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Transition Metal-Catalyzed Carbon-Carbon Bond Formation Utilizing Transfer Hydrogenation

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Transition Metal-Catalyzed Carbon-Carbon Bond Formation Utilizing Transfer Hydrogenation

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May 2015

Dedication

To Micca:

my loving wife and best friend.

Acknowledgements

First and foremost, I must thank my advisor, Prof. Michael J. Krische for your mentorship over the last five years. Your passion for chemistry is both inspirational and contagious. You have provided an environment that is conducive to the development of a young scientist, and for that I am forever appreciative.

I would also like to thank the members of the Krische group for your camaraderie and friendship. I must acknowledge Abbas, Jason and Joseph for showing me how to be efficient in the laboratory. Without your guidance, I am certain that I would have struggled to be productive during my time in the Krische group. I must also thank those who I have had the pleasure to collaborate with during my tenure in the Krische group: Abbas, Brannon, Boyoung, Ivan, Laina, Ryan, Ryosuke, Taka, Tony and Victoria. Specifically Brannon, we have been each other's sharpening stones, and I know that the many conversations we have had at the chalk board has furthered my learning and understanding of chemistry.

To my parents, you have given me the tools that I need to succeed at anything in life. You taught me the meaning of tenacity and an unyielding pursuit to achieve whatever goals I may set. Your love and support could never be replaced.

To Micca, you are the love of my life, my confidant and my best friend. You have sacrificed much so that I could pursue my passion in chemistry, and I am eternally grateful to have you as my wife.

Transition Metal-Catalyzed Carbon-Carbon Bond Formation Utilizing Transfer Hydrogenation

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The University of Texas at Austin, 2015

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A central tenant of organic synthesis is the construction of carbon-carbon bonds. One of the traditional methods for carrying out such transformations is that of carbonyl addition. Unfortunately, traditional carbonyl addition chemistry suffers various drawbacks: preactivation, moisture sensitivity, and the generation of stoichiometric organometallic waste. The research presented in this dissertation focuses on the development of methods that make use of nucleophile-electrophile pairs generated *in situ via* transfer hydrogenation, which allow the formation of carbonyl or imine addition products from the alcohol or amine oxidation level; streamlining the construction of complex molecules from simple, readily available starting materials. Additionally, studies toward the total synthesis of the fibrinogen receptor inhibitor tetrafibricin, utilizing the methods developed in catalytic carbon-carbon bond formation through the addition, transfer or removal of hydrogen, are presented.

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Chapter 1: Transition-Metal Catalyzed Transformations of Reactants Containing Internal Redox Activity

1.1 Introduction

As the field of organic chemistry has exploded into the twenty-first century, the synthetic chemist's toolbox continues to develop. The question has evolved from "Can we make this molecule;" to "How efficient can we construct this structure". One of the concepts born out of this quest is atom economy. Atom economy is the idea of maximizing the number of atoms in the reactants that appear in the product.[1] This concept is of the utmost importance when considering "process-relevant" methods. When conducting transformations on the process scale, a chemist must consider a number of facets including economic and environmental issues.[2] A major contributor to these issues is that of waste disposal. Waste disposal has garnered much attention recently and has even fostered the development of a new area of chemistry, Green Chemistry. The Environmental Protection Agency defines Green Chemistry as "the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances."[3]

Minimizing waste can be attacked at many different angles (solvent used, purification methods, mediating reactions by using catalyst, etc.)[2,4], but this review will focus on eliminating external oxidants or reductants used to complete the catalytic cycle by employing reagents that contain the necessary redox activity needed by the transition-metal catalyst in the catalytic cycle. This review will discuss the recent advancements made in the fields of C-H activation, amination and diamination, aziridination and carbonyl addition reactions.

This review is not meant to be a comprehensive document containing all transformations relative to its subject matter; nevertheless, it is a means to discuss the prospect of improving known transformations by rendering them more atom- and redox-efficient through the elimination of external oxidants and

reductants. Each section will present known transformations and their counterpart, which utilizes reagent-contained redox activity in the catalytic cycle.

1.2 C-H Functionalization Utilizing Internal Oxidants

1.2.1 Background

The ability to selectively functionalize unreactive C-H bonds gives rise to enormous possibilities when considering how to construct a molecule.[5] Unfortunately, there remains many unmet challenges. Many of these transformations require a directing group to enhance regioselectivity.[6] Another drawback of these transformations is the requirement of an external oxidant to complete the catalytic cycle, thus generating a stoichiometric amount of the reduced oxidant after the reaction is completed, limiting the process-relevance of such transformations. Many groups have addressed this problem by including the oxidant in the reagent. Pioneers such as Cui, Fagnou, Glorius, Hartwig and Yu, have developed strategies that utilize a directing group as the internal oxidant, avoiding the need for an external oxidant all together.

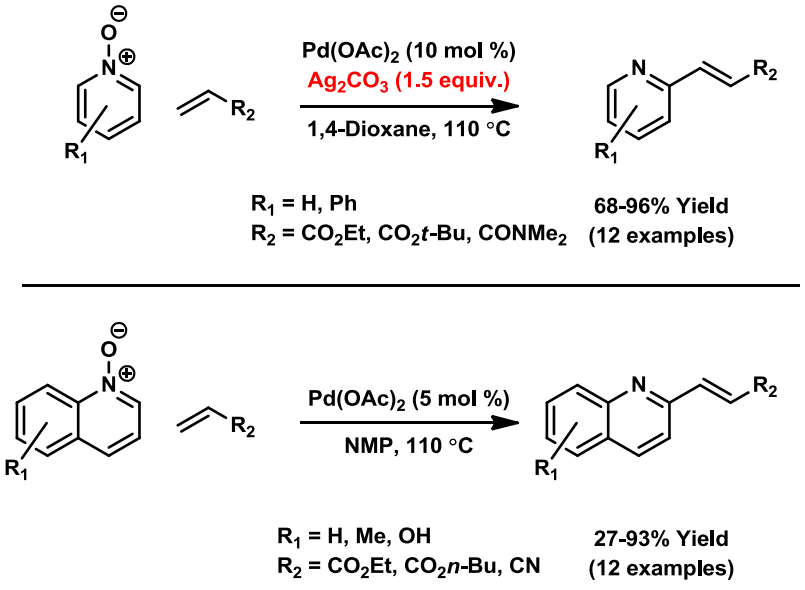
1.2.2 *N*-Oxides

The *N*-oxide group is a commonly used directing group in the area of C-H activation, and the groups of Fagnou, Hiyama, and Cho have demonstrated its utility.[7–9] Specifically, Cho and coworkers used the *N*-oxide to functionalize pyridine-*N*-oxides at the 2-position (Scheme 1.1 top).[9] They obtained products of palladium catalyzed alkenylation utilizing both acrylates and unactivated olefins. Unfortunately Ag_2CO_3 must be used as the stoichiometric oxidant. Cui and coworkers improved on this protocol by utilizing the *N*-oxide as both the directing group and the internal oxidant (Scheme 1.1 bottom).[10] They were able to alkenylate at the 2-position of various quinolone-*N*-oxides, forming 2-alkenylated

quinolones. These studies showed comparable reactivity and selectivity to the original work across a similar range of olefins.

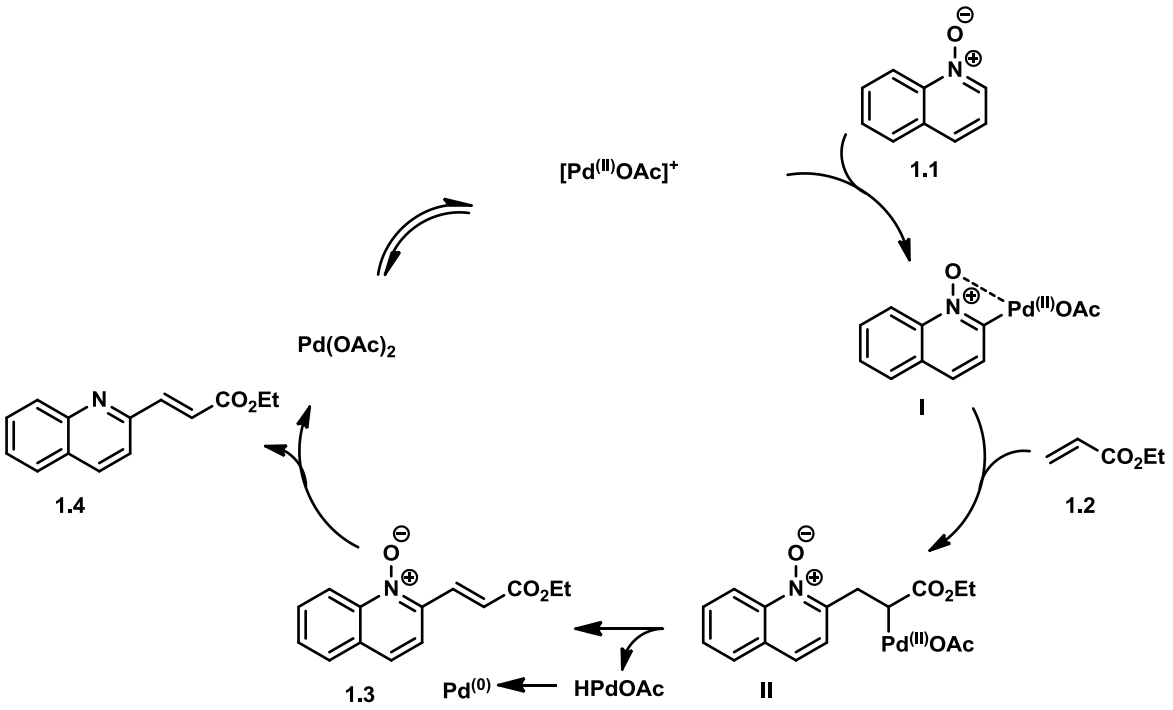
A plausible mechanism is shown in Figure 1.1. Initially, *N*-oxide **1.1** coordinates the cationic palladium(II), allowing an electrophilic attack at the

Scheme 1.1. Comparing Cho's methodology with Cui's use of *N*-Oxides as internal oxidants.



2-position of intermediate **I**. Next coordination of the olefin **1.2**, followed by *syn* insertion forms intermediate **II**. β-Hydride elimination generates *N*-oxide **1.3** and the palladium-hydride species which reductively eliminates to form palladium(0). *N*-oxide **1.3** then oxidizes the palladium(0) back to palladium(II) closing the catalytic cycle and releasing desired quinoline **1.4**.

Figure 1.1. A plausible mechanism for the formation of 2-alkenylated quinolones from quinolone-*N*-Oxide.

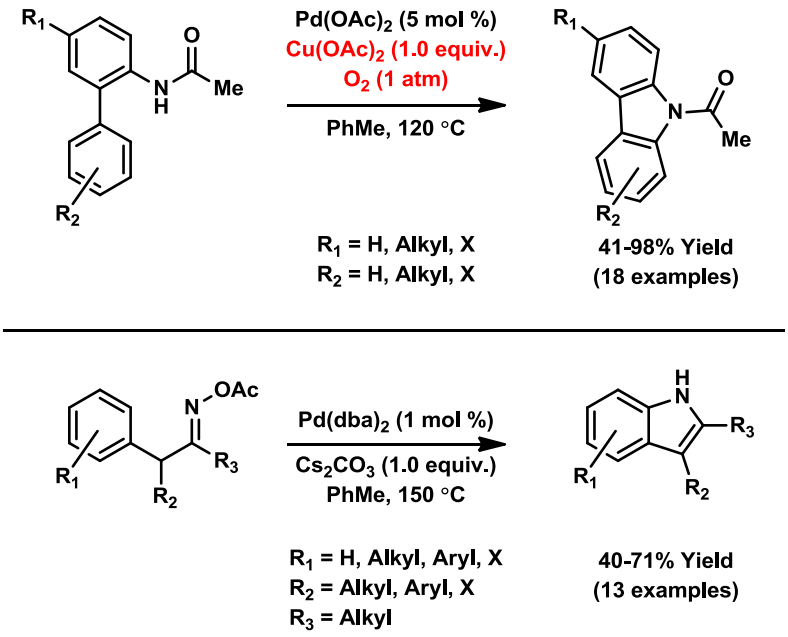


1.2.3 *N*-Acyloxy Groups

Another group that could be used as both a directing group and an internal oxidant is the *N*-acyloxy group. Hartwig and coworkers examined the use of this functionality in the amination of aromatic C-H bonds.[11] This transformation is similar to an approach published from the Buchwald group that aminates aromatic C-H bonds using an acetamide as the directing group forming carbazoles (Scheme 1.2 top).[12] Buchwald and coworkers obtained moderate to excellent reactivity using $Pd(OAc)_2$, and the reaction displayed a wide scope. However, this reaction required the addition of stoichiometric amounts of $Cu(OAc)_2$ and 1 atm O_2 to proceed. It was later discovered that a catalytic

amount of $Cu(OAc)_2$ could be used in the presence of 1 atm of O_2. By employing the *N*-acyloxy group as both a directing group and internal oxidant, Hartwig and coworkers obtained moderate reactivity over a wide scope of oxime-acetates to form various substituted indoles (Scheme 1.2 bottom). They found $Pd(dba)_2$ to be the optimum catalyst for this transformation.

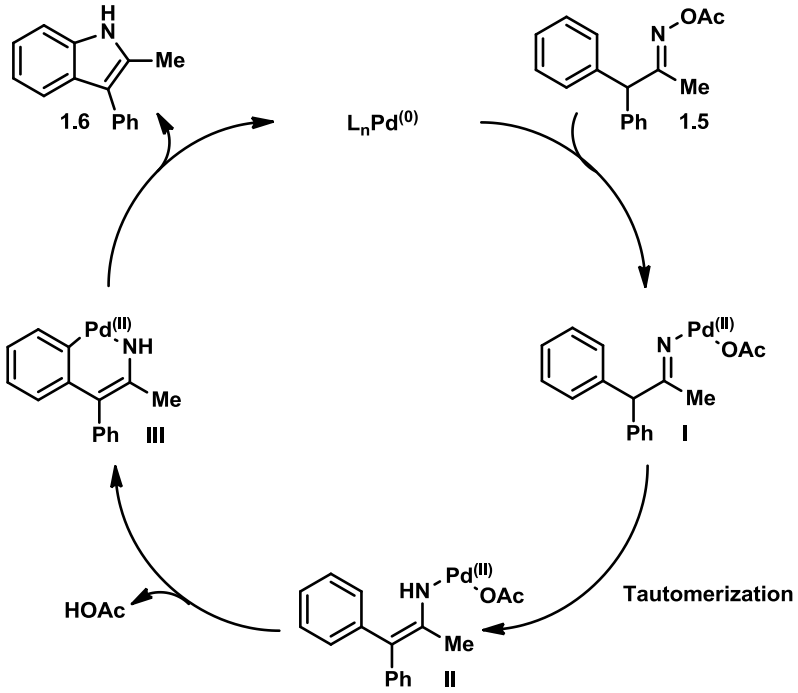
Scheme 1.2. Comparing Buchwald's methodology with Hartwig's use of *N*-acyloxy groups as internal oxidants.



A proposed mechanism of this transformation is presented in Figure 1.2. Unlike the Cui mechanism (Figure 1.1), it is believed that the palladium inserts into the N-O bond of oxime-acetate **1.5** to begin the cycle, immediately oxidizing palladium(0) to palladium(II) and generating intermediate **I**. Tautomerization of intermediate **I** furnishes intermediate **II**. Next, C-H bond cleavage occurs to give intermediate **III**, also producing an equivalent of acetic acid. Lastly, C-N reductive

elimination furnishes indole **1.6** and regenerates palladium(0) to complete the catalytic cycle.

Figure 1.2. A plausible mechanism for the formation of indoles utilizing *N*-acyloxy groups as both directing groups and internal oxidants.

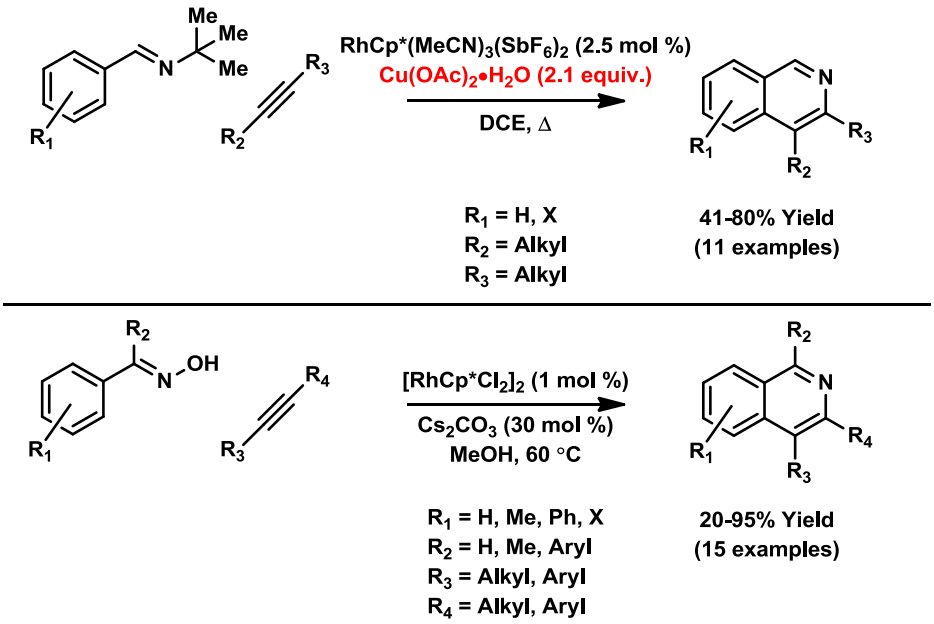


1.2.4 Oximes

Oximes have also played a role in C-H activation for the formation of synthetically or medicinally relevant products such as isoquinolines, which have shown to be an important class of natural products due to their bioactivity.[13] Li and coworkers were able to employ oximes as reagent-contained redox active groups with a rhodium(III) catalyst in the formation of isoquinolines.[14] Comparing this with the established protocol for the formation of these useful moieties from the Fagnou group, illustrates the role of oximes. Fagnou and coworkers used a rhodium(II) catalyst to promote C-C and C-N bond formation between aryl imines

and alkynes (Scheme 1.3 top).[15] This transformation showed a wide scope and utilized a rhodium(V) intermediate to enhance C-N reductive elimination. Unfortunately, to harness an intermediate at such a high oxidation level, an external oxidant was used in the form of $Cu(OAc)_2 \bullet H_2O$. As previously mentioned, Li and coworkers further developed this methodology by utilizing the potential of oximes along with a rhodium(III) catalyst (Scheme 1.3 bottom). They obtained the desired isoquinolines in moderate to high yields across a wide scope. Additionally, no external oxidant was needed to complete the catalytic cycle because of the versatility of oximes as both a directing group and redox active reagent.

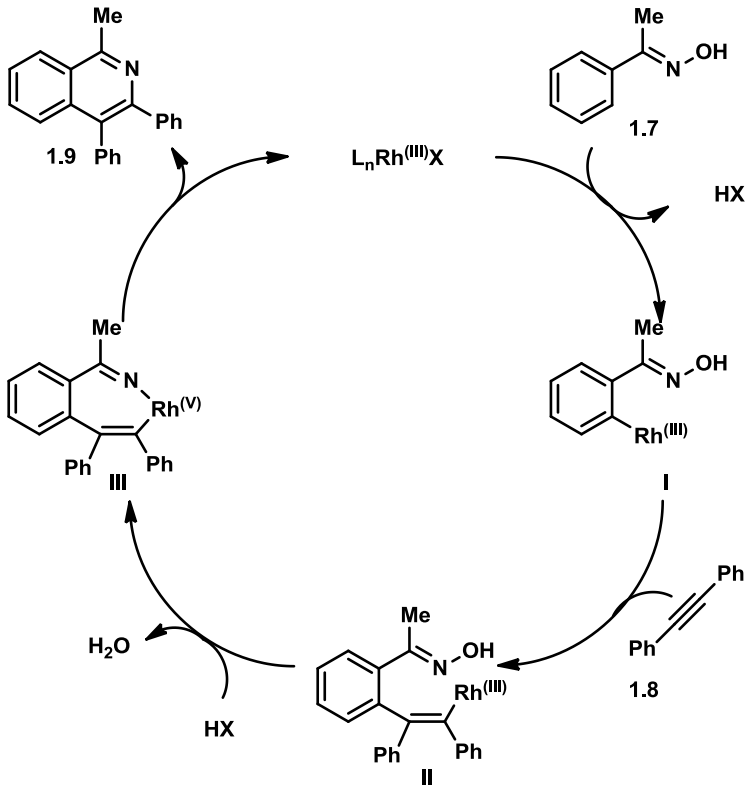
Scheme 1.3. Comparing methodologies used to form isoquinolines from Fagnou and Li.



A potential mechanism is proposed in Figure 1.3. Initially, it is believe that the rhodium(III) species, coordinated by oxime **1.7**, activates the *ortho* C-H bond to generate intermediate **I** and release an equivalent of acid. Next, alkyne

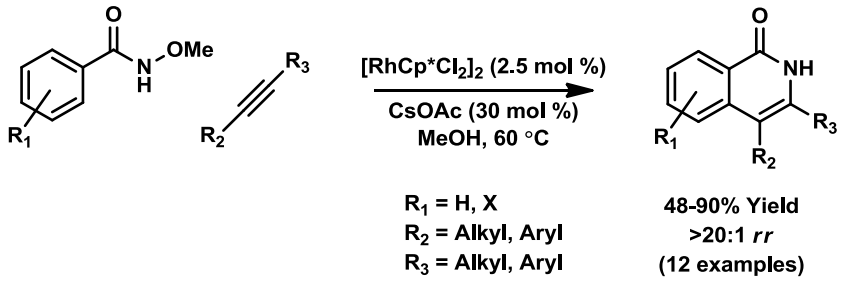
insertion forms 7-membered rhodacycle intermediate **II**. It is thought that the acid generated can then protonate the oxime, inducing water loss and unveiling rhodium(V) intermediate **III**. Reductive elimination then occurs forming desired isoquinoline **1.9** and regenerating rhodium(III) to close the catalytic cycle. This methodology should not be considered an iteration of that reported by Cheng, since that transformation is believed to generate an olefin intermediate, which is reported isolable, and subsequently undergoes electrocyclization to reveal the desired isoquinoline.[16]

Figure 1.3. A plausible mechanism for the formation of isoquinolines utilizing the redox potential of oximes.



Related to the use of oximes in these transformations is the work reported by the Fagnou group that utilizes N-OMe as the reagent-contained redox active component.[17] Fagnou and coworkers were able to harness the activity of this group to generate isoquinolones in good yields (Scheme 1.4). Also, this methodology shows good tolerance for heteroatoms attached to the aryl ring. Initially they screened conditions that utilized $Cu(OAc)_2 \bullet H_2O$ as an oxidant, but observed an interesting mixture of a 1:1 ratio between the desire product and the product still containing the intact N-OMe. This is believed to signify the competition between $Cu(OAc)_2 \bullet H_2O$ and the N-OMe group as catalyst oxidants. Ultimately Fagnou and coworkers opted to utilize the oxidizing characteristics of the N-OMe group since the primary amide was desired.

Scheme 1.4. Generation of isoquinolones reported by Fagnou.

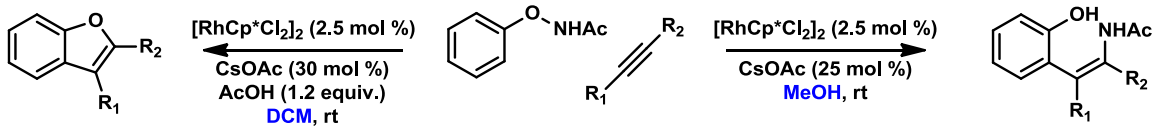


1.2.5 N-Group as Leaving Group

As many examples have been discussed that utilize the N-O bond as the internal oxidant, only those have been analyzed leaving products of C-N bond formation. These groups can be flipped so that the oxygen atom remains in place and the nitrogen leaves. The Lu group reported the use of *N*-phenoxyacetamides as the internal oxidant in the formation of enamides and benzofurans (Scheme 1.5).[18] Amazingly this system showed incredible tunability to partition between pathways of generating either the enamides or benzofurans. It was

Strongly coordinating solvents, such as DMSO or DMF, shut the reaction down. Weakly coordinating solvents such as methanol favored the formation of the enamide, while noncoordinating solvents such as dichloromethane favored the benzofurans.

Scheme 1.5. Formation of enamides and benzofurans utilizing *N*-phenoxyacetimides as the internal oxidant.



47-90% Yield
>20:1 *rr*
(14 examples)

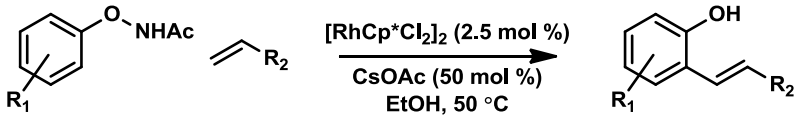
R_1 = Alkyl, Aryl, Ester
R_2 = Aryl, Ester

R_1 = Alkyl, Aryl, Ester
R_2 = Alkyl, Aryl, Ester

51-83% Yield
>20:1 *rr*
(15 examples)

The Lu group has also reported a protocol for the synthesis of *ortho*-alkenyl phenols, which are considered important building blocks in synthetic chemistry (Scheme 1.6).[19] They were able to eliminate the requirement for aryl preactivation needed in the Mizoroki-Heck by using C-H activation and removed the necessity of an external oxidant by using *N*-phenoxyacetamides as the internal oxidant. This methodology was expanded to include a wide scope of phenolic motifs as well as alkenyl reagents.

Scheme 1.6. Formation of *ortho*-alkenyl phenols reported by Lu.



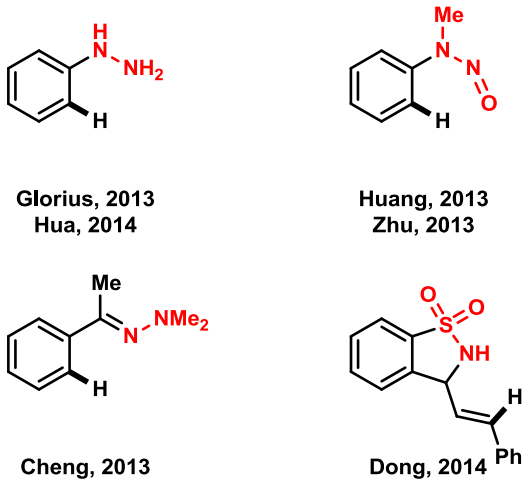
R_1 = H, Akyl, Aryl, X
R_2 = Aryl, Ester, CN

45-85% Yield
(24 examples)

1.2.6 Miscellaneous Groups

Utilizing other directing groups besides those that contain N-O bonds used as internal oxidants has been reported (Figure 1.4). Glorius and coworkers reported the use of aryl hydrazines in the formation of indoles.[20] Hua and coworkers also published the use of hydrazones in the formation of indoles.[21] Both the Huang and Zhu groups used nitrous amides in the formation of indoles.[22,23] Cheng and coworkers used hydrazones as well in the synthesis of isoquinolines.[24]

Figure 1.4. Various directing groups which contain internal oxidant activity.



1.2.7 Conclusion

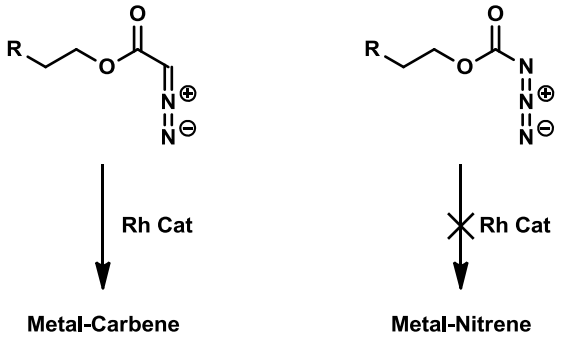
This section discussed many of the recent advancements that have been made in the field of C-H activation in which reagent-contained redox activity was utilized to eliminate the need for an external oxidant. This was not a comprehensive list of all the marvelous work reported in this area. For a more complete story of what has been accomplished, recent reviews of this topic by Cui and Jiang should be consulted.[25,26]

1.3 *N*-Tosyloxycarbamates as Nitrene Precursors in C-H Aminations

1.3.1 Background

The activation of diazo compounds utilizing transition-metal complexes derived from metals such as rhodium, have allowed for the discovery of a variety of transformations.[27] Unfortunately the of use azides as nitrenoid precursors has shown less promise.[28] In fact it has been postulated that instead of coordinating to the internal nitrogen (analogous to the generation of metal-carbenes), the metal catalyst coordinates to the terminal nitrogen of the azide group, preventing the expulsion of nitrogen gas and formation of the metal-nitrenoid species (Scheme 1.7).[28] To circumvent this issue a number of hypervalent-iodine species

Scheme 1.7. Displaying the problems in Nitrenoid formation when compared to that of carbenoid formation.



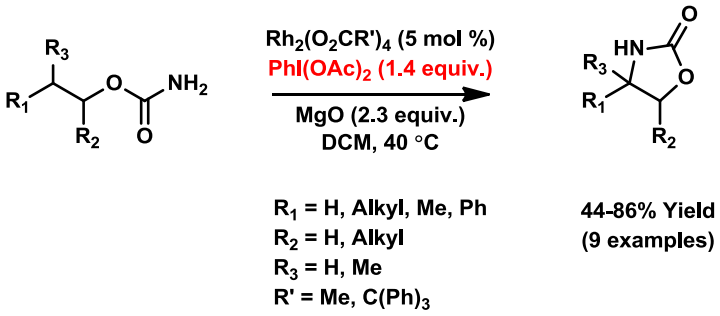
have been employed as oxidants.[29,30] These have worked well, but unfortunately there is the drawback of generating an equivalent of iodobenzene once the reaction is completed. This limits the use of this type of transformation on scale because of the massive amount of waste generated as iodobenzene. Lebel and coworkers discovered a way to circumvent this issue. They postulated that using a less coordinating leaving group would favor metal coordination to the internal

nitrogen, and the nitrene could be formed directly.[28] They accomplished this feat by utilizing the anion derived from a tosyloxycarbamate, allowing direct access to the metal-nitrenoid.[31]

1.3.2 C-H Amination Using *N*-Tosyloxycarbamates

Utilizing a rhodium(II) catalyst and PhI=$(OAc)_2$ as the oxidant, Du Bois and coworkers uncovered a unique transformation that allows for the conversion of easily accessed carbamate starting materials to oxazolidinones, which can be opened to 1,2-amino alcohols (Scheme 1.8 top).[32] By forming the iodoimine *in*

Scheme 1.8. Comparing the C-H amination strategies of Du Bois and Lebel.

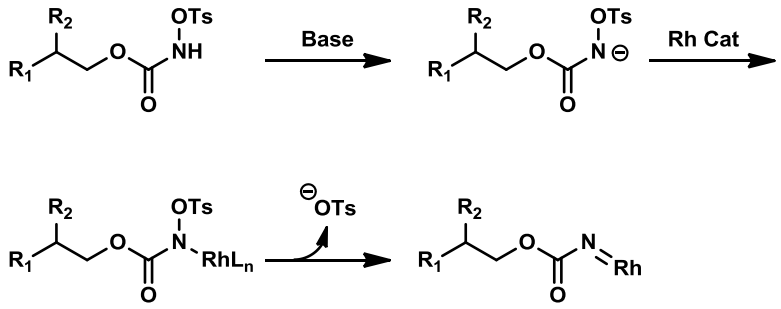


situ, the use of iodoimines is not restricted by preformed reagents with a poor shelf life and limited scope. This method allowed access to a variety of

oxazolidinones, but it is not without drawbacks: stoichiometric amount of iodobenzene is produced.

Lebel and coworkers improved on this issue by utilizing a *N*-tosyloxycarbamate as the nitrene precursor to perform C-H aminations (Scheme 1.8 bottom).[31] This replaced the need for an external oxidant such as a hypervalent iodide species by applying reagent-contained oxidative activity to this transformation. It is thought that the tosyloxy motif acts to sufficiently acidify the nitrogen, promoting its deprotonation and enhancing its ability to coordinate the rhodium.[28] The tosylate can then leave, generating the metal-nitrene, oxidizing the rhodium in the process (Scheme 1.9).[28] This idea allowed Lebel and coworkers to access many of the same substrates with similar efficiency as Du Bois and coworkers, precluding the need for hypervalent iodide species.

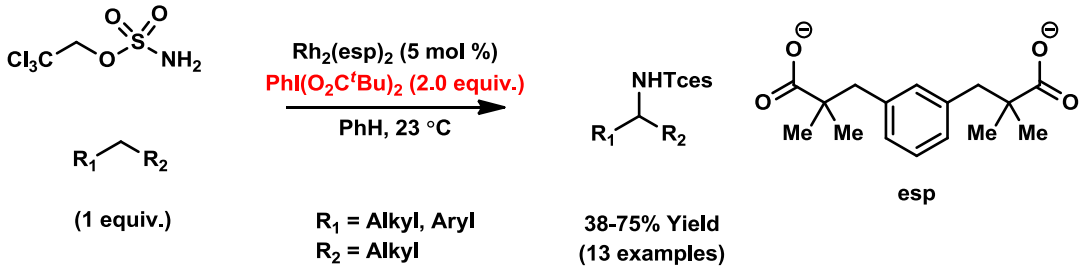
Scheme 1.9. Formation of the rhodium-nitrene using *N*-tosyloxycarbamates.

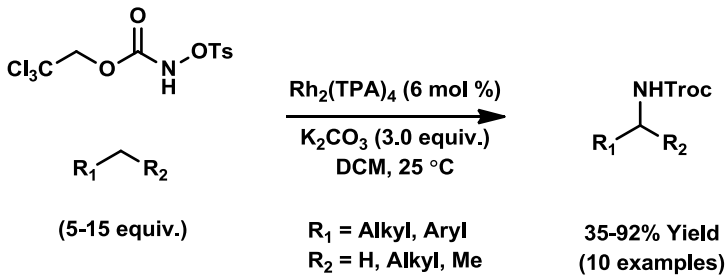


After they disclosed the C-H aminations performed using the unique ability to form the iodoimine *in situ*, Du Bois and coworkers uncovered an intermolecular variant (Scheme 1.10 top).[33,34] They initially discovered an intermolecular variant in 2004,[33] but found that the system needed further optimization to be applied to a more diverse scope. It was reported that two important modifications must be made. First, a rhodium(II) catalyst modified by esp (Scheme 1.10 top) needed to be employed. Next, usage of a sulfamate ester, such as trichloroethyl sulfamate,

proved to be crucial. Du Bois and coworkers were able to take these new findings and apply them to a wide range of hydrocarbons and obtain products of

Scheme 1.10. Comparing intermolecular C-H amination methodologies from Du Bois and Lebel.





intermolecular C-H amination reactions in good yields, but there still is the prevailing problem of using hypervalent iodide oxidants in this transformation.

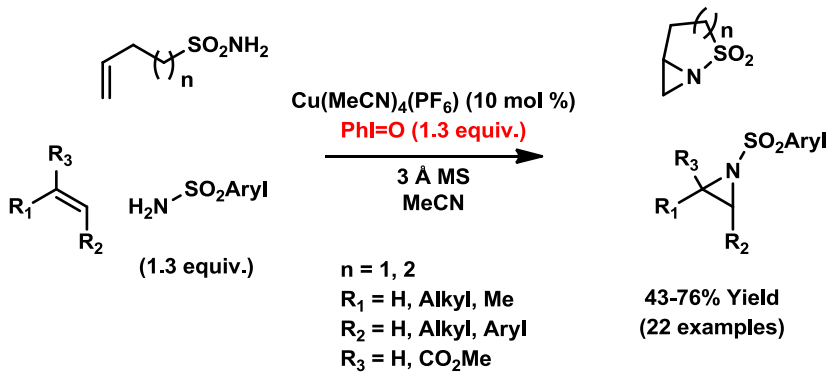
Lebel and coworkers were able to expand their methodology to include the intermolecular variant of the C-H amination reaction they discovered. They found it imperative to utilize the Troc protected *N*-tosyloxycarbamates. This group allowed them to access similar products to those obtained by the Du Bois group in comparable yields, all the while eliminating the need for a hypervalent iodide oxidant in this transformation.

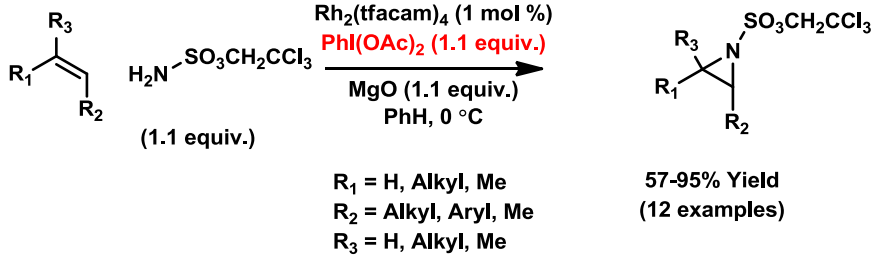
1.3.3 Aziridination Using *N*-Tosyloxycarbamates

Transformations that functionalize olefins through catalytic oxidation in a very selective and precise manner have become indispensable for the synthetic organic chemist.[35] Furthermore, olefin epoxidation has become one of these major pathways. The formation of nitrogen-containing three-membered rings, aziridines, has gained much attention due to the prevalence of nitrogen containing functional groups in biologically active molecules.[36] Among the methods used to create aziridines is one disclosed from the Dauban group that utilizes a copper(II) catalyst to perform azirdinations of olefins with sulfonamides (Scheme 1.11 top).[37] They were able to generate the desired aziridines in good yield across a wide range of substrates.

Likewise, Du Bois and coworkers employed a rhodium(II) catalyst modified by tfacam across a similar range of substrates (Scheme 1.11 bottom).[38] Impressively, both methods performed well for the intermolecular case. Unfortunately, both methods also make use of a hypervalent iodide source as oxidant: Dauban using iodosylbenzene and Du Bois using $PhI(OAc)_2$.

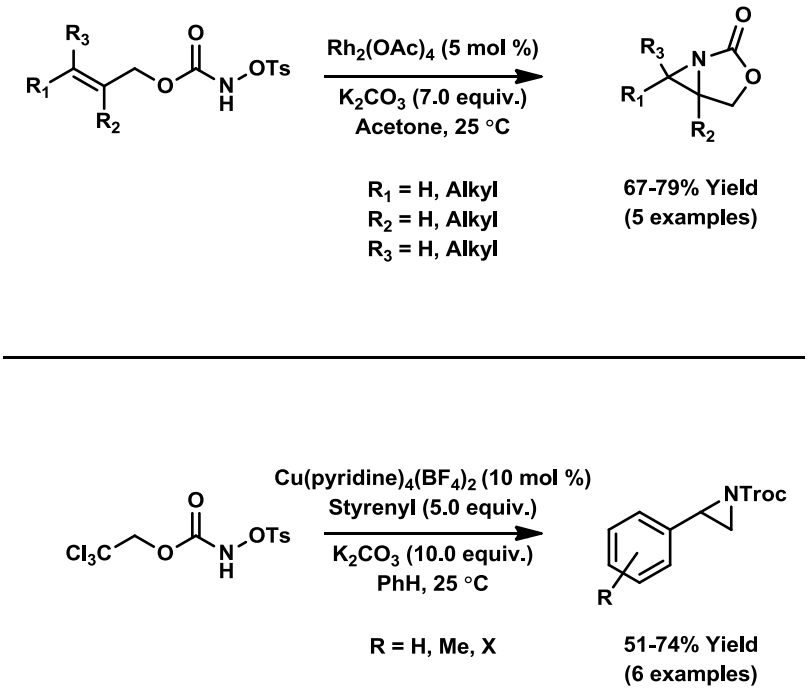
Scheme 1.11. Aziridination methods from the Dauban group and Du Bois group.





As before, Lebel and coworkers saw an opportunity to improve on the usability of these transformations. Initially they disclosed a method for performing intramolecular aziridinations utilizing a rhodium(II) catalyst and various alkenyl-*N*-tosyloxycarbamates (Scheme 1.12 top).[31] They found that the aziridination worked with equal facility when using both disubstituted and trisubstituted olefins, and the transformation was stereospecific, forming only one observable diastereomer.

Scheme 1.12. Lebel's methods for aziridination.



As seen above, Lebel and coworkers were forced to employ quite different conditions to achieve the intermolecular variant of the aziridination (Scheme 1.12 bottom).[39] First they utilized the Troc protected *N*-tosyloxycarbamate that functioned in the intermolecular C-H amination reactions. Lebel and coworkers also changed the catalyst completely, using a copper(II) catalyst modified by pyridine. These new conditions proved fruitful, allowing access to aryl aziridines in moderate yield, barring the need for an external oxidant in the transformation.

1.3.4 Conclusion

This section presented some of the pioneering work from the Lebel group that precludes the need for hypervalent iodide oxidants in both C-H amination reactions as well as aziridination reactions. The employment of *N*-tosyloxycarbamates functions through reagent-contained redox activity of the

N-O bond. For a more complete picture, reviews from the Lebel group can be consulted.[28,40]

1.4 N-N Bond as Oxidant in Diamination Reactions

1.4.1 Background

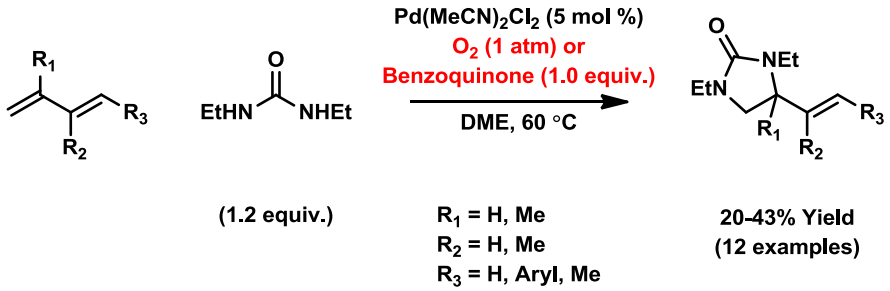
Since Bäckvall reported one of the first transition-metal catalyzed diaminations of olefins in the late 1970's,[41] these motifs have garnered tremendous attention. They are not only privileged structures in the world of pharmaceuticals and agrochemicals,[42] but they are also crucial as catalyst and ligands in the area of organo- and transition-metal catalysis.[43] Thus, the synthesis of this structure has been the subject of many studies. This section will focus on some of the transition-metal catalyzed transformations to produce vicinal diamines by way of diaziridinones and their related structures from the Shi group. These new methods utilize the reagent-contained redox activity in the N-N bond of diaziridinones to circumvent the need for an external oxidant.

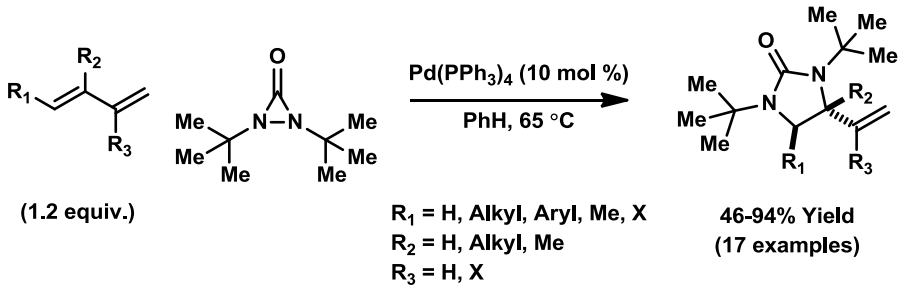
1.4.2 Diamination of Conjugated Dienes

Because of the importance of vicinal diamines in biologically active molecules, as well as, their use in catalysis, they have been the subject of extensive investigation. One such example was unveiled by the Booker-Milburn group in which they report a novel palladium-catalyzed intermolecular diamination of dienes using ureas (Scheme 1.13 top).[44] This work makes use of the diverted Wacker-type pathway that was invoked in the earlier work by Bäckvall.[41] Booker-Milburn and coworkers were able to expand this technology across a wide scope of dienes in good yield and good regioselectivity. However, the problem of an external oxidant persisted. In some cases O_2 was used, and in other cases, benzoquinone was used.

Shi and coworkers discovered a novel transformation that utilized the internal oxidant activity of diaziridinones *via* the N-N bond to eliminate the need for some external oxidant (Scheme 1.13 bottom).[45] By exposing the diaziridinone to a variety of dienes in the presence of a palladium(0) catalyst, they obtained similar products as those seen in the Booker-Milburn report in excellent yields. Also this transformation tolerated some heteroatom functionality not seen in the earlier reports.

Scheme 1.13. Comparing the diamination reactions of Booker-Milburn and Shi.

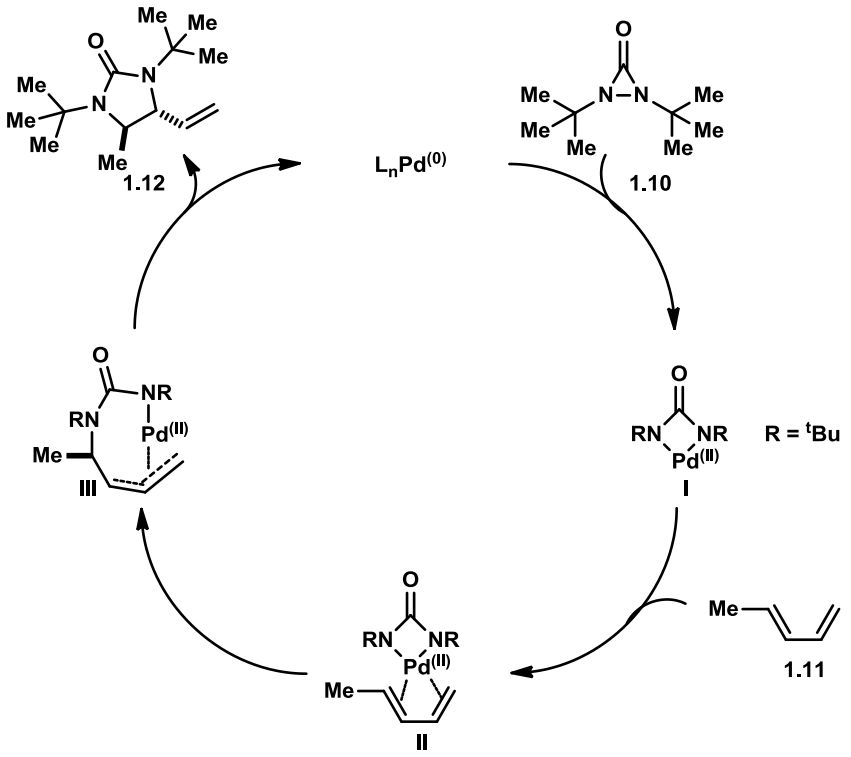




To understand how the diaziridinone affects this transformation a potential mechanism is presented in Figure 1.5.[45] Initially, it is thought that the

palladium(0) inserts into the N-N bond of aziridinone **1.10** forming palladium(II) intermediate **I**. Next, diene **1.11** complexes intermediate **I** to generate intermediate **II**. Migratory insertion occurs to form the π-allyl palladium complex **III**. Reductive elimination ensues to release desired diamination product **1.12** and regenerate the palladium(0) catalyst to close out the catalytic cycle. So, the oxidative addition of the palladium to the N-N bond serves the same role as the oxidant in the transformation presented by Booker-Milburn and coworkers, thus eliminating the need for an external oxidant.

Figure 1.5. A plausible mechanism for Shi's deamination of dienes.

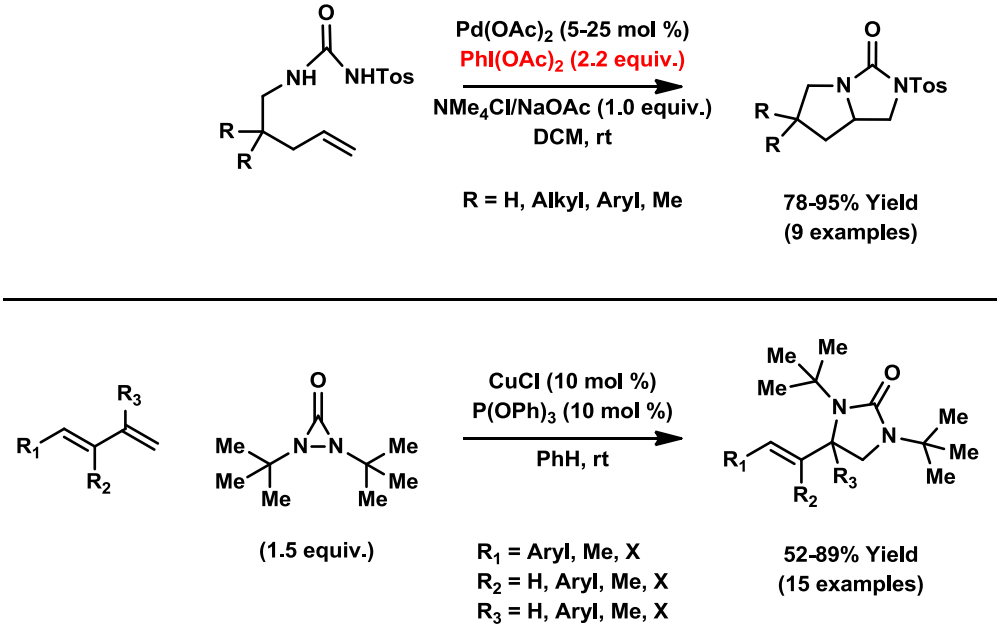


The two transformations presented from Booker-Milburn and Shi were regioselective for coupling at the internal olefins. Muñiz and coworkers disclosed an intramolecular, regioselective diamination of terminal olefins by employing a

palladium(II) catalyst and substituted ureas, which allowed access to cyclic ureas and cyclic diamines (Scheme 1.14 top).[46] They noticed that substitution on the ureas was important. If the urea contained a primary amine, after the amination occurred, the secondary amine could still coordinate the palladium, rendering it inactive. Furthermore, this transformation also required the addition of $PhI(OAc)_2$ as an external oxidant to induce the second amination and regenerate the catalyst.

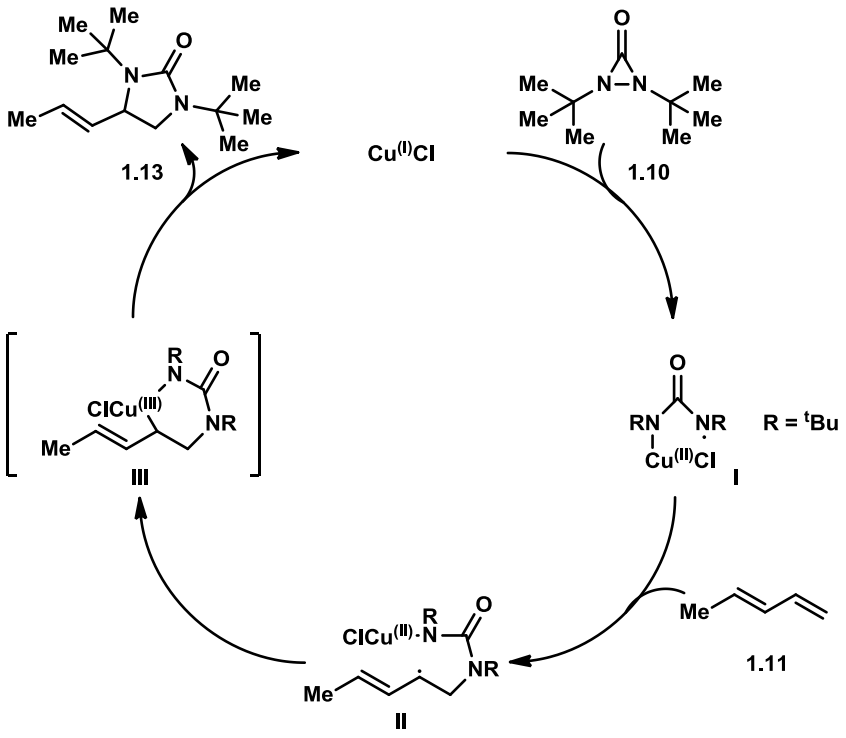
Later the Shi group further expanded the originally developed diamination transformation utilizing diaziridinones to include the complementary regioselectivity to their earlier work: diamination at terminal olefins (Scheme 1.14 bottom).[47] They had to employ an entirely different catalytic system than before, moving from palladium to a copper(I) salt. Fortunately the same diaziridinone performed beautifully when paired with the copper(I) catalyst, allowing access to a variety of different diamination products.

Scheme 1.14. Comparing the diamination of terminal olefins from Muñiz and Shi.



A plausible mechanism can be seen in Figure 1.6. This transformation is believed to proceed by way of a radical pathway. It is thought that the copper(I) species reductively cleaves the N-N bond of **1.10** to generate radical intermediate **I**. Radical addition of intermediate **I** to the diene forms intermediate **II**. Homolytic cleavage of the Cu-N bond could occur, followed by C-N bond formation to generate product **1.13**. An alternative to this could be the formation of copper(III) intermediate **III**, which could then reductively eliminate to give product **1.13** and regenerate the copper(I) catalyst.

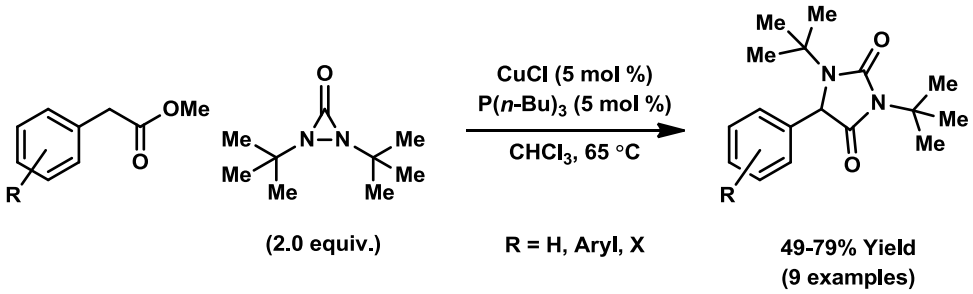
Figure 1.6. A plausible mechanism for the regioselective diamination of terminal olefins.



1.4.3 Miscellaneous Uses of Diaziridinones and Their Analogues in Diaminations

After discovering that the N-N bond in diaziridinones can be used as reagent-contained oxidants in diamination reactions, Shi and coworkers began exploring their application in the synthesis of a variety of different structures. One such application was the development of a hydantoin synthesis utilizing diaziridinones (Scheme 1.15).[48] The Shi group found that when exposing diaziridinones to a copper(I) catalyst in the presence of esters, they were able to isolate hydantoin products in moderate yields. Unfortunately this transformation does not tolerate aliphatic methyl esters. It is believed that this transformation first proceeds through a copper-catalyzed α-amination followed by a simple acyl substitution to generate the hydantoin product.

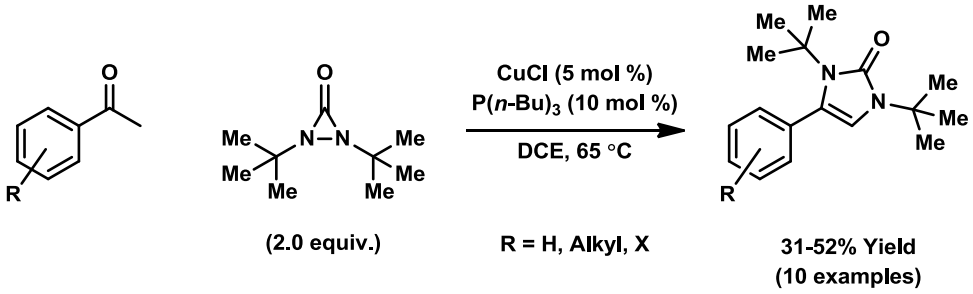
Scheme 1.15. Formation of hydantoins using diaziridinones.



The Shi group also investigated the formation of imidazolinones utilizing a copper(I) catalyst and diaziridinones (Scheme 1.16).[49] The conditions used were similar to those also employed in the formation of hydantoins, only differing in the solvent used. These transformations proceeded in an analogous fashion to the hydantoins. First, a copper-catalyzed α-amination occurred, which was followed by an acyl substitution to generate the imidazolinones. The substrate scope

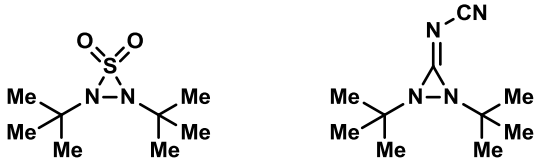
favored a variety of methyl aryl ketones, but only produced the desired products in moderate yields.

Scheme 1.16. Formation of imidazolinones using diaziridinones.



Not only has the Shi group investigated the use of diaziridinones in diamination reactions, but they have also investigated the use of other N-N containing reagents such as thiadiaziridine[50] and diaziridinimines[51], which form products of cycloguanidation (Figure 1.7).

Figure 1.7. Other N-N containing reagents used in diamination reactions.



1.4.4 Conclusion

This section has covered many of the early reports from Shi and coworkers concerning the use of reagent-contained redox activity in diamination transformations. By utilizing the reagent-contained redox activity of diaziridinones enclosed in the N-N bond, diaminations proceed without the need for some

external oxidant. A recent review from the Shi group paints a more extensive picture of the use of N-N bonds as internal oxidants in these transformations.[52]

1.5 Alcohols as Reductants in Carbonyl Addition Reactions

1.5.1 Background

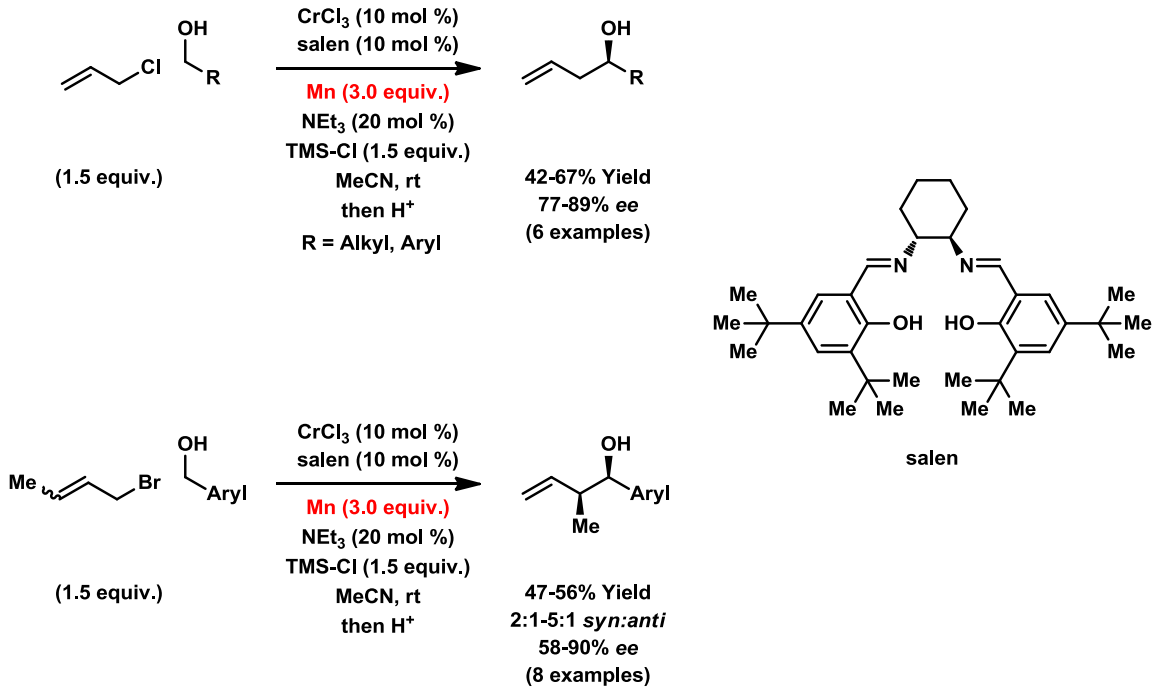
Carbonyl addition chemistry has had a great influence on organic synthesis. Since Victor Grignard first used an organomagnesium reagent to add to a carbonyl group,[53] many methods of carbonyl addition have arisen. Many of these require the discreet formation of an organometallic which then adds to a carbonyl, generating stoichiometric metal waste or necessitating the use of a reductant to reform the next organometallic species, equipped to perform carbonyl addition. Recent work out of the Krische group has shown that the native reducing power of a primary alcohol (alcohols can be oxidized to ketones) can also mediate carbonyl addition. This idea represents reagent-contained reducing ability of a compound which could render a transformation involving an external reductant obsolete.

1.5.2 Alcohol Redox Activity Mediating Carbonyl Additions

One of the traditional methods to perform transition metal catalyzed carbonyl addition is the Nozaki-Hyama-Kishi reaction.[54] In the original report, chromium(II) salts were used to couple allyl chloride and benzaldehyde, furthermore stoichiometric chromium was used. More recent reports use manganese as a reductant, allowing chromium to be used catalytically. The first catalytic enantioselective Nozaki-Hiyama-Kishi was reported by Cozzi and coworkers (Scheme 1.17).[55,56] Using conditions inspired by the Jacobsen group,[57] they found that a chromium catalyst modified by a salen ligand was able to catalyze the addition of allyl halides to aldehydes in moderate yields and

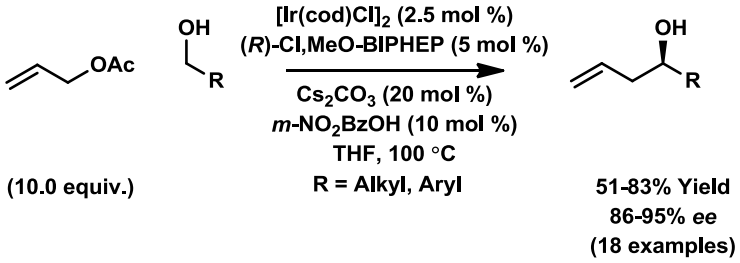
moderate selectivity. In order for this transformation to be catalytic in chromium, manganese was used as an external reductant, which inhibits its efficiency.

Scheme 1.17. First asymmetric Nozaki-Hiyama-Kishi reaction.



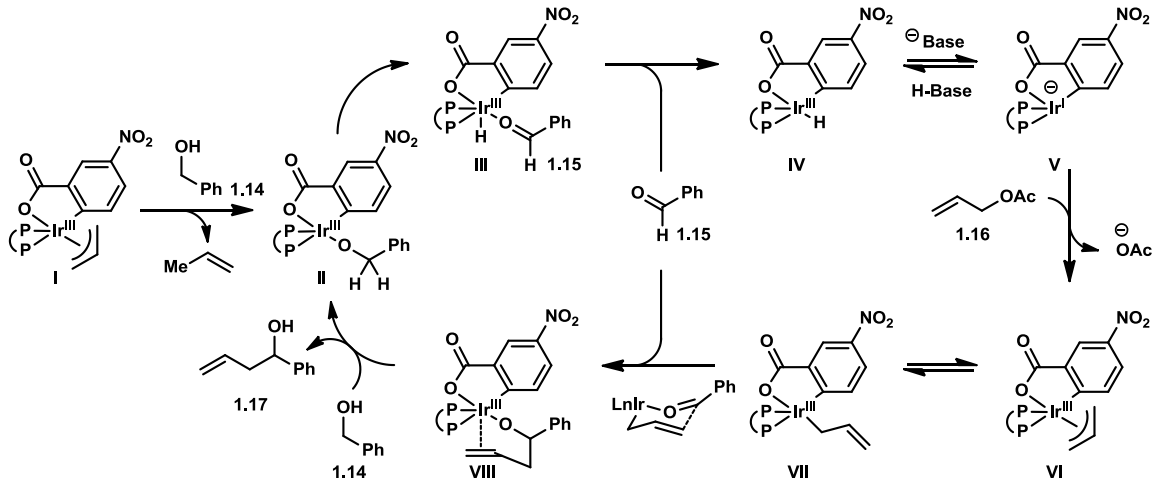
Krische and coworkers discovered a method to perform these transformations by employing an iridium catalyst and excluding the need for an external reductant by using the native reducing ability of a primary alcohol (Scheme 1.18).[58,59] By employing an iridium(I) catalyst, they are able to perform carbonyl additions to a variety of aliphatic, allylic and benzylic alcohols with allyl acetate. The homoallylic alcohol products were obtained in good yields and excellent enantioselectivity. It may seem counter-intuitive to be able to perform carbonyl addition to an alcohol, but by utilizing the redox activity of an alcohol, this is possible.

Scheme 1.18. Iridium-catalyzed carbonyl addition to primary alcohols.



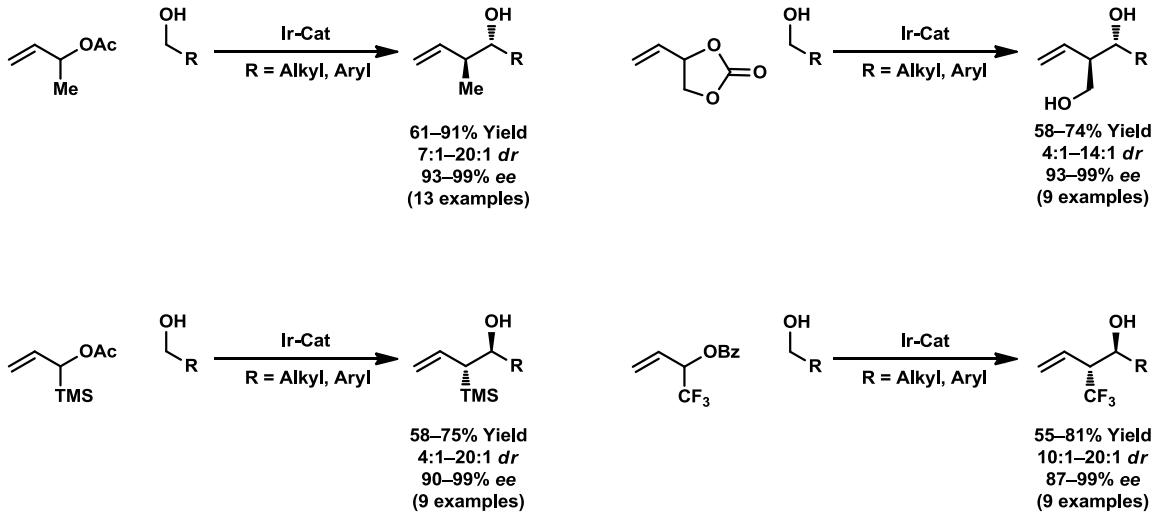
A plausible mechanism is in Figure 1.8. It is believed that the catalyst enters into the catalytic cycle through protonation of allyl species **I** by alcohol **1.14** to generate iridium alkoxide **II**. Iridium alkoxide **II** can undergo β-hydride elimination to generate intermediate **III**. Aldehyde **1.15** can then dissociate unveiling unsaturated iridium hydride **IV**. Base can then deprotonate iridium hydride **IV** forming anionic iridium(I) (species **V**). Oxidative addition of allyl acetate **1.16** produces allyl species **VI**, which is in equilibrium with allyl species **VII**. It is believed that species **VII** is the active catalyst, since it is coordinatively unsaturated. The aldehyde re-associates, and carbonyl addition is thought to occur through a closed six-centered transition state generating species **VIII**. Alcohol exchange releases desired homoallylic alcohol **1.17** and regenerates iridium alkoxide **II**. It can be seen that the oxidation of the alcohol to the aldehyde is what functions to reduce the iridium. This is an incredible way to utilize reagent-contained reductant activity all the while unveiling a new reactive intermediate, a carbonyl.

Figure 1.8. A plausible mechanism for iridium-catalyzed carbonyl addition of primary alcohols with allyl acetate.

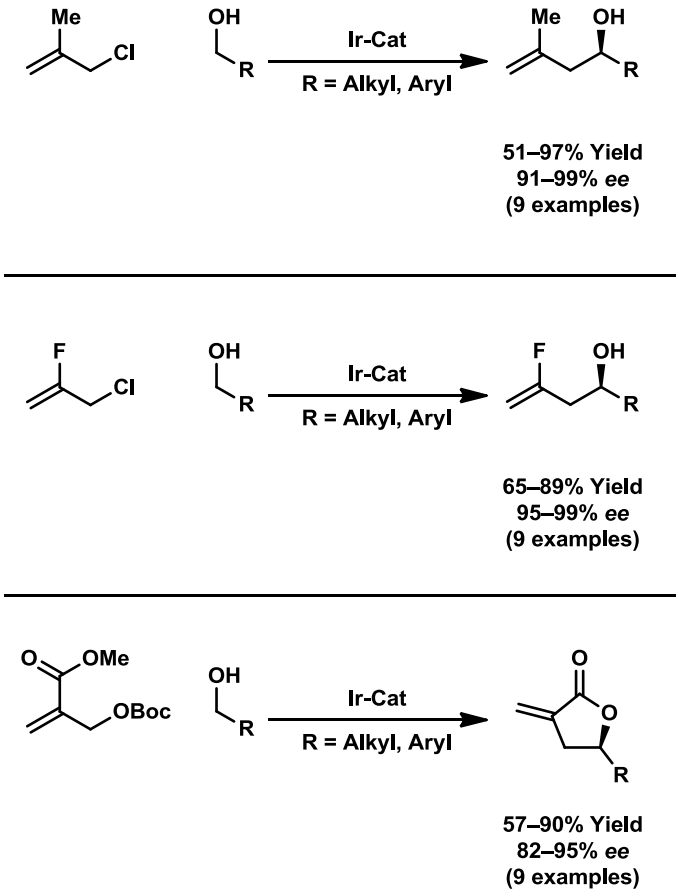


Krische and coworkers have had much success applying this technology to encompass a large family of these types of reactions to generate synthetically useful products. The have obtained products of crotylation,[60,61] hydroxymethyl allylation,[62] trifluoromethyl allylation[63] and silylallylation[64] (Scheme 1.19). They have also been able to utilize disubstituted allyl donor species in these types of transformations that have allowed access to products of methallylation,[65] fluoroallylation[66] and α-exo-methylene-γ-butyrolactones[67] (Scheme 1.20).

Scheme 1.19. Family of allylation transformations utilizing primary alcohols as reductants.



Scheme 1.20. Utilization of disubstituted allyl donors in primary alcohol mediated carbonyl additions.



1.5.3 Conclusion

This section has covered many of the early reports from Krische and coworkers concerning the use of reagent-contained redox activity in carbonyl addition reactions. They have also a developed a suite of transformations that employ various ruthenium catalyst and make use of hydrometallation or oxidative coupling pathways. Recent reviews from the Krische group tell a more complete story of the research conducted in this area.[68–70]

1.6 Summary

Reagent-contained redox activity has already begun to play a role in the way synthetic chemist are approaching problems. This review has highlighted some incredible work in which the redox activity of reagents have improved the atom economy and the ability of these transformations to become more process relevant. Although none of these transformations are perfectly atom efficient, they represent steps taken in the right direction to performing more sustainable chemistry in the future.

Again, this review is not meant to be completely comprehensive, as some transformations were excluded such as borrowing hydrogen chemistry.[71,72] This review is meant to consider some of the more recent discoveries that have been applied to solving such problems as the use of external oxidants or reductants.

Chapter 2: 2,2-Disubstituted Allyl Donors in Iridium-Catalyzed Stereoselective Allylations*

2.1 Introduction

Process-relevant methods are able to transform abundant, renewable feedstocks to valuable products without the generation of stoichiometric amounts of waste.[1] This is embodied by catalytic hydrogenation, which has found wide use across all areas of chemical industry.[2] Likewise, alkene hydroformylation can be seen as the prototypical carbon-carbon bond forming hydrogenation, epitomizing process-relevant methods.[3] Currently alkene hydroformylation is the largest volume application of homogeneous metal catalysis.[4]

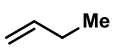
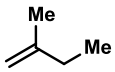
Considering the importance of catalytic hydrogenation and hydroformylation, the Krische group has made efforts to discover C-C bond forming reactions beyond hydroformylation. By hydrogenating olefins in the presence of carbonyl compounds, products of carbonyl allylation can be obtained[5,6] without substrate preactivation or generation of stoichiometric amounts of byproducts as with traditional carbonyl allylation methods.[7–11] This protocol inspired a number of related iridium-catalyzed transformations that allowed access to interesting structural motifs,[12–18] which could be used as building blocks for complex molecule synthesis. Despite the success of 1-substituted carbonyl allylation reactions via transfer hydrogenation, 2,2-disubstituted products (containing vinyl substitution) have proven elusive. It is known that the stability of late transition metal-olefin π-complexes decreases as

*Hassan, A.; Montgomery, T. P.; Krische, M. J. *Chem. Commun.* **2012**, *48* (39), 4692. Acknowledgement is made to A. H. for reaction discovery and M. J. K. for supervision.
Montgomery, T. P.; Hassan, A.; Park, B. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134* (27), 11100. Acknowledgment is made to A. H. for reaction discovery and development, B. Y. Park for scope evaluation and M. J. K. for supervision.

olefin substitution increases (Figure 2.1),[19–21] yet this problem can be avoided by the use of a more reactive leaving group or LUMO-lowering substituents on the olefin (Scheme 2.1), as evidenced by the vinylogous aldol and methallylation recently published from this lab.[22,23] Using the knowledge gained from these

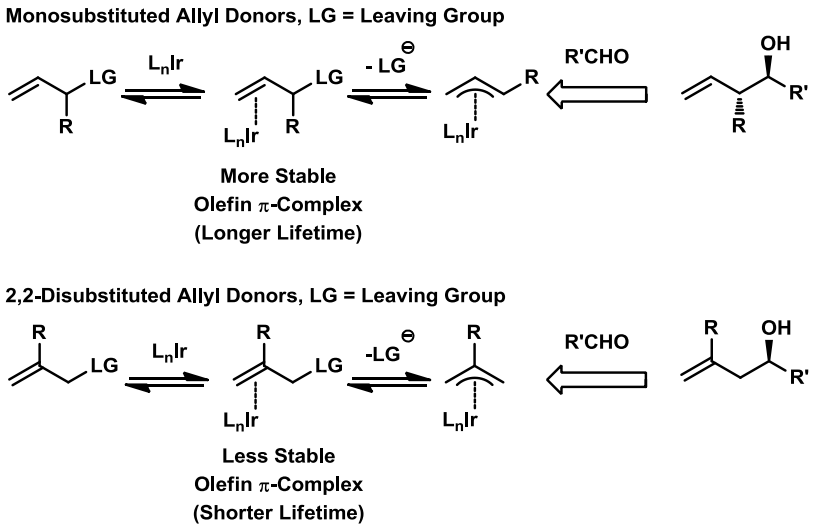
Figure 2.1. Stability of metal-olefin π-complexes using a rhodium(I) catalyst.

Relative Stability Constants of Rh(I) Olefin-Metal π-Complex

Olefin	K
	23.19
	3.40
	3.62
	0.15
	0.12

developments, attempts to further expand the scope of iridium-catalyzed allylations utilizing 2,2-disubstituted allyl donors began.

Scheme 2.1. More reactive leaving groups or LUMO lowering substituents compensate for decreased metal-olefin π-complex stability.

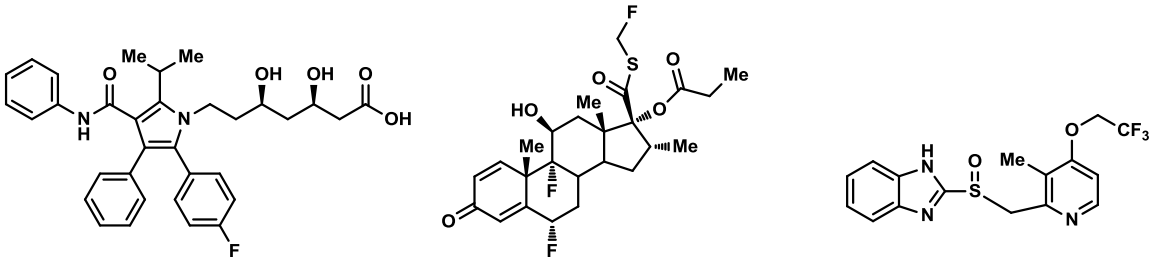


2.2 Iridium-Catalyzed (2-Fluoro)Allylation of Primary Alcohols

2.2.1 Background

Organofluorine chemistry has recently emerged as an important and lucrative area of research for both the pharmaceutical and agrochemical sectors. Since the 1950's, when the first fluorinated pharmaceutical (fludrocortisone) was introduced, over one hundred and fifty drugs have come to market which contain a fluorine atom.[24,25] This represents over twenty percent of all pharmaceutical agents. In fact, in the year 2008, pharmaceuticals containing fluorine made up three of the top five selling pharmaceuticals (Figure 2.2), with lipitor being the top selling pharmaceutical that year.[26] Fluorine has also gained importance in the

Figure 2.2. Top selling pharmaceuticals in 2008.



agrochemical industry, comprising an estimated thirty to forty percent of all agrochemicals sold.[24] It is thought that fluorine can have many different effects on molecules in a biological environment: enhanced metabolic stability, effects on lipophilicity and molecule binding in the enzyme active site.[24]

Considering the importance of fluorine in the pharmaceutical and agrochemical industry, it is quite unfortunate that organofluorine compounds are the least naturally occurring organohalogen.[27] In fact, less than twenty naturally occurring organofluorine compounds are known.[28] Furthermore, despite decades of investigations on enantioselective carbonyl allylations, enantioselective carbonyl (2-fluoro)allylations have not been reported until this work.[29]

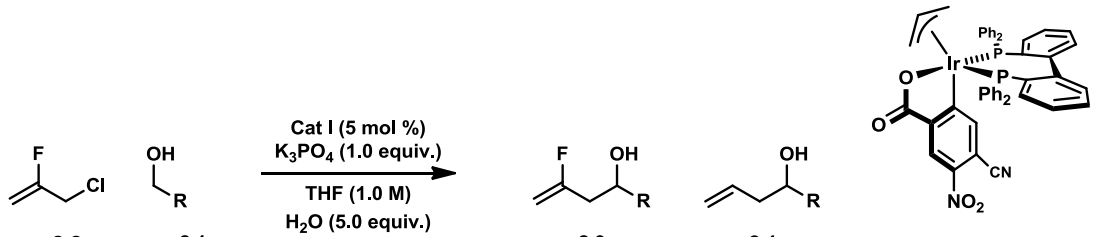
2.2.2 Reaction Development and Scope

Studies commenced with a screen of the commercially available 3-chloro-2-fluoropropene **2.2** and alcohol **2.1a** using the cyclometallated iridium π-allyl complex of 4-cyano-3-nitrobenzoic acid and BIPHEP (**Cat I**) with the conditions optimized for the coupling of methallyl chloride[23] and primary alcohols. Surprisingly, **Cat I**, as well as other iridium catalyst from our group are stable to column chromatography, so the catalyst can be isolated without any inorganic impurities.[13] Product **2.3a** was obtained in good yield, but defluorinated side

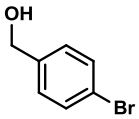
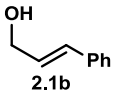
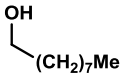
product **2.4a** was also detected. Attempts were made to minimize the formation of this side product, but variation of base, concentration and solvent showed no improvement from the initial conditions applied. Reaction temperature showed a noticeable effect (Table 2.1). For benzylic alcohol **2.1a** and allylic alcohol **2.1b**, the reaction proceeded as low as 40 °C, maximizing the ratio of the desired product to that of the defluorinated product. When coupling aliphatic alcohols, such as **2.1c**, a slightly higher temperature was used to maximize this ratio.

To evaluate the trends discovered for the racemic couplings, coupling attempts between 3-chloro-2-fluoropropene **2.2** and alcohols **2.1a-i** were made using a cyclometallaed iridium catalyst modified by Cl-MeO-BIPHEP (**Cat II**). We found that benzylic alcohols **2.1a, d** and **e**, allylic alcohols **2.1b, f** and **g** and aliphatic alcohols **2.1c, h** and **i** all participate in the highly enantioselective coupling to form products **2.3a-i** of (2-fluoro)allylation (Table 2.2). The products of (2-fluoro)allylation were able to be separated by column chromatography, but to ensure correct ratios of desired product to defluorinated product was determined, products **2.3a-i** and defluorinated products **2.4a-i** were isolated as a

Table 2.1. Optimization of reaction temperature.

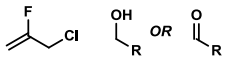


2.2 (3.0 equiv.) | 2.1 | 2.3 Yield (%) | 2.4 Defuorinated Yield (%) | Cat I

2.1		2.3 Yield (%)	2.4 Defuorinated Yield (%)
 2.1a	40 °C	85	6
	50 °C	78	8
 2.1b	40 °C	74	trace
	50 °C	55	7
 2.1c	40 °C	10	6
	50 °C	60	8
	60 °C	75	8

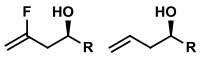
mixture. As expected, this reaction performs similarly from the aldehyde oxidation level. Using aldehydes **2.5a-i** and employing isopropanol as the reductant, we obtained products **2.4a-i** in similar reactivity and similar enantioselectivity, now allowing carbonyl (2-fluoro)allylation to be accomplished from both the alcohol and aldehyde oxidation levels.

Table 2.2. Scope of (2-fluoro)allylation.

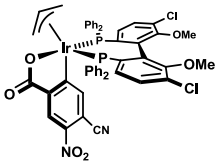


2.2
(1.5 equiv.)

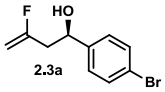
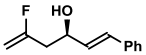
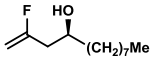
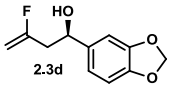
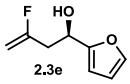
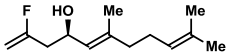
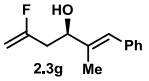
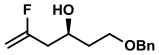
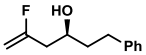
2.1 or 2.5



2.3 2.4

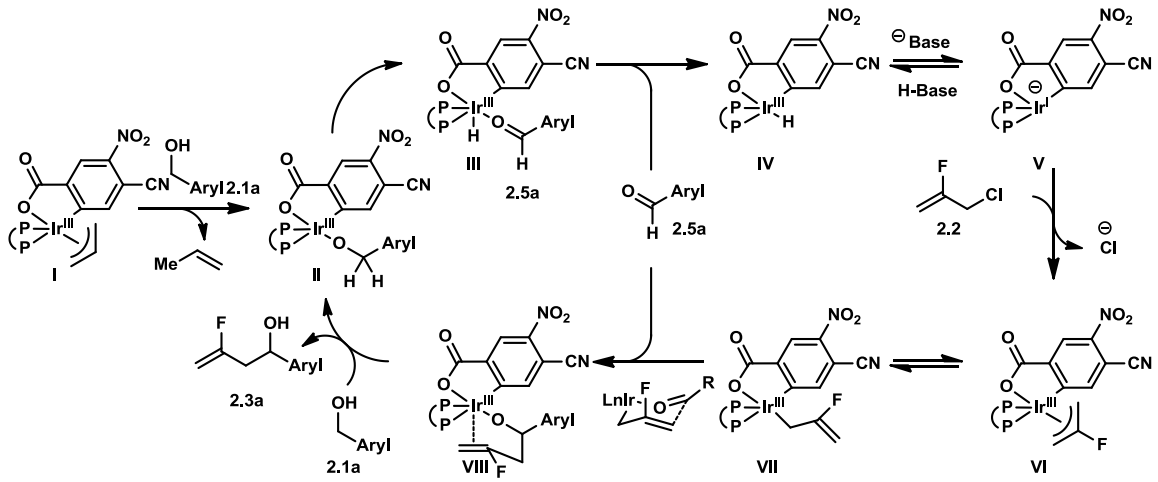


Cat II

Product	[o] Level	Yield (%) 2.3a-i (2.4a-i)	*ee* (%)
 2.3a	Alcohol Aldehyde	76 (10) 61 (5)	99 99
 2.3b	Alcohol Aldehyde	65 (6) 55 (6)	98 98
 2.3c	Alcohol Aldehyde	89 (5) 65 (6)	99 98
 2.3d	Alcohol Aldehyde	76 (4) 74 (3)	98 98
 2.3e	Alcohol Aldehyde	80 (5) 93 (4)	98 98
 2.3f	Alcohol Aldehyde	75 (4) 74 (3)	95 96
 2.3g	Alcohol Aldehyde	86 (7) 89 (5)	99 99
 2.3h	Alcohol Aldehyde	81 (3) 88 (5)	99 99
 2.3i	Alcohol Aldehyde	65 (5) 73 (5)	99 99

A potential mechanism is aligned with that presented in Figure 1.8 and can be seen in Figure 2.3. It is believed that the catalyst enters into the catalytic cycle by protonation of allyl species **I** by alcohol **2.1a** to generate iridium alkoxide **II**. Iridium alkoxide **II** can undergo β-hydride elimination to generate intermediate **III**. Aldehyde **2.5a** can then dissociate unveiling unsaturated iridium hydride **IV**. It is believed that a base can then deprotonate iridium hydride **IV** forming anionic iridium(I) (species **V**). Oxidative addition of 3-chloro-2-fluoropropene **2.2** produces allyl species **VI**, which is in equilibrium with allyl species **VII**. It is believed that species **VII** is the active catalyst, since it is coordinatively

Figure 2.3. A plausible mechanism for the (2-fluoro)allylation of primary alcohols.

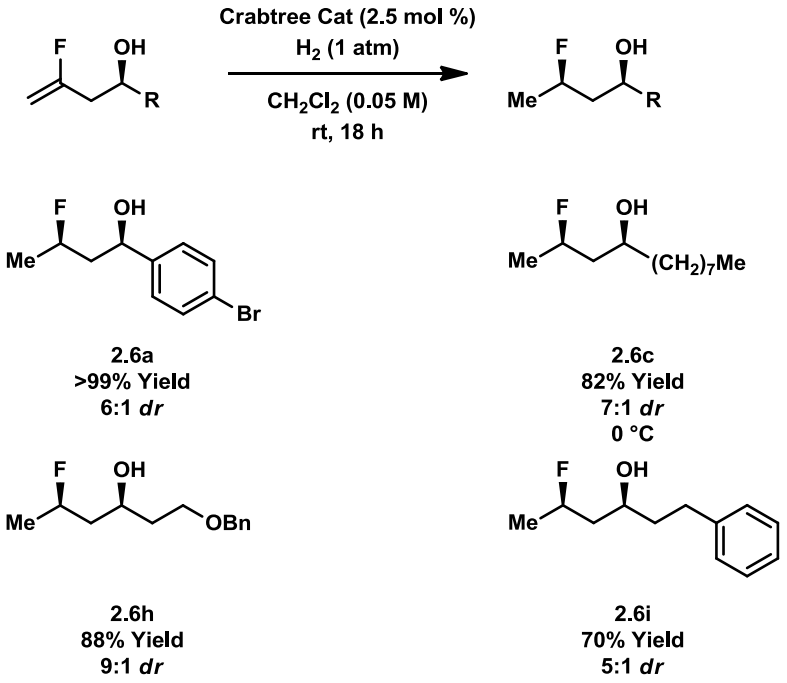


unsaturated. Aldehyde **2.5a** reassociates, and carbonyl addition is thought to occur through a closed six-centered transition state generating species **VIII**. Alcohol exchange occurs to release desired homoallylic alcohol **2.3a** and regenerate iridium alkoxide **II**. Although no studies were undertaken, it was thought that defluorination products **2.4** are formed after release of products **2.3**, since the amount of **2.4** seemed to increase with time.

2.2.3 Product Elaboration

With a developed method to obtain compounds **2.3a-i** available, further elaboration of these adducts were pursued. Initially, an attempt at Heck coupling was made with product **2.3i** and iodobenzene. Unfortunately the yield was not satisfactory. Further investigation unveiled the potential to stereoselectively set the C-F bond through hydrogenation. Preliminary methods used included Pd/C in the presence of 1 atm of hydrogen. Desired product **2.6i** was isolated but in only a 1:1 mixture of diastereomers. Next, Crabtree's catalyst[30,31] was examined as a potential catalyst. Crabtree's catalyst worked delightfully, furnishing desired *syn*-3-fluoro-1-alcohols **2.6a**, **c**, **h** and **i** (Table 2.3). It was discovered that lowering the catalyst loading and performing the reaction more dilute improved the diastereoselectivity. Fortunately, fluoroalcohol **2.6a** was crystalline, which

Table 2.3. Hydrogenation to generate *syn*-3-fluoro-1-alcohols **2.6a**, **c**, **h** and **I** *via* Crabtree hydrogenation.



allowed absolute and relative stereochemical assignment using single crystal X-ray diffraction analysis by anomalous dispersion method (Figure 2.4). It is believed that the relative stereochemistry is set from asymmetric induction of the alcohol. The alcohol can coordinate to the iridium center, forcing the addition of the hydrogen to come from the *anti*-face, furnishing the *syn*-3-fluoro-1-alcohols (Figure 2.5).

Figure 2.4. X-ray crystal structure of **2.6a** to determine absolute and relative stereochemistry.

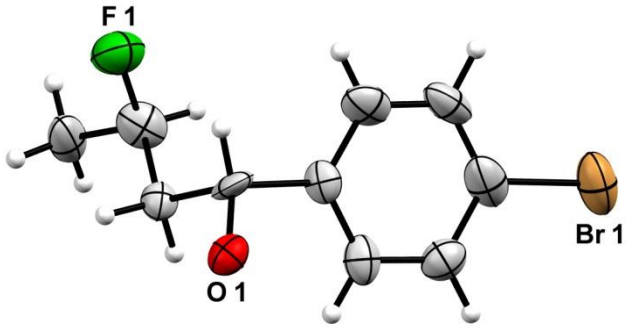
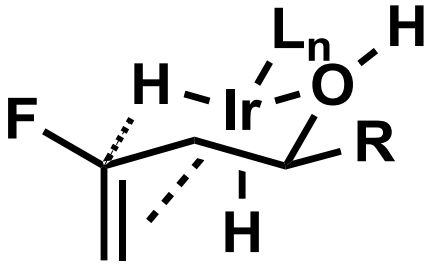


Figure 2.5. Stereochemical model of the formation of *syn*-3-fluoro-1-alcohols.



2.2.4 Conclusion

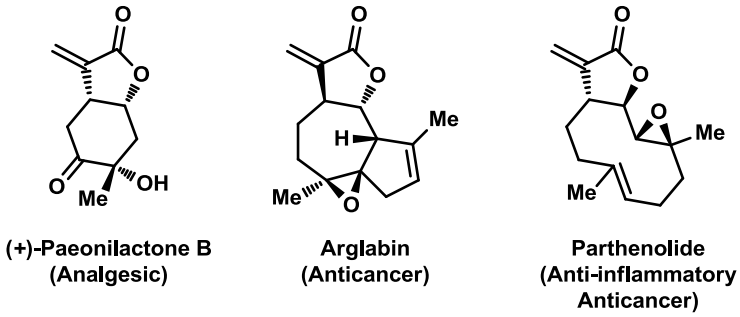
Using the commercially available 3-chloro-2-fluoropropene, direct enantioselective iridium-catalyzed (2-fluoro)allylation of alcohols **2.1a-i** has been achieved. As expected, (2-fluoro)allylation of aldehydes in the presence of isopropanol generated an identical set of products, **2.3a-i**. Diastereoselective Crabtree hydrogenation of products **2.3a**, **c**, **h** and **i** furnished *syn*-3-fluoro-1-alcohols **2.6a**, **c**, **h** and **i** in good yield and diastereoselectivity. Thus consecutive iridium-catalyzed C-C and C-H bond formation has been utilized to generate chiral fluorine containing building blocks, precluding the need for stoichiometric metallic reagents, thus eliminating the generation of stoichiometric metallic waste.

2.3 Iridium-Catalyzed Formation of α-*exo*-Methylene γ-Butyrolactones

2.3.1 Introduction

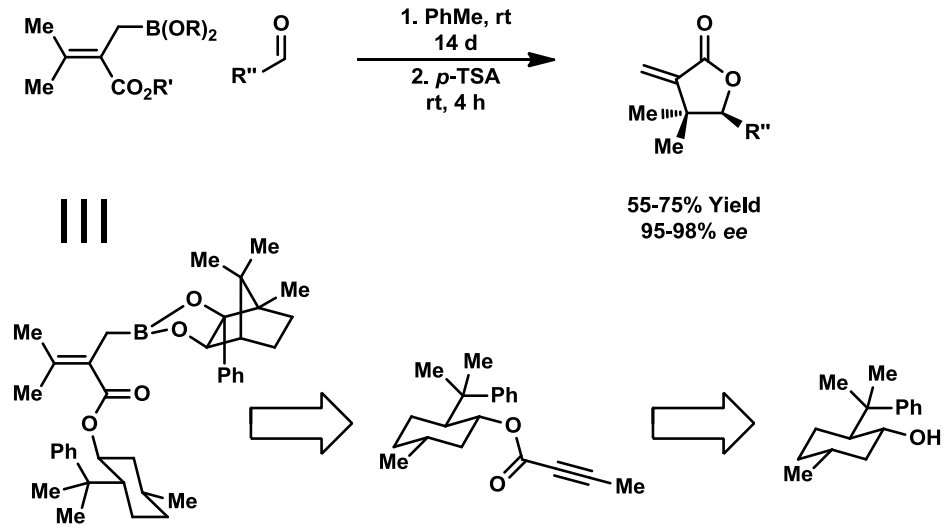
α-*exo*-Methylene γ-butyrolactones compose one of the largest known classes of natural products, constituting an estimatied ten precent of the more than thirty thousand known natural products (Figure 2.6).[32–37] In fact, Arglabin is actually in clinical use in some near eastern countries. Because of their importance in nature, α-*exo*-methylene γ-butyrolactones have been the subject of

Figure 2.6. Select α-*exo*-methylene γ-butyrolactone examples and their activity.



much investigation over the years. Among the many methods for their preparation, (2-alkoxycarbonyl)allylmetal reagents have served as reliable protocols for the formation of this common motif. Presently, methods that employ (2-alkoxycarbonyl)allylmetal reagents based on boron,[38–50] silicon,[51–58] tin,[59–63] zinc[64] and nickel[65] have found success. Umpoled reactions of (2-alkoxycarbony)allyl halides also stimulate the formation of α-*exo*-methylene γ-butyrolactones, such as Reformatsky and Nozaki-Hiyama type reactions.[66–79] Asymmetric methods for the formation of α-*exo*-methylene γ-butyrolactones rely heavily on stoichiometric chirality transfer from chiral auxiliaries.[38,39,41,42,49,75] The state of the art was developed by Hall and coworkers, which employs two chiral auxiliaries: one as the boronate ester derived from camphor and another as the phenyl menthol derivative on the ester of the olefin (Figure 2.7).[39,41] They obtain reasonable yields, but achieve exceptional levels of asymmetry. Unfortunately their method is not without drawbacks. As previously stated, they must use two chiral auxiliaries. Furthermore, this process is not atom-economic. To transfer six carbon atoms and one oxygen atom, such a huge mass intensive reagent must be used.

Figure 2.7. Hall's enantioselective synthesis of α-*exo*-methylene γ-butyrolactones.



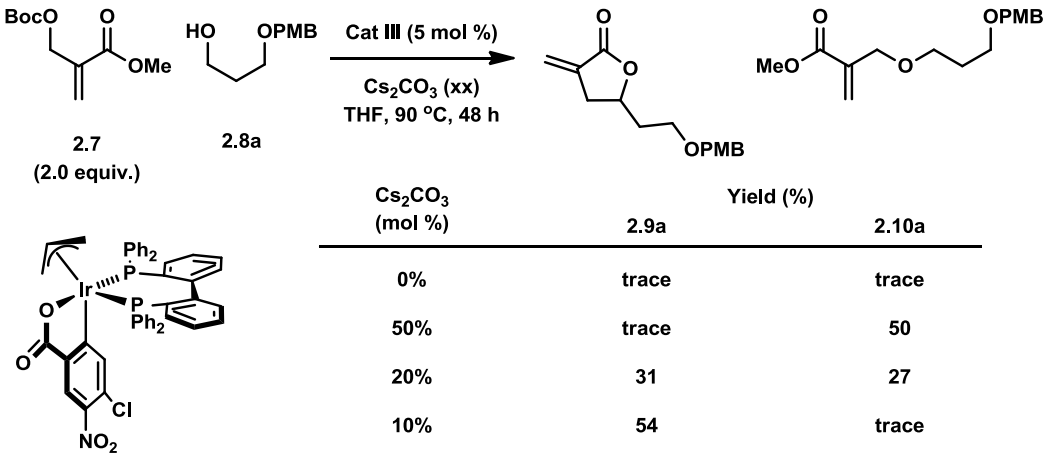
It is known that the stability of the metal-olefin π-complex decreases with increasing substitution of the olefin;[19,20] however, it was recently found that π-backbonding[81–85] can be enhanced with carboxy substitution, thus compensating for the destabilization of a metal-olefin π-complex, enabling vinylogous aldol addition.[22] With this in mind, acrylic ester **2.7** was designed to participate in the iridium-catalyzed formation of α-*exo*-methylene γ-butyrolactones. This work represents the first highly enantioselective catalytic (2-alkoxycarbonyl)allylation to form α-*exo*-methylene γ-butyrolactones, which utilizes iridium catalyzed C-C bond formation.[80]

2.3.2 Reaction Development and Scope

Initial attempts at the formation of α-*exo*-methylene γ-butyrolactones commenced with the coupling of acrylic ester **2.7** and alcohol **2.8a** in the presence of the chromatographically purified iridium catalyst (**Cat III**) modified by 4-chloro-3-nitrobenzoic acid and BIPHEP ligand and using half an equivalent of

base (Cs_2CO_3). Surprisingly only trace amounts of desired lactone **2.9a** were detectable. Reconsidering the previously mentioned vinylogous aldol technology, it was recalled that the catalyst used in that transformation was not column purified, thus most likely contaminated with small amounts of inorganic base. This hypothesis encouraged attempting the reaction again, but with lowering amounts of base (Table 2.4). It was found that as the base loading was

Table 2.4. Optimazation of base loadings in the formation of α-*exo*-methylene γ-butyrolactones.

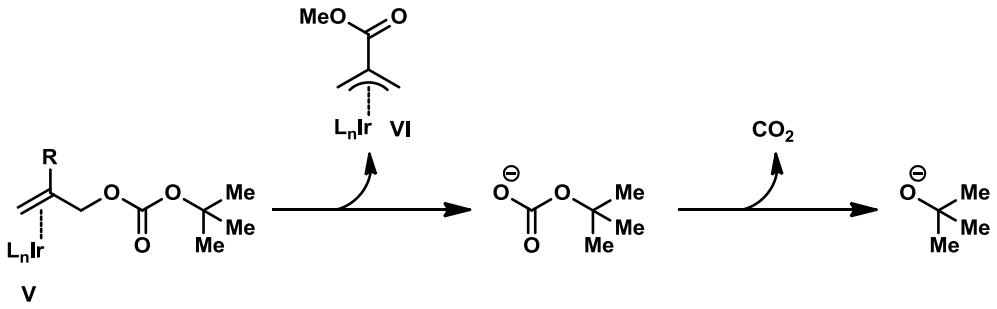


Cs_2CO_3 (mol %)	Yield (%) 2.9a	2.10a
0%	trace	trace
50%	trace	50
20%	31	27
10%	54	trace
5%	65	trace

decreased, the formation desired product **2.9a** increased and the formation of byproduct **2.10a** decreased. It was determined that 5 mol % of Cs_2CO_3 gave the best result, forming the product in 65% yield. Considering the reaction mechanism presented in Figure 2.2 (it is believed that this transformation proceeds through an analogous mechanism, substituting acrylic ester **2.7** for 3-chloro-2-fluoropropene **2.2**), it is important to understand why a catalytic amount of base is necessary. Upon oxidative addition of acrylic ester **2.7** to iridium species **V**, iridium species **VI** then goes on to complete the catalytic cycle while

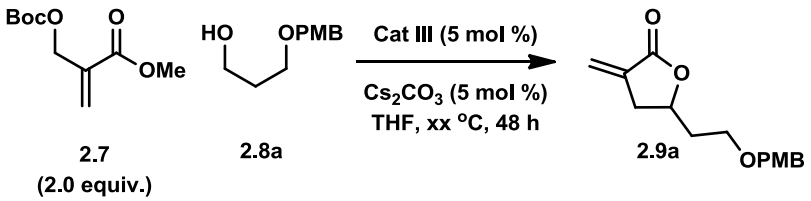
the generated carbonate can persist as base, or the carbonate can decarboxylate at the reaction temperature, producing an equivalent of *tert*-butoxide which could also act as base (Figure 2.8). Nonetheless, for each catalytic turnover, an equivalent of base is produced, thus necessitating a catalytic amount to get the cycle going.

Figure 2.8. Understanding the need for only catalytic base.



Next, reaction temperature was assayed. As the reaction temperature was increased, formation of product **2.9a** decreased, but as the temperature was lowered, an increase in the formation of product **2.9a** was observed (Table 2.5). A minimal efficiency temperature was discovered at 80 °C.

Table 2.5. Optimazation of temperature in the formation of α-*exo*-methylene γ-butyrolactones.

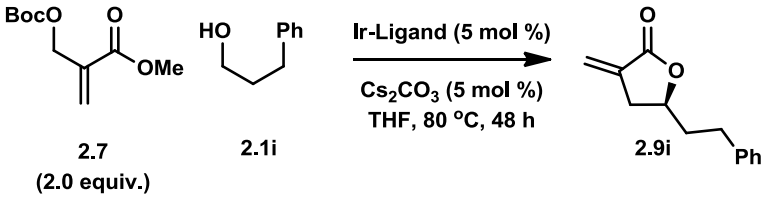


2.7 (2.0 equiv.) 2.8a 2.9a

Temp. xx °C	Yield (%)
70	48
80	77
90	65
100	39

Using the optimal conditions found by employing **Cat III**, the asymmetric variant was attempted assaying a variety of axially chiral chelating phosphine ligands (Table 2.6). Many commonly used binaphthyl and biphenyl based ligands were assessed to no avail (alcohol **2.8a** was switched to **2.1i** because **2.1i** showed lower *ee*, thus making it a better substrate to optimize). Fortunately, the iridium catalyst modified by (-)-TMBTP (**Cat IV**) showed an increase in *ee* for the formation of product **2.9i**. Lastly, attempts were made to further enhance the enantioselectivity of the system by altering solvent (Table 2.7). The isolated yields and enantioselctivity of the transformation proved to be solvent dependent. Reactions performed in 2-Me-THF returned a lower yield and enantioselectivity than the reactions performed in THF. While 1,4-dioxane delivered product **2.9i** in only 33% yield and 72% *ee*, acetonitrile furnished lactone **2.9i** in 34% yield and 92% *ee*. To balance the yield and enantioselectivity, a mixed solvent was used over the course of 72 hours. It is believed that, since acetonitrile is lewis basic, it can coordinate the iridium during the bond forming step, potentially enhancing the chiral pocket of the desired enantiomer over the undesired enantiomer.

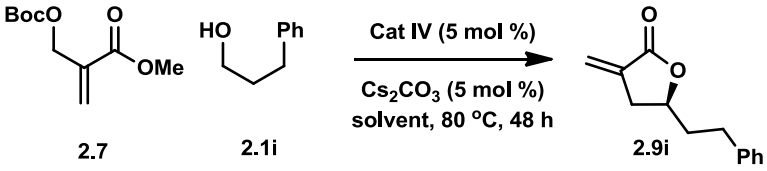
Table 2.6. Ligand optimization in the asymmetric synthesis of α-*exo*-methylene γ-butyrolactones.



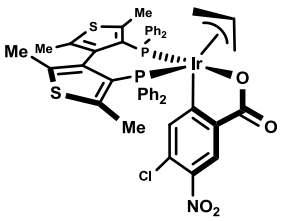
2.7 (2.0 equiv.) 2.1i 2.9i

Ligand	Yield (%)	*ee* (%)
(*R*)-MeO-BIPHEP	83	71
(*R*)-Cl-OMe-BIPHEP	72	69
(*R*)-BINAP	75	69
(*R*)-Xylyl-BINAP	74	69
(*R*)-C3-TunePhos	67	58
(*R*)-SEGPHOS	74	71
(*R*)-DM-SEGPHOS	67	80
(*R*)-SYNPHOS	79	69
CTH-(*R*)-P-Phos	50	80
(-)-TMBTP	79	88

Table 2.7. Solvent optimization in the asymmetric synthesis of α-*exo*-methylene γ-butyrolactones.



2.7 (2.0 equiv.) 2.1i 2.9i



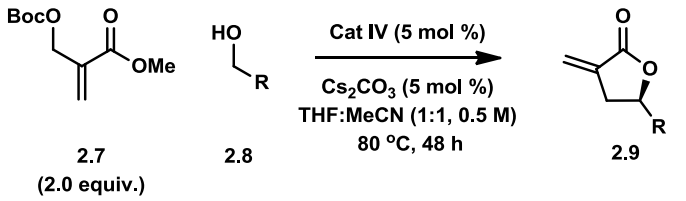
Cat IV

Solvent (0.5 M)	Yield (%)	*ee* (%)
THF	79	88
2-Me-THF	68	77
1,4-Dioxane	33	72
MeCN	34	92
1:1 THF:MeCN	52	90
1:1 THF:MeCN (90 °C)	47	86
1:1 THF:MeCN (72 h)	57	90

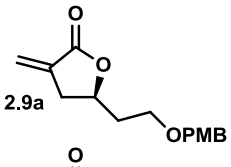
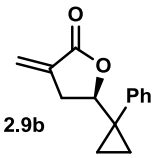
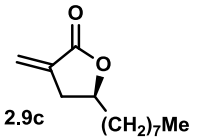
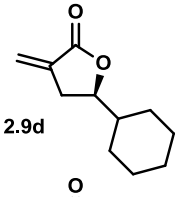
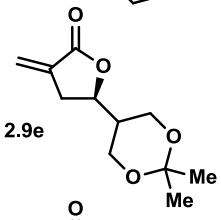
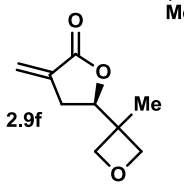
With the optimal conditions now identified, the scope of this transformation was evaluated. Using a variety of aliphatic alcohols, α-*exo*-methylene γ-butyrolactones **2.9a-i** were generated in moderate to excellent yields and good to high enantioselectivities (Table 2.8). Unfortunately these conditions were not uniform across all types of primary alcohols. Benzylic and allylic alcohols participated in the coupling, but the enantioselectivty of lactone products **2.9j** and **k** was 63% *ee* and 57% *ee* respectively. Products **2.9c** and **2.9i** were previously made and have assigned stereochemistry; therefore absolute stereoconfiguration was assigned based on literature value.[60,86] For product **2.9a**, the iridium catalyst derived from 4-cyano-3-nitro benzoic acid was used (**Cat V**). For product **2.9g**, iridium catalyst modified by (*R*)-DM-SEGPHOS (**Cat VI**) was used, and the reaction was conducted in THF.

Surprisingly, this transformation did not work well from the aldehyde oxidation level. The desired lactone products were formed, but the enantioselectivities were quite low in most cases. Only in the case of product **2.9g** was the enantioselectivity good (Scheme 2.2). The reason for this is unknown at the moment, but it could be speculated that there is typically only a catalytic amount of aldehyde in the reaction mixture at any single time, but when starting from the aldehyde oxidation level, there is a surplus of aldehyde in the reaction. Further, this could potentially hasten the carbonyl addition step, thus diminishing the selectivity in the reaction. Unfortunately no mechanistic studies were undertaken, and this issue remains only a partially met challenge for this technology.

Table 2.8. Scope of (2-alkoxycarbony)allylation to form α-*exo*-methylene γ-butyrolactones.

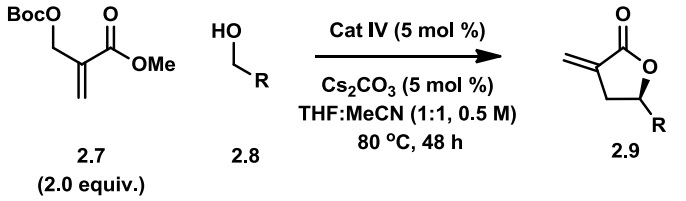


2.7 (2.0 equiv.) 2.8 2.9

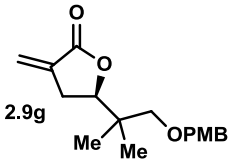
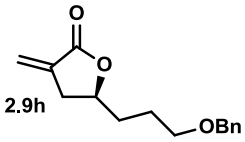
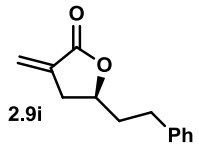
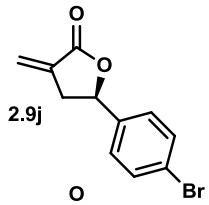
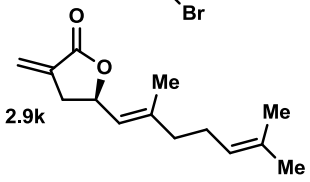
Product	Yield (%) 2.9a-f	*ee* (%)
 2.9a	67	90
 2.9b	73	90
 2.9c	66	90
 2.9d	73	95
 2.9e	65	94
 2.9f	84	87

Cat V was used in the formation of 2.9a

Table 2.8, cont.

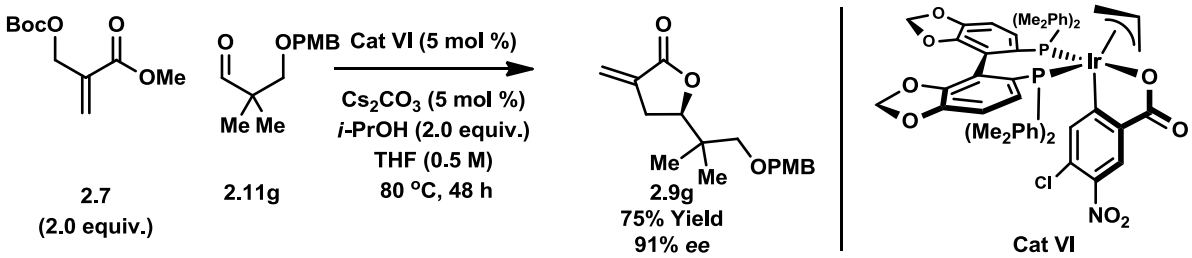


2.7 (2.0 equiv.) 2.8 2.9

Product	Yield (%) 2.9g-k	*ee* (%)
 2.9g	90	92
 2.9h	67	82
 2.9i	57	90
 2.9j	76	63
 2.9k	50	57

Cat VI was used in the formation of 2.9g

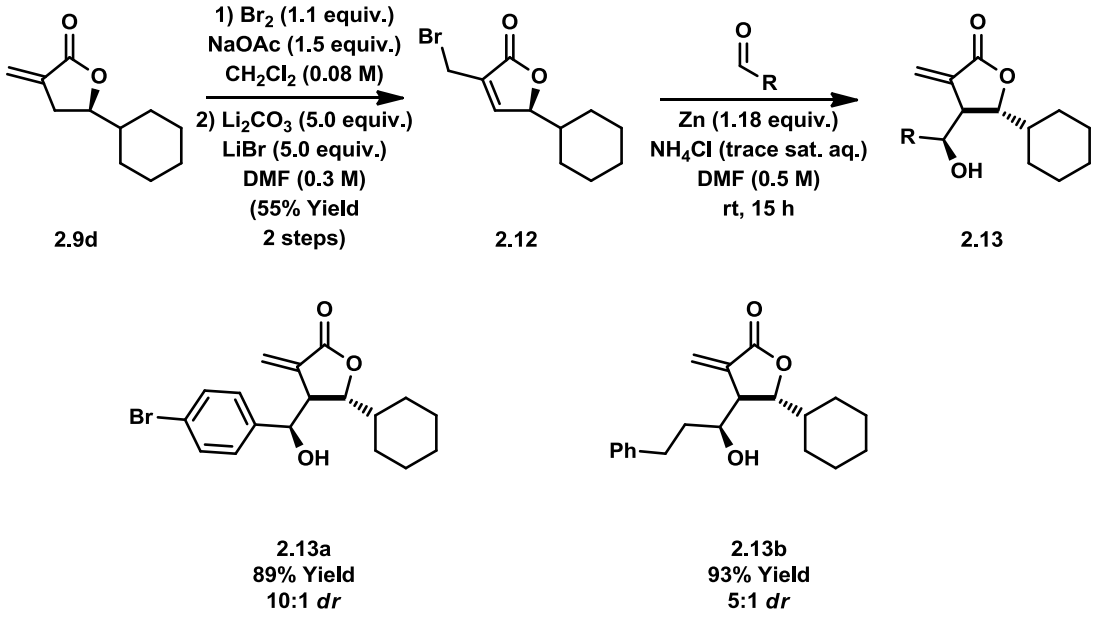
Scheme 2.2. Formation of α-*exo*-methylene γ-butyrolactones from the aldehyde oxidation level.



2.3.3 Product Elaboration

To illustrate the potential utility of this transformation, product **2.9d** was elaborated to disubstituted lactones **2.13a** and **2.13b** (Scheme 2.3). Initially, product **2.9d** was brominated followed by a selective elimination to generate allyl bromide **2.12**.[87] A zinc-mediated reductive coupling of alcohols **2.1a** and **2.1i** was each performed on allyl bromide **2.12**, furnishing lactones **2.13a** and **2.13b**.[88] This synthesis allows access to disubstituted α-*exo*-methylene γ-butyrolactones with control of both absolute and relative stereochemistry.

Scheme 2.3. Access to disubstituted α-*exo*-methylene γ-butyrolactones.



2.3.4 Conclusion

α-*exo*-Methylene γ-butyrolactones represent an enormous family of naturally occurring compounds; however the catalytic enantioselective formation of such motifs *via* carbonyl (2-alkoxycarbonyl)allylation was hitherto unknown. Here, the first catalytic enantioselective carbonyl (2-alkoxycarbonyl)allylation utilizing iridium-catalyzed transfer hydrogenative C-C bond formation for the preparation of α-*exo*-methylene γ-butyrolactones was reported. Furthermore, entry into the disubstituted α-*exo*-methylene γ-butyrolactones motif with control of both absolute and relative stereochemistry is possible.

2.4 Summary

Iridium-catalyzed carbonyl allylations have proven of exceptional importance in the field of synthetic organic chemistry, many having been applied to total syntheses of both natural and unnatural products. Being able to expand

this technology to include 2,2-disubstituted olefins as allyl donor species has not only allowed entry into novel structures, but made traditional structures more accessible. Furthermore the knowledge gained from mechanistic details, such as ways to enhance the metal-olefin π-complex, is paramount. Going forward, new allyl donor species could be investigated that allow direct access to disubstituted α-*exo*-methylene γ-butyrolactones. Additionally, the use of trisubstituted allyl donors remains an unmet challenge.

2.5 Experimental Section

2.5.1 Experimental Details for Section 2.2

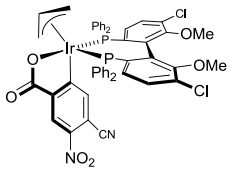
General Information

All reactions were run under an atmosphere of argon. Sealed tubes (13x100m^2) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Tetrahydrofuran was dried over sodium metal, benzophenone, and distilled immediately prior to use. Dichloromethane was dried over $CaCl_2$ and distilled immediately prior to use. Anhydrous solvents were transferred by oven-dried syringes. All ligands and $[Ir(cod)Cl]_2$ were used as received from Strem Chemical Inc. Alcohols were distilled or recrystallized prior to use. Both allyl acetate and 3-chloro-2-fluoroprop-1-ene were distilled prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in p-anisaldehyde solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm).

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, M-H, or M-F) or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz). For $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer. For CDCl3 solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_C (77.0 ppm). ^{19}F Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Chemical

shifts are reported as parts per million (ppm). Optical rotations were performed on an Automatic Polarimeter AP-300 using dichloromethane as solvent. Melting points were taken on a Stuart SMP3 melting point apparatus.

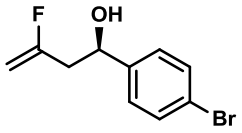
Synthesis of Cat II



To a mixture of $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 1.0 equiv.), (*R*)-Cl,MeO-BIPHEP (260.6 mg, 0.40 mmol, 2.0 equiv.), Cs_2CO_3 (260.6 mg, 0.80 mmol, 4.0 equiv.), and 4-CN-3-NO_2BzOH (153.7 mg, 0.89 mmol, 4.0 equiv.) in a sealed tube under an atmosphere of argon was added THF (4.0 mL, 0.05 M) and allyl acetate (100.1 mg, 1.0 mmol, 5.0 equiv.). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 °C, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered with the aid of tetrahydrofuran (10 mL). The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography (dichloromethane:ether, 3:1). The residue obtained upon chromatographic isolation was dissolved in tetrahydrofuran (2 mL) and hexane (50 mL) was added. The resulting yellow precipitate was collected by filtration and dried under vacuum to provide **Cat II** (344.0 mg, 0.320 mmol) in 80% yield.

Experimental Using Alcohols 2.1a-i

Synthesis of (4R)-4-(4-Bromophenyl)-2-fluorobuta-1-ene-4-ol (2.3a).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added alcohol **2.1a** (37.4 mg, 0.2 mmol, 1.0 equiv.), **Cat II** (10.7 mg, 0.01 mmol, 5 mol %), and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3a** (42.0 mg, 0.171 mmol) as a white solid in 86% yield and **2.4a** (3.1 mg, 0.014 mmol) as a white solid in 7% yield.

TLC (SiO_2): R_f= 0.24 (ethyl acetate:hexanes, 1:9)

$[\alpha]_D^{23}$=+56.3°

^{1}H NMR (400 MHz, CDCl3): δ 7.51-7.47 (m, 2H), 7.27-7.24 (m, 2H), 4.95-4.91 (m, 1H), 4.67 (dd, *J*=17.2, 3.2 Hz, 1H), 4.34 (dd, *J*=50.0, 2.8 Hz, 1H), 2.62-2.54 (m, 2H), 2.16 (d, *J*=2.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl3): δ 162.8 (d, *J*=255.2 Hz), 142.0, 131.6, 131.6, 127.4, 127.4, 121.7, 93.2 (d, *J*=19.3 Hz), 70.3, 42.3 (d, *J*=26.1 Hz).

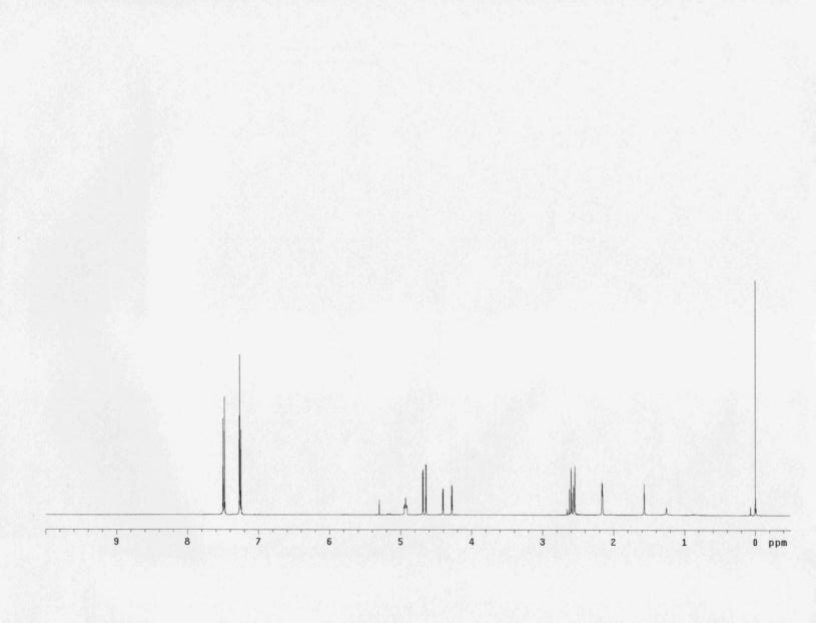
^{19}F NMR (400 MHz, CDCl3): δ -95.99 (ddt, *J*=52.8, 40.4, 17.6 Hz).

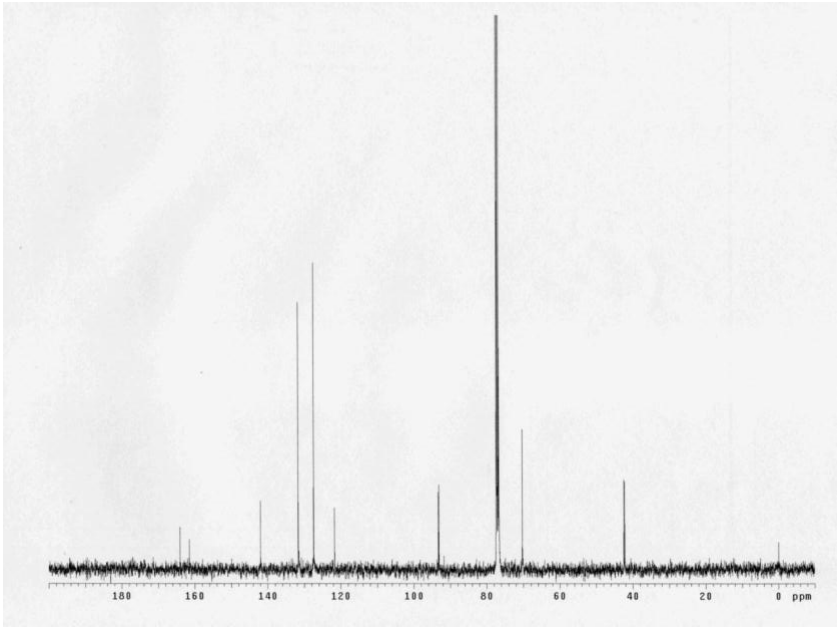
HRMS (CI) Calcd. for $C_{10}H_{11}BrFO$ $[M+H]^+$: 244.9977, Found: 244.9977.

FTIR (neat): 3408, 2920, 1676, 1593, 1488, 1406, 1305, 1242, 1171, 1103, 1070, 1009, 937, 856, 816, 776, 672, 658 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 12.2 min, t_{major} = 13.1 min; ee = 99%

MP 67-69°C

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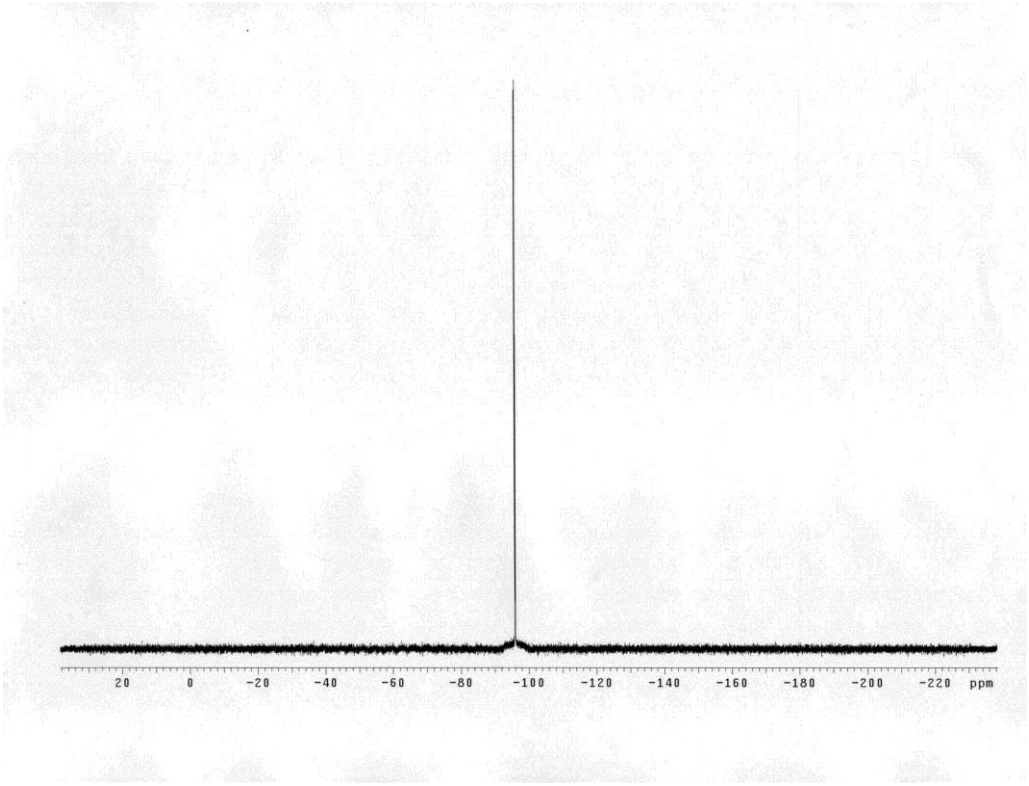
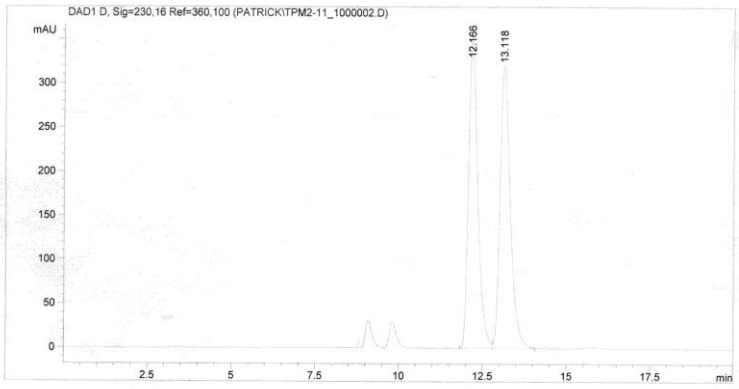
160
140
120
100
80
60
40
20
0 ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220 ppm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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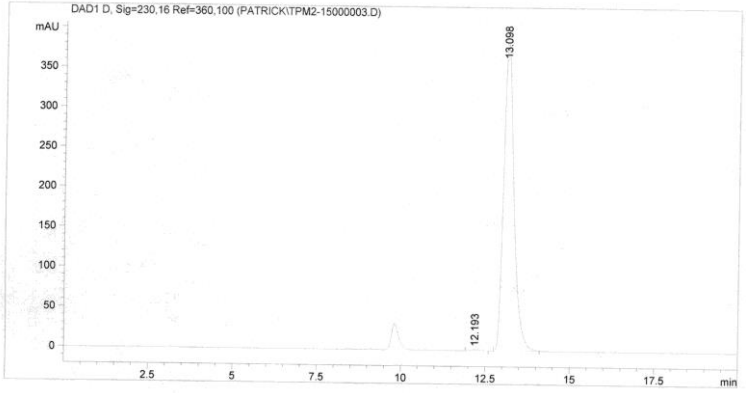
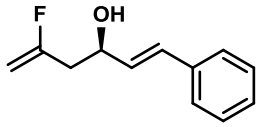
2	13.118	VB	0.3206	6776.39941	320.61572	50.1882



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.193	BB	0.2518	28.13190	1.62619	0.3413
2	13.098	BB	0.3219	8214.97168	386.67972	99.6587

Synthesis of (3R)-5-Fluoro-1-phenylhexa-1,5-diene-3-ol (2.3b).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1,0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1b** (26.8 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl/hexanes, 1:9) to furnish the title compound **2.3b** (29.4 mg, 0.153 mmol) as a colorless oil in 76% yield and **2.4b** (1.3 mg, 0.007 mmol) as a colorless oil in 4% yield.

