

# **METAL-CATALYZED ANNULATIONS OF STRAINED CYCLOALKANES**

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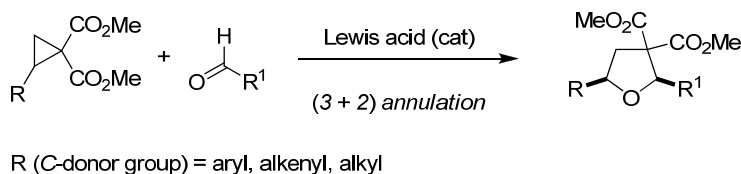
## ABSTRACT

ANDREW THOMAS PARSONS: Metal-Catalyzed Annulations of Strained Cycloalkanes

(Under the direction of Jeffrey S. Johnson)

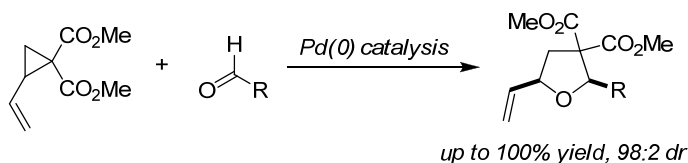
### I. Lewis Acid-Catalyzed (3 + 2) Annulation of Malonate-Derived Donor-Acceptor Cyclopropanes and Aldehydes

An overview of the development, scope, and mechanism of the (3 + 2) annulation of malonate-derived donor-acceptor cyclopropanes and aldehydes is presented.



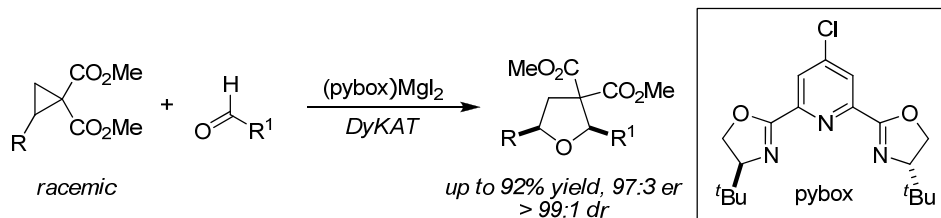
### II. Palladium(0)-Catalyzed Annulation of Dimethyl 2-Vinylcyclopropane-1,1-Dicarboxylate and Aldehydes: The Synthesis of Tetrahydrofurans through an Aldol-Allylic Etherification Sequence

The synthesis of tetrahydrofurans via palladium(0)-catalyzed annulation of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate and aldehydes is described. Carbon-carbon bond cleavage of the cyclopropane was achieved through  $\pi$ -allylpalladium formation. Aldol reaction with an aldehyde and subsequent ring-closure provides the desired 2,5-*cis*-disubstituted tetrahydrofurans with high diastereoselectivity.



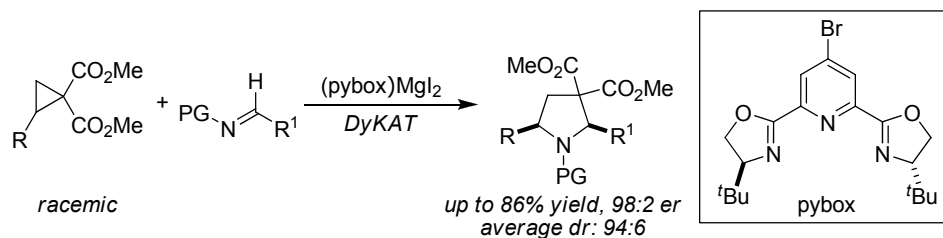
### III. Enantioselective Synthesis of Tetrahydrofurans via Dynamic Kinetic Asymmetric (3 + 2) Annulation of Racemic Cyclopropanes and Aldehydes

The synthesis of enantioenriched 2,5-*cis*-disubstituted tetrahydrofurans was achieved through a dynamic kinetic asymmetric transformation (DyKAT) of racemic cyclopropanes. Use of a catalytic amount of 4-chloro-*tert*-butylpybox/MgI<sub>2</sub> facilitated the enantioselective annulation of electron-rich donor-acceptor cyclopropanes and aldehydes. The electron-deficient 4-chloro-pybox ligand provided an increase in yield while maintaining high levels of stereoselectivity.



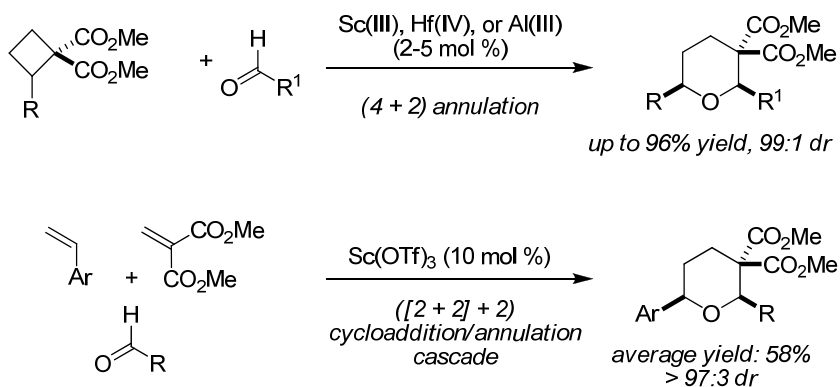
### IV. Dynamic Kinetic Asymmetric Synthesis of Pyrrolidines from Racemic Cyclopropanes and Aldimines: Reaction Development and Mechanistic Insights

The use of a (pybox)MgI<sub>2</sub> catalyst for the dynamic kinetic asymmetric synthesis of pyrrolidines from donor-acceptor cyclopropanes and aldimines is described. The choice of *N*-protecting group and 4-substituted-*tert*-butyl-pybox ligand was essential to achieving high yields and selectivities. Mechanistic investigations suggest that the reaction occurs via annulation with the (*E*)-aldimine dipolarophile exclusively and minimal *E*—*Z*-isomerization occurs prior to annulation.



## V. Lewis Acid-Catalyzed (4 + 2) Annulation of Donor-Acceptor Cyclobutanes and Aldehydes

The diastereoselective synthesis of 2,6-*cis*-disubstituted tetrahydropyrans via (4 + 2) annulation of D–A cyclobutanes and aldehydes is described.  $\text{Sc}(\text{OTf})_3$  and  $\text{Hf}(\text{OTf})_4$  catalyze the annulation with cinnamyl and aryl aldehydes. Extension of this methodology to alkyl aldehydes required the use of a bulky aluminum(III) Lewis acid. A one-pot cycloaddition/annulation cascade was achieved, providing access to tetrahydropyrans directly from an olefin, dimethyl 2-methylenemalonate, and an aldehyde.



## ACKNOWLEDGEMENTS

First, I need to thank the people who have provided me with their unwavering support throughout my life, Kimberly and Donald Parsons, my mother and father. Words cannot even begin to describe how grateful I am to have such wonderful parents. They have always done everything in their power and made selfless sacrifices to help me achieve my goals. They taught me the importance of leading by example and having a strong work ethic. They allowed me to make my own decisions and always trusted that I'd make the best choice given the circumstances. While I can't say that I've always made the most intelligent decisions, my parents have always stood by my side and taught me how to learn from my mistakes. I am grateful that they set a great example for both my brother and I, and there's no doubt that the reason this dissertation exists is because of the love and support that they continue to provide me. I thank them both dearly.

By mere chance, my brother, Don, and I both ended up only 30 miles apart in North Carolina. While we only saw each other once every month or two, the time that we spent together over the last five years has really impacted our relationship in a positive manner. Both of our lives have undergone substantial transformations, and I am especially proud of what Don has achieved since I arrived to Chapel Hill. I am thankful for his generosity over the years, and with that being said, I probably still owe him a few 5:00 am rides to the airport. I am going to miss our trips to Carrburritos and my weekend getaways to Raleigh or Cary to watch the Patriots game or go cycling.

I have been very fortunate that my grandparents, Bob and Louise Parsons and Fred and Winnie Thomas, have been a strong presence in my life. I have fond memories of my childhood, vacationing in Maine and northern New Hampshire. I didn't realize it at the time, but it was a lot of work being the grandparents of my brother and me. Between baseball, football, and karate there was no real off-season for them and I appreciate all of the time and energy that they put into supporting our activities. I am especially grateful for the quality time I was fortunate enough to spend with my late grandfather, Fred Thomas. He was the most generous person I have had the pleasure of knowing. While I'm still sad about his recent passing, I feel lucky to be the grandson of such a wonderful person.

It's hard to believe that it's been over six years since my girlfriend, Kiele Mauricio, and I met in an anthropology class at Bowdoin College. Spending the majority of our relationship in long distance has been difficult at times, but I feel fortunate that we developed such strong communication as a result. I am grateful for her patience, love, and support over the years. Her compassion made my sometimes treacherous path through graduate school much smoother. Even when I was not having my finest moment, she found a way to pick me up and regain perspective. I'm happy that we made it this far and look forward to the future.

Ben Stranges, my former Bowdoin classmate, and I made an interesting roommate combination for the past three years. He has been a great source of entertainment and support, and I am fortunate that we both ended up in Chapel Hill for our graduate studies. He

introduced me to some of the finer things in life, such as the joy of cooking with bacon fat, vintage Bob Dylan records, and old western and classic movies. I'd like to think I had an equally positive influence on Ben's life, but unfortunately I think he'll only be coming out of this experience with bad memories of repeating "24" plotlines and an addiction to coffee.

I owe a great deal of thanks to my undergraduate advisor at Bowdoin College, Rick Broene. When I was on the verge of transferring schools, Rick convinced me to instead postpone my decision and spend the summer working in his lab at Bowdoin. At the time, I didn't realize that this would have such an impact on the course of my life. The opportunity that Rick provided me resulted in my decision to stay at Bowdoin and apply to graduate school. Since arriving at UNC, Rick has continued to be a great mentor and friend. I am forever indebted to him for all he has done for me.

Thanks are extended to my defense committee members: Professors Maurice Brookhart, Joseph Templeton, Michel Gagné, and Marcey Waters. I owe Maurice Brookhart and Mike Gagné special thanks for their letters of support in my postdoctoral and fellowship application processes. The congeniality of this department made it a wonderful place to conduct my graduate studies and the open-door policy of faculty proved to be a valuable resource. Additionally, the Gagné, Waters, and Crimmins research groups are thanked for generously allowing for the use of their chemicals and instruments.

There never seemed to be a dull moment in the Johnson Group. For contributing to this great experience, I'd like to thank Johnson group members, past and present: Cory Bausch, Ash Berman, Andy Satterfield, Steve Greszler, Chris Tarr, Mike Slade, Dan Schmitt, Austin Smith, Kimberly Steward, and Justin Malinowski. I personally thank Dave Nicewicz and Matthew Campbell for their invaluable insight and unique perspectives on chemistry and life. As a new member of the lab, observing their work ethic and enthusiasm for chemistry was inspirational. Along with being excellent mentors, they have also been great friends, and I'm lucky to have shared this experience with them.

I would like to thank Matthew Campbell for enduring the pain of the palladium project with me. Neither of us really knew what we were in for when we began the optimization studies of this reaction (we should be finished by Thanksgiving, right?). The effort he put into completing this project is appreciated. I am also thankful to Austin Smith and my undergraduate colleague, Andrew Neel, who joined me as coworkers on the aldimine DyKAT project. The collaborative efforts on these projects made their completion much less daunting and led to some stimulating discussions that surely benefitted us all. Additionally, I would also like extend my thanks to those group members who proofread portions of this dissertation: Matthew Campbell, Chris Tarr, Dan Schmitt, Mike Slade, and Austin Smith.

Finally, I'd like to express gratitude to my research advisor, Jeffrey Johnson. His enthusiasm for chemistry has been an incredible source of motivation during my time conducting research in his laboratory. I am thankful for his patient, respectful, and humble manner, which promotes the free-speaking of ideas without fear of judgment. Even when I (frequently) proposed bad ideas that were based on faulty logic, he'd correct my reasoning without disparage. The successes I have experienced during my graduate career are largely a result of Jeff's constant intellectual and moral support, for which I am truly grateful. I've come to realize that having an advisor like Jeff is a rarity, and I feel privileged to have worked under his guidance.

*To my family  
and  
in loving memory of my grandfather,  
W. Frederic Thomas  
(1925 – 2009)*



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## LIST OF ABBREVIATIONS AND SYMBOLS

|                     |  |
|---------------------|--|
| A                   | acceptor                                       |
| A <sup>1,3</sup>    | 1,3-allylic strain                             |
| Ac                  | acetate  |
| Ad                  | adamantyl                                      |
| Anal.               | elemental analysis                             |
| Ar                  | aryl   |
| aq                  | aqueous  |
| atm                 | atmospheres                                    |
| bipy                | 2,2'-dipyridyl                                 |
| Bn                  | benzyl   |
| bphen               | bathophenanthroline                            |
| br                  | broad  |
| bs                  | broad singlet                                  |
| <sup>n</sup> Bu     | <i>normal</i> -butyl                           |
| <sup>t</sup> Bu     | <i>tert</i> -butyl                             |
| <sup>13</sup> C NMR | carbon nuclear magnetic resonance spectroscopy |
| C–C                 | carbon-carbon bond                             |
| calcd.              | calculated                                     |
| cat                 | catalytic amount or catalyst                   |
| COD                 | cyclooctadiene                                 |
| conv                | conversion                                     |
| d                   | doublet or days                                |

|            |  |
|------------|--|
| dd         | doublet of doublet                         |
| ddt        | doublet of doublet of triplet              |
| dq         | doublet of quartet                         |
| dec        | decomposition                              |
| dtd        | doublet of triplet of doublet              |
| D          | donor                                      |
| D–A        | donor-acceptor                             |
| DAST       | diethylaminosulfur trifluoride             |
| dba        | dibenzylideneacetone                       |
| DBFOX      | 4,6-dibenzofurandiyl-2,2'-bis(oxazoline)   |
| DCC        | dicyclohexylcarbodiimide                   |
| <i>dig</i> | digonal                                    |
| DKR        | dynamic kinetic resolution                 |
| DMAP       | 4- <i>N,N</i> -dimethylaminopyridine       |
| DME        | dimethoxyethane                            |
| DMF        | <i>N,N</i> -dimethylformamide              |
| DMM        | dimethyl 2-methylenemalonate               |
| DMSO       | dimethyl sulfoxide                         |
| dppf       | 1,1'-bis(diphenylphosphino)ferrocene       |
| dppe       | 1,2-bis(diphenylphosphino)ethane           |
| dr         | diastereomeric ratio                       |
| dt         | doublet of triplet                         |
| DTBM       | 3,5-di- <i>tert</i> -butyl-4-methoxyphenyl |

|                    |  |
|--------------------|--|
| DyKAT              | dynamic kinetic asymmetric transformation      |
| E                  | electron withdrawing group                     |
| <i>E</i>           | <i>entgegen</i>                                |
| El(+)              | electrophile                                   |
| <i>endo</i>        | endocyclic                                     |
| eq                 | equation                                       |
| equiv              | equivalents                                    |
| er                 | enantiomeric ratio                             |
| ESI                | electrospray ionization                        |
| Et                 | ethyl  |
| Et <sub>2</sub> O  | diethyl ether                                  |
| EtOAc              | ethyl acetate                                  |
| EWG                | electron withdrawing group                     |
| <i>exo</i>         | exocyclic                                      |
| FID                | flame ionization detector                      |
| GLC                | gas-liquid chromatography                      |
| h                  | hour   |
| <sup>1</sup> H NMR | proton nuclear magnetic resonance spectroscopy |
| <i>n</i> -hexanal  | <i>normal</i> -hexanal                         |
| HMPA               | hexamethylphosphoramide                        |
| HOMO               | highest occupied molecular orbital             |
| HPLC               | high performance liquid chromatography         |
| HRMS               | high resolution mass spectroscopy              |

|         |  |
|---------|--|
| Hz      | hertz  |
| IR      | infrared spectroscopy  |
| $J$     | coupling constant  |
| $k$     | reaction rate  |
| kcal    | kilocalorie  |
| $L^*$   | chiral ligand  |
| LA      | Lewis acid   |
| $LA^*$  | chiral Lewis acid  |
| LAH     | lithium aluminum hydride   |
| LRMS    | low resolution mass spectroscopy                                 |
| LUMO    | lowest unoccupied molecular orbital                              |
| M       | metal or molarity  |
| m       | multiplet  |
| MAD     | methylaluminum bis(2,6-di- <i>tert</i> -butyl-4-methylphenoxide) |
| Me      | methyl   |
| MeCN    | acetonitrile   |
| Menth   | menthyl  |
| MeOH    | methanol   |
| Mes     | mesityl  |
| 2-MeTHF | 2-methyltetrahydrofuran  |
| mg      | milligram  |
| MHz     | megahertz  |
| min     | minutes  |

|                        |   |
|------------------------|---|
| mL                     | milliliter                                      |
| mmol                   | millimole                                       |
| mp                     | melting point                                   |
| MS                     | molecular sieves                                |
| <i>n</i>               | <i>normal</i> or number of atoms or counterions |
| NBS                    | <i>N</i> -bromosuccinimide                      |
| nd                     | not determined                                  |
| nOe                    | nuclear Overhauser enhancement                  |
| NOESY                  | nuclear Overhauser enhancement spectroscopy     |
| NpOH                   | naphthol  |
| nr                     | no reaction                                     |
| Nu(–)                  | nucleophile                                     |
| op                     | optical purity                                  |
| PG                     | protecting group                                |
| Ph                     | phenyl  |
| pmdba                  | 4,4'-dimethoxydibenzylideneacetone              |
| ppm                    | parts per million                               |
| <sup><i>i</i></sup> Pr | <i>iso</i> -propyl                              |
| PTFE                   | polytetrafluoroethylene                         |
| pybox                  | pyridine-2,6-bis(oxazoline)                     |
| q                      | quartet   |
| qd                     | quartet of doublet                              |
| qn                     | quintuplet                                      |

|            |   |
|------------|---|
| R          | substituent                                     |
| $R_f$      | retention factor                                |
| $R_L$      | large substituent                               |
| $R_S$      | small substituent                               |
| <i>rac</i> | racemic   |
| RCHO       | aldehyde  |
| rt         | room temperature                                |
| s          | singlet   |
| SFC        | supercritical fluid chromatography              |
| $S_E2$     | bimolecular electrophilic substitution          |
| $S_N2$     | bimolecular nucleophilic substitution           |
| SPhos      | 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| T          | temperature                                     |
| t          | triplet   |
| $t_{1/2}$  | half-life                                       |
| $t_r$      | retention time                                  |
| td         | triplet of doublet                              |
| Tf         | trifluoromethanesulfonyl                        |
| THF        | tetrahydrofuran                                 |
| THP        | tetrahydropyran                                 |
| TLC        | thin layer chromatography                       |
| TM         | transition metal                                |
| TMS        | trimethylsilyl                                  |



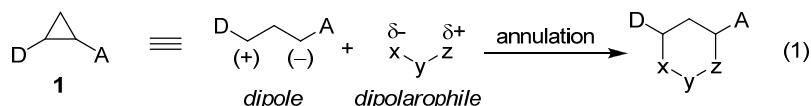
|               |  |
|---------------|--|
| triflate      | trifluoromethanesulfonate                      |
| <i>trig</i>   | trigonal                                       |
| Troc          | trichloroethyloxycarbonyl                      |
| Ts            | <i>para</i> -toluenesulfonyl                   |
| UV            | ultraviolet                                    |
| X             | anionic ligand, halide, substituent, or number |
| <i>Z</i>      | <i>zusammen</i>                                |
| Å             | Ångstrom                                       |
| [ $\alpha$ ]  | optical rotation                               |
| $\Delta$      | heat   |
| $\delta$      | chemical shift or partial charge               |
| $\mu\text{L}$ | microliter                                     |
| $\mu\text{m}$ | micrometer                                     |

## CHAPTER ONE

# LEWIS ACID-CATALYZED (3 + 2) ANNULATION OF MALONATE-DERIVED DONOR-ACCEPTOR CYCLOPROPANES AND ALDEHYDES

### 1.1 Introduction

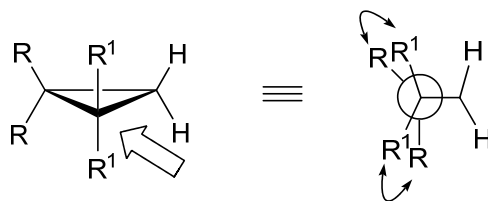
Polysubstituted heterocyclic moieties are prevalent in naturally occurring and pharmaceutically relevant molecules. For this reason, development of efficient methods for their stereoselective preparation is an important challenge for synthetic organic chemists. The ideal synthetic operation would be one-step, high yielding, and provide several bond-forming events with absolute control of regio- and stereoselectivity; cycloadditions represent an attractive class of reactions to achieve this end. In this context, (3 + *n*) cycloaddition (more generally, annulation) reactions of *vicinal* donor-acceptor (D–A) cyclopropanes **1** represent valuable methods for the preparation of five-, six-, and seven-membered heterocycles (eq 1).<sup>1</sup> Recent advances in the catalytic stereoselective synthesis of myriad D–A cyclopropanes from simple starting materials<sup>2,3</sup> has facilitated the exploration of these compounds as building blocks for complex molecules.<sup>4,5</sup>



Cyclopropanes represent a unique class of reagents due to their unusually strained architecture and exceptional reactivity when compared to other cycloalkanes. The ease with

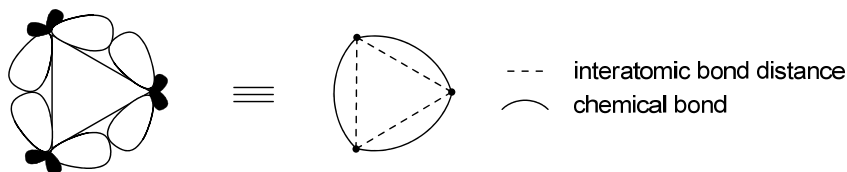
which the cyclopropyl carbon-carbon (C–C)  $\sigma$ -bond undergoes cleavage can be attributed to its particularly high strain energy. Several structural attributes lead to this high degree of strain. One contributing source is the required distortion of the  $sp^3$ -hybridized carbon atoms from the preferred  $109.5^\circ$  to  $60^\circ$ , resulting in a significant amount of Baeyer (angular) strain. The three-membered carbocycle exists as rigid planar molecule with a minimal degree of conformational freedom. Consequently the cyclopropyl substituents are forced to eclipse, resulting in a high degree of Pitzer (torsional) strain (**Figure 1-1**).<sup>5</sup>

**Figure 1-1.** Torsional Strain of Cyclopropane



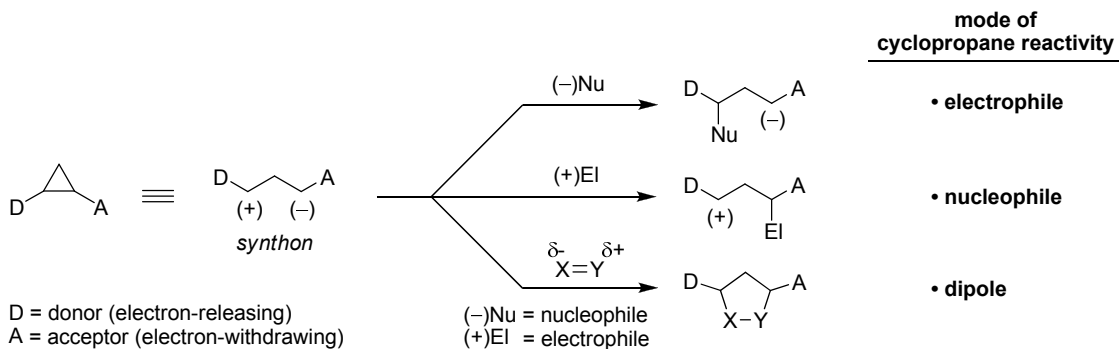
Geometric constraints of the cyclopropane C- $sp^3$  orbitals affect the nature of the  $\sigma$ -C–C bonds and significant distortion occurs. Despite having weak bonds, the interatomic bond distance (distance in space between each cyclopropyl carbon atom) is shorter than that of ethane.<sup>6</sup> This seemingly inconsistent characteristic can be attributed to a lack of axial symmetry of the C–C  $\sigma$ -bonds.<sup>6</sup> The  $sp^3$ -hybridicity of the carbon atoms causes the bonding orbitals of cyclopropane to overlap in a fashion that results in approximately 20% less overlap when compared to the C–C bonding interaction in ethane.<sup>5</sup> It has been proposed by Coulson and Moffitt that these bonds are best described as “bent” due to this asymmetric overlap (**Figure 1-2**).<sup>7</sup> This hypothesis provides an explanation consistent with the observed shortened interatomic bond distance and weakened chemical bond of cyclopropane.

**Figure 1-2.** Carbon-Carbon Bonding in Cyclopropane



*Vicinal* donor-acceptor cyclopropanes have been extensively studied over the past decade due to their enhanced reactivity and increased functionality.<sup>1,3,8-12</sup> Elevation in reactivity is derived from the simultaneous stabilization of transient charged intermediates by the donor and acceptor group upon heterolytic C–C  $\sigma$ -bond cleavage. The ease in which D–A cyclopropanes undergo ring-opening allows them to serve as synthetic equivalents to all-carbon 1,3-dipoles under mild reaction conditions. This dipolar nature causes cyclopropanes **1** to display a diverse array of reactivities, facilitating their implementation in numerous complexity-building synthetic operations (**Scheme 1-1**).

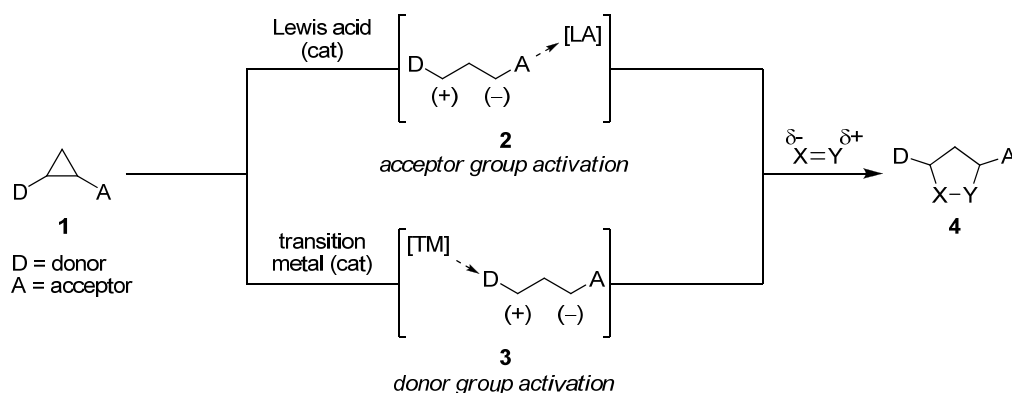
**Scheme 1-1.** Modes of Reactivity for *Vicinal* Donor-Acceptor Cyclopropanes



The development of  $(3 + n)$  annulations of *vicinal* D–A cyclopropanes **1** with dipolarophiles provides a method to access a range of hetero- and carbocyclic products. These reactions are commonly conducted using Lewis acid-catalyzed activation of the acceptor group, rendering **1** electrophilic (activation is schematically represented as complex **2**, **Scheme 1-2**, top). Trapping with nucleophilic dipolarophiles furnishes annulation

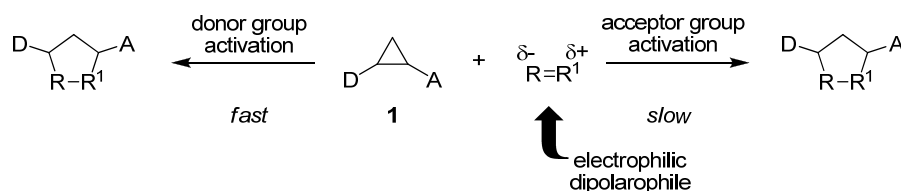
products of type **4**. An alternative approach to achieving this transformation involves donor group activation using an electron-rich transition metal (**Scheme 1-2**, bottom). Counter to the Lewis acid-activated complex **2**, the transition metal-activated species **3** is nucleophilic, requiring a sufficiently electron-deficient dipolarophile to undergo annulation. Thus, these modes of activation are electronically complementary.

**Scheme 1-2.** Catalytic Modes of D–A Cyclopropane Activation and Subsequent Annulation with a Dipolarophile



In cyclopropane annulations, the choice of activation mode can significantly alter the rate of reaction depending on dipolarophile electronics. For example, the optimal dipole/dipolarophile orbital overlap in an annulation utilizing acceptor group activation exists between the  $\text{LUMO}_{\text{dipole}}$  and the  $\text{HOMO}_{\text{dipolarophile}}$ .<sup>13</sup> Thus, annulations of a *vicinal* D–A cyclopropane **1** and an electrophilic dipolarophile using acceptor group activation will result in a slow reaction rate due to the low energy HOMO of the dipolarophile. Alternatively, if **1** is subjected to donor group activation, use of an electrophilic dipolarophile will result in rate acceleration due to an increased energy of the  $\text{HOMO}_{\text{dipole}}$ , providing better orbital overlap with the low energy  $\text{LUMO}_{\text{dipolarophile}}$  (**Scheme 1-3**).

**Scheme 1-3.** Relative Reaction Rates of Donor and Acceptor Group Activated *Vicinal* D–A Cyclopropanes with Electrophilic Dipolarophiles



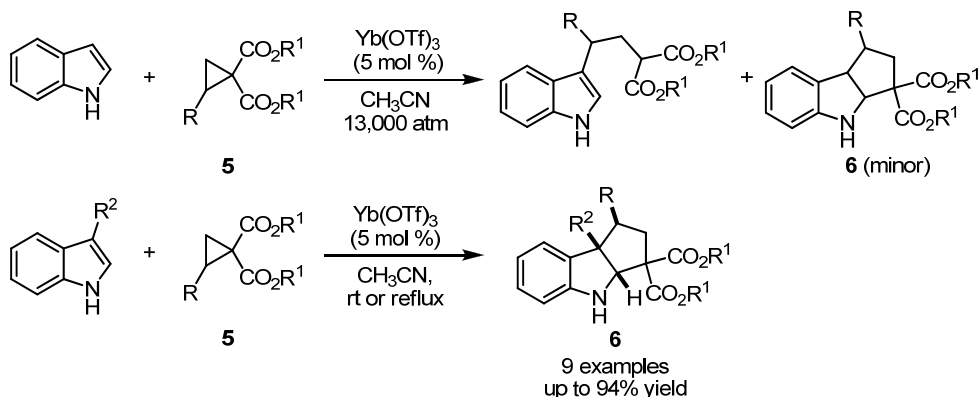
## 1.2 Background

### 1.2.1 Initial Discovery

Early studies of *vicinal* donor-acceptor cyclopropanes conducted by Cram and Danishefsky relied on thermal activation to achieve sufficient reactivity. This seminal work most importantly led to an increased understanding of the mechanistic intricacies involved in ring-opening reactions of D–A cyclopropanes.<sup>14-16</sup> The development of mild Lewis acid-catalyzed methods to achieve ring-opening has led to their widespread application in organic synthesis. D–A cyclopropanes derived from malonic esters have gained considerable attention due to their ease of preparation, bench top stability, and *geminal* diester motif that serves as a functional handle for Lewis acid activation.

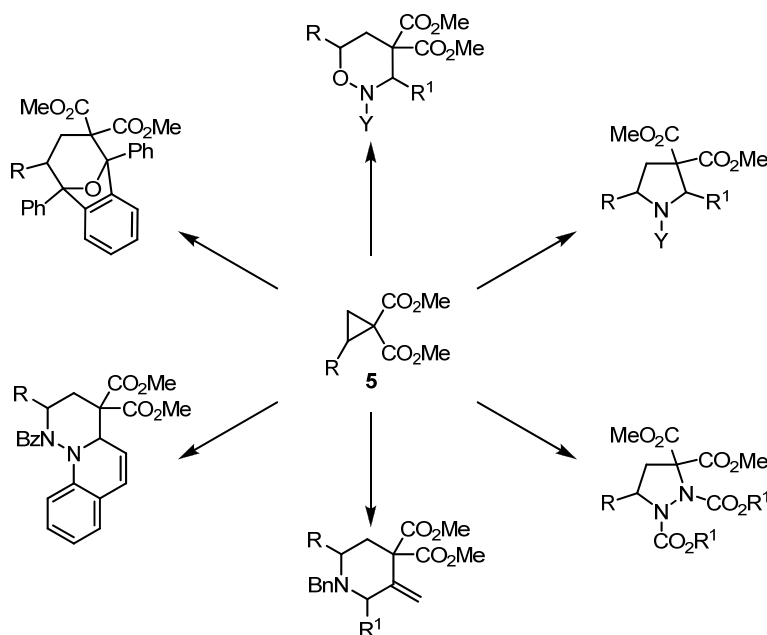
Current methods for the synthesis of hetero- and carbocycles from **5** rely predominantly on the use of Lewis acid catalysis. The initial discovery of this process was reported by Kerr when byproduct **6** was observed in the Yb(OTf)<sub>3</sub>-catalyzed nucleophilic ring opening of **5** with indole nucleophiles under high pressure (eq 3).<sup>17</sup> Subsequent studies demonstrated that reaction conditions could be optimized to give **6** as the major product.<sup>18</sup>

**Scheme 1-4.** Initial Discovery and Development of Lewis Acid-Catalyzed Annulation of **5** with Indole Dipolarophiles



Since this discovery, numerous methods have been developed to transform **5** into complex heterocycles via catalytic annulation with dipolarophiles (**Scheme 1-5**).<sup>19-24</sup> In these processes, the donor and acceptor groups assume dual roles: 1) stabilize transient charged intermediates resulting from cyclopropyl C–C  $\sigma$ -bond cleavage; and 2) provide a point for cyclopropane activation via donor or acceptor group stabilization (**Scheme 1-2**, *vide supra*).

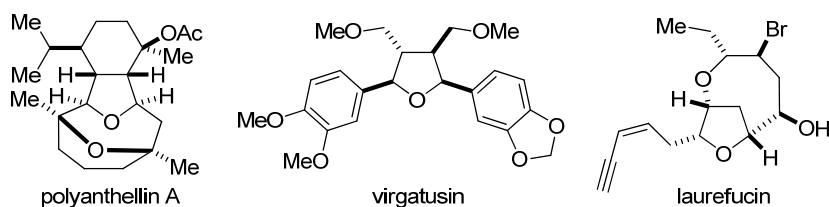
**Scheme 1-5.** Selected Heterocycles Accessed via Annulation of **5** with Dipolarophiles



### 1.2.2 Aldehyde/Cyclopropane Annulation via Lewis Acid Catalysis

Tetrahydrofuran (THF) moieties are ubiquitous in naturally occurring and pharmaceutically relevant molecules (**Figure 1-3**). The importance of developing methods for their preparation is evidenced by the continued interest in this area of research.<sup>25</sup> The preparation of THFs through the (3 + 2) annulation of malonate-derived donor–acceptor cyclopropanes and aldehydes would provide an attractive route to these motifs for several reasons: a) malonate-derived cyclopropanes are readily accessible; b) many aldehydes are commercially available or easily prepared; and c) annulation reactions are highly convergent.

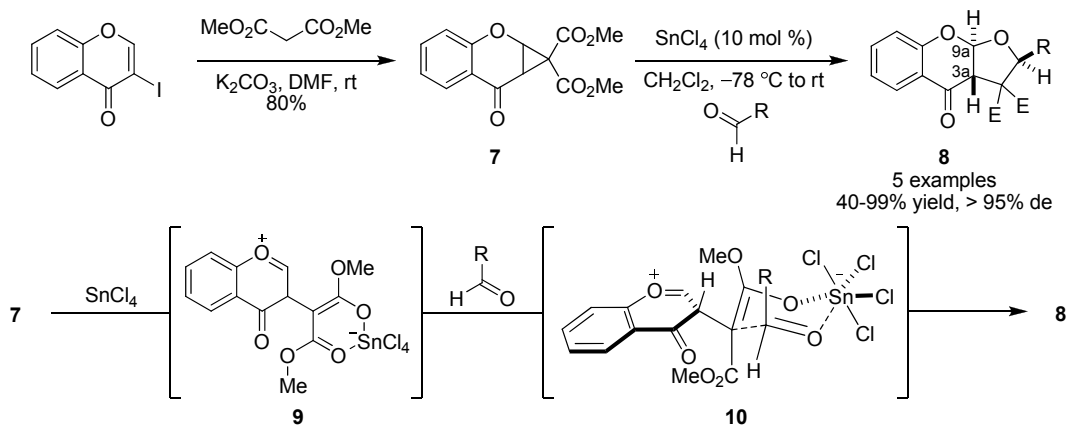
**Figure 1-3.** Representative Tetrahydrofuran-Containing Natural Products



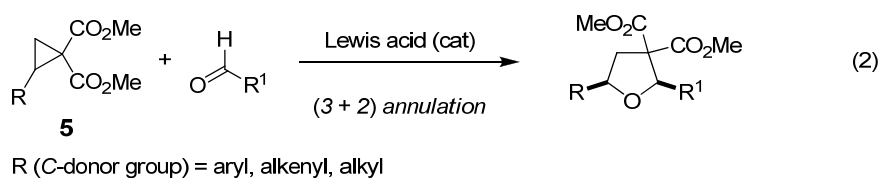
The participation of aldehydes in annulation reactions with D–A cyclopropanes is not an unknown process. Most reported methodologies involving aldehyde/cyclopropane annulations require the use of stoichiometric Lewis acid promoters and largely focuses on the preparation of lactones<sup>26-29</sup> rather than tetrahydrofurans.<sup>30,31</sup> Recently, Sugita and coworkers reported the annulation of malonate-derived methanochromanone **7** and aldehydes using catalytic SnCl<sub>4</sub>, providing *trans*-fused tetrahydrofuro[2,3-*b*][1]benzopyranones **8** in a highly diastereoselective manner.<sup>32</sup> Although no mechanistic studies were reported, it was proposed that the reaction is initiated by SnCl<sub>4</sub>-promoted ring opening to zwitterion **9**. Coordination with an aldehyde and organization into chair-like transition state **10** places the aldehyde substituent R in a pseudo-axial position, minimizing steric hindrance. A diastereoselective aldol addition followed by ring-closure of the resultant alkoxide yields adduct **8**.



**Scheme 1-6.** SnCl<sub>4</sub>-Catalyzed Annulation of Malonate-Derived Methanochromanone **7** and Aldehydes



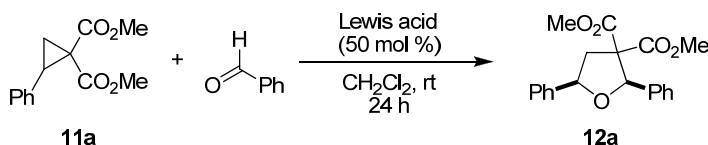
Precedents established by Kerr have demonstrated that use of an appropriate Lewis acid allows for catalytic annulations **5** bearing non-heteroatomic donor groups under mild reaction conditions (*vide supra*).<sup>18,19</sup> Extension of this methodology to aldehyde dipolarophiles would provide broad access to substituted THFs in a convergent one-step process. In recognizing the utility of this transformation, the Johnson group sought to develop an annulation of **5** with aldehyde dipolarophiles to access tetrahydrofuran derivatives (eq 2).



Initial efforts in the Johnson group involved the examination of a range of Lewis acids to achieve the annulation of cyclopropane **11a** with benzaldehyde (**Table 1-1**). Cyclopropane **11a** was prepared in two steps from benzaldehyde and dimethyl malonate in through a Knoevenagel/Corey-Chaykovsky sequence.<sup>33-35</sup> Subjection of **11a** to substoichiometric Lewis acid promoters in the presence of excess benzaldehyde provided THF derivative **12a** in varying yields and diastereoselectivities. The results of this analysis

proved that  $\text{Sn}(\text{OTf})_2$  was an efficient catalyst, requiring only 5 mol % loading to achieve the desired annulation in excellent yield and stereoselectivity (entry 13). While stronger Lewis acids such as  $\text{AlCl}_3$  and  $\text{Sc}(\text{OTf})_3$  provided **12a** in good yield, the diastereoselectivity was poor (entries 3 and 10).

**Table 1-1.** Examination of Lewis Acid Promoters for the Annulation of Cyclopropane **11a** and Benzaldehyde



| entry | Lewis acid                | yield (%) <sup>a</sup> | dr <sup>b</sup> | entry           | Lewis acid                | yield (%) <sup>a</sup> | dr <sup>b</sup> |
|-------|---------------------------|------------------------|-----------------|-----------------|---------------------------|------------------------|-----------------|
| 1     | $\text{AgOTf}$            | < 5                    | nd              | 11              | $\text{SnCl}_2$           | 84                     | 99:1            |
| 2     | $\text{AgNTf}_2$          | 73                     | 99:1            | 12              | $\text{Sn}(\text{OTf})_2$ | 97                     | 99:1            |
| 3     | $\text{AlCl}_3$           | 81                     | 67:33           | 13 <sup>c</sup> | $\text{Sn}(\text{OTf})_2$ | 98                     | 99:1            |
| 4     | $\text{Ce}(\text{OTf})_3$ | 75                     | 99:1            | 14              | $\text{SnCl}_4$           | 90                     | 97:3            |
| 5     | $\text{Cu}(\text{OTf})_2$ | 94                     | 98:2            | 15              | $\text{Tb}(\text{OTf})_3$ | 32                     | 99:1            |
| 6     | $\text{Dy}(\text{OTf})_3$ | 28                     | 98:2            | 16              | $\text{Tm}(\text{OTf})_3$ | 44                     | 99:1            |
| 7     | $\text{Er}(\text{OTf})_3$ | 20                     | nd              | 17              | $\text{Yb}(\text{OTf})_3$ | 74                     | 99:1            |
| 8     | $\text{Hf}(\text{OTf})_4$ | 30                     | 67:33           | 18              | $\text{ZnCl}_2$           | 54                     | 98:2            |
| 9     | $\text{Ho}(\text{OTf})_3$ | 23                     | 98:2            | 19              | $\text{Zn}(\text{OTf})_2$ | 70                     | 98:2            |
| 10    | $\text{Sc}(\text{OTf})_3$ | 96                     | 67:33           |                 |                           |                        |                 |

a) Determined by  $^1\text{H}$  NMR spectroscopy using a mesitylene internal standard. b) Determined by  $^1\text{H}$  NMR spectroscopy. c) 5 mol % of the catalyst was used. Abbreviations: dr = diastereomeric ratio, nd = not determined. (Reprinted in part with permission from Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, 130, 8642-8650. © 2008 American Chemical Society)

Subsequent studies sought to examine the scope of the Lewis acid-catalyzed cyclopropane/aldehyde annulation. Early reaction development was carried out using cyclopropane **11a** bearing an electron-neutral phenyl donor group. The identity of the donor group was extended to numerous electronically diverse substituents (**Table 1-2**). Cyclopropanes bearing electron deficient 4-MeO<sub>2</sub>CPh and 4-AcOPh donor groups were successful only with increased catalyst loadings and reaction times (entries 5-6). Relative

stereochemistry of **12** was determined to be 2,5-*cis* by the presence of a strong nuclear Overhauser effect between the two methine protons at the C2' and C5' positions.

**Table 1-2.** Effect of the Cyclopropyl Donor Group on Reaction Rate and Diastereoselectivity

| <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math>\text{11a-i}</math> </div> <div>+</div> <div style="text-align: center;"> <math>\text{O}=\text{C}-\text{Ph}</math> </div> <div> <math>\xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{Sn(OTf)}_2 (5 \text{ mol } \%)}</math> </div> <div style="text-align: center;"> <math>\text{12a-i}</math> </div> </div> |                        |          |         |                        |                 |
|--|------------------------|----------|---------|------------------------|-----------------|
| entry  | R                      | time (h) | product | yield (%) <sup>a</sup> | dr <sup>b</sup> |
| 1  | Ph                     | 2.25     |         | 100                    | 99:1            |
| 2  | 4-MeOPh                | 0.1      |         | 85                     | 98:2            |
| 3  | 4-MePh                 | 1.25     |         | 60                     | 99:1            |
| 4 <sup>c</sup>   | 4-BrPh                 | 25       |         | 61                     | 99:1            |
| 5 <sup>d</sup>   | 4-AcOPh                | 24       |         | 91                     | 99:1            |
| 6 <sup>d</sup>   | 4-MeO <sub>2</sub> CPh | 24       |         | 83                     | 99:1            |
| 7  | 2-thienyl              | 0.75     |         | 97                     | 96:4            |
| 8  | ( <i>E</i> )-CH=CHPh   | 1        |         | 94                     | 70:30           |
| 9  | HC=CH <sub>2</sub>     | 8        |         | 94                     | 90:10           |

a) Isolated yield. b) Determined by <sup>1</sup>H NMR spectroscopy of the unpurified product. c) 10 mol % of Sn(OTf)<sub>2</sub> was used. d) 30 mol % of Sn(OTf)<sub>2</sub> was used.

While the cyclopropane scope demonstrated the ability to use diverse carbon-donor groups, it was necessary to examine the electronic affects of the aldehyde to develop a mechanistic hypothesis (**Table 1-3**). These studies indicated that the identity of the aldehyde had a large influence on reaction time. For example, the electron-poor 4-nitrobenzaldehyde requires an elevated catalyst loading of 20 mol % and a longer reaction time to go to completion (entry 3). Aliphatic aldehydes required the use of catalytic  $\text{SnCl}_4$  rather than  $\text{Sn}(\text{OTf})_2$  (entry 6).

**Table 1-3.** An Examination of Electronically Diverse Aldehydes

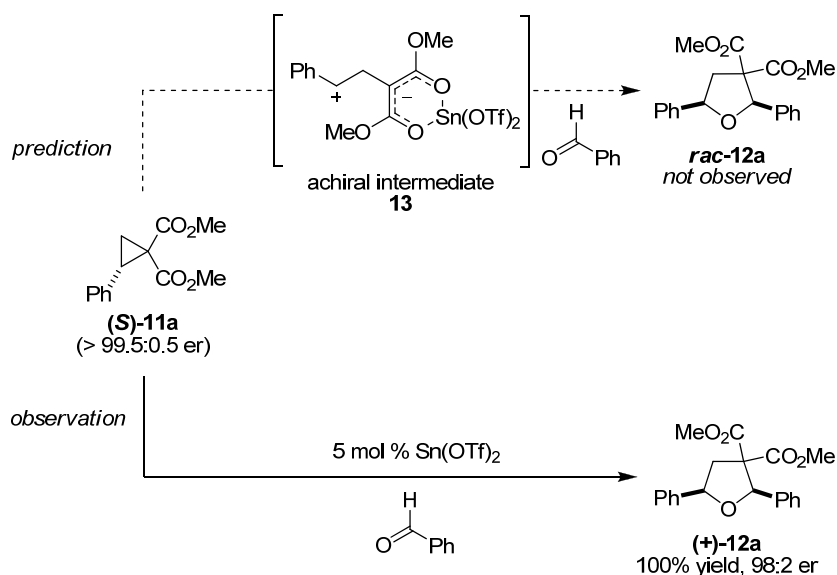
Reaction scheme showing the conversion of cyclopropane **11a** (with two  $\text{CO}_2\text{Me}$  groups and a  $\text{Ph}$  group) and an aldehyde ( $\text{R}-\text{CHO}$ ) to a bicyclic acetal product **12j-n** using  $\text{Sn}(\text{OTf})_2$  (5 mol %) in  $\text{CH}_2\text{Cl}_2$  at room temperature.

| entry          | R                    | time (h) | product        | yield (%) <sup>a</sup> | dr <sup>b</sup> |
|----------------|----------------------|----------|----------------|------------------------|-----------------|
| 1              | 4-MeOPh              | 3.5      | <br><b>12j</b> | 99                     | 99:1            |
| 2              | 4-ClPh               | 4.75     | <br><b>12k</b> | 97                     | 99:1            |
| 3 <sup>c</sup> | 4-NO <sub>2</sub> Ph | 15       | <br><b>12l</b> | 89                     | 95:5            |
| 5              | ( <i>E</i> )-HC=CHPh | 3.5      | <br><b>12m</b> | 97                     | 94:6            |
| 5 <sup>d</sup> | Et                   | 1.75     | <br><b>12n</b> | 100                    | 97:3            |

a) Isolated yield. b) Determined by  $^1\text{H}$  NMR spectroscopy of the unpurified product. c) 20 mol % of  $\text{Sn}(\text{OTf})_2$  was used. d) 5 mol % of  $\text{SnCl}_4$  was used.

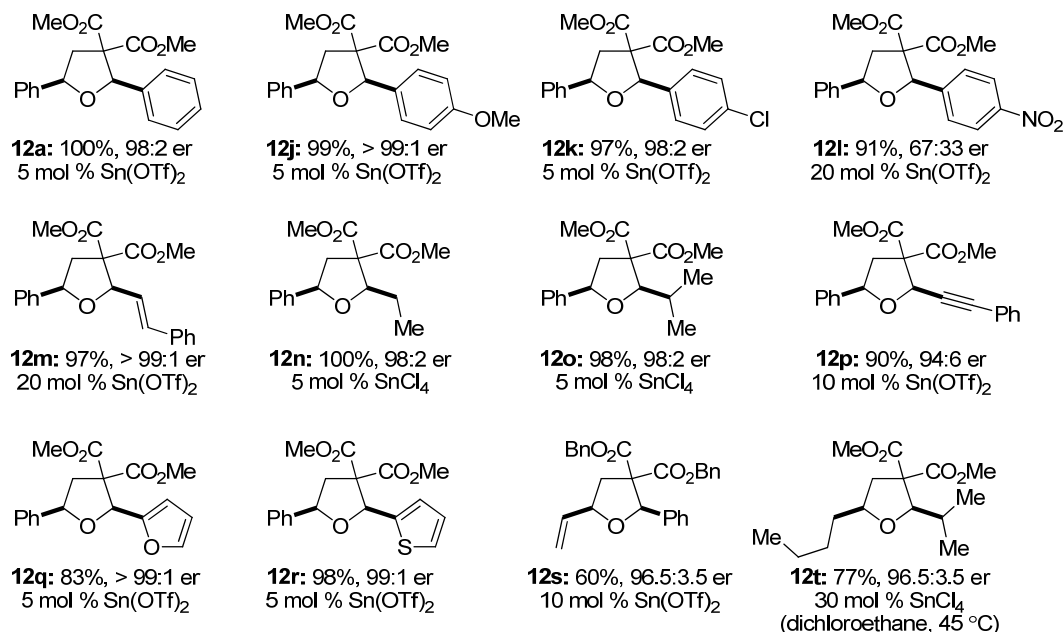
Key mechanistic information was obtained when Pohlhaus prepared enantioenriched **11a** to examine the stereochemical outcome of annulation with aldehyde dipolarophiles. At the onset of these studies, the authors hypothesized that the reaction would proceed through achiral intermediate **13**, resulting in the formation of *racemic*-**12a** (Scheme 1-7). Interestingly, near complete stereochemical transfer was observed in **12a** (er = 98:2) suggesting that the formation of an achiral reaction intermediate is not significant.

**Scheme 1-7.** Annulation of (*S*)-**11a** with Benzaldehyde

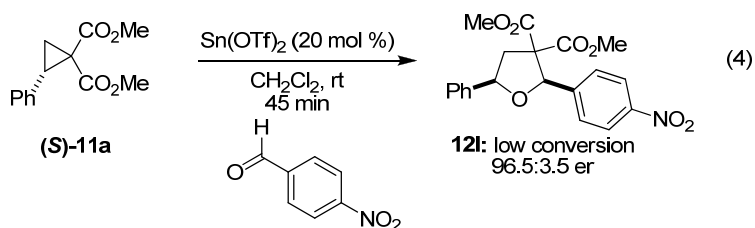
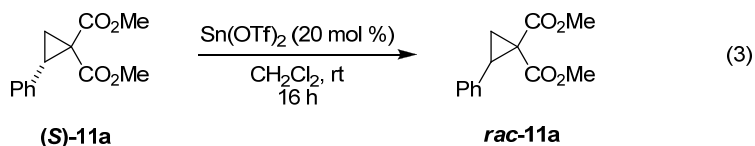


The scope of the enantiospecific (3 + 2) annulation was shown to be general for electron-rich and -neutral aldehydes, resulting in near complete transfer of chirality to the THF products. Use of highly electron-deficient aldehydes that required increased catalyst loadings and reaction times resulted in low levels of chirality transfer. This suggests that an alternative mechanism may be operable when electron-deficient aldehydes are used. The versatility of this reaction was demonstrated with the extension to enantioenriched cyclopropanes bearing vinyl and butyl donor groups. (Figure 1-4).

**Figure 1-4.** Scope of the Enantiospecific Sn(II)- and Sn(IV)-Catalyzed Annulation of Enantioenriched Cyclopropanes and Aldehydes

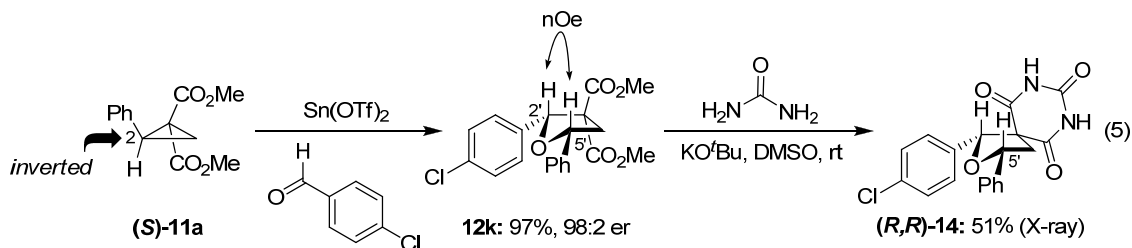


Additional experimentation was conducted in order to determine the nature of stereochemical erosion during the annulation of (*S*)-**11a** with electron-poor aldehydes. Evidence for competing Sn(OTf)<sub>2</sub>-catalyzed cyclopropane racemization was obtained when (*S*)-**11a** was exposed to a catalytic amount of Sn(OTf)<sub>2</sub> in the absence of an aldehyde. After monitoring the reaction for 16 h, the enantiomeric ratio (er) of **11a** had degraded to 50:50 (eq 3). Furthermore, when the annulation of (*S*)-**11a** and 4-nitrobenzaldehyde was quenched at low conversion, **12l** was obtained in 96.5:3.5 er (eq 4). This provides evidence that the annulation of electron-poor aldehydes proceeds through an enantiospecific mechanism, but cyclopropane racemization is a significant competing process.



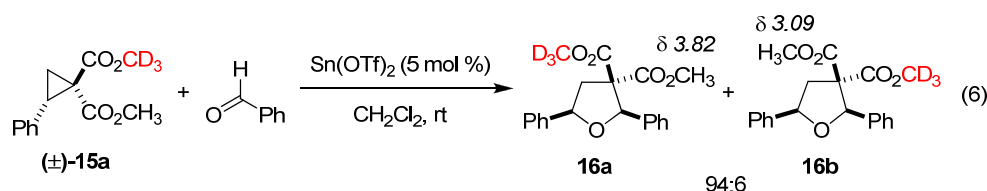
It was necessary to determine the absolute configuration of **12** in order to elucidate the mechanism of stereochemical transfer. Conversion of **12k** to barbituric acid derivative **14** provided crystals suitable for single-crystal X-ray diffraction analysis (**Scheme 1-8**).<sup>36</sup> The absolute stereochemistry was determined to be (2*R*, 5*R*), indicating that the mechanistic pathway involves inversion of the cyclopropyl C2 stereocenter (C5' of **12**). This inversion also provides further evidence that nucleophilic addition by the aldehyde is a mechanistic possibility in this transformation.

