METAL-CATALYZED ANNULATIONS OF STRAINED CYCLOALKANES

Andrew Thomas Parsons

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

Chapel Hill 2010

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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 π-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/MgI₂ 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)MgI₂ 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. Sc(OTf)_3 and Hf(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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<th>Abbreviation</th>
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<tr>
<td>A</td>
<td>acceptor</td>
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<tr>
<td>A&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>1,3-allylic strain</td>
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<tr>
<td>Ac</td>
<td>acetate</td>
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<tr>
<td>Ad</td>
<td>adamantyl</td>
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<tr>
<td>Anal.</td>
<td>elemental analysis</td>
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<td>bipy</td>
<td>2,2′-dipyridyl</td>
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<tr>
<td>&quot;Bu</td>
<td><em>normal</em>-butyl</td>
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<td>′Bu</td>
<td><em>tert</em>-butyl</td>
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<tr>
<td>&lt;sup&gt;13&lt;/sup&gt;C NMR</td>
<td>carbon nuclear magnetic resonance spectroscopy</td>
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<tr>
<td>C–C</td>
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<tr>
<td>calcd.</td>
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<tr>
<td>cat</td>
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<td>COD</td>
<td>cyclooctadiene</td>
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<td>doublet or days</td>
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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-dibenzofurandiy1-2,2′-bis(oxazoline)
DCC dicyclohexylcarbodiimide
dig digonal
DKR dynamic kinetic resolution
DMAP 4-\(N,N\)-dimethylaminopyridine
DME dimethoxyethane
DMF \(N,N\)-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-\textit{tert}-butyl-4-methoxyphenyl
DyKAT  dynamic kinetic asymmetric transformation
E  electron withdrawing group
E  entgegen
El(+)  electrophile
endo  endocyclic
eq  equation
equiv  equivalents
er  enantiomeric ratio
ESI  electrospray ionization
Et  ethyl
Et₂O  diethyl ether
EtOAc  ethyl acetate
EWG  electron withdrawing group
exo  exocyclic
FID  flame ionization detector
GLC  gas-liquid chromatography
h  hour
¹H NMR  proton nuclear magnetic resonance spectroscopy
n-hexanal  normal-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-tert-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
n normal or number of atoms or counterions
NBS N-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
′Pr iso-propyl
PTFE polytetrafluoroethylene
pybox pyridine-2,6-bis(oxazoline)
q quartet
qd quartet of doublet
qn quintuplet
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<td>RF</td>
<td>retention factor</td>
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<td>large substituent</td>
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<td>small substituent</td>
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<td>RCHO</td>
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<td>room temperature</td>
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<td>SN2</td>
<td>bimolecular nucleophilic substitution</td>
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<td>SPhos</td>
<td>2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl</td>
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<td>t</td>
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<td>t1/2</td>
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<td>trifluoromethanesulfonyl</td>
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<td>tetrahydrofuran</td>
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<td>THP</td>
<td>tetrahydropyran</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TM</td>
<td>transition metal</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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<td>Symbol</td>
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<tr>
<td>triflate</td>
<td>trifluoromethanesulfonate</td>
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<tr>
<td>Troc</td>
<td>trichloroethyloxycarbonyl</td>
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<td>Ts</td>
<td>para-toluenesulfonyl</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>X</td>
<td>anionic ligand, halide, substituent, or number</td>
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<td>Z</td>
<td>zusammen</td>
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<tr>
<td>Å</td>
<td>Ångstrom</td>
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<tr>
<td>[α]</td>
<td>optical rotation</td>
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<tr>
<td>Δ</td>
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<tr>
<td>δ</td>
<td>chemical shift or partial charge</td>
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<tr>
<td>µL</td>
<td>microliter</td>
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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). Recent advances in the catalytic stereoselective synthesis of myriad D–A cyclopropanes from simple starting materials has facilitated the exploration of these compounds as building blocks for complex molecules.

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° to 60°, 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).

**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.\(^6\) This seemingly inconsistent characteristic can be attributed to a lack of axial symmetry of the C–C \(\sigma\)-bonds.\(^6\) 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.\(^5\) It has been proposed by Coulson and Moffitt that these bonds are best described as “bent” due to this asymmetric overlap (Figure 1-2).\(^7\) 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

![Diagram of carbon-carbon bonding in cyclopropane](image)

*Vicinal* donor-acceptor cyclopropanes have been extensively studied over the past decade due to their enhanced reactivity and increased functionality.\(^1\),\(^3\),\(^8\)-\(^12\) Elevation in reactivity is derived from the simultaneous stabilization of transient charged intermediates by the donor and acceptor group upon heterolytic C–C σ-bond cleavage. The ease in which D–A cyclopropanes undergo ring-opening allows them to serve as a 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

\[
\begin{align*}
\text{D} &= \text{donor (electron-releasing)} \\
\text{A} &= \text{acceptor (electron-withdrawing)} \\
\text{synthon} &= \text{mode of cyclopropane reactivity}
\end{align*}
\]

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 LUMO_dipole and the HOMO_dipolarophile. 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 HOMO_dipole, providing better orbital overlap with the low energy LUMO_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.\(^{14-16}\) 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)\(_3\)-catalyzed nucleophilic ring opening of 5 with indole nucleophiles under high pressure (eq 3).\(^{17}\) Subsequent studies demonstrated that reaction conditions could be optimized to give 6 as the major product.\(^{18}\)
**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**). In these processes, the donor and acceptor groups assume dual roles: 1) stabilize transient charged intermediates resulting from cyclopropyl C–C σ-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. The preparation of THFs through the (3 + 2) annihilation 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) annihilation reactions are highly convergent.

Figure 1-3. Representative Tetrahydrofuran-Containing Natural Products

The participation of aldehydes in annihilation 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 rather than tetrahydrofurans. Recently, Sugita and coworkers reported the annulation of malonate-derived methanochromanone 7 and aldehydes using catalytic SnCl₄, providing trans-fused tetrahydrofuro[2,3-b][1]benzopyranones 8 in a highly diastereoselective manner. Although no mechanistic studies were reported, it was proposed that the reaction is initiated by SnCl₄-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.
Precedents established by Kerr have demonstrated that use of an appropriate Lewis acid allows for catalytic annihilations 5 bearing non-heteroatomic donor groups under mild reaction conditions (vide supra). 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. 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 Sn(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 AlCl₃ and Sc(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

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>yield (%)a</th>
<th>drb</th>
<th>entry</th>
<th>Lewis acid</th>
<th>yield (%)a</th>
<th>drb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>&lt; 5</td>
<td>nd</td>
<td>11</td>
<td>SnCl₂</td>
<td>84</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>AgNTf₂</td>
<td>73</td>
<td>99:1</td>
<td>12</td>
<td>Sn(OTf)₂</td>
<td>97</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>81</td>
<td>67:33</td>
<td>13</td>
<td>Sn(OTf)₂</td>
<td>98</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>Ce(OTf)₃</td>
<td>75</td>
<td>99:1</td>
<td>14</td>
<td>SnCl₄</td>
<td>90</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)₂</td>
<td>94</td>
<td>98:2</td>
<td>15</td>
<td>Tb(OTf)₃</td>
<td>32</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>Dy(OTf)₃</td>
<td>28</td>
<td>98:2</td>
<td>16</td>
<td>Tm(OTf)₃</td>
<td>44</td>
<td>99:1</td>
</tr>
<tr>
<td>7</td>
<td>Er(OTf)₃</td>
<td>20</td>
<td>nd</td>
<td>17</td>
<td>Yb(OTf)₃</td>
<td>74</td>
<td>99:1</td>
</tr>
<tr>
<td>8</td>
<td>Hf(OTf)₄</td>
<td>30</td>
<td>67:33</td>
<td>18</td>
<td>ZnCl₂</td>
<td>54</td>
<td>98:2</td>
</tr>
<tr>
<td>9</td>
<td>Ho(OTf)₃</td>
<td>23</td>
<td>98:2</td>
<td>19</td>
<td>Zn(OTf)₂</td>
<td>70</td>
<td>98:2</td>
</tr>
<tr>
<td>10</td>
<td>Sc(OTf)₃</td>
<td>96</td>
<td>67:33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Determined by ¹H NMR spectroscopy using a mesitylene internal standard. b) Determined by ¹H 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-MeO₂CPh 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

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)</th>
<th>dr</th>
<th>a)</th>
<th>b)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2.25</td>
<td><img src="image" alt="12a" /></td>
<td>100</td>
<td>99:1</td>
<td>a)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-MeOPh</td>
<td>0.1</td>
<td><img src="image" alt="12b" /></td>
<td>85</td>
<td>98:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-MePh</td>
<td>1.25</td>
<td><img src="image" alt="12c" /></td>
<td>60</td>
<td>99:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-BrPh</td>
<td>25</td>
<td><img src="image" alt="12d" /></td>
<td>61</td>
<td>99:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4-AcOPh</td>
<td>24</td>
<td><img src="image" alt="12e" /></td>
<td>91</td>
<td>99:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4-MeO&lt;sub&gt;2&lt;/sub&gt;CPh</td>
<td>24</td>
<td><img src="image" alt="12f" /></td>
<td>83</td>
<td>99:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2-thienyl</td>
<td>0.75</td>
<td><img src="image" alt="12g" /></td>
<td>97</td>
<td>96:4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(E)-CH=CHPh</td>
<td>1</td>
<td><img src="image" alt="12h" /></td>
<td>94</td>
<td>70:30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>HC=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>8</td>
<td><img src="image" alt="12i" /></td>
<td>94</td>
<td>90:10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 SnCl₄ rather than Sn(OTf)₂ (entry 6).

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

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)ᵃ</th>
<th>drᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeOPh</td>
<td>3.5</td>
<td><img src="image" alt="Product 1j" /></td>
<td>99</td>
<td>99:1</td>
</tr>
<tr>
<td>2</td>
<td>4-ClPh</td>
<td>4.75</td>
<td><img src="image" alt="Product 1k" /></td>
<td>97</td>
<td>99:1</td>
</tr>
<tr>
<td>3ᶜ</td>
<td>4-NO₂Ph</td>
<td>15</td>
<td><img src="image" alt="Product 1l" /></td>
<td>89</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>(E)-HC=CHPh</td>
<td>3.5</td>
<td><img src="image" alt="Product 1m" /></td>
<td>97</td>
<td>94:6</td>
</tr>
<tr>
<td>5ᵈ</td>
<td>Et</td>
<td>1.75</td>
<td><img src="image" alt="Product 1n" /></td>
<td>100</td>
<td>97:3</td>
</tr>
</tbody>
</table>

ᵃ) Isolated yield.ᵇ) Determined by ¹H NMR spectroscopy of the unpurified product.ᶜ) 20 mol % of Sn(OTf)₂ was used.ᵈ) 5 mol % of SnCl₄ 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) annihilation 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)₂-catalyzed cyclopropane racemization was obtained when (S)-11a was exposed to a catalytic amount of Sn(OTf)₂ 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). The absolute stereochemistry was determined to be (2R, 5R), 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 of the ester group trans to the phenyl substituent of 11a and subsequent reesterification using perdeuterated dimethyl sulfate yielded diastereopure isotopically-labeled 15a. 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 $^1$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). Inversion has been observed for the methanolysis and aminolysis of activated optically pure (op) cyclopropanes at elevated temperatures (eq 7, 8). Cram has proposed carbanion-carbenium ions as transient configurally stable intermediates in reactions with D-A cyclopropanes of this type. Next, an $S_{E2}$-process occurring by a “corner” attack mechanism would proceed with inversion at the cyclopropane 1-position and afford the tetrahydrofuran (mechanism B);
However, this is the minor diastereomer observed from the labeling experiment (eq 6). 41-44

The cyclopropane could also undergo “edge” attack by the aldehyde (mechanism C). This $S_{E}2$ process would occur with retention of configuration at the 1-position. 30 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 $[\pi 2_a + \sigma 2_a]$ pathway (mechanism D). 45-47 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.;
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. 

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 reaction is directly related to the nucleophilicity of the aldehyde (eq 9). A 120° rotation about the C2–C3 σ-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 C1–C3 σ-bond prior to ring closure. It is noted that scrambling of the ester groups would require a 180° C1–C3 bond rotation to be faster than the 120° C2–C3 bond rotation. Additionally, this 180° rotation would involve an eclipsing butane interaction between C2 and one carboxyester group, while the 120° rotation would not suffer similar torsional strain. (Reprinted in part with permission from Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li,

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_N$2-type mechanism is not operative. 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). An $S_N$2-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 σ-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.
1.4 References


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.\textsuperscript{1} 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.\textsuperscript{2,3} Recent research in this area has shown aldehydes to be competent dipolarophiles in these reactions, providing 2,5-\textit{cis}-disubstituted tetrahydrofurans (THFs) 2 in high diastereoselectivity (eq 1).\textsuperscript{4-6}

\[
\begin{align*}
\text{R (C-donor group)} & = \text{aryl, alkenyl, alkyl} \\
\text{R} & \quad \text{Lewis acid (cat)} \\
\text{1} & \quad \text{(3 + 2) annulation} \\
\text{2} & \quad \text{R} \\
\text{R} & \quad \text{O} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{H} & \quad \text{H} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

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)-1\textit{a} to
catalytic Sn(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.¹

**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).⁶

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 π-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 η³-5 with its corresponding η¹ complexes (Scheme 2-2). Since η¹—η³ interconversion proceeds through achiral complex η¹-5a, 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.\textsuperscript{7-10} 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 Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (eq 2).\(^{11-13}\)

\[
\begin{array}{c}
\text{CO}_2\text{Me} & \text{CO}_2\text{Me} \\
Pd_{2}(\text{dba})_{3} \cdot \text{CHCl}_3 (2.5 \text{ mol \%}) & \text{R} \\
\end{array}
\]

(2)

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).\(^{11}\) 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

\[
\begin{array}{c}
\text{CO}_2\text{Me} & \text{CO}_2\text{Me} \\
Pd_{2}(\text{dba})_{3} \cdot \text{CHCl}_3 (2.5 \text{ mol \%}) & \text{E} \quad \text{E}^1 \\
\text{R}^1 \quad \text{R}^2 \\
\end{array}
\]

7: 8 examples 23-89% yield

(R groups omitted for clarity)
Additional experimentation in the Tsuji lab revealed that Pd(0)-catalyzed annulation of 3 could be extended to aryl isocyanate dipolarophiles, providing access to δ-lactams 9. Use of alkyl isocyanates failed to react under these conditions. The authors note that use of the electron-rich PnBu₃ 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 3.¹²

\[
\text{R, R'} = \text{H or Me}
\]

Tsuji’s demonstrations that vinylcyclopropanes 3 participate in annulation reactions through π-allylpalladium complexes 5 provide a basis on which to expand this method to other dipolarophiles. Use of aldehydes in (3 + 2) annulations with π-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.⁶ 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 HOMOdipole—LUMOdipolarophile, 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).

