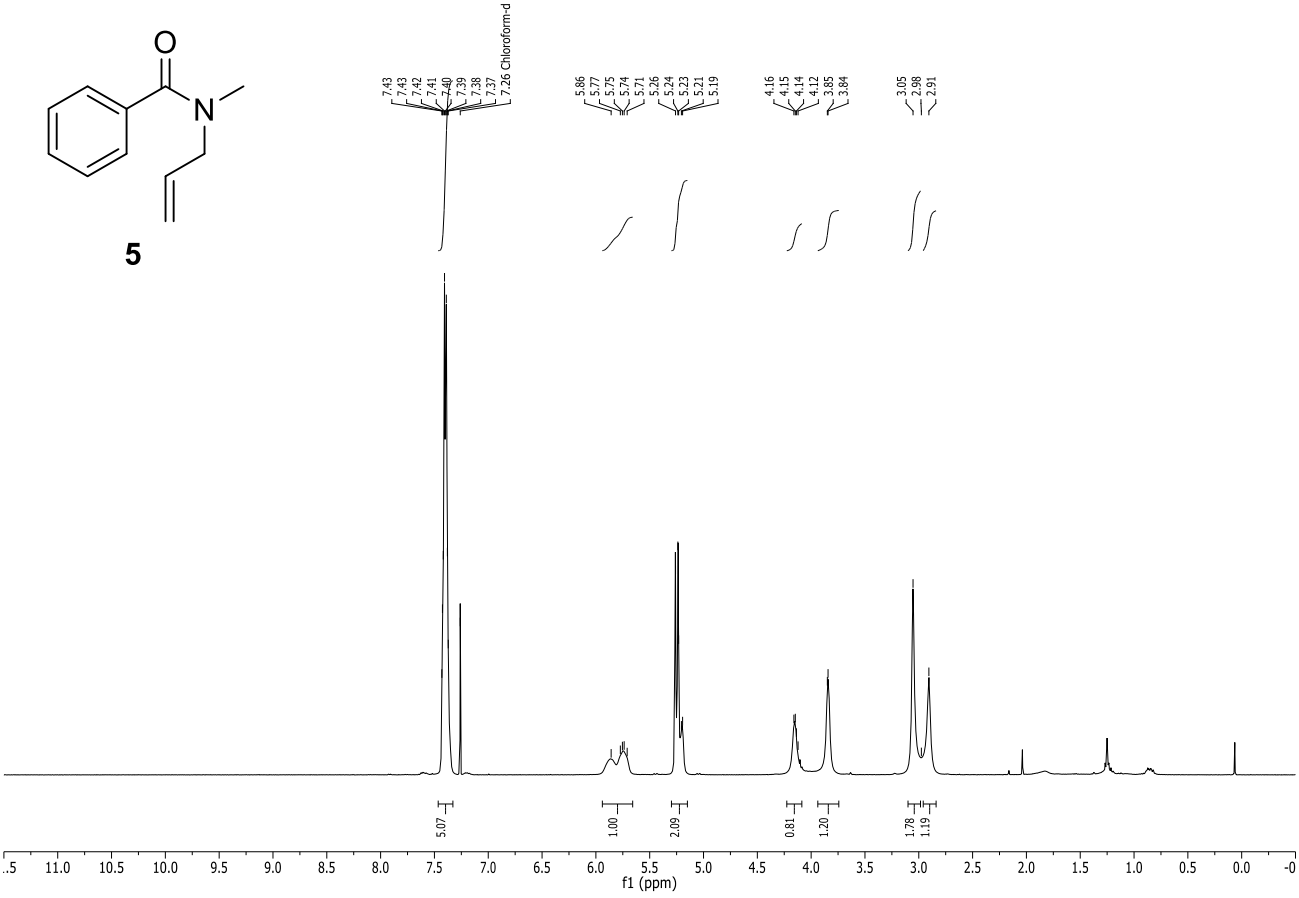


(3S,8S,9S,10R,13R,14S,17R)-3-(Allyloxy)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (**3f**)



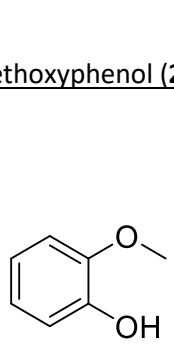


N-Allyl-*N*-methylbenzamide (**5**)

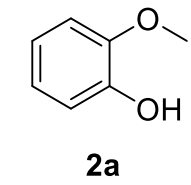


5. NMR SPECTRA: PRODUCTS

2-Methoxyphenol (**2a**)

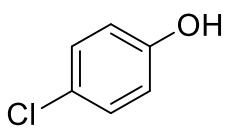


2a

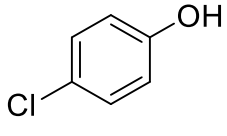


2a

4-Chlorophenol (**2b**)

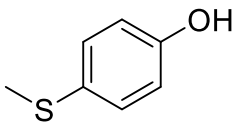


2b

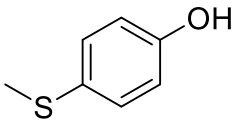


2b

4-(Methylthio)phenol (**2c**)

