ASYMMETRIC PERICYCLIC TRANSFORMATIONS FROM REACTIVE PALLADIUM INTERMEDIATES

Thesis by

Alexander Quinn Cusumano

In Partial Fulfillment of the Requirements for

the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY
Pasadena, California

2024
(Defended June 5, 2023)
To my loving parents
ACKNOWLEDGEMENTS

There are numerous people I wish to thank for their support, encouragement, mentorship, and friendship during my time in graduate school. The culmination of all of these interactions and memories has made this time a truly unique experience – one far more exhilarating and rewarding than I could have ever imagined.

First, I have to thank Professor Brian Stoltz for his guidance, support, and unwavering enthusiasm over the past five years. Brian is an amazing scientist. He is always thinking outside the box, taking on hard challenges, and getting everyone else excited about chemistry. I also want to acknowledge how Brian is a role model of a PI. During my time in the Stoltz group, I have been continually impressed with his people skills – his patience, optimism, ability to foster scientific growth in his mentees, and his genuine investment in our personal development as young adults. Brian offers us an immense amount of freedom in our research directions and the types of challenges we wish to pursue. This level of autonomy allows us to explore our unique interests and define our own scientific identities, all while still benefiting from his support and guidance. I am extremely grateful to have had the opportunity to pursue doctoral studies in the Stoltz group.

I would also like to thank Professor William (Bill) Goddard for being a second mentor to me on the fronts of theoretical and computational chemistry. Bill has unique insights, perspectives, and is always excited to talk about research. I have especially enjoyed taking and TA-ing the Ch120–CH121 series. The concepts we talked about and the intuitive picture of quantum mechanics painted from these courses has changed the way I think about chemistry at the deepest level. I would also like express my appreciation for the members of my thesis committee. In addition to being a supportive thesis chair, Professor Gregory Fu
was always there to offer professional advice and chemistry wisdom. From our chats about postdoc plans and grantsmanship to kinetic queries, Greg has been a phenomenal resource. I would also like to thank Professors Ryan Hadt, Theo Agapie, and Sarah Reisman for their support over the years.

We are lucky at Caltech to have amazing staff that make everyone’s research possible. To that end, I am grateful for the plethora of help and guidance I have received over the years from Dr. Scott Virgil. I need to thank Dr. David VanderVelde, Dr. Mike Takase, and Dr. Mona Shahgholi for their expertise and assistance in NMR spectroscopy, X-ray crystallography, and mass spectrometry. Beth Marshall, Joe Drew, Alison Ross, and Tomomi Kano are all thanked for keeping everything in Schlinger running.

I am lucky to have had a number of outstanding project partners during my time in the Stoltz group. The guidance of Dr. Eric Alexy and Dr. Tyler Fulton were critical when I first arrived. From teaching me laboratory techniques to offering big-picture career advice, their direction was treasured. I am thankful to Dr. Trevor Lohrey for all of the help with organometallic-related synthesis and questions, as well as insights on life as a postdoc. I have learned a ton from our conversations and had a great time working with Ni and Pd together. Working with Adrian Samkian and Zack Sercel on the synthesis of OSDAs has been a pleasure. I have also had the opportunity to work with Dr. Steven Sardini and Dr. Veronica Hubble on a variety of projects over the last years, all of which have been an awesome time (besides our “asymmetric” protonation). I am thankful for our “[4+2] team” – Kali Flesch, Ruby Chen, and Christian Strong – for being an amazingly supportive group in our efforts to hijack Pd enolates. Lastly, I am grateful for the opportunity to mentor Tianyi Zhang, an
amazingly talented undergraduate, over the past two years. Tianyi continually impressed me with his intellect, fun personality, and ability to rapidly acquire and apply new skills.

The Stoltz group is full of interesting characters that make coming to work each day that much more enjoyable. I got lucky to have an awesome cohort, with Alexia Kim, Zack Sercel, and Tyler Casselman (TC). Officer Kim has been the perfect hood-mate and partner on our bad boy police force over these 5 years. If you are reading this, I am sorry for the embarrassing photos in my defense. Thank you for putting up with me and blessing our bay with good tunes – sorry for the dances. Zack has been not only a source of encouragement, but also a great sounding board for wacky ideas, a fun project partner, and just a pleasure to talk to about life. Hopefully we get to cross paths again someday. TC was the addition to our cohort that we needed. From random fist-bumps when I looked stressed at my desk to hilarious one-liners, Tyler has been a great moral booster. I am also thankful for the following class, Melinda Chan and Ally Stanko. I need to thank Melinda for support and friendship over the years. I remember when we first met, you almost called the police because you didn’t have my number saved and I convinced you over text that you were being roped in to a cocaine smuggling ring in the Cats. Anyways, thank you for the Ting Ting workouts, letting me babysit Poo, and the life advice. Our group then rapidly expanded two classes of seven graduate students. Jay Barbor, Kali Flesch, Kevin Gonzales, Elliot Hicks, Farbod Moghadam, Samir Rezgui, and Adrian Samkian were all amazing additions to the group. The following year we were blessed with Ruby Chen, Ben Gross, Kim Sharp, Christian Strong, Camila Suarez, Marva Tariq, and Hao Yu. It was fun watching all of this new talent flood into the group as the size of our family grew dramatically. I am excited to see what our
most recent class, Adrian de Almenara, Sydney Bottcher, Chloe Cerione, and Jonathan Farhi, will accomplish over the next few years.

I am grateful for the talented group of postdocs I have overlapped with over the years. Dr. Stephen Sardini has been an awesome friend and project partner. Stephen is a talented chemist and has started and developed several exciting projects in his time in the Stoltz group. Thank you for helping me out whenever I got stuck and always pushing me to be a hard little worker. Dr. Veronica Hubble has been another key figure during my time in the Stoltz group. I remember chatting on the phone about Brian and research in the Stoltz group when you were considering pursuing a postdoc here. Fortunately, you decided to come to Caltech, and the rest is history. Dr. Melissa Ramirez has been an awesome addition to the group. Our conversations on academia, science, and life never failed to offer me a new perspective on things – this I value a ton. In addition to the former group members mentioned earlier, I have to give a special thanks to Dr. Chris Reimann for being a “fatherly” figure to me and Alexia when we were baby G1s. Thank you for always supporting us regardless of whatever wild situation in which we found ourselves. Long live “Bible Club.”

My years prior to Caltech were formative. I am indebted to Professor Markus Etzkorn at UNC Charlotte for welcoming me into his research group during my high school years. Those early experiences introduced me to the exciting field that is organic chemistry, about which I have remained passionate ever since. Following this, I had the great fortune of working with Professor Joshua Pierce during my undergraduate years at NC State. His guidance and support (and patience) were crucial to my development as a young scientist and ultimately led to me pursuing graduate school. I would also especially like to thank Dr.
Yasamin Moazami and the entirety of the Pierce group for being amazing mentors during these years.

Lastly, I would like to extend my gratitude to my loving family, without whom none of this would be possible. My parents, and sister Nicki, have been an amazing support system every step of the way. To this day, without fail, I receive embarrassingly decorated “care packages” all the way from North Carolina for even the smallest of holidays. Thank you for always encouraging me to pursue my passions, and for the endless love. Of course, I have to thank my amazing girlfriend, Meagan Castañeda, for being by my side through this crazy journey. Meeting you was the best thing to happen to me during my time here. I am so lucky to have you and I am excited for the next steps in our life together. At last, mga anak natin Pingu, Koala, at Kokak – salamat sa support.
ABSTRACT

Research in the Stoltz group is centered around the development of novel tactics and strategies for the synthesis of complex organic molecules. The Pd-catalyzed decarboxylative asymmetric allylic alkylation of enolate nucleophiles is a cornerstone of our groups’ efforts to develop methodologies that directly facilitate the synthesis of stereochemically complex molecular building blocks. This thesis first focuses on our efforts to deepen our mechanistic understanding of these transformations. We then employ our insights as a base from which we expand the scope of the decarboxylative asymmetric allylic alkylation reaction, as well as develop entirely novel reaction paradigms.

   A.Q.C. participated in manuscript preparation.


   A.Q.C. carried out computational studies, experimental work, data analysis, and manuscript preparation.


   A.Q.C. carried out computational studies, data analysis, and manuscript preparation.


   A.Q.C. carried out computational studies, data analysis, and manuscript preparation.

A.Q.C. carried out experimental work, computational studies, data analysis, and manuscript preparation.
TABLE OF CONTENTS

Dedication ........................................................................................................... iii
Acknowledgements ........................................................................................... iv
Abstract ............................................................................................................. ix
Published Content and Contributions ......................................................... x
Table of Contents ............................................................................................. xii
List of Figures .................................................................................................... xvi
List of Schemes .................................................................................................. xxxv
List of Tables ..................................................................................................... xxxvii
List of Abbreviations ........................................................................................ xxxix

CHAPTER 1
Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

1.1 Introduction .................................................................................................. 1
1.2 Computational Methods ........................................................................... 5
1.3 Results ........................................................................................................ 6
  1.3.1 Oxidative Addition ............................................................................... 7
  1.3.2 Decarboxylation .................................................................................. 13
  1.3.3 C–C Bond Formation via Reductive Elimination ............................. 23
  1.3.4 Complete Catalytic Cycle ................................................................... 35
  1.3.5 Experiment and Discussion ................................................................. 39
1.4 Conclusions .................................................................................................. 43
1.5 Supporting Information ............................................................................. 46
  1.5.1 General Computational Details ............................................................ 46
  1.5.2 Initial Benchmarking ........................................................................... 49
  1.5.3 Decarboxylation and Control Experiments ....................................... 52
  1.5.4 Prediction of Enantioselectivity ......................................................... 53
  1.5.5 Additional Notes .................................................................................. 57
  1.5.6 Experimental Procedures and Spectroscopic Data ........................... 63
1.6 References and Notes ................................................................................ 67
**APPENDIX 1**

*Spectra Relevant to Chapter 1*

---

### CHAPTER 2

*Analysis of the Pd $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ Pericyclic Reaction*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Introduction</td>
<td>83</td>
</tr>
<tr>
<td>2.2 Results and Discussion</td>
<td>84</td>
</tr>
<tr>
<td>2.3 Conclusions</td>
<td>95</td>
</tr>
<tr>
<td>2.4 Supporting Information</td>
<td>95</td>
</tr>
<tr>
<td>2.4.1 General Computational Details</td>
<td>95</td>
</tr>
<tr>
<td>2.4.2 NEVPT2/CASSCF Active Spaces and Results</td>
<td>97</td>
</tr>
<tr>
<td>2.4.3 Additional Notes on NEVPT2/CASSCF Calculations</td>
<td>115</td>
</tr>
<tr>
<td>2.4.4 Discussion on Other Main Group Chelefuges</td>
<td>115</td>
</tr>
<tr>
<td>2.4.5 Exploring Exchange Coupling in Diradical Intermediate</td>
<td>117</td>
</tr>
<tr>
<td>2.4.6 Redox Innocence of the PHOX Ligand in the $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ Reaction</td>
<td>122</td>
</tr>
<tr>
<td>2.4.7 Nucleus Independent Chemical Shift (NICS) Calculations</td>
<td>124</td>
</tr>
<tr>
<td>2.4.8 Intrinsic Bonding Orbital (IBO) Analysis</td>
<td>125</td>
</tr>
<tr>
<td>2.5 References</td>
<td>126</td>
</tr>
</tbody>
</table>

---

### CHAPTER 3

*Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Introduction</td>
<td>136</td>
</tr>
<tr>
<td>3.2 Results and Discussion</td>
<td>138</td>
</tr>
<tr>
<td>3.2.1 Reaction Design and Optimization</td>
<td>138</td>
</tr>
<tr>
<td>3.2.2 Proposed Mechanism</td>
<td>143</td>
</tr>
<tr>
<td>3.2.3 Substrate Scope</td>
<td>144</td>
</tr>
<tr>
<td>3.2.4 [4+2] Cycloaddition</td>
<td>149</td>
</tr>
<tr>
<td>3.2.5 Catalyst Turnover</td>
<td>152</td>
</tr>
<tr>
<td>3.2.6 Further Mechanism-based Developments</td>
<td>153</td>
</tr>
<tr>
<td>3.2.7 Product Derivatizations</td>
<td>155</td>
</tr>
<tr>
<td>3.3 Conclusions</td>
<td>158</td>
</tr>
<tr>
<td>3.4 Supporting Information</td>
<td>158</td>
</tr>
<tr>
<td>3.4.1 Materials and Methods</td>
<td>158</td>
</tr>
</tbody>
</table>
3.4.2 Experimental Procedures and Spectroscopic Data ...................... 160
3.4.3 Determination of Absolute and Relative Stereochemistry by VCD Spectroscopy ................................................................. 262
3.4.4 2D NMR Analysis of Select Compounds ................................ 287
3.4.5 General Computational Details ............................................. 294
3.5 References and Notes ............................................................... 303

APPENDIX 2
Spectra Relevant to Chapter 3

CHAPTER 4
Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A
4.1 Introduction ............................................................................. 537
4.2 Computational Methods ......................................................... 539
4.3 Results and Discussion ............................................................ 540
4.3.1 Step 1: Photoexcitation ..................................................... 541
4.3.2 Step 2: First C–C Bond Formation ....................................... 544
4.3.3 Step 3: Second C–C Bond Formation ................................. 549
4.3.4 Complete Mechanism ......................................................... 553
4.4 Conclusions ............................................................................. 556
4.5 Supporting Information .......................................................... 557
4.5.1 General Computational Details ........................................... 557
4.6 References and Notes ............................................................... 574

CHAPTER 5
Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles
5.1 Introduction ............................................................................. 586
5.2 Mechanism and Development ................................................. 588
5.3 Substrate Scope ...................................................................... 590
5.4 Product Transformations ......................................................... 593
5.5 Conclusions ............................................................................. 593
5.6 Supporting Information .......................................................... 594
5.6.1 Materials and Methods ....................................................... 594
5.6.2 Experimental Procedures and Spectroscopic Data............................. 596
5.7 References and Notes ........................................................................... 639

APPENDIX 3 .................................................................................................................. 644
Spectra Relevant to Chapter 5

APPENDIX 4 .................................................................................................................. 753
Notebook Cross-Reference for New Compounds

ABOUT THE AUTHOR ................................................................................................. 757
LIST OF FIGURES

CHAPTER 1
Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation of a C(sp³)–C(sp³) Cross-Coupling

Figure 1.1 Pd-catalyzed Decarboxylative Asymmetric Allylic Alkylation ........... 2
Figure 1.2 Four classes of Pd⁰ allyl carboxylate oxidative addition................... 8
Figure 1.3 Isomeric transition state for the anti-displacement-type oxidative addition ................................................................. 9
Figure 1.4 Relative free energies of constitutional isomers of η¹– and η³–allyl Pd complexes from masked enolate synthons .................. 12
Figure 1.5 Experimentally-derived parameters for decarboxylation and decarboxylation pathways considered ........................................... 14
Figure 1.6 Structures of rate-limiting transition states for decarboxylation ..... 19
Figure 1.7 Inner-sphere C–C bond forming transition states considered ........ 23
Figure 1.8 Reductive elimination from Pd enolate 13................................. 25
Figure 1.9 Structures of the two lowest energy diastereomeric transition states of TS20 ................................................................. 26
Figure 1.10 Complete catalytic cycle for the inner-sphere allylic alkylation reaction ............................................................................. 36
Figure 1.11 Free energy profile of minimum energy pathway through full catalytic cycle ........................................................................ 38
Figure 1.12 Conversion of 1 to (S)-2 under standard reaction conditions .... 40
Figure 1.13 Effect of decarboxylation mechanism on downstream enantioselectivity ........................................................................ 41
Figure 1.14 Effect of solvation and ligand electronics on enantioselectivity .... 43
Figure 1.15 Select frontier MOs of a model Pt⁰ complex highlighting potential hybridization of 2a’ and 3a’. .............................................. 60

APPENDIX 1
Spectra Relevant to Chapter 1

Figure A1.1 ¹H NMR (400 MHz, CDCl₃) of compound 20 ................................. 81
CHAPTER 2
Analysis of the Pd [π2s + π2s + σ2s + σ2s] Pericyclic Reaction

Figure 2.1 Seven-centered cyclic transition states in Pd catalysis. ......................... 84
Figure 2.2 Orbital correlation diagram for the [π2s + π2s + σ2s + σ2s] quasi-
cheletropic reaction of diallyl sulfone .............................................. 86
Figure 2.3 Orbital correlation diagram for the pericyclic reaction of 26 to 28 .... 90
Figure 2.4 FMO perspective of the [π2s + π2s + σ2s + σ2s] reaction ..................... 91
Figure 2.5 IBO analysis the Pd [π2s + π2s + σ2s + σ2s] reaction ................................ 94
Figure 2.6 MCSCF active space orbitals and energies of complex 13........ 99
Figure 2.7 MCSCF active space orbitals and energies of complex TS20 ...... 100
Figure 2.8 MCSCF active space orbitals and energies of complex 19 .......... 101
Figure 2.9 MCSCF active space orbitals and energies of 23 ...................... 102
Figure 2.10 MCSCF active space orbitals and energies of TS27 ................. 103
Figure 2.11 MCSCF active space orbitals and energies of diradical 30 .... 104
Figure 2.12 MCSCF active space orbitals and energies of TS28 ................. 105
Figure 2.13 MCSCF active space orbitals and energies of SO3 (24) ............ 106
Figure 2.14 MCSCF active space orbitals and energies of (s-cis)-1,5-hexadiene
(25_cis) ......................................................................................... 107
Figure 2.15 MCSCF active space orbitals and energies of (s-trans)-1,5-hexadiene
(25_trans) ....................................................................................... 108
Figure 2.16 MCSCF active space orbitals and energies of complex 26 ........ 109
Figure 2.17 MCSCF active space orbitals and energies of complex 27 .... 110
Figure 2.18 MCSCF active space orbitals and energies of TS25 .......... 111
Figure 2.19 MCSCF active space orbitals and energies of TS26 ............. 112
Figure 2.20 MCSCF active space orbitals and energies of 28 .............. 113
Figure 2.21 MCSCF active space orbitals and energies of 29 .............. 114
Figure 2.22 Orbital correlation diagram for the ground-state symmetry-forbidden
[π2s + π2s + σ2s + σ2s] extrusion of CO from hepta-1,6-dien-4-one
.............................................................................................................. 116
Figure 2.23 Exchange coupling via IDDCI .............................................. 121
Figure 2.24 Orbitals involved in the vertical transitions to the lowest energy singlet
and triplet excited states at TS20. ....................................................... 124
CHAPTER 3
Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

Figure 3.1 Examples of chiral Pd enolate reactivity and proposed reaction ..... 137
Figure 3.2 General reactivity paradigm from Pd enolate 43 .................................. 139
Figure 3.3 Sacrificial additives to enable catalyst turnover and additive-free reaction with prenyl ester 40a ................................................................. 141
Figure 3.4 Eyring analysis of 41/49 product ratio for propylene and butylene tethered substrates 40a and 40f ................................................................. 147
Figure 3.5 Irreversibility of C–C bond formation and origins of enantioinduction in the [4+2] cycloaddition step ................................................................. 151
Figure 3.6 Two lowest-energy pathways for catalyst turnover ................................ 153
Figure 3.7 KIE study and prenyl ester modification ............................................. 154
Figure 3.8 Product derivatizations of [4+2] products ............................................. 157
Figure 3.9 Three diastereomers 41a, 41q, and 41q′ to be compared to spectra computed from all eight possible stereoisomers ........................................... 264
Figure 3.10 Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_endo-trans ................................................. 265
Figure 3.11 Overlaid experimental and calculated VCD spectra for 41a – assigned as ent-A_endo-trans .................................................................................. 265
Figure 3.12 Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_exo-trans ......................................................... 266
Figure 3.13 Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_endo-cis ......................................................... 267
Figure 3.14 Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_exo-cis ......................................................... 268
Figure 3.15 Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_endo-trans ......................................................... 269
Figure 3.16 Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_exo-trans ......................................................... 270
Figure 3.17 Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_endo-cis ......................................................... 271
Figure 3.18 Overlaid experimental and calculated VCD spectra for 41q – assigned as ent-A_endo-cis .................................................................................. 271
Figure 3.19 Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_exo-cis ......................................................... 272
Figure 3.20  Comparison of experimental VCD and IR spectra for product \(41q'\) to computed spectra for \textit{A_\text{endo-trans}} .......................................................... 273
Figure 3.21  Comparison of experimental VCD and IR spectra for product \(41q'\) to computed spectra for \textit{A_\text{exo-trans}} .......................................................... 274
Figure 3.22  Comparison of experimental VCD and IR spectra for product \(41q'\) to computed spectra for \textit{A_\text{endo-cis}} .......................................................... 275
Figure 3.23  Comparison of experimental VCD and IR spectra for product \(41q'\) to computed spectra for \textit{A_\text{exo-cis}} .......................................................... 276
Figure 3.24  Overlayed experimental and calculated VCD spectra for \(41q'\) – assigned as \textit{ent-A_\text{exo-cis}} ........................................................................... 276
Figure 3.25  Three diastereomers \(41k\), \(41k'\), and \(41k''\) to be compared to spectra computed from all eight possible stereoisomers. ..................................... 277
Figure 3.26  Experimental VCD and IR spectra for product \(41k\) compared to computed spectra for \textit{B_\text{endo-trans}} .......................................................... 278
Figure 3.27  Overlayed experimental and calculated VCD spectra for \(41k\) – assigned as \textit{B_\text{endo-trans}} .......................................................... 278
Figure 3.28  Experimental VCD and IR spectra for product \(41k\) compared to computed spectra for \textit{B_\text{exo-trans}} .......................................................... 279
Figure 3.29  Experimental VCD and IR spectra for product \(41k\) compared to computed spectra for \textit{B_\text{endo-cis}} .......................................................... 280
Figure 3.30  Experimental VCD and IR spectra for product \(41k\) compared to computed spectra for \textit{B_\text{exo-cis}} .......................................................... 281
Figure 3.31  Experimental IR spectrum for product \(41k'\) compared to computed spectra for isomers of \(B \) ............................................................. 282
Figure 3.32  Experimental VCD and IR spectra for product \(41k''\) compared to computed spectra for \textit{B_\text{endo-trans}} .......................................................... 283
Figure 3.33  Experimental VCD and IR spectra for product \(41k''\) compared to computed spectra for \textit{B_\text{exo-trans}} .......................................................... 284
Figure 3.34  Experimental VCD and IR spectra for product \(41k''\) compared to computed spectra for \textit{B_\text{endo-cis}} .......................................................... 285
Figure 3.35  Overlayed experimental and calculated VCD spectra for \(41k''\) – assigned as \textit{B_\text{endo-cis}} .......................................................... 285
Figure 3.36  Experimental VCD and IR spectra for product \(41k''\) compared to computed spectra for \textit{B_\text{exo-cis}} .......................................................... 286
Figure 3.37  \(^1\text{H}-^1\text{H}\) COSY NMR spectrum of \(41a\) (400 MHz, CDCl\(_3\)) ....................................................... 287
Figure 3.38  \(^1\text{H}-^{13}\text{C}\) HSQC NMR spectrum of \(41a\) (400 MHz, CDCl\(_3\)) ....................................................... 288
Figure 3.39  \(^1\text{H}-^1\text{H}\) NOESY NMR spectrum of \(41a\) (400 MHz, CDCl\(_3\)) ....................................................... 288
APPENDIX 2

Spectra Relevant to Chapter 3

Figure A2.1  
$^1$H NMR (400 MHz, CDCl$_3$) of compound 41a.......................... 316

Figure A2.2  
Infrared spectrum (Thin Film, NaCl) of compound 41a ................... 317

Figure A2.3  
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41a ..................... 317

Figure A2.4  
$^1$H NMR (400 MHz, CDCl$_3$) of compound 41b....................... 318

Figure A2.5  
Infrared spectrum (Thin Film, NaCl) of compound 41b ................ 319

Figure A2.6  
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41b ..................... 319

Figure A2.7  
$^1$H NMR (400 MHz, CDCl$_3$) of compound 41c ....................... 320

Figure A2.8  
Infrared spectrum (Thin Film, NaCl) of compound 41c ................ 321

Figure A2.9  
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41c ..................... 321

Figure A2.10  
$^1$H NMR (400 MHz, CDCl$_3$) of compound 41d....................... 322
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.11</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41d</td>
<td>323</td>
</tr>
<tr>
<td>A.12</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41d</td>
<td>323</td>
</tr>
<tr>
<td>A.13</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41f</td>
<td>324</td>
</tr>
<tr>
<td>A.14</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41f</td>
<td>325</td>
</tr>
<tr>
<td>A.15</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41f</td>
<td>325</td>
</tr>
<tr>
<td>A.16</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41j</td>
<td>326</td>
</tr>
<tr>
<td>A.17</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41j</td>
<td>327</td>
</tr>
<tr>
<td>A.18</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41j</td>
<td>327</td>
</tr>
<tr>
<td>A.19</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41k</td>
<td>328</td>
</tr>
<tr>
<td>A.20</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41k</td>
<td>329</td>
</tr>
<tr>
<td>A.21</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41k</td>
<td>329</td>
</tr>
<tr>
<td>A.22</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41k'</td>
<td>330</td>
</tr>
<tr>
<td>A.23</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41k'</td>
<td>331</td>
</tr>
<tr>
<td>A.24</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41k'</td>
<td>331</td>
</tr>
<tr>
<td>A.25</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41k''</td>
<td>332</td>
</tr>
<tr>
<td>A.26</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41k''</td>
<td>333</td>
</tr>
<tr>
<td>A.27</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41k''</td>
<td>333</td>
</tr>
<tr>
<td>A.28</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41l</td>
<td>334</td>
</tr>
<tr>
<td>A.29</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41l</td>
<td>335</td>
</tr>
<tr>
<td>A.30</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41l</td>
<td>335</td>
</tr>
<tr>
<td>A.31</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41m</td>
<td>336</td>
</tr>
<tr>
<td>A.32</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41m</td>
<td>337</td>
</tr>
<tr>
<td>A.33</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41m</td>
<td>337</td>
</tr>
<tr>
<td>A.34</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41m'</td>
<td>338</td>
</tr>
<tr>
<td>A.35</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41m'</td>
<td>339</td>
</tr>
<tr>
<td>A.36</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41m'</td>
<td>339</td>
</tr>
<tr>
<td>A.37</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41n</td>
<td>340</td>
</tr>
<tr>
<td>A.38</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41n</td>
<td>341</td>
</tr>
<tr>
<td>A.39</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41n</td>
<td>341</td>
</tr>
<tr>
<td>A.40</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41o</td>
<td>342</td>
</tr>
<tr>
<td>A.41</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41o</td>
<td>343</td>
</tr>
<tr>
<td>A.42</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41o</td>
<td>343</td>
</tr>
<tr>
<td>A.43</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41o'</td>
<td>344</td>
</tr>
<tr>
<td>A.44</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41o'</td>
<td>345</td>
</tr>
<tr>
<td>A.45</td>
<td>$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41o'</td>
<td>345</td>
</tr>
<tr>
<td>A.46</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) of compound 41p</td>
<td>346</td>
</tr>
<tr>
<td>A.47</td>
<td>Infrared spectrum (Thin Film, NaCl) of compound 41p</td>
<td>347</td>
</tr>
</tbody>
</table>
Figure A.48
13C NMR (100 MHz, CDCl3) of compound 41p .................. 347
Figure A.49
1H NMR (400 MHz, CDCl3) of compound 41p’ .................. 348
Figure A.50
Infrared spectrum (Thin Film, NaCl) of compound 41p’ ........ 349
Figure A.51
13C NMR (100 MHz, CDCl3) of compound 41p’ ............... 349
Figure A.52
1H NMR (400 MHz, CDCl3) of compound 41q .................. 350
Figure A.53
Infrared spectrum (Thin Film, NaCl) of compound 41q ....... 351
Figure A.54
13C NMR (100 MHz, CDCl3) of compound 41q ............... 351
Figure A.55
1H NMR (400 MHz, CDCl3) of compound 41q’ ................. 352
Figure A.56
Infrared spectrum (Thin Film, NaCl) of compound 41q’....... 353
Figure A.57
13C NMR (100 MHz, CDCl3) of compound 41q’ ............... 353
Figure A.58
1H NMR (400 MHz, CDCl3) of compound 41r .................. 354
Figure A.59
Infrared spectrum (Thin Film, NaCl) of compound 41r ....... 355
Figure A.60
13C NMR (100 MHz, CDCl3) of compound 41r ............... 355
Figure A.61
1H NMR (400 MHz, CDCl3) of compound 41s .................. 356
Figure A.62
Infrared spectrum (Thin Film, NaCl) of compound 41s ....... 357
Figure A.63
13C NMR (100 MHz, CDCl3) of compound 41s ............... 357
Figure A.64
1H NMR (400 MHz, CDCl3) of compound 41t .................. 358
Figure A.65
Infrared spectrum (Thin Film, NaCl) of compound 41t ....... 359
Figure A.66
13C NMR (100 MHz, CDCl3) of compound 41t ............... 359
Figure A.67
1H NMR (400 MHz, CDCl3) of compound 41t’ ................. 360
Figure A.68
Infrared spectrum (Thin Film, NaCl) of compound 41t’ ...... 361
Figure A.69
13C NMR (100 MHz, CDCl3) of compound 41t’ ............... 361
Figure A.70
1H NMR (400 MHz, CDCl3) of compound 41u .................. 362
Figure A.71
Infrared spectrum (Thin Film, NaCl) of compound 41u ....... 363
Figure A.72
13C NMR (100 MHz, CDCl3) of compound 41u ............... 363
Figure A.73
1H NMR (400 MHz, CDCl3) of compound D-41f .............. 364
Figure A.74
Infrared spectrum (Thin Film, NaCl) of compound D-41f ..... 365
Figure A.75
13C NMR (100 MHz, CDCl3) of compound D-41f ............. 365
Figure A.76
2H NMR (61 MHz, CHCl3) of compound D-41f ............... 366
Figure A.77
1H NMR (400 MHz, CDCl3) of compound 44 .................. 367
Figure A.78
Infrared spectrum (Thin Film, NaCl) of compound 44 ....... 368
Figure A.79
13C NMR (100 MHz, CDCl3) of compound 44 .................. 368
Figure A.80
1H NMR (400 MHz, CDCl3) of compound 40a .................. 369
Figure A.81
Infrared spectrum (Thin Film, NaCl) of compound 40a ...... 370
Figure A.82
13C NMR (100 MHz, CDCl3) of compound 40a .................. 370
Figure A.83
1H NMR (400 MHz, CDCl3) of compound 40b .................. 371
Figure A.84
Infrared spectrum (Thin Film, NaCl) of compound 40b ..... 372
| Figure A2.85 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40b | 372 |
| Figure A2.86 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40c | 373 |
| Figure A2.87 | Infrared spectrum (Thin Film, NaCl) of compound 40c | 374 |
| Figure A2.88 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40c | 374 |
| Figure A2.89 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40d | 375 |
| Figure A2.90 | Infrared spectrum (Thin Film, NaCl) of compound 40d | 376 |
| Figure A2.91 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40d | 376 |
| Figure A2.92 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40e | 377 |
| Figure A2.93 | Infrared spectrum (Thin Film, NaCl) of compound 40e | 378 |
| Figure A2.94 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40e | 378 |
| Figure A2.95 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40f | 379 |
| Figure A2.96 | Infrared spectrum (Thin Film, NaCl) of compound 40f | 380 |
| Figure A2.97 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40f | 380 |
| Figure A2.98 | $^1$H NMR (400 MHz, CDCl$_3$) of compound D-40f | 381 |
| Figure A2.99 | Infrared spectrum (Thin Film, NaCl) of compound D-40f | 382 |
| Figure A2.100 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-40f | 382 |
| Figure A2.101 | $^2$H NMR (61 MHz, CHCl$_3$) of compound D-40f | 383 |
| Figure A2.102 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40g | 384 |
| Figure A2.103 | Infrared spectrum (Thin Film, NaCl) of compound 40g | 385 |
| Figure A2.104 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40g | 385 |
| Figure A2.105 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40h | 386 |
| Figure A2.106 | Infrared spectrum (Thin Film, NaCl) of compound 40h | 387 |
| Figure A2.107 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40h | 387 |
| Figure A2.108 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40i | 388 |
| Figure A2.109 | Infrared spectrum (Thin Film, NaCl) of compound 40i | 389 |
| Figure A2.110 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40 | 389 |
| Figure A2.111 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40j | 390 |
| Figure A2.112 | Infrared spectrum (Thin Film, NaCl) of compound 40j | 391 |
| Figure A2.113 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40j | 391 |
| Figure A2.114 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40k | 392 |
| Figure A2.115 | Infrared spectrum (Thin Film, NaCl) of compound 40k | 393 |
| Figure A2.116 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40k | 393 |
| Figure A2.117 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40l | 394 |
| Figure A2.118 | Infrared spectrum (Thin Film, NaCl) of compound 40l | 395 |
| Figure A2.119 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40l | 395 |
| Figure A2.120 | $^1$H NMR (400 MHz, CDCl$_3$) of compound 40m | 396 |
| Figure A2.121 | Infrared spectrum (Thin Film, NaCl) of compound 40m | 397 |
Figure A.122 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40m .......................... 397
Figure A.123 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40n .......................... 398
Figure A.124 Infrared spectrum (Thin Film, NaCl) of compound 40n .................... 399
Figure A.125 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40n .......................... 399
Figure A.126 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40o .......................... 400
Figure A.127 Infrared spectrum (Thin Film, NaCl) of compound 40o .................... 401
Figure A.128 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40o .......................... 401
Figure A.129 $^1$H NMR (400 MHz, CDCl$_3$) of compound 99 ............................ 402
Figure A.130 Infrared spectrum (Thin Film, NaCl) of compound 99 ..................... 403
Figure A.131 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 99 ............................ 403
Figure A.132 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40p .......................... 404
Figure A.133 Infrared spectrum (Thin Film, NaCl) of compound 40p .................... 405
Figure A.134 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40p .......................... 405
Figure A.135 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40q .......................... 406
Figure A.136 Infrared spectrum (Thin Film, NaCl) of compound 40q .................... 407
Figure A.137 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40q .......................... 407
Figure A.138 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40r .......................... 408
Figure A.139 Infrared spectrum (Thin Film, NaCl) of compound 40r .................... 409
Figure A.140 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40r .......................... 409
Figure A.141 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40s .......................... 410
Figure A.142 Infrared spectrum (Thin Film, NaCl) of compound 40s .................... 411
Figure A.143 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40s .......................... 411
Figure A.144 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40t .......................... 412
Figure A.145 Infrared spectrum (Thin Film, NaCl) of compound 40t .................... 413
Figure A.146 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40t .......................... 413
Figure A.147 $^1$H NMR (400 MHz, CDCl$_3$) of compound 40u .......................... 414
Figure A.148 Infrared spectrum (Thin Film, NaCl) of compound 40u .................... 415
Figure A.149 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40u .......................... 415
Figure A.150 $^1$H NMR (400 MHz, CDCl$_3$) of compound 42 ............................ 416
Figure A.151 Infrared spectrum (Thin Film, NaCl) of compound 42 ..................... 417
Figure A.152 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 42 ............................ 417
Figure A.153 $^1$H NMR (400 MHz, CDCl$_3$) of compound 47 ............................ 418
Figure A.154 Infrared spectrum (Thin Film, NaCl) of compound 47 ..................... 419
Figure A.155 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 47 ............................ 419
Figure A.156 $^1$H NMR (400 MHz, CDCl$_3$) of compound 101 .......................... 420
Figure A.157 Infrared spectrum (Thin Film, NaCl) of compound 101 .................... 421
Figure A.158 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 101 .......................... 421
Figure A2.159 $^1$H NMR (400 MHz, CDCl$_3$) of compound 102 .................. 422
Figure A2.160 Infrared spectrum (Thin Film, NaCl) of compound 102 ........... 423
Figure A2.161 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 102 .................. 423
Figure A2.162 $^1$H NMR (400 MHz, CDCl$_3$) of compound 85 .................. 424
Figure A2.163 Infrared spectrum (Thin Film, NaCl) of compound 85 ........... 425
Figure A2.164 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 85 .................. 425
Figure A2.165 $^1$H NMR (400 MHz, CDCl$_3$) of compound 86 .................. 426
Figure A2.166 Infrared spectrum (Thin Film, NaCl) of compound 86 ........... 427
Figure A2.167 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 86 .................. 427
Figure A2.168 $^1$H NMR (400 MHz, CDCl$_3$) of compound D-86 ............... 428
Figure A2.169 Infrared spectrum (Thin Film, NaCl) of compound D-86 ....... 429
Figure A2.170 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-86 ............... 429
Figure A2.171 $^2$H NMR (61 MHz, CHCl$_3$) of compound D-86 ................. 430
Figure A2.172 $^1$H NMR (400 MHz, CDCl$_3$) of compound 87 ................. 431
Figure A2.173 Infrared spectrum (Thin Film, NaCl) of compound 87 ........... 432
Figure A2.174 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 87 ................. 432
Figure A2.175 $^1$H NMR (400 MHz, CDCl$_3$) of compound 93 ................. 433
Figure A2.176 Infrared spectrum (Thin Film, NaCl) of compound 93 ......... 434
Figure A2.177 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 93 ................. 434
Figure A2.178 $^1$H NMR (400 MHz, CDCl$_3$) of compound 88 ................. 435
Figure A2.179 Infrared spectrum (Thin Film, NaCl) of compound 88 ......... 436
Figure A2.180 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 88 ................. 436
Figure A2.181 $^1$H NMR (400 MHz, CDCl$_3$) of compound 89 ................. 437
Figure A2.182 Infrared spectrum (Thin Film, NaCl) of compound 89 .......... 438
Figure A2.183 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 89 ................. 438
Figure A2.184 $^1$H NMR (400 MHz, CDCl$_3$) of compound 90 ................. 439
Figure A2.185 Infrared spectrum (Thin Film, NaCl) of compound 90 .......... 440
Figure A2.186 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 90 ................. 440
Figure A2.187 $^1$H NMR (400 MHz, CDCl$_3$) of compound 91 ................. 441
Figure A2.188 Infrared spectrum (Thin Film, NaCl) of compound 91 .......... 442
Figure A2.189 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 91 ................. 442
Figure A2.190 $^1$H NMR (400 MHz, CDCl$_3$) of compound 92 ................. 443
Figure A2.191 Infrared spectrum (Thin Film, NaCl) of compound 92 .......... 444
Figure A2.192 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 92 ................. 444
Figure A2.193 $^1$H NMR (400 MHz, CDCl$_3$) of compound 96 ................. 445
Figure A2.194 Infrared spectrum (Thin Film, NaCl) of compound 96 .......... 446
Figure A2.195 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 96 ................. 446
Figure A.196 ¹H NMR (400 MHz, CDCl₃) of compound 95

Figure A.197 Infrared spectrum (Thin Film, NaCl) of compound 95

Figure A.198 ¹³C NMR (100 MHz, CDCl₃) of compound 95

Figure A.199 ¹H NMR (400 MHz, CDCl₃) of compound 94

Figure A.200 Infrared spectrum (Thin Film, NaCl) of compound 94

Figure A.201 ¹³C NMR (100 MHz, CDCl₃) of compound 94

Figure A.202 ¹H NMR (400 MHz, CDCl₃) of compound 98

Figure A.203 Infrared spectrum (Thin Film, NaCl) of compound 98

Figure A.204 ¹³C NMR (100 MHz, CDCl₃) of compound 98

Figure A.205 ¹H NMR (400 MHz, CDCl₃) of compound 97

Figure A.206 Infrared spectrum (Thin Film, NaCl) of compound 97

Figure A.207 ¹³C NMR (100 MHz, CDCl₃) of compound 97

Figure A.208 ¹H NMR (400 MHz, CDCl₃) of compound D-100

Figure A.209 Infrared spectrum (Thin Film, NaCl) of compound D-100

Figure A.210 ¹³C NMR (100 MHz, CDCl₃) of compound D-100

Figure A.211 ¹H NMR (400 MHz, CDCl₃) of compound D-100

Figure A.212 Infrared spectrum (Thin Film, NaCl) of compound D-100

Figure A.213 ¹³C NMR (100 MHz, CDCl₃) of compound D-100

Figure A.214 ²H NMR (61 MHz, CHCl₃) of compound D-100

Figure A.215 ¹H NMR (400 MHz, CDCl₃) of compound 103

Figure A.216 Infrared spectrum (Thin Film, NaCl) of compound 103

Figure A.217 ¹³C NMR (100 MHz, CDCl₃) of compound 103

Figure A.218 ¹H NMR (400 MHz, CDCl₃) of compound 107

Figure A.219 Infrared spectrum (Thin Film, NaCl) of compound 107

Figure A.220 ¹³C NMR (100 MHz, CDCl₃) of compound 107

Figure A.221 ¹H NMR (400 MHz, CDCl₃) of compound 105

Figure A.222 Infrared spectrum (Thin Film, NaCl) of compound 105

Figure A.223 ¹³C NMR (100 MHz, CDCl₃) of compound 105

Figure A.224 ¹H NMR (400 MHz, CDCl₃) of compound 106

Figure A.225 Infrared spectrum (Thin Film, NaCl) of compound 106

Figure A.226 ¹³C NMR (100 MHz, CDCl₃) of compound 106

Figure A.227 ¹H NMR (400 MHz, CDCl₃) of compound 113

Figure A.228 Infrared spectrum (Thin Film, NaCl) of compound 113

Figure A.229 ¹³C NMR (100 MHz, CDCl₃) of compound 113

Figure A.230 ¹H NMR (400 MHz, CDCl₃) of compound 104

Figure A.231 Infrared spectrum (Thin Film, NaCl) of compound 104

Figure A.232 ¹³C NMR (100 MHz, CDCl₃) of compound 104
Figure A2.233 $^1$H NMR (400 MHz, CDCl$_3$) of compound 108 ......................... 472
Figure A2.234 Infrared spectrum (Thin Film, NaCl) of compound 108 .......... 473
Figure A2.235 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 108 ................. 473
Figure A2.236 $^1$H NMR (400 MHz, CDCl$_3$) of compound 109 ................. 474
Figure A2.237 Infrared spectrum (Thin Film, NaCl) of compound 109 .......... 475
Figure A2.238 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 109 ................. 475
Figure A2.239 $^1$H NMR (400 MHz, CDCl$_3$) of compound 110 ................. 476
Figure A2.240 Infrared spectrum (Thin Film, NaCl) of compound 110 .......... 477
Figure A2.241 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 110 ................. 477
Figure A2.242 $^1$H NMR (400 MHz, CDCl$_3$) of compound 111 ................. 478
Figure A2.243 Infrared spectrum (Thin Film, NaCl) of compound 111 .......... 479
Figure A2.244 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 111 ................. 479
Figure A2.245 $^1$H NMR (400 MHz, CDCl$_3$) of compound 112 ................. 480
Figure A2.246 Infrared spectrum (Thin Film, NaCl) of compound 112 .......... 481
Figure A2.247 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 112 ................. 481
Figure A2.248 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49a .................. 482
Figure A2.249 Infrared spectrum (Thin Film, NaCl) of compound 49a .......... 483
Figure A2.250 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49a ................. 483
Figure A2.251 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49e ................ 484
Figure A2.252 Infrared spectrum (Thin Film, NaCl) of compound 49e .......... 485
Figure A2.253 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49e ................. 485
Figure A2.254 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49f ................. 486
Figure A2.255 Infrared spectrum (Thin Film, NaCl) of compound 49f .......... 487
Figure A2.256 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49f ................. 487
Figure A2.257 $^1$H NMR (400 MHz, CDCl$_3$) of compound D-49f ............... 488
Figure A2.258 Infrared spectrum (Thin Film, NaCl) of compound D-49f ........ 489
Figure A2.259 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-49f ............... 489
Figure A2.260 $^2$H NMR (61 MHz, CHCl$_3$) of compound D-49f ............... 490
Figure A2.261 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49g ................. 491
Figure A2.262 Infrared spectrum (Thin Film, NaCl) of compound 49g .......... 492
Figure A2.263 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49g ................. 492
Figure A2.264 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49h ................. 493
Figure A2.265 Infrared spectrum (Thin Film, NaCl) of compound 49h .......... 494
Figure A2.266 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49h ................. 494
Figure A2.267 $^1$H NMR (400 MHz, CDCl$_3$) of compound 49i ................ 495
Figure A2.268 Infrared spectrum (Thin Film, NaCl) of compound 49i .......... 496
Figure A2.269 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49i ................. 496
Figure A2.270  $^1$H NMR (400 MHz, CDCl$_3$) of compound 83.......................... 497
Figure A2.271  Infrared spectrum (Thin Film, NaCl) of compound 83 ................. 498
Figure A2.272  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 83 ................. 498
Figure A2.273  $^1$H NMR (400 MHz, CDCl$_3$) of compound 84 ................... 499
Figure A2.274  Infrared spectrum (Thin Film, NaCl) of compound 84 ............... 500
Figure A2.275  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 84 ................... 500
Figure A2.276  $^1$H NMR (400 MHz, CDCl$_3$) of compound 59 ..................... 501
Figure A2.277  Infrared spectrum (Thin Film, NaCl) of compound 59 .............. 502
Figure A2.278  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 59 ..................... 502
Figure A2.279  $^1$H NMR (400 MHz, CDCl$_3$) of compound 63 ..................... 503
Figure A2.280  Infrared spectrum (Thin Film, NaCl) of compound 63 .............. 504
Figure A2.281  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 63 ..................... 504
Figure A2.282  $^1$H NMR (400 MHz, CDCl$_3$) of compound 64 ..................... 505
Figure A2.283  Infrared spectrum (Thin Film, NaCl) of compound 64 .............. 506
Figure A2.284  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 64 ..................... 506
Figure A2.285  $^1$H NMR (400 MHz, CDCl$_3$) of compound 65 ..................... 507
Figure A2.286  Infrared spectrum (Thin Film, NaCl) of compound 65 .............. 508
Figure A2.287  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 65 ..................... 508
Figure A2.288  $^1$H NMR (400 MHz, CDCl$_3$) of compound 66 ..................... 509
Figure A2.289  Infrared spectrum (Thin Film, NaCl) of compound 66 .............. 510
Figure A2.290  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 66 ..................... 510
Figure A2.291  $^1$H NMR (400 MHz, CDCl$_3$) of compound 67 ..................... 511
Figure A2.292  Infrared spectrum (Thin Film, NaCl) of compound 67 .............. 512
Figure A2.293  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 67 ..................... 512
Figure A2.294  $^1$H NMR (400 MHz, CDCl$_3$) of compound 68 ..................... 513
Figure A2.295  Infrared spectrum (Thin Film, NaCl) of compound 68 .............. 514
Figure A2.296  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 68 ..................... 514
Figure A2.297  $^1$H NMR (400 MHz, CDCl$_3$) of compound 114 ..................... 515
Figure A2.298  Infrared spectrum (Thin Film, NaCl) of compound 114 ............. 516
Figure A2.299  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 114 ..................... 516
Figure A2.300  $^1$H NMR (400 MHz, CDCl$_3$) of compound 69 ..................... 517
Figure A2.301  Infrared spectrum (Thin Film, NaCl) of compound 69 .............. 518
Figure A2.302  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 69 ..................... 518
Figure A2.303  $^1$H NMR (400 MHz, CDCl$_3$) of compound 70 ..................... 519
Figure A2.304  Infrared spectrum (Thin Film, NaCl) of compound 70 .............. 520
Figure A2.305  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 70 ..................... 520
Figure A2.306  $^1$H NMR (400 MHz, CDCl$_3$) of compound 75 ..................... 521
Figure A2.307 Infrared spectrum (Thin Film, NaCl) of compound 75 .......... 522
Figure A2.308 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 75 .......... 522
Figure A2.309 $^1$H NMR (400 MHz, CDCl$_3$) of compound 76 .................. 523
Figure A2.310 Infrared spectrum (Thin Film, NaCl) of compound 76 .......... 524
Figure A2.311 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 76 .......... 524
Figure A2.312 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77 .......... 525
Figure A2.313 Infrared spectrum (Thin Film, NaCl) of compound 77 .......... 526
Figure A2.314 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 77 .......... 526
Figure A2.315 $^1$H NMR (400 MHz, CDCl$_3$) of compound 78 .......... 527
Figure A2.316 Infrared spectrum (Thin Film, NaCl) of compound 78 .......... 528
Figure A2.317 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 78 .......... 528
Figure A2.318 $^1$H NMR (400 MHz, CDCl$_3$) of compound 79 .......... 529
Figure A2.319 Infrared spectrum (Thin Film, NaCl) of compound 79 .......... 530
Figure A2.320 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 79 .......... 530
Figure A2.321 $^1$H NMR (400 MHz, CDCl$_3$) of compound 80 .......... 531
Figure A2.322 Infrared spectrum (Thin Film, NaCl) of compound 80 .......... 532
Figure A2.323 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 80 .......... 532
Figure A2.324 $^1$H NMR (400 MHz, CDCl$_3$) of compound 81 .......... 533
Figure A2.325 Infrared spectrum (Thin Film, NaCl) of compound 81 .......... 534
Figure A2.326 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 81 .......... 534
Figure A2.327 $^1$H NMR (400 MHz, CDCl$_3$) of compound 82 .......... 535
Figure A2.328 Infrared spectrum (Thin Film, NaCl) of compound 82 .......... 536
Figure A2.329 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 82 .......... 536

CHAPTER 4
Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

Figure 4.1 Complete mechanism describing formation of unexpected product 124 from the intramolecular [2+2] photocycloaddition of enone 121 ..... 555

CHAPTER 5
Development of a Branched-selective Asymmetric Allylic Alklylation of Hard Pd-Enolate Nucleophiles

Figure 5.1 Asymmetric allylic alkylation of tetrasubstituted enolate nucleophiles
**Figure 5.2**  Computational studies and initial reaction development ........................................ 587
**Figure 5.3**  Substrate scope of branched-selective allylic alkylation ........................................ 589
**Figure 5.4**  Branched allylic alkylation product derivatizations ................................................. 592

**APPENDIX 3**

* Spectra Relevant to Chapter 5 *

**Figure A3.1**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160a ........................................... 645
**Figure A3.2**  Infrared spectrum (Thin Film, NaCl) of compound 160a ........................................... 646
**Figure A3.3**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160a ........................................... 646
**Figure A3.4**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160b ........................................... 647
**Figure A3.5**  Infrared spectrum (Thin Film, NaCl) of compound 160b ........................................... 648
**Figure A3.6**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160b ........................................... 648
**Figure A3.7**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160c ........................................... 649
**Figure A3.8**  Infrared spectrum (Thin Film, NaCl) of compound 160c ........................................... 650
**Figure A3.9**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160c ........................................... 650
**Figure A3.10**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160d ........................................... 651
**Figure A3.11**  Infrared spectrum (Thin Film, NaCl) of compound 160d ........................................... 652
**Figure A3.12**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160d ........................................... 652
**Figure A3.13**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160e ........................................... 653
**Figure A3.14**  Infrared spectrum (Thin Film, NaCl) of compound 160e ........................................... 654
**Figure A3.15**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160e ........................................... 654
**Figure A3.16**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160f ........................................... 655
**Figure A3.17**  Infrared spectrum (Thin Film, NaCl) of compound 160f ........................................... 656
**Figure A3.18**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160f ........................................... 656
**Figure A3.19**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160g ........................................... 657
**Figure A3.20**  Infrared spectrum (Thin Film, NaCl) of compound 160g ........................................... 658
**Figure A3.21**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160g ........................................... 658
**Figure A3.22**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160h ........................................... 659
**Figure A3.23**  Infrared spectrum (Thin Film, NaCl) of compound 160h ........................................... 660
**Figure A3.24**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160h ........................................... 660
**Figure A3.25**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160i ........................................... 661
**Figure A3.26**  Infrared spectrum (Thin Film, NaCl) of compound 160i ........................................... 662
**Figure A3.27**  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160i ........................................... 662
**Figure A3.28**  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160j ........................................... 663
**Figure A3.29**  Infrared spectrum (Thin Film, NaCl) of compound 160j ........................................... 664
Figure A.30  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160j ........................................ 664
Figure A.31  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160k ........................................ 665
Figure A.32  Infrared spectrum (Thin Film, NaCl) of compound 160k .................. 666
Figure A.33  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160k .......................... 666
Figure A.34  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160l ............................... 667
Figure A.35  Infrared spectrum (Thin Film, NaCl) of compound 160l ................. 668
Figure A.36  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160l ............................... 668
Figure A.37  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160m ............................. 669
Figure A.38  Infrared spectrum (Thin Film, NaCl) of compound 160m ................. 670
Figure A.39  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160m ............................. 670
Figure A.40  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160m ............................. 671
Figure A.41  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160n ............................... 672
Figure A.42  Infrared spectrum (Thin Film, NaCl) of compound 160n ................. 673
Figure A.43  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160n ............................... 673
Figure A.44  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160n ............................. 674
Figure A.45  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160o ............................... 675
Figure A.46  Infrared spectrum (Thin Film, NaCl) of compound 160o .................. 676
Figure A.47  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160o ............................. 676
Figure A.48  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160o ............................. 677
Figure A.49  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160p .................................. 678
Figure A.50  Infrared spectrum (Thin Film, NaCl) of compound 160p .................. 679
Figure A.51  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160p ............................. 679
Figure A.52  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160p ............................. 680
Figure A.53  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160p_linear .................. 681
Figure A.54  Infrared spectrum (Thin Film, NaCl) of compound 160p_linear .... 682
Figure A.55  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160p_linear .................. 682
Figure A.56  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160p_linear .................. 683
Figure A.57  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160q_mixture .............. 684
Figure A.58  $^1$H NMR (400 MHz, CDCl$_3$) of compound 160q ......................... 685
Figure A.59  Infrared spectrum (Thin Film, NaCl) of compound 160q .................. 686
Figure A.60  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160q ............................. 686
Figure A.61  $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160q ............................. 687
Figure A.62  $^1$H NMR (400 MHz, CDCl$_3$) of compound 158a ............................... 688
Figure A.63  Infrared spectrum (Thin Film, NaCl) of compound 158a .................. 689
Figure A.64  $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158a ............................. 689
Figure A.65  $^1$H NMR (400 MHz, CDCl$_3$) of compound 158b ............................... 690
Figure A.66  Infrared spectrum (Thin Film, NaCl) of compound 158b .................. 691
| Figure A3.67 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158b}$ ..................... 691 |
| Figure A3.68 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158c}$ ..................... 692 |
| Figure A3.69 | Infrared spectrum (Thin Film, NaCl) of compound $^{158c}$ ........... 693 |
| Figure A3.70 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158c}$ ..................... 693 |
| Figure A3.71 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158d}$..................... 694 |
| Figure A3.72 | Infrared spectrum (Thin Film, NaCl) of compound $^{158d}$ ........... 695 |
| Figure A3.73 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158d}$ ..................... 695 |
| Figure A3.74 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158e}$ ..................... 696 |
| Figure A3.75 | Infrared spectrum (Thin Film, NaCl) of compound $^{158e}$ ........... 697 |
| Figure A3.76 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158e}$ ..................... 697 |
| Figure A3.77 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158f}$ ..................... 698 |
| Figure A3.78 | Infrared spectrum (Thin Film, NaCl) of compound $^{158f}$ ........... 699 |
| Figure A3.79 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158f}$ ..................... 699 |
| Figure A3.80 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158g}$..................... 700 |
| Figure A3.81 | Infrared spectrum (Thin Film, NaCl) of compound $^{158g}$ ........... 701 |
| Figure A3.82 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158g}$ ..................... 701 |
| Figure A3.83 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158h}$ ..................... 702 |
| Figure A3.84 | Infrared spectrum (Thin Film, NaCl) of compound $^{158h}$ ........... 703 |
| Figure A3.85 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158h}$ ..................... 703 |
| Figure A3.86 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158i}$ ..................... 704 |
| Figure A3.87 | Infrared spectrum (Thin Film, NaCl) of compound $^{158i}$ ........... 705 |
| Figure A3.88 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158i}$ ..................... 705 |
| Figure A3.89 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158j}$..................... 706 |
| Figure A3.90 | Infrared spectrum (Thin Film, NaCl) of compound $^{158j}$ ........... 707 |
| Figure A3.91 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158j}$ ..................... 707 |
| Figure A3.92 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158k}$ ..................... 708 |
| Figure A3.93 | Infrared spectrum (Thin Film, NaCl) of compound $^{158k}$ ........... 709 |
| Figure A3.94 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158k}$ ..................... 709 |
| Figure A3.95 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158l}$ ..................... 710 |
| Figure A3.96 | Infrared spectrum (Thin Film, NaCl) of compound $^{158l}$ ........... 711 |
| Figure A3.97 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158l}$ ..................... 711 |
| Figure A3.98 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158m}$ ..................... 712 |
| Figure A3.99 | Infrared spectrum (Thin Film, NaCl) of compound $^{158m}$ ........... 713 |
| Figure A3.100 | $^{13}$C NMR (100 MHz, CDCl$_3$) of compound $^{158m}$ ..................... 713 |
| Figure A3.101 | $^{19}$F NMR (282 MHz, CDCl$_3$) of compound $^{158m}$ ............... 714 |
| Figure A3.102 | $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{158n}$ ..................... 715 |
| Figure A3.103 | Infrared spectrum (Thin Film, NaCl) of compound $^{158n}$ ........... 716 |
Figure A.104  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158n .................. 716

Figure A.105  

$^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158n ................. 717

Figure A.106  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 158o ................... 718

Figure A.107  

Infrared spectrum (Thin Film, NaCl) of compound 158o .......... 719

Figure A.108  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158o ................. 719

Figure A.109  

$^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158o ................ 720

Figure A.110  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 158p .................. 721

Figure A.111  

Infrared spectrum (Thin Film, NaCl) of compound 158p ......... 722

Figure A.112  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158p ............... 722

Figure A.113  

$^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158p ................ 723

Figure A.114  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 158q ............... 724

Figure A.115  

Infrared spectrum (Thin Film, NaCl) of compound 158q .......... 725

Figure A.116  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158q ............... 725

Figure A.117  

$^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158q ................ 726

Figure A.118  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165a ............... 727

Figure A.119  

Infrared spectrum (Thin Film, NaCl) of compound 165a .......... 728

Figure A.120  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165a ............... 728

Figure A.121  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165b ............... 729

Figure A.122  

Infrared spectrum (Thin Film, NaCl) of compound 165b .......... 730

Figure A.123  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165b ............... 730

Figure A.124  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165c ............... 731

Figure A.125  

Infrared spectrum (Thin Film, NaCl) of compound 165c .......... 732

Figure A.126  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165c ............... 732

Figure A.127  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165d ............... 733

Figure A.128  

Infrared spectrum (Thin Film, NaCl) of compound 165d .......... 734

Figure A.129  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165d ............... 734

Figure A.130  

$^1$H NMR (400 MHz, C$_6$D$_6$) of compound 165e ............... 735

Figure A.131  

Infrared spectrum (Thin Film, NaCl) of compound 165e .......... 736

Figure A.132  

$^{13}$C NMR (100 MHz, C$_6$D$_6$) of compound 165e ............... 736

Figure A.133  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165f ............... 737

Figure A.134  

Infrared spectrum (Thin Film, NaCl) of compound 165f .......... 738

Figure A.135  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165f ............... 738

Figure A.136  

$^1$H NMR (400 MHz, CDCl$_3$) of compound 165g ............... 739

Figure A.137  

Infrared spectrum (Thin Film, NaCl) of compound 165g .......... 740

Figure A.138  

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165g ............... 740

Figure A.139  

$^1$H NMR (400 MHz, CDCl$_3$) of compound L4.................. 741

Figure A.140  

Infrared spectrum (Thin Film, NaCl) of compound L4 ........... 742
Figure A3.141 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L4 ....................... 742
Figure A3.142 $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L4 .......................... 743
Figure A3.143 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L4 .......................... 743
Figure A3.144 $^1$H NMR (400 MHz, CDCl$_3$) of compound L5 .......................... 744
Figure A3.145 Infrared spectrum (Thin Film, NaCl) of compound L5 .................. 745
Figure A3.146 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L5 .......................... 745
Figure A3.147 $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L5 .......................... 746
Figure A3.148 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L5 .......................... 746
Figure A3.149 $^1$H NMR (400 MHz, CDCl$_3$) of compound L6 .......................... 747
Figure A3.150 Infrared spectrum (Thin Film, NaCl) of compound L6 .................. 748
Figure A3.151 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L6 .......................... 748
Figure A3.152 $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L6 .......................... 749
Figure A3.153 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L6 .......................... 749
Figure A3.154 $^1$H NMR (400 MHz, CDCl$_3$) of compound L7 .......................... 750
Figure A3.155 Infrared spectrum (Thin Film, NaCl) of compound L7 .................. 751
Figure A3.156 $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L7 .......................... 751
Figure A3.157 $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L7 .......................... 752
Figure A3.158 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L7 .......................... 752
LIST OF SCHEMES

CHAPTER 1
Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation of a C(sp$^3$)–C(sp$^3$) Cross-Coupling

- Scheme 1.1 Free energy network from resting state 3 through decarboxylation... 15
- Scheme 1.2 Relative energy of select η$^1$– and η$^3$–allyl intermediates 22
- Scheme 1.3 Various C–C bond forming pathways 30

CHAPTER 3
Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

- Scheme 3.1 Proposed divergent catalytic cycle 144

CHAPTER 4
Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

- Scheme 4.1 Photochemical [2+2] approach to scabrolide A 538
- Scheme 4.2 General four-step mechanism for the olefin/α,β-unsaturated carbonyl [2+2] photocycloaddition 550
- Scheme 4.3 Photoexcitation of 3_S0 and conversion to reactive triplet diradical 121$^3$(ππ*) 543
- Scheme 4.4 Eight lowest energy reaction pathways from 121$^3$(ππ*) 546
- Scheme 4.5 Predicted reactivity from diradical 126 550
- Scheme 4.6 Predicted reactivity from diradical 125 551
- Scheme 4.7 All four diastereomeric 5-exo-trig β-attack transition states and products 562
- Scheme 4.8 All four diastereomeric 4-exo-trig β-attack transition states and products 563
- Scheme 4.9 All diastereomeric products for 6-exo-trig α-attack (144–147), 6-endo-trig β-attack (148–149), 5-endo-trig β-attack (150–151), and 5-exo-trig α-attack (152–155) 564
Scheme 4.10 Conformational influence on outcome post-ISC .......................... 565
Scheme 4.11 PESs generated from single point calculations along the BS-DFT IRC trajectories of $^{126}$ to TS54 to $^{124}$ ................................................................. 568
Scheme 4.12 Comparison of performance in relaxed surface scan of ring closure of diradical $^{126}$ to form observed but undesired product $^{124}$ of various DFT functionals with respect to NEVPT2 ............................................ 570
Scheme 4.12 Comparison of performance in relaxed surface scan of ring closure of diradical $^{125}$ to form observed but undesired product $^{120}$ of various DFT functionals with respect to NEVPT2 ............................................ 571
Scheme 4.12 Comparison of performance in relaxed surface scan of ring closure of diradical $^{125}$ to form observed but undesired product $^{120}$ of various DFT functionals with respect to NEVPT2 ............................................ 571
LIST OF TABLES

CHAPTER 1
Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation of a C(sp^3)–C(sp^3) Cross-Coupling

Table 1.1 Qualitative comparison of relative free energy barrier heights along reductive elimination pathways ........................................... 35
Table 1.2 Comparison of geometric parameters obtained from geometry optimization with various functionals and basis sets .................. 50
Table 1.3 Decarboxylation barrier heights with geometries optimized in gas phase and with CPCM(THF) ......................................................... 52
Table 1.4 Decarboxylation barrier heights of complexes derived from the (R) enantiomer of 1 ........................................................................... 53
Table 1.5 Comparison of relative free energies obtained across a variety of density functional methods ..................................................... 54
Table 1.6 Comparison of relative free energies obtained at the DLPNO-CCSD(T) level of theory ................................................................. 56
Table 1.7 Optimization without D3 corrections (BP86) ............................... 56
Table 1.8 Optimization with B3LYP-D3 .................................................. 57
Table 1.9 Relative free energies (in kcal/mol) of isomeric oxidative addition transition states at various levels of theory ...................... 59
Table 1.10 Comparison of barrier heights to decarboxylation with the standard (S)-t-BuPHOX and electron poor (S)-(CF_3)_3-t-BuPHOX ligands ... 61
Table 1.11 Inner-sphere reductive elimination transition states with α-phenyl substrate ................................................................. 61

CHAPTER 2
Analysis of the Pd [π2s + π2s + σ2s + σ2s] Pericyclic Reaction

Table 2.1 Calculation of spin exchange coupling constant (J) between spin centers in 1,4-diradical 30 ......................................................... 119
Table 2.2 TD-DFT vertical excitations at stationary points 13, TS20, and 19 ... 123
CHAPTER 3
Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

Table 3.1 Optimization of [4+2] reaction conditions ........................................... 142
Table 3.2 Substrate scope of the [4+2] reaction ....................................................... 145

CHAPTER 4
Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (–)-Scabrolide A

Table 4.1 Comparison of vertical excitation energies calculated at the 121_S0 with various state-averaging schemes................................................................. 560
Table 4.2 Free energy barriers to C–C bond formation/cleavage from 126........................ 567
Table 4.3 Partitioning of five lowest-energy conformers of singlet diradical 126 between four outcomes based on picosecond-scale AIMD calculations ................................................................. 572
Table 4.4 Partitioning of five lowest-energy conformers of singlet diradical 125 between four outcomes based on picosecond-scale AIMD calculations ................................................................. 573
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation at wavelength of sodium D line</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>$\text{tert-}$-butyloxy carbonyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>$c$</td>
<td>concentration for specific rotation measurements</td>
</tr>
<tr>
<td>calc’d</td>
<td>calculated</td>
</tr>
<tr>
<td>cm$^{-1}$</td>
<td>wavenumber(s)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>D</td>
<td>deuterium</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>$ee$</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
</tbody>
</table>
ESI  electrospray ionization
Et   ethyl
EtOAc ethyl acetate
G    grams
GC   gas chromatography
h    hours
HPLC high-performance liquid chromatography
HRMS high-resolution mass spectrometry
Hz   hertz
IPA  isopropanol
IR   infrared (spectroscopy)
J    coupling constant (NMR), exchange coupling constant (diradicals)
K    Kelvin (absolute temperature)
kecal kilocalorie
KHMDS potassium hexamethyldisilazide
L    liter; ligand
LDA  lithium diisopropylamide
m/z  mass to charge ratio
Me   methyl
mg   milligram(s)
MHz  megahertz
min  minutes
mol  mole(s)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$-Bu</td>
<td>$n$-butyl</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PHOX</td>
<td>phosphinooxazoline (ligand)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>R</td>
<td>generic for any atom or functional groups</td>
</tr>
<tr>
<td>SCF</td>
<td>self-consistent field</td>
</tr>
<tr>
<td>SFC</td>
<td>supercritical fluid chromatography</td>
</tr>
</tbody>
</table>
CHAPTER 1

Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

1.1 INTRODUCTION

The construction of chiral all-carbon quaternary centers remains a forefront challenge in synthetic chemistry.\(^1\) Over the years, our group has pursued the development of the decarboxylative asymmetric allylic alkylation reaction as a practical entry into these highly sought-after structural motifs (Figure 1.1A).\(^2\) This approach has proved fruitful in asymmetric synthesis,\(^3\) particularly in the early-stage preparation of chiral building blocks. However, our efforts to further extend the scope of these transformations have highlighted limitations of the current catalytic systems.\(^4\) We recognize that a comprehensive mechanistic understanding is crucial in our ability to address these shortcomings and to realize general improvements. Owing to the interplay of several plausible inner- and outer-sphere processes (Figure 1.1B), the unification of a comprehensive, stereochemically complete mechanistic hypothesis has remained elusive for the Pd(PHOX) system. Determination of inner- or outer-sphere nucleophilic attack through observation of retention (outer-sphere) or inversion (inner-sphere) of stereochemistry when employing chiral cyclic allyl electrophiles is not applicable as such substitution patterns are not

\(^{†}\)This research was performed under the co-advisory of Prof. William A. Goddard III. Portions of this chapter have been reproduced with permission from Cusumano, A. Q.; Stoltz, B. M.; Goddard, W. A. III. J. Am. Chem. Soc. 2020, 142, 13917–13933. © 2020 American Chemical Society.
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

tolerated by the system at hand. Surprisingly, allylic alkylation with the Pd(PHOX) system demonstrates remarkable tolerance to exogenous water, with reaction yields and enantioselectivity largely unaffected. These results suggest that the presence of an unbound enolate with a conjugate acid pKₐ significantly higher than that of water is unlikely. Given the tolerance to water, an inner-sphere mechanism for C–C bond formation is generally invoked for the Pd(PHOX) system.

Figure 1.1. (A) Original report of the decarboxylative asymmetric allylic alkylation of \( \beta \)-ketoesters by Stoltz.\textsuperscript{2a} (B) Inner- and outer-sphere allylic alkylation. (C) Isolation of the catalyst resting state.\textsuperscript{5} (D) This research.

A. Allylic alkylation of \( \beta \)-ketoesters to forge chiral all-carbon quaternary centers:\textsuperscript{2a}

B. Outer- versus inner-sphere allylic alkylation.

C. Mechanistic Developments.\textsuperscript{5}

D. This research.
In contrast, mechanistic studies by Trost and coworkers with the bis-phosphine \((R,R)\)-ANDEN-phenyl ligand on related substrates suggest alkylation occurs via an outer-sphere mechanism.\(^6\) As anticipated with an ionic outer-sphere mechanism, highly charge stabilized “soft” enolates perform well in these systems.\(^7\) Unlike the outer-sphere conditions of Trost, the Pd(PHOX) catalytic manifold provides low levels of enantioselectivity with stabilized enolate nucleophiles,\(^4,8\) yet the Pd(PHOX) system excels with basic “hard” enolates, as well as substrates that contain heteroatoms.\(^9\)

Key to the inner-sphere C–C bond formation hypothesis is the intermediacy of a square planar C- or O-bound Pd\(^{\text{II}}\) enolate complex. In our efforts to directly observe such a species, our group isolated a unique \(\eta^1\)-allyl Pd\(^{\text{II}}\) carboxylate complex \((3)\) from the reaction of Pd\(_2\)(dba)\(_3\), \((S)\)-t-BuPHOX, and \(\beta\)-ketoester \(1\) (Figure 1.1C). The carboxylate complex was determined to be the catalyst resting state, with decarboxylation as the rate-limiting process \((k = 1.58 \times 10^{-3} \text{ s}^{-1} \text{ at } 24 \degree \text{C}, \text{corresponding to a free energy barrier of } 21.2 \text{ kcal/mol})\).\(^5\)

In addition to experimental studies, our groups have turned to quantum mechanics (QM) calculations as a powerful tool to interrogate the mechanism of the stereoablative transformation of \((\pm)-1\) to \((S)-2\).\(^{10}\) These investigations focused on post-decarboxylation intermediates, and ultimately led to the discovery of a low energy pathway for inner-sphere C–C bond formation via a seven-centered cyclic reductive elimination transition state (Figure 1.1D). Analogous fully carbocyclic mechanisms have been proposed by Morken and Echavarren.\(^{11}\) While these initial studies offer an invaluable knowledge base, the
mechanism of decarboxylation and the precise origins of enantioinduction remained unclear. To address these questions, we returned to computational and experimental studies. During our group’s ongoing efforts to explore the mechanism, Sargent and coworkers reported an all-DFT-based investigation of the Pd(PHOX)-catalyzed transformation of 1 to 2. Unfortunately, the computationally-derived barrier to decarboxylation was significantly less than that of experiment, with the rate-limiting step as an isomerization to a pre-decarboxylation intermediate. Nevertheless, other aspects of their study regarding decarboxylation and C–C bond formation corroborate our computational and experimental findings herein. Taken together, these studies bring an unprecedented level of clarity to the mechanism of the decarboxylative asymmetric allylic alkylation reaction.

Herein, we outline a detailed QM investigation into each step of the reaction mechanism: oxidative addition, decarboxylation, and C–C bond formation, revealing a mechanistic picture that unites all current experimental observations, including enantioinduction, reaction rate, identity of the catalyst resting state, enolate cross-over, water tolerance, and solvent effects on the interplay between inner- and outer-sphere pathways in the PHOX system (Figure 1.1D). To provide useful insight into factors underlying enantiomeric selectivity, very high quantum mechanical accuracy is required. Given this, we use this study as an opportunity to compare the efficacy of various modern computational methods (density functional theory and localized coupled-cluster theory) in the context of asymmetric Pd⁰/PdII catalysis. Further experiments are carried out to explore the mechanistic hypotheses derived from the ab initio calculations. Lastly, we address the
shortcomings of the present state-of-the-art catalyst systems and offer theory-based insight into future development.

1.2 COMPUTATIONAL METHODS

Density functional theory (DFT) geometry optimizations, energy, vibrational frequency, and coupled-cluster calculations were performed using Orca version 4.1.2.13 Geometry optimizations were carried out with the BP86 generalized gradient approximation (GGA) functional14 with Becke-Johnson damped D3 dispersion corrections (herein referred to as D3).15 A mixed basis set was implemented, in which Pd is described by the small core LANL2TZ(f) basis set with the Hay–Wadt effective core potential (ECP),16 while the 6-31G(d) basis set was used on all other atoms. Key structures were optimized at various levels of theory and compared to crystallographic data to ensure that consistent results are obtained across multiple methodologies (see 1.5 Supporting Information for details).

Triple-ζ quality single point calculations were carried out on all stationary points with a variety of density functionals, including BP86-D3,14 B3LYP-D3,17 PBE0-D3,18 M06,19 and DSD-BLYP-D320 with the def2-TZVP basis set21 on all atoms (including the small core ECP28MWB pseudopotential22 on Pd). Corrections for solvation (THF or otherwise as specified) were carried out for single point calculations with the implicit Conductor-like Polarizable Continuum Model (CPCM).23 Unless otherwise noted, all energies reported are G$_{298}^\circ$ values from single point calculations at the M06/def2-TZVP/CPCM(THF) level of theory on BP86-D3/LANL2TZ(f)–6-31G(d) optimized
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

geometries with thermodynamic corrections applied from frequency calculations obtained at the optimization level of theory. The Quasi-RRHO method is applied to correct for the breakdown of the harmonic oscillator approximation for low frequency vibrations. All stationary points are characterized by the appropriate number of imaginary vibrational modes (zero for optimized geometries and one for transition states). Intrinsic reaction coordinate (IRC) analyses were carried out to ensure all transition states connect the appropriate starting materials and products. Molecular illustrations were made from CLYview.

Additional single point calculations were performed on all optimized structures with the domain based local pair natural orbital coupled-cluster (DLPNO-CCSD(T), “NormalPNO” settings unless otherwise noted) method as described by Neese and coworkers and as implemented in Orca (further details included in Supporting Information). The cc-pVTZ basis set is used on all atoms in the DLPNO-CCSD(T) calculations, with the SK-MCDHF-RSC effective core potential on Pd. Throughout the text, free energies calculated from electronic energies at the DLPNO-CCSD(T)/cc-pVTZ/CPCM(THF) level of theory are provided in brackets next to the DFT (M06/CPCM(THF)) values for comparison.

1.3 RESULTS

Our investigation began with the experimental observation of the [(PHOX)Pd(η^1-allyl)(RCO_2)] complex (3) as the resting state of the catalyst (Figure 1.2). The structure of this unusual η^1–allyl complex was previously confirmed by X-ray crystallography while
the solution phase behavior was studied by NMR spectroscopy. Importantly, 3 is competent in the reaction, and affords the ketone product 2 from β-ketoester 1 in similar yield and enantioselectivity to that obtained from the catalytic transformation. Kinetic studies revealed first order rate dependence of this process in 3 with an overall rate constant measured to be 1.58 x 10^{-3} s^{-1} (at 24 ºC in THF-d8). Given that loss of CO₂ is the rate limiting step, the experimental ΔG‡ of decarboxylation is calculated to be 21.2 kcal/mol.

1.3.1 OXIDATIVE ADDITION

To better understand the role of the catalyst resting state (3) in the overall mechanistic picture, we first sought to examine the mechanism of oxidative addition of allyl β-ketoester 1 to the Pd⁰(PHOX) precatalyst. Oxidative addition of allyl acetate to Pd⁰ complexes is generally represented as directly generating the [LₙPd(η³-allyl)](OAc) ion pair in situ in a reversible fashion. This prompted us to question whether oxidative addition proceeds through a unique mechanism in which 3 is yielded directly, or if an analogous [(PHOX)Pd(η³-allyl)]⁺(RCO₂⁻) ion pair (4) is first formed followed by rapid equilibration to 3 (Figure 1.2A).

While the stereoablative transformation employs racemic substrate (1), the chiral center is not directly involved but rather appended to the site of oxidative addition through freely rotatable bonds. Hence, we expect comparable energies of the diastereomeric transition states arising from both enantiomers of 1. Our initial explorations considered the (S) enantiomer of 1, but the relevant oxidative addition pathways were also evaluated for
(R)-1. A similar consideration is employed with regard to the orientation of the allyl fragment in the \( \eta^3 \)–bound form. Here, the prefix *endo* describes the \( \eta^3 \)–(allyl) conformer in which the apical carbon (*i.e.*, C2) of the allyl group is *cis* to the \( t \)-Bu group of the PHOX ligand, and *exo* corresponds to the *trans* isomer. Experimentally the *endo* and *exo* isomers were found to be nearly identical in energy. Both *endo* and *exo* geometries will be considered. Unless otherwise stated, free energy comparisons are from the lowest energy conformer.

**Figure 1.2.** (A) Four general classes of Pd\(^0\) allyl carboxylate oxidative addition mechanisms (B) Stereoretentive three-centered (TS1), seven-centered (TS2), and syn \( S_N2' \)-like (TS3) transition states.\(^a\)

---

\[ \begin{array}{l}
\text{A. Oxidative addition mechanisms considered.} \\
\text{Resting state} \\
\text{3-coordinate (TS1) or pericyclic (TS2)} \\
\text{S_N2'-like (TS3) or S_N2'-like (TS4)} \\
\end{array} \]

\[ \begin{array}{l}
\text{TS1} \quad \Delta G^\ddagger = 56.1 \ [63.2] \\
\text{TS2} \quad \Delta G^\ddagger = 26.9 \ [31.6] \\
\text{TS3} \quad \Delta G^\ddagger = 21.6 \ [22.1] \\
\end{array} \]

\[ \begin{array}{l}
\text{Stereoretentive mechanisms not operative} \\
\end{array} \]

---

\[ \begin{array}{l}
\text{B. Stereoretantive mechanisms (TS1–TS3).} \\
\end{array} \]

---

\[ \begin{array}{l}
[a] \text{ Relative Gibbs free energies in kcal/mol (M06). Free energies derived from DLPNO-CCSD(T) calculations in brackets.} \\
\end{array} \]
Starting from olefin-bound Pd$^0$(PHOX) complex 5, a variety of transition states that achieve C–O bond cleavage were considered (Figure 1.2A). Three- (TS1)$^{29,30}$ and seven-membered (TS2) cyclic transition states,$^{31}$ as well as a $\text{syn}$ conjugate displacement-type mechanism (TS3) afford barrier heights greater than that of the rate-limiting step ($\Delta G^\ddagger = 21.2$ kcal/mol) (Figure 1.2B).$^5$

**Figure 1.3.** Isomeric transition states for the anti displacement-type oxidative addition mechanisms.$^a$

\[ \begin{align*}
(t-N): & 0.0 [0.0] \\
(t-N)-TS: & 6.4 [4.8] \\
(t-P): & 0.1 [0.7] \\
(t-P)-TS: & 12.6 [11.2]
\end{align*} \]

$^a$ Relative Gibbs free energies in kcal/mol (M06). Free energies derived from DLPNO-CCSD(T) calculations in brackets. Endo $\eta^1$-allyl 4 is 0.3 [0.4] kcal/mol higher in energy than its exo isomer depicted above.

Analogous to TS3, an anti displacement-type mechanism (TS4) via electrophilic addition to Pd$^0$ presents a substantially lower barrier than that of the other pathways
considered (Figure 1.3). Unlike TS3, in which C–O bond breaking occurs through the filling of $\sigma^*(C–O)$ by the olefin-based $\pi(C–C)$ orbital, TS4 achieves the same overall result with direct overlap between $\sigma^*(C–O)$ and the Pd d($x^2–y^2$)-based HOMO.

Isomeric transition states are possible, in which the displacement event occurs trans to either the nitrogen or phosphorus of the PHOX ligand. The abbreviations t-N and t-P refer to C–O bond breaking occurring trans to N and trans to P, respectively. Here, we assume free equilibration between the isomers of 5. Therefore, we consider the apparent barrier height to be that of the lowest energy transition state from the lowest energy isomer (t-N)-5.

From the corresponding olefin-bound Pd precursors (5), we found a barrier height of 12.6 [11.2] kcal/mol for (t-P)-TS4. Interestingly, considerably lower energy pathways were obtained for displacements trans to nitrogen, with a barrier of 6.4 [4.8] kcal/mol for (t-N)-TS4. A similar energetic preference for displacement trans to nitrogen is observed across several DFT methods. Oxidative addition via these mechanisms leads directly to ion pair 4. Additionally, as anticipated by experiment, the energy of endo and exo isomers of 4 were found to be nearly identical, with the exo-isomer favored by 0.3 [0.4] kcal/mol. Henceforth, reference to TS4 will specifically refer to the lowest energy isomer, (t-N)-TS4.

In summary, of the oxidative addition pathways considered, olefin binding, followed by anti displacement (TS4) affords the lowest barrier height by a considerable margin. The displacement is stereospecific to inversion of chirality with respect to that of the leaving group, whereas the pathways involving a three-centered transition state (TS1),
a seven-membered pericyclic transition state (TS2), or a syn conjugate displacement (TS3) would be anticipated to retain the configuration of the carboxylate leaving group (when substitution is present on the allyl terminus). We emphasize that consideration of each mechanistic pathway is crucial in order to reliably interpret net inversion/retention of stereochemistry as a general mechanistic probe in the Tsuji–Trost reaction.\textsuperscript{32}

Furthermore, the two lowest energy pathways (direct/anti and conjugate/syn displacement) directly afford ion pair 4 rather than 3 as the product of oxidative addition. These results suggest that the observed $\eta^1$–allyl catalyst resting state (3) is not the direct product of oxidative addition but is generated through a subsequent equilibration from ion pair 4. Curious as to the magnitude of the difference in energy between $\eta^1$–allyl 3 and ion pair 4, we compared the calculated free energies of the two isomeric complexes. In accord with experiment, $\text{[(PHOX)Pd}(\eta^1$–allyl)(RCO$_2$)] (3) is computed to be favored over the $\text{[(PHOX)Pd}(\eta^3$–allyl)]$^+$‌(RCO$_2^-$) ion pair (4) by 5.4 kcal/mol (Figure 1.4). Single point calculations with several other density functionals give rise to similar results ($\Delta G =$ 4.6 to 9.3 kcal/mol), showing that this outcome is not an artifact of the DFT functional. In agreement with the DFT values, a difference in free energy of 5.2 kcal/mol favoring 3 over 4 is obtained at the DLPNO-CCSD(T) level of theory and is taken to be our reference value.