TLC (SiO_2): R_f= 0.2 (ethyl acetate:hexanes, 1:9)

$[\alpha]_D^{23}$=+25.8°

^{1}H NMR (400 MHz, CDCl3): δ 7.33-7.16 (m, 5H), 6.59 (d, *J*=16.0 Hz, 1H), 6.17 (dd, *J*=16.0, 8.0 Hz, 1H), 4.61 (dd, *J*=17.2, 2.8 Hz, 1H), 4.52-4.48 (m, 1H), 4.33 (dd, *J*=50.0, 2.8 Hz, 1H), 2.49-2.42 (m, 1H), 1.84 (br, 1H).

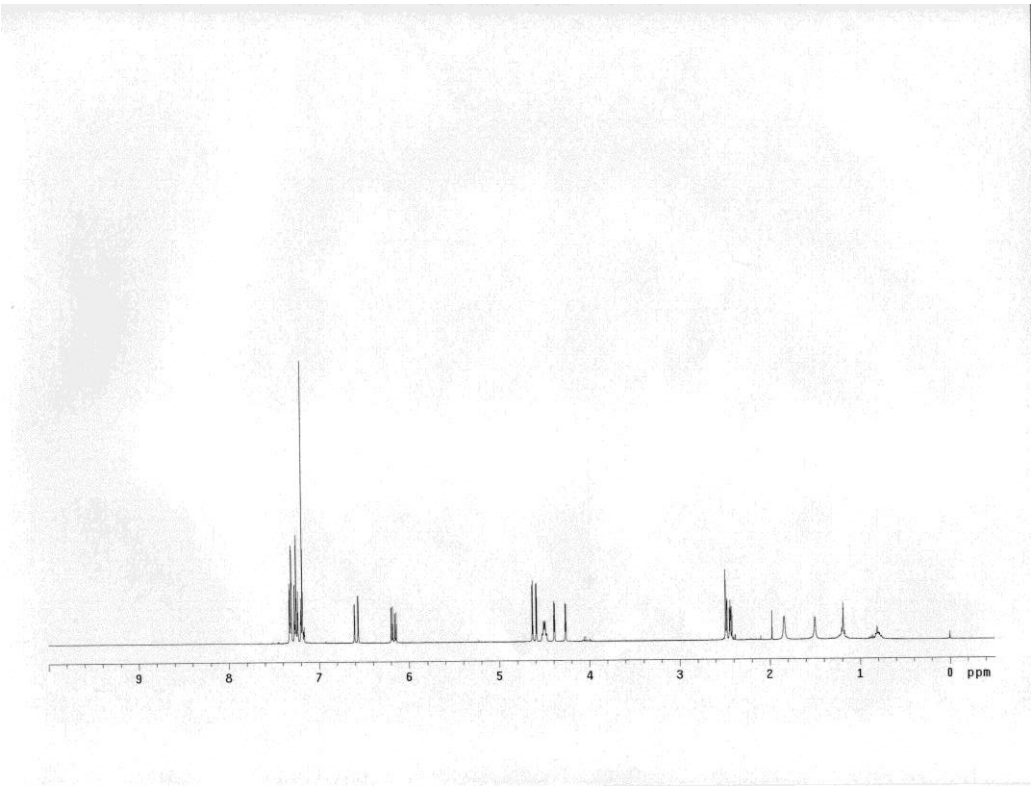
^{13}C NMR (100 MHz, CDCl3): δ 156.0 (d, *J*=256.0 Hz), 129.3, 124.0, 123.5, 121.6, 120.9, 119.5, 85.9 (d, *J*=19.4 Hz), 62.5, 33.4 (d, *J*=26.0 Hz).

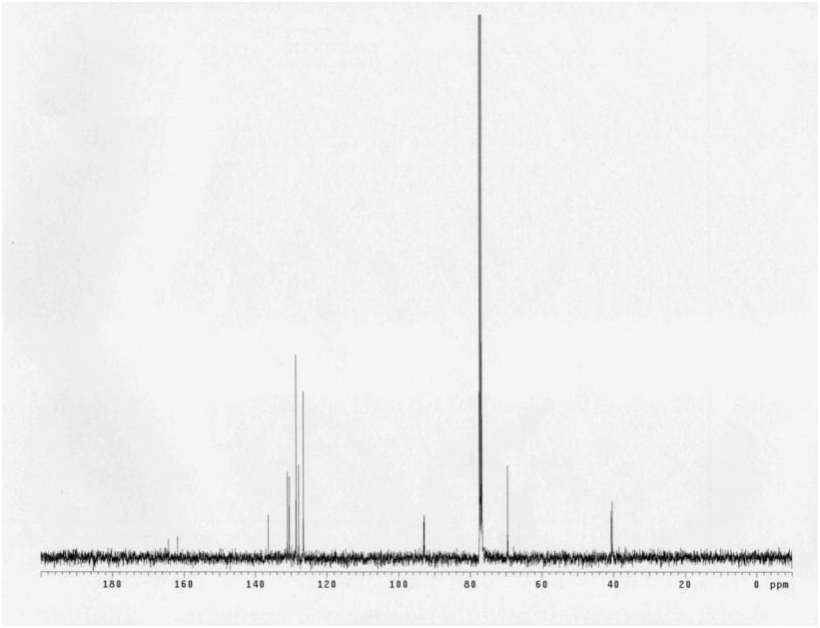
^{19}F NMR (400 MHz, CDCl3): δ -94.97 (ddt, *J*=52.8, 40.0, 18.0 Hz).

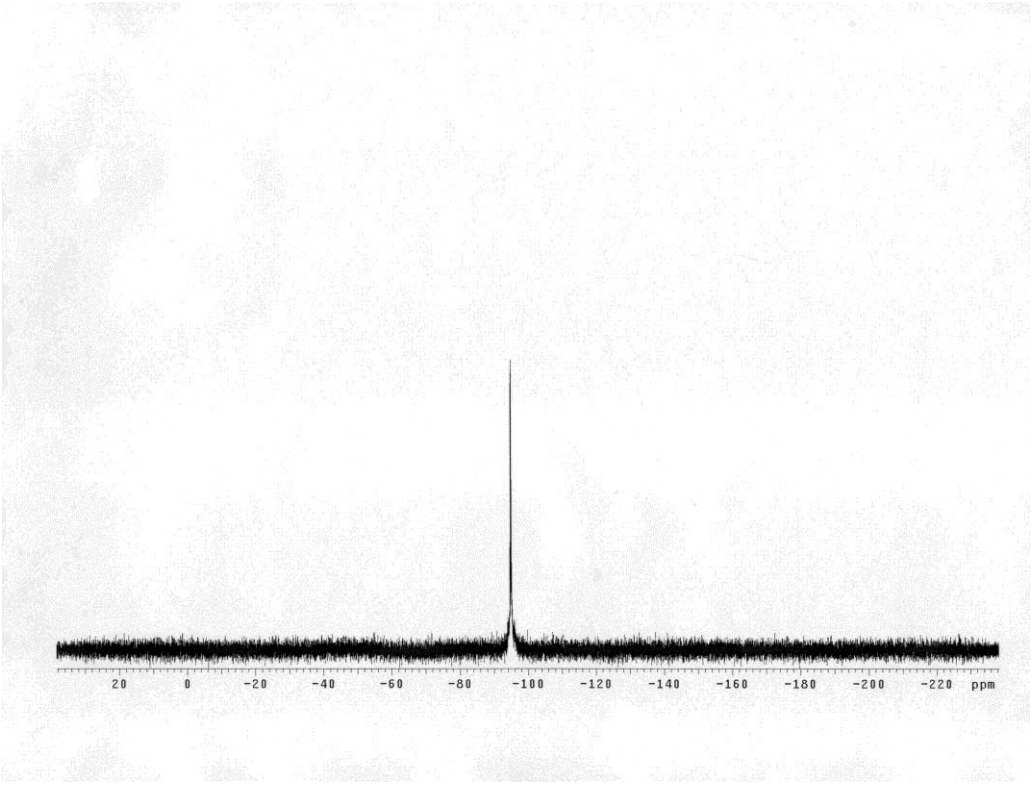
HRMS (CI) Calcd. for $C_{12}H_{12}FO$ $[M-H]^+$: 191.0871, Found: 191.0872.

FTIR (neat): 3400, 3028, 2926, 1674, 1601, 1495, 1453, 1422, 1243, 1178, 1070, 1029, 968, 938, 854, 749, 699, 659 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 14.6 min, t_{major} = 16.0 min; ee = 98%




180
160
140
120
100
80
60
40
20
0 ppm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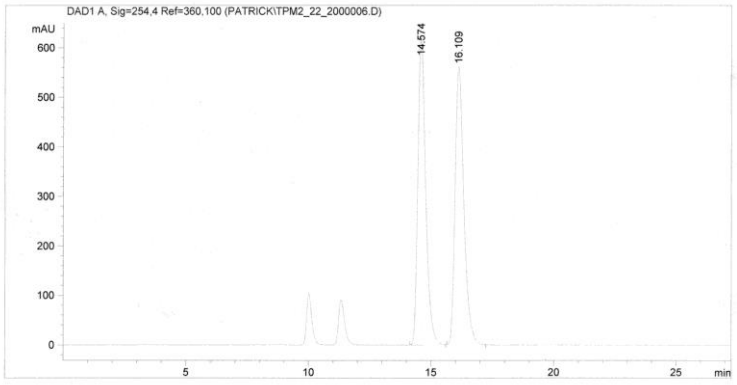
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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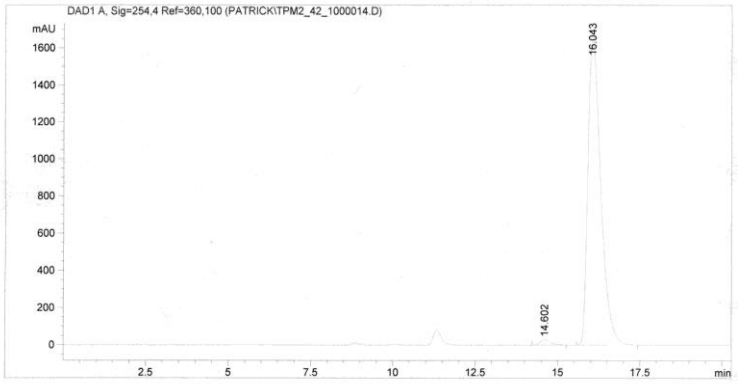
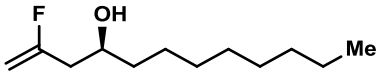
2	16.109	BB	0.3756	1.39510e4	561.95593	50.2283



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.602	BB	0.3285	634.24323	29.07792	1.3910
2	16.043	BB	0.4178	4.49604e4	1650.49707	98.6090

Synthesis of (4S)-2-Fluoro-dodec-1-ene-4-ol (2.3c).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1c** (28.9 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:19) to furnish the title compound **2.3c** (30.9 mg, 0.153 mmol) as a colorless oil in 76% yield and **2.4c** (3.5 mg, 0.019 mmol) as a colorless oil in 10% yield.

TLC (SiO_2): R_f=0.38 (ethyl acetate:hexanes, 1:9)

$[\alpha]_D^{23}$=-5.5°

^{1}H NMR (400 MHz, CDCl3): δ 4.65 (dd, *J*=17.6, 2.8 Hz, 1H), 4.35 (dd, *J*=50.4, 2.8 Hz, 1H), 3.88-3.82 (m, 1H), 2.44-2.22 (m, 2H), 1.50-1.44 (m, 2H), 1.28-1.21 (m, 12H), 0.88 (t, *J*=2.8 Hz, 3H).

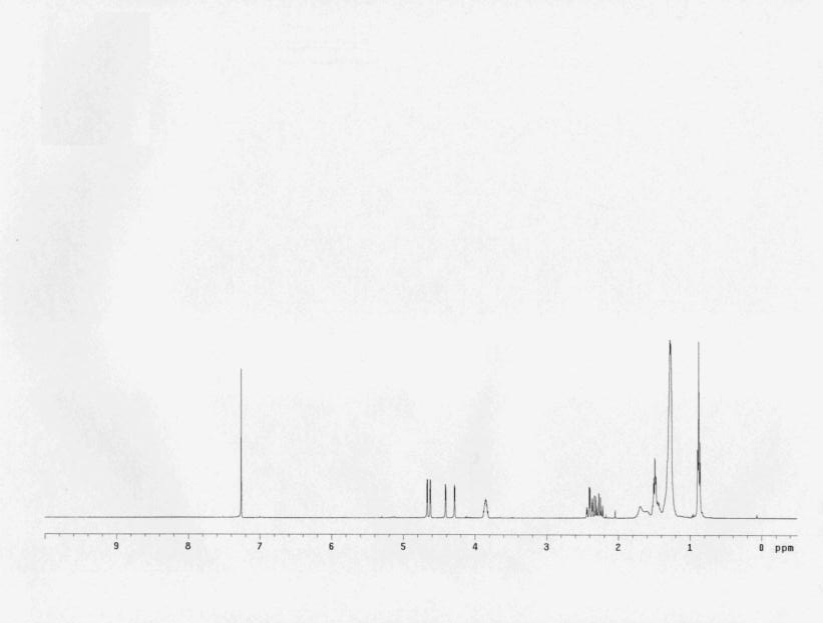
^{13}C NMR (100 MHz, CDCl3): δ 163.9 (d, *J*=256.0 Hz), 92.4 (d, *J*=19.3 Hz), 68.5, 40.3 (d, *J*=26.1), 36.8, 31.8, 29.5, 29.5, 29.2, 25.5, 22.6, 14.1

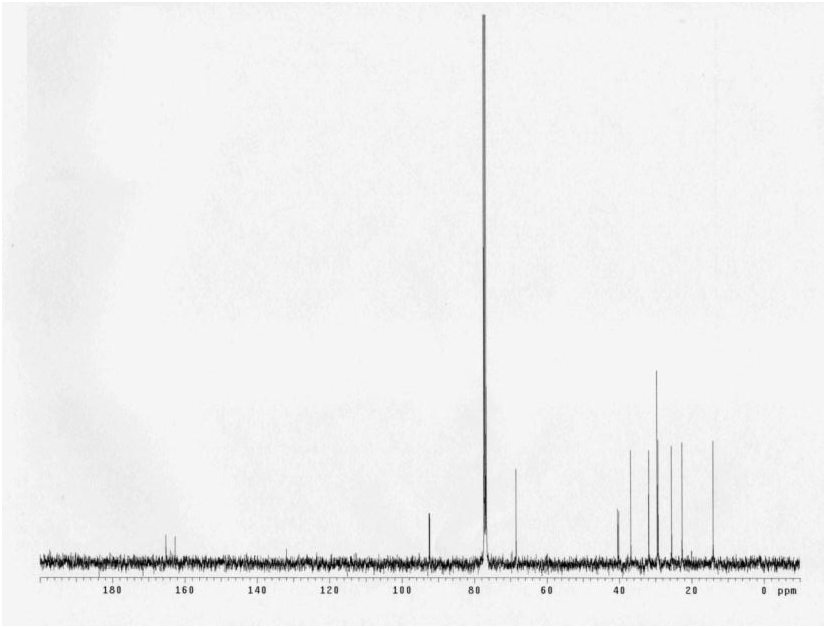
^{19}F NMR (400 MHz, CDCl3): δ -94.55 (ddt, *J*=53.2, 44.0, 18.0 Hz).

HRMS (CI) Calcd. for $C_{12}H_{23}0$ $[M-F]^+$: 183.1747, Found: 183.1749.

FTIR (neat): 3352, 2955, 2925, 2855, 1672, 1466, 1247, 1181, 1085, 939, 847 cm^{-1}.

HPLC Enantiomeric excess was determined by the analysis of the 3,5-dinitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{minor} = N/A, t_{major} = 9.1 min; ee = 99%

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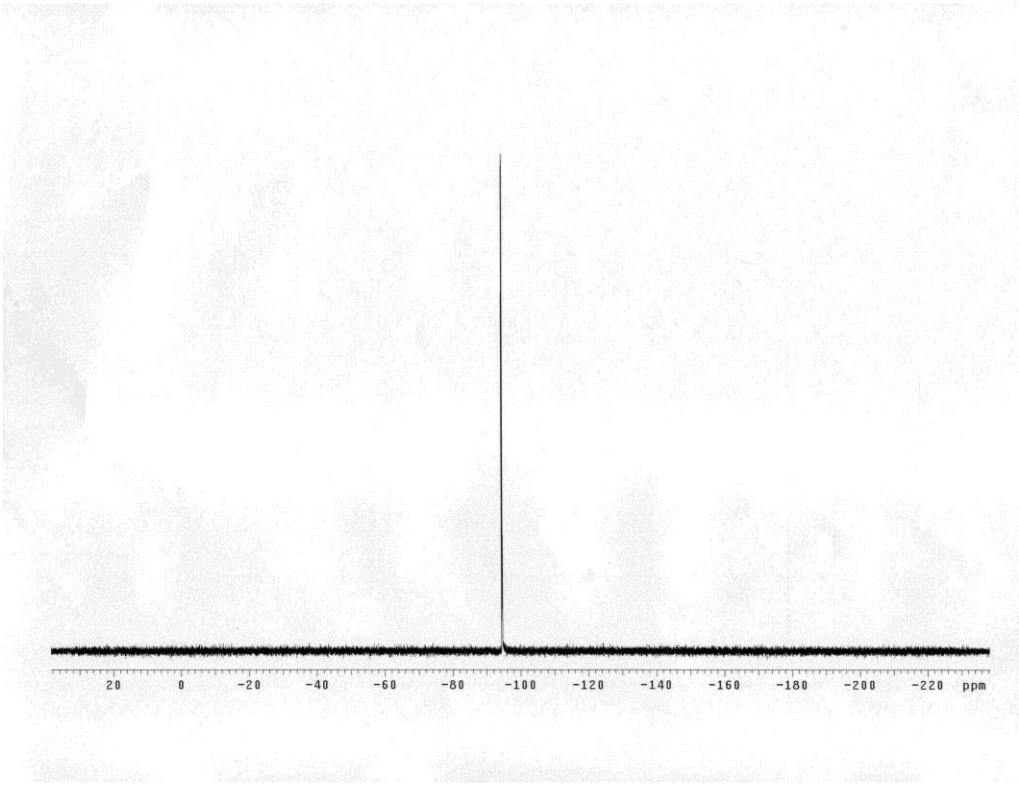
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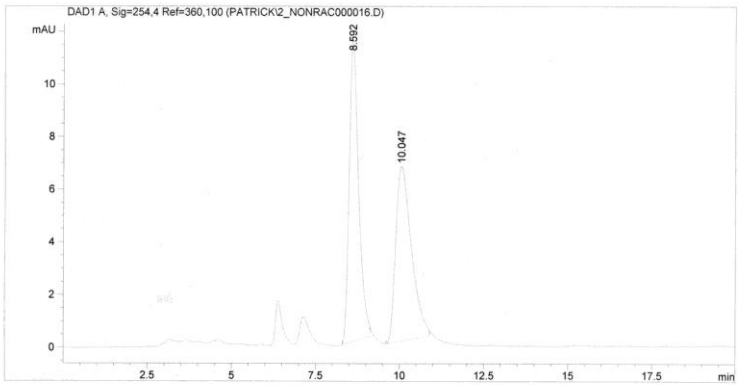
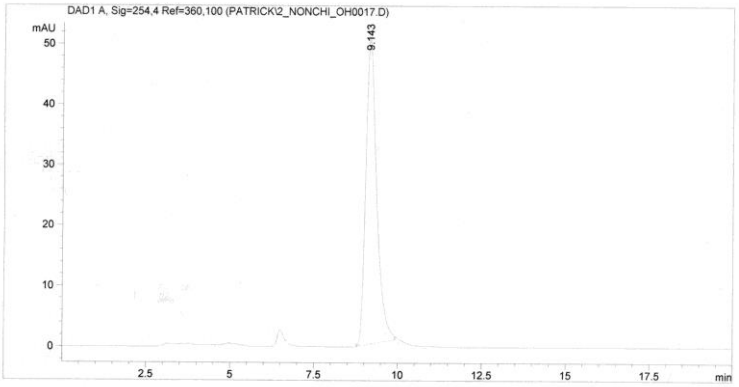
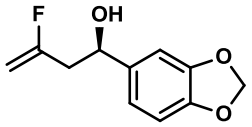


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.592	BB	0.2918	224.01506	11.47397	51.0517
2	10.047	BB	0.4822	214.78491	6.62501	48.9483



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.143	BB	0.3402	1141.51648	50.40371	100.0000

Synthesis of (1R)-1-(Benzo[*d*][1,3]dioxo-5-yl)-3-fluorobuta-3-ene-1-ol (2.3d).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added alcohol **2.1d** (30.4 mg, 0.2 mmol, 1.0 equiv.), **Cat II** (10.7 mg, 0.01 mmol, 5 mol %), and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3d** (34.2 mg, 0.163 mmol) as a colorless oil in 81% yield and **2.4d** (1.0 mg, 0.005 mmol) as a colorless oil in 3% yield.

TLC (SiO_2): R_f=0.18 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=+119.2°

^{1}H NMR (400 MHz, CDCl3): δ 6.89 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=8.0, 2.0 Hz, 1H), 6.79 (t, *J*=8.0 Hz, 1H), 5.96 (s, 1H), 4.89-4.86 (m, 1H), 4.65 (dd, *J*=17.2, 2.8 Hz, 1H), 4.34 (dd, *J*=50.0, 2.8 Hz, 1H), 2.67-2.50 (m, 2H), 2.06 (br, 1H).

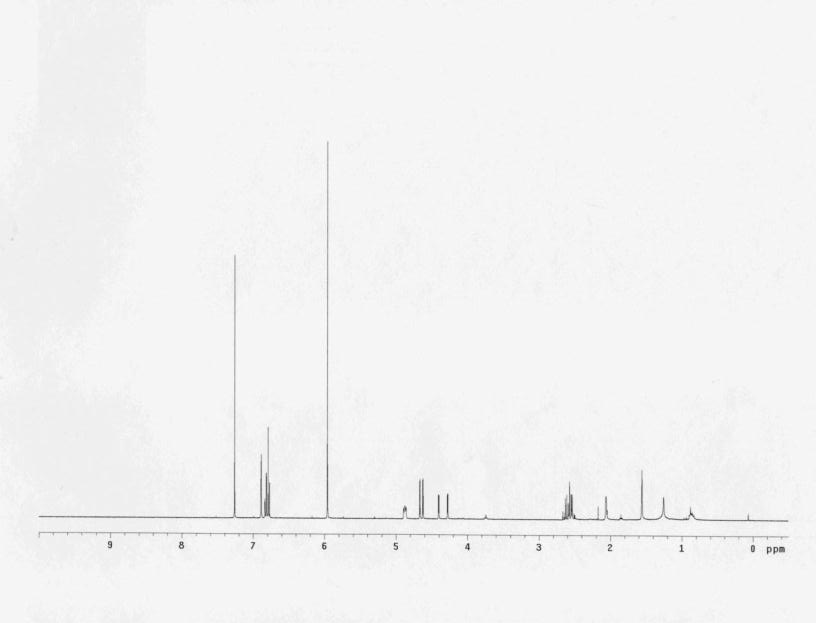
^{13}C NMR (100 MHz, CDCl3): δ 163.1 (d, *J*=255.2), 147.8, 147.2, 137.1, 119.2, 108.1, 106.2, 101.0, 92.7 (d, *J*=19.4), 70.8, 42.3 (d, *J*=26.0).

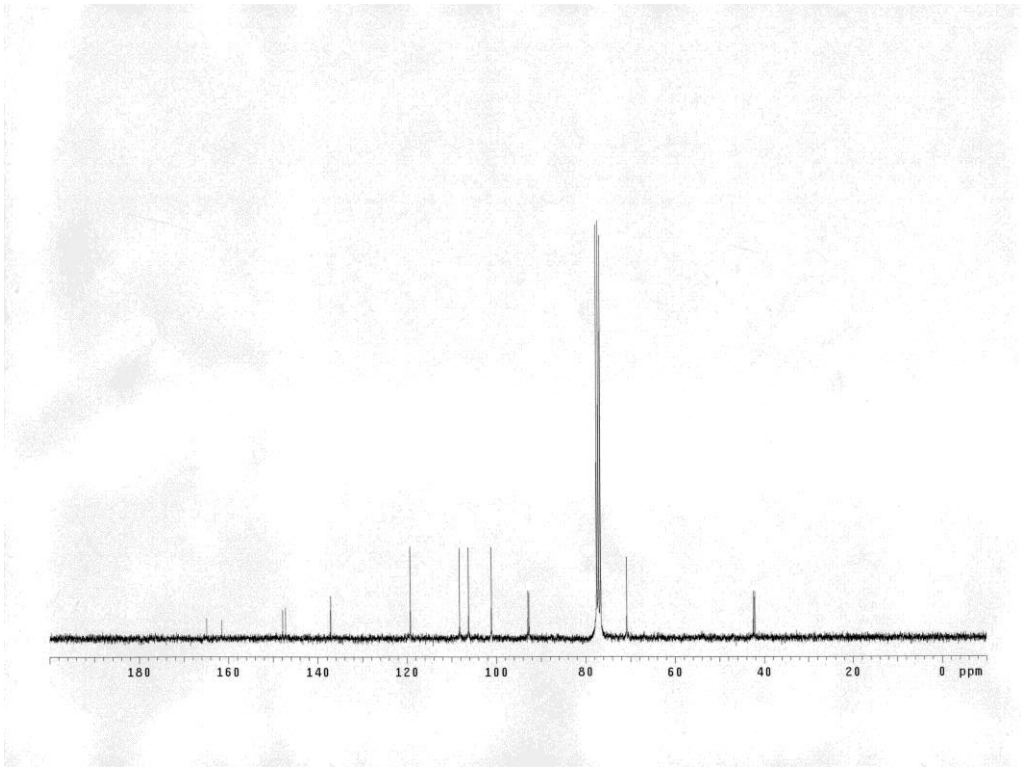
^{19}F NMR (400 MHz, CDCl3): δ -95.86 (ddt, *J*=53.2, 40.4, 18.0 Hz).

HRMS (CI) Calcd. for $C_{11}H_{11}FO_3$ $[M]^+$: 210.0693, Found: 210.0692.

FTIR (neat): 3402, 2897, 1675, 1503, 1488, 1443, 1238, 1188, 1123, 1095, 1037, 932, 900, 856, 811, 786, 728 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 280 nm), t_{minor} = 19.8 min, t_{major} = 21.5 min; ee = 99%

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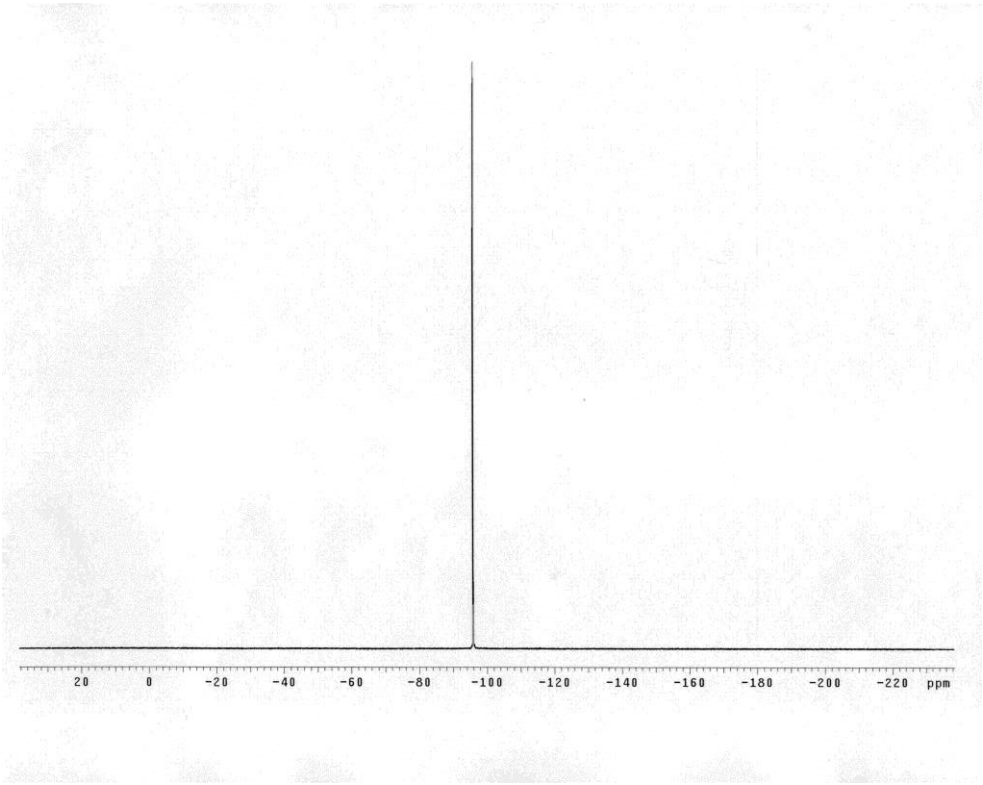
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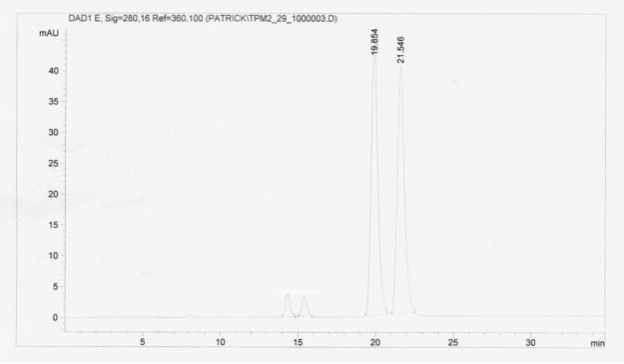

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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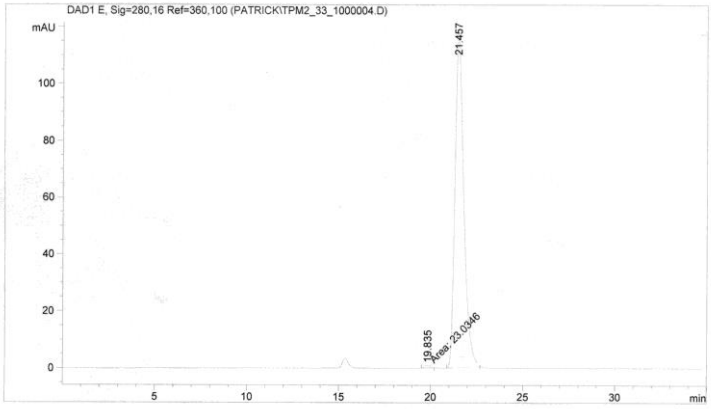
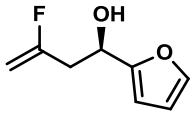
2	21.546	BB	0.4868	1290.00415	40.15759	46.8851



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.835	MM	0.4127	23.03462	9.30159e-1	0.5895
2	21.457	BB	0.5107	3884.46851	115.41161	99.4105

Synthesis of (1R)-3-Fluoro-1-furfurylbuta-3-ene-1-ol (2.3e).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1e** (19.6 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3e** (20.3 mg, 0.130 mmol) as a yellow oil in 65% yield and **2.4e** (1.4 mg, 0.01 mmol) as a yellow oil in 5% yield.

TLC (SiO_2): R_f= 0.19 (ethyl acetate:hexane, 1:9)

[α]$_D^{23}$=+23.4°

^{1}H NMR (400 MHz, CDCl3): δ 7.39 (dd,*J*=1.6, 0.4 Hz, 1H), 6.35 (dd, *J*=3.2, 2 Hz, 1H), 6.30 (d, *J*=3.2 Hz, 1H), 5.00-4.05 (m, 1H), 4.67 (dd, *J*=17.2, 2.8 Hz, 1H), 4.39 (dd, *J*=49.6, 2.8 Hz, 1H), 2.78 (d, *J*=6.8 Hz, 1H), 2.74-2.72 (m, 1H), 2.12 (br, 1H).

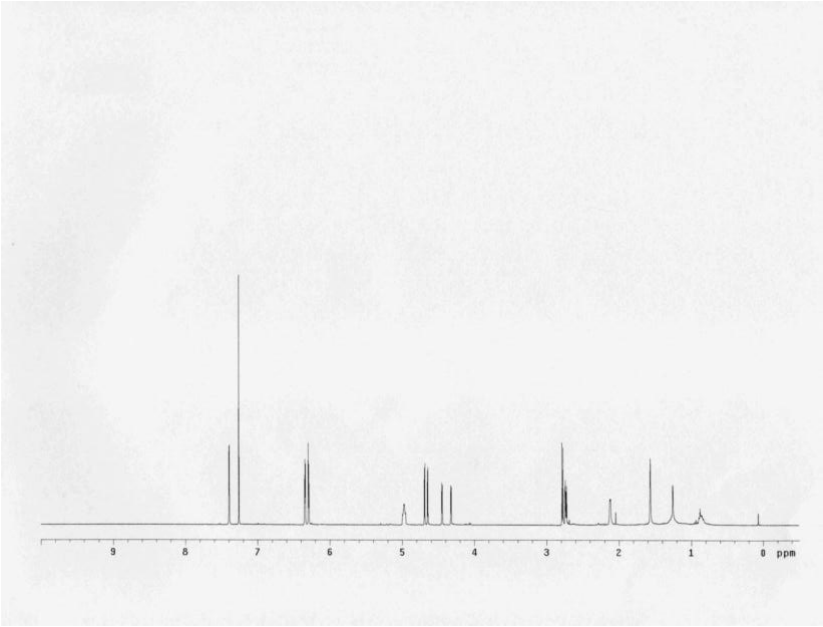
^{13}C NMR (100 MHz, CDCl3): δ 163.4 (d, *J*=255.2 Hz), 155.0, 142.3, 110.3, 106.5, 93.0 (d, *J*=19.3 Hz), 64.6, 38.6 (d, *J*=26.8 Hz).

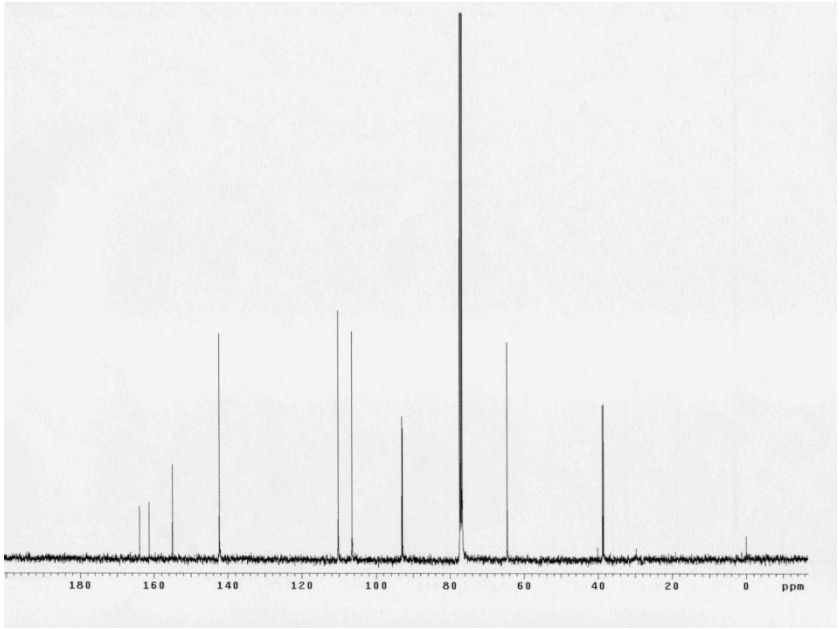
^{19}F NMR (400 MHz, CDCl3): δ -96.15 (ddt, *J*=53.6, 39.6, 18.8 Hz).

HRMS (CI) Calcd. for $C_8H_9FO_2$ $[M]^+$: 156.0587, Found: 156.0587.

FTIR (neat): 3384, 2919, 1676, 1505, 1429, 1344, 1290, 1244, 1144, 1058, 1010, 937, 913, 884, 856 813, 739, 657 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 10.6 min, t_{major} = 11.3 min; ee = 99%

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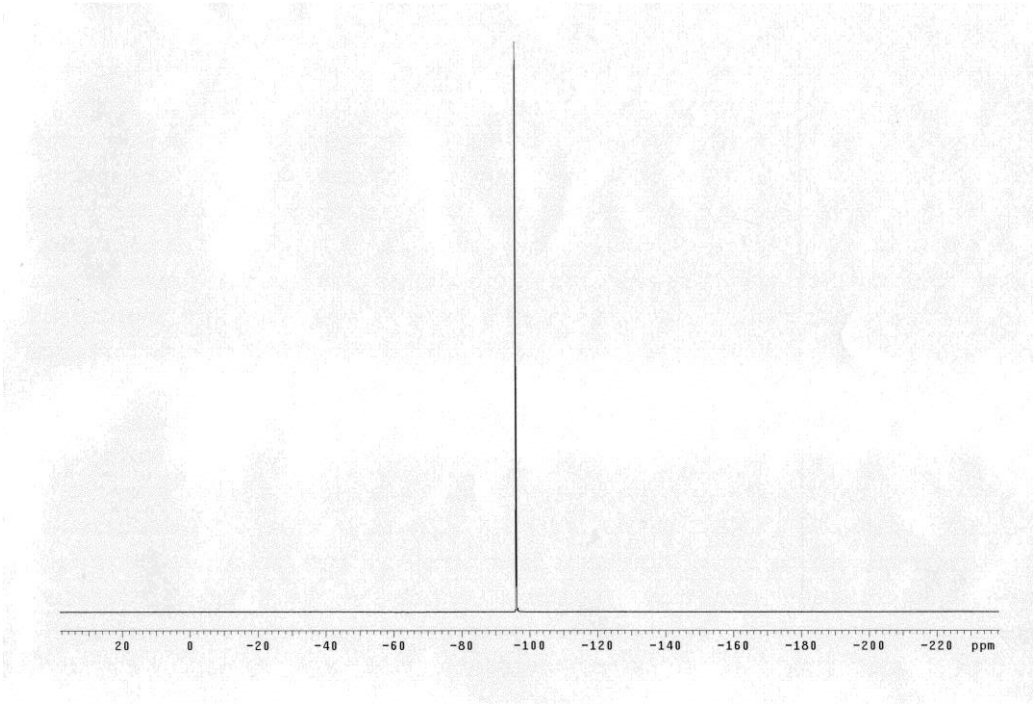
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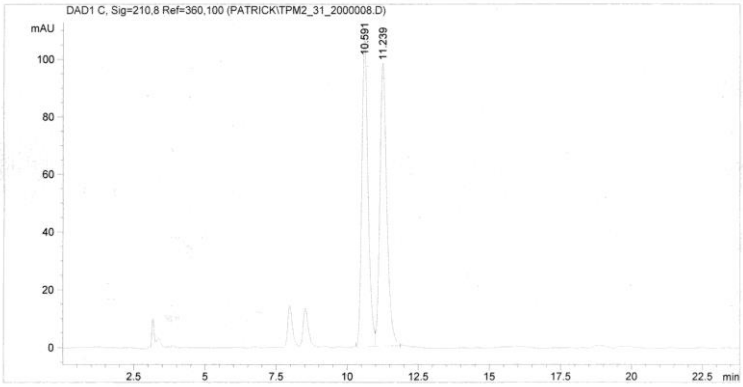
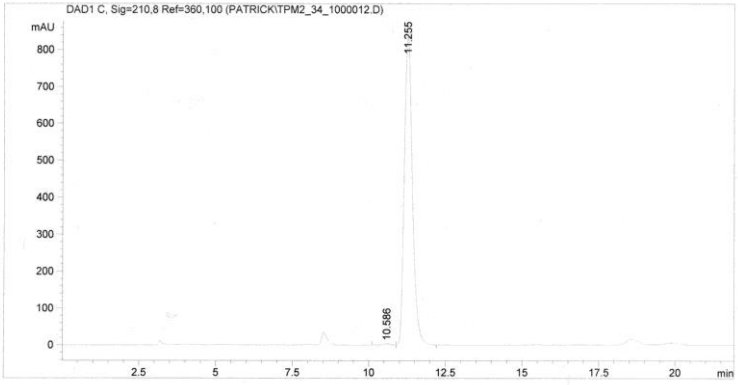
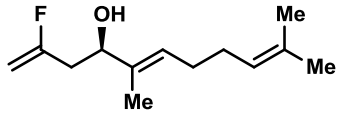


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.591	BV	0.2305	1639.01404	107.12891	49.6174
2	11.239	VB	0.2540	1664.29041	98.08391	50.3826



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.586	BV	0.2617	71.36349	3.93333	0.4595
2	11.255	VB	0.2881	1.54594e4	834.61639	99.5405

Synthesis of (4R)-2-Fluoro-6,10-dimethylundeca-1,5,9-triene-4-ol (2.3f).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1f** (30.9 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3f** (31.8 mg, 0.150 mmol) as a yellow oil in 75% yield and **2.4f** (1.4 mg, 0.007 mmol) as a yellow oil in 4% yield.

TLC (SiO_2): R_f= 0.28 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=+7.9°

^{1}H NMR (400 MHz, CDCl3): δ 5.21 (d, *J*=8.4 Hz, 1H), 5.1-5.06 (m, 1H), 4.66-4.61 (m, 1H), 4.63 (dd, *J*=17.2, 2.8 Hz, 1H), 4.34 (dd, *J*=50.0, 2.4 Hz, 1H), 2.49-2.30 (m, 2H), 2.12-2.07 (m, 2H), 2.05-2.00 (m, 1H), 1.69 (dd, *J*=8.8, 1.2 Hz, 6H), 1.60 (s, 3H), 1.59 (br, 1H).

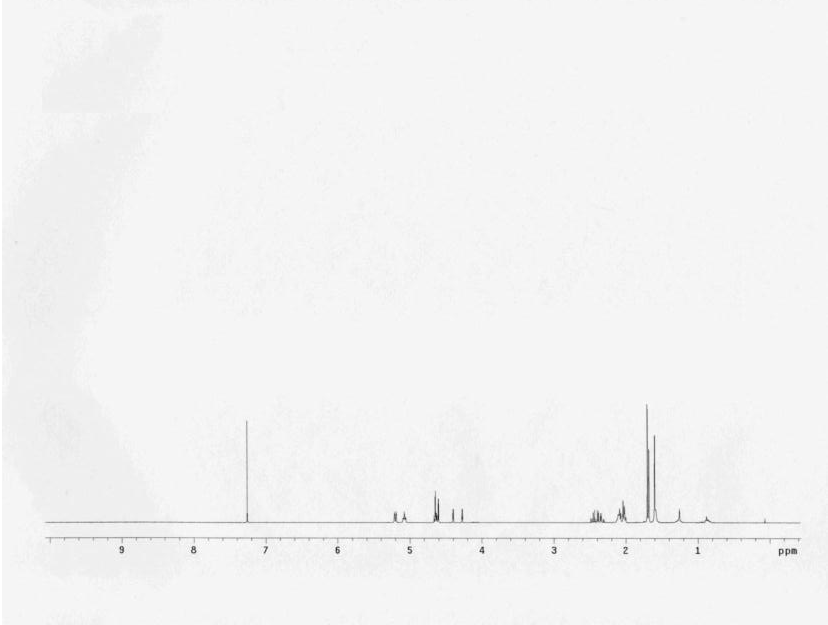
^{13}C NMR (100 MHz, CDCl3): δ 163.5 (d, *J*=256.0 Hz), 139.8, 131.8, 126.1, 123.8, 92.4 (d, *J*=19.3 Hz), 65.4, 40.4 (*J*=25.3 Hz), 39.5, 26.3, 25.7, 17.7, 16.6.

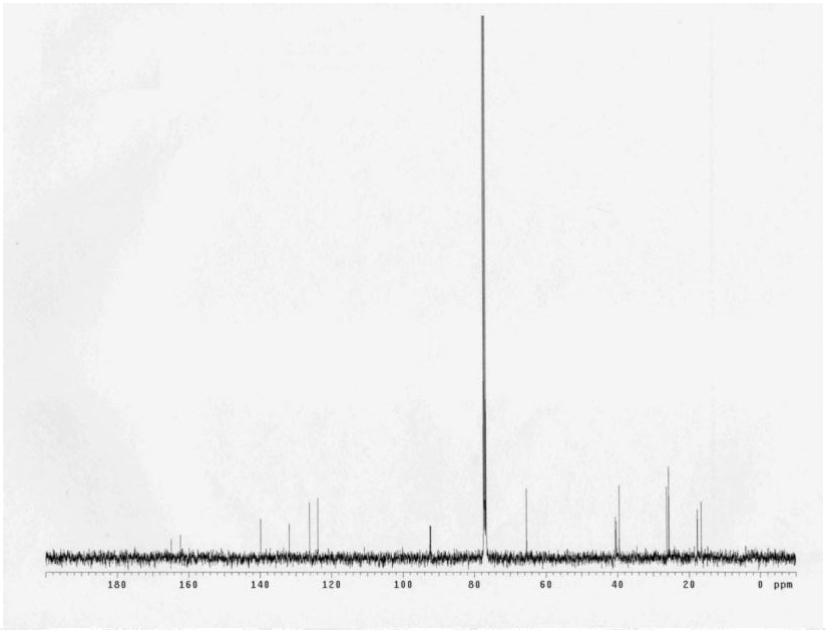
^{19}F NMR (400 MHz, CDCl3): δ -94.88 (ddt, *J*=53.2, 41.2, 18.0).

HRMS (CI) Calcd. for $C_{13}H_{20}FO$ $[M-H]^+$: 211.1501, Found: 211.1498.

FTIR (neat): 3382, 2964, 2916, 2857, 2361, 1672, 1442, 1377, 1261, 1241, 1192, 1108, 1037, 940, 847, 821, 810 cm^{-1}.

HPLC Enantiomeric excess was determined by the analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{minor} = 5.8 min, t_{major} = 5.4 min; ee = 95%

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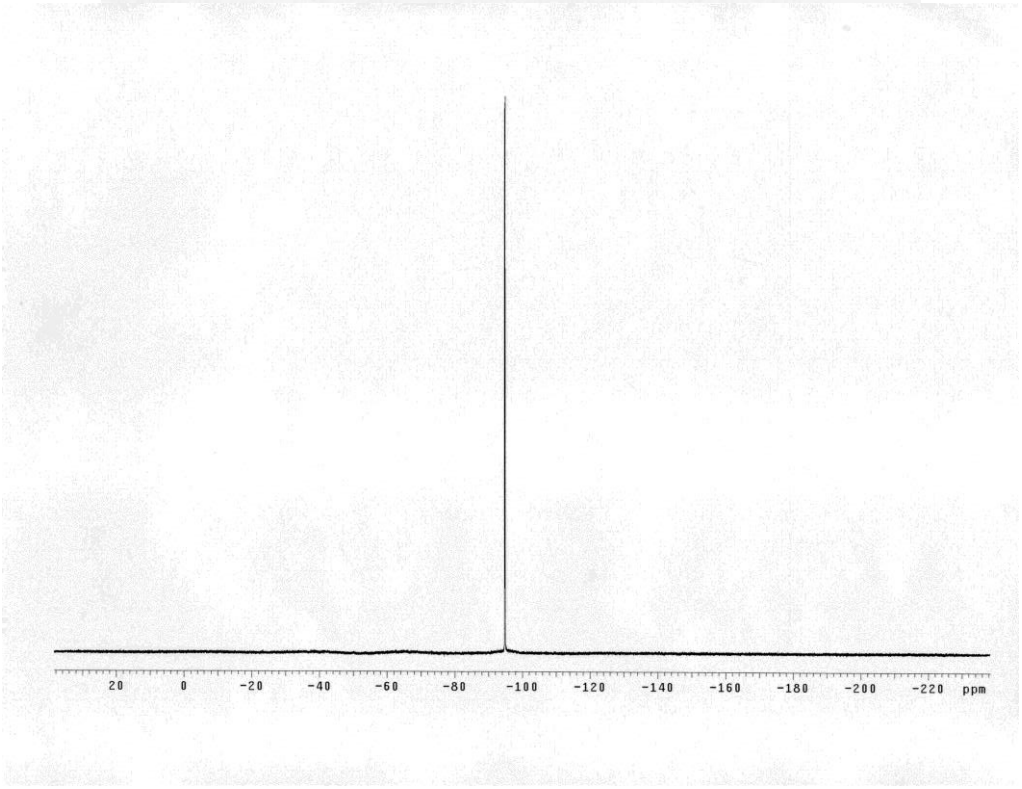
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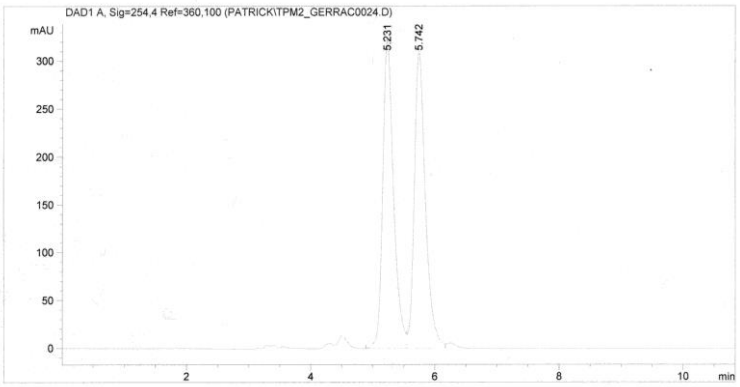

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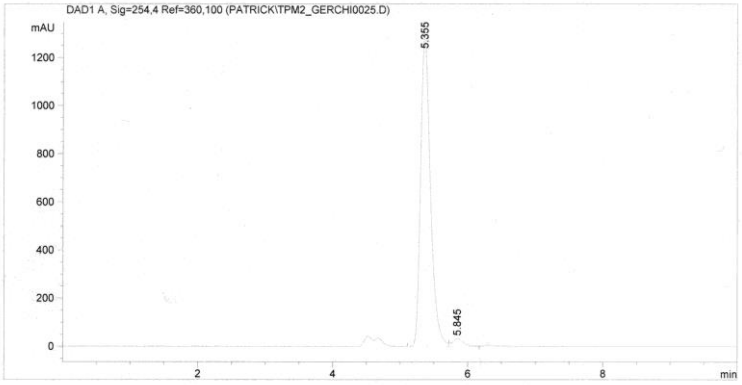
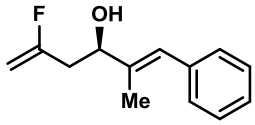


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.355	BV	0.1571	1.31098e4	1284.17468	97.3068
2	5.845	VV	0.1724	362.84540	31.49163	2.6932

Synthesis of (3R)-5-Fluoro-2-methyl-1phenylhexa-1,5-diene-3-ol (2.3g).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1g** (29.2 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate/hexanes, 1:9) to furnish the title compound **2.3g** (32.8 mg, 0.159 mmol) as a colorless oil in 80% yield and **2.4g** (2.0 mg, 0.011 mmol) as a colorless oil in 5% yield.

TLC (SiO_2): R_f= 0.25 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=+1.5°

^{1}H NMR (400 MHz, CDCl3): δ 7.36-7.21 (m, 5H), 6.58 (br, 1H), 4.68 (dd, *J*=17.6, 2.8 Hz, 1H), 4.45-4.44 (m, 1H), 4.41 (dd, *J*=50, 2.8 Hz, 1H), 2.58-2.46 (m, 1H), 1.90 (br, 1H), 1.90 (d, *J*=1.6 Hz, 3H).

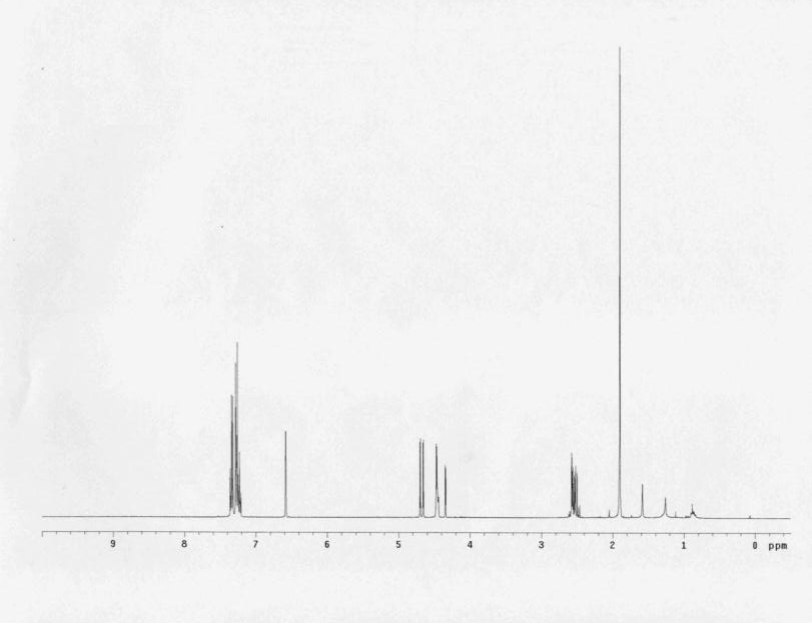
^{13}C NMR (100 MHz, CDCl3): δ 163.4 (d, *J*=256.0 Hz), 138.7, 137.2, 129.0, 128.1, 126.6, 126.3, 92.6 (d, *J*=19.3 Hz), 74.3, 38.7 (d, *J*=26.0 Hz), 13.4.

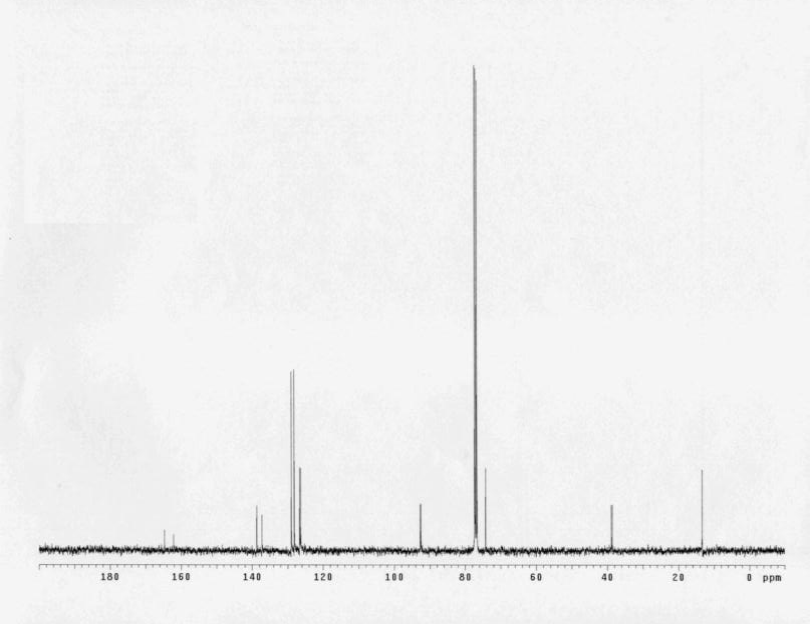
^{19}F NMR (400 MHz, CDCl3): δ -95.39 (ddt, *J*=52.8, 40.8, 17.6 Hz).

HRMS (CI) Calcd. for $C_{13}H_{15}FO$ $[M]^+$: 206.1109, Found: 206.1107.

FTIR (neat): 3390, 2920, 1674, 1491, 1445, 1380, 1333, 1242, 1178, 1015, 940, 920, 854, 749, 699 cm^{-1}.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 10.3 min, t_{major} = 12.3 min; ee = 98%

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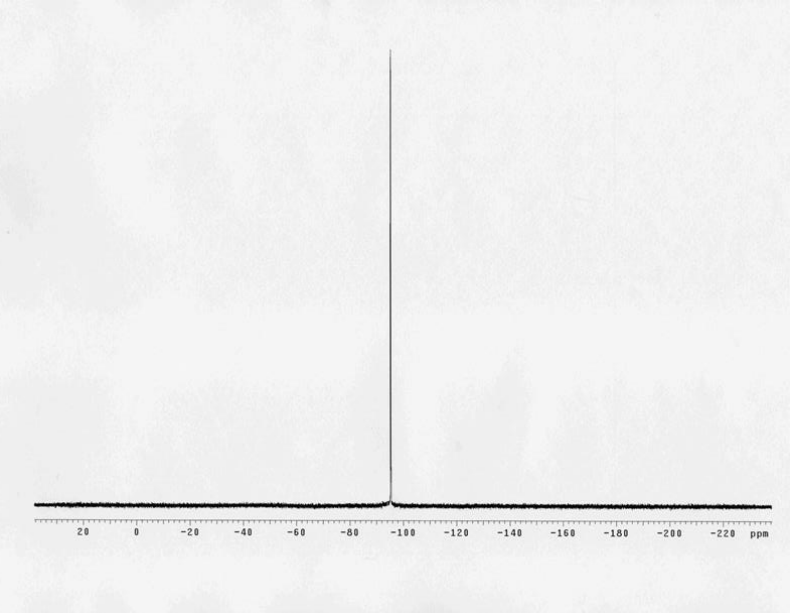
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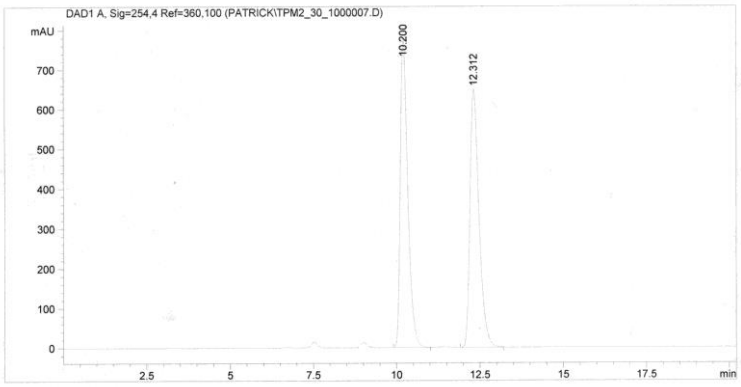
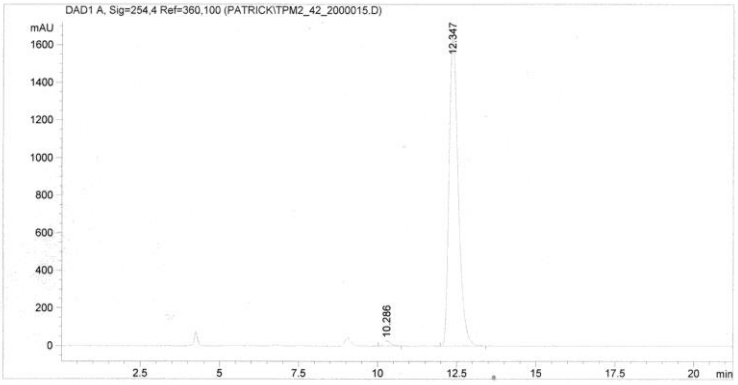
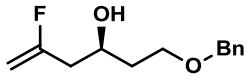


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.200	BB	0.2375	1.21983e4	775.59875	49.9786
2	12.312	VB	0.2833	1.22088e4	649.35803	50.0214



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.286	BB	0.2326	416.54034	27.21012	1.2367
2	12.347	BB	0.3128	3.32647e4	1638.81714	98.7633

Synthesis of (4S)-6-Benzyloxy-2-fluorohexa-1-ene-4-ol (2.3h).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1h** (33.2 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3h** (29.3 mg, 0.131 mmol) as a colorless oil in 65% yield and **2.4h** (2.4 mg, 0.012 mmol) as a colorless oil in 6% yield.

TLC (SiO_2) : R_f=0.22 (ethyl acetate:hexanes, 1:9)

$[\alpha]_D^{23}$=-39.3°

^{1}H NMR (400 MHz, CDCl3): δ 7.37-7.28 (m, 5H), 4.63 (dd, *J*=17.6, 2.8 Hz, 1H), 4.53 (s, 2H), 4.34 (dd, *J*=50.0, 2.8 Hz, 1H), 4.11-4.05 (m, 1H), 3.77-3.64 (m, 2H), 3.10 (br, 1H), 2.46-2.29 (m, 2H), 1.85-1.78 (m, 2H).

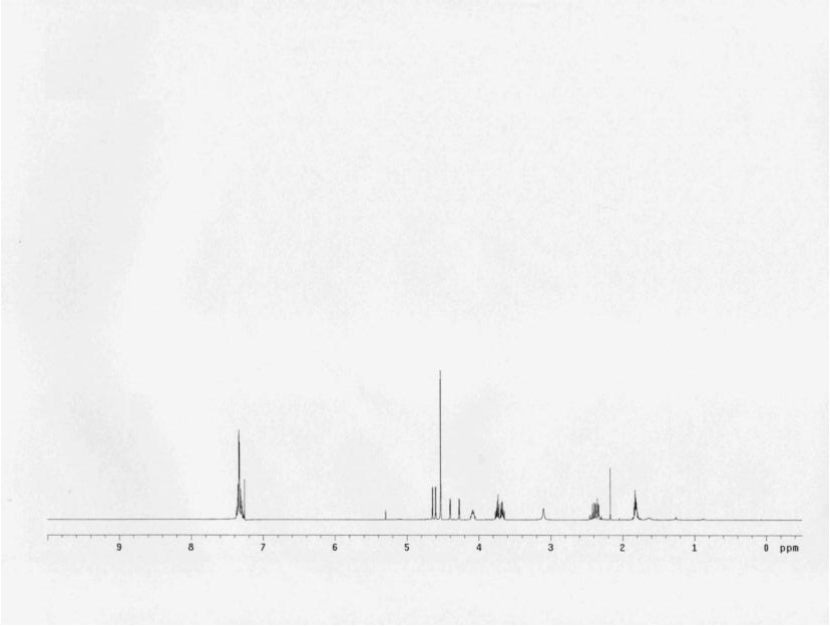
^{13}C NMR (100 MHz, CDCl3): δ 163.8 (d, *J*=255.0 Hz), 137.8, 128.5, 128.5, 127.8, 127.7, 127.7, 92.2 (d, *J*=20.1 Hz), 73.4, 68.9, 68.3, 40.1 (d, *J*=26.1 Hz), 35.8.

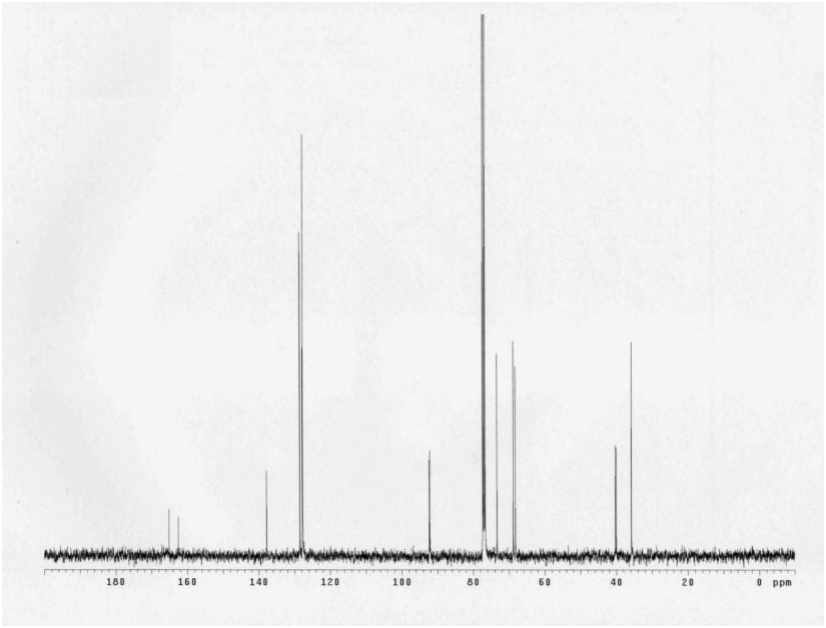
^{19}F NMR (400 MHz, CDCl3): δ -94.60 (ddt, *J*=53.2, 36.8, 4.6 Hz).

HRMS (CI) Calcd. for $C_{13}H_{17}FO_2$ $[M]^+$: 224.1210, Found: 224.1213.

FTIR (neat): 3444, 3063, 2954, 2865, 2359, 1674, 1636, 1452, 1275, 1176, 1113, 1072, 935, 852, 749, 714, 699 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 210 nm), t_{minor}=11.8 min, t_{major}=12.4 min; ee = 98%

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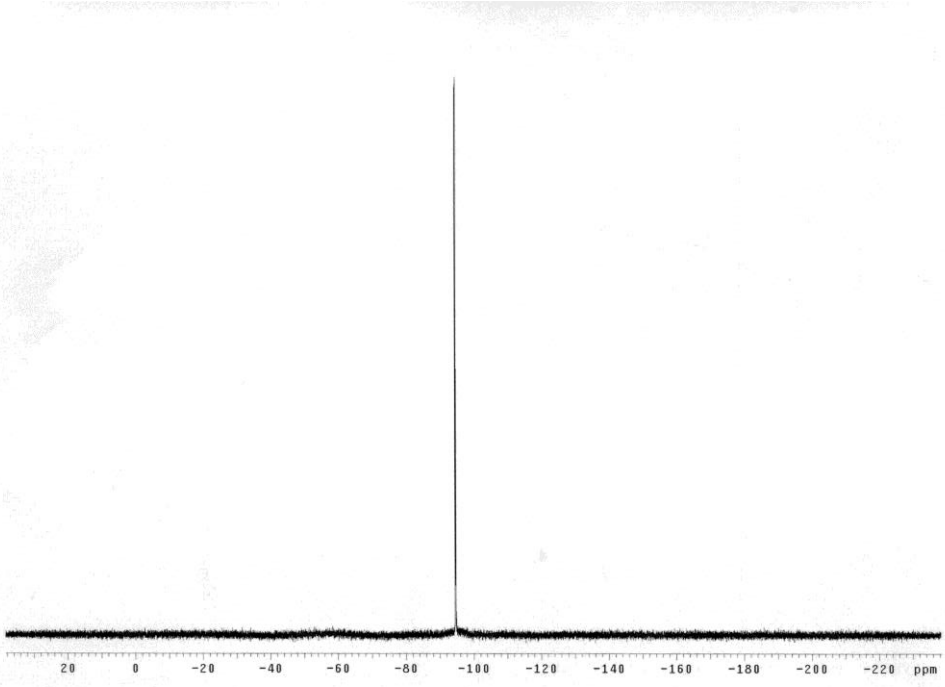
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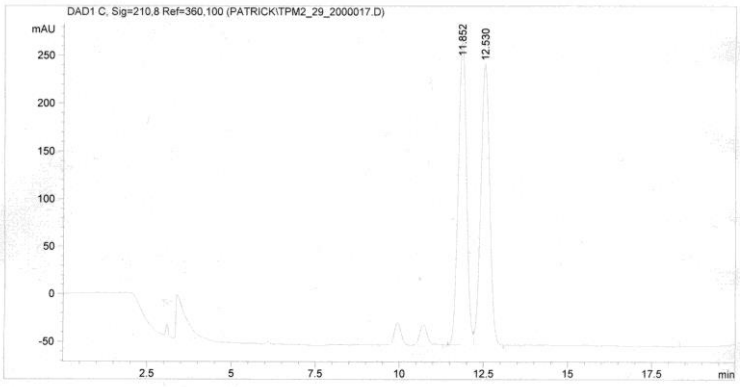
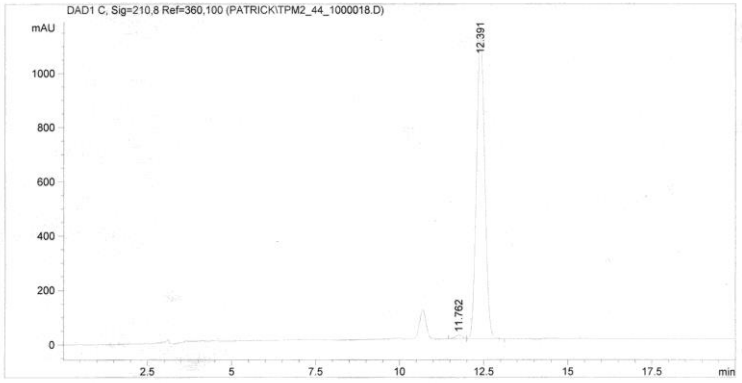
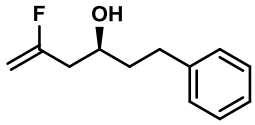


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.619	BB	0.3250	226.03453	10.50771	0.8050
2	16.095	BB	0.3943	2.78515e4	1074.86841	99.1950



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.762	BV	0.2386	215.47427	14.07298	1.1183
2	12.391	VB	0.2677	1.90525e4	1113.05432	98.8817

Synthesis of (4S)-2-Fluoro-6-phenylhexa-1-en-4-ol (2.3i).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), alcohol **2.1i** (27.2 mg, 0.2 mmol, 1.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3i** (34.6 mg, 0.178 mmol) as a yellow oil in 89% yield and **2.4i** (1.8 mg, 0.010 mmol) as a yellow oil in 5% yield.

TLC (SiO_2): R_f=0.2 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=-28.4°

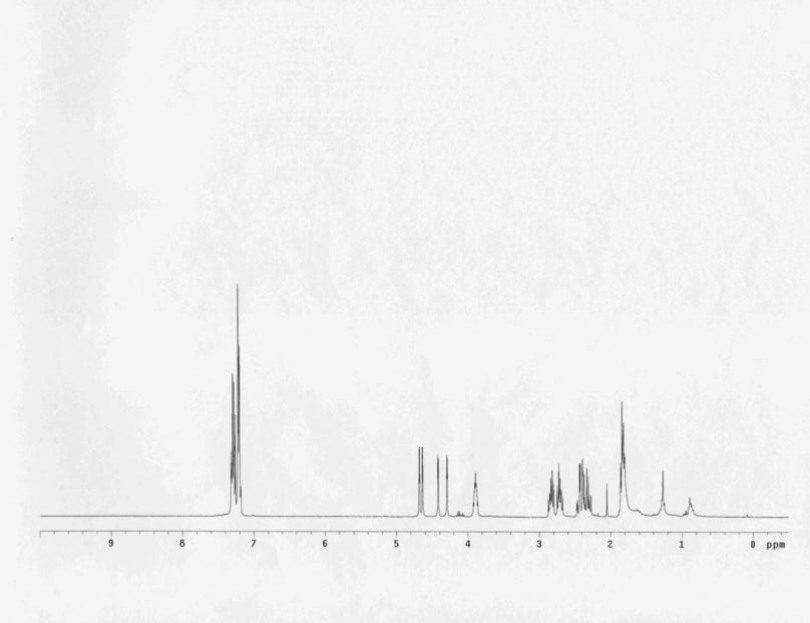
^{1}H NMR (400 MHz, CDCl3): δ 7.32-7.22 (m, 5H), 4.66 (dd, *J*=17.6, 2.8 Hz, 1H), 4.35 (dd, *J*=50.0, 2.8 Hz, 1H), 3.92-3.86 (m, 1H), 2.87-2.80 (m, 2H), 2.47-2.27 (m, 2H), 1.86-1.80 (m, 3H).

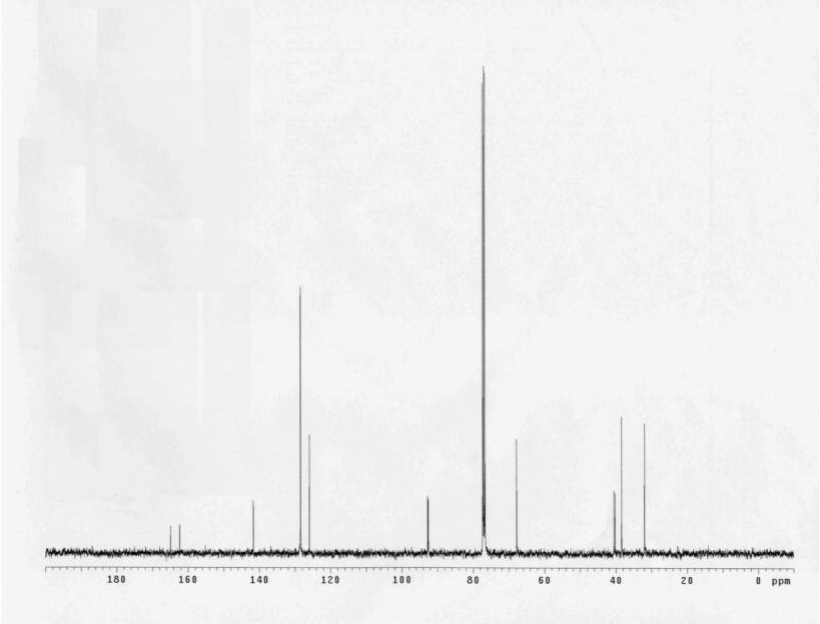
^{13}C NMR (100 MHz, CDCl3): δ 163.6 (d, *J*=255.2 Hz), 141.8, 128.4, 128.4, 125.9, 92.7 (d, *J*=19.3 Hz), 67.8, 40.4 (d, *J*=25.3 Hz), 38.4, 31.9.

^{19}F NMR (400 MHz, CDCl3): δ -94.50 (ddt, *J*=52.8, 42.8, 17.2 Hz).

HRMS (CI) Calcd. for $C_{12}H_{15}FO$ $[M]^+$: 194.1107, Found: 194.1107.

FTIR (neat): 3335, 2952, 2921, 2902, 2889, 1678, 1493, 1451, 1435, 1343, 1299, 1254, 1230, 1181, 1074, 1058, 1028, 1015, 941, 932, 854, 845, 749, 699 cm^{-1}.
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 9.8 min, t_{major} = 14.2 min; ee = 99%

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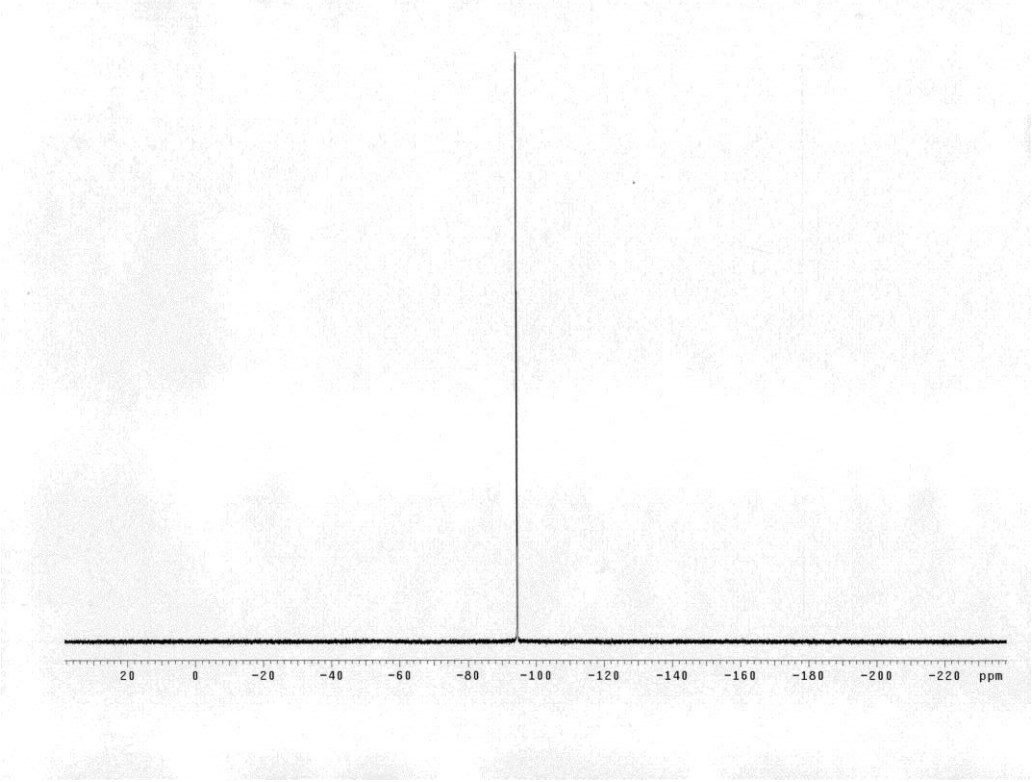
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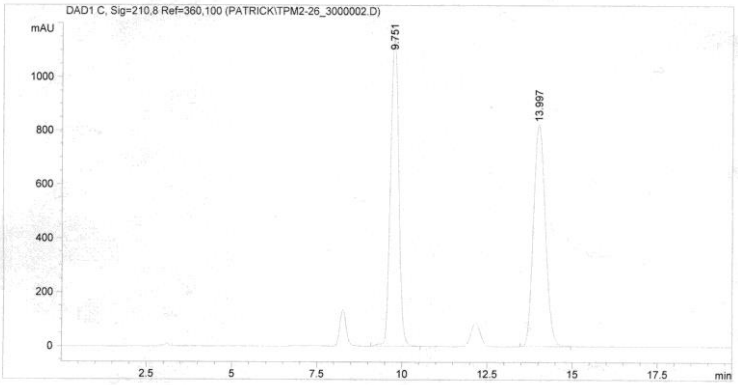
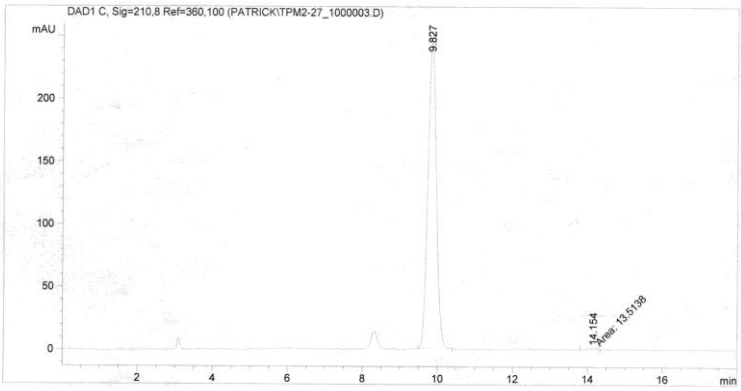


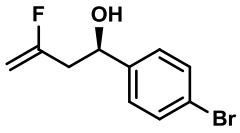
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.751	BB	0.2661	1.93873e4	1141.80164	49.0733
2	13.997	BB	0.3813	2.01195e4	822.76782	50.9267



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.827	BB	0.2417	3828.17358	245.84146	99.6482
2	14.154	MM	0.2876	13.51383	7.83075e-1	0.3518

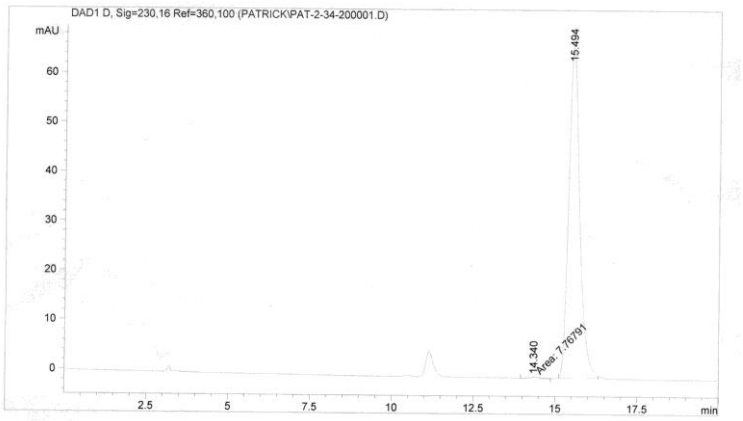
Experimental Using Aldehydes 2.5a-i

Synthesis of (4R)-4-(4-Bromophenyl)-2-fluorobuta-1-ene-4-ol (2.3a).



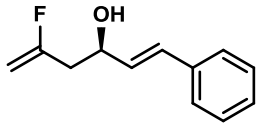
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added aldehyde **2.5a** (37.0 mg, 0.2 mmol, 1.0 equiv.), **Cat II** (10.7 mg, 0.01 mmol, 5 mol %), and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3a** (43.6 mg, 0.178 mmol) as a white solid in 89% yield and **2.4a** (2.2 mg, 0.010 mmol) as a white solid in 5% yield.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 14.3 min, t_{major} = 15.5 min; ee = 99%



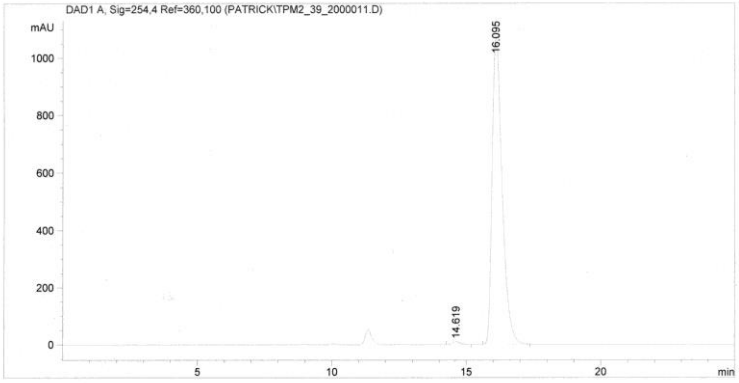
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.340	MM	0.4186	7.76791	3.09274e-1	0.4925
2	15.494	BB	0.3520	1569.31580	67.30836	99.5075

Synthesis of (3R)-5-Fluoro-1-phenylhexa-1,5-diene-3-ol (2.3b).



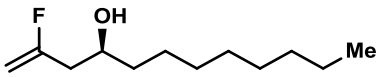
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5b** (26.4 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3b** (28.5 mg, 0.148 mmol) as a colorless oil in 74% yield and **2.4b** (1 mg, 0.006 mmol) as a colorless oil in 3% yield.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 14.6 min, t_{major} = 16.1 min; ee = 98%



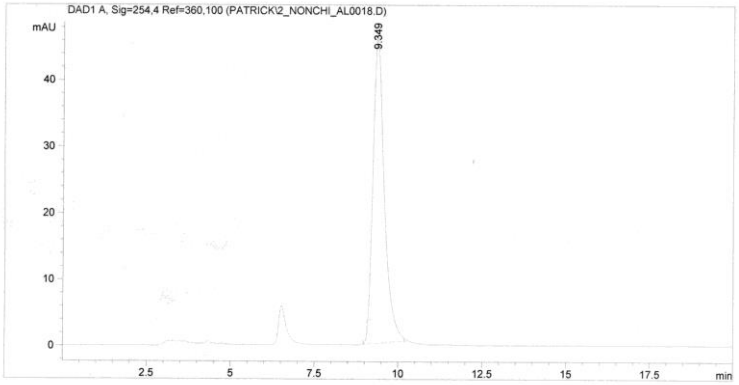
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.619	BB	0.3250	226.03453	10.50771	0.8050
2	16.095	BB	0.3943	2.78515e4	1074.86841	99.1950

Synthesis of (4S)-2-Fluoro-dodec-1-ene-4-ol (2.3c).



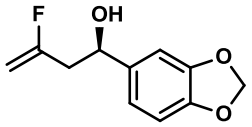
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5c** (28.4 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes 1:19) to furnish the title compound **2.3c** (24.5 mg, 0.116 mmol) as a colorless oil in 61% yield and **2.4c** (1.9 mg, 0.010 mmol) as a colorless oil in 5% yield.

HPLC Enantiomeric excess was determined by the analysis of the 3,5-dintorbenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{minor} = N/A, t_{major} = 9.3 min; ee = 99%



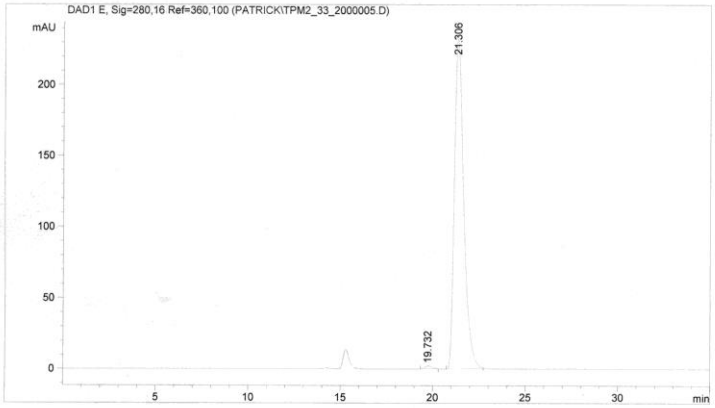
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.349	BB	0.3551	1091.71729	45.96155	100.0000

Synthesis of (1R)-1-(Benzo[*d*][1,3]dioxo-5-yl)-3-fluorobuta-3-ene-1-ol (2.3d).



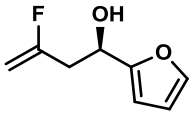
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added aldehyde **2.5d** (30.3 mg, 0.2 mmol, 1.0 equiv.), **Cat II** (10.7 mg, 0.01 mmol, 5 mol %), and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3d** (36.8 mg, 0.175 mmol) as a colorless oil in 88% yield and **2.4d** (1.9 mg, 0.010 mmol) as a colorless oil in 5% yield.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 280 nm), t_{minor} = 19.7 min, t_{major} = 21.3 min; ee = 99%



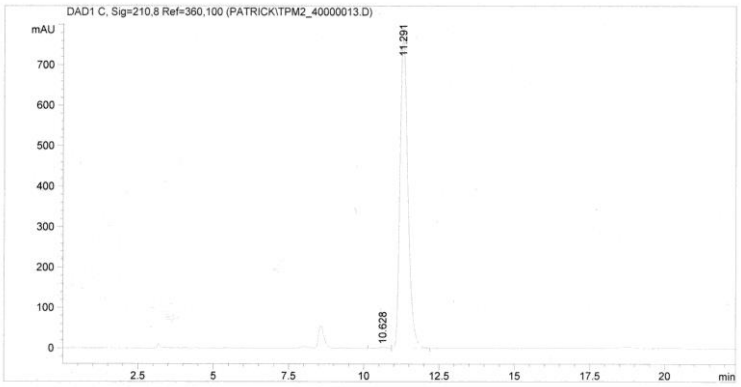
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.732	BB	0.4016	60.00493	2.20407	0.7261
2	21.306	BB	0.5356	8204.38965	232.52441	99.2739

Synthesis of (1R)-3-Fluoro-1-furfurylbuta-3-ene-1-ol (2.3e).



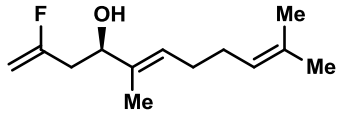
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5e** (19.2 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3e** (22.8 mg, 0.146 mmol) as a yellow oil in 73% yield and **2.4e** (1.4 mg, 0.010 mmol) as a yellow oil in 5% yield.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 10.6 min, t_{major} = 11.3 min; ee = 99%



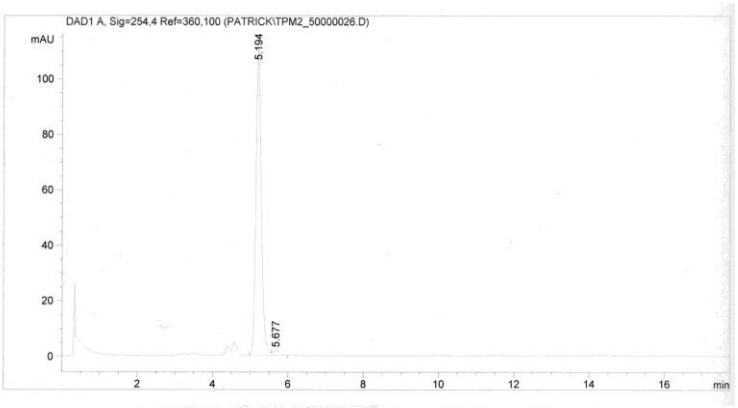
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.628	BV	0.2707	49.70620	2.67561	0.3519
2	11.291	VB	0.2850	1.40742e4	763.77069	99.6481

Synthesis of (4R)-2-Fluoro-6,10-dimethylundeca-1,5,9-triene-4-ol (2.3f).



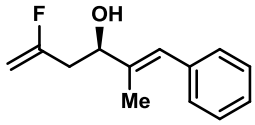
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5f** (30.4 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3f** (31.6 mg, 0.149 mmol) as a yellow oil in 74% yield and **2.4f** (1.3 mg, 0.007 mmol) as a yellow oil in 3% yield.

HPLC Enantiomeric excess was determined by the analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{minor} = 5.7 min, t_{major} = 5.2 min; ee = 96%



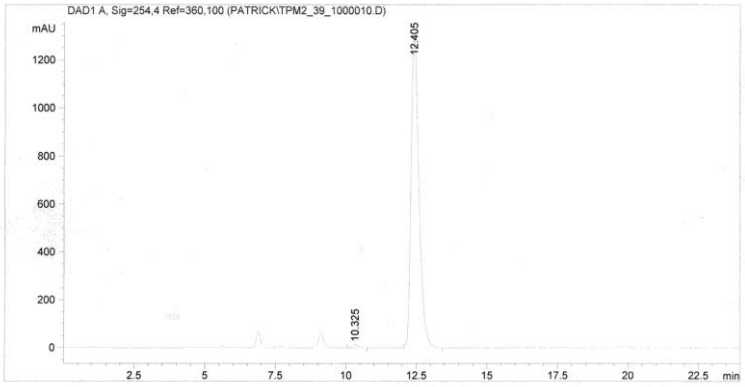
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.194	BV	0.1497	1093.51599	110.29647	98.2468
2	5.677	VB	0.1635	19.51354	1.75776	1.7532

Synthesis of (3R)-5-Fluoro-2-methyl-1phenylhexa-1,5-diene-3-ol (2.3g).



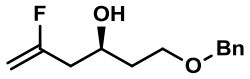
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5g** (29.6 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 40 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3g** (38.5 mg, 0.187 mmol) as a colorless oil in 93% yield and **2.4g** (1.4 mg, 0.007 mmol) as a colorless oil in 4% yield.

HPLC (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 10.3 min, t_{major} = 12.4 min; ee = 98%



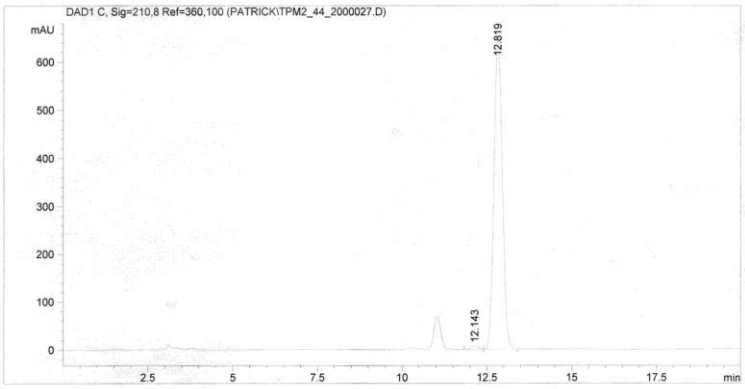
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.325	BB	0.2316	196.07742	12.87925	0.7695
2	12.405	BB	0.2983	2.52845e4	1291.81689	99.2305

Synthesis of (4S)-6-Benzyloxy-2-fluorohexa-1-ene-4-ol (2.3h).



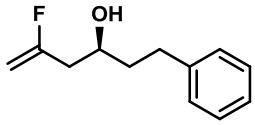
To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5h** (32.8 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3h** (24.8 mg, 0.111 mmol) as a colorless oil in 55% yield and **2.4h** (2.3 mg, 0.011 mmol) as a colorless oil in 6% yield.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 210 nm), t_{minor} = 12.1 min, t_{major} = 12.8 min; ee = 98%



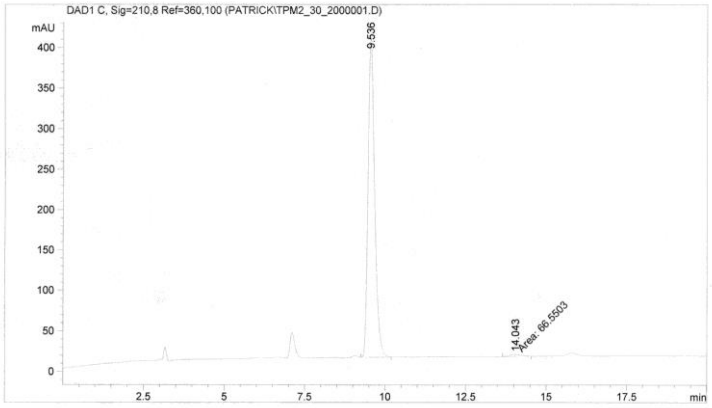
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.143	BV	0.2417	128.30276	8.32924	1.1385
2	12.819	VB	0.2691	1.11416e4	646.51965	98.8615

Synthesis of (4S)-2-Fluoro-6-phenylhexa-1-en-4-ol (2.3i).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar was added **Cat II** (10.7 mg, 0.01 mmol, 5 mol %) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL), 3-chloro-2-fluoroprop-1-ene **2.2** (28.4 mg, 0.3 mmol, 1.5 equiv.), aldehyde **2.5i** (26.8 mg, 0.2 mmol, 1.0 equiv.), isopropanol (24.0 mg, 0.4 mmol, 2.0 equiv.), and water (18.0 mg, 1.0 mmol, 5.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 60 °C for 24 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.3i** (25.2 mg, 0.0.130 mmol) as a yellow oil in 65% yield and **2.4i** (2.2 mg, 0.012 mmol) as a yellow oil in 6% yield.

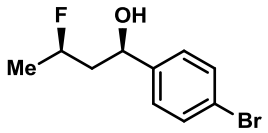
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 9.5 min, t_{major} = 14.0 min; ee = 98%



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.536	VB	0.2177	5653.99951	393.39713	98.8366
2	14.043	MM	0.4264	66.55029	2.60149	1.1634

Experimental Procedures and Spectroscopic Data for Hydrogenation Products 2.6

Synthesis of (1*R*)-1-(4-bromophenyl)-3-fluorobutan-1-ol (2.6a).



To a vial containing a magnetic stir bar was added alcohol **2.3a** (0.125 mmol, 30.6 mg) followed by Crabtree's catalyst (0.003 mmol, 2.5 mg). The vial was charged with dichloromethane (0.05M, 2.5 mL). The vial was capped with a septum, and purged with hydrogen gas (1 atm) for five minutes. The reaction was allowed to stir for 16 hours at room temperature. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.6a** (49 mg, 0.2 mmol) as a white solid in >99% yield and 6:1 *dr*.

TLC (SiO_2): R_f= 0.19 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=38.1°

^{1}H NMR (400 MHz, CDCl3): δ 7.49 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=4.4 Hz, 2H), 4.89 (t, 6.0 Hz, 1H), 4.77-4.59 (m, 1H), 2.27 (dd, *J*=5.2, 2.4 Hz, 1H), 2.24-2.17 (m, 1H), 1.89-1.74 (m, 1H), 1.36 (dd, *J*=24.4, 6.0 Hz, 3H).

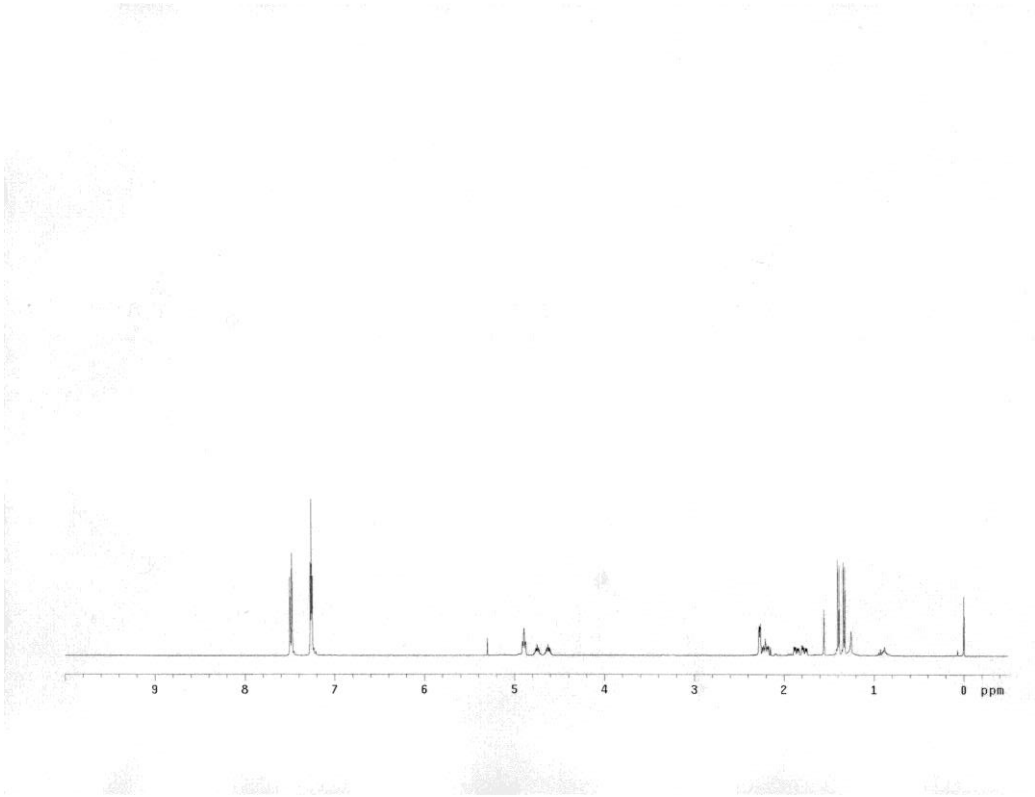
^{13}C NMR (100 MHz, CDCl3): δ 142.7, 131.7, 127.7, 121.6, 90.0 (d, *J*=162.2 Hz), 71.8, 46.1 (d, *J*=19.4 Hz), 21.3 (d, *J*=22.6 Hz).

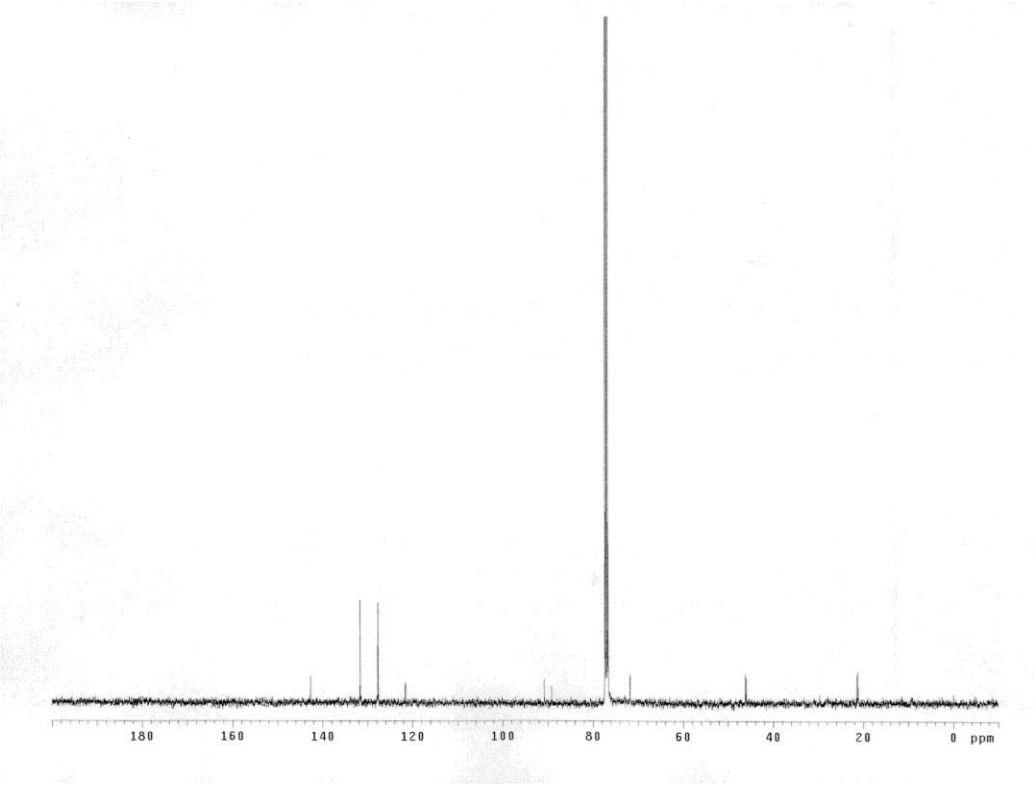
^{19}F NMR (400 MHz, CDCl3): δ -173.68 - -174.14 (m), -175.65 - -176.05 (m).

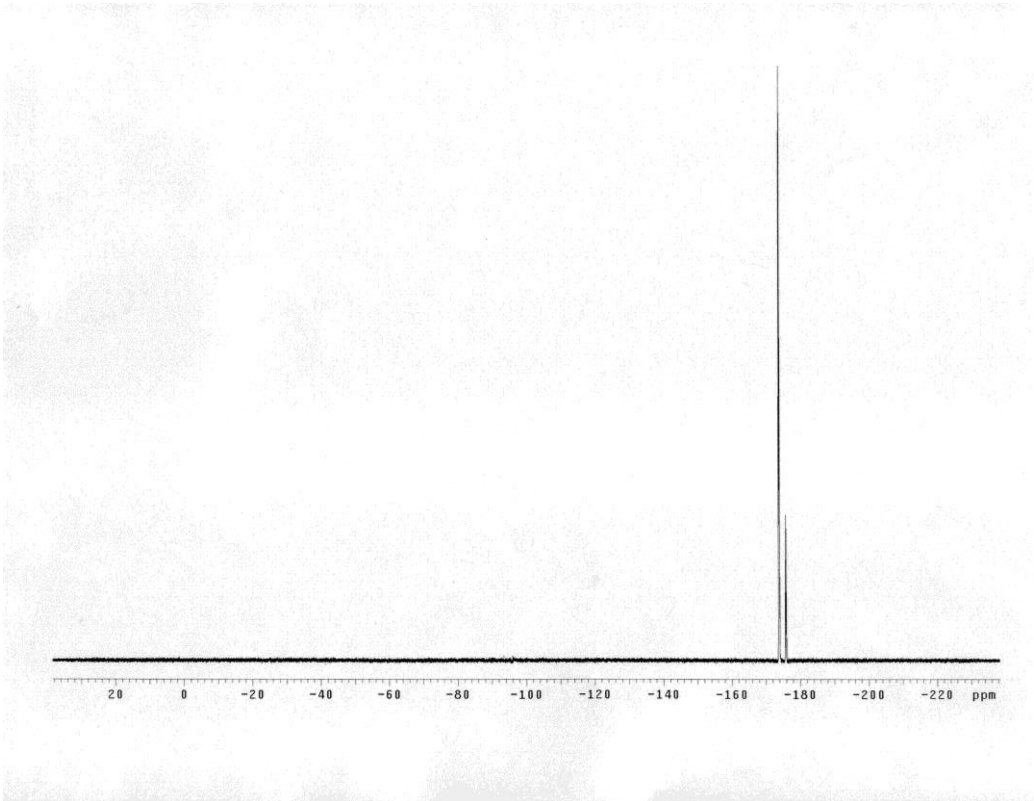
HRMS (CI) Calcd. for $C_{10}H_{12}FO$ $[M+]^+$: 246.0056, Found: 246.0056.

FTIR (neat): 3365.05, 2932.50, 1485.54, 1457.05, 1384.94, 1135.50, 1070.51, 1010.36, 829.09 cm^{-1}.

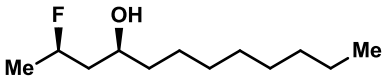
MP 54-56 °C




180
160
140
120
100
80
60
40
20
0 ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220 ppm

Synthesis of (4*S*)-2-fluorododecan-4-ol (2.6c).



To a vial containing a magnetic stir bar was added Crabtree's catalyst (0.0025 mmol, 2 mg). The vial was charged with dichloromethane (0.05M, 2 mL) followed by alcohol **2.3c** (20.2 mg, 0.1 mmol). The vial was capped with a septum, and purged with hydrogen gas (1 atm). The reaction was allowed to stir for 16 hours at 0 °C. The reaction mixture was allowed to warm to ambient temperature, then concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.6c** (16.8 mg, 0.082 mmol) as a colorless oil in 82% yield and 7:1 *dr*.

TLC (SiO_2): R_f= 0.19 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=-5.9°

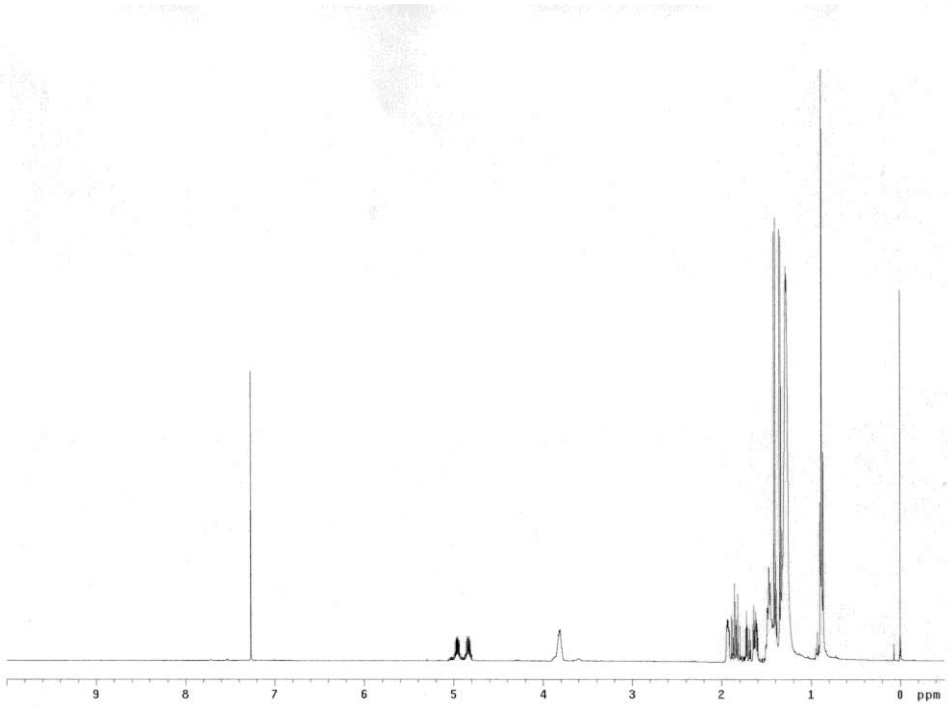
^{1}H NMR (400 MHz, CDCl3): δ 4.99-4.80 (m, 1H), 3.86-3.78 (m, 1H), 1.93 (br, 1H), 1.89-1.60 (m, 2H), 1.51-1.42 (m, 2H), 1.38 (dd, *J*=24.4, 6.4 Hz, 3H), *J*= 1.28-1.27 (m, 12H), 0.88 (t, *J*=6.8 Hz, 3H).

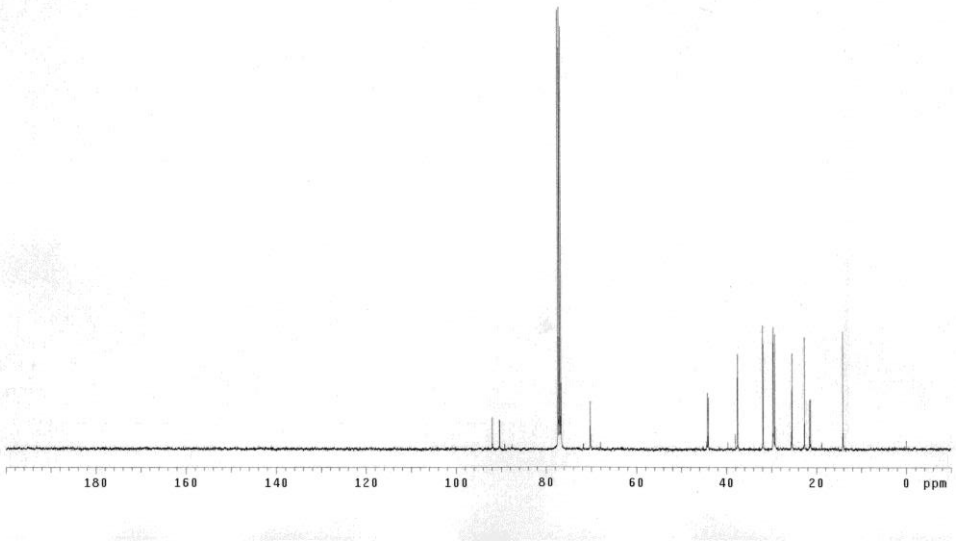
^{13}C NMR (100 MHz, CDCl3): δ 91.1 (d, *J*=160.7 Hz), 70.2, 44.1 (d, *J*=18.6 Hz), 37.5, 31.9, 29.6, 29.5, 29.2, 25.4, 22.7, 21.4 (d, *J*=22.3 Hz), 14.1.

^{19}F NMR (400 MHz, CDCl3): δ -172.24 - -172.71 (m), -175.37 - -175.70 (m).

HRMS (CI) Calcd. for $C_{12}H_{24}FO$ $[M-H]^+$: 203.1810, Found: 203.1811.

FTIR (neat): 3374, 2925, 2854, 1463, 1385, 1129, 1082, 924, 819 cm^{-1}.


9
8
7
6
5
4
3
2
1
0 ppm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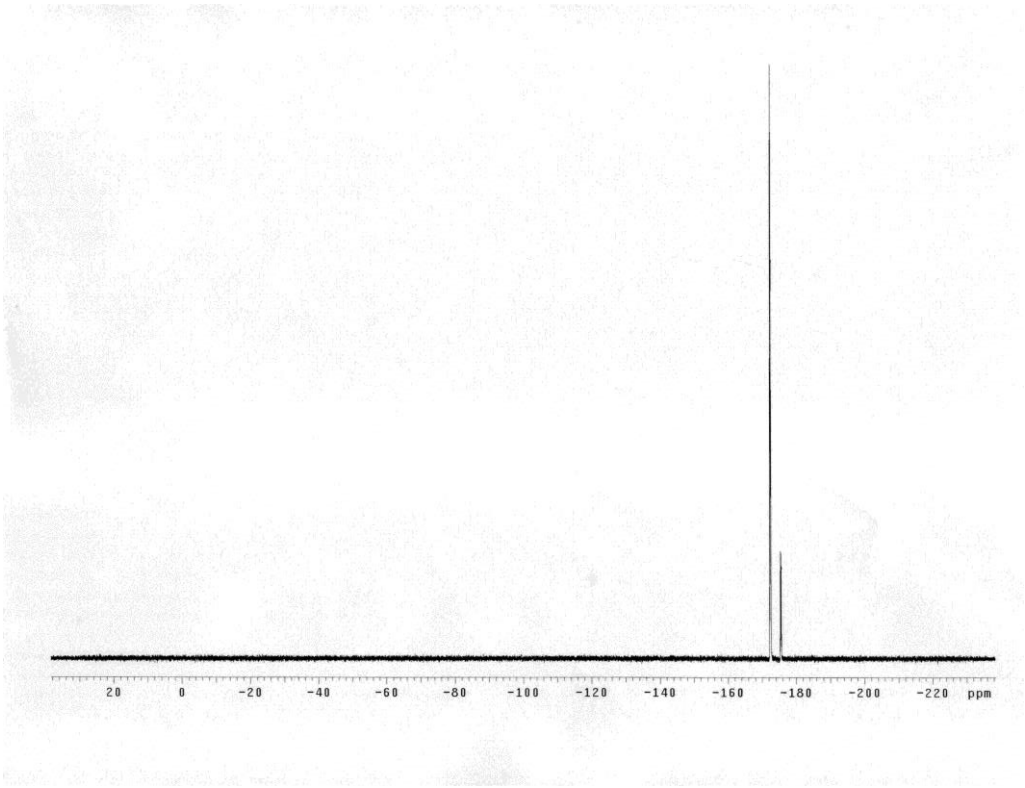
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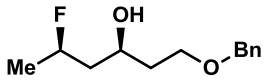
Synthesis of (3S)-1-(benzyloxy)-5-fluorohexan-3-ol (2.6h).



To a vial containing a magnetic stir bar was added Crabtree's catalyst (0.0025 mmol, 2 mg). The vial was charged with dichloromethane (0.05M, 2 mL) followed by alcohol **2.3h** (22.4 mg, 0.1 mmol). The vial was capped with a septum, and purged with hydrogen gas (1 atm). The reaction was allowed to stir for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.6h** (19.9 mg, 0.087 mmol) as a colorless oil in 88% yield and 9:1 *dr*.

TLC (SiO_2): R_f= 0.19 (ethyl acetate:hexanes, 1:5)

[α]$_D^{23}$=-13.0°

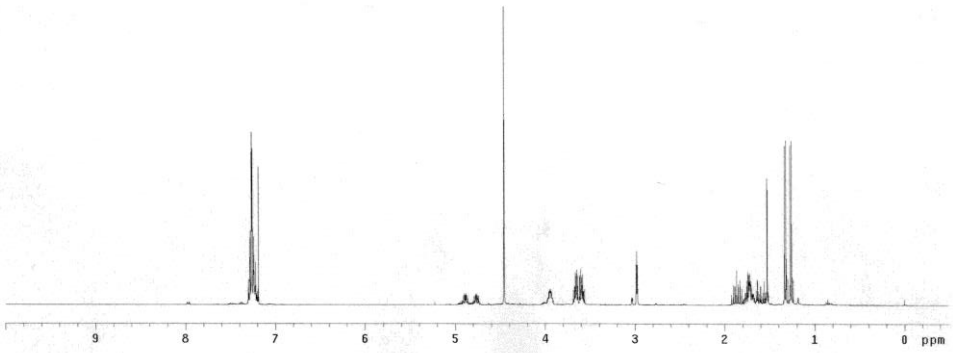
^{1}H NMR (400 MHz, CDCl3): δ 7.30-7.19 (m, 5H), 4.92-4.73 (m, 1H), 4.46 (s, 2H), 3.99-3.91 (m, 1H), 3.69-3.56 (m, 2H), 1.92-1.52 (m, 4H), 1.30 (dd, *J*=24.4, 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 137.8, 128.5, 127.8, 127.7, 89.7 (d, *J*=85.96 Hz), 73. 4, 68.9, 44.0 (d, *J*=102 Hz), 36.4, 21.2 (d, *J*=119.2 Hz).

^{19}F NMR (400 MHz, CDCl3): δ -172.12 - -172.57 (m), -175.28 - -175.62 (m).

HRMS (CI) Calcd. for $C_{13}H_{20}FO_2$ $[M+H]^+$: 227.1445, Found: 227.1447.

FTIR (neat): 3430, 2923, 2866, 1454, 1385, 1206, 1094, 1027, 923, 822, 737, 697 cm^{-1}.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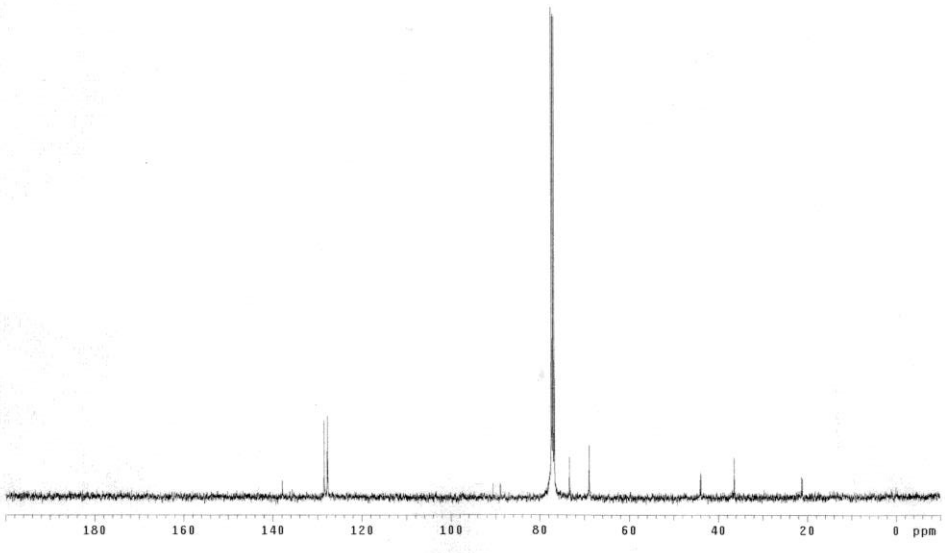
5
4
3
2
1
0 ppm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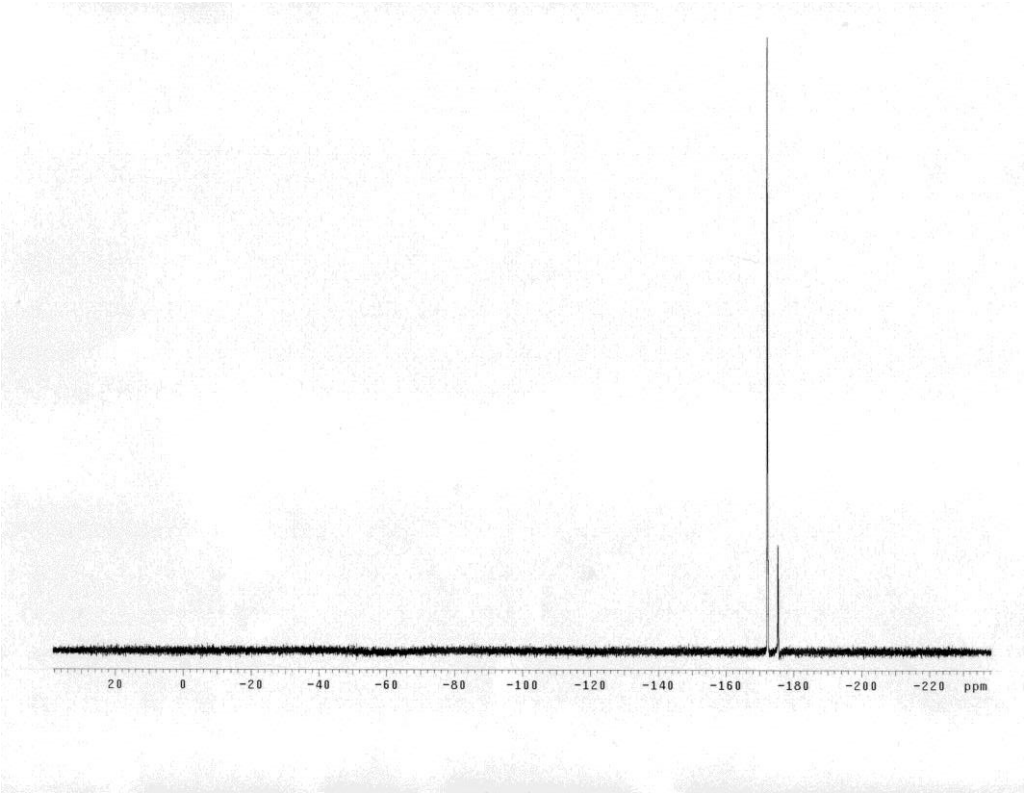
0 ppm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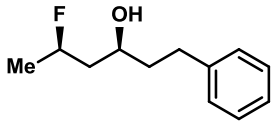
-220
ppm

Synthesis of (3*S*)-5-fluoro-1-phenylhexan-3-ol (2.6i).



To a vial containing a magnetic stir bar was added Crabtree's catalyst (0.0025 mmol, 2 mg). The vial was charged with dichloromethane (0.05M, 2 mL) followed by alcohol **2.3i** (19.6 mg, 0.1 mmol). The vial was capped with a septum, and purged with hydrogen gas (1 atm).The reaction was allowed to stir for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to furnish the title compound **2.6i** (13.5 mg, 0.0688 mmol) as a yellow oil in 70% yield 5:1 *dr*.

TLC (SiO_2): R_f= 0.19 (ethyl acetate:hexanes, 1:9)

[α]$_D^{23}$=-14.2°

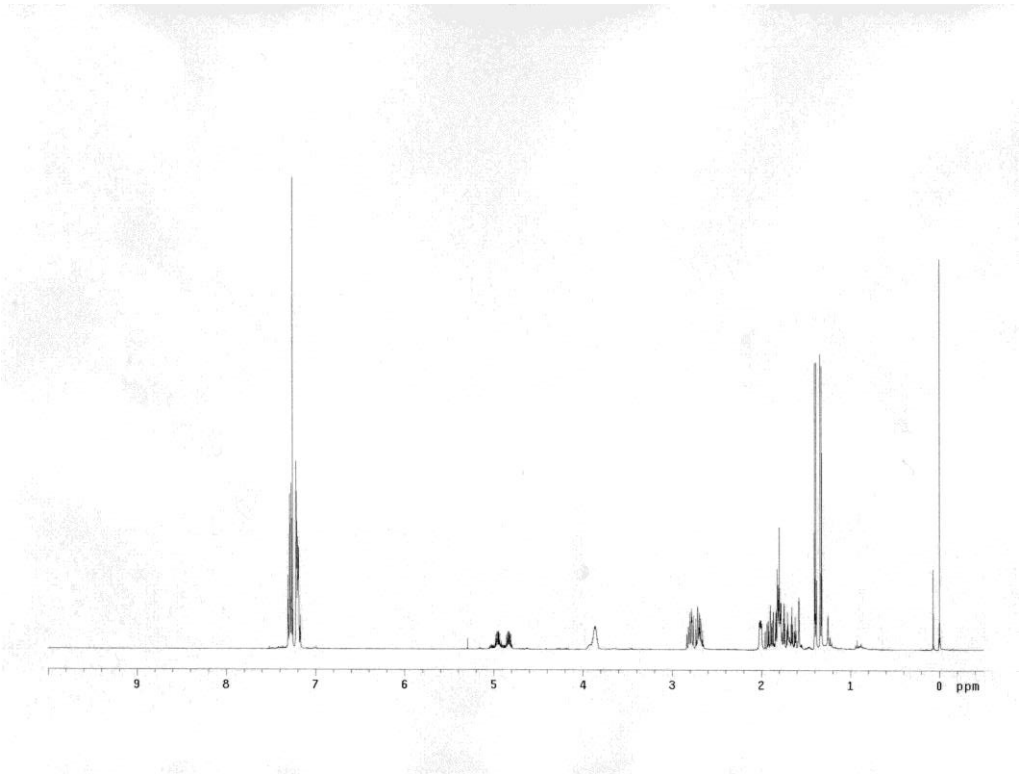
^{1}H NMR (400 MHz, CDCl3): δ 7.27 (t, *J*=6.4 Hz, 2H), 7.19 (dd, *J*=6.4, 2.4 Hz, 3H), 4.96-4.78 (m, 1H), 3.88-3.81 (m, 1H), 2.82-2.64 (m, 2H), 2.01-1.98 (m, 1H), 1.94-1.57 (m, 4H), 1.35 (dd, *J*=24.4, 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 141.9, 128.4, 125.9, 91.2 (dd, *J*=160.7 Hz), 69.6, 44.1 (d, *J*=18.6 Hz), 39.1, 31.8, 21.4 (d, *J*=22.4 Hz).

^{19}F NMR (400 MHz, CDCl3): δ -172.33 - -172.80 (m), -175.39 - -175.78 (m).

HRMS (CI) Calcd. for $C_{12}H_{16}FO$ $[M-H]^+$: 195.1184, Found: 195.1185.