![Chemical structure](image)

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).14,15

**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 Pd(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)2/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). 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 π-backbonding, which results in an increased lability of the dba and readily provides catalytically-active Pd(0).
Next, a comparison of Pd$_2$(pmdba)$_3$ (pmdba = 4,4′-dimethoxydibenzylideneacetone)$^{17}$ to Pd(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 Pd(dba)$_2$ was used. In contrast to the 28 h required for Pd(dba)$_2$, Pd$_2$(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 % Pd$_2$(pmdba)$_3$ and various dipyridyl and phenanthryl ligands (Scheme 2-7).
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/Pd$_2$(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.
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 $^1$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\(^{18}\) nucleophiles\(^{19}\) are known add directly to the cationic metal center.\(^9\)

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 though the neutral palladacyclic chair 11, the vinyl group would prefer to adopt a pseudo-equatorial position to avoid A\(^{1,3}\) 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

\[ \text{Scheme 2-9. Proposed Catalytic Cycle for the Pd(0)-Catalyzed Annulation of } 3a \text{ and Aldehydes} \]

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)\(^6\) 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).\(^{14}\) 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

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>time (h)</th>
<th>solvent</th>
<th>conversion (%)</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>22</td>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;</td>
<td>100</td>
<td>62:38</td>
<td>50:50</td>
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<tr>
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<td>21</td>
<td>2-MeTHF</td>
<td>50</td>
<td>45:55</td>
<td>nd&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Ligand 3" /></td>
<td>25</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>62:38</td>
<td>53:47</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Ligand 4" /></td>
<td>29</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>48</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>55:45</td>
<td>64:36</td>
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<td><img src="image7" alt="Ligand 7" /></td>
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<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;</td>
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<td>67:33</td>
<td>64.5:35.5</td>
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<tr>
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<td>14</td>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
<td>77:23</td>
<td>50:50</td>
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<tr>
<td>9</td>
<td><img src="image9" alt="Ligand 9" /></td>
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<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;</td>
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<td>64:36</td>
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<td>80&lt;sup&gt;d&lt;/sup&gt;</td>
<td>60:40</td>
<td>71.5:28.5</td>
</tr>
</tbody>
</table>

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 (\(^1\)H NMR and \(^13\)C NMR) were recorded on a Bruker model DRX 500 or a Bruker model DRX 400 (\(^1\)H NMR at 500 MHz and \(^13\)C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (\(^1\)H NMR: CDCl\(_3\) at 7.26 ppm; \(^13\)C NMR: CDCl\(_3\) at 77.0 ppm). \(^1\)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 µm) 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 N₂ 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. Pd₂(pmdba)₃ was prepared according to the method of Fu.¹⁷ 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):**

```
MeO₂C─CO₂Me + Br─CH₂─Br─Br → NaH (50% in oil) THF, 0°C to rt 18 h
```

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\textsubscript{2} for 18 h. The reaction was partitioned between Et\textsubscript{2}O (100 mL) and H\textsubscript{2}O (100 mL). The aqueous layer was extracted with Et\textsubscript{2}O (2 x 100 mL). The combined organic layers were washed with H\textsubscript{2}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\textsubscript{2}O/hexanes) and was distilled (0.05 torr, 60 °C) to give pure \textit{3a} as a clear, colorless oil (4.95 g, 27.1 mmol, 71% yield). The \textsuperscript{1}H NMR spectrum matched the reported data.\textsuperscript{20}

**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\textsubscript{2}(pmdba)\textsubscript{3} (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 (3\textit{a}, 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\textsubscript{2}. 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\textsubscript{2}. 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 \( \text{N}_2 \) for the indicated time period. The reaction mixture was worked up by eluting through a 1” Monstr-Pette silica plug with \( \sim 15 \) mL dichloromethane. Diastereomeric ratios were determined \( ^1\text{H} \) 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-vinylidihydrofuran-3,3(2H)-dicarboxylate (4a):**

![4a](image)

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), \( \text{Pd}_2(\text{pmdba})_3 \) (0.0027 g, 0.0025 mmol), and bathophenanthroline (0.0033 g, 0.0099 mmol). After 25 h at 40 °C and workup, \( ^1\text{H} \) 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\(^{-1}\)) 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; \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) major diastereomer: \( \delta \) 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: \( \delta \) 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); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) major diastereomer:
δ 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: δ 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% Et₂O/hexanes) Rᵣ 0.26; Anal. Calcd. for C₁₆H₁₈O₅: C, 66.19; H, 6.25. Found: C, 66.46; H, 6.39.

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

![Image of compound 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), Pd₂(pmdba)₃ (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 4 h at room temperature and workup, ¹H 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⁻¹) 2998, 2956, 1737, 1436, 1328, 1273, 1231, 1210, 1165, 1125, 1086, 1067, 1019, 936, 919, 855, 735; ¹H NMR (500 MHz, CDCl₃) major diastereomer: δ 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: δ 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); ¹³C NMR (100 MHz, CDCl₃) major diastereomer: δ 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: δ 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% Et₂O/hexanes) Rf 0.23; Anal. Calcd. for C₁₇H₁₇F₃O₅: C, 56.98; H, 4.78. Found: C, 57.05; H, 4.87.

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

![4d](image)

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), Pd₂(pmdba)₃ (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, ¹H 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⁻¹) 3080, 3006, 2954, 2889, 2846, 1733, 1607, 1511, 1436, 1335, 1273, 1223, 1208, 1158, 1111, 1100, 1084, 1052, 1015, 936, 919, 847, 807; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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,
\[ J = 8.1 \text{ Hz}, \ 116.1, \ 82.8, \ 79.8, \ 66.0, \ 52.7, \ 52.2, \ 40.5; \ \text{TLC} \ (15\% \ \text{Et}_2\text{O/hexanes}) \ R_f \ 0.26; \]

**Anal.** Calcd. for C_{16}H_{17}FO_5: C, 62.33; H, 5.56. Found: C, 62.14; H, 5.60.

**Dimethyl 2-p-tolyl-5-vinylidihydrofuran-3,3(2H)-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\textsubscript{2}(pmdba)_3 (0.0090 g, 0.0082 mmol), and batho phenanthroline (0.0110 g, 0.0326 mmol). After 96 h at room temperature and workup, \textsuperscript{1}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\textsuperscript{-1}) 3014, 2998, 2952, 2871, 1733, 1517, 1436, 1368, 1337, 1272, 1231, 1206, 1181, 1156, 1136, 1106, 1086, 1054, 1021, 992, 936, 919, 836, 799; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) major diastereomer: \( \delta \) 7.27 (d, \( J = 7.8 \text{ Hz}, 2\text{H} \)), 7.09 (d, \( J = 7.8 \text{ Hz}, 2\text{H} \)), 6.09 (ddd, \( J = 17.1, 10.3, 6.8 \text{ Hz}, 1\text{H} \)), 5.65 (s, 1H), 5.40 (d, \( J = 17.2 \text{ Hz}, 1\text{H} \)), 5.26 (d, \( J = 10.4 \text{ Hz}, 1\text{H} \)), 4.39 (ddd, \( J = 11.3, 6.6, 5.9 \text{ Hz}, 1\text{H} \)), 3.75 (s, 3H), 3.21 (s, 3H), 2.75 (dd, \( J = 13.3, 10.5 \text{ Hz}, 1\text{H} \)), 2.49 (dd, \( J = 13.3, 6.0 \text{ Hz}, 1\text{H} \)), 2.30 (s, 3H); minor diastereomer: \( \delta \) 7.31 – 7.24 (m, 2H), 7.12 – 7.07 (m, 1H), 5.90 (ddd, \( J = 17.0, 10.3, 6.1 \text{ Hz}, 1\text{H} \)), 5.74 (s, 1H), 5.33 (d, \( J = 17.1 \text{ Hz}, 1\text{H} \)), 5.16 (d, \( J = 10.4 \text{ Hz}, 1\text{H} \)), 5.09 – 5.02 (m, 1H), 3.75 (s, 3H), 3.21 (s, 3H), 3.01 (dd, \( J = 13.1, 7.0 \text{ Hz}, 1\text{H} \)), 2.30 (s, 3H), 2.19 (dd, \( J = 13.2, 7.0 \text{ Hz}, 1\text{H} \)); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) 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\textsubscript{17}H\textsubscript{20}O\textsubscript{5}: C, 67.09; H, 6.62. Found: C, 67.47; H, 6.70.
Dimethyl 2-(4-bromophenyl)-5-vinylidencyclohex-3-ene-1,1-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$_2$(pmdba)$_3$ (0.0045 g, 0.0041 mmol), and bathophenantroline (0.0055 g, 0.0163 mmol). After 24 h at room temperature and workup, $^1$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$^{-1}$) 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; $^1$H NMR (500 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) major diastereomer: $\delta$ 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) $R_f$ 0.27; Anal. Calcd. for C$_{16}$H$_{17}$BrO$_5$: C, 52.05; H, 4.64. Found: C, 52.35; H, 4.67.
**Dimethyl 2-(4-chlorophenyl)-5-vinyldihydrofuran-3,3(2H)-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$_2$(pmdba)$_3$ (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 12 h at 40 °C and workup, $^1$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$^{-1}$) 3083, 2997, 2954, 2883, 2846, 1914, 1739, 1600, 1493, 1436, 1272, 1229, 1206, 1158, 1086, 1057, 1015, 936, 843, 803, 704; **$^1$H NMR** (500 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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); **$^{13}$C NMR** (100 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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) $R_f$ 0.32; **Anal.** Calcd. for C$_{16}$H$_{17}$ClO$_5$: C, 59.17; H, 5.28. Found: C, 59.53; H, 55.66.
**Dimethyl 2-(4-(methoxycarbonyl)phenyl)-5-vinylidihydrofuran-3,3(2H)-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$_2$(pmdba)$_3$ (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 27 h at 40 °C and workup, $^1$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$^{-1}$) 3000, 2956, 2848, 1729, 1613, 1436, 1279, 1208, 1113, 1059, 1019, 938, 868, 766, 731, 704; $^1$H NMR (500 MHz, CDCl$_3$) 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); $^{13}$C NMR (100 MHz, CDCl$_3$) 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$_2$Cl$_2$) $R_f$ 0.15; Anal. Calcd. for C$_{18}$H$_{20}$O$_7$: C, 62.06; H, 5.79. Found: C, 61.89; H, 5.77.
Dimethyl 2-(4-cyanophenyl)-5-vinylidihydrofuran-3,3(2H)-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$_2$(pmdba)$_3$ (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 5.5 h at room temperature and workup, $^1$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$^{-1}$) 3006, 2956, 2885, 2231, 1733, 1611, 1505, 1436, 1275, 1231, 1208, 1086, 1054, 936, 853, 808, 737; $^1$H NMR (500 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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$_2$Cl$_2$) $R_f$ 0.20; Anal. Calcd. for C$_{17}$H$_{17}$NO$_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.49; H, 5.44; N, 4.17.
Dimethyl 2-(4-nitrophenyl)-5-vinylidihydrofuran-3,3(2H)-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$_2$(pmdba)$_3$ (0.0009 g, 0.0008 mmol), and bathophenantroline (0.0011 g, 0.0033 mmol). After 5 h at room temperature and workup, $^1$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$^{-1}$) 3085, 3002, 2956, 2850, 1735, 1607, 1526, 1436, 1349, 1273, 1208, 1054, 1015, 936, 863, 749, 697; $^1$H NMR (500 MHz, CDCl$_3$) 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); $^{13}$C NMR (100 MHz, CDCl$_3$) 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$_2$Cl$_2$/petroleum ether) R$_f$ 0.12; Anal. Calcd. for C$_{16}$H$_{17}$NO$_7$: C, 57.31; H, 5.11. Found: C, 57.43; H, 5.11.
**Dimethyl 2-(3-chlorophenyl)-5-vinyldihydrofuran-3,3(2H)-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$_2$(pmdba)$_3$ (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 21 h at 40 °C and workup, $^1$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$^{-1}$) 3085, 3000, 2954, 2883, 2844, 1733, 1600, 1574, 1478, 1434, 1333, 1273, 1229, 1206, 1084, 1057, 934, 890, 783, 693; $^1$H NMR (500 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) major diastereomer: $\delta$ 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: $\delta$ 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$_f$ 0.23; Anal. Calcd. for C$_{16}$H$_{17}$ClO$_5$: C, 59.17; H, 5.28. Found: C, 59.46; H, 5.48.
Dimethyl 2-(3-nitrophenyl)-5-vinylidihydrofuran-3,3(2H)-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), Pd₂(pmdba)₃ (0.0018 g, 0.0017 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 2 h at room temperature and workup, ¹H 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⁻¹) 2954, 2881, 2846, 1733, 1532, 1480, 1436, 1353, 1275, 1229, 1210, 1158, 1113, 1092, 1081, 1055, 936, 901, 816, 805, 737, 685; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂Cl₂) Rₗ 0.12; Anal. Calcd. for C₁₆H₁₇NO₇: 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(2H)-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_2(pmdba)_3 (0.0090 g, 0.0082 mmol), and bathophenanthroline (0.0108 g, 0.0326 mmol). After 3.5 h at 40 °C and workup, ^1H 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⁻¹) 3074, 2997, 2954, 2877, 2846, 1737, 1650, 1596, 1574, 1476, 1436, 1331, 1270, 1229, 1200, 1090, 1046, 1034, 938, 919, 872, 812, 756, 712; ^1H NMR (500 MHz, CDCl₃) 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); ^13C NMR (100 MHz, CDCl₃) 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_f 0.29; Anal. Calcd. for C₁₆H₁₇ClO₅: C, 59.17; H, 5.28. Found: C, 59.40; H, 5.36.

Dimethyl 2-(2-fluorophenyl)-5-vinyldihydrofuran-3,3(2H)-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_2(pmdba)_3 (0.0019 g, 0.0016 mmol), and bathophenanthroline (0.0022 g, 0.0066 mmol). After 20 h at room temperature
and workup, \textsuperscript{1}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: \textbf{IR} (thin film, cm\textsuperscript{-1}) 3085, 2995, 2954, 2846, 1737, 1619, 1590, 1492, 1457, 1436, 1272, 1231, 1098, 1052, 938, 805, 762, 737; \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{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); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{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; \textbf{TLC} (20% EtOAc/hexanes) $R_f$ 0.19; \textbf{Anal.} Calcd. for C\textsubscript{16}H\textsubscript{17}FO\textsubscript{5}: C, 62.33; H, 5.56. Found: C, 62.54; H, 5.49.

**Dimethyl 2-(2-nitrophenyl)-5-vinylidihydrofuran-3,3(2\textsubscript{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), Pd$_2$(pmdba)$_3$ (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 3 h at room temperature and workup, \textsuperscript{1}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 °C. Analytical data for 4o: mp 47-49 °C; IR (thin film, cm⁻¹) 3056, 2989, 2956, 1737, 1531, 1266, 1202, 1158, 1092, 1052, 938, 897, 739, 706; ¹H NMR (500 MHz, CDCl₃) major diastereomer: δ 7.91 (dd, J = 8.1, 1.0 Hz, 1H), 7.73 (dd, J = 7.9, 0.9 Hz, 1H), 7.58 (td, J = 7.7, 0.9 Hz, 1H), 7.42 (td, J = 8.2, 1.3 Hz, 1H), 6.42 (s, 1H), 6.05 (dd, J = 17.1, 10.4, 6.6 Hz, 1H), 5.42 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.51 (ddd, J = 11.2, 5.8, 5.4 Hz, 1H), 3.82 (s, 3H), 3.15 (s, 3H), 2.75 (dd, J = 13.3, 11.2 Hz, 1H), 2.45 (dd, J = 13.3, 5.2 Hz, 1H); minor diastereomer: δ 7.84 (d, J = 9.1 Hz, 1H), 7.63 (d, J = 7.9 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 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 5.06 – 5.00 (m, 1H), 3.74 (s, 3H), 3.24 (s, 3H), 3.00 (dd, J = 13.1, 7.0 Hz, 1H), 2.30 (dd, J = 13.1, 7.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) major diastereomer: δ 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: δ 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 (CH₂Cl₂) R₇ 0.17; Anal. Calcd. for C₁₆H₁₇NO₇: 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-vinylidihydrofuran-3,3(2H)-dicarboxylate (4p):

The title compound was prepared according to General Procedure A using dimethyl 2-vinylecyclopropane-1,1-dicarboxylate (3a, 0.060 g, 0.33 mmol), hexanal (0.196 g, 1.96 mmol), Pd₂(pmdba)₃ (0.0045 g, 0.0041 mmol), and bathophenanthroline (0.0055 g, 0.0163 mmol). After 22 h at room temperature and workup, ¹H 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, cm⁻¹) 3083, 2987, 2956, 2861, 1737, 1436, 1268, 1204, 1077, 1028, 928; ¹H NMR (500 MHz, CDCl₃) major diastereomer: δ 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: δ 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); ¹³C NMR (100 MHz, CDCl₃) major diastereomer: δ 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: δ 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) Rf 0.35; Anal. Calcd. for C₁₅H₂₄O₅: C, 63.36; H, 8.51. Found: C, 63.49; H, 8.62.