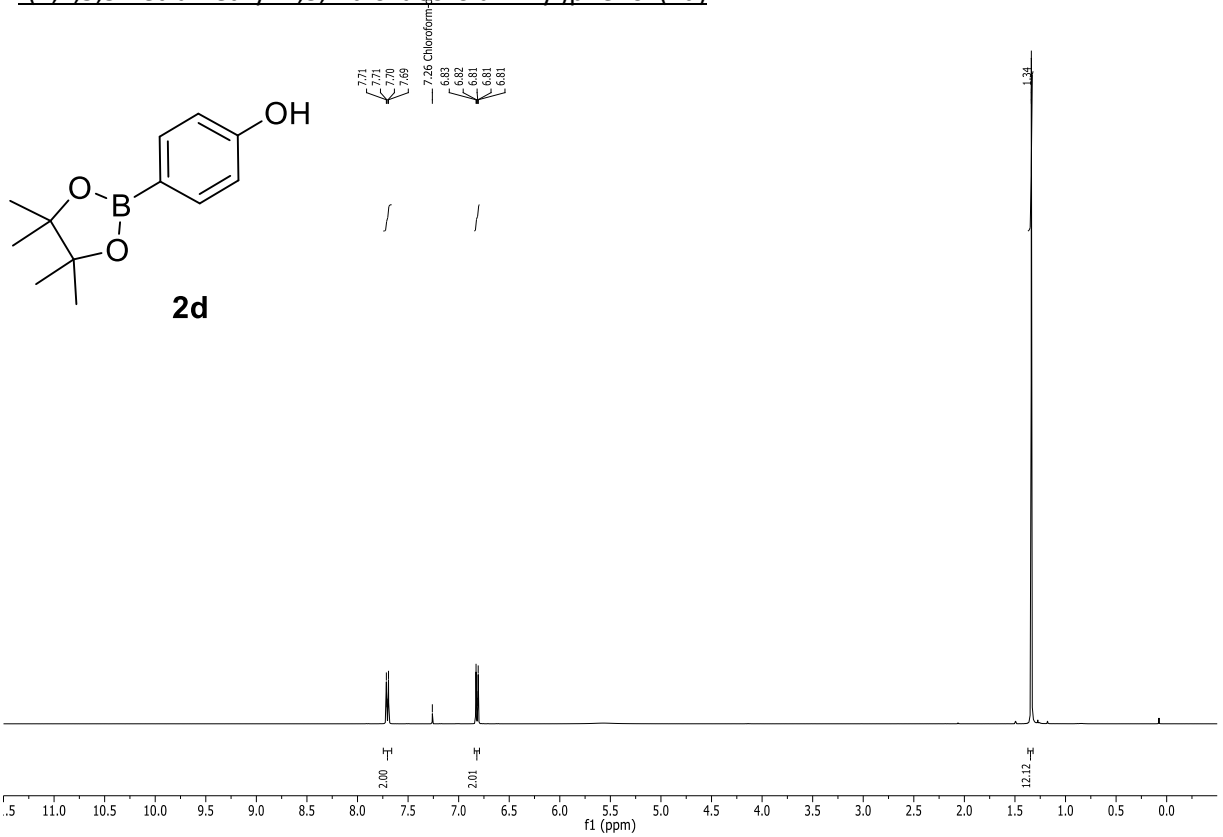


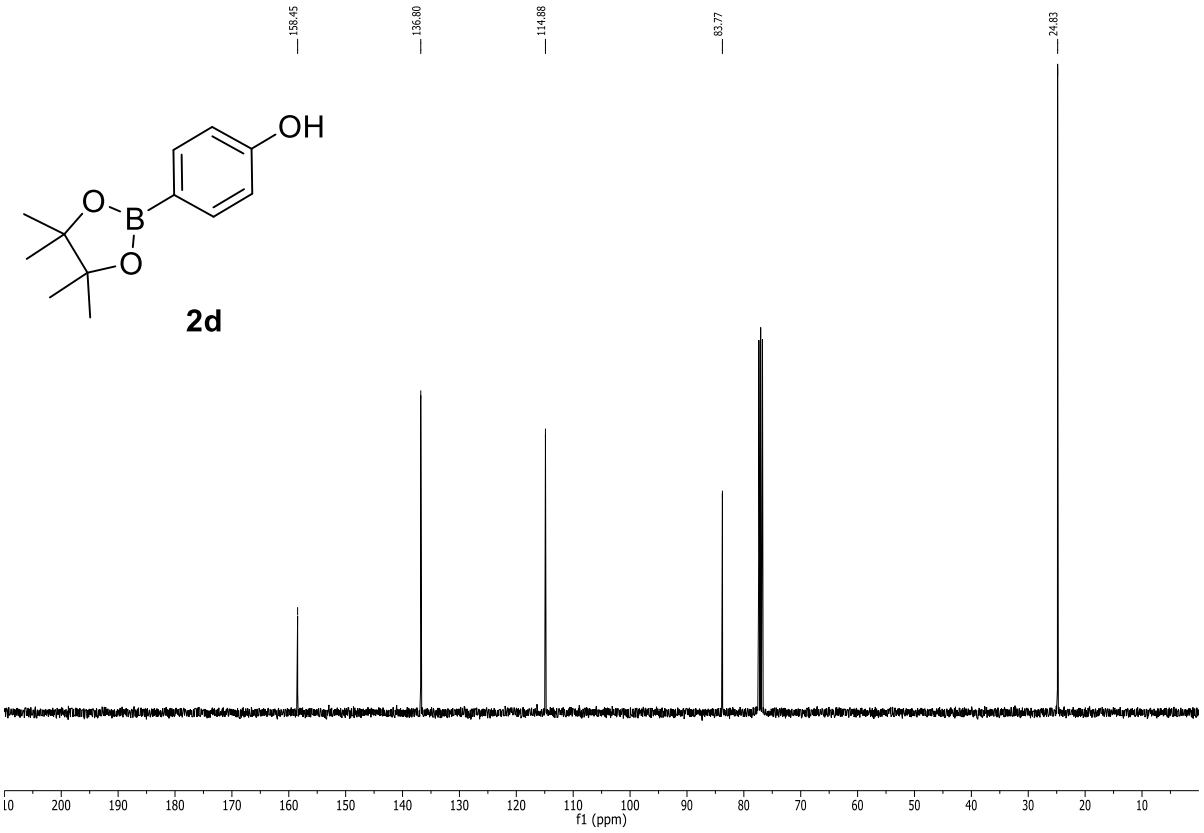
2c



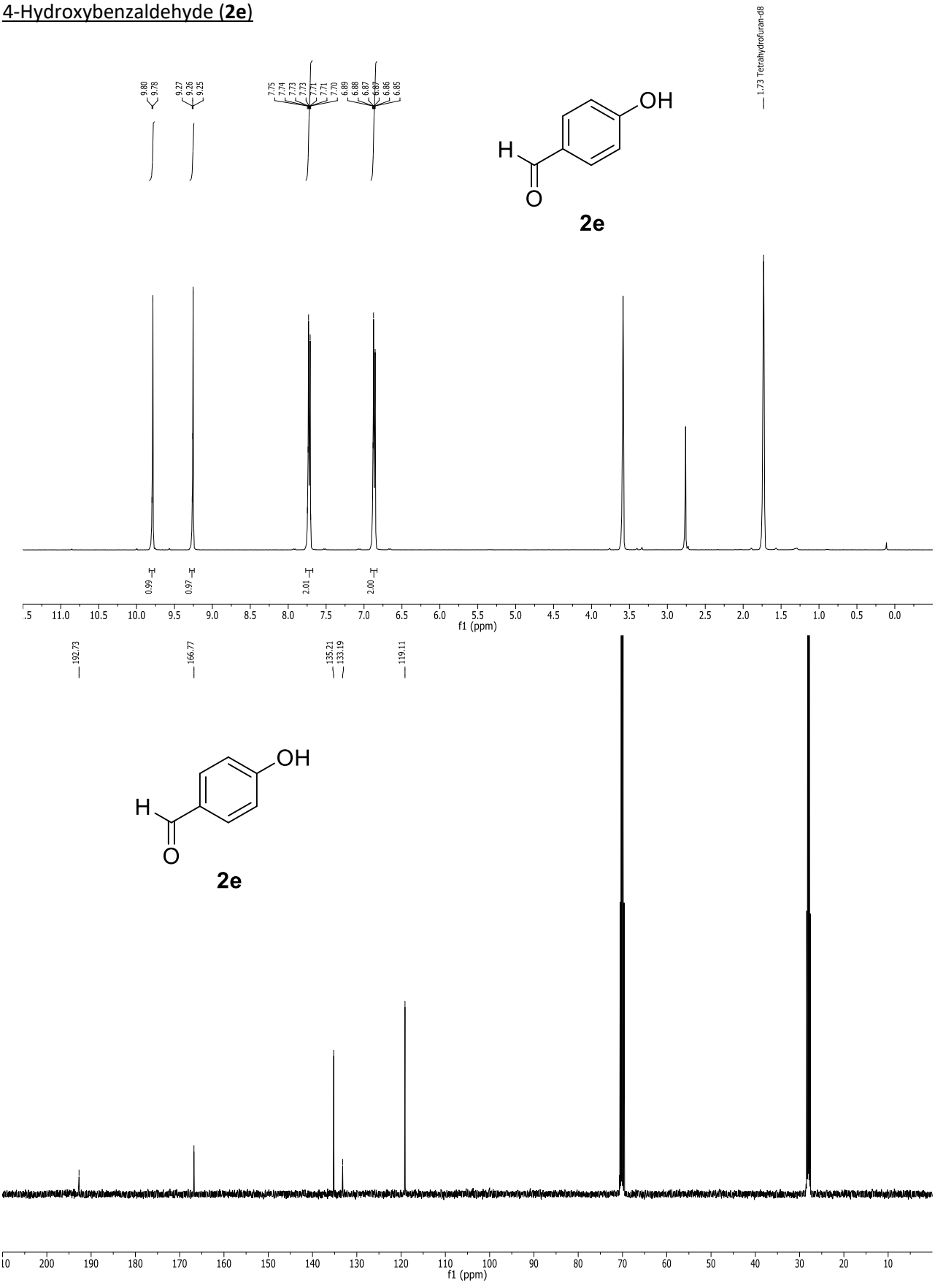
2c

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**2d**)

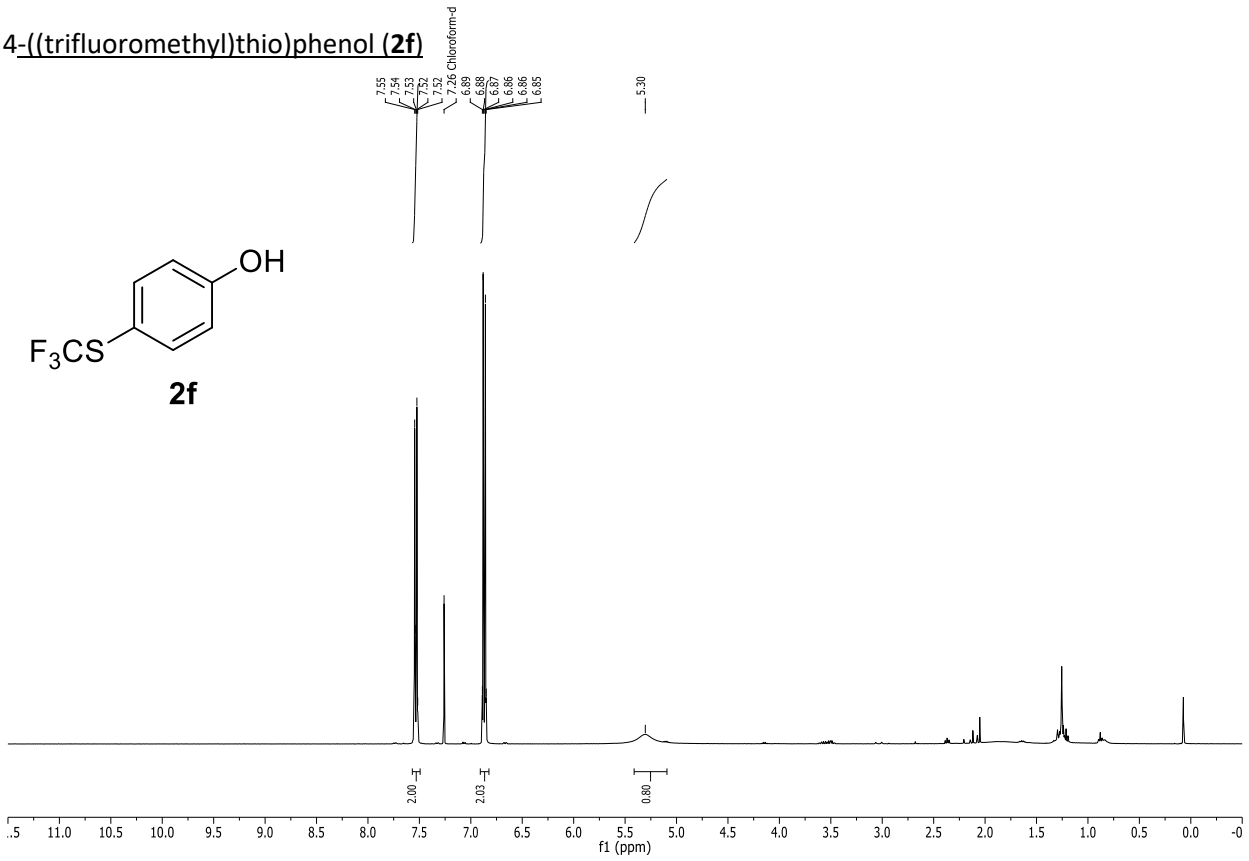


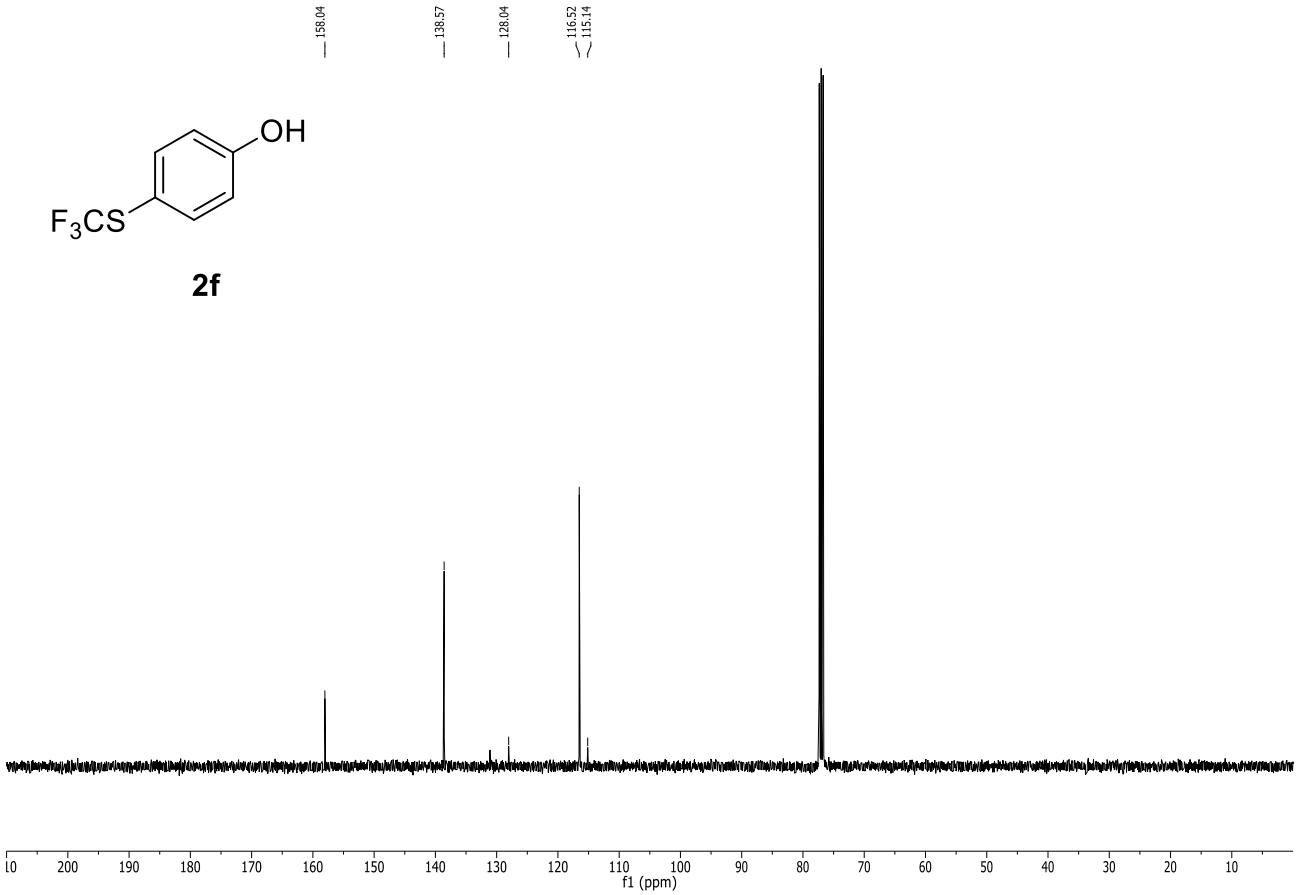


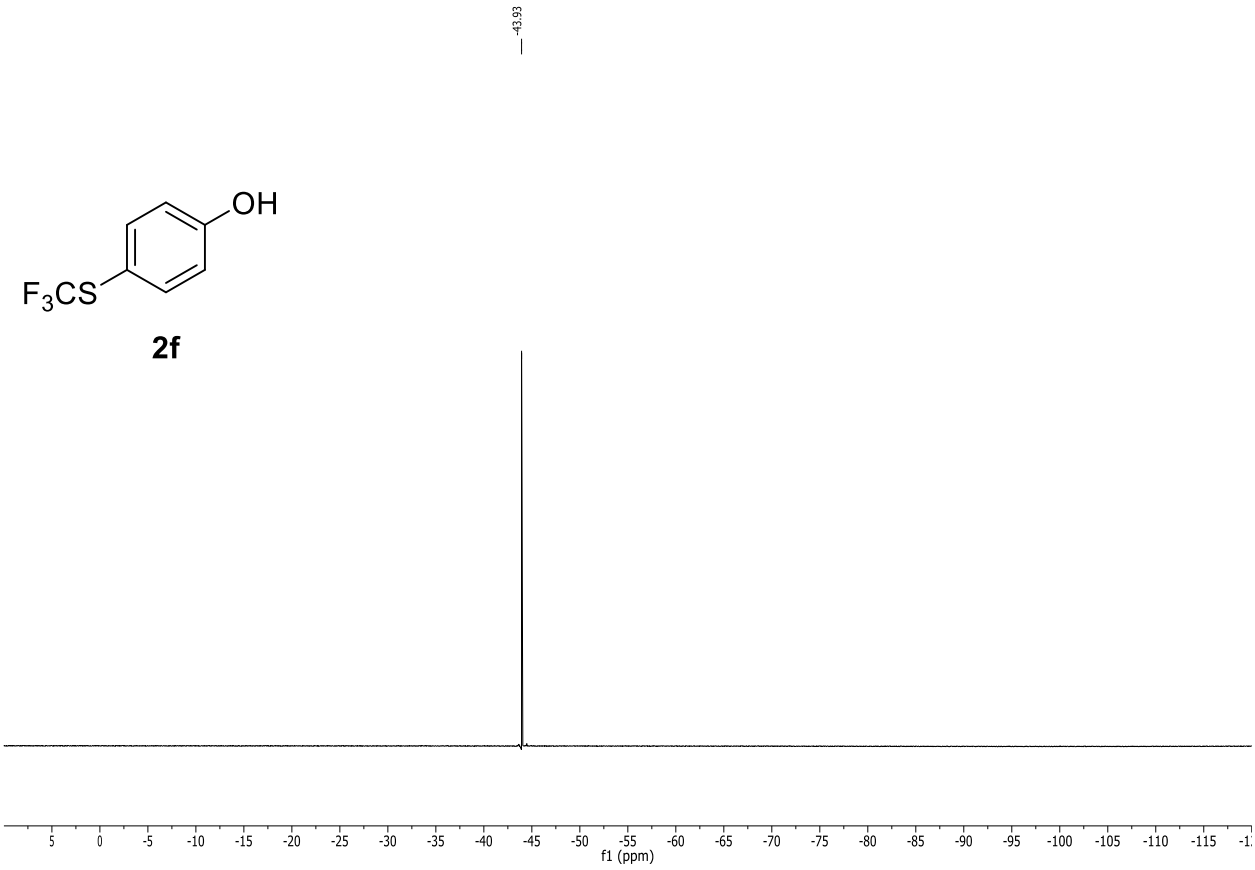
4-Hydroxybenzaldehyde (**2e**)



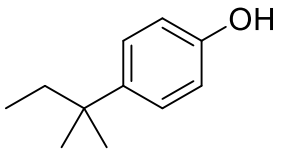
4-((trifluoromethyl)thio)phenol (**2f**)



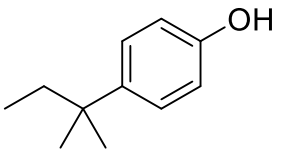



-43.93
OH
F3CS
2f
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
f1 (ppm)

4-(*tert*-Pentyl)phenol (**2g**)