**Scheme 1-8.** Determination of the Absolute Configuration of Tetrahydrofurans

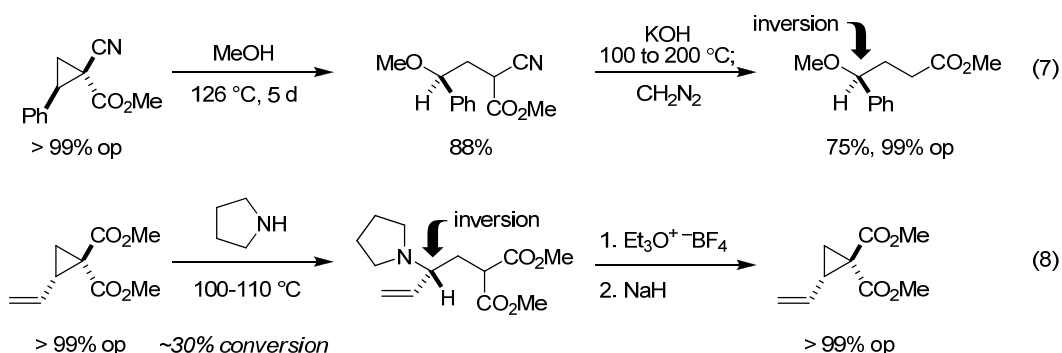


A labeling study was conducted to provide additional stereochemical data for the development of a mechanistic hypothesis. Selective hydrolysis<sup>37</sup> of the ester group *trans* to the phenyl substituent of **11a** and subsequent reesterification using perdeuterated dimethyl sulfate yielded diastereopure isotopically-labeled **15a**.<sup>38</sup> Reaction with benzaldehyde gave a mixture of products in which 94% of label in the major product **16a** was found *cis* to the

phenyl groups (eq 6). A significant upfield shift in the  $^1\text{H}$  NMR spectrum is regularly observed for the methyl group *cis* to the C2 phenyl group of the tetrahydrofurans **12** due to shielding ring currents. This spectral characteristic allowed for facile assignment of the ester groups. (Reprinted in part with permission from Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650. © 2008 American Chemical Society)



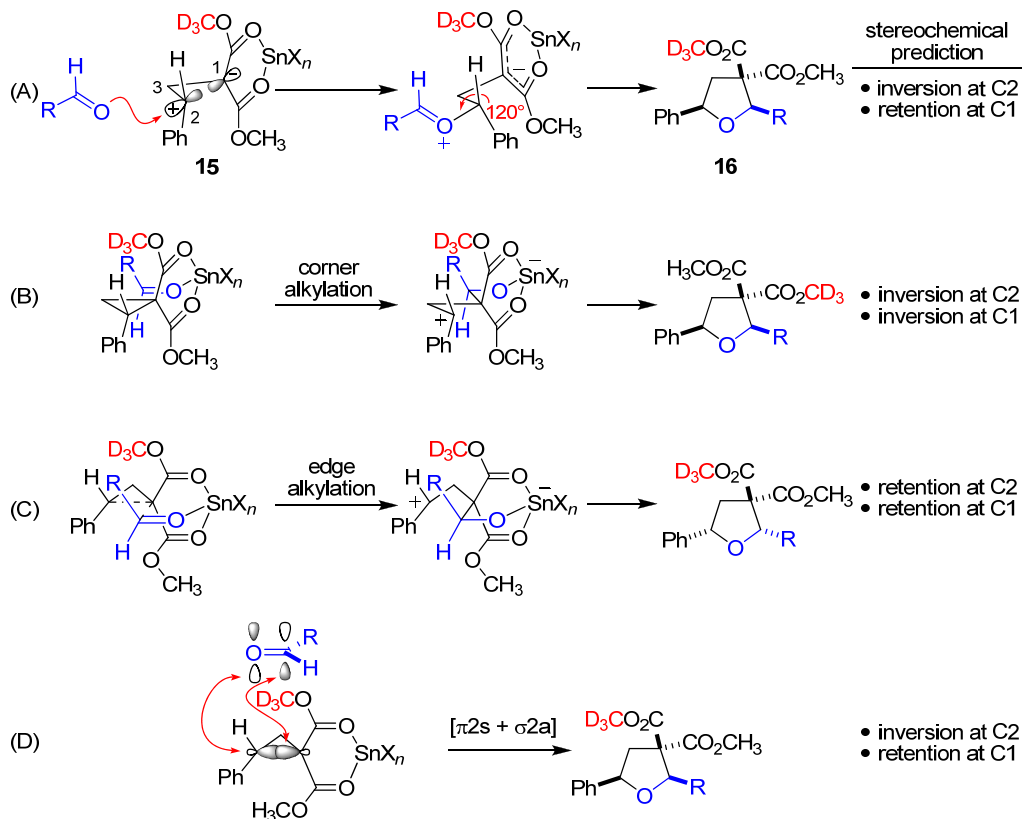
The authors evaluated four possible mechanisms for the (3 + 2) annulation in the context of their experimental observations (**Scheme 1-9**). First, a substitution process where the aldehyde acts as a nucleophile, causing inversion of the stereochemistry at the activated C2 carbon of the cyclopropane (mechanism A).<sup>8,15,39</sup> Inversion has been observed for the methanolysis<sup>15</sup> and aminolysis<sup>16</sup> of activated optically pure (op) cyclopropanes at elevated temperatures (eq 7, 8). Cram has proposed carbanion-carbenium ions as transient



configurationally stable intermediates in reactions with D-A cyclopropanes of this type.<sup>14,40</sup> Next, an  $\text{S}_{\text{E}}2$ -process occurring by a “corner” attack mechanism would proceed with inversion at the cyclopropane 1-position and afford the tetrahydrofuran (mechanism B);



**Scheme 1-9.** Mechanistic Considerations for the (3 + 2) Annulation of **15a** with Aldehydes

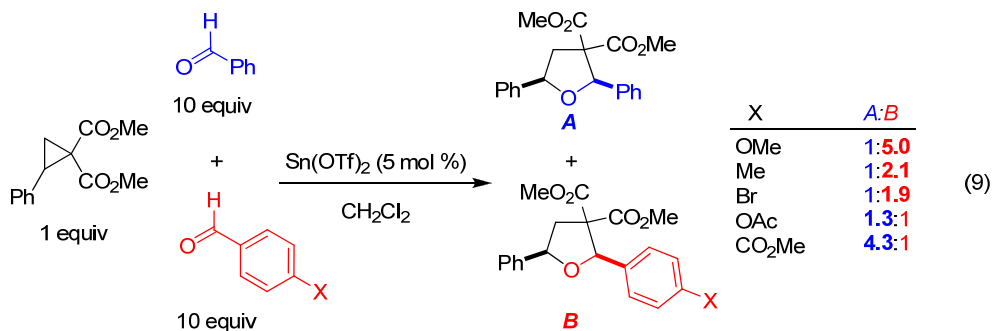


however, this is the minor diastereomer observed from the labeling experiment (eq 6).<sup>41-44</sup>

The cyclopropane could also undergo “edge” attack by the aldehyde (mechanism C). This S<sub>E</sub>2 process would occur with retention of configuration at the 1-position.<sup>30</sup> Placing the large group of the aldehyde away from the phenyl group on the cyclopropane would lead to the incorrect absolute stereochemistry. If a concerted mechanism is considered, the reaction would need to occur via a symmetry allowed  $[\pi 2_s + \sigma 2_a]$  pathway (mechanism D).<sup>45-47</sup> There is only one coplanar orientation of reactants that is consistent with the observed relative and absolute stereochemistry and would not suffer from significant unfavorable steric interactions. Both mechanisms A and D predict a stereochemical outcome that is consistent with experimental observations. (Reprinted in part with permission from Pohlhaus, P. D.;

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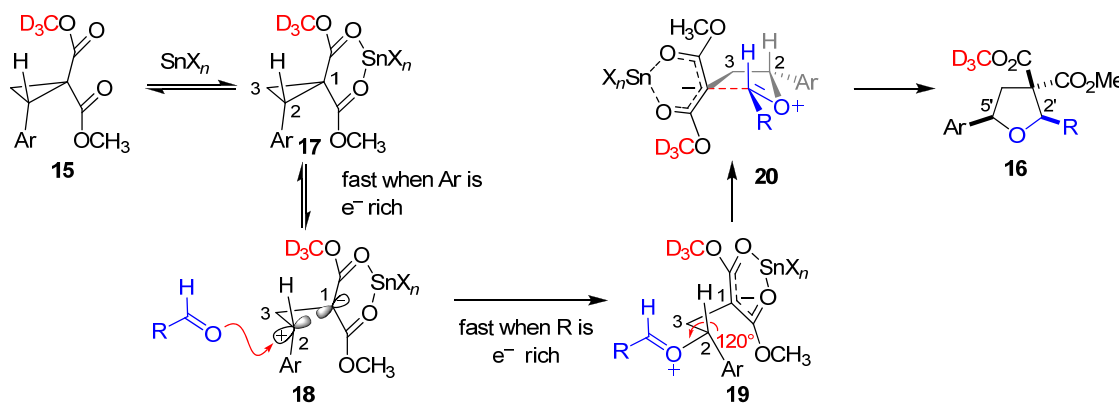
The Pohlhaus and coworkers conducted further experimentation to distinguish mechanisms A and D. Competition experiments were performed using substituted benzaldehydes of varying electronic character versus benzaldehyde (eq 9). When electron-rich aldehydes were used the product ratio favors the tetrahydrofuran derived from the electron-rich aldehyde, product **B**; however, when electron-poor aldehydes are used the product ratio reverses and favors tetrahydrofuran **A** derived from benzaldehyde. In mechanism A (**Scheme 1-9**), electron-rich aldehydes should react faster if the key step is nucleophilic attack of the oxygen lone pair on the activated cyclopropane, thus the



competition experiments' ratios support this mode of action. This piece of evidence disfavors a concerted mechanism (mechanism D) in which the primary orbital interaction would be between the HOMO of the cyclopropane and the LUMO of the aldehyde. This is not congruent with the sluggish reactivity of electron-poor aldehydes, which have lower LUMO energies and should therefore react faster if such a mechanism were operative. (Reprinted in part with permission from Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650. © 2008 American Chemical Society)

The origin of the *cis*-diastereoselectivity in these annulation reactions was analyzed in the context of mechanism A (**Scheme 1-9**) where the aldehyde serves as a nucleophilic dipolarophile. It was proposed that the more accessible *trans* lone pair on the carbonyl oxygen attacks the configurationally stable carbenium-carbanion **18** in the initial substitution reaction (**Scheme 1-10**). Experimental observations suggest that the rate of this

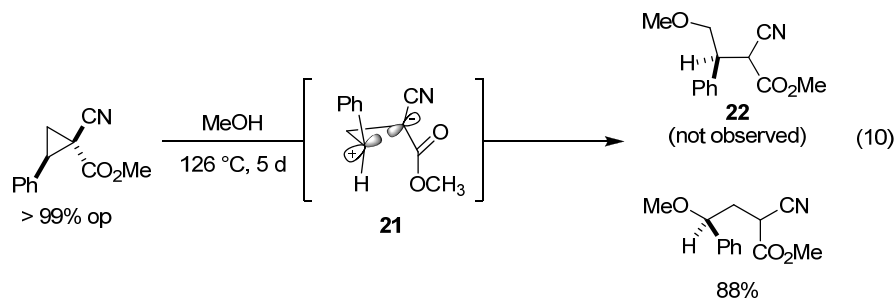
**Scheme 1-10.** Proposed Mechanism and Rational for the Observed 2,5-*cis* Diastereoselection



(*E*)-oxocarbenium (**19**) formation is directly related to the nucleophilicity of the aldehyde (eq 9). A  $120^\circ$  rotation about the  $\text{C2-C3}$   $\sigma$ -bond would place the zwitterion in an envelope conformation **20** where substituents from the cyclopropane and aldehyde occupy pseudo-equatorial positions. Quenching of the oxocarbenium ion by addition of the proximal tin enolate completes ring closure to tetrahydrofuran **16**. That **16** is formed with the labeled carbomethoxy group *cis* to the 2'- and 5'-substituents suggests that little rotation occurs about the  $\text{C1-C3}$   $\sigma$ -bond prior to ring closure. It is noted that scrambling of the ester groups would require a  $180^\circ$   $\text{C1-C3}$  bond rotation to be faster than the  $120^\circ$   $\text{C2-C3}$  bond rotation. Additionally, this  $180^\circ$  rotation would involve an eclipsing butane interaction between  $\text{C2}$  and one carboxyester group, while the  $120^\circ$  rotation would not suffer similar torsional strain. (Reprinted in part with permission from Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li,

W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650. © 2008 American Chemical Society)

An interesting aspect of this annulation is that aldehyde addition does not occur at the unsubstituted C3 cyclopropyl methylene carbon in any instances. This observation suggests that an  $S_N2$ -type mechanism is not operative.<sup>48</sup> Furthermore, experiments with enantioenriched cyclopropanes (**11**) clearly indicate that a naked carbocation is not formed at C2; stereochemical information is transferred to the products with high fidelity. These results are consistent with Cram's proposal that configurationally-stable intimate carbenium-carbanion formation (**21**) facilitates ring opening of a D–A cyclopropane via nucleophilic substitution (eq 10).<sup>14,40</sup> An  $S_N2$ -type mechanism would result in generation of **22**, which is not an observed product. Intimate ion pair formation provides a reasonable explanation for the regioselectivity of cyclopropane/aldehyde annulations.



### 1.3 Conclusion

The Johnson research group has successfully implemented aldehyde dipolarophiles in Lewis acid-catalyzed (3 + 2) annulation reactions with malonate-derived donor-acceptor cyclopropanes. This transformation provides a convergent method for the preparation of 2,5-*cis*-disubstituted tetrahydrofurans. Numerous Lewis acids were shown to achieve the desired annulation, with Sn(II) and Sn(IV) catalysts providing the most efficient transformation.

Simple carbon donor groups are capable of stabilizing the transient carbocation generated upon cyclopropyl C–C  $\sigma$ -bond cleavage, which allowed for substantial broadening of the range of accessible products. The aldehyde scope demonstrated that both electron-rich and -poor aryl, unsaturated, and alkyl aldehydes serve as competent dipolarophiles.

Mechanistic studies revealed that this annulation is interesting in that the initial bond-forming event involves an unusual nucleophilic attack by an aldehyde on a configurationally-stable intimate ion pair of the D–A cyclopropane. This mode of reactivity allowed for this reaction to proceed with high levels of stereoselectivity; use of an enantioenriched cyclopropane results in nearly complete transfer of stereochemical information, providing facile access to optically active tetrahydrofurans.

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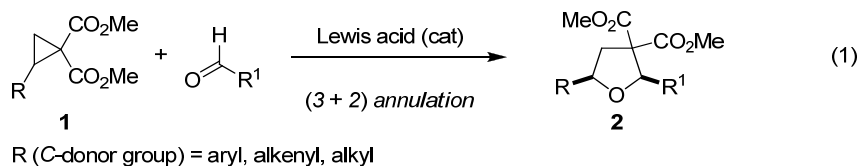
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## CHAPTER TWO

# PALLADIUM(0)-CATALYZED ANNULATION OF DIMETHYL 2-VINYLCYCLOPROPANE-1,1-DICARBOXYLATE AND ALDEHYDES: THE SYNTHESIS OF TETRAHYDROFURANS THROUGH AN ALDOL–ALLYLIC ETHERIFICATION SEQUENCE

## 2.1 Introduction and Background

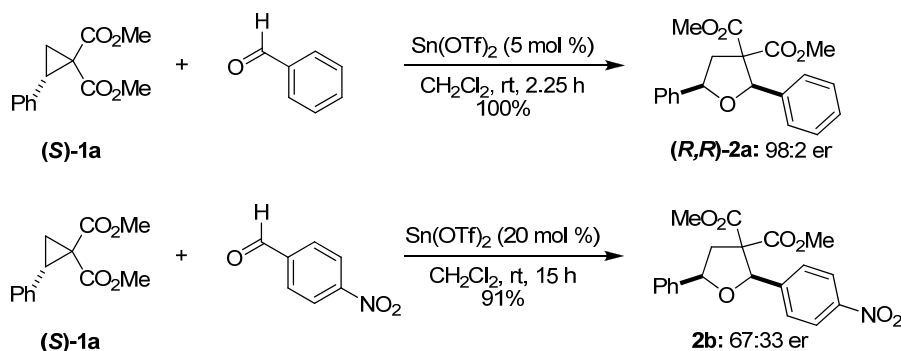
Dipolar cycloadditions (more generally, annulations) are versatile reaction that are useful for the convergent synthesis of hetero- and carbocyclic products.<sup>1</sup> The use of malonate-derived donor-acceptor (D–A) cyclopropane **1** as a three-carbon dipole equivalent in Lewis acid-catalyzed annulations with dipolarophiles is a well-studied process.<sup>2,3</sup> Recent research in this area has shown aldehydes to be competent dipolarophiles in these reactions, providing 2,5-*cis*-disubstituted tetrahydrofurans (THFs) **2** in high diastereoselectivity (eq 1).<sup>4-6</sup>



An interesting aspect of Lewis acid-catalyzed cyclopropane/aldehyde annulations is that use of an enantioenriched cyclopropane results in the transfer of stereochemical information to the tetrahydrofuran product. For example, exposure of enantiopure (*S*)-**1a** to

catalytic  $\text{Sn}(\text{OTf})_2$  in the presence of benzaldehyde produces THF **(R,R)-2a** with an enantiomeric ratio (er) of 98:2 (**Scheme 2-1**, top). In this transformation the dominant orbital overlap is between non-bonding aldehyde lone pair and LUMO of the cyclopropane.<sup>1</sup>

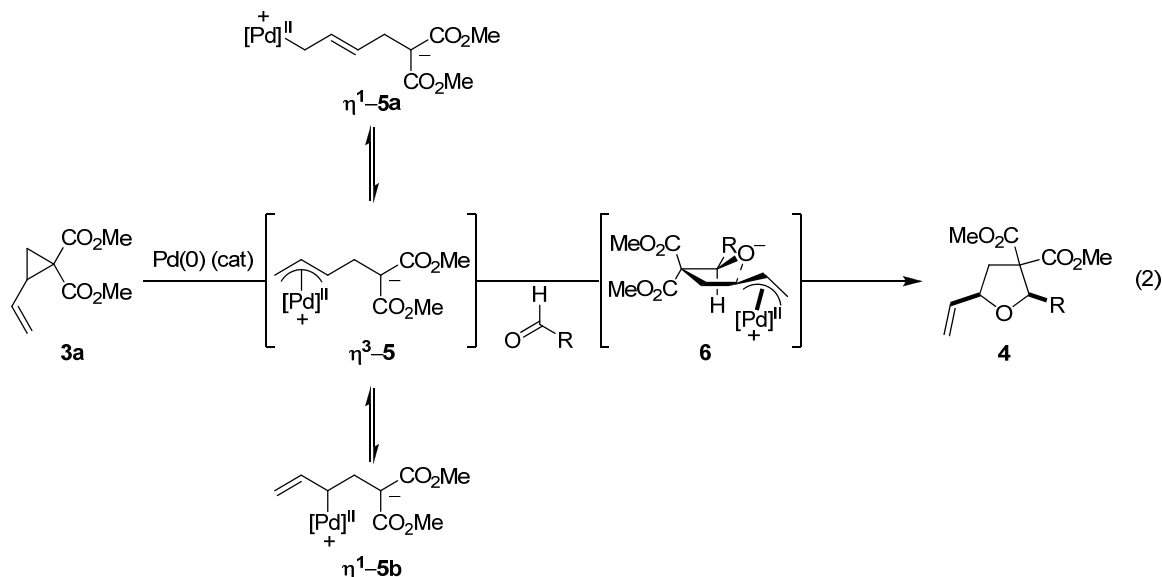
**Scheme 2-1.** Lewis Acid-Catalyzed (3 + 2) Annulation of **(S)-1a** and Aldehydes



A consequence of this mode of reactivity is that use of electron-deficient aldehydes results in low transfer of stereochemical information to the product. Thus, while annulation of **(S)-1a** with 4-nitrobenzaldehyde results in a high chemical yield of **2b**, most of the stereochemical information is lost due to competing cyclopropane racemization (**Scheme 2-1**, bottom).<sup>6</sup>

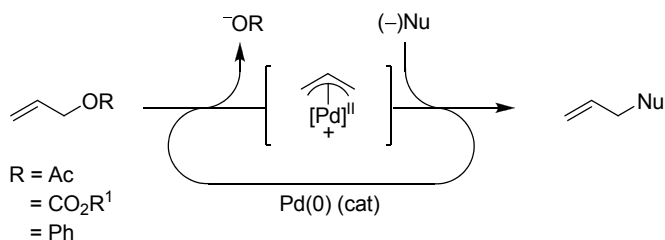
Lewis acid-catalyzed cyclopropane/aldehyde annulations do not proceed through achiral intermediates, limiting the opportunities for dynamic kinetic asymmetric catalysis. An alternative method to facilitate this reaction is through donor group activation of **3a** (see **Chapter One**) using  $\pi$ -allylpalladium chemistry. Development of this type of synthetic method would have the advantage of increasing the rate in which electron-deficient aldehydes undergo annulation with malonate-derived D–A cyclopropanes. Furthermore, the mechanistic aspects of this transformation create an opportunity for asymmetric catalysis; racemization of **3a** occurs via interconversion of  $\eta^3$ -**5** with its corresponding  $\eta^1$  complexes (**Scheme 2-2**). Since  $\eta^1$ — $\eta^3$  interconversion proceeds through achiral complex  $\eta^1$ -**5a**, use of a chiral ancillary ligand may allow for an enantioselective transformation to be achieved.

**Scheme 2-2.** Proposed Pd(0)-Catalyzed (3 + 2) Annulation of **3a** with Aldehydes



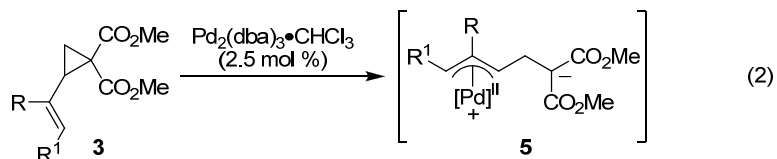
The use of  $\pi$ -allylpalladium complexes for the electrophilic allylation of nucleophiles is a well studied reaction manifold.<sup>7-10</sup> Most methods for generation of  $\pi$ -allylpalladium reaction intermediates typically involve oxidative addition of Pd(0) into allylic alcohol derivatives (**Scheme 2-3**). This transformation has proven to be a versatile tool for the allylation of nucleophiles in complex reaction systems.

**Scheme 2-3.** Generic Catalytic Cycle for Electrophilic Allylation Using  $\pi$ -Allylpalladium Methodology



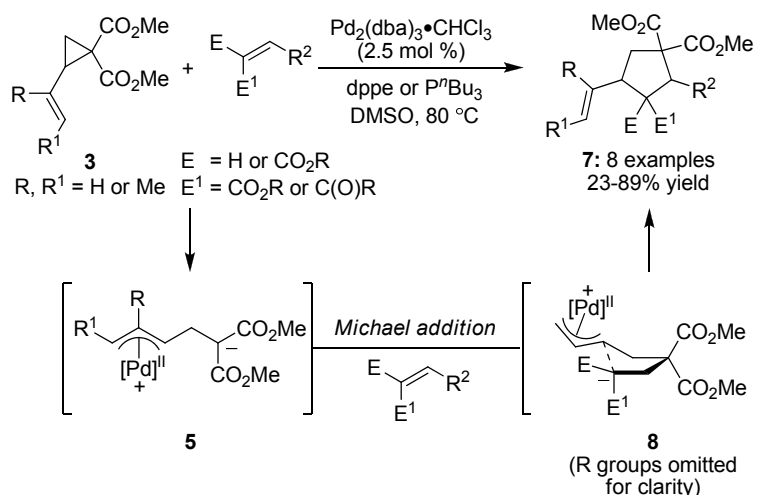
Traditional  $\pi$ -allylpalladium methodology produces a stoichiometric amount of waste by loss of the allylic leaving group. A strategy to circumvent the generation of this by-product and increase the molecular complexity of allylated products involves tethering of the

allylic leaving group. Tsuji recognized the potential for using cyclopropane **3** as a substrate for  $\pi$ -allylpalladium generation. This mode of reactivity is unique in that the oxidative addition results in loss of a *carbon* leaving group, which is made possible by the high strain energy of cyclopropanes. Access to the  $\pi$ -allylpalladium zwitterion **5** was achieved through ring-opening of **3** by catalytic  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (eq 2).<sup>11-13</sup>

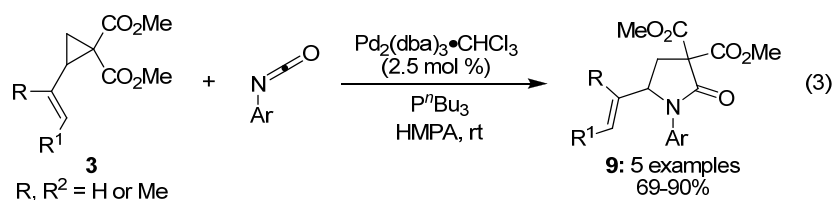


In initial investigations, Tsuji employed  $\pi$ -allylpalladium complexes **5** for use as dipoles in (3 + 2) annulations with electron-deficient olefin dipolarophiles (**Scheme 2-3**). These reactions resulted in the formation of polysubstituted cyclopentanes **7** in high chemical yields (diastereoselectivity was not disclosed).<sup>11</sup> The mechanism of this transformation involves oxidative addition of the Pd(0) catalyst with cyclopropane **3**. Michael addition into an electron-deficient olefin generates zwitterion **8** and subsequent ring closure furnishes cyclopentane **7** and regenerates the Pd(0) catalyst.

**Scheme 2-4.** (3 + 2) Annulation of Cyclopropane **3** via Pd(0)-Catalyzed Michael Addition/Allylic Alkylation Sequence



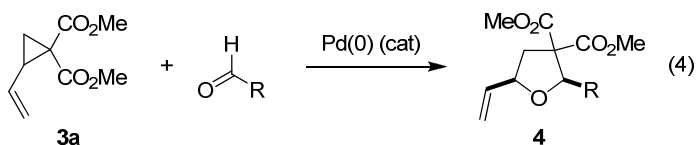
Additional experimentation in the Tsuji lab revealed that Pd(0)-catalyzed annulation of **3** could be extended to aryl isocyanate dipolarophiles, providing access to  $\delta$ -lactams **9**. Use of alkyl isocyanates failed to react under these conditions. The authors note that use of the electron-rich  $P^tBu_3$  ligand was required for the reaction to occur with sufficient efficiency. Similarly, a solvent screen indicated that a polar aprotic solvent was necessary for successful annulation to occur, presumably to facilitate oxidative addition of Pd(0) with **3**.<sup>12</sup>



Tsuji's demonstrations that vinylcyclopropanes **3** participate in annulation reactions through  $\pi$ -allylpalladium complexes **5** provide a basis on which to expand this method to other dipolarophiles. Use of aldehydes in (3 + 2) annulations with  $\pi$ -allylpalladium complex **5** to provide tetrahydrofurans **4** (eq 2) would complement the established Lewis acid-catalyzed route to tetrahydrofurans from malonate-derived D–A cyclopropanes.<sup>6</sup> This Pd(0)-catalyzed methodology would demonstrate high reactivity towards electron-poor aldehydes, which normally display poor reactivity in Lewis acid-catalyzed systems. This complementary reactivity is a result of a shift in the dominant orbital overlap to occur between the HOMO<sub>dipole</sub>—LUMO<sub>dipolarophile</sub>, which is a result of activation the donor group of **3** (see **Chapter One**). Additionally, similar annulations are proposed to proceed through achiral intermediates, suggesting that a dynamic kinetic asymmetric transformation may be achievable by implementing chiral ancillary ligands.

## 2.2 Pd(0)-Catalyzed Tetrahydrofuran Synthesis: Results and Discussion

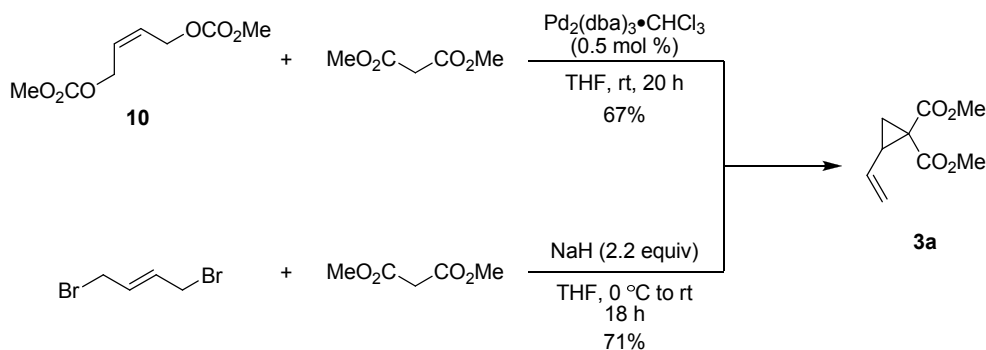
This study examined the use of electrophilic aldehyde dipolarophiles in Pd(0)-catalyzed (3 + 2) annulation reactions with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, eq 4).



### 2.2.1 Substrate Synthesis and Reaction Development

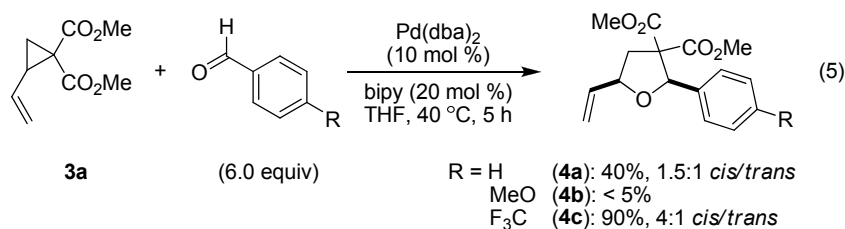
Several methods are available for the preparation of **3a**. Tsuji achieved this transformation using a one-step inter/intramolecular Pd(0)-catalyzed double allylation of dimethyl malonate with dicarbonate **10** (Scheme 2-5, top). Alternatively, vinylcyclopropane **3a** is accessible in one step through a double alkylation of dimethylmalonate with commercially available 1,4-dibromo-2-butene (Scheme 2-5, bottom).<sup>14,15</sup>

**Scheme 2-5.** Methods for the Preparation of Vinylcyclopropane **3a**



Tsuji's success using dibenzylidene acetone (dba)-ligated Pd(0) to achieve ring opening of **3a** provides an appropriate starting point for early investigations. Thus, initial efforts toward achieving annulation of **3a** with benzaldehyde commenced using  $\text{Pd}(\text{dba})_2$ . A focused screen of ancillary ligands revealed that use of 2,2'-dipyridyl (bipy) provided

tetrahydrofuran **4a** in 40% yield and low *cis/trans* diastereoselectivity (eq 5). Attempts to catalyze this transformation using Ni(0), Mo(0), W(0), and Ir(I) failed to produce more than trace quantities of tetrahydrofuran **4a**.

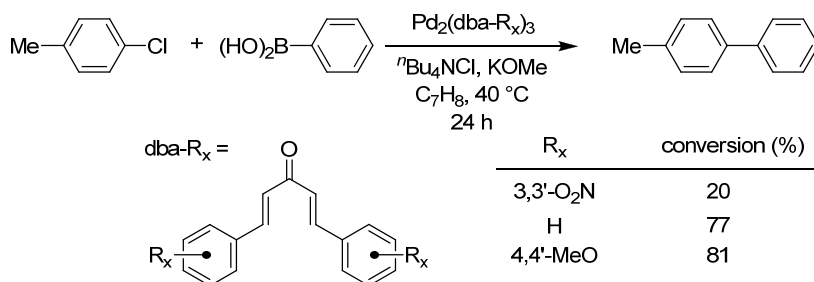


With promising preliminary reaction conditions identified, several electronically diverse aldehydes were evaluated. In comparing the performance of 4-methoxybenzaldehyde and 4-trifluoromethylbenzaldehyde in annulation with **3a**, it was evident that electron-deficient aldehydes were optimal dipolarophiles for this transformation (eq 5). The reaction of electron-rich 4-methoxybenzaldehyde furnished only trace amounts of tetrahydrofuran **4b** and significant cyclopropane oligomerization occurred. Conversely, 4-trifluoromethylbenzaldehyde underwent smooth annulation to tetrahydrofuran **4c**. These results are consistent with observations previously disclosed by Tsuji (*vide supra*).

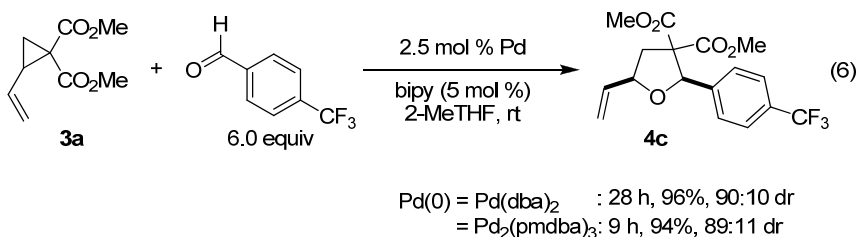
Due to the need for electron-deficient aldehydes using the Pd(dba)<sub>2</sub>/bipy catalyst system, more extensive catalyst development was pursued in hopes of broadening the scope of this transformation. Recent studies conducted in the Fairlamb laboratory examined the activity of Pd(0) catalysts supported by substituted dba ligands in Suzuki–Miyaura cross coupling reactions (**Scheme 2-6**).<sup>16</sup> It was demonstrated that Pd(0) catalysts bearing electron-rich dba ligands show a marked increase in reactivity. They propose that this is a consequence of decreased Pd  $\pi$ -backbonding, which results in an increased lability of the dba and readily provides catalytically-active Pd(0).



**Scheme 2-6.** dba-R<sub>x</sub> Ligand Effects on Pd(0)-Catalyzed Suzuki–Miyaura Cross Coupling Reactions

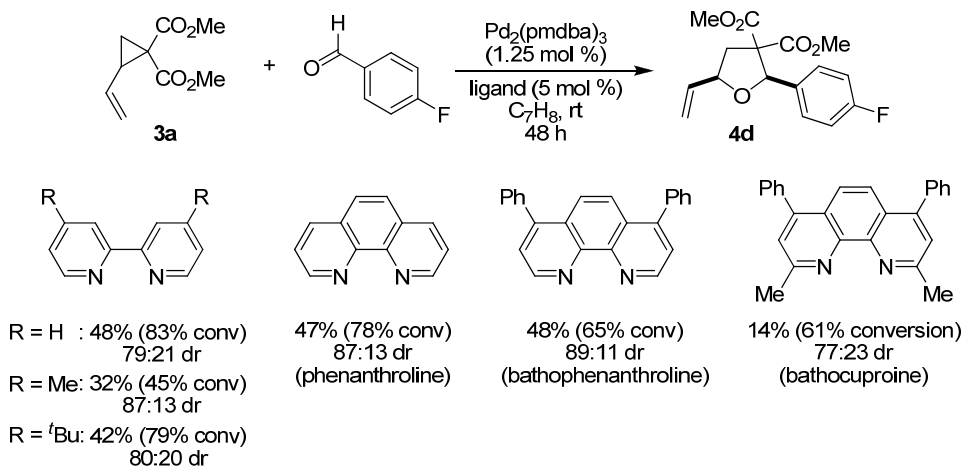


Next, a comparison of  $\text{Pd}_2(\text{pmdba})_3$  ( $\text{pmdba}$  = 4,4'-dimethoxydibenzylideneacetone)<sup>17</sup> to  $\text{Pd}(\text{dba})_2$  as catalysts for the annulation of **3a** with 4-trifluoromethylbenzaldehyde was conducted (eq 6). While both catalysts furnished tetrahydrofuran **4c** in excellent yield and good diastereoselectivity, the reaction was sluggish when  $\text{Pd}(\text{dba})_2$  was used. In contrast to the 28 h required for  $\text{Pd}(\text{dba})_2$ ,  $\text{Pd}_2(\text{pmdba})_3$  proved to be much more active, requiring only 9 h to reach completion.



While excellent results were obtained using 4-trifluoromethylbenzaldehyde as a dipolarophile, use of this aldehyde as a model for reaction development was discontinued to focus on improving more problematic aldehydes. In particular, we found annulation of 4-fluorobenzaldehyde to proceed poorly under the conditions shown in eq 6. Further reaction optimization was attempted by altering the exogenous ligand added to the reaction mixture. Preliminary studies revealed that *N,N'*-bidentate ligands provided the highest yields and diastereoselectivities. Thus, annulation of 4-fluorobenzaldehyde and **3a** was examined using 1.25 mol %  $\text{Pd}_2(\text{pmdba})_3$  and various dipyridyl and phenanthryl ligands (**Scheme 2-7**).

**Scheme 2-7.** Evaluation of Bipyridyl and Phenanthryl Ligands

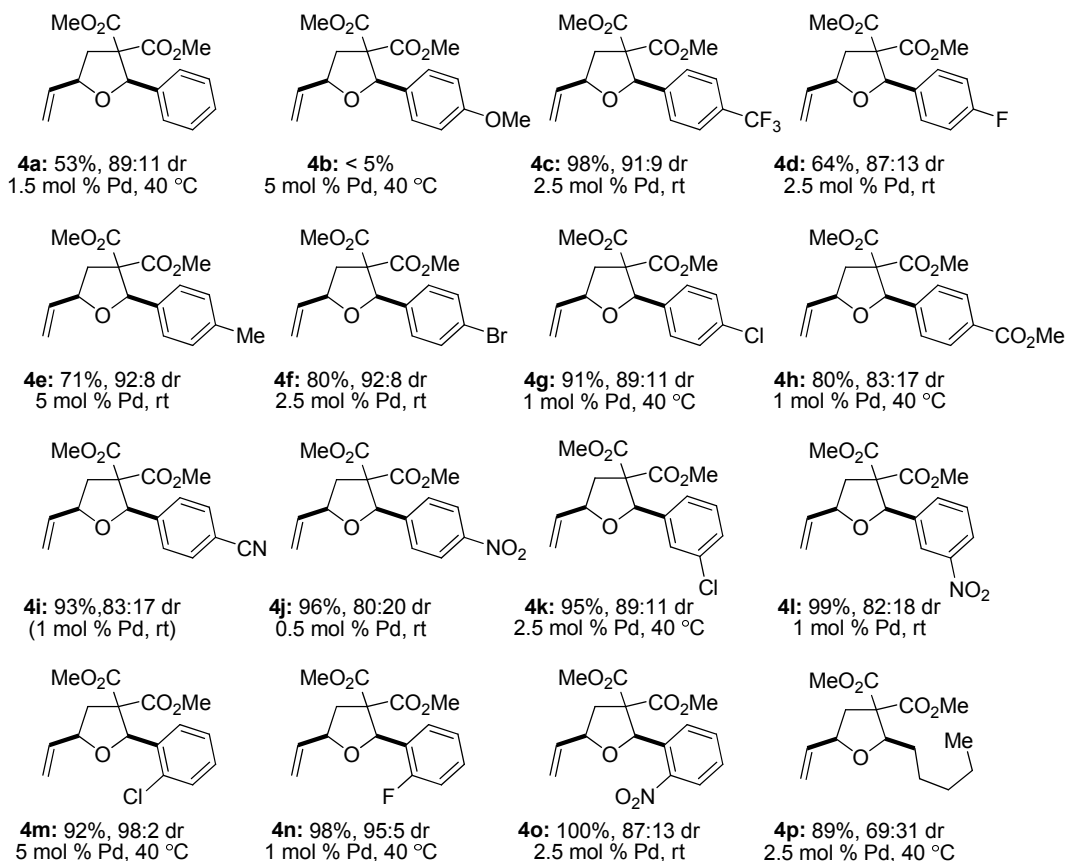


Although the efficiency of this transformation remained lower than the annulation with 4-trifluoromethylbenzaldehyde, we discovered that bathophenanthroline (bphen) provides a marked increase in efficacy over bipy.

With both the diastereoselectivity and the product/oligomer ratio maximized using the bathophenanthroline/ $\text{Pd}_2(\text{pmdba})_3$ -derived complex, we examined a variety of electronically diverse aromatic aldehydes with this catalyst system (**Figure 2-1**). As expected, this methodology works best for electron-poor aldehydes, providing high yields and short reaction times. Electron-rich aldehydes are problematic, with only trace product obtained with 4-methoxybenzaldehyde despite complete consumption of cyclopropane. *n*-Hexanal was a competent dipolarophile, providing the desired THF product in high yield, although the diastereoselection was poor. Aliphatic aldehydes containing  $\alpha$ -branching were unreactive. While reaction rates can often be increased by boosting the catalyst loading, nonproductive oligomerization increases as well. Catalyst loading and reaction temperature were variables found to be in a delicate balance that required some fine-tuning for each substrate; therefore, the reaction conditions in **Figure 2-1** vary slightly as the aldehyde partner changes.

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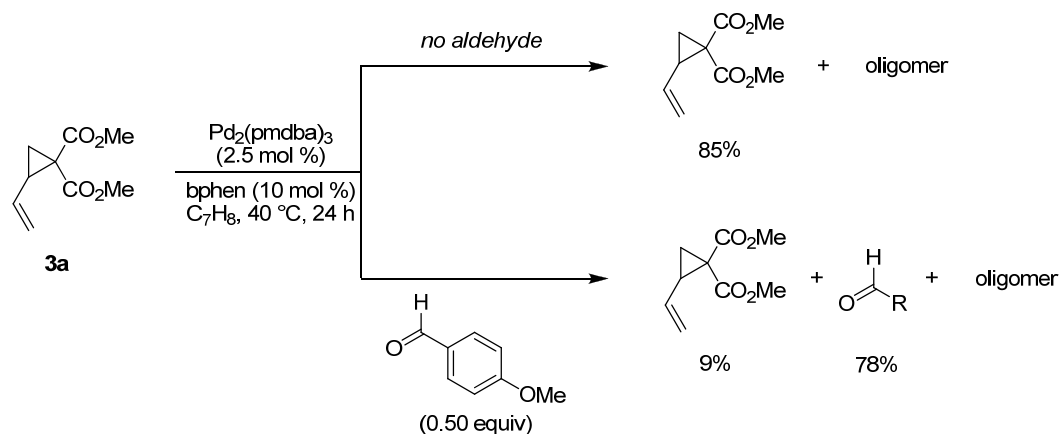
**Figure 2-1.** Aldehyde Scope in the Pd(0)-Catalyzed (3 + 2) Annulation of **3a**



To probe the nature of cyclopropane oligomerization, **3a** was subjected to the reaction conditions in the absence of aldehyde (**Scheme 2-8**). It is interesting that in this experiment, only 15% conversion of the cyclopropane to oligomer occurs. To examine the effect of the aldehyde on oligomerization, we conducted the reaction using 0.50 equivalents of 4-methoxybenzaldehyde (relative to **3a**). Analysis by <sup>1</sup>H NMR spectroscopy revealed 91% of **3a** and 22% of the aldehyde were consumed. The reaction was accompanied by significant oligomer formation, suggesting that 4-methoxybenzaldehyde plays some role in co-promoting the oligomerization. (Reprinted in part with permission from Parsons, A. T.;

Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541-2544. © 2008 American Chemical Society)

**Scheme 2-8.** Examination of the Aldehyde Role in Cyclopropane Oligomerization



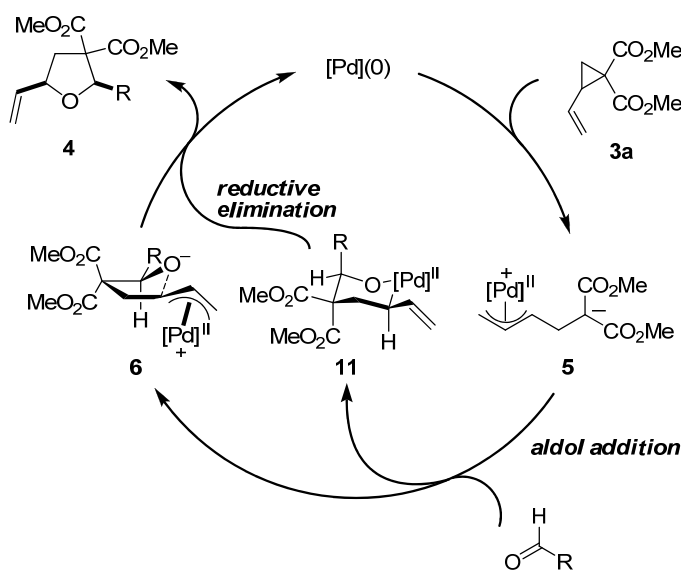
### 2.2.2 Mechanistic Analysis

Data from the aldehyde screen provided mechanistic insight into this reaction. Electron-poor aldehydes react at a much faster rate and allow for a lower catalyst loading. This is a result of the low energy LUMO of electron-deficient aldehydes, providing a smaller energy gap between the high energy HOMO of **3a**. This data supports Tsuji's hypothesis that Pd(0)-catalyzed (3 + 2) annulations of **3a** proceed via nucleophilic attack on electron-deficient dipolarophiles by  $\pi$ -allylpalladium complex **5**. Similarly, attack by **5** on an aldehyde produces zwitterionic alkoxide **6**. Ring closure and dissociation of the Pd(0) catalyst yields the tetrahydrofuran product **4**. Alternatively, generation of neutral palladacycle **11** followed by reductive elimination is also a viable pathway since "hard" alkoxide<sup>18</sup> nucleophiles<sup>19</sup> are known add directly to the cationic metal center.<sup>9</sup>

The diastereoselectivity of Pd(0)-catalyzed annulations of **3a** and aldehydes is believed to arise from organization into an envelope-like transition state **6**, orienting the  $\pi$ -allylpalladium complex and aldehyde substituent in pseudo-equatorial arrangements.

Proceeding through the neutral palladacyclic chair **11**, the vinyl group would prefer to adopt a pseudo-equatorial position to avoid A<sup>1,3</sup> strain with the carbomethoxy group. In this case, the observed *cis* diastereoselectivity would require the aldehyde substituent to occupy a pseudo-axial position. The reason for the substrate-dependent variability in the diastereomeric ratio is unclear since no apparent trend exists.

**Scheme 2-9.** Proposed Catalytic Cycle for the Pd(0)-Catalyzed Annulation of **3a** and Aldehydes

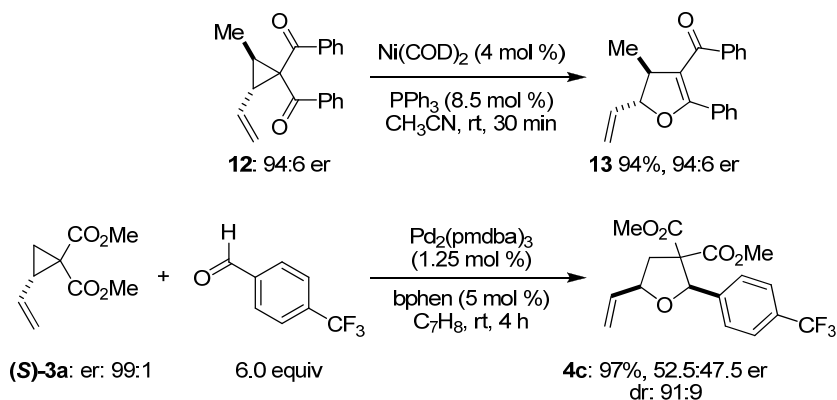


### 2.2.3 Stereochemical Analysis

Next, we were interested in examining the stereochemical outcome of the Pd(0)-catalyzed (3 + 2) annulation when enantioenriched (**S**)-**3a** (er: 99:1)<sup>6</sup> was used. Previously, our group reported that the Ni(0)-catalyzed rearrangement of enantioenriched cyclopropane **12** to dihydrofuran **13** proceeded without loss of stereochemical information (**Scheme 2-10**, top).<sup>14</sup> Conversely, under the standard annulation conditions (**Scheme 2-10**, bottom), we observed nearly complete degradation of enantioenrichment in the product (er: 52.5:47.5).

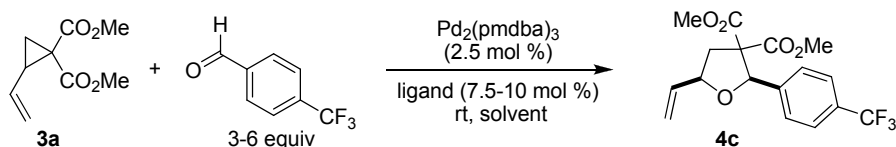
This result suggests the mechanism involves intermediacy of an achiral intermediate and/or racemization of the starting material.

**Scheme 2-10.** Rearrangement and Annulation of Enantioenriched Vinylcyclopropanes Using Ni(0) or Pd(0) Catalysis



Data indicating the formation of an achiral reaction intermediate/or fast racemization of **3a** prior to annulation led us to investigate the use of chiral ancillary ligands on the Pd(0) catalyst to achieve an asymmetric annulation. Several chiral *P,P*-, *P,N*-, and *N,N'*-bidentate ligands were examined (selected examples: **Table 2-1**). While many Pd(0)/ligand complexes maintained high catalytic activity, none provided acceptable levels of enantioselectivity. Furthermore, unusually low diastereoselectivities were obtained in all cases. A possible explanation for the difficulties in rendering this process stereoselective is that the distant chiral metal complex may be unable to instill a high degree of asymmetry in the initial bond-forming step (**Scheme 2-9**). Then if the ring closure is non-selective, a mixture of the *cis* and *trans* products will be observed in a level of enantioenrichment determined by the selectivity in the aldol reaction. If ring closure is selective, one would expect products to be formed with high enantioselectivity as a ratio of diastereomers determined by the degree of selectivity in the initial aldol addition. The results reported in **Table 2-1** suggest that little or no selectivity is achieved in either bond-forming event.

**Table 2-1.** Selected Chiral Ligands Examined for the Asymmetric Pd(0)-Catalyzed Annulation of **3a** and 4-Trifluoromethylbenzaldehyde



| entry | ligand | time<br>(h)            | solvent                         | conversion<br>(%)               | dr <sup>a</sup> | er <sup>b</sup> |           |
|-------|--------|------------------------|---------------------------------|---------------------------------|-----------------|-----------------|-----------|
| 1     |        | 22                     | C <sub>7</sub> H <sub>8</sub>   | 100                             | 62:38           | 50:50           |           |
| 2     |        | 21                     | 2-MeTHF                         | 50                              | 45:55           | nd <sup>c</sup> |           |
| 3     |        | 25                     | CH <sub>2</sub> Cl <sub>2</sub> | 100                             | 62:38           | 53:47           |           |
| 4     |        | Ar = Ph                | 29                              | CH <sub>2</sub> Cl <sub>2</sub> | 85 <sup>d</sup> | 52:48           | 72:28     |
| 5     |        | Ar = DTBM <sup>e</sup> | 48                              | CH <sub>2</sub> Cl <sub>2</sub> | 100             | 55:45           | 64:36     |
| 7     |        | R = <sup>i</sup> Pr    | 22                              | C <sub>7</sub> H <sub>8</sub>   | 100             | 67:33           | 64.5:35.5 |
| 8     |        | R = <sup>t</sup> Bu    | 14                              | C <sub>7</sub> H <sub>8</sub>   | 85 <sup>d</sup> | 77:23           | 50:50     |
| 9     |        | R = Ph                 | 13                              | C <sub>7</sub> H <sub>8</sub>   | 87 <sup>d</sup> | 68:32           | 55:45     |
| 10    |        | R = <sup>i</sup> Pr    | 5                               | CH <sub>2</sub> Cl <sub>2</sub> | 100             | 64:36           | 60.5:39.5 |
| 11    |        | R = <sup>t</sup> Bu    | 72                              | CH <sub>2</sub> Cl <sub>2</sub> | 80 <sup>d</sup> | 60:40           | 71.5:28.5 |

a) Determined by <sup>1</sup>H NMR spectroscopy of the unpurified product. b) Determined for the *cis* isomer by chiral SFC analysis after reduction of the esters to alcohols. c) nd = not determined. d) Isolated yield. e) DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl.

## 2.3 Conclusion

In summary, an efficient and diastereoselective method to synthesize racemic tetrahydrofuran derivatives via Pd(0)-catalyzed (3 + 2) annulation of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate and aldehydes has been developed. This reaction

works well for electron-poor aldehydes, which is complementary to the Lewis acid-catalyzed annulations developed in our lab. Studies using an enantioenriched cyclopropane suggest that the reaction proceeds through an achiral intermediate or racemization occurs more rapidly than annulation. Attempts to develop an asymmetric methodology using chiral Pd(0) complexes were unsuccessful.

## 2.4 Experimental

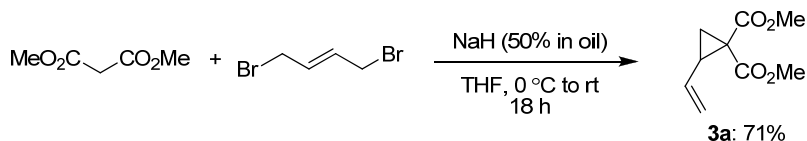
**Methods.** Infrared (IR) spectra were obtained using an ASI ReactIR 1000. Proton and carbon magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker model DRX 500 or a Bruker model DRX 400 ( $^1\text{H}$  NMR at 500 MHz and  $^{13}\text{C}$  NMR at 100 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, t = triplet, br t = broad triplet, td = triplet of doublet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Combustion analyses were performed by Atlantic Microlab Inc. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and ethanolic *p*-anisaldehyde solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless



otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials.** Toluene was dried by passage through a column of neutral alumina under nitrogen prior to use. 2-Methyltetrahydrofuran (2-MeTHF) and tetrahydrofuran (THF) were distilled from a sodium/benzophenone ketyl under N<sub>2</sub> prior to use. Dimethylformamide (DMF) was distilled from phosphorous pentoxide under reduced pressure prior to use. Benzaldehyde, 4-fluorobenzaldehyde, and 4-methylbenzaldehyde were purified by the following procedure: the neat aldehydes were washed sequentially with a 1 M sodium hydroxide solution and a saturated aqueous sodium bicarbonate solution, dried with magnesium sulfate, and distilled under reduced pressure. 4-Chlorobenzaldehyde was sublimed under reduced pressure. 4-Trifluoromethylbenzaldehyde was purchased from Oakwood Products, Inc. and used without further purification. Pd<sub>2</sub>(pmdba)<sub>3</sub> was prepared according to the method of Fu.<sup>17</sup> All other reagents were obtained from Acros or Sigma-Aldrich and used without further purification unless otherwise noted.

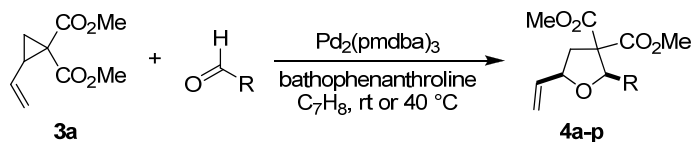
**Preparation of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (3a):**



A flame-dried two-neck 250 mL round-bottomed flask was charged with NaH (50% in oil, 4.0 g, 83.6 mmol, 2.2 equiv) and THF (85 mL). The suspension was cooled to 0 °C and dimethyl malonate (5.0 g, 38.0 mmol, 1.0 equiv) was added dropwise via syringe (Caution: gas evolution). The suspension was allowed to warm to room temperature stirred for 45 min

and 1,4-dibromo-2-butene (8.1 g, 38.0 mmol, 1.0 equiv) was added in one portion. The reaction was allowed to stir under N<sub>2</sub> for 18 h. The reaction was partitioned between Et<sub>2</sub>O (100 mL) and H<sub>2</sub>O (100 mL). The aqueous layer was extracted with Et<sub>2</sub>O (2 x 100 mL). The combined organic layers were washed with H<sub>2</sub>O (100 mL), brine (100 mL), dried over magnesium sulfate, and concentrated by rotary evaporation to afford a light brown oil. The crude product was purified by column chromatography (20% Et<sub>2</sub>O/hexanes) and was distilled (0.05 torr, 60 °C) to give pure **3a** as a clear, colorless oil (4.95 g, 27.1 mmol, 71% yield). The <sup>1</sup>H NMR spectrum matched the reported data.<sup>20</sup>

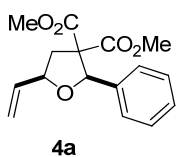
**General Procedure A for the palladium(0)-catalyzed annulation of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**) and aldehydes:**



In a glove box, a flame-dried vial (vial #1) equipped with a magnetic stir bar was charged with Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.5-5.0% Pd), bathophenanthroline, and anhydrous toluene (90 μL). The vial was sealed with a rubber septum and then stirred for 30 minutes to allow for ligand coordination. A second flame-dried vial (vial #2) was charged with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol, 1.0 equiv) and anhydrous toluene (210 μL). Liquid aldehydes (6.0 equiv) were also added to vial #2 followed by sealing with a rubber septum. Both vials were removed from the glove box and placed under N<sub>2</sub>. Solid aldehydes (3.0 or 6.0 equiv) were added to the vial #1, containing Pd and ligand, followed by purging the vial for several minutes with a stream of dry N<sub>2</sub>. The contents of vial #2 were cannulated to the first vial quickly. The reaction was stirred at the indicated

temperature (room temperature or 40 °C) under an atmosphere of dry N<sub>2</sub> for the indicated time period. The reaction mixture was worked up by eluting through a 1" Monstr-Pette silica plug with ~15 mL dichloromethane. Diastereomeric ratios were determined <sup>1</sup>H NMR spectrometric analysis of the unpurified products. Analytically pure products were obtained by purification using flash chromatography, eluting with the indicated solvent system.

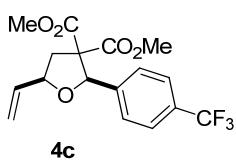
**Dimethyl 2-phenyl-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4a**):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), benzaldehyde (0.207 g, 1.95 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0027 g, 0.0025 mmol), and bathophenanthroline (0.0033 g, 0.0099 mmol). After 25 h at 40 °C and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 89:11. Flash chromatography (10% ethyl acetate/hexanes) provided pure **4a** (0.050 g, 0.17 mmol, 53% yield) as a clear, colorless oil. Analytical data for **4a**: **IR** (thin film, cm<sup>-1</sup>) 3081, 2998, 2952, 2883, 2844, 1739, 1594, 1488, 1434, 1409, 1335, 1272, 1229, 1206, 1179, 1158, 1136, 1102, 1084, 1071, 1059, 1011, 990, 936, 917, 841, 801, 733; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.44 – 7.37 (m, 2H), 7.32 – 7.22 (m, 3H), 6.10 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.68 (s, 1H), 5.41 (dt, *J* = 17.2, 1.0 Hz, 1H), 5.28 (dt, *J* = 10.6, 0.9 Hz, 1H), 4.41 (ddd, *J* = 10.4, 6.7, 6.1 Hz, 1H), 3.81 (s, 3H), 3.11 (s, 3H), 2.78 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.50 (dd, *J* = 13.4, 6.0 Hz, 1H); minor diastereomer: δ 7.44 – 7.37 (m, 2H), 7.32 – 7.22 (m, 3H), 5.91 (ddd, *J* = 17.0, 10.3, 6.0 Hz, 1H), 5.79 (s, 1H), 5.35 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.18 (dt, *J* = 10.4, 1.1 Hz, 1H), 5.11 – 5.04 (m, 1H), 3.77 (s, 3H), 3.17 (s, 3H), 3.02 (dd, *J* = 13.1, 7.0 Hz, 1H), 2.20 (dd, *J* = 13.1, 7.2 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer:

$\delta$  171.1, 168.9, 137.7, 136.4, 128.0, 127.7, 126.9, 117.5, 84.2, 79.2, 66.1, 52.9, 52.1, 40.3; minor diastereomer:  $\delta$  170.3, 169.0, 138.2, 138.1, 127.9, 127.8, 126.4, 116.0, 83.4, 79.9, 66.1, 52.7, 52.1, 40.5; **TLC** (15% Et<sub>2</sub>O/hexanes) *R<sub>f</sub>* 0.26; **Anal.** Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub>: C, 66.19; H, 6.25. Found: C, 66.46; H, 6.39.

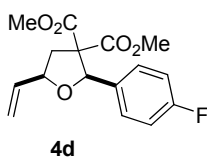
**Dimethyl 2-(4-(trifluoromethyl)phenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (4c):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-trifluoromethylbenzaldehyde (0.340 g, 1.95 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 4 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 90:10. Flash chromatography (15% diethyl ether/hexanes) provided pure **4c** (0.114 g, 0.32 mmol, 98% yield) as a clear, colorless oil. Analytical data for **4c**: **IR** (thin film, cm<sup>-1</sup>) 2998, 2956, 1737, 1436, 1328, 1273, 1231, 1210, 1165, 1125, 1086, 1067, 1019, 936, 919, 855, 735; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  7.58 – 7.54 (m, 4H), 6.09 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.69 (s, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.44 (ddd, *J* = 10.0, 6.6, 6.4 Hz, 1H) 3.81 (s, 3H), 3.11 (s, 3H), 2.75 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.53 (dd, *J* = 13.4, 6.3 Hz, 1H); minor diastereomer:  $\delta$  7.58 – 7.54 (m, 4H), 5.91 (ddd, *J* = 17.0, 10.4, 6.2 Hz, 1H), 5.80 (s, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.11 – 5.06 (m, 1H), 3.77 (s, 3H), 3.16 (s, 3H), 3.01 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.20 (dd, *J* = 13.1, 10.3 Hz); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  170.8, 168.6, 141.8, 136.1, 129.1 (q, *J* = 32.1 Hz), 127.3, 124.6, 124.6, 117.8, 83.4, 79.4, 66.0, 52.9, 52.1, 40.2; minor diastereomer:  $\delta$  170.0, 168.7, 142.4, 137.7, 126.9, 125.3, 122.6,

116.3, 82.6, 80.1, 66.1, 52.8, 52.0, 40.5; **TLC** (15% Et<sub>2</sub>O/hexanes) *R<sub>f</sub>* 0.23; **Anal.** Calcd. for C<sub>17</sub>H<sub>17</sub>F<sub>3</sub>O<sub>5</sub>: C, 56.98; H, 4.78. Found: C, 57.05; H, 4.87.

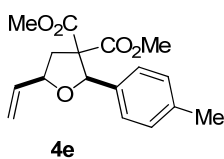
**Dimethyl 2-(4-fluorophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4d**):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-fluorobenzaldehyde (0.242 g, 1.95 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol) in anhydrous 2-methyltetrahydrofuran as solvent. After 72 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 82:14. Flash chromatography (10% ethyl acetate/hexanes) provided pure **4d** (0.072 g, 0.23 mmol, 72% yield) as a clear, colorless oil. Analytical data for **4d**: **IR** (thin film, cm<sup>-1</sup>) 3080, 3006, 2954, 2889, 2846, 1733, 1607, 1511, 1436, 1335, 1273, 1223, 1208, 1158, 1111, 1100, 1084, 1052, 1015, 936, 919, 847, 807; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.39 (d, *J* = 8.5, 5.5 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 6.08 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.64 (s, 1H), 5.40 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.27 (dt, *J* = 10.4, 0.8 Hz, 1H), 4.40 (ddd, *J* = 10.2, 6.7, 6.3 Hz, 1H), 3.80 (s, 3H), 3.16 (s, 3H), 2.74 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.50 (dd, *J* = 13.4, 6.2 Hz, 1H); minor diastereomer: δ 7.45 – 7.37 (m, 2H), 7.01 – 6.95 (m, 2H), 5.90 (ddd, *J* = 16.7, 10.4, 6.2 Hz, 1H), 5.73 (s, 1H), 5.33 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.18 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.09 – 5.02 (m, 1H), 3.76 (s, 3H), 3.21 (s, 3H), 3.00 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.18 (dd, *J* = 13.2, 7.3 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 171.0, 168.9, 162.5 (d, *J* = 244.9 Hz), 136.3, 133.4, 128.7 (d, *J* = 8.1 Hz), 117.7, 114.6 (d, *J* = 21.3 Hz), 83.5, 79.2, 66.0, 52.9, 52.2, 40.3; minor diastereomer: δ 170.2, 169.0, 138.0, 133.7, 128.2 (d,

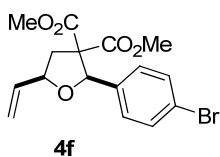
$J = 8.1$  Hz), 116.1, 82.8, 79.8, 66.0, 52.7, 52.2, 40.5; **TLC** (15% Et<sub>2</sub>O/hexanes)  $R_f$  0.26; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>FO<sub>5</sub>: C, 62.33; H, 5.56. Found: C, 62.14; H, 5.60.

**Dimethyl 2-*p*-tolyl-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4e**):**



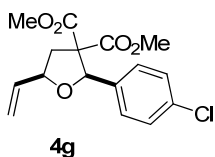
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-methylbenzaldehyde (0.235 g, 1.95 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0090 g, 0.0082 mmol), and bathophenanthroline (0.0110 g, 0.0326 mmol). After 96 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 93:7. Flash chromatography (10% ethyl acetate/hexanes) provided pure **4e** (0.070 g, 0.23 mmol, 71% yield) as a clear, colorless oil. Analytical data for **4e**: **IR** (thin film, cm<sup>-1</sup>) 3014, 2998, 2952, 2871, 1733, 1517, 1436, 1368, 1337, 1272, 1231, 1206, 1181, 1156, 1136, 1106, 1086, 1054, 1021, 992, 936, 919, 836, 799; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  7.27 (d,  $J = 7.8$  Hz, 2H), 7.09 (d,  $J = 7.8$  Hz, 2H), 6.09 (ddd,  $J = 17.1$ , 10.3, 6.8 Hz, 1H), 5.65 (s, 1H), 5.40 (d,  $J = 17.2$  Hz, 1H), 5.26 (d,  $J = 10.4$  Hz, 1H), 4.39 (ddd,  $J = 11.3$ , 6.6, 5.9 Hz, 1H), 3.75 (s, 3H), 3.21 (s, 3H), 2.75 (dd,  $J = 13.3$ , 10.5 Hz, 1H), 2.49 (dd,  $J = 13.3$ , 6.0 Hz, 1H), 2.30 (s, 3H); minor diastereomer:  $\delta$  7.31 – 7.24 (m, 2H), 7.12 – 7.07 (m, 1H), 5.90 (ddd,  $J = 17.0$ , 10.3, 6.1 Hz, 1H), 5.74 (s, 1H), 5.33 (d,  $J = 17.1$  Hz, 1H), 5.16 (d,  $J = 10.4$  Hz, 1H), 5.09 – 5.02 (m, 1H), 3.75 (s, 3H), 3.21 (s, 3H), 3.01 (dd,  $J = 13.1$ , 7.0 Hz, 1H), 2.30 (s, 3H), 2.19 (dd,  $J = 13.2$ , 7.0 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  171.2, 169.0, 137.7, 136.5, 134.7, 128.4, 126.8, 117.5, 84.1, 79.1, 66.1, 52.9, 52.1, 40.2, 21.1; **TLC** (10% EtOAc/hexanes)  $R_f$  0.13; **Anal.** Calcd. for C<sub>17</sub>H<sub>20</sub>O<sub>5</sub>: C, 67.09; H, 6.62. Found: C, 67.47; H, 6.70.