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

![Diagram of the preparation of (S)-dimethyl-2-vinylcyclopropane-1,1-dicarboxylate [(S)-3a]]
Preparation of cinchonidine salt 15:

The diacid 14 (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 Et₂O. 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 N₂. After 16 h, the reaction was quenched with H₂O (25 mL). The resulting solution was extracted with CH₂Cl₂ (3 x 85 mL). The combined organic extracts were washed with H₂O (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-vinyl dihydrofuran-3,3(2H)-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), Pd2(pmdba)3 (0.0051 g, 0.0047 mmol), and bathophenanthroline (0.0062 g, 0.0187 mmol). After 4 h at room temperature and workup, 1H 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 LiAlH4 (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 Et2O, quenched with 0.5 mL H2O, 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 Et2O. The filtrate was dried over MgSO4, 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: \textbf{IR} (thin film, cm\textsuperscript{-1}) 3384, 2243, 2883, 1619, 1420, 1326, 1165, 1127, 1067, 1017, 932, 849, 735; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) major diastereomer: δ 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); \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) major diastereomer: δ 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\textsubscript{f} 0.16.
2.5 References


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.$^{1,2}$ 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” 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 \([S(S)_{\text{cat}}\text{, Scheme 3-1, left}].\) Selectivity is also dependent on the rate of catalyst complexation \([k_{S(R/S)_{\text{cat}}}]\) and interconversion of each enantiomer \([k_{X(R/S)_{\text{cat}}}].\)
through the common enantiomeric intermediate $X_{\text{cat}}$. 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 $S_{(R)\text{cat}}$. 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$^3$ (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 $X_{\text{cat}}$; the relative rates of $X_{\text{cat}}$ 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.
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\textsuperscript{*})-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).

$$\text{rac-1} \xrightarrow{(\text{pybox})\text{Mgl}_2} \text{DyKAT} \xrightarrow{\text{eq 1}} \text{up to 92% yield, 97:3 er > 99:1 dr}$$

### 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
Generation of enantioenriched products using this reaction manifold has typically required the use of nonracemic cyclopropane starting materials in reactions proceeding via stereospecific pathways. While numerous methods are available for the enantioselective preparation of cyclopropanes, 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). Thus, a method to access tetrahydrofurans of type 2 through a DyKAT would result in an overall shorter synthetic sequence.

Recently, Sibi and coworkers reported the first catalytic asymmetric transformation of malonate-derived cyclopropanes 1. Inspired by the previously reported racemic synthesis of tetrahydro-1,2-oxazines 3 via Yb(OTf)₃-catalyzed nitrone/cyclopropane annulation (eq 2), 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 Ni(ClO$_4$)$_2$/Ph-DBFOX (4) provided excellent yields and enantioselectivities (Scheme 3-5). While unsubstituted cyclopropanes of type 1 (R = H) provide products in good yield and enantioselectivities, poor diastereoselectivities are observed when R $\neq$ H. Although no mechanistic proposal is reported, it is possible that the low diastereoselectivity is a result of enantiodifferentiation after the first irreversible step.$^{19}$ Thus, non-selective nucleophilic attack by the nitrone 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/Nitrone Annulation Reported by Sibi$^{17}$
More recently, Tang reported the ability to differentiate enantiomers of 1 using a Ni(ClO₄)₂/trisoxazoline (5)-catalyzed annulation with nitrones to achieve a kinetic resolution.²⁰ 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 Ni(ClO₄)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 1,¹¹,¹² 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 Tang²⁰
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.\textsuperscript{12,13} 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.\textsuperscript{21}

![Chemical structure](image)

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.\textsuperscript{22,23} 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 MgI\(_2\)/ligand complexes.
**Table 3-1.** Initial Examination of Chiral Lewis Acids for the Annulation of 1b with Benzaldehyde

![Diagram](image_url)

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>Lewis acid</th>
<th>conversion (%)</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image_url" alt="Image" /></td>
<td>Ni(ClO₄)₂</td>
<td>100</td>
<td>54:46</td>
</tr>
<tr>
<td>2</td>
<td><img src="image_url" alt="Image" /></td>
<td>Mg(ClO₄)₂</td>
<td>95</td>
<td>57:43</td>
</tr>
<tr>
<td>3</td>
<td><img src="image_url" alt="Image" /></td>
<td>Sn(OTf)₂</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td><img src="image_url" alt="Image" /></td>
<td>Zn(OTf)₂</td>
<td>10</td>
<td>50:50</td>
</tr>
<tr>
<td>5</td>
<td><img src="image_url" alt="Image" /></td>
<td>Cu(SbF₆)₂</td>
<td>100</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td><img src="image_url" alt="Image" /></td>
<td>Sn(OTf)₂</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td><img src="image_url" alt="Image" /></td>
<td>Sc(OTf)₃</td>
<td>100</td>
<td>50:50</td>
</tr>
<tr>
<td>8</td>
<td><img src="image_url" alt="Image" /></td>
<td>Yb(OTf)₃</td>
<td>100</td>
<td>50:50</td>
</tr>
<tr>
<td>9</td>
<td><img src="image_url" alt="Image" /></td>
<td>MgI₂</td>
<td>100</td>
<td>65:35</td>
</tr>
</tbody>
</table>

Conditions: 1b (1.0 equiv), benzaldehyde (2.0 equiv), MgI₂ (0.10 equiv), ligand (0.12 equiv), [1b]₀ = 0.30 M in CH₂Cl₂, rt, 48 h. a) Determined by ¹H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis.

An examination of oxazoline-complexed MgI₂ catalysts revealed that cyclopropane decomposition limited the yield of 2a (**Table 3-2**). For example, while ‘Bu-pybox (7a)/MgI₂ 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 ‘Bu-pybox/Lewis acid complexes was examined (> 25 metals, data not shown). The result of this analysis indicated that MgI₂ remained the most promising catalyst; additional optimization of this system was pursued.
Table 3-2. Selected Ligands Examined for the MgI₂-Catalyzed Asymmetric Annulation of 1b with Benzaldehyde

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>solvent</th>
<th>yield (%)</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Ligand 1" /></td>
<td>CH₂Cl₂</td>
<td>44&lt;sup&gt;d&lt;/sup&gt;</td>
<td>67:33</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Ligand 2" /></td>
<td>CH₂Cl₂</td>
<td>nd&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55:45</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ligand 3" /></td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>80:20</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ligand 4" /></td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Ligand 5" /></td>
<td>CH₂Cl₂</td>
<td>&lt; 5</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Ligand 6" /></td>
<td>CH₂Cl₂</td>
<td>&lt; 5</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Ligand 7" /></td>
<td>CH₂Cl₂</td>
<td>10</td>
<td>77:23</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Ligand 8" /></td>
<td>CH₂Cl₂</td>
<td>&lt; 5</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Ligand 9" /></td>
<td>CCl₄</td>
<td>5</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Ligand 10" /></td>
<td>CCl₄</td>
<td>15</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Ligand 11" /></td>
<td>C₆H₆</td>
<td>&lt; 5</td>
<td>nd</td>
</tr>
</tbody>
</table>

Conditions: 1b (1.0 equiv), benzaldehyde (2.0 equiv), MgI₂ (0.10 equiv), ligand (0.12 equiv), [1b]<sub>0</sub> = 0.30 M in the indicated solvent, rt, 48 h.  a) Determined by ¹H 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

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

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 annihilation of $1b$ with 4-methoxybenzaldehyde (eq 4). As $[1b]_0$ decreased, there was a marked increase in both yield and enantioselectivity. Further dilution below $[1b]_0 = 0.050 \text{ M}$ 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.

![Chemical Reaction](image)

### 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 tBu-pybox framework, we explored perturbations of the ligands at the 4-position of the pyridine.

Preparation of 4-X-tBu-pybox ligands commenced with dehydration of commercially available chelidamic acid (13) using PX$_5$ ($X = \text{Cl}^{24}$ or Br$^{25}$) followed by a methanol quench, providing pyridines 14a-b. An addition-elimination reaction using NaI transformed 14b to
the corresponding iodide\textsuperscript{26} and subsequent Pd(0)-catalyzed/Cu(I)-promoted coupling with methyl-2,2-difluoro-2-(fluorosulfonyl)acetate\textsuperscript{27} yielded trifluoromethylated pyridine 14c in 73\% overall yield. Condensation with tert-leucinol provided bisamides 15a-c. Arylation of 15a using a Suzuki–Miyaura\textsuperscript{28} coupling provided 15d-e. Cyclization of the amides to

\textit{Scheme 3-7.} Preparation of 4-X'-Bu-Pybox Ligands from Chelidamic Acid (13)

oxazolines was achieved by treating 15a-e with diethylamino sulfur trifluoride, furnishing 4-X'-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 MgI₂-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-F₃C-^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**

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>conversion (%)</th>
<th>yield (%)</th>
<th>er (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>93</td>
<td>62</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>100</td>
<td>74</td>
<td>96:4</td>
</tr>
<tr>
<td>3d</td>
<td>Cl</td>
<td>100</td>
<td>16</td>
<td>82.5:17.5</td>
</tr>
<tr>
<td>4e</td>
<td>Br</td>
<td>100</td>
<td>40</td>
<td>96:4</td>
</tr>
<tr>
<td>5</td>
<td>CF₃</td>
<td>100</td>
<td>75</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>100</td>
<td>57</td>
<td>95.5:3.5</td>
</tr>
<tr>
<td>7</td>
<td>Mes</td>
<td>95</td>
<td>57</td>
<td>94.6</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>26</td>
<td>5</td>
<td>nd⁷</td>
</tr>
<tr>
<td>10</td>
<td>N₃</td>
<td>100</td>
<td>67</td>
<td>96:4</td>
</tr>
<tr>
<td>11</td>
<td>N₃</td>
<td>100</td>
<td>55</td>
<td>93.5:6.5</td>
</tr>
</tbody>
</table>

Conditions: 1b (1.0 equiv), benzaldehyde (2.0 equiv), MgI₂ (0.10 equiv), ligand (0.12 equiv), [1b]₀ = 0.05 M in CCl₄, rt, 48 h. a) Determined by ^¹^H NMR spectroscopy using a mesitylene internal standard. b) Determined by chiral SFC analysis. c) Average isolated yield of two independent trials. d) With CH₂Cl₂ as the solvent. e) With C₇H₈ 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-tBu-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 MgI2-Catalyzed DyKAT of Cyclopropanes 1b-e 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 α-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.11 Unreacted 1a was isolated and determined to be enriched in the (R)-configuration by comparison to an authentic sample29 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.
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 \textit{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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure3-3}
\caption{Enantiomeric Analysis of \(1b\) and \(2b\) as a Function of Conversion}
\end{figure}

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 \textbf{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.\(^\text{30}\) 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\(_2\) 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 \((R)-17\) and \((S)-17\) undergo Cu(OTf)\(_2\)/6-catalyzed Diels-Alder reactions at different rates.\(^{31}\) 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 \(\text{tert}\)-butyl of the oxazoline ligand in complex \(\text{syn-18}\) (Scheme 3-9, top). The enhanced reactivity is caused by a synergistic blocking of the \(\text{Si}\) face by both the imide and ligand substituents, providing unobstructed access of the cyclopentadiene to the \(\text{Re}\) face. While complexation of \((S)-17\) with Cu(OTf)\(_2\)/6 avoids the unfavorable ligand/substrate interactions in \(\text{anti-18}\), the approach of cyclopentadiene is hindered from both the \(\text{Si}\) and \(\text{Re}\) faces, resulting in a slow reaction rate.

**Scheme 3-9.** Evans Precedent for the Preference of a Destabilized Reactive Intermediate
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). 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 (1H NMR and 13C NMR) were recorded on a
Bruker model DRX 400 ($^1$H NMR at 400 MHz and $^{13}$C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard ($^1$H NMR: CDCl$_3$ at 7.26 ppm, DMSO at 2.54 ppm; $^{13}$C NMR: CDCl$_3$ at 77.0 ppm, DMSO at 40.45 ppm). $^1$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 µm 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 µm) 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 N$_2$ prior to use. $N,N$-Dimethyl formamide was distilled from phosphorous pentoxide under reduced pressure prior to use. Acetonitrile was distilled from CaH$_2$ under N$_2$ prior to use. Methylene chloride was dried by passage through a column of activated alumina under N$_2$ prior to use. Cyclopropanes 1a-d were prepared according to the method of Wood.$^{33}$ Cyclopropanes ($R$)- and ($S$)-1a were prepared according
to the method of Pohlhaus. 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\(_4\) and distilled under N\(_2\) 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, Goto, and Rotello, respectively. \( tert \)-Leucinol was prepared from \( tert \)-leucine according to the method of Meyers. Methyl-2,2-difluoro-2-(fluorosulfonyl)acetate was purchased from Oakwood Products. Pd(OAc)\(_2\) and (dppf)PdCl\(_2\)•CH\(_2\)Cl\(_2\) 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):**

![Chemical structure](image)

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 (1.22 g, 3.8 mmol, 1.0 equiv), Cul (4.24 g, 22.3 g, 5.9 equiv), and (dppf)PdCl\(_2\)•CH\(_2\)Cl\(_2\) (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\(_2\). 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 N₂. The reaction was cooled to room temperature, diluted with CH₂Cl₂ (120 mL), and filtered through celite to afford a dark brown solution which was subsequently washed with H₂O (2 x 200 mL), 50% saturated aqueous NaCl solution (300 mL), and brine (300 mL). The solution was dried over NaSO₄, 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⁻¹) 3082, 3009, 2959, 1726, 1448, 1415, 1381, 1281, 1146, 984, 971, 937, 785, 634; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (s, 2H), 4.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) 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) Rf 0.20; LRMS (ESI) calcd. for C₁₀H₈F₃NO₄⁺H: 264.0, Found: 264.0.

General Procedure A for the synthesis of N²,N⁶-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-N₂,N⁶-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⁻¹) 3380, 2963, 1668, 1525, 1477, 1402, 1368, 1339, 1299, 1275, 1232, 1090, 1055, 894, 772, 680;¹H NMR (400 MHz, CDCl₃) 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);¹³C NMR (100 MHz, CDCl₃) δ 163.1, 150.2, 148.1, 125.4, 62.9, 60.0, 34.0, 27.0; HRMS (ESI) calcd. For C₁₉H₃₀ClN₃O₄+H 400.2003, Found: 400.1997; [α]D²⁹ –9.3 (c = 0.40, CHCl₃).

4-Bromo-N₂,N⁶-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⁻¹) 3380, 3053, 2965, 1682, 1518, 1399, 1368, 1338, 1233, 1091, 1055, 893, 778, 760, 715, 679; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 163.1, 149.8, 136.5, 128.5, 62.9, 60.0, 34.0, 27.0; LRMS (ESI) calcd. for C₁₉H₃₀BrN₃O₄+: 444.1, Found: 444.1; [α]D⁻²⁸ –11.7 (c = 0.255, CHCl₃).