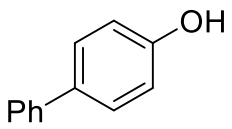


2g

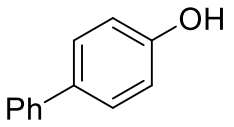


2g

4-Phenylphenol (**2h**)

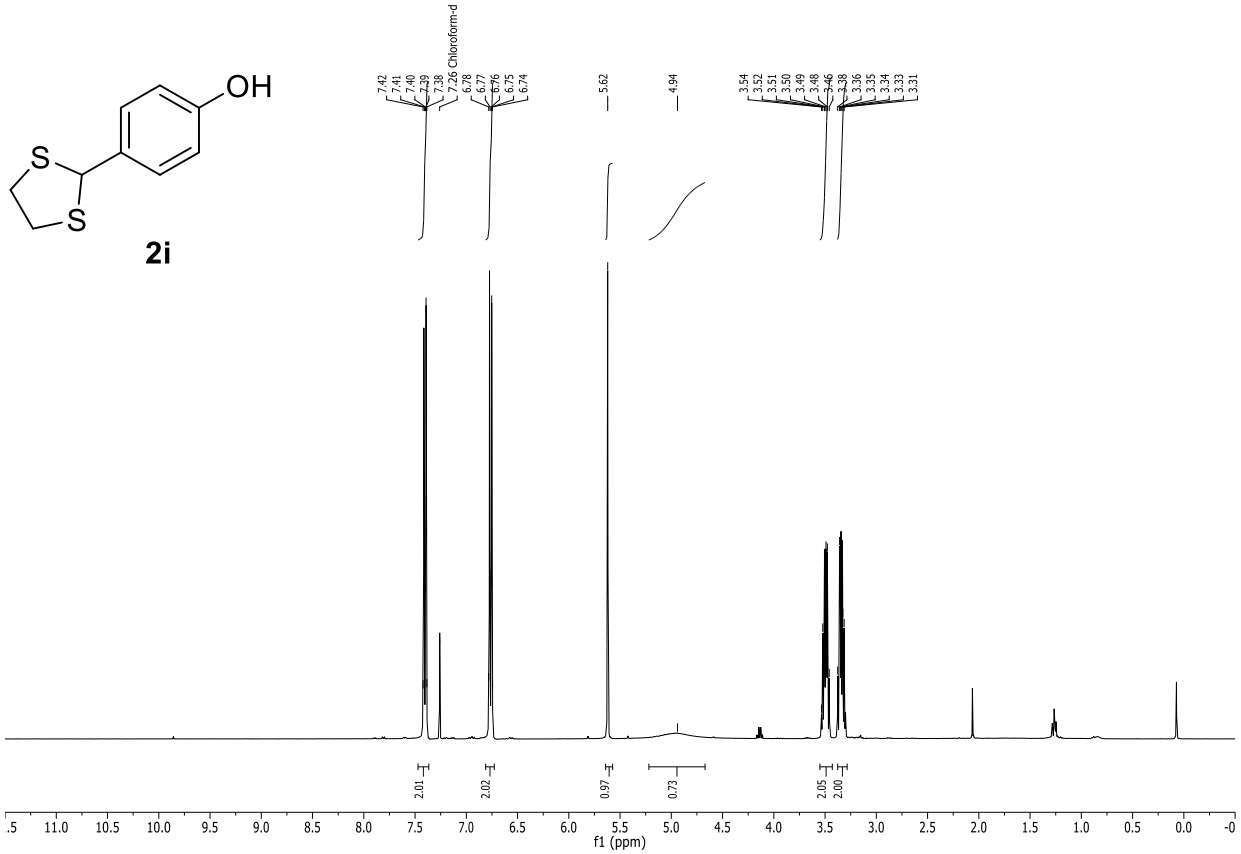


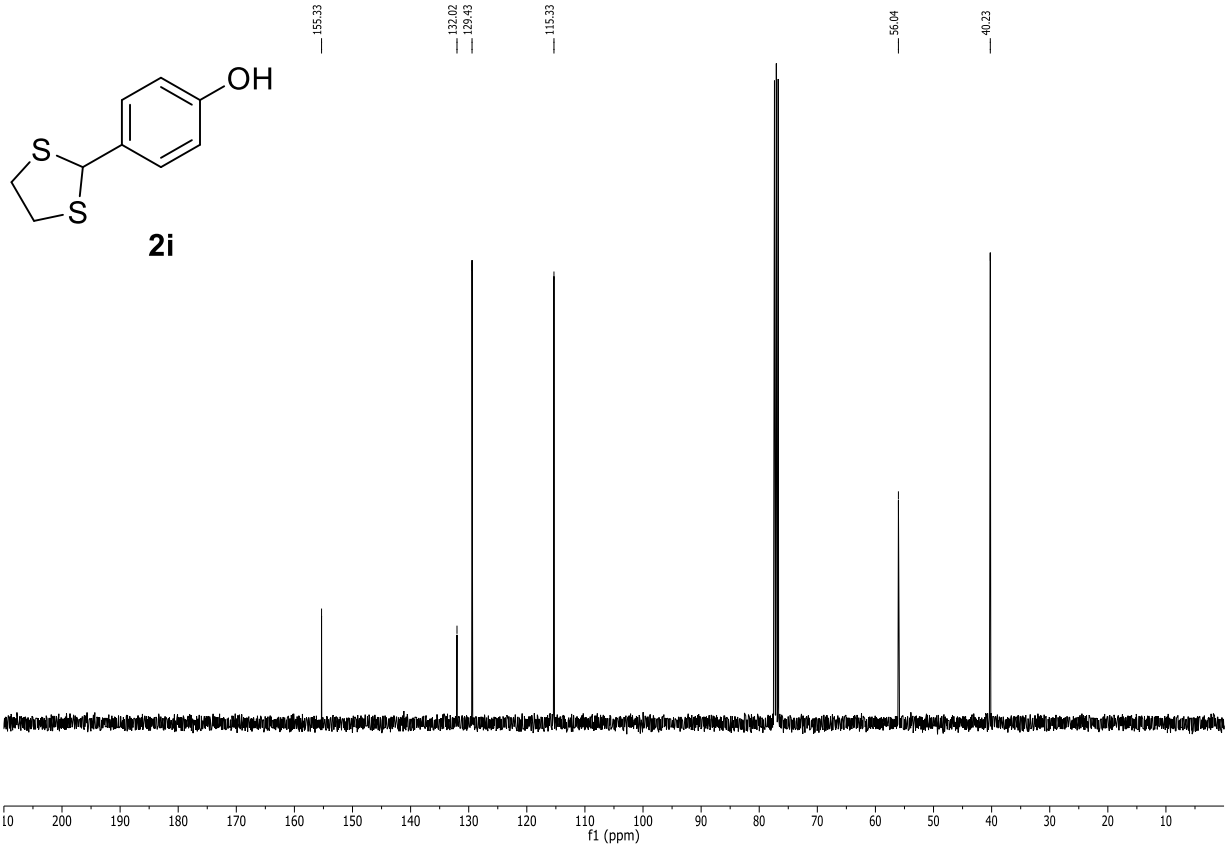
2h



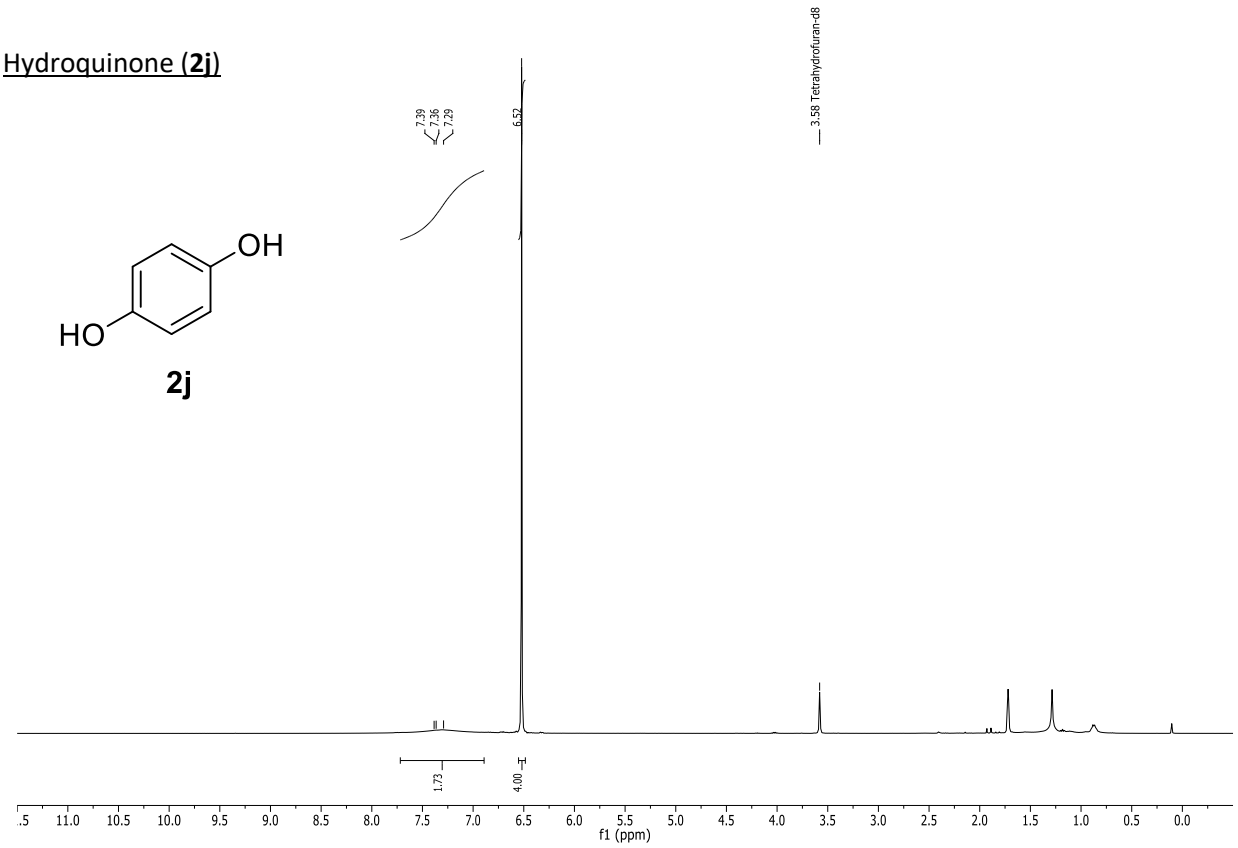
2h

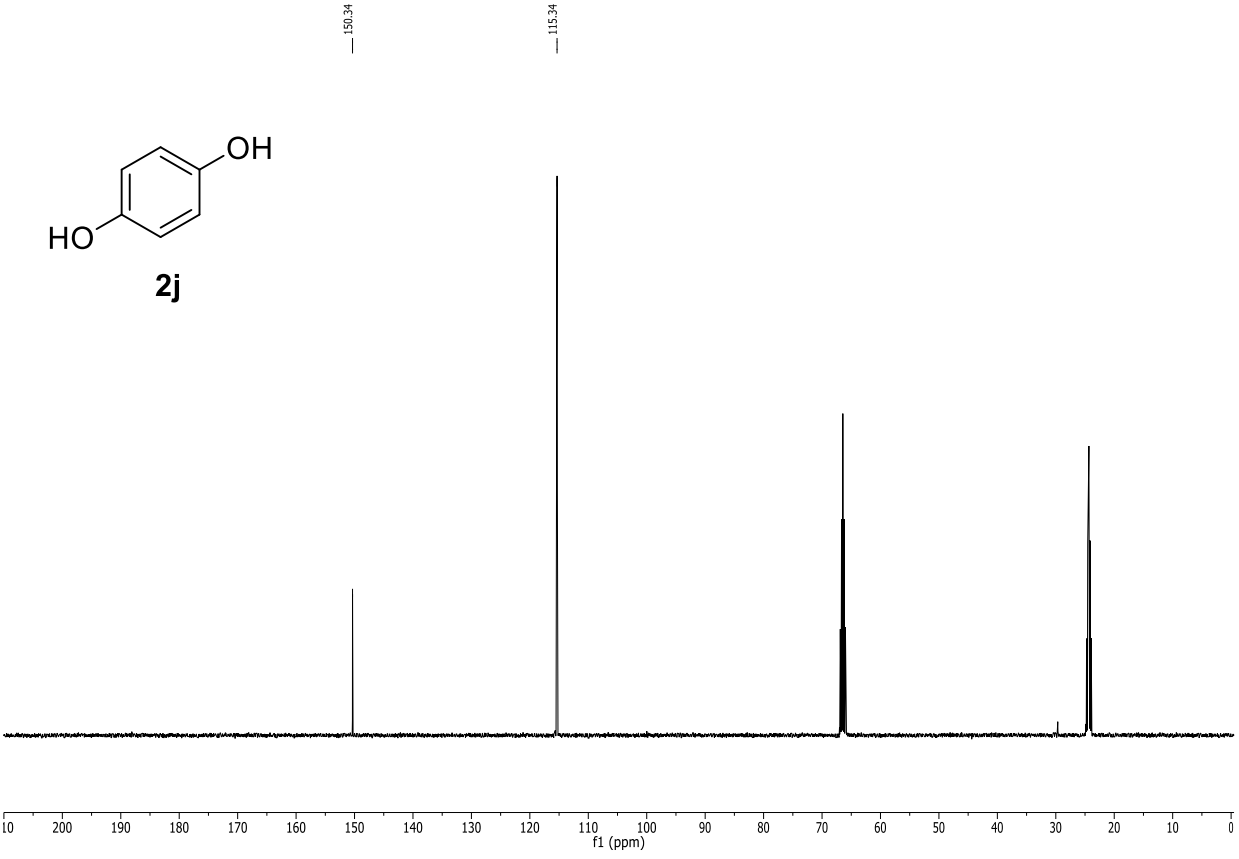
4-(1,3-Dithiolan-2-yl)phenol (**2i**)