Interestingly, this trend appears not to be due to an extraneous effect of the $\beta$-ketocarboxylate leaving group, but rather a general feature of the Pd(PHOX) system with allyl acetates. Control experiments have been previously reported by our group in which the allyl $\beta$-ketoester was replaced with allyl acetate to similar effect.\textsuperscript{5} The corresponding
[(PHOX)Pd(η^1–allyl)(OAc)] complex (6) was isolated and characterized by X-ray crystallography and solution-phase NMR spectroscopy. Accordingly, the difference in free energies between 6 and ion pair 7 was calculated to be 6.6 [6.0] kcal/mol, favoring the η^1–allyl form (Figure 1.4).

Figure 1.4. Relative free energies of constitutional isomers of η^1– and η^3–allyl Pd complexes from masked enolate synthons, and acetate for comparison.^[a]

<table>
<thead>
<tr>
<th>β-ketoesters</th>
<th>acetates</th>
<th>enol carbonates</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /> 3 0.0 [0.0]</td>
<td><img src="image" alt="Diagram" /> 4 5.4 [5.2]</td>
<td><img src="image" alt="Diagram" /> 5 9.7 [9.7]</td>
</tr>
<tr>
<td><img src="image" alt="Diagram" /> 6 0.0 [0.0]</td>
<td><img src="image" alt="Diagram" /> 7 6.6 [6.0]</td>
<td><img src="image" alt="Diagram" /> 8 9.7 [9.7]</td>
</tr>
<tr>
<td><img src="image" alt="Diagram" /> 9 10.3 [12.2]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Relative Gibbs free energies in kcal/mol (M06). Free energies derived from DLPNO-CCSD(T) calculations in brackets.

We then sought to explore these trends for the allyl enol carbonate substrate class,^[2b] for which a crystal structure of the catalyst resting state has yet to be obtained. As with the β-ketocarboxylates, the corresponding η^1–allyl carbonate complex (8) was predicted to be favored over the η^3–allyl carbonate ion pair (9) (Figure 1.4). Calculations with the M06 density functional predict a 0.6 kcal/mol preference for the η^1-allyl form, while DLPNO-CCSD(T) theory refines the energy difference to 2.5 kcal/mol, still favoring the η^1–allyl form. Accordingly, ^31^P NMR studies suggest the catalyst resting state may be an analogous η^1–allyl complex.^[5] Taking experimental and theoretical results into account, we anticipate
that the η¹–allyl form similarly dominates the solution phase character of the catalyst resting state.

Complexes 3, 4, 8, and 9, are constitutional isomers. Since the subsequent reaction yields identical Pd enolate intermediates, we note that the enol carbonate substrate is predicted to undergo a more exergonic reaction than the β-ketocarboxylate isomer by ca. 10 kcal/mol. While investigation into the mechanism of decarboxylation of the enol carbonates 8/9 lies outside the scope of this investigation, we postulate the following: If the resting state of the catalyst in the enol carbonate system is described by 8/9 (analogous to the carboxylates), and if the absolute energy of the barrier to decarboxylation is similar to that of 3, then a significantly higher reaction rate is anticipated. We therefore wish to highlight the design of the enolate synthon as one avenue by which future improvements to the reaction rate may be achieved.

1.3.2 DECARBOXYLATION

We then sought to explore the mechanism through which decarboxylation occurs. Loss of CO₂ was experimentally determined to be the rate-limiting step of catalyst turnover. Deriving inspiration from the canonical decarboxylation of β-ketocarboxylic acids, we explored analogous cases for a PdⅡ β-ketocarboxylate (Figure 1.5). Two isomeric square pyramidal transition states may be envisioned: one in which the carboxylate group is apically bound to Pd (TS5), and another with an equatorially bound carboxylate (TS6). Alternatively, decarboxylation could occur through a Zwitterionic square planar complex wherein the ketone of the β-ketocarboxylate is coordinated to η¹–allyl Pd (TS14) or the
analogous \( \eta^1 \)-allyl case (TS15). As noted previously, the minimum energy pathway through oxidative addition directly affords ion pair 4, rather than the catalyst resting state 3. To explore the interconnectivity between these intermediates, as well as our postulated decarboxylative pathways, we constructed the free energy network depicted in Scheme 1.1.

Beginning from the product of oxidative addition, ion pair 4, the catalyst resting state (3) can be reached via square pyramidal intermediate 11 (a higher energy conformer of 3) with an overall effective barrier of 4.3 [5.0] kcal/mol and \( \Delta G \) of \(-5.4 \) [\(-5.2\)] kcal/mol (Scheme 1.1).

**Figure 1.5.** (A) Experimentally-derived parameters for decarboxylation. (B) Decarboxylation pathways considered.

**A. Experimental rate and corresponding barrier for rate-limiting decarboxylation.**

**B. Possible decarboxylation mechanisms.**
Scheme 1.1. Free energy network from resting state 3 to decarboxylation pathways.\(^{a}\)

\[\text{Resting state} \xrightarrow{TS9} 10: 16.1 [16.9] \xrightarrow{TS5} (Si)-13: 0.6 [5.4]\]

\[\text{Pathway 1} \]

\[\text{Pathway 2} \]

\[\text{Pathway 3} \]

\[\text{Pathway 4} \]

[a] Free energies in kcal/mol (M06) with energies derived from DLPNO-CCSD(T) calculations in brackets. Minimum energy pathways through decarboxylation colored with higher energy alternatives in grey. Lowest energy conformers depicted.

We then turned our attention to decarboxylation. Transition states TS5 and TS6 require the square pyramidal precursors 10 and 11, respectively (Scheme 1.1). Sufficiently low energy pathways connecting the resting state (3) to 10 and 11 are found. Decarboxylation is observed only through transition states in which the carboxylate group is poised axially on the six-membered ring, whether it be in a boat ((boat)-TS5) or chair ((chair)-TS5). This may result from the C–CO$_2^-$ $\sigma$ orbital experiencing enhanced overlap.
with the $\pi^*$ of the ketone when occupying an axial position. While the chair conformers dominate the equilibrium geometries of 10, both M06 and DLPNO-CCSD(T) methods predict decarboxylation through (boat)-TS5 to be lower in energy than (chair)-TS5 by 1.8 and 2.8 kcal/mol, respectively. An apparent $\Delta G^\ddagger$ value of 22.0 [26.8] kcal/mol is calculated from resting state 3 to TS5. We will henceforth refer to this sequence as decarboxylative pathway 1.

While the barrier to decarboxylation via TS5 is quite low with respect to 10 (5.9 [9.9] kcal/mol), decarboxylation directly from 11 (via TS6) is not observed. This result is not unexpected, since weak axial binding is generally observed in square planar d$^8$ complexes (in the absence of $\pi$ back bonding) by virtue of the filled, axially-oriented metal-based d($z^2$) orbital, here of slight Pd–O $\sigma^*$ character. Considering the role of the Pd$^{II}$ center as a Lewis acid in promoting the decarboxylation, the weak axial binding of the ketone carbonyl in 11 to the metal center results in a complex that is poorly predisposed to decarboxylation. Furthermore, the LUMO of the square planar/square pyramidal d$^8$ complexes are largely of metal-based d($x^2$–$y^2$) character. As such, compared to 11, the equatorially-bound carbonyl of 10 exhibits greater overlap with the Pd-based LUMO, allowing for more effective charge transfer to the electropositive metal center. This, combined with the greater positive partial charge of the Pd center in 10 due to the weakly bound axial carboxylate counterion, results in facile decarboxylation.

Analogous to the highly charge-separated cyclic form of 10, we were intrigued to find an acyclic variant, 12, as a stable intermediate on the potential energy surface.
Calculations reveal 12 equilibrates with resting state 3 via TS11–11–TS12–4–TS13 (Scheme 1.1). The highest barrier is that of TS13 at 14.0 [16.3] kcal/mol, with 12 at 12.7 [15.9] kcal/mol higher in energy than 3. As with 10, decarboxylation from 12 may then occur with the carboxylate oriented axially in either a chair or boat conformer, with the chair being lowest in energy (TS14). From 12, a barrier height of 4.4 [6.1] kcal/mol through TS14 is found. With respect to resting state 3, the overall barrier to decarboxylation through this pathway is 17.1 [22.0] kcal/mol. As with TS5, decarboxylation through this route directly affords the η1–allyl O–bound Pd enolate (Re)-13 (a rotamer of (Si)-13). We will henceforth denote this sequence as decarboxylative pathway 2.

We next envisioned the possibility for decarboxylation to occur directly from the [η3–(allyl)Pd(PHOX)]+(RCO2-) ion pair, 4. We will term this sequence decarboxylative pathway 3. In pathway 3, the overall barrier height through decarboxylation was found to be 17.5 [23.2] kcal/mol via the lowest energy conformer of TS15. Dissimilar to pathways 1 and 2, pathway 3 does not lead directly to (Re/Si)-13 but rather the η3–allyl isomer 14. The relevance of this detail becomes apparent below in the free energy networks through which C–C bond forming occurs (Scheme 1.3).

Loss of CO2 is the overall rate determining step for pathways 1, 2, and 3. Of the three, we found pathway 2 to have the lowest barrier at 17.1 [22.0] kcal/mol; however, pathway 3 is comparable in energy, with a barrier height of 17.5 [23.2] kcal/mol, and the difference between these pathways is likely within the accuracy of DFT. Single point calculations with B3LYP-D3, PBE0-D3 and DSD-BLYP-D3 favor TS14 by 5.0, 2.0, and
0.4 kcal/mol, respectively. Moreover, DLPNO-CCSD(T) calculations favor TS14 by 1.2 kcal/mol. Thus, we suggest an energetic preference for pathway 2. However, both pathways 2 and 3 remain mechanistically relevant under the reaction conditions.

As previously mentioned, NMR experiments determined the rate constant of decarboxylation of isolated 3 to be $1.58 \times 10^{-3}$ s$^{-1}$ at 24 ºC, corresponding to $\Delta G^\ddagger$ of 21.2 kcal/mol, which is consistent with the observed reaction time of a few hours. This experimental data affords an opportunity to compare the computational methods utilized in this study. Interestingly, all density functionals employed predict lower barriers than that of experiment. The most accurate values are obtained with the global hybrid PBE0-D3 and the spin-component-scaled double-hybrid DSD-BLYP-D3, with calculated barriers of 20.2 kcal/mol and 18.6 kcal/mol, respectively. The popular B3LYP-D3 density functional affords the least accurate $\Delta G^\ddagger$ of 16.5 kcal/mol. With a barrier of 17.1 kcal/mol, M06 also overestimates the rate of decarboxylation. High-quality coupled-cluster calculations with DLPNO-CCSD(T) provide an accurate barrier height of 22.0 kcal/mol, within 1.0 kcal/mol of experiment. Employing “TightPNO” cutoff criteria refines this value to 21.9 kcal/mol.

Since the dipole moment of TS15 (19.7 D) is large compared to that of TS5 (12.2 D) and TS14 (13.6 D) (with M06/CPCM(THF)) we investigated the effect of solvation on the relative free energy barriers of the three pathways. Experimentally, high yields and enantioselectivities are observed across a variety of non-polar aprotic solvents, while yields and enantioselectivities diminish in polar, aprotic solvents.
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 19 Comprehensive Quantum Mechanics Investigation

Figure 1.6. Structures of rate-limiting transition states for decarboxylation pathways 1–3 and apparent barriers as a qualitative function of solvation.

<table>
<thead>
<tr>
<th></th>
<th>Toluene (ε = 2.4)</th>
<th>Et₂O (ε = 4.3)</th>
<th>THF (ε = 7.3)</th>
<th>DMF (ε = 38.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS14</td>
<td>15.4</td>
<td>16.5</td>
<td>17.1</td>
<td>17.9</td>
</tr>
<tr>
<td>TS15</td>
<td>19.6</td>
<td>18.3</td>
<td>17.5</td>
<td>16.6</td>
</tr>
<tr>
<td>TS15</td>
<td>21.9</td>
<td>22.0</td>
<td>22.0</td>
<td>22.0</td>
</tr>
<tr>
<td>TS16</td>
<td>–</td>
<td>–</td>
<td>20.3b</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] Apparent barriers to decarboxylation (ΔG‡ from 3). Free energies reported in kcal/mol, calculated with M06/def2-TZVP/CPCM(solvent) on gas phase geometries. [b] With respect to the corresponding β-ketoacid (16-H).

Our initial efforts to assess solvent dependence focused on solvent effects from single point calculations using the implicit Conductor-like Polarizable Continuum Model (CPCM) for geometries optimized in the gas phase. As stated above, we found net barrier heights of 17.1, 17.5, and 22.0 kcal/mol in THF (ε = 7.3) for decarboxylation pathways 2, 3, and 1, respectively. Control computation experiments were carried out in which
optimizations of select intermediates were additionally carried out in THF (see 1.5 Supporting Information), yielding similar results but with an even greater preference for pathway 2.

In addition to THF ($\varepsilon = 7.3$), we compared the barrier heights of the three decarboxylative pathways in the less polar solvents toluene ($\varepsilon = 2.4$) and diethyl ether ($\varepsilon = 4.3$), along with the more polar DMF ($\varepsilon = 38.3$). A clear trend arises in which a continuum with a reduced charge permittivity ($\varepsilon < 8$) favors pathway 2 ($\text{TS14}$), while pathway 3 ($\text{TS15}$) is preferred in solvents with higher dielectric constants ($\varepsilon > 8$) (Figure 1.6).

Specifically, $\text{TS14}$ is 4.2 kcal/mol lower in energy than $\text{TS15}$ in toluene, compared to a $\Delta\Delta G^\ddagger$ of 1.8 and 0.4 kcal/mol (favoring $\text{TS14}$) in Et$_2$O and THF, respectively. In DMF, pathway 3 is predicted to be most favorable, with $\text{TS15}$ 1.3 kcal/mol lower in energy than $\text{TS14}$. Furthermore, we found these trends to be a result of the simultaneous lowering of the barrier of $\text{TS14}$ and raising that of $\text{TS15}$ with decreasing solvent polarity. For example, $\Delta G^\ddagger$ of decarboxylation through $\text{TS14}$ with M06/def2-TZVP/CPCM(toluene) was found to be 15.4 kcal/mol, compared to 17.1 kcal/mol in THF. Meanwhile, the barrier height to $\text{TS15}$ is 19.6 kcal/mol in toluene, compared to 17.5 kcal/mol in THF. In conclusion, less polar solvents afford greater selectivity for pathway 2 while lowering the overall barrier height to decarboxylation through this pathway.

Since the polarizable continuum implicit solvation model considers electrostatics as the sole component of solute-solvent interaction, it may be inadequate to quantitatively capture all effects in the experimental solvent variations – particularly when comparing
solute with very different cavities. We expect the general trends to remain qualitatively consistent with these findings, and thus, valuable for considerations in future reaction development. Recently, a new CPCM model was developed and implemented in ORCA (versions 5 and above) that employs a polarization charge density made of spherical Gaussians, rather than point charges, spread over the surface of the solute cavity resulting in a smoother potential. For future investigations, we recommend the use of this improved Gaussian charge scheme (GCS) for geometry optimization and single-point energy evaluation.

As racemic allyl β-ketoester 1 is employed in the stereoablative transformation, we carried out an analogous investigation from the other diastereomer of 3, derived for the (R)-1. A qualitatively similar situation is encountered (see 1.5 Supporting Information).

Previous mechanistic studies found both the reaction yield and product enantioenrichment to be tolerant of super-stoichiometric equivalencies of water. This result formed the basis of evidence for an inner-sphere mechanism. Additionally, crossover experiments with deuterium labeling of both the allyl fragment and enolate were performed. Since nearly equal quantities of the crossed products were observed, the involvement of an outer-sphere mechanism in which a solvated free enolate is indifferent to attacking either the labeled or unlabeled η3-allyl complexes may be considered but is inconsistent with the water-stability of the system. These results may also be accommodated within the inner-sphere mechanistic hypothesis as well when considering the carboxylate/carbonate intermediates are sufficiently stable to undergo exchange prior to decarboxylation.
Scheme 1.2. Relative energy of select $\eta^1$- and $\eta^3$-allyl intermediates.$^{a}$

\[
\begin{array}{ccc}
3: 0.0 [0.0] & \underset{\text{\textbullet}}{\text{\textbullet}} & 4: 5.4 [5.2] \\
15 + 16: 6.2 [9.6]
\end{array}
\]

\[a\] Relative Gibbs free energies in kcal/mol (M06). Free energies derived from DLPNO-CCSD(T) calculations in brackets.

For the $\beta$-ketocarboxylate intermediate, this mechanism appears to take place. Comparing the difference in free energy between ion pair 4 and solvent separated ions 15 and 16, it is reasonable that free exchange between the carboxylate anion and Pd cation may occur at a rate superseding that of decarboxylation (Scheme 1.2). Both inner and outer-sphere mechanisms may thus accommodate the results of the crossover experiments. Therefore, under these conditions, the observation of enolate/allyl electrophile crossover is irrelevant to differentiation between the two mechanistic pathways.

With regard to water tolerance, we compared the barrier heights to decarboxylation for the conjugate acid of $\beta$-ketocarboxylate 16 ($16-H$) via the canonical six-membered cyclic transition state to those of the Pd-catalyzed pathways mentioned above. With $\Delta G^\ddagger = 20.3$ [26.1] kcal/mol for TS16, the lowest apparent barriers to decarboxylation remain those involving the Pd catalyst (pathways 2 and 3). Furthermore, the lower pKa of $16-H$ compared to water (ca. 10 units) affords a low effective concentration $16-H$, and thus, a substantially slower reaction than would be indicated from the relative $\Delta G^\ddagger$ from $16-H$ is expected. This offers an explanation as to why, in the Pd(PHOX)-catalyzed systems, the
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 23 Comprehensive Quantum Mechanics Investigation

decarboxylated but non-alkylated starting material is not observed. Hence, the experimentally observed water tolerance is well explained for this system.

1.3.3 C–C BOND FORMATION VIA REDUCTIVE ELIMINATION

Given post-decarboxylation Pd enolate intermediates 14, (Re)-13, and (Si)-13, we then sought to explore possible mechanisms for C(sp³)–C(sp³) bond formation. We further exploit this opportunity to revise and expand upon previous investigations in this area.¹⁰

Figure 1.7. Inner-sphere C–C bond forming transition states considered.

First, inner-sphere mechanisms are considered. We envisioned four unique classes of transition states through which reductive elimination may occur: (1) a three-membered ring transition state from a C–bound Pd enolate (TS17), (2) a five-membered cyclic transition state from a C–bound Pd enolate in which the carbon atom of the Pd enolate migrates to the distal carbon of the η¹-allyl fragment (TS18), (3) a five-membered ring transition state from an O–bound Pd enolate in which the carbon atom of the enolate bonds with the proximal carbon of the η¹-allyl fragment (TS19), and (4) a seven-membered cyclic transition state (TS20)³³ (Figure 1.7). Previous investigation suggests the isomerization between oxygen and carbon-bound Pd enolates to be facile.¹⁰ Thus, we initially focused on evaluating the barrier to the C(sp³)–C(sp³) bond forming event.
Consistent with previous observations,\textsuperscript{10} three-centered transition state TS\textsubscript{17} was calculated to be intractably high in energy, with an apparent barrier of 33.7 [46.4] kcal/mol. To determine whether a lower energy transition state could be found by expanding the ring size, we considered the vinylogous case of the 5-centered transition state (TS\textsubscript{18}). However, the planarity of the allyl fragment in the transition state mandates a still highly strained five-membered ring. Despite our best efforts, a transition state fitting this connectivity was never found on the PES, and any transformation similar would likely be intractably high in energy. Next, we turn our attention to an alternative five-membered cyclic transition state, TS\textsubscript{19}. Beginning from O–bound Pd enolate 13, the barrier to TS\textsubscript{19} is found to be 32.6 [46.3] kcal/mol, and thus, likely not responsible for C–C bond formation.

Lastly, we considered the fully expanded seven-membered cyclic transition state, TS\textsubscript{20}. Here, the seven-membered ring may adopt either a boat or chair conformer for both \textit{Re} and \textit{Si} faces of the enolate. Additionally, the six-membered ring of the cyclohexanone enolate fragment may adopt two unique half chair conformers, giving rise to eight total transition states to be considered (Figure 1.8). Here, bond formation from the \textit{Re} and \textit{Si} faces afford the \textit{S} and \textit{R} enantiomer of product, respectively. The prefixes \textit{chair}/\textit{boat} refer to the conformation of the seven-membered ring, and \textit{axial}/\textit{equatorial} denote the half chair geometry of the cyclic enolate (Figure 1.8A).
**Figure 1.8.** (A) Reductive elimination from axial versus equatorial Pd enolate half-chairs. (B) Lowest energy chair and boat conformers for each diastereomeric seven-centered C–C bond forming transition state.\(^a\)

[A. Axial versus equatorial attack from Pd enolate half-chairs.]

\[
\begin{align*}
\text{Axial attack (favored)} & & \text{Equatorial attack (disfavored)} \\
\end{align*}
\]

[B. Four lowest energy (axial attack) transition states.]

\[
\begin{align*}
\text{To (S)-2 [Major]} & \quad \text{(Re)-13} \quad \text{(Re/chair)-TS20} \quad \Delta G^\ddagger_{\text{rel}} = 0.0 \ [0.0] \quad \text{or} \quad \text{(Re/boat)-TS20} \quad \Delta G^\ddagger_{\text{rel}} = 3.6 \ [5.9] \\
\text{To (R)-2 [Minor]} & \quad \text{(Si)-13} \quad \text{(Si/chair)-TS20} \quad \Delta G^\ddagger_{\text{rel}} = 2.1 \ [2.8] \quad \text{or} \quad \text{(Si/boat)-TS20} \quad \Delta G^\ddagger_{\text{rel}} = 1.3 \ [1.9]
\end{align*}
\]

\[a\] Relative free energies given in kcal/mol from final electronic energies at the M06/def2-TZVP/CPCM(THF) level of theory with DLPNO-CCSD(T) values in brackets. For \((\text{Si/boat})\)-TS20, the DLPNO-CCSD(T) value was refined with TightPNO settings.

Transition states that feature *equatorial* attack of the allyl fragment by the enolate half chair are all higher in energy than their *axial* counterparts by 0.4 to 1.5 kcal/mol. Henceforth, in our discussion the *axial/equatorial* suffix will be omitted with all references...
being to the favorable axial transition states. In comparison with the previously mentioned inner-sphere transition states, all eight of the seven-membered cyclic transition states (TS20) offer substantially lower barriers to C–C bond formation, with $\Delta G^\ddagger$ ranging from 10.8 [18.5] to 15.1 [24.6] kcal/mol.

**Figure 1.9. Structures of the two lowest energy diastereomeric transition states of TS20.**

![Figure 1.9](image)

[a] Relative free energies given in kcal/mol from final electronic energies at the M06/def2-TZVP/CPCM(THF) level of theory with DLPNO-CCSD(T) values in brackets.

Experimentally, the (S)-enantiomer of the $t$-BuPHOX ligand yields (S)-2-allyl-2-methylcyclohexan-1-one ((S)-2) as the major product with 88% ee. At a reaction temperature of 25 °C, this corresponds to an effective energetic difference of 1.6 kcal/mol between the enantiodetermining transition states. From O-bound Pd enolate (Si/Re)-13, we found the lowest energy difference between Re/Si diastereomeric transition states to be (Re/chair)-TS20 and (Si/boat)-TS20, with barrier heights of 10.8 and 12.1 kcal/mol,
respectively ($\Delta\Delta G^\ddagger = 1.3 [1.9]$ kcal/mol) (Figure 1.8B). This initial result is in good agreement with the experimentally observed enantioselectivities.

Because reliably obtaining relative energies within a sub-kcal/mol error from QM is challenging, we performed a variety of control calculational experiments. Single point calculations on the BP86-D3/LANL2TZ(f)-6-31G(d) optimized geometries were carried out with a suite of 15 density functionals, encompassing several classes of functionals. Electronic energies obtained at the DLPNO-CCSD(T) level of theory (with both NormalPNO and TightPNO settings) were employed for benchmarking. The four lower energy axial conformations of TS20 (Figure 1.8B) were also optimized with a subset of density functionals (with and without empirical dispersion corrections (D3)), followed by single point calculations as previously described (see 1.5 Supporting Information). All results from the control experiments correctly predict (Re/chair)-TS20 to be the overall lowest energy transition state, with (Si/boat)-TS20 as the lowest energy pathway for the formation of the minor product (R)-2. Thus, we propose C–C bond formation via TS20 to be the enantiodetermining step in the decarboxylative asymmetric allylic alkylation reaction with the Pd(PHOX) catalyst (Figure 1.9).

An investigation of a related system by our groups highlighted internal rearrangements of a Pd enolate as a potential mechanism by which product enantioselectivity is determined.\textsuperscript{10b} Although outside the scope of that investigation, the authors noted that a subsequent equilibration between (Si/Re) enolates may be facile. Thus, a definite conclusion as to the origin of the enantioinduction was not drawn. Accordingly, we found a facile interconversion between (Si)-13 and (Re)-13, with a rotational barrier
several kcal/mol lower in energy than that of C–C bond formation (TS24) (vide infra, Scheme 1.3). Therefore, the rate of kinetic quenching of intermediates (Si)-13 and (Re)-13 will not be sufficient to preserve any stereochemical induction of previous mechanistic steps. A similar conclusion was posited by McPherson and coworkers.12

Upon further examination, it becomes clear that in the case of the favored (Re)-TS20 geometries, adverse interaction between the α-methyl substituent of the enolate fragment and the t-Bu group of the PHOX ligand is minimal compared to the analogous clash between the t-Bu group and the carbocyclic backbone of the enolate found in (Si)-TS20. The four atoms ligating Pd, along with the two carbon termini of the newly forming σ (C–C) bond, are nearly coplanar (Figure 1.9). In the Si transition states, the resulting steric clash between the ligand and substrate leads to a distorted chair/boat transition state as well as deviation from square planarity at the Pd center. We performed a control calculation in which the t-Bu group of the PHOX ligand was replaced with a hydrogen atom, followed by subsequent transition state optimization. The optimized (Si)-des-t-Bu transition state regained planarity resembling the favored (Re)-TS20 geometry. These results suggest that the steric interaction from the carbocyclic scaffold and the t-Bu group of the PHOX ligand, along with the accompanying distortion from square planarity, is the primary origin of enantioinduction.

Although previous work suggests an inner-sphere mechanism to be prevalent, we do not discount the possibility that a competing outer-sphere mechanism is also present. In fact, with the Pd(PHOX) system, stabilized “soft” enolates generally remain competent in
the reaction, albeit with substantially reduced enantioselectivities.\textsuperscript{4} In the canonical Tsuji–Trost allylic alkylation, differentiation between inner- and outer-sphere pathways is highly reliant on the nature of the nucleophile,\textsuperscript{34} with hard nucleophiles proceeding through inner-sphere attack and soft nucleophiles via outer-sphere mechanisms. As such, we hypothesize that the poor enantioselectivities observed with stabilized enolates are likely the result of a less selective outer-sphere mechanism dominating the C–C bond formation step. In an effort to continue the development of this methodology to include previously inaccessible substrate classes, we sought to explore the intricacies of the interplay between outer-sphere and inner-sphere mechanisms.

From O–bound enolates \textit{(Si)}-\textbf{13} and \textit{(Re)}-\textbf{13}, an associative displacement of the enolate by the olefin of the allyl fragment \textit{(Si}/\textit{Re})-\textbf{TS21} directly affords \textbf{14} (as two inconsequential rotamers) (Scheme 1.3). Its noteworthy that \textbf{14} is also the product of decarboxylation through \textbf{TS15} (decarboxylative pathway 3) (Scheme 1.1). As expected, in \textbf{14}, bonding between the axial enolate oxygen and Pd is dominated by electrostatic attraction. Intermediate \textbf{14} presents a Pd–O bond length of 2.72 Å and Löwden bond order of 0.23, compared to the 2.08 Å Pd–O bond length and bond order of 0.60 as observed in \textit{(Re)}-\textbf{13}. As such, disassociated ions \textbf{15} and \textbf{17} are comparable in free energy to \textbf{14}. This was found to be the lowest energy entry into the outer-sphere mechanistic space (Scheme 1.3).
Scheme 1.3. Various C–C bond forming pathways.\textsuperscript{a}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme13.png}
\end{figure}

\textsuperscript{a} Free energies relative to 3 (in kcal/mol) obtained with M06/def2-TZVP/PCPC(THF), with energies derived from electronic energies at the DLPNO-CCSD(T)/cc-pVTZ/PCPC(THF) level of theory in brackets. Lowest energy conformers depicted. $\Delta \Delta G^\ddagger$ refined to 1.9 kcal/mol with TightPNO settings.

In considering C–C bond formation through an outer-sphere attack of enolate 17 on the $[\eta^3-(\text{allyl})\text{Pd(PHOX)}]^+$ complex (15), we note that attack may occur either \textit{trans} to N or P, from the \textit{Si} or \textit{Re} face of the enolate, in both enolate half chairs, and to either \textit{exo}- or \textit{endo}-allyl 15. Based on our previous findings, we considered only the enolate half chair which gives rise to the favored axial attack. Here, we found six of the eight hypothesized transition states for this outer-sphere process (TS22).

Unlike the inner-sphere transition states TS20, which give rise to $\Delta \Delta G^\ddagger$ of 1.3 [1.9] kcal/mol between the lowest energy diastereomeric transition states, the outer-sphere
transition states afford reduced selectivity. From transition states (Si)-TS22 and (Re)-TS22, a ΔΔG‡ of 0.6 [1.4] kcal/mol was calculated. We note that the presence of numerous nearly degenerate rotameric transition states complicated obtaining accurate ΔΔG‡ for this pathway.

In addition to reactivity at the π-allyl carbon termini, nucleophilic attack at the central carbon of the allyl fragment to afford palladacyclobutane species is known.\textsuperscript{35} Previous experimental and computational studies find the mode of reactivity to be highly dependent on the σ-donating/π-accepting nature of the ancillary ligand and the basicity of the nucleophile. Palladacyclobutane complexes have been proposed as mechanistic intermediates in palladium-mediated cyclopropanation reactions,\textsuperscript{36} as well as isolated and characterized by X-ray crystallography.\textsuperscript{37}

Of relevance to this work, we considered that 15 and 17 may combine in such a way that the oxygen atom of 17 forms a covalent bond with the β carbon of the allyl fragment to afford metallacyclobutane 18. The C–C π orbitals of the enolate fragment are in potentially good overlap with the Pd–C σ* of the allyl terminus. Thus, we envisioned intermediate 18 may be a competent precursor to the desired C–C bond formation via (Si/Re)-TS23. IRC analysis reveals (Si/Re)-TS23 directly connects metallacyclobutane 18 and the complexed ketone product (R/S)-19 on the potential energy surface without the intermittency of ion pair 15+17. Therefore, TS23 represents a C–C bond forming pathway unique to that of TS22. Complex 18 is well poised for reductive elimination to form 19.
The apparent barrier to this process (relative to enolate (Si)-13) is 16.4 [20.5] and 16.1 [20.8] kcal/mol for (Si)-TS23 and (Re)-TS23, respectively.

From analysis of the free energy network encompassing Pd enolates (Si)-13, (Re)-13, and 14, with the accompanying C–C bond forming pathways, the following conclusions are drawn:

1. Given facile rotation about the Pd–O and C–O σ bonds in Pd enolates (Si)-13 and (Re)-13, preservation of stereochemical information through differentiation in energy between prior diastereomeric transition states should largely be erased. We found the rotational barrier from (Si)-13 to (Re)-13 to be 5.1 [6.6] kcal/mol (via TS24), whereas the minimum energy barrier to C–C bond formation is 10.8 [18.5] kcal/mol. Therefore, the rate of kinetic quenching of intermediates (Si)-13 and (Re)-13 will not be sufficient to preserve any stereochemical induction from previous mechanistic steps. However, this feature of the PES may be substrate specific and more extrapolated scaffolds may experience rotational barriers similar to or greater than that of C–C bond formation.

2. The mechanism through which decarboxylation of the β-ketoester occurs plays an important role in determining the predisposition for C–C bond formation to occur through either an inner or outer-sphere process. As previously mentioned, decarboxylation via TS5, TS14, and TS15, yield Pd enolates (Si)-13, (Re)-13, and 14, respectively. From (Re/Si)-13, direct C–C bond formation through the inner-sphere transition states (Re/chair)-TS20 or (Si/boat)-TS20 represent the lowest energy pathway to the product. From (Re/Si)-13, the apparent barrier height to C–C bond formation via an outer-sphere
mechanism corresponds to the isomerization of \((\text{Re}/\text{Si})-13\) to the axially-bound enolate \(14\) via \((\text{Re}/\text{Si})\)-TS21, as \((\text{Re}/\text{Si})\)-TS21 are found to be higher in energy than the outer-sphere C–C bond forming transition states (TS22). Therefore, decarboxylation through TS5 or TS14 (pathway 1 or 2) to directly afford \((\text{Re}/\text{Si})-13\) carries a predisposition for inner-sphere C–C bond formation.

Alternatively, decarboxylation via TS15 (pathways 3) directly leads to apical enolate \(14\). When this is the case, C–C bond formation through both inner and outer-sphere processes becomes highly competitive. From \(14\), the highest barrier to the outer-sphere mechanism is that of the outer-sphere C–C bond forming event (TS22). While the barrier heights for the inner-sphere C–C bond forming transition states are lower in energy than those of the outer-sphere mechanism, the Pd enolate must first undergo an isomerization from apically-bound \(14\) to square planar complexes \((\text{Re}/\text{Si})-13\). In fact, the barrier heights of these isomerizations (via \((\text{Re}/\text{Si})\)-TS21) are comparable to that of the outer-sphere C–C bond formation. Therefore, less preference for the inner over outer-sphere mechanism is expected for the case in which decarboxylation proceeds through TS15 (pathway 3). Qualitatively similar results are obtained across a variety of density functional methods.

3. We previously discussed the effects of solvation on differentiating between decarboxylative pathways. We find that nonpolar solvents such as toluene impose a large preference for decarboxylation through the less polar TS14, while polar solvents result in preference for the more charge-separated TS15. Given the similarities in the free energies of the inner- and outer-sphere mechanisms, along with the experimentally observed solvent dependencies described in the literature, an analogous investigation into the solvent effects
on differentiation of the inner- and outer-sphere mechanistic pathways was carried out. For the reasons described above, this investigation is qualitative in nature, highlighting the expected reactivity trends.

First, we note the relative free energies between the low energy Pd enolates \((\text{Re/Si})-13\) and the transition states for their isomerization to \(14\) are independent of the continuum dielectric constant (Table 1.1). However, the barrier for C–C bond formation via inner-sphere TS20 demonstrates a dependence on solvent polarity in which less polar solvents afford reduced barrier heights. As anticipated, the generation of solvent separated ions 15 and enolate 17 from 14 becomes increasingly unfavorable with decreasing dielectric constant of the solvent. As the relative free energy of 15 and 17 increases dramatically in nonpolar solvents, the outer-sphere C–C bond formation from the separate ions via TS22 is anticipated to become less prevalent. In contrast, solvation in a continuum with a high dielectric constant favors the separate ions 15 and 17 over Pd enolate 14. The barriers to outer-sphere C–C bond formation also decrease, now favoring an outer-sphere mechanism from 14.

Taken together with the results for solvent effects on decarboxylation, we conclude that in polar solvent, decarboxylation via TS15 is favored, affording intermediate 14. From 14, the minimum energy pathway to C–C bond formation is via a less enantioselective outer-sphere mechanism (TS22). Conversely, nonpolar solvents favor loss of CO\(_2\) through TS14, yielding enolate \((\text{Si})\)-13. Reductive elimination via the 7-membered pericyclic transition state TS20 then ensues. Given the sensitivity of relative barrier heights to changes in solvation, we highlight the need to consider both the mechanism of
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 35 Comprehensive Quantum Mechanics Investigation

decarboxylation and that of the C–C bond forming pathways in determining the inner-sphere or outer-sphere mechanism to be more favorable.

**Table 1.1. Qualitative comparison of relative free energy barrier heights along reductive elimination pathways.**

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>PhMe</th>
<th>Et₂O</th>
<th>THF</th>
<th>DMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re)-13</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>(Si)-13</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>14</td>
<td>8.8</td>
<td>9.3</td>
<td>9.5</td>
<td>9.8</td>
</tr>
<tr>
<td>15 + 17</td>
<td>33.2</td>
<td>17.5</td>
<td>9.2</td>
<td>-0.5</td>
</tr>
<tr>
<td>(Re)-TS21</td>
<td>13.5</td>
<td>13.5</td>
<td>13.5</td>
<td>13.6</td>
</tr>
<tr>
<td>(Si)-TS21</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
</tr>
<tr>
<td>(Re/chair)-TS20</td>
<td>9.5</td>
<td>10.3</td>
<td>10.8</td>
<td>11.5</td>
</tr>
<tr>
<td>(Si/boat)-TS20</td>
<td>10.9</td>
<td>11.7</td>
<td>12.1</td>
<td>12.7</td>
</tr>
<tr>
<td>(endo/Re/t-P)-TS22</td>
<td>14.9⁺</td>
<td>13.9⁺</td>
<td>13.3</td>
<td>12.6</td>
</tr>
<tr>
<td>(exo/Si/t-N)-TS22</td>
<td>16.0⁺</td>
<td>14.7⁺</td>
<td>13.9</td>
<td>12.9</td>
</tr>
<tr>
<td>(endo/Re/t-P)-TS23</td>
<td>19.8</td>
<td>17.8</td>
<td>16.6</td>
<td>15.1</td>
</tr>
<tr>
<td>(endo/Si/t-P)-TS23</td>
<td>19.1</td>
<td>17.2</td>
<td>16.1</td>
<td>14.8</td>
</tr>
</tbody>
</table>

[a] Relative free energies given in kcal/mol at the M06/def2-TZVP/CPCM(solvent) level of theory on geometries obtained in the gas phase. [b] Barrier less than free energy of separated ions 15 and 17.

1.3.4 COMPLETE CATALYTIC CYCLE

Considering the findings for each step of the decarboxylative allylic alkylation reaction, we now construct a mechanistic picture that unites theoretical and experimental findings (Figure 1.10). First, the π-basic Pd⁰(PHOX) precatalyst coordinates to the olefin
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

of the allyl β-ketoester starting material (1), followed by oxidative addition to form the [Pd(PHOX)(η^3-allyl)]^+(RCO_2^-) ion pair (4). Oxidative addition occurs trans to the nitrogen of the PHOX ligand via direct displacement of the carboxylate leaving group (TS4). Validation of this displacement-type mechanism supports the basis from which previous claims have been made using inversion/retention of stereochemistry as a probe for determination of inner versus outer-sphere mechanisms (when substitution on the allyl terminus is present).^6,32 The mechanism of Bäckvall was found to be unlikely for these substrates.^31 Furthermore, both enantiomers of the starting material have similar barriers to oxidative addition. This is in accordance with experimental evidence that a kinetic resolution of the allyl β-ketoester starting material is generally not observed to great extent.^38

Figure 1.10. Complete catalytic cycle for the inner-sphere allylic alkylation reaction.
Ion pair 4 readily equilibrates to the more thermodynamically stable [Pd(PHOX)(η^1–allyl)(RCO₂)] complex (3). Experiment and computation agree in identifying 3 as the resting state of the catalyst. We further extend the analogous comparison to that of the enol carbonate substrate class (8/9). Given the equilibration between 3 and 4, along with the similar relative energies of the separated ions, we conclude that observation of crossover products in deuterium labeling experiments does not necessarily indicate an outer-sphere C–C bond forming mechanism, but rather is still accommodated within the inner-sphere mechanistic hypothesis. That is, charge-separated ion pairs may undergo facile anion exchange to afford the observed cross-products. Additionally, the pK_b of the carboxylate/carbonate anions is such that quenching with water to render an inactive or decomposed species is not anticipated, in accordance with the observed water tolerance experiments.

Subsequent loss of CO₂ occurs through one (or more) of three unique decarboxylative transition states, each leading to a different Pd enolate intermediate. Our investigation determines that ion pair 4 (the initial product of oxidative addition) is a common intermediate along the two lowest energy pathways through decarboxylation. Therefore, the catalyst resting state (3) is best described as an off-cycle intermediate (Figure 1.11). In agreement with experiment, decarboxylation is determined here to be rate-limiting. Furthermore, the calculated rate of decarboxylation (4.65 x 10⁻⁴ s⁻¹, ΔG‡ = 21.9 kcal/mol) is in excellent agreement with that of experiment (1.58 x 10⁻³ s⁻¹, ΔG‡ = 21.2 kcal/mol).
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

**Figure 1.11.** Free energy profile of minimum energy pathway through full catalytic cycle (green) as well as pathway for equilibration to off-cycle resting state 3 (orange).\(^{a}\)

From the four-coordinate Pd enolates \((\text{Re/Si})-13\), the most facile pathway to C–C bond formation is inner-sphere reductive elimination via a seven-membered pericyclic transition state \((\text{TS20})\). We establish that this C–C bond forming event is the enantiodetermining step (Figure 1.8). Calculated enantioselectivities agree with experiment and are assessed across a variety of computational methods.

\(^{a}\) Note that decarboxylation is considered irreversible as \(\text{CO}_2\) is lost to reaction headspace/atmosphere.
We investigated the interplay of inner and outer-sphere mechanisms. In particular, we assess effects of solvation on the differentiation of these two processes. The highly enantioselective inner-sphere process is favored in nonpolar solvents, whereas the less selective outer-sphere mechanisms become increasingly relevant in polar solvents. The origin of this solvent dependence is two-fold. In addition to stabilization of charged intermediates encountered in the outer-sphere processes, we find that increasingly polar solvents favor decarboxylation via the formally charge-separated transition state \( \text{TS15} \), leading directly to the square pyramidal enolate complex 14. Above, we discuss the implications of this in the context of a more facile entry into the outer-sphere mechanistic space.

1.3.5 EXPERIMENT AND DISCUSSION

We then sought to experimentally evaluate the mechanistic predictions obtained in our computational investigation. In the case of \( \alpha \)-methyl allyl enol carbonate 8, prior research reveals that the reaction rate is increased with the use of the more electron poor \((S)-(\text{CF}_3)_3-t\)-BuPHOX ligand.\(^\text{39}\) While a similar trend for the analogous \( \beta \)-ketoester (1) may be anticipated, reaction time course studies reveal that the same rate enhancement is not observed (Figure 1.12). In fact, when the catalyst resting state (3), and both low energy transition states responsible for decarboxylation (\( \text{TS14} \) and \( \text{TS15} \)) are re-optimized with the \((S)-(\text{CF}_3)_3-t\)-BuPHOX ligand, the barrier to decarboxylation is calculated to be 22.2 kcal/mol (DLPNO-CCSD(T), TightPNO) — within error of the 21.9 kcal/mol (DLPNO-CCSD(T), TightPNO) barrier height of the original system. This experiment further
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

highlights the fidelity of the computational methods employed in this study in describing the reactivity trends in the catalytic system.

**Figure 1.12.** Conversion of 1 to (S)-2 under standard reaction conditions.\(^a\)

![Conversion graph](image)

\(^a\) Conversion as determined by GC-FID with respect to tetradecane internal standard.

We prepared α-phenyl allyl β-ketoester substrate 20 to probe the interplay of inner and outer-sphere processes (Figure 1.13). Compared to α-methylated β-ketoester 1, the enolate derived from 20 experiences significant electronic stabilization through conjugation. As anticipated from the discussion provided above, as well as prior experimental trends, substrate 20 affords the desired product (S)-22 in 99% yield, however, in a modest 23% ee. It is worth noting that the reduction in enantioselectivity is likely not exclusively a consequence of steric interactions. A variety of sterically encumbered substrates, which do not provide significant electronic stabilization, such as the analogous α-i-Bu, α-Bn, α-prenyl, etc., compounds afford the corresponding allylic alkylation products in 82–91% ee.\(^2\) Error! Bookmark not defined. Furthermore, we compute a
\[ \Delta \Delta G^\ddagger \] of 1.3 kcal/mol between the enantiodetermining inner-sphere transition states derived from substrate 20 (corresponding to 80% ee at 25 °C). These results suggest that an enantioselective inner-sphere pathway persists, however, under the standard reaction conditions, the less selective outer-sphere mechanisms dominate.

**Figure 1.13.** Effect of decarboxylation mechanism on downstream enantioselectivity.\(^a\)

In addition to \(\alpha\)-phenyl \(\beta\)-ketoester 20, the corresponding \(\alpha\)-phenyl allyl enol carbonate (21) was also evaluated in the transformation (Figure 1.13). Interestingly, under identical conditions to those employed with \(\beta\)-ketoester 20, enol carbonate 21 affords (S)-22 in a reduced 15% ee, compared to 23% ee as obtained starting from 20.\(^8\) After decarboxylation, both 20 and 21 share access to the same network of enolate intermediates (Scheme 1.3). However, by virtue of the differing mechanisms of decarboxylation, the point at which the intermediates derived from each substrate enter the post-decarboxylation mechanistic space is anticipated to vary. As prefaced by our computational investigation, this may lead to altered levels of product enantioenrichment due to the resulting predisposition for C–C bond formation to occur via inner- or outer-sphere mechanisms to varying extent (vida supra). Naturally, differences in enantioselectivities based on enolate

---

\(^{a}\) Enantiomeric excess determined by chiral SFC analysis.
synthon (i.e., \( \beta \)-ketoester versus enol carbonate) are expected to be increasingly pronounced in the case of stabilized enolates (20/21), for which an outer-sphere mechanism is readily accessible. These results highlight the importance in considering the effect of the mechanism of decarboxylation and subsequent behavior of enolate intermediates in the overall enantioselectivity of the transformation.

With compound 20 in hand, we then sought to probe the effects of solvation and ligand electronics on observed enantioselectivity (Figure 1.14). As previously mentioned, the enantioselective inner-sphere pathway to C–C bond formation to (S)-22 is expected to be largely outcompeted by less selective outer-sphere mechanisms. Our computational investigations suggest that, for allyl \( \beta \)-ketoesters, inner-sphere mechanisms are favored by: (1) disfavoring the charge-separated intermediates required for an outer-sphere approach, and (2) favoring decarboxylative mechanisms that lead directly to \( \eta^1 \)-allyl square planar palladium enolates (i.e., via decarboxylation pathways 1 and 2). Calculations further predicted that this may be accomplished by utilizing nonpolar solvents, as well as through the installation of electron withdrawing groups on the PHOX ligand framework.

Indeed, we observe an increase from 23 to 28% ee simply by implementing toluene \((\varepsilon = 2.4)\) in place of THF \((\varepsilon = 7.3)\) as the reaction solvent (entries 1–2, Figure 1.14). Utilizing the more electron poor (S)-(CF\(_3\))\(_3\)-t-BuPHOX ligand in toluene (entry 3) and a 2:1 methylcyclohexane/toluene solvent mixture \((\varepsilon = 2.1)\), enantioselectivity was further enhanced to 32% and 36% ee, respectively (entries 3–4). Given the initial improvements from perturbations of ligand electronics and solvation alone, we suggest in silico high-
throughput screening of ligands with different steric environments as a practical next step in future developmental efforts.

**Figure 1.14.** Effect of solvation and ligand electronics on enantioselectivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>ee (‰)</th>
<th>Yield 22 (‰)</th>
<th>$\Delta G_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-t-BuPHOX</td>
<td>THF [7.4]</td>
<td>23</td>
<td>99</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>(S)-t-BuPHOX</td>
<td>PhMe [2.4]</td>
<td>28</td>
<td>96</td>
<td>24.0</td>
</tr>
<tr>
<td>3</td>
<td>(S)-(CF$_3$)$_3$-t-BuPHOX</td>
<td>PhMe [2.4]</td>
<td>32</td>
<td>90</td>
<td>31.0</td>
</tr>
<tr>
<td>4</td>
<td>(S)-(CF$_3$)$_3$-t-BuPHOX</td>
<td>2:1 MeCy/PhMe [2.1]</td>
<td>36</td>
<td>69$^d$</td>
<td>35.2</td>
</tr>
</tbody>
</table>

[a] Determined by chiral SFC analysis. [b] Determined by $^1$H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [c] Change in free energy (in kcal/mol, 1 M standard state) from square pyramidal enolate to separated ions. [d] 34% of 20 remaining after 12 hours.

### 1.4 CONCLUSIONS

We report a detailed quantum mechanics investigation into the three mechanistic steps (oxidative addition, decarboxylation, and reductive elimination) of the decarboxylative asymmetric allylic alkylation with the Pd(PHOX) catalyst system. Experiments were carried out to explore the mechanistic hypotheses derived from the ab initio calculations.

Beginning with allyl $\beta$-ketoester 1, oxidative addition of Pd$^0$(PHOX) proceeds through pre-coordination of the olefin of the allyl fragment of 1 (to give 5), followed by an $S_N2$-like electrophilic addition to Pd to yield the $[(PHOX)Pd(\eta^3$-allyl)]$^+$$(RCO_2)^-$ ion pair.
(4). Ion pair 4 then rapidly equilibrates to the catalyst resting state, [(PHOX)Pd(η¹-allyl)(RCO₂)] (3). Complex 3 is best described as an off-cycle intermediate. Given the equilibration between 3 and 4, along with the similar relative energies of the separated ions, we corroborate that the results from our previously reported cross-over experiments are not necessarily indicative of an outer-sphere mechanism, but still are accommodated within the inner-sphere mechanistic hypothesis.

From the catalyst resting state (3), we find three dominant pathways (1, 2, and 3) through which decarboxylation may occur. Each pathway leads to a unique palladium enolate with the ability for subsequent interconversion between the three. However, ensuing analysis of the C–C bond forming potential energy surface reveals that the enolates derived from pathways 1 and 2 are more predisposed to undergo an inner-sphere C–C bond formation via the seven-membered pericyclic transition state, TS20. On the other hand, decarboxylation via pathway 3 directly affords square pyramidal enolate 14 which may undergo a more facile dissociation and enter the outer-sphere mechanistic space.

We predict relative barrier heights among the decarboxylative and C(sp³)–C(sp³) bond forming pathways to be highly solvent dependent. Decreasing solvent polarity favors inner-sphere processes by destabilizing the ionic intermediates of the outer-sphere mechanism, as well as promoting decarboxylation via Pathway 2. Decarboxylation is determined to be rate-limiting in accordance with experiment. Furthermore, the calculated decarboxylation rate constant in THF obtained with DLPNO-CCSD(T) (4.65x10⁻⁴ s⁻¹; ΔG‡ = 21.9 kcal/mol) is in excellent agreement with that of experiment (1.58x10⁻³ s⁻¹; ΔG‡ =
21.2 kcal/mol). In comparison, the DFT methods applied in this study all predict a rate constant $10^3$–$10^7$ times larger in magnitude ($\Delta G^\ddagger = 12.5$–$18.9$ kcal/mol) than experimentally observed.

We considered several inner-sphere reductive elimination transition states. In accordance with previous research in our group, the seven-membered, doubly-vinylogous transition state (TS20) provides the lowest energy pathway to C–C bond formation in nonpolar solvents. We establish that the C(sp$^3$)–C(sp$^3$) bond forming event is the enantiodetermining step. Calculated $\Delta \Delta G^\ddagger$ are in excellent agreement with experimentally observed enantioselectivities and are assessed across a variety of computational methods. A model is proposed for the origin of the enantioinduction.

We also investigated outer-sphere processes, which we found to be competitive in barrier height with the inner-sphere reactions, albeit slightly less favorable. Unlike the inner-sphere transition states, however, severely degraded enantiocontrol is anticipated for outer sphere mechanisms.

Additionally, enolate synthon design is highlighted as an area for future development. Herein, we compare the relative thermodynamics of catalyst resting states derived from different enolate precursors. From this, we suggest that in conjunction with catalyst design, the development of more activated masked enolates may achieve a desirable increase in reaction rate. With a complete mechanistic picture in hand, in silico development may now accompany ensuing experimental efforts.

In order to evaluate the fidelity of the mechanistic hypotheses, a stabilized enolate equivalent (20) was employed as a probe for inner and outer-sphere competition.
Experimental results support the computation-based predictions in solvent trends as well as effects of ligand substitution. Furthermore, comparison between 20 and 21 demonstrates the intricacies in the equilibration of the palladium enolate intermediates as described herein. While α-methyl ketone 1 is employed throughout the majority of this study as a “standard” substrate, many of the experimentally observed trends mentioned throughout the text remain consistent amongst more highly decorated heterocyclic scaffolds alike. Thus, the conclusions presented herein are expected to serve as robust first-order approximations to a broad variety of substrate classes.

Density functional theory and localized coupled-cluster theory are employed in this study. We find the DLPNO-CCSD(T) method of Neese et al. highly effective in obtaining accurate barrier heights and thermodynamic relations. Thus, we recommend DLPNO-CCSD(T) for routine use in future quantum mechanics-based investigations in asymmetric catalysis.

These avenues of thought, coupled with the detailed mechanistic hypothesis presented herein, provide a powerful tool in addressing the current limitations and aiding in the future development of the decarboxylative asymmetric allylic alkylation reaction.

1.5 SUPPORTING INFORMATION

1.5.1 GENERAL COMPUTATIONAL DETAILS

Density functional theory calculations

All quantum mechanical calculations were performed with ORCA version 4.1 and 4.2. Unless otherwise noted, geometry optimizations were carried out with the BP86
generalized gradient approximation (GGA) functional\textsuperscript{14} [Becke ’88 exchange functional paired with the Perdew ’86 correlation functional] with Becke–Johnson damped D3 dispersion corrections (henceforth referred to as D3).\textsuperscript{15} A mixed basis set was implemented, in which palladium is described by the small core LANL2TZ(f) basis set with the Hay Wadt effective core potential\textsuperscript{16} (ECP) [28 core electrons on Pd], and the 6-31G(d) basis set was used on all other atoms. Thermal corrections (at 298 K) were calculated from the unscaled vibrational frequencies at this level of theory. The Quasi-RRHO method was applied to correct for the breakdown of the harmonic oscillator approximation for low frequency vibrations.\textsuperscript{24} All stationary points are characterized by the appropriate number of imaginary vibrational modes (zero for optimized geometries and one for transition states). Intrinsic reaction coordinate (IRC) analyses were carried out to ensure all transition states connect the appropriate starting materials and products.

Triple-ζ quality single point calculations were carried out on all stationary points with the BP86-D3, B3LYP-D3,\textsuperscript{17} PBE0-D3,\textsuperscript{18} M06,\textsuperscript{19} and DSD-BLYP-D3\textsuperscript{20} functionals with the def2-TZVP basis set\textsuperscript{21} on all atoms (with the small core ECP28MWB pseudopotential\textsuperscript{22} on Pd). The Conductor-like Polarizable Continuum Model (CPCM)\textsuperscript{23} was employed in these single point calculations to include effects of solvation. Thermal corrections obtained at the previous level of theory are then applied to these electronic energies to obtain the reported free energies ($G_{298}$). Calculated free energy changes are for a 1 M standard state at 25 ℃, apart from decarboxylation where CO$_2$ is given a standard state of 1 atm.
These methods encompass a range of functional classes, including GGA (BP86-D3), hybrid GGA (B3LYP-D3), non-empirical hybrid GGA (PBE0-D3), hybrid meta-GGA (M06), and spin-component-scaled double hybrid (DSD-BLYP-D3), where effects from dispersion are accounted for either in parameterization or empirically with \textit{ad-hoc} corrections. As the M06 density functional is parameterized to offer a suitable balance between transition metals and main group elements, we report these energies in the text of the manuscript. However, we encourage comparison of these results to those obtained with the other methods. The values obtained from all quantum mechanical calculations are included in the supporting excel file available online (https://pubs.acs.org/doi/10.1021/jacs.0c06243?ref=pdf).

The resolution of identity (RI) and chain-of-spheres\textsuperscript{40} (keyword = RIJCOSX) approximations were utilized for coulomb and exchange integrals, respectively, where applicable. Automatic generation of the auxiliary basis sets was employed (keyword = AutoAux).\textsuperscript{41} The finest integration grid settings (Grid7, GridX9, NoFinalGrid) were utilized in all calculations.

\textbf{DLPNO-CCSD(T) Calculations}

Additional single point calculations were performed on all optimized structured with the domain based local pair natural orbital coupled-cluster (DLPNO-CCSD(T)) method as described by Neese \textit{et. al.} and as implemented in ORCA.\textsuperscript{26} Here, we find the cc-pVTZ basis set (with the corresponding cc-pVTZ/C and def2/J auxiliary basis sets), along with the small core SK-MCDHF-RSC effective core potential\textsuperscript{27} on Pd (\textit{i.e.}, the cc-pVTZ-PP main basis set with cc-pVTZ-PP/C and def2/J auxiliary basis sets) with the
“NormalPNO” cutoffs to offer an appropriate balance between cost and accuracy for routine use. As before, the CPCM(THF) was employed to account for effects of solvation. Thermal corrections obtained at the BP86-D3/LANL2TZ(f)–6-31G(d) are applied to the DLPNO-CCSD(T)/cc-pVTZ/CPCM(THF) electronic energies to afford the corresponding free energies. The “TightPNO” settings are employed to further refine correlation energy for comparison of select structures.

Notes:

- Similar results are obtained with the def2-TZVP basis set in control experiments, although we elected to employ Dunning’s cc-pVnZ family of basis sets for ease of basis set extrapolation with further calculations should the need arise.
- “NormalPNO”: $T_{\text{CutPairs}} = 10^{-3}$, $T_{\text{CutDO}} = 1 \times 10^{-2}$, $T_{\text{CutPNO}} = 3.33 \times 10^{-7}$, $T_{\text{CutMKN}} = 10^{-3}$
- “TightPNO”: $T_{\text{CutPairs}} = 10^{-5}$, $T_{\text{CutDO}} = 5 \times 10^{-3}$, $T_{\text{CutPNO}} = 1.00 \times 10^{-7}$, $T_{\text{CutMKN}} = 10^{-3}$
- “TightPNO” settings may be employed, however, the computational cost increases dramatically. Thus, we have found an efficient approach is to perform routine single point calculations with “NormalPNO” cutoffs, then refine these values for key intermediates with the “TightPNO” settings.
- When CPCM implicit solvation is employed (ORCA 4), the Hartree–Fock reference is optimized self-consistently with respect to the solvent reaction field, but the subsequent optimization of the cluster amplitudes is not. [An alternative is to apply $\Delta G(\text{solv})$ from DFT calculations to a gas phase DLPNO-CCSD(T) energy.]
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 50 Comprehensive Quantum Mechanics Investigation

1.5.2 INITIAL BENCHMARKING

We explore density functional and basis set dependence on the geometry optimization of the PdII resting state complex 3. These calculated geometries are then compared to that of the recently reported crystallographic structure (CCDC 695531) (Table 1.2). While slight discrepancies between crystallographic and solution phase structure may persist, we utilize this data as a reference point to which we may calibrate our methodology, as well as explore general trends in basis set and functional dependencies.

Table 1.2. Comparison of geometric parameters obtained from geometry optimization with various functionals and basis sets.

<table>
<thead>
<tr>
<th>Basis Set</th>
<th>Functional</th>
<th>Pd–P</th>
<th>Pd–N</th>
<th>Pd–O</th>
<th>Pd–C</th>
<th>d1</th>
<th>MUEa</th>
<th>MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal XRD</td>
<td></td>
<td>2.189</td>
<td>2.133</td>
<td>2.136</td>
<td>2.055</td>
<td>4.687</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LNAL2DZ[Pd]6-31G(d)</td>
<td>BP86-D3</td>
<td>2.217</td>
<td>2.201</td>
<td>2.159</td>
<td>2.082</td>
<td>4.610</td>
<td>3.65</td>
<td>3.65</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>BP86-D3</td>
<td>2.206</td>
<td>2.148</td>
<td>2.107</td>
<td>2.067</td>
<td>4.598</td>
<td>1.83</td>
<td>0.38</td>
</tr>
<tr>
<td>def2-TZVP [all atoms]</td>
<td>BP86-D3</td>
<td>2.182</td>
<td>2.136</td>
<td>2.111</td>
<td>2.070</td>
<td>4.632</td>
<td>1.25</td>
<td>-0.35</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>PBE-D3</td>
<td>2.214</td>
<td>2.162</td>
<td>2.117</td>
<td>2.069</td>
<td>4.701</td>
<td>2.17</td>
<td>1.22</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>TPSS-D3</td>
<td>2.217</td>
<td>2.154</td>
<td>2.101</td>
<td>2.071</td>
<td>4.673</td>
<td>2.50</td>
<td>0.75</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>BLYP-D3</td>
<td>2.233</td>
<td>2.208</td>
<td>2.152</td>
<td>2.095</td>
<td>4.645</td>
<td>4.38</td>
<td>4.38</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>B3LYP-D3</td>
<td>2.228</td>
<td>2.209</td>
<td>2.134</td>
<td>2.066</td>
<td>4.683</td>
<td>3.20</td>
<td>3.10</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>B3PW-D3</td>
<td>2.204</td>
<td>2.145</td>
<td>2.088</td>
<td>2.045</td>
<td>4.586</td>
<td>2.13</td>
<td>-0.78</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>PBE0-D3</td>
<td>2.211</td>
<td>2.150</td>
<td>2.086</td>
<td>2.040</td>
<td>4.673</td>
<td>2.60</td>
<td>-0.65</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>TPSSh-D3</td>
<td>2.215</td>
<td>2.153</td>
<td>2.091</td>
<td>2.059</td>
<td>4.653</td>
<td>2.37</td>
<td>0.12</td>
</tr>
<tr>
<td>LNAL2TZ(f) [Pd]6-31G(d)</td>
<td>wB97X-D3</td>
<td>2.226</td>
<td>2.179</td>
<td>2.097</td>
<td>2.033</td>
<td>4.612</td>
<td>2.75</td>
<td>-0.80</td>
</tr>
</tbody>
</table>
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 51 Comprehensive Quantum Mechanics Investigation

<table>
<thead>
<tr>
<th>LANL2DZ [Pd]/6-31G(d)</th>
<th>B3LYP</th>
<th>2.278</th>
<th>2.234</th>
<th>2.133</th>
<th>2.079</th>
<th>5.102</th>
<th>5.43</th>
<th>5.28</th>
</tr>
</thead>
</table>

[a] Geometric parameters (Pd-X bond lengths, and \(d_1\)) given in angstrom (Å). MUE and MSE (excluding \(d_1\)) given in pm. Optimization carried out beginning from the known X-ray crystal structure.  

[b] CCDC 695531 (ref. 5).

From these controls, the following trends are observed:

1. Greatly reduced errors in Pd–X bond lengths with minimal increase in computational cost are obtained by employing the larger triple-\(\zeta\) quality basis set with polarization functions, LANL2TZ(f), on Pd in place of the double-\(\zeta\) (LANL2DZ) basis set.

2. The use of Becke-Johnson D3 damped dispersion corrections (-D3) in the optimization greatly aids in capturing perturbations of the ligand geometry arising from noncovalent interactions (see \(d_1\)).

3. Density functionals constructed with the Lee–Yang–Parr correlation functional (BLYP, B3LYP) present elongated Pd–X bonds and are among the functionals with the highest MUEs. This trend has been previously described in the literature\(^{19}\) and has been attributed to the LYP functional underestimating correlation at the uniform electron gas (UEG) limit.\(^{42}\)

Thus, for geometry optimization we employ the BP86 density functional with Becke–Johnson damped dispersion corrections (BP86-D3), with a mixed basis set comprised of the LANL2TZ(f) basis set on Pd with 6-31G(d) on all other atoms. *We do not recommend the use of the B3LYP/LANL2DZ–6-31G(d) level of theory as is employed in select literature investigations. We believe more suitable geometries may be obtained with D3BJ dispersion*
corrections and triple-ζ basis sets with polarization functions on the metal center. Apart
from B3LYP and BLYP, all other functionals evaluated perform comparably well.

1.5.3 DECARBOXYLATION AND CONTROL EXPERIMENTS

In order to obtain accurate barrier heights for the rate determining decarboxylative
step, geometry/transition state optimizations were also carried out with CPCM(THF) for
comparison to the structures optimized in the gas phase (Table 1.3).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BP86-D3</td>
<td>16.5</td>
<td><strong>12.5</strong></td>
<td>16.4</td>
<td>15.1</td>
<td><strong>11.5</strong></td>
<td>21.7</td>
</tr>
<tr>
<td>B3LYP-D3</td>
<td>18.4b</td>
<td><strong>16.5</strong></td>
<td>21.5</td>
<td>19.2</td>
<td><strong>15.4</strong></td>
<td>27.7</td>
</tr>
<tr>
<td>PBE0-D3</td>
<td>21.0c</td>
<td><strong>18.9</strong></td>
<td>21.0</td>
<td>23.9</td>
<td><strong>19.0</strong></td>
<td>27.8</td>
</tr>
<tr>
<td>M06</td>
<td>22.0</td>
<td><strong>17.1</strong></td>
<td>17.5</td>
<td>21.8</td>
<td><strong>15.2</strong></td>
<td>19.8</td>
</tr>
<tr>
<td>DSD-BLYP-D3</td>
<td>20.6d</td>
<td><strong>18.6</strong></td>
<td>19.0</td>
<td>22.5</td>
<td><strong>17.1</strong></td>
<td>24.1</td>
</tr>
<tr>
<td>DLPNO-CCSD(T)c</td>
<td>26.8</td>
<td><strong>22.0</strong></td>
<td>23.2c</td>
<td>26.8</td>
<td><strong>19.8</strong></td>
<td>28.2</td>
</tr>
</tbody>
</table>

[a] Comparison of barrier heights obtained across a variety of methods with geometries optimized in
gas phase and with CPCM(THF). Barrier heights given in kcal/mol from “Method”/def2-TZVP–
CPCM(THF)/BP86-D3/LANL2TZ(f)–6-31G(d) (with or without CPCM(THF)). [b] (chair/ax)-TS5. [c]
(boat/ax)-TS14. [d] (exo/boat/ax)-TS15. [e] Single point with the cc-pVTZ basis set (with SK-MCDHF-
RSC pseudopotential on Pd; i.e., cc-pVTZ-PP), “NormalPNO” settings.

For completeness, intermediates derived from the R enantiomer of starting material 1 were also investigated (Table 1.4). An analogous result was obtained. Note: Transition
state geometries obtained with CPCM(THF) solvation were prone to an additional small imaginary vibrational mode (<5 cm⁻¹) corresponding to a rocking of the ligand backbone. With the point charge CPCM scheme these were unable to be eliminated, however they bear no consequences on the final results.

**Table 1.4.** Decarboxylation barrier heights of complexes derived from the (R) enantiomer of 1.a

<table>
<thead>
<tr>
<th>Method</th>
<th>(chair/ax)-TS14_diast2</th>
<th>(exo/chair/ax)-TS15_diast2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP86-D3</td>
<td>12.3</td>
<td>18.5</td>
</tr>
<tr>
<td>B3LYP-D3</td>
<td>16.7</td>
<td>24.8</td>
</tr>
<tr>
<td>PBE0-D3</td>
<td>21.0</td>
<td>25.5</td>
</tr>
<tr>
<td>M06</td>
<td>17.4</td>
<td>21.5</td>
</tr>
<tr>
<td>DSD-BLYP-D3</td>
<td>18.8</td>
<td>23.1</td>
</tr>
<tr>
<td>DLPNO-CCSD(T)ᵇ</td>
<td>21.6</td>
<td>27.7</td>
</tr>
</tbody>
</table>

[a] Barrier heights reported in kcal/mol from single point calculations with the listed functional/method, the def2-TZVP basis set on all atoms and CPCM(THF) on geometries obtained with BP86-D3/LANL2TZ(f)–6-31G(d). [ᵇ] Single point with the cc-pVTZ basis set (with SK-MCDHF-RSC pseudopotential on Pd; i.e., cc-pVTZ-PP) and “NormalPNO” settings.

1.5.4 **PREDICTION OF ENANTIOSELECTIVITY**

Given the challenge of calculating energies to within the sub-kcal/mol level of accuracy required for accurate prediction of reaction enantioselectivity, we chose to employ a variety of control experiments to assess the fidelity of our results. With geometries obtained at the BP86-D3/LANL2TZ(f)–6-31G(d) level, we began by evaluating single point energies with a variety of density functional methods (Table 1.5). These methods include generalized gradient approximation (GGA), meta-GGA, hybrid...
meta-GGA, range-separated hybrid GGA, and double hybrid functionals. Similar trends in relative free energies are obtained across each of the methods tested.

**Table 1.5. Comparison of relative free energies obtained across a variety of density functional methods.**

<table>
<thead>
<tr>
<th></th>
<th>BP86-D3</th>
<th>BLYP-D3</th>
<th>revPBE-D3</th>
<th>M06-L</th>
<th>B3LYP-D3</th>
<th>B3LYP-D3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>5.4</td>
<td>6.0</td>
<td>5.3</td>
<td>4.2</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>(Re/chair/eq)-TS20</td>
<td>1.6</td>
<td>2.2</td>
<td>1.7</td>
<td>1.4</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>(Re/boat/eq)-TS20</td>
<td>5.5</td>
<td>5.3</td>
<td>5.0</td>
<td>4.3</td>
<td>5.6</td>
<td>5.2</td>
</tr>
<tr>
<td>(Si/chair/ax)-TS20</td>
<td>2.0</td>
<td>2.4</td>
<td>1.9</td>
<td>1.8</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>(Si/boat/ax)-TS20</td>
<td>1.0</td>
<td>0.8</td>
<td>0.9</td>
<td>0.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>(Si/chair/eq)-TS20</td>
<td>4.2</td>
<td>5.0</td>
<td>4.1</td>
<td>3.7</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>(Si/boat/eq)-TS20</td>
<td>3.2</td>
<td>3.4</td>
<td>2.9</td>
<td>2.6</td>
<td>3.6</td>
<td>3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PBE0-D3</th>
<th>TPSSh-D3</th>
<th>M06</th>
<th>M06-2X</th>
<th>oB97X-D3</th>
<th>mPW2PLYP-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>5.2</td>
<td>5.9</td>
<td>3.6</td>
<td>4.3</td>
<td>6.1</td>
<td>5.1</td>
</tr>
<tr>
<td>(Re/chair/eq)-TS20</td>
<td>1.2</td>
<td>1.7</td>
<td>0.4</td>
<td>1.2</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>(Re/boat/eq)-TS20</td>
<td>5.6</td>
<td>5.8</td>
<td>4.0</td>
<td>4.4</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>(Si/chair/ax)-TS20</td>
<td>2.5</td>
<td>2.2</td>
<td>2.1</td>
<td>2.8</td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td>(Si/boat/ax)-TS20</td>
<td>1.5</td>
<td>1.0</td>
<td>1.3</td>
<td>1.0</td>
<td>0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>(Si/chair/eq)-TS20</td>
<td>4.1</td>
<td>4.2</td>
<td>3.2</td>
<td>4.0</td>
<td>4.3</td>
<td>4.0</td>
</tr>
<tr>
<td>(Si/boat/eq)-TS20</td>
<td>3.5</td>
<td>3.3</td>
<td>2.8</td>
<td>2.8</td>
<td>3.0</td>
<td>4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PWBP95-D3</th>
<th>DSD-BLYP-D3</th>
<th>DSD-PBE-P86-D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>5.5</td>
<td>5.1</td>
<td>5.0</td>
</tr>
<tr>
<td>(Re/chair/eq)-TS20</td>
<td>1.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>(Re/boat/eq)-TS20</td>
<td>5.5</td>
<td>5.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 55 Comprehensive Quantum Mechanics Investigation

<table>
<thead>
<tr>
<th></th>
<th>Z1</th>
<th>Z2</th>
<th>Z3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Si/chair/ax)-TS20</td>
<td>2.4</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>(Si/boat/ax)-TS20</td>
<td>1.4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>(Si/chair/eq)-TS20</td>
<td>3.9</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>(Si/boat/eq)-TS20</td>
<td>3.3</td>
<td>3.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

[a] Relative free energies reported in kcal/mol from single point calculations with the listed functional, the def2-TZVP basis set on all atoms and CPCM(THF) on geometries obtained with BP86-D3/LANL2TZ(f)–6-31G(d). [b] A mixed basis set consisting of LANL2TZ(f) on palladium and 6-311+G(d) on all other atoms utilized.

Given the potentially significant role of noncovalent interactions in differentiating the energy between diastereomeric transition states, we sought to further refine our calculated \( \Delta \Delta G^\ddagger \) by employing single point calculations with domain based local pair natural orbital coupled-cluster theory (DLPNO-CCSD(T)) (Table 1.6). For these calculations, we employ the cc-pVTZ basis set on all atoms, with the SK-MCDHF-RSC relativistic effective core potential on palladium. Calculations are additionally carried out with the “TightPNO” criteria for the two lowest energy diastereomeric transition states found from calculations with the “NormalPNO” settings.

Under standard conditions at 25 °C, an enantiomeric excess of 88% is experimentally observed, corresponding to an apparent \( \Delta \Delta G^\ddagger \) of 1.6 kcal/mol. Comparing the relative energies of only the two lowest energy diastereomeric transition states with “NormalPNO” and “TightPNO” cutoffs affords a calculated \( \Delta \Delta G^\ddagger \) of 2.3 and 1.9 kcal/mol, respectively, corresponding to 96% ee and 92% ee. From a Boltzmann-weighted average over unique transition states (with “NormalPNO”), 94% ee is calculated. These results are
in good agreement with experimentally obtained values, and thus highlight the efficacy of
the DLPNO-CCSD(T) in the context of asymmetric catalysis.

**Table 1.6. Comparison of relative free energies obtained at the DLPNO-CCSD(T) level of theory.**

<table>
<thead>
<tr>
<th></th>
<th>DLNO-CCSD(T)</th>
<th>DLNO-CCSD(T)</th>
<th>DLNO-CCSD(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NormalPNO</td>
<td>NormalPNO</td>
<td>TightPNO</td>
</tr>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>6.6</td>
<td>5.9</td>
<td>–</td>
</tr>
<tr>
<td>(Re/chair/eq)-TS20</td>
<td>1.4</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>(Re/boat/eq)-TS20</td>
<td>6.6</td>
<td>6.1</td>
<td>–</td>
</tr>
<tr>
<td>(Si/chair/ax)-TS20</td>
<td>3.0</td>
<td>2.8</td>
<td>–</td>
</tr>
<tr>
<td>(Si/boat/ax)-TS20</td>
<td>2.2</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>(Si/chair/eq)-TS20</td>
<td>4.5</td>
<td>4.0</td>
<td>–</td>
</tr>
<tr>
<td>(Si/boat/eq)-TS20</td>
<td>4.4</td>
<td>4.2</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] Relative free energies reported in kcal/mol with DLPNO-CCSD(T)/cc-pVTZ–PCPM(THF)//BP86-
D3/LANL2TZ(f)–6-31G(d). bUsing the def2-TZVP basis set on all atoms.

Further controls were carried out in which transition state optimizations were
carried out without D3 dispersion correction (Table 1.7), and with the B3LYP-D3 hybrid
functional (Table 1.8). Both of these trials offer similar overall results to those obtained
with BP86-D3 geometries.

**Table 1.7. Optimization without D3 corrections (BP86).**

<table>
<thead>
<tr>
<th></th>
<th>M06 b</th>
<th>DLNO-CCSD(T) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>4.4</td>
<td>5.9</td>
</tr>
<tr>
<td>(Re/chair/eq)-TS20</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>(Re/boat/eq)-TS20</td>
<td>5.3</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

<table>
<thead>
<tr>
<th></th>
<th>M06</th>
<th>DLNO-CCSD(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/ax)-TS20</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Re/boat/ax)-TS20</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>(Si/chair/ax)-TS20</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>(Si/boat/ax)-TS20</td>
<td>1.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>


**Table 1.8. Optimization with B3LYP-D3.**

Facile interconversion between (Re)-13 and (Si)-13

A previous computational investigation into the reaction mechanism of a truncated system (beginning from enolate intermediates) highlights internal rearrangements of palladium enolates prior to C–C bond formation as a possible origin of enantioinduction.21 This hypothesis is dependent on kinetic quenching (rather than equilibration) of enolates (Re)-13 and (Si)-13 by their corresponding C–C bond forming events. However, the authors of that study recognize that a transition state leading to the facile equilibration of
(Re/Si)-13 may exist, but do not explore further, leaving the origins of enantioinduction unresolved. In this investigation, a low energy transition state connecting (Re)-13 and (Si)-13 on the PES is found (TS24, ΔG‡ ~ 5 kcal/mol). TS24 is significantly lower in energy than the next lowest transition states, which are those of C–C bond formation (TS20). Thus, enolates (Re)-13 and (Si)-13 are expected to be in thermal equilibrium. Hence, internal rearrangements of palladium enolates, followed by kinetic quenching via C–C bond formation, is not responsible for enantioinduction.

Additional potentially lower energy transition states for the interconversion of (Re)-13 and (Si)-13 likely persist, however are challenging to optimize given the flat nature of the PES and conformational flexibility of the enolate fragment. It is worth noting that highly decorated, sterically encumbered substrates may experience a barrier to enolate equilibration similar or greater in magnitude to that of C–C bond formation. Should this be the case, the mechanism of decarboxylation and/or choice of masked enolate synthon would play a large role in the resultant product enantioselectivity. The pathways, intermediates, and consideration described in this research provide a framework from which this would be evaluated.

Trans Influence in Oxidative Addition

Our investigations into the mechanism of oxidative addition reveal the lowest energy process for C–O bond cleavage to be that of an anti displacement-type of mechanism (Figure 1.3). The lowest energy conformer of four unique transition states are considered, in which displacement of the carboxylate leaving group occurs trans to either
the nitrogen (\(t\)-N) or phosphorus (\(t\)-P) of the PHOX ligand, with either exo or endo approach of the allylic fragment.

Table 1.9. Relative free energies (in kcal/mol) of isomeric oxidative addition transition states at various levels of theory.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>BP86-D3</th>
<th>B3LYP-D3</th>
<th>PBE0-D3</th>
<th>M06</th>
<th>DLPNO-CCSD(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(exo/t-N)-TS4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(endo/t-N)-TS4</td>
<td>1.4</td>
<td>2.0</td>
<td>1.9</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>(exo/t-P)-TS4</td>
<td>5.9</td>
<td>7.6</td>
<td>7.3</td>
<td>7.5</td>
<td>9.3</td>
</tr>
<tr>
<td>(endo/t-P)-TS4</td>
<td>3.8</td>
<td>4.8</td>
<td>5.5</td>
<td>6.2</td>
<td>6.5</td>
</tr>
</tbody>
</table>

[a] Relative free energies reported in kcal/mol with geometries obtained with BP86-D3/LANL2TZ(f)–6-31G(d). Single point calculation with def2-TZVP basis set on all atoms (def2-ECP on Pd) and CPCM(THF). [b] Single point calculation with DLPNO-CCSD(T)/cc-pVTZ/CPCM(THF) with “NormalPNO” settings.

An energetic preference of 3.8–6.5 kcal/mol is found for the \(t\)-N transition states across the various levels of theory investigated (Table 1.9). While this may be in part due to steric interactions between the carboxylate leaving group and the phenyl rings of the triaryl phosphine ligand, we also consider electronic effects. In accordance with the anticipated trans influence, elongated Pd–X bond lengths trans to phosphorus are observed (Figure 1.3). As a hypothesis for the origins of the preference for \(t\)-N transition states, we consider the research of De Proft and co-workers,\(^43\) who provide a ligand-field-based rational for the trans influence in related square planar Pt(II) complexes. In brief, the authors suggest the repulsion between a strong trans ligand (T) and the ligand trans to T (L) arises from further hybridization (in unsymmetrical d\(^8\) complexes) between the occupied 2a’ and
virtual 3a’ MOs (Figure 1.15) resulting in a net decreas in Pt–L σ-bonding character, and thus, a longer bond length.

Figure 1.15. Select frontier MOs of a model PtII complex highlighting potential hybridization of 2a’ and 3a’.

In the case of the (PHOX)Pd complexes, we consider this effect may play a role in the calculated preference for displacement trans to nitrogen. The reduced Pd–C(OCOR) bond length in the t-N transitions states should be conducive to enhanced overlap with the σ*(C–O), thus, facilitating displacement of the carboxylate leaving group.

Additional Computations for “Experiment and Discussion” Section of Manuscript

Experimentally, it was determined that for β-ketoester substrate 1, employing the more electron poor (S)-(CF₃)₃-t-BuPHOX ligand in place of the standard (S)-t-BuPHOX ligand, with otherwise identical reaction conditions, did not result in a significant change in reaction rate. Computationally, an identical result was obtained. Henceforth, the suffix “_CF₃” denotes structures that are re-optimized using the (R)-(CF₃)₃-t-BuPHOX ligand. The apparent barrier heights of the two lowest energy decarboxylation pathways (Pathways 2 and 3, see text) were then compared with both ligands at the DLPNO-CCSD(T) level of
theory. Similar results are obtained with “NormalPNO” and “TightPNO” cutoffs (Table 1.10).

**Table 1.10.** Comparison of barrier heights to decarboxylation with the standard (S)-t-BuPHOX and electron poor (S)-(CF₃)₃-t-BuPHOX ligands.⁴

<table>
<thead>
<tr>
<th></th>
<th>TS14</th>
<th>TS15</th>
<th>TS14_CF₃</th>
<th>TS15_CF₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>NormalPNO</td>
<td>22.0</td>
<td>23.5</td>
<td>22.4</td>
<td>21.6</td>
</tr>
<tr>
<td>TightPNO</td>
<td>21.9</td>
<td>24.3</td>
<td>22.2</td>
<td>22.4</td>
</tr>
</tbody>
</table>

[a] Free energies reported in kcal/mol with geometries obtained with BP86-D3/LANL2TZ(f)–6-31G(d).
Single point calculation with DLPNO-CCSD(T)/cc-pVTZ–PCM(THF).