FTIR (neat): 3363, 2976, 2935, 1652, 1539, 1515, 1506, 1455, 1435, 1417, 1386, 1136, 1091, 1053, 922, 864, 825, 813, 747, 699 cm^{-1}.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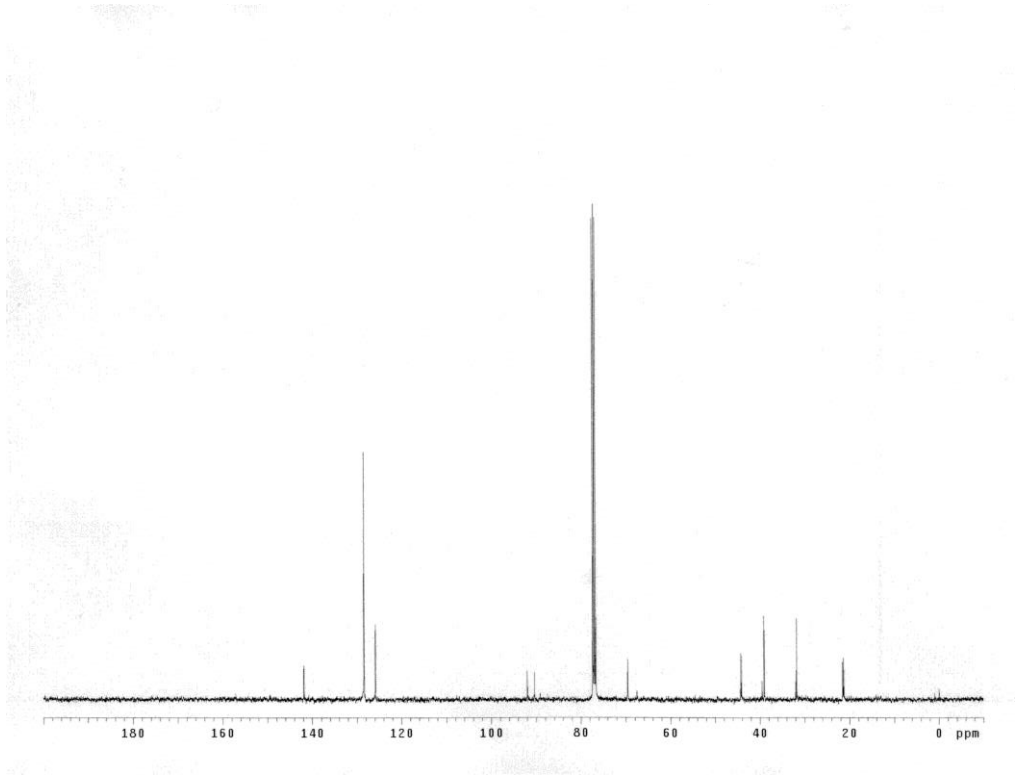
4
3
2
1
0 ppm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160
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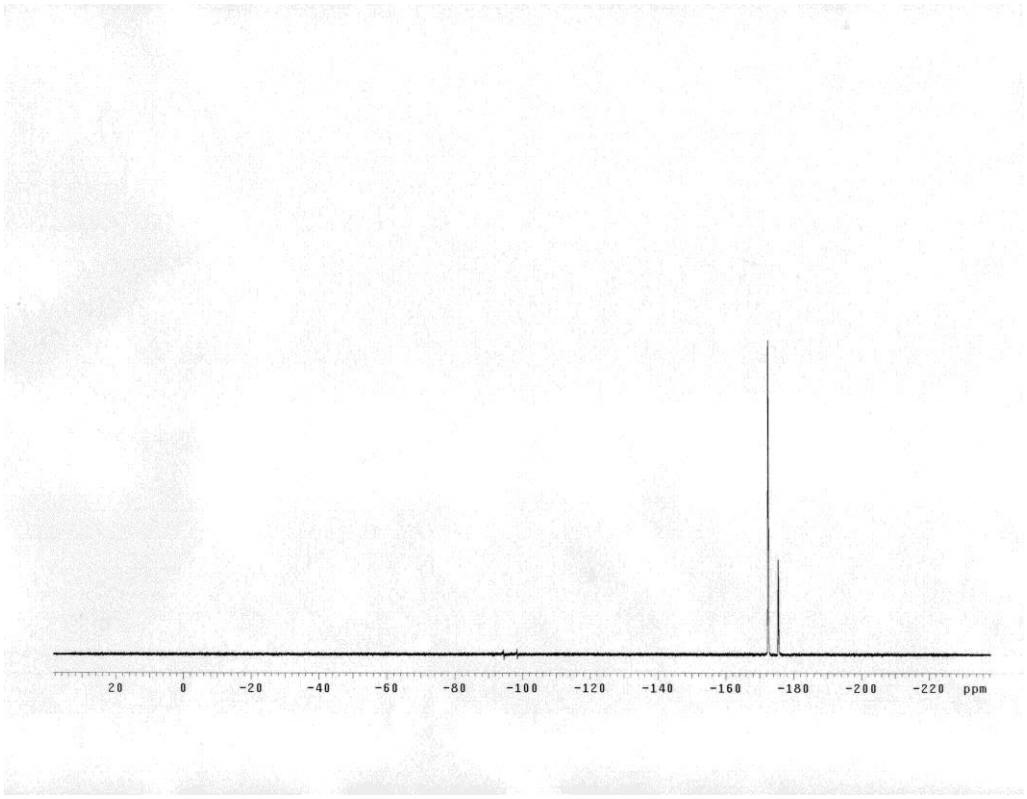
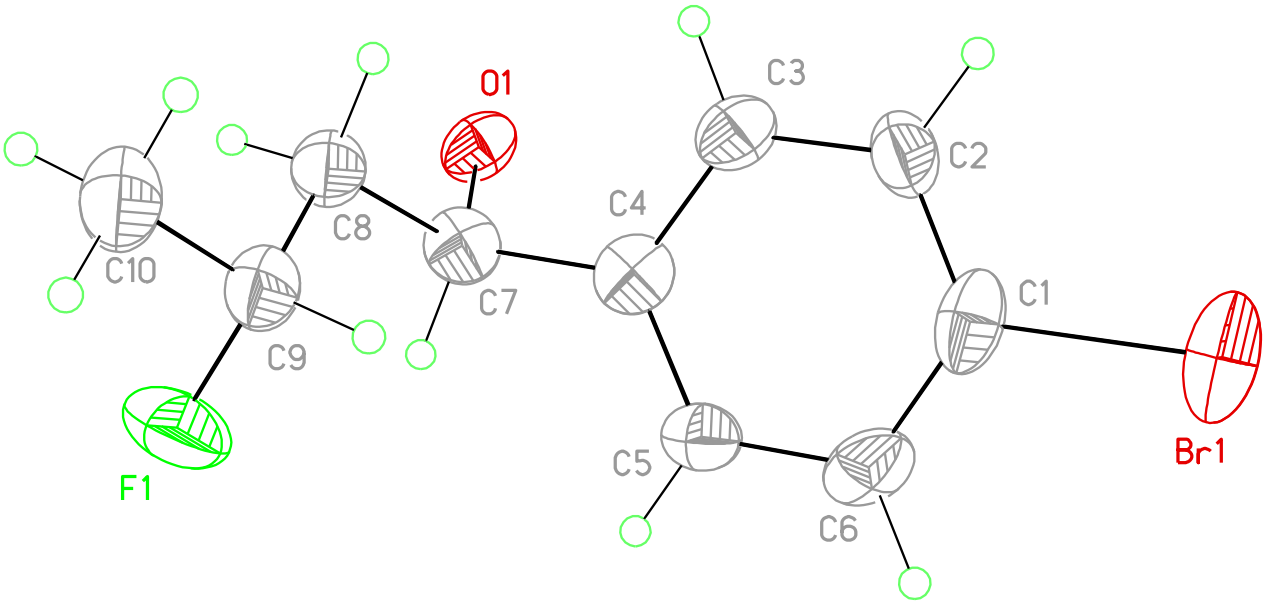
100
80
60
40
20
0 ppm


20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

Absolute and relative Stereochemical determination

The absolute and relative stereochemistry was determined by x-ray analysis of product **2.6a** and was found to be *R,R*.

View of molecule showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The configuration at C7 and C9 is *R, R*.



Crystal data and structure refinement for 1.

Empirical formula	C10 H12 Br F O	
Formula weight	247.11	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.6093(12) Å	α = 90°.
	b = 14.340(2) Å	β = 90°.
	c = 39.901(4) Å	γ = 90°.
Volume	3209.5(9) $Å^3$	
Z	12	
Density (calculated)	1.534 Mg/m^3	
Absorption coefficient	3.816 mm^{-1}	
F(000)	1488	
Crystal size	0.60 x 0.02 x 0.02 mm	
Theta range for data collection	3.02 to 25.00°.	
Index ranges	-6<=h<=6, -17<=k<=12, -40<=l<=46	
Reflections collected	17775	
Independent reflections	5541 [R(int) = 0.0888]	
Completeness to theta = 25.00°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.714	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5541 / 0 / 355	
Goodness-of-fit on F^2	1.129	
Final R indices [I>2sigma(I)]	R1 = 0.0764, wR2 = 0.1259	
R indices (all data)	R1 = 0.1404, wR2 = 0.1521	

Absolute structure parameter	-0.01(2)
Largest diff. peak and hole	0.775 and -0.572 e.Å^{-3}

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br1	9529(2)	9022(1)	8009(1)	61(1)
F1	10953(10)	6092(4)	6357(2)	61(2)
O1	10346(11)	8937(4)	6279(1)	37(2)
C1	9870(20)	8754(6)	7533(2)	41(3)
C2	8149(18)	9052(7)	7314(2)	44(3)
C3	8344(18)	8843(7)	6974(2)	37(3)
C4	10280(20)	8322(6)	6854(2)	36(2)
C5	11998(18)	8036(7)	7086(2)	36(3)
C6	11810(20)	8240(7)	7429(3)	43(3)
C7	10451(19)	8094(6)	6479(2)	38(2)
C8	8582(17)	7437(7)	6356(2)	37(3)
C9	8831(19)	6464(7)	6496(2)	42(3)
C10	6820(20)	5823(7)	6402(3)	54(3)
Br2	5324(2)	5387(1)	5379(1)	53(1)
F2	2452(12)	11556(5)	5340(2)	72(2)
O2	7067(11)	9872(4)	5916(2)	40(2)
C11	5765(19)	6685(6)	5443(2)	35(3)
C12	7786(18)	7108(7)	5313(2)	35(3)
C13	8041(18)	8065(7)	5352(2)	38(3)
C14	6399(19)	8587(7)	5525(2)	33(3)
C15	4430(20)	8137(6)	5665(2)	36(2)

C16	4139(19)	7176(7)	5624(2)	43(3)
C17	6697(18)	9626(7)	5565(2)	40(3)
C18	4570(20)	10176(6)	5429(2)	50(3)
C19	4760(20)	11221(6)	5446(2)	46(3)
C20	6510(20)	11649(9)	5227(3)	69(4)
Br3	9944(3)	14049(1)	5792(1)	66(1)
F3	15959(12)	11430(4)	7275(2)	62(2)
O3	14120(11)	9953(4)	6439(1)	39(2)
C21	11360(20)	13075(7)	6045(3)	55(4)
C22	10200(20)	12223(7)	6061(2)	45(3)
C23	11129(19)	11516(7)	6252(2)	42(3)
C24	13320(18)	11622(7)	6416(2)	33(2)
C25	14440(20)	12465(7)	6397(2)	49(3)
C26	13470(20)	13205(7)	6215(3)	49(3)
C27	14277(18)	10821(6)	6626(2)	39(3)
C28	12972(17)	10683(6)	6960(2)	34(3)
C29	13430(20)	11437(8)	7215(3)	49(3)
C30	12250(20)	11281(7)	7549(2)	53(3)

Bond lengths [Å] and angles [°] for 1.

Br1-C1	1.946(8)	C11-C16	1.361(12)
F1-C9	1.417(11)	C11-C12	1.387(13)
O1-C7	1.451(10)	C12-C13	1.389(13)
C1-C2	1.371(14)	C12-H12	0.95
C1-C6	1.380(14)	C13-C14	1.374(13)
C2-C3	1.396(13)	C13-H13	0.95
C2-H2	0.95	C14-C15	1.395(14)
C3-C4	1.403(14)	C14-C17	1.508(13)
C3-H3	0.95	C15-C16	1.397(12)
C4-C5	1.397(13)	C15-H15	0.95
C4-C7	1.534(12)	C16-H16	0.95
C5-C6	1.403(13)	C17-C18	1.532(14)
C5-H5	0.95	C17-H17	1.00
C6-H6	0.95	C18-C19	1.504(12)
C7-C8	1.493(13)	C18-H18A	0.99
C7-H7	1.00	C18-H18B	0.99
C8-C9	1.510(12)	C19-C20	1.448(14)
C8-H8A	0.99	C19-H19	1.00
C8-H8B	0.99	C20-H20A	0.98
C9-C10	1.503(14)	C20-H20B	0.98
C9-H9	1.00	C20-H20C	0.98
C10-H10A	0.98	Br3-C21	1.898(12)
C10-H10B	0.98	F3-C29	1.437(12)
C10-H10C	0.98	O3-C27	1.455(10)
Br2-C11	1.895(9)	C21-C26	1.376(16)
F2-C19	1.445(12)	C21-C22	1.384(14)
O2-C17	1.460(10)	C22-C23	1.371(13)

C22-H22	0.95	C27-H27	1.00
C23-C24	1.401(14)	C28-C29	1.505(13)
C23-H23	0.95	C28-H28A	0.99
C24-C25	1.364(13)	C28-H28B	0.99
C24-C27	1.521(12)	C29-C30	1.507(14)
C25-C26	1.399(13)	C29-H29	1.00
C25-H25	0.95	C30-H30A	0.98
C26-H26	0.95	C30-H30B	0.98
C27-C28	1.535(12)	C30-H30C	0.98

C2-C1-C6	122.0(9)	C8-C7-C4	114.4(8)
C2-C1-Br1	119.4(8)	O1-C7-H7	107.6
C6-C1-Br1	118.6(8)	C8-C7-H7	107.6
C1-C2-C3	119.9(10)	C4-C7-H7	107.6
C1-C2-H2	120.1	C7-C8-C9	113.3(8)
C3-C2-H2	120.1	C7-C8-H8A	108.9
C2-C3-C4	120.5(10)	C9-C8-H8A	108.9
C2-C3-H3	119.7	C7-C8-H8B	108.9
C4-C3-H3	119.7	C9-C8-H8B	108.9
C5-C4-C3	117.6(9)	H8A-C8-H8B	107.7
C5-C4-C7	122.7(10)	F1-C9-C10	107.7(8)
C3-C4-C7	119.6(10)	F1-C9-C8	106.3(8)
C4-C5-C6	122.3(10)	C10-C9-C8	113.8(9)
C4-C5-H5	118.9	F1-C9-H9	109.6
C6-C5-H5	118.9	C10-C9-H9	109.6
C1-C6-C5	117.7(10)	C8-C9-H9	109.6
C1-C6-H6	121.2	C9-C10-H10A	109.5
C5-C6-H6	121.2	C9-C10-H10B	109.5
O1-C7-C8	108.4(8)	H10A-C10-H10B	109.5
O1-C7-C4	110.9(7)	C9-C10-H10C	109.5

H10A-C10-H10C	109.5	C19-C18-H18B	108.3
H10B-C10-H10C	109.5	C17-C18-H18B	108.3
C16-C11-C12	121.5(9)	H18A-C18-H18B	107.4
C16-C11-Br2	119.5(8)	F2-C19-C20	106.8(8)
C12-C11-Br2	119.0(7)	F2-C19-C18	104.6(9)
C11-C12-C13	118.2(9)	C20-C19-C18	116.4(10)
C11-C12-H12	120.9	F2-C19-H19	109.6
C13-C12-H12	120.9	C20-C19-H19	109.6
C14-C13-C12	121.8(10)	C18-C19-H19	109.6
C14-C13-H13	119.1	C19-C20-H20A	109.5
C12-C13-H13	119.1	C19-C20-H20B	109.5
C13-C14-C15	118.7(9)	H20A-C20-H20B	109.5
C13-C14-C17	121.2(10)	C19-C20-H20C	109.5
C15-C14-C17	120.1(9)	H20A-C20-H20C	109.5
C14-C15-C16	120.1(10)	H20B-C20-H20C	109.5
C14-C15-H15	119.9	C26-C21-C22	120.1(11)
C16-C15-H15	119.9	C26-C21-Br3	121.4(9)
C11-C16-C15	119.6(10)	C22-C21-Br3	118.5(10)
C11-C16-H16	120.2	C23-C22-C21	120.0(11)
C15-C16-H16	120.2	C23-C22-H22	120.0
O2-C17-C14	110.9(8)	C21-C22-H22	120.0
O2-C17-C18	109.0(8)	C22-C23-C24	120.8(11)
C14-C17-C18	112.7(9)	C22-C23-H23	119.6
O2-C17-H17	108.1	C24-C23-H23	119.6
C14-C17-H17	108.1	C25-C24-C23	118.4(10)
C18-C17-H17	108.1	C25-C24-C27	122.4(10)
C19-C18-C17	116.1(10)	C23-C24-C27	119.0(9)
C19-C18-H18A	108.3	C24-C25-C26	121.4(11)
C17-C18-H18A	108.3	C24-C25-H25	119.3

C26-C25-H25	119.3	C27-C28-H28B	108.7
C21-C26-C25	119.2(10)	H28A-C28-H28B	107.6
C21-C26-H26	120.4	F3-C29-C28	106.1(9)
C25-C26-H26	120.4	F3-C29-C30	106.6(10)
O3-C27-C24	109.9(7)	C28-C29-C30	114.4(9)
O3-C27-C28	107.9(7)	F3-C29-H29	109.9
C24-C27-C28	114.2(8)	C28-C29-H29	109.9
O3-C27-H27	108.2	C30-C29-H29	109.9
C24-C27-H27	108.2	C29-C30-H30A	109.5
C28-C27-H27	108.2	C29-C30-H30B	109.5
C29-C28-C27	114.2(8)	H30A-C30-H30B	109.5
C29-C28-H28A	108.7	C29-C30-H30C	109.5
C27-C28-H28A	108.7	H30A-C30-H30C	109.5
C29-C28-H28B	108.7	H30B-C30-H30C	109.5

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	86(1)	66(1)	32(1)	-8(1)	2(1)	-22(1)
F1	39(4)	49(4)	93(5)	-3(4)	5(4)	13(3)
O1	36(4)	47(4)	29(3)	7(3)	-3(3)	-4(4)
C1	44(7)	49(6)	30(5)	-6(4)	4(6)	-24(7)
C2	34(7)	53(7)	45(7)	-21(6)	5(5)	0(6)
C3	30(6)	43(7)	40(6)	1(5)	-4(5)	-7(6)
C4	33(6)	37(6)	38(5)	6(4)	4(6)	-9(6)
C5	30(7)	34(6)	43(7)	2(5)	-2(5)	1(5)
C6	58(8)	31(6)	42(7)	14(5)	-16(6)	-1(6)
C7	34(6)	38(6)	42(6)	0(4)	5(6)	-4(6)
C8	32(6)	42(7)	38(6)	-4(5)	2(5)	-2(5)
C9	50(8)	42(7)	35(6)	-5(5)	-5(5)	3(6)
C10	65(8)	50(8)	48(7)	-12(6)	-8(6)	1(7)
Br2	79(1)	39(1)	41(1)	1(1)	-4(1)	4(1)
F2	70(5)	62(5)	84(5)	7(4)	-15(4)	13(4)
O2	41(4)	49(5)	30(4)	-6(3)	3(3)	-3(4)
C11	43(7)	43(6)	18(5)	2(4)	12(5)	0(6)
C12	29(7)	52(7)	24(5)	-7(5)	-11(5)	20(6)
C13	28(6)	57(8)	28(5)	-3(5)	-5(5)	-1(6)
C14	35(7)	43(7)	21(5)	4(4)	-5(5)	0(5)
C15	41(7)	35(6)	32(5)	-6(4)	-6(5)	4(6)
C16	45(8)	59(8)	25(5)	3(5)	-3(5)	-8(6)
C17	39(7)	54(8)	28(6)	-1(5)	12(5)	-12(6)
C18	69(8)	47(7)	35(5)	3(4)	-9(6)	12(7)

C19	42(7)	46(7)	50(6)	2(5)	-12(6)	-5(7)
C20	64(9)	80(10)	63(9)	11(7)	18(7)	-2(8)
Br3	98(1)	44(1)	54(1)	11(1)	14(1)	14(1)
F3	59(5)	69(5)	58(4)	-12(3)	-5(4)	-11(4)
O3	33(4)	46(4)	37(4)	-3(3)	-1(3)	7(3)
C21	90(11)	34(7)	39(7)	-6(5)	13(7)	-1(7)
C22	43(7)	50(7)	43(5)	-8(5)	-2(6)	3(7)
C23	46(8)	44(7)	35(6)	5(5)	10(5)	11(6)
C24	34(7)	29(6)	37(6)	0(5)	6(5)	11(5)
C25	66(8)	42(6)	40(5)	-18(5)	8(6)	-11(7)
C26	67(9)	34(7)	47(7)	-10(5)	19(7)	-18(6)
C27	36(7)	39(6)	41(5)	-9(4)	-24(5)	-3(5)
C28	29(6)	39(7)	34(5)	3(4)	3(5)	2(5)
C29	51(9)	44(8)	52(8)	-12(6)	15(6)	3(6)
C30	90(9)	39(7)	29(6)	-4(5)	2(6)	-9(6)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

	x	y	z	U(eq)
H2	6824	9400	7394	53
H3	7156	9054	6822	45
H5	13336	7690	7009	43
H6	12984	8031	7584	52
H7	12038	7796	6439	46
H8A	8664	7406	6108	45
H8B	6994	7685	6417	45
H9	8978	6494	6745	51
H10A	6641	5812	6158	81
H10B	5336	6048	6505	81
H10C	7163	5192	6484	81
H12	8966	6751	5199	42
H13	9387	8366	5256	45
H15	3291	8485	5789	43
H16	2813	6868	5723	52
H17	8146	9819	5436	49
H18A	4316	9996	5192	60
H18B	3127	9985	5555	60
H19	5069	11417	5682	55
H20A	6172	11474	4994	103
H20B	8106	11434	5288	103
H20C	6423	12329	5249	103
H22	8767	12128	5939	54
H23	10274	10947	6273	50
H25	15915	12550	6510	59

H26	14255	13792	6208	59
H27	15995	10947	6675	47
H28A	11237	10652	6916	41
H28B	13462	10077	7057	41
H29	12943	12056	7121	59
H30A	12612	10650	7629	79
H30B	10519	11351	7524	79
H30C	12842	11739	7711	79

Torsion angles [°] for 1.

C6-C1-C2-C3	-0.7(16)	C14-C15-C16-C11	-0.9(14)
Br1-C1-C2-C3	-178.3(7)	C13-C14-C17-O2	-114.8(9)
C1-C2-C3-C4	0.6(15)	C15-C14-C17-O2	65.1(11)
C2-C3-C4-C5	-0.7(14)	C13-C14-C17-C18	122.7(10)
C2-C3-C4-C7	179.5(9)	C15-C14-C17-C18	-57.4(11)
C3-C4-C5-C6	0.9(14)	O2-C17-C18-C19	59.0(11)
C7-C4-C5-C6	-179.3(9)	C14-C17-C18-C19	-177.5(8)
C2-C1-C6-C5	0.9(15)	C17-C18-C19-F2	-173.6(8)
Br1-C1-C6-C5	178.5(7)	C17-C18-C19-C20	68.8(12)
C4-C5-C6-C1	-1.0(15)	C26-C21-C22-C23	1.7(16)
C5-C4-C7-O1	-124.6(9)	Br3-C21-C22-C23	-177.5(7)
C3-C4-C7-O1	55.3(12)	C21-C22-C23-C24	-4.2(15)
C5-C4-C7-C8	112.5(11)	C22-C23-C24-C25	3.9(14)
C3-C4-C7-C8	-67.7(11)	C22-C23-C24-C27	179.8(8)
O1-C7-C8-C9	168.3(8)	C23-C24-C25-C26	-1.2(14)
C4-C7-C8-C9	-67.4(11)	C27-C24-C25-C26	-176.9(9)
C7-C8-C9-F1	-67.6(9)	C22-C21-C26-C25	1.0(16)
C7-C8-C9-C10	174.0(8)	Br3-C21-C26-C25	-179.8(7)
C16-C11-C12-C13	-4.4(14)	C24-C25-C26-C21	-1.3(16)
Br2-C11-C12-C13	177.9(7)	C25-C24-C27-O3	-136.4(9)
C11-C12-C13-C14	2.4(14)	C23-C24-C27-O3	47.9(11)
C12-C13-C14-C15	0.2(13)	C25-C24-C27-C28	102.2(11)
C12-C13-C14-C17	-179.9(9)	C23-C24-C27-C28	-73.5(10)
C13-C14-C15-C16	-1.0(13)	O3-C27-C28-C29	167.0(8)
C17-C14-C15-C16	179.1(9)	C24-C27-C28-C29	-70.4(11)
C12-C11-C16-C15	3.7(14)	C27-C28-C29-F3	-60.1(11)
Br2-C11-C16-C15	-178.6(7)	C27-C28-C29-C30	-177.2(9)

2.5.2 Experimental Details for Section 2.3

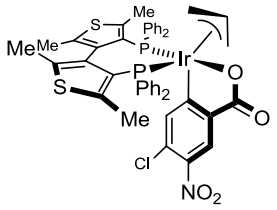
General Information

All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Tetrahydrofuran was dried over sodium metal, benzophenone, and distilled immediately prior to use. Dichloromethane was dried over $CaCl_2$ and distilled immediately prior to use. *N,N*-Dimethylformamide was distilled from 4 Å mol sieves under vacuum. Anhydrous solvents were transferred by oven-dried syringes. All ligands and $[Ir(cod)Cl]_2$ were used as received from Strem Chemical Inc or Merck and Co., Inc. Alcohols and aldehydes were distilled or recrystallized prior to use. Allyl acetate was distilled prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm).

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, or M-H), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_C (77.0 ppm). Optical rotations were performed on an Automatic Polarimeter AP-300 using dichloromethane (unless

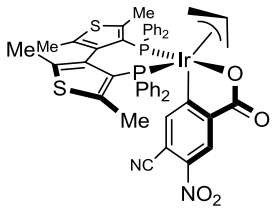
otherwise noted) as solvent. Melting points were taken on a Stuart SMP3 melting point apparatus.

Synthesis of Cat IV



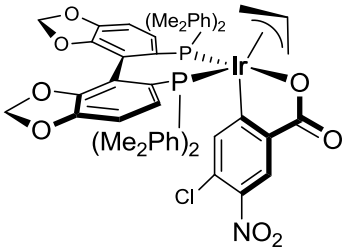
To a resealable pressure tube equipped with a magnetic stir bar were added $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 1.0 equiv.), (-)-TMBTP (236.3 mg, 0.40 mmol, 2.0 equiv.), Cs_2CO_3 (260.6 mg, 0.80 mmol, 4.0 equiv.), and 4-Cl-3-NO_2BzOH (161.2 mg, 0.80 mmol, 4.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (4.0 mL, 0.05 M with respect to $[Ir(cod)Cl]_2$) allyl acetate (100.1 mg, 1.0 mmol, 5.0 equiv.) were added, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 °C, at which point it was allowed to cool to ambient temperature. The reaction mixture was filtered through filter paper and washed with tetrahydrofuran (10 mL). The filtrate was concentrated *in vacuo*, and the residue was subjected to flash column chromatography (dichloromethane:ether, 3:1). The residue obtained upon chromatographic isolation was dissolved in THF (2 mL) and hexane (50 mL) was added. The resulting yellow powder was collected by filtration and dried under vacuum to provide **Cat IV** (282.5 mg, 0.276 mmol) in 69% yield.

Synthesis of Cat V



To a resealable pressure tube equipped with a magnetic stir bar were added $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 1.0 equiv.), (-)-TMBTP (236.3 mg, 0.40 mmol, 2.0 equiv.), Cs_2CO_3 (260.6 mg, 0.80 mmol, 4.0 equiv.), and 4-CN-3-NO_2BzOH (153.7 mg, 0.80 mmol, 4.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (4.0 mL, 0.05 M with respect to $[Ir(cod)Cl]_2$) and allyl acetate (100.1 mg, 1.0 mmol, 5.0 equiv.) were added, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 °C, at which point it was allowed to cool to ambient temperature. The reaction mixture was filtered through filter paper and washed with tetrahydrofuran (10 mL). The filtrate was concentrated *in vacuo*, and the residue was subjected to flash column chromatography (dichloromethane:ether, 3:1). The residue obtained upon chromatographic isolation was dissolved in THF (2 mL) and hexane (50 mL) was added. The resulting yellow powder was collected by filtration and dried under vacuum to provide **Cat V** (180.9 mg, 0.178 mmol) in 45% yield.

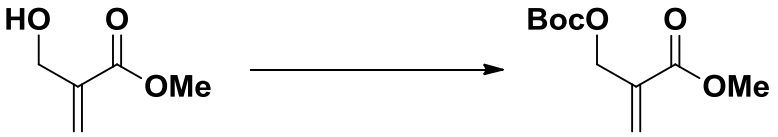
Synthesis of Cat VI



To a resealable pressure tube equipped with a magnetic stir bar were added $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 1.0 equiv.), (*R*)-DM-SEGPHOS (289.1 mg, 0.40 mmol, 2.0 equiv.), Cs_2CO_3 (260.6 mg, 0.80 mmol, 4.0 equiv.), and 4-Cl-3-NO_2BzOH (161.2 mg, 0.80 mmol, 4.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (4.0 mL, 0.05 M with respect to $[Ir(cod)Cl]_2$) and allyl acetate (100.1 mg, 1.0 mmol, 5.0 equiv.) were added, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 °C, at which point it was allowed to cool to ambient temperature. The reaction mixture was filtered through filter paper and washed with tetrahydrofuran (10 mL). The filtrate was concentrated *in vacuo*, and the residue was subjected to flash column chromatography (dichloromethane:ether, 3:1). The residue obtained upon chromatographic isolation was dissolved in THF (2 mL) and hexane (50 mL) was added. The resulting yellow powder was collected by filtration and dried under vacuum to provide **Cat VI** (300 mg, 0.260 mmol) in 65% yield.

Synthesis of Acrylic Ester 2.7

methyl 2-(((tert-butoxycarbonyl)oxy)methyl)acrylate (2.7).

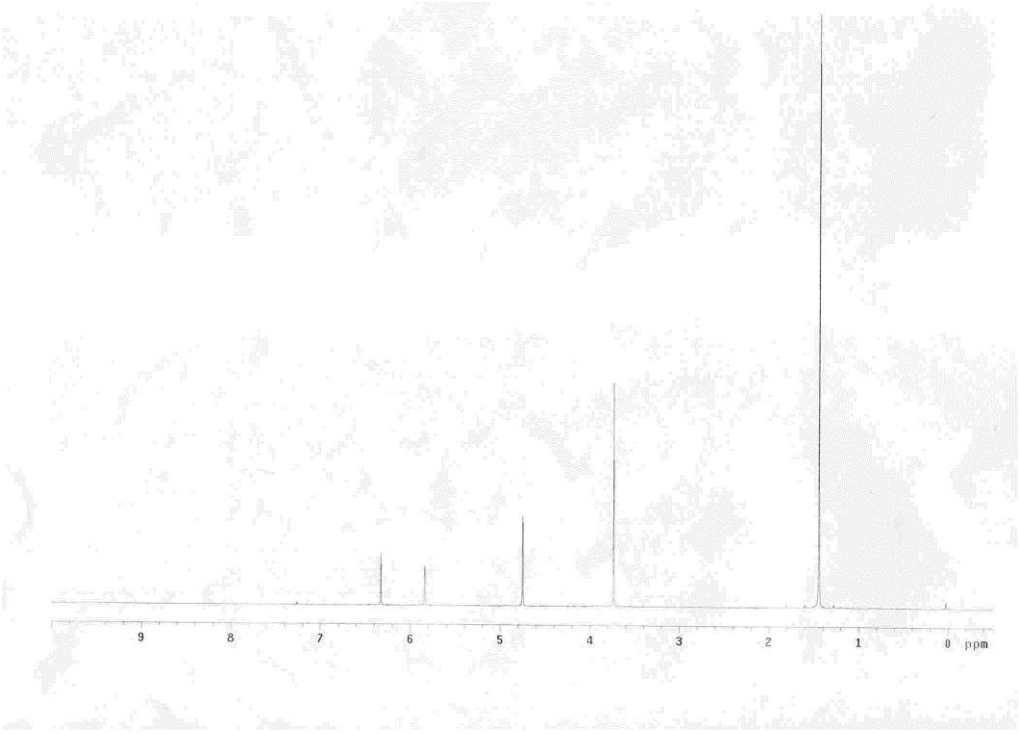


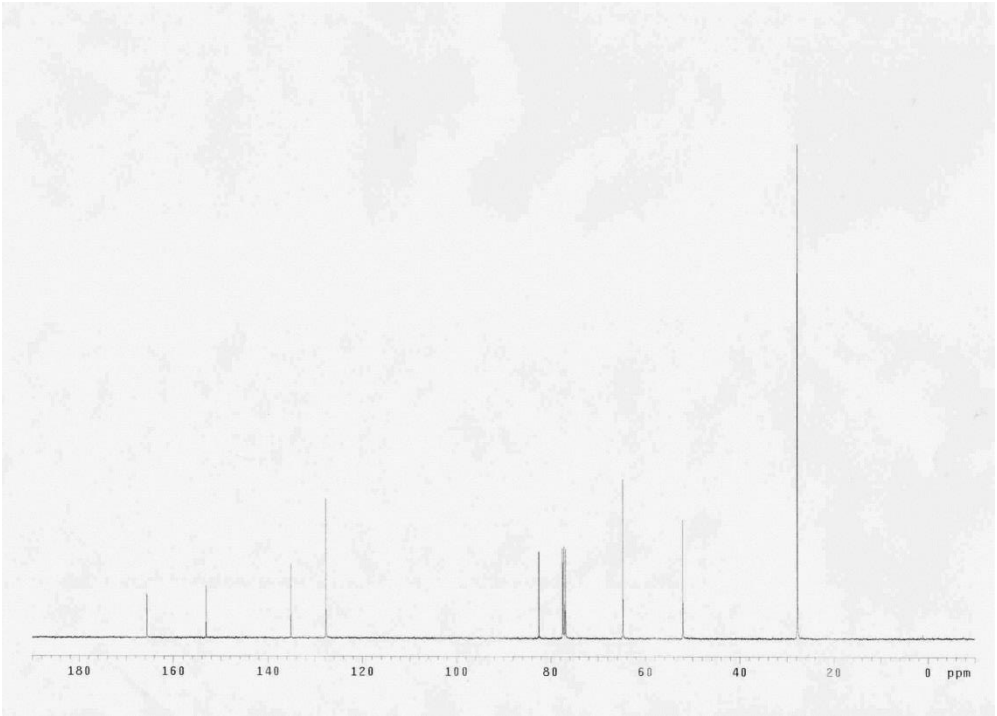
2.14 **2.7**

Methyl 2-(hydroxymethyl)acrylate **2.14** was prepared in accordance with a previous synthesis.[89]

To an oven-dried round bottom flask equipped with a magnetic stir bar were added methyl 2-(hydroxymethyl)acrylate **2.14** (4.25 g, 36.6 mmol, 1.0 equiv.), di-*tert*-butyl dicarbonate (8.79 g, 40.3 mmol, 1.1 equiv.), and DMAP (0.447 g, 3.66 mmol, 10 mol %), followed by dichloromethane (140 mL, 0.2 M with respect to the alcohol). The reaction mixture was stirred at room temperature for 2 hours, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (diethyl ether:hexanes, 1:19) to give the desired acrylic ester **2.7** (5.46 g, 25.3 mmol) as a colorless oil in 69% yield.

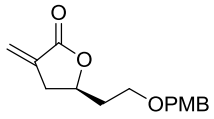
TLC (SiO_2): R_f = 0.31 (diethyl ether:hexanes, 1:9).
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (d, *J* = 0.8 Hz, 1H), 5.84 (d, *J* = 0.8 Hz, 1H), 4.75 (s, 2H), 3.73 (s, 3H), 1.45 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 152.9, 134.9, 127.5, 82.3, 64.6, 51.9, 27.6.
LRMS (CI) Calcd. for $C_{10}H_{15}0_5$ $[M-H]^+$: 215, Found: 215.
FTIR (neat): 2981, 1742, 1642, 1439, 1395, 1369, 1311, 1276, 1254, 1197, 1155, 1101, 1084, 948, 859, 816, 792, 772, 750 cm^{-1}.


9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Experimental Using Alcohols 2.8a-i

Synthesis of (*R*)-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylenedihydrofuran-2(3*H*)-one (2.9a).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat V** (10.1 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.4 mL, 0.5 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8a** (39.2 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 48 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to furnish the title compound **2.9a** (35.1 mg, 0.134 mmol) as a pale yellow oil in 67% yield.

TLC (SiO_2): R_f = 0.29 (ethyl acetate:hexanes, 1:2).

[α]$_D^{23}$ = -42.0°.

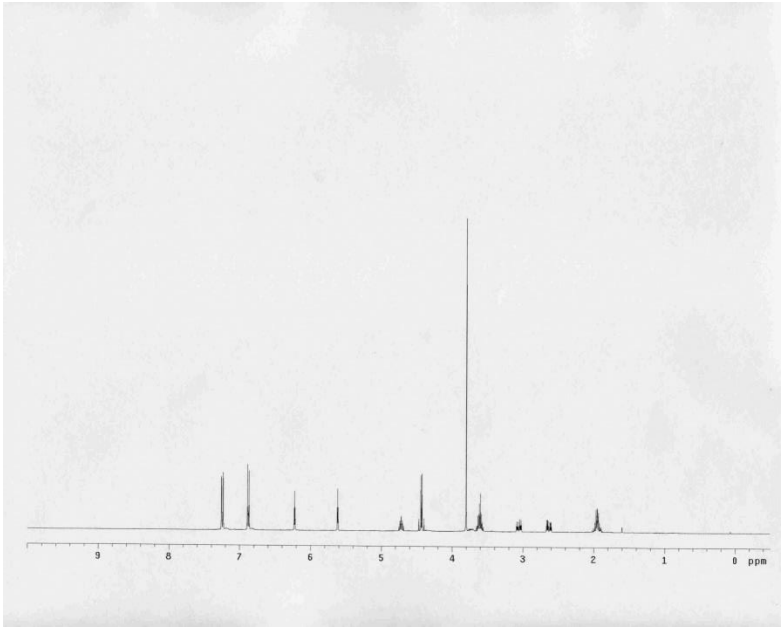
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.22 (t, *J* = 2.8 Hz, 1H), 5.62 (t, *J* = 2.8 Hz, 1H), 4.75-4.68 (m, 1H), 4.47-4.40 (m, 2H), 3.80 (s, 3H), 3.66-3.56 (m, 2H), 3.06 (ddt, *J* = 17.2, 7.6, 2.8 Hz, 1H), 2.63 (ddt, *J* = 17.2, 6.0, 2.8 Hz, 1H), 1.99-1.93 (m, 2H).

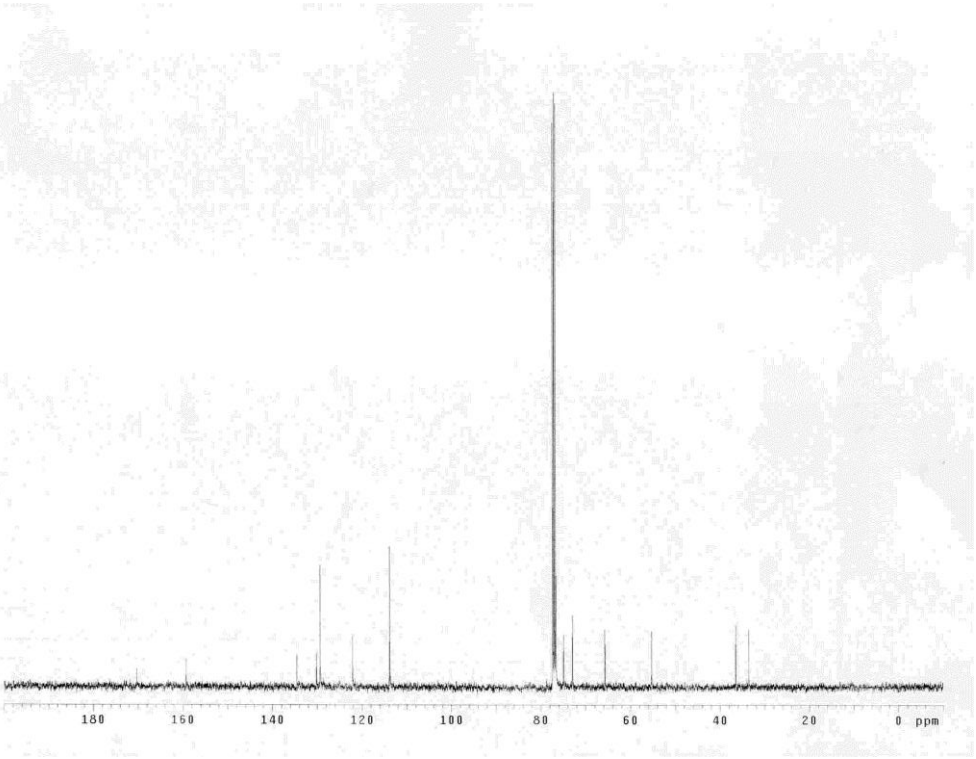
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 159.2, 134.5, 130.1, 129.3, 122.1, 113.8, 74.9, 72.9, 65.7, 55.3, 36.5, 33.6.

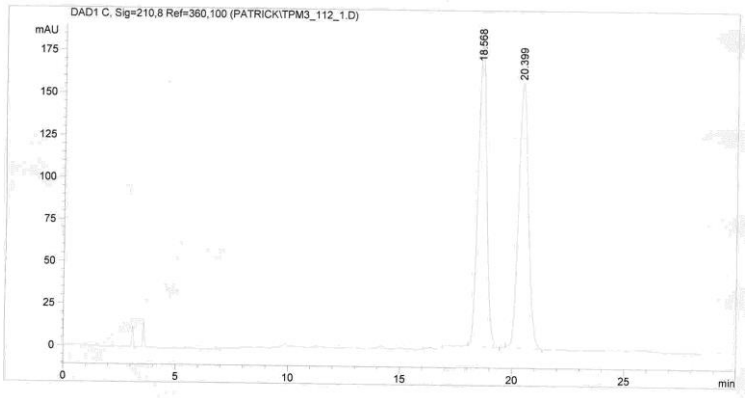
LRMS (CI) Calcd. for $C_{15}H_{18}0_4$ $[M]^+$: 262, Found: 262.

FTIR (neat): 2970, 1739, 1513, 1440, 1365, 1229, 1216, 1093, 1033 cm^{-1}.

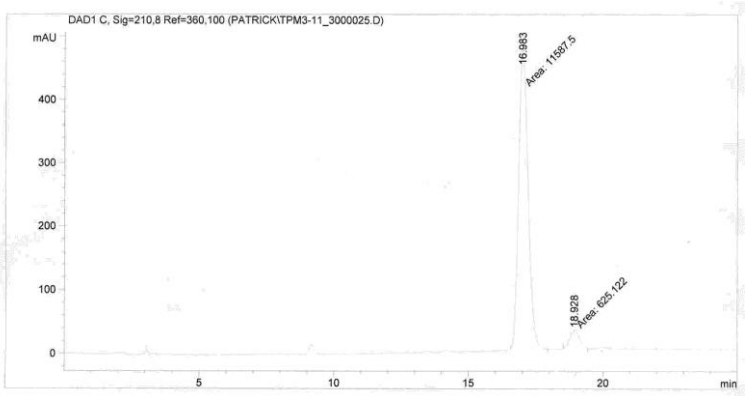
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 33.6 min, t_{minor} = 37.5 min; ee = 90%.





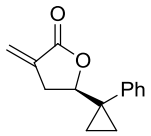


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.568	BB	0.4129	4764.60449	178.77997	50.0263
2	20.399	BB	0.4700	4759.59863	156.87640	49.9737



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.983	MM	0.4074	1.15875e4	474.09460	94.8813
2	18.928	MM	0.3913	625.12225	26.62897	5.1187

Synthesis of (*R*)-3-methylene-5-(1-phenylcyclopropyl)dihydrofuran-2(3*H*)-one (2.9b).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %), Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %), and alcohol **2.8b** (29.6 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), and acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to furnish the title compound **2.9b** (31.3 mg, 0.146 mmol) as a white solid in 73% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:3).

[α]$_D^{23}$ = -15.0°.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.30-7.21 (m, 3H), 5.98 (t, *J* = 2.8 Hz, 1H), 5.39 (t, *J* = 2.8 Hz, 1H), 4.23 (dd, J = 8.0, 6.2 Hz, 1H), 2.90 (ddt, *J* = 17.4, 8.0, 2.8 Hz, 1H), 2.75 (ddt, *J* = 17.4, 6.2, 2.8 Hz 1H), 1.04-1.01 (m, 1H), 0.95-0.91 (m, 3H).

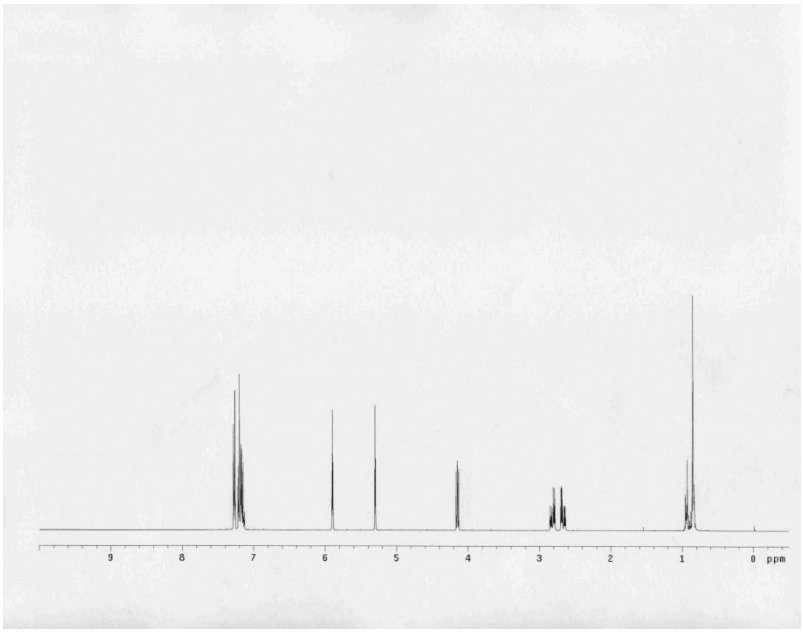
^{13}C NMR (100 MHz, CDCl3): δ 170.2, 139.0, 134.4, 131.2, 128.3, 127.3, 121.3, 82.7, 31.4, 28.9, 10.9, 9.5.

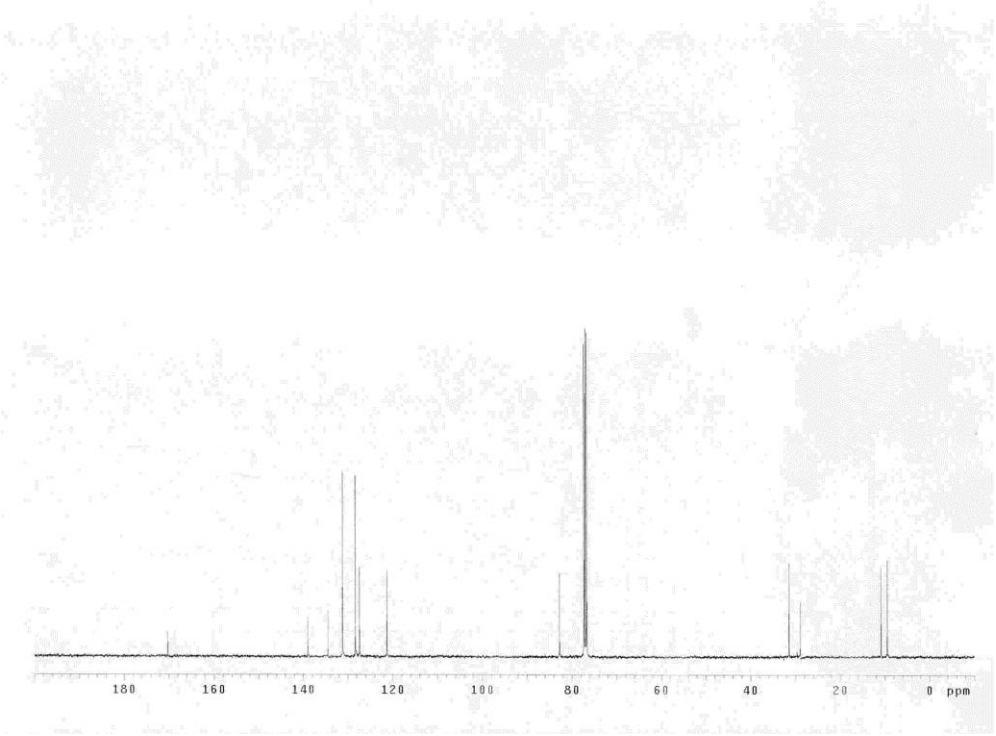
LRMS (CI) Calcd. for $C_{14}H_{15}0_2$ $[M+H]^+$: 215, Found: 215.

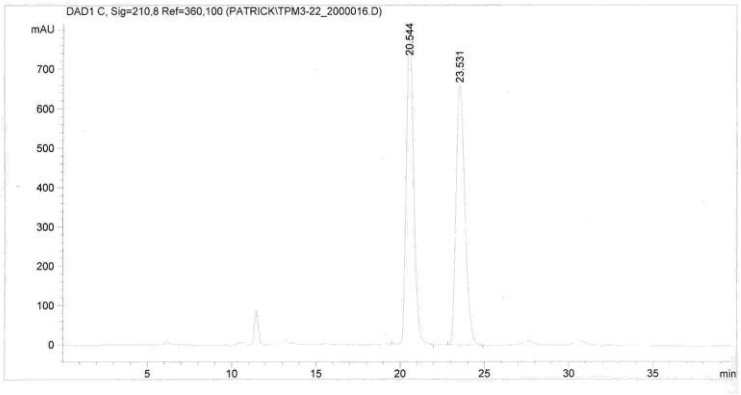
FTIR (neat): 3000, 1759, 1279, 1242, 1132, 1028, 975, 940, 703 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 20.5 min, t_{minor} = 23.7 min; ee = 90%.

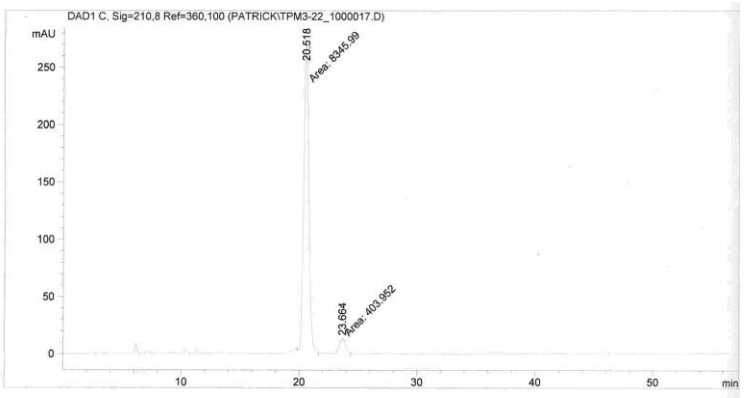
MP 80-82 °C.





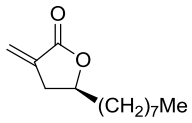


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.544	VB	0.4839	2.41309e4	777.84991	50.0827
2	23.531	BB	0.5685	2.40512e4	657.84906	49.9173



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.518	MM	0.5141	8345.98926	270.59091	95.3834
2	23.664	MM	0.5344	403.95163	12.59922	4.6166

Synthesis of (*S*)-3-methylene-5-octyldihydrofuran-2(3*H*)-one (2.9c).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.4 mL, 0.5 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8c** (28.9 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 48 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to furnish the title compound **2.9c** (27.6 mg, 0.132 mmol) as a colorless oil in 66% yield.

TLC (SiO_2): R_f = 0.35 (ethyl acetate:hexanes, 1:3).

[α]$_D^{23}$ = -36.6° in dichloromethane (accepted **[α]$_D^{25}$** = -38.4° in EtOH)[2].

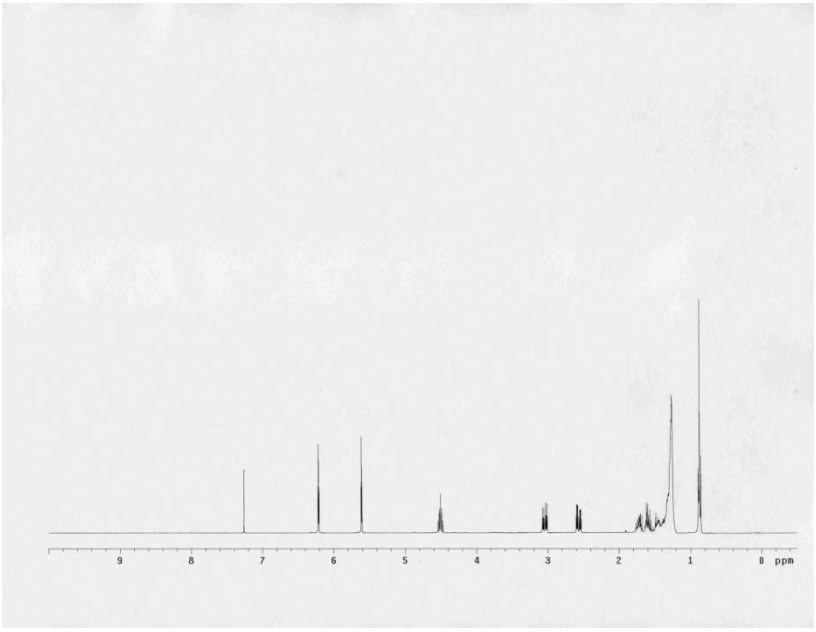
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (t, *J* = 2.8 Hz, 1H), 5.61 (t, *J* = 2.8 Hz, 1H), 4.50 (dddd, *J* = 21.2, 13.6, 7.6, 6.0 Hz, 1H), 3.04 (ddt, *J* = 17.2, 7.6, 2.8 Hz, 1H), 2.56 (ddt, *J* = 17.2, 6.0, 2.8 Hz, 1H), 1.76-1.55 (m, 2H), 1.36-1.26 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

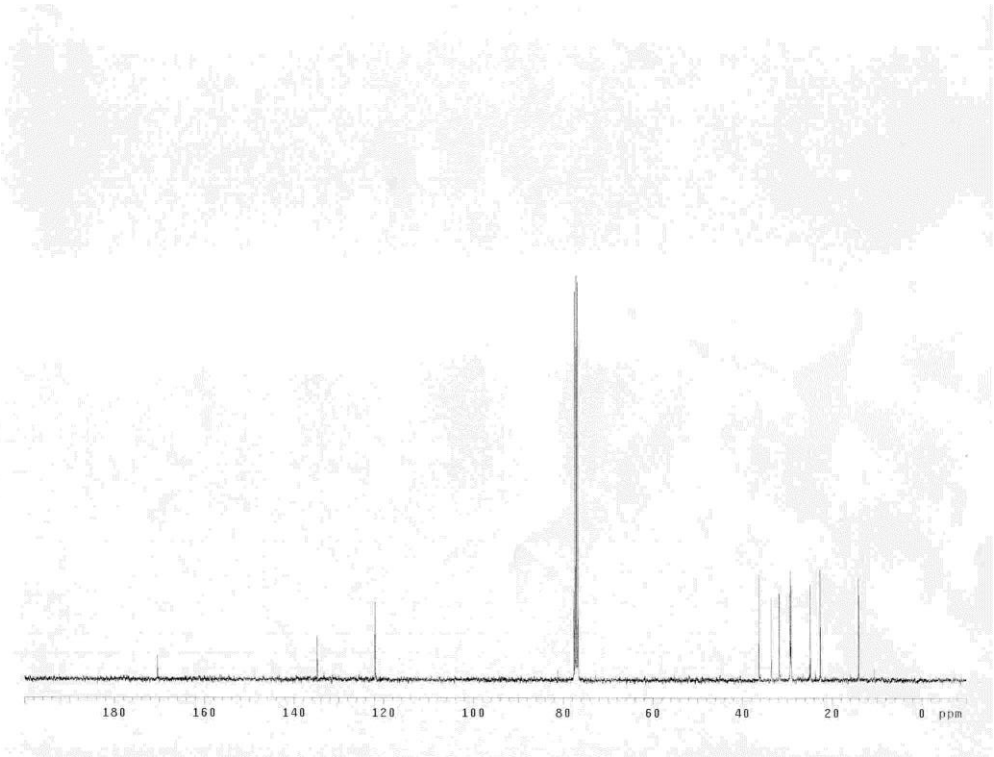
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 134.8, 121.9, 77.6, 36.2, 33.5, 31.8, 29.4, 29.3, 29.1, 24.8, 22.6, 14.1.

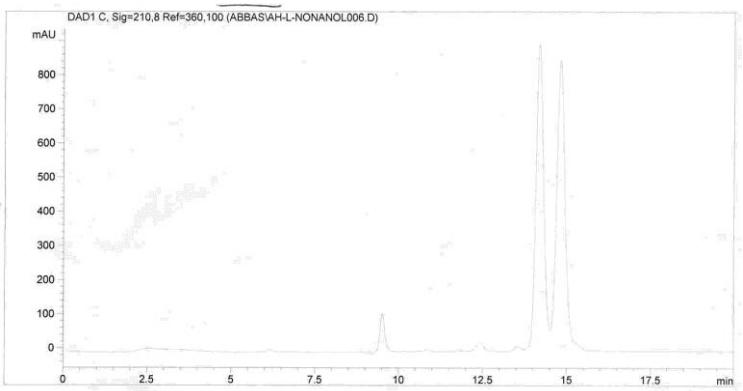
LRMS (CI) Calcd. for $C_{13}H_{23}0_2$ $[M+H]^+$: 211, Found: 211.

FTIR (neat): 2925, 2855, 1761, 1724, 1276, 1256, 1205, 1142, 1116, 1002 cm^{-1}.

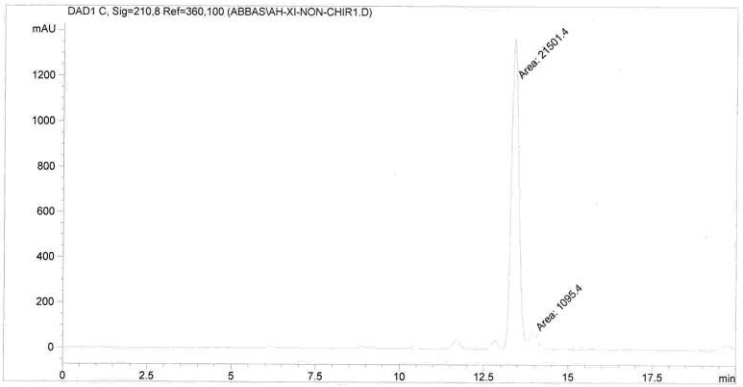
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 210 nm), t_{major} = 13.4 min, t_{minor} = 14.0 min; ee = 90%.





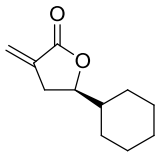


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.174	VV	0.2516	1.46039e4	898.75342	48.7419
2	14.802	VB	0.2739	1.53578e4	853.75470	51.2581



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.395	MF	0.2633	2.15014e4	1361.09631	95.1524
2	13.979	FM	0.2704	1095.40002	67.51331	4.8476

Synthesis of (*R*)-5-cyclohexyl-3-methylenedihydrofuran-2(3*H*)-one (2.9d).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8d** (22.8 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to furnish the title compound **2.9d** (26.3 mg, 0.146 mmol) as a white solid in 73% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexanes, 1:2).

[α]$_D^{23}$ = -34.2°.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (t, *J* = 2.8 Hz, 1H), 5.60 (t, *J* = 2.8 Hz, 1H), 4.24 (ddd (seen as broad quartet), *J* = 14.4, 7.2, 6.4 Hz, 1H), 2.95 (ddt, *J* = 17.2, 7.2, 2.8 Hz, 1H), 2.67 (ddt, *J* = 17.2, 6.4, 2.8 Hz, 1H), 1.92-1.88 (m, 1H), 1.78-1.61 (m, 4H), 1.53-1.48 (m, 1H), 1.26-1.00 (m, 5H).

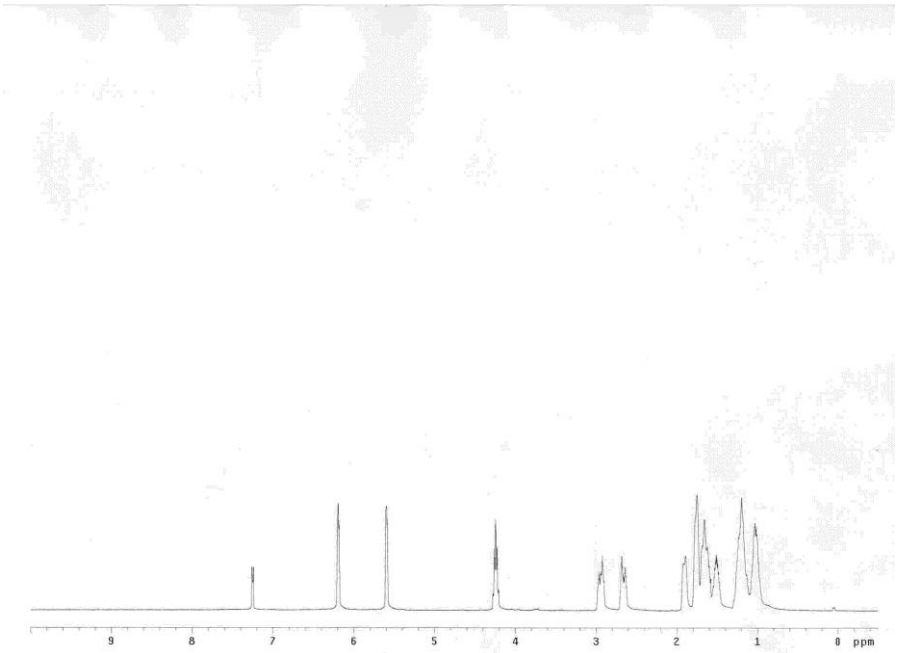
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 134.9, 121.6, 81.4, 43.0, 31.3, 28.1, 27.7, 26.2, 25.7, 25.5.

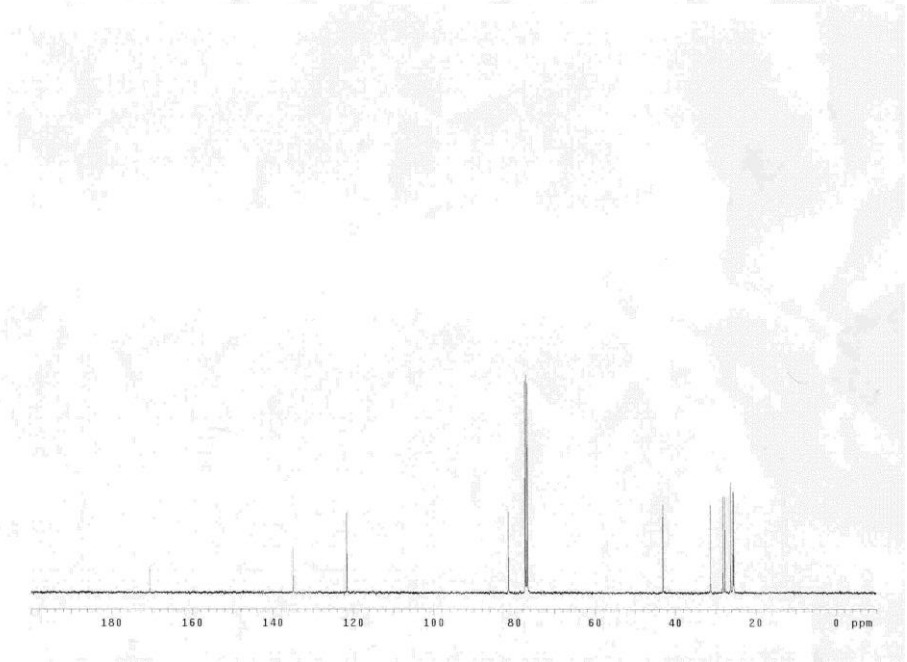
LRMS (CI) Calcd. for $C_{11}H_{16}0_2$ $[M+H]^+$: 181, Found: 181.

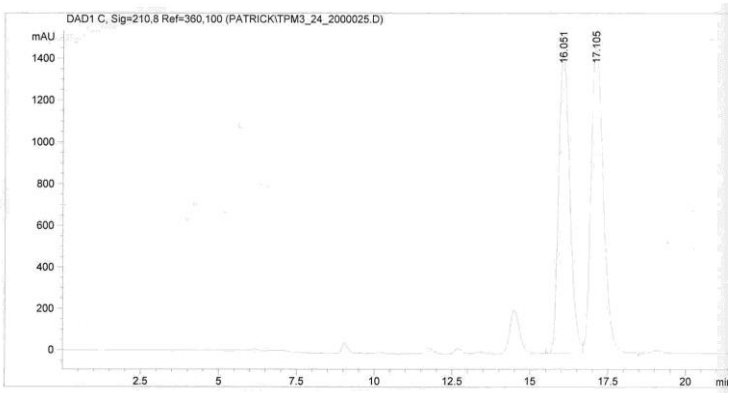
FTIR (neat): 2925, 2853, 1757, 1277, 1255, 1121, 1028, 993 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 210 nm), t_{major} = 16.1 min, t_{minor} = 17.1 min; ee = 95%.

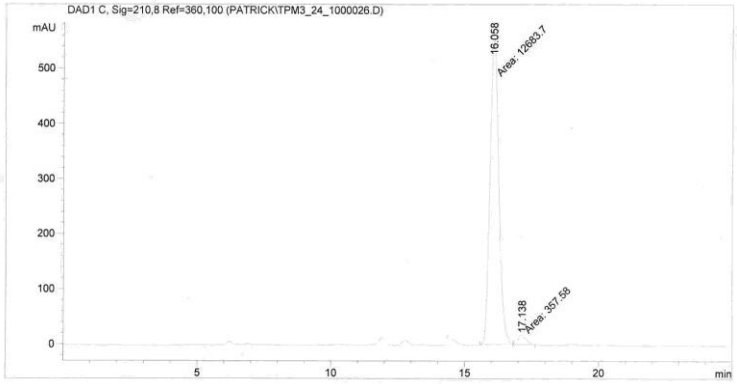
MP 56-58 °C.





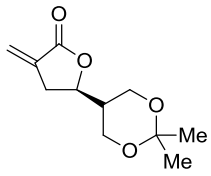


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.051	BV	0.3942	3.61041e4	1431.54822	47.1179
2	17.105	VB	0.4310	4.05209e4	1472.67725	52.8821



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.058	MM	0.3805	1.26837e4	555.61346	97.2581
2	17.138	MM	0.3783	357.57953	15.75177	2.7419

Synthesis of (*R*)-5-(2,2-dimethyl-1,3-dioxan-5-yl)-3-methylenedihydrofuran-2(3*H*)-one (2.9e).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8e** (29.2 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 2:3) to furnish the title compound **2.9e** (27.6 mg, 0.130 mmol) as a colorless oil in 65% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate:hexanes, 2:3).

$[\alpha]_D^{23}$ = -19.9°.

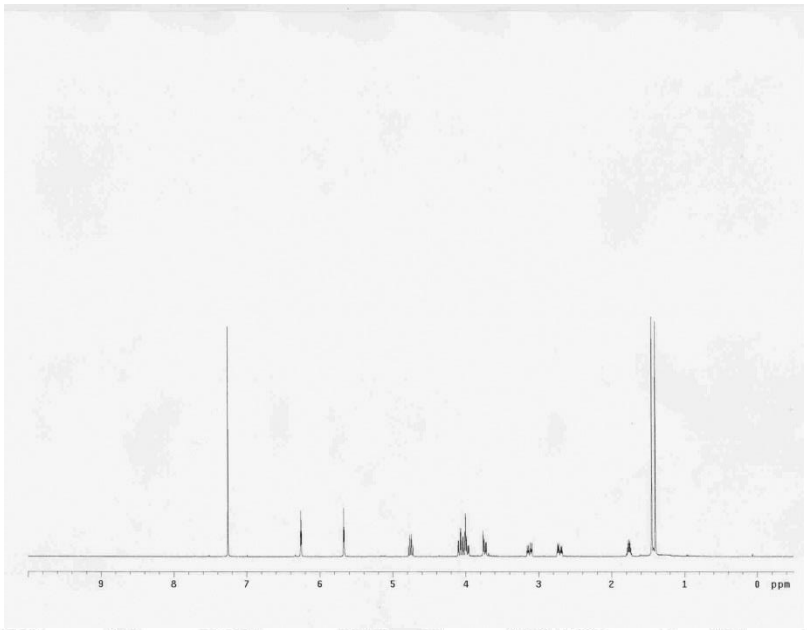
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (t, *J* = 2.6 Hz, 1H), 5.65 (t, *J* = 2.6 Hz, 1H), 4.73 (ddd (seen as broad quartet), *J* = 16.0, 8.0, 6.8 Hz, 1H), 4.10-3.96 (m, 3H), 3.76-3.72 (m, 1H), 3.10 (ddt, *J* = 17.2, 8.0, 2.6 Hz, 1H), 2.68 (ddt, *J* = 17.2, 6.8, 2.6 Hz, 1H), 1.80-1.73 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H).

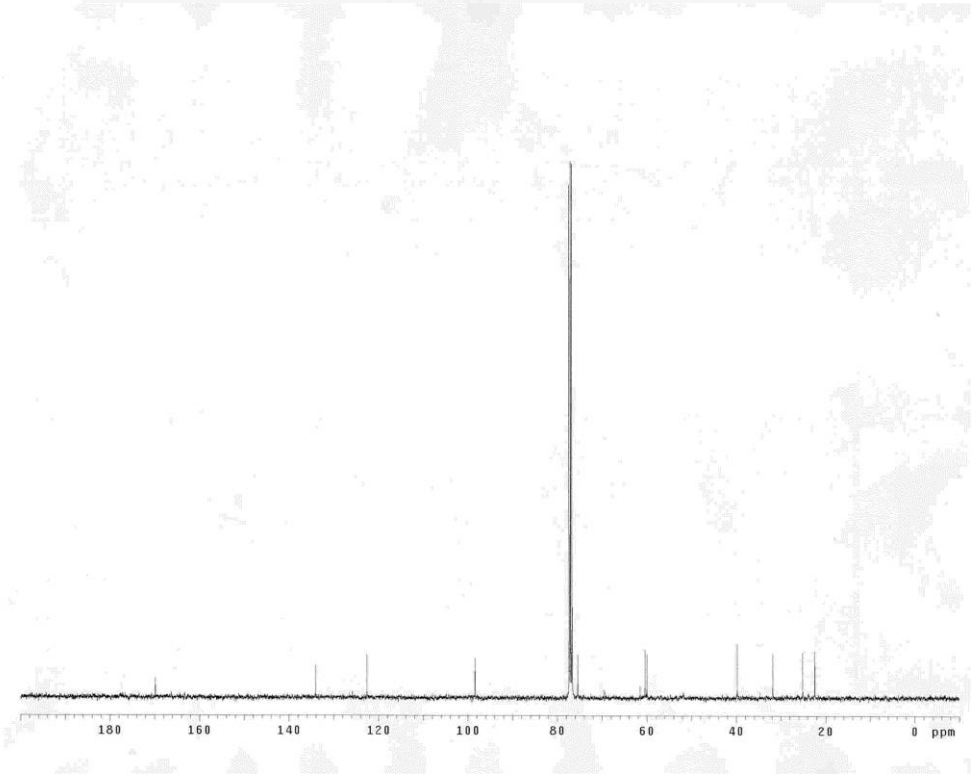
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 134.0, 122.6, 98.4, 75.4, 60.4, 60.0, 39.8, 31.9, 25.2, 22.4.

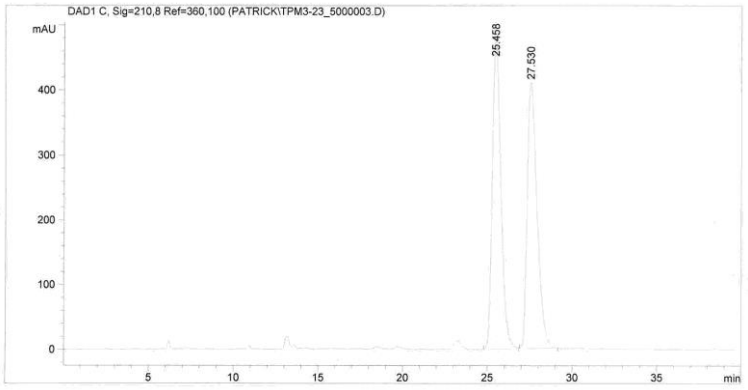
LRMS (CI) Calcd. for $C_{11}H_{17}O_4$ $[M+H]^+$: 213, Found: 213.

FTIR (neat): 2991, 1763, 1721, 1438, 1371, 1249, 1197, 1155, 1089, 1007, 826 cm^{-1}.

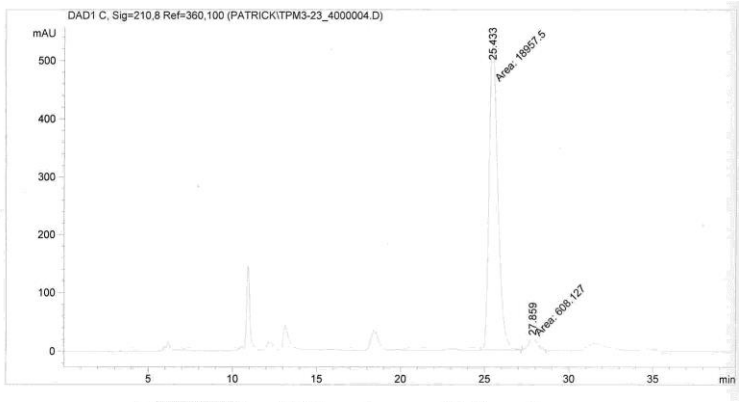
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 0.5 mL/min, 210 nm), t_{major} = 25.4 min, t_{minor} = 27.9 min; ee = 94%.


9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

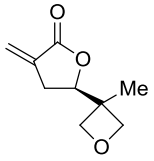


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.458	BB	0.5437	1.69546e4	478.15036	50.5888
2	27.530	BB	0.6085	1.65599e4	410.66696	49.4112



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.433	MM	0.5989	1.89575e4	527.55505	96.8919
2	27.859	MM	0.5450	608.12695	18.59683	3.1081

Synthesis of (*R*)-3-methylene-5-(3-methyloxetan-3-yl)dihydrofuran-2(3*H*)-one (2.9f).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8f** (20.4 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 2:3) to furnish the title compound **2.9f** (28.3 mg, 0.168 mmol) as a colorless oil in 84% yield.

TLC (SiO_2): R_f = 0.22 (ethyl acetate:hexanes, 2:3).

$[\alpha]_D^{23}$ = -24.9°.

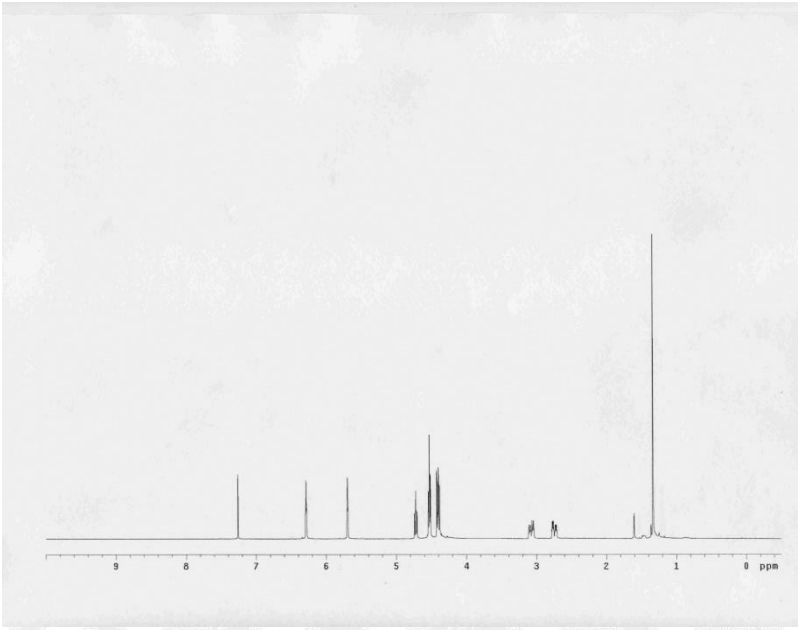
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (t, *J* = 2.8 Hz, 1H), 5.69 (t, *J* = 2.8 Hz, 1H), 4.70 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.40 (d, *J* = 6.4 Hz, 1H), 4.37 (d, *J* = 6.4 Hz, 1H), 3.06 (ddt, *J* = 17.4, 8.0, 2.8 Hz, 1H), 2.73 (ddt, *J* = 17.4, 6.4, 2.8 Hz, 1H), 1.33 (s, 3H).

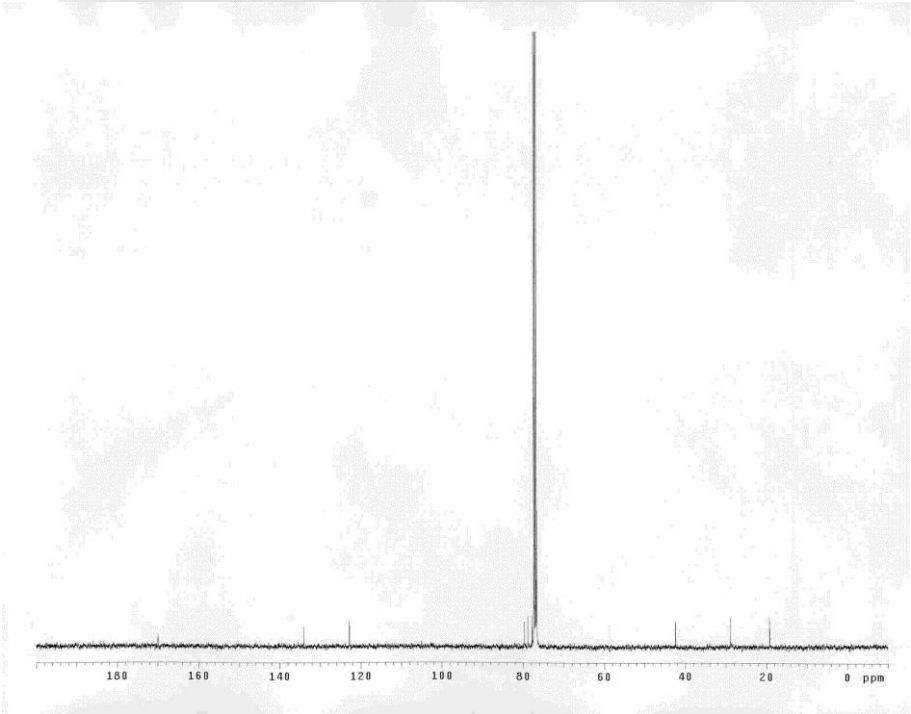
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 134.0, 122.8, 79.7, 78.8, 77.9, 42.4, 28.8, 19.2.

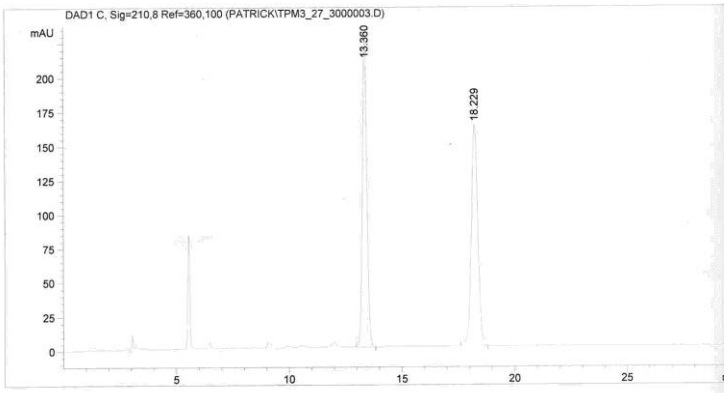
LRMS (CI) Calcd. for $C_9H_{12}O_3$ $[M+H]^+$: 189, Found: 169.

FTIR (neat): 2273, 1761, 1724, 1333, 1282, 1253, 1197, 1125, 1039, 1007, 980, 815 cm^{-1}.

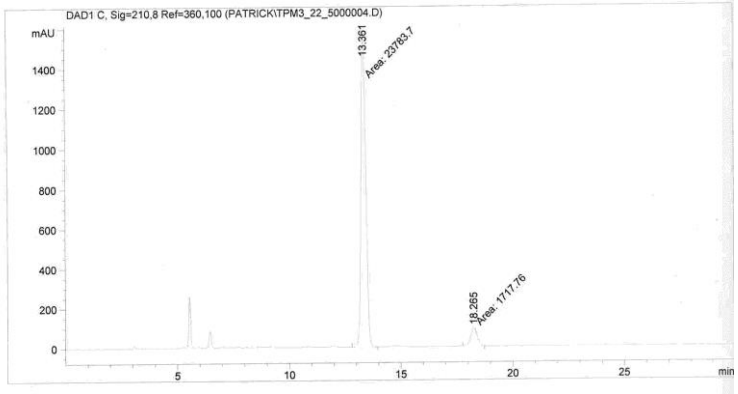
HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 13.4 min, t_{minor} = 18.3 min; ee = 87%.





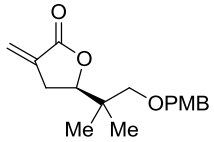


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.360	BB	0.2200	3189.02686	224.08011	49.6979
2	18.229	BB	0.3084	3227.80029	162.06041	50.3021



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.361	MM	0.2568	2.37837e4	1543.58215	93.2641
2	18.265	MM	0.3177	1717.75537	90.12621	6.7359

Synthesis of (*R*)-5-(1-((4-methoxybenzyl)oxy)-2-methylpropan-2-yl)-3-methylenedihydrofuran-2(3*H*)-one (2.9g).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat VI** (11.7 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.4 mL, 0.5 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8g** (44.9 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 48 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to furnish the title compound **2.9g** (52.3 mg, 0.180 mmol) as a colorless oil in 90% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes,1:4).

[α]$_D^{23}$ = -17.9°.

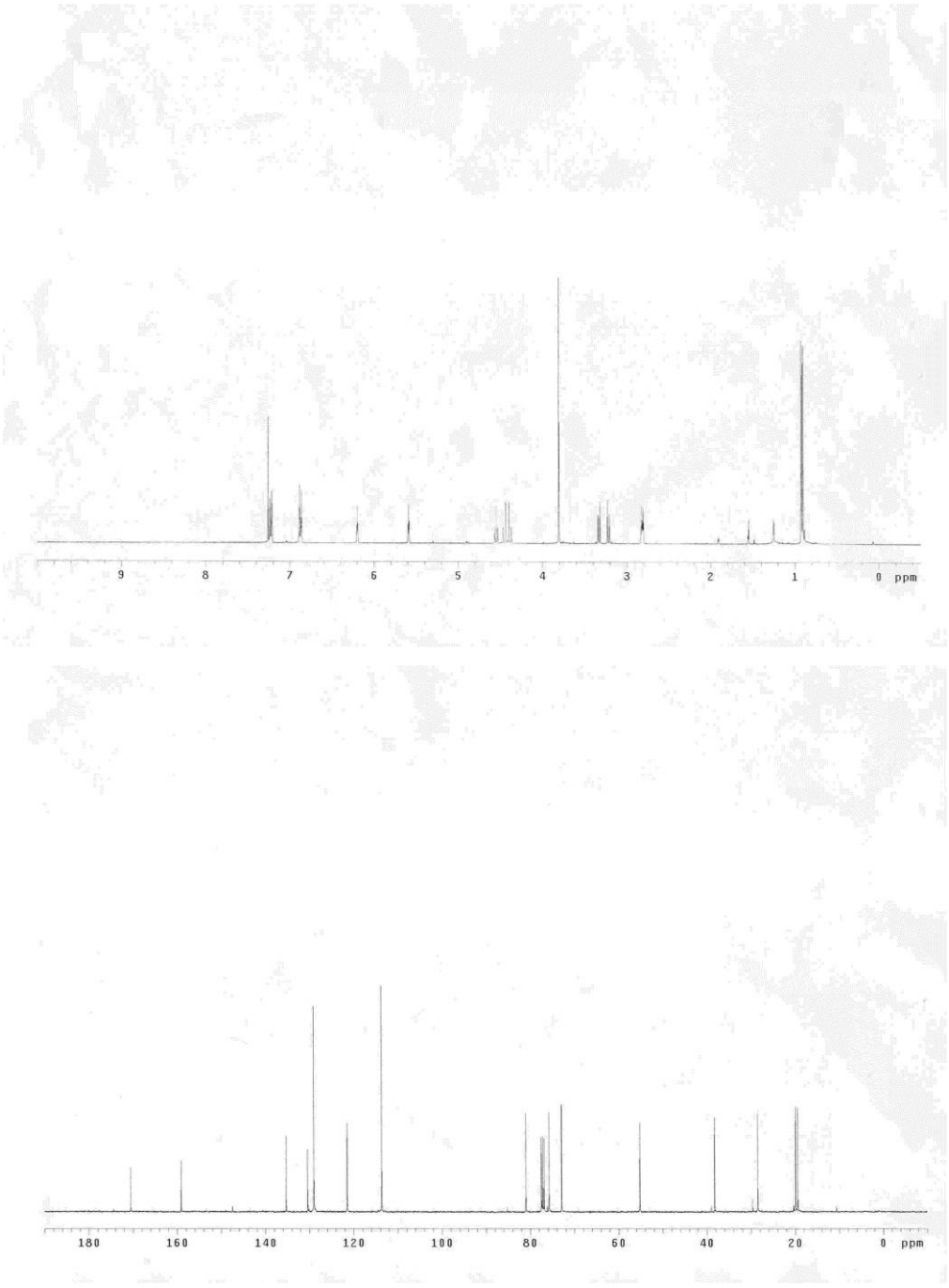
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.20 (t, *J* = 2.6 Hz, 1H), 5.59 (t, *J* = 2.6 Hz, 1H), 4.55 (dd, *J* = 7.6 Hz, 1H), 4.46-4.37 (m, 2H), 3.81 (s, 3H), 3.34-3.32 (m, 1H), 3.23-3.21 (m, 1H), 2.82 (dt, *J* = 7.2, 2.8 Hz, 2H), 0.92 (d, *J* = 7.6 Hz, 6H).

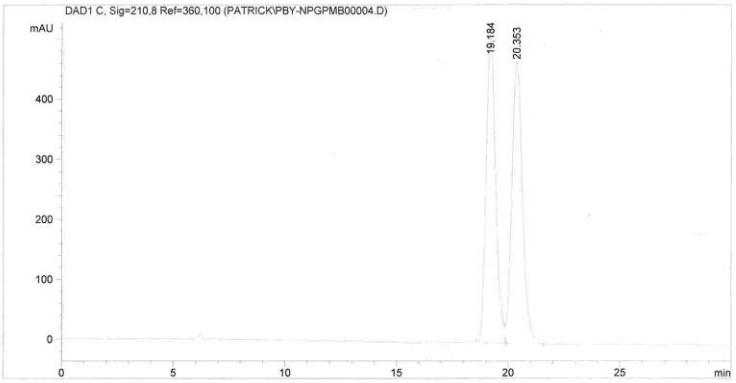
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 158.9, 135.1, 130.2, 128.8, 121.3, 113.5, 80.809, 75.6, 72.8, 54.9, 38.0, 28.3, 19.7, 19.2.

LRMS (CI) Calcd. for $C_{17}H_{21}0_4Na$ $[M-H+Na]^+$: 313, Found: 313.

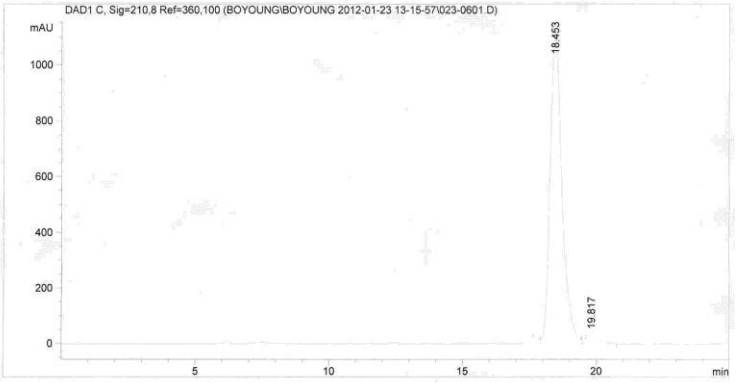
FTIR (neat): 2962, 1758, 1611, 1512, 1465, 1399, 1366, 1338, 1301, 1279, 1246, 1172, 1131, 1091, 1033, 998, 935, 814, 754 cm^{-1}.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 18.5 min, t_{minor} = 19.8 min; ee = 92%.



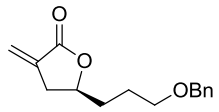


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.184	VV	0.4582	1.51236e4	509.63657	49.5449
2	20.353	VB	0.5056	1.54014e4	468.45010	50.4551



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.453	VV	0.4755	3.44768e4	1100.43677	96.0874
2	19.817	VB	0.4967	1403.85706	41.92266	3.9126

Synthesis of (*S*)-5-(3-(benzyloxy)propyl)-3-methylenedihydrofuran-2(3*H*)-one (2.9h).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.8h** (36.0 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to furnish the title compound **2.9h** (33.0 mg, 0.134 mmol) as a colorless oil in 67% yield.

TLC (SiO_2): R_f = 0.31 (ethyl acetate:hexanes, 1:4).

[α]$_D^{23}$ = -10.5°.

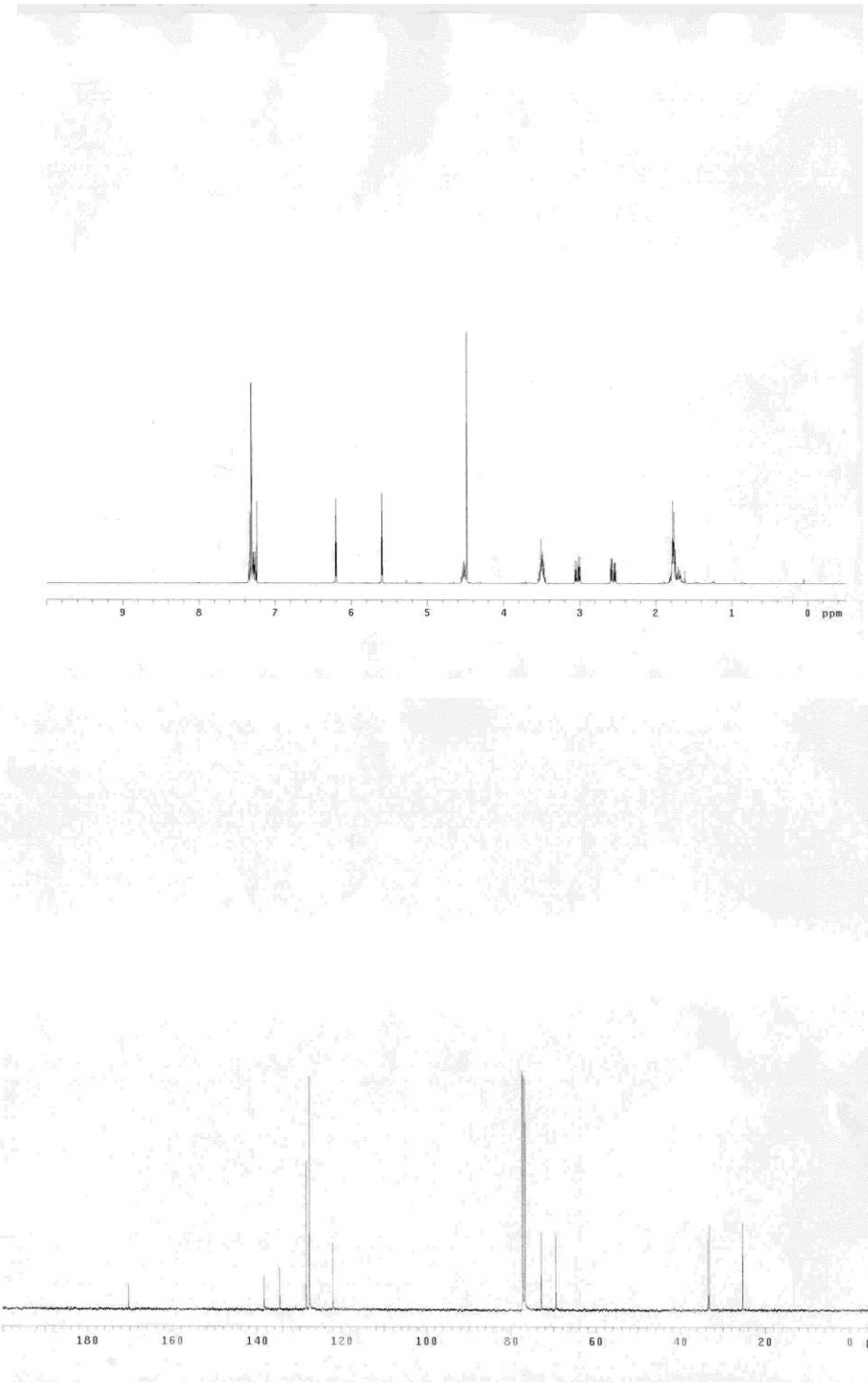
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 6.22 (t, *J* = 2.8 Hz, 1H), 5.61 (t, *J* = 2.8 Hz, 1H), 4.57-4.48 (m, 3H), 3.56-3.47 (m, 2H), 3.05 (ddt, *J* = 17.2, 7.6, 2.8 Hz, 1H), 2.58 (ddt, *J* = 17.2, 6.4, 2.8 Hz, 1H), 1.84-1.67 (m, 4H).

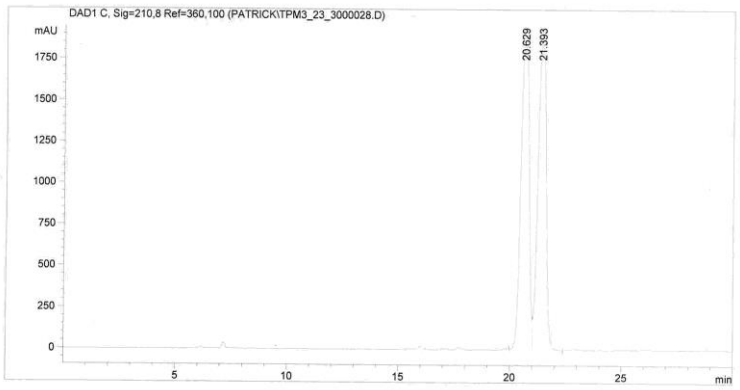
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 138.3, 134.6, 128.4, 127.6, 122.0, 72.9, 69.5, 33.5, 33.2, 25.3.

LRMS (CI) Calcd. for $C_{15}H_{19}0_3$ $[M+H]^+$: 247, Found: 247.

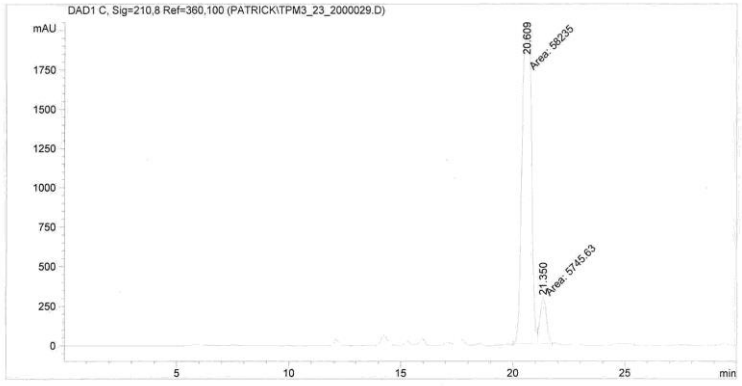
FTIR (neat): 2945, 1759, 1454, 1364, 1276, 1229, 1216, 1203, 1100, 1000, 729, 698 cm^{-1}.

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 93:7, 0.5 mL/min, 210 nm), t_{major} = 20.6 min, t_{minor} = 21.4 min; ee = 82%.



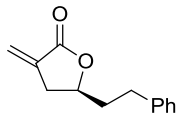


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.629	VV	0.4156	4.81535e4	1850.64539	50.1648
2	21.393	VB	0.4143	4.78370e4	1846.00513	49.8352



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.609	MM	0.4999	5.82350e4	1941.64966	91.0197
2	21.350	MM	0.3312	5745.62842	289.13873	8.9803

Synthesis of (*S*)-3-methylene-5-phenethyldihydrofuran-2(3*H*)-one (2.9i).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat IV** (10.2 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.2 mL, 1.0 M with respect to the alcohol), acetonitrile (0.2 mL, 1.0 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), and alcohol **2.1i** (27.2 mg, 0.2 mmol, 1.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 72 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to furnish the title compound **2.9i** (23.1 mg, 0.114 mmol) as a colorless oil in 57% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

[α]$_D^{23}$ = -33.3° (accepted **[α]$_D^{25}$**=-31.5°)[3] both in $CHCl_3$.

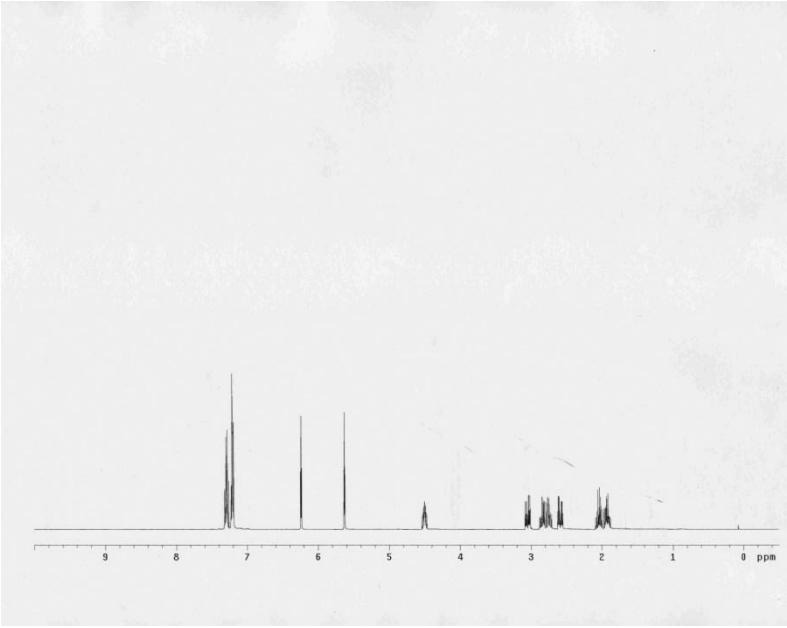
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 6.24 (t, *J* = 2.8 Hz, 1H), 5.63 (t, *J* = 2.8 Hz, 1H), 4.54-4.47 (m, 1H), 3.05 (ddt, *J* = 17.0, 7.6, 2.8 Hz, 1H), 2.88-2.71 (m, 2H), 2.59 (ddt, *J* = 17.0, 6.0, 2.8 Hz, 1H), 2.09-1.88 (m, 2H).

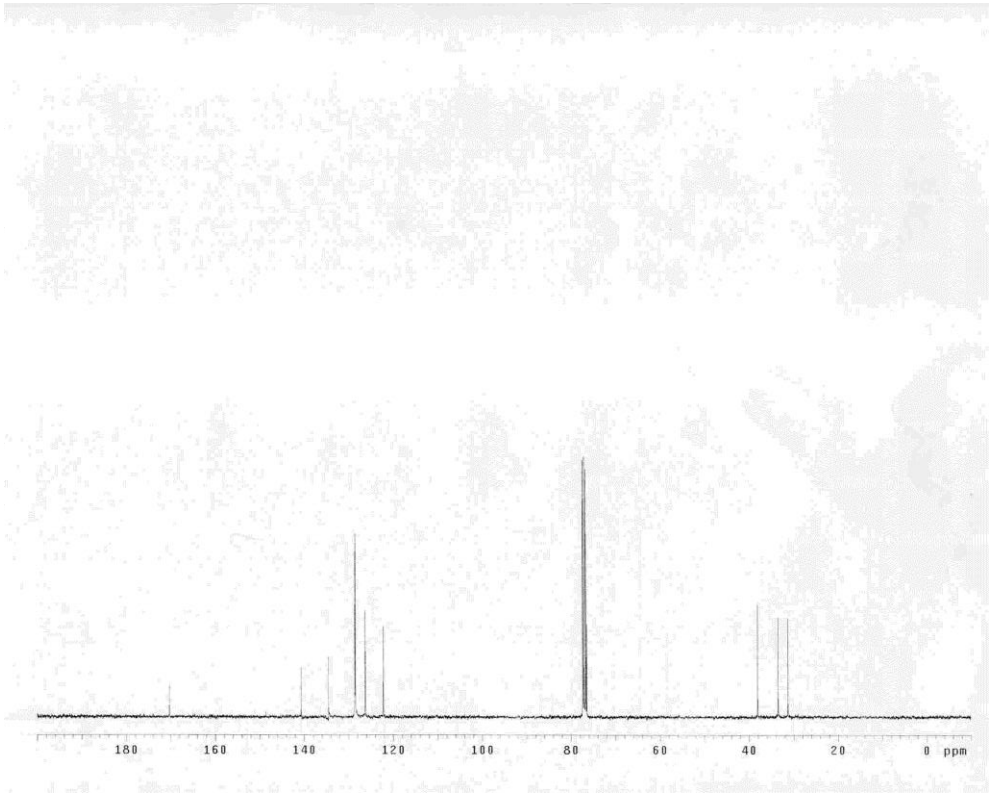
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 140.6, 134.5, 128.5, 128.4, 126.1, 122.2, 76.5, 38.0, 33.5, 31.3.

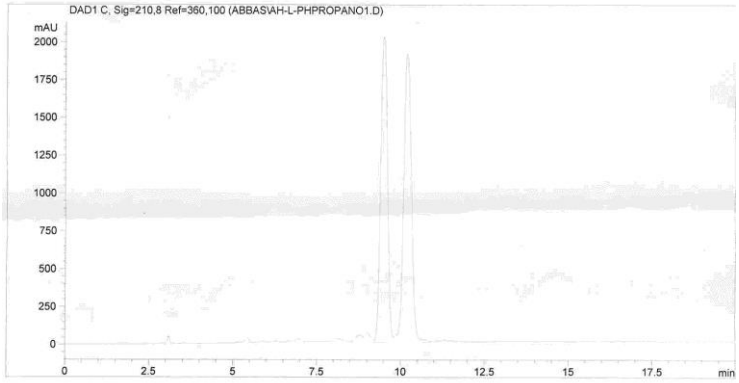
LRMS (CI) Calcd. for $C_{13}H_{15}0_2$ $[M+H]^+$: 203, Found: 203.

FTIR (neat): 2929, 1756, 1454, 1398, 1352, 1276, 1163, 1126, 1023, 936, 813, 751, 700 cm^{-1}.

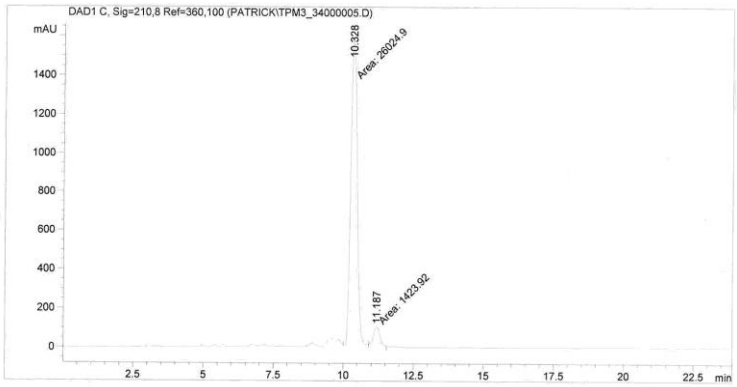
HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 210 nm), t_{major} = 10.3 min, t_{minor} = 11.2 min; ee = 90%.







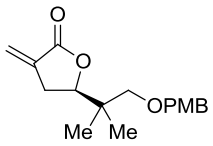
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.481	VV	0.2287	2.88169e4	2017.09143	48.2711
2	10.178	VV	0.2545	3.08811e4	1911.36707	51.7289



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.328	MM	0.2744	2.60249e4	1580.74524	94.8125
2	11.187	MM	0.2467	1423.91785	96.18800	5.1875

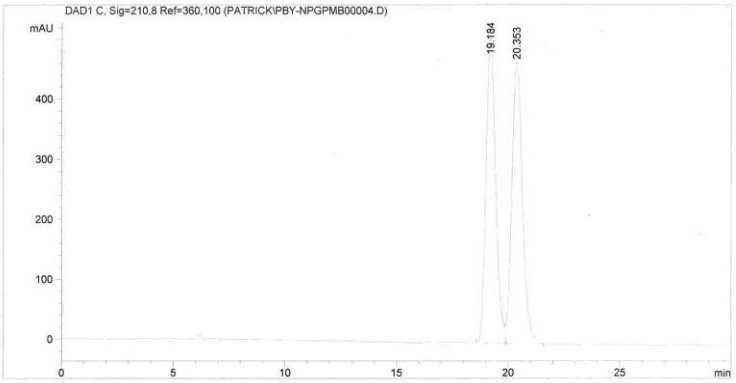
Experimental Using Aldehyde 2.11g

Synthesis of (*R*)-5-(1-((4-methoxybenzyl)oxy)-2-methylpropan-2-yl)-3-methylenedihydrofuran-2(3*H*)-one (2.9g).

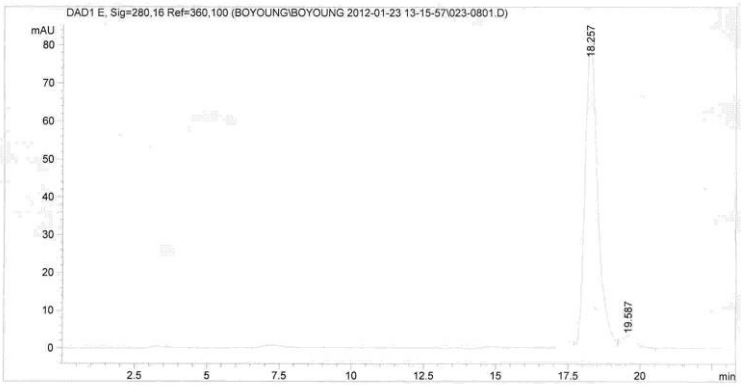


To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added **Cat VI** (11.7 mg, 0.01 mmol, 5 mol %) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with argon. Tetrahydrofuran (0.4 mL, 0.5 M with respect to the alcohol), acrylic ester **2.7** (86.5 mg, 0.4 mmol, 2.0 equiv.), aldehyde **2.11g** (44.9 mg, 0.2 mmol, 1.0 equiv.), and isopropyl alcohol (24.0 mg, 0.4 mmol, 2.0 equiv.) were added to the purged tube, and the rubber septum was quickly replaced with a screw cap. The reaction mixture was heated in an oil bath at 80 °C for 48 hours, at which point it was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to furnish the title compound **2.9g** (52.3 mg, 0.18 mmol) as a colorless oil in 75% yield.

HPLC (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 18.5 min, t_{minor} = 19.8 min; ee = 91%.



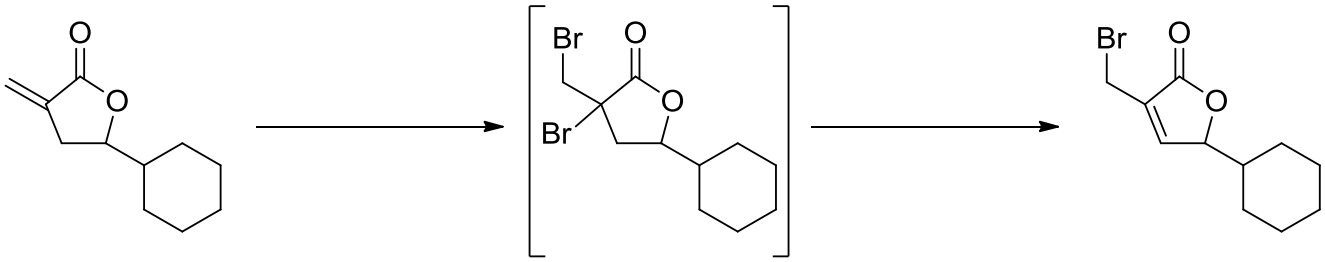
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.184	VV	0.4582	1.51236e4	509.63657	49.5449
2	20.353	VB	0.5056	1.54014e4	468.45010	50.4551



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.257	VB	0.4634	2500.07837	81.15117	96.0837
2	19.587	BB	0.4518	101.90097	3.03404	3.9163

Elaboration of Lactone 2.9d.

Synthesis of (S)-3-(bromomethyl)-5-cyclohexylfuran-2(5H)-one (2.12)

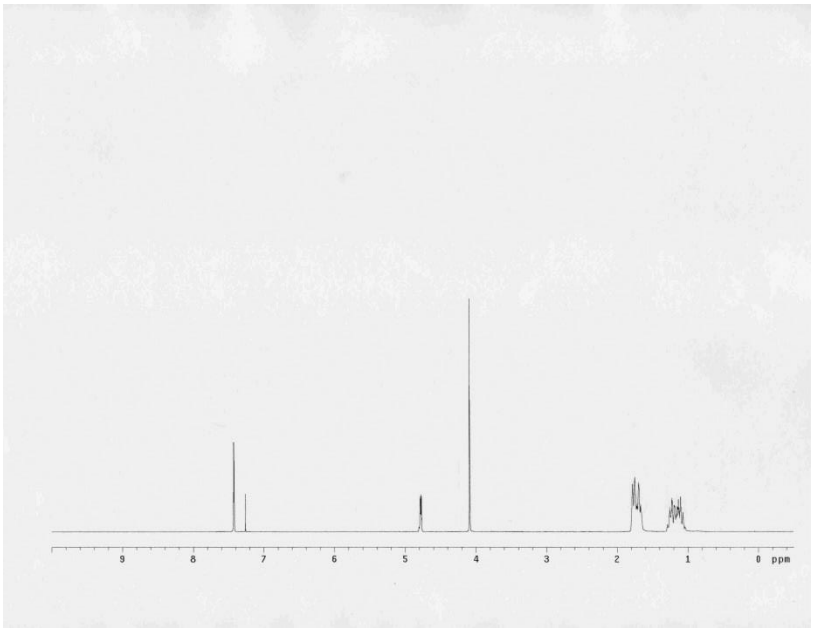


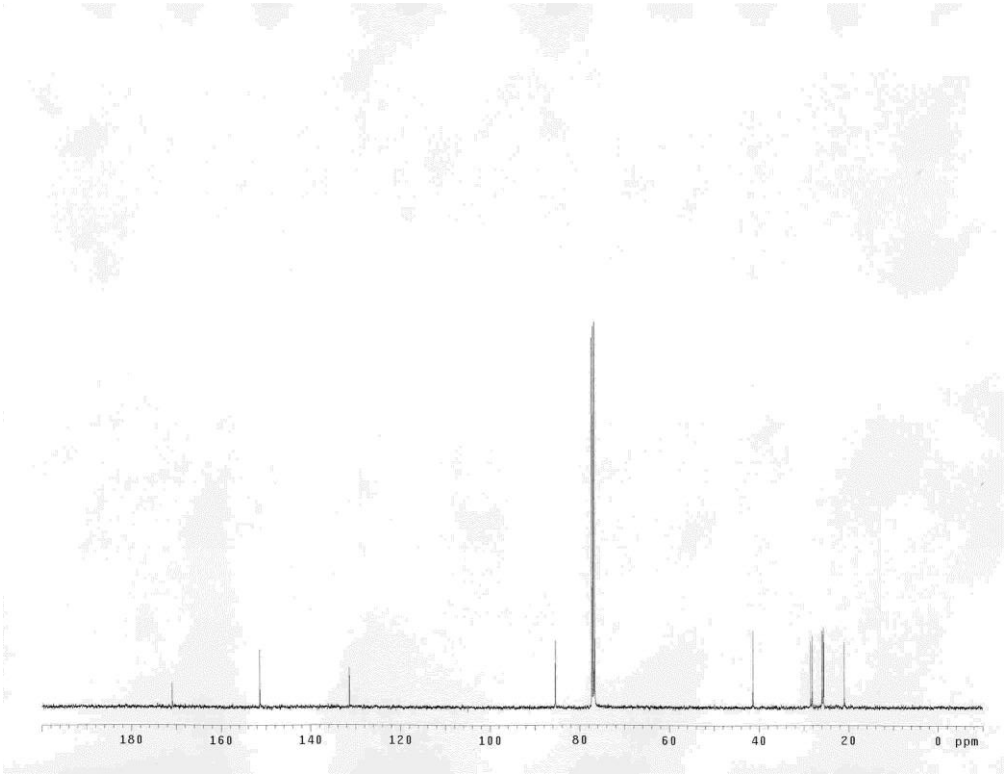
To an oven-dried round-bottom flask equipped with a magnetic stir bar were added butyrolactone *rac*-**2.9d** (138.1 mg, 0.77 mmol, 1.0 equiv.) and anhydrous sodium acetate (95.2 mg, 1.16 mmol, 1.5 equiv.). The round-bottom flask was sealed with a rubber septum and purged with argon. Dichloromethane (10.5 mL, 0.073 M with respect to *rac*-**2.9d**) was added to the round-bottom flask, and the flask was cooled to 0 °C in an ice bath. Bromine (135.3 mg, 0.847 mmol, 1.1 equiv.) dissolved in dichloromethane (0.25 mL, 3.4 M with respect to bromine) was added to the reaction mixture over 10 minutes. The round-bottom flask was allowed to warm to room temperature and stir for 3 hours. The reaction was quenched with saturated sodium thiosulfate (aq.) and washed with water. The organic extract was dried ($MgSO_4$) and concentrated. The dibromo-butyrolactone product was used without further purification.

To an oven-dried round-bottom flask equipped with a magnetic stir bar were added anhydrous lithium carbonate (284.5 mg, 3.85 mmol, 5.0 equiv.) and anhydrous lithium bromide (334.4 mg, 3.85 mmol, 5.0 equiv.). The round-bottom flask was sealed with a rubber septum and purged with argon. A solution of crude dibromo-lactone (0.77 mmol) in *N*,*N*-dimethylformamide (2.6 mL, 0.3 M

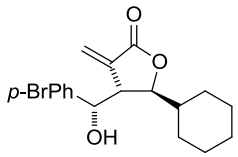
with respect to the dibromo-lactone) was added to the round-bottom flask. The reaction mixture was stirred at 60 °C for 15 hours. Upon completion of the reaction as determine by TLC analysis, the reaction was quenched with water and extracted with ethyl acetate 3 times. The organic extracts were combined, dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to furnish the title compound **2.12** (107.8 mg, 0.416 mmol) as a white solid in 54% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:3).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.77-4.75 (m, 1H), 4.08-4.07 (m, 2H), 1.70-1.64 (m, 6H), 1.25-1.06 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 151.4, 131.3, 85.4, 41.3, 28.5, 28.1, 26.0, 25.7, 25.6, 21.0.
LRMS (CI) Calcd. for $C_{11}H_{15}O_2$ $[M-Br]^+$: 179, Found: 179.
FTIR (neat): 2926, 2853, 1751, 1450, 1229, 1069, 1026, 980, 791 cm^{-1}.
MP 70-72 °C.


9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of (4S,5S)-4-((S)-(4-bromophenyl)(hydroxy)methyl)-5-cyclohexyl-3-methylenedihydrofuran-2(3H)-one (2.13a).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added bromo-lactone **2.12** (25.9 mg, 0.1 mmol, 1.0 equiv.), zinc dust <10 µm (7.72 mg, 0.118 mmol, 1.18 equiv.), and *p*-bromobenzaldehyde **2.5a** (18.9 mg, 0.1 mmol, 1.0 equiv.). The tube was sealed with a rubber septum and purged with argon. *N*,*N*-dimethylformamide (0.2 mL, 0.5 M with respect to bromo-lactone **2.12**) and ammonium chloride (10 µL, saturated aqueous solution) were added to the purged tube, and the septum was quickly replaced with a screw cap. The reaction mixture was stirred for 15 hours at room temperature. Upon completion of the reaction as determine by TLC analysis, the reaction mixture was quenched with ammonium chloride (1 mL, saturated aqueous solution), diluted with water, and extracted with ethyl acetate 3 times. The organic extracts were combined, dried with sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:2) to furnish the title compound **2.13a** (32.5 mg, 0.089 mmol) as a colorless oil in 89% yield and 10:1 *dr*.

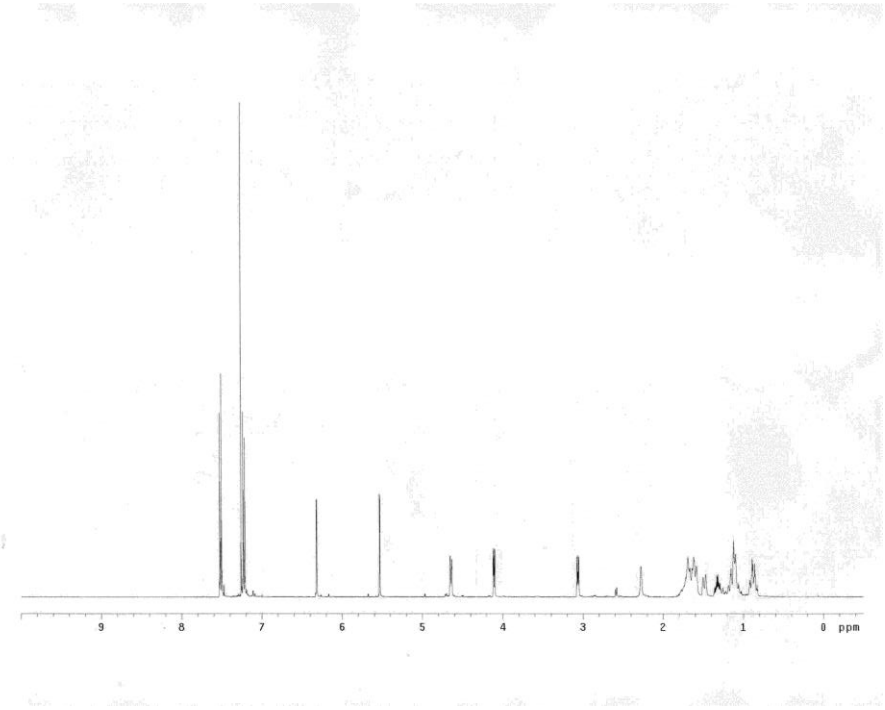
TLC (SiO_2): R_f = 0.41(ethyl acetate:hexanes, 1:2).

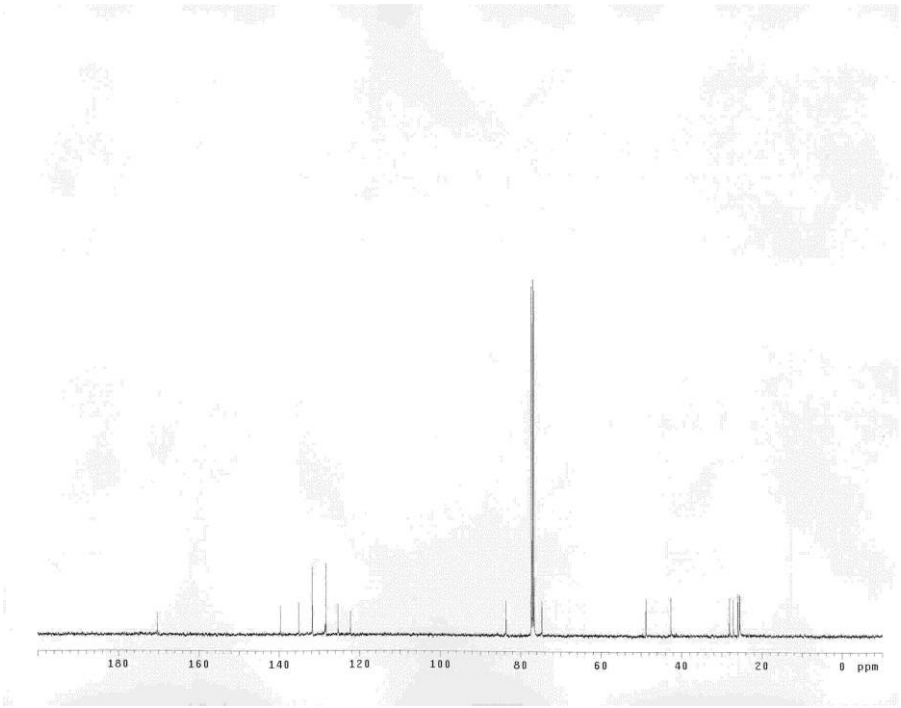
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 1.8 Hz, 1H), 5.48 (d, *J* = 1.8 Hz, 1H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.09 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.05-3.02 (m, 1H), 2.51-2.50 (br, 1H), 1.69-1.56 (m, 4H), 1.46 (d, *J* = 12.8 Hz, 1H), 1.34-1.29 (m, 1H), 1.36-1.07 (m, 3H), 0.90-0.83 (m, 2H).

^{13}C NMR (100 MHz, CDCl3): δ 170.2, 139.6, 135.1, 131.7, 128.3, 125.3, 122.3, 83.6, 74.7, 48.8, 42.6, 28.1, 27.1, 26.0, 25.6, 25.5.

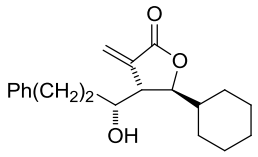
LRMS (CI) Calcd. for $C_{18}H_{22}BrO_3$ $[M+H]^+$: 366, Found: 366.

FTIR (neat): 3450, 2923, 2853, 1742, 1487, 1450, 1273, 1134, 1070, 1010, 819 cm^{-1}.




180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of (4S,5S)-5-cyclohexyl-4-((R)-1-hydroxy-3-phenylpropyl)-3-methylenedihydrofuran-2(3H)-one (2.13b).



To a resealable pressure tube (13x100 mm) equipped with a magnetic stir bar were added bromo-lactone **2.12** (25.9 mg, 0.1 mmol, 1.0 equiv.) and zinc dust <10 μm (7.72 mg, 0.118 mmol, 1.18 equiv.). The tube was sealed with a rubber septum and purged with argon. *N*,*N*-dimethylformamide (0.2 mL, 0.5 M with respect to bromo-lactone **2.12**), ammonium chloride (10 μL, saturated aqueous solution), and 3-phenylpropanal **2.5i** (13.4 mg, 0.1 mmol, 1.0 equiv.) were added to the purged tube, and the septum was quickly replaced with a screw cap. The reaction mixture was stirred for 15 hours at room temperature. Upon completion of the reaction as determine by TLC analysis, the reaction mixture was quenched with ammonium chloride (1 mL, saturated aqueous solution), diluted with water, and extracted with ethyl acetate 3 times. The organic extracts were combined, dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:2) to furnish the title compound **2.13b** (29.1 mg, 0.093 mmol) as a colorless oil in 93% yield and 5:1 *dr*.

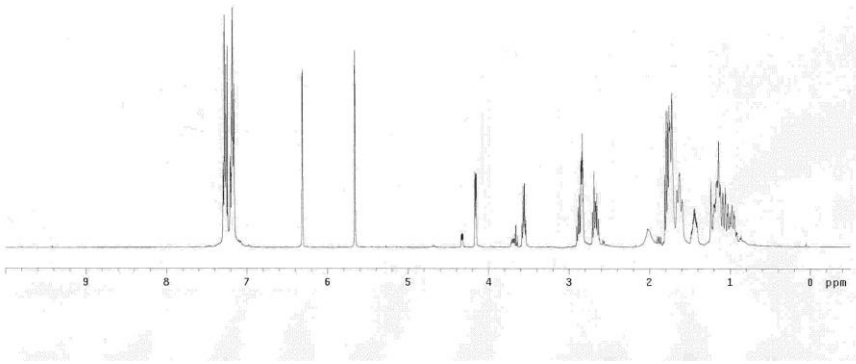
TLC (SiO_2): R_f = 0.41 (ethyl acetate:hexanes, 1:2).

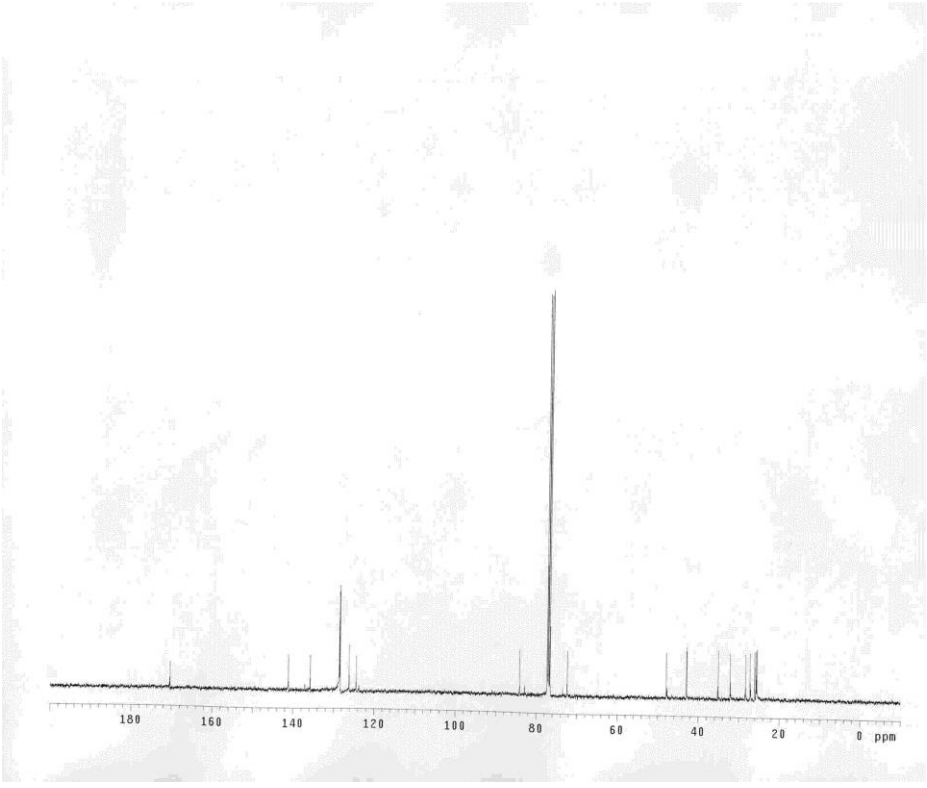
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.20-7.16(m, 3H), 6.31 (d, *J* = 1.8 Hz, 1H), 5.66 (d, *J* = 1.8 Hz, 1H), 4.16 (dd, *J* = 5.6, 2.0 Hz, 1H), 3.56 (ddd (seen as broad quartet), *J* = 12.4, 6.0, 6.0 Hz, 1H), 2.90-2.82 (m, 2H), 2.71-2.63 (m, 1H), 1.81-1.72 (m, 6H), 1.66-1.60 (m, 2H), 1.47-1.41 (m, 1H), 1.24-0.94 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.34, 141.1, 135.7, 128.6, 128.4, 126.2, 124.4, 84.1, 72.4, 47.9, 42.9, 35.1, 32.2, 28.3, 27.2, 26.1, 25.7, 25.6.

LRMS (CI) Calcd. for $C_{20}H_{27}O_3$ $[M+H]^+$: 315, Found: 315.

FTIR (neat): 3443, 2926, 2853, 1743, 1496, 1451, 1273, 1133, 1030, 747, 700 cm^{-1}.


9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Chapter 3: The Formation of CF_3-Bearing All-Carbon Quaternary Centers *via* Ruthenium Catalyzed Couplings of Allenes and Paraformaldehyde[*]

3.1 Introduction

The formation of all-carbon quaternary centers has received significant attention in organic synthesis, largely through the construction of steroids and other biologically active natural products, which contain all-carbon quaternary centers in their structures. Recently, methods for the formation of all-carbon quaternary centers have been reported utilizing transition metal catalysis and hydrogen auto-transfer conditions to enforce the coupling between 1,1-disubstituted allenes and primary alcohols or aldehydes (Scheme 3.1).[1–8] Further, the methods for alcohol mediated reductive coupling of allenes and paraformaldehyde[2] offer an alternative to traditional diene hydroformylation,[9–13] since regioselectivity is often an issue in the hydroformylation of compounds with more than one unit of unsaturation.[14–21]

As previously mentioned, organofluorine chemistry has greatly impacted the realm of both the pharmaceutical and agrochemical industry.[22,23] Hence, methods for the incorporation of fluorine or fluorine containing functional groups have been developed.[24–34] Despite many efforts, there are limited ways to form all-carbon quaternary centers which contain a trifluoromethyl group.[35–39] Henceforth investigations into the formation of homoallylic alcohols containing a trifluoromethyl substituted all-carbon quaternary center by way of transition metal-catalyzed reductive coupling of paraformaldehyde with 1-aryl-1-trifluoromethylallenes commenced.[40]

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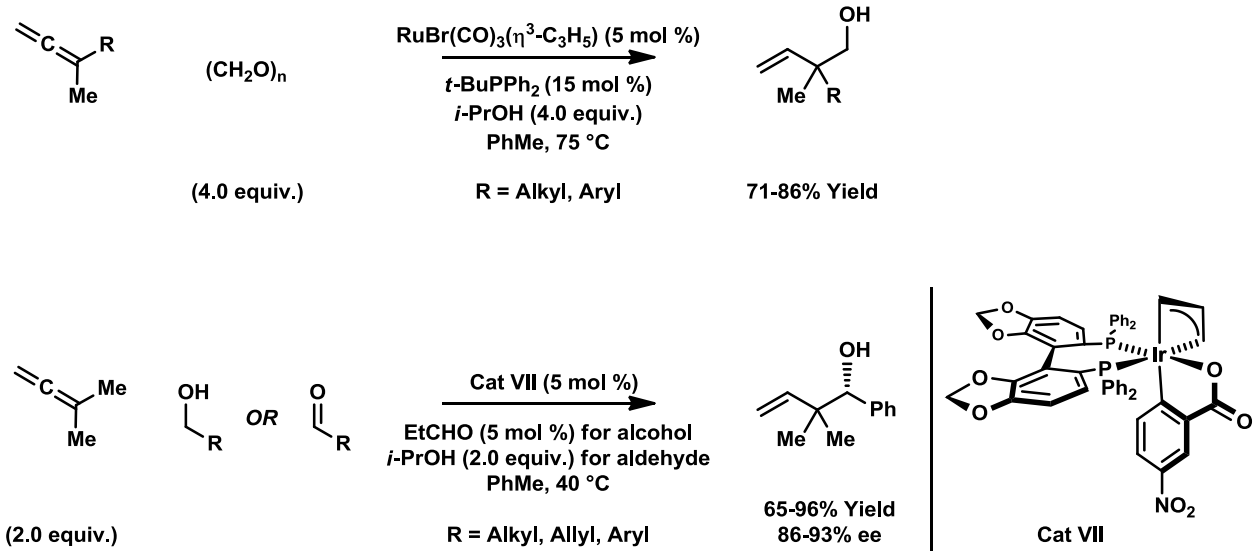
[*]Sam, B.; Montgomery, T. P.; Krische, M. J. *Org. Lett.* **2013**, *15* (14), 3790. Acknowledgement is made to B. S. for reaction discovery, development, scope evaluation and product elaboration and M. J. K. for supervision.

