LEWIS ACID-PROMOTED CYCLOADDITION REACTIONS OF AZIRIDINES AND CYCLOPROPANES

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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

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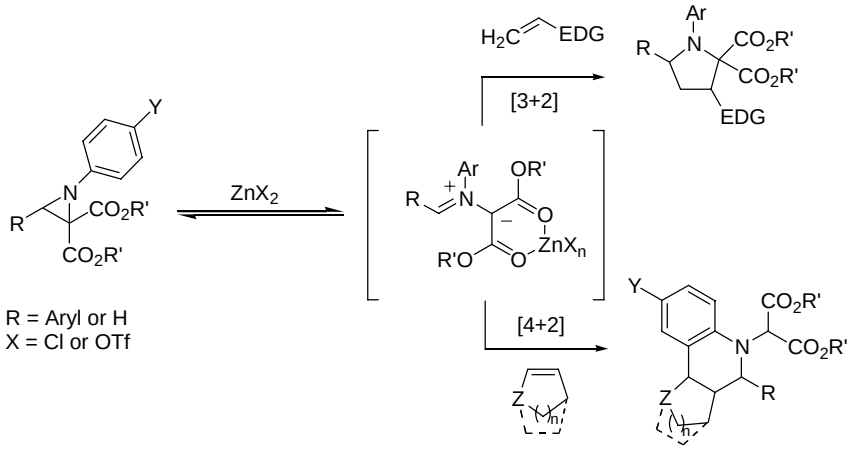
ABSTRACT

PATRICK DENNIS POHLHAUS: Lewis Acid-Promoted Cycloaddition Reactions of Aziridines and Cyclopropanes
(Under the direction of Jeffrey Scott Johnson)

I. Lewis Acid-Promoted Carbon-Carbon Bond Cleavage of Aziridines: Divergent Cycloaddition Pathways of the Derived Ylides

The formation of azomethine ylides from aziridines under Lewis acidic conditions and the productive reactivity of these species are described. Efficient carbon-carbon bond cleavage of aziridines through treatment with stoichiometric or catalytic amounts of Zn(II) salts has been shown to occur under relatively mild conditions. Depending on the constitution of the dipolarophile, the resulting azomethine ylides undergo cycloadditions with electron-rich olefins in either a [3+2] or [4+2] manner producing pyrrolidine or tetrahydroquinoline derivatives.

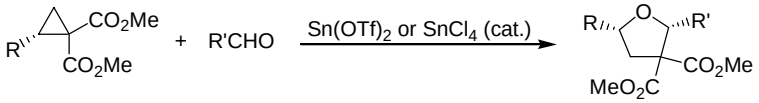


II. Heterocycle Synthesis Via [3+2] Reactions of Cyclopropanes

A review of the literature concerning the use of cyclopropanes in the one-step synthesis of five-membered heterocycles is presented. Methodology for the convenient, stereoselective preparation of substituted γ-lactones, γ-lactams, tetrahydrofurans, pyrrolidines, and various other heterocycles from simple cyclopropane precursors is described. Lewis acid-promotion/catalysis, as well as thermal methods for the ring cleavage of cyclopropanes are discussed. Where possible, proposed models are given for the stereochemical outcome of these annulation reactions.

III. Enantiospecific and Diastereoselective Tin-Catalyzed Cycloaddition Reactions of Aldehydes and Donor-Acceptor Cyclopropanes: The Synthesis of 2,5-Disubstituted Tetrahydrofurans

The diastereoselective synthesis of a variety of *cis*-2,5-disubstituted tetrahydrofurans via Sn(II)- or Sn(IV)-catalyzed cycloaddition reactions of donor-acceptor (D-A) cyclopropanes with aldehydes is described. In some cases, the use of enantioenriched cyclopropane has been shown to afford optically active tetrahydrofuran derivatives with excellent stereochemical transfer. Evidence is presented supporting an S_N2 reaction in which the aldehyde participates as a nucleophilic species.



R = Aryl, heteroaryl, alkenyl, alkyl
R' = Aryl, heteroaryl, alkenyl, alkynyl, alkyl

IV. Application of the Tin-Catalyzed Cyclopropane/Aldehyde Cycloaddition Reaction: Progress Towards the 2-Oxabicyclo[4.3.0]nonane Core of the Cladiellin Diterpenes

Efforts towards the construction of the hydroisobenzofuran core common to the cladiellin diterpenes are discussed. The use of a model system in the catalytic cyclopropane/aldehyde cycloaddition manifold has been explored. The stereochemical results of this successful reaction are discussed in the context of possible extension to a more sophisticated system. Synthetic efforts herein have disclosed a potential straightforward route for the preparation electron-poor alkenylidene cyclopropanes via an unprecedented 3-*exo*-*dig* cyclization pathway.

To my parents, Timothy and Rosina Pohlhaus, for whose
constant love I am forever grateful

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I would like to thank Professor Jeffrey Johnson for allowing me to be one of the students in his first graduating class. I can't begin to imagine the difficulty of training new students, securing money, and jump-starting a lab, all at the same time. As hard as it may have been, Jeff was always willing to lend a hand when it was needed. I remember Jeff telling me when I started working in lab, "I'm willing to help you as much or as little as you wish," and he kept his word throughout my graduate career. I am deeply grateful for the guidance Jeff has given me over the past five years and grateful as well for the humble manner in which he gave it.

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I give my thanks to the members of by defense committee, Professors James Morken, Joseph Templeton, Maurice Brookhart, and Valerie Sheares Ashby. Additionally, I would like to thank Professors Michael Gagné, and Joseph DeSimone for their presence on my preliminary orals committee.

Above all, I extend my deepest love and thanks to my parents, Timothy and Rosina, and my brother Tim. There is no way to express how grateful I am to my family, and I know that I would not be where I am today without them. They have been selfless in their sacrifices and have done so much to help me fulfill my dreams.

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LIST OF ABBREVIATIONS AND SYMBOLS

p-ABSA	*p*-acetamidobenzenesulfonyl azide
aq.	aqueous
BINOL	1,1'-bi-2-naphthol
br	broad
n-Bu	*n*-butyl
n-BuLi	*n*-butyl lithium
t-Bu	*tert*-butyl
cat.	catalytic amount or catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
conv.	conversion
COSY	correlated spectroscopy
d	days or doublet
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
S-DOSP	*N*-[(4-dodecylphenyl)sulfonyl]-(*L*)-prolinato
d.r.	diastereomeric ratio
E^+	electrophile
ee	enantiomeric excess
eq	equation
equiv	equivalents
Et	ethyl
Et_2O	diethyl ether

EtOAc	ethyl acetate
FID	flame ionization detector
GC	gas chromatography
h	hour
hν	light
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
kPa	kilopascal
L	ligand
L.A.	Lewis acid
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
Me	methyl
mg	milligram
MHz	megahertz

min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MS	molecular sieves
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
NR	no reaction
Nu^-	nucleophile
[O]	oxidation
ORTEP	Oak Ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
rac	racemic
R_f	retention factor
r.t.	room temperature
SFC	supercritical fluid chromatography
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS	trimethylsilyl
t_r	retention time
TsOH	*p*-toluenesulfonic acid
δ	chemical shift
μL	microliter

CHAPTER 1

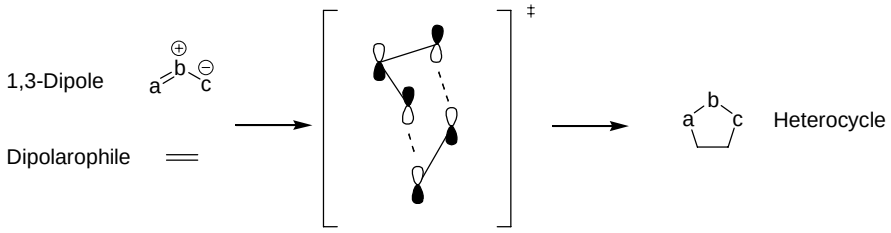
LEWIS ACID-PROMOTED CARBON-CARBON BOND CLEAVAGE OF AZIRIDINES: DIVERGENT CYCLOADDITION PATHWAYS OF THE DERIVED YLIDES

1.1 Introduction

Pyrrolidines and pyrrolines represent extremely important structural motifs in organic chemistry due to their frequent occurrence in biologically active compounds and natural products. The significance of these five-membered heterocycles has led to the development of numerous methods for their preparation.[1] However, when considering the synthesis of pyrrolidine derivatives, the number of bonds that can be made in a single synthetic step and the stereochemical control of these connections must be carefully considered. This is especially important as the complexity of the target substrate increases. In a single synthetic operation, the 1,3-dipolar cycloaddition reaction of an azomethine ylide with an alkene (or alkyne) forms two new carbon-carbon bonds with up to four new stereocenters.[2,3] Moreover, these constructions are typically made in a very stereo- and regio-controlled fashion. It is for this reason that the dipolar cycloaddition of azomethine ylides is arguably the most powerful method for the synthesis of pyrrolidines.[4]

A 1,3-dipolar cycloaddition reaction involves the interaction of 4 π electrons delocalized over a three-atom fragment (the dipole) and a π–bond (the dipolarophile), with bond formation at the termini of the two fragments, thereby forming a 5-membered ring. At least one atom in the dipole must be a heteroatom, and consequently a heterocycle is always produced. Dipolar cycloaddition reactions are pericyclic reactions and therefore adhere to the Woodward-Hoffman rules. The cycloaddition obeys a $[_{\pi}4_s + _{\pi}2_s]$ concerted mechanism where bond formation is suprafacial in both the dipole and dipolarophile (**Scheme 1-1**).[5-7]

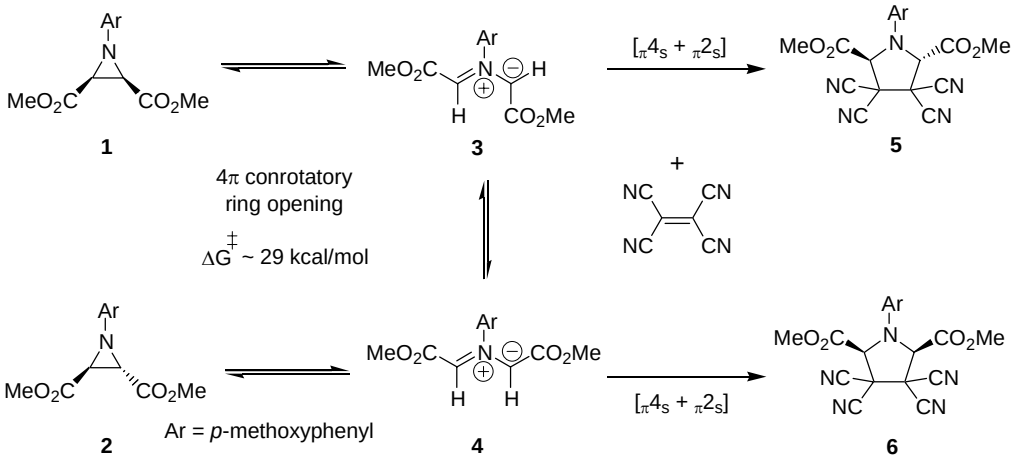
Scheme 1-1. Bond Formation in 1,3-Dipolar Cycloaddition Reactions



Pioneering work on the use of 1,3-dipoles, specifically azomethine ylides, was carried out by Huisgen in the 1960's.[8-13] It was found that upon separately heating epimeric *cis*- and *trans*-dimethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylates **1** and **2** in the presence of a highly active dipolarophile, single stereoisomeric pyrrolidines **5** and **6**, respectively, were produced (**Scheme 1-2**). This result is one of the first reports on the generation of an azomethine ylide. The stereodefined 1,3-dipoles **3** and **4** are produced upon electrocyclic ring opening of the aziridine in a conrotatory fashion in accordance with the Woodward-Hoffman rules for a 4π-system. The azomethine ylides then undergo cycloaddition with the dipolarophile in a $[_{\pi}4_s + _{\pi}2_s]$ fashion, directly transferring the relative stereochemical

information in the aziridine to the stereochemistry of the pyrrolidine. The rate of the reaction was shown to be independent of the concentration of dipolarophile, indicating that the rate-limiting step of this process was initial cleavage of the carbon-carbon bond. The activation energy for this process, leading to the intermediate azomethine ylide from either **1** or **2**, was calculated to be approximately 29 kcal/mol at 100 °C, which translates to rather forcing conditions. In the absence of a very active dipolarophile (dialkyl azodicarboxylates, tetracyanoethylene or dimethyl acetylenedicarboxylate), isomerization between the *anti*-dipole **3** and the *syn*-dipole **4** occurs and a mixture of pyrrolidine stereoisomers is produced from diastereomerically pure aziridine.

Scheme 1-2. Stereospecific Ring Opening of Aziridines with Stereospecific Cycloaddition of the Derived Azomethine Ylides

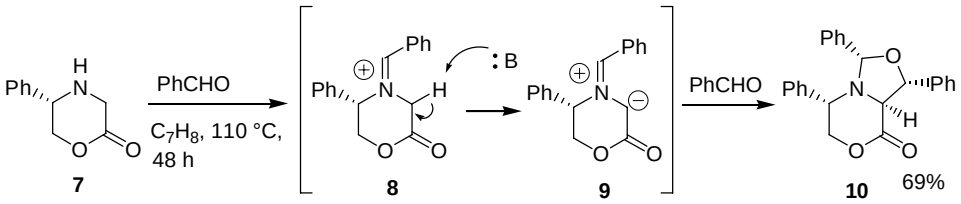


The obvious value of the azomethine ylide in the expeditious construction of nitrogen containing five-membered rings has spurred the development of a number of unique methods for their generation.[3,4] The majority of procedures involve the formation of stabilized azomethine ylides, that is, ylides with one or more electron-withdrawing groups attached to a

terminus. Due to their instability, the ylides are typically generated *in situ* and treated directly with a dipolarophile.

