Title
Studies Towards the Synthesis of Optically Active Bicyclo[2.2.2]octa-2,5-dienes

Author
Lybbert, Breeyawn Nycole

Publication Date
2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Studies Towards the Synthesis of Optically Active Bicyclo[2.2.2]octa-2,5-dienes

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Chemistry

by

Breeyawn Nycole Lybbert

2012

ABSTRACT OF THE DISSERTATION

Studies Towards the Synthesis of
Optically Active Bicyclo[2.2.2]octa-2,5-dienes

by

Breeyawn Nycole Lybbert
Doctor of Philosophy in Chemistry
University of California, Los Angeles, 2012
Professor Michael E. Jung, Chair

Optically active 2,5-disubstituted bicyclo[2.2.2]octa-2,5-dienes (bod) have found use within synthetic organic chemistry as chiral ligands for rhodium asymmetric catalysis reactions. These chiral ligands often provide greater enantioselectivity than their phosphorus-based chiral ligand cousins when employed in the formation of carbon-carbon bonds under rhodium catalysis. The drawback to using these types of 2,5-disubstituted bicyclo[2.2.2]octa-2,5-diene ligands is that they are very expensive to buy if they are commercially available or they must be synthesized if they are not commercially available. Present literature syntheses of these bod ligands rely on the physical separation of diastereomeric derivatives via recrystallization with low recovery or the separation of enantiomers via chiral HPLC, in which only small amounts of material may be separated.

We have devised a synthesis of phenyl, benzyl, and methyl substituted bod ligands based on a bridged Robinson annulation reaction of 1,5-diketones and 1,5-ketoaldehydes, which gives the bicyclic core necessary for the bod ligand. Furthermore, our synthesis is designed to create optically active 1,5-diketones and 1,5-ketoaldehydes which transfer their chirality to the bicyclic core of the molecule. Our synthesis does not rely upon separation of racemic material at any step; instead we provide a method to synthesize any optically active bod ligand that is desired.

We successfully synthesized the chiral 3-allylcyclohexanone (>95% ee), a key intermediate in our synthesis, using a chiral conjugate allylation of α,β-unsaturated β-ketoesters using $Cu(OTf)_2$ and the chiral *t*Bu-box ligand. We then successfully completed the racemic synthesis of 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod) over 11 steps in 4.4% yield. The chiral Ph-bod ligand is projected to take 14 steps and proceed in a 1.1% overall yield. We also synthesized the racemic 2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene (Bn-bod) over 7 steps in 1.4% overall yield. The synthesis of 2,5-dimethylbicyclo[2.2.2]ocat-2,5-diene (Me-bod) was attempted but was unsuccessful at this time. Ultimately we proved the utility of the bridged Robinson annulation reaction for the synthesis of various bicyclo[2.2.2]octa-2,5-dienes.

The dissertation of Breeyawn Nycole Lybbert is approved.

Jing Huang

Neil Garg

Michael E. Jung, Committee Chair

University of California, Los Angeles

2012

To my beloved husband Adam who has been my support through all the hurdles of graduate school. To my parents, my brother, and Sterling and Sally who have always believed in me and supported me.

7/27/12

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

ACKNOWLEDGEMENTS

I am thankful for the many people that God has brought into my life that have given me their support in helping me obtain this degree. The road has not always been easy and straight and I have needed all of their support at one point or another along this journey. I first would like to thank my research advisor, Dr. Michael E. Jung. Thank you Boss for taking a chance on me and for accepting me into your research group. I sincerely could not have completed this degree without your support and encouragement. Thank you for your patience in mentoring me these last 6 years. I had my fair share of difficulties during my time in graduate school and you have stood by me through all of them. I will remember many things you told me in graduate school, but perhaps most of all I will remember that you once told me that "the point of choosing your career is to choose something that you love and that you are good at." That one piece of advice during a difficult time in graduate school changed my life and my career path. You helped me realize that teaching is my passion and it is something that I love and that I am good at. Thank you for helping me to obtain my doctorate degree so that I can live my passion and love my career as much as I know you love yours. You knowledge, your patience, and your love for your students are all things that I hope to bring to my own classroom in the future. Thank you for being my mentor.

Thank you to my doctoral committee members, Dr. Michael E. Jung, Dr. Neil Garg, and Dr. Jing Huang for the time you have spent reading this manuscript and helping me edit and prepare it. Thank you to my many lab mates over the last 6 years in the Jung group. The support and guidance that I received from many of you was essential to me completing this degree. Thank you to my fellow Jung group member and friend, Tim Dong, for all of your help and support. We started graduate school together and jumped all of the hoops together to finally be

able to finish our degrees together. Your friendly ear during both the good and bad times of graduate school really helped me keep things in perspective.

Thank you to Dr. Arlene Russell for giving me the opportunity to explore research in chemical education for the last 3 years. Dr. Jung helped me discover my passion for teaching and he sent me to you for guidance. You stoked the flames of my passion for teaching and I cannot thank you enough for being such a fantastic mentor, advisor, confidante, and source of direction to a wayward and discouraged graduate student. You helped me find the light and my own strength to complete my degree and reach for my goal of becoming a chemistry professor. Thank you for your encouragement and your friendship. I could not have done it without you.

Thank you to those people who have no idea what I do and what I want to teach for the rest of my life, to those people to who don't quite understand why I love school so much, to those people that supported me anyway and cheered me along when things got tough and rejoiced with me when things were great. Thank you to my family. First, thank to my beloved husband Adam. You have been with me through all of the good and the bad of graduate school. You have seen me at my lowest points and at my highest points. Thank you for being my support and for always having faith when I couldn't see the light. It is a joy to come home to you and to know how much I am loved. I look forward to this next chapter in our lives. Second, thank you to my parents and my twin brother. You have really been with me through everything. All of you have always seen the path ahead of me before I realized I was on it. When I told you I wanted to be a chemistry professor, you all laughed and told me that you always knew I would be a teacher, but that I needed to figure it out on my own. Mom and Dad, you always joke that you don't know where my brains came from, but I know they came from you. Mom, your quiet determination to get through anything life throws at you was your gift to me. Dad, your type-A

personality and your drive to succeed gave me strength to persevere. Brayland, our relationship and the support of my twin brother can never be replaced or replicated. Your confidence in me was always reassuring and helped me strive for excellence. Last, thank you to my second set of parents, Sterling and Sally. I would not have made it through my undergraduate degree if it wasn't for you two. You cosigned my student loans when I needed you to so I could focus on school and complete my Bachelor's degree in 4 years. If it wasn't for you, I may not have been able to complete college at all, and may have never made it to graduate school and onto a career that I love. Your support and confidence in me always drove me to succeed. Thank you.

Thank you to my undergraduate advisor and mentors, Dr. Thomas Hoye for introducing me to research and helping me get to graduate school, and to Dr. Gary Gray, the man who first taught me to love organic chemistry and advised me all through college. When I told Dr. Gray that I was taking a year off from school after undergrad to help my family, he told me "don't get comfortable, because you are going back [to graduate school]!" Well, Dr. Gray, I did go back and I succeeded in achieving not only my degree but all of the life lessons along the way.

Thank you to everyone who helped get me here. I didn't do this alone, and I will be eternally grateful for your support, encouragement, and your love.

VITA

2005	B.S. Chemistry Department of Chemistry University of Minnesota, Twin Cities Minneapolis, MN
2005-2006	Ecolab (contracted by Aerotek) Technician in Floorcare Department
2006-2010	Teaching Assistant/Associate Department of Chemistry and Biochemistry University of California, Los Angeles
2009	Award for Excellence in Teaching Department of Chemistry and Biochemistry University of California, Los Angeles
2010-2012	Graduate Research Assistant Department of Chemistry and Biochemistry University of California, Los Angeles Los Angeles, CA

Chapter 1: Introduction to Bicyclo[2.2.2]octa-2,5-dienes

Introduction and Literature Survey of the Use of Bicyclo[2.2.2]octa-2,5-dienes

The formation of carbon-carbon bonds is perhaps the central tenet of organic chemistry. The use of transition metals to catalyze the formation of carbon-carbon bonds is a wide and ever-developing field of chemistry. Within this field lies the desire to not only form carbon-carbon bonds with the help of transition metals, but to also complete these reactions in a stereocontrolled manner. The use of various small chiral molecules to act as ligands around the metal center is not a new concept in transition-metal-catalyzed asymmetric reactions. The use of chiral phosphorus-based molecules used as ligands is very well developed in this subfield of chemistry. The chiral phosphorus-based ligands have varying levels of success both in terms of reaction yield and enantioselectivity. In 2003, Hayashi and coworkers at Kyoto University in Japan reported their synthesis of (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.1]hepta-2,5-diene (Bn-nbd) **2**, a C_2-symmetric chiral diene ligand, that displayed high enantioselectivity (88-99%) in the rhodium-based asymmetric addition reactions between organoboronic acids and α,β-unsaturated carbonyl compounds (Figure 1).[1] This discovery helped launch the development of a new series of chiral ligands for rhodium metal based asymmetric catalysis reactions.

Although Hayashi had previously synthesized and used the chiral Bn-nbd ligand, he soon found that when synthesizing various other norbordiene ligands with aryl group substituents at the 2 and 5 positions, that these new chiral ligands **3** were not air or light stable. Therefore he devised and tested a new, more stable, bicyclic skeleton for the chiral diene ligands. Beginning in 2004, Hayashi reported the use of molecules containing the bicyclo[2.2.2]octa-2,5-diene scaffold **4** as chiral ligands for rhodium-based asymmetric catalysis reactions. Ligands like **4** with various R groups create a chiral environment around the rhodium metal center which then

allows for various chemical reactions to occur in a stereocontrolled manner. The use of chiral 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod) **5** and chiral 2,5-di(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene (Bn-bod) **6** ligands (as well as other variations) continues to be explored by Hayashi under rhodium-based catalysis conditions. In the last 8 years, Hayashi has written many articles detailing a variety of uses for various bicyclo[2.2.2]octa-2,5-diene ligands **4**.

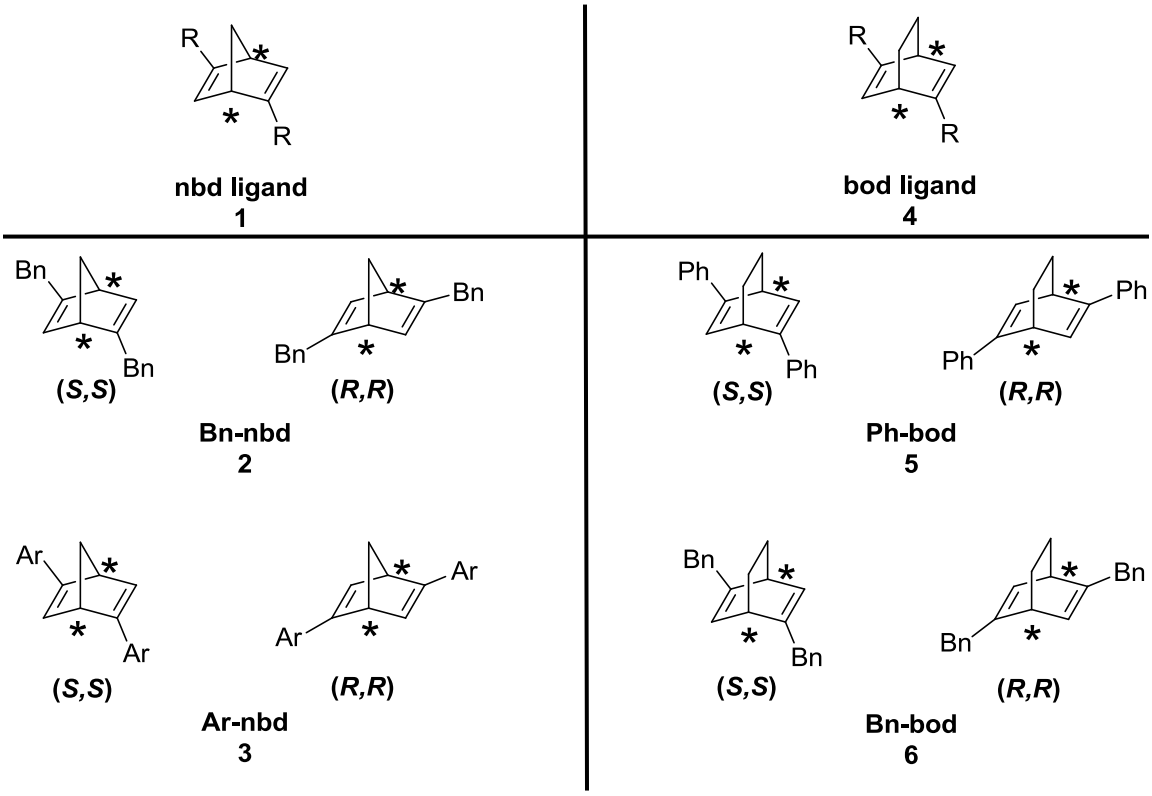


Figure 1. Bicyclo[2.2.1]hepta-2,5-diene **1** and Bicyclo[2.2.2]octa-2,5-diene **4** ligands.

The enantioselectivity of these reactions comes from the chiral environment created when the bicyclo[2.2.2]octa-2,5-diene is coordinated to the rhodium-metal center. As depicted in Figure 2, the rhodium-metal complexes the bod ligand, the enone, and the phenyl group, which

will be added enantioselectively to the β-position of the enone. The olefin of the enone is coordinated such that the carbonyl moiety is oriented away from the aryl substituent of the bod ligand. Interestingly, alkyl substitution at the β-position of the enone is not a major factor in determining the enantioface of the olefin coordination. As shown, both cyclic and acyclic enones are complexed from their α*re*-face which gives the 1,4-phenylated products with the observed configuration. Similar pictures can be drawn for various bicyclo[2.2.2]octa-2,5-diene based ligands complexed to a rhodium-metal center with various olefinic substrates.

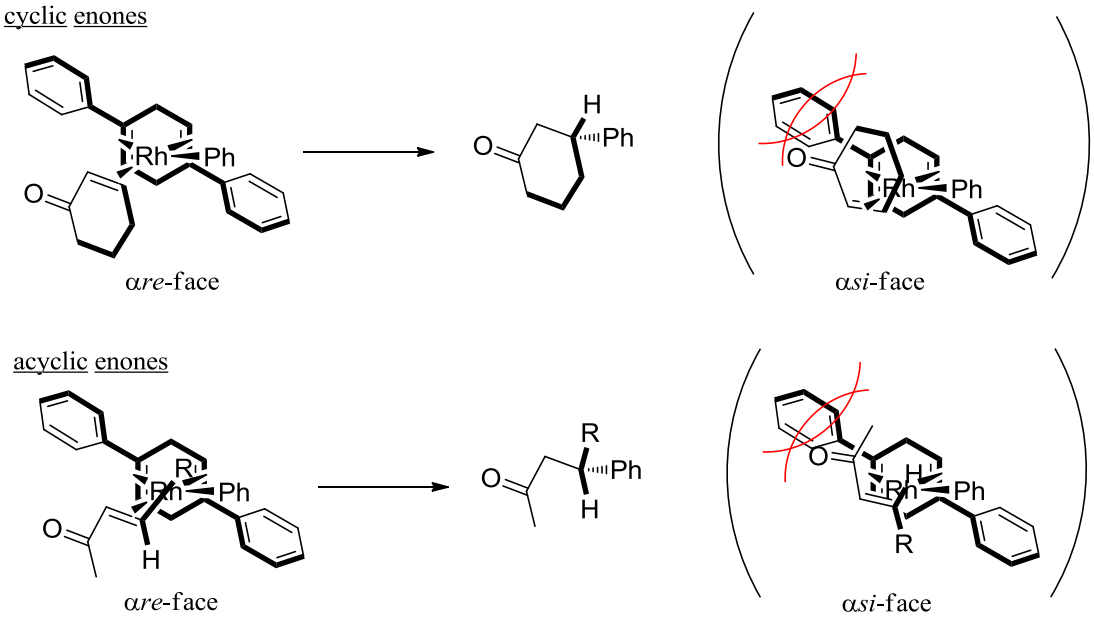


Figure 2. Rhodium complex coordinated with chiral Ph-bod ligand and cyclic/acyclic enones.

The most common type of reaction Hayashi has explored is the 1,4-addition of aryl groups to various α,β-unsaturated carbonyl compounds. In 2005, Hayashi reported the successful 1,4-addition of aryl groups to enones,[2] α,β-unsaturated Weinreb amides,[3] and β-silyl enones.[4] As shown in Figure 3, Hayashi reported the chiral β-phenylation of acyclic and cyclic enones **7** under rhodium-based asymmetric reaction conditions with phenylboronic acid using either the

Ph-bod **5** or the Bn-bod **6** ligand. In the case of the acyclic enones tested, Hayashi found the best results using the Bn-bod **6** ligand, which afforded the chiral β-phenyl ketone **8** in 94-97% yield and 94-98% enantiomeric excess. However, when cyclic enones were tested, it was found that the Ph-bod **5** ligand gave the best results. The corresponding chiral β-phenylated acyclic ketones **8** were isolated in 95-97% yield and 92-99% e.e. Hayashi makes specific note that the reactions were completed within 1 hour at 30 °C, which provided evidence that the rhodium/chiral diene complex's catalytic activity is higher than the rhodium/chiral binap complex typically used in such reactions previously in the literature.

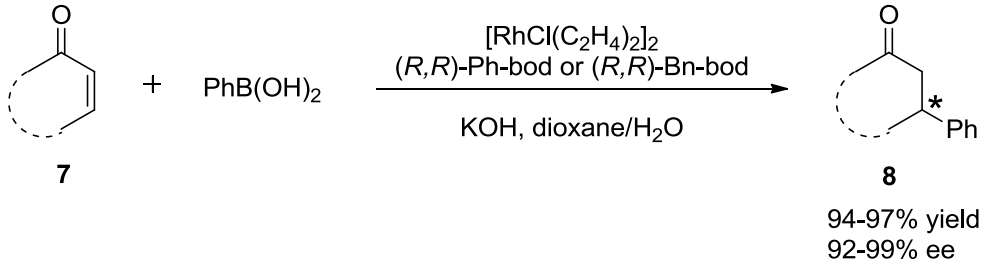


Figure 3. Enantioselective 1,4-addition of a phenyl group to cyclic/acyclic enones **7** using Rh/bod catalyst system.

Hayashi further demonstrated the successful advantage of the same rhodium/bod catalyst system over the rhodium/chiral binap catalyst system on α,β-unsaturated Weinreb amides. As shown in Figure 4, the chiral β-arylation of α,β-unsaturated Weinreb amides **9** was successful, both in yield and e.e., with the use of the (*S*,*S*)-Bn-bod ligand. The Bn-bod ligand gave higher yield (92%) and e.e. (90%) compared to the Ph-bod ligand (75% yield, 70% ee), as was expected for an acyclic substrate as revealed in Figure 3. The chiral β-arylated Weinreb amides **10** were isolated in 74-92% yield and 80-90% e.e. using various arylboronic acids.

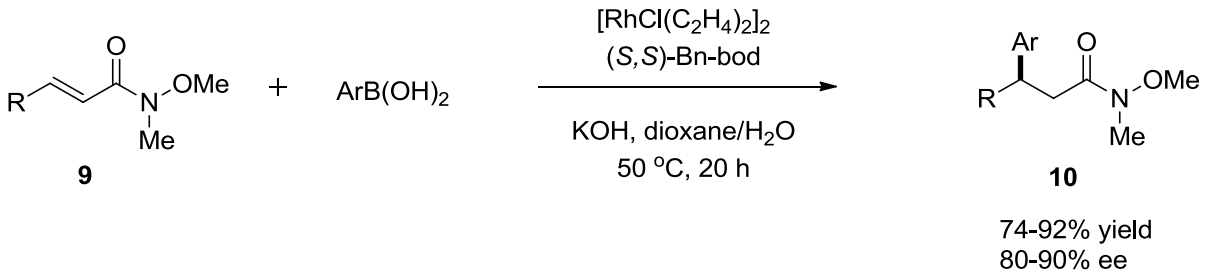


Figure 4. Enantioselective 1,4-addition of aryl groups to α, β-unsaturated Weinreb amides **11** using Rh/Bn-bod catalyst system.

Also in 2005, Hayashi reported the chiral β-arylation of β-silyl enones **11** under the rhodium/bod catalyst system with various arylboronic acids. Initial testing with phosphorus-based chiral ligands, (*R*)-binap and (*S*)-phosphoramidite, gave poor to moderate enantiomeric excess (14% and 72% respectively). Testing the phenyl and benzyl substituted bicyclo[2.2.2]octa-2,5-diene ligands gave a marked improvement in enantiomeric excess as well as yield (Ph-bod: 90% yield, 97% e.e. and Bn-bod: 94% yield, 99% e.e.). As expected, given the acyclic substrate, the Bn-bod ligand produced a better enantiomeric excess than the Ph-bod ligand and both bod ligands outperformed the phosphine based ligands. Overall, the chiral β-silyl β-arylated ketones **12** were isolated in 86-96% yield and 93-99% e.e. (Figure 5) using the rhodium/Bn-bod catalyst system.

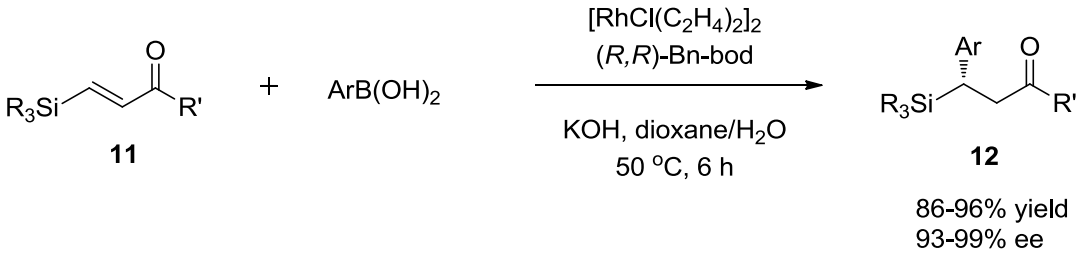


Figure 5. Enantioselective 1,4-addition of aryl groups to acyclic β-silyl enones **11** using Rh/Bn-bod catalyst system.

In 2006, Hayashi reported the asymmetric addition of aryl groups to 3-substituted maleimides **16** (Figure 6).[5] Interestingly, he found that the use of phosphorus-based chiral ligands ((*R*)-binap and (*R*)-H_8-binap) versus the chiral bod ligands gave different regioisomers of the succinimide product (**14** vs. **15**) and both types of ligands gave high e.e.'s. It was found that the phosphorus based binap ligands gave predominately asymmetric phenylation at C3, forming a quaternary carbon center, whereas the Ph-bod and Bn-bod ligands gave predominately phenylation at C4, forming a mixture of *cis/trans* isomeric succinimide products **15**. Although the *cis/trans* ratio for the bod ligands was not very good, the e.e.'s were high for both bod ligands (83-99%). Likewise, the binap ligands gave high e.e.'s as well (96-97%). Overall, Hayashi showed the usefulness of the chiral binap ligands as well as the chiral bod ligands in the selective formation of different regioisomeric succinimide products.

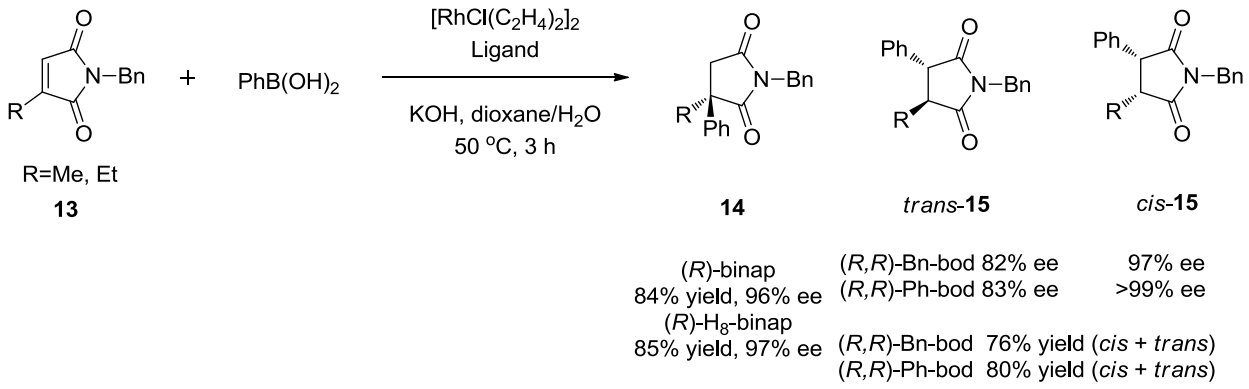


Figure 6. Enantioselective 1,4-addition of a phenyl group to 3-substituted maleimides **13**.

The following year, in 2007, Hayashi reported the asymmetric 1,4-addition of aryl and alkenyl groups to quinone monoketals[6] using organoboronic acids. He also reported the asymmetric 1,4-addition of aryl and alkenyl groups to β-silyl enones[7] and to cyclic and acyclic enones[8] via aryl

and alkenyl silanes. As an extension of the chiral β-arylation of various enones, Hayashi demonstrated the successful chiral arylation and alkenylation of quinone monoketals **16** (Figure 7). Similar to previous papers, Hayashi tested the chiral Ph-bod and Bn-bod ligands as well as the phosphorus-based chiral ligands (*R*)-binap and (*S*)-phosphoramidite. As seen previously, the chiral bod ligands outperformed the phosphorus-based ligands in both yield and e.e. The chiral Ph-bod ligand was ideal for the cyclic enones giving 86-98% yield and excellent enantiomeric excess (96-99%) with a variety of aryl and alkenyl boronic acids.

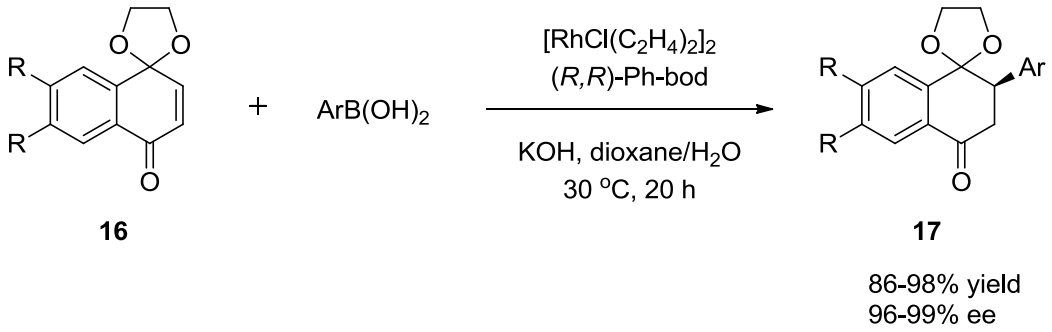
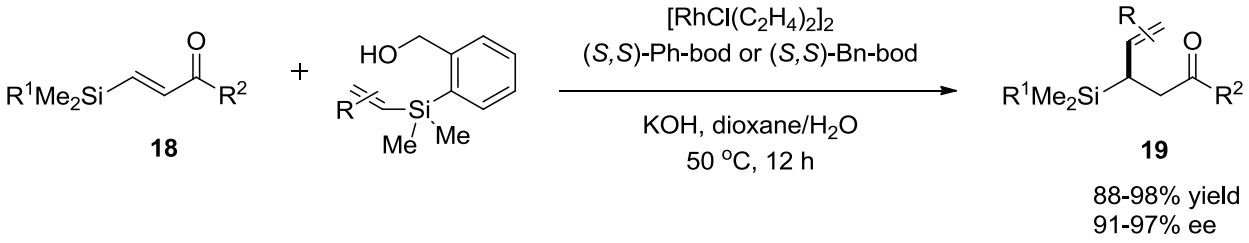


Figure 7. Enantioselective 1,4-addition of aryl groups to quinone monoketals **16**.

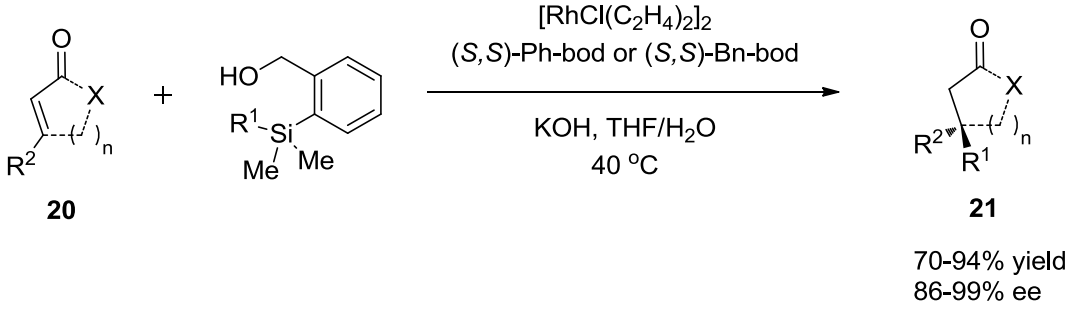
In a pair of papers published in 2007, Hayashi showcased the versatility of the rhodium/chiral bod ligand catalyst system by exploring the 1,4-addition reactions of α,β-unsaturated carbonyl compounds with aryl and alkenyl silanes instead of organoboronic acids.[7,8] As shown in Figure 8, the successful chiral β-alkenylation of β-silyl enones **18** using various alkenyl silanes gave the corresponding β-allyl silane products **19** in 88-98% yield and 91-97% e.e. Similarly to his previous papers, Hayashi showed that the phosphorus based chiral ligands (binap and phosphoramidite) gave poor yields and enantioselectivity. Luckily, both the Ph-bod and Bn-bod ligands gave indentical yields and enantioselectivity of the products. Interestingly in this case, the Ph-bod ligand, which precedent had shown tended to work better on cyclic substrates rather

than acyclic substrates, worked well here. Similar to Figure 8, the 1,4-addition of aryl and alkenyl groups to cyclic and acyclic α,β-unsaturated carbonyl compounds **20**, shown in Figure 9, also proceeded in high yield (70-94%) and high e.e. (86-99%). The precedented distinction between the Ph-bod and the Bn-bod ligands reacting preferentially with cyclic and acyclic substrates, respectively, is not evidenced here either. There seems to be no correlation between the ligand substitution and whether the substrate is cyclic or acyclic when dealing with aryl or alkenyl silane donors.



18 **19**

Figure 8. Enantioselective β-alkenylation of β-silyl enones **18**.



20 **21**

Figure 9. Enantioselective β-arylation of β-substituted cyclic/acyclic enones **20**.

Showcasing the utility of his catalytic system, in 2008 Hayashi reported the asymmetric 1,4-addition of aryl groups to the electron deficient olefins (*E*)-methyl 2-cyano-3-aryl

propenoates **22** (Figure 10). [9] The construction of a chiral diarylmethane center is of particular importance due to its presence in pharmaceuticals and natural products. The use of the Ph-bod ligand and various aryl boronic acids under rhodium catalysis gave the chiral β-diaryl substituted product **23** in >90% yield and 96-99% e.e. Again, the use of bod ligands was required to produce products with high e.e., since the phosphorus based (*R*)-binap ligand gave poor yields and poor enantioselectivity.

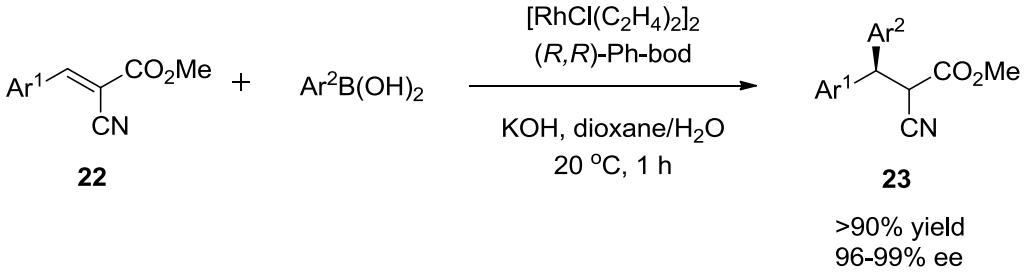


Figure 10. Enantioselective 1,4-addition of aryl groups to (*E*)-methyl 2-cyano-3-aryl propenoates **22** using Rh/bod catalyst system.

While continuing to explore variations on the 1,4-addition reaction motif, in 2005 Hayashi reported on the power of his standard reaction conditions in the addition/cyclization of arylboronic acids to alkynals **24** (Figure 11). [10] Multiple carbon-carbon bonds were formed under asymmetric reaction conditions to give the products **25** containing a tetrasubstituted olefin and a chiral secondary alcohol in good yield (71-89%) and high e.e. (93-96%). The Bn-bod ligand gave slightly better yields and enantioselectivity than the Bn-nbd ligand. The use of phosphine based ligands gave low yields and moderate enantioselectivity.

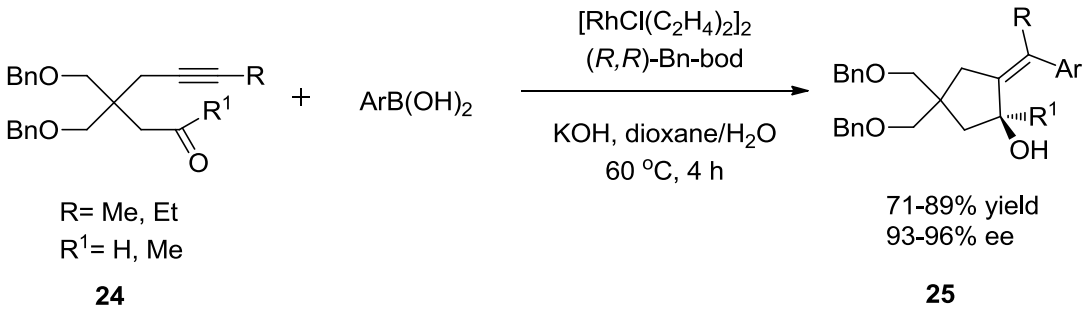


Figure 11. Enantioselective addition/cyclization of arylboronic acids to alkynals **24**.

Five years later, in 2010, Hayashi reported the asymmetric synthesis of spirocarbocycles from the arylation/cyclization of alkynyl enones **26** (Figure 12).[11] Use of the Ph-bod ligand gave only a moderate yield but excellent e.e. (95%). However, the use of the Bn-bod ligand gave an improvement in the yield and a slight improvement in e.e. (97%). Various aryl alkynyl groups and various tetraarylborates were submitted to the rhodium/Bn-bod reaction conditions and gave the trisubstituted olefinic spirocyclic products **27** in good yields (70-75%) and high enantiomeric excess (91-97%).

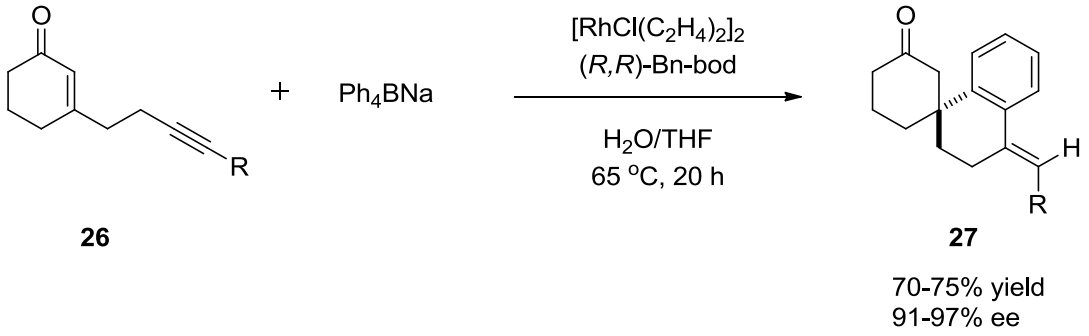


Figure 12. Enantioselective arylation/cyclization of alkynyl enones **26**.

In 2004 and 2006, early on in Hayashi's exploration of the chiral bod ligands in rhodium asymmetric catalyst reactions, he discovered the asymmetric 1,2-arylation[12] and methylation[13] of *N*-tosylarylimines **28**. The asymmetric arylation of various *N*-tosylarylimines with aryl boroxines gave the corresponding chiral amines **29** in 94-99% yield and 95-99% e.e. (Figure 13). Similarly the use of dimethylzinc gave chiral amines **30** in 61-91% yield and 94-98% e.e. (Figure 14). The phosphorus-based chiral ligands (*R*)-binap, (*R*)-segphos, and (*S*)-phosphoramidite all gave poor to moderate yields and e.e.'s of the chiral amine product.