**Dimethyl 2-(4-bromophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4f**):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-bromobenzaldehyde (0.181 g, 0.98 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 24 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 93:7. Flash chromatography (10% ethyl acetate/hexanes) provided pure **4f** (0.100 g, 0.27 mmol, 83% yield) as a clear, colorless oil. Analytical data for **4f**: **IR** (thin film, cm<sup>-1</sup>) 3081, 2998, 2952, 2883, 2844, 1739, 1594, 1488, 1434, 1409, 1335, 1272, 1229, 1206, 1179, 1158, 1136, 1102, 1084, 1071, 1059, 1011, 990, 936, 917, 841, 801, 733; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.42 (d, *J* = 8.4, 2H), 7.33 – 7.24 (m, 2H), 6.07 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.60 (s, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.40 (ddd, *J* = 10.1, 6.6, 6.5 Hz, 1H), 3.79 (s, 3H), 3.17 (s, 3H), 2.72 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.50 (dd, *J* = 13.4, 6.2 Hz, 1H); minor diastereomer: δ 7.44 – 7.39 (m, 2H), 7.33 – 7.24 (m, 2H), 5.89 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.70 (s, 1H), 5.33 (d, *J* = 17.1, 1H), 5.17 (d, *J* = 10.4, 1H), 5.08 – 5.01 (m, 1H), 3.75 (s, 3H), 3.22 (s, 3H), 2.99 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.2, 7.4 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.9, 168.8, 136.7, 136.2, 130.9, 128.6, 122.0, 117.8, 83.5, 79.3, 65.9, 53.0, 52.2, 40.3; **TLC** (15% EtOAc/hexanes) R<sub>f</sub> 0.27; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>BrO<sub>5</sub>: C, 52.05; H, 4.64. Found: C, 52.35; H, 4.67.

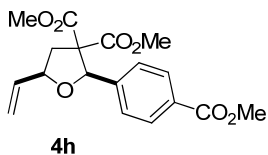
**Dimethyl 2-(4-chlorophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4g**):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-chlorobenzaldehyde (0.275 g, 1.96 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 12 h at 40 °C and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 89:11. Flash chromatography (10% ethyl acetate/hexanes) provided pure **4g** (0.097 g, 0.30 mmol, 92% yield) as a clear, colorless oil. Analytical data for **4g**: IR (thin film, cm<sup>-1</sup>) 3083, 2997, 2954, 2883, 2846, 1914, 1739, 1600, 1493, 1436, 1272, 1229, 1206, 1158, 1086, 1057, 1015, 936, 843, 803, 704; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.10 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.65 (s, 1H), 5.42 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.43 (ddd, *J* = 6.6, 6.4, 3.4 Hz, 1H), 3.83 (s, 3H), 3.20 (s, 3H), 2.76 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.53 (dd, *J* = 13.4, 6.2 Hz, 1H); minor diastereomer: δ 7.39 (m, 2H), 7.29 (m, 2H), 5.92 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.75 (s, 1H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.08 (m, 1H), 3.80 (s, 3H), 3.25 (s, 3H), 3.02 (dd, *J* = 13.2, 6.9 Hz, 1H), 2.21 (dd, *J* = 13.2, 7.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.9, 168.8, 136.3 (two overlapping resonances), 133.8, 128.3, 127.9, 117.7, 83.5, 79.2, 66.0, 52.9, 52.2, 40.3; minor diastereomer: δ 170.1, 168.9, 137.9, 136.7, 133.7, 116.1, 82.7, 79.9, 65.0, 52.8, 52.2, 40.5; TLC (10% EtOAc/hexanes) R<sub>f</sub> 0.32; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>ClO<sub>5</sub>: C, 59.17; H, 5.28. Found: C, 59.53; H, 5.66.

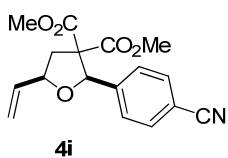


**Dimethyl 2-(4-(methoxycarbonyl)phenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4h**):**



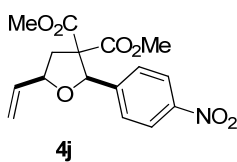
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-formyl methylbenzoate (0.161 g, 0.98 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 27 h at 40 °C and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 83:17. Flash chromatography (methylene chloride) provided pure **4h** (0.094 g, 0.27 mmol, 83% yield) as a clear, colorless oil. Analytical data for **4h**: **IR** (thin film, cm<sup>-1</sup>) 3000, 2956, 2848, 1729, 1613, 1436, 1279, 1208, 1113, 1059, 1019, 938, 868, 766, 731, 704; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.07 (ddd, *J* = 17.1, 10.3, 7.3 Hz 1H), 5.68 (s, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.40 (ddd, *J* = 6.8, 6.3, 3.9 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.08 (s, 3H), 2.73 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.50 (dd, *J* = 13.3, 6.0 Hz, 1H); minor diastereomer: δ 7.95 (m, 2H), 7.48 (m, 2H), 5.88 (ddd, *J* = 16.9, 10.3, 6.2 Hz, 1H), 5.79 (s, 1H), 5.32 (d, *J* = 16.8 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.06 (m, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.13 (s, 3H), 2.98 (dd, *J* = 13.0, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.2, 7.6 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.9, 168.6, 166.7, 142.9, 136.2, 129.8, 129.0, 126.9, 117.8, 83.7, 79.4, 66.1, 52.9, 52.1, 51.9, 40.4; minor diastereomer: δ 170.1, 168.7, 166.7, 143.5, 137.8, 129.7, 129.0, 126.5, 116.2, 83.0, 80.1, 66.2, 52.8, 52.1 (two overlapping resonances), 40.6; **TLC** (CH<sub>2</sub>Cl<sub>2</sub>) R<sub>f</sub> 0.15; **Anal.** Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>7</sub>: C, 62.06; H, 5.79. Found: C, 61.89; H, 5.77.

**Dimethyl 2-(4-cyanophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4i**):**



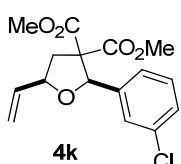
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-cyanobenzaldehyde (0.129 g, 0.98 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 5.5 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 83:17. Flash chromatography (methylene chloride) provided pure **4i** (0.095 g, 0.30 mmol, 92% yield) as a clear, colorless oil. Analytical data for the title compound: **IR** (thin film, cm<sup>-1</sup>) 3006, 2956, 2885, 2231, 1733, 1611, 1505, 1436, 1275, 1231, 1208, 1086, 1054, 936, 853, 808, 737; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 6.06 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.64 (s, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.42 (ddd, *J* = 6.7, 6.6, 3.3 Hz, 1H), 3.80 (s, 3H), 3.13 (s, 3H), 2.72 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.53 (dd, *J* = 13.4, 6.4 Hz, 1H); minor diastereomer: δ 7.58 (m, 2H), 7.54 (m, 2H), 5.88 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.75 (s, 1H), 5.33 (dt, *J* = 17.1, 1.1 Hz, 1H), 5.19 (dt, *J* = 10.4, 1.0 Hz, 1H), 5.06 (m, 1H), 3.76 (s, 3H), 3.17 (s, 3H), 2.98 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.19 (dd, *J* = 13.2, 7.7 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.6, 168.5, 143.0, 137.5, 131.5, 127.6, 118.5, 117.9, 111.8, 83.2, 79.4, 66.0, 53.0, 52.2, 40.4; minor diastereomer: δ 169.8, 168.5, 143.7, 137.5, 131.5, 127.3, 118.6, 116.4, 111.6, 82.5, 80.2, 66.2, 52.9, 52.1, 40.6; **TLC** (CH<sub>2</sub>Cl<sub>2</sub>) *R<sub>f</sub>* 0.20; **Anal.** Calcd. for C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.49; H, 5.44; N, 4.17.

**Dimethyl 2-(4-nitrophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4j**):**



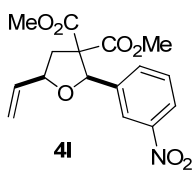
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 4-nitrobenzaldehyde (0.148 g, 0.98 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0009 g, 0.0008 mmol), and bathophenanthroline (0.0011 g, 0.0033 mmol). After 5 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 80:20. Flash chromatography (80% methylene chloride/petroleum ether) provided pure **4j** (0.100 g, 0.30 mmol, 95% yield) as a clear, colorless oil. The oil solidifies upon standing at −30 °C. Analytical data for **4j**: **mp** 67-69 °C; **IR** (thin film, cm<sup>−1</sup>) 3085, 3002, 2956, 2850, 1735, 1607, 1526, 1436, 1349, 1273, 1208, 1054, 1015, 936, 863, 749, 697; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.09 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.70 (s, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.45 (ddd, *J* = 6.7, 6.7, 3.2 Hz, 1H), 3.82 (s, 3H), 3.15 (s, 3H), 2.74 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.56 (dd, *J* = 13.4, 6.4 Hz, 1H); minor diastereomer: δ 8.16 (m, 2H), 7.64 (m, 2H), 5.90 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.81 (s, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.09 (m, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 3.00 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.22 (dd, *J* = 13.2, 7.8 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.7, 168.5, 147.7, 145.0, 136.0, 127.8, 122.9, 118.0, 83.1, 79.6, 66.1, 53.1, 52.3, 40.4; minor diastereomer: δ 169.9, 168.6, 147.6, 145.8, 137.5, 127.5, 122.9, 116.6, 82.4, 80.3, 66.3, 53.0, 52.2, 40.7; **TLC** (80% CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether) R<sub>f</sub> 0.12; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>NO<sub>7</sub>: C, 57.31; H, 5.11. Found: C, 57.43; H, 5.11.

**Dimethyl 2-(3-chlorophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4k**):**



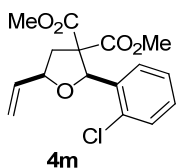
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 3-chlorobenzaldehyde (0.275 g, 1.96 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 21 h at 40 °C and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 89:11. Flash chromatography (15% ethyl acetate/hexanes) provided pure **4k** (0.103 g, 0.317 mmol, 97% yield) as a clear, colorless oil. Analytical data for **4k**: **IR** (thin film, cm<sup>-1</sup>) 3085, 3000, 2954, 2883, 2844, 1733, 1600, 1574, 1478, 1434, 1333, 1273, 1229, 1206, 1084, 1057, 934, 890, 783, 693; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.40 (s, 1H), 7.30 (m, 1H), 7.23 (m, 2H), 6.08 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.62 (s, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.40 (ddd, *J* = 6.7, 6.3, 3.8 Hz, 1H), 3.80 (s, 3H), 3.18 (s, 3H), 2.73 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.50 (dd, *J* = 13.4, 6.2 Hz, 1H); minor diastereomer: δ 7.42 (s, 1H), 7.30 (m, 1H), 7.22 (m, 2H), 5.89 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.72 (s, 1H), 5.34 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.18 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.06 (m, 1H), 3.76 (s, 3H), 3.23 (s, 3H), 2.99 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.2, 7.4 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.8, 168.6, 139.8, 136.2, 133.7, 129.0, 128.1, 127.0, 125.1, 117.8, 83.4, 79.3, 66.1, 52.9, 52.2, 40.2; minor diastereomer: δ 170.0, 168.7, 140.4, 137.8, 133.8, 129.1, 128.0, 126.6, 124.8, 116.2, 82.7, 80.0, 66.1, 52.8, 52.2, 40.5; **TLC** (15% EtOAc/hexanes) R<sub>f</sub> 0.23; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>ClO<sub>5</sub>: C, 59.17; H, 5.28. Found: C, 59.46; H, 5.48.

**Dimethyl 2-(3-nitrophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4l**):**



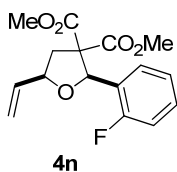
The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 3-nitrobenzaldehyde (0.147 g, 0.98 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0018 g, 0.0017 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 2 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 82:18. Flash chromatography (dichloromethane increasing to 1.5% methanol/dichloromethane) provided pure **4l** (0.108 g, 0.32 mmol, 99% yield) as a clear, colorless oil. The oil solidifies upon standing at −30 °C. Analytical data for **4l**: **mp** 79-81 °C; **IR** (thin film, cm<sup>−1</sup>) 2954, 2881, 2846, 1733, 1532, 1480, 1436, 1353, 1275, 1229, 1210, 1158, 1113, 1092, 1081, 1055, 936, 901, 816, 805, 737, 685; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 8.29 (s, 1H), 8.12 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 6.10 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.71 (s, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.45 (ddd, *J* = 9.9, 6.8, 6.6 Hz, 1H), 3.82 (s, 3H), 3.16 (s, 3H), 2.73 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.56 (dd, *J* = 13.5, 6.4 Hz, 1H); minor diastereomer: δ 8.31 (s, 1H), 8.15 – 8.10 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.45 (m, 1H), 5.90 (ddd, *J* = 16.8, 10.4, 6.2 Hz, 1H), 5.80 (s, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.13 – 5.06 (m, 1H), 3.78 (s, 3H), 3.22 (s, 3H), 3.01 (dd, *J* = 13.2, 6.9 Hz, 1H), 2.22 (dd, *J* = 13.2, 7.6 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.6, 168.5, 147.9, 140.0, 136.0, 133.0, 128.7, 123.0, 122.0, 118.0, 83.0, 79.5, 66.0, 53.1, 52.3, 40.2; minor diastereomer: δ 169.8, 140.6, 137.6, 132.7, 122.9, 121.6, 116.4, 82.3, 80.1, 66.1, 53.0, 40.5; **TLC** (CH<sub>2</sub>Cl<sub>2</sub>) *R<sub>f</sub>* 0.12; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>NO<sub>7</sub>: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.08; H, 5.01; N, 4.10.

#### Dimethyl 2-(2-chlorophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4m**):



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 2-chlorobenzaldehyde (0.275 g, 1.96 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0090 g, 0.0082 mmol), and bathophenanthroline (0.0108 g, 0.0326 mmol). After 3.5 h at 40 °C and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio: 98:2. Flash chromatography (20% ethyl acetate/hexanes) provided pure **4m** (0.097 g, 0.30 mmol, 92% yield) as a clear, colorless oil. Analytical data for **4m**: IR (thin film, cm<sup>-1</sup>) 3074, 2997, 2954, 2877, 2846, 1737, 1650, 1596, 1574, 1476, 1436, 1331, 1270, 1229, 1200, 1090, 1046, 1034, 938, 919, 872, 812, 756, 712; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 (d, *J* = 7.29, 1H), 7.22 (t, *J* = 6.6, 1H), 7.17 (t, *J* = 7.7, 1.6 Hz), 6.29 (s, 1H), 6.025 (ddd, *J* = 17.1 Hz, 10.4, 6.5 Hz, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.42 (m, 1H), 3.81 (s, 3H), 3.13 (s, 3H), 2.79 (dd, *J* = 13.1, 11.7 Hz, 1H), 2.42 (dd, *J* = 13.3, 4.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) major diastereomer: δ 170.8, 168.5, 136.4, 135.8, 133.3, 129.1, 129.0, 128.9, 126.4, 117.8, 80.5, 79.1, 65.8, 53.1, 52.0, 41.1; TLC (20% EtOAc/hexanes) R<sub>f</sub> 0.29; **Anal.** Calcd. for C<sub>16</sub>H<sub>17</sub>ClO<sub>5</sub>: C, 59.17; H, 5.28. Found: C, 59.40; H, 5.36.

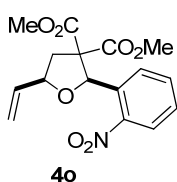
#### Dimethyl 2-(2-fluorophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4n**):



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 2-fluorobenzaldehyde (0.243 g, 1.96 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 20 h at room temperature

and workup,  $^1\text{H}$  NMR analysis of the unpurified product gave the diastereomeric ratio: 95:5. Flash chromatography (20% ethyl acetate/hexanes) provided pure **4n** (0.097 g, 0.315 mmol, 97% yield) as a clear, colorless oil. Analytical data for **4n**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3085, 2995, 2954, 2846, 1737, 1619, 1590, 1492, 1457, 1436, 1272, 1231, 1098, 1052, 938, 805, 762, 737;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  7.40 (td,  $J = 7.5, 1.5$  Hz, 1H), 7.24 (m, 1H), 7.10 (t,  $J = 7.7$  Hz, 1H), 6.99 (dd,  $J = 18.6, 10.2$  Hz, 1H), 6.09 (s, 1H), 6.05 (ddd,  $J = 17.1, 10.4, 6.7$  Hz, 1H), 5.41 (d,  $J = 17.2$  Hz, 1H), 5.27 (d,  $J = 10.4$  Hz, 1H), 4.42 (m, 1H), 3.82 (s, 3H), 3.18 (s, 3H), 2.80 (dd,  $J = 13.3, 11.1$  Hz, 1H), 2.46 (dd,  $J = 18.6, 5.3$  Hz, 1H); minor diastereomer:  $\delta$  7.40 (m, 1H), 7.24 (m, 1H), 7.10 (m, 1H), 6.99 (m, 1H), 6.14 (s, 1H), 5.89 (ddd,  $J = 16.9, 10.5, 6.1$  Hz, 1H), 5.35 (dt,  $J = 17.1, 1.2$  Hz, 1H), 5.18 (dt,  $J = 10.4, 1.1$  Hz, 1H), 5.02 (m, 1H), 3.77 (s, 3H), 3.26 (s, 3H), 3.08 (dd,  $J = 13.1, 7.0$  Hz, 1H), 2.27 (dd,  $J = 13.0, 6.7$  Hz, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  170.7, 168.6, 161.3, 158.8, 136.0, 129.7, 128.7, 125.7, 125.6, 123.7, 123.7, 117.8, 114.9, 114.7, 79.2, 78.0, 77.9, 65.8, 53.0, 52.1, 40.6; **TLC** (20% EtOAc/hexanes)  $R_f$  0.19; **Anal.** Calcd. for  $\text{C}_{16}\text{H}_{17}\text{FO}_5$ : C, 62.33; H, 5.56. Found: C, 62.54; H, 5.49.

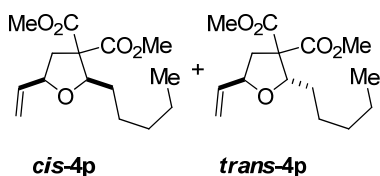
**Dimethyl 2-(2-nitrophenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4o**):**



The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), 2-nitrobenzaldehyde (0.147 g, 0.98 mmol),  $\text{Pd}_2(\text{pmdba})_3$  (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 3 h at room temperature and workup,  $^1\text{H}$  NMR analysis of the unpurified product gave the diastereomeric ratio: 87:13. Flash chromatography (80% dichloromethane/hexanes increasing to 100% dichloromethane)

provided pure **4o** (0.110 g, 0.33 mmol, 100% yield) as a clear, colorless oil. The oil solidifies upon standing at  $-30\text{ }^{\circ}\text{C}$ . Analytical data for **4o**: **mp** 47-49  $^{\circ}\text{C}$ ; **IR** (thin film,  $\text{cm}^{-1}$ ) 3056, 2989, 2956, 1737, 1532, 1437, 1351, 1266, 1202, 1158, 1092, 1052, 938, 897, 739, 706;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  7.91 (dd,  $J = 8.1, 1.0\text{ Hz}$ , 1H), 7.73 (dd,  $J = 7.9, 0.9\text{ Hz}$ , 1H), 7.58 (td,  $J = 7.7, 0.9\text{ Hz}$ , 1H), 7.42 (td,  $J = 8.2, 1.3\text{ Hz}$ , 1H), 6.42 (s, 1H), 6.05 (ddd,  $J = 17.1, 10.4, 6.6\text{ Hz}$ , 1H), 5.42 (d,  $J = 17.2\text{ Hz}$ , 1H), 5.29 (d,  $J = 10.4\text{ Hz}$ , 1H), 4.51 (ddd,  $J = 11.2, 5.8, 5.4\text{ Hz}$ , 1H), 3.82 (s, 3H), 3.15 (s, 3H), 2.75 (dd,  $J = 13.3, 11.2\text{ Hz}$ , 1H), 2.45 (dd,  $J = 13.3, 5.2\text{ Hz}$ , 1H); minor diastereomer:  $\delta$  7.84 (d,  $J = 9.1\text{ Hz}$ , 1H), 7.63 (d,  $J = 7.9\text{ Hz}$ , 1H), 7.60 – 7.54 (m, 1H), 7.45 – 7.39 (m, 1H), 6.49 (s, 1H), 5.90 (ddd,  $J = 16.7, 10.4, 6.1\text{ Hz}$ , 1H), 5.35 (d,  $J = 17.1\text{ Hz}$ , 1H), 5.18 (d,  $J = 10.4\text{ Hz}$ , 1H), 5.06 – 5.00 (m, 1H), 3.74 (s, 3H), 3.24 (s, 3H), 3.00 (dd,  $J = 13.1, 7.0\text{ Hz}$ , 1H), 2.30 (dd,  $J = 13.1, 7.0\text{ Hz}$ , 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  170.8, 168.6, 148.4, 135.6, 133.8, 132.8, 129.2, 128.9, 124.2, 118.2, 79.4, 79.3, 66.1, 53.2, 52.4, 41.3; minor diastereomer:  $\delta$  169.7, 168.7, 148.9, 137.5, 132.4, 128.6, 124.3, 116.5, 80.6, 66.3, 53.1, 40.9; **TLC** ( $\text{CH}_2\text{Cl}_2$ )  $R_f$  0.17; **Anal.** Calcd. for  $\text{C}_{16}\text{H}_{17}\text{NO}_7$ : C, 57.31; H, 5.11; N, 4.18. Found: C, 57.41; H, 5.16; N, 4.28.

***cis*- and *trans*-Dimethyl 2-pentyl-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4p**):**

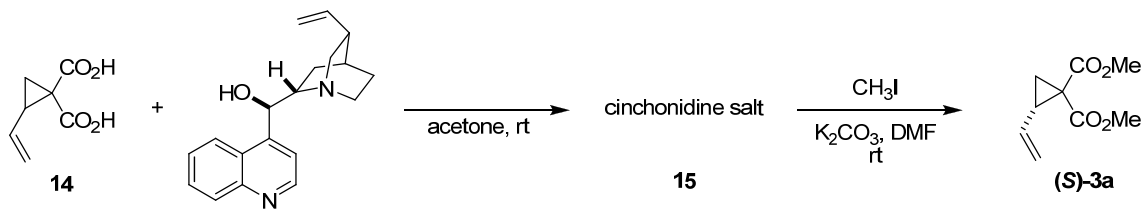


The title compound was prepared according to General Procedure A using dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**3a**, 0.060 g, 0.33 mmol), hexanal (0.196 g, 1.96 mmol),  $\text{Pd}_2(\text{pmdba})_3$  (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 22 h at room temperature and workup,  $^1\text{H}$  NMR analysis of the

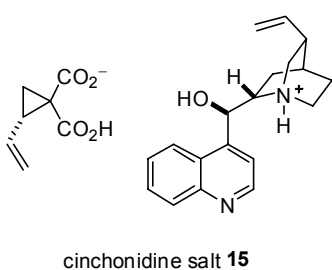


unpurified product gave the diastereomeric ratio: 69:31. Flash chromatography (15% ethyl acetate/hexanes) provided pure **4p** (0.085 g, 0.30 mmol, 92% yield) as a clear, colorless oil. Analytical data **4p**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3083, 2987, 2956, 2861, 1737, 1436, 1268, 1204, 1077, 1028, 928;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  5.91 (ddd,  $J = 17.0$ , 9.5, 7.0 Hz, 1H), 5.25 (d,  $J = 17.5$  Hz, 1H), 5.14 (d,  $J = 10.5$  Hz, 1H), 4.30 (d,  $J = 9.0$  Hz, 1H), 4.22 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.50 – 2.41 (m, 2H), 1.56 – 1.54 (m, 2H), 1.30 – 1.20 (m, 6H), 0.84 (m, 3H); minor diastereomer:  $\delta$  5.78 (ddd,  $J = 16.5$ , 10.0, 6.0 Hz, 1H), 5.21 (d,  $J = 18.5$  Hz, 1H), 5.07 (d,  $J = 10.5$  Hz, 1H), 4.66 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.83 (dd,  $J = 13.0$ , 7.5 Hz, 1H), 2.04 (dd,  $J = 13.0$ , 7.0 Hz, 1H), 1.60 – 1.58 (m, 2H), 1.35 – 1.31 (m, 6H), 0.84 (m, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  170.9, 169.9, 137.5, 117.0, 82.8, 78.8, 63.4, 52.6, 52.4, 40.2, 31.6 (two overlapping resonances), 26.3, 22.4, 13.9; minor diastereomer:  $\delta$  170.3, 169.7, 138.5, 115.3, 82.0, 78.1, 63.5, 52.5, 52.4, 31.3, 26.5; **TLC** (15% EtOAc/hexanes)  $R_f$  0.35; **Anal.** Calcd. for  $\text{C}_{15}\text{H}_{24}\text{O}_5$ : C, 63.36; H, 8.51. Found: C, 63.49; H, 8.62.

#### Preparation of (*S*)-dimethyl-2-vinylcyclopropane-1,1-dicarboxylate [(*S*)-**3a**]:

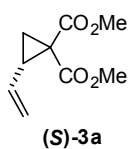


### Preparation of cinchonidine salt **15**:



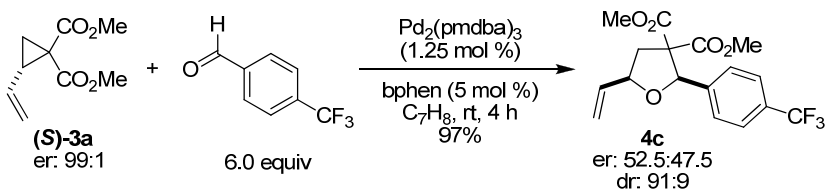
The diacid **14**<sup>21</sup> (10 g, 62.4 mmol, 1.0 equiv) was dissolved in 85 mL of acetone at room temperature and was allowed to stir for a few minutes. Cinchonidine (62.4 mmol, 18.37 g, 1.0 equiv) was then added with stirring. The solution became a clear yellow and with continued stirring a white precipitate crashed out of solution. The precipitate was isolated by Büchner filtration and washed with small portions of Et<sub>2</sub>O. The material was then dried under vacuum. The cyclopropane salt **15** was recrystallized from ethanol. After six recrystallizations, the salt was obtained in 99:1 dr (6% yield).

### (*S*)-Dimethyl-2-vinylcyclopropane-1,1-dicarboxylate [(*S*)-**3a**]:



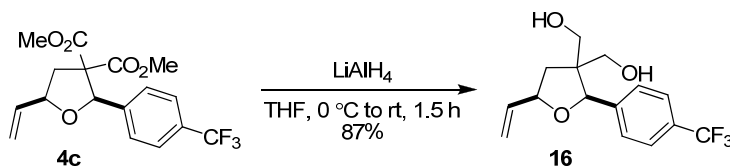
A flame dried flask containing a magnetic stir bar was purged with nitrogen and charged with the cyclopropane salt **15** (2.0 g, 4.4 mmol), potassium carbonate (1.3 g, 9.7 mmol) and dry dimethylformamide (12 mL). The mixture was allowed to stir for 30 minutes. The reaction mixture was then charged with iodomethane (3.1 g, 22 mmol) and was allowed to proceed under N<sub>2</sub>. After 16 h, the reaction was quenched with H<sub>2</sub>O (25 mL). The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 85 mL). The combined organic extracts were washed with H<sub>2</sub>O (3 x 85 mL), brine (1 x 85 mL), and dried over sodium sulfate. After rotary evaporation 608 mg (75%) of the cyclopropane was obtained as a yellow oil, which was purified by flash chromatography with 20% diethyl ether /hexanes prior to use. Care must be taken if material is dried *in vacuo* as the material is volatile.

**Dimethyl 2-(4-(trifluoromethyl)phenyl)-5-vinyldihydrofuran-3,3(2*H*)-dicarboxylate (**4c**):**



The title compound was prepared according to General Procedure A using (*S*)-dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (0.069 g, 0.38 mmol), 4-trifluoromethylbenzaldehyde (0.391 g, 2.25 mmol), Pd<sub>2</sub>(pmdba)<sub>3</sub> (0.0051 g, 0.0047 mmol), and bathophenanthroline (0.0062 g, 0.0187 mmol). After 4 h at room temperature and workup, <sup>1</sup>H NMR analysis of the unpurified product gave the diastereomeric ratio of 91:9. Flash chromatography (15% diethyl ether/hexanes) provided pure **4c** (0.130 g, 0.36 mmol, 97% yield) as a clear, colorless oil. Analytical data was identical to that reported for the cycloaddition with *rac*-**3a**.

**Preparation of 2-(4-(trifluoromethyl)phenyl)-5-vinyltetrahydrofuran-3,3-diyl dimethanol (**16**):**



A solution of **4c** (0.130 g, 0.36 mmol) in tetrahydrofuran (1.1 mL) was cooled to 0 °C and treated with a solution of LiAlH<sub>4</sub> (2.18 mL of a 1.0 M solution in THF, 6 equiv) by dropwise addition via syringe. After addition, the reaction was allowed to warm to room temperature with stirring. After 1.5 h, the reaction was cooled to 0 °C and diluted with 5 mL Et<sub>2</sub>O, quenched with 0.5 mL H<sub>2</sub>O, 0.25 mL of a 10% NaOH (aq.) solution. The mixture was filtered through a fritted funnel and the filter cake was washed with several portions of Et<sub>2</sub>O. The filtrate was dried over MgSO<sub>4</sub>, filtered, and concentrated by rotary evaporation. Flash

chromatography (55% EtOAc/hexanes) provided pure **16** (0.096 g, 0.32 mmol, 87% yield) as a clear, colorless oil in 52.5:47.5 er as determined by chiral SFC analysis (Chiralpak AS, 3.0% MeOH, 2.0 mL/min, 200 bar, 27 °C, 220 nm,  $t_r$ -major 10.4 min,  $t_r$ -minor 11.2 min). Analytical data for the title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3384, 2243, 2883, 1619, 1420, 1326, 1165, 1127, 1067, 1017, 932, 849, 735;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  7.57 (d,  $J = 8.17$  Hz, 2H), 7.50 (d,  $J = 8.13$  Hz, 2H), 6.01 (ddd,  $J = 17.0$ , 10.4, 6.2 Hz, 1H), 5.38 (d,  $J = 17.2$  Hz, 1H), 5.23 (d,  $J = 10.4$  Hz), 4.86 (s, 1H), 4.48 (ddd,  $J = 9.5$ , 6.3, 6.3, 1H), 3.87 (s, 2H), 3.23 (dd,  $J = 23.4$ , 10.9, 2H), 2.10 (dd,  $J = 6.5$ , 13.1, 1H), 1.66 (dd,  $J = 12.9$ , 9.7, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  143.0, 137.6, 127.0 (two overlapping resonances), 125.0 (q,  $J = 3.8$ ), 116.6, 84.2, 78.7, 67.5, 66.7, 52.4, 38.9; TLC (55% EtOAc/hexanes)  $R_f$  0.16.

## 2.5 References

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**CHAPTER THREE**

**ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROFURANS VIA DYNAMIC  
KINETIC ASYMMETRIC (3 + 2) ANNULATION OF RACEMIC CYCLOPROPANES  
AND ALDEHYDES**

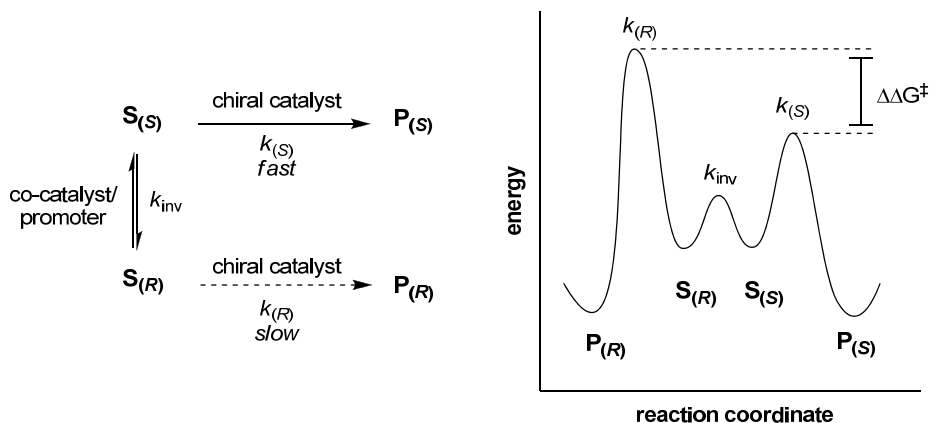
### **3.1 Introduction**

The efficiency of a chemical transformation is measured by several characteristics: a) chemical yield; b) the amount of non-product molecules present, either as waste or excess reagent, upon completion of the reaction; c) the number of bonds formed per synthetic operation; and d) the degree of chemo- and stereoselectivity. While these goals have been elegantly addressed in many complex systems, there still remain numerous challenges in achieving reaction efficiency. Advances in enantioselective catalysis have greatly increased the efficiency of stereoselective transformations by circumventing the required use of stoichiometric resolving agents employed in classical kinetic resolutions or chiral auxiliaries.

Dynamic kinetic asymmetric transformations (DyKATs) are one of the most valuable reaction classes in organic synthesis.<sup>1,2</sup> Unlike traditional kinetic resolutions where the theoretical yield is 50%, DyKATs have a theoretical yield of 100%. This greatly increases the efficiency in which enantiopure products can be accessed. Similarly to DyKATs, dynamic kinetic resolutions (DKRs) also have a theoretical yield of 100% but require the use

of a co-promoter or co-catalyst to interconvert the enantiomers of a racemic substrate in order to achieve a dynamic transformation (**Figure 3-1**).

**Figure 3-1.** Kinetics of a Dynamic Kinetic Resolution



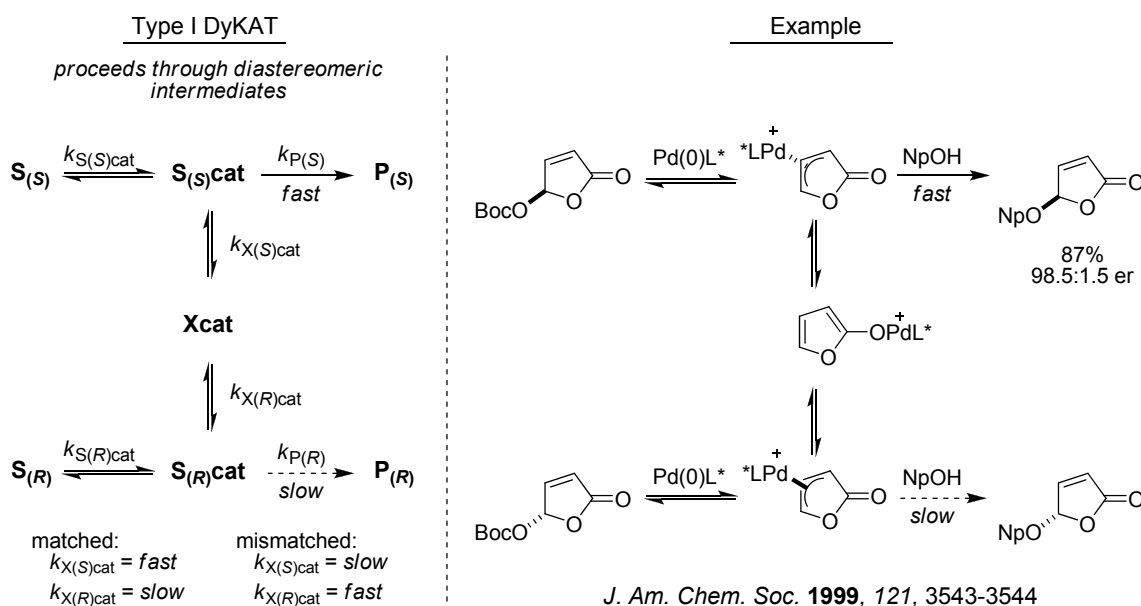
Converse to dynamic kinetic resolutions, DyKATs use a single catalyst to achieve both the interconversion of substrate enantiomers and the asymmetric transformation. This is an advantageous characteristic since it avoids reagent compatibility issues that may arise in developing a DKR. While several classes of DyKATs exist, only processes that involve the transformation of a racemic substrate mixture to a single enantioenriched product will be discussed in this chapter. This “de-racemization of enantiomers”<sup>2</sup> through a DyKAT can be categorized into two different classes based on the reaction mechanism: type I and type II.

Type I dynamic kinetic asymmetric transformations are characterized by the procession of the irreversible product-forming steps through diastereomeric substrate/catalyst complexes (**Scheme 3-1**). Product distributions are, in part, determined by the relative reactivities of these complexes. Thus, in type I DyKATs the absolute configuration of the product is determined by the absolute configuration of the reactive diastereomeric substrate/catalyst complex [**S<sub>S</sub>cat**, **Scheme 3-1**, left]. Selectivity is also dependent on the rate of catalyst complexation [ $k_{S(R/S)cat}$ ] and interconversion of each enantiomer [ $k_{X(R/S)cat}$ ]



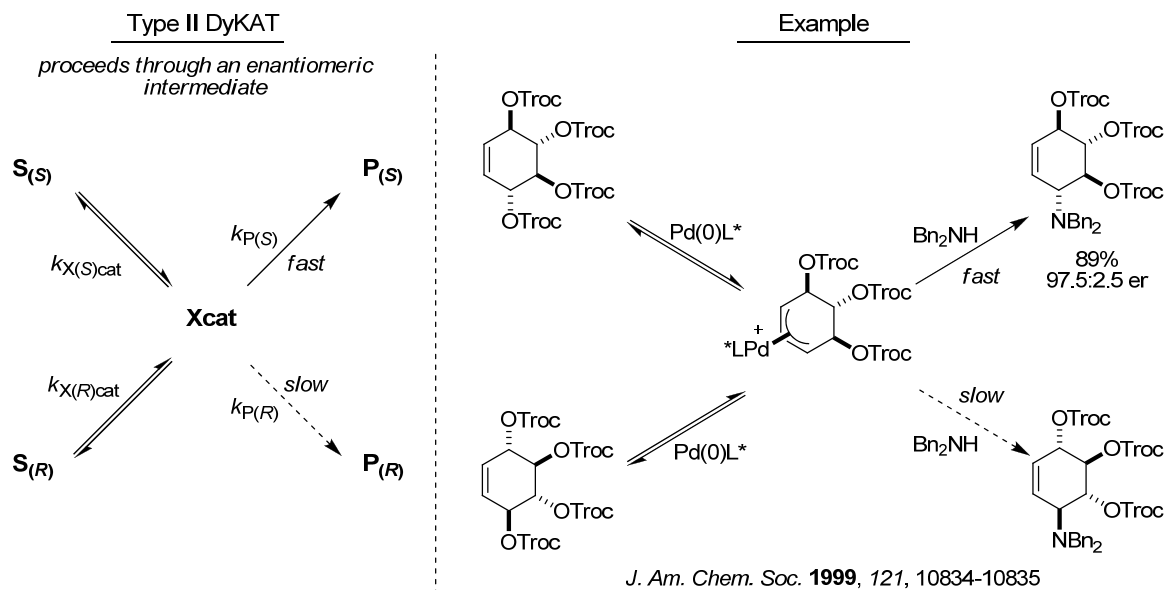
through the common enantiomeric intermediate **Xcat**. For example, if the transformation in **Scheme 3-1** displayed kinetics in which  $k_{X(R)\text{cat}}$  is fast but  $k_{X(S)\text{cat}}$  is slow, only moderate selectivity will be achieved since there will be a high population of **S<sub>(R)</sub>cat**. This is known as a “mismatched” case. If the kinetics of this reaction were “matched,” then  $k_{X(R)\text{cat}}$  would be slow and  $k_{X(S)\text{cat}}$  would be fast, resulting in a highly selective transformation.

**Scheme 3-1.** Kinetic Representation of a Type I DyKAT (left) and a Literature Example Reported by Trost<sup>3</sup> (right)



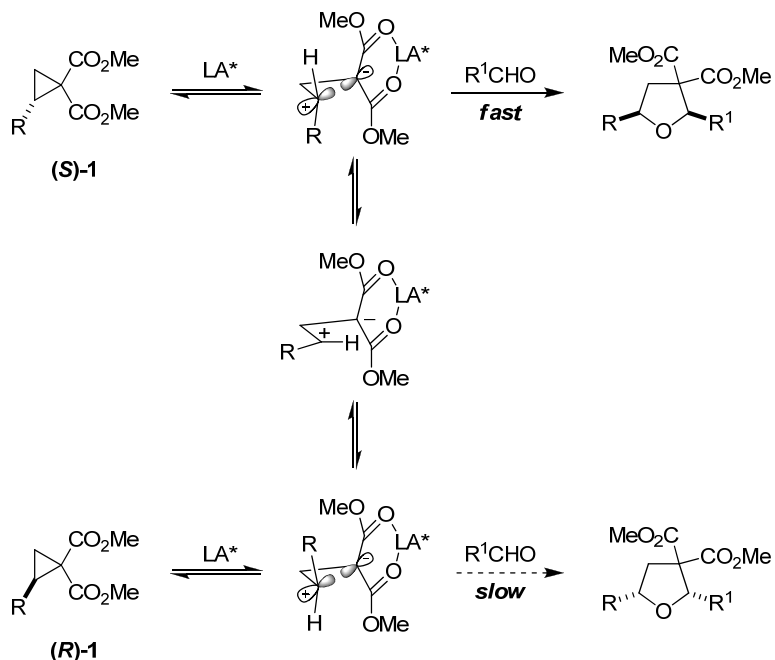
Type II DyKATs differ from type I variants in that the reaction proceeds through a single enantiomeric intermediate that is generated directly from two enantiomeric starting materials (**Scheme 3-2**). Selectivity is dependent only on the relative rates of product formation,  $k_{P(S)}$  and  $k_{P(R)}$ , from **Xcat**; the relative rates of **Xcat** formation [ $k_{X(S)\text{cat}}$  and  $k_{X(R)\text{cat}}$ ] from each enantiomeric substrate only affects the overall rate of the transformation, not the selectivity. The absolute configuration of products is determined by any non-fluxional stereocenters present and/or ligand control.

**Scheme 3-2.** Kinetic Representation of a Type II DyKAT (left) and a Literature Example Reported by Trost<sup>4</sup> (right)

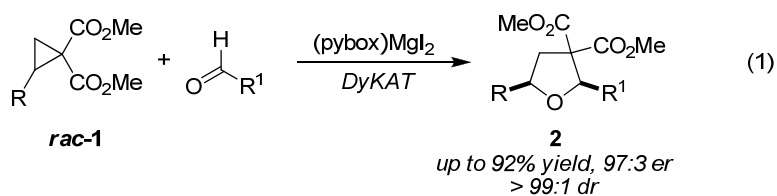


While dynamic kinetic asymmetric transformations represent a powerful tool in asymmetric synthesis, substrates for these reactions are limited to molecules with planes of symmetry (mirror or  $C_2$ ) or fluxional stereogenic centers. Previous work on Lewis acid-catalyzed annulations of malonate-derived donor-acceptor (D–A) cyclopropanes (see **Chapter One**) demonstrated that enantioenriched substrates are prone to racemization under the reaction conditions. While this process is undesired for enantiospecific annulations, it is favorable when considering opportunities for dynamic asymmetric reaction development. In the realm of DyKATs, the Lewis acid-catalyzed interconversion of cyclopropane enantiomers is a requirement needed to achieve a type I transformation (**Scheme 3-3**).

**Scheme 3-3.** Proposed Chiral Lewis Acid (LA<sup>\*</sup>)-Catalyzed Type I DyKAT of **1** via Asymmetric Annulation with Aldehydes



The work reported herein describes the preparation of enantioenriched tetrahydrofuran (THF) derivatives through a type I dynamic kinetic asymmetric transformation of racemic malonate-derived D–A cyclopropanes **1** via asymmetric (3 + 2) annulation with aldehydes (eq 1).

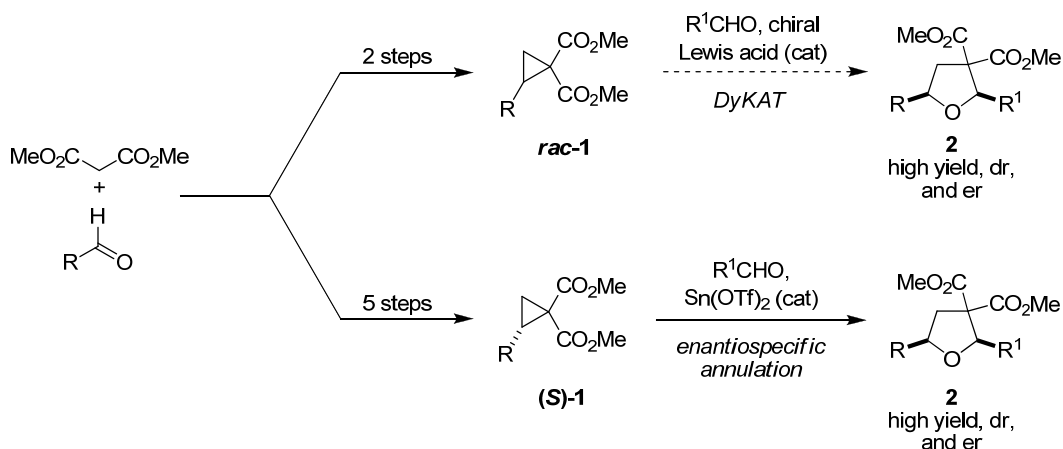


## 3.2 Background

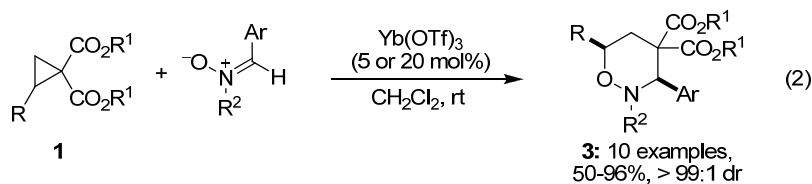
Recent literature reports have demonstrated that malonate-derived D–A cyclopropanes are useful reagents for the preparation of carbo- and heterocycles through Lewis acid-catalyzed (3 + *n*) annulations with appropriate dipolarophiles (see **Chapter**

**One).**<sup>5-10</sup> Generation of enantioenriched products using this reaction manifold has typically required the use of nonracemic cyclopropane starting materials in reactions proceeding via stereospecific pathways.<sup>11-14</sup> While numerous methods are available for the enantioselective preparation of cyclopropanes,<sup>15</sup> a more attractive route to enantioenriched annulation products would be through an asymmetric ( $3 + n$ ) annulation of a racemic cyclopropane. This method would have the advantage of introducing asymmetry at a later stage, rendering the cyclopropane a less-valuable starting material. For example, racemic preparation of **1** can be achieved in two steps from dimethyl malonate and an aldehyde whereas preparation of (*S*)-**1** requires five steps, including a classical resolution (**Scheme 3-4**).<sup>16</sup> Thus, a method to access tetrahydrofurans of type **2** through a DyKAT would result in an overall shorter synthetic sequence.

**Scheme 3-4.** Preparation of Enantioenriched Tetrahydrofurans through a Proposed DyKAT (top) and Enantiospecific Annulation Reported by Pohlhaus<sup>11</sup> (bottom)

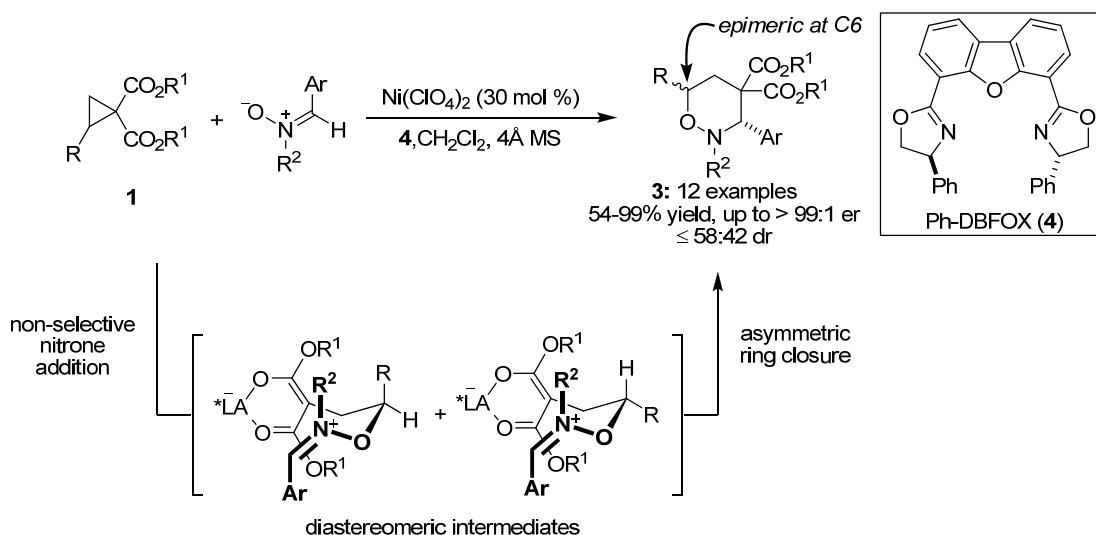


Recently, Sibi and coworkers reported the first catalytic asymmetric transformation of malonate-derived cyclopropanes **1**.<sup>17</sup> Inspired by the previously reported racemic synthesis of tetrahydro-1,2-oxazines **3** via  $Yb(OTf)_3$ -catalyzed nitron/cyclopropane annulation (eq 2),<sup>18</sup> Sibi sought to extend this method to an asymmetric variant through the use of a chiral



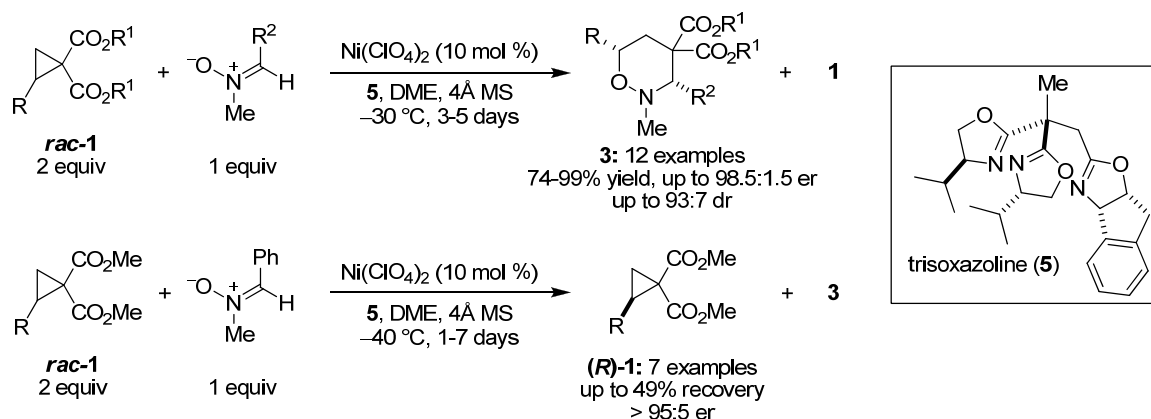
Lewis acid. A thorough investigation of Lewis acid/ligand complexes revealed  $\text{Ni}(\text{ClO}_4)_2/\text{Ph-DBFOX}$  (**4**) provided excellent yields and enantioselectivities (**Scheme 3-5**). While unsubstituted cyclopropanes of type **1** ( $\text{R} = \text{H}$ ) provide products in good yield and enantioselectivities, poor diastereoselectivities are observed when  $\text{R} \neq \text{H}$ . Although no mechanistic proposal is reported, it is possible that the low diastereoselectivity is a result of enantiodifferentiation after the first irreversible step.<sup>19</sup> Thus, non-selective nucleophilic attack by the nitron results in formation of two diastereomeric substrate/Lewis acid intermediates (**Scheme 3-5**). An asymmetric ring closure would result in the formation of a diastereomeric product mixture with high enantioenrichment. This work reveals a significant challenge in developing a DyKAT or even a simple kinetic resolution of **1** using chiral Lewis acid catalysis: differentiation between cyclopropane enantiomers.

**Scheme 3-5.** Enantioselective Cyclopropane/Nitron Annulation Reported by Sibi<sup>17</sup>



More recently, Tang reported the ability to differentiate enantiomers of **1** using a  $\text{Ni}(\text{ClO}_4)_2$ /trioxazoline (**5**)-catalyzed annulation with nitrones to achieve a kinetic resolution.<sup>20</sup> This was the first example of enantiodifferentiation of malonate-derived cyclopropanes using Lewis acid catalysis. Slight modifications of the reaction conditions allowed for access to either highly enantioenriched **3** or recovery of enantioenriched **1** (**Scheme 3-6**). Since this transformation achieves a kinetic resolution, it must be true that  $\text{Ni}(\text{ClO}_4)_2$ /(**5**) does not interconvert the enantiomers of **1** under the reaction conditions. This methodology is significant to future advancements in catalytic asymmetric transformations of **1**. Coupled with the precedent previously established for Lewis acid-catalyzed racemization of enantioenriched **1**,<sup>11,12</sup> this report provides evidence that a DyKAT of **1** is possible in a carefully designed system.

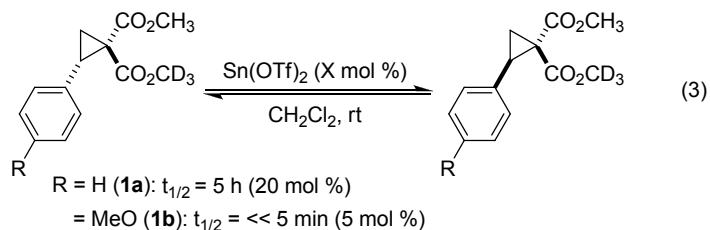
**Scheme 3-6.** Kinetic Resolution of Cyclopropanes *rac*-**1** via Asymmetric Annulation with Nitrones as Reported by Tang<sup>20</sup>



### 3.3 Reaction Development

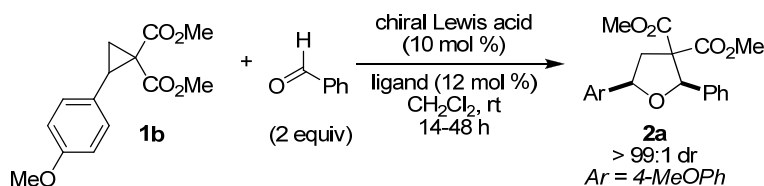
#### 3.3.1 Early Investigations

Previous studies on Lewis acid-catalyzed annulations of malonate-derived cyclopropanes (**1**) provided insight into the nature of undesired racemization occurring over the course of the reaction.<sup>12,13</sup> These studies suggested that the rate of racemization is dependent on the cation-stabilizing ability of the donor group (eq 3). Based on the relative rates of Lewis acid-catalyzed cyclopropane ring-opening, we chose to proceed with 4-methoxyphenyl-substituted cyclopropane **1b** since previous experiments had demonstrated its increased rate of ring-opening. Furthermore, the occurrence of a number of 2,5-diaryltetrahydrofuran natural products bearing electron-rich aromatic moieties further recommended **1b** as an appropriate point of departure for this study.<sup>21</sup>



Early experiments examined annulation of **1b** with excess benzaldehyde in the presence of chiral Lewis acid catalysts that have been useful in facilitating other asymmetric processes (**Table 3-1**). The ease of preparation and proven utility of oxazoline-containing ligands prompted us to narrow our focus to complexes derived from ligands of this class.<sup>22,23</sup> Evaluation of several Lewis acid/ligand combinations led to the discovery that while most complexes catalyzed this reaction to high conversion and diastereoselectivity, enantioselectivities were poor in all cases. Magnesium iodide complexed with bis(oxazoline) ligand **8** provided the most encouraging results, yielding tetrahydrofuran **2a** in 65:35 er. With these results in hand, we set out to examine a range of  $\text{MgI}_2$ /ligand complexes.

**Table 3-1.** Initial Examination of Chiral Lewis Acids for the Annulation of **1b** with Benzaldehyde



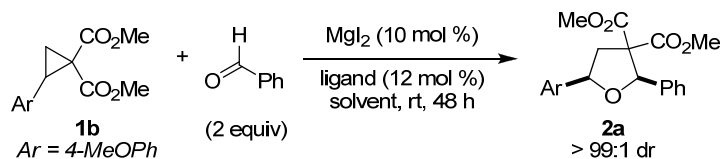
| entry | ligand          | Lewis acid                         | conversion (%) <sup>a</sup> | er <sup>b</sup> |
|-------|-----------------|------------------------------------|-----------------------------|-----------------|
| 1     | <br><b>(4)</b>  | Ni(ClO <sub>4</sub> ) <sub>2</sub> | 100                         | 54:46           |
| 2     |                 | Mg(ClO <sub>4</sub> ) <sub>2</sub> | 95                          | 57:43           |
| 3     | <br><b>(6)</b>  | Sn(OTf) <sub>2</sub>               | 0                           | —               |
| 4     |                 | Zn(OTf) <sub>2</sub>               | 10                          | 50:50           |
| 5     |                 | Cu(SbF <sub>6</sub> ) <sub>2</sub> | 100                         | 50:50           |
| 6     | <br><b>(7a)</b> | Sn(OTf) <sub>2</sub>               | 0                           | —               |
| 7     |                 | Sc(OTf) <sub>3</sub>               | 100                         | 50:50           |
| 8     |                 | Yb(OTf) <sub>3</sub>               | 100                         | 50:50           |
| 9     | <br><b>(8)</b>  | MgI <sub>2</sub>                   | 100                         | 65:35           |

Conditions: **1b** (1.0 equiv), benzaldehyde (2.0 equiv), MgI<sub>2</sub> (0.10 equiv), ligand (0.12 equiv), [**1b**]<sub>0</sub> = 0.30 M in CH<sub>2</sub>Cl<sub>2</sub>, rt, 48 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis.

An examination of oxazoline-complexed MgI<sub>2</sub> catalysts revealed that cyclopropane decomposition limited the yield of **2a** (Table 3-2). For example, while <sup>t</sup>Bu-pybox (**7a**)/MgI<sub>2</sub> provided a marked increase in enantioselectivity (er: 80:20) the yield was poor despite complete consumption of **1b** (entry 3). In an attempt to increase the yield of **2a**, a broad range of <sup>t</sup>Bu-pybox/Lewis acid complexes was examined (> 25 metals, data not shown). The result of this analysis indicated that MgI<sub>2</sub> remained the most promising catalyst; additional optimization of this system was pursued.



**Table 3-2.** Selected Ligands Examined for the MgI<sub>2</sub>-Catalyzed Asymmetric Annulation of **1b** with Benzaldehyde

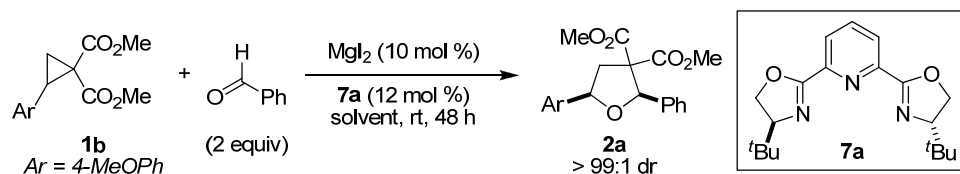


| entry | ligand |                          | solvent                         | yield (%) <sup>a</sup> | er <sup>b</sup> |
|-------|--------|--------------------------|---------------------------------|------------------------|-----------------|
| 1     |        | (4)                      | CH <sub>2</sub> Cl <sub>2</sub> | 44 <sup>d</sup>        | 67:33           |
| 2     |        | (6)                      | CH <sub>2</sub> Cl <sub>2</sub> | nd <sup>c</sup>        | 55:45           |
| 3     |        | R = <sup>t</sup> Bu (7a) | CH <sub>2</sub> Cl <sub>2</sub> | 30                     | 80:20           |
| 4     |        | R = <sup>i</sup> Pr (7b) | CH <sub>2</sub> Cl <sub>2</sub> | 18                     | nd              |
| 5     |        | R = Ph (7c)              | CH <sub>2</sub> Cl <sub>2</sub> | < 5                    | nd              |
| 6     |        | R = Bn (7d)              | CH <sub>2</sub> Cl <sub>2</sub> | < 5                    | nd              |
| 7     |        | R = Ad (7e) <sup>e</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 10                     | 77:23           |
| 8     |        | (9)                      | CH <sub>2</sub> Cl <sub>2</sub> | < 5                    | nd              |
| 9     |        | (10)                     | CCl <sub>4</sub>                | 5                      | nd              |
| 10    |        | (11)                     | CCl <sub>4</sub>                | 15                     | nd              |
| 11    |        | (12)                     | C <sub>6</sub> H <sub>6</sub>   | < 5                    | nd              |

Conditions: **1b** (1.0 equiv), benzaldehyde (2.0 equiv), MgI<sub>2</sub> (0.10 equiv), ligand (0.12 equiv), [**1b**]<sub>0</sub> = 0.30 M in the indicated solvent, rt, 48 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis. c) nd = not determined. d) 4Å molecular sieves were added. e) Ad = adamantyl.

With a workable catalyst system selected, efforts toward improving the yield and enantioselectivity of this transformation were focused on modification of the reaction conditions (temperature, solvent, concentration). While deviations from room temperature resulted in decreased yields, an extensive screen of solvents resulted in substantial variance in reaction efficiency (**Table 3-3**). Chloroform furnished **2a** in the highest yield and benzene the highest enantioselectivity (entries 9 and 15), both providing marked increases over methylene chloride (entry 1). Binary mixtures of these solvents did not produce a synergistic effect. Carbon tetrachloride resulted in the most balanced increase in yield and er (entry 12) and was chosen for subsequent optimization experiments.