Condensation of aldehydes with secondary α-amino esters is a common route to stabilized azomethine ylides. Reaction of amino ester **7** with benzaldehyde produces a stabilized azomethine ylide (**9**) upon deprotonation of the intermediate iminium ion (**8**). This ylide can be trapped with an alkene or added to a second equivalent of aldehyde affording an oxazolidine (**10**) (**Scheme 1-3**).[14]

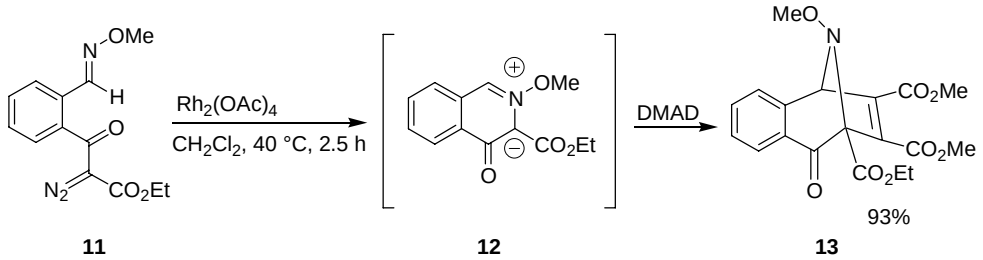
Scheme 1-3. Azomethine Ylide Generation from a Secondary α-Amino Ester and Aldehyde



7 **8** **9** **10**

Azomethine ylides can also be formed via metal induced decomposition of an α-diazo carbonyl compound in the presence of an imine or oxime.[15,16] When *E*-diazo *O*-methyloxime **11** is treated with $Rh_2(OAc)_4$, the keto carbenoid that is formed reacts intramolecularly with the oxime nitrogen lone pair to form cyclic azomethine ylide **12** (**Scheme 1-4**). This dipole then reacts intermolecularly with dimethyl acetylenedicarboxylate producing methoxylamine **13**.

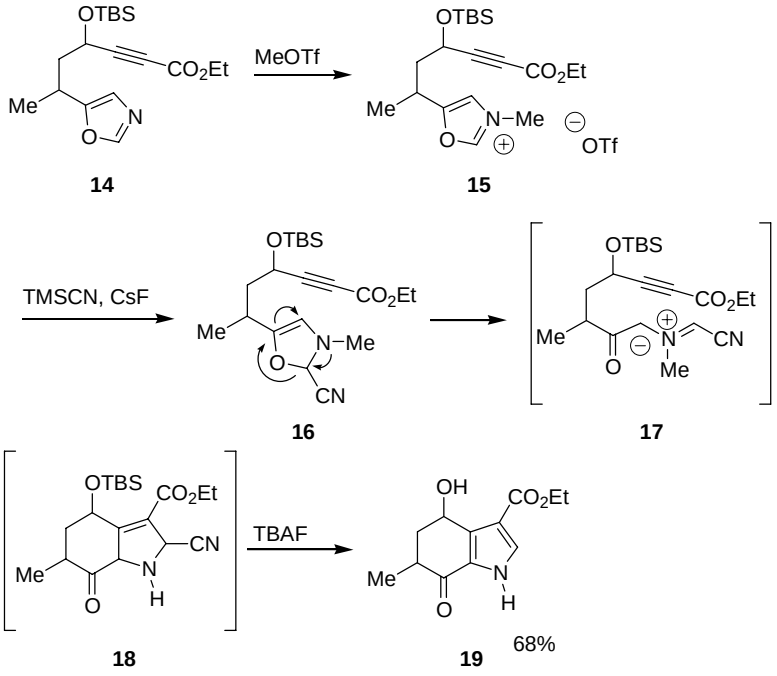
Scheme 1-4. Azomethine Ylide Generation from a Carbenoid and Oxime



11 **12** **13**

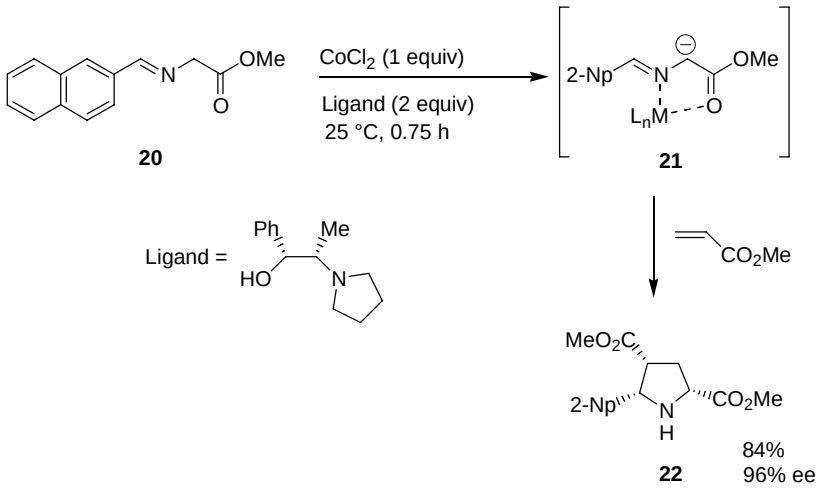
Thermally unstable 4-oxazolines may also be used for the generation of stabilized azomethine ylides.[17,18] These precursors are easily prepared via *N*-alklyation of an oxazole followed by hydride reduction or nucleophilic attack at the 2-position. The generation and intramolecular trapping of an azomethine ylide from oxazole **14** demonstrates this methodology (**Scheme 1-5**).[19] The oxazole is treated with methyl triflate affording oxazolium salt **15**. Upon exposure to a cyanide source, the salt is converted to 4-oxazoline **16**, which spontaneously opens to azomethine ylide **17**. Trapping by the tethered dipolarophile affords tetrahydroindolone **19** after elimination of hydrogen cyanide and subsequent treatment with TBAF.

Scheme 1-5. Azomethine Ylide Generation from a 4-Oxazoline



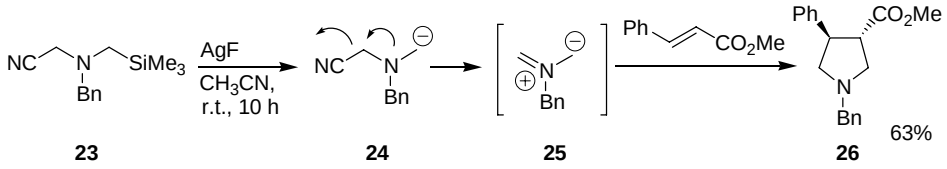
Grigg originally showed that the treatment of an α-amino acid derived imine with a metal salt and a tertiary amine is a very mild way of generating an azomethine ylide in which the nitrogen atom is coordinated to a metal center.[20] These species have a reactivity profile similar to that of standard azomethine ylides and are frequently referred to as metallo-azomethine ylides. In a quintessential reaction, glycine imine **20** is treated with $CoCl_2$ and an ephedrine derived ligand in a methyl acrylate solution, affording pyrrolidine **22** as a single regioisomer and diastereomer in 96% ee (**Scheme 1-6**). The active species is believed to be *syn*-metallo-azomethine ylide **21**, formed via nitrogen-metal coordination, followed by deprotonation. Since the initial discovery of these metallo-ylides, a number of methods for their catalytic generation and asymmetric trapping have been developed.[21-23]

Scheme 1-6. Metallo-Azomethine Ylide Generation from an Imine and Metal Salt/Amine



Nonstabilized azomethine ylides may also be generated. An example of this is the desilylation of α-cyanoaminosilanes developed by Padwa.[24] Desilylation of **23** by AgF induces cyanide loss to form symmetrical azomethine ylide **25**. This intermediate undergoes intermolecular cycloaddition with methyl cinnamate to furnish *trans*-3,4-pyrrolidine **26** exclusively (**Scheme 1-7**). Several other methods for the generation of nonstabilized azomethine ylides have been developed based on desilylation strategies.[3]

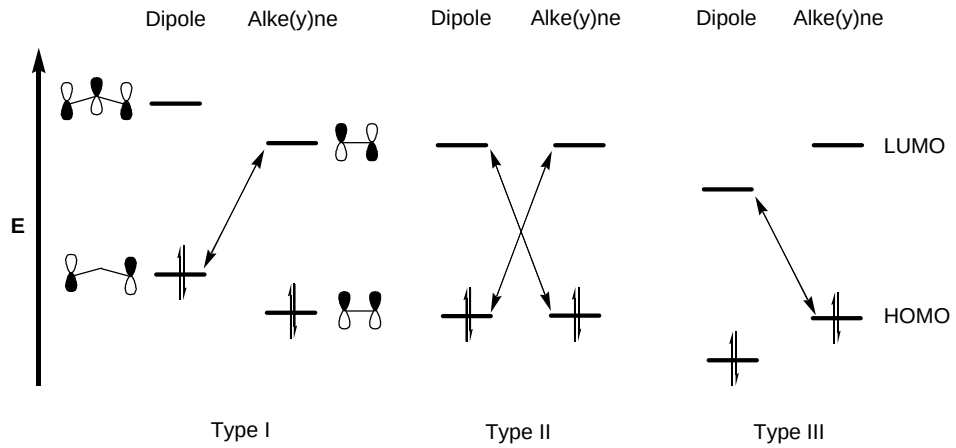
Scheme 1-7. Generation of a Nonstabilized Azomethine Ylide via Desilylation/Elimination



The pericyclic nature of 1,3-dipolar cycloaddition reactions allows transition state examination using frontier molecular orbital (FMO) analysis.[5-7,25] Thus, the HOMO and LUMO interactions of the dipole and dipolarophile are primarily responsible for reactivity.

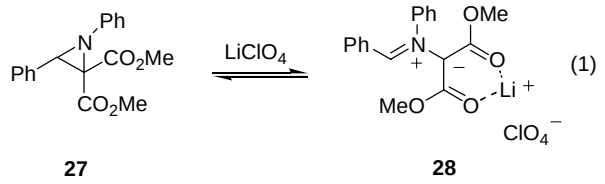
More specifically, the frontier molecular orbitals that are closest in energy in both of the partners contribute most to the stabilization of the transition state, and their interaction is considered to be dominant. The frontier orbital arrangement of a 1,3-dipole and dipolarophile corresponds to that of the all-carbon allyl anion system and ethylene, respectively. In this system both HOMO and LUMO pairs on the reactants possess the correct symmetry for interaction, and therefore the dominant interaction is determined by the electronics of the particular pair of reactants in question (**Figure 1-1**). In a type I cycloaddition, the dominant interaction is between the HOMO of the dipole and the LUMO of the dipolarophile. The rate of cycloaddition with a dipole exhibiting this behavior will increase as the dipolarophile becomes more electron deficient and the orbital energy gap decreases. The vast majority of azomethine ylide cycloadditions are type I. Conversely, the dominant interaction in a type III cycloaddition is between the LUMO of the dipole and HOMO of the dipolarophile. Thus, the rate of cycloaddition will increase as the dipolarophile becomes more electron rich and these orbitals become closer in energy. If the rate of cycloaddition increases with a particular dipole as the dipolarophile becomes either more electron rich or deficient, the reactions are considered to be Type II. In this case, both of the symmetry allowed orbital interactions ($HOMO_{dipole}$-$LUMO_{dipolarophile}$ and $LUMO_{dipole}$-$HOMO_{dipolarophile}$) are deemed important in the reactivity. Additionally, analysis of the orbital coefficients in the dominant interaction allows prediction of the regiochemistry in 1,3-dipolar cycloaddition reactions. The favored transition state will be the one in which the terminal atoms with the largest coefficients in the dominant interacting orbitals overlap.

Figure 1-1. Frontier Molecular Orbital Interactions in 1,3-Dipolar Cycloaddition Reactions



1.2 Background

The chemistry of aziridines is dominated by the reactivity of the carbon-nitrogen bonds.[26] The most notable exception to this reactivity pattern is the thermal or photochemical electrocyclic ring opening of aziridines to give azomethine ylides as transient intermediates resulting from carbon-carbon bond cleavage (see **1.1**). This reaction manifold enjoys a prominent role in pyrrolidine synthesis due to the facility with which the derived 1,3-dipoles may be trapped in [3+2] cycloaddition reactions; however, the development of mild variants of this C–C bond heterolysis is largely unexplored. It was therefore of interest to develop a mild, selective [3+2] cycloaddition of aziridines. A report by Carrie suggested that this indeed was possible.[27] In this report, the authors described $LiClO_4$ as a Lewis acid capable of achieving carbon-carbon bond cleavage in aziridine **27**. ^1H NMR spectroscopy indicated quantitative conversion of that aziridine to its derived lithium coordinated azomethine ylide **28** (eq 1). Despite the large effective concentration of the ylide complex in that system, two separate experiments showed a rate decrease in the cycloaddition with



27 28

electron-poor dimethyl fumarate, relative to the same reaction carried out in the absence of $LiClO_4$. These results suggest that the cycloaddition producing pyrrolidine **30** was occurring through free azomethine ylide **29**, and that $LiClO_4$ served only to reduce the effective concentration of **29** through the equilibrium with metal-bound azomethine ylide **28** (**Scheme 1-8**). It was hypothesized that a metal-coordinated ylide such as **28** would be extremely electron-poor; thus, its cycloaddition reactions would be of type III in the Sustmann classification system of 1,3-dipolar cycloadditions. HOMO/LUMO matching suggested that rate acceleration should be observed with electron-rich dipolarophiles. (**Figure 1-2**).[5]

Scheme 1-8. Retardation of Cycloaddition with Dimethyl Fumarate Through Metal Coordinated Azomethine Ylide **28**