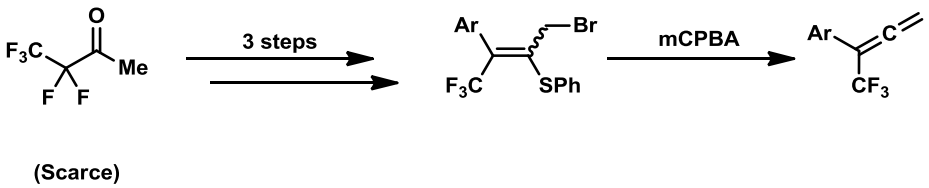
Scheme 3.1. Select examples of allene couplings with carbonyl groups mediated by hydrogen auto-transfer.



3.2 Synthesis of CF_3-Containing Allenes

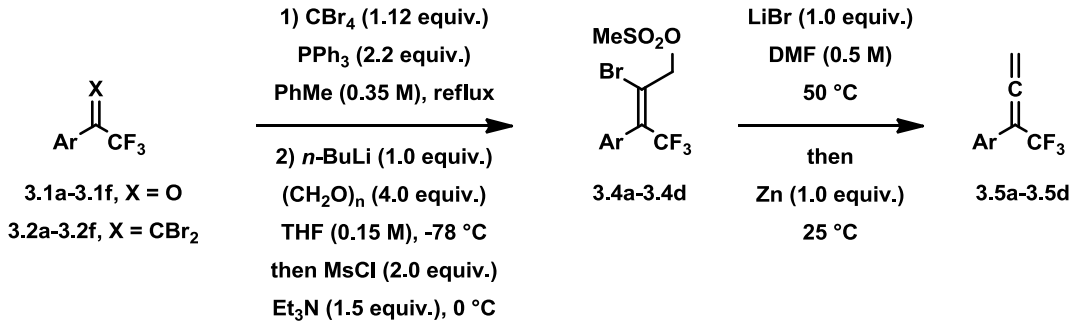
Studies in the coupling of paraformaldehyde with 1-aryl-1-trifluoromethylallenes first required a method to synthesize the desired allenes. Synthesis involving substitution on propargyl leaving groups with a trifluoromethyl nucleophile are reported,[41–43] but these methods do not allow for the formation of aryl substituted allenes. Also, syntheses which introduce the trifluoromethyl group at an early stage can be found (Scheme 3.2); however, the starting materials for these methods were not readily available.[44–46]

Scheme 3.2. Known route to 1-aryl-1-trifluoromethylallenes.

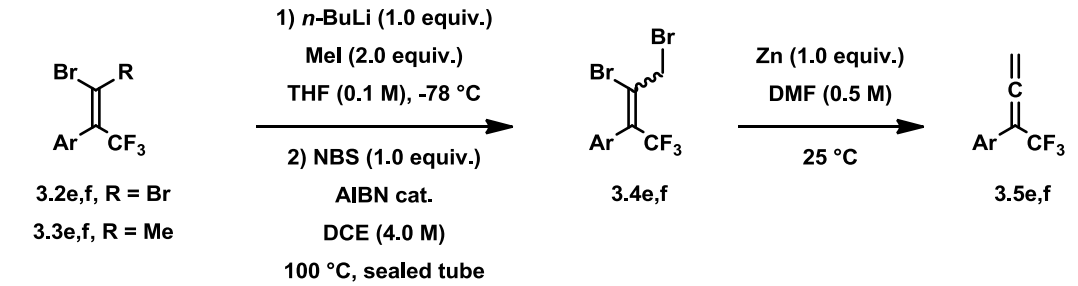


Classical approaches for allene synthesis, such as the Doering-LaFlamme method,[47] were unsuccessful, thus an effective route for the synthesis of 1-aryl-1-trfluoromethyl allenes required development (Figure 3.1).

Figure 3.1. Synthetic routes to 1-aryl-1-trifluoromethylallenes.



aryl group	3.2a-3.2f, Yield	3.4a-3.4d, Yield	3.5a-3.5d, Yield
3.1a, Ar = C_6H_5	3.2a, 81%	3.4a, 49%	3.5a, 78%
3.1b, Ar = 3-MeC_6H_4	3.2b, 82%	3.4b, 37%	3.5b, 86%
3.1c, Ar = 4-$MeOC_6H_4$	3.2c, 91%	3.4c, 48%	3.5c, 72%
3.1d, Ar = 2-napthyl	3.2d, 84%	3.4d, 38%	3.5d, 77%
3.1e, Ar = 3,5-$Cl_2C_6H_3$	3.2e, 82%		
3.1f, Ar = 4-ClC_6H_4	3.2f, 84%		



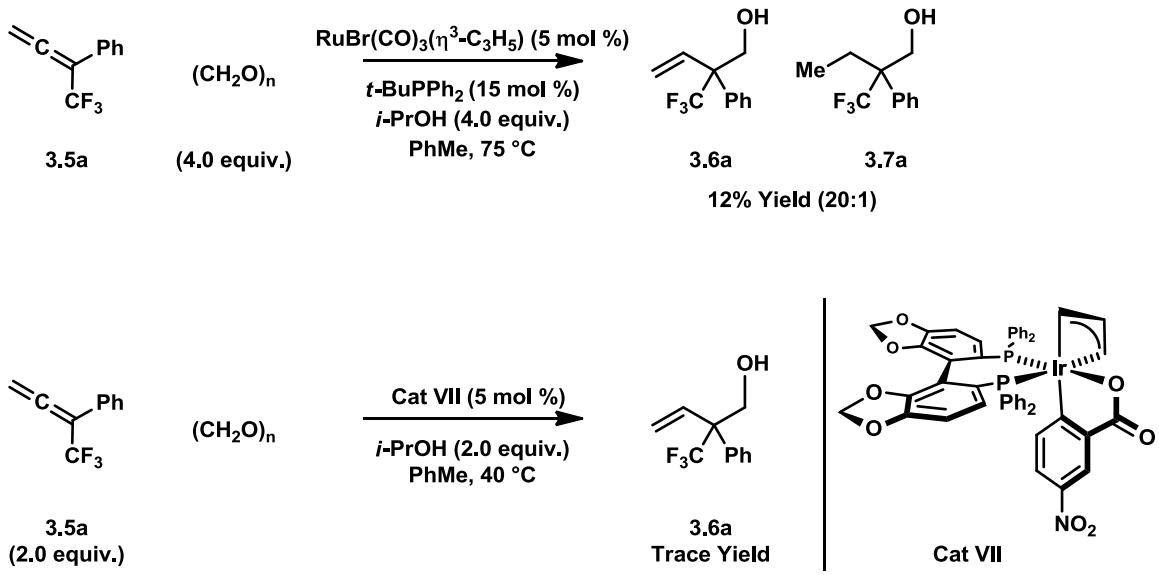
aryl group	3.3e,f, Yield	3.4e,f, Yield	3.5e,f, Yield
3.1e, Ar = 3,5-$Cl_2C_6H_3$	3.3e, 73%	3.4e, 56%	3.5e, 56%
3.1f, Ar = 4-ClC_6H_4	3.3f, 81%	3.4f, 43%	3.5f, 84%

Corey-Fuchs olefination of aryl trifluormethyl ketones **3.1a-f**[48–50] furnished methylene dibromides **3.2a-f**. Lithiation[51] of methylene dibromides **3.2a-d** and subsequent treatment with paraformaldehyde followed by quenching with methanesulfonyl chloride delivered allylic sulfonates **3.4a-d**, which were generated as a single geometrical isomer. Allylic sulfonates **3.4a-d** were first converted to the bromide *in situ* and then exposed to freshly washed zinc dust to furnish 1-aryl-1-trifluoromethylallenes **3.5a-d** in good isolated yield. The vinyl lithium species derived from dibromides **3.2e** and **3.2f** did not efficiently react with paraformaldehyde, thus an alteration to the synthesis had to be made. These adducts could be methylated with methyl iodide to form vinyl bromides **3.3e** and **3.3f** as a single geometrical isomer. Allylic bromination, which scrambles olefin geometry, followed by treatment with freshly washed zinc dust, furnished 1-aryl-1-trifluoromethylallenes **3.5e** and **3.5f**.

3.3 Reaction Development and Scope

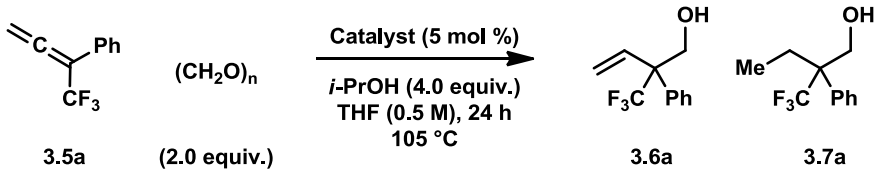
With a serviceable route to allenes **3.5a-f**, investigations into the reductive coupling with paraformaldehyde ensued. Initial attempts utilized conditions previously developed for the coupling of 1,1-disubstituted allenes and paraformaldehyde (Scheme 3.3).[2] Unfortunately these conditions failed to generate the desired product in reasonable yield (only 12%) while including the hydrogenated coupling product as an inseparable side product. Furthermore, employing the previous conditions that use **Cat VII** resulted in trace product formation (Scheme 3.3).[4] Examining additional conditions that have found success in couplings of this type provided more promising results.[1–8] By utilizing the catalytic system that includes $RuHCl(CO)(PPh_3)_3$ and DiPPF (similar conditions to what was previously reported[7]) and performing the reaction at 105 °C, desired coupling product **3.6a** was obtained in 46% yield as a single compound.

Scheme 3.3. Initial screens for the reductive coupling of allene **3.5a** and paraformaldehyde.



Further optimization of the catalytic system followed by assessing various ruthenium complexes without the use of exogenous ligand to examine the background reaction was continued (Table 3.1). $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ delivered the desired product in highest yield, but unfortunately small quantities of hydrogenated side product **3.7a** were detected. Therefore, $RuHCl(CO)(PPh_3)_3$ was determined the optimum catalyst to move forward with since it provided desired product **3.6a** in 37% yield without any detectable side product **3.7a**.

Table 3.1. Screens of various ruthenium complexes in the coupling of allene **3.5a** and paraformaldehyde.



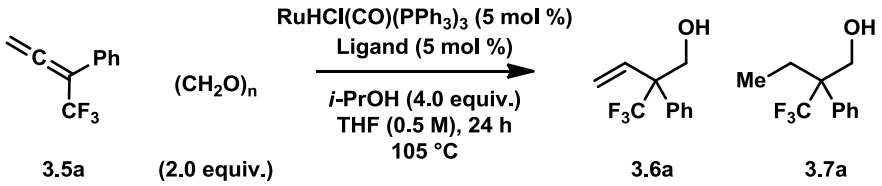
3.5a (2.0 equiv.) 3.6a 3.7a

Catalyst	loading	Yield (%)	3.6a:3.7a
none	-	-	-
$RuBr(CO)_3(\eta^3\text{-}C_3H_5)$	5 mol %	Trace	n.d.
$RuH_2(CO)(PPh_3)_3$	5 mol %	18	>20:1
$RuHCl(CO)(PPh_3)_3$	5 mol %	37	>20:1
$Ru(O_2CCF_3)_2(CO)(PPh_3)_3$	5 mol %	51	13:1
$[RuCl_2(p\text{-cymene})]_2$	2.5 mol %	48	4:1

*Ratios determined by ^{19}F NMR analysis of crude reaction mixtures

As previously mentioned, the combination of $RuHCl(CO)(PPh_3)_3$ with DiPPF furnished desired product **3.6a** in higher yield (46%) than $RuHCl(CO)(PPh_3)_3$ alone, so other ligands were examined (Table 3.2). It was found that bidentate ferrocene based ligands, such as DPPF and DB^{t}PF, improved the overall yield of the coupling product, 68% and 58% respectively. Regrettably, DPPF generated side product **3.7a** in higher quantities. Thus, it appears that more electron-rich ferrocene-based phosphines (DiPPF and DB^{t}PF) suppress the formation of side product **3.7a** when compared to DPPF. The screening of alkyl-linked phosphines displayed an interesting trend: the amount of side product **3.7a** formed appeared to be proportional to the bite angle of the ligand, the larger the bite angle, the more **3.7a** formed. The ligand with a single methylene spacer, DPPM, suppressed the formation of **3.7a**, while the ligand with a four-carbon linker, DPPB, generated the largest amount of **3.7a**. Both of these ligands generated coupling product in 70% yield. Rationalization for this trend is given in Figure 3.2. Once desired product **3.6a** is formed, a

Table 3.2. Select ligand screen in the coupling of allene **3.5a** and paraformaldehyde.



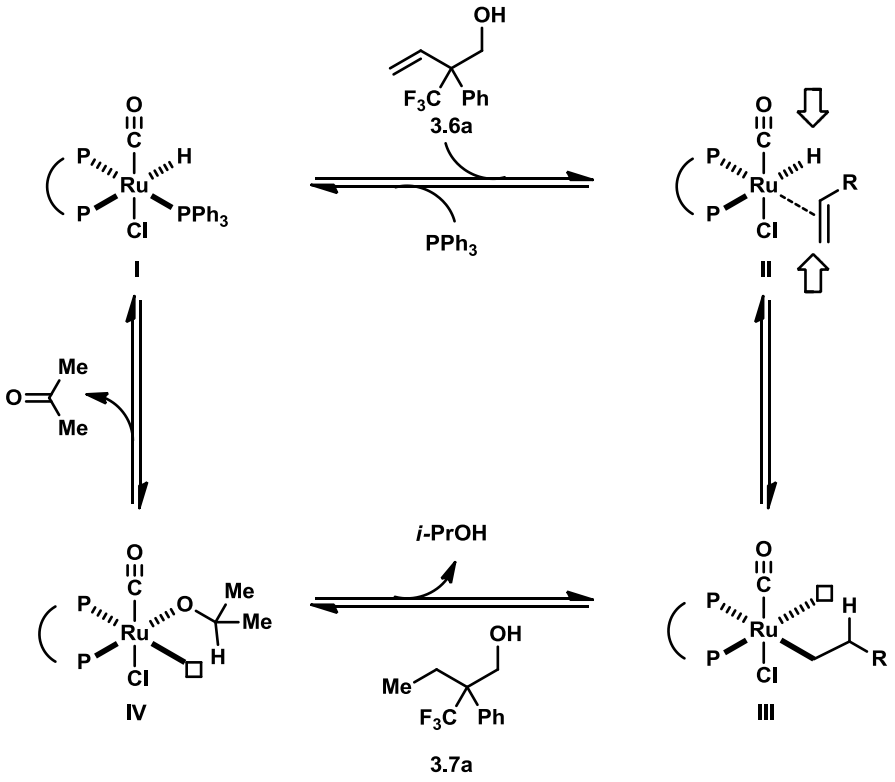
3.5a (2.0 equiv.) 3.6a 3.7a

Ligand	Yield (%)	3.6a:3.7a
DiPPF	46	>20:1
DPPF	68	12:1
DB^{t}PF	58	>20:1
BINAP	31	10:1
DCyPM	68	10:1
DPPM	70	>20:1
DPPE	70	9:1
DPPP	35	3:1
DPPB	70	1:4

*Ratios determined by ^{19}F NMR analysis of crude reaction mixtures

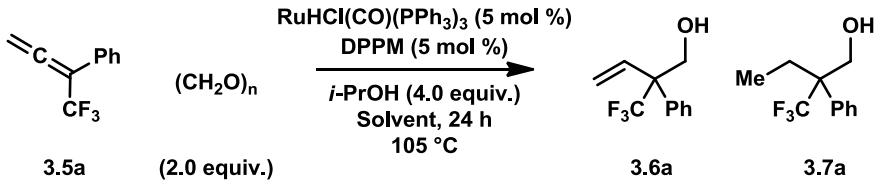
triphenylphosphine ligand can dissociate and the olefin can coordinate to the ruthenium, forming intermediate **II**. As the carbon linker of the ligand increases, the hydride in intermediate **II** is forced closer to the olefin. Thus, hydrometallation can occur, generating intermediate **III**. Protonolysis from isopropanol present in the reaction mixture releases side product **3.7a** and forms intermediate **IV**. β-Hydride elimination can occur to generate acetone and reform ruthenium catalyst **I**.

Figure 3.2. Rationale for ligand influence in formation of side product **3.7a**.



After a short solvent screen (Table 3.3), it was found that using toluene provided similar reactivity to THF, delivering the product in 70% yield. Because toluene has a boiling point near the reaction conditions, it was chosen as the solvent going forward, thus allowing the transformation to proceed outside of a pressured environment. It should be noted, select ligands were reexamined in this transformation using toluene as solvent, but no significant changes in reactivity or selectivity were observed.

Table 3.3. Screen of various solvents in the coupling of allene **3.5a** and paraformaldehyde.



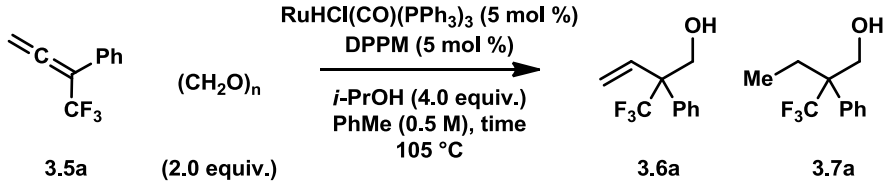
3.5a (2.0 equiv.) 3.6a 3.7a

Solvent	Concentration (M)	Yield (%)	3.6a:3.7a
THF	0.5	70	>20:1
THF	1.0	67	>20:1
PhMe	0.5	70	>20:1
1,4-Dioxane	0.5	69	>20:1
DCE	0.5	64	>20:1
MeCN	0.5	28	>20:1

*Ratios determined by ^{19}F NMR analysis of crude reaction mixtures

Reaction time was also examined (Table 3.4). To our amazement, ^{19}F NMR of crude reaction mixture showed that the reaction was 98% complete after only ten minutes. No starting material was detected after thirty minutes. One hour was selected as the best condition assayed to carry across a wide scope of 1-aryl-1-trifluoromethylallenes, since extended reaction times did not seem to negatively affect the product. Because this reaction was completed in such a short period of time, it was hypothesized that lower catalyst loadings or lower temperatures could be employed. Unfortunately, these ideas were proven incorrect as significantly lower yields of the coupling product were observed.

Table 3.4. Screening reaction times in the coupling of allene **3.5a** and paraformaldehyde.



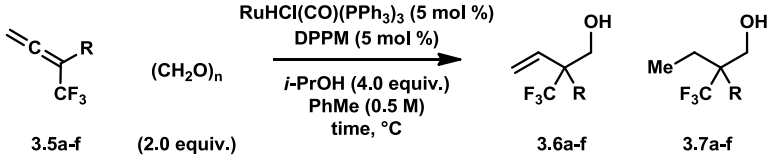
3.5a (2.0 equiv.) 3.6a 3.7a

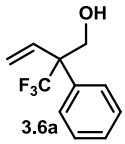
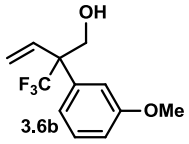
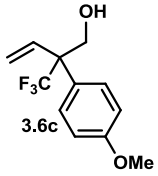
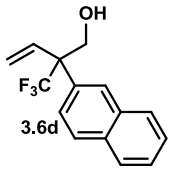
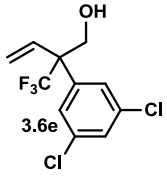
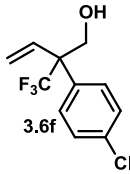
Time	Conversion (%)	3.6a:3.7a
3 min	49	>20:1
5 min	74	>20:1
10 min	98	>20:1
20 min	99	>20:1
30 min	100	>20:1
1 h	100	>20:1
2 h	100	>20:1

*Conversion and Ratios determined by ^{19}F NMR analysis of crude reaction mixtures

With optimized conditions ready to be employed, the scope of this transformation was evaluated (Table 3.5). A variety of electron-rich,-neutral and moderately -poor aryl groups were tolerated by this transformation, furnishing desired alcohols **3.6a-f** in good yield. In all cases, complete levels of branched regioselectivity were observed, and only in the case of allene **3.5e** was any significant quantity of hydrogenated side product detected. Regrettably, it seemed as though this transformation necessitated the use of an aryl substituent. When examining an allene with methylene heteroatom (-CH_2OTBS) substitution, low yield was observed. Also, to gauge the scalability of this transformation, allene **3.5a** was subjected to the optimized reaction conditions and furnished approximately one gram of alcohol **3.6a** without loss of yield or selectivity.

Table 3.5. Scope of hydrohydroxymethylation of allenes **3.5a-f**.

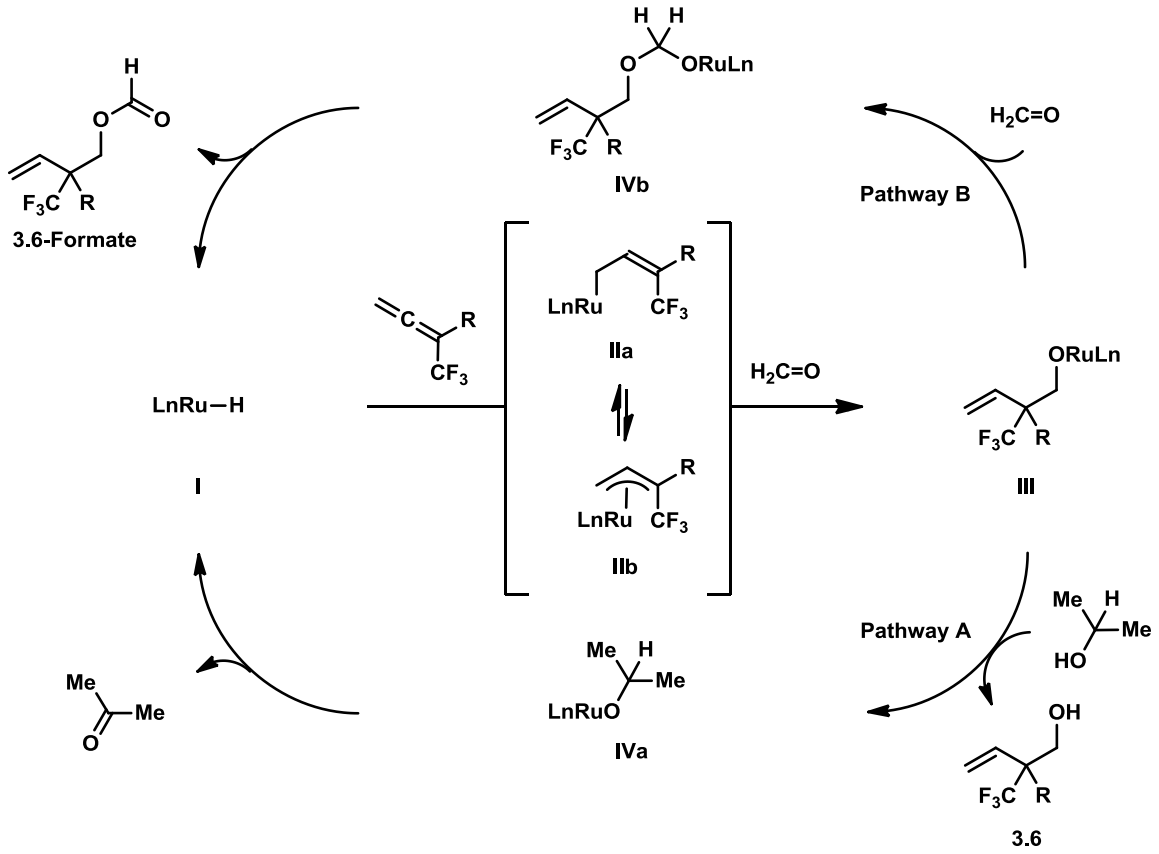


Product	Time	Temperature (°C)	Yield (%)	Ratio (3.6:3.7)
 3.6a	1 h	105	78	20:1
 3.6b	30 min	120	65	>20:1
 3.6c	1 h	105	75	>20:1
 3.6d	1 h	105	67	>20:1
 3.6e	30 min	120	73	16:1
 3.6f	30 min	120	68	>20:1

*Ratios determined by ^{19}F NMR analysis of crude reaction mixtures
Yields of isolated material

A plausible catalytic cycle for the reductive coupling of 1-aryl-1-trfluoromethyallenes is proposed in Figure 3.3. Ruthenium hydride enters into the catalytic cycle by hydrometallating the allene to furnish allylruthenium haptomers **IIa** and **IIb**.[52–58] Addition to formaldehyde occurs from the primary *σ*-allylruthenium haptomer **IIa** furnishing ruthenium alkoxide intermediate **III**. At this stage, the pathways can diverge, but ultimately result in the same product. If pathway **A** is taken, isopropanol can protonolytically cleave ruthenium alkoxide **III** generating product alcohol **3.6** and ruthenium isopropoxide **IVa**. β-Hydride

Figure 3.3. Proposed mechanism for the hydrohydroxymethylation of allenes **3.5a-f**.

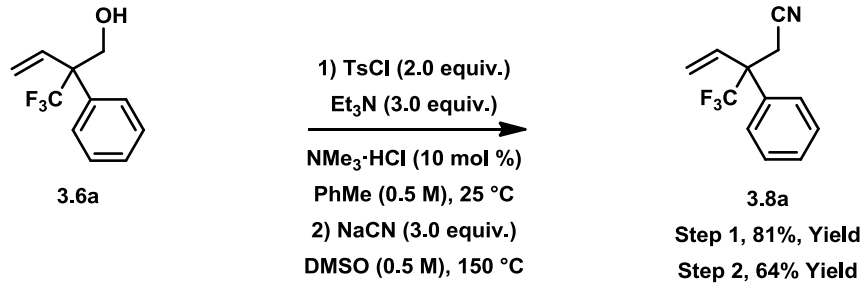


elimination can then occur, reforming ruthenium precatalyst **I** and acetone. If pathway **B** is taken, ruthenium intermediate **III** can undergo formaldehyde addition, forming ruthenium alkoxide **IVb**. Subsequent β-hydride elimination can occur, releasing **3.6**-formate and regenerating ruthenium hydride **I**. Dealing with formate esters are not uncommon in the chemistry from this group, including reactions of allenes.[2,59,60] **3.6**-Formate can be cleaved to the desired product by simple workup with methanolic sodium hydroxide.

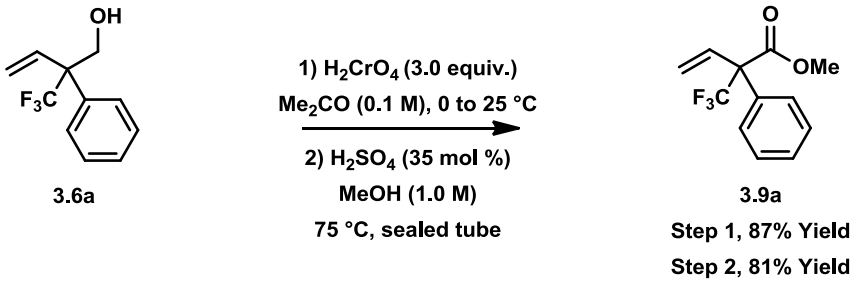
3.4 Product Elaboration

To illustrate the utility of these coupling products, alcohol **3.6a** was converted to the corresponding *p*-toluenesulfonate and reacted with sodium cyanide in DMSO. Despite the notoriously low rates normally observed for S_N2 reactions of neopentyl electrophiles, nitrile **3.8a** was formed in moderate yield (Scheme 3.4). Jones oxidation of product alcohol **3.6a**, followed by Fischer esterification produced methyl ester **3.9a** (Scheme 3.5).

Scheme 3.4. Formation of nitrile **3.8a** from alcohol **3.6a**.



Scheme 3.5. Formation of methyl ester **3.9a** from alcohol **3.6a**.



3.5 Summary

Novel synthetic routes have been reported, allowing access to 1-aryl-1-trifluoromethyl allenes. A ruthenium-catalyzed reductive coupling of 1-aryl-1-trifluoromethylallenes to paraformaldehyde forming homoallylic alcohols which contain a trifluoromethyl-bearing all-carbon quaternary center has been revealed. This transformation occurs by way of hydrogen auto-transfer, mediated by isopropanol. This methodology represents one of only a few methods available for the construction of all-carbon quaternary centers bearing a trifluomethyl group, allowing incorporation of the much desired fluorinated functional group into synthetic building blocks. Future investigations should focus on the development of an asymmetric variant of this methodology, as well as, couplings to higher alcohols and aldehydes.

3.5 Experimental Details

General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringes. Reaction tubes and flasks were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Toluene (PhMe) and tetrahydrofuran (THF) were distilled from sodium and benzophenone. 1,2-dichloroethane (DCE) was distilled from CaH_2. $RuHCl(CO)(PPh_3)_3$was prepared according to literature procedure.[61] 2-propanol (99.8%, extra dry), methanesulfonyl chloride (MsCl) 99.5% and lithium bromide 99%+, anhydrous were obtained from Acros Organics. Paraformaldehyde was used as received from Aldrich Chemical Company, Inc. MsCl was distilled over phosphorous pentoxide (P_2O_5) prior to use. Triethylamine was purchased from Fischer Scientific and stored over sodium hydorxide. Carbon tetrabromide and *p*-toluenesulfonyl chloride were purchased and used as received from TCI America. Triphenylphosphine (PPh_3), 1,1-bis(diphenylphosphino)methane (DPPM), 1,1-bis(dicyclohexylphosphino)methane (DCyPM), 1,2-bis(dicyclohexylphosphino)ethane (DCyPE), N-Bromosuccinimide (NBS), and Zn dust, <10 μm, were purchased from Sigma-Aldrich. 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF), 1,1′-bis(di-tert-butylphosphino)ferrocene (DB^tPF), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) were obtained from Strem Chemicals Inc. All ligands were used as received. NBS was recrystallized according to the method of McCoy.[62] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F_{254}) and products were visualized by UV, $KMnO_4$

and/or anisaldehyde stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[63] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for chloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for chloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer.

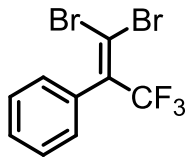
Representative Procedure for the Preparation of Dibromides 3.2a-f

2-Aryl-1,1-dibromo-3,3,3-trifluoropropenes **3.2a-f** were prepared in accordance with the literature procedure reported by Uno.[64]

To a 500mL three-necked round bottom flask equipped with a magnetic stir bar and reflux condenser was added PPh_3 (14.4 g, 55 mmol, 2.2 equiv.). The flask was sealed with rubber septa, purged with argon, and toluene (71 mL, 0.35 M) was added. The mixture was stirred until PPh_3 dissolved, at which point CBr_4 (9.3g, 28 mmol, 1.12 equiv.) was quickly added under a flow of argon. After stirring for an additional 30 minutes, at which point the mixture was bright yellow, the trifluoracetyl compound **3.1b** (5.0 g, 25 mmol, 1.0 equiv.) was added drop

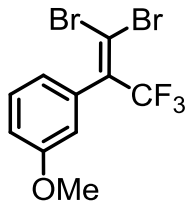
wise via syringe over 15 minutes. The mixture was stirred for an additional 30 minutes and then refluxed overnight. The reaction mixture was allowed to cool to room temperature, at which point hexane (50 mL) was added to precipitate salts. The suspension was filtered through a pad of silica, washing with 5% ethyl acetate/hexane. Then the filtrate was quenched with water (100 mL). The organics were removed and the aqueous layer was extracted twice with toluene (2 × 100 mL). The combined organics were washed with water (100 mL), sat. $NaHCO_3$ (2 × 100 mL), and brine (100 mL), dried (Na_2SO_4), filtered and evaporated to dryness. Purification under the noted conditions furnished the title compound **3.2b**.

Synthesis of (1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2a).



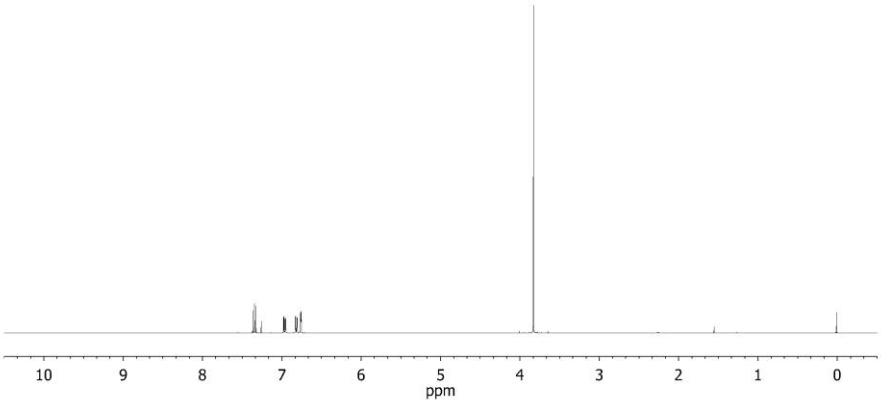
The reaction was conducted on a 150 mmol scale (via ketone **3.1a**). After aqueous work-up, the crude residue was purified by distillation (bp 38 °C/0.15 mmHg) (lit,[65] 94-104 °C/11 mmHg) to furnish the title compound **3.2a** (40.0 g, 81%) as a colorless oil. Spectral data is consistent with the reported literature data.[64,65]

Synthesis of 1-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)-3-methoxybenzene (3.2b).



The reaction was conducted on a 25 mmol scale (via ketone **3.1b**). After aqueous work-up, the crude residue was purified by distillation (bp 82 °C/0.15 mmHg) to furnish the title compound **3.2b** (7.2 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 1H), 6.97 (ddd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 6.85-6.80 (m, 1H), 6.78-6.74 (m, 1H), 3.83 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 137.4 (q, *J* = 32.7 Hz), 136.5, 129.9, 120.8, 121.8 (q, *J* = 276.1 Hz), 114.9, 114.1, 101.6 (q, *J* = 2.8 Hz), 55.3.
^{19}F NMR (376 MHz, $CDCl_3$): δ -58.6.
LRMS (EI): m/z 361 $[M+H]^+$
FTIR (neat): 2943, 2837, 1598, 1580, 1487, 1465, 1431, 1298, 1284, 1240, 1179, 1128, 1043, 995, 983, 875, 854, 802, 782, 747, 703, 676 cm^{-1}.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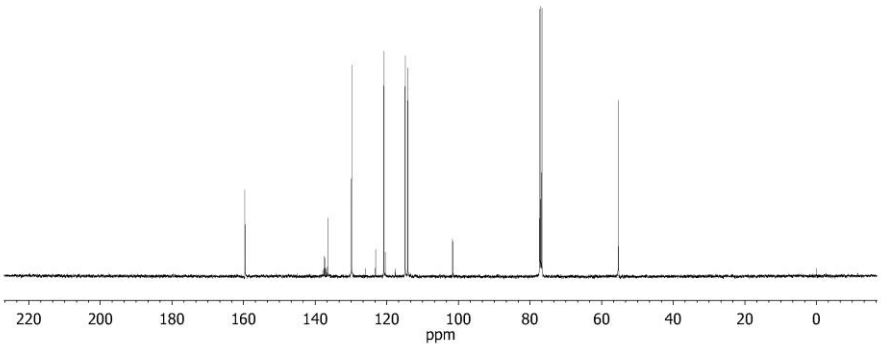
ppm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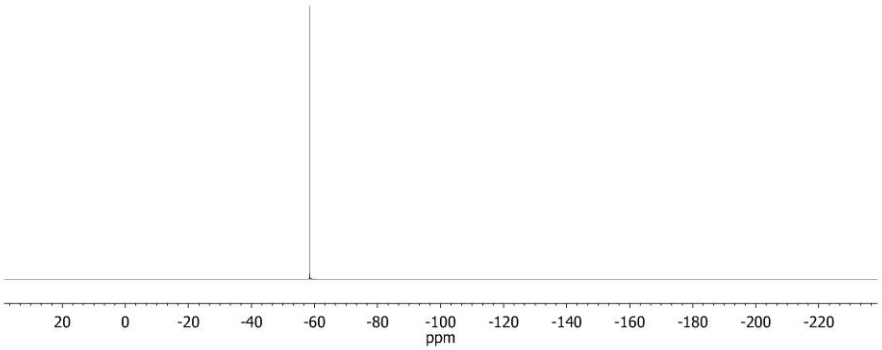
ppm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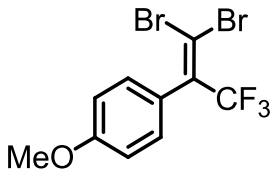
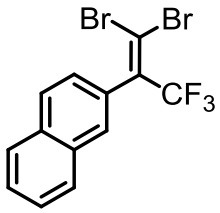
ppm

Synthesis of 1-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)-4-methoxybenzene (3.2c).



The reaction was conducted on a 25 mmol scale (via ketone **3.1c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.2c** (8.1 g, 91%) as a colorless oil. Spectral data is consistent with the reported literature data.[64]

Synthesis of 2-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)naphthalene (3.2d).



The reaction was conducted on a 22 mmol scale (via ketone **3.1d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.2d** (7.0 g, 84%) as a colorless oil.

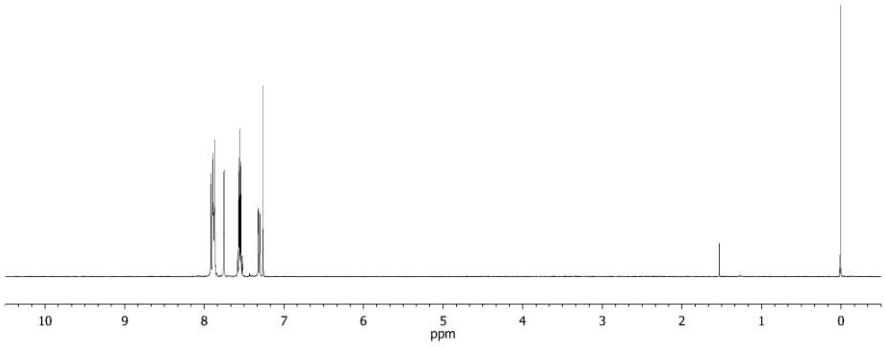
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.85 (m, 3H), 7.75 (d, *J* = 1.4 Hz, 1H), 7.60-7.51 (m, 2H), 7.31 (dd, *J* = 8.5, 1.7 Hz, 1H).

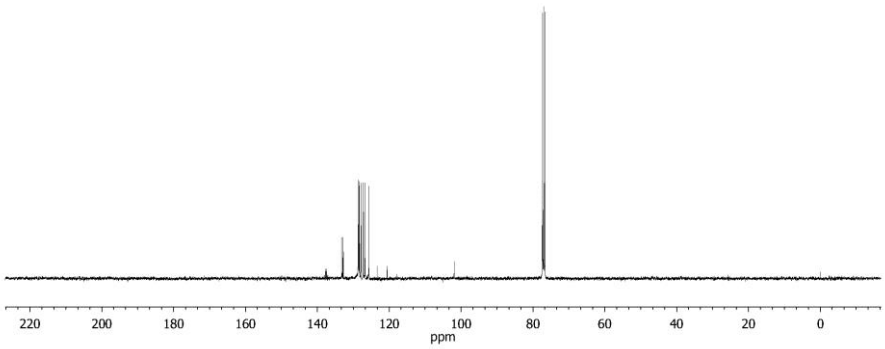
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6 (q, *J* = 32.6 Hz), 133.2, 132.9, 132.8, 128.6, 128.5, 128.3, 127.8, 127.2, 126.7, 125.6, 121.96 (q, *J* = 276.2 Hz), 101.9 (q, *J* = 3.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3.

LRMS (EI): m/z 381 $[M+H]^+$

FTIR (neat): 3059, 1599, 1581, 1505, 1289, 1269, 1243, 1204, 1180, 1166, 1124, 1017, 991, 962, 898, 866, 853, 816, 801, 769, 751, 736, 688 cm^{-1}.

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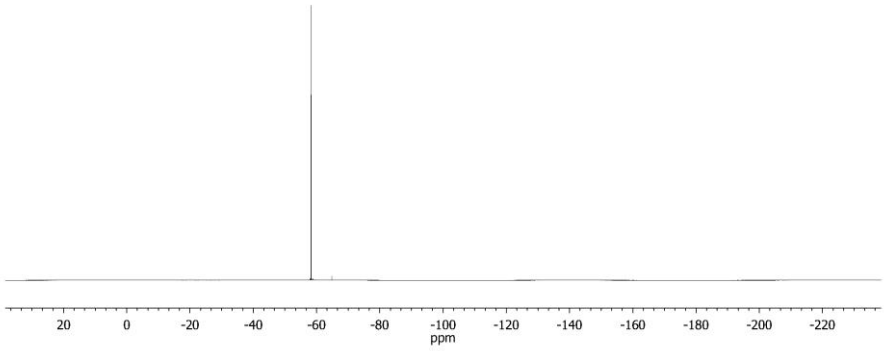
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-160
-180
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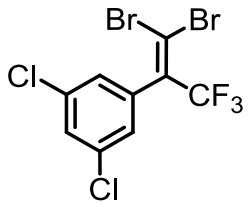
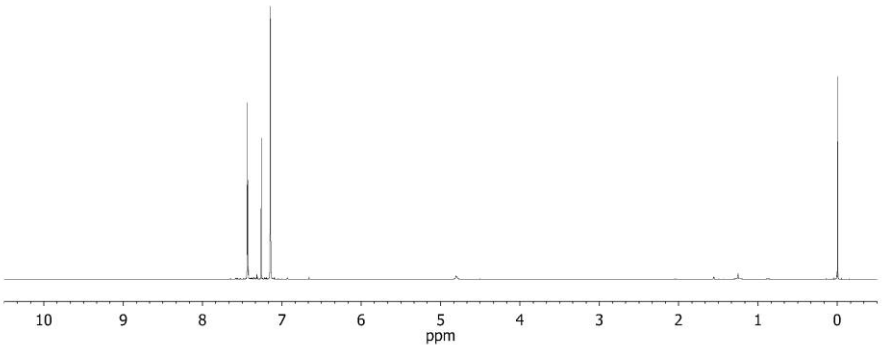
ppm

Synthesis of 1,3-dichloro-5-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2e).



The reaction was conducted on a 25 mmol scale (via ketone **3.1e**). After aqueous work-up, the crude residue was purified by distillation (bp 84 °C/0.1 mmHg) to furnish the title compound **3.2e** (8.2 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 1.9 Hz, 1H), 7.14 (d, *J* = 1.9 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 135.5, 135.2 (q, *J* = 33.4 Hz), 129.7, 127.2, 121.4 (q, *J* = 276.2 Hz), 103.6 (q, *J* = 2.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -58.4.
LRMS (CI): m/z 399 $[M]^+$
FTIR (neat): 1589, 1561, 1413, 1295, 1203, 1177, 1135, 1103, 1008, 867, 838, 803, 705, 690, 661 cm^{-1}.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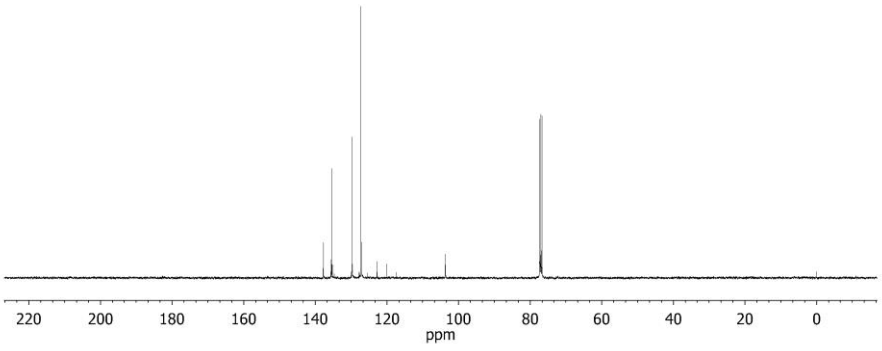
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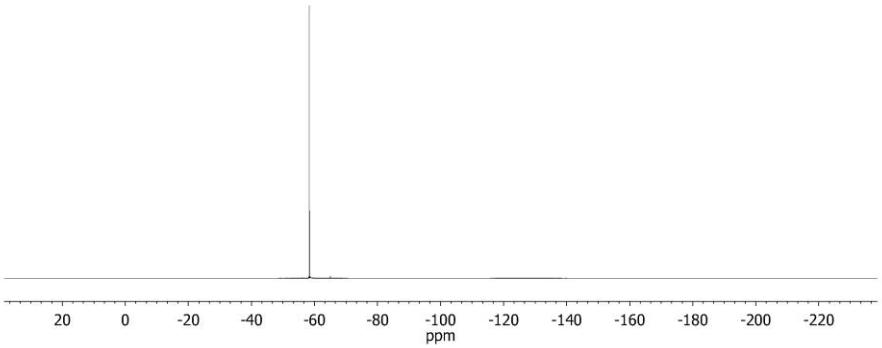
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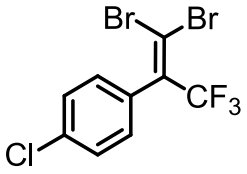
Synthesis of 1-chloro-4-(1,1-dibromo-3,3,3-trifluoroprop-1-en-2-yl)benzene (3.2f).



The reaction was conducted on a 25 mmol scale (via ketone **3.1f**). After aqueous work-up, the crude residue was purified by distillation (bp 79 °C/ 0.15 mmHg) (lit,[64] 123 °C/12 mmHg) to furnish the title compound **3.2f** (7.6 g, 84%) as a colorless oil. Spectral data is consistent with the reported literature data.[68]

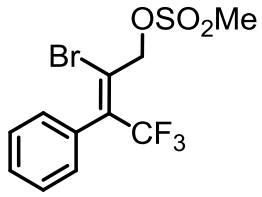
Representative Procedure for the Preparation of Methansulfonates 3.4a-d

Methanesulfonates **4a**-**4d** were prepared by modifying a literature procedure reported by Li and co-workers.[66]

To a 1 L three-neck round bottom flask equipped with a magnetic stir bar was added **3.2a** (14.2 g, 43 mmol, 1.0 equiv.). The flask was sealed with rubber septa, purged with argon, and THF (430 mL, 0.1 M) was added. Upon cooling to -78 ºC, *n*-butyl lithium (2.5 M in hexanes, 17.0 mL, 43 mmol) was slowly added to the mixture and stirred for 30 minutes at this temperature. Paraformaldehyde (5.2 g, 172 mmol, 4.0 equiv.) was added and let warm to room temperature while stirring overnight. The reaction mixture was cooled to 0 ºC. Triethylamine (9.0 mL, 65 mmol, 1.5 equiv.) was added and stirred for 30 min, followed by dropwise addition of MsCl (6.7 mL, 86 mmol, 2.0 equiv.) and stirring for 2 hours at this temperature. The reaction mixture was quenched with 1 M HCl (200 mL) and extracted with diethyl ether (3 × 150 mL). The organic phase was washed with water (150 mL), brine (150 mL) and dried (Na_2SO_4). The crude residue was

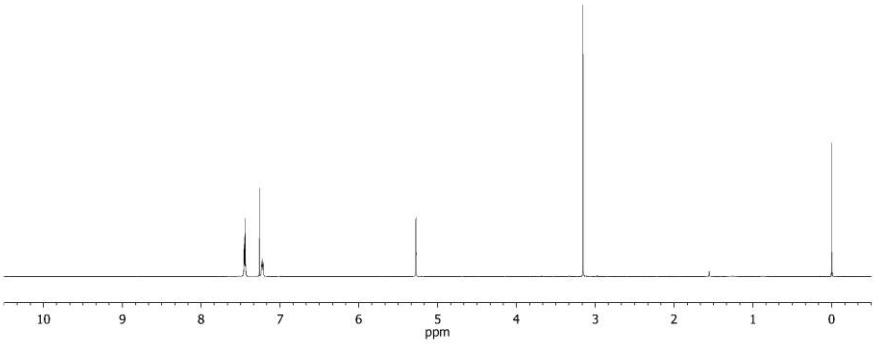
purified by flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compounds **3.4a**.

Synthesis of (E)-2-bromo-4,4,4-trifluoro-3-phenylbut-2-en-1-yl methanesulfonate (3.4a).



The reaction was conducted on a 43 mmol scale (via **3.2a**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% ethyl acetate/hexane) to furnish the title compound **3.4a** (7.7 g, 49%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.42 (m, 3H), 7.25-7.19 (m, 2H), 5.27 (q, *J* = 1.0 Hz, 2H), 3.16 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (q, *J* = 31.8 Hz), 134.6, 130.1 (q, *J* = 2.8 Hz), 129.4, 128.6 (d, *J* = 22.2 Hz), 121.8 (q, *J* = 277.1 Hz), 69.0 (q, *J* = 3.5 Hz), 38.2.
^{19}F NMR (376 MHz, $CDCl_3$): δ -55.7.
LRMS (CI): m/z 360 $[M]^+$
FTIR (neat): 3028, 1643, 1381, 1349, 1332, 1297, 1261, 1202, 1171, 1117, 1032, 1016, 999, 988, 978, 957, 928, 912, 834, 783, 761, 748, 697, 658 cm^{-1}.
MP (air): 81-83 °C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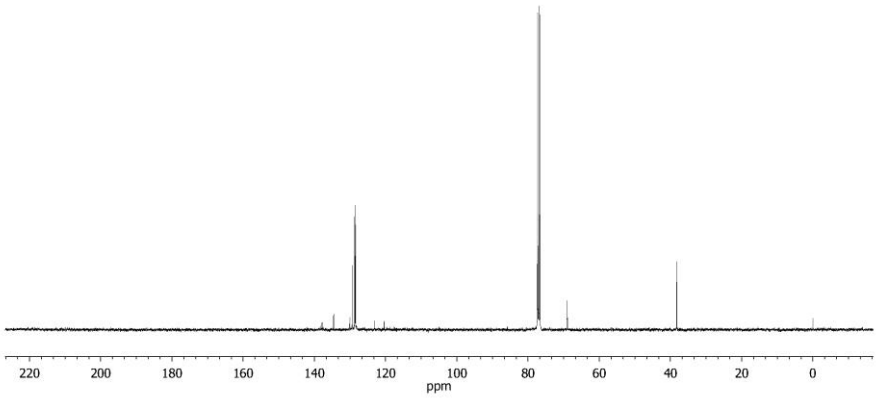
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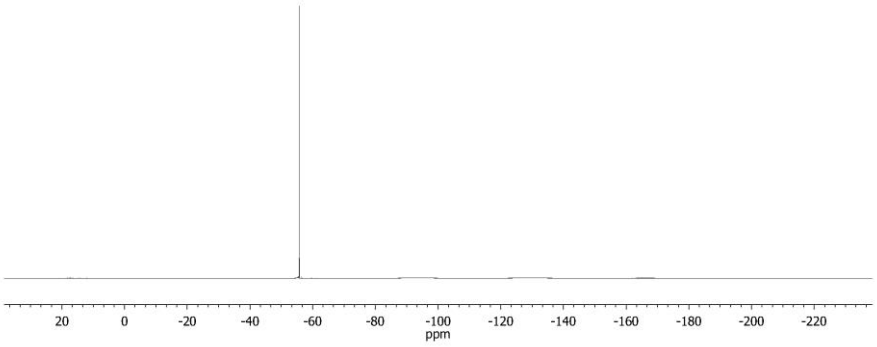
40
20
0
ppm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-100
ppm
-120
-140
-160
-180
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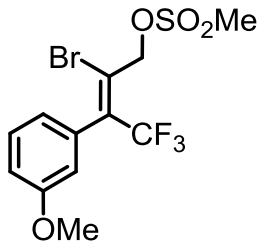
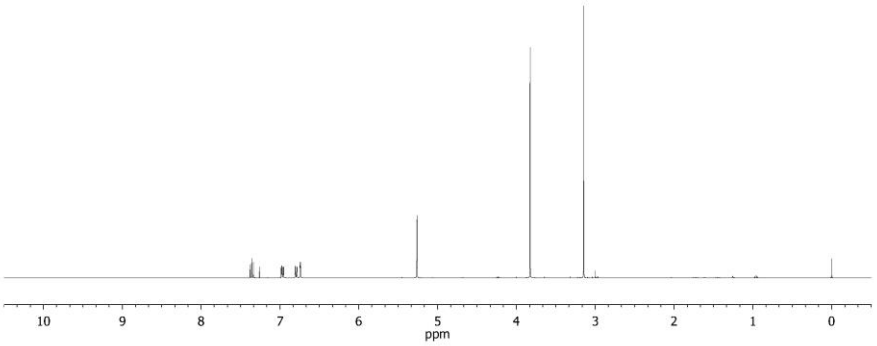
-220

Synthesis of (E)-2-bromo-4,4,4-trifluoro-3-(3-methoxyphenyl)but-2-en-1-yl methanesulfonate (3.4b).



The reaction was conducted on a 5.5 mmol scale (via **3.2b**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% ethyl acetate/hexane) to furnish the title compound **3.4b** (787 mg, 37%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.4 Hz, 1H), 6.97 (dddd, *J* = 8.4, 3.6, 2.8, 0.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.75-6.74 (m, 1H), 5.27-5.26 (m, 2H), 3.83 (s, 3H), 3.15 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 137.7 (q, *J* = 32.0 Hz), 135.7, 130.0, 129.8, 121.7 (q, *J* = 275.3 Hz), 120.6, 114.9, 114.1, 69.0 (q, *J* = 3.0 Hz), 55.4, 38.2.
^{19}F NMR (376 MHz, $CDCl_3$): δ -55.7.
LRMS (EI): m/z 295 $[M\text{-}CH_3O_3S]^+$
FTIR (neat): 1599, 1580, 1489, 1466, 1431, 1360, 1302, 1243, 1172, 1125, 1046, 951, 818, 737, 705 cm^{-1}.
MP (air): 73-75 °C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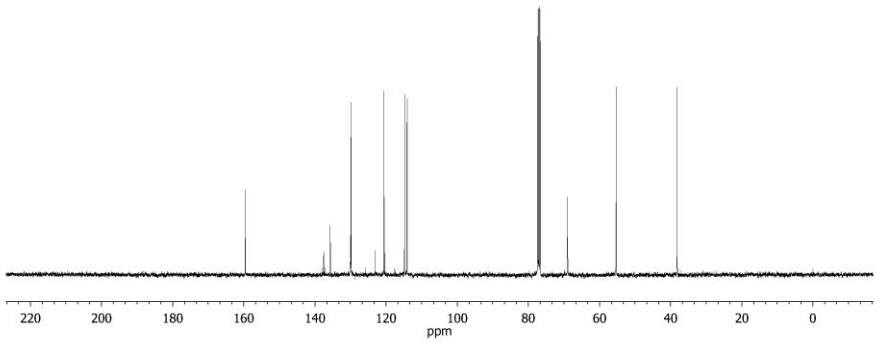
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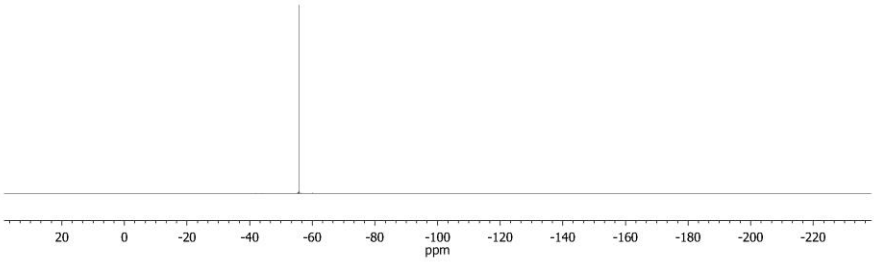
ppm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-100
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-160
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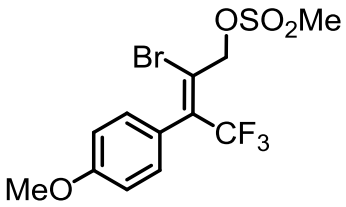
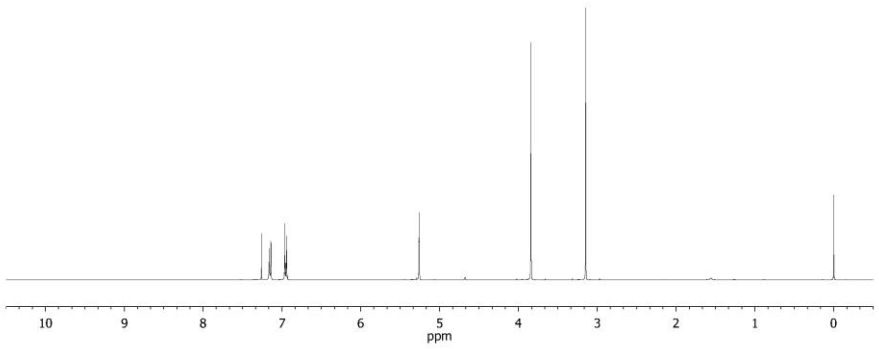
-200
-220
ppm

Synthesis of (E)-2-bromo-4,4,4-trifluoro-3-(4-methoxyphenyl)but-2-en-1-yl methanesulfonate (3.4c).



The reaction was conducted on a 16 mmol scale (via **3.2c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 20% ethyle acetate/hexane) to furnish the title compound **3.4c** (3.1 g, 48%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.14 (m, 2H), 6.97-6.94 (m, 2H), 5.26 (q, *J* = 0.8 Hz, 2H), 3.84 (s, 3H), 3.15 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 137.7 (q, *J* = 31.1 Hz), 130.2, 130.0, 126.8, 121.9 (q, *J* = 275.5 Hz), 114.0, 69.1, 55.3, 38.2.
^{19}F NMR (400 MHz, CDCl3): δ -55.8.
LRMS (EI) m/z 295 $[M\text{-}CH_3O_3S]^+$
FTIR (neat): 1637, 1608, 1512, 1458, 1353, 1302, 1250, 1208, 1166, 1107, 1026, 984, 961, 921, 850, 834, 769, 664 cm^{-1}.
MP (air): 119-120 °C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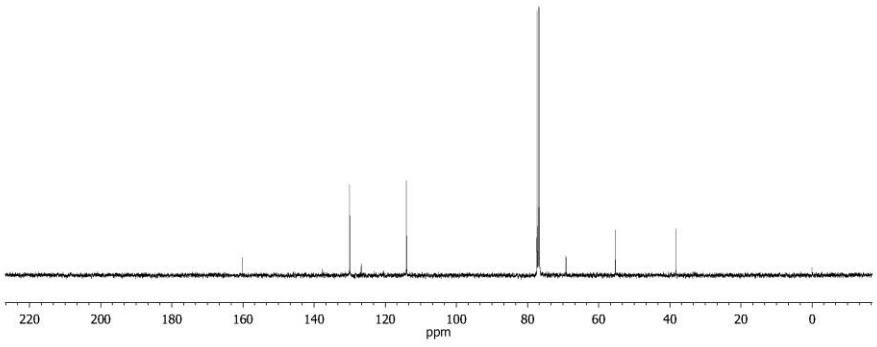
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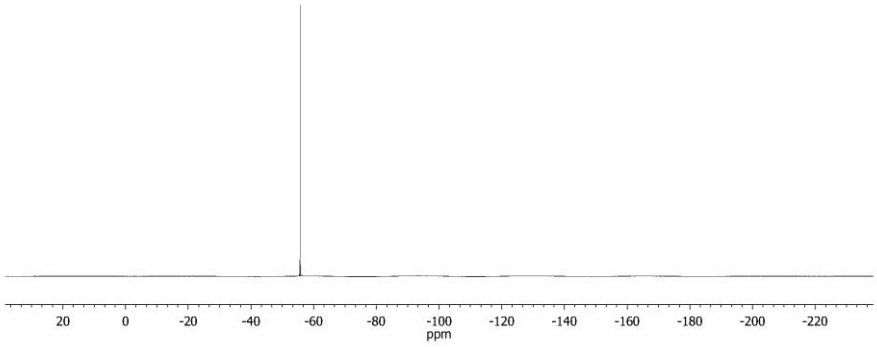
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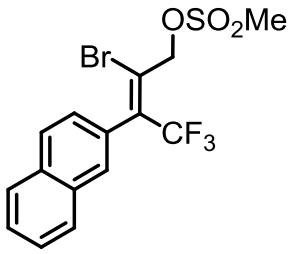
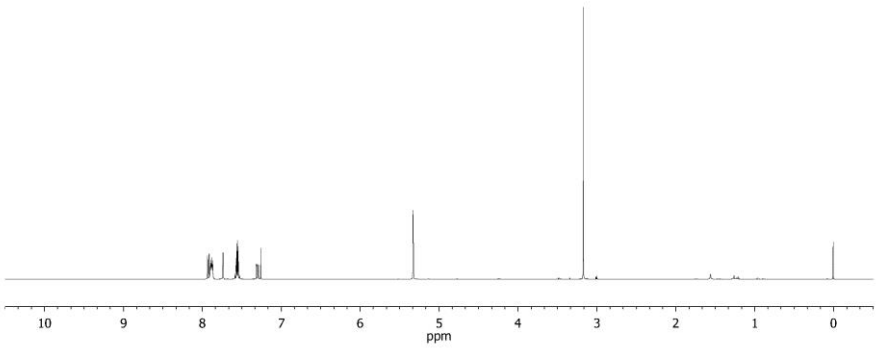
Synthesis of (E)-2-bromo-4,4,4-trifluoro-3-(naphthalen-2-yl)but-2-en-1-yl methanesulfonate (3.4d).



The reaction was conducted on a 2.6 mmol scale (via **3.2d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexane) to furnish the title compound **3.4d** (404 mg, 38%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.90-7.86 (m, 2H), 7.74 (s, 1H), 7.56 (dddd, *J* = 12.0, 9.2, 6.8, 2.0 Hz, 2H), 7.30 (dd, *J* = 2.0, 8.6 Hz, 1H) 5.33 (s, 2H), 3.17 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (q, *J* = 32.0 Hz), 133.3, 132.9, 131.9, 130.4, 128.6, 128.3, 127.8, 127.2, 126.8, 125.5, 121.9 (q, *J* = 276.1 Hz), 69.0 (q, *J* = 3.7 Hz), 38.3.
^{19}F NMR(400 MHz, CDCl3): δ -55.5.
LRMS (CI): m/z 315 $[M\text{-}CH_3O_3S]^+$
FTIR (neat): 2360, 1635, 1361, 1295, 1246, 1169, 1129, 954, 818, 750, 685 cm^{-1}.
MP (air): 106-109 °C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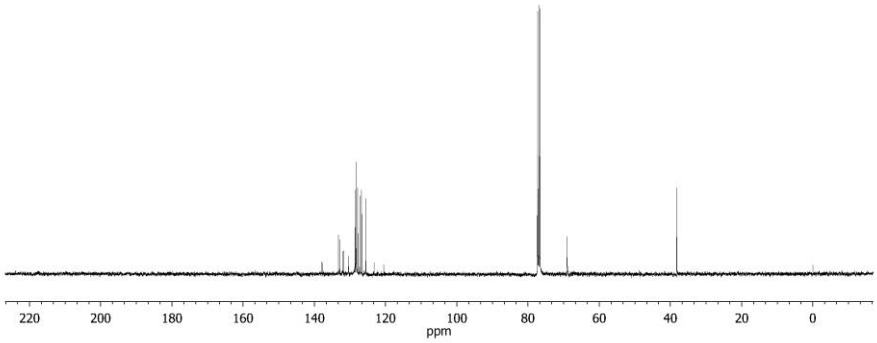
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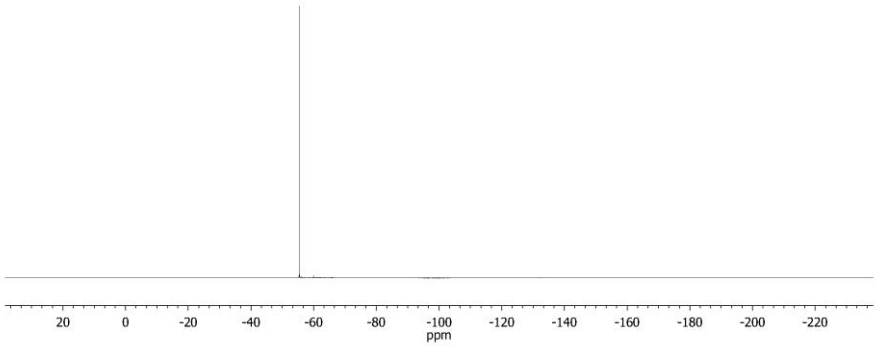
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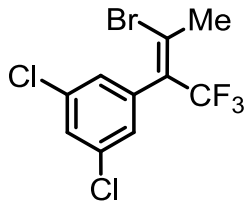
-220
ppm

Representative Procedure for the Preparation of 3.3e,f

1,1,1-trifluorobut-2-enes **3e**,**f** were prepared by modifying a literature procedure reported by Li and co-workers.[66]

To a 250 mL round bottom flask equipped with a magnetic stir bar was added **3.2e** (3.0 g, 7.5 mmol, 1.0 equiv.). The flask was sealed with a rubber septum, purged with argon, and THF (75 mL, 0.1 M) was added. Upon cooling to -78 ºC, *n*-butyl lithium (2.5 M in hexanes, 3.0 mL, 7.5 mmol) was slowly added to the mixture and stirred for 30 minutes at this temperature. Methyl iodide (0.9 mL, 15 mmol, 200 mol%) was added and stirring continued at -78 ºC for 2 hours. The reaction mixture was quenched with distilled water (50 mL) and extracted with diethyl ether (3 × 50 mL). The organic phase was washed brine (100 mL), and dried (Na_2SO_4).The crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.3e**.

Synthesis of (E)-1-(3-bromo-1,1,1-trifluorobut-2-en-2-yl)-3,5-dichlorobenzene (3.3e).



The reaction was conducted on a 7.5 mmol scale (via **2e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3e** (1.8 g, 73%) as a colorless oil.

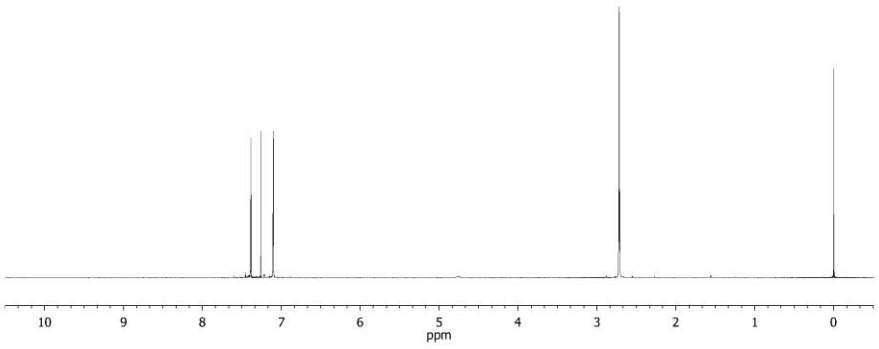
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 1.8 Hz, 2H), 2.72 (q, *J* = 2.2 Hz, 3H).

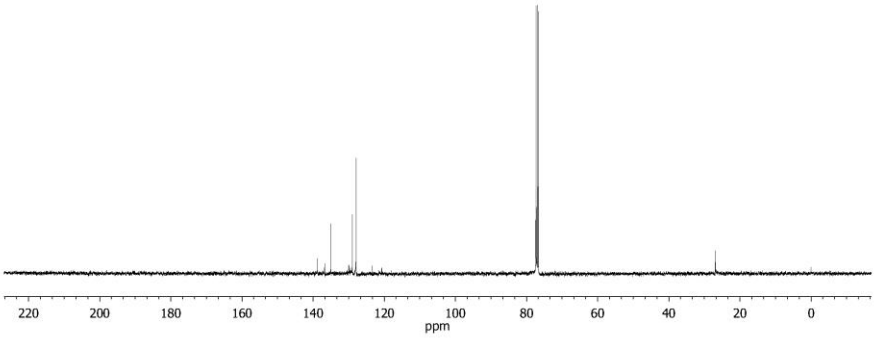
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 136.8, 135.0, 128.9, 127.9, 122.1 (q, *J* = 276.1 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ-56.1.

LRMS (CI): m/z 335 $[M+H]^+$

FTIR (neat): 1644, 1588, 1562, 1434, 1413, 1385, 1298, 1256, 1219, 1176, 1124, 1103, 1025, 999, 980, 862, 805, 762, 711, 697, 656 cm^{-1}.

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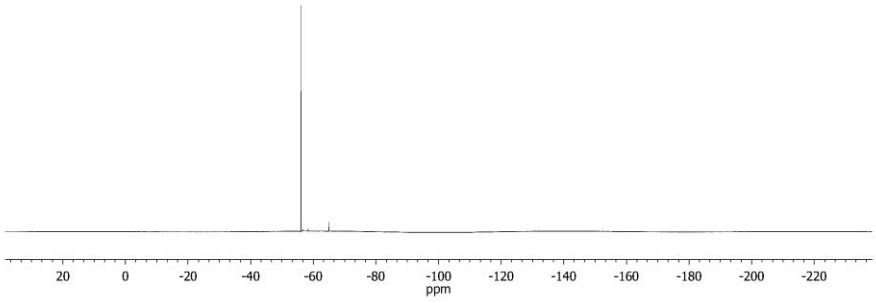
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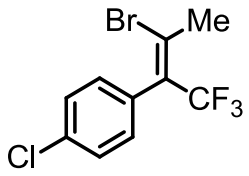
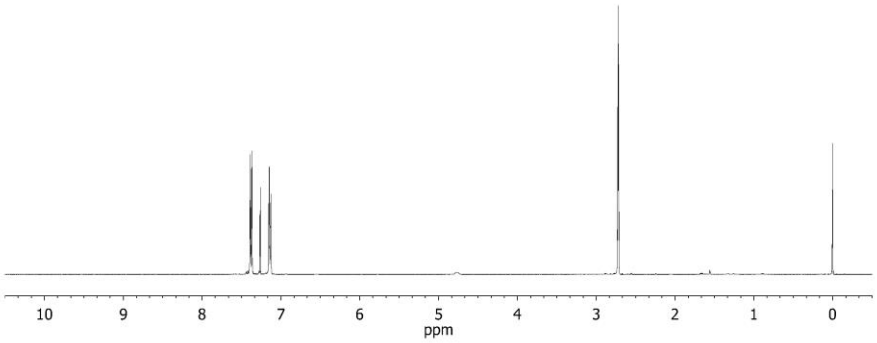
ppm

Synthesis of (E)-1-(3-bromo-1,1,1-trifluorobut-2-en-2-yl)-4-chlorobenzene (3.3f).



The reaction was conducted on a 7.5 mmol scale (via **3.2f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.3f** (1.8 g, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.34 (m, 2H), 7.17-7.10 (m, 2H), 2.82-2.55 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.7, 130.7, 128.7, 122.4 (q, J = 276.1 Hz), 26.9.
^{19}F NMR (376 MHz, $CDCl_3$): δ -56.2.
LRMS (CI): m/z 301 $[M+H]^+$
FTIR (neat): 3091, 2970, 1738, 1604, 1507, 1366, 1317, 1296, 1220, 1158, 1095, 1037, 1014, 991, 899, 838, 818, 735, 663 cm^{-1}.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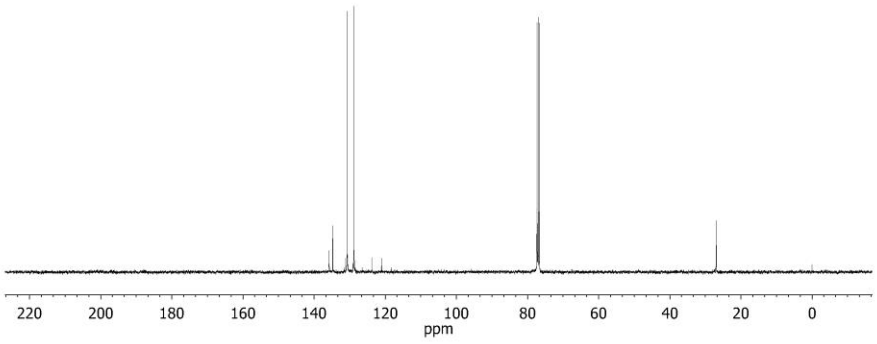
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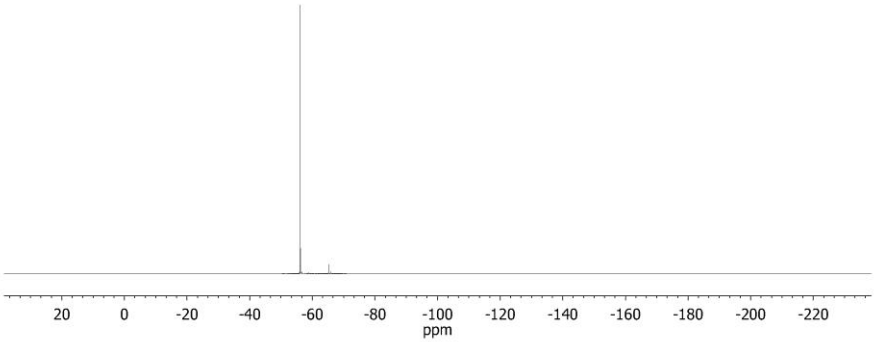
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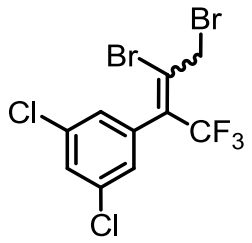
-220
ppm

Representative Procedure for the Preparation of 3.4e,f

To an oven-dried pressure tube equipped with magnetic stir bar was added **3.3e** (1.0 g, 3 mmol, 1.0 equiv.), NBS (590 mg, 3.3 mmol, 1.1 equiv.), and AIBN cat. The flask was sealed with a rubber septum, purged with argon, and DCE (0.75 mL, 4.0 M) was added. The rubber septum was quickly replaced with a screw cap, and the reaction was heated to 100 ºC for 24 hours. The reaction mixture was allowed to cool to room temperature, at which point 10% $Na_2S_2O_3$ (3 mL) was added and stirred for 30 min. The mixture was diluted with distilled water (15 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was washed with distilled water (15 mL), brine (15 mL) and dried (Na_2SO_4). The crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4e**.

Synthesis of 1,3-dichloro-5-(3,4-dibromo-1,1,1-trifluorobut-2-en-2-yl)benzene (3.4e).



The reaction was conducted on a 3 mmol scale (via **3.3e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4e** (690mg, 56%, *E*/*Z* : 54/46) as a colorless oil.

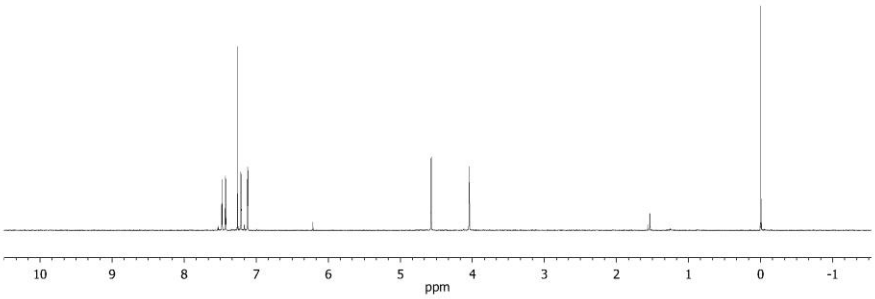
^{1}H NMR (400 MHz, $CDCl_3$): (*E*-isomer) δ 7.43 (t, *J* = 1.9 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 2H), 4.58 (q, *J* = 1.0 Hz, 2H). (*Z*-isomer) δ 7.48 (t, *J* = 1.9 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 2H), 4.05 (q, *J* = 0.9 Hz, 2H)

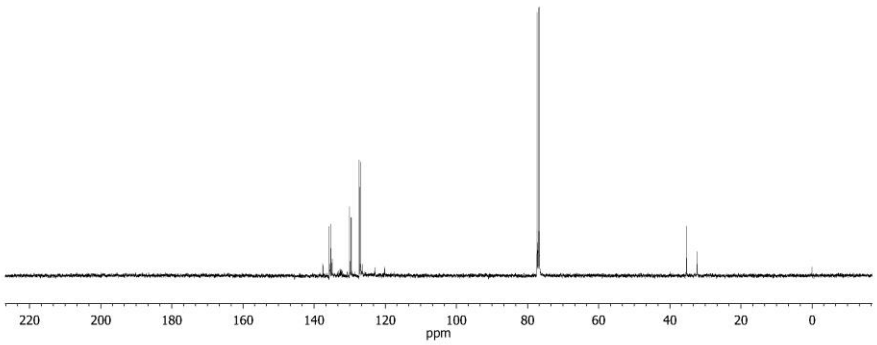
^{13}C NMR (100 MHz, $CDCl_3$): (*E*/*Z*-isomers) δ 137.5, 135.8, 135.6, 135.3, 134.9, 130.0, 129.6, 127.3, 126.9, 121.6 (q, *J* = 277.0 Hz), 121.6 (q, *J* = 276.4 Hz), 35.3, 32.3 (q, *J* = 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): (*E*-isomer) δ -56.6. (*Z*-isomer) δ -59.5.

LRMS (CI): m/z 413 $[M+H]^+$

FTIR (neat): 1621, 1586, 1561, 1429, 1412, 1389, 1300, 1219, 1183, 1219, 1129, 999, 979, 916, 899, 863, 836, 807, 721, 708, 696, 684, 656 cm^{-1}.

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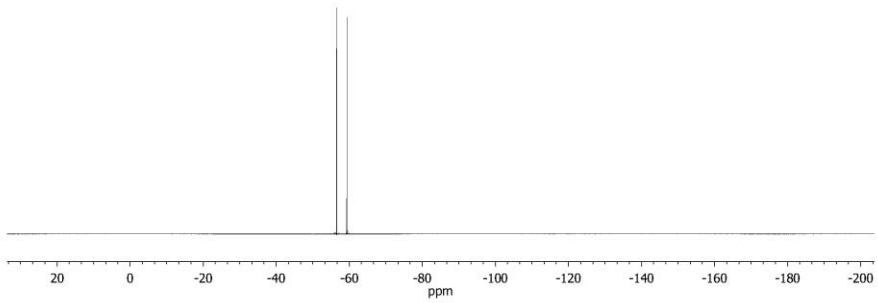
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-120
-140
-160
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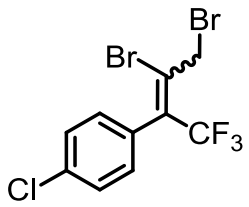
-200
ppm

Synthesis of 1-chloro-4-(3,4-dibromo-1,1,1-trifluorobut-2-en-2-yl)benzene (3.4f).



The reaction was conducted on a 3 mmol scale (via **3.3f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.4f** (469 mg, 43%, *E*/*Z* : 39/61) as a colorless oil.

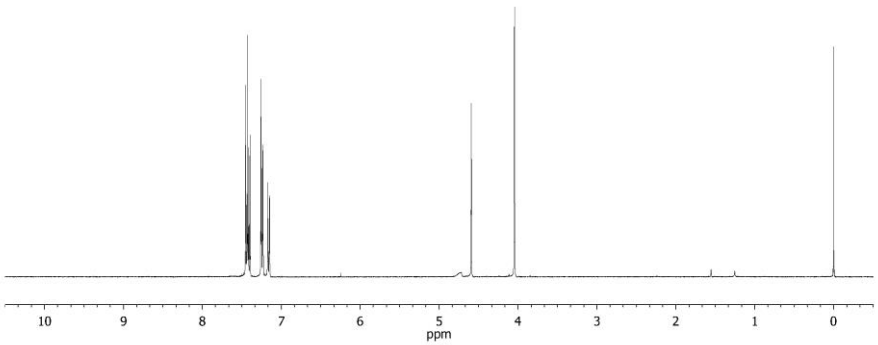
^{1}H NMR (400 MHz, $CDCl_3$): (*E*-isomer) δ 7.42-7.38 (m, 2H), 7.18-7.13 (m, 2H), 4.59 (q, *J* = 1.9 Hz, 2H). (*Z*-isomer) δ 7.47-7.42 (m, 2H), 7.26-7.21 (m, 2H), 4.04 (q, *J* = 1.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): (*E*/*Z*-isomers) δ 135.9, 135.4, 134.7, 134.5, 134.2, 133.5, 130.8, 130.2, 129.9, 129.3, 128.9, 128.8, 121.9 (q, *J* = 277.1 Hz), 121.8 (d, *J* = 276.4 Hz), 35.8, 32.7 (q, *J* = 3.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): (*E*-isomer) δ -56.7. (*Z*-isomer) δ -59.7.

LRMS (CI): m/z 381 $[M+H]^+$

FTIR (neat): 1623, 1593, 1490, 1427, 1398, 1309, 1263, 1217, 1178, 1126, 1091, 1017, 954, 931, 892, 827, 771, 733, 725, 655 cm^{-1}.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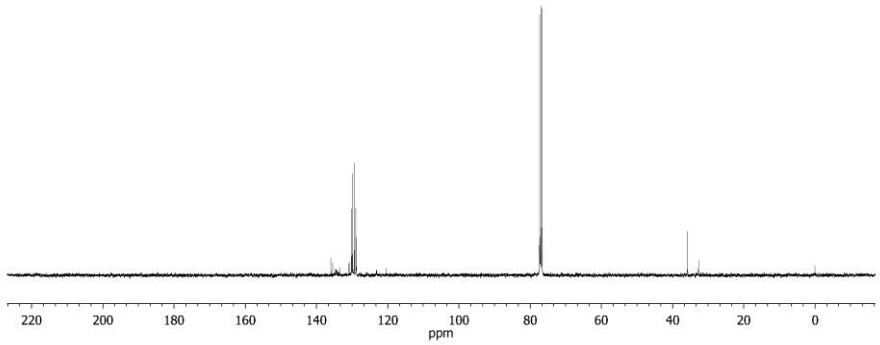
0
ppm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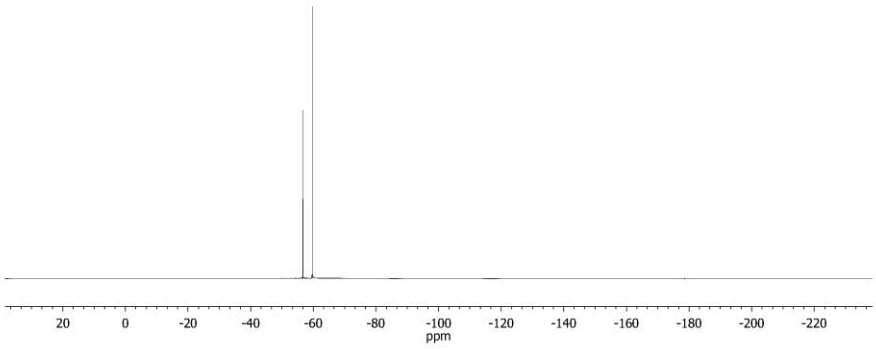
ppm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-140
-160
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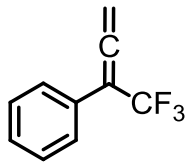
-220
ppm

Representative Procedure for the Preparation of Allenes 3.5a-d

Trifluoromethyl-containing allenes **3.5a**-**d** were prepared by modifying an existing literature procedure reported by Knochel.[67]

To a 250 mL three-necked round bottom flask equipped with a magnetic stir bar and reflux condenser was added methanesulfonate **3.4a** (7.7 g, 21 mmol, 1.0 equiv.) and lithium bromide (1.9 g, 21 mmol, 1.0 equiv.). The flask was sealed with rubber septa, purged with argon and DMF (43 mL, 0.5 M) was added, and the mixture was heated to 50 ºC for 5 hours. Upon cooling to room temperature, Zn dust (1.5 g, 23.5 mmol, 1.1 equiv.) was added and stirred for 24 hours. The reaction mixture was quenched with 1 M HCl (50 mL) and extracted with diethyl ether (3 × 50 mL). The organic phase was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to furnish the title compound **3.5a** as a colorless oil.

Synthesis of (1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5a)



The reaction was conducted on a 21 mmol scale (via **3.4a**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to furnish the title compound **3.5a** (3.1 g, 78%) as a colorless oil.

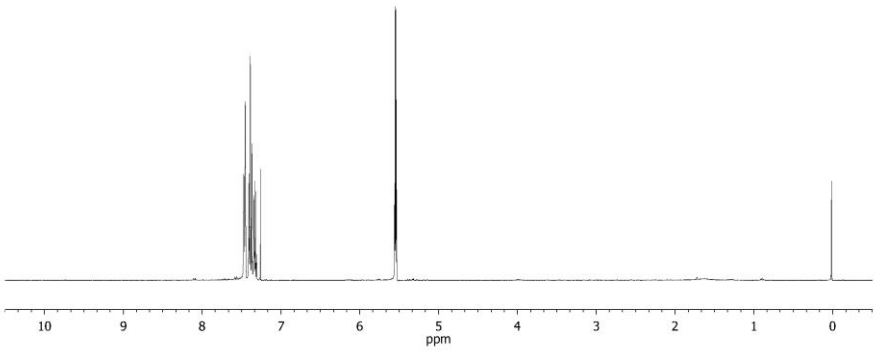
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.29 (m, 5H), 5.54 (q, *J* = 3.4 Hz, 2H).

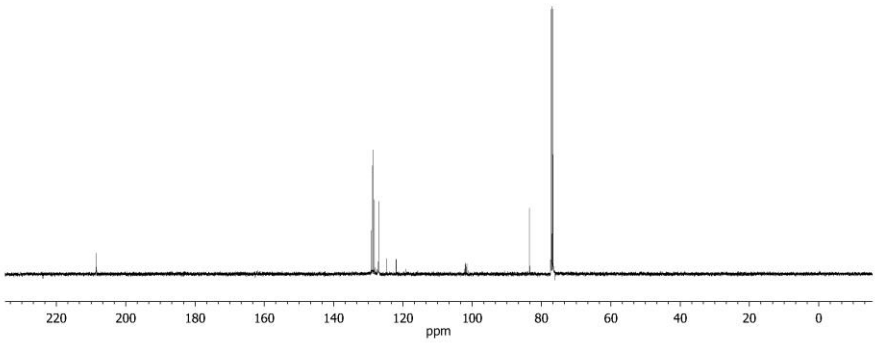
^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5 (q, *J* = 4.1 Hz), 128.7, 128.2, 123.3 (q, *J* = 273.8 Hz), 101.8 (q, *J* = 34.4 Hz), 83.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.47.

LRMS (CI): m/z 185 $[M+H]^+$

FTIR (neat): 3066.5, 1974, 1720, 1600, 1498, 1454, 1304, 1270, 1170, 1034, 1001, 937, 914, 866, 764, 739, 693, 693, 660 cm^{-1}.

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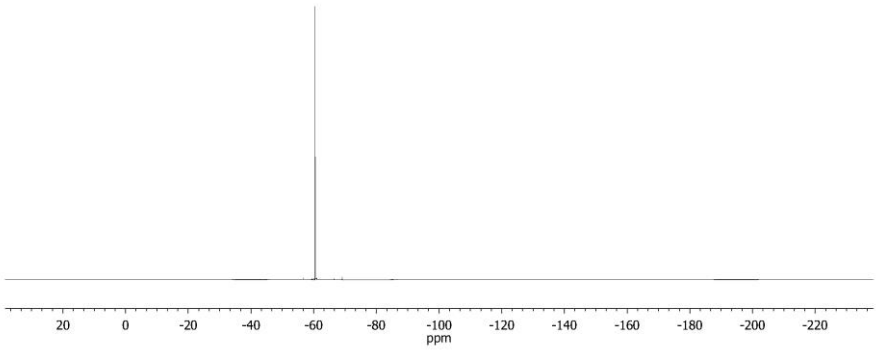
ppm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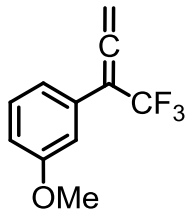
-220
ppm

Synthesis of 1-methoxy-3-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5b).



The reaction was conducted on a 1.8 mmol scale (via **3.4b**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5b** (334 mg, 86%) as a pale yellow oil.

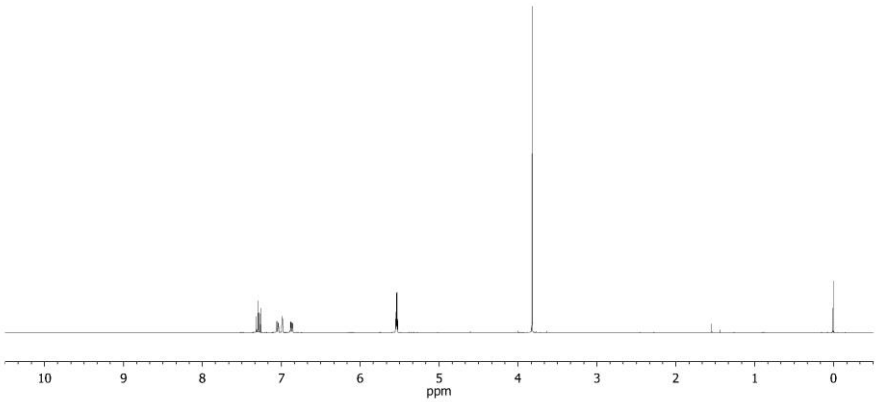
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.0, 16.0 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.86 (dd, *J* = 2.4, 8.0 Hz, 1H), 5.53 (q, *J* = 3.6 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ δ 208.6 (q, *J* = 3.7 Hz), 159.8, 130.5, 129.7, 123.3 (q, *J* = 272.3 Hz), 119.5, 113.6, 113.0, 101.7 (q, *J* =34.2 Hz), 83.5, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.3.

LRMS (EI): m/z 215 [M+H]

FTIR (neat): 1601, 1582, 1491, 1312, 1283, 1235, 1184, 1116, 1051, 974, 961, 868, 780, 729, 696 cm^{-1}.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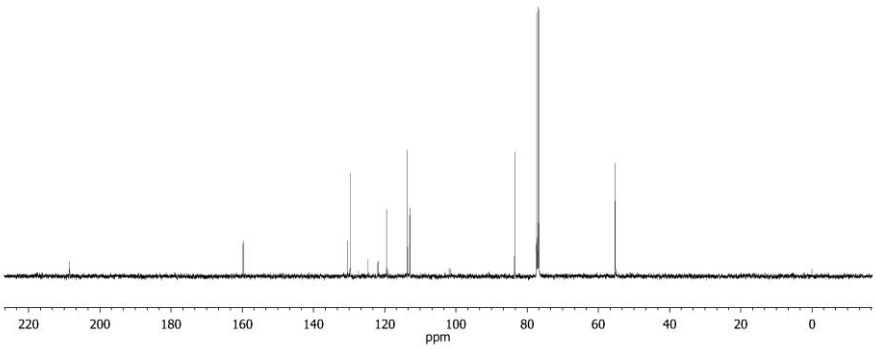
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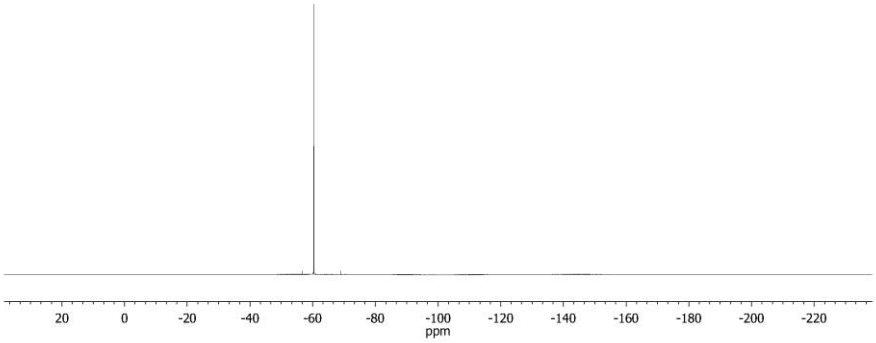
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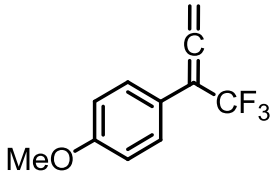
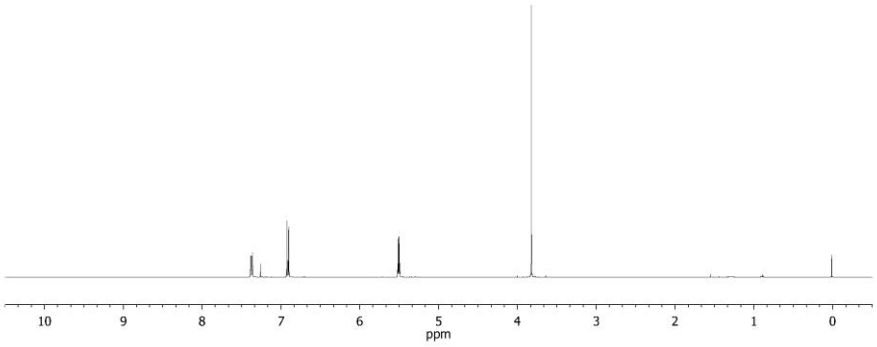
-220
ppm

Synthesis of 1-methoxy-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5c).



The reaction was conducted on a 5.1 mmol scale (via **3.4c**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5c** (792 mg, 72%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 9.2 Hz, 2H), 6.90 (ddd, *J* = 3.2, 5.2, 9.2 Hz, 2H), 5.50 (q, *J* = 3.2 Hz, 2H), 3.81 (s, 3H).
^{13}C NMR(100 MHz, $CDCl_3$): 208.1 (q, *J* = 3.7 Hz), 159.5, 128.4, 123.4 (q, *J* = 272.3 Hz), 121.2, 114.2, 101.4 (q, *J* = 34.0 Hz), 83.3, 55.3.
^{19}F NMR (376 MHz, $CDCl_3$): δ -60.7.
LRMS (EI): m/z 215 [M+H]
FTIR (neat): 1712, 1609, 1306, 1250, 1165, 1117, 1102, 1032, 938, 831, 731 cm^{-1}.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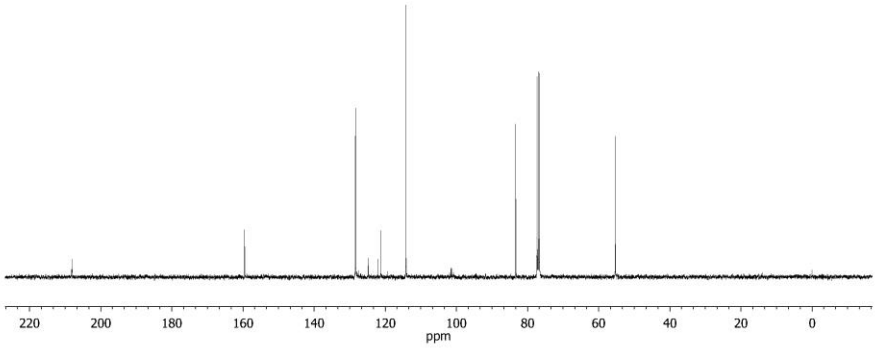
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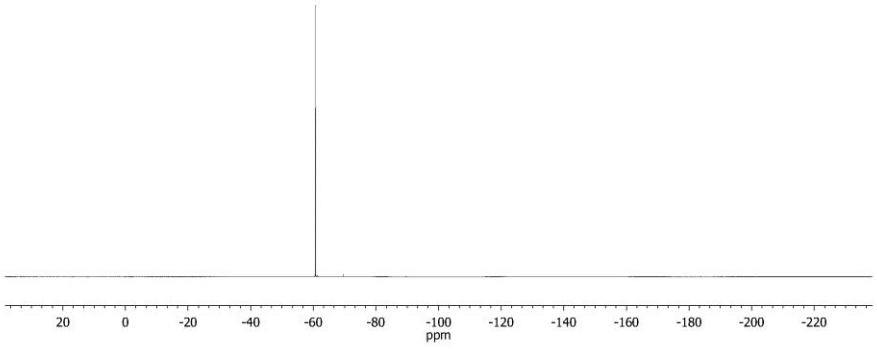
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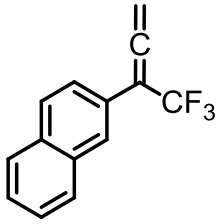
-220

Synthesis of 2-(1,1,1-trifluorobuta-2,3-dien-2-yl)naphthalene (3.5d).



The reaction was conducted on a 1.3 mmol scale (via **3.4d**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5d** (241 mg, 77%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.85-7.80 (m, 3H), 7.54-7.47 (m, 3H), 5.62 (q, *J* = 3.6 Hz, 2H).

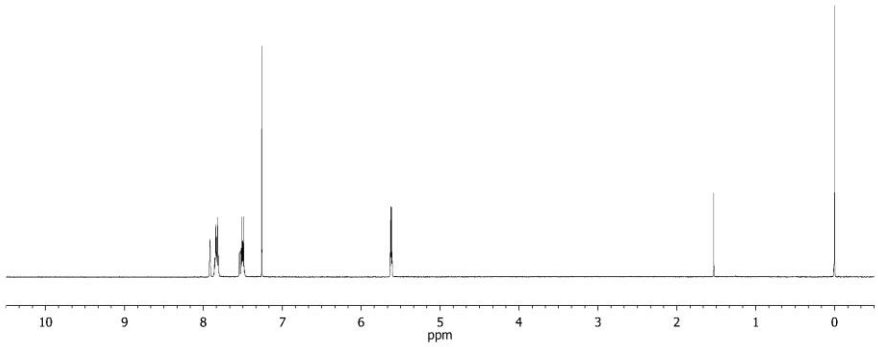
^{13}C NMR (100 MHz, $CDCl_3$ δ 208.9 (q, *J* = 4.5 Hz, 1C), 133.3, 132.8, 128.4, 128.3, 127.6, 126.6, 126.6, 126.3, 126.0 (q, *J* = 1.5 Hz, 1C), 124.8, 123.5 (q, *J* = 272.5 Hz), 102.1 (q, *J* = 34.2 Hz), 83.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.22.

LRMS (CI): m/z 235 $[M+H]^+$

FTIR (neat): 3046, 1969, 1935, 1598, 1507, 1307, 1265, 1245, 1209, 1163, 1133, 1108, 1022, 968, 925, 874, 861, 854, 834, 818, 747, 727 cm^{-1}.

MP (air): 54-56 °C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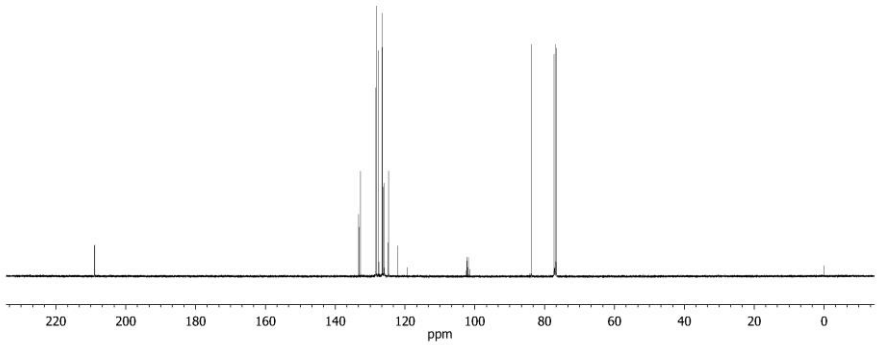
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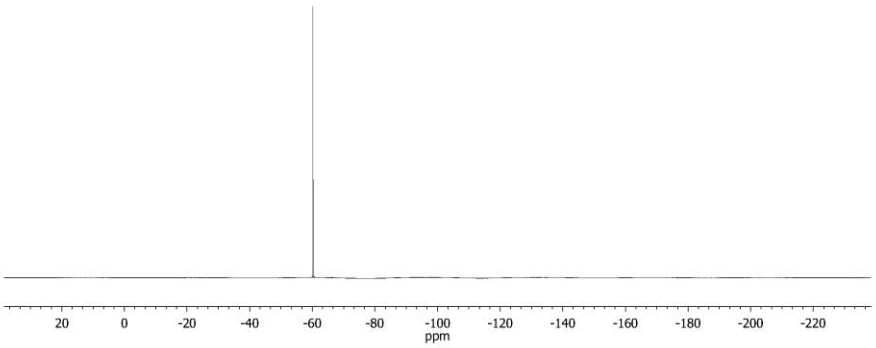
ppm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-160
-180
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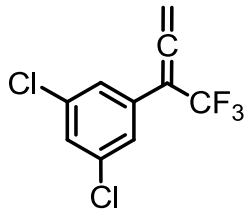
-220
ppm

Representative Procedure for the Preparation of Allenes 3.5e,f

Trifluoromethyl-substituted allenes **5e**,**f** were prepared by modifying an existing literature procedure reported by Lin.[68]

To a 25 mL three-neck round bottom flask equipped with a magnetic stir bar was added 3,4-dibromo-1,1,1-trifluorobut-2-enes **3.4e** (549 mg, 1.3 mmol, 1.0 equiv.). The flask was sealed with rubber septa, purged with argon, and DMF (2.6 mL, 0.5 M) was added, followed by Zn dust (87 mg, 1.33 mmol, 1.0 equiv.) and stirred for 48 hours at 25 °C. The reaction mixture was quenched with 1 M HCl (15 mL) and extracted with diethyl ether (3 × 10 mL). The organic phase was washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compounds **3.5e**.

Synthesis of 1,3-dichloro-5-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5e).



The reaction was conducted on a 1.3 mmol scale (via **3.4e**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5e** (194 mg, 56%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 3H), 5.64 (q, *J* = 3.2 Hz, 2H).

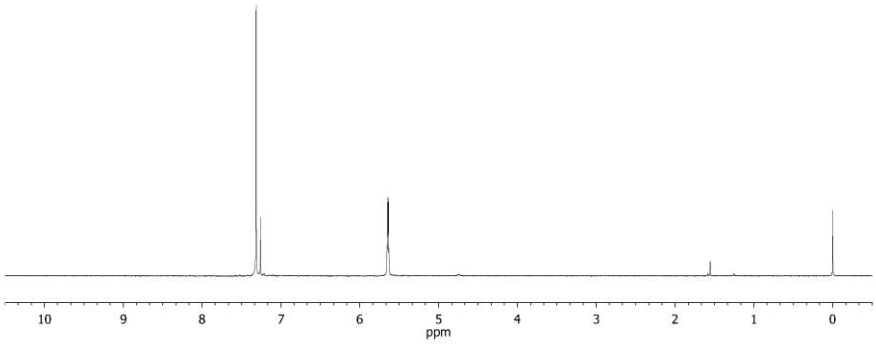
^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6 (q, *J* = 3.8 Hz), 135.4, 132.3, 128.3, 125.4, 122.8 (q, *J* = 273.9 Hz), 100.4 (q, *J* = 35.5 Hz), 84.7.

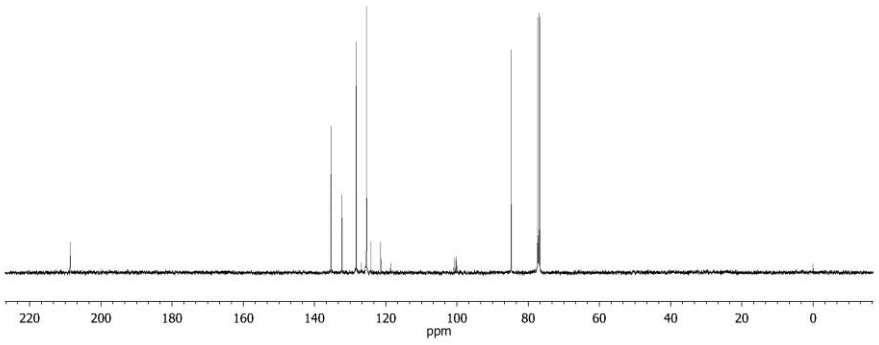
^{19}F NMR (376 MHz, $CDCl_3$): δ -60.5.

LRMS (CI): m/z 253 $[M+H]^+$

FTIR (neat): 3077, 2994, 1962, 1928, 1750, 1589, 1562, 1445, 1438, 1408, 1316, 1289, 1242, 1173, 1109, 986, 873, 857, 800, 775, 699, 685, 659 cm^{-1}.

MP (air): 51-55 °C

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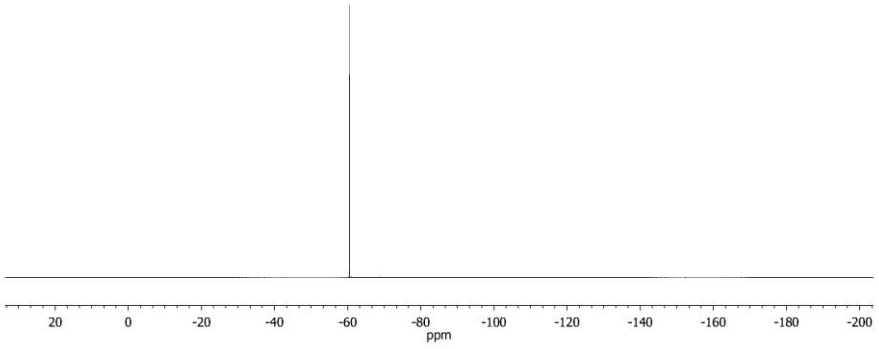
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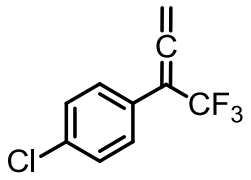
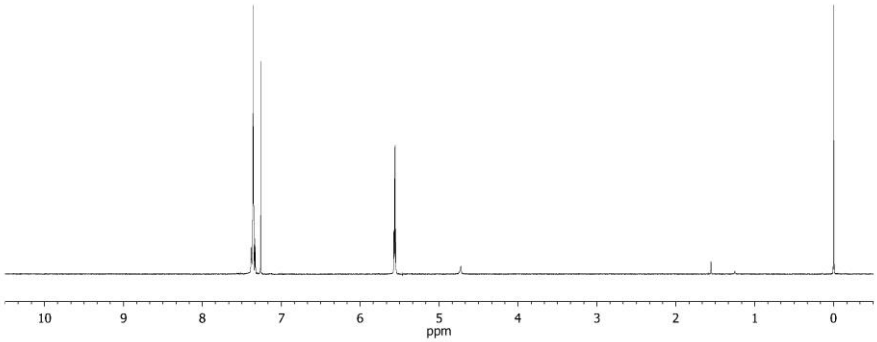
ppm

Synthesis of 1-chloro-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (3.5f).



The reaction was conducted on a 5.3 mmol scale (via **3.4f**). After aqueous work-up, the crude residue was purified by flash column chromatography (SiO_2, 100% hexane) to furnish the title compound **3.5f** (1.0 g, 84%) as a colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 4H), 5.56 (q, *J* = 3.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4 (q, *J* = 4.2 Hz), 134.2, 128.9, 128.3, 127.6, 123.1 (q, *J* = 273.8 Hz), 101.1 (q, *J* = 34.9 Hz), 83.9.
^{19}F NMR (376 MHz, $CDCl_3$): δ -60.6.
LRMS (CI): m/z 219 $[M+H]^+$
FTIR (neat): 1972, 1936, 1595, 1494, 1317, 1305, 1289, 1255, 1172, 1117, 1101, 1092, 1016, 935, 867, 828, 751, 735, 718, 707 cm^{-1}.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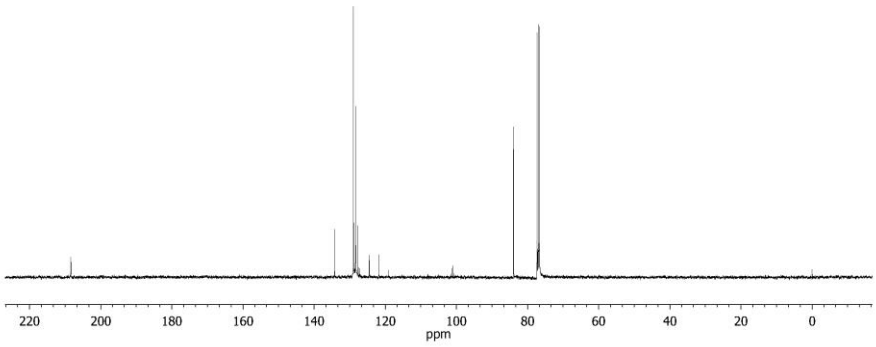
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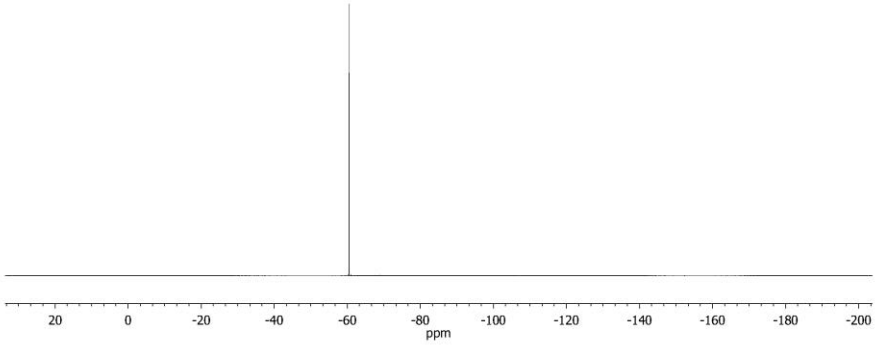
ppm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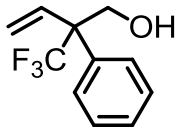
ppm

General Procedure for the Coupling of Allenes 3.5a-f to Paraformaldehyde

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.6 mg, 0.010 mmol, 5 mol %), DPPM (3.8 mg, 0.010 mmol, 5 mol %), and paraformaldehyde (12.0 mg, 0.40 mmol, 2.0 equiv.). The tube was sealed with a rubber septum, purged with argon, and toluene (0.4 mL, 0.5 M with respect to allene), allene (0.200 mmol, 1.0 equiv.) and 2-propanol (61 μL, 0.8 mmol, 4.0 equiv.) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. The reaction mixture was concentrated *in vacuo,* then diluted with diethyl ether (20 mL), and washed with 1 M HCl. The organics were removed and the aqueous layer was extracted diethyl ether (2 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2) to furnish the title compounds.

Synthesis of 2-phenyl-2-(trifluoromethyl)but-3-en-1-ol (3.6a)



The reaction was conducted in accordance with General Procedure (via allene **3.5a**) at 105°C for 1 hour. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexane) to furnish the title compound (33.6 mg, 78%, 20:1 (**3.6a**:**3.7a**)) as a yellow oil.

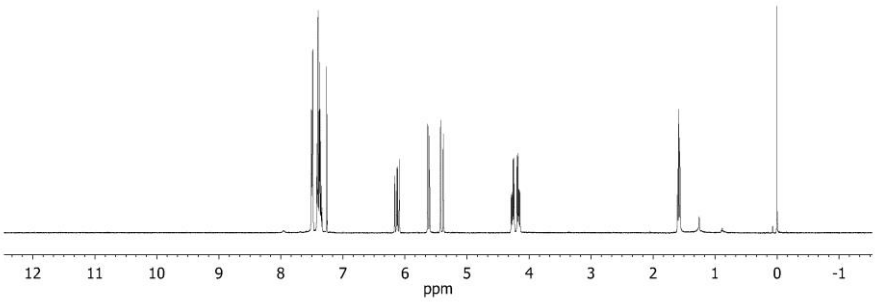
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.46 (m, 2H), 7.44-7.32 (m, 3H), 6.13 (dd, *J* = 17.9, 11.3 Hz, 1H), 5.62 (d, *J* = 11.3 Hz, 1H), 5.40 (d, *J* = 17.8 Hz, 1H), 4.26 (dd, *J* = 11.8, 6.7 Hz, 1H), 4.17 (dd, *J* = 11.8, 7.2 Hz, 1H), 1.59 (t, *J* = 7.1 Hz, 1H).

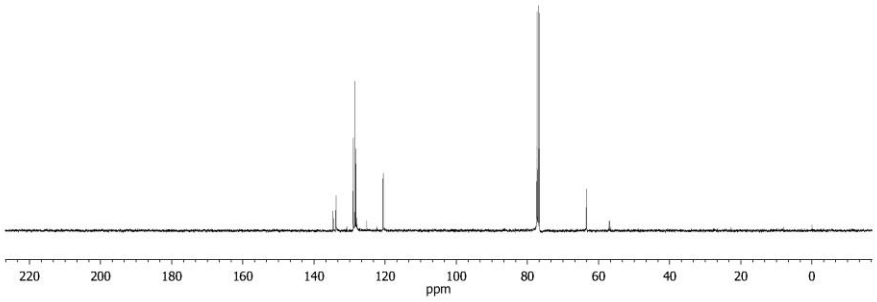
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 133.8, 129.0, 128.5, 128.2, 126.6 (q, *J* = 284.7 Hz), 120.6, 63.4, 56.9 (q, *J* = 22.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.9.

LRMS (CI): m/z 199 $[M\text{-}H_2O+H]^+$

FTIR (neat): 3411, 1640, 1498, 1449, 1250, 1145, 1047, 1012, 935, 877, 761, 733, 699 cm^{-1}.

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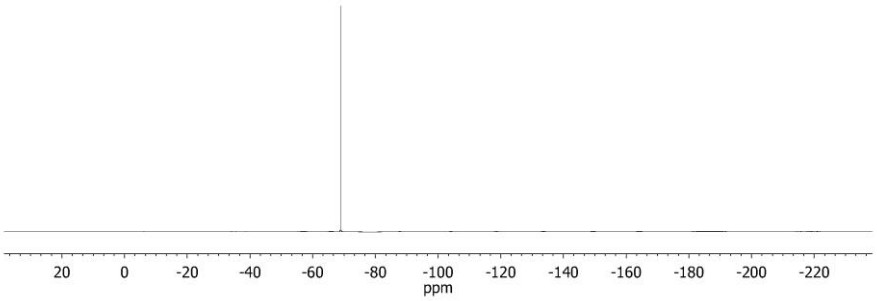
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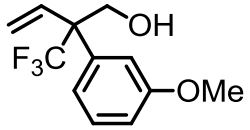
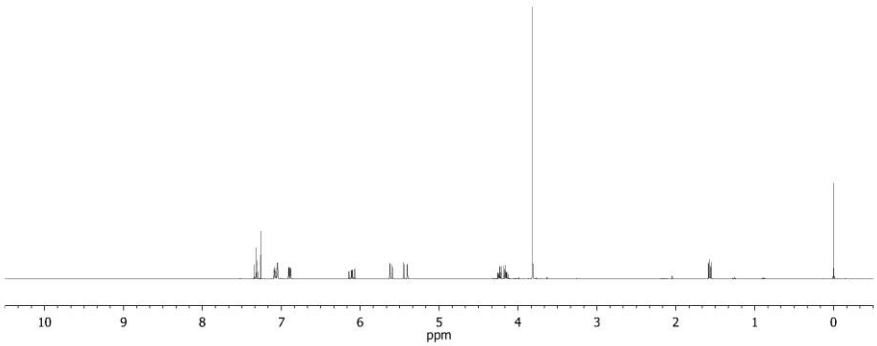
-220
ppm

Synthesis of 2-(3-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6b).



The reaction was conducted in accordance with General Procedure (via allene **3.5b**) at 120°C for 30 minutes. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexane) to furnish the title compound (32.1 mg, 65%, >20:1 (**3.6b**:**3.7b**)) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.09-7.07 (m, 1H), 7.05-7.04 (m, 1H), 7.89 (dddd, *J* = 8.2, 3.4, 2.8, 0.8 Hz, 1H), 6.11 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 5.42 (d, *J* = 17.8 Hz, 1H), 4.24 (dd, *J* = 11.8, 7.2 Hz, 1H), 4.15 (dd, *J* = 11.8, 7.2 Hz, 1H), 3.81 (s, 3H), 1.59-1.55 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 136.2, 133.7, 129.5, 126.5 (d, *J* = 282.7 Hz), 121.1, 120.5, 115.7, 113.0, 63.6, 56.9 (q, *J* = 22.3 Hz), 55.2.
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.6.
LRMS (CI): m/z 229 $[M\text{-}OH]^+$
FTIR (neat): 3458, 29.45, 2360, 1603, 1584, 1492, 1253, 1168, 1140, 1041, 940, 881, 816, 780, 732, 700 cm^{-1}.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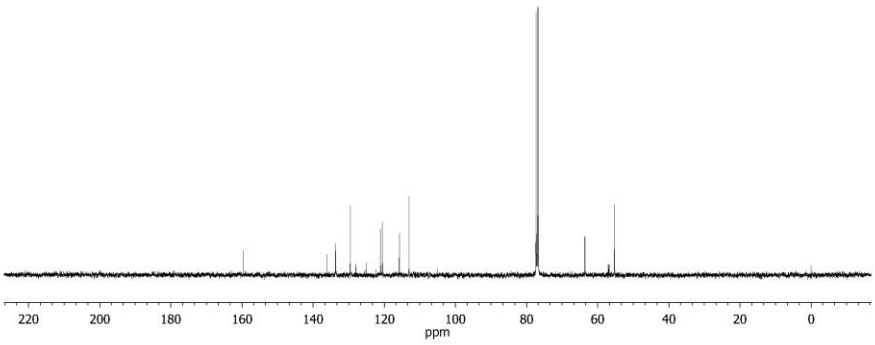
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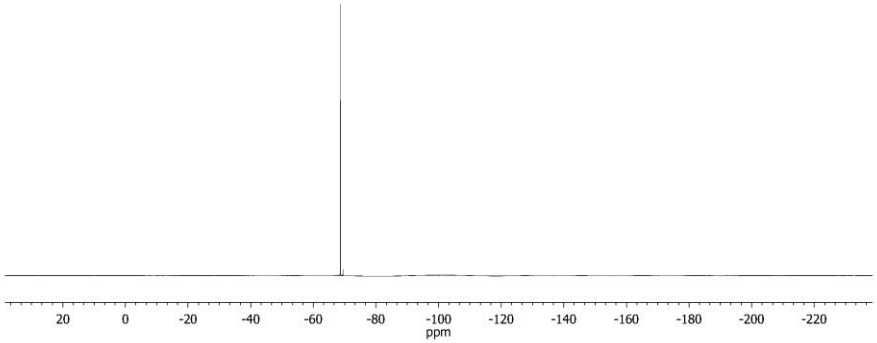
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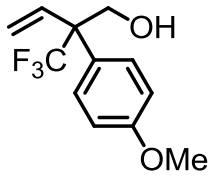
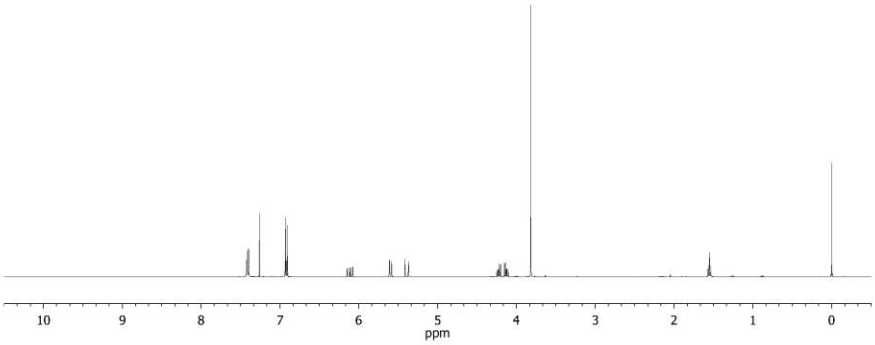
Synthesis of 2-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6c).



The reaction was conducted in accordance with General Procedure (via allene **3.5c**) at 105°C for 1 hour. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexane) to furnish the title compound (36.8 mg, 75%, >20:1 (**3.6c**:**3.7c**)) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.91 (ddd, *J* = 10.8, 6.4, 4.0 Hz, 2H), 6.11 (dd, *J* = 17.8, 11.4 Hz, 1H), 5.60 (d, *J* = 11.4 Hz, 1H), 5.39 (d, *J* = 17.8 Hz, 1H), 4.23 (dd, *J* = 11.6, 7.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.82 (s, 3H), 1.55 (t, *J* = 7.0 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 134.0, 130.3, 126.6 (q, *J* = 283.5 Hz), 126.3, 120.4, 113.9, 63.3, 56.4 (q, *J* = 23.1 Hz), 55.2.
^{19}F NMR (376 MHz, $CDCl_3$): δ -69.3.
LRMS (CI): m/z 229 $[M\text{-}OH]^+$
FTIR (neat): 3454, 1612, 1582, 1466, 1253, 1144, 1034, 932, 827, 738, 667 cm^{-1}.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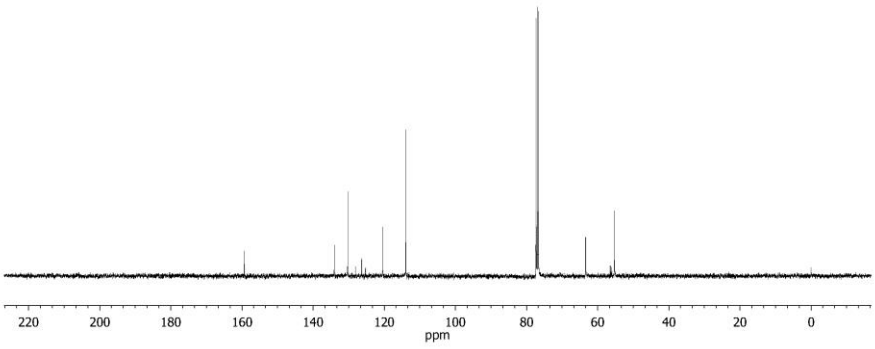
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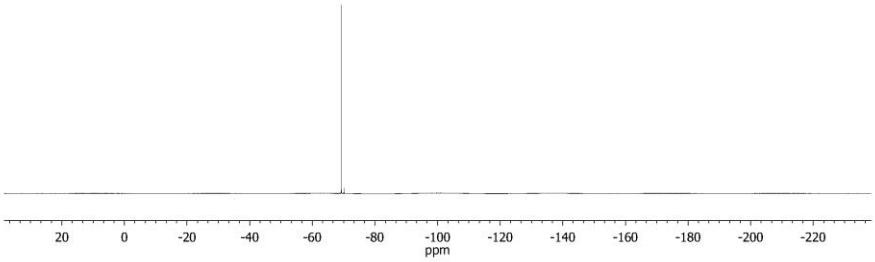
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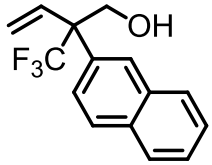
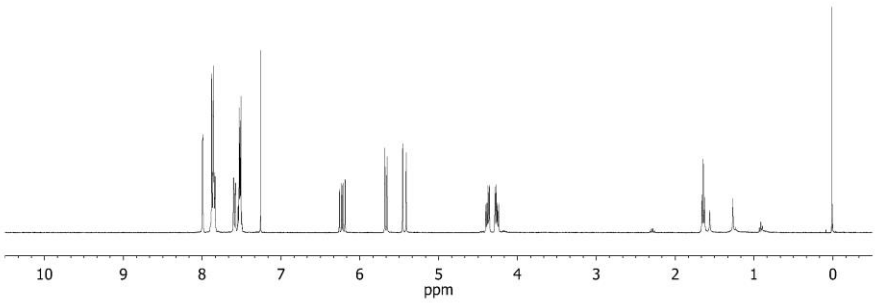
Synthesis of 2-(naphthalen-2-yl)-2-(trifluoromethyl)but-3-en-1-ol (3.6d).



The reaction was conducted in accordance with General Procedure (via allene **3.5d**) at 105 °C for 1 hour. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexane) to furnish the title compound (35.7 mg, 67%, >20:1 (**6d**:**7d**)) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.92-7.81 (m, 3H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.56-7.47 (m, 2H), 6.22 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.67 (d, *J* = 11.2 Hz, 1H), 5.43 (d, *J* = 17.8 Hz, 1H), 4.38 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.26 (dd, *J* = 11.9, 7.0 Hz, 1H), 1.64 (t, *J* = 7.0 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 133.0, 132.7, 131.9, 128.9, 128.4, 128.1, 127.4, 126.8, 126.7 (q, *J* = 285.1 Hz), 126.4, 126.1, 120.9, 63.5, 57.1 (q, *J* = 22.8 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.6.
LRMS (EI): m/z 266 $[M]^+$
FTIR (neat): 3332, 2918, 1596, 1510, 1413, 1363, 1325, 1255, 1209, 1168, 1145, 1125, 1081, 10501, 994, 964, 935, 909, 864, 810, 751, 728, 685, 660 cm^{-1}.
MP (air): 64-67 °C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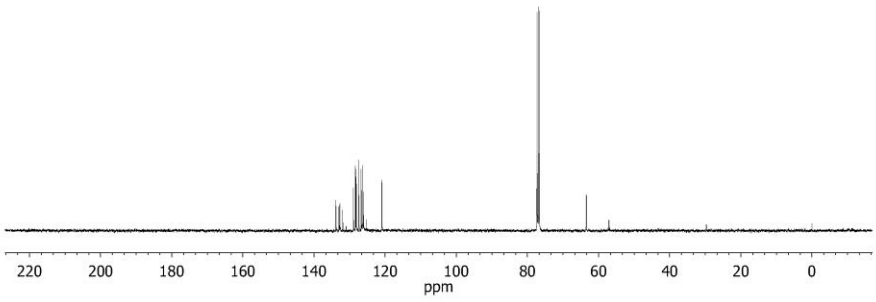
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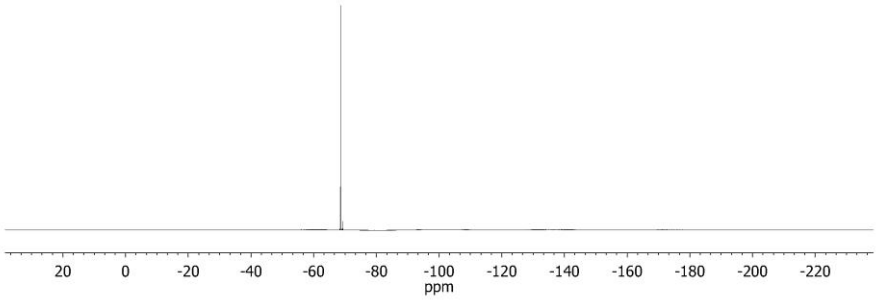
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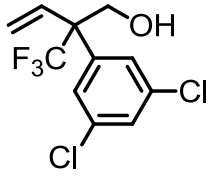
Synthesis of 2-(3,5-dichlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6e).