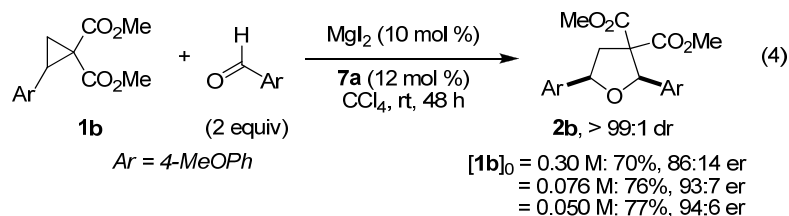
**Table 3-3.** Examination of Solvent Effects on Yield and Enantioselectivity



| entry | solvent                         | yield (%) <sup>a</sup> | er <sup>b</sup> | entry | solvent              | yield (%) <sup>a</sup> | er <sup>b</sup> |
|-------|---------------------------------|------------------------|-----------------|-------|----------------------|------------------------|-----------------|
| 1     | methylene chloride              | 30                     | 80:20           | 9     | chloroform           | 68                     | 84:16           |
| 2     | 2-methyl tetrahydrofuran        | 40                     | 88:12           | 10    | chlorobenzene        | 51                     | 90:10           |
| 3     | cyclopentyl methyl ether        | 25                     | 88:12           | 11    | ethyl acetate        | 24 (72) <sup>c</sup>   | nd              |
| 4     | <i>tert</i> -butyl methyl ether | 38 (80) <sup>c</sup>   | nd <sup>d</sup> | 12    | carbon tetrachloride | 64                     | 92.5:7.5        |
| 5     | diethyl ether                   | 43                     | 84:16           | 13    | toluene              | 27                     | nd              |
| 6     | benzotrifluoride                | 57                     | 88:12           | 14    | tetrahydrofuran      | 30                     | 75:25           |
| 7     | dichloroethane                  | 33                     | nd              | 15    | benzene              | 49                     | 93:7            |
| 8     | 1,4-dioxane                     | 27                     | nd              |       |                      |                        |                 |

Conditions: **1b** (1.0 equiv), benzaldehyde (2.0 equiv), MgI<sub>2</sub> (0.10 equiv), **7a** (0.12 equiv), [**1b**]<sub>0</sub> = 0.30 M in the indicated solvent, rt, 48 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis. c) Numbers in parentheses refer to % conversion of **1b**. d) nd = not determined

In previous experiments, we had encountered difficulty when using 4-methoxybenzaldehyde as the dipolarophile. In these reactions, this aldehyde provided increased yields of the THF product when compared to benzaldehyde, but the enantioselectivity was greatly diminished. We proceeded to vary the reaction concentration and examine the yield and enantioselectivity for the annulation of **1b** with 4-methoxybenzaldehyde (eq 4). As  $[\mathbf{1b}]_0$  decreased, there was a marked increase in both yield and enantioselectivity. Further dilution below  $[\mathbf{1b}]_0 = 0.050$  M did not result in additional improvement of yield and enantioselectivity. The results obtained under dilute reaction conditions represented a substantial improvement, justifying the continuation of reaction development using a more intensive approach.



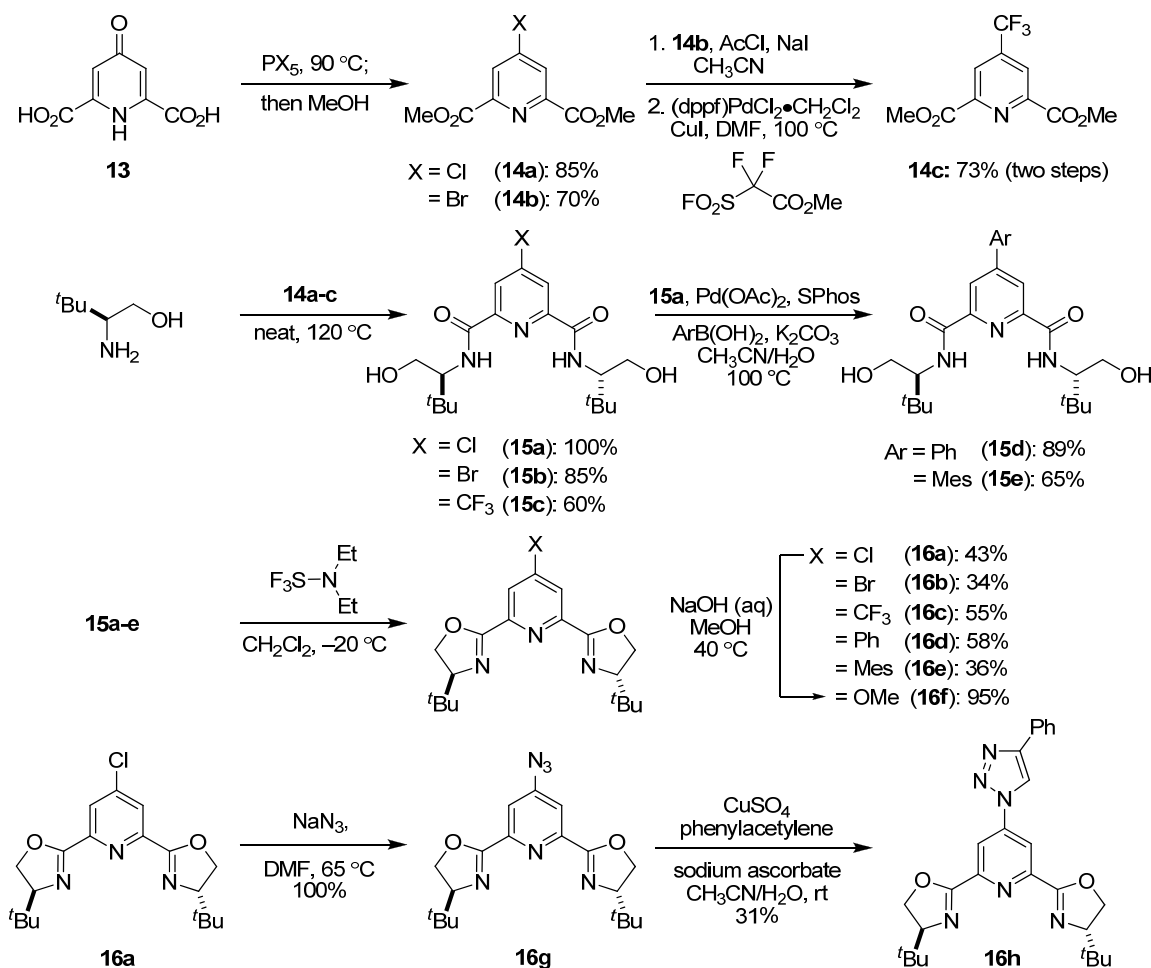
### 3.3.2 Ligand Development

The preliminary conditions developed in section 3.3.1 represent the culmination of standard approaches available for reaction optimization. To achieve further improvement in yield and enantioselectivity, we considered a ligand-based approach. The results presented in **Table 3-2** revealed that the *tert*-butyl group on the pybox ligand was necessary for sufficient selectivity and yield (entries 3-7). In order to achieve variability within the *t*Bu-pybox framework, we explored perturbations of the ligands at the 4-position of the pyridine.

Preparation of 4-X-*t*Bu-pybox ligands commenced with dehydration of commercially available chelidamic acid (**13**) using  $\text{PX}_5$  ( $\text{X} = \text{Cl}^{24}$  or  $\text{Br}^{25}$ ) followed by a methanol quench, providing pyridines **14a-b**. An addition-elimination reaction using NaI transformed **14b** to

the corresponding iodide<sup>26</sup> and subsequent Pd(0)-catalyzed/Cu(I)-promoted coupling with methyl-2,2-difluoro-2-(fluorosulfonyl)acetate<sup>27</sup> yielded trifluoromethylated pyridine **14c** in 73% overall yield. Condensation with *tert*-leucinol provided bisamides **15a-c**. Arylation of **15a** using a Suzuki–Miyaura<sup>28</sup> coupling provided **15d-e**. Cyclization of the amides to

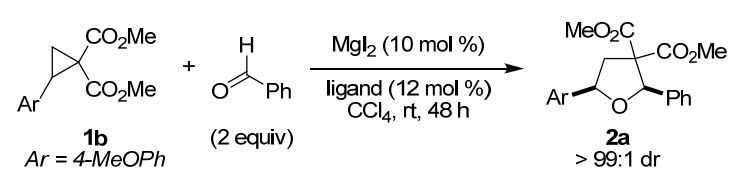
**Scheme 3-7.** Preparation of 4-X-*t*Bu-Pybox Ligands from Chelidamic Acid (**13**)

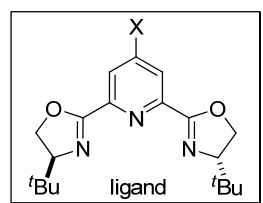


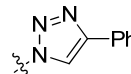
oxazolines was achieved by treating **15a-e** with diethylaminosulfur trifluoride, furnishing 4-X-*t*Bu-pybox ligands **16a-e** in 34–58% yield (not optimized). Additional ligand diversity was accessed through modifications of **16a**. Thus, nucleophilic displacement of chloride with methoxide or azide gave **16f-g** in near quantitative yield. A copper-catalyzed azide/alkyne cycloaddition of **16g** with phenylacetylene gave the triazole-substituted pybox **16h**.

With an electronically diverse set of 4-substituted-*t*Bu-pybox ligands prepared, we conducted MgI<sub>2</sub>-catalyzed annulation reactions of **1b** with benzaldehyde using ligands **16a-h** (Table 3-4). Variation in the electronic characteristics of 4-X-*t*Bu-pybox ligands had a negligible effect on enantioselectivity, but induced significant variation in yield. The electron-rich 4-MeO-*t*Bu-pybox (**16f**) resulted in low conversion of **1b**, presumably due to its stronger binding, causing a decrease in Lewis acidity of the Mg(II) catalyst. Conversely, the electron-deficient 4-F<sub>3</sub>C-*t*Bu-pybox (**16c**) provided the highest enantioselectivity, but the yield suffered due to decomposition of **1b** (entry 6). The moderately electron-deficient ligands **16a** (X = Cl) and **16b** (X = Br) provided the highest yields and levels of enantiocontrol (entries 2, 5).

**Table 3-4.** Evaluation of 4-Substituted-*t*Bu-Pybox Ligands





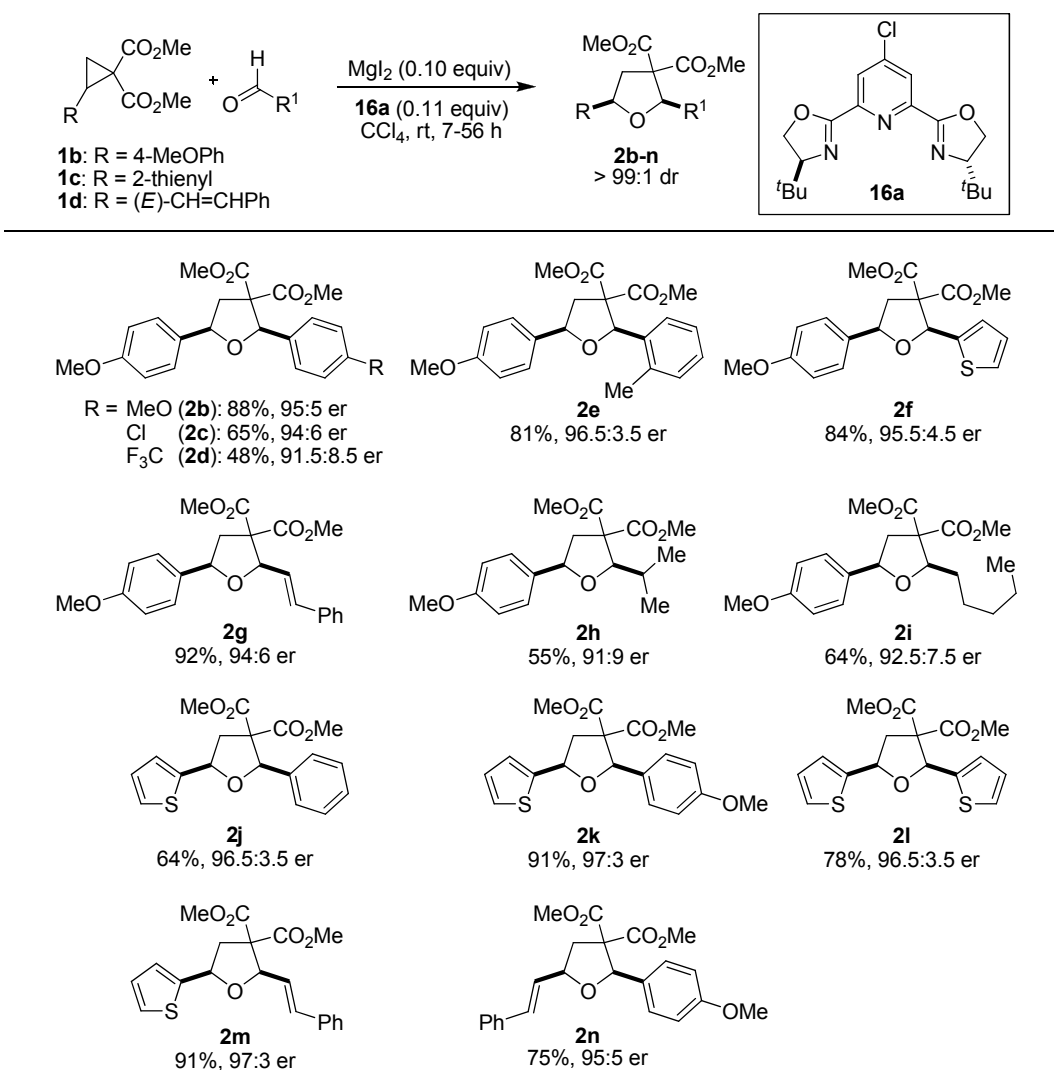
| entry          | X  | conversion (%) <sup>a</sup> | yield (%) <sup>a</sup> | er <sup>b</sup> |
|----------------|--|-----------------------------|------------------------|-----------------|
| 1              | H ( <b>7a</b> )  | 93                          | 62                     | 95.5:4.5        |
| 2              | Cl ( <b>16a</b> )  | 100                         | 74 <sup>c</sup>        | 96:4            |
| 3 <sup>d</sup> | Cl ( <b>16a</b> )  | 100                         | 16                     | 82.5:17.5       |
| 4 <sup>e</sup> | Cl ( <b>16a</b> )  | 100                         | 40                     | 96:4            |
| 5              | Br ( <b>16b</b> )  | 100                         | 75                     | 95:5            |
| 6              | CF <sub>3</sub> ( <b>16c</b> )   | 100                         | 57                     | 96.5:3.5        |
| 7              | Ph ( <b>16d</b> )  | 100                         | 43                     | 95.5:4.5        |
| 8              | Mes ( <b>16e</b> )   | 95                          | 57                     | 94:6            |
| 9              | OMe ( <b>16f</b> )   | 26                          | 5                      | nd <sup>f</sup> |
| 10             | N <sub>3</sub> ( <b>16g</b> )  | 100                         | 67                     | 96:4            |
| 11             |  ( <b>16h</b> ) | 100                         | 55                     | 93.5:6.5        |

Conditions: **1b** (1.0 equiv), benzaldehyde (2.0 equiv), MgI<sub>2</sub> (0.10 equiv), ligand (0.12 equiv), [**1b**]<sub>0</sub> = 0.05 M in CCl<sub>4</sub>, rt, 48 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis. c) Average isolated yield of two independent trials. d) With CH<sub>2</sub>Cl<sub>2</sub> as the solvent. e) With C<sub>7</sub>H<sub>8</sub> as the solvent. f) nd = not determined

### 3.3.3 Reaction Scope

Next, we explored the scope of the cyclopropane/aldehyde annulation under the conditions outlined in **Table 3-4** with 4-Cl-*t*-Bu-pybox (**16a**). Cyclopropane **1a** bearing a phenyl donor group was not a successful substrate due to an insufficient rate of racemization (*vide infra*). We identified 2-thienyl- and styryl-substituted cyclopropanes **1c** and **1d** as competent substrates for this transformation, a further indication that the donor group must be sufficiently cation-stabilizing to display dynamic character. Attempts to expand the

**Figure 3-2.** Substrate Scope for the MgI<sub>2</sub>-Catalyzed DyKAT of Cyclopropanes **1b-c** via Annulation with Aldehydes



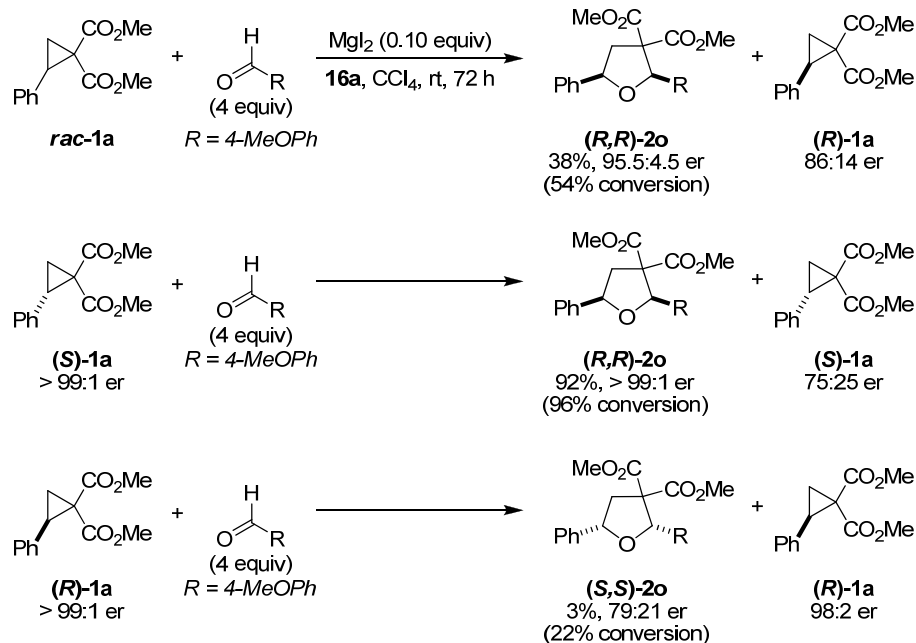
cyclopropane scope to encompass other electron-rich cyclopropanes (e.g. donor group = 2-furyl, 2-methoxyphenyl, 4-methylphenyl) were not successful. Cinnamyl and electron-rich aryl aldehyde dipolarophiles gave the highest chemical yield and enantioselection of tetrahydrofuran products (up to 92% yield, 97:3 er). Linear and  $\alpha$ -branched aliphatic aldehydes furnished products in diminished yields but maintained good levels of enantioselectivity. Electron-poor aldehydes typically gave lower yields, presumably due to their poor nucleophilicity and competing cyclopropane decomposition. These reactions afforded a complex mixture of by-products.

### 3.3.4 Stereochemical and Mechanistic Analysis

During the course of our studies, we observed that the enantiomers of phenyl-substituted cyclopropane **1a** did not readily interconvert under the optimized reaction conditions. Thus, **1a** is a substrate for a kinetic resolution. We sought to use this property of **1a** as a mechanistic probe (**Scheme 3-8**).

Reaction of *rac*-**1a** with 4-methoxybenzaldehyde produced THF (*R,R*)-**2o** in 38% yield (54% conversion) in 95.5:4.5 er. Absolute stereochemistry was determined by comparison of the optical rotation and SFC retention times to previously reported data for **2o**.<sup>11</sup> Unreacted **1a** was isolated and determined to be enriched in the (*R*)-configuration by comparison to an authentic sample<sup>29</sup> using chiral gas chromatography. Similar reactions were conducted using enantiopure samples of (*S*)- and (*R*)-**1a**. As expected from the results obtained using *rac*-**1a**, reaction with (*S*)-**1a** went to near complete conversion to (*R,R*)-**2o** in 99:1 er. Conversely, use of (*R*)-**1a** resulted in low conversion, furnishing **2o** in low yield and in the (*S,S*)-configuration.

**Scheme 3-8.** Stereochemical Analysis



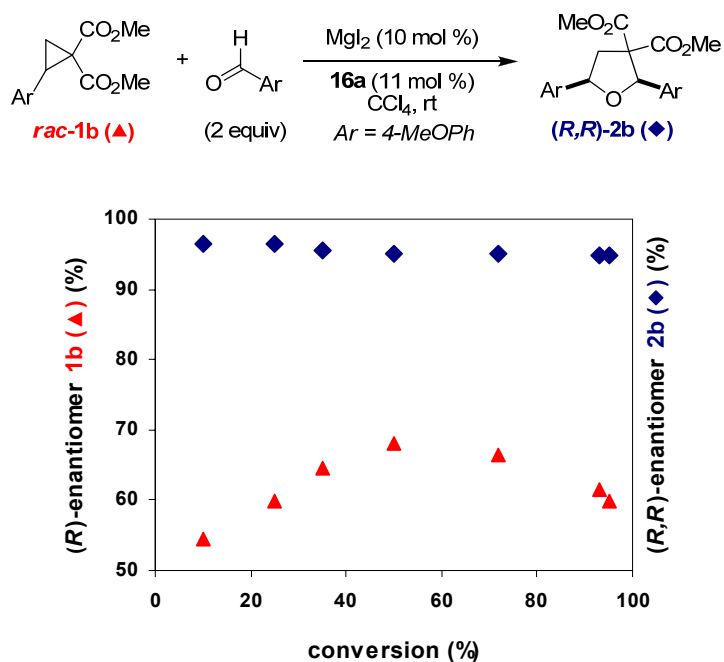
Several conclusions may be drawn from the data described in **Scheme 3-8**. Based on the relative rates of reaction for racemic and enantiopure samples of **1a**, the aldehyde dipolarophile preferentially undergoes annulation with **(*S*)-1a**. This conclusion is in agreement with the observed stereochemical configuration of tetrahydrofuran **2o** when *rac*-**1a** undergoes annulation; reaction of **(*S*)-1a** provides product **(*R,R*)-2o**, which is consistent with an enantiospecific reaction mechanism (see **Chapter One**). Annulation with **(*R*)-1a** provided evidence that a type I DyKAT is operative (**Scheme 3-1**). If the DyKAT of racemic cyclopropanes **1** proceeded through a common enantiomeric intermediate (type II DyKAT, **Scheme 3-2**), it is expected that use of enantioenriched **1** would result in the production identical product enantiomers regardless of the absolute configuration of the starting cyclopropane. While **1a** is not a perfect model due to its slow rate of racemization, it provides evidence against a type II DyKAT mechanism since its annulation with 4-



methoxybenzaldehyde does not provide **2o** with the same absolute configuration obtained with *rac*-**1d** and (*S*)-**1d**.

To obtain additional mechanistic information, we examined the annulation of **1b** with 4-methoxybenzaldehyde and monitored the enantioenrichment of **1b** (▲) and **2b** (◆) as a function of conversion (**Figure 3-3**). At 10% conversion, tetrahydrofuran **2b** was obtained in 96.5:3.5 er. There was a slow degradation of the product enantiomeric ratio until completion of the reaction, where **2b** is isolated in 94.5:5.5 er. Enrichment of **1b** remained elevated in the slower-reacting (*R*)-enantiomer for the duration of the reaction. Since the

**Figure 3-3.** Enantiomeric Analysis of **1b** and **2b** as a Function of Conversion



selectivity of a type II DyKAT is based solely on the transformation of a common enantiomeric intermediate to the product, the enantiomeric ratio of the products should be conserved throughout the duration of the reaction. In conjunction with the data in **Scheme 3-8**, the data in **Figure 3-3** further suggests that a type II DyKAT is not operative. Degradation in the product er is most likely due to mechanistic characteristics consistent with a

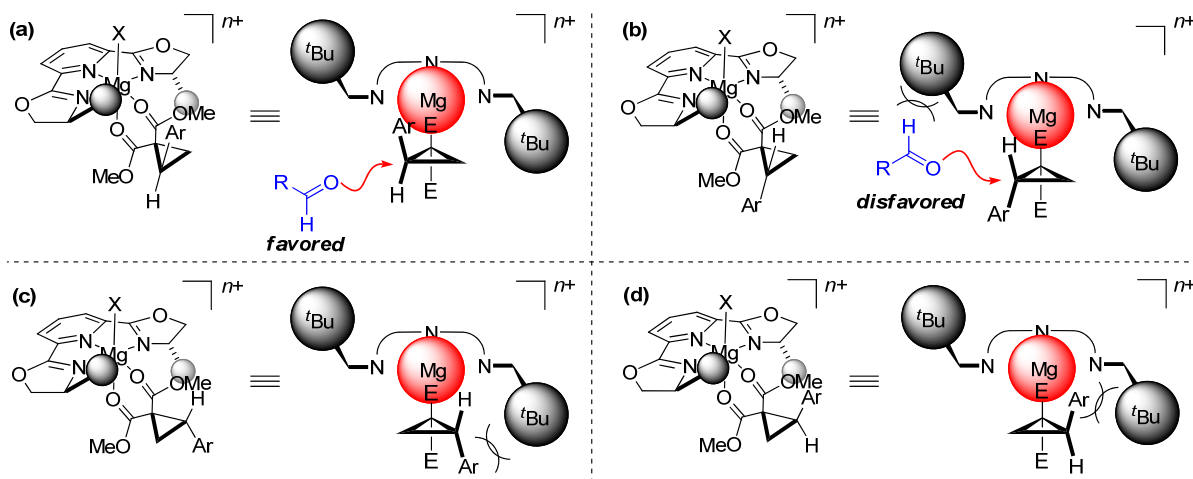
mismatched type I DyKAT, which would also account for the high enrichment of (*R*)-**1b** during the reaction (*vide supra*).

### 3.3.5 Stereochemical Model

Previous studies of Mg(II)/2,2':6',2''-terpyridine complexes have shown these structures to be dicationic and accommodate a six-coordinate octahedral geometry in the presence of coordinating solvents, as confirmed by single X-ray diffraction analysis.<sup>30</sup> We believe that this data suggests a similar octahedral orientation for the Mg(II)/pybox complex. In the absence of a coordinating solvent, the *geminal* diesters of **1** accompany two coordination sites. The final open site may contain either iodide or a neutral aldehyde ligand, resulting in a monocationic or dicationic complex, respectively.

Coordination of the racemic mixture of cyclopropane **1** with the (pybox)MgI<sub>2</sub> catalyst can result in the formation of four diastereomeric complexes (**Figure 3-4**). Complexes (**c**) and (**d**) are unlikely to form in any appreciable amounts due to substantial steric interactions between the cyclopropyl substituent and the *tert*-butyl group of the oxazoline. Nucleophilic attack by the aldehyde would also be blocked by the *tert*-butyl group. Conversely,

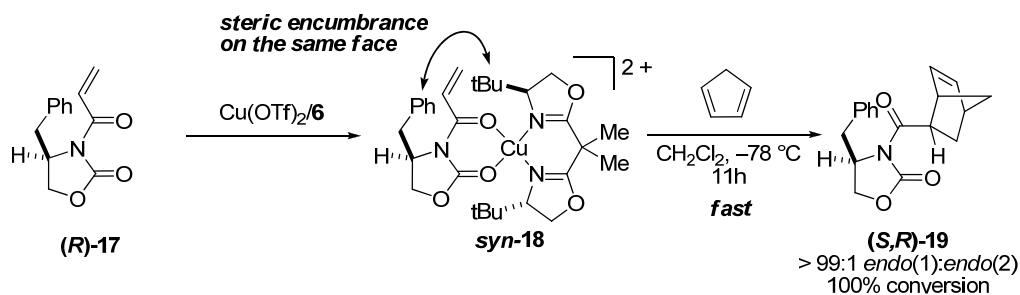
**Figure 3-4.** Hypothetical Model for the Observed Stereochemistry



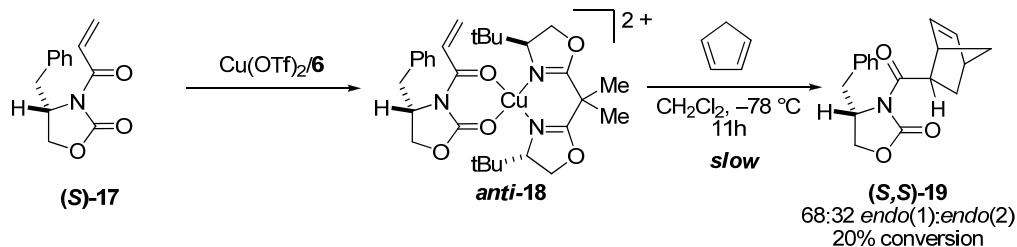
complexes **(a)** and **(b)** experience much less steric crowding. Nucleophilic attack by an aldehyde on complex **(a)** would yield tetrahydrofuran **(R,R)-2**, consistent with the observed stereochemical outcomes described in **Figure 3-3**. While **(a)** appears to be more sterically congested than **(b)**, it does provide a clear path for nucleophilic attack by the aldehyde. A similar phenomenon was recently reported by Evans where enantiomeric imides **(R)**- and **(S)**-**17** undergo Cu(OTf)<sub>2</sub>/6-catalyzed Diels-Alder reactions at different rates.<sup>31</sup> It was observed that reaction of **(R)**-**17** is rapid even though the benzyl group of the imide experiences a high-energy steric interaction with the *tert*-butyl of the oxazoline ligand in complex **syn-18** (**Scheme 3-9**, top). The enhanced reactivity is caused by a synergistic blocking of the *Si* face by both the imide and ligand substituents, providing unobstructed access of the cyclopentadiene to the *Re* face. While complexation of **(S)**-**17** with Cu(OTf)<sub>2</sub>/6 avoids the unfavorable ligand/substrate interactions in **anti-18**, the approach of cyclopentadiene is hindered from both the *Si* and *Re* faces, resulting in a slow reaction rate.

**Scheme 3-9.** Evans Precedent for the Preference of a Destabilized Reactive Intermediate

• **Matched case for a square-planar Cu center**



• **Mismatched case for a square-planar Cu center**



A mechanism proceeding through complex **(b)** would suffer from an unfavorable steric interaction between the aldehyde and the oxazoline *tert*-butyl group. The observations reported by Evans suggest that while complex **(a)** may be more sterically congested, the ease of nucleophilic attack by the aldehyde on this complex allows for this transformation to proceed. Additionally, computational studies on a related system suggest that the angle of aldehyde nucleophilic attack is important for annulation to occur, possibly reinforcing the preference for the aldehyde to react with complex **(a)**.<sup>32</sup> Further experimentation will be necessary to adjust and confirm this working stereochemical hypothesis and determine the nature of cyclopropane enantiomer interconversion.

### 3.4 Conclusion

In summary, a simple protocol for the preparation of enantioenriched tetrahydrofuran derivatives through a dynamic kinetic asymmetric (3 + 2) annulation of racemic malonate-derived D–A cyclopropanes and aldehydes has been developed. A variety of cyclopropanes bearing electron-rich donor groups undergo annulation with aryl, cinnamyl, and aliphatic aldehydes to afford products in good yield, dr and er. Stereochemical data obtained through use of cyclopropane **1a** provided insight into reaction kinetics and allowed for the development of a working mechanistic hypothesis. Further experimentation will be necessary to fully elucidate the mechanistic details of this transformation.

### 3.5 Experimental

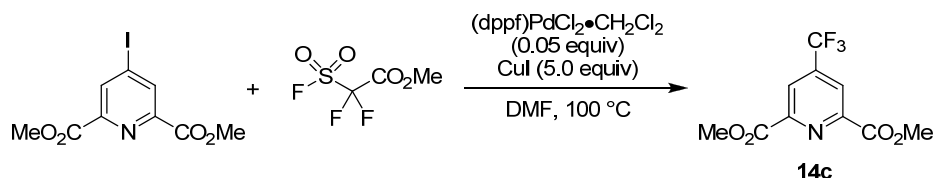
**Methods.** Infrared (IR) spectra were obtained using a JASCO FT/IR 460-plus spectrometer. Proton and carbon magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were recorded on a

Bruker model DRX 400 ( $^1\text{H}$  NMR at 400 MHz and  $^{13}\text{C}$  NMR at 100 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm, DMSO at 2.54 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm, DMSO at 40.45 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Spectra may have been obtained from racemic samples, and therefore diastereomeric ratios may vary from values reported in tables. Combustion analyses were performed by Atlantic Microlab Inc. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 200  $\mu\text{m}$  silica G TLC plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials.** All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Carbon tetrachloride was purified by distillation from phosphorous pentoxide under  $\text{N}_2$  prior to use. *N,N*-Dimethyl formamide was distilled from phosphorous pentoxide under reduced pressure prior to use. Acetonitrile was distilled from  $\text{CaH}_2$  under  $\text{N}_2$  prior to use. Methylene chloride was dried by passage through a column of activated alumina under  $\text{N}_2$  prior to use. Cyclopropanes **1a-d** were prepared according to the method of Wood.<sup>33</sup> Cyclopropanes (**R**)- and (**S**)-**1a** were prepared according

to the method of Pohlhaus.<sup>12</sup> Benzaldehyde, *p*-anisaldehyde, 2-methylbenzaldehyde, 2-thiophenecarboxaldehyde, and *trans*-cinnamaldehyde were purified by the following procedure: The neat aldehydes were washed sequentially with a 1 M sodium hydroxide solution and a saturated aqueous sodium bicarbonate solution, dried with magnesium sulfate, and distilled under reduced pressure. 4-Chlorobenzaldehyde was sublimed under reduced pressure. Isobutyraldehyde and *n*-hexanal were dried over CaSO<sub>4</sub> and distilled under N<sub>2</sub> prior to use. Dimethyl 4-iodopyridine-2,6-dicarboxylate, dimethyl 4-chloropyridine-2,6-dicarboxylate (**14a**), and dimethyl 4-bromopyridine-2,6-dicarboxylate (**14b**) were prepared from chelidamic acid according to the methods of Chessa,<sup>26</sup> Goto,<sup>24</sup> and Rotello,<sup>25</sup> respectively. *tert*-Leucinol was prepared from *tert*-leucine according to the method of Meyers.<sup>34</sup> Methyl-2,2-difluoro-2-(fluorosulfonyl)acetate was purchased from Oakwood Products. Pd(OAc)<sub>2</sub> and (dppf)PdCl<sub>2</sub>•CH<sub>2</sub>Cl<sub>2</sub> was purchased from Strem Chemical. Mesitylboronic acid and *tert*-leucine were obtained from TCI America. All other reagents were obtained from Acros or Sigma-Aldrich and used without further purification.

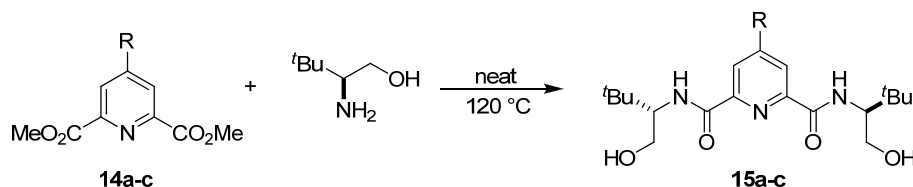
#### Preparation of dimethyl 4-(trifluoromethyl)pyridine-2,6-dicarboxylate (**14c**):<sup>27</sup>



In an inert atmosphere glove box, a flame-dried three-necked 250 mL round-bottomed flask containing a magnetic stir bar was charged with dimethyl 4-iodopyridine-2,6-dicarboxylate<sup>26</sup> (1.22 g, 3.8 mmol, 1.0 equiv), CuI (4.24 g, 22.3 g, 5.9 equiv), and (dppf)PdCl<sub>2</sub>•CH<sub>2</sub>Cl<sub>2</sub> (0.16 g, 0.19 mmol, 0.05 equiv). The flask was removed from the glove box, affixed with a reflux condenser, and placed under N<sub>2</sub>. To this flask was added DMF (60 mL) followed by a

solution of methyl-2,2-difluoro-2-(fluorosulfonyl)acetate (4.27 g, 22.3 mmol, 5.9 equiv) in DMF (14 mL) via cannula. The resulting mixture was heated to 100 °C and was allowed to proceed for 24 h under N<sub>2</sub>. The reaction was cooled to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (120 mL), and filtered through celite to afford a dark brown solution which was subsequently washed with H<sub>2</sub>O (2 x 200 mL), 50% saturated aqueous NaCl solution (300 mL), and brine (300 mL). The solution was dried over NaSO<sub>4</sub>, filtered, and was concentrated *in vacuo* and purified by flash chromatography (30% EtOAc/hexanes) to provide pure **14c** (0.79 g, 3.00 mmol, 79% yield, not optimized) as a white solid. Analytical data for **14c**: mp 122-124 °C; IR (thin film, cm<sup>-1</sup>) 3082, 3009, 2959, 1726, 1448, 1415, 1381, 1281, 1146, 984, 971, 937, 785, 634; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.52 (s, 2H), 4.07 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.8, 149.6, 141.0 (q, *J* = 35.1 Hz), 123.6 (d, *J* = 3.1 Hz), 121.9 (q, *J* = 273.6 Hz), 53.4; TLC (30% EtOAc/hexanes) R<sub>f</sub> 0.20; LRMS (ESI) calcd. for C<sub>10</sub>H<sub>8</sub>F<sub>3</sub>NO<sub>4</sub>+H: 264.0, Found: 264.0.

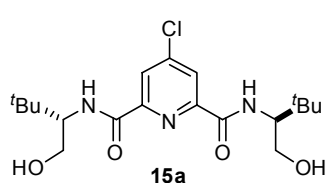
**General Procedure A for the synthesis of *N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-pyridine-2,6-dicarboxamides **15a-c**:**



To a 20-mL scintillation vial containing a magnetic stir bar was added the 4-substituted dimethyl pyridine-2,6-carboxylate (**14**, 1.0 equiv) and *tert*-leucinol (2.0-2.2 equiv). The vial was sealed with a screw cap and the neat mixture was heated to 120 °C in an oil bath until a solid formed (approximately 2 h) at which point the cap was removed and the vial was placed under high-vacuum (< 0.10 mm Hg) for 2 h at 120 °C. The resulting amorphous white solids

are typically of sufficient purity for subsequent transformations. Analytically pure samples can be obtained by heating the unpurified product to 120 °C, dissolving in a minimal amount of boiling EtOAc and pouring into a large excess of hexanes (25 °C). The product can then be isolated by Büchner filtration and dried *in vacuo*.

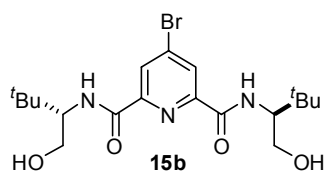
**4-Chloro-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (15a):**



The title compound was prepared according to General Procedure

A using dimethyl 4-chloropyridine-2,6-dicarboxylate (**14a**, 0.89 g, 3.88 mmol, 1 equiv) and *tert*-leucinol (1.0 g, 8.53 mmol, 2.2 equiv). After stirring for 2 h at 120 °C and placement under high-vac for 2 h, 1.55 g (3.88 mmol, 100% yield) of the title compound was obtained as an amorphous white solid of sufficient purity for subsequent transformations. Analytical data for **15a**: mp 119-122 °C; IR (thin film, cm<sup>-1</sup>) 3380, 2963, 1668, 1525, 1477, 1402, 1368, 1339, 1299, 1275, 1232, 1090, 1055, 894, 772, 680; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.29 (s, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 3.96 (m, 4H), 3.75 (dd, *J* = 11.2, 7.2 Hz, 2H), 1.04 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.1, 150.2, 148.1, 125.4, 62.9, 60.0, 34.0, 27.0; HRMS (ESI) calcd. For C<sub>19</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>4</sub>+H 400.2003, Found: 400.1997; [α]<sub>D</sub><sup>29</sup> -9.3 (*c* = 0.40, CHCl<sub>3</sub>).

**4-Bromo-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (15b):**



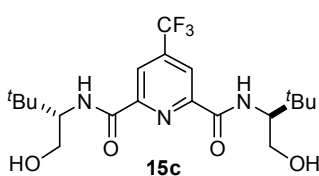
The title compound was prepared according to General Procedure

A using dimethyl 4-bromopyridine-2,6-dicarboxylate (**14b**, 1.0 g, 3.65 mmol, 1 equiv) and *tert*-leucinol (0.86 g, 7.3 mmol, 2 equiv). After stirring for 2 h at 120 °C and placement under high-vac, the resulting amorphous white



solid was dissolved in EtOAc (15 mL) at 120 °C and was poured into hexanes (50 mL, 25 °C). The solution was allowed to sit for 4 h as a precipitate slowly formed, which was then isolated by Büchner filtration and dried *in vacuo* to afford 1.38 g (3.10 mmol, 85% yield, not optimized) of the title compound as a fine white powder. Analytical data for **15b**: mp 162-164 °C; IR (thin film, cm<sup>-1</sup>) 3380, 3053, 2965, 1682, 1518, 1399, 1368, 1338, 1233, 1091, 1055, 893, 778, 760, 715, 679; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.42 (s, 2H), 7.99 (d, *J* = 9.20 Hz, 2H), 3.96 (m, 4H), 3.74 (dd, *J* = 11.2, 7.20 Hz, 2H), 2.78 (bs, 2H), 1.03 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.1, 149.8, 136.5, 128.5, 62.9, 60.0, 34.0, 27.0; LRMS (ESI) calcd. for C<sub>19</sub>H<sub>30</sub>BrN<sub>3</sub>O<sub>4</sub>+H: 444.1, Found: 444.1; [α]<sub>D</sub><sup>28</sup> -11.7 (*c* = 0.255, CHCl<sub>3</sub>).

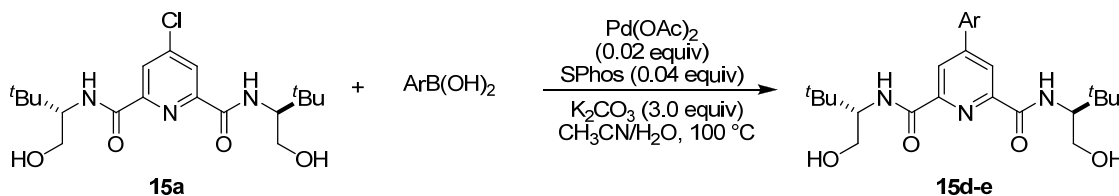
**4-(Trifluoromethyl)-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (15c):**



The title compound was prepared according to General Procedure A using dimethyl 4-(trifluoromethyl)pyridine-2,6-dicarboxylate (**14c**, 1.9 mmol, 2.0 equiv). After stirring for 1 h at 120 °C and placement under high-vac, the resulting amorphous white solid was dissolved in EtOAc (15 mL) at 120 °C and was poured into room temperature hexanes (30 mL). The solution was allowed to sit for 4 h as a precipitate slowly formed which was then isolated by Büchner filtration and dried *in vacuo* to afford 0.268 g (1.14 mmol, 60% yield, not optimized) of the title compound as a fine white powder. Analytical data for **15c**: mp 178-180 °C; IR (thin film, cm<sup>-1</sup>) 3322, 3072, 2966, 1666, 1539, 1477, 1435, 1399, 1366, 1334, 1285, 1220, 1179, 1141, 1096, 1046, 1023, 999, 932, 903, 628; <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.45 (d, *J* = 9.6 Hz, 2H), 8.42 (s, 2H), 4.69 (t, *J* = 5.6 Hz, 2H), 3.87 (m, 2H), 3.72 (m, 2H), 3.61 (m, 2H), 1.01 (s, 18H); <sup>13</sup>C NMR (100 MHz, DMSO) δ 163.2, 152.3, 140.7 (d, *J* = 30.2 Hz), 123.3 (q,

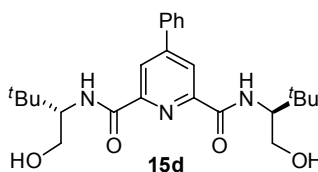
$J = 273.6$  Hz), 120.6 (d,  $J = 3.4$  Hz), 61.1, 60.3, 35.0, 27.7; **LRMS** (ESI) calcd. for  $C_{20}H_{30}F_3N_3O_4 + H$ : 434.2, Found: 434.1;  $[\alpha]_D^{28} +6.32$  ( $c = 0.27$ , MeOH).

**General Procedure B for the synthesis of 4-aryl  $N^2,N^6$ -bis((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamides **15d-e**:**<sup>28</sup>



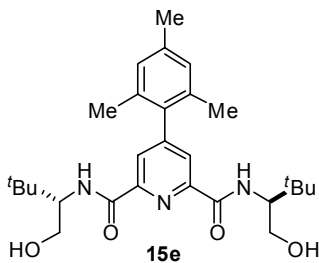
In an inert atmosphere glove box, a flame-dried 20-mL scintillation vial containing a magnetic stir bar was charged with 4-chloro- $N^2,N^6$ -bis((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15a**, 1.0 equiv), the boronic acid (1.2 equiv),  $Pd(OAc)_2$  (0.02 equiv), SPhos (0.04 equiv), and  $K_2CO_3$  (3.0 equiv). The vial was fitted with a rubber septum and was removed from the box and placed under  $N_2$ . To this vial was added acetonitrile and  $H_2O$  (degassed by sonication under high-vacuum for two minutes). The rubber septum was replaced with a screw cap and the reaction was heated to  $100\text{ }^\circ C$  in an oil bath for 24 h and was then allowed to cool to room temperature. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were dried over magnesium sulfate, filtered through a 1-cm Monstr-Pette plug of celite, and concentrated *in vacuo*. The resulting foam was purified by flash chromatography with the indicated solvent system.

***N*<sup>2</sup>,*N*<sup>6</sup>-Bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-4-phenylpyridine-2,6-dicarboxamide (15d):**



The title compound was prepared according to General Procedure B with 4-chloro-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15a**, 0.25 g, 0.625 mmol), phenylboronic acid (0.091 g, 0.75 mmol), Pd(OAc)<sub>2</sub> (0.0028 g, 0.0125 mmol), SPhos (0.010 g, 0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (0.260 g, 1.88 mmol), acetonitrile (1.0 mL), and H<sub>2</sub>O (0.625 mL). After stirring for 24 h and work up, the residue was purified by flash chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.246 g (0.556 mmol, 89% yield, not optimized) of the title compound as a white powder. Analytical data for **15d**: mp 108-111 °C; IR (thin film, cm<sup>-1</sup>) 3398, 3060, 2965, 2872, 1670, 1605, 1531, 1368, 1052, 1002, 906, 765, 738, 696, 626; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.53 (s, 2H), 8.12 (d, *J* = 9.2 Hz, 2H), 7.73 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.50 (m, 3H), 3.99 (m, 4H), 3.75 (m, 2H), 2.96 (br t, *J* = 4.8 Hz, 2H), 1.06 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 164.4, 151.9, 149.3, 136.5, 130.0, 129.3, 127.2, 122.7, 63.2, 60.1, 33.0, 27.0; LRMS (ESI) calcd. for C<sub>25</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>+Na: 464.3, Found: 464.3; [α]<sub>D</sub><sup>29</sup> -15.6 (*c* = 0.29, CHCl<sub>3</sub>).

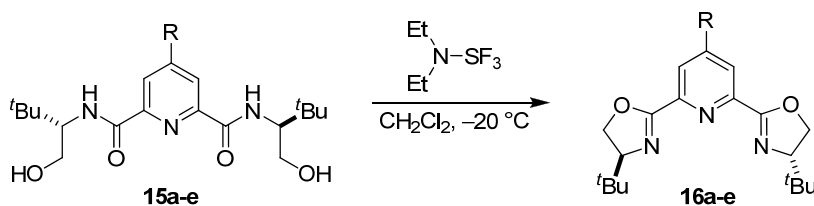
***N*<sup>2</sup>,*N*<sup>6</sup>-Bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-4-mesityl pyridine-2,6-dicarboxamide (15e):**



The title compound was prepared according to General Procedure B with 4-chloro-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15a**, 0.25 g, 0.625 mmol), phenylboronic acid (0.091 g, 0.75 mmol), Pd(OAc)<sub>2</sub> (0.0028 g, 0.0125 mmol), SPhos (0.010 g, 0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (0.260 g, 1.88 mmol), acetonitrile (1.0 mL), and H<sub>2</sub>O (0.625 mL). After stirring for 24 h and work up, the residue was purified by

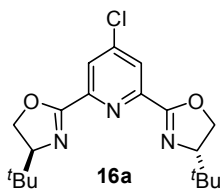
flash chromatography (50% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.0195 g (0.406 mmol, 65% yield, not optimized) of the title compound as a white powder. Analytical data for **15e**: mp 128-131 °C; IR (thin film, cm<sup>-1</sup>) 3399, 2964, 1671, 1613, 1531, 1478, 1401, 1368, 1232, 1050, 854; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.18 (s, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 2H), 4.00 (m, 4H), 3.76 (m, 2H), 2.68 (bs, 2H), 2.33 (s, 3H), 1.96 (s, 6H), 1.08 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 164.4, 153.9, 148.9, 138.1, 135.0, 134.8, 128.5, 126.4, 63.4, 60.0, 33.9, 27.1, 21.0, 20.6; TLC (50% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) R<sub>f</sub> 0.26; LRMS (ESI) calcd. for C<sub>28</sub>H<sub>41</sub>N<sub>3</sub>O<sub>4</sub>+Na: 506.3, Found: 506.3; [α]<sub>D</sub><sup>28</sup> -5.3 (*c* = 0.24, CHCl<sub>3</sub>).

**General Procedure C for the synthesis of 4-substituted-*t*Bu-pybox ligands 16a-e:**



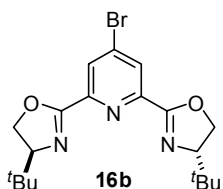
A flame-dried round-bottomed flask containing a magnetic stir bar under N<sub>2</sub> was charged with the appropriate 4-substituted-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15**, 1.0 equiv) and CH<sub>2</sub>Cl<sub>2</sub>. The resulting solution was cooled to -20 °C in a mechanical cooling bath and was charged with diethylaminosulfur trifluoride (DAST, 3.0 equiv) by dropwise addition over 5 min. The reaction was allowed to proceed under N<sub>2</sub> for 24 h at -20 °C, at which time a solution of 3.0 M aqueous NH<sub>4</sub>OH was added and reaction mixture was removed from the bath and diluted with H<sub>2</sub>O. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting yellow solid was purified by recrystallization from hot methanol.

**(4*S*,4'*S*)-2,2'-(4-Chloropyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16a):**



The title compound was prepared according to General Procedure C using 4-chloro-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15a**, 1.0 g, 2.5 mmol), DAST (1.21 g, 7.5 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (16 mL). After stirring for 24 h at −20 °C, the reaction was worked up with 3.0 M aqueous NH<sub>4</sub>OH (2.75 mL) and H<sub>2</sub>O (55 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and the combined organics were dried and concentrated. Recrystallization from hot methanol provided 0.392 g (1.08 mmol, 43% yield, not optimized) of the title compound as a white solid. Analytical data for this compound has been previously reported.<sup>35</sup>

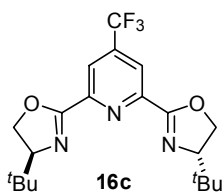
**(4*S*,4'*S*)-2,2'-(4-Bromopyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16b):**



The title compound was prepared according to General Procedure C using 4-bromo-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15b**, 0.606 g, 1.36 mmol), DAST (0.66 g, 4.1 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (8.7 mL). After stirring for 24 h at −20 °C, the reaction was worked up with 3.0 M aqueous NH<sub>4</sub>OH (1.5 mL) and H<sub>2</sub>O (30 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL) and the combined organics were dried and concentrated. Recrystallization from hot methanol provided 0.189 g (0.462 mmol, 34% yield, not optimized) of the title compound as a white solid. Analytical data for **16b**: mp 179-181 °C; IR (thin film, cm<sup>−1</sup>) 3087, 2957, 2905, 2869, 1644, 1560, 1477, 1377, 1362, 1329, 1297, 1209, 1196, 1123, 978, 937, 886; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.41 (s, 2H), 4.47 (dd, *J* = 10.0, 8.8 Hz, 2H), 4.32 (t, *J* = 8.8 Hz, 2H), 4.11 (dd, *J* = 10.4, 8.8 Hz, 2H), 0.96 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.3,

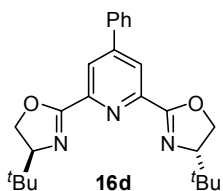
147.9, 133.5, 128.9, 76.5, 69.7, 34.0, 26.0; **LRMS** (ESI) calcd. for C<sub>19</sub>H<sub>26</sub>BrN<sub>3</sub>O<sub>2</sub>+H: 408.1, Found: 408.1; [ $\alpha$ ]<sub>D</sub><sup>28</sup> -121.1 (*c* = 0.22, CHCl<sub>3</sub>).

**(4*S*,4'*S*)-2,2'-(4-(Trifluoromethyl)pyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16c):**



The title compound was prepared according to General Procedure C using 4-trifluoromethyl-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15c**, 0.202 g, 0.47 mmol), DAST (0.225 g, 1.4 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL). After stirring for 24 h at -20 °C, the reaction was quenched with 3.0 M aq NH<sub>4</sub>OH (0.5 mL) and H<sub>2</sub>O (10 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL) and the combined organic extracts were dried and concentrated. Recrystallization from hot methanol provided 0.102 g (0.259 mmol, 55% yield, not optimized) of the title compound as a white solid. Analytical data for **16c**: **mp** 212-214 °C; **IR** (thin film, cm<sup>-1</sup>) 2960, 2907, 2871, 1648, 1574, 1479, 1291, 1181, 1148, 980, 963, 932, 909, 821, 690; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (s, 2H), 4.52 (t, *J* = 9.6 Hz, 2H), 4.35 (t, *J* = 8.8 Hz, 2H), 4.14 (t, *J* = 9.2 Hz, 2H), 0.96 (s, 18H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.3, 148.4, 139.8 (d, *J* = 139.2 Hz), 121.5 (d, *J* = 274.4), 121.4 (d, *J* = 3.4 Hz), 76.6, 69.9, 34.0, 26.0; **LRMS** (ESI) calcd. for C<sub>20</sub>H<sub>26</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>+H: 398.2, Found: 398.2; [ $\alpha$ ]<sub>D</sub><sup>28</sup> -155.3 (*c* = 0.20, CHCl<sub>3</sub>).

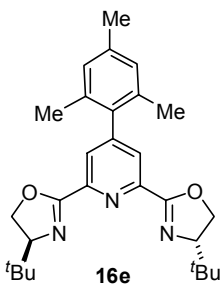
**(4*S*,4'*S*)-2,2'-(4-Phenylpyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16d):**



The title compound was prepared according to General Procedure C using 4-phenyl-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15d**, 0.200 g, 0.453 mmol), DAST (0.219 g, 1.36 mmol),

and CH<sub>2</sub>Cl<sub>2</sub> (2.8 mL). After stirring for 24 h at –20 °C, the reaction was worked up with 3.0 M aqueous NH<sub>4</sub>OH (0.5 mL) and H<sub>2</sub>O (10 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL) and the combined organics were dried and concentrated. Recrystallization from hot methanol provided 0.107 g (0.263 mmol, 58% yield, not optimized) of the title compound as a white solid. Analytical data for **16d**: mp 280 °C (dec.); IR (thin film, cm<sup>-1</sup>) 2953, 2903, 2867, 1647, 1608, 1550, 1497, 1479, 1403, 1361, 1331, 1299, 1242, 1109, 1059, 978, 936; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.48 (s, 2H), 7.77 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.48 (m, 3H), 4.50 (dd, *J* = 10.0, 8.8 Hz, 2H), 4.35 (t, *J* = 8.4 Hz, 2H), 4.13 (dd, *J* = 10.0, 8.4 Hz, 2H), 0.97 (s, 18H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.4, 149.9, 137.0, 129.6, 129.1, 127.3, 123.6, 76.5, 69.5, 34.0, 26.0; LRMS (ESI) calcd for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>+H: 406.3, Found: 406.3; [α]<sub>D</sub><sup>28</sup> –69.5 (c = 0.29, CHCl<sub>3</sub>).

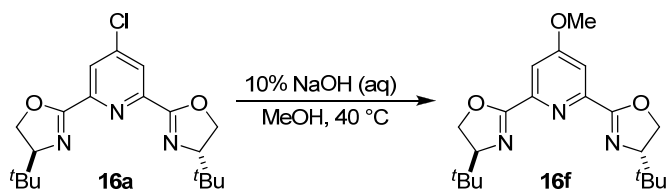
**(4*S*,4'*S*)-2,2'-(4-Mesitylpyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16e):**



The title compound was prepared according to General Procedure C using 4-mesityl-*N*<sup>2</sup>,*N*<sup>6</sup>-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (**15e**, 0.165 g, 0.341 mmol), DAST (0.164 g, 1.02 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (2.1 mL). After stirring for 24 h at –20 °C, the reaction was quenched with 3.0 M aq NH<sub>4</sub>OH (0.4 mL) and H<sub>2</sub>O (7 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL) and the combined organic extracts were dried and concentrated. Recrystallization from hot methanol provided 0.055 g (0.123 mmol, 36% yield, not optimized) of the title compound as a white solid. Analytical data for **16e**: mp 265 °C (dec.); IR (thin film, cm<sup>-1</sup>) 3046, 2957, 2869, 1650, 1613, 1542, 1477, 1397, 1363, 1296, 1237, 1208, 1113, 1054, 1030, 983, 939, 851, 780, 620, 560; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ

8.04 (s, 2H), 6.94 (s, 2H), 4.48 (t,  $J = 9.2$  Hz, 2H), 4.32 (t,  $J = 8.8$  Hz, 2H), 4.11 (dd,  $J = 10.0, 8.4$  Hz, 2H), 2.32 (s, 3H), 1.99 (s, 6H), 0.95 (s, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2, 151.2, 147.3, 137.9, 135.1, 135.0, 128.4, 126.8, 76.4, 69.5, 34.0, 25.9, 21.0, 20.6; LRMS (ESI) calcd. for  $\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_2 + \text{H}$ : 448.3, Found: 448.3;  $[\alpha]_{\text{D}}^{28} -57.7$  ( $c = 0.20$ ,  $\text{CHCl}_3$ ).

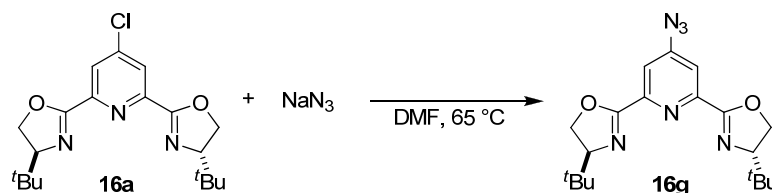
**Preparation of (4*S*,4'*S*)-2,2'-(4-methoxypyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16f):**



A 1-dram screw cap vial containing a magnetic stir bar was charged with (4*S*,4'*S*)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (**16a**, 0.020 g, 0.055 mmol), MeOH (0.50 mL), and 10% aqueous NaOH (0.30 mL). The vial was sealed with a PTFE-lined cap and heated to 40 °C. After stirring for 14 h, the reaction was allowed to cool to room temperature and was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined  $\text{CH}_2\text{Cl}_2$  extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 0.019 g (0.052 mmol, 95% yield) of the title compound as a white solid. Analytical data for **16f**: mp 138-141 °C; IR (thin film,  $\text{cm}^{-1}$ ) 2956, 2869, 1651, 1598, 1566, 1478, 1398, 1362, 1300, 1210, 1092, 1045, 981, 937, 865;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (s, 2H), 4.47 (dd,  $J = 10.0, 9.2$  Hz, 2H), 4.32 (t,  $J = 8.8$  Hz, 2H), 4.11 (dd,  $J = 10.4, 8.8$  Hz, 2H), 3.97 (s, 3H), 0.99 (s, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5, 162.3, 148.4, 111.8, 76.4, 69.5, 55.8, 34.0, 26.0; LRMS (ESI) calcd. for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_3 + \text{H}$ : 360.2, Found: 360.2;  $[\alpha]_{\text{D}}^{28} -74.0$  ( $c = 0.25$ ,  $\text{CHCl}_3$ ).

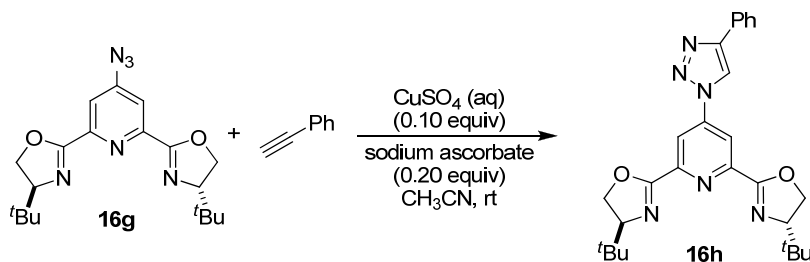


**Preparation of (4*S*,4'*S*)-2,2'-(4-Azidopyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16g):**



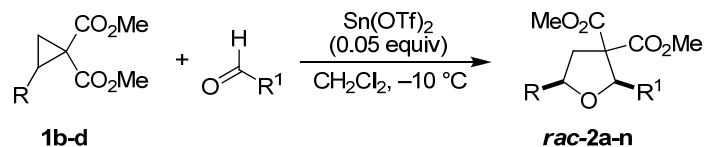
A 20-mL scintillation vial containing a magnetic stir bar was charged with (4*S*,4'*S*)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (**16a**, 0.10 g, 0.275 mmol, 1 equiv) and DMF (1.75 mL). To this suspension was added  $\text{NaN}_3$  (0.179 g, 2.75 mmol, 10 equiv) and the vial was capped and heated to 65 °C for 3 h. The reaction mixture was allowed to cool to room temperature, and was then concentrated *in vacuo*. The resulting yellow residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (12 mL) and was filtered through a 1-cm Monstr-Pette plug of celite. The resulting yellow solution was concentrated *in vacuo* to afford 0.100 g (0.275 mmol, 100% yield) of the title compound as a yellow solid. Analytical data for **16g**: mp 169-171 °C; IR (thin film,  $\text{cm}^{-1}$ ) 2960, 2907, 2871, 2128, 1647, 1584, 1563, 1480, 1401, 1365, 1291, 1243, 1138, 1092, 970, 932, 870, 729, 702;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (s, 2H), 4.47 (t,  $J = 9.2$  Hz, 2H), 4.31 (t,  $J = 8.4$  Hz, 2H), 4.10 (t,  $J = 8.8$  Hz, 2H), 0.95 (s, 18H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7, 150.2, 148.6, 115.8, 76.4, 69.7, 33.9, 25.9; LRMS (ESI) calcd. for  $\text{C}_{19}\text{H}_{26}\text{N}_6\text{O}_2 + \text{H}$ : 371.2, Found: 371.2;  $[\alpha]_{\text{D}}^{28} -104.8$  ( $c = 0.395$ ,  $\text{CHCl}_3$ ).