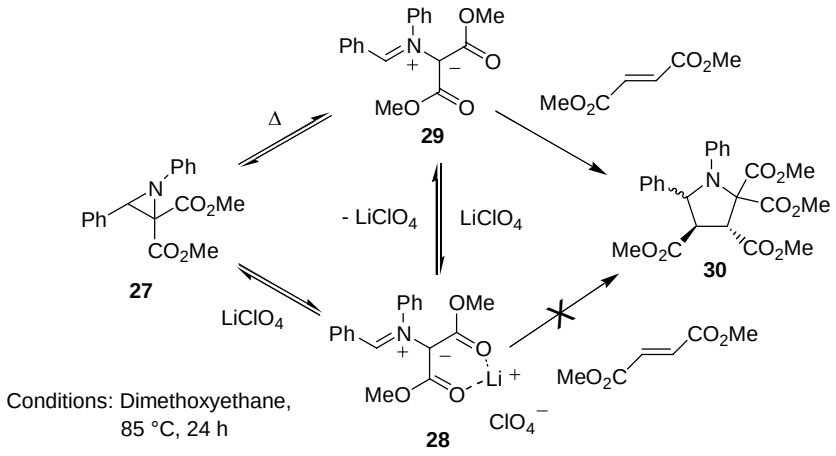
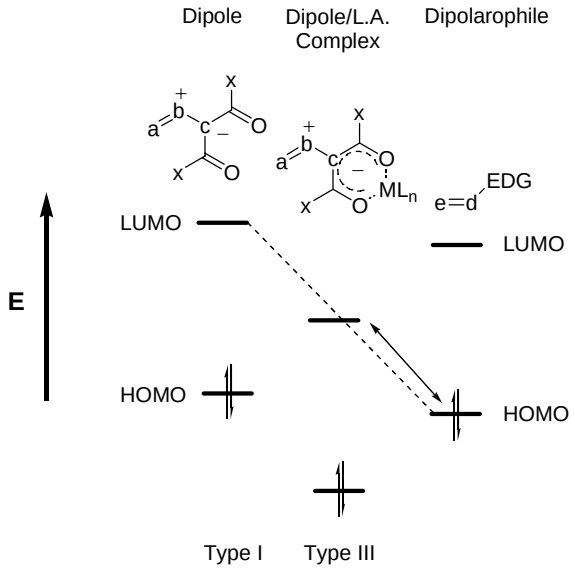
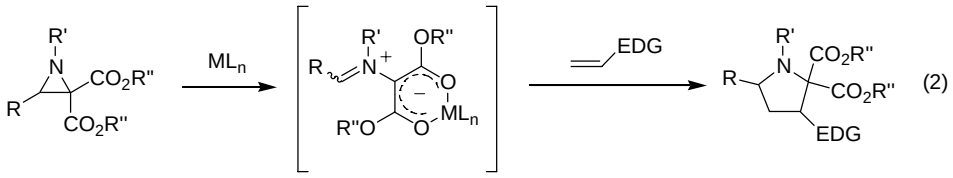


Figure 1-2. Perturbation of 1,3-Dipole Frontier Molecular Orbitals Upon Lewis Acid Complexation



1.3 Results and Discussion[28]

This study focused on Lewis acid assistance in the carbon-carbon bond cleavage of aziridines and subsequent cycloadditions of the metal-bound azomethine ylides to electron-rich dipolarophiles (eq 2).[29]

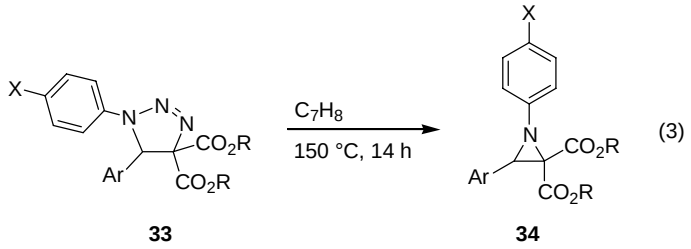


(2)

1.3.1 Substrate Synthesis

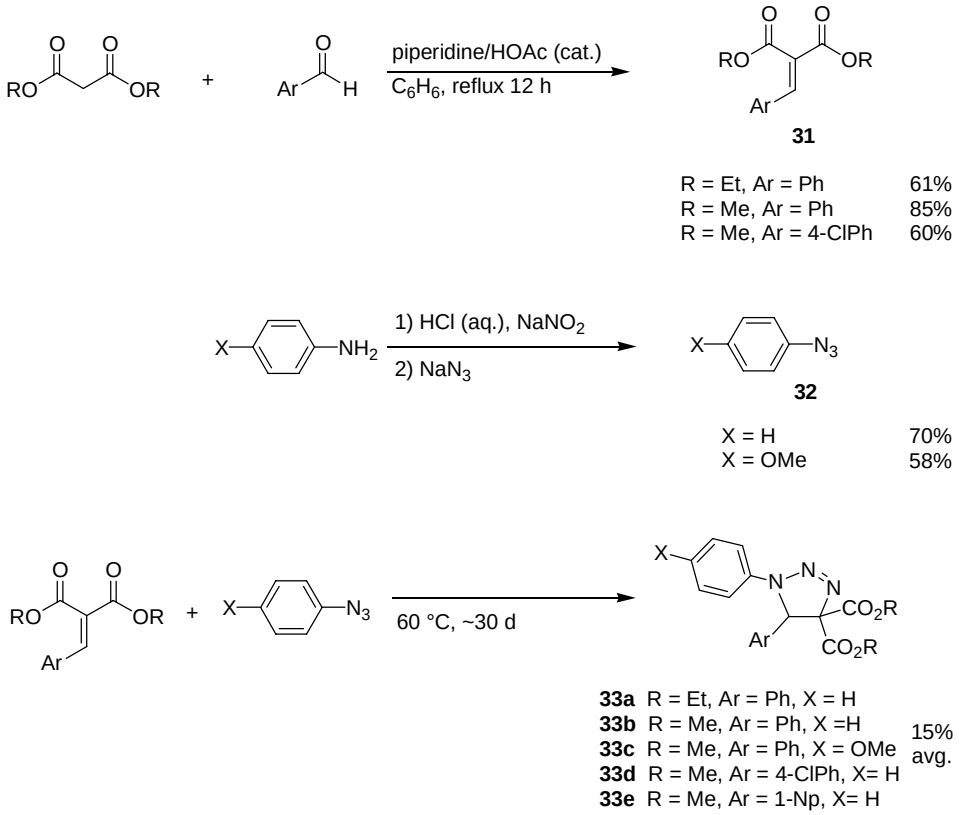
Based on the results of Carrie, 1,3-diaryl-2,2-dicarboxylic acid dialkyl ester aziridines (**34**) were initially chosen for this study. Their syntheses were achieved by the thermolysis of appropriately substituted triazolines (**33**) immediately prior to use without purification (eq

3).[30] The triazolines were each synthesized in three steps (**Scheme 1-9**). Benzylidene malonates (**31**) were prepared from the corresponding aldehydes and dialkyl malonates under Knoevenagel condensation conditions employing a catalytic amount of piperidinium acetate with azeotropic removal of water.[31] Aryl azides (**32**) were prepared from the appropriate aniline by treatment of the *in situ* formed diazonium salt with sodium azide.[32] Triazolines (**33a-33e**) were synthesized by cycloaddition of the aryl azides with benzylidene malonates at an elevated temperature.[30,33] These reactions were not complete but were stopped after 30 days in the interest of time. Purification by flash chromatography afforded the pure triazolines in a typical yield of about 15%.



33 **34** (3)

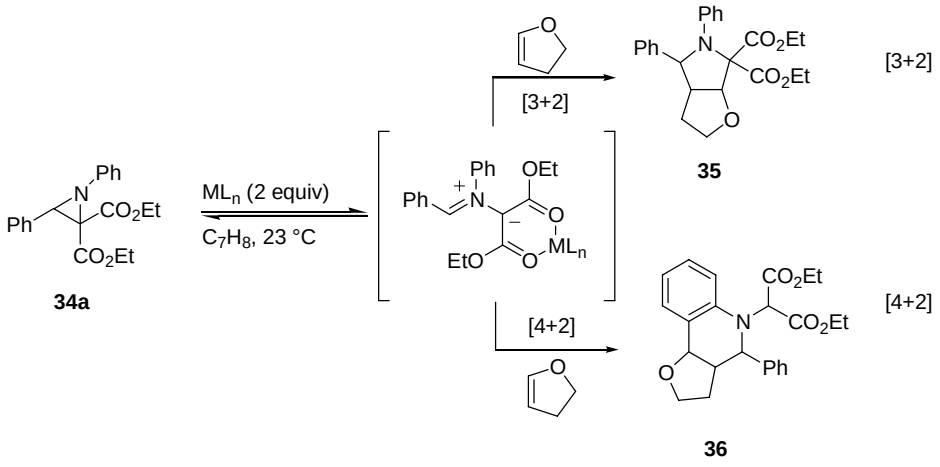
Scheme 1-9. Synthesis of Aziridine Precursors



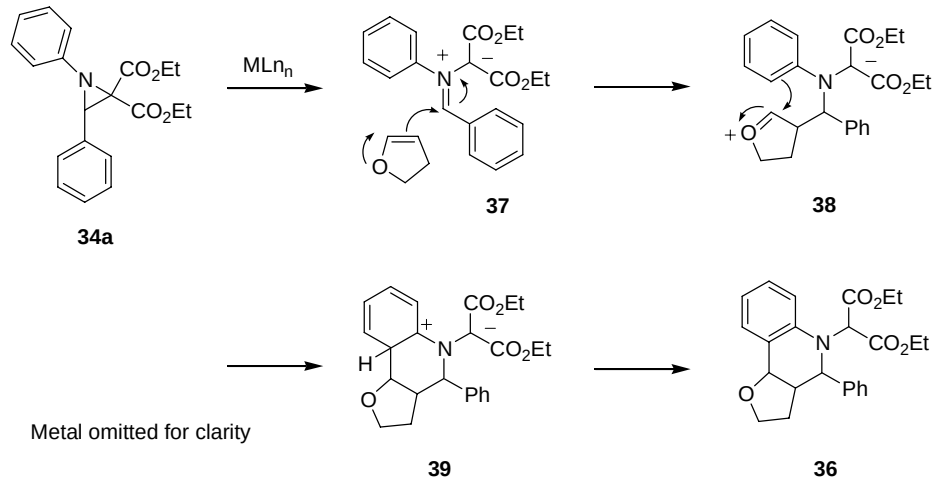
1.3.2 Reaction Development

To evaluate the possibility of effecting metal-promoted cycloadditions involving aziridine **34a**, a representative selection of Lewis acids including $Mg(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, and $SnCl_2$ were tested in their ability to form adduct **35** in the presence of dihydrofuran. In addition to the anticipated [3+2] cycloadduct **35**, a [4+2] cycloadduct (**36**) was concurrently formed (**Scheme 1-10**). This adduct is most likely derived from a Mannich-type addition of dihydrofuran to the initially formed ylide **37**, followed by intramolecular Friedel-Crafts alkylation of species **38**. Zwitterion **39** then undergoes proton transfer to restore aromaticity affording [4+2] adduct **36** (**Scheme 1-11**).

Scheme 1-10. Test Reaction for Lewis Acid Survey

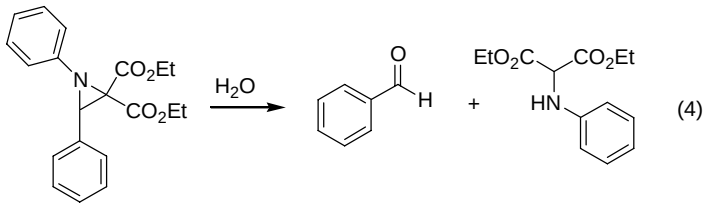


Scheme 1-11. Proposed Mechanism for the Formation of the [4+2] Cycloadduct **36**



At the outset of studying this system, it became apparent that aziridine **34a** undergoes instantaneous quantitative decomposition to benzaldehyde and to substituted aniline **40** upon exposure to water (eq 4).[30] It was therefore necessary to operate under rigorously anhydrous conditions. The primary focus of the initial screen was to optimize the ratio of (**35**+**36**):**40**. This ratio was taken as a measure of reaction efficiency, since any unreacted aziridine is immediately hydrolyzed upon workup, affording the aniline (**40**). Zn(II) salts, in particular

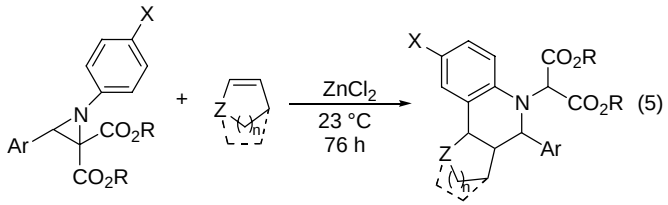
$ZnCl_2$, were most suitable promoters of the cycloaddition and were selected for further examination.

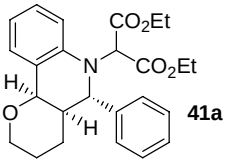
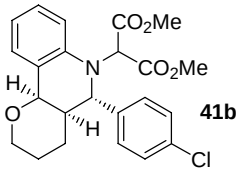
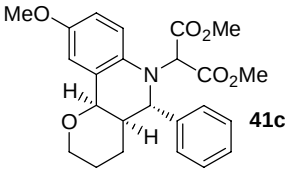
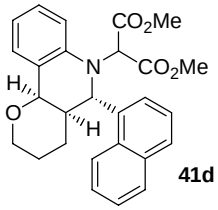


34a **40**

Under optimal conditions, cycloadditions were performed using a variety of aziridines and electron-rich alkenes (eq 5). Cyclic dipolarophiles were observed to proceed primarily or exclusively through the [4+2] pathway yielding highly substituted tetrahydroquinolines with excellent diastereoselectivity (**Table 1-1**). Only in the case of 2,3-dihydrofuran (entry 8) does the [3+2] pathway become substantial.