The reaction was conducted in accordance with General Procedure (via allene **3.5e**) at 120 °C for 30 minutes. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% ethyl acetate/hexane) to furnish the title compound (38.7 mg, 68%, 16:1 **3.**(**6e**:**3.7e**)) as a yellow oil.

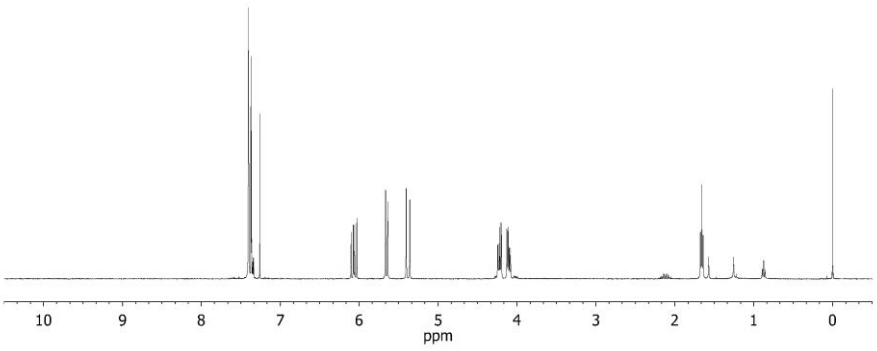
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 2H), 7.37 (t, *J* = 1.8 Hz, 1H), 6.07 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.65 (d, *J* = 11.3 Hz, 1H), 5.38 (d, *J* = 17.8 Hz, 1H), 4.22 (dd, *J* = 11.9, 6.9 Hz, 1H), 4.11 (dd, *J* = 11.9, 6.5 Hz, 1H), 1.66 (t, *J* = 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 135.1, 132.8, 128.6, 127.9, 126.0 (q, *J* = 284.8 Hz), 121.7, 63.1, 56.8 (q, *J* = 23.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.9.

LRMS (EI): m/z 285 $[M+H]^+$

FTIR (neat): 3398, 1589, 1564, 1420, 1258, 1156, 1051, 997, 941, 859, 801, 771, 731, 688 cm^{-1}.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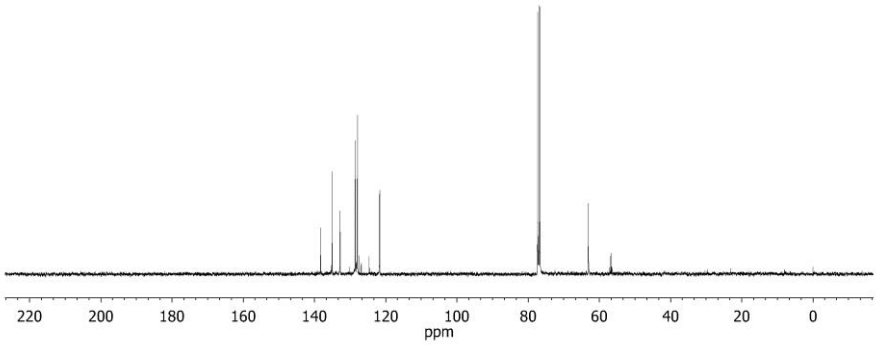
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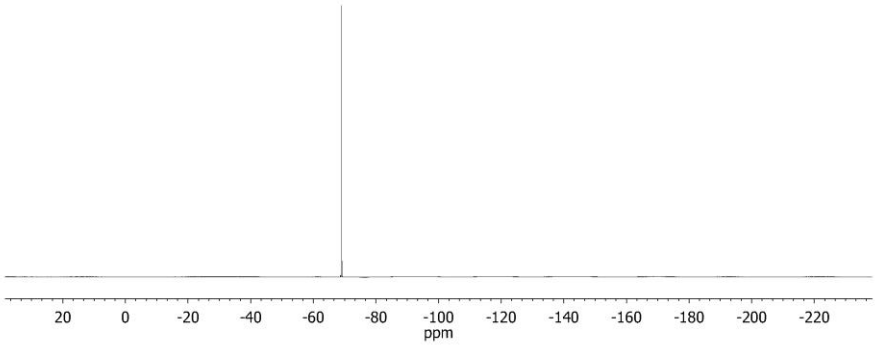
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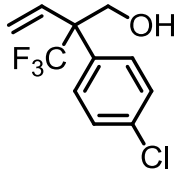
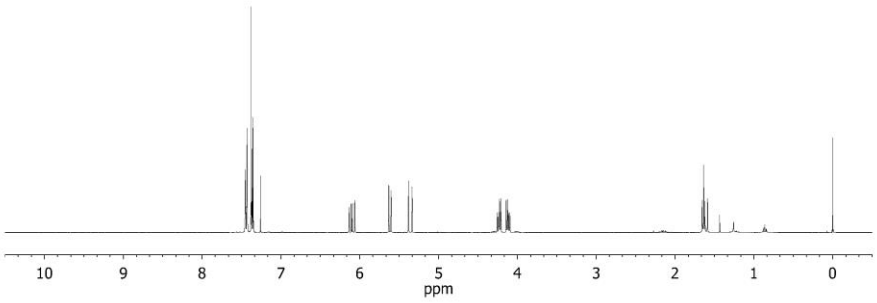
-220
ppm

Synthesis of 2-(4-chlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (3.6f).



The reaction was conducted in accordance with General Procedure (via allene **3.5f**) at 120°C for 30 minutes. The mixture was allowed to cool to room temperature, at which point methanolic KOH (2.0 M) was added and stirred for 4 hours. After aqueous workup, the crude residue was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 10% ethyl acetate/hexane) to furnish the title compound (36.3 mg, 73%, >20:1(**3.6f**:**3.7f**)) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.40 (m, 2H), 7.39-7.33 (m, 2H), 6.10 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.62 (d, *J* = 11.2 Hz, 1H), 5.36 (d, *J* = 17.8 Hz, 1H), 4.23 (dd, *J* = 11.9, 7.0 Hz, 1H), 4.12 (dd, *J* = 11.9, 6.7 Hz, 1H), 1.64 (t, *J* = 7.0 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 133.5, 133.2, 130.6, 128.7, 126.4 (q, *J* = 284.8 Hz), 121.1, 63.2, 56.7 (q, *J* = 22.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -69.2.
LRMS (CI): m/z 233 $[M\text{-}H_2O+H]^+$
FTIR (neat): 3429, 2908, 1642, 1597, 1496, 1258, 1150, 1098, 1047, 1013, 935, 878, 821, 747, 732, 662 cm^{-1}.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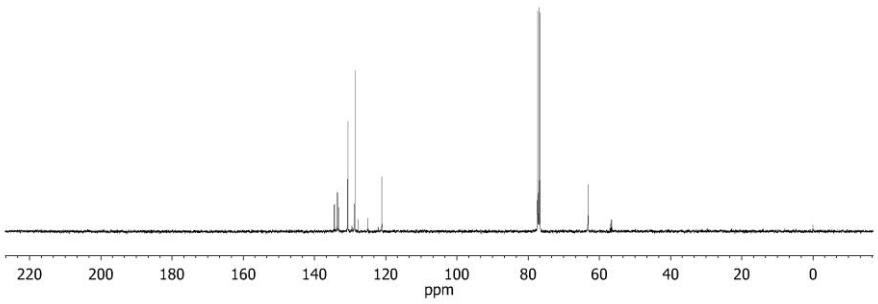
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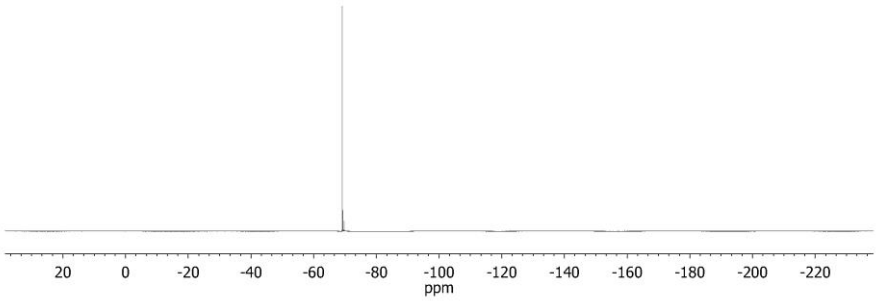
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-160
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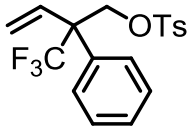
-220
ppm

Elaboration of Product 3.6a

Synthesis of 2-phenyl-2-(trifluoromethyl)but-3-en-1-yl 4-methylbenzenesulfonate.

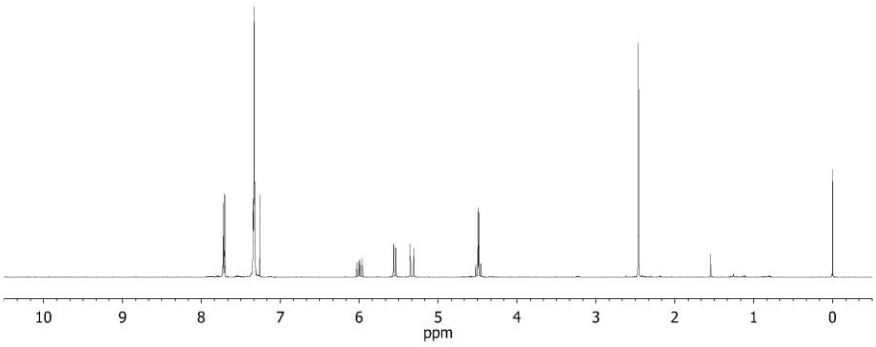


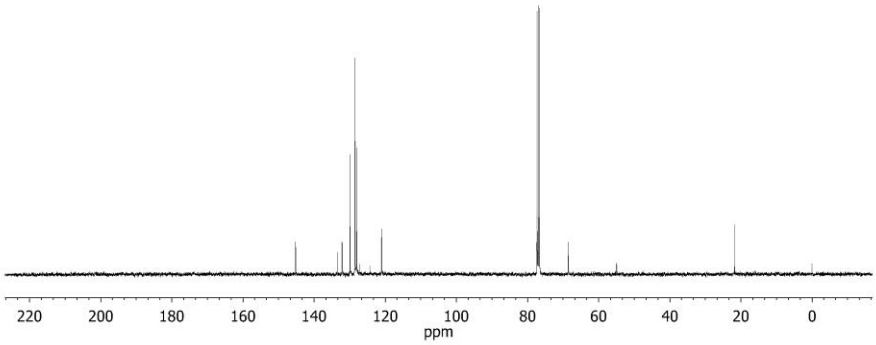
To an oven-dried pressure tube equipped with magnetic stir bar was added **3.6a** (153 mg, 0.708 mmol, 1.0 equiv.) and trimethylamine hydrogen chloride (6.8 mg, 0.071 mmol, 10 mol %). The flask was sealed with a rubber septum, purged with argon, and toluene (0.7 mL, 1.0 M with respect to **3.6a**) and triethylamine (0.3 mL, 2.124 mmol, 3.0 equiv.) were added. Then, *p*-toluenesulfonyl chloride (270 mg, 1.416 mmol) in toluene (0.7 mL, 2.0 M with respect to *p*-toluenesulfonyl chloride) was dropwise added over 5 min. The rubber septum was quickly replaced with a screw cap and the reaction was stirred at 25 °C for 20 hours, at which point distilled water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 20% ethyl acetate/hexane) to afford the title compound (211 mg, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.36-7.29 (m, 7H), 6.00 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.55 (d, *J* = 11.3 Hz, 1H), 5.33 (d, *J* = 17.8 Hz, 1H), 4.55 – 4.41 (m, 2H), 2.46 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 133.5, 132.2, 132.1, 129.9, 128.5, 128.0, 125.7 (q, *J* = 285.0 Hz), 121.0, 68.5, 55.0 (q, *J* = 24.6 Hz), 21.7.
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.7.

LRMS (CI): m/z 371 $[M+H]^+$

FTIR (neat): 3064, 1598, 1496, 1450, 1367, 1294, 1250, 1189, 1175, 1153, 1096, 1070, 990, 939, 885, 825, 812, 791, 763, 739, 699, 665 cm^{-1}.

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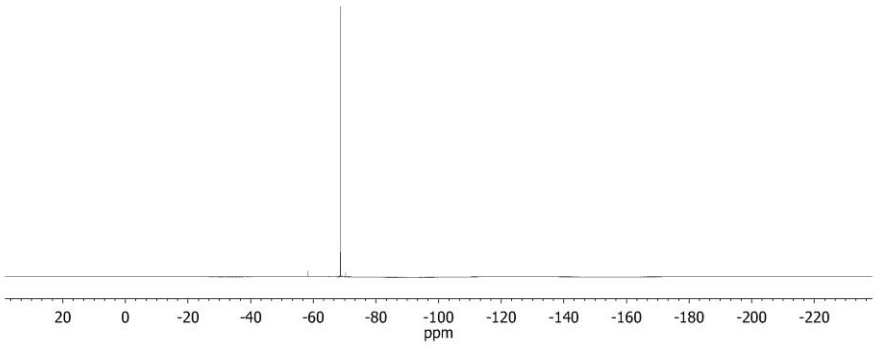
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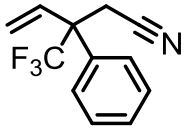
-220
ppm

Synthesis of 3-phenyl-3-(trifluoromethyl)pent-4-enenitrile (3.8a).



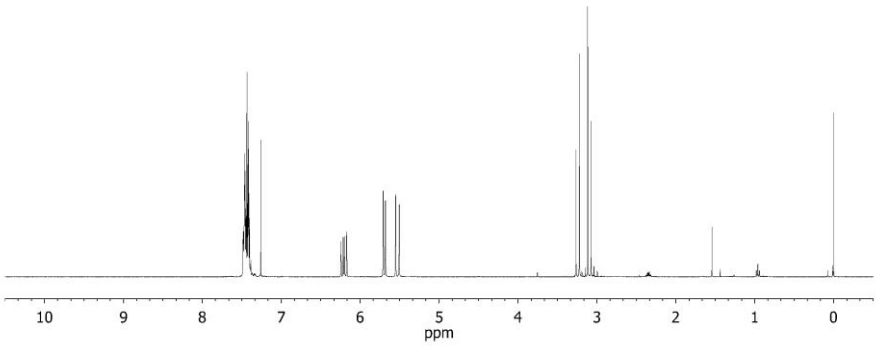
3-phenyl-3-(trifluoromethyl)pent-4-enenitrile was prepared by modifying a literature procedure reported by Kuwahara.[69]

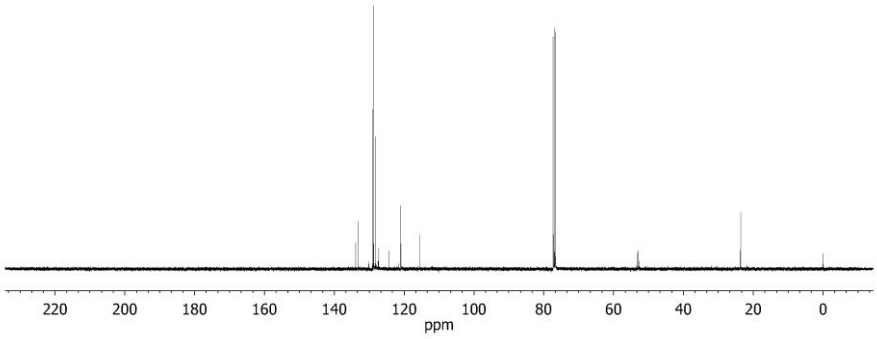
To an oven-dried pressure tube equipped with magnetic stir bar was added 2-phenyl-2-(trifluoromethyl)but-3-en-1-yl-4-methylbenzenesulfonate (180 mg, 0.486 mmol, 1.0 equiv.) and sodium cyanide (NaCN) (71.5 mg, 1.458 mmol, 3.0 equiv.). The tube was sealed with a rubber septum, purged with argon and DMSO (1.0 mL, 0.5 M with respect to tosylate) was added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to 150 °C for 45 hours. The reaction mixture was allowed to cool to room temperature, at which point diethyl ether (20 mL) and water (20 mL) were added. The organics were removed and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 15% diethyl ether/pentane) to afford the title compound **3.8a** (70.0 mg, 64%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.36 (m, 5H), 6.21 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.69 (d, *J* = 11.2 Hz, 1H), 5.53 (d, *J* = 17.7 Hz, 1H), 3.43-3.00 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 133.1 (q, *J* = 1.5 Hz), 129.0, 128.8, 128.3 (q, *J* = 1.2 Hz), 125.8 (q, *J* = 284.5 Hz), 121.0, 115.6, 53.0 (q, *J* = 25.1 Hz), 23.6 (q, *J* = 2.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -71.6.

LRMS (CI): m/z 266 $[M+H]^+$

FTIR (neat): 2255, 1497, 1150, 1251, 1153, 1004, 975, 941, 904, 763, 733, 698 cm^{-1}.

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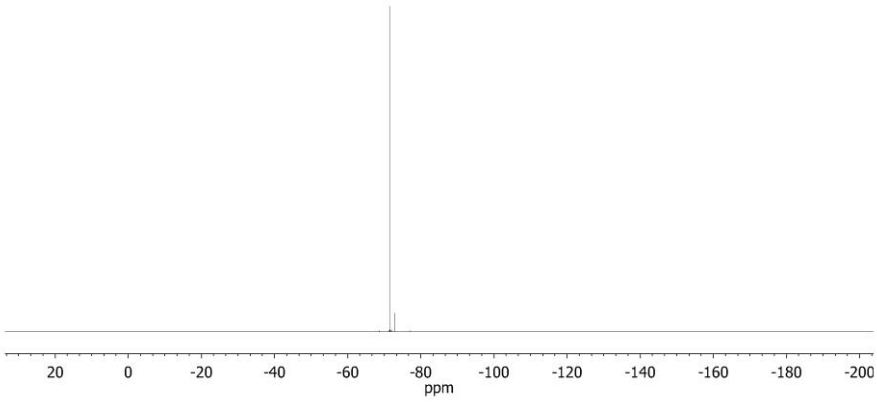
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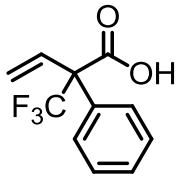
ppm

Synthesis of 2-phenyl-2-(trifluoromethyl)but-3-enoic acid.



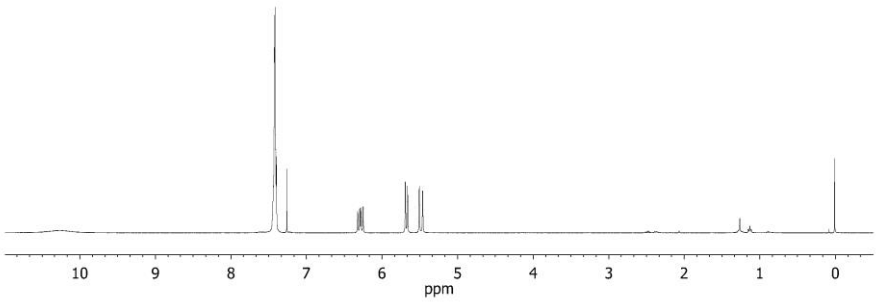
2-phenyl-2-(trifluoromethyl)but-3-enoic acid was prepared by modifying an oxidation procedure reported by Berkowitz.[70]

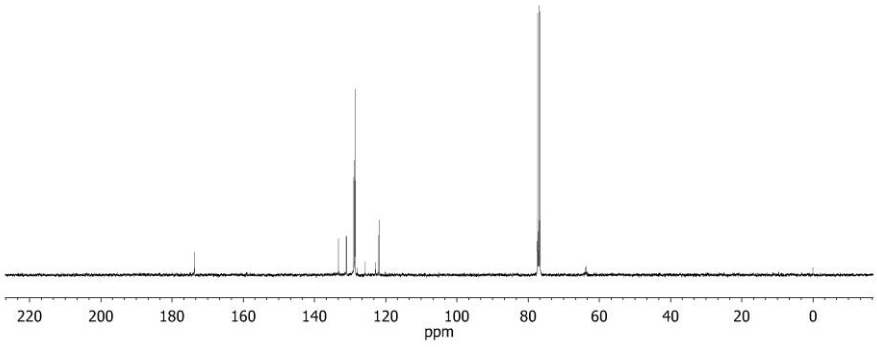
To a flame-dried round bottom flask equipped with magnetic stir bar was added **3.6a** (153 mg, 0.708 mmol, 1.0 equiv.). The flask was sealed with a rubber septum, purged with argon, and acetone (7.0 mL, 0.1 M with respect to **3.6a**) was added. The mixture was cooled to 0 °C, at which point freshly prepared H_2CrO_4 (0.58 mL, 3.66 M, 3.0 equiv.) was drop wise added. The reaction mixture was allowed to warm to room temperature and stir for 2 hours, at which point 2-propanol (10 mL) was slowly added. The precipitated salts were filtered through a pad of cotton, washing with dichloromethane (30 mL). The filtrate was washed with 1 M HCl (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 40% ethyl acetate/hexane) to afford the title compound (141 mg, 87%) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (brs, 1H), 7.52-7.33 (m, 5H), 6.29 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.68 (d, *J* = 11.0 Hz, 1H), 5.48 (d, *J* = 18.0 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 133.3, 131.1, 128.9, 128.7, 128.6, 124.3 (q, *J* = 283.9 Hz), 121.9, 63.8 (q, *J* = 25.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.5.
LRMS (CI): m/z 231 $[M+H]^+$

FTIR (neat): 2918, 1716, 1638, 1494, 1452, 1394, 1328, 1266, 1219, 1177, 1155, 1124, 1082, 1015, 1004, 992, 937, 917, 876, 762, 709, 697, 671, 655 cm^{-1}.

MP (air): 98-100 °C

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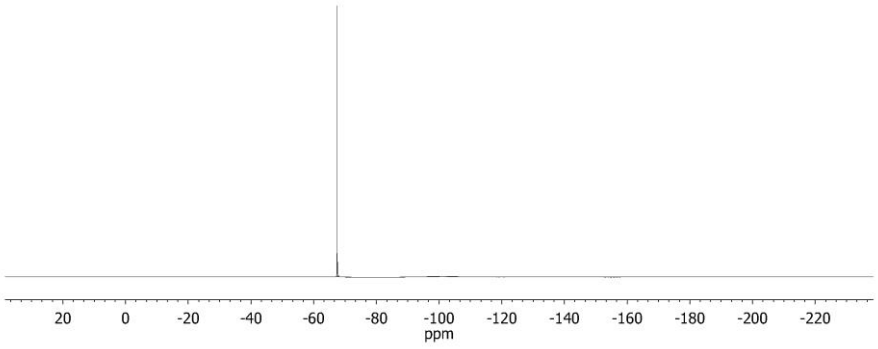
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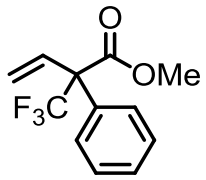
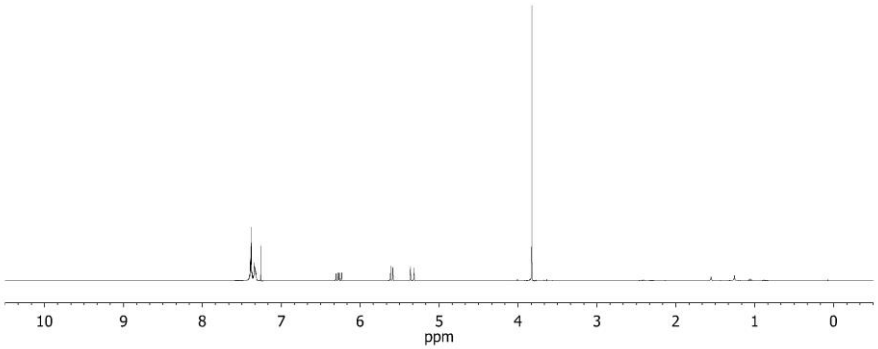
ppm

Synthesis of methyl 2-phenyl-2-(trifluoromethyl)but-3-enoate (3.9a).



To an oven-dried pressure tube equipped with magnetic stir bar was added 2-phenyl-2-(trifluoromethyl)but-3-enoic acid (46.0 mg, 0.2 mmol, 1.0 equiv.). The tube was sealed with a rubber septum, purged with argon, and methanol (0.2 mL, 1 M with respect to acid) and conc. Sulfuric acid (4 µL) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated at 75°C for 18.5 hours. The reaction mixture was allowed to cool to room temperature, at which point dichloromethane (10 mL) was added and quenched with distilled water. The organics were removed and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (SiO_2, 5% ethyl acetate/hexane) to afford the title compound **3.9a** (39.4 mg, 81%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.29 (m, 5H), 6.27 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.60 (d, *J* = 11.1 Hz, 1H), 5.34 (d, *J* = 17.7 Hz, 1H), 3.82 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 133.9, 131.7, 128.6, 128.6, 128.5, 124.5 (q, *J* = 283.7 Hz), 121.2 , 64.0 (q, *J* = 25.3 Hz), 53.1.
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.4.
LRMS (CI): m/z 245 $[M+H]^+$
FTIR (neat): 2957, 1745, 1640, 1498, 1451, 1436, 1331, 1267, 1238, 1163, 1125, 1084, 1031, 1006, 940, 903, 800, 766, 719, 697, 655 cm^{-1}.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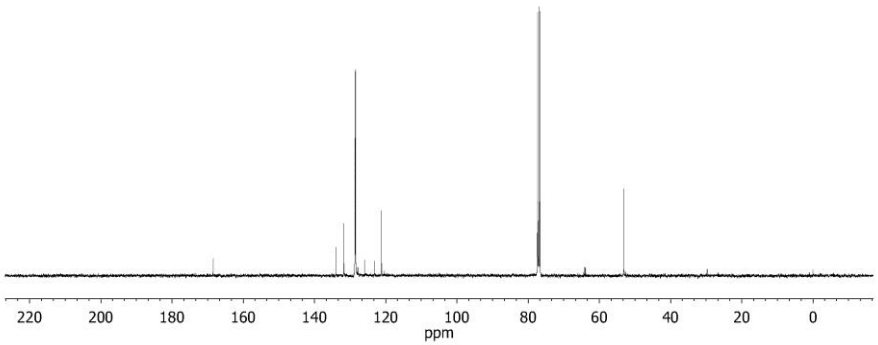
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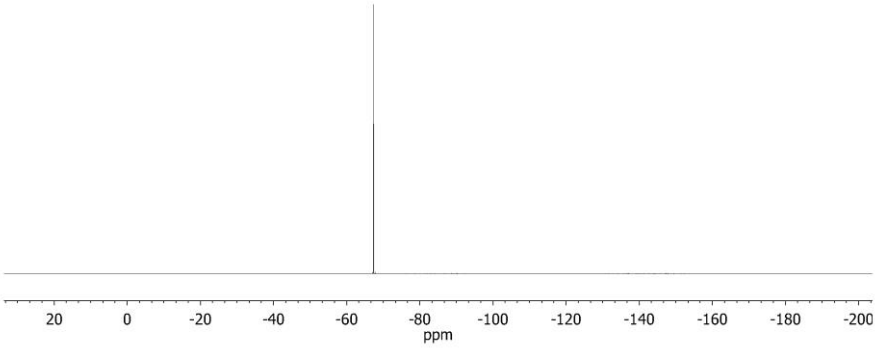
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Chapter 4: Ruthenium-Catalyzed Oxidative Coupling of Secondary Alcohols and Dienes*

4.1 Introduction

Redox-triggered C-C bond formation between primary alcohols and π-unsaturates has been intensely investigated by the Krische group.[1–3] Furthermore, the reductive coupling variants between aldehydes and π-unsaturates have also been well established. Despite advancements in the understanding of these couplings, the related redox-triggered couplings between secondary alcohols with π-unsaturates remained elusive. Although dehydrogenation of secondary alcohols has occurred to generate the ketone as the electrophile in the redox pair, subsequent carbonyl addition has proven challenging, presumably due to the low electrophilicity of ketones when compared to aldehydes. It seemed as though a new catalytic system must be examined, which could further expand the scope of redox-triggered C-C bond formation to include secondary alcohols. A new catalyst must serve two roles: it should function to dehydrogenate the secondary alcohol to a ketone, thus forming a redox pair with a π-unsaturate, and it should promote the coupling between the generated nucleophile-electrophile pair (π-unsaturate and ketone).

After a survey of literature, a ruthenium catalyst was found which could serve both roles. Murai and coworkers employed $(Ru)_3(CO)_{12}$ in a [2+2+1] oxidative coupling reaction of ethylene, carbon monoxide and 1,2-

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*Park, B. Y.; Montgomery, T. P.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135* (44), 16320. Acknowledgement is made to B. Y. P. for reaction discovery, development and scope evaluation, V. J. G. for scope evaluation and M. J. K. for supervision.
Geary, L. M.; Chen, T.-Y.; Montgomery, T. P.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136* (16), 5920. Acknowledgement is made to L. M. G. for reaction discovery, development and scope evaluation, T.-Y. C. for reaction development and scope evaluation and M. J. K. for supervision.

dicarbonyl compounds to form spirolactones (Scheme 4.1).[4] It has been known for some time that $(Ru)_3(CO)_{12}$ can catalyze the oxidation of both primary and secondary alcohols,[5–7] but one set of findings revealed by Beller and coworkers showed exceptional promise due to their structural similarities to the ones used by Murai and coworkers. Beller and coworkers found that α-hydroxy amides participate in borrowing hydrogen chemistry when exposed to $(Ru)_3(CO)_{12}$ in the presence of a variety of different anilines (Figure 4.1).[8] It is believed the alcohol is first oxidized to the α-ketoamide, generating a ruthenium hydride. Condensation of the amine on the ketone generates the imine, which is then reduced to the amine by the previously generated ruthenium-hydride.

Scheme 4.1. Ruthenium(0) catalyzed spirolactonization of 1,2-dicarbonyls with ethylene and carbon monoxide.

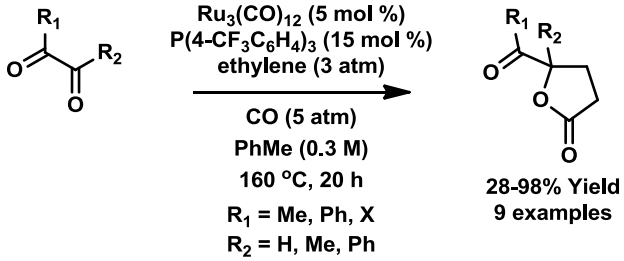
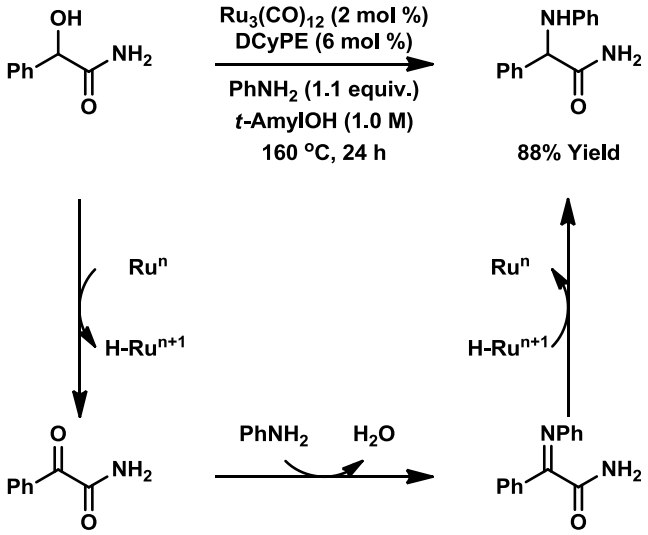
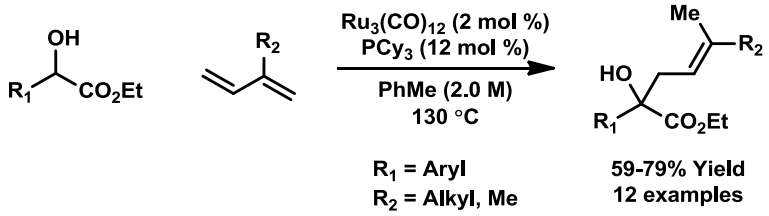


Figure 4.1. Borrowing hydrogen amination of α-hydroxy amides.



Using this newly identified catalyst, redox-neutral C-C bond formations between α-hydroxy esters with isoprene and myrcene were attempted. Fortuitously, $(Ru)_3(CO)_{12}$, when paired with PCy_3, smoothly catalyzes this transformation, permitting access to products of prenylation and geranylation of secondary alcohols from the alcohol oxidation level (Scheme 4.2).[9]

Scheme 4.2. Ruthenium catalyzed prenylation and geranylation of secondary alcohols.



Surprisingly, the products showed coupling at the four-position of the diene, a previously unobserved regioselectivity when employing a ruthenium catalyst. This regioselectivity is indicative of an oxidative coupling-type mechanism. By slightly modifying these conditions, this technology was expanded to include

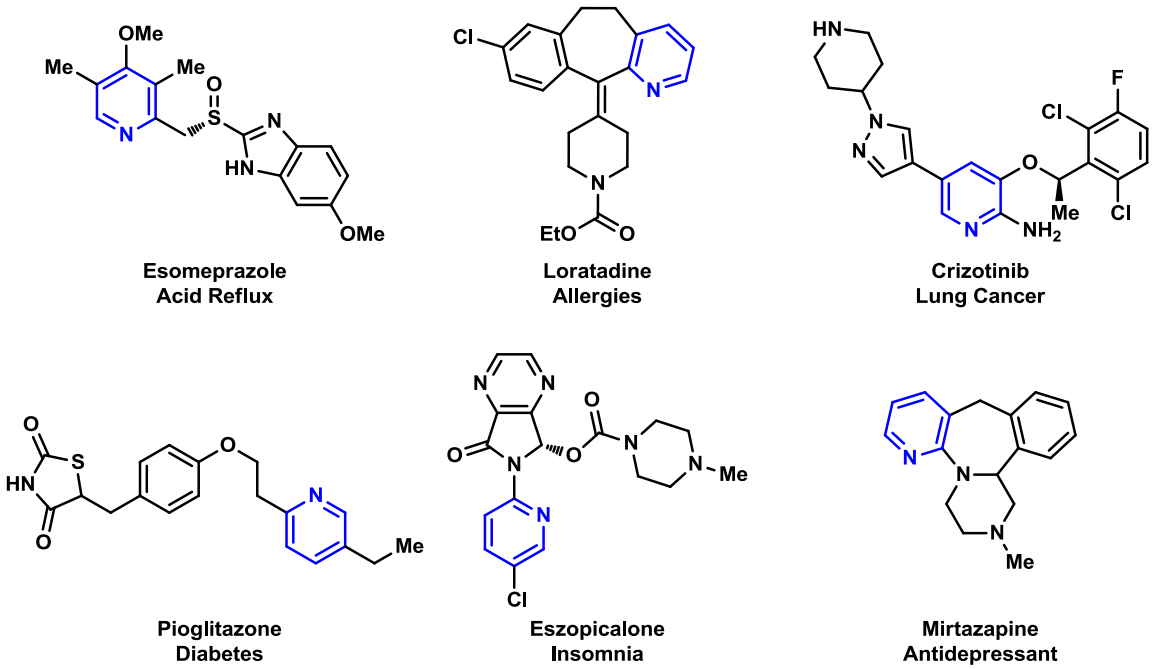
coupling of 3-hydroxyoxindoles, 1,2-diols and pyridyl-methanols with dienes[10–13] and acrylates,[14] as well as 1,2-diols with alkynes[15] and 3-hydroxyoxindoles with α-olefins.[16]

4.2 Ruthenium Catalyzed Hydrohydroxyalkylation of Isoprene with Heteroaromatic Secondary Alcohols

4.2.1 Background

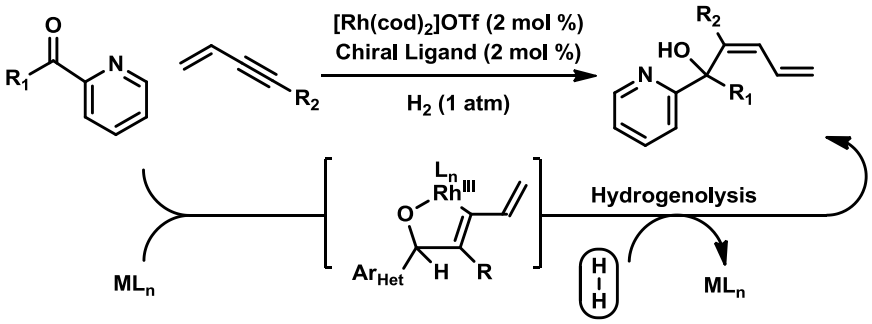
Nitrogen-containing heterocycles have a permeating presence in active pharmaceutical ingredients.[17] Further, the pyridine ring reigns supreme in the realm of nitrogen-containing heterocycles.[18] It is present in more than one hundred drugs on the market, including blockbuster drugs esomeprazole (Nexium) and loratidine (Claritin) (Figure 4.2).[19] Because of its privileged nature in pharmaceuticals, numerous methods have been developed to

Figure 4.2. Pharmaceuticals on the market which contain a pyridine ring.



access functionalized derivatives of this substructure. The majority of these methods exist to functionalize at the heteroaromatic nucleus through metal catalyzed cross-couplings or related C-H activation initiated processes.[20–23] Metal catalyzed C-C bond forming transformations that make use of the LUMO-lowering effect of pyridines and higher azines, enabling extranuclear functionalizations, are less common. These types of transformations include rhodium catalyzed addition of organoboron reagents to 2-vinyl azines[24–27] and 2-alkynyl azines[28–30] as well as reductive aldol and Mannich type couplings of 2-vinyl azines.[31,32] In one example of rhodium(I) catalyzed reductive C-C coupling mediated by hydrogen gas, the LUMO-lowering effect of pyridine, which is augmented by their ability to chelate, was indispensable in promoting an alkyne-carbonyl oxidative coupling pathway (Scheme 4.3).[33]

Scheme 4.3. Rhodium catalyzed coupling of alkynes and carbonyls.

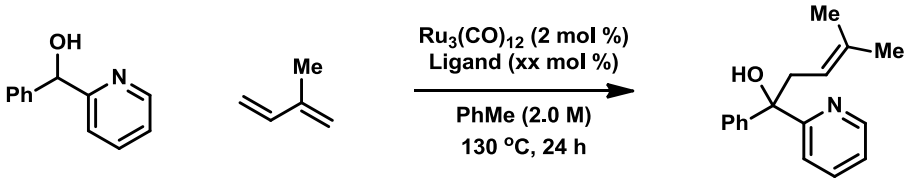


Inspired by work employing $(Ru)_3(CO)_{12}$ as a catalyst to promote a similar transformation that utilizes transfer hydrogenative C-C bond formation to couple α-hydroxy esters (Scheme 4.2) and 1,2-diols with dienes,[9,11] which is believed to proceed through the coupling of dienes and the transient α-ketoester and 1,2-dione respectively, it was postulated that certain heteroaromatic ketones could serve as vicinal dicarbonyl groups to engage heteroaromatic secondary alcohols in diene hydrohydroxyalkylation.

4.2.2 Reaction Development and Scope

The prospect of adapting conditions from the previously developed transformation that coupled α-hydroxy esters with isoprene and myrcene[9] (Scheme 4.2) to the corresponding coupling of heteroaromatic secondary alcohols **4.1a-o** was rendered uncertain because of the strong chelating ability of pyridyl ligands to ruthenium, which could inhibit catalytic turnover. Despite this concern, studies on this transformation commenced. Initially, various ligands were screened with $(Ru)_3(CO)_{12}$ as catalyst (Table 4.1). It became apparent that nitrogen based ligands, as well as bidentate phosphine ligands were inadequate for this reaction, but on the other hand, the monodentate phosphine ligand PCy_3 provided the product in good yield (85%). It was important that the PCy_3 was freshly recrystallized, so not to be contaminated with any of the phosphine oxide, to ensure consistent results.

Table 4.1. Select ligands assayed in the coupling of isoprene with alcohol **4.1a**.



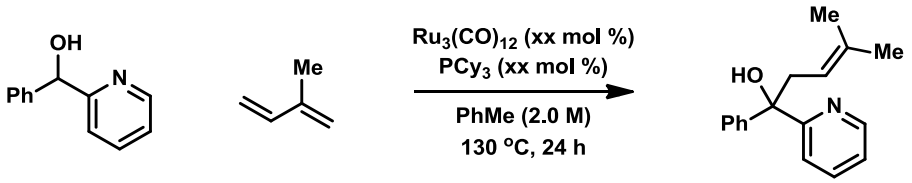
4.1a **4.2a (2.0 equiv.)** **4.3a**

Ligand	mol %	Yield (%)
-	-	49
bipy	6	52
terpy	6	50
phen	6	45
(*rac*)-BINAP	6	38
PCy_3	12	85

Catalyst and ligand loading were also assayed (Table 4.2). The ruthenium catalyst proved to be particularly active, allowing loadings of the

trimer to be reduced to 1 mol % (3 mol % of the monomer). Also, loading of PCy_3 could be reduced to only 5 mol %, delivering product **4.3a** in 91% yield. Unfortunately, reduction of the loading of the ruthenium trimer below 1 mol % led to reduced yields. After a brief temperature screen, it was found that 130 °C was the optimum temperature, and the reaction time could be lowered to eighteen hours without any significant drop in yield.

Table 4.2. Select catalyst loading and ligand loading assay in the coupling of isoprene with alcohol **4.1a**.



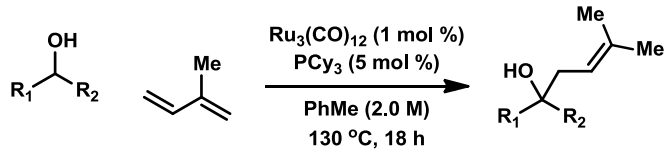
4.1a **4.2a (2.0 equiv.)** **4.3a**

$(Ru)_3(CO)_{12}$ (mol %)	PCy_3 (mol %)	Yield (%)
2.0	12	85
2.0	10	90
2.0	8	87
2.0	6	76
2.0	4	72
1.0	5	91
0.5	2.5	75
0.25	1.25	42

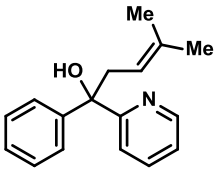
With these optimized conditions at the ready, the scope of this transformation was evaluated (Table 4.3). Interestingly, electron-neutral (**4.1a**), electron-deficient (**4.1b-e**) and electron-rich (**4.1f** and **g**) alcohols participated in the coupling, providing products **4.3a-g** in high yields. Also, pyridyl-methanols with a heteroaryl group (**4.1h** and **i**) participated in the coupling. For the first time when using the $(Ru)_3(CO)_{12}$ as catalyst, alkyl substituted α-hydroxy carbonyl-type substrates (**4.1j-l**) were tolerated in the transformation, albeit with slightly higher loadings of catalyst (2 mol %) and ligand (10 mol %)

and with extended reaction times (48 h). Alcohol **4.1c** required the same loading of catalyst and ligand as substrates **4.1j-l** but only twenty-four hours of reaction time was needed.

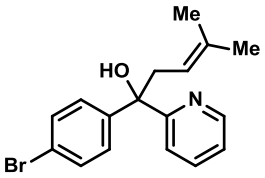
Table 4.3. Scope of hydrohydroxylation of alcohols **4.1a-o** and isoprene.



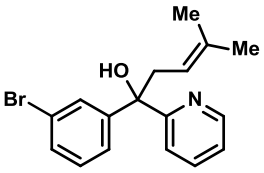
4.1 | 4.2a (2.0 equiv.) | 4.3



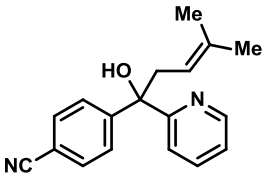
4.3a
90% Yield



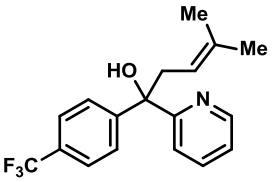
4.3b
92% Yield



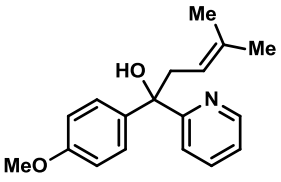
4.3c
90% Yield



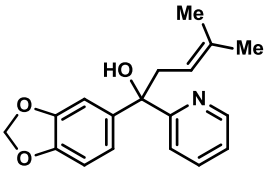
4.3d
99% Yield



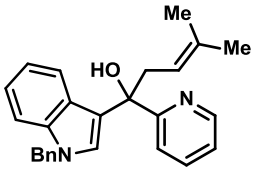
4.3e
95% Yield



4.3f
90% Yield

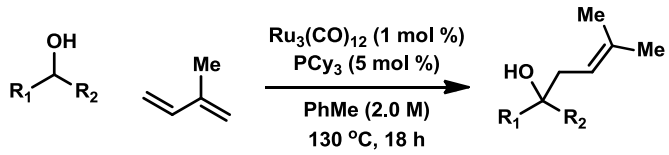


4.3g
85% Yield

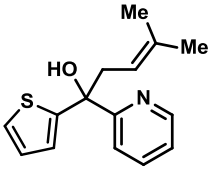


4.3h
62% Yield

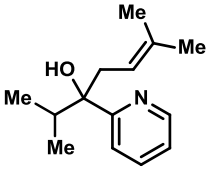
Table 4.3, cont.



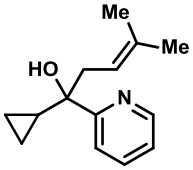
4.1 | 4.2a (2.0 equiv.) | 4.3



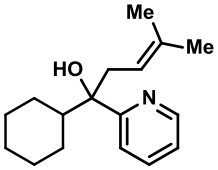
4.3i
90% Yield



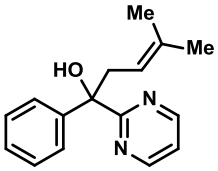
4.3j
66% Yield



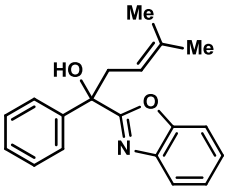
4.3k
66% Yield



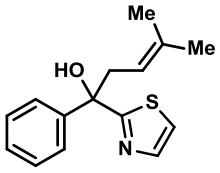
4.3l
50% Yield



4.3m
91% Yield



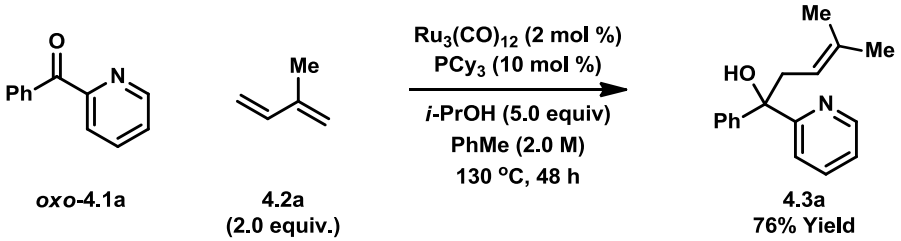
4.3n
88% Yield



4.3o
86% Yield

Beyond the 2-pyridyl group, it was found that other heteroaryl substituted benzyl alcohols engaged in this transformation (Table 4.3). Pyrimidine, benzoxazole and thiazole containing secondary alcohols (**4.1m-o**) were converted to the desired products in good yield. Furthermore, coupling from the ketone oxidation level proceeded when employing isopropanol as the reductant, providing product **4.3a** in 76% yield (Scheme 4.4).

Scheme 4.4. Hydrohydroxyalkylation from the ketone oxidation level.



oxo-4.1a | 4.2a (2.0 equiv.) | 4.3a 76% Yield

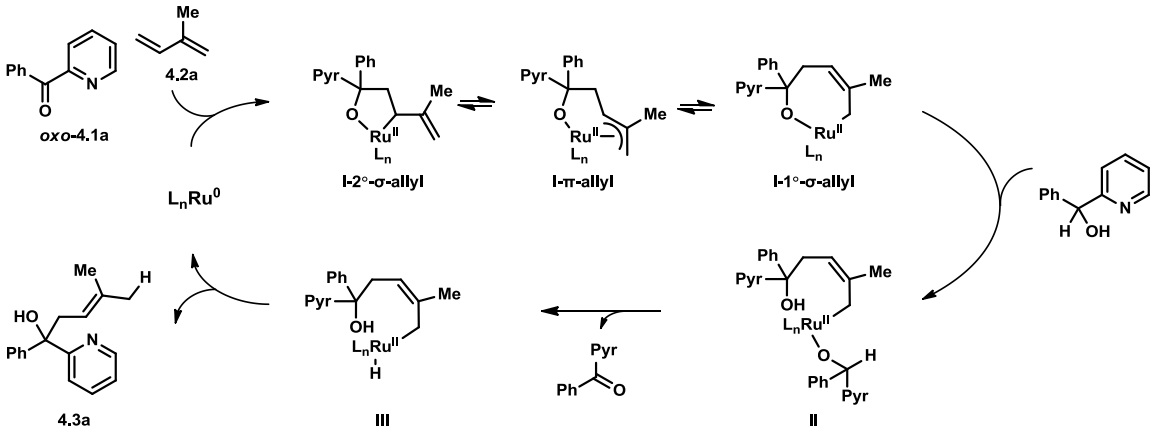
The scope of the transformation was also assayed using other dienes such as butadiene and myrcene, but the *E*/*Z* selectivity was poor. It was believed that the chelation ability of the pyridyl group could have reduced the selectivity of the reaction. Additionally, other isomers of pyridyl methanols were used, but only dehydrogenation occurred to furnish the ketones. No coupling product was detected, necessitating carbonyl character adjacent to the ketone for LUMO-lowering effects to enhance electrophilicity of the ketone.

4.2.3 Mechanistic Investigations

Based on recent studies of the ruthenium(0) catalyzed hydrohydroxyalkylation of α-hydroxy esters and dienes,[9] a catalytic mechanism that utilized diene-carbonyl oxidative coupling was proposed (Figure 4.3). A discrete monometallic ruthenium(0) complex should form as a result of the combination of $(Ru)_3(CO)_{12}$ and PCy_3 in solution.[34] To initiate the catalytic pathway, alcohol **4.1a** must be oxidized to the corresponding ketone

(*oxo*-**4.1a**). Diene-carbonyl oxidative coupling of isoprene and *oxo*-**4.1a** furnishes ruthenium intermediate **I**-2°-σ-allyl. It is believed that **I**-2°-σ-allyl exist in equilibrium with **I**-π-allyl and **I**-1°-σ-allyl. Protonation of **I**-1°-σ-allyl by alcohol **4.1a** generates ruthenium alkoxide **II**, which can undergo β-hydride elimination, releasing *oxo*-**4.1a** and forming ruthenium hydride **III**. C-H reductive elimination furnishes product **4.3a** and regenerates the ruthenium(0) catalyst to close the catalytic cycle.

Figure 4.3. A plausible catalytic cycle in the hydrohydroxyalkylation of isoprene and alcohol **4.1a**.



To corroborate this mechanism, an attempt was made to isolate allyl-oxaruthenacycle **I**. With this objective in mind, *oxo*-**4.1a**, $(Ru)_3(CO)_{12}$ (33 mol %) and isoprene **4.2a** (2.0 equiv.) were combined in a sealed vessel and stirred for one hour at 130 °C (Scheme 4.5). After cooling the reaction, vapor-vapor diffusion was initiated to induce crystallization. Amazingly, a crystal was obtained, and single crystal X-ray diffraction revealed oxaruthenacycle **Ia**-π-allyl (Figure 4.4). In the crystal structure, there is a water molecule hydrogen-

Scheme 4.5. Attempts at forming allyl-oxaruthenacycle **I.**

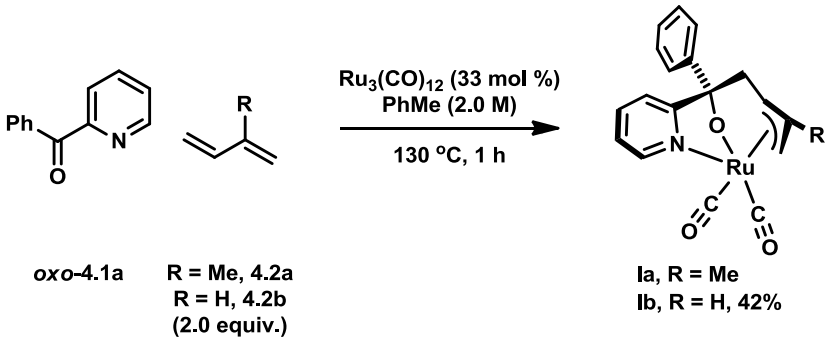
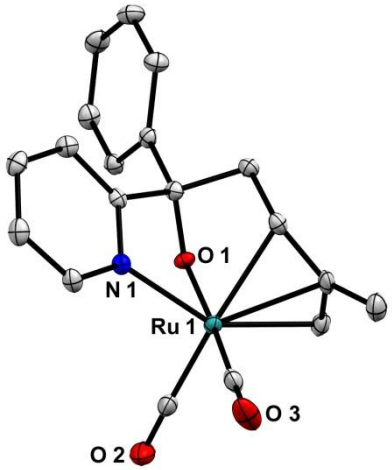


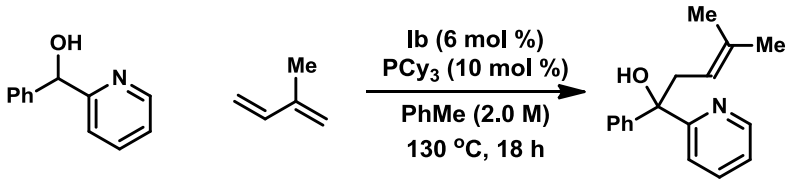
Figure 4.4. X-ray crystal structure of oxaruthenacycle **Ia**-π-allyl.



bonded to the alkoxide, suggestive of the protonation of **I**-1°-σ-allyl to form **II**. This complex proved to be somewhat stable and could even be isolated from the crude reaction mixture by conventional silica gel chromatography; however, significant loss of material occurred. Oxaruthenacycle **Ib**-π-allyl, derived from butadiene, proved to be more robust compared to **Ia**-π-allyl and could be isolated by silica gel chromatography in 42% yield. To substantiate the proposal that this was indeed an intermediate in the catalytic cycle, alcohol **4.1a** was combined with isoprene in the presence of **Ib**-π-allyl (6

mol %) and PCy_3 (10 mol %) (Scheme 4.6). Delightfully, hydrohydroxyalkylation product **4.3a** was isolated in 77% yield.

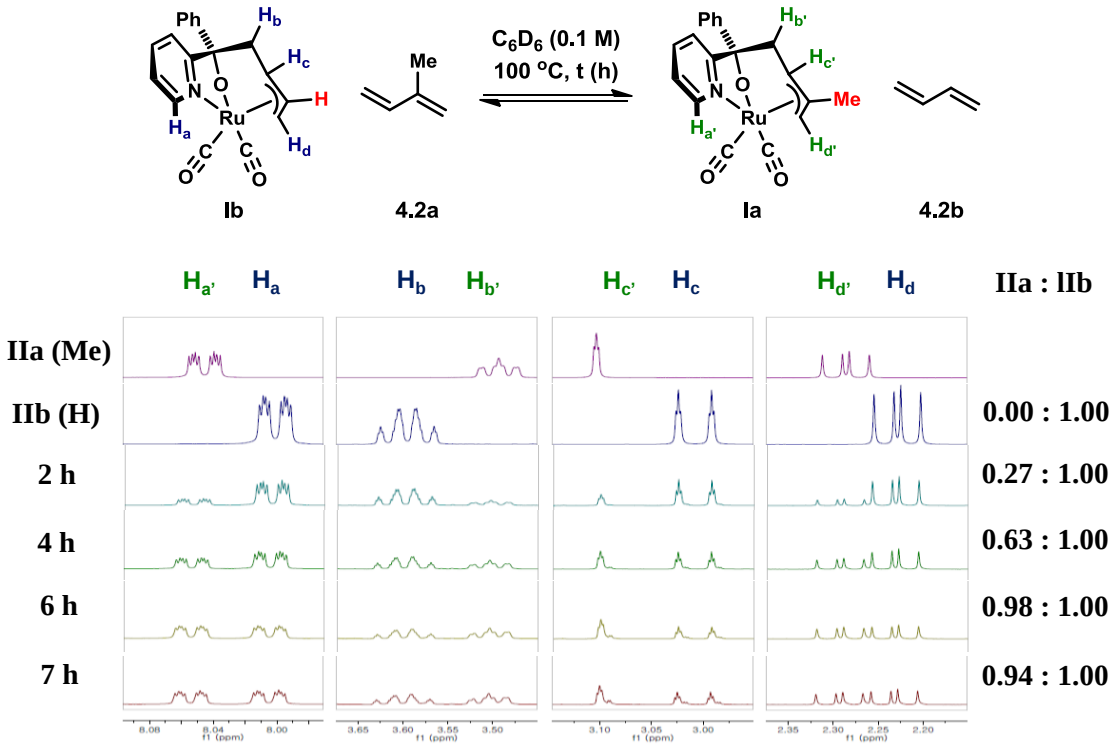
Scheme 4.6. Examination of **Ib**-π-allyl as an intermediate in the catalytic cycle.



4.1a **4.2a (2.0 equiv.)** **4.3a 77% Yield**

Although complexes **Ia**-π-allyl and **Ib**-π-allyl could exist as diastereomeric mixtures, a single stereoisomer was observed for each allyl species by ^{1}H NMR and ^{13}C NMR. This better enabled exchange experiments intended to probe the reversibility of the oxaruthenacycle formation. Supporting this postulate is the report of reversible oxidative coupling of dienes and aldehydes with stoichiometric nickel(0).[35] Upon the exposure of **Ib**-π-allyl (1.0 equiv.) to isoprene (88 mol %) in benzene-d_6 at 100 °C, the gradual formation of **Ia**-π-allyl could be observed by ^{1}H NMR (Figure 4.5). At two hours, formation of **Ia**-π-allyl is visible, but still only in a 1:4 ratio with **Ib**-π-allyl. At four hours, a more significant portion of **Ia**-π-allyl has formed. By six hours, it appeared equilibration had been reached and no further conversion was observed.

Figure 4.5. Probing the reversibility of the oxidative coupling between isoprene and alcohol **4.1a**.



4.2.4 Conclusion

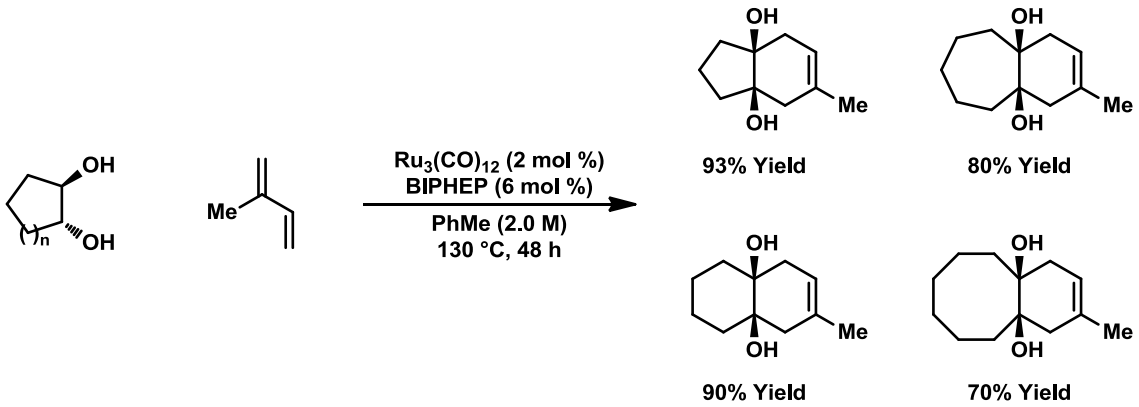
The technology of coupling secondary alcohols and dienes utilizing a ruthenium(0) catalyst has been expanded to include heteroaryl substituted secondary alcohols. This methodology allows for the direct conversion of secondary to tertiary alcohols, precluding the use of premetalated reagents and the generation of stoichiometric waste. Furthermore, the oxaruthenacycle postulated as a mechanistic intermediate was isolated and characterized for the first time, and the observed reversible oxidative coupling provided more profound insight into the structural-interactional features of this catalytic system.

4.3 Ruthenium-Catalyzed Diol-Diene Benzannulation

4.3.1 Background

Continuing the investigations of C-C couplings of alcohols,[1–3] a byproduct-free method for the formal [4+2] cycloaddition of 1,2 diols with dienes, utilizing a ruthenium(0) catalyst, was reported (Scheme 4.7).[11] This

Scheme 4.7. Ruthenium(0) catalyzed [4+2] cycloaddition of 1,2-diols and dienes.

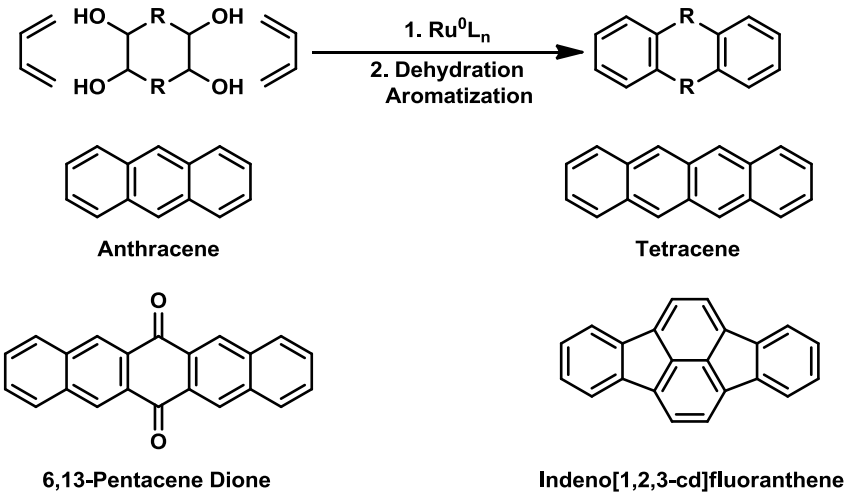


protocol allowed access to cis diols, which could be oxidatively cleaved in an effective ring expansion.[36] Another potential use for this methodology is the aromatization of the cycloadducts through a double dehydration, constituting a novel strategy for benzannulation. Furthermore, investigation of a two-directional benzannulation strategy would allow access to polycyclic aromatic hydrocarbons (PAHs) (Figure 4.5).[12]

Polycyclic aromatic hydrocarbons, such as fluoranthenes and acenes, have garnered the interest of theoretical, physical experimental and materials chemists because of their electronic structure and potential utility with regard to optoelectronic devices.[37–45] Unfortunately, current methods for the construction of PAHs typically rely on lengthy syntheses and methods that are

not well suited for implementation on scale,[46–52] obstructing the long-term goal of developing commercial manufacturing routes. Deployment of ruthenium-catalyzed benzannulation strategy could enhance the scalability of syntheses to generate PAHs.

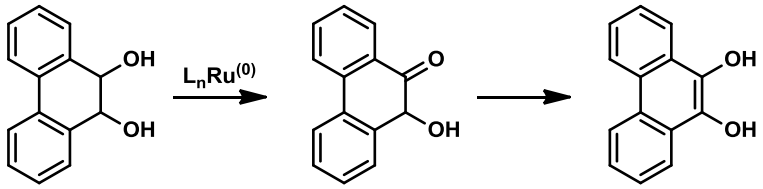
Figure 4.6. Potential two-directional benzannulation strategy permitting access to PAHs.



4.3.2 Reaction Development and Scope

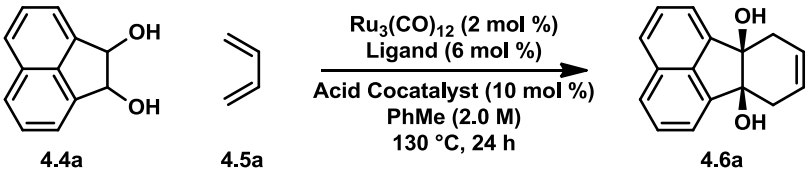
Investigations into this transformation commenced by applying the conditions from the first generation [4+2] cycloaddition[11] with butadiene **4.5a** and 9,10-dihydroxy-9,10-dihydrophenanthrene; however, no coupling product was detected. After further investigation, it was determined that 9,10-dihydroxy-9,10-dihydrophenanthrene was actually being converted to phenanthrenehydroquinone. It is believed that this happens once the first alcohol oxidation has occurred. With the α-hydroxy ketone, tautomerization can follow, aromatizing the product compound, thus generating the unreactive phenanthrenehydroquinone (Scheme 4.8). With this in mind,

Scheme 4.8. Formation of phenanthrenehydroquinone.



acenaphthene-1,2-diol **4.4a** was chosen as a potential substrate since its tautomerization would lead to an anti-aromatic intermediate which was less likely to form. Application of the previously used conditions in the presence of diene **4.5a** yielded the desired cycloadduct in 47% yield. Select ligands were screened to determine the optimum one for this transformation (Table 4.4). It was found that both DPPP and BIPHEP perform similarly. DPPP was used because it is much more cost efficient. The yield of **4.6a** was still much lower than desired, so an acid cocatalyst was added to the reaction. Acid cocatalyst have been known to enhance the rate of such ruthenium(0) catalyzed oxidative coupling transformations.[14,16] By employing DPPP in the presence of 3,5-dimethylbenzoic acid, product **4.6a** was isolated in 82% yield.

Table 4.4. Select ligands and acid cocatalysts assayed in the formation of **4.6a**.

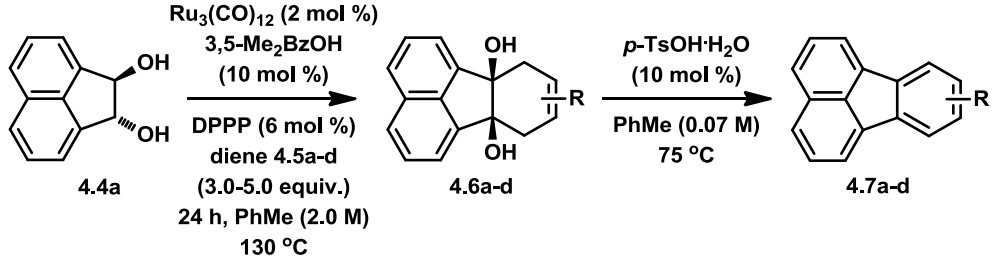


4.4a 4.5a 4.6a

Ligand	Acid Cocatalyst	Yield (%)
PCy_3	-	Trace
DPPPh	-	30
BIPHEP	-	47
DPPP	-	49
DPPP	$C_{10}CO_2H$	52
DPPP	3,5-Me_2BzOH	82

With serviceable conditions to deliver desired cycloadduct **4.6a**, methods for dehydration were examined. After a survey of literature, it was discovered that *p*-toluenesulfonic acid can participate in acid catalyzed dehydrations.[53,54] Luckily, treatment of **4.6a** with *p*-toluenesulfonic acid delivered the fully aromatized fluoranthene **4.7a**. The scope of the reaction was evaluated using the optimized conditions (Table 4.5). A number of substituted dienes participated in the coupling with diol **4.4a**. Diene **4.5d** proved somewhat problematic and required additional ligand assays to determine the optimum conditions, using DPPPh and no additional acid cocatalyst (Table 4.6). Subsequent dehydration occurred seamlessly, furnishing the desired fluoranthenes in excellent yields.

Table 4.5. Benzannulation of diol **4.4a** with dienes **4.5a-d**.



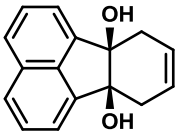
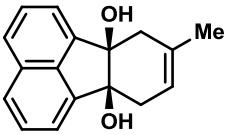
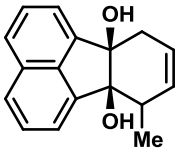
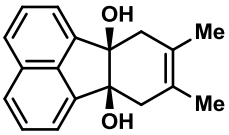
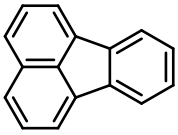
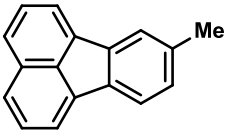
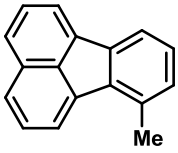
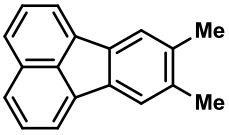
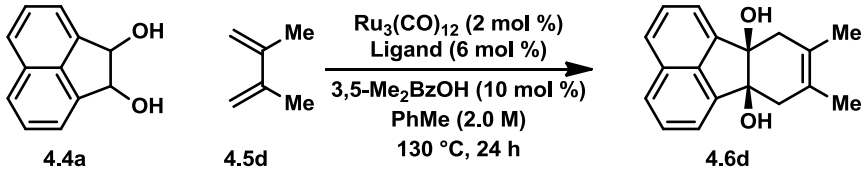
4.5a, butadiene	4.5b, isoprene	4.5c, 1,3-pentadiene	4.5d, 2,3-Me_2-butadiene
			
4.6a, 82% Yield	4.6b, 81% Yield	4.6c, 82% Yield 1:1.3 dr	4.6d, 81% Yield
			
4.7a, 90% Yield	4.7b, 92% Yield	4.7c, 90% Yield	4.7d, 95% Yield

Table 4.6. Additional optimization for diene **4.5d**.



4.4a 4.5d 4.6d

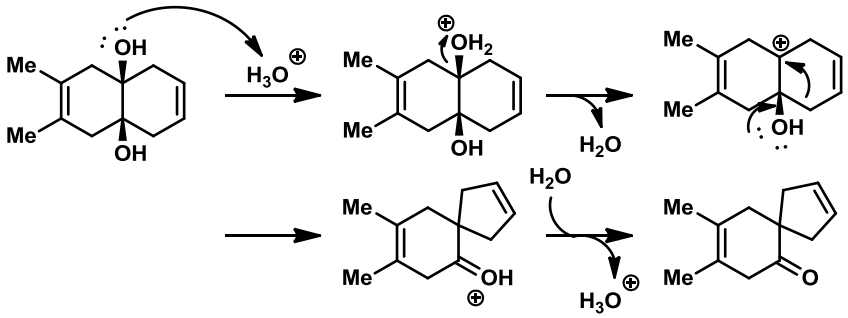
Ligand	Yield (%)
PCy_3	25
BIPHEP	13
DPPP	31
DPPPE	41
DPPM	Trace
DPPB	Trace
DCyPE	18
DCyPM	13
DPPF	Trace
XantPhos	Trace
DPPPh	69
DPPPh (48 h)	81

To further evaluate the scope of this benzannulation methodology, the coupling of diol **4.4b** and dienes **4.5a-e** was attempted. Because the oxidative coupling is thought to proceed through the transient 1,2-dione, the feasibility of diol **4.4b** was uncertain. Once *tetradehydro*-**4.4b** is formed, tautomerization could occur, forming 4,5-dimethyl catechol, which would be unreactive in the catalytic cycle. Amazingly, using the optimized conditions except for the acid cocatalyst, cycloadducts **4.8a-c** and **e** were formed in excellent yield with complete levels of *syn*-diastereoselectivity (Table 4.7). Only in the case of diene **4.5d** was cycloaddition impeded due to the formation of 4,5-dimethyl catechol. Because diene **4.5d** does not contain a monosubstituted olefin, it is postulated that oxidative coupling is slow with respect to the formation of 4,5-dimethyl catechol.[55,56]

Aromatization by double dehydration was attempted using *p*-tolunesulfonic acid, but the desired PAHs were not obtained. This is not surprising, considering that the substrates are not at the appropriate oxidation

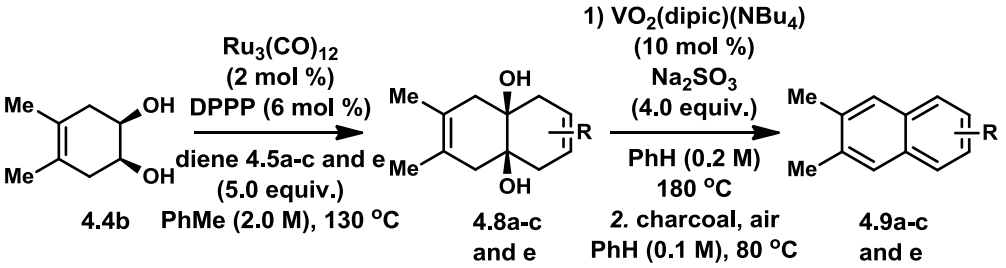
level. Among the products isolated, pinacol rearrangement was a major component. (Scheme 4.9).

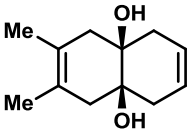
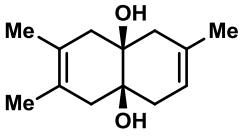
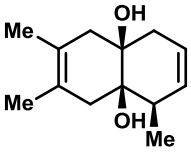
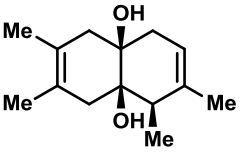
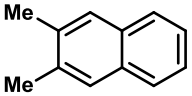
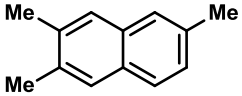
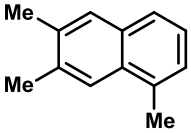
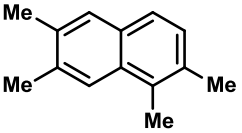
Scheme 4.9. Pinacol rearrangement observed in double dehydration attempt.



Consequently, diol deoxydehydration (DODH)[57–62] followed by aerobic dehydrogenative aromatization of the resulting trienes was explored as a way to access naphthalenes **4.9a-c** and **e**. Using Nicholas's DODH,[62] cycloadducts **4.8a-c** and **e** were converted to the corresponding trienes in good yield. The crude DODH reaction mixture was filtered through celite and then exposed to activated charcoal (DARCO KB) in the presence of air, furnishing the desired naphthalenes **4.9a-c** and **e** (Table 4.7).

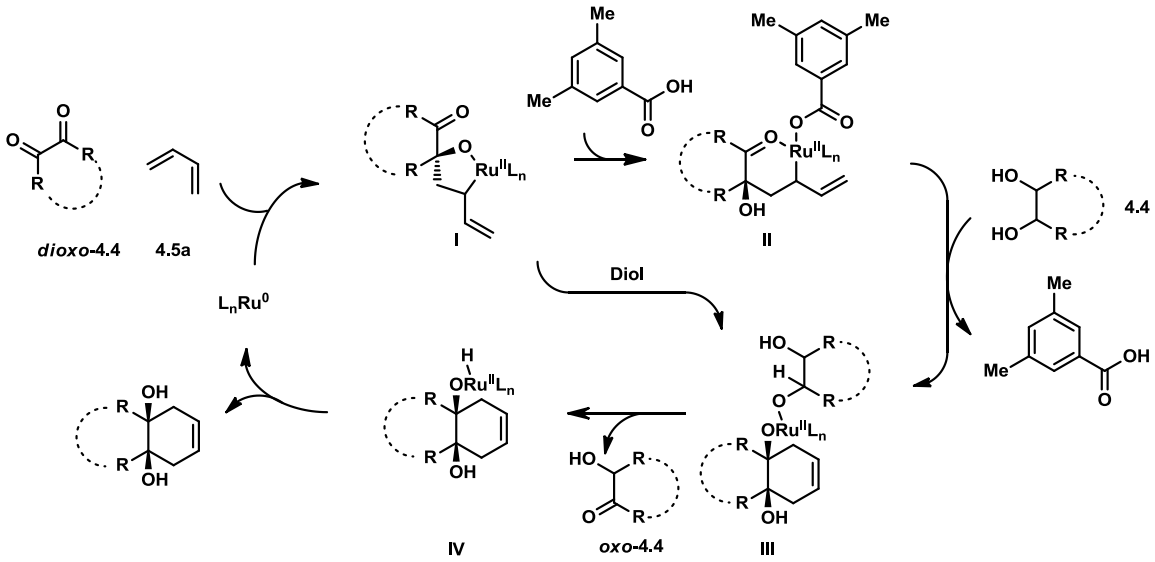
Table 4.7. Benzannulation of diol **4.4b** with dienes **4.5a-c** and **e**.



4.5a, butadiene	4.5b, isoprene	4.5c, 1,3-pentadiene	4.5e, 3-Me-1,3-pentadiene
			
4.8a, 94% Yield	4.8b, 98% Yield	4.8c, 85% Yield 16:1 dr	4.8e, 88% Yield >20:1 dr
			
4.9a, 89% Yield	4.9b, 76% Yield	4.9c, 75% Yield	4.9e, 75% Yield

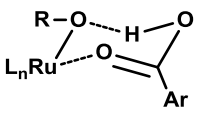
A plausible catalytic cycle is believed to be analgous to that proposed in the original [4+2] cycloaddition report[11] and is proposed in Figure 4.6. A discrete monometallic ruthenium(0) complex should form as a result of the combination of $(Ru)_3(CO)_{12}$ and PCy_3 in solution.[34] To initiate the catalytic pathway, alcohol **4.4a** must be oxidized to the corresponding 1,2-dione (*dioxo*-**4.4**). Diene-carbonyl oxidative coupling of butadiene **4.5a** and *dioxo*-**4.4** furnishes ruthenium intermediate **I**. Here is where the pathways can momentarily diverge. If no acid cocatalyst is used, protonolytic cleavage of oxaruthenacycle **I** by diol **4.4** (or *oxo*-**4.4**) triggers allylruthenation onto the remaining ketone, forming intermediate **III**. If an acid cocatalyst is used, then intermediate **I** is protonolytically cleaved to generate intermediate **II**. Diol **4.4** (or *oxo*-**4.4**) can then protonate the benzoate, triggering allylruthenation onto

Figure 4.7. A plausible catalytic cycle for the benzannulation of diol **4.4** and diene **4.5a**.



the remaining ketone, also forming intermediate **III**. β-Hydride elimination can occur to release *oxo*-**4.4** (or *dioxo*-**4.4**) and generate intermediate **IV**. Finally, O-H reductive elimination can occur to furnish the desired product and regenerate the ruthenium(0) catalyst. It is believed that the acid cocatalyst can enhance reactivity because its protonation/deprotonation can occur by way of a six-membered ring (Figure 4.7) (diol mediated protonation/deprotonation would most likely go through a four-membered ring).

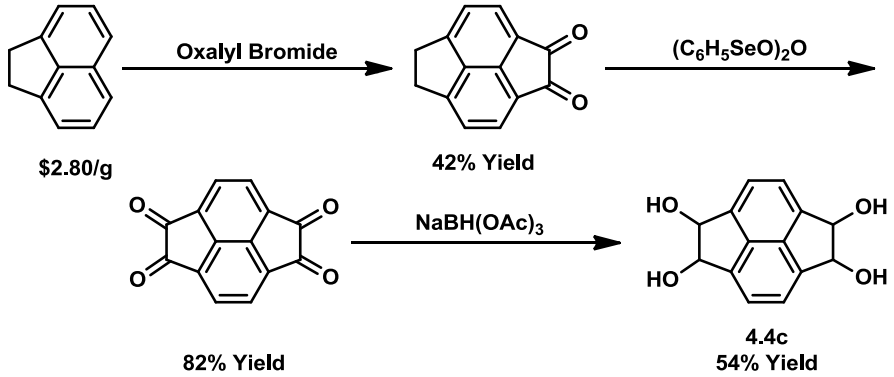
Figure 4.8. Acid cocatalyst mediated protonation/deprotonation.



4.3.3 Two-Directional Benzannulation

With a functioning protocol for one-directional benzannulation, the capability of this method to extend to two-directional benzannulation was explored through the coupling of diene **4.5a** and tetraol **4.4c**. To test this transformation, tetraol **4.4c** must be prepared. Fortunately, 1,2,5,6-tetraketopyracene is a known compound. Starting from acenaphthene, a double Friedel-Crafts acylation was performed using $AlBr_3$ and oxalyl bromide, forming diketopyracene in 42% yield (Figure 4.8).[63] Oxidation of the acenaphthalene backbone was achieved through the use of benzeneselenic anhydride.[64] Reduction of 1,2,5,6-tetraketopyracene seemed trivial, but more reactive hydride sources such as $NaBH_4$, $LiAlH_4$ and $LiBHEt_3$ led to decomposition, so $NaBH(OAc)_3$ was employed, furnishing tetraol **4.4c** in moderate yield.

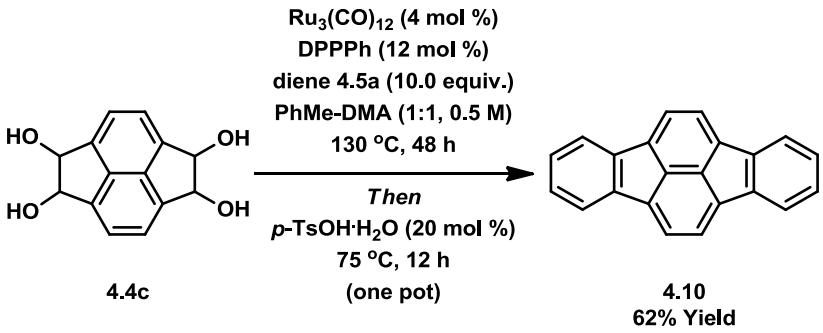
Figure 4.9. Synthesis of tetraol **4.4c**.



For the two-directional benzannulation, it was found that DPPPh was the optimum ligand when coupling tetraol **4.4c** and diene **4.5a**. Interestingly, a mixed solvent system consisting of toluene:dimethylacetamide (1:1) was used to ensure solubility. Solubility also was an issue in the isolation of the cycloadduct. It appeared that there was product by TLC observation, but nothing could be isolated from conventional silica gel chromatography,

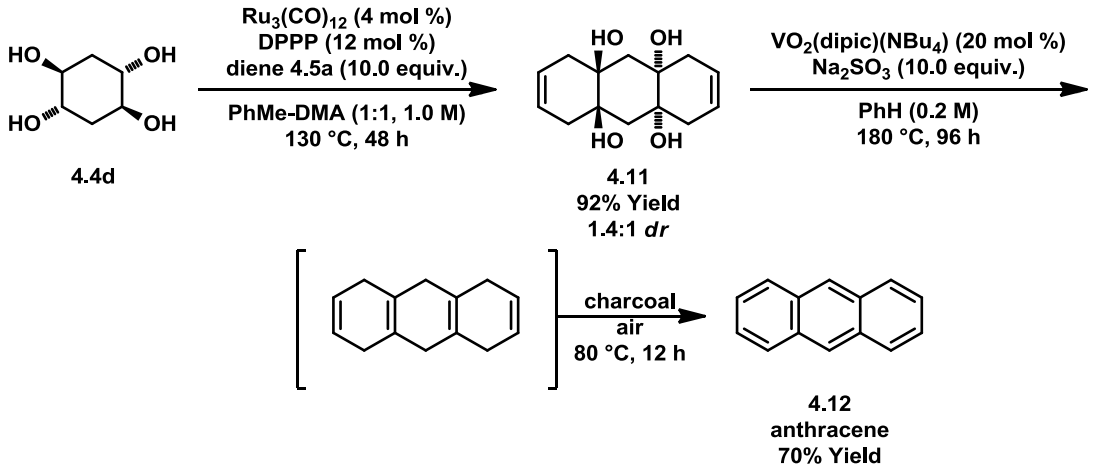
presumably because the product wasn't soluble on the silica gel column. Therefore, aromatization using *p*-toluensulfonic acid was attempted with the crude reaction mixture, which furnished desired indeno[1,2,3-*cd*]-fluoranthene **4.10a** in 62% yield (Scheme 4.10).

Scheme 4.10. Formation of indeno[1,2,3-*cd*]-fluoranthene **4.10**.

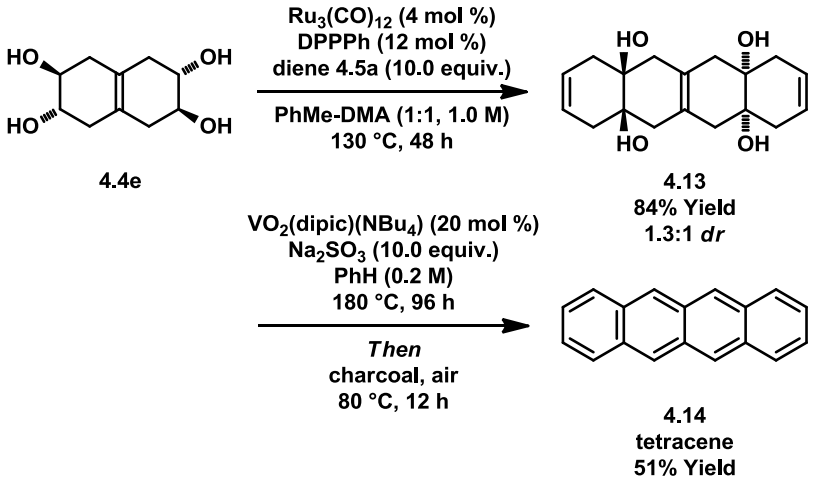


Inspired by the success of the two-directional synthesis of **4.10**, two-directional syntheses of a homologous series of acenes were examined. Tetraol **4.4d** was synthesized by double dihydroxylation of 1,4-cyclohexadiene using selenium dioxide and a 30% solution of H_2O_2.[65] With tetraol **4.4d** in hand, ruthenium(0) catalyzed double cycloaddition was attempted with diene **4.5a**. Remarkably, adduct **4.11** was obtained in 92% yield (Scheme 4.11). Further conversion of adduct **4.11** by DODH and aerobic dehydrogenative aromatization furnished anthracene **4.12** (Scheme 4.11). Tetraol **4.4e** was synthesized by first oxidizing 1,4,5,8-tetrahydronaphthalene to the bisepoxide through an iodine mediated oxidation with Ag_2O, followed by epoxide opening in aqueous trifluoroacetic acid. Tetraol **4.4e** was subjected to the same two-step sequence as tetraol **4.4d**, delivering tetracene **4.14** in moderate yield over a two-step protocol (Scheme 4.12). The use of tetraol **4.4f** was also investigated.

Scheme 4.11. Synthesis of anthracene *via* ruthenium-catalyzed coupling, double DODH and dehydrogenative aromatization.



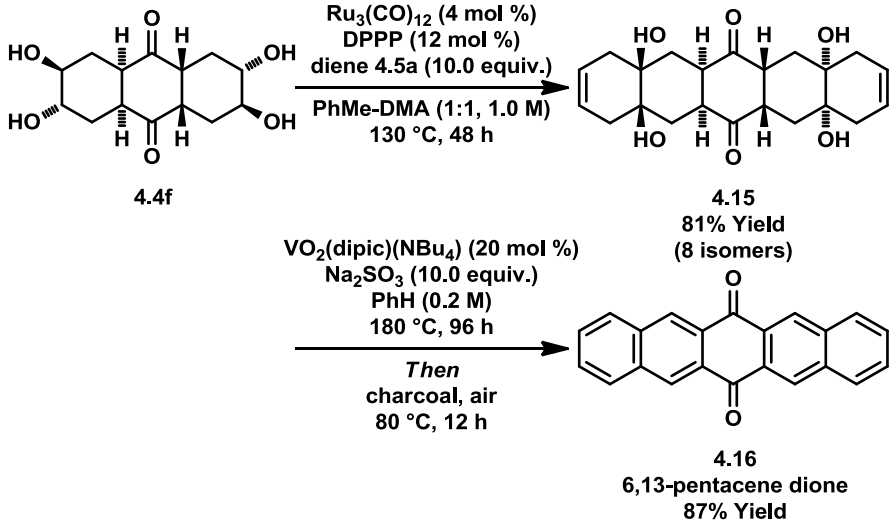
Scheme 4.12. Synthesis of tetracene *via* ruthenium-catalyzed coupling, double DODH and dehydrogenative aromatization.



The synthesis of **4.4f** began with a Diels-Alder reaction of diene **4.5a** and benzoquinone, followed by bisepoxidation with mCPBA and subsequent opening with glacial acetic acid.[66,67] An analogous strategy for the cycloaddition, DODH and aerobic dehydrogenative aromatization to

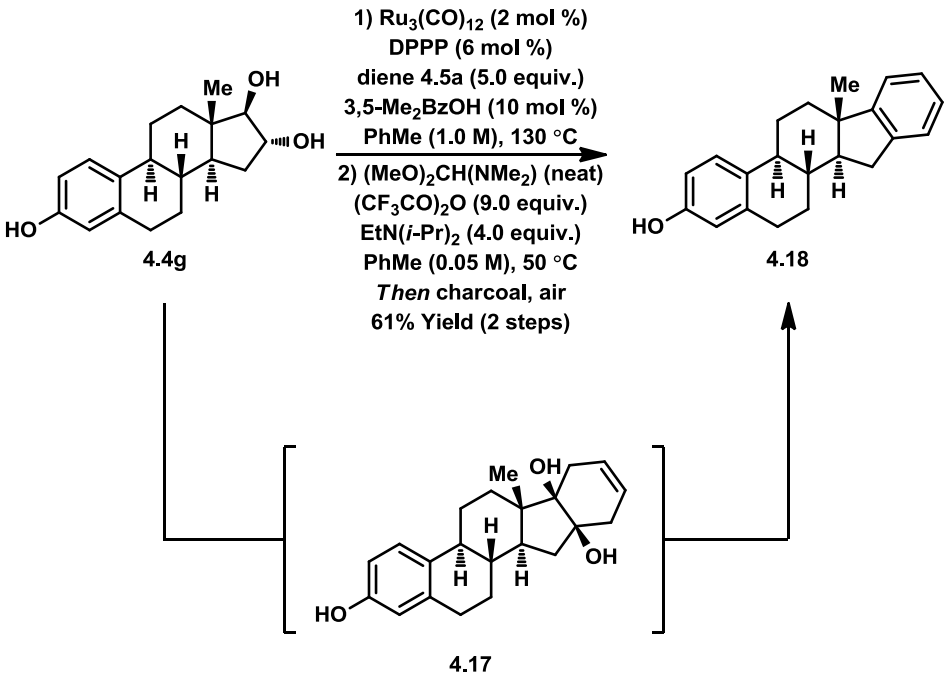
anthracene and tetracene was applied to furnish 6,13-pentacene dione **4.16** in good yield over two steps (Scheme 4.13). One thing to consider in these sequences is the poor diastereoselectivity for the cycloaddition is irrelevant since the stereochemistry is destroyed in the aromatization.

Scheme 4.13. Synthesis of 6,13-pentacene dione *via* ruthenium-catalyzed coupling, double DODH and dehydrogenative aromatization.



Lastly, it was desired to evaluate the capabilities of this methodology beyond the construction of PAHs. To this end, the benzannulation of estriol **4.4g**, was attempted, examining this methodology in a more functionalized system. Amazingly, the cycloaddition occurred efficiently, even in the presence of a free phenol. The resulting cycloadduct was converted to the benzannulated steroid **4.18** in 87% yield (Scheme 4.14).

Scheme 4.14. Ruthenium-catalyzed coupling and double DODH and dehydrogenative aromatization of estriol **4.4g**.



4.3.4 Conclusion

A new methodology was developed that utilizes a ruthenium(0) catalyst to promote [4+2] cycloadditions between 1,2-diols and dienes. Further elaboration of the products by way of double dehydration aromatization or DODH followed by aerobic dehydrogenative aromatization to furnish fluoranthenes and naphthalene derivatives has been achieved. This methodology has also been successfully applied to tetraols, allowing two-directional benzannulation to be realized. This methodology represents a new synthetic pathway to access a variety PAH's in an efficient manner.

4.4 Summary

Redox-triggered C-C bond formation of secondary alcohols by employing a ruthenium(0) catalyst has been achieved. This catalyst has

allowed access to a vast array of structural motifs that were previously untouched through the use of redox-triggered C-C bond formation mediated by transition metal catalysis. Specifically, methods for the coupling of α-hydroxy esters, 3-hydroxyoxindoles, 1,2-diols and pyridyl-methanols with dienes[10–13] and acrylates,[14] 1,2-diols with alkynes[15] and 3-hydroxyoxindoles with α-olefins[16] have been reported. One unmet challenge in all of these couplings is the establishment of an asymmetric variant to these transformations; however, this could prove quite challenging, since it has been shown that the oxidative coupling step is reversible. Extraordinarily high kinetic selectivities would be required to offset erosion of enantiomeric excess due to this reversibility.

4.5 Experimental Section

4.5.1 Experimental Details for Section 4.2

General Information

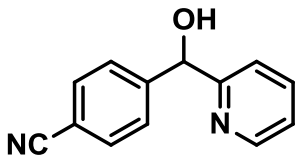
All reactions were run under an atmosphere of argon. Pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator. Toluene was dried over sodium metal, benzophenone and distilled immediately prior to use. Anhydrous solvents were transferred by oven-dried syringes. Tricyclohexylphosphine was recrystallized prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40–63 μm).

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H or M+Na), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_C (77.0 ppm). Melting points were taken on a Stuart SMP3 melting point apparatus.

Procedure for the Preparation of Pyridyl Methanols 4.1a-o

2-Bromopyridine (0.48 mL, 5 mmol) was added to *i*-PrMgCl (5 mmol) in THF (5 mL) at rt. After 2 hours, aldehyde (6 mmol) was added. After an additional 2 hours at rt, water (25 mL) was added. Extraction with dichloromethane (3 x 10 mL), drying over sodium sulfate, concentration *in vacuo* and purification by flash column chromatography (SiO_2, 25% EtOAc/hexanes) furnished the title compounds **4.1a**,[68] **4.1b**,[69] **4.1c**,[70] **4.1e**,[69] **4.1f**,[68] **4.1i**,[71] **4.1j**,[72] **4.1k**,[73] **4.1l**,[72] **4.1m**[74] and **4.1n**.[75]

Synthesis of 4-Cyanophenyl Pyridyl Methanol (4.1d).



In accordance with the general procedure, 2-Bromopyridine (0.48 mL, 5 mmol) was added to *i*-PrMgCl (5 mmol) in THF (5 mL) at rt. After 2 hours, 4-cyanobenzaldehyde (828.0 mg, 6 mmol) was added. After 2 hours at rt, water (25 mL) was added. Extraction with dichloromethane (3 x 10 mL), drying over sodium sulfate, concentration *in vacuo* and purification by flash column chromatography (SiO_2, 25% EtOAc/hexanes) furnished the title compound (796.9 mg, 76%) as a brown solid.

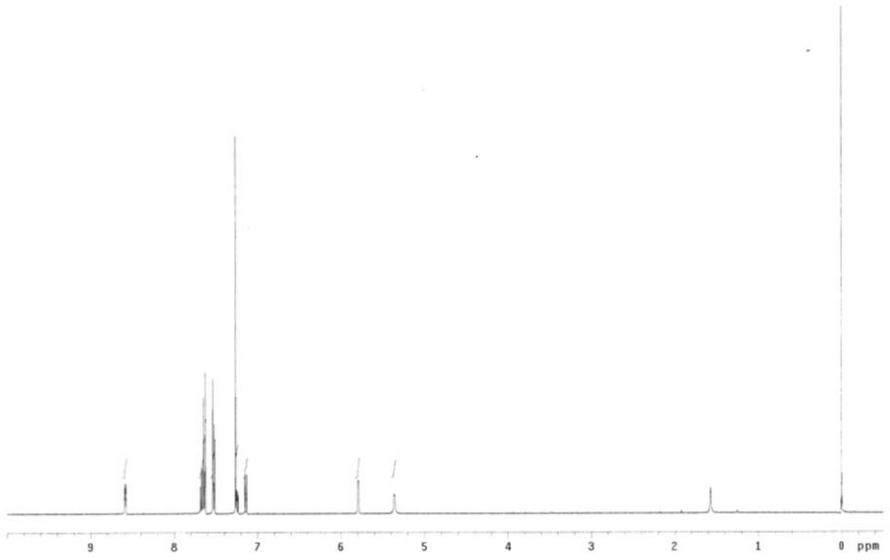
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60-8.58 (m, 1H), 7.69-7.62 (m, 3H), 7.54-7.52 (m, 2H), 7.26-7.23 (m, 1H), 7.15-7.13 (m, 1H), 5.79 (s, 1H), 5.36 (s, 1H).

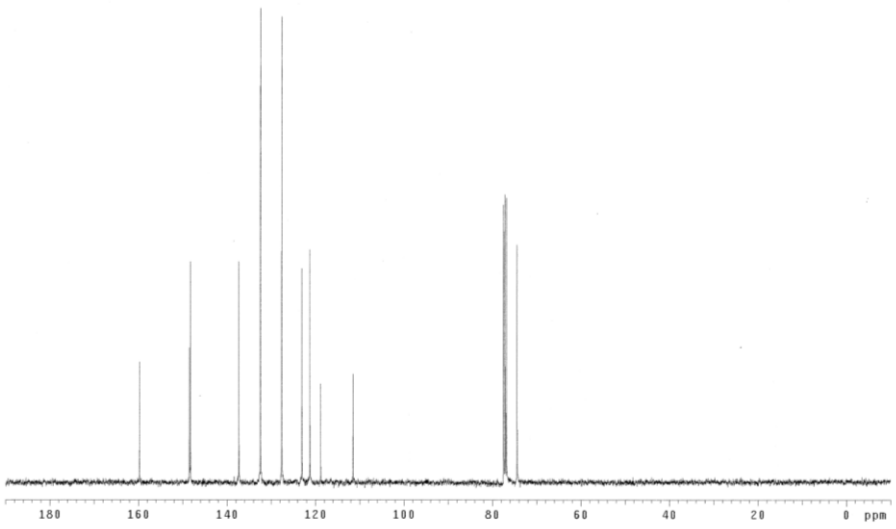
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.5, 148.3, 137.3, 132.4, 127.6, 123.0, 121.2, 118.8, 111.5, 74.5.

LRMS (CI) Calcd. for $C_{13}H_{11}N_2O$ $[M+H]^+$: 211, Found: 211.

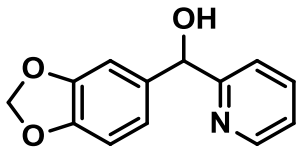
FTIR (neat): v 3181, 2359, 2342, 2228, 1593, 1571, 1503, 1436, 1408, 1275, 1261, 1195, 1097, 1059, 1019, 1003, 870, 811, 764, 750, 668 cm^{-1}.

MP 76.0–77.0 ^{o}C.



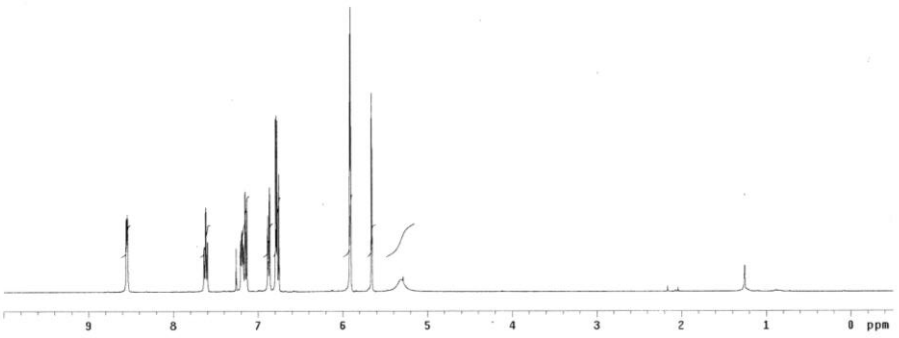


Synthesis of 1,3-Benzodioxole Pyridyl Methanol (4.1g).



In accordance with the general procedure, 2-Bromopyridine (0.48 mL, 5 mmol) was added to *i*-PrMgCl (5 mmol) in THF (5 mL) at rt. After 2 hours, piperonal (910.0 mg, 6 mmol) was added. After 2 hours at rt, water (25 mL) was added. Extraction with dichloromethane (3 x 10 mL), drying over sodium sulfate, concentration *in vacuo* and purification by flash column chromatography (SiO_2, 25% EtOAc/hexanes) furnished the title compound (861.4 mg, 75%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 4.4 Hz, 1H), 7.64-7.60 (m, 1H), 7.21-7.18 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.79-6.76 (m, 2H), 5.91 (dd, *J* = 4.0, 1.2 Hz, 2H), 5.66 (s, 1H), 5.31 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 148.0, 147.9, 147.3, 137.4, 137.0, 122.5, 121.4, 120.8, 108.2, 107.5, 101.1, 74.8.
LRMS (CI) Calcd. for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230, Found: 230.
FTIR (neat): v 3148, 2891, 1593, 1571, 1503, 1487, 1470, 1436, 1372, 1334, 1293, 1248, 1214, 1187, 1124, 1102, 1055, 1038, 1003, 928, 869, 846, 802, 765, 742, 724, 716, 667 cm^{-1}.
MP 71.5**–**72.5 ^oC.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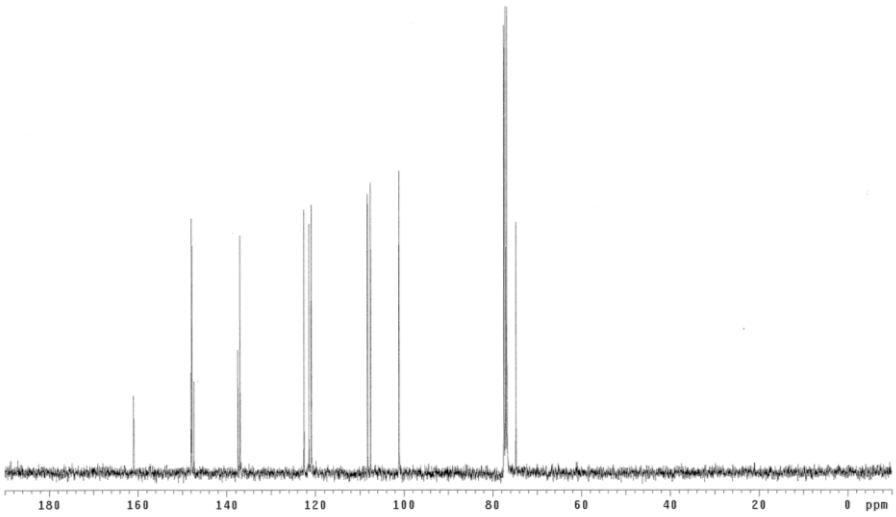
0 ppm


180
160
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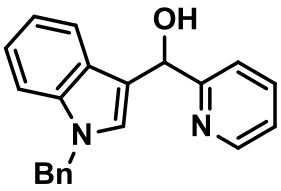
0 ppm

Synthesis of 2-(*N*-Bn-indolyl) Pyridyl Methanol (4.1h).



In accordance with the general procedure, 2-Bromopyridine (0.48 mL, 5 mmol) was added to *i*-PrMgCl (5 mmol) in THF (5 mL) at rt. After 2 hours, 1-benzyl-1H-indole-3-carbaldehyde (1.4 g, 6 mmol) was added. After 2 hours at rt, water (25 mL) was added. Extraction with dichloromethane (3 x 10 mL), drying over sodium sulfate, concentration *in vacuo* and purification by flash column chromatography (SiO_2, 25% EtOAc/hexanes) furnisedh the title compound (1.1 g, 72%) as a yellow solid.

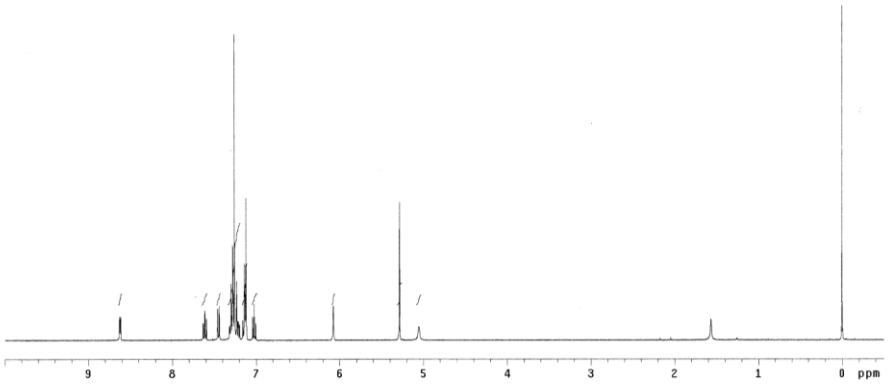
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63-8.61 (m, 1H), 7.61 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32-7.20 (m, 7H), 7.16–7.14 (m, 3H), 7.04-7.00 (m, 1H), 6.08 (s, 1H), 5.28 (s, 2H), 5.04 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 147.8, 137.3, 137.2, 136.8, 128.8, 127.7, 127.4, 126.9, 126.6, 122.4, 122.1, 121.4, 120.1, 119.7, 117.5, 109.9, 69.2, 50.1.

LRMS (CI) Calcd. for $C_{21}H_{19}N_2O$ $[M+H]^+$: 315, Found: 315.

FTIR (neat): v 3115, 1593, 1572, 1544, 1494, 1465, 1452, 1437, 1397, 1351, 1334, 1307, 1238, 1171, 1095, 1046, 1025, 1001, 761, 733, 707, 693, 664 cm^{-1}.

MP 113.5–114.0 ^oC.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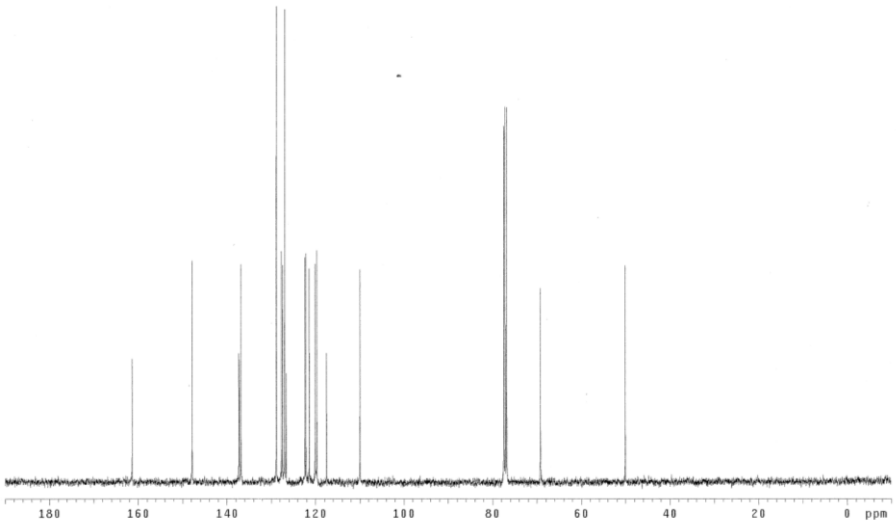
0 ppm


180
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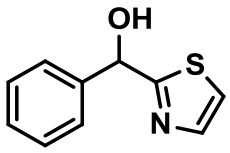
0 ppm

Synthesis of Thiazolyl Pyridyl Methanol (4.1o).



In accordance with the general procedure, 2-Bromothiazole (0.46 mL, 5 mmol) was added to *i*-PrMgCl (5 mmol) in THF (5 mL) at rt. After 2 hours, benzaldehyde (0.62 mL, 6 mmol) was added. After 2 hours at rt, water (25 mL) was added. Extraction with dichloromethane (3 x 10 mL), drying over sodium sulfate, concentration *in vacuo* and purification by flash column chromatography (SiO_2, 25% EtOAc/hexanes) furnished the title compound (621.0 mg, 65%) as a white solid.

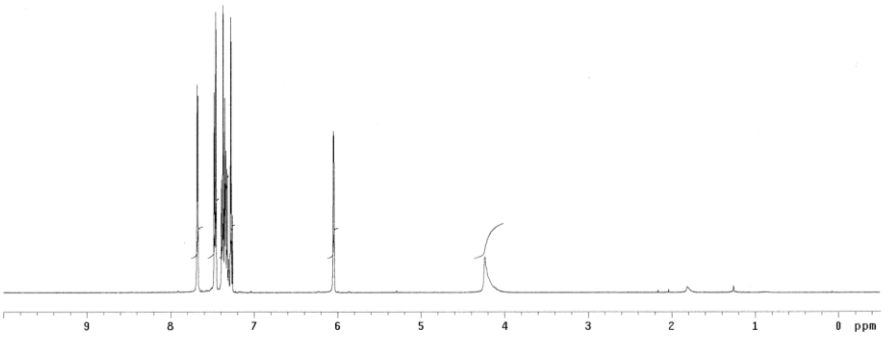
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 3.2 Hz 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 1.2 Hz, 1H), 7.39-7.30 (m, 3H), 7.28 (d, *J* = 3.2 Hz, 1H), 6.04 (s, 1H), 4.23 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 142.3, 141.5, 128.7, 128.5, 126.6, 119.6, 73.8.

LRMS (CI) Calcd. for $C_{10}H_9NaNOS$ $[M+H]^+$: 214, Found: 214.

FTIR (neat): v 3124, 2853, 1738, 1509, 1495, 1454, 1341, 1282, 1249, 1196, 1183, 1141, 1088, 1064, 1049, 1027, 921, 831, 795, 770, 702, 662 cm^{-1}.

MP 108.5–109.5 ^{o}C.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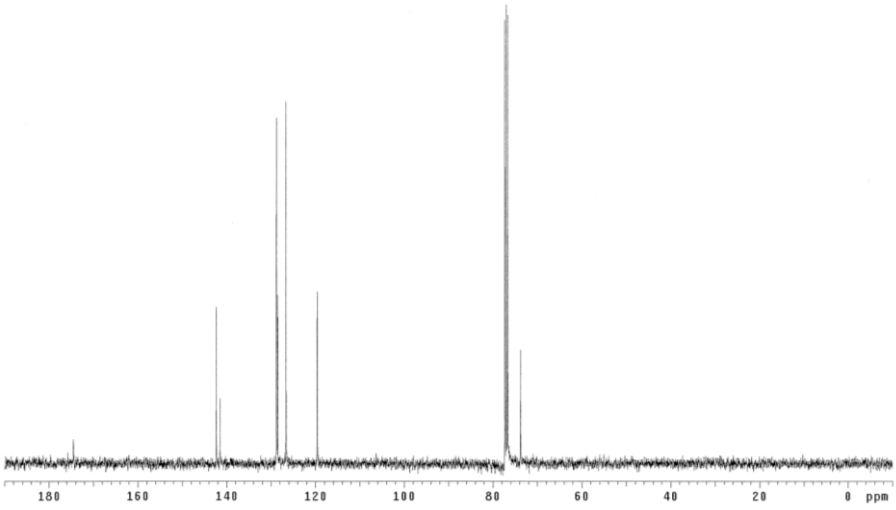
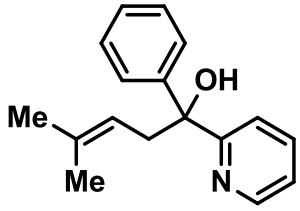

180
160
140
120
100
80
60
40
20
0 ppm

General Procedure for the Coupling of Isoprene to Pyridyl Methanol 4.1a-o

To a pressure tube equipped with magnetic stir bar was added $Ru_3(CO)_{12}$ (1.9 mg, 0.003 mmol, 1 mol %) and PCy_3 (4.2 mg, 0.015 mmol, 5 mol %). The tube was then sealed with a rubber septum, purged with argon. At this stage, pyridyl methanol **4.1a-o** (0.3 mmol, 1.0 equiv.), and PhMe (0.15 mL, 2.0 M concentration with respect to pyridyl methanol), and isoprene (60 µL, 0.600 mmol, 2.0 equiv.) were added. The rubber septum was quickly replaced with a screw cap. The reaction was heated to 130 ^oC for the indicated time. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2) under the condition noted to furnish prenylated pyridyl methanols.

Synthesis of Phenyl Pyridyl Prenyl Methanol (4.3a).



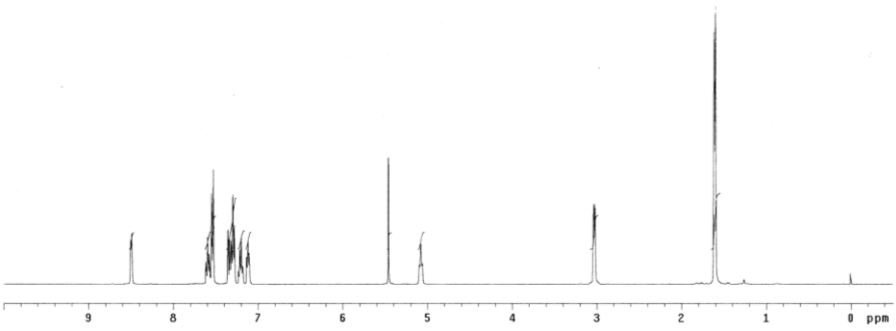
In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 18 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (68.6 mg, 90%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51-8.49 (m, 1H), 7.62-7.58 (m, 1H), 7.56-7.53 (m, 2H), 7.36-7.28 (m, 3H), 7.23-7.18(m, 1H), 7.14-7.11 (m, 1H), 5.46 (d, *J* = 1.6 Hz, 1H), 5.10-5.06 (m, 1H), 3.03 (d, *J* = 7.2 Hz, 2H), 1.62 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 144.4, 142.5, 138.8, 128.3, 127.4, 125.5, 119.5, 117.7, 78.3, 41.9, 26.2, 18.4.

LRMS (CI) Calcd. for $C_{17}H_{20}NO$ $[M+H]^+$: 254, Found: 254.

FTIR (neat): v 3351, 2969, 2913, 1590, 1571, 1468, 1446, 1432, 1376, 1293, 1189, 1152, 1109, 1090, 1065, 998, 886, 838, 789, 748, 698, 665 cm^{-1}.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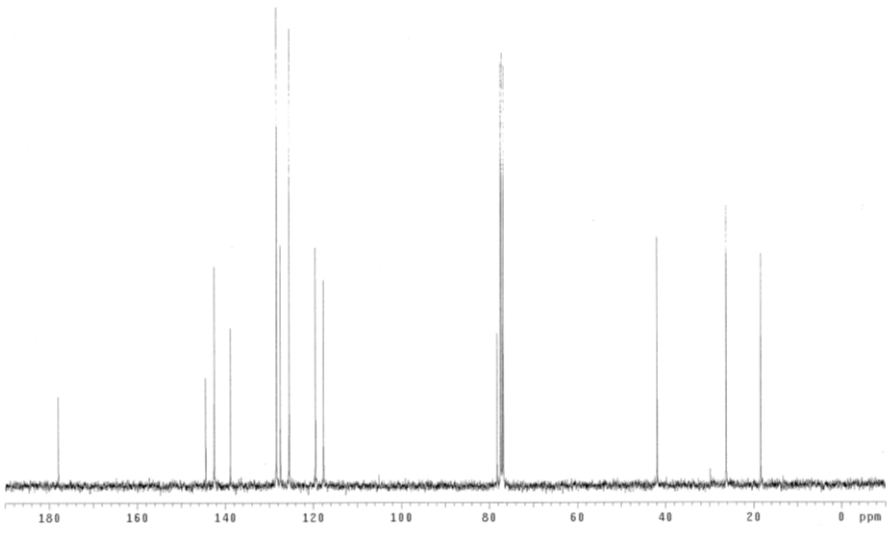
180
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100
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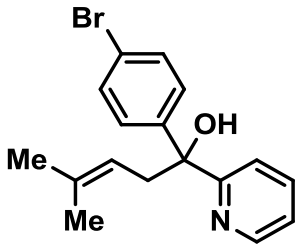
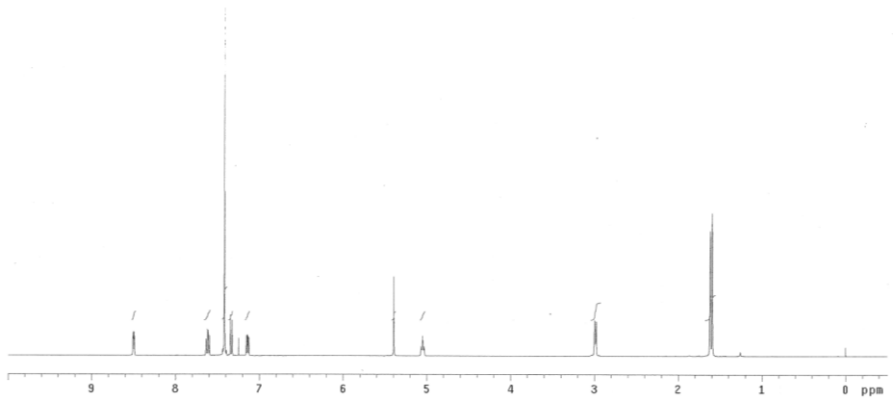
0 ppm

Synthesis of 4-Bromophenyl Pyridyl Prenyl Methanol (4.3b).



In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 18 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (91.7 mg, 92%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51-8.49 (m, 1H), 7.64-7.60 (m, 1H), 7.44-7.39 (m, 4H), 7.35-7.32 (m, 1H), 7.16-7.12 (m, 1H), 5.39 (s, 1H), 5.07-5.03 (m, 1H), 2.99 (dd, *J* = 6.8, 0.8 Hz, 2H), 1.62 (d, *J* = 1.6 Hz, 3H), 1.60 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 147.6, 145.4, 137.0, 135.4, 131.2, 128.1, 122.2, 121.0, 120.5, 118.7, 40.0, 26.0, 18.3.
LRMS (CI) Calcd. for $C_{17}H_{19}BrNO$ $[M+H]^+$: 332, Found: 332.
FTIR (neat): v 3375, 2969, 2912, 1738, 1590, 1570, 1485, 1468, 1433, 1393, 1375, 1291, 1216, 1152, 1102, 1072, 1052, 1008, 936, 886, 820, 781, 749, 735, 716, 669 cm^{-1}.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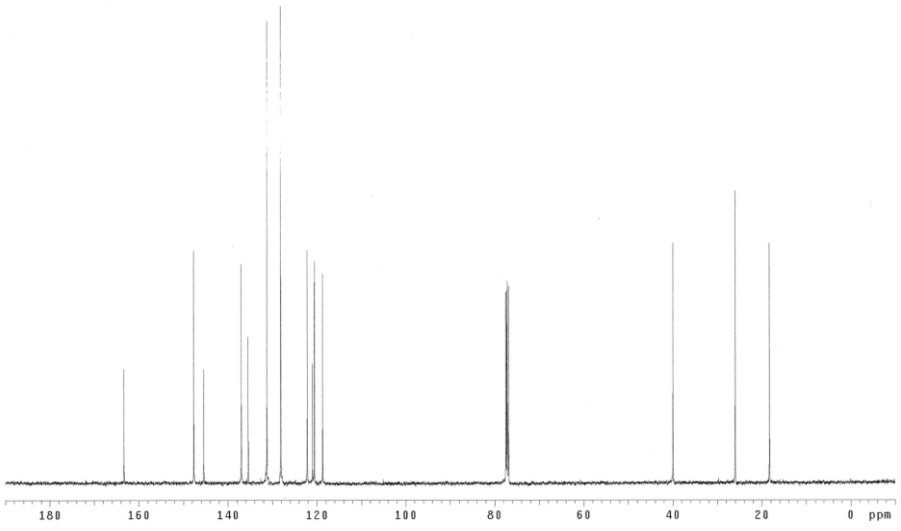
0 ppm


180
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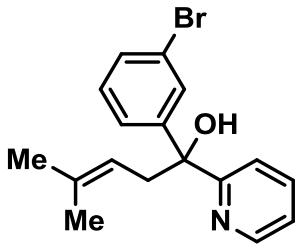
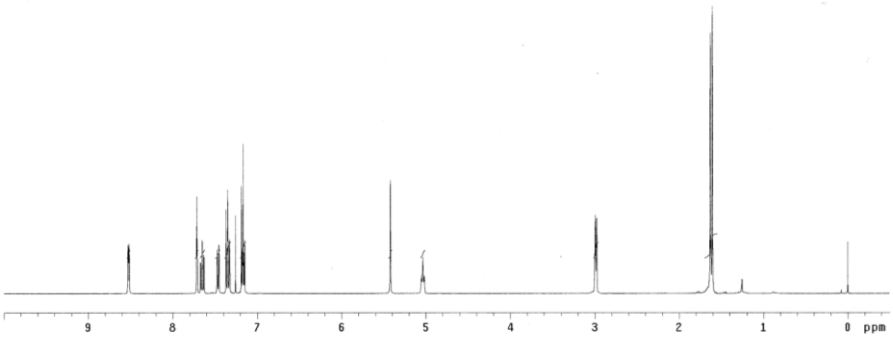
0 ppm

Synthesis of 3-Bromophenyl Pyridyl Prenyl Methanol (4.3c).



In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 24 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (89.0 mg, 90%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.65 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.37-7.32 (m, 2H), 7.19-7.15 (m, 2H), 5.42 (s, 1H), 5.06-5.02 (m, 1H), 2.99 (d, *J* = 6.8 Hz, 2H), 1.63 (d, *J* =1.2 Hz, 3H), 1.61 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 148.8, 147.7, 137.1, 135.6, 130.1, 129.8, 129.5, 124.9, 122.6, 122.3, 120.7, 118.6, 40.0, 26.0, 18.4.
LRMS (CI) Calcd. for $C_{17}H_{19}BrNO$ $[M+H]^+$: 332, Found: 332.
FTIR (neat): v 3352, 2970, 2913, 2355, 1738, 1588, 1568, 1467, 1433, 1416, 1375, 1294, 1169, 1112, 1096, 1072, 1052, 996, 892, 839, 792, 775, 749, 697, 683, 657 cm^{-1}.


9
8
7
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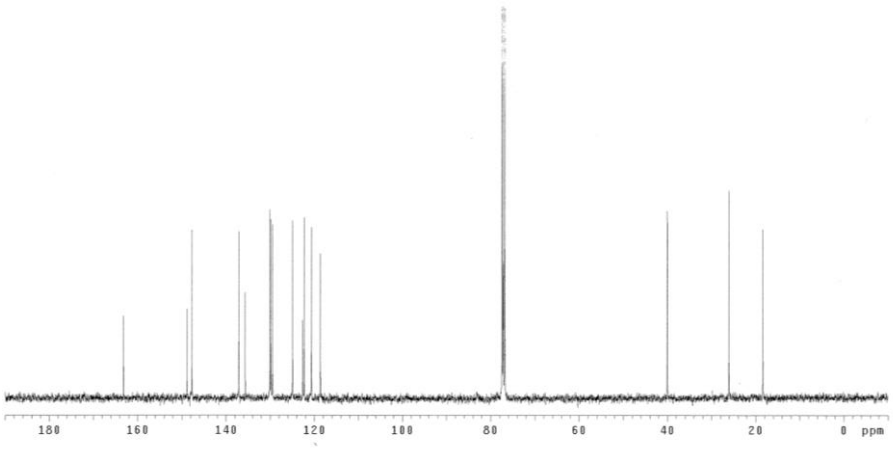
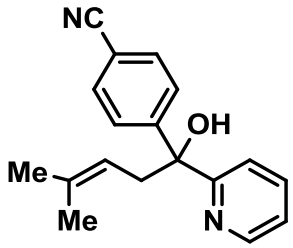
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of 4-Cyanophenyl Pyridyl Prenyl Methanol (4.3d).



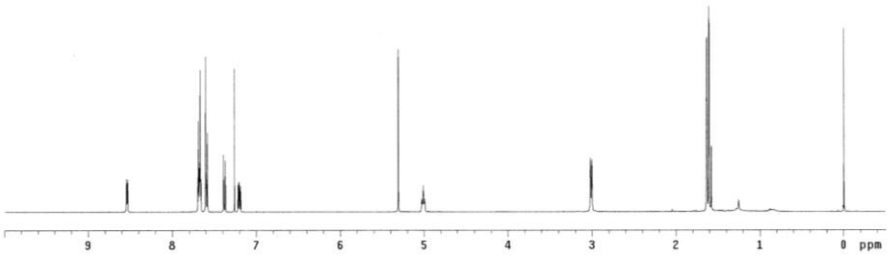
In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 18 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (83.0 mg, 99%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 7.70-7.65 (m, 3H), 7.61-7.58 (m, 2H), 7.38 (dt, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.20 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 5.31 (s, 1H), 5.03-4.99 (m, 1H), 3.01 (d, *J* = 7.2 Hz, 2H), 1.63 (d, *J* = 0.8 Hz, 3H), 1.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 151.5, 147.7, 137.0, 135.9, 131.9, 126.8, 122.3, 120.3, 118.8, 118.0, 110.5, 39.7, 25.8, 18.1.

LRMS (CI) Calcd. for $C_{18}H_{19}N_2O$ $[M+H]^+$: 279, Found: 279.

FTIR (neat): v 2915, 2227, 1606, 1589, 1573, 1504, 1469, 1454, 1434, 1403, 1384, 1292, 1191, 1153, 1105, 1079, 1052, 996, 888, 832, 787, 751, 710, 685 cm^{-1}.