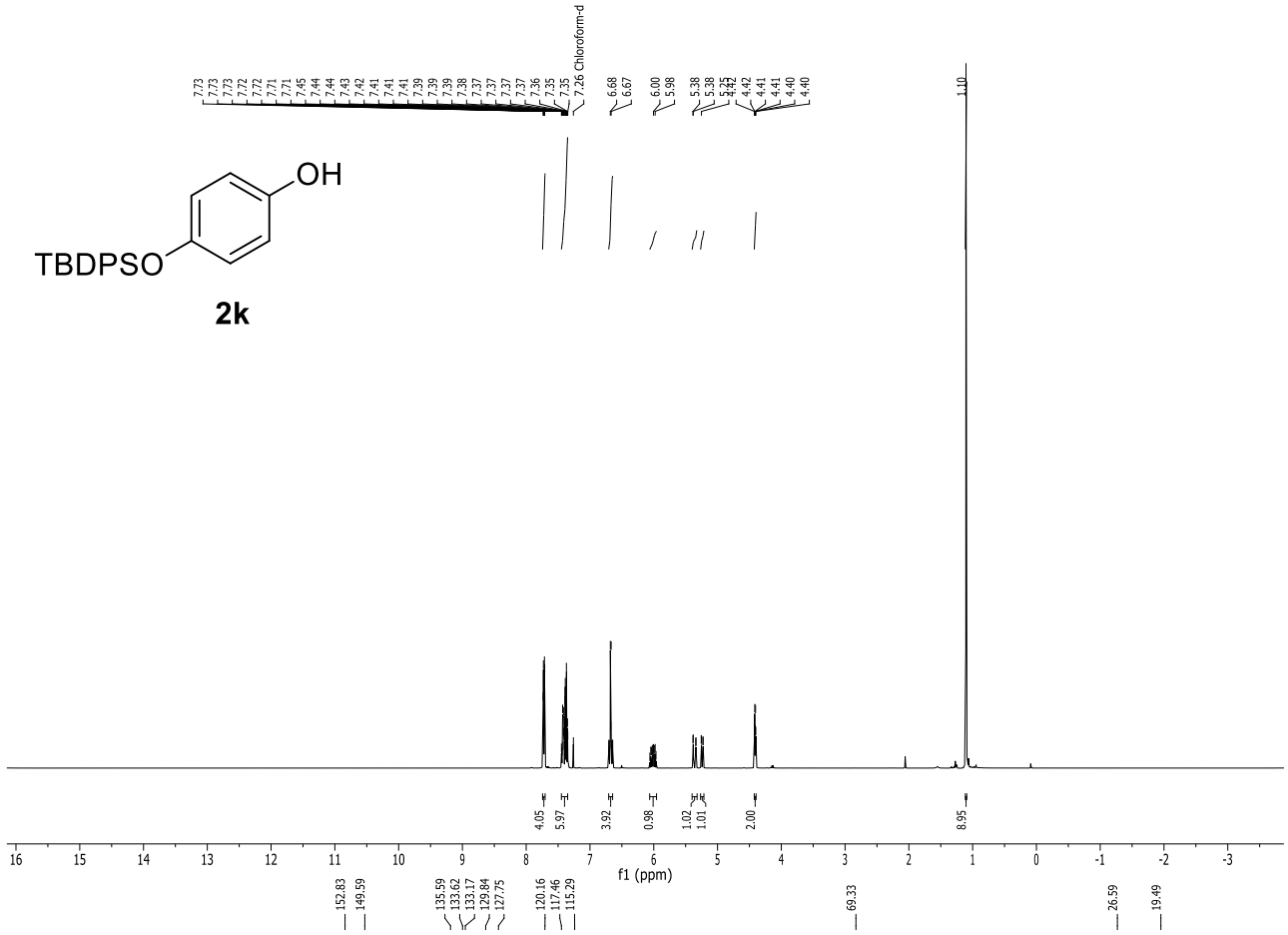


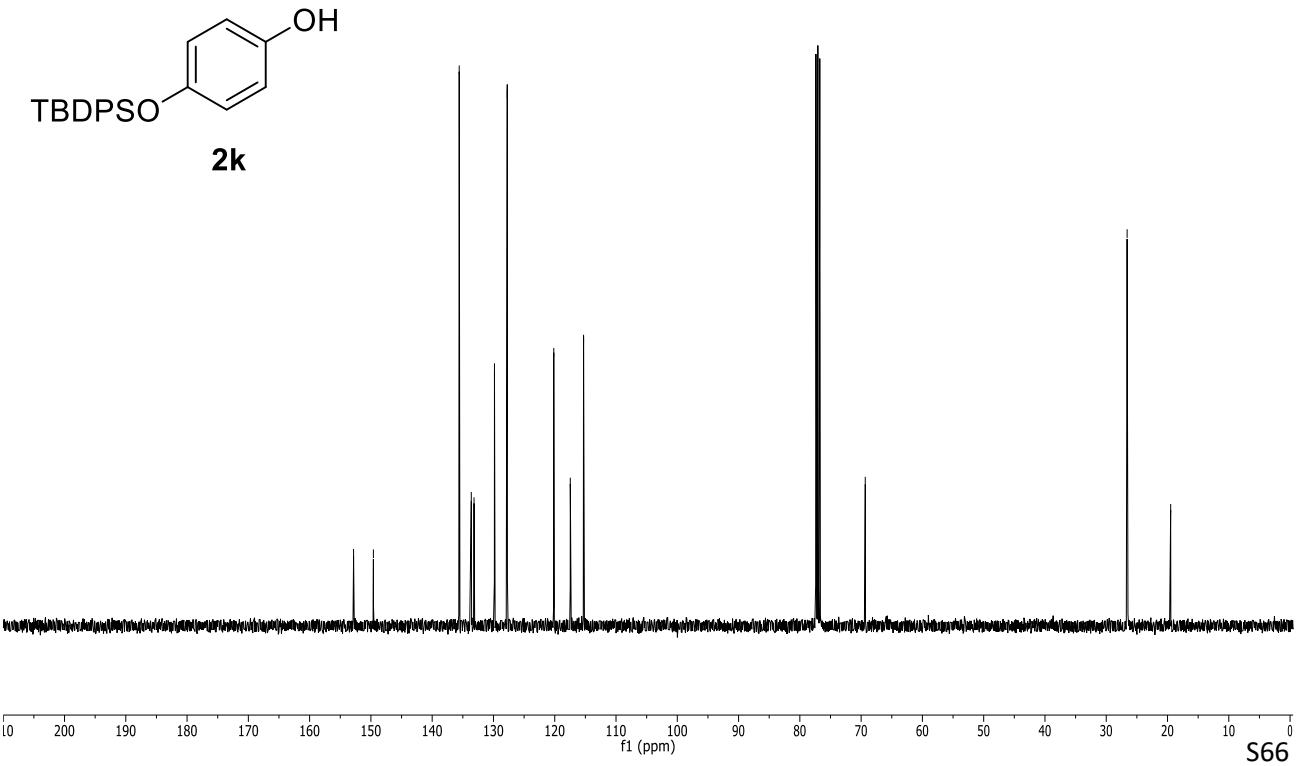
Hydroquinone (**2j**)



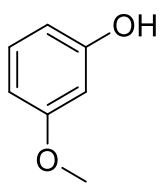


(4-(allyloxy)phenoxy)(tert-butyl)diphenylsilane (**2k**)

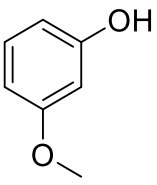




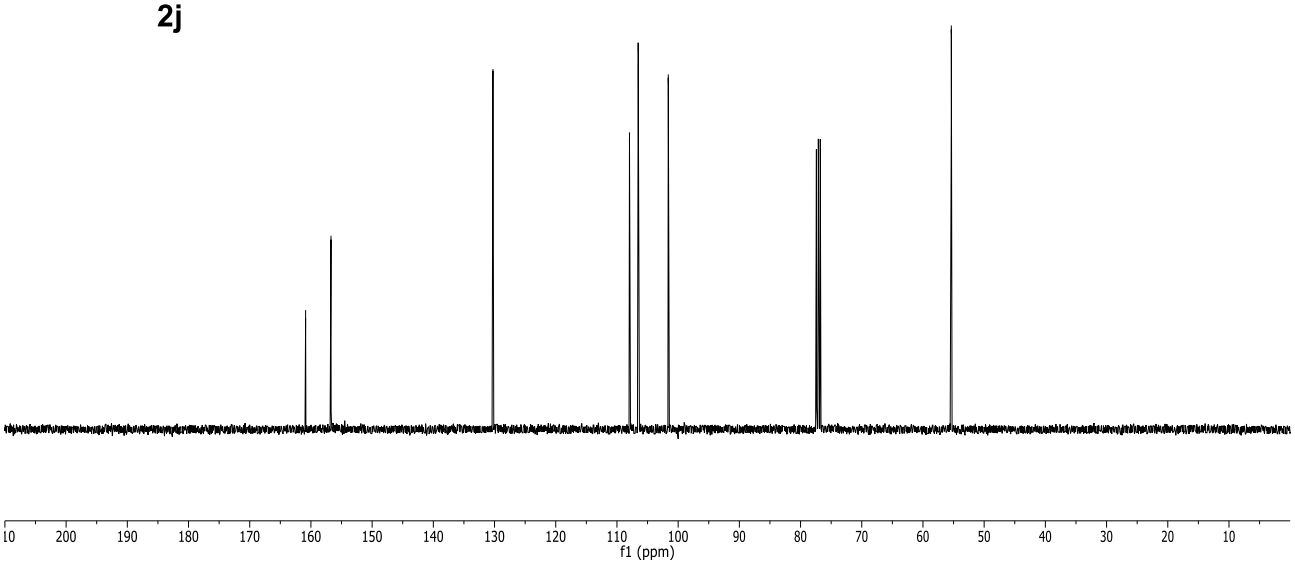
3-Methoxyphenol (**2l**)



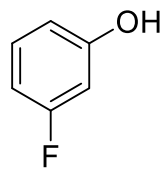
2l



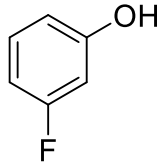
2j



3-Fluorophenol (**2m**)