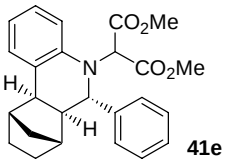
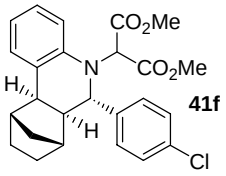
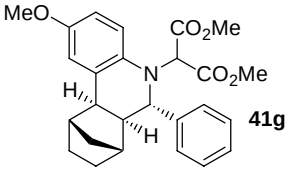
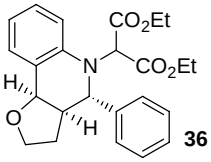
Table 1-1. Zn(II)-Promoted [4+2] Cycloadditions of Aziridines and Electron-Rich Alkenes (Eq 5)[a]



Entry	Olefin (eqiuv)	X, Ar	Product	d.r.	yield[b] ([4+2]/[3+2])
1[e]	 (15.1)	H, Ph	 **41a**	>99:1	79% (15:1)
2	 (15.1)	H, 2-ClPh	 **41b**	>99:1	72% (7.8:1)
3	 (15.1)	MeO, Ph	 **41c**	>99:1	65% (26:1)
4	 (15.1)	H, 1-Np	 **41d**	5.1:1	49%[c]

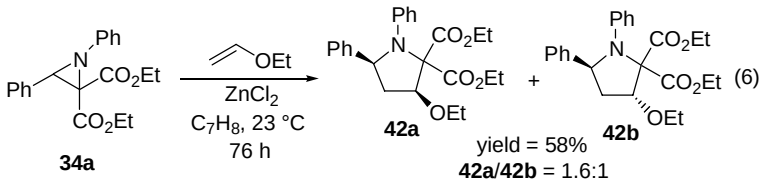
a) Aziridine (1.0 equiv), $ZnCl_2$ (1.2 equiv). b) Isolated yield of analytically pure [4+2] adducts only, except where noted. c) Diastereomers inseparable. d) Yield is combined for both [4+2] and [3+2] products. e) Solvent for entries 1-4 is THF. f) Solvent for entries 5-7 is CH_2Cl_2. g) Solvent for entry 8 is toluene.

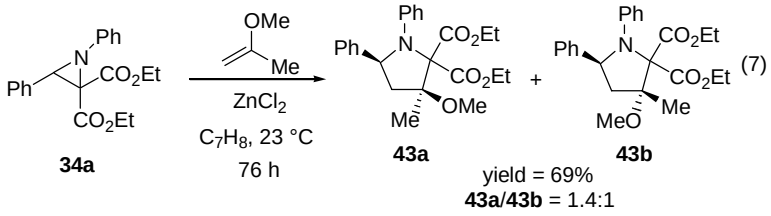
Table 1-1, continued. Zn(II)-Promoted [4+2] Cycloadditions of Aziridines and Electron-Rich Alkenes (Eq 5)[a]

Entry	Olefin	X, Ar	Product	d.r.	yield[b] ([4+2]/[3+2])
5[f]	 (3.0)	H, Ph	 **41e**	9:1	82%
6	 (3.0)	H, 2-ClPh	 **41f**	2.8:1	71%
7	 (3.0)	MeO, Ph	 **41g**	>99:1	80%
8[g]	 (21.7)	H, Ph	 **36**	10:1	55%[d] (3.5:1)

a) Aziridine (1.0 equiv), $ZnCl_2$ (1.2 equiv). b) Isolated yield of analytically pure [4+2] adducts only, except where noted. c) Diastereomers inseparable. d) Yield is combined for both [4+2] and [3+2] products. e) Solvent for entries 1-4 is THF. f) Solvent for entries 5-7 is CH_2Cl_2. g) Solvent for entry 8 is toluene.

Acyclic enol ethers intercept the metal-coordinated ylide via a different mechanistic pathway: in the cases of ethyl vinyl ether (eq 6) and 2-methoxypropene (eq 7) only the [3+2] pathway is observed. The derived pyrrolidines are produced in 58 and 69% yield, respectively, with modest diastereocontrol. It is important to note that these cycloadditions cannot be effectively performed in the absence of Lewis acid. Dihydrofuran yields none of the [4+2] or [3+2] adduct under thermal conditions (toluene, sealed tube, 160 °C, 2 d) in the presence of **34a**, while [3+2] adduct **43** is obtained in only 16% yield under the same conditions using 2-methoxypropene. These experiments indicate that Lewis acid promotion is essential and provide additional support for the type III classification of this family of cycloadditions. It is not clear from the available data whether **42** and **43** are formed by concerted or stepwise mechanisms. The cause for bifurcation in mechanism from [4+2] to [3+2] is also not known, but may be steric in nature.

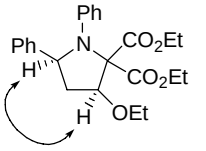




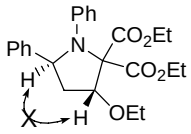
The relative stereochemistries of [3+2] cycloadducts **42** and **43** were determined by NOESY analysis. The relative stereochemistries of [4+2] adducts **36** and **41a-c** were also determined by NOESY analysis. The pertinent resonances in the ^{1}H NMR spectra of **41d**

were not sufficiently resolved for direct analysis, therefore this assignment was made by analogy to **41a-c**. Representative NOE enhancements are shown in **Figure 1-3**. Single crystal X-ray analysis was employed in the determination of the relative stereochemistry of norbornylene adduct **41f**, and the stereochemistries of compounds **41e** and **41g** were assigned by analogy. The X-ray structure of **41f** is shown in **Figure 1-4**.

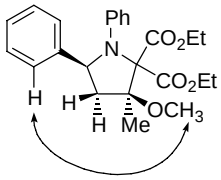
Figure 1-3. Observed NOE Enhancements in [3+2] and [4+2] Cycloadducts



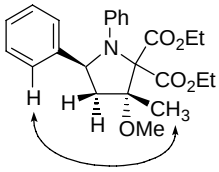
42a



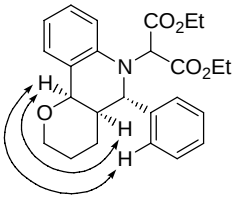
42b



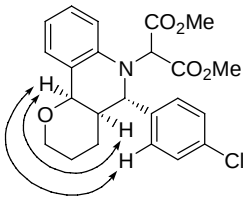
43a



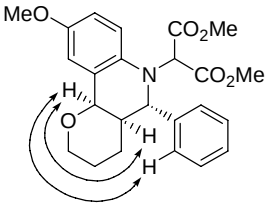
43b



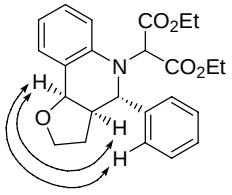
41a



41b

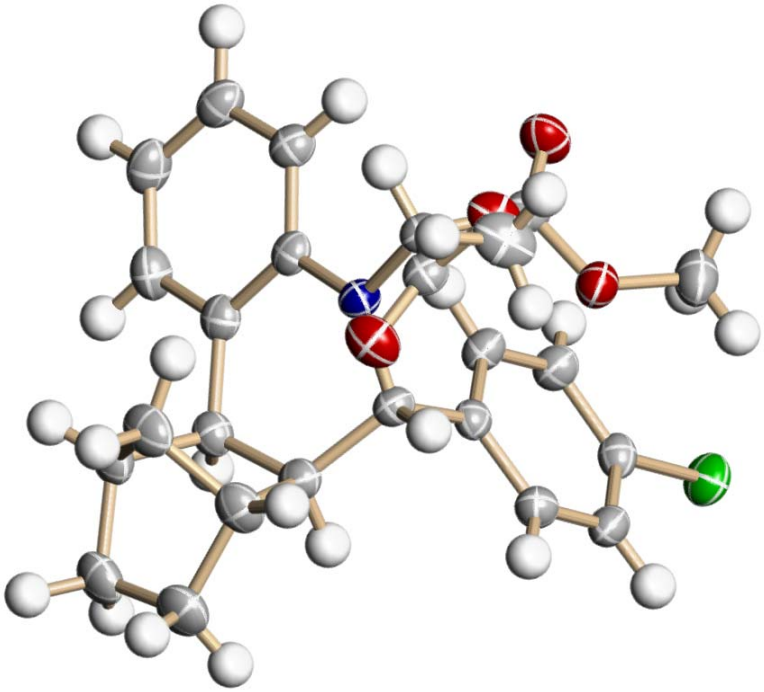


41c

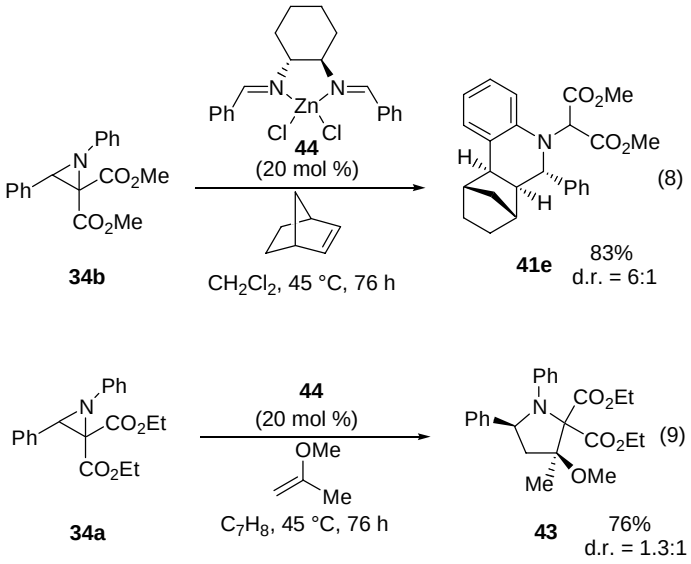


36

Figure 1-4. ORTEP of **41f**



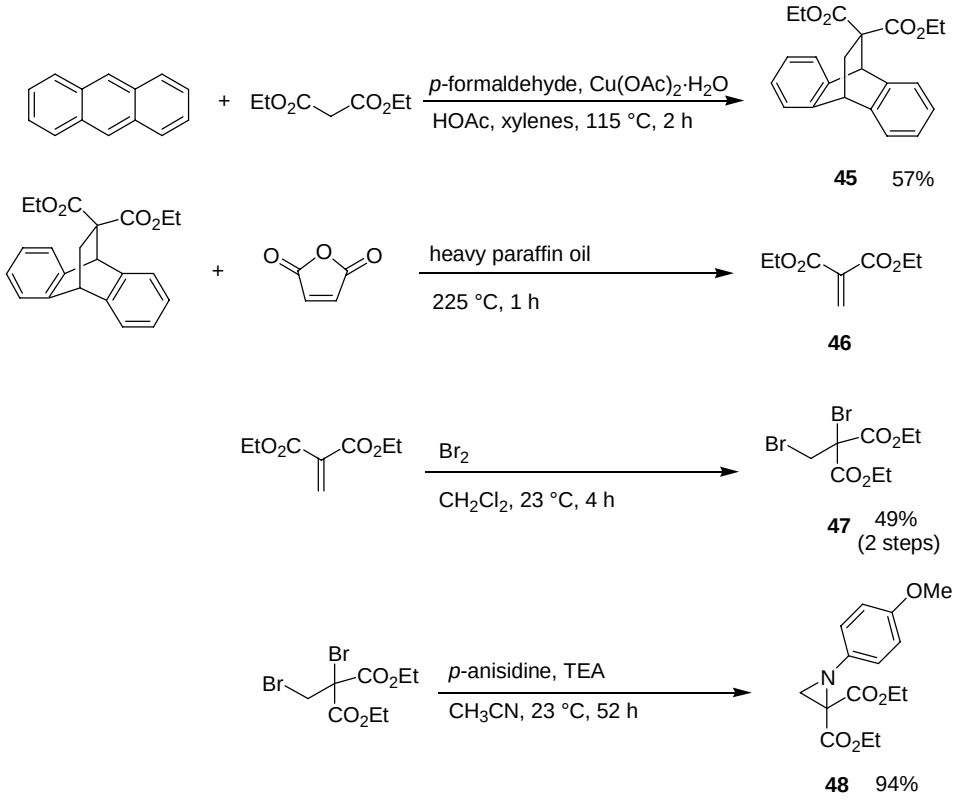
Efforts to render the reaction catalytic in Lewis acid have been successful. $ZnCl_2$ alone provides only modest yields, but the derived bis(imine) complex (*N*,*N*'-dibenzylidene-cyclohexane-1,2-diamine)$ZnCl_2$ (**44**) provided good yields in both the [4+2] and [3+2] cycloadditions at 20 mol % catalyst loading (eq 8 and 9). The $ZnCl_2$ complex was more effective than the analogous $Zn(OTf)_2$ complex. While the products exhibited <5% enantiomeric enrichment, the results demonstrate that these mild cycloadditions may be conducted under catalytic conditions.



Owing to the necessity of generating aziridines **34** immediately prior to use and the need to handle them in an inert atmosphere (glove box), a more air stable aziridine structure was sought. It was thought that removal of the aryl group in the 3-position would reduce nucleophilic attack by water and hence aziridine decomposition. It was also postulated that retaining the geminal diester moiety would still allow bidentate coordination to a Lewis acid and stabilization of a latent azomethine ylide. It was found that large quantities of aziridines unsubstituted at the 3-position could be prepared employing methodology developed by De Keyser for the synthesis of methylene malonates (**Scheme 1-12**).[34] The methylene malonate derived from diethyl malonate (**46**) is highly unstable under the conditions of its synthesis but may be protected as its stable Diels-Alder adduct (**45**) by *in situ* by trapping with anthracene. The product (**46**) is then liberated through a retro Diels-Alder/Diels-Alder sequence and distilled directly from the reaction pot. Dibromination, followed by a double alkylation of *p*-anisidine with **47**,[35] affords the desired unsubstituted aziridine **48** in good yield. As predicted, aziridine **48** is completely bench-stable and shows no appreciable decomposition

when stored in the freezer for months. *N-para*-methoxyphenyl aziridine **48** was chosen to allow simple oxidative *N*-deprotection of pyrrolidine products.