**Preparation of (4*S*,4'*S*)-2,2'-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (16h):**



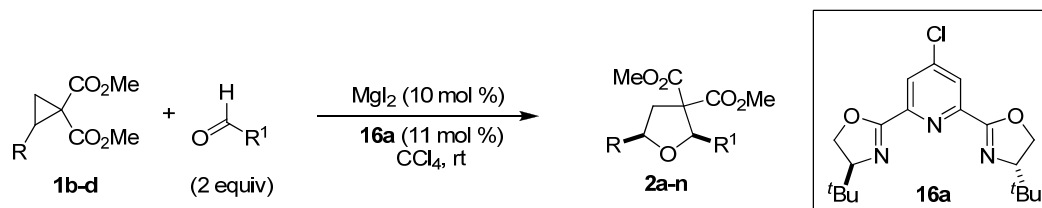
A 1-dram screw cap vial was charged with (4*S*,4'*S*)-2,2'-(4-azidopyridine-2,6-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) (**16g**, 0.050 g, 0.135 mmol, 1.0 equiv), CH<sub>3</sub>CN (0.50 mL), phenylacetylene (0.0137 g, 0.135 mmol, 1.0 equiv), CuSO<sub>4</sub> (0.0034 g, 0.014 mmol, 0.10 equiv) in H<sub>2</sub>O (0.050 mL), and sodium ascorbate (0.0053 g, 0.027 mmol, 0.20 equiv). The vial was capped and held at room temperature for 21 h, at which time the solvent was removed *in vacuo*. The resulting dark purple solid was suspended in H<sub>2</sub>O and was isolated by Büchner filtration. Recrystallization from hot MeOH provided 0.020 g (0.042 mmol, 31% yield, not optimized) of the title compound as a white solid. Analytical data for **16h**: **mp** 260 °C (dec.); **IR** (thin film, cm<sup>-1</sup>) 3129, 3103, 3052, 2959, 2905, 2868, 2359, 1649, 1604, 1577, 1478, 1448, 1413, 1363, 1243, 1106, 1039, 936, 766, 694; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.70 (s, 2H), 8.48 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 4.53 (t, *J* = 9.2 Hz, 2H), 4.37 (t, *J* = 8.40 Hz, 2H), 4.17 (t, *J* = 9.60 Hz, 2H), 0.99 (s, 18H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 161.6, 149.3, 149.2, 144.1, 129.5, 129.0, 128.9, 126.1, 117.0, 115.3, 76.6, 69.9, 34.0, 26.0; **LRMS** (ESI) calcd. for C<sub>27</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub>+H: 473.3, Found: 473.3; [α]<sub>D</sub><sup>28</sup> -45.8 (*c* = 0.21, CHCl<sub>3</sub>).

#### General Procedure D for the preparation of *rac*-tetrahydrofurans 2a-n:



In an inert atmosphere glove box, a 3.5-mL shell vial (vial #1) containing a magnetic stir bar was charged with  $\text{Sn}(\text{OTf})_2$  (0.015 mmol, 0.05 equiv). A second 3.5-mL shell vial (vial #2) was charged with the cyclopropane (0.303 mmol, 1.0 equiv), aldehyde (0.909 mmol, 3.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (0.50 mL). The vials were removed from the box, placed under  $\text{N}_2$ , and cooled to  $-10^\circ\text{C}$ . The contents of vial #2 were then transferred to vial #1 via syringe. The reaction was allowed to proceed until disappearance of the starting material was confirmed by TLC analysis using  $\text{CH}_2\text{Cl}_2$  or 25% EtOAc/hexanes as the mobile phase. Upon completion, the contents of the vial were passed through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and was concentrated to give the crude products as colorless oils, which were then purified by flash chromatography using the solvent system indicated in General Procedure E.

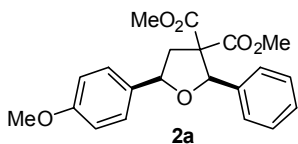
#### General Procedure E for the enantioselective preparation tetrahydrofurans 2a-n:



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with  $\text{MgI}_2$  (0.10-0.20 equiv), 4-Cl-*t*Bu-pybox (**16a**, 0.11-0.22 equiv), and  $\text{CCl}_4$  (0.20-0.40 mL). The vial was sealed with PTFE-lined cap and was allowed to stir until ligand coordination is complete as evidenced by formation of a yellow complex (approx. 30 min).

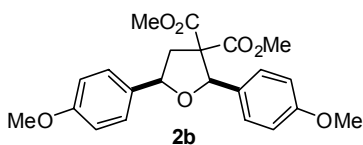
To this complex, a solution of the cyclopropane (0.151 mmol, 1.0 equiv) and aldehyde (2.0-4.0 equiv) in CCl<sub>4</sub> (2.60-2.80 mL) was added. The vial was recapped, removed from the glove box, and was allowed to proceed until the disappearance of the starting material was confirmed by TLC analysis using CH<sub>2</sub>Cl<sub>2</sub> or 25% EtOAc/hexanes as the mobile phase. Upon completion, the contents of the vial were passed through a 1-inch Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and concentrated *in vacuo*. The resulting product was then purified by flash chromatography with the indicated solvent system.

**(2*R*,5*R*)-Dimethyl 5-(4-methoxyphenyl)-2-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (2a):**



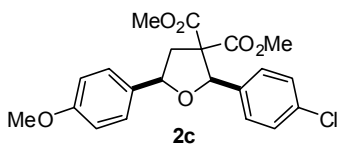
The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and benzaldehyde (0.032 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 26 h, the reaction was worked up. The product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2a** (0.0415 g, 0.112 mmol, 74% yield) of the title compound as a white solid as a single diastereomer in 96.5:3.5 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 4.0 min, *t<sub>r</sub>*-minor 4.9 min). Analytical data for this compound has been previously reported.<sup>12</sup> [ $\alpha$ ]<sub>D</sub><sup>29</sup> +83.5 (*c* = 0.33, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,5*R*)-Dimethyl 2,5-bis(4-methoxyphenyl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2b**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (0.042 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 7 h, the reaction was worked up. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2b** (0.0554 g, 0.138 mmol, 92% yield) as a white solid as a single diastereomer in 95:5 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 5.2 min, *t<sub>r</sub>*-minor 6.5 min). Analytical data has been previously reported.<sup>12</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +67.1 (*c* = 0.50, CH<sub>2</sub>Cl<sub>2</sub>).

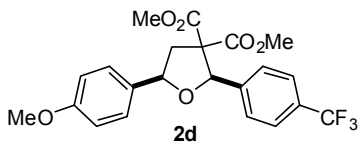
**(2*R*,5*R*)-Dimethyl 2-(4-chlorophenyl)-5-(4-methoxyphenyl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2c**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (0.064 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 25 h, the reaction was worked up. The product was purified by flash chromatography (15% EtOAc/hexanes) to pure **2c** (0.0418 g, 0.103 mmol, 68% yield) as a clear colorless oil as a single diastereomer in 94:6 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-

major 4.6 min,  $t_{\text{r}}$ -minor 5.3 min). Analytical data for **2c**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3067, 3004, 2953, 2902, 2839, 1732, 1614, 1516, 1492, 1436, 1384, 1348, 1278, 1249, 1176, 1085, 1057, 940, 834, 803;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (d,  $J = 8.8$  Hz, 2H), 7.44 Hz (d,  $J = 8.4$  Hz, 2H), 7.29 (d,  $J = 8.4$  Hz, 2H), 6.94 (d,  $J = 8.8$  Hz, 2H), 5.72 (s, 1H), 4.90 (dd,  $J = 10.4$ , 6.4 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.18 (s, 3H), 2.99 (dd,  $J = 13.6$ , 10.8 Hz, 1H), 2.70 (dd,  $J = 13.6$ , 6.4 Hz, 2H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 169.2, 159.6, 136.2, 133.9, 131.6, 128.4, 128.0 (two overlapping resonances), 114.0, 83.7, 79.8, 66.2, 55.3, 53.0, 52.3, 42.6; **TLC** (15% EtOAc/hexanes)  $R_f$  0.15; **Anal.** Calcd. for  $\text{C}_{21}\text{H}_{21}\text{ClO}_6$ : C, 62.3; H, 5.23; Found: C, 62.21; H, 5.27;  $[\alpha]_{\text{D}}^{27} +57.3$  ( $c = 0.52$ ,  $\text{CH}_2\text{Cl}_2$ ).

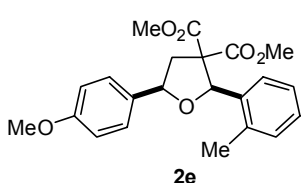
**(2*R*,5*R*)-Dimethyl 5-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2d**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and 4-trifluoromethylbenzaldehyde (0.106 g, 0.60 mmol, 4.0 equiv) dissolved in  $\text{CCl}_4$  (2.8 mL) and  $\text{MgI}_2$  (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl- $t$ Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in  $\text{CCl}_4$  (0.20 mL). After work up, the product was purified by flash chromatography (20% EtOAc/hexanes) to **2d** (0.031 g, 0.071 mmol, 46% yield) as a clear colorless oil as a single diastereomer in 91:9 er as determined by chiral SFC analysis (Chiralpack AD, 2.0% MeOH, 2.0 mL/min, 200 bar, 40  $^\circ\text{C}$ , 220 nm,  $t_{\text{r}}$ -major 6.8 min,  $t_{\text{r}}$ -minor 7.5 min). Analytical data for **2d**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3074, 3005, 2955, 2841, 1732, 1615, 1588, 1517, 1436, 1326, 1280, 1248, 1172, 1124, 1066, 941, 853;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 8.0$  Hz, 2H), 7.59 (d,  $J = 8.0$  Hz, 2H), 7.50 (d,  $J = 8.4$  Hz, 2H), 6.96 (d,

$J = 8.4$  Hz, 2H), 5.79 (s, 1H), 4.94 (dd,  $J = 10.0, 6.0$  Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.01 (m, 1H), 2.73 (dd,  $J = 13.6, 6.4$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 169.1, 159.7, 141.7, 131.4, 130.2 (q,  $J = 32.1$  Hz), 128.1 (d,  $J = 14.0$ ), 127.4, 124.6 (d,  $J = 3.7$  Hz), 124.1 (q,  $J = 270.5$ ), 114.0, 83.6, 79.9, 66.3, 55.2, 53.0, 52.1, 42.7; TLC (20% EtOAc/hexanes)  $R_f$  0.22; LRMS (ESI) calcd. for  $\text{C}_{22}\text{H}_{21}\text{F}_3\text{O}_6 + \text{Na}$ : 461.1, found 461.2;  $[\alpha]_{\text{D}}^{25} +61.4$  ( $c = 0.29$ ,  $\text{CH}_2\text{Cl}_2$ ).

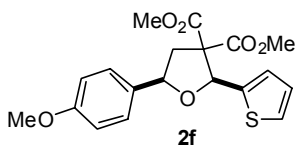
**(2*R*,5*R*)-dimethyl 5-(4-methoxyphenyl)-2-*o*-tolylidihydrofuran-3,3(2*H*)-dicarboxylate (2e):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and *o*-tolualdehyde (0.036 g, 0.30 mmol, 2.0 equiv) dissolved in  $\text{CCl}_4$  (2.8 mL) and  $\text{MgI}_2$  (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-*t*Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in  $\text{CCl}_4$  (0.20 mL). After 18 h, the reaction was worked up. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2e**, (0.048 g, 0.125 mmol, 83% yield) of the title compound as a white solid as a single diastereomer in 96.5:3.5 er as determined by chiral SFC analysis (Chiralpack AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm,  $t_{\text{r}}$ -major 4.4 min,  $t_{\text{r}}$ -minor 4.8 min). Analytical data: Analytical data for **2e**: mp 79-82 °C; IR (thin film,  $\text{cm}^{-1}$ ) 3067, 3002, 2953, 2839, 1731, 1614, 1587, 1516, 1435, 1283, 1245, 1174, 1084, 1052, 936, 908, 831, 760, 681;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (m, 3H), 7.15 (m, 3H), 6.94 (d,  $J = 8.4$  Hz, 2H), 6.20 (s, 1H), 4.90 (dd,  $J = 11.6, 4.8$  Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.08 (dd,  $J = 13.2, 12.0$  Hz, 1H), 3.06 (s, 3H), 2.61 (dd,  $J = 13.6, 4.8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.6, 168.9, 159.5, 136.6, 136.3, 131.3, 129.8, 127.8, 127.7,

127.2, 125.6, 113.9, 80.6, 79.3, 66.2, 55.3, 53.0, 52.0, 43.3, 19.7; **TLC** (20% EtOAc/hexanes)  $R_f$  0.24; **LRMS** (ESI) calcd. for  $C_{22}H_{24}O_6+Na$ : 407.2, found 407.1;  $[\alpha]_D^{27} +61.4$  ( $c = 0.51$ ,  $CH_2Cl_2$ ).

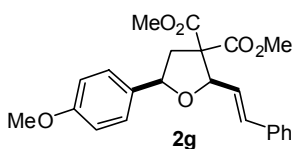
**(2*S*,5*R*)-dimethyl 5-(4-methoxyphenyl)-2-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2f**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (0.034 g, 0.30 mmol, 2.0 equiv) dissolved in  $CCl_4$  (2.8 mL) and  $MgI_2$  (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl- $t$ -Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in  $CCl_4$  (0.20 mL). After 12 h, the reaction was worked up. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide pure **2f** (0.048 g, 0.128 mmol, 84% yield) as a white solid as a single diastereomer in 95.5:4.5 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm,  $t_r$ -major, 4.8 min,  $t_r$ -minor 5.8 min). Analytical data for **2f**: **mp** 91-93 °C; **IR** (thin film,  $cm^{-1}$ ) 3061, 3005, 2954, 2840, 1733, 1614, 1587, 1516, 1436, 1368, 1278, 1249, 1176, 1086, 1038, 833, 701;  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.48 (d,  $J = 8.8$  Hz, 2H), 7.25 (dd,  $J = 5.2, 1.2$  Hz, 1H), 7.10 (d,  $J = 3.2$ , 1H), 6.96 (m, 3H), 6.05 (s, 1H), 4.90 (dd,  $J = 10.8, 6.0$  Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.34 (s, 3H), 2.98 (dd,  $J = 13.6, 10.8$  Hz, 1H), 2.70 (dd,  $J = 13.6, 6.0$  Hz, 1H);  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  170.9, 168.8, 159.5, 141.0, 131.5, 127.9, 126.3, 125.5, 125.2, 113.9, 80.8, 79.8, 66.4, 55.2, 53.0, 52.5, 41.9; **TLC** (15% EtOAc/hexanes)  $R_f$  0.16; **Anal.** Calcd. for  $C_{19}H_{20}O_6S$ : C, 60.62; H, 5.36. Found: C, 60.83; H, 5.29;  $[\alpha]_D^{27} +103.2$  ( $c = 0.215$ ,  $CH_2Cl_2$ ).

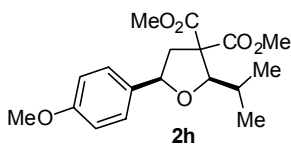


**(2*R*,5*R*)-Dimethyl 5-(4-methoxyphenyl)-2-styryldihydrofuran-3,3(2*H*)-dicarboxylate (2*g*):**



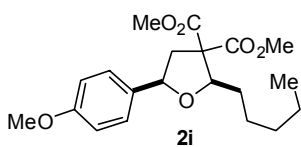
The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and *trans*-cinnamaldehyde (0.040 g, 0.302 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-ybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 12 h, the reaction was worked up. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2g** (0.055 g, 0.139 mmol, 92% yield) as a clear colorless oil as a single diastereomer in 94:6 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major, 5.7 min, *t<sub>r</sub>*-minor 6.6 min). Analytical data for **2g**: **IR** (thin film, cm<sup>-1</sup>) 3063, 3029, 3004, 2954, 2840, 1733, 1614, 1516, 1449, 1436, 1277, 1249, 1175, 1079, 1037, 971, 832, 741, 694; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.26 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 14.0, 6.4 Hz, 1H), 5.25 (dd, *J* = 6.8, 0.8 Hz, 1H), 4.88 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.64 (s, 3H), 2.87 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.73 (dd, *J* = 13.6, 6.0 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 170.9, 169.4, 159.5, 136.5, 132.9, 132.0, 128.5, 127.9, 127.8, 126.6, 125.0, 113.9, 82.9, 79.8, 65.2, 55.3, 53.0, 52.7, 42.1; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.18; **LRMS** (ESI) calcd. for C<sub>23</sub>H<sub>24</sub>O<sub>6</sub>+Na: 419.2, found 419.2; [α]<sub>D</sub><sup>26</sup> +72.5 (*c* = 0.375, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,5*R*)-Dimethyl 2-isopropyl-5-(4-methoxyphenyl)dihydrofuran-3,3(2*H*)-dicarboxylate (2*h*):**



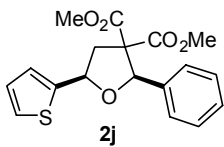
The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and isobutyraldehyde (0.044 g, 0.604 mmol, 4.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 46 h, the reaction was worked up. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2h** (0.028 g, 0.083 mmol, 55% yield) as a clear colorless oil as a single diastereomer in 91.5:8.5 er as determined by chiral SFC analysis (Chiralcel OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 4.1 min, *t<sub>r</sub>*-minor 4.5 min). Analytical data for **2h**: **IR** (thin film, cm<sup>-1</sup>) 3067, 2999, 2955, 2874, 2840, 1732, 1614, 1516, 1436, 1277, 1248, 1198, 1176, 1114, 1091, 1056, 833; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.71 (dd, *J* = 9.2, 6.8 Hz, 1H), 4.28 (d, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.68 (m, 2H), 1.95 (m, 1 H), 1.01 (m, 6H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.7, 170.44, 159.3, 132.5, 127.7, 113.8, 88.2, 78.6, 63.2, 55.2, 52.7, 52.4, 44.2, 30.0, 20.5, 18.9; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.32; **Anal.** Calcd. for C<sub>18</sub>H<sub>24</sub>O<sub>6</sub>: C, 64.27; H, 7.19; Found: C, 63.98; H, 7.08; [α]<sub>D</sub><sup>26</sup> +70.7 (*c* = 0.22, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,5*R*)-Dimethyl 5-(4-methoxyphenyl)-2-pentyldihydrofuran-3,3(2*H*)-dicarboxylate (2i):**



The title compound was prepared according to General Procedure E with dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and hexanal (0.060 g, 0.60 mmol, 4.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 30 h, the reaction was worked up. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide pure **2i** (0.035 g, 0.096 mmol, 63% yield) as a clear slightly yellow oil in 93:7 er as determined by chiral SFC analysis (Chiralcel OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 7.3 min, *t<sub>r</sub>*-minor 8.5 min). Analytical data for **2i**: **IR** (thin film, cm<sup>-1</sup>) 3065, 3004, 2955, 2861, 1733, 1614, 1516, 1458, 1436, 1281, 1246, 1175, 1074, 1035, 952, 833; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.73 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.44 (d, *J* = 8.6 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H), 2.68 (m, 2H), 1.63 (m, 2H), 1.47 (m, 2H), 3.11 (m, 4H), 0.89 (m, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.3, 170.3, 159.4, 132.6, 127.9, 113.8, 83.0, 79.4, 63.8, 55.2, 52.7, 52.4, 42.8, 31.7 (two overlapping resonances), 26.5, 22.5, 14.0; **TLC** (15% EtOAc/hexanes) *R<sub>f</sub>* 0.25; **LRMS** (ESI) calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>6</sub>+Na: 387.2, found 387.2; [α]<sub>D</sub><sup>27</sup> +88.9 (*c* = 0.375, CH<sub>2</sub>Cl<sub>2</sub>).

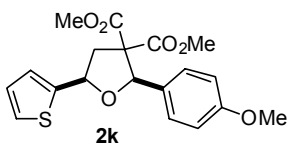
**(2*R*,5*R*)-Dimethyl 2-phenyl-5-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (2j):**



The title compound was prepared according to General Procedure E with dimethyl 2-(thien-2-yl)cyclopropane-1,1-dicarboxylate (**1c**, 0.036 g, 0.151 mmol, 1.0 equiv) and benzaldehyde (0.032 g, 0.30 mmol, 2.0

equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 30 h, the reaction was worked up. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to provide pure **2j** (0.034 g, 0.098 mmol, 65% yield) as a white solid as a single diastereomer in 96.5:3.5 er as determined by chiral SFC analysis (Chiralpack AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 4.1 min, *t<sub>r</sub>*-minor 4.7 min). Analytical data for this compound has been previously reported.<sup>12</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +77.8 (*c* = 0.265, CH<sub>2</sub>Cl<sub>2</sub>).

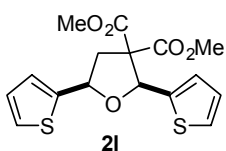
**(2*R*,5*R*)-Dimethyl 2-(4-methoxyphenyl)-5-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2k**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(thien-2-yl)cyclopropane-1,1-dicarboxylate (**1c**, 0.036 g, 0.151 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (0.042 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 8 h, the reaction was worked up. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide pure **2k** (0.053 g, 0.141 mmol, 93% yield) as a clear colorless oil in 97.5:2.5 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t<sub>r</sub>*-major 4.5 min, *t<sub>r</sub>*-minor 5.1 min). Analytical data for **2k**: **IR** (thin film, cm<sup>-1</sup>) 3004, 2953, 2839, 1732, 1613, 1586, 1515, 1436, 1280, 1249, 1174, 1086, 1053, 1035, 932, 841, 805; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 4.8 Hz, 1H), 7.15 (d, *J* = 3.2 Hz, 1H), 7.01 (dd, *J* = 4.8, 3.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.75 (s, 1H), 5.21 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.83 (s, 3H), 3.78

(s, 3H), 3.20 (s, 3H), 3.11 (dd,  $J = 13.6, 10.4$  Hz, 1H), 2.76 (dd,  $J = 13.2, 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 168.9, 159.5, 142.8, 129.6, 128.4, 126.6, 125.5, 125.4, 113.3, 84.2, 75.6, 66.2, 55.2, 53.0, 52.3, 42.7; TLC (15% EtOAc/hexanes)  $R_f$  0.19; LRMS (ESI) calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_6\text{S}+\text{Na}$ : 399.1, found 399.1;  $[\alpha]_{\text{D}}^{27} +57.8$  ( $c = 0.415$ ,  $\text{CH}_2\text{Cl}_2$ ).

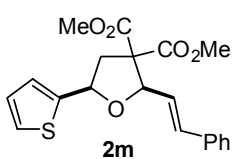
**(2*S*,5*R*)-Dimethyl 2,5-di(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (**2l**):**



The title compound was prepared according to General Procedure E with dimethyl 2-(thien-2-yl)cyclopropane-1,1-dicarboxylate (**1c**, 0.036 g, 0.151 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (0.034 g, 0.30 mmol, 2.0 equiv) dissolved in  $\text{CCl}_4$  (2.8 mL) and  $\text{MgI}_2$  (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl- $t$ -Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in  $\text{CCl}_4$  (0.20 mL). After work up, the crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide pur **2l** (0.042 g, 0.119 mmol, 78% yield) as a clear colorless oil as a single diastereomer in 96.5:3.5 er as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm,  $t_r$ -major 4.3 min,  $t_r$ -minor 4.9 min). Analytical data for **2l**: IR (thin film,  $\text{cm}^{-1}$ ) 3109, 3074, 3003, 2953, 2882, 1796, 1732, 1682, 1436, 1281, 1235, 1087, 1049, 855, 840, 714, 699;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (dd,  $J = 4.8, 0.8$  Hz, 1H), 7.26 (dd,  $J = 2.0, 0.8$  Hz, 1H), 7.15 (d,  $J = 3.2$  Hz, 1H), 7.07 (d,  $J = 3.6$  Hz, 1H), 7.01 (dd,  $J = 4.8, 3.6$  Hz), 6.96 (dd,  $J = 5.2, 3.6$  Hz, 1H), 6.07 (s, 1H), 5.21 (dd,  $J = 10.8, 5.6$  Hz, 1H), 5.86 (s, 3H), 3.73 (s, 3H), 3.11 (dd,  $J = 13.6, 11.2$  Hz, 1H), 2.79 (dd,  $J = 13.6, 5.6$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 168.2, 142.4, 140.9, 126.6, 126.4, 125.7, 125.6, 125.5, 125.4, 80.7, 75.8, 66.4, 53.2, 52.6, 41.8; TLC (15% EtOAc/hexanes)  $R_f$

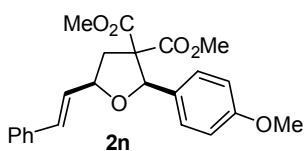
0.19; **Anal.** Calcd. for C<sub>16</sub>H<sub>16</sub>O<sub>5</sub>S<sub>2</sub>: C, 54.53; H, 4.58. Found: C, 54.78; H, 4.66; [ $\alpha$ ]<sub>D</sub><sup>26</sup> +102.2 (*c* = 0.31, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,5*R*)-Dimethyl 2-styryl-5-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (2*m*):**



The title compound was prepared according to General Procedure E with dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (**1c**, 0.036 g, 0.151 mmol, 1.0 equiv) and *trans*-cinnamaldehyde (0.040 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 18 h, the reaction was worked up. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to provide pure **2m** (0.0535 g, 0.144 mmol, 95% yield) as a clear slightly yellow oil as a single diastereomer in 97:3 er as determined by chiral SFC analysis (Chiralpack AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t*<sub>r</sub>-major 5.4 min, *t*<sub>r</sub>-minor 6.1 min). Analytical data for **2m**: **IR** (thin film, cm<sup>-1</sup>) 3063, 3028, 3004, 2953, 2880, 1734, 1496, 1448, 1436, 1278, 1226, 1200, 1174, 1137, 738, 694; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 (d, *J* = 7.6 Hz, 2H), 7.31-7.25 (m, 4H), 7.12 (d, *J* = 1.2 Hz, 1H), 7.01 (d, *J* = 3.2 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.20 (dd, *J* = 10.0, 6.4 Hz), 3.85 (s, 3H), 3.65 (s, 3H), 2.99 (t, *J* = 13.2, 1H), 2.82 (dd, *J* = 13.6, 6.4 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 168.8, 143.1, 136.4, 133.2, 128.5, 127.9, 126.7, 126.6, 125.5, 125.4, 124.8, 82.9, 75.7, 65.2, 53.1, 52.7, 42.1; **TLC** (10% EtOAc/hexanes) R<sub>f</sub> 0.12; **LRMS** (ESI) calcd. for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>S+Na: 419.2, found 419.1; [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 83.2 (*c* = 0.23, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,5*R*)-Dimethyl 2-(4-methoxyphenyl)-5-styryldihydrofuran-3,3(2*H*)-dicarboxylate (2n):**



The title compound was prepared according to General Procedure E with (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1d**, 0.039 g, 0.151 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (0.041 g, 0.30 mmol, 2.0 equiv) dissolved in CCl<sub>4</sub> (2.8 mL) and MgI<sub>2</sub> (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>t</sup>Bu-pybox (**16a**, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl<sub>4</sub> (0.20 mL). After 24 h, the reaction was worked up. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide pure **2n** (0.0456 g, 0.115 mmol, 76% yield as a clear colorless oil in > 25:1 dr and 95:5 er (of the major diastereomer) as determined by chiral SFC analysis (Chiralpack AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 220 nm, *t*<sub>r</sub>-major 5.3 min, *t*<sub>r</sub>-minor 7.6 min). Analytical data for **2n**: **IR** (thin film, cm<sup>-1</sup>) 3063, 3028, 3003, 2953, 2840, 1731, 1614, 1514, 1436, 1359, 1282, 1247, 1174, 1035, 968, 933, 841, 805; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.36 (m, 4H), 7.27 (m, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.25 (d, *J* = 16.0 Hz, 1H), 6.45 (dd, *J* = 16.0, 7.2 Hz, 1H), 5.69 (s, 1H), 4.59 Hz (ddd, *J* = 10.0, 6.4, 6.4 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.21 (s, 3H), 2.86 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.56 (dd, *J* = 13.6, 6.4 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.2, 169.1, 159.4, 136.4, 132.8, 129.8, 128.5, 128.2, 127.9, 127.6, 126.6, 113.2, 84.0, 78.8, 66.0, 55.1, 52.8, 52.2, 40.6; **TLC** (15% EtOAc/hexanes) *R*<sub>f</sub> 0.16; **LRMS** (ESI) calcd. for C<sub>23</sub>H<sub>24</sub>O<sub>6</sub>+Na: 419.2, found 419.1; [α]<sub>D</sub><sup>27</sup> +54.7 (*c* = 0.27, CH<sub>2</sub>Cl<sub>2</sub>).

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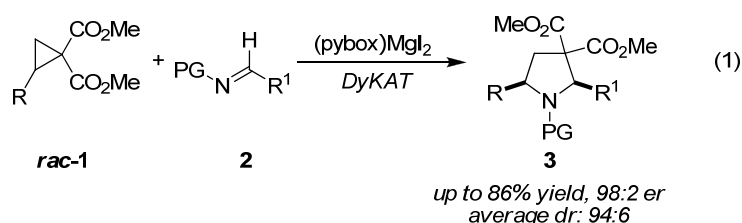
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# CHAPTER FOUR

## DYNAMIC KINETIC ASYMMETRIC SYNTHESIS OF PYRROLIDINES FROM RACEMIC CYCLOPROPANES AND ALDIMINES: REACTION DEVELOPMENT AND MECHANISTIC INSIGHTS

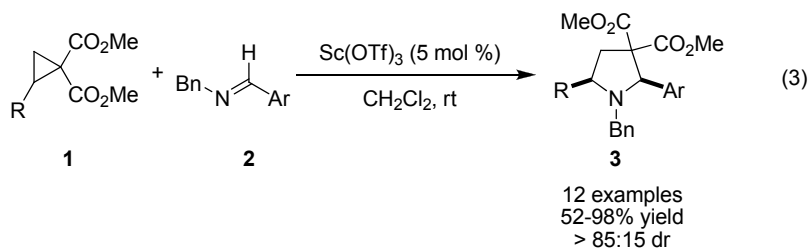
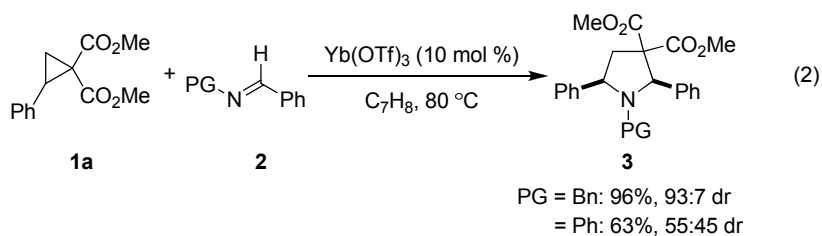
### 4.1 Introduction

Nitrogen-containing heterocycles are abundant in naturally occurring and pharmaceutically relevant molecules.<sup>1</sup> In particular, substituted pyrrolidine derivatives are ubiquitous and their value is reflected by continued interest in developing methods for their preparation.<sup>2-7</sup> Efforts in our lab<sup>8-11</sup> and others<sup>12,13</sup> have focused on the asymmetric synthesis of hetero- and carbocycles via ring-opening reactions of malonate-derived donor-acceptor (D–A) cyclopropanes **1**. We recently reported a dynamic kinetic asymmetric transformation (DyKAT) of *rac*-**1** via (pybox)MgI<sub>2</sub>-catalyzed (3 + 2) annulation with aldehydes to afford 2,5-*cis*-disubstituted tetrahydrofurans in a highly enantioselective manner.<sup>11</sup> Herein, we report the asymmetric synthesis of pyrrolidines from racemic cyclopropanes **1** and (*E*)-aldimines **2** (eq 1, PG = protecting group) and experiments that reveal a surprising mechanistic dichotomy with the extant cyclopropane/aldehyde annulations.



## 4.2 Background

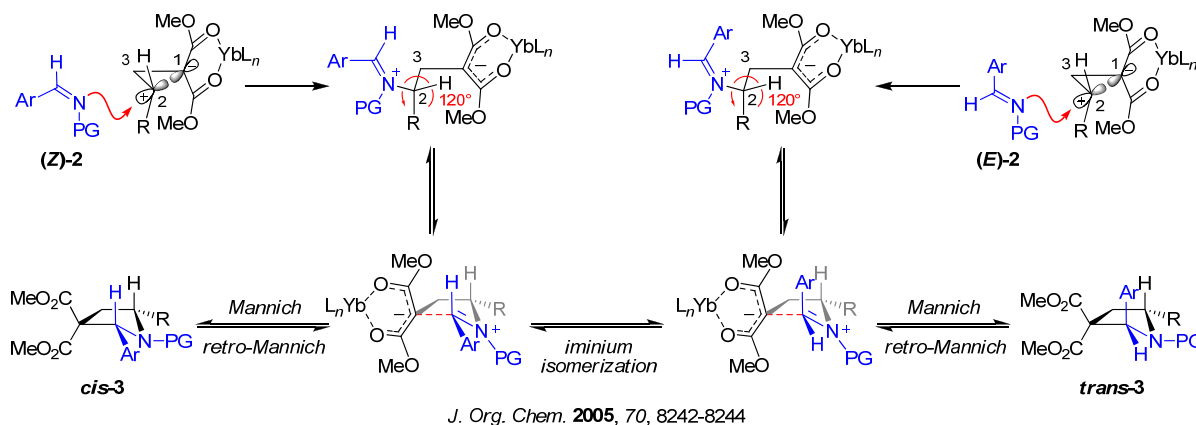
Lewis acid-catalyzed (3 + *n*) annulations of malonate-derived donor-acceptor cyclopropanes (**1**) are an extensively studied class of reactions. While our laboratory has focused its efforts on the mechanistic elucidation of cyclopropane annulations using aldehyde dipolarophiles (see **Chapter One**)<sup>10,14,15</sup> and Kerr has examined annulations with nitrones in great detail,<sup>16-18</sup> annulations of aldimine dipolarophiles have not been thoroughly investigated. Initial developments of (3 + 2) annulations of **1** with aldimine dipolarophiles were independently reported by Kerr<sup>19</sup> and Tang.<sup>20</sup> Similar to the conditions used for their previously developed annulation with nitrones,<sup>16</sup> Kerr found Yb(OTf)<sub>3</sub> to be an optimal Lewis acid (eq 2). Tang discovered that Sc(OTf)<sub>3</sub> catalyzed this transformation at ambient temperatures with only 5 mol % loading (eq 3). Unlike the high *cis* diastereoselectivity obtained when using nitron or aldehyde dipolarophiles, aldimines gave inconsistent diastereoselectivities that showed a dependence on the identity of the aldimine protecting group (PG).



Based on previous mechanistic studies on cyclopropane/aldehyde annulations conducted in our laboratory (see **Chapter One**), the Kerr group proposed that aldimine

annulations proceed through an analogous reaction mechanism. This hypothesis is based on several assumptions: a) the aldimine undergoes reversible *E*—*Z* isomerization prior to nucleophilic ring-opening of **1** or b) *E*—*Z* iminium isomerization occurs, and c) retro-Mannich ring-opening allows for equilibration of the *cis*/*trans* products (**Scheme 4-1**).

**Scheme 4-1.** Kerr's Proposed Mechanism for Yb(OTf)<sub>3</sub>-Catalyzed Cyclopropane/Aldimine Annulations<sup>19</sup>



Furthermore the hypothesis proposes: a) the (*Z*)-aldimine/iminium furnishes the *cis* product; b) the (*E*)-aldimine/iminium furnishes the *trans* product; and c) the *N*-protecting group of the aldimine does not influence the angle of nucleophilic attack by **2**.

The aforementioned research on racemic aldimine annulations reported by Kerr and Tang and our development of a dynamic kinetic asymmetric (3 + 2) annulation of **1** with aldehydes (see **Chapter Three**), prompted us to explore the coupling of our DyKAT methodology with aldimine dipolarophiles. During the course of our reaction development, we also sought to address questions that arose from the mechanistic hypothesis described in **Scheme 4-1**. Namely, we wanted to determine what role *E*—*Z* aldimine/iminium isomerization plays in cyclopropane/aldimine annulations and whether it is reasonable to assume aldimines react in an analogous manner to aldehydes.

## 4.3 Reaction Development

### 4.3.1 Evaluation of the Aldimine Protecting Group

Early efforts in the development of a dynamic kinetic asymmetric (3 + 2) annulation of cyclopropanes and aldimines used the previously optimized conditions for the analogous aldehyde annulation of **1b** using  $\text{MgI}_2$ /4-Cl-*t*-Bu-pybox (**L1**) as the catalyst. The reported influence of the aldimine *N*-protecting group on diastereoselectivity led us to first evaluate annulations of various *N*-protected benzaldehyde-derived aldimines (**Table 4-1**). Similar to Kerr's observations, when PG = Ph the *cis/trans* diastereoselectivity was low at

**Table 4-1.** An Examination of Aldimine *N*-Protecting Groups

$\text{rac-1b}$  (R = 4-MeOPh) + **2a-g**  $\xrightarrow[\text{CCl}_4, \text{rt}, 24 \text{ h}]{\text{MgI}_2 (10 \text{ mol } \%), \text{L1} (12 \text{ mol } \%)}$  **3**

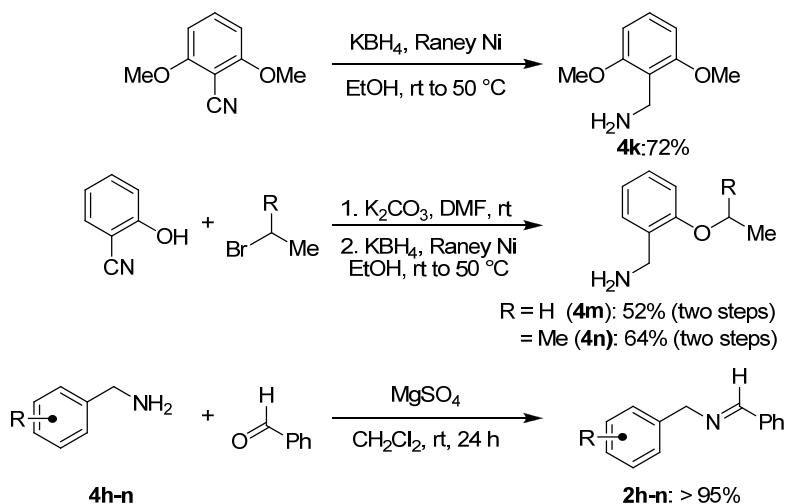
| entry          | protecting group (PG) | yield (%) <sup>a</sup> | dr <sup>b</sup> | er <sup>c</sup> |                 |
|----------------|-----------------------|------------------------|-----------------|-----------------|-----------------|
| 1              |                       | <b>2a</b>              | 77              | 55:45           | nd <sup>d</sup> |
| 2              |                       | <b>2b</b>              | — <sup>e</sup>  | —               | —               |
| 3              |                       | <b>2c</b>              | — <sup>e</sup>  | —               | —               |
| 4              |                       | <b>2d</b>              | 0 <sup>f</sup>  | —               | —               |
| 5              |                       | <b>2e</b>              | 0 <sup>f</sup>  | —               | —               |
| 6              |                       | <b>2f</b>              | 27              | > 99:1          | nd              |
| 7              |                       | <b>2g</b>              | 83              | 97:3            | 85.5:14.5       |
| 8 <sup>g</sup> |                       | <b>2g</b>              | 74              | 95:5            | 91:9            |

Conditions: **1b** (1.0 equiv), aldimine (2.0 equiv),  $\text{MgI}_2$  (0.10 equiv), **L1** (0.12 equiv),  $[\text{1b}]_0 = 0.050$  M in  $\text{CCl}_4$ , rt, 24 h. a) Determined by  $^1\text{H}$  NMR spectroscopy using a mesitylene internal standard. b) Determined by  $^1\text{H}$  NMR spectroscopy. c) Determined by chiral SFC analysis. d) nd = not determined. e) No reaction occurred. f) Decomposition of **1b** occurred. g) 1.1 equiv of the aldimine was used.

55:45 (entry 1). A range of other protecting groups either resulted in no reaction (entries 2-3) or decomposition of **1b** (entries 4-5). The benzhydryl-protected aldimine **2f** provided excellent diastereoselectivity, but the yield was poor due to decomposition of **1b** (entry 6). We found that annulation with an *N*-benzyl-protected aldimine **2g** provided good yields and enantioselectivity with high 2,5-*cis*-diastereoselectivity (entry 7). Decreasing the aldimine equivalents from 2.0 to 1.1 (relative to **1b**) resulted in a lower yield, but enantioselectivity increased substantially (entry 8).

The superior results obtained with *N*-benzyl-protected aldimine **2g** led us to continue our reaction optimization by examining a range of substituted benzyl protecting groups. We focused our attention on electron-rich alkoxy-substituted benzyl groups since they are more easily removed under hydrogenolytic conditions. Many of the parent benzylamines were commercially available for the preparation of aldimines **2h-n**. Benzylamines **4k, m-n** are not available from commercial sources and were prepared according to the synthetic route outlined in **Scheme 4-2**. The corresponding aldimines were prepared by condensation of the benzylamine with benzaldehyde and used without purification.

**Scheme 4-2.** Preparation of Benzylamines and Substituted *N*-Benzyl-Protected Aldimines



With a range of alkoxy-substituted *N*-benzyl-protected aldimines in hand, we examined the annulation of **1b** and aldimines **2h-n** using the  $\text{MgI}_2/\text{L1}$  catalyst (**Table 4-2**). Annulation of 4-methoxybenzyl-protected aldimine **2h** resulted in a moderately higher yield, but the enantioselectivity remained unchanged (entry 1). Moving to 2-methoxybenzyl-protected **2i** furnished pyrrolidine **3bi** with a substantial increase in the enantiomeric ratio to 95:5 (entry 2). Exploration of bulkier 2-alkoxy- or di-substituted-aldimines provided mixed results. 2-Ethoxy- and -isopropoxybenzyl-protected aldimines yielded comparable results to **2i**, but the parent benzylamines are not commercially available (entries 6-7). With this in mind, we chose to proceed with aldimines bearing a 2-methoxybenzyl protecting group.

**Table 4-2.** An Examination of Substituted Aldimine *N*- Benzyl Protecting Groups

**rac-1b** + **2h-n**  $\xrightarrow[\text{L1 (12 mol \%)}]{\text{MgI}_2 (10 \text{ mol \%})}$  **3bh-3bn**  
 $\text{Ar} = 4\text{-MeOPh}$

| entry | protecting group (PG) | yield (%) <sup>a</sup> | dr <sup>b</sup> | er <sup>c</sup> |
|-------|-----------------------|------------------------|-----------------|-----------------|
| 1     |                       | 77 ( <b>3bh</b> )      | 96:4            | 90.5:9.5        |
| 2     |                       | 71 ( <b>3bi</b> )      | 96:4            | 95:5            |
| 3     |                       | 75 ( <b>3bj</b> )      | 96:4            | 93:7            |
| 4     |                       | 69 ( <b>3bk</b> )      | 99:1            | 89.5:10.5       |
| 5     |                       | 68 ( <b>3bl</b> )      | 80:20           | 92:8            |
| 6     |                       | 76 ( <b>3bm</b> )      | 95:5            | 94:6            |
| 7     |                       | 73 ( <b>3bn</b> )      | 94:6            | 96:4            |

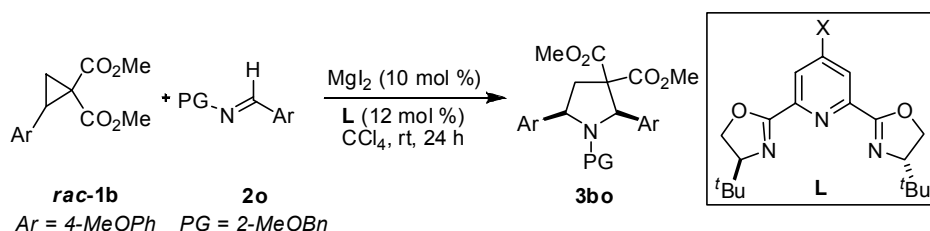
Conditions: **1b** (1.0 equiv), aldimine (1.1 equiv),  $\text{MgI}_2$  (0.10 equiv), **L1** (0.12 equiv),  $[\mathbf{1b}]_0 = 0.050$  M in  $\text{CCl}_4$ , rt, 24 h. a) Determined by  $^1\text{H}$  NMR spectroscopy using a mesitylene internal standard. b) Determined by  $^1\text{H}$  NMR spectroscopy. c) Determined by chiral SFC analysis.



### 4.3.2 Ligand Optimization

Previous optimization studies conducted for the development of a dynamic kinetic asymmetric (3 + 2) annulation of cyclopropanes and aldehydes revealed that the pybox ligand electronics have a significant influence on the chemical yield of tetrahydrofuran products.<sup>11</sup> We sought to further improve the cyclopropane/aldimine DyKAT using this strategy. Thus, unsubstituted and 4-substituted-*t*Bu-pybox ligands (**L0-L6**) were examined under the standard reaction conditions (**Table 4-3**). Previous difficulties in obtaining high enantioselectivity with the electron-rich 4-methoxybenzaldehyde-derived aldimine **2o** (data not shown) prompted us to conduct this optimization study using this dipolarophile.

**Table 4-3.** An Examination of 4-Substituted-*t*Bu-Pybox Ligands



| entry | X               |               | conversion (%) <sup>a</sup> | yield (%) <sup>a</sup> | dr <sup>b</sup> | er <sup>c</sup> |
|-------|-----------------|---------------|-----------------------------|------------------------|-----------------|-----------------|
| 1     | H               | ( <b>L0</b> ) | 44                          | 39                     | 84:16           | 74:26           |
| 2     | Cl              | ( <b>L1</b> ) | 100                         | 66                     | 96:4            | 89.5:10.5       |
| 3     | Br              | ( <b>L2</b> ) | 100                         | 79 <sup>d</sup>        | 97:3            | 93:7            |
| 4     | CF <sub>3</sub> | ( <b>L3</b> ) | 100                         | 69                     | 96:4            | 92:8            |
| 5     | Ph              | ( <b>L4</b> ) | 93                          | 63                     | 94.5:5.5        | 83:17           |
| 6     | Mes             | ( <b>L5</b> ) | 64                          | 56                     | 91:9            | 89:11           |
| 7     |                 | ( <b>L6</b> ) | 100                         | 76                     | 94.5:5.5        | 80:20           |

Conditions: **1b** (1.0 equiv), **2o** (1.1 equiv), MgI<sub>2</sub> (0.10 equiv), ligand (0.12 equiv), [**1b**]<sub>0</sub> = 0.050 M in CCl<sub>4</sub>, rt, 24 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by <sup>1</sup>H NMR spectroscopy. c) Determined by chiral SFC analysis. d) Average isolated yield of two independent trials.

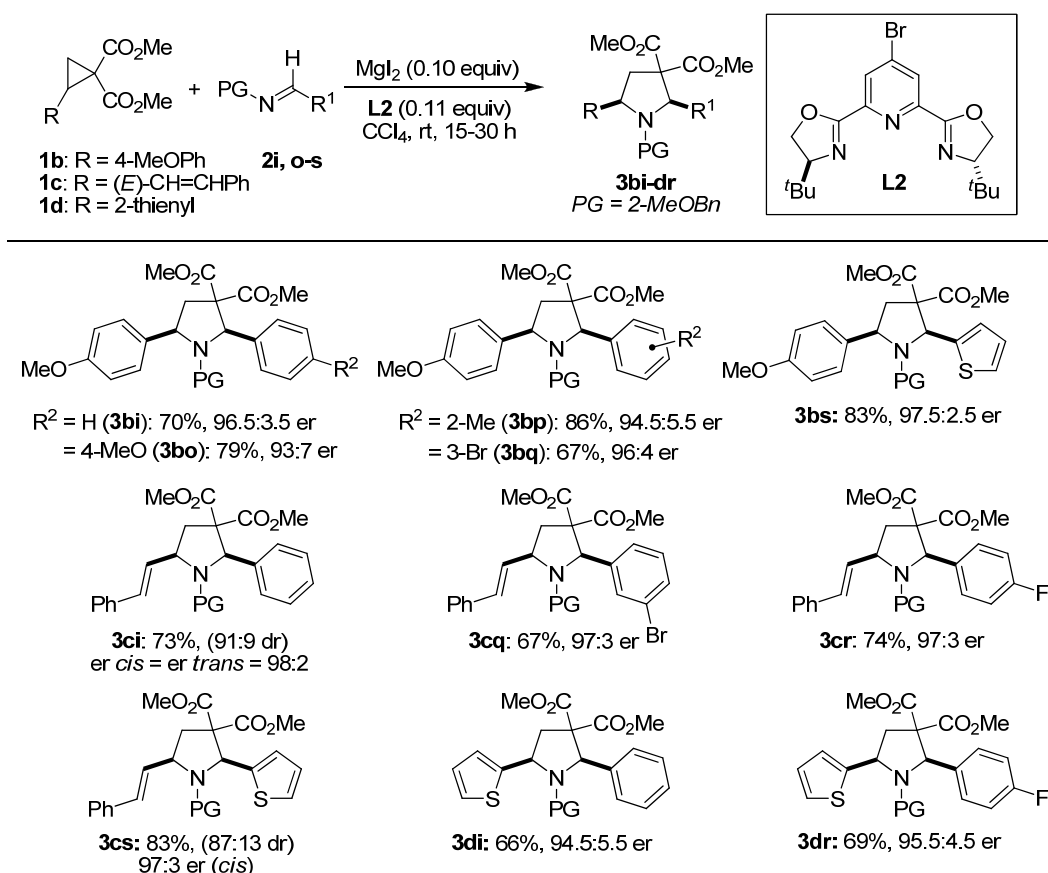
Interestingly, we found that **L2** (X = Br) provided superior results to the other ligands examined. Along with a substantially improved yield over **L1**, there was also a marked increase in enantioselectivity. This is in contrast to the annulation with aldehydes, where

only the yield was significantly impacted by substitution on the pybox. The optimal reaction conditions for the asymmetric annulation of cyclopropanes and aldimines were found to be remarkably similar to our previously developed aldehyde annulation. Minor adjustments in the 4-X-*t*Bu-pybox ligand substitution (Br instead of Cl) and lowering the dipolarophile equivalents from 2.0 to 1.1 allowed for the successful transition to aldimine dipolarophiles.

### 4.3.3 Substrate Scope

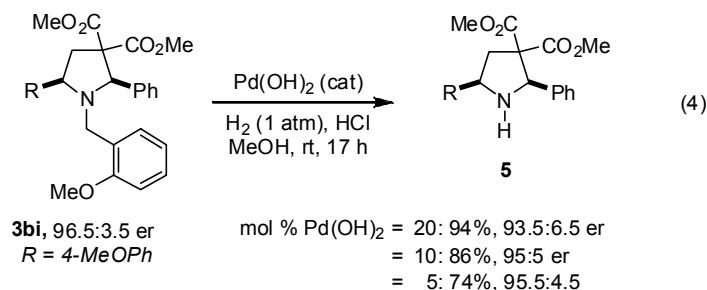
We sought to explore the generality of this method and began by examining the cyclopropanes known to display dynamic behavior under the  $\text{MgI}_2/4\text{-X-}^t\text{Bu-pybox}$  reaction conditions; thus cyclopropanes bearing 4-methoxyphenyl (**1b**), styryl (**1c**), and 2-thienyl (**1d**) donor groups were employed (**Figure 4-1**). Several 2-methoxybenzyl-protected substituted

**Figure 4-1** Substrate Scope



aryl and heteroaromatic aldimines were successful dipolarophiles in this transformation. Yields were generally good (66-86%) with high enantioselectivities, up to 98:2 er. Use of electron-deficient aryl, unsaturated, or aliphatic aldimines were not successful coupling partners, which is consistent with Kerr's results in the racemic series.

In an attempt to cleave the 2-methoxybenzyl-protected pyrrolidine products, we subjected **3bi** (96.5:3.5 er) to standard hydrogenolytic conditions using Pd/C under a hydrogen atmosphere. Under these conditions, only protected pyrrolidine was recovered. Moving to more active Pd(OH)<sub>2</sub> (Pearlman's catalyst), we cleanly obtained the free pyrrolidine **5** using 20 mol % catalyst loading, albeit with some loss in enantioenrichment (eq 4). We found a correlation between catalyst loading and enantioenrichment. Using a 10 mol % loading of Pd(OH)<sub>2</sub> provided the optimal balance of product yield and enantioenrichment.<sup>21</sup>

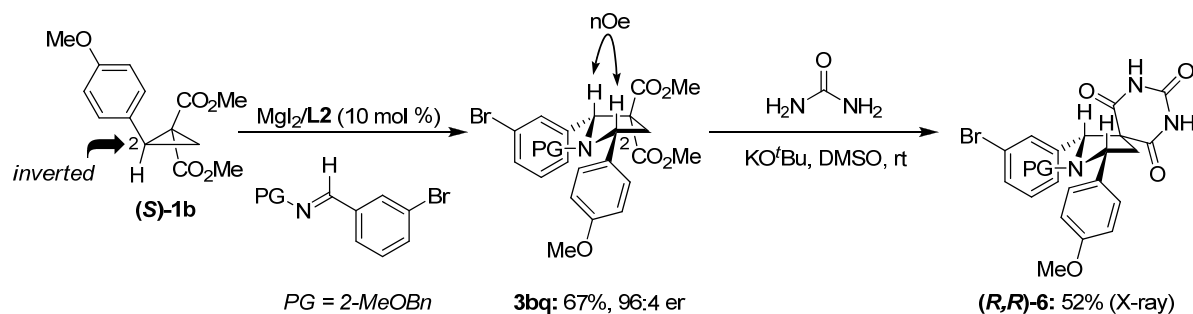


#### 4.4 Stereochemical and Mechanistic Analysis

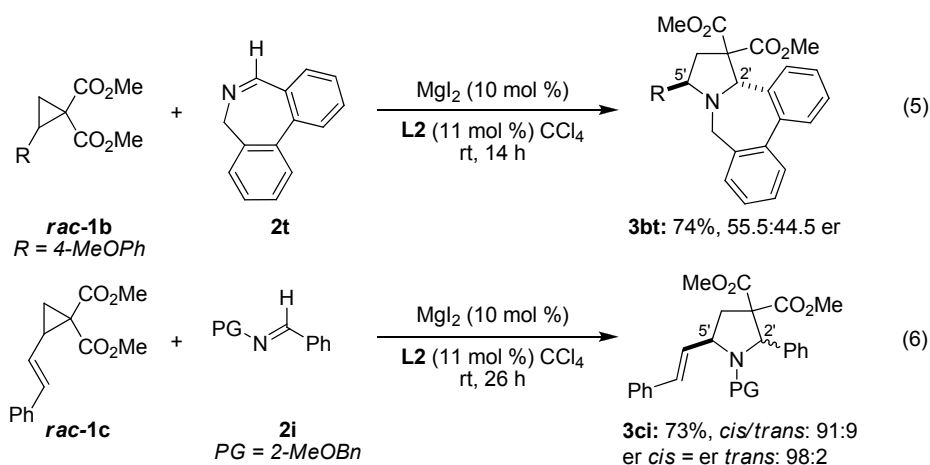
Annulations of enantioenriched D–A cyclopropanes with aldehydes have been shown to proceed through an enantiospecific pathway.<sup>8,10</sup> While it has been assumed a similar mode of reactivity exists for aldimine dipolarophiles,<sup>19,20</sup> it has never been experimentally proven. Previous efforts in our group demonstrated that dipolarophiles selectively react with the (*S*)-enantiomer of cyclopropanes **1** under MgI<sub>2</sub>/L1 catalysis, resulting in inversion of the

cyclopropyl stereocenter. To determine if analogous reactivity is displayed by aldimines, we converted pyrrolidine **3bq** into its corresponding barbituric acid derivative (**Scheme 4-3**).<sup>22</sup> Single crystal X-ray diffraction analysis confirmed the absolute stereochemical configuration of the product (***R,R***-**6**). This data provides evidence that MgI<sub>2</sub>/**L2**-catalyzed annulations of aldimines proceed with an identical stereochemical outcome to the corresponding aldehyde annulation.

**Scheme 4-3.** Absolute Stereochemical Determination through Single Crystal X-ray Diffraction Analysis of Barbituric Acid Derivative **6**



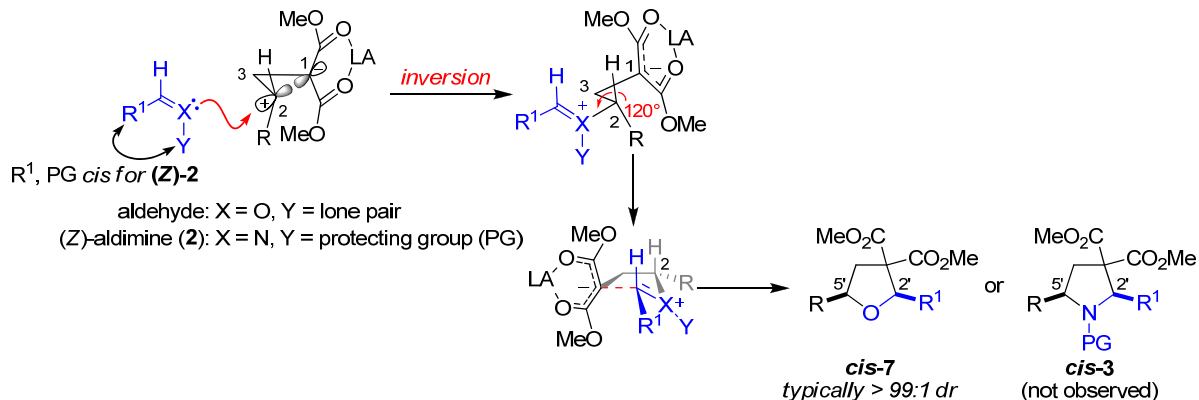
With the absolute stereochemical configuration determined, we sought to examine the source of diastereoselectivity for aldimine/cyclopropane annulations. Kerr previously hypothesized that the source of variation in diastereoselectivity is a result of the fluxional *E/Z*-geometry of the aldimines or corresponding iminiums generated during the course of the reaction (**Scheme 4-1**). This hypothesis predicts that (*E*)-aldimines/iminiums furnish the *trans* pyrrolidine products. In order to test this hypothesis we selected (*Z*)-aldimine **2t**<sup>23</sup> as a reaction partner that, through cyclic constraint, would preclude *E*—*Z* isomerization (eq 5). Strikingly, Lewis acid-catalyzed annulation of **2t** and cyclopropane **1b** delivered pyrrolidine **3bt** exclusively as the 2,5-*trans* isomer with poor enantiomeric discrimination (diastereoselection > 95:5, 55.5:44.5 er). The low level of enantioselectivity for annulation



of **1b** and **2t** reveals nucleophile dependence in the discrimination of (*S*)-**1b** over the (*R*)-enantiomer. Conversely, the minor 2,5-*trans* adduct obtained from annulation of (*E*)-aldimine **2i** and cyclopropane **1c** was produced with high enantioselectivity (eq 6). If *trans*-**3ci** is formed as a result of isomerization of (*E*)-**2i** to the (*Z*)-isomer prior to annulation with cyclopropane **1c**, we would expect the enantioenrichment to be low based on our studies with (*Z*)-aldimine **2t**. This analysis suggests that *E*—*Z* isomerization of the aldimines is not a significant pathway leading to the production of *trans* pyrrolidine products.

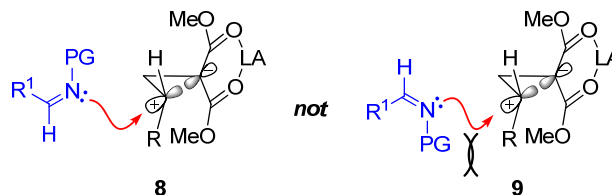
The results obtained using aldimine **2t** are surprising when one considers the similarities between a (*Z*)-aldimine and an aldehyde. On the surface, it appears that annulations with these dipolarophiles should provide heterocyclic products with identical relative stereochemistries. Experimentally, this is not the case; where aldehydes provide *cis* tetrahydrofurans **7**, (*Z*)-aldimines selectively furnish *trans* pyrrolidines (**Scheme 4-4**). This observation highlights a more subtle influence on diastereoselectivity: orientation of the incoming dipolarophile. It is likely that the aldimine protecting group prevents a nucleophilic attack with a trajectory analogous to aldehydes (*vide infra*).

**Scheme 4-4.** Proposed Trajectory of Aldehyde and (Z)-Aldimine Nucleophilic Attack



The absolute stereochemical relationship established by X-ray crystallographic analysis (**Scheme 4-3**) and the results obtained in eq 6 indicate that the epimeric stereocenter is located at C2' of the pyrrolidine. Furthermore, the analysis displayed in **Scheme 4-4** suggests that (Z)-aldimine **2t** must adopt an alternative orientation prior to nucleophilic attack (**Figure 4-2**). Approach **8** avoids an unfavorable interaction between the aldimine protecting group and the cyclopropyl C2 substituent, R, which would be present if the attack was analogous to that of an aldehyde. In addition to being sterically disfavored, annulation via approach **9** would result in formation of 2,5-*cis* pyrrolidines, which are not experimentally observed with (Z)-aldimines.