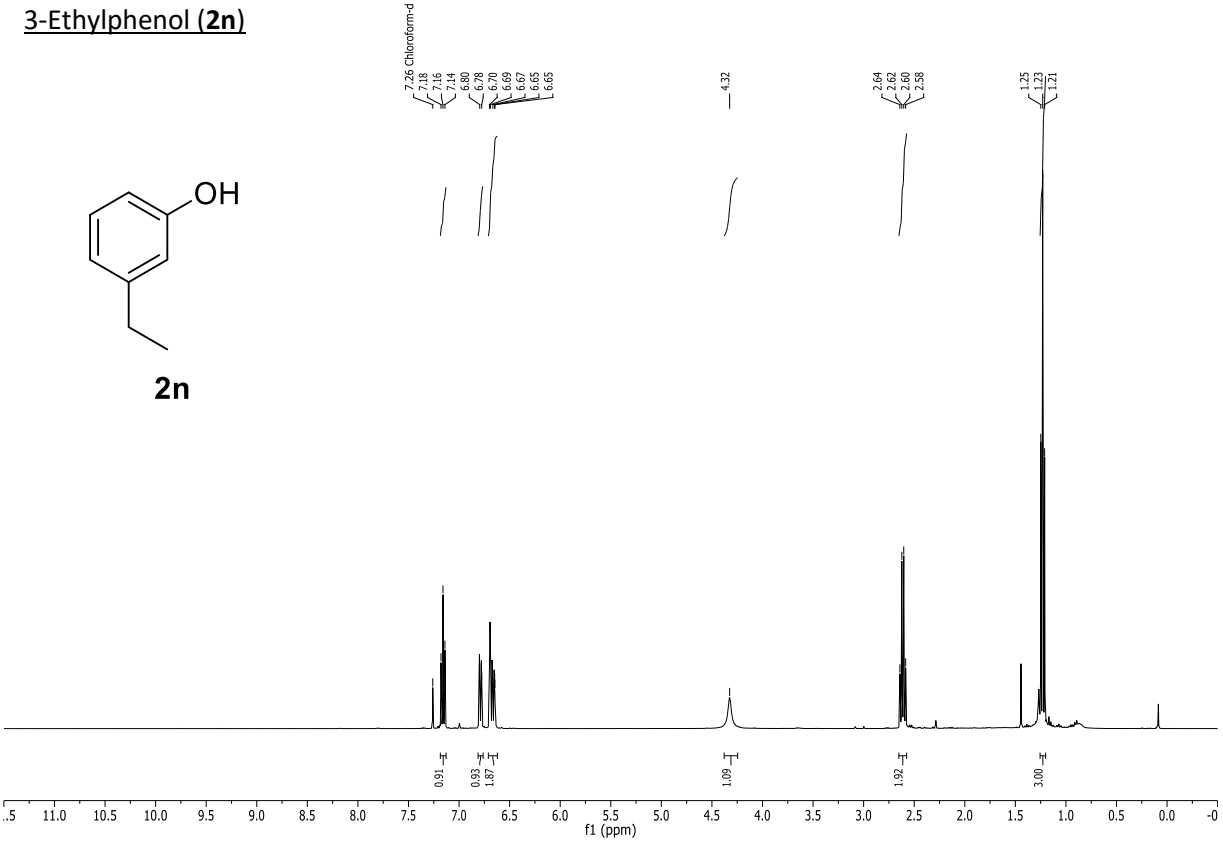
2m

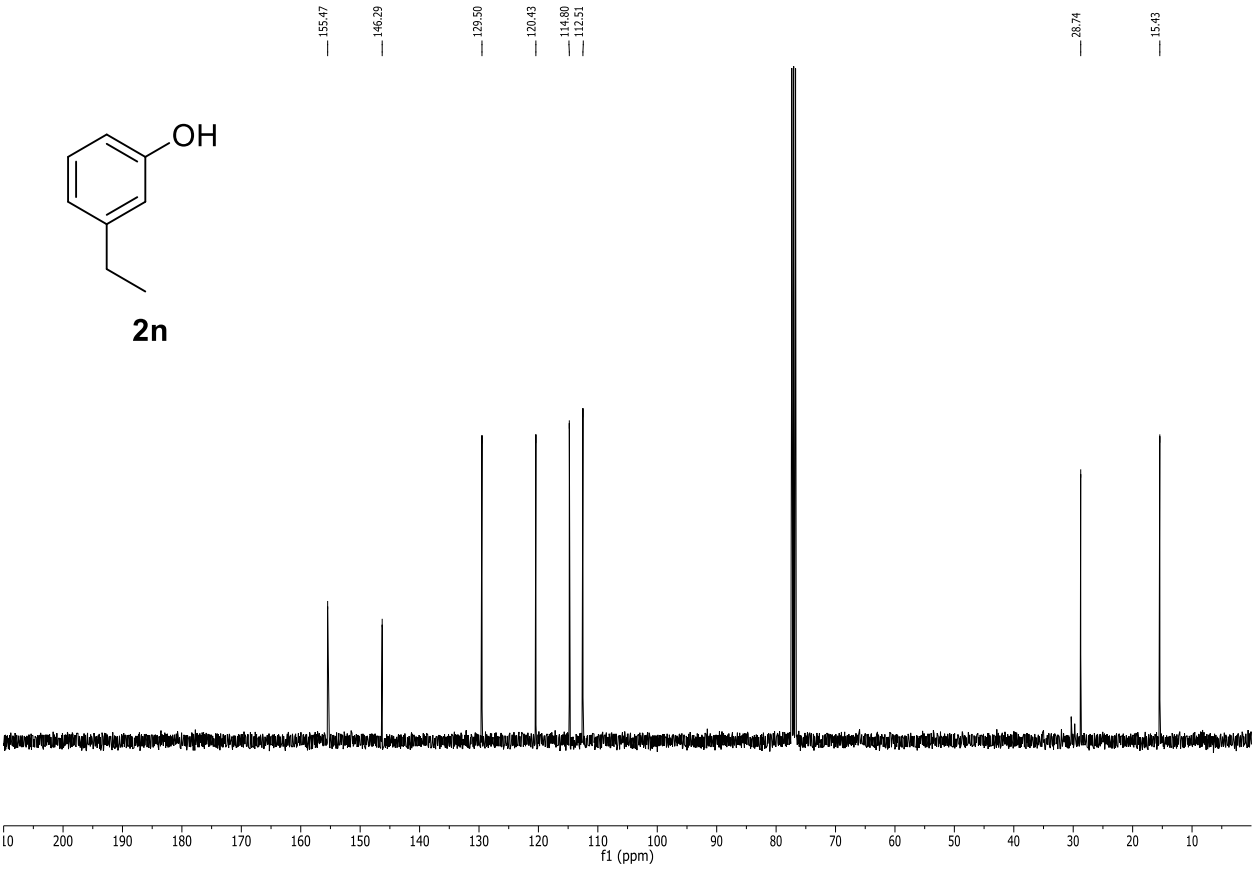


2m

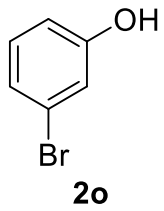

-111.60
-111.62
-111.63
-111.65
-111.67
-111.68
OH
F
2m
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

3-Ethylphenol (**2n**)

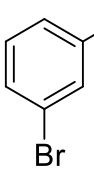




3-Bromophenol (**2o**)