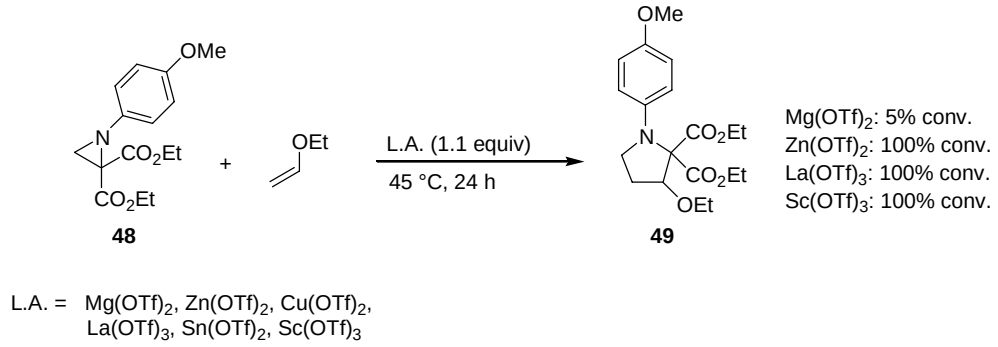
Scheme 1-12. Synthesis of Aziridines Unsubstituted at the 3-Position



A Lewis acid screen was then conducted for the cycloaddition of aziridine **48** with ethyl vinyl ether (**Scheme 1-13**). The results of this screen indicate that this more robust aziridine does in fact undergo Lewis acid assisted azomethine ylide formation and dipolar cycloaddition to an electron-rich dipolarophile. The reaction is also very dependent on the metal used. While $Zn(OTf)_2$, $La(OTf)_3$, and $Sc(OTf)_3$, give relatively clean conversion to the desired product, the use of $Cu(OTf)_2$ and $Sn(OTf)_2$ result in decomposition of the aziridine

with no product formation. $Mg(OTf)_2$ gives only slight conversion to the pyrrolidine, with recovered starting material. It was necessary to carry out these reactions at a slightly elevated temperature (45 °C) relative to the 3-aryl aziridines (**34**), which reacted at room temperature. Due to its low poly(ethyl vinyl ether) formation compared to other Lewis acids, $Zn(OTf)_2$ was chosen for further study. The reaction was shown to be catalytic in this metal as well. Treatment of aziridine **48** with 20 mol % $Zn(OTf)_2$ in the presence of ethyl vinyl ether at 40 °C for 40 h afforded pyrrolidine **49** in 71% yield.

Scheme 1-13. Lewis Acid Screen for the Cycloaddition of Aziridine **48** and Ethyl Vinyl Ether

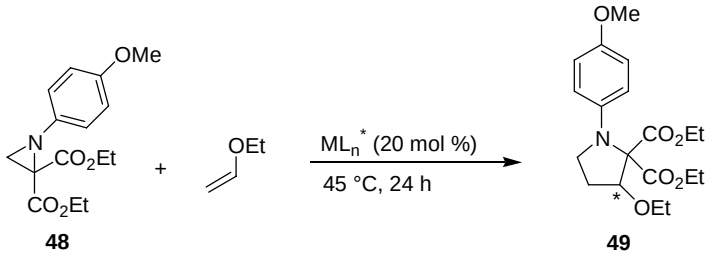


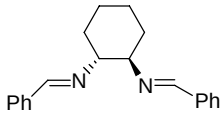
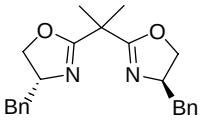
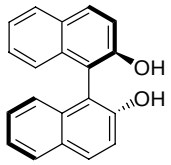
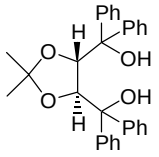
1.3.3 Efforts Towards Asymmetric Induction

With the discovery of the catalytic cycloaddition of **48** with an electron-rich dipolarophile, an asymmetric version of this chemistry was then sought. A screen was subsequently conducted employing Zn(II) salts in combination with chiral bidentate ligands (**Table 1-2**). The use of the complex derived from *N*,*N*'-dibenzylidene-cyclohexane-1,2-diamine and $Zn(OTf)_2$ showed a drastic decrease in conversion relative to free $Zn(OTf)_2$ (entries 1 and 2). Generation of the cationic bis(imine)$ZnSbF_6Cl$ complex through the addition of $AgSbF_6$ to the analogous $ZnCl_2$ complex provided no increase in catalyst activity

(entries 3 and 4). The benzylbisoxazoline/$Zn(OTf)_2$ complex gave full conversion to the product (entry 5), though the enantioselectivity was poor. Due to their successful use in asymmetric Diels-Alder chemistry, chiral titanates were then examined.[36] Although Cl_2Ti-BINOLate showed almost no reactivity (entry 6), Cl_2Ti-TADDOLate exhibited modest reactivity in CH_2Cl_2 (entry 7). This small but noticeable increase in reactivity warranted further investigation, and it was found that very good conversions could be achieved in Et_2O and toluene. A number of TADDOL ligands with aryl groups of differing sterics and electronics were then surveyed for their effect on enantioselectivity (**Table 1-3**). Regardless of the TADDOL ligand employed, the conversion to product was good but the enantioselectivity remained universally low.

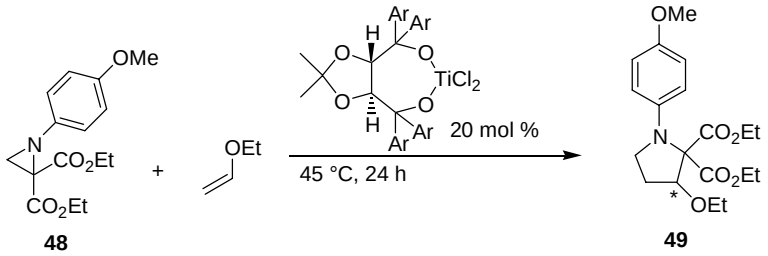
Table 1-2. Metal/Ligand Screen for the Catalytic Asymmetric Synthesis of Pyrrolidine **49**[a]



Entry	Ligand	Lewis Acid	Solvent	Result
1		$Zn(OTf)_2$	CH_2Cl_2	NR
2		$Zn(OTf)_2$	THF	slight conv.
3		$ZnCl_2/AgSbF_6$	C_7H_8	slight conv.
4		$ZnCl_2/AgSbF_6$	CH_2Cl_2	NR
5		$Zn(OTf)_2$	THF	100% conv., 8% ee
6		$TiCl_2(O^iPr)_2$	CH_2Cl_2	slight conv.
7		$TiCl_2(O^iPr)_2$	CH_2Cl_2	29% conv.
8		$TiCl_2(O^iPr)_2$	THF	slight conv.

a) Aziridine (1.0 equiv), ML_n (0.2 equiv), ethyl vinyl ether (15.0 equiv).

Table 1-3. Effect of TADDOL Sterics/Electronics on Enantioselectivity of Cycloaddition[a]

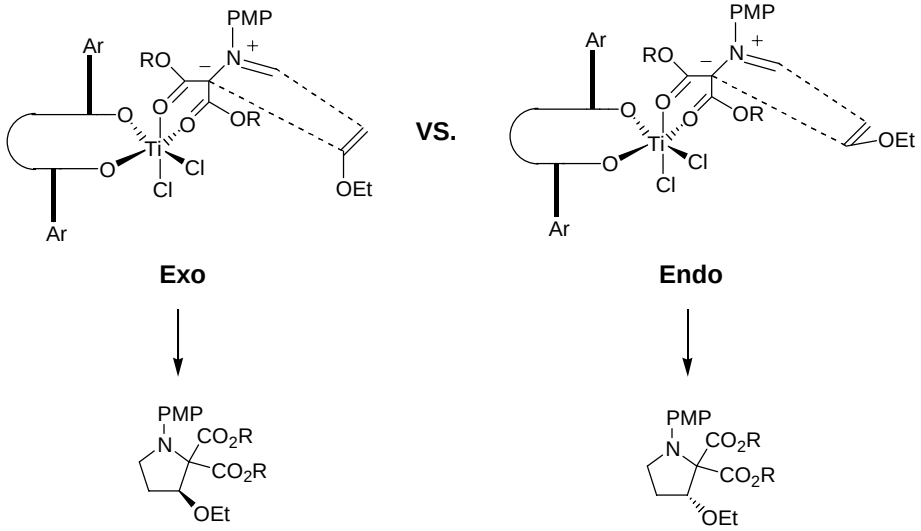


Entry	Ar	Solvent	% Conv.	% ee
1	Ph	Et_2O	60	12
2	Ph	C_7H_8	74	6
3	F_5Ph	C_7H_8	79	6
4	2-Np	C_7H_8	75	6
5	2-FPh	C_7H_8	78	3

a) Aziridine (1.0 equiv), ML_n (0.2 equiv), ethyl vinyl ether (15.0 equiv).

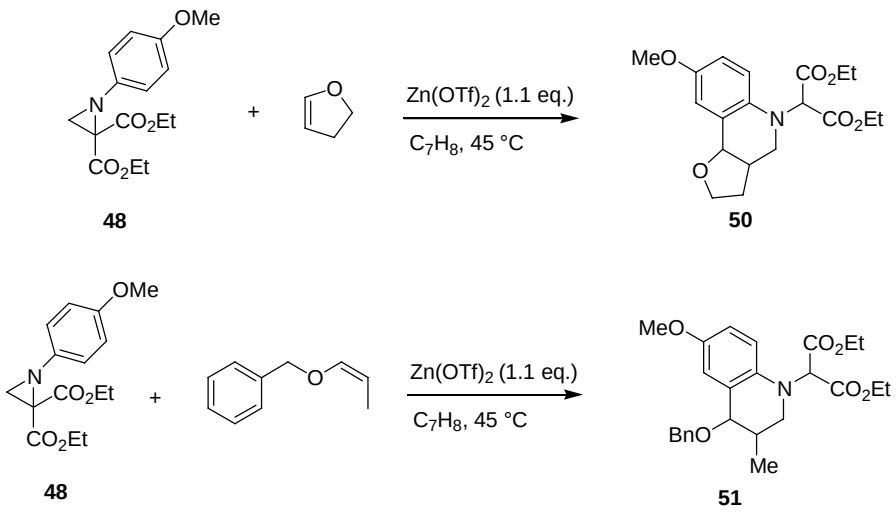
Studies on the stereoselectivity of related Ti-BINOLate and Ti-TADDOLate catalyzed reactions were used to explore the possible stereochemical course of this reaction. A desirable scenario would be one in which only one azomethine ylide geometry predominates, and the TADDOL ligand effectively blocks one face of the 1,3-dipole against dipolarophile attack. In this situation the sole determinant of asymmetric induction may be the interaction between the dipole and dipolarophile (**Scheme 1-14**). Hence, the degree of enantioselectivity would be determined by the energetic difference between the endo and exo transition states.

Scheme 1-14. Possible Transition States in the Cl_2Ti-TADDOLate Catalyzed Cycloaddition of Aziridine **48** with Ethyl Vinyl Ether



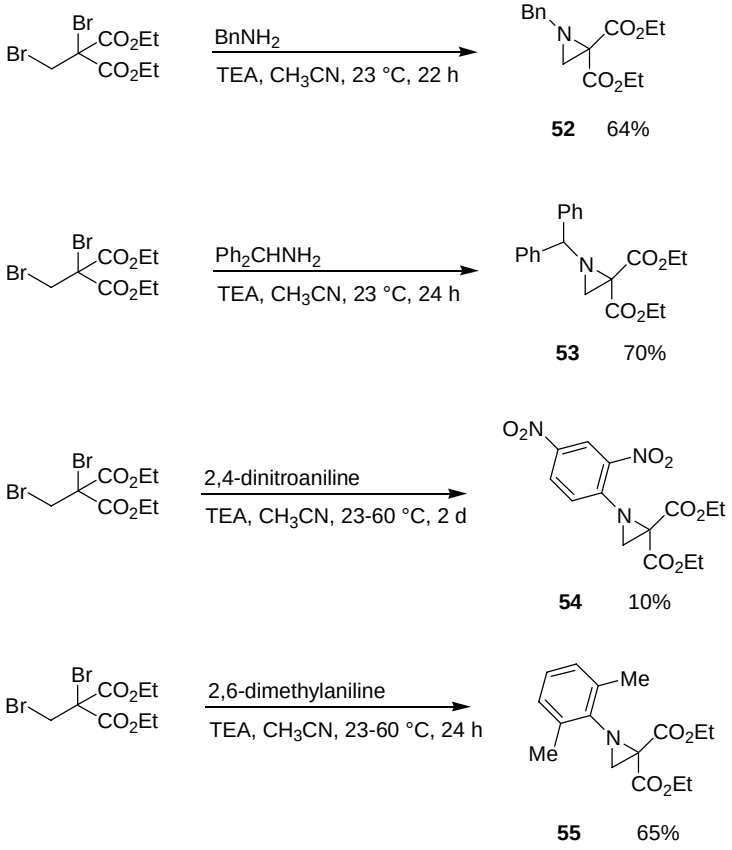
It was anticipated that the addition of a β-substituent on the dipolarophile may increase the energetic difference between possible transition states. However, upon attempted cycloaddition with both cyclic and acyclic dipolarophiles, 2,3-dihydrofuran and *Z*-propenyloxymethyl-benzene, respectively, the [4+2] adducts (**50** and **51**) were again realized (**Scheme 1-15**). The formation of **51** provides the most compelling evidence that β-substitution, and not just the cyclic nature of a dipolarophile, induces the [4+2] reaction pathway.