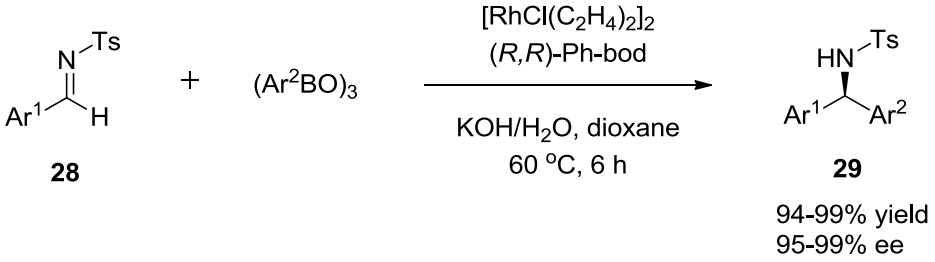


Figure 13. Enantioselective arylation of *N*-tosylarylimines **28**.

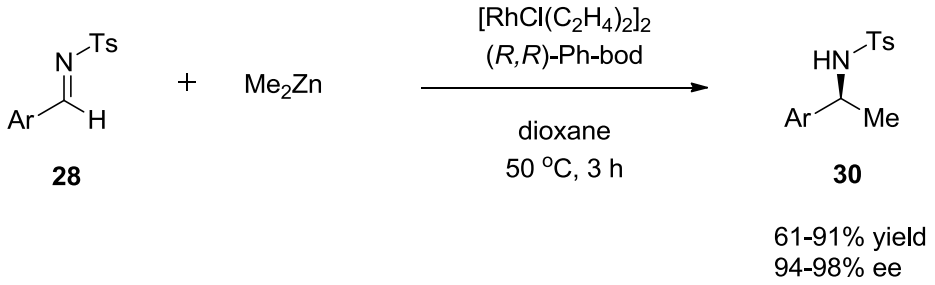


Figure 14. Enantioselective methylation of *N*-tosylarylimines **30**.

In a unique application of Hayashi's catalyst system, in 2011 Yoshida and Yanagisawa used Hayashi's work on the 1,2-addition of *N*-tosylarylimines **28**, and used the chiral zinc-

complexed tosylamine intermediate **31** as a catalyst for the asymmetric alkylation of aldehydes to form chiral alcohols **33** (Figure 15).[14] They found the optimal reaction conditions proceeded when the aryl substitution on the *N*-tosylamine was a 2,3-dimethoxyphenyl group. Subsequent use of the chiral zinc complex as the catalyst gave good to high yields (60-90%) and generally high e.e.'s (75-96%) of product.

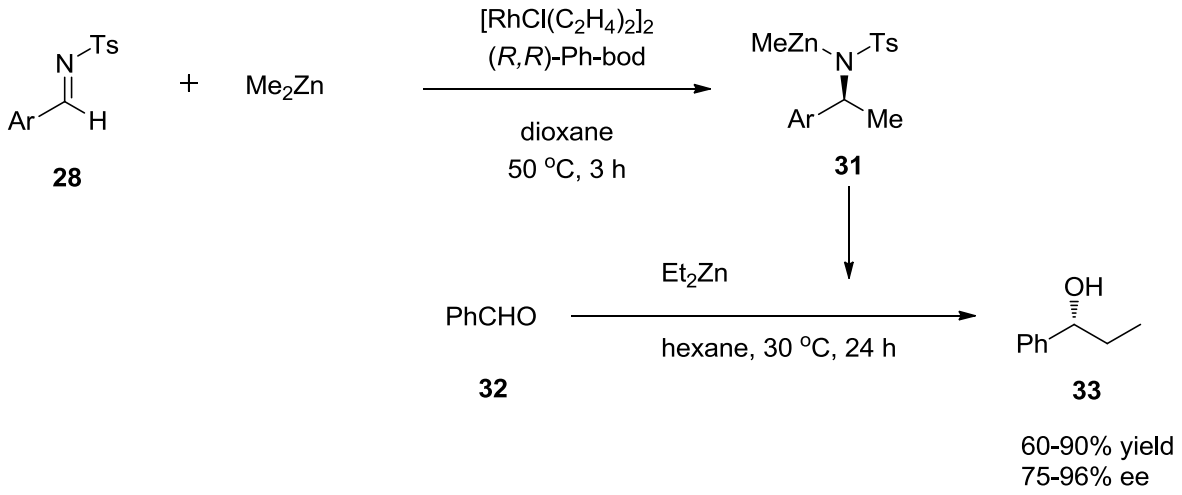


Figure 15. Use of chiral zinc-complexed tosylamines **31** as a catalyst for the asymmetric alkylation of benzaldehyde **32**.

Another unique application of the rhodium/chiral diene catalyst system was reported in 2007 by Hayashi to affect a 1,3-migration of an alkynyl silane of an α,β-unsaturated tertiary alcohol **34**, which resulted in the chiral β-alkynylsilyl ketone **35** in 91% yield and 97% e.e. when the (*S,S*)-Ph-bod was used as the chiral ligand (Figure 16).[15] When the (*R*)-binap ligand was used, the enantiomeric excess suffered, as it only produced product in 71% e.e.

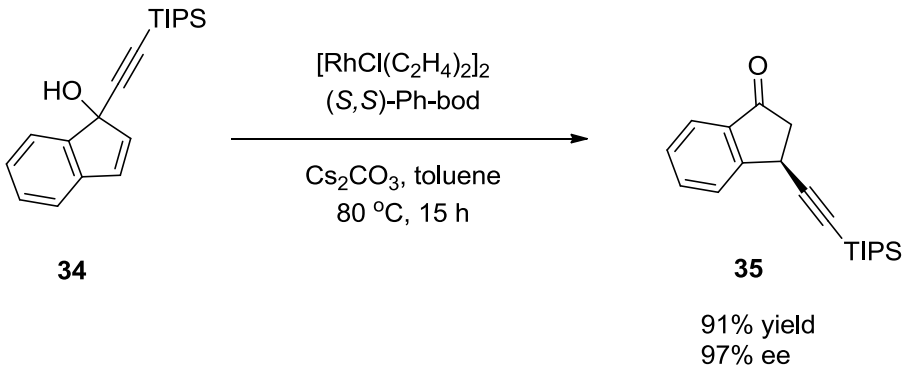


Figure 16. Asymmetric 1,3-migration of an alkynyl silane using Rh/bod catalyst system.

The power of the bicyclo[2.2.2]octa-2,5-diene scaffold in asymmetric rhodium-based arylation reactions has been and will continue to be explored in the chemical literature. Similar reactions have been used by others in rhodium-based asymmetric catalysis reactions that also rely on the bicyclo[2.2.2]octa-2,5-diene scaffold for their chiral ligands, but which are not C_2-symmetric. Carreira has written several papers which use bicyclooctadiene ligands which are derived from enantiomerically pure carvone.[16,17,18] Similar to Hayashi's chemistry, Carreira reports the successful asymmetric 1,4-addition of aryl groups to α,β-unsaturated aldehydes **36** using aryl boronic acids, which produced chiral β-diarylated aldehydes **38** in yields from 63-90% and high e.e.'s of 89-93% (Figure 17).[18]

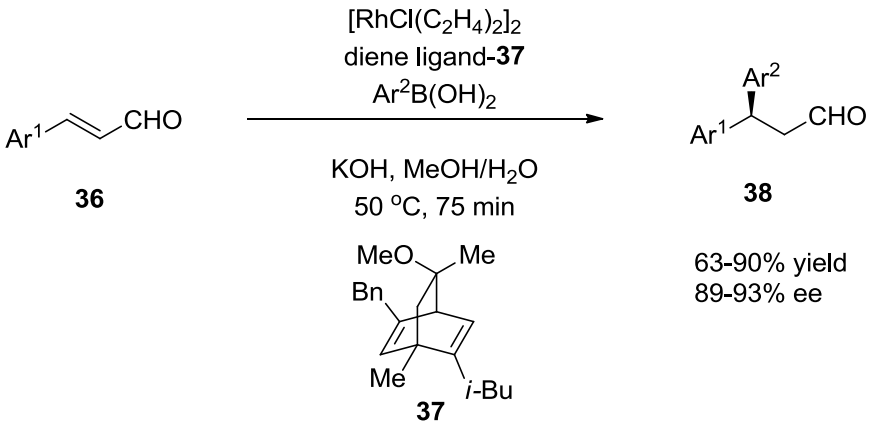


Figure 17. Enantioselective 1,4-addition of aryl groups to α,β-unsaturated aldehydes **36** using Rh/bod-**37** catalyst system.

Carreira also reported the use of a similar bicyclooctadiene ligand **41** containing an additional olefin substitution under the typical rhodium asymmetric catalysis conditions for the 1,4-addition of aryl groups to cyclic and acyclic α,β-unsaturated carbonyl compounds (**39** and **40**) (Figure 18). [16] High yields (78-98%) and high ee's (88-98%) for a variety of α,β-unsaturated carbonyls (ketones, lactones, amides, and esters) (**42** and **43**) were realized.

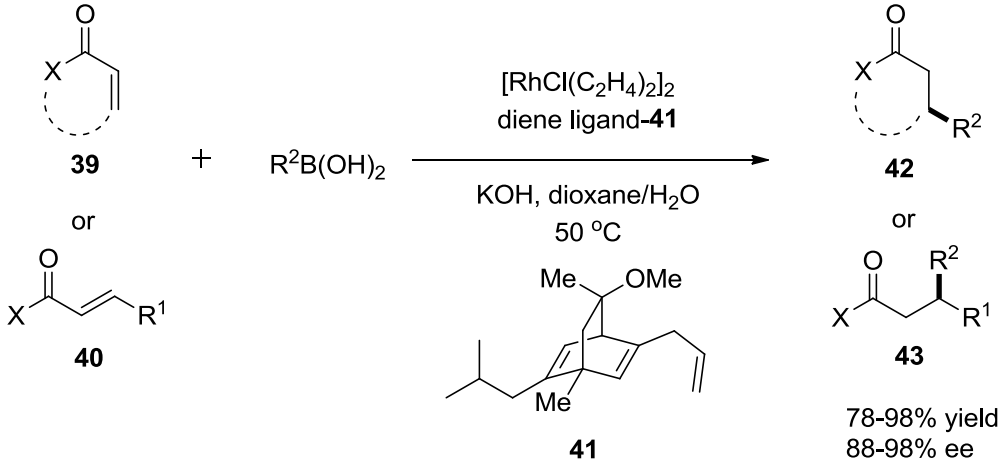


Figure 18. Enantioselective 1,4-addition of aryl groups to cyclic/acyclic α,β-unsaturated carbonyl compounds **39** & **40**.

As a different application of his bicyclo[2.2.2]octa-2,5-diene ligands, Carriera reported their use in the iridium catalyzed kinetic resolution of allyl carbonates **44** in up to 93% e.e. (Figure 19).[17]

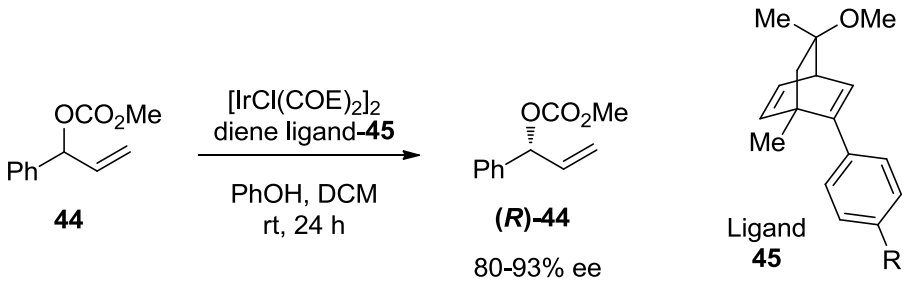


Figure 19. Kinetic resolution of allyl carbonates **44** using Ir/bod-**45** catalyst system.

Similar to Carriera, Hayashi and Rawal also reported a facile synthesis of a non-C_2 symmetric ligand based on the bicyclo[2.2.2]octa-2,5-diene scaffold in 2008. Hayashi and Rawal created their ligand from enantiomerically pure (*R*)-(-)-α-phellandrene in reaction with methyl propiolate to create the substituted bicyclic diene in 98% e.e.[19] Two more simple steps converted the ester moiety to the tertiary alcohol in good yield. This new ligand **47** was subsequently used under the standard asymmetric rhodium catalysis reaction conditions with aryl boronic acids and various enones **46**, both cyclic and acyclic, which gave high yields (87-96%) and high e.e.'s (81-99%) of the chiral β-arylated ketones **48** (Figure 20).

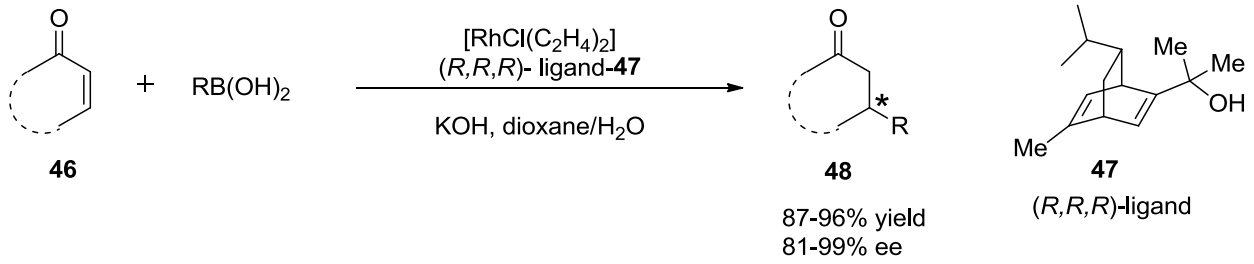


Figure 20. β-arylation of various enones **46** using Rh/bod-**47** catalyst stystem.

The advantage to Carreira's and Hayashi's non-C_2 symmetric bicyclo[2.2.2]octa-2,5-dienes is the scalability of the synthesis. Carreira's ligands are easily synthesized in 4-7 steps from a cheap, widely available, and enantiomerically pure starting material, (-)-carvone. Likewise, Hayashi and Rawal's non-C_2 symmetric bicyclo[2.2.2]octa-2,5-diene ligand is also available in 3 steps from a enantiomerically pure starting material, (*R*)-(-)-α-phellandrene. The Ph-bod ligand **5** is commercially available from Aldrich, but is very expensive, whereas the Bn-bod ligand **6** is not commercially available. These ligands must be synthesized when their use is desired and unlike their non-C_2 symmetric cousins, their synthesis is not as easily scalable and suffers from an overall low yield.

Synthesis of Bicyclo[2.2.2]octa-2,5-diene Ligands in the Literature

Hayashi cites the chemical literature in his synthesis of the various bod ligands he uses. The common method of synthesizing the bod ligands starts from the racemic bicyclo[2.2.2]octane-2,5-dione ***dl*-49** (Figure 21).[2] Hayashi gives two methods for the synthesis of Ph-bod and Bn-bod chiral ligands. Route A involves the creation of hydrazone diastereomers **50** from the racemic diketone and subsequent resolution of the diastereomers via recrystallization from methanol. Hydrolysis of the hydrazone and recrystallization gives the pure enantiomers of the diketone ***(R,R)*-49**. Vinyl triflate formation and cross-coupling with the appropriate Grignard reagent then gives the Ph-bod ***(R,R)*-5** and the Bn-bod ***(R,R)*-6**. Route B first creates the vinyl triflate ***dl*-51** of the racemic diketone and then cross couples it with the appropriate Grignard reagent giving a racemic mixture of the chiral Ph-bod **5** or Bn-bod **6**. The enantiomers are separated via chiral HPLC. Both routes have their drawbacks in terms of scalability. Route A suffers from a poor yield in the recrystallization step of the diastereomeric hydrazones (12%) as well as a poor yield in the hydrolysis of the hydrazone and recrystallization of the enantiomerically pure diketone (4%). Route B generally has good reaction yields, but suffers from the use of preperative chiral HPLC, in which only small amounts of crude product can be purified at one time in order to isolate each of the chiral bod ligands.

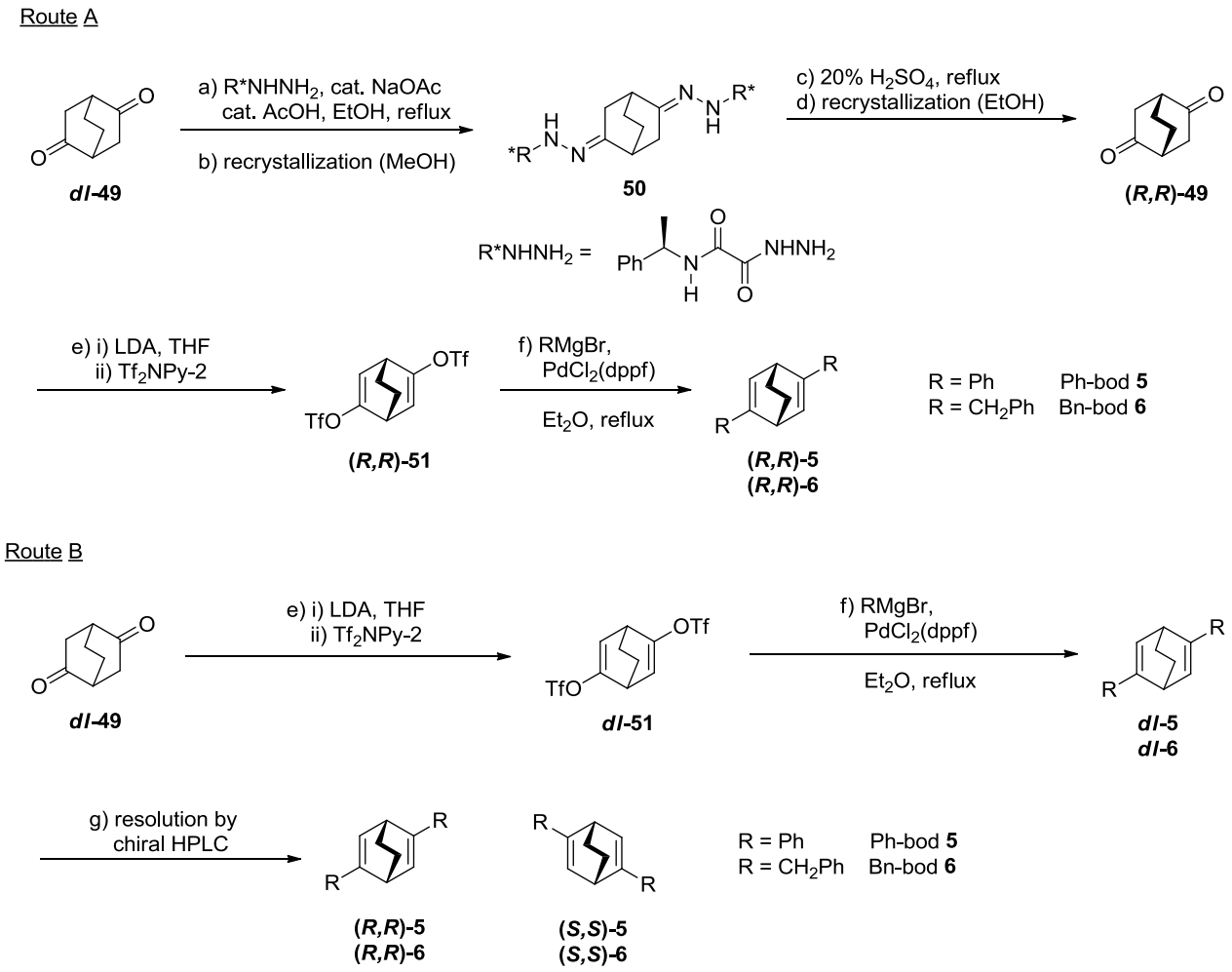


Figure 21. Synthesis of chiral Ph-bod **5** and Bn-bod **6**.

The racemic diketone ***dl*-49** starting material is typically obtained by a Diels-Alder cycloaddition of 2-acetoxypropenenitrile **53** and the trimethylsilyl enol ether of 2-cyclohexen-1-one **52** in 51% yield (Figure 22).[20] Another alternative in the synthesis of the diketone is the Diels-Alder cycloaddition between hydroquinone **55** and maleic anhydride **56** which after hydrolysis and reduction gives the bicyclic diketone ***dl*-49** in 3% yield from very cheap starting materials (Figure 23). [21] As can be seen from the general synthesis from the literature, the overall yield of either Ph-bod **5** or Bn-bod **6** is very low and suffers from a lack of general scalability.

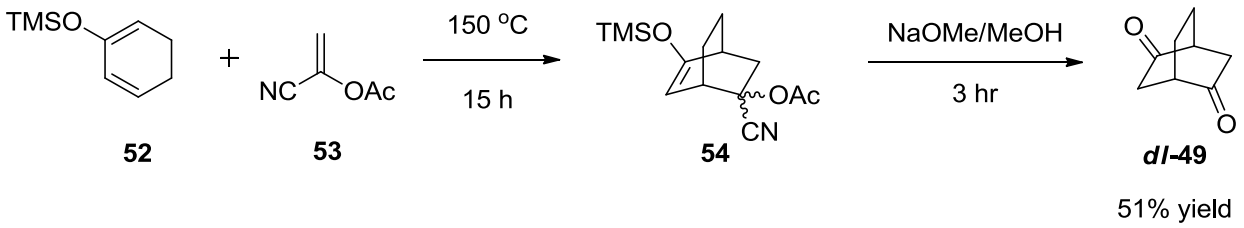


Figure 22. Synthesis of racemic bicyclo[2.2.2]octa-2,5-dione ***dl*-49** by Werstiuk.

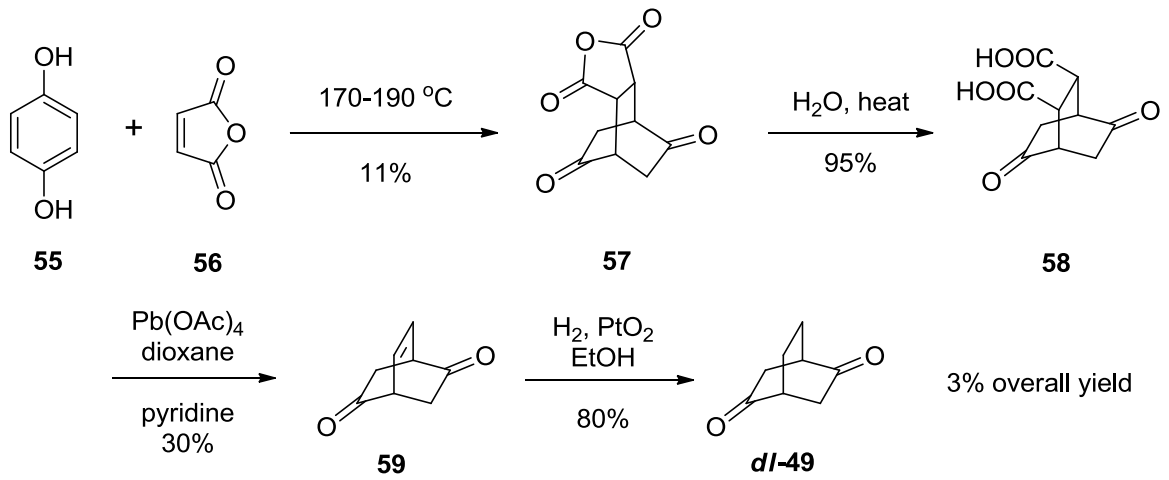


Figure 23. Synthesis of racemic bicyclo[2.2.2]octa-2,5-dione ***dl*-49** by Paquette.

Recently in 2012, a pharmaceutical company (Actelion Pharmaceuticals Ltd.) in Switzerland published a scalable synthesis of enantiomerically pure Ph-bod ***(R,R)*-5** as well as many non-C_2 symmetric variations (Figure 24).[22, 23] Their synthesis relies on an enantioselective Michael reaction between 2-cyclohexen-1-one **60** and dimethyl malonate catalyzed by the Shibasaki catalyst,[24,25] (R)- ALB (Al-Li-bis(binaphthoxide complex)), which gave the enantiomerically pure malonate product on a multi-kilogram scale. Subsequent ketalization of the cyclic ketone proceeded in high yield to give the pure malonate ketal product **61** in 85% yield over two steps. The next 9 steps all proceeded in good to high yields, with the exception of the

oxidation of the primary alcohol **64** to the aldehyde **65** and then the acid catalyzed aldol cyclization of the ketal aldehyde, which only proceeded in a 45% yield over two steps. Conversion of the bicyclic enone **68** to the desired Ph-bod ***(R,R)*-5** was then accomplished in 2 steps, via Grignard addition to the ketone and subsequent mesylation and elimination of the tertiary alcohol, in 65% yield. The overall yield for this process starting from 2-cyclohexen-1-one **60** to synthesis the chiral Ph-bod ***(R,R)*-5** ligand is 14%, which is an improvement over any previous literature procedures. However, the synthesis of the Bn-bod **6** ligand is not reported, only ligands with at least one phenyl substitution on the diene were synthesized. Therefore a good, scalable synthesis of Bn-bod **6** is still needed.

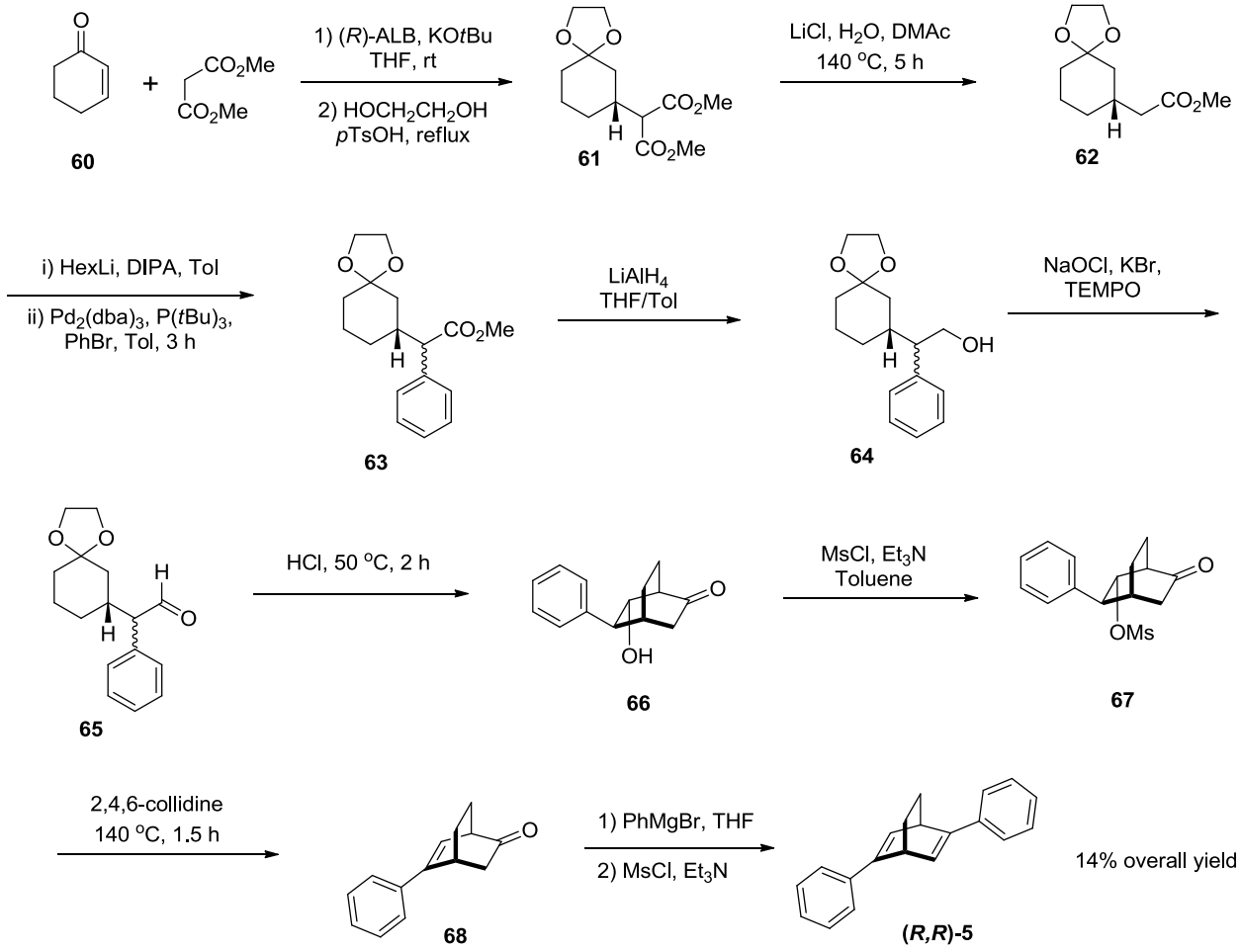


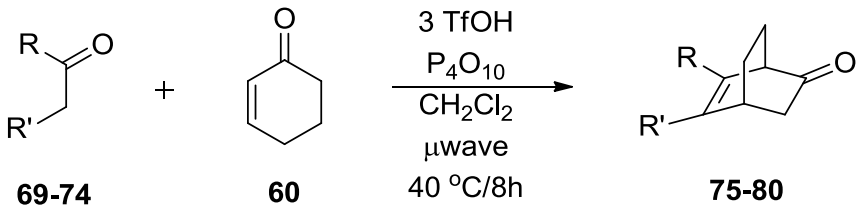
Figure 24. Industrial synthesis of (*R,R*)-Ph-bod **5** ligand.

In 2006, when we embarked on our own synthesis of various C_2-symmetric bicyclo[2.2.2]octa-2,5-dienes, we did so only with the knowledge of Hayashi's reported synthesis of these types of ligands which relied upon a physical separation of either diastereomers via recrystallization techniques or the separation of enantiomers via chiral HPLC, as described previously. Although as we now know in 2012, others were also working on a better synthetic route to these ligands, we started our own journey by recognizing work done within our own laboratory. We describe

here our proposed synthetic route to Ph-bod **5** and Bn-bod **6** using a bridged Robinson annulation reaction to create the necessary bicyclic core.

Our Synthetic Plan

Previous work in our lab led to the discovery that bicyclo[2.2.2]oct-5-en-2-ones **75-80**, possible precursors to the bicyclo[2.2.2]octa-2,5-dienes (bod), could be synthesized via a tandem intermolecular Michael addition-intramolecular aldol condensation process, effectively a bridged Robinson annulation, between 2-cyclohexen-1-one **60** and various ketones **69-74** (see Table 1) in a one-step process.[26]



69-74 **60** **75-80**

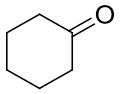
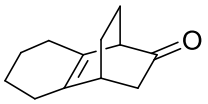
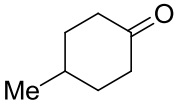
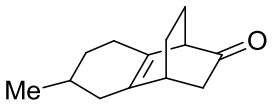
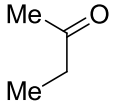
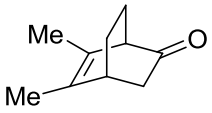
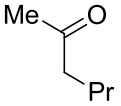
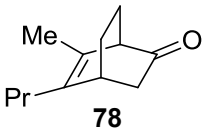
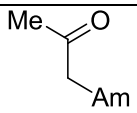
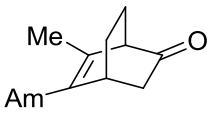
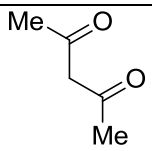
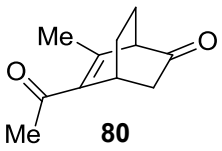
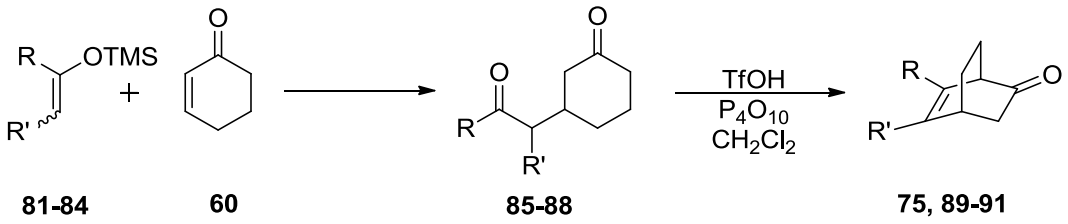
Entry	Ketone	Enone Product	Yield (%)
1	 **69**	 **75**	57
2	 **70**	 **76**	50
3	 **71**	 **77**	51
4	 **72**	 **78**	32
5	 **73**	 **79**	31
6	 **74**	 **80**	40

Table 1. One-step bridged Robinson annulation reaction.

It was discovered that simple methyl ketones gave poor yields and a two-step process was developed to circumvent this problem. In the case of methyl ketones, they were first converted to their corresponding trimethylsilyl enol ethers **81-84** and then subsequently reacted with 2-

cyclohexen-1-one **60** using $TiCl_4$ as a Lewis acid to facilitate the reaction. This gave the intermediate 1,5-diketones **85-88** as shown in Table 2. The 1,5-diketones were then subjected to the same acidic conditions as the one-step process to give the bicyclo[2.2.2]octa-5-ene-2-one products **75** and **89-91** in good yields.



81-84 **60** **85-88** **75, 89-91**

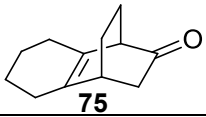
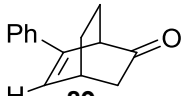
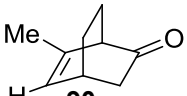
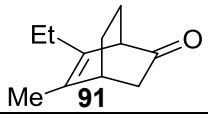
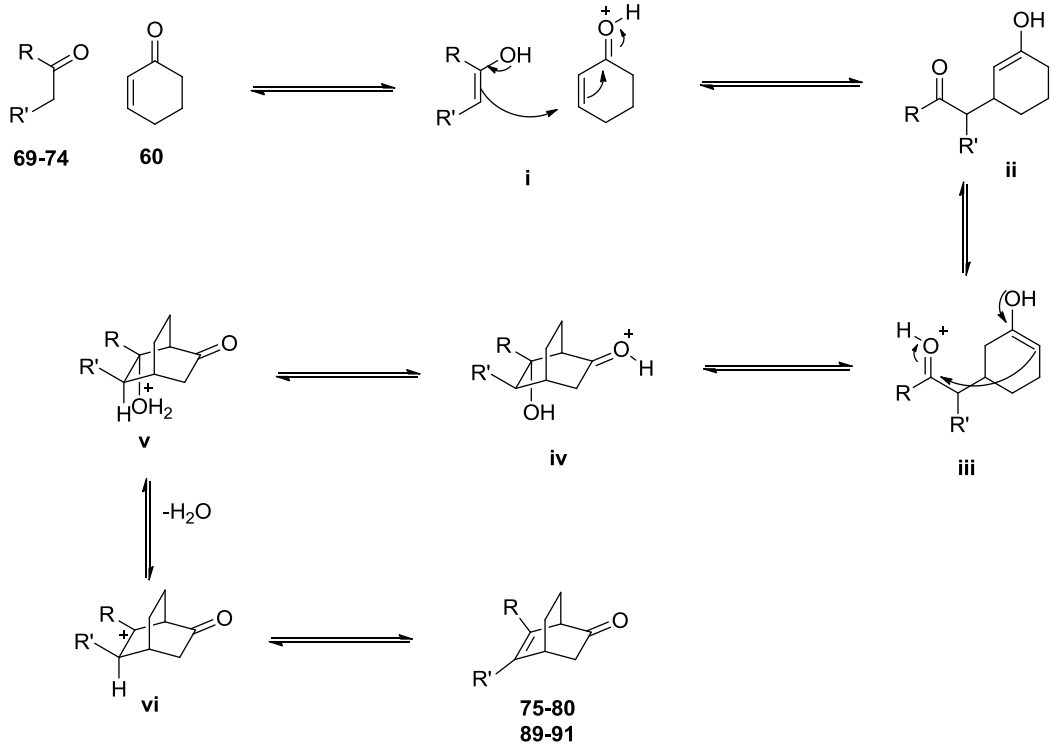
R, R'	Diketone Yield	Enone Product	Conditions	Enone Yield
$(CH_2)_4$ **81**	70%	 **75**	Microwave/40 °C/2 h	82%
Ph, H **82**	92%	 **89**	0 °C/30 min; 23 °C/45 min	78%
Me, H **83**	78%	 **90**	0 °C/1 h; 23 °C/40 min	51%
Et, Me **84**	93%	 **91**	Microwave/40 °C/8 h	40%

Table 2. Two-step bridged Robinson annulation.