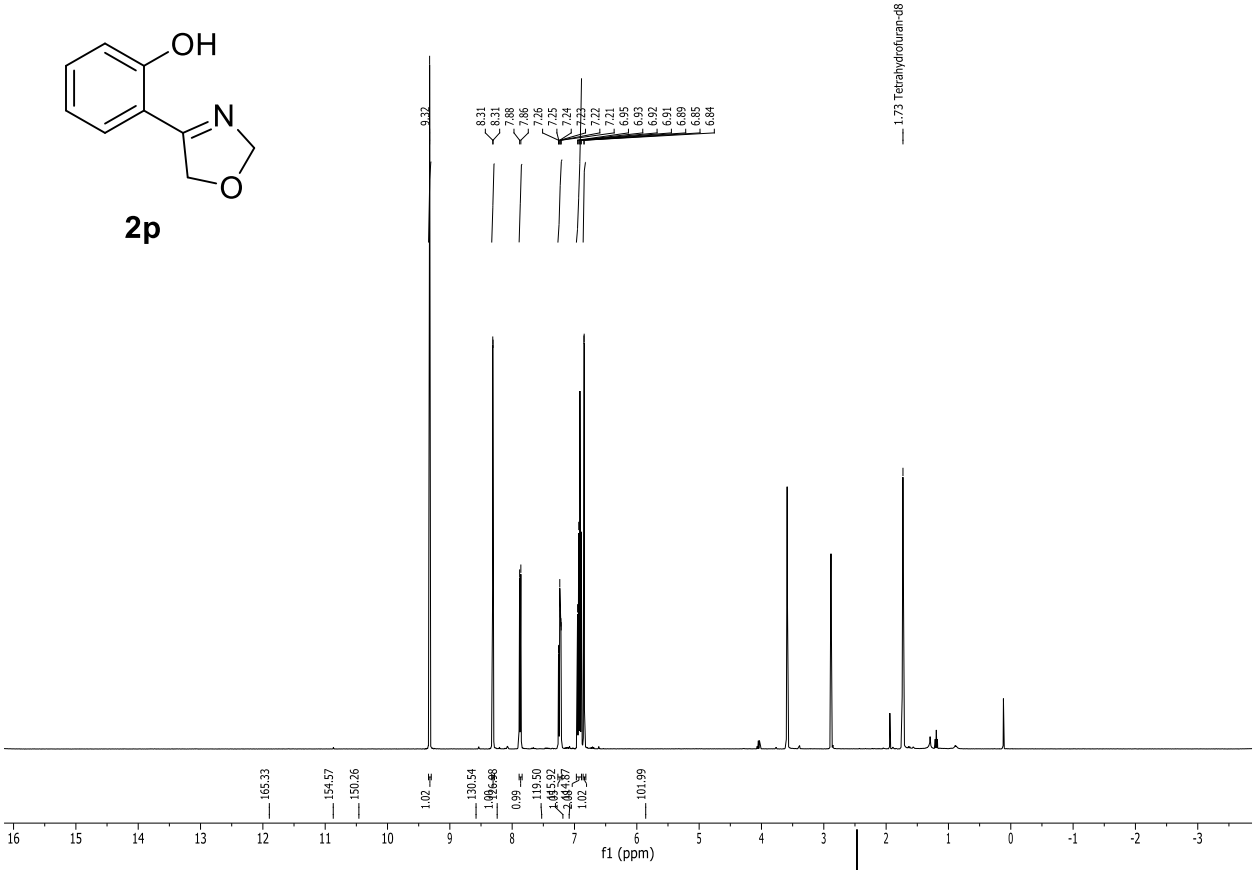


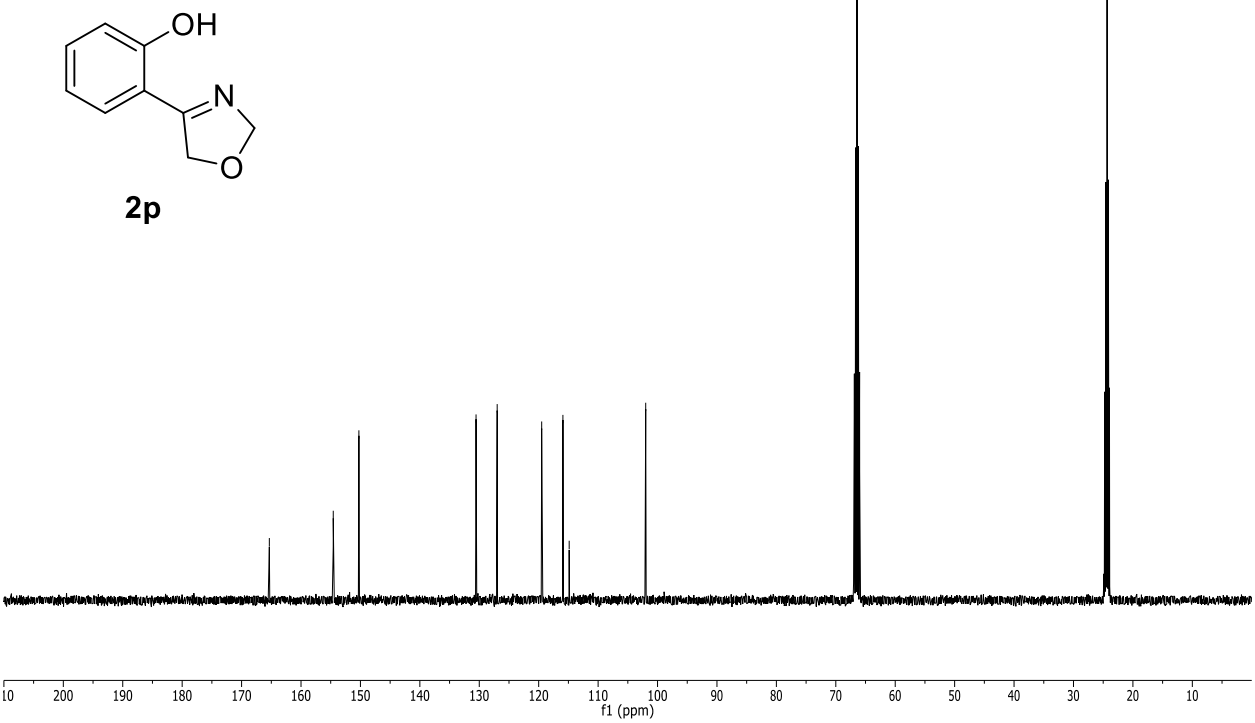
2o



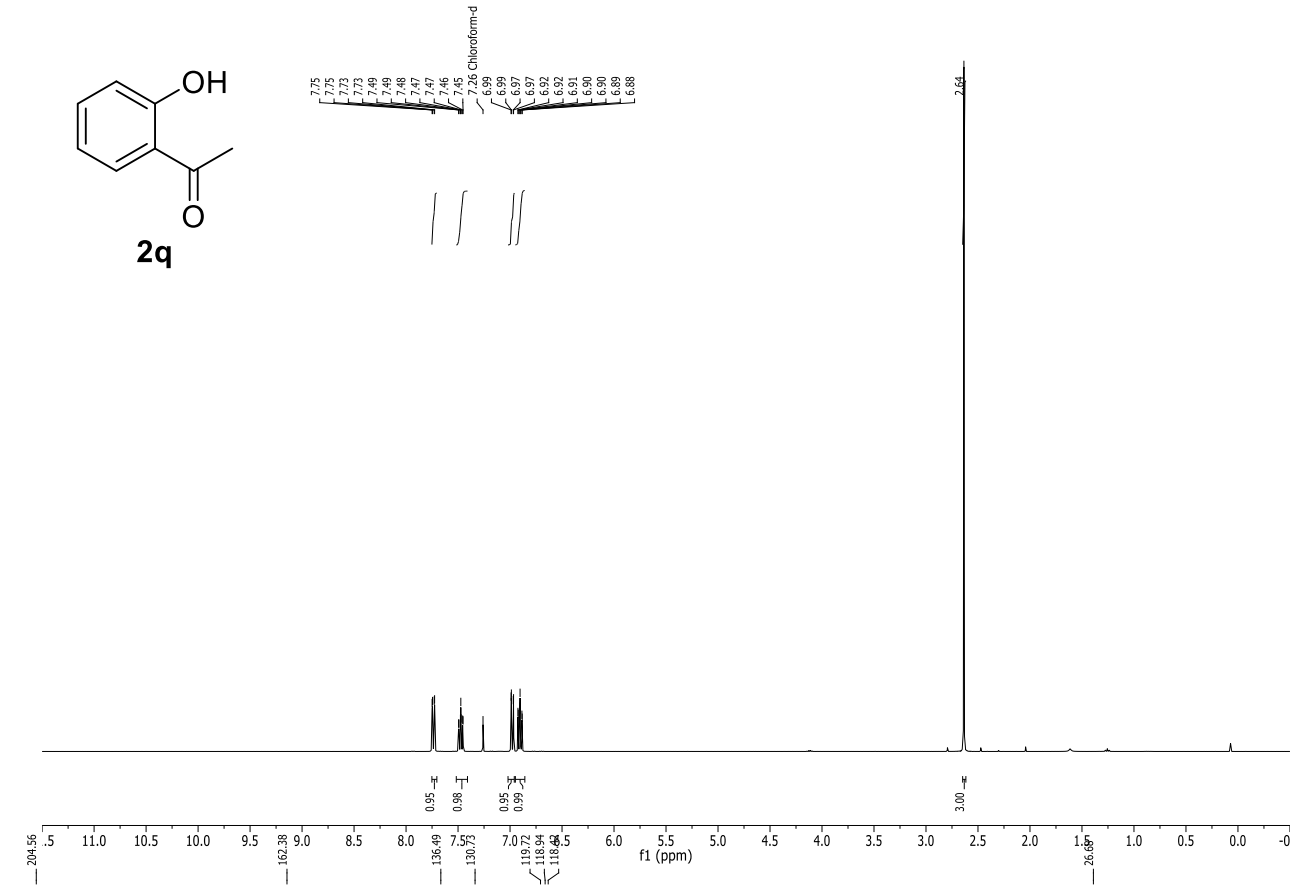
2o

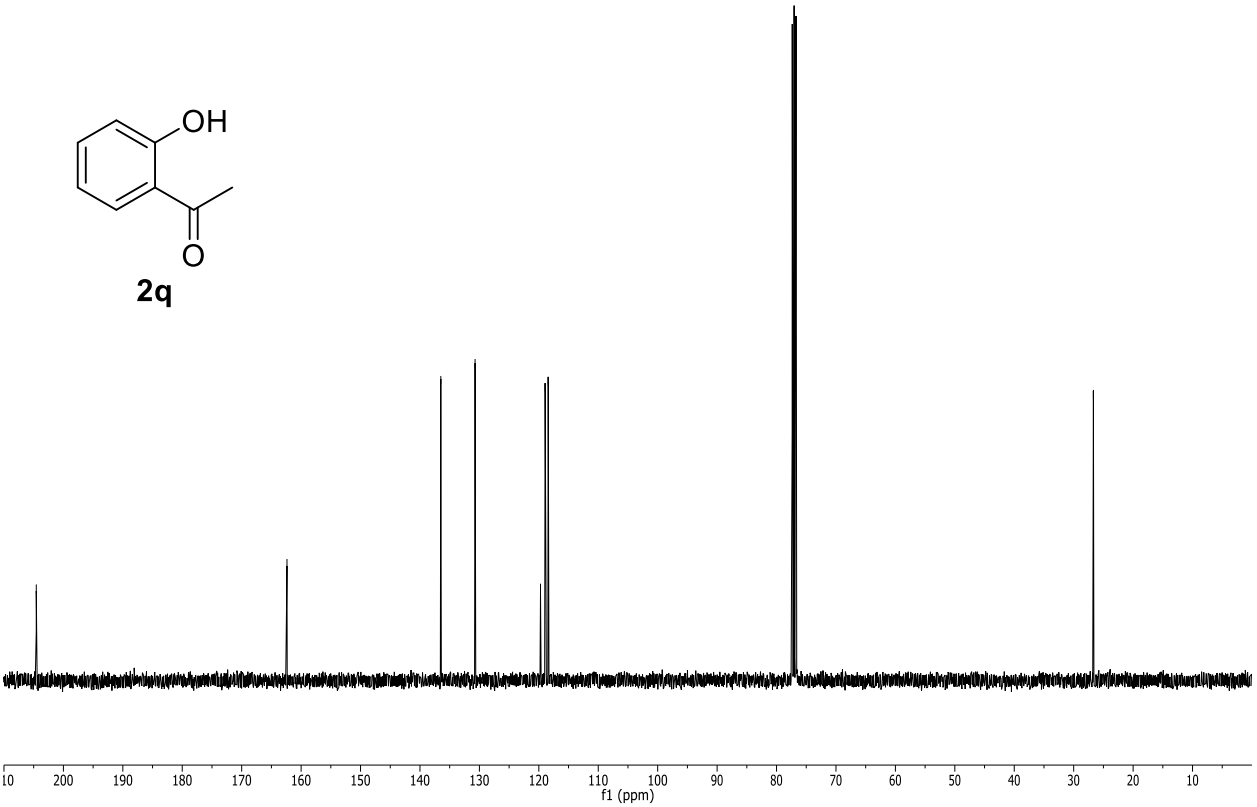
2-(2,5-Dihydrooxazol-4-yl)phenol (**2p**)



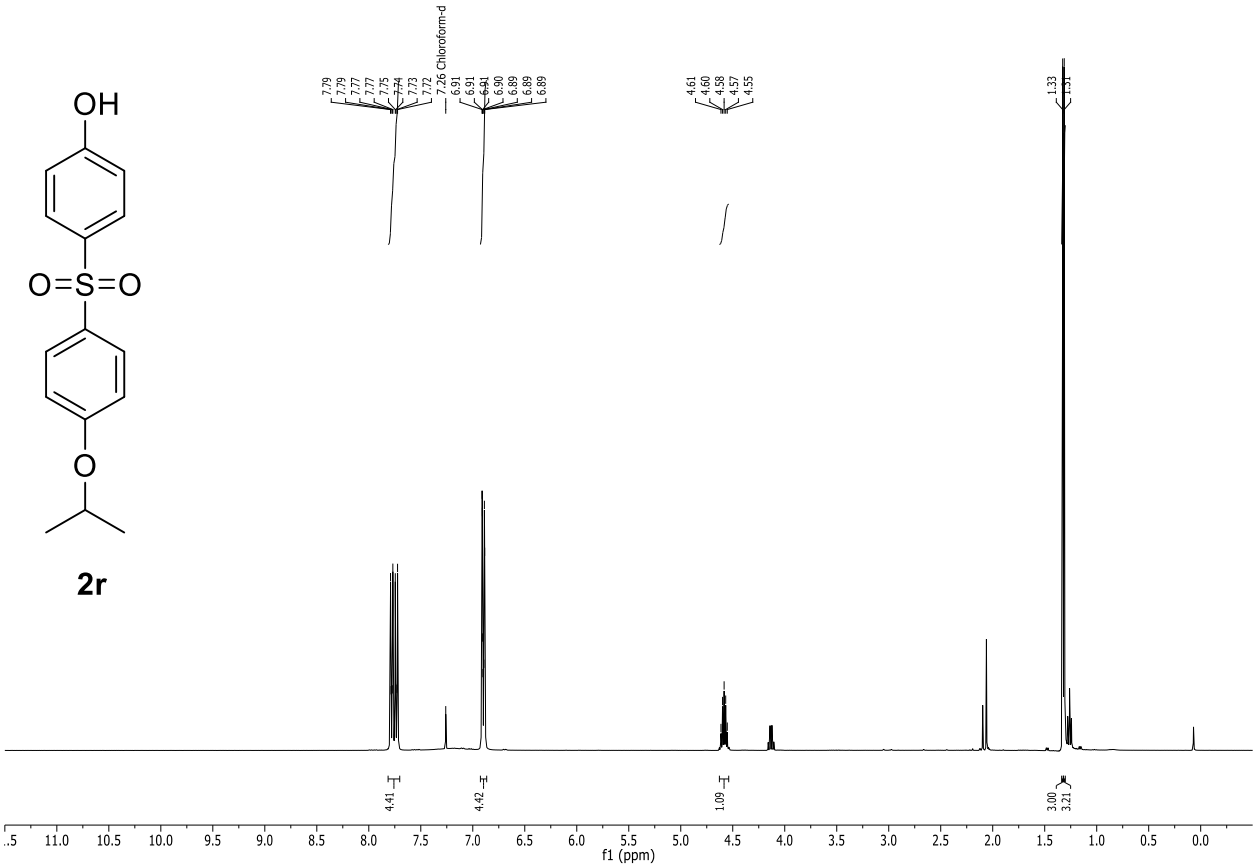


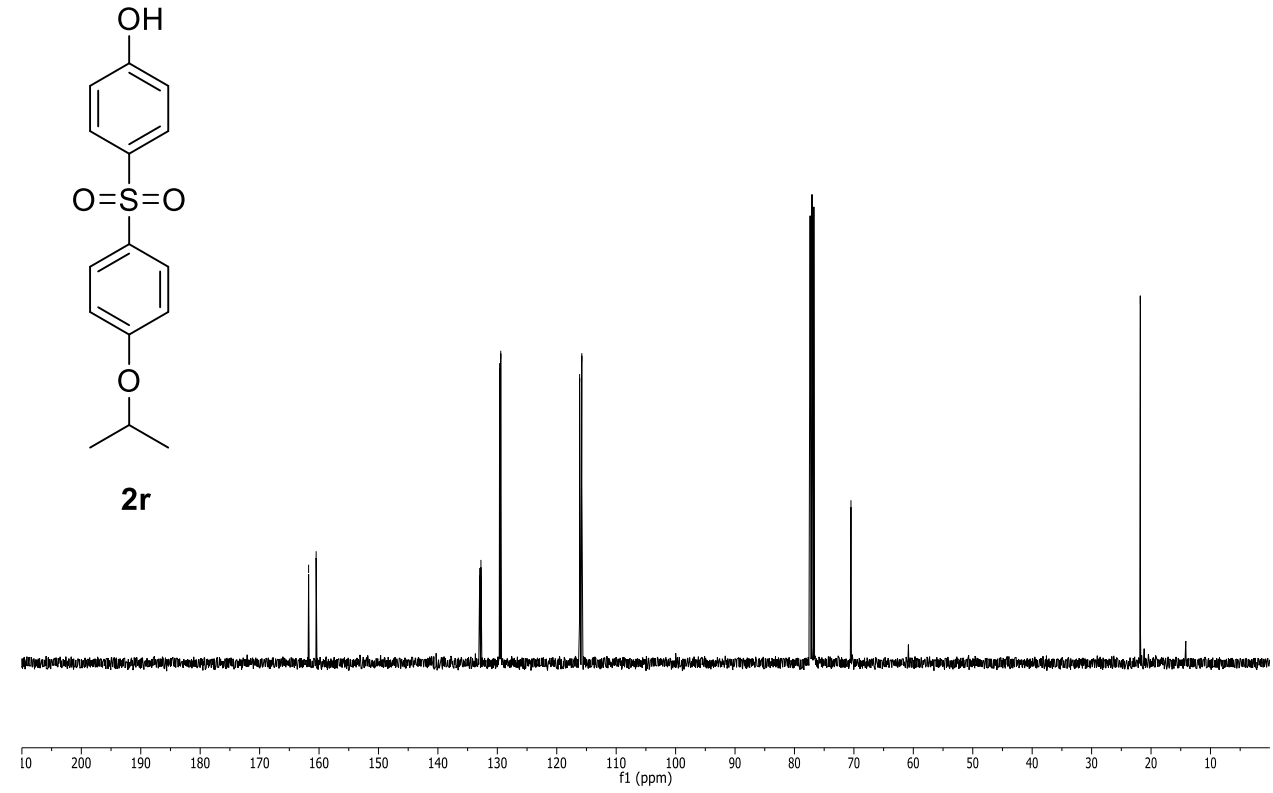
2-Hydroxyacetophenone (**2q**)