4-(Trifluoromethyl)-N²,N⁶-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⁻¹) 3322, 3072, 2966, 1666, 1539, 1477, 1435, 1399, 1366, 1334, 1285, 1220, 1179, 1141, 1096, 1046, 1023, 999, 932, 903, 628; ¹H 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); ¹³C NMR (100 MHz, DMSO) δ 163.2, 152.3, 140.7 (d, J = 30.2 Hz), 123.3 (q,
\[ J = 273.6 \text{ Hz}, \ 120.6 \ (d, \ J = 3.4 \text{ Hz}), \ 61.1, \ 60.3, \ 35.0, \ 27.7; \ \text{LRMS (ESI) calcd. for} \ C_{20}H_{30}F_{3}N_{3}O_{4}+: 434.2, \ \text{Found: 434.1; } [\alpha]_{D}^{28} +6.32 \ (c = 0.27, \ \text{MeOH}). \]

**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:28**

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\(_2\)CO\(_3\) (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\(_2\)O (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 °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.
**N₂,N₆-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-N₂,N₆-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)₂ (0.0028 g, 0.0125 mmol), SPhos (0.010 g, 0.025 mmol), K₂CO₃ (0.260 g, 1.88 mmol), acetonitrile (1.0 mL), and H₂O (0.625 mL). After stirring for 24 h and work up, the residue was purified by flash chromatography (5% MeOH/CH₂Cl₂) 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⁻¹) 3398, 3060, 2965, 2872, 1670, 1605, 1531, 1368, 1052, 1002, 906, 765, 738, 696, 626; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₅H₃₅N₃O₄+Na: 464.3, Found: 464.3; [α]D²⁹ –15.6 (c = 0.29, CHCl₃).

**N₂,N₆-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-N₂,N₆-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)₂ (0.0028 g, 0.0125 mmol), SPhos (0.010 g, 0.025 mmol), K₂CO₃ (0.260 g, 1.88 mmol), acetonitrile (1.0 mL), and H₂O (0.625 mL). After stirring for 24 h and work up, the residue was purified by
flash chromatography (50% EtOAc/CH2Cl2) to afford 0.0195 g (0.406 mmol, 65% yield, not optimized) of the title compound as a white powder. Analytical data for 15e: \( \text{mp} \) 128-131 °C; \( \text{IR} \) (thin film, \( \text{cm}^{-1} \)) 3399, 2964, 1671, 1613, 1531, 1478, 1401, 1368, 1232, 1050, 854; \( ^1\text{H NMR} \) (400 MHz, CDCl3) \( \delta \) 8.18 (s, 2H), 8.15 (d, \( J = 8.8 \text{ Hz} \), 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); \( ^{13}\text{C NMR} \) (100 MHz, CDCl3) \( \delta \) 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/CH2Cl2) \( R_f \) 0.26; \( \text{LRMS} \) (ESI) calcd. for C28H41N3O4+Na: 506.3, Found: 506.3; \([\alpha]^2_{D\text{28}}\) −5.3 (\( c = 0.24, \text{CHCl}_3 \)).

**General Procedure C for the synthesis of 4-substituted-\text{tBu-pybox ligands 16a-e}**:  

A flame-dried round-bottomed flask containing a magnetic stir bar under \( \text{N}_2 \) was charged with the appropriate 4-substituted-\( N^2,N^6 \)-bis((\text{S})-1-hydroxy-3,3-dimethylbutan-2-yl)pyridine-2,6-dicarboxamide (15, 1.0 equiv) and CH2Cl2. The resulting solution was cooled to \(-20 \degree \text{C} \) 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 \( \text{N}_2 \) for 24 h at \(-20 \degree \text{C} \), at which time a solution of 3.0 M aqueous NH4OH was added and reaction mixture was removed from the bath and diluted with H2O. The aqueous layer was extracted with CH2Cl2, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting yellow solid was purified by recrystallization from hot methanol.
(4S,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-\(N_2N_6\)-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\(_2\)Cl\(_2\) (16 mL). After stirring for 24 h at \(-20^\circ\)C, the reaction was worked up with 3.0 M aqueous NH\(_4\)OH (2.75 mL) and H\(_2\)O (55 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (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.\(^{35}\)

(4S,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-\(N_2N_6\)-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\(_2\)Cl\(_2\) (8.7 mL). After stirring for 24 h at \(-20^\circ\)C, the reaction was worked up with 3.0 M aqueous NH\(_4\)OH (1.5 mL) and H\(_2\)O (30 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (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\(^{-1}\)) 3087, 2957, 2905, 2869, 1644, 1560, 1477, 1377, 1362, 1329, 1297, 1209, 1196, 1123, 978, 937, 886; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 161.3,
The title compound was prepared according to General Procedure C using 4-trifluoromethyl-\(N^2,N^6\)-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\(_2\)Cl\(_2\) (3.0 mL). After stirring for 24 h at \(-20^\circ\)C, the reaction was quenched with 3.0 M aq NH\(_4\)OH (0.5 mL) and H\(_2\)O (10 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (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\(^{-1}\)) 2960, 2907, 2871, 1648, 1574, 1479, 1291, 1181, 1148, 980, 963, 932, 909, 821, 690; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 161.3, 148.4, 139.8 (d, \(J = 139.2\) Hz), 121.5 (d, \(J = 274.4\) Hz), 121.4 (d, \(J = 3.4\) Hz), 76.6, 69.9, 34.0, 26.0; LRMS (ESI) calcd. for C\(_{20}\)H\(_{26}\)F\(_3\)N\(_3\)O\(_2\)+H: 398.2, Found: 398.2; \([\alpha]_D^{28}\) –155.3 (c = 0.20, CHCl\(_3\)).

The title compound was prepared according to General Procedure C using 4-phenyl-\(N^2,N^6\)-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$_2$Cl$_2$ (2.8 mL). After stirring for 24 h at $-20 \, ^\circ$C, the reaction was worked up with 3.0 M aqueous NH$_4$OH (0.5 mL) and H$_2$O (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (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$^{-1}$) 2953, 2903, 2867, 1647, 1608, 1550, 1497, 1479, 1403, 1361, 1331, 1299, 1242, 1109, 1059, 978, 936; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_{25}$H$_{31}$N$_3$O$_2$+H: 406.3, Found: 406.3; $[\alpha]_D^{28}$ –69.5 (c = 0.29, CHCl$_3$).

(4S,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-$N^2,N^6$-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$_2$Cl$_2$ (2.1 mL). After stirring for 24 h at $-20 \, ^\circ$C, the reaction was quenched with 3.0 M aq NH$_4$OH (0.4 mL) and H$_2$O (7 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (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$^{-1}$) 3046, 2957, 2869, 1650, 1613, 1542, 1477, 1397, 1363, 1296, 1237, 1208, 1113, 1054, 1030, 983, 939, 851, 780, 620, 560; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$
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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{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; \textbf{LRMS} (ESI) calcd. for C\textsubscript{28}H\textsubscript{37}N\textsubscript{3}O\textsubscript{2}+H: 448.3, Found: 448.3; \([\alpha]_D^{28} – 57.7 (c = 0.20,\text{ CHCl}_3)\).

**Preparation of (4S,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 (4S,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 CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The combined CH\textsubscript{2}Cl\textsubscript{2} extracts were dried over sodium sulfate, filtered, and concentrated \textit{in vacu} 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; \textbf{IR} (thin film, cm\textsuperscript{-1}) 2956, 2869, 1651, 1598, 1566, 1478, 1398, 1300, 1210, 1092, 1045, 981, 937, 865; \textbf{1H NMR} (400 MHz, CDCl\textsubscript{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); \textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 166.5, 162.3, 148.4, 111.8, 76.4, 69.5, 55.8, 34.0, 26.0; \textbf{LRMS} (ESI) calcd. for C\textsubscript{29}H\textsubscript{30}N\textsubscript{3}O\textsubscript{2}+H: 360.2, Found: 360.2; \([\alpha]_D^{28} – 74.0 (c = 0.25,\text{ CHCl}_3)\).
Preparation of \((4S,4'S)-2,2'-(4-Azidopyridine-2,6-diyl)bis(4-\text{tert}-butyl-4,5-dihydrooxazole)\) (16g):

A 20-mL scintillation vial containing a magnetic stir bar was charged with \((4S,4'S)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-\text{tert}-butyl-4,5-dihydrooxazole)\) (16a, 0.10 g, 0.275 mmol, 1 equiv) and DMF (1.75 mL). To this suspension was added 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 \textit{in vacuo}. The resulting yellow residue was dissolved in CH\(_2\)Cl\(_2\) (12 mL) and was filtered through a 1-cm Monstr-Pette plug of celite. The resulting yellow solution was concentrated \textit{in vacuo} to afford 0.100 g (0.275 mmol, 100% yield) of the title compound as a yellow solid. Analytical data for 16g:

\textbf{mp} 169-171 °C; \textbf{IR} (thin film, cm\(^{-1}\)) 2960, 2907, 2871, 2128, 1647, 1584, 1563, 1480, 1365, 1291, 1243, 1138, 1092, 970, 932, 870, 729, 702; \textbf{\(^1\)H NMR} (400 MHz, 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); \textbf{\(^{13}\)C NMR} (100 MHz, CDCl\(_3\)) \(\delta\) 161.7, 150.2, 148.6, 115.8, 76.4, 69.7, 33.9, 25.9; \textbf{LRMS} (ESI) calcd. for C\(_{19}\)H\(_{26}\)N\(_6\)O\(_2\)+H: 371.2, Found: 371.2; \([\alpha]\)\(^{28}\) \(-104.8\) (\(c = 0.395\), CHCl\(_3\)).
Preparation of (4S,4'S)-2,2'-(4-(4-phenyl-1H-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 (4S,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$_3$CN (0.50 mL), phenylacetylene (0.0137 g, 0.135 mmol, 1.0 equiv), CuSO$_4$ (0.0034 g, 0.014 mmol, 0.10 equiv) in H$_2$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$_2$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$^{-1}$) 3129, 3103, 3052, 2959, 2905, 2868, 2359, 1649, 1604, 1577, 1478, 1448, 1413, 1363, 1243, 1106, 1039, 936, 766, 694; $^1$H NMR (400 MHz, CDCl$_3$) 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); $^{13}$C NMR (100 MHz, CDCl$_3$) 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$_{27}$H$_{32}$N$_6$O$_2$+H: 473.3, Found: 473.3; [$\alpha$]$_D^{28}$ = −45.8 (c = 0.21, CHCl$_3$).
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 Sn(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 CH$_2$Cl$_2$ (0.50 mL). The vials were removed from the box, placed under N$_2$, and cooled to $-10 \, ^\circ$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 CH$_2$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 CH$_2$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 MgI$_2$ (0.10-0.20 equiv), 4-Cl-$^5$Bu-pybox (16a, 0.11-0.22 equiv), and 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$_4$ (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$_2$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 CH$_2$Cl$_2$ (12 mL) and concentrated \textit{in vacuo}. The resulting product was then purified by flash chromatography with the indicated solvent system.

\textbf{(2R,5R)-Dimethyl 5-(4-methoxyphenyl)-2-phenyldihydrofuran-3,3(2H)-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$_4$ (2.8 mL) and MgI$_2$ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-tBu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl$_4$ (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 \textit{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 4.0 min, $t_r$-minor 4.9 min). Analytical data for this compound has been previously reported.$^{12}$ $[\alpha]_D^{29}$ +83.5 ($c = 0.33$, CH$_2$Cl$_2$).
(2R,5R)-Dimethyl 2,5-bis(4-methoxyphenyl)dihydrofuran-3,3(2H)-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$_4$ (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 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, $t_r$-major 5.2 min, $t_r$-minor 6.5 min). Analytical data has been previously reported.$^{12}$ \[\alpha\]$_D^{25}$ +67.1 (c = 0.50, CH$_2$Cl$_2$).

(2R,5R)-Dimethyl 2-(4-chlorophenyl)-5-(4-methoxyphenyl)dihydrofuran-3,3(2H)-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$_4$ (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 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, $t_r$-
major 4.6 min, \( t_r \)-minor 5.3 min). Analytical data for 2c: **IR** (thin film, cm\(^{-1}\)) 3067, 3004, 2953, 2902, 2839, 1732, 1614, 1516, 1492, 1436, 1384, 1348, 1278, 1249, 1176, 1085, 1057, 940, 834, 803; **\(^1\)H NMR** (400 MHz, 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); **\(^{13}\)C NMR** (100 MHz, 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 C\(_{21}\)H\(_{21}\)ClO\(_6\): C, 62.3; H, 5.23; Found: C, 62.21; H, 5.27; \([\alpha]_D^{27} +57.3 \) (\( c = 0.52 \), CH\(_2\)Cl\(_2\)).

\((2R,5R)\)-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 CCl\(_4\) (2.8 mL) and MgI\(_2\) (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-\(^1\)Bu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in 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 °C, 220 nm, \( t_r \)-major 6.8 min, \( t_r \)-minor 7.5 min). Analytical data for 2d: **IR** (thin film, cm\(^{-1}\)) 3074, 3005, 2955, 2841, 1732, 1615, 1588, 1517, 1436, 1326, 1280, 1248, 1172, 1124, 1066, 941, 853; **\(^1\)H NMR** (400 MHz, 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,
\( J = 8.4 \text{ Hz, 2H}, 5.79 \text{ (s, 1H)}, 4.94 \text{ (dd, } J = 10.0, 6.0 \text{ Hz, 1H}), 3.84 \text{ (s, 3H)}, 3.83 \text{ (s, 3H)}, 3.01 \text{ (m, 1H)}, 2.73 \text{ (dd, } J = 13.6, 6.4 \text{ Hz, 1H}); ^{13}\text{C NMR (100 MHz, CDCl}_3 \delta 171.1, 169.1, 159.7, 141.7, 131.4, 130.2 \text{ (q, } J = 32.1 \text{ Hz), 128.1 \text{ (d, } J = 14.0 \text{), 127.4, 124.6 \text{ (d, } J = 3.7 \text{ Hz), 124.1 \text{ (q, } J = 270.5 \text{), 114.0, 83.6, 79.9, 66.3, 55.2, 53.0, 52.1, 42.7; TLC (20\% EtOAc/hexanes) } R_f 0.22; \text{ LRMS (ESI) calcd. for C}_{22}\text{H}_{21}\text{F}_3\text{O}_6+\text{Na}: 461.1, found 461.2; \left[ \alpha \right]_D^{25} +61.4 \text{ (c = 0.29, CH}_2\text{Cl}_2)\).

\textbf{(2R,5R)-dimethyl 5-(4-methoxyphenyl)-2-o-tolyldihydrofuran-3,3(2H)-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 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 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, \( t_r\)-major 4.4 min, \( t_r\)-minor 4.8 min). Analytical data: Analytical data for 2e: \textbf{mp} 79-82 °C; \textbf{IR} (thin film, cm\(^{-1}\)) 3067, 3002, 2953, 2839, 1731, 1614, 1587, 1516, 1435, 1283, 1245, 1174, 1084, 1052, 936, 908, 831, 760, 681; \textbf{\(^1\)H NMR} (400 MHz, CDCl\(_3\)) \( \delta 7.49 \text{ (m, 3H), 7.15 \text{ (m, 3H), 6.94 \text{ (d, } J = 8.4 \text{ Hz, 2H), 6.20 \text{ (s, 1H), 4.90 \text{ (dd, } J = 11.6, 4.8 \text{ Hz, 1H), 3.84 \text{ (s, 3H), 3.83 \text{ (s, 3H), 3.08 \text{ (dd, } J = 13.2, 12.0 \text{ Hz, 1H), 3.06 \text{ (s, 3H), 2.61 \text{ (dd, } J = 13.6, 4.8 \text{ Hz, 1H); ^{13}\text{C NMR} (100 MHz, CDCl}_3 \delta 171.6, 168.9, 159.5, 136.6, 136.3, 131.3, 129.8, 127.8, 127.7,}

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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) Rf 0.24; LRMS (ESI) calcd. for C22H24O6+Na: 407.2, found 407.1; [α]D 27° +61.4 (c = 0.51, CH2Cl2).