Our proposed mechanism is shown in Scheme 1. Under the strongly acidic reaction conditions, the ketone is in equilibrium with its enol form and can subsequently attack the protonated enone **60** which gives intermediate **ii**. Intermediate **ii** then rearranges via proton transfers to intermediate **iii**, which is the starting point for the bridged Robinson annulation in the two step process. The enol portion of intermediate **iii** attacks the protonated carbonyl (an acid-catalyzed aldol reaction) to form the bicyclic intermediate **iv**. Intermediate **iv** is converted to

intermediate **v** via proton transfer. The intermediate **v** is dehydrated leaving the carbocation intermediate **vi**, which is deprotonated to give the final product, the bicyclic enone.



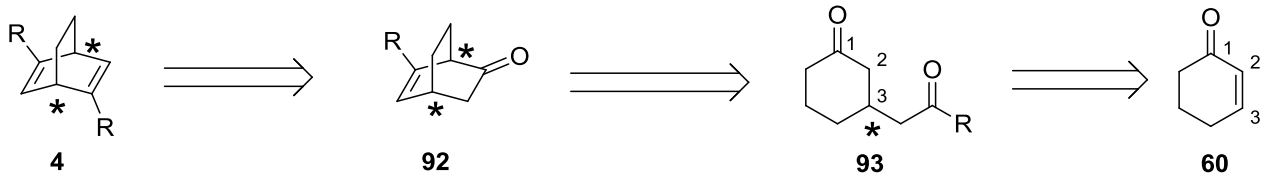
Scheme 1. Proposed mechanism for the bridged Robinson annulation.

These results prompted our exploration of the synthesis of bicyclo[2.2.2]octa-2,5-dienes (bod) ligands using the bridged Robinson annulation procedure to build the bicyclic framework. Of particular interest was the case using the silyl enol ether of acetophenone (R=Ph, **82**) since the bicyclic product **89** could be a reasonable precursor to the Ph-bod ligand **5** used extensively by Hayashi and others. Our task at hand was to devise a synthesis of various bod ligands, with particular emphasis on R=Ph and R=Bn as these ligands are the most commonly used in the literature. We also sought to investigate the synthesis of the alkyl bod ligands using R=Me.

Particularly we designed our synthesis in a stereocontrolled manner which would allow us to avoid having to separate racemic material at any step, as is done today.

Retrosynthetic Analysis

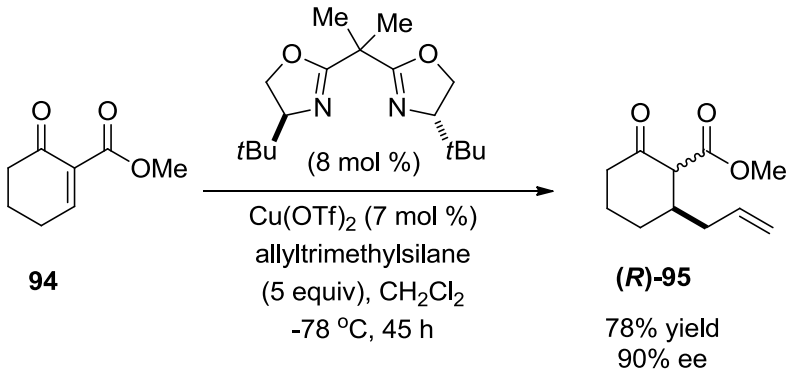
We turned our attention to the two-step procedure that was previously developed for the synthesis of these bicyclo[2.2.2]oct-5-en-2-ones since the intermediate 1,5-diketone looked to be a reasonable substrate in which we could impart stereocontrol. As shown in Scheme 2, if we could control the chirality of the stereocenter at C3 of 2-cyclohexen-1-one **60**, then that stereocenter would dictate the chirality of the bicyclic product **92** from the bridged Robinson annulation and the chirality of the molecule would be preserved through the final steps of the synthesis of the bod ligands **4**. The success of this proposed synthesis was reliant upon the enantioselectivity of the Michael reaction between 2-cyclohexen-1-one **60** and an appropriate small molecule that could provide a function group handle for further synthesis.



Scheme 2. Retrosynthetic Analysis.

While searching the literature for enantioselective Michael-type reactions with high enantiomeric excesses, we discovered a paper from the Snapper lab in which he reported the

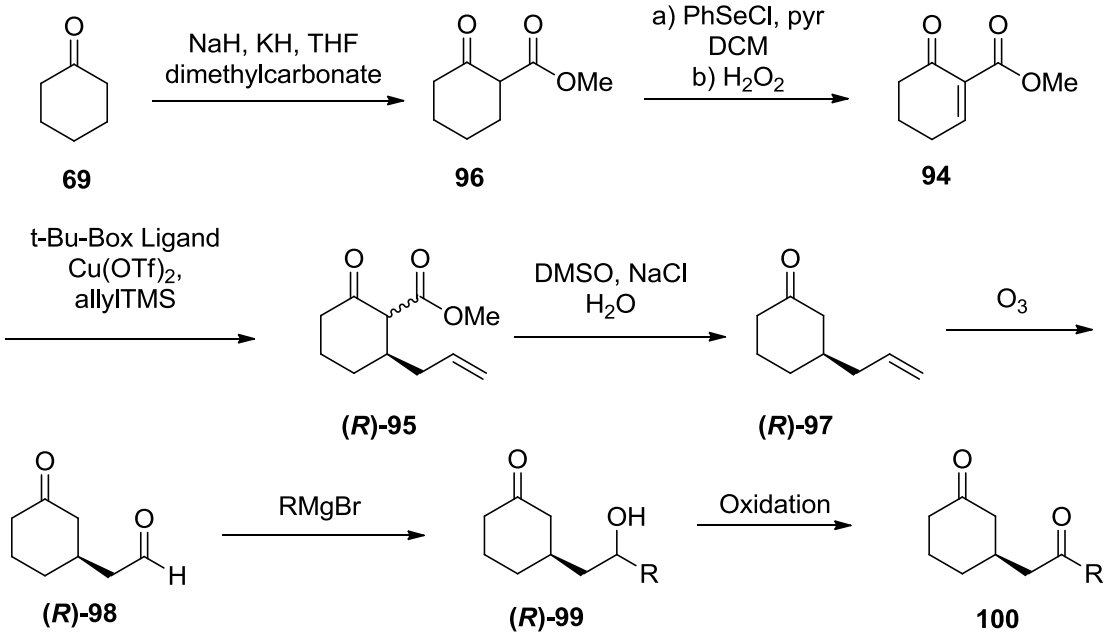
catalytic enantioselective Hosomi-Sakurai conjugate allylation of cyclic unsaturated β-ketoesters.[27] Snapper reported a 78% yield and 90% ee for the allylation of methyl 6-oxocyclohex-1-enecarboxylate **94** under copper catalyzed reaction conditions using the (*S,S*)-2,2'-methylenebis(4-*tert*-butyl-2-oxazoline) (*t*Bu-box) ligand to control the stereochemistry (Scheme 3). Snapper's conditions for the enantioselective Michael-type reaction were attractive to us due to the fact that the cyclic enone starting material was similar to that which we had originally envisioned, as well as the use of a well-known and simple catalyst system ((*S,S*)-*t*Bu-box and $Cu(OTf)_2$). Likewise, the addition of the allyl group at the C3 position of the enone gave us the necessary functionality that we would need to further synthesize the 1,5-diketones we desired.



Scheme 3. Snapper's enantioselective Hosomi-Sakurai conjugate allylation.

With Snapper's method in mind, we devised the following synthesis to allow us access to a variety of 1,5-diketones, in particular those where R=Ph, Bn, and Me (Scheme 4). The requisite methyl 6-oxocyclohex-1-enecarboxylate **94** was synthesized via a two-step process from cyclohexanone **69** by installation of the methyl ester and subsequent formation of the enone by elimination of the phenylselenenic acid. Snapper's Hosomi-Sakurai conjugate allylation

followed by decarboxylation of the methyl ester would yield the optically active allylcyclohexanone **(*R*)-97**. From the allylcyclohexanone we envisioned an ozonolysis step to remove the excess carbon as well as install an aldehyde which could then be further functionalized with the addition of various Grignard reagents. Oxidation of the secondary alcohols **(*R*)-99** would then yield the targeted optically active 1,5-diketones **100**.

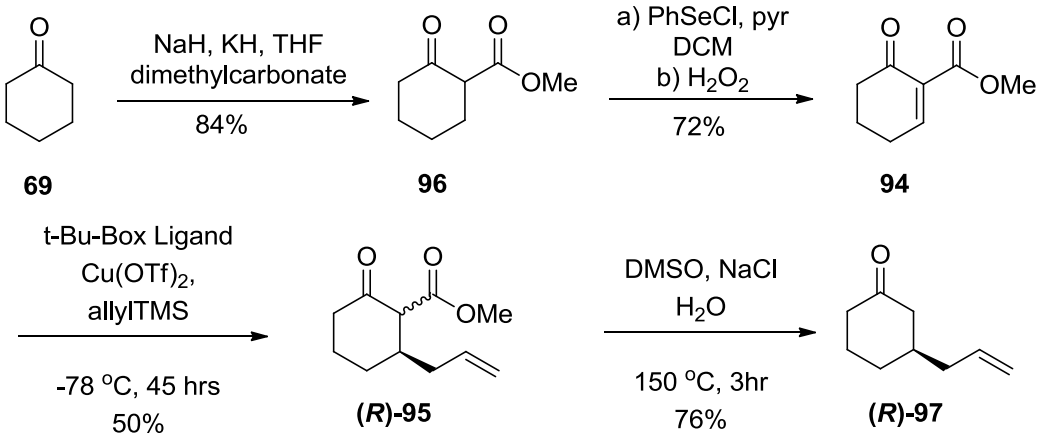


Scheme 4. Proposed synthesis of chiral 1,5-diketones **100**.

Chapter 2: Synthesis of Bicyclo[2.2.2]octa-2,5-dienes

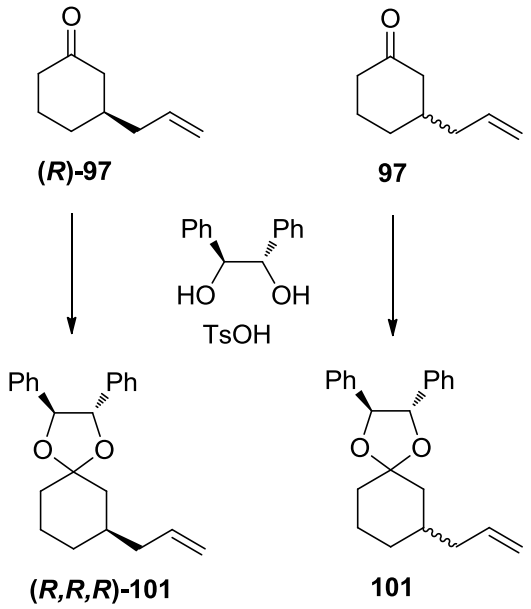
Synthesis of Chiral 3-Allylcyclohexanone and Proof of Optical Activity

As the first step in exploring this synthesis, we sought to duplicate Snapper's results by synthesizing the optically active 3-allylcyclohexanone **(*R*)-97**. Cyclohexanone is a cheap and widely available starting material, so the choice was made to start with it and create the necessary unsaturated β-keto ester **94** in two steps (Scheme 5). Addition of the methyl ester to cyclohexanone **69** was accomplished easily using NaH and dimethyl carbonate yielding the β-keto ester **96** in 84% yield.[28] The formation of methyl 6-oxocyclohex-1-enecarboxylate **94** was accomplished in 74% yield by elimination of the phenylselenic acid using hydrogen peroxide.[29] It was imperative in this reaction process to perform an intermediate acidic workup to remove all traces of pyridine from the reaction prior to the oxidation step to avoid accidental epoxidation of the resulting enone. With the unsaturated β-keto ester **94** in hand, we treated it with $Cu(OTf)_2$, (*S,S*)-*t*Bu-box, and allyl trimethylsilane at -78 °C for 45 hours. A slight modification from Snapper's original procedure, the addition of 4 Å molecular sieves to the reaction, helped ensure that the catalyst system was dry before addition of the unsaturated β-keto ester **94**. We isolated the allyl β-keto ester **(*R*)-95** in 50% yield compared to Snapper's reported 78% yield. Krapcho decarboxylation at 150 °C in DMSO provided the desired 3-allylcyclohexanone product **(*R*)-97** as mainly a single enantiomer (>95% ee) in 76% yield.



Scheme 5. Synthesis of optically active 3-allylcyclohexanone **(*R*)-97**.

To test the enantioselectivity of the Hosomi-Sakurai conjugate allylation, we synthesized the diastereomeric ketal of 3-allylcyclohexanone **(*R*)-97** by treating it with *R,R*-hydrobenzoin in the presence of *p*-toluenesulfonic acid (Scheme 6).[30] Analogously we created the same diastereomeric ketal of a racemic sample of 3-allylcyclohexanone **97**. Comparison of the ^{13}C NMR spectra of the two ketals showed a distinct difference between the two molecules. The ^{13}C NMR of the desired chiral allyl cyclohexanone ketal **(*R,R,R*)-101** showed a single set of peaks as would be expected of a pure sample (one diastereomer) (Figure 25). The ^{13}C NMR of the racemic allyl cyclohexanone ketal **101** showed a double set of peaks for the corresponding olefin signals as well as the alkyl carbon signals upfield (Figure 26). In the absence of a reliable optical rotation measurement, the evidence provided by ^{13}C NMR analysis assured us of the validity of Snapper's method to produce enantiomerically pure (>95% ee) allyl cyclohexanone **(*R*)-97**.



Scheme 6. Proof of optical activity of 3-allylcyclohexanone **(*R*)-97**.

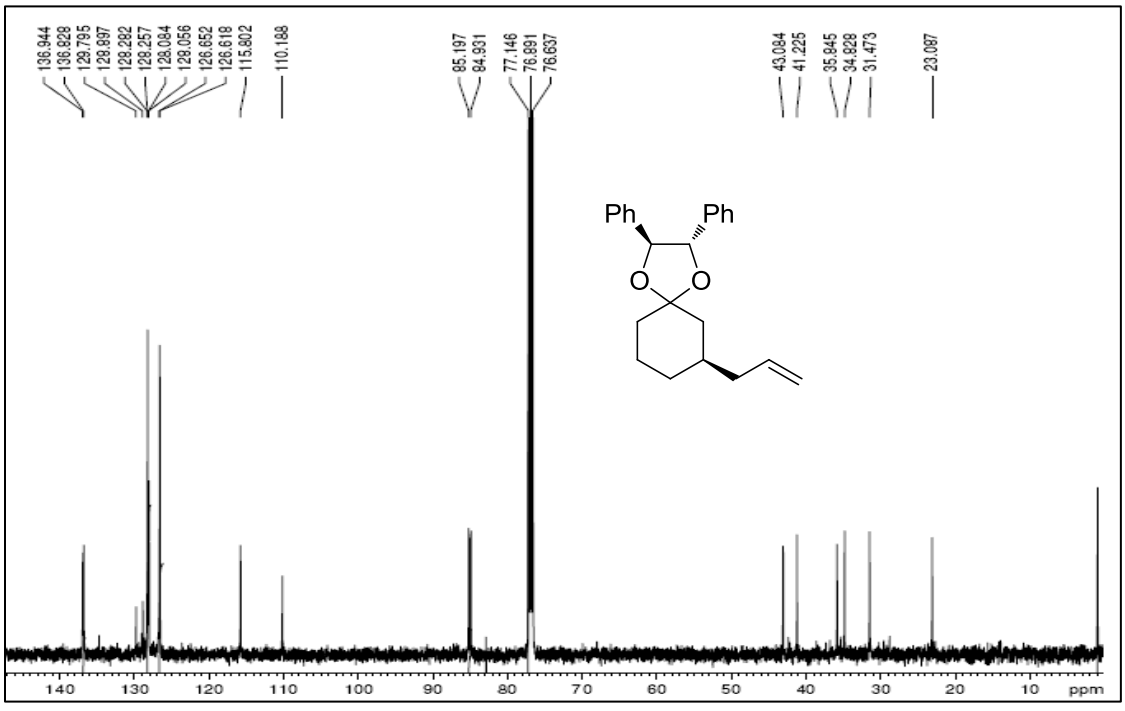


Figure 25. ^{13}C NMR of **(*R*,*R*,*R*)-101**.

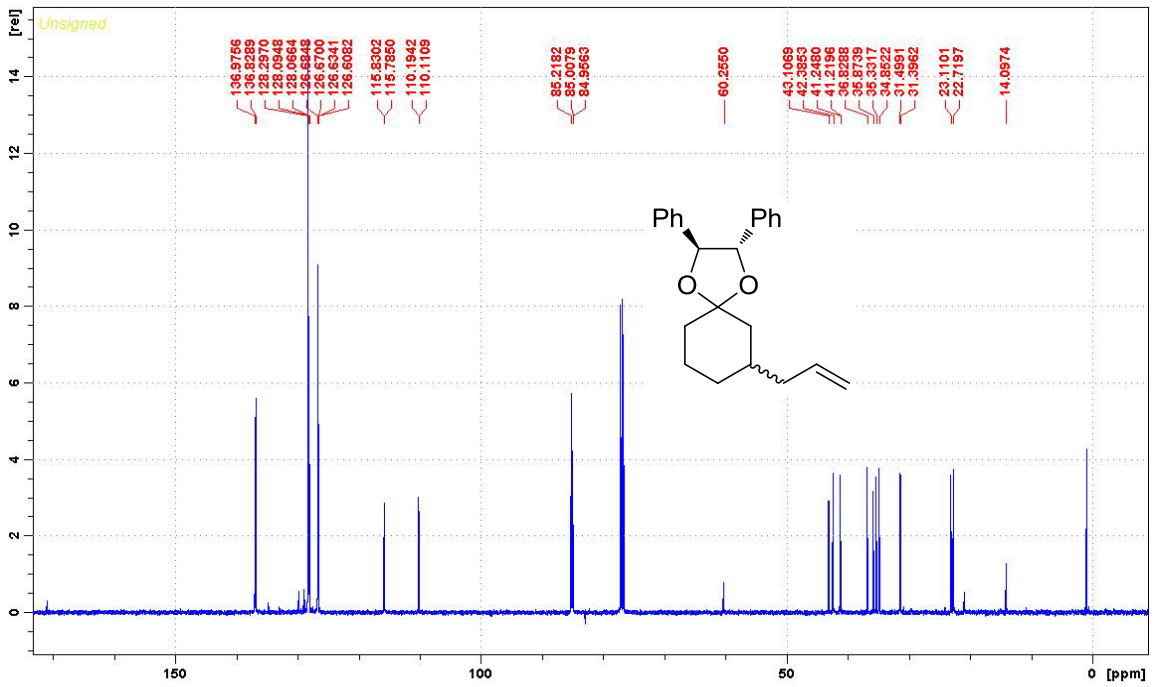


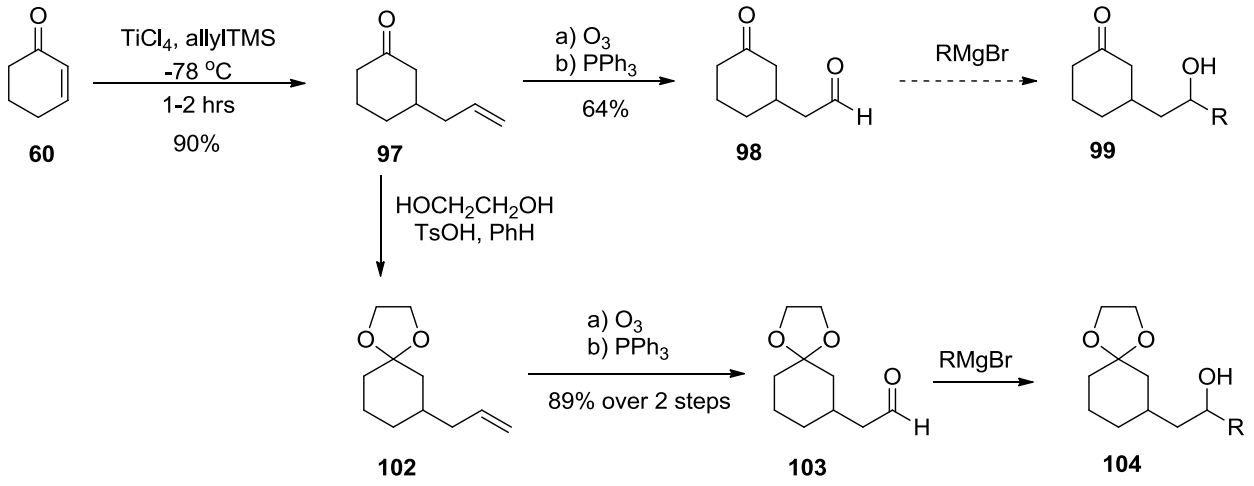
Figure 26. ^{13}C NMR of **101**.

Once we had proven that the enantioselective synthesis of 3-allylcyclohexanone **(*R*)-97** was possible in our hands, we set out to devise a synthesis of the requisite 1,5-diketones (R=Ph, Bn, and Me) and then to subsequently synthesize the corresponding bicyclooctadiene ligands via a bridged Robinson annulation. We elected to work out the synthesis using racemic material to avoid having to make multi-gram quantities of the expensive *t*Bu-box ligand.

Racemic Synthesis of Intermediate Ketal-Aldehyde 103

Creating multi-gram quantities of our desired starting material, racemic 3-allylcyclohexanone **97**, was easily accomplished in 90% yield in one step starting with 2-cyclohexen-1-one and treating with the Lewis acid $TiCl_4$ and allyltrimethylsilane (Scheme 7).[31]

Formation of 2-(3-oxocyclohexyl)acetaldehyde **98** was accomplished through ozonolysis of the allylcyclohexanone **97**.[32] We were originally hopeful that reaction conditions could be found that would allow for selective Grignard addition to the aldehyde carbonyl and not the ketone carbonyl. However, through many repeated trials, we discovered that the Grignard reagents were not selective in their attack on the two available carbonyls. We commonly isolated the cyclohexane moiety with R groups attached at both the ketone and aldehyde carbonyl carbons. Therefore, protection of the ketone functionality was deemed necessary. Protection of the ketone was accomplished by treating the allylcyclohexanone **97** with ethylene glycol and *p*TsOH in refluxing benzene to form the ketal **102**.[30] The protected product **102** was then subjected to ozonolysis conditions which produced the ketal aldehyde product **103**.[32]



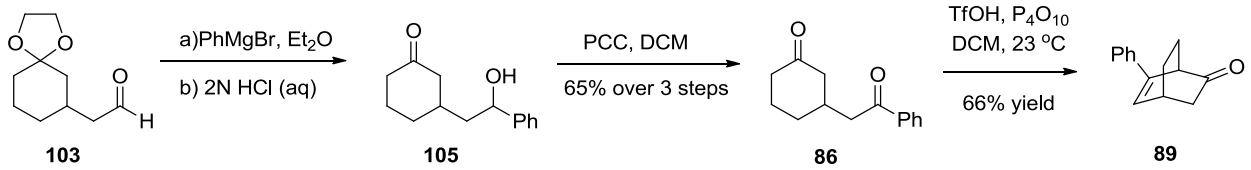
Scheme 7. Synthesis of racemic 3-allylcyclohexanone **97** and racemic ketal aldehyde **103**.

At this point in the synthesis, we had reached a fork in the road, in which separate paths would be taken to produce the Ph-bod ligand and the Bn-bod ligand from the common ketal

aldehyde intermediate **103**. Synthesis of the Me-bod ligand would be explored as well to test the viability of our synthesis using smaller alkyl substituents.

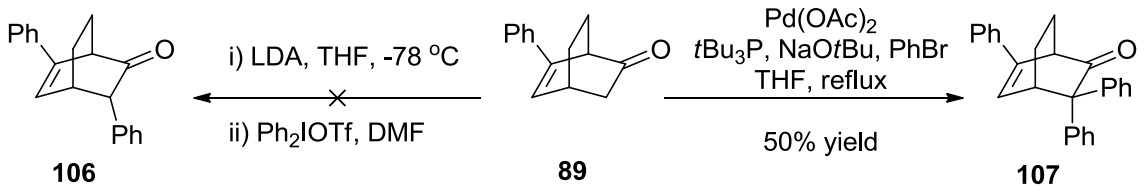
Synthesis of Racemic (1*R*,4*R*)-2,5-Diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod)

The ketal aldehyde **103** was treated with a freshly prepared solution of phenylmagnesium bromide in diethyl ether and then the reaction was quenched with a 2N HCl solution which not only quenched the Grignard reaction but also facilitated removal of the ketal moiety to produce the keto secondary alcohol **105** (Scheme 8).[33] Oxidation of the alcohol to the phenyl ketone **86** was possible with many oxidizing agents, but we found that pyridinium chlorochromate (PCC) gave the best results.[34] The phenyl substituted 1,5-diketone **86** was isolated in 65% yield over 3 steps. The 1,5-diketone underwent the bridged Robinson annulation via treatment with 2 equivalents of trifluoromethanesulfonic acid (TfOH) in dichloromethane at 23 °C in the presence of phosphorus pentoxide as a dessicant.[26] This dessicant is necessary since the reaction produces an equivalent of water due to dehydration of the initial aldol product. The bicyclic product **89** was isolated in 66% yield along with 10% of the unreacted 1,5-diketone **86**, which could be recycled.



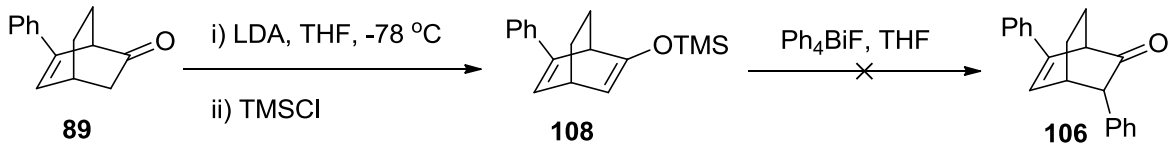
Scheme 8. Synthesis of bicyclic enone **89**.

Our next challenge was to introduce a phenyl group next to the carbonyl. A survey of the literature revealed that the common methods for the addition of "Ph^+" was to use either Buchwald conditions (aryl halide, palladium catalysis, and sodium *tert*-butoxide)[35] or use basic conditions and diphenyliodonium triflate (Ph_2IOTf).[36] In our circumstances, the Buchwald conditions worked too well, giving us the diphenylated product **107** instead of the monophenylated product **106** we desired (Scheme 9). Mechanistically this was not surprising due to the enhanced acidity of the proton α to the ketone once one phenyl group has been added. The second addition of phenyl was highly favored and faster than continued monophenylation of the remaining starting ketone. As such, the reaction proceeded to 50% conversion of the ketone and then stopped once all of the bromobenzene had been consumed. We elected to test other conditions for the phenyl addition rather than attempt to optimize the Buchwald conditions. Our next approach was to synthesize diphenyliodonium triflate and under basic conditions to effect the addition of phenyl α to the ketone. Multiple attempts were made with different bases (LDA, LiHMDS), and reaction times and temperatures to encourage formation of our desired phenylated product. However, none of these attempts were successful as they all returned unreacted starting material. Formation of the enolate was not thought to be a problem; instead we believed the issue was the addition of the Ph_2IOTf reagent. The diphenyliodonium triflate reagent was only soluable in *N,N*-dimethylformamide (DMF), and although steps were taken to ensure complete absence of water from the reagent and solvent, we believe the reagent addition was quenching the enolate and not allowing any further reaction.



Scheme 9. Attempted mono-phenylation of **89**.

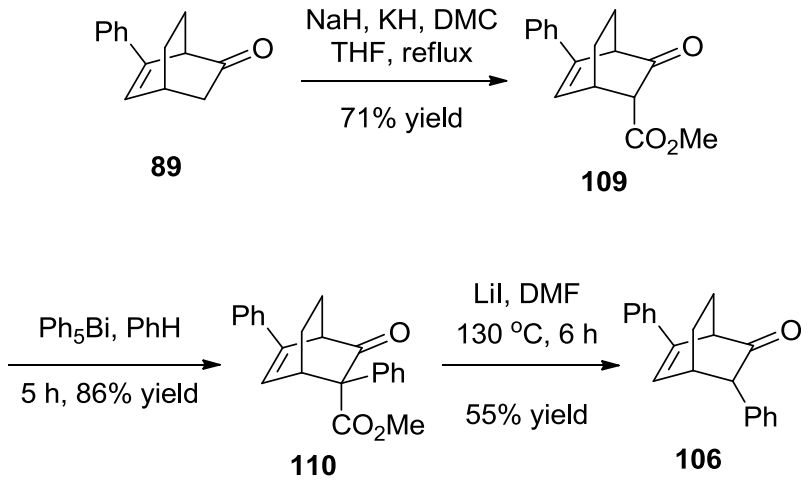
Our next recourse was to look into bismuth chemistry, popularized by Barton. During our search of the literature, a paper by Maruoka was found detailing their use of fluorotetraphenylbismuth for the monophenylation of the silyl enol ethers of various ketones.[37] This method was attractive due to multiple examples of monophenylation rather than diphenylation of substrates without a blocking group to prevent it. Also, formation of the silyl enol ether **108** of our starting ketone **89** was easily accomplished with LDA and TMSCl. Formation of Ph_4BiF was problematic due to poor yields in the conversion of Ph_3BiF_2 to the $[Ph_4Bi]^+$ $[BF_4]^-$ salt and then subsequent ion exchange to afford Ph_4BiF. The small amount of Ph_4BiF that was isolated was used in an attempt to form our monophenylated product **106** but this reaction was unsuccessful (Scheme 10).



Scheme 10. Attempted mono-phenylation of **89** with Ph_4BiF.

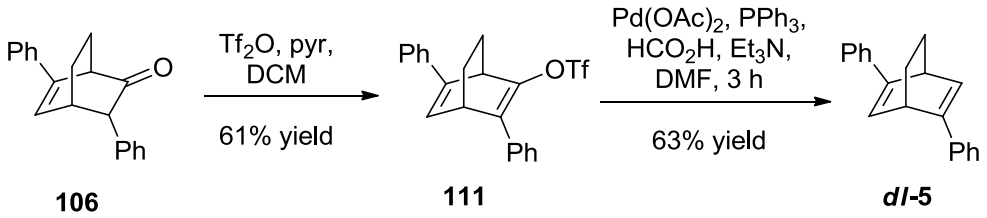
While we were exploring this bismuth based chemistry, a Barton paper was found detailing the addition of a phenyl group to the α-carbon of various β-keto esters using

pentaphenylbismuth (Ph_5Bi).[38] We had originally discarded this method due to the presence of the ester group which our system lacked. However, after many unsuccessful attempts with other phenylation systems, we decided to attempt these conditions. Creation of the β-keto ester **109** was effected by treating the starting ketone **89** under basic conditions with dimethyl carbonate in THF at reflux for 2 hours (Scheme 11).[28] The β-keto ester **109** was isolated in 71% yield as a 2:1 mixture of diastereomers with the α-ester being the major product. The newly installed ester serves two purposes: 1) it does not allow for our substrate to be diphenylated and 2) the ester is needed to provide the necessary acidity to the α-hydrogen for the bismuth reagent to abstract it. Happily, we found under mild reaction conditions that the α-phenylation of the β-keto ester **109** was easily effected, providing the desired phenyl substituted β-keto ester **110** in 86% yield as a single diastereomer. Calculations support our proposed diastereomer where the ester is in the α-position rather than the β-position. Ultimately, for our purposes, it does not matter which diastereomer we obtained, since we would be introducing an olefin at that position later in the synthesis. Subsequent removal of the extraneous ester moiety was accomplished under Krapcho decarboxylation conditions giving the diphenylated bicyclic product **106** in 55% yield as a 1:1 separable mixture of diastereomers.[33]



Scheme 11. Synthesis of diphenylbicyclic enone **106**.

To finish the synthesis of racemic (1*R*, 4*R*) 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ***dl*-5** (Ph-bod), the two final steps were readily completed (Scheme 12). Formation of the vinyl triflate **111** was achieved using trifluoromethanesulfonic anhydride and pyridine in dichloromethane giving the desired product in 61% yield. The final cross coupling step replaced the vinyl triflate group with a hydrogen atom under palladium catalysis with formic acid and triethylamine, which gave the desired Ph-bod ***dl*-5** in 63% yield.[39]



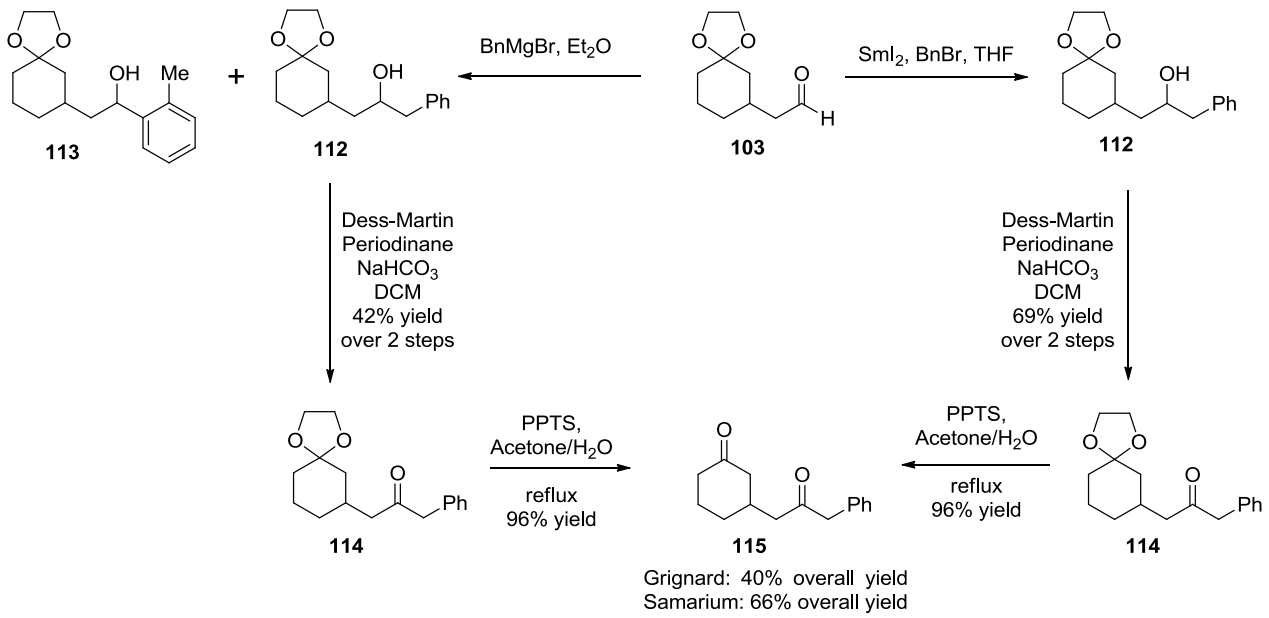
Scheme 12. Final steps in the synthesis of racemic Ph-bod **5**.

Our synthesis of racemic (1*R*, 4*R*) 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ***dl*-5** (Ph-bod) involved 11 steps, starting from 2-cyclohexen-1-one, with a 4.4% overall yield. The proposed synthesis using these same reactions for the synthesis of chiral (1*R*, 4*R*) 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene **(*R,R*)-5** would contain 14 steps, starting with cyclohexanone, with a 1.1% overall yield. The 10 steps to synthesize Ph-bod ***dl*-5** from 3-allylcyclohexanone are accomplished in 4.9% overall yield. The common intermediate in both syntheses is the 3-allylcyclohexanone **97**, after which the synthesis of Ph-bod becomes congruent. The disparity in overall yields is accounted for by the extra steps necessary to synthesize the unsaturated β-keto ester to apply Snapper's chemistry to create the enantiomerically pure 3-allylcyclohexanone **(*R*)-97**.