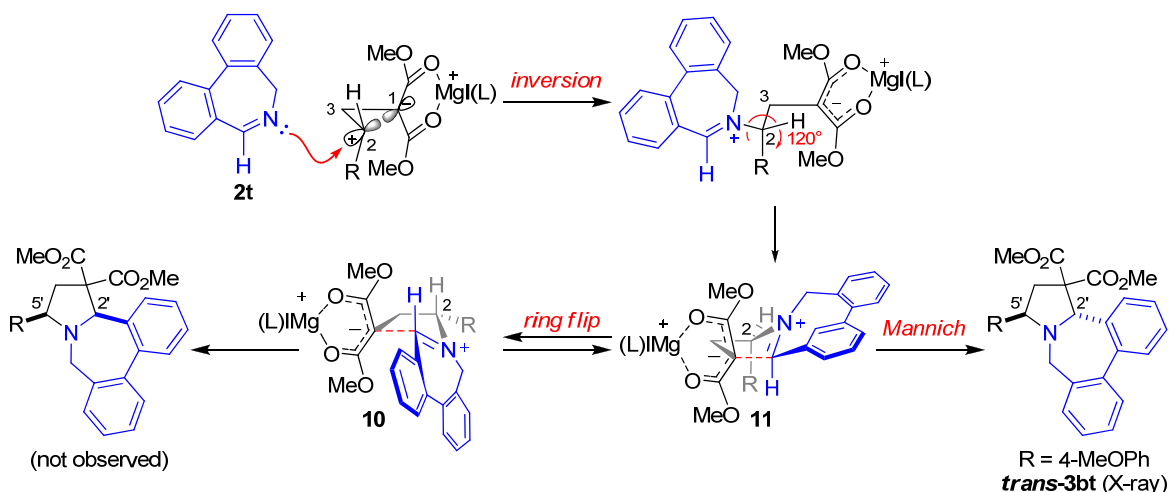
**Figure 4-2.** Steric Considerations in the Nucleophilic Attack of (Z)-Aldimines on Cyclopropanes



We further hypothesize that the configuration of the C2' pyrrolidine stereocenter, which arises via Mannich cyclization, varies as a result of at least two different factors: (a)

ring flip prior to ring closure; and (b) iminium isomerization prior to ring closure. The application of the non-fluxional (*Z*)-aldimine **2t** allows us to separately examine (a) and (b) since iminium isomerization is precluded. In conjunction with the results from eq 5, the analysis in **Scheme 4-5** reveals that the “meridional” transition structure **10** leading to the *cis* isomer is not competitive. Nonbonded steric compression apparently favors placing R (the C5'-substituent) in the axial position (transition state **11**). We therefore conclude that formation of 2,5-*cis* pyrrolidines from transient (*Z*)-aldimines or iminiums is unlikely since the non-fluxional (*Z*)-aldimine **2t** furnishes the 2,5-*trans* pyrrolidine **3bt** exclusively.

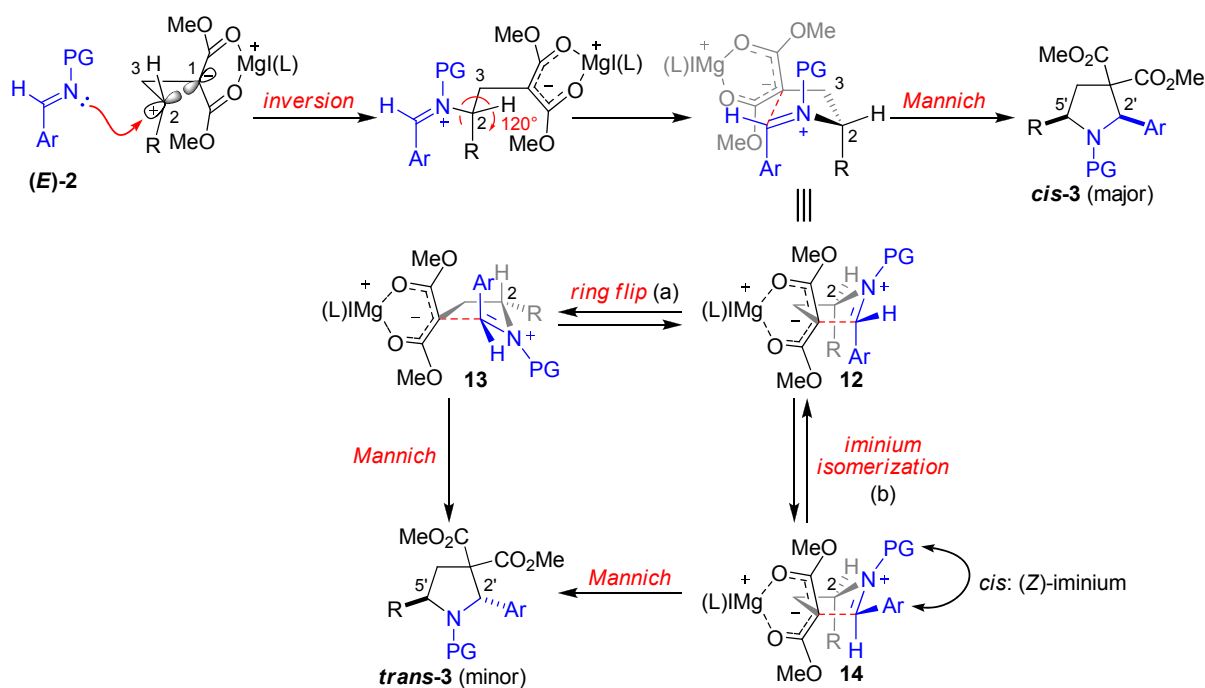
**Scheme 4-5.** Mechanistic Hypothesis for the Formation of *trans* Pyrrolidines from (*Z*)-Aldimine **2t**



A similar analysis can be applied to the (3 + 2) annulation of **1** and (*E*)-aldimines (**Scheme 4-6**). An attack trajectory that minimizes steric interactions between the protecting group and cyclopropyl substituent and maximizes orbital overlap is analogous to that shown in **Scheme 4-5**. In contrast to reactions with aldehydes, the nucleophilic lone pair is *syn* to the Ar group. Counter to the annulation of **1** with **2t**, a 120° rotation of the C2–C3 bond places both R and Ar in pseudo-axial orientations within the envelope transition state (**12**),<sup>24</sup>

presumably minimizing steric penalties associated with structures **13** ( $R \leftrightarrow PG$ ) and **14** ( $Ar \leftrightarrow PG$ ). Ring closure provides the major 2,5-*cis*-disubstituted pyrrolidines **cis-3**. The minor *trans* adducts (**trans-3**) can arise from as yet indistinguishable ring flip (path a) or iminium isomerization (path b) prior to ring closure. Regardless, these analyses and the results obtained with **2t** suggest that the previously-proposed isomerization to the (*Z*)-iminium prior to ring closure would result in formation of the minor 2,5-*trans*-disubstituted pyrrolidine, not the major *cis* isomer.

**Scheme 4-6.** Mechanistic Hypothesis for the Annulation of Cyclopropanes **1** and (*E*)-Aldimines



## 4.5 Conclusion

In summary, we have developed an enantioselective synthesis of 2,5-*cis*-disubstituted pyrrolidines through a dynamic kinetic asymmetric (3 + 2) annulation of racemic cyclopropanes and (*E*)-aldimines. Careful selection of the substituted *N*-benzyl protecting



group of the aldimine allowed for an increase in enantioselectivity and selective deprotection of the pyrrolidine cycloadduct in the presence of other electron-rich benzyl substituents. Simple mechanistic studies and stereochemical observations suggest that the aldimine dipolarophiles react through the (*E*)-geometry via the unusual diaxial transition state **12** to furnish 2,5-*cis*-disubstituted pyrrolidine products. We also postulate that the orientation of the aldimine during nucleophilic attack differs from that of an aldehyde due to steric repulsion between the aldimine protecting group and cyclopropyl substituent.

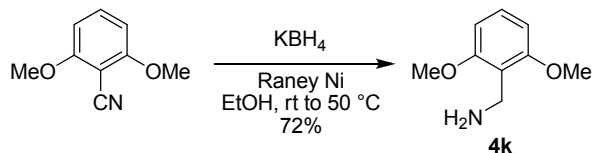
## 4.6 Experimental

**Methods.** Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker model DRX 400 or 500 ( $^1\text{H}$  NMR at 400 MHz or 500 MHz and  $^{13}\text{C}$  NMR at 100 or 125 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm, DMSO- $d_6$  at 2.54 ppm,  $\text{CD}_2\text{Cl}_2$  at 5.32 ppm, and  $\text{C}_6\text{D}_6$  at 7.15 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm, DMSO- $d_6$  at 40.45 ppm,  $\text{CD}_2\text{Cl}_2$  at 54.0 ppm, and  $\text{C}_6\text{D}_6$  at 128.6 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250°C) with helium gas as carrier. Supercritical fluid chromatography was performed on a Berger SFC system. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a

Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields, enantiomeric ratios (er) and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials.** Dichloromethane was dried by passage through a column of neutral alumina under nitrogen prior to use. Dichloroethane was distilled from calcium hydride under  $\text{N}_2$  and stored in a Schlenk flask. Carbon tetrachloride was purified by distillation from phosphorous pentoxide under  $\text{N}_2$ . All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

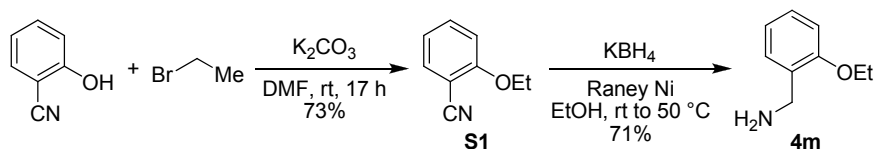
**Preparation of (2,6-dimethoxyphenyl)methanamine (4k):**



A 100-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (36 mL), potassium borohydride (2.65 g, 49.0 mmol, 4.0 equiv), Raney Ni (1.8 mL of a 50% suspension in  $\text{H}_2\text{O}$ , approx. 1.0 equiv), and 2,6-dimethoxybenzonitrile (2.0 g, 12.26 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 1.5 h at

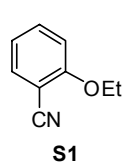
room temperature. The reaction was warmed to 50 °C and stirred for 5.5 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (75 mL), washed with H<sub>2</sub>O (3 x 75 mL), dried over magnesium sulfate, and concentrated to afford **4k** (1.48 g, 7.03 mmol, 72% yield) as a clear colorless oil. Analytical data for **4k**: IR (thin film, cm<sup>-1</sup>) 2940, 2837, 1593, 1476, 1316, 1256, 1155, 1091, 882, 799, 778, 587; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.19 (t, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 2H), 3.85 (s, 6H), 1.49 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.1, 127.8, 120.1, 103.7, 55.6, 34.6; LRMS (ESI) Calcd. for C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub>+H: 168.1, Found: 168.1.

#### Preparation of (2-ethoxyphenyl)methanamine (**4m**):

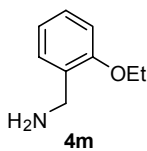


#### Preparation of 2-ethoxybenzonitrile (**S1**):

A 100-mL round bottomed flask containing a magnetic stir bar was charged with **S1** (0.90 g, 6.12 mmol, 73% yield) as a clear yellow oil. Analytical data for **S1** has been previously reported.<sup>25</sup>

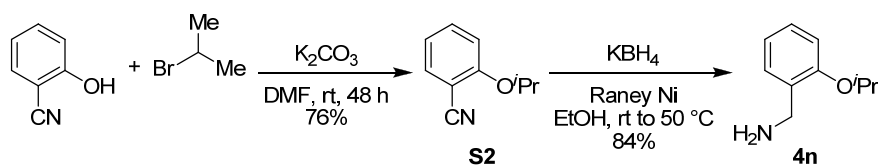

 A 100-mL round bottomed flask containing a magnetic stir bar was charged with *N,N*-dimethylformamide (DMF, 15 mL), potassium carbonate (2.32 g, 16.8 mmol, 2.0 equiv), 2-hydroxybenzonitrile (1.0 g, 8.40 mmol, 1.0 equiv), and bromoethane (0.915 g, 0.622 mL, 8.40 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 17 h, at which point H<sub>2</sub>O (30 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were then washed with H<sub>2</sub>O (30 mL), dried over magnesium sulfate, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded **S1** (0.90 g, 6.12 mmol, 73% yield) as a clear yellow oil. Analytical data for **S1** has been previously reported.<sup>25</sup>

### Preparation of (2-ethoxyphenyl)methanamine (**4m**):

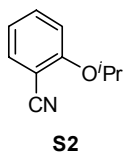


A 100-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (18 mL), potassium borohydride (1.32 g, 24.5 mmol, 4.0 equiv), Raney Ni (0.90 mL of a 50% suspension in H<sub>2</sub>O, approx. 1.0 equiv), and 2-ethoxybenzonitrile (**S1**, 0.90 g, 6.12 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 0.5 h at room temperature. The reaction was warmed to 50 °C and stirred for 3 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (40 mL), washed with H<sub>2</sub>O (3 x 40 mL), dried over magnesium sulfate, and concentrated to afford **4m** (0.658 g, 4.35 mmol, 71% yield) as a clear colorless oil. Analytical data for **4m**: IR (thin film, cm<sup>-1</sup>) 3376, 2979, 2928, 1600, 1588, 1493, 1454, 1118, 1046, 928, 753, 462; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.20 (t, *J* = 6.8 Hz, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 2H), 1.60 (s, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.7, 132.0, 128.4, 127.9, 120.3, 111.1, 63.3, 42.8, 14.9; LRMS (ESI) Calcd. For C<sub>9</sub>H<sub>13</sub>NO+H: 152.1, Found: 152.1.

### Preparation of (2-isopropoxyphenyl)methanamine (**4n**):



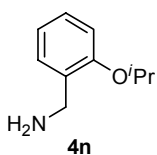
### Preparation of 2-isopropoxybenzonitrile (**S2**):



A 250-mL round bottomed flask containing a magnetic stir bar was charged with *N,N*-dimethylformamide (DMF, 30 mL), potassium carbonate (4.64 g, 33.6 mmol, 2.0 equiv), 2-hydroxybenzonitrile (2.0 g, 16.80 mmol, 1.0 equiv), and 2-bromopropane (2.01 g, 1.58 mL, 16.80 mmol, 1.0 equiv). The reaction was allowed to stir at

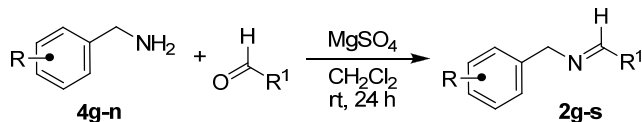
room temperature for 17 h, at which point H<sub>2</sub>O (60 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then washed with H<sub>2</sub>O (60 mL), dried over magnesium sulfate, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded **S2** (2.049 g, 12.71 mmol, 76% yield) as a clear colorless oil. Analytical data for **S2** has been previously reported.<sup>25</sup>

**Preparation of (2-isopropoxyphenyl)methanamine (4n):**



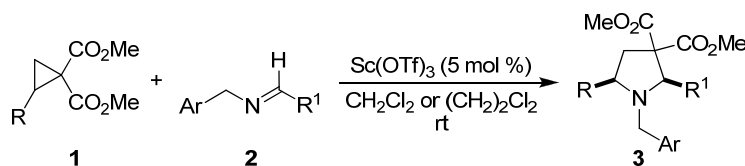
A 250-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (37 mL), potassium borohydride (2.71 g, 24.5 mmol, 4.0 equiv), Raney Ni (1.90 mL of a 50% suspension in H<sub>2</sub>O, approx. 1.0 equiv), and 2-isopropoxybenzonitrile (**S2**, 2.025 g, 12.56 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 0.5 h at room temperature. The reaction was warmed to 50 °C and stirred for 2 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (75 mL), washed with H<sub>2</sub>O (3 x 75 mL), dried over magnesium sulfate, and concentrated to afford **4n** (1.748 g, 10.58 mmol, 84% yield) as a clear colorless oil. Analytical data for **4n**: **IR** (thin film, cm<sup>-1</sup>) 3377, 2977, 2931, 1599, 1488, 1455, 1286, 1237, 1119, 957, 751; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.19 (dd, *J* = 11.8, 4.4 Hz, 2H), 6.87 (dd, *J* = 12.2, 4.6 Hz, 2H), 4.65 – 4.54 (m, 1H), 3.79 (s, 2H), 1.56 (s, 2H), 1.36 (s, 3H), 1.35 (s, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 155.7, 132.9, 128.6, 127.8, 120.2, 112.6, 69.7, 42.9, 22.1; **LRMS** (ESI) Calcd. for C<sub>9</sub>H<sub>11</sub>NO+H: 166.1, Found: 166.1.

**General Procedure A for the preparation of substituted *N*-benzyl-protected aldimines **2g-s**:**



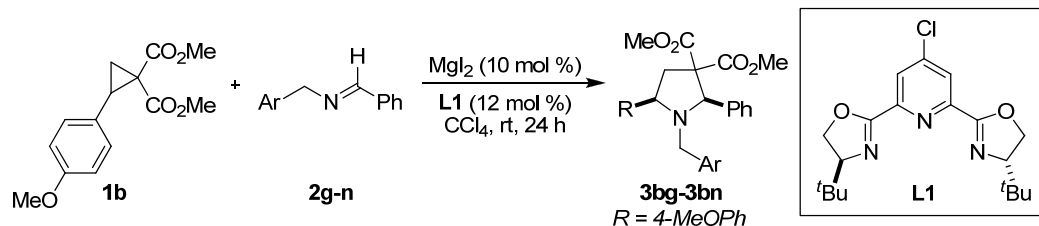
A flame-dried flask was charged with the amine (1.0 equiv), magnesium sulfate (1.5 equiv), and dichloromethane (0.20 – 0.46 M in the amine, concentration is inconsequential). The suspension was stirred for 5 min, at which time the aldehyde (1.0 equiv) was added. The reaction was stirred for 24 h and was then filtered through celite and concentrated to afford aldimines **2g-s** of sufficient purity for subsequent transformations.

**General Procedure B for the preparation of racemic pyrrolidines of type **3**:**



In an inert atmosphere glove box, a 1-dram vial was charged with scandium(III) triflate (0.05 equiv) followed by a solution of cyclopropane **1** and aldimine **2** in dichloromethane or dichloroethane [0.60 M in **1**, CH<sub>2</sub>Cl<sub>2</sub> and (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub> can be used interchangeably]. The vial was removed from the glove box and the reaction was allowed to stir until disappearance of **1** is confirmed by thin layer chromatography (25% EtOAc/hexanes or dichloromethane as the mobile phase) and was quenched by filtration through a 1-inch Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub>. Concentration *in vacuo* affords pyrrolidine **3**, which is purified by flash chromatography using the indicated solvent systems (*vide infra*).

**General Procedure C for the enantioselective  $\text{MgI}_2/\text{L1}$ -catalyzed annulation of cyclopropane **1a** and aldimines **2g-n** to afford pyrrolidines **3bg-3bn** (Table 4-2):**



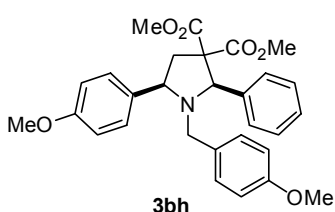
In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar is charged with  $\text{MgI}_2$  (0.0021 g, 0.0076 mmol, 0.10 equiv), **L1** (0.0033 g, 0.0091 mmol, 0.12 equiv), and carbon tetrachloride (0.10 mL). The resulting suspension was allowed to stir vigorously for 1 h, at which point a solution of cyclopropane **1b** (0.020 g, 0.0760 mmol, 1.0 equiv) and aldimine **2** (0.0840 mmol, 1.10 equiv) in carbon tetrachloride (1.40 mL) was added. The vial was removed from the glove box and allowed to stir at room temperature. Upon disappearance of **1b** as confirmed by thin layer chromatography, the reaction was filtered through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (approx 10 mL) and concentrated. Yields were determined by  $^1\text{H}$  NMR using a mesitylene internal standard. Analytically pure material was obtained by purification using flash chromatography.

**Analytical data for (2*R*,5*R*)-dimethyl 1-benzyl-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (**3bg**):**

**IR** (thin film,  $\text{cm}^{-1}$ ) 3027, 2950, 2836, 1732, 1511, 1455, 1283, 1243, 1172, 1032, 832;  **$^1\text{H}$  NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.88 (d,  $J = 7.2$  Hz, 2H), 7.68 (d,  $J = 8.5$  Hz, 2H), 7.30 (t,  $J = 7.5$  Hz, 2H), 7.22 – 7.08 (m, 6H), 6.99 (d,  $J = 8.5$  Hz, 2H), 5.22 (s, 1H), 3.93 – 3.78 (m, 3H), 3.49 (s, 3H), 3.38 (s, 3H), 3.33 (d,  $J = 10.8$  Hz, 1H), 2.95 (s, 3H), 2.59 (dd,  $J = 13.3$ , 6.5 Hz, 1H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 169.8, 159.0, 139.2, 134.7, 133.5, 130.2,

129.1, 129.0, 127.8, 127.6, 127.5, 126.8, 114.0, 69.2, 63.7, 63.2, 55.3, 52.7, 51.9, 51.9, 42.1; **TLC** (20% EtOAc/hexanes)  $R_f$  0.45; **LRMS** (ESI) Calcd. for  $C_{28}H_{29}NO_5+H$ : 460.2, Found: 460.2; SFC analysis (Chiralpack, AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 91:9 er,  $t_r$ -major 4.67 min,  $t_r$ -minor 5.16 min;  $[\alpha]_D^{28} = +44.9$  ( $c = 0.560$ ,  $CHCl_3$ ).

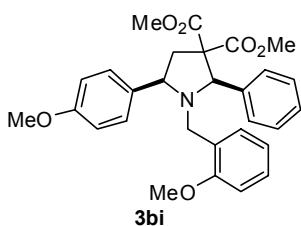
**Analytical data for (2*R*,5*R*)-dimethyl 1-(4-methoxybenzyl) 5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bh):**



**IR** (thin film,  $cm^{-1}$ ) 2951, 2835, 1731, 1611, 1510, 1455, 1434, 1246, 1175, 1034, 830;  **$^1H$  NMR** (400 MHz,  $C_6D_6$ )  $\delta$  7.79 (t,  $J = 12.7$  Hz, 2H), 7.58 (t,  $J = 10.1$  Hz, 2H), 7.22 (t,  $J = 7.5$  Hz, 2H), 7.09 (t,  $J = 7.2$  Hz, 1H), 6.97 (d,  $J = 8.4$  Hz, 2H), 6.90 (d,  $J = 8.5$  Hz, 2H), 6.68 (d,  $J = 8.4$  Hz, 2H), 5.12 (s, 1H), 3.80 (dd,  $J = 10.3, 6.4$  Hz, 1H), 3.73 (d,  $J = 6.9$  Hz, 2H), 3.39 (s, 3H), 3.27 (s, 6H), 3.24 – 3.19 (m, 1H), 2.84 (s, 3H), 2.49 (dd,  $J = 13.3, 6.6$  Hz, 1H);  **$^{13}C$  NMR** (125 MHz,  $CDCl_3$ )  $\delta$  172.0, 169.9, 159.0, 158.4, 139.1, 133.6, 131.4, 129.1, 129.0, 127.8, 127.5, 126.6, 114.0, 113.0, 69.0, 63.6, 62.8, 55.2, 55.1, 52.7, 51.9, 50.7, 42.1; **TLC** (20% EtOAc/hexanes)  $R_f$  0.37; **LRMS** (ESI) Calcd. for  $C_{29}H_{31}NO_6+H$ : 490.2, Found: 490.2. SFC analysis (Chiralpack, AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 90.5:9.5 er,  $t_r$ -major 4.72 min,  $t_r$ -minor 5.35 min;  $[\alpha]_D^{29} = +46.1$  ( $c = 0.550$ ,  $CHCl_3$ ).

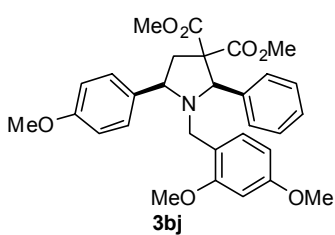


**Analytical data for (2*R*,5*R*)-dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bi):**



**IR** (thin film,  $\text{cm}^{-1}$ ) 2952, 2836, 1731, 1511, 1435, 1282, 1243, 1173, 1032, 832;  **$^1\text{H}$  NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.75 (d,  $J = 7.3$  Hz, 2H), 7.57 (d,  $J = 8.6$  Hz, 2H), 7.19 – 7.15 (m, 2H), 7.06 (dt,  $J = 11.1, 4.8$  Hz, 2H), 7.00 – 6.93 (m, 1H), 6.87 (d,  $J = 8.6$  Hz, 2H), 6.72 (t,  $J = 7.3$  Hz, 1H), 6.40 (t,  $J = 8.8$  Hz, 1H), 5.29 (s, 1H), 4.02 (d,  $J = 13.7$  Hz, 1H), 3.97 – 3.85 (m, 2H), 3.38 (s, 3H), 3.28 (s, 3H), 3.22 (s, 3H), 3.19 (m, 1H), 2.83 (s, 3H), 2.57 (dd,  $J = 13.2, 6.1$  Hz, 1H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 170.0, 140.4, 134.3, 132.3, 128.9, 128.8, 128.2, 127.3, 127.1, 124.5, 119.4, 113.6, 109.8, 69.7, 64.2, 55.3, 54.5, 52.7, 51.8, 47.3, 42.5; **TLC** (15% EtOAc/hexanes)  $R_f$  0.17; **LRMS** (ESI) Calcd. for  $\text{C}_{29}\text{H}_{31}\text{NO}_6 + \text{H}$ : 490.2, Found: 490.2. SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 95:5 er,  $t_r$ -major 7.41 min,  $t_r$ -minor 8.14 min;  $[\alpha]_D^{29} = +60.4$  ( $c = 0.580$ ,  $\text{CHCl}_3$ ).

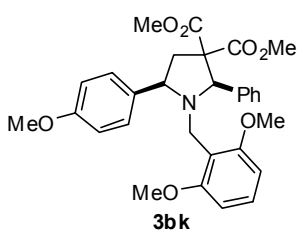
**Analytical data for (2*R*,5*R*)-dimethyl 1-(2,4-dimethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bj):**



**IR** (thin film,  $\text{cm}^{-1}$ ) 3001, 2952, 2836, 1732, 1611, 1509, 1291, 1245, 1209, 1172, 1038, 832, 701;  **$^1\text{H}$  NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.92 (d,  $J = 7.4$  Hz, 2H), 7.72 (d,  $J = 8.5$  Hz, 2H), 7.32 (t,  $J = 7.5$  Hz, 2H), 7.20 (t,  $J = 7.2$  Hz, 1H), 7.08 (d,  $J = 8.2$  Hz, 1H), 7.02 (d,  $J = 8.5$  Hz, 2H), 6.39 (s, 1H), 6.34 (d,  $J = 8.2$  Hz, 1H), 5.43 (s, 1H), 4.12 (d,  $J = 13.9$  Hz, 1H), 4.06 (dd,  $J = 10.8, 6.3$  Hz, 1H), 4.00 (d,  $J = 13.9$  Hz, 1H), 3.51 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 3.36 (d,  $J = 13.2$  Hz, 1H), 3.31 (s, 3H), 2.95 (s, 3H), 2.71 (dd,  $J = 13.2, 6.2$  Hz, 1H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 169.8, 158.7, 140.3, 134.4, 132.8, 128.9, 128.8, 127.3, 127.1, 116.9, 113.6, 103.1, 97.7, 69.5, 64.1, 63.8, 55.2, 55.2, 54.5, 52.7, 51.8, 46.5,

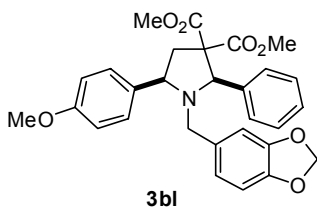
42.5; **TLC** (20% EtOAc/hexanes)  $R_f$  0.27; **LRMS** (ESI) Calcd. for  $C_{30}H_{33}NO_7+H$ : 520.2, Found: 520.2. SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 93:7 er,  $t_r$ -major 8.79 min,  $t_r$ -minor 9.56 min;  $[\alpha]_D^{28} = +57.6$  ( $c = 0.610$ ,  $CHCl_3$ ).

**Analytical data for (2*R*,5*R*)-dimethyl 1-(2,6-dimethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bk):**



**mp** 49-52 °C; **IR** (thin film,  $cm^{-1}$ ) 2951, 2836, 1733, 1595, 1511, 1474, 1245, 1173, 1116, 831;  **$^1H$  NMR** (400 MHz,  $C_6D_6$ )  $\delta$  7.83 (d,  $J = 7.3$  Hz, 2H), 7.69 (d,  $J = 8.6$  Hz, 2H), 7.23 (t,  $J = 7.5$  Hz, 2H), 7.14 (t,  $J = 7.2$  Hz, 1H), 6.97 (dd,  $J = 8.4, 6.2$  Hz, 3H), 6.18 (d,  $J = 8.3$  Hz, 2H), 5.54 (s, 1H), 4.23 (dd,  $J = 28.3, 12.5$  Hz, 2H), 4.12 (dd,  $J = 11.3, 5.8$  Hz, 1H), 3.53 (s, 3H), 3.45 (s, 3H), 3.38 (s, 6H), 3.31 (dd,  $J = 13.0, 11.5$  Hz, 1H), 2.95 (s, 3H), 2.77 (dd,  $J = 13.2, 5.8$  Hz, 1H).;  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  172.3, 169.5, 158.9, 158.6, 141.4, 135.3, 128.6, 128.4, 128.1, 126.7, 114.1, 113.2, 102.7, 70.6, 65.9, 64.7, 55.2, 54.9, 52.7, 51.6, 43.0, 42.6; **TLC** (20% EtOAc/hexanes)  $R_f$  0.23; **LRMS** (ESI) Calcd. for  $C_{30}H_{33}NO_7+H$ : 520.2, Found: 520.2. SFC analysis (Chiralcel, OD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 89.5:10.5 er,  $t_r$ -major 7.38 min,  $t_r$ -minor 8.21 min;  $[\alpha]_D^{29} = +60.5$  ( $c = 0.270$ ,  $CHCl_3$ ).

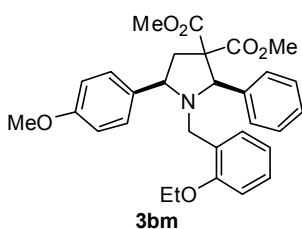
**Analytical data for (2*R*,5*R*)-dimethyl 1-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bl):**



**mp** 58-60 °C; **IR** (thin film,  $cm^{-1}$ ) 2952, 2891, 2837, 1731, 1511, 1488, 1440, 1243, 1039, 930, 833, 737, 702;  **$^1H$  NMR** (400 MHz,  $C_6D_6$ )  $\delta$  7.85 (d,  $J = 7.4$  Hz, 2H), 7.65 (d,  $J = 8.5$  Hz, 2H), 7.29 (t,  $J = 6.0$  Hz, 2H), 7.17 (t,  $J = 7.3$  Hz, 1H), 6.96 (d,  $J = 8.6$  Hz, 2H), 6.74 (s, 1H), 6.67 (d,  $J =$

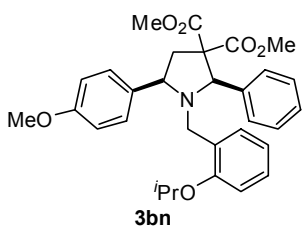
7.8 Hz, 1H), 6.57 (d,  $J = 7.8$  Hz, 1H), 5.38 (dd,  $J = 9.4, 1.2$  Hz, 2H), 5.22 (s, 1H), 3.92 (dd,  $J = 10.7, 6.5$  Hz, 1H), 3.82 – 3.71 (m, 2H), 3.48 (s, 3H), 3.40 (s, 3H), 3.37 – 3.31 (m, 1H), 2.94 (s, 3H), 2.61 (dd,  $J = 13.3, 6.5$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 169.7, 159.1, 147.0, 146.3, 139.4, 133.6, 129.0, 127.8, 127.5, 123.3, 114.0, 110.5, 107.4, 100.6, 69.6, 63.9, 63.7, 55.3, 52.6, 52.3, 51.8, 42.2; **TLC** (20% EtOAc/hexanes)  $R_f$  0.27; **LRMS** (ESI) Calcd. for  $\text{C}_{29}\text{H}_{29}\text{NO}_7 + \text{H}$ : 504.2, Found: 504.2. SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 92:8 er,  $t_r$ -major 7.29 min,  $t_r$ -minor 7.84 min;  $[\alpha]_D^{27} = +45.0$  ( $c = 0.280$ ,  $\text{CHCl}_3$ ).

**Analytical data for (2*R*,5*R*)-dimethyl 1-(2-ethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bm):**



**IR** (thin film,  $\text{cm}^{-1}$ ) 3027, 2950, 2837, 1732, 1511, 1493, 1455, 1289, 1241, 1172, 1049, 831;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.70 (d,  $J = 7.4$  Hz, 2H), 7.57 (d,  $J = 8.5$  Hz, 2H), 7.17 – 7.15 (m, 1H), 7.12 – 7.09 (m, 2H), 7.02 (t,  $J = 7.5$  Hz, 2H), 6.93 (m, 1H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.71 (t,  $J = 7.3$  Hz, 1H), 6.35 (d,  $J = 8.2$  Hz, 1H), 5.47 (s, 1H), 4.07 (d,  $J = 13.3$  Hz, 1H), 3.98 – 3.93 (m, 2H), 3.52 – 3.42 (m, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 3.22 (dd,  $J = 13.1, 11.4$  Hz, 1H), 2.82 (s, 3H), 2.62 (dd,  $J = 13.2, 5.9$  Hz, 1H), 1.11 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 169.5, 158.8, 157.2, 140.6, 134.2, 132.1, 128.8, 128.7, 128.0, 127.1, 126.9, 125.4, 119.2, 113.6, 110.6, 70.2, 65.2, 64.4, 63.0, 55.3, 52.8, 51.8, 48.8, 42.5, 14.8; **TLC** (15% EtOAc/hexanes)  $R_f$  0.23; **LRMS** (ESI) Calcd. for  $\text{C}_{30}\text{H}_{33}\text{NO}_6 + \text{H}$ : 504.2, Found: 504.2; SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 94:6 er,  $t_r$ -major 7.43 min,  $t_r$ -minor 8.11 min;  $[\alpha]_D^{28} = +58.3$  ( $c = 0.260$ ,  $\text{CHCl}_3$ ).

**Analytical data for (2*R*,5*R*)-dimethyl 1-(2-isopropoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bn):**



**IR** (thin film,  $\text{cm}^{-1}$ ) 2951, 2837, 1734, 1512, 1490, 1455, 1286,

1243, 1173, 957, 831;  **$^1\text{H}$  NMR** (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.73 (d,  $J$  = 7.4 Hz, 2H), 7.58 (d,  $J$  = 8.4 Hz, 2H), 7.18 (d,  $J$  = 7.2 Hz, 1H), 7.13 (d,

$J$  = 7.6 Hz, 2H), 7.03 (t,  $J$  = 7.3 Hz, 1H), 6.93 (t,  $J$  = 7.5 Hz, 1H),

6.87 (d,  $J$  = 8.4 Hz, 2H), 6.69 (t,  $J$  = 7.3 Hz, 1H), 6.47 (d,  $J$  = 8.2 Hz, 1H), 5.39 (s, 1H), 4.06

(d,  $J$  = 13.4 Hz, 1H), 4.02 (dd,  $J$  = 13.2, 6.4 Hz, 1H), 3.97 (d,  $J$  = 13.7 Hz, 2H), 3.37 (s, 3H),

3.31 (s, 3H), 3.25 – 3.18 (m, 1H), 2.82 (s, 3H), 2.62 (dd,  $J$  = 13.2, 5.9 Hz, 1H), 1.10 (d,  $J$  =

6.0 Hz, 3H), 1.01 (d,  $J$  = 6.0 Hz, 3H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 169.5, 158.7,

156.4, 140.6, 134.2, 132.4, 128.8, 128.7, 127.9, 127.1, 126.9, 126.1, 119.2, 113.7, 112.6,

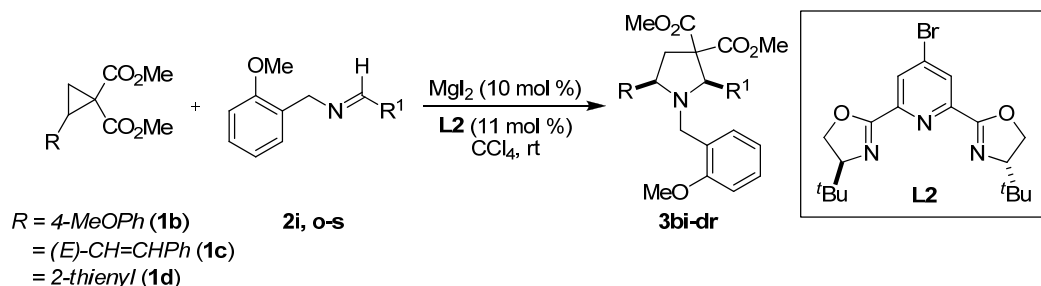
70.2, 69.8, 64.8, 64.4, 55.3, 52.8, 51.8, 48.5, 42.4, 22.1, 22.0; **TLC** (15% EtOAc/hexanes)  $R_f$

0.22; **LRMS** (ESI) Calcd. for  $\text{C}_{31}\text{H}_{35}\text{NO}_6 + \text{H}$ : 518.2, Found: 518.3; SFC analysis (Chiralcel,

OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 94:6 er,  $t_r$ -major 8.82 min,  $t_r$ -minor 9.79

min;  $[\alpha]_D^{27} = +53.0$  ( $c$  = 0.230,  $\text{CHCl}_3$ ).

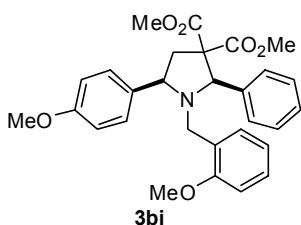
**General Procedure D for the enantioselective  $\text{MgI}_2/\text{L2}$ -catalyzed annulation of cyclopropanes 1b-d and aldimines 2i, o-s to afford pyrrolidines 3bi-3dr (Figure 4-1):**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with  $\text{MgI}_2$  (0.0042 g, 0.0151 mmol, 0.10 equiv), **L2** (0.0068 g, 0.0166 mmol, 0.11 equiv),

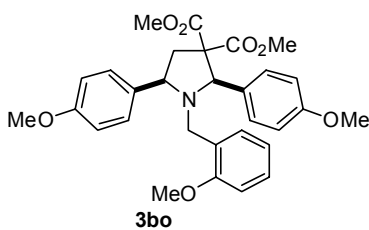
and carbon tetrachloride (0.20 mL). The vial was sealed with a PTFE-lined screw cap and the suspension was stirred vigorously until a pale yellow complex is formed (approx. 1 h) at which point a solution of cyclopropane (0.151 mmol, 1.0 equiv) and aldimine (0.166 mmol, 1.10 equiv) in carbon tetrachloride (2.80 mL) was added. The vial was recapped, removed from the box, and allowed to stir. When disappearance of the cyclopropane was confirmed by thin layer chromatography, the contents of the vial were filtered through a 1-inch Monstr-Pette plug of silica gel with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The resulting solution was concentrated and purified by flash chromatography using the indicated solvent system.

**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (**3bi**):**



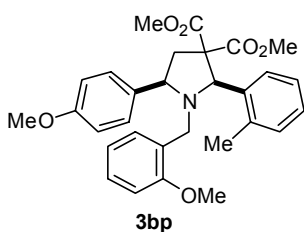
The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**2i**, 0.038 g, 0.166 mmol, 1.10 equiv). After 15 h, the reaction was worked up and **3bi** was obtained in 97:3 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided **3bi** (0.052 g, 0.106 mmol, 70% yield) as a waxy white solid in 96.5:3.5 er as determined by SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t*<sub>r</sub>-major 7.41 min, *t*<sub>r</sub>-minor 8.14 min; [α]<sub>D</sub><sup>26</sup> = +76.6 (*c* = 0.280, CHCl<sub>3</sub>).

**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-2,5-bis(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (**3bo**):**



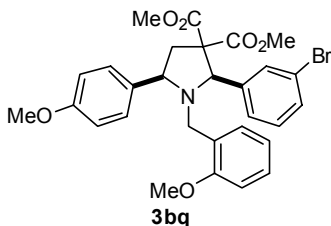
The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(4-methoxybenzylidene)-1-(2-methoxyphenyl)methanamine (**2o**, 0.042 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **3bo** was obtained in 96:4 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3bo** (0.063 g, 0.121 mmol, 80% yield) as a white solid in 92.5:7.5 er as determined by SFC analysis (Chiralcel, OD, 10.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 5.7 min, *t<sub>r</sub>*-minor 6.3 min. Analytical data for **3bo**: mp 50-52 °C; IR (thin film, cm<sup>-1</sup>) 2953, 2837, 1732, 1510, 1273, 1245, 1172, 1034, 831, 759; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.14 – 7.08 (m, 1H), 6.99 (dd, *J* = 11.1, 4.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.74 (dd, *J* = 13.9, 6.6 Hz, 1H), 6.42 (d, *J* = 8.1 Hz, 1H), 5.26 (s, 1H), 4.04 (d, *J* = 13.8 Hz, 1H), 3.94 (d, *J* = 13.4 Hz, 1H), 3.92 (dd, *J* = 10.4, 6.7 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 3.23 – 3.17 (m, 1H), 2.90 (s, 3H), 2.58 (dd, *J* = 13.2, 6.2 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.2, 169.8, 158.7, 158.6, 157.9, 134.3, 132.3, 132.3, 129.9, 128.7, 128.2, 124.5, 119.4, 113.6, 112.7, 109.8, 69.2, 64.0, 64.0, 55.2, 55.1, 54.5, 52.7, 51.9, 47.0, 42.4; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.14; LRMS (ESI) Calcd. for C<sub>30</sub>H<sub>33</sub>NO<sub>7</sub>+H: 520.2, Found: 520.2; [α]<sub>D</sub><sup>26</sup> = +38.8 (*c* = 0.370, CHCl<sub>3</sub>).

**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-2,5-bis(2-methylphenyl)pyrrolidine-3,3-dicarboxylate (**3bp**):**



The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(2-methylbenzylidene)-1-(2-methoxyphenyl)methanamine (**2p**, 0.040 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **3bp** was obtained in 98:2 dr as determined by  $^1\text{H}$  NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3bp** (0.067 g, 0.134 mmol, 89% yield) as a white solid in 94.5:5.5 er as determined by SFC analysis (Chiralcel, OD, 6.0% MeOH, 2.0 mL/min, 200 bar, 220 nm)  $t_{\text{r}}$ -major 7.6 min,  $t_{\text{r}}$ -minor 8.2 min. Analytical data for **3bp**: IR (thin film,  $\text{cm}^{-1}$ ) 2952, 1731, 1512, 1266, 1246, 1173, 1034, 832, 738, 704;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.16 (d,  $J = 7.8$  Hz, 1H), 7.56 (d,  $J = 8.5$  Hz, 2H), 7.14 (s, 1H), 7.07 (d,  $J = 7.3$  Hz, 1H), 6.99 (t,  $J = 7.3$  Hz, 1H), 6.96 – 6.89 (m, 2H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.68 (t,  $J = 7.4$  Hz, 1H), 6.32 (d,  $J = 8.2$  Hz, 1H), 5.60 (s, 1H), 4.06 (dd,  $J = 11.8, 5.0$  Hz, 1H), 4.01 (d,  $J = 13.4$  Hz, 1H), 3.90 (d,  $J = 13.4$  Hz, 1H), 3.37 (s, 3H), 3.33 (d,  $J = 12.6$  Hz, 1H), 3.29 (s, 3H), 3.21 (s, 3H), 2.80 (s, 3H), 2.62 (dd,  $J = 13.1, 5.1$  Hz, 1H), 2.44 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 169.4, 158.9, 157.7, 138.9, 137.0, 134.0, 131.8, 129.1, 128.8, 128.7, 128.2, 126.6, 125.3, 124.9, 119.4, 113.6, 109.5, 65.1, 65.0, 64.0, 55.3, 54.5, 52.9, 51.6, 48.8, 43.4, 19.5; TLC (15% EtOAc/hexanes)  $R_f$  0.20; LRMS (ESI) Calcd. for  $\text{C}_{30}\text{H}_{33}\text{NO}_6 + \text{H}$ : 504.3, Found: 504.3;  $[\alpha]_{\text{D}}^{27} = +76.9$  ( $c = 0.300$ ,  $\text{CHCl}_3$ ).

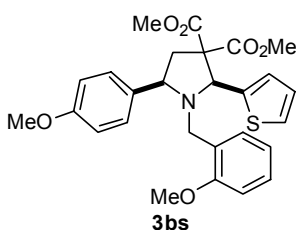
**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-2,5-bis(3-bromophenyl)pyrrolidine-3,3-dicarboxylate (**3bq**):**



The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(3-bromobenzylidene)-1-(2-methoxyphenyl)methanamine (**2q**, 0.050 g, 0.166 mmol, 1.10 equiv). After 24 h, the reaction was worked up and **3bq** was obtained in 98:2 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **3bq** (0.055 g, 0.097 mmol, 64% yield) as a white solid in 96:4 er as determined by SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 12.1 min, *t<sub>r</sub>*-minor 13.2 min. Analytical data for **3bq**: mp 48-51 °C; IR (thin film, cm<sup>-1</sup>) 2952, 2835, 1733, 1511, 1465, 1434, 1247, 1174, 1033, 832, 737; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 8.05 (s, 1H), 7.70 – 7.60 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.06 (dd, *J* = 10.7, 4.9 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.94 – 6.86 (m, 1H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.29 (s, 1H), 4.09 (d, *J* = 13.3 Hz, 1H), 3.95 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.30 – 3.21 (m, 1H), 2.96 (s, 3H), 2.63 (dd, *J* = 13.3, 6.1 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.9, 169.3, 159.0, 157.9, 143.1, 133.8, 132.1, 131.9, 130.0, 128.8, 128.7, 128.5, 127.4, 124.6, 121.2, 119.5, 113.8, 69.7, 64.8, 64.3, 55.3, 54.6, 52.8, 51.9, 48.3, 42.3; TLC (10% EtOAc/hexanes) *R<sub>f</sub>* 0.16; LRMS (ESI) Calcd. for C<sub>29</sub>H<sub>30</sub>NO<sub>6</sub>+Cs: 700.1, Found: 700.0; [α]<sub>D</sub><sup>26</sup> = +35.7 (*c* = 0.280, CHCl<sub>3</sub>).

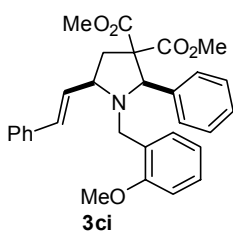


**(2*S*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (**3bs**):**



The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-1-(2-methoxyphenyl)-*N*-(thiophen-2-ylmethylene)methanamine (**2s**, 0.038 g, 0.166 mmol, 1.10 equiv). After 22 h, the reaction was worked up and **3bs** was obtained in 93:7 dr as determined by  $^1\text{H}$  NMR spectroscopy. Flash chromatography (20% EtOAc/hexanes) provided pure **3bs** (0.063 g, 0.127 mmol, 84% yield) as a white solid in 98:2 er as determined by SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm)  $t_{\text{r}}$ -major 12.9 min,  $t_{\text{r}}$ -minor 14.4 min. Analytical data for **3bs**: mp 44-47 °C; IR (thin film,  $\text{cm}^{-1}$ ) 2953, 2837, 1733, 1512, 1272, 1245, 1173, 1034, 832, 703;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.60 (d,  $J = 8.5$  Hz, 2H), 7.19 – 7.16 (m, 1H), 7.04 – 6.98 (m, 2H), 6.92 (d,  $J = 5.0$  Hz, 1H), 6.87 (d,  $J = 8.5$  Hz, 2H), 6.79 – 6.72 (m, 2H), 6.47 (d,  $J = 8.1$  Hz, 1H), 5.73 (s, 1H), 4.23 (d,  $J = 13.7$  Hz, 1H), 4.00 (d,  $J = 13.8$  Hz, 1H), 3.96 (dd,  $J = 11.4, 5.4$  Hz, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 3.26 (s, 3H), 3.24 – 3.18 (m, 1H), 3.04 (s, 3H), 2.61 (dd,  $J = 13.0, 5.4$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7, 168.9, 158.9, 158.0, 147.3, 133.7, 132.2, 128.8, 128.4, 126.0, 124.8, 124.6, 119.5, 113.6, 109.9, 64.6, 64.6, 64.0, 55.2, 54.7, 52.9, 52.2, 47.6, 41.8; TLC (20% EtOAc/hexanes)  $R_{\text{f}}$  0.20; LRMS (ESI) Calcd. for  $\text{C}_{27}\text{H}_{29}\text{NO}_6\text{S}+\text{H}$ : 496.2, Found: 496.3;  $[\alpha]_{\text{D}}^{28} = +82.3$  ( $c = 0.470$ ,  $\text{CHCl}_3$ ).

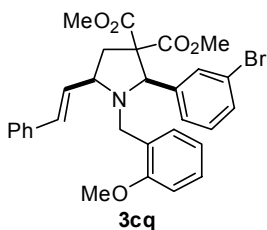
**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-2-phenyl-5-styrylpyrrolidine-3,3-dicarboxylate (**3ci**):**



The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**2i**, 0.038 g, 0.166 mmol, 1.10 equiv).

After 26 h, the reaction was worked up and **3ci** was obtained in 91:9 dr as determined by  $^1\text{H}$  NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3ci** (0.054 g, 0.112 mmol, 74% yield) as a clear colorless oil with both diastereomers enriched to 98:2 er as determined by SFC analysis (Chiralcel, OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 220 nm)  $t_{\text{r-major (cis)}}$  24.8 min,  $t_{\text{r-minor (cis)}}$  27.3 min,  $t_{\text{r-major (trans)}}$  21.7 min,  $t_{\text{r-minor (trans)}}$  22.9 min. Analytical data for **3ci**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3028, 2951, 2836, 1733, 1493, 1435, 1268, 1246, 966, 753, 701;  $^1\text{H}$  **NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 7.2$  Hz, 2H), 7.21 (d,  $J = 4.0$  Hz, 4H), 7.15 (dd,  $J = 9.5, 4.8$  Hz, 3H), 7.11 – 7.06 (m, 2H), 6.98 (t,  $J = 7.8$  Hz, 1H), 6.70 (t,  $J = 7.4$  Hz, 1H), 6.54 (d,  $J = 8.2$  Hz, 1H), 6.47 (d,  $J = 15.9$  Hz, 1H), 6.09 (dd,  $J = 15.9, 8.0$  Hz, 1H), 4.70 (s, 1H), 3.76 – 3.66 (m, 2H), 3.64 (s, 3H), 3.56 (s, 3H), 3.34 (dt,  $J = 10.4, 7.1$  Hz, 1H), 2.97 (s, 3H), 2.70 (dd,  $J = 13.1, 10.9$  Hz, 1H), 2.19 (dd,  $J = 13.2, 6.0$  Hz, 1H);  $^{13}\text{C}$  **NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 169.5, 157.7, 140.2, 137.3, 132.2, 131.7, 131.1, 128.8, 128.4, 128.0, 127.4, 127.2, 126.3, 126.2, 119.7, 110.0, 71.3, 64.7, 64.4, 54.9, 52.7, 51.8, 48.7, 39.5; **TLC** (15% EtOAc/hexanes)  $R_f$  0.22; **LRMS** (ESI) Calcd. for  $\text{C}_{30}\text{H}_{31}\text{NO}_5 + \text{H}$ : 486.2, Found: 486.2;  $[\alpha]_{\text{D}}^{28} = +125.4$  ( $c = 0.430$ ,  $\text{CHCl}_3$ ).

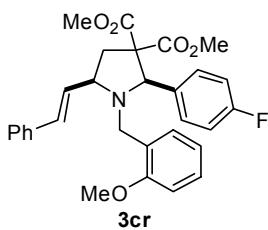
**(2*R*,5*R*)-Dimethyl 2-(3-bromophenyl)-1-(2-methoxybenzyl)-5-styrylpyrrolidine-3,3-dicarboxylate (**3cq**):**



The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(3-bromobenzylidene)-1-(2-methoxyphenyl)methanamine (**2q**, 0.050 g, 0.166 mmol, 1.10 equiv).

After 39 h, the reaction was worked up and **3cq** was obtained in 93:7 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **3cq** (0.060 g, 0.106 mmol, 70% yield) as a white solid in 96.5:3.5 er as determined by SFC analysis (Chiralcel, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 19.7 min, *t<sub>r</sub>*-minor 21.8 min. Analytical data for **3cq**: mp 41-44 °C; IR (thin film, cm<sup>-1</sup>) 2952, 1733, 1493, 1435, 1266, 1198, 1174, 1070, 967, 737, 695; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.55 (s, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 14.5, 7.2 Hz, 3H), 7.31 – 7.24 (m, 2H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.66 (s, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.76 (s, 1H), 3.87 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.71 (d, *J* = 10.5 Hz, 1H), 3.69 (s, 3H), 3.44 (dt, *J* = 10.2, 7.6 Hz, 1H), 3.16 (s, 3H), 2.76 (dd, *J* = 13.0, 11.1 Hz, 1H), 2.31 (dd, *J* = 13.3, 6.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.8, 169.2, 157.7, 142.8, 137.0, 131.8, 131.7, 131.6, 130.1, 128.8, 128.5, 128.3, 127.4, 127.3, 126.3, 125.5, 121.4, 119.6, 109.8, 70.3, 64.3, 64.3, 54.8, 52.9, 52.0, 48.9, 39.2; TLC (10% EtOAc/hexanes) R<sub>f</sub> 0.18; LRMS (ESI) Calcd. for C<sub>30</sub>H<sub>30</sub>BrNO<sub>5</sub>+Cs: 696.1, Found: 696.0; [α]<sub>D</sub><sup>28</sup> = +124.6 (*c* = 0.290, CHCl<sub>3</sub>).

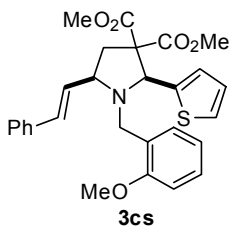
**(2*R*,5*R*)-Dimethyl 2-(4-fluorophenyl)-1-(2-methoxybenzyl)-5-styrylpyrrolidine-3,3-dicarboxylate (**3cr**):**



The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(4-fluorobenzylidene)-1-(2-methoxyphenyl)methanamine (**2r**, 0.050 g, 0.166 mmol, 1.10 equiv).

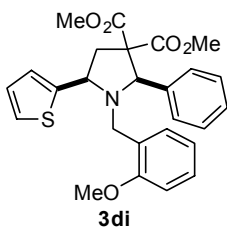
After 39 h, the reaction was worked up and **3cr** was obtained in 93:7 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **3cr** (0.055 g, 0.109 mmol, 73% yield) as a waxy slightly yellow solid in 97.5:2.5 er as determined by SFC analysis (Chiralcel, OD, 1.5% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 33.6 min, *t<sub>r</sub>*-minor 38.6 min. Analytical data for **3cr**: IR (thin film, cm<sup>-1</sup>) 2952, 2837, 1733, 1602, 1507, 1278, 1245, 1222, 966, 850, 692; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 4H), 7.23 (t, *J* = 6.4 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 8.7 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.18 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.76 (s, 1H), 3.80 (d, *J* = 13.8 Hz, 1H), 3.73 (s, 3H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.65 (s, 3H), 3.42 (dt, *J* = 10.4, 7.9 Hz, 1H), 3.12 (s, 3H), 2.75 (dd, *J* = 13.2, 10.9 Hz, 1H), 2.28 (dd, *J* = 13.3, 6.1 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.0, 169.5, 163.0, 161.1, 157.6, 137.1, 135.8, 131.9, 131.7, 131.4, 130.3, 130.2, 128.4, 128.1, 127.4, 126.3, 125.8, 119.7, 114.2, 114.0, 109.9, 70.4, 64.6, 64.2, 54.8, 52.9, 52.0, 48.7, 39.3; TLC (10% EtOAc/hexanes) *R<sub>f</sub>* 0.10; LRMS (ESI) Calcd. for C<sub>30</sub>H<sub>30</sub>FNO<sub>5</sub>+H: 504.2, Found: 504.2; [α]<sub>D</sub><sup>29</sup> = +107.8 (*c* = 0.400, CHCl<sub>3</sub>).

**(2*S*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-5-styryl-2-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (**3cs**):**



The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-1-(2-methoxyphenyl)-*N*-(thiophen-2-ylmethylene)methanamine (**2s**, 0.038 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **3cs** was obtained in 87:13 dr as determined by <sup>1</sup>H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3cs** (0.061 g, 0.124 mmol, 82% yield) as a waxy slightly yellow solid in 97.5:2.5 er as determined by SFC analysis (Chiralcel, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 33.6 min, *t<sub>r</sub>*-minor 38.6 min. Analytical data for **3cs**: **IR** (thin film, cm<sup>-1</sup>) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.35 – 7.28 (m, 4H), 7.26 – 7.24 (m, 1H), 7.24 – 7.20 (m, 1H), 7.17 – 7.15 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 3.6 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.0 Hz, 1H), 5.15 (s, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.85 (d, *J* = 13.9 Hz, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.45 – 3.38 (m, 1H), 3.32 (s, 3H), 2.77 (dd, *J* = 12.9, 11.2 Hz, 1H), 2.29 (dd, *J* = 13.2, 5.6 Hz, 1H); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 171.6, 169.0, 157.7, 146.4, 137.1, 131.8, 131.7, 131.2, 128.4, 128.1, 127.3, 126.3, 126.1, 126.0, 125.0, 124.8, 119.7, 110.0, 66.0, 64.5, 64.2, 54.9, 52.9, 52.3, 48.6, 38.8; **TLC** (15% EtOAc/hexanes) *R<sub>f</sub>* 0.14; **LRMS** (ESI) Calcd. for C<sub>28</sub>H<sub>29</sub>NO<sub>5</sub>S+H: 492.2, Found: 492.2; [α]<sub>D</sub><sup>28</sup> = +126.7 (*c* = 0.370, CHCl<sub>3</sub>).

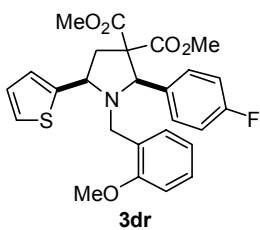
**(2*R*,5*R*)-Dimethyl 1-(2-methoxybenzyl)-2-phenyl-5-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (**3di**):**



The title compound was prepared according to General Procedure D using dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (**1d**, 0.036 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**2i**, 0.038 g, 0.166 mmol, 1.10 equiv).

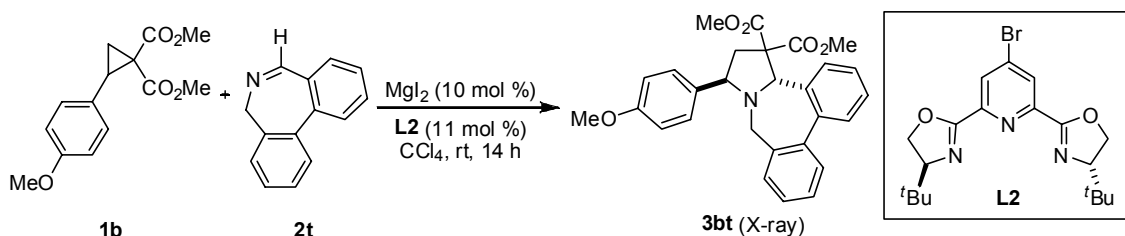
After 24 h, the reaction was worked up and **3di** was obtained in 87:13 dr as determined by  $^1\text{H}$  NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3di** (0.046 g, 0.100 mmol, 66% yield) as a clear slightly yellow oil with the major (*cis*) diastereomer in 97.5:2.5 er as determined by SFC analysis (Chiralcel, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm)  $t_{\text{r}}$ -major 9.5 min,  $t_{\text{r}}$ -minor 10.3 min. Analytical data for **3di**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 7.2$  Hz, 2H), 7.31 (d,  $J = 4.5$  Hz, 1H), 7.25 (t,  $J = 7.0$  Hz, 3H), 7.19 (d,  $J = 7.2$  Hz, 1H), 7.17 – 7.08 (m, 2H), 7.04 – 6.94 (m, 2H), 6.80 – 6.72 (m, 1H), 6.70 (d,  $J = 8.1$  Hz, 1H), 4.91 (s, 1H), 4.19 (dd,  $J = 10.7, 6.0$  Hz, 1H), 3.82 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.06 (s, 3H), 2.93 (dd,  $J = 13.3, 10.9$  Hz, 1H), 2.48 (dd,  $J = 13.3, 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8, 169.0, 158.0, 147.8, 140.4, 132.3, 128.8, 128.3, 127.2, 126.1, 124.7, 124.4, 119.5, 110.0, 69.5, 64.4, 60.6, 54.6, 52.7, 51.8, 47.7, 42.9; **TLC** (15% EtOAc/hexanes)  $R_f$  0.25; **LRMS** (ESI) Calcd. for  $\text{C}_{26}\text{H}_{27}\text{NO}_5\text{S}+\text{H}$ : 466.2, Found: 466.2;  $[\alpha]_{\text{D}}^{26} = +80.9$  ( $c = 0.400$ ,  $\text{CHCl}_3$ ).