In order to experimentally probe the interplay of inner- and outer-sphere mechanistic pathways, we prepared α-phenyl β-ketoester 20 as well as the corresponding enol carbonate 21. Highlighting the role of decarboxylative pathway on subsequent C–C bond formation, compounds 20 and 21 both yield α-phenyl product 22, however with differing degrees of enantioenrichment. In analogous fashion to intermediates derived from substrate 1 (R = Me), the corresponding set of seven-membered pericyclic inner-sphere C–C bond forming transition states (TS20_Ph) are considered. These initial results suggest that inner-sphere C–C bond formation for these α-phenyl enolates may give rise to a similar degree of product enantioenrichment as the α-methyl case (Table 1.11).

**Table 1.11.** Inner-sphere reductive elimination transition states with α-phenyl substrate.

<table>
<thead>
<tr>
<th>Transition State</th>
<th>G(rel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/axial)-TS20_Ph_i</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Relative Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Re/chair/axial)-TS20_Ph_ii</td>
<td>1.3</td>
</tr>
<tr>
<td>(Re/boat/axial)-TS20_Ph_i</td>
<td>4.9</td>
</tr>
<tr>
<td>(Re/boat/axial)-TS20_Ph_ii</td>
<td>3.6</td>
</tr>
<tr>
<td>(Si/chair/axial)-TS20_Ph_i</td>
<td>4.1</td>
</tr>
<tr>
<td>(Si/chair/axial)-TS20_Ph_ii</td>
<td>4.1</td>
</tr>
<tr>
<td>(Si/boat/axial)-TS20_Ph_i</td>
<td>1.3</td>
</tr>
<tr>
<td>(Si/boat/axial)-TS20_Ph_ii</td>
<td>1.3</td>
</tr>
</tbody>
</table>

[a] Relative free energies reported in kcal/mol from the M06/def2-TZVP–CPMC(THF)//BP86-D3/LANL2TZ(f)–6-31G(d) level of theory. Note that Re and Si exchange compared to TS20 with α-Me groups due to the priority of the Ph substituent.

1.5.6 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

**Allyl 2-oxo-1-phenylcyclohexane-1-carboxylate (20)**

Compound 20 was prepared in following literature precedent. To a flame dried flask equipped with a stir bar under a nitrogen atmosphere were added phenylboronic acid (1.46 g, 12.1 mmol, 1.10 equiv), lead(IV) acetate (5.34 g, 12.1 mmol, 1.10 equiv), and mercury(II) acetate (0.38 g, 1.21 mmol). The solids were dissolved in anhydrous chloroform (20 mL) and the solution was heated to 40 °C. After one hour at 40 °C, a solution of allyl 2-oxocyclohexane-1-carboxylate (2.00 g, 11.0 mmol, 1.00 equiv) in pyridine (11.0 mL, 1.0 M) was added to the reaction, and stirring at 40 °C was continued for 18 hours. Upon complete consumption of β-ketoester starting material, as determined by TLC (10%
EtOAc/hexanes), the reaction mixture was let cool, then filtered through a plug of Celite® washing with chloroform. The combined organic phase was washed with aqueous H$_2$SO$_4$ (3 M, 20 mL). The resulting aqueous layer was extracted twice with chloroform (20 mL). The combined organic layer was once again washed with water (20 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and volatiles were removed in vacuo. The crude oil was purified by flash column chromatography (10% EtOAc/hexanes) to afford β-ketoester 20 (2.00 g, 70% yield) as a colorless oil, which solidifies to an amorphous solid upon refrigeration.

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 7.27 – 7.23 (m, 2H), 5.86 (ddt, $J = 17.2$, 10.5, 5.6 Hz, 1H), 5.25 – 5.17 (m, 2H), 4.65 (dq, $J = 5.6$, 1.5 Hz, 2H), 2.81 – 2.73 (m, 1H), 2.60 – 2.53 (m, 2H), 2.48 – 2.40 (m, 1H), 2.03 – 1.93 (m, 1H), 1.90 – 1.73 (m, 3H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 206.8, 171.1, 136.6, 131.6, 128.6, 128.0, 127.8, 118.6, 66.7, 66.1, 40.8, 35.2, 27.8, 22.1

**IR (Neat Film, NaCl):** 2989, 1714, 1434, 1214 cm$^{-1}$.

**HRMS (MM: FD+):** m/z calc’d for C$_{16}$H$_{18}$O$_3$ [M]$^+$: 258.1256, found 258.1265.

---

**General procedure for asymmetric allylic alkylation screening**

The procedure for the Pd-catalyzed dicarboxylic allylic alkylation is followed as described in our previous reports. In a nitrogen filled glovebox, an oven dried
vial is charged with a stir bar, tris(dibenzylideneacetone)dipalladium(0) (2.28 mg, 2.50 µmol), and ligand (6.25 µmol). Solvent (1.0 mL) is added, and the catalyst stock solution is pre-stirred for 30 minutes at 25 °C. To a separate vial equipped with a stir bar is added a solution of substrate (0.05 mmol) in solvent (1.0 mL, 0.05 M). To the solution of substrate is added 0.50 mL of the pre-stirred catalyst stock solution [1.25 µmol Pd\(_2\)(dba)\(_3\), 3.13 µmol ligand]. The reaction vessel is then sealed with electrical tape and removed from the glovebox. Stirring is continued at 25 °C for 12 hours (unless otherwise noted). Volatiles are then removed in vacuo and the product is purified by silica gel flash column chromatography or preparatory-scale TLC.

(S)-2-allyl-2-methylcyclohexan-1-one ((S)-2)

Known compound – Spectral data matches that of prior literature reports.\(^2\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 5.69\) (ddt, \(J = 16.2, 10.9, 7.4\) Hz, 1H), 5.07 – 5.01 (m, 2H), 2.42 – 2.33 (m, 3H), 2.23 (dd, \(J = 13.8, 7.2\) Hz, 1H), 1.91 – 1.67 (m, 5H), 1.64 – 1.55 (m, 1H), 1.07 (s, 3H).

Note: Compound is moderately volatile, and care should be exercised when removing solvent in vacuo.
(S)-2-allyl-2-phenylcyclohexan-1-one ((S)-22)

Known compound – Spectral data matches that of prior literature reports.\(^45\)

\(^1\text{H} \text{NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 7.35 (t, \(J = 7.7\) Hz, 2H), 7.26 – 7.22 (m, 1H), 7.15 (d, \(J = 7.5\) Hz, 2H), 5.44 (dddd, \(J = 17.0, 10.2, 7.9, 6.7\) Hz, 1H), 4.92 (d, \(J = 10.2\) Hz, 1H), 4.88 (d, \(J = 17.0\) Hz, 1H), 2.67 (dq, \(J = 14.4, 3.0\) Hz, 1H), 2.51 (dd, \(J = 14.0, 6.7\) Hz, 2H), 2.44 (dd, \(J = 14.0, 8.0\) Hz, 2H), 2.38 – 2.26 (m, 2H), 1.99 – 1.91 (m, 1H), 1.83 – 1.63 (m, 4H).

**SFC conditions:** 5% IPA, 2.5 mL/min, Chiralpak OJ-H column, \(\lambda = 210\) nm, \(t_R\) (min): minor = 3.31, major = 3.07.

**Racemic 22:**

**From enol carbonate 21:**
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation

From $\beta$-ketoester 20:

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.046</td>
<td>MF</td>
<td>0.0731</td>
<td>842.69116</td>
<td>192.14436</td>
<td>56.8607</td>
</tr>
<tr>
<td>2</td>
<td>3.287</td>
<td>FM</td>
<td>0.0768</td>
<td>639.33521</td>
<td>138.66087</td>
<td>43.1393</td>
</tr>
</tbody>
</table>

From $\beta$-ketoester 20 with optimal conditions (entry 4 in Figure 1.14):

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.169</td>
<td>MN</td>
<td>0.0760</td>
<td>269.91296</td>
<td>59.16746</td>
<td>61.6800</td>
</tr>
<tr>
<td>2</td>
<td>3.420</td>
<td>FM</td>
<td>0.0784</td>
<td>167.68944</td>
<td>35.64637</td>
<td>38.3200</td>
</tr>
<tr>
<td>3</td>
<td>3.867</td>
<td>MF</td>
<td>0.0608</td>
<td>255.43756</td>
<td>135.37050</td>
<td>68.0706</td>
</tr>
<tr>
<td>4</td>
<td>3.027</td>
<td>PF</td>
<td>0.0634</td>
<td>237.08202</td>
<td>62.32189</td>
<td>31.9234</td>
</tr>
</tbody>
</table>
1.6 REFERENCES AND NOTES


Enantioselective Decarboxylative Allylic Alkylation Reactions of Ketones. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843. Note that product enantioenrichment follows a linear correlation with PHOX ligand enantioenrichment. An error was found in a unit conversion (minutes to seconds) in the supporting information data. The correct rate in inverse seconds is $k = 1.58 \times 10^{-3} \text{ s}^{-1}$. While this error was initially propagated it is minor and does not affect any subsequent conclusions.


(15) (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the


(19) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 74 Comprehensive Quantum Mechanics Investigation


(c) Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. Evidence of the
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 76 Comprehensive Quantum Mechanics Investigation


Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 78
Comprehensive Quantum Mechanics Investigation

(36) Hegedus, L. S.; Darlington, W. H.; Russell, C. E. Cyclopropanation of Ester
5196.

(37) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. Isolation
and X-Ray Crystal Structure of a Palladacyclobutane: Insight into the Mechanism

(38) Note that in reference 2h a slight kinetic resolution was observed.

(39) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. A Facile and Modular

(40) Neese, F.; Wennmohs, F.; Hansen, A.; Becker, U. Efficient, Approximate and
Parallel Hartree-Fock and Hybrid DFT Calculations. A ‘Chain-of-Spheres’

(41) Stoychev, G. L.; Auer, A. A.; Neese, F. Automatic Generation of Auxiliary Basis

(42) (a) Chéron, N.; Jacquemin, D.; Fleurat-Lessard, P. A Qualitative Failure of B3LYP
(b) Burke, K.; Perdew, J. P.; Ernzerhof, M. Why the Generalized Gradient
Approximation Works and How to Go beyond It. International Journal of Quantum
Chemistry 1997, 61, 287–293.
Chapter 1 – Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A 79
Comprehensive Quantum Mechanics Investigation

(43) Pinter, B.; Speybroek, V. V.; Waroquier, M.; Geerlings, P.; De Proft, F. trans effect

(44) Akula, R.; Doran, R.; Guiry, P. J. Highly Enantioselective Formation of α- Allyl-α- 
Arylcyclopentanones via Pd-Catalysed Decarboxylative Asymmetric Allylic

(45) Trost, B. M.; Schroeder, G. M.; Kristensen, J. Palladium-Catalyzed Asymmetric
APPENDIX 1

Spectra Relevant to Chapter 1: Mechanism of the Pd-catalyzed Asymmetric Allylic Alkylation: A Comprehensive Quantum Mechanics Investigation
Figure A1.1. $^1$H NMR (400 MHz, CDCl$_3$) of compound 20.
Figure A1.2. Infrared spectrum (Thin Film, NaCl) of compound 20.

Figure A1.3. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 20.
CHAPTER 2

Analysis of the Pd $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction†

2.1 INTRODUCTION

Selectivity in pericyclic reactions is a tangible manifestation of the quantum mechanical wave-like behavior of electrons. Bringing an acyclic system to a cyclic transition state introduces constructive/destructive interferences amongst the spatial wavefunctions of the component electrons, which are governed by orbital orthogonality requirements as prescribed by the Pauli principle. With proper constructive overlaps, the bond order of the transition state will match that of the reactant(s) and product(s) – i.e., net covalent bonding is maintained through the transition state. Alternatively, destructive interferences are incurred that do not allow for continual bonding – i.e., a covalent bonding interaction is lost, and the electronic configuration is that of a diradical. Several conceptual frameworks are commonly employed to analyze the nature of bonding in pericyclic transition states, though these are simply different projections of the same underlying physics. These tools include orbital and state correlation diagrams, frontier molecular orbital (FMO) theory,¹ the orbital phase continuity principle² in valence bonding wavefunctions, and the concept of transition state (anti)aromaticity.³

Pericyclic reactivity is also commonplace in organometallic systems.⁴ In fact, the elementary step responsible for enantioinduction in the inner-sphere asymmetric Tsuji

¹Performed under the co-advisory of Prof. William A. Goddard III. This chapter has been reproduced with permission from J. Am. Chem. Soc. 2020, 142, 19033–19039. © 2020 American Chemical Society.
allylic alkylation is C–C bond formation through a synchronous, seven-membered pericyclic transition state (TS20) (Figure 2.1A). Since the original computational reports by our groups and others, the relationship between this class of seven-membered transition states to those of the canonical pericyclic reactions as described by Woodward and Hoffmann is underexplored. Exemplifying the peculiar nature of the reaction, an analogous transformation in a system comprised of main group elements remains elusive.

Given the key role of this seven-membered pericyclic process in asymmetric catalysis, we sought to delineate the underlying reactivity paradigm that enables this unique transformation (Figure 2.1B).

**Figure 2.1.** Seven-centered cyclic transition states in Pd catalysis.

A. Seven-membered transition state in C–C bond formation:

B. This research: \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reactions.

---

2.2 RESULTS AND DISCUSSION

To obtain a general understanding of this bond forming event, we first examined an analogous system comprised of main group elements, namely the reaction of diallyl sulfone (23) to sulfur dioxide (24) and 1,5-hexadiene (25) (Figure 2.1B). If the geometry of the seven-membered cheletropic transition state (TS24) is constrained to match that of TS20, then a suprafacial relationship amongst the eight correlating orbitals with linear departure of the cheleleuge is mandated. Thus, the transformation of 23 to 24 + 25 is designated \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reactions.
Chapter 2 – Analysis of the Pd-catalyzed \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) Pericyclic Reaction

+ \pi 2s + \sigma 2s + \sigma 2s] and the reverse as \([\omega 2s + \pi 2s + \pi 2s + \sigma 2s]\). With four suprafacial two-electron terms, the ground-state pericyclic reaction of 23 to 24 + 25 is anticipated to be symmetry-forbidden by the generalized Woodward–Hoffmann rules.\(^8\) An identical conclusion is reached for chelefugues such as CO and N\(_2\) in the ground state.\(^10\) Given the low thermal barriers with which the Pd-catalyzed transformations proceed (\(\Delta G^\ddagger = 10–20\) kcal/mol),\(^5\) we became curious as to whether the transformation is similarly forbidden for a L\(_n\)Pd\(^{0}\)-like chelefuge.

To uncover the electronic origins that enable the transition metal-mediated pericyclic processes, we turned to ab initio Quantum Mechanics (QM) calculations. Calculations were carried out with the ORCA ab initio package (see 2.4. Supporting Information for full details).\(^11\) Complete active space self-consistent field (CASSCF) theory is utilized to capture the multiconfigurational nature of the potential energy surface (PES), where the (8,8) active space is defined to be the eight valence electrons in eight correlating orbitals as described by orbital correlation diagrams. Dynamical correlation is accounted for via N-electron valence state perturbation theory\(^12\) (NEVPT2) single point calculations on the CASSCF wavefunctions. All geometry optimizations and frequency calculations were carried out with the triple-\(\zeta\) quality def2-TZVP basis set\(^13\) on all atoms (with the small core ECP28MWB pseudopotential\(^14\) on Pd, \textit{i.e.}, 18 explicit electrons including the 4s and 4p core electrons). For transition metal complexes with insignificant multiconfigurational character, geometries were obtained with density functional theory (DFT) (PBE0-D3(BJ)/def2-TZVP)\(^15\) followed by CASSCF/NEVPT2 single point calculations with the def2-TZVPP basis set. Solvation was accounted for in single point
**Figure 2.2.** (A) Orbital correlation diagram for the $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ quasi-cheletropic reaction of diallyl sulfone.\(^a\) (B) Symmetry-forbidden C–C bond formation from diallyl sulfone 23.\(^b\)

A. Orbital correlation diagram for the $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction of diallyl sulfone:

B. Ground state reaction of 23 to 24 + 25:

C. Electronic structure of diradical 30:

[a] Select natural orbitals from the CAS(8,8) active space shown. [b] CASSCF-based free energy estimates in kcal/mol with the NEVPT2 corrected values in parentheses.

calculation with the SMD model for THF.\(^{16}\) All energies reported are solvated free energies at 298.15 K.
Beginning with main group analog diallyl sulfone (23), generation of symmetry-adapted linear combinations of correlating valence orbitals under approximate C\textsubscript{2} symmetry affords symmetric (\(a\)) and antisymmetric (\(b\)) sets of \(\sigma/\sigma^*\)(C–S) and \(\pi/\pi^*\)(C–C) orbitals (Figure 2.2A). Correlating these orbitals to those of the product implies an avoided crossing along the ground state potential energy surface (PES) as the diabatic state describing 23, \(|\Phi_A\rangle\), corresponds to a doubly excited state of the products. Likewise, a single transition state connecting 23 to 24 + 25 was not found on the CASSCF potential energy surface. Rather, a stepwise process involving singlet diradical intermediate 30 was found (Figure 2.2B).\textsuperscript{17} At this point, the ground state configuration interaction (CI) vector possesses nearly equal contributions of configurations \(|\Phi_S\rangle\) and \(|\Phi_A\rangle\), leading to a diradical index \(d = 98.0\%\) (Figure 2.2C).\textsuperscript{18} Calculations with multreference iterative Difference Dedicated CI (IDDCI) theory provide \(d = 95.4\%\) and a singlet/triplet exchange coupling constant (\(J\)) of 83 cm\(^{-1}\).\textsuperscript{19}

In summary, the required crossing of the starting material (23) and product (24 + 25) diabatic ground states renders the concerted \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reaction symmetry-forbidden. The ground state PES of 23 \(\rightarrow\) 24 + 25 is characterized by a stepwise mechanism involving weakly coupled diradical 30, with an overall \(\Delta G^\ddagger\) of \(>50\) kcal/mol — contrasting the low thermal barriers of Pd-catalyzed transformations (\(\Delta G^\ddagger = 10–20\) kcal/mol).\textsuperscript{5} Given this, we became curious as to whether the Pd-catalyzed transformation is similarly symmetry-forbidden, proceeding through a low energy diradical intermediate/state, or whether a unique set of symmetry elements describe the transformation that conserves orbital symmetry through the reaction.
In order to probe this hypothesis, we first considered the case of a simplified bis-(η^1-allyl)Pd(II) complex 26 (Figure 2.3A). Contrary to 23, we find a single low energy transition state (TS_25), with ΔG‡ = 13.4 kcal/mol, on the spin-restricted DFT (PBE0-D3(BJ)/def2-TZVP) PES connecting 26 to 28 (Figure 2.3B). We obtain a similar result for (η^1-allyl)Pd(II) enolate 27. We find that the ground-state single-determinant wavefunction along the PES is stable with respect to symmetry breaking, suggesting a single closed-shell singlet (CSS) configuration is dominant. The existence of a saddle point smoothly connecting 26 to 28 on a PES derived from the CSS state of a single-determinant wavefunction points to the absence of an avoided crossing. Moreover, this suggests that simple DFT geometries should be reliable for these Pd complexes and will be used in the following.

For comparison to the symmetry-forbidden transformation of 23 to 24 + 25, we construct the corresponding orbital correlation diagram for the conversion of 26 to 28 (Figure 2.3A). The four occupied correlating orbitals of starting complex 6 are identical in symmetry to those of diallyl sulfone 13 (two a and two b symmetry elements). However, unlike the products of the thermally-forbidden reaction (24 + 25), complex 28 maintains the symmetry of ground-state minimum 26. This is further evident in the composition of the ground-state CASSCF wavefunction at TS_25, with weights of 0.86 and 0.02 for the dominant CSS configuration and second largest contributor, respectively. Note the absence of configurations corresponding Zwitterionic states or mixing of ground and doubly excited states describing a diradical configuration. Control experiments do not find evidence of redox noninnocence of the PHOX ligand scaffold. Thus, our calculations suggest the Pd
Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction

$[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction is symmetry-allowed. While introducing heteroatoms into the system formally lowers the symmetry, this has no effect on the underlying physics. Hence, the transformation of Pd$^{II}$ enolate complex 27 to 29 is also symmetry-allowed in the ground-state (Figure 2.3B).

The symmetry of the lone pair-like orbital of the chelefuge differentiates between the thermally-allowed and forbidden scenarios. In ground state SO$_2$, the lone pair occupies a symmetric sp$^2$ valence orbital ($2a$ in Figure 2.2A), whereas in 8/9, this corresponds to the antisymmetric Pd-based d(x$^2$–y$^2$) orbital ($2b$ in Figure 2.3A). Thus, the eight-electron seven-membered pericyclic transition is thermally-allowed in the case of Pd complexes 27, 29, and 13 by virtue of the parity of the d(x$^2$–y$^2$) orbital involved in $\sigma$ bonding with the organic scaffold (Figure 2.3C).$^{20}$ Other metal-based d orbitals can be included in this analysis but bear no consequence as these orbitals remain doubly occupied throughout the transformation.

From the perspective of frontier molecular orbital (FMO) theory, the transformation is readily interpreted as the (in)ability of the chelefuge HOMO/donor to constructively interact with the antisymmetric LUMO/acceptor of the 1,5-hexadiene in the appropriate geometry (Figure 2.4A). If constructive overlap is achieved, then net bonding is preserved through the transition state and the reaction is symmetry-allowed.$^{20a-b}$ This is the case for the Pd-catalyzed transformation as the Pd-based d(x$^2$–y$^2$) HOMO of hypothetical L$_2$Pd$^0$ chelefuge $\sigma$ bonds with the diene in a suprafacial/antaranodal fashion, i.e., with phase inversion, constructively mixing with the diene LUMO (Figure 2.4A).$^{21}$ This is not the case for the symmetric nucleophile lone pair orbitals of SO$_2$ and CO.$^{10}$
Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction

Figure 2.3. (A) Orbital correlation diagram for the pericyclic reaction of 26 to 28. Select natural orbitals of CAS(8,8) wavefunction shown. (B) Free energy changes and barriers (in kcal/mol). (C) Orbital topologies.

A. Orbital correlation diagram for the $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction of bis-$[\pi{1\text{-}}\text{allyl}]$Pd$^{II}$ complex 26:

B. The $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction of 6/7 to 8/9:

C. Relevant orbital topologies:

[a] Free energies calculated using NEVPT2 electronic energies with thermal corrections and geometries from DFT (PBE0-D3(BJ)). Full DFT energies in parenthesis.
Figure 2.4. (A) FMO perspective of the \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reaction. (B) Relevant MOs from the CAS(8,8) active space that contribute to the aromaticity of TS25. (C) NICS analysis of TS25 (green and red spheres denote negative and positive NICS values).\(^a\)

<table>
<thead>
<tr>
<th>A. Reactivity paradigm from FMOs:</th>
<th>B. Elements of Craig–Möbius aromaticity in TS25:</th>
<th>C. NICS analysis of TS25:</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="FMO" /></td>
<td><img src="image2" alt="Elements" /></td>
<td><img src="image3" alt="NICS" /></td>
</tr>
</tbody>
</table>

\(^a\) NICS values in ppm with sphere radius depicting magnitude of the shift \(r = (|\delta_{ppm}|)^{1/3}\).

It is well understood that concerted, symmetry-allowed pericyclic reactions proceed through aromatic transition states.\(^3\) Thus, if the Pd \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reaction of 26 to 28 is indeed symmetry-allowed, then TS25 should be aromatic in nature. From analysis of the active space MOs at TS25 we find elements of Craig–Möbius-like aromaticity within the \(\sigma\) bonding framework.\(^2^2\) Of particular interest, the HOMO and HOMO–2 conform to a Möbius topology with the Pd \(d(x^2–y^2)\) generating a phase inversion and an odd number of nodes (1 and 3) along the ring (Figure 2.4B).\(^2^3\) To probe this suspected aromaticity, we
employ the Nucleus-Independent Chemical Shift (NICS) method of Schleyer and coworkers.\textsuperscript{24} A NICS(0) of –19.4 ppm is calculated at the geometric center of the seven-membered ring of TS\textsuperscript{25}, indicating aromaticity.\textsuperscript{25} Likewise, a positive NICS is found at various points along the external periphery. For enhanced visualization, the NICS at points along 2D grids are displayed in Figure 2.4C.

A principal objective of our investigation is to relate electronic structure to intuitive concepts in chemical bonding. As such, we sought to explore whether the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ transformation could be properly described by valence bonding concepts such as the ubiquitous “arrow–pushing” formalism of Robinson and Ingold.\textsuperscript{26} Given the single-configurational nature of the ground state density, the concept of bond reorganization is addressed through analysis of Intrinsic Bonding Orbitals (IBOs) as described by Knizia and co-workers.\textsuperscript{27} Previously, IBO analysis was implemented to highlight “electron flow” through transition states, discern between classes of mechanisms, and evaluate synchronicity of bond making/breaking in these events.\textsuperscript{27} Generation of IBOs proceeds through a Pipek–Mezey-style localization of Kohn–Sham orbitals where orbital charge contribution to an atomic center is measured by Intrinsic Atomic Orbital (IAO) charge.\textsuperscript{27a–b} At no point in the localization are empirical concepts of valence bonding introduced, yet IBOs correspond well to two-center two-electron bonds (or lone pairs) as depicted in Lewis structures. IBOs of forming/breaking bonds at transition structures generally resemble three-center two-electron bonds describing the transformation of one localized bond to another. Hence, the progression of IBOs along a reaction coordinate offers a connection to the “arrow–pushing” formalism of Robinson and Ingold. So long as
the localized orbitals are adequately portrayed by a Lewis structure and the system is well described by a single reference wavefunction then there is utility in such analysis.

IBO analysis was carried out with the full (PHOX)Pd enolate system (Figure 2.5). Four IBOs ($\phi_i$) undergo significant displacement along the intrinsic reaction coordinate (IRC) through $13 \rightarrow \text{TS}20 \rightarrow 19$. The first of these, $\phi_1$, corresponds to the localized $\pi$(C–C) bond of the enolate fragment, which smoothly progresses to encapsulate the density of the newly formed $\sigma$(C–C) bond of the product. Likewise, $\phi_2$, $\phi_3$, and $\phi_4$ track the transformations of $\pi$(C–C) → $\pi$(C–C)', $\sigma$(Pd–C) → $n$(Pd; d(x²–y²)), and $\sigma$(Pd–O) → $\pi$(C–O), respectively. Considering these transformations together reveals an intrinsic directionality to the evolution of the local orbitals in the Pd-catalyzed $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ reaction. Inspection of the relative magnitudes of net orbital displacement along the IRC further suggests synchronicity in the bond making/breaking events of the $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ process (Figure 2.5). In accord with the initial reports of Knizia and co-workers, we also find the localized IBOs obtained from the ground state densities closely resemble valence orbitals as portrayed in simple Lewis structures. Thus, tracking the net flow of electron density is carried out in the same valence bonding framework. The result is a mechanism described by the synchronous movement of valence bonding electron pairs, or more precisely, a first principles-derived “arrow-pushing” mechanism that accounts for the net change in bonding along the reaction coordinate in a chemically intuitive orbital basis (Figure 2.5).
Figure 2.5. IBO analysis the Pd $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction.

[a] Note that the $R$ enantiomer of the $t$-BuPHOX ligand employed. Select atoms omitted for clarity.
2.3 CONCLUSIONS

In conclusion, we find the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction to be symmetry-allowed in the ground-state owing to phase inverting role of the Pd $d(x^2-y^2)$ orbital in the $\sigma$ bonding framework of the transition state. Insights from this investigation are contextualized within the Woodward–Hoffmann rules, orbital correlation diagrams, and FMO theory. As with prototypical thermally-allowed pericyclic reactions, we find the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ reaction proceeds through an aromatic transition state. Lastly, we describe a first principles-derived “arrow-pushing” mechanism from analysis the transformation of IBOs along the reaction coordinate. These efforts highlight the connection between ab initio electronic structure calculations and empirical bonding concepts, thus, facilitating a natural conceptualization of chemical bonding in these unique systems.

2.4 SUPPORTING INFORMATION

2.4.1 GENERAL COMPUTATIONAL DETAILS

All quantum mechanical calculations were performed with ORCA version 4.1 and 4.2. Geometries of open-shell species (TS27, 30, and TS28) and their precursors (23, 24 and 25) were optimized with complete active space self-consistent field (CASSCF) theory. The active space was defined as the correlating valence electrons and orbitals as obtained by the corresponding orbital correlation diagrams (see below). The triple-$\zeta$ quality def2-TZVP basis set was used on all atoms. Further details on choice of active spaces are provided below. Results obtained via broken-symmetry density functional theory (BS-DFT) are provided below for comparison. For transition metal complexes with insignificant
multiconfigurational character \( (26, 27, \text{TS}25, \text{TS}26, 28, \text{and} 29) \), geometries were obtained from dispersion-corrected DFT. The PBE0 global hybrid density functional\(^1\) paired with Becke–Johnson damped D3 dispersion corrections (henceforth referred to as PBE0-D3(BJ)) and the def2-TZVP basis set on all atoms was employed. The small-core ECP28MWB pseudopotential\(^1\) was used on Pd (18 explicit electrons including the 4s and 4p core shells are defined).

To account for dynamical correlation, N-electron valence state perturbation theory\(^1\) (NEVPT2) single point calculations were carried out on all stationary points (CASSCF and DFT geometries) from the corresponding CAS references. The strongly contracted variant of NEVPT2 was employed. Solvation was accounted for in these single point calculations with the SMD model for THF.\(^1\) In addition to single point calculations with NEVPT2/def2-TZVP/SMD(THF), for the compounds that were optimized with PBE0-D3(BJ)/def2-TZVP, additional single point calculations were carried out with PBE0-D3(BJ)/def2-TZVP/SMD(THF) for comparison.

Thermal corrections were obtained from the unscaled vibrational frequencies computed at the level of theory employed for geometry optimization. The Quasi-RRHO method\(^\text{30}\) was applied to correct for the breakdown of the harmonic oscillator approximation in low frequency vibrations. For CASSCF and DFT calculations these frequencies were computed numerically and analytically, respectively. All stationary points were characterized by the appropriate number of imaginary vibrational modes (zero for optimized geometries and one for transition states). Intrinsic reaction coordinate (IRC) analyses were carried out to ensure all transition states connect saddle points to the
appropriate minima. Conformer searching was carried out manually and energies reported are from lowest energy conformers. All energies reported in the manuscript are free energies calculated at 298.15 K and at a 1 atm standard state. Applying thermal corrections obtained at the optimization level of theory to the single point electronic energies (and solvation free energies), final Gibbs free energies are accordingly:

$$G_{\text{solv}} = E(\text{el})^{\text{SP}} + \text{ZPE} + E(\text{vib}) + E(\text{rot}) + E(\text{trans}) + k_b T - TS + \Delta G(\text{solv})^{\text{SP}}$$

The resolution of identity (RI) and chain-of-spheres\(^{31}\) (keyword = RIJCOSX) approximations were utilized for coulomb and exchange integrals, respectively. Automatic generation of auxiliary basis sets was employed (keyword = AutoAux).\(^{32}\) [Note that in geometry optimization, frequency, and IRC calculations with CASSCF, the RI and COS approximations were not used as they are not implemented with analytical (nuclear) gradients in ORCA version 4.2.0]. The finest integration grid settings (Grid7, GridX9, NoFinalGrid) were utilized in all calculations.

### 2.4.2 NEVPT2/CASSCF ACTIVE SPACE RESULTS

Unless otherwise specified, energies provided below are solvated CASSCF and NEVPT2 free energies (in Hartree) with the def2-TZVP basis set and SMD implicit solvation model for THF. Energies further refined with the def2-TZVPP basis set are provided in the text and supporting excel document (nearly identical results were obtained). Weights ($C_i^2$) of the three configurations with the largest contributions to the ground state CI coefficient vector are provided. The notation [2200] corresponds to a configuration with double occupancy of the first and second MOs of the active space and zero occupancy of the third and fourth active space MOs. Unless otherwise noted, active space MOs are
depicted as the natural orbitals of the CAS wavefunction and are rendered with a contour value of 0.07. Active spaces were chosen to include the correlating valence orbitals as determined by the corresponding Woodward–Hoffmann orbital correlation diagrams. The active space may be localized to confirm the correct active space compositions. Unless otherwise specified, state-averaging was not employed, and results are that of the lowest energy singlet state. Occupancy numbers are provided in parentheses next to MO numbers. Orbital energy eigenvalues (from NEVPT2) are listed when the ordering of the active space MOs by occupancy number is different than the ordering by energies.
Figure 2.6. MCSCF active space orbitals and energies of complex 13.

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(8,8)</td>
<td>-2022.394386</td>
</tr>
<tr>
<td>NEVPT2(8,8)</td>
<td>-2030.146571</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.87749</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.02871</td>
<td>[21211010]</td>
</tr>
<tr>
<td>0.02357</td>
<td>[22020200]</td>
</tr>
</tbody>
</table>

[a] Geometry taken from reference 5 (BP86-D3/LANL2TZ(f)[Pd],6-31G(d)). Energies above are CASSCF and NEVPT2 solvated electronic energies in Hartree. Orbital energy eigenvalues (by ascending MO) in eV: -0.5516, -0.4294, -0.2868, -0.3067, 0.1907, 0.3014, 0.3116, 0.9729. Isosurface level adjusted to 0.03 for ease of visualization.
**Figure 2.7.** MCSCF active space orbitals and energies of \( \text{TS20} \).\(^a\)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85071</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.03808</td>
<td>[22202000]</td>
</tr>
<tr>
<td>0.00849</td>
<td>[22111100]</td>
</tr>
</tbody>
</table>

[a] Geometry taken from reference 5 (BP86-D3/LANL2TZ(f)\([\text{Pd}],6-31G(d))\). Energies above are CASSCF and NEVPT2 solvated electronic energies in Hartree. Orbital energy eigenvalues (by ascending MO) in eV: \(-0.5101, -0.4084, -0.3196, -0.2322, 0.1617, 0.2167, 0.3781, 0.7215\). Isosurface level adjusted to 0.04 for ease of visualization.
Figure 2.8. MCSCF active space orbitals and energies of complex 19.\(^a\)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90785</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.02896</td>
<td>[22020200]</td>
</tr>
<tr>
<td>0.02830</td>
<td>[22202000]</td>
</tr>
</tbody>
</table>

[a] Geometry taken from reference 5 (BP86-D3/LANL2TZ(f)[Pd],6-31G(d)). Energies above are CASSCF and NEVPT2 solvated electronic energies in Hartree. Orbital energy eigenvalues (by ascending MO) in eV: -0.6097, -0.4323, -0.4795, -0.3032, 0.2540, 0.2951, 0.7745, 0.5139. Isosurface level adjusted to 0.04 for ease of visualization.
Figure 2.9. MCSCF active space orbitals and energies of diallyl sulfone 23.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
<th>CASSCF(8,8)</th>
<th>NEVPT2(8,8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90106</td>
<td>[22220000]</td>
<td>-780.349971</td>
<td>-782.106985</td>
</tr>
<tr>
<td>0.03843</td>
<td>[22111100]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01005</td>
<td>[22202000]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MO35 (1.98)  MO36 (1.98)  MO37 (1.98)  MO38 (1.08)  MO39 (0.92)  MO40 (0.02)  MO41 (0.02)  MO42 (0.02)
**Figure 2.10.** MCSCF active space orbitals and energies of TS27.

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(8,8)</td>
<td>-780.258382</td>
</tr>
<tr>
<td>NEVPT2(8,8)</td>
<td>-782.031183</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.68584</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.26002</td>
<td>[22202000]</td>
</tr>
<tr>
<td>0.01996</td>
<td>[22111100]</td>
</tr>
</tbody>
</table>

MO35 (1.98)  MO36 (1.98)  MO37 (1.95)  MO38 (1.44)

MO39 (0.56)  MO40 (0.05)  MO41 (0.02)  MO42 (0.02)
Figure 2.11. MCSCF active space orbitals and energies of diradical 30.
Figure 2.12. MCSCF active space orbitals and energies of TS28.

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy (hartree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(8,8)</td>
<td>-780.244658</td>
</tr>
<tr>
<td>NEVPT2(8,8)</td>
<td>-782.024561</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.61644</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.29502</td>
<td>[22202000]</td>
</tr>
<tr>
<td>0.04355</td>
<td>[22111100]</td>
</tr>
</tbody>
</table>

MO35 (1.98)  MO36 (1.98)  MO37 (1.92)  MO38 (1.33)  MO39 (0.67)  MO40 (0.08)  MO41 (0.03)  MO42 (0.02)
**Figure 2.13.** MCSCF active space orbitals and energies of $SO_2$ (24).

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(2,2)</td>
<td>-547.345604</td>
</tr>
<tr>
<td>NEVPT2(2,2)</td>
<td>-548.090971</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.98002</td>
<td>[20]</td>
</tr>
<tr>
<td>0.01998</td>
<td>[02]</td>
</tr>
</tbody>
</table>

MO15 (1.96)  MO16 (0.04)
**Figure 2.14.** MCSCF active space orbitals and energies of (s-cis)-1,5-hexadiene (25_cis).\(^a\)

![Diagram of 25_cis]

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.91161</td>
<td>[222000]</td>
</tr>
<tr>
<td>0.03853</td>
<td>[211110]</td>
</tr>
<tr>
<td>0.01066</td>
<td>[220200]</td>
</tr>
</tbody>
</table>

\(^a\) Active space orbitals for compound 25_cis. (Not visible at isosurface printed above: MO23 and MO24 experience slight mixing with MO25 and MO20, respectively, such that the resulting orbital energy eigenvalue for MO23 is lower than that of the symmetric MO24 (0.2332 eV and 0.2374 eV).
Figure 2.15. MCSCF active space orbitals and energies of (s-trans)-1,5-hexadiene (25_trans).

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.92057</td>
<td>[222000]</td>
</tr>
<tr>
<td>0.03724</td>
<td>[211110]</td>
</tr>
<tr>
<td>0.00985</td>
<td>[202200]</td>
</tr>
</tbody>
</table>

CASSCF(6,6) -233.004232
NEVPT2(6,6) -234.022461
Chapter 2 – Analysis of the Pd-catalyzed [$\pi 2s + \pi 2s + \sigma 2s + \sigma 2s$] Pericyclic Reaction

**Figure 2.16.** MCSCF active space orbitals and energies of complex 26.$^a$

![Diagram of complex 26 with orbitals](image)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88527</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.01649</td>
<td>[22111100]</td>
</tr>
<tr>
<td>0.01002</td>
<td>[21211010]</td>
</tr>
</tbody>
</table>

CASSCF(8,8) -1044.976965
NEVPT2(8,8) -1047.103294

[a] Active space orbitals for compound 26. Orbital energy eigenvalues (by ascending MO) in eV: –0.4110, –0.4486, –0.3197, –0.3230, 0.1931, 0.2702, 0.3169, 0.6241. In this (low energy) conformation, the antisymmetric Pd–L $\sigma^*$ and the antisymmetric C–C $\pi^*$ symmetry adapted linear combinations mix to give rise to MO50 and MO52.
Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction

**Figure 2.17.** MCSCF active space orbitals and energies of complex 27.a

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(8,8)</td>
<td>-1080.874182</td>
</tr>
<tr>
<td>NEVPT2(8,8)</td>
<td>-1083.041153</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88716</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.03125</td>
<td>[22111100]</td>
</tr>
<tr>
<td>0.02575</td>
<td>[20220020]</td>
</tr>
</tbody>
</table>

[a] Active space orbitals for compound 27. Orbital energy eigenvalues (by ascending MO) in eV: –0.5622, –0.3144, –0.4403, –0.3213, 0.1826, 0.2975, 0.2983, 0.9742. In this conformation, the $\eta^1$-allyl ligand C–C $\pi$ orbitals are nearly coplanar and further mix with the Pd-based d$(x^2–y^2)$ (MO48–MO51). If the active space is localized (Foster–Boys) the C–C $\pi/\pi^*$ and Pd–C $\sigma/\sigma^*$ may be separated for ease of interpretation.
Figure 2.18. MCSCF active space orbitals and energies of TS25.$^a$

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85693</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.01682</td>
<td>[22202000]</td>
</tr>
<tr>
<td>0.01094</td>
<td>[22111100]</td>
</tr>
</tbody>
</table>

[a] Active space orbitals for compound TS25. Isosurface value adjusted to 0.04 for ease of visualization. Orbital energy eigenvalues (by ascending MO) in eV: $-0.4443, -0.4016, -0.3064, -0.2400, 0.1574, 0.2046, 0.3684, 0.5126$. 

[Image of molecular structures and orbitals]
Figure 2.19. MCSCF active space orbitals and energies of TS26.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.86058</td>
<td>[22220000]</td>
<td>-1080.838314</td>
</tr>
<tr>
<td>0.03715</td>
<td>[22202000]</td>
<td>-1083.018807</td>
</tr>
<tr>
<td>0.00724</td>
<td>[22020200]</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Active space orbitals for compound TS26. Isosurface value adjusted to 0.04 for ease of visualization. Orbital energy eigenvalues (by ascending MO) in eV: -0.5448, -0.4209, -0.3126, -0.2783, 0.1404, 0.2406, 0.3519, 0.7700.
Figure 2.20. MCSCF active space orbitals and energies of 28.\(^a\)

| CASSCF(8,8) | -1045.009114 |
| NEVPT2(8,8) | -1047.148494 |

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88527</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.01649</td>
<td>[22111100]</td>
</tr>
<tr>
<td>0.01002</td>
<td>[21211010]</td>
</tr>
</tbody>
</table>

[a] Active space orbitals for compound 28. Isosurface value adjusted to 0.04 for ease of visualization.

Orbital energy eigenvalues (by ascending MO) in eV: −0.6193, −0.4392, −0.3288, −0.3509, 0.2247, 0.2579, 0.8061, 0.4683.
Figure 2.21. MCSCF active space orbitals and energies of 29.

<table>
<thead>
<tr>
<th>Method</th>
<th>Energy (a.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSCF(8,8)</td>
<td>-1080.909107</td>
</tr>
<tr>
<td>NEVPT2(8,8)</td>
<td>-1083.101216</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.92253</td>
<td>[22220000]</td>
</tr>
<tr>
<td>0.02687</td>
<td>[22202000]</td>
</tr>
<tr>
<td>0.01400</td>
<td>[22020200]</td>
</tr>
</tbody>
</table>

[a] Active space orbitals for compound 29. Isosurface value adjusted to 0.06 for ease of visualization.

Orbital energy eigenvalues (by ascending MO) in eV: −0.6342, −0.4444, −0.3324, −0.5055, 0.2854, 0.2572, 0.8066, 0.4687.
2.4.3 ADDITIONAL NOTES ON NEVPT2/CASSCF CALCULATIONS

The frozen core approximation was not used in the NEVPT2 calculations (keyword: "! NoFrozenCore"). Solvated free energies include the cavitation, dispersion, structure (CDS) terms as calculated in the SMD model.\textsuperscript{16} \textit{Practical note to users}: For efficiently converging active spaces with weakly correlated valence-bond-like orbitals (such as the C–C $\sigma/\sigma^*$) in the starting complexes and products, we recommend use of the PMO virtual orbital optimization feature in ORCA. A standard procedure involved converging the MCSCF with an active space excluding the weakly correlating pair, localization of the internal space, locating the valence bond orbital of interest, then optimization of a corresponding virtual orbital (using the PMO methodology (RefMO)). Generally, expanding the active space to include the natural orbital-like pair affords smoothly convergence of the MCSCF.

2.4.4 DISCUSSION ON OTHER MAIN GROUP CHELEFUGES

In our investigation of the $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ reaction, we employ diallyl sulfone (23) as a main group analog to bis($\eta^1$-allyl)Pd(PH$_3$)$_2$ complex 26. In addition to SO$_2$, CO and N$_2$ are also viable main group chelefuges. Thus, the $[\pi2s + \pi2s + \sigma2s + \sigma2s]$ reactions of hepta-1,6-dien-4-one or diallyl isodiazene may be considered. For these scenarios, there are \textit{nine} correlating valence orbitals – occupied by 10 valence electrons (see Chapter 3 of reference 8). Both reactions are similarly symmetry forbidden. As a representative example, the orbital correlation diagram for the reaction of hepta-1,6-dien-4-one to CO and 1,5-hexadiene is provided below (Figure 2.22). In the general $[\pi2s + \pi2s + \sigma2s + \sigma2a]$ reaction, we only consider linear departure/approach of the chelefuge due to
the geometric/steric constraints of the seven-membered transition state. An exception to this may be methylene carbene, which could possibly undergo the thermally allowed \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2a]/[\omega 2a + \pi 2s + \pi 2s + \sigma 2s]\) reaction, \textit{i.e.}, with non-linear departure/approach of the carbene.

\textbf{Figure 2.22.} Orbital correlation diagram for the ground state symmetry-forbidden \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) extrusion of CO from hepta-1,6-dien-4-one.

From the FMO perspective, it is important to note that the \(\pi\) systems of CO and \(N_2\) are of the correct symmetry to constructively interact with the diene LUMO (in its reactive conformer), but these \(\pi\) orbitals ultimately correlate to lone pairs on O (in CO) and N (in \(N_2\)) and thus cannot serve as the “donor” in the donor-acceptor relationship.
Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction

2.4.5 EXCHANGE COUPLING IN DIRADICAL INTERMEDIATE 30

The RI and COS integral approximations were not used in calculations evaluating exchange coupling. All computations were carried out in the gas phase. State averaging over the relevant singlet and triplet diradical states was employed in CASSCF calculations. Results obtained with the minimal (2,2) active space, i.e., including only the local spin centers, are provided for comparison. Hypothetical diradical species 30 is a metastable intermediate on the singlet CAS(8,8) and BS-DFT ($M_s = 0$) potential energy surfaces. In the case of BS-DFT, the diradical was found as an intermediate regardless of choice of functional ((U)PBE0-D3(BJ), (U)PBE-D3(BJ), (U)M06-2X).33

Exchange coupling interaction may be described through the phenomenological Heisenberg–Dirac–van Vleck Hamiltonian34:

$$\hat{H}_{\text{HDVV}} = -2J\hat{S}_A\hat{S}_B$$

where $\hat{S}_A$ and $\hat{S}_B$ are “local” spin operators on spin sites $A$ and $B$. $J$ is defined as the exchange coupling constant. Thus, for the coupling of two spin-1/2 magnetic sites, $J$ is expressed as:

$$J = -\frac{1}{2}(E_T - E_S)$$

where $E_T$ and $E_S$ are the energies of the triplet- and singlet-coupled diradical states, respectively. When $J > 0$, i.e., $E_T < E_S$, the interaction is termed ferromagnetic. Likewise, $J < 0$ implies an antiferromagnetic coupling of the two spins. As a consequence of a single determinant formulation, the broken-symmetry DFT solution of an open-shelled singlet state is a mixture of the $M_s = 0$ singlet and triplet states.35 Thus, calculation of exchange
coupling was performed after removal of spin contamination. The spin projection to the “true” singlet energy was carried out via the Yamaguchi equation:

\[ E_T - E_S = \frac{2}{\langle S^2 \rangle_T - \langle S^2 \rangle_{BS}} (E_T - E_{BS}) \]

As such, the \( J \) values we report via BS-DFT are calculated as:

\[ J = -\frac{E_T - E_{BS}}{\langle S^2 \rangle_T - \langle S^2 \rangle_{BS}} \]

Single point calculations with SA-CAS(8,8) on the CAS(8,8) PES initially suggest an antiferromagnetic coupling between the two spin-1/2 centers (\( J = -12.1 \text{ cm}^{-1} \)) of 30. However, inclusion of dynamical correlation via SC-NEVPT2, with the SA-CAS(8,8) reference, reveals a weak ferromagnetic coupling (\( J = 3.2 \text{ cm}^{-1} \)) (Table 2.1, entry 5). BS-DFT single point calculations carried out on the CAS(8,8) geometry also suggest a singlet-coupled diradical, with \( J = -38.9 \text{ cm}^{-1} \). Conversely, DFT single point calculations at both the high spin and broken-symmetry (BS-)DFT-optimized geometries suggest ferromagnetism (Table 2.1, entries 9 and 10). Unsurprisingly, these data suggest the treatment of dynamical electron correlation is crucial in obtaining qualitatively meaningful results.
Table 2.1. Calculation of spin exchange coupling constant (J) between spin centers in 1,4-diradical 30.

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Method</th>
<th>J (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SA-CAS(2,2)</td>
<td>59.1</td>
</tr>
<tr>
<td>2</td>
<td>SA-CAS(8,8)</td>
<td>-12.1</td>
</tr>
<tr>
<td>3</td>
<td>SC-NEVPT2/SA-CAS(2,2)</td>
<td>-14.1</td>
</tr>
<tr>
<td>4</td>
<td>FIC-NEVPT2/SA-CAS(2,2)</td>
<td>-14.0</td>
</tr>
<tr>
<td>5</td>
<td>SC-NEVPT2/SA-CAS(8,8)</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>FIC-NEVPT2/SA-CAS(8,8)</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>IDDCI⁶</td>
<td>82.9</td>
</tr>
<tr>
<td>8</td>
<td>(U)PBE0-D3(BJ)⁶</td>
<td>-38.9</td>
</tr>
<tr>
<td>9</td>
<td>(U)PBE0-D3(BJ)⁴</td>
<td>30.0</td>
</tr>
<tr>
<td>10</td>
<td>(U)PBE0-D3(BJ)⁵</td>
<td>37.0</td>
</tr>
</tbody>
</table>

[a] Unless otherwise noted, performed on the singlet CAS(8,8)/def2-TZVP geometry 30. All calculations above employ the def2-TZVP basis set on all atoms, no integral approximations, and are carried out in the gas phase. Pictured above are the two natural orbitals in the CAS(8,8) active space describing bonding and antibonding pairing in diradical 30. [b] IDDCI (see below) starting from the SA-CAS(2,2) wavefunction. [c] BS-DFT single point calculation on CAS(8,8)/def2-TZVP geometry. [d] Single point calculation on broken-symmetry (Mₚ = 0) (U)PBE0-D3(BJ)/def2-TZVP optimized geometry. [e] Single point calculation on high spin (S = 1) (U)PBE0-D3(BJ)/def2-TZVP optimized geometry.

For a more rigorous treatment of static and dynamic correlation, multireference calculations were carried out with the Iterative Difference Dedicated Configuration
Interaction (IDDCI) method.\textsuperscript{37} The standard DDCI approach resembles that of an uncontracted MRCI (singles and doubles), where completely inactive double excitations are omitted. The reference states were defined to be the singlet and triplet diradical states. The state-averaged CAS(2,2) wavefunction was taken to be the initial orbitals. The results obtained with DDCI are highly depended on the choice of reference orbitals. To help alleviate this starting orbital dependence and generally obtain more accurate results, we employed the Iterative DDCI method (IDDCI) of Malrieu and coworkers.\textsuperscript{11b} In IDDCI, an iterative MO improvement strategy is utilized in which a DDCI calculation is first converged, followed by construction of the state-averaged single-particle density matrix and diagonalization to give a set of new set of state-averaged natural orbital-like MOs. These MOs then serve as the starting orbital basis for a subsequent DDCI calculation. The process is repeated until self-consistency (\textit{i.e.}, the energies of the states stabilize).

As implemented in the ORCA program, convergence of the calculated exchange coupling constant and state energies is achieved with the parameters $T_{\text{sel}} = 1 \times 10^{-11}$ (default $1 \times 10^{-6}$) and $T_{\text{pre}} = 1 \times 10^{-4}$ (default $1 \times 10^{-4}$). A sample input for the IDDCI calculation is provided below:

```plaintext
! def2-TZVP NoPop Grid7 NoFinalGrid
! MORead VeryTightSCF NoIter AllowRHF
%base "SampleName"
%moinp "SampleStart.gbw"
%method
FrozenCore fc_ewin
end

%mrdci
   EWin -10,1000
   CIType MRDDCI3
```

Due to the rapid increase in computational cost with increase in the size of the active space, we elected to employ the (2,2) active space consisting of the two local magnetic orbitals. Calculations with the (8,8) active space were explored; however, it was found that convergence of the exchange coupling constant and state energies was not fully achieved with values of $T_{\text{sel}}$ that yield a reasonable computational cost. Thus, we suggest the results obtained from the tightly converged (2,2) active space to be more robust. *Note that the results are qualitatively similar regardless – both (2,2) and (8,8) active spaces afford $J > 0$.* After five iterations, the IDDCI(2,2) method converges to an exchange coupling constant of 82.9 cm$^{-1}$ (Figure 2.23). These results are in accord with that of NEVPT2(8,8) and BS-DFT, suggesting a triplet ground state of diradical 30.

In summary, the concerted ground state \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) reaction of diallyl sulfone 23 to SO$_2$ (24) and 1,5-hexadiene (25) is symmetry forbidden. Owing to the triplet
ground state of diradical 30, the individual steps of the stepwise mechanism are formally spin forbidden — granted the singlet and triplet states are nearly degenerate (ΔE_{T-S} of ca. 0.5 kcal/mol) in the weakly coupled diradical.

**Figure 2.23.** Exchange coupling via IDDCI.\(^a\)

![Graph showing exchange coupling via IDDCI](image)

\(^a\) Convergence of exchange coupling and state energies via iterative MO optimization in DDCI (IDDCI).

### 2.4.6 REDOX INNOCENCE OF THE PHOX LIGAND

The general Pd-catalyzed \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) pericyclic reaction is symmetry allowed without mandatory implication of ligand-based excited states/configurations. However, in the case of Pd(PHOX) complexes, we sought to evaluate whether the π system of the PHOX ligand is capable of facilitating the reductive elimination through ligand-based redox activity. First, we note that the ground state densities obtained with PBE0-D3(BJ)/def2-TZVP are stable with respect to spin symmetry breaking. Thus, at the DFT level, the ground state along the reaction path 13 → TS20 → 19 is well represented as a
closed-shell singlet (CSS). Time-dependent density functional theory (TD-DFT) calculations were then carried out on stationary points 13, TS20, and 19 at the PBE0-D3(BJ)/def2-TZVP/SMD(THF) level of theory. The TD-DFT calculations suggest no low energy excited states along the ground state PES. The lowest of these vertical transitions is that of the $^3(M/L→L)$ at TS20, which is calculated to be nearly 1.0 eV (Table 2.2). All other excitations (M→M, L→M/L, etc.) are found to be > 2 eV. The PHOX π*-based LUMO (Figure 2.24) serves as a common acceptor in each of the lowest energy transitions in Table 2. These results suggest that redox contribution of the PHOX ligand along the ground state PES is likely trivial.

**Table 2.2. TD-DFT vertical excitations at stationary points 13, TS20, and 19.**

<table>
<thead>
<tr>
<th></th>
<th>13</th>
<th>TS20</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excitation</td>
<td>Energy (eV)</td>
<td>Excitation</td>
</tr>
<tr>
<td>Singlet</td>
<td>L → L</td>
<td>1.463</td>
<td>M/L → L</td>
</tr>
<tr>
<td></td>
<td>L → L</td>
<td>1.014</td>
<td>M/L → L</td>
</tr>
<tr>
<td>Triplet</td>
<td>MLCT</td>
<td>2.264</td>
<td>MLCT</td>
</tr>
</tbody>
</table>

[a] Lowest energy TD-DFT vertical excitations with PBE0-D3(BJ)/def2-TZVP/SMD(THF) and adapted triplets from the RKS reference. L = ligand, M = metal, M/L = mixed metal/ligand.
Figure 2.24. Orbitals involved in the vertical transitions to the lowest energy singlet and triplet excited states at TS20.

2.4.7 NUCLEUS INDEPENDENT CHEMICAL SHIFT CALCULATIONS

Calculations of Nucleus Independent Chemical Shift (NICS) were carried out in order to probe the aromatic character of TS25. In this investigation, the formalism of Schleyer and coworkers is followed. Reported NICS values are the negative of the calculated isotropic chemical shift/shielding at the geometric center of the ring in question. These calculations were carried out with the NMR module in ORCA. Calculations of NICS were conducted in the gas phase at the PBE0-D3(BJ)/def2-TZVP level of theory. Gauge independent atomic orbitals (GIAO) were used and the relevant one-electron and two-electron integrals were evaluated analytically and with the RIJK approximation, respectively. A ghost atom (“H:”, no nuclear charge nor electrons) was used to define a point in space at which shielding was to be determined. A highly contracted basis (and auxiliary basis) function was then assigned to the ghost atom. This procedure was used to ensure the proper grid points were assigned to the point in space without significantly perturbing the ground state density. Note that the results are independent of the chosen
exponent as long as the exponent is large. For example, the following would be added to
the geometry block of an input file to define a point with cartesian coordinates (0.00, 1.00, 2.00):

H: 0.00 1.00 2.00 newgto S 1 1 1000000 1 end newauxJKgto S 1 1 2000000 1 end

At the PBE0-D3(BJ)/def2-TZVP level of theory, NICS values of −8.9 and 28.8 ppm
were obtained for benzene and cyclobutadiene, respectively. These controls are in good
agreement with literature values of −9.7 and 27.6 ppm (HF/6-31+G(d)).24 As described in
the text, an NICS value of −19.4 ppm is found at the geometric center of the seven-
membered ring of TS25 (Figure 2.4C). A NICS value of −19.4 ppm reveals a significant
diatropic ring current. Thus, TS25 is characterized as aromatic.25

2.4.8 INTRINSIC BONDING ORBITAL ANALYSIS

Analysis of the net flow of electron density through the Pd-catalyzed [π2s + π2s + σ2s + σ2s] pericyclic reaction was carried out by Intrinsic Bonding Orbital (IBO)
analysis.27 IBO analysis was carried out along the IRC describing 19 → TS20 → 19. SCF
densities were obtained at the M06/def2-TZVP/CPCM(THF) level of theory and on BP86-
D3(BJ)/LANL2TZ(f)[Pd]–6-31G(d) geometries, consistent with reference 5. Localization
of the SCF density, frame alignment, and calculation of IBO displacement were carried out
with the IBOView program. For further details of this procedure and additional discussion
of the relevant theory, see the seminal reports of Knizia and coworkers.27 Note that results
are largely independent of choice in density functional, and qualitatively identical results
may be obtained with densities from an ab initio wavefunction method.
2.5 REFERENCES AND NOTES


(4) Such as three-centered reductive elimination and [2+2] cycloadditions in olefin metathesis.


(9) Despite our best efforts, we are unable to find literature examples of an identical main group analog fitting $\Delta \pi = 0$ and $\Delta \sigma = 1$ in this seven-membered geometry.

(10) See Supporting Information for a discussion on N$_2$ as a chelefuge. For examples of


(15) PBE0-D3: PBE0 hybrid density functional coupled with Becke–Johnson damped D3 dispersion correction. PBE0: (a) Adamo, C.; Barone, V. Toward Reliable Density Functional Methods without Adjustable Parameters: The PBE0 Model. *J.
Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction


(17) Similar results were obtained with broken-symmetry DFT (see supporting information for details). We are unable to find a concerted closed-shell singlet $[\pi 2a + \pi 2s + \sigma 2s + \sigma 2s]$ transition state. Additionally, singlet diradical 10 is in the boat conformation collapses to the corresponding cyclobutene.

(18) Diradical index defined as described by Neese and coworkers, with $d = 98.0\%$ indicating of 98% diradical character. Here, $c_0$ and $c_d$ are the factional contributions of the relevant bonding and antibonding configurations to the ground-state CI wavefunction.

$$d = 200 \sqrt{\frac{c_0^2 c_d^2}{c_0^2 + c_d^2}}$$

Herebian, D.; Wieghardt, K. E.; Neese, F. Analysis and Interpretation of Metal-Radical Coupling in a Series of Square Planar Nickel Complexes: Correlated Ab

Note that through-bond coupling of $2b$ with $\sigma^*(C\cdots C)$ and $3a$ with $\sigma(C\cdots C)$ gives rise to $2b$ being lower in energy than the symmetric $3a$. For further discussion see: Stuyver, T.; Chen, B.; Zeng, T.; Geerlings, P.; De Proft, F.; Hoffmann, R. Do Diradicals Behave Like Radicals? *Chem. Rev.* **2019**, *119*, 11291–11351.


(20) A similar effect was observed by Steigerwald and Goddard in studying the thermally allowed $[2s + 2s]$ sigma bond metathesis of D$_2$ by transition metal hydrides. (a) Steigerwald, M. L.; Goddard III, W. A. The $2s + 2s$ Reactions at
Chapter 2 – Analysis of the Pd-catalyzed \([\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]\) Pericyclic Reaction

(21) LUMO as derived qualitatively for FMO analysis from two interacting three electron allyl fragments.


(23) Hua, Y.; Zhang, H.; Xia, H.; Houk, K. N. Three Classes of \(\pi\)-Aromaticity **2020**, submitted. Received as a personal communication.


(29) Final IBO at 2 is of $d(x^2-y^2)$ parentage with $\pi$-back-bonding to the olefin observed.


Chapter 2 – Analysis of the Pd-catalyzed $[\pi 2s + \pi 2s + \sigma 2s + \sigma 2s]$ Pericyclic Reaction


CHAPTER 3

_Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates_†

### 3.1 INTRODUCTION

Enantioselective construction of all-carbon quaternary stereogenic centers represents a central and ongoing challenge in synthetic organic chemistry. The asymmetric allylic alkylation of enolate nucleophiles serves as a powerful strategy for accessing such motifs.

A unique aspect of the Pd-catalyzed allylic alkylation methods developed by our group is the inner-sphere reductive elimination from a chiral O-bound Pd enolate intermediate (32), yielding enantioenriched ketones (33) (Figure 3.1A). This intermediate is generated catalytically from achiral or racemic enolate precursors, such as allyl enol carbonates and \(\beta\)-ketoesters (31). The Pd enolate is accessed in the absence of a base, under neutral conditions, and in a regiospecific fashion. Conversely, canonical conditions for enolate formation are plagued by regioselectivity challenges and typically require the use of a strong base or Lewis acid. Given the inherent advantages of Pd enolates, we sought to exploit their reactivity beyond simple allylic alkylations in more general asymmetric transformations.

Highlighting the utility of this concept, our lab has demonstrated the enantioselective protonation of Pd enolates as a valuable strategy to access ketones with

---

†This research was carried out with Flesch, K. N.; Chen, P.-J.; Strong, C. S. Portions of this chapter have been reproduced with permission from Stoltz, et al. _J. Am. Chem. Soc._ **2023**, _In press_. © 2023 American Chemical Society.
tertiary stereocenters (34). Building upon this success, we subsequently developed methods to construct quaternary centers via enantioselective conjugate additions (35) and intramolecular aldol reactions (36). Taken together, these advances underscore the feasibility of employing Pd enolates as stereogenic nucleophiles.

**Figure 3.1.** (A) Examples of chiral Pd enolate reactivity. (B) Lithium base-promoted intramolecular formal [4+2] cycloaddition. (C) Proposed asymmetric intramolecular [4+2] reaction. (D) Divergent catalytic cycle.
In a unique example of enolate reactivity, Fukumoto and coworkers reported a formal [4+2] reaction from in situ generated conjugated lithium enolate 38, forging tricyclic adduct 39 in a racemic fashion (Figure 3.1B).\textsuperscript{10} We envisioned that an analogous asymmetric transformation would be tractable from a chiral, conjugated Pd enolate – derived from the decarboxylation of unsaturated \( \beta \)-ketoester 40a using an asymmetric ligand on Pd (Figure 3.1C).

To realize this transformation, we sought to develop a conceptual framework based on our mechanistic understanding to expand the general utility of the Pd enolate. As such, we employed a strategy of divergent catalysis (Figure 3.1D), where deviation occurs at the common Pd enolate \( \text{i.e.}, \ C \), Figure 3.1D, cf. Scheme 3.1, vide infra), allowing for desired alternative reactivity in the diverged cycle. Subsequent re-entry into the original catalytic cycle turns over the catalyst allowing regeneration of the Pd enolate.

Applying this strategy of divergent catalysis, we developed a catalytic decarboxylative asymmetric intramolecular [4+2] cycloaddition from conjugated Pd enolates. Mechanistic studies including quantum mechanics calculations, Eyring analysis, and KIE studies offer insights into the reaction mechanism. This transformation enables access to tricyclic scaffolds bearing at least four contiguous stereocenters, at least one of which is quaternary.

3.2 RESULTS AND DISCUSSION

3.2.1 REACTION DESIGN AND OPTIMIZATION

Employing unsaturated \( \beta \)-ketoester 42 as a precursor for conjugated Pd enolate 43, we hypothesized that the precededented allylic alkylation forming 44 could be interrupted by
a [4+2] cycloaddition to generate 45 (Figure 3.2A). Alkylation of the transposed enolate (45) would then turn over the catalyst and forge tricyclic product 46.

**Figure 3.2.** (A) General reactivity paradigm from Pd enolate 43. (B) Computed substituent effects on the rate of C–C bond formation and successful application.\(^a\)

[A] See 3.4 Supporting Information for computational details and discussion of other isomeric transition states. Yield determined by \(^1\)H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excess determined by chiral SFC.
Unfortunately, the rate direct allylic alkylation of enolate 43 supersedes the desired divergent reactivity. Treatment of β-ketoester 42 under our standard conditions produces ketone 44 in 98% yield and 84% ee (Figure 3.2B). This prompted us to redesign our exit strategy (Figure 3.1D). Increasing the rate of the cycloaddition through modification of the diene or dienophile could circumvent formation of premature allylic alkylation product 44 but would limit the generality of this transformation. Therefore, we sought to impede alkylation through modification of the allyl moiety.

Computational investigation of a model system (TS29) suggested that introducing terminal substitution on the allyl group raises the barrier to reductive elimination, decreasing the rate of allylic alkylation (Figure 3.2B, see 3.4 Supporting Information for computational details).

For example, phenyl substitution (entry 2, Figure 3.2B) slows the rate of inner-sphere reductive elimination by roughly three orders of magnitude. Inspired by these computational results, we explored the efficacy of cinnamyl ester substrate 47 in the transformation. In line with our hypothesis, the desired tricyclic core was observed (48), albeit as a complex mixture of isomers – hampering the synthetic utility. To this end, we sought to develop an alternative strategy for catalyst turnover that could potentially simplify the product outcomes.

Building upon previous findings from our group, we sought to employ stoichiometric acidic additives for catalyst turnover. The exogenous acid serves the dual purpose of protonating the final enolate (analogous to 45) and turning over the catalyst by trapping the cinnamyl group. Addition of 3,5-dimethylphenol9 exclusively yielded undesired protonation product 49a along with aryl ether 50 (Figure 3.3A). To our delight,
replacing the phenol additive with 4-methylaniline afforded the desired endo \([4+2]\) cycloadduct (41a) as a single diastereomer in 83% yield and 88% ee.

**Figure 3.3.** (A) Sacrificial additives to enable catalyst turnover.\(^a\) (B) Additive-free reaction with prenyl ester 40a.\(^b\)

![Chemical diagram](image)

[a] Equivalents includes mixture of branched and linear constitutional isomers, as well as double-alkylation of aniline. [b] Isoprene (52) observed in 0.94:1 ratio with 41a by \(^1\)H NMR (J Young tube, toluene-\(d_8\)).

Seeking to improve the reaction yield, the competency of \(\beta\)-ketoester 40a, derived from the commodity chemical prenyl alcohol, was explored. According to our computations, a substrate containing a di-substituted allyl fragment would be similarly effective in hindering premature allylic alkylation by increasing the barrier to reductive elimination (Figure 3.2B, entry 3). Perplexingly, while the desired tricyclic product was
generated in 73% isolated yield and 88% ee, no alkylated 4-methylaniline (analogous to 51) was observed as a byproduct.

**Table 3.1. Optimization of [4+2] reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Yield 41a (%)</th>
<th>ee 41a (%)</th>
<th>Yield 49a (%)</th>
<th>ee 49a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>96 (83)</td>
<td>87 (87)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>86</td>
<td>81</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>benzene</td>
<td>92</td>
<td>87</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1,4-dioxane</td>
<td>12</td>
<td>–</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>40 ºC</td>
<td>51</td>
<td>89</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>(S)-(CF$_3$)$_3$-t-BuPHOX</td>
<td>12</td>
<td>89</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>(S)-(OMe)$_3$-t-BuPHOX</td>
<td>40</td>
<td>88</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>4-methylaniline (1 equiv)</td>
<td>93 (73)</td>
<td>87 (88)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>4-methylaniline (2 equiv)</td>
<td>78</td>
<td>87</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>3,5-dimethylphenol (1 equiv)</td>
<td>0</td>
<td>–</td>
<td>100</td>
<td>71</td>
</tr>
</tbody>
</table>

[a] Conditions: 0.02 mmol 40a, 2.5 mol % Pd$_2$(dba)$_3$, 6.5 mol % ligand, in 1.0 mL of solvent (0.02 M). [b] Yields determined by $^1$H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. Isolated yields on 0.2 mmol scale in parentheses.

A control reaction excluding 4-methylaniline was carried out, and surprisingly, desired product 41a was formed in 83% yield and 87% ee (Figure 3.3B). This suggests that an alternative catalyst turnover mechanism is operative. Further NMR experiments revealed the stoichiometric evolution of isoprene (52) accompanying formation of product 41a. Intrigued by this unexpected finding and clean reaction profile, we pursued optimization of additive-free reaction conditions.
The reaction proceeds in THF and benzene albeit in slightly diminished yield and enantioselectivity (entries 2–3, Table 3.1). Employing 1,4-dioxane as the solvent, protonation product 49a was obtained as the major product in 63% yield and 49% ee, while cycloadduct 41a was observed in only 12% yield (entry 4, Table 3.1). Lowering the temperature to 40 ºC slightly improved the ee to 89% at the cost of decreased conversion (entry 5, Table 3.1). Modification of the electronic properties of the PHOX ligand deleteriously impacted the product distribution (entries 6–7, Table 3.1). Phenol and aniline additives do not improve the reaction (entries 8–10, Table 3.1). Ultimately, optimized reaction conditions were determined to be additive-free with (S)-t-BuPHOX in toluene at 60 ºC. The reaction affords 41a, a bridged bicycle with a pendant fused ring, in 83% isolated yield and 87% ee. The transformation allows for the simultaneous construction of four contiguous stereocenters, including one all-carbon quaternary center. Gratifyingly, the reaction can be performed with reduced catalyst loading (0.625 mol %) on 1.0 mmol scale to afford 41a in 59% yield and 89% ee. The ability to efficiently construct these complex building blocks on scale highlights the synthetic utility of this transformation.

3.2.2 PROPOSED MECHANISM

We sought to capitalize on these initial exciting results by constructing a mechanistic framework to inform rational design. Based on our lab’s prior investigations of Pd-catalyzed decarboxylative asymmetric allylic alkylation reactions, we propose that oxidative addition of Pd⁰ to β-ketoester 40a proceeds through complex 53 to afford the η¹-allyl carboxylate resting state 54 (Scheme 3.1).¹² Rate-limiting decarboxylation ensues, affording O-bound Pd enolate 55.³,¹² This chiral conjugated enolate then serves as the diene
in a [4+2] cycloaddition (TS30) with the pendant dienophile to form tricyclic enolate 56. Subsequent proton transfer would generate product 41a. Concomitant isoprene generation, followed by ligand exchange, allows for re-entry into the original catalytic cycle at 53. We posit that the formation of undesired ketone 49a arises from an off-cycle pathway, where catalyst turnover occurs prior to cycloaddition via premature proton transfer to 55.

**Scheme 3.1.** Proposed divergent catalytic cycle. Undesired reaction pathways in grey.

### 3.2.3 SUBSTRATE SCOPE

With a working mechanistic hypothesis in hand, we sought to draw further mechanistic insights from substrate design, while simultaneously exploring limits of the reaction. Considering the inverse relationship between diene ring size and Diels–Alder
Table 3.2. Substrate scope of the [4+2] reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40a</td>
<td>41a (endo) 83% yield, 87% ee</td>
</tr>
<tr>
<td>40b</td>
<td>41b (endo) 85% yield, 88% ee</td>
</tr>
<tr>
<td>40c</td>
<td>41c (endo) 65% yield, 65% ee</td>
</tr>
<tr>
<td>40d</td>
<td>41d (endo) 83% yield, 97% ee</td>
</tr>
<tr>
<td>40e</td>
<td>41e (endo) (not observed) 81% yield, 47% ee</td>
</tr>
<tr>
<td>40f</td>
<td>41f (endo) 42% yield, 92% ee</td>
</tr>
<tr>
<td></td>
<td>41f' (exo) 45% yield, 51% ee</td>
</tr>
<tr>
<td>40g</td>
<td>41g (endo) (not observed) 74% yield, 56% ee</td>
</tr>
<tr>
<td></td>
<td>41g' (exo)</td>
</tr>
<tr>
<td>40h</td>
<td>41h (endo)</td>
</tr>
<tr>
<td>40i</td>
<td>41i (endo) 80% yield, 7% ee</td>
</tr>
<tr>
<td>40j</td>
<td>41j (endo) 50% yield, 87% ee</td>
</tr>
<tr>
<td>40k</td>
<td>41k (endo) 82% yield, 10.4:1.4:1 dr, 88% ee (endo)</td>
</tr>
<tr>
<td></td>
<td>41k' (exo)</td>
</tr>
<tr>
<td>40l</td>
<td>41l (endo)</td>
</tr>
<tr>
<td>40m</td>
<td>41m (endo) 65% yield, 1.4:1 dr\textsuperscript{b}</td>
</tr>
<tr>
<td></td>
<td>41m' (exo) 62% ee (endo), 62% ee (exo)</td>
</tr>
<tr>
<td>40n</td>
<td>41n (endo) 88% yield, 14.3:1 dr, 91% ee</td>
</tr>
</tbody>
</table>
reaction rate$^{13,2}$, we explored whether this trend impacts the generality of our transformation. However, with cyclopentyl diene derived from enone $40c$, a decrease in yield and ee, relative to six-membered parent substrate $40a$, was noted (Table 3.2). In comparison to smaller ring sizes, seven-membered cyclic dienes require increased distortion energy to reach the desired transition state.$^{13}$ Despite this, seven-membered ring substrate $40d$ leads to a high yield and improved ee. Thus, this transformation represents a powerful method to synthesize various challenging bicyclic cores.

[a] Conditions: 0.2 mmol $40a$, 2.5 mol % Pd$_2$(dba)$_3$, 6.5 mol % ligand, in toluene (10 mL, 0.02 M), isolated yields, dr determined by $^1$H NMR analysis of reaction crude. [b] dr determined by isolated yields of endo/exo products.
Figure 3.4. Eyring analysis of 41/49 product ratio for propylene and butylene tethered substrates 40a and 40f.\(^a\)

\[
\begin{array}{cccc}
\text{Substrate} & n & \Delta\Delta H^\dagger (\text{kcal/mol}) & \Delta\Delta S^\dagger (\text{eu}) \\
\hline
40a & 1 & 7 \pm 1 & 14 \pm 3 \\
40f & 2 & 7 \pm 1 & 20 \pm 2 \\
\end{array}
\]

\(^a\) All data points collected in triplicate, error bars and ranges reflect a 95% confidence interval.\(^{14}\) Reactions carried out on 0.02 mmol scale with product ratios determined by crude \(^1\)H NMR analysis.

The dienophile tether length was subsequently modulated to test its influence on product distribution. The ethylene tethered substrate 40e yields solely the premature protonation product 49e, likely due to insurmountable developing ring strain in the cycloaddition transition state. In contrast to the propylene tethered substrate 40a, the
butylene tethered substrate 40f leads to a near equal distribution of cycloadduct 41f (42% yield) and prematurely protonation product 49f (45% yield). Following this trend, the pentylene tethered substrate 40g leads only to protonation product 49g. Rationalizing this phenomenon, we propose that lengthening the tether increases conformational flexibility and imposes a greater entropic penalty to the highly organized [4+2] transition state. In contrast, increased tether length is inconsequential to the protonation process, which does not involve the dienophile.

Eyring analysis of product distributions from reactions of 40a and 40f further supports the hypothesis of an entropic preference for the formation of 49a/f over 41a/f (Figure 3.4). With 40a, cycloaddition (41a) is enthalpically favored (ΔΔH‡ = 7 kcal/mol) but entropically disfavored (ΔΔS‡ = 14 eu) over protonation (49a). As anticipated, increasing the tether length to four methylene units (40f) further increases the relative entropic penalty for cycloaddition (ΔΔS‡ = 20 eu), while the differential enthalpy of activation remains similar (ΔΔH‡ = 7 kcal/mol). Hence, entropy differences associated with tether length lead to the formation of differential amounts of undesired ketones 49a and 49f.

We then surveyed the scope of functional groups that are tolerated in this reaction (Table 3.2). The cycloaddition does not proceed in the absence of a π-acceptor (40h), and carboxylic acid 40i exclusively affords undesired ketone 49i. To our delight, a variety of functional groups are compatible, including ethyl ester 10b, phenyl ketone 10j, phenyl ester 40k, mesityl ester 40l, N-hydroxyphthalimido (NHP) ester 40m, enecarbamate 40n, and N-acyl oxazolidinone 40o. Additionally, further conjugated cinnamic ester dienophile 40p
affords tetracycle 41p. These results demonstrate the ability to tolerate varying dienophile electronics, incorporate additional functional handles, and access alternate ring systems.

The majority of the substrate scope is reflective of a stereospecific process, yielding only *endo* and *exo* diastereomers. We sought to exploit this property of the reaction to access other diastereomers of 41a by employing (Z)-olefin dienophile 40q. Gratifyingly, desired cycloadducts 41q (*endo*) and 41q’ (*exo*) are furnished in a 1.6:1 ratio with a 92% combined yield, in 84% and 29% ee, respectively.

Further substitution patterns on the substrate were explored with the aim of increasing the stereochemical complexity of the products. Trisubstituted benzyl ester dienophile 40r furnished cycloadduct 41r, featuring two all-carbon quaternary centers, in 47% yield and 90% ee. β-Methyl (40s) and β-ethoxy (40t) α,β-unsaturated enones are also competent substrates, forging additional tetrasubstituted bridgehead stereocenters. Finally, we explored α-methyl substituted enone 40u. The corresponding product 41u was produced, bearing five contiguous stereocenters in >20:1 dr.

In summary, the transformation described herein represents a versatile method for the preparation of a variety of enantioenriched polycyclic scaffolds. Inspired by these results, we sought to explore the origins of enantioinduction and the mechanism by which catalyst turnover is achieved.

### 3.2.4 [4+2] CYCLOADDITION

In order to probe the origins of enantioinduction in the transformation, we first aimed to elucidate the enantiodetermining step in the catalytic cycle. We hypothesized that either the cycloaddition is irreversible and dictates the stereochemical outcome, or a
reversible [4+2] is coupled to a subsequent enantiodetermining step. First, we computationally evaluated the energetics of the [4+2] process. Cycloaddition directly from conjugated enolate 55 to transposed enolate 56 via TS30 is achieved with a $\Delta G^\dagger$ of 9.8 and $\Delta G$ of −22.3 kcal/mol (Figure 3.5A). The 32.1 kcal/mol barrier to the reverse process renders the cycloaddition step irreversible under the reaction conditions. Hence, our computations suggest that the cycloaddition step is enantiodetermining.

To assess this hypothesis experimentally, reaction product 41a was converted to its corresponding prenyl enol carbonate 59. Under the standard reaction conditions, Pd$^0$ undergoes oxidative addition to 59, and decarboxylation affords target common intermediate 56 (Figure 3.5B). When enantioenriched or racemic 59 is subjected to the reaction conditions, cycloadduct 41a is obtained in high yield and identical enantiopurity to that of the respective enol carbonate precursor (59) (Figure 3.5B). No stereochemical resolution in product 41a is observed from racemic enol carbonate 59, indicating that a post-cycloaddition process is not responsible for enantioinduction. In addition to verifying the irreversibility of the cycloaddition step, these experiments also support the viability of enolate 56 as an intermediate in the catalytic cycle (Scheme 3.1).

Considering the [4+2] cycloaddition as the enantiodetermining process, the origin of enantioinduction in this step was investigated. As such, the lowest energy endo transition states giving rise to each enantiomer of 41a were evaluated (Figure 3.5C). The minimum energy pathway to each enantiomer of product features a transition state in which the dienophile tether is syn to the $t$-Bu group of the PHOX ligand – in accord with prior observations in inner-sphere allylic alkylation transition states.$^{3,15}$ From this orientation,
Figure 3.5. (A) Computed barriers.\textsuperscript{a} (B) Experimentally verifying irreversibility of the C–C bond formation. (C) Origins of enantioinduction in the [4+2] cycloaddition step.

A. Thermodynamics of C–C bond formation.

\[
\begin{align*}
\Delta G^\text{rel} & = 0.0 \\
\Delta G^\text{rel} & = 9.8 \\
\Delta G^\text{rel} & = -22.3
\end{align*}
\]

B. Enantioenrichment as readout of reversibility.

\[
\begin{align*}
\text{Pd}_2(\text{dba})_3 & \text{ (2.5 mol %)} \\
(5) + \text{BuPHOX} & \text{ (6.5 mol %)} \\
\text{toluene, 60 °C}
\end{align*}
\]

[4+2] step is irreversible and enantiodetermining

C. Origins of enantioinduction \((R = \text{CO}_2\text{Bn})\).

\[
\begin{align*}
\Delta G^\text{rel} & = 0.0 \\
\Delta G^\text{rel} & = 1.6
\end{align*}
\]

[a] Gibbs free energies in kcal/mol. See supporting information in section 3.4 for details.
the dienophile preferentially approaches the externally-exposed enantiotopic face of the diene to avoid steric clash between the benzyl ester and the phenyl groups of the PHOX ligand scaffold (Figure 3.5C). A 1.6 kcal/mol preference for external (TS30) over internal (TS31) approach is calculated, in accord with the experimentally observed 87% ee.\(^\text{16}\) The major enantiomer of product (41a) predicted by computations matches that of the major enantiomer obtained experimentally, as confirmed by vibrational circular dichroism (VCD) spectroscopy (see 3.4 Supporting Information for details).

In summary, our investigations reveal C–C bond formation to be the enantiodetermining step, with enantioselectivity achieved by biasing external over internal dienophile approach (Figure 3.5).

### 3.2.5 CATALYST TURNOVER

Our [4+2] transformation is rendered catalytic by a unique reduction of Pd\(^{\text{II}}\) to Pd\(^0\) that occurs concomitantly with formation of isoprene (52) and ketone 41a. This observation motivated computational investigations to elucidate the catalyst turnover mechanism.

Of the numerous mechanisms explored, the minimum energy pathway involves isomerization of 56 to an N-detached π-allyl Pd species (60) and subsequent inner-sphere proton transfer (TS4) (Figure 3.6). Additionally, a pathway featuring outer-sphere proton transfer (TS5) was found to be highly competitive for catalyst turnover. These two processes present very similar free energy barriers of 22.3 and 22.4 kcal/mol, respectively, which are readily surmountable at 60 °C. A single favored pathway is not identified as the energy difference between the two mechanisms is within error of computations. In both pathways, subsequent ligand exchange of isoprene (52) for starting material 40a completes
the catalytic cycle. Analysis of Intrinsic Bonding Orbitals (IBOs)\(^\text{17}\) along the reaction coordinate suggest these processes are best conceptualized as the transfer of a proton, rather than a hydride, to the Pd enolate (see 3.4 Supporting Information for details).\(^\text{18}\) Analogous mechanisms were found to be operative from pre-cycloaddition enolate 55, giving rise to premature protonation product 49a.