Synthesis of Racemic (1*R*,4*R*)-2,5-Bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene (Bn-bod)

The synthesis of racemic (1*R*,4*R*)-2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene ***dl*-6** (Bn-bod) was envisioned to be completely analogous to the synthesis of Ph-bod **5** (Scheme 13). Therefore, beginning with the ketal aldehyde **103**, we proposed an analogous Grignard reaction using benzylmagnesium bromide to create the necessary benzyl alcohol **112**.[40] We soon discovered that although the Grignard reaction does work, it comes with some drawbacks. We found that the commercially available solutions of benzylmagnesium bromide (1.0 M in diethyl ether) commonly resulted in formation of the desired alcohol but also the formation of a side product wherein the Grignard reagent had rearranged to a tolyl Grignard reagent. To avoid this issue, we made our own benzylmagnesium bromide in diethyl ether, but at a much lower concentration (0.05-0.10 M) and the reagent solution was always prepared fresh and never

stored. With this dilute reagent solution we avoided the issue of the tolyl rearrangement as well as minimized the amount of the 1,2-diphenylethane byproduct that was formed during the formation of the reagent. Various oxidation reaction conditions were tested and it was found that Dess-Martin periodinane (DMP) not only provided the highest yield but also had the benefit of being the fastest reaction (10-15 minutes).[41] The overall yield for the Grignard reaction followed by oxidation by DMP was 42%. Since the Grignard route had the drawbacks of a low yield as well as a highly dilute reaction conditions (0.05 M), we sought to find an alternative to it. A publication by Kagan reported the reaction of benaldehyde with benzyl bromide under samarium diiodide conditions to give a 78% yield of the alcohol product with a reaction time of 3 minutes.[42] Applying these conditions to our system, we found that the reaction of the ketal aldehyde **103** and benzyl bromide proceeded cleanly with 2 equivalents of SmI_2 in THF (0.1 M) in under 5 minutes to give the expected benzyl alcohol **112**. Oxidation with DMP gave the benzyl ketone **114** in an overall yield of 69% over 2 steps.

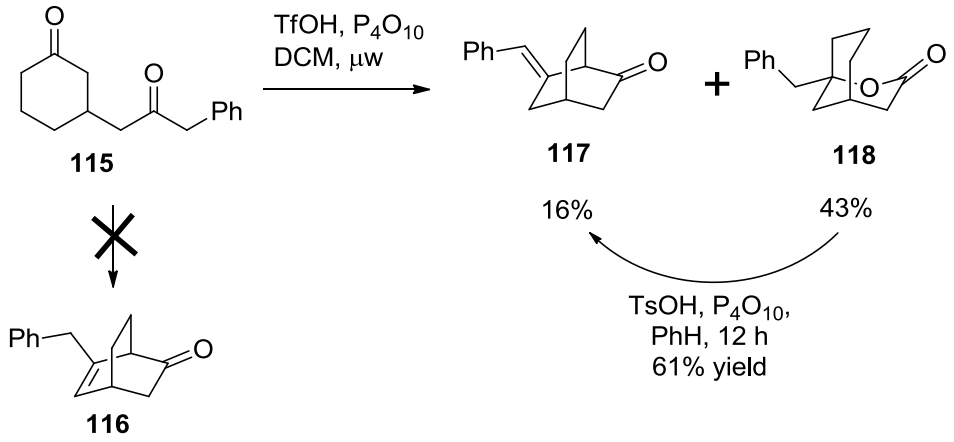


Scheme 13. Synthesis of benzyl 1,5-diketone **115**.

Ideally the deprotection of the ketal could have been effected either during the acidic quench or workup of the Grignard or SmI_2 reaction or during the oxidation step; however it was found that the overall yields of the benzyl diketone suffered when any of the intermediates were treated with a 1-2 M HCl solution. Quenching the SmI_2 reaction with 2M HCl commonly destroyed the molecule and low yields of product (10-20%) were recovered. Subsequently, the oxidation reaction of the alcohol with Dess-Martin periodinane was buffered with sodium bicarbonate to avoid any degradation of the product due to residual acetic acid in the DMP. The overall yields were increased by protecting the ketal from strongly acidic conditions until it was necessary to remove it. The ketal was removed under mildly acidic conditions using pyridinium *p*-toluenesulfonate (PPTS) in refluxing acetone and water (56 °C) for 5 hours.[43] The desired benzyl diketone **115** was isolated in 96% yield. Due to the ease of the SmI_2 reaction conditions

as well as the higher overall yield compared to the Grignard conditions, we elected to use the SmI_2 conditions to continue with the synthesis.

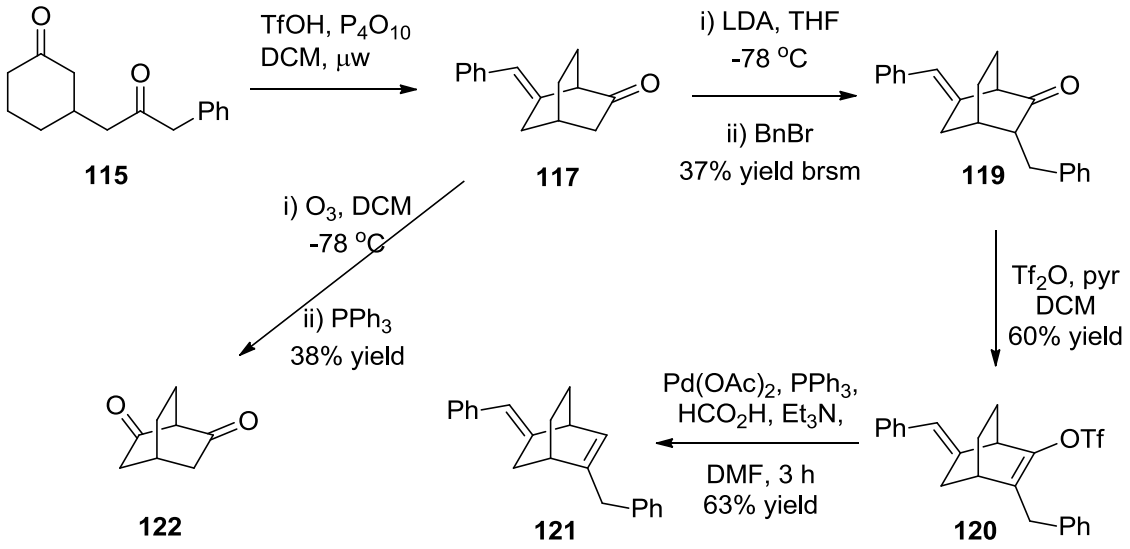
The benzyl 1,5-diketone **115** underwent the bridged Robinson annulation easily (Scheme 14). However, the elimination step did not give us the olefin product we expected. Instead of giving us the endocyclic olefin **116**, the reaction gave us the exocyclic olefin **117** in 16% yield as well as a lactone side product **118** in 61% yield. The side product could be turned into the exocyclic olefin in 61% yield by treating it with an excess of *p*-toluenesulfonic acid and phosphorus pentoxide in benzene for 12 hours. The formation of the rearranged product, the lactone **118**, will be described separately later in this thesis.



Scheme 14. Bridged Robinson annulation of benzyl 1,5-diketone **115**.

During the synthesis, however, we failed to initially recognize that the wrong olefin had been formed during the bridged Robinson annulation. Moving forward with the exocyclic olefin product **117**, we completed the final three steps of the synthesis as shown in Scheme 15. The alkylation α to the ketone was accomplished in moderate yield (37% based on recovered starting material).[44] The formation of the vinyl triflate **120** and its subsequent elimination were both

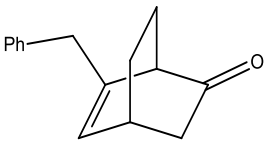
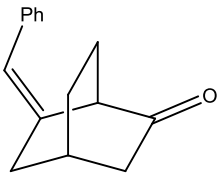
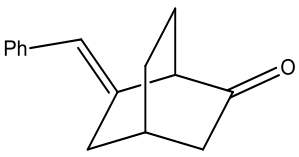
accomplished under the same reaction conditions as those used for the Ph-bod ***dl*-5** synthesis and both reactions gave comparable yields, 60% and 63% respectively.[39] Once we reached the final di-olefin product, which we had assumed to be the correct Bn-bod ligand, we realized that the compound we had made was not C_2 symmetric and in fact had no symmetry at all. Reviewing the proton NMR of the bridged Robinson annulation product, we realized that the olefinic proton was shown as a triplet instead of the expected doublet of doublets that we had seen previously in the Ph-bod synthesis. To confirm our suspicions that we did indeed have the exocyclic olefin **121** we reacted it with ozone to create the bicyclic diketone **122** which has a simple and symmetric proton NMR spectrum. [32]



Scheme 15. Synthesis of **121** and **122**.

With our suspicions confirmed and the exocyclic olefin bicycle **117** in hand we then needed to know if it was possible to isomerize the olefin to the endocyclic position in order to form our desired product **116**. Calculations were done comparing the free energy of each

molecule, the two olefinic isomers of the exocyclic olefin as well as our desired olefin within the bicycle. As shown in Table 3, the calculations confirmed that the exocyclic alkenes were both more stable than the endocyclic alkene, presumably due to the extra ring strain in the endocyclic alkene. The energy cost to isomerize the olefin from the most stable exocyclic isomer to the endocyclic one (2.3 kcal) was deemed too high to overcome. The olefin is most stable when conjugated with the phenyl ring and we were unable to come up with a method to avoid this product within the framework of our proposed synthesis.

Olefin	 **116**	 **(*Z*)-117**	 **(*E*)-117**
Calculated Relative Free Energy (kcal)	2.3	1.8	0

B3LYP/6-13G*

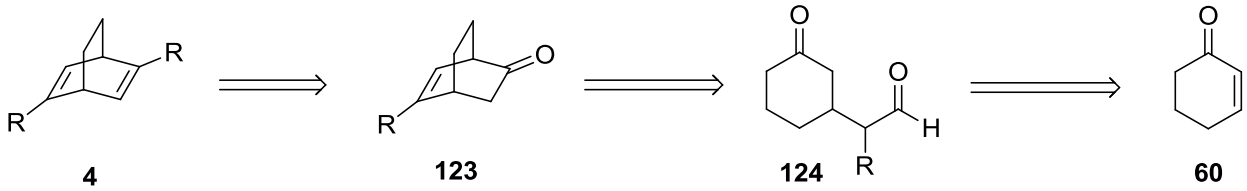
Table 3. Calculated relative free energies of Bn-BRA adducts **116** & **117**.

New Retrosynthesis and Proposed Synthesis of Bn-bod

We know that the acid-catalyzed portion of the bridged Robinson annulation works to give us the bicyclic aldol product we desired. However, the exo vs. endo problem arises during the elimination step. After the aldol reaction the bicycle has a tertiary alcohol that is removed under the acidic conditions leaving a tertiary carbocation. At this point there is a choice of which α-proton to eliminate to create the olefin. We have seen that the molecule prefers to eliminate a benzylic proton in order to extend the conjugation and give the most stable alkene. Therefore, we

needed to devise a new synthesis that would allow us to avoid the tertiary carbocation leading to the exocyclic bicyclic alkene **117**.

With this goal in mind we devised a new retrosynthesis to avoid this problem (Scheme 16). In this new synthesis, instead of submitting a 1,5-diketone to the bridged Robinson annulation conditions, we proposed to submit a substituted 1,5-keto-aldehyde to the same conditions. The final bicyclo[2.2.2]octa-2,5-diene **4** would be the enanatiomer of the bod ligand we had planned to synthesize from our previous route.

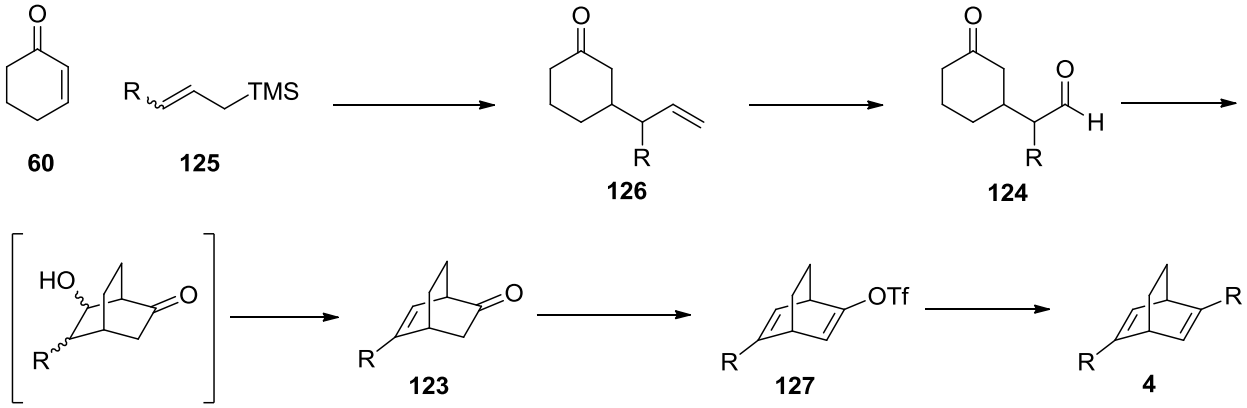


4 **123** **124** **60**

Scheme 16. Retrosynthesis #2.

Wishing to maintain a synthesis similar to the Ph-bod synthesis and wanting to maintain the use of Snapper's chemistry to create the enantiomerically pure allylcyclohexanone, we envisioned the following synthesis (Scheme 17). A modification from our previous synthesis was the use of a substituted allylsilane **125**, which would create a similar 3-allylcyclohexanone but with the desired substituent (R) already attached **126**. Ozonolysis would create the 1,5-keto aldehyde **124** which would then be submitted to our bridged Robinson annulation conditions. Since the substitution (R group) is next to the aldehyde, instead of being a substituted ketone, this would create an intermediate during the bridged Robinson annulation containing a secondary alcohol which is one carbon removed from the R group. This compound could only eliminate to give the endocyclic olefin **123** we desired. Vinyl triflate formation and then cross-coupling under

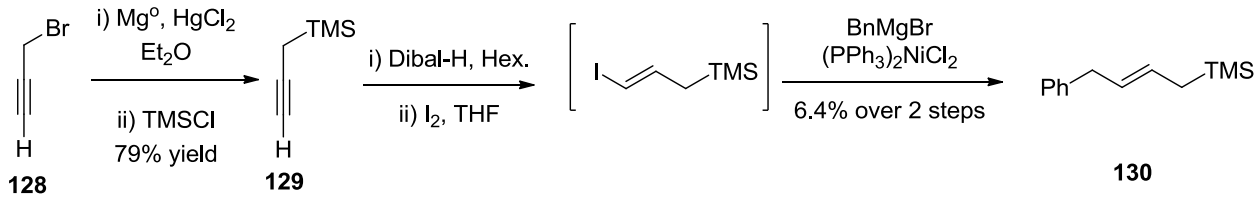
palladium catalysis with an appropriate Grignard reagent would give our final bicyclo[2.2.2]octa-2,5-diene product **4**.



Scheme 17. Proposed synthesis of bod ligands **4** using substituted allylsilanes **125**.

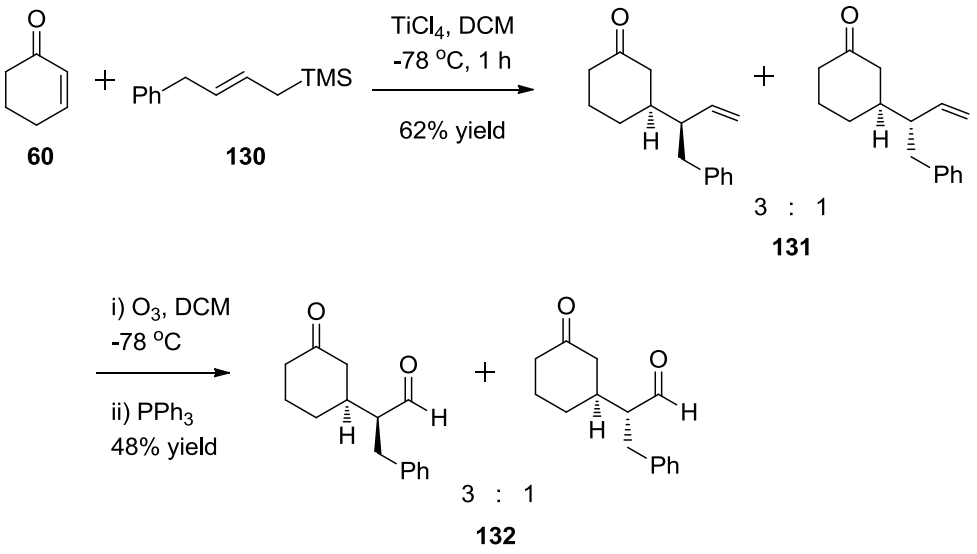
Racemic Synthesis #2 of (1*R*,4*R*)-2,5-Bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene (Bn-bod)

The required benzylic allylsilane **130** was synthesized via literature conditions starting with propargyl bromide (Scheme 18).[45] Creation of the Grignard reagent from propargyl bromide followed by quenching with trimethylsilyl chloride produced propargyl trimethylsilane **129** in 79% yield. The propargyl trimethylsilane **129** was then reacted with Dibal-H and iodine to give the vinyl iodide intermediate, which was not isolated, and was immediately cross-coupled with benzylmagnesium bromide under nickel catalysis reaction conditions to yield the *trans* benzylallylsilane, (*E*)-trimethyl(4-phenylbut-2-en-1-yl)silane **130**.



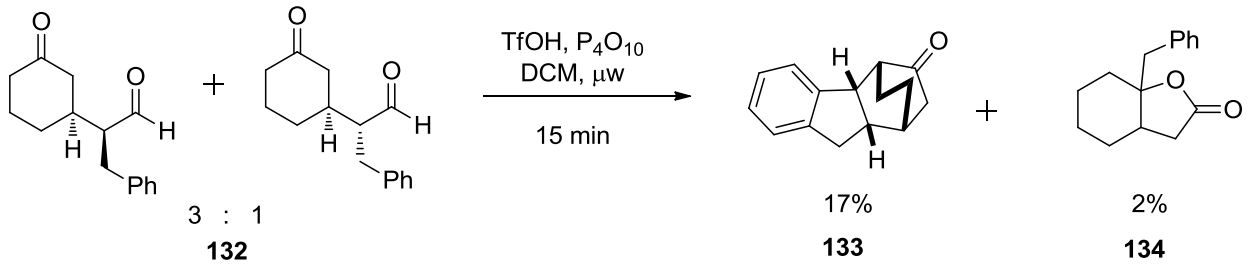
Scheme 18. Synthesis of (*E*)-trimethyl(4-phenylbut-2-en-1-yl)silane **130**.

In analogy to the Ph-bod synthesis, 2-cyclohexen-1-one **60** was reacted with (*E*)-trimethyl(4-phenylbut-2-en-1-yl)silane **130** under Lewis acid conditions using $TiCl_4$,[31] which yielded the benzyl substituted 3-allylcyclohexanone product, (*S*)-3-((*R*)-1-phenylbut-3-en-2-yl)cyclohexanone **131**, in 62% yield and in a 3:1 diastereomeric ratio (Scheme 19). The structure of the major diastereomer was assigned based on the likely mechanism of the Hosomi-Sakurai reaction and the literature precedence.[31] Ozonolysis of the two diastereomeric 3-allylcyclohexanones **131** generated the corresponding keto-aldehydes, (*S*)-2-((*S*)-3-oxocyclohexyl)-3-phenylpropanal **132** and the 2*R* isomer, in 48% yield, still as a 3:1 diastereomeric ratio. [32]



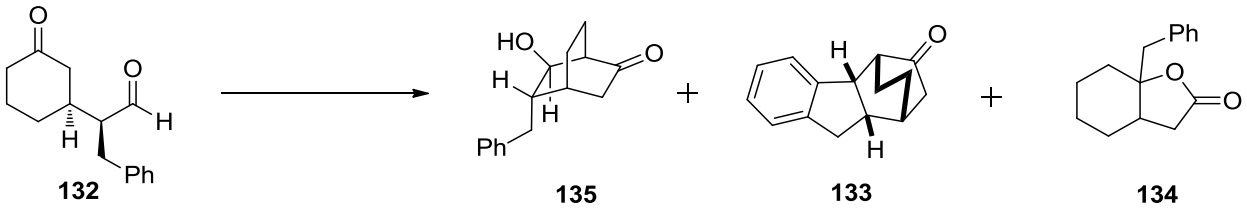
Scheme 19. Synthesis of benzyl-substituted 1,5-ketoaldehydes **132**.

Submitting the diastereomeric mixture of keto-aldehydes **132** to our standard reaction conditions for the bridged Robinson annulation, namely 2 equivalents of trifluoromethanesulfonic acid and 2 equivalents of phosphorus pentoxide as a dessicant in dichloromethane under microwave conditions for 15 minutes, resulted in only formation of the undesired side products (**133** and **134**) with low yields (Scheme 20). A more detailed discussion of the mechanism of the formation of these side products will be presented later. However, based upon the structures of the side products, we theorized that the problem arose from the formation of the very reactive secondary carbocation necessary for olefin formation. To investigate this issue, we redevised the bridge Robinson annulation conditions to only form the alcohol and to avoid elimination of the alcohol via a carbocation.



Scheme 20. Bridged Robinson annulation of benzyl-substituted 1,5-ketoaldehydes **132**.

In our efforts to identify suitable reaction conditions to provide us with the desired bicyclic ketone framework while maintaining the secondary alcohol, we screened 6 different reaction conditions with 3 different acids without the addition of phosphorus pentoxide (see Table 4). We found that the use of triflic acid, under either microwave or normal reaction conditions, gave only side products. We next tested *p*-toluenesulfonic acid, both the monohydrate and the anhydrous material, and found that both conditions provided us with the desired bicyclic alcohol **135**. However after a reaction time of 90 minutes there was still a significant amount of the starting keto-aldehyde **132** remaining. We next tested hydrochloric acid as a 1.0 M solution in water and as a 4.0 M solution in dioxane. After a reaction time of 90 minutes the 1.0 M HCl solution in water showed no reaction by TLC. However, after a reaction time of 30 minutes, the 4.0 M HCl solution in dioxane gave no starting material and only our desired bicyclic alcohol **135** was isolated in 85% yield.

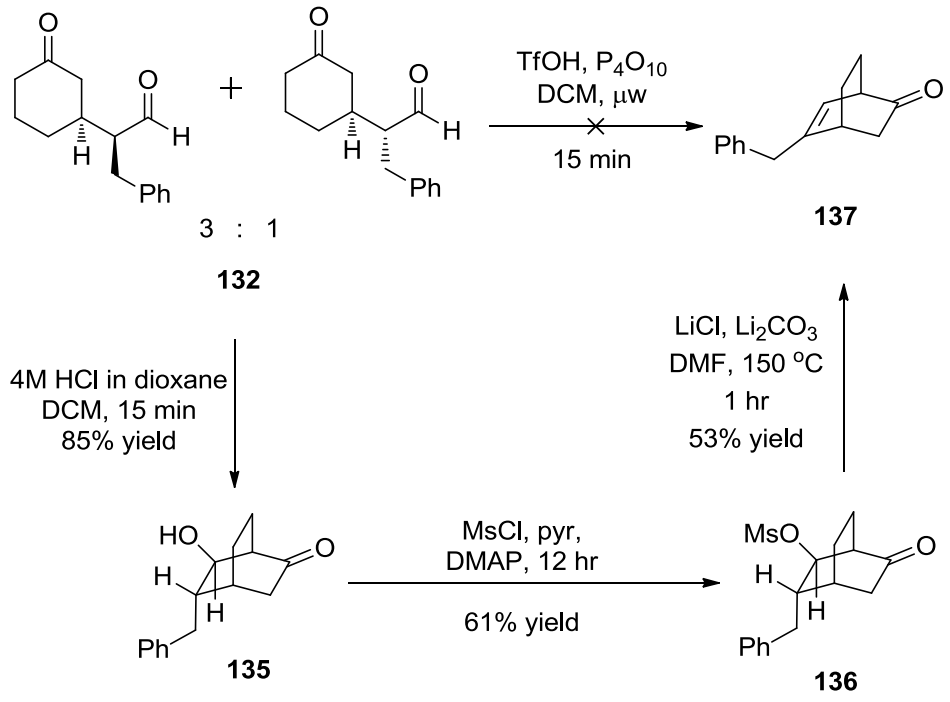


Acid	Temp.	Time (min)	Results
TfOH	μw, 40 °C	15	**133** + **134**
TfOH	23 °C	15	**133** + **134**
TsOH (•H_2O)	23 °C	90	**135** + **132**
TsOH (anhydrous)	23 °C	90	**135** + **132**
HCl (1.0M in H_2O)	23 °C	90	**132**
HCl (4.0M in dioxane)	23 °C	30	**135** (85% yield)

Table 4. Screening of various acids for the bridged Robinson annulation reaction of **132**.

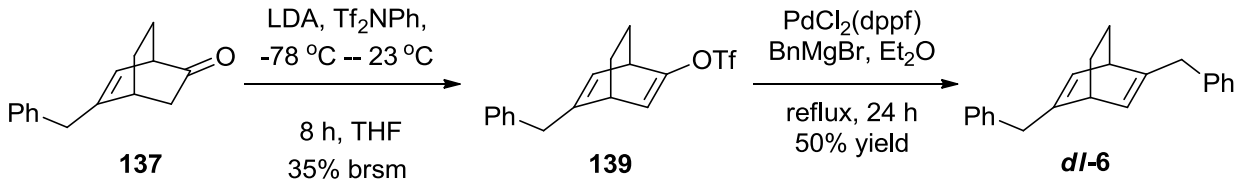
From our screening of revised bridged Robinson annulation conditions, we chose to move forward using 4.0 M HCl in dioxane because it gave the best yields of all of the conditions tested, with no side product formation. In addition, the conversion was complete in less than 30 minutes. Therefore, treating the diastereomeric mixture of benzyl substituted keto-aldehydes **132** under those conditions gave an 85% yield of the *trans* bicyclic alcohol, 5-(phenylmethyl)-6-hydroxybicyclo[2.2.2]octan-2-one **135** (Scheme 21). The structure assignment of the hydroxyl bicycle **135** is tentative and is based on the assumption that the *trans* isomer would be more stable under these formation conditions. However, it could be the opposite *trans* isomer instead or indeed one of the two *cis* isomers. Wishing to avoid the elimination of the alcohol under acidic conditions, we converted the secondary alcohol to a mesylate to facilitate elimination under basic conditions instead.[46] The conversion of the alcohol to the mesylate was accomplished easily using methanesulfonyl chloride and pyridine with a catalytic amount of 4-

(dimethylamino)-pyridine (DMAP) in 61% yield. Elimination of the mesylate was found to proceed best under the basic conditions of lithium chloride and lithium carbonate in DMF at 150 °C for 1 hour.[33] The desired bicyclic enone, (±)-(1*R*,4*R*)-5-(phenylmethyl)bicyclo[2.2.2]oct-5-en-2-one **137**, was isolated in 53% yield.



Scheme 21. Synthesis of the benzyl substituted bicyclic enone **137**.

The final two steps of the synthesis of (±)-(1*R*,4*R*)-2,5-bis(phenylmethyl) bicyclo[2.2.2]octa-2,5-diene ***dl*-6** (Bn-bod) were accomplished via vinyl triflate formation[47] of the benzyl bicyclic enone **137** in 35% yield followed by the cross-coupling of the vinyl triflate **139** with benzylmagnesium bromide under palladium catalysis in refluxing ether for 24 hours.[48] The final product ***dl*-6** was isolated in 50% yield from the vinyl triflate **139** (Scheme 22).



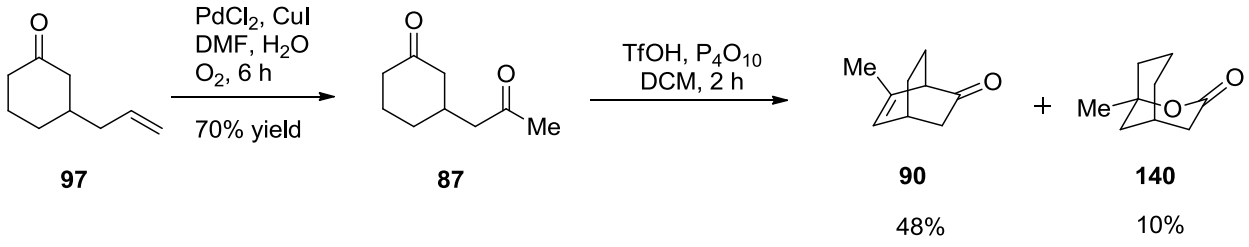
Scheme 22. Final steps to synthesize Bn-bod ***dl*-6**.

Our synthesis of racemic (1*R*,4*R*)-2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene ***dl*-6** (Bn-Bod) involved 7 steps, starting from 2-cyclohexen-1-one, with a 1.4% overall yield. The reactions within this synthesis can be optimized to increase the overall yield of the ligand. The proposed synthesis using the same reactions for the synthesis of optically pure (1*R*,4*R*)-2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene **(*R*,*R*)-6** (Bn-bod) would involve 10 steps as outlined, starting with cyclohexanone. The Hosomi-Sakurai reaction described by Snapper focused on the addition of allyltrimethylsilane to the enone system. We would like to extend the use of that chemistry by including the use of substituted allylsilanes to create optically active substituted allylcyclohexanone substrates.

Attempted Synthesis of Racemic (1*R*,4*R*)-2,5-Dimethylbicyclo[2.2.2]octa-2,5-diene (Me-bod)

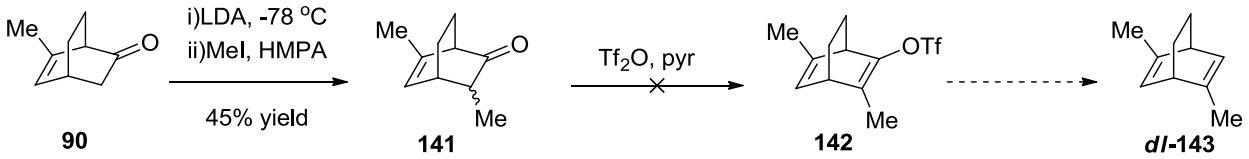
The synthesis of (1R,4R)-2,5-dimethylbicyclo[2.2.2]octa-2,5-diene (Me-bod) was undertaken due to its simplicity as well as to broaden the scope of our synthetic plan using the bridged Robinson annulation to synthesize various bicyclo[2.2.2]octa-2,5-dienes. The Me-bod ligand is not used in the literature in the same manner as the phenyl and benzyl bod ligands. We chose to synthesize it nonetheless since the bridged Robinson annulation was already proven to work. [26]

The requisite methyl 1,5-diketone **87** was easily synthesized via a Wacker oxidation reaction of the simple 3-allylcylcohexanone **97** intermediate in 70% yield.[49] The bridged Robinson annulation was effected via our standard (non-microwave) conditions using trifluoromethanesulfonic acid and phosphorus pentoxide in dichloromethane. The desired methyl bicyclic enone **90** was isolated in 48% yield. The lactone side product **140** was isolated in 10% yield as well. Again, the mechanism of the formation of this lactone byproduct will be discussed later.



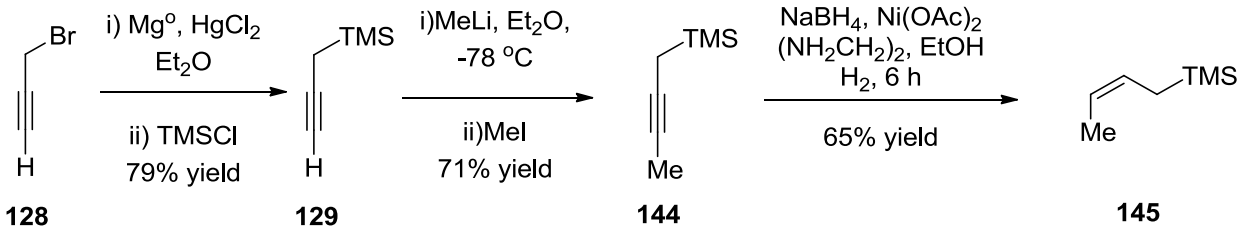
Scheme 23. Bridged Robinson annulation reaction of the methyl 1,5-diketone **87**.

From the methyl bicyclic enone **90**, it should take an additional three steps to successfully synthesize the Me-bod ***dl*-143** (Scheme 24). Addition of a methyl group α to the ketone was accomplished under enolate conditions using LDA and methyl iodide with HMPA to yield the dimethyl product **141** in 45% yield, as a mixture of diastereomers.[50] In analogy to our other bod syntheses, we wanted to synthesize the vinyl triflate and then reduce it to finish the synthesis. However, when we submitted the dimethyl bicyclic enone **141** to the triflic anhydride and pyridine conditions that were used previously, we isolated an unknown trimer side product in 77% yield and none of the desired vinyl triflate product. We still have not determined the structure of this trimeric material. Since this direct route was unsuccessful, we decided to explore the synthesis of Me-bod via the 1,5-ketoaldehyde route that we used for the synthesis of Bn-bod ***dl*-6**.



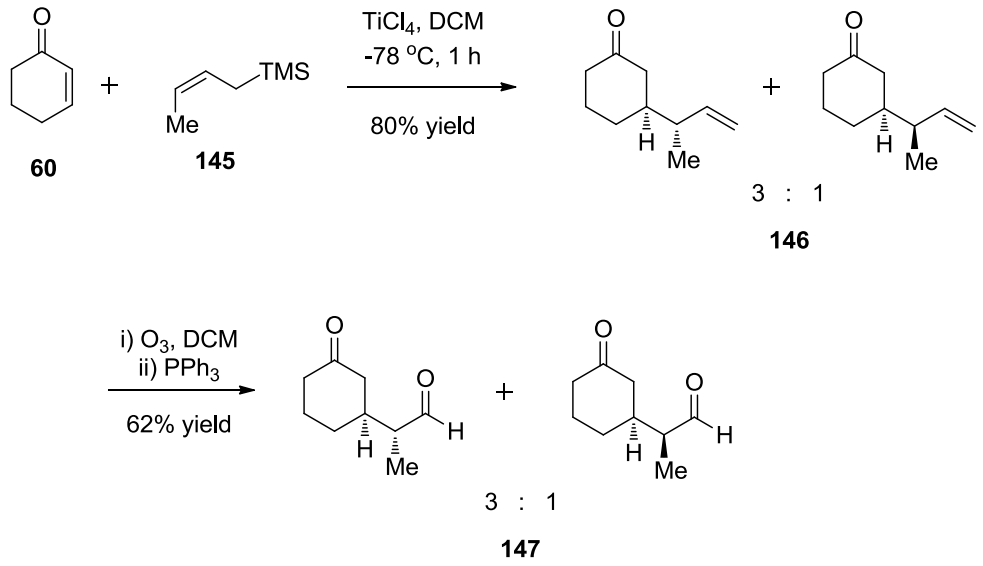
Scheme 24. Attempted synthesis of the Me-bod ***dl*-143**.

In analogy to the synthesis of Bn-bod ***dl*-6**, we sought to synthesize the Me-bod ***dl*-143** according to Scheme 16. We first had to synthesize (*Z*)-crotyl trimethylsilane **145**, which was done according to literature procedures, as shown (Scheme 25).[45] Methylation of propargyl TMS **129** was readily accomplished by reaction with methyllithium and methyl iodide in 71% yield. Alkyne **144** was reduced to crotyl trimethylsilane **145** in 65% yield using the nickel-boride catalyst system under a hydrogen atmosphere.



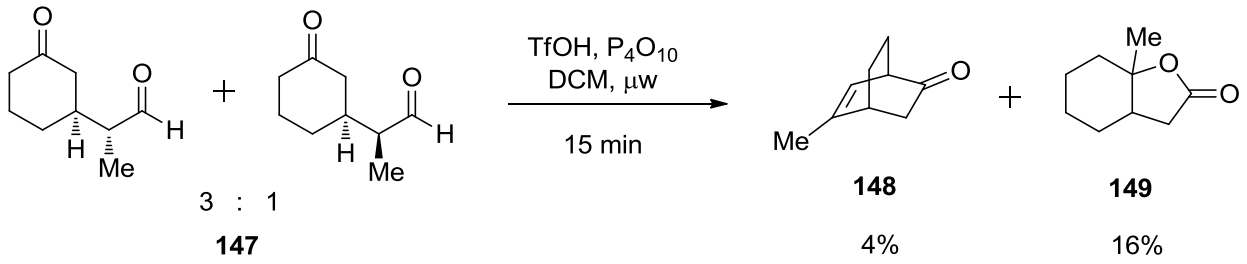
Scheme 25. Synthesis of (*Z*)-crotyl trimethylsilane **145**.