9
8
7
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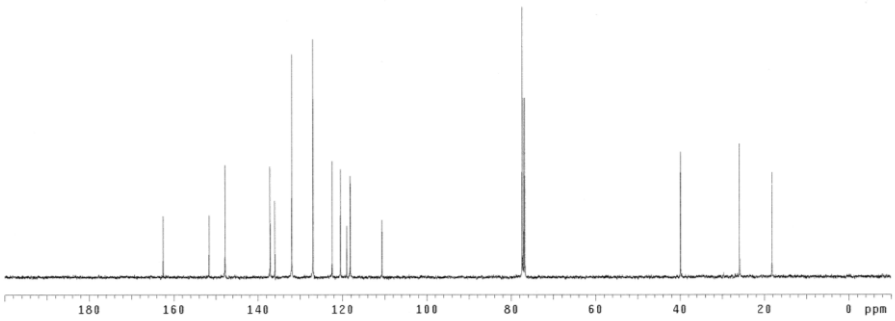
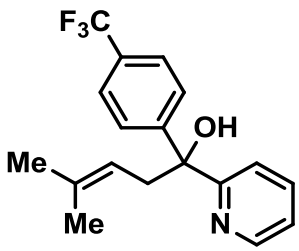
4
3
2
1
0 ppm

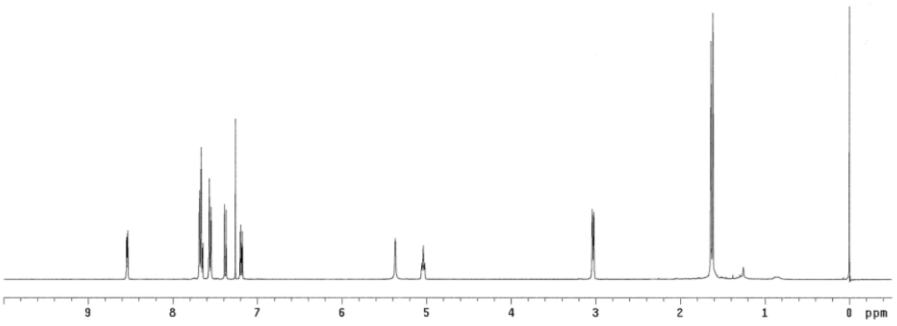

180
160
140
120
100
80
60
40
20
0 ppm

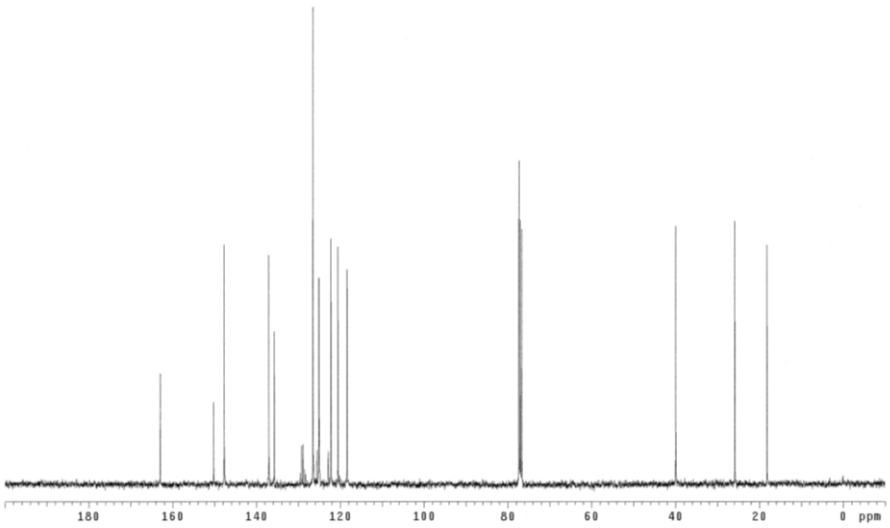
Synthesis of 4-Trifluoromethylphenyl Pyridyl Prenyl Methanol (4.3e).

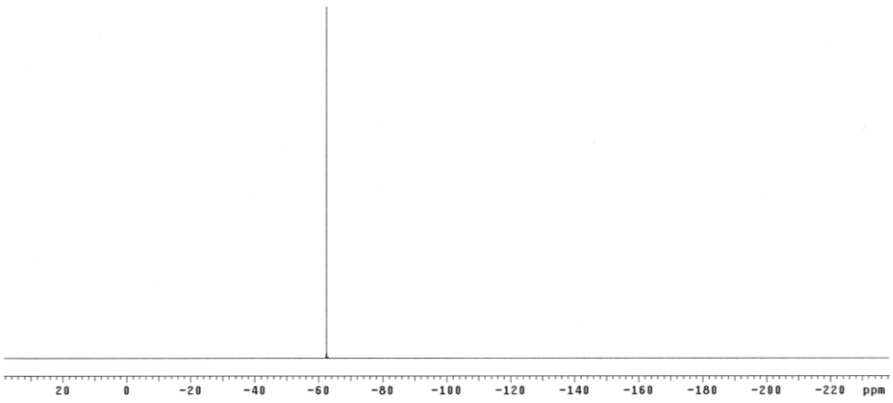


In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 18 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (91.1 mg, 95%) as a yellow oil.

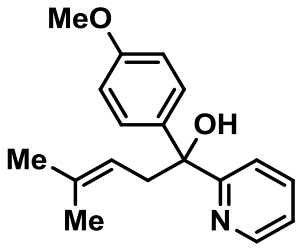
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 7.69-7.65 (m, 3H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.39-7.37 (m, 1H), 7.21-7.17 (m, 1H), 5.37 (s, 1H), 5.06-5.02 (m, 1H), 3.03 (dd, *J* = 6.8, 1.2 Hz, 2H), 1.64 (d, *J* = 0.8 Hz, 3H), 1.61 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): 163.0, 150.2, 147.7, 137.0, 135.7, 126.5, 125.1, 125.1, 122.9, 122.2, 120.5, 118.4, 39.9, 25.9, 18.2.
^{19}F NMR (376 MHz, CDCl3): δ -62.4.
LRMS (CI) Calcd. for $C_{18}H_{19}F_3NO$ $[M+H]^+$: 322, Found: 322.
FTIR (neat): v 3377, 2917, 1618, 1590, 1572, 1468, 1434, 1409, 1324, 1163, 1120, 1067, 1017, 999, 887, 835, 787, 751, 724, 670 cm^{-1}.


9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

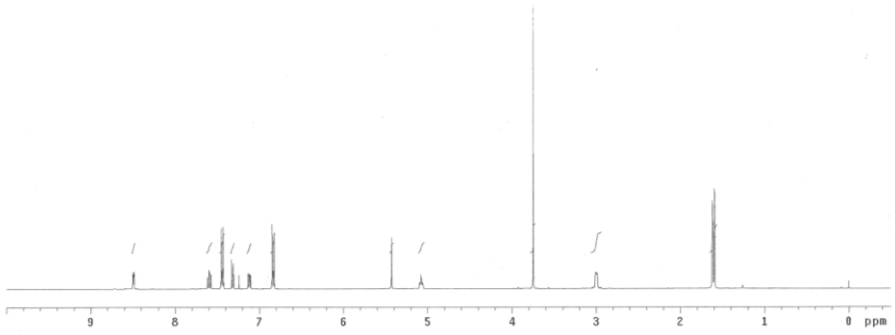

20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

Synthesis of 4-Methoxyphenyl Pyridyl Prenyl Methanol (4.3f).



In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 24 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 5% EtOAc/hexanes) to furnish the title compound (76.2 mg, 90%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50-8.48 (m, 1H), 7.60 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.46-7.42 (m, 2H), 7.32 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.12 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H), 6.85-6.82 (m, 2H), 5.43 (s, 1H), 5.10–5.06 (m, 1H), 3.75 (s, 3H), 3.01-2.99 (m, 2H), 1.62 (d, *J* = 1.2 Hz, 3H), 1.59 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 158.5, 147.4, 138.5, 136.8, 134.8, 127.4, 121.9, 120.7, 119.2, 113.5, 55.2, 40.1, 26.0, 18.3.
LRMS (CI) Calcd. for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284, Found: 284.
FTIR (neat): v 3376, 2910, 2835, 1737, 1609, 1590, 1570, 1509, 1465, 1433, 1375, 1301, 1247, 1177, 1105, 1076, 1034, 998, 940, 887, 829, 797, 783, 750 cm^{-1}.


9
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6
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4
3
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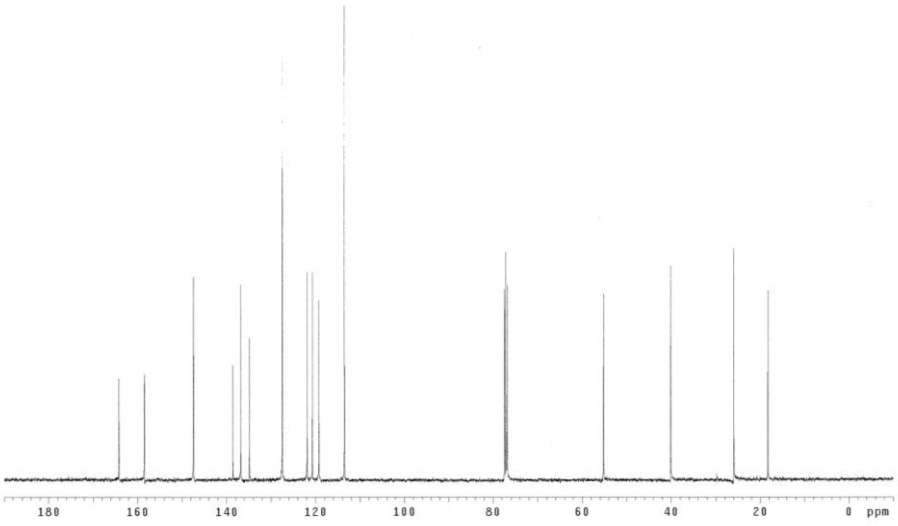
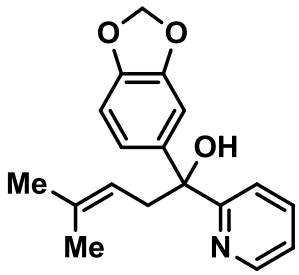
1
0 ppm

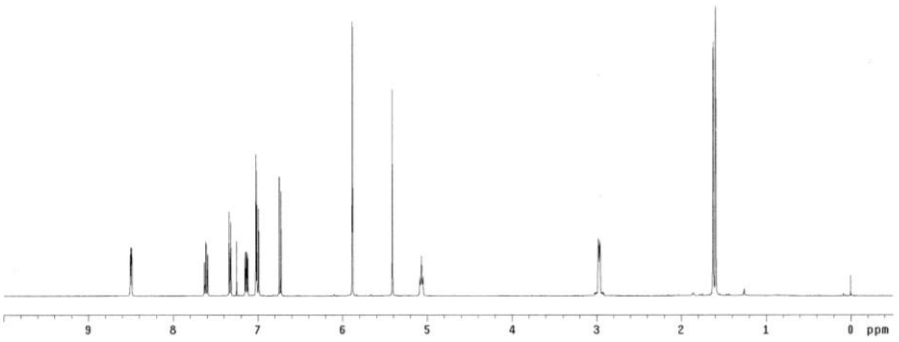

180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of 1,3-Benzodioxole Pyridyl Prenyl Methanol (4.3g).



In modification to the general procedure, 2.0 equiv. of isoprene was employed and the reaction was heated for 18 hours, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (76.0 mg, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51-8.49 (m, 1H), 7.61 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.34-7.32 (m, 1H), 7.13 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.89-5.88 (m, 2H), 5.41 (s, 1H), 5.09-5.05 (m, 1H), 2.97 (d, *J* =6.8 Hz, 2H), 1.62 (d, *J* = 0.8 Hz, 3H), 1.60 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 147.6, 147.5, 146.4, 140.6, 136.8, 135.0, 122.0, 120.6, 119.3, 119.0, 107.8, 107.3, 111.0, 40.1, 26.0, 18.3.
LRMS (CI) Calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298, Found: 298.
FTIR (neat): v 3373, 2912, 1742, 1590, 1570, 1502, 1486, 1468, 1433, 1376, 1293, 1235, 1152, 1106, 1078, 1038, 998, 935, 912, 865, 812, 782, 750, 735, 715, 678 cm^{-1}.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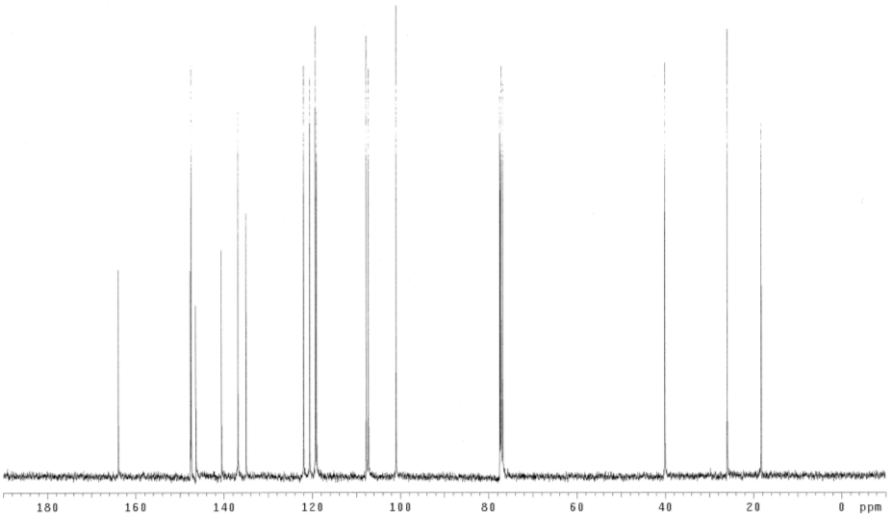
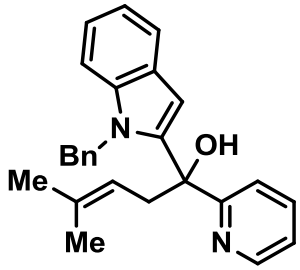
0 ppm

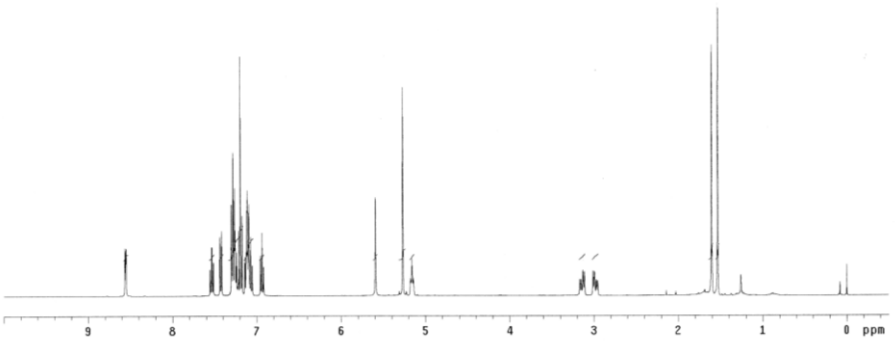

180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of 2-(*N*-Bn-indolyl) Pyridyl Prenyl Methanol (4.3h).



In a modification to the general procedure, $Ru_3(CO)_{12}$ (2 mol %) was employed. After 24 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 10% EtOAc/hexanes) to furnish the title compound (71.3 mg, 62% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 8.56-8.55 (m, 1H), 7.54 (td, *J* = 8.0, 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30-7.17 (m, 6H), 7.14-7.05 (m, 4H), 6.96-6.92 (m, 1H), 5.59 (s, 1H), 5.27 (s, 2H), 5.18-5.14 (m, 1H), 3.15 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.99 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.61 (s, 3H), 1.53 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 147.2, 137.6, 137.3, 136.7, 134.4, 128.8, 127.7, 126.9, 126.6, 126.4, 121.9, 121.8, 121.4, 121.0, 120.8, 119.4, 109.7, 75.4, 50.1, 40.7, 26.0, 18.2.
LRMS (CI) Calcd. for $C_{26}H_{27}N_2O$ $[M+H]^+$: 383, Found: 383.
FTIR (neat): v 3371, 2914, 1738, 1591, 1569, 1548, 1496, 1466, 1453, 1433, 1355, 1331, 1293, 1217, 1178, 1106, 1049, 1028, 1016, 998, 908, 872, 787, 733, 696 cm^{-1}.


9
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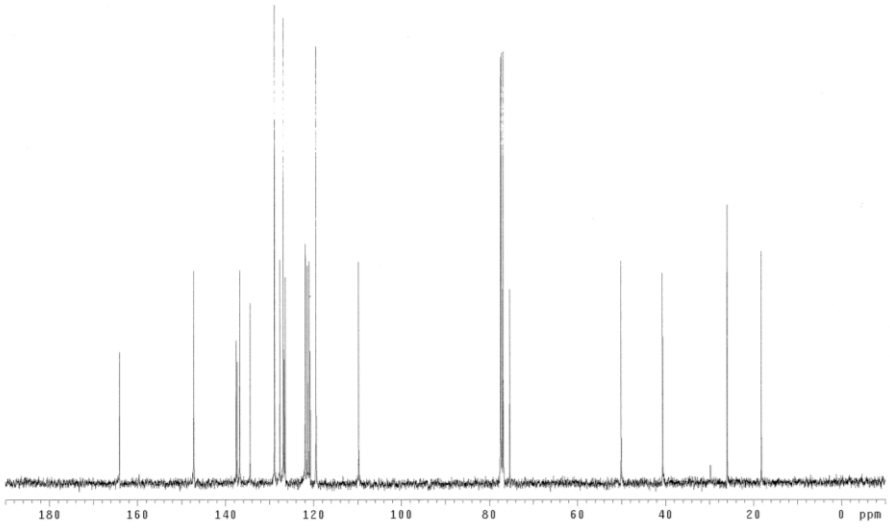
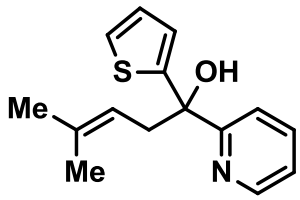
1
0 ppm

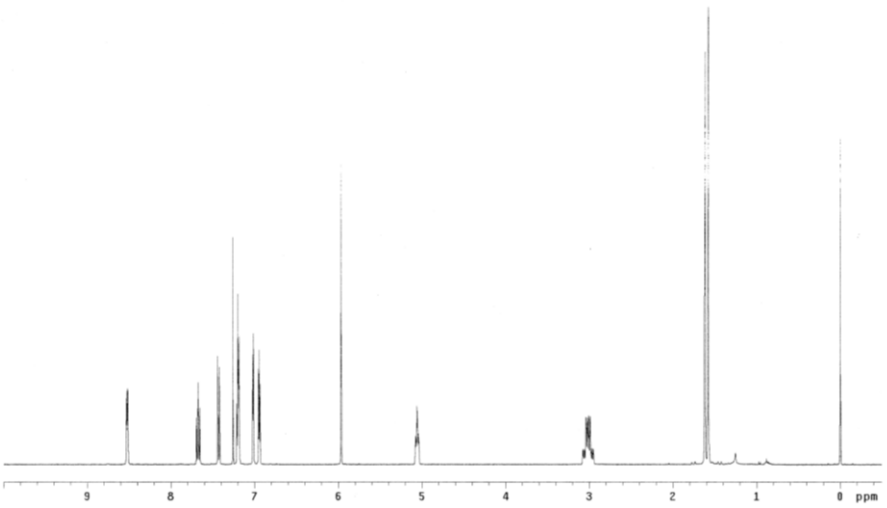

180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of 2-Thienyl Pyridyl Prenyl Methanol (4.3i).



The reaction was performed in accordance with the general procedure. After 18 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (63.0 mg, 90% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 7.68 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.44-7.42 (m, 1H), 7.22-7.18 (m, 2H), 7.02-7.01 (m, 1H), 6.94 (dd, *J* = 5.0, 3.4 Hz, 1H), 5.97 (s, 1H), 5.08-5.04 (m, 1H), 3.05 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.98 (dd, *J* = 14.8, 2.4 Hz, 1H), 1.62 (s, 3H), 1.58 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 152.1, 147.1, 136.9, 135.1, 126.6, 124.6, 123.3, 122.2, 120.3, 118.4, 41.6, 25.8, 18.2.
LRMS (CI) Calcd. for $C_{15}H_{18}NOS$ $[M+H]^+$: 260, Found: 260.
FTIR (neat): v 3331, 2916, 1591, 1571, 1468, 1433, 1383, 1349, 1294, 1234, 1152, 1108, 1077, 1048, 999, 874, 848, 827, 781, 750, 697 cm^{-1}.


9
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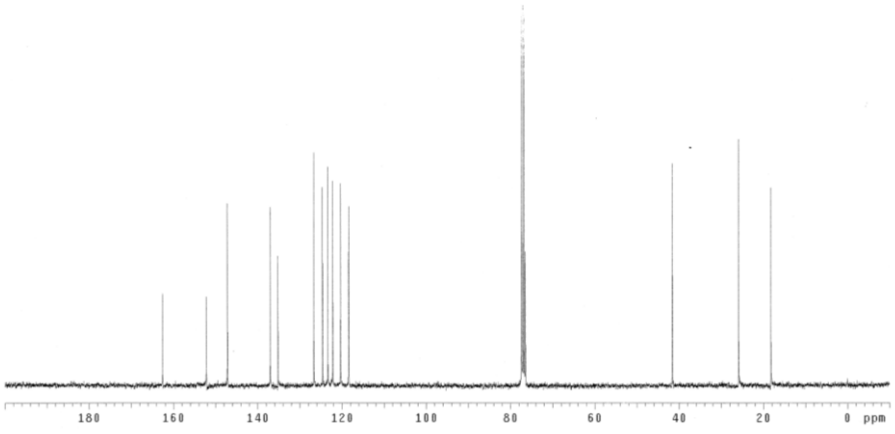
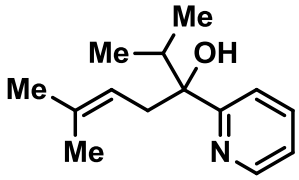
0 ppm

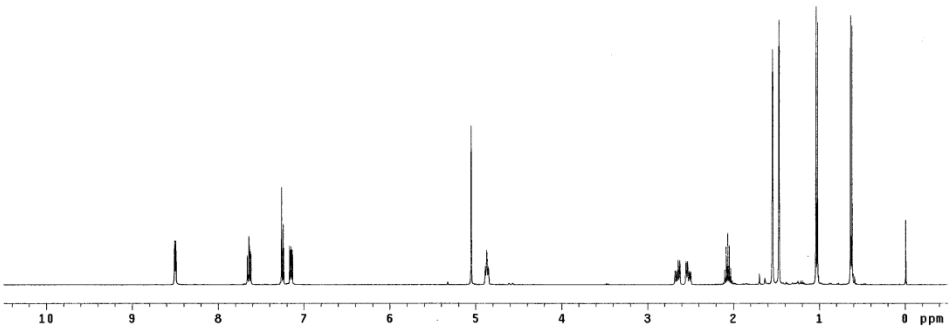

180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of Isopropyl Pyridyl Prenyl Methanol (4.3j).



In a modification to the general procedure, $Ru_3(CO)_{12}$ (2 mol %) and PCy_3 (10 mol %) were employed. After 48 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (43.7 mg, 66% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51-8.49 (m, 1H), 7.64 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.15 (ddd, *J* = 6.0, 4.8, 1.4 Hz, 1H), 5.05 (s, 1H), 4.89-4.85 (m, 1H), 2.65 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.05 (heptet, *J* = 6.8 Hz, 1H), 1.55 (s, 3H), 1.47 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.63 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 147.0, 136.2, 133.8, 121.5, 120.2, 119.4, 78.1, 37.7, 37.2, 25.8, 18.0, 17.3, 16.8.
LRMS (CI) Calcd. for $C_{14}H_{23}NO$ $[M+H]^+$: 220, Found: 220.
FTIR (neat): v 3381, 2965, 2914, 2360, 1593, 1570, 1471, 1434, 1384, 1362, 1293, 1179, 1146, 1052, 1025, 999, 895, 838, 784, 751, 727 cm^{-1}.


10
9
8
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3
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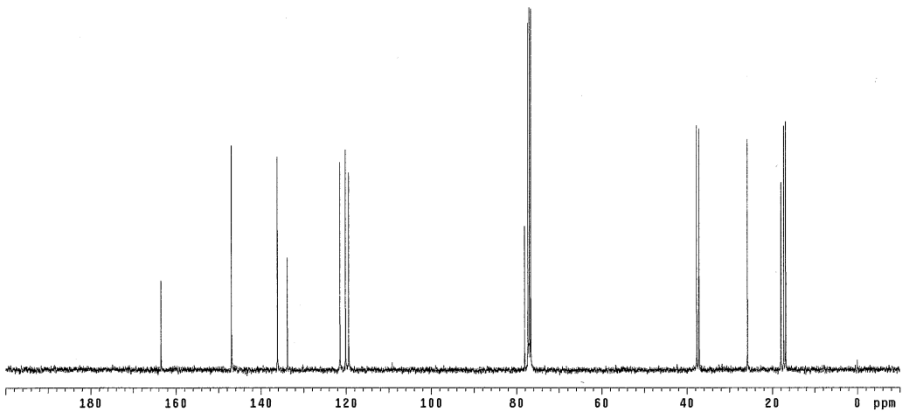
1
0 ppm


180
160
140
120
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80
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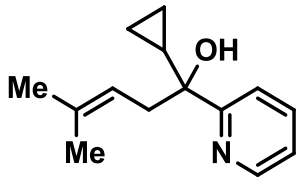
40
20
0 ppm

Synthesis of Cyclopropyl Pyridyl Prenyl Methanol (4.3k).



In a modification to the general procedure, $Ru_3(CO)_{12}$ (2 mol %) and PCy_3 (10 mol %) were employed. After 48 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (43.2 mg, 66%) as a yellow oil.

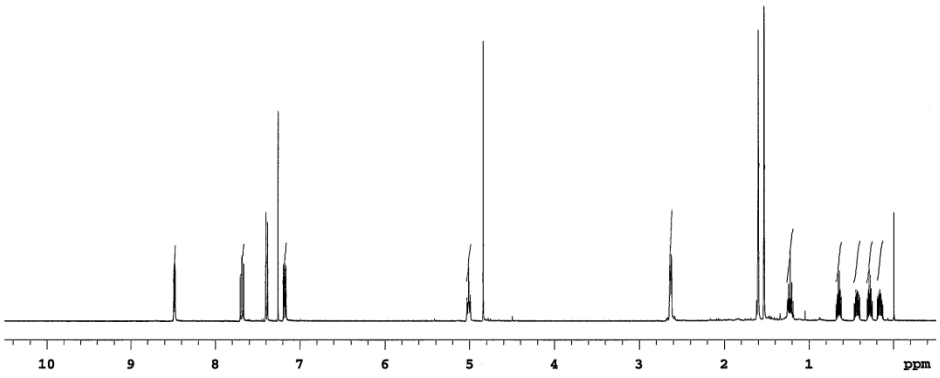
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49-8.48 (m, 1H), 7.71-7.67 (m, 1H), 7.39 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.19 (ddd, *J* = 4.8, 7.6, 1.2 Hz, 1H), 5.03-4.99 (m, 1H), 4.84 (s, 1H), 2.63 (d, *J* = 7.2 Hz, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.26-1.19 (m, 1H), 0.68-0.62 (m, 1H), 0.47-0.40 (m, 1H), 0.32-0.26 (m, 1H), 0.20-0.13 (m, 1H).

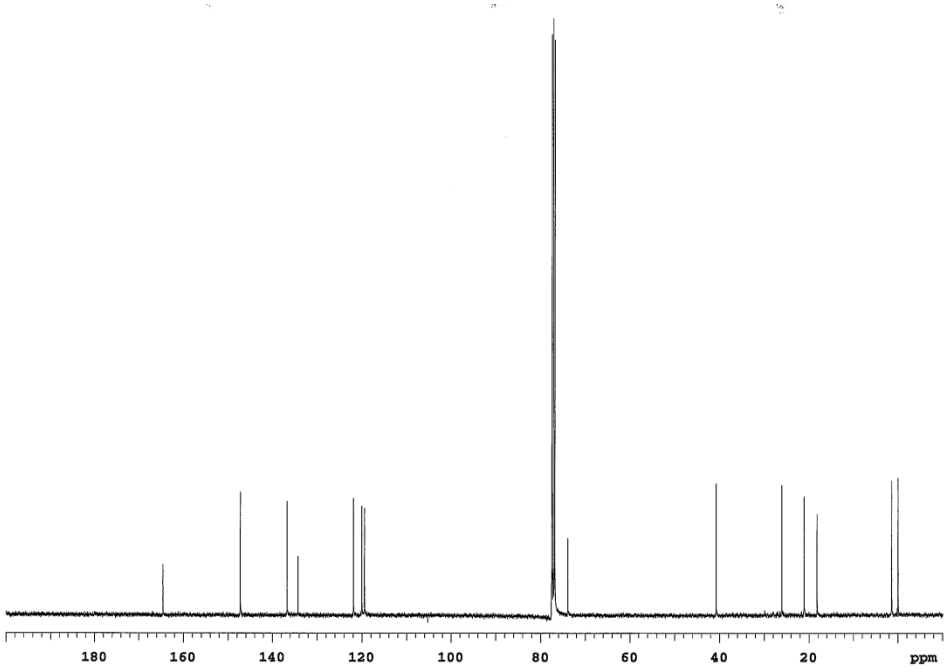
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 147.2, 136.8, 134.3, 121.9, 120.1, 119.5, 74.0, 40.8, 26.1, 21.1, 18.2, 1.4.

LRMS (CI) Calcd. for $C_{14}H_{20}NO$ $[M+H]^+$: 218, Found: 218.

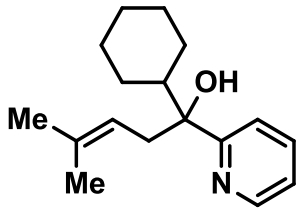
FTIR (neat): v 3429, 3275, 3004, 2963, 2915, 1587, 1570, 1468, 1434, 1397, 1376, 1353, 1292, 1246, 1208, 1190, 1156, 1140, 1113, 1069, 1051, 1038, 1024, 1011, 999, 990, 915, 896, 836, 777, 751, 727 cm^{-1}.

MP 44–46 ^oC.


10
9
8
7
6
5
4
3
2
1
ppm

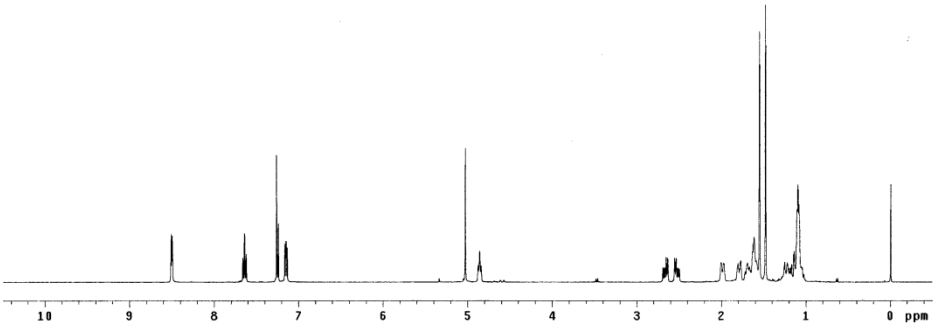

180
160
140
120
100
80
60
40
20
ppm

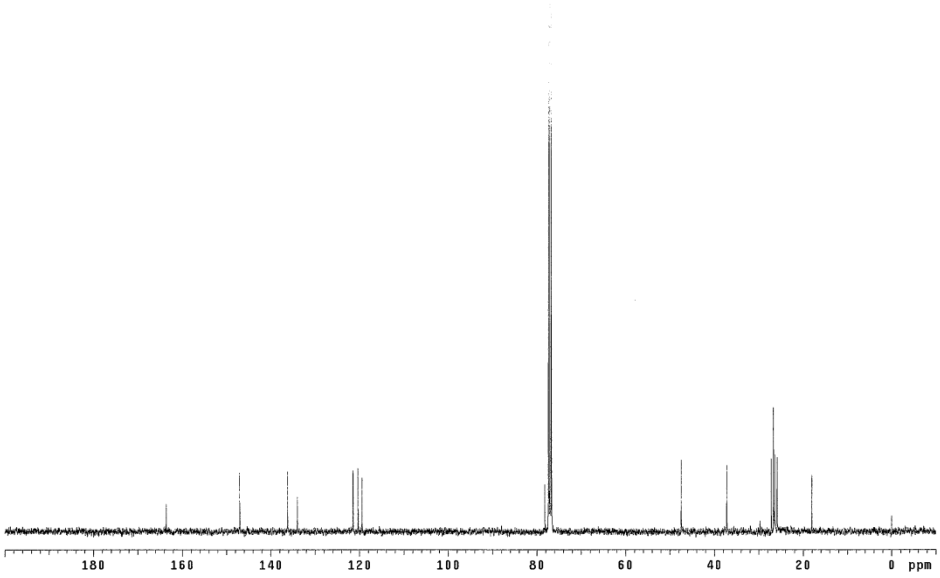
Synthesis of Cyclohexyl Pyridyl Prenyl Methanol (4.3l).



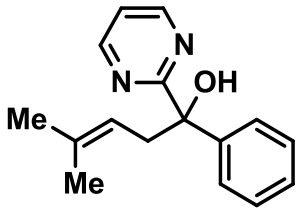
In modification to the general procedure, $Ru_3(CO)_{12}$ (2 mol %) and PCy_3 (10 mol %) were employed. After 48 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (39.2 mg, 50% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.64 (dt, *J* = 6.4, 1.4 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.15 (dd, *J* = 7.6, 5.6 Hz, 1H), 5.03 (s, 1H), 4.88-4.84 (m, 1H), 2.66 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.00-1.97 (m, 1H), 1.80-1.77 (m, 1H), 1.73-1.59 (m, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.25-1.17 (m, 2H), 1.14-1.13 (m, 1H), 1.11-1.08 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 147.0, 136.2, 133.9, 121.4, 120.3, 119.4, 78.2, 47.4, 37.2, 27.2, 26.7, 26.6, 26.4, 25.9, 18.0.
LRMS (CI) Calcd. for $C_{17}H_{26}NO$ $[M+H]^+$: 260, Found: 260.
FTIR (neat): v 2928, 2853, 2359, 1592, 1570, 1471, 1434, 1394, 1114, 1087, 777, 751, 667 cm^{-1}.


10
9
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of Pyrimidinyl Prenyl Methanol (4.3m).



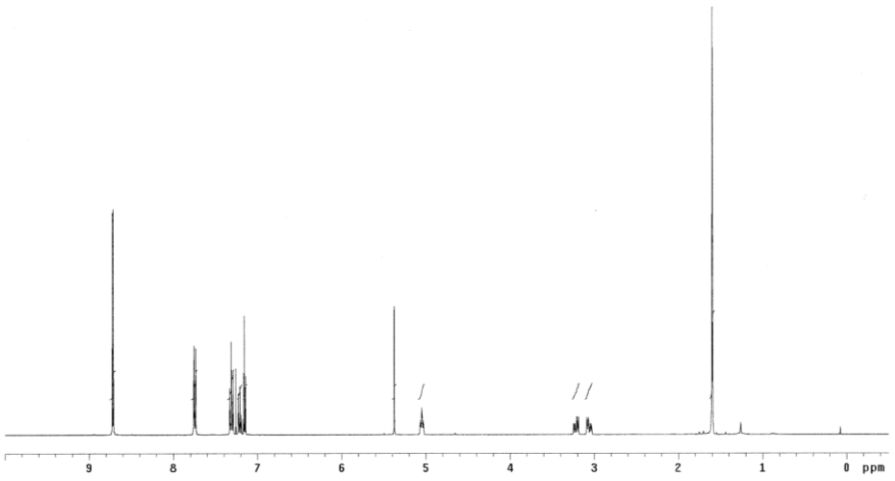
In modification to the general procedure, the reaction was conducted at 120 ^{o}C. After 18 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (69.4 mg, 91% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.8 Hz, 2H), 7.76-7.73 (m, 2H), 7.34-7.29 (m, 2H), 7.23-7.19 (m, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 5.37 (s, 1H), 5.07-5.02 (m, 1H), 3.22 (dd, *J* =14.4, 7.2 Hz, 1H), 3.06 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.60 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 156.8, 145.5, 134.7, 128.1, 127.0, 126.1, 119.1, 119.1, 78.7, 40.3, 26.0, 18.3.

LRMS (CI) Calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255, Found: 255.

FTIR (neat): v 3439, 2969, 2913, 1738, 1672, 1572, 1562, 1492, 1447, 1418, 1374, 1263, 1199, 1118, 1090, 1066, 1032, 997 cm^{-1}.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8
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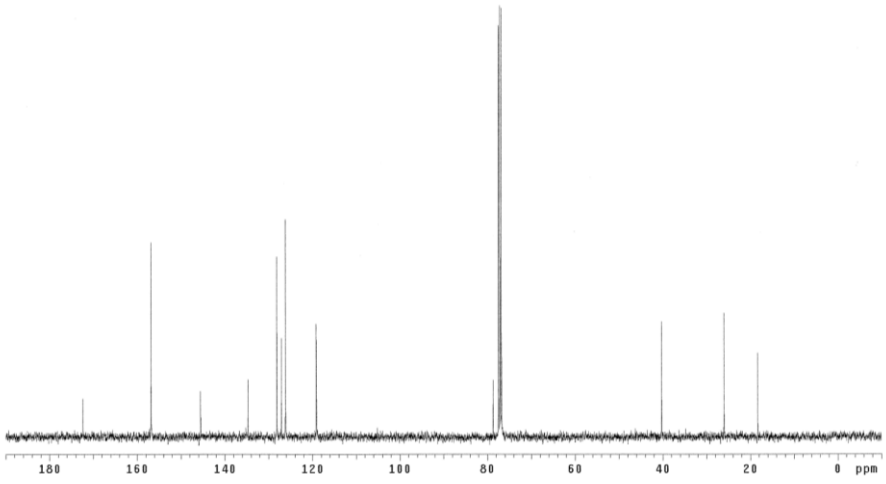
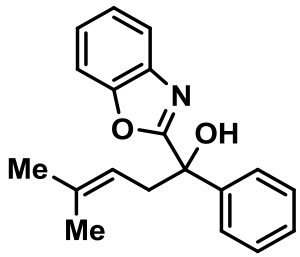
6
5
4
3
2
1
0 ppm

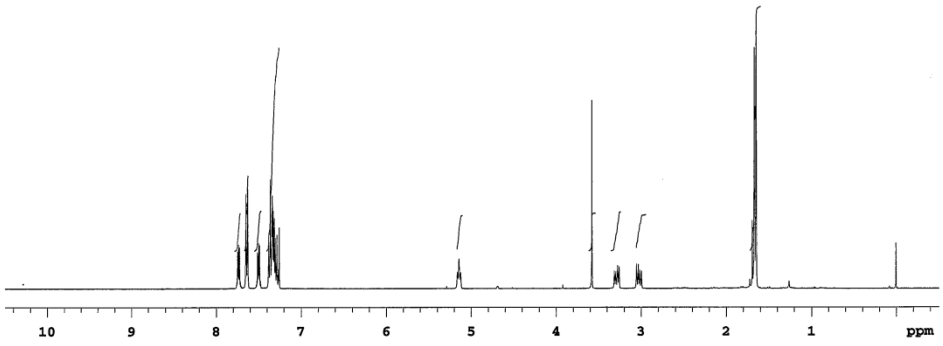

180
160
140
120
100
80
60
40
20
0 ppm

Synthesis of Benzoxazolyl Pyridyl Prenyl Methanol (4.3n).



In modification to the general procedure, $Ru_3(CO)_{12}$ (2 mol %) was employed. After 24 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (77.4 mg, 88% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 1H), 7.86-7.83 (m, 1H), 7.75-7.72 (m, 2H), 7.51-7.49 (m, 1H), 7.38-7.33 (m, 3H), 7.29-7.25 (m, 1H), 5.14-5.09 (m, 1H), 3.56 (s, 1H), 3.43 (dd, *J* = 14.4, 6.8 Hz, 1H), 3.10 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.67 (s, 3H), 1.65 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 151.2, 142.4, 140.6, 138.1, 128.5, 128.4, 127.8, 125.4, 125.1, 124.6, 124.5, 120.2, 117.1, 110.9, 75.7, 40.1, 26.0, 18.2.
LRMS (ESI) Calcd. for $C_{19}H_{19}NaNO_2$ $[M+Na]^+$: 316, Found: 316.
FTIR (neat): v 3414, 3058, 2914, 2357, 1610, 1560, 1494, 1474, 1454, 1376, 1241, 1159, 1096, 1069, 1033, 1003, 929, 908, 879, 840, 794, 761, 746, 726, 698, 667 cm^{-1}.


10
9
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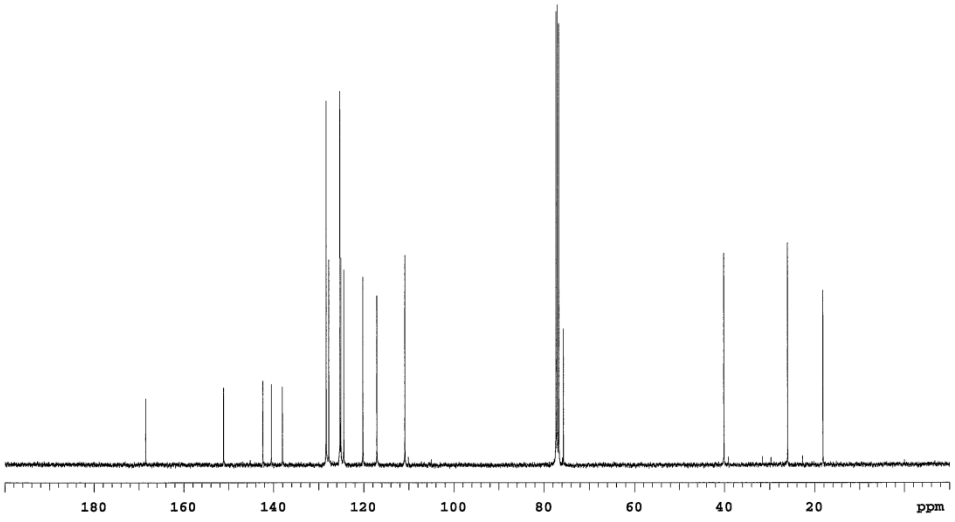
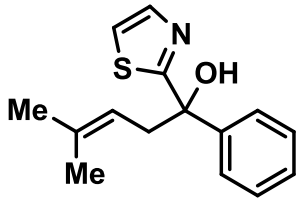
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

Synthesis of Thiazolyl Pyridyl Prenyl Methanol (4.3o).



The reaction was performed in accordance with the general procedure. After 18 hours, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (76.5 mg, 86% yield) as a brown solid.

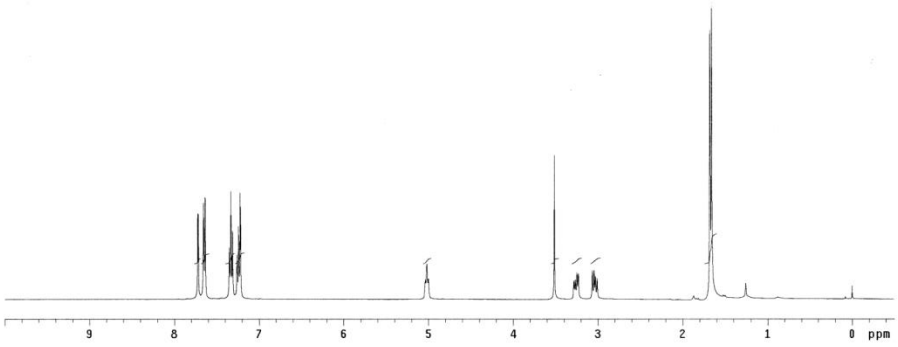
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 3.2 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 1H), 7.22 (d, *J* = 3.2 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 3.51 (s, 1H), 3.26 (dd, *J* = 14.4, 6.8 Hz, 1H), 3.04 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.68 (s, 3H), 1.66 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 144.4, 142.5, 138.8, 128.3, 127.4, 125.5, 119.5, 117.7, 78.2, 41.9, 26.2, 18.4.

LRMS (CI) Calcd. for $C_{15}H_{18}NOS$ $[M+H]^+$: 260, Found: 260.

FTIR (neat): v 3117, 2970, 2912, 2852, 1739, 1506, 1495, 1444, 1378, 1232, 1204, 1150, 1097, 1061, 984, 938, 918, 856, 821, 781, 765, 725, 696, 670 cm^{-1}.

MP 97.3–98.3 ^oC.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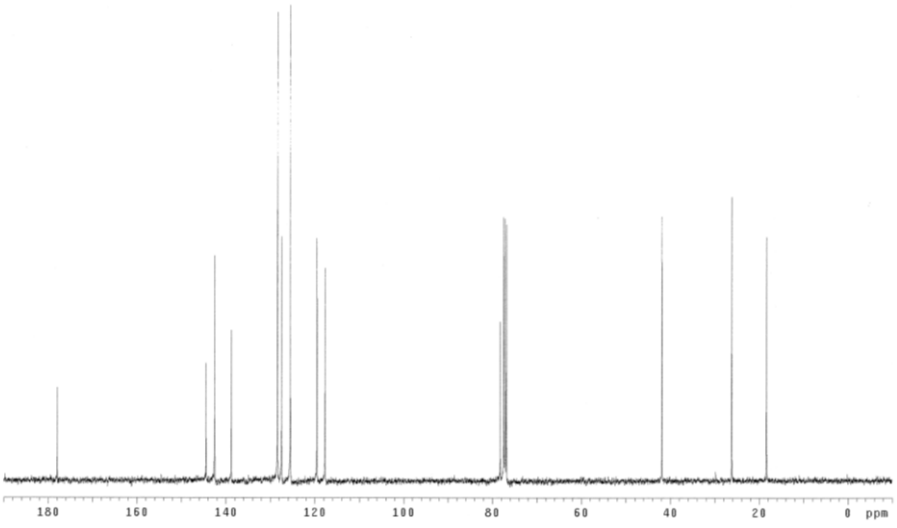
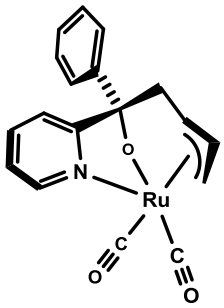
8
7
6
5
4
3
2
1
0 ppm


180
160
140
120
100
80
60
40
20
0 ppm

Charaterization of π-Allyl Oxaruthenacycle complex Ib-π-allyl.

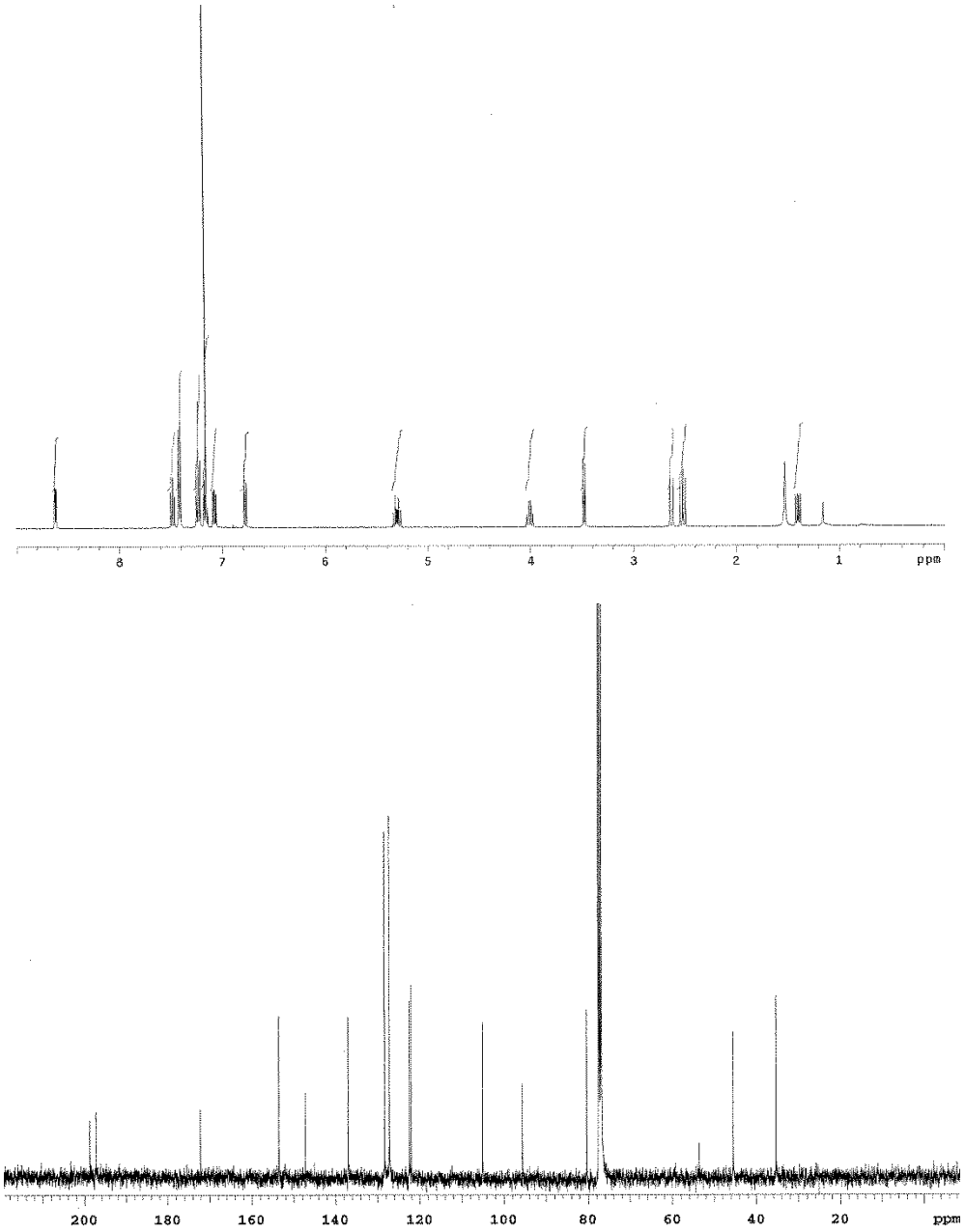


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63-8.61 (m, 1H), 7.48 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.25-7.21 (m, 2H), 7.18-7.14 (m, 1H), 7.09-7.06 (m, 1H), 6.78 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 5.34-5.27 (m, 1H), 4.04-3.98 (m, 1H), 3.48 (ddd, *J* = 7.6, 1.2, 1.2 Hz, 1H), 2.65-2.61 (m, 1H), 2.52 (dd, *J* = 11.6, 8.4 Hz, 1H), 1.42-1.37 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 197.3, 172.1, 153.5, 147.2, 137.0, 128.3, 127.2, 122.5, 122.1, 105.0, 95.6, 80.3, 53.6, 45.5, 35.4.

HRMS (CI) Calcd. for $C_{19}H_{18}NO_3Ru$ $[M+H]^+$:396.0095, Found: 396.0181.

FTIR (neat): v 2014, 1941 cm^{-1}.


8
7
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ppm
200
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160
140
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80
60
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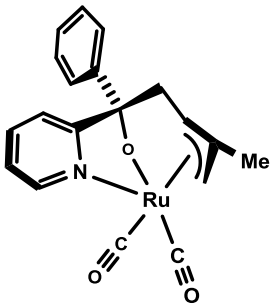
20
ppm

Charaterization of π-Allyl Oxaruthenacycle complex Ia-π-allyl.

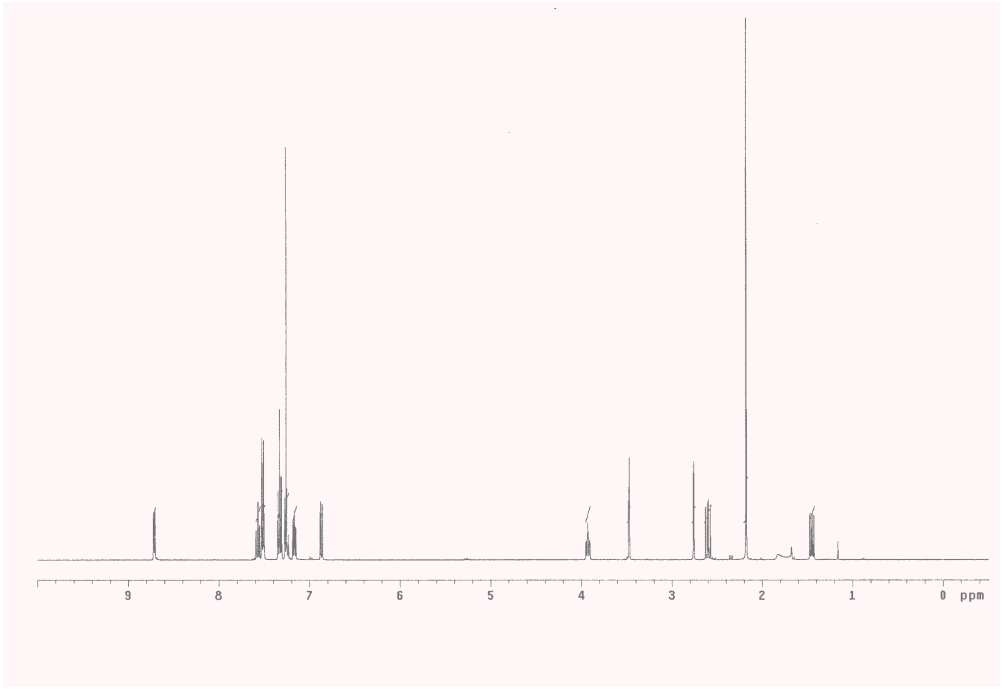


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (ddd, *J* = 5.2, 0.8, 0.8 Hz, 1H), 7.57 (td, *J* = 7.6, 1.6 Hz, 1H), 7.53-7.50 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.19-7.15 (m, 1H), 6.88-6.86 (m, 1H), 3.95-3.91 (m, 1H), 3.47 (dd, *J* = 1.6, 1.6 Hz, 1H), 2.76 (dd, *J* = 1.2, 0.8 Hz, 1H), 2.60 (dd, *J* = 12.0, 8.8 Hz, 1H), 2.18 (s, 3H), 1.45 (dd, *J* = 12.0, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 198.1, 172.0, 153.2, 147.0, 136.7, 128.1, 127.1, 127.0, 122.3, 121.8, 121.7, 94.9, 79.2, 47.1, 35.9, 28.5.

HRMS (CI) Calcd. for $C_{19}H_{18}NO_3Ru$ $[M+H]^+$: 410.0252, Found: 410.0340

FTIR (neat): v 2008, 1929 cm^{-1}.


9
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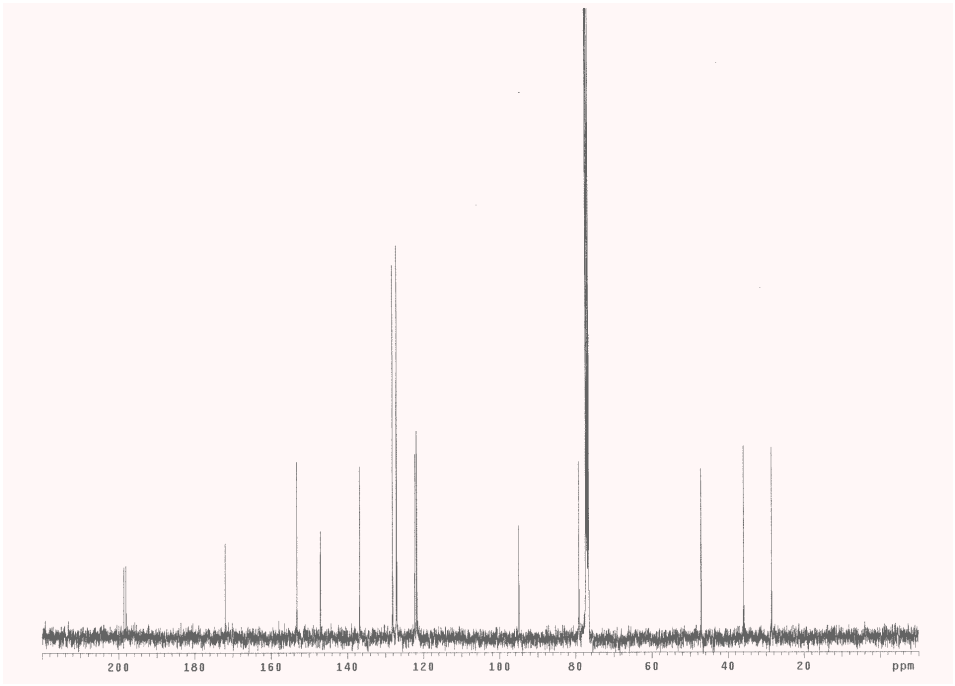
0 ppm


200
180
160
140
120
100
80
60
40
20
ppm

Crystallographic Material for π-Allyl Oxaruthenacycle complex derived from isoprene.

Crystal data and structure refinement for π-Allyl Oxaruthenacycle complex derived from isoprene.

Identification code	shelxl
Empirical formula	C19 H17.20 N O3.10 Ru
Formula weight	410.21
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 8.0576(18) Å α= 90°. b = 9.927(2) Å β= 93.986(3)°. c = 21.084(5) Å γ = 90°.
Volume	1682.5(6) $Å^3$
Z	4
Density (calculated)	1.619 Mg/m^3
Absorption coefficient	0.949 mm^{-1}
F(000)	828
Crystal size	0.24 x 0.05 x 0.04 mm^3
Theta range for data collection	1.94 to 27.50°.
Index ranges	-10<=h<=10, -12<=k<=12, -27<=l<=27
Reflections collected	24210
Independent reflections	3865 [R(int) = 0.0338]
Completeness to theta = 27.50°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.875
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3865 / 0 / 234
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0246, wR2 = 0.0583
R indices (all data)	R1 = 0.0279, wR2 = 0.0604

Largest diff. peak and hole	0.829 and -0.620 e.Å^{-3}

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for π-Allyl Oxaruthenacycle complex derived from isoprene. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	-421(2)	4945(2)	1742(1)	15(1)
C2	-1423(2)	4892(2)	2249(1)	18(1)
C3	-693(2)	4591(2)	2848(1)	18(1)
C4	1022(2)	4398(2)	2924(1)	16(1)
C5	1970(2)	4512(2)	2402(1)	12(1)
C6	3880(2)	4405(2)	2403(1)	13(1)
C7	4713(2)	4811(2)	3046(1)	13(1)
C8	4892(2)	3913(2)	3556(1)	17(1)
C9	5635(3)	4311(2)	4140(1)	21(1)
C10	6231(2)	5615(2)	4223(1)	20(1)
C11	6073(2)	6513(2)	3718(1)	18(1)
C12	5320(2)	6119(2)	3135(1)	14(1)
C13	4357(2)	2953(2)	2211(1)	14(1)
C14	3657(2)	2600(2)	1550(1)	14(1)
C15	4428(2)	2724(2)	971(1)	16(1)
C16	5416(2)	3862(2)	844(1)	18(1)
C17	3940(3)	1742(2)	442(1)	22(1)
C18	3052(2)	6427(2)	807(1)	19(1)
C19	1657(3)	4069(2)	413(1)	20(1)
N1	1236(2)	4748(2)	1814(1)	12(1)
O1	4384(2)	5253(1)	1924(1)	12(1)
O2	3127(2)	7498(2)	619(1)	28(1)
O3	821(2)	3696(2)	-16(1)	34(1)
Ru1	3019(1)	4626(1)	1115(1)	12(1)
O1W	6490(20)	6941(17)	1280(8)	32(4)

Bond lengths [Å] and angles [°] for π-Allyl Oxaruthenacycle complex derived from isoprene.

C1-N1	1.347(2)
C1-C2	1.385(3)
C1-H1	0.9500
C2-C3	1.388(3)
C2-H2	0.9500
C3-C4	1.393(3)
C3-H3	0.9500
C4-C5	1.387(3)
C4-H4	0.9500
C5-N1	1.356(2)
C5-C6	1.543(2)
C6-O1	1.397(2)
C6-C7	1.526(3)
C6-C13	1.553(3)
C7-C12	1.396(3)
C7-C8	1.395(3)
C8-C9	1.389(3)
C8-H8	0.9500
C9-C10	1.387(3)
C9-H9	0.9500
C10-C11	1.387(3)
C10-H10	0.9500
C11-C12	1.389(3)
C11-H11	0.9500
C12-H12	0.9500
C13-C14	1.508(3)
C13-H13A	0.9900
C13-H13B	0.9900
C14-C15	1.414(3)
C14-Ru1	2.255(2)
C14-H14	0.92(2)

C15-C16	1.418(3)
C15-C17	1.512(3)
C15-Ru1	2.2346(19)
C16-Ru1	2.1878(19)
C16-H16B	0.96(2)
C16-H16A	0.95(2)
C17-H17A	0.9800
C17-H17B	0.9800
C17-H17C	0.9800
C18-O2	1.139(3)
C18-Ru1	1.903(2)
C19-O3	1.150(2)
C19-Ru1	1.865(2)
N1-Ru1	2.1316(16)
O1-Ru1	2.0592(13)
O1-O1W	2.799(16)
O2-O1W	3.01(17)

N1-C1-C2	122.33(18)
N1-C1-H1	118.8
C2-C1-H1	118.8
C1-C2-C3	118.49(18)
C1-C2-H2	120.8
C3-C2-H2	120.8
C2-C3-C4	119.20(18)
C2-C3-H3	120.4
C4-C3-H3	120.4
C5-C4-C3	119.65(18)
C5-C4-H4	120.2
C3-C4-H4	120.2
N1-C5-C4	120.66(17)
N1-C5-C6	112.63(15)
C4-C5-C6	126.71(17)
O1-C6-C7	110.59(15)

O1-C6-C5	107.32(14)
C7-C6-C5	111.12(15)
O1-C6-C13	106.40(14)
C7-C6-C13	112.01(15)
C5-C6-C13	109.19(15)
C12-C7-C8	118.36(17)
C12-C7-C6	119.54(16)
C8-C7-C6	122.10(17)
C9-C8-C7	121.07(19)
C9-C8-H8	119.5
C7-C8-H8	119.5
C8-C9-C10	120.06(19)
C8-C9-H9	120.0
C10-C9-H9	120.0
C11-C10-C9	119.39(19)
C11-C10-H10	120.3
C9-C10-H10	120.3
C10-C11-C12	120.63(19)
C10-C11-H11	119.7
C12-C11-H11	119.7
C11-C12-C7	120.49(18)
C11-C12-H12	119.8
C7-C12-H12	119.8
C14-C13-C6	111.85(15)
C14-C13-H13A	109.2
C6-C13-H13A	109.2
C14-C13-H13B	109.2
C6-C13-H13B	109.2
H13A-C13-H13B	107.9
C15-C14-C13	128.30(17)
C15-C14-Ru1	70.87(11)
C13-C14-Ru1	103.24(12)
C15-C14-H14	113.5(13)
C13-C14-H14	114.3(13)

Ru1-C14-H14	116.8(13)
C14-C15-C16	121.21(18)
C14-C15-C17	118.26(18)
C16-C15-C17	119.70(17)
C14-C15-Ru1	72.41(11)
C16-C15-Ru1	69.52(11)
C17-C15-Ru1	122.46(13)
C15-C16-Ru1	73.10(11)
C15-C16-H16B	117.6(15)
Ru1-C16-H16B	123.6(14)
C15-C16-H16A	119.9(14)
Ru1-C16-H16A	98.9(14)
H16B-C16-H16A	115.7(19)
C15-C17-H17A	109.5
C15-C17-H17B	109.5
H17A-C17-H17B	109.5
C15-C17-H17C	109.5
H17A-C17-H17C	109.5
H17B-C17-H17C	109.5
O2-C18-Ru1	177.68(18)
O3-C19-Ru1	178.48(19)
C1-N1-C5	119.56(16)
C1-N1-Ru1	129.89(13)
C5-N1-Ru1	110.45(12)
C6-O1-Ru1	104.51(10)
C19-Ru1-C18	91.66(9)
C19-Ru1-O1	176.18(7)
C18-Ru1-O1	88.80(7)
C19-Ru1-N1	100.23(8)
C18-Ru1-N1	102.04(7)
O1-Ru1-N1	75.98(6)
C19-Ru1-C16	99.87(8)
C18-Ru1-C16	101.70(8)
O1-Ru1-C16	83.74(7)

N1-Ru1-C16	148.24(7)
C19-Ru1-C15	85.27(8)
C18-Ru1-C15	136.69(8)
O1-Ru1-C15	96.99(6)
N1-Ru1-C15	121.05(7)
C16-Ru1-C15	37.38(8)
C19-Ru1-C14	99.40(8)
C18-Ru1-C14	165.60(8)
O1-Ru1-C14	80.78(6)
N1-Ru1-C14	85.14(6)
C16-Ru1-C14	67.46(7)
C15-Ru1-C14	36.72(7)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for π-Allyl Oxaruthenacycle complex derived from isoprene. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	12(1)	16(1)	17(1)	-4(1)	-2(1)	1(1)
C2	12(1)	18(1)	24(1)	-4(1)	1(1)	-2(1)
C3	14(1)	21(1)	19(1)	-2(1)	5(1)	-3(1)
C4	15(1)	16(1)	16(1)	0(1)	0(1)	-2(1)
C5	11(1)	8(1)	15(1)	-1(1)	0(1)	-1(1)
C6	10(1)	14(1)	14(1)	1(1)	1(1)	0(1)
C7	9(1)	16(1)	13(1)	-1(1)	1(1)	1(1)
C8	18(1)	16(1)	17(1)	2(1)	-1(1)	-2(1)
C9	22(1)	25(1)	15(1)	5(1)	-2(1)	0(1)
C10	17(1)	28(1)	14(1)	-4(1)	-4(1)	1(1)
C11	16(1)	17(1)	20(1)	-4(1)	-2(1)	0(1)
C12	12(1)	16(1)	16(1)	1(1)	0(1)	2(1)
C13	14(1)	15(1)	14(1)	1(1)	0(1)	2(1)
C14	12(1)	13(1)	17(1)	-1(1)	-2(1)	2(1)
C15	13(1)	19(1)	17(1)	-3(1)	0(1)	8(1)
C16	13(1)	26(1)	16(1)	-2(1)	3(1)	4(1)
C17	21(1)	24(1)	22(1)	-8(1)	-1(1)	5(1)
C18	19(1)	22(1)	14(1)	-2(1)	3(1)	4(1)
C19	21(1)	18(1)	22(1)	-2(1)	-1(1)	8(1)
N1	11(1)	12(1)	14(1)	-2(1)	0(1)	-1(1)
O1	11(1)	15(1)	10(1)	0(1)	0(1)	-2(1)
O2	42(1)	21(1)	23(1)	4(1)	12(1)	4(1)
O3	38(1)	30(1)	30(1)	-13(1)	-20(1)	13(1)
Ru1	11(1)	15(1)	10(1)	-1(1)	0(1)	2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for π-Allyl Oxaruthenacycle complex derived from isoprene.

	x	y	z	U(eq)
H1	-919	5126	1330	18
H2	-2584	5059	2189	22
H3	-1355	4517	3202	22
H4	1539	4189	3330	19
H8	4499	3016	3502	21
H9	5736	3690	4483	25
H10	6742	5890	4621	24
H11	6483	7406	3772	21
H12	5218	6745	2794	17
H13A	5584	2871	2232	17
H13B	3933	2305	2518	17
H17A	4745	1001	450	33
H17B	3929	2207	32	33
H17C	2829	1382	502	33
H14	2820(30)	1960(20)	1537(10)	12(5)
H16B	5790(30)	3950(20)	425(11)	24(6)
H16A	6110(30)	4250(20)	1175(11)	20(6)

Torsion angles [°] for π-Allyl Oxaruthenacycle complex derived from isoprene.

N1-C1-C2-C3	-1.7(3)
C1-C2-C3-C4	2.2(3)
C2-C3-C4-C5	0.1(3)
C3-C4-C5-N1	-3.0(3)
C3-C4-C5-C6	176.59(17)
N1-C5-C6-O1	31.7(2)
C4-C5-C6-O1	-147.92(18)
N1-C5-C6-C7	152.73(15)
C4-C5-C6-C7	-26.9(3)
N1-C5-C6-C13	-83.22(18)
C4-C5-C6-C13	97.1(2)
O1-C6-C7-C12	22.1(2)
C5-C6-C7-C12	-97.00(19)
C13-C6-C7-C12	140.57(17)
O1-C6-C7-C8	-157.97(16)
C5-C6-C7-C8	83.0(2)
C13-C6-C7-C8	-39.5(2)
C12-C7-C8-C9	0.8(3)
C6-C7-C8-C9	-179.13(18)
C7-C8-C9-C10	-0.7(3)
C8-C9-C10-C11	0.2(3)
C9-C10-C11-C12	0.3(3)
C10-C11-C12-C7	-0.2(3)
C8-C7-C12-C11	-0.4(3)
C6-C7-C12-C11	179.57(16)
O1-C6-C13-C14	-53.92(19)
C7-C6-C13-C14	-174.88(15)
C5-C6-C13-C14	61.61(19)
C6-C13-C14-C15	93.5(2)
C6-C13-C14-Ru1	17.61(17)
C13-C14-C15-C16	-40.4(3)
Ru1-C14-C15-C16	51.59(16)

C13-C14-C15-C17	150.04(19)
Ru1-C14-C15-C17	-117.96(17)
C13-C14-C15-Ru1	-92.00(19)
C14-C15-C16-Ru1	-52.88(16)
C17-C15-C16-Ru1	116.52(17)
C2-C1-N1-C5	-1.1(3)
C2-C1-N1-Ru1	174.79(14)
C4-C5-N1-C1	3.5(3)
C6-C5-N1-C1	-176.15(16)
C4-C5-N1-Ru1	-173.14(14)
C6-C5-N1-Ru1	7.20(17)
C7-C6-O1-Ru1	-176.35(11)
C5-C6-O1-Ru1	-55.00(14)
C13-C6-O1-Ru1	61.78(14)
C6-O1-Ru1-C19	52.1(11)
C6-O1-Ru1-C18	149.08(12)
C6-O1-Ru1-N1	46.36(11)
C6-O1-Ru1-C16	-109.01(12)
C6-O1-Ru1-C15	-73.97(11)
C6-O1-Ru1-C14	-40.90(11)
C1-N1-Ru1-C19	-25.08(18)
C5-N1-Ru1-C19	151.12(13)
C1-N1-Ru1-C18	68.85(18)
C5-N1-Ru1-C18	-114.95(13)
C1-N1-Ru1-O1	154.53(18)
C5-N1-Ru1-O1	-29.27(11)
C1-N1-Ru1-C16	-153.56(17)
C5-N1-Ru1-C16	22.6(2)
C1-N1-Ru1-C15	-115.70(17)
C5-N1-Ru1-C15	60.50(14)
C1-N1-Ru1-C14	-123.78(17)
C5-N1-Ru1-C14	52.42(12)
C15-C16-Ru1-C19	-68.57(13)
C15-C16-Ru1-C18	-162.35(12)

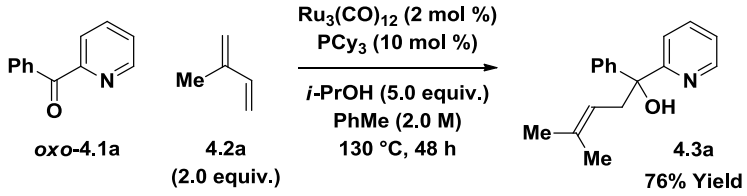
C15-C16-Ru1-O1	110.18(11)
C15-C16-Ru1-N1	59.99(18)
C15-C16-Ru1-C14	27.59(11)
C14-C15-Ru1-C19	-112.64(13)
C16-C15-Ru1-C19	113.05(13)
C17-C15-Ru1-C19	0.14(17)
C14-C15-Ru1-C18	159.97(12)
C16-C15-Ru1-C18	25.65(17)
C17-C15-Ru1-C18	-87.26(19)
C14-C15-Ru1-O1	64.27(11)
C16-C15-Ru1-O1	-70.05(12)
C17-C15-Ru1-O1	177.04(16)
C14-C15-Ru1-N1	-13.54(13)
C16-C15-Ru1-N1	-147.85(11)
C17-C15-Ru1-N1	99.24(16)
C14-C15-Ru1-C16	134.32(17)
C17-C15-Ru1-C16	-112.9(2)
C16-C15-Ru1-C14	-134.32(17)
C17-C15-Ru1-C14	112.8(2)
C15-C14-Ru1-C19	68.80(13)
C13-C14-Ru1-C19	-164.87(12)
C15-C14-Ru1-C18	-70.9(3)
C13-C14-Ru1-C18	55.4(3)
C15-C14-Ru1-O1	-115.06(11)
C13-C14-Ru1-O1	11.26(11)
C15-C14-Ru1-N1	168.39(12)
C13-C14-Ru1-N1	-65.29(12)
C15-C14-Ru1-C16	-28.05(11)
C13-C14-Ru1-C16	98.27(13)
C13-C14-Ru1-C15	126.32(17)

Symmetry transformations used to generate equivalent atoms:

X-ray Experimental for $(C_{17}H_{17}NO)Ru(CO)_2$ – 0.1 H_2O: Crystals grew as clusters of large colorless needless by slow evaporation from toluene. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.24 x 0.05 x 0.04 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71075Å). A total of 1344 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 45 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed above. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40. The structure was solved by direct methods using SIR97 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97. Structure analysis was aided by use of the programs PLATON98 and WinGX. Most of the hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on the allylic carbon atoms were observed in a ΔF map and refined with isotropic displacement parameters. A small peak, 1.3 $e^-/Å^3$, persisted in the final ΔF map. This peak was within H-bonding distance to two oxygen atoms, O1 and O2. As a result, it was assumed to represent a small amount of water that co-crystallized along with the complex. The site occupancy factor for this atom, O1W, was refined while fixing an isotropic displacement parameter to 0.05 yielded an approximate occupancy of close to 10%.

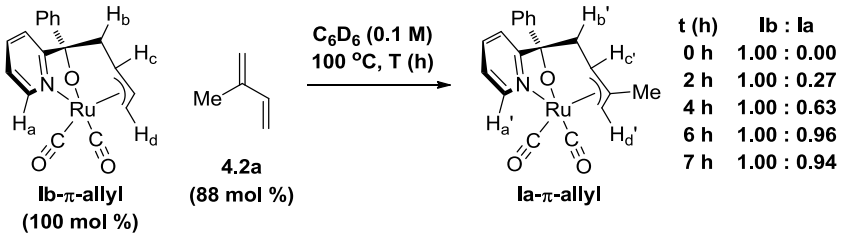
The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0343*P)^2 + (0.8933*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.0604, with R(F) equal to 0.0246 and a goodness of fit, S, = 1.00. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992). All figures were generated using SHELXTL/PC. Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Synthesis of 4.3a from Ketone Oxidation Level.



To a pressure tube equipped with magnetic stir bar was added benzoylpyridine (0.3 mmol, 1.0 equiv.), $Ru_3(CO)_{12}$ (3.9 mg, 0.006 mmol, 2 mol %) and PCy_3 (8.4 mg, 0.03 mmol, 10 mol %). The tube was sealed with a rubber septum and purged with argon. Toluene (0.15 mL, 2.0 M concentration with respect to benzoylpyridine), isopropanol (115 µL, 1.5 mmol, 5.0 equiv.), and isoprene (60 µL, 0.6 mmol, 2.0 equiv.) were added. The rubber septum was quickly replaced with a screw cap. The reaction was heated to 130 ^oC for 48 hours. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 2.5% EtOAc/hexanes) to furnish the title compound (57.9 mg, 90% yield) as a yellow oil.

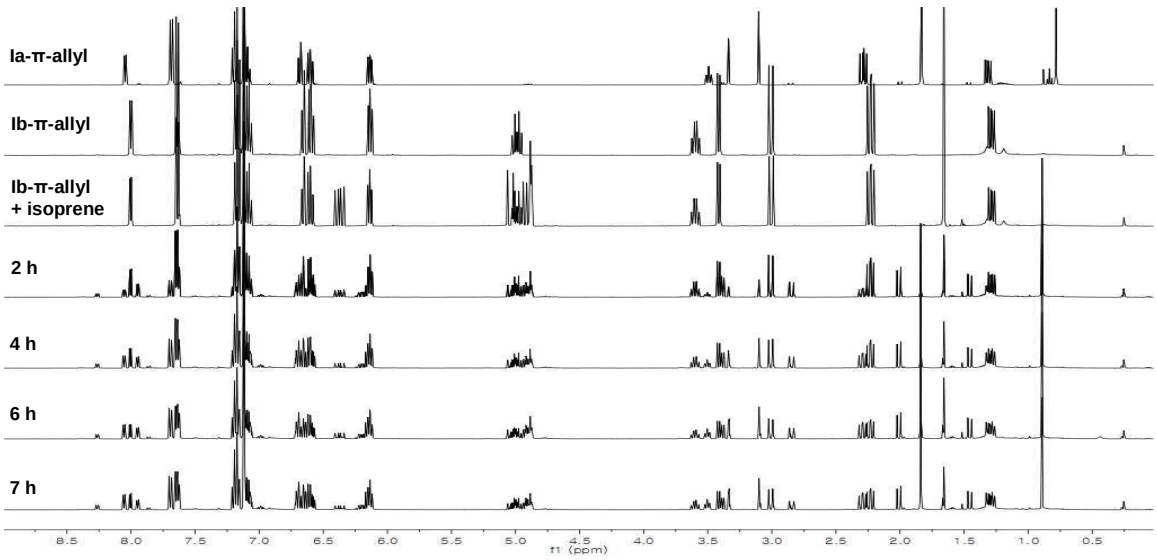
^{1}H NMR-Exchange Data.



Ib-π-allyl (100 mol %) | **4.2a (88 mol %)** | **Ia-π-allyl**

t (h)	Ib : Ia
0 h	1.00 : 0.00
2 h	1.00 : 0.27
4 h	1.00 : 0.63
6 h	1.00 : 0.96
7 h	1.00 : 0.94

To a pressure NMR tube was added **Ib**-π-allyl (0.060 mmol, 100 mol %). The tube was sealed with a rubber septum, purged with argon. At this stage, C_6D_6 (0.60 mL, 0.1 M concentration with respect to **Ib**-π-allyl), and isoprene (5.3 µL, 0.053 mmol, 88 mol %) were added. The rubber septum was quickly replaced with a screw cap. The reaction was heated to 100 ^{o}C and ^{1}H NMR were recorded every hour (at 25 ^{o}C).



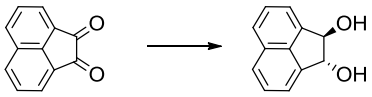
4.5.2 Experimental Details for Section 4.3

General Comments

All glassware was oven dried at 140 °C overnight and cooled under argon or nitrogen gas before use. All ruthenium catalyzed reactions were carried in sealed pressure tubes (13 x 100 mm). Toluene was dried by distillation from sodium and benzophenone immediately before use. $Ru_3(CO)_{12}$, and all ligands and additives were purchased from commercial suppliers and used as received.

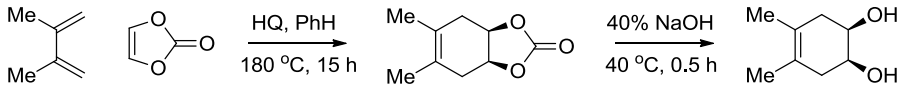
Butadiene **4.5a** was freshly condensed immediately before use. All other dienes (**4.5b-e**) were distilled immediately prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was accomplished with UV light followed by dipping in a *p*-anisaldehyde solution and heating. Purification of reaction products was carried out by flash column chromatography using 40-63 μm silica gel. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a Varian Gemini spectrometer in $CDCl_3$ solutions unless otherwise noted. ^{13}C NMR spectra were routinely run with broadband decoupling. Chemical shifts for ^1H and ^{13}C are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm and triplet at 77.0 ppm, respectively). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), etc. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z. Masses are reported for the molecular ion (M-H, M, M+H or M+Na) or suitable ion.

Synthesis of 1,2-dihydroacenaphene-1,2-diol (4.4a).



Diol **4.4a** was synthesized according to a literature procedure.[76] To a stirred suspension of acenaphthylene-1,2-dione (2.62 g, 14.4 mmol, 1.0 equiv.) in MeOH (44 mL, 0.33 M) at 0 °C, was added sodium borohydride (1.10 g, 28.8 mmol, 2.0 equiv.) in small portions. The reaction was stirred overnight. The solvent was evaporated *in vacuo*, and the crude oil was washed with water to afford the vicinal diol (1.10 g, 5.91 mmol) as a white solid in 41% yield. ^{1}H and ^{13}C NMR data were consistent with the literature report.[76]

Synthesis of (1R*,2R*)-4,5-Dimethylcyclohex-4-ene-1,2-diol (4.4b).

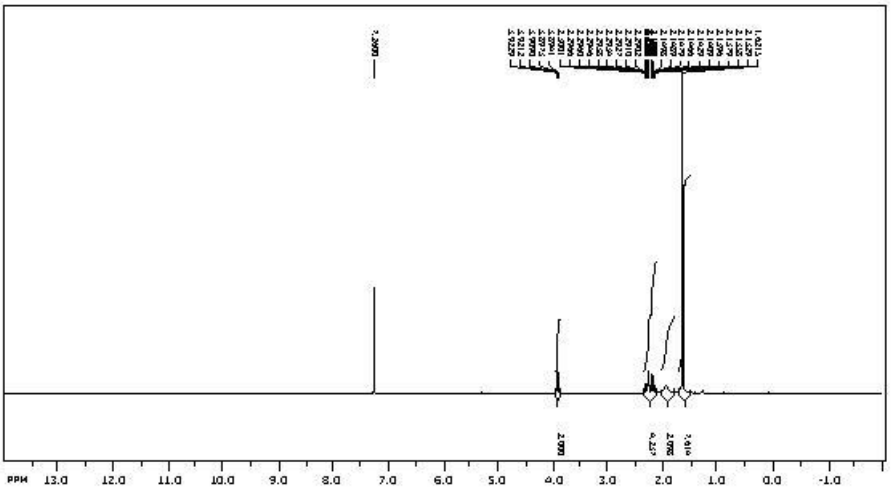


Diol **4.4b** was synthesized according to a literature procedure.[77] Vinylidene carbonate (4.29 g, 49.9 mmol, 3.8 equiv.) and freshly distilled 2,3-dimethylbutadiene (1.5 mL, 13.1 mmol, 1.0 equiv.) were combined with 10 mg hydroquinone and 1.25 mL benzene in a pressure tube. The tube was sealed under nitrogen and placed in a 180 °C oil bath. After 15 hours, the pressure tube was removed from the oil bath and allowed to cool to room temperature. The benzene was removed *in vacuo*, and the excess vinylidene carbonate was removed via Kugelrohr short path distillation to give (3a*R**,7a*S**)-5,6-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]-dioxol-2-one (4.55 g, 7.99 mmol) as an oil in 61% yield, which was used in the next step without further purification.

The oil was suspended in 40 mL of 40% aqueous NaOH, placed in an oil bath

at 40 ^{o}C and stirred for approximately 30 minutes. The reaction vessel was then removed from the oil bath and allowed to cool to room temperature. The reaction was acidified to pH 4 with 6M HCl. The aqueous mixture was extracted with three volumes of diethyl ether. The organic fractions were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude oil. The crude residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexane, 3:2) to provide the diol **4.4b** (2.36 g, 4.87 mmol) as a colorless solid in 61% yield. The melting point of the colorless solid was consistent with that reported in the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (m, 2H), 2.39 (m, 2H), 2.19 (m, 2H), 1.75 (s, 6H), 1.64 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 122.3, 69.3, 36.9, 18.7.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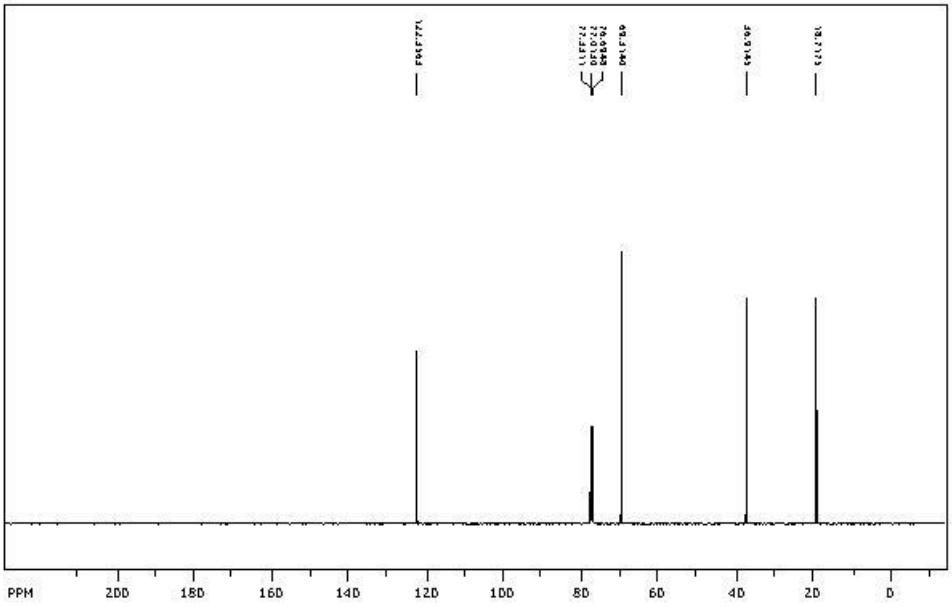
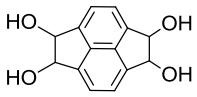
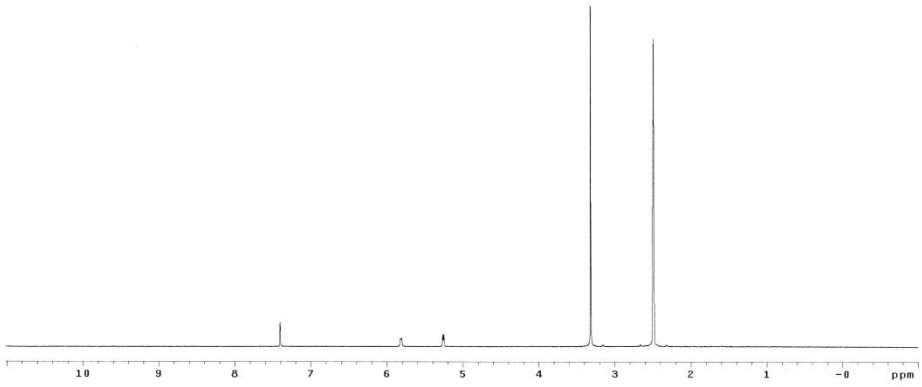

PPM 200 180 160 140 120 100 80 60 40 20 0

Synthesis of 1,2,5,6-tetrahydropenta[fg]acenaphthylene-1,2,5,6-tetraol (4.4c).



To a solution of 1,2,5,6-tetraketopyracene[64] (0.5 g, 2.1 mmol, 1.0 equiv.) in ethanol (40 mL, 0.05 M with respect to the tetraketopyracene) at 0 ^{o}C was added sodium triacetoxy borohydride (1.7 g, 8.4 mmol, 4.0 equiv.) in small portions. The mixture was allowed to warm to room temperature. After 4 hours, the reaction mixture was cooled to 0 ^{o}C, and water was added. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromato graphy (SiO_2: ethanol:dichloromethane, 1:4). The resulting solid was recry stallized from methanol to give the title compound **4.4c** (260 mg, 1.13 mmol) as a pale gray solid in 54% yield and 2:1 dr.

^{1}H NMR (400 MHz, d_6-DMSO): δ 7.40 (s, 4H), 5.82-5.80 (m, 4H), 5.26 (d, *J* = 5.6 Hz, 4H).
^{13}C NMR (100 MHz, d_6-DMSO): δ 140.8, 140.7, 121.7, 121.6, 84.9.
FTIR (neat): v. 3166, 2908, 1560, 1457, 1398, 1320, 1257, 1206, 1143, 1 078, 1001 cm^{-1}.
TLC Rf: 0.5 (isopropyl alcohol:dichloromethane, 2:3).
LRMS (Cl) Calculated for $C_{14}H_{12}NaO_4$ $[M+Na]^+$: 267.1; Found: 267.1.
MP: 244.9-245.6 ^{o}C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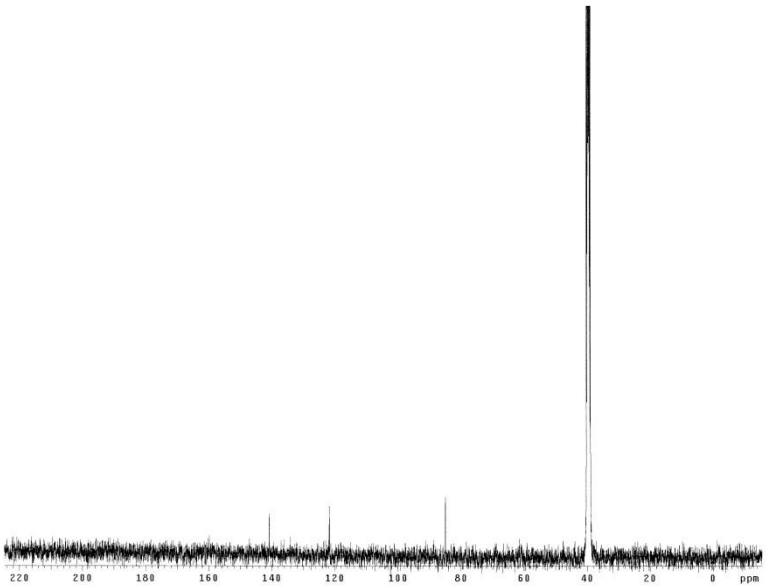
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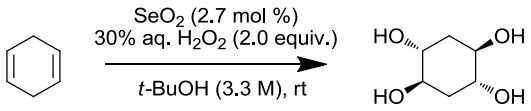
ppm

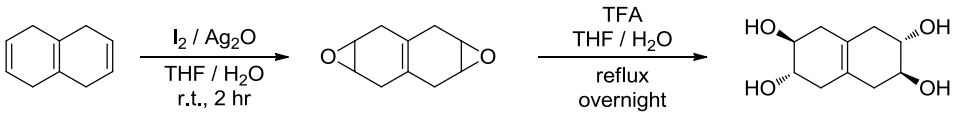
Synthesis of (1R*,2R*,4R*,5R*)-Cyclohexane-1,2,4,5-tetraol (4.4d).



Tetraol **4.4d** was prepared according to a published procedure.[65] To a stirred solution of selenium dioxide (5.6 mg, 0.63 mmol) in tert-butyl alcohol (7.5 mL) was added 1,4- cyclohexadiene (2.00 g, 25 mmol). To the resulting mixture 30% H_2O_2 (5.60 g, 50 mmol) was added dropwise over 20 minutes at room temperature. The mixture was stirred for 24 hours at room temperature. $NaHSO_3$ (500 mg) was added to reduce the possibly of unreacted H_2O_2. The solid precipitate was filtered and washed with ethanol. The filtrates were combined and concentrated *in vacuo* to give a viscous oil. The residue was taken up in hot ethanol (50 mL), the mixture was filtered and the ethanol was removed by rotary evaporatation under reduced pressure to give tetrol **4.4d**. Tetraol **4.4d** was further purified by recrystallizing from ethanol to give a colourless solid (1.89 g, 13.5 mmol) in 54% yield. ^{1}H and ^{13}C spectral data were consistent with published values.[65]

^{1}H NMR (400 MHz, D_2O): δ 3.76 (m, 4H), 1.84 (m, 4H).
^{13}C NMR (100 MHz, D_2O): δ 74.4, 38.3.

Synthesis of 1,2,3,4,5,6,7,8-Octahydronaphthalene-2,3,6,7-tetraol (4.4e).



1,4,5,8-tetrahydronaphthalene was prepared according to a published procedure.[79]

1a,2,3,3a,4a,5,6,6a-octahydronaphtho[2,3-b:6,7-b']bis(oxirene)

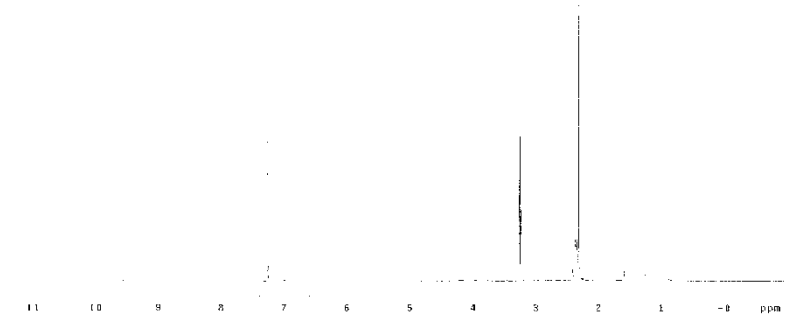
To a stirred solution of 1,4,5,8-tetrahydronaphthalene (1.0 g, 7.6 mmol, 1.0 equiv.) in tetrahydrofuran:water (9:1, 253 ml, 0.03 M with respect to the naphthalene) were added iodine (3.8 g, 15.2 mmol, 2.0 equiv.) and Ag_2O (3.5 g, 15.2 mmol, 2.0 equiv.), and stirring was continued till the mixture completely decolorized (2 hours). Precipitated silver iodide was removed by filtration, and the filtrate was diluted with dichloromethane (2 -fold volume) and dried ($MgSO_4$). The organic extracts were filtered and concentrated *in vacuo* to give a solid residue. The crude residue was subjected to flash column chromatography (SiO2: ethyl acetate:dichloromethane, 1:4) to give octahydronaphtho[2,3-b:6,7-b']bisoxir ene (1.03 g, dr = 1.3:1) as a white solid product in 83%yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (d, *J* = 6.8 Hz, 4H), 2.41-2.93 (m, 8H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 117.62, 117.58, 51.3, 50.9, 30.0, 29.9.
FTIR (neat): v. 3392, 3001, 2876, 2361, 1736, 1437, 1340, 1237, 1025, 1001, 805 cm^{-1}.
TLC Rf: 0.6 (ethyl acetate:dichloromethane, 1:4).
LRMS (Cl) Calculated for $C_{10}H_{12}NaO_2$ $[M+Na]^+$:187.1; Found:187.1
MP: 84.7-85.1 ^{o}C

1,2,3,4,5,6,7,8-octahydronaphthalene-2,3,6,7-tetraol (4.4e).

Octahydronaphtho[2,3-b:6,7-b']bisoxirene (0.88 g, 5.4 mmol, 1.0 equiv.) and trifluoroacetic acid (0.17 mL, 2.16 mmol, 40 mol %) were combined in tetrahydrofuran:water (1:1, 72 ml, 0.075 M with respect to the oxirene) and refluxed overnight. After cooling the mixture to room temperature, the solvents were concentrated *in vacuo* and the crude solid product was recrystallized from methanol and hexane to give 1,2,3,4,5,6,7,8-octahydronaphthalene-2,3,6,7-tetraol **4.4e** (0.82 g,4.10 mmol) as white solid product in 76% yield and 1.3:1 dr.

^{1}H NMR (400 MHz, d_6-DMSO): δ 4.58-4.55 (m, 4H), 3.41 (s, 2H), 3.36 (s, 2H), 2.08-2.03 (m, 4H), 1.78-1.74 (s, 4H).
^{13}C NMR (100 MHz, d_6-DMSO): δ 125.5, 70.5, 69.9, 37.4, 37.0.
FTIR (neat): v. 3280, 2903, 2837, 1443, 1375, 1117, 1050, 1020 cm^{-1}.
TLC Rf: 0.7 (ethanol: dichloromethane, 1:1).
LRMS (Cl) Calculated for $C_{10}H_{16}NaO_4$ $[M+Na]^+$: 223.1; Found: 223.1.
MP: 251.2-251.7 ^{o}C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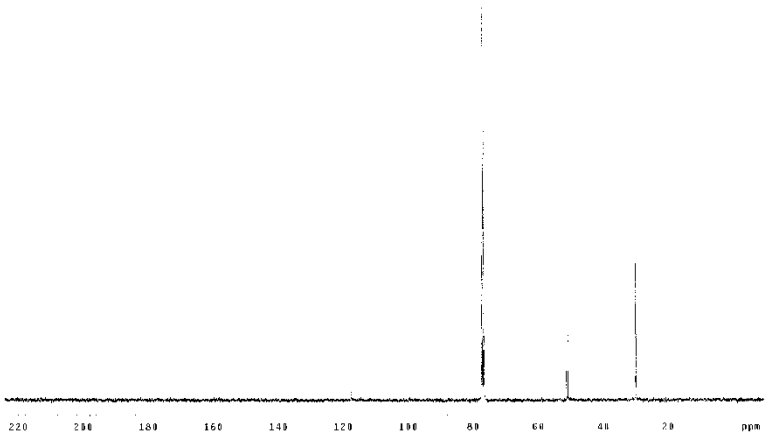
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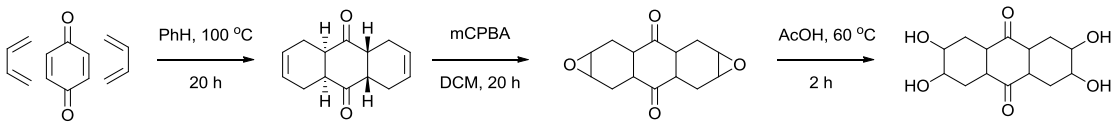
Synthesis of 2,3,6,7-Tetrahydroxydodecahydroanthracene-9,10-dione (4.4f).



Dienedione was synthesized according to a reported procedure.[66] Benzoquinone (2.86 g, 26.5 mmol) was taken up in benzene (5.5 mL, 5.9 M with respect to benzoquinone) in a sealed tube fitted with a septum. Butadiene (6.0 mL, 68.8 mmol, 2.6 equiv.) was added, and the septum was replaced with a screw cap. The reaction was placed in a preheated 100 ^{o}C oil bath. After 24 hours, the sealed tube was removed from the oil bath and allowed to cool to room temperature. The product that precipitated out was collected as a solid, furnishing the dienedione (2.91 g, 13.3 mmol) in 50% yield. The melting point and ^{1}H NMR were consistent with literature reports.[66]

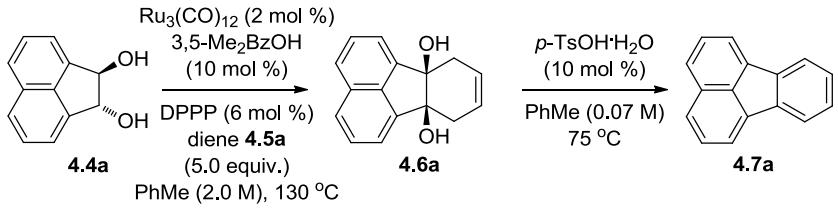
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.67 (m, 4H), 3.05 (m, 4H), 2.48 (m, 4H), 2.21 (m, 4H).
MP: 154-155 ^{o}C.

The bisepoxide was synthesized according to a reported procedure.[67] The diene (2.00 g, 9.25 mmol, 1.0 equiv.) was dissolved in dichloromethane (105 mL, 0.9 M with respect to the diene) and cooled to 0 ^{o}C. Separately, mCPBA (5.02 g, 20.3 mmol, 2.2 equiv.) was dissolved in dichloromethane (50 mL, 0.185 M with respect to diene) and added drop wise to the chilled solution of diene. The reaction was allowed to gradually warm to room temperature and stirred overnight. After approximately 15 hours, the reaction was quenched with half saturated $NaHCO_3$. The layers were separated, and the aqueous layer was washed three times with additional dichloromethane. The organic

layers were combined and washed sequentially with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($NaSO_4$), filtered and concentrated *in vacuo*. The crude reaction mixture was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4 to 2:3) to give the desired epoxides (1.40 g, 5.64 mmol) in 61% yield and a mixture of approximately 5 different isomers in an undetermined ratio, and were used as is. The compound [9,9'-bianthracene]-10,10'-diol was also isolated as a byproduct of this reaction.

The mixture of epoxides was opened to tetraols via heating in acetic acid. The epoxide mixture (0.528 g, 2.12 mmol) was taken up in glacial acetic acid (50 mL, 0.04 M with respect to the epoxide) and placed in a preheated 60 ^{o}C oil bath. After approximately 3 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The acetic acid was removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: methanol:dichloromethane, 1:4) to provide a mixture of tetraols.

Synthesis of Fluoranthene (4.7a).



6b,7,10,10a-tetrahydrofluoranthene-6b,10a-diol (4.6a)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %), 3,5-dimethylbenzoic acid (4.5 mg, 0.03 mmol, 10 mol %) and acenaphthenediol **4.4a** (55.8 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon and toluene (0.15 mL, 2.0 M with respect to **4.4a**) was added via syringe, followed by freshly condensed butadiene **4.5a** (0.127 mL, 1.5 mmol, 5.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^oC oil bath. After 24 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:1) to provide the cycloadduct **4.6a** (58.5 mg, 0.25 mmol)as a white solid in 82% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 7.68 (dd, *J* = 0.8, 7.8 Hz, 2H), 7.54 (dd, *J* = 6.8, 7.8 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 2H), 5.61 (ddd, *J* = 1.6, 4.0 Hz, 2H), 4.86 (residual H_2O), 2.87 (ddd, *J* = 2.0, 4.0, 16.0 Hz, 2H), 2.72 (dd, *J* = 2.0, 13.6 Hz, 2H).

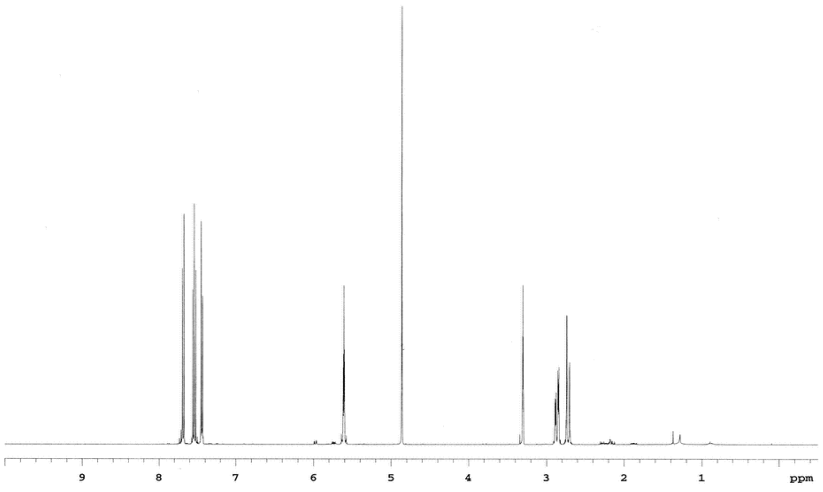
^{13}C NMR (100 MHz, CD_3OD): δ 149.9, 137.2, 128.0, 127.7, 123.8, 118.5, 81.9, 36.9.

FTIR (neat): v 3315, 3045, 2940, 1497, 1413, 1375, 1307, 1244, 1203, 1123, 1096, 1054, 993, 835, 787, 773 cm^{-1}.

TLC Rf: 0.46 (ethyl acetate:hexanes, 1:1).

LRMS (CI) Calculated for $C_{16}H_{14}NaO_2$ $[M+Na]^+$: 289; Found: 289.

MP: 181-183 °C.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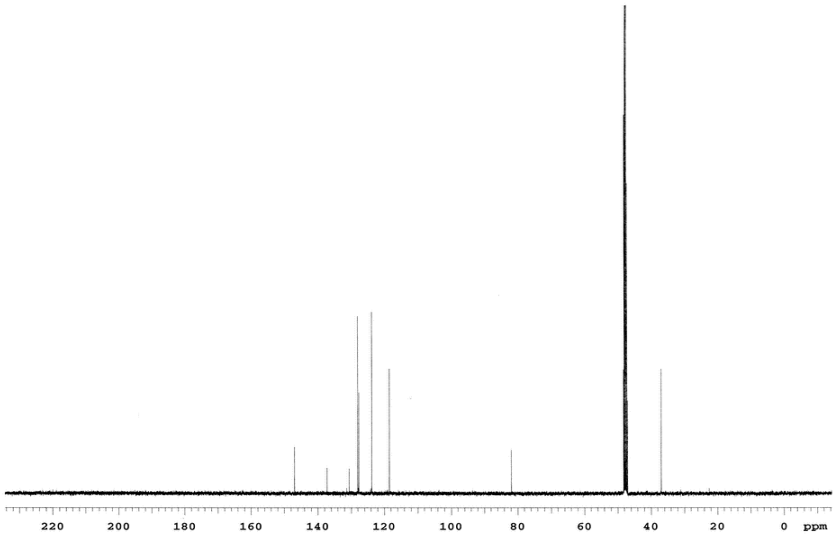
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Fluoranthene (4.7a)

To a round bottomed flask was added cycloadduct **4.6a** (23.8 mg, 0.1 mmol, 1.0 equiv.) followed by *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol, 10 mol %). Toluene was added (1.4 mL, 0.07 M with respect to **4.6a**). The round bottomed flask was fitted with a reflux condenser, and the reaction vessel was placed in a 75 ^{o}C oil bath. When judged complete by TLC (6.5 hours), the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The toluene was removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: hexanes) to provide fluoranthene **4.7a** (18.2 mg, 0.09 mmol) as a white solid in 90% yield. The NMR spectra were consistent with a literature report.[79]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.6 Hz, 2H), 7.93 (ddd, *J* = 1.0, 4.0, 6.6 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 1.0, 8.4 Hz, 2H), 7.40 (ddd, *J* = 1.0, 4.0, 6.6 Hz, 2H).

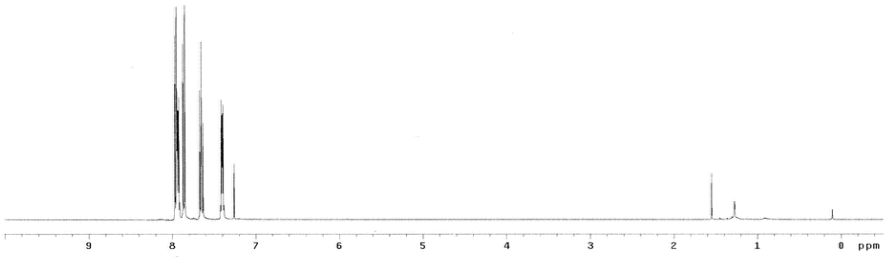
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 136.9, 132.4, 130.0, 127.9, 127.5, 126.6, 121.5, 120.0.

FTIR (neat): v 3051, 2922, 1452, 1439, 1420, 1184, 1159, 1151, 1016, 970, 912, 772, 746 cm^{-1}.

TLC Rf: 0.57 (ethyl acetate:hexanes, 1:19).

HRMS (CI) Calculated for $C_{16}H_{10}$ $[M]^{+}$: 202.0783; Found: 202.0776.

MP: 111-112 °C.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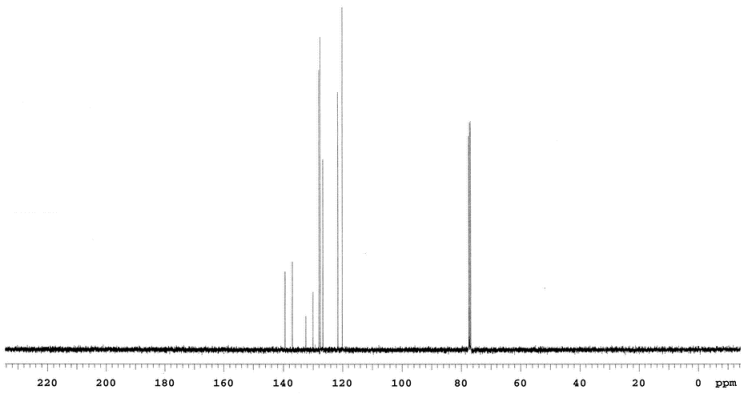
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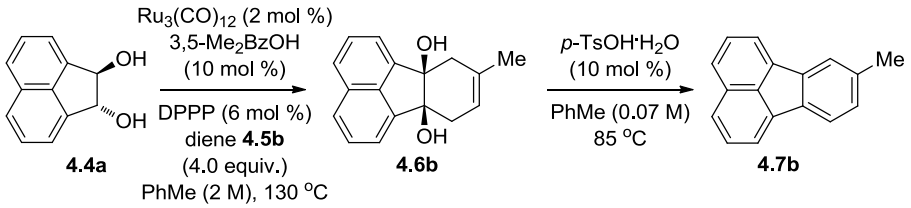
Synthesis of 8-Methylfluoranthene (4.7b).



8-Methyl-6b,7,10,10a-tetrahydrofluoranthene-6b,10a-diol (4.6b)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %), 3,5-dimethyl-benzoic acid (4.5 mg, 0.03 mmol, 10 mol %) and acenaphthenediol **4.4a** (55.9 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 2.0 M with respect to **4.4a**) was added via syringe, followed by freshly distilled isoprene **4.5b** (0.12 mL, 1.2 mmol, 4.0 equiv.). The septum was replaced with a screw cap and the reaction was placed in a 130 ^oC oil bath. After 24 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to provide the cycloadduct **4.6b** (61.3 mg, 0.24 mmol) as a colourless solid in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.58-7.54 (m, 2H), 7.47 (d, *J* = 6.8 Hz, 2H), 5.38-5.35 (m, 1H), 3.10-3.06 (d, *J* = 15.2 Hz, 2H), 2.79-2.64 (m, 4H), 1.58 (d, *J* = 0.8 Hz, 3H).

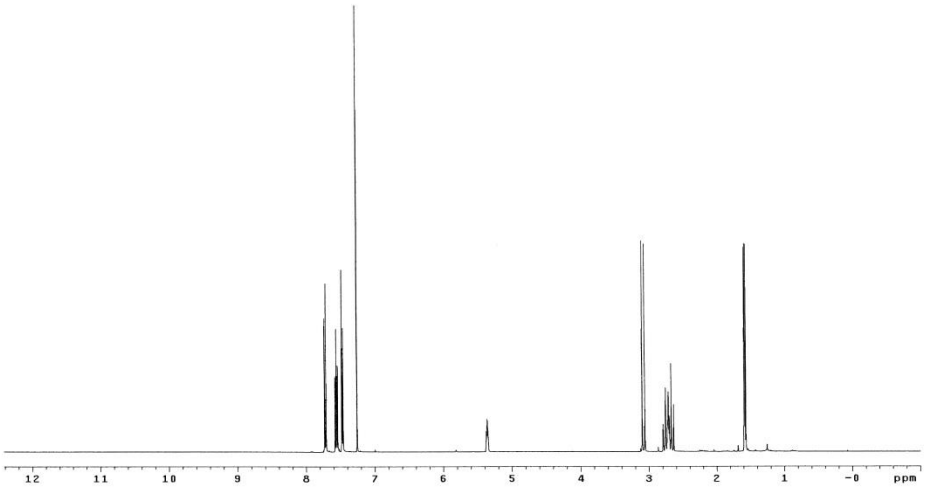
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 145.7, 126.9, 130.7, 128.6, 124.7, 119.9, 118.9, 118.8, 82.6, 82.5, 77.2, 42.0, 37.7, 23.3.

FTIR (neat): v 3318, 3033, 2936, 2850, 2361, 1443, 1405, 1179, 1121, 1071, 834 cm^{-1}.

TLC Rf: 0.7 (ethyl acetate:hexanes 1:4).

LRMS (Cl) Calculated for $C_{17}H_{15}O$ $[M\text{-}OH]^+$: 235; Found: 235.

MP: 172.6-173.4 ^oC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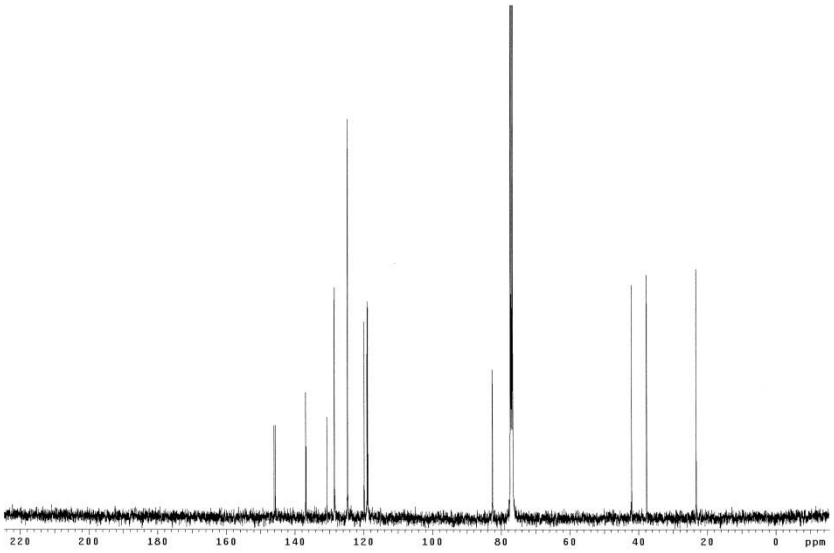
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8-Methylfluoranthene (4.7b)

To a round bottomed flask was added cycloadduct **4.6b** (25.2 mg, 0.1 mmol, 1.0 equiv.) followed by *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol, 10 mol %). Toluene was added (1.4 mL, 0.07 M with respect to **4.6b**). The round bottomed flask was fitted with a reflux condenser, and the reaction vessel was placed in an 85 ^{o}C oil bath. When judged complete by TLC (2 hours), the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The toluene was removed *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes) to provide 8-methylfluoranthene **4.7b** (19.9 mg, 0.092 mmol) as a colourless oil in 92% yield.

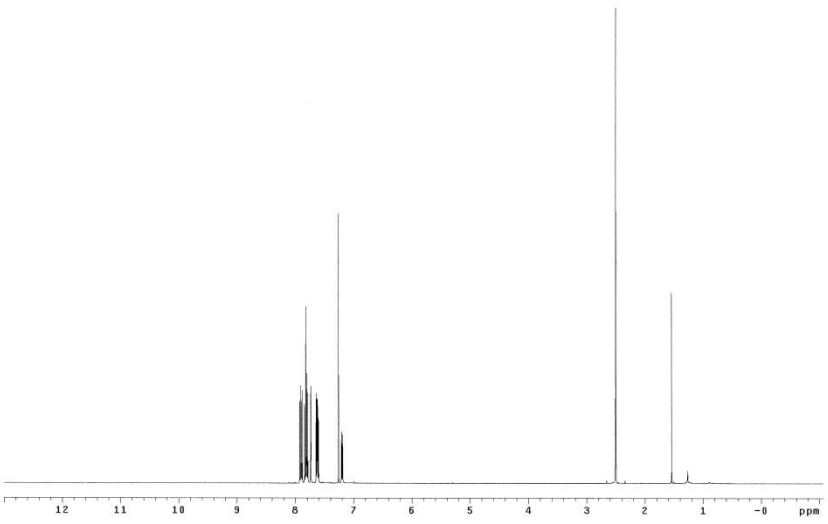
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.88 (m, 2H), 7.84-7.79 (m, 3H), 7.74-7.73 (m, 1H), 7.65-7.60 (m, 2H), 7.21-7.19 (m, 1H), 2.50 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 137.5, 137.1, 136.9, 132.6, 129.9, 128.3, 127.9, 127.8, 126.5, 126.1, 122.3, 121.2, 119.8, 119.5, 77.2, 21.8.

FTIR (neat): v 3039, 2920, 2362, 2342, 1736, 1455, 1427, 1179, 886, 808, 770 cm^{-1}.

TLC Rf: 0.6 (hexanes).

HRMS (Cl) Calculated for $C_{17}H_{12}$: 216.0939; Found: $[M]^{+}$: 216.0934.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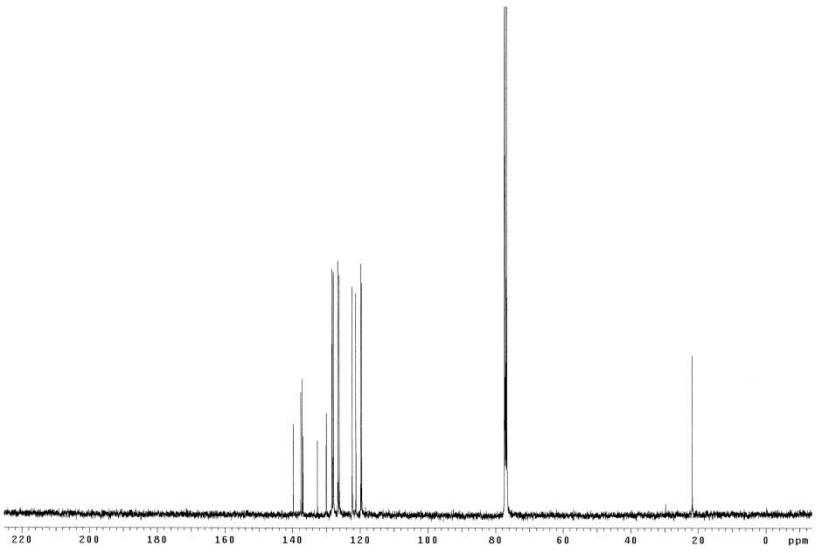
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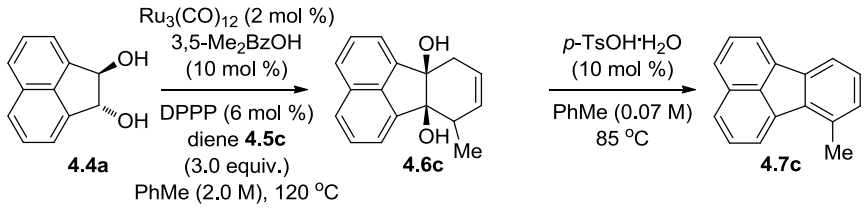
ppm

Synthesis of7-Methylfluoranthene (4.7c).



7-Methyl-6b,7,10,10a-tetrahydrofluoranthene-6b,10a-diol (4.6c)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %), 3,5-dimethylbenzoic acid (4.5 mg, 0.03 mmol, 10 mol %) and acenaphthenediol **4.4a** (55.9 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 2.0 M with respect to **4.4a**) was added via syringe, followed by freshly distilled 1,3-pentadiene **4.5c** (0.09 mL, 0.9 mmol, .3.0 equiv.). The septum was replaced with a screw cap and the reaction was placed in a 120 ^oC oil bath. After 24 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to provide the cycloadduct **4.6c** (62 mg, 0.25 mmol) as white solid in 82% yield and 1.3:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.72 (m, 4H), 7.60-7.45 (m, 8H), 6.23 (dd, *J* = 10.0, 0.8 Hz, 1H), 6.03-5.98 (m, 1H), 5.83-5.79 (m, 1H), 5.35-5.31 (m, 1H), 3.32 (s, 1H), 3.11 (s, 1H), 3.10-3.05 (m, 1H), 2.88 (s, 1H), 2.57-2.50 (m, 3H), 2.34-2.26 (m, 1H), 2.04-1.89 (m, 2H), 1.54 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H).

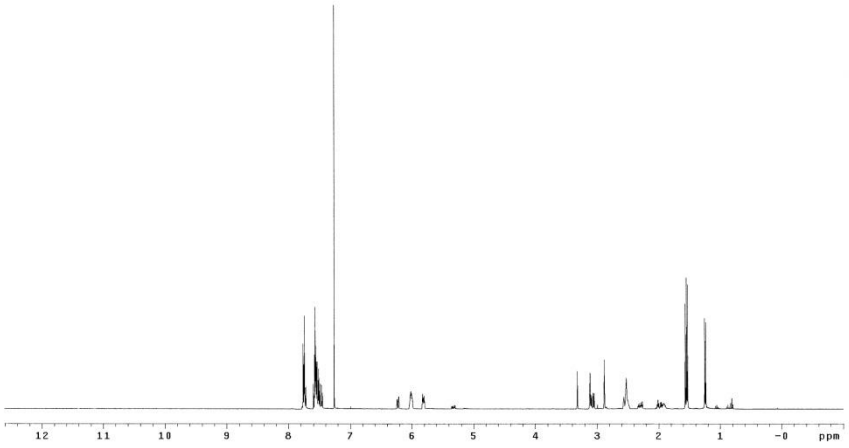
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 145.1, 145.0, 144.4, 135.8, 134.9, 131.5, 131.1, 130.2, 128.5, 128.3, 128.2, 128.0, 127.5, 126.9, 125.2, 124.9, 124.8, 124.5, 121.1, 120.4, 119.4, 119.1, 85.1, 83.5, 83.2, 79.9, 39.4, 37.3, 36.7, 29.9, 14.5, 13.7.

FTIR (neat): v 3330, 3039, 2975, 2940, 2883, 1499, 1426, 1367, 1297, 1217, 1002 cm^{-1}.

TLC Rf: 0.7 (4:1 hexanes:ethyl acetate).

LRMS (Cl) Calculated for $C_{17}H_{15}O$ $[M\text{-}OH]^+$: 235; Found: 235.

MP: 135.8-136.5 ^oC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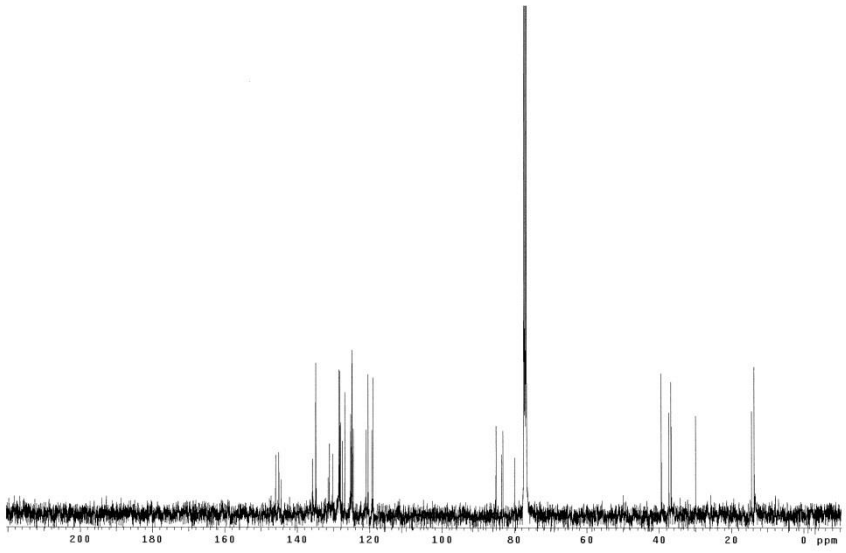
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0 ppm

7-Methylfluoranthene (4.7c)

To a round bottomed flask was added cycloadduct **4.6c** (25.2 mg, 0.1 mmol, 1.0 equiv.) followed by *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol, 10 mol %). Toluene was added (1.4 mL, 0.07 M with respect to **4.6c**). The round bottomed flask was fitted with a reflux condenser, and the reaction vessel was placed in an 85 ^{o}C oil bath. When judged complete by TLC (2 hours), the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The toluene was removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: hexanes) to provide 7-methylfluoranthene **4.7c** (19.3 mg, 0.09 mmol) as a colourless oil in 90% yield. The NMR spectra were consistent with that of a literature report.[80]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.95 (m, 2H), 7.87-7.84 (m, 2H), 7.80 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.68-7.63 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.20-7.18 (m, 1H), 2.78 (s, 3H).

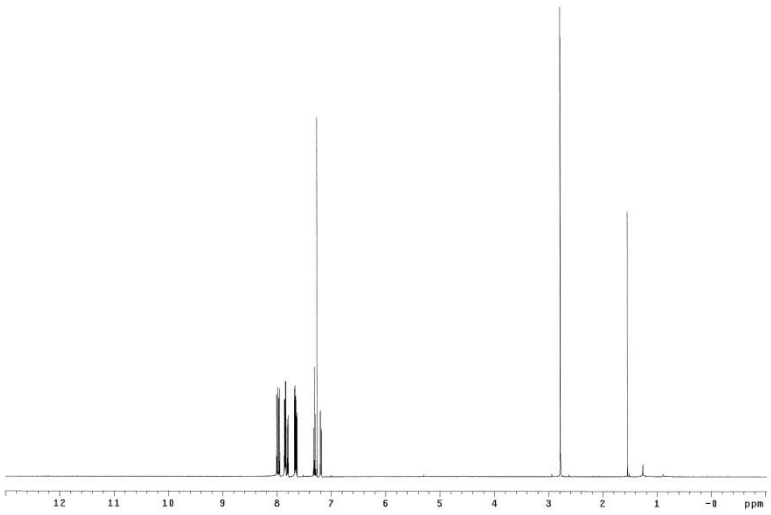
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 137.8, 137.3, 136.9, 134.3, 132.4, 129.8, 128.0, 127.8, 127.3, 126.6, 126.2, 123.0, 119.9, 119.1, 77.2, 20.5.

FTIR (neat): v 3048, 2920, 2851, 2360, 1920, 1586, 1443, 1424, 1185, 823, 770 cm^{-1}.

TLC Rf: 0.5 (hexanes).

HRMS (Cl) Calculated for $C_{17}H_{12}$: 216.0939; Found: $[M]^{+}$: 216.0933.

MP: 130.0-130.4 ^{o}C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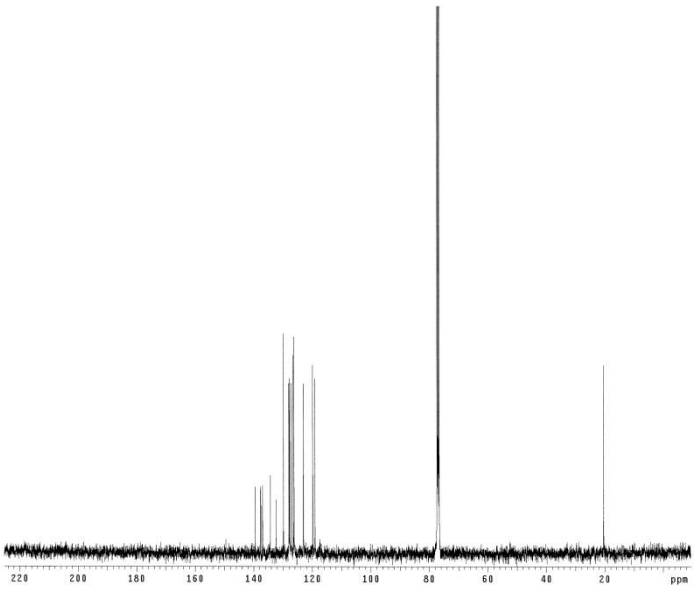
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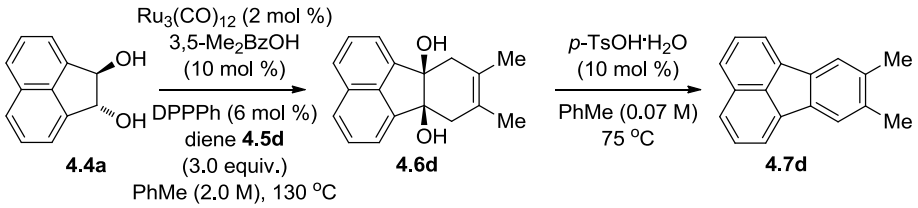
ppm

Synthesis of 8,9-Dimethylfluoranthene (4.7d).



8,9-Dimethyl-6b,7,10,10a-tetrahydrofluoranthene-6b,10a-diol (4.6d) .

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPPh (8.0 mg, 0.018 mmol, 6 mol %) and acenaphthenediol **4.4a** (55.8 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon and toluene (0.15 mL, 2.0 M with respect to **4.4a**) was added via syringe, followed by freshly distilled dimethylbutadiene **4.5d** (0.102 mL, 0.9 mmol, 3.0 equiv.). The septum was replaced with a screw cap and the reaction was placed in a 130 ^{o}C oil bath. After 48 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate: hexanes, 1:1) to provide the cycloadduct **4.6d** (66.2 mg, 0.24 mmol) as a white solid in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 6.6, 8.2 Hz, 2H), 7.47 (d, *J* = 6.6 Hz, 2H), 3.03 (s, 2H), 2.76 (d, *J* = 13.6 Hz, 2H), 2.60 (d, *J* = 13.6 Hz, 2H), 1.50 (s, 6H).