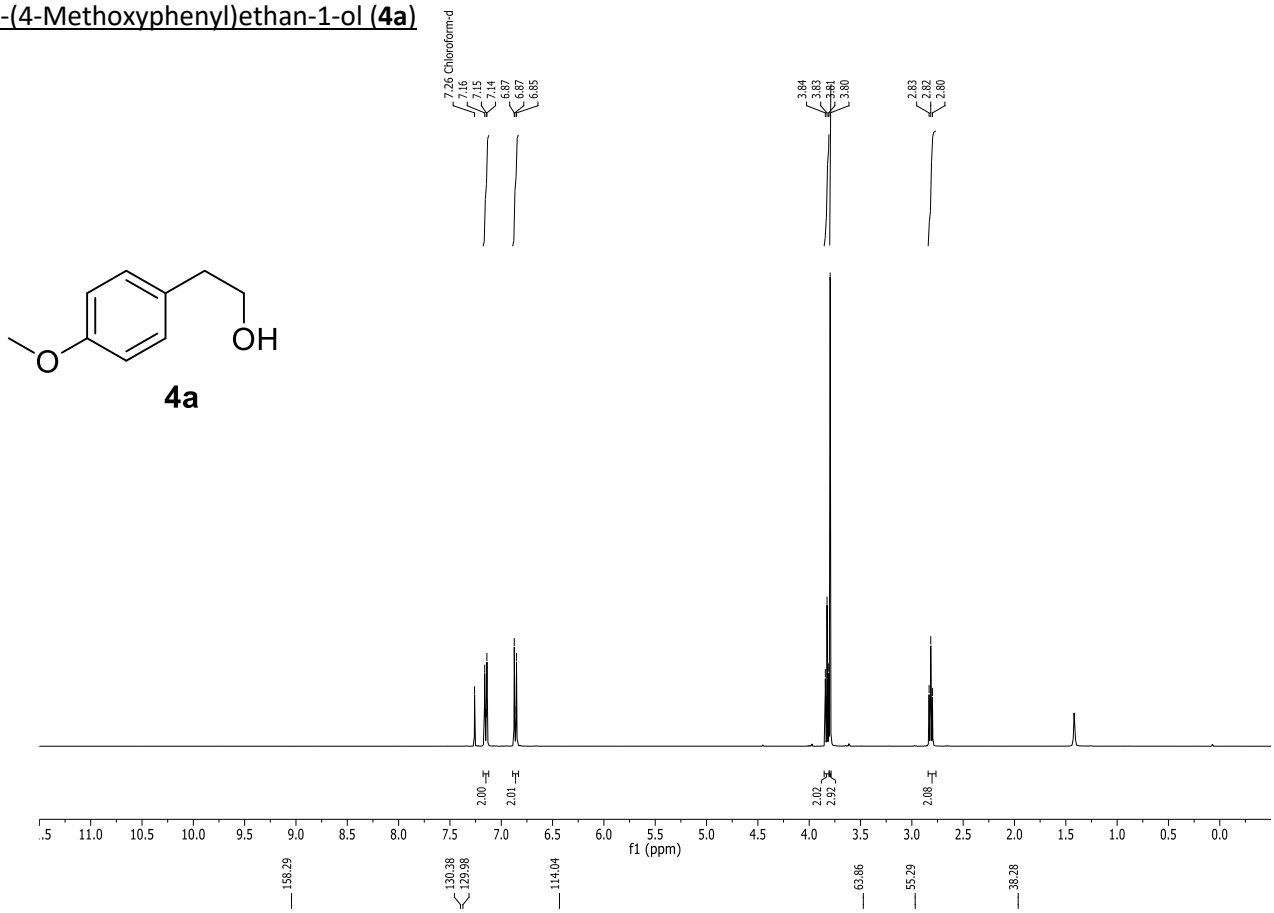


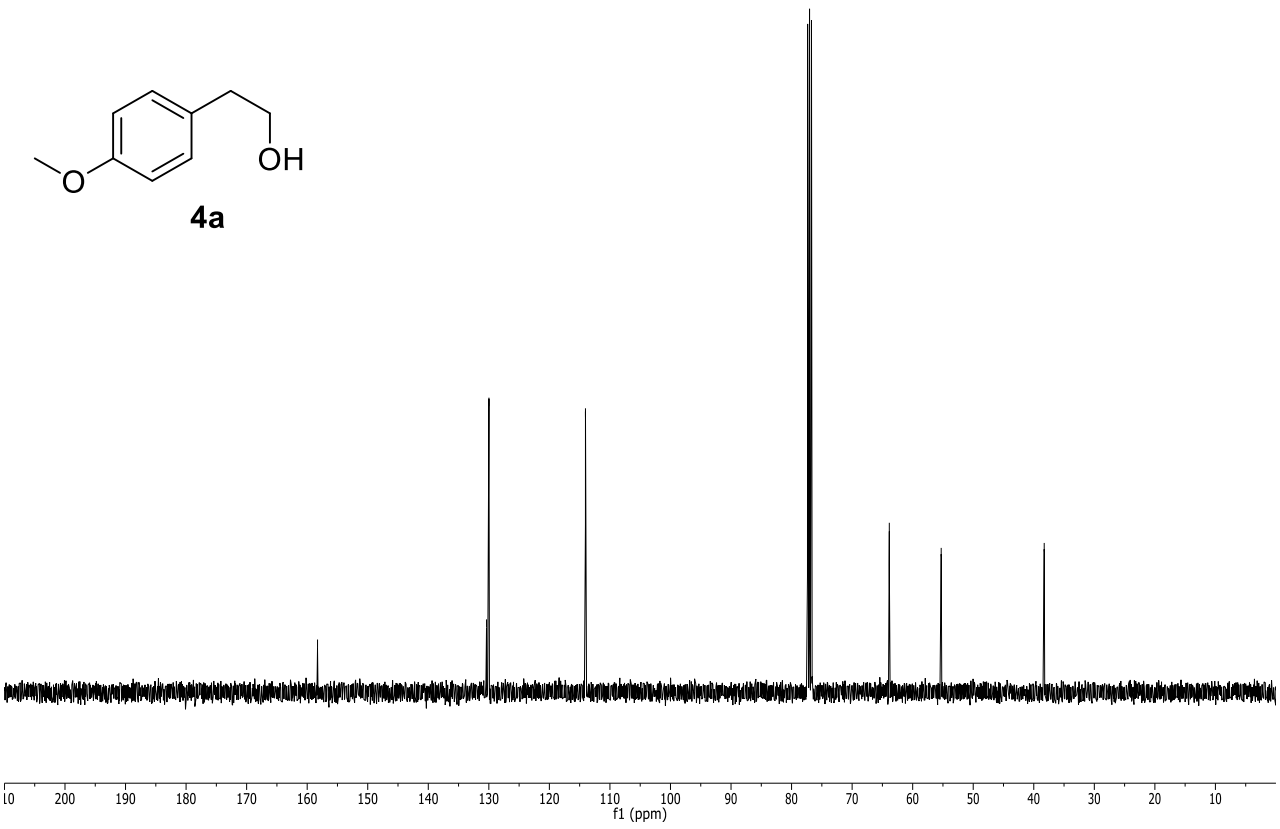
4-((4-Isopropoxyphenyl)sulfonyl)phenol (**2r**)



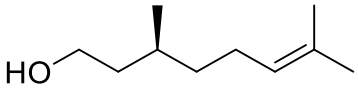


2-(4-Methoxyphenyl)ethan-1-ol (**4a**)

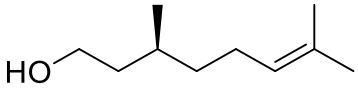




(*S*)-3,7-Dimethyloct-6-en-1-ol (**4b**)

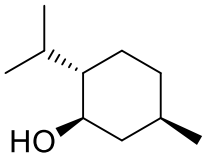


4b

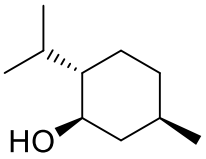


4b

Menthol (**4c**)

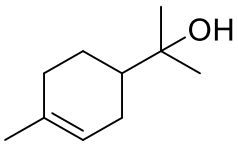

HO

7.26 Chloroform-d
3.43
3.42
3.40
3.39
3.38
3.37
2.18
2.17
2.16
2.15
2.14
1.97
1.94
1.94
1.67
1.66
1.63
1.62
1.62
1.61
1.58
1.58
1.36
1.34
1.10
1.07
0.92
0.91
0.89
0.81
0.79
1.00
1.06
1.13
2.12
1.32
1.02
0.98
10.96
f1 (ppm)

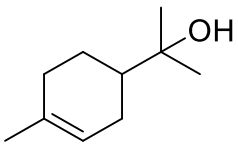

HO

71.55
50.12
45.02
34.54
31.65
25.81
23.11
22.23
21.03
16.08
f1 (ppm)

2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol (**4d**)

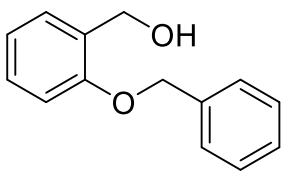


4d

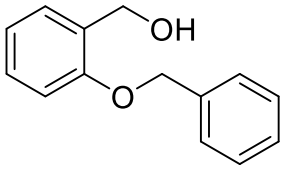


4d

(2-(Benzyloxy)phenyl)methanol (**4e**)