As before, 2-cyclohexen-1-one **60** was reacted with (*Z*)-crotyl trimethylsilane **145** under Lewis acid conditions using $TiCl_4$,[31] which yielded the methyl substituted 3-allylcyclohexanone product, (*S*)-3-((*S*)-but-3-en-2-yl)cyclohexanone **146**, in 80% yield and again in a 3:1 diastereomeric ratio (Scheme 26). Again, the structure of the major diastereomer was assigned based on the mechanism of the Hosomi-Sakurai reaction and literature precedent. [31] Ozonolysis of the diastereomeric mixture of 3-(3-butenyl)cyclohexanones **146** generated the corresponding ketoaldehydes, (*R*)-2-((*S*)-3-oxocyclohexyl)propanal **147**, in 62% yield with the same 3:1 diastereomeric ratio.[32]



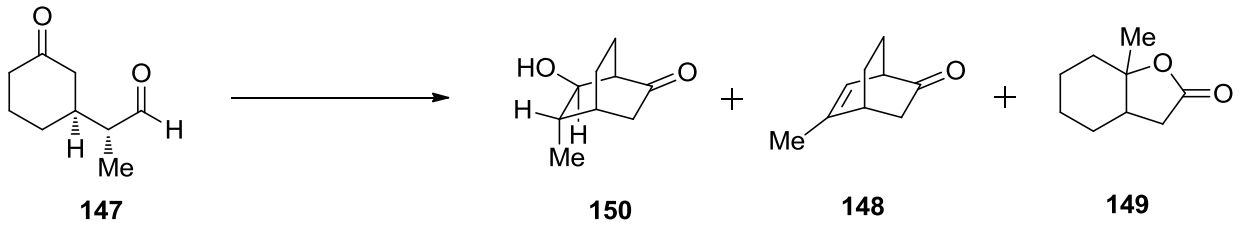
Scheme 26. Synthesis of methyl substituted 1,5-ketoaldehydes **147**.

Submitting the diastereomeric mixture of ketoaldehydes **147** to our standard reaction conditions for the bridged Robinson annulation, namely 2 equivalents of trifluoromethanesulfonic acid and 2 equivalents of phosphorus pentoxide as a dessicant in dichloromethane for 15 minutes at 23 °C, resulted in mostly side product formation **149** and very little formation of the desired methyl bicyclic enone **148** (Scheme 27). A more detailed discussion of the mechanism of formation of the side product will be presented later. However, based upon the structure of the side product, we theorized that the problem arose from the inefficient removal of water from the reaction. To investigate this issue, we followed the same protocol set forward for the synthesis of the Bn-bod ***dl*-6** ligand; that is to control the formation of the bicyclic alcohol first, then to address any elimination issues.



Scheme 27. Bridged Robinson annulation of methyl substituted 1,5-ketoaldehydes **147**.

Similar to our results in the synthesis of Bn-bod, we subjected the diastereomeric mixture of ketoaldehydes **147** to various acidic conditions (Table 5). We found similar results in this case. The use of triflic acid gave predominantly side product **149** formation and very little of our desired product **148**. *p*-Toluenesulfonic acid conditions successfully produced the bicyclic alcohol **150**. However, like in the Bn-bod synthesis, a significant amount of starting material remained after 90 minutes reaction time. The use of aqueous hydrochloric acid (1.0 M) was ineffective. The use of non-aqueous hydrochloric acid (4.0 M in dioxane) gave an excellent yield (91%) of our desired hydroxyl bicyclic ketone **150**.



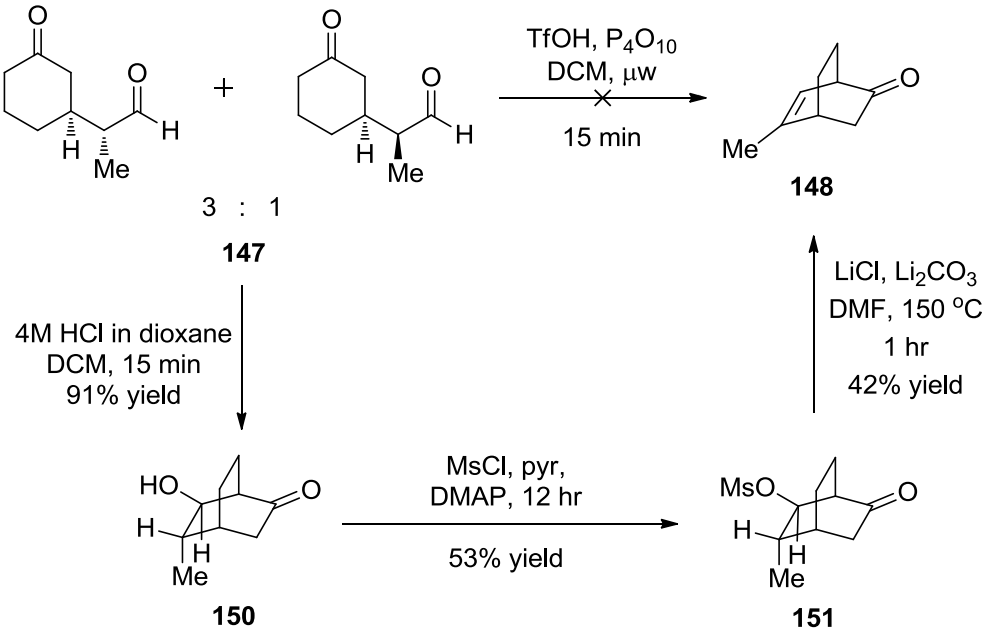
147 **150** **148** **149**

Acid	Temp	Time (min)	Results
TfOH	µw, 40 °C	15	**148** + **149**
TfOH	23 °C	15	**148** + **149**
TsOH (·H_2O)	23 °C	90	**150** + **147**
TsOH (anhydrous)	23 °C	90	**150** + **147**
HCl (1.0M in H_2O)	23 °C	90	**147**
HCl (4.0M in dioxane)	23 °C	30	**150** (91% yield)

Table 5. Screening of various acids for the bridged Robinson annulation reaction of **147**.

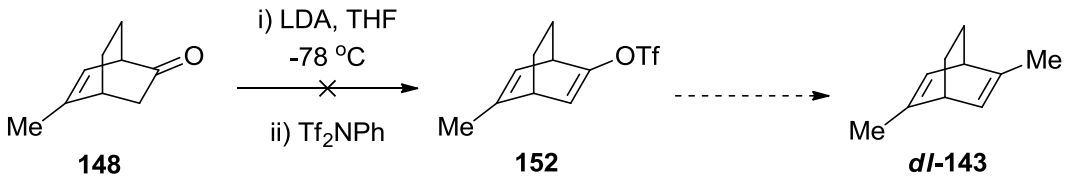
Analogous to the Bn-bod synthesis, we elected to move forward with the synthesis of Me-bod ***dl*-143** by using the revised bridged Robinson annulation conditions of 4.0 M HCl in dioxane (Scheme 28). Treating the diastereomeric mixture of methyl substituted ketoaldehydes **147** under those conditions gave an 91% yield of the *trans* bicyclic alcohol, 6-hydroxy-5-methylbicyclo[2.2.2]octan-2-one **150**. As before, the structural assignment of **150** is tentative and is based on the theory that under these conditions the most stable product should predominate and we assume that is the *trans* isomer. Avoiding the use of acidic conditions for the elimination, we converted the secondary alcohol to a mesylate, which would eliminate under basic conditions.[46] The conversion of the alcohol to the mesylate was accomplished easily using methanesulfonyl chloride and pyridine with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in 53% yield. Elimination of the mesylate proceeded best under the basic conditions of

lithium chloride and lithium carbonate in DMF at 150 °C for 1 hour.[33] The desired bicyclic enone, (±)-(1*R*,4*R*)-5-methylbicyclo[2.2.2]oct-5-en-2-one **148**, was isolated in 42% yield.



Scheme 28. Synthesis of methyl substituted bicyclic enone **148**.

The final two steps of the synthesis of (±) (1R,4R)-2,5-dimethylbicyclo[2.2.2]octa-2,5-diene (Me-bod ***dl*-143**) were envisioned to be analogous to the Bn-bod synthesis. However, we encountered a similar issue when attempting to convert the methyl bicyclic ketone **148** to the vinyl triflate **152**. We were unable to isolate any of the desired vinyl triflate under the expected conditions. Instead we isolated a mixture of two compounds, which we have surmised are likely a dimer or trimer of our starting ketone.



Scheme 29. Attempted synthesis of the Me-bod ***dl*-143**.

Although our initial goal of synthesizing the Me-bod ***dl*-143** was to provide support for being able to synthesis alkyl derivatives of the bicyclo[2.2.2]octa-2,5-diene core using the bridged Robinson annulation approach, more work needs to be done to ensure a versatile synthesis of various bod ligands.

Chapter 3: Rearrangements

Rearrangements

During our exploration of the syntheses of Bn-bod ***dl*-6** and Me-bod ***dl*-143** we came across several unexpected side products during the bridged Robinson annulation step (Figure 27). The common thread of the rearranged products was that all of them were created under the standard strongly acidic conditions of trifluoromethanesulfonic acid (pKa = -15). We have proposed a possible mechanism for each rearrangement reaction we encountered. The insights gained from the formation of these products helped guide our eventual final synthesis.

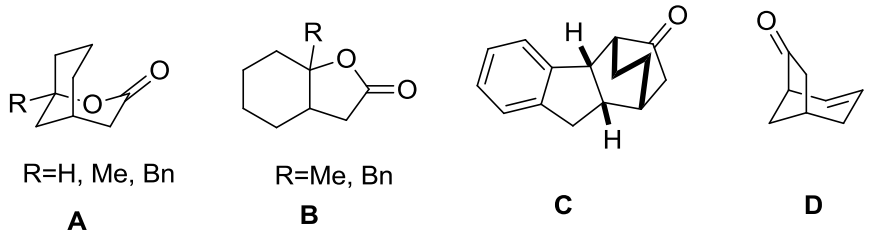
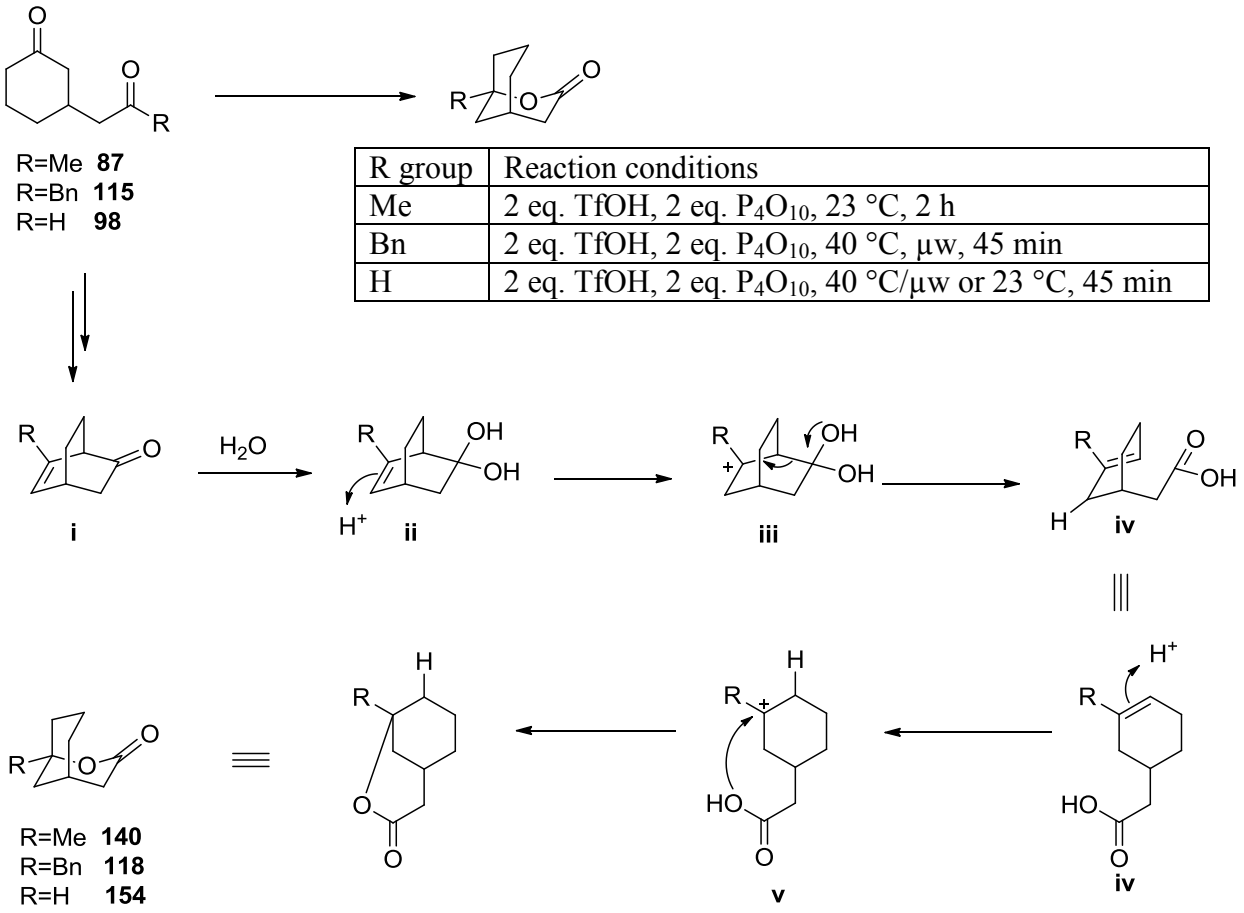


Figure 27. Rearrangement products from the bridged Robinson annulation with triflic acid.

Rearrangement A occurred in the cases of the methyl ketone **87**, benzyl ketone **115**, and the 1,5-ketoaldehyde **98** as shown in Figure 28. The mechanistic steps for the formation of the intended bicyclic enone products are purposefully omitted here as they were cited in the general mechanism for the bridged Robinson annulation described earlier. Our proposed mechanism postulates that the formation of the bridged Robinson annulation product was indeed successful, but that due to the reaction conditions an over-reaction occurred resulting in the undesired side products. As shown in the mechanism, we predict that a molecule of water initially hydrates the ketone of the bicycle giving intermediate **ii**. Protonation of the olefin gives tertiary carbocation **iii**, which allows for the formation of the carboxylic acid and breaking of the bridge-head carbon-

carbon bond giving a new olefin **iv**. Protonation of the olefin gives another tertiary carbocation **v**, which is attacked by the carboxylic acid and after deprotonation gives the bicyclic lactone product **140**, **118**, or **154**.



R group	Reaction conditions
Me	2 eq. TfOH, 2 eq. P_4O_{10}, 23 °C, 2 h
Bn	2 eq. TfOH, 2 eq. P_4O_{10}, 40 °C, µw, 45 min
H	2 eq. TfOH, 2 eq. P_4O_{10}, 40 °C/µw or 23 °C, 45 min

Figure 28. Proposed mechanism for rearrangement **A**

Our proposed mechanism for rearrangement **A** highlights two facts of the reaction conditions that we were subsequently able to adjust to avoid the formation of the lactone side product. The fact that water was still present in solution such that it could hydrate the ketone, led us to believe that the phosphorus pentoxide inefficiently dried the solution. To avoid this issue it was necessary to use fresh phosphorus pentoxide that had been protected well against absorption

of water from the air as well as the use of a big enough stir bar in the reaction vessel and rapid stirring to encourage efficient suspension of the phosphorus pentoxide throughout the solution. The excess acid used in the reaction conditions cannot be avoided. Previously it was found that a 2-3 fold excess of acid is necessary to produce the best yields of the desired bicyclic enone. However, the amount of time that the reaction is left to run was found to be a factor in the formation of the cyclic lactone. Previous work done by Jung and Maderna (unpublished) demonstrated that at higher temperatures and longer reaction times, formation of the lactone product is favorable. While our reaction conditions of dichloromethane at 23 °C or 40 °C are hardly deemed as high temperature conditions, the fact that we saw the lactone product formation after 45 minutes seems to suggest that our reaction time is too long. The bridged Robinson annulation is likely complete in a much shorter time period and as such, further bridged Robinson annulation reactions were carefully monitored to find the optimal reaction time.

Rearrangement **B** occurred in the cases of the methyl substituted and benzyl substituted 1,5-ketoaldehydes (**147** and **132**) as shown in Figure 29. Like in rearrangement **A**, the mechanistic steps for the formation of the intended bicyclic enone products are omitted as they were described earlier. We proposed that the bridged Robinson annulation product **i** is hydrated to give intermediate **ii**. Protonation of the olefin gives intermediate **iii**, which then allows for the formation of the carboxylic acid intermediate **iv**. The new olefin of intermediate **iv** is protonated followed by a 1,2-hydride shift resulting in the formation of the tertiary carbocation **vi**. Attack by the carboxylic acid on the carbocation and deprotonation gives the lactone side product **149** and **134**.

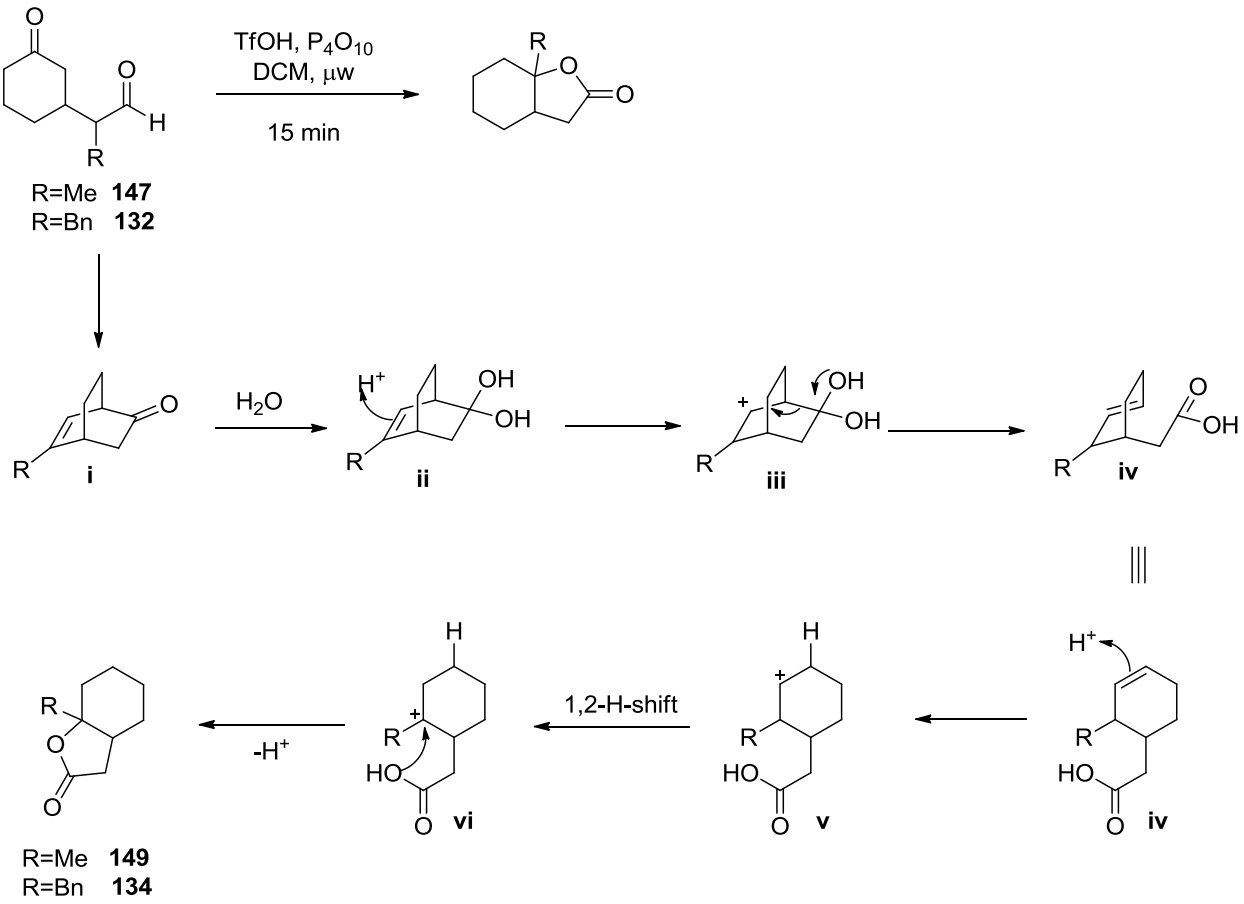


Figure 29. Proposed mechanism for rearrangement **B**

The same conclusions arose from our proposed mechanism for rearrangement **B**. The phosphorus pentoxide was still inefficient in removing water from the reaction solution and excess acid in solution helps to promote the rearrangement. As was stated earlier, it is essential that excess acid is used to promote formation of the desired bicyclic enone (**i**). We also know that the reaction time is a predictor for the amount of lactone that could be formed. However, in light of the 45 minute reaction times done previously, the reaction time for the 1,5-ketoaldehydes was limited to 15 minutes, at which time all of the starting material was consumed. We therefore

postulate that the 1,5-ketoaldehydes are more reactive under the strongly acidic conditions and are more susceptible to over-reaction.

Rearrangement **C** occurred in the case of the benzyl substituted 1,5-ketoaldehyde **132** as shown in Figure 30. As in rearrangement **A**, many of the mechanistic steps for the formation of the expected bicyclic enone products are purposefully omitted since the general mechanism for the bridged Robinson annulation was described earlier. Our proposed mechanism postulates that the bridged Robinson annulation occurred as predicted up until intermediate **i**, which is one step away from creating the desired bicyclic enone **137**. Instead we postulate that the elimination of a water molecule occurs to give the secondary carbocation **ii** as expected. However, at this point, the carbocation is attacked by the benzene ring via electrophilic aromatic substitution (intramolecular Friedel-Crafts alkylation) to give carbocation **iii**, which upon deprotonation gives the side product **133**. The participation of the benzene ring, although unexpected, is not unreasonable given the favorability of the formation of a 5-membered carbocycle. The stereochemical assignment of **133** is tentative. We assume that the stereochemistry of the benzyl group in **ii** can be equilibrated via a deprotonation-reprotonation sequence involving the enone **137**. We then argue that protonation occurs to place the benzyl group on the less hindered face (syn to the ketone). Cyclization would then give the proposed structure.

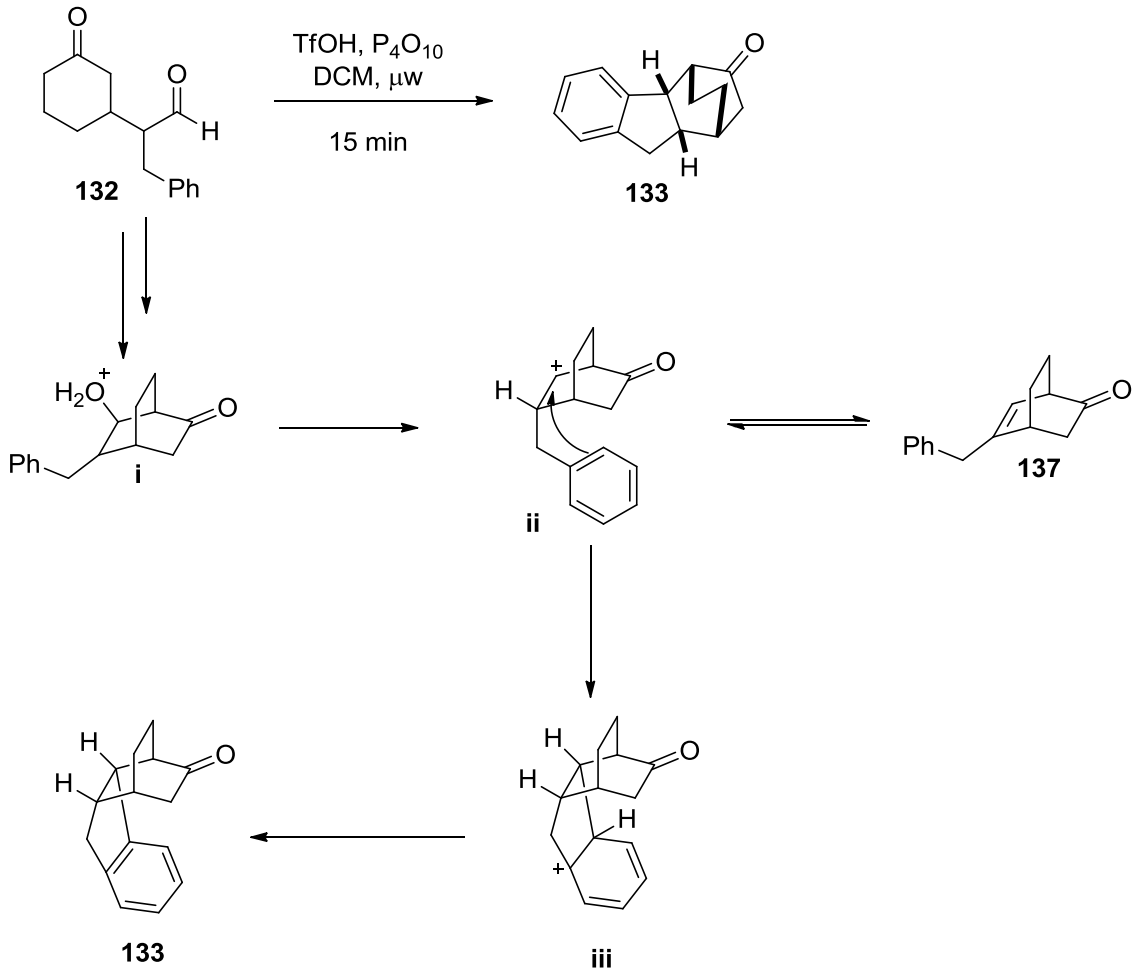


Figure 30. Proposed mechanism for rearrangement **C**.

Given the reaction conditions of rearrangement **C**, we are unable to avoid the formation of this side product. The short reaction time as well as the previous inefficiency of phosphorus pentoxide to absorb water does not seem to have any obvious effect within our proposed mechanism. Instead, the inherent structure of the molecule is the best predictor of this rearrangement, and therefore the rearrangement likely cannot be avoided under these conditions. It may be possible however to alter the acidity of the reaction, i.e., use a weaker acid, to avoid the formation of the carbocation and instead stop the bridged Robinson annulation reaction at the

bicyclic alcohol. This approach was ultimately used as was previously demonstrated in the final synthesis of Bn-bod ***dl*-6**.

Rearrangement **D** occurred in the case of the unsubstituted 1,5-ketoaldehyde **98** as shown in Figure 31. Although ultimately of no significance to the final synthesis of the Bn-bod ligand ***dl*-6**, when we were forced to use 1,5-ketoaldehydes in the bridged Robinson annulation to complete the Bn-bod synthesis, we first tested our standard bridged Robinson annulation reaction conditions on the unsubstituted 1,5-ketoaldehyde **98**. As shown in Figure 31, the bridged Robinson annulation reaction produced two side products instead of the desired bicyclic enone. The lactone side product was already discussed via rearrangement **A**. Our proposed mechanism for the bicyclic enone side product **153** postulates that the bridged Robinson annulation occurred as predicted up until intermediate **i**. The bicyclic alcohol is protonated to give intermediate **ii**. The carbon-carbon bond between the carbonyl carbon and the bridge-head carbon is broken to form a new double bond with the elimination of water. This rearrangement forms the stable carbonyl carbocation **iii**. The carbocation is then attacked by the double bond preferentially forming the 5-membered ring to give intermediate carbocation **iv**. Elimination of the adjacent proton gives the final double bond resulting in the rearranged bicyclic enone product **153**. The structure of this product was confirmed by comparison of its ^{13}C NMR spectrum with that reported in the literature.[51]

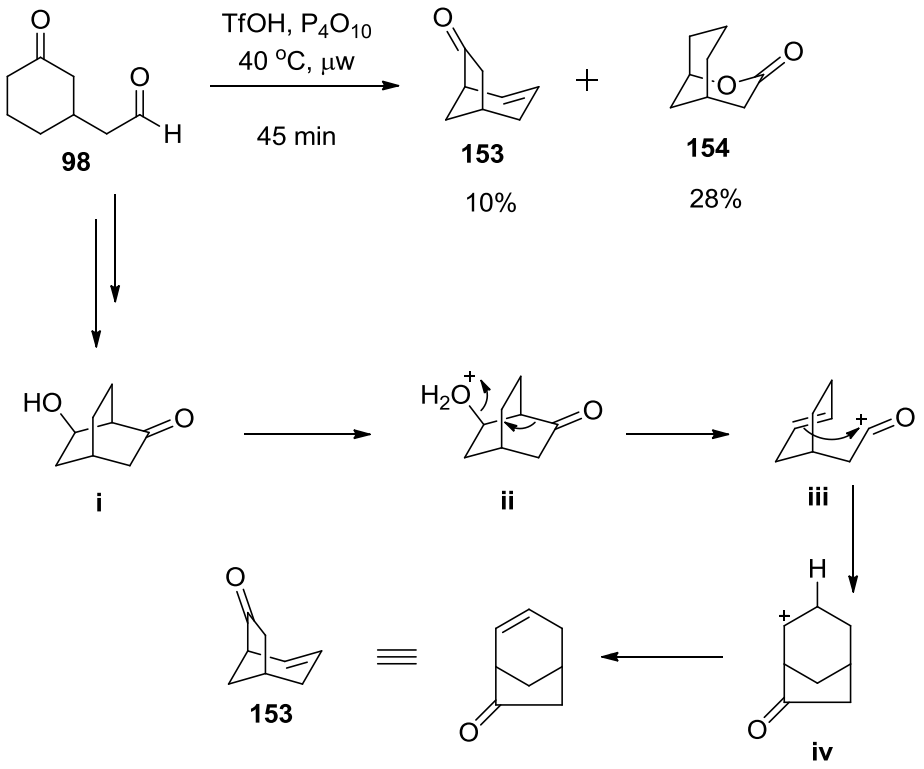


Figure 31. Proposed mechanism for rearrangement **D**.

The mechanism proposed for rearrangement **D** led us to the same conclusions from rearrangement **C**. The structure of the molecule determined the outcome of the reaction, not the reaction conditions. So therefore, it is unlikely that the rearrangement can be avoided under these reaction conditions. Altering the acidity of the reaction became the solution to this problem, as was demonstrated in our final synthesis of Bn-bod ***dl*-6**.

Conclusions and Future Work

The general syntheses of racemic (1*R*, 4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ***dl*-5** (Ph-bod) and racemic (1*R*,4*R*)-2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene ***dl*-6** (Bn-bod) have been completed. Some optimization of reaction conditions could still be carried out to increase the overall yield of each synthesis. We propose the use of the substituted allylsilanes, (*Z*)-but-2-en-1-yltrimethylsilane **145** and (*E*)-trimethyl(4-phenylbut-2-en-1-yl)silane **130**, to synthesize the corresponding Me-bod ***dl*-143** and Bn-bod ***dl*-6**. However, at this time, there is no literature precedence for the use of Snapper's conditions with these substituted allylsilanes to give optically active 3-allylcylohexanones. We believe that Snapper's conditions will give reasonable enantiomeric excess. However, at this time there is no way to predict the extent of the enantioselectivity possible under these conditions and with these reagents. Clearly, testing and optimization of those conditions would need to be done in the future to complete the synthesis of the optically active Me-bod ***dl*-143** and Bn-bod ***dl*-6**. The syntheses as described are amenable to further study of the electronic or steric factors of various substituents on the benzene rings of the ligands.

The synthesis of racemic (1*R*,4*R*)-2,5-dimethylbicyclo[2.2.2]octa-2,5-diene (Me-bod ***dl*-143**) was not successful at this time. Further work needs to be done to explore the viability of alkyl groups for the bod ligands within this synthetic scheme. Quite possibly an optimization of the reaction conditions would yield positive results in the final synthesis of Me-bod. We do not believe that this synthesis is prohibitive of a variety of alkyl substitution on the bicyclo[2.2.2]octa-2,5-diene core, only that more work needs to be done to finish the synthesis.

Experimental Section

All glassware was flame-dried under vacuum unless otherwise noted. All reactions were carried out under an argon atmosphere. Tetrahydrofuran (THF) and diethyl ether were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane (DCM), toluene, benzene, pyridine, triethylamine, and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. DMF was used directly from a commercial EMB DriSolv bottle. DMSO was used directly from a commercial Acros Organics bottle (extra dry, stored over Molecular Sieves, <50 ppm H_2O). All other solvents or reagents were purified according to literature procedures. All chemicals and anhydrous solvents were purchased from Aldrich Chemical Company, Acros Organics, Strem, or Alfa Aesar and used as obtained. Microwave reactions were performed in a CEM Discover microwave system under pressure in 10 mL sealed reaction tubes. ^{1}H NMR and ^{13}C NMR spectra were obtained on AV300, ARX-400, ARX-500 or AV500 spectrometers. The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) and the resonance patterns are reported with the following notations: br (broad), s (singlet), d (double), t (triplet), q (quartet) and m (multiplet). Thin-layer chromatography (TLC) was carried out using precoated silica gel sheets (Merck 60 F_{254}). Visual detection was performed with ultraviolet light (short wave and long wave), *p*-anisaldehyde stain, vanillin stain, magic stain, and potassium permanganate stain. Flash chromatography was performed using SilicaFlash™ P60 (60 A, 40-63 μm) silica gel from SiliCycle Inc. with compressed air.

(±)-(1*R*, 4*R*)- 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (*dl*-5).

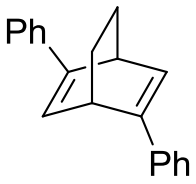
(±) (1*R*,4*S*) 3,6-diphenylbicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethanesulfonate (**111**) (268 mg, 0.66 mmol, 1 equiv) was dissolved in dry dimethylformamide (DMF) (7 mL) under an argon atmosphere. $Pd(OAc)_2$ (18 mg, 0.03 mmol, 4 mol%), PPh_3 (14 mg, 0.05 mmol, 8 mol%), triethylamine (0.55 mL, 3.95 mmol, 6 equiv), and formic acid (0.10 mL, 2.64 mmol, 4 equiv) were added to the solution and it was stirred at 23 °C for 3 h. The black solution was quenched by the addition of water (15 mL) and was subsequently extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 30:1 pentane:diethyl ether as the eluent. The product was isolated as a white solid (258 mg, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.52 (4H, d, *J* = 7.5 Hz)

7.41 (4H, dd , *J* = 7.5, 7.5 Hz)

7.30 (2H, t, *J* = 7.5 Hz)



6.72 (2H, dd, *J* = 6.25, 1.7 Hz)

4.30 (2H, bd, *J* = 6.5 Hz)

1.64 (4H, bs).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.9, 138.3, 129.3, 128.6, 126.9, 124.9, 40.1, 25.9.

(±)-(1*R*,4*R*)-2,5-bis(phenylmethyl)bicyclo[2.2.2]octa-2,5-diene (*dl*-6).

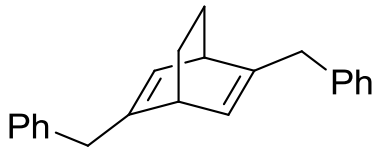
The racemic mixture of (1*R*,4*R*)-5-(phenylmethyl)bicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethanesulfonate (**139**) (7 mg, 0.02 mmol, 1 equiv) and $PdCl_2$(dppf) (1.5 mg, 0.002 mmol, 0.10 equiv) were dissolved in dry diethyl ether (0.25 mL). A freshly prepared solution of benzylmagnesium bromide (0.24 mL, 0.12 mmol, 6 equiv, 0.5 M solution in ether) was added to the reaction mixture. The resultant bright yellow solution was heated to reflux for 24 h. The reaction mixture was quenched with water (1 mL) and then extracted with diethyl ether (3 x 5 mL). The ether layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel using 100% pentane as the eluent. The bicyclooctadiene product was isolated as a colorless oil (3 mg, 0.01 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.27 (4H, t, *J* = 7.5 Hz)

7.19 (2H, t, *J* = 7.5 Hz)

7.13 (4H, t, *J* = 7.5 Hz)



5.82 (2H, dd, *J* = 6.0, 1.0 Hz)

3.45 (2H,b d, *J* = 15.5 Hz)

3.42 (2H, bd, J = 15.5 Hz)

3.27-3.24 (2H, m)

1.26-1.19 (2H, m)

1.14-1.08 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.2, 139.7, 129.0, 128.3, 128.2, 125.9, 41.1, 40.1, 26.0.