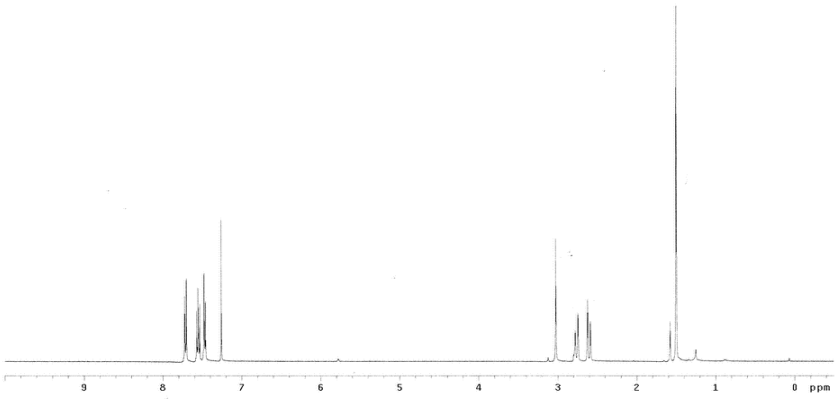
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 136.8, 130.6, 128.5, 126.6, 124.6, 118.8, 82.7, 43.9, 19.2.

FTIR (neat): v 3329, 2928, 1437, 1407, 1105, 1063, 994, 835, 796, 777, 762, 707 cm^{-1}.

TLC Rf: 0.46 (ethyl acetate:hexanes, 1:1).

LRMS (CI) Calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$: 289; Found: 289.

MP: 211-214 °C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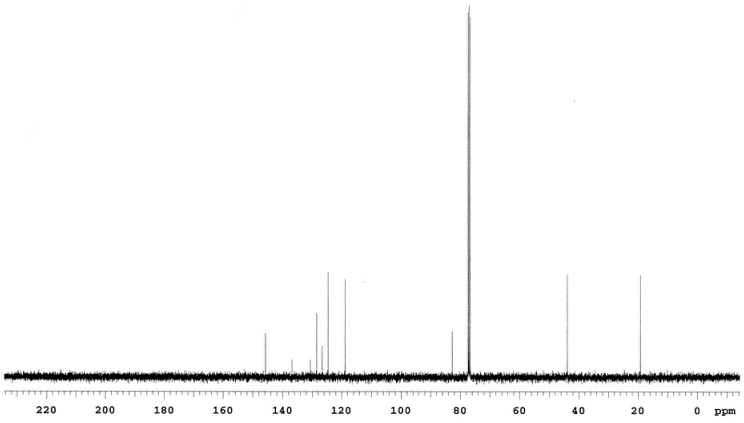
220
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0 ppm

8,9-Dimethylfluoranthene (4.7d)

To a round bottomed flask was added cycloadduct **4.6d** (26.6 mg, 0.1 mmol, 1.0 equiv.) followed by *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol, 10 mol %). Toluene was added (1.4 mL, 0.07 M with respect to **4.6d**). The round bottomed flask was fitted with a reflux condenser, and the reaction vessel was placed in a 75 ^{o}C oil bath. When judged complete by TLC (6.5 hours), the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The toluene was removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: hexanes) to provide 8,9-dimethylfluoranthene **4.7d** (21.9 mg, 0.095 mmol) as a yellow solid in 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 6.8 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.69 (s, 2H), 7.61 (dd, *J* = 6.8, 7.8 Hz, 2H), 2.40 (s, 6H).

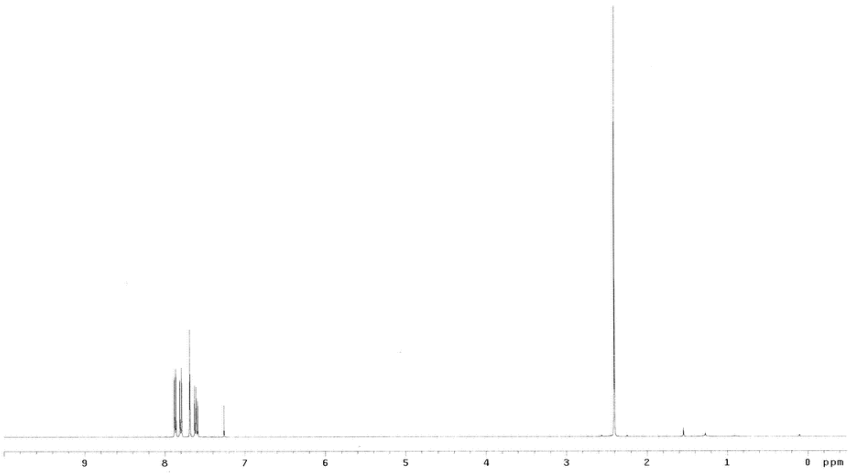
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 137.3, 132.6, 129.9, 127.9, 126.1, 122.8, 119.4, 20.3.

FTIR (neat): v 3040, 3005, 2964, 2917, 1612, 1464, 1446, 1411, 1086, 1017, 997, 875, 817, 771 cm^{-1}.

TLC Rf: 0.57 (ethyl acetate:hexanes, 1:19).

HRMS (CI) Calculated for $C_{18}H_{14}$ $[M]^{+}$: 230.1096; Found: 230.1091.

MP: 146-112 °C.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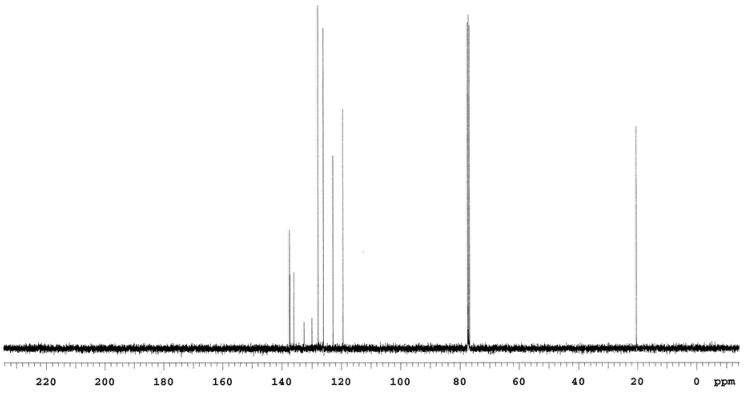
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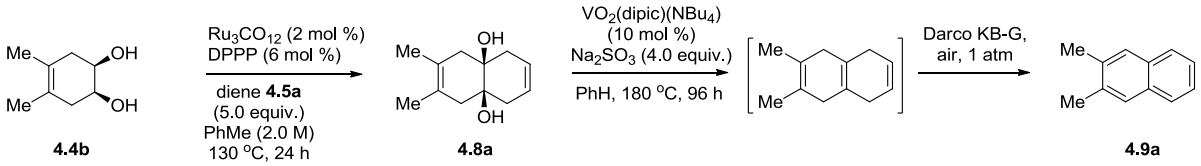
Synthesis of 2,3-Dimethylnaphthalene (4.9a)



2,3-Dimethyl-1,4,4a,5,8,8a-hexahydronaphthalene-4a,8a-diol (4.8a)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (7.6 mg, 0.012 mmol, 2 mol %), DPPP (14.8 mg, 0.036 mmol, 6 mol %) and dimethylcyclohexenediol **4.4b** (85.3 mg, 0.6 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.30 mL, 2.0 M with respect to **4.4b**) was added via syringe, followed by freshly condensed butadiene **4.5a** (0.26 mL, 3.0 mmol, 5.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 24 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 2:3) to provide the cycloadduct **4.8a** (103.5 mgn 0.28 mmol) as a colourless crystalline solid in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.55 (m, 2H), 2.29-2.16 (m, 8H), 1.61 (s, 6H), 1.59-1.54 (br s, 2H).

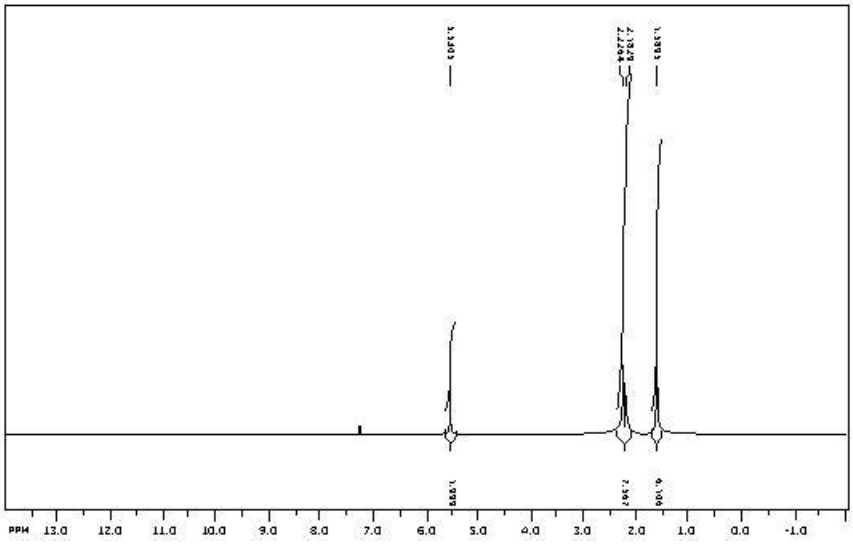
^{13}C NMR (100 MHz, $CDCl_3$): δ 124.2, 122.6, 72.1, 42.7, 36.3, 18.6.

FTIR (neat): v 3319, 2902, 1432, 1007, 895, 663 cm^{-1}.

TLC Rf: 0.27 (3:2 hexanes:ethyl acetate).

LRMS (Cl) Calculated for $C_{12}H_{18}NaO_2$ $[M+Na]^+$: 217.1; Found: 217.1.

MP: 91-93 ^{o}C.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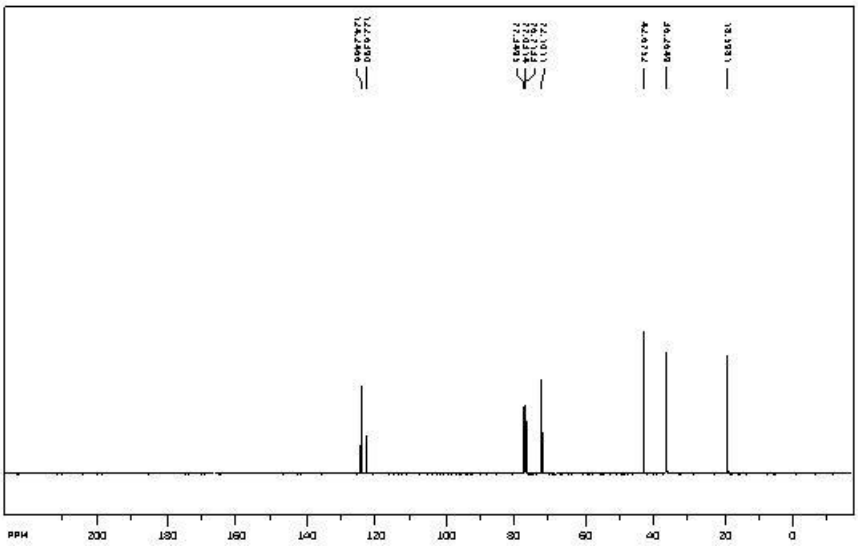

PPM 200 180 160 140 120 100 80 60 40 20 0

2,3-Dimethylnaphthalene (4.9a)

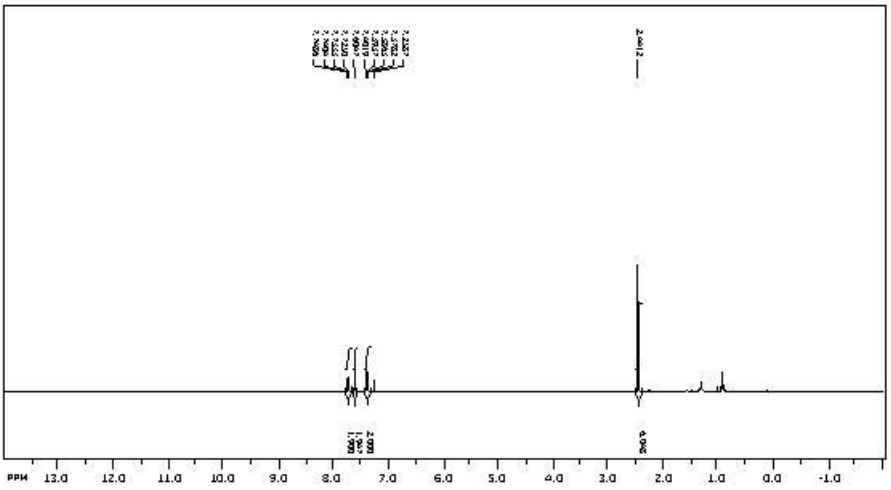
To a dry pressure tube sealed with a septum was added diol **4.8a** (20.0 mg, 0.1 mmol), $VO_2(dipic)(NBu_4)$ (4.9 mg, 0.01 mmol, 10 mol %) and Na_2SO_3 (50.4 mg, 0.4 mmol, 4.0 equiv.). Benzene (0.5 mL, 0.2 M with respect to **4.8a**) was added, and the septum was replaced with a screw cap, and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed and the crude reaction mixture was filtered through a short pad of silica and the product was eluted with hexanes to give the tetrahydronaphthalene (14.2 mg, 0.091 mmol) in 91% yield as a mixture of isomers. The isolated material was taken up in benzene (0.5 mL) and Darco KB-G (15 mg) was added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^oC oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: 100% hexanes) to provide naphthalene **4.9a** (13.8 mg, 0.089 mmol) as a colourless solid in 98% yield. The ^1H and ^{13}C spectral data were consistent with that previously reported.[81]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, 2H, J^1 = 3.4 Hz, J^2 = 6.1 Hz), 7.61 (s, 2H), 7.39 (dd, 2H, J^1 = 3.4 Hz, J^2 = 6.1 Hz), 2.43 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 132.4, 127.3, 126.8, 125.0, 20.2.

TLC Rf: 0.70 (ethyl acetate:hexanes, 2:3).

HRMS (Cl) Calculated for $C_{12}H_{12}$: 156.0939; Found: $[M]^+$: 156.0936.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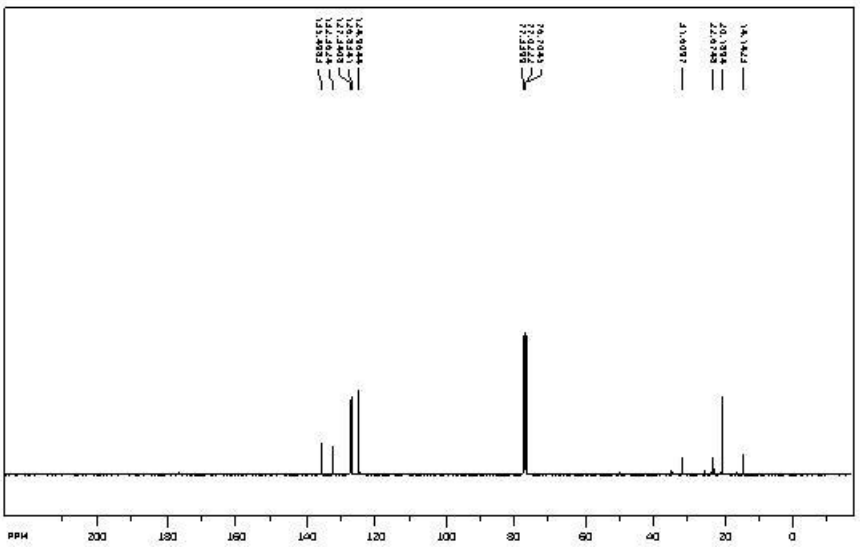
PPM
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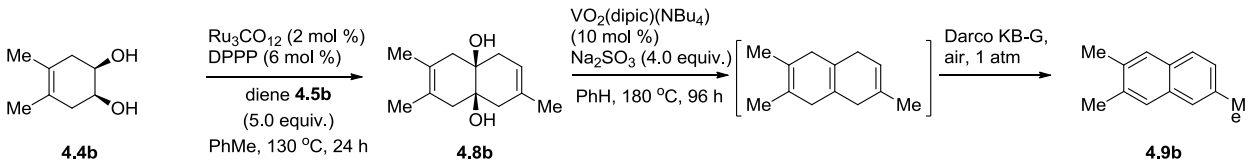
140
120
100
80
60
40
20
0

Synthesis of 2,3,6-Trimethylnaphthalene (4.9b).



2,3,6-Trimethyl-1,4,4a,5,8,8a-hexahydronaphthalene-4a,8a-diol (4.8b)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %) and dimethylcyclohexenediol **4.4b** (42.7 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon and toluene (0.15 mL, 2.0 M with respect to **4.4b**) was added via syringe, followed by freshly distilled isoprene **4.5b** (0.15 mL, 1.5 mmol, 5.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 24 hours, the reaction vessel was removed from the oil bath and was allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexane, 2:3) to provide the cycloadduct **4.8b** (61.3 mg, 0.29 mmol) as a colourless crystalline solid in 98% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (m, 1H), 2.26-2.05 (m, 10H), 1.65 (s, 3H), 1.59 (s, 6H).

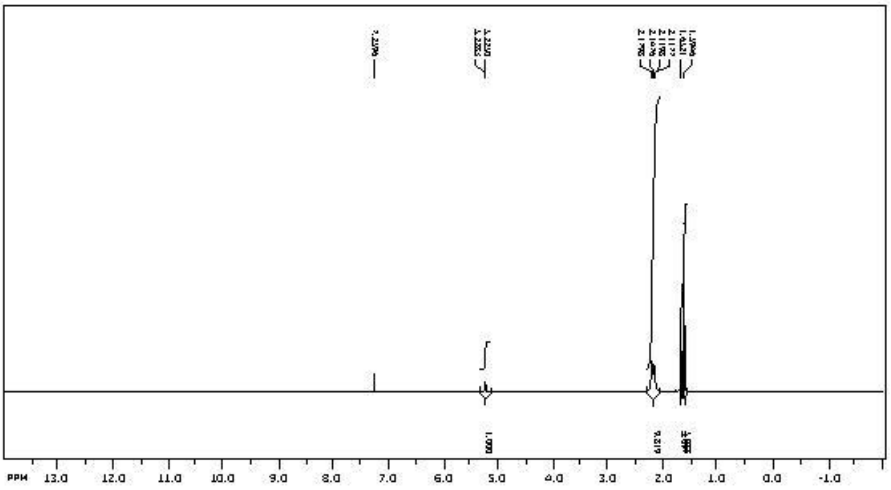
^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 122.73, 122.68, 118.0, 72.3, 71.9, 42.7, 42.5, 41.1, 36.2, 23.1, 18.6.

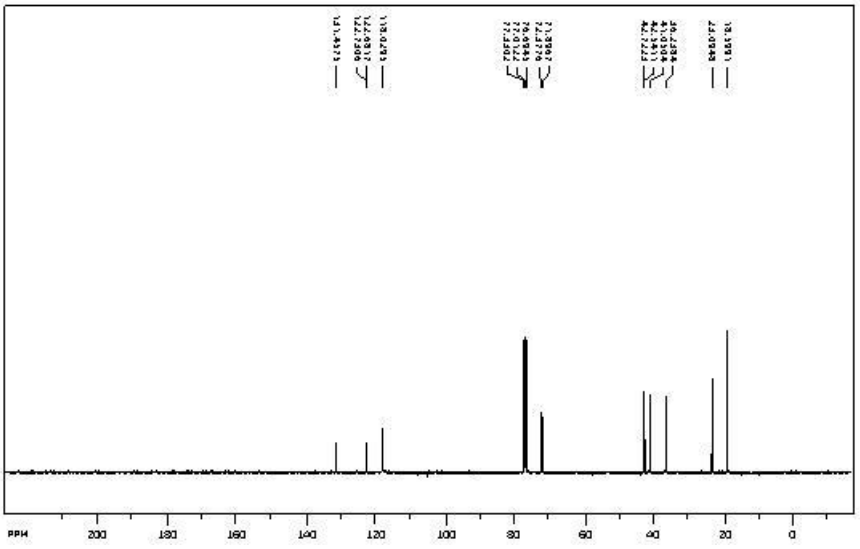
FTIR (neat): v 3363, 2892, 1436, 1070, 958 cm^{-1}.

TLC Rf: 0.21 (ethyl acetate:hexane, 2:3).

LRMS (Cl) Calculated for $C_{13}H_{20}NaO_2$ $[M+Na]^+$: 231.1; Found: 231.1.

MP: 82-84 ^{o}C.





2,3,6-Trimethylnaphthalene (4.9b)

To a dry pressure tube sealed with a septum was added diol **4.8b** (50.0 mg, 0.24 mmol), $VO_2(dipic)(NBu_4)$ (11.8 mg, 0.024 mmol, 10 mol %) and Na_2SO_3 (121.0 mg, 0.96 mmol, 4.0 equiv.). Benzene (0.96 mL, 0.25 M with respect to **4.8b**) was added, and the septum was replaced with a screw cap, and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed, and Darco KB-G (50 mg) was added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^oC oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: hexanes) to provide naphthalene **4.9b** (37.4 mg, 0.18 mmol) as a colourless solid in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 1H, *J* = 8.2 Hz), 7.53 (d, 2H, *J* = 16 Hz), 7.51 (s, 1H), 7.23 (m, 1H), 2.50 (s, 3H), 2.42 (s, 6H).

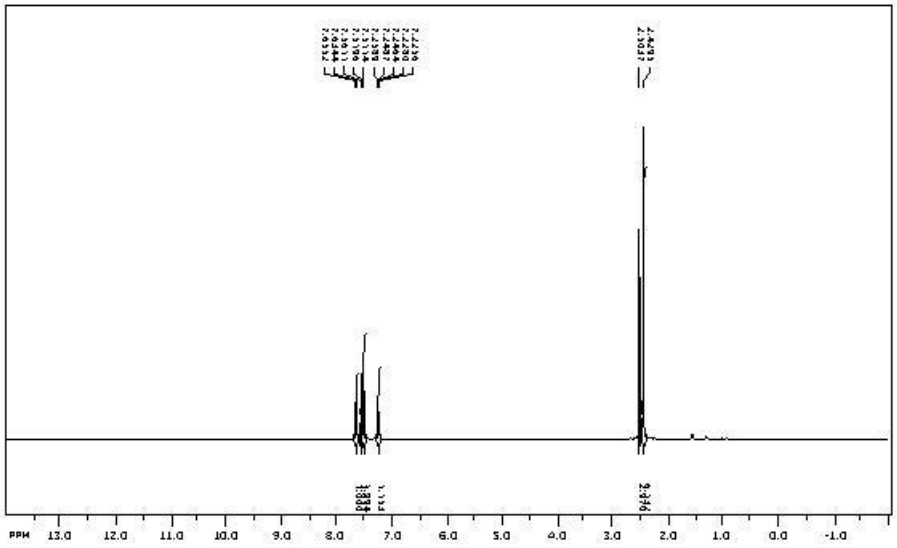
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 134.5, 134.4, 132.6, 130.6, 127.2, 127.1, 126.8, 126.7, 125.8, 21.7, 20.2, 20.1.

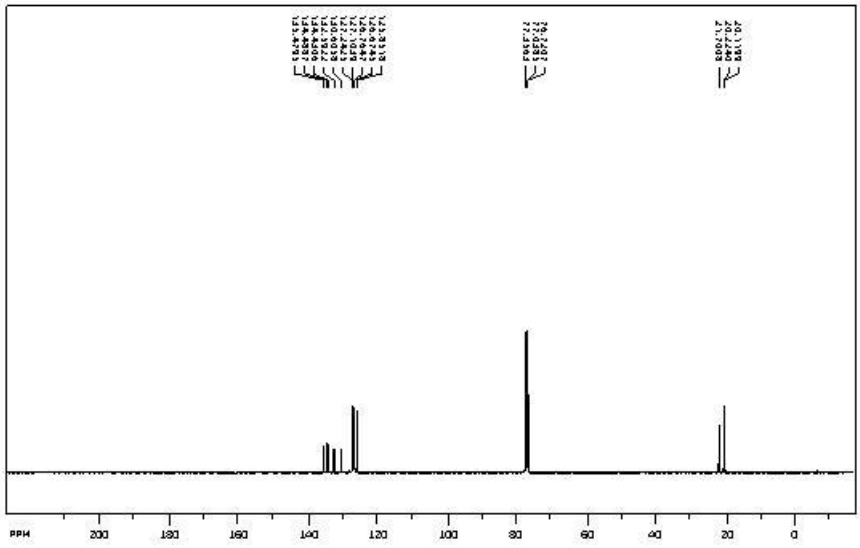
FTIR (neat): v 2915, 1613, 1502, 1440, 881, 800 cm^{-1}.

TLC Rf: 0.40 (ethyl acetate:hexane, 2:3).

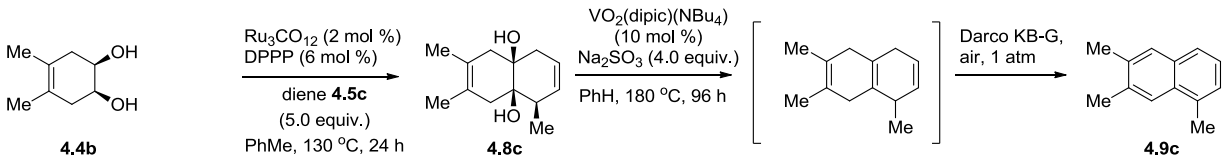
HRMS (Cl) Calculated for $C_{13}H_{14}$: 170.1096; Found: $[M]^+$: 170.1095.

MP: 99-102 ^oC.





Synthesis of 1,6,7-Trimethylnaphthalene (4.9c).



1,6,7-Trimethyl-1,4,4a,5,8,8a-hexahydronaphthalene-4a,8a-diol (4.8c)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %) and dimethylcyclohexenediol **4.4b** (42.7 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon and toluene (0.15 mL, 2.0 M with respect to **4.4b**) was added via syringe, followed by freshly distilled 1.3-pentadiene **4.5c** (0.15 mL, 1.5 mmol, 5.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 24 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexane, 2:3) to provide the cycloadduct **4.8c** (53.0 mg, 0.255 mmol) as a colourless crystalline solid in 85% yield and 16:1 dr).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56-5.50 (m, 1H), 5.33-5.28 (m, 1H), 2.45-2.32 (m, 3H), 2.28-2.14 (m, 3H), 2.09-1.88 (m, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.04 (d, 3H, *J* = 7.4 Hz).

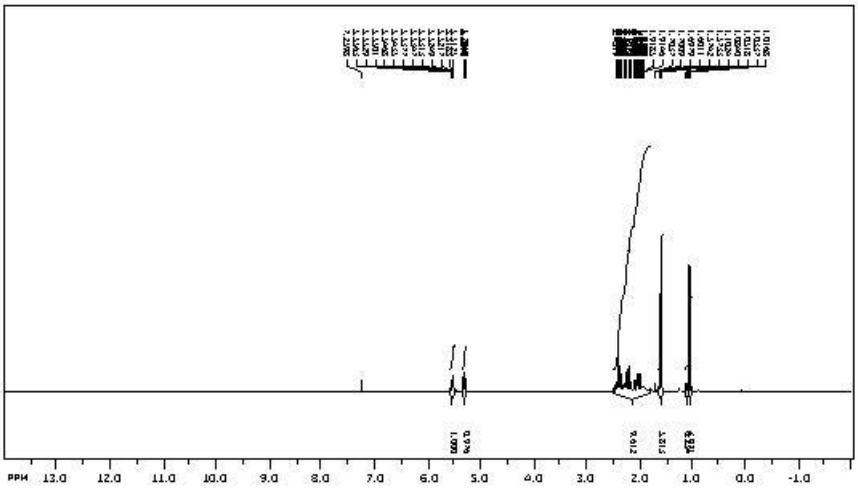
^{13}C NMR (100 MHz, $CDCl_3$): δ 130.6, 123.4, 123.3, 122.1, 73.7, 72.8, 42.8, 38.7, 36.2, 35.7, 18.9, 18.4, 14.3.

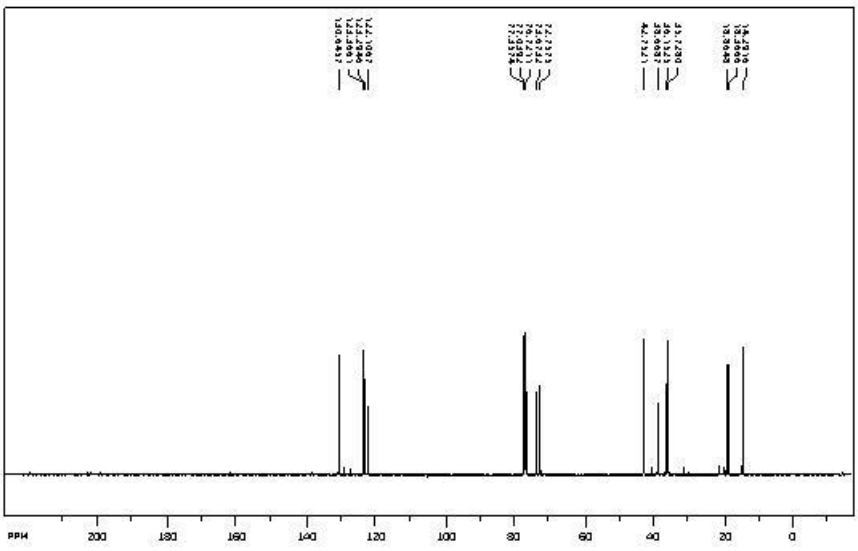
FTIR (neat): υ 3531, 3378, 2992, 1436, 1117, 980, 654 cm $^{-1}$.

TLC Rf: 0.25 (ethyl acetate:hexane, 2:3).

LRMS (Cl) Calculated for $C_{13}H_{20}NaO_2$ $[M+Na]^+$: 231.1; Found: 231.1.

MP: 124-129 ^{o}C





1,6,7-Trimethylnaphthalene (4.9c)

To a dry pressure tube sealed with a septum was added diol **4.8c** (50.0 mg, 0.24 mmol), $VO_2(dipic)(NBu_4)$ (11.8 mg, 0.024 mmol, 10 mol %) and Na_2SO_3 (121.0 mg, 0.96 mmol, 4.0 equiv.). Benzene (0.96 mL, 0.25 M) was added, and the septum was replaced with a screw cap and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed, and 50 mg of Darco KB-G was added. The pressure tube was sealed with a septum and the reaction vessel was placed in an 80 ^oC oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: 100% hexanes) to provide naphthalene **4.9c** as a colourless solid in 75% yield (31.6 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.60 (t, 2H, *J* = 4 Hz), 7.28 (t, 1H, *J* = 8 Hz), 7.23 (m, 1H).

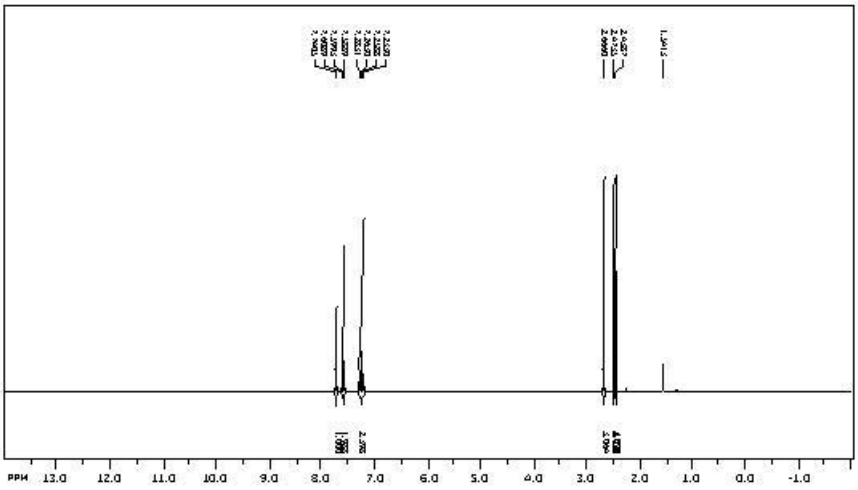
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 135.1, 133.3, 132.4, 131.4, 128.0, 125.7, 125.3, 124.7, 123.8, 20.5, 20.0, 19.4.

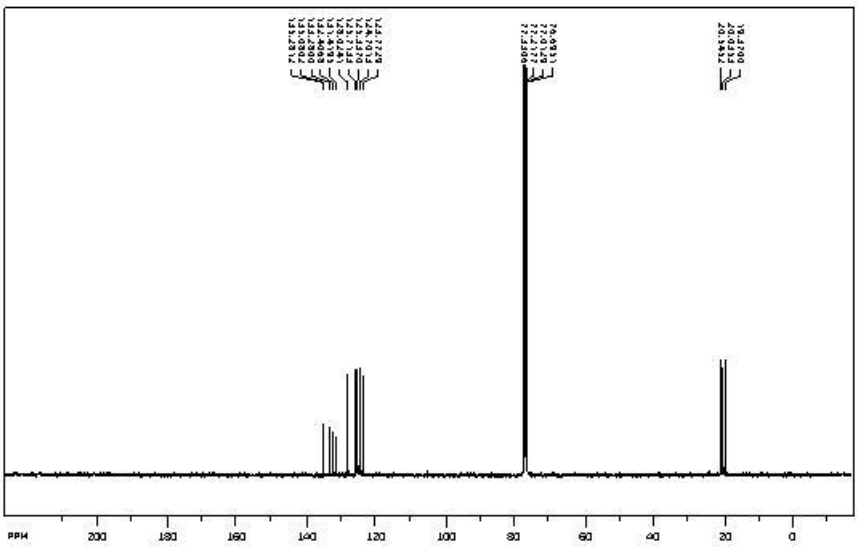
FTIR (neat): v 2913, 1502, 1438, 1074, 882, 799 cm^{-1}.

TLC Rf: 0.42 (ethyl acetate:hexane, 2:3).

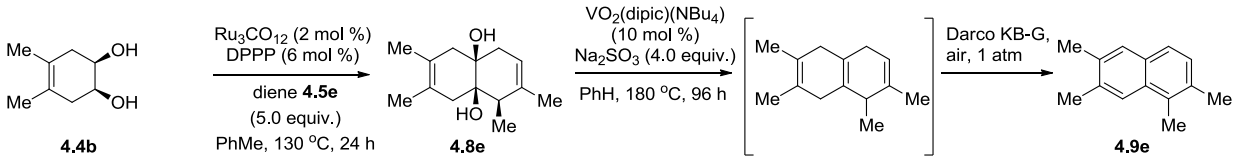
HRMS (Cl) Calculated for $C_{13}H_{14}$: 170.1096; Found: $[M]^+$: 170.1093.

MP: 103-105 ^oC





Synthesis of 1,2,6,7-Tetramethylnaphthalene (4.9e).



1,2,6,7-tetramethyl-1,4,4a,5,8,8a-hexahydronaphthalene-4a,8a-diol (4.8e)

To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 2 mol %), DPPP (7.4 mg, 0.018 mmol, 6 mol %) and dimethylcyclohexenediol **4.4b** (42.7 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 2.0 M) was added via syringe, followed by freshly distilled 3-methyl-1,3-pentadiene **4.5e** (0.16 mL, 1.5 mmol, 5.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 24 hours, the reaction vessel was removed from the oil bath and was allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: 40% ethyl acetate:hexane) to provide the cycloadduct **4.8e** (58.8 mg, 0.26 mmol) as a colourless crystalline solid in 88% yield >20:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27 (m, 1H), 5.33-5.28 (m, 1H), 2.36-2.26 (m, 2H), 2.25-2.14 (m, 3H), 2.09-1.91 (m, 4H), 1.65 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.11 (d, 3H, J = 7.4 Hz).

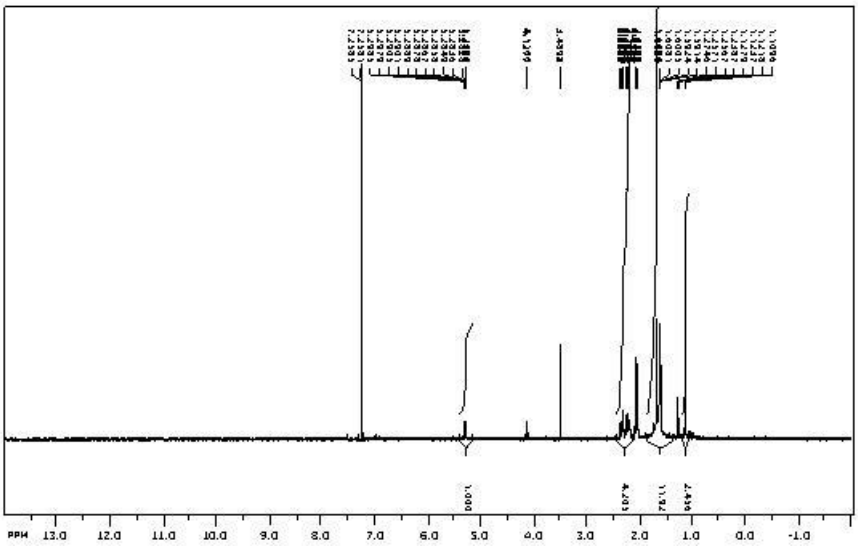
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 123.1, 122.5, 118.5, 74.0, 72.8, 42.7, 40.4, 40.1, 36.5, 21.8, 18.8, 18.4, 12.5.

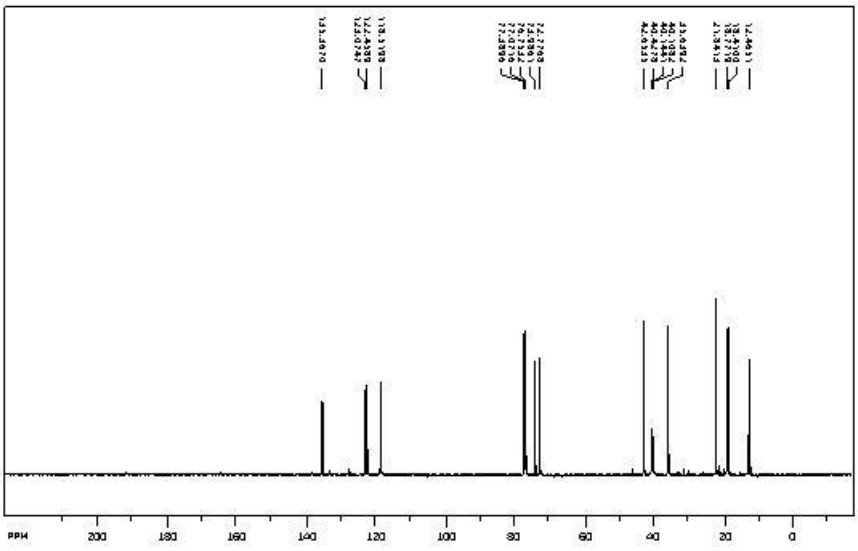
FTIR (neat): v 3309, 2911, 1441, 1382, 1087, 973 cm $^{-1}$.

TLC Rf: 0.30 (ethyl acetate:hexane, 2:3).

LRMS (Cl) Calculated for $C_{13}H_{20}NaO_2$ $[M+Na]^+$: 231.1; Found: 231.1.

MP: 111-113 ^{o}C.





1,2,6,7-Tetramethylnaphthalene (4.9e)

To a dry pressure tube sealed with a septum was added diol **4.8e** (60.0 mg, 0.27 mmol), VO_2(dipic)(NBu_4) (13.2 mg, 0.027 mmol, 10 mol %) and Na_2SO_3 (136.1 mg, 1.08 mmol, 4.0 equiv.). Benzene (1.1 mL, 0.25 M with respect to **4.8e**) was added, and the septum was replaced with a screw cap, and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed, and 60 mg of Darco KB-G was added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^oC oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: hexanes) to provide naphthalene **4.9e** (50.2 mg, 0.20 mmol) as a colourless solid in 75% yield.

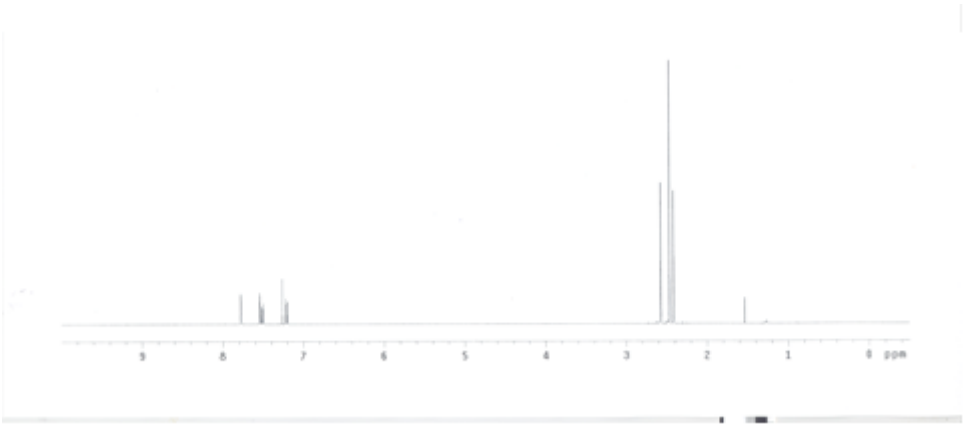
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.55 (s, 1H), 7.52 (d, 1H, *J* = 8 Hz), 7.22 (d, 1H, *J* = 8 Hz), 2.58 (s, 3H), 2.47 (s, 6H), 2.43 (s, 3H).

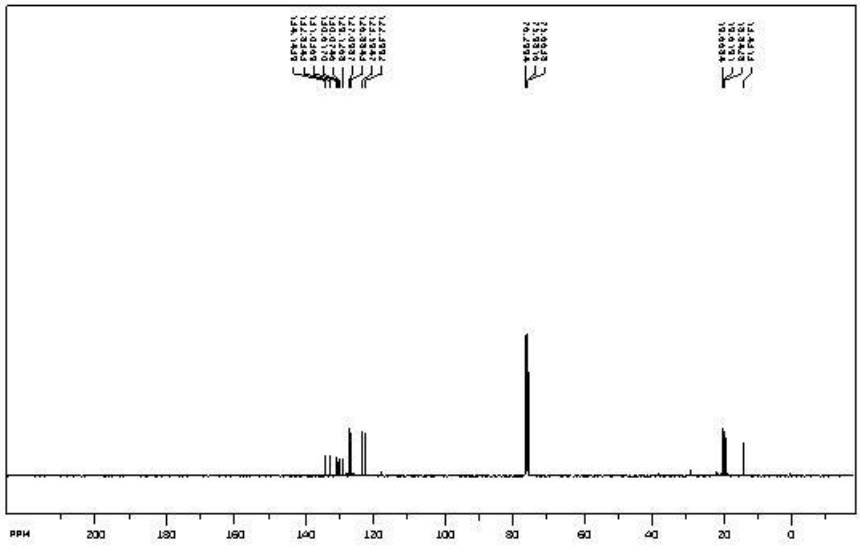
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 132.8, 131.0, 130.6, 130.1, 129.1, 127.1, 126.9, 123.6, 122.4, 19.7, 19.6, 18.8, 13.4.

FTIR (neat): v 2919, 1498, 1445, 1026, 862, 798 cm^{-1}.

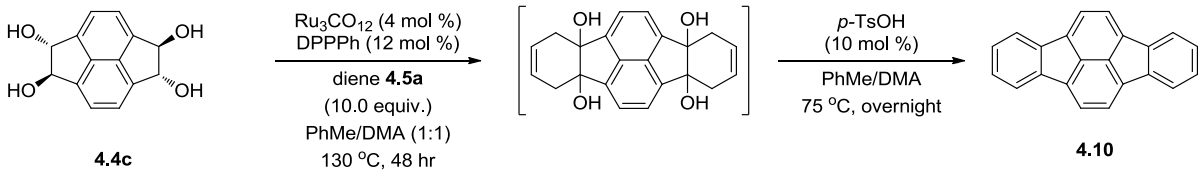
TLC Rf: 0.76 (ethyl acetate:hexane, 2:3).

HRMS (Cl) Calculated for $C_{14}H_{16}$ $[M]^+$: 184.1252; Found: 184.1246.





Synthesis of Indeno[1,2,3-cd]fluoranthene (4.10).



To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (5.1 mg, 0.008 mmol, 4 mol %), DPPPh (10.7 mg, 0.024 mmol, 12 mol %) and tetraol **4.4c** (48.8 mg, 0.2 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.2 mL, 1.0 M with respect to **4.4c**) and freshly distilled dimethylacetamide (0.2 mL, 1.0 M with respect to **4.4c**) were added via syringe, followed by freshly condensed butadiene **4.5a** (0.176 mL, 2.0 mmol, 10.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 48 hours, the reaction vessel was removed from the oil bath and was allowed to cool to room temperature. *p*-Toluenesulfonic acid (7.6 mg, 0.04 mmol, 20 mol %) and toluene (2.0 mL, 0.1 M with respect to **4.4c**) were added into the mixture, and the reaction was placed in a 75 ^{o}C oil bath. When judged complete by TLC (overnight), the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The solvents were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: DCM was used for a short column first and toluene was used for the second column) to provide indeno[1,2,3-cd]fluoranthene **4.10** (33.9 mg, 0.12 mmol) as dark yellow solid in 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 4H), 7.55 (s, 4H), 7.18-7.16 (m, 4H).

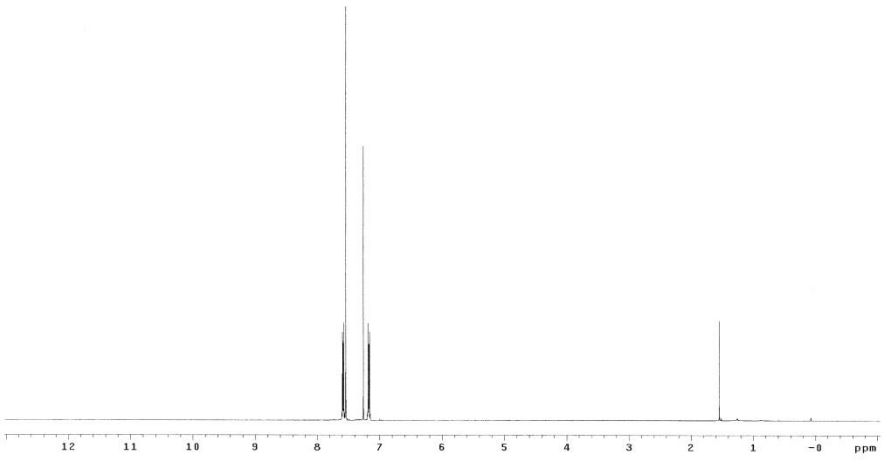
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 137.6, 132.8, 128.1, 122.8, 121.8.

FTIR (neat): v 2925.5, 2361.5, 1456.0, 1260.4, 1012.1, 904.8, 801.5, 728.4 cm^{-1}.

TLC Rf: 0.3 (hexanes).

HRMS (Cl) Calculated for $C_{22}H_{12}$: 276.0939; Found: $[M]^+$: 276.0941.

MP: 253.2-254.0 ^oC (literature[83] mp 255-258 ^oC).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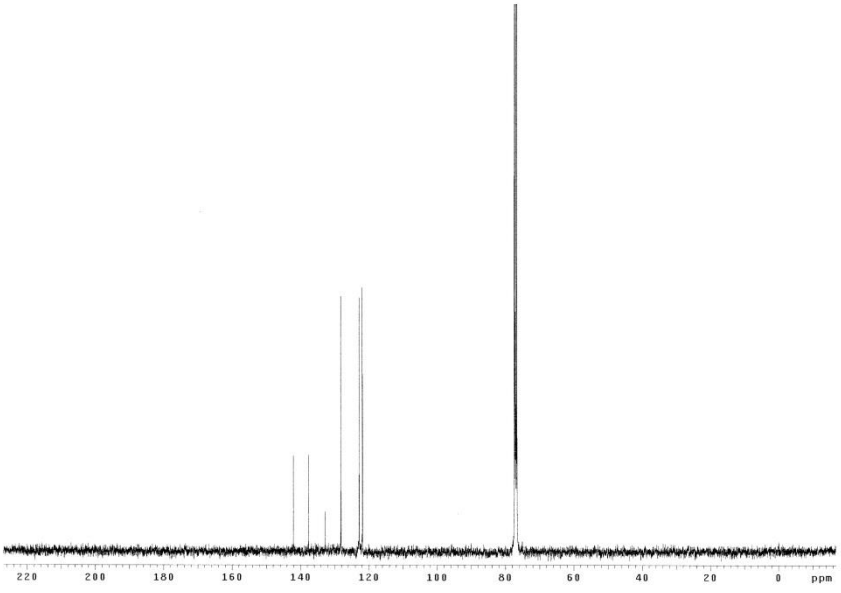
11
10
9
8
7
6
5
4
3
2
1
-0
ppm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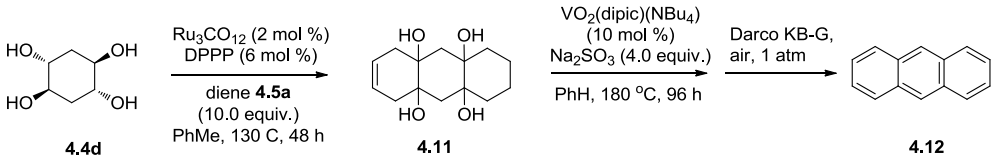
200
180
160
140
120
100
80
60
40
20
0
ppm

Synthesis of Anthracene (4.12).



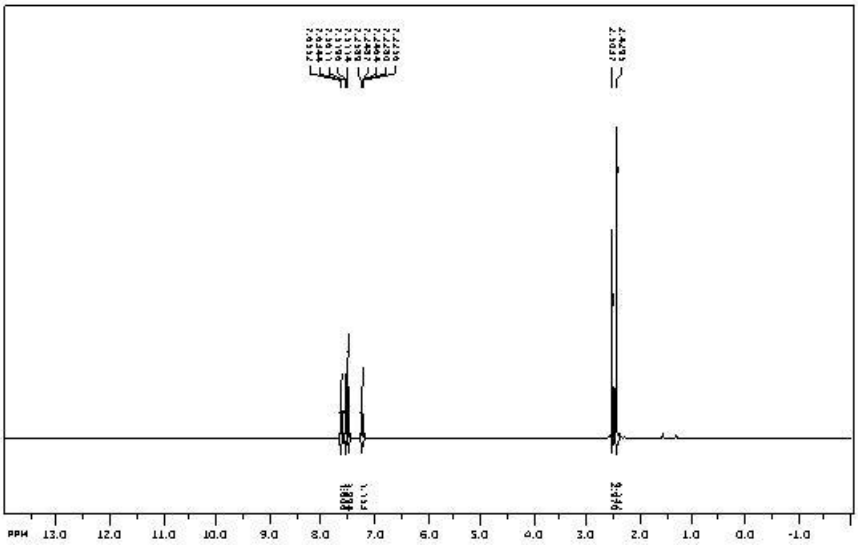
To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (7.6 mg, 0.012 mmol, 4 mol %), DPPP (14.8 mg, 0.036 mmol, 12 mol %) and tetraol **4.4d** (44.5 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.30 mL, 2.0 M with respect to **4.4d**) was added via syringe, followed by freshly condensed butadiene **4.5a** (0.26 mL, 3.0 mmol, 10.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 48 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: methanol:dichlormethane, 1:19) to provide the cycloadduct **4.11** (71.4 mg, 0.28 mmol) as a colourless solid in 92% yield and 1.4:1 dr. The material was characterized by ^{1}H NMR only.

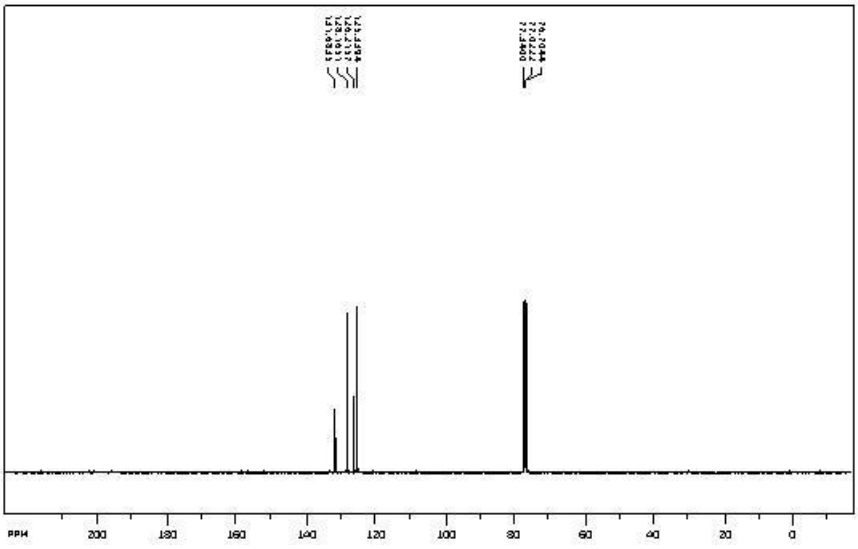
^{1}H NMR (400 MHz, acetone-d_6): δ 5.49 (m, 1.75 H), 5.45 (m, 1.30 H), 2.85-2.78 (m, 8H), 2.32-2.62 (m, 4H).

To a dry pressure tube sealed with a septum was added the intermediate tetraol **4.11** (20.0 mg, 0.068 mmol), VO_2(dipic)(NBu_4) (6 mg, 0.0012 mmol, 15 mol %) and Na_2SO_3 (40 mg, 0.312 mmol, 4.0 equiv.). Benzene (0.31 mL, 0.25 M with respect to the tetraol) was added. The septum was replaced with a screw cap, and the reaction was placed in a 180 ^{o}C oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed and 10 mg of Darco KB-G was

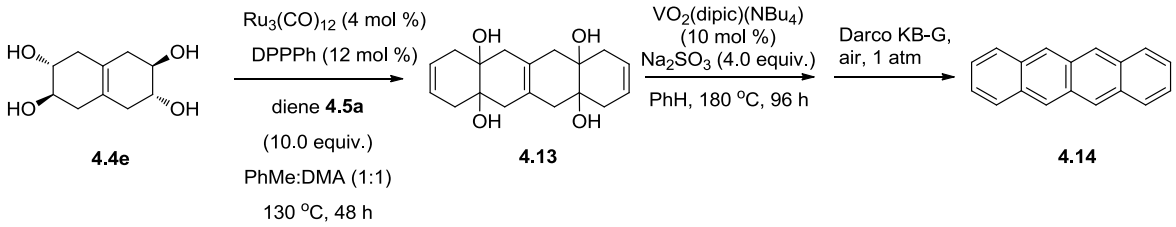
added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^{o}C oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: hexanes) to provide anthracene **4.12** (10.2 mg, 0.048 mmol) as a colourless solid in 70% yield. The ^{1}H and ^{13}C NMR spectra were a match to that of commercially available material.

^{1}H NMR (400 MHz): δ 8.44 (s, 2H), 8.02 (m, 4H), 7.48 (m, 4H).
^{13}C NMR (100 MHz): δ 131.7, 128.2, 126.2, 125.3.
TLC Rf: 0.32 (hexanes).
HRMS (Cl) Calculated for $C_{14}H_{10}$: 178.0783; Found: $[M]^{+}$: 178.0782





Synthesis of Tetracene (4.14).



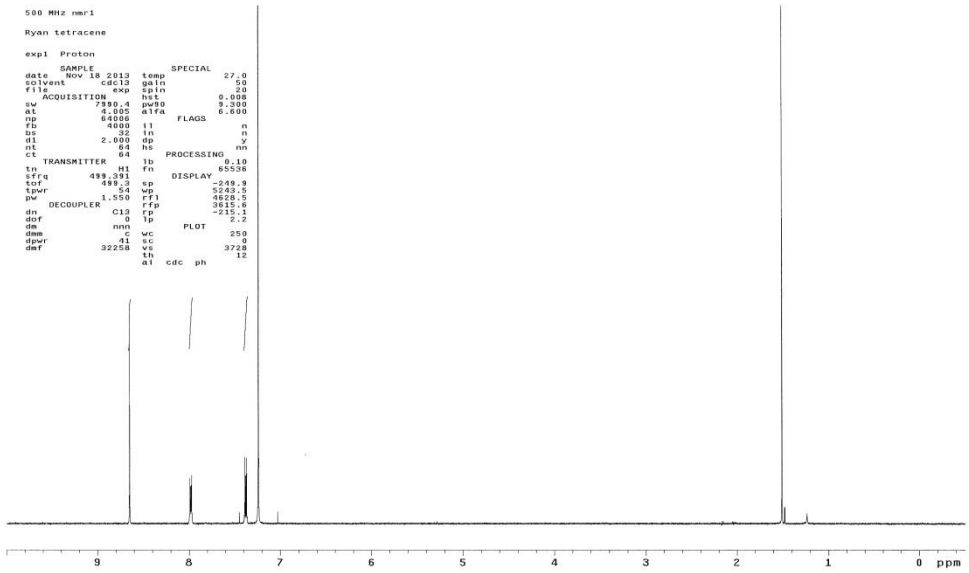
To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (7.7 mg, 0.012 mmol, 4 mol %), DPPPh (16.1 mg, 0.036 mmol, 12 mol %) and tetraol **4.4e** (60.0 mg, 0.3 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 2.0 M with respect to **4.4e**) and dimethylacetamide (0.15 mL, 2.0 M with respect to **4.4e**) were added via syringe, followed by freshly condensed butadiene **4.5a** (0.264 mL, 3.0 mmol, 10.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^{o}C oil bath. After 48 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the residue was subjected to flash column chromatography (SiO_2: ethanol:dichloromethane, 1:4) to provide the intermediate cycloadduct **4.13** (76.7 mg, 0.25 mmol) as white solid in 84% yield 1.3:1 dr.

^{1}H NMR (400 MHz, d_4-MeOH): δ 5.49 (s, 4H), 2.22-2.06 (m, 16H).
^{13}C NMR (100 MHz, d_4-MeOH): δ 125.4, 72.9, 72.8, 42.3, 42.2, 37.8.
FTIR (neat): v 3327, 3025, 2899, 2833, 1421, 1321, 1221, 1090, 891, 804 cm^{-1}.
TLC Rf: 0.7 (ethanol:dichloromethane, 1:1).
LRMS (Cl) Calculated for $C_{18}H_{24}NaO_4$ $[M+Na]^+$: 327.16; Found: 327.16.
MP: 202.3-202.8 ^{o}C

To a dry pressure tube sealed with a septum was added the intermediate tetraol **4.13** (60.8 mg, 0.2 mmol), VO_2(dipic)(NBu_4) (19.6 mg, 0.04 mmol, 20 mol %) and Na_2SO_3 (252 mg, 2.0 mmol, 10.0 equiv.). Benzene (1.0 mL, 0.2 M with respect to the tetraol) was added. The septum was replaced with a screw cap, and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed and 60.8 mg of Darco KB-G was added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^oC oil bath and stirred under a balloon of air. After 72 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: toluene) and recrystallized from dichloromethane to provide tetracene **4.14** (23.2 mg, 0.10 mmol) as an orange solid in 51% yield.

***The entire process needs to be performed in the dark, otherwise the photooxidation will provide a mixture of naphthacene and 5,12-naphthacenequinone as the final product.**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 4H), 8.00 (m, 4H), 8.67 (s, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 128.3, 126.3, 125.1.
FTIR (neat): v 3044, 1807, 1628, 1537, 1462, 1386, 1296, 1162, 1122, 958, 900, 737 cm^{-1}.
TLC Rf: 0.3 (hexanes).
HRMS (Cl) Calculated for $C_{18}H_{12}$: 228.0939; Found: $[M]^+$: 228.0936.
MP: 345-346 ^oC


500 MHz nmr1
Ryan tetracene
exp1 Proton
SAMPLE
date Nov 18 2013
solvent cdcl3
file exp
ACQUISITION
sw 7390.4
at 4.005
np 64006
fb 4000
bs 32
d1 2.000
nt 64
ct 64
TRANSMITTER
tn H1
sfrq 499.391
tof 499.3
tpwr 54
pw 1.550
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 41
dmf 32258
SPECIAL
temp 27.0
gain 50
spin 20
hst 0.008
pw90 9.300
alfa 6.600
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.10
fn 65536
DISPLAY
sp -249.9
wp 5243.5
rf1 4628.5
rfp 3615.6
rp -215.1
lp 2.2
PLOT
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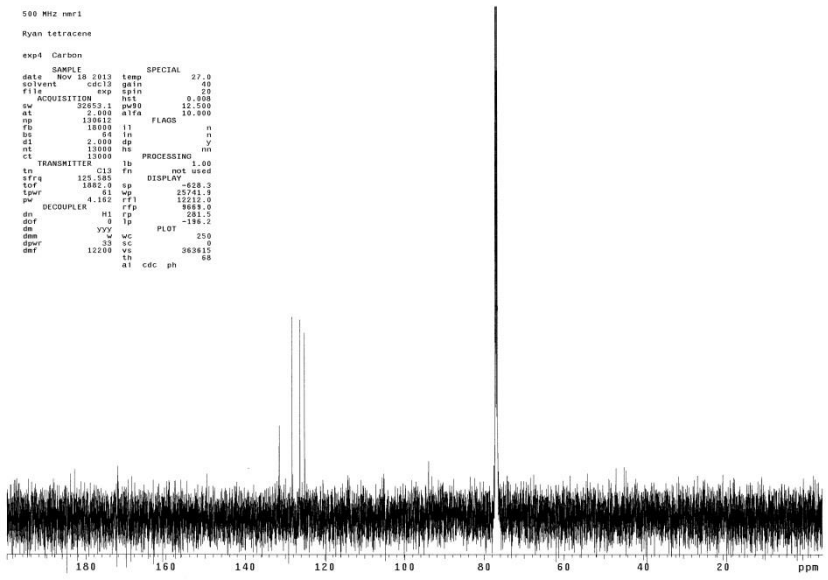
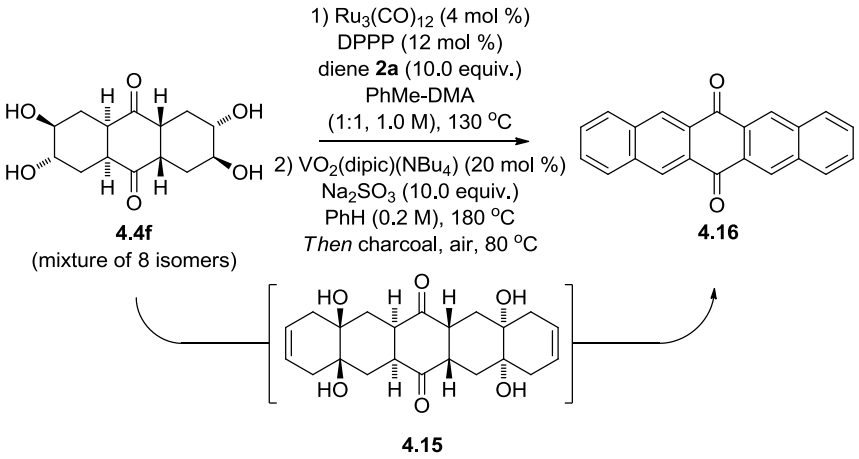
sc 0
vs 3728
th 12
al cdc ph
9
8
7
6
5
4
3
2
1
0 ppm


500 MHz nmr1
Ryan tetracene
exp4 Carbon
SAMPLE
date Nov 18 2013
solvent cdcl3
file exp
ACQUISITION
sw 32653.1
at 2.000
np 130612
fb 18000
bs 64
d1 2.000
nt 13000
ct 13000
TRANSMITTER
tn C13
sfrq 125.585
tof 1882.0
tpwr 61
pw 4.162
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 33
dmf 12200
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 12.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.3
wp 25741.9
rf1 12212.0
rfp 9663.0
rp 281.5
lp -196.2
PLOT
wc 250
sc 0
vs 363615
th 68
al cdc ph
180
160
140
120
100
80
60
40
20
ppm

Synthesis of 6,13-Pentacenedione (4.16).



To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 4 mol %), DPPP (7.4 mg, 0.018 mmol, 12 mol %) and tetraol **4.4f** (42.6 mg, 0.15 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 1.0 M with respect to **4.4f**) and dimethylacetamide (0.15 mL, 1.0 M with respect to **4.4f**) were added via syringe, followed by freshly condensed butadiene **4.5a** (0.13 mL, 1.5 mmol, 10.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^oC oil bath. After 48 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The solvents were removed *in vacuo*. Cycloadduct **4.15** was not purified or characterized, and was used directly in the next step.

Cycloadduct **4.15** was suspended in toluene (0.6 mL, 0.25 M with respect to **4.15**) in a pressure tube and $VO_2(dipic)(NBu_4)$ (7.4 mg, 0.015 mmol, 10 mol %) and Na_2SO_3 (75.6 mg, 0.60 mmol, 4.0 equiv.) were added. The pressure tube was sealed with a screw cap, and the reaction was placed in a 180 ^oC oil bath. After 96 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was removed, and 32 mg of

Darco KB-G was added. The pressure tube was sealed with a septum, and the reaction vessel was placed in an 80 ^{o}C oil bath and stirred under a balloon of air. After 12 hours, the reaction vessel was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to provide pentacenedione **4.16** (40.5 mg, 0.13 mmol) as a colourless solid in 87% yield. The ^{1}H spectrum and FTIR were in accordance with that of commercially available material.

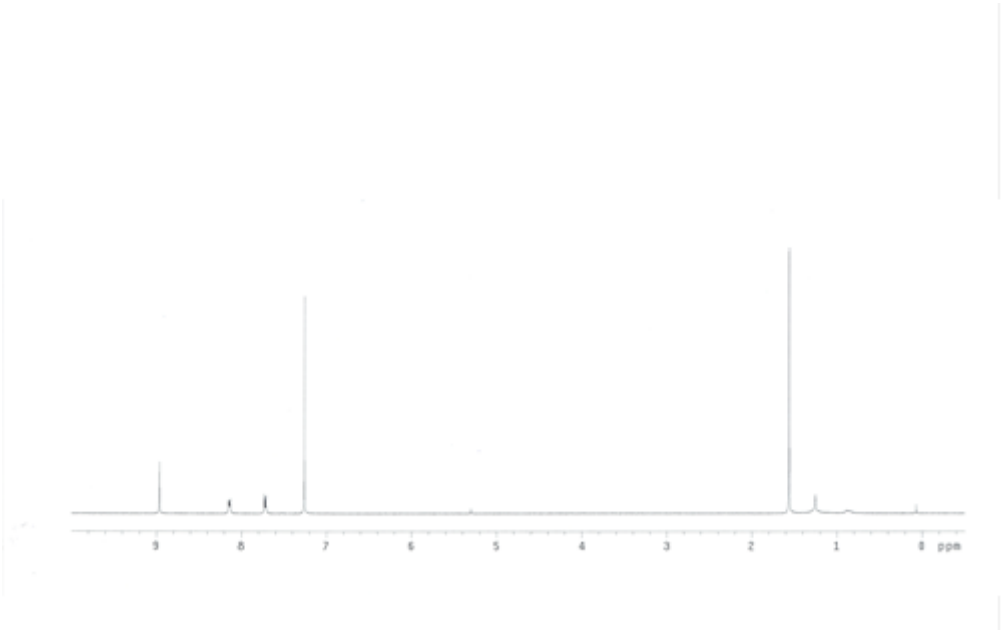
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 4H), 8.17-8.11 (m, 4H), 7.74-7.80 (m, 4H).

FTIR (neat): v 3054, 1671, 1612, 1442, 1275, 758 cm^{-1}.

TLC Rf: 0.23 (ethyl acetate:hexanes, 1:9).

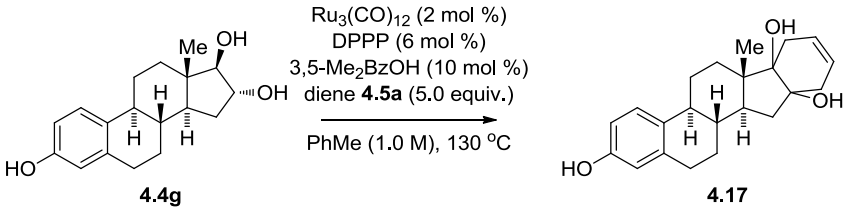
HRMS (Cl) Calculated for $C_{22}H_{12}O_2$: 308.0837; Found: $[M]^+$: 308.0840.

MP: >350 ^{o}C



Synthesis of Benzannulated Estriol (4.18).

(6bS, 8aS, 13aS)-4-Hydroxy-8a-methyl-2,6b,7,8,8a,13,13b-octahydro-1H-indeno[2,1-a]phenanthrene (4.17)



To a dry pressure tube sealed with a septum under an argon atmosphere was added $Ru_3(CO)_{12}$ (3.8 mg, 0.006 mmol, 4 mol %), DPPP (7.4 mg, 0.018 mmol, 12 mol %), 3,5-dimethylbenzoic acid (4.5 mg, 0.03 mmol, 10 mol %) and triol **4.4g** (86.5 mg, 0.15 mmol, 1.0 equiv.). The pressure tube was purged with argon, and toluene (0.15 mL, 2.0 M with respect to **4.4g**) and dimethylacetamide (0.15 mL, 2.0 M with respect to **4.4g**) were added via syringe, followed by freshly condensed butadiene **4.5a** (0.13 mL, 1.5 mmol, 10.0 equiv.). The septum was replaced with a screw cap, and the reaction was placed in a 130 ^oC oil bath. After 48 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The solvents were removed *in vacuo*. The cycloadducts were subjected to flash column chromatography (SiO_2: ethyl acetate: hexanes, 2:3) to give the title compound (35.9 mg, 0.11 mmol) in 70% yield and 2:1 dr, which were used as a mixture in the following steps. A pure sample of the major diasteromer, which is more polar, was isolated and has the following characteristics.

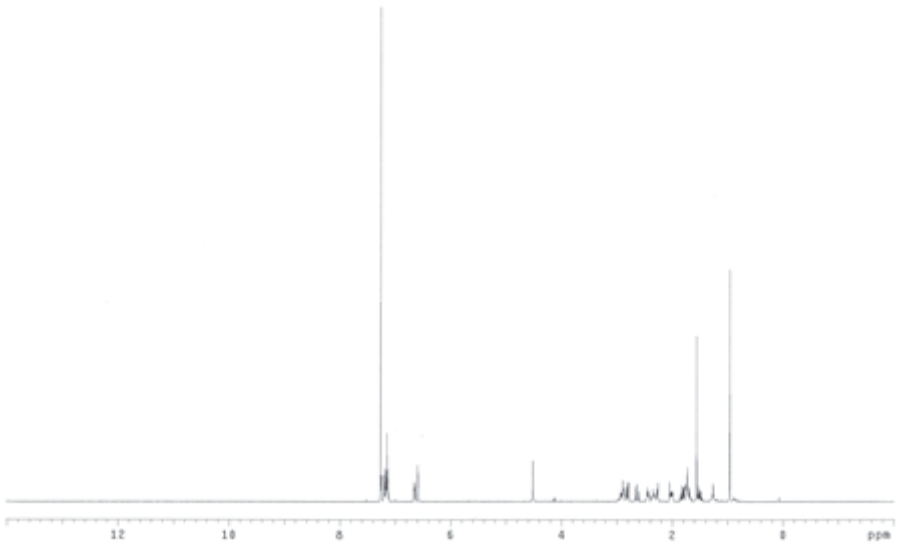
^{1}H NMR (400 MHz, $CDCl_3$+acetone-d_6): δ 8.13 (s, 1H), 6.55 (d, 1H, *J* = 8 Hz), 6.06 (dd, 1H, *J* = 2.5, 8 Hz), 5.99 (d, 1H, *J* = 2.5 Hz), 5.46-5.32 (m, 2H), 4.20 (br s, 1H), 3.43 (br s, 1H), 2.31-2.21 (m, 2H), 1.93-1.86 (m, 1H), 1.81-1.70 (m,

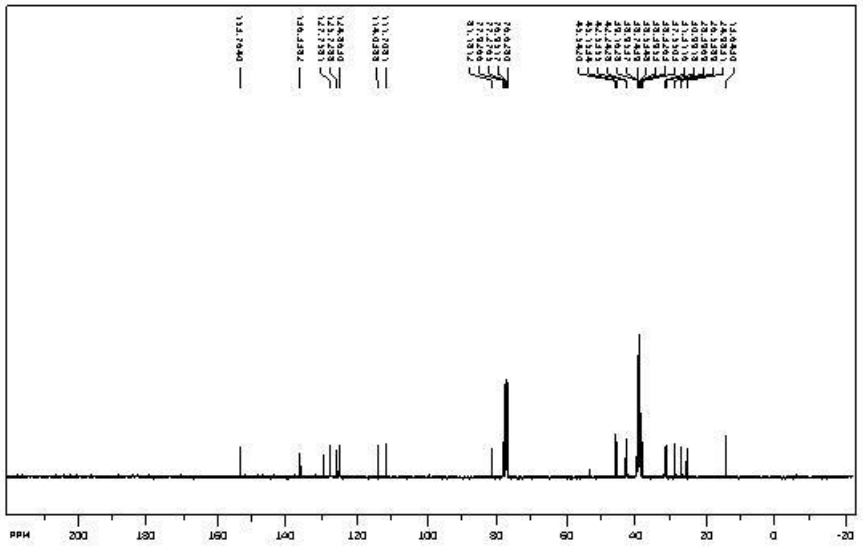
2H), 1.66-1.57 (m, 1H), 1.54-1.28 (m, 5H), 1.19-0.88 (m, 5H), 0.83-0.71 (m, 2H), 0.38 (s, 3H).

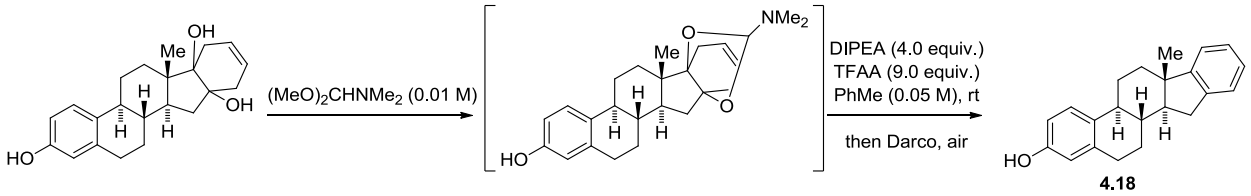
^{13}C NMR (100 MHz, $CDCl_3$+acetone-d_6): δ 153.8, 136.3, 129.7, 127.8, 125.7, 124.9, 114.0, 111.7, 81.2, 77.9, 45.5, 45.2, 42.5, 42.2, 38.4, 37.6, 31.3, 31.0, 28.4, 26.5, 25.0, 13.6.

TLC Rf: 0.17 (ethyl acetate:hexanes, 2:3).

LRMS (Cl) Calculated for $C_{23}H_{30}O_3$ $[M]^+$: 340; Found: 340.


12
10
8
6
4
2
0
ppm


PPM
200
180
160
140
120
100
80
60
40
20
0
-20



In accordance with the known practice of DMF-acetal mediated DODH protocol,[83] the diastereomeric mixture of cycloadduct **4.17** (20 mg, 0.0588 mmol) were suspended in *N*,*N*-dimethylformamide dimethyl acetal (5 mL 0.01 M with respect to the cycloadducts) and stirred at room temperature. The suspension gradually became homogeneous. After 12 hours, the solvent was removed *in vacuo*. The resulting dimethylformamide estriol acetal was not purified or characterized. This material was taken up in toluene (1.2 mL 0.05 M with respect to the cycloadducts), and trifluoroacetic acid anhydride (74 µL, 0.529 mmol, 9.0 equiv.) and diisopropylethylamine (41 µL, 0.235 mmol, 4.0 equiv.) were added. The solution was heated at 50 ^{o}C overnight. After approximately 20 hours, Darco-KB-G (10 mg) was added, and the reaction was stirred another 5 hours under an atmosphere of air. The solvents and residual reagents were removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: ethyl acetate: hexanes, 1:9) to provide the benzannulated estriol **4.18** (15.7 mg, 0.05 mmol) as a colourless oil in 87% yield.

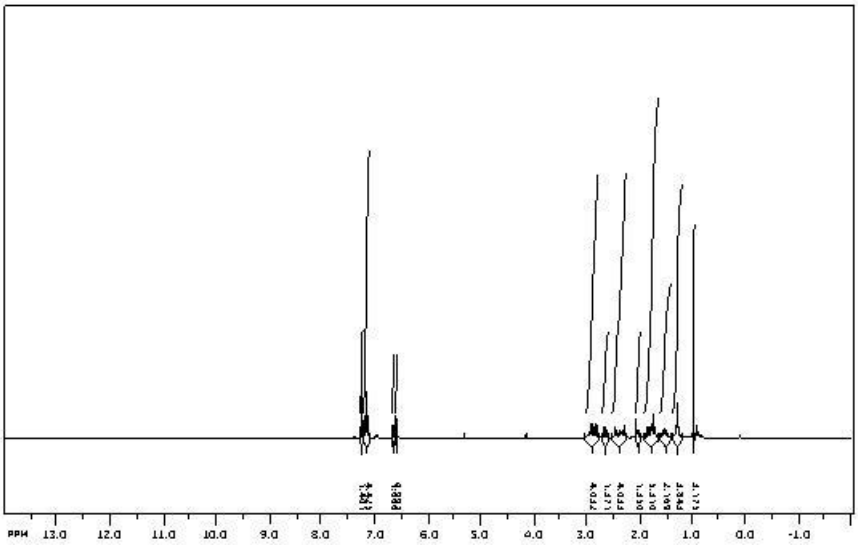
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.22-7.11 (m, 4H), 6.66 (dd, 1H, *J* = 2.5, 8 Hz), 6.60 (d, 1H, *J* = 2.5 Hz), 3.00-2.79 (m, 4H), 2.64 (m, 1H), 2.51-2.26 (m, 4H), 2.02 (m, 1H), 1.87-1.66 (m, 5H), 1.58-1.44 (m, 2H), 1.28 (m, 3H), 0.97 (s, 3H).

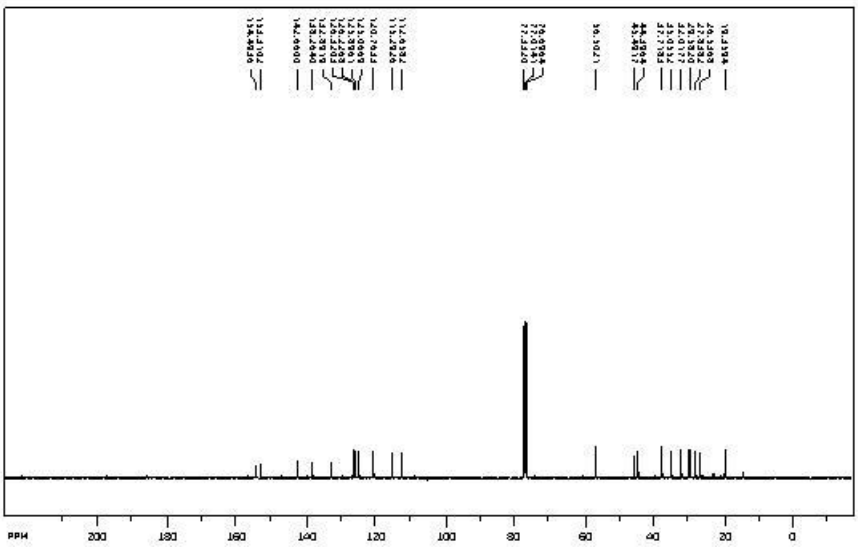
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.3, 142.7, 138.3, 132.9, 126.3, 126.2, 125.9, 125.1, 120.8, 115.3, 112.7, 56.5, 45.5, 44.4, 37.7, 35.1, 32.0, 29.6, 27.8, 26.5, 19.4.

FTIR (neat): v 3330, 2921, 1610, 1451, 1155, 762, 737 cm $^{-1}$.

TLC Rf: 0.92 (ethyl acetate:hexanes, 2:3).

HRMS (Cl) Calculated for $C_{22}H_{24}O$: 304.1827; Found: $[M]^+$: 304.1828.



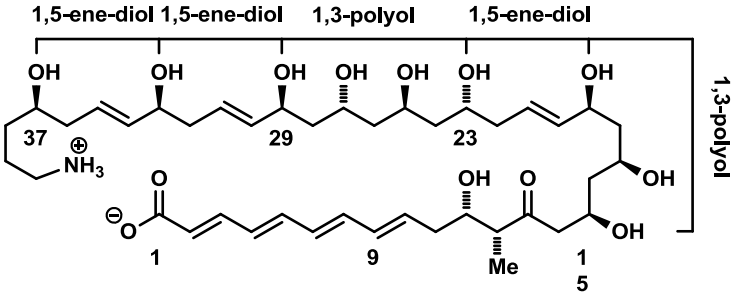


Chapter 5: Synthesis of C9-C20 Fragment of Tetrafibricin *via* Asymmetric Alcohol C-H Allylation and *syn*-Crotylation*

5.1 Introduction

Catalytic C-C bond formation through the addition, transfer or removal of hydrogen[1–4] has been paramount in streamlining the syntheses of 6-deoxyerythronolide B,[5] bryostatin 7,[6] trienomycins A and F,[7] cyanolide A[8] and roxaticin.[9] Owing to the redox economy of the methods employed in their construction, the aforementioned syntheses represent the most concise routes to any member of their respective natural product family reported to date.[4] Considering the structural complexity of tetrafibricin (Figure 5.1), it was determined that a synthetic exercise in the construction of this molecule would be a worthy challenge to examine the utility of the developed C-C bond forming methodology previously mentioned.

Figure 5.1. Structure of the fibrinogen receptor inhibitor tetrafibricin.



Tetrafibricin is a potent fibrinogen receptor inhibitor isolated from *Streptomyces neyagawaensis* NR0775[10–12] that functions by blocking GPIIb/IIIa

*Itoh, T.; Montgomery, T. P.; Recio, A.; Krische, M. J. *Org. Lett.* **2014**, *16* (3), 820. Acknowledgement is given to T. I. and A. R. for route development and optimization and M. J. K. for supervision.

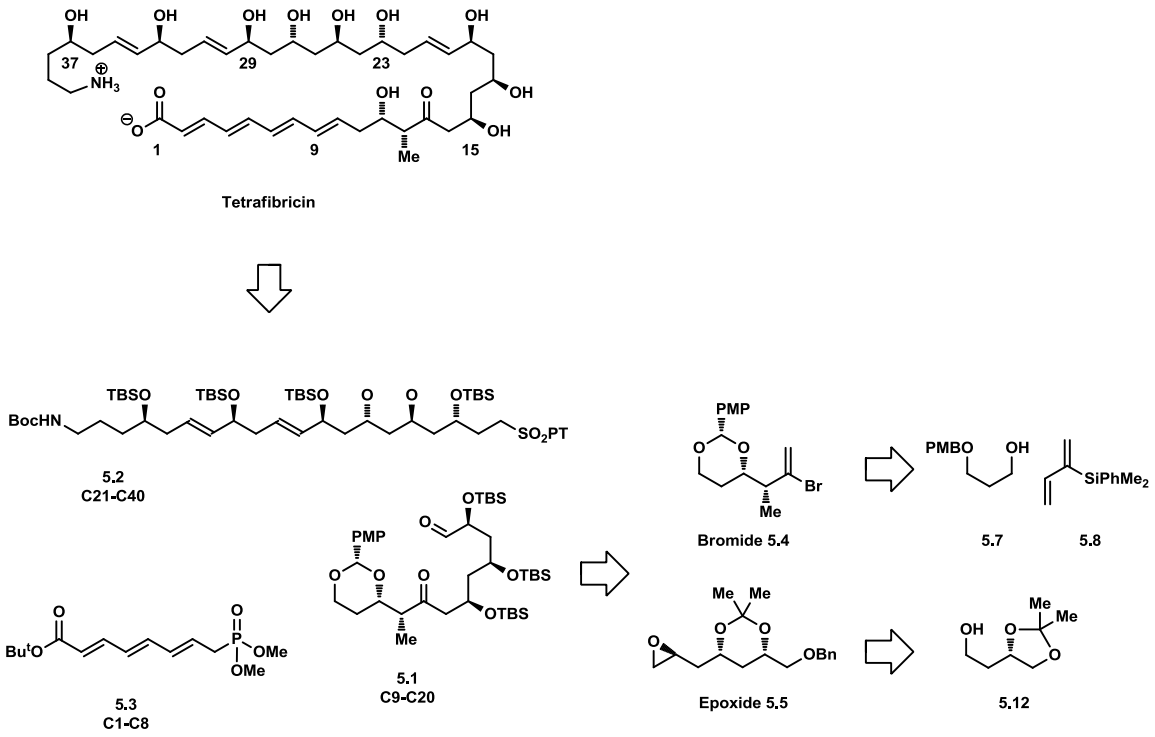
receptors on the platelet surface, thus inhibiting platelet aggregation.[13,14] While biosynthetically related to the oxo-polyene macrolide antibiotic lienomycin,[15] tetrafibricin is acyclic and inactive against *Bacillus subtilis* and *Escherichia coli*. Further, the structure of tetrafibricin, including 1,5-ene-diol and 1,3-diol motifs, primary amine and tetraenoic acid moieties, represents a significant departure from all other naturally occurring fibrinogen receptor antagonists; therefore, tetrafibricin could serve as a useful tool in the study of platelet aggregation, fibrinogen binding and treatment of arterial thrombosis.[14,16,17] For these reasons, tetrafibricin has garnered interest in its preparation through total synthesis. It has been the target of synthetic studies from the laboratories of Cossy,[18] Curran,[19–22] Friestad,[23] Roush[24–26] and Krische.[27,28] Although the total synthesis of a protected derivative of the natural product by Curran[22] and *N*-acetyl dihydrotetrafibricin methyl ester by Roush[26] have been reported, the total synthesis of tetrafibricin remains an unmet challenge.

5.2 Retrosynthetic Analysis of Tetrafibricin

It was envisioned that tetrafibricin could arise from the Julia-Kocienski olefination of C9-C20 fragment **5.1** and C21-C40 fragment **5.2**, and Horner-Wadsworth-Emmons of C9-C20 fragment **5.1** and C1-C8 fragment **5.3** (Figure 5.2). C1-C8 fragment **5.3** could be constructed using known chemistry through a series of manipulations that include a Horner-Wadsworth Emmons olefination.[24,29] An elegant synthesis for the C21-C40 fragment was revealed in an earlier report by Krische and coworkers, which made use of an iridium-catalyzed C-C bond formation mediated by hydrogen auto-transfer,[1–3] aiding in the rapid construction of this fragment (12 linear and 17 total steps).[27] The C21-C40 fragment reported was only three steps away from the sulfone needed for the Julia-Kocienski olefination. The construction of C9-C20 fragment **5.1** was envisioned to arise from a coupling of two main pieces, vinyl bromide **5.4** and epoxide **5.5**. It was thought that vinyl bromide **5.4** could be constructed using the

ruthenium-catalyzed *syn*-crotylation methodology,[30] and epoxide **5.5** would ultimately arise from the iridium-catalyzed carbonyl allylation methodology.[31,32]

Figure 5.2. Retrosynthetic Analysis of tetrafibricin and fragment **5.1**.



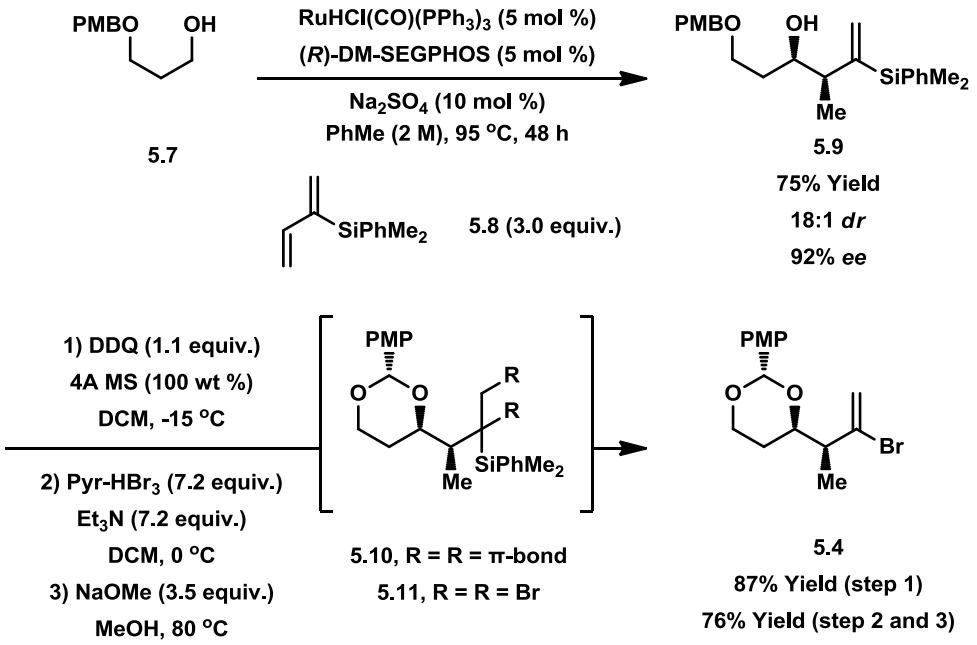
5.3 Synthesis of C9-C20 of Tetrafibricin

5.3.1 Synthesis of Bromide 5.4

Synthesis of bromide **5.4** was accomplished using the previously reported ruthenium-catalyzed hydrohydroxyalkylation of diene **5.8** and alcohol **5.7**. A modification of the previously reported conditions,[30] involving use of the catalyst generated from $RuHCl(CO)(PPh_3)_3$ and (*R*)-DM-SEGPHOS in the presence of substoichiometric sodium sulfate, furnished homoallylic alcohol **5.9** in 75% yield,

good *syn*-diastereomeric control and high enantioselectivity (18:1 *dr* and 92% *ee*) (Figure 5.3). Using DDQ oxidation, alcohol **5.9** was converted to the

Figure 5.3. Synthesis of vinyl bromide **5.4**.



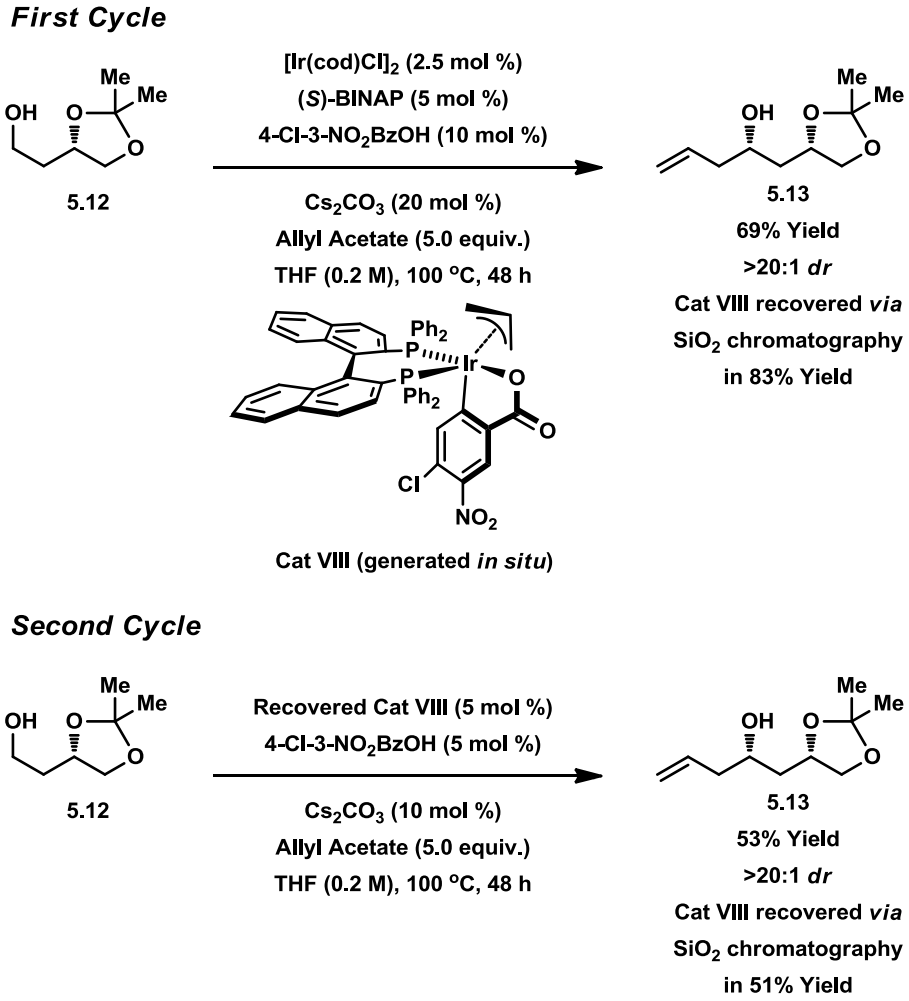
p-methoxybenzilidene acetal **5.10** in 87% yield[33] and then to dibromide **5.11** *via* treatment with pyridinium bromide perbromide. Crude dibromide **5.11** was exposed to sodium methoxide, generating vinyl bromide **5.4**.

5.3.2 Synthesis of Epoxide 5.5

Synthesis of epoxide **5.5** commenced by employment of the iridium-catalyzed alcohol C-H allylation[31,32] of commercially available alcohol **5.12**, which is derived from (*S*)-malic acid (Figure 5.4). Using the cyclometalated iridium catalyst, **Cat VIII**, generated *in situ* from $[Ir(cod)Cl]_2$, 4-chloro-3-nitrobenzoic acid, allyl acetate and (*S*)-BINAP, homoallylic alcohol **5.13** was produced in 69% yield as a single diastereomer, determined by ^1H NMR of the crude reaction mixture.

As previously noted,[34] cyclometalated iridium catalyst such as **Cat VIII** have shown increased stability to conventional silica gel chromatography. Given the evidence that carbonyl addition is turnover limiting,[32] it could be interpreted that stable π-allyl complex **Cat VIII** is a resting state for the catalyst, prompting the recovery and re-subjection of **Cat VIII** to the reaction conditions. Upon

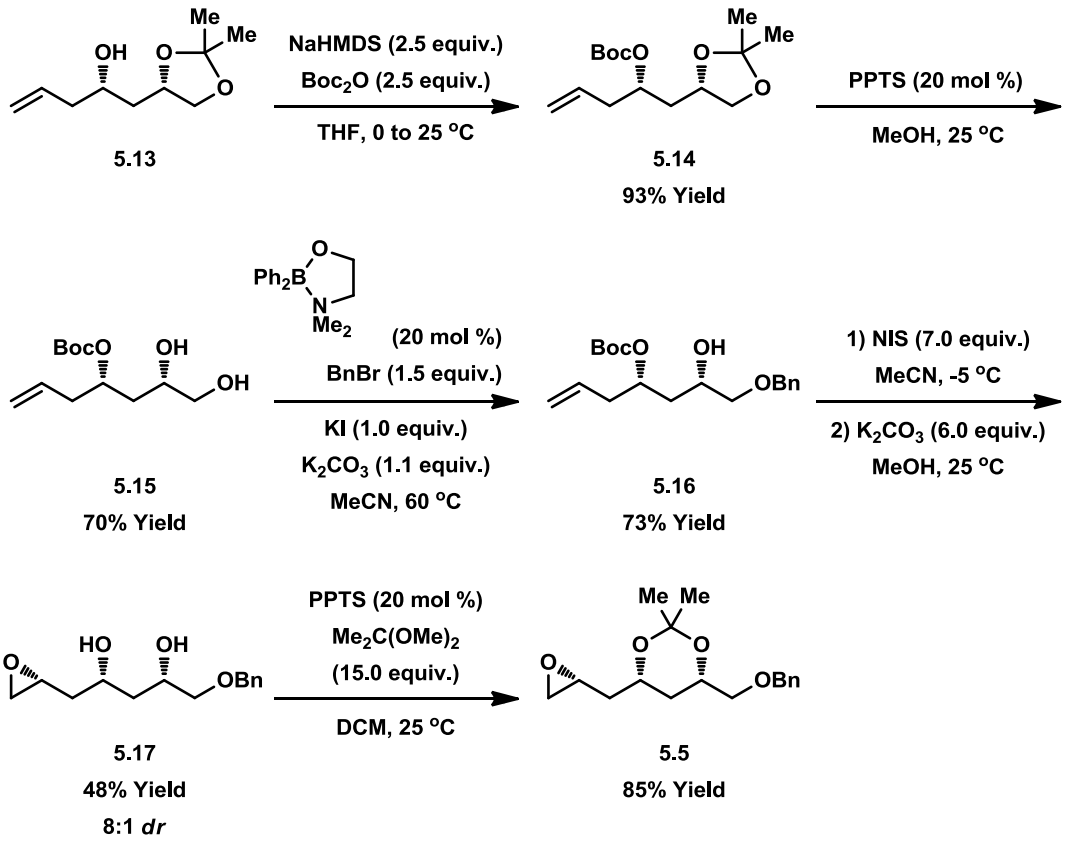
Figure 5.4. Formation of alcohol **5.13** in addition to catalyst recovery and recycling.



re-subjection of **Cat VIII** to the reaction conditions, homoallylic alcohol **5.13** was obtained in 53% yield and equally high diastereomeric ratio as obtained before (Figure 5.4). This represents a novel concept for iridium catalyst of this type. Catalyst recovery and recycling, along with the ability to bypass discrete alcohol-to-aldehyde redox transformations, has rendered this allylation technology more efficient and cost-effective.

To complete the synthesis of epoxide **5.5**, homoallylic alcohol **5.13** was converted to carbonate **5.14**, followed by acid catalyzed methanolysis to remove the acetal protecting group, forming diol **5.15** (Figure 5.5). Primary benzyl protection of diol **5.15** using Taylor's diphenyl borinic acid catalyst[35] was achieved with excellent levels of site-selectivity, furnishing *mono*-benzyl ether *mono*-Boc-carbonate **5.16**. Modified Bartlett halocyclization[36–38] of *mono*-benzyl ether *mono*-Boc-carbonate **5.16** followed by exposure of the crude mixture to potassium carbonate in methanol furnished epoxy diol **5.17** in 48% yield and 8:1 *dr*, favoring the *syn*-diastereomer. Acetonide protection of diol **5.17** delivered epoxide **5.5** in seven steps.

Figure 5.5. Synthesis of epoxide **5.5**.

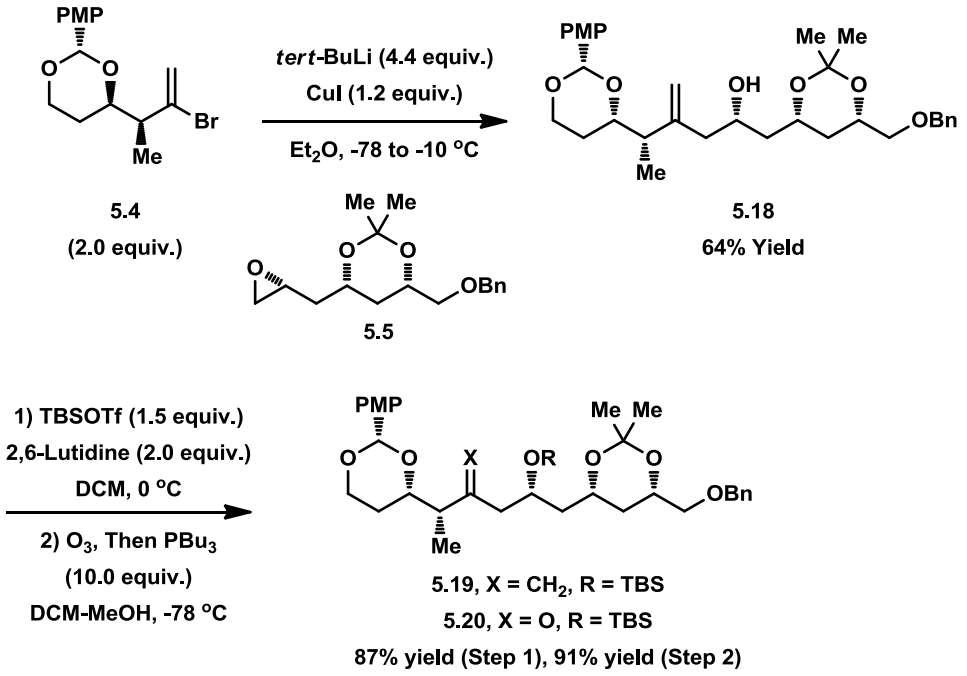


5.3.3 Coupling of Bromide 5.4 and Epoxide 5.5 to Form C9-C20 of Tetrafibricin

To form fragment C9-C20 of tetrafibricin, the cuprate derived from vinyl bromide **5.4** was reacted with epoxide **5.5** (Figure 5.6).[39–42] Initially, it was desired to use the commercially available lithium 2-thienyl(cyano)cuprate solution to form the higher order mixed organocuprate reagent,[40,42] thus limiting the stoichiometry of vinyl bromide **5.4** used in the transformation. Unfortunately this method failed to provide serviceable quantities of alcohol **5.18**. Conversely, using cuprous iodide as the copper source with two equivalents of vinyl bromide **5.4**, product **5.18** was obtained in good yield based on the amount of epoxide **5.5**

used.[39,41] Silyl protection of alcohol **5.18**, followed by ozonolysis of olefin **5.19**, furnished fragment **5.20** in ten linear steps from commercially available alcohol **5.12** and fifteen total steps.

Figure 5.6. Coupling of bromide **5.4** and epoxide **5.5** to form fragment **5.20**.



5.4 Summary

A synthetic route to fragment **5.20** C9-C20 of tetrafibricin has been reported. Only benzyl deprotection and oxidation of the resulting alcohol to the aldehyde remain before fragment **5.1** is delivered, allowing the Julia-Kociensky olefination to be attempted with fragment **5.2** C21-C40 of tetrafibricin. Studies toward the total synthesis of tetrafibricin remain ongoing in the Krische group.

Furthermore, this synthetic exercise led to the observation that the cycolmetalated iridium complex employed in the carbonyl allylation of primary alcohols may be recovered and recycled. The ability to perform multiple rounds

of catalyst recovery and recycling, coupled with the capacity to engage alcohols directly as coupling partners for catalytic C-C bond formation in the absence of alcohol-to-aldehyde redox reactions, makes the present iridium-catalyzed protocol both cost-effective and step-economical.

5.5 Experimental Details

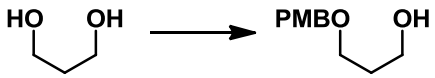
General Information

All reactions were run under inert atmosphere. Tetrahydrofuran was dried over sodium benzophenone ketyl radical and distilled prior to use. Dichloromethane was dried over calcium hydride and distilled prior to use. Other solvents were freshly distilled using standard drying methods prior to use. Commercially available allyl acetate (Sigma-Aldrich) was used directly without further purification. $[Ir(cod)Cl]_2$ and ligands were used as received from Strem Chemicals ((*S*)-BINAP) or Takasago International Corp. ((*R*)-DM-SEGPHOS). Cesium carbonate was purchased from Alfa Aesar and used directly without further purification. Pyridinium bromide perbromide (Sigma-Aldrich) was recrystallized with glacial acetic acid prior to use. All other commercially available reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in p-anisaldehyde solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm).

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, M-H) or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.0 ppm). Optical rotations were performed on an Automatic Polarimeter AP-300 using dichloromethane as

solvent. Enantiomeric excess was measured by Agilent 1200 Series HPLC device using Daicel Chiralcel OJ-H column.

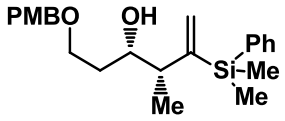
Synthesis of 3-((4-methoxybenzyl)oxy)propan-1-ol (5.7).



5.6 **5.7**

Alcohol **5.7** was prepared from alcohol **5.6** in accordance with the literature procedure.[43]

Synthesis of (3*S*,4*R*)-5-(Dimethyl(phenyl)silyl)-1-(4-methoxybenzyloxy)-4-methylhex-5-en-3-ol (5.9).



To a resealable pressure tube equipped with a magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (727 mg, 0.75 mmol, 5 mol %) and (*R*)-DM-SEGPHOS (550 mg, 0.75 mmol, 5 mol %). The tube was sealed with a rubber septum and purged with nitrogen. Toluene (7.6 mL, 2.0 M concentration with respect to alcohol **1**), diene **5.8** (9.0 mL, 45.7 mmol, 3.0 equiv.), alcohol **5.7** (3.0 g, 15.1 mmol, 1.0 equiv.) and Na_2SO_4 (216 mg, 1.5 mmol, 10 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 95 °C for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated in *vacuo.* The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4)

to give product **5.9** (4.40 g, 11.3 mmol) as a colorless oil in 75% yield and 18:1 dr (*syn*:*anti*).

TLC (SiO_2): R_f = 0.36 (ethyl acetate:hexanes, 1:4).

$[\alpha]_D^{21}$ = +56.9 (*c* 1.0, CH_2Cl_2).

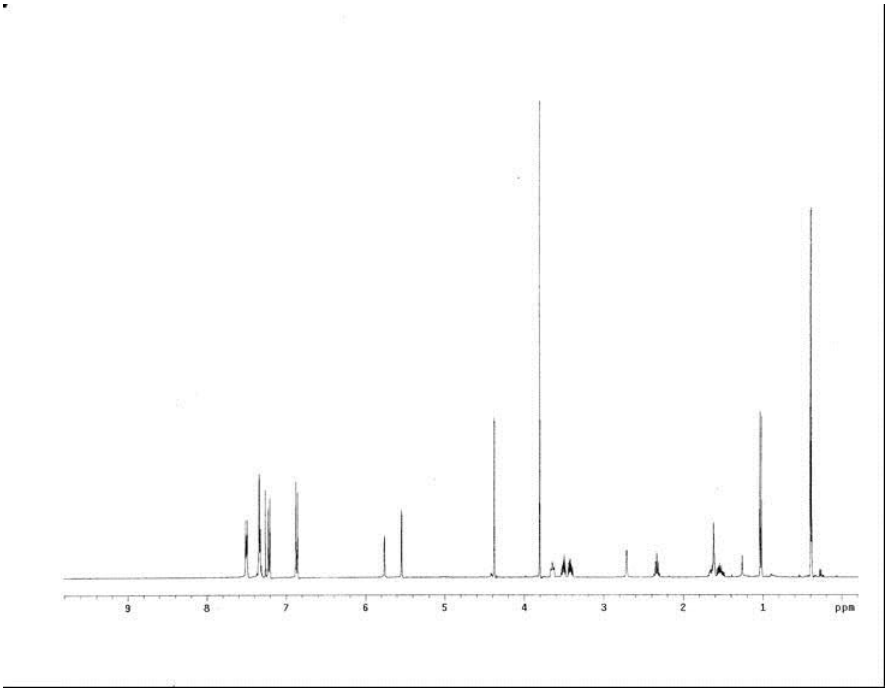
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.47 (m, 2H), 7.38-7.29 (m, 3H), 7.21 (dd, *J* = 2.0, 6.8 Hz, 2H), 6.92-6.82 (m, 2H), 5.76 (dd, *J* = 1.2, 2.8 Hz, 1H), 5.54 (d, *J* = 2.8 Hz, 1H), 4.37 (s, 2H), 3.80 (s, 3H), 3.68-3.60 (m, 1H), 3.50 (ddd, *J* = 4.4, 5.2, 9.2 Hz, 1H), 3.42 (ddd, *J* = 4.4, 8.4, 9.2 Hz, 1H), 2.71 (brs, 1H), 2.33 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.69-1.60 (m, 1H), 1.59-1.47 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.39 (s, 3H), 0.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 153.9, 138.0, 133.9, 130.1, 129.2, 129.0, 127.7, 126.7, 113.7, 73.3, 72.8, 69.0, 55.2, 44.2, 34.3, 15.9, -2.6, -2.7.

FT-IR (neat): v 2956, 1586, 1512, 1427, 1246, 1081, 1035, 815, 774, 733, 700 cm^{-1}.

HPLC Chiralcel OJ-H column, hexanes : *i*-PrOH = 99 : 1, 1.0 mL/min, 254 nm, t_{major} = 71.0 min, t_{minor} = 82.7 min; 92% *ee*

HRMS (ESI) Calcd. for $C_{23}H_{32}NaO_3Si$ $[M+Na]^+$: 407.2012, found: 407.2014.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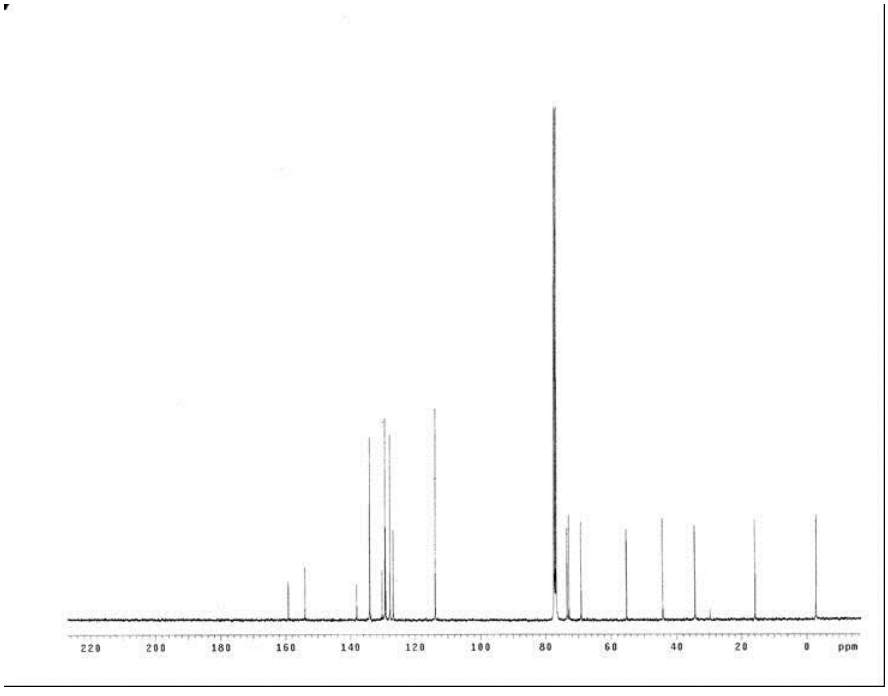
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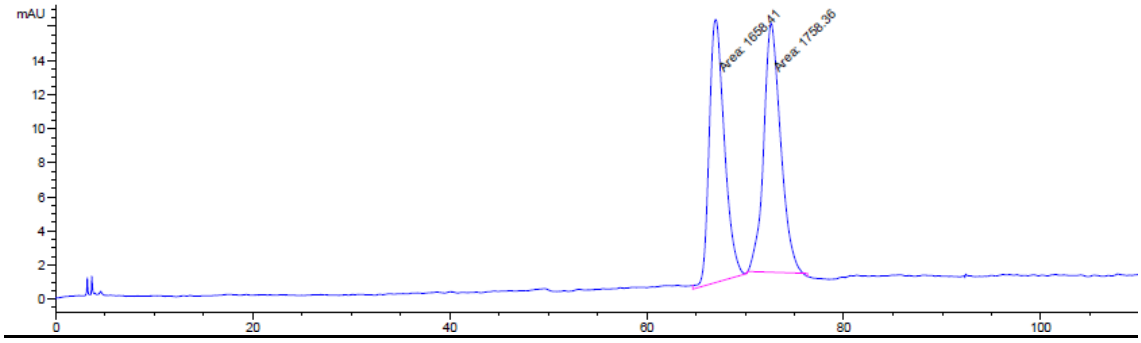
ppm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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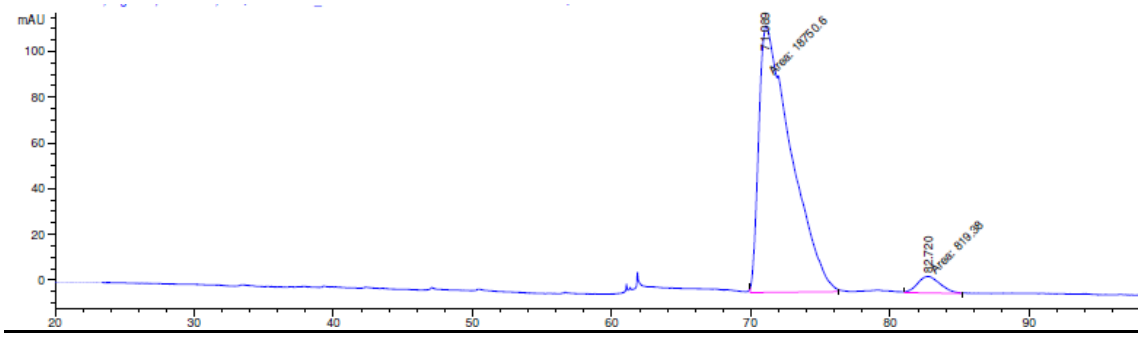
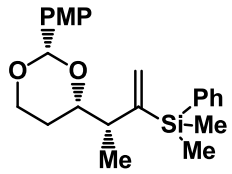
2	72.609	MM	2.0036	1758.35974	14.62631	51.4627
Totals :				3416.76782	30.08223	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	71.089	MM	2.6841	1.87506e4	116.42996	95.8131
2	82.720	MM	1.8878	819.37958	7.23390	4.1869
Totals :				1.95700e4	123.66387	

Synthesis of ((*R*)-3-((2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)but-1-en-2-yl)dimethyl(phenyl)silane (5.10).



To a solution of alcohol **5.9** (2.50 g, 6.5 mmol, 1.0 equiv.), in dichloromethane (50 ml, 0.13 M with respect to alcohol **5.9**) at -15 ^{o}C was added 4Å molecular sieves (2.50 g, 100 wt % with respect to alcohol **5.9**). Then DDQ (1.62 g, 7.1 mmol, 1.1 equiv.) was added in three portions over 5 minutes. The reaction mixture was then stirred for 10 hours, filtered through a pad of celite and washed with dichloromethane (2 × 20 ml). The organics were washed with water, brine, and dried ($MgSO_4$). The organics were concentrated *in vacuo* to give the crude vinyl silane as a yellow oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give vinyl silane **5.10** (2.16 g, 5.66 mmol) as a pale yellow oil in 87% yield.

TLC (SiO_2): R_f = 0.57 (ethyl acetate:hexanes, 1:4).

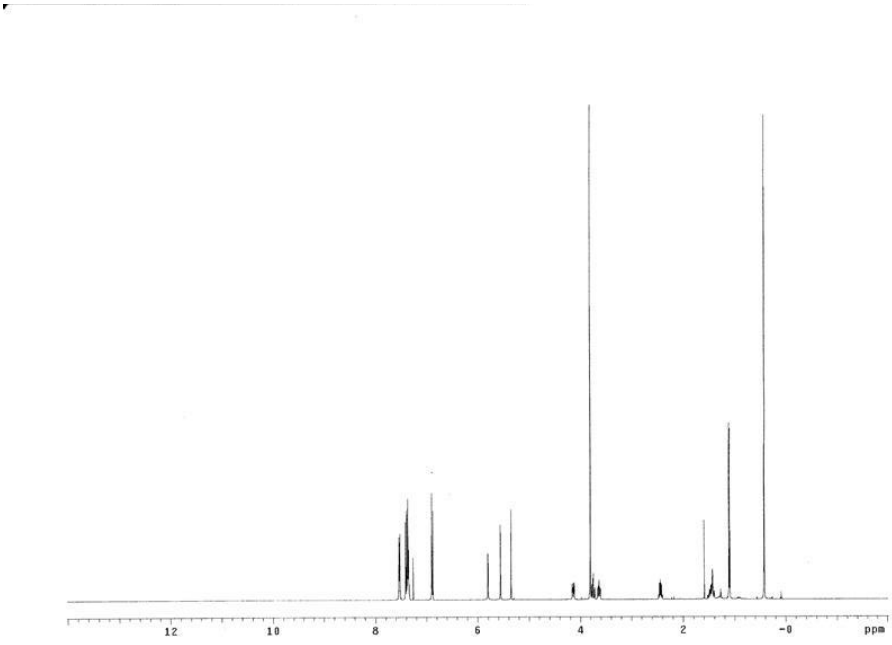
$[\alpha]_D^{22}$ = +25.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.43-7.32 (m, 5H), 6.91-6.86 (m, 2H), 5.80 (dd, *J* = 0.8, 2.4 Hz, 1H), 5.55 (d, *J* = 2.4 Hz, 1H), 5.35 (s, 1H), 4.13 (ddd, *J* = 1.6, 4.8, 11.6 Hz, 1H), 0.41 (s, 3H), 3.80 (s, 3H), 3.75 (dt, *J* = 3.6, 11.6 Hz, 1H), 3.63 (ddd, *J* = 3.2, 8.4, 13.6 Hz, 1H), 2.43 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.54-1.38 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 152.7, 137.8, 133.9, 131.5, 129.0, 127.6, 127.1, 127.0, 113.3, 110.7, 80.4, 67.0, 55.1, 43.9, 29.6, 18.1, -2.7, -2.8.

FT-IR (neat): v 2958, 1615, 1517, 1391, 1247, 1170, 1099, 1035, 816, 775 cm^{-1}.

HRMS (ESI) Calcd. for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$: 405.1856, found: 405.1857.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6
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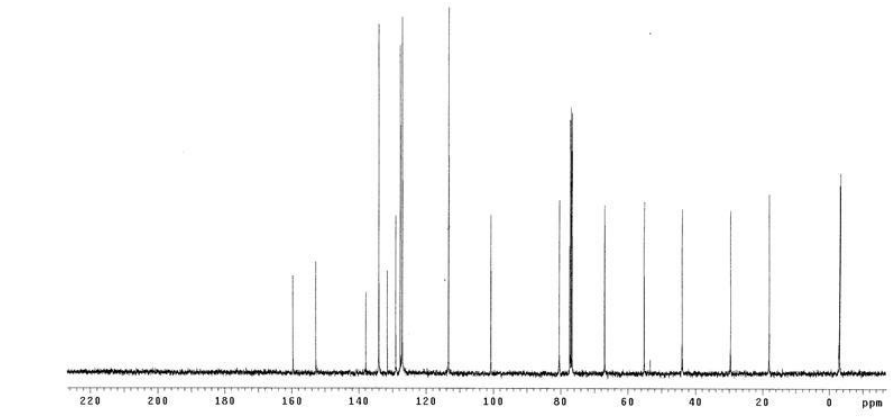
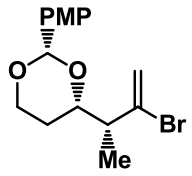
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

Synthesis of (2*S*,4*S*)-4-((*R*)-3-Bromobut-3-en-2-yl)-2-(4-methoxyphenyl)-1,3-dioxane (5.4).



To a solution of vinyl silane **5.10** (1.12 g, 2.95 mmol, 1.0 equiv.) and triethylamine (0.49 mL, 3.54 mmol, 1.2 equiv.) in dichloromethane (14.7 mL, 0.2 M with respect to vinyl silane **5.10**) at 0 °C was added pyridinium bromide perbromide (1.13 g, 3.54 mmol, 1.2 equiv.). The resultant solution was stirred for 0.5 hours and then allowed to warm to ambient temperature. Once at ambient temperature, the reaction solution was charged with triethylamine (0.49 mL, 3.25 mmol, 1.2 equiv.) and a white precipitate formed. The reaction vessel was cooled to 0 °C and pyridinium bromide perbromide (1.13 g, 3.54 mmol, 1.2 equiv.) was added again. The above was repeated 5 more times, or until TLC suggested consumption of starting material. The reaction was quenched with triethylamine (1 mL) and 4% aqueous sodium hydrogen sulfite and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried (Na_2SO_4). The organic layer was concentrated *in vacuo,* and the crude product was taken to the next step.

The dibrominated crude product **5.11** (1.63 g, 2.95 mmol, 1.0 equiv.) was dissolved in methanol (9.8 mL, 0.3 M with respect to product **5.11**) and solid sodium methoxide (0.55 g, 10.33 mmol, 3.5 equiv.) was added. The reaction flask was then fixed with a reflux condenser and placed in an oil bath at 80 °C for 3 hours. The reaction was then allowed to cool to ambient temperature and quenched with water. The reaction was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The

crude material was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:19) to give vinyl bromide **5.4** (756 mg, 2.24 mmol) as a colorless oil in 76% yield.

TLC (SiO_2): R_f = 0.47 (ethyl acetate:hexanes, 1:4).

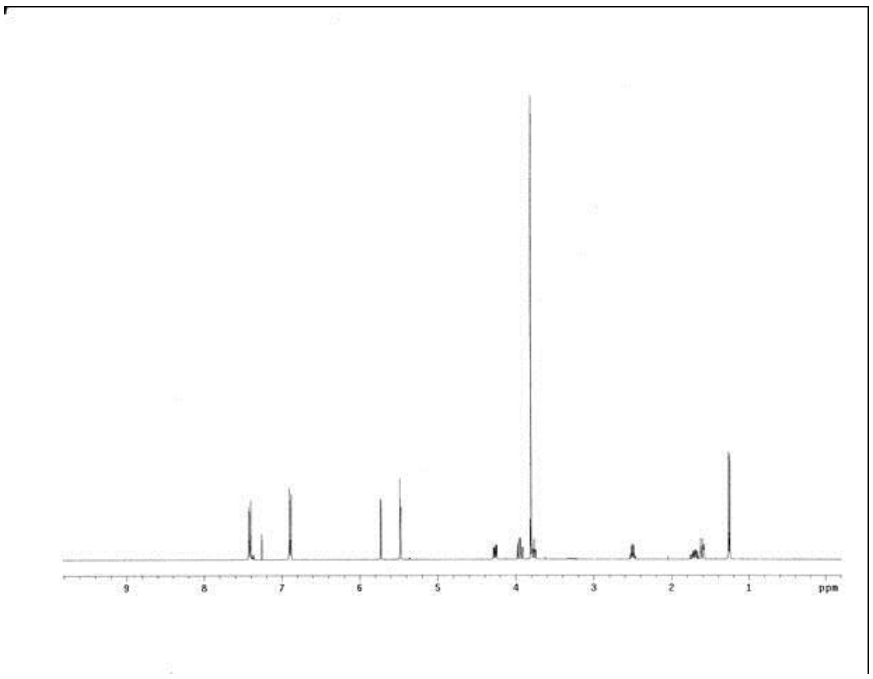
$[\alpha]_D^{25}$ = +21.8 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.39 (m, 2H), 6.92-6.87 (m, 2H), 5.73 (d, *J* = 1.6 Hz, 1H), 5.48 (d, *J* = 0.8 Hz, 1H), 5.47 (d, *J* = 1.6 Hz, 1H), 4.26 (ddd, *J* = 1.2, 4.8, 12.8 Hz, 1H), 3.94 (dt, *J* = 2.8, 12.0 Hz, 1H), 3.80 (s, 3H), 3.77 (tt, *J* = 2.8, 10.8 Hz, 1H), 2.50 (dq, *J* = 6.4, 12.8 Hz, 1H), 1.77-1.66 (m, 1H), 1.64-1.57 (m, 1H), 1.26 (dd, J = 0.8, 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 136.4, 131.2, 127.1, 118.1, 113.4, 100.9, 78.6, 66.8, 55.2, 49.4, 29.4, 16.1.

FT-IR (neat): v 2967, 2836, 1614, 1587, 1427, 1372, 1244, 1211, 1158, 1100, 1033, 978, 945, 826, 779 cm^{-1}.

HRMS (ESI) Calcd. for $C_{15}H_{19}BrNaO_3$ $[M+Na]^+$: 349.0409, found: 349.0405.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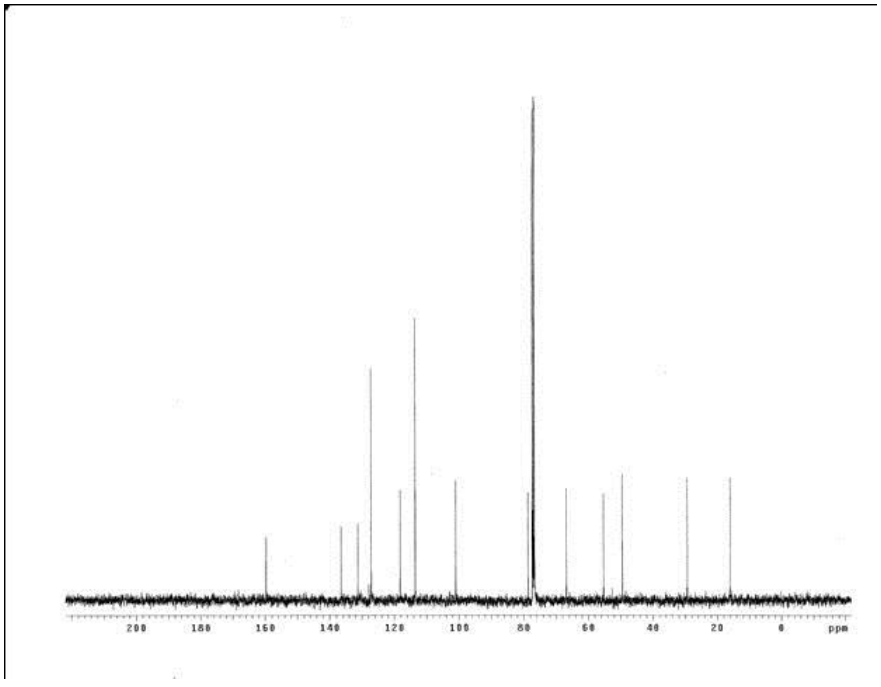
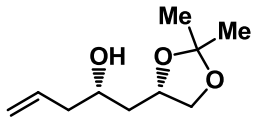

200
180
160
140
120
100
80
60
40
20
0
ppm

Synthesis of (*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (5.13).



A pressure tube was charged with alcohol **5.12** (2.000 g, 13.6 mmol, 1.0 equiv.), $[Ir(cod)Cl]_2$ (0.229 g, 0.34 mmol, 2.5 mol %), (*S*)-BINAP (0.425 g, 0.68 mmol, 5 mol %), 4-chloro-3-nitrobenzoic acid (0.276 g, 1.36 mmol, 10 mol %), and cesium carbonate (0.892 g, 2.73 mmol, 20 mol %). The pressure tube was carefully purged with argon, and tetrahydrofuran (68 mL, 0.2 M with respect to alcohol **5.12**) was added, followed by allyl acetate (8.5 mL, 68.4 mmol, 5.0 equiv.). The pressure tube was sealed and heated at 100 ^{o}C for 72 hours. The reaction mixture was allowed to cool to ambient temperature and then diluted with dichloromethane (50 mL). Solids were filtered off using a pad of celite and rinsed with dichloromethane (2 x 20 mL). The crude reaction mixture was concentrated *in vacuo* to give a brown oil. The crude material was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give alcohol **5.13** (1.74 g, 9.38 mmol) as a single diastereomer in 69% yield. The column was then flushed (ethyl acetate:dichloromethane, 1:1 folowed by diethyl ether:dichloromethane, 1:2) to give catalyst **Cat VIII** (634 mg, 0.59 mmol) as a yellow solid in 83% yield.