**(2*R*,5*R*)-Dimethyl 2-(4-fluorophenyl)-1-(2-methoxybenzyl)-5-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (**3dr**):**



The title compound was prepared according to General Procedure D using (*E*)-dimethyl dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (**1d**, 0.036 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(2-fluorobenzylidene)-1-(2-methoxyphenyl)methanamine (**2r**, 0.050 g, 0.166 mmol, 1.10 equiv). After 30 h, the reaction was worked up and **3dr** was obtained in 97:3 dr as determined by  $^1\text{H}$  NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **3dr** (0.050 g, 0.103 mmol, 68% yield) as a clear slightly yellow oil with the major (*cis*) diastereomer in 95.5:4.5 er as determined by SFC analysis (Chiralcel, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm)  $t_{\text{r}}$ -major 8.9 min,  $t_{\text{r}}$ -minor 9.8 min. Analytical data for **3dr**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3070, 3001, 2952, 2837, 1734, 1602, 1507, 1281, 1244, 849, 823, 517;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.35 (m, 2H), 7.31 (d,  $J$  = 4.9 Hz, 1H), 7.15 – 7.07 (m, 2H), 6.99 (dt,  $J$  = 6.3, 3.1 Hz, 1H), 6.96 (d,  $J$  = 7.4 Hz, 1H), 6.90 (t,  $J$  = 8.7 Hz, 2H), 6.74 (t,  $J$  = 7.3 Hz, 1H), 6.66 (d,  $J$  = 8.2 Hz, 1H), 4.87 (s, 1H), 4.16 (dd,  $J$  = 10.8, 6.0 Hz, 1H), 3.78 (d,  $J$  = 6.1 Hz, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.11 (s, 3H), 2.90 (dd,  $J$  = 13.3, 10.9 Hz, 1H), 2.48 (dd,  $J$  = 13.4, 6.0 Hz, 1H)  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8, 169.0, 163.3, 160.8, 157.9, 147.5, 136.1, 132.2, 130.4, 130.3, 128.4, 126.2, 124.9, 124.7, 124.5, 119.6, 114.1, 113.9, 110.0, 69.0, 64.3, 60.8, 54.7, 52.8, 51.9, 48.0, 42.7; **TLC** (15% EtOAc/hexanes)  $R_{\text{f}}$  0.18; **LRMS** (ESI) Calcd. for  $\text{C}_{26}\text{H}_{26}\text{FNO}_5\text{S}+\text{Na}$ : 506.2, Found: 506.2;  $[\alpha]_{\text{D}}^{29} = +46.7$  ( $c$  = 0.400,  $\text{CHCl}_3$ ).

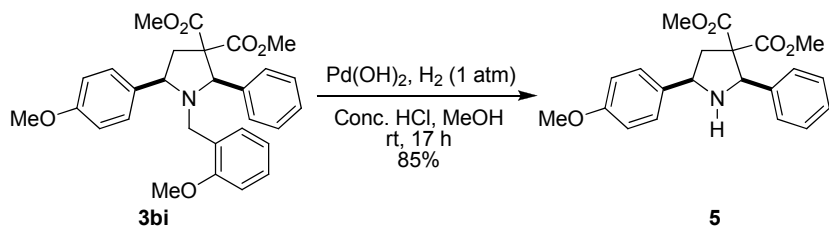
**Preparation of (dimethyl 7-(4-methoxyphenyl)-6,7-dihydro-4b*H*-dibenzo[c,e]pyrrolo [1,2-*a*]azepine-5,5(9*H*)-dicarboxylate (**3bt**):**



The title compound was prepared according to General Procedure D using 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.020 g, 0.076 mmol, 1.0 equiv) and 5*H*-dibenzo[c,e]azepine<sup>23</sup> (**2t**, 0.016 g, 0.083 mmol, 1.10 equiv). After 14 h, the reaction was worked up and **3bt** was obtained as a single diastereomer in a 2:1 mixture of conformers in 71% yield as determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. Flash chromatography (20% EtOAc/hexanes) provided pure **3bt** as a white solid in 55.5:44.5 er as determined by SFC analysis (Chiralcel, OD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) *t<sub>r</sub>*-major 13.6 min, *t<sub>r</sub>*-minor 11.7 min. Analytical data for **3bt**: **mp** 83-84 °C; **IR** (thin film, cm<sup>-1</sup>) 2848, 2685, 2305, 1694, 1597, 1439, 1197, 825, 741; [Note: <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained by analyzing the trifluoroacetic acid (TFA) salt of **3bt**, prepared by adding 1.0 equiv of neat TFA to a chloroform solution of **3bt**] **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.90 (d, *J* = 7.2, 1H), 7.66 – 7.65 (m, 2H), 7.59 – 7.52 (m, 4H), 7.49 – 7.44 (m, 2H), 7.00 – 6.98 (m, 2H), 6.62 (s, 1H), 4.66 (dd, *J* = 12.0, 6.8 Hz), 4.25 (d, *J* = 14.0 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.85 (s, 3H), 3.25 (s, 3H), 2.79 – 2.68 (m, 2H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 168.1, 167.9, 161.1, 140.3, 138.3, 134.0, 131.7, 131.0, 130.7, 130.6, 130.3, 129.5, 128.8, 128.6, 114.8, 71.3, 66.3, 62.7, 55.4, 53.3, 52.9, 50.4, 39.2; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.20; **LRMS** (ESI) Calcd. for C<sub>28</sub>H<sub>27</sub>NO<sub>5</sub>+H: 458.2, Found: 458.2; [α]<sub>D</sub><sup>26</sup> = −1.95 (*c* = 0.25, CHCl<sub>3</sub>). X-ray quality crystals were obtained by slow evaporation of methanol.

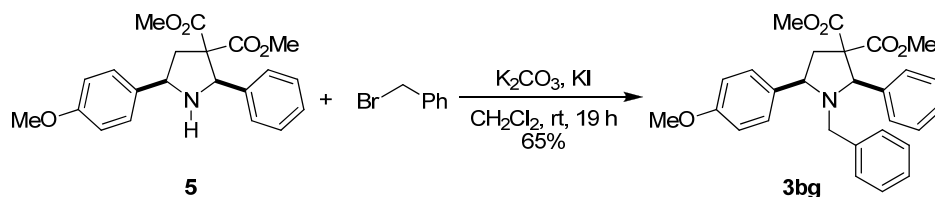


**Pd(OH)<sub>2</sub>-catalyzed reductive debenzylization of pyrrolidine **3bi** to provide pyrrolidine **5**:**



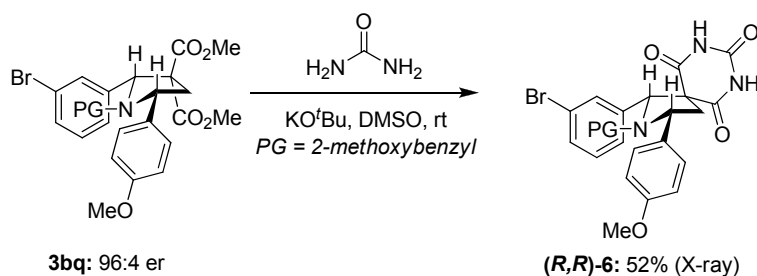
A flame-dried 5-mL round bottomed flask containing a magnetic stir bar was purged with N<sub>2</sub> and charged with a solution of pyrrolidine **3bi** (0.025 g, 0.051 mmol, 1.0 equiv) in methanol (0.50 mL) containing 1 drop of concentrated hydrochloric acid. To this solution was added Pd(OH)<sub>2</sub> (0.0036 g, 0.0051 mmol, 0.10 equiv). The flask was purged with a balloon of H<sub>2</sub> and was placed under a balloon atmosphere of H<sub>2</sub>. The reaction was allowed to stir for 17 h and was filtered through a 1-cm Monstr-Pette plug of celite with methanol (10 mL). The solution was concentrated *in vacuo* and the resulting residue taken up in saturated aq. NaHCO<sub>3</sub> solution (5 mL) and extracted with CHCl<sub>3</sub> (3 x 5 mL), dried over magnesium sulfate and concentrated to provide **5** (0.016 g, 0.043 mmol, 85% yield) as a clear colorless oil. Analytical data for **5**: **IR** (thin film, cm<sup>-1</sup>) 3054, 2987, 2305, 1730, 1612, 1512, 1421, 1265, 895, 744; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.54 (t, *J* = 7.4 Hz, 4H), 7.39 – 7.22 (m, 4H), 6.94 (d, *J* = 8.2 Hz, 2H), 5.22 (s, 1H), 4.25 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.12 (s, 3H), 2.86 (dd, *J* = 13.3, 10.7 Hz, 1H), 2.54 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.30 (s, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 172.3, 170.0, 159.2, 139.9, 134.3, 128.2, 127.9, 127.8, 127.7, 114.0, 67.0, 65.7, 60.3, 55.3, 52.7, 51.9, 42.9; **LRMS** (ESI) Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>5</sub>+H: 370.2, Found: 370.2; Enantiomeric ratio [determined by converting to the *N*-benzyl derivative (**3bg**), *vide infra*] 95.5:4.5 er; [α]<sub>D</sub><sup>25</sup> = +33.5 (*c* = 0.350, CHCl<sub>3</sub>).

### Preparation of **3bg** by *N*-benzylation of **5**:



A flame-dried 1-dram vial containing a magnetic stir bar was charged with a solution of **5** (0.017 g, 0.046 mmol, 1.0 equiv) in dichloromethane (0.230 mL). To this solution was added potassium carbonate (0.061 g, 0.437 mmol, 9.5 equiv), benzylbromide (0.024 g, 0.017 mL, 0.138 mmol, 3.0 equiv), and potassium iodide (0.0017 g, 0.010 mmol, 0.22 equiv). The vial was sealed with a PTFE-lined screw cap and was allowed to stir for 19 h. The reaction mixture was diluted with H<sub>2</sub>O (10 mL) and extracted with Et<sub>2</sub>O (3 x 5 mL). The combined organic extracts were washed with H<sub>2</sub>O (10 mL), brine (10 mL), dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography provided **3bg** (0.0137 g, 0.029 mmol, 65%). SFC analysis (Chiralpack, AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 95.5:4.5 er, *t<sub>r</sub>*-major 4.7 min, *t<sub>r</sub>*-minor 5.2 min.

### Preparation of (*R,R*)-1-(3-bromophenyl)-2-(2-methoxybenzyl)-3-(4-methoxyphenyl)-2,7,9-triazaspiro[4.5]decane-6,8,10-trione (**6**):



A solution of **3bq** (0.094 g, 0.165 mmol, 1.0 equiv, 96:4 er) in 0.8 mL DMSO was treated with urea (0.060 g, 0.992 mmol, 6.0 equiv) and KO<sup>t</sup>Bu (0.041 g, 0.364 mmol, 2.2 equiv). After stirring for 1 h, the reaction was diluted with 15 mL of EtOAc and washed with 20 mL

of a 0.1 N HCl (aq.) solution. The aqueous phase was extracted with three 20 mL portions of EtOAc. The combined organic extracts were washed with two 20 mL portions of water and 25 mL of brine, dried over MgSO<sub>4</sub>, and concentrated by rotary evaporation affording a white solid. Flash chromatography (40% EtOAc/hexanes) provided pure **6** (0.048 g, 0.085 mmol, 52%) as a white solid. This material was dissolved in a small amount of THF and recrystallized by slow diffusion of petroleum ether vapor into the solution. The initial batch of crystals was discarded and this process was repeated. A third crystallization provided a single crystal suitable for X-ray analysis. Analytical data for **6**: mp 200 °C (dec); IR (thin film, cm<sup>-1</sup>) 3369, 3214, 3055, 2986, 2961, 2937, 2838, 2305, 1729, 1512, 1422, 1353, 1246, 1173, 1033; <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 8.51 (s, 1H), 7.83 (bs, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.76 – 6.72 (m, 2H), 6.66 (d, 8.0 Hz, 1H), 4.03 (s, 1H), 3.99 (t, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.68 (d, *J* = 14.0 Hz, 2H), 3.54 – 3.51 (m, 2H), 3.51 (s 3H), 2.67 (dd, *J* = 13.0, 8.0 Hz, 1H), 2.50 (dd, *J* = 13.0, 9.5 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 172.5, 169.9, 159.7, 158.4, 148.8, 139.7, 134.5, 132.9, 132.2, 131.8, 129.8, 129.4, 127.6, 123.4, 120.1, 114.3, 110.5, 78.8, 68.2, 62.1, 55.8, 55.0, 40.6, 26.1; TLC (40% EtOAc/hexanes) R<sub>f</sub> 0.18; LRMS (ESI) Calcd. for C<sub>28</sub>H<sub>26</sub>BrN<sub>3</sub>O<sub>5</sub>+H: 564.1, Found: 564.1; [α]<sub>D</sub><sup>28</sup> = +38.1 (*c* = 0.305, THF).

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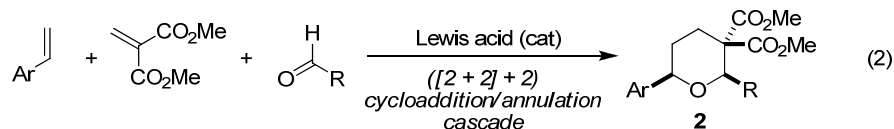
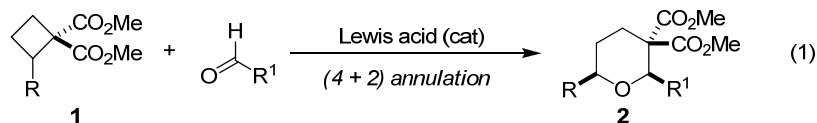
## CHAPTER FIVE

### LEWIS ACID-CATALYZED (4 + 2) ANNULATION OF DONOR-ACCEPTOR

#### CYCLOBUTANES AND ALDEHYDES

##### 5.1 Introduction

The previous chapters of this dissertation highlighted the value of malonate-derived donor-acceptor (D–A) cyclopropanes as synthetic building blocks for the preparation of highly substituted carbo- and heterocyclic products via (3 + *n*) annulation reactions with dipolarophiles.<sup>1,2</sup> Studies in our laboratory have demonstrated aldehydes to be competent dipolarophiles in Lewis acid-catalyzed (3 + 2) annulations with D–A cyclopropanes, furnishing tetrahydrofuran derivatives in a stereoselective manner.<sup>3–6</sup> Despite the potential utility of homologous products, reports that extend this methodology to (4 + *n*) annulations of D–A cyclobutanes are rare. Herein, we report the preparation of tetrahydropyrans (THPs) **2** through a Lewis acid-catalyzed (4 + 2) annulation of malonate-derived cyclobutanes (**1**) and aldehydes (eq 1). Extension of this methodology to a ([2 + 2] + 2) cycloaddition/annulation cascade that circumvents the necessity to isolate and purify **1** is also described (eq 2).

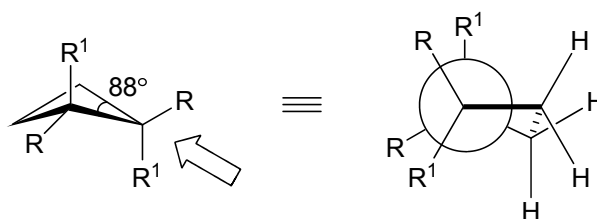


## 5.2 Background

Strained cycloalkanes represent an important class of reagents due to their unique reactivity. Studies of strained rings have largely focused on cyclopropanes due to their ease of preparation<sup>7</sup> and proven synthetic utility.<sup>8-10</sup> Cyclobutanes have gained much less attention, presumably due to the relative dearth of methods available for their preparation. Furthermore, while the strain energy of cyclobutane [26.3 kcal/mol (6.6 kcal/mol/C–C bond)] is considerable when compared to cyclohexane, cyclopropane is significantly more strained [27.5 kcal/mol (9.2 kcal/mol/C–C bond)].<sup>11</sup> This fact has led to the continued perception that cyclobutane reactivity is “unremarkable.”<sup>9</sup>

Several factors contribute to the high strain energy of cyclobutane. Similar to cyclopropane, the C–C bonds are forced to deviate from the preferred 109.5° for sp<sup>3</sup>-hybridized carbon atoms. A planar cyclobutane would be expected to possess a C–C–C bond angle of 90°, but the bond angles have been experimentally determined to be 88°.<sup>12,13</sup> This increase in angular strain is caused by an adoption of a puckered conformation (**Figure 5-1**). This conformation is favored since it results in a decrease in the torsional strain caused by unfavorable eclipsing substituents that would be present in a planar cyclobutane.

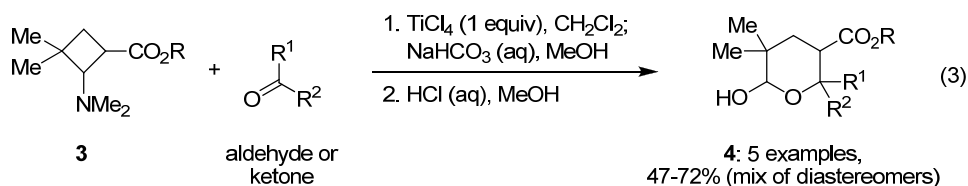
**Figure 5-1.** Illustrations of the Puckered Conformation of Cyclobutane



The use of cyclobutanes as reagents in organic synthesis has generally been in intramolecular transformations such as electrocyclization reactions or rearrangements.<sup>14</sup> Use of *vicinal* donor-acceptor cyclobutanes as saturated 1,4-dipole equivalents in intermolecular

annulation reactions is not a thoroughly investigated reaction manifold. Furthermore, most literature examples demonstrating cyclobutyl C–C heterolytic bond cleavage under Lewis acidic conditions required the presence of heteroatom donor groups.

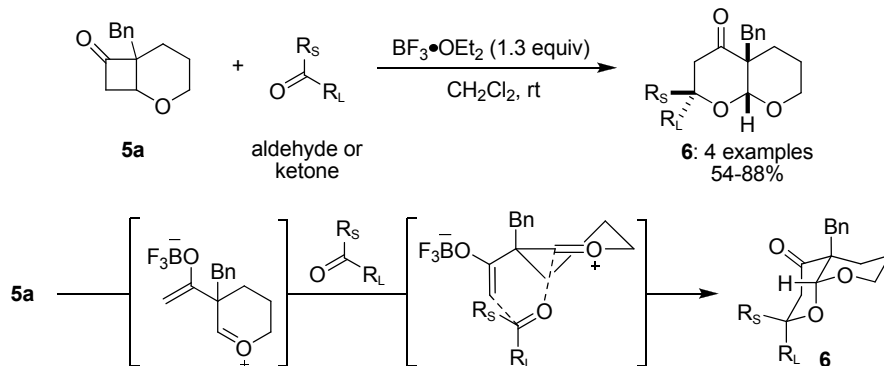
The first reported intermolecular annulation of *vicinal* D–A cyclobutanes was reported by Shimada and coworkers in 1991.<sup>15</sup> In this transformation, *N,N*-dimethylamino-substituted acrylate-derived D–A cyclobutanes **3** underwent annulation with aldehydes and ketones under Lewis acid promotion (eq 3). The researchers found that optimal yields were obtained when **3** was added to a premixed solution of stoichiometric titanium(IV) chloride and an aldehyde or ketone at room temperature. An aqueous basic workup provided cyclic aminal or ketal products. Subsequent hydrolysis furnished  $\delta$ -lactol products **4** as a mixture of diastereomers.



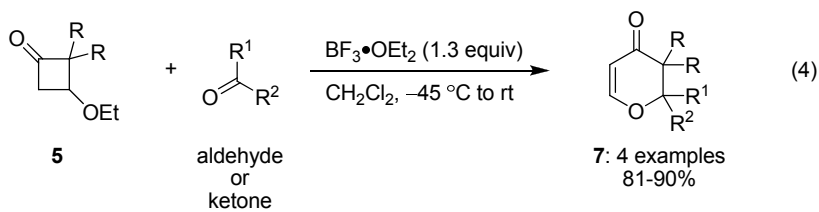
More recently, Matsuo and coworkers have explored the use of alkoxycyclobutanones **5** as 1,4-dipole equivalents in (4 + 2) annulations of dipolarophiles. The initial report of this transformation demonstrated that aldehydes and ketones undergo annulation with **5a** using  $\text{BF}_3 \cdot \text{OEt}_2$  as a stoichiometric promoter, affording hexahydropyranones **6** (Scheme 5-1).<sup>16</sup> The transformation proceeded with high chemo- and diastereoselectivity. The proposed mechanism involves oxocarbenium formation/C–C bond cleavage facilitated by cyclobutanone coordination to  $\text{BF}_3$ . Approach of the carbonyl dipolarophile orients  $\text{R}_\text{L}$  ( $\text{L} = \text{large}$ ) in a pseudo-equatorial position and (4 + 2) annulation occurs to form the *cis*-fused hexahydropyranone products.



**Scheme 5-1.** Annulation of Alkoxycyclobutanones with Aldehydes and Ketones



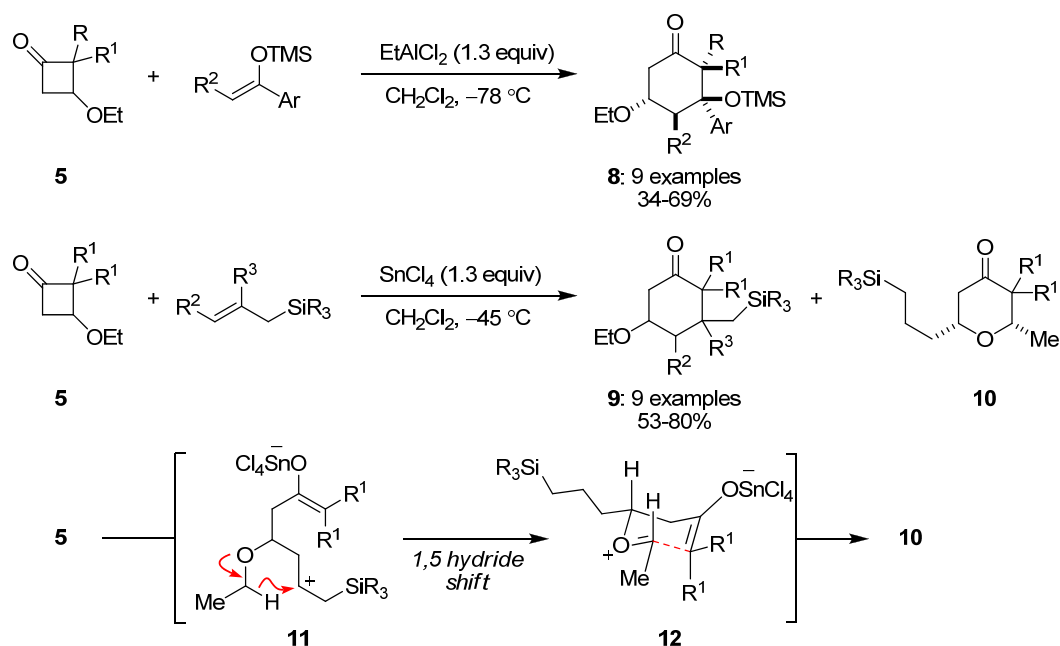
Attempts to extend this transformation to acyclic alkoxycyclobutanones resulted in elimination of the alkoxide to form dihydro- $\gamma$ -pyronones **7**. Optimization of this process through temperature control allowed for efficient access to dihydro- $\gamma$ -pyronone products in excellent yield (eq 4). While most transformations were conducted using superstoichiometric  $\text{BF}_3 \cdot \text{OEt}_2$ , the authors note that annulations of **5** and benzaldehyde can be conducted using a catalytic amount of Lewis acid (30 mol %) with equal success.



Subsequent reports from Matsuo demonstrated electron-rich olefins such as silyl enol ethers<sup>17</sup> and allylsilanes<sup>18</sup> are competent dipolarophiles, forming substituted cyclohexanones upon annulation with **5** (**Scheme 5-2**). Several Lewis acids were examined for the annulation of silyl enol ethers and it was found the transformation proceeded most efficiently when promoted with stoichiometric  $\text{EtAlCl}_2$ . Other Lewis acids such as  $\text{SnCl}_4$  and  $\text{Sc}(\text{OTf})_3$  provided the desired cyclohexanone **8** in diminished yields. Conversely, when the dipolarophile was switched to allylsilanes,  $\text{SnCl}_4$  was the preferred Lewis acid promoter. Products were obtained in good yields but in low diastereoselectivity (< 80:20) and the

relative stereochemistry was not determined. Interestingly, tetrahydro- $\gamma$ -pyranone **10** was obtained as a by-product in some cases. It is proposed that ene addition of the allyl silane into the Sn(IV)-activated cyclobutanone forms zwitterion **11**. A 1,5-hydride shift generates oxocarbenium ion **12**. Orientation into a chair-like transition state and ring closure provides **10** with high 2,6-*cis* diastereoselectivity.

**Scheme 5-2.** Annulation of Alkoxy-cyclobutanones with Electron-Rich Olefins as Reported by Matsuo



The work by Shimada and Matsuo demonstrates D–A cyclobutanes undergo C–C bond cleavage under Lewis acidic conditions. The successful intermolecular (4 + 2) annulations of D–A cyclobutanes with carbonyl and olefin dipolarophiles provides a basis for the development of more challenging transformations. Similar to the examples by Shimada and Matsuo, most ring-opening reactions of cyclobutanes are achieved using the aid of heteroatom donor groups or embedded ketones (i.e. cyclobutanones).<sup>19,20</sup> Extension of this methodology to D–A cyclobutanes possessing a *carbon* donor group is desirable since it

would provide an advancement over the current limitations in structural variability of the cyclobutane reagents. Furthermore, development of catalytic methods is a desired improvement over the standard use of stoichiometric Lewis acid promoters in most transformations of D–A cyclobutanes.

Previous work in our group has investigated aldehyde dipolarophiles in Lewis acid-catalyzed (3 + 2) annulations with D–A cyclopropanes, furnishing tetrahydrofuran derivatives in a stereoselective manner. Based on this precedent and those of Shimada and Matsuo, we sought to access tetrahydropyrans through a Lewis acid-catalyzed (4 + 2) annulation of malonate-derived D–A cyclobutanes **1** and aldehydes (eq 1). The resulting THP products are of interest due to their prevalence in biologically relevant and structurally interesting molecules.<sup>21,22</sup>

## 5.3 Reaction Development

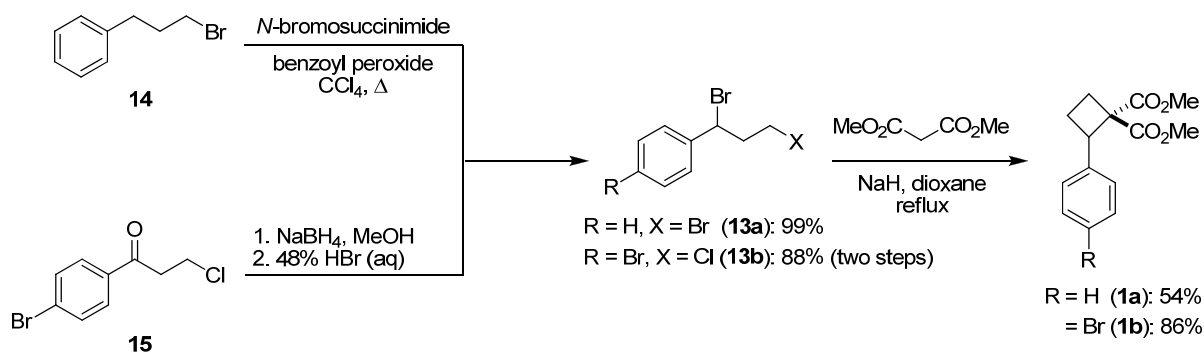
### 5.3.1 Substrate Synthesis

Preparation of malonate-derived donor-acceptor cyclobutanes **1** bearing a diverse range of donor groups requires the use of several different methods. Unlike the corresponding cyclopropanes of this class, there is no Corey–Chaykovsky reaction available for the preparation of cyclobutanes. We sought to draw from a pool of diverse reactions such as double-alkylations, [2 + 2] cycloadditions, and allylic alkylations that have been reported for the preparation of similarly substituted cyclobutanes.

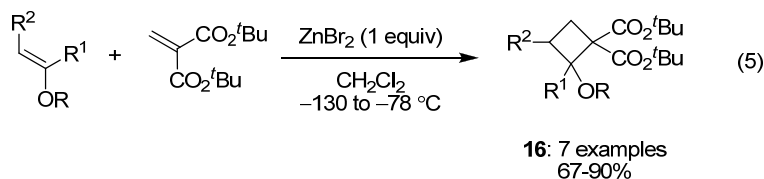
Electron-neutral and -rich aryl substituted malonate-derived cyclobutanes have previously been accessed through double alkylation of (1,3-dihalopropyl)arenes **13**.<sup>23</sup> We chose to prepare phenyl- and 4-bromophenyl-substituted cyclobutanes **1a** and **1b** using this

route. Thus, **13a** was prepared by radical bromination of commercially available (3-bromopropyl)benzene (**14**) in nearly quantitative yield.<sup>24</sup> Reduction of commercially available ketone **15** followed by bromination with aqueous HBr furnished **13b** in 86% over two steps.<sup>23</sup> Double alkylation of dimethylmalonate with **13** provides cyclobutanes **1a** and **1b** in moderate and good yield, respectively.

**Scheme 5-3.** Preparation of Cyclobutanes **1a** and **1b**

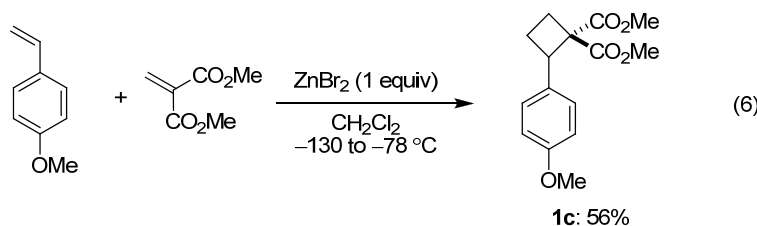


Preparation of the electron-rich 4-methoxyphenyl-substituted cyclobutane **1c** was problematic when using the route outlined in **Scheme 5-3**. A report by Roberts outlined a method to prepare cyclobutanes via Lewis acid-promoted [2 + 2] cycloaddition of enol ethers and di-*tert*-butyl 2-methylenemalonate (eq 5).<sup>25</sup> The bulky *tert*-butyl esters and a stoichiometric amount of Lewis acid prevented decomposition of the malonate through



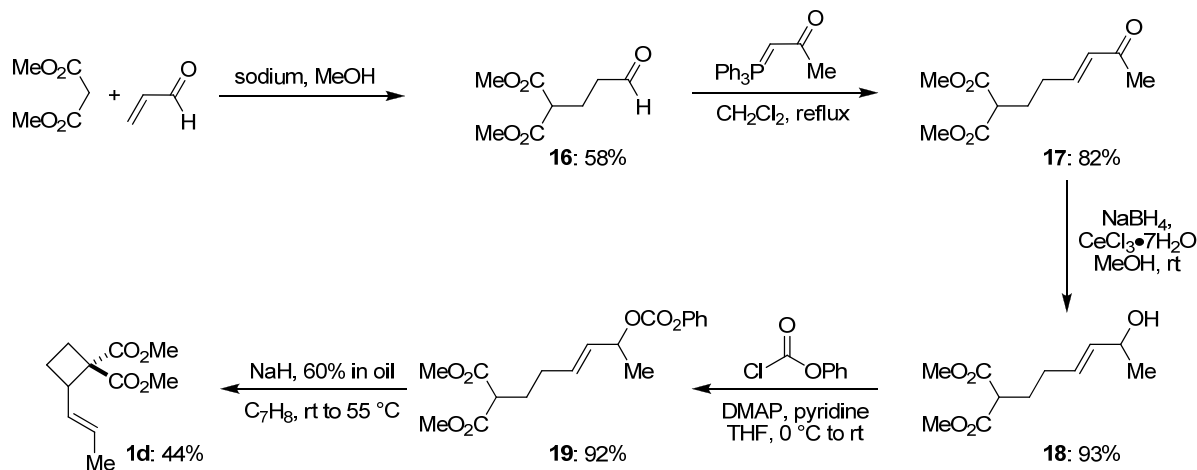
polymerization. The prerequisite that the nucleophilic olefin be sufficiently electron-rich led us to consider the use of 1-methoxy-4-vinylbenzene as the nucleophilic olefin in this methodology. Thus, a suspension of dimethyl 2-methylenemalonate (DMM) and stoichiometric  $\text{ZnBr}_2$  was treated with a solution of 1-methoxy-4-vinylbenzene at  $-130$  to  $-$

78 °C (eq 6). The desired [2 + 2] cycloaddition occurred under these conditions, furnishing cyclobutane **1c** in moderate yield.



With the preparation of electronically-diverse arylcyclobutanes achieved, efforts were focused on preparing a cyclobutane containing a donor group that can serve as a functional handle. Boeckman previously developed a route to cyclobutanes of type **1** bearing an olefinic donor group via intramolecular  $S_N2'$  allylation.<sup>26</sup> Due to the synthetic value of alkenes, we proceeded to synthesize propenylcyclobutane **1d** according to Boeckman's method. This sequence began with a conjugate addition of dimethylmalonate to acrolein.<sup>27</sup> The resultant aldehyde **16** was treated with 1-(triphenylphosphoranylidene)-2-propanone, providing unsaturated ketone **17**. A Luche reduction of **17** furnished alcohol **18**, which was treated with phenyl chloroformate to yield allylic carbonate **19**. Deprotonation of the malonate using sodium hydride facilitated the 4-*exo-trig* cyclization to yield cyclobutane **1d**.

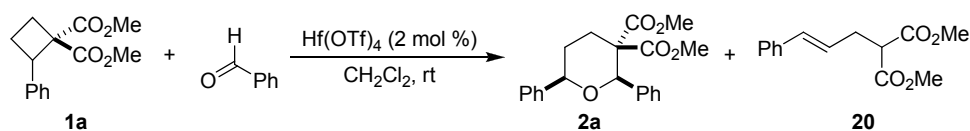
**Scheme 5-4.** Preparation of Propenylcyclobutane **1d**



### 5.3.2 Method Development

Our initial investigations focused on the annulation of phenylcyclobutane **1a** and benzaldehyde under Lewis acid catalysis. We presumed that the decreased strain energy of cyclobutanes relative to cyclopropanes would require a stronger Lewis acid to undergo annulation. Previous studies on (3 + 2) cyclopropane/aldehyde annulations revealed that hafnium(IV) triflate was more active than tin(II) triflate in this transformation. After preliminary experiments indicated Hf(OTf)<sub>4</sub> was an effective catalyst for the annulation of **1a** with benzaldehyde, we examined a range of solvents in order to optimize the chemical yield and diastereoselectivity of this transformation (**Table 5-1**). Reactions with non-coordinating

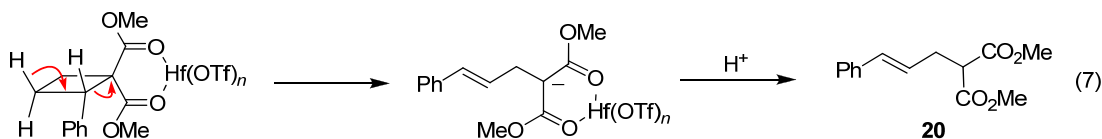
**Table 5-1.** Solvent Optimization



| entry | solvent                  | yield (%) <sup>a</sup> | dr <sup>b</sup> | entry | solvent              | yield (%) <sup>a</sup> | dr <sup>b</sup> |
|-------|--------------------------|------------------------|-----------------|-------|----------------------|------------------------|-----------------|
| 1     | methylene chloride       | 95                     | 92:8            | 8     | chloroform           | 76                     | 94:6            |
| 2     | 2-methyl tetrahydrofuran | nr <sup>c</sup>        | nd <sup>d</sup> | 9     | chlorobenzene        | 85                     | 96:4            |
| 3     | cyclopentyl methyl ether | (< 5) <sup>e</sup>     | nd              | 10    | carbon tetrachloride | 60 (89) <sup>e</sup>   | 95:5            |
| 4     | diethyl ether            | 29 (46) <sup>e</sup>   | 94:6            | 11    | toluene              | 80                     | 95:5            |
| 5     | benzotrifluoride         | 84                     | 95:5            | 12    | tetrahydrofuran      | nr                     | nd              |
| 6     | dichloroethane           | 93                     | 96:4            | 13    | benzene              | 73                     | 96:4            |
| 7     | 1,4-dioxane              | (< 5) <sup>e</sup>     | nd              | 14    | hexanes              | 71                     | 96:4            |

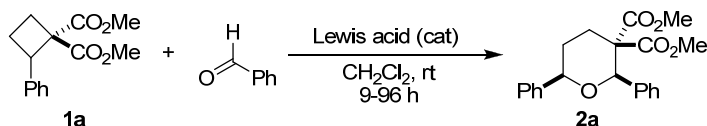
Conditions: **1a** (1.0 equiv), benzaldehyde (3.0 equiv), Hf(OTf)<sub>4</sub> (0.02 equiv), [**1a**]<sub>0</sub> = 0.25 M in the indicated solvent, rt, 12-18 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by <sup>1</sup>H NMR spectroscopy. c) nr = no reaction. d) nd = not determined. e) Numbers in parentheses refer to % conversion of **1a**.

solvents proved to be the most effective in this system. While many solvents facilitated high yields and diastereoselectivities of **2a**, we found methylene chloride to be the most convenient. In many cases, we observed the formation of styrene derivative **20** as a by-product, largely accounting for the discrepancy between yield and conversion (eq 7).



With an optimal solvent system selected, efforts were focused on increasing the diastereoselectivity of this transformation. We examined several Lewis acids that have proven useful in cyclopropane/aldehyde annulations (**Table 5-2**). Interestingly, Sn(OTf)<sub>2</sub> was not an effective catalyst for the annulation of cyclobutane **1a** and benzaldehyde, even with a 20 mol % loading. This is in stark contrast to the cyclopropane/aldehyde annulations in which this was the Lewis acid of choice, typically requiring only a 5 mol % loading. Scandium(III) triflate yielded tetrahydropyran **2a** with the highest yield and diastereoselection; therefore, the scope of this reaction was explored using this Lewis acid.

**Table 5-2.** Examination of Lewis Acids



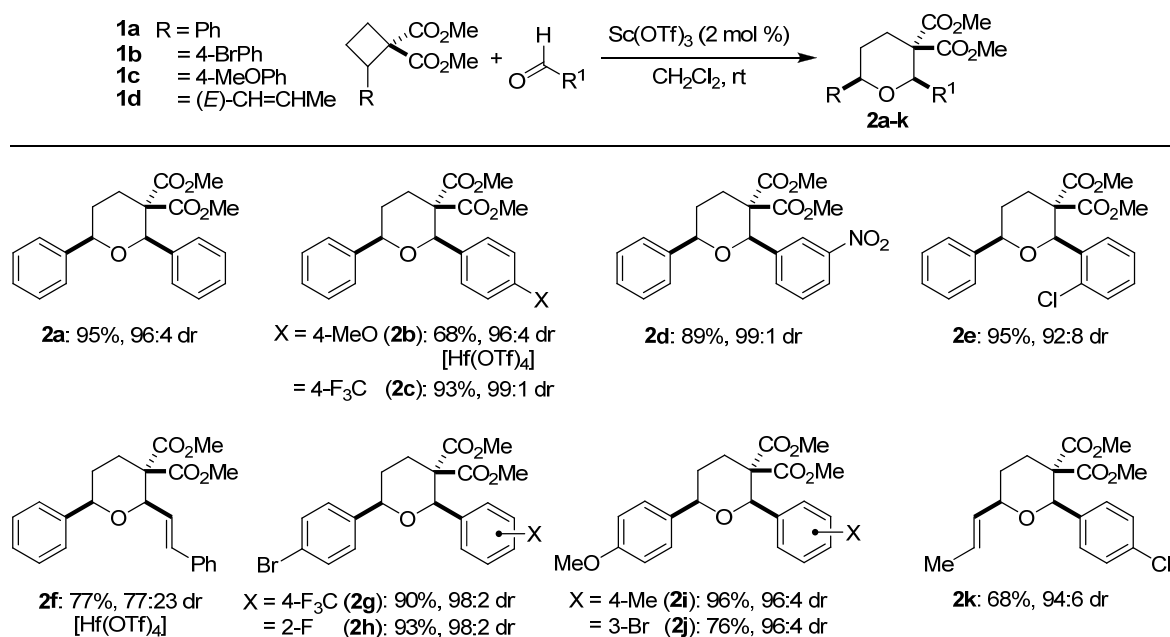
| entry | Lewis acid           | mol % | yield (%) <sup>a</sup> | conversion (%) <sup>a</sup> | dr <sup>b</sup> |
|-------|----------------------|-------|------------------------|-----------------------------|-----------------|
| 1     | AlCl <sub>3</sub>    | 5     | 93                     | 100                         | 96:4            |
| 2     | Cu(OTf) <sub>2</sub> | 5     | 13                     | 19                          | 94:6            |
| 3     | Sc(OTf) <sub>3</sub> | 5     | 98                     | 100                         | 96:4            |
| 4     | Sn(OTf) <sub>2</sub> | 20    | 28                     | 45                          | 95:5            |
| 5     | Yb(OTf) <sub>3</sub> | 5     | 0                      | 0                           | —               |
| 6     | Zn(OTf) <sub>2</sub> | 5     | 0                      | 0                           | —               |

Conditions: **1a** (1.0 equiv), benzaldehyde (3.0 equiv), Lewis acid (0.05-0.20 equiv), [**1a**]<sub>0</sub> = 0.25 M in CH<sub>2</sub>Cl<sub>2</sub>, rt, 9-96 h. a) Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene internal standard. b) Determined by <sup>1</sup>H NMR spectroscopy.

### 5.3.3 Cyclobutane and Aldehyde Scope

With a highly efficient reaction system identified, exploration of the cyclobutane and aldehyde scope was conducted using our optimized conditions. Cyclobutanes **1a-d** were successful in undergoing annulation with a range of electron-poor to electron-rich aryl aldehydes (**Figure 5-2**). Annulation of **1a** with the electron-rich 4-methoxybenzaldehyde and cinnamaldehyde was sluggish and required the use of  $\text{Hf}(\text{OTf})_4$  as the catalyst. This highlights an interesting characteristic of cyclobutane/aldehyde annulations: electron-deficient aldehydes react more rapidly (see **5.6 Experimental**). This is in contrast to cyclopropane/aldehyde annulations in which electron-rich aldehydes react more rapidly. A more detailed discussion of this observation is discussed in section **5.4**.

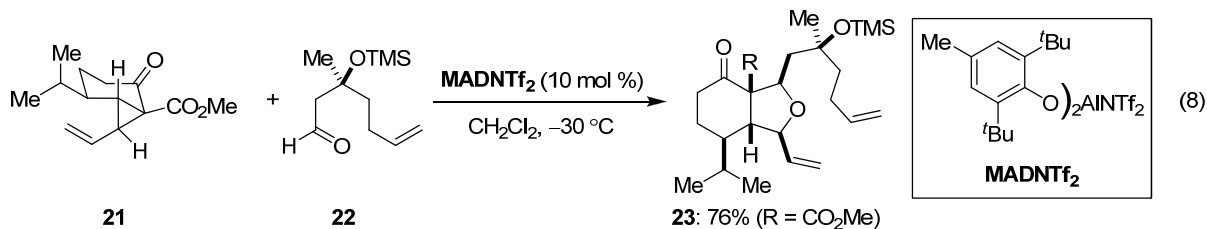
**Figure 5-2.** Annulation of Cyclobutanes **1a-d** with Cinnamyl and Aryl Aldehydes



Attempts to extend the  $\text{Sc}(\text{OTf})_3$  and  $\text{Hf}(\text{OTf})_4$  conditions to aliphatic aldehydes were not successful. We were prompted to evaluate alternative Lewis acids in order to achieve the annulation of **1** with aliphatic aldehydes. Campbell and Johnson recently reported the use of

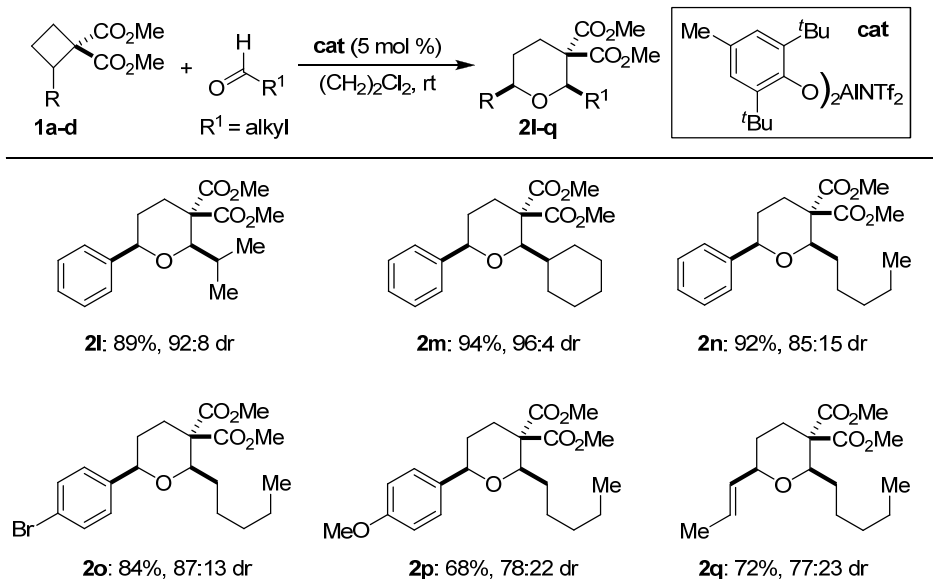


a methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)<sup>28</sup> derivative (MADNTf<sub>2</sub>) to catalyze the annulation of cyclopropane **21** with sensitive aldehyde **22** en route to the natural product polyanthellin A (eq 8).<sup>29</sup> We examined this complex as a



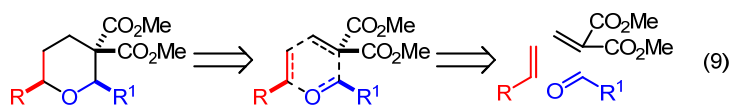
possible alternative to Sc(OTf)<sub>3</sub> and found it was effective in catalyzing the annulation of linear, branched, and cyclic aliphatic aldehydes (**Figure 5-3**). The diastereomeric ratio of the THP products varied, with branched and cyclic aldehydes providing the highest levels of diastereoselection (up to 96:4 dr). Linear aliphatic aldehydes tended to display low diastereoselectivity regardless of the identity of cyclobutane (Reprinted in part with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society).

**Figure 5-3.** MADNTf<sub>2</sub>-Catalyzed Annulation of Cyclobutanes **1a-d** with Aliphatic Aldehydes



### 5.3.4 Development of a $[2 + 2] + 2$ Cycloaddition/Annulation Cascade

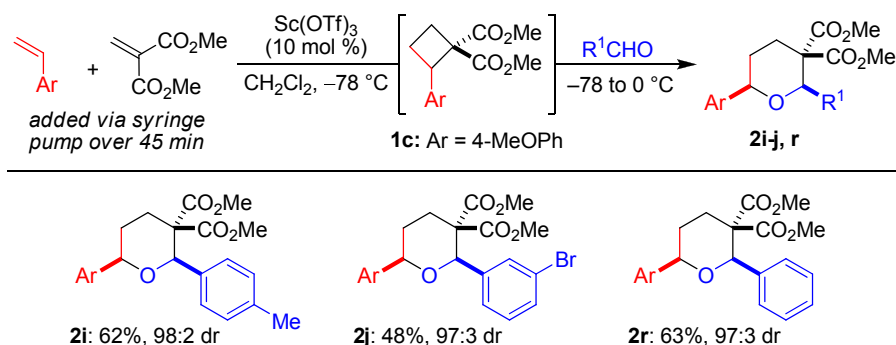
Given that the cyclobutane starting materials can themselves arise from a Lewis acid-catalyzed cycloaddition of dimethyl 2-methylenemalonate (DMM) and a nucleophilic olefin (eq 6), we became interested in testing the notion that the title THP synthesis could be streamlined into a one-pot operation. A sequenced alkene/alkene  $[2 + 2]$  cycloaddition–cyclobutane/aldehyde  $(4 + 2)$  annulation could in principle directly deliver THP products from simple linear starting materials with no processing of intermediates (eq 9). (Reprinted in part with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society).



Early efforts in the development of this sequence focused on achieving the  $[2 + 2]$  cycloaddition of DMM and 1-methoxy-4-vinylbenzene using a catalytic amount of  $\text{Sc}(\text{OTf})_3$ . This study revealed that DMM decomposition was severely limiting cyclobutane formation. In our previous preparation of cyclobutane **1c**, the stoichiometric amount of  $\text{ZnBr}_2$  served to promote  $[2 + 2]$  cycloaddition and also prevent DMM decomposition. These experimental results suggest that two equivalents of Lewis acid-coordinated DMM are less likely to oligomerize than one coordinated and one non-coordinated DMM. Thus, we conducted the initial  $[2 + 2]$  cycloaddition by slow addition of DMM and 1-methoxy-4-vinylbenzene to a suspension of  $\text{Sc}(\text{OTf})_3$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ . Formation of cyclobutane **1c** was confirmed by thin layer chromatography and subsequent addition of the aldehyde resulted in the formation of the desired THP products (**Figure 5-4**). This one-pot method furnished THPs in greater overall yield than the two-step cyclobutane formation/ $(4 + 2)$  annulation sequence. Attempts to conduct initial alkene/alkene  $[2 + 2]$  cycloaddition in the presence of an aldehyde resulted

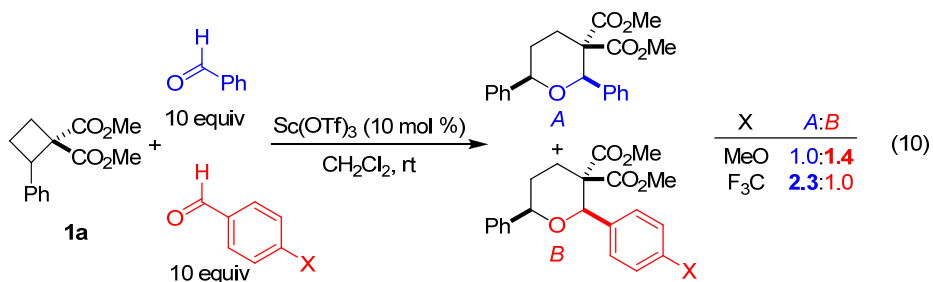
in a moderately lower yield of THP products. (Reprinted in part with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society).

**Figure 5-4.** Sc(OTf)<sub>3</sub>-Catalyzed ([2 + 2] + 2) Cycloaddition/Annulation Cascade to Tetrahydropyrans (Reprinted in part with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society)



## 5.4 Mechanistic and Stereochemical Analysis

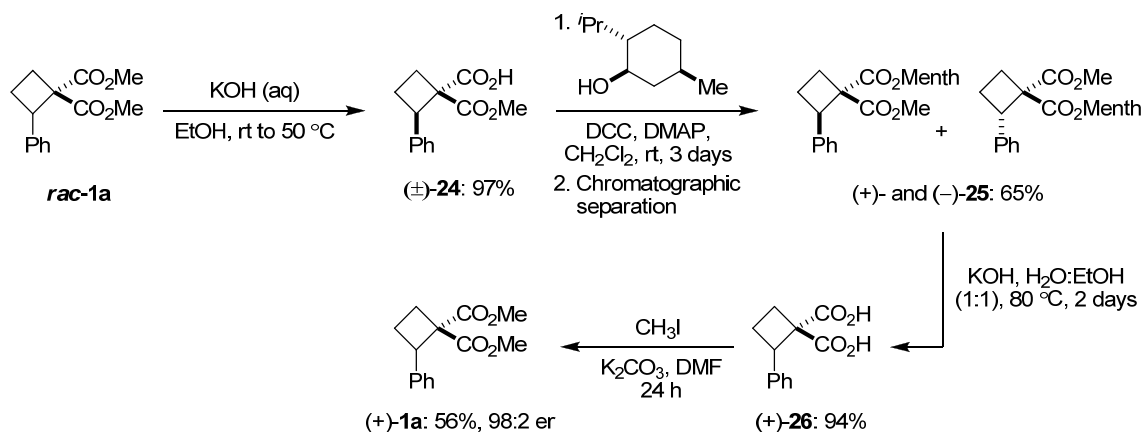
During the course of our studies, it was observed that annulations of electron-poor benzaldehydes with D–A cyclobutanes proceed most rapidly. This is in contrast to the analogous cyclopropane/aldehyde (3 + 2) annulations where electron-rich aldehydes result in the greatest reaction rates.<sup>5</sup> In an effort to probe this phenomenon more closely, we performed direct competition experiments between electron-rich and -poor aldehydes versus benzaldehyde (eq 10). Interestingly, this study revealed that there is a preference for



reaction with the more electron-rich aldehyde. These seemingly conflicting results may indicate an increased propensity of electron-rich aldehydes to coordinate the Sc(III) catalyst, causing a decrease in Lewis acidity [via (RCHO)<sub>n</sub>Sc(OTf)<sub>3</sub>]. Thus, reaction times are not necessarily indicative of native aldehyde reactivity; the difference in reaction rates may be due to varying degrees of catalyst inhibition. (Reprinted in part with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society).

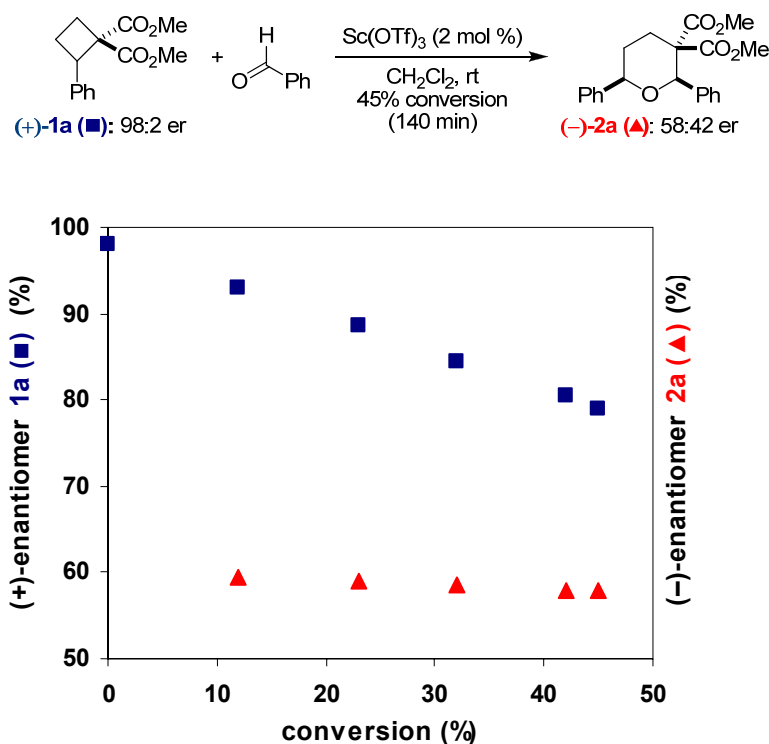
Next, we sought to gain additional stereochemical and mechanistic insight through annulation with an enantioenriched cyclobutane. Since no methods are currently available for the catalytic enantioselective preparation of cyclobutanes of type **1**, we developed a classical resolution of **1a** (**Scheme 5-5**). Diastereoselective mono-saponification of *rac*-**1a** furnished carboxylic acid (±)-**24**.<sup>30</sup> Esterification using dicyclohexylcarbodiimide and (–)-menthol yielded a chromatographically-separable mixture of diastereomeric cyclobutanes (+)- and (–)-**25**. Saponification of the methyl and menthyl esters provides diacid (+)-**26**. Esterification of the resulting carboxylic acids with iodomethane furnished cyclobutane (+)-**1a** in 98:2 er (the absolute configuration was not determined).

**Scheme 5-5.** Preparation of Enantioenriched Cyclobutane (+)-**1a**



With enantioenriched **1a** prepared, we subjected this cyclobutane to the standard reaction conditions using benzaldehyde as the dipolarophile and monitored the er of **1a** (■) and **2a** (▲) as a function of conversion (**Figure 5-5**). At 12% conversion (–)-**2a** is formed with a 59.5:40.5 er while (+)-**1a** remained highly enriched (er = 93:7). Moreover, while slow loss of cyclobutane enantioenrichment occurred over time, the product enantiomer ratio remained surprisingly constant. From the electronic profiling (eq 10), it would appear that there is a nucleophilic substitution component to the reaction, but **Figure 5-5** reveals that the issue of chirality transfer is more ambiguous than for the analogous D–A cyclopropanes. Further experimentation will be necessary to elucidate the mechanism of this transformation. (Reprinted with permission from Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202-14203. © 2009 American Chemical Society).

**Figure 5-5.** Stereochemical Analysis of the Sc(OTf)<sub>3</sub>-Catalyzed (4 + 2) Annulation of (+)-**1a** and Benzaldehyde



## 5.5 Conclusion

The development of a (4 + 2) annulation of donor-acceptor cyclobutanes and aldehydes to furnish *cis*-2,6-disubstituted tetrahydropyran derivatives has been achieved. We streamlined this methodology by developing a ([2 + 2] + 2) cycloaddition/annulation sequence where *in situ* generation of the cyclobutane allows access to THPs directly from dimethyl 2-methylenemalonate, 1-methoxy-4-vinylbenzene, and an aldehyde. Mechanistic insights into this transformation were obtained through the use of competition experiments, revealing that there is a preference for annulation with electron-rich aldehydes. This result is in contrast to the experimentally observed reaction rates where electron-poor aldehydes react more rapidly, suggesting Lewis acid deactivation occurs in the presence of coordinating electron-rich aldehydes. Annulation of enantioenriched cyclobutane **1a** (er = 98:2) resulted in a low level of chirality transfer to the THP product. Additional studies are necessary in order to develop a mechanistic proposal to account for the high diastereoselectivity and low stereospecificity of this transformation.

## 5.6 Experimental

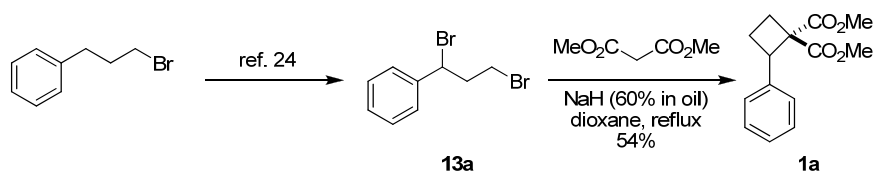
**Methods.** Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker model DRX 400 or 500 ( $^1\text{H}$  NMR at 400 MHz or 500 MHz and  $^{13}\text{C}$  NMR at 100 or 125 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm,  $\text{DMSO-d}_6$  at 2.54 ppm, and  $\text{C}_6\text{D}_6$  at 7.15 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm,  $\text{DMSO-d}_6$  at 40.45 ppm, and  $\text{C}_6\text{D}_6$  at 128.6 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d =

doublet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dtd = doublet of triplet of doublet, t = triplet, bt = broad triplet, td = triplet of doublet, q = quartet, qd = quartet of doublet, qn = quintet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C) with helium gas as carrier. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralpack WO column (modifier = 2.0% MeOH, flow = 2.0 mL/min, pressure = 200 bar, detector = UV, 210 nm, temperature = 40 °C). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Elemental analysis was performed by Atlantic Microlab, Inc. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63  $\mu$ m) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials.** Tetrahydrofuran, toluene, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Dioxane was distilled from a

sodium/benzophenone ketyl under N<sub>2</sub> and stored in a Schlenk flask. Dichloroethane was purified by distillation from calcium hydride under N<sub>2</sub> prior to use. Benzaldehyde, *p*-anisaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde, 2-fluorobenzaldehyde, and *trans*-cinnamaldehyde were purified by the following procedure: The neat aldehydes were washed sequentially with a 1 M sodium hydroxide solution and a saturated aqueous sodium bicarbonate solution, dried with magnesium sulfate, and distilled under reduced pressure. 4-Chlorobenzaldehyde was sublimed under reduced pressure. Isobutyraldehyde, cyclohexanecarboxaldehyde, and hexanal were dried over CaSO<sub>4</sub> and distilled under N<sub>2</sub> prior to use. Dimethyl 2-methylenemalonate was prepared according to the method of De Keyser<sup>31</sup> and was stored at −30 °C. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

**Preparation of dimethyl 2-phenylcyclobutane-1,1-dicarboxylate (1a):**



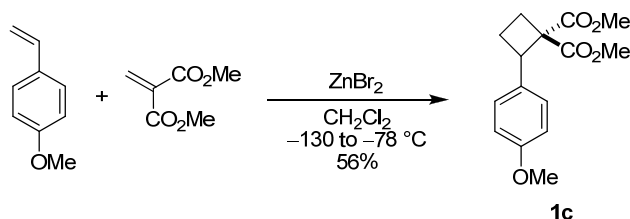
Under N<sub>2</sub>, a flame dried 500-mL 2-neck round-bottomed flask containing a magnetic stir bar was charged with (1,3-dibromopropyl)benzene<sup>24</sup> (**13a**, 13.95 g, 50.2 mmol, 1.0 equiv), dimethyl malonate (7.3 g, 55.3 mmol, 1.1 equiv), and 161 mL anhydrous dioxane. The flask was affixed with a reflux condenser and the solution was heated to reflux. Sodium hydride [2.06 g (60% in mineral oil), 51.7 mmol, 1.03 equiv) was added in small portions over approximately 10 minutes. The reaction was allowed to reflux for 1 h, at which point additional sodium hydride [2.06 g (60% in mineral oil), 51.7 mmol, 1.03 equiv] was added in





1435, 1281, 1201, 1107, 1073, 1011, 831; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 4.29 (t, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.29 (s, 3H), 2.75 – 2.62 (m, 1H), 2.62 – 2.48 (m, 1H), 2.28 (dd, *J* = 20.1, 9.1 Hz, 1H), 2.22 – 2.10 (m, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.9, 169.5, 138.2, 131.1, 129.3, 120.9, 59.8, 59.5, 52.5, 52.0, 44.6, 25.7, 20.7; **TLC** (10% EtOAc/hexanes) *R<sub>f</sub>* 0.18; **Anal.** Calcd. for C<sub>14</sub>H<sub>15</sub>O<sub>4</sub>: C, 51.40; H, 4.62. Found: C, 51.58; H, 4.54.