**Figure 3.6.** Two lowest-energy pathways for catalyst turnover.\(^\text{a}\)

![Diagram](Image)

[a] Gibbs free energies in kcal/mol. See section 3.4 supporting information for details.

### 3.2.6 FURTHER MECHANISM-BASED DEVELOPMENTS

While this method allows access to a variety of complex scaffolds, premature protonation remains an outstanding challenge we sought to address. As such, we aimed to leverage our mechanistic insights surrounding this process to inhibit byproduct formation.
Figure 3.7. (A) KIE study. (B) Prenyl ester modification.

A. Leveraging kinetic isotope effect (KIE) to slow proton transfer.\textsuperscript{a}

\[
\begin{array}{c}
\text{O} & \text{O} & \text{CD}_{3} \\
\text{Pd}(\text{dba})_{2} \text{ (2.5 mol %)} & \text{(S)-t-BuPHOX (6.5 mol %)} \\
toluene, 60 ^\circ \text{C}, 14 \text{ h} \\
\text{D-40f} & \text{D-41f} & \text{D-49f} \\
& 93\% \text{ D}^\circ & 64\% \text{ D}^\circ
\end{array}
\]

B. Modification of prenyl ester via cyclic and benzylic analogs.\textsuperscript{c}

\[
\begin{array}{c}
\text{O} & \text{O} & \text{OR} \\
\text{Pd}(\text{dba})_{2} \text{ (2.5 mol %)} & \text{(S)-t-BuPHOX (6.5 mol %)} \\
toluene, 60 ^\circ \text{C}, 14 \text{ h} \\
\text{41f} & \text{49f}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield 41f (%)</th>
<th>ee 41f (%)</th>
<th>Yield 49f (%)</th>
<th>ee 49f (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-Me</td>
<td>(40f) 44</td>
<td>91</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>2\textsuperscript{d}</td>
<td></td>
<td>(63) 25</td>
<td>92</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(64) 8</td>
<td>–</td>
<td>89</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(65) 63</td>
<td>92</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>(66) 48</td>
<td>92</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>6\textsuperscript{e}</td>
<td>Ph-Ph</td>
<td>(67) 14</td>
<td>94</td>
<td>86</td>
<td>60</td>
</tr>
</tbody>
</table>

[a] Conditions: 0.20 mmol D-40f, 2.5 mol % Pd\textsubscript{2}(dba)\textsubscript{3}, 6.5 mol % ligand, in 10 mL of solvent (0.02 M). [b] Deuterium incorporation determined by HRMS. [c] Conditions: 0.02 mmol substrate, 2.5 mol % Pd\textsubscript{2}(dba)\textsubscript{3}, 6.5 mol % ligand, in 1.0 mL of solvent (0.02 M). Yield determined by \textsuperscript{1}H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. [d] 21% of allylic alkylation product was also observed. [e] The corresponding benzylic diene was also observed (see 3.4 Supporting Information for details).
To that end, we turned our attention to butylene tethered substrate \textit{40f} given its similar yield of desired \textit{41f} (44\%) and byproduct \textit{49f} (42\%). We envisioned favoring the formation of \textit{41f} by modification of the ancillary prenyl moiety. By introducing a kinetic isotope effect, we aimed to slow down the protonation processes. To our delight, employing hexa-deutero prenyl ester \textit{D-40f} (Figure 3.7A) increases the yield of desired cycloadduct \textit{D-41f} to 66\%, with 91\% ee.\textsuperscript{19} Next, cyclic analogs of the prenyl ester \textit{40f} were prepared (Figure 3.7B). At one extreme, seven-membered exocycle \textit{66} affords a product distribution which closely mirrors that of parent substrate \textit{40f} (entry 5). Excitingly, contracting the ring by one methylene (\textit{65}) shifts the distribution favorably toward \textit{41f} (entry 4, 3:1 ratio of \textit{41f:49f}). However, five- and four-membered exocycles (\textit{64} and \textit{63}), as well as acyclic bis-benzylic allylic ester \textit{67}, afford unfavorable product distributions.

In summary, we find appropriate modification of the prenyl moiety to be effective in suppressing deleterious side reactions. This is particularly important as the ring system generated in this reaction is a scaffold relevant to natural product synthesis.

\textbf{3.2.7 PRODUCT DERIVATIZATIONS}

To assess the utility of the asymmetric intramolecular [4+2] products, we started by altering the oxidation state of ketone \textit{41a} (Figure 3.8A) through a 1,2-reduction, which provided alcohol \textit{68} in quantitative yield and in 1.5:1 dr. Subsequently, we explored ring expansion strategies to incorporate heteroatoms and to furnish different ring systems (Figure 3.8A). From ketone \textit{41a}, oxime condensation and subsequent Beckmann rearrangement afforded lactam \textit{69} as a single isomer in 56\% yield over two steps.
Analogously, Baeyer–Villiger oxidation furnished lactone 70 in 41% yield as a single isomer.

Furthermore, the tricyclic cycloaddition products closely resemble many members of the atisane family of diterpenoids (Figure 3.8B, 71-74). Therefore, reactions to further functionalize these scaffolds were explored. First, hydrogenolysis followed by persulfate-mediated radical decarboxylation of 41f afforded ketone 75 in 27% yield over two steps.20 We were delighted to find that the exo-cyclic methylene motif presented in both crotogoudin (71) and campylopin (74) could be achieved through aldol condensations from both 75 and 41f to yield crotogoudin-like enone 76 in 41% yield and analogous enone 77 in 26% yield.21 Enone 77 can be further functionalized through dihydroxylation to furnish the primary and tertiary alcohol centers of the acochlearine (72) core in 13% yield and 10:1 dr (78).22 A wider spectrum of natural product cores could also be accessed through oxidation at different sites of the tricyclic hydrocarbon backbone. For example, Riley oxidation of 41f provided diketone 79 in 50% yield,23 which can then be selectively mono-protected as acetal 80 in 41% yield.24 Further manipulations to the exposed ketone of 80 could yield spiramilactam B (73)-like oxidation patterns. To that end, directed C–H oxidation following an oxime condensation of 41f yielded oxime 81 in 30% yield. Deprotection of the oxime afforded the desired acetate on campylopin (74)-like tricycle 82 in 19% yield as a single diastereomer.25 Overall, derivatization of the Diels–Alder product 41f allowed access to four natural product-like motifs, demonstrating the potential of applying this transformation to asymmetric natural product syntheses.
Figure 3.8. (A) Oxidation state alterations, ring system adjustments, and heteroatom incorporation on 41a. (B) Reaction sequences to construct natural product-like cores.
3.3 CONCLUSIONS

We developed an asymmetric decarboxylative [4+2] cycloaddition employing a key catalytically-generated chiral Pd enolate intermediate – analogous to those implicated in inner-sphere allylic alkylation reactions. To enable this transformation, we first systematically modified the allyl moiety to disfavor undesired allylic alkylation. This allows the conjugated Pd enolate to engage in a [4+2] cycloaddition with a pendant dienophile. Computational and experimental analysis supports the role of C–C bond formation as the enantiodetermining step. Further computational investigation reveals that the catalyst turnover occurs through a proton transfer from the prenyl group directly to the transposed enolate, forming the desired product and releasing isoprene. Building upon these mechanistic insights, we were able to further favor the desired [4+2] cycloaddition over premature protonation for challenging substrates relevant to complex natural product synthesis. In summary, our approach of divergent catalysis serves as a powerful framework for rational design in asymmetric catalytic reactions. Studies applying this strategy more broadly in other synthetically relevant transformations are currently underway.

3.4 SUPPORTING INFORMATION

3.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and
visualized by UV fluorescence quenching or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. \(^1\)H NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). \(^1\)C NMR spectra were recorded on a Bruker 400 MHz spectrometer (100 MHz) and are reported relative to CHCl₃ (δ 77.16 ppm). \(^2\)H NMR spectra were recorded on a Bruker 400 MHz (61 MHz) spectrometer and are reported relative to residual CDCl₃ (δ 7.26 ppm). Data for \(^1\)H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as the peaks appear as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for \(^1\)C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. \(^1\)C NMR spectra of deuterated compounds are complicated by the low intensity of peaks of deuterium-substituted carbon atoms. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm\(^{-1}\)). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing Chiralpak (AD-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd.
High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in Field Desorption (FD+) mode. Absolute stereochemical assignments were made by vibrational circular dichroism analysis for select compounds with related compounds assigned by analogy.

Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligands were prepared according to literature procedures.27


3.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Pd-Catalyzed Decarboxylative Cycloadditions

General Procedure A: Asymmetric Pd-Catalyzed Decarboxylative Cycloadditions.

In a nitrogen filled glovebox, an oven-dried 20 mL vial was charged with a stir bar, Pd$_2$(dba)$_3$ (4.6 mg, 0.005 mmol, 2.5 mol %), (S)-t-BuPHOX (5.0 mg, 0.013 mmol, 6.5 mol %), and toluene (5 mL). The catalyst solution was stirred at 23 ºC for 20 min. A solution of substrate 40 (0.2 mmol, 1 equiv) in toluene (5 mL) was added to the vial. The resultant solution was then heated to 60 ºC for 14 h. The solution was then cooled to 23 ºC and concentrated under reduced pressure. The crude reaction mixture was loaded directly
onto a flash column and the product (41) was isolated by silica gel flash column chromatography.

benzyl (3aR,6R,7S,7aR)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41a)

Prepared from 40a following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (49.7 mg, 0.167 mmol, 83% yield, 87% ee). Absolute and relative stereochemistry were assigned by VCD (vida infra). 2D NMR studies independently confirm the relative stereochemistry (vida infra).

\[1^H\text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 7.40 – 7.31 (m, 5H), 5.14 (d, J = 1.6 Hz, 2H), 2.54 (dt, J = 18.8, 2.3 Hz, 1H), 2.51 – 2.47 (m, 2H), 2.21 (dddd, J = 10.6, 8.7, 7.2, 1.7 Hz, 1H), 2.14 – 2.04 (m, 3H), 1.86 (ddd, J = 13.0, 11.1, 6.8 Hz, 1H), 1.81 – 1.72 (m, 2H), 1.70 – 1.52 (m, 3H), 1.44 (ddt, J = 12.9, 10.9, 1.8 Hz, 1H), 1.22 (ddd, J = 13.9, 9.2, 4.9 Hz, 1H).

\[1^3\text{C NMR (100 MHz, CDCl}_3\text{)}: \delta 215.1, 174.7, 136.0, 128.8, 128.5, 128.2, 66.7, 54.2, 47.5, 43.3, 41.3, 32.9, 29.1, 27.4, 26.5, 25.1, 22.6.

\text{IR (Neat Film, NaCl):} 2947, 2873, 1726, 1455, 1267, 1160 \text{ cm}^{-1}.

\text{HRMS (MM: FD+):} m/z \text{ calc’d for C}_{19}\text{H}_{22}\text{O}_3 [M]^+: 298.1564, \text{ found 298.1576}.

\text{Optical Rotation:} [\alpha]_D^{21} = -20.3 (c 1.00, CHCl}_3\text{).

\text{SFC conditions:} 15\% \text{ IPA, 2.5 mL/min, Chiralpak AD-H column, } \lambda = 210 \text{ nm, } t_R \text{ (min):} \text{ minor = 4.21, major = 5.30}
ethyl \((3aR,6R,7S,7aR)-4\text{-}\text{o xo octahydro-3a,6-ethanoindene-7-carboxylate (41b)}\)

Prepared from \textit{40b} following General Procedure A. Purification by flash column chromatography (5–30\% EtOAc/hexanes) afforded the title compound as a colorless oil (39.9 mg, 0.169 mmol, 84\% yield, 88\% ee).

\(^1\text{H NMR (400 MHz, CDCl}_3\)): \(\delta 4.15 \text{ (q, } J = 7.1 \text{ Hz, 2H), 2.55 \text{ (dt, } J = 18.8, 2.6 \text{ Hz, 1H), 2.49 – 2.44, 2.42 (d, } J = 8.6 \text{ Hz, 1H), 2.23 – 2.14 (m, 1H), 2.15 – 2.04 (m, 3H), 1.91 – 1.71 (m, 3H), 1.71 – 1.52 (m, 3H), 1.50 – 1.40 (m, 1H), 1.26 (t, } J = 7.1 \text{ Hz, 3H), 1.21 (dt, } J = 9.2, 4.9 \text{ Hz, 1H).}

\(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \(\delta 215.2, 174.9, 60.8, 54.2, 47.5, 43.3, 41.3, 32.9, 29.1, 27.4, 26.5, 25.1, 22.6, 14.4.

\text{IR (Neat Film, NaCl): } 2947, 2873, 1725, 1270, 1170 \text{ cm}^{-1}.

\text{HRMS (MM: FD+: } \text{m/z calc’d for } C_{14}H_{20}O_3 [M]^+: 236.1412, \text{ found 236.1415.}

\text{Optical Rotation: } [\alpha]_D^{21} = -34.2 \text{ (c 1.00, CHCl}_3\).

\textit{Enantiomeric excess determined by converting ethyl ester to benzyl ester through saponification and Steglich esterification.}

\textit{SFC conditions: } 15\% \text{ IPA, 2.5 mL/min, Chiralpak AD-H column, } \lambda = 210 \text{ nm, } t_R \text{ (min): minor = 4.21, major = 5.30.}
benzyl (3aR,6R,7S,7aR)-4-oxooctahydro-3a,6-methanoindene-7-carboxylate (41c)

Prepared from 40c following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (37.0 mg, 0.130 mmol, 65% yield, 65% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.29 (m, 5H), 5.13 (dd, $J$ = 12.3, 7.9 Hz, 2H), 2.96 (t, $J$ = 4.2, 1H), 2.92 (ddd, $J$ = 5.2, 3.7, 1.4, 1H), 2.42 – 2.35 (m, 1H), 2.22 – 2.17 (m, 1H), 2.16 – 2.05 (m, 3H), 1.95 (dddt, $J$ = 12.9, 8.4, 5.1, 2.2 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.66 (dt, $J$ = 10.6, 1.6 Hz, 1H), 1.52 – 1.37 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.9, 173.3, 136.0, 128.8, 128.5, 128.3, 67.8, 66.6, 52.4, 48.5, 41.8, 40.6, 40.5, 32.2, 27.5, 22.1.

IR (Neat Film, NaCl): 2960, 2358, 1739, 1164, 730, 668 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{20}$O$_3$ [M]$^+$: 284.1414, found 284.1407.

Optical Rotation: $[\alpha]_D^{21}$ +20.0 (c 1.00, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 3.97, major = 4.33.

benzyl (3aR,7R,8S,8aR)-10-oxooctahydro-1H-3a,7-ethanoazulene-8-carboxylate (41d)
Prepared from 40d following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (51.8 mg, 0.166 mmol, 83% yield, 97% ee).

\[^1^H\text{NMR (400 MHz, CDCl}_3\):} \delta 7.40 – 7.31 (m, 5H), 5.16 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.64 – 2.56 (m, 1H), 2.25 (ddd, J = 18.5, 2.0, 1.0 Hz, 1H), 2.08 (td, J = 10.5, 7.8 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.79 (m, 3H), 1.78 – 1.60 (m, 4H), 1.59 – 1.43 (m, 4H).

\[^{13}C\text{NMR (100 MHz, CDCl}_3\):} \delta 215.7, 175.8, 136.0, 128.8, 128.3, 66.7, 58.0, 50.2, 45.4, 41.0, 35.7, 33.6, 33.3, 32.0, 28.0, 21.8, 21.2.

\text{IR (Neat Film, NaCl):} 2934, 2873, 1727, 1713, 1455, 1161 cm\textsuperscript{-1}.

\text{HRMS (MM: FD\textsuperscript{+}):} m/z \text{calc’d for C}_{20}\text{H}_{24}\text{O}_3 [M+H]\textsuperscript{+}: 312.1720, found 312.1734.

\text{Optical Rotation:} [\alpha]_D^{21} +21.4 (c 1.00, CHCl\textsubscript{3}).

\text{SFC conditions:} 15\% IPA, 2.5 mL/min, Chiralpak AD-H column, \lambda = 210 nm, t_R (min): minor = 4.70, major = 6.23.

benzyl (1S,2R,4aR,8aR)-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (41f).

Prepared from 40f following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (26.3 mg, 0.084 mmol, 42% yield, 92% ee).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.29 (m, 5H), 5.16 (d, $J$ = 12.4 Hz, 1H), 5.10 (d, $J$ = 12.2 Hz, 1H), 2.47 (dt, $J$ = 17.0, 2.8 Hz, 2H), 2.28 – 2.19 (m, 2H), 2.14 (ddd, $J$ = 19.7, 3.8, 1.8 Hz, 1H), 2.01 (ddddd, $J$ = 11.8, 6.8, 4.5, 1.7 Hz, 1H), 1.87 (dddt, $J$ = 12.8, 4.5, 3.4, 1.6 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.71 – 1.56 (m, 4H), 1.51 – 1.11 (m, 5H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 216.3, 174.5, 136.0, 128.7, 128.4, 128.2, 66.7, 49.8, 45.1, 40.5, 37.1, 30.9, 30.0, 28.9, 26.2, 25.6, 21.7, 21.1.

IR (Neat Film, NaCl): 2928, 2856, 1721, 1170 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc'd for C$_{20}$H$_{24}$O$_3$ [M]$^+$: 312.1720, found 312.1732.

Optical Rotation: $[\alpha]$$_{D}^{21}$ -15.5 (c 1.00, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 4.70, major = 6.23.

$^{3a\text{R,6\text{R,7\text{S,7a\text{R}}}}}$-7-benzoylhexahydro-3\text{a,6-ethanoinden-4(1H)-one (41j)}

Prepared from 40j following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (27.1 mg, 0.101 mmol, 50% yield, 87% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.97 – 7.94 (m, 2H), 7.61 – 7.56 (m, 1H), 7.51 – 7.46 (m, 2H), 3.42 (d, $J$ = 8.5 Hz, 1H), 2.58 – 2.50 (m, 2H), 2.41 – 2.38 (m, 1H), 2.16 (ddd, $J$ = 13.7, 11.1, 6.2 Hz, 1H), 2.08 – 1.87 (m, 4H), 1.82 – 1.74 (m, 1H), 1.70 – 1.50 (m, 4H), 1.25 (ddd, $J$ = 14.0, 9.2, 5.1 Hz, 1H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.9, 201.0, 136.4, 133.4, 128.9, 128.5, 54.2, 49.4, 41.4, 40.8, 34.1, 28.9, 27.8, 26.5, 25.6, 22.7.

IR (Neat Film, NaCl): 2945, 2871, 1720, 1677, 1447, 1217 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{20}$O$_2$ [M]$^+$: 268.1463, found 268.1463.

Optical Rotation: $[\alpha]_D^{21}$ – 32.7 (c 1.00, CHCl$_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 2.55, major = 3.40.

phenyl (3a$R$,6$R$,7$S$,7a$R$)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41k, 41k’ and 41k’’)

Prepared from 40k following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (47.2 mg, 0.166 mmol, 83% yield, 14.8:1.6:1.0 endo-trans/endo-cis/exo-trans, 88% ee (endo-trans)). Crude analysis by $^1$H NMR affords a 10.4:1.4:1.0 ratio of endo-trans/exo-trans/endo-cis. The diastereomers were subsequently separated by preparative HPLC (15% IPA/hexanes, 25 mL/min, Chiralpak AD-H column) for independent characterization. Absolute and relative stereochemistry were assigned/confirmed by VCD where applicable (vida infra) in addition to 2D NMR.

41k (endo-trans):
$^1$H NMR (400 MHz, CDCl$_3$): δ 7.41 – 7.34 (m, 2H), 7.25 – 7.20 (m, 1H), 7.09 – 7.04 (m, 2H), 2.70 (d, $J = 8.7$ Hz, 1H), 2.67 – 2.60 (m, 2H), 2.31 (dddd, $J = 10.6, 8.8, 7.3, 1.7$ Hz, 1H), 2.23 – 2.09 (m, 3H), 1.97 – 1.76 (m, 3H), 1.67 (dddd, $J = 13.5, 11.1, 9.0, 6.2, 4.5$ Hz, 3H), 1.50 (ddt, $J = 12.5, 10.6, 1.7$ Hz, 1H), 1.31 – 1.17 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 214.8, 173.4, 150.7, 129.6, 126.0, 121.5, 54.2, 47.5, 43.4, 41.2, 32.9, 29.1, 27.3, 26.5, 25.0, 22.5.

IR (Neat Film, NaCl): 2948, 2872, 1750, 1721, 1592, 1492, 1192, 1144 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{20}$O$_3$ [M]$^+$: 284.1412, found 284.1411.

Optical Rotation: $[\alpha]_D^{21}$ –16.7 (c 0.20, CHCl$_3$). (single major enantiomer of 11j)

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.09, major = 6.08.

41k’ (exo-trans):

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.39 – 7.34 (m, 2H), 7.25 – 7.19 (m, 1H), 7.06 – 7.01 (m, 2H), 3.30 (dt, $J = 12.0, 2.3$ Hz, 1H), 3.08 (dt, $J = 19.5, 2.8$ Hz, 1H), 2.58 (h, $J = 2.8$ Hz, 1H), 2.47 – 2.33 (m, 2H), 2.21 (dt, $J = 19.6, 2.4$ Hz, 1H), 2.08 – 2.01 (m, 2H), 1.93 – 1.71 (m, 5H), 1.70 – 1.59 (m, 1H), 1.04 (ddd, $J = 12.8, 11.4, 6.7$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 215.2, 171.8, 150.6, 129.6, 126.0, 121.7, 54.6, 45.8, 44.0, 40.1, 31.4, 28.4, 28.2, 27.0, 26.3, 21.8.

IR (CDCl$_3$ solution): 2951, 2870, 1751, 1717, 1194, 1163, 1146 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{20}$O$_3$ [M]$^+$: 284.1412, found 284.1417.

41k” (endo-cis):
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.43 – 7.36\) (m, 2H), 7.27 – 7.22 (m, 1H), 7.12 – 7.07 (m, 2H), 2.76 – 2.67 (m, 1H), 2.58 (dt, \(J = 8.3, 1.7\) Hz, 1H), 2.48 – 2.33 (m, 4H), 2.12 – 2.01 (m, 2H), 1.91 – 1.63 (m, 5H), 1.10 (ddd, \(J = 13.0, 11.2, 6.5\) Hz, 1H), 1.01 (ddd, \(J = 12.4, 9.5, 2.8\) Hz, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 215.1, 172.9, 150.9, 129.6, 126.1, 121.6, 53.8, 49.4, 46.0, 44.2, 32.7, 32.0, 28.6, 27.4, 22.6, 21.5\).

IR (CDCl\(_3\) solution): 2945, 2872, 1751, 1717, 1194, 1163, 1130 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{18}\)H\(_{20}\)O\(_3\) [M\(^+\)]: 284.1412, found 284.1407.

Mesityl (3a\(R\),6\(R\),7\(S\),7\(a\)\(R\))-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41l)

Prepared from 40l following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (58.6 mg, 0.180 mmol, 90% yield, 89% ee).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 6.87\) (s, 2H), 2.75 (d, \(J = 8.8\) Hz, 1H), 2.72 – 2.65 (m, 2H), 2.36 (dddd, \(J = 10.6, 8.9, 7.3, 1.6\) Hz, 1H), 2.26 (s, 3H), 2.24 – 2.09 (m, 3H), 2.08 (s, 6H), 1.98 – 1.78 (m, 3H), 1.75 – 1.61 (m, 3H), 1.55 – 1.48 (m, 1H), 1.31 – 1.24 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 214.8, 172.8, 145.9, 135.6, 129.5, 129.5, 129.5, 54.2, 47.4, 43.5, 41.3, 33.2, 29.2, 27.5, 26.5, 25.1, 22.6, 20.9, 16.4\).

IR (Neat Film, NaCl): 2946, 2873, 1747, 1723, 1485, 1458, 1189, 1137 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{21}\)H\(_{26}\)O\(_3\) [M\(^+\)]: 326.1877, found 326.1886.
Optical Rotation: $[\alpha]_{D}^{21} -25.8$ (c 1.00, CHCl$_3$).

**SFC conditions:** 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.06, major = 4.33.

1,3-dioxoisindolin-2-yl (3a$R$,6$R$,7$S$,7a$R$)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41m and 41m')

Prepared from 40m following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compounds as colorless oils (Endo: 37.7 mg, 0.106 mmol, 53% yield, 62% ee; Exo: 8.6 mg, 0.024 mmol, 12% yield, 62% ee).

**41m (endo):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.92 – 7.85 (m, 2H), 7.83 – 7.75 (m, 2H), 2.84 (dd, $J = 8.7$, 1.3 Hz, 1H), 2.71 (m, 1H), 2.64 (dt, $J = 18.9$, 2.5 Hz, 1H), 2.46 – 2.28 (m, 1H), 2.28 – 2.18 (m, 2H), 2.13 (m, 1H), 1.98 – 1.76 (m, 3H), 1.76 – 1.60 (m, 3H), 1.56 – 1.48 (m, 1H), 1.34 – 1.19 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.0, 171.4, 162.1, 135.0, 129.0, 124.2, 54.1, 44.8, 43.3, 41.0, 33.2, 28.9, 27.2, 26.4, 24.9, 22.4.

IR (Neat Film, NaCl): 2948, 2873, 1782, 1742, 1718, 1466, 1362, 1185 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{20}$H$_{19}$NO$_5$ [M]$^+$: 353.1263, found 353.1251.
**Optical Rotation:** $[\alpha]_D^{21} -0.2$ (c 1.00, CHCl$_3$).

**SFC conditions:** 30% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): minor $= 4.03$, major $= 3.00$

**41m' (exo):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.90 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.81 (dd, $J = 5.5, 3.1$ Hz, 2H), 2.77 (tt, $J = 3.9, 2.2$ Hz, 1H), 2.73 (d, $J = 8.4$ Hz, 1H), 2.47 – 2.28 (m, 4H), 2.19 – 2.02 (m, 2H), 1.92 – 1.71 (m, 4H), 1.71 – 1.61 (m, 1H), 1.11 (ddd, $J = 13.1, 11.2, 6.6$ Hz, 1H), 1.08 – 0.95 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.2, 170.8, 162.1, 135.0, 129.1, 124.2, 53.7, 46.7, 46.0, 44.1, 32.9, 31.8, 28.4, 27.2, 22.5, 21.2.

**IR (Neat Film, NaCl):** 2947, 2868, 1809, 1784, 1743, 1717, 1466, 1362, 1185 cm$^{-1}$.

**HRMS (MM: FD+):** $m/z$ calc’d for C$_{20}$H$_{19}$NO$_5$ [M]$^+$: 353.1263, found 353.1261.

**Optical Rotation:** $[\alpha]_D^{21} -13.6$ (c 0.81, CHCl$_3$).

**SFC conditions:** 30% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): minor $= 4.98$, major $= 4.29$.

![Diagram](image)

dibenzyl (3aR,4R,5R,7aS)-7-oxooctahydro-5,7a-(epiminomethano)indene-4,9-dicarboxylate (41n)
Prepared from 40n following General Procedure A. Purification by flash column chromatography (0–40 % EtOAc/hexanes) afforded the title compound as a colorless oil (76.1 mg, 0.176 mmol, 88% yield, 14.3:1 endo/exo, 91% ee (endo)).

1H NMR (400 MHz, CDCl3): δ 7.35 (dd, J = 7.1, 4.9 Hz, 10H), 5.21 – 5.07 (m, 4H), 4.90 – 4.74 (m, 1H), 3.49 (dd, J = 12.1, 5.8 Hz, 1H), 3.40 – 3.27 (m, 1H), 2.88 (t, J = 8.9 Hz, 1H), 2.66 – 2.42 (m, 2H), 2.30 (p, J = 9.3 Hz, 1H), 2.23 – 2.10 (m, 2H), 1.91 – 1.56 (m, 3H), 1.33 – 1.14 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 210.1, 209.7, 172.2, 154.4, 136.3, 135.5, 128.9, 128.7, 128.7, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 67.6, 67.2, 55.9, 55.8, 50.4, 50.0, 48.8, 48.6, 45.7, 45.6, 42.6, 42.6, 41.7, 41.6, 29.0, 28.9, 24.1, 22.9.

IR (Neat Film, NaCl): 3399, 2963, 2874, 2357, 1729, 1700, 1652, 1414, 1288, 1156, 1115, 748, 681 cm⁻¹.

HRMS (MM: FD+): m/z calc’d for C26H27NO5 [M]+: 433.1889, found 433.1874.

Optical Rotation: [α]D²¹ −39.8 (c 0.75, CHCl3).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, tR (min): minor = 9.19, major = 11.59.

3-((3aR,6R,7S,7aR)-4-oxooctahydro-3a,6-ethanoindene-7-carbonyl)oxazolidin-2-one (41o and 41o’)

![Diagram of 41o (endo) and 41o' (exo)]
Prepared from 40o following General Procedure A. Purification by flash column chromatography (0–90 % EtOAc/hexanes) afforded the title compound as a colorless oil (51.2 mg, 0.185 mmol, 92% yield, 1.1:1 endo/exo (ratio from crude 1H NMR analysis), 84% ee (endo), 79% ee (exo)).

41o (endo):

1H NMR (400 MHz, CDCl3): δ 4.43 (t, J = 8.1 Hz, 2H), 4.15 – 4.00 (m, 2H), 3.54 – 3.47 (m, 1H), 2.66 (ddd, J = 12.4, 8.3, 6.9 Hz, 1H), 2.52 – 2.25 (m, 4H), 1.92 – 1.68 (m, 5H), 1.67 – 1.53 (m, 2H), 1.08 (ddd, J = 12.9, 11.2, 6.4 Hz, 1H), 0.89 (tt, J = 12.3, 9.5 Hz, 1H).

13C NMR (100 MHz, CDCl3): δ 215.5, 173.8, 153.4, 62.1, 53.7, 48.3, 44.1, 44.0, 43.1, 33.8, 31.3, 28.7, 27.3, 22.8, 20.8.

IR (Neat Film, NaCl): 2942, 2867, 1775, 1714, 1693, 1387, 1267, 1222, 1040 cm⁻¹.


Optical Rotation: [α]D²¹ –39.5 (c 1.00, CHCl₃).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, tR (min): minor = 4.15, major = 5.17.

41o’ (exo):

1H NMR (400 MHz, CDCl3): δ 4.43 (t, J = 8.1 Hz, 2H), 4.13 – 3.97 (m, 2H), 3.71 (d, J = 8.8 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.35 (dd, J = 3.5, 2.3 Hz, 1H), 2.19 – 1.84 (m, 5H), 1.81 – 1.41 (m, 6H), 1.27 – 1.18 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 214.9, 174.6, 153.5, 62.13, 54.1, 45.6, 43.1, 41.2, 40.6, 34.5, 28.4, 27.3, 26.5, 25.3, 22.7.

IR (Neat Film, NaCl): 2949, 2872, 1775, 1718, 1692, 1387, 1221, 1040, 759 cm⁻¹.
HRMS (MM: FD+): \( m/z \) calc’d for \( C_{15}H_{19}NO_4 \) [M\(^+\)]: 277.1314, found 277.1317.

**Optical Rotation:** \([\alpha]_D^{21} \) –5.8 (c 1.00, CHCl\(_3\)).

**SFC conditions:** 15\% IPA, 2.5 mL/min, Chiralpak AD-H column, \( \lambda = 210 \text{ nm, } t_R \) (min):
mminor = 6.80, major = 6.38.

**benzyl \( (3R,4S,4aS,9aS)-1\text{-oxo-}1,2,3,4,4a,9\text{-hexahydro-3,9a-ethanofluorene-4-carboxylate} \) (41p and 41p’)**

Prepared from 40p following General Procedure A. Purification by flash column chromatography (0–35\% EtOAc/hexanes) afforded the title compounds as colorless oils (Endo: 56.8 mg, 0.156 mmol, 78\% yield, 72\% ee; Exo: 2.0 mg, 5.48 \( \mu \)mol, 3\% yield).

**41p (endo):**

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \( \delta \) 7.28 – 7.20 (m, 5H), 7.14 – 7.05 (m, 4H), 5.13 (d, \( J = 2.4 \) Hz, 2H), 3.53 (dd, \( J = 9.4, 1.0 \) Hz, 1H), 3.16 (d, \( J = 15.7 \) Hz, 1H), 2.74 (dt, \( J = 9.3, 1.1 \) Hz, 1H), 2.61 (dt, \( J = 18.8, 2.4 \) Hz, 1H), 2.51 (ttt, \( J = 3.5, 2.2, 1.1 \) Hz, 1H), 2.31 (d, \( J = 15.8 \) Hz, 1H), 2.11 (ddd, \( J = 18.8, 3.5, 1.2 \) Hz, 1H), 1.70 – 1.56 (m, 2H), 1.54 – 1.45 (m, 1H), 1.42 – 1.34 (m, 1H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\):} \( \delta \) 214.0, 174.6, 142.3, 140.6, 135.8, 128.8, 128.6, 128.4, 127.3, 127.0, 125.5, 124.3, 125.5, 67.1, 56.6, 47.8, 45.6, 42.1, 35.0, 33.2, 27.0, 24.8.

**IR (Neat Film, NaCl):** 2942, 2869, 1726, 1457, 1164 cm\(^{-1}\).

**HRMS (MM: FD+):** \( m/z \) calc’d for \( C_{23}H_{22}O_3 \) [M+H\(^+\)]: 346.1564, found 346.1571.
**Optical Rotation:** $[\alpha]_D^{21} +1.4$ (c 1.00, CHCl$_3$).

**SFC conditions:** 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 6.74, major = 6.28.

$41q'$ (exo):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 – 7.34 (m, 5H), 7.24 (d, $J = 7.1$ Hz, 1H), 7.14 – 7.07 (m, 3H), 5.30 (d, $J = 12.3$ Hz, 1H), 5.25 (d, $J = 12.3$ Hz, 1H), 3.85 (d, $J = 9.4$ Hz, 1H), 3.46 (d, $J = 14.7$ Hz, 1H), 2.75 (d, $J = 9.3$ Hz, 1H), 2.69 – 2.65 (m, 1H), 2.44 (d, $J = 14.9$ Hz, 1H), 2.37 (dd, $J = 18.7$, 2.1 Hz, 1H), 2.19 (ddd, $J = 18.6$, 3.4, 2.1 Hz, 1H), 2.15 – 2.07 (m, 2H), 1.90 – 1.84 (m, 1H), 1.81 – 1.76 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.5, 174.0, 143.8, 142.7, 135.9, 128.8, 128.6, 128.4, 127.2, 126.6, 124.8, 122.5, 67.1, 56.4, 49.9, 48.3, 44.1, 35.3, 31.9, 27.5, 21.8.

**IR (Neat Film, NaCl):** 2918, 1727, 1161 cm$^{-1}$.

**HRMS (MM: FD+):** $m/z$ calc’d for C$_{23}$H$_{22}$O$_3$ [M+H]$^+$: 346.1569, found 346.1568.

benzyl (3aR,6R,7S,7aS)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate ($41q$ and $41q'$)

Prepared from 40q following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (54.9 mg, 0.183 mmol, 92% yield, 1.6:1 endo/exo, 84% ee (endo), 29% ee (exo)). The endo ($41q$) and exo ($41q'$) diastereomers were subsequently separated by preparative TLC (25%
EtOAc/hexanes) for independent characterization. Absolute and relative stereochemistry were assigned/confirmed by VCD (see below).

**41q (endo):**

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] : \( \delta 7.39–7.31 \text{ (m, 5H), 5.13–5.02 (m, 2H), 3.10–2.99 (m, 2H), 2.47 (h, } J = 2.9 \text{ Hz, 1H), 2.36–2.21 (m, 2H), 2.15 (dt, } J = 19.3, 2.3 \text{ Hz, 1H), 1.86–1.63 (m, 6H), 1.56–1.48 (m, 1H), 1.06–0.92 (m, 2H).} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3\] : \( \delta 215.5, 172.9, 135.9, 128.7, 128.7, 128.5, 66.3, 54.4, 45.9, 44.0, 40.2, 31.4, 28.3, 28.1, 27.0, 26.4, 21.8. \]

**IR (Neat Film, NaCl):** 2940, 2868, 1728, 1456, 1174, 1166, 1146 cm\(^{-1}\).  
**HRMS (MM: FD+):** \( m/z \) calc’d for C\(_{19}\)H\(_{22}\)O\(_3\) [M]\(^+\): 298.1564, found 298.1578.  
**Optical Rotation:** \( [\alpha]_D^{21} = -32.4 \text{ (c 1.00, CHCl}_3\] \).

**SFC conditions:** 15% IPA, 2.5 mL/min, Chiralpak AD-H column, \( \lambda = 210 \text{ nm, t}_R \text{ (min): minor = 5.44, major = 6.53.} \)

**41q’ (exo):**

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] : \( \delta 7.40–7.31 \text{ (m, 5H), 5.14 (d, } J = 12.3 \text{ Hz, 1H), 5.09 (d, } J = 12.2 \text{ Hz, 1H), 3.01 (ddd, } J = 11.7, 3.3, 1.4 \text{ Hz, 1H), 2.46 (h, } J = 3.3 \text{ Hz, 1H), 2.35–2.25 (m, 3H), 2.14 (tdd, } J = 11.6, 7.9, 1.6 \text{ Hz, 1H), 2.07–1.94 (m, 2H), 1.88–1.69 (m, 3H), 1.63–1.57 (m, 1H), 1.47–1.34 (m, 2H), 1.16 (ddd, } J = 13.9, 9.1, 5.0 \text{ Hz, 1H).} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3\] : \( \delta 215.5, 173.1, 136.0, 128.8, 128.5, 128.5, 66.3, 53.6, 45.4, 42.7, 41.2, 32.0, 26.4, 25.3, 24.4, 22.3, 21.8. \]

**IR (Neat Film, NaCl):** 2946, 2847, 1720, 1457, 1154 cm\(^{-1}\).  
**HRMS (MM: FD+):** \( m/z \) calc’d for C\(_{19}\)H\(_{22}\)O\(_3\) [M]\(^+\): 298.1564, found 298.1578.
Optical Rotation: \([\alpha]_D^{21} -5.1 \text{ (c 1.00, CHCl}_3\).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, \(\lambda = 210\) nm, \(t_R\) (min): minor = 7.01, major = 7.42.

benzyl \((3aR,6R,7S,7aS)-7\)-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41r)

Prepared from 40r following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (29.4 mg, 0.094 mmol, 47% yield, 89% ee).

\(^1\)H NMR (400 MHz, CDCl$_3$): \(\delta 7.39 – 7.29\) (m, 5H), 5.16 (d, \(J = 12.4\) Hz, 1H), 5.10 (d, \(J = 12.4\) Hz, 1H), 2.49 – 2.38 (m, 2H), 2.32 (dt, \(J = 18.9, 2.8\) Hz, 1H), 2.19 – 2.10 (m, 2H), 2.01 – 1.92 (m, 1H), 1.85 – 1.66 (m, 4H), 1.65 – 1.55 (m, 1H), 1.49 – 1.31 (m, 5H), 1.13 (ddd, \(J = 14.5, 9.1, 6.0\) Hz, 1H).

\(^13\)C NMR (100 MHz, CDCl$_3$): \(\delta 215.2, 177.8, 136.1, 128.7, 128.4, 128.0, 66.8, 54.37, 45.8, 44.7, 43.4, 37.3, 26.5, 24.4, 24.1, 22.7, 22.4, 20.8\).

IR (Neat Film, NaCl): 2951, 2875, 1723, 1454, 1239, 1212, 1106 cm$^{-1}$.

HRMS (MM: FD+): \(m/z\) calc’d for C$_{20}$H$_{24}$O$_3$ [M]$^+$: 312.1725, found 312.1732.

Optical Rotation: \([\alpha]_D^{21} -15.3 \text{ (c 1.00, CHCl}_3\).

SFC conditions: 40% IPA, 2.5 mL/min, Chiralpak IC column, \(\lambda = 210\) nm, \(t_R\) (min): minor = 2.68, major = 3.51.
benzyl (3aR,6R,7R,7aR)-6-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41s)

Prepared from 40s following General Procedure A. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the title compound as a colorless oil (43.6 mg, 0.140 mmol, 69% yield, 83% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.29 (m, 5H), 5.13 (d, $J = 1.1$ Hz, 2H), 2.86 (dd, $J = 18.5$, 3.5 Hz, 1H), 2.37 (dd, $J = 8.8$, 1.4 Hz, 1H), 2.29 – 2.15 (m, 1H), 2.15 – 2.04 (m, 1H), 2.01 – 1.70 (m, 3H), 1.84 (dd, $J = 18.7$, 1.4 Hz, 1H), 1.68 – 1.36 (m, 4H), 1.30 – 1.15 (m, 2H), 0.94 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.5, 174.9, 135.9, 128.8, 128.5, 128.5, 66.7, 54.2, 52.6, 47.0, 44.9, 38.0, 36.0, 28.7, 26.3, 26.0, 23.8, 22.8.

IR (Neat Film, NaCl): 2949, 2873, 1750, 1498, 1454, 1384, 1324, 1155, 1114, 977, 754, 698, 678, 556 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{20}$H$_{24}$O$_3$ [M]$^+$: 312.1703, found 312.1720.

Optical Rotation: $[\alpha]_D^{21}$ –68.2 (c 0.75, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): minor = 10.23, major = 12.31.
benzyl (3aR,6S,7R,7aR)-6-ethoxy-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41t and 41t’)

Prepared from 40t following General Procedure A. Purification by flash column chromatography (0–50% EtOAc/hexanes) afforded the title compounds as colorless oils (Endo: 44.0 mg, 0.128 mmol, 64% yield, 85% ee; Exo: 17.0 mg, 0.050 mmol, 25% yield, 72% ee). Absolute and relative stereochemistry were assigned/confirmed by VCD (see below).

41t (endo):

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.38 – 7.28 \text{ (m, 5H)}, 5.16 \text{ (d, } J = 1.5 \text{ Hz, 2H)}, 3.55 – 3.32 \text{ (m, 2H)}, 3.17 \text{ (dd, } J = 18.5, 3.1 \text{ Hz, 1H)}, 2.86 \text{ (dd, } J = 8.5, 1.5 \text{ Hz, 1H)}, 2.38 – 2.25 \text{ (m, 2H)}, 2.16 – 2.02 \text{ (m, 1H)}, 2.02 – 1.86 \text{ (m, 3H)}, 1.87 – 1.39 \text{ (m, 5H)}, 1.20 \text{ (ddd, } J = 14.1, 9.1, 5.1 \text{ Hz, 1H)}, 1.03 \text{ (t, } J = 7.0 \text{ Hz, 3H}).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 210.8, 173.7, 136.0, 128.7, 128.4, 128.3, 78.2, 66.8, 58.0, 54.2, 51.9, 45.1, 45.1, 30.7, 28.8, 25.8, 24.8, 22.9, 15.8.

IR (Neat Film, NaCl): 2944, 2875, 1726, 1458, 1390, 1320, 1282, 1153, 1110, 1039, 746, 700 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{21}\)H\(_{26}\)O\(_4\) [M]: 342.1832, found 342.1826.

Optical Rotation: \([\alpha]_D^{21} – 47.4 \text{ (c 0.75, CHCl}_3)\).
SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, \( \lambda = 210 \) nm, \( t_R \) (min): minor = 4.73, major = 5.13.

41t' (exo):

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.42 – 7.28 (m, 5H), 5.19 (d, \( J = 1.1 \) Hz, 2H), 3.57 – 3.35 (m, 2H), 2.69 (dd, \( J = 7.8, 1.7 \) Hz, 1H), 2.60 – 2.47 (m, 1H), 2.47 – 2.44 (m, 2H), 2.39 (ddd, \( J = 12.5, 7.9, 6.9 \) Hz, 1H), 2.28 (ddd, \( J = 13.5, 9.4, 4.6 \) Hz, 1H), 1.92 – 1.78 (m, 3H), 1.77 – 1.66 (m, 1H), 1.67 – 1.58 (m, 1H), 1.11 (ddd, \( J = 11.3, 6.6, 3.7 \) Hz, 1H), 1.03 (t, \( J = 6.9 \) Hz, 3H), 0.89 (tt, \( J = 12.4, 9.6 \) Hz, 1H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 211.5, 173.4, 136.0, 128.7, 128.4, 128.3, 66.9, 58.1, 54.1, 52.8, 47.5, 46.8, 31.0, 27.7, 26.5, 25.9, 23.1, 15.7.

IR (Neat Film, NaCl): 2946, 1721, 1451, 1390, 1328, 1154, 1117, 767, 698 cm\(^{-1}\).

HRMS (MM: FD+): \( m/z \) calc’d for C\(_{21}\)H\(_{26}\)O\(_4\) [M]: 342.1833, found 342.1826.

Optical Rotation: \([\alpha]_D^{21} +1.8 \) (c 0.75, CHCl\(_3\)).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, \( \lambda = 210 \) nm, \( t_R \) (min): minor = 3.29, major = 4.04.

benzyl (3aR,6R,7S,7aR)-5-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (41u)
Prepared from 40u following General Procedure A. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the title compound as a colorless oil (13.6 mg, 0.044 mmol, 22% yield, 61% ee).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 7.39 - 7.32 (m, 5H), 5.14 (ddd, \text{ }^J = 17.8, 12.2 \text{ Hz}, 2H), 2.61 (dd, \text{ }^J = 3.7, 2.1 \text{ Hz}, 1H), 2.45 - 2.30 (m, 3H), 2.21 - 2.06 (m, 4H), 1.90 - 1.63 (m, 3H), 1.61 - 1.35 (m, 2H), 1.32 - 1.16 (m, 1H), 0.97 (d, \text{ }^J = 7.7 \text{ Hz}, 3H). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{)}: \delta 217.7, 174.8, 135.9, 128.7, 128.6, 128.5, 66.8, 54.2, 48.3, 46.9, 42.2, 38.1, 29.7, 28.9, 26.6, 24.1, 22.5, 15.8. \]

\[ \text{IR (Neat Film, NaCl): 2943, 2873, 1718, 1455, 1197, 1171 cm}^{-1}. \]

\[ \text{HRMS (MM: FD+): } m/z \text{ calc'd for C}_{20}\text{H}_{24}\text{O}_3 [M]^+: 312.1725, \text{ found 312.1730}. \]

\[ \text{Optical Rotation: } [\alpha]_D^{21} +10.9 (c 0.75, \text{ CHCl}_3). \]

\[ \text{SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, } \lambda = 210 \text{ nm, } t_R \text{ (min): minor = 5.84, major = 5.43.} \]

\[ \text{benzyl (1S,2R,4aR,8aR)-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate-3-d (D-41f)} \]

Prepared from \textbf{D-40f} following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (41.3 mg, 0.132 mmol, 66% yield, 91% ee).
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.39 – 7.30 (m, 5H), 5.16 (d, $J = 12.4$ Hz, 1H), 5.11 (d, $J = 12.2$ Hz, 1H), 2.51 – 2.41 (m, 1.6H), 2.36 – 2.10 (m, 2.7H), 2.02 (dddd, $J = 11.8$, 9.1, 5.3, 2.9 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.71 (m, 1H), 1.70 – 1.55 (m, 4H), 1.52 – 1.11 (m, 5H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 216.4, 174.5, 136.0, 128.8, 128.4, 128.2, 77.5, 77.2, 76.8, 66.7, 49.9, 45.1, 40.5, 37.1, 31.0, 30.9, 30.8, 30.0, 28.9, 26.2, 25.6, 21.8, 21.2.

*Partial deuteration complicates $^{13}$C NMR spectrum. Peaks are listed as they appear.

$^2$H NMR (61 MHz, CHCl$_3$): δ 2.46, 2.14.

*Trace $D$-exchanged water observed in spectrum.

IR (Neat Film, NaCl): 2928, 2858, 1723, 1169 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{20}$H$_{23}$DO$_3$ [M+H]$^+$: 313.1783, found 313.1795.

Optical Rotation: $[\alpha]_D$ –21.3 (c 1.00, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 5.07, major = 6.38.

benzyl ($S,E$)-6-(1-allyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (44)

Prepared from 42 (0.02 mmol) following General Procedure A. Purification by preparatory thin layer chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (10.1 mg, 0.0196 mmol, 98% yield, 84% ee).
1H NMR (400 MHz, CDCl₃): δ 7.40 – 7.29 (m, 5H), 6.97 (dt, J = 15.6, 6.9 Hz, 1H), 6.85 (dt, J = 10.1, 3.9 Hz, 1H), 5.91 (dt, J = 10.0, 2.0 Hz, 1H), 5.85 (dt, J = 15.7, 1.6 Hz, 1H), 5.69 (ddt, J = 16.6, 10.5, 7.3 Hz, 1H), 5.17 (s, 2H), 5.09 – 5.00 (m, 2H), 2.41 – 2.29 (m, 3H), 2.26 – 2.13 (m, 3H), 1.87 (t, J = 6.1 Hz, 2H), 1.63 – 1.23 (m, 4H).

13C NMR (100 MHz, CDCl₃): δ 202.9, 166.6, 149.6, 148.7, 136.3, 134.0, 129.0, 128.7, 128.3, 128.3, 121.4, 118.3, 66.2, 47.6, 39.1, 33.9, 32.9, 30.8, 23.1, 22.4.

IR (Neat Film, NaCl): 2936, 2358, 1718, 1669, 1262, 992 cm⁻¹.

HRMS (MM: FD+): m/z calc’d for C_{22}H_{26}O₃ [M]⁺: 338.1881, found 338.1877.

Optical Rotation: [α]_D²¹ = −0.69 (c 0.62, CHCl₃).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, tᵣ (min): minor = 14.49, major = 11.94.

benzyl (E)-7-(1-(2-cyclobutylideneethyl)-2-oxocyclohex-3-en-1-yl)hept-2-enoateenoate (83)

Prepared from 63 following General Procedure A, with the modification of being on 0.1 mmol scale. Purification by preparatory thin layer chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (2.4 mg, 0.006 mmol, 6% yield).

1H NMR (400 MHz, CDCl₃): δ 7.41 – 7.29 (m, 5H), 6.99 (dt, J = 15.6, 6.9 Hz, 1H), 6.85 (dt, J = 10.0, 3.9 Hz, 1H), 5.92 – 5.81 (m, 2H), 5.17 (s, 2H), 5.01 – 4.92 (m, 1H), 2.67 –
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

2.54 (m, 3H), 2.40 – 2.30 (m, 2H), 2.27 – 1.99 (m, 4H), 1.96 – 1.82 (m, 3H), 1.63 – 1.49 (m, 3H), 1.49 – 1.36 (m, 3H), 1.32 – 1.13 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 203.6, 166.6, 150.1, 148.5, 143.1, 136.3, 129.1, 128.7, 128.3, 128.3, 121.1, 115.4, 66.2, 48.3, 34.1, 33.1, 32.3, 31.2, 30.8, 29.6, 28.8, 23.6, 23.2, 17.1.

IR (Neat Film, NaCl): 2929, 1720, 1670, 1185 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{26}$H$_{32}$O$_3$ [M]$^+$: 392.2351, found 392.2341.

(2-vinylprop-1-ene-1,3-diyldibenzene (84)

Prepared from 67 following General Procedure A, with the modification of being on 0.1 mmol scale. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (6.5 mg, 0.03 mmol, 29% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.18 (m, 11.5H), 6.91 – 6.80 (m, 1.15H), 6.56 (ddd, $J = 17.4$, 10.8, 0.9 Hz, 0.15H), 6.45 (s, 1H), 5.42 – 5.33 (m, 1H), 5.19 – 5.13 (m, 1.15H), 5.11 – 5.06 (m, 0.15H), 3.90 (s, 0.3H), 3.73 (s, 2H).

*Isolated as an apparent 1:0.15 mixture of alkene isomers.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.5, 140.2, 139.9, 137.7, 137.5, 137.3, 134.2, 133.8, 131.8, 129.6, 128.9, 128.8, 128.7, 128.5, 128.2, 128.2, 127.3, 127.0, 126.2, 126.1, 116.4, 114.8, 40.3, 33.2.

*Isolated as an apparent 1:0.15 mixture of alkene isomers.

IR (Neat Film, NaCl): 3060, 3023, 2919, 1601, 1493, 1455, 1165, 1074 cm$^{-1}$. 


Preparation of Unsaturated β-Ketoester Starting Materials

*General Procedure B: Horner–Wadsworth–Emmons Olefination*

To a suspension of NaH (60% by weight in mineral oil, 1.1 equiv) in THF (0.5 M) at 0 ºC was dropwise added a solution of the appropriate phosphonate ester (1.1 equiv) in THF (1.0 M). Stirred at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of aldehyde 85 (1.0 equiv) in THF (0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of NaHCO₃ and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product (10) was purified by silica gel flash column chromatography.

3-methylbut-2-en-1-yl (E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40a)

Prepared from 85 and benzyl 2-(diethoxyphosphoryl)acetate following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.410 g, 1.00 mmol, 67 % yield).
\(^{1}\text{H NMR (400 MHz, CDCl}_3\):} \(\delta 7.38 - 7.29 (m, 5H), 6.98 (dt, J = 15.7, 6.9 Hz, 1H), 6.90 - 6.84 (m, 1H), 6.02 (ddd, J = 10.1, 2.5, 1.5 Hz, 1H), 5.87 (dt, J = 15.6, 1.6 Hz, 1H), 5.31 - 5.24 (m, 1H), 5.17 (s, 2H), 4.58 (dt, J = 7.2, 1.0 Hz, 2H), 2.55 - 2.41 (m, 2H), 2.37 - 2.27 (m, 1H), 2.22 (qd, J = 7.3, 1.6 Hz, 2H), 1.97 - 1.86 (m, 2H), 1.77 - 1.69 (m, 4H), 1.67 (d, J = 1.4 Hz, 3H), 1.55 - 1.38 (m, 2H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\):} \(\delta 196.3, 171.6, 166.5, 149.3, 149.3, 139.7, 136.3, 129.4, 128.7, 128.3, 128.3, 121.5, 118.3, 66.2, 62.3, 57.0, 33.5, 32.7, 30.5, 25.8, 23.9, 23.2, 18.2.

IR (Neat Film, NaCl): 3034, 2938, 1723, 1684, 1653, 1455, 1384, 1246, 1174, 1166 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{25}\)H\(_{30}\)O\(_5\) [M]\(^+\): 410.2088, found 410.2097.

3-methylbut-2-en-1-yl (E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40b)

Prepared from 85 and ethyl 2-(diethoxyphosphoryl)acetate following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.291 g, 0.835 mmol, 47 % yield).

\(^{1}\text{H NMR (400 MHz, CDCl}_3\):} \(\delta 6.97 - 6.85 (m, 2H), 6.02 (ddd, J = 10.0, 2.6, 1.5 Hz, 1H), 5.81 (dt, J = 15.6, 1.6 Hz, 1H), 5.31 - 5.24 (m, 1H), 4.64 - 4.54 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.55 - 2.41 (m, 2H), 2.37 - 2.27 (m, 1H), 2.21 (qd, J = 7.3, 1.6 Hz, 2H), 1.98 –
1.87 (m, 2H), 1.78 – 1.69 (m, 4H), 1.68 (s, 3H), 1.55 – 1.37 (m, 2H), 1.28 (t, \( J = 7.1 \) Hz, 3H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta \) 196.3, 171.6, 166.8, 149.3, 148.5, 139.7, 129.4, 121.8, 118.3, 62.3, 60.3, 57.0, 33.5, 32.6, 30.5, 25.8, 23.9, 23.3, 18.2, 14.4.

\( \text{IR (Neat Film, NaCl):} \) 2934, 1714, 1682, 1168 cm\(^{-1}\).

\( \text{HRMS (MM: FD+):} \) \( m/z \) calc’d for C\( _{20} \)H\( _{28} \)O\( _5 \)[M]\(^+\): 348.1937, found 348.1943.

3-methylbut-2-en-1-yl \((E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohept-3-ene-1-carboxylate (40d)\)

Prepared from cyclohept-2-en-1-one following General Procedures B–D. Note that inseparable impurities plagued the \( \beta \)-ketoester and aldehyde intermediates. Fortunately, these intermediates could be brought through the sequence in sub-optimal purity to still afford the title compound 40d as a colorless oil (265 mg, 0.62 mmol, 3.2% yield from cyclohept-2-en-1-one) after a final purification by flash column chromatography (20% EtOAc/hexanes).

\( ^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta \) 7.39 – 7.30 (m, 5H), 6.97 (dt, \( J = 15.6, 6.9 \) Hz, 1H), 6.36 (ddd, \( J = 12.3, 5.5, 3.9 \) Hz, 1H), 5.98 (ddd, \( J = 12.3, 2.4, 1.4 \) Hz, 1H), 5.86 (dt, \( J = 15.6, 1.6 \) Hz, 1H), 5.28 (ddp, \( J = 8.6, 5.7, 1.4 \) Hz, 1H), 5.17 (s, 2H), 4.57 (d, \( J = 7.2 \) Hz, 2H), 2.47 – 2.27 (m, 3H), 2.19 (qd, \( J = 7.2, 1.6 \) Hz, 2H), 1.99 – 1.79 (m, 3H), 1.77 – 1.69 (m, 4H), 1.69 – 1.61 (m, 4H), 1.43 – 1.32 (m, 2H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.1, 172.9, 166.5, 149.3, 143.2, 139.7, 136.3, 131.6, 128.7, 128.3, 128.3, 121.5, 118.2, 66.2, 63.9, 62.2, 36.5, 32.6, 32.3, 31.2, 25.8, 24.3, 23.0, 18.2.

IR (Neat Film, NaCl): 2927, 1720, 1686, 1453, 1162 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{26}$H$_{32}$O$_5$ [M]$^+$: 424.2244, found 424.2241.

3-methylbut-2-en-1-yl (E)-1-(7-(benzylxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40f)

Prepared from 86 and benzyl 2-(diethoxyphosphoryl)acetate$^{28}$ following General Procedure B. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (652 mg, 1.54 mmol, 69% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.30 (m, 5H), 6.99 (ddd, $J = 15.5, 7.3, 6.3$ Hz, 1H), 6.90 – 6.84 (m, 1H), 6.01 (d, $J = 10.1$ Hz, 1H), 5.85 (d, $J = 15.6$ Hz, 1H), 5.30 – 5.25 (m, 1H), 5.17 (s, 2H), 4.58 (d, $J = 6.6$ Hz, 2H), 2.55 – 2.40 (m, 2H), 2.36 – 2.26 (m, 1H), 2.24 – 2.16 (m, 2H), 1.96 – 1.86 (m, 2H), 1.77 – 1.65 (m, 7H), 1.47 (p, $J = 7.4$ Hz, 2H), 1.38 – 1.24 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.2, 171.6, 166.5, 149.7, 149.2, 139.4, 136.2, 129.2, 128.6, 128.2, 128.2, 121.1, 118.2, 66.0, 62.1, 56.9, 33.5, 32.0, 30.2, 28.4, 25.7, 24.2, 23.7, 18.1.

IR (Neat Film, NaCl): 2932, 2861, 1722, 1684, 1653, 1456, 1263, 1181 cm$^{-1}$.
HRMS (MM: FD+): \(m/z\) calc’d for C\(_{26}\)H\(_{32}\)O\(_5\) [M]\(^+\): 424.2244, found 424.2247.

3-(methyl-\(d_3\))but-2-en-1-yl-4,4,4-\(d_3\) (\(E\))-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (\(D\)-40f)

Prepared from \(D\)-86 and benzyl 2-(diethoxyphosphoryl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (201 mg, 0.467 mmol, 48 % yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39 – 7.30 (m, 5H), 6.99 (dt, \(J = 15.6, 6.9\) Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, \(J = 10.1, 2.6, 1.5\) Hz, 1H), 5.85 (dt, \(J = 15.6, 1.5\) Hz, 1H), 5.27 (t, \(J = 7.1\) Hz, 1H), 5.17 (s, 2H), 4.58 (dd, \(J = 7.2, 1.7\) Hz, 2H), 2.55 – 2.41 (m, 2H), 2.36 – 2.27 (m, 1H), 2.25 – 2.15 (m, 2H), 1.98 – 1.85 (m, 2H), 1.73 (ddd, \(J = 13.6, 11.2, 5.3\) Hz, 1H), 1.51 – 1.42 (m, 2H), 1.37 – 1.25 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.4, 171.7, 166.6, 149.8, 149.3, 139.4, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.3, 57.0, 33.6, 32.2, 30.3, 28.5, 24.3, 23.9.

\(^2\)H NMR (61 MHz, CHCl\(_3\)): \(\delta\) 1.69, 1.65.

IR (Neat Film, NaCl): 2930, 1720, 1683, 1264, 1167 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{26}\)H\(_{26}\)D\(_6\)O\(_5\) [M]\(^+\): 430.2621, found 430.2622.
3-methylbut-2-en-1-yl (E)-1-(8-(benzyloxy)-8-oxooct-6-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40g)

Prepared from 87 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (773 mg, 1.76 mmol, 65 % yield).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ 7.40 – 7.29 (m, 5H), 6.99 (dt, $J = 15.6, 6.9$ Hz, 1H), 6.89 – 6.84 (m, 1H), 6.01 (ddd, $J = 10.0, 2.5, 1.5$ Hz, 1H), 5.85 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.28 (ddp, $J = 8.6, 5.7, 1.4$ Hz, 1H), 5.17 (s, 2H), 4.63 – 4.53 (m, 2H), 2.55 – 2.40 (m, 2H), 2.36 – 2.26 (m, 1H), 2.19 (qd, $J = 7.1, 1.6$ Hz, 2H), 1.98 – 1.84 (m, 2H), 1.77 – 1.69 (m, 4H), 1.67 (s, 3H), 1.49 – 1.41 (m, 2H), 1.36 – 1.23 (m, 4H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta$ 196.5, 171.7, 166.6, 150.1, 149.3, 139.5, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.2, 57.1, 33.7, 32.3, 30.3, 29.6, 27.8, 25.8, 24.4, 23.9, 18.2.

IR (Neat Film, NaCl): 2929, 2858, 1721, 1684, 1654, 1456, 1264, 1168 cm\textsuperscript{-1}.

HRMS (MM: FD\textsuperscript{+}): $m/z$ calc’d for C\textsubscript{27}H\textsubscript{34}O\textsubscript{5} [M]\textsuperscript{+}: 438.2401, found 438.2396.

![Structural diagram of 3-methylbut-2-en-1-yl (E)-2-oxo-1-(6-oxo-6-phenoxyhex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (40k)](image_url)
Prepared from 85 and benzyl 2-(diethoxyphosphoryl)acetate following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (409 mg, 1.03 mmol, 57% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (t, $J = 8.0$ Hz, 2H), 7.22 (t, $J = 7.4$ Hz, 1H), 7.18 – 7.10 (m, 3H), 6.91 – 6.87 (m, 1H), 6.05 – 6.00 (m, 2H), 5.29 (tt, $J = 7.1, 1.3$ Hz, 1H), 4.61 (d, $J = 7.1$ Hz, 2H), 2.56 – 2.44 (m, 2H), 2.37 – 2.27 (m, 3H), 2.00 – 1.92 (m, 2H), 1.82 – 1.73 (m, 4H), 1.69 (s, 3H), 1.63 – 1.46 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.3, 171.6, 165.1, 150.9, 150.9, 149.3, 139.7, 129.5, 129.4, 125.8, 121.8, 121.1, 118.3, 62.4, 57.0, 33.6, 32.8, 30.5, 25.8, 23.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2930, 1732, 1684, 1652, 1458, 1245, 1195 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{24}$H$_{38}$O$_5$ [M]$^+$: 396.1931, found 396.1945.

3-methylbut-2-en-1-yl (E)-1-(6-(mesityloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40l)

Prepared from 85 and mesityl 2-(diethoxyphosphoryl)acetate following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (597 mg, 1.36 mmol, 76% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (dt, $J = 15.7, 6.8$ Hz, 1H), 6.92 – 6.84 (m, 3H), 6.09 – 6.01 (m, 2H), 5.32 – 5.26 (m, 1H), 4.61 (d, $J = 5.6$ Hz, 2H), 2.57 – 2.43 (m, 2H), 2.39 –
2.27 (m, 3H), 2.26 (s, 3H), 2.09 (s, 6H), 2.01 – 1.92 (m, 2H), 1.79 (dd, J = 13.6, 11.9, 4.8 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.64 – 1.46 (m, 2H).

^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 196.3, 171.6, 164.6, 150.7, 149.3, 146.0, 139.7, 135.3, 130.0, 129.4, 129.3, 120.7, 118.3, 62.4, 57.0, 33.6, 32.8, 30.5, 25.8, 23.9, 23.2, 20.9, 18.2, 16.4.

IR (Neat Film, NaCl): 2920, 1733, 1684, 1458, 1248, 1192, 1140 cm\textsuperscript{-1}.

HRMS (MM: FD\textsuperscript{+}): m/z calc’d for C\textsubscript{27}H\textsubscript{34}O\textsubscript{5}\textsuperscript{+}: 438.2401, found 438.2401.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

1-benzyl 3-(3-methylbut-2-en-1-yl) (E)-3-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-4-oxo-3,4-dihydropyridine-1,3(2\textsubscript{H})-dicarboxylate (40n)

Prepared from 88 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (20-30% EtOAc/hexanes) afforded the title compound as a colorless oil (181.3 mg, 0.332 mmol, 55% yield).

\(^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.79 (s, 1H), 7.44 – 7.28 (m, 10H), 6.94 (dt, J = 15.5, 6.8 Hz, 1H), 5.85 (dt, J = 15.7, 1.6 Hz, 1H), 5.42 – 5.21 (m, 4H), 5.17 (s, 2H), 4.67 – 4.51 (m, 3H), 3.71 (d, J = 13.6 Hz, 1H), 2.20 (q, J = 7.3 Hz, 2H), 2.07 – 1.92 (m, 1H), 1.69 – 1.58 (m, 1H), 1.71 (s, 3H), 1.66 (s, 3H), 1.49 – 1.40 (m, 2H).

\(^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 190.5, 169.5, 166.4, 148.7, 142.7, 140.1, 136.2, 135.0, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 121.7, 118.0, 106.5, 69.4, 66.2, 62.8, 55.3, 48.3, 32.4, 31.3, 25.8, 23.0, 18.2.
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

IR (Neat Film, NaCl): 2938, 2338, 1726, 1676, 1388, 1303, 1201, 975 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{32}\)H\(_{35}\)NO\(_7\) [M]: 545.2414, found 545.2408.

3-methylbut-2-en-1-yl (E)-2-oxo-1-(6-oxo-6-(2-oxooxazolidin-3-yl)hex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (40o)

Prepared from 85 and diethyl (2-oxo-2-(2-oxooxazolidin-3-yl)ethyl)phosphonate \(^{31}\) following General Procedure B. Purification by flash column chromatography (0-80\% EtOAc/hexanes) afforded the title compound as a colorless oil (275.1 mg, 0.706 mmol, 71\% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.23 (d, \(J = 15.6\) Hz, 1H), 7.12 (dt, \(J = 15.4, 6.7\) Hz, 1H), 6.87 (ddd, \(J = 7.8, 6.0, 3.9\) Hz, 1H), 6.01 (dt, \(J = 10.3, 2.0\) Hz, 1H), 5.28 (tt, \(J = 7.2, 1.3\) Hz, 1H), 4.62 – 4.54 (m, 2H), 4.41 (dd, \(J = 8.5, 7.6\) Hz, 2H), 4.11 – 4.02 (m, 2H), 2.55 – 2.40 (m, 2H), 2.38 – 2.25 (m, 3H), 2.00 – 1.86 (m, 2H), 1.82 – 1.69 (m, 2H), 1.73 (s, 3H), 1.68 (s, 3H), 1.50 (dt, \(J = 17.3, 12.4, 7.6\) Hz, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.3, 171.6, 165.3, 153.6, 150.9, 149.4, 139.4, 139.6, 129.3, 120.5, 118.3, 62.3, 62.2, 57.0, 42.8, 33.4, 33.1, 30.3, 25.8, 23.9, 23.3, 18.2.

IR (Neat Film, NaCl): 2927, 1774, 1724, 1684, 1636, 1385, 1359, 1222, 1042 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{21}\)H\(_{27}\)NO\(_6\) [M]: 389.1838, found 389.1827.
3-methylbut-2-en-1-yl 

(E)-1-(6-(benzyloxy)-5-methyl-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40r)

Prepared from 85 and benzyl 2-(diethoxyphosphoryl)propanoate\textsuperscript{32} following General Procedure B. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (220 mg, 0.518 mmol, 29% yield).

\textbf{1H NMR (400 MHz, CDCl\textsubscript{3}):} \(\delta 7.39 – 7.29 (m, 5H), 6.87 \text{ (ddddd, } J = 10.1, 4.9, 3.0, 1.1 \text{ Hz, 1H}), 6.78 \text{ (tq, } J = 7.5, 1.5 \text{ Hz, 1H}), 6.01 \text{ (ddd, } J = 10.1, 2.5, 1.5 \text{ Hz, 1H}), 5.31 – 5.24 \text{ (m, 1H), 5.18 \ (s, 2H), 4.58 \ (d, } J = 6.9 \text{ Hz, 2H}), 2.55 – 2.41 \text{ (m, 2H), 2.36 – 2.26 \ (m, 1H), 2.19 \ (qd, } J = 7.5, 1.1 \text{ Hz, 2H}), 1.98 – 1.87 \text{ (m, 2H), 1.85 \ (s, 3H), 1.79 – 1.69 \ (m, 4H), 1.67 \ (s, 3H), 1.53 – 1.37 \ (m, 2H)).

\textbf{13C NMR (100 MHz, CDCl\textsubscript{3}):} \(\delta 196.3, 171.6, 168.0, 149.3, 142.3, 139.6, 136.5, 129.3, 128.6, 128.2, 128.1, 128.1, 118.3, 66.3, 62.3, 57.0, 33.7, 30.4, 29.2, 25.8, 23.9, 23.9, 18.2, 12.6.

IR (Neat Film, NaCl): 2930, 1711, 1686, 1452, 1265, 1180 cm\textsuperscript{-1}.

HRMS (MM: FD\textsuperscript{+}): \textit{m/z} calc’d for C\textsubscript{26}H\textsubscript{32}O\textsubscript{5} [M]\textsuperscript{+}: 424.2250, found 424.2250.
3-methylbut-2-en-1-yl (E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-4-methyl-2-oxocyclohex-3-ene-1-carboxylate (40s)

Prepared from 89 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (15–20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (827.2 mg, 2.16 mmol, 64% yield).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.39 – 7.28 (m, 5H), 6.98 (dt, \(J = 15.6, 6.8 \) Hz, 1H), 5.87 (dq, \(J = 2.7, 1.3 \) Hz, 1H), 5.86 (dt, \(J = 15.6, 1.6 \) Hz, 1H), 5.27 (tp, \(J = 7.1, 1.4 \) Hz, 1H), 5.16 (s, 2H), 4.64 – 4.51 (m, 2H), 2.52 – 2.36 (m, 2H), 2.28 – 2.14 (m, 3H), 1.98 – 1.83 (m, 5H), 1.72 (s, 4H), 1.67 (s, 3H), 1.54 – 1.34 (m, 2H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 195.9, 171.7, 166.5, 161.4, 149.3, 139.6, 136.3, 128.7, 128.3, 128.3, 126.1, 121.5, 118.4, 66.2, 62.3, 55.9, 33.5, 32.7, 30.2, 28.8, 25.8, 24.2, 23.3, 18.2.

IR (Neat Film, NaCl): 3032, 2938, 1723, 1674, 1438, 1379, 1264, 1212, 1168, 1013, 741, 698 cm\textsuperscript{-1}.

HRMS (MM: FD\textsuperscript{+}): \(m/z\) calc’d for C\textsubscript{26}H\textsubscript{32}O\textsubscript{5} [M]\textsuperscript{+}: 424.2235, found 424.2244.
Prepared from 90 and benzyl 2-(diethoxyphosphoryl)acetate\(^\text{28}\) following General Procedure B. Purification by flash column chromatography (30% EtOAc/hexanes) afforded the title compound as a colorless oil (814.7 mg, 1.79 mmol, 88% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.40 - 7.28\) (m, 5H), 6.98 (dt, \(J = 15.6, 6.8\) Hz, 1H), 5.86 (dt, \(J = 15.7, 1.6\) Hz, 1H), 5.34 (d, \(J = 1.2\) Hz, 1H), 5.28 (dddt, \(J = 7.0, 5.6, 2.8, 1.4\) Hz, 1H), 5.16 (s, 2H), 4.66 – 4.52 (m, 2H), 3.89 (qd, \(J = 7.1, 1.6\) Hz, 2H), 2.61 (dddd, \(J = 17.9, 10.1, 4.9, 1.2\) Hz, 1H), 2.46 – 2.27 (m, 2H), 2.21 (qd, \(J = 7.3, 1.6\) Hz, 2H), 2.02 – 1.83 (m, 2H), 1.82 – 1.72 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.45 (dddd, \(J = 13.3, 11.2, 6.4, 2.7\) Hz, 2H), 1.35 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 195.8, 176.6, 171.8, 166.5, 149.4, 139.5, 136.3, 128.7, 128.3, 128.3, 121.4, 118.5, 102.3, 66.2, 64.5, 62.3, 56.0, 33.8, 32.7, 28.7, 26.6, 25.8, 23.3, 18.2, 14.3.

IR (Neat Film, NaCl): 2939, 1721, 1655, 1608, 1446, 1380, 1342, 1242, 1190, 1026, 736 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(/m/z/\) calc’d for C\(_{27}\)H\(_{34}\)O\(_6\) [M\(^+\)]: 454.2349, found 454.2350.

3-methylbut-2-en-1-yl \((E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-3-methyl-2-oxocyclohex-3-ene-1-carboxylate (40u)\)
Prepared from 91 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (1176.8 mg, 2.77 mmol, 71% yield).

\textbf{1\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta 7.41 – 7.26\) (m, 5H), 6.98 (dt, \(J = 15.6, 6.8\) Hz, 1H), 6.59 (ddt, \(J = 4.7, 3.1, 1.3\) Hz, 1H), 5.87 (dt, \(J = 15.6, 1.6\) Hz, 1H), 5.27 (tdq, \(J = 7.1, 2.8, 1.5\) Hz, 1H), 5.17 (s, 2H), 4.57 (d, \(J = 6.7\) Hz, 2H), 2.50 – 2.36 (m, 2H), 2.33 – 2.16 (m, 3H), 1.98 – 1.83 (m, 2H), 1.78 (q, \(J = 1.7\) Hz, 3H), 1.77 – 1.64 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H) 1.61 – 1.34 (m, 3H).

\textbf{13\textsuperscript{C} NMR (100 MHz, CDCl\textsubscript{3})}: \(\delta 197.0, 171.9, 166.5, 149.4, 143.8, 139.6, 136.3, 135.4, 128.7, 128.3, 128.3, 121.5, 118.3, 66.2, 62.2, 56.9, 33.6, 32.7, 30.9, 25.8, 23.6, 23.4, 18.2, 16.6.

\textbf{IR (Neat Film, NaCl)}: 2921, 1721, 1677, 1450, 1377, 1248, 1168, 728 cm\textsuperscript{-1}.

\textbf{HRMS (MM: FD+)}: \(m/z\) calc’d for C\textsubscript{26}H\textsubscript{32}O\textsubscript{5} [M]+: 424.2244, found 424.2244.

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

\textbf{allyl (E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (42)}

Prepared from 92 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (599.1 mg, 1.41 mmol, 46% yield).

\textbf{1\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta 7.41 – 7.26\) (m, 5H), 6.98 (dt, \(J = 15.6, 6.9\) Hz, 1H), 6.89 (ddddd, \(J = 10.1, 4.8, 3.1, 1.0\) Hz, 1H), 6.03 (ddd, \(J = 10.1, 2.5, 1.6\) Hz, 1H), 5.93 – 5.77 (m,
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

2H), 5.27 (dq, \( J = 17.2, 1.5 \) Hz, 1H), 5.21 (dq, \( J = 10.4, 1.3 \) Hz, 1H), 5.17 (s, 2H), 4.60 (dq, \( J = 5.6, 1.6 \) Hz, 2H), 2.57 – 2.42 (m, 2H), 2.39 – 2.27 (m, 1H), 2.22 (qd, \( J = 7.3, 1.6 \) Hz, 2H), 2.02 – 1.87 (m, 2H), 1.77 (ddd, \( J = 13.7, 11.7, 5.2 \) Hz, 1H), 1.57 – 1.40 (m, 2H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta 196.0, 171.2, 166.5, 149.5, 149.1, 136.2, 131.7, 129.3, 128.7, 128.3, 128.3, 127.8, 127.1, 121.6, 118.7, 66.2, 65.9, 57.0, 33.4, 32.6, 30.3, 23.8, 23.2.

IR (Neat Film, NaCl): 2937, 2357, 1723, 1684, 1456, 1262, 1165, 992 cm\(^{-1}\).

HRMS (MM: FD+): \( m/z \) calc’d for C\(_{23}\)H\(_{27}\)O\(_5\) [M]\(^+\): 383.1871, found 383.1853.

1\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.37 – 7.34 \) (m, 6H), 7.34 – 7.29 (m, 3H), 7.27 – 7.24 (m, 1H), 6.97 (dt, \( J = 15.6, 6.9 \) Hz, 1H), 6.89 (dddd, \( J = 10.1, 4.8, 3.1, 1.0 \) Hz, 1H), 6.62 (d, \( J = 15.9 \) Hz, 1H), 6.22 (dt, \( J = 15.9, 6.4 \) Hz, 1H), 6.04 (dd, \( J = 10.1, 2.5, 1.6 \) Hz, 1H), 5.86 (dt, \( J = 15.7, 1.6 \) Hz, 1H), 5.16 (s, 2H), 4.76 (dt, \( J = 6.4, 1.4 \) Hz, 2H), 2.56 – 2.45 (m, 2H), 2.37 – 2.28 (m, 1H), 2.22 (ddd, \( J = 7.4, 7.4, 1.6 \) Hz, 2H), 1.95 (ddt, \( J = 16.8, 7.9, 5.7 \) Hz, 2H), 1.78 (ddd, \( J = 13.7, 11.7, 5.0 \) Hz, 1H), 1.56 – 1.42 (m, 2H).

cinnamyl 1-((E)-6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (47)

Prepared from 93 and benzyl 2-(diethoxyphosphoryl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (569 mg, 1.24 mmol, 67% yield).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.0, 171.4, 166.5, 149.5, 149.1, 136.2, 136.2, 134.7, 129.3, 128.7, 128.7, 128.3, 128.3, 126.8, 122.6, 121.6, 66.2, 65.9, 57.0, 33.4, 32.6, 30.3, 23.8, 23.2.

IR (Neat Film, NaCl): 3034, 2942, 1718, 1700, 1684, 1247, 1166 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{29}\)H\(_{30}\)O\(_5\) [M\(^+\): 458.2088, found 458.2082.

22-cyclobutylideneethyl \((E)\)-1-(7-(benzylloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylatecarboxylate (63)

Prepared from 94 and benzyl 2-(diethoxycarbonyl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the title compound as a colorless oil (354 mg, 0.81 mmol, 39.8% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40 – 7.29 (m, 5H), 6.99 (dt, \(J = 14.9, 1.0\) Hz, 1H), 6.91 – 6.84 (m, 1H), 6.02 (d, \(J = 1.2\) Hz, 1H), 5.86 (d, \(J = 15.7\) Hz, 1H), 5.24 – 5.13 (m, 3H), 4.51 – 4.41 (m, 2H), 2.75 – 2.62 (m, 4H), 2.56 – 2.39 (m, 2H), 2.36 – 2.27 (m, 1H), 2.25 – 2.16 (m, 2H), 2.02 – 1.84 (m, 4H), 1.73 (ddd, \(J = 13.6, 11.2, 5.3\) Hz, 1H), 1.47 (p, \(J = 7.5\) Hz, 2H), 1.40 – 1.23 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.4, 171.6, 166.6, 149.8, 149.3, 148.8, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 114.0, 66.2, 62.3, 57.1, 33.6, 32.2, 31.2, 30.3, 29.6, 28.5, 24.3, 23.9, 17.1.

IR (Neat Film, NaCl): 2945, 1722, 1687, 1446, 1169 cm\(^{-1}\).
HRMS (MM: FD+): \( m/z \) calc’d for C\(_{27}\)H\(_{32}\)O\(_5\) \([M]^+\): 436.2250, found 436.2222.

2-cyclopentylideneethyl \((E)\)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (64)

Prepared from 95 and benzyl 2-(diethoxyphosphoryl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 4.41 mmol, 38.9% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.40 – 7.28 (m, 5H), 6.99 (dt, \( J = 15.6, 6.9 \) Hz, 1H), 6.91 – 6.83 (m, 1H), 6.01 (ddd, \( J = 10.1, 2.6, 1.5 \) Hz, 1H), 5.85 (dt, \( J = 15.6, 1.6 \) Hz, 1H), 5.37 (tp, \( J = 7.0, 2.2 \) Hz, 1H), 5.17 (s, 2H), 4.60 – 4.53 (m, 2H), 2.56 – 2.39 (m, 2H), 2.37 – 2.15 (m, 7H), 1.98 – 1.85 (m, 2H), 1.78 – 1.54 (m, 5H), 1.53 – 1.41 (m, 2H), 1.40 – 1.22 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 196.4, 171.7, 166.6, 151.1, 149.8, 149.3, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 113.8, 66.2, 63.7, 57.1, 33.9, 33.6, 32.2, 30.3, 29.0, 28.5, 26.4, 26.2, 24.3, 23.9.

IR (Neat Film, NaCl): 2946, 1719, 1686, 1457, 1165 cm\(^{-1}\).

HRMS (MM: FD+): \( m/z \) calc’d for C\(_{28}\)H\(_{34}\)O\(_5\) \([M]^+\): 450.2406, found 450.2394.
2-cyclohexylideneethyl \((E)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (65)\)

Prepared from 96 and benzyl 2-(diethoxyphosphoryl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (81 mg, 0.17 mmol, 32.9% yield).