(2S,5R)-dimethyl 5-(4-methoxyphenyl)-2-(thiophen-2-yl)dihydrofuran-3,3(2H)-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 CCl4 (2.8 mL) and MgI2 (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-Bu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl4 (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, tR-major, 4.8 min, tR-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, CDCl3) δ 7.48 (d, J = 8.8 Hz, 2H), 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); ¹³C NMR (100 MHz, CDCl3) δ 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) Rf 0.16; Anal. Calcd. for C19H20O6S: C, 60.62; H, 5.36. Found: C, 60.83; H, 5.29; [α]D 27° +103.2 (c = 0.215, CH2Cl2).
(2R,5R)-Dimethyl 5-(4-methoxyphenyl)-2-styryldihydrofuran-3,3(2H)-dicarboxylate (2g):

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 CCl₄ (2.8 mL) and MgI₂ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-4Bu-ybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl₄ (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_r-major, 5.7 min, t_r-minor 6.6 min). Analytical data for 2g: IR (thin film, cm⁻¹) 3063, 3029, 3004, 2954, 2840, 1733, 1614, 1516, 1449, 1436, 1277, 1249, 1175, 1079, 1037, 971, 832, 741, 694;¹H NMR (400 MHz, CDCl₃) 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);¹³C NMR (100 MHz, CDCl₃) δ 170.9, 169.4, 159.5, 136.5, 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) R₂ 0.18; LRMS (ESI) calcd. for C_{23}H_{24}O_{6}+Na: 419.2, found 419.2; [α]_{D}^{26} +72.5 (c = 0.375, CH₂Cl₂).
(2R,5R)-Dimethyl 2-isopropyl-5-(4-methoxyphenyl)dihydrofuran-3,3(2H)-dicarboxylate (2h):

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 CCl₄ (2.8 mL) and MgI₂ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-4-Bu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl₄ (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, tᵣ-major 4.1 min, tᵣ-minor 4.5 min). Analytical data for 2h: IR (thin film, cm⁻¹) 3067, 2999, 2955, 2874, 2840, 1732, 1614, 1516, 1436, 1277, 1248, 1198, 1176, 1114, 1091, 1056, 833; ¹H NMR (400 MHz, CDCl₃) 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, 1H), 1.01 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) 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) Rᵣ 0.32; Anal. Calcd. for C₁₈H₂₄O₆: C, 64.27; H, 7.19; Found: C, 63.98; H, 7.08; [α]D²⁶ +70.7 (c = 0.22, CH₂Cl₂).
(2R,5R)-Dimethyl 5-(4-methoxyphenyl)-2-pentyldihydrofuran-3,3(2H)-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 CCl4 (2.8 mL) and MgI2 (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-tBu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl4 (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_r-major 7.3 min, t_r-minor 8.5 min).

Analytical data for 2i: IR (thin film, cm⁻¹) 3065, 3004, 2955, 2861, 1733, 1614, 1516, 1458, 1436, 1281, 1246, 1175, 1074, 1035, 952, 833; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) Rₚ 0.25; LRMS (ESI) calcd. for C₂₀H₂₈O₆⁺Na: 387.2, found 387.2; [α]D²⁷ +88.9 (c = 0.375, CH₂Cl₂).

(2R,5R)-Dimethyl 2-phenyl-5-(thiophen-2-yl)dihydrofuran-3,3(2H)-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 CCl₄ (2.8 mL) and MgI₂ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>1</sup>Bu-pybox (<b>16a</b>, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl₄ (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 <b>2j</b> (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, <i)t_r</i>-major 4.1 min, <i>t_r</i>-minor 4.7 min). Analytical data for this compound has been previously reported.<sup>12</sup> <i>[α]<sub>D</sub></i><sup>25</sup> +77.8 (<i>c</i> = 0.265, CH₂Cl₂).

<b>(2R,5R)-Dimethyl 2-(4-methoxyphenyl)-5-(thiophen-2-yl)dihydrofuran-3,3(2H)-dicarboxylate (2k):</b>

The title compound was prepared according to General Procedure E with dimethyl 2-(thien-2-yl)cyclopropane-1,1-dicarboxylate (<b>1c</b>, 0.036 g, 0.151 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (0.042 g, 0.30 mmol, 2.0 equiv) dissolved in CCl₄ (2.8 mL) and MgI₂ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-<sup>1</sup>Bu-pybox (<b>16a</b>, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl₄ (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 <b>2k</b> (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, <i>t_r</i>-major 4.5 min, <i>t_r</i>-minor 5.1 min). Analytical data for <b>2k</b>: 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, CDCl₃) δ 7.38 (d, <i>J</i> = 8.4 Hz, 2H), 7.34 (d, <i>J</i> = 4.8 Hz, 1H), 7.15 (d, <i>J</i> = 3.2 Hz, 1H), 7.01 (dd, <i>J</i> = 4.8, 3.2 Hz, 1H), 6.84 (d, <i>J</i> = 8.8 Hz, 2H), 5.75 (s, 1H), 5.21 (dd, <i>J</i> = 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); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 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 C$_{19}$H$_{20}$O$_6$S$^+$Na: 399.1, found 399.1; $[\alpha]_D^{27} +57.8$ (c = 0.415, CH$_2$Cl$_2$).

(2S,5R)-Dimethyl 2,5-di(thiophen-2-yl)dihydrofuran-3,3(2H)-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 CCl$_4$ (2.8 mL) and MgI$_2$ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl'-Bu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in 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, cm$^{-1}$) 3109, 3074, 3003, 2982, 1796, 1732, 1682, 1436, 1281, 1235, 1087, 1049, 855, 840, 714, 699; $^1$H NMR (400 MHz, CDCl$_3$) δ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 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) $R_f$
Anal. Calcd. for C_{16}H_{16}O_{5}S_{2}: C, 54.53; H, 4.58. Found: C, 54.78; H, 4.66; [α]_{D}^{26} +102.2 (c = 0.31, CH_{2}Cl_{2}).

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

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_{4} (2.8 mL) and MgI_{2} (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-Bu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl_{4} (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_{r}-major 5.4 min, t_{r}-minor 6.1 min). Analytical data for 2m: IR (thin film, cm⁻¹) 3063, 3028, 3004, 2953, 2880, 1734, 1496, 1448, 1436, 1278, 1226, 1200, 1174, 1137, 738, 694; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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_{f} 0.12; LRMS (ESI) calcd. for C_{20}H_{20}O_{5}S+Na: 419.2, found 419.1; [α]_{D}^{26} + 83.2 (c = 0.23, CH₂Cl₂).
(2R,5R)-Dimethyl 2-(4-methoxyphenyl)-5-styryldihydrofuran-3,3(2H)-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 CCl₄ (2.8 mL) and MgI₂ (0.0042 g, 0.0151 mmol, 0.10 equiv) and 4-Cl-tBu-pybox (16a, 0.0061, 0.0166 mmol, 0.11 equiv) coordinated in CCl₄ (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, tᵣ-major 5.3 min, tᵣ-minor 7.6 min). Analytical data for 2n: IR (thin film, cm⁻¹) 3063, 3028, 3003, 2953, 2840, 1731, 1614, 1514, 1436, 1359, 1282, 1247, 1174, 1035, 968, 933, 841, 805; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) Rf 0.16; LRMS (ESI) calcd. for C₂₃H₂₄O₆⁺Na: 419.2, found 419.1; [α]D²⁷ +54.7 (c = 0.27, CH₂Cl₂).
3.6 References


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.1 In particular, substituted pyrrolidine derivatives are
ubiquitous and their value is reflected by continued interest in developing methods for their
preparation.2-7 Efforts in our lab8-11 and others12,13 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)MgI₂-catalyzed (3 + 2) annulation with aldehydes to afford
2,5-cis-disubstituted tetrahydrofurans in a highly enantioselective manner.11 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.

\[
\begin{align*}
\text{rac-1} & \quad \text{2} \quad \text{DyKAT} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{R} & \quad \text{R}^1 \\
\text{PG} & \quad \text{PG} \\
\end{align*}
\]

(1) up to 86% yield, 98.2 er
average dr: 94:6
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)\(^{10,14,15}\) and Kerr has examined annulations with nitrones in great detail,\(^ {16-18}\) 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\(^ {19}\) and Tang.\(^ {20}\) Similar to the conditions used for their previously developed annulation with nitrones,\(^ {16}\) Kerr found Yb(OTf)\(_3\) to be an optimal Lewis acid (eq 2). Tang discovered that Sc(OTf)\(_3\) catalyzed this transformation at ambient temperatures with only 5 mol % loading (eq 3). Unlike the high cis diastereoselectivity obtained when using nitrone 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 aldime 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)$_3$-Catalyzed Cyclopropane/Aldimine Annulations

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 aldime does not influence the angle of nucleophilic attack by 2.

The aforementioned research on racemic aldime 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 aldime 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 $E$—$Z$ aldime/iminium isomerization plays in cyclopropane/aldimine annulations and whether it is reasonable to assume aldimes 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 MgI₂/4-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

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<thead>
<tr>
<th>entry</th>
<th>protecting group (PG)</th>
<th>yield (%)</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>2a</td>
<td>77</td>
<td>55.45</td>
<td>nd</td>
</tr>
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<td>2</td>
<td>2b</td>
<td>— e</td>
<td>—</td>
<td>—</td>
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<tr>
<td>3</td>
<td>2c</td>
<td>— e</td>
<td>—</td>
<td>—</td>
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<td>0'</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>27</td>
<td>&gt;99:1</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>83</td>
<td>97.3</td>
<td>85.5:14.5</td>
</tr>
<tr>
<td>8</td>
<td>2g</td>
<td>74</td>
<td>95.5</td>
<td>91.9</td>
</tr>
</tbody>
</table>

Conditions: 1b (1.0 equiv), aldimine (2.0 equiv), MgI₂ (0.10 equiv), L₁ (0.12 equiv), [1b]₀ = 0.050 M in CCl₄, rt, 24 h. a) Determined by ¹H NMR spectroscopy using a mesitylene internal standard. b) Determined by ¹H 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 Benzyllamines 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 \( \text{MgI}_2/L1 \) 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**

<table>
<thead>
<tr>
<th>entry</th>
<th>protecting group (PG)</th>
<th>yield (%)(^a)</th>
<th>( \text{dr}^b )</th>
<th>( \text{er}^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( 2h )</td>
<td>77 (3bh)</td>
<td>96:4</td>
<td>90.5:9.5</td>
</tr>
<tr>
<td>2</td>
<td>( 2i )</td>
<td>71 (3bi)</td>
<td>96:4</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>( 2j )</td>
<td>75 (3bj)</td>
<td>96:4</td>
<td>93:7</td>
</tr>
<tr>
<td>4</td>
<td>( 2k )</td>
<td>69 (3bk)</td>
<td>99:1</td>
<td>89.5:10.5</td>
</tr>
<tr>
<td>5</td>
<td>( 2l )</td>
<td>68 (3bl)</td>
<td>80:20</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>( 2m )</td>
<td>76 (3bm)</td>
<td>95:5</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td>( 2n )</td>
<td>73 (3bn)</td>
<td>94:6</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Conditions: \( 1b \) (1.0 equiv), aldimine (1.1 equiv), \( \text{MgI}_2 \) (0.10 equiv), \( L1 \) (0.12 equiv), \( [1b]_0 = 0.050 \) M in \( \text{CCl}_4 \), rt, 24 h. \( a \) Determined by \(^1\)H NMR spectroscopy using a mesitylene internal standard. \( b \) Determined by \(^1\)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.\textsuperscript{11} We sought to further improve the cyclopropane/aldimine DyKAT using this strategy. Thus, unsubstituted and 4-substituted-\textsuperscript{t}Bu-pybox ligands (L\textsubscript{0}-L\textsubscript{6}) were examined under the standard reaction conditions (Table 4-3). Previous difficulties in obtaining high enantioselectivity with the electron-rich 4-methoxybenzaldehyde-derived aldimine 2\texttextsuperscript{o} (data not shown) prompted us to conduct this optimization study using this dipolarophile.

Table 4-3. An Examination of 4-Substituted-\textsuperscript{t}Bu-Pybox Ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>conversion (%)\textsuperscript{a}</th>
<th>yield (%)\textsuperscript{a}</th>
<th>dr\textsuperscript{b}</th>
<th>er\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>44</td>
<td>39</td>
<td>84:16</td>
<td>74:26</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>100</td>
<td>66</td>
<td>96:4</td>
<td>89.5:10.5</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>100</td>
<td>79\textsuperscript{d}</td>
<td>97:3</td>
<td>93:7</td>
</tr>
<tr>
<td>4</td>
<td>CF\textsubscript{3}</td>
<td>100</td>
<td>69</td>
<td>96:4</td>
<td>92:8</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>93</td>
<td>63</td>
<td>94.5:5.5</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>Mes</td>
<td>64</td>
<td>56</td>
<td>91:9</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>N\textsubsuperscript{3}N\textsubsuperscript{3}-Ph</td>
<td>100</td>
<td>76</td>
<td>94.5:5.5</td>
<td>80:20</td>
</tr>
</tbody>
</table>

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

Interestingly, we found that L\textsubscript{2} (X = Br) provided superior results to the other ligands examined. Along with a substantially improved yield over L\textsubscript{1}, 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-tBu-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 MgI₂/4-X-tBu-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)₂ (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)₂ provided the optimal balance of product yield and enantioenrichment.²¹

\[
\begin{array}{c}
\text{3bi, 96.5:3.5 er} \\
R = 4-	ext{MeOPh} \\
\begin{array}{c}
\text{Pd(OH)₂ (cat)} \\
\text{H₂ (1 atm), HCl} \\
\text{MeOH, rt, 17 h}
\end{array}
\end{array} \quad \begin{array}{c}
\text{5} \\
\begin{array}{c}
\text{mol % Pd(OH)₂} = 20: 94\%, 93.5:6.5 \text{ er} \\
= 10: 86\%, 95.5 \text{ er} \\
= 5: 74\%, 95.5:4.5
\end{array}
\end{array}
\]

\[ \text{(4)} \]

### 4.4 Stereochemical and Mechanistic Analysis

Annulations of enantioenriched D–A cyclopropanes with aldehydes have been shown to proceed through an enantiospecific pathway.⁸,¹⁰ While it has been assumed a similar mode of reactivity exists for aldimine dipolarophiles,¹⁹,²⁰ it has never been experimentally proven. Previous efforts in our group demonstrated that dipolarophiles selectively react with the (S)-enantiomer of cyclopropanes 1 under MgI₂/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).\textsuperscript{22} Single crystal X-ray diffraction analysis confirmed the absolute stereochemical configuration of the product (\textit{R,R})-6. This data provides evidence that MgI\textsubscript{2}/L\textsubscript{2}-catalyzed annihilations of aldimines proceed with an identical stereochemical outcome to the corresponding aldehyde annihilation.