Scheme 1-15. Zn(II) Promoted [4+2] Cycloadditions of Aziridine **48** with β-Substituted Dipolarophiles



Realizing the obvious limitations of this chemistry if only dipolarophiles unsubstituted at the β-position could participate in the [3+2] cycloadditions, a number of other aziridines were synthesized in the hopes that the [4+2] pathway would be disfavored for these substrates. These aziridines were prepared in the same manner as **48**, from the double alkylation of an appropriate amine with dibromide **47** (**Scheme 1-16**). Alkyl amino substrates **52** and **53** were chosen to afford *N*-protected pyrrolidines while eliminating the [4+2] pathway. Dinitroaziridine **54** was expected to be completely deactivated towards electrophilic aromatic substitution, while 2,6-substitution on the aryl ring of aziridine **55** would block the ring closure necessary for the formation of the [4+2] adduct. Employing the same reaction conditions used in the TADDOL ligand screen (**Table 1-3**, **entry 2**), aziridines **52-55** afforded no productive [3+2] cycloaddition. Starting material was recovered in each case.

Scheme 1-16. Preparation of Aziridines Disfavored for the [4+2] Reaction Manifold



1.4 Conclusions

This study has documented the first productive metal-promoted and metal-catalyzed aziridine carbon-carbon bond cleavage reactions. It has been shown that the electronic properties of a metal bound azomethine ylide differ greatly from those of a free azomethine ylide generated thermolytically or photochemically from an aziridine, or otherwise. This generation of an azomethine ylide exhibiting type III behavior adds to the few documented examples of these 1,3-dipoles undergoing cycloadditions with electron-rich dipolarophiles.[37-41] A divergence in cycloaddition pathway has been shown to be highly dependent upon the

constitution of the dipolarophile employed. While dipolarophiles that are unsubstituted at the β-position undergo [3+2] cycloadditions affording substituted pyrrolidines, cyclic and acyclic dipolarophiles substituted at the β-position undergo cycloadditions primarily or exclusively through a very diastereoselective [4+2] pathway producing tetrahydroquinoline derivatives. Attempts to assuage the [4+2] reaction mode have resulted in a loss of reactivity. All of the cycloaddition reactions documented here are conducted under very mild conditions, generally at or slightly above room temperature. Finally, the possibility of rendering this metal catalyzed 1,3-dipolar cycloaddition reaction asymmetric has proven unfruitful. The lack of absolute stereochemical induction is believed to arise from energetically similar transition states that are possible with simple terminal alkene dipolarophiles.

1.5 Experimental

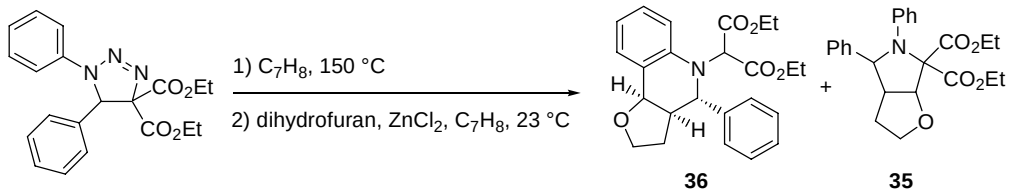
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard for ^{1}H NMR at 0.00 ppm and $CDCl_3$ solvent resonance as the internal standard for ^{13}C NMR at 77.16 ppm. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Structural assignments were made using a combination of COSY and NOESY experiments. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was

performed on Whatman 0.25 mm silica gel 60 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 Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables and equations, which are averages of at least two experiments. Toluene, tetrahydrofuran, and methylene chloride were dried by passage through a column of neutral alumina under nitrogen prior to use. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Zinc(II) chloride was dried at 150 °C under vacuum overnight.

General Procedure (A) for Aziridine Synthesis and Lewis Acid-Promoted Cycloaddition. In an inert atmosphere glove box, a flame-dried Schlenk tube with a magnetic stir bar was charged with 0.22 mmol of the triazoline (1.0 equiv), and 3 mL of toluene. Outside of the glove box, this solution was heated to 150 °C for 14 h. After cooling, the tube was transferred into the glove box where the mixture was concentrated *in vacuo*. To the remaining residue was added 0.26 mmol of $ZnCl_2$ (1.2 equiv), 1.6 mL of solvent, and 0.71-4.7 mmol of the dipolarophile (3-22 equiv). The tube was sealed and the reaction was stirred for 76 h at 23 °C outside of the glove box. The reaction was diluted with 20 mL of CH_2Cl_2 and washed with 10 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 10 mL of CH_2Cl_2. The organic extracts were combined, washed with 20 mL of saturated aqueous NaCl, dried over Na_2SO_4, and the solvent was removed with a

rotary evaporator. The product was purified by flash chromatography, eluting with the indicated solvent system to afford the pure pyrrolidine or tetrahydroquinoline product.

General Procedure (B) for Aziridine Synthesis and Lewis Acid–Catalyzed Cycloaddition. In an inert atmosphere glove box, a flame-dried Schlenk tube with a magnetic stir bar was charged with 0.22 mmol of the triazoline (1.0 equiv) and 3 mL of toluene. Outside of the glove box, this solution was heated to 150 °C for 14 h. After cooling, the tube was transferred into the glove box where the mixture was concentrated *in vacuo*. The catalyst was prepared in the glovebox by stirring 0.04 mmol of $ZnCl_2$ (0.20 equiv) and 0.04 mmol of *N,N*-dibenzylidene-cyclohexane-1,2-diamine (0.20 equiv) in 2 mL of THF for 1 h. To the aziridine generated from the triazoline thermolysis was added (*N,N*-dibenzylidene-cyclohexane-1,2-diamine)$ZnCl_2$ (0.20 equiv) as a heterogeneous mixture in THF and concentrated *in vacuo*. The residue was treated with 1.6 mL of solvent and 0.71-3.3 mmol the dipolarophile (3-15 equiv). The tube was sealed and the reaction was stirred for 76 h at 45 °C outside of the glove box. The reaction was diluted with 20 mL of CH_2Cl_2 and washed with 10 ml of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 10 mL of CH_2Cl_2. The organic extracts were combined, washed with 20 mL of saturated aqueous NaCl, dried over Na_2SO_4, and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography, eluting with the indicated solvent system to afford the pure pyrrolidine or tetrahydroquinoline product.

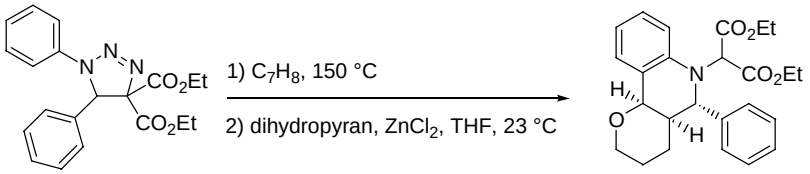


2-(4-Phenyl-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]quinolin-5-yl)-malonic acid diethyl ester (36). The title compound was prepared according to General Procedure **A** using 80.0 mg of triazoline, 3 mL of C_7H_8, then 35.3 mg of $ZnCl_2$, 360 μL of dihydrofuran, and 1.6 mL of C_7H_8. After 76 h at 23 °C and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 4.66 vs. δ 5.14) gave the isomeric composition of the product: **36/35** = 3.2:1. ^{1}H NMR (δ 4.66 vs. δ 5.04) gave the diastereomer ratio of **36** with respect to another [4+2] isomer of unknown relative stereochemistry: 10:1. The isomers were separated and purified by flash chromatography with a 5-20% EtOAc/hexanes linear gradient to afford 49.5 mg (55%) of the product (**36+35**), as clear oils which contained 3% of a [4+2] adduct of unknown relative stereochemistry.

Analytical data for **36**: **IR** (thin film, cm^{-1}) 3057, 2983, 2937, 2872, 1755, 1738, 1605, 1581, 1497, 1456, 1369, 1265, 1178, 1161, 1103, 1032, 737, 704; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.35-7.24 (m, 5H), 7.15 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 6.83 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.83 (s, 1H), 4.66 (d, *J* = 5.7 Hz, 1H), 4.41 (d, *J* = 7.8 Hz, 1H), 4.23-4.12 (m, 2H), 3.98-3.76 (m, 4H), 2.66 (dddd, *J* = 7.7, 7.7, 5.7, 5.7 Hz, 1H), 2.16-2.04 (m, 1H), 2.00-1.89 (m, 1H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.72, 167.69, 143.7, 141.7, 130.9, 128.9, 128.8, 128.1, 128.0, 122.3, 118.8, 113.2, 74.4, 65.7, 65.0, 63.2, 61.8, 44.1, 29.82,

29.77, 14.2, 13.9; TLC (20% EtOAc/petroleum ether) R_f 0.31; **Anal.** Calcd. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.07; H, 6.65; N, 3.34.

Analytical data for **4,5-diphenyl-hexahydro-furo[2,3-c]pyrrole-6,6-dicarboxylic acid diethyl ester (35)**: **IR** (thin film, cm^{-1}) 3061, 3028, 2980, 2937, 2895, 1755, 1720, 1601, 1581, 1504, 1454, 1389, 1367, 1292, 1267, 1225, 1176, 1138, 1117, 1059, 1034, 928, 862, 750, 704; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.28-7.24 (m, 2H), 7.20-7.16 (m, 1H), 7.07-7.02 (m, 2H), 6.85-6.82 (m, 2H), 6.78 (tt, *J* = 7.3, 1.1 Hz, 1H), 5.14 (d, *J* = 9.0 Hz, 1H), 4.97 (d, *J* = 6.4 Hz, 1H), 4.51-4.43 (m, 1H), 4.37-4.29 (m, 1H), 4.06-3.98 (m, 1H), 3.92-3.84 (m, 1H); 3.64 (ddd, *J* = 8.1, 8.1, 4.4 Hz, 1H), 3.54-3.45 (m, 2H), 1.73-1.57 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 167.6, 145.2, 140.0, 128.5, 128.3, 127.7, 127.2, 121.0, 119.8, 88.0, 81.5, 69.4, 67.8, 61.6, 61.4, 47.1, 28.8, 14.4, 13.8; TLC (20% EtOAc/petroleum ether) R_f 0.36; **Anal.** Calcd. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.25; H, 6.73; N, 3.35.

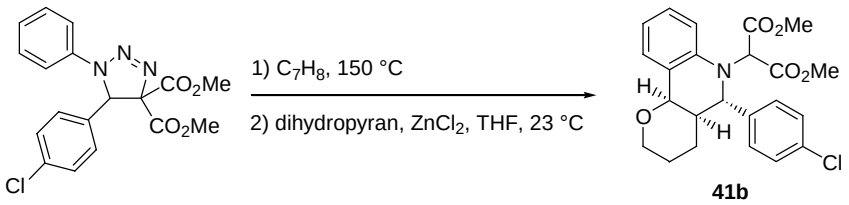


41a

2-(5-Phenyl-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]quinolin-6-yl)-malonic acid diethyl ester (41a). The title compound was prepared according to General Procedure **A** using 80.0 mg of triazoline, 3 mL of C_7H_8, then 35.6 mg of $ZnCl_2$, 300 μL of dihydropyran, and 1.6 mL of THF. After 76 h at 23 °C and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 4.50 vs. δ 4.94) gave the ratio of **41a** with respect to a [3+2] isomer of

unknown relative stereochemistry: 12:1. The crude product was purified by flash chromatography with a 7.5-17.5% EtOAc/hexanes linear gradient to afford 77.0 mg (83%) of the product as a clear oil.

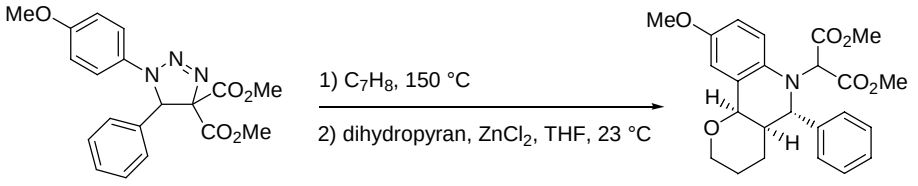
Analytical data for **41a**: **IR** (thin film, cm^{-1}) 3062, 3030, 2980, 2939, 2862, 1759, 1736, 1603, 1579, 1495, 1464, 1454, 1390, 1367, 1304, 1271, 1217, 1176, 1159, 1090, 1072, 1041, 1030, 943, 916, 893, 866, 779, 739, 704; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.4 Hz, 1H), 7.30-7.21 (m, 5H), 7.15 (ddd, *J* = 8.6, 7.4, 1.8 Hz, 1H), 6.80 (ddd, *J* = 7.4, 7.4, 0.6 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 4.81 (s, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.50 (d, *J* = 3.7 Hz, 1H), 4.21-4.09 (m, 2H), 3.92-3.71 (m, 3H), 3.67-3.61 (m, 1H), 2.19 (dddd, *J* = 6.3, 6.3, 4.1, 4.1 Hz, 1H), 1.78-1.68 (m, 2H), 1.57-1.47 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.9, 167.5, 143.9, 142.2, 129.4, 128.8, 128.6, 127.7, 127.6, 121.9, 118.2, 112.6, 71.3, 66.2, 64.8, 64.6, 61.8, 61.7, 39.3, 25.4, 24.0, 14.1, 13.8; TLC (20% EtOAc/petroleum ether) R_f 0.40; **Anal.** Calcd. for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.69; H, 6.95; N, 3.24.