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.41 – 7.27 (m, 5H), 6.99 (dt, \(J = 15.6, 6.9\) Hz, 1H), 6.87 (ddddd, \(J = 10.1, 5.2, 2.5, 1.1\) Hz, 1H), 6.01 (ddd, \(J = 10.1, 2.6, 1.5\) Hz, 1H), 5.85 (dt, \(J = 15.6, 1.6\) Hz, 1H), 5.23 (tp, \(J = 7.3, 1.2\) Hz, 1H), 5.17 (s, 2H), 4.59 (d, \(J = 7.2\) Hz, 2H), 2.56 – 2.39 (m, 2H), 2.36 – 2.26 (m, 1H), 2.25 – 2.13 (m, 4H), 2.12 – 2.03 (m, 2H), 1.98 – 1.84 (m, 2H), 1.78 – 1.66 (m, 1H), 1.63 – 1.42 (m, 8H), 1.41 – 1.21 (m, 2H).

\(^13C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.4, 171.6, 166.6, 149.8, 149.3, 147.7, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 114.9, 66.2, 61.5, 57.0, 37.1, 33.6, 32.2, 30.4, 29.2, 28.5, 28.5, 27.9, 26.7, 24.3, 23.9.

IR (Neat Film, NaCl): 2929, 2853, 1723, 1681, 1456, 1385, 1266, 1184 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for \(C_{29}H_{36}O_5\) [M]: 464.2563, found 464.2543.

![Chemical Structure Image]

2-cycloheptylideneethyl \((E)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (66)\)
Prepared from 97 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (5–70% EtOAc/hexanes) afforded the title compound as a colorless oil (135 mg, 0.28 mmol, 30% yield).

\textsuperscript{1}H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 – 7.29 (m, 5H), 6.99 (dt, $J = 15.7$, 6.9 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.01 (ddd, $J = 10.2$, 2.6, 1.5 Hz, 1H), 5.85 (dt, $J = 15.6$, 1.6 Hz, 1H), 5.27 (tt, $J = 7.1$, 1.3 Hz, 1H), 5.17 (s, 2H), 4.59 (d, $J = 7.1$ Hz, 2H), 2.57 – 2.39 (m, 2H), 2.36 – 2.16 (m, 7H), 1.98 – 1.84 (m, 2H), 1.73 (ddd, $J = 13.6$, 11.3, 5.2 Hz, 1H), 1.61 – 1.43 (m, 10H), 1.31 (dddd, $J = 13.2$, 11.8, 8.6, 6.2 Hz, 2H).

\textsuperscript{13}C NMR (100 MHz, CDCl$_3$): $\delta$ 196.4, 171.7, 166.6, 149.8, 149.3, 149.0, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.0, 57.0, 37.7, 33.6, 32.2, 30.4, 30.2, 29.8, 29.1, 28.9, 28.5, 27.3, 24.3, 23.9.

IR (Neat Film, NaCl): 2919, 2361, 1722, 1682, 1651, 1443, 1234, 1187 cm\textsuperscript{-1}.

HRMS (MM: FD\textsuperscript{+}): $m/z$ calc’d for C\textsubscript{30}H\textsubscript{38}O\textsubscript{5} [M]\textsuperscript{+}: 478.2719, found 478.2716.

3-benzyl-4-phenylbut-2-en-1-yl (\textit{E})-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (67)

Prepared from 98 and benzyl 2-(diethoxyphosphoryl)acetate\textsuperscript{28} following General Procedure B. Purification by flash column chromatography (5–70% EtOAc/hexanes) afforded the title compound as a colorless oil (205 mg, 0.36 mmol, 39% yield).
**1H NMR (400 MHz, CDCl₃):** δ 7.39 – 7.24 (m, 9H), 7.23 – 7.17 (m, 2H), 7.09 (dd, J = 11.6, 7.3 Hz, 4H), 6.98 (dt, J = 15.6, 6.9 Hz, 1H), 6.89 – 6.80 (m, 1H), 6.02 (d, J = 10.1 Hz, 1H), 5.85 (d, J = 16.1 Hz, 1H), 5.51 (t, J = 7.2 Hz, 1H), 5.17 (s, 2H), 4.83 – 4.69 (m, 2H), 3.36 (s, 2H), 3.23 (s, 2H), 2.55 – 2.40 (m, 2H), 2.37 – 2.24 (m, 1H), 2.18 (q, J = 7.2 Hz, 2H), 2.00 – 1.85 (m, 2H), 1.75 (ddd, J = 13.5, 11.1, 5.2 Hz, 1H), 1.46 (p, J = 7.4 Hz, 1H), 1.38 – 1.22 (m, 2H).

**13C NMR (100 MHz, CDCl₃):** δ 196.2, 171.6, 166.6, 149.8, 149.3, 144.8, 139.0, 138.8, 136.3, 129.4, 129.3, 128.8, 128.7, 128.7, 128.5, 128.3, 128.3, 126.5, 126.4, 121.7, 121.3, 66.2, 61.9, 57.1, 42.9, 35.8, 33.6, 32.1, 30.3, 28.5, 24.3, 23.9.

**IR (Neat Film, NaCl):** 3027, 2931, 1722, 1682, 1493, 1387, 1264, 1165 cm⁻¹.

**HRMS (MM: FD+):** m/z calc’d for C₃₈H₄₀O₅ [M]⁺: 576.2876, found 576.2857.

(E)-6-(1-(((3-methylbut-2-en-1-yl)oxy)carbonyl)-2-oxocyclohex-3-en-1-yl)hex-2-enoic acid (40i)³³

To a suspension of Zn(OTf)₂ (6.6 mmol, 2.2 equiv) in THF (15 mL) was added (diethoxyphosphinyl)acetic acid (3 mmol, 1 equiv), followed by the addition of TMEDA (1.89 mmol, 0.63 equiv), DBU (12 mmol, 4 equiv), and then a solution of aldehyde 85 (3 mmol, 1 equiv) in THF (2 mL). The solution was stirred at 23 °C for 18 h, and the reaction was diluted with 1 M HCl and extracted with dichloromethane (4x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure.
Purification by silica gel flash column chromatography (35% EtOAc/hexanes with 3% AcOH) afforded the title compound as a white solid (137.4 mg, 0.43 mmol, 43% yield).

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_{3}]: \delta 7.04 (dt, J = 15.7, 6.8 Hz, 1H), 6.93 – 6.84 (m, 1H), 6.03 (ddd, J = 10.2, 2.6, 1.5 Hz, 1H), 5.83 (dt, J = 15.6, 1.6 Hz, 1H), 5.28 (tp, J = 7.2, 1.4 Hz, 1H), 4.66 – 4.53 (m, 2H), 2.58 – 2.40 (m, 2H), 2.37 – 2.28 (m, 1H), 2.25 (qd, J = 7.3, 1.6 Hz, 2H), 1.98 – 1.87 (m, 2H), 1.80 – 1.68 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.61 – 1.37 (m, 3H). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_{3}]: \delta 196.3, 171.6, 170.2, 151.4, 149.3, 139.7, 129.4, 120.8, 118.3, 62.4, 57.0, 33.5, 32.7, 30.5, 25.8, 23.9, 23.1, 18.2. \]

\[ \text{IR (Neat Film, NaCl): 2929, 1725, 1694, 1424, 1384, 1236, 1171 cm}^{-1}. \]

\[ \text{HRMS (MM: FD+): } m/z \text{ calc’d for C}_{18}H_{24}O_5 [M]^+: 320.1624, \text{ found 320.1636.} \]

3-methylbut-2-en-1-yl (E)-1-(6-((1,3-dioxoisindolin-2-yl)oxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40m)\textsuperscript{34}

To a round bottom flask was added crude acid 40i (assumed quantitative yield from previous reaction, 1 mmol, 1 equiv), DMAP (1.1 mmol, 1.1 equiv), NHP (2 mmol, 2 equiv), dichloromethane (9.5 mL), and triethylamine (1.1 mmol, 1.1 equiv). EDC•HCl (1.1 mmol, 1.1 equiv) was then added under N\textsubscript{2} atmosphere in a single portion, and the reaction was stirred vigorously at 23 °C for 12 h. The reaction mixture was diluted with dichloromethane and washed with 0.5 N HCl, saturated aqueous NaHCO\textsubscript{3}, and brine. The combined organic
layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography (30–35% EtOAc/hexanes) afforded the title compound as a colorless oil (109.6 mg, 0.48 mmol, 24% yield over two steps).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.96 – 7.84 (m, 2H), 7.79 (dd, $J = 5.5$, 3.1 Hz, 2H), 7.30 (dd, $J = 15.8$, 6.7 Hz, 1H), 6.89 (ddddd, $J = 10.1$, 4.9, 3.0, 1.1 Hz, 1H), 6.10 (dt, $J = 15.8$, 1.6 Hz, 1H), 6.04 (dd, $J = 10.1$, 2.5, 1.5 Hz, 1H), 5.29 (tddd, $J = 5.7$, 2.8, 1.4 Hz, 1H), 4.67 – 4.55 (m, 2H), 2.58 – 2.40 (m, 2H), 2.35 (m, 3H), 2.03 – 1.89 (m, 2H), 1.87 – 1.74 (m, 1H), 1.74 (s, 3H), 1.69 (d, $J = 1.3$ Hz, 3H), 1.66 – 1.45 (m, 3H).

$^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 196.2, 162.4, 162.2, 155.2, 149.3, 139.8, 134.8, 129.4, 129.1, 124.1, 118.3, 116.0, 62.4, 57.0, 33.5, 33.3, 30.6, 25.9, 23.9, 23.0, 18.3.

IR (Neat Film, NaCl): 1771, 1744, 1682 cm$^{-1}$.

HRMS (MM: FD+): m/z calc’d for C$_{26}$H$_{27}$NO$_7$ [M]$^+$: 465.1788, found 465.1779.

3-methylbut-2-en-1-yl (Z)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40q)

To a solution of benzyl 2-(bis(2-(tert-butyl)phenoxy)phosphoryl)acetate$^{35}$ (890 mg, 1.80 mmol, 1.00 equiv) in MeCN (18 mL, 0.1 M) was added K$_2$CO$_3$ (783 mg, 3.69 mmol, 2.05 equiv). The reaction was cooled to 0 ºC and a solution of 85 (500 mg, 1.80 mmol, 1.00 equiv) in MeCN (18 mL, 0.1 M) was dropwise added. The reaction was gradually warmed
to 25 ºC and stirring was continued until consumption of 85 as determined by TLC (around 16 h). The reaction mixture was filtered through a plug of Celite® to remove solids and volatiles were removed in vacuo. Purification by flash column chromatography (0–40% EtOAc/hexanes) afforded the title compound as a colorless oil (482 mg, 1.17 mmol, 65% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.29 (m, 5H), 6.90 – 6.84 (m, 1H), 6.24 (dt, J = 11.5, 7.4 Hz, 1H), 6.01 (ddd, J = 10.1, 2.5, 1.6 Hz, 1H), 5.83 (dt, J = 11.5, 1.7 Hz, 1H), 5.28 (ddp, J = 8.6, 5.7, 1.4 Hz, 1H), 5.15 (s, 2H), 4.59 (d, J = 7.2 Hz, 2H), 2.68 (qd, J = 7.4, 1.8 Hz, 2H), 2.53 – 2.41 (m, 2H), 2.35 – 2.26 (m, 1H), 1.98 – 1.87 (m, 2H), 1.79 – 1.71 (m, 4H), 1.67 (s, 3H), 1.52 – 1.37 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 196.4, 171.7, 166.2, 150.5, 149.3, 139.5, 136.3, 129.3, 128.7, 128.3, 128.3, 119.9, 118.4, 65.9, 62.3, 57.1, 33.4, 30.3, 29.4, 25.8, 24.2, 23.8, 18.2.

IR (Neat Film, NaCl): 2918, 1714, 1447, 1178, 1161 cm⁻¹.


3-methylbut-2-en-1-yl (E)-2-oxo-1-(6-oxo-6-phenylhex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (40j)

(2-oxo-2-phenylethyl)triphenylphosphonium bromide³⁶ (996 mg, 2.16 mmol, 1.2 equiv) was stirred in 26 mL of a 3:2 CH₂Cl₂/2 M aq. NaOH mixture for 30 minutes at 23 ºC. The layers were separated, and the aqueous layer was extracted twice with CH₂Cl₂. The
combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and solvent was removed in vacuo. To a solution of this crude ylide in DCE (22 mL, 0.1 M) was added aldehyde 85 (500 mg, 1.80 mmol, 1 equiv). The reaction was stirred at 65 ºC for 36 hours. Upon complete consumption of 85, as determined by TLC, volatiles were removed in vacuo. Purification by flash column chromatography (30% EtOAc/hexanes) afforded the title compound as a colorless oil (330 mg, 0.867 mmol, 48% yield).

\(^{1}H\) NMR (400 MHz, CDCl₃):  δ 7.95 – 7.90 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (tt, J = 6.8, 1.5 Hz, 2H), 7.02 (dt, J = 15.4, 6.7 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.03 (ddd, J = 10.2, 2.6, 1.5 Hz, 1H), 5.30 – 5.25 (m, 1H), 4.59 (d, J = 7.1 Hz, 2H), 2.55 – 2.43 (m, 2H), 2.38 – 2.27 (m, 3H), 2.01 – 1.91 (m, 2H), 1.80 (ddd, J = 13.6, 12.0, 4.7 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.63 – 1.47 (m, 2H).

\(^{13}C\) NMR (100 MHz, CDCl₃):  δ 196.3, 191.0, 171.6, 149.3, 149.1, 139.7, 138.1, 132.8, 129.4, 128.7, 128.7, 126.4, 118.3, 62.4, 57.0, 33.6, 33.2, 30.5, 25.8, 23.9, 23.4, 18.2.

IR (Neat Film, NaCl): 2931, 1724, 1671, 1619, 1447, 1229, 1177 cm⁻¹.

An oven dried round bottom flask was charged with KHMDS (837 mg, 4.20 mmol, 1.05 equiv), 18-crown-6 (1.06 g, 4.00 mmol, 1.0 equiv), and THF (21 mL). The mixture was cooled to –78 ºC and a solution of enone 100 (830 mg, 4.00 mmol, 1.0 equiv) in THF (10 mL) was added. The reaction mixture was stirred for 15 minutes then (2-(bromomethyl)phenyl)methylene diacetate\(^{37}\) (1.86 g, 6.00 mmol, 1.5 equiv) was added in a minimal amount of THF (ca 5 mL). The solution was slowly warmed to 45 ºC and stirred for 14 h. Upon complete consumption of starting material (as determined by TLC), the solution was cooled to 23 ºC, diluted with a saturated aqueous solution of NH\(_4\)Cl, and the reaction mixture was extracted thrice with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.00 g, 2.33 mmol, 58% yield).
**Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates**

1H NMR (400 MHz, CDCl₃): δ 7.87 (s, 1H), 7.58 – 7.52 (m, 1H), 7.30 – 7.24 (m, 2H), 7.21 – 7.16 (m, 1H), 6.88 – 6.82 (m, 1H), 6.07 (ddd, J = 10.1, 2.8, 1.3 Hz, 1H), 5.24 (ddq, J = 8.6, 5.7, 1.4 Hz, 1H), 4.56 (d, J = 7.2 Hz, 2H), 3.52 (d, J = 14.8 Hz, 1H), 3.45 (d, J = 14.8 Hz, 1H), 2.53 – 2.41 (m, 1H), 2.36 (dddd, J = 13.6, 4.9, 2.6, 1.3 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 1.86 (ddd, J = 13.6, 10.4, 5.3 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H).

13C NMR (100 MHz, CDCl₃): δ 195.4, 171.1, 168.8, 168.8, 149.6, 139.7, 135.5, 134.9, 131.5, 129.6, 129.5, 127.6, 127.2, 118.2, 88.4, 62.5, 58.2, 34.2, 30.2, 25.9, 24.1, 21.0, 21.0, 18.2.

IR (Neat Film, NaCl): 2935, 1759, 1731, 1682, 1447, 1371, 1236, 1206 cm⁻¹.


3-methylbut-2-en-1-yl (E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohept-3-ene-1-carboxylate (40p)

To a solution of diacetate 99 (500 mg, 1.17 mmol, 1 equiv) in benzene (11.7 mL, 0.1 M) was added bismuth chloride (38 mg, 0.12 mmol, 0.1 equiv). The reaction mixture was heated to 35 ºC for 3 hours. Upon cooling to 25 ºC, the reaction mixture was diluted with water and the layers were separated. The aqueous layer was extracted twice with chloroform. The combined organic layers were washed with brine, dried over Na₂SO₄, and volatiles were removed in vacuo. The crude aldehyde was used directly in the subsequent Horner–Wadsworth–Emmons olefination.
To a suspension of NaH (52 mg, 1.29 mmol, 60% by weight in mineral oil, 1.1 equiv) in THF (2.6 mL, 0.5 M) at 0 ºC was dropwise added a solution of benzyl 2-(diethoxyphosphoryl)acetate$^{28}$ (369 mg, 1.29 mmol, 1.1 equiv) in THF (1.3 mL, 1.0 M). Stirring at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of the crude aldehyde in THF (2.4 mL, 0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of NaHCO$_3$ and extracted with EtOAc (3x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (230 mg, 0.502 mmol, 43% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.08 (d, J = 15.7 Hz, 1H), 7.57 (dd, J = 7.5, 1.9 Hz, 1H), 7.44 – 7.31 (m, 5H), 7.27 – 7.17 (m, 3H), 6.85 – 6.80 (m, 1H), 6.40 (d, J = 15.7 Hz, 1H), 6.06 (ddd, J = 10.1, 2.9, 1.2 Hz, 1H), 5.28 – 5.21 (m, 3H), 4.56 – 4.49 (m, 2H), 3.57 (d, J = 14.3 Hz, 1H), 3.31 (d, J = 14.4 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.30 – 2.16 (m, 2H), 1.82 – 1.70 (m, 4H), 1.65 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 195.1, 170.4, 166.7, 149.7, 143.2, 139.7, 136.7, 136.2, 134.7, 132.1, 130.0, 129.3, 128.7, 128.4, 128.3, 127.5, 126.8, 119.4, 118.2, 66.5, 62.5, 58.4, 35.4, 30.2, 25.9, 24.1, 18.2.

IR (Neat Film, NaCl): 3028, 2927, 1720, 1686, 1629, 1168 cm$^{-1}$.

HRMS (MM: FD+): m/z calc’d for C$_{29}$H$_{30}$O$_5$ [M]+: 458.2088, found 458.2086.
3-methylbut-2-en-1-yl \((E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclopentane-1-carboxylate \(102\)

Prepared from \(101\) and benzyl 2-(diethoxyphosphoryl)acetate\(^{28}\) following General Procedure B. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 3.51 mmol, 70% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.76 (dt, \(J = 5.6, 2.7 \text{ Hz, 1H}\)), 7.42 – 7.26 (m, 5H), 6.95 (dt, \(J = 15.6, 6.9 \text{ Hz, 1H}\)), 6.16 (dt, \(J = 5.8, 2.2 \text{ Hz, 1H}\)), 5.85 (dt, \(J = 15.6, 1.6 \text{ Hz, 1H}\)), 5.27 (tdq, \(J = 7.2, 2.9, 1.5 \text{ Hz, 1H}\)), 5.16 (s, 2H), 4.59 (d, \(J = 7.1 \text{ Hz, 2H}\)), 3.33 – 3.19 (m, 1H), 2.68 – 2.51 (m, 1H), 2.21 (qd, \(J = 7.3, 1.6 \text{ Hz, 2H}\)), 1.99 (ddd, \(J = 13.7, 12.3, 4.5 \text{ Hz, 1H}\)), 1.82 – 1.70 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.53 – 1.23 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 205.7, 170.6, 166.4, 163.9, 148.9, 139.6, 136.2, 132.4, 128.7, 128.4, 128.3, 121.7, 118.3, 66.2, 62.7, 58.0, 39.5, 34.0, 32.4, 25.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2932, 2356, 1715, 1623, 1164, 976, 754 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{24}\)H\(_{28}\)O\(_5\) [M]\(^+\): 396.1920, found 396.1931.

3-methylbut-2-en-1-yl \((E)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclopent-3-ene-1-carboxylate \(40c\)

A flame dried round bottom flask was charged with \(i\)-Pr\(_2\)NH (0.35 mL, 2.5 mmol, 1.25 equiv) and THF (8.0 mL, 0.25 M). The solution was cooled to \(-78\) °C and \(n\)-BuLi (0.96 mL, 2.4 mmol, 1.2 equiv) was added dropwise and the resultant solution was stirred for 30
min. Ketoester 102 (797 mg, 2.00 mmol, 1.0 equiv) in THF (8.0 mL, 0.25 M) was added dropwise and the mixture was stirred for 1 h. *N*-tert-Butylbenzenesulfinimidoyl chloride\(^{38}\) (560.9 mg, 2.6 mmol, 1.3 equiv) in THF (4.0 mL, 0.5 M) was added dropwise and the solution was slowly warmed to 23 °C. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with saturated aqueous NaHCO\(_3\) solution and extracted with Et\(_2\)O (25 mL x 3). The combined organic layers were dried with Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO\(_2\), 0–40% EtOAc/Hexanes) to afford enone 40b as a colorless oil (100 mg, 0.25 mmol, 13% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.76 (dt, \(J = 5.6, 2.7\) Hz, 1H), 7.42 – 7.26 (m, 5H), 6.95 (dt, \(J = 15.6, 6.9\) Hz, 1H), 6.16 (dt, \(J = 5.8, 2.2\) Hz, 1H), 5.85 (dt, \(J = 15.6, 1.6\) Hz, 1H), 5.27 (tdq, \(J = 7.2, 2.9, 1.5\) Hz, 1H), 5.16 (s, 2H), 4.59 (d, \(J = 7.1\) Hz, 2H), 3.33 – 3.19 (m, 1H), 2.68 – 2.51 (m, 1H), 2.21 (qd, \(J = 7.3, 1.6\) Hz, 2H), 1.99 (ddd, \(J = 13.7, 12.3, 4.5\) Hz, 1H), 1.82 – 1.70 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.53 – 1.23 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 205.7, 170.6, 166.4, 163.9, 148.9, 139.6, 136.2, 132.4, 128.7, 128.4, 128.3, 121.7, 118.3, 66.2, 62.7, 58.0, 39.5, 34.0, 32.4, 25.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2932, 2356, 1715, 1263, 1164, 976, 754 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{24}\)H\(_{38}\)O\(_5\) [M]\(^+\): 396.1920, found 396.1931.
3-methylbut-2-en-1-yl (E)-1-(5-(benzyloxy)-5-oxopent-3-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (40e)

To a solution of enone 100 (1.04 g, 5.00 mmol, 1.0 equiv) in DMF (10 mL, 0.5 M) at 25°C was added dropwise triethylamine (0.07 mL, 0.50 mmol, 0.1 equiv) followed by acrolein (0.50 mL, 7.50 mmol, 1.5 equiv). Upon consumption of starting material (as determined by TLC), the reaction mixture was diluted with water and extracted thrice with diethyl ether. The combined organic layers were washed with water followed by brine, dried over Na₂SO₄, and volatiles were removed in vacuo. The crude aldehyde was used directly in the subsequent Horner–Wadsworth–Emmons olefination. To a suspension of NaH (132 mg, 3.30 mmol, 60% by weight in mineral oil, 1.1 equiv) in THF (6 mL, 0.5 M) at 0 ºC was dropwise added a solution of benzyl 2-(diethoxyphosphoryl)acetate (945 mg, 3.30 mmol, 1.1 equiv) in THF (3.0 mL, 1.0 M). Stirred at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of the crude aldehyde in THF (6.0 mL, 0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of NaHCO₃ and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (490 mg, 1.24 mmol, 41% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.41 – 7.29 (m, 5H), 6.99 (dt, J = 15.7, 6.8 Hz, 1H), 6.93 – 6.84 (m, 1H), 6.03 (ddd, J = 10.1, 2.5, 1.5 Hz, 1H), 5.88 (dt, J = 15.6, 1.6 Hz, 1H), 5.27 (ddt, J = 7.2, 5.8, 1.4 Hz, 1H), 5.17 (s, 2H), 4.59 (d, J = 7.1 Hz, 2H), 2.56 – 2.41 (m, 2H), 2.38 – 2.13 (m, 3H), 2.08 – 1.81 (m, 3H), 1.73 (s, 3H), 1.67 (s, 3H).
\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 196.0, 171.4, 166.4, 149.3, 148.9, 139.9, 136.2, 129.4, 128.7, 128.3, 121.5, 118.2, 66.2, 62.4, 56.6, 32.2, 30.7, 27.6, 25.8, 23.8, 18.2. \]

\[ \text{IR (Neat Film, NaCl): } 3032, 2934, 1737, 1681, 1445, 1384, 1265, 1175, 1137 \text{ cm}^{-1}. \]

\[ \text{HRMS (MM: FD+): } m/z \text{ calc'd for C}_{24}\text{H}_{28}\text{O}_5 [\text{M}]^+: 396.1937, \text{ found 396.1926.} \]

**Preparation of Aldehyde Precursors**

*General Procedure C: Alkylation of \( \beta \)-Ketoesters*

An oven dried round bottom flask was charged with KHMDS (1.05 equiv), 18-crown-6 (1.0 equiv), and THF (0.2 M with respect to KHMDS). The mixture was cooled to −78 °C and a solution of acylated enone 100 (1.0 equiv) in THF (0.4 M) was added. The reaction mixture was stirred for 15 minutes and then the appropriate alkyl bromide (1.5 equiv) was added neat dropwise. The solution was slowly warmed to 45 °C and stirred for 14 h. Upon complete consumption of starting material (as determined by TLC), the solution was cooled to 23 °C, diluted with a saturated aqueous solution of NH\(_4\)Cl and the reaction mixture was extracted thrice with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to afford the crude diethyl acetal which was used directly in the next step. A round bottom flask was charged with the crude acetal and acetone (0.5 M), then cooled to 0 °C. Aqueous 1 M HCl (1:1 volume with respect to acetone) was added and stirring was continued for 1 h. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was extracted with EtOAc (3x). The
combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to afford the respective aldehyde product (85).

3-methylbut-2-en-1-yl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (85)

Prepared from 100 and 4-bromo-1,1-diethoxybutane$^{19}$ following General Procedure C. Purification by flash column chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.81 g, 6.50 mmol, 49% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.75 (t, $J$ = 1.5 Hz, 1H), 6.89 (dddd, $J$ = 10.1, 4.4, 3.1, 1.1 Hz, 1H), 6.02 (dd, $J$ = 10.1, 2.5, 1.6 Hz, 1H), 5.31 – 5.25 (m, 1H), 4.59 (d, $J$ = 6.8 Hz, 2H), 2.55 – 2.43 (m, 4H), 2.39 – 2.30 (m, 1H), 2.02 – 1.94 (m, 1H), 1.89 (ddd, $J$ = 12.5, 11.7, 4.5 Hz, 1H), 1.78 (dd, $J$ = 11.6, 4.9 Hz, 1H), 1.73 (s, 3H), 1.71 – 1.59 (m, 5H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 202.2, 196.2, 171.5, 149.5, 139.7, 129.3, 118.3, 62.4, 57.0, 44.2, 33.2, 30.3, 25.8, 23.8, 18.2, 17.5.

IR (Neat Film, NaCl): 2942, 1732, 1716, 1456, 1180 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{16}$H$_{22}$O$_4$ [M]$^+$: 278.1518, found 278.1509.

3-methylbut-2-en-1-yl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (86)
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

Prepared from 100 and 5-bromo-1,1-diethoxypentane superscript 39 following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (648 mg, 2.22 mmol, 38% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 9.75\) (s, 1H), 6.91 – 6.84 (m, 1H), 6.01 (ddd, \(J = 10.1, 2.6, 1.6\) Hz, 1H), 5.27 (tdq, \(J = 7.1, 2.8, 1.4\) Hz, 1H), 4.58 (d, \(J = 7.1\) Hz, 2H), 2.54 – 2.40 (m, 4H), 2.36 – 2.27 (m, 1H), 1.98 – 1.86 (m, 2H), 1.78 – 1.60 (m, 10H), 1.40 – 1.26 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 202.6, 196.4, 171.7, 149.4, 139.6, 129.3, 118.3, 62.3, 57.0, 43.7, 33.6, 30.4, 25.8, 24.3, 23.8, 22.5, 18.2.

IR (Neat Film, NaCl): 2941, 1733, 1717, 1456, 1219 cm\(^{-1}\)

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{16}\)H\(_{22}\)O\(_4\) [M]\(+\): 293.1747, found 293.1768.

\[
\begin{align*}
\text{3-}(\text{methyl-}d_3)\text{but-2-en-1-yl-4,4,4-d}_3 & \quad \text{2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (D-86)}
\end{align*}
\]

Prepared from D-100 and 5-bromo-1,1-diethoxypentane superscript 39 following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (290 mg, 0.971 mmol, 42% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 9.75\) (t, \(J = 1.7\) Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, \(J = 10.1, 2.6, 1.6\) Hz, 1H), 5.27 (t, \(J = 7.2\) Hz, 1H), 4.58 (dd, \(J = 7.2, 1.8\) Hz, 2H), 2.55 – 2.41 (m, 4H), 2.36 – 2.26 (m, 1H), 1.97 – 1.86 (m, 2H), 1.74 (ddd, \(J = 13.6, 11.6, 5.1\) Hz, 1H), 1.68 – 1.60 (m, 2H), 1.40 – 1.24 (m, 2H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.6, 196.4, 171.7, 149.4, 139.4, 129.3, 118.4, 62.3, 57.0, 43.7, 33.6, 30.4, 24.3, 23.9, 22.5.

$^2$H NMR (61 MHz, CHCl$_3$): $\delta$ 1.69, 1.65.

IR (Neat Film, NaCl): 2941, 1726, 1682, 1238, 1186 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{18}$D$_6$O$_4$ [M]$^+$: 298.2051, found 298.2052.

3-methylbut-2-en-1-yl 2-oxo-1-(6-oxohexyl)cyclohex-3-ene-1-carboxylate (87)

Prepared from 100 and 6-bromo-1,1-diethoxyhexane$^{39}$ following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (838 mg, 2.73 mmol, 32% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.75 (t, $J = 1.8$ Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, $J = 10.0$, 2.5, 1.5 Hz, 1H), 5.30 – 5.25 (m, 1H), 4.62 – 4.55 (m, 2H), 2.54 – 2.39 (m, 4H), 2.36 – 2.27 (m, 1H), 1.98 – 1.84 (m, 2H), 1.73 (t, $J = 1.2$ Hz, 4H), 1.69 – 1.59 (m, 5H), 1.39 – 1.24 (m, 4H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.8, 196.5, 171.7, 149.3, 139.5, 129.4, 118.4, 62.3, 57.1, 43.9, 33.6, 30.3, 29.6, 25.8, 24.4, 23.9, 21.9, 18.2.

IR (Neat Film, NaCl): 2934, 2864, 1733, 1717, 1684, 1456, 1220 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{26}$O$_4$ [M]$^+$: 306.1831, found 306.1854.
cinnamyl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (93)

Prepared from 103 and 4-bromo-1,1-diethoxybutane following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.607 g, 1.86 mmol, 49% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.74 (t, $J$ = 1.5 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.35 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 6.91 (dddd, $J$ = 10.1, 4.3, 3.1, 1.1 Hz, 1H), 6.63 (dt, $J$ = 16.0, 1.4 Hz, 1H), 6.23 (dt, $J$ = 15.8, 6.4 Hz, 1H), 6.05 (dddd, $J$ = 10.1, 2.4, 1.7 Hz, 1H), 4.77 (dt, $J$ = 6.5, 1.1 Hz, 2H), 2.57 – 2.45 (m, 4H), 2.42 – 2.32 (m, 1H), 2.05 – 1.98 (m, 1H), 1.93 (ddd, $J$ = 13.2, 11.7, 5.1 Hz, 1H), 1.80 (ddd, $J$ = 13.2, 11.1, 5.5 Hz, 1H), 1.73 – 1.63 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.1, 196.0, 171.3, 149.7, 136.2, 134.7, 129.2, 128.8, 128.3, 126.8, 122.7, 66.0, 57.1, 44.1, 33.3, 30.1, 23.8, 17.5.

IR (Neat Film, NaCl): 2941, 1732, 1717, 1700, 1181, 734, 701 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{20}$H$_{22}$O$_4$ [M]$^+$: 326.1513, found 326.1510.

1-benzyl 3-(3-methylbut-2-en-1-yl) 4-oxo-3-(4-oxobutyl)-3,4-dihydropyridine-1,3(2H)-dicarboxylate (88)
Prepared from 104 and 4-bromo-1,1-diethoxybutane\textsuperscript{39} following General Procedure C. Purification by flash column chromatography (15–30\% EtOAc/hexanes) afforded the title compound as a colorless oil (603.9 mg, 1.46 mmol, 60\% yield).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):} δ 9.73 (t, \textit{J} = 1.4 Hz, 1H), 7.80 (s, 1H), 7.40 (d, \textit{J} = 3.5 Hz, 5H), 5.27 (m, 4H), 4.61 (m, 3H), 3.78 (d, \textit{J} = 13.6 Hz, 1H), 2.45 (tt, \textit{J} = 6.8, 1.7 Hz, 2H), 2.03 – 1.90 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.70 – 1.60 (m, 1H).

\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}):} δ 201.6, 190.5, 169.4, 142.7, 140.1, 135.0, 129.0, 128.9, 128.6, 118.0, 106.5, 69.4, 62.8, 55.4, 48.2, 43.9, 31.1, 25.8, 18.2, 17.2.

\textbf{IR (Neat Film, NaCl):} 2945, 2338, 1727, 1670, 1604, 1389, 1302, 1201, 932 cm\textsuperscript{-1}.

\textbf{HRMS (MM: FD\textsuperscript{+}):} \textit{m/z} calc’d for C\textsubscript{23}H\textsubscript{27}NO\textsubscript{6}[M]\textsuperscript{+}: 413.1838, found 413.1852.

![89]

3-methylbut-2-en-1-yl 4-methyl-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (89)

Prepared from 105 and 4-bromo-1,1-diethoxybutane\textsuperscript{39} following General Procedure C. Purification by flash column chromatography (25–50\% EtOAc/hexanes) afforded the title compound as a colorless oil (1141.4 mg, 3.90 mmol, 78\% yield).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):} δ 9.74 (s, 1H), 5.87 (dt, \textit{J} = 2.6, 1.2 Hz, 1H), 5.27 (tp, \textit{J} = 7.1, 1.4 Hz, 1H), 4.58 (d, \textit{J} = 7.2 Hz, 2H), 2.45 (ddd, \textit{J} = 8.0, 4.8, 1.7 Hz, 4H), 2.29 – 2.18 (m, 1H), 1.92 (s, 3H), 2.00 – 1.84 (m, 2H), 1.72 (s, 3H), 1.67 (s, 3H), 1.79 – 1.54 (m, 3H).
13C NMR (100 MHz, CDCl3): δ 202.2, 195.9, 171.7, 161.6, 139.6, 126.0, 118.3, 62.3, 56.0, 44.2, 33.2, 30.0, 28.7, 25.8, 24.2, 18.2, 17.5.

IR (Neat Film, NaCl): 3426, 2936, 2730, 1725, 1672, 1637, 1440, 1380, 1348, 1311, 1272, 1233, 1214, 1177, 1104, 1050, 1016, 986, 939, 870, 842, 820, 776 cm⁻¹.

HRMS (MM: FD+): m/z calc’d for C_{17}H_{24}O_{4} [M]: 292.1682, found 292.1669.

3-methylbut-2-en-1-yl 4-ethoxy-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (90)

Prepared from 106 and 4-bromo-1,1-diethoxybutane following General Procedure C. Purification by flash column chromatography (30–40% EtOAc/hexanes) afforded the title compound as a colorless oil (653.2 mg, 2.03 mmol, 21% yield).

1H NMR (400 MHz, CDCl3): δ 9.75 (t, J = 1.5 Hz, 1H), 5.34 (d, J = 1.1 Hz, 1H), 5.29 (tp, J = 7.2, 1.4 Hz, 1H), 4.66 – 4.53 (m, 2H), 3.86 (q, J = 7.18, 2H), 2.61 (dddd, J = 17.8, 10.3, 4.7, 1.3 Hz, 1H), 2.50 – 2.30 (m, 4H), 2.02 – 1.87 (m, 2H), 1.82 – 1.73 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.67 – 1.58 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H).

13C NMR (100 MHz, CDCl3): δ 201.9, 195.5, 176.5, 171.5, 139.1, 118.1, 101.9, 64.3, 62.0, 55.7, 43.9, 33.1, 28.2, 26.3, 25.5, 17.9, 17.2, 13.9.

IR (Neat Film, NaCl): 2939, 2728, 1723, 1659, 1608, 1447, 1380, 1315, 1242, 1179, 1108, 1027, 942, 816, 769 cm⁻¹.

HRMS (MM: FD+): m/z calc’d for C_{18}H_{26}O_{5} [M]: 322.1790, found 322.1775.
3-methylbut-2-en-1-yl 3-methyl-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (91)

Prepared from 107 and 4-bromo-1,1-diethoxybutane following General Procedure C. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (1.14 g, 3.90 mmol, 70% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.75 (s, 1H), 6.64 – 6.57 (m, 1H), 5.27 (tt, $J = 7.1, 1.4$ Hz, 1H), 4.64 – 4.51 (m, 2H), 2.51 – 2.36 (m, 4H), 2.36 – 2.22 (m, 1H), 2.01 – 1.92 (m, 1H), 1.87 (m, 1H), 1.83-1.53 (m, 3H) 1.78 (s, 3H), 1.73 (s, 3H), 1.67 (d, $J = 1.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.2, 196.9, 171.9, 143.9, 139.6, 135.3, 118.3, 62.2, 57.0, 44.2, 33.3, 30.7, 25.8, 23.5, 18.2, 17.7, 16.6.

IR (Neat Film, NaCl): 3500, 2925, 2333, 1725, 1681, 1449, 1361, 1182 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{24}$O$_4$ [M]$^+$: 292.1680, found 292.1669.

allyl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (92)

Prepared from allyl 2-oxocyclohex-3-ene-1-carboxylate and 4-bromo-1,1-diethoxybutane following General Procedure C. Purification by flash column
chromatography (15–30% EtOAc/hexanes) afforded the title compound as a colorless oil (773.2 mg, 3.09 mmol, 21% yield).

\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{): } \delta 9.75 (t, J = 1.4 \text{ Hz, } 1\text{H}), 6.91 (dddd, J = 10.1, 4.4, 3.1, 1.1 \text{ Hz, } 1\text{H}), 6.03 (dt, J = 10.1, 2.0 \text{ Hz, } 1\text{H}), 5.86 (ddt, J = 17.1, 10.2, 5.6 \text{ Hz, } 1\text{H}), 5.28 (dq, J = 17.2, 1.6 \text{ Hz, } 1\text{H}), 5.22 (dq, J = 10.4, 1.3 \text{ Hz, } 1\text{H}), 4.60 (dq, J = 5.4, 1.6 \text{ Hz, } 2\text{H}), 2.58 – 2.43 (m, 4\text{H}), 2.43 – 2.30 (m, 1\text{H}), 2.07 – 1.95 (m, 1\text{H}), 1.91 (ddd, J = 13.2, 11.6, 5.2 \text{ Hz, } 1\text{H}), 1.79 (ddd, J = 13.2, 10.9, 5.6 \text{ Hz, } 1\text{H}), 1.75 – 1.56 (m, 2\text{H}). \]

\[ ^{13}C \text{NMR (100 MHz, CDCl}_3\text{): } \delta 202.1, 196.0, 171.2, 149.7, 131.7, 129.2, 118.7, 65.9, 57.1, 44.1, 33.1, 30.1, 23.7, 17.4. \]

IR (Neat Film, NaCl): 2947, 2732, 1726, 1680, 1238, 1184 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for \(C_{14}H_{19}O_4 [M]^+\): 251.1281, found 251.1278.

3-methylbut-2-en-1-yl 2-oxo-1-(pent-4-en-1-yl)cyclohex-3-ene-1-carboxylate (40h)

Prepared from 100 and 5-bromopent-1-ene following General Procedure C (without hydrolysis step). Purification by flash column chromatography (0-20% EtOAc/hexanes) afforded the title compound as a colorless oil (93.8 mg, 0.34 mmol, 23% yield).

\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{): } \delta 6.87 (dddd, J = 10.1, 4.8, 3.1, 1.1 \text{ Hz, } 1\text{H}), 6.01 (ddd, J = 10.1, 2.5, 1.6 \text{ Hz, } 1\text{H}), 5.78 (ddt, J = 16.9, 10.2, 6.6 \text{ Hz, } 1\text{H}), 5.28 (tdq, J = 7.1, 2.9, 1.4 \text{ Hz, } 1\text{H}), 5.00 (dq, J = 17.1, 1.6 \text{ Hz, } 1\text{H}), 4.94 (ddt, J = 10.2, 2.2, 1.2 \text{ Hz, } 1\text{H}), 4.59 (dd, J = 7.2, 3.7 \text{ Hz, } 1\text{H}), 4.64 – 4.53 (m, 2\text{H}), 2.57 – 2.41 (m, 2\text{H}), 2.38 – 2.24 (m, 2\text{H}), 2.12 – 2.01 (m,}
2H), 2.00 – 1.86 (m, 2H), 1.77 – 1.69 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.51 – 1.28 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 196.5, 171.7, 149.3, 139.5, 138.4, 129.4, 118.4, 114.9, 62.2, 57.1, 34.2, 33.4, 30.3, 25.8, 24.0, 23.9, 18.2.

IR (Neat Film, NaCl): 2928, 1726, 1683, 1440, 1383, 1186, 912 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{24}$O$_3$ [M]$^+$: 276.1725, found 276.1718.

3-methylbut-2-en-1-yl 2-oxo-1-(4-oxobutyl)cyclopentane-1-carboxylate (101)

Prepared from 3-methylbut-2-en-1-yl 2-oxocyclopentane-1-carboxylate$^{41}$ and 4-bromo-1,1-diethoxybutane$^{39}$ following General Procedure C. Purification by flash column chromatography (20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.86 g, 6.97 mmol, 87% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.74 (t, $J$ = 1.4 Hz, 1H), 5.29 (tp, $J$ = 7.3, 1.4 Hz, 1H), 4.59 (d, $J$ = 7.2 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.44 (tt, $J$ = 7.0, 1.5 Hz, 2H), 2.44 – 2.36 (m, 1H), 2.31 – 2.18 (m, 1H), 2.11 – 1.85 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.67 – 1.48 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 214.8, 201.9, 171.0, 139.7, 118.2, 62.5, 60.4, 44.0, 38.0, 33.2, 33.0, 25.9, 19.8, 18.2, 17.6.

IR (Neat Film, NaCl): 3456, 2954, 2724, 1745, 1721, 1446, 1406, 1384, 1154, 953 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{15}$H$_{22}$O$_4$ [M]$^+$: 266.1525, found 266.1513.
2-cyclohexylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (96)

Prepared from 108 and 5-bromo-1,1-diethoxypentane\textsuperscript{39} following General Procedure C. Purification by flash column chromatography (10–50\% EtOAc/hexanes) afforded the title compound as a colorless oil (177 mg, 0.53 mmol, 25\% yield).

\textbf{1H NMR (400 MHz, CDCl$_3$):} $\delta$ 9.75 (t, $J = 1.7$ Hz, 1H), 6.93 – 6.83 (m, 1H), 6.02 (ddd, $J = 10.1$, 2.6, 1.6 Hz, 1H), 5.23 (tt, $J = 7.2$, 1.2 Hz, 1H), 4.60 (d, $J = 7.2$ Hz, 2H), 2.56 – 2.39 (m, 4H), 2.37 – 2.26 (m, 1H), 2.20 – 2.13 (m, 2H), 2.12 – 2.05 (m, 2H), 1.99 – 1.85 (m, 2H), 1.74 (ddd, $J = 13.6$, 11.7, 5.0 Hz, 1H), 1.64 (p, $J = 7.5$ Hz, 2H), 1.58 – 1.46 (m, 6H), 1.43 – 1.20 (m, 2H).

\textbf{13C NMR (100 MHz, CDCl$_3$):} $\delta$ 202.6, 196.4, 171.6, 149.3, 147.7, 129.4, 114.8, 61.5, 57.0, 43.7, 37.1, 33.6, 30.4, 29.2, 28.5, 27.9, 26.7, 24.3, 23.9, 22.5.

\textbf{IR (Neat Film, NaCl):} 2929, 2858, 1731, 1446, 1170, 938 cm$^{-1}$.


2-cyclopentylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (95)
Prepared from 109 and 5-bromo-1,1-diethoxypentane\(^\text{39}\) following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 4.40 mmol, 39% yield).

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 9.75 (t, J = 1.7 Hz, 3H), 6.92 – 6.83 (m, 1H), 6.02 (ddd, J = 10.1, 2.6, 1.6 Hz, 1H), 5.41 – 5.32 (m, 1H), 4.64 – 4.50 (m, 2H), 2.56 – 2.39 (m, 4H), 2.37 – 2.20 (m, 5H), 1.99 – 1.83 (m, 2H), 1.80 – 1.57 (m, 7H), 1.45 – 1.22 (m, 2H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): } \delta 202.6, 196.4, 171.7, 151.1, 149.4, 129.4, 113.8, 63.8, 57.0, 43.7, 33.9, 33.6, 30.4, 29.0, 26.4, 26.2, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2947, 2725, 1729, 1697, 1456, 1356, 1215 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): m/z calc’d for C\(_{19}\)H\(_{26}\)O\(_4\) [M\(^+\): 318.1831, found 318.1809.

2-cyclobutylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (94)

Prepared from 110 and 5-bromo-1,1-diethoxypentane\(^\text{39}\) following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (649 mg, 2.13 mmol, 29% yield).

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 9.75 (t, J = 1.7 Hz, 1H), 6.94 – 6.83 (m, 1H), 6.02 (ddd, J = 10.1, 2.6, 1.5 Hz, 1H), 5.20 (tp, J = 7.1, 2.3 Hz, 1H), 4.46 (ddt, J = 7.4, 2.3, 1.1 Hz, 2H), 2.69 (dt, J = 16.0, 8.4 Hz, 4H), 2.56 – 2.40 (m, 4H), 2.37 – 2.26 (m, 1H), 2.03 – 1.84 (m, 4H), 1.75 (ddd, J = 13.6, 11.6, 5.1 Hz, 1H), 1.64 (p, J = 7.5 Hz, 2H), 1.42 – 1.26 (m, 2H).
13C NMR (100 MHz, CDCl3): δ 202.6, 196.4, 171.6, 149.4, 148.9, 129.4, 114.0, 62.3, 57.0, 43.7, 33.6, 31.2, 30.4, 29.6, 24.3, 23.9, 22.5, 17.1.

IR (Neat Film, NaCl): 2941, 1726, 1681, 1446, 1387, 1240, 1171, 1103 cm−1.


3-benzyl-4-phenylbut-2-en-1-yl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (98)

Prepared from 111 and 5-bromo-1,1-diethoxypentane39 following General Procedure C. Purification by flash column chromatography (10–60% Et2O/hexanes) afforded the title compound as a colorless oil (425 mg, 0.955 mmol, 18% yield).

1H NMR (400 MHz, CDCl3): δ 9.73 (t, J = 1.7 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.21 (tt, J = 7.5, 2.3 Hz, 2H), 7.15 – 7.03 (m, 4H), 6.90 – 6.82 (m, 1H), 6.02 (ddd, J = 10.2, 2.5, 1.6 Hz, 1H), 5.51 (d, J = 7.4 Hz, 1H), 4.83 – 4.70 (m, 2H), 3.36 (s, 2H), 3.24 (s, 2H), 2.54 – 2.24 (m, 5H), 2.00 – 1.86 (m, 2H), 1.77 (ddd, J = 13.6, 11.6, 5.1 Hz, 1H), 1.63 (p, J = 7.5 Hz, 2H), 1.44 – 1.22 (m, 2H).

13C NMR (100 MHz, CDCl3): δ 202.5, 196.2, 171.6, 149.4, 144.8, 139.0, 138.8, 129.4, 129.3, 128.8, 128.7, 128.5, 126.5, 126.4, 121.7, 62.0, 57.0, 43.7, 42.9, 35.8, 33.6, 30.4, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2923, 1723, 1684, 1493, 1451, 1386, 1231 cm−1.

2-cycloheptylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (97)

Prepared from 112 and 5-bromo-1,1-diethoxypentane following General Procedure C. Purification by flash column chromatography (10–70% Et2O/hexanes) afforded the title compound as a colorless oil (349 mg, 1.01 mmol, 15% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.75 (t, $J$ = 1.7 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.02 (ddd, $J$ = 10.1, 2.6, 1.6 Hz, 1H), 5.28 (tt, $J$ = 7.1, 1.3 Hz, 1H), 4.60 (d, $J$ = 7.1 Hz, 2H), 2.56 – 2.40 (m, 4H), 2.38 – 2.20 (m, 5H), 1.98 – 1.87 (m, 2H), 1.76 (ddd, $J$ = 13.7, 12.0, 4.8 Hz, 1H), 1.65 (p, $J$ = 7.5 Hz, 2H), 1.57 (q, $J$ = 5.4 Hz, 4H), 1.50 (dt, $J$ = 5.2, 2.4 Hz, 4H), 1.42 – 1.27 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.6, 196.4, 171.7, 149.4, 149.0, 129.4, 118.4, 62.1, 57.0, 43.7, 37.7, 33.6, 30.4, 30.2, 29.8, 29.1, 28.9, 27.3, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2923, 2854, 1737, 1681, 1443, 1385, 1235, 1172 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{21}$H$_{30}$O$_4$ [M]$^+$: 346.2144, found 346.2139.

$\beta$-Ketoesters Synthesis

*General Procedure D: Prenyl $\beta$-ketoesters Synthesis through Acylation*
A flame dried round bottom flask was charged with iPr₂NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 °C and n-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 °C. The corresponding cyclohexenone (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 °C for 30 minutes. The solution was cooled to −78 °C, and the appropriate N-acyl imidazole (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 °C and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the corresponding acylated enone.

3-methylbut-2-en-1-yl 2-oxocyclohex-3-ene-1-carboxylate (100)

Prepared from 2-cyclohexen-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate following General Procedure D. Purification by flash column chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (6.65 g, 31.9 mmol, 41% yield).

^1H NMR (400 MHz, CDCl₃): δ 7.02 – 6.97 (m, 1H), 6.07 (dt, J = 10.2, 2.0 Hz, 1H), 5.37 – 5.32 (m, 1H), 4.65 (d, J = 7.1 Hz, 2H), 3.42 – 3.39 (m, 1H), 2.55 – 2.45 (m, 1H), 2.44 – 2.34 (m, 2H), 2.26 – 2.18 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 194.1, 170.2, 150.7, 139.6, 129.3, 118.4, 62.3, 53.6, 25.9, 25.8, 24.5, 18.2.

IR (Neat Film, NaCl): 3033, 2934, 1736, 1682, 1447, 1387, 1302, 1233, 1159, 1123 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{12}$H$_{16}$O$_3$ [M]$^+$: 208.1099, found 208.1090.

3-(methyl-$d_3$)but-2-en-1-yl-4,4,4-$d_3$ 2-oxocyclohex-3-ene-1-carboxylate (D-100)

Prepared from 2-cyclohexen-1-one and 3-(methyl-$d_3$)but-2-en-1-yl-4,4,4-$d_3$ 1H-imidazole-1-carboxylate following General Procedure D. Purification by flash column chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.00 g, 4.67 mmol, 37% yield). *Note that 1.0 equiv of the N-acyl imidazole can be employed.*

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.99 (dt, $J = 10.0$, 3.7 Hz, 1H), 6.06 (dt, $J = 10.2$, 2.1 Hz, 1H), 5.34 (t, $J = 7.2$ Hz, 1H), 4.65 (d, $J = 7.2$ Hz, 2H), 3.40 (dd, $J = 9.7$, 5.0 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.32 (m, 2H), 2.22 (ddt, $J = 13.7$, 8.8, 3.0 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 194.1, 170.2, 150.7, 139.4, 129.3, 118.4, 62.3, 53.6, 25.8, 24.5.

$^2$H NMR (61 MHz, CHCl$_3$): δ 1.72, 1.67.

IR (Neat Film, NaCl): 2942, 1736, 1681, 1388, 1164 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{12}$H$_{10}$D$_6$O$_3$ [M]$^+$: 214.1476, found 214.1476.
cinnamyl 2-oxocyclohex-3-ene-1-carboxylate (103)

Prepared from 2-cyclohexen-1-one and cinnamyl 1H-imidazole-1-carboxylate\(^{42}\) following General Procedure D. Purification by flash column chromatography (15–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.98 g, 3.82 mmol, 39% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40 – 7.37 (m, 2H), 7.34 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 7.01 (dt, \(J = 10.3, 3.8\) Hz, 1H), 6.67 (dt, \(J = 15.9, 1.3\) Hz, 1H), 6.29 (dt, \(J = 15.9, 6.4\) Hz, 1H), 6.09 (dt, \(J = 10.2, 2.0\) Hz, 1H), 4.83 (d, \(J = 6.5\) Hz, 2H), 3.47 (dd, \(J = 10.2, 4.9\) Hz, 1H), 2.57 – 2.47 (m, 1H), 2.47 – 2.34 (m, 2H), 2.28 – 2.21 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 193.9, 169.9, 150.8, 136.3, 134.6, 129.3, 128.7, 128.2, 126.8, 122.9, 65.9, 53.6, 25.8, 24.5.

IR (Neat Film, NaCl): 3024, 2940, 1734, 1676, 1304, 1223, 1157, 1123, 969 cm\(^{-1}\)

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{16}\)H\(_{16}\)NaO\(_3\) [M+Na]\(^+\): 279.0997, found 279.0983.

3-methylbut-2-en-1-yl 3-methyl-2-oxocyclohex-3-ene-1-carboxylate (107)

Prepared from 2-methylcyclohex-2-en-1-one\(^{44}\) and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate\(^{42}\) following General Procedure D. Purification by flash column
chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (1.09 g, 4.90 mmol, 23% yield).

\[ ^{1}\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta 6.78 – 6.69 (m, 1H), 5.35 (tdq, J = 7.2, 2.9, 1.5 Hz, 1H), 4.65 (d, J = 7.2 Hz, 2H), 3.42 – 3.36 (m, 1H), 2.48 – 2.11 (m, 5H), 1.79 (d, J = 1.6 Hz, 3H), 1.75 (s, 3H), 1.70 (s, 3H). \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)}: \delta 194.7, 170.6, 145.5, 139.5, 135.4, 118.5, 62.2, 53.8, 26.3, 25.9, 24.6, 18.2, 16.2. \]

IR (Neat Film, NaCl): 2925, 1736, 1676, 1449, 1381, 1249, 1151 cm\(^{-1}\).

HRMS (MM: FD\(^{+}\)): \(m/z\) calc’d for C\(_{13}\)H\(_{18}\)O\(_3\) [M]\(^{+}\): 222.1255, found 222.1251.

3-methylbut-2-en-1-yl 4-methyl-2-oxocyclohex-3-ene-1-carboxylate (105)

Prepared from 3-methylcyclohex-2-en-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate\(^{42}\) following General Procedure D. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (2.95 g, 13.3 mmol, 17% yield).

\[ ^{1}\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta 5.91 (h, J = 1.4 Hz, 1H), 5.35 (tp, J = 7.1, 1.6 Hz, 1H), 4.65 (d, J = 7.2 Hz, 2H), 3.37 – 3.27 (m, 1H), 2.48 – 2.24 (m, 3H), 2.21 – 2.15 (m, 1H), 1.97 (s, 3H), 1.75 (d, J = 1.3 Hz, 3H), 1.70 (s, 3H). \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)}: \delta 193.9, 170.5, 163.0, 139.5, 126.0, 118.5, 62.3, 52.6, 29.5, 25.9, 25.7, 24.5, 18.2. \]
IR (Neat Film, NaCl): 2938, 1732, 1668, 1634, 1378, 1357, 1302, 1246, 1216, 1170, 1152, 1018 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{13}\)H\(_{18}\)O\(_3\) [M]\(^+\): 222.1257, found 222.1251.

3-methylbut-2-en-1-yl 4-ethoxy-2-oxocyclohex-3-ene-1-carboxylate (106)

Prepared from 3-ethoxycyclohex-2-en-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate\(^{42}\) following General Procedure D. Purification by flash column chromatography (25–30\% EtOAc/hexanes) afforded the title compound as a colorless oil (2.84 g, 9.51 mmol, 19\% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.38 (s, 1H), 5.37 – 5.32 (m, 1H), 4.72 – 4.59 (m, 2H), 3.91 (qd, \(J = 7.0, 2.3\) Hz, 2H), 3.36 – 3.27 (m, 1H), 2.56 (ddd, \(J = 16.6, 6.2, 4.5\) Hz, 1H), 2.47 – 2.27 (m, 2H), 2.24 – 2.08 (m, 1H), 1.75 (s, 3H), 1.70 (s, 3H), 1.36 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.0, 177.7, 170.6, 139.4, 118.5, 102.3, 64.6, 62.3, 52.5, 27.5, 25.9, 24.3, 18.2, 14.2.

IR (Neat Film, NaCl): 2980, 2357, 1730, 1648, 1605, 1380, 1192, 1026, 668 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{14}\)H\(_{20}\)O\(_4\) [M]\(^+\): 252.1363, found 252.1356.
A flame dried round bottom flask was charged with i-Pr$_2$NH (2.52 mL, 18.0 mmol, 1.2 equiv) and THF (167 mL, 0.1 M). The solution was cooled to –78 ºC and n-BuLi (7.20 mL, 18.0 mmol, 1.2 equiv) was added dropwise. The resultant solution was slowly warmed to 0 ºC over 1 h and then cooled to – 78 ºC. The LDA solution was added dropwise to a solution of 1-benzoyl-2,3-dihydropyridin-4(1H)-one$^{45}$ (3.47 g, 15.0 mmol, 1.0 equiv) in THF (239 mL, 0.06 M) at –78 ºC. The resultant solution was stirred for 1 h. Then methyl cyanoformate (1.37 mL, 17.25 mmol, 1.15 equiv) was added dropwise. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH$_4$Cl and the product was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO$_2$, 20–30% EtOAc/Hexanes) to afford acylated enone 113 (1.17 g, 4.05 mmol, 27% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.88 (s, 1H), 7.39 (d, $J$ = 2.3 Hz, 5H), 5.40 (s, 1H), 5.28 (s, 1H), 4.39 (dd, $J$ = 13.6, 8.9 Hz, 1H), 4.18 (dd, $J$ = 13.6, 5.4 Hz, 1H), 3.76 (s, 3H), 3.51 (dd, $J$ = 8.9, 5.4 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.8, 168.2, 143.6, 134.8, 129.1, 128.9, 128.8, 128.7, 106.8, 69.6, 52.9, 50.6, 44.4.

IR (Neat Film, NaCl): 2952, 2332, 1734, 1670, 1601, 1388, 1293, 1213 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{15}$H$_{15}$NO$_5$ [M]$^+$: 289.0950, found 289.0948.

1-benzyl 3-(3-methylbut-2-en-1-yl) 4-oxo-3,4-dihydropyridine-1,3(2H)-dicarboxylate (104)
A flame dried round bottom flask equipped with a reflux condenser was charged with Zn$^0$ dust (51.5 mg, 0.787 mmol, 0.2 equiv), acylated enone 113 (1.14 g, 3.40 mmol, 1.0 equiv), and toluene (19.7 mL, 0.2 M). To the stirred solution, prenyl alcohol was added neat (2.00 mL, 19.68 mmol, 5.0 equiv). The resultant solution was heated to reflux for 3 days. The solution was cooled to 23 °C, filtered through a celite plug and eluted with CH$_2$Cl$_2$, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO$_2$, 15–25% EtOAc/Hexanes) to afford acylated enone 104 (883 mg, 2.57 mmol, 65% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (s, 1H), 7.39 (m, 5H), 5.39 (s, 1H), 5.32 (tp, $J = 7.3$, 1.4 Hz, 1H), 5.27 (s, 2H), 4.65 (dd, $J = 7.3$, 2.9 Hz, 2H), 4.38 (dd, $J = 13.6$, 8.9 Hz, 1H), 4.17 (dd, $J = 13.5$, 5.4 Hz, 1H), 3.48 (dd, $J = 9.1$, 5.3 Hz, 1H), 1.74 (s, 3H), 1.69 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.9, 167.8, 143.5, 140.1, 134.9, 129.0, 128.9, 128.8, 128.7, 118.0, 106.9, 69.5, 62.8, 50.8, 44.5, 25.9, 18.2.

IR (Neat Film, NaCl): 2965, 1727, 1676, 1599, 1388, 1293, 1209, 940 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{19}$H$_{21}$O$_5$ [M$^+$]: 343.1420, found 343.1420.
**General Procedure E: Substituted β-Ketoesters Synthesis through Acylation**

To a solution of di(1H-imidazol-1-yl)methanone (2.0 equiv) in THF (2.0 M) at 0 °C was added dropwise a solution of the corresponding alcohol (1.0 equiv) in CH₂Cl₂ (1.0 M). After 3 h, the reaction mixture was gradually warmed to 25 °C. Upon consumption of starting material (as determined by TLC), the reaction mixture was concentrated under reduced pressure then filtered through a silica plug and eluted with 50% EtOAc/Hexanes. The resulting solution was concentrated under reduced pressure.

A flame dried round bottom flask was charged with iPr₂NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 °C and n-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 °C. 2-cyclohexen-1-one (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 °C for 30 minutes. The solution was cooled to –78 °C, and the corresponding crude 1H-imidazole-1-carboxylate (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 °C and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were
washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the corresponding acylated enone.

![Structure](image)

**2-cyclohexylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (108)**

Prepared from 2-cyclohexen-1-one and 2-cyclohexylideneethan-1-ol$^{46}$ following General Procedure E, with the modification of 1.5 equiv of di(1H-imidazol-1-yl)methanone and 1.2 equiv of 2-cyclohexylideneethyl 1H-imidazole-1-carboxylate being used. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (535 mg, 2.15 mmol, 28% yield).

$^1$H NMR (400 MHz, CDCl$_3$): 8 7.04 – 6.95 (m, 1H), 6.07 (dt, J = 10.1, 2.0 Hz, 1H), 5.29 (tt, J = 7.2, 1.2 Hz, 1H), 4.67 (d, J = 7.2 Hz, 2H), 3.45 – 3.36 (m, 1H), 2.56 – 2.30 (m, 3H), 2.27 – 2.15 (m, 3H), 2.14 – 2.08 (m, 2H), 1.60 – 1.48 (m, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 194.1, 170.2, 150.6, 147.5, 129.3, 115.0, 61.5, 53.6, 37.1, 29.2, 28.5, 27.9, 26.7, 25.8, 24.5.

IR (Neat Film, NaCl): 2930, 2852, 1735, 1683, 1447, 1388, 1298, 1169, 1122 cm$^{-1}$.

HRMS (MM: FD+): m/z calc’d for C$_{15}$H$_{20}$O$_3$ [M]$^+$: 248.1412, found 248.1418.

![Structure](image)

**2-cyclopentylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (109)**
Prepared from 2-cyclohexen-1-one and 2-cyclopentyldeneethan-1-ol following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.69 g, 11.46 mmol, 31.9% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.99 (dt, $J = 10.1$, 3.8 Hz, 1H), 6.07 (dt, $J = 10.2$, 2.0 Hz, 1H), 5.50 – 5.40 (m, 1H), 4.64 (dt, $J = 7.2$, 1.1 Hz, 2H), 3.45 – 3.37 (m, 1H), 2.57 – 2.15 (m, 8H), 1.75 – 1.58 (m, 4H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.1, 170.2, 151.2, 150.7, 129.3, 113.8, 63.8, 53.6, 34.0, 29.0, 26.4, 26.2, 25.8, 24.5.

IR (Neat Film, NaCl): 2946, 2869, 1782, 1681, 1455, 1387, 1304, 1224, 1156 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{14}$H$_{18}$O$_3$ [M]$^+$: 234.1256, found 234.1255.

2-cyclobutylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (110)

Prepared from 2-cyclohexen-1-one and 2-cyclobutylideneethan-1-ol following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.02 g, 9.19 mmol, 31.7% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.00 (dt, $J = 10.1$, 3.7 Hz, 1H), 6.07 (dt, $J = 10.2$, 2.0 Hz, 1H), 5.27 (tp, $J = 6.9$, 2.2 Hz, 1H), 4.53 (d, $J = 7.2$ Hz, 2H), 3.45 – 3.36 (m, 1H), 2.80 – 2.65 (m, 4H), 2.56 – 2.31 (m, 3H), 2.28 – 2.15 (m, 1H), 1.98 (p, $J = 8.0$ Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.1, 170.1, 150.7, 148.9, 129.3, 114.1, 62.3, 53.6, 31.2, 29.6, 25.8, 24.5, 17.1.

IR (Neat Film, NaCl): 2947, 1737, 1681, 1457, 1397, 1301, 1229, 1163, 1123 cm$^{-1}$. 
HRMS (MM: FD+): m/z calc’d for C_{13}H_{16}O_3 [M]^+: 220.1099, found 220.1093.

3-benzyl-4-phenylbut-2-en-1-yl 2-oxocyclohex-3-ene-1-carboxylate (111)

Prepared from 2-cyclohexen-1-one and 3-benzyl-4-phenylbut-2-en-1-ol following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (1.96 g, 5.43 mmol, 21.3% yield).

^1^H NMR (400 MHz, CDCl_3): δ 7.33 – 7.25 (m, 4H), 7.24 – 7.18 (m, 2H), 7.17 – 7.07 (m, 4H), 7.03 – 6.97 (m, 1H), 6.08 (dt, J = 10.1, 2.0 Hz, 1H), 5.59 (tt, J = 7.1, 1.1 Hz, 1H), 4.86 – 4.80 (m, 2H), 3.48 – 3.35 (m, 3H), 3.26 (s, 2H), 2.55 – 2.32 (m, 3H), 2.30 – 2.15 (m, 1H).

^13^C NMR (100 MHz, CDCl_3): δ 193.9, 170.1, 150.7, 144.4, 139.0, 138.9, 129.3, 129.3, 128.9, 128.7, 128.5, 126.5, 126.4, 121.9, 62.0, 53.6, 42.9, 35.9, 25.8, 24.5.

IR (Neat Film, NaCl): 3026, 2927, 1738, 1681, 1493, 1388, 1304, 1230, 1157, 1123 cm^{-1}.

HRMS (MM: FD+): m/z calc’d for C_{24}H_{24}O_3 [M]^+: 360.1725, found 360.17302.

2-cycloheptylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (112)
Prepared from 2-cyclohexen-1-one and 2-cycloheptylideneethan-1-ol following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (1.73 g, 5.43 mmol, 28.1% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.99 (dt, $J = 10.0$, 3.8 Hz, 1H), 6.07 (dt, $J = 10.1$, 2.0 Hz, 1H), 5.34 (tt, $J = 7.1$, 1.3 Hz, 1H), 4.66 (d, $J = 7.0$ Hz, 2H), 3.45 – 3.37 (m, 1H), 2.57 – 2.15 (m, 8H), 1.63 – 1.44 (m, 8H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 194.1, 170.2, 150.6, 148.8, 129.3, 118.5, 62.1, 53.6, 37.8, 30.2, 29.9, 29.1, 28.8, 27.3, 25.8, 24.5.

IR (Neat Film, NaCl): 2923, 2853, 1736, 1681, 1442, 1388, 1300, 1231, 1155, 1122, 1076 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{26}$H$_{22}$O$_3$ [M$^+$]: 262.1569, found 262.1577.

**Protonated Enone Byproducts**

benzyl ($R,E$)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (49a)

In a nitrogen filled glovebox, an oven-dried 20 mL vial was charged with a stir bar, Pd$_2$(dba)$_3$ (0.46 mg, 0.50 µmol, 2.5 mol %), (S)-t-BuPHOX (0.50 mg, 1.3 µmol, 6.5 mol %), and toluene (0.5 mL). The catalyst solution was stirred at 23 ºC for 20 min. A solution of substrate 40a (8.2 mg, 0.020 mmol, 1 equiv) and 3,5-dimethylphenol (2.4 mg, 0.020 mmol, 1 equiv) in toluene (0.5 mL) was added to the vial. The resultant solution was then heated to 60 ºC for 14 h. The solution was then cooled to 23 ºC and concentrated under reduced
pressure. NMR analysis of the crude reaction mixture affords an NMR yield of 100% (with respect to 1,3,5-trimethoxybenzene as an internal standard). The sample was purified by preparatory TLC (25% EtOAc/hexanes) to afford 49a (71% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.29 (m, 5H), 7.01 (dt, $J = 15.7, 6.9$ Hz, 1H), 6.92 (ddddd, $J = 10.1, 4.5, 3.5, 0.9$ Hz, 1H), 5.98 (ddd, $J = 10.1, 2.3, 1.7$ Hz, 1H), 5.88 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.17 (s, 2H), 2.46 – 2.34 (m, 2H), 2.32 – 2.20 (m, 3H), 2.09 (dqd, $J = 13.3, 4.8, 1.0$ Hz, 1H), 1.89 – 1.80 (m, 1H), 1.75 (ddddd, $J = 13.3, 11.0, 8.4, 5.8$ Hz, 1H), 1.55 – 1.35 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.6, 166.6, 149.7, 149.6, 136.3, 129.7, 128.7, 128.3, 128.3, 121.4, 66.2, 46.5, 32.5, 29.0, 28.0, 25.6, 25.3.

IR (Neat Film, NaCl): 2921, 1712, 1673, 1257 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{19}$H$_{22}$O$_3$ [M]+: 298.1569, found 298.1565.

Optical Rotation: $[\alpha]_D^{21}$ +3.5 (c 0.20, CHCl$_3$).

SFC conditions: 40% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): minor = 3.81, major = 4.34.

benzyl (R,E)-7-(2-oxocyclohex-3-en-1-yl)hept-2-enoate (49d)

Isolated as a byproduct from the reaction of 40d to 41d as a colorless oil (10.4 mg, 0.0332 mmol, 17% yield, 67% ee).
\[^{1}\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3)\]: \(\delta 7.32 - 7.22 \ (m, \ 5H), \ 6.93 \ (dt, \ J = 15.7, 6.9 \ Hz, \ 1H), \ 6.53 \ (\text{ddd, } J = 12.0, 6.7, 4.0 \ Hz, \ 1H), \ 5.94 \ (\text{ddd, } J = 11.9, 2.5, 0.9 \ Hz, \ 1H), \ 5.80 \ (dt, \ J = 15.6, 1.6 \ Hz, \ 1H), \ 5.10 \ (s, \ 3H), \ 2.59 - 2.49 \ (m, \ 1H), \ 2.42 - 2.25 \ (m, \ 2H), \ 2.14 \ (tdd, \ J = 7.7, 4.8, 1.4 \ Hz, \ 2H), \ 1.90 - 1.48 \ (m, \ 5H), \ 1.44 - 1.29 \ (m, \ 4H)\).

\[^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3)\]: \(\delta 205.7, \ 166.5, \ 149.6, \ 146.0, \ 136.2, \ 132.8, \ 128.6, \ 128.2, \ 128.2, \ 121.2, \ 66.0, \ 51.7, \ 32.4, \ 31.1, \ 29.9, \ 29.5, \ 25.8, \ 25.4\).

\text{IR (Neat Film, NaCl): } 2917, \ 1719, \ 1671, \ 1266, \ 1165 \ cm^{-1}.

\text{HRMS (MM: FD+): } m/z \ \text{calc'd for C}_{20}\text{H}_{24}\text{O}_3 [M]^+: 312.1720, \ \text{found} \ 312.1734.

\text{Optical Rotation: } [\alpha]_D^{21} -0.6 \ (c \ 1.00, \ \text{CHCl}_3).

\text{SFC conditions: } 15\% \ \text{IPA, 2.5 mL/min, Chiralpak AD-H column, } \lambda = 210 \ nm, \ t_R \ (\text{min}): \ \text{minor} = 8.23, \ \text{major} = 7.63.

\[\text{benzyl (}S,E\text{-5-(2-oxocyclohex-3-en-1-yl)pent-2-enoate (49e)}\]

Isolated as the major byproduct from the reaction of 40e to 41e. Purification by flash column chromatography (0–45\% EtOAc/hexanes) afforded the title compound as a colorless oil (46.1 mg, 0.16 mmol, 81\% yield, 47\% ee).

\[^{1}\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3)\]: \(\delta 7.42 - 7.28 \ (m, \ 5H), \ 7.01 \ (dt, \ J = 15.6, 6.9 \ Hz, \ 1H), \ 6.92 \ (\text{ddd, } J = 10.0, 4.4, 3.6, 1.0 \ Hz, \ 1H), \ 5.98 \ (dt, \ J = 10.0, 2.0 \ Hz, \ 1H), \ 5.90 \ (dt, \ J = 15.7, 1.6 \ Hz, \ 1H), \ 5.17 \ (s, \ 2H), \ 2.44 - 2.24 \ (m, \ 5H), \ 2.15 - 1.96 \ (m, \ 2H), \ 1.82 - 1.69 \ (m, \ 1H), \ 1.62 - 1.44 \ (m, \ 1H)\).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.3, 166.5, 149.6, 149.4, 136.2, 129.7, 128.7, 128.3, 128.3, 121.6, 66.2, 45.9, 29.7, 28.2, 27.8, 25.4.

IR (Neat Film, NaCl): 3032, 2932, 1719, 1675, 1455, 1386, 1265, 1171 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{18}$H$_{20}$O$_3$ [M]$^+$: 284.1412, found 284.1407.

Optical Rotation: $[\alpha]_D^{21} +11.8$ (c 1.00, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AS-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 5.69, major = 6.54.

benzyl (R,E)-7-(2-oxocyclohex-3-en-1-yl)hept-2-enoate (49f)

Isolated as a byproduct from the reaction of 40f to 41f as a colorless oil (28.1 mg, 0.090 mmol, 45% yield, 51% ee). Absolute stereochemistry proposed based on VCD analysis (vide infra).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.29 (m, 5H), 7.00 (dt, $J$ = 15.6, 6.9 Hz, 1H), 6.90 (ddddd, $J$ = 10.0, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (dt, $J$ = 10.1, 2.0 Hz, 1H), 5.86 (dt, $J$ = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.42 – 2.33 (m, 2H), 2.29 – 2.18 (m, 3H), 2.08 (dqd, $J$ = 13.3, 4.8, 0.9 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.78 – 1.69 (m, 1H), 1.52 – 1.29 (m, 5H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.8, 166.6, 150.0, 149.5, 136.3, 129.6, 128.6, 128.3, 128.3, 121.2, 66.1, 46.6, 32.2, 29.0, 28.2, 27.9, 26.6, 25.2.

IR (Neat Film, NaCl): 2927, 2859, 1716, 1675, 1652, 1262, 1172 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{20}$H$_{24}$O$_3$ [M]$^+$: 312.1725, found 312.1737.

Optical Rotation: $[\alpha]_D^{21} +4.1$ (c 1.00, CHCl$_3$).
SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t<sub>R</sub> (min):
minor = 7.77, major = 8.44.

benzyl (R,E)-7-(2-oxocyclohex-3-en-1-yl-1-d)hept-2-enoate (D-49f)

Isolated as a byproduct from the reaction of D-40f to D-41f as a colorless oil (14.9 mg, 0.0475 mmol, 24% yield, 55% ee).

^1H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.39 – 7.29 (m, 5H), 7.00 (dt, J = 15.6, 7.0 Hz, 1H), 6.91 (ddddd, J = 10.1, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (ddddd, J = 10.0, 2.3, 1.6, 0.6 Hz, 1H), 5.86 (dt, J = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.44 – 2.33 (m, 2H), 2.28 – 2.18 (m, 2.5H), 2.09 (dddt, J = 13.3, 5.8, 4.5 Hz, 1H), 1.87 – 1.70 (m, 2H), 1.53 – 1.27 (m, 5H).

^13C NMR (100 MHz, CDCl<sub>3</sub>): δ 201.9, 166.6, 150.0, 149.6, 129.7, 129.7, 128.7, 128.3, 128.3, 121.2, 66.2, 46.6, 32.3, 29.0, 28.9, 28.2, 27.9, 27.8, 26.7, 26.6, 25.3, 25.2.

^3H NMR (61 MHz, CHCl<sub>3</sub>): δ 2.25.

IR (Neat Film, NaCl): 2929, 2857, 1714, 1697, 1174 cm<sup>-1</sup>.

HRMS (MM: FD+): m/z calc’d for C<sub>20</sub>H<sub>23</sub>DO<sub>3</sub> [M+H]<sup>+</sup>: 313.1783, found 313.1788.

Optical Rotation: [α]<sub>D</sub><sup>21</sup> +5.8 (c 0.50, CHCl<sub>3</sub>).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t<sub>R</sub> (min):
minor = 7.96, major = 8.67.
benzyl (R,E)-8-(2-oxocyclohex-3-en-1-yl)oct-2-enoate (49g)

Isolated as the major product from the reaction of 40g to 41g as a colorless oil (50.5 mg, 0.155 mmol, 77% yield, 56% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 – 7.29 (m, 5H), 7.01 (dt, $J = 15.6$, 6.9 Hz, 1H), 6.91 (dddd, $J = 10.0$, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (dt, $J = 10.0$, 2.0 Hz, 1H), 5.86 (dt, $J = 15.6$, 1.6 Hz, 1H), 5.17 (s, 2H), 2.45 – 2.33 (m, 2H), 2.30 – 2.16 (m, 3H), 2.09 (dqd, $J = 14.5$, 5.0, 0.9 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.51 – 1.42 (m, 2H), 1.41 – 1.28 (m, 5H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.0, 166.7, 150.2, 149.5, 136.3, 129.7, 128.7, 128.3, 128.3, 121.1, 66.1, 46.6, 32.3, 29.3, 29.1, 28.0, 27.9, 26.8, 25.2.

IR (Neat Film, NaCl): 2927, 2859, 1718, 1677, 1555, 1450, 1257, 1165 cm$^{-1}$

HRMS (MM: FD+): m/z calc’d for C$_{21}$H$_{26}$O$_3$ [M]$^+$: 326.1877, found 326.1891.

Optical Rotation: $[\alpha]_D^{21} +7.0$ (c 1.00, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 9.70, major = 10.46.

6-(pent-4-en-1-yl)cyclohex-2-en-1-one (49h)

Isolated as the major product from the reaction of 40h to 41h as a colorless oil. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the title compound as a colorless oil (11.0 mg, 0.067 mmol, 33% yield, 58% ee).
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

¹H NMR (400 MHz, CDCl₃): δ 6.91 (dddd, J = 10.1, 4.4, 3.5, 0.9 Hz, 1H), 5.97 (dt, J = 10.0, 2.1 Hz, 1H), 5.81 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (dq, J = 17.2, 1.8 Hz, 1H), 4.94 (dd, J = 10.1, 1.3 Hz, 1H), 2.45 – 2.24 (m, 3H), 2.16 – 1.98 (m, 2=3H), 1.95 – 1.69 (m, 2H), 1.55 – 1.31 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 202.0, 149.5, 138.8, 129.7, 114.7, 46.6, 34.0, 28.8, 27.9, 26.4, 25.2.

IR (Neat Film, NaCl): 2925, 2859, 1677, 1639, 1456, 1387, 1215, 912 cm⁻¹.


Optical Rotation: [α]²¹D –111.5 (c 1.00, CHCl₃).

SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): minor = 4.41, major = 4.11.

(E)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoic acid (49i)

Isolated as the major product from the reaction of 40i to 41i as a colorless oil. Purification by flash column chromatography (35% EtOAc/hexanes with 3% AcOH) afforded the title compound as a white solid (33.2 mg, 0.16 mmol, 80% yield, 9% ee).

¹H NMR (400 MHz, CDCl₃): δ 7.07 (dtd, J = 15.5, 7.0, 1.5 Hz, 1H), 6.97 – 6.87 (m, 1H), 5.98 (dq, J = 10.1, 1.9 Hz, 1H), 5.84 (dt, J = 15.6, 1.6 Hz, 1H), 2.49 – 2.35 (m, 2H), 2.34 – 2.19 (m, 3H), 2.16 – 2.04 (m, 1H), 1.92 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.63 – 1.48 (m, 2H), 1.48 – 1.35 (m, 1H).
\textbf{13C NMR (100 MHz, CDCl₃):} δ 201.7, 171.5, 151.9, 149.7, 129.7, 120.9, 46.5, 32.5, 29.0, 28.0, 25.5.

\textbf{IR (Neat Film, NaCl):} 2928, 2857, 1731, 1454, 1155 cm⁻¹

\textbf{HRMS (MM: FD+):} m/z calc’d for C₁₂H₁₇O₅ [M]⁺: 209.1178, found 209.1168.

\textbf{Optical Rotation:} [α]_D^{21} 2.2 (c 1.00, CHCl₃).

\textbf{SFC conditions:} 30% IPA, 2.5 mL/min, Chiralpak IC column, l = 210 nm, t_R (min): minor = 3.30, major = 4.02

\begin{center}
\includegraphics[width=0.5\textwidth]{49m.png}
\end{center}

\textbf{1,3-dioxoisoindolin-2-yl (E)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (49m)}

Isolated as a byproduct product from the reaction of 40m to 41m as a colorless oil.

Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a white solid (7.7 mg, 0.022 mmol, 11% yield).

\textbf{1H NMR (400 MHz, CDCl₃):} δ 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.79 (dd, J = 5.5, 3.1 Hz, 2H), 7.32 (dt, J = 15.8, 6.9 Hz, 1H), 6.93 (dddd, J = 10.1, 4.5, 3.5, 1.0 Hz, 1H), 6.10 (dt, J = 15.8, 1.6 Hz, 1H), 5.99 (ddd, J = 10.0, 2.3, 1.7 Hz, 1H), 2.50 – 2.25 (m, 5H), 2.12 (m, 1H), 1.95 – 1.84 (m, 1H), 1.78 (m, 1H), 1.59 (m, 2H), 1.45 (m, 1H).

\textbf{13C NMR (100 MHz, CDCl₃):} δ 201.5, 162.5, 162.2, 155.6, 149.7, 134.9, 129.7, 129.1, 124.1, 115.9, 46.5, 33.2, 29.1, 28.1, 25.4, 25.3.

\textbf{IR (Neat Film, NaCl):} 2931, 1770, 1745, 1673, 1466, 1360, 1186 cm⁻¹.