3*RS*-(2-Oxo-2-phenylethyl)cyclohexanone (86).

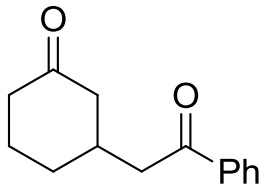
A 1 L round-bottom flask was charged with oxalyl chloride (5.53 mL, 63.37 mmol, 2 equiv) in dichloromethane (320 mL) at -78 °C. Dimethyl sulfoxide (8.99 mL, 126.73 mmol, 4 equiv) was added slowly and the reaction mixture stirred for 30 min. A solution of 3*RS*-(2*RS*-hydroxy-2-phenylethyl)cyclohexanone (**105**) (6.92 g, 31.68 mmol, 1 equiv) in dichloromethane (10 mL) was added and the reaction stirred for 1 h at -78 °C. Triethylamine (17.66 mL, 126.73 mmol, 4 equiv) was then added and the reaction mixture was stirred for 2 h. TLC analysis (2:1 hexanes:ethyl acetate) showed complete consumption of the starting material. The reaction was allowed to warm slowly to 0 °C and quenched with water (75 mL). The layers were separated and the water later extracted with diethyl ether (3 x 75 mL). The combined organic layers were washed with 1N HCl solution (50 mL), water (50 mL), and brine (75 mL), then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified on silica gel flash column chromatography using 2:1 hexanes:ethyl acetate as eluent. The diketone product was isolated as a pale yellow oil (4.45 g, 65% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.93 (2H, dd, *J* = 8.8, 1.6 Hz)

7.56 (1H, tt, *J* = 7.4, 1.6 Hz)

7.46 (2H, t, *J* = 7.8 Hz)



3.06 (1H, dd, *J* = 16.4, 6.8 Hz)

2.94 (1H, dd, *J* = 16.4, 6.0 Hz)

2.58-2.48 (2H, m)

2.42-2.36 (1H, dm, *J* = 14.4 Hz)

2.27 (1H, dddd, *J* = 14.2, 12.0, 6.0, 1.0 Hz)

2.14 (1H, ddd, *J* = 14.4, 12.8, 1.0 Hz)

2.09-1.96 (2H, m)

1.78-1.67 (1H, m)

1.50-1.40 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.7, 198.4, 137.0, 133.2, 128.7, 128.1, 47.8, 44.7, 41.3, 34.9, 31.1, 24.9.

3-(2-Oxopropyl)cyclohexanone (87).

In a 250 mL round-bottom flask, palladium (II) chloride (256 mg, 1.45 mmol, 0.1 equiv), copper (I) chloride (1.43 g, 14.47 mmol, 1 equiv), DMF (30 mL) and water (30 mL) were combined. Oxygen gas was bubbled through the solution for 10 min to saturate the solution. 3-(2-Propenyl)-cyclohexanone (**97**) (3.30 g, 23.88 mmol, 1 equiv) was dissolved in DMF (5 mL) and added in one portion to the reaction mixture. The reaction mixture was stirred under an oxygen atmosphere for 6 h. The mixture was poured into 3M HCl (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic layers were washed with 0.5N HCl (5 x 50 mL) and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified via flash column chromatography on silica gel using 6:1 pentane:diethyl ether as the eluent. The product was isolated as a pale yellow oil (2.58 g, 3.68 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

2.42 (2H, m)

2.38-2.29 (3H, m)

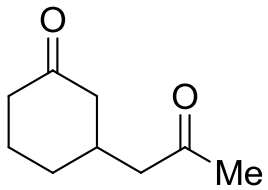
2.22 (1H, m)

2.11 (3H, s)

2.05-1.96 (2H, m)

1.92-1.86 (1H, m)

1.69 (1H, m)



1.34 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.6, 206.9, 49.7, 47.5, 41.2, 34.3, 30.9, 30.5, 24.9.

(1*R*, 4*R*) and (1*S*, 4*S*)-6-Phenylbicyclo[2.2.2]oct-5-en-2-one (89).

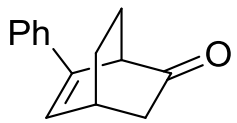
A 500 mL round-bottom flask was charged with phosphorus pentoxide (12.5 g, 44.13 mmol, 2 equiv) and dichloromethane under an argon atmosphere. 3*RS*-(2-oxo-2-phenylethyl)cyclohexanone (**86**) (4.77 g, 22.06 mmol, 1 equiv) in dichloromethane (5 mL) was then added to the stirred solution at 0 °C. Trifluoromethanesulfonic acid (3.91 mL, 44.13 mmol, 2 equiv) was added quickly and the resultant red-orange solution was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for another hour until TLC (1:1 pentane:diethyl ether) showed complete disappearance of the starting material. The reaction was then filtered and washed with dichloromethane to remove the phosphorus pentoxide. Triethylamine was added to the red solution with swirling until the solution turned yellow and was subsequently concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel using 2:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless or pale yellow oil (2.89 g, 66% yield). A small amount of the starting diketone (up to 10%) was also isolated and could be recycled.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.41-7.38 (2H, m)

7.36-7.31 (2H, m)

7.28-7.24 (1H, m)



6.72 (1H, dd, *J* = 6.8, 2.0 Hz)

3.70 (1H, ddd, *J* =2.8, 2.0, 2.0 Hz)

3.14 (1H, ddddd, *J* = 6.8, 2.8, 2.8, 2.8, 2.8 Hz)

2.14 (2H, m)

2.01 (1H, m)

1.85-1.69 (2H, m)

1.66-1.59 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.7, 140.0, 137.5, 130.7, 128.6, 127.6, 125.1, 51.2, 40.6, 32.6, 24.6, 22.8.

(±) (1*R*,4*R*)-6-Methylbicyclo[2.2.2]oct-5-en-2-one (90)

(±) (1*R*,5*S*)-1-methyl-2-oxabicyclo[3.3.1]nonan-3-one (140).

In a 100 mL round-bottom flask, phosphorus pentoxide (P_4O_{10}, 6.26 g, 22.05 mmol, 2 equiv) was suspended in dry dichloromethane (DCM, 30 mL) under an argon atmosphere. 3-(2-Oxopropyl)cyclohexanone (**87**) (1.70 g, 11.02 mmol, 1 equiv) was dissolved in DCM (5 mL) and

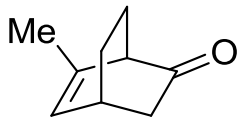
the solution added to the P_4O_{10} suspension in one portion. Trifluoromethanesulfonic acid (1.95 mL, 22.05 mmol, 2 equiv) was added quickly and the reaction mixture was stirred vigorously at 23 °C for 2 h. The reaction was filtered by gravity to remove the P_4O_{10} and the residue washed with DCM. Triethylamine was added to the filtrate with swirling until the solution changed from red to yellow. The reaction mixture was concentrated *in vacuo* and the residue was purified via flash column chromatography on silica gel using 1:1 pentane:diethyl ether as the eluent. The bicyclic product was islolated as a pale yellow oil (720 mg, 5.29 mmol, 48% yield). A side product, (1*R*,5*S*)-1-methyl-2-oxabicyclo[3.3.1]nonan-3-one (**140**), was isolated as well (150 mg, 1.10 mmol, 10% yield).

(±) (1*R*,4*R*)-6-Methylbicyclo[2.2.2]oct-5-en-2-one (90)

^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.96 (1H, bd, *J* = 6.5 Hz)

2.83 (1H, m)



2.78 (1H, d of pentet, *J* = 6.0, 3.0 Hz)

1.90-1.89 (2H, m)

1.75-1.70 (1H, m)

1.70 (3H, s)

1.59-1.52 (1H, m)

1.47 (1H, dddd, J = 12.0, 12.0, 4.0, 3.0 Hz)

1.41-1.35 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.1, 137.2, 129.2, 53.8, 41.0, 31.9, 25.0, 22.1, 19.9.

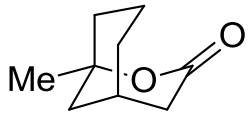
(±) (1*R*,5*S*)-1-methyl-2-oxabicyclo[3.3.1]nonan-3-one (140).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

2.51 (1H, dd, J = 18.5, 7.0 Hz)

2.26 (1H, d, J = 18.0 Hz)

2.21-2.17 (1H, m)



1.75 (1H, d, J = 12.5 Hz)

1.67 (1H, d, J = 13.5 Hz)

1.59-1.51 (3H, m)

1.46-1.29 (3H, m)

1.23 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 80.8, 37.1, 36.3, 35.0, 30.3, 28.9, 26.5, 17.3.

Methyl 6-oxocyclohex-1-enecarboxylate (94).

Phenylselenyl chloride (3.86g, 20.17 mmol, 1.05 equiv) was dissolved in dichloromethane (330 mL) in a 500 mL round-bottom flask. The flask was cooled to 0 °C, pyridine (2.32 mL, 28.82 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 15 min. A solution of methyl 2-oxocyclohexanecarboxylate (**96**) (3.0 g, 19.21 mmol, 1 equiv) in dichloromethane (20 mL) was added dropwise to the reaction mixture over 1 h at 0 °C. The reaction mixture was stirred at 0 °C for 4 h then it was allowed to warm to 23 °C and stirred for 12 h. Water (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined ether and dichloromethane layers were washed with 1N HCl (3 x 75 mL) and brine (1 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was dissolved in dry dichloromethane (200 mL) and cooled to 0 °C. Hydrogen peroxide (30% solution in water) was added in 1 mL increments every 10 minutes to the vigorously stirred solution. After 6 mL had been added, the reaction was stirred at 0 °C for a further 30 min. Water was added (100 mL) to the reaction mixture and the layers were separated. The dichloromethane layer was washed with water (2 x 75 mL), 1N HCl (1 x 75 mL), saturated $NaHCO_3$ solution (1 x 75 mL), and brine (1 x 75 mL), then dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate as the eluent. Methyl 6-oxocyclohex-1-enecarboxylate (**94**) (2.12 g, 13.57 mmol, 72% yield) was isolated as a yellow oil.

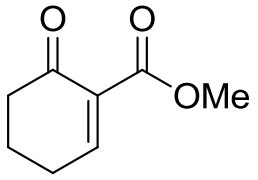
^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.64 (1H, t, *J* = 4.0 Hz)

3.72 (3H, s)

2.48-2.42 (4H, m)

1.98 (2H, pentet, *J* = 6.0 Hz).



^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.5, 165.1, 156.7, 132.8, 52.1, 38.7, 26.1, 22.1.

(2*R*)-Methyl 2-allyl-6-oxocyclohexanecarboxylate (*R*-95).

A 25 mL test-tube equipped with a small stirbar was flame dried, capped with a septum and placed in a dry atmosphere (glove-box). $Cu(OTf)_2$ (94 mg, 0.26 mmol, 0.20 equiv), 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane (*t*Bu-Box,85 mg, 0.29 mmol, 0.22 equiv), and 4 Å molecular sieves (100 mg) were placed in the test tube and it was sealed with a septum and Teflon tape before being removed from the glove-box. Dichloromethane (6 mL) was added and the solution was allowed to stir for 15 min. Methyl 6-oxocyclohex-1-enecarboxylate (**94**) (200 mg, 1.30 mmol, 1 equiv) was dissolved in dichloromethane (1 mL) and was added to the catalyst reaction mixture which immediately turned the solution from a light blue-green solution to a dark brown/purple solution. The reaction mixture was then cooled to -78 °C in a tall Dewar flask and allyltrimethylsilane (1.03 mL, 6.5 mmol, 5 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 45 h, then quenched with a saturated solution of NH_4Cl (2 mL) at -78 °C and

the tube was allowed to warm to 23 °C. The reaction mixture was then extracted with dichloromethane (3 x 10 mL), and the organic layer was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate as the eluent. The product was isolated as a colorless oil (128 mg, 0.65 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

12.31 (1H, s)

5.76-5.66 (1H, m)

4.98-4.89 (2H, m)

3.72 (3H, s)

2.56-2.54 (1H, m)

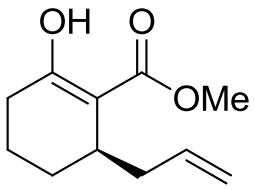
2.30-2.21 (3H, m)

1.94 (1H, m)

1.71-1.66 (2H, m)

1.65-1.55 (1H, m)

1.40-1.35 (1H, m).



^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.9, 137.5, 115.6, 101.6, 51.2, 38.6, 31.2, 28.7, 24.9, 16.7.

Methyl 2-oxocyclohexanecarboxylate (96).

A 500 mL 3-necked round-bottom flask equipped with a reflux condenser was charged with sodium hydride (NaH, 7.73 g, 193.20 mmol, 2 equiv, 60% suspension in mineral oil), dimethyl carbonate (22.0 mL, 261.08 mmol, 2.7 equiv), and dry tetrahydrofuran (350 mL). The mixture was heated to reflux and cyclohexanone (10.0 mL, 96.60 mmol, 1 equiv) was added dropwise over 1 h. Potassium hydride (KH, 1.29 g, 9.66 mmol, 0.10 equiv) was added in one portion to the refluxing mixture after 1 mL of cyclohexanone was added. The reaction mixture was refluxed for 4 h, then cooled to 23 °C and was stirred an additional 12 h. The reaction was poured into 3M acetic acid (100 mL) and brine (100 mL). The mixture was extracted with dichloromethane (3 x 200 mL) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via vacuum distillation giving methyl 2-oxocyclohexanecarboxylate (**96**) (12.67 g, 81.14 mmol, 84% yield, bp 75-78 °C @ 0.63 mm Hg). Proton NMR shows the product to be comprised of a 1:0.4 mixture of the enol and keto tautomers.

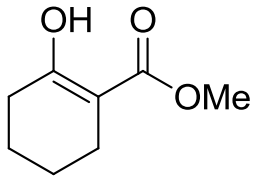
^{1}H NMR (500 MHz, $CDCl_3$) δ:

Enol:

12.12 (1H, s)

3.71 (3H, s)

2.23 (2H, td, *J* = 6.5, 1.0 Hz)



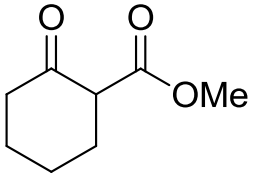
2.17 (2H, td, *J* = 6.5, 1.0 Hz)

1.66-1.62 (2H, m)

1.59-1.54 (2H, m).

Keto:

3.71 (3H, s)



3.36 (1H, dd, *J* = 9.5, 6.0 Hz)

2.49-2.44 (1H, ddd, *J* = 14.0, 5.0, 5.0 Hz)

2.36-2.30 (1H, ddd, *J* = 14.0, 10.5, 6.0 Hz)

2.14-2.04 (2H, m)

1.97-1.92 (1H, m)

1.87-1.75 (2H, m)

1.69-1.64 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.2, 173.1, 172.1, 97.6, 52.1, 51.3, 41.5, 29.9, 29.0, 27.1, 23.3, 22.4, 22.3, 21.9.

3-(2-propenyl)-cyclohexanone (97).

Cyclohexenone (16.0 g, 166.45 mmol, 1 equiv) was dissolved in dry dichloromethane (350 mL) in a 1L round-bottom flask under argon atmosphere with stirring at -78 °C. $TiCl_4$ (1.0 M solution in dichloromethane) (200 mL, 199.74 mmol, 1.2 equiv) was added slowly over 30 min. The red solution was allowed to stir at -78 °C for 1 h. A solution of allyltrimethylsilane (29 mL, 183.10 mmol, 1.1 equiv) in dichloromethane (10 mL) was added to the reaction mixture slowly over 1 h. The reaction was stirred at -78 °C until complete (2-3 h by TLC (4:1 hexane: ethyl acetate)). Water was added at -78 °C to quench the reaction and the reaction was allowed to warm to 0 °C. The organic and aqueous layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce a yellow oil. The crude mixture was purified by flash column chromatography on silica gel (4:1 hexanes: ether eluent) to give the pure product as a colorless oil (22.425 g, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

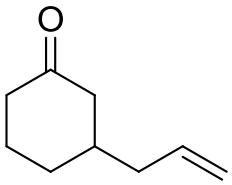
5.74 (1H, ddt, *J* = 16.0, 9.2, 7.0 Hz)

5.03 (1H, bd, *J* = 9.2 Hz)

5.02 (1H, bd, *J* = 16.0 Hz)

2.41 (1H, dddd, *J* = 13.6, 4.0, 2.0, 2.0 Hz)

2.35 (1H, dm, *J* = 14.0 Hz)



2.25 (1H, dddd, *J* = 14.0, 12.4, 6.0, 1.2 Hz)

2.15-1.99 (4H, m)

1.94-1.80 (2H, m)

1.70-1.59 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.7, 135.7, 116.8, 47.7, 41.4, 40.8, 38.8, 30.9, 25.1.

3*R*-(2-propenyl)-cyclohexanone (*R*-97).

In a 100 mL round-bottom flask equipped with a condenser, (2*R*)-methyl 2-allyl-6-oxocyclohexanecarboxylate (***R*-95**) (120 mg, 0.61 mmol, 1 equiv), NaCl (35 mg, 0.61 mmol, 1 equiv), dimethyl sulfoxide (DMSO, 10 mL), and water (10 drops) were added and the mixture was heated to 150 °C for 3 h. The reaction was then cooled to 23 °C and extracted with 2:1 pentane:diethyl ether mixture (5 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel with 2:1 hexanes:ethyl acetate. The product was isolated as a colorless oil (64 mg, 0.47 mmol, 76% yield).

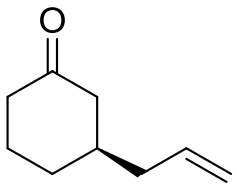
^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.72 (1H, ddt, *J* = 18.0, 11.0, 7.0 Hz)

5.02 (1H, d, *J*= 11.5 Hz)

5.00 (1H, d, J = 18.0 Hz)

2.40 (1H, dm, J = 13.5 Hz)



2.34 (1H, m)

2.23 (1H, ddd, J = 10.4, 10.4, 6.5 Hz)

2.09-2.01 (4H, m)

1.87-1.79 (2H, m)

1.60 (1H, dddd, J = 13.5, 12.5, 3.5, 3.5 Hz)

1.33 (1H, dddd, J = 13.5, 3.5, 3.5, 3.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.7, 135.7, 116.8, 47.7, 41.4, 40.8, 38.8, 30.9, 25.1.

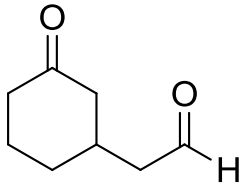
3-Oxocyclohexaneacetaldehyde (98).

In a 250 mL round-bottom flask, 3-allylcyclohexanone (**97**) (2.0 g, 14.47 mmol, 1 equiv) was dissolved in dry dichloromethane (150 mL) and cooled to -78 °C. Ozone was bubbled through the solution until the solution turned blue, then oxygen was then bubbled through the solution until the blue color dissipated. Triphenylphosphine (3.8 g, 14.47 mmol, 1 equiv) was added with stirring and the reaction was placed under an argon atmosphere and allowed to warm to 23 °C overnight. Water was added to reaction and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over

anhydrous $MgSO_4$ and concentrated *in vacuo*. To remove the triphenylphosphine oxide, the residue was suspended in a 1:1 mixture of pentane and diethyl ether and filtered through Celite while washing with a small amount of cold diethyl ether. The filtrate was concentrated again and the suspension/filtration step repeated if necessary. The crude product was purified via flash column chromatography on silica gel using 2:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless oil (1.317 g, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

9.74 (1H, t, *J* = 1.2 Hz)



2.52-2.36 (5H, m)

2.29-2.22 (1H, dddd, *J* = 14.5, 12.5, 6.0, 1.2 Hz)

2.11-2.01 (2H, m)

1.95-1.92 (1H, bd, *J* = 13.0 Hz)

1.76-1.66 (1H, ddddd, *J* = 13.5, 10.5, 10.5, 4.5, 4.0 Hz)

1.46- 1.37 (1H, dddd, *J* = 12.0, 12.0, 10.5, 4.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.3, 200.7, 50.0, 47.5, 41.1, 33.2, 31.0, 24.9.

(±) 7-(2-Propenyl)-2,3-diphenyl-1,4-dioxaspiro[4.5]decane (101).

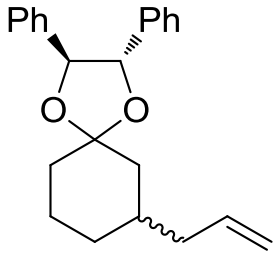
3-(2-Propenyl)cyclohexanone (**97**) (53 mg, 0.36 mmol, 1 equiv) was dissolved in benzene (50 mL) in a 100 mL round-bottom flask with a Dean Stark trap and condenser. *p*-Toluenesulfonic acid (14 mg, 0.07 mmol, 0.2 equiv) and *R,R*-hydrobenzoin (116 mg, 0.54 mmol, 1.5 equiv) were added the reaction mixture. The reaction mixture was heated to reflux for 1 h. After the flask was cooled to 23 °C, a saturated solution of $NaHCO_3$ (50 mL) was added. The mixture was extracted with ethyl acetate (3 x 50 mL) and the organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate which gave the product as a white solid (121 mg, 0.36 mmol, 100% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.35-7.22 (10H, m)

5.86 (0.5H, dddd, *J* = 16.5, 10.5, 7.0, 7.0 Hz)

5.82 (0.5H, dddd, *J* = 16.5, 10.5, 7.0, 7.0 Hz)



5.09-5.01 (2H, m)

4.75 (2H, m)

2.19-2.05 (4H, m)

1.95-1.69 (5H, m)

1.46 (0.5H, dd, J = 12.5, 12.5 Hz)

1.44 (0.5H, dd, J = 12.5, 12.5 Hz)

1.05-0.89 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.0, 136.8, 128.3, 128.10, 128.07, 126.69, 126.67, 126.63, 126.61, 115.83, 115.79, 110.2, 110.1, 85.2, 85.01, 85.00, 43.1, 42.4, 41.24, 41.22, 36.8, 35.9, 35.3, 34.9, 31.5, 31.4, 23.1, 22.7.

(2*R*,3*R*,7*R*)-7-(2-Propenyl)-2,3-diphenyl-1,4-dioxaspiro[4.5]decane (*R*,*R*,*R*-101)

(3*R*)-3-(2-Propenyl)cyclohexanone (***R*-97**) (25 mg, 0.18 mmol, 1 equiv) was dissolved in benzene (25 mL) in a 50 mL round-bottom flask with a Dean Stark trap and condenser. *p*-Toluenesulfonic acid (7 mg, 0.04 mmol, 0.2 equiv) and *R,R*-hydrobenzoin (58 mg, 0.27 mmol, 1.5 equiv) were added the reaction mixture. The reaction mixture was heated to reflux for 1 h. After the flask was cooled to 23 °C, a saturated solution of $NaHCO_3$ (25 mL) was added. The mixture was extracted with ethyl acetate (3 x 25 mL) and the organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate which gave the product as a white solid (36 mg, 0.12 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.35-7.20 (10H, m)

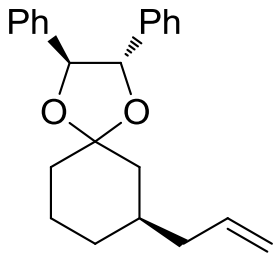
5.84 (1H, dddd, *J* = 17.6, 10.5, 7.0, 7.0 Hz)

5.04 (1H, d, *J* = 16.5 Hz)

5.03 (1H, d, *J* = 10.5 Hz)

4.74 (1H, d, *J* = 8.5 Hz)

4.71 (1H, d, *J* = 8.5 Hz)



2.16-2.03 (4H, m)

1.93-1.85 (1H, m)

1.80-1.61 (4H, m)

1.41 (1H, dd, *J* = 12.8, 12.8 Hz)

1.00-0.87 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.9, 136.8, 128.3, 128.08, 128.06, 126.7, 126.6, 115.8, 110.2, 85.2, 84.9, 43.1, 41.2, 35.8, 34.8, 31.5, 23.1. (1 low-field carbon not resolved)

7-(2-propenyl)-1,4-dioxaspiro[4.5]decane (102).

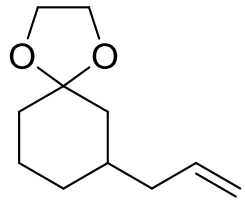
3-(2-propenyl)cyclohexanone (**97**) (18.4 g, 133.13 mmol, 1 equiv) was dissolved in benzene (350 mL) in a 500 mL round-bottom flask equipped with a Dean-Stark trap and condenser. Ethylene glycol (12.40 g, 199.71 mmol, 1.5 equiv) and *p*-toluenesulfonic acid monohydrate (5.06 g, 26.63 mmol, 0.2 equiv) were added and the reaction mixture was heated to reflux. The reaction was allowed to run for 12 h until it was complete as evidenced by TLC. The mixture was allowed to cool and was quenched by the addition of saturated $NaHCO_3$ solution (50 mL). Water was added to dissolve any precipitate. The mixture was extracted with diethyl ether (3 x 100 mL). The organic layer was washed with brine (100 mL) and then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The pale yellow oil (16.79 g, 82% yield) was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.74 (1H, ddt, J = 16.4, 10.8, 7.2 Hz)

4.99 (1H, bd, J = 16.4 Hz)

4.98 (1H, bd, J = 10.8 Hz)



3.93 (4H, s)

2.04-1.96 (2H, m)

1.80-1.60 (5H, m)

1.56-1.36 (2H, m)

1.17 (1H, dd, J = 12.3, 12.3 Hz)

0.86 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.9, 115.8, 109.4, 64.3, 64.1, 41.35, 41.31, 35.4, 34.8, 31.5, 23.2.

2-(1,4-dioxaspiro[4.5]decan-7-yl)acetaldehyde (103).

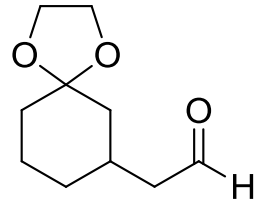
7-(2-propenyl)-1,4-dioxaspiro[4.5]decane (**102**) (17.286 g, 94.846 mmol, 1 equiv) was dissolved in dichloromethane (470 mL) in a 1L round bottom flask at -78 °C. Ozone was bubbled through the solution until the solution turned blue, then oxygen was bubbled through the solution until the blue color dissipated. To quench, triphenylphosphine (24.88 g, 94.846 mmol, 1 equiv) was added to the stirred solution at -78 °C. The solution was allowed to stir for 12 h under an argon atmosphere to ensure complete destruction of the ozonide. Water was added to the solution (200 mL) and the layers separated. The water layer was extracted twice with dichloromethane (50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was contaminated with triphenylphosphine oxide (white solid). The triphenylphosphine oxide was removed by swirling the crude product in a solvent mixture of 1:1 pentane: diethyl ether (100 mL). The suspension was filtered through Celite, washing with a small amount of cold diethyl ether. The filtrate was then concentrated *in vacuo.* If there was still a significant amount of triphenylphosphine oxide remaining, the process was repeated. Once the majority of the triphenylphosphine oxide was removed, the residue was purified via flash chromatography on silica gel using 4:1 hexane: ethyl

acetate as the eluent. The product was a colorless oil (12.496 g, 72% yield) which was stored under argon in the freezer until ready to be used.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

9.73 (1H, t, J = 2.0 Hz)

3.92 (4H, s)



2.34 (1H, ddd, J = 17.8, 7.8, 2.1 Hz)

2.31 (1H, ddd, J = 17.8, 6.0, 2.1 Hz)

2.28-2.15 (1H, m)

1.79-1.67 (4H, m)

1.62-1.51 (1H, m)

1.46-1.38 (1H, m)

1.25 (1H, dd, J = 12.2, 12.2 Hz)

1.01-0.91 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.1, 108.7, 64.3, 64.2, 50.6, 41.3, 34.6, 31.6, 30.5, 22.9.

3*RS*-(2*RS*-Hydroxy-2-phenylethyl)cyclohexanone (105).

Magnesium turnings (3.85 g, 158.42 mmol, 5 equiv) were placed in a flame dried 1 L round-bottom flask under argon. Dry diethyl ether (320 mL) and a crystal of iodine were added. A small portion of bromobenzene (1 mL) was added and the reaction was heated to reflux. Once the solution turned grey and cloudy, the remaining bromobenzene (6.66 mL total, 63.368 mmol, 2 equiv) was added slowly and the reaction mixture was refluxed for 1 h to ensure complete formation of the Grignard reagent. A solution of 2-(1,4-dioxaspiro[4.5]decan-7-yl)acetaldehyde (**103**) (5.84 g, 31.68 mmol, 1 equiv) in diethyl ether (15ml) was then added slowly to the reaction flask and stirred for 30 min until TLC analysis (2:1 hexanes: ethyl acetate) indicated complete consumption of the starting material. The reaction was cooled to 23 °C, quenched with 3N HCl (200 mL), and allowed to stir overnight. Water was added to the reaction mixture and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude oil was used in the following step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

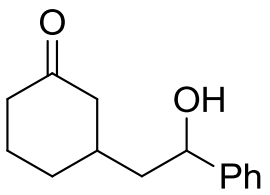
7.34-7.25 (5H, m)

4.73 (1H, dd, *J* = 8.8, 8.8 Hz)

2.49 (1H, bdd, *J* = 12.4, 12.4 Hz)

2.33 (1H, m)

2.24 (1H, bddd, *J* = 12.4, 12.4, 5.8 Hz)



2.20-2.05 (1H, m)

2.09-1.76 (5H, m)

1.71-1.56 (2H, m)

1.39 (1H, bdd, J = 11.2, 11.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.71, 211.66, 144.77, 144.67, 128.64, 128.61, 128.3, 127.8, 127.7, 127.2, 125.8, 125.7, 72.0, 71.7, 48.4, 47.6, 45.78, 45.77, 41.42, 41.37, 35.72, 35.67, 31.8, 30.9, 25.1, 25.0.

(±) (1*R*, 3*R*, 4*S*) 3,6-Diphenylbicyclo[2.2.2]oct-5-en-2-one (106).

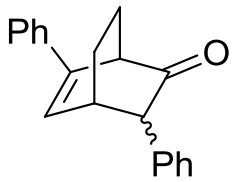
The diastereomeric mixture of methyl 3-oxo-2,5-diphenylbicyclo[2.2.2]oct-5-ene-2-carboxylates (**110**) (484 mg, 1.46 mmol, 1 equiv) was dissolved in dry dimethylformamide (5 mL) in a 10 mL round-bottom flask. Lithium iodide (1.36 g, 10.19 mmol, 7 equiv) was added and the mixture was heated to 130 °C and stirred for 6 h. The reaction was quenched by pouring into crushed ice and was stirred for a further 12 h. The reaction mixture was extracted with ethylacetate (3 x 10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified via column chromatography on silica gel using 4:1 pentane:diethyl ether as the eluent. Two isomers (diastereomers) of the product were isolated, one as a white powder (100 mg) and the other as a colorless oil (121 mg), for an overall yield of 55%.

Isomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.51 (2H, bd, *J* = 9.6 Hz)

7.42 (2H, bdd, *J* = 7.2, 8 Hz)



7.36- 7.24 (4H, m)

7.17 (2H, bd, *J* = 6.8 Hz)

6.75 (1H, dd, *J* = 6.4, 1.6 Hz)

3.93 (1H, ddd, *J* = 2.8, 2.8, 1.6 Hz)

3.44 (1H, bs)

3.27 (1H, dddd, *J* = 6.4, 2.8, 2.8, 2.8 Hz)

2.24-2.17 (1H, dddd, *J* = 12.4, 10.8, 4.8, 2.4 Hz)

2.05 (1H, dddd, *J* = 12.8, 9.8, 3.2, 3.2 Hz)

1.87 (1H, dddd, *J* = 12.4, 12, 3.6, 3.6 Hz)

1.74 (1H, dddd, *J* = 12.0, 12.0, 4.4, 3.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.6, 140.3, 138.5, 137.5, 130.0, 128.8, 128.43, 128.40, 127.8, 126.8, 125.3, 55.7, 51.7, 40.4, 25.7, 22.4.

Isomer 2:

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.48 (2H, bd, *J* = 7.2 Hz)

7.40-7.35 (4H, m)

7.34- 7.26 (2H, m)

7.19 (2H, bd, *J* = 7.2 Hz)

6.91 (1H, dd, *J* = 6.8, 1.6 Hz)

3.87 (1H, m)

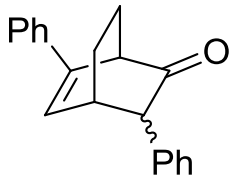
3.51 (1H, bs)

3.19 (1H, dddd, *J* = 6.0, 2.8, 2.8, 2.8 Hz)

2.15-2.07 (1H, m)

1.88-1.76 (2H, m)

1.46-1.35 (1H, m).



^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.6, 140.7, 138.3, 137.4, 131.5, 128.73, 128.69, 128.5, 127.7, 126.9, 125.2, 53.9, 51.7, 40.4, 22.6, 19.2.

(1*R*, 4*R*) and (1*S*, 4*S*)-3,3,6-Triphenylbicyclo[2.2.2]oct-5-en-2-one (107).

Under an inert atmosphere (dry box) $Pd(OAc)_2$ (48 mg, 0.071 mmol, 0.05 equiv), NaOtBu (204 mg, 2.12 mmol, 1.5 equiv), and tri(*tert*-butyl)phosphine (0.18 mL, 0.49M solution in hexanes, 0.088 mmol, 0.63 equiv) were added with dry tetrahydrofuran (8 mL) to a flame dried 50 mL round-bottom flask equipped with a stirbar. Bromobenzene (0.15 mL, 1.41 mmol, 1 equiv) and (1*R*, 4*R*)/(1*S*, 4*S*)-6-phenylbicyclo[2.2.2]oct-5-en-2-one (**89**) (308 mg, 1.55 mmol, 1.1 equiv) in tetrahydrofuran (3 mL) were added to the flask containing the catalyst and the reaction was heated to 50 °C. The reaction was monitored by TLC (4:1 hexanes: ethyl acetate) and allowed to reflux for 24 h, after which some starting material still remained as evidenced by TLC. The reaction was cooled to 23 °C, diluted with diethyl ether, washed with 1N HCl (3 mL), water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to yield the diphenylated product (221 mg, 52% yield, yellow solid) and unreacted starting material (127 mg, 41% recovered).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

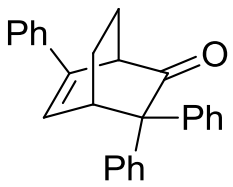
7.49 (2H, d, *J* = 7.9 Hz)

7.36 (2H, d, *J* = 7.8 Hz)

7.33-7.18 (10H, m)

7.13 (1H, t, *J* = 7.3 Hz)

7.0 (1H, bd, *J* = 6.4 Hz)



3.91 (1H, m)

3.82 (1H, dd, J = 6.8, 2.4, 2.4 Hz)

2.09-2.02 (1H, m)

1.77 (1H, dddd, J = 12.8, 12.8, 3.2, 3.2 Hz)

1.66-1.60 (1H, dddd, J = 10.0, 10.0, 3.2, 3.2 Hz)

1.51-1.42 (1H, dddd, J = 12.4, 12.4, 5.6, 3.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.9, 131.1, 129.7, 128.5, 128.3, 128.2, 127.6, 127.4, 126.4, 126.1, 125.2, 60.5, 52.1, 43.2, 21.9, 21.4 (several low field carbons not resolved).

(±) (1*S*,4*R*)-Methyl 3-oxo-5-phenylbicyclo[2.2.2]oct-5-ene-2-carboxylate (109).