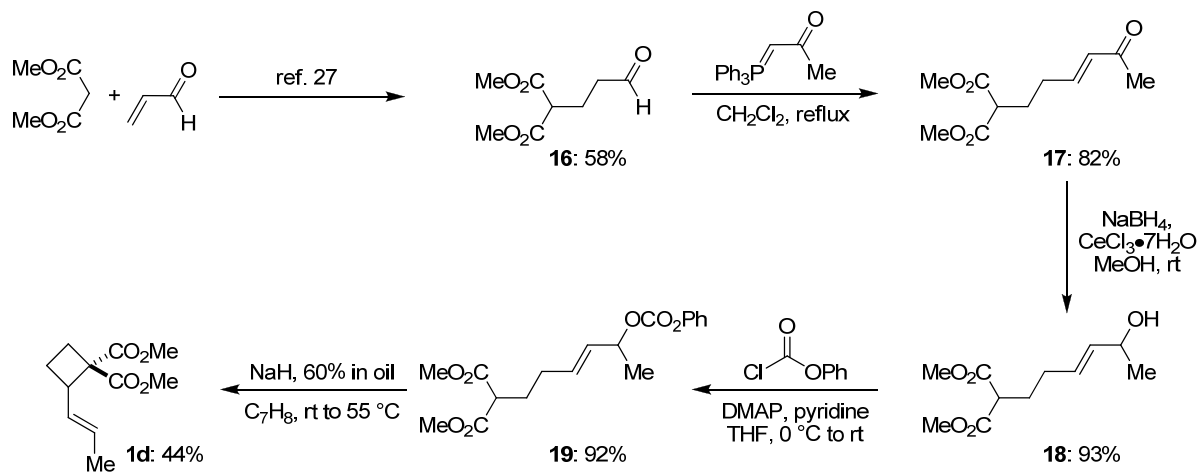
**Preparation of dimethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (1c):**



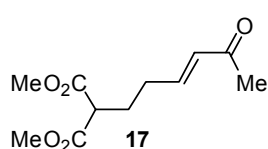
In an inert atmosphere glove box, a 100-mL round-bottomed flask was charged with ZnBr<sub>2</sub> (1.32 g, 5.9 mmol, 1.0 equiv), a magnetic stir bar, and was fitted with a rubber septum. A scintillation vial was charged with dimethyl 2-methylenemalonate<sup>31</sup> (DMM, 0.85 g, 5.9 mmol, 1.0 equiv) and fitted with a rubber septum. Both vessels were removed from the glove box and placed under N<sub>2</sub>. Outside of the glove box, a flame scintillation vial under N<sub>2</sub> was charged with 1-methoxy-4-vinylbenzene (0.933 g, 0.933 mL, 6.9 mmol, 1.2 equiv). All vials were charged with CH<sub>2</sub>Cl<sub>2</sub> (13.5 mL, 40.5 mL total). The flask containing ZnBr<sub>2</sub> was cooled to -130 °C in a pentane/liquid N<sub>2</sub> bath. To the ZnBr<sub>2</sub> was added DMM followed by 1-methoxy-4-vinylbenzene (both added via cannula over approximately 5 min). The reaction was warmed to -78 °C in an isopropanol/dry ice bath and was allowed to stir for 1 h. A solution of pyridine (1.82 g, 1.85 mL, 23.1 mmol, 4.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (13.0 mL) pre-cooled to -78 °C was added to the reaction via syringe. The reaction was allowed to warm to room

temperature, washed with saturated aq. Na<sub>2</sub>EDTA (2 x 60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Flash chromatography (7.5% EtOAc/hexanes) afforded **1c** (0.926 g, 3.33 mmol, 56% yield) as a white solid. Analytical data for **1c**: mp 55-56 °C; IR (thin film, cm<sup>-1</sup>) 3000, 2952, 2839, 1732, 1612, 1515, 1435, 1275, 1253, 1107, 1037, 835; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.30 (t, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (s, 3H), 2.71 – 2.65 (m, 1H), 2.57 (qn, *J* = 10.0 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.18 – 2.11 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.1, 169.8, 158.6, 131.3, 128.7, 113.4, 59.8, 55.2, 52.4, 51.8, 44.7, 25.5, 21.0; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.18; Anal. Calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>5</sub>: C, 64.74; H, 6.52. Found: C, 64.90; H, 6.58.

#### Preparation of (*E*)-dimethyl 2-(prop-1-enyl)cyclobutane-1,1-dicarboxylate (**1d**):



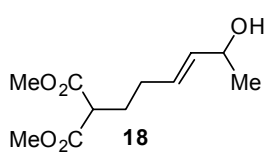
#### (*E*)-Dimethyl 2-(5-oxohex-3-enyl)malonate (**17**)



A 250-mL round-bottomed flask containing a magnetic stir bar was charged with dimethyl 2-(3-oxopropyl)malonate<sup>27</sup> (**16**, 9.9 g, 52.6 mmol, 1.0 equiv, 80% pure), 1-(triphenylphosphoranylidene)-2-propanone (20.1 g, 63.13 mmol, 1.2 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (111 mL). The flask was affixed

with a reflux condenser and was heated to reflux for 42 h. The reaction was allowed to cool to room temperature and was concentrated *in vacuo*. The resulting residue was suspended in 30% EtOAc/hexanes and stirred for 2 h and was filtered through celite and concentrated. Flash chromatography (40% EtOAc/hexanes) afforded (*E*)-dimethyl 2-(5-oxohex-3-enyl)malonate (**17**) (7.84 g, 82% yield based on 80% pure starting material) as a clear colorless oil. Analytical data for **17**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3006, 2956, 1735, 1675, 1437, 1361, 1157, 980;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.71 (dt,  $J = 16.0, 6.8$  Hz, 1H), 6.06 (d,  $J = 16.0$  Hz, 1H), 3.72 (s, 6H), 3.36 (t,  $J = 7.6$  Hz, 1H), 2.28 – 2.23 (m, 2H), 2.22 (s, 3H), 2.06 (q,  $J = 8.0$  Hz, 2H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  198.1, 169.3, 145.5, 132.1, 52.5, 50.8, 29.8, 27.0, 26.9; **TLC** (40% EtOAc/hexanes)  $R_f$  0.28; **Anal.** Calcd. for  $\text{C}_{11}\text{H}_{16}\text{O}_5$ : C, 57.88; H, 7.07. Found: C, 57.73; H, 7.04.

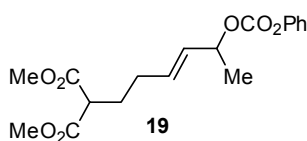
**(*E*)-Dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**18**):**



A 250-mL round-bottomed flask containing a magnetic stir bar was charged with  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (1.75 g, 35.19 mmol, 1.75 equiv) and MeOH (50 mL). The suspension was stirred vigorously until homogeneous (approximately 5 min), at which point (*E*)-dimethyl 2-(5-oxohex-3-enyl)malonate (**17**, 4.59 g, 20.01 mmol, 1.0 equiv) in MeOH (50 mL) was added. The resulting solution was stirred for 5 min and  $\text{NaBH}_4$  (0.837 g, 22.12 mmol, 1.1 equiv) was added in 10 portions over 15 min. The reaction mixture was allowed to stir for 1.5 h and was then diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL) and poured into a 2 M aq. HCl solution (150 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 75 mL). The combined  $\text{CH}_2\text{Cl}_2$  extracts were washed with 2 M aq. HCl (75 mL), brine (75 mL), dried

over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The product was purified by flash chromatography (20% EtOAc/hexanes) to afford (*E*)-dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**18**) (4.28 g, 18.59 mmol, 93%) as a clear colorless oil. Analytical data for **18**: **IR** (thin film, cm<sup>-1</sup>) 3421, 2957, 1734, 1438, 1287, 1245, 1158, 1062, 971; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.62 – 5.41 (m, 2H), 4.29 – 4.13 (m, 1H), 3.70 (s, 6H), 3.34 (t, *J* = 7.2 Hz, 1H), 2.03 (dt, *J* = 9.9, 3.8 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.88 (s, 1H), 1.20 (d, *J* = 6.4 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 169.6, 135.9, 128.3, 68.4, 52.3, 50.9, 29.6, 28.1, 23.3; **TLC** (40% EtOAc/hexanes) R<sub>f</sub> 0.19; **Anal.** Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>: C, 57.38; H, 7.88. Found: C, 57.35; H, 7.85.

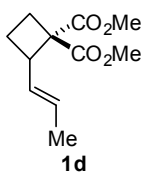
**(*E*)-Dimethyl 2-(5-(phenoxycarbonyloxy)hex-3-enyl)malonate (**19**):**



A flame-dried 250-mL round-bottomed flask was charged with a solution of (*E*)-dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**18**, 4.18 g, 18.15 mmol, 1.0 equiv) in tetrahydrofuran (74 mL). The flask was purged with N<sub>2</sub> and cooled to 0 °C in an ice-water bath. 4-Dimethylaminopyridine (0.22 g, 1.82 mmol, 0.10 equiv) was added in one portion followed by dropwise addition of pyridine (3.59 g, 3.66 mL, 45.38 mmol, 2.5 equiv) via syringe over 10 min. Phenyl chloroformate (5.68 g, 4.55 mL, 36.31 mmol, 2.0 equiv) was added via syringe over 10 min. The reaction was allowed to stir for 30 min at 0 °C and was then warmed to room temperature and was stirred for an additional 4.5 h. The reaction was cooled to 0 °C and quenched with 2 M aq. HCl (75 mL). The organic layer was separated and the aqueous layer extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic extracts were washed with 2 M aq. HCl (2 x 75 mL), 2 M aq. NaOH (2 x 75 mL), dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to afford pure (*E*)-dimethyl 2-(5-(phenoxycarbonyloxy)hex-3-enyl)malonate (**19**) (5.88 g,

16.79 mmol, 92%) as a clear colorless oil. Analytical data for **19**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 1756, 1496, 1437m 1250, 1210, 1154, 1044, 970, 780, 688;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (td,  $J = 7.7, 1.8$  Hz, 2H), 7.25 – 7.19 (m, 1H), 7.17 (dd,  $J = 8.6, 1.0$  Hz, 2H), 5.76 (dt,  $J = 13.6, 6.6$  Hz, 1H), 5.56 (dd,  $J = 15.5, 7.1$  Hz, 1H), 5.23 (qn,  $J = 6.5$  Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.38 (t,  $J = 7.3$  Hz, 1H), 2.10 (dd,  $J = 14.5, 6.7$  Hz, 2H), 2.00 (dt,  $J = 7.4, 4.4$  Hz, 2H), 1.42 (d,  $J = 6.5$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 152.9, 151.2, 132.4, 130.1, 129.3, 125.8, 121.0, 75.9, 52.3, 50.8, 29.6, 27.8, 29.6, 27.8, 20.2; **TLC** (20% EtOAc/hexanes)  $R_f$  0.21; **Anal.** Calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_7$ : C, 61.71; H, 6.33. Found: C, 61.79; H, 6.45.

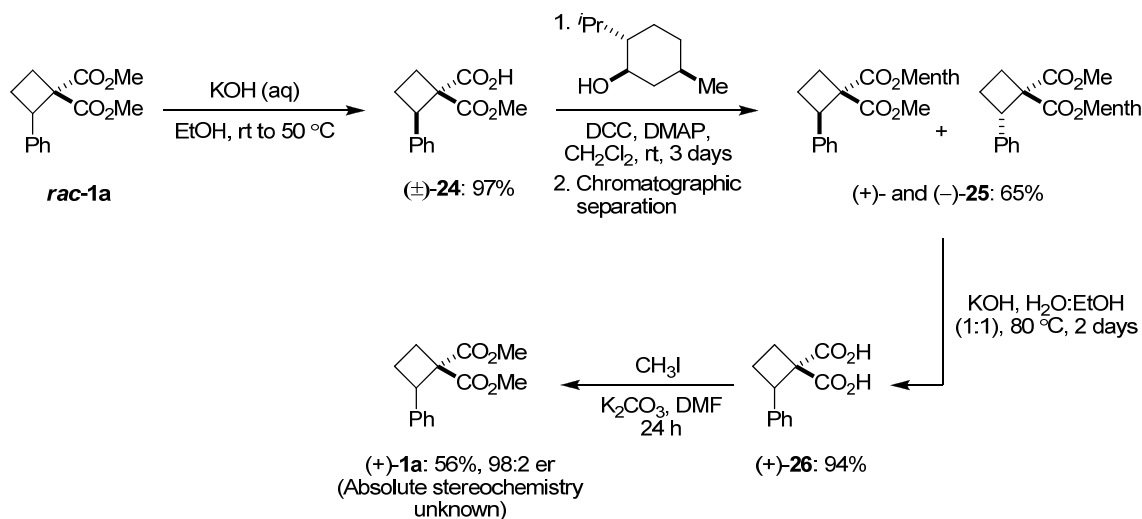
**(*E*)-Dimethyl 2-(prop-1-enyl)cyclobutane-1,1-dicarboxylate (**1d**):**



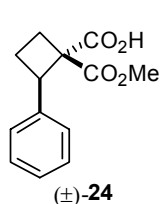
A flame-dried 100 mL round-bottomed flask containing a magnetic stir bar was charged with sodium hydride [0.285 g (60% in oil), 7.13 mmol, 2.0 equiv] under  $\text{N}_2$ . The sodium hydride was washed with hexanes to remove the oil and was suspended in  $\text{C}_7\text{H}_8$  (7.0 mL). To this suspension was added a solution of (*E*)-dimethyl 2-(5-(phenoxy carbonyloxy)hex-3-enyl)malonate (**19**, 1.25 g, 3.57 mmol, 1.0 equiv) in  $\text{C}_7\text{H}_8$  (10 mL) via cannula over 20 min followed by a  $\text{C}_7\text{H}_8$  wash (4 mL). The reaction was stirred at room temperature for 30 min and then warmed to 55  $^\circ\text{C}$  for an additional 5 h. The reaction was then cooled to room temperature and poured into 50 mL  $\text{H}_2\text{O}$ . The organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (3 x 25 mL). The combined organic layers were washed with 2 M aq. NaOH (2 x 25 mL), dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. Purification by flash chromatography (7.5% EtOAc/hexanes) afforded **1d** (0.33 g, 1.55 mmol, 44% yield) as a volatile clear colorless oil. (Note: While analyzing the flash

column fractions using thin layer chromatography, it is necessary to elute the TLC plate twice in 7.5% EtOAc/hexanes to visualize an undesired impurity). Analytical data for **1d**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2998, 2953, 1733, 1436, 1275, 1256, 1201, 1115, 970;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.60 – 5.49 (m, 1H), 5.44 (dd,  $J = 15.8, 6.6$  Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.60 (dd,  $J = 16.0, 8.1$  Hz, 1H), 2.61 – 2.55 (m, 1H), 2.21 – 2.10 (m, 1H), 2.10 – 1.95 (m, 2H), 1.65 (d,  $J = 6.2$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 170.2, 129.5, 127.6, 58.2, 52.3, 52.0, 43.2, 25.7, 22.1, 17.8; **TLC** (7.5% EtOAc/hexanes)  $R_f$  0.16; **LRMS** (ESI) Calcd. for  $\text{C}_{11}\text{H}_{16}\text{O}_4 + \text{Na}$ : 235.1, Found: 235.1.

### Preparation of (+)-dimethyl 2-phenylcyclobutane-1,1-dicarboxylate [(+)-1a]:



### (±)-1-(Methoxycarbonyl)-2-phenylcyclobutanecarboxylic acid (24):

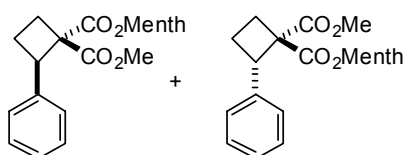


This compound was prepared from **rac-1a** according to the protocol reported by Burger and Coyne<sup>30</sup> and was of sufficient purity for subsequent transformations. Analytical data for **24**: **mp** 139–141  $^\circ\text{C}$ ; **IR** (thin film,  $\text{cm}^{-1}$ )

3005, 2952, 1743, 1706, 1496, 1419, 1287, 1204, 1122, 943, 792, 700;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 – 7.30 (m, 4H), 7.25 – 7.22 (m, 1H), 4.37 (t,  $J = 9.5$  Hz, 1H), 3.32 (s, 3H),

2.76 – 2.64 (m, 2H), 2.48 – 2.42 (m, 1H), 2.24 – 2.19 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 169.8, 138.6, 128.1, 127.4, 127.1, 59.5, 52.1, 45.6, 25.5, 20.6; LRMS (ESI) Calcd. for  $\text{C}_{13}\text{H}_{14}\text{O}_4+\text{Na}$ : 257.1, Found: 257.1.

**(+)- and (-)-1-(2-isopropyl-5-methylcyclohexyl) 1-methyl 2-phenylcyclobutane-1,1-dicarboxylate (25):**

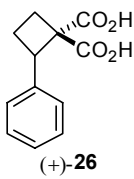


A 100-mL round-bottomed flask was charged with ( $\pm$ )-(methoxycarbonyl)-2-phenylcyclobutanecarboxylic acid (**24**, 0.900 g, 3.84 mmol, 1.0 equiv), dicyclohexylcarbodiimide (1.02 g, 4.95 mmol, 1.3 equiv), 4-dimethylaminopyridine (0.469 g, 3.84 mmol, 1.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (20 mL). The resulting solution was allowed to stir for 30 min, at which time finely ground (-)-menthol (0.650 g, 4.27 mmol, 1.10 equiv) was added in one portion. The flask was sealed with a polypropylene stopper and was allowed to stir for 3 days. The reaction was filtered through celite and the filtrate was washed with saturated aq.  $\text{NH}_4\text{Cl}$  (2 x 20 mL),  $\text{H}_2\text{O}$  (2 x 20 mL), and brine (1 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Partial separation of the isomers was achieved by flash chromatography (30 – 60%  $\text{CH}_2\text{Cl}_2$ /hexanes) to afford (-)-1-methyl 2-phenylcyclobutane-1,1-dicarboxylate (0.200 g, 0.537 mmol), (+)-1-methyl 2-phenylcyclobutane-1,1-dicarboxylate (0.174 g, 0.467 mmol), and a mixture of the two isomers (0.560 g, 1.503 mmol), all present as clear slightly yellow oils (total combined yield: 0.934 g, 2.504 mmol, 65%). Analytical data for (-)-**25**:  $[\alpha]_{\text{D}}^{29} = -115.2$  ( $c = 0.440$ ,  $\text{CHCl}_3$ ); IR (thin film,  $\text{cm}^{-1}$ ) 2953, 2871, 1726, 1435, 1198, 1182, 1109, 1037, 956, 757, 698;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.26 (m, 4H), 7.24 – 7.16 (m, 1H), 4.70 (td,  $J = 10.9, 4.3$  Hz, 1H), 4.36 (t,  $J = 8.7$  Hz, 1H), 3.20 (s, 3H), 2.72 (t,  $J = 8.8$  Hz, 1H), 2.58 (dd,  $J = 17.6$ ,



10.5 Hz, 1H), 2.27 – 2.12 (m, 2H), 2.07 (d,  $J = 11.5$  Hz, 1H), 1.86 – 1.74 (m, 1H), 1.74 – 1.62 (m, 2H), 1.57 – 1.45 (m, 1H), 1.43 – 1.32 (m, 1H), 1.13 – 0.79 (m, 3H), 0.93 (d,  $J = 6.5$  Hz, 3H), 0.84 (d,  $J = 7.1$  Hz, 3H) 0.72 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 169.9, 139.3, 128.0, 127.7, 126.8, 75.4, 59.9, 51.4, 47.0, 45.0, 40.5, 34.3, 31.4, 25.9, 25.7, 23.3, 22.0, 20.7, 20.7, 16.0; **TLC** (60%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.39; **LRMS** (ESI) Calcd. for  $\text{C}_{23}\text{H}_{32}\text{O}_4 + \text{Na}$ : 395.2, Found: 395.2. Analytical data for (+)-**25**:  $[\alpha]_{\text{D}}^{29} = + 24.9$  ( $c = 0.400$ ,  $\text{CHCl}_3$ ); **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2871, 1726, 1456, 1435, 1271, 1199, 1109, 1037, 957, 757;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.22 (m, 4H), 7.20 (t,  $J = 6.5$  Hz, 1H), 4.75 (td,  $J = 10.9, 4.3$  Hz, 1H), 4.35 (t,  $J = 9.4$  Hz, 1H), 3.23 (s, 3H), 2.75 – 2.55 (m, 2H), 2.31 – 2.11 (m, 2H), 2.02 (d,  $J = 11.9$  Hz, 1H), 1.91 (dq,  $J = 6.6, 4.3$  Hz, 1H), 1.69 (d,  $J = 11.4$  Hz, 2H), 1.58 – 1.47 (m, 1H), 1.40 (dd,  $J = 23.8, 12.4$  Hz, 1H), 1.08 (dd,  $J = 23.0, 12.7$  Hz, 1H), 1.00 – 0.83 (m, 9H), 0.79 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 170.0, 139.2, 127.9, 127.6, 126.8, 75.2, 60.1, 51.6, 47.0, 45.1, 40.3, 34.2, 31.4, 26.1, 25.6, 23.4, 22.0, 20.7, 20.6, 16.1; **TLC** (60%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.35; **LRMS** (ESI) Calcd. for  $\text{C}_{23}\text{H}_{32}\text{O}_4 + \text{Na}$ : 395.2, Found: 395.2.

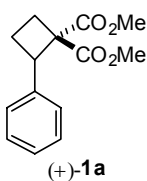
**(+)-2-Phenylcyclobutane-1,1-dicarboxylic acid (26):**



Potassium hydroxide pellets (0.203 g, 3.62 mmol, 9.0 equiv) were dissolved in  $\text{H}_2\text{O}$  (3.25 mL) and diluted with EtOH (3.25 mL). This KOH solution was added to a 25-mL round-bottomed flask containing a magnetic stir bar and (+)-methyl 2-phenylcyclobutane-1,1-dicarboxylate (**25**, 0.150 g, 0.403 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and the reaction was heated at reflux for 2 d at which point the reaction was cooled to room temperature and the majority of the ethanol was

removed by rotary evaporation. The resulting solution was diluted with H<sub>2</sub>O (20 mL) and washed with Et<sub>2</sub>O (4 x 20 mL). The aqueous solution was brought to pH = 1 by addition of concentrated HCl. The acidic solution was extracted with Et<sub>2</sub>O (4 x 15 mL) and the combined organic extracts were dried over MgSO<sub>4</sub> and concentrated to afford pure (+)-2-phenylcyclobutane-1,1-dicarboxylic acid (**26**) (0.083 g, 0.381 mmol, 94%) as a white powder. Analytical data for (+)-**26**:  $[\alpha]_D^{27} = +65.5$  ( $c = 0.300$ , CHCl<sub>3</sub>); **mp** 125-128 °C (dec.); **IR** (thin film, cm<sup>-1</sup>) 2953, 2688, 2573, 1699, 1419, 1290, 1222, 1116, 928, 785, 697; **<sup>1</sup>H NMR** (400 MHz, DMSO)  $\delta$  12.56 (bs, 2H), 7.31 – 7.28 (m, 4H), 7.22 – 7.17 (m, 1H), 4.18 (t,  $J = 9.6$  Hz, 1H), 2.50 – 2.40 (m, 2H), 2.25 – 2.19 (m, 1H), 2.12 – 2.06 (m, 1H); **<sup>13</sup>C NMR** (100 MHz, DMSO)  $\delta$  174.0, 171.7, 140.9, 128.7, 128.4, 127.3, 60.0, 45.1, 26.4, 21.4; **LRMS** (ESI) Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>+Na: 243.1, Found: 243.1.

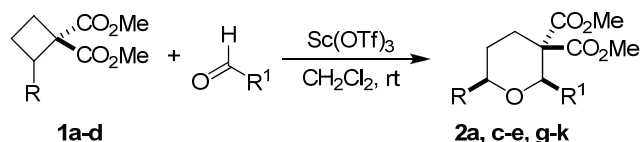
**(+)-Dimethyl 2-phenylcyclobutane-1,1-dicarboxylate (**1a**):**



A flame-dried 1-dram vial containing a magnetic stir bar was charged with (+)-2-phenylcyclobutane-1,1-dicarboxylic acid (**26**, 0.083 g, 0.381 mmol, 1.0 equiv), potassium carbonate (0.208 g, 0.151 mmol, 4.0 equiv), and dimethylformamide (1.75 mL). The resulting suspension was stirred for 30 min and then iodomethane (0.321 g, 0.141 mL, 2.26 mmol, 6.0 equiv) was added in one portion. The reaction was allowed to stir for 24 h and was then poured into a separatory funnel containing H<sub>2</sub>O (10 mL). The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic extracts were washed with H<sub>2</sub>O (3 x 15 mL) and 50% saturated aq. NaCl solution (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The product was purified by flash chromatography (10% EtOAc/hexanes) to afford (+)-**1a** (0.052 g, 0.209 mmol, 56%) as a

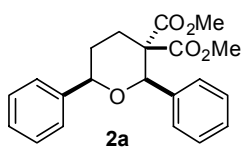
slightly yellow clear oil in 98:2 er as determined by GC analysis (Chiradex B-DM column, 30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C).  $[\alpha]_D^{27} = +93.9$  ( $c = 0.360$ ,  $\text{CHCl}_3$ ).

**General Procedure A for the  $\text{Sc}(\text{OTf})_3$ -catalyzed (4 + 2) annulation of cyclobutanes **1a-d** with aryl aldehydes to afford tetrahydropyrans **2a, c-e, g-k**:**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with  $\text{Sc}(\text{OTf})_3$  (0.02 equiv). To this vial was added a solution of the cyclobutane (1.0 equiv) and aldehyde (3.0 equiv) in  $\text{CH}_2\text{Cl}_2$  ( $[\mathbf{1}]_0 = 0.25 \text{ M}$ ). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and allowed to stir. Upon disappearance of the cyclobutane as indicated by TLC analysis (with 25% EtOAc/hexanes or  $\text{CH}_2\text{Cl}_2$  as the mobile phase), the reaction was filtered through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and concentrated. The resulting tetrahydropyrans **2a, c-e, g-k** were purified by flash chromatography using the indicated solvent system.

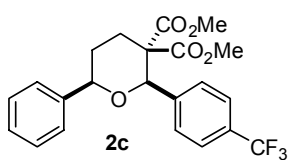
**Dimethyl 2,6-diphenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**2a**):**



The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), benzaldehyde (0.103 g, 0.967 mmol, 3.0 equiv),  $\text{Sc}(\text{OTf})_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 6.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15%

EtOAc/hexanes) to afford **2a** (0.111 g, 0.313 mmol, 97% yield) as a white waxy solid in 96:4 dr. Analytical data for **2a**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3032, 2952, 2857, 1729, 1452, 1435, 1257, 1091, 1068, 700;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (d,  $J = 7.3$  Hz, 2H), 7.43 (d,  $J = 7.4$  Hz, 2H), 7.36 (t,  $J = 7.4$  Hz, 2H), 7.33 – 7.20 (m, 4H), 5.17 (s, 1H), 4.69 (dd,  $J = 11.4, 2.2$  Hz, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 2.77 – 2.62 (m, 1H), 2.34 (td,  $J = 13.3, 4.3$  Hz, 1H), 2.12 (ddd,  $J = 17.0, 13.5, 4.0$  Hz, 1H), 2.01 – 1.89 (m, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 142.3, 139.5, 128.3, 127.5, 127.4, 127.2, 125.8, 82.3, 80.7, 58.6, 52.4, 51.5, 32.8, 30.0; **TLC** (15% EtOAc/hexanes)  $R_f$  0.18; **Anal.** Calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_5$ : C, 71.17; H, 6.26. Found: C, 71.16; H, 6.32.

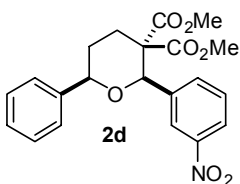
**Dimethyl 6-phenyl-2-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (**2c**):**



The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv),  $\text{Sc}(\text{OTf})_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 4.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2c** (0.126 g, 0.298 mmol, 92% yield) as a clear colorless oil in 99:1 dr. Analytical data for **2c**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 2858, 1731, 1436, 1327, 1166, 1121, 1068, 1019, 856;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d,  $J = 8.3$  Hz, 2H), 7.56 (d,  $J = 8.4$  Hz, 2H), 7.47 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 5.22 (s, 1H), 4.70 (dd,  $J = 11.5, 2.5$  Hz, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 2.73 (dt,  $J = 13.4, 3.2$  Hz, 1H), 2.35 (td,  $J = 13.4, 4.4$  Hz, 1H), 2.21 – 2.06 (m, 1H), 2.03 – 1.93 (m, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 168.7, 143.6, 141.9, 129.7 (q,  $J = 32.3$  Hz), 128.4,

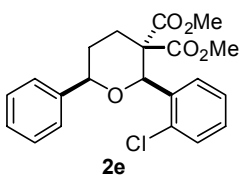
127.9, 127.7, 125.8, 124.3 (q,  $J = 271.5$  Hz), 124.15 (q,  $J = 4.0$  Hz), 81.7, 80.8, 58.6, 52.5, 51.6, 32.7, 29.8; **TLC** (15% EtOAc/hexanes)  $R_f$  0.15; **Anal.** Calcd. for  $C_{22}H_{21}F_3O_5$ : C, 62.56; H, 5.01. Found: C, 62.81; H, 5.12.

**Dimethyl 2-(3-nitrophenyl)-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2d):**



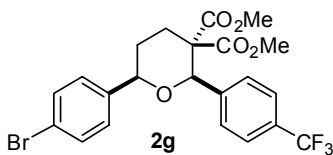
The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 3-nitrobenzaldehyde (0.146 g, 0.967 mmol, 3.0 equiv),  $Sc(OTf)_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $CH_2Cl_2$  (1.28 mL). After stirring for 6.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2d** (0.116 g, 0.290 mmol, 90% yield) as yellow crystals in 98:2 dr. Analytical data for **2d**: **mp** 122–123 °C; **IR** (thin film,  $cm^{-1}$ ) 3032, 2953, 2860, 1731, 1530, 1349, 1275, 1256, 1092, 1069, 806, 699;  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  8.30 (s, 1H), 8.17 – 8.08 (m, 1H), 7.86 (d,  $J = 7.8$  Hz, 1H), 7.47 (t,  $J = 8.0$  Hz, 1H), 7.44 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.24 (s, 1H), 4.71 (dd,  $J = 11.5, 2.7$  Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 2.78 – 2.70 (m, 1H), 2.36 (td,  $J = 13.4, 4.5$  Hz, 1H), 2.17 – 2.05 (m, 1H), 1.99 (ddt,  $J = 13.9, 4.5, 2.8$  Hz, 1H);  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  171.0, 168.6, 147.7, 141.6 (two overlapping resonances), 133.8, 128.5, 128.1, 127.8, 125.8, 122.6, 122.5, 81.4, 81.1, 58.6, 52.7, 51.9, 32.6, 29.9; **TLC** (20% EtOAc/hexanes)  $R_f$  0.19; **Anal.** Calcd. for  $C_{21}H_{21}NO_7$ : C, 63.15; H, 5.30; N, 3.51. Found: C, 63.08; H, 5.30; N, 3.51.

**Dimethyl 2-(4-chlorophenyl)-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2e):**



The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 2-chlorobenzaldehyde (0.136 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 7.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2e** (0.122 g, 0.314 mmol, 97% yield) as a white solid in 92:8 dr. Analytical data for **2e**: mp 90-92 °C; IR (thin film, cm<sup>-1</sup>) 3031, 2952, 2856, 1735, 1437, 1276, 1254, 1166, 1092, 1032, 759, 701; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.38 – 7.24 (m, 5H), 7.23 – 7.17 (m, 1H), 5.31 (s, 1H), 4.69 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 2.65 – 2.55 (m, 2H), 1.99 (ddd, *J* = 13.9, 6.6, 3.5 Hz, 1H), 1.82 (dtd, *J* = 14.0, 11.5, 6.1 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.5, 168.8, 142.2, 136.4, 133.2, 131.8, 128.9, 128.3, 128.2, 127.6, 126.1, 125.8, 81.0, 78.9, 57.5, 52.7, 51.9, 32.4, 30.6; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.21; **Anal.** Calcd. for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>: C, 64.87; H, 5.44. Found: C, 65.15; H, 5.49.

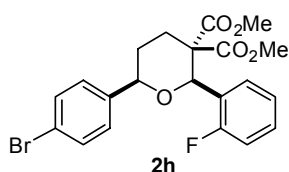
**Dimethyl 6-(4-bromophenyl)-2-(4-(trifluoromethyl) phenyl) dihydro-2H-pyran-3,3(4H)-dicarboxylate (2g):**



The title compound was prepared according to General Procedure A using **1b** (0.105 g, 0.322 mmol, 1.0 equiv), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 15 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2g** (0.146 g, 0.291

mmol, 90% yield) as a yellow powder in 98:2 dr. Analytical data for **2g**: mp 107-109 °C; IR (thin film, cm<sup>-1</sup>) 3003 2954, 2858, 1731, 1436, 1327, 1166, 1122, 1068, 1011, 856, 815; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 (q, *J* = 8.5 Hz, 4H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 1H), 4.64 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.70 (s, 3H), 3.54 (s, 3H), 2.71 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.31 (td, *J* = 13.3, 4.4 Hz, 1H), 2.08 (ddd, *J* = 16.8, 13.4, 4.0 Hz, 1H), 2.00 – 1.88 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.0, 168.6, 143.3, 140.8, 131.5, 129.7 (q, *J* = 32.0 Hz), 127.8, 127.5, 124.2 (d, *J* = 270.0 Hz), 125.6 – 122.7 (m), 121.5, 81.7, 80.0, 58.3, 52.6, 51.7, 32.5, 29.7; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.23; Anal. Calcd. for C<sub>22</sub>H<sub>20</sub>BrF<sub>3</sub>O<sub>5</sub>: C, 52.71; H, 4.02. Found: C, 52.78; H, 4.05.

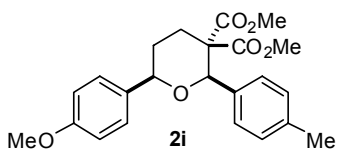
**Dimethyl 6-(4-bromophenyl)-2-(2-fluorophenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2h):**



The title compound was prepared according to General Procedure A using **1b** (0.105 g, 0.322 mmol, 1.0 equiv), 2-fluorobenzaldehyde (0.120 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 16.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2h** (0.136 g, 0.301 mmol, 94% yield) as a clear colorless oil in 99:1 dr. Analytical data for **2h**: IR (thin film, cm<sup>-1</sup>) 2953, 2857, 1735, 1490, 1274, 1255, 1086, 1011, 764; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.88 (t, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.21 (m, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.02 – 6.88 (m, 1H), 5.17 (s, 1H), 4.62 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.66 (s, 6H), 2.65 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.52 (td, *J* = 13.7, 4.0 Hz, 1H), 1.95 (dd, *J* = 13.6, 2.9 Hz, 1H), 1.82 (ddd, *J* = 25.6, 13.8, 3.9 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.6, 168.7, 161.0, 158.6, 141.1, 131.4, 131.1 (d,

$J = 3.7$  Hz), 129.3 (d,  $J = 8.7$  Hz), 127.5, 125.8 (d,  $J = 12.6$  Hz), 123.3 (d,  $J = 3.1$  Hz), 121.4, 114.2, 113.9, 80.2, 76.8, 57.7, 52.5, 51.8, 32.1, 30.3; **TLC** (20% EtOAc/hexanes)  $R_f$  0.24; **LRMS** (ESI) Calcd. for  $C_{21}H_{20}BrFO_5 + Na$ : 473.1, Found: 473.0.

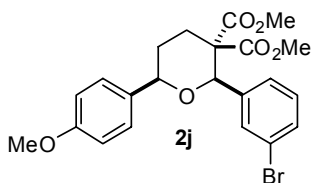
**Dimethyl 6-(4-methoxyphenyl)-2-p-tolyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2i):**



The title compound was prepared according to General Procedure A using **1c** (0.090 g, 0.322 mmol, 1.0 equiv), 4-methylbenzaldehyde (0.116 g, 0.967 mmol, 3.0 equiv),  $Sc(OTf)_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $CH_2Cl_2$  (1.28 mL). After stirring for 15 min, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2i** (0.120 g, 0.301 mmol, 93% yield) as colorless crystals in 96:4 dr. Analytical data for **2i**: **mp** 126-127 °C; **IR** (thin film,  $cm^{-1}$ ) 3003, 2952, 2839, 1728, 1515, 1435, 1250, 1083, 1035, 826;  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.34 (d,  $J = 8.0$  Hz, 4H), 7.10 (d,  $J = 7.7$  Hz, 2H), 6.88 (d,  $J = 8.4$  Hz, 2H), 5.11 (s, 1H), 4.62 (d,  $J = 10.0$  Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 2.68 (d,  $J = 13.3$  Hz, 1H), 2.36 – 2.28 (m, 1H), 2.32 (s, 3H), 2.09 (dq,  $J = 13.6, 3.8$  Hz, 1H), 1.91 (d,  $J = 12.0$  Hz, 1H);  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  171.3, 169.2, 159.0, 137.0, 136.5, 134.7, 127.9, 127.3, 127.1, 113.7, 82.4, 80.3, 58.6, 55.2, 52.3, 51.5, 32.8, 29.9, 21.1; **TLC** (15% EtOAc/hexanes)  $R_f$  0.16; **Anal.** Calcd. for  $C_{23}H_{26}O_6$ : C, 69.33; H, 6.58. Found: C, 69.10; H, 6.61.

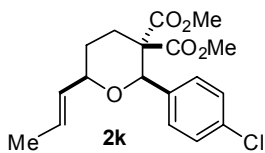


**Dimethyl 6-(4-methoxyphenyl)-2-(3-bromophenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2j):**



The title compound was prepared according to General Procedure A using **1c** (0.090 g, 0.322 mmol, 1.0 equiv), 3-bromobenzaldehyde (0.179 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 15 min, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2j** (0.118 g, 0.255 mmol, 79% yield) as a clear colorless oil in 97:3 dr. Analytical data for **2j**: IR (thin film, cm<sup>-1</sup>) 3002, 2952, 2838, 1730, 1614, 1515, 1434, 1250, 1082, 1035, 829, 776; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59 (s, 1H), 7.43 – 7.29 (m, 4H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.11 (s, 1H), 4.61 (dd, *J* = 11.5, 2.2 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.58 (s, 3H), 2.69 (dt, *J* = 13.2, 3.1 Hz, 1H), 2.30 (td, *J* = 13.3, 4.2 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.96 – 1.85 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.1, 168.8, 159.2, 141.8, 134.2, 130.6, 130.5, 128.7, 127.1, 126.2, 121.3, 113.8, 81.6, 80.5, 58.5, 55.2, 52.4, 51.6, 32.7, 29.7; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.13; LRMS (ESI) Calcd. for C<sub>22</sub>H<sub>23</sub>BrO<sub>6</sub>+Na: 485.1, Found: 485.1.

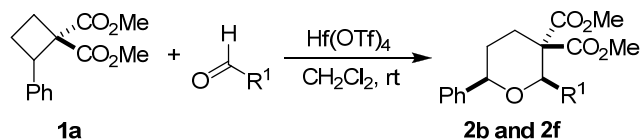
**Dimethyl 2-(4-chlorophenyl)-6-((*E*)-prop-1-enyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2k):**



The title compound was prepared according to General Procedure A using **1d** (0.040 g, 0.188 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.079 g, 0.564 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0018 g, 0.0037 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (0.75 mL). After stirring for 6.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (60% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) to afford **2k** (0.047 g, 0.133 mmol, 70% yield) as a

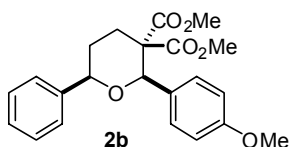
clear colorless oil in 94:6 dr. Analytical data for **2k**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2360, 2342, 1731, 1492, 1436, 1090, 1014, 846, 808;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 8.5$  Hz, 2H), 7.23 (d,  $J = 8.5$  Hz, 2H), 5.74 (dq,  $J = 12.9, 6.3$  Hz, 1H), 5.55 (dd,  $J = 15.4, 6.1$  Hz, 1H), 4.96 (s, 1H), 4.16 – 3.97 (m, 1H), 3.65 (s, 3H), 3.53 (s, 3H), 2.68 – 2.50 (m, 1H), 2.14 (td,  $J = 13.4, 4.4$  Hz, 1H), 1.95 – 1.79 (m, 1H), 1.70 – 1.65 (m, 1H), 1.69 (d,  $J = 6.4$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 168.9, 138.2, 133.2, 131.3, 128.9, 127.4, 127.3, 81.4, 79.4, 58.5, 52.4, 51.6, 32.3, 28.0, 17.7; **TLC** (60%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.28; **Anal.** Calcd. for  $\text{C}_{18}\text{H}_{21}\text{ClO}_5$ : C, 61.28; H, 6.00. Found: C, 61.51; H, 6.04.

**General Procedure B for the  $\text{Hf}(\text{OTf})_4$ -catalyzed (4 + 2) annulation of cyclobutane **1a** with 4-methoxybenzaldehyde and cinnamaldehyde to afford tetrahydropyrans **2b** and **2f**:**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with  $\text{Hf}(\text{OTf})_4$  (0.0050 g, 0.0064 mmol, 0.02 equiv). To this vial was added a solution of cyclobutane **1a** (0.080 g, 0.322 mmol, 1.0 equiv) and the aldehyde (0.967 mmol, 3.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.28 mL). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and allowed to stir. After disappearance of the cyclobutane was confirmed by TLC analysis, the reaction was filtered through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and concentrated. The resulting tetrahydropyran products were purified by flash chromatography using the indicated solvent system.

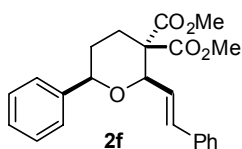
**Dimethyl 2-(4-methoxyphenyl)-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2b):**



The title compound was prepared according to General Procedure B using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-methoxybenzaldehyde

(0.132 g, 0.967 mmol, 3.0 equiv), Hf(OTf)<sub>4</sub> (0.0050 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 11 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (80 – 90 – 100% CH<sub>2</sub>Cl<sub>2</sub>/hexanes gradient) to afford **2b** (0.084 g, 0.219 mmol, 68% yield) as a clear colorless oil in 96:4 dr. Analytical data for **2b**: **IR** (thin film, cm<sup>-1</sup>) 2952, 2930, 1851, 1729, 1613, 1514, 1453, 1435, 1250, 1177, 1069, 1033, 700; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.41 (dd, *J* = 7.6, 6.1 Hz, 4H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.23 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.11 (s, 1H), 4.67 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 2.76 – 2.58 (m, 1H), 2.32 (td, *J* = 13.3, 4.3 Hz, 1H), 2.19 – 2.02 (m, 1H), 2.02 – 1.88 (m, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.3, 169.2, 159.0, 142.4, 131.7, 128.6, 128.2, 127.5, 125.8, 112.7, 82.1, 80.7, 58.6, 55.1, 52.3, 51.6, 32.7, 30.0; **TLC** (80% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) R<sub>f</sub> 0.18; **Anal.** Calcd. for C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>: C, 68.74; H, 6.29. Found: C, 69.00; H, 6.28.

**Dimethyl 6-phenyl-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (2f):**

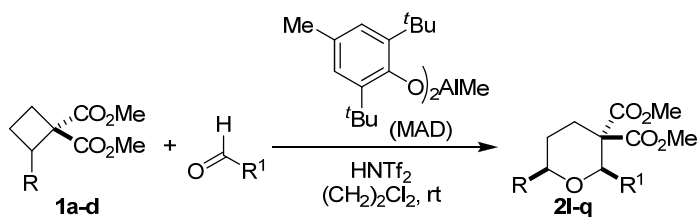


The title compound was prepared according to General Procedure B using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), *trans*-cinnamaldehyde (0.128 g, 0.967 mmol, 3.0 equiv), Hf(OTf)<sub>4</sub> (0.0050 g, 0.0064 mmol, 0.02

equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 22 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2f** (0.095 g, 0.264 mmol, 82% yield) as a

clear colorless oil in 79:21 dr. Analytical data for **2f**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3030, 2953, 1732, 1451, 1435, 1236, 1171, 1066, 1026, 696;  **$^1\text{H}$  NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.41 (d,  $J = 7.4$  Hz, 2H), 7.31 (d,  $J = 7.3$  Hz, 2H), 7.19 (t,  $J = 7.5$  Hz, 2H), 7.12 – 6.97 (m, 5H), 6.86 (d,  $J = 16.1$  Hz, 1H), 4.73 (d,  $J = 5.7$  Hz, 1H), 4.32 (dd,  $J = 11.6, 2.2$  Hz, 1H), 3.36 (s, 3H), 3.25 (s, 3H), 2.71 – 2.58 (m, 1H), 2.15 (ddd,  $J = 25.2, 13.4, 4.0$  Hz, 1H), 1.95 (td,  $J = 13.3, 4.2$  Hz, 1H), 1.62 – 1.50 (m, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 169.2, 142.0, 137.1, 131.3, 128.4, 128.3, 127.6, 127.4, 127.4, 126.6, 125.9, 82.2, 80.4, 58.1, 52.5, 52.1, 32.0, 29.9; **TLC** (15% EtOAc/hexanes)  $R_f$  0.23; **Anal.** Calcd. for  $\text{C}_{22}\text{H}_{24}\text{O}_6$ : C, 72.61; H, 6.36. Found: C, 72.67; H, 6.44.

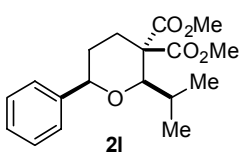
**General Procedure C for the MADNTf<sub>2</sub>-catalyzed (4 + 2) annulation of cyclobutanes 1a-d with alkyl aldehydes to afford tetrahydropyrans 2l-q:**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)<sup>28</sup> (MAD, 0.07 equiv), HNTf<sub>2</sub> (0.05 equiv) and (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub> (0.180 mL). The resulting solution was stirred until the evolution of methane gas ceases, approximately 5 min. To this vial is added a solution of the cyclobutane (0.322 mmol, 1.0 equiv) and aldehyde (0.967 mmol, 3.0 equiv) in (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub> (1.00 mL). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and stirred. Upon disappearance of the cyclobutane as indicated by TLC analysis (with 25% EtOAc/hexanes or CH<sub>2</sub>Cl<sub>2</sub> as the mobile phase), the reaction was filtered through a 1-inch

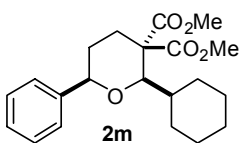
Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and concentrated. The resulting tetrahydropyrans **2l-q** were purified by flash chromatography using the indicated solvent system.

**Dimethyl 2-isopropyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2l):**



The title compound was prepared according to General Procedure C using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), isobutyraldehyde (0.070 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and dichloroethane (1.28 mL). After stirring for 22.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (7.5% EtOAc/hexanes) to afford **2l** (0.091 g, 0.284 mmol, 88% yield) as a clear colorless oil in 91:9 dr. Analytical data for **2l**: **IR** (thin film, cm<sup>-1</sup>) 2953, 2871, 1731, 1450, 1435, 1254, 1092, 1068, 1013, 698; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.38 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 4.48 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.72 – 3.66 (m, 1H), 2.62 (dt, *J* = 12.8, 3.1 Hz, 1H), 2.51 – 2.28 (m, 1H), 2.07 (td, *J* = 12.8, 4.8 Hz, 1H), 2.01 – 1.80 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 172.2, 169.7, 142.6, 128.2, 127.3, 125.7, 86.9, 80.1, 56.2, 52.3, 52.0, 33.6, 31.7, 29.7, 20.2, 19.8; **TLC** (7.5% EtOAc/hexanes) *R<sub>f</sub>* 0.16; **Anal.** Calcd. For C<sub>18</sub>H<sub>24</sub>O<sub>5</sub>: C, 67.48; H, 7.55. Found: C, 67.44; H, 7.67.

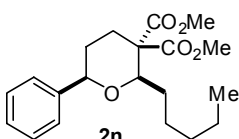
**Dimethyl 2-cyclohexyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2m):**



The title compound was prepared according to General Procedure C using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), cyclohexanecarboxaldehyde (0.108 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045

g, 0.0161 mmol, 0.05 equiv), and dichloroethane (1.28 mL). After stirring for 24.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2m** (0.109 g, 0.302 mmol, 94% yield) as a clear colorless oil in 96:4 dr. Analytical data for **2m**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2927, 2852, 1730, 1450, 1435, 1093, 1068, 1029, 1009;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 4.45 (dd,  $J = 10.7, 3.0$  Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.72 – 3.61 (m, 1H), 2.69 – 2.51 (m, 1H), 2.05 (td,  $J = 12.6, 4.8$  Hz, 3H), 1.99 – 1.80 (m, 2H), 1.76 – 1.53 (m, 4H), 1.35 – 1.09 (m, 3H), 1.09 – 0.91 (m, 2H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 169.7, 142.6, 128.2, 127.3, 125.7, 86.2, 80.2, 56.1, 52.3, 52.0, 41.6, 33.7, 30.4, 30.1, 29.8, 26.8, 26.6, 26.3; **TLC** (10% EtOAc/hexanes)  $R_f$  0.32; **Anal.** Calcd. For  $\text{C}_{18}\text{H}_{24}\text{O}_5$ : C, 69.98; H, 7.83. Found: C, 69.80; H, 7.99.

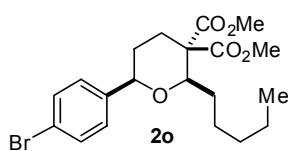
**Dimethyl 2-pentyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2n):**



The title compound was prepared according to General Procedure C using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv),  $\text{HNTf}_2$  (0.0045 g, 0.0161 mmol, 0.05 equiv), and dichloroethane (1.28 mL). After stirring for 6.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2n** (0.103 g, 0.296 mmol, 92% yield) as a clear colorless oil in 85:15 dr. Analytical data for **2n**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 2929, 2859, 1732, 1452, 1435, 1256, 1092, 1068, 698;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.30 (m, 4H), 7.28 (dd,  $J = 7.7, 4.5$  Hz, 1H), 4.55 – 4.37 (m, 1H), 3.87 (d,  $J = 9.0$  Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.73 – 2.52 (m, 1H), 2.14 – 1.95 (m, 2H), 1.95 – 1.77 (m, 2H), 1.77 – 1.49 (m, 2H), 1.30 (d,  $J = 3.4$  Hz, 5H), 0.88 (bs, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,

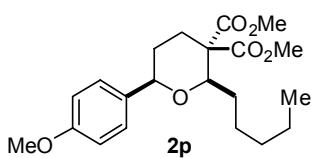
CDCl<sub>3</sub>)  $\delta$  171.6, 169.7, 142.4, 128.2, 127.4, 125.9, 82.2, 80.2, 56.8, 52.4, 51.9, 32.6, 31.6, 29.7, 26.9, 22.6, 14.0; **TLC** (10% EtOAc/hexanes)  $R_f$  0.25; **Anal.** Calcd. For C<sub>20</sub>H<sub>28</sub>O<sub>5</sub>: C, 68.94; H, 8.10. Found: C, 69.17; H, 8.06.

**Dimethyl 6-(4-bromophenyl)-2-pentyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2o):**



The title compound was prepared according to General Procedure C using **1b** (0.105 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and dichloroethane (1.28 mL). After stirring for 20 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2o** (0.116 g, 0.271 mmol, 84% yield) as a clear colorless oil in 87:13 dr. Analytical data for **2o**: **IR** (thin film, cm<sup>-1</sup>) 2953, 2928, 2859, 1732, 1489, 1435, 1255, 1233, 1083, 1011, 804; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 (d,  $J$  = 8.4 Hz, 2H), 7.20 (d,  $J$  = 8.3 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.84 (dd,  $J$  = 9.7, 1.3 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.66 – 2.53 (m, 1H), 2.08 – 1.89 (m, 2H), 1.89 – 1.75 (m, 2H), 1.75 – 1.62 (m, 1H), 1.62 – 1.48 (m, 1H), 1.40 – 1.19 (m, 5H), 0.87 (bt,  $J$  = 5.9 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.5, 169.6, 141.4, 131.3, 127.6, 121.2, 82.1, 79.5, 56.6, 52.4, 52.0, 32.5, 32.4, 31.6, 29.7, 26.9, 22.5, 14.0; **TLC** (10% EtOAc/hexanes)  $R_f$  0.23; **Anal.** Calcd. For C<sub>20</sub>H<sub>27</sub>BrO<sub>5</sub>: C, 56.21; H, 6.37. Found: C, 56.51; H, 6.47.

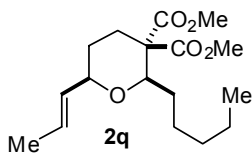
**Dimethyl 6-(4-methoxyphenyl)-2-pentyldihydro-2H-pyran-3,3 (4H)-dicarboxylate (2p):**



Note: This reaction was run at 0 °C. The title compound was prepared according to General Procedure C using **1c** (0.090 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv),

MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and dichloroethane (1.28 mL). After stirring for 3.5 h at 0 °C, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2p** (0.081 g, 0.214 mmol, 66% yield) as a clear colorless oil in 78:22 dr. Analytical data for **2p**: IR (thin film, cm<sup>-1</sup>) 2954, 2930, 2858, 1731, 1614, 1515, 1436, 1249, 1175, 1081, 1034, 825; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.90 – 3.82 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 2.67 – 2.51 (m, 1H), 2.11 – 1.94 (m, 2H), 1.92 – 1.75 (m, 2H), 1.73 – 1.48 (m, 2H), 1.29 (m, *J* = 3.1 Hz, 5H), 0.87 (bs, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.7, 169.7, 159.1, 134.6, 127.2, 113.7, 82.2, 79.9, 56.9, 55.3, 52.3, 51.9, 32.6, 31.6, 29.4, 27.0, 22.6, 14.0; TLC (15% EtOAc/hexanes) R<sub>f</sub> 0.22; **Anal.** Calcd. For C<sub>21</sub>H<sub>30</sub>O<sub>6</sub>: C, 66.65; H, 7.99. Found: C, 66.81; H, 8.02.

**Dimethyl 2-pentyl-6-((*E*)-prop-1-enyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2q):**



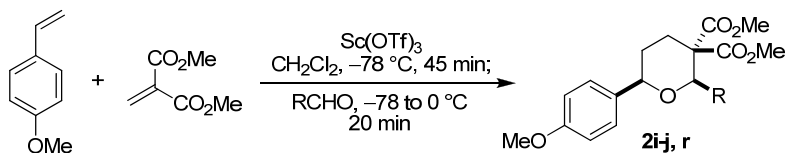
The title compound was prepared according to General Procedure C using **1d** (0.040 g, 0.188 mmol, 1.0 equiv), hexanal (0.056 g, 0.564 mmol, 3.0 equiv), MAD (0.0063 g, 0.013 mmol, 0.07 equiv), HNTf<sub>2</sub>

(0.0027 g, 0.0094 mmol, 0.05 equiv), and dichloroethane (0.75 mL). After stirring for 3.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2q** (0.050 g, 0.156 mmol,



85% yield) as a clear colorless oil in 77:23 dr containing an inseparable cyclobutane decomposition product (16%, by mass). Corrected yield: 0.042 g, 0.134 mmol, 72%. Analytically pure material was obtained by HPLC purification. Analytical data for **2q**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2955, 2929, 2858, 1733, 1436, 1256, 1230, 1085, 1068, 1016, 966;  **$^1\text{H}$  NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.68 – 5.56 (m, 1H), 5.52 (dd,  $J = 15.6, 4.6$  Hz, 1H), 4.00 – 3.83 (m, 1H), 3.74 (d,  $J = 6.4$  Hz, 1H), 3.38 (s, 3H), 3.27 (s, 3H), 2.71 – 2.52 (m, 1H), 2.17 (dtd,  $J = 14.5, 9.8, 4.9$  Hz, 1H), 2.10 – 1.93 (m, 2H), 1.92 – 1.70 (m, 2H), 1.54 (m, 1H), 1.48 (d,  $J = 6.0$  Hz, 3H), 1.44 – 1.20 (m, 5H), 0.86 (t,  $J = 7.0$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  172.4, 170.2, 133.4, 126.6, 82.8, 79.7, 57.7, 52.4, 52.1, 33.9, 33.3, 32.7, 29.4, 28.2, 23.6, 18.3, 14.8; **TLC** (10% EtOAc/hexanes)  $R_f$  0.27; **LRMS** (ESI) Calcd. For  $\text{C}_{17}\text{H}_{28}\text{O}_5 + \text{Na}$ : 335.2, Found: 335.2.

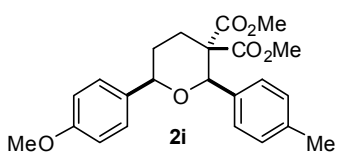
**General Procedure D for the  $\text{Sc}(\text{OTf})_3$ -catalyzed  $([2 + 2] + 2)$  cycloaddition/annulation of 1-methoxy-4-vinylbenzene, dimethyl 2-methylenemalonate, and aldehydes to afford tetrahydropyrans **2i-j, r**:**



In an inert atmosphere glove box, a 1-dram shell vial containing a magnetic stir bar was charged with  $\text{Sc}(\text{OTf})_3$  (0.0171 g, 0.0347 mmol, 0.10 equiv). A second shell vial was charged with dimethyl 2-methylenemalonate<sup>31</sup> (DMM, 0.050 g, 0.347 mmol, 1.0 equiv) and fitted with a rubber septum. Both vessels were removed from the glove box and placed under  $\text{N}_2$ . The  $\text{Sc}(\text{OTf})_3$  was suspended in  $\text{CH}_2\text{Cl}_2$  (0.25 mL) and cooled to  $-78\text{ }^\circ\text{C}$  in an isopropanol/dry ice bath. The DMM was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) and 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv) was added via syringe. The resulting solution

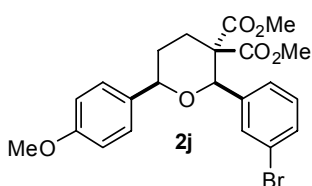
was drawn into a syringe and added to the  $\text{Sc}(\text{OTf})_3$  by syringe pump over 45 min. When the disappearance of DMM was confirmed by TLC (using 20% EtOAc/hexanes, approx 5-10 min), the aldehyde (1.04 mmol, 3.0 equiv) was added neat via syringe. The reaction was held at  $-78\text{ }^\circ\text{C}$  for 20 min and was then warmed to  $0\text{ }^\circ\text{C}$  for an additional 20 min at which point disappearance of **1c** can be observed by TLC (20% EtOAc/hexanes). The reaction was filtered through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and concentrated. The resulting tetrahydropyrans **2i-j, r** were purified by flash chromatography using the indicated solvent system.

**Dimethyl 6-(4-methoxyphenyl)-2-*p*-tolylidihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (**2i**):**



The title compound was prepared according to General Procedure D using  $\text{Sc}(\text{OTf})_3$  (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.050 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), 4-methylbenzaldehyde (0.125 g, 0.124 mL, 1.04 mmol, 3.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (2.25 mL). Work up and purification by flash chromatography (15% EtOAc/hexanes) provide pure **2i** (0.096 g, 0.241 mmol, 69% yield) as colorless crystals in 99:1 dr.

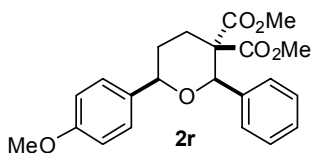
**Dimethyl 6-(4-methoxyphenyl)-2-(3-bromophenyl)dihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (**2j**):**



The title compound was prepared according to General Procedure D using  $\text{Sc}(\text{OTf})_3$  (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.050 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), 3-bromobenzaldehyde (0.192 g, 0.122 mL, 1.04 mmol, 3.0

equiv), and CH<sub>2</sub>Cl<sub>2</sub> (2.25 mL). Work up and purification by flash chromatography (15% EtOAc/hexanes) provided pure **2j** (0.076 g, 0.164 mmol, 47% yield) as a clear colorless oil in 97:3 dr.

**Dimethyl 6-(4-methoxyphenyl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2r):**



The title compound was prepared according to General Procedure D using Sc(OTf)<sub>3</sub> (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.050 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), benzaldehyde (0.110 g, 0.105 mL, 1.04 mmol, 3.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (2.25 mL). Work up and purification by flash chromatography (20% EtOAc/hexanes) provided pure **2r** (0.079 g, 0.205 mmol, 59% yield) as a clear colorless oil in 98:2 dr. Analytical data for **2r**: **IR** (thin film, cm<sup>-1</sup>) 2952, 2838, 1730, 1614, 1515, 1435, 1250, 1176, 1082, 1033, 828, 700; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 7.5 Hz, 4H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.29 (m, 3H), 7.29 – 7.24 (m, 2H), 5.18 (s, 1H), 4.66 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 2.72 – 2.70 (m, 1H), 2.34 (dt, *J* = 13.5, 4.5 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.96 – 1.93 (m, 1H).; **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 171.3, 169.1, 159.0, 139.4, 134.5, 127.5, 127.4, 127.2, 127.1, 113.6, 82.3, 80.3, 58.5, 55.2, 52.4, 51.6, 32.7, 29.9; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.23; **LRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>+Na: 407.2, Found: 407.2.

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