2-[5-(4-Chloro-phenyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]quinolin-6-yl]-malonic acid dimethyl ester (41b). The title compound was prepared according to General Procedure **A** using 81.5 mg of triazoline, 3 mL of C_7H_8, then 35.6 mg of $ZnCl_2$, 300 μL of dihydropyran, and 1.6 mL of THF. After 76 h at 23 °C and extractive workup, ^{1}H NMR

analysis of the unpurified product (δ 4.51 vs. δ 4.93) gave the ratio of **41b** with respect to a [3+2] isomer of unknown relative stereochemistry: 7.6:1. The crude product was purified by flash chromatography with a 10-20% EtOAc/hexanes gradient to afford 68.3 mg (73%) of the product as a white foam.

Analytical data for **41b**: **IR** (thin film, cm^{-1}) 3654, 3488, 3044, 2951, 2861, 2724, 1907, 1743, 1603, 1578, 1492, 1496, 1435, 1397, 1368, 1305, 1162, 1090, 1041, 1014, 921, 896, 839, 826, 750, 705, 660, 645, 608; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 1H), 7.29-7.24 (m, 2H), 7.20-7.14 (m, 3H), 6.83 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 4.88 (s, 1H), 4.69 (d, *J* = 6.2 Hz, 1H), 4.51 (d, *J* = 4.1 Hz, 1H), 3.80-3.71 (m, 1H), 3.71 (s, 3H), 3.66-3.59 (m, 1H), 3.37 (s, 3H), 2.19-2.11 (m, 1H), 1.80-1.49 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 167.7, 143.4, 140.7, 133.5, 129.4, 128.9, 128.7 (two overlapping resonances), 121.5, 118.5, 112.0, 70.6, 65.3, 64.2, 63.9, 52.7, 52.6, 39.3, 25.2, 24.3; TLC (20% EtOAc/petroleum ether) R_f 0.26; **Anal.** Calcd. for $C_{25}H_{28}ClNO_5$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.03; H, 5.73; N, 3.15.

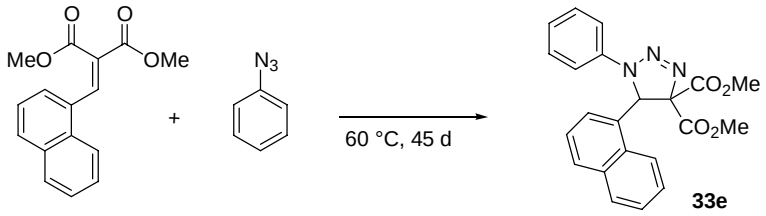


41c

2-(9-Methoxy-5-phenyl-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]quinolin-6-yl)-malonic acid dimethyl ester (41c). The title compound was prepared according to General Procedure **A** using 80.5 mg of triazoline, 3 mL of C_7H_8, then 35.6 mg of $ZnCl_2$, 300 μL of dihydropyran, and 1.6 mL of THF. After 76 h at 23 °C and extractive workup, ^{1}H NMR

analysis of the unpurified product (δ 4.49 vs. δ 4.89) gave the ratio of **41c** with respect to a [3+2] isomer of unknown relative stereochemistry: 26:1. The crude product was purified by flash chromatography with a 15-25% EtOAc/hexanes linear gradient to afford 60.8 mg (66%) of the product as a white foam.

Analytical data for **41c**: **IR** (thin film, cm^{-1}) 2999, 2950, 2859, 1742, 1505, 1453, 1434, 1357, 1229, 1160, 1087, 1066, 1043, 923, 905, 870, 805, 760, 737, 704; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.25-7.21 (m, 3H), 6.95 (d, *J* = 2.9 Hz, 1H), 6.77 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 4.84 (s, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 4.0 Hz, 1H), 3.84-3.77 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.68-3.62 (m, 1H), 3.37 (s, 3H), 2.19 (dddd, *J* = 7.1, 7.1, 4.1, 4.1 Hz, 1H), 1.77-1.69 (m, 2H), 1.59-1.48 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 168.1, 152.4, 142.2, 137.7, 128.6, 127.7, 127.4, 122.7, 115.1, 114.4, 113.2, 71.3, 65.7, 64.7, 64.4, 55.8, 52.52, 52.50, 39.5, 25.4, 24.0; TLC (20% EtOAc/petroleum ether) R_f 0.16; **Anal.** Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.83; H, 6.48; N, 3.28.

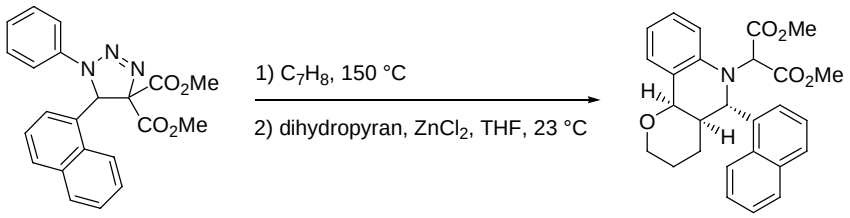


33e

5-Naphthalen-1-yl-1-phenyl-1,5-dihydro-[1,2,3]triazole-4,4-dicarboxylic acid dimethyl ester (33e). The title compound was prepared by combining 2-naphthalen-1-ylmethylene-malonic acid dimethyl ester (2.9 g, 10.9 mmol, 1.0 equiv) and phenyl azide (2.6 g, 21.8 mmol, 2.0 equiv) in a small vial. After 42 d at 60 °C, the crude product was purified by flash

chromatography with a 15-20% EtOAc/hexanes gradient to afford 667 mg (16%) of the product as a yellow solid.

Analytical data for **33e**: **IR** (Nujol mull, cm^{-1}) 1742, 1598, 1461, 1377, 1282, 1228, 1130, 750; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.30 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.20-7.14 (m, 4H), 7.09 (dd, *J* = 7.2, 0.98 Hz, 1H), 6.98 (tt, *J* = 6.7, 1.8 Hz, 1H), 6.79 (s, 1H), 3.96 (s, 3H), 2.84 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.1, 164.8, 138.6, 133.8, 131.4, 129.6, 129.4, 129.0, 128.8, 127.3, 126.3, 125.8, 125.3, 123.7, 123.3, 115.8, 96.0, 59.2, 54.5, 52.4; TLC (20% EtOAc/petroleum ether) R_f 0.22; **Anal.** Calcd. for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.93; H, 5.05; N, 10.55.

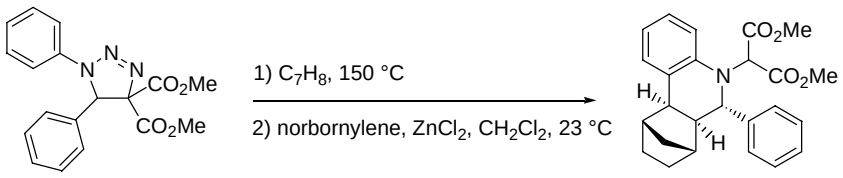


41d

2-(5-Naphthalen-1-yl-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]quinolin-6-yl)-malonic acid dimethyl ester (41d). The title compound was prepared according to General Procedure **A** using 84.9 mg of triazoline, 3 mL of C_7H_8, then 33.0 mg of $ZnCl_2$, 300 μL of dihydropyran, and 1.6 mL of THF. After 76 h at 23 °C and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 4.64 vs. δ 4.90) gave the diastereomer ratio of **41d** with respect to another isomer of unknown relative stereochemistry: 4.2:1. The material was

purified by flash chromatography with a 5-20% EtOAc/hexanes linear gradient to afford 49.0 mg (51%) of the product as clear crystals that contained 13% of a diastereomer.

Analytical data for **41d**: **IR** (Nujol mull, cm^{-1}) 2357, 1753, 1742, 1604, 1501, 1460, 1377, 1335, 1242, 1202, 1170, 1126, 1081, 1067, 783, 748; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.87 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.61-7.55 (m, 1H), 7.53-7.50 (m, 1H), 7.45 (ddd, *J* = 7.5, 1.3, 1.3 Hz, 1H), 7.37-7.29 (m, 2H), 7.26-7.19 (m, 1H), 6.87 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.49 (d, *J* = 3.1 Hz, 1H), 5.07 (s, 1H), 4.64 (d, *J* = 4.9 Hz, 1H), 3.73 (s, 3H), 3.59-3.56 (m, 2H), 3.05 (s, 3H), 2.47-2.39 (m, 1H), 1.98-1.93(m, 1H), 1.82-1.58 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 167.4, 143.7, 137.3, 134.1, 130.6, 129.3, 128.6, 128.1, 126.7, 125.7, 125.2 (two overlapping resonances), 124.6, 122.4, 120.3, 118.1, 110.7, 69.4, 64.5, 61.9, 60.8, 52.7, 52.5, 37.8, 25.8, 25.2; TLC (20% EtOAc/petroleum ether) R_f 0.31; **Anal.** Calcd. for $C_{27}H_{27}NO_5$: C,72.79; H, 6.11; N, 3.14. Found: C, 72.55; H, 6.15; N, 3.09.



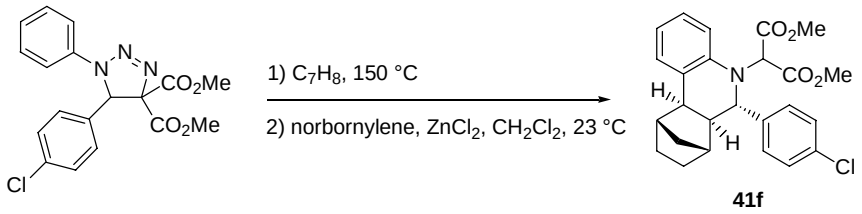
41e

2-((6α,6aβ,7α,10α,10aβ)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methano-6-phenyl-phenanthridin-5-yl)malonic acid dimethyl ester (41e). The title compound was prepared according to General Procedure **A** using 80 mg of triazoline, 3 mL of C_7H_8, then 35 mg of $ZnCl_2$, 67.0 mg of norbornylene, and 1.6 mL of CH_2Cl_2. After 76 h at 23 °C and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 2.80 vs. δ 2.72) gave the diastereomer

ratio of **41e** with respect to another isomer of unknown relative stereochemistry: 9:1. The isomers were purified by flash chromatography with a 15-22.5% EtOAc/hexanes linear gradient to afford 80.9 mg (85%) of the product as a white foam which contained 10% of a diastereomer.

Alternatively, the title compound was prepared according to General Procedure **B** using 80 mg of triazoline, 3 mL of C_7H_8, then 20 mg of (*N,N*-dibenzylidene-cyclohexane-1,2-diamine)$ZnCl_2$, 67.0 mg of norbornylene, and 1.6 mL of CH_2Cl_2. After 76 h at 45 °C and extractive workup, the crude product was purified by flash chromatography with a 15-22.5% EtOAc/hexanes linear gradient to afford 83.0 mg (86%) of the product as a white foam which contained 15% of a diastereomer.

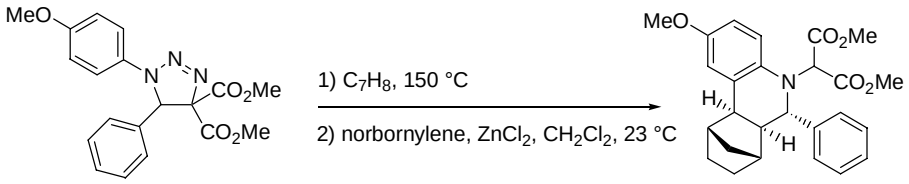
Analytical data for **41e**: **IR** (thin film, cm^{-1}), 3060, 3027, 2952, 2869, 1762, 1741, 1598, 1496, 1452, 1434, 1371, 1340, 1282, 1247, 1230, 1193, 1120, 1072, 1029, 938, 929, 890, 827, 806, 750, 736, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19-7.03 (m, 7H), 6.83-6.80 (m, 2H), 5.07 (s, 1H), 4.49 (d, *J* = 3.5 Hz, 1H), 3.69 (s, 3H), 3.24 (s, 3H), 2.80 (d, *J* = 12.0 Hz, 1H), 2.41-2.38 (m, 2H), 2.24 (dd, *J* = 9.1, 3.6 Hz, 1H), 1.79 (d, *J* = 9.7 Hz, 1H), 1.67-1.60 (m, 1H), 1.56-1.48 (m, 1H), 1.39-1.26 (m, 2H), 1.04 (d, *J* = 9.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 168.0, 144.8, 144.1, 130.5, 129.7, 128.4, 127.6, 126.9, 126.6, 119.3, 113.6, 63.9 (two overlapping resonances), 52.9, 52.6, 52.1, 47.3, 44.0, 43.8, 34.3, 30.8, 28.9; TLC (20% EtOAc/petroleum ether) R_f 0.42; **Anal.** Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.20; H, 6.77; N, 3.49.



41f

2-((6α,6aβ,7α,10α,10aβ)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methano-6-(4-chlorophenyl)-phenanthridin-5-yl)malonic acid dimethyl ester (41f). The title compound was prepared according to General Procedure **A** using 88 mg of triazoline, 3 mL of C_7H_8, then 35 mg of $ZnCl_2$, 67.0 mg of norbornylene, and 1.6 mL of CH_2Cl_2. After 76 h at 23 °C and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 2.78 vs. δ 2.70) gave the diastereomer ratio of **41f** with respect to another isomer of unknown relative stereochemistry: 2.8:1. The isomers were purified by flash chromatography with a 10-25% EtOAc/hexanes linear gradient to afford 78 mg (75%) of the product as a white foam which contained 23% of a diastereomer.