A 100 mL round-bottom flask was charged with NaH (908 mg, 22.70 mmol, 3 equiv, 60% suspension in mineral oil), dimethyl carbonate (1.91 mL, 22.70 mmol, 3 equiv) and tetrahydrofuran (25 mL). The reaction mixture was heated to reflux and then a solution of 3-(1*R*, 4*R*)/(1*S*, 4*S*)-6-phenylbicyclo[2.2.2]oct-5-en-2-one (**89**) (1.5 g, 7.57 mmol, 1 equiv) in 5 mL tetrahydrofuran was added slowly. A catalytic amount of KH (100 mg, 0.76 mmol, 0.1 equiv, 80% suspension in mineral oil) was added to the flask after 0.5 mL of the (1*R*, 4*R*)/(1*S*, 4*S*)-6-phenylbicyclo[2.2.2]oct-5-en-2-one (**89**) solution was added. The reaction mixture was refluxed for 4 h then cooled to 23 °C. Water was added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with 1N

HCl (1 x 25 mL) and brine (1 x 25 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified via flash column chromatography on silica gel using 4:1 hexanes:ethyl acetate as the eluent. The product was isolated as a powder (1.372 g, 71% yield) as a 2:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.42-7.38 (2H, m)

7.37-7.31 (2H, m)

7.31-7.25 (1H, m)

6.81 (0.67H, dd, J = 6.6, 1.8 Hz)

6.75 (0.33H, dd, J = 6.8, 1.6 Hz)

3.77 (1H, s)

3.68 (2H, s)

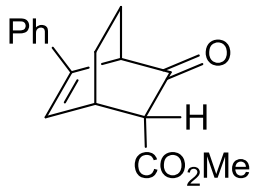
3.40-3.36 (1H, m)

3.19 (0.67H, d, J = 1.6 Hz)

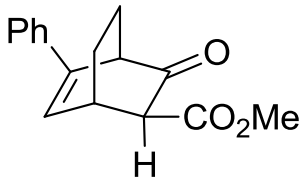
3.10 (0.33H, bdd, J = 2.2, 1.6 Hz)

2.17-2.10 (0.33H, dddd, J = 12.4, 9.6, 4.6, 2.2 Hz)

2.08-2.01 (1H, m)



Major Isomer



Minor Isomer

1.87-1.72 (2H, m)

1.68-1.61 (0.67H, m)

1.56-1.48 (0.33H, m).

Major isomer-^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.5, 168.3, 138.0, 137.0, 130.0, 128.6, 127.8, 125.3, 55.4, 52.5, 50.5, 35.6, 23.9, 22.5.

Minor isomer-^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.2, 169.6, 140.8, 137.0, 130.0, 128.7, 128.0, 125.1, 53.0, 52.4, 50.7, 35.9, 21.7, 20.8.

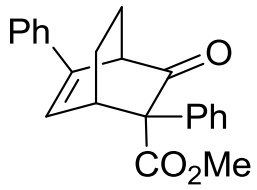
(±) (1*S*,4*R*)-Methyl 3-oxo-2,5-diphenylbicyclo[2.2.2]oct-5-ene-2-carboxylate (110).

The diastereomeric mixture of methyl 3-oxo-5-phenylbicyclo[2.2.2]oct-5-ene-2-carboxylates (**109**) (900 mg, 3.51 mmol, 1 equiv) and pentaphenylbismuth (3.133 g, 5.27 mmol, 1.5 equiv) were dissolved in benzene (70 mL) and the solution stirred at 23 °C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue purified via silica gel column chromatography using 4:1 pentane:diethyl ether as the eluent. The product was isolated as a white solid (1.0 g, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.50 (2H, d, *J* = 7.5 Hz)

7.33-7.21 (8H, m)



6.73 (1H, dd, *J* = 6.8, 1.3 Hz)

3.87 (1H, m)

3.83 (1H, ddd, *J* = 6.3, 3.0, 3.0 Hz)

3.72 (3H, s)

2.25-2.19 (1H, m)

2.00 (1H, dddd, *J* = 12.5, 9.5, 3.0, 3.0 Hz)

1.81 (1H, dddd, *J* = 12.8, 12.8, 3.5, 3.5 Hz)

1.69 (1H, dddd, *J* = 12.8, 12.8, 5.0, 3.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.8, 171.2, 138.4, 137.8, 136.8, 129.3, 128.6, 128.2, 127.9, 127.3, 127.2, 125.3, 62.3, 52.9, 51.3, 41.0, 22.3, 21.8.

(±) (1*R*,4*S*) 3,6-Diphenylbicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethanesulfonate (111).

The diastereomeric mixture of 3,6-Diphenylbicyclo[2.2.2]oct-5-en-2-**ones** (**106**) (307 mg, 1.12 mmol, 1 equiv) and trifluoromethanesulfonic anhydride (0.28 mL, 1.68 mmol, 1.5 equiv)

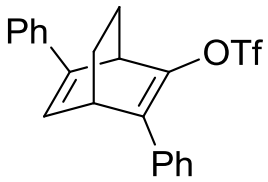
were dissolved in pyridine (0.14 mL, 1.79 mmol, 1.6 equiv) and the reaction mixture was stirred for 24 h. The reaction mixture was concentrated *in vacuo* and purified via flash column chromatography on silica gel using 6:1 pentane:diethyl ether as eluent. The product was isolated as a colorless oil (268 mg, 0.67 mmol, 61% yield, 68% yield brsm).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.54 (2H, bd, J = 6.8 Hz)

7.48-7.42 (6H, m)

7.39-7.32 (2H, m)



6.70 (1H, dd, J = 6.2, 2.2 Hz)

4.39 (1H, m)

4.17 (1H, ddd, J = 6.0, 2.6, 2.6 Hz)

2.13 (1H, dddd, J = 10.0, 10.0, 3.2, 3.2 Hz)

1.89-1.82 (1H, dddd, J = 11.2, 11.2, 4.0, 2.4 Hz)

1.75 (1H, dddd, J = 9.8, 9.2, 3.2, 3.2 Hz)

1.68 (1H, dddd, J = 9.4, 9.4, 2.6, 2.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.5, 146.3, 136.4, 134.5, 133.8, 128.8, 128.6, 128.5, 128.1, 127.7, 127.5, 125.1, 118.4 (q, J = 3188.8 Hz), 43.6, 43.5, 26.0, 25.6.

1-Phenyl-3-(1,4-dioxaspiro[4.5]decan-7-yl)propan-2-ol (112).

Under an argon atmosphere (dry box), samarium metal (5.43 g, 36.10 mmol, 2.5 equiv) was weighed out and covered with dry tetrahydrofuran (140 mL). Once removed from the dry box, 1,2-diiodoethane (5.09 g, 18.10 mmol, 1.25 equiv) was added to the flask and the reaction mixture was stirred at 23 °C for 30 min until the solution became dark blue indicating formation of samarium diiodide (SmI_2). 2-(1,4-Dioxaspiro[4.5]decan-7-yl)acetaldehyde (**103**) (2.66 g, 14.44 mmol, 1 equiv) and benzyl bromide (3.43 mL, 28.88 mmol, 2 equiv) were premixed in THF (10 mL) and added in one portion to the SmI_2 mixture. Within 2 min, the reaction mixture became a yellow-green color and slowly returned to a dark blue color. The reaction mixture was stirred at 23 °C for 30 min before being quenched by the addition of 1N HCl (50 mL). The aqueous and organic layers were separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with a saturated solution of $Na_2S_2O_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material could be used in the next step without purification or could be purified by flash column chromatography on silica gel using 2:1 hexanes:ethyl acetate as the eluent. The pure product was isolated as a colorless viscous oil (2.52 g, 9.14 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

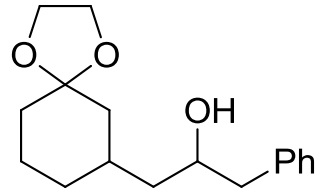
7.31 (2H, bdd, *J* = 7.6, 6.8 Hz)

7.25-7.19 (3H, m)

3.93 (5H, bs)

2.81 (1H, dd, *J* = 13.4, 4.2 Hz)

2.64 (1H, ddd, *J* = 13.4, 8.4, 4.0 Hz)



1.88-1.69 (5H, m)

1.56-1.36 (5H, m)

1.23 (0.5H, dd, *J* = 13.0, 13.0 Hz)

1.15 (0.5H, dd, *J* = 13.0, 13.0 Hz)

0.93 (0.5H, dddd, *J* = 12.4, 12.4, 12.4, 3.2 Hz)

0.84 (0.5H, dddd, *J* = 12.4, 12.4, 12.4, 3.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5, 129.44, 129.42, 128.6, 126.5, 109.19, 109.17, 70.1, 70.0, 64.32, 64.29, 64.2, 44.6, 44.5, 44.0, 42.2, 41.3, 34.9, 34.8, 32.5, 32.3, 31.4, 23.2, 23.1.

1-Phenyl-3-(1,4-dioxaspiro[4.5]decan-7-yl)propan-2-one (114).

In a 500 mL round-bottom flask, 1-phenyl-3-(1,4-dioxaspiro[4.5]decan-7-yl)propan-2-ol (**112**) (3.399 g, 12.30 mmol, 1 equiv) was dissolved in dichloromethane (125 mL). Sodium bicarbonate ($NaHCO_3$, 1.34 g, 15.99 mmol, 1.3 equiv) and Dess-Martin periodinane (6.78 g, 15.99 mmol, 1.3 equiv) were added and the reaction mixture was stirred at 23 °C for 10 min. The mixture was diluted with diethyl ether (75 mL) and a 1:1 mixture of a saturated solution of $Na_2S_2O_3$ and saturated solution of $NaHCO_3$ was added and the resultant reaction mixture stirred for 15 min. The aqueous and organic layers were separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using 2:1 hexanes:ethyl acetate as the eluent. The product was isolated as a colorless oil (3.14 mg, 12.08 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.31 (2H, bt, J = 6.8 Hz)

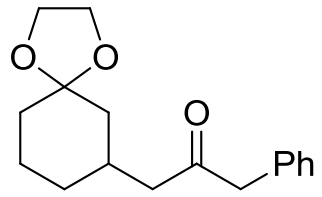
7.27-7.23 (1H, m)

7.18 (2H, bd, J = 6.8 Hz)

3.93-3.89 (4H, m)

3.66 (2H, bs)

2.38 (1H, dd, J = 16.4, 7.2 Hz)



2.34 (1H, dd, J = 16.4, 6.4 Hz)

2.22-2.09 (1H, m)

1.73-1.60 (4H, m)

1.59- 1.47 (1H, m)

1.39 (1H, ddd, J = 12.4, 12.4, 4.0 Hz)

1.13 (1H, dd, J = 12.4, 12.4 Hz)

0.84 (1H, dddd, J = 12.4, 12.4, 12.4, 3.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.4, 134.2, 129.4, 128.7, 127.0, 108.8, 64.3, 64.2, 50.5, 48.8, 41.0, 34.7, 31.52, 31.49, 22.9.

3-(2-Oxo-3-phenylpropyl)cyclohexanone (115).

1-Phenyl-3-(1,4-dioxaspiro[4.5]decan-7-yl)propan-2-one (**114**) (3.14 g, 11.43 mmol, 1 equiv) was dissolved in acetone (60 mL) and water (30 mL). Pyridinium *p*-toluenesulfonate (PPTS, 287 mg, 1.14 mmol, 0.1 equiv) was added and the reaction mixture was refluxed for 5 h. The reaction mixture was diluted with water (50 mL) and diethyl ether (50 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated

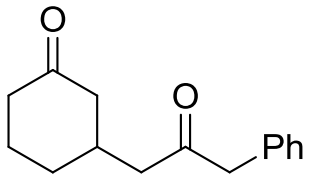
in vacuo. The product was isolated as a pale yellow oil (2.52 g, 96% yield) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.33 (2H, bdd, *J* = 6.8, 6.8 Hz)

7.29-7.25 (1H, tt, *J* = 7.4, 1.7 Hz)

7.18 (2H, bd, *J* = 6.8 Hz)



3.66 (2H, s)

2.46 (1H, dd, *J* = 16.8, 7.0 Hz)

2.42 (1H, dd, *J* = 16.8, 5.6 Hz)

2.38- 2.31 (3H, m)

2.23- 2.15 (1H, m)

1.99-1.91 (2H, m)

1.86-1.80 (1H, bd, *J* = 13.2 Hz)

1.71-1.60 (1H, m)

1.32-1.19 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.7, 206.4, 133.8, 129.4, 128.8, 127.2, 50.8, 47.7, 47.4, 41.2, 34.2, 30.8, 24.8.

(±) (1*R*,4*S*,*E*)-6-Phenylmethylidenebicyclo[2.2.2]octan-2-one (117)

(±) (1*R*,5*S*)-1-Benzyl-2-oxabicyclo[3.3.1]nonan-3-one (118).

A stock solution was created by dissolving 3-(2-oxo-3-phenylpropyl)cyclohexanone (**115**) (2.0 g, 8.68 mmol, 1 equiv) in dichloromethane (30 mL). The stock solution was divided into 10 equal portions. In a 10 mL microwave vial equipped with a stirbar was placed P_4O_{10} (493 mg, 1.74 mmol, 2 equiv) and 3 mL of the starting material stock solution. Trifluoromethanesulfonic acid (0.16 mL, 1.74 mmol, 2 equiv) was added to the stirred solution. The microwave vial was capped securely and stirred at 40 °C for 45 min under microwave conditions. The contents of the vial were filtered by gravity and the solid P_4O_{10} rinsed with dichloromethane. This process was repeated nine more times with the remaining starting material stock solution. All of the organic filtrates were combined and then quenched with the addition of triethylamine until the red solution turned yellow. The mixture was then concentrated *in vacuo* and the residue purified via flash column chromatography on silica gel using 1:1 pentane:diethyl ether as the eluent. The enone product was isolated as a pale yellow oil (295 mg, 1.39 mmol, 16.0% yield). An unintended lactone side product, (±) (1*R*,5*S*)-1-benzyl-2-oxabicyclo[3.3.1]nonan-3-one (**118**), was isolated as the major product (860 mg, 3.73 mmol, 43.0% yield). (±) (1*R*,5*S*)-1-benzyl-2-oxabicyclo[3.3.1]nonan-3-one (**118**) can be converted to (±) (1R,4S,E)-6-(phenylmethyl)idenebicyclo[2.2.2]octan-2-one (**117**) by refluxing in benzene with *p*-toluenesulfonic acid (2 equiv) and P_4O_{10} (2 equiv) for 12 h.

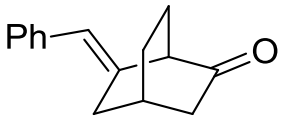
(±) (1*R*,4*S*,*E*)-6-Phenylmethylidenebicyclo[2.2.2]octan-2-one (117)

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.32-7.13 (5H, m)

6.33 (1H, dd, *J* = 2.8, 2.4 Hz)

3.00 (1H, dd, *J* = 2.8, 2.8 Hz)



2.76 (1H, dddd, *J* =17.6, 2.6, 2.6, 2.6 Hz)

2.66 (1H, dddd, *J* = 17.6, 2.6, 2.6, 2.6 Hz)

2.41 (1H, app heptet, *J* = 2.8 Hz)

2.32 (1H, ddd, *J* = 18.8, 2.8, 2.4 Hz)

2.28 (1H, ddd, *J* = 18.8, 2.8, 2.4 Hz)

2.05-1.97 (2H, m)

1.81-1.64 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.6, 137.3, 136.7, 128.6, 128.3, 126.6, 126.1, 55.9, 44.0, 34.5, 28.4, 24.7, 24.2.

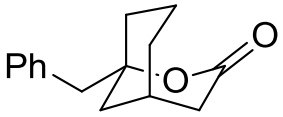
(±) (1*R*,5*S*)-1-Benzyl-2-oxabicyclo[3.3.1]nonan-3-one (118)

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.28-7.19 (5H, m)

2.96 (1H, d, *J* = 14.0 Hz)

2.70 (1H, d, *J* = 14.0 Hz)



2.52 (1H, dd, *J* = 18.8, 6.8 Hz)

2.34 (1H, d, *J* = 18.8 Hz)

2.23 (1H, m)

1.88 (1H, bd, *J* = 12.0 Hz)

1.66-1.54 (4H, m)

1.51- 1.41 (3H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 135.6, 130.7, 128.1, 126.7, 82.7, 48.0, 36.0, 35.2, 33.9, 30.6, 26.4, 17.4.

(±) (1*R*,4*S*,*E*)-3-(phenylmethyl)-6-phenylmethylidinebicyclo[2.2.2]octan-2-one (119).

In a flame-dried round-bottom flask, diisopropylamine (0.59 mL, 4.19 mmol, 1.2 equiv) was dissolved in dry tetrahydrofuran (9 mL) and the flask was cooled to -78 °C. *n*Butyllithium

(1.67 mL, 4.19 mmol, 2.5M in hexanes, 1.2 equiv) was added slowly to the reaction mixture and it was then stirred at 0 °C for 10 min. The solution became pale yellow and was cooled to -78 °C and stirred for a further 30 min. (±) (1*R*,*4S*,*E*)-6-phenylmethylidenebicyclo[2.2.2]octan-2-one (**117**) solution (741 mg, 3.49 mmol, 1 equiv) in 1 mL THF was added dropwise at -78 °C and the reaction mixture was stirred for 1 h. Benzyl bromide (0.83 mL, 6.98 mmol, 2 equiv) in 2 mL THF was added dropwise at -78 °C and the reaction mixture was allowed to warm slowly to 23 °C and was stirred for 15 h. Water was added to quench the reaction and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the organic layers were dried over anhydrous $MgSO_4$. The crude residue was purified via flash column chromatography on silica gel using 10:1 pentane:diethyl ether as the eluent. Two diastereomeric products were separated and isolated as a pale yellow oil and a yellow solid (306 mg, 29% combined yield, 37% yield brsm). The starting material was also isolated (163 mg, 22% recovered) and could be recycled.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

Major Isomer:

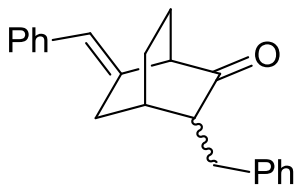
7.40-7.18 (10H, m)

6.34 (1H, dd, J = 2.4, 2.4 Hz)

3.38 (1H, dd, J = 14.0, 3.6 Hz)

3.04 (1H, m)

2.64-2.24 (2H, m)



2.19-1.97 (4H, m)

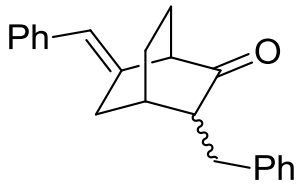
1.83-1.59 (3H, m).

Minor Isomer:

7.40-7.07 (10H, m)

6.39 (1H, dd, J = 2.4, 2.4 Hz)

3.25 (1H, dd, J = 13.6, 3.4 Hz)



3.04 (1H, m)

2.96-2.83 (1H, m)

2.70-2.40 (3H, m)

2.12-2.00 (2H, m)

1.84-1.20 (3H, m).

^{13}C NMR (100 MHz, $CDCl_3$) of a 1:1 mixture δ: 213.6, 139.8, 137.2, 136.6, 128.7, 128.5, 128.4, 128.2, 126.5, 126.2, 125.9, 55.8, 54.1, 35.8, 33.6, 30.0, 24.9, 19.9.

(±)(1*R*,4*S*,*E*)-3-(phenylmethyl)-6-phenylmethylidenebicyclo[2.2.2]oct-2-en-2-yl trifluoromethanesulfonate (120).

The diastereomeric mixture of (1*R*,4*S*,*E*)-3-(phenylmethyl)-6-phenylmethylidenebicyclo[2.2.2]octan-2-ones (**119**) (71 mg, 0.24 mmol, 1 equiv) and pyridine (0.03 mL, 0.38 mmol, 1.6 equiv) were dissolved in dichloromethane (1 mL) in a 10 mL round-bottom flask. Trifluoromethanesulfonic anhydride (0.06 mL, 0.35 mmol, 1.5 equiv) was added and the reaction mixture was stirred at 23 °C for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was purified via flash column chromatography on silica gel using 6:1 pentane:diethyl ether as eluent. The product was isolated as a white solid (61 mg, 0.14 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.39-7.21 (10H, m)

6.38 (1H, m)

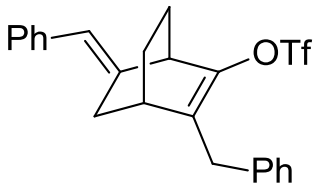
3.67 (1H, d, *J* = 15.0 Hz)

3.63 (1H, d, *J* = 15.0 Hz)

3.44 (1H, dd, *J* = 2.8, 2.4 Hz)

2.81 (1H, dd, *J* = 2.8, 2.4 Hz)

2.46 (1H, ddd, *J* = 16.8, 2.4, 2.4 Hz)



2.25 (1H, dddd, J = 17.2, 2.8, 2.8, 2.8 Hz)

1.99-1.91 (1H, m)

1.89-1.80 (1H, m)

1.59-1.50 (1H, m)

1.40-1.32 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.8, 141.0, 137.8, 137.2, 132.8, 129.1, 128.7, 128.4, 128.3, 126.8, 126.4, 122.2, 118.7 (q, J = 319.0 Hz), 46.9, 36.5, 34.6, 34.1, 28.2, 25.3.

(±) (1*S*,4*S*,*E*)-2-(Phenylmethyl)-5-phenylmethylidenebicyclo[2.2.2]oct-2-ene (121).

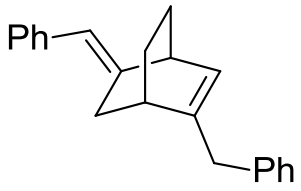
The racemic mixture of (1*R*,4*S*,*E*)-3-(phenylmethyl)-6-phenylmethylidenebicyclo[2.2.2]oct-2-en-2-yl trifluoromethanesulfonates (**120**) was dissolved in *N*, *N*-dimethylformamide (DMF, 1.4 mL) in a 10 mL round-bottom flask. Palladium (II) acetate (4 mg, 0.06 mmol, 0.04 equiv), PPh_3 (3 mg, 0.01 mmol, 0.08 equiv), triethylamine (0.12 mL, 0.84 mmol, 6 equiv), and formic acid (0.02 mL, 0.56 mmol, 4 equiv) were added to the reaction flask and the reaction mixture was stirred at 23 °C for 20 h. Water (5 mL) was added to the reaction mixture and this mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using pentane as the eluent. The product was isolated as a white solid (25 mg, 0.09 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.33-7.15 (10H, m)

6.25 (1H, bdd, *J* = 2.8, 2.4 Hz)

6.02 (1H, bd, *J* = 6.4, Hz)



3.48 (2H, bs)

3.16 (1H, ddd, *J* = 6.4, 3.2, 2.8 Hz)

2.66 (1H, m)

2.47 (1H, ddd, *J* = 16.8, 2.4, 2.4 Hz)

2.27 (1H, dddd, *J* = 16.8, 2.8, 2.8, 2.8 Hz)

1.77-1.70 (1H, m)

1.57- 1.46 (2H, m)

1.32-1.22 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ:145.6, 145.5, 139.3, 138.7, 129.1, 128.3, 128.2, 128.1, 126.6, 126.1, 125.6, 119.8, 43.7, 41.2, 35.7, 35.5, 27.6, 25.3.

Bicyclo[2.2.2]octane-2,6-dione (122).

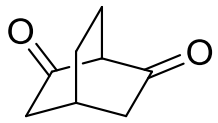
The racemic mixture of (1*R*,4*S*,*E*)-6-benzylidenebicyclo[2.2.2]octan-2-one (**117**) (20 mg, 0.09 mmol, 1 equiv) was dissolved in dichloromethane (1 mL) and the flask was cooled to -78 °C. Ozone was bubbled through the solution until the solution turned blue, then oxygen was bubbled through the solution until the blue color dissipated. Triphenylphosphine (25 mg, 0.09 mmol, 1 equiv) was added to the stirred solution at -78 °C under an argon atmosphere. The solution was allowed to warm to 23 °C over 16 h. Water was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel with 2:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless oil (5 mg, 0.04 mmol, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

3.19 (1H, dd, *J* = 2.7, 2.7 Hz)

2.66 (1H, app heptet, *J* = 3.0 Hz)

2.53 (2H, ddd, *J* = 21.0, 3.0, 1.9 Hz)



2.49 (2H, bd, *J* = 21.0 Hz)

2.39 (1H, m)

2.36 (1H, m)

2.12 (2H, m)

1.89-1.85 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.9, 63.8, 44.0, 28.0, 23.7, 22.2.

Trimethyl(prop-2-yn-1-yl)silane (129).

A 1 L 3-necked, round-bottom flask equipped with a stirbar, condenser, and addition funnel was flame dried under vacuum and then charged with magnesium turnings (13 g, 538.00 mmol, 2 equiv) and dry diethyl ether (100 mL). Mercury (II) chloride (1.46 g, 5.38 mmol, 0.02 equiv) and propargyl bromide (1 mL) were added and the mixture was stirred until the reaction initiated as evidenced by the formation of a gray cloudy solution (usually 10-15 min). The remaining propargyl bromide (total amount: 32 g, 80 wt% in toluene, 269.00 mmol, 1 equiv) was dissolved in diethyl ether (270 mL) and the solution was added dropwise (2-4 drops/sec) via the addition funnel to the initiated Grignard solution. After complete addition of the propargyl bromide, the reaction was stirred for 30 min at 23 °C. The suspension was then allowed to settle and the supernatant solution was transferred via cannula to a 1 L flame-dried round-bottom flask. The flask was cooled to 0 °C, the solution was stirred vigorously, and then chlorotrimethylsilane (TMSCl, 34 mL, 269.00 mmol, 1 equiv) was added slowly over 20 min using a syringe pump. The reaction mixture was stirred at 0 °C for a further 45 min, then allowed to warm to 23 °C, and was stirred for 1 h. The supernatant solution was transferred to a 500 mL round-bottom flask via cannula and placed in the freezer overnight. The colorless solution was transferred to a new flask and the diethyl ether removed via distillation (36 °C, 1 atm) with a Vigereux column. The remaining solution was comprised of 37.88% product (11.96 g, 106.56 mmol, 79% yield) in

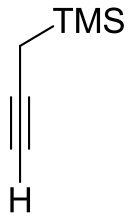
toluene and residual diethyl ether. The solution of trimethyl(prop-2-yn-1-yl)silane (**129**) was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

1.80 (1H, t, J = 3.0 Hz)

1.45 (2H, d, J = 3.2 Hz)

0.10 (9H, s).



^{13}C NMR (100 MHz, $CDCl_3$) δ: 82.5, 66.7, 6.7, -2.3.

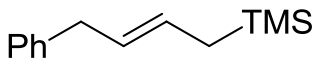
(*E*)-Trimethyl(4-phenylbut-2-en-1-yl)silane (130).

The solution of trimethyl(prop-2-yn-1-yl)silane (**129**) (10 g, 89.09 mmol, 1 equiv) in toluene and diethyl ether was placed in a 500 mL round-bottom flask equipped with a reflux condenser. Diisobutylaluminum hydride (DIBAL, 89 mL, 89.09 mmol, 1.0 M solution in hexanes) was added to the starting material solution and the reaction mixture was heated to 50 °C for 3.5 h. The flask was then cooled to 23 °C and the solvent removed *in vacuo*. The reaction flask was wrapped in aluminum foil and the residue dissolved in dry tetrahydrofuran (35 mL). The flask was cooled to -50 °C and a solution of iodine (22.6 g, 10 mL THF) was added slowly to the reaction mixture. Once addition was complete, the reaction was allowed to warm to 23 °C, diethyl ether (75 mL) was added and water was added very slowly to quench the reaction

mixture. Once the reaction was quenched, saturated $Na_2S_2O_3$ (50 mL) solution was added and the mixture was extracted with dichloromethane (3 x 50 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* in a flask wrapped with aluminum foil. The residue (11.56 g, 48.13 mmol, estimated) was immediately dissolved in diethyl ether (160 mL) and bis(triphenylphosphine)nickel dichloride (787 mg, 1.20 mmol, 2.5 mol %) was added and the reaction mixture was cooled to -35 °C. A solution of benzylmagnesium chloride (53 mL, 52.94 mmol, 1.1 equiv) in diethyl ether (1.0 M) was added slowely over 30 min. The reaction mixture was stirred in the dark (wrapped in aluminum foil) at -35 °C for 3.5 h and then at -10 °C for a further 12 h. The reaction was quenched by the addition of saturated NH_4Cl solution (50 mL). The organic layer was washed with NH_4Cl and the combined aqueous layers were extracted with pentane (3 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 x 100 mL) and brine (1 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified on plug of alumina, washed with hexanes, and concentrated *in vacuo*. The final product was isolated as a solution in toluene (50%, 1.16 g, 5.68 mmol, 6.4% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.34-7.2 (5H, m)



5.57-5.38 (2H, m)

3.34 (2H, d, *J* = 6.4 Hz)

1.47 (2H, d, *J* = 7.6 Hz)

0.01 (9H, s).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 128.4, 128.3, 127.9, 127.3, 125.8, 39.3, 22.7, -1.9.

(*S*)-3-((*R*)-1-Phenylbut-3-en-2-yl)cyclohexanone (131).

Cyclohexenone (589 mg, 6.13 mmol, 1 equiv) was dissolved in dichloromethane (DCM, 25 mL) and the reaction flask was cooled to -78 °C. Titanium (IV) chloride (7.36 mL, 7.36 mmol, 1.2 equiv, 1 M in DCM) was added slowly over 10 min and the reaction mixture was stirred for 30 min at -78 °C. A solution of (*E*)-trimethyl(4-phenylbut-2-en-1-yl)silane (**130**) (1.38 g, 6.74 mmol, 1.1 equiv) in DCM (5 mL) was added dropwise to the reaction solution over 40 min. The reaction mixture was allowed to stir for 1 h until TLC analysis showed complete disappearance of cyclohexenone. The cooling bath was removed and water was added to quench the reaction, and the flask was allowed to warm to 23 °C. The aqueous and organic layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 4:1 hexanes:ethyl acetate as the eluent. The product, 3-(1-phenylbut-3-en-2-yl)cyclohexanone (**131**), was isolated as a colorless oil (868 mg, 3.80 mmol, 62% yield, 3:1 dr).

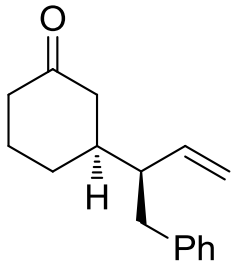
^{1}H NMR (400 MHz, $CDCl_3$) δ:

Major Isomer:

7.26 (2H, t, *J* = 7.6 Hz)

7.17 (1H, t, *J* = 7.2 Hz)

7.11 (2H, d, *J* = 6.8 Hz)



5.64 (1H, ddd, *J* = 17.2, 10.0, 10.0 Hz)

5.04 (1H, dd, *J* = 10.2, 1.8 Hz)

4.87 (1H, dd, *J* = 17.2, 1.2 Hz)

2.80 (1H, dd, *J* = 13.6, 6.0 Hz)

2.64 (1H, dd, *J* = 13.6, 8.4 Hz)

2.38-2.30 (2H, m)

2.28-2.18 (3H, m)

2.13-2.04 (1H, m)

1.98 (1H, dm, *J* = 13.2 Hz)

1.83 (1H, m)

1.67-1.50 (1H, m)

1.37 (1H, dddd, *J* = 12.4, 12.4, 12.4, 3.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.0, 140.1, 138.4, 129.14, 129.09, 128.2, 126.0, 50.9, 46.9, 41.8, 41.5, 38.7, 26.8, 25.3.

(*S*)-2-((*S*)-3-Oxocyclohexyl)-3-phenylpropanal (132).

(*S*)-3-((*R*)-1-Phenylbut-3-en-2-yl)cyclohexanone (**131**) (824 mg, 3.61 mmol, 1 equiv) was dissolved in dichloromethane (DCM, 36 mL) in a 100 mL 3-necked round-bottom flask. The flask was cooled to -78 °C and ozone (O_3) was bubbled through the solution until it turned blue. Oxygen was then bubbled through the solution until the blue color dissipated. Triphenylphosphine (PPh_3, 947 mg, 3.61 mmol, 1 equiv) was added to the stirred solution to quench the ozonide. An argon atmosphere was introduced and the reaction flask was allowed to warm to 23 °C slowly over 12 h. Water (30 mL) was added to the reaction, the aqueous and organic layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combine organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 2:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless oil (404 mg, 1.75 mmol, 48% yield, 3:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

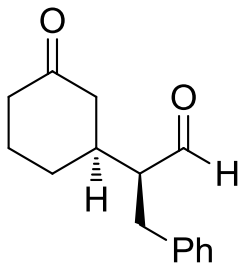
Major Isomer:

9.68 (1H, d, J = 2.5 Hz)

7.28 (2H, t, J = 7.5 Hz)

7.20 (1H, t, *J* = 7.5 Hz)

7.14 (2H, d, *J* = 7.5 Hz)



3.01 (1H, dd, *J* = 14.0, 9.0 Hz)

2.85 (1H, dd, *J* = 14.5, 5.5 Hz)

2.62 (1H, dddd, *J* = 9.0, 9.0, 5.5, 2.5 Hz)

2.47-2.38 (2H, m)

2.30 (1H, dd, *J* = 13.0, 13.0 Hz)

2.21-2.08 (2H, m)

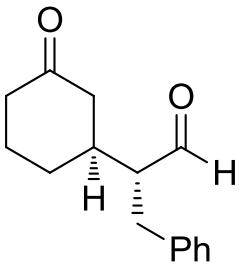
1.94-1.90 (1H, m)

1.67-1.59 (2H, m)

1.54 (1H, dddd, *J* = 12.5, 12.5, 12.5, 3.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1, 203.6, 138.4, 128.84, 128.76, 126.7, 57.8, 45.4, 41.3, 38.7, 32.5, 28.5, 25.2.

Minor Isomer (selected peaks):



9.71 (1H, d, *J* = 2.0 Hz)

3.03 (1H, dd, *J* = 14.0, 9.0 Hz)

2.80 (1H, dd, *J* = 14.0, 5.5 Hz)

2.69-2.65 (1H, m).

4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-3(2H)-one (133)

7a-Benzylhexahydrobenzofuran-2(3H)-one (134).

(*S*)-2-((*S*)-3-Oxocyclohexyl)-3-phenylpropanal (**132**) (85 mg, 0.37 mmol, 1 equiv) and phosphorus pentoxide (210 mg, 0.74 mmol, 2 equiv) were dissolved in dichloromethane (3.5 mL) in a 10 mL microwave vial equipped with a stirbar. Trifluoromethanesulfonic acid (0.07 mL, 0.74, 2 equiv) was added and the reaction mixture was heated to 40 °C in the microwave for 45 min. The reaction mixture was filtered and washed with dichloromethane. The red filtrate solution was quenched with triethylamine until it turned yellow. The mixture was concentrated *in vacuo* and immediately purified via flash column chromatography on silica gel using 1:1 pentane:diethyl ether as the eluent. Two products were isolated, 4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-3(2H)-one (**133**) (13 mg, 0.06 mmol, 17% yield) and 7a-Benzylhexahydrobenzofuran-2(3H)-one (**134**) (11 mg, 0.05 mmol, 2% yield).

4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-3(2H)-one (133)

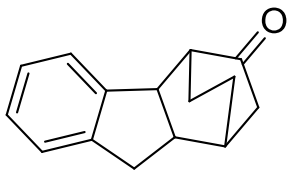
^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.21-7.13 (3H, m)

7.04 (1H, d, *J* = 7.5 Hz)

3.21 (1H, dd, *J* = 18.5, 8.0 Hz)

3.07 (1H, bs)



2.99 (1H, d, *J* = 18.5 Hz)

2.57-2.52 (2H, m)

2.41 (1H, dd, *J* = 18.0, 6.5 Hz)

2.45-2.37 (1H, m)

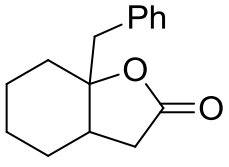
2.24 (1H, d, *J* = 18.0 Hz)

2.00 (1H, dddd, *J* = 13.5, 13.5, 5.5, 5.5 Hz)

1.64 (1H, ddd, *J* = 13.5, 13.5, 5.5 Hz)

1.43-1.36 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 220.8, 139.5, 135.2, 128.4, 128.1, 126.5, 126.1, 48.2, 44.5, 37.8, 37.6, 36.1, 28.7, 27.8, 22.0.



7a-Benzylhexahydrobenzofuran-2(3H)-one (134)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.5, 135.8, 130.5, 128.41, 128.38, 43.2, 37.6, 34.4, 32.8, 25.7, 21.9, 20.4.