\textbf{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 annihilations. Kerr previously hypothesized that the source of variation in diastereoselectivity is a result of the fluxional \textit{E/Z}-geometry of the aldimines or corresponding iminiums generated during the course of the reaction (Scheme 4-1). This hypothesis predicts that (\textit{E})-aldimines/iminiums furnish the \textit{trans} pyrrolidine products. In order to test this hypothesis we selected (\textit{Z})-aldimine 2t\textsuperscript{23} as a reaction partner that, through cyclic constraint, would preclude \textit{E}—\textit{Z} isomerization (eq 5). Strikingly, Lewis acid-catalyzed annihilation of 2t and cyclopropane 1b delivered pyrrolidine 3bt exclusively as the 2,5-\textit{trans} isomer with poor enantiomeric discrimination (diastereoselection > 95:5, 55.5:44.5 er). The low level of enantioselectivity for annihilation
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 aldimeines is not a significant pathway leading to the production of trans pyrrolidine products.

The results obtained using aldime 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 aldimeine 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

![Scheme 4-4](image)

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

![Figure 4-2](image)

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).
presumably minimizing steric penalties associated with structures 13 (R ↔ PG) and 14 (Ar ↔ 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-\textit{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 (\(^1\)H NMR and \(^13\)C NMR) were recorded on a Bruker model DRX 400 or 500 (\(^1\)H NMR at 400 MHz or 500 MHz and \(^13\)C NMR at 100 or 125 MHz) spectrometer with solvent resonance as the internal standard (\(^1\)H NMR: CDCl\(_3\) at 7.26 ppm, DMSO-d6 at 2.54 ppm, CD\(_2\)Cl\(_2\) at 5.32 ppm, and C\(_6\)D\(_6\) at 7.15 ppm; \(^13\)C NMR: CDCl\(_3\) at 77.0 ppm, DMSO-d6 at 40.45 ppm, CD\(_2\)Cl\(_2\) at 54.0 ppm, and C\(_6\)D\(_6\) at 128.6 ppm). \(^1\)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. GC 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\(^\circ\)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 µm) 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 N₂ and stored in a Schlenk flask. Carbon tetrachloride was purified by distillation from phosphorous pentoxide under N₂. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

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

\[
\begin{array}{c}
\text{MeO} \\
\text{CN} \\
\text{MeO} \\
\end{array}
\xrightleftharpoons[\text{KBH}_4, \text{EtOH, rt to 50 °C}]{\text{Raney Ni}}
\begin{array}{c}
\text{MeO} \\
\text{H}_2\text{N} \\
\text{MeO} \\
\end{array}
\]

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 H₂O, 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 H₂O (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⁻¹) 2940, 2837, 1593, 1476, 1316, 1256, 1155, 1091, 882, 799, 778, 587; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 127.8, 120.1, 103.7, 55.6, 34.6; LRMS (ESI) Calcd. for C₉H₁₃NO₂+H: 168.1, Found: 168.1.

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

![Reaction Scheme]

Preparation of 2-ethoxybenzonitrile (S1):

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 H₂O (30 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were then washed with H₂O (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.
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 H₂O, 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 H₂O (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⁻¹) 3376, 2979, 2928, 1600, 1588, 1493, 1454, 1118, 1046, 928, 753, 462; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 132.0, 128.4, 127.9, 120.3, 111.1, 63.3, 42.8, 14.9; LRMS (ESI) Calcd. For C₉H₁₃NO⁺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 H₂O (60 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then washed with H₂O (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.²⁵

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

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O}^{\text{Pr}} \\
\text{H}_2\text{N} & \quad \text{O}^{\text{Pr}} \\
\text{H}_2\text{N} & \quad \text{O}^{\text{Pr}}
\end{align*}
\]

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 H₂O, 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 H₂O (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⁻¹) 3377, 2977, 2931, 1599, 1488, 1455, 1286, 1237, 1119, 957, 751; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 155.7, 132.9, 128.6, 127.8, 120.2, 112.6, 69.7, 42.9, 22.1; LRMS (ESI) Calcd. for C₅H₁₅NO+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, CH₂Cl₂ and (CH₂)₂Cl₂ 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 CH₂Cl₂. 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 MgI₂/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 MgI₂ (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 CH₂Cl₂ (approx 10 mL) and concentrated. Yields were determined by ¹H NMR using a mesitylene internal standard. Analytically pure material was obtained by purification using flash chromatography.

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

IR (thin film, cm⁻¹) 3027, 2950, 2836, 1732, 1511, 1455, 1283, 1243, 1172, 1032, 832; ¹H NMR (400 MHz, C₆D₆) δ 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); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 169.8, 159.0, 139.2, 134.7, 133.5, 130.2, 134.5, 133.5, 132.5.
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-phenylpyrroloidine-3,3-dicarboxylate (3bh):

\[ \text{IR (thin film, cm}^{-1}\text{)} 2951, 2835, 1731, 1611, 1510, 1455, 1434, 1246, 1175, 1034, 830; \text{H NMR (400 MHz, C}_6\text{D}_6\text{)} \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); \text{C NMR (125 MHz, CDCl}_3\text{)} \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 (2R,5R)-dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bi):

IR (thin film, cm\(^{-1}\)) 2952, 2836, 1731, 1511, 1435, 1282, 1243, 1173, 1032, 832; \(^1\)H NMR (400 MHz, C\(_6\)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); \(^1\)C NMR (125 MHz, 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 C\(_{29}\)H\(_{31}\)NO\(_6\)+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, CHCl\(_3\)).

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

IR (thin film, cm\(^{-1}\)) 3001, 2952, 2836, 1732, 1611, 1509, 1291, 1245, 1209, 1172, 1038, 832, 701; \(^1\)H NMR (400 MHz, C\(_6\)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); \(^1\)C NMR (125 MHz, 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) Rf 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; [α]_{D}^{28} = +57.6 (c = 0.610, CHCl_{3}).

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

![Image of molecule 3bk]

mp 49-52 °C; IR (thin film, cm^{-1}) 2951, 2836, 1733, 1595, 1511, 
1474, 1245, 1173, 1116, 831; \textbf{^1}H NMR (400 MHz, C_{6}D_{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).; \textbf{^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) Rf 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; [α]_{D}^{29} = +60.5 (c = 0.270, CHCl_{3}).

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

![Image of molecule 3bl]

mp 58-60 °C; IR (thin film, cm^{-1}) 2952, 2891, 2837, 1731, 1511, 
1488, 1440, 1243, 1039, 930, 833, 737, 702; \textbf{^1}H NMR (400 MHz, 
C_{6}D_{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, 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; \( \text{TLC} \) (20% EtOAc/hexanes) \( R_f \) 0.27; \( \text{LRMS} \) (ESI) Calcd. for C\(_{29}\)H\(_{29}\)NO\(_7\)+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):**

\[
\text{IR (thin film, cm}^{-1}) \ 3027, 2950, 2837, 1732, 1511, 1493, 1455, 1289, 1241, 1172, 1049, 831; \ \text{\(^1\text{H NMR} \) (500 MHz, C}_6\text{D}_6) \ \delta \ 7.70 \ (d, \ J = 7.4 \ \text{Hz, 2H}), \ 7.57 \ (d, \ J = 8.5 \ \text{Hz, 2H}), \ 7.17 – 7.15 \ (m, 1H), \ 7.12 \ (t, \ J = 7.5 \ \text{Hz, 2H}), \ 6.93 \ (m, 1H), \ 6.86 \ (d, \ J = 8.6 \ \text{Hz, 2H}), \ 6.71 \ (t, \ J = 7.3 \ \text{Hz, 1H}), \ 6.35 \ (d, \ J = 8.2 \ \text{Hz, 1H}), \ 5.47 \ (s, 1H), \ 4.07 \ (d, \ J = 13.3 \ \text{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 \ \text{Hz, 1H}), \ 2.82 \ (s, 3H), \ 2.62 \ (dd, \ J = 13.2, 5.9 \ \text{Hz, 1H}), \ 1.11 \ (t, \ J = 7.0 \ \text{Hz, 3H}); \ \text{\(^{13}\text{C NMR} \) (125 MHz, 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; \ \text{TLC (15% EtOAc/hexanes) \ R_f \ 0.23; \ LRMS (ESI) Calcd. for C\(_{30}\)H\(_{33}\)NO\(_6\)+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 (2R,5R)-dimethyl 1-(2-isopropoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (3bn):

**IR** (thin film, cm⁻¹) 2951, 2837, 1734, 1512, 1490, 1455, 1286, 1243, 1173, 957, 831; ¹H NMR (500 MHz, C₆D₆) δ 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); ¹³C NMR (125 MHz, CDCl₃) δ 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) Rₗf 0.22; LRMS (ESI) Calcd. for C₃₁H₃₅NO₆⁺H: 518.2, Found: 518.3; SFC analysis (Chiralcel, OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 94:6 er, tᵣ-major 8.82 min, tᵣ-minor 9.79 min; [α]D²⁷ = +53.0 (c = 0.230, CHCl₃).

**General Procedure D** for the enantioselective MgI₂/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 MgI₂ (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 CH₂Cl₂ (10 mL). The resulting solution was concentrated and purified by flash chromatography using the indicated solvent system.

(2R,5R)-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 ¹H 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) tᵣ-major 7.41 min, tᵣ-minor 8.14 min; [α]D²⁶ = +76.6 (c = 0.280, CHCl₃).
(2R,5R)-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 1H 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) $t_r$-major 5.7 min, $t_r$-minor 6.3 min. Analytical data for 3bo: mp 50-52 °C; IR (thin film, cm⁻¹) 2953, 2837, 1732, 1510, 1273, 1245, 1172, 1034, 831, 759; ¹H NMR (400 MHz, C₆D₆) 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); ¹³C NMR (125 MHz, CDCl₃) 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) Rf 0.14; LRMS (ESI) Calcd. for C₃₀H₃₃NO₇⁺H: 520.2, Found: 520.2; $[\alpha]_D^{26} = +38.8$ (c = 0.370, CHCl₃).
(2R,5R)-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 $^1$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) $t_r$-major 7.6 min, $t_r$-minor 8.2 min. Analytical data for 3bp: IR (thin film, cm$^{-1}$) 2952, 1731, 1266, 1173, 1034, 738, 704; $^1$H NMR (500 MHz, C$_6$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); $^{13}$C NMR (125 MHz, 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 C$_{30}$H$_{33}$NO$_6$+H: 504.3, Found: 504.3; [$\alpha$]$_D$$^{27}$ = +76.9 (c = 0.300, CHCl$_3$).
(2R,5R)-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 \(^1\)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) \(t_r\)-major 12.1 min, \(t_r\)-minor 13.2 min. Analytical data for 3bq: mp 48-51 °C; IR (thin film, cm\(^{-1}\)) 2952, 2835, 1733, 1511, 1465, 1434, 1247, 1174, 1033, 832, 737; \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 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); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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) \(R_f\) 0.16; LRMS (ESI) Calcd. for C\(_{29}\)H\(_{30}\)NO\(_6\)+Cs: 700.1, Found: 700.0; \([\alpha]_D^{26}\) = +35.7 (c = 0.280, CHCl\(_3\)).
(2S,5R)-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 \(^1\)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) \(t_r\)-major 12.9 min, \(t_r\)-minor 14.4 min. Analytical data for 3bs: \(\text{mp} 44-47 \degree\text{C}; \text{IR} (\text{thin film, cm}^{-1}) 2953, 2837, 1733, 1512, 1272, 1245, 1173, 1034, 832, 703; \text{\(^1\)H NMR (500 MHz, 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), 3.73 (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); \text{\(^{13}\)C NMR (125 MHz, 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; \text{TLC (20% EtOAc/hexanes) R}_f 0.20; \text{LRMS (ESI) Calced. for C}_{27}\text{H}_{29}\text{NO}_6\text{S+H: 496.2, Found: 496.3; } \left[\alpha\right]_D^{28} = +82.3 (c = 0.470, \text{CHCl}_3).
(2R,5R)-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 $^1$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) $t_r$-major (cis) 24.8 min, $t_r$-minor (cis) 27.3 min, $t_r$-major (trans) 21.7 min, $t_r$-minor (trans) 22.9 min. Analytical data for 3ci: IR (thin film, cm$^{-1}$) 3028, 2951, 2836, 1733, 1493, 1435, 1268, 1246, 966, 753, 701; $^1$H NMR (400 MHz, 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); $^{13}$C NMR (100 MHz, 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 C$_{30}$H$_{31}$NO$_5$+H: 486.2, Found: 486.2; [$\alpha$]$_D^{28} = +125.4$ (c = 0.430, CHCl$_3$).
(2R,5R)-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 $^1$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) $t_r$-major 19.7 min, $t_r$-minor 21.8 min. Analytical data for 3cq: mp 41-44 °C; IR (thin film, cm$^{-1}$) 2952, 1733, 1493, 1435, 1266, 1198, 1174, 1070, 967, 737, 695; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 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) $R_f$ 0.18; LRMS (ESI) Calcd. for C$_{30}$H$_{30}$BrNO$_5$+Cs: 696.1, Found: 696.0; $[\alpha]_D^{28} = +124.6$ (c = 0.290, CHCl$_3$).
(2R,5R)-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 $^1$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) $t_r$-major 33.6 min, $t_r$-minor 38.6 min. Analytical data for 3cr: IR (thin film, cm$^{-1}$) 2952, 2837, 1733, 1602, 1507, 1278, 1245, 1222, 966, 850, 692; $^1$H NMR (500 MHz, CDCl$ _3 $) $\delta$ 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); $^{13}$C NMR (125 MHz, CDCl$ _3 $) $\delta$ 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$_f$ 0.10; LRMS (ESI) Calcd. for C$_{30}$H$_{30}$FNO$_5$+H: 504.2, Found: 504.2; [$\alpha$]$_D^{29}$ = +107.8 (c = 0.400, CHCl$_3$).
(2S,5R)-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 1H 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_r-major 33.6 min, t_r-minor 38.6 min. Analytical data for 3cs: IR (thin film, cm⁻¹) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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) Rₚ 0.14; LRMS (ESI) Calcd. for C₂₈H₂₉NO₅S+H: 492.2, Found: 492.2; [α]_D²⁸ = +126.7 (c = 0.370, CHCl₃).
(2R,5R)-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 $^1$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) $t_r$-major 9.5 min, $t_r$-minor 10.3 min. Analytical data for 3di: IR (thin film, cm$^{-1}$) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702; $^1$H NMR (400 MHz, 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); $^{13}$C NMR (100 MHz, 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 C$_{26}$H$_{27}$NO$_5$S+H: 466.2, Found: 466.2; $[\alpha]_D^{26}$ = +80.9 (c = 0.400, CHCl$_3$).
(2R,5R)-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 $^1$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) $t_r$-major 8.9 min, $t_r$-minor 9.8 min. Analytical data for 3dr: IR (thin film, cm$^{-1}$) 3070, 3001, 2952, 2837, 1734, 1507, 1281, 1244, 849, 823, 517; $^1$H NMR (400 MHz, 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) $^{13}$C NMR (100 MHz, 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, 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) $R_f$ 0.18; LRMS (ESI) Calcd. for C$_{26}$H$_{26}$FNO$_5$S$^+$Na: 506.2, Found: 506.2; [$\alpha$]$_D^{29}$ = +46.7 ($c = 0.400$, CHCl$_3$).
Preparation of (dimethyl 7-(4-methoxyphenyl)-6,7-dihydro-4b\text{H}-dibenzo[c,e]pyrrolo[1,2-a]azepine-5,5(9H)-dicarboxylate (3bt):

\[
\text{MeO} \quad \text{MeO} \\
\text{MeO} \quad \text{MeO} \\
\text{MeO} \quad \text{MeO}
\]

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\text{H}-dibenzo[c,e]azepine (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 \textsuperscript{1}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) \( t_r \)-major 13.6 min, \( t_r \)-minor 11.7 min. Analytical data for 3bt: mp 83-84 °C; IR (thin film, cm\(^{-1}\)) 2848, 2685, 2305, 1694, 1597, 1439, 1197, 825, 741; [Note: \textsuperscript{1}H and \textsuperscript{13}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] \textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 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) \( R_f \) 0.20; LRMS (ESI) Calcd. for C\(_{28}\)H\(_{27}\)NO\(_5\)+H: 458.2, Found: 458.2; [\( \alpha \)]\(_D\)^{26} = −1.95 (c = 0.25, CHCl\(_3\)). X-ray quality crystals were obtained by slow evaporation of methanol.
Pd(OH)$_2$-catalyzed reductive debenzylation of pyrrolidine 3bi to provide pyrrolidine 5:

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{MeO} \\
\text{3bi} & \quad \text{N} \\
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{MeO} \\
\text{5} & \quad \text{N} \\
Pd(OH)$_2$, H$_2$ (1 atm) & \quad \text{Conc. HCl, MeOH} \\
\text{rt, 17 h} & \quad \text{85%}
\end{align*}
\]

A flame-dried 5-mL round bottomed flask containing a magnetic stir bar was purged with N$_2$ 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)$_2$ (0.0036 g, 0.0051 mmol, 0.10 equiv). The flask was purged with a balloon of H$_2$ and was placed under a balloon atmosphere of H$_2$. 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 \textit{in vacuo} and the resulting residue taken up in saturated \textit{aq} NaHCO$_3$ solution (5 mL) and extracted with CHCl$_3$ (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$^{-1}$) 3054, 2987, 2305, 1730, 1612, 1512, 1421, 1265, 895, 744; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_{21}$H$_{23}$NO$_5$+H: 370.2, Found: 370.2; Enantiomeric ratio [determined by converting to the N-benzyl derivative (3bg), \textit{vide infra}] 95.5:4.5 er; [$\alpha$]$_D^{25}$ = +33.5 (c = 0.350, CHCl$_3$).
Preparation of 3bg by N-benzylation of 5:

\[
\begin{align*}
\text{MeO}_2C & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{Br} & \quad \text{Ph}
\end{align*}
\]

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 H₂O (10 mL) and extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with H₂O (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, \(t_r\)-major 4.7 min, \(t_r\)-minor 5.2 min.