\textbf{HRMS (MM: FD+):} m/z calc’d for C₂₀H₁₉NO₅ [M]⁺: 353.1263, found 353.1242.
benzyl \((R,E)\)-2-methyl-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (49r)

Isolated as a byproduct from the reaction of 40r to 41r as a colorless oil (23.2 mg, 0.0743 mmol, 37% yield, 59% ee).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.40 – 7.29\) (m, 5H), 6.91 (dddd, \(J = 10.1, 4.5, 3.5, 0.9\) Hz, 1H), 6.81 (td, \(J = 7.5, 1.5\) Hz, 1H), 5.97 (dt, \(J = 10.0, 1.9\) Hz, 1H), 5.18 (s, 2H), 2.45 – 2.34 (m, 2H), 2.32 – 2.17 (m, 3H), 2.09 (dqd, \(J = 13.4, 4.9, 1.0\) Hz, 1H), 1.90 – 1.81 (m, 4H), 1.80 – 1.71 (m, 1H), 1.55 – 1.36 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 201.7, 168.1, 149.6, 142.7, 136.6, 129.7, 128.6, 128.2, 128.1, 127.9, 66.3, 46.6, 29.2, 29.0, 28.0, 26.2, 25.2, 12.6\).

IR (Neat Film, NaCl): 3033, 2932, 2861, 1710, 1677, 1256 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{20}\)H\(_{24}\)O\(_3\) [M]: 312.1725, found 312.1729.

Optical Rotation: \([\alpha]_{D}^{21} +8.6\) (c 1.00, CHCl\(_3\)).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, \(\lambda = 210\) nm, \(t_r\) (min): minor = 5.89, major = 6.22.

benzyl \((E)\)-6-(4-ethoxy-2-oxocyclohex-3-en-1-yl)hex-2-enoate (49t)

Isolated as a byproduct from the reaction of 40t to 41t as a colorless oil (5.2 mg, 0.015 mmol, 8% yield, 45% ee).
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 – 7.27 (m, 5H), 7.01 (dt, $J = 15.6, 6.9$ Hz, 1H), 5.87 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.31 (s, 1H), 5.17 (s, 2H), 3.88 (qd, $J = 7.1, 1.4$ Hz, 2H), 2.41 (dd, $J = 7.2, 5.3$ Hz, 2H), 2.29 – 2.13 (m, 3H), 2.06 (dq, $J = 13.2, 5.2$ Hz, 1H), 1.86 (ddt, $J = 13.3, 11.1, 5.2$ Hz, 1H), 1.78 – 1.64 (m, 1H), 1.59 – 1.37 (m, 3H), 1.35 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.4, 176.9, 166.6, 149.7, 136.3, 128.7, 128.3, 128.3, 121.3, 102.3, 66.1, 64.4, 45.1, 32.5, 29.3, 28.2, 26.4, 25.7, 14.3.

IR (Neat Film, NaCl): 2919, 1718, 1648, 1605, 1456, 1377, 1260, 1190, 732 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{21}$H$_{26}$O$_4$ [M]$^+$: 342.1828, found 342.1826.

Optical Rotation: $[\alpha]_D^{21}$ –5.5 (c 0.34, CHCl$_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 10.17, major = 11.69.

[Diagram of benzyl (E)-6-(3-methyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (49u)]

benzyl (E)-6-(3-methyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (49u)

Isolated as a byproduct from the reaction of 40u to 41u as a colorless oil (23.6 mg, 0.075 mmol, 37% yield, 46% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 – 7.28 (m, 5H), 7.01 (dt, $J = 15.5, 6.9$ Hz, 1H), 6.71 – 6.63 (m, 1H), 5.88 (dt, $J = 15.6, 1.6$ Hz, 1H), 5.17 (s, 2H), 2.33 (ddq, $J = 6.3, 4.8, 2.0$ Hz, 2H), 2.29 – 2.19 (m, 3H), 2.10 – 2.01 (m, 1H), 1.88 – 1.77 (m, 1H), 1.76 (q, $J = 1.7$ Hz, 3H), 1.74 – 1.69 (m, 1H), 1.56 – 1.34 (m, 3H).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 201.9, 166.6, 149.8, 144.5, 136.3, 135.3, 128.68, 128.3, 128.3, 121.3, 66.2, 46.6, 32.5, 29.2, 28.4, 25.7, 25.2, 16.3\).

IR (Neat Film, NaCl): 2925, 1718, 1670, 1455, 1262, 1172, 1013 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc'd for C\(_{20}\)H\(_{24}\)O\(_3\) [M]\(^+\): 312.1725, found 312.1721.

Optical Rotation: \([\alpha]_D^{21} -14.7\) (c 0.35, CHCl\(_3\)).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, \(\lambda = 210\) nm, \(t_R\) (min): minor = 7.18, major = 7.62.

Product Derivatizations

\[
\begin{align*}
\text{benzyl (3aR,6R,7S,7aR)-4-hydroxyoctahydro-3a,6-ethanoindene-7-carboxylate (68)}
\end{align*}
\]

To a solution of ketone 41a (0.125 mmol, 1 equiv) in methanol (4.4 mL) was added NaBH\(_4\) (0.25 mmol, 2 equiv) at 0 \(^\circ\)C. The reaction was allowed to stir for 10 min at 0 \(^\circ\)C and then was diluted with water. The aqueous layer was extracted with dichloromethane (3x), and the combined organic layers were dried over Na\(_2\)SO\(_4\). Concentration under reduced pressure afforded the title compound as a colorless oil (37.6 mg, 0.125 mmol, 99% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.42 – 7.30\) (m, 5H), 5.19 – 5.05 (m, 2H), 3.76 (dd, \(J = 8.9, 5.3\) Hz, 0.4H, minor), 3.69 (dt, \(J = 8.9, 1.5\) Hz, 0.6H, major), 2.35 – 2.24 (m, 1H), 2.15 – 1.95 (m, 2H), 1.95 – 1.83 (m, br, 1H), 1.83 – 1.56 (m, 6H), 1.53 – 1.23 (m, 5H), 1.15 – 1.01 (m, 1H).
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.8, 175.6, 136.3, 128.6, 128.2, 128.2, 128.0, 128.0, 75.6, 70.3, 66.3, 66.3, 49.21, 48.1, 44.5, 44.2, 43.2, 36.8, 35.0, 34.9, 34.0, 30.5, 30.3, 30.1, 29.6, 29.0, 26.7, 26.3, 22.8, 22.8, 20.3.

IR (Neat Film, NaCl): 3438, 3032, 2942, 2865, 1730, 1455, 1162 cm$^{-1}$

HRMS (MM: FD+): $m/z$ calc’d for C$_{19}$H$_{24}$O$_3$ [M]$^+$: 300.1725, found 300.1730.

Optical Rotation: $[\alpha]_D^{21}$ –31.1 (c 1.00, CHCl$_3$).

![Chemical Reaction](attachment:image)

benzyl (3a$R$,6$R$,7$S$,7a$R$,E)-4-(hydroxyimino)octahydro-3a,6-ethanoindene-7-carboxylate (114)

To a stirred solution of ketone 41a (0.125 mmol, 1 equiv) in methanol (1.25 mL) was added NaOAc (0.3 mmol, 2.4 equiv), NH$_2$OH•HCl (0.15 mmol, 1.17 equiv), and water (0.05 mL). The reaction was brought to reflux for 2 h and was subsequently cooled to 23 ºC and concentrated under reduced pressure. The crude mixture was then diluted with water and extracted with EtOAc (3x), washed with a saturated aqueous solution of NaHCO$_3$ and brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The material was used in the next step without further purification assuming quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.28 (m, 5H), 5.20 – 5.06 (m, 2H), 2.52 – 2.46 (m, 2H), 2.43 – 2.39 (m, 1H), 2.39 – 2.36 (m, 1H), 2.15 (dtd, $J = 10.2, 8.2, 1.8$ Hz, 1H), 2.07 (ddt, $J = 11.9, 8.3, 4.1$ Hz, 1H), 1.98 (ddd, $J = 13.0, 11.0, 8.0$ Hz, 1H), 1.82 – 1.71 (m, 3H),
1.67 (ddd, \(J = 10.9, 3.6, 1.8\) Hz, 1H), 1.48 (ddd, \(J = 12.5, 7.8, 6.5, 3.7\) Hz, 2H), 1.36 (ddddd, \(J = 23.6, 11.1, 8.8, 2.6\) Hz, 2H).

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 174.8, 165.4, 136.2, 128.7, 128.4, 128.2, 66.5, 48.2, 45.7, 44.4, 30.6, 29.2, 28.9, 28.1, 27.2, 25.5, 22.6.

IR (Neat Film, NaCl): 2945, 1731, 1161 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{19}\)H\(_{23}\)NO\(_3\) [M]\(^+\): 313.1678, found 313.1676.

Optical Rotation: \([\alpha]_D^{21}\) –22.0 (c 0.37, CHCl\(_3\)).

benzyl \((4R,5S,5aR,8aR)-2\)-oxooctahydro-\(1H\)-4,8a-ethanocyclopenta[\(b\)]azepine-5-carboxylate (69)

To a solution of 114 (0.125 mmol, 1 equiv) in THF (1.25 mL) at 0 °C was added a solution of SOCl\(_2\) (0.625 mmol, 5 equiv) in THF (0.23 mL). The reaction was stirred for 3 h at 0 °C, followed by dilution with water. Aqueous solution NH\(_4\)OH was added to the reaction mixture until neutral, and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with water and brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. Purification by flash column chromatography (35% EtOAc/hexanes) afforded the title compound as a colorless oil (22 mg, 0.167 mmol, 56% yield over two steps).
1H NMR (400 MHz, CDCl3): δ 7.41 – 7.27 (m, 5H), 6.67 (s, 1H, br), 5.15 (q, J = 12.3 Hz, 2H), 2.73 (dt, J = 18.1, 1.6 Hz, 1H), 2.62 (tdd, J = 9.9, 8.0, 1.4 Hz, 1H), 2.48 (dd, J = 18.4, 6.9 Hz, 1H), 2.40 – 2.32 (m, 2H), 2.29 – 2.16 (m, 1H), 1.95 (dtd, J = 12.7, 8.7, 2.2 Hz, 1H), 1.82 – 1.62 (m, 7H), 1.62 – 1.52 (m, 1H), 1.44 – 1.30 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 174.6, 174.2, 135.9, 128.8, 128.4, 128.3, 66.7, 59.9, 48.8, 48.5, 39.2, 33.3, 31.1, 29.8, 25.1, 23.3.

IR (Neat Film, NaCl): 3182, 3055, 2934, 1727, 1648, 1456, 1398, 1167 cm⁻¹.

HRMS (MM: FD+): m/z calc’d for C19H23NO3 [M]+: 313.1678, found 313.1678.

Optical Rotation: [α]D²¹ –5.5 (c 0.89, CHCl₃).

benzyl (4R,5S,5aR,8aR)-2-oxooctahydro-4,8a-ethanocyclopenta[b]oxepine-5-carboxylate (70)

To a solution ketone 41a (37 mg, 0.13 mmol, 1 equiv) in CH₂Cl₂ (1.25 mL, 0.1 M) at 0°C was added NaHCO₃ (30.8 mg, 0.37 mmol, 2.9 equiv). Subsequently, m-CPBA (31 mg, 0.15 mmol, 1.2 equiv) was added and the reaction was allowed to warm to 25°C. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of Na₂S₂O₃ and extracted with Et₂O (3x). The combined organic layers were washed with a saturated solution of NaHCO₃ followed by brine, dried over Na₂SO₄, and volatiles were removed in vacuo. Purification by preparatory
thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a clear oil (16 mg, 0.05 mmol, 41% yield).

1H NMR (400 MHz, CDCl3): δ 7.43 – 7.29 (m, 5H), 5.22 – 5.10 (m, 2H), 2.97 (ddd, J = 19.0, 2.5, 1.4 Hz, 1H), 2.83 – 2.61 (m, 2H), 2.41 – 2.32 (m, 2H), 2.28 – 2.09 (m, 3H), 2.05 – 1.93 (m, 1H), 1.81 – 1.56 (m, 5H), 1.40 – 1.26 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 173.9, 172.9, 135.7, 128.8, 128.6, 128.3, 88.4, 66.9, 47.8, 46.5, 39.6, 39.1, 32.8, 30.4, 29.7, 24.9, 22.7.

IR (Neat Film, NaCl): 2943, 2873, 1722, 1255, 1189, 1167 cm⁻¹.


Optical Rotation: [α]D²¹ –15.8 (c 1.00, CHCl₃).

(2S,4aR,8aR)-octahydro-2H-2,4a-ethanonaphthalen-9-one (75)

A vial containing ketone 41f (0.72 mmol, 1 equiv) and Pd/C (10 wt. % with 67% H₂O, 0.072 mmol, 0.1 equiv) was evacuated and backfilled with H₂. Methanol (1.06 mL) was subsequently added, and the reaction was stirred at 23 °C overnight. The crude reaction mixture was filtered through a silica plug and concentrated under reduced pressure to afford the corresponding acid as a white solid, which was used without further purification.

To a solution of the crude acid (0.62 mmol, 1 equiv) in DMSO (1.24 mL) was added (NH₄)₂S₂O₈ (1.86 mmol, 3 equiv) and 2,4,6-collidine (1.86 mmol, 3 equiv). The mixture was purged with N₂ for 5 min and was subsequently sealed and heated to 60 °C for 2 h with
stirring. The reaction mixture was diluted with dichloromethane, washed with brine (1x), and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine (3x), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a white solid (30.2 mg, 0.167 mmol, 27% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.33 – 2.21 (m, 3H), 2.13 – 2.07 (m, 1H), 1.93 (dddd, $J$ = 13.3, 10.6, 3.8, 2.8 Hz, 1H), 1.75 – 1.58 (m, 6H), 1.53 (dd, $J$ = 13.6, 4.0 Hz, 1H), 1.47 – 1.38 (m, 2H), 1.38 – 1.28 (m, 1H), 1.27 – 1.17 (m, 1H), 1.17 – 1.05 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 218.6, 44.9, 43.9, 34.5, 34.1, 30.6, 29.0, 27.7, 25.9, 25.9, 21.8, 21.4.

IR (Neat Film, NaCl): 2925, 1716 cm$^{-1}$

HRMS (MM: F+): $m/z$ calc’d for C$_{12}$H$_{18}$O [M]$^+$: 178.1358, found 178.1359.

Optical Rotation: $[\alpha]_{D}^{21}$ – 59.9 (c 0.89, CHCl$_3$).

(2S,4aR,8aR)-10-methyleneoctahydro-2H-2,4a-ethanonaphthalen-9-one (76)

To a solution of ketone 75 (0.056 mmol, 1 equiv) and ethyl formate (4 mmol, 71.4 equiv) in toluene (3.2 mL) was added a solution of KHMDS (0.5 M in toluene, 1.6 mmol, 28 equiv) at 23 ºC. The reaction mixture was stirred at 70 ºC for 16 h. Upon cooling to 0 ºC, THF (6.4 mL) and formalin (37% in water, 3.2 mL) was added, and then the reaction was heated to 50 ºC for 4 h. The reaction mixture was diluted with a saturated aqueous solution
of \( \text{NH}_4\text{Cl} \), extracted with EtOAc (3x), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes, 2x) afforded the title compound as a yellow oil (4.4 mg, 0.023 mmol, 41% yield).

**\(^1\text{H NMR (400 MHz, CDCl}_3\):** \( \delta \) 5.93 (d, \( J = 1.8 \text{ Hz}, 1\text{H} \)), 5.15 (d, \( J = 1.8 \text{ Hz}, 1\text{H} \)), 2.66 (p, \( J = 3.0 \text{ Hz}, 1\text{H} \)), 2.39 – 2.19 (m, 1H), 1.98 (dddd, \( J = 13.2, 10.6, 3.9, 2.8 \text{ Hz}, 1\text{H} \)), 1.81 – 1.61 (m, 6H), 1.51 – 1.42 (m, 2H), 1.41 – 1.31 (m, 2H), 1.23 – 1.15 (m, 2H), 1.11 (dt, \( J = 12.9, 3.6 \text{ Hz}, 1\text{H} \)).

**\(^{13}\text{C NMR (100 MHz, CDCl}_3\):** \( \delta \) 205.3, 147.9, 116.3, 45.0, 36.1, 35.0, 34.7, 30.8, 29.0, 26.5, 26.0, 21.6, 21.3.

**IR (Neat Film, NaCl):** 2926, 2859, 1708, 1630, 1464, 1449 cm\(^{-1}\)

**HRMS (MM: FD+):** \( m/z \) calc’d for C\(_{13}\)H\(_{18}\)O [M\(^+\): 190.1358, found 190.1353.

**Optical Rotation:** \([\alpha]_D^{21} = -34.2 \text{ (c } 0.29, \text{ CHCl}_3\).

**ethyl (1S,2S,4aR,8aR)-3-methylene-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (77)**

To a solution of 41f (0.192 mmol, 1 equiv) and ethyl formate (13.71 mmol, 71.4 equiv) in toluene (11.1 mL) was added a solution of KHMDS (0.5 M in toluene, 5.49 mmol, 28 equiv) at 23 °C. The reaction mixture was stirred at 70 °C for 16 h. Upon cooling to 0 °C, THF (22.2 mL) and formalin (37% in water, 11.1 mL) was added, and then the reaction was heated to 50 °C for 4 h. The reaction mixture was diluted with a saturated aqueous solution
of NH₄Cl, extracted with EtOAc (3x), dried over Na₂SO₄, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes, 2x) afforded the title compound as a yellow oil (13.1 mg, 0.05 mmol, 26% yield).

**¹H NMR (400 MHz, CDCl₃):** δ 5.99 (d, J = 1.7 Hz, 1H), 5.17 (d, J = 1.7 Hz, 1H), 4.21 – 4.01 (m, 2H), 3.04 (td, J = 3.1, 2.0 Hz, 1H), 2.27 (ddd, J = 14.2, 11.4, 5.4 Hz, 1H), 2.21 (dd, J = 6.8, 2.0 Hz, 1H), 2.01 (dddd, J = 11.6, 6.5, 4.4, 1.7 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.73 – 1.65 (m, 2H), 1.56 – 1.50 (m, 1H), 1.47 – 1.31 (m, 2H), 1.29 – 1.16 (m, 6H).

**¹³C NMR (100 MHz, CDCl₃):** δ 203.7, 173.8, 144.3, 119.0, 60.8, 51.1, 45.0, 39.1, 37.2, 30.3, 28.9, 26.2, 25.8, 21.3, 21.1, 14.4.

**IR (Neat Film, NaCl):** 2927, 2867, 1732, 1708, 1449, 1180 cm⁻¹.

**HRMS (MM: FD+):** m/z calc’d for C₁₆H₂₂O₃ [M]: 262.1569, found 262.1576.

**Optical Rotation:** [α]D²¹ –3.9 (c 0.38, CHCl₃).

**ethyl (1R,2S,4aR,8aR)-3-hydroxy-3-(hydroxymethyl)-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (78)**

A flame dried vial was charged with enone 77 (14.7 mg, 0.056 mmol, 1 equiv) and acetone (2.3 mL, 0.024 M) and water (0.6 mL, 0.094 M). NMO (50 wt. % in H₂O) (23 µL, 0.112 mmol, 2 equiv) was added and the solution was cooled to 0 °C. K₂OsO₄·2H₂O (2.1 mg, 0.006 mmol, 0.1 equiv) was added to the solution. The resultant solution was slowly warmed to 23 °C. Upon complete consumption of starting material (as determined by TLC),
the reaction was quenched with a saturated solution of Na₂S₂O₃ and stirred for 30 min. The mixture was then diluted with CH₂Cl₂ and the product was extracted with CH₂Cl₂ (2 x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.1 mg, 0.007 mmol, 13% yield, 10:1 dr). In the ¹H NMR, peaks that correspond to the minor diastereomer closely resemble the major diastereomer. dr was determine through integration of ¹H NMR peaks 2.69 ppm (major) and 2.96 ppm (minor).

¹H NMR (400 MHz, CDCl₃): δ 4.15 (q, J = 7.1 Hz, 2H), 3.81 (dd, J = 11.8, 2.6 Hz, 1H), 3.54 (dd, J = 11.9, 2.7 Hz, 1H), 2.71 – 2.67 (m, 1H), 2.38 – 2.24 (m, 2H), 2.10 (d, J = 7.3 Hz, 1H), 1.94 – 1.64 (m, 7H), 1.47 – 1.18 (m, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 218.4, 174.8, 75.8, 65.8, 61.0, 48.9, 45.4, 37.3, 37.2, 30.3, 28.3, 25.6, 22.5, 21.0, 14.3.

IR (Neat Film, NaCl): 3468, 2930, 2355, 1716, 1197, 1033 cm⁻¹.

HRMS (MM: FD⁺): m/z calc’d for C₁₆H₂₄O₅ [M⁺]: 296.1624, found 296.1619.

Optical Rotation: [α]D²¹ 2.1 (c 0.24, CHCl₃).

\[ \text{benzyl (1R,2S,4aR,8aR)-3,4-dioxoctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (79)} \]
To a solution of 41f (0.064 mmol, 1 equiv) in glacial acetic acid (0.1 mL) was added SeO$_2$ (0.077 mmol, 1.2 equiv). The reaction was brought to reflux for 19 h. After cooling to 23 ºC, the reaction mixture was filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in EtOAc and washed with water (5x), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (10.4 mg, 0.031 mmol, 48% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 – 7.28 (m, 5H), 5.19 – 5.04 (m, 2H), 3.00 (m, 1H), 2.54 (dd, $J = 6.4$, 2.3 Hz, 1H), 2.40 (ddd, $J = 14.6$, 10.3, 6.9 Hz, 1H), 2.02 (m, 3H), 1.80 – 1.69 (m, 2H), 1.68 – 1.50 (m, 3H), 1.48 – 1.38 (m, 1H), 1.33 (dt, $J = 13.4$, 3.5 Hz, 1H), 1.29 – 1.15 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.7, 196.1, 173.2, 135.4, 128.8, 128.6, 128.4, 67.4, 49.9, 48.0, 46.3, 37.9, 30.2, 28.3, 25.5, 22.7, 20.5, 20.2.

IR (Neat Film, NaCl): 2932, 2857, 1731, 1454, 1155 cm$^{-1}$.

HRMS (MM: FD+): m/z calc’d for C$_{20}$H$_{22}$O$_4$ [M$^+$]: 326.1518, found 326.1532.

Optical Rotation: $[\alpha]_D^{21} = -49.2$ (c 1.04, CHCl$_3$).

benzyl (1$R$,2$S$,4$a$R,8$a$R)-3,3-dimethoxy-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (80)
To a solution of diketone 79 (0.031 mmol, 1 equiv) in methanol (0.13 mL) was added HC(OMe)$_3$ (1.2 mmol, 38 equiv) and $p$-TsOH$\cdot$H$_2$O (0.031 mmol, 1 equiv). The reaction was stirred for 19 h at 40 °C, followed by dilution with a saturated aqueous solution of NaHCO$_3$. The aqueous layer was extracted with EtOAc (4x), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (4.7 mg, 0.013 mmol, 41% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.29 (m, 5H), 5.26 (d, $J$ = 12.3 Hz, 1H), 5.02 (d, $J$ = 12.3 Hz, 1H), 3.20 (s, 3H), 3.06 (s, 3H), 2.93 (dt, $J$ = 4.2, 2.2 Hz, 1H), 2.29 – 2.11 (m, 3H), 1.98 – 1.89 (m, 1H), 1.83 (dddd, $J$ = 13.8, 11.4, 6.7, 2.4 Hz, 1H), 1.70 – 1.58 (m, 4H), 1.54 (d, $J$ = 3.9 Hz, 1H), 1.31 (dd, $J$ = 10.8, 2.4 Hz, 1H), 1.27 – 1.19 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 209.0, 173.5, 136.5, 128.6, 128.5, 128.2, 97.4, 66.4, 50.4, 48.8, 48.4, 45.5, 36.4, 34.9, 30.0, 29.1, 25.5, 23.1, 21.0, 21.0.

IR (Neat Film, NaCl): 2933, 2855, 1736, 1449, 1172 cm$^{-1}$

HRMS (MM: FD+): m/z calc’d for C$_{22}$H$_{28}$O$_5$ [M$^+$]: 372.1937, found 372.1931.

Optical Rotation: $[\alpha]_{D}^{21}$ –26.2 (c 0.42, CHCl$_3$).

benzyl (1S,2R,4aS,8aR,E)-5-acetoxy-4-(acetoxyimino)octahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (81)
To a stirred solution of ketone 41f (0.096 mmol, 1 equiv) in methanol (0.93 mL) was added NaOAc (0.23 mmol, 2.4 equiv), NH$_2$OH•HCl (0.111 mmol, 1.17 equiv), and water (0.033 mL). The reaction was brought to reflux for 3.5 h and was subsequently cooled to 23 °C and concentrated under reduced pressure. The crude mixture was then diluted with water and extracted with EtOAc (3x), washed with a saturated aqueous solution of NaHCO$_3$ and brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The crude oxime was dissolved in a 1:1 mixture of AcOH/Ac$_2$O (0.78 mL). The reaction vessel was sealed and stirred at 23 °C for 2 h. Pd(OAc)$_2$ (0.0048 mmol, 0.05 equiv) and PhI(OAc)$_2$ (0.288 mmol, 3 equiv) were subsequently added, and the reaction was heated to 100 °C for 16 h. The reaction mixture was cooled to 23 °C, filtered through a silica plug, and the filtrate was diluted with EtOAc. The organic layer was washed with a saturated solution of NaHCO$_3$ until not acidic, washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound (81) as a yellow oil (12.3 mg, 0.0288 mmol, 30% yield over two steps).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 – 7.27 (m, 5H), 5.31 – 5.20 (m, 1H), 5.20 – 5.02 (m, 2H), 2.62 (dt, $J = 20.2$, 3.5 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.27 – 2.17 (m, 1H), 2.14 (s, 3H), 2.02 (s, 3H), 1.89 (m, 1H), 1.83 – 1.69 (m, 4H), 1.62 (t, $J = 2.8$ Hz, 2H), 1.46 – 1.28 (m, 4H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.9, 170.6, 170.4, 168.9, 135.9, 128.8, 128.5, 128.2, 71.7, 66.9, 49.6, 42.2, 39.1, 29.5, 28.9, 28.6, 26.9, 25.5, 23.0, 21.4, 20.2, 16.7.

IR (Neat Film, NaCl): 2930, 1764, 1731, 1456, 1371, 1248, 1210 cm$^{-1}$. 

Optical Rotation: [α]_D^21 –27.6 (c 1.00, CHCl₃).

benzyl (1S,2R,4aR,8aR)-5-acetoxy-4-oxooctahydro-2H-2,4a-ethanonaphthalene-1-carboxylate (82)

To a solution of 81 (0.029 mmol, 1 equiv) in methanol (0.06 mL) in a loosely capped vial was added K₂CO₃ (0.013 mmol, 0.45 equiv) at 23 ºC in three portions over 6 h. NaHSO₃ (0.1 mmol, 3.5 equiv) and water (0.06 mL) were subsequently added, and the vial was sealed and heated to 80 ºC for 3 h. The reaction mixture was diluted with CHCl₃, rinsed with 1 M HCl, and the aqueous layer was extracted with CHCl₃ (3x). The combined organic layers were neutralized with a saturated solution of NaHCO₃, washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (35% EtOAc/hexanes) afforded the title compound as a colorless oil (1.8 mg, 0.0056 mmol, 19% yield).

^1H NMR (400 MHz, CDCl₃): δ 7.41 – 7.30 (m, 5H), 5.19 – 5.06 (m, 3H), 2.48 (m, 1H), 2.41 (dt, J = 19.2, 2.8 Hz, 1H), 2.29 (dt, J = 6.9, 2.0 Hz, 1H), 2.16 – 2.04 (m, 3H), 1.98 (s, 3H), 1.94 – 1.89 (m, 1H), 1.87 – 1.79 (m, 3H), 1.78 – 1.73 (m, 1H), 1.71 (m, 2H), 1.46 – 1.29 (m, 3H).

^13C NMR (100 MHz, CDCl₃): δ 212.2, 173.9, 170.2, 135.9, 128.8, 128.5, 128.3, 70.8, 66.9, 49.4, 48.5, 40.5, 37.9, 30.7, 29.0, 26.7, 25.8, 22.9, 21.3, 15.7.
IR (Neat Film, NaCl): 2928, 1781, 1375, 1246, 1173 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{22}\)H\(_{26}\)O\(_5\) [M\(^+\): 370.1780, found 370.1774.

Optical Rotation: \([\alpha]_D^{21}\) \(-18.3\) (c 0.18, CHCl\(_3\)).

Preparation of Additional Compounds

benzyl (3\(R\),6\(R\),7\(S\),7\(a\)\(R\))-4-oxooctahydro-3\(a\),6-ethanoindene-7-carboxylate (59)\(^{42}\)

To a solution of KHMDS (40 mg, 0.20 mmol, 1.0 equiv) and 18-crown-6 (53 mg, 0.20 mmol, 1 equiv) in THF (2.0 mL) at \(-78^\circ\)C was added a solution of 41\(a\) (60 mg, 0.20 mmol, 1 equiv). Stirring was continued at \(-78^\circ\)C for 30 minutes, then a pre-mixed solution of 3-methylbut-2-en-1-yl 1\(H\)-imidazole-1-carboxylate (43 mg, 0.24 mmol, 1.2 equiv) and boron trifluoride diethyl etherate (30 \(\mu\)L, 0.24 mmol, 1.2 equiv) in THF (1.2 mL) was added dropwise. After two additional hours of stirring at \(-78^\circ\)C, EtOAc and saturated aqueous NH\(_4\)Cl were added. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and solvent was removed in vacuo. The crude mixture was purified by silica gel flash column chromatography (0–40% EtOAc/hexanes) to afford enol carbonate 59 as a colorless oil (44 mg, 0.11 mmol, 55% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39 – 7.29 (m, 5H), 5.70 (d, \(J = 6.8\) Hz, 1H), 5.42 – 5.36 (m, 1H), 5.09 (d, \(J = 3.6\) Hz, 2H), 4.65 (d, \(J = 7.3\) Hz, 2H), 3.08 – 2.96 (m, 1H), 2.25 (d, \(J\)
= 5.6 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.91 – 1.79 (m, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.63 – 1.54 (m, 2H), 1.52 – 1.38 (m, 3H), 1.35 – 1.28 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 174.9, 155.6, 153.5, 140.6, 136.4, 128.7, 128.2, 128.0, 117.9, 112.8, 66.3, 65.3, 51.3, 48.1, 48.1, 35.5, 28.4, 28.4, 27.3, 25.9, 24.6, 22.8, 18.3.

IR (Neat Film, NaCl): 2953, 2870, 1754, 1735, 1241, 1226, 1150 cm⁻¹


SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, tR (min): minor = 3.05, major = 3.40.

4.4.3 DETERMINATION OF ABSOLUTE AND RELATIVE STEREOCHEMISTRY BY VCD SPECTROSCOPY

Experimental Protocol: A solution of the compound of interest (50 mg/mL) in CDCl3 was loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF2 windows and a 100 mm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a set of 24 one-hour blocks (24 blocks, 3120 scans per block) in dual PEM mode. A 15-minute acquisition of neat (+)-α-pinene control yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background corrected using a 30-minute block IR acquisition of the empty instrument chamber under gentle N2 purge, and were solvent corrected using a 16-hour (16 blocks, 3120 scans per block) IR/VCD acquisition of CDCl3 in the same 100 μm BaF2 cell. The reported spectra represent the result of block averaging.

Both enantiomers of compounds 41a, 41q, and 41q’ were prepared from the (S) and (R) enantiomers of the t-BuPHOX ligand. Data were collected for both enantiomers of
compounds at identical concentration and the final reported VCD spectra are the half-difference of the spectra of the compounds derived from the (S) minus (R) enantiomer of ligand. Due to limited sample size, spectra of cycloadducts 41k’ and 41k” were collected at concentrations of 11.7 and 9.3 mg/mL, respectively.

**Computational Protocol:** An arbitrarily chosen enantiomer of the compound of interest was subjected to an exhaustive initial molecular mechanics-based conformational search (OPLS_2005 force field, CHCl₃ solvent, 10.0 kcal/mol cutoff, “Enhanced” torsional sampling) as implemented in MacroModel program. The resulting ensemble of conformers was subsequently optimized using the B3PW91 functional, cc-pVTZ(-f) basis, and implicit PBF solvation model for chloroform using the Jaguar program. Harmonic frequencies computed at the B3PW91/cc-pVTZ(-f)/PBF(chloroform) level were scaled by 0.98. The resultant structurally unique conformers possessing all positive Hessian eigenvalues were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities of the retained conformers were convolved using Lorentzian line shapes (γ = 4 cm⁻¹) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra. The predicted VCD of the opposite enantiomer was generated by inversion of sign.
VCD Analysis for diastereomers 41a, 41p, and 41p’

Figure 3.9. Three diastereomers 41a, 41q, and 41q’ to be compared to spectra computed from all eight possible stereoisomers.
Figure 3.10. Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_endo-trans.\(^a\)

[109x674]Figure 3.10. Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_endo-trans.\(^a\)

[126x361][a] Experimental IR spectrum in good agreement with computed spectrum. Experimental VCD spectrum for 41a is in excellent agreement with computed spectrum for ent-A_endo-trans.

Figure 3.11. Overlayed experimental and calculated VCD spectra for 41a – assigned as ent-A_endo-trans.
Figure 3.12. Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_exo-trans.\textsuperscript{a}

[a] A shift of –3 cm\textsuperscript{-1} along x-axis applied to computed spectra in fitting. Experimental data from 41a do not match computed data of A_exo-trans.
Figure 3.13. Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_endo-cis.^[a]

[a] Experimental data from 41a do not match computed data of A_endo-cis.
Figure 3.14. Comparison of experimental VCD and IR spectra for product 41a to computed spectra for A_exo-cis.\textsuperscript{a}

\textsuperscript{a} A shift of –3 cm\textsuperscript{-1} along x-axis applied to computed spectra in fitting. Experimental data from 41a do not match computed data of A_exo-cis.
**Figure 3.15.** Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_{endo-trans}.\(^a\)

[a] A shift of +14 cm\(^{-1}\) along x-axis applied to computed spectra in fitting. The IR spectrum of 41q contains similar features to the calculated spectrum for A_{endo-trans}; however, the VCD spectrum displays large discrepancies at 1174, 1152, 1330, 1076, and 992 cm\(^{-1}\). 41q is not assigned as A_{endo-trans}.  

---
Figure 3.16. Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_exo-trans.

[a] Experimental data from 41q do not match computed data of A_exo-trans.
Figure 3.17. Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_endo-cis.

[a] A shift of +5 cm\(^{-1}\) along x-axis applied to computed spectra in fitting. The IR spectrum of 41q is in good agreement with that of the computed IR spectrum of A_endo-cis. Experimental VCD spectrum for 41q is in excellent agreement with computed spectrum for ent-A_endo-cis.

Figure 3.18. Overlayed experimental and calculated VCD spectra for 41q – assigned as ent-A_endo-cis.
Figure 3.19. Comparison of experimental VCD and IR spectra for product 41q to computed spectra for A_exo-cis.\textsuperscript{a}

\textsuperscript{a} Experimental data from 41q do not match computed data of A_exo-cis.
Figure 3.20. Comparison of experimental VCD and IR spectra for product 41q' to computed spectra for A_endo-trans.\textsuperscript{a}

\textsuperscript{a} The VCD spectrum was baseline-corrected with a shift of +7 cm\textsuperscript{-1} along y-axis. Experimental data from 41q' do not match computed data of A_endo-trans.
**Figure 3.21.** Comparison of experimental VCD and IR spectra for product $41q'$ to computed spectra for $A_{exo-trans}$.

[a] The VCD spectrum of $41q'$ was baseline-corrected with a shift of +7 cm$^{-1}$ along y-axis. A shift of -15 cm$^{-1}$ along x-axis applied to computed spectra in fitting. Experimental data from $41q'$ do not match computed data of $A_{exo-trans}$. 
**Figure 3.22.** Comparison of experimental VCD and IR spectra for product 41q' to computed spectra for A_endo-cis.\(^a\)

[a] The VCD spectrum of 41q' was baseline-corrected with a shift of +7 cm\(^{-1}\) along y-axis. Experimental data from 41q' do not match computed data of A_endo-cis.
**Figure 3.23.** Comparison of experimental VCD and IR spectra for product 41q’ to computed spectra for A_exo-cis.\(^a\)

![Comparison of experimental VCD and IR spectra for product 41q’ to computed spectra for A_exo-cis.](image)

\(^a\) The VCD spectrum of 41q’ was baseline-corrected with a shift of +7 cm\(^{-1}\) along y-axis. A shift of +7 cm\(^{-1}\) along x-axis applied to computed spectra in fitting. Experimental VCD spectrum for 41q’ is in good agreement with computed spectrum for ent-A_exo-cis.

**Figure 3.24.** Overlayed experimental and calculated VCD spectra for 41q’ – assigned as ent-A_exo-cis.

![Overlayed experimental and calculated VCD spectra for 41q’](image)
Figure 3.25. Three diastereomers $41k$, $41k'$, and $41k''$ to be compared to spectra computed from all eight possible stereoisomers.
**Figure 3.26.** Experimental VCD and IR spectra for product 41k compared to computed spectra for B_endo-trans.^[a]

[a] Experimental IR spectrum in good agreement with computed spectrum. Experimental VCD spectrum for 41k is in excellent agreement with computed spectrum for B_endo-trans.

**Figure 3.27.** Overlaid experimental and calculated VCD spectra for 41k – assigned as B_endo-trans.
Figure 3.28. Experimental VCD and IR spectra for product 41k compared to computed spectra for B_exo-trans.\textsuperscript{a}

\textsuperscript{a} Experimental IR spectrum in good agreement with computed spectrum. However, VCD spectrum contain key sign mismatches in regions around 1400 and 1100 cm\textsuperscript{-1}. Hence, 41k is not assigned as B_exo-trans.
**Figure 3.29.** Experimental VCD and IR spectra for product \(41k\) compared to computed spectra for \(B_{endo-cis}\).\(^a\)

\[\text{Experimental data do not match computed data and } 41k \text{ is not assigned as } B_{endo-cis}.\]

\(^a\) Experimental data do not match computed data and \(41k\) is not assigned as \(B_{endo-cis}\).
Figure 3.30. Experimental VCD and IR spectra for product 41k compared to computed spectra for B_exo-cis.\(^a\)

[a] Experimental data do not match computed data and 41k is not assigned as B_exo-cis.

Due to limited sample size (< 3 mg), useful VCD spectra of 41k’ were unable to be obtained. Enantiomeric series was assigned by analogy to the 41a, 41q and 41q’ series. The 1000–1500 cm\(^{-1}\) region of the IR spectra are still analyzed to support relative stereochemical assignments made by 2D NMR.
Figure 3.31. Experimental IR spectrum for product $41k'$ compared to computed spectra for $\text{B}_\text{endo-trans}$ (top left), $\text{B}_\text{exo-trans}$ (top right), $\text{B}_\text{endo-cis}$ (bottom left), $\text{B}_\text{exo-cis}$ (bottom right).\(^a\)

[a] The trans relationship is supported, in accord with 2D NMR data. In contrast to endo-cis and exo-cis, the computed IR spectra for both endo-trans and exo-trans are similar and do not offer key features for distinguishing the two. Given the trans stereochemistry, with $41k$ known as $\text{B}_\text{endo-trans}$, $41k'$ is assigned as $\text{B}_\text{exo-trans}$ with absolute stereochemistry assigned based on analogy to $41q'$. 


Figure 3.32. Experimental VCD and IR spectra for product $41k''$ compared to computed spectra for $\text{B}_\text{endo-trans}$.$^a$

[a] Experimental data do not match computed data and $41k''$ is not assigned as $\text{B}_\text{endo-trans}$. 
Figure 3.33. Experimental VCD and IR spectra for product \(41k''\) compared to computed spectra for B\_exo\_trans.\(^a\)

[a] Experimental data do not match computed data and \(41k''\) is not assigned as B\_exo\_trans.
Figure 3.34. Experimental VCD and IR spectra for product 41k'' compared to computed spectra for B_endo-cis.\(^a\)

[a] Experimental IR spectrum is in agreement with the computed spectrum of B_endo-cis. Assignment of absolute stereochemistry is based on the sign of the three most intense peaks in VCD spectrum, 1368, 1350, and 1085 cm\(^{-1}\). These match B_endo-cis, the same enantiomeric series as 41k.

Figure 3.35. Overlayed experimental and calculated VCD spectra for 41k'' – assigned as B_endo-cis.
Figure 3.36. Experimental VCD and IR spectra for product 41k” compared to computed spectra for B_exo-cis.\textsuperscript{a}

[a] Experimental data do not match computed data and 41k” is not assigned as B_exo-cis.
3.4.4 2D NMR ANALYSIS OF SELECT COMPOUNDS

Figure 3.37. $^1H-^1H$ COSY NMR spectrum of 41a (400 MHz, CDCl$_3$).
Figure 3.38. $^1$H-$^{13}$C HSQC NMR spectrum of 41a (400 MHz, CDCl₃).

Figure 3.39. $^1$H-$^1$H NOESY NMR spectrum of 41a (400 MHz, CDCl₃).
Figure 3.40. $^1$H–$^1$H COSY NMR spectrum of 41p (400 MHz, CDCl$_3$).

Figure 3.41. $^1$H–$^{13}$C HSQC NMR spectrum of 41p (400 MHz, CDCl$_3$).
**Figure 3.42.** $^1$H-$^1$H NOESY NMR spectrum of 41p (400 MHz, CDCl$_3$).

**Figure 3.43.** $^1$H-$^1$H COSY NMR spectrum of 41q (400 MHz, CDCl$_3$).
**Figure 3.44.** $^1H$-$^13C$ HSQC NMR spectrum of 41q (400 MHz, CDCl$_3$).

**Figure 3.45.** $^1H$-$^1H$ NOESY NMR spectrum of 41q (400 MHz, CDCl$_3$).
Figure 3.46. $^1$H–$^1$H COSY NMR spectrum of 41q' (400 MHz, CDCl$_3$).

Figure 3.47. $^1$H–$^{13}$C HSQC NMR spectrum of 41q' (400 MHz, CDCl$_3$).
Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates

Figure 3.48. $^1$H–$^1$H NOESY NMR spectrum of 41q’ (400 MHz, CDCl₃).

3.4.5 GENERAL COMPUTATIONAL DETAILS

General Notes

All quantum mechanics calculations were carried out with the ORCA program. All geometry optimizations, harmonic frequency calculations, and single-point energy evaluations were carried out with density functional theory (DFT). The PBE0 functional paired with Becke–Johnson damped D4 dispersion corrections, henceforth referred to as PBE0-D4, was used as it has proven a robust method for such systems in our prior studies. For geometry optimization and harmonic frequency calculations, Pd is described by the def2-TZVP basis set and the ECP28MWB small-core (18 explicit valence electrons) quasi-relativistic pseudopotential, while C, H, N, and P are assigned the def2-SVP basis. Diffuse functions are added to oxygen (ma-def2-SVP). Herein, we refer to this composite...
basis set as BS1. Geometry optimization and harmonic frequency calculations were carried out with the CPCM implicit solvation model for toluene (PhMe, \( \varepsilon = 2.4 \)). For all calculations employing CPCM, surface charges are described by the improved Gaussian charge scheme of Neese and coworkers with a scaled Van der Waals cavity \( (\alpha = 1.2) \). All Hessians were computed analytically. Stationary points are characterized by the correct number of imaginary vibrational modes (zero for minima and one for saddle points). Intrinsic reaction coordinate (IRC) analysis confirms the nature of transition states. Cartesian coordinates of all optimized structures are included as “.xyz” files are available online in a compressed zip file format.

Electronic energies are further refined with single-point calculations employing the PBE0-D4 functional and the def2-TZVPP basis set on all atoms (with the ECP28MWB pseudopotential for Pd) with additional diffuse functions on O (ma-def2-TZVPP). This mixed basis is henceforth referred to as BS2. Solvation was accounted for with CPCM as mentioned above (PhMe, \( \varepsilon = 2.4 \)). Final Gibbs free energies were obtained by applying thermodynamic corrections obtained at the optimization level of theory to these refined electronic energies. Thermodynamic corrections from harmonic frequency calculations employ the quasi-ridged rotor harmonic oscillator approach to correct for the breakdown of the harmonic oscillator approximation at low vibrational frequencies. Note that free energies are adjusted to a 1 M standard state. The translational \( (S_{\text{trans}}) \) and rotational entropy \( (S_{\text{rot}}) \) contributions to the Gibbs free energy calculated for a complex in condensed phase are \( ca. 40\text{–}60\% \) of the values obtained assuming an ideal gas. As suggested in the literature, \( S_{\text{trans}} \) and \( S_{\text{rot}} \) obtained by ideal gas treatment are scaled by a factor of 0.5 to
obtain the final condensed phase values.\textsuperscript{63} Hence, the Gibbs free energy at 333.15 K is calculated as:

$$
G_{solv}^* = E_{el,solv}^{BS2} + ZPE + E_{trans} + E_{rot} + E_{vib} + k_B T - T \left( S_{el} + S_{vib} + \frac{1}{2} S_{trans} + \frac{1}{2} S_{rot} \right)
$$

$$
+ \Delta G^{0\rightarrow*}
$$

The resolution of identity (RI) and Chain-of-Spheres (COS) approximations are employed for efficient evaluation of Coulomb and exchange integrals, respectively.\textsuperscript{64} The def2/J auxiliary basis\textsuperscript{65} is employed for all atoms except oxygen, for which a suitable auxiliary was obtained via the automatic generation algorithm in the ORCA program (keyword: \textit{AutoAux}).\textsuperscript{66} Very fine grid settings are employed in all calculations (optimization/frequency calculations: DefGrid2, single point calculations: DefGrid3).

Conformer searching was carried out for each stationary point using the meta-dynamics-based CREST program (using GNF-FF) from the Grimme group. Duplicate conformers were removed, and low energy conformers were subsequently optimized and energies evaluated at the cheaper PBE0-D4/def2-TZVP (Pd), ma-def2-SVP (O), def2-SVP/CPCM(PhMe)//PBE-D4/def2-TZVP (Pd), ma-def2-SV(P) (O), def2-SV(P) level of theory. The final low energy conformers were further optimized at the level of theory mentioned prior. Note that for enantiodetermining transition states (such as TS2 and TS3) conformer searching also explicitly includes rotation about the Pd–O–C–C(enolate) dihedral, consideration of s-cis and s-trans ester conformations, as well as all permutations of the considered stereochemical elements.
Finally, conformational entropy\(^6\) (entropy arising from multiple low energy thermally populated conformers) is accounted for by the \textit{mixture of components} model of DeTar.\(^8\) Conformational entropy \(S_{\text{conf}}\) is defined as:

\[
S_{\text{conf}} = -R \sum \chi_i \ln (\chi_i)
\]

where \(\chi_i\) is the mole fraction (thermal population) of the \(i\)th conformer based on its relative free energy within the conformer ensemble. Given the computational demand for computing free energies for large ensembles of conformers, \(\chi_i\) was derived from the free energies initially computed during the conformer screening process (PBE0-D4/def2-TZVP (Pd), ma-def2-SVP (O), def2-SVP/PCM(PhMe)//PBE-D4/def2-TZVP (Pd), ma-def2-SV(P) (O), def2-SV(P))

\[
G_{\text{final}} = G_{\text{solv}}^* - T S_{\text{conf}}
\]

For the systems at hand, values of \(TS_{\text{conf}}\) (at 333.15 K) can be on the order of magnitude of a few kcal/mol.

**Comparison of Barrier Heights to Inner-sphere Reductive Elimination**

Employing cyclohexanone-derived Pd enolate as a model system\((13, 116, 117)\), the barrier to inner-sphere reductive elimination was investigated while varying substitution on the allyl moiety (Figure 3.49). For further discussion on the seven-centered cyclic reductive elimination process, see Chapters 1–2.
Figure 3.49. Relative free energies for various inner-sphere reductive elimination transition states from allyl (13), cinnamyl (116), and prenyl (117) complexes.  

<table>
<thead>
<tr>
<th>Starting Enolate</th>
<th>“Me up” (Si face) [Disfavored]</th>
<th>“Me down” (Re face) [Favored]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="13" /></td>
<td><img src="image" alt="TS20" /></td>
<td><img src="image" alt="TS20" /></td>
</tr>
<tr>
<td>$G_{rel} = 0.0$</td>
<td>$G_{rel} = 16.0$</td>
<td>$G_{rel} = 14.9$</td>
</tr>
<tr>
<td><img src="image" alt="116" /></td>
<td><img src="image" alt="TS29" /></td>
<td><img src="image" alt="TS29" /></td>
</tr>
<tr>
<td>$G_{rel} = 0.0$</td>
<td>$G_{rel} = 22.4$</td>
<td>$G_{rel} = 21.6$</td>
</tr>
<tr>
<td><img src="image" alt="117" /></td>
<td><img src="image" alt="TS29" /></td>
<td><img src="image" alt="TS29" /></td>
</tr>
<tr>
<td>$G_{rel} = 0.0$</td>
<td>$G_{rel} = 25.1$</td>
<td>$G_{rel} = 25.1$</td>
</tr>
</tbody>
</table>

[a] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.

Mechanism of Catalyst Turnover

Of all the sampled transition states, we found the outer-sphere and N-detached inner-sphere pathways to be highly competitive and lowest in energy. Additional transition states were
also explored, and the lowest energy pathway of each type of mechanism are shown in the following table.

**Figure 3.50.** Relative free energies for various proton transfer transition states from post-cycloaddition enolate 56.

<table>
<thead>
<tr>
<th>Starting Enolate</th>
<th>Inner-Sphere Pathways</th>
<th>Pd–H Transfer to Enolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS34 $G_{rel} = 32.5$</td>
<td>TS35 $G_{rel} = 45.2$</td>
</tr>
<tr>
<td>$G_{rel} = 0.0$</td>
<td></td>
<td>TS36 $G_{rel} = 31.8$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-Hydride Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS37 $G_{rel} = 64.5$</td>
</tr>
<tr>
<td>TS38 $G_{rel} = 55.6$</td>
</tr>
<tr>
<td>TS39 $G_{rel} = -29-30$</td>
</tr>
</tbody>
</table>

[a] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.

**Mechanism of Premature Protonation**

Analogous to the catalyst turnover mechanism, N-detached inner-sphere pathways were found to be lowest-energy for premature protonation. Of these transition states (TS40a and TS40b) that would yield enantiomeric protonation products, the lowest-energy TS40a provides the enantiomer consistent with the major reaction product. In addition, an outer-sphere pathway (TS41) was also found to be competitive.
Figure 3.51. Relative free energies for various proton transfer transition states from pre-cycloaddition enolate 55.\[^a\]

<table>
<thead>
<tr>
<th>Starting Enolate</th>
<th>N-Detached Inner-Sphere Pathways</th>
<th>Outer-Sphere Pathway</th>
</tr>
</thead>
</table>
| ![Structure 55](image)  
\[G_{\text{rel}} = 0.0\] | ![Structure TS40a](image)  
\[G_{\text{rel}} = 20.2\] | ![Structure TS41](image)  
\[G_{\text{rel}} = 23.4\] |

\[^a\] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.
Intrinsic Bonding Orbital (IBO) Analysis of Inner-sphere Proton Transfer

IBO analysis along the reaction coordinate of the N-detached inner-sphere proton transfer to post-cycloaddition enolate confirms the role of prenyl as a proton source.

Figure 3.52. IBO analysis of N-detached inner-sphere mechanism and corresponding derived arrow-pushing mechanism.
pKa Calculations and Thermodynamics of Outer-Sphere Proton Transfer

The pKₐ values of the π-allyl Pd complex 118 and ketones were calculated, and the results verify that the proton transfers to both pre- and post-cycloaddition enolates are thermodynamically favorable.

**Figure 3.53.** Computed pKₐ values of cationic π-allyl Pd complex 119 and ketones 49a and 41a.
Enantiodetermining [4+2] cycloaddition

**Figure 3.54.** (A) Comparison of internal versus external dienophile approach to both enantiotopic diene faces. (B) Select low energy conformers of TS31 (allyl isomers not pictured). (C) Additional space-filling models for TS30 and TS31.

**A. External versus internal dienophile approach in pathways to 41a and (ent)-41a.**

<table>
<thead>
<tr>
<th></th>
<th>TS leading to 41a</th>
<th>TS leading to ent-41a (minor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS30</td>
<td><img src="TS30.png" alt="Image" /></td>
<td><img src="TS30_ent.png" alt="Image" /></td>
</tr>
<tr>
<td>∆G‡_{rel}</td>
<td>0.0 kcal/mol [Favored]</td>
<td>6.4 kcal/mol</td>
</tr>
</tbody>
</table>

**B. Select low energy conformers of TS31:**

- ![Image](TS31_1.png) (G_{rel} = 1.6 kcal/mol)
- ![Image](TS31_2.png) (G_{rel} = 2.3 kcal/mol)
- ![Image](TS31_3.png) (G_{rel} = 2.3 kcal/mol)

**C. Additional space-filling models for TS30 versus TS31:**

- TS30 [Favored]
- TS31 [Disfavored]
4.5 REFERENCES AND NOTES


Chapter 3 – Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates


(10) (a) Ihara, M.; Ishida, Y.; Abe, M.; Toyota, M.; Fukumoto, K.; Kametani, T. Stereocontrolled Synthesis of the CDF Part of Aconitum Alkaloids via

(11) All quantum mechanics calculations were carried out with the ORCA program. Neese, F. Software Update: The ORCA Program System—Version 5.0. *WIREs Computational Molecular Science* 2022, 12, e1606.


(14) Error bars are present for 40f to 41f/49f – they are smaller than the marker size in the figure.


(16) Unfortunately, attempts to further disfavor TS31 by ortho-substitution of the PHOX ligand phenyl groups thwarted reactivity.


(19) Note that on smaller scales (0.02 mmol) the ratio of D-41f to D-49f is 6.7:1 – in accord with a primary KIE. We hypothesize this may arise from the highly temperature-dependent nature of the product distribution paired with less homogenous reaction solution temperature on larger scales.


(22) Kim, K. E.; Sakazaki, Y.; Stoltz, B. M. Synthesis of Non-Natural Cyanthiwigin–Gagunin Hybrids through Late-Stage Diversification of the Cyanthiwigin Natural Product Core. Tetrahedron 2020, 76, 130755.


(34) Fulton, T. J.; Cusumano, A. Q.; Alexy, E. J.; Du, Y. E.; Zhang, H.; Houk, K. N.; Stoltz, B. M. Global Diastereoconvergence in the Ireland–Claisen Rearrangement...


(49) Yang, J.; Lu, K.; Li, C.; Zhao, Z.; Zhang, X.; Zhang, F.; Tu, Y. Chiral 1,2,3-Triazolium Salt Catalyzed Asymmetric Mono- and Dialkylation of 2,5-Diketopiperazines with the Construction of Tetrasubstituted Carbon Centers. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114129.

(50) **Schrödinger Release 2021-4**: MacroModel, Schrödinger, LLC, New York, NY, 2021.


(60) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of


APPENDIX 2

Spectra Relevant to Chapter 3: Catalytic Asymmetric [4+2] Cycloaddition of Pd Enolates
Figure A2.1. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41a.
Figure A2.2. Infrared spectrum (Thin Film, NaCl) of compound 41a.

Figure A2.3. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41a.
Figure A2.4. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41b.
Figure A2.5. Infra-red spectrum (Thin Film, NaCl) of compound 41b.

Figure A2.6. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41b.
Figure A2.7. $^1H$ NMR (400 MHz, CDCl$_3$) of compound 41c.
Figure A2.8. Infrared spectrum (Thin Film, NaCl) of compound 41c.

Figure A2.9. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41c.
Figure A2.10. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41d.
Figure A2.11. Infrared spectrum (Thin Film, NaCl) of compound 41d.

Figure A2.12. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41d.
Figure A2.13. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41f.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.14. Infrared spectrum (Thin Film, NaCl) of compound 41f.

Figure A2.15. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41f.
Figure A2.16. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41j.
Figure A2.17. Infrared spectrum (Thin Film, NaCl) of compound 41j.

Figure A2.18. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41j.
Figure A2.19. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41k.
Figure A2.20. Infrared spectrum (Thin Film, NaCl) of compound 41k.

Figure A2.21. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41k.
Figure A2.22. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41k'.
**Figure A2.23.** Infrared spectrum (CDCl₃ solution) of compound 41k'.

**Figure A2.24.** ¹³C NMR (100 MHz, CDCl₃) of compound 41k'.
Figure A2.5. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41k".
Figure A2.26. Infrared spectrum (CDCl₃ solution) of compound 41k''.

Figure A2.27. $^{13}$C NMR (100 MHz, CDCl₃) of compound 41k''.
Figure A2.28. $^1$H NMR (400 MHz, CDCl$_3$) of compound 411.
Figure A2.29. Infrared spectrum (Thin Film, NaCl) of compound 41l.

Figure A2.30. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41l.
Figure A2.31. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41m.
Figure A2.32. Infrared spectrum (Thin Film, NaCl) of compound 41m.

Figure A2.33. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41m.
Figure A2.34. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41m'.

Structure of 41m'.
Figure A2.35. Infrared spectrum (Thin Film, NaCl) of compound 41m'.

Figure A2.36. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41m'.
Figure A2.37. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41n.
Figure A2.38. Infrared spectrum (Thin Film, NaCl) of compound 41n.

Figure A2.39. $^1$C NMR (100 MHz, CDCl$_3$) of compound 41n.
Figure A2.40. $^1$H NMR (400 MHz, CDCl$_3$) of compound 410.
Figure A2.41. Infrared spectrum (Thin Film, NaCl) of compound 41o.

Figure A2.42. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41o.
Figure A2.43. $^1$H NMR (400 MHz, CDCl$_3$) of compound 410'.
Figure A2.44. Infrared spectrum (Thin Film, NaCl) of compound 41o'.

Figure A2.45. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41o'.
Figure A2.46. $^1$H NMR (400 MHz, CDCl$_3$) of compound $41p$. 
Figure A2.47. Infrared spectrum (Thin Film, NaCl) of compound 41p.

Figure A2.48. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41p.
Figure A2.49. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41p'.

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41p':

- $\delta$ (ppm) 125.5 (s, C=O)
- $\delta$ (ppm) 128.2 (s, C=O)
- $\delta$ (ppm) 134.1 (s, C=O)
- $\delta$ (ppm) 138.4 (s, C=O)
- $\delta$ (ppm) 142.7 (s, C=O)

$^1$H NMR (400 MHz, CDCl$_3$) of compound 41p':

- $\delta$ (ppm) 1.0 (s, 3H, Me)
- $\delta$ (ppm) 2.0 (s, 3H, Me)
- $\delta$ (ppm) 3.5 (s, 3H, Me)
- $\delta$ (ppm) 4.5 (s, 3H, Me)
- $\delta$ (ppm) 5.5 (s, 3H, Me)
- $\delta$ (ppm) 6.5 (s, 3H, Me)
- $\delta$ (ppm) 7.5 (s, 3H, Me)
- $\delta$ (ppm) 8.5 (s, 3H, Me)
**Figure A2.50.** Infrared spectrum (Thin Film, NaCl) of compound 41p'.

**Figure A2.51.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41p'.
Figure A2.52. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41q.
Figure A2.53. Infrared spectrum (Thin Film, NaCl) of compound 41q.

Figure A2.54. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41q.
Figure A2.55. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41q'.
Figure A2.56. Infrared spectrum (Thin Film, NaCl) of compound 41q'.

Figure A2.57. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41q'.
Figure A2.5.8. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41r.
Figure A2.59. Infrared spectrum (Thin Film, NaCl) of compound 41r.

Figure A2.60. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41r.
Figure A2.61. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41s.
Figure A2.62. Infrared spectrum (Thin Film, NaCl) of compound 41s.

Figure A2.63. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41s.
Figure A2.6.4. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41t.
Figure A2.65. Infrared spectrum (Thin Film, NaCl) of compound 41t.

Figure A2.66. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41t.
Figure A2.67. $^1$H NMR (400 MHz, CDCl₃) of compound 41t'.

Appendix 2 – Spectra Relevant to Chapter 3
Figure A2.68. Infrared spectrum (Thin Film, NaCl) of compound 41t'.

Figure A2.69. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41t'.
Figure A2.70. $^1$H NMR (400 MHz, CDCl$_3$) of compound 41u.
Figure A2.71. Infrared spectrum (Thin Film, NaCl) of compound 41u.

Figure A2.72. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 41u.
Figure A2.73. $^1$H NMR (400 MHz, CDCl$_3$) of compound D-41f.
Figure A2.74. Infrared spectrum (Thin Film, NaCl) of compound D-41f.

Figure A2.75. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-41f.
Figure A2.76. $^2$H NMR (61 MHz, CDCl$_3$) of compound D-41f.
Figure A2.77. $^1$H NMR (400 MHz, CDCl$_3$) of compound 44.
Figure A2.78. Infrared spectrum (Thin Film, NaCl) of compound 44.

Figure A2.79. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 44.
Figure A2.80. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40a.
Figure A2.81. Infrared spectrum (Thin Film, NaCl) of compound 40a.

Figure A2.82. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40a.
Figure A2.83. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40b.
Figure A2.84. Infrared spectrum (Thin Film, NaCl) of compound 40b.

Figure A2.85. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40b.
Figure A2.86. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40c.
Figure A2.87. Infrared spectrum (Thin Film, NaCl) of compound 40c.

Figure A2.88. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40c.
Figure A2.89. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40d.
Figure A2.90. Infrared spectrum (Thin Film, NaCl) of compound 40d.

Figure A2.91. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40d.
Figure A2.92. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40e.
Figure A2.93. Infrared spectrum (Thin Film, NaCl) of compound 40e.

Figure A2.94. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40e.
Figure A2.95. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40f.
Figure A2.96. Infrared spectrum (Thin Film, NaCl) of compound 40f.

Figure A2.97. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40f.
Figure A2.98. $^1\text{H}$ NMR (400 MHz, CDCl$_3$) of compound D-40f.
Figure A2.99. Infrared spectrum (Thin Film, NaCl) of compound D-40f.

Figure A2.100. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-40f.
Figure A2.101. $^2$H NMR (61 MHz, CDCl$_3$) of compound D-40f.
Figure A2.102: $^1$H NMR (400 MHz, CDCl$_3$) of compound 40g.
Figure A2.103. Infrared spectrum (Thin Film, NaCl) of compound 40g.

Figure A2.104. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40g.
Figure A2.105. $^1H$ NMR (400 MHz, CDCl$_3$) of compound 40h.
Figure A2.106. Infrared spectrum (Thin Film, NaCl) of compound 40h.

Figure A2.107. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40h.
Figure A2.108. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40i.
Figure A2.109. Infrared spectrum (Thin Film, NaCl) of compound 40i.

Figure A2.110. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40i.
Figure A2.111. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40j.
Figure A2.112. Infrared spectrum (Thin Film, NaCl) of compound 40j.

Figure A2.113. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40j.
Figure A2.114. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40k.
Figure A2.115. Infrared spectrum (Thin Film, NaCl) of compound 40k.

Figure A2.116. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40k.
Figure A2.117. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40l.
Figure A2.118. Infrared spectrum (Thin Film, NaCl) of compound 40l.

Figure A2.119. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40l.
Figure A2.120. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40m.
Figure A2.121. Infrared spectrum (Thin Film, NaCl) of compound 40m.

Figure A2.122. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40m.
Figure A2.123. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40n.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.124. Infrared spectrum (Thin Film, NaCl) of compound 40n.

Figure A2.125. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40n.
Figure A2.126. $^1$H NMR (400 MHz, CDCl$_3$) of compound 400.
Figure A2.127. Infrared spectrum (Thin Film, NaCl) of compound 40o.

Figure A2.128. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40o.
Figure A2.129. $^1$H NMR (400 MHz, CDCl$_3$) of compound 99.
Figure A2.130. Infrared spectrum (Thin Film, NaCl) of compound 99.

Figure A2.131. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 99.
Figure A2.132. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40p.
Figure A2.133. Infrared spectrum (Thin Film, NaCl) of compound 40p.

Figure A2.134. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40p.
Figure A2.135. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40q.
Figure A2.136. Infrared spectrum (Thin Film, NaCl) of compound 40q.

Figure A2.137. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40q.
Figure A2.138. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40r.
Appendix 2 – Spectra Relevant to Chapter 3

**Figure A2.139.** Infrared spectrum (Thin Film, NaCl) of compound 40r.

**Figure A2.140.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40r.
Figure A2.141. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40s.
Figure A2.142. Infrared spectrum (Thin Film, NaCl) of compound 40s.

Figure A2.143. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40s.
Figure A2.144. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40t.
Figure A2.145. Infrared spectrum (Thin Film, NaCl) of compound 40t.

Figure A2.146. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40t.
Figure A2.147. $^1$H NMR (400 MHz, CDCl$_3$) of compound 40u.
Figure A2.148. Infrared spectrum (Thin Film, NaCl) of compound 40u.

Figure A2.149. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 40u.
Figure A2.150. $^1$H NMR (400 MHz, CDCl$_3$) of compound 42.
Figure A2.151. Infrared spectrum (Thin Film, NaCl) of compound 42.

Figure A2.152. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 42.
Figure A2.153. $^1$H NMR (400 MHz, CDCl$_3$) of compound 47.
Figure A2.154. Infrared spectrum (Thin Film, NaCl) of compound 47.

Figure A2.155. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 47.
Figure A2.156. $^1$H NMR (400 MHz, CDCl$_3$) of compound 101.
Figure A2.157. Infrared spectrum (Thin Film, NaCl) of compound 101.

Figure A2.158. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 101.
Figure A2.159. $^1$H NMR (400 MHz, CDCl$_3$) of compound 102.
**Figure A2.160.** Infrared spectrum (Thin Film, NaCl) of compound 102.

**Figure A2.161.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 102.
Figure A2.162. $^1$H NMR (400 MHz, CDCl$_3$) of compound 85.
Figure A2.163. Infrared spectrum (Thin Film, NaCl) of compound 85.

Figure A2.164. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 85.
Figure A2.165. $^1$H NMR (400 MHz, CDCl$_3$) of compound 86.
Figure A2.166. Infrared spectrum (Thin Film, NaCl) of compound 86.

Figure A2.167. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 86.
Figure A2.168. $^1$H NMR (400 MHz, CDCl$_3$) of compound D-86.
Figure A2.169. Infrared spectrum (Thin Film, NaCl) of compound D-86.

Figure A2.170. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-86.
**Figure A2.171.** $^1$H NMR (61 MHz, CHCl$_3$) of compound **D-86**.
Figure A2.172. $^1$H NMR (400 MHz, CDCl$_3$) of compound 87.
Figure A2.173. Infrared spectrum (Thin Film, NaCl) of compound 87.

Figure A2.174. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 87.
Figure A2.175. $^1$H NMR (400 MHz, CDCl$_3$) of compound 93.
Figure A2.176. Infrared spectrum (Thin Film, NaCl) of compound 93.

Figure A2.177. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 93.
Figure A2.178. $^1$H NMR (400 MHz, CDCl$_3$) of compound 88.
Figure A2.179. Infrared spectrum (Thin Film, NaCl) of compound 88.

Figure A2.180. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 88.
Figure A2.181. $^1$H NMR (400 MHz, CDCl$_3$) of compound 89.
Figure A2.182. Infrared spectrum (Thin Film, NaCl) of compound 89.

Figure A2.183. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 89.
Figure A2.184. $^1$H NMR (400 MHz, CDCl$_3$) of compound 90.
Figure A2.185. Infrared spectrum (Thin Film, NaCl) of compound 90.

Figure A2.186. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 90.
Figure A2.187. $^1$H NMR (400 MHz, CDCl$_3$) of compound 91.
Figure A2.188. Infrared spectrum (Thin Film, NaCl) of compound 91.

Figure A2.189. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 91.
Figure A2.190. $^1H$ NMR (400 MHz, CDCl$_3$) of compound 92.
Figure A2.191. Infrared spectrum (Thin Film, NaCl) of compound 92.

Figure A2.192. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 92.
Figure A2.193. $^1$H NMR (400 MHz, CDCl$_3$) of compound 96.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.194. Infrared spectrum (Thin Film, NaCl) of compound 96.

Figure A2.195. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 96.
Figure A2.196. $^1$H NMR (400 MHz, CDCl$_3$) of compound 95.
Figure A2.197. Infrared spectrum (Thin Film, NaCl) of compound 95.

Figure A2.198. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 95.
Figure A2.199. $^1$H NMR (400 MHz, CDCl$_3$) of compound 94.
Figure A2.200. Infrared spectrum (Thin Film, NaCl) of compound 94.

Figure A2.201. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 94.
Figure A2.202. $^1H$ NMR (400 MHz, CDCl$_3$) of compound 98.
Figure A2.203. Infrared spectrum (Thin Film, NaCl) of compound 98.

Figure A2.204. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 98.
Figure A2.205. $^1$H NMR (400 MHz, CDCl$_3$) of compound 97.
Figure A2.206. Infrared spectrum (Thin Film, NaCl) of compound 97.

Figure A2.207. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 97.
Figure A2.208. $^1$H NMR (400 MHz, CDCl$_3$) of compound 100.
Figure A2.209. Infrared spectrum (Thin Film, NaCl) of compound 100.

Figure A2.210. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 100.
Figure A2.211. $^1$H NMR (400 MHz, CDCl$_3$) of compound D-100.
Figure A2.212. Infrared spectrum (Thin Film, NaCl) of compound D-100.

Figure A2.213. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-100.
**Figure A2.214.** $^2$H NMR (61 MHz, CHCl$_3$) of compound **D-100**.
Figure A2.215. $^1$H NMR (400 MHz, CDCl$_3$) of compound 103.
Figure A2.216. Infrared spectrum (Thin Film, NaCl) of compound 103.

Figure A2.217. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 103.
Figure A2.218. $^1$H NMR (400 MHz, CDCl$_3$) of compound 107.
Figure A2.219. Infrared spectrum (Thin Film, NaCl) of compound 107.

Figure A2.220. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 107.
Figure A2.221. $^1$H NMR (400 MHz, CDCl$_3$) of compound 105.
Figure A2.222. Infrared spectrum (Thin Film, NaCl) of compound 105.

Figure A2.223. $^{13}$C NMR (100 MHz, CDCl₃) of compound 105.
Figure A2.224. $^1$H NMR (400 MHz, CDCl$_3$) of compound 106.
Figure A2.225. Infrared spectrum (Thin Film, NaCl) of compound 106.

Figure A2.226. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 106.
Figure A2.227. $^1$H NMR (400 MHz, CDCl$_3$) of compound 113.
Figure A2.228. Infrared spectrum (Thin Film, NaCl) of compound 113.

Figure A2.229. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 113.
Figure A2.30. $^1$H NMR (400 MHz, CDCl$_3$) of compound 104.
Figure A2.231. Infrared spectrum (Thin Film, NaCl) of compound 104.

Figure A2.232. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 104.
Figure A2.233. $^1$H NMR (400 MHz, CDCl$_3$) of compound 108.
Figure A2.234. Infrared spectrum (Thin Film, NaCl) of compound 108.

Figure A2.235. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 108.
Figure A2.236. $^1$H NMR (400 MHz, CDCl$_3$) of compound 109.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.237. Infrared spectrum (Thin Film, NaCl) of compound 109.

Figure A2.238. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 109.
Figure A2.239. $^1$H NMR (400 MHz, CDCl$_3$) of compound 110.
**Figure A2.240.** Infrared spectrum (Thin Film, NaCl) of compound 110.

**Figure A2.241.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 110.
Figure A2.242. $^1$H NMR (400 MHz, CDCl$_3$) of compound 111.
Figure A2.243. Infrared spectrum (Thin Film, NaCl) of compound 111.

Figure A2.244. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 111.
Figure A2.245. $^1$H NMR (400 MHz, CDCl$_3$) of compound 112.
Figure A2.246. Infrared spectrum (Thin Film, NaCl) of compound 112.

Figure A2.247. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 112.
Figure A2.248. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49a.
Figure A2.249. Infrared spectrum (Thin Film, NaCl) of compound 49a.

Figure A2.250. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49a.
Figure A2.251. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49e.
Figure A2.252. Infrared spectrum (Thin Film, NaCl) of compound 49e.

Figure A2.253. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49e.
Figure A2.254. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49f.
Figure A2.255. Infrared spectrum (Thin Film, NaCl) of compound 49f.

Figure A2.256. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49f.
Figure A2.257. $^1$H NMR (400 MHz, CDCl$_3$) of compound D-49f.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.258. Infrared spectrum (Thin Film, NaCl) of compound D-49f.

Figure A2.259. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound D-49f.
Figure A2.260. $^2$H NMR (61 MHz, CHCl$_3$) of compound D-49f.
Figure A2.261. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49g.
Figure A2.262. Infrared spectrum (Thin Film, NaCl) of compound 49g.

Figure A2.263. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49g.
Figure A2.264. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49h.
Figure A2.265. Infrared spectrum (Thin Film, NaCl) of compound 49h.

Figure A2.266. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49h.
Figure A2.267. $^1$H NMR (400 MHz, CDCl$_3$) of compound 49i.
Figure A2.268. Infrared spectrum (Thin Film, NaCl) of compound 49i.

Figure A2.269. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 49i.
Figure A2.270. $^1$H NMR (400 MHz, CDCl$_3$) of compound 83.
Figure A2.271. Infrared spectrum (Thin Film, NaCl) of compound 83.

Figure A2.272. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 83.
Figure A2.273. $^1$H NMR (400 MHz, CDCl$_3$) of compound 84.
Figure A2.274. Infrared spectrum (Thin Film, NaCl) of compound 84.

Figure A2.275. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 84.
Figure A2.276. $^1$H NMR (400 MHz, CDCl$_3$) of compound 59.
Figure A2.277. Infrared spectrum (Thin Film, NaCl) of compound 59.

Figure A2.278. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 59.
Figure A2.279. $^1$H NMR (400 MHz, CDCl$_3$) of compound 63.
Figure A2.280. Infrared spectrum (Thin Film, NaCl) of compound 63.

Figure A2.281. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 63.
Figure A2.282. $^1$H NMR (400 MHz, CDCl$_3$) of compound 64.
Figure A2.283. Infrared spectrum (Thin Film, NaCl) of compound 64.

Figure A2.284. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 64.
Figure A2.285. $^1$H NMR (400 MHz, CDCl$_3$) of compound 65.
Figure A2.286. Infrared spectrum (Thin Film, NaCl) of compound 65.

Figure A2.287. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 65.
Figure A2.288. $^1$H NMR (400 MHz, CDCl$_3$) of compound 66.
Figure A2.289. Infrared spectrum (Thin Film, NaCl) of compound 66.

Figure A2.290. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 66.
Figure A2.291. $^1$H NMR (400 MHz, CDCl$_3$) of compound 67.
Figure A2.292. Infrared spectrum (Thin Film, NaCl) of compound 67.

Figure A2.293. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 67.
Figure A2.294. $^1$H NMR (400 MHz, CDCl$_3$) of compound 68.
Figure A2.295. Infrared spectrum (Thin Film, NaCl) of compound 68.

Figure A2.296. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 68.
Figure A2.297. $^1$H NMR (400 MHz, CDCl$_3$) of compound 114.
**Figure A2.298.** Infrared spectrum (Thin Film, NaCl) of compound 114.

**Figure A2.299.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 114.
Figure A2.300. $^1$H NMR (400 MHz, CDCl$_3$) of compound 69.
Figure A2.301. Infrared spectrum (Thin Film, NaCl) of compound 69.

Figure A2.302. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 69.
Figure A2.303. $^1$H NMR (400 MHz, CDCl$_3$) of compound 70.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.304. Infrared spectrum (Thin Film, NaCl) of compound 70.

Figure A2.305. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 70.
Figure A2.306. $^1$H NMR (400 MHz, CDCl$_3$) of compound 75.
Figure A2.307. Infrared spectrum (Thin Film, NaCl) of compound 75.

Figure A2.308. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 75.
Figure A2.309. $^1$H NMR (400 MHz, CDCl$_3$) of compound 76.
**Figure A2.310.** Infrared spectrum (Thin Film, NaCl) of compound 76.

**Figure A2.311.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 76.
Figure A2.312. $^1$H NMR (400 MHz, CDCl$_3$) of compound 77.
Figure A2.313. Infrared spectrum (Thin Film, NaCl) of compound 77.

Figure A2.314. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 77.
Figure A2.315. $^1$H NMR (400 MHz, CDCl$_3$) of compound 78.
Figure A2.316. Infrared spectrum (Thin Film, NaCl) of compound 78.

Figure A2.317. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 78.
Figure A2.318. $^1$H NMR (400 MHz, CDCl$_3$) of compound 79.
Figure A2.319. Infrared spectrum (Thin Film, NaCl) of compound 79.

Figure A2.320. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 79.
Figure A2.321. $^1$H NMR (400 MHz, CDCl$_3$) of compound 80.
Figure A2.322. Infrared spectrum (Thin Film, NaCl) of compound 80.

Figure A2.323. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 80.
Figure A2.324. $^1$H NMR (400 MHz, CDCl$_3$) of compound 81.
Figure A2.325. Infrared spectrum (Thin Film, NaCl) of compound 81.

Figure A2.326. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 81.
Figure A2.327. $^1$H NMR (400 MHz, CDCl$_3$) of compound 82.
Appendix 2 – Spectra Relevant to Chapter 3

Figure A2.328. Infrared spectrum (Thin Film, NaCl) of compound 82.

Figure A2.329. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 82.
Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A†

4.1 INTRODUCTION

The [2+2] photocycloaddition serves as a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds. The versatility of this transformation has led to numerous applications in the context of natural product synthesis, particularly as the four-membered cycloadducts can be further employed in ring expansion processes through strain-release and C–C bond activation.

In our recent total synthesis of (−)-scabrolide A (119), we sought to construct the 7-membered ring in the natural product through an oxidation/fragmentation sequence from cyclobutane 120. Intermediate 120 would be accessed through an intramolecular photochemical [2+2] cycloaddition of an enone with a pendant vinyl silane (121) – derived from 122 and 123 – to forge the [4–5] ring system (120) (Scheme 4.1A). Surprisingly, the desired [4–5] ring system (120) was not formed in this process; rather, a cis-fused [4–4] product 124 was produced as the exclusive product (Scheme 4.1B). The observed selectivity contrasts the “rule of five” generally attributed to enone-olefin cycloadditions, wherein the formation of five-membered rings is considered to be kinetically facile. As a consequence of the undesirable reactivity, three additional steps to protect and

†This research was carried out with Zhang T. Y. Portions of this chapter have been reproduced with permission from Stoltz, et al. J. Org. Chem. 2022, 87, 14115–14124. © 2023 American Chemical Society.
subsequently deprotect the isopropenyl olefin had to be incorporated into the synthesis. Rectifying the chemoselectivity of the [2+2] photocycloaddition from 121 would improve material throughput, support future synthetic efforts, and enable derivative-based biological studies. To explore this issue, we employ quantum mechanical calculations to understand the mechanism by which the unexpected product 124 is formed and uncover the origins of chemo- and diastereoselectivity.

Scheme 4.1. Photochemical [2+2] approach to scabrolide A.
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

4.2 COMPUTATIONAL METHODS

All quantum mechanics calculations were carried out with the Orca program.\(^7\) Geometries were optimized by density functional theory (DFT) using the B3LYP functional\(^8\) paired with Grimme’s D4 dispersion correction\(^9\) and the def2-SV(P) basis set.\(^10\) Vibrational frequency calculations were carried out at the same level of theory for all stationary points to verify their nature as minima or saddle points and to obtain thermal Gibbs free energy corrections at 298 K. Intrinsic reaction coordinate (IRC) analysis was performed to confirm that transition states lead to the appropriate minima.\(^11\) Additional DFT single point calculations were carried out with the ωB97M-V functional\(^12\) and the def2-TZVPP basis set with the SMD implicit solvation model for benzene.\(^13\) Multiconfigurational single point calculations were carried out using complete active space self-consistent field (CASSCF) theory, with subsequent treatment of dynamical correlation by second order N-electron valence state perturbation theory (NEVPT2).\(^14\) For state-averaged calculations, the Nakano quasi-degenerate (QD) formulation was employed.\(^15\) These calculations employed the def2-TZVPP basis set with the SMD model for benzene. The (8,8) active space (eight electrons and eight orbitals) was chosen to contain the enone π system, the isopropenyl π/π* and the vinyl silane π/π*. The enone oxygen lone pair was included to obtain the (10,9) active space where nπ* states are relevant. Unless otherwise specified, final Gibbs free energies are NEVPT2/def2-TZVPP/SMD(benzene) electronic energies with thermodynamical corrections obtained from the optimization level of theory. For full computational details, see section 4.5.
4.3 RESULTS AND DISCUSSION

The mechanism of the enone-olefin [2+2] photocycloaddition has been the subject of numerous theoretical and experimental investigations.\textsuperscript{1b,16,17} The general mechanism begins with UVA irradiation to promote the \( n \rightarrow \pi^* \) excitation of \( \alpha,\beta \)-unsaturated carbonyl \textit{127} (Scheme 4.2, Step 1). The \( \textit{1}^\text{(n}\pi^*) \) excited state undergoes intersystem crossing (ISC) primarily to the \( \textit{3}(\pi\pi^*) \) state (\textit{128} \_\textit{3}(\pi\pi^*)) (El Sayed’s rule).\textsuperscript{18} Occupation of the antibonding \( \pi^* \) orbital would then result in elongation of the C=O and C=C bonds. For conformationally flexible enones, the adiabatically relaxed \( \textit{3}(\pi\pi^*) \) state leads to a torsion about the \( \alpha \) and \( \beta \) positions and typically becomes lower in energy than the \( \textit{3}(n\pi^*) \) state. Prior studies unambiguously determined that the first C–C bond formation occurs from triplet excited states,\textsuperscript{1b,17} preferentially from the \( \textit{3}(\pi\pi^*) \) state.\textsuperscript{16a} For intermolecular cases, the ensuing C–C bond formation between the enone and olefin typically occurs via \( \beta \)-attack of the enone (Scheme 4.2, Step 2), \textit{i.e.}, an attack by the less stabilized spin center, to afford a triplet 1,4-diradical (\textit{3} \textit{129}). Half-lives of the 1,4-triplet diradicals intermediates have been measured to range from 10 to 1,000 ns.\textsuperscript{19} Subsequent ISC to the corresponding singlet diradical (\textit{1} \textit{129}) then enables either productive ring closure to form \textit{131} or unproductive C–C scission to return to enone \textit{127} (Scheme 4.2, Steps 3 and 4). Weedon and coworkers find that the intermediacy of \( \alpha \)-radicals (sp\textsuperscript{2}), such as \textit{1} \textit{129}, tends to favor C–C bond scission, while ring closure is more likely with \( \beta \)-radicals (sp\textsuperscript{3}), such as \textit{1} \textit{130}.\textsuperscript{20}
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

**Scheme 4.2.** General four-step mechanism for the olefin/α,β-unsaturated carbonyl [2+2] photocycloaddition.

### 4.3.1 STEP 1: PHOTOEXCITATION

The [2+2] photocycloaddition of enone 121 (Scheme 4.1B) is achieved upon irradiation with a standard UVA mercury vapor gas-discharge lamp (λ<sub>max</sub> ~ 350 nm). The initial singlet n → π* vertical excitation was calculated to be 3.96 eV (313 nm) (Scheme 4.3A) – in accord with known values for aliphatic cyclic enones.<sup>19b</sup> Energies of 3.73 and 4.01 eV were calculated for the vertical n → π* and π → π* excitations to the 3(^nπ*) and 3(^ππ*) states, respectively, from the ground state minimum (121_S0) (Scheme 4.3C).<sup>21</sup> The second lowest singlet excitation is significantly higher in energy at 7.45 eV and is of 1(^ππ*) character.<sup>22</sup> In accord with prior studies, the singlet n → π* excitation is accessible under UVA irradiation and is the excited state from which productive reactivity ensues.