Second cycle

A pressure tube was charged with alcohol **5.12** (1.748 g, 11.9 mmol, 1.0 equiv.), 4-chloro-3-nitrobenzoic acid (0.120 g, 0.59 mmol, 5 mol %), and cesium carbonate (0.389 g, 1.2 mmol, 10 mol %) and then purged with argon. Catalyst **Cat VIII** (0.634 g, 0.59 mmol, 5 mol %) was dissolved in tetrahydrofuran (20 mL, 0.6 M with respect to alcohol **5.12**) and cannulated into the reaction vessel. Tetrahydrofuran (40 mL, 0.3 M with respect to alcohol **5.12**) was added followed

by allyl acetate (7.4 mL, 59.8 mmol, 5.0 equiv.). The tube was sealed avoiding air contamination and heated to 100 °C for 72 hours. The reaction mixture was allowed to cool to ambient temperature and then diluted with dichloromethane (50 mL). Solids were filtered off using a pad of celite and rinsed with dichloromethane (2 x 20 mL). Solvents were concentrated *in vacuo* to give a brown oil. The crude material was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give alcohol **5.13 (**1.18 g, 6.3 mmol) as clear oil in 53% yield. The column was then flushed (ethyl acetate:dichloromethane, 1:1 folowed by diethyl ether:dichloromethane, 1:2) to give pure catalyst **Cat VIII** (321 mg, 0.30 mmol) as a yellow solid in 51% yield.

TLC (SiO_2): R_f = 0.56 (ethyl acetate:hexanes, 1:1).

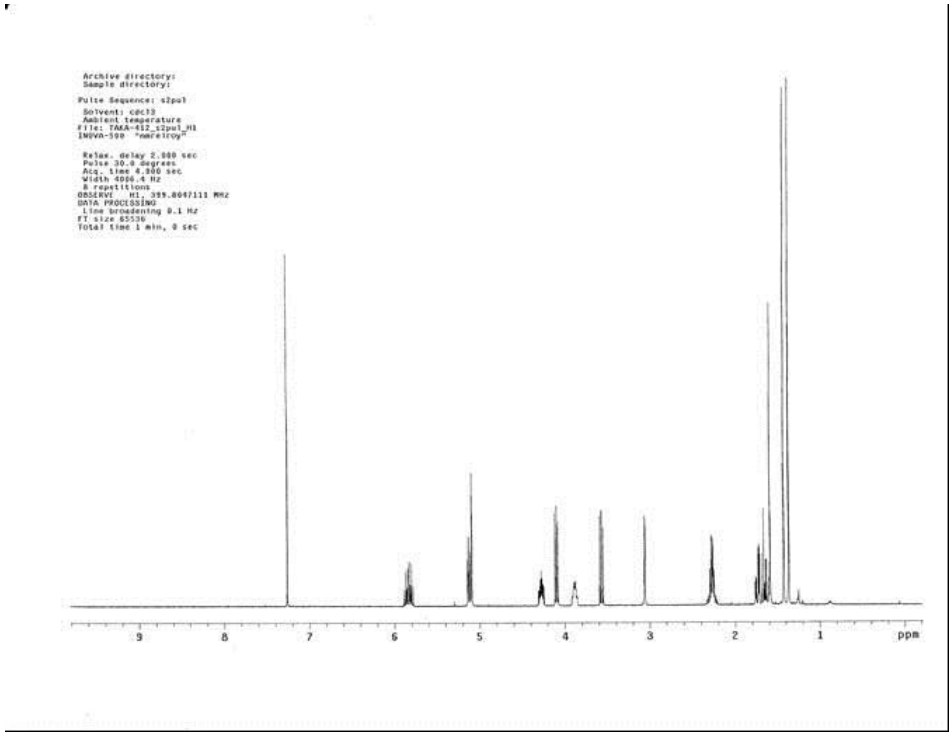
$[\alpha]_D^{26}$ = +12.6 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (ddt, *J* = 7.2, 10.4, 17.6 Hz, 1H), 5.16-5.12 (m, 1H), 5.11-5.04 (m, 1H), 4.32-4.22 (m, 1H), 4.09 (dd, *J* = 7.2, 8.0 Hz, 1H), 3.92-3.84 (m, 1H), 3.56 (dd, *J* = 7.2, 8.0 Hz, 1H), 3.05 (d, *J* = 1.6 Hz, 1H), 2.34-2.20 (m, 2H), 1.73 (ddd, *J* = 2.8, 3.6, 14.0 Hz, 1H), 1.65 (dt, *J* = 9.2, 14.0 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 117.7, 109.3, 75.6, 70.1, 69.6, 41.8, 39.6, 26.8, 25.7.

FT-IR (neat): v 2984, 2935, 1774, 1370, 1215, 1157, 1057, 996, 915, 862 cm^{-1}.

HRMS (ESI) Calcd. for $C_{10}H_{18}NaO_3$ $[M+Na]^+$: 209.1148, found: 209.1147.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Sample directory:
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Solvent: cpcl3
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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 4006.4 Hz
8 repetitions
OBSERVE H1, 399.8047111 MHz
DATA PROCESSING
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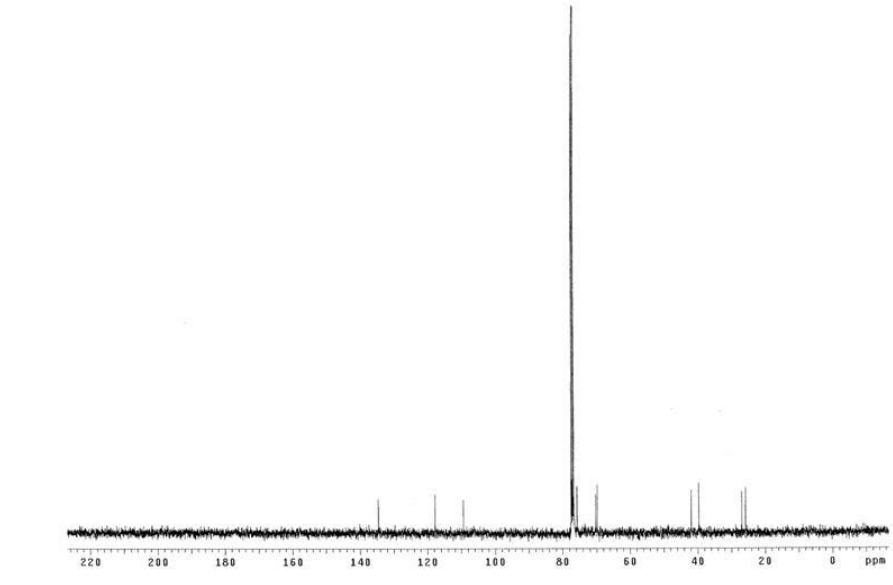
3
2
1
ppm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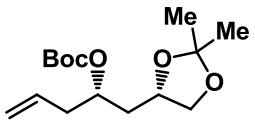
ppm

Synthesis of *tert*-Butyl (*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-yl carbonate (5.14).



Sodium bis(dimethylsilyl)amide (1.0 M in tetrahydrofuran, 21.8 mL, 21.8 mmol, 2.5 equiv.) was added to a solution of alcohol **5.13** (1.62 g, 8.73 mmol, 1.0 equiv.) in tetrahydrofuran (44 mL, 0.2 M with respect to alcohol **5.13**) at 0 °C. After 30 min, di-*tert*-butyldicarbonate (6.29 g, 21.8 mmol, 2.5 equiv.) was added to the reaction mixture at 0 °C. After 10 minutes, the reaction was warmed to ambient temperature and stirred for 1 hour. The reaction was quenched with saturated aqueous sodium chloride and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:19) to give carbonate **5.14** (2.32 g, 8.12 mmol) as a colorless oil in 93% yield.

TLC (SiO_2): R_f = 0.56 (ethyl acetate:hexanes, 1:4).

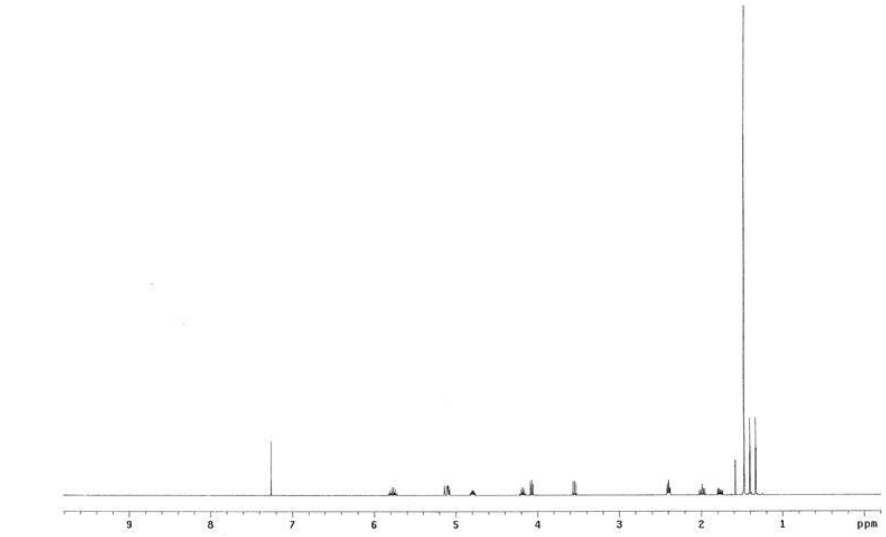
$[\alpha]_D^{20}$ = +22.4 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (ddt, *J* = 7.2, 10.0, 17.2 Hz, 1H), 5.11 (ddd, *J* = 1.2, 3.2, 17.2 Hz, 1H), 5.09 (ddt, *J* = 1.2, 2.0, 10.0 Hz, 1H), 4.79 (dddd, *J* = 4.4, 6.4, 7.6, 12.4 Hz, 1H), 4.22-4.14 (m, 1H), 4.07 (dd, *J* = 5.6, 7.6 Hz, 1H), 3.54 (dd, *J* = 7.2, 7.6 Hz, 1H), 2.43-2.36 (m, 2H), 1.98 (ddd, *J* = 6.4, 7.6, 14.0 Hz, 1H), 1.33 (s, 3H), 1.76 (ddd, *J* = 4.4, 6.4, 14.0 Hz, 1H), 1.47 (s, 9H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 133.1, 118.2, 108.8, 81.9, 73.6, 72.7, 69.3, 38.7, 37.1, 27.7 (3C), 26.9, 25.6.

FT-IR (neat): v 2982, 1736, 1368, 1252, 1159, 1092, 1061, 829, 752 cm^{-1}.

HRMS (ESI) Calcd. for $C_{15}H_{26}NaO_5$ $[M+Na]^+$: 309.1672, found: 309.1668.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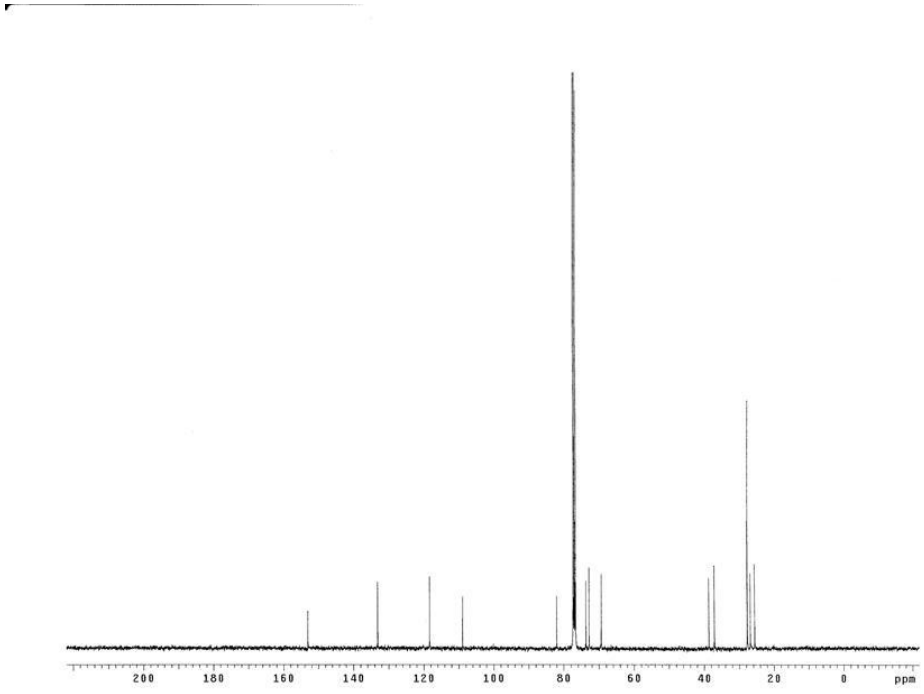
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0
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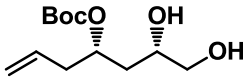
Synthesis of *tert*-Butyl (4*S*,6*S*)-6,7-dihydroxyhept-1-en-4-yl carbonate (5.15).



A solution of carbonate **5.14** (2.0 g, 0.69 mmol, 1.0 equiv.) and pyridinium *p*-toluenesulfonate (400 mg, 20% w/w) in methanol (10 mL, 0.07 M with respect to carbonate **5.14**) was stirred at ambient temperature under argon for 24 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:1) to give diol **5.15** (1.20 g, 0.48 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 2:1).

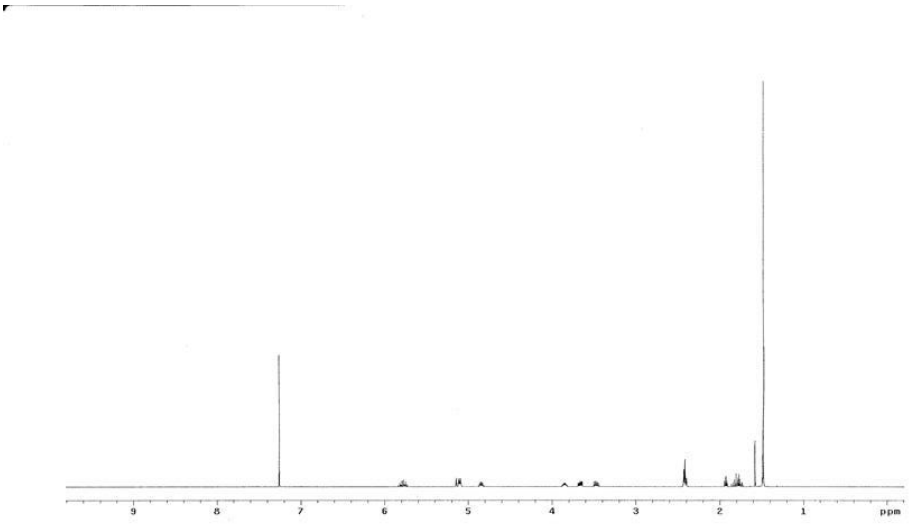
$[\alpha]_D^{21}$ = +28.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 7.2, 10.4, 17.2 Hz, 1H), 5.13 (ddd, *J* = 1.6, 3.6, 12.8 Hz, 1H), 5.10-5.07 (m, 1H), 4.80-4.89 (m, 1H), 3.90-3.80 (m, 1H), 3.66 (ddd, *J* = 3.6, 6.4, 11.2 Hz, 1H), 3.47 (ddd, *J* = 5.6, 7.6, 11.2 Hz, 1H), 2.44-2.38 (m, 3H), 1.92 (t, *J* = 6.0 Hz, 1H), 1.81 (ddd, *J* = 7.6, 14.8, 22.4 Hz, 1H), 1.75 (ddd, *J* = 4.8, 10.0, 14.8 Hz, 1H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 133.0, 118.3, 82.2, 74.4, 69.6, 66.4, 38.8, 37.0, 27.7.

FT-IR (neat): v 3375, 2980, 1735, 1394, 1276, 1252, 1159, 1089, 915, 879, 732 cm^{-1}.

HRMS (ESI) Calcd. for $C_{12}H_{22}NaO_5$ $[M+Na]^+$: 269.1359, found: 269.1356.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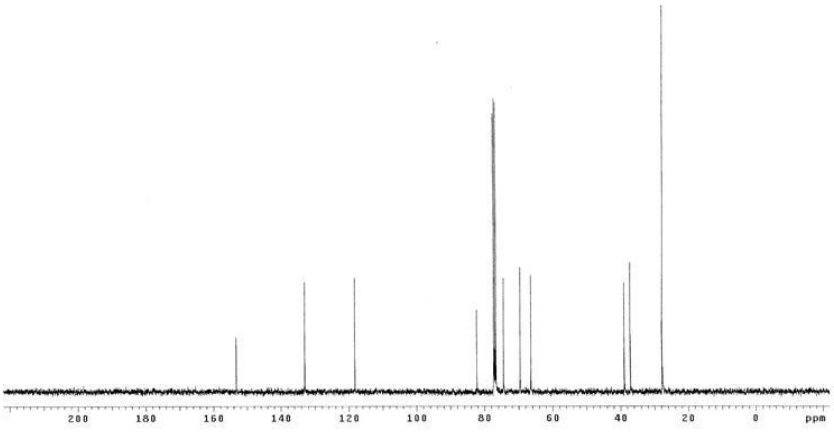
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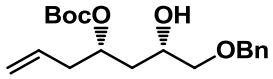
Synthesis of (4S,6S)-7-(benzyloxy)-6-hydroxyhept-1-en-4-yl tert-butyl carbonate (5.16).



To an oven-dried round-bottom flask equipped with a magnetic stir bar was added diphenyl borinic acid (54.8 mg, 0.12 mmol, 20 mol %), potassium iodide (202.2 mg, 1.22 mmol, 1.0 equiv.), and potassium carbonate (185.2 mg, 1.34 mmol, 1.1 equiv.). The round-bottom flask was sealed with a rubber septum and purged with argon. Dry acetonitrile (6.0 ml, 0.2 M with respect to diol **5.15**) followed by diol **5.15** (300 mg, 1.22 mmol, 1.0 equiv.) and benzyl bromide (0.211 ml, 1.83 mmol, 1.5 equiv.) were added, and the reaction was stirred for 48 hours at 60 °C. The reaction was allowed to cool to ambient temperature, poured into a separatory funnel containing water, and extracted with ethyl acetate. The organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give carbonate **5.16** (303 mg, 0.89 mmol) as a colorless oil in 73% yield.

TLC (SiO_2): R_f = 0.44 (ethyl acetate:hexanes, 1:4).

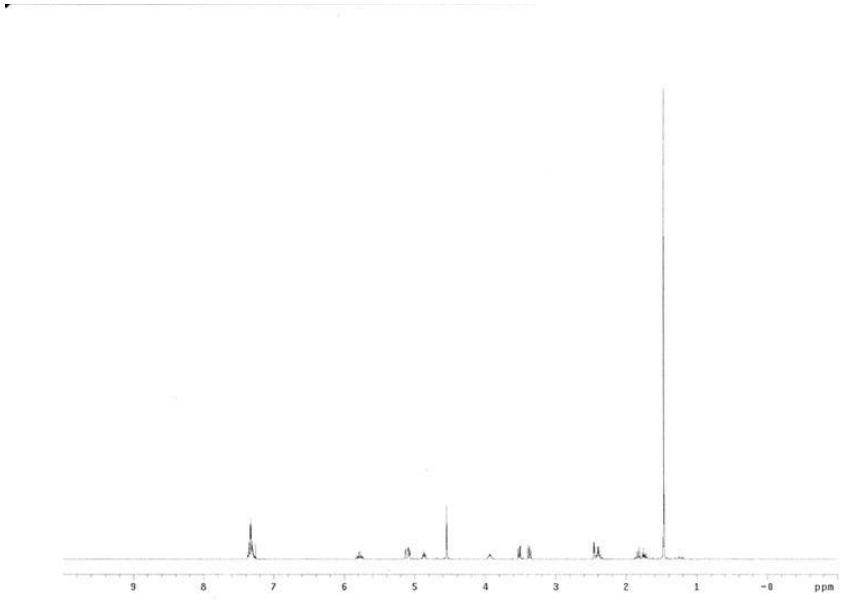
$[\alpha]_D^{22}$ = +7.0(*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.78 (ddt, *J* = 5.6, 10.0, 17.2 Hz, 1H), 5.15-5.07 (m, 2H), 4.87 (ddd, *J* = 5.6, 7.2, 12.8 Hz, 1H), 4.55 (s, 2H), 3.97-3.90 (m, 1H), 3.52 (dd, *J* = 3.2, 9.2 Hz, 1H), 3.37 (dd, *J* = 6.8, 9.2 Hz, 1H), 2.46-2.35 (m, 3H), 1.92-1.79 (m, 1H), 1.74 (ddd, *J* = 5.2, 10.4, 19.6 Hz, 1H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 137.9, 133.2, 128.4, 127.8, 127.7, 127.7, 118.1, 81.9, 74.1, 74.0, 67.8, 42.0, 38.7, 37.1, 27.8.

FT-IR (neat): v 3457, 2979, 2922, 1735 1454, 1368, 1277, 1253, 1162, 1093, 996, 918, 831, 792, 738, 698 cm^{-1}.

HRMS (ESI) Calcd. for $C_{19}H_{28}NaO_5$ $[M+Na]^+$: 359.1838, found: 359.1829.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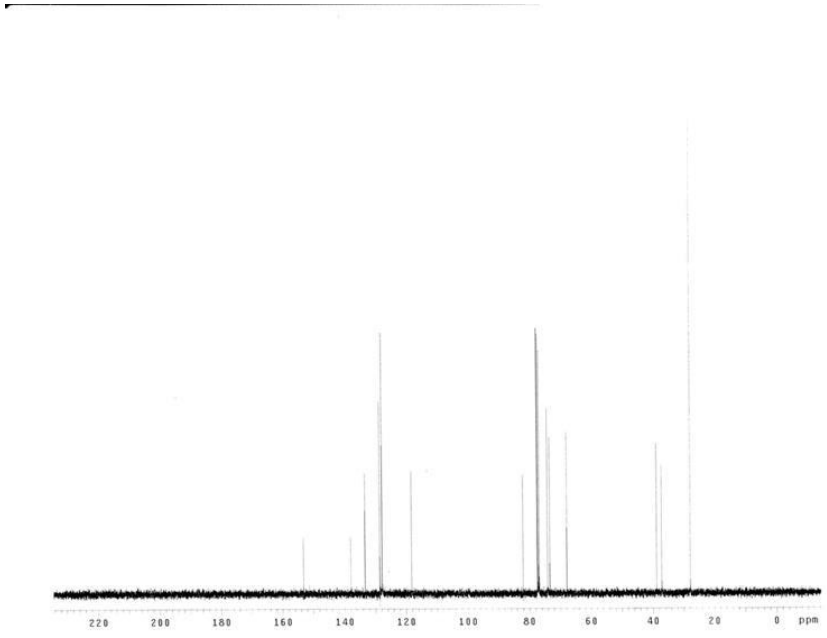
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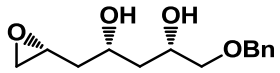
ppm

Synthesis of (2S,4R)-1-(benzyloxy)-5-((R)-oxiran-2-yl)pentane-2,4-diol (5.17).



To a solution of carbonate **5.16** (100 mg, 0.3 mmol, 1.0 equiv.) in dry acetonitrile (1.7 mL, 0.18 M with respect to carbonate **5.16**) at -40 °C was added *N*-iodosuccinamide (472 mg, 2.1 mmol, 7.0 equiv.). The reaction mixture was allowed to warm to 0 °C and stirred for 16 hours, at which point it was quenched with aqueous sodium thiosulfate and extracted with diethyl ether. The organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil that was subjected to the next step.

The crude reaction mixture was then dissolved in methanol (6.0 mL, 0.05 M with respect to carbonate **5.16**) and potassium carbonate (250 mg, 1.8 mmol, 6.0 equiv.) was added to the solution. The reaction was stirred at ambient temperature for 2 hours, quenched with a 1:1 saturated sodium thiosulfate: saturated sodium bicarbonate solution, and extracted with diethyl ether. The organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as an opaque oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:1) to give epoxide **5.17** (36 mg, 0.14 mmol) as a colorless oil in 48% yield over two steps and 8:1 dr (*syn*:*anti*).

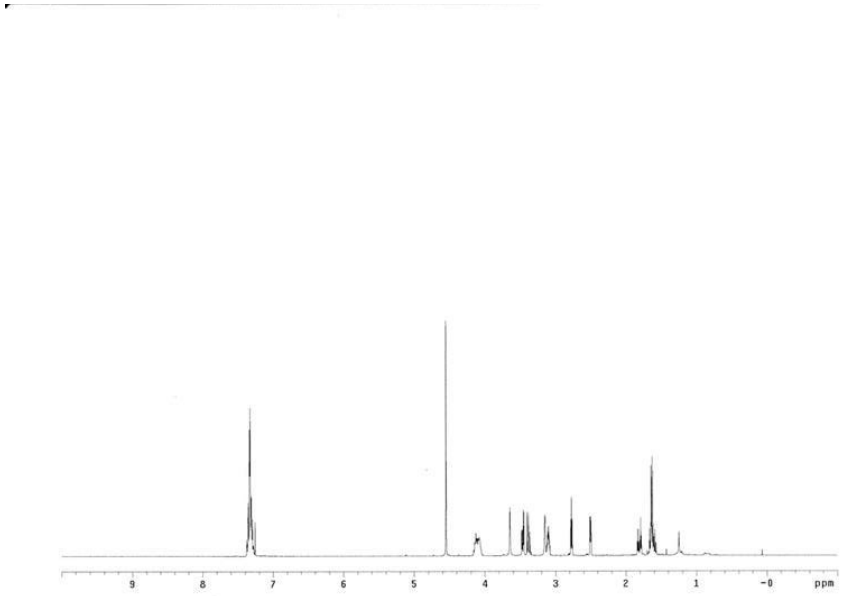
TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:1).
$[\alpha]_D^{22}$ = +4.4 (*c* 1.0, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 4.56 (s, 2H), 4.16-4.07 (m, 2H), 3.6 (brs, 1H), 3.47 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.39 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.13-

3.08 (m, 2H), 2.78 (dd, *J* = 4.0, 4.8 Hz, 1H), 2.51 (dd, *J* = 2.8, 4.8 Hz, 1H), 1.82 (dt, *J* = 4.4, 14.4 Hz, 1H), 1.67-1.58 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 128.5, 127.9, 127.8, 74.2, 73.4, 71.2, 70.1, 49.8, 46.6, 40.0, 39.0.

FT-IR (neat): v 3415, 2922, 2855, 1496, 1453, 1364, 1316, 1259, 1206, 1097, 1028, 845, 740, 699 cm^{-1}.

HRMS (ESI) Calcd. for $C_{14}H_{20}NaO_4$ $[M+Na]^+$: 275.1261 found: 275.1254.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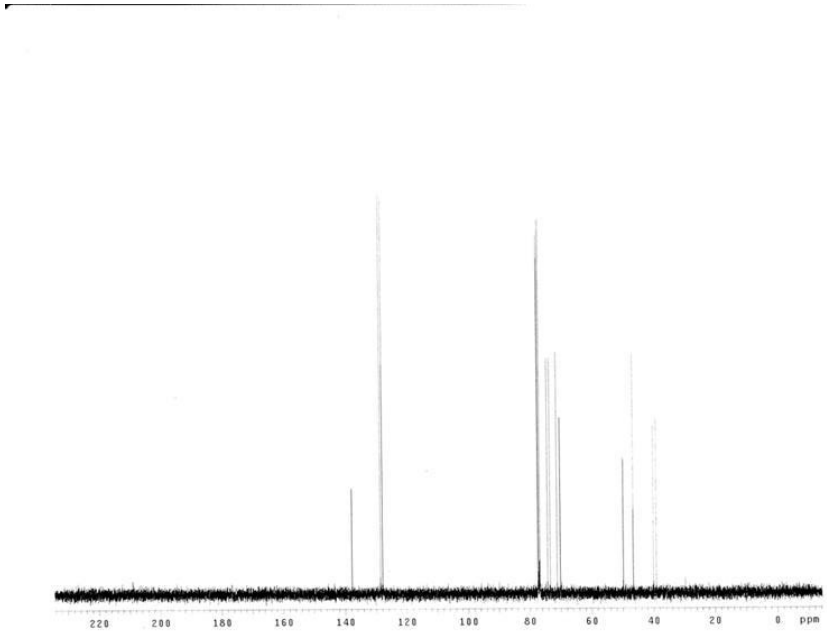
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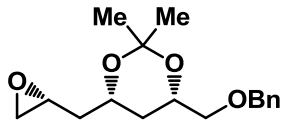
Synthesis of (4S,6S)-4-((benzyloxy)methyl)-2,2-dimethyl-6-((R)-oxiran-2-ylmethyl)-1,3-dioxane (5.5).



To a solution of epoxide **5.17** (98.4 mg, 0.39 mmol, 1.0 equiv.) in dichloromethane (3.9 ml, 0.1 M with respect to epoxide **5.17**) was added 2,2-dimethoxypropane (0.725 mL, 5.85 mmol, 15.0 equiv.) followed by pyridinium *p*-toluenesulfonate (19.6 mg, 0.078 mmol, 20 mol%). The reaction mixture was stirred for 14 hours at ambient temperature then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as a colorless oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give epoxide **5.5** (96.9 mg, 0.33 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.57 (ethyl acetate:hexanes, 1:4).

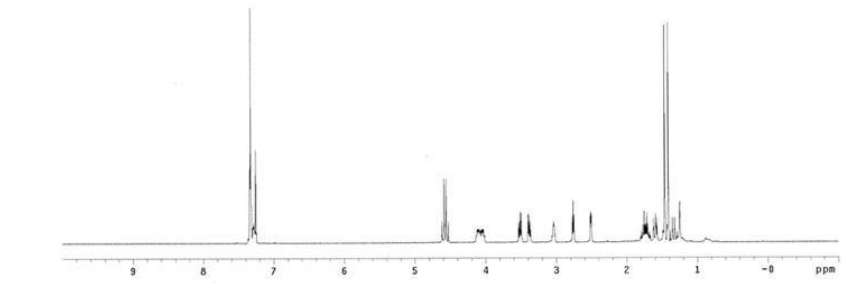
$[\alpha]_D^{22}$ = -13.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.14-4.01 (m, 2H), 3.51 (dd *J* = 6.0, 10.0 Hz, 1H), 3.39 (dd, *J* = 5.2, 10.0 Hz, 1H), 3.06-3.02 (m, 1H), 2.76 (dd, *J* = 4.4, 5.2 Hz, 1H), 2.51 (dd *J* = 2.8, 4.8 Hz, 1H), 1.81-1.67 (m, 2H), 1.63-1.59 (m, 2H), 1.47 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.4, 127.7, 127.6, 98.7, 73.5, 73.5, 68.4, 66.1, 48.8, 46.7, 38.8, 33.4, 30.1, 19.8.

FT-IR (neat): v 2992, 2918, 2861, 1454, 1380, 1263, 1200, 1171, 1106, 1028, 944, 837, 739, 699 cm^{-1}

HRMS (ESI) Calcd. for $C_{17}H_{28}NO_4$ $[M+NH_4]^+$: 310.2016, found: 310.2013.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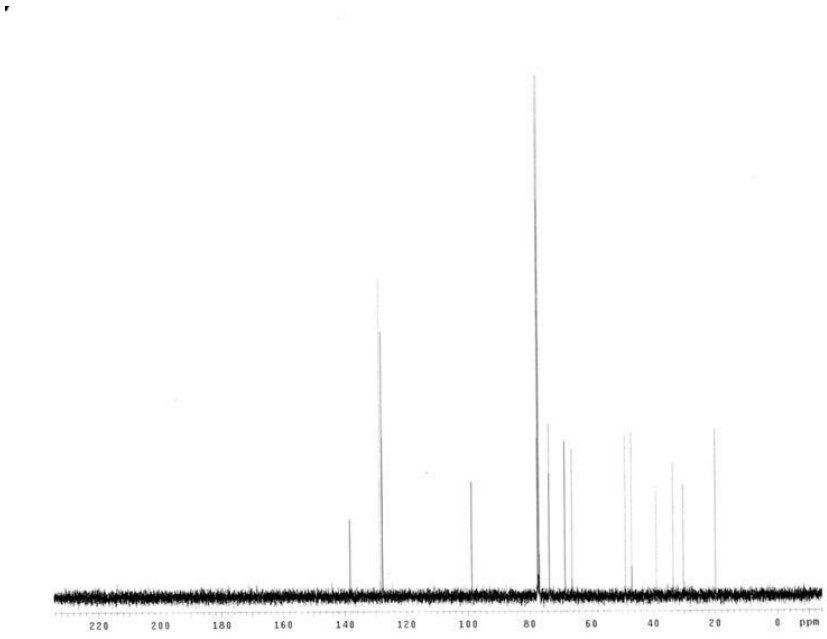
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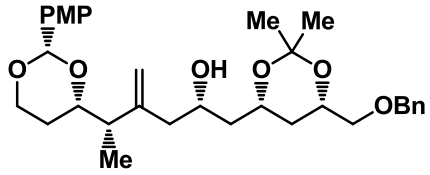
Synthesis of (2*S*,5*S*)-1-((4*S*,6*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-((2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-4-methylenehexan-2-ol (5.18).



To a solution of vinyl bromide **5.4** (200 mg, 0.61 mmol, 2.0 equiv.), in diethyl ether (1.01 ml, 0.284 M with respect to epoxide **5.5**) at -78 ^{o}C was added a solution of *tert*-butyl lithium (0.792 ml, 1.35mmol, 1.7 M, 4.4 equiv.). The reaction mixture was stirred for 2 hours at -78 °C. Then a heterogeneous solution of cuprous iodide (69.7 mg, 0.37 mmol, 1.2 equiv.) in diethyl ether (1.13 ml, 0.271 M with respect to epoxide **5.5**) was added, and the reaction was allowed to warm from -78 to -40 °C over two hours, during which the reaction turned black. Next, the reaction mixture was cooled to -78 °C, and a solution of epoxide **5.5** (89.4 mg, 0.31 mmol, 1.0 equiv.) in diethyl ether (0.735 ml, 0.416 M with respect to epoxide **5.5**) was added. The reaction mixture was allowed to warm to -10 °C over 2 hours. The reaction was then quenched with aqueous ammonium chloride and extracted with ethyl acetate. The organics were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as dark-colored oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:4) to give alcohol **5.18** (99.3 mg, 0.18 mmol) as a colorless oil in 64% yield.

TLC (SiO_2): R_f = 0.17 (ethyl acetate:hexanes, 1:4).

$[\alpha]_D^{22}$ = -21.8 (*c* 1.0, CH_2Cl_2).

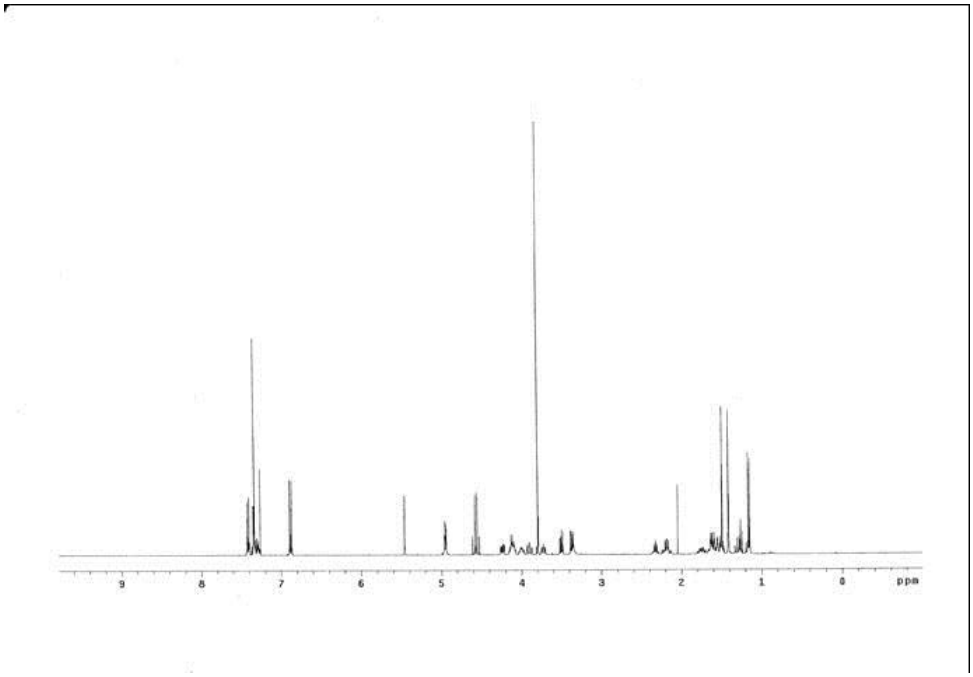
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.39 (m, 2H), 7.38-7.32 (m, 4H), 7.31-7.26 (m, 1H), 6.90-6.87 (m, 2H), 5.45 (s, 1H), 4.95 (s, 1H), 4.91 (s, 1H), 4.59 (d, *J* =

12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.23 (ddd, *J* = 1.2, 4.8, 11.2 Hz, 1H), 4.16-4.05 (m, 2H), 4.04-3.95 (m, 1H), 3.90 (dt, *J* = 2.4, 12.0 Hz, 1H), 3.79 (s, 3H), 3.72 (ddd, *J* = 2.4, 8.0, 10.4 Hz, 1H), 3.49 (dd, *J* = 5.6, 10.0 Hz, 1H), 3.36 (dd, *J* = 4.8, 10.0 Hz, 1H), 3.35 (brs, 1H), 2.38-2.28 (m, 1H), 2.21 (dd, *J* = 7.6, 14.4 Hz, 1H), 2.15 (dd, *J* = 5.2, 14.4 Hz, 1H), 1.81-1.69 (m, 1H), 1.68-1.58 (m, 3H), 1.49 (s, 3H), 1.57-1.46 (m, 1H), 1.41 (s, 3H), 1.34-1.23 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.0, 138.0, 131.4, 128.3, 127.7, 127.6, 127.1, 113.4, 112.6, 100.9, 98.7, 80.1, 73.4, 73.3, 69.6, 69.3, 68.3, 67.0, 55.2, 45.2, 43.4, 42.6, 33.8, 30.3, 29.2, 19.8, 16.4.

FT-IR (neat): v 2914, 2858, 1587, 1428, 1380, 1246, 1200, 1099, 1033, 873, 778, 730 cm^{-1}.

HRMS (ESI) Calcd. for $C_{32}H_{44}NaO_7$ $[M+Na]^+$: 563.2976, found: 563.2979.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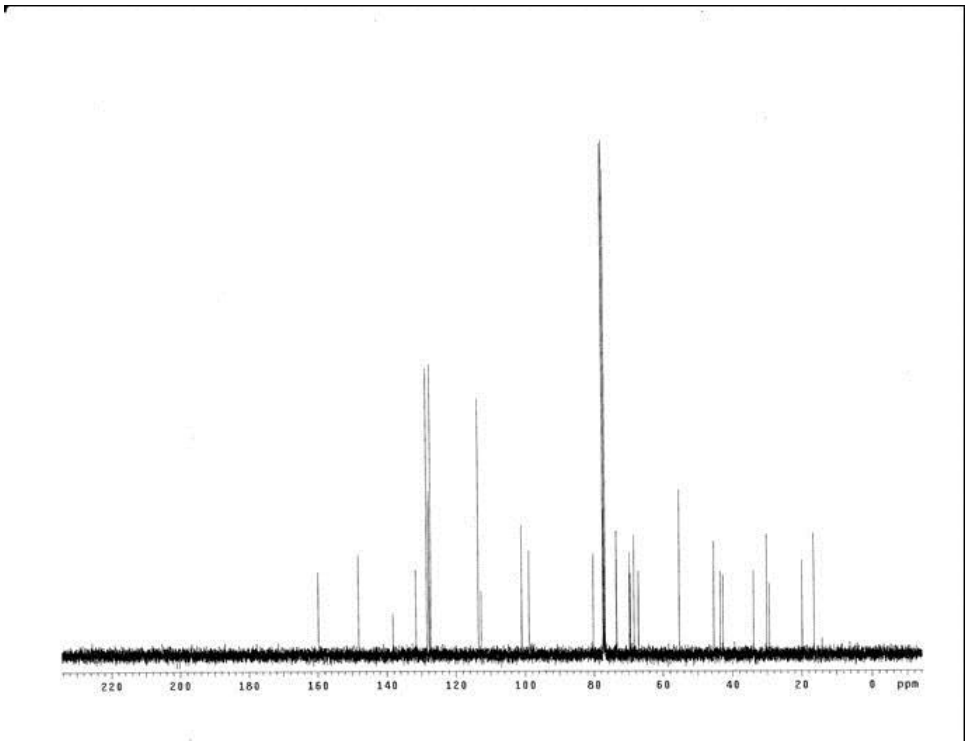
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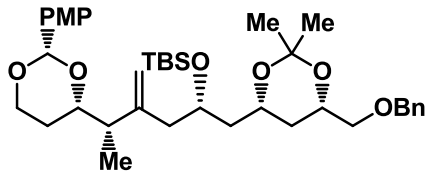
Synthesis of ((2*S*,5*S*)-1-((4*R*,6*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-((2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-4-methylenehexan-2-yloxy)(tert-butyl)dimethylsilane (5.19).



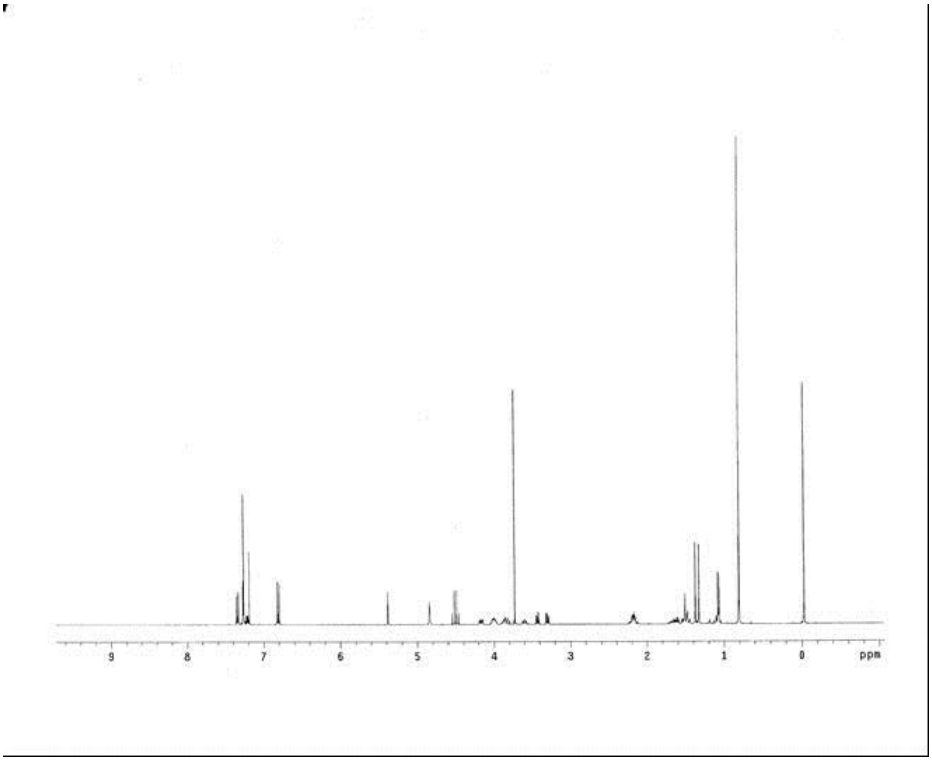
To a solution of alcohol **5.18** (242 mg, 0.35 mmol, 1.0 equiv.) and 2,6-lutidine (82 µL, 0.70 mmol, 2.0 equiv.) in dry dichloromethane (3.5 mL, 0.1 M with respect to alcohol **5.18**) at 0 °C under an atmosphere of argon was added TBSOTf (130 µL, 0.52 mmol, 1.5 equiv.). The reaction was stirred at 0 °C for 1 hour, warmed to ambient temperature and quenched with water. The reaction mixture was extracted with ethyl acetate. The organics were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to give olefin **5.19** (264 mg, 0.31 mmol) as a colorless oil in 87% yield.

TLC (SiO_2): R_f = 0.65 (ethyl acetate:hexanes, 1:3).

$[\alpha]_D^{22}$ = 5.62 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H), 7.36-7.32 (m, 4H), 7.32-7.26 (m, 1H), 6.92-6.85 (m, 2H), 5.45 (s, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.23 (ddd, *J* = 1.2, 5.2, 11.6 Hz, 1H), 4.14-4.02 (m, 2H), 3.88-3.84 (m, 2H), 3.79 (s, 3H), 3.67 (ddd, *J* = 2.0, 7.6, 10.8 Hz, 1H), 3.49 (dd, *J* = 5.6, 10.0 Hz, 1H), 3.37 (dd, *J* = 4.8, 10.0 Hz, 1H), 2.32-2.18 (m, 3H), 1.81-1.65 (m, 2H), 1.63-1.50 (m, 4H), 1.44 (s, 3H), 1.40 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 147.6, 138.2, 131.4, 128.3, 127.6, 127.5, 127.1, 113.4, 113.1, 100.9, 98.5, 80.7, 73.6, 73.3, 68.5, 67.5, 67.0, 65.7, 55.2, 44.9, 44.6, 43.2, 33.7, 30.1, 29.3, 25.8 (3C), 19.6, 17.9, 16.4, -4.0, -4.4.
FT-IR (neat): v 2928, 2854, 1517, 1378, 1247, 1101, 1035, 774, 733, 697 cm^{-1}.
HRMS (ESI) Calcd. for $C_{38}H_{62}NO_7Si$ $[M+NH_3]^+$: 672.4295, found: 672.4290.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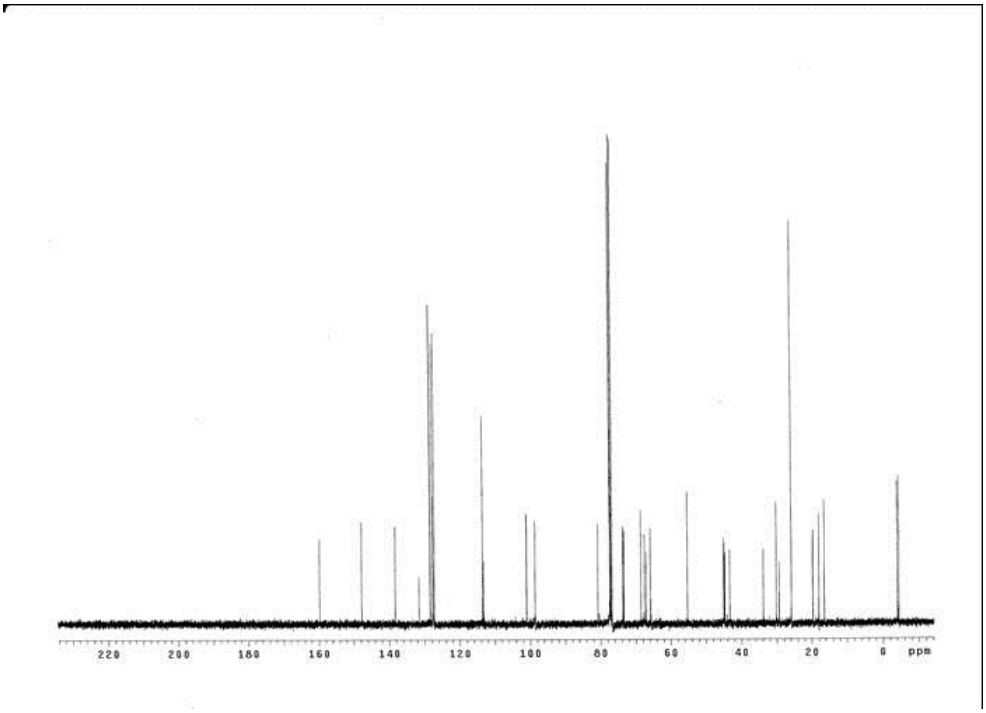
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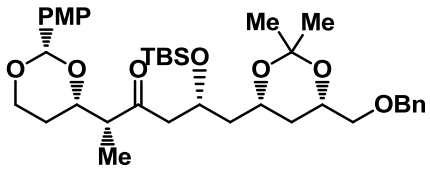
Synthesis of (2R,5R)-6-((4R,6S)-6-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-((tert-butyldimethylsilyl)oxy)-2-((2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)hexan-3-one (5.20).



To a solution of olefin **5.19** (50 mg, 0.076 mmol, 1.0 equiv.) in methanol (0.38 ml, 0.2 M with respect to olefin **5.19**) and dichloromethane (0.38 ml, 0.2 M with respect to olefin **5.19**) was added two drops of a saturated solution of Sudan III in MeOH. The reaction mixture was cooled to -78 °C and ozone was bubble through the solution until the color began to lighten (~8 min). Next, two balloons of argon gas were bubbled through the solution. Tributylphosphine (0.2 ml, 0.81 mmol, 10.5 equiv.) was then added, and the reaction mixture was stirred at –78 °C for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as an orange oil. The crude product was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:9) to give ketone **5.20** (45.6 mg, 0.069 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:4).

$[\alpha]_D^{22}$ = -17.2 (*c* 1.0, CH_2Cl_2).

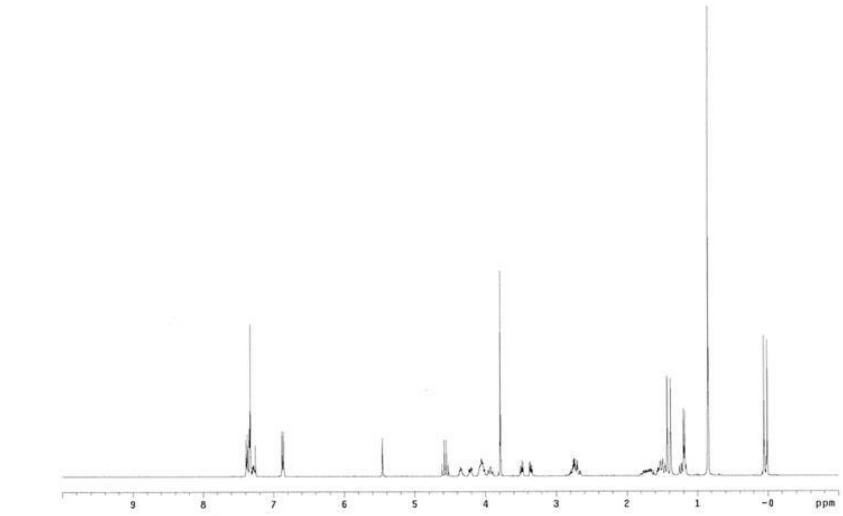
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (m, 2H), 7.35-7.32 (m, 4H), 7.31-7.27 (m, 1H), 6.89-6.85 (m, 2H), 5.46 (s, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.38-4.32 (m, 1H), 4.22 (ddd, *J* = 1.2, 4.8, 11.6 Hz, 1H), 4.10-4.01 (m, 3H), 3.97-3.90 (m, 1H), 3.79 (s, 3H), 3.49 (dd, *J* = 6.0, 10.0 Hz, 1H), 3.36 (dd,

J = 5.2, 10.4 Hz, 1H), 2.87-2.66 (m, 3H), 1.80-1.65 (m, 2H), 1.57-1.46 (m, 4H), 1.43 (s, 3H), 1.38 (s, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 159.8, 138.2, 131.2, 128.4, 127.7, 127.6, 127.3, 127.2, 113.5, 101.1, 98.5, 77.6, 73.4, 68.6, 66.7, 65.2, 65.1, 55.3, 52.0, 50.1, 43.7, 34.0, 30.2, 28.9, 25.8 (3C), 19.7, 17.9, 12.4, -4.6.

FT-IR (neat): v 2955, 2927, 2854, 1713, 1615, 1518, 1463, 1379, 1249, 1201, 1170, 1105, 1035, 832, 777, 737, 698 cm^{-1}.

HRMS (ESI) Calcd. for $C_{37}H_{60}NO_8Si$ $[M+NH_4]^+$: 674.4089, found: 674.4083.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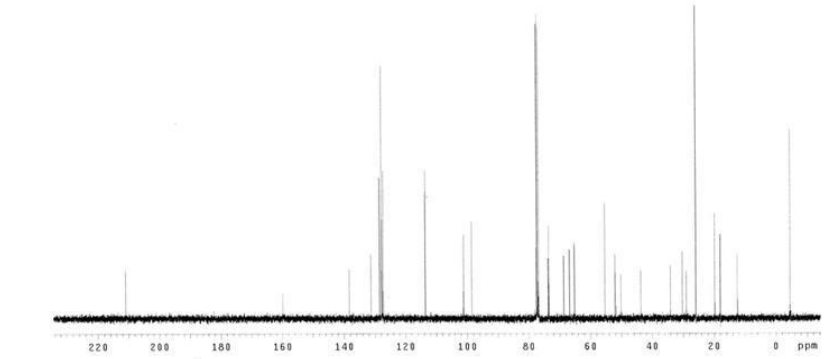
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Chapter 6: Ruthenium-Catalyzed Hydroaminoalkylation: Utilizing Pyrrolidine as an Imine Surrogate

6.1 Introduction

A fundamental issue in organic chemistry remains the efficient construction of carbon-carbon bonds. It has been found that the hydrogenation of π-unsaturates in the presence of carbonyl compounds promotes C-C bond formation through reductive coupling.[1] Furthermore, a collection of redox-triggered carbonyl additions have been introduced, wherein hydrogen transfer from alcohols to π-unsaturates delivers transient carbonyl-organometallic pairs, which combine to furnish products of formal alcohol C-H activation or "hydrohydroxyalkylation."[1–4] Expanding the scope of this technology to include the reductive coupling of π-unsaturates and imines as coupling partners has been demonstrated.[5–9] Unfortunately, the idea of using amines as transient imines has proven much more futile.

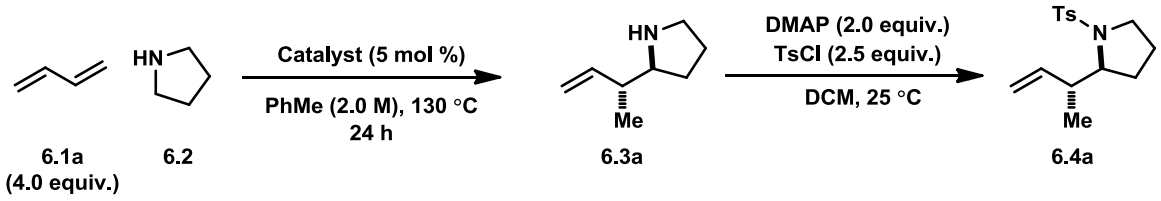
Although several early transition metal-based catalyst for hydroaminoalkylation have been described,[10–14] the development of related late transition metal-catalyzed amine C-H functionalizations have proven challenging.[10–23] With the exception of the ruthenium(0) catalyzed hydroaminoalkylation of dienes with hydantoins,[24] all other late-transition-metal catalyst for the coupling of amines and π-unsaturates require pyridine directing groups in combination with mono-olefin reactants.[15–23] One interesting example of reductive coupling of a diene with an imine utilizes a ruthenium(II) catalyst and 4-aminobutanol to promote Schiff base formation[25,26] through alcohol oxidation, followed by coupling of the imine and resultant π-allyl species, which is formed by hydrogen auto-transfer from alcohol to diene hydrometallation.[27] Direct hydroaminoalkylation of dienes and unactivated amines remains rarely charted territory in late transition metal catalysis.

6.2 Reaction Development and Scope

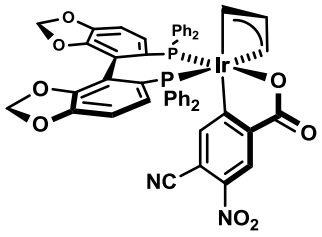
Inspired by the results of formal hydroaminoalkylation that make use of the Schiff base generated *in situ* from 4-aminobutanol to couple with dienes, it was reasoned that such nucleophile-electrophile pairs could be generated through the redox-triggered coupling of butadiene **6.1a** and pyrrolidine **6.2**. However, one significant challenge observed is the dehydrogenation of amines, which does not occur in the coupling of 4-aminobutanol and dienes,[27] nevertheless, this transformation was investigated.

After a brief survey of literature, studies commenced with the screening of various catalyst at 130 °C in the coupling of diene **6.1a** and pyrrolidine **6.2** (Table 6.1). Although cyclometalated iridium catalyst **Cat IX** and Shvo's catalyst

Table 6.1. Select assay of catalyst screened in the formation of **6.4a**.



6.1a (4.0 equiv.) | 6.2 | 6.3a | 6.4a



Cat IX

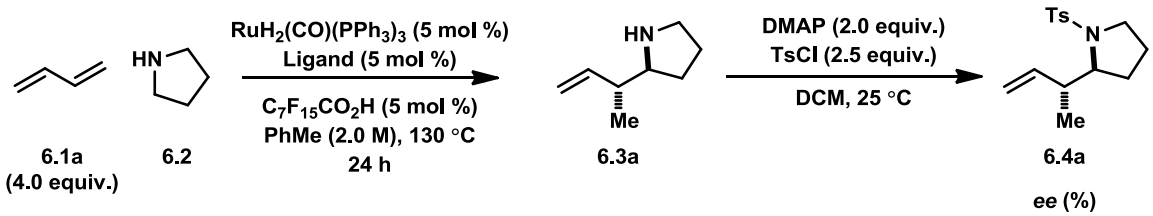
Catalyst	Yield (%)	*dr*
Cat IX	Trace	ND
Shvo's Catalyst	Trace	ND
$RuHCl(CO)(PPh_3)_3$	>10	ND
$RuHCl(CO)(PPh_3)_3$ (with DPPP)	24	2.0:1
$RuH_2(CO)(PPh_3)_3$	8	3.6:1
$RuH_2(CO)(PPh_3)_3$ (with DPPP and $C_7F_{15}CO_2H$)	51	2.4:1

provided no detectable product, both $RuHCl(CO)(PPh_3)_3$ and $RuH_2(CO)(PPh_3)_3$ provided 2-substituted pyrrolidine **6.4a** in low yield and low diasteroselectivity. However, when DPPP was added as ligand (and an acid additive for

$RuH_2(CO)(PPh_3)_3$), the reactivity dramatically increased, furnishing product **6.4a** in 24% yield and 2.0:1 *dr* and 51% yield and 2.4:1 *dr* respectively in favor of the *anti*-diastereomer. To facilitate isolation, the crude coupling product was tosylated *in situ* with *p*-toluenesulfonyl chloride.

With these results, $RuH_2(CO)(PPh_3)_3$ was chosen for subsequent optimization, so a vast array of ligands were examined with the addition of $C_7F_{15}CO_2H$ as an additive. Chiral phosphines were screened to assess the asymmetric transformation (Table 6.2). Unfortunately, the chiral phosphines assayed did not provide the major diastereomer in good enantioenrichment, while the minor diastereomer was isolated in high enantioselectivity. After an

Table 6.2. Select assay of chiral ligands screened in the formation of **6.4a**.



6.1a (4.0 equiv.) 6.2 6.3a 6.4a

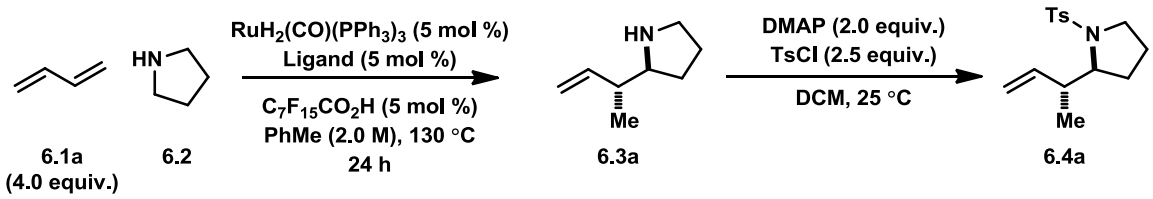
Ligand	Yield (%)	*dr*	*ee* (%) major (minor)
(*S*)-BINAP	20	2.5:1	16 (72)
(*S*)-SEGPHOS	21	2.8:1	19 (75)
(*R*)-Cl-MeO-BIPHEP	16	3.4:1	24 (73)
(*R*)-MonoPhos	Trace	ND	ND
(*R*)-XylyI-P-Phos	20	3.8:1	10 (80)
(*S,S*)-DIOP	21	5.9:1	6 (32)
(1*R*,1'*R*,2*S*,2'*S*)-DuanPhos	37	2.3:1	10 (84)
(*R*)-QuinoxP	38	2.4:1	8 (46)
Walphos SL-W005-1	Trace	ND	ND
Josiphos-SL-J015-1	37	2.2:1	6 (46)

intensive chiral ligand screen, focus was switched from the enantioselective variant to the diastereoselective transformation.

Further assays examining the carbon linker between phosphines revealed interesting results (Table 6.3). It appeared that steric effects played a role in the

diastereoselectivity of the transformation. Both DCyPE and DCyPP provided product **6.4a** in better diasteroselectivity than DPPP, but unfortunately the yield was diminished. After an exhaustive ligand screening, it was determined that DPPP was indeed the optimum ligand for this transformation. It was then postulated that preforming the catalyst derived from $RuH_2(CO)(PPh_3)_3$ and DPPP[28] could enhance the reactivity of the catalyst because coordination of excess pyrrolidine **6.2** could prevent the formation of the active catalyst, thus lowering the yield. Delightfully this proved successful, delivering product **6.4a** in 61% yield and 2.4:1 *dr* (Scheme 6.1).

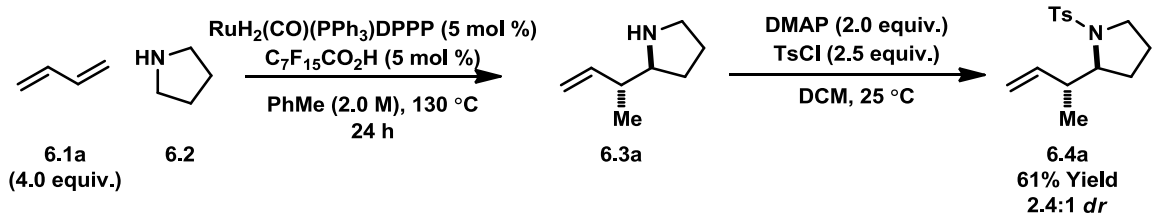
Table 6.3. Select assay of ligands screened in the formation of **6.4a**.



6.1a (4.0 equiv.) | 6.2 | 6.3a | 6.4a

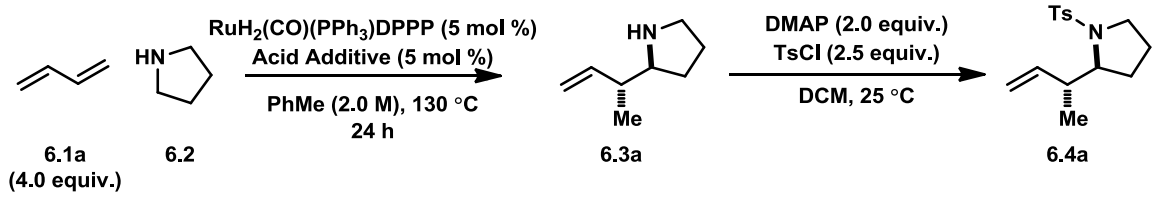
Ligand	Yield (%)	*dr*
DPPP	51	2.4:1
DPPM	Trace	ND
DPPE	24	1.6:1
DPPB	16	4.5:1
DPPF	Trace	ND
DCyPM	35	1.9:1
DCyPE	36	5.9:1
DCyPP	14	>20:1
DCyPB	Trace	ND

Scheme 6.1. Employment of the preformed ruthenium catalyst in the formation of **6.4a**.



With this result in hand, a variety of different acid additives were assayed in order to increase reaction efficiency (Table 6.4). After an exhaustive screen (chiral-phosphoric and chiral-BINOL based acids that have shown promise in previous reports[29,30] were screened, but no appreciable effects were observed) it was found that ferrocenecarboxylic acid furnished product **6.4a** in the best overall yield and diastereoselectivity, 57% yield and 8.1:1 *dr*. Unfortunately, some of the acids, such as 3,5-dimethylbenzoic acid, 1-adamantanecarboxylic acid and pivalic acid, which provided better diastereoselectivity, were further assayed, but the yield remained insufficient.

Table 6.4. Select assay of acid additives screened in the formation of **6.4a**.



Acid Additive	Yield (%)	*dr*
$C_7F_{15}CO_2H$	61	2.4:1
3,5-Me_2BzOH	51	10.0:1
Ferr. CO_2H	57	8.1:1
$C_{10}H_{15}CO_2H$	47	9.7:1
Pivalic Acid	47	9.0:1
N-Me-Pyrrole-2-CO_2H	52	8.3:1

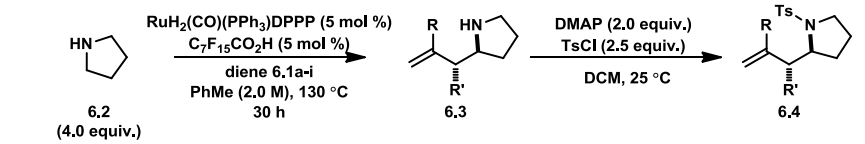
Variations in temperature and solvent were examined, but no changes were needed. Toluene proved to be the ideal solvent for this transformation. Although 130 °C remained the optimum temperature for this transformation, interesting effects that further proved the difficulty of amine dehydrogenation were revealed. As the temperature was only slightly decreased to 120 °C, a large decrease in the yield occurred (loss of 20-30% depending on the catalytic system). Reaction time also had a slight effect. By increasing the reaction time to thirty hours, the yield of **6.4a** jumped to 66%, but if the reaction was allowed to continue beyond thirty hours, the yield began to decrease. It is believed that the product was decomposing, but nothing significant could be identified.

With these conditions, the scope of hydroaminoalkylation was examined. Unfortunately, conditions for butadiene hydroaminoalkylation were not applicable across a wide range of higher dienes. The conditions that employed $C_7F_{15}CO_2H$ proved to be much more robust, thus generating products **6.4b-f**. in reasonable yields (Tabel 6.5). One manipulation was made with respect to the stoichiometry. For dienes **6.1c-i** the stoichiometry was inverted so that the diene was the limiting reagent. This was not an issue considering availability of pyrrolidine. The scope of this transformation proved quite limited; only 2-substituted dienes **6.1b-e** that did not contain a bulky substituent participated well in the coupling. Dienes **6.1h-l**, which did contain steric bulk at the 2-position, showed limited reactivity. Furthermore, no other amine substrates engaged in the coupling, including aziridines, azetidine, piperidine, indoline, *iso*-indoline and *N*-methylanisidine.

A plausible catalytic mechanism is believed to mirror that proposed for diene hydrohyroxyalkylation (Figure 6.1).[29–33] It is proposed that ruthenium hydride **I** enters into the catalytic cycle through hydrometalation of diene **6.1a** to form π-allyl ruthenium species **II**. Ruthenium species **II** can isomerize to the σ-allyl ruthenium species, which opens a coordination site on the metal, allowing coordination of imine **6.5**, furnishing intermediate **III**. Subsequent C-C bond formation generates ruthenium amide **IV**. Proton exchange from pyrrolidine **6.2**

releases coupling product **6.3a** and forms intermediate **V**. β-Hydride elimantion of intermediate **V** releases imine **6.5** and regenerates ruthenium hydride **I**. To further probe the catalytic mechanism, it was hypothesized that imine **6.5** could be directly employed, in the presence of a reductant such as H_2 gas, in the coupling reaction. Imine **6.5** was prepared according to the known procedure that oxidizes pyrrolidine using sodium persulfate and silver nitrate.[34] It is known that imine **6.5** resides as the trimer at room temperature. When *trimeric*-**6.5** was exposed to diene **6.1a** under reductive coupling conditions, utilizing H_2 gas as reductant, product **6.4a** was delivered in moderate yield (Scheme 6.2). Interestingly, because amine dehydrogenation was not needed, the reaction proceeded at a much lower temperature (80 °C). T*rimeric*-**6.5** is known to begin decomposing to the monomer around 60 °C.[34]

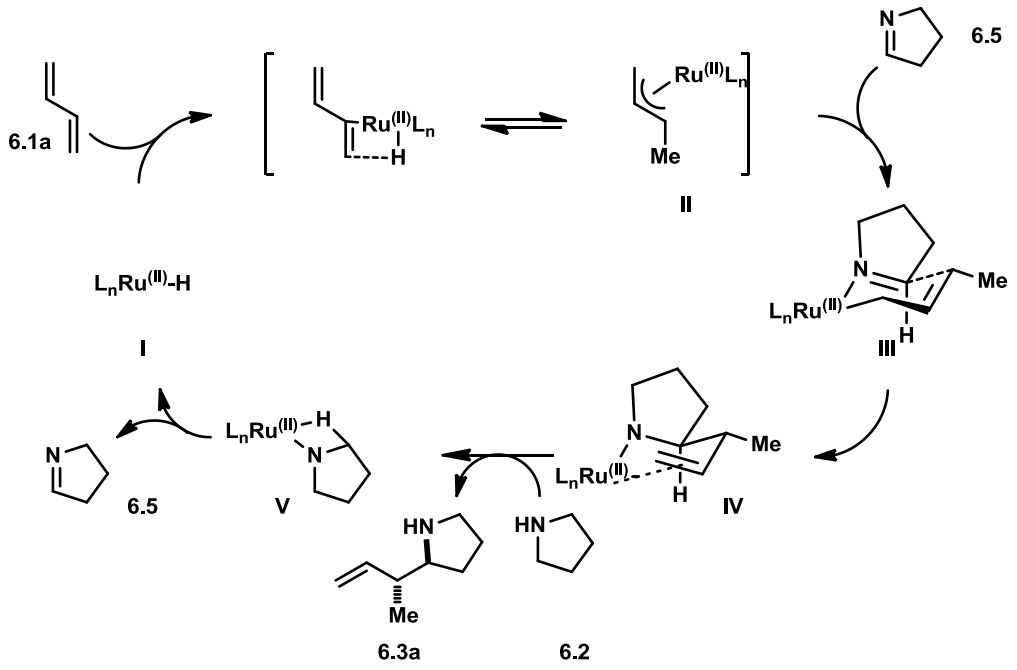
Table 6.5. Scope of ruthenium-catalyzed hydroaminoalkylation.



diene	Product	Yield	*dr*
6.1a*	6.4a	66	8:1
6.1b*	6.4b	60	5:1
6.1c	6.4c	54	3:1
6.1d	6.4d	60	3:1
6.1e	6.4e	56	2.4:1
6.1f	6.4f	53	2.5:1
6.1g	6.4g	~15	mixture
6.1h	6.4h	trace	ND
6.1i	6.4i	13	1:1

*For dienes 6.1a-b, 4.0 equiv. of diene was used and 1.0 equiv. of pyrrolidine 6.2 was used

Figure 6.1. A plausible catalytic cycle for the hydroaminoalkylation of diene **6.1a** with pyrrolidine **6.2**.



The *anti*-diastereoselectivity can be explained in stereochemical models A-D (Figure 6.2). Imine addition is believed to occur by way of the primary σ-allylruthenium haptomer with allylic inversion through a closed transition state. Because stereochemical models **A** and **B** would generate *syn*-diastereomers, these pathways can be excluded. Stereochemical model **D** requires intervention of the (*Z*)-σ-allylruthenium isomer, which is unlikely due to the steric effects involved from the large metal center. Thus, stereochemical model **C**, wherein imine addition occurs through a chair-like transition structure by way of the (*E*)-σ-allylruthenium isomer, is preferred.

Scheme 6.2. Reductive coupling of *trimeric*-**6.5** with diene **6.1a**.

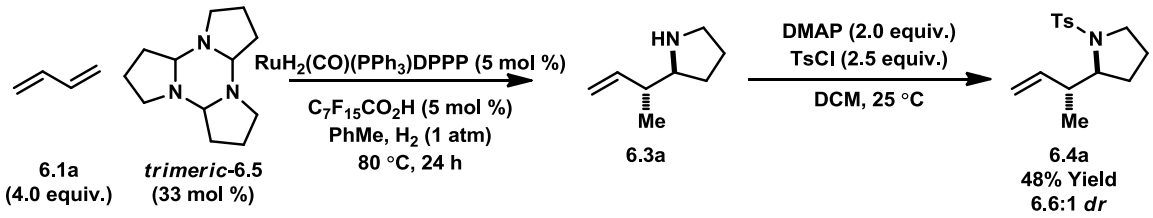
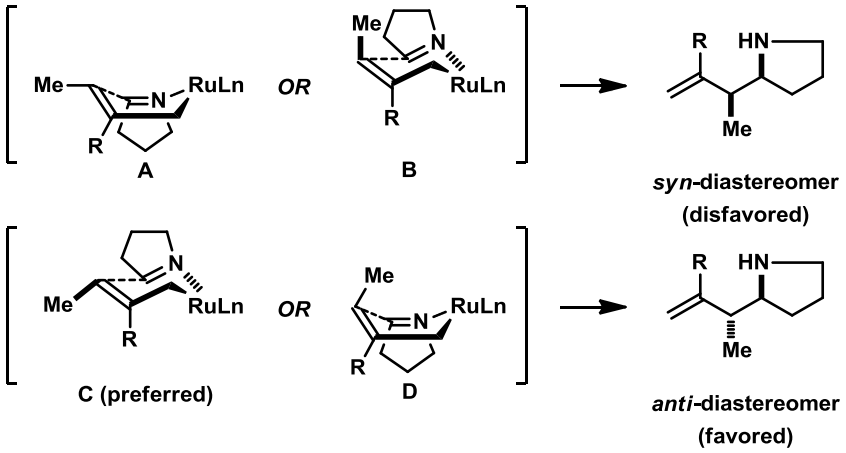


Figure 6.2. Stereochemical models A-D for imine addition.



6.3 Summary

A rare example of late transition metal-catalyzed hydroaminoalylation of 2-substituted dienes with pyrrolidine in the absence of directing groups has been reported. Unfortunately, the scope of this transformation is quite limited, probably due to the energetics needed in amine dehydrogenation, which has proven much more difficult than alcohol dehydrognenation.[27] No other amines assayed participated to much extent with the dienes employed. With regards to diene, substrate scope was also quite limited, only allowing substitution at the 2-position, with substituents consisting of small electro-neutral groups. More investigations into a catalytic system that is better suited for amine

dehydrogenation while still retaining the ability to hydrometalate π-unsaturates are necessary.

6.4 Experimental Details

General Information

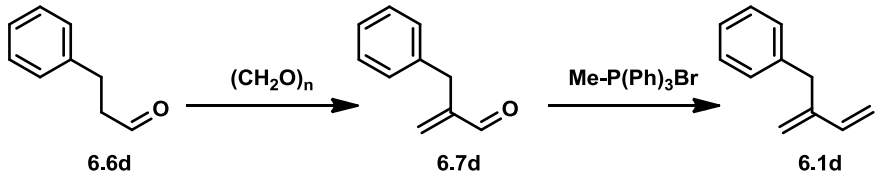
All glassware was oven dried at 140 °C overnight and cooled under argon gas before use. All ruthenium catalyzed reactions were carried out in sealed pressure tubes (13 x 100 mm). Toluene was purified by distillation from sodium and benzophenone immediately before use. All ligands and additives were purchased from commercial suppliers and used as received.

$[RuH_2(CO)(PPh_3)(dppp)]$ was prepared according to the literature procedure.[28]

1,3-Butadiene **6.1a** was freshly condensed immediately before use. Pyrrolidine **6.2** and dienes (**6.1b**, **6.1c** and **6.1g**) were distilled in a Hickman still immediately prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was accomplished with UV light followed by dipping in a *p*-anisaldehyde solution and heating. Purification of reaction products was carried out by flash column chromatography using 40-63 μm silica gel. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini 400 (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Dienes **6.1h**[35] and **i**[32] were prepared according to the literature procedures. *Trimeric*-**6.5a** was prepared according to its known protocol.[34]

Synthesis of (2-methylenebut-3-en-1-yl)benzene (6.1d).

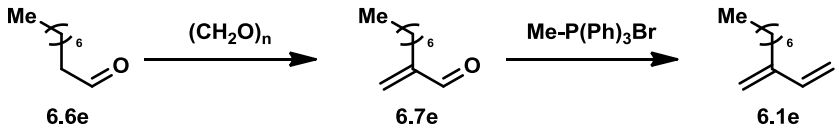


6.6d **6.7d** **6.1d**

Aldehyde **6.7d** was prepared according to its known protocol.[36]

To a solution of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol) in tetrahydrofuran (50 mL, 0.16 M with respect to aldehyde **6.7d**) at 0 °C was added *n*-BuLi (2.3 M, 4.35 mL, 10.0 mmol) and stirred for 15 minutes. A solution of aldehyde **6.7d** (1.17 g, 8.0 mmol) in tetrahydrofuran (10 mL, 0.8 M with respect to aldehyde **6.7d**) was added to the basic solution and stirred for one hour at 0 °C, then four hours at room temperature. The reaction was quenched with an aqueous solution of ammonium chloride and extracted with diethyl ether three times. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2: 2% ether:hexane) to afford diene **6.1d** in 80% yield (0.923 g, 6.4 mmol). The characterization matched what has been reported in the literature.[37]

Synthesis of 3-methylenedec-1-ene (6.1e).



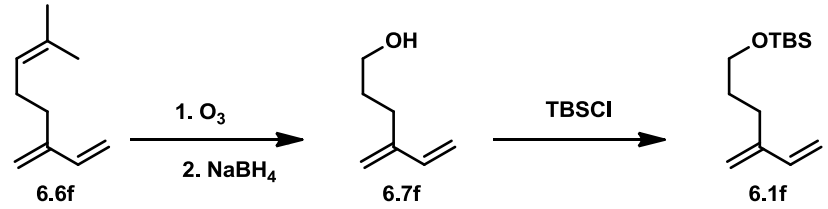
6.6e 6.7e 6.1e

To a solution of pyrrolidine (159.5 mg, 2.29 mmol) and *N,N*-dimethylaminobenzoic acid (740.0 mg, 4.48 mmol) in refluxing dichloromethane (22.0 mL, 1.0 M with respect to aldehyde **6.6e**) was added aldehyde **6.6e** (3.2 g, 22.4 mmol) and aqueous formaldehyde 37% (672.7 mg, 22.4 mmol). The solution continued to stir at reflux for 40 minutes. After cooling to room temperature, the reaction was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane three times. The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2: 5% ether:hexane) to afford aldehyde **6.7e** in 81% yield (0.2.8 g, 18.2 mmol).

To a solution of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol) in tetrahydrofuran (50 mL, 0.16 M with respect to aldehyde **6.7e**) at 0 °C was added *n*-BuLi (2.3 M, 4.35 mL, 10.0 mmol) and stirred for 15 minutes. A solution of aldehyde **6.7e** (1.23 g, 8.0 mmol) in tetrahydrofuran (10 mL, 0.8 M with respect to aldehyde **6.7e**) was added to the basic solution and stirred for one hour at 0 °C, then four hours at room temperature. The reaction was quenched with an aqueous solution of ammonium chloride and extracted with diethyl ether three times. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2: 2% ether:hexane) to afford diene

6.1e in 80% yield (0.975 g, 6.4 mmol). The characterization matched what has been reported in the literature.[38]

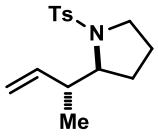
Synthesis of *tert*-butyldimethyl((4-methylenehex-5-en-1-yl)oxy)silane (6.1f).



Alcohol **6.7f** was prepared according to its known protocol.[39]

To a solution of alcohol **6.7f** (680 mg, 6.06 mmol) and imidazole (825 mg, 12.12 mmol) in *N*,*N*-dimethylformamide (30 mL, 0.2 M with respect to alcohol **6.7f**) at 0 °C was added *tert*-butyldimethylsilyl chloride (1.1 g, 7.27 mmol) and stirred overnight. The reaction mixture was diluted with water and extracted with diethyl ether three times. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2: 2% ether:hexane) to afford diene **6.1f** in 82% yield (1.12 g, 4.94 mmol). The characterization matched what has been reported in the literature.[40]

Synthesis of 2-(but-3-en-2-yl)-1-tosylpyrrolidine (6.4a).



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (24.2 mg, 0.03 mmol, 5 mol %), ferrocenecarboxylic acid (6.9 mg, 0.03 mmol, 5 mol %). Toluene (0.3 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (50 µL, 0.6 mmol, 1.0 equiv.) was added to the reaction mixture. The pressure tube was cooled to −78 °C, and freshly condensed 1,3-butadiene **6.1a** (0.2 mL, 2.4 mmol, 4.0 equiv.) was added. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (184 mg, 1.5 mmol, 2.5 equiv.), *p*-toluenesulfonyl chloride (228 mg, 1.2 mmol, 2.0 equiv.) and dichloromethane (2.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5%, ethyl acetate:hexane) to provide **6.4a** as a colorless solid in 66% yield (110.6 mg, *anti*:*syn* = 8:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.75 (ddd, *J* = 16.0, 12.0, 8.0 Hz, 1H), 5.08–5.00 (m, 2H), 3.66–3.62 (m, 1H),

3.34–3.24 (m, 2H), 2.86–2.78 (m, 1H), 2.41 (s, 3H), 1.71–1.58 (m, 2H), 1.54–1.44 (m, 1H), 1.37–1.29 (m, 1H), 1.01 (d, *J* = 8.0 Hz, 3H).

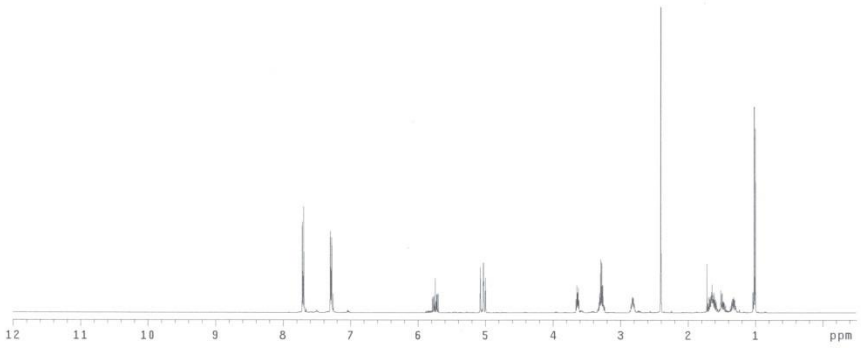
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 140.9, 134.8, 129.6, 127.5, 114.7, 63.8, 49.8, 41.7, 26.6, 24.6, 21.5, 13.2.

FTIR (neat): v 2924, 1910, 1597, 1447, 1341, 1156, 1091, 1041, 999, 915, 814, 664 cm^{-1}.

TLC Rf: 0.60 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{15}H_{21}NO_2SNa^+$ $[M+Na]^+$: 302.1185; Found: 302.1187.

MP: 95–95 °C.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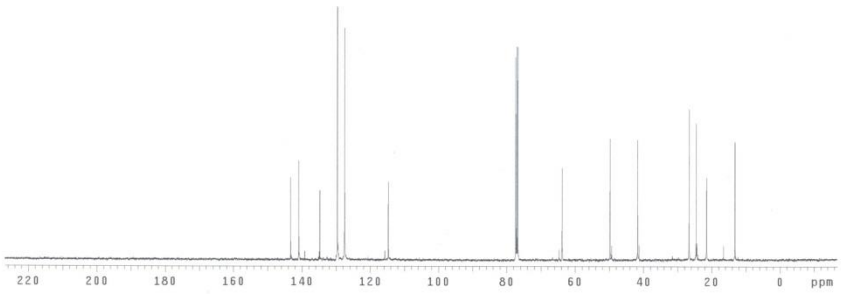
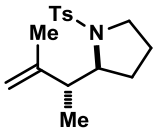
10
9
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

Synthesis of 2-(3-methylbut-3-en-2-yl)-1-tosylpyrrolidine (6.4b).



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (12.1 mg, 0.015 mmol, 5 mol %), pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol %). Toluene (0.15 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (25 µL, 0.3 mmol, 1.0 equiv.) and freshly distilled isoprene **6.1b** (0.12 mL, 1.2 mmol, 4.0 equiv.) were added to the reaction mixture. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (92 mg, 0.75 mmol, 2.5 equiv.), *p*-toluenesulfonyl chloride (114 mg, 0.6 mmol, 2.0 equiv.) and dichloromethane (1.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5% ethyl acetate:hexane) to provide **6.4b** as a colorless solid in 60% yield (53.0 mg, *anti*:*syn* = 5:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 1H), 4.72 (s, 1H), 3.78–3.74 (m, 1H), 3.37–3.25 (m, 2H), 2.88–2.81 (m,

1H), 2.42 (s, 3H), 1.79 (s, 3H), 1.71–1.59 (m, 2H), 1.47–1.31 (m, 2H), 1.02 (d, *J* = 8.0 Hz, 3H).

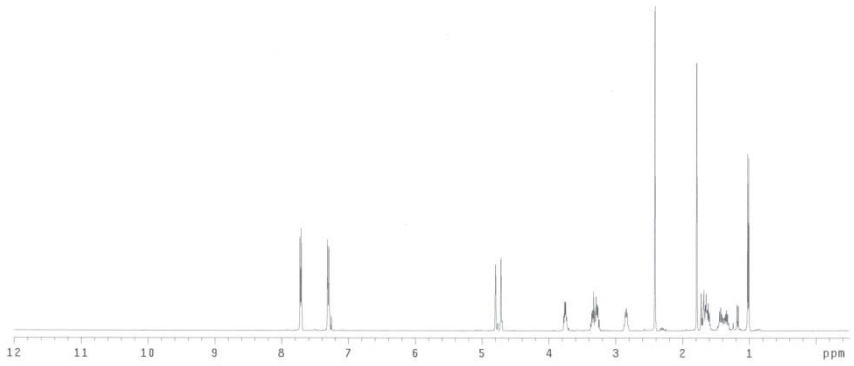
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 143.3, 134.6, 129.6, 127.6, 110.8, 61.8, 49.9, 43.9, 26.1, 24.7, 22.2, 21.5, 11.9.

FTIR (neat): v 2970, 2872, 1597, 1449, 1336, 1153, 1089, 1043, 996, 986, 897, 816, 710 cm^{-1}.

TLC Rf: 0.55 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{16}H_{23}NO_2SNa^+$ $[M+Na]^+$: 316.1342; Found: 316.1342.

MP: 68–70 °C.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9
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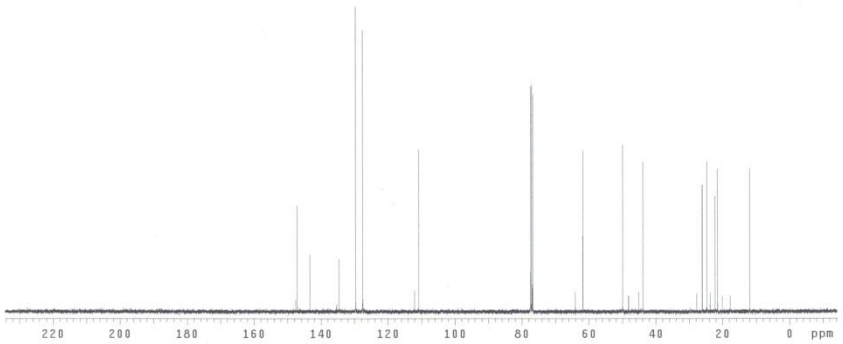
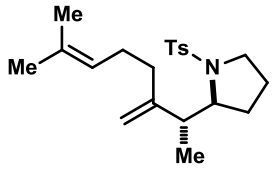
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

Synthesis of 2-(7-methyl-3-methyleneoct-6-en-2-yl)-1-tosylpyrrolidine (6.4c)



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (12.1 mg, 0.015 mmol, 5 mol %), pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol %). Toluene (0.15 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (0.1 mL, 1.2 mmol, 4.0 equiv.) and freshly distilled myrcene **6.1c** (51.5 µL, 0.3 mmol, 1.0 equiv.) were added to the reaction mixture. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (258 mg, 2.0 mmol, 7.0 equiv.), *p*-toluenesulfonyl chloride (342 mg, 1.8 mmol, 6.0 equiv.) and dichloromethane (2.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5% ethyl acetate:hexane) to provide **6.4c** as a colorless oil in 54% yield (58.6 mg, *anti*:*syn* = 3:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.33–7.29 (m, 2H), 5.15–5.11 (m, 1H), 4.84 (s, 1H), 4.78 (d, *J* = 1.2 Hz, 1H), 3.79–3.73 (m, 1H),

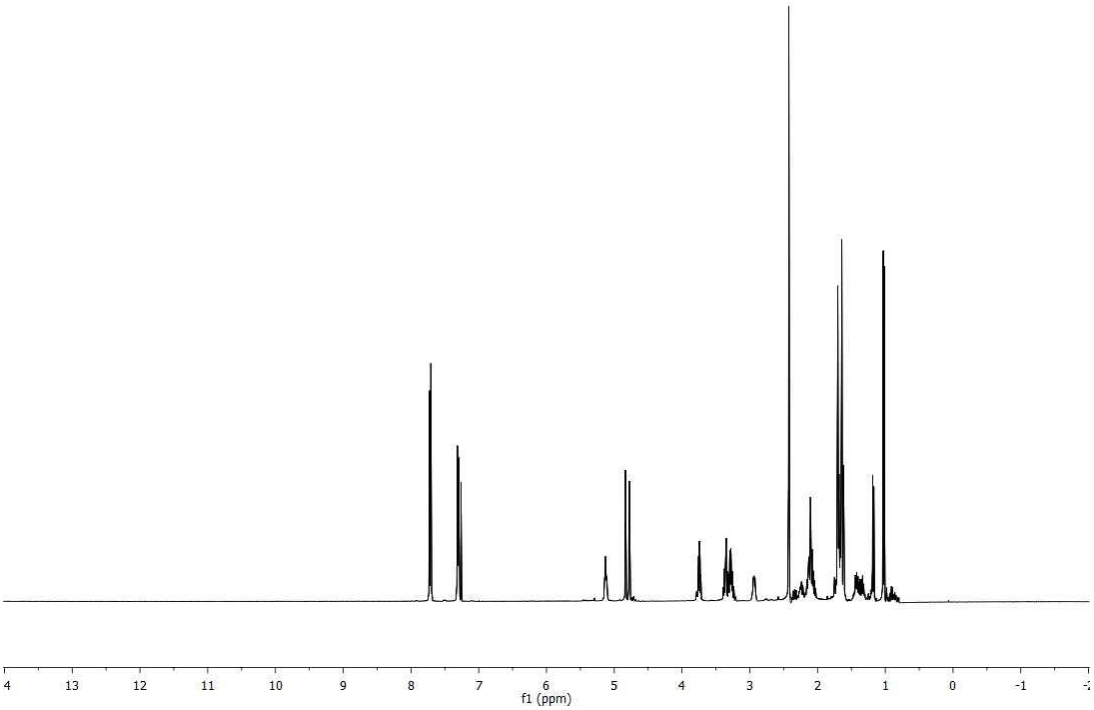
3.39–3.33 (m, 1H), 3.32–3.23 (m, 1H), 2.97–2.91 (m, 1H), 2.43 (s, 3H), 2.27–2.19 (s, 1H), 2.18–2.03 (m, 3H), 1.71 (s, 3H), 1.69–1.67 (m, 2H), 1.65 (s, 3H), 1.48–1.30 (m, 2H), 1.03 (d, *J* = 7.2 Hz, 3H).

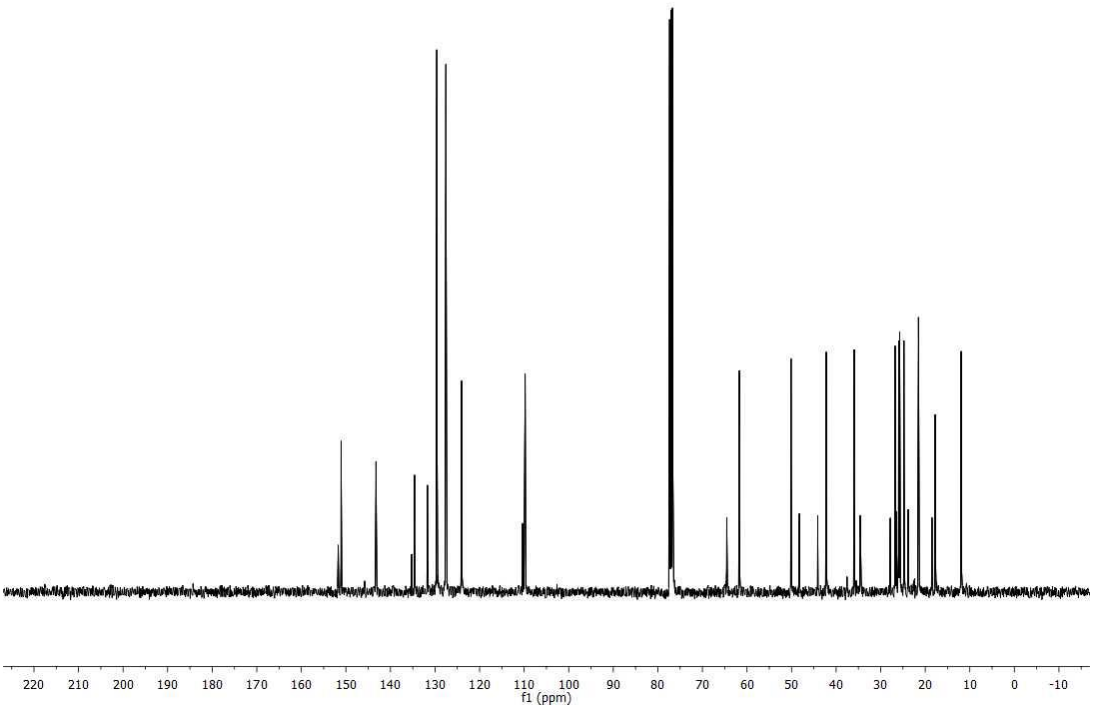
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 143.2, 134.7, 131.7, 129.6, 127.6, 124.0, 109.8, 61.7, 50.1, 42.2, 35.9, 26.8, 26.0, 25.7, 24.8, 21.5, 17.8, 11.9.

FTIR (neat): ν 2969, 2363, 1736, 1597, 1449, 1343, 1202, 1157, 1091, 1040, 996, 893, 814, 708, 664 cm^{-1}.

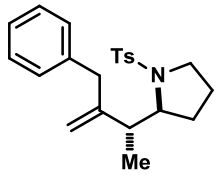
TLC Rf: 0.65 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{21}H_{31}NO_2SNa^+$ $[M+Na]^+$: 384.1980; Found: 384.1970.


14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Synthesis of 2-(3-benzylbut-3-en-2-yl)-1-tosylpyrrolidine (6.4d).



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (12.1 mg, 0.015 mmol, 5 mol %), pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol %). Toluene (0.15 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (0.1 mL, 1.2 mmol, 4.0 equiv.) and diene **6.1d** (43.3 mg, 0.3 mmol, 1.0 equiv.) were added to the reaction mixture. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (258 mg, 2.0 mmol, 7.0 equiv.), *p*-toluenesulfonyl chloride (342 mg, 1.8 mmol, 6.0 equiv.) and dichloromethane (2.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5% ethyl acetate:hexane) to provide **6.4d** as a colorless oil in 60% yield (66.5 mg, *anti*:*syn* = 3:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.34-7.21 (m, 7H), 4.92 (s, 1H), 4.82 (s, 1H), 3.77 (dt, *J* = 4.0, 8.0 Hz, 1H), 3.43 (s, 2H), 3.37-3.22 (m, 2H),

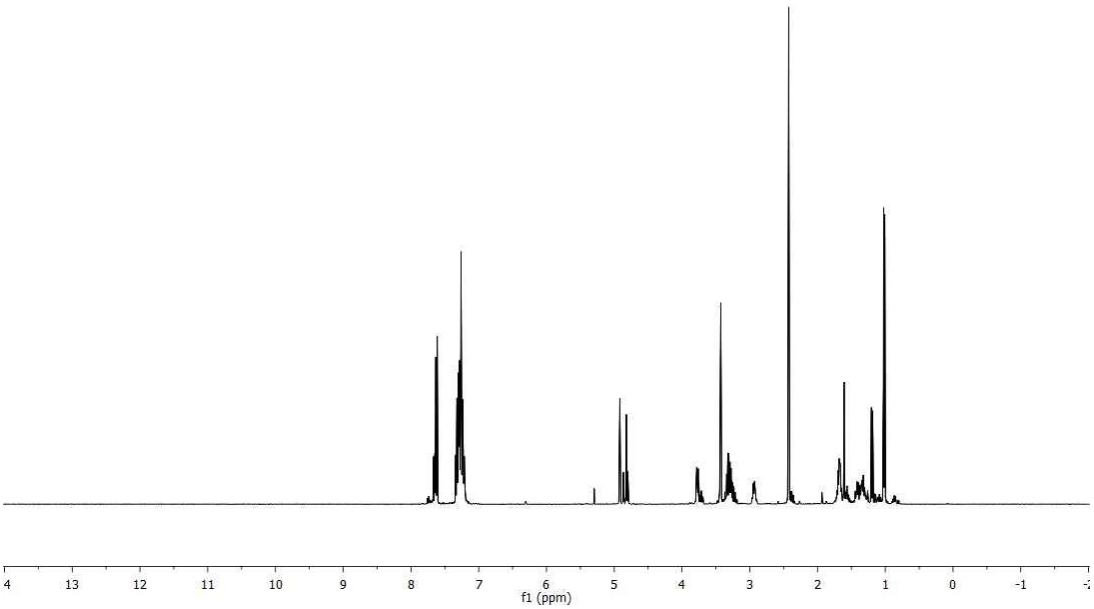
2.96-2.90 (m, 1H), 2.43 (s, 3H), 1.71-1.64 (m, 2H), 1.45-1.29 (m, 2H), 1.02 (d, *J* = 4.0 Hz, 3H).

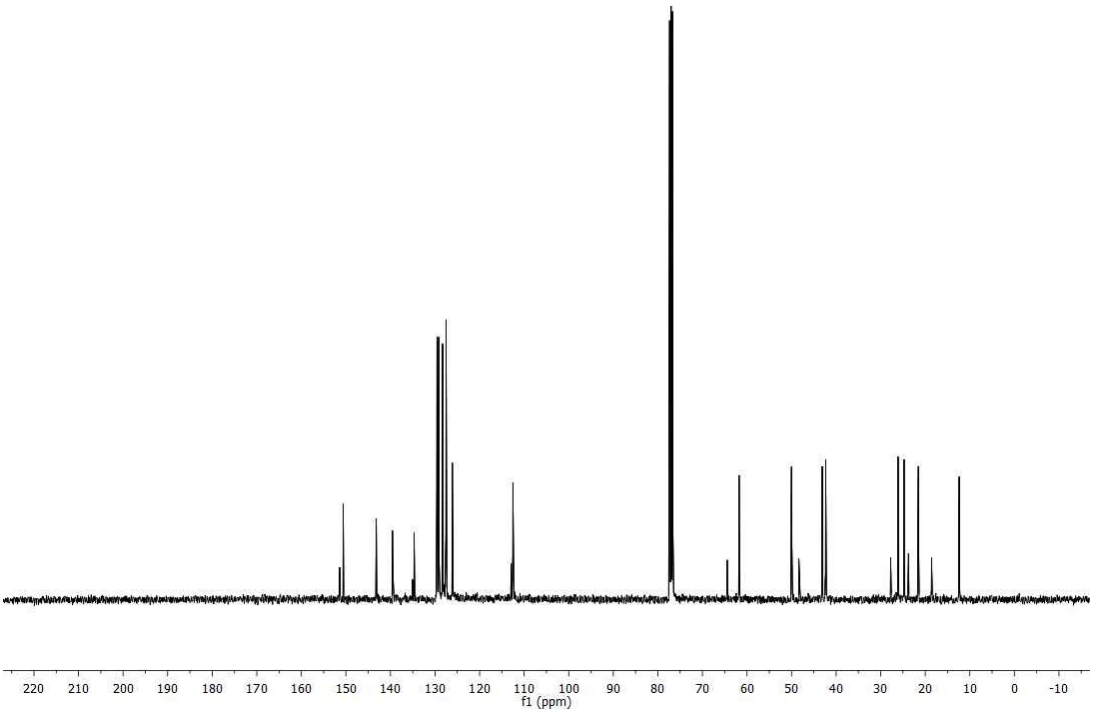
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.2, 139.6, 134.7, 129.6, 129.2, 128.3, 127.5, 126.1, 112.5, 61.8, 50.0, 43.1, 42.3, 26.1, 24.8, 21.5, 12.4.

FTIR (neat): v 2970, 1598, 1494, 1343, 1157, 1092, 1040, 996, 898, 815, 738, 700, 665 cm^{-1}.

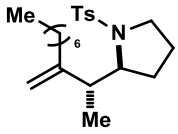
TLC Rf: 0.52 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{22}H_{27}NO_2SNa^+$ $[M+Na]^+$: 362.1655; Found: 362.1659.


4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Synthesis of 2-(3-methylenedecan-2-yl)-1-tosylpyrrolidine (6.4e).



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (12.1 mg, 0.015 mmol, 5 mol %), pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol %). Toluene (0.15 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (0.1 mL, 1.2 mmol, 4.0 equiv.) and diene **6.1e** (45.7 mg, 0.3 mmol, 1.0 equiv.) were added to the reaction mixture. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (258 mg, 2.0 mmol, 7.0 equiv.), *p*-toluenesulfonyl chloride (342 mg, 1.8 mmol, 6.0 equiv.) and dichloromethane (2.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5% ethyl acetate:hexane) to provide **6.4e** as a colorless oil in 56% yield (63.2 mg, *anti*:*syn* = 2.4:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.32-7.29 (m, 2H), 4.81 (s, 1H), 4.75 (s, 1H), 3.72 (dt, *J* = 4.0, 8.0 Hz, 1H), 3.40-3.23 (m, 2H), 2.96-2.90 (m,

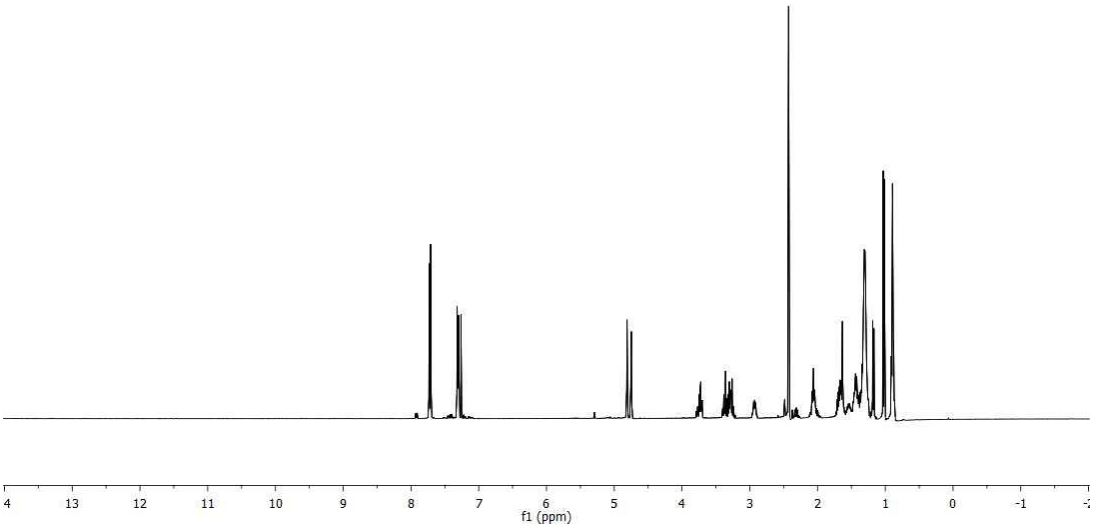
1H), 2.43 (s, 3H), 2.08-2.04 (m, 2H), 1.71-1.61 (m, 2H), 1.58-1.25 (m, 12H) 1.02 (d, *J* = 8.0 Hz, 3H), 0.91-0.87 (m, 3H).

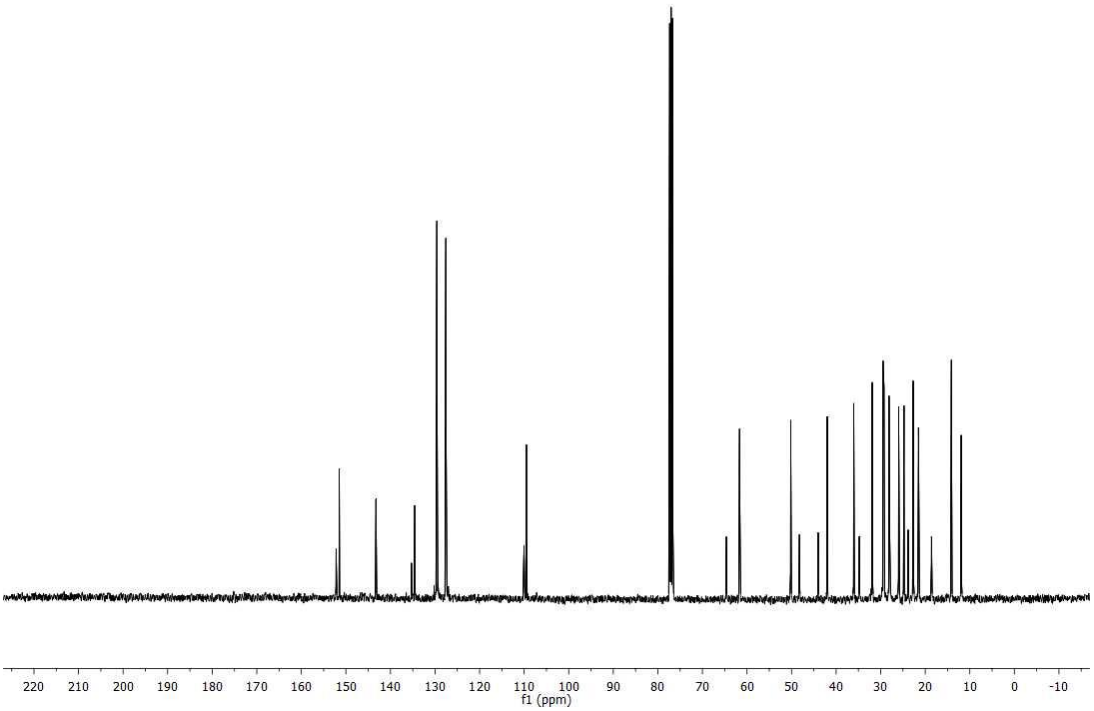
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 143.3, 134.6, 129.6, 127.6, 109.5, 61.7, 50.2, 42.0, 36.0, 31.9, 29.5, 29.3, 28.1, 26.0, 24.8, 22.7, 21.5, 14.1, 11.9.

FTIR (neat): v 2926, 2855, 1462, 1345, 1202, 1159, 1092, 1040, 998, 893, 815, 709, 666 cm^{-1}.

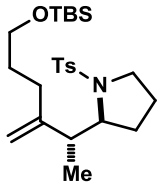
TLC Rf: 0.65 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{22}H_{35}NO_2SNa^+$ $[M+Na]^+$: 400.2281; Found: 400.2284.


4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Synthesis of 2-(6-((tert-butyldimethylsilyl)oxy)-3-methylenehexan-2-yl)-1-tosylpyrrolidine (6.4f).



To a dry pressure tube purged with argon were added $RuH_2(CO)(PPh_3)DPPP$ (12.1 mg, 0.015 mmol, 5 mol %), pentadecafluorooctanoic acid (6.2 mg, 0.015 mmol, 5 mol %). Toluene (0.15 mL, 2.0 M) was added via syringe, and the pressure tube was sealed with a screw cap. The reaction was placed in a 130 °C oil bath and stirred for 25 minutes. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The screw cap was replaced with a septum, and the pressure tube was purged with argon. Freshly distilled pyrrolidine **6.2** (0.1 mL, 1.2 mmol, 4.0 equiv.) and diene **6.1f** (67.9 mg, 0.3 mmol, 1.0 equiv.) were added to the reaction mixture. The septum was replaced with a screw cap, and the reaction was placed in a 130 °C oil bath. After 30 hours, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. 4-(*N*,*N*-dimethlyamino)pyridine (258 mg, 2.0 mmol, 7.0 equiv.), *p*-toluenesulfonyl chloride (342 mg, 1.8 mmol, 6.0 equiv.) and dichloromethane (2.0 mL) were added to the mixture, and the reaction was stirred at room temperature for 16 hours. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2: 2% to 5% ethyl acetate:hexane) to provide **6.4f** as a colorless oil in 53% yield (71.7 mg, *anti*:*syn* = 2.5:1).

For the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.84 (s, 1H), 4.78 (s, 1H), 3.77-3.72 (m, 1H), 3.65 (t, *J* = 8.0 Hz, 2H), 3.39-3.25

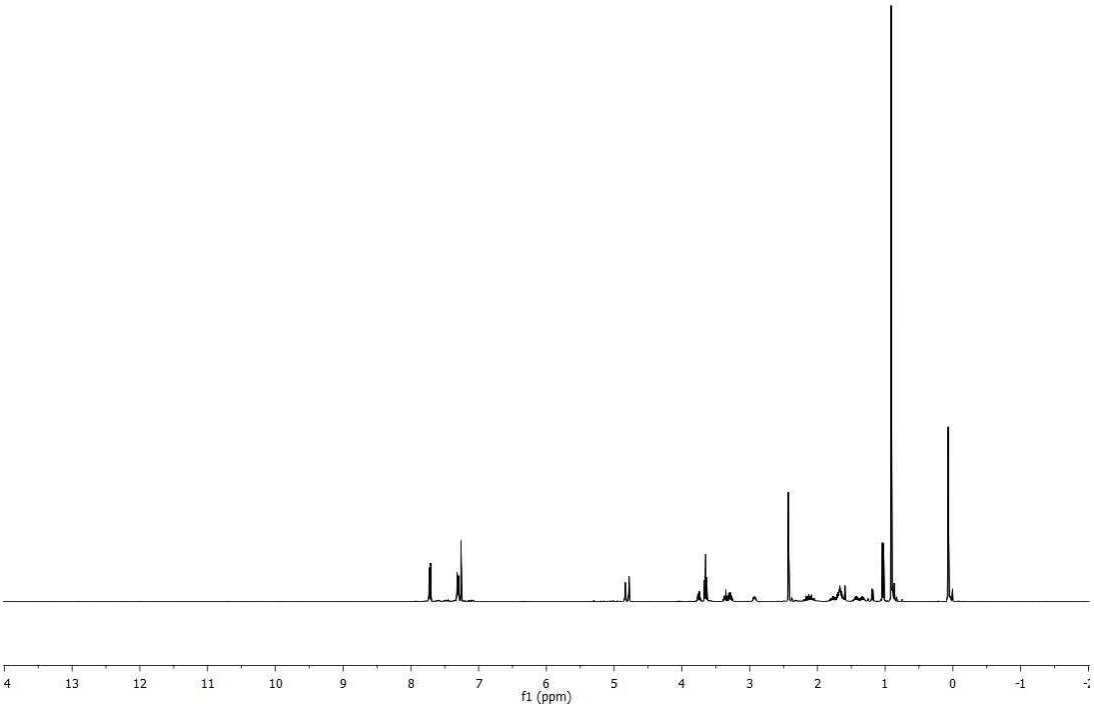
(m, 2H), 2.96-2.89 (m, 1H), 2.43 (s, 3H), 2.21-2.05 (m, 2H), 1.81-1.62 (m, 4H), 1.48-1.30 (m, 2H), 1.03 (d, *J* = 8.0 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

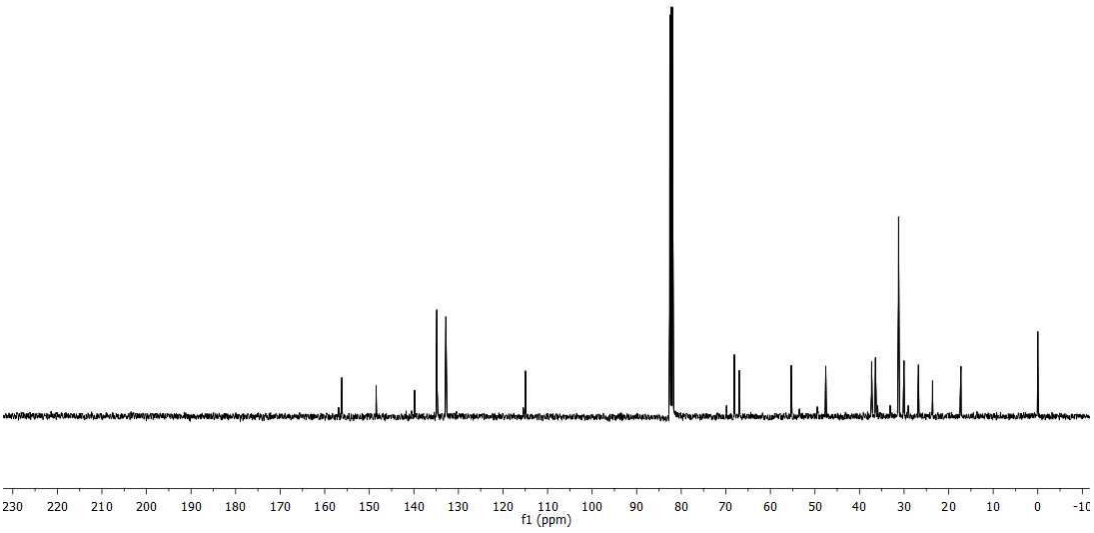
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 148.5, 139.9, 134.9, 132.8, 115.0, 68.1, 67.0, 55.3, 47.6, 37.3, 36.4, 31.2, 30.0, 26.8, 23.6, 17.2, 0.0.

FTIR (neat): v 2928, 2856, 2357, 1738, 1641, 1598, 1462, 1346, 1252, 1203, 1159, 1093, 999, 895, 835, 814, 775, 709, 665 cm^{-1}.

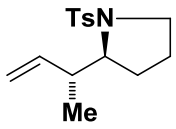
TLC Rf: 0.45 (4:1 hexanes:ethyl acetate).

HRMS (ESI): Calculated for $C_{24}H_{41}NO_3SSiNa^+$ $[M+Na]^+$: 474.2469; Found: 474.2469.

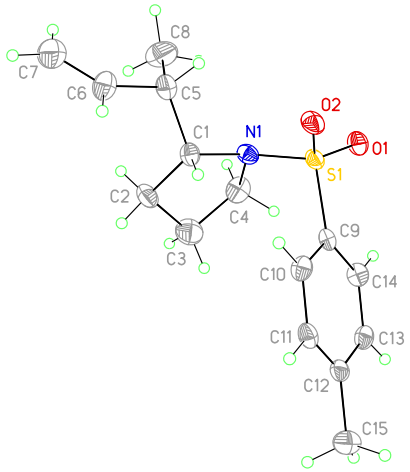

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Crystal Structure of Product (*S*)-2-((*R*)-but-3-en-2-yl)-1-tosylpyrrolidine (6.4a).



compound 6.4a



Crystal data and structure refinement for 1.

Empirical formula	C15 H21 N O2 S	
Formula weight	279.39	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 6.2588(7) Å	α= 90°.
	b = 14.0040(16) Å	β= 101.959(7)°.
	c = 8.5176(9) Å	γ = 90°.
Volume	730.35(14) $Å^3$	
Z	2	
Density (calculated)	1.270 Mg/m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	300	
Crystal size	0.270 x 0.200 x 0.100 mm	
Theta range for data collection	2.845 to 24.992°.	
Index ranges	-7<=h<=7, -16<=k<=16, -10<=l<=10	
Reflections collected	?	
Independent reflections	2570 [R(int) = ?]	

Completeness to theta = 25.242°	96.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.778
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2570 / 1 / 175
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0610, wR2 = 0.1339
R indices (all data)	R1 = 0.0885, wR2 = 0.1440
Absolute structure parameter	-0.2(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.338 and -0.283 e.$Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	6930(9)	5804(6)	5156(7)	21(1)
C2	7672(12)	6693(5)	4338(9)	29(2)
C3	6579(13)	7524(6)	4980(10)	39(2)
C4	4405(12)	7126(5)	5147(9)	30(2)
C5	6466(12)	4918(5)	4090(9)	30(2)
C6	8526(12)	4586(5)	3609(9)	31(2)
C7	8737(15)	4339(6)	2141(11)	47(2)
C8	4557(12)	5055(7)	2674(11)	51(3)
C9	6130(10)	6573(5)	8854(7)	18(1)
C10	8348(11)	6386(5)	9391(8)	22(2)
C11	9612(11)	7028(5)	10415(8)	23(2)
C12	8716(11)	7857(5)	10917(7)	22(2)
C13	6494(12)	8013(5)	10386(8)	22(2)
C14	5201(11)	7393(5)	9351(7)	20(2)

C15	10105(12)	8540(5)	12039(9)	32(2)
N1	4901(9)	6124(3)	5669(7)	21(1)
O1	2274(7)	6013(3)	7439(6)	29(1)
O2	5327(7)	4860(3)	7696(5)	26(1)
S1	4516(3)	5814(1)	7421(2)	20(1)

Bond lengths [Å] and angles [°] for 1.

C1-N1	1.495(8)	C7-H7B	0.95
C1-C5	1.529(10)	C8-H8A	0.98
C1-C2	1.544(10)	C8-H8B	0.98
C1-H1	1.00	C8-H8C	0.98
C2-C3	1.509(10)	C9-C14	1.392(9)
C2-H2A	0.99	C9-C10	1.394(9)
C2-H2B	0.99	C9-S1	1.769(7)
C3-C4	1.504(11)	C10-C11	1.382(9)
C3-H3A	0.99	C10-H10	0.95
C3-H3B	0.99	C11-C12	1.395(9)
C4-N1	1.485(8)	C11-H11	0.95
C4-H4A	0.99	C12-C13	1.388(10)
C4-H4B	0.99	C12-C15	1.497(10)
C5-C6	1.505(10)	C13-C14	1.375(10)
C5-C8	1.524(11)	C13-H13	0.95
C5-H5	1.00	C14-H14	0.95
C6-C7	1.330(11)	C15-H15A	0.98
C6-H6	0.95	C15-H15B	0.98
C7-H7A	0.95	C15-H15C	0.98

N1-S1	1.620(6)	O2-S1	1.431(5)
O1-S1	1.434(5)		

N1-C1-C5	110.4(5)	C3-C4-H4A	111.0
N1-C1-C2	104.1(5)	N1-C4-H4B	111.0
C5-C1-C2	115.1(5)	C3-C4-H4B	111.0
N1-C1-H1	109.0	H4A-C4-H4B	109.0
C5-C1-H1	109.0	C6-C5-C8	113.5(6)
C2-C1-H1	109.0	C6-C5-C1	110.1(6)
C3-C2-C1	104.9(6)	C8-C5-C1	112.9(6)
C3-C2-H2A	110.8	C6-C5-H5	106.6
C1-C2-H2A	110.8	C8-C5-H5	106.6
C3-C2-H2B	110.8	C1-C5-H5	106.6
C1-C2-H2B	110.8	C7-C6-C5	126.4(8)
H2A-C2-H2B	108.8	C7-C6-H6	116.8
C4-C3-C2	103.6(6)	C5-C6-H6	116.8
C4-C3-H3A	111.0	C6-C7-H7A	120.0
C2-C3-H3A	111.0	C6-C7-H7B	120.0
C4-C3-H3B	111.0	H7A-C7-H7B	120.0
C2-C3-H3B	111.0	C5-C8-H8A	109.5
H3A-C3-H3B	109.0	C5-C8-H8B	109.5
N1-C4-C3	104.0(6)	H8A-C8-H8B	109.5
N1-C4-H4A	111.0	C5-C8-H8C	109.5

H8A-C8-H8C	109.5	C13-C14-H14	120.4
H8B-C8-H8C	109.5	C9-C14-H14	120.4
C14-C9-C10	120.4(6)	C12-C15-H15A	109.5
C14-C9-S1	119.4(5)	C12-C15-H15B	109.5
C10-C9-S1	120.0(5)	H15A-C15-H15B	109.5
C11-C10-C9	119.0(6)	C12-C15-H15C	109.5
C11-C10-H10	120.5	H15A-C15-H15C	109.5
C9-C10-H10	120.5	H15B-C15-H15C	109.5
C10-C11-C12	121.4(6)	C4-N1-C1	109.5(5)
C10-C11-H11	119.3	C4-N1-S1	117.9(4)
C12-C11-H11	119.3	C1-N1-S1	119.1(4)
C13-C12-C11	118.1(6)	O2-S1-O1	119.6(3)
C13-C12-C15	121.2(6)	O2-S1-N1	106.6(3)
C11-C12-C15	120.7(7)	O1-S1-N1	106.9(3)
C14-C13-C12	121.8(6)	O2-S1-C9	108.4(3)
C14-C13-H13	119.1	O1-S1-C9	107.2(3)
C12-C13-H13	119.1	N1-S1-C9	107.6(3)
C13-C14-C9	119.2(6)		

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(3)	24(3)	24(3)	1(4)	5(2)	5(4)
C2	28(4)	30(4)	32(4)	3(3)	12(3)	-9(4)
C3	48(5)	24(4)	47(5)	3(3)	15(4)	-2(4)
C4	36(5)	28(4)	26(4)	6(3)	5(3)	9(3)
C5	27(4)	32(4)	35(4)	-3(3)	15(4)	-3(4)
C6	32(4)	33(4)	30(4)	0(3)	10(4)	7(3)
C7	39(5)	49(6)	58(6)	-15(4)	18(5)	-5(4)
C8	19(4)	62(6)	71(6)	-35(5)	5(4)	-3(4)
C9	15(3)	19(3)	20(3)	4(3)	7(3)	0(3)
C10	23(4)	21(4)	23(4)	1(3)	7(3)	7(3)
C11	15(3)	30(4)	24(4)	5(3)	6(3)	1(3)
C12	23(4)	25(4)	17(3)	3(3)	5(3)	-5(3)
C13	28(4)	22(4)	19(3)	3(3)	8(3)	3(3)
C14	17(3)	18(4)	25(4)	5(3)	4(3)	8(3)
C15	32(4)	29(4)	32(4)	-1(3)	3(3)	-4(4)
N1	17(3)	19(3)	27(3)	1(2)	4(2)	0(2)

O1	16(2)	35(3)	38(3)	-7(2)	14(2)	-2(2)
O2	29(3)	15(2)	37(3)	1(2)	14(2)	0(2)
S1	17(1)	19(1)	26(1)	-1(1)	9(1)	-2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

	x	y	z	
H1	8067	5644	6130	25
H2A	9281	6760	4617	35
H2B	7202	6649	3156	35
H3A	7438	7738	6030	47
H3B	6390	8068	4221	47
H4A	3807	7486	5959	36
H4B	3341	7149	4110	36
H5	6030	4401	4769	36
H6	9801	4550	4435	37
H7A	7509	4363	1273	57
H7B	10116	4138	1960	57
H8A	4996	5484	1888	76
H8B	3319	5333	3052	76
H8C	4130	4435	2170	76
H10	8982	5824	9059	26
H11	11124	6902	10784	27
H13	5848	8563	10748	27

H14	3690	7523	8979	24
H15A	9410	9171	11944	47
H15B	11547	8589	11765	47
H15C	10269	8309	13144	47

Torsion angles [°] for 1.

N1-C1-C2-C3	20.8(7)	S1-C9-C14-C13	-175.9(5)
C5-C1-C2-C3	141.8(6)	C3-C4-N1-C1	-23.9(7)
C1-C2-C3-C4	-35.5(7)	C3-C4-N1-S1	116.6(5)
C2-C3-C4-N1	36.4(7)	C5-C1-N1-C4	-122.2(6)
N1-C1-C5-C6	-178.7(5)	C2-C1-N1-C4	1.9(7)
C2-C1-C5-C6	63.8(8)	C5-C1-N1-S1	97.9(5)
N1-C1-C5-C8	53.3(8)	C2-C1-N1-S1	-138.0(5)
C2-C1-C5-C8	-64.2(8)	C4-N1-S1-O2	-174.0(5)
C8-C5-C6-C7	-6.0(12)	C1-N1-S1-O2	-37.4(5)
C1-C5-C6-C7	-133.6(8)	C4-N1-S1-O1	57.0(5)
C14-C9-C10-C11	-0.4(9)	C1-N1-S1-O1	-166.4(5)
S1-C9-C10-C11	175.0(5)	C4-N1-S1-C9	-57.9(5)
C9-C10-C11-C12	-0.1(9)	C1-N1-S1-C9	78.7(5)
C10-C11-C12-C13	1.4(9)	C14-C9-S1-O2	-150.8(5)
C10-C11-C12-C15	179.4(6)	C10-C9-S1-O2	33.7(6)
C11-C12-C13-C14	-2.2(9)	C14-C9-S1-O1	-20.4(6)
C15-C12-C13-C14	179.8(6)	C10-C9-S1-O1	164.2(5)
C12-C13-C14-C9	1.8(9)	C14-C9-S1-N1	94.3(5)
C10-C9-C14-C13	-0.4(9)	C10-C9-S1-N1	-81.2(5)

Appendix

List of Abbreviations and Acronyms

2-Me-THF	2-methyltetrahydrofuran
Ag_2O	silver(I) oxide
$AlBr_3$	aluminum bromide
atm	atmosphere
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BIPHEP	2,2’-bis(diphenylphosphino)-1,1’-biphenyl
(*R*)-Cl-MeO-BIPHEP	(*R*)-(+)-5,5’-dichloro-6,6’-dimethoxy-2,2’-bis((diphenylphosphino)-1,1’-bipenyl
Cs_2CO_3	cesium carbonate
$Cu(OAc)_2$	copper(II) acetate
$Cu(OAc)_2•H_2O$	copper(II) acetate monohydrate
DB^tPF	1,1’-bis(di-*tert*-butylphosphino)ferrocene
DCyPB	1,4-bis(dicyclohexylphosphino)butane
DCyPE	1,2-bis(dicyclohexylphosphino)ethane
DCyPM	bis(dicyclohexylphosphino)methane
DCyPP	1,3-bis(dicyclohexylphosphino)propane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DiPPF	1,1’-bis(di-*i*-propylphosphino)ferrocene
DMF	*N,N*-dimethylformamide
(*R*)-DM-SEGPHOS	(*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
DMSO	dimethyl sulfoxide
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1’-bis(diphenylphosphino)ferrocene

DPPM	bis(diphenylphosphino)methane
DPPP	1,3-bis(diphenylphosphino)propane
DPPPh	1,2-bis(diphenylphosphino)benzene
ee	enantiomeric excess
i-PrMgCl	isopropylmagnesium chloride
KOH	potassium hydroxide
$LiAlH_4$	lithium aluminum hydride
$LiBHEt_3$	lithium triethylborohydride
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
Na_2SO_4	sodium sulfate
$NaBH(OAc)_3$	sodium triacetoxyborohydride
$NaBH_4$	sodium borohydride
O_2	oxygen
PCy_3	tricyclohexylphosphine
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium(0)
$Pd(OAc)_2$	palladium(II) acetate
Pd/C	palladium on carbon
$PhI(OAc)_2$	(diacetoxyiodo)benzene
$Rh_2(tpa)_4$	rhodium(II) triphenylacetate dimer
tfacam	trifluoroacetamidate
THF	tetrahydrofuran
(-)-TMBTP	(-)-4,4’-bis(diphenylphosphino)-2,2’,5,5’-tetramethyl-3,3’-bithiophene

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