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

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{CO}_2\text{Me} & \quad \text{H} \\
\text{MeO} & \quad \text{PG} \\
\text{PG} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{CO}_2\text{Me} & \quad \text{H} \\
\text{MeO} & \quad \text{H}_2\text{N} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

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\(^t\)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 MgSO₄, 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⁻¹) 3369, 3214, 3055, 2986, 2961, 2937, 2838, 2305, 1729, 1512, 1422, 1353, 1246, 1173, 1033; ¹H NMR (500 MHz, CD₂Cl₂) 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); ¹³C NMR (125 MHz, CD₂Cl₂) 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) Rₜ 0.18; LRMS (ESI) Calcd. for C₂₈H₂₃BrN₃O₅+H: 564.1, Found: 564.1; [α]D¹⁸⁺ = +38.1 (c = 0.305, THF).
4.7 References


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.\textsuperscript{1,2} 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.\textsuperscript{3-6} 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 tetrahydropyran (THP) 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\(^7\) and proven synthetic utility.\(^8-10\) 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)].\(^11\) This fact has led to the continued perception that cyclobutane reactivity is “unremarkable.”\(^9\)

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\(^3\)-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°.\(^12,13\) 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.\(^14\) 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. 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 δ-lactol products 4 as a mixture of diastereomers.

![Reaction equation](image)

More recently, Matsuo and coworkers have explored the use of alkoxy-cyclobutanones 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 BF₃•OEt₂ as a stoichiometric promoter, affording hexahydropyranones 6 (Scheme 5-1). The transformation proceeded with high chemo- and diastereoselectivity. The proposed mechanism involves oxocarbenium formation/C–C bond cleavage facilitated by cyclobutanone coordination to BF₃. Approach of the carbonyl dipolarophile orients R_L (L = 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-γ-pyronones 7. Optimization of this process through temperature control allowed for efficient access to dihydro-γ-pyronone products in excellent yield (eq 4). While most transformations were conducted using superstoichiometric BF₃•OEt₂, 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 ethers¹⁷ and allylsilanes¹⁸ 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 EtAlCl₂. Other Lewis acids such as SnCl₄ and Sc(OTf)₃ provided the desired cyclohexanone 8 in diminished yields. Conversely, when the dipolarophile was switched to allylsilanes, SnCl₄ 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 Alkoxycyclcobutanones 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). 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.21,22

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 13.23 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.\(^2^4\) Reduction of commercially available ketone 15 followed by bromination with aqueous HBr furnished 13b in 86\% over two steps.\(^2^3\) 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).\(^2^5\) 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 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. 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. 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 phenylecyclobutane 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)₄ 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

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
<th>dr</th>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methylene chloride</td>
<td>95</td>
<td>92:8</td>
<td>8</td>
<td>chloroform</td>
<td>76</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>2-methyl tetrahydrofuran</td>
<td>nr</td>
<td>nd</td>
<td>9</td>
<td>chlorobenzene</td>
<td>85</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>cyclopentyl methyl ether</td>
<td>(&lt; 5)</td>
<td>nd</td>
<td>10</td>
<td>carbon tetrachloride</td>
<td>60 (89)</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>diethyl ether</td>
<td>29 (46)</td>
<td>94:6</td>
<td>11</td>
<td>toluene</td>
<td>80</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>benzotrifluoride</td>
<td>84</td>
<td>95:5</td>
<td>12</td>
<td>tetrahydrofuran</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>dichloroethane</td>
<td>93</td>
<td>96:4</td>
<td>13</td>
<td>benzene</td>
<td>73</td>
<td>96:4</td>
</tr>
<tr>
<td>7</td>
<td>1,4-dioxane</td>
<td>(&lt; 5)</td>
<td>nd</td>
<td>14</td>
<td>hexanes</td>
<td>71</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Conditions: 1a (1.0 equiv), benzaldehyde (3.0 equiv), Hf(OTf)₄ (0.02 equiv), [1a]₀ = 0.25 M in the indicated solvent, rt, 12-18 h. a) Determined by ¹H NMR spectroscopy using a mesitylene internal standard. b) Determined by ¹H 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 annihilations (Table 5-2). Interestingly, Sn(OTf)\(_2\) 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 annihilations 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

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>mol %</th>
<th>yield (%)(^a)</th>
<th>conversion (%)(^a)</th>
<th>dr(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl(_3)</td>
<td>5</td>
<td>93</td>
<td>100</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)(_2)</td>
<td>5</td>
<td>13</td>
<td>19</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)(_3)</td>
<td>5</td>
<td>98</td>
<td>100</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>Sn(OTf)(_2)</td>
<td>20</td>
<td>28</td>
<td>45</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)(_3)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)(_2)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Conditions: 1a (1.0 equiv), benzaldehyde (3.0 equiv), Lewis acid (0.05-0.20 equiv), \([1a]_0 = 0.25\ \text{M in CH}_2\text{Cl}_2, \text{rt, 9-96 h.}\) \(^a\) Determined by \(^1\)H NMR spectroscopy using a mesitylene internal standard. \(^b\) Determined by \(^1\)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 \textbf{1a-d} were successful in undergoing annulation with a range of electron-poor to electron-rich aryl aldehydes (\textbf{Figure 5-2}). Annulation of \textbf{1a} with the electron-rich 4-methoxybenzaldehyde and cinnamaldehyde was sluggish and required the use of Hf(OTf)$_4$ as the catalyst. This highlights an interesting characteristic of cyclobutane/aldehyde annulations: electron-deficient aldehydes react more rapidly (see \textbf{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 \textbf{5.4}.

\textbf{Figure 5-2.} Annulation of Cyclobutanes \textbf{1a-d} with Cinnamyl and Aryl Aldehydes

\begin{center}
\begin{align*}
\textbf{1a} & \quad \text{R} = \text{Ph} \\
\textbf{1b} & \quad \text{R} = \text{4-BrPh} \\
\textbf{1c} & \quad \text{R} = \text{4-MeOPh} \\
\textbf{1d} & \quad \text{R} = \text{(E)-CH=CHMe} \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\textbf{2a} & \quad \text{R} = \text{Ph} \quad \text{95\%}, \text{96:4 dr} \\
\textbf{2b} & \quad \text{R} = \text{4-MeO} \quad \text{68\%}, \text{96:4 dr} \\
\textbf{2c} & \quad \text{R} = \text{4-F} \quad \text{93\%}, \text{99:1 dr} \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\textbf{2d} & \quad \text{R} = \text{NO}_2 \quad \text{99\%}, \text{99:1 dr} \\
\textbf{2e} & \quad \text{R} = \text{Cl} \quad \text{95\%}, \text{92:8 dr} \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\textbf{2f} & \quad \text{R} = \text{Ph} \quad \text{77\%}, \text{77:23 dr} \\
\end{align*}
\end{center}

Attempts to extend the Sc(OTf)$_3$ and Hf(OTf)$_4$ conditions to aliphatic aldehydes were not successful. We were prompted to evaluate alternative Lewis acids in order to achieve the annulation of \textbf{1} with aliphatic aldehydes. Campbell and Johnson recently reported the use of
a methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD)\textsuperscript{28} derivative (MAD\textsubscript{NTf\textsubscript{2}}) to catalyze the annulation of cyclopropane \textsuperscript{21} with sensitive aldehyde \textsuperscript{22} en route to the natural product polyanthellin A (eq 8).\textsuperscript{29} We examined this complex as a possible alternative to Sc(OTf)\textsubscript{3} 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).

\textbf{Figure 5-3.} MAD\textsubscript{NTf\textsubscript{2}}-Catalyzed Annulation of Cyclobutanes 1a-d with Aliphatic Aldehydes

\begin{align*}
\text{MAD\textsubscript{NTf\textsubscript{2}}} &\rightarrow \text{products} \\
\end{align*}
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).

\[
\begin{align*}
\text{DMM} & \quad \xrightarrow{\text{Sc(OTf)}_3} \quad \text{cyclobutane} \quad \xrightarrow{\text{aldehyde}} \quad \text{THPs}
\end{align*}
\]

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 Sc(OTf)₃. This study revealed that DMM decomposition was severely limiting cyclobutane formation. In our previous preparation of cyclobutane 1c, the stoichiometric amount of ZnBr₂ 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 Sc(OTf)₃ in CH₂Cl₂ at −78 °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

**Figure 5-4.** Sc(OTf)₃-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.⁵ 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)$_n$Sc(OTf)$_3$]. 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. 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)₃-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 \textit{cis}-2,6-disubstituted tetrahydropyran derivatives has been achieved. We streamlined this methodology by developing a \([(2 + 2) + 2]\) cycloaddition/annulation sequence where \textit{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 \((^1\text{H NMR: CDCl}_3 \text{ at } 7.26 \text{ ppm, DMSO-d6 at } 2.54 \text{ ppm, and C}_6\text{D}_6 \text{ at } 7.15 \text{ ppm}; ^{13}\text{C NMR: CDCl}_3 \text{ at } 77.0 \text{ ppm, DMSO-d6 at } 40.45 \text{ ppm, and C}_6\text{D}_6 \text{ at } 128.6 \text{ ppm})\). \(^1\text{H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d =}

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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 µm) 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 N₂ and stored in a Schlenk flask. Dichloroethane was purified by distillation from calcium hydride under N₂ 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 CaSO₄ and distilled under N₂ prior to use. Dimethyl 2-methylenemalonate was prepared according to the method of De Keyser³¹ 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 N₂, a flame dried 500-mL 2-neck round-bottomed flask containing a magnetic stir bar was charged with (1,3-dibromopropyl)benzene²⁴ (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
an analogous manner. The reaction was heated at reflux for an additional 12 h, at which point it was slowly cooled to room temperature. The resulting heterogeneous mixture was filtered through celite. The filter cake was washed with copious Et₂O and the filtrate was concentrated. Flash chromatography (2.5 – 3.3 – 5.0% EtOAc/hexanes) provided 1a (6.67 g, 26.87 mmol, 54% yield) as a slightly yellow clear oil. Unreacted (1,3-dibromopropyl)benzene was also recovered (2.5 g, 8.99 mmol, 18%). Analytical data for 1a:

IR (thin film, cm⁻¹) 3030, 3000, 2952, 1732, 1496, 1435, 1275, 1201, 1107, 791, 699; ¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.28 (m, 4H), 7.22 – 7.18 (m, 1H), 4.37 (t, J = 9.2 Hz, 1H), 3.77 (s, 3H), 3.23 (s, 3H), 2.28 (qd, J = 9.2, 2.4 Hz, 1H), 2.17 (qd, J = 8.8, 2.0 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 172.0, 169.6, 139.1, 128.0, 127.5, 126.9, 59.7, 52.4, 51.7, 45.1, 25.6, 20.7; TLC (10% EtOAc/hexanes) Rf 0.31; Anal. Calcd. for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.60.

**Preparation of dimethyl 2-(4-bromophenyl)cyclobutane-1,1-dicarboxylate (1b):**

Dimethyl 2-(4-bromophenyl)cyclobutane-1,1-dicarboxylate (1b) was prepared from 1-bromo-4-(1-bromo-3-chloropropyl)benzene²³ (13b, 1.13 g, 3.6 mmol, 1.0 equiv), dimethyl malonate (0.530 g, 0.458 mL, 4.01 mmol, 1.1 equiv) and sodium hydride [0.36 g (60% in oil), 9.0 mmol] in an analogous manner to the synthesis of 1a. The product was purified by flash chromatography (10% EtOAc/hexanes) to afford 1b (1.01 g, 3.10 mmol 86% yield) as a slightly yellow oil. Analytical data for 1b: IR (thin film, cm⁻¹) 3000, 2952, 1732, 1489,
1435, 1281, 1107, 1073, 1011, 831; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 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) \( R_f \) 0.18; Anal. Calcd. for C\textsubscript{14}H\textsubscript{15}O\textsubscript{4}: C, 51.40; H, 4.62. Found: C, 51.58; H, 4.54.

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

![Chemical reaction diagram]

In an inert atmosphere glove box, a 100-mL round-bottomed flask was charged with ZnBr\textsubscript{2} (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-methylene malonate\textsuperscript{31} (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\textsubscript{2}. Outside of the glove box, a flame scintillation vial under N\textsubscript{2} 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\textsubscript{2}Cl\textsubscript{2} (13.5 mL, 40.5 mL total). The flask containing ZnBr\textsubscript{2} was cooled to \(-130 \) °C in a pentane/liquid N\textsubscript{2} bath. To the ZnBr\textsubscript{2} 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\textsubscript{2}Cl\textsubscript{2} (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. Na₂EDTA (2 x 60 mL), dried over Na₂SO₄, 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⁻¹) 3000, 2952, 2839, 1732, 1515, 1435, 1275, 1253, 1107, 1037, 835; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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_f 0.18; Anal. Calcd. for C₁₅H₁₈O₅: 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)malonate²⁷ (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 CH₂Cl₂ (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, cm\(^{-1}\)) 3006, 2956, 1735, 1675, 1437, 1361, 1157, 980; \(^1\)H NMR (400 MHz, 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); \(^13\)C NMR (100 MHz, 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 C\(_{11}\)H\(_{16}\)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 CeCl\(_3\)•7H\(_2\)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 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 CH\(_2\)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 CH\(_2\)Cl\(_2\) (3 x 75 mL). The combined CH\(_2\)Cl\(_2\) extracts were washed with 2 M aq. HCl (75 mL), brine (75 mL), dried
over Na₂SO₄ 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⁻¹) 3421, 2957, 1734, 1438, 1287, 1245, 1158, 1062, 971; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 135.9, 128.3, 68.4, 52.3, 50.9, 29.6, 28.1, 23.3; TLC (40% EtOAc/hexanes) Rₚ 0.19; Anal. Calcd. for C₁₁H₁₈O₅: C, 57.38; H, 7.88. Found: C, 57.35; H, 7.85.