5-(Phenylmethyl)-6-hydroxybicyclo[2.2.2]octan-2-one (135).

(*S*)-2-((*S*)-3-Oxocyclohexyl)-3-phenylpropanal (**132**) (100mg, 0.43 mmol, 1 equiv) was dissolved in dichloromethane (4 mL) in a 25-mL round-bottom flask. Hydrochloric acid (HCl, 4M in dioxane, 0.13 mL, 0.52 mmol, 1.2 equiv) was added to the flask and the reaction mixture was stirred for 15 min at 23 °C. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material could be used in the following step without further purification or can be purified via flash column chromatography on silica gel (1:1 pentane:diethyl ether). 5-(Phenylmethyl)-6-hydroxybicyclo[2.2.2]octan-2-one (**135**) was isolated as a white solid (85 mg, 0.37 mmol, 85% yield). We have tentatively assigned this last major diastereomer as one of the *trans* isomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.31 (2H, t, *J* = 7.5 Hz)

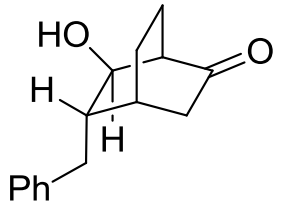
7.24-7.21 (3H, m)

3.79 (1H, bs)

2.94 (1H, dd, *J* = 13.7, 7.2 Hz)

2.69 (1H, dd, *J* = 13.7, 9.2 Hz)

2.42 (1H, ddd, *J* = 3.0, 3.0, 3.0 Hz)



2.17-2.27 (2H, m)

1.99 (2H, m)

1.95-1.73 (4H, m)

1.49-1.41 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.3, 139.9, 128.9, 128.6, 126.4, 75.3, 51.2, 48.9, 45.5, 39.3, 30.6, 20.1, 18.4.

Selected peaks from other isomers:

^{1}H NMR (500 MHz, $CDCl_3$) δ:

4.26 (1H, m) (major)

4.21 (1H, m) (minor)

2.77 (1H, dd, *J*= 13.5, 8.0 Hz).

(±)-(1*R*,2*R*,3*S*,4*R*)-3-(Phenylmethyl)-6-oxobicyclo[2.2.2]octan-2-yl methanesulfonate (136).

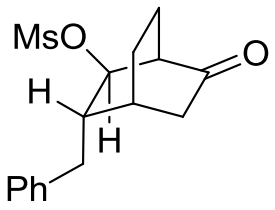
5-(Phenylmethyl)-6-hydroxybicyclo[2.2.2]octan-2-one (**135**) (566 mg, 2.46 mmol, 1 equiv) was dissolved in dichloromethane (12 mL) in a 50 mL round-bottom flask. Pyridine (0.40 mL, 4.92 mmol, 2 equiv), 4-(dimethylamino)pyridine (DMAP, 60 mg, 0.49 mmol, 0.2 equiv), and methanesulfonyl chloride (0.57 mL, 7.37 mmol, 3 equiv) were added and the reaction

mixture was stirred for 12 h at 23 °C. The reaction mixture was poured into brine (25 mL) and was extracted with diethyl ether (3 x 25 mL). The ether layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate as the eluent. Two spots were isolated from the column. The higher R_f spot (0.62) contained a mixture of 3 diastereomers as a yellow oil (135 mg, 0.44 mmol, 18% yield) and the lower R_f spot (0.48) was isolated as a single diastereomer as a yellow solid (326 mg, 1.06 mmol, 43% yield). We have tentatively assigned this last major diastereomer as one of the *trans* isomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.34-7.29 (2H, m)

7.25-7.20 (3H, m)



4.72 (1H, dd, *J* = 3.5, 3.5 Hz)

3.07 (1H, dd, *J* = 13.5, 7.0 Hz)

2.77 (3H, s)

2.74 (1H, m)

2.71 (1H, dd, *J* = 13.5, 10.0 Hz)

2.31 (1H, dd, *J* = 19.0, 3.5 Hz)

2.26-2.22 (2H, m)

2.07 (1H, m)

1.97-1.82 (3H, m)

1.53-1.46 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.5, 138.8, 129.0, 128.8, 126.7, 83.3, 48.5, 46.5, 45.4, 38.8, 38.5, 30.5, 20.0, 18.3.

Selected peaks from other isomers:

^{1}H NMR (500 MHz, $CDCl_3$) δ:

4.59 (1H, dd, *J* = 3.5, 3.5 Hz)

2.56 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9, 210.7, 206.5, 138.5, 133.8, 129.4, 129.2, 128.9, 128.8, 127.2, 126.8, 81.3, 50.8, 49.7, 47.7, 47.4, 45.8, 41.2, 38.9, 38.4, 37.9, 34.2, 30.8, 30.6, 25.3, 24.8, 16.0.

(±)-(1*R*,4*R*)-5-(Phenylmethyl)bicyclo[2.2.2]oct-5-en-2-one (137).

The diastereomeric mixture of (1*R*,2*R*,3*S*,4*R*)-3-(phenylmethyl)-6-oxobicyclo[2.2.2]octan-2-yl methanesulfonate (**136**) (292 mg, 0.95 mmol, 1 equiv) was dissolved in *N*, *N*-dimethylformamide (12 mL). LiBr (329 mg, 3.79 mmol, 4 equiv) and lithium

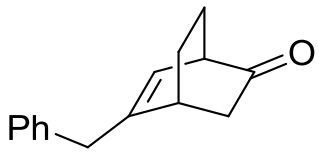
carbonate (420 mg, 5.68 mmol, 6 equiv) were added and the reaction mixture was stirred at heated to 150 °C. After 1 h the reaction mixture was cooled to 23 °C and poured into water (50 mL). The quenched reaction mixture was extracted with diethyl ether (3 x 50 mL). The combined ether layers were washed with 0.5 N HCl (5 x 40 mL) and brine (50 mL), then dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 1:1 pentane:diethyl ether as the eluent. (±)-(1*R*,4*R*)-5-(phenylmethyl)bicyclo[2.2.2]oct-5-en-2-one (**137**) was isolated as a white solid (106 mg, 0.50 mmol, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.29 (2H, t, *J* = 7.5 Hz)

7.22 (1H, t, *J* = 7.5 Hz)

7.15 (2H, d, *J* = 7.0 Hz)



5.83 (1H, dd, *J* = 6.5, 1.0 Hz)

3.48 (1H, d, *J* = 15.5 Hz)

3.45 (1H, dd, *J* = 15.0, 1.0 Hz)

3.09 (1H, ddd, *J* = 6.5, 2.7, 2.7 Hz)

2.73 (1H, dddd, *J* = 2.7, 2.7, 2.7, 2.7 Hz)

1.94 (1H, dd, *J* = 18.5, 2.5 Hz)

1.86 (1H, ddd, J = 18.5, 3.0, 3.0 Hz)

1.85-1.81 (1H, m)

1.65-1.58 (2H, m)

1.41-1.34 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.5, 149.1, 138.1, 129.0, 128.5, 126.4, 121.6, 48.8, 41.1, 40.6, 36.2, 24.4, 23.4.

(±)-(1*R*,4*R*)-5-(Phenylmethyl)bicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethanesulfonate (139).

Diisopropylamine (0.10 mL, 0.75 mmol, 1.5 equiv) was dissolved in dry tetrahydrofuran (1.2 mL) in a 25 mL round-bottom flask and the reaction was cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 0.30 mL, 0.76 mmol, 1.52 equiv) was added dropwise to the cooled reaction flask. After warming the reaction flask to 0 °C for 10 min, the flask was cooled to -78 °C and stirred for 30 min. The racemic mixture of (1*R*,4*R*)-5-(phenylmethyl)bicyclo[2.2.2]oct-5-en-2-one (**137**) (106 mg, 0.50 mmol, 1 equiv) in tetrahydrofuran (1 mL) was added to the lithium diisopropylamine (LDA) solution and the mixture was stirred at -78 °C for 1 h. Phenyl triflimide (802 mg, 2.25 mmol, 4.5 equiv) was added in one portion to the reaction flask and the mixture was allowed to warm slowly to 23 °C over 8 h. The reaction mixture was quenched by adding water (5 mL). The mixture was extracted with dichloromethane (3 x 5 mL) and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude

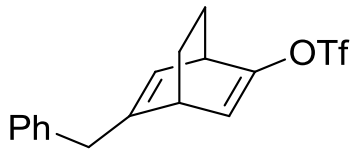
residue was purified via flash column chromatography on silica gel with 100% pentane as the eluent. The product was isolated as a colorless oil (47 mg, 0.14 mmol, 27% yield, 35% brsm).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.28 (2H, t, *J* = 7.2 Hz)

7.21 (1H, t, *J* = 7.5 Hz)

7.10 (2H, d, *J* = 7.0 Hz)



5.97 (1H, dd, *J* = 7.0, 2.5 Hz)

5.96 (1H, dd, *J* = 6.0, 1.5 Hz)

3.54 (1H, dddd, *J* = 6.0, 2.7, 2.7, 2.7 Hz)

3.45 (1H, bd, *J* = 15.5 Hz)

3.43 (1H, bd, *J* = 15.5 Hz)

3.39 (1H, dddd, *J* = 7.0, 2.5, 2.5, 2.5 Hz)

1.72-1.67 (1H, m)

1.46-1.41 (1H, m)

1.39-1.34 (1H, m)

1.27 (1H, dddd, *J* = 12.0, 9.5, 4.0, 3.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.2, 147.3, 138.5, 128.9, 128.4, 127.0, 126.3, 120.4, 118.6 (q, J = 319 Hz), 40.6, 40.3, 39.5, 26.3, 24.4.

(±) (1*R*,4*S*)-3,6-Dimethylbicyclo[2.2.2]oct-5-en-2-one (141).

In a 25 mL flame-dried round-bottom flask, diisopropylamine (0.38 mL, 2.66 mmol, 1.2 equiv) was dissolved in dry tetrahydrofuran (THF, 4 mL) and the solution was cooled to -78 °C. *n*-Butyllithium (1.06 mL, 2.66 mmol, 1.2 equiv) was added dropwise and the solution was warmed to 0 °C and stirred for 10 min. The pale yellow solution was then cooled to -78 °C and (±) (1*R*,4*R*)-6-methylbicyclo[2.2.2]oct-5-en-2-one (**90**) (302 mg, 2.22 mmol, 1 equiv) in THF (1 mL) was added dropwise. After the reaction mixture had stirred for 1 h, hexamethylphosphoramide (HMPA, 0.77 mL, 4.44 mmol, 2 equiv) and methyl iodide (0.28 mL, 4.44 mmol, 2 equiv) were added and the reaction mixture was allowed to warm slowly to 23 °C and was stirred for 12 h. Water was added to quench the reaction and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel using 10:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless oil (150 mg, 1.00 mmol, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ:

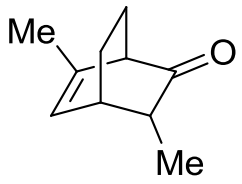
6.0 (1H, bd, J = 6.4 Hz)

2.91 (1H, m)

2.66-2.64 (1H, m)

1.95 (1H, dq, J = 7.2, 1.6 Hz)

1.84-1.78 (1H, m)



1.80 (3H, s)

1.75-1.64 (1H, m)

1.60-1.45 (2H, m)

1.03 (3H, d, J = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.0, 136.1, 128.2, 53.8, 44.8, 38.8, 25.7, 21.5, 19.8, 17.4.

But-2-yn-1-yltrimethylsilane (144).

The solution of trimethyl(prop-2-yn-1-yl)silane (**129**) (4.47 g, 39.82 mmol) in toluene and diethyl ether was mixed with dry tetrahydrofuran (55 mL) in a 250 mL round-bottom flask and the mixture was cooled to -78 °C under an argon atmosphere. Methyllithium (32.4 mL, 51.77 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred for 3 h at -78 °C. Methyl iodide (5 mL, 79.64 mmol, 2 equiv) was added slowly to the reaction mixture and the reaction was allowed to warm slowly to 23 °C and then stirred at 23 °C for 5 h. Water was added to quench the reaction and the solution was extracted with pentane (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. The pentane solvent

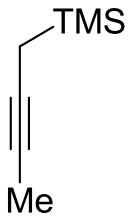
was removed via distillation (with a Vigereux column). The remaining solution was comprised of 25.91% but-2-yn-1-yltrimethylsilane (**144**) (3.56 g, 28.19 mmol, 71% yield) in a solution of toluene and THF. The product solution was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

1.77 (3H, t, *J* = 2.8 Hz)

1.39 (2H, q, *J* = 2.8 Hz)

0.09 (9H, s).



^{13}C NMR (100 MHz, $CDCl_3$) δ: 76.3, 73.8, 21.4, 6.9, -2.2.

(*Z*)-But-2-en-1-yltrimethylsilane (145).

In a 500 mL round-bottom flask, $NaBH_4$ (1.33 g, 35.24 mmol, 1.25 equiv) was dissolved in 35 mL of ethanol (95%). Ethylene diamine (6.36 mL, 95.16 mmol, 3.38 equiv) and $Ni(OAc)_2$ (tetrahydrate) (8.77 g, 35.24 mmol, 1.25 equiv) were added to the solution and the reaction mixture was covered with a H_2 atmosphere. Ethanol (250 mL) was added to dilute the reaction mixture and a solution of but-2-yn-1-yltrimethylsilane (**144**) (3.56 g, 28.19 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred under an H_2 atmosphere for 6 h until the reaction was shown to be complete by TLC (100% pentane, R_f = 0.95). The reaction mixture was filtered through a pad of Celite and washed with pentane. The filtrate was washed with water (3

x 150 mL) and dried over anhydrous Na_2SO_4. The pentane solvent was removed via distillation (with a Vigereux column). The remaining solution comprised of 59.88% (*Z*)-but-2-en-1-yltrimethylsilane (**145**) (2.36 g, 18.42 mmol, 65% yield), (*E*)-but-2-en-1-yltrimethylsilane (685 mg, 5.34 mmol, 19% yield), and toluene. The product solution was used without further purification.

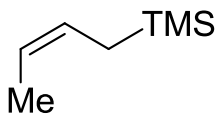
^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.50-5.34 (2H, m)

1.57 (3H, d, J = 6.4 Hz)

1.49 (2H, d, J = 8.0 Hz)

0.03 (9H, s).



^{13}C NMR (100 MHz, $CDCl_3$) δ: 126.5, 121.2, 18.0, 12.6, -1.8.

(*S*)-3-((*S*)-But-3-en-2-yl)cyclohexanone (146).

2-Cyclohexen-1-one (1.47 g, 15.33 mmol, 1 equiv) was dissolved in dichloromethane (DCM, 65 mL) and the reaction flask was cooled to -78 °C. Titanium (IV) chloride (30.66 mL, 30.66 mmol, 1.2 equiv, 1 M in DCM) was added slowly over 10 min and the reaction mixture was stirred for 30 min at -78 °C. A solution of (*Z*)-but-2-en-1-yltrimethylsilane (**145**) in DCM

(10 mL) was added dropwise to the reaction solution over 40 min. The reaction mixture was allowed to stir for 1 h until TLC analysis showed complete disappearance of 2-cyclohexen-1-one. The cooling bath was removed and water was added to quench the reaction, and the flask was allowed to warm to 23 °C. The aqueous and organic layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 4:1 hexanes:ethyl acetate as the eluent. The product, 3-(but-3-en-2-yl)cyclohexanone (**146**), was isolated as a colorless oil (1.86 g, 12.22 mmol, 80% yield, 3:1 dr).

^1H NMR (400 MHz, $CDCl_3$) δ:

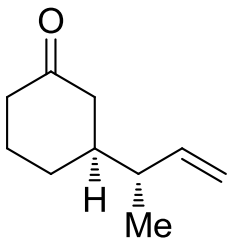
Major Isomer:

5.65 (1H, ddd, J = 17.2, 10.4, 8.0 Hz)

5.03-4.95 (2H, m)

2.40-2.31 (1H, m)

2.23 (1H, ddd, J = 13.2, 13.2, 6.2 Hz)



2.14- 2.00 (3H, m)

1.85 (1H, m)

1.71-1.62 (1H, m)

1.59 (1H, ddddd, J = 13.2, 13.2, 13.2, 4.0, 4.0 Hz)

1.37 (1H, dddd, J = 12.4,12.4, 12.4, 3.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 141.4, 114.7, 45.4, 43.9, 42.7, 41.2, 28.7, 25.3, 17.0.

(*R*)-2-((*S*)-3-Oxocyclohexyl)propanal (147).

(*S*)-3-((*S*)-But-3-en-2-yl)cyclohexanone (**146**) (1.79 g, 11.79 mmol, 1 equiv) was dissolved in dichloromethane (DCM, 120 mL) in a 250 mL 3-necked round-bottom flask. The flask was cooled to -78 °C and ozone (O_3) was bubbled through the solution until it turned blue. Oxygen was then bubbled through the solution until the blue color dissipated. Triphenylphosphine (PPh_3, 3.09 g, 11.79 mmol, 1 equiv) was added to the stirred solution to quench the ozonide. An argon atmosphere was introduced and the reaction flask was allowed to warm to 23 °C slowly over 12 h. Water (50 mL) was added to the reaction, the aqueous and organic layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combine organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was suspended in 1:1 pentane:diethyl ether and filtered to remove the triphenylphosphine oxide contaminant. The filtrate solution was concentrated *in vacuo* and the crude residue was purified via flash column chromatography on silica gel using 2:1 pentane:diethyl ether as the eluent. The product was isolated as a colorless oil (1.14 g, 7.36 mmol, 62% yield, 5:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

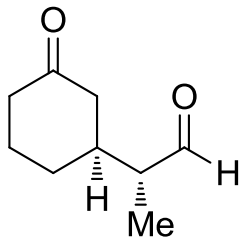
Major Isomer:

9.65 (1H, d, *J* = 1.5 Hz)

2.39-2.31 (3H, m)

2.30-2.20 (3H, m)

2.12-2.05 (1H, m)



1.79-1.74 (1H, m)

1.64 (1H, ddddd, *J* = 13.0, 13.0, 13.0, 4.0, 4.0 Hz)

1.54-1.41 (1H, m)

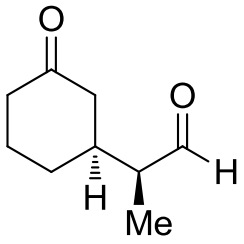
1.10 (3H, d, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5, 203.8, 50.7, 45.9, 41.2, 38.8, 27.3, 25.2, 9.8.

Minor Isomer (selected peaks):

9.62 (1H, d, *J* = 2.5 Hz)

1.87 (1H, dm, *J* = 13.5 Hz)



1.09 (3H, d, *J* = 7.0 Hz).

(±)-(1*R*,4*R*)-5-Methylbicyclo[2.2.2]oct-5-en-2-one (148).

The diastereomeric mixture of 3-methyl-6-oxobicyclo[2.2.2]octan-2-yl methanesulfonate (**151**) (103 mg, 0.44 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (DMF, 5.5 mL) in a 25 mL round-bottom flask. Lithium carbonate (197 mg, 2.66 mmol, 6 equiv) and LiBr (154 mg, 1.77 mmol, 4 equiv) were added to the flask and the reaction mixture was heated to 150 °C and monitored by TLC (1:1 pentane:diethyl ether). The reaction was complete after 30 min and the flask was cooled to 23 °C. The reaction mixture was diluted with brine (15 mL) and the mixture was extracted with diethyl ether (3 x 20 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was isolated as a pale yellow oil (25 mg, 0.19 mmol, 42% yield) that could be used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.75 (1H, bd, *J* = 6.8 Hz)

3.00 (1H, ddd, *J* = 6.4, 2.8, 2.8 Hz)

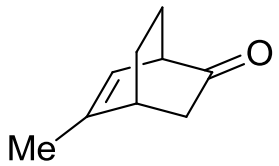
2.69 (1H, m)

2.03 (1H, ddd, *J* = 18.4, 2.8, 2.8 Hz)

1.97 (1H, dd, *J* = 18.4, 2.2 Hz)

1.82 (3H, d, *J* = 1.6 Hz)

1.85-1.78 (1H, m)



1.69-1.47 (3H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.6, 146.5, 120.5, 48.5, 40.1, 37.8, 23.9, 23.2, 20.2.

7a-Methylhexahydrobenzofuran-2(3H)-one (149).

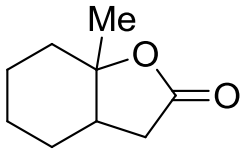
(*R*)-2-((*S*)-3-Oxocyclohexyl)propanal (xx) (25 mg, 0.16 mmol, 1 equiv) was dissolved in dichloromethane (1.6 mL) in a 10 mL microwave vial equipped with a stirbar. Trifluoromethanesulfonic acid (0.03 mL, 0.32 mmol, 2 equiv) was added and the reaction mixture was heated to 40 °C in the microwave for 15 min. Triethylamine was added to the red reaction mixture until it turned yellow. The mixture was concentrated *in vacuo* and immediately purified via flash column chromatography on silica gel using 1:1 pentane:diethyl ether as the eluent. Two products were isolated from the reaction mixture, the expected product (±)-(1*R*,4*R*)-5-methylbicyclo[2.2.2]oct-5-en-2-one (**148**) (1 mg, 0.01 mmol, 4% yield) and a rearranged product 7a-Methylhexahydrobenzofuran-2(3H)-one (**149**) (4 mg, 0.03 mmol, 16% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

2.60 (1H, dd, *J* = 17.2, 7.7 Hz)

2.39 (1H, dd, *J* = 17.5, 8.0 Hz)

2.28-2.23 (1H, m)



1.78 (1H, ddd, J = 14.0, 9.5, 4.5 Hz)

1.72-1.66 (2H, m)

1.61-1.56 (2H, m)

1.52-1.44 (2H, m)

1.41 (3H, s)

1.40-1.33 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.8, 85.1, 40.3, 35.2, 34.7, 26.5, 25.6, 22.0, 21.2.

6-Hydroxy-5-methylbicyclo[2.2.2]octan-2-one (150).

(*R*)-2-((*S*)-3-Oxocyclohexyl)propanal (**147**) (200 mg, 1.29 mmol, 1 equiv) was dissolved in dichloromethane (12 mL) in a 25 mL round-bottom flask. Hydrochloric acid (0.39 mL, 1.55 mmol, 1.2 equiv, 4.0 M in dioxane) was added and the reaction mixture was stirred at 23 °C for 15 min. The reaction mixture was quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL) and then extracted with dichloromethane (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material could be used in the following step without further purification or could be purified via flash column chromatography on silica gel (1:1 pentane:diethyl ether). The product was isolated as a mixture of two diastereomers (181 mg, 1.17 mmol, 90.5% yield). We have tentatively assigned them as the two possible *trans* isomers.

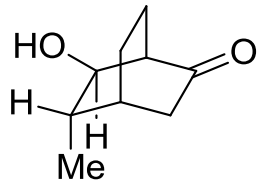
^{1}H NMR (500 MHz, $CDCl_3$) δ:

Major Isomer:

4.20 (1H, dd, *J* = 8.0, 5.0 Hz)

2.51-2.46 (1H, ddd, *J* = 18.0, 2.5, 2.5 Hz)

2.48 (1H, m)



2.20-2.07 (1H, m)

2.02 (1H, dm, *J* = 18.0 Hz)

1.90 (1H, bs)

1.84-1.50 (5H, m)

1.08 (3H, d, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.8, 70.6, 51.1, 40.1, 35.1, 34.7, 26.0, 20.0, 12.9.

Minor Isomer:

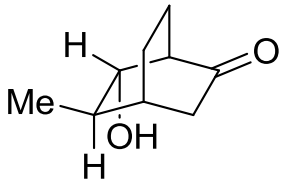
3.63 (1H, bs)

2.38 (1H, m)

2.20-2.15 (1H, ddd, *J* = 18.0, 2.5, 2.5 Hz)

2.20-2.07 (1H, m)

1.90 (1H, bs)



1.84-1.48 (6H, m)

1.08 (3H, d, J = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.8, 74.1, 52.3, 40.6, 38.9, 33.8, 26.1, 18.7, 15.5.

3-Methyl-6-oxobicyclo[2.2.2]octan-2-yl methanesulfonate (151).

6-Hydroxy-5-methylbicyclo[2.2.2]octan-2-one (**150**) (555 mg, 3.60 mmol, 1 equiv) was dissolved in dichloromethane (12 mL). Pyridine (0.39 mL, 4.82 mmol, 1.3 equiv), 4-(dimethylamino)pyridine (DMAP, 59 mg, 0.48 mmol, 0.13 equiv) and methanesulfonyl chloride (0.56 mL, 7.23 mmol, 2 equiv) were added and the reaction mixture was stirred at 23 °C for 14 h. The reaction was quenched by pouring the mixture into a saturated brine solution (20 mL). The mixture was extracted with diethyl ether (3 x 20 mL). The ether layer was washed with a solution of 3 N HCl (1 x 25 mL), then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified via flash column chromatography on silica gel using 1:1 hexanes:ethyl acetate as the eluent. The product was isolated as two spots, one diastereomer (87 mg, 0.37 mmol, 10% yield) and a mixture of the other 3 diastereomers (362 mg, 1.56 mmol, 43% yield).

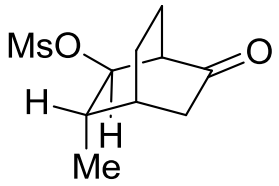
^{1}H NMR (500 MHz, $CDCl_3$) δ: *(1 pure diastereomer)*

4.46 (1H, ddd, *J* = 4.0, 4.0, 1.0 Hz)

3.01 (3H, s)

2.67 (1H, ddd, *J* = 3.2, 2.4, 2.4 Hz)

2.31 (1H, ddd, *J* = 19.2, 2.8, 2.8 Hz)



2.16-2.10 (1H, m)

2.10 (1H, ddd, *J* = 19.2, 2.4, 2.4 Hz)

2.08-1.98 (2H, m)

1.84-1.74 (1H, m)

1.71-1.59 (2H, m)

1.12 (3H, d, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9, 83.0, 49.6, 38.79, 38.77, 38.5, 33.1, 25.4, 17.8, 15.8.

Selected peaks from other isomers:

^{1}H NMR (500 MHz, $CDCl_3$) δ: *(3 isomers)*

5.17 (1H, dd, *J* = 8.5, 4.5 Hz)

4.60 (1H, dd, *J* = 3.5, 3.5 Hz)

3.03 (3H, s)

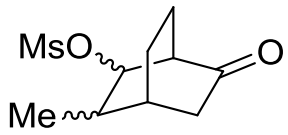
2.98 (3H, s)

2.70 (1H, m)

2.70 (1H, m)

1.25 (3H, d, *J* = 7.5 Hz)

1.13 (3H, d, *J* = 7.0 Hz).



(±)-(1*R*,5*R*)-Bicyclo[3.2.1]oct-3-en-6-one (153)

(±)-(1*R*,5*S*)-2-Oxabicyclo[3.3.1]nonan-3-one (154).

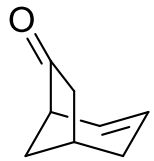
In a 10 mL microwave vial equipped with a stir bar was added phosphorus pentoxide (1.01 g, 3.57 mmol, 2 equiv) and dichloromethane (3 mL). A solution of racemic 2-(3-oxocyclohexyl)acetaldehyde (**98**) (250 mg, 1.78 mmol, 1 equiv) in dichloromethane (3 mL) was then added to the vial followed by trifluoromethanesulfonic acid (0.32 mL, 3.57 mmol, 2 equiv). The vial was microwaved at 40 °C for 45 min. TLC analysis (1:1 pentane:diethyl ether) showed disappearance of the starting material. The reaction mixture was filtered to remove the solid P_2O_5 and was rinsed with dichloromethane. Triethylamine was added to the red filtrate solution until the solution turned pale yellow. The solution was concentrated *in vacuo* and immediately purified via flash column chromatography on silica gel with 1:1 pentane:diethyl ether as the eluent. (±)-(1*R*,5*S*)-2-Oxabicyclo[3.3.1]nonan-3-one (**154**) (60 mg, 0.49 mmol, 28% yield, R_f = 0.43) was isolated as well an unexpected eliminated product (±)-(1*R*,5*R*)-bicyclo[3.2.1]oct-3-en-6-one (**153**) (26 mg, 0.19 mmol, 10% yield, R_f = 0.82).

(±)-(1*R*,4*R*)-Bicyclo[2.2.2]oct-5-en-2-one (153)

^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.72 (1H, d, *J* = 8.5 Hz)

5.71 (1H, d, *J* = 8.5 Hz)



2.82 (1H, m)

2.57 (2H, m)

2.36 (1H, dd, *J* = 14.8, 6.0 Hz)

2.17 (1H, dd, *J* = 14.8, 2.4 Hz)

2.00 (1H, d, *J* = 14.4 Hz)

1.91 (1H, ddd, *J* = 9.2, 4.6, 3.6 Hz)

1.74 (1H, dd, *J* = 9.0, 2.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.0, 128.4, 126.0, 46.8, 43.7, 34.4, 32.0, 30.3.

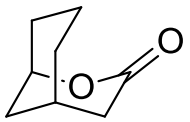
(±)-(1*R*,5*S*)-2-oxabicyclo[3.3.1]nonan-3-one (154)

^{1}H NMR (500 MHz, $CDCl_3$) δ:

4.48 (1H, ddd, *J* = 4.0, 4.0, 4.0 Hz)

2.58 (1H, dd, *J* = 17.0, 7.0 Hz)

2.36 (1H, bm)



2.21 (1H, dd, *J* = 17.0, 3.0 Hz)

2.07-1.98 (1H, dddd, 15.0, 3.0, 3.0, 3.0 Hz)

1.72-1.57 (3H, m)

1.50-1.39 (2H, m)

1.28-1.21 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.6, 79.2, 37.5, 34.8, 27.7, 27.1, 22.8, 19.9.

References

(1) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K., *J. Am. Chem. Soc.* **2003,** *125* (38), 11508-11509.

(2) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T., *J. Org. Chem.* **2005,** *70* (7), 2503-2508.

(3) Shintani, R.; Kimura, T.; Hayashi, T., *Chem. Commun.* **2005,** (25), 3213-3214.

(4) Shintani, R.; Okamoto, K.; Hayashi, T., *Org. Lett.* **2005,** *7* (21), 4757-4759.

(5) Shintani, R.; Duan, W.-L.; Hayashi, T., *J. Am. Chem. Soc.* **2006,** *128* (17), 5628-5629.

(6) Tokunaga, N.; Hayashi, T., *Adv. Synth. Catal.* **2007,** *349* (4-5), 513-516.

(7) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T., *Org. Lett.* **2007,** *9* (22), 4643-4645.

(8) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T., *J. Am. Chem. Soc.* **2007,** *129* (29), 9137-9143.

(9) Sorgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T., *Org. Lett.* **2008,** *10* (4), 589-592.

(10) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T., *J. Am. Chem. Soc.* **2004,** *127* (1), 54-55.

(11) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T., *Angew. Chem.Int. Ed.* **2010,** *49* (22), 3795-3798.

(12) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T., *J. Am. Chem. Soc.* **2004,** *126* (42), 13584-13585.

(13) Nishimura, T.; Yasuhara, Y.; Hayashi, T., *Org. Lett.* **2006,** *8* (5), 979-981.

(14) Yoshida, K.; Akashi, N.; Yanagisawa, A., *Tetrahedron: Asymmetry* **2011,** *22* (11), 1225-1230.

(15) Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T., *J. Am. Chem. Soc.* **2007,** *129* (46), 14158-14159.

(16) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M., *Org. Lett.* **2004,** *6* (21), 3873-3876.

(17) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M., *J. Am. Chem. Soc.* **2004,** *126* (6), 1628-1629.

(18) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M., *J. Am. Chem. Soc.* **2005,** *127* (31), 10850-10851.

(19) Okamoto, K.; Hayashi, T.; Rawal, V. H., *Org. Lett.* **2008,** *10* (19), 4387-4389.

(20) Werstiuk, N. H.; Yeroushalmi, S.; Guan-Lin, H., *Can. J. Chem.* **1992,** *70* (3), 974-980.

(21) Hill, R. K.; Morton, G. H.; Peterson, J. R.; Walsh, J. A.; Paquette, L. A., *J. Org. Chem.* **1985,** *50* (26), 5528-5533.

(22) Abele, S.; Inauen, R.; Spielvogel, D.; Moessner, C., *J. Org. Chem.* **2012,** *77* (10), 4765-4773.

(23) Abele, S.; Inauen, R.; Funel, J.-A.; Weller, T., *Org. Process Res. Dev.* **2011,** *16* (1), 129-140.

(24) Jiricek, J.; Blechert, S., *J. Am. Chem. Soc.* **2004,** *126* (11), 3534-3538.

(25) Ohshima, T.; Xu, Y.; Takita, R.; Shibasaki, M., *Tetrahedron* **2004,** *60* (43), 9569-9588.

(26) Jung, M. E.; Maderna, A., *Tetrahedron Lett.* **2005,** *46* (30), 5057-5061.

(27) Shizuka, M.; Snapper, M. L., *Angew. Chem.Int. Ed.* **2008,** *47* (27), 5049-5051.

(28) Alderdice, M.; Sum, F. W.; Weiler, L., *Org. Synth.* **1990,** *Coll. Vol. 7*.

(29) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., *J. Org. Chem.* **1981,** *46* (14), 2920-2923.

(30) Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I., *J. Am. Chem. Soc.* **1994,** *116* (20), 8937-8951.

(31) Tokoroyama, T.; Pan, L.-R., *Tetrahedron Lett.* **1989,** *30* (2), 197-200.

(32) Harrowven, D. C.; Lucas, M. C.; Howes, P. D., *Tetrahedron* **2001,** *57* (4), 791-804.

(33) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J., *Tetrahedron Lett.* **1967,** *8* (3), 215-217.

(34) Chen, S.; Patrick, B. O.; Scheffer, J. R., *Can. J. Chem.* **2005,** *83* (9), 1460-1472.

(35) Kawatsura, M.; Hartwig, J. F., *J. Am. Chem. Soc.* **1999,** *121* (7), 1473-1478.

(36) Aggarwal, V. K.; Olofsson, B., *Angew. Chem.Int. Ed.* **2005,** *44* (34), 5516-5519.

(37) Ooi, T.; Goto, R.; Maruoka, K., *J. Am. Chem. Soc.* **2003,** *125* (35), 10494-10495.

(38) Barton, D. H. R.; Finet, J.-P.; Giannotti, C.; Halley, F., *J. Chem. Soc., Perkin Trans. 1* **1987**, 241-249.

(39) Fu, J.-m.; Snieckus, V., *Can. J. Chem.* **2000,** *78* (6), 905-919.

(40) Driver, T. G.; Franz, A. K.; Woerpel, K. A., *J. Am. Chem. Soc.* **2002,** *124* (23), 6524-6525.

(41) Ohno, H.; Okumura, M.; Maeda, S.-i.; Iwasaki, H.; Wakayama, R.; Tanaka, T., *J. Org. Chem.* **2003,** *68* (20), 7722-7732.

(42) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B., *J. Organomet. Chem.* **1983,** *250* (1), 227-236.

(43) Blase, F. R.; Le, H., *Tetrahedron Lett.* **1995,** *36* (26), 4559-4562.

(44) Singh, V.; Iyer, S. R., *Tetrahedron* **2005,** *61* (2), 457-462.

(45) Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M., *Chem. Eur. J.* **2001,** *7* (6), 1304-1308.

(46) Riveira, M. n. J.; La-Venia, A.; Mischne, M. P., *J. Org. Chem.* **2008,** *73* (21), 8678-8681.

(47) Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S. J.; Stille, J. K., *J. Org. Chem.* **1985,** *50* (13), 2302-2308.

(48) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S., *Angew. Chem.Int. Ed.* **2008,** *47* (40), 7669-7672.

(49) Tsuji, J.; Shimizu, I.; Yamamoto, K., *Tetrahedron Lett.* **1976,** *17* (34), 2975-2976.

(50) Santiago, A. N.; Takeuchi, K. i.; Ohga, Y.; Nishida, M.; Rossi, R. A., *J. Org. Chem.* **1991,** *56* (4), 1581-1584.

(51) Stothers, J. B.; Swenson, J. R.; Tan, C. T., *Can. J. Chem.* **1975,** *53* (4), 581-588.