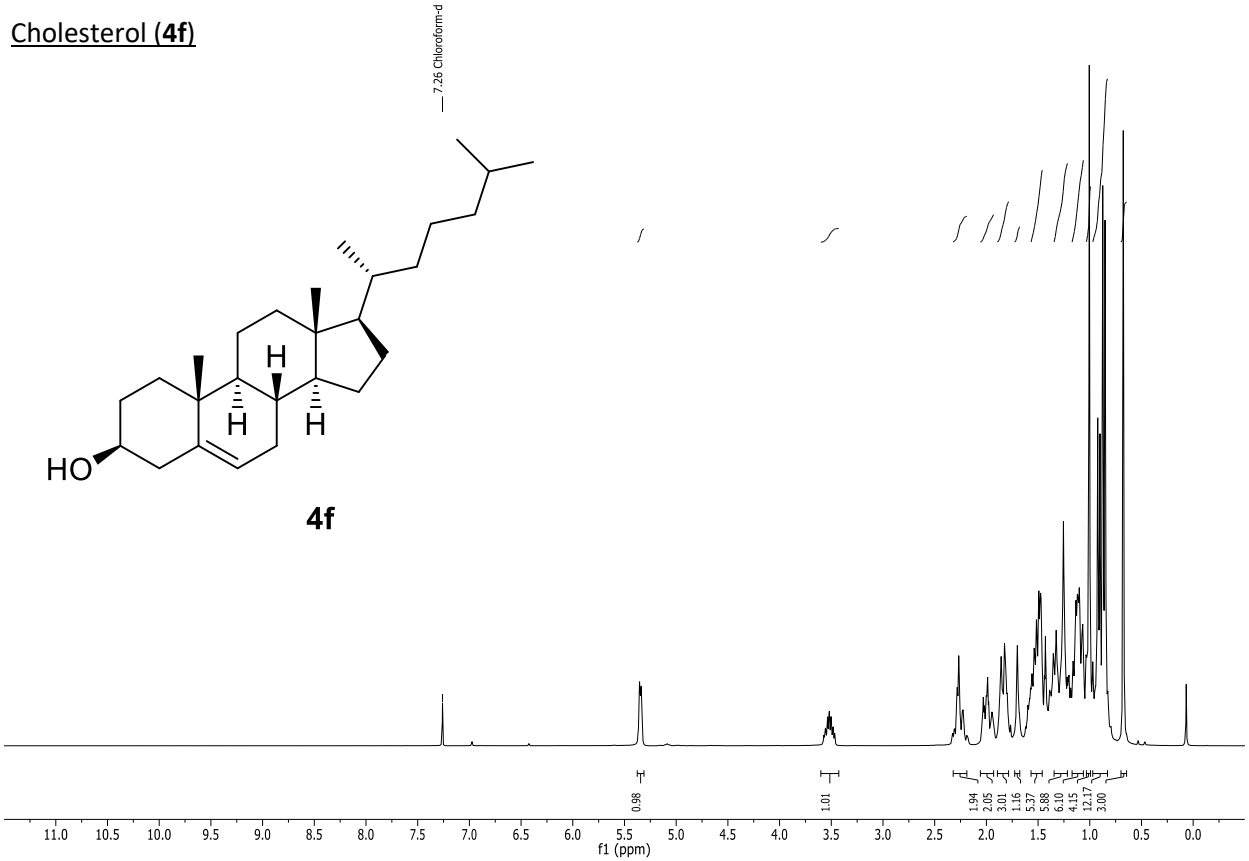


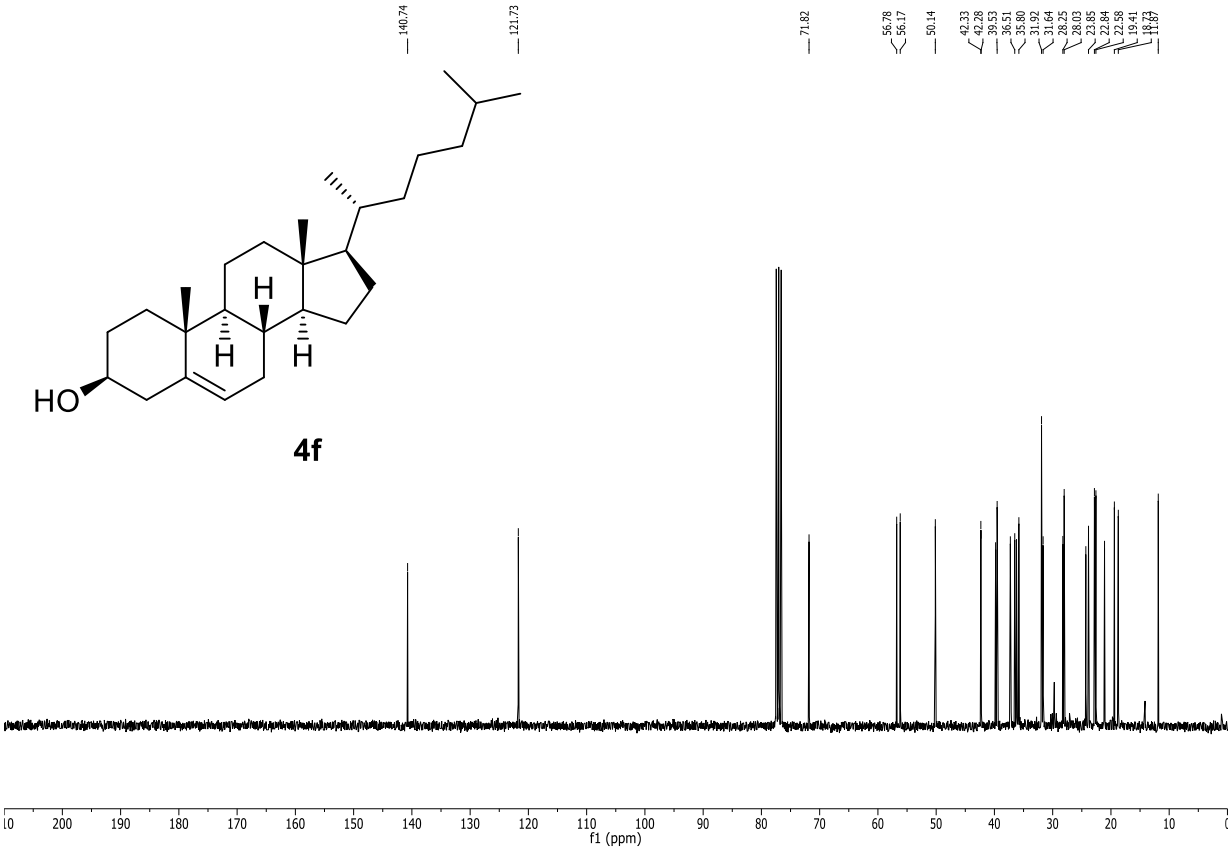
4e



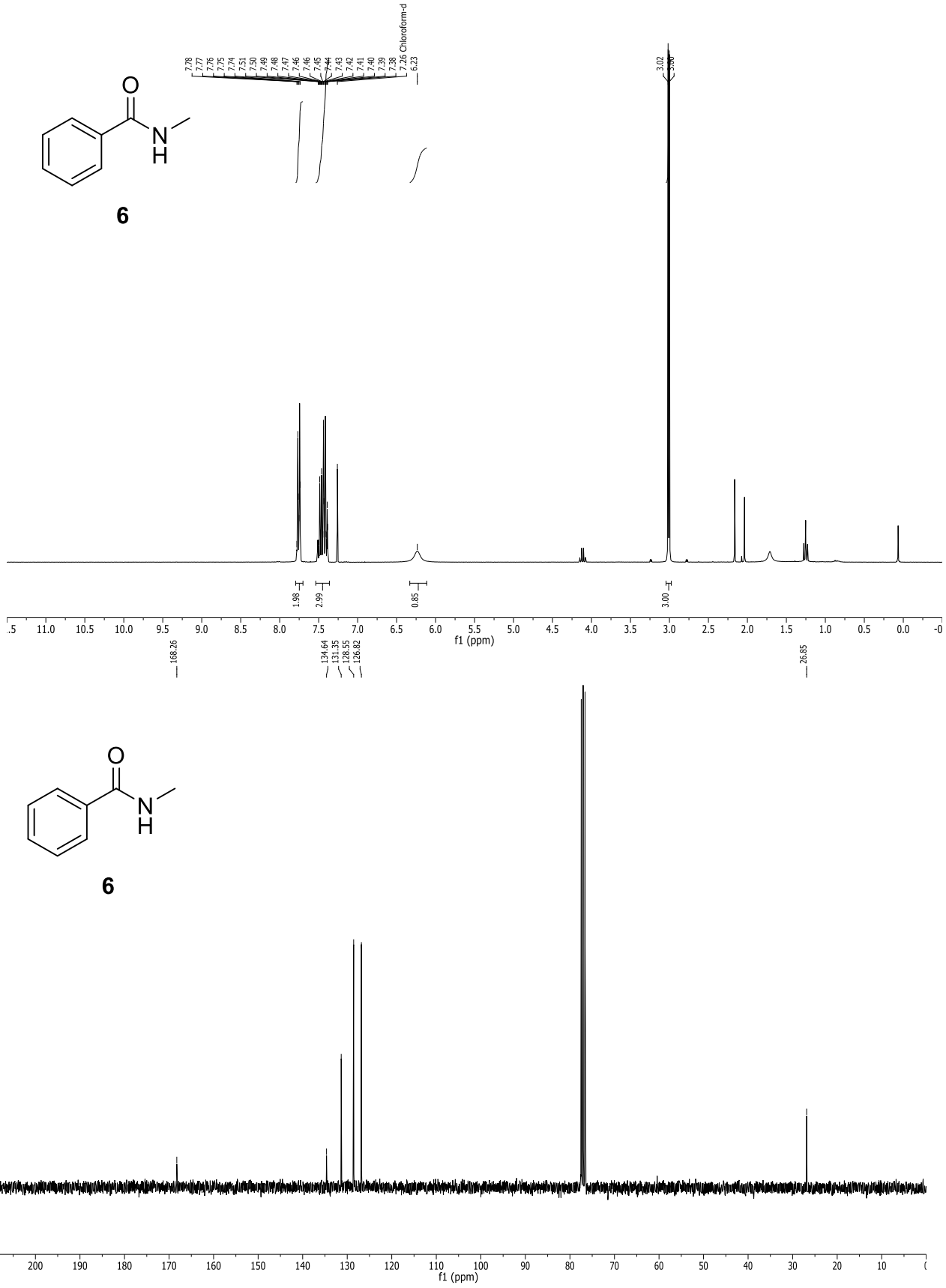
4e

Cholesterol (**4f**)





N-Methylbenzamide (**6**)



6

6. REFERENCES

[1] F. Koch, A. Berkefeld, *Dalton Transactions* **2018**, *47*, 10561-10568.
[2] Y. Mao, Y. Liu, Y. Hu, L. Wang, S. Zhang, W. Wang, *ACS Catal.* **2018**, *8*, 3016-3020.
[3] K. Huang, H. Wang, V. Stepanenko, M. De Jesús, C. Torruellas, W. Correa, M. Ortiz-Marciales, *J. Org. Chem* **2011**, *76*, 1883-1886.
[4] C. Huang, J. Feng, R. Ma, S. Fang, T. Lu, W. Tang, D. Du, J. Gao, *Org. Lett.* **2019**, *21*, 9688-9692.
[5] B. Gaspar, E. M. Carreira, *Angew. Chem. Int. Ed.* **2007**, *46*, 4519-4522.
[6] L. Kong, Q. Lin, X. Lv, Y. Yang, Y. Jia, Y. Zhou, *Green Chem.* **2009**, *11*, 1108-1111.
[7] S. Naik, R. Gopinath, M. Goswami, B. K. Patel, *Org. Biomol. Chem.* **2004**, *2*, 1670-1677.
[8] H.-C. Yang, J. Yu, K.-B. Oh, D.-S. Shin, W.-J. Cho, J. Shin, S. Kim, *Arch. Pharmacal Res.* **2007**, *30*, 955-961.
[9] J. B. McManus, D. A. Nicewicz, *J. Am. Chem. Soc.* **2017**, *139*, 2880-2883.
[10] L. Jiménez-González, S. García-Muñoz, M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Eur. J.* **2006**, *12*, 8762-8769.
[11] T. Delaine, V. Bernardes-Génisson, A. Quémard, P. Constant, B. Meunier, J. Bernadou, *Eur. J. Med. Chem* **2010**, *45*, 4554-4561.
[12] C. J. Bennett, S. T. Caldwell, D. B. McPhail, P. C. Morrice, G. G. Duthie, R. C. Hartley, *Bioorg. Med. Chem* **2004**, *12*, 2079-2098.
[13] P. Xu, F. Wang, G. Fan, X. Xu, P. Tang, *Angew. Chem. Int. Ed.* **2017**, *56*, 1101-1104.
[14] S. Kyasa, R. N. Meier, R. A. Pardini, T. K. Truttmann, K. T. Kuwata, P. H. Dussault, *J. Org. Chem* **2015**, *80*, 12100-12114.
[15] C. Su, P. G. Williard, *Org. Lett.* **2010**, *12*, 5378-5381.
[16] N. Ohmura, A. Nakamura, A. Hamasaki, M. Tokunaga, *Eur. J. Org. Chem* **2008**, *2008*, 5042-5045.
[17] L. X. Song, H. M. Wang, Y. Yang, P. Xu, *Bull. J. Chem. Soc* **2007**, *80*, 2185-2195.
[18] P. Bovonsombat, R. Ali, C. Khan, J. Leykajarakul, K. Pla-on, S. Aphimanchindakul, N. Pungcharoenpong, N. Timsuea, A. Arunrat, N. Punpongjareorn, *Tetrahedron* **2010**, *66*, 6928-6935.
[19] M. Selva, P. Tundo, *J. Org. Chem* **2006**, *71*, 1464-1470.
[20] W. Zhu, D. Ma, *Org. Lett.* **2006**, *8*, 261-263.
[21] K. Gao, M. Xu, C. Cai, Y. Ding, J. Chen, B. Liu, Y. Xia, *Org. Lett.* **2020**, *22*, 6055-6060.
[22] R.-Y. Tang, P. Zhong, Q.-L. Lin, *J. Fluor. Chem* **2007**, *128*, 636-640.
[23] D. Łażewska, X. Ligneau, J.-C. Schwartz, W. Schunack, H. Stark, K. Kieć-Kononowicz, *Bioorg. Med. Chem* **2006**, *14*, 3522-3529.
[24] L. Bai, J.-X. Wang, *Adv. Synth. Catal.* **2008**, *350*, 315-320.
[25] R. Bernini, A. Coratti, G. Provenzano, G. Fabrizi, D. Tofani, *Tetrahedron* **2005**, *61*, 1821-1825.
[26] A. Stern, J. S. Swenton, *J. Org. Chem.* **1987**, *52*, 2763-2768.
[27] T. Utsumi, K. Noda, D. Kawauchi, H. Ueda, H. Tokuyama, *Adv. Synth. Catal.* **2020**, *362*, 3583-3588.
[28] J. Xu, X. Wang, C. Shao, D. Su, G. Cheng, Y. Hu, *Org. Lett.* **2010**, *12*, 1964-1967.
[29] R. Shen, T. Chen, Y. Zhao, R. Qiu, Y. Zhou, S. Yin, X. Wang, M. Goto, L.-B. Han, *J. Am. Chem. Soc.* **2011**, *133*, 17037-17044.
[30] M. G. Saulnier, M. Dodier, D. B. Frennesson, D. R. Langley, D. M. Vyas, *Org. Lett.* **2009**, *11*, 5154-5157.
[31] B. S. Takale, V. N. Telvekar, *Chem. Lett* **2010**, *39*, 1279-1280.
[32] R. Kuruto-Niwa, R. Nozawa, T. Miyakoshi, T. Shiozawa, Y. Terao, *Environ. Toxicol. Pharmacol* **2005**, *19*, 121-130.

[33] R. R. Behera, R. Ghosh, S. Panda, S. Khamari, B. Bagh, *Org. Lett.* **2020**, *22*, 3642-3648.
[34] A. Dahlén, A. Sundgren, M. Lahmann, S. Oscarson, G. Hilmersson, *Org. Lett.* **2003**, *5*, 4085-4088.
[35] T. M. Maier, S. Sandl, P. Melzl, J. Zweck, A. Jacobi von Wangelin, R. Wolf, *Chem. Eur. J.* **2020**, *26*, 6113-6117.
[36] K. N. Gurudutt, M. A. Pasha, B. Ravindranath, P. Srinivas, *Tetrahedron* **1984**, *40*, 1629-1632.
[37] J. Lee, J.-H. Lee, S. Y. Kim, N. A. Perry, N. E. Lewin, J. A. Ayres, P. M. Blumberg, *Bioorg. Med. Chem* **2006**, *14*, 2022-2031.
[38] C. Meng, H. Niu, J. Ning, W. Wu, J. J. M. Yi, *Chem* **2020**, *25*, 602.
[39] Y. Jo, J. Ju, J. Choe, K. H. Song, S. Lee, *J. Org. Chem* **2009**, *74*, 6358-6361.

5. Appendix: List of Acronyms

Ar	Aryl
bipy	bipyridine
BHT	Butylated hydroxy toluene
Boc	Benzyloxycarbonyl
cod	1,4-cyclooctadiene
CPA	Chiral Phosphoric Acid
DEAD	diethylazodicarboxylate
dba	dibenzylideneacetone
dtbpx	1,2-bis((di-tert-butylphosphaneyl)methyl)benzene
DMP	Dess-Martin Periodinane
DMF	Dimethylformamide
DMA	Dimethylacetamide
DMSO	Dimethylsulfoxide
DME	Dimethoxyethane
EPR	Electron Paramagnetic Resonance
HAT	Hydrogen Atom Transfer
HMDS	Hexamethyldisilazane
IR	Infrared
Pd	Palladium
Ru	Ruthenium
KIE	Kinetic Isotope Effect
LAH	Lithium Aluminium Hydride
MsOH	Methanesulfonic acid
NBS	N-bromosuccinimide
pin	pinacolato
SEM	Scanning Electron Microscopy
SET	Single Electron Transfer
TMSCl	Trimethylsilylchloride
TBDPSCl	tert-butyldiphenylsilyl
TfOH	Triflic acid
THPI	Tetrahydropyran-indole
TMEDA	N,N,N‘,N‘-tetramethylethylenediamine
TON	Turnover Number
TOF	Turnover Frequency
UV	Ultraviolet
XRD	X-ray Diffraction
Xantphos	(9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)