Despite our best efforts, pervasive root-flipping made adiabatic optimization on the 1(^nπ*) surface challenging. As such, we employed the optimized 3(^nπ*) geometry as a surrogate for the 1(^nπ*) minimum.<sup>23</sup> The resulting adiabatic excitation energies of 3.34 and 3.37 eV (77.0 and 81.1 kcal/mol) are obtained for the 3(^nπ*) and 1(^nπ*) states, respectively. Apart from elongation of the C(2)–O(1) and C(3)–C(4) bonds, the 3(^nπ*) geometry is
similar to that of the ground state enone (Scheme 4.3D). At the 121\textsuperscript{1}(nπ\*) stationary point, the \(3(ππ\*)\) surface lies 4.8 kcal/mol above the \(1(nπ\*)\) surface. The \(3(nπ\*)\) is the lowest energy triplet state at the 121\textsubscript{S}s and 121\textsubscript{1}(nπ\*) stationary points (Scheme 4.3A); however, the adiabatic \(3(ππ\*)\) excitation energies of simple enones are typically lower than that of the \(3(nπ\*)\) state. Although it has been hypothesized that for highly rigid, cyclic systems the \(3(ππ\*)\) state may remain higher in energy,\textsuperscript{24} optimization of the \(3(ππ\*)\) state of 121 yields a total adiabatic excitation energy of 3.26 eV (75.2 kcal/mol), 1.8 kcal/mol lower than the \(3(nπ\*)\) minimum despite the rigidity of the tricyclic core. Given its comparative thermodynamic favorability, we hypothesized that the \(3(ππ\*)\) surface can be readily accessed from the initially excited \(1(nπ\*)\) state and account for the subsequent C–C bond formation. Hence, we sought to further interrogate the interaction of the excited state surfaces.

Beginning from the minimized 121\textsuperscript{1}(nπ\*) geometry (still employing the \(3(nπ\*)\) minimum as a surrogate), the nuclear coordinates were relaxed with energies and forces obtained from the \(3(ππ\*)\) surface.\textsuperscript{25} Single point calculations at the QD-NEVPT2 level of theory were carried out at points along the optimization trajectory to plot the corresponding energies of the \(1(nπ\*), \ 3(nπ\*)\), and \(3(ππ\*)\) surfaces. Moving along the reaction coordinate, the \(3(ππ\*)\) state energy decreases, with elongation of the C(2)–O(1) and C(3)–C(4) bonds and subsequent twisting along the C(2)–C(3)–C(4)–C(5) dihedral (Scheme 4.3D). The nπ\* states increase in energy as a result of these distortions, with the \(1(nπ\*)\) crossing the \(3(ππ\*)\) surface at C(2)–O(1) and C(3)–C(4) bond lengths of 1.33 and 1.45 Å, respectively.\textsuperscript{26} Non-zero spin-orbit coupling (SOC) between the \(1(nπ\*)\) and \(3(ππ\*)\) states results in an avoided
crossing with a barrier ($E_a$) of 1.4 kcal/mol (Scheme 4.3B). In contrast to the $^1(n\pi^*)$ to $^3(\pi\pi^*)$ crossing, ISC from the $^1(n\pi^*)$ state to the $^3(n\pi^*)$ state is symmetry-forbidden. Additionally, non-productive phosphorescence from the $^3(n\pi^*)$ state to the closed-shell singlet ground state is symmetry-allowed and is anticipated to be rapid. In summary, an $n \rightarrow \pi^*$ transition at 3.96 eV (313 nm) followed by ISC to the $^3(\pi\pi^*)$ surface yields intermediate $121_3(\pi\pi^*)$ – which is 1.8 kcal/mol lower in energy than $121_3(n\pi^*)$ – poised to undergo the first C–C bond formation.

Scheme 4.3. Photoexcitation of $121_{S0}$ and conversion to reactive triplet diradical $121_3^3(n\pi^*)$. 

![Scheme 4.3](image-url)
4.3.2 STEP 2: FIRST C–C BOND FORMATION

Triplet diradical $121_3^{3}(\pi\pi^*)$ may then undergo C–C bond formation with either of the pendant olefins. A single reference approach such as DFT should provide a good description of the triplet surface where the lowest triplet state is well isolated from other excited states, as is the case for the $121_3^{3}(\pi\pi^*)$ (vide supra). Moreover, spin contamination is generally minor.

As mentioned above, radical cyclizations during the first C–C bond formation may occur from either the $\alpha$ or $\beta$ positions (Scheme 4.2, Step 2). In the analogous reaction between acrolein and ethylene, Houk and coworkers find a 3–4 kcal/mol preference for $\beta$-attack due to the greater stability of the resulting delocalized $\alpha$-acyl radical.\textsuperscript{16}a In the system at hand, $\beta$-attack may occur from the isopropenyl olefin in a 5-exo-trig fashion ($\text{TS}_{44}$, $\text{TS}_{45}$) or the vinyl silane in a 4-exo-trig ($\text{TS}_{46}$, $\text{TS}_{47}$) fashion, respectively (Scheme 4.4A).\textsuperscript{28} The corresponding 5-endo-trig and 6-endo-trig cyclizations that give rise to spirocyclic 1,4-diradicals were also considered (see section 4.5). The cyclizations may occur from either the $Re$ or $Si$ face of the enone in conjunction with either face of the olefin (Schemes 4.7 and 4.8). In total, twelve diastereomeric transition states were considered for the $\beta$-attack mechanism.

For reaction pathways involving $\alpha$-attack, twelve diastereomeric transition states were similarly derived from approach to either face of the enone with the isopropenyl olefin in a 6-endo-trig ($\text{TS}_{48}$, $\text{TS}_{49}$) or 5-exo-trig cyclization (Scheme 4.7), or with the pendant vinyl silane in a 7-endo-trig ($\text{TS}_{50}$, $\text{TS}_{51}$) or 6-exo-trig cyclization (Scheme 4.9).\textsuperscript{29} All
diastereomeric transition states for α- and β-attack pathways were considered because the new stereocenters forged from the [2+2] photocycloaddition will be ablated during the ensuing synthetic transformations (oxidation and fragmentation, Scheme 4.1A). This causes diastereomeric diradicals – such as $^3\text{132}$ and $^3\text{133}$ (Scheme 4.4A) – to eventually give rise to the same [6–4–5] ring-containing synthetic intermediate. Therefore, only the chemoselectivity – not the diastereoselectivity – of the first C–C bond formation is relevant to the final synthetic outcome.

Given the vast number of energetically accessible conformers for each of the 24 relevant diastereomeric transition states, pre-screening with DFT ((U)ωB97M-V/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P)) was carried out to efficiently eliminate high energy pathways. The eight most relevant pathways are discussed below (Scheme 4.4A) with additional discussion on alternative pathways in section 4.5.

During the course of our synthetic planning, we envisioned that the system would preferentially undergo β-attack in a 5-exo-trig cyclization with the vinyl silane ($\text{TS44}$), forging the 5-membered ring of a desirable cycloaddition adduct ($^3\text{132}$). Approach of the enone $\text{Si}$ face to give 1,4-diradical intermediate $^3\text{132}$ is met with a barrier of 8.0 kcal/mol. The analogous 5-exo-trig transition state corresponding to approach of the $\text{Re}$ face ($\text{TS45}$) was not found. Rather, diradical $^3\text{133}$ converts to $^{121}_3(\pi\pi^*)$ via a stepwise mechanism from cycloheptyl diradical $^3\text{125}$ (Scheme 4.4B).
Scheme 4.4. Eight lowest energy reaction pathways from 121⁻^(3π⁺).*[a]

A. Eight lowest energy reaction pathways from triplet diradical 121⁻^(3π⁺).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Reaction</th>
<th>Desired/Not Observed</th>
<th>α-attack on isopropenyl olefin (6-endo-trig)</th>
<th>β-attack on vinyl silane (5-exo-trig)</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>4-endo</td>
<td>Re-face</td>
<td>TS48</td>
<td>TS32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G_{rel} = 3.0</td>
<td>G_{rel} = -8.7</td>
</tr>
<tr>
<td>122</td>
<td>6-endo</td>
<td>Re-face</td>
<td>TS49</td>
<td>TS33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G_{rel} = 5.0</td>
<td>G_{rel} = -8.7</td>
</tr>
<tr>
<td>123</td>
<td>5-exo</td>
<td>Si-face</td>
<td>TS45</td>
<td>TS34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G_{rel} = -11.9</td>
<td>G_{rel} = 1.4</td>
</tr>
<tr>
<td>124</td>
<td>4-exo</td>
<td>Si-face</td>
<td>TS46</td>
<td>TS35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G_{rel} = 5.2</td>
<td>G_{rel} = 1.4</td>
</tr>
<tr>
<td>125</td>
<td>3-exo</td>
<td>Si-face</td>
<td>TS47</td>
<td>TS36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G_{rel} = 3.0</td>
<td>G_{rel} = 1.4</td>
</tr>
</tbody>
</table>

B. 5-exo-trig Transition States

<table>
<thead>
<tr>
<th>Transition State</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS44</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS45</td>
<td>Not Observed</td>
</tr>
<tr>
<td>TS46</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS47</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS48</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS49</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS50</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS51</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS52</td>
<td>5-exo-trig</td>
</tr>
<tr>
<td>TS53</td>
<td>5-exo-trig</td>
</tr>
</tbody>
</table>

[a] Gibbs free energies (in kcal/mol) are calculated at the NEVPT2/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory. –SiR₃ = SiMe₃Ph. [b] All attempts to find a saddle point corresponding to TS45 ultimately lead to TS52 connecting ¹25 to ¹133.
Prior studies suggest that bond formation occurs from the $^3(\pi\pi^*)$ state rather than along the higher energy $^3(n\pi^*)$ surface. Indeed, the $^3(n\pi^*)$ state is found to lie 1.69 eV (39.0 kcal/mol) above the $^3(\pi\pi^*)$ ground state triplet PES at the TS44 saddle point.\textsuperscript{31} At TS44, $^3(n\pi^*)$ character in the ground state triplet is negligible, contributing < 0.5\% to the configuration interaction (CI) wavefunction.

Surprisingly, a barrier of 5.2 kcal/mol was found for Re face $\beta$-attack in a 4-exo-trig cyclization with the isopropenyl olefin (TS46), lower than that of the minimum energy 5-exo-trig pathway (TS44). Approaching from the Re face of the enone is favored (TS46), with a $\Delta G^\ddagger$ to Si face approach of 14.0 kcal/mol (TS47) (Scheme 4.4A). Unlike the generation of cyclopentanes \textsuperscript{3}132 and \textsuperscript{3}133, the formation of both cyclobutane 1,4-diradicals (\textsuperscript{3}134 and \textsuperscript{3}135) is thermodynamically unfavorable, with a change in reaction free energy ($\Delta G$) of 1.4 and 3.0 kcal/mol, respectively.

We then turned our attention to reaction pathways featuring $\alpha$-attack of the triplet enone diradical. Productive C–C bond formation may occur through either a 6-endo-trig or 7-endo-trig radical cyclization from either the Re or Si face of the enone (Scheme 4.4).\textsuperscript{32} Barriers of 3.0 and 5.0 kcal/mol were found for 6-endo-trig cyclization from the Re (TS48) or Si face (TS49), respectively. Higher barriers were obtained for the 7-endo-trig cyclization at 8.0 and 7.4 kcal/mol for approach from the Re (TS50) or Si face (TS51), respectively. Triplet 1,4-diradical intermediates resulting from 6-endo-trig (\textsuperscript{3}126) or 7-endo-trig (\textsuperscript{3}137) radical cyclization are lower in free energy than \textsuperscript{121}_3(\pi\pi^*) by at least 13 kcal/mol.
In summary, the global minimum energy pathway for the first C–C bond formation from $121_3(\pi\pi^*)$ is via 6-endo-trig cyclization with the isopropenyl olefin to forge triplet diradical $^{3}126$. This process is accompanied by a $\Delta G^\ddagger$ of 3.0 kcal/mol and a $\Delta G$ of $-15.6$ kcal/mol, relative to $121_3(\pi\pi^*)$. The transition state describing this minimum energy pathway ($TS_{48}$) resides on the $^3(\pi\pi^*)$ surface, with a vertical excitation energy of 1.96 eV (45.2 kcal/mol) to the $^3(n\pi^*)$ state. At $TS_{48}$, $^3(n\pi^*)$ character in the ground state triplet is negligible, contributing < 0.5% to the CI wavefunction.$^{33}$

Prior studies suggest that in photochemical [2+2] cycloadditions, the first C–C bond formation on the triplet surface occurs irreversibly ($i.e.$, before ISC).$^{1b,16}$ We found forward and reverse barriers to C–C bond formation along the minimum energy pathway to be 3.0 and 18.6 kcal/mol, with rate constants at 298.15 K of $3.9 \times 10^{10}$ s$^{-1}$ and $1.4 \times 10^{-1}$ s$^{-1}$, respectively. For simple enones, lifetimes of triplet 1,4-diradical intermediates derived from [2+2] photocycloadditions are on the scale of 10 to 1,000 ns, $i.e.$, unimolecular decay rate constants are on the order of magnitude of $10^6 - 10^8$ s$^{-1}$. Thus, C–C bond formation through $TS_{48}$ is irreversible, with the reverse process ($k \sim 10^{-1}$ s$^{-1}$) being outcompeted by ISC ($k \sim 10^8 - 10^6$ s$^{-1}$). Meanwhile, productive bond formation ($k \sim 10^{10}$ s$^{-1}$) is anticipated to be more rapid than ISC, and thus, proceeds on the triplet surface. Still, we consider the effect of a competitive ISC. Starting from the $121_3(\pi\pi^*)$ geometry, optimization along the ground state singlet surface smoothly affords the closed-shell singlet starting material $121_{S0}$. Hence, premature spin flip would lower the efficiency of the overall process but likely does not lead to undesired reactivity.$^{16d}$
4.3.3 STEP 3: SECOND C–C BOND FORMATION

The first ring closure generates a triplet 1,4-diradical, which was shown to be almost energetically degenerate with its singlet counterpart. The singlet-triplet gap for diradical 126 is calculated to be less than 1 kcal/mol, favoring anti-ferromagnetically coupled spins (Scheme 4.5). After ISC to the singlet 1,4-diradical surface, the system undergoes relaxation to a stable diradical intermediate or a C–C bond cleavage to re-form 121 (Scheme 4.5). We hypothesized that the partitioning between the two outcomes depends on the conformation of the 1,4-diradical at the point at which ISC occurs (Scheme 4.10). Starting from the triplet diradical geometries of low-energy conformers, relaxation of the nuclear coordinates on the broken-symmetry (Ms = 0) DFT (BS-DFT) surface yields either singlet diradicals or enone 121. For diradical 126 (Scheme 4.5), five of the 14 lowest-energy conformers relaxed to enone 121 (including the globally lowest-energy conformer), which accounts for 70% of the Boltzmann-weighted population of conformers. As such, only 30% of the triplet diradical population will relax to stable singlet diradicals.

Unlike multi-configurational methods (such as NEVPT2/CASSCF), single-determinantal methods (such as BS-DFT) are unable to properly describe open-shell singlet states. Hence, we sought to compare the final energies calculated on the BS-DFT potential energy surface (PES) to those from the NEVPT2 surface. We found significant discrepancies in the BS-DFT and NEVPT2 PESs along the reaction coordinate of the second C–C bond formation (see section 4.5), with BS-DFT calculations favoring a later transition state than NEVPT2. Consequently, a more accurate barrier was derived from a
PES obtained by calculating NEVPT2 electronic energies along the BS-DFT intrinsic reaction coordinate (IRC) trajectory for the transition state in question.

**Scheme 4.5.** Predicted reactivity from diradical 126.

[a] Gibbs free energies (in kcal/mol) are calculated at the NEVPT2/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SVP level of theory. –SiR$_3$ = SiMe$_3$Ph.
Scheme 4.6. Predicted reactivity from diradical 125.

A. Predicted reactivity from 7-membered cyclic diradical 125

B. [2+2] Photocycloaddition with masked isoprenyl olefin

[a] Gibbs free energies (in kcal/mol) are calculated at the NEVPT2/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory. –SiR₃ = SiMe₂Ph.
From the relaxed singlet diradical geometry, the second C–C bond formation could then occur. For diradical 126, the formation of which is most facile during the first C–C bond formation (Scheme 4.4), the open-shell singlet PES for its lowest-energy conformer (Scheme 4.5) suggests that formation of the experimentally observed product 124 involves a barrier of 1.8 kcal/mol via \(^1\text{TS54}\). This is significantly lower than the 3.9 kcal/mol barrier ('\(^1\text{TS54}'\)) for the formation of the corresponding diastereomer 124' or the 3.7 kcal/mol barrier ('\(^1\text{TS53}\)') for the reversion back to enone 121. This is consistent with exclusive formation of product 6, as was observed experimentally.\(^4\)

It was observed in the original synthesis of scabrolide A that protecting the isopropenyl olefin as an epoxide (138) afforded the desired [6–4–5] ring system as the \(R\) epimer at C(3) (139) (Scheme 4.6A). Analogously, we analyzed the open-shell singlet surface for diradical 125, which would lead to the desired but experimentally non-observed product 120 containing the [6–4–5] ring system with the same stereochemistry at C(3). Its precursor triplet diradical \(^3\text{125}\) is generated via 7-endo-trig cyclization (TS50) of 121\(^3(\pi\pi^*)\) (Scheme 4.4A) and all of its low-energy conformers remained as stable singlet diradicals after ISC (with a singlet-triplet gap of less than 1.0 kcal/mol). NEVPT2 calculations suggest a highly flat open-shell singlet PES around the diradical geometry, with an approximately barrierless formation of target product 120 via \(^1\text{TS56}\), or its diastereomer 120' via \(^1\text{TS56}'\), or re-formation of enone 121 via \(^1\text{TS55}\) (Scheme 4.6B).

The relative flat nature of the open-shell singlet PES introduces the possibility that dynamical effects might dictate the partitioning of reaction pathways from diradicals \(^1\text{126}\) and \(^1\text{125}\). Ergo, ab initio molecular dynamics (AIMD) simulations were performed,
beginning from optimized triplet-diradical geometries (see section 4.5). AIMD were carried out with the PBE functional, as our controlled studies found that omission of Hartree–Fock exchange leads to a more qualitatively correct open-shell singlet PES with respect to NEVPT2 as a reference (Schemes 4.12 and 4.13). For $^1 \text{126}$, AIMD reveals an equal partitioning of low-energy conformers between substrate regeneration and product formation, which is qualitatively consistent with the distribution of outcomes from relaxation of nuclear coordinates of low-energy conformers along the broken-symmetry PES (Table 4.3). Similarly, AIMD trajectories suggest that the majority of the population of diradical $^1 \text{125}$ terminate as the desired product $\text{120}$, while <1% affords substrate $\text{121}$ or diastereomer $\text{120'}$ (Table 4.4). These results suggest that dynamic effects on the singlet surface are not significant and the aforementioned results from relaxation of nuclear coordinates after the ISC are reliable.

In summary, our results demonstrate that if ISC from the triplet to the open-shell singlet surface affords a stable singlet diradical, then the second C–C bond formation (ring closure) will occur, albeit with variable efficiencies depending on the conformation of the singlet diradical. Equipped with this understanding, we hypothesized that the desired product $\text{120}$ (or $\text{120'}$) can be accessed, as long as formation of triplet diradical $^3 \text{125}$ is favored during the first C–C bond formation.

4.3.4 COMPLETE MECHANISM

As a result of these findings, we propose a mechanism that accounts for the chemo- and diastereoselectivity in the unexpected formation of $\text{124}$ from enone $\text{121}$ (Figure 4.1). The initial $n \rightarrow \pi^*$ excitation followed by intersystem crossing (ISC) to the $^3(\pi\pi^*)$ state
and geometric relaxation, characterized by twisting of the enone, affords triplet diradical 121\(\cdot^3(\pi\pi^*)\) (Scheme 4.3). From 121\(\cdot^3(\pi\pi^*)\), cyclizations can occur from \(\alpha\)- or \(\beta\)-attack of the enone triplet diradical with either the pendant isopropenyl olefin or vinyl silane. Considering all modes of cyclization and \(Re/Si\) facial selectivity, a total of eight possible ring-closed products are relevant (Scheme 4.4A). From 121\(\cdot^3(\pi\pi^*)\) the most kinetically favorable of these pathways is a 6-\textit{endo}\-trig cyclization involving \(\alpha\)-attack of the enone onto the isopropenyl olefin to give 3\textit{126}, with \(\Delta G^\ddag\) of 3.0 kcal/mol (TS\textit{48}, Scheme 4.4A) and \(\Delta\Delta G^\ddag\) of 4.4 kcal/mol (relative to the second lowest activation barrier). This initial C–C bond formation is thermodynamically favored by 15.6 kcal/mol. Experimentally derived excited state lifetimes for related 3\(\cdot^3(\pi\pi^*)\) 1,4-diradical intermediates range from 10 to 1,000 ns. As a result, the initial C–C bond formation is irreversible. ISC from 3\textit{126} affords the corresponding singlet 1,4-diradical 1\textit{126}. Along the singlet surface, C–C bond cleavage to regenerate 121 or radical recombination to forge a second C–C bond may occur to form ring-closed species 124 or 124\'. Given the flat nature of the singlet PES, the ultimate outcome of ISC was found to be influenced by the conformation of the triplet diradical prior to spin-flip. Relaxation to the ground state enone 121 was observed in a subset of conformers accounting for approximately 70% of the Boltzmann population of the conformer ensemble of 3\textit{126}. For the conformers that persisted as singlet diradicals, radical recombination to forge experimentally observed product 124 is favored over formation of 124\' or 121 (Scheme 4.5).
Figure 4.1. Complete mechanism describing formation of unexpected product 124 from the intramolecular [2+2] photocycloaddition of enone 121.

[a] Relative free energies (in kcal/mol) calculated at the (QD-)NEVPT2/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory. Relative energies in eV given in parentheses. Vertical excitation energies at selected stationary points are calculated with a state-averaged wavefunction. $^1(\pi\pi^*)/S_0$ intersection is not depicted.
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (–)-Scabrolide A

4.4 CONCLUSIONS

We report a detailed quantum mechanics investigation of the mechanism of the intramolecular enone-olefin [2+2] photocycloaddition employed in our recent synthesis of (–)-scabrolide A (119). In our prior report, enone 121 was subjected to UV irradiation with the intent to forge a [6–4–5] ring system, which upon oxidative ring opening, would afford the fused [6–7] carbocyclic framework of (–)-scabrolide A (119). To our surprise, instead of forming the desired [6–4–5] ring scaffold (i.e., 120), 121 undergoes an unexpected cyclization to afford an undesired [6–4–4] ring system (i.e., 124). As a consequence of the undesirable reactivity, three additional synthetic steps to mask and subsequently reveal the isopropenyl olefin were incorporated into the synthesis.

Our QM calculations reveal that the preferential formation of the [6–4–4] ring system is a result of a facile 6-endo-trig radical cyclization on the $^3\pi\pi^*$ surface, outcompeting the alternative 7-endo-trig, 6-exo-trig, 5-exo/endo-trig, and 4-exo-trig pathways. Analysis of the open-shell singlet surfaces describing the hypothetical 1,4-diradical intermediates post-ISC reveals that C–C bond formation by radical recombination is favorable in each case. Moreover, our study has showcased the practicality and accuracy of combining ab initio wavefunction methods (CASSCF/NEVPT2) with DFT in modeling multiconfigurational and multideterminental open-shell systems. This approach thus serves as a model for future computational endeavors aiming at real-world systems involving complex spin configurations.
4.5 SUPPORTING INFORMATION

4.5.1 GENERAL COMPUTATIONAL DETAILS

All quantum mechanical calculations were performed with ORCA version 4.2. The resolution of identity (RI) and chain-of-spheres approximations were utilized for Coulomb and exchange integrals, respectively, with the def2/J auxiliary basis set. Ultra-fine integration grids were employed throughout (keywords: “Grid7 NoFinalGrid GridX9”). The CYLview and Chimera programs were used to generate graphical images in the main text.

**DFT Calculations:** Unless otherwise noted, geometry optimizations were carried out with the B3LYP global hybrid generalized gradient approximation (GGA) functional with Grimme’s D4 dispersion corrections (henceforth referred to as B3LYP-D4) with the def2-SV(P) basis set on all atoms. For open-shell species, unrestricted Kohn–Sham orbitals were employed. Spin contamination is generally minor. Thermal corrections at 298.15 K were calculated from the unscaled vibrational frequencies at this level of theory. The Quasi-RRHO method was applied to correct for the breakdown of the harmonic oscillator approximation for low frequency vibrations. All stationary points are characterized by the appropriate number of imaginary vibrational modes (zero for optimized geometries and one for transition states). Intrinsic reaction coordinate (IRC) analyses were carried out to ensure all transition states connect the appropriate starting materials and products. DFT electronic energies were further refined with the oB97M-V functional, def2-TZVPP basis set on all atoms, and the SMD implicit solvation model for benzene. Outlying charge corrections were included in the final solvated energies. Final
(DFT) Gibbs free energies were derived by applying thermodynamic corrections obtained at the optimization level of theory to these refined electronic energies. While these DFT energies are found to be reliable for high-spin ($S = 1$) intermediates where the $n\pi^*$ and $\pi\pi^*$ surfaces are well separated, multiconfigurational calculations (here, CASSCF/NEVPT2) are employed for a more rigorous description of the electronic structure. However, DFT remains a cost-effective tool for rapid evaluation/screening of conformers. Hence, calculations at the (U)$\omega$B97M-V/def2-TZVPP/SMD(benzene)/(U)-B3LYP-D4/def2-SV(P) level of theory were employed for exploring reactivity along the triplet $\pi\pi^*$ surface (see Schemes 4.7–4.9).

**CASSCF/NEVPT2 Calculations:** CASSCF calculations were performed in order to properly describe the multiconfigurational nature of the system in regions of state crossings, as well as open-shell singlet intermediates. The active space is chosen to incorporate the necessary bonding/anti-bonding orbitals. For enone $121_S0$, this affords a 10 electron in 9 orbital active space [enone $\pi/\pi^*$ orbitals, isopropyl $\pi/\pi^*$, vinyl silane $\pi/\pi^*$, carbonyl oxygen lone pair], henceforth abbreviated as (10,9). For intermediates where C–C bonds are formed from reactivity of these $\pi$ systems, the corresponding C–C $s/s^*$ are included to maintain a consistent active space. The carbonyl oxygen lone pair of $121$ and its subsequent intermediates is included only when necessary (i.e., describing $n\pi^*$ states), as the lone pair is otherwise weakly correlated (occupation number > 1.999) leading to convergence issues. Additional dynamical correlation is recovered by subsequent N-Electron Valence State Perturbation Theory$^{14}$ (NEVPT2) calculations using the CASSCF wavefunction as a reference. For cases where state-averaged CASSCF wavefunctions are
employed, the quasi-degenerate formalism of Nakano\textsuperscript{15} (QD-NEVPT2) was employed, allowing for re-mixing of CI coefficients under the effect of dynamical correlation. Unless otherwise noted, all energies in the main text are relative Gibbs free energies in kcal/mol derived from electronic energies at the NEVPT2/def2-TZVPP/SMD(benzene) level of theory with thermodynamic corrections from the (U)B3LYP/def2-SV(P) optimization level.

**Excited State Surfaces in Scheme 4.3.**

The initial singlet n → π* vertical excitation energy of 3.96 eV (313 nm) was obtained from QD-NEVPT2-corrected CASSCF wavefunction with the (10,9) active space with averaging over two triplets (nπ* and ππ*) and three singlet states (closed-shell singlet (ground state), nπ*, and ππ*). Nearly identical results are obtained regardless of state averaging scheme employed (see Table 4.1). From the ground state closed-shell singlet (S\textsubscript{0}), the singlet n → π* (S\textsubscript{1}) and π → π* (S\textsubscript{1}) excitations are 3.96 and 7.45 eV, respectively (Table S1).
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

Table 4.1. Comparison of vertical excitation energies calculated at the $^{121}_S_0$ with various state-averaging schemes.\(^{a}\)

<table>
<thead>
<tr>
<th>State</th>
<th>2 triplets</th>
<th>2 singlets</th>
<th>3 singlets</th>
<th>2 triplets 3 singlets</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_0$</td>
<td>–</td>
<td>0.00 [0.0]</td>
<td>0.00 [0.0]</td>
<td>0.00 [0.0]</td>
</tr>
<tr>
<td>$S_1$</td>
<td>–</td>
<td>4.01 [92.6]</td>
<td>3.99 [92.0]</td>
<td>3.96 [91.4]</td>
</tr>
<tr>
<td>$S_2$</td>
<td>–</td>
<td>–</td>
<td>7.42 [171.2]</td>
<td>7.45 [171.7]</td>
</tr>
<tr>
<td>$T_1$</td>
<td>0.00 [0.0]</td>
<td>–</td>
<td>–</td>
<td>3.73 [85.9]</td>
</tr>
<tr>
<td>$T_2$</td>
<td>0.28 [6.6]</td>
<td>–</td>
<td>–</td>
<td>4.01 [92.4]</td>
</tr>
</tbody>
</table>

\(^{a}\) Calculations at the QD-NEVPT2/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory with the (10,9) active space at $^{121}_S_0$.

In order to calculate the energy difference between the $^3(n\pi^*)$ and $^3(\pi\pi^*)$ minima (\textit{i.e.}, $^{121}_3(n\pi^*)$ and $^{121}_3(\pi\pi^*)$), single point calculations at the QD-NEVPT2/CASSCF level of theory with state averaging ($^3(n\pi^*)$ and $^3(\pi\pi^*)$) were carried out at the $^{121}_3(n\pi^*)$ and $^{121}_3(\pi\pi^*)$ stationary points. State averaging was employed as at $^{121}_3(\pi\pi^*)$ the carbonyl oxygen lone pair is not significantly correlated in the ground-state triplet at $^{121}_3(\pi\pi^*)$ (occupation number > 1.999). This results in convergence issues in orbital optimization when included in the active space. Accordingly, the lowest triplet state at $^{121}_3(\pi\pi^*)$ does not contain significant $^3(n\pi^*)$ character and is well described by a single configuration of $\pi\pi^*$ character. Single point calculations with DFT ((U)oB97M-V/def2-TZVPP/SMD(benzene)) also predict the $^{121}_3(\pi\pi^*)$ minimum to be 1.8 kcal/mol lower in energy than $^{121}_3(n\pi^*)$.

An analogous strategy was employed when calculating the vertical excitation energies at the other relevant stationary points in Scheme 4.3 ($^{121}_3(\pi\pi^*)$), scheme 4.4.
(TS48), and when computing the vertical energy difference between \( ^3(n\pi^*) \) and \( ^3(\pi\pi^*) \) at C–C bond forming transition states. For computing the energy difference between stationary points with the same ground state (for example, \( \Delta G^\ddagger \) between 121\_3(\( \pi\pi^* \)) and TS48, both with \( ^3(\pi\pi^*) \) ground state), state-averaging is not employed.

**Additional Stereochemical Considerations**

In addition to the two 5-exo-trig \( \beta \)-attack pathways highlighted in the main discussion (TS44 and TS45 in Scheme 4.4), two additional diastereomeric pathways (TS57 and TS58) are possible (Scheme 4.7). These pathways present higher barriers and are not accessible given the estimated kinetics of ISC. Moreover, the ensuing ring closure (after ISC) of the diradical intermediates would forge highly strained trans [4–5] fused ring systems. Hence, even if triplet diradical intermediates 140 and 141 were formed, C–C bond scission after ISC is anticipated, reforming starting material 121\_S0.

In analogy to the discussion above, two additional diastereomeric 4-exo-trig \( \beta \)-attack transition states are possible (TS59 and TS60, Scheme 4.8). These pathways are high in energy relative to the minimum energy pathways (Scheme 4.4) and are not responsible for the observed reactivity. Moreover, the formation of the resulting cyclobutane-containing products is accompanied by a positive change in free energy. Hence, equilibration prior to ISC will preferentially reform 121\_3(\( \pi\pi^* \)).
Scheme 4.7. All four diastereomeric 5-exo-trig β-attack transition states and products.\(^a\)

[a] All diradicals are in the triplet spin state. Gibbs free energies in kcal/mol from the (U)\(\omega\)B97M-V/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory.
Scheme 4.8. All four diastereomeric 4-exo-trig β-attack transition states and products.

[a] All diradicals are in the triplet spin state. Gibbs free energies in kcal/mol from the (U)\textit{oB97M-V}/def2-TZVPP/SMD(benzene)/(U)\textit{B3LYP-D4/def2-SV(P)} level of theory.
**Scheme 4.9.** All diastereomeric products for 6-exo-trig α-attack (144–147), 6-endo-trig β-attack (148–149), 5-endo-trig β-attack (150–151), and 5-exo-trig α-attack (152–155).\(^a\)

\[\text{β-attack of enone} \]

\[\begin{array}{c}
\text{6-endo-trig} \\
148 (ΔG = -25.0) \\
149 (ΔG = -29.5) \\
\text{6-exo-trig} \\
146 (ΔG = -13.7) \\
147 (ΔG = -15.0) \\
144 (ΔG = -16.2) \\
145 (ΔG = -14.6) \\
\text{5-exo-trig} \\
152 (ΔG = -9.1) \\
153 (ΔG = -7.5) \\
154 (ΔG = -10.6) \\
155 (ΔG = -2.6) \\
\text{5-endo-trig} \\
150 (ΔG = -20.0) \\
151 (ΔG = -14.9) \\
\end{array}\]

\[\text{α-attack of enone} \]

\[\text{[a] All diradicals are in the triplet spin state. Gibbs free energies in kcal/mol from the (U)ωB97M-V/def2-TZVPP/SMD(benzene)//(U)B3LYP-D4/def2-SV(P) level of theory.}\]

While the formation of cross adducts is not experimentally observed, the free energy of triplet diradicals derived from 6-exo-trig α-attack (24–27), 6-endo-trig β-attack (28–29), 5-endo-trig β-attack (30–31), and 5-exo-trig α-attack (32–35) were evaluated for reference (Scheme 4.9). Wolf and Agosta have also previously found that substitution on the internal carbon of pendant olefins leads to “straight” adducts rather than crossed products.\(^{44}\)
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

Open-shell Singlet Potential Energy Surfaces

As the triplet diradical (such as $^3\text{126}$) undergoes a spin flip (ISC), whether it geometrically relaxes to the stable open-shell singlet diradical (such as $^1\text{126}$) or undergoes C–C bond cleavage back to the substrate 121 may be influenced by conformation (Scheme 4.10).

**Scheme 4.10.** Conformational influence on outcome post-ISC.$^a$

[a] Outcome of ISC would depend on the exact conformation of each conformer of triplet-spin diradical ($^3\text{126}$). This led to a partitioning between geometry relaxation to a stable diradical ($^1\text{126}$), or C–C bond cleavage to re-form substrate 121, as illustrated by the example of diradical 126.

Unfortunately, a single Slater determinant, as is used in DFT, does not afford a proper spin eigenfunction for an open-shell singlet state. However, the broken-symmetry formalism may be employed to obtain an $M_s = 0$ wavefunction with a qualitatively correct character. While the resulting wavefunction is spin contaminated, the energy of the “pure” singlet state can be estimated by a variety of spin projection methods. Here, we employ that of Yamaguchi.$^{45}$
$$E_T - E_S = \frac{2}{\langle S^2 \rangle_T - \langle S^2 \rangle_{BS}} (E_T - E_{BS})$$

When applying this approach to calculate barriers for C–C bond formation/cleavage from the singlet diradical intermediates (1126, 1125, etc.), some spin-projected values resulted in barriers of < 0 kcal/mol (Table 4.2). This indicates that the broken-symmetry (BS) DFT PES may be qualitatively incorrect, i.e., stationary points on the BS-PES may not be stationary points on the true singlet surface. To test this, single point calculations with CASSCF/NEVPT2 were carried out along the IRC trajectories from the suspected saddle points (as obtained by BS-DFT) (Scheme 4.11). While BS-DFT predicts TS11 to be a stationary point between 18 and 6, the NEVPT2 PES reveals no well-defined saddle point, and hence, ∆E(el) ~ 0.0 kcal/mol.

While the relative energies along the BS-DFT PES are not necessarily accurate, the molecular geometries obtained along the IRC describing the simple C–C bond stretching/compressing should otherwise remain reliable. As such, a refined PES is derived from single point calculations with CASSCF/NEVPT2 carried out along the IRC trajectories from the saddle points as obtained by BS-DFT. ∆E(el) is then calculated from this new PES and thermodynamical corrections are applied accordingly to obtain free energy barriers (∆G‡).
Table 4.2. Free energy barriers to C–C bond formation/cleavage from $^{1126}$.a

<table>
<thead>
<tr>
<th>Species formed</th>
<th>$\Delta G^\ddagger$ (kcal/mol)</th>
<th>BS-DFT</th>
<th>SP-BS-DFT</th>
<th>QD-NEVPT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>124</td>
<td>5.0</td>
<td></td>
<td>-1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>124'</td>
<td>6.6</td>
<td>1.8</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>6.5</td>
<td>2.5</td>
<td>3.7</td>
<td></td>
</tr>
</tbody>
</table>

[a] Significant discrepancies between broken-symmetry DFT (BS-DFT), spin-projected BS-DFT, and QD-NEVPT2 calculations in the activation barrier for second C–C bond formation (TS54 and TS54') and reversion to substrate (TS53), as illustrated by the example of diradical 126. Single-point energies were obtained using (U)B3LYP-D4/def2-SV(P) geometries at either the QD-NEVPT2/CASSCF/def2-TZVPP/SMDBzene) or (U)B3LYP-D4/def2-TZVPP/SMDBzene) level of theory. For SP-BS-DFT, Yamaguchi’s formula for spin projection was applied.
Scheme 4.11. PESs generated from single point calculations along the BS-DFT IRC trajectories of $^{1}126$ to TS54 to $^{1}124$.\(^{a}\)

[a] The CASSCF PES is included for comparison, but the NEVPT2 PES should be taken as reference.

Considering the relatively flat nature of many of the open-shell singlet potential energy surfaces, we sought to explore by means of ab initio molecular dynamics (AIMD) simulations whether dynamic effects play a role in the final product distributions. For the system at hand, AIMD would not be practical at the CASSCF/NEVPT2 level. Constrained to DFT, we returned to the approach described above, now comparing the performance of a variety of functionals to NEVPT2 references. This was carried out for the ring closure step of diradicals $^{1}126$ (Scheme 4.12) and $^{1}125$ (Scheme 4.13). These results show that the PBE-D4 functional bears the best resemblance to the NEVPT2 potential energy surface.
Employing the PBE-D4 functional, AIMD simulations were initiated from the lowest energy conformers (within a 1.0 kcal/mol window) of $^3$125 (Table 4.4) and $^3$126 (Table 4.3). AIMD simulations were propagated with a 1.0 fs timestep for up to 10 ps or until a bond formation/cleavage occurred. A Berendsen thermostat was employed with a time constant of 50 fs. Randomized initial velocities were set at 20 K, followed by a temperature ramp to 298 K.
Scheme 4.12. Comparison of performance in relaxed surface scan of ring closure of diradical 1126 to form observed but undesired product 124 of various DFT functionals with respect to NEVPT2.

[a] Scans were performed from the lowest-energy conformer of 1126. All single point energies were calculated from each respective functional with the def2-TZVPP basis set and with the SMD(benzene) implicit solvation.
Scheme 4.13. Comparison of performance in relaxed surface scan of ring closure of diradical \(^1\text{125}\) to form observed but undesired product \(\text{120}\) of various DFT functionals with respect to NEVPT2.\(^a\)

[a] Scans were performed from the lowest-energy conformer of \(^1\text{125}\). All single point energies were calculated from each respective functional with the def2-TZVPP basis set and with the SMD(benzene) implicit solvation.
Table 4.3. Partitioning of five lowest-energy conformers of singlet diradical $^{1}$126 between four outcomes based on picosecond-scale AIMD calculations.$^{a}$

<table>
<thead>
<tr>
<th>Conformer #</th>
<th>$G_{\text{rel}}$ (kcal/mol)</th>
<th>% Boltzmann population</th>
<th>% $^{1}$126</th>
<th>% 124</th>
<th>% 124'</th>
<th>% 121</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.9</td>
<td>8.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>6.6</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>16.8</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.0</td>
<td>38.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>7.1</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0.4</td>
<td>20.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

$^{a}$ Percent remaining as diradical $^{1}$126, product 124 formation, diastereomer 124' formation, and substrate 121 formation. AIMD calculations were performed at (U)PBE-D4/def2-SV(P) level of theory.
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A

Table 4.4. Partitioning of five lowest-energy conformers of singlet diradical $^{1}{^{125}}$ between four outcomes based on picosecond-scale AIMD calculations.$^a$

![Diagram showing the reaction and structures](image.png)

<table>
<thead>
<tr>
<th>Conformer #</th>
<th>Δ$G_{\text{rel}}$ (kcal/mol)</th>
<th>% Boltzmann population</th>
<th>% $^{1}{^{125}}$</th>
<th>% 120</th>
<th>% 120'</th>
<th>% 121</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.00</td>
<td>28.8</td>
<td>32</td>
<td>68</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.84</td>
<td>6.9</td>
<td>10</td>
<td>80</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>0.37</td>
<td>15.4</td>
<td>25</td>
<td>75</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.50</td>
<td>12.3</td>
<td>35</td>
<td>65</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0.01</td>
<td>28.4</td>
<td>23</td>
<td>77</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Percent remaining as diradical $^{1}{^{125}}$, product 120 formation, diastereomer 120' formation, and substrate 121 formation. AIMD calculations were performed at (U)PBE-D4/def2-SV(P) level of theory.
REFERENCES AND NOTES

Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A


Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the
Synthesis of (−)-Scabrolide A

Rodríguez-Santiago, L.; Sodupe, M. [2 + 2] Photocycloaddition of 2(5H)-Furanone
to Unsaturated Compounds. Insights from First Principles Calculations and
Reguero, M.; Olivucci, M.; Bernardi, F.; Robb, M. A. Excited-State Potential
Surface Crossings in Acrolein: A Model for Understanding the Photochemistry and

(a) Lam, E. Y. Y.; Valentine, Donald.; Hammond, G. S. Mechanisms of
Photochemical Reactions in Solution. XLIV. Photodimerization of
Nelson, P. J.; Brown, E. L. Photochemical Transformations. XXV. Two Triplet
Mechanisms in Photochemical Addition of 2-Cyclohexenones to 1,1-
Photochemical Cycloaddition Reactions of Enones to Alkenes; Synthetic
Applications. *Synthesis* 1970, 287–300. For a review, see: (e) Schuster, D. I.; Lem,
George.; Kaprinidis, N. A. New Insights into an Old Mechanism: [2 + 2]
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A


(21) Similar results are obtained regardless of the state averaging scheme employed.

(22) \( \Delta E_{ST}(\pi\pi^*) \) is larger in magnitude than \( \Delta E_{ST}(n\pi^*) \) as the overlap of the \( \pi/\pi^* \) orbitals is greater than that of the \( n/\pi^* \) orbitals.

(23) The \( ^3(n\pi^*) \) and \( ^3(n\pi^*) \) minima are expected to be qualitatively similar in geometry. The similarity of their PES is highlighted in Scheme 4.3B.

(25) Root-flipping between $^3(\pi\pi^*)$ and $^3(n\pi^*)$ states complicates this matter. In order to approximate the diabatic surface obtained by relaxation of the nuclear coordinates of the $^3(\pi\pi^*)$ state, the carbonyl oxygen lone pair is removed from the active space, rendering the $^3(\pi\pi^*)$ state the lowest energy triplet state for the portion of the PES of interest. Starting from the $^{120}_3(n\pi^*)$ minimum geometry, triplet state geometries were then relaxed at the CASSCF(8,8)/def2-SV(P) level of theory. Points along the optimization trajectory were then taken for analysis.

(26) The crossing point is not rigorously the minimum energy crossing point, rather the approximate surface rather serves as an upper bound.

(27) At the $^3(\pi\pi^*)/^1(n\pi^*)$ minimum energy crossing point, SOC creates an energy gap of ca. 1 kcal/mol between the adiabatic surfaces.

(28) For $\beta$-attack, 2 diastereomeric transition states arise from each of 4-exo-, 5-endo-, 5-exo-, and 6-endo-trig cyclizations, as the pendant olefin of interest approaches the $\beta$-radical from either the *Si* or *Re* face of the enone. There are 2 more diastereomeric transition states for each of the 4-exo- and 5-exo-trig cyclizations, as the $\beta$-radical can approach the more substituted and prochiral carbon in the isopropenyl olefin and the vinyl silane from either of the diastereotopic faces of the olefin.
(29) For α-attack, 2 diastereomeric transition states arise from each of 5-exo-, 6-endo-, 6-exo-, and 7-endo-trig cyclizations, as the pendant olefin of interest approaches the β-radical from either the Si or Re face of the enone. There are 2 more diastereomeric transition states for each of the 5-exo- and 6-exo-trig cyclizations, as the α-radical can approach the more substituted and prochiral carbon in the isopropenyl olefin and the vinyl silane from either of the diastereotopic faces of the olefin.

(30) No first-order saddle point exists describing TS45, not that the formation of $^3\text{133}$ is barrierless, but rather that the saddle structure that would have corresponded to TS45 maintains non-zero energy gradient until ultimately reaching TS52. In other words, bringing the vinyl silane olefin to the $^3(\pi\pi^*)$ enone would more readily give rise to TS50. This is likely due to the steric congestion of forming vicinal tetrasubstituted centers in TS45. We note that there may be non-statistical dynamical affects that are not accounted for here – TS52 may be near an inflection point on a bifurcated PES which could lead to $^3\text{133}$ or $^3\text{125}$ from $^3\text{121}$.

(31) The $^3(n\pi^*)$ transition structure is different than that along the $^3(\pi\pi^*)$ surface. However, the vertical excitation of ca. 40 kcal/mol at the $^3(\pi\pi^*)$ saddle point highlights the significant divergence of the two surfaces at this region of the PES.

(32) Similar reactivity has been proposed in intermolecular enone/olefine photocycloadditions. Bowman, R. M.; Calvo, C.; McCullough, J. J.; Rasmussen, P.
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A


(33) Note that its <0.5% of QD-NEVPT2 wavefunction.

(34) The vertical singlet-triplet gap was calculated at the same geometry optimized by (U)B3LYP-D4/def2-SV(P) on the open-shell singlet surface. Energy of the lowest singlet and triplet state was calculated with state-averaging using the QD-NEVPT2 method with an (8,8) active space.

(35) Note the relative rates of ISC also depend on the geometry of the 1,4-diradical, with increasingly perpendicular valence orbitals giving rise to stronger SOC. Increased ionic character in the singlet state and decreasing distance between the two radical centers also serve to maximize SOC. See also: Carlacci, L.; Doubleday, C.; Furlani, T. R.; King, H. F.; McIver, J. W. Spin-Orbit Coupling in Biradicals. Ab Initio MCSCF Calculations on Trimethylene and the Methyl-Methyl Radical Pair. J. Am. Chem. Soc. 1987, 109, 5323–5329.


(37) Broken symmetry energies were spin decontaminated following the approach of Yamaguchi and coworkers to approximate the energy of the pure singlet states.
Chapter 4 – Quantum Mechanics Investigations of the [2+2] Photocycloaddition in the Synthesis of (−)-Scabrolide A


CHAPTER 5


5.1 INTRODUCTION

The construction of chiral all-carbon quaternary centers featuring vicinal tertiary stereocenters exemplifies a prevalent challenge in synthetic chemistry. We envisioned the transition metal-catalyzed branched-selective allylic alkylation of prochiral hard enolate nucleophiles as a promising strategy for accessing such motifs. However, a multitude of challenges must be overcome, including regioselectivity in enolate formation, and regio-, enantio-, and diastereoselectivity in the alkylation event.\(^1\) Ir catalyst systems have proven to be privileged for the branched-selective allylic alkylation of soft carbon nucleophiles.\(^2\) Extending this reactivity paradigm to hard, prochiral enolate nucleophiles has remained a challenge.\(^3\) To address this, Hartwig employed the in situ generation of Ba enolates to enable the branched-selective allylic alkylation of α-tetralone nucleophiles (156) (Figure 5.1A).\(^4\) However, this approach is limited to select ketones due to the challenge of regioselective deprotonation. Related transformations are subject to similar constraints.\(^5\) The Pd-catalyzed decarboxylative allylic alkylation of β-ketoesters represents a general, regiospecific-at-nucleophile strategy for the asymmetric allylic alkylation of hard enolates (Figure 5.1B).\(^6\) However, canonical Pd-catalyzed decarboxylative allylic alkylation

\(^1\) Unpublished research conducted with Dr. Stephen Sardini and Dr. Veronica Hubble
employing tetrasubstituted nucleophiles and substituted allyl esters (158a) gives rise to undesired regioselectivity, yielding linear alkylation products (159a) (Figure 5.1C).^3^7

**Figure 5.1. Asymmetric allylic alkylation of tetrasubstituted enolate nucleophiles.**

---

[a] Reaction conditions: 158a (0.05 mmol), Pd\(_2\)(dba)_3 (2.5 mol %), (S,S)-DACH-Ph (6.5 mol %), and THF (2 mL) at 60 °C for 14 h. NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. Enantioselectivity measured by chiral SFC analysis.

Aided by our prior mechanistic studies, we sought to favor the formation of branched products through the design of ligands that bias key interactions in the inner-sphere seven-membered reductive elimination transition state. Ultimately, we achieve a general approach to chiral all-carbon vicinal quaternary/tertiary stereocenters (Figure 5.1D). High diastereoo- (>20:1) and enantioselectivity (>80% ee) are obtained, with the
majority of products featuring >20:1 branched/linear selectivity. Subsequent derivatization of these compounds highlights their utility as synthetic building blocks.

5.2 MECHANISM AND DEVELOPMENT

We began our investigation by considering the inner-sphere transition states that lead to the formation of the desired branched (160a) and undesired linear (159a) products from β-ketoester 158a (Figure 5.2A). The two lowest energy transition states leading to linear (159a) and branched (160a) products are TS61 and TS62, respectively. Unfortunately, with the prototypical (S)-t-BuPHOX ligand (L1), linear TS61 is favored by 2.6 kcal/mol over its branched counterpart. Noting the proximity of the allyl substituent to the phenyl group of the PHOX backbone (red arrows in TS61 at top of Figure 5.2A), we explored di-ortho substitution of the ligand aryl groups as a means to disfavor TS61 by sterics. Accordingly, with (S)-Mes-t-BuPHOX (L2), TS62 now becomes favored over TS61 by 3.5 kcal/mol. Enantioselectivity of the branched product (160a) from inner-sphere reactivity is computed to remain high, with ΔΔG‡ between diastereomeric transition states of 2.4 and 3.9 kcal/mol with L1 and L2, respectively. Moreover, 2.5 and 1.2 kcal/mol preferences for the chair-like over the boat-like transition states ensures good diastereoselectivity. In summary, our preliminary in silico studies highlight that (1) ortho substitution of the ligand arenes will introduce a bias for the desired branched product (160a), and (2) a purely inner-sphere reaction will maintain both high diastereo- and enantioselectivity.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

**Figure 5.2.** Computational studies and initial reaction development.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield</th>
<th>B:L</th>
<th>dr</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-t-BuPHOX (L1)</td>
<td>THF</td>
<td>54</td>
<td>1.2:1</td>
<td>2.1:1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>(S)-t-BuPHOX (L1)</td>
<td>PhMe</td>
<td>97</td>
<td>1.1:9</td>
<td>7.0:1</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>(S)-CF$_3$-BuPHOX (L3)</td>
<td>PhMe</td>
<td>88</td>
<td>1.1:1</td>
<td>14:1</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>(S)-Mes-t-BuPHOX (L2)</td>
<td>PhMe</td>
<td>38</td>
<td>1.1:1</td>
<td>1.5:1</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>L4</td>
<td>PhMe</td>
<td>25</td>
<td>3:1:1</td>
<td>12:1</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>PhMe</td>
<td>85</td>
<td>11:1</td>
<td>14:1</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>L6</td>
<td>PhMe</td>
<td>70</td>
<td>1:7:1</td>
<td>16:1</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>L7</td>
<td>PhMe</td>
<td>62</td>
<td>5:9:1</td>
<td>&gt;20:1</td>
<td>76</td>
</tr>
</tbody>
</table>

[a] Gibbs free energies in kcal/mol. [b] Reaction conditions: 158a (0.05 mmol), Pd$_2$(dba)$_3$ (2.5 mol %), ligand (6.5 mol %), and solvent (2 mL) at 60 ºC for 14 h. NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. B:L and dr determined by crude $^1$H NMR analysis. Enantioselectivity measured by chiral SFC analysis. [c] Isolated yield from 0.1 mmol of 158a at 50 ºC.

Encouraged by the prospect of rational ligand design as a means to affect branched-selective alkylation, we began our experimental investigations. As anticipated, subjecting β-ketoester 158a to standard reaction conditions with (S)-t-BuPHOX (L1) in THF afforded the undesired linear isomer (159a) as the major reaction product with a branched-to-linear ratio (B/L) of 1:2.1 (Figure 5.2B, entry 1). Surprisingly, the branched ketone (160a) was furnished in poor enantio- and diastereoselectivity. Our computational studies found that branched product formation from inner-sphere reductive elimination to proceed with both high enantio- and diastereoselectivity. Hence, we suspected a deleterious outer-sphere...
mechanism to be competitive with said inner-sphere processes. To disfavor charge-separated outer-sphere intermediates, a less polar solvent, such as toluene, and the electron-poor \((S)-(CF_3)_3-t\)-BuPHOX (L3) ligand were explored. Under these conditions, the desired branched product is obtained in 86% yield, 80% ee, and an improved 14:1 dr (entries 2–3). As anticipated, regioselectivity remains poor, with a B/L ratio of 1:1.1. To improve branched-selectivity, \((S)\)-Mes-\(t\)-BuPHOX (L2) from our in silico studies was explored; however, the electron rich nature of the ligand likely supports outer-sphere processes, affording 160a in 6% ee and 1.9:1 dr (entry 4). Hence, a series of ligands that keep ortho aryl substitution yet feature electron-withdrawing groups were evaluated (L4–L7, entries 5–8). Ultimately, \(o\)-trifluoromethylether-containing PHOX ligand L7 was found to be optimal for the branched-selective allylic alkylation of 158a, affording the desired product (160a) in 62% isolated yield, 82% ee, >20:1 dr, and in a 9.1:1 B/L ratio at 50 °C in toluene (entry 9).

**5.3 SUBSTRATE SCOPE**

With respect to the scope of the transformation, substrates that incorporate \(\alpha,\beta\)-unsaturation led to a marked increase in the branched selectivity to 20:1 or greater (160b and 160c) (Figure 5.3). We were delighted to find the increasingly electron-rich enolate nucleophiles derived from synthetically useful vinylogous esters are well tolerated, affording the corresponding products (160d–160h) in generally good yield, >20:1 B/L, >20:1 dr, and 82–87% ee. Both ligands L6 and L7 perform well for the vinylogous ester substrate class. A vinylogous thioester was also explored, albeit reduced branched selectivity was observed (160i). \(\alpha\)-Enaminone-containing product 160j was obtained in
lower yield but excellent diastereo- and enantioselectivity (>20:1 dr, 94% ee). We were excited to observe that aliphatic substituted allyl electrophiles are competent coupling partners. Crotyl alcohol-derived β-ketoester 158k affords enone 160k in 59% yield, 8.3:1 dr, and 73% ee, albeit with a diminished 2.5:1 B/L ratio. The reduction in branched selectivity likely arises from the smaller steric profile of the methyl substituent, making distinction between TS61 and TS62 more challenging. Employing a larger alkyl substituent restores branched-selectivity (160l). Additionally, α-fluoro enolate nucleophiles are highly competent substrates in this transformation. A variety of fluorinated tetrasubstituted/tertiary vicinal stereocenter-containing products (160m–160q) were furnished in generally good yield as predominantly a single isomer with high enantioselectivity (82–87% ee). Hence, the branched-selective decarboxylative allylic alkylation described herein represents a powerful strategy to access diverse, stereochemically rich building blocks.
Figure 5.3. Substrate scope of branched-selective allylic alkylation.

\[
\begin{align*}
\text{Substrate scope for branched-selective allylic alkylation forging quaternary centers} \\
\end{align*}
\]

[a] Reaction conditions: \(158\) (0.1 mmol), \(\text{Pd}_2(\text{dba})_3\) (2.5 mol %), \(L7\) (6.5 mol %), and toluene (4 mL) at 50 \(^\circ\)C for 14 h. [b] \(\text{Pd}_2(\text{pmdba})_3\) can be employed as a Pd source when dba is difficult to separate from desired product. [c] \(L6\) employed (comparable performance between \(L7\) and \(L6\)). [d] \(L3\) employed. [e] Reaction carried out at 60 \(^\circ\)C.
5.4 PRODUCT TRANSFORMATIONS

Derivatization of allylic alkylation products showcases the synthetic utility of these building blocks. Stork–Danheiser ketone transposition of vinylogous ester 160d afforded \(\gamma\)-substituted \(\alpha,\beta\)-unsaturated ketone 161. Selective olefin hydrogenation of 160d smoothly furnishes vicinal stereocenter-containing product 162 in nearly quantitative yield. Wacker oxidation of the terminal olefin of 160c yielded ketone 163, now bearing a 1,4-dioxygenation pattern.

*Figure 5.4. Branched allylic alkylation product derivatizations.*

\[
\begin{align*}
\text{EtO} & \quad \text{Ph} & \quad \text{Me} & \quad \text{EtO} \\
\text{H} & \quad \text{C} & \quad \text{H} & \quad \text{Cl} \\
\text{Me} & \quad \text{O} & \quad \text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{Ph} & \quad \text{Me} \\
\text{DIBAL-H, CH}_2\text{Cl}_2, 0 \degree \text{C} & \quad \text{then, } \text{H}_2\text{SO}_4, 23 \degree \text{C} & \quad \text{57% yield} \\
\text{H}_2 (1 \text{ atm}), \text{Pd/C} & \quad \text{MeOH, 23 \degree C} & \quad \text{99% yield} \\
\text{PdCl}_2, \text{CuCl}_2 & \quad \text{O}_2 (1 \text{ atm}) & \quad \text{DMF/H}_2\text{O, 60 \degree C} & \quad \text{30% yield}
\end{align*}
\]

5.5 CONCLUSIONS

We report the development of a branched-selective Pd-catalyzed decarboxylative asymmetric allylic alkylation of *hard* enolate nucleophiles. Building on our prior studies on the inner-sphere seven-centered reductive elimination, we derive a set of design principles for rational ligand design that ultimately overturns the innate selectivity in prior systems. The transformation employs readily accessible \(\beta\)-ketoester precursors to furnish products containing vicinal all-carbon quaternary/tertiary stereocenters. Branched products
are obtained in up to 80% yield, >20:1 dr, and 87% ee. Studies further expanding the utility and scope of this transformation are underway and will be reported in due course.

5.6 SUPPORTING INFORMATION

5.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer (100 MHz) and are reported relative to CHCl₃ (δ 77.16 ppm). ²H NMR spectra were recorded on a Bruker 400 MHz (61 MHz) spectrometer and are reported relative to residual CDCl₃ (δ 7.26 ppm). Data for ¹H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as the peaks appear as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

silicon grease (δ 0.07 ppm), which do not impact product assignments. $^{13}$C NMR spectra of deuterated compounds are complicated by the low intensity of peaks of deuterium-substituted carbon atoms. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO$_2$ analytical chromatography system utilizing Chiralpak (AD-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in Field Desorption (FD$^+$) mode. Absolute stereochemical assignments were made by vibrational circular dichroism analysis for select compounds with related compounds assigned by analogy.

Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligands were prepared according to literature procedures.$^{12}$

5.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation

General Procedure A: Asymmetric Pd-Catalyzed Decarboxylative Allylic Alkylation

In a nitrogen filled glovebox, an oven-dried 1 dram vial was charged with a stir bar, Pd$_2$(dba)$_3$ or Pd$_2$(pmdba)$_3$ (2.5 µmol, 2.5 mol %), ligand (0.0065 mmol, 6.5 mol %), and toluene (1.0 mL). The catalyst solution was stirred at 23 ºC for 20 min, then added to a solution of substrate 158 in toluene (3 mL) in a 2 dram vial. The reaction vial was then sealed with electrical tape, removed from the glovebox, and heated to 50 ºC for 14 h. The reaction mixture was let cool to ambient temperature, passed through a plug of silica gel, and concentrated under reduced pressure. The crude reaction mixture was loaded directly onto a flash column and the product (160) was isolated by silica gel flash column chromatography.

(S)-2-methyl-2-((S)-1-phenylallyl)cyclohexan-1-one (160a)

Prepared from 158a (27.2 mg, 100 µmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the title compound as a colorless oil (14.2 mg, 62.2 µmol, 62% yield, 9.1:1 B/L, >20:1 dr (B), 82% ee(B)).
*Crude $^1$H NMR analysis reveals a B/L of 5.6:1 prior to chromatography.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 6.21 – 6.07 (m, 1H), 5.09 – 5.03 (m, 2H), 3.93 (d, $J$ = 9.4 Hz, 1H), 2.56 – 2.32 (m, 2H), 2.10 – 1.98 (m, 2H), 1.87 – 1.62 (m, 3H), 1.35 – 1.24 (m, 1H), 0.98 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 215.0, 140.0, 136.6, 129.8, 128.2, 126.9, 117.2, 53.0, 52.5, 39.7, 37.4, 27.8, 21.1, 19.6.

IR (Neat Film, NaCl): 3062, 3027, 2933, 2863, 1704, 1453, 1124 cm$^{-1}$.

HRMS (MM: EI$^+$): $m/z$ calc’d for C$_{16}$H$_{20}$O [M]$^+$: 228.1514, found 228.1515.

Optical Rotation: $[\alpha]_D^{21}$ –25.1 (c 1.00, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda$ = 210 nm, $t_r$ (min): minor = 3.59, major = 2.81.

(S)-6-methyl-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160b)

Prepared from 158b (27.2 mg, 1.00 mmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–100% CH$_2$Cl$_2$/hexanes) afforded the title compound as a colorless oil (11.5 mg, 0.05 mmol, 51% yield, 20:1 B/L, >20:1 dr (B), 78% ee(B)).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32 – 7.17 (m, 5H), 6.84 (dt, $J$ = 10.0, 3.9 Hz, 1H), 6.20 (dt, $J$ = 16.8, 9.9 Hz, 1H), 5.91 (dt, $J$ = 10.0, 2.1 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.86 (d, $J$ =
Chapter 5 - Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

9.7 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.40 – 2.29 (m, 1H), 1.85 (dt, J = 13.8, 5.7 Hz, 1H), 1.73 (ddd, J = 13.9, 7.3, 5.5 Hz, 1H), 1.10 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 203.0, 148.2, 140.8, 137.0, 129.8, 129.1, 128.1, 126.6, 117.4, 52.9, 48.8, 31.1, 23.4, 20.5.

IR (Neat Film, NaCl): 3028, 2935, 2343, 2357, 1699, 1670, 1636, 1387, 1222, 695 cm$^{-1}$.

HRMS [M+H]$^+$: m/z calc’d for C$_{16}$H$_{19}$O: 227.14359, found 227.14317.

Optical Rotation: [α]$_D^{22}$ +39.0° (c 0.48, CHCl$_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t$_R$ (min): minor = 4.45, major = 4.08.

(S)-3,6-dimethyl-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160c)

Prepared from 158c (28.4 mg, 100 µmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–20% EtOAc/hexanes) afforded the title compound as a colorless oil (16.8 mg, 69.9 µmol, 70% yield, >20:1 B/L, >20:1 dr, 80% ee).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.37 – 7.24 (m, 5H), 6.28 (dt, J = 16.8, 9.9 Hz, 1H), 5.83 (q, J = 1.4 Hz, 1H), 5.17 (dd, J = 10.0, 1.8 Hz, 1H), 5.11 (ddd, J = 16.8, 1.8, 0.9 Hz, 1H), 3.94 (d, J = 9.7 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.37 – 2.28 (m, 1H), 1.98 (s, 3H), 1.92 (ddd, J = 13.8, 6.9, 5.4 Hz, 1H), 1.78 (ddd, J = 13.8, 7.0, 5.4 Hz, 1H), 1.16 (s, 3H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.8, 159.9, 141.0, 137.1, 129.8, 128.1, 126.5, 126.0, 117.4, 53.1, 47.5, 30.9, 28.3, 24.1, 20.8.

IR (Neat Film, NaCl): 3062, 3028, 2969, 2932, 1663, 1637, 1452, 1377, 1213 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{20}$O [M]: 240.1514, found 240.1522.

Optical Rotation: $[\alpha]_D^{21} +38.1$ (c 1.00, CHCl$_3$)

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 2.95, major = 3.31.

(S)-3-ethoxy-6-methyl-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160d)

Prepared from 158d (31.4 mg, 100 µmol) following General Procedure A using Pd$_2$(dba)$_3$ and L7. Purification by flash column chromatography (0–40% EtOAc/hexanes) afforded the title compound as a colorless oil (18.8 mg, 70 µmol, 70% yield, >20:1 dr, 84% ee). Ligand L6 afforded identical results.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28 – 7.16 (m, 5H), 6.23 (dt, $J = 16.8, 9.9$ Hz, 1H), 5.23 (s, 1H), 5.12 (dd, $J = 10.1, 1.8$ Hz, 1H), 5.06 (ddd, $J = 16.8, 1.9, 0.9$ Hz, 1H), 3.90 (d, $J = 9.7$ Hz, 1H), 3.87 (dd, $J = 7.0, 2.8$ Hz, 1H), 3.83 (dd, $J = 7.0, 2.7$ Hz, 1H), 2.48 (ddd, $J = 18.1, 7.0, 5.6$ Hz, 1H), 2.44 – 2.34 (m, 1H), 1.87 (ddd, $J = 13.4, 7.6, 5.6$ Hz, 1H), 1.73 – 1.66 (m, 2H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.11 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.8, 175.5, 141.2, 137.1, 129.8, 128.1, 126.5, 117.4, 102.0, 64.3, 53.5, 47.5, 29.5, 26.1, 21.3, 14.3.
(S)-3-ethoxy-6-ethyl-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160e)

Prepared from 158e (34.4 mg, 104 µmol) following General Procedure A using Pd$_2$(dba)$_3$ and L6. Purification by flash column chromatography (5–20% EtOAc/hexanes) afforded the title compound as a colorless oil (21.0 mg, 74 µmol, 70% yield, >20:1 dr, 87% ee).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.26 – 7.21 (m, 4H), 7.19 – 7.13 (m, 1H), 6.26 (dt, J = 16.8, 10.1 Hz, 1H), 5.22 (s, 1H), 5.14 – 5.07 (m, 2H), 4.02 (d, J = 10.0 Hz, 1H), 3.86 – 3.78 (m, 2H), 2.47 – 2.33 (m, 2H), 1.96 – 1.74 (m, 3H), 1.50 (dq, J = 14.5, 7.4 Hz, 1H), 1.31 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 201.0, 175.2, 141.6, 137.0, 130.1, 128.0, 126.3, 117.3, 103.0, 64.2, 51.7, 50.7, 26.7, 26.3, 26.0, 14.3, 8.3.

IR (Neat Film, NaCl): 2978, 2937, 1650, 1612, 1380, 1189 cm$^{-1}$.

HRMS (MM: ESI+): m/z calc’d for C$_{19}$H$_{25}$O$_2$ [M+H]$^+$: 285.1849, found 285.1859.

Optical Rotation: $[\alpha]_D^{21}$ +16.0 (c 1.00, CHCl$_3$).
SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, \( t_R \) (min):
minor = 2.93, major = 3.50.

[methyl 3-((R)-4-ethoxy-2-oxo-1-((S)-1-phenylallyl)cyclohex-3-en-1-yl)propanoate (160f)]

Prepared from 158f (38.2 mg, 98.9 \( \mu \)mol) following General Procedure A using Pd\(_2\)(dba)\(_3\) and L6. Purification by flash column chromatography (5–20% EtOAc/hexanes) afforded the title compound as a colorless oil (14.3 mg, 41.8 \( \mu \)mol, 42% yield, >20:1 dr, 84% ee).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.26 – 7.20 (m, 4H), 7.18 – 7.13 (m, 1H), 6.25 (dt, \( J = 16.8, 10.1 \) Hz, 1H), 5.20 (s, 1H), 5.19 – 5.10 (m, 2H), 4.07 (d, \( J = 10.1 \) Hz, 1H), 3.86 – 3.77 (m, 2H), 3.63 (s, 3H), 2.52 – 2.33 (m, 3H), 2.25 (ddd, \( J = 16.3, 11.4, 4.8 \) Hz, 1H), 2.00 (ddd, \( J = 14.0, 11.5, 5.2 \) Hz, 1H), 1.95 – 1.79 (m, 3H), 1.31 (t, \( J = 7.0 \) Hz, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 200.2, 175.3, 174.3, 141.0, 136.2, 130.0, 128.0, 126.4, 117.9, 102.6, 64.2, 51.6, 51.0, 49.6, 28.3, 28.1, 27.0, 25.7, 14.1.

IR (Neat Film, NaCl): 2980, 2946, 1737, 1643, 1610, 1381, 1191 cm\(^{-1}\).

HRMS (MM: ESI+): \( m/z \) calc’d for C\(_{21}\)H\(_{27}\)O\(_4\) [M+H]\(^+\): 343.1904, found 343.1909.

Optical Rotation: \([\alpha]_D^{21} +24.6\) (c 1.00, CHCl\(_3\)).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, \( t_R \) (min):
minor = 2.54, major = 3.00.
3-((S)-4-ethoxy-2-oxo-1-((S)-1-phenylallyl)cyclohex-3-en-1-yl)propanenitrile (160g)

Prepared from 158g (35.3 mg, 100 µmol) following General Procedure A using Pd₂(dba)₃ and L₆. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (23.9 mg, 77.2 µmol, 77% yield, >20:1 B/L, >20:1 dr, 84% ee).

¹H NMR (400 MHz, CDCl₃): δ 7.29 – 7.23 (m, 2H), 7.19 (td, J = 7.8, 1.4 Hz, 3H), 6.23 (dt, J = 16.9, 10.1 Hz, 1H), 5.24 (s, 1H), 5.20 (d, J = 10.2 Hz, 1H), 5.13 (d, J = 16.9 Hz, 1H), 3.97 (d, J = 9.9 Hz, 1H), 3.89 – 3.80 (m, 2H), 2.51 – 2.39 (m, 3H), 2.28 – 2.12 (m, 2H), 1.93 – 1.76 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 199.5, 175.8, 140.2, 135.8, 129.8, 128.3, 126.9, 120.4, 118.5, 102.6, 64.6, 51.0, 49.8, 29.3, 26.7, 25.7, 14.2, 12.1.

IR (Neat Film, NaCl): 2980, 2937, 2246, 1643, 1606, 1381, 1190 cm⁻¹.

HRMS (MM: ESI⁺): m/z calc’d for C₂₀H₂₄O₂N [M+H]⁺: 310.1802, found 310.1804.

Optical Rotation: [α]D²¹ +13.1 (c 1.00, CHCl₃).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, tᵣ (min): minor = 2.06, major = 3.05.

(S)-3-(benzyloxy)-6-methyl-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160h)
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

Prepared from 158h following General Procedure A using Pd$_2$(dba)$_3$ and L6. Purification by flash column chromatography (0–40% EtOAc/hexanes) afforded the title compound as a colorless oil (23.4 mg, 0.704 mmol, 70% yield, >20:1 dr, 82% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.32 (m, 5H), 7.30 – 7.24 (m, 4H), 7.19 (ddd, $J = 8.4, 5.3, 2.2$ Hz, 1H), 6.24 (dt, $J = 16.8, 9.9$ Hz, 1H), 5.37 (s, 1H), 5.12 (dd, $J = 10.1, 1.9$ Hz, 1H), 5.06 (d, $J = 16.8$ Hz, 1H), 4.87 – 4.80 (m, 2H), 3.92 (d, $J = 9.7$ Hz, 1H), 2.55 (dt, $J = 18.1, 6.1$ Hz, 1H), 2.45 (ddd, $J = 18.1, 7.5, 5.6$ Hz, 1H), 1.91 (ddd, $J = 13.3, 7.6, 5.6$ Hz, 1H), 1.73 (ddd, $J = 13.7, 7.0, 5.6$ Hz, 1H), 1.14 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.6, 175.0, 141.1, 137.0, 135.2, 129.8, 128.8, 128.7, 128.1, 128.0, 126.5, 117.5, 102.6, 70.5, 53.5, 47.6, 29.4, 26.1, 21.3.

IR (Neat Film, NaCl): 2932, 1652, 1610, 1362, 1186 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{23}$H$_{24}$O$_2$ [M]$^+$: 332.1776, found 332.1773.

Optical Rotation: $[\alpha]_D^{21} = -5.0$ (c 1.00, CHCl$_3$).

SFC conditions: 25% IPA, 2.5 mL/min, Chiralpak OD-H column, $\lambda = 254$ nm, $t_R$ (min): minor = 4.10, major = 3.72.

(S)-6-methyl-6-((S)-1-phenylallyl)-3-(phenylthio)cyclohex-2-en-1-one (160i)

Prepared from 158i following General Procedure A using Pd$_2$(dba)$_3$ and L6. Purification by flash column chromatography (0–40% EtOAc/hexanes) afforded the title compound as a colorless oil (29.2 mg, 0.873 mmol, 87% yield, 7.5:1 B/L, >20:1 dr, 78% ee).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.47 – 7.38 (m, 5H), 7.27 – 7.18 (m, 5H), 6.18 (dt, $J = 16.8$, 9.9 Hz, 1H), 5.37 (s, 1H), 5.11 (dd, $J = 10.1$, 1.9 Hz, 1H), 5.05 (d, $J = 16.8$ Hz, 1H), 3.91 (d, $J = 9.7$ Hz, 1H), 2.63 – 2.46 (m, 2H), 1.94 (ddd, $J = 13.3$, 7.7, 5.3 Hz, 1H), 1.78 (ddd, $J = 13.7$, 6.7, 5.2 Hz, 1H), 1.11 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 199.3, 164.0, 143.5, 140.9, 136.8, 135.6, 130.2, 129.9, 129.8, 128.1, 126.5, 120.3, 117.6, 53.3, 47.9, 31.0, 27.2, 21.3.

IR (Neat Film, NaCl): 2927, 1650, 1579, 1212 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{22}$H$_{22}$O$_2$S $[M]^+$: 334.1391, found 334.1392.

Optical Rotation: $[\alpha]_{D}^{21}$ = –64.9 (c 1.00, CHCl$_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.45, major = 4.08.

(S)-6-methyl-2-morpholino-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160j)

Prepared from 158j following General Procedure A using Pd$_2$(dba)$_3$ and L$_3$. Purification by preparatory TLC (10% acetone/toluene) afforded the title compound as a colorless oil (9.2 mg, 0.030 mmol, 30% yield, 9.1:1 B/L, >20:1 dr, 94% ee).

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.18 – 7.16 (m, 3H), 7.14 – 7.08 (m, 2H), 7.06 – 7.01 (m, 1H), 6.13 (dt, $J = 16.8$, 9.9 Hz, 1H), 5.24 (t, $J = 4.4$ Hz, 1H), 4.98 – 4.90 (m, 2H), 3.90 (d, $J = 9.6$ Hz, 1H), 3.77 – 3.58 (m, 4H), 2.91 – 2.83 (m, 2H), 2.39 – 2.32 (m, 2H), 2.22 – 2.10
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

(m, 1H), 1.96 – 1.84 (m, 1H), 1.61 (dt, J = 13.8, 5.4 Hz, 1H), 1.33 (ddd, J = 13.8, 8.2, 5.6 Hz, 1H), 1.08 (s, 3H).

\(^{13}\text{C NMR (100 MHz, C}_6\text{D}_6\): } \delta 198.3, 146.3, 141.1, 137.6, 130.0, 128.2, 126.8, 121.6, 117.2, 67.0, 53.4, 50.5, 49.4, 31.5, 22.0, 20.5.

IR (Neat Film, NaCl): 3027, 2928, 2853, 1681, 1615, 1450, 1263, 1210, 1119 cm\(^{-1}\).

HRMS (MM: ESI\(^{+}\)): \(m/z\) calc’d for C\(_{20}\)H\(_{27}\)O\(_2\)N [M+H]\(^{+}\): 312.1958, found 312.1961.

Optical Rotation: \([\alpha]_D^{21} +8.9\) (c 0.90, CHCl\(_3\)).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak OJ-H column, \(\lambda = 280\) nm, \(t_R\) (min): minor = 3.89, major = 2.05.

\[(S)-6\text{-methyl-2-morpholino-6-\((S)-1\text{-phenylallyl)cyclohex-2-en-1-one} (160k)\]

Prepared from \(158k\) (0.094 mmol) following General Procedure A using Pd\(_2\)(pmdba)\(_3\) and L\(_6\). Purification by preparatory TLC (25% Et\(_2\)O/hexanes) afforded the title compound as a colorless oil (10.0 mg, 0.056 mmol, 59% yield, 2.5:1 B/L, 9.0:1 dr, 73% ee).

\(^1\text{H NMR (400 MHz, C}_6\text{D}_6\): } \delta 5.81 – 5.75 (m, 1.4H (linear + both branched)), 5.69 (ddd, \(J = 16.5, 10.7, 8.4\) Hz, 0.9H (branched)), 5.62 – 5.53 (m, 0.4H (linear)), 5.39 – 5.29 (m, 0.4H (linear)), 5.08 – 4.95 (m, 2H (branched major + branched minor)), 2.75 – 2.63 (m, 0.9H (branched major)), 2.64 – 2.56 (m, 0.1H (branched minor)), 2.31 – 2.21 (m, 3.6H), 2.01 (ddd, \(J = 13.7, 7.3, 6.3\) Hz, 1H), 1.95 – 1.87 (m, 5H), 1.76 – 1.58 (m, 3.3H), 1.06 (s,
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

1.2H(linear), 0.99 (s, 2.7H(branched major)), 0.98 (s, 0.4H(branched minor)), 0.94 (d, J = 6.8 Hz, 2.7H(branched major)), 0.88 (d, J = 7.0 Hz, 0.4H(branched minor)).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 5.79 (s, 1H), 5.67 (dt, J = 16.9, 9.9 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.47 (d, J = 2.4 Hz, 2H), 3.57 – 3.40 (m, 2H), 2.97 (ddd, J = 9.4, 7.4, 5.6 Hz, 1H), 2.37 – 2.17 (m, 2H), 2.08 – 1.97 (m, 1H), 1.91 (s, 3H), 1.70 – 1.61 (m, 2H), 1.02 (s, 3H).

$^13$C NMR (100 MHz, CDCl$_3$): δ 204.0, 203.8, 160.5, 160.2, 140.4, 139.9, 126.8, 126.1, 125.8, 125.6, 125.5, 115.6, 115.4, 46.3, 46.0, 43.9, 41.6, 40.2, 33.8, 33.1, 31.9, 30.5, 29.8, 29.5, 28.4, 28.1, 28.0, 24.2, 24.1, 21.9, 20.3, 18.1, 15.3, 14.4, 13.1.

IR (Neat Film, NaCl): 2965, 2930, 1666, 1638, 1433, 1378, 1213 cm$^{-1}$.

HRMS (MM: F1+): $m/z$ calc’d for C$_{12}$H$_{18}$O [M]$^+$: 178.1358, found 178.1362.

Optical Rotation: $[\alpha]_D^{21}$ +2.3 (c 1.00, CHCl$_3$).

SFC conditions: 4% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda$ = 210 nm, $t_R$ (min): minor = 7.16, major = 8.11.

(S)-6-methyl-2-morpholino-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160l)

Prepared from 158l (0.105 mmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–20% EtOAc/hexanes) afforded the title compound as a colorless oil (10.6 mg, 0.037 mmol, 35% yield, >20:1 B/L, >20:1 dr, 82% ee).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 202.7, 159.9, 138.6, 136.0, 128.3, 127.5, 127.4, 125.9, 118.5, 72.8, 70.6, 48.1, 45.1, 29.7, 28.0, 24.1, 20.9.

IR (Neat Film, NaCl): 3026, 2918, 1665, 1453, 1214, 1096 cm$^{-1}$.

HRMS (MM: ESI$^+$): $m/z$ calc’d for C$_{19}$H$_{24}$O$_2$ [M]$^+$: 284.1766, found 284.1776.

Optical Rotation: $[\alpha]_D^{21}$ +33.2 (c 1.05, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 3.77, major = 2.81.

(S)-2-fluoro-2-((S)-1-phenylallyl)cyclohexan-1-one (160m)

Prepared from 158m (28.6 mg, 103 $\mu$mol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the title compound as a colorless crystalline solid (17.1 mg, 73.6 $\mu$mol, 71% yield, >20:1 B/L, >20:1 dr, 85% ee) as well as a fraction (1.5 mg, 6.5 $\mu$mol, 6% yield) containing mixed E/Z linear isomers with trace of the major diastereomer of the branched isomer. Overall yield: 18.6 mg, 80.1 $\mu$mol, 77% yield, 13:1 B/L, >20:1 dr (B), 85% ee (B)).