(E)-Dimethyl 2-(5-(phenoxy carbonyloxy) 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 N₂ 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 Et₂O (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 MgSO₄, and concentrated in vacuo to afford pure (E)-dimethyl 2-(5-(phenoxy carbonyloxy)hex-3-enyl)malonate (19) (5.88 g,
16.79 mmol, 92%) as a clear colorless oil. Analytical data for 19: IR (thin film, cm⁻¹) 2954, 1756, 1496, 1437m 1250, 1210, 1154, 1044, 970, 780, 688; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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) Rf 0.21; Anal. Calcd. for C₁₈H₂₂O₇: 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 N₂. The sodium hydride was washed with hexanes to remove the oil and was suspended in C₇H₈ (7.0 mL). To this suspension was added a solution of (E)-dimethyl 2-(5-(phenoxycarbonyloxy)hex-3-enyl)malonate (19, 1.25 g, 3.57 mmol, 1.0 equiv) in C₇H₈ (10 mL) via cannula over 20 min followed by a C₇H₈ wash (4 mL). The reaction was stirred at room temperature for 30 min and then warmed to 55 °C for an additional 5 h. The reaction was then cooled to room temperature and poured into 50 mL H₂O. The organic layer was separated and the aqueous layer extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with 2 M aq. NaOH (2 x 25 mL), dried over MgSO₄, 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, cm\(^{-1}\)) 2998, 2953, 1733, 1436, 1275, 1256, 1201, 1115, 970; **\(^1\)H NMR** (400 MHz, 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); **\(^{13}\)C NMR** (100 MHz, 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 C\(_{11}\)H\(_{16}\)O\(_4\)+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\(^{30}\) and was of sufficient purity for subsequent
transformations. Analytical data for 24: mp 139-141 °C; **IR** (thin film, cm\(^{-1}\))
3005, 2952, 1743, 1706, 1496, 1419, 1287, 1204, 1122, 943, 792, 700; **\(^1\)H NMR** (500 MHz,
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); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 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 C$_{13}$H$_{14}$O$_4$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 (+)- (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 CH$_2$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. NH$_4$Cl (2 x 20 mL), H$_2$O (2 x 20 mL), and brine (1 x 20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Partial separation of the isomers was achieved by flash chromatography (30 – 60% CH$_2$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: $[\alpha]_D^{29} = -115.2$ (c = 0.440, CHCl$_3$); IR (thin film, cm$^{-1}$) 2953, 2871, 1726, 1435, 1198, 1182, 1109, 1037, 956, 757, 698; $^1$H NMR (400 MHz, CDCl$_3$) δ 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, $J = 17.6$, 4.3 Hz, 1H).
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, 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; \(\text{TLC}\) (60% CH\(_2\)Cl\(_2\)/hexanes) \(R_f\) 0.39; \(\text{LRMS}\) (ESI) Calcd. for C\(_{23}\)H\(_{32}\)O\(_4\)Na: 395.2, Found: 395.2. Analytical data for (+)-25: \([\alpha]_D^{29} = + 24.9\) (c = 0.400, CHCl\(_3\)); \(\text{IR}\) (thin film, cm\(^{-1}\)) 2953, 2871, 1726, 1456, 1435, 1271, 1199, 1109, 1037, 957, 757; \(^1\text{H NMR}\) (400 MHz, 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, 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; \(\text{TLC}\) (60% CH\(_2\)Cl\(_2\)/hexanes) \(R_f\) 0.35; \(\text{LRMS}\) (ESI) Calcd. for C\(_{23}\)H\(_{32}\)O\(_4\)Na: 395.2, Found: 395.2.

\((+)-2\text{-Phenylcyclobutane-1,1-dicarboxylic acid (26)}:\)

\[
\text{\textbullet CO}_2\text{H} \quad \text{H}_2\text{O} \quad \text{EtOH} \quad \text{KOH} \quad \text{Magnetic stir bar} \quad (+)-\text{methyl 2-phenylcyclobutane-1,1-dicarboxylate (25)}
\]

Potassium hydroxide pellets (0.203 g, 3.62 mmol, 9.0 equiv) were dissolved in H\(_2\)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 H₂O (20 mL) and washed with Et₂O (4 x 20 mL). The aqueous solution was brought to pH = 1 by addition of concentrated HCl. The acidic solution was extracted with Et₂O (4 x 15 mL) and the combined organic extracts were dried over MgSO₄ 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: [α]D²⁷ = + 65.5 (c = 0.300, CHCl₃); mp 125-128 °C (dec.); IR (thin film, cm⁻¹) 2953, 2688, 2573, 1699, 1419, 1290, 1222, 1116, 928, 785, 697; ¹H NMR (400 MHz, DMSO) δ 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); ¹³C NMR (100 MHz, DMSO) δ 174.0, 171.7, 140.9, 128.7, 128.4, 127.3, 60.0, 45.1, 26.4, 21.4; LRMS (ESI) Calcd. for C₁₂H₁₂O₄+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 H₂O (10 mL). The resulting solution was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with H₂O (3 x 15 mL) and 50% saturated aq. NaCl solution (15 mL), dried over Na₂SO₄, and concentrated in vacuo. The product was purified by flash chromatography (10% EtOAc/hexanes) to afford (+)-1а (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). [α]D27 = + 93.9 (c = 0.360, CHCl3).

**General Procedure A for the Sc(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 Sc(OTf)3 (0.02 equiv). To this vial was added a solution of the cyclobutane (1.0 equiv) and aldehyde (3.0 equiv) in CH2Cl2 ([I]0 = 0.25 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 CH2Cl2 as the mobile phase), the reaction was filtered through a 1-inch Monstr-Pette plug of silica with CH2Cl2 (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), Sc(OTf)3 (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH2Cl2 (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: \textbf{IR} (thin film, cm\(^{-1}\)) 3032, 2952, 2857, 1729, 1452, 1435, 1257, 1091, 1068, 700; \textbf{\(^1\)H NMR} (400 MHz, 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); \textbf{\(^{13}\)C NMR} (100 MHz, 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; \textbf{TLC} (15% EtOAc/hexanes) \(R_f\) 0.18; \textbf{Anal.} Calcd. for C\(_{21}\)H\(_{22}\)O\(_5\): C, 71.17; H, 6.26. Found: C, 71.16; H, 6.32.

**Dimethyl 6-phenyl-2-(4-(trifluoromethyl)phenyl)dihydro-2\(H\)-pyran-3,3(4\(H\))-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), Sc(OTf)\(_3\) (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH\(_2\)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: \textbf{IR} (thin film, cm\(^{-1}\)) 2954, 2858, 1731, 1436, 1327, 1166, 1121, 1068, 1019, 856; \textbf{\(^1\)H NMR} (400 MHz, 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); \textbf{\(^{13}\)C NMR} (100 MHz, CDCl\(_3\)) \(\delta\) 171.1, 168.7, 143.6, 141.9, 129.7 (q, \(J = 32.3\) Hz), 128.4, 187
127.9, 127.7, 125.8, 124.3 (q, δ = 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_{3}O_{5}: C, 62.56; H, 5.01. Found: C, 62.81; H, 5.12.

**Dimethyl 2-(3-nitrophenyl)-6-phenyl dihydro-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) δ 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); ^13C NMR (100 MHz, CDCl_3) δ 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)$_3$ (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH$_2$Cl$_2$ (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$^{-1}$) 3031, 2952, 2856, 1735, 1437, 1276, 1254, 1166, 1092, 1032, 759, 701; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_f$ 0.21; Anal. Calcd. for C$_{21}$H$_{21}$ClO$_5$: 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)$_3$ (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH$_2$Cl$_2$ (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⁻¹) 3003 2954, 2858, 1731, 1436, 1327, 1166, 1122, 1068, 1011, 856, 815;
¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) Rf 0.23; Anal. Calcd. for
C₂₂H₂₀BrF₃O₅: 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)₃ (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH₂Cl₂ (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⁻¹) 2953, 2857, 1735,
1490, 1274, 1255, 1086, 1011, 764; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 168.7, 161.0, 158.6, 141.1, 131.4, 131.1 (d,
$J = 3.7 \text{ Hz}$, 129.3 (d, $J = 8.7 \text{ Hz}$), 127.5, 125.8 (d, $J = 12.6 \text{ Hz}$), 123.3 (d, $J = 3.1 \text{ Hz}$), 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-2$H$-pyran-3,3(4$H$)-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$_2$Cl$_2$ (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; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 (d, $J = 8.0 \text{ Hz}$, 4H), 7.10 (d, $J = 7.7 \text{ Hz}$, 2H), 6.88 (d, $J = 8.4 \text{ Hz}$, 2H), 5.11 (s, 1H), 4.62 (d, $J = 10.0 \text{ Hz}$, 1H), 3.80 (s, 3H), 3.68 (d, 3H), 3.58 (s, 3H), 2.68 (d, $J = 13.3 \text{ Hz}$, 1H), 2.36 – 2.28 (m, 1H), 2.32 (s, 3H), 2.09 (d, $J = 13.6$, 3.8 Hz, 1H), 1.91 (d, $J = 12.0 \text{ Hz}$, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.3, 169.2, 159.0, 157.0, 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)$_3$ (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH$_2$Cl$_2$ (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 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$^{-1}$) 3002, 2952, 2838, 1730, 1614, 1515, 1434, 1250, 1082, 1035, 829, 776; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_f$ 0.13; LRMS (ESI) Calcd. for C$_{22}$H$_{23}$BrO$_6$+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)$_3$ (0.0018 g, 0.0037 mmol, 0.02 equiv) and CH$_2$Cl$_2$ (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$_2$Cl$_2$/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, cm\(^{-1}\)) 2953, 2360, 2342, 1731, 1492, 1436, 1090, 1014, 846, 808; **\(^1\)H NMR** (400 MHz, 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); **\(^{13}\)C NMR** (100 MHz, 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% CH\(_2\)Cl\(_2\)/hexanes) \(R_f\) 0.28; **Anal.** Calcd. for C\(_{18}\)H\(_{21}\)ClO\(_5\): C, 61.28; H, 6.00. Found: C, 61.51; H, 6.04.

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

![Chemical structure](image)

In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with Hf(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 CH\(_2\)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 CH\(_2\)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)₄ (0.0050 g, 0.0064 mmol, 0.02 equiv) and CH₂Cl₂ (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% CH₂Cl₂/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⁻¹) 2952, 2930, 1851, 1729, 1613, 1514, 1435, 1250, 1177, 1069, 1033, 700; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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% CH₂Cl₂/hexanes) Rₚ 0.18; Anal. Calcd. for C₂₂H₂₄O₆: 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)₄ (0.0050 g, 0.0064 mmol, 0.02 equiv) and CH₂Cl₂ (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, cm$^{-1}$) 3030, 2953, 1732, 1451, 1435, 1236, 1171, 1066, 1026, 696; $^1$H NMR (400 MHz, C$_6$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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 169.2, 142.0, 137.1, 131.3, 128.4, 128.3, 127.6, 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 C$_{22}$H$_{24}$O$_6$: C, 72.61; H, 6.36. Found: C, 72.67; H, 6.44.

**General Procedure C for the MADNTf$_2$-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)$_{28}$ (MAD, 0.07 equiv), HNTf$_2$ (0.05 equiv) and (CH$_2$)$_2$Cl$_2$ (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$_2$)$_2$Cl$_2$ (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$_2$Cl$_2$ as the mobile phase), the reaction was filtered through a 1-inch
Monstr-Pette plug of silica with CH₂Cl₂ (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):**

![Image of compound 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), HNTf₂ (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⁻¹) 2953, 2871, 1731, 1450, 1435, 1254, 1092, 1068, 1013, 698; **¹H NMR** (400 MHz, CDCl₃) 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); **¹³C NMR** (100 MHz, CDCl₃) 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) Rₚ 0.16; **Anal.** Calcd. For C₁₈H₂₄O₅: 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):**

![Image of compound 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), HNTf₂ (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, cm\(^{-1}\)) 2927, 2852, 1730, 1435, 1093, 1068, 1029, 1009; \(^1\)H NMR (400 MHz, 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); \(^{13}\)C NMR (100 MHz, 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 C\(_{18}\)H\(_{24}\)O\(_5\): C, 69.98; H, 7.83. Found: C, 69.80; H, 7.99.

**Dimethyl 2-pentyl-6-phenyldihydro-2\(^{\text{H}}\)-pyran-3,3(4\(^{\text{H}}\))-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), 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, cm\(^{-1}\)) 2954, 2929, 2859, 1732, 1452, 1435, 1256, 1092, 1068, 698; \(^1\)H NMR (400 MHz, 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); \(^{13}\)C NMR (100 MHz,
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), HNTf₂ (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⁻¹) 2953, 2928, 2859, 1732, 1489, 1435, 1255, 1233, 1083, 1011, 804; ¹H NMR (400 MHz, CDCl₃) δ 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, 3H), 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); ¹³C NMR (100 MHz, CDCl₃) δ 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) Rₚ 0.23; Anal. Calcd. For C₂₀H₂₇BrO₅: 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), HNTf₂ (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⁻¹) 2954, 2930, 2858, 1731, 1614, 1515, 1436, 1249, 1175, 1081, 1034, 825; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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_f 0.22; Anal. Calcd. For C₂₁H₃₀O₆: 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), HNTf₂ (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, cm⁻¹) 2955, 2929, 2858, 1733, 1436, 1256, 1230, 1085, 1068, 1016, 966; H NMR (400 MHz, C₆D₆) δ 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 (dt, 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); C NMR (100 MHz, C₆D₆) δ 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) Rₙ 0.27; LRMS (ESI) Calcd. For C₁₇H₂₈O₅⁺Na: 335.2, Found: 335.2.

**General Procedure D for the Sc(OTf)₃-catalyzed ([2 + 2] + 2) cycloaddition/annulation of 1-methoxy-4-vinylbenzene, dimethyl 2-methylene malonate, 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 Sc(OTf)₃ (0.0171 g, 0.0347 mmol, 0.10 equiv). A second shell vial was charged with dimethyl 2-methylene malonate (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 N₂. The Sc(OTf)₃ was suspended in CH₂Cl₂ (0.25 mL) and cooled to –78 °C in an isopropanol/dry ice bath. The DMM was dissolved in CH₂Cl₂ (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 Sc(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 °C for 20 min and was then warmed to 0 °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 CH₂Cl₂ (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-tolyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2i):**

The title compound was prepared according to General Procedure D using Sc(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 CH₂Cl₂ (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-2H-pyran-3,3(4H)-dicarboxylate (2j):**

The title compound was prepared according to General Procedure D using Sc(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$_2$Cl$_2$ (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)$_3$ (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), benzaldehyde (0.110 g, 0.105 mL, 1.04 mmol, 3.0 equiv), and CH$_2$Cl$_2$ (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$^{-1}$) 2952, 2838, 1730, 1614, 1515, 1435, 1250, 1176, 1082, 1033, 828, 700; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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, 2H), 2.34 (dt, $J = 13.5$, 4.5 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.96 – 1.93 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 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) $R_f$ 0.23; LRMS (ESI) Calcd. For C$_{22}$H$_{24}$O$_6$+Na: 407.2, Found: 407.2.
5.7 References