*Crude $^1$H NMR analysis reveals a B/L of 12.5:1 prior to chromatography.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.24 (m, 5H), 6.18 (ddd, $J$ = 17.1, 10.3, 8.8 Hz, 1H), 5.12 (d, $J$ = 10.3 Hz, 1H), 5.08 (d, $J$ = 17.1 Hz, 1H), 3.88 (dd, $J$ = 32.4, 8.8 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.54 – 2.45 (m, 1H), 2.06 – 1.98 (m, 1H), 1.86 – 1.68 (m, 5H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

*Trace isolated peaks of minor diastereomer (<5%) observed as 5.26 – 5.19 (m, 2H), 2.88 – 2.75 (m, 2H), 2.43 – 2.30 (m, 2H). Others overlap with major diastereomer.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 207.5 (d, $J_{C-F}$ = 18.2 Hz), 137.9, 135.3 (d, $J_{C-F}$ = 5.4 Hz), 129.6 (d, $J$ = 2.6 Hz), 128.8, 127.5, 117.9, 100.7 (d, $J_{C-F}$ = 194.8 Hz), 53.1 (d, $J_{C-F}$ = 20.0 Hz), 40.3, 36.7 (d, $J_{C-F}$ = 21.7 Hz), 27.8, 22.2 (d, $J_{C-F}$ = 9.1 Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$): δ –166.45 (d, $J$ = 32.5 Hz).

IR (Neat Film, NaCl): 2948, 1724, 1454, 1047 cm$^{-1}$.

HRMS (MM: EI$^+$): $m/z$ calc’d for C$_{15}$H$_{17}$OF [M]$^+$: 232.1263, found 232.1259.

Optical Rotation: [α]$_D^{21}$ –23.3 (c 1.00, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 3.23, major = 2.65.

(S)-2-fluoro-2-((S)-1-phenylallyl)cyclohexan-1-one (160n)

Prepared from 158n (27.0 mg, 98.4 µmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L7. Purification by flash column chromatography (0–20% EtOAc/hexanes) afforded the title compound as a colorless oil (17.1 mg, 74.3 µmol, 75% yield, >20:1 B/L, >20:1 dr, 82% ee).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.37 – 7.27 (m, 5H), 6.95 – 6.90 (m, 1H), 6.23 (ddd, $J$ = 17.0, 10.1, 8.7 Hz, 1H), 6.06 (dddd, $J$ = 10.0, 4.0, 2.8, 1.3 Hz, 1H), 5.11 (d, $J$ = 10.1 Hz, 1H), 4.96 (d, $J$ = 17.0 Hz, 1H), 3.67 (dd, $J$ = 31.1, 8.7 Hz, 1H), 2.58 – 2.38 (m, 2H), 2.19 – 2.07 (m, 1H), 2.00 – 1.92 (m, 1H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 195.6 (d, $J_{C-F} = 17.2$ Hz), 149.0, 138.5, 135.3 (d, $J_{C-F} = 5.5$ Hz), 129.2 (d, $J_{C-F} = 2.8$ Hz), 128.9, 128.2, 127.6, 118.0, 97.4 (d, $J_{C-F} = 194.5$ Hz), 53.0 (d, $J_{C-F} = 20.2$ Hz), 31.2 (d, $J_{C-F} = 22.1$ Hz), 25.1 (d, $J_{C-F} = 11.3$ Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$): $-168.84$ (d, $J = 31.5$ Hz).

IR (Neat Film, NaCl): 3031, 2922, 1695, 1489, 1452, 1425, 1383, 1219, 1060 cm$^{-1}$.

HRMS (MM: EI+): $m/z$ calc’d for C$_{15}$H$_{15}$OF [M]: 230.1107, found 230.1113.

Optical Rotation: $[\alpha]_{D}^{21} +41.1$ (c 1.00, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.74, major = 3.92.

(R)-3-ethoxy-6-fluoro-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160o)

Prepared from 158o (31.8 mg, 100 $\mu$mol) following General Procedure A using Pd$_2$(dba)$_3$ and L6. Purification by flash column chromatography (5–20% EtOAc/hexanes) afforded the title compound as a colorless oil (21.9 mg, 79.8 $\mu$mol, 80% yield, >20:1 dr, 87% ee).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.37 – 7.26 (m, 5H), 6.36 – 6.22 (m, 1H), 5.35 – 5.32 (m, 1H), 5.13 (d, $J = 10.2$ Hz, 1H), 4.97 (d, $J = 17.0$ Hz, 1H), 3.92 (q, $J = 7.1$ Hz, 2H), 3.71 (dd, $J = 29.7$, 8.5 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.45 – 2.36 (m, 1H), 2.16 – 2.03 (m, 1H), 1.94 – 1.85 (m, 1H), 1.38 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.4 (d, $J_{C-F} = 18.1$ Hz), 194.3, 175.6 (d, $J_{C-F} = 1.6$ Hz), 138.8, 135.4 (d, $J_{C-F} = 5.6$ Hz), 129.3 (d, $J_{C-F} = 2.5$ Hz), 128.8, 127.5, 117.8, 100.8, 96.4.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

(d, $J_{	ext{C-F}} = 191.3$ Hz), 65.1, 53.3 (d, $J_{	ext{C-F}} = 20.8$ Hz), 29.3 (d, $J_{	ext{C-F}} = 23.5$ Hz), 27.2 (d, $J_{	ext{C-F}} = 11.0$ Hz), 14.2.

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –168.60– –168.67 (m, 1F).

IR (Neat Film, NaCl): 2981, 2938, 1672, 1603, 1379, 1243, 1193 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{17}$H$_{20}$O$_2$F [M+H]$^+$: 275.1442, found 275.1440.

Optical Rotation: $[\alpha]_{D}^{21}$ –11.2 (c 0.70, CHCl$_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda$ = 254 nm, $t_R$ (min): minor = 2.25, major = 2.58.

(R)-6-((S)-1-(benzyloxy)but-3-en-2-yl)-6-fluoro-3-methylcyclohex-2-en-1-one (160p)

Prepared from 158p (36.0 mg, 108 $\mu$mol) following General Procedure A using Pd$_2$(dba)$_3$ and L7. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the branched product (160p) as a colorless oil (14.8 mg, 51.3 $\mu$mol, 48% yield, 14.3:1 dr, 84% ee) and the (Z)-linear product (160p_linear) also as a colorless oil (2.9 mg, 10.1 $\mu$mol, 9% yield, >20:1 Z/E, 53% ee)). Overall yield: 17.7 mg, 61.4 $\mu$mol, 57% yield, 5.1:1 B/L, >16.1 dr (B), 84% ee (B)).

*Crude $^1$H NMR analysis reveals a B/L of 5.6:1 and a dr (B) of 12.9:1 prior to chromatography. In the tabulated NMR data for 160p, the minor diastereomer is denoted.

160p:
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.36 - 7.27 (m, 5H), 5.88 - 5.74 (m, 2H), 5.34 - 5.24 (m, 0.15H(minor)), 5.17 (d, \(J = 10.3, 1.7\) Hz, 1H), 5.12 (d, \(J = 17.8\) Hz, 1H), 4.50 (s, 2H), 4.45 (d, \(J = 11.8\) Hz, 0.07H(minor)), 4.34 (d, \(J = 11.7\) Hz, 0.07H(minor)), 3.76 (dd, \(J = 9.8, 6.7\) Hz, 1H), 3.65 (dd, \(J = 9.6, 6.3\) Hz, 0.07H(minor)), 3.52 (ddd, \(J = 9.8, 5.6, 0.9\) Hz, 1H), 2.99 (ddt, \(J = 21.4, 9.2, 6.1\) Hz, 1H), 2.91 - 2.82 (m, 0.07H(minor)), 2.53 - 2.33 (m, 3H), 2.26 - 2.14 (m, 1H), 1.96 (s, 3H), 1.93 (s, 0.19H(minor)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 194.0\) (d, \(J_{C-F} = 17.9\) Hz), 162.3, 138.2, 133.8 (d, \(J_{C-F} = 4.6\) Hz), 128.5, 127.8, 127.7, 125.1, 119.1, 95.6 (d, \(J_{C-F} = 185.9\) Hz), 73.3, 69.7 (d, \(J_{C-F} = 5.7\) Hz), 47.1 (d, \(J_{C-F} = 21.4\) Hz), 30.6 (d, \(J_{C-F} = 22.7\) Hz), 29.6 (d, \(J_{C-F} = 9.5\) Hz), 24.2.

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta -167.64 - -167.85\) (m).

IR (Neat Film, NaCl): 2923, 1681, 1633, 1104 cm\(^{-1}\).

HRMS (MM: FD+): \(m/z\) calc’d for C\(_{18}\)H\(_{21}\)O\(_2\)F\(^+\): 289.1604, found 289.1590.

Optical Rotation: \([\alpha]_D^{21} - 34.2\) (c 1.00, CHCl\(_3\)).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, \(\lambda = 210\) nm, \(t_R\) (min): minor = 4.59, major = 3.43.

\(160p\_linear:\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.37 - 7.27 (m, 5H), 5.89 - 5.80 (m, 2H), 5.66 (dddt, \(J = 11.2, 8.4, 6.9, 1.5\) Hz, 1H), 4.54 - 4.48 (m, 2H), 4.13 - 4.08 (m, 1H), 4.09 - 4.00 (m, 1H), 2.68 - 2.49 (m, 2H), 2.48 - 2.30 (m, 2H), 2.28 - 2.09 (m, 2H), 1.94 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 194.3\) (d, \(J_{C-F} = 17.9\) Hz), 162.8, 138.3, 130.6, 128.6, 128.0, 127.8, 125.5 (d, \(J_{C-F} = 4.5\) Hz), 124.9, 93.9 (d, \(J_{C-F} = 183.0\) Hz), 72.5, 65.8, 32.1 (d, \(J_{C-F} = 23.8\) Hz), 31.6 (d, \(J_{C-F} = 22.9\) Hz), 29.2 (d, \(J_{C-F} = 9.0\) Hz), 24.3.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ −161.29 −161.59 (m).

IR (Neat Film, NaCl): 2917, 1682, 1631, 1072 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc'd for C$_{18}$H$_{21}$O$_2$F $[M]^{+}$: 289.1604, found 289.1597.

Optical Rotation: $[\alpha]_{D}^{21}$ −5.3 (c 0.30, CHCl$_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 6.68, major = 5.86.

(R)-3-ethoxy-6-fluoro-6-((S)-1-phenylallyl)cyclohex-2-en-1-one (160q)

Prepared from 158q (23.3 mg, 103 µmol) following General Procedure A using Pd$_2$(pmdba)$_3$ and L3. Purification by flash column chromatography (5–20% Et$_2$O/hexanes) afforded the title compound as a colorless oil (14.7 mg, 80.8 µmol, 78% yield, >20:1 dr, 87% ee). For further characterization, the mixture of isomers was subsequently purified by C18 reverse-phase preparatory HPLC (40–65% MeCN/H$_2$O) to afford the major diastereomer of 160q as a single isomer.

*Compound 160q was found to be volatile, avoid excessive exposure to high vacuum.

Yields are corrected for trace Et$_2$O in sample after purification.*

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.93 – 5.83 (m, 2H), 5.10 – 5.01 (m, 2H), 2.91 – 2.74 (m, 1H), 2.47 (dt, $J$ = 18.9, 5.6 Hz, 1H), 2.36 (dt, $J$ = 19.0, 6.5 Hz, 1H), 2.29 – 2.18 (m, 2H), 1.97 (s, 3H), 1.09 (d, $J$ = 7.0 Hz, 3H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 194.3 (d, \(J_{C-F} = 18.0\) Hz), 162.0, 137.5, 125.4, 116.5, 95.8 (d, \(J_{C-F} = 184.7\) Hz), 40.29 (d, \(J_{C-F} = 21.9\) Hz), 30.5, 29.8, 29.5, 29.3, 29.2, 29.1, 14.2 (d, \(J_{C-F} = 5.7\) Hz).

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta -168.13--168.31\) (m, 1F).

IR (Neat Film, NaCl): 2919, 2849, 1681, 1633, 1434, 1380, 1225 cm\(^{-1}\).

HRMS (MM: FI\(^+\)): \(m/z\) calc’d for C\(_{11}\)H\(_{15}\)OF [M]: 182.1107, found 182.1107.

Optical Rotation: \([\alpha]_{D}^{21} -32.3\) (c 0.40, CHCl\(_3\)).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, \(\lambda = 254\) nm, \(t_R\) (min): minor = 4.76, major = 5.45.

Synthesis of \(\beta\)-ketoester substrates (158a–158q)

General Procedure B: Alkylation of \(\beta\)-ketoesters.

\[
\begin{array}{c}
\text{165a–xx} \\
\begin{array}{c}
\text{R} \quad \text{R}^2 \\
\text{O} \quad \text{O} \\
\text{K}_2\text{CO}_3 \ (2\ \text{equiv}) \\
\text{electrophile} \ (2\ \text{equiv}) \\
\end{array}
\end{array}
\xrightarrow{\text{acetone, 50 °C}}
\begin{array}{c}
\text{158a–q} \\
\begin{array}{c}
\text{R} \quad \text{R}^2 \\
\text{O} \quad \text{O} \\
\end{array}
\end{array}
\]

To a solution of \(\beta\)-ketoester 165 (1 equiv) in acetone (0.5 M) is added anhydrous K\(_2\)CO\(_3\) (2 equiv), followed by the relevant electrophile (2 equiv). The reaction is heated to 50 °C and stirring is continued until complete consumption of starting material is observed (typically 24–36 h). The reaction mixture is then filtered, and volatiles are removed in vacuo. Purification by flash silica gel column chromatography affords the desired alkylated \(\beta\)-ketoester.
cinnamyl 1-methyl-2-oxocyclohexane-1-carboxylate (158a)

Prepared from cinnamyl 2-oxocyclohexane-1-carboxylate and methyl iodide following General Procedure B. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (0.458 g, 1.39 mmol, 84% yield).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.45 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.22 (m, 1H), 6.65 (d, $J = 15.9$ Hz, 1H), 6.26 (dt, $J = 15.9$, 6.5 Hz, 1H), 4.81 (ddd, $J = 12.8$, 6.4, 1.2 Hz, 1H), 4.77 (ddd, $J = 12.8$, 6.4, 1.2 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.51 – 2.43 (m, 2H), 2.06 – 1.98 (m, 1H), 1.79 – 1.61 (m, 3H), 1.53 – 1.44 (m, 1H), 1.33 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 208.3, 173.0, 136.2, 135.0, 128.8, 128.4, 126.8, 126.6, 65.9, 57.4, 40.8, 38.4, 27.6, 22.8, 21.4.

IR (Neat Film, NaCl): 2938, 1714, 1453 (m), 1142 (m), 961 (m) cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{20}$O$_3$ [M]$^+$: 272.1412, found 272.1410.

![Image](158b)

cinnamyl 1-methyl-2-oxocyclohex-3-ene-1-carboxylate (158b)

Prepared from cinnamyl 2-oxocyclohex-3-ene-1-carboxylate (prepared following General Procedure D and used crude) and methyl iodide following General Procedure B. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (0.48 g, 1.78 mmol, 23% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 – 7.27 (m, 5H), 6.92 (dddd, $J = 10.1$, 4.4, 3.3, 1.0 Hz, 1H), 6.62 (d, $J = 15.9$ Hz, 1H), 6.23 (dt, $J = 15.9$, 6.3 Hz, 1H), 6.07 (ddd, $J = 10.1$, 2.4, 1.7 Hz, 1H), 5.23 (dd, $J = 15.9$, 11.8 Hz, 1H), 4.89 (ddd, $J = 12.8$, 6.4, 1.2 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.51 – 2.43 (m, 2H), 2.06 – 1.98 (m, 1H), 1.79 – 1.61 (m, 3H), 1.53 – 1.44 (m, 1H), 1.33 (s, 3H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

Hz, 1H), 4.83 – 4.70 (m, 2H), 2.57 – 2.43 (m, 2H), 2.40 – 2.30 (m, 1H), 1.92 (ddd, $J = 14.6, 8.9, 5.2$ Hz, 1H), 1.42 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 197.0, 172.6, 149.6, 136.3, 134.5, 129.0, 128.8, 128.3, 126.8, 122.8, 65.9, 53.6, 33.5, 23.8, 20.8.

IR (Neat Film, NaCl): 3025, 1731, 1681, 1250, 1096 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{17}$H$_{18}$O$_3$ [M]$^+$: 270.1256, found 270.1259.

cinnamyl 1,4-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (158c)

Prepared from 165a and methyl iodide following General Procedure B. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a colorless oil (0.65 g, 2.1 mmol, 63% yield).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37 (d, $J = 7.5$ Hz, 2H), 7.31 (d, $J = 7.4$ Hz, 2H), 7.28 – 7.23 (m, 1H), 6.61 (d, $J = 15.8$ Hz, 1H), 6.23 (dt, $J = 15.8, 6.4$ Hz, 1H), 5.92 (s, 1H), 4.81 – 4.70 (m, 2H), 2.51 (dt, $J = 13.3, 4.8$ Hz, 1H), 2.48 – 2.39 (m, 1H), 2.25 (dt, $J = 19.0, 5.3$ Hz, 1H), 1.94 (s, 3H), 1.92 – 1.86 (m, 1H), 1.41 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 196.7, 172.8, 161.7, 136.3, 134.3, 128.7, 128.2, 126.8, 125.7, 122.9, 65.8, 52.5, 33.3, 28.7, 24.3, 20.5.

IR (Neat Film, NaCl): 3026, 2935, 1731, 1668, 1448, 1253 cm$^{-1}$.

cinnamyl 4-ethoxy-1-methyl-2-oxocyclohex-3-ene-1-carboxylate (158d)

Prepared from 165b and methyl iodide following General Procedure B. Purification by flash column chromatography (10–50% EtOAc/hexanes) afforded the title compound as a colorless oil (0.65 g, 2.1 mmol, 63% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 – 7.25 (m, 5H), 6.62 (d, $J = 15.9$ Hz, 1H), 6.24 (dt, $J = 15.9$, 6.3 Hz, 1H), 5.37 (s, 1H), 4.82 – 4.72 (m, 2H), 3.90 (q, $J = 7.0$ Hz, 2H), 2.61 – 2.47 (m, 2H), 2.38 (dt, $J = 17.1$, 5.3 Hz, 1H), 1.88 (ddd, $J = 13.7$, 8.5, 5.2 Hz, 1H), 1.43 (s, 3H), 1.34 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.9, 176.7, 172.9, 136.3, 134.3, 128.7, 128.2, 126.8, 123.0, 101.9, 65.8, 64.6, 52.6, 31.9, 26.6, 20.7, 14.2.

IR (Neat Film, NaCl): 2980, 2942, 1731, 1656, 1606, 1377, 1250, 1195 cm$^{-1}$.

HRMS (MM: FD+): $m/z$ calc’d for C$_{19}$H$_{22}$O$_4$ [M]$^+$: 314.1518, found 314.1516.

cinnamyl 4-ethoxy-1-ethyl-2-oxocyclohex-3-ene-1-carboxylate (158e)

Prepared from 165b and ethyl iodide following General Procedure B. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (0.458 g, 1.39 mmol, 84% yield).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.38 – 7.35 (m, 2H), 7.33 – 7.29 (m, 2H), 7.27 – 7.23 (m, 1H), 6.62 (d, \(J = 15.9\) Hz, 1H), 6.24 (dt, \(J = 15.8, 6.3\) Hz, 1H), 5.36 (s, 1H), 4.77 (dd, \(J = 6.3, 1.4\) Hz, 2H), 3.93 – 3.84 (m, 2H), 2.64 (dddd, \(J = 17.9, 9.8, 5.0, 1.2\) Hz, 1H), 2.45 (dt, \(J = 13.3, 5.0\) Hz, 1H), 2.36 (dt, \(J = 17.9, 5.0\) Hz, 1H), 2.13 – 2.01 (m, 1H), 1.93 (dd, \(J = 13.3, 9.6, 5.2\) Hz, 1H), 1.83 (dq, \(J = 13.9, 7.5\) Hz, 1H), 1.33 (t, \(J = 7.0\) Hz, 3H), 0.92 (t, \(J = 7.5\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 196.0, 176.7, 171.8, 136.4, 134.3, 128.7, 128.2, 126.8, 123.1, 102.3, 65.7, 64.5, 56.5, 27.9, 27.1, 26.6, 14.2, 9.2.

IR (Neat Film, NaCl): 3025, 2979, 2938, 1728, 1659, 1603, 1446, 1378, 1235, 1186 cm\(^{-1}\).

HRMS (MM: ESI+): m/z calc’d for C\(_{20}\)H\(_{25}\)O\(_4\) [M+H]\(^+\): 329.1747, found 329.1747.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{cinnamyl4-ethoxy-1-(3-methoxy-3-oxopropyl)-2-oxocyclohex-3-ene-1-carboxylate.png}
\caption{cinnamyl 4-ethoxy-1-(3-methoxy-3-oxopropyl)-2-oxocyclohex-3-ene-1-carboxylate (158f)}
\end{figure}

Prepared from 165b and methyl acrylate following General Procedure B. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (0.48 g, 1.24 mmol, 75% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.39 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 6.62 (d, \(J = 15.9\) Hz, 1H), 6.23 (dt, \(J = 15.9, 6.3\) Hz, 1H), 5.36 (s, 1H), 4.82 – 4.72 (m, 2H), 3.88 (qd, \(J = 7.1, 2.0\) Hz, 2H), 3.65 (s, 3H), 2.64 – 2.53 (m, 1H), 2.49 – 2.36 (m, 4H),
2.33 – 2.25 (m, 1H), 2.13 (ddd, \( J = 13.9, 10.0, 6.1 \) Hz, 1H), 1.95 – 1.87 (m, 1H), 1.34 (t, \( J = 7.0 \) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 195.4, 176.6, 173.7, 171.5, 136.3, 134.6, 128.7, 128.2, 126.8, 122.8, 102.2, 66.0, 64.7, 55.4, 51.8, 29.8, 29.0, 28.9, 26.4, 14.2.

IR (Neat Film, NaCl): 2946, 1737, 1731, 1659, 1651, 1606, 1246, 1192 cm\(^{-1}\).

HRMS (MM: ESI\(^+\)): \( m/z \) calc’d for C\(_{22}\)H\(_{27}\)O\(_6\) [M+H\(^+\)]: 387.1802, found 387.1806.

cinnamyl 1-(2-cyanoethyl)-4-ethoxy-2-oxocyclohex-3-ene-1-carboxylate (158g)

Prepared from 165b and acrylonitrile following General Procedure B. Purification by flash column chromatography (5–30\% EtOAc/hexanes) afforded the title compound as a colorless oil (349 mg, 0.987 mmol, 59\% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.40 – 7.27 (m, 5H), 6.64 (d, \( J = 15.9 \) Hz, 1H), 6.23 (dt, \( J = 15.9, 6.5 \) Hz, 1H), 5.38 (s, 1H), 4.85 – 4.74 (m, 2H), 3.96 – 3.86 (m, 2H), 2.65 – 2.39 (m, 5H), 2.31 – 2.13 (m, 2H), 2.01 – 1.94 (m, 1H), 1.35 (t, \( J = 7.0 \) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 194.8, 176.9, 171.0, 136.1, 135.2, 128.8, 128.4, 126.8, 122.3, 119.8, 102.2, 66.4, 64.9, 55.1, 30.0, 29.4, 26.4, 14.2, 13.4.

IR (Neat Film, NaCl): 2981, 2939, 1730, 1651, 1605, 1381, 1186 cm\(^{-1}\).

HRMS (MM: EI\(^+\)): \( m/z \) calc’d for C\(_{21}\)H\(_{23}\)O\(_4\)N [M\(^+\)]: 353.1629, found 353.1627.
cinnamyl 4-(benzyloxy)-1-methyl-2-oxocyclohex-3-ene-1-carboxylate (158h)

Prepared from 165c and methyl iodide following General Procedure B. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (179 mg, 0.475 mmol, 57% yield).

^1^H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.41 – 7.26 (m, 10H), 6.63 (d, J = 15.9 Hz, 1H), 6.25 (dt, J = 15.9, 6.3 Hz, 1H), 5.52 (s, 1H), 4.89 (s, 2H), 4.83 – 4.72 (m, 2H), 2.65 (dddd, J = 17.6, 9.8, 4.5, 1.1 Hz, 1H), 2.56 – 2.41 (m, 2H), 1.92 (dd, J = 12.8, 8.8, 4.7 Hz, 1H), 1.44 (s, 3H).

^1^C NMR (100 MHz, CDCl\textsubscript{3}): δ 196.7, 176.4, 172.8, 136.3, 135.0, 134.4, 128.9, 128.8, 128.7, 128.2, 128.0, 126.8, 123.0, 102.5, 70.8, 65.9, 52.6, 31.9, 26.6, 20.7.

IR (Neat Film, NaCl): 3027, 2935, 1730, 1659, 1607, 1251, 1189, 1170 cm\textsuperscript{-1}.

HRMS (MM: ESI+): m/z calc’d for C\textsubscript{24}H\textsubscript{24}O\textsubscript{4} [M]^+: 376.1675, found 376.1665.

\[\text{158i}\]

cinnamyl 1-methyl-2-oxo-4-(phenylthio)cyclohex-3-ene-1-carboxylate (158i)

Prepared from 165d and methyl iodide following General Procedure B. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (232 mg, 0.853 mmol, 62% yield).

^1^H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.46 – 7.27 (m, 10H), 6.62 (d, J = 15.9 Hz, 1H), 6.24 (dt, J = 15.9, 6.3 Hz, 1H), 5.52 (s, 1H), 4.81 (dd, J = 12.9, 6.3 Hz, 1H), 4.73 (dd, J = 13.0, 6.3 Hz, 1H), 2.73 – 2.64 (m, 1H), 2.59 – 2.46 (m, 2H), 2.01 – 1.93 (m, 1H), 1.41 (s, 3H).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 193.3, 172.5, 165.9, 136.2, 135.5, 134.3, 130.3, 129.9, 128.6, 128.1, 127.8, 126.7, 122.7, 119.9, 65.8, 52.8, 33.6, 27.6, 20.4.

IR (Neat Film, NaCl): 2934, 1729, 1655, 1577, 1303, 1250, 1167, 1108 cm$^{-1}$.

HRMS (MM: FD$^+$): $m/z$ calc’d for C$_{23}$H$_{22}$O$_3$S $[M]^+$: 378.1290, found 378.1293.

![Cinnamyl 1-methyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (158i)](image)

cinnamyl 1-methyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (158i)

Prepared from 165e and methyl iodide following General Procedure B. Purification by flash column chromatography (15–50% EtOAc/hexanes) afforded the title compound as a colorless oil (0.43 g, 1.24 mmol, 81% yield).

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.14 – 7.10 (m, 2H), 7.09 – 6.99 (m, 3H), 6.36 (d, $J = 15.9$ Hz, 1H), 6.00 (dt, $J = 15.9$, 6.4 Hz, 1H), 5.17 (ddd, $J = 4.9$, 3.5, 1.0 Hz, 1H), 4.56 (ddd, $J = 12.9$, 6.5, 1.4 Hz, 1H), 4.50 (ddd, $J = 12.8$, 6.3, 1.4 Hz, 1H), 3.67 (ddd, $J = 11.2$, 6.4, 3.0 Hz, 1H), 3.58 (ddd, $J = 11.2$, 6.4, 2.9 Hz, 1H), 2.91 (ddd, $J = 11.5$, 6.3, 2.9 Hz, 1H), 2.47 – 2.30 (m, 4H), 1.92 – 1.81 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H).

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 192.8, 172.4, 146.9, 136.5, 134.7, 128.9, 128.6, 126.9, 123.0, 121.8, 66.9, 65.6, 54.4, 50.2, 33.3, 22.7, 20.9.

IR (Neat Film, NaCl): 2936, 2856, 1736, 1730, 1692, 1613, 1448 cm$^{-1}$.

HRMS (MM: ESI$^+$): $m/z$ calc’d for C$_{21}$H$_{26}$O$_4$N $[M+H]^+$: 356.1856, found 356.1867.
(E)-but-2-en-1-yl 1,4-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (158k)

Prepared from 165g and methyl iodide following General Procedure B. Purification by flash column chromatography (5–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.29 g, 1.30 mmol, 55% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.89 (s, 1H), 5.74 (dqt, $J = 15.3$, 6.5, 1.2 Hz, 1H), 5.57 – 5.47 (m, 1H), 4.56 – 4.47 (m, 2H), 2.51 – 2.37 (m, 2H), 2.28 – 2.19 (m, 1H), 1.94 (s, 3H), 1.90 – 1.82 (m, 1H), 1.70 (d, $J = 6.5$ Hz, 3H), 1.37 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.9, 172.8, 161.6, 131.4, 125.8, 124.8, 65.9, 52.4, 33.3, 28.7, 24.3, 20.4, 17.9.

IR (Neat Film, NaCl): 3027, 2938, 2917, 1730, 1679, 1636, 1440, 1250 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{13}$H$_{18}$O$_3$Na [M+Na]$^+$: 245.1148, found 245.1159.

(Z)-4-(benzyloxy)but-2-en-1-yl 1,4-dimethyl-2-oxocyclohex-3-ene-1-carboxylate (158l)

Prepared from 165f and methyl iodide following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (361 mg, 1.1 mmol, 73% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39 – 7.31 (m, 1H), 7.31 – 7.26 (m, 1H), 5.88 (q, $J = 1.5$ Hz, 1H), 5.80 (dtt, $J = 11.2$, 6.2, 1.4 Hz, 1H), 5.70 – 5.59 (m, 1H), 4.72 – 4.59 (m, 2H), 4.11 (ddd, $J = 6.3$, 1.6, 0.8 Hz, 1H), 2.47 (dt, $J = 13.2$, 5.1 Hz, 1H), 2.43 – 2.35 (m, 1H),
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

2.24 (dt, $J = 18.9, 5.2$ Hz, 1H), 1.94 (d, $J = 1.4$ Hz, 1H), 1.87 (ddd, $J = 13.2, 8.3, 5.1$ Hz, 1H), 1.37 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 196.6, 172.7, 161.6, 138.1, 131.2, 128.6, 127.9, 127.8, 126.4, 125.6, 72.6, 65.8, 61.1, 52.4, 33.2, 28.7, 24.3, 20.3.

IR (Neat Film, NaCl): 3031 (m), 2933 (m), 1731 (s), 1681 (s), 1454 (m), 1214 (m) cm$^{-1}$.

HRMS (MM: ESI$^+$): $m/z$ calc’d for C$_{20}$H$_{24}$O$_4$Na [M+Na]$^+$: 351.1567, found 351.1565.

General Procedure C: Fluorination of $\beta$-ketoesters.

To a solution of $\beta$-ketoester (1 equiv) in anhydrous acetonitrile (0.2 M) at 23 ºC is added neat titanium(IV) chloride (0.1 equiv). After 5 minutes, Selectfluor® was added in one portion. The reaction mixture is stirred at 23 ºC until complete consumption of starting material as observed by TLC (typically 2 hours). Water is then added, and the reaction mixture is extracted three times with Et$_2$O. The combined organic layers was washed with saturated aqueous brine, dried over anhydrous sodium sulfate, and volatiles were removed in vacuo. The crude reaction mixture was purified by silica gel flash column chromatography to yield the desired $\alpha$-fluoro-$\beta$-ketoester.

cinnamyl 1-fluoro-2-oxocyclohexane-1-carboxylate (158m)
Prepared from cinnamyl 2-oxocyclohexane-1-carboxylate following General Procedure C. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (0.80 g, 2.9 mmol, 75% yield).

**1H NMR (400 MHz, CDCl₃):** δ 7.40 (d, J = 7.3 Hz, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.26 (m, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 6.6 Hz, 1H), 4.89 (d, J = 6.5 Hz, 2H), 2.81 – 2.69 (m, 1H), 2.67 – 2.56 (m, 1H), 2.57 – 2.40 (m, 1H), 2.25 – 2.11 (m, 1H), 1.99 – 1.82 (m, 4H).

**13C NMR (100 MHz, CDCl₃):** δ 201.9 (d, J_C-F = 20.0 Hz), 166.9 (d, J_C-F = 24.9 Hz), 136.0, 135.6, 128.8, 128.5, 126.9, 121.9, 96.6 (d, J_C-F = 197.2 Hz), 66.9, 39.7, 36.2 (d, J_C-F = 21.7 Hz), 26.7, 21.0 (d, J_C-F = 5.7 Hz).

**19F NMR (282 MHz, CDCl₃):** δ –160.82 (ddd, J = 21.5, 13.5, 5.1 Hz, 1F).

**IR (Neat Film, NaCl):** 2943, 1731, 1457, 1281 cm⁻¹


---

cinnamyl 1-fluoro-2-oxocyclohex-3-ene-1-carboxylate (158n)

Prepared from cinnamyl 2-oxocyclohex-3-ene-1-carboxylate (prepared following General Procedure D and used crude) following General Procedure C. Purification by flash column chromatography (0–20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.54 g, 2.0 mmol, 50% yield).

**1H NMR (400 MHz, CDCl₃):** δ 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.10 (dt, J = 10.2, 4.0 Hz, 1H), 6.69 (d, J = 15.9 Hz, 1H), 6.27 (dt, J = 15.8, 6.5 Hz,
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

1H), 6.18 (dq, J = 10.2, 2.0 Hz, 1H), 4.94 – 4.84 (m, 2H), 2.72 – 2.58 (m, 3H), 2.48 – 2.39 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.9 (d, J = 18.7 Hz), 167.0 (d, J = 25.9 Hz), 151.9, 153.9, 135.4, 128.7, 128.4, 127.7, 126.8, 121.8, 92.9 (d, J = 194.8 Hz), 66.8, 31.3 (d, J = 22.5 Hz), 23.3 (d, J = 7.2 Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$): δ –164.30 (dd, J = 22.8, 12.5 Hz).

IR (Neat Film, NaCl): 3027, 2940, 1759, 1693, 1265 cm$^{-1}$.

HRMS (MM: FD+): m/z calc’d for C$_{16}$H$_{15}$O$_3$F [M]$^+$: 274.1005, found 274.1004.

cinnamyl 4-ethoxy-1-fluoro-2-oxocyclohex-3-ene-1-carboxylate (158o)

Prepared from 165b following General Procedure C. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.16 g, 0.50 mmol, 31% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.42 – 7.35 (m, 2H), 7.36 – 7.27 (m, 2H), 7.31 – 7.22 (m, 2H), 6.68 (d, J = 15.9 Hz, 1H), 6.28 (dd, J = 16.0, 6.2 Hz, 1H), 5.46 (s, 1H), 4.94 – 4.85 (m, 2H), 3.97 (q, J = 7.1 Hz, 2H), 2.72 – 2.53 (m, 3H), 2.44 – 2.33 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.6 (d, J$_{C-F}$ = 18.9 Hz), 178.2, 167.7 (d, J$_{C-F}$ = 26.0 Hz), 136.1, 135.3, 128.7, 128.4, 126.9, 122.0, 101.0, 92.3 (d, J$_{C-F}$ = 193.6 Hz), 66.8, 65.3, 29.7 (d, J$_{C-F}$ = 23.0 Hz), 25.7 (d, J$_{C-F}$ = 6.0 Hz), 14.2.

$^{19}$F NMR (282 MHz, CDCl$_3$): δ –163.76 – –163.93 (m).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

IR (Neat Film, NaCl): 2983, 2943, 1765, 1666, 1599, 1382, 1264 cm\(^{-1}\)

HRMS (MM: ESI+): \(m/z\) calc’d for C\(_{18}\)H\(_{19}\)O\(_4\)FNa [M+Na]\(^+\): 341.1148, found 341.1158.

\((Z)-4\)-(benzyloxy)but-2-en-1-yl 1-fluoro-4-methyl-2-oxocyclohex-3-ene-1-carboxylate (158p)

Prepared from \(165f\) following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (0.39 g, 1.2 mmol, 75% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38 – 7.27 (m, 5H), 6.00 (s, 1H), 5.89 – 5.82 (m, 1H), 5.73 – 5.66 (m, 1H), 4.79 (d, \(J = 6.7\) Hz, 2H), 4.51 (s, 2H), 4.13 (d, \(J = 6.2\) Hz, 2H), 2.63 – 2.33 (m, 4H), 2.03 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 188.5 (d, \(J_{C-F} = 18.6\) Hz), 167.4 (d, \(J_{C-F} = 25.8\) Hz), 164.6, 138.1, 132.1, 128.6, 128.0, 127.9, 125.6, 124.7, 92.2 (d, \(J_{C-F} = 194.0\) Hz), 72.7, 65.8, 62.0, 31.1 (d, \(J_{C-F} = 22.5\) Hz), 28.0 (d, \(J_{C-F} = 6.5\) Hz), 24.7.

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta\) –165.21 (dd, \(J = 26.4, 12.0\) Hz).

IR (Neat Film, NaCl): 2914, 1764, 1681, 1627, 1264, 1088 cm\(^{-1}\)

HRMS (MM: ESI+): \(m/z\) calc’d for C\(_{19}\)H\(_{22}\)O\(_4\)F [M+H]\(^+\): 333.1502, found 333.1491.

\((E)-\)but-2-en-1-yl 1-fluoro-4-methyl-2-oxocyclohex-3-ene-1-carboxylate (158q)
Prepared from 165g following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (326 mg, 1.44 mmol, 60% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.00 (s, 1H), 5.87 – 5.77 (m, 1H), 5.58 (dtq, $J = 15.0$, 6.7, 1.7 Hz, 1H), 4.64 (ddt, $J = 6.7$, 2.5, 1.2 Hz, 2H), 2.65 – 2.49 (m, 3H), 2.43 – 2.33 (m, 1H), 2.03 (s, 3H), 1.72 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 188.7 (d, $J_{C-F} = 18.6$ Hz), 167.4 (d, $J_{C-F} = 25.7$ Hz), 164.5, 132.8, 124.7, 124.1, 92.3 (d, $J_{C-F} = 194.1$ Hz), 67.0, 31.2 (d, $J_{C-F} = 22.5$ Hz), 28.2 (d, $J_{C-F} = 6.8$ Hz), 24.6, 18.0.

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –165.04 (d, $J = 22.2$ Hz).

IR (Neat Film, NaCl): 3029, 2940, 1760, 1681, 1631, 1436, 1271, 1263, 1019 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{12}$H$_{15}$O$_3$FNa [M+Na]$^+$: 249.0897, found 249.0901.

General Procedure D: $\beta$-ketoester synthesis through ketone acylation.

A flame dried round bottom flask was charged with iPr$_2$NH (2.2 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and $n$-BuLi (2.5 M in hexanes, 2.1 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. The corresponding cyclohexenone (2.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the appropriate N-acyl imidazole (1.0 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was
gradually warmed to 23 °C and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the corresponding acylated enone.

\[
\text{cinnamyl 4-methyl-2-oxocyclohex-3-ene-1-carboxylate (165a)}
\]

Prepared from 3-methylcyclohex-2-en-1-one and cinnamyl 1H-imidazole-1-carboxylate following General Procedure D. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (5.5 g, 20.3 mmol, 51% yield).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.42 – 7.36 (m, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.29 – 7.19 (m, 1H), 6.67 (d, $J = 15.8$ Hz, 1H), 6.28 (dt, $J = 15.8$, 6.4 Hz, 1H), 5.94 (d, $J = 1.5$ Hz, 1H), 4.82 (d, $J = 6.4$ Hz, 2H), 3.46 – 3.28 (m, 1H), 2.49 – 2.25 (m, 4H), 2.25 – 2.17 (m, 1H), 1.97 (d, $J = 1.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 193.7, 170.2, 163.1, 136.3, 134.5, 128.7, 128.2, 126.8, 126.0, 123.0, 65.8, 52.7, 29.6, 25.6, 24.5.

IR (Neat Film, NaCl): 3026, 2935, 1737, 1666, 1445, 970 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{17}$H$_{18}$O$_3$Na [M+Na]$^+$: 293.1148, found 293.1152.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

\(165b\)

**cinnamyl 4-ethoxy-2-oxocyclohex-3-ene-1-carboxylate (165b)**

Prepared from 3-ethoxycyclohex-2-en-1-one following General Procedure D. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (2.13 g, 7.09 mmol, 35% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.41 – 7.37 \text{ (m, 2H)}, 7.32 \text{ (tt, } J = 6.5, 1.0 \text{ Hz, 2H}), 7.28 – 7.23 \text{ (m, 1H)}, 6.67 \text{ (d, } J = 15.9 \text{ Hz, 1H}), 6.29 \text{ (dt, } J = 15.9, 6.4 \text{ Hz, 1H}), 5.40 \text{ (s, 1H)}, 4.82 \text{ (dd, } J = 6.4, 1.4 \text{ Hz, 2H}), 3.96 – 3.88 \text{ (m, 2H)}, 3.41 – 3.36 \text{ (m, 1H)}, 2.62 – 2.52 \text{ (m, 1H)}, 2.48 – 2.33 \text{ (m, 2H)}, 2.25 – 2.15 \text{ (m, 2H)}, 1.37 \text{ (t, } J = 7.0 \text{ Hz, 3H}).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 193.6, 177.6, 170.2, 136.2, 134.3, 128.6, 128.1, 126.7, 122.9, 102.1, 65.8, 64.6, 52.4, 27.4, 24.2, 14.1.\)

IR (Neat Film, NaCl): 2980, 2942, 1736, 1654, 1602, 1380, 1192 cm\(^{-1}\).

HRMS (MM: FD\(^+\)): \(m/z\) calc’d for C\(_{18}\)H\(_{20}\)O\(_4\) \([M]^+\): 300.1362, found 300.1353.

\(165c\)

**cinnamyl 4-(benzyloxy)-2-oxocyclohex-3-ene-1-carboxylate (165c)**

Prepared from 3-(benzyloxy)cyclohex-2-en-1-one following General Procedure D. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (0.79 g, 2.2 mmol, 22% yield).
**Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles**

**H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.42 – 7.27 (m, 10H), 6.68 (d, $J = 15.9$ Hz, 1H), 6.29 (dt, $J = 15.9$, 6.4 Hz, 1H), 5.54 (s, 1H), 4.91 (d, $J = 2.5$ Hz, 2H), 4.83 (dd, $J = 6.4$, 1.3 Hz, 2H), 3.41 (dd, $J = 9.0$, 5.0 Hz, 1H), 2.65 (ddd, $J = 17.5$, 6.4, 5.0 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.41 (dtd, $J = 13.7$, 8.7, 5.0 Hz, 1H), 2.23 (ddt, $J = 13.5$, 6.6, 5.0 Hz, 1H).

**C NMR (100 MHz, CDCl$_3$):** $\delta$ 193.6, 177.3, 170.1, 136.2, 134.7, 134.4, 128.8, 128.7, 128.6, 128.1, 127.9, 126.7, 122.9, 102.8, 70.8, 65.8, 52.4, 27.4, 24.2.

**IR (Neat Film, NaCl):** 3030, 2942, 1736, 1657, 1603, 1362, 1186, 1150 cm$^{-1}$.

**HRMS (MM: FD+):** $m/z$ calc’d for C$_{23}$H$_{22}$O$_4$ [M]$^+$: 362.1518, found 362.1510.

**Cinnamyl 2-oxo-4-(phenylthio)cyclohex-3-ene-1-carboxylate (165d)**

Prepared from 3-(phenylthio)cyclohex-2-en-1-one following General Procedure D. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.59 g, 4.36 mmol, 44% yield).

*trace 3-(phenylthio)cyclohex-2-en-1-one coeluted with 165d. The material can be carried through alkylation and separated without issue*

**H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.49 – 7.37 (m, 8H), 7.34 – 7.25 (m, 2H), 6.66 (d, $J = 15.9$ Hz, 1H), 6.27 (dt, $J = 15.9$, 6.3 Hz, 1H), 5.53 (s, 1H), 4.81 (dd, $J = 6.4$, 1.4 Hz, 2H), 3.41 (dd, $J = 9.3$, 4.9 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.62 – 2.51 (m, 1H), 2.50 – 2.36 (m, 1H), 2.32 – 2.25 (m, 1H).

**C NMR (100 MHz, CDCl$_3$):** $\delta$ 190.2, 169.9, 167.5, 136.3, 135.6, 134.5, 130.5, 130.1, 128.7, 128.2, 127.7, 126.8, 122.9, 120.1, 65.9, 52.9, 28.6, 26.1.
IR (Neat Film, NaCl): 3054, 2939, 1736, 1656, 1576, 1300, 1167, 1146 cm\(^{-1}\).

HRMS (MM: FD\(+\)): \(m/z\) calc’d for C\(_{22}\)H\(_{20}\)O\(_3\)S \([\text{M}^+]: 364.1133\), found 364.1133.

Cinnamyl 3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (165e)

Prepared from 2-morpholinocyclohex-2-en-1-one\(^{13}\) following General Procedure D. Purification by flash column chromatography (30–60\% EtOAc/hexanes) afforded the title compound as a colorless oil (1.34 g, 3.92 mmol, 33\% yield).

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta 7.16 – 7.13\) (m, 2H), 7.10 – 6.98 (m, 3H), 6.43 (d, \(J = 15.9\) Hz, 1H), 6.12 (dt, \(J = 15.9, 6.4\) Hz, 1H), 5.22 (t, \(J = 4.5\) Hz, 1H), 4.71 – 4.61 (m, 2H), 3.64 – 3.56 (m, 4H), 3.28 (dd, \(J = 9.6, 4.6\) Hz, 1H), 2.67 – 2.55 (m, 4H), 2.20 – 2.12 (m, 1H), 2.02 (dq, \(J = 17.5, 4.9, 4.3\) Hz, 1H), 1.81 – 1.65 (m, 2H).

\(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \(\delta 190.4, 169.7, 146.5, 136.7, 134.5, 128.8, 128.2, 127.0, 124.3, 123.4, 66.9, 65.6, 55.2, 50.3, 26.0, 23.6.

IR (Neat Film, NaCl): 3024, 2953, 2854, 1736, 1685, 1610, 1448, 1262, 1118 cm\(^{-1}\).

HRMS (MM: ESI\(+\)): \(m/z\) calc’d for C\(_{20}\)H\(_{24}\)O\(_4\)N \([\text{M+H}^+]: 342.1700\), found 342.1710.

\((Z)-4-(benzyloxy)but-2-en-1-yl\) 4-methyl-2-oxocyclohex-3-ene-1-carboxylate (165f)

Prepared from 3-methylcyclohex-2-en-1-one and \((Z)-4-(benzyloxy)\)but-2-en-1-yl 1H-imidazole-1-carboxylate following General Procedure D. Purification by flash column
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (5.5 g, 20.3 mmol, 51% yield). *Due to difficult separation, the NMR contains signals associated with the starting material. However, this can be used in the next step without consequence.*

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.41 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 5.91 (t, $J = 1.5$ Hz, 1H), 5.86 – 5.78 (m, 1H), 5.76 – 5.63 (m, 1H), 4.72 (dd, $J = 6.6, 1.3$ Hz, 2H), 4.51 (s, 2H), 4.13 (dd, $J = 6.2, 1.5$ Hz, 2H), 3.40 – 3.21 (m, 1H), 2.48 – 2.25 (m, 5H), 2.25 – 2.14 (m, 1H), 2.05 – 1.96 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 193.6, 170.2, 163.1, 138.1, 131.2, 128.6, 127.9, 127.8, 126.5, 126.0, 72.6, 65.8, 61.1, 52.6, 29.5, 25.6, 24.5.

IR (Neat Film, NaCl): 3457, 3031, 2936, 1738, 1667, 1453 cm$^{-1}$.

HRMS (MM: ESI+): m/z calc’d for C$_{19}$H$_{23}$O$_4$Na [M+Na]$^+$: 337.1410, found 337.1415.

(E)-but-2-en-1-yl 4-methyl-2-oxocyclohex-3-ene-1-carboxylate (165g)

Prepared from 3-methylcyclohex-2-en-1-one following General Procedure D. Purification by flash column chromatography (20–40% EtOAc/hexanes) afforded the title compound as a colorless oil (1.98 g, 9.49 mmol, 63% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 5.92 (q, $J = 1.4$ Hz, 1H), 5.84 – 5.74 (m, 1H), 5.63 – 5.54 (m, 1H), 4.58 (dt, $J = 6.5, 1.1$ Hz, 2H), 3.32 (dd, $J = 9.6, 5.1$ Hz, 1H), 2.45 – 2.27 (m, 3H), 2.21 – 2.16 (m, 1H), 1.97 (s, 3H), 1.71 (dq, $J = 6.5, 1.2$ Hz, 3H).
13C NMR (100 MHz, CDCl3): δ 193.8, 170.2, 163.0, 131.7, 126.0, 124.9, 66.0, 52.6, 29.5, 25.6, 24.5, 17.9.

IR (Neat Film, NaCl): 3027, 2941, 1737, 1671, 1632, 1439, 1166, 1153 cm⁻¹.

HRMS (MM: ESI+): m/z calc’d for C_{12}H_{16}O_{3}Na [M+Na]⁺: 231.0992, found 231.1000.

**General Procedure E: Preparation of Novel (S)-t-BuPHOX Ligands.**

A flame-dried 3-neck round-bottom flask attached to a reflux condenser under nitrogen atmosphere was charged with CuI (0.15 equiv). Anhydrous toluene (0.03 M) was added followed by DMEDA (1.1 equiv), and the reaction mixture was stirred at ambient temperature for 20 minutes. To the pre-stirred catalyst solution was added the requisite aryl bromide (1.0 equiv), Cs₂CO₃ (3.0 equiv), and the aryl phosphine (1.3 equiv). Minimal additional toluene was added to rinse any solids off the sides of the flask. The reaction mixture was heated to reflux (ca. 130 °C) and stirred for a minimum of 21 h. Upon completion, the reaction mixture was cooled to ambient temperature, filtered through a pad of celite, and washed with CH₂Cl₂. The filtrate was concentrated and purified by flash silica gel column chromatography.

**General Procedure F: Preparation of Novel (S)-t-BuPHOX Ligands.**
A flame-dried 3-neck round-bottom flask attached to a reflux condenser under nitrogen atmosphere was charged with Cul (0.15 equiv). Anhydrous toluene (0.03 M) was added followed by DMEDA (1.1 equiv), and the reaction mixture was stirred at ambient temperature for 20 minutes. To the pre-stirred catalyst solution was added aryl bromide (1.0 equiv), Cs₂CO₃ (3.8 equiv), and aryl phosphine oxide (1.8 equiv). Minimal additional toluene was added to rinse any solids off the sides of the flask. The reaction mixture was heated to reflux (ca. 130 °C) and stirred for a minimum of 21 h. Upon completion, the reaction mixture was cooled to ambient temperature, filtered through a pad of celite, and washed with CH₂Cl₂. The filtrate was concentrated and purified by flash silica gel column chromatography.

The isolated phosphine oxide was placed in an oven-dried vial along with a magnetic stir bar and degassed using an Argon balloon for 10 min. Ph₂SiH₂ (1.2 mL, 6.5 mmol, 7.0 equiv) was added to the reaction vial, which fully dissolved the phosphine oxide residue. The reaction vial was then placed in a pre-heated oil bath at 140 °C and stirred until complete reduction of phosphine oxide (typically 24–120 h). Once complete as determined by ³¹P NMR, the reaction was cooled to ambient temperature adsorbed onto silica gel then purified by flash silica gel column chromatography.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

(S)-2-(2-(bis(2,6-difluorophenyl)phosphaneyl)-5-(trifluoromethyl)phenyl)-4-(tert-buty1)-4,5-dihydrooxazole (L4)

Prepared from bis(2,6-difluorophenyl)phosphate (190 mg, 0.74 mmol, 1.2 equiv) following General Procedure E. Purification by flash column chromatography (0–50% CH₂Cl₂/hexanes) afforded the title compound as a white solid (67 mg, 0.13 mmol, 20% yield).

*Note: Ullmann coupling using the aryl phosphine oxide does not yield any product.

\(^{1}\)H NMR (300 MHz, CDCl₃): \(\delta 8.23\) (dd, \(J = 4.4, 2.0\) Hz, 1H), 7.61 – 7.50 (m, 1H), 7.42 – 7.26 (m, 3H), 6.83 (qd, \(J = 7.8, 2.3\) Hz, 4H), 4.30 (dd, \(J = 10.1, 8.5\) Hz, 1H), 4.13 (t, \(J = 8.7\) Hz, 1H), 3.94 (dd, \(J = 10.1, 8.9\) Hz, 1H), 0.69 (s, 9H).

\(^{13}\)C NMR (101 MHz, CDCl₃): \(\delta 165.8\) (td, \(J = 9.0, 3.7\) Hz), 163.3 (td, \(J = 9.0, 4.1\) Hz), 161.2 (d, \(J = 4.9\) Hz), 140.9 (d, \(J = 28.6\) Hz), 133.1, 132.1, 131.6 (dt, \(J = 28.6, 10.9\) Hz), 130.5 (qd, \(J = 33.2, 1.6\) Hz), 128.0, 126.4 (q, \(J = 3.7\) Hz), 126.2 – 126.0 (m), 125.3, 122.6, 119.8, 114.7 – 113.3 (m), 111.9 – 111.2 (m), 68.9, 33.5, 25.8.

\(^{31}\)P NMR (121 MHz, CDCl₃): \(\delta -55.81 – -56.51\) (m).

\(^{19}\)F NMR (282 MHz, CDCl₃): \(\delta -62.83 – -62.88\) (m, 3F), \(-100.06 – -100.19\) (m, 1F), \(-100.24 – -100.34\) (m, 1F), \(-100.43 – -100.54\) (m, 1F), \(-100.58 – -100.70\) (m, 1F).
IR (Neat Film, NaCl): 3080, 2958, 2907, 2870, 1657, 1607, 1574, 1454, 1326, 1228, 1176, 1131, 1083, 986, 784 cm\(^{-1}\).

HRMS (MM: ESI\(^{+}\)):\text{ m/z calc'd for } \text{C}_{26}\text{H}_{21}\text{NOF}_7\text{P } [\text{M}]^{+}: 527.12490, \text{ found } 527.12391.

Optical Rotation:[\alpha]_D^{21} +18.1^\circ (c 0.10, \text{CHCl}_3)

(S)-4-(\text{tert-butyl})-2-(2-(\text{di-o-tolylphosphaneyl})-5-(\text{trifluoromethyl})phenyl)-4,5-dihydrooxazole (L5)

Prepared from di-o-tolylphospane (240 mg, 1.1 mmol, 1.3 equiv) following General Procedure E. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a tan solid (130 mg, 0.27 mmol, 31% yield).

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \delta 8.21 (t, J = 2.7 Hz, 1H), 7.51 (dd, J = 8.1, 2.0 Hz, 1H), 7.26 – 7.16 (m, 4H), 7.11 – 6.97 (m, 3H), 6.73 – 6.64 (m, 2H), 4.13 (dd, J = 10.1, 8.5 Hz, 1H), 4.04 (t, J = 8.3 Hz, 1H), 3.94 (dd, J = 10.1, 8.3 Hz, 1H), 2.38 (dd, J = 4.1, 1.7 Hz, 6H), 0.70 (s, 9H).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\):} \delta 161.61, 143.48 – 143.01 (m), 142.75 (d, J = 27.4 Hz), 142.31 (d, J = 28.0 Hz), 135.93 – 135.60 (m), 134.81, 133.49, 133.26, 133.05, 130.85, 130.53, 130.25 (d, J = 4.9 Hz), 128.90 (d, J = 15.1 Hz), 126.81 (dq, J = 11.3, 3.7 Hz), 126.38 (d, J = 16.2 Hz), 125.30, 122.59, 68.63, 33.76, 25.79, 21.48, 21.25.

\(^{31}\text{P NMR (121 MHz, CDCl}_3\):} \delta –20.8 (s).
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –62.8 (s).

IR (Neat Film, NaCl): 3056, 2957, 2867, 2356, 1653, 1471, 1454, 1341, 1324, 1169, 1130, 1079, 970 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{28}$H$_{29}$NOF$_3$P [M+H]$^+$: 483.19389, found 483.19472.

Optical Rotation: $[\alpha]_{D}^{22}$ –55.4 ° (c 0.28, CHCl$_3$).

(S)-2-(2-(bis(2-fluorophenyl)phosphanylyl)-5-(trifluoromethyl)phenyl)-4-(tert-butyl)-4,5-dihydrooxazole (L6)

Prepared from bis(2-fluorophenyl)phosphine oxide (408 mg, 1.7 mmol, 1.8 equiv) following General Procedure F. Purification by flash column chromatography (0–50% EtOAc/hexanes) afforded the title compound as a white solid (408 mg, 0.81 mmol, 85% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.28 (t, $J$ = 2.8 Hz, 1H), 7.59 (dd, $J$ = 8.2, 2.0 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.20 (dd, $J$ = 8.2, 3.0 Hz, 1H), 7.11 – 7.02 (m, 4H), 6.88 – 7.84 (m, 1H), 6.82 – 6.77 (m, 1H), 4.26 (dd, $J$ = 10.1, 8.6 Hz, 1H), 4.12 (t, $J$ = 8.6 Hz, 1H), 4.00 (dd, $J$ = 10.1, 8.6 Hz, 1H), 0.74 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 165.7 (dd, $J$ = 17.9, 16.1 Hz), 163.5 – 163.0 (m), 161.3, 141.6 (d, $J$ = 29.5 Hz), 135.0 – 134.8 (m), 134.7 – 134.4 (m), 132.3 (d, $J$ = 21.8 Hz), 131.4
(dd, $J = 25.3$, 8.3 Hz), 131.0 (d, $J = 33.2$ Hz), 127.0 (q, $J = 3.7$ Hz), 126.7 (t, $J = 3.5$ Hz), 125.2, 124.8 (dd, $J = 9.7$, 3.3 Hz), 124.4 – 123.7 (m), 122.5, 68.9, 33.7, 25.8.

$^{31}$P NMR (121 MHz, CDCl$_3$): $\delta$ –32.10 (t, $J = 63.2$ Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –62.90 (s, 3F), –103.64 – –103.88 (m, 1), –103.88 – –104.11 (m, 1F).

IR (Neat Film, NaCl): 3069, 2956, 2357, 1654, 1469, 1324, 1170, 1132, 1081, 756 cm$^{-1}$.

HRMS (MM: ESI+): $m/z$ calc’d for C$_{26}$H$_{23}$NOF$_5$P [M+H]$^+$: 491.14374, found 491.14451.

Optical Rotation: $[\alpha]_D^{22}$ –20.5° ($c$ 0.73, CHCl$_3$).

(S)-2-(2-(bis(2-(trifluoromethoxy)phenyl)phosphaneyl)-5-(trifluoromethyl)phenyl)-4-(tert-butyl)-4,5-dihydrooxazole (L7)

Prepared from bis(2-(trifluoromethoxy)phenyl)phosphine oxide (700 mg, 1.9 mmol, 1.8 equiv) following General Procedure F. Purification by flash column chromatography (0–50% EtOAc/hexanes) afforded the title compound as a tan solid (632 mg, 0.99 mmol, 94% yield).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.25 – 8.23 (m, 1H), 7.62 – 7.50 (m, 1H), 7.45 – 7.37 (m, 2H), 7.31 – 7.27 (m, 2H), 7.20 – 7.14 (m, 2H), 7.03 (dd, $J = 8.2$, 2.7 Hz, 1H), 6.90 – 6.74 (m, 2H), 4.21 (dd, $J = 10.2$, 8.5 Hz, 1H), 4.12 (t, $J = 8.2$ Hz, 1H), 3.98 (dd, $J = 10.2$, 7.8 Hz, 1H), 0.71 (s, 9H).
\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}: \delta 161.24, 151.82 (dd, J = 27.3, 19.9 \text{ Hz}), 141.42 (d, J = 30.8 \text{ Hz}), 135.41 (d, J = 2.8 \text{ Hz}), 135.00, 134.49, 133.09 (d, J = 23.3 \text{ Hz}), 131.50, 131.18, 130.94, 130.85, 130.66, 130.45 (d, J = 17.5 \text{ Hz}), 130.23, 129.78 (d, J = 21.2 \text{ Hz}), 128.00, 127.86 (d, J = 1.3 \text{ Hz}), 126.95 – 126.41 (m), 125.16, 124.33 (d, J = 3.0 \text{ Hz}), 122.45, 121.76 (d, J = 3.0 \text{ Hz}), 119.60, 119.27 – 119.01 (m), 116.60, 69.01, 33.82, 25.66. \]

\[ ^{31}\text{P NMR (121 MHz, CDCl}_3\text{)}: \delta -27.4 \text{ (m).} \]

\[ ^{19}\text{F NMR (282 MHz, CDCl}_3\text{)}: \delta -56.5 \text{ (s, 6F)}, -62.9 \text{ (s, 3F).} \]

\[ \text{IR (Neat Film, NaCl): 3062, 2964, 2870, 2363, 2342, 1653, 1472, 1326, 1251, 1216, 1200, 1168, 1160, 1128, 1081 cm}^{-1}. \]

\[ \text{HRMS (MM: ESI+): } m/z \text{ calc’d for C}_{28}\text{H}_{23}\text{NO}_{3}\text{F}_9\text{P [M+H]}^+: 623.12718, \text{ found 623.12455.} \]

\[ \text{Optical Rotation: } [\alpha]_{D}^{21} -20.3 ^{\circ} \text{ (c 1.48, CHCl}_3\text{).} \]
5.7 REFERENCES AND NOTES


(a) Reaction conditions: 158a (0.05 mmol), Pd₂dba₃ (2.5 mol %), (S,S)-DACH-Ph (6.5 mol %), and THF (2 mL) at 60 ºC for 14 h. (b) An analogous result was found by Wolfe and coworkers: Bornowski, E. C.; Hinds, E. M.; White, D. R.; Nakamura, Y.; Wolfe, J. P. Pd-Catalyzed Alkene Difunctionalization Reactions of Enolates for the Synthesis of Substituted Bicyclic Cyclopentanes. Org. Process Res. Dev. 2019, 23, 1610–1630.

Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles


(10) Free energies at the PBE0-D4/def2-TZVPP/SMD(PhMe)//PBE-D4/def2-TZVP[Pd], ma-def2-SVP[O], def2-SV(P) level of theory at 333.15 K.
Chapter 5 – Development of a Branched-selective Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles


APPENDIX 3

Spectra Relevant to Chapter 5: Development of a Branched-selective
Asymmetric Allylic Alkylation of Hard Pd-Enolate Nucleophiles
Figure A3.1. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160a.
Figure A3.2. Infrared spectrum (Thin Film, NaCl) of compound 160a.

Figure A3.3. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160a.
Figure A3.4. $^1\text{H}$ NMR (400 MHz, CDCl$_3$) of compound 160b.
Figure A3.5. Infrared spectrum (Thin Film, NaCl) of compound 160b.

Figure A3.6. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160b.
Figure A3.7. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160c.
Figure A3.8. Infrared spectrum (Thin Film, NaCl) of compound 160c.

Figure A3.9. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160c.
Figure A3.10. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160d.
**Figure A3.11.** Infrared spectrum (Thin Film, NaCl) of compound 160d.

**Figure A3.12.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160d.
Figure A3.13. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160e.
**Figure A3.14.** Infrared spectrum (Thin Film, NaCl) of compound 160e.

**Figure A3.15.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160e.
Figure A3.16. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160f.
Figure A3.17. Infrared spectrum (Thin Film, NaCl) of compound 160f.

Figure A3.18. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160f.
Figure A3.19. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160g.
Figure A3.20. Infrared spectrum (Thin Film, NaCl) of compound 160g.

Figure A3.21. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160g.
Figure A3.22. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160h.
Figure A3.23. Infrared spectrum (Thin Film, NaCl) of compound 160h.

Figure A3.24. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160h.
Figure A3.25. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160i.
Figure A3.26. Infrared spectrum (Thin Film, NaCl) of compound 160i.

Figure A3.27. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160i.
Figure A3.28. $^1$H NMR (400 MHz, C$_6$D$_6$) of compound 160j.
**Figure A3.29.** Infrared spectrum (Thin Film, NaCl) of compound 160j.

**Figure A3.30.** $^{13}$C NMR (100 MHz, C$_6$D$_6$) of compound 160j.
Figure A3.28. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160k.
**Figure A3.32.** Infrared spectrum (Thin Film, NaCl) of compound 160k.

**Figure A3.33.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160k.
Figure A3.34. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160l.
Figure A3.35. Infrared spectrum (Thin Film, NaCl) of compound 160l.

Figure A3.36. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160l.
Figure A3.37. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160m.
Figure A3.38. Infrared spectrum (Thin Film, NaCl) of compound 160m.

Figure A3.39. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160m.
Figure A3.40. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160m.
Figure A3.41. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160n.
Figure A3.42. Infrared spectrum (Thin Film, NaCl) of compound 160n.

Figure A3.43. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160n.
Figure A3.44. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160n.
Figure A3.45. $^1\text{H}$ NMR (400 MHz, CDCl$_3$) of compound 160$^o$. 
Figure A3.46. Infrared spectrum (Thin Film, NaCl) of compound 160o.

Figure A3.47. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160o.
Figure A3.48. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160o.
Figure A3.49. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160p.
Figure A3.50. Infrared spectrum (Thin Film, NaCl) of compound 160p.

Figure A3.51. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160p.
Figure A3.52. $^{19}\text{F} \text{NMR} \ (282 \text{ MHz, CDCl}_3)$ of compound 160p.
Figure A3.53. $^1$H NMR (400 MHz, CDCl$_3$) of compound 160p_linear.
Figure A3.54. Infrared spectrum (Thin Film, NaCl) of compound 160p_linear.

Figure A3.55. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160p_linear.
Figure A3.56. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160p_linear.
Figure A3.57. $^1$H NMR (500 MHz, CDCl$_3$) of compound 160q (mixture).
Figure A3.58. $^1$H NMR (400 MHz, CDCl$_3$) of compound $^{160q}$. 
Figure A3.59. Infrared spectrum (Thin Film, NaCl) of compound 160q.

Figure A3.60. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 160q.
Figure A3.61. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 160q.
Figure A3.62. $^1$H NMR (600 MHz, CDCl$_3$) of compound 158a.
Figure A3.63. Infrared spectrum (Thin Film, NaCl) of compound 158a.

Figure A3.64. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158a.
Figure A3.65. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158b.
Figure A3.66. Infrared spectrum (Thin Film, NaCl) of compound 158b.

Figure A3.67. $^{13}$C NMR (100 MHz, CDCl₃) of compound 158b.
Figure A3.6.8. $^1$H NMR (600 MHz, CDCl$_3$) of compound 158c.
**Figure A3.69.** Infrared spectrum (Thin Film, NaCl) of compound 158c.

**Figure A3.70.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158c.
Figure A3.71. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158d.
Figure A3.72. Infrared spectrum (Thin Film, NaCl) of compound 158d.

Figure A3.73. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158d.
Figure A3.74. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158e.
Figure A3.75. Infrared spectrum (Thin Film, NaCl) of compound 158e.

Figure A3.76. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158e.
Figure A3.77. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158f.
Figure A3.78. Infrared spectrum (Thin Film, NaCl) of compound 158f.

Figure A3.79. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158f.
Figure A3.80. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158g.
Figure A3.81. Infrared spectrum (Thin Film, NaCl) of compound 158g.

Figure A3.82. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158g.
Figure A3.83. $^1$H NMR (400 MHz, CDCl$_3$) of compound $158\text{h}$. 
Figure A3.84. Infrared spectrum (Thin Film, NaCl) of compound 158h.

Figure A3.85. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158h.
Figure A3.86. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158i.
Figure A3.87. Infrared spectrum (Thin Film, NaCl) of compound 158i.

Figure A3.88. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158i.
Figure A3.89. $^1$H NMR (400 MHz, CD$_3$OD) of compound 158j.
Figure A3.90. Infrared spectrum (Thin Film, NaCl) of compound 158j.

Figure A3.91. $^{13}$C NMR (100 MHz, C$_6$D$_6$) of compound 158j.
Figure A3.92. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158k.
Figure A3.93. Infrared spectrum (Thin Film, NaCl) of compound 158k.

Figure A3.94. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158k.
Figure A3.95. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158I.
Figure A3.96. Infrared spectrum (Thin Film, NaCl) of compound 158l.

Figure A3.97. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158l.
Figure A3.9. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158m.
Figure A3.99. Infrared spectrum (Thin Film, NaCl) of compound 158m.

Figure A3.100. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158m.
Figure A3.101. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158m.
Figure A3.102. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158n.
Figure A3.103. Infrared spectrum (Thin Film, NaCl) of compound $158n$.  

Figure A3.104. $^{13}C$ NMR (100 MHz, CDCl$_3$) of compound $158n$.  

Figure A3.105. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158n.
Figure A3.106. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158o.
Figure A3.107. Infrared spectrum (Thin Film, NaCl) of compound 158o.

Figure A3.108. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158o.
Figure A3.10. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound $158o$. 
Figure A3.110. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158p.
Figure A3.11. Infrared spectrum (Thin Film, NaCl) of compound 158p.

Figure A3.112. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158p.
Figure A3.113. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158p.
Figure A3.114. $^1$H NMR (400 MHz, CDCl$_3$) of compound 158q.
Figure A3.115. Infrared spectrum (Thin Film, NaCl) of compound 158q.

Figure A3.116. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 158q.
Figure A3.117. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound 158q.
Figure A3.11. $^1$H NMR (400 MHz, CDCl$_3$) of compound 165a.
Figure A3.119. Infrared spectrum (Thin Film, NaCl) of compound 165a.

Figure A3.120. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165a.
Figure A3.121. $^1$H NMR (400 MHz, CDCl$_3$) of compound 165b.
Figure A3.12. Infrared spectrum (Thin Film, NaCl) of compound 165b.

Figure A3.13. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165b.
Figure A3.124. $^1H$ NMR (400 MHz, CDCl$_3$) of compound 165c.
Figure A3.125. Infrared spectrum (Thin Film, NaCl) of compound 165c.

Figure A3.126. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165c.
Figure A3.127. $^1$H NMR (400 MHz, CDCl$_3$) of compound 165d.
**Figure A3.128.** Infrared spectrum (Thin Film, NaCl) of compound 165d.

**Figure A3.129.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165d.
Figure A3.130. $^1$H NMR (400 MHz, C$_6$D$_6$) of compound 165e.
Figure A3.131. Infrared spectrum (Thin Film, NaCl) of compound 165e.

Figure A3.132. $^{13}$C NMR (100 MHz, C$_6$D$_6$) of compound 165e.
Figure A3.133. $^1$H NMR (400 MHz, CDCl$_3$) of compound 165f.
Figure A3.134. Infrared spectrum (Thin Film, NaCl) of compound 165f.

Figure A3.135. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165f.
Figure A3.136. $^1$H NMR (400 MHz, CDCl$_3$) of compound 165g.
Appendix 3 – Spectra Relevant to Chapter 5

Figure A3.137. Infrared spectrum (Thin Film, NaCl) of compound 165g.

Figure A3.138. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound 165g.
Figure A3.139. $^1$H NMR (400 MHz, CDCl$_3$) of compound L4.
Figure A3.140. Infrared spectrum (Thin Film, NaCl) of compound L4.

Figure A3.141. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L4.
Figure A3.142. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L4.

Figure A3.143. $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L4.
Figure A3.144. $^1$H NMR (400 MHz, CDCl$_3$) of compound L5.
Figure A3.145. Infrared spectrum (Thin Film, NaCl) of compound L5.

Figure A3.146. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L5.
Figure A3.147. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L5.

Figure A3.148. $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L5.
Figure A3.149. $^1$H NMR (400 MHz, CDCl$_3$) of compound L6.
Figure A3.150. Infrared spectrum (Thin Film, NaCl) of compound L6.

Figure A3.151. $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L6.
Figure A3.152. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L6.

Figure A3.153. $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L6.
Figure A3.154. $^1\text{H} \text{NMR (400 MHz, CDCl}_3$) of compound L7.
**Figure A3.155.** Infrared spectrum (Thin Film, NaCl) of compound L7.

**Figure A3.156.** $^{13}$C NMR (100 MHz, CDCl$_3$) of compound L7.
Figure A3.157. $^{19}$F NMR (282 MHz, CDCl$_3$) of compound L7.

Figure A3.158. $^{31}$P NMR (121 MHz, CDCl$_3$) of compound L7.
APPENDIX 4

*Notebook Cross-Reference for New Compounds.*
<table>
<thead>
<tr>
<th>Compound</th>
<th>Notebook Ref.</th>
<th>Compound</th>
<th>Notebook Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>40a</td>
<td>AQC3-189</td>
<td>41n</td>
<td>KNF-3-043-B</td>
</tr>
<tr>
<td>40b</td>
<td>AQC5-245</td>
<td>41o</td>
<td>KNF-2-221A</td>
</tr>
<tr>
<td>40c</td>
<td>KNF-2-145</td>
<td>41o'</td>
<td>KNF-2-221B</td>
</tr>
<tr>
<td>40d</td>
<td>AQC4-33</td>
<td>41p</td>
<td>AQC4-61</td>
</tr>
<tr>
<td>40e</td>
<td>CS-I-153</td>
<td>41p'</td>
<td>AQC4-181_p2</td>
</tr>
<tr>
<td>40f</td>
<td>AQC4-274</td>
<td>41q</td>
<td>AQC3-275_p2</td>
</tr>
<tr>
<td>40g</td>
<td>AQC3-213</td>
<td>41r</td>
<td>AQC4-69_p1</td>
</tr>
<tr>
<td>40h</td>
<td>KNF-2-219</td>
<td>41s</td>
<td>KNF-1-295</td>
</tr>
<tr>
<td>40i</td>
<td>RC-I-99</td>
<td>41t</td>
<td>KNF-2-161_A</td>
</tr>
<tr>
<td>40j</td>
<td>AQC4-109</td>
<td>41t'</td>
<td>KNF-2-161_B</td>
</tr>
<tr>
<td>40k</td>
<td>AQC3-263</td>
<td>41u</td>
<td>KNF-2-229_C</td>
</tr>
<tr>
<td>40l</td>
<td>AQC3-277</td>
<td>42</td>
<td>KNF-1-289</td>
</tr>
<tr>
<td>40m</td>
<td>RC-I-75</td>
<td>44</td>
<td>KNF-1-293</td>
</tr>
<tr>
<td>40n</td>
<td>KNF-3-033</td>
<td>47</td>
<td>AQC3-137</td>
</tr>
<tr>
<td>40o</td>
<td>KNF-2-207</td>
<td>49a</td>
<td>AQC3-229</td>
</tr>
<tr>
<td>40p</td>
<td>AQC4-55</td>
<td>49e</td>
<td>CS-I-163</td>
</tr>
<tr>
<td>40q</td>
<td>AQC3-281</td>
<td>49f</td>
<td>AQC4-19_p2</td>
</tr>
<tr>
<td>40r</td>
<td>AQC4-67</td>
<td>49g</td>
<td>AQC4-21</td>
</tr>
<tr>
<td>40s</td>
<td>KNF-1-287</td>
<td>49h</td>
<td>KNF-3-031</td>
</tr>
<tr>
<td>40t</td>
<td>KNF-2-157</td>
<td>49i</td>
<td>RC-I-119A</td>
</tr>
<tr>
<td>40u</td>
<td>ED-2-043</td>
<td>63</td>
<td>CS-I-225</td>
</tr>
<tr>
<td>41a</td>
<td>AQC3-291</td>
<td>64</td>
<td>CS-I-223</td>
</tr>
<tr>
<td>41b</td>
<td>AQC5-251</td>
<td>65</td>
<td>CS-I-183</td>
</tr>
<tr>
<td>41c</td>
<td>KNF-2-151</td>
<td>66</td>
<td>CS-I-271</td>
</tr>
<tr>
<td>41d</td>
<td>AQC4-35_p1</td>
<td>67</td>
<td>CS-I-257</td>
</tr>
<tr>
<td>41f</td>
<td>AQC4-19_p1</td>
<td>68</td>
<td>RC-I-111</td>
</tr>
<tr>
<td>41j</td>
<td>AQC4-117</td>
<td>69</td>
<td>RC-I-129</td>
</tr>
<tr>
<td>41k</td>
<td>AQC3-265B_p4</td>
<td>70</td>
<td>CS-I-51</td>
</tr>
<tr>
<td>41k’</td>
<td>AQC3-265B_p3</td>
<td>75</td>
<td>RC-II-35</td>
</tr>
<tr>
<td>41k”</td>
<td>AQC3-265B_p1</td>
<td>76</td>
<td>RC-II-39</td>
</tr>
<tr>
<td>41l</td>
<td>AQC3-287</td>
<td>77</td>
<td>RC-II-41</td>
</tr>
<tr>
<td>41m</td>
<td>RC-I-181A</td>
<td>78</td>
<td>KNF-3-177</td>
</tr>
<tr>
<td>41m’</td>
<td>RC-I-181A</td>
<td>79</td>
<td>RC-I-301</td>
</tr>
<tr>
<td>80</td>
<td>RC-II-67</td>
<td>D-40f</td>
<td>AQC4-143</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>81</td>
<td>RC-II-65</td>
<td>D-41f</td>
<td>AQC4-153_p1</td>
</tr>
<tr>
<td>82</td>
<td>RC-II-77</td>
<td>D-49f</td>
<td>AQC4-153_p2</td>
</tr>
<tr>
<td>83</td>
<td>CS-I-229</td>
<td>D-86</td>
<td>AQC4-139</td>
</tr>
<tr>
<td>84</td>
<td>CS-I-279</td>
<td>D-100</td>
<td>AQC4-133</td>
</tr>
<tr>
<td>85</td>
<td>AQC3-187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>AQC3-201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>AQC3-203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>KNF-1-283</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>KNF-2-155</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>KNF-1-275-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>AQC3-129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>CS-I-217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>CS-I-215</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>CS-I-179</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>CS-I-267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>CS-I-249</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>AQC4-159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>AQC3-183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>KNF-2-121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>KNF-2-123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>AQC3-117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>KNF-2-155</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>KNF-1-279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>KNF-2-147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>ED-2-035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>108</td>
<td>CS-I-175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>CS-I-203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>CS-I-207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>CS-I-237</td>
<td></td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>CS-I-253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>KNF-2-283</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>RC-I-113</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table A4.2 Notebook cross-reference for Chapter 5.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Notebook Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>158a</td>
<td>SRS-II-294</td>
</tr>
<tr>
<td>158b</td>
<td>AQC5-65</td>
</tr>
<tr>
<td>158c</td>
<td>SRS-III-128</td>
</tr>
<tr>
<td>158d</td>
<td>AQC5-47</td>
</tr>
<tr>
<td>158e</td>
<td>AQC5-193</td>
</tr>
<tr>
<td>158f</td>
<td>AQC5-173</td>
</tr>
<tr>
<td>158g</td>
<td>AQC5-235</td>
</tr>
<tr>
<td>158h</td>
<td>AQC5-117</td>
</tr>
<tr>
<td>158i</td>
<td>AQC5-115</td>
</tr>
<tr>
<td>158j</td>
<td>AQC5-87</td>
</tr>
<tr>
<td>158k</td>
<td>AQC5-123</td>
</tr>
<tr>
<td>158l</td>
<td>SRS-III-31</td>
</tr>
<tr>
<td>158m</td>
<td>AQC5-41</td>
</tr>
<tr>
<td>158n</td>
<td>AQC5-67</td>
</tr>
<tr>
<td>158o</td>
<td>AQC5-153</td>
</tr>
<tr>
<td>158p</td>
<td>AQC5-103</td>
</tr>
<tr>
<td>158q</td>
<td>AQC5-125</td>
</tr>
<tr>
<td>160a</td>
<td>AQC5-265</td>
</tr>
<tr>
<td>160b</td>
<td>VH-II-197</td>
</tr>
<tr>
<td>160c</td>
<td>AQC5-271</td>
</tr>
<tr>
<td>160d</td>
<td>AQC5-143</td>
</tr>
<tr>
<td>160e</td>
<td>AQC5-201</td>
</tr>
<tr>
<td>160f</td>
<td>AQC5-181</td>
</tr>
<tr>
<td>160h</td>
<td>AQC5-145</td>
</tr>
<tr>
<td>160i</td>
<td>AQC5-147</td>
</tr>
<tr>
<td>160j</td>
<td>AQC6-147</td>
</tr>
<tr>
<td>160k</td>
<td>AQC6-151</td>
</tr>
<tr>
<td>160l</td>
<td>AQC6-151</td>
</tr>
<tr>
<td>160m</td>
<td>AQC5-267</td>
</tr>
<tr>
<td>160n</td>
<td>AQC5-269</td>
</tr>
<tr>
<td>160o</td>
<td>AQC5-171</td>
</tr>
<tr>
<td>160p</td>
<td>AQC5-257_p1</td>
</tr>
<tr>
<td>160p_linear</td>
<td>AQC5-107B_p2</td>
</tr>
<tr>
<td>160q</td>
<td>AQC6-145_p1</td>
</tr>
<tr>
<td>165a</td>
<td>SRS-III-16</td>
</tr>
<tr>
<td>165b</td>
<td>AQC5-37</td>
</tr>
<tr>
<td>165c</td>
<td>AQC5-111</td>
</tr>
<tr>
<td>165d</td>
<td>AQC5-109</td>
</tr>
<tr>
<td>165e</td>
<td>AQC6-83</td>
</tr>
<tr>
<td>165f</td>
<td>SRS-III-30</td>
</tr>
<tr>
<td>165g</td>
<td>AQC6-113</td>
</tr>
<tr>
<td>L4</td>
<td>VH-II-264</td>
</tr>
<tr>
<td>L5</td>
<td>VH-II-195</td>
</tr>
<tr>
<td>L6</td>
<td>VH-II-281</td>
</tr>
<tr>
<td>L7</td>
<td>VH-II-291</td>
</tr>
</tbody>
</table>
ABOUT THE AUTHOR

Alexander Quinn Cusumano was born in St. Petersburg, Florida on June 7th, 1997 to Dave and Dale Cusumano. After 10 years in Florida, Alex, his parents, and his younger sister Nicki moved to Charlotte, North Carolina. His interest in organic chemistry began in high school after carrying out research in the lab of Professor Markus Etzkorn at the University of North Carolina at Charlotte.

In the fall of 2014, Alex started attending North Carolina State University in Raleigh, North Carolina as a chemistry major. While an undergraduate at NCSU, he conducted research under the advisory of Professor Joshua Pierce regarding the development of methods for the synthesis of functionalized heterocycles in the context of natural product synthesis. With the continued support and guidance from Dr. Pierce, his passion for academic research was solidified, leading him to continue his studies in graduate school.

Upon completion of his studies at NCSU, Alex moved to Pasadena, California to pursue graduate studies at the California Institute of Technology under the advisory of Professor Brian Stoltz, with additional guidance from Professor William A. Goddard III. His research focused on the development of novel asymmetric transformations, with an emphasis on transition-metal catalysis and computational chemistry. Upon completion of his Ph.D. at Caltech in June 2023, Alex will continue to broaden his research horizons with a postdoctoral appointment under the guidance of Professor Abigail Doyle at the University of California at Los Angeles.