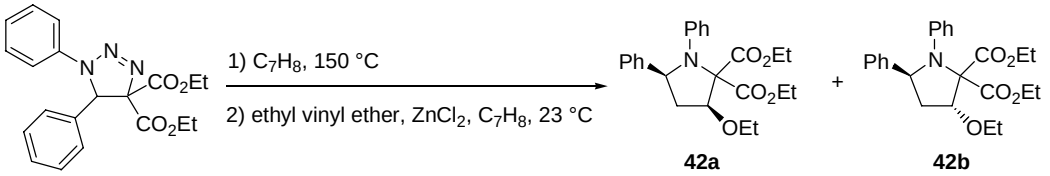
Analytical data for **41f**: **IR** (thin film, cm^{-1}), 3062, 2952, 2869, 1764, 1739, 1598, 1579, 1490, 1454, 1434, 1396, 1371, 1340, 1295, 1282, 1232, 1170, 1091, 1031, 1014, 910, 823, 750, 730; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15-7.06 (m, 4H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.84-6.80 (m, 2H), 5.10 (s, 1H), 4.55 (d, *J* = 2.5 Hz, 1H), 3.71 (s, 3H), 3.28 (s, 3H), 2.78 (d, *J* = 9.0 Hz, 1H), 2.44 (s, 1H), 2.34 (d, *J* = 3.5 Hz, 1H), 2.19-2.11 (m, 1H), 1.77 (d, *J* = 9.9 Hz, 1H), 1.68-1.60 (m, 1H), 1.57-1.49 (m, 1H), 1.39-1.26 (m, 2H), 1.04 (d, *J* = 9.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 167.8, 144.3, 142.9, 132.4, 130.4, 129.9, 128.9, 128.4, 126.8, 119.5, 113.5, 63.8, 62.8, 52.9, 52.6, 52.2, 47.7, 43.9 (two overlapping resonances), 34.3, 30.9, 28.8; TLC (20% EtOAc/petroleum ether) R_f 0.41; **Anal.** Calcd. for $C_{25}H_{26}NO_4Cl$: C, 68.25; H, 5.96; N, 3.18. Found: C, 67.99; H, 5.99; N, 3.20.



41g

2-((6α,6aβ,7α,10α,10aβ)-5,6,6a,7,8,9,10,10a-octahydro-7,10-methano-2-methoxy-6-phenyl-phenanthridin-5-yl)malonic acid dimethyl ester (41g). The title compound was prepared according to General Procedure **A** using 87 mg of triazoline, 3 mL of C_7H_8, then 35 mg of $ZnCl_2$, 67.0 mg of norbornylene, and 1.6 mL of CH_2Cl_2. After 76 h at 23 °C and extractive workup, the crude product was purified by flash chromatography with a 10-25% EtOAc/hexanes linear gradient to afford 85 mg (82%) of the product as a white foam.

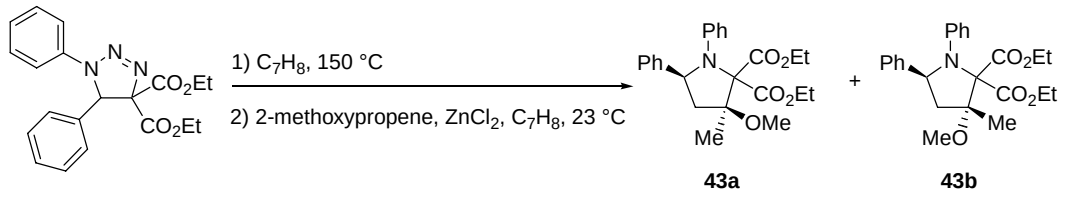
Analytical data for **41g**: **IR** (thin film, cm^{-1}), 2950, 2869, 2834, 1762, 1739, 1506, 1452, 1432, 1303, 1295, 1226, 1195, 1162, 1043, 1031, 910, 802, 734, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.14 (m, 3H), 7.07 (d, *J* = 6.6 Hz, 2H), 6.79-6.76 (m, 2H), 6.64 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.94 (s, 1H), 4.38 (d, *J* = 4.2 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.29 (s, 3H), 2.78 (d, *J* = 9.3 Hz, 1H), 2.43 (d, *J* = 3.8 Hz, 1H), 2.33 (d, *J* = 2.2 Hz, 1H), 2.26 (dd, *J* = 9.1, 4.7 Hz, 1H), 1.79 (d, *J* = 10.3 Hz, 1H), 1.69-1.61 (m, 1H), 1.57-1.49 (m, 1H), 1.41-1.27 (m, 2H), 1.05 (d, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.3, 168.2, 153.0, 143.6, 138.8, 131.9, 128.4, 127.9, 127.0, 115.2, 115.0, 111.7, 64.3, 64.2, 55.6, 52.6, 52.5, 52.1, 46.7, 44.5, 43.4, 34.3, 30.6, 29.0; TLC (20% EtOAc/petroleum ether) R_f 0.32; **Anal.** Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.51; H, 6.72; N, 3.14.



(±)-(3*S*,5*S*)-3-Ethoxy-1,5-diphenyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (42a). The title compound was prepared according to General Procedure **A** using 80.0 mg of triazoline, 3 mL of C_7H_8, then 35.6 mg of $ZnCl_2$, 340 μL of ethyl vinyl ether, and 1.6 mL of C_7H_8. After 76 h at 23 °C, and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 4.97 vs. δ 5.05) gave the diastereomer ratio of the product: **42a**/**42b** = 1.6:1. The isomers were separated and purified by adsorption onto SiO_2 followed by flash chromatography with a 5-20% EtOAc/hexanes linear gradient to afford 54.5 mg (61%) of the product (**42a**+**42b**) as clear oils.

Analytical data for **42a**: **IR** (thin film, cm^{-1}) 3062, 3026, 2980, 2929, 2902, 2873, 1741, 1732, 1601, 1504, 1454, 1367, 1350, 1327, 1302, 1242, 1178, 1128, 1080, 1061, 1028, 926, 868, 816, 750, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.28-7.23 (m, 2H), 7.18-7.14 (m, 1H), 7.05-7.00 (m, 2H), 6.68 (tt, *J* = 7.2, 1.0 Hz, 1H), 6.55-6.51 (m, 2H), 4.97 (dd, *J* = 7.6, 6.3 Hz, 1H), 4.51 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.47-4.41 (m, 1H), 4.37-4.29 (m, 1H), 4.12-3.99 (m, 2H), 3.55-3.48 (m, 1H), 3.39-3.32 (m, 1H), 2.79 (ddd, *J* = 12.7, 7.6, 5.5 Hz, 1H), 2.18 (ddd, *J* = 12.7, 6.1, 6.1 Hz, 1H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.6, 167.8, 144.9, 143.5, 128.4, 128.3, 126.9, 126.8, 118.8, 116.6, 85.1, 79.6, 65.9, 64.0, 61.8, 61.6, 40.3, 15.1, 14.4, 13.9; TLC (10% EtOAc/petroleum ether) R_f 0.18; **Anal.** Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: Combustion analysis failed.

Analytical data for **(±)-(3*R*,5*S*)-3-ethoxy-1,5-diphenyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (42b)**: **IR** (thin film, cm^{-1}) 2981, 2924, 1741, 1601, 1504, 1450, 1350, 1329, 1242, 1211, 1178, 1161, 1122, 1095, 1063, 748, 692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.33-7.30 (m, 2H), 7.25-7.21 (m, 1H) 7.08-7.03 (m, 2H), 6.68 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.54-6.50 (m, 2H), 5.05 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.62 (dd, *J* = 9.6, 6.5 Hz, 1H), 4.42-4.30 (m, 2H), 4.30-4.15 (m, 2H), 3.77-3.69 (m, 1H), 3.55-3.48 (m 1H), 2.74 (ddd, *J* = 12.1, 9.4, 9.4 Hz, 1H), 2.24 (ddd, *J* = 12.1, 6.3, 2.7 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.2, 167.7, 145.4, 144.1, 128.8, 128.4, 127.1, 126.1, 118.0, 114.7, 84.1, 66.9, 63.9, 62.1, 61.8, 39.9, 29.9, 15.4, 14.24, 14.22; TLC (10% EtOAc/petroleum ether) R_f 0.20; **Anal.** Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: Combustion analysis failed.



(±)-(3*S*,5*S*)-3-Methoxy-3-methyl-1,5-diphenyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (43a). The title compound was prepared according to General Procedure **A** using 80.0 mg of triazoline, 3 mL of C_7H_8, then 33.0 mg of $ZnCl_2$, 313 μL of 2-methoxypropene, and 1.6 mL of C_7H_8. After 76 h at 23 °C, and extractive workup, ^{1}H NMR analysis of the unpurified product (δ 4.99 vs. δ 5.12) gave the diastereomer ratio of the product: **43a**/**43b** = 1.4:1. The isomers were separated and purified by adsorption onto SiO_2 followed by flash

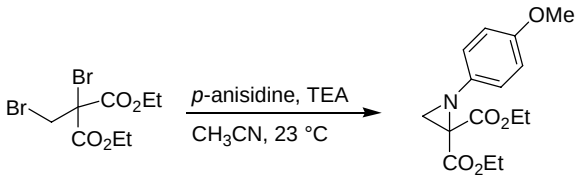
chromatography with a 5-20% EtOAc/hexanes linear gradient to afford 67.0 mg (75%) of the product (**43a**+**43b**) as clear oils.

Alternatively, the title compound was prepared according to General Procedure **B** using 80.0 mg of triazoline, 3 mL of C_7H_8, then 18.6 mg of (*N,N*-dibenzylidene-cyclohexane-1,2-diamine)$ZnCl_2$, 313 μL of 2-methoxypropene, and 1.6 mL of C_7H_8. After 76 h at 23 °C, and extractive workup, ^{1}H NMR analysis of the unpurified product gave the diastereomer ratio of the product: **43a**/**43b** = 1.2:1. The isomers were separated and purified by adsorption onto SiO_2 followed by flash chromatography with a 5-20% EtOAc/hexanes linear gradient to afford 68.0 mg (76%) of the product (**43a**+**43b**) as clear oils.

Analytical data for **43a**: **IR** (thin film, cm^{-1}) 3061, 3026, 2980, 2937, 2902, 2829, 1751, 1601, 1578, 1506, 1464, 1452, 1379, 1350, 1329, 1261, 1232, 1205, 1192, 1167, 1136, 1109, 1078, 1039, 993, 891, 866, 764, 748, 702, 646; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.31-7.25 (m, 2H), 7.20-7.15 (m, 1H), 7.09-7.02 (m, 2H), 6.66 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.40-6.36 (m, 2H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.47-4.23 (m, 2H), 4.22-4.11 (m, 2H), 2.73 (dd, *J* = 13.5, 9.8 Hz, 1H), 2.62 (s, 3H), 2.38 (dd, *J* = 13.2, 1.0 Hz, 1H), 1.42 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 166.6, 146.1, 144.1, 128.4, 128.2, 126.7, 126.4, 117.5, 114.2, 88.8, 83.5, 65.2, 61.9, 61.2, 49.3, 40.0, 17.9, 14.3, 14.1; TLC (20% EtOAc/petroleum ether) R_f 0.41; **Anal.** Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: Combustion analysis failed.

Analytical data for **(±)-(3*R*,5*S*)-3-methoxy-3-methyl-1,5-diphenyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (43b)**: **IR** (thin film, cm^{-1}) 3061, 3026, 2981, 2956, 2931, 2850, 1763, 1743, 1601, 1504, 1450, 1377, 1365, 1323, 1265, 1219, 1186, 1155, 1126, 1076, 1038, 908, 864, 750, 704, 692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.32-7.28

(m, 2H), 7.23-7.19 (m, 1H), 7.06-7.01 (m, 2H), 6.67 (tt, *J* = 7.3, 0.9 Hz, 1H), 6.36-6.33 (m, 2H), 5.12 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.47-4.29 (m, 2H), 4.23-4.10 (m, 2H), 3.32 (s, 3H), 3.13 (dd, *J* = 11.9, 9.5 Hz, 1H), 2.17 (dd, *J* = 12.3, 3.5 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.29 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 168.0, 145.9, 143.8, 128.6, 128.4, 126.8, 126.6, 117.9, 114.9, 86.4, 82.2, 63.6, 61.9, 61.5, 51.2, 45.4, 20.5, 14.3, 14.1; TLC (20% EtOAc/petroleum ether) R_f 0.34; **Anal**. Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.10; H, 7.03; N, 3.40.

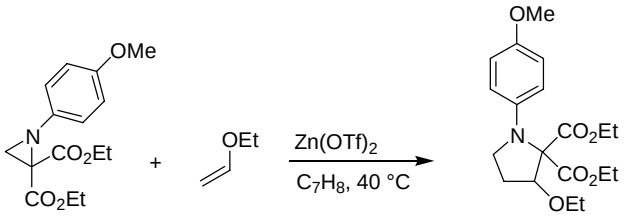


48

1-(4-Methoxy-phenyl)-aziridine-2,2-dicarboxylic acid diethyl ester (48). A solution of the dibromide (5.8 g, 17.5 mmol, 1.0 equiv) in 15 mL of acetonitrile was treated with a solution of *p*-anisidine (2.2 g, 17.5 mmol, 1.0 equiv) in 15 mL of acetonitrile. Triethylamine (3.9 g, 38.5 mmol, 2.2 equiv) was then added and the mixture was stirred for 52 h at 23 °C. The reaction mixture was diluted with 50 mL of Et_2O and washed with 50 mL of saturated aqueous NaCl. The aqueous layer was extracted with two 40 mL portions of Et_2O and the combined organic extracts were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator. The crude material was purified by flash chromatography with 20% EtOAc/petroleum ether to afford 4.8 g (94%) of the product as a tangerine oil.

Analytical data for **48**: **IR** (thin film, cm^{-1}) 2982, 2938, 2909, 2837, 1740, 1611, 1586, 1509, 1466, 1445, 1372, 1319, 1297, 1242, 1199, 1171, 1104, 1126, 967, 860, 834,

765, 723, 660; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.17 (q, *J* = 6.9 Hz, 4H), 3.75 (s, 3H), 2.86 (s, 2H), 1.20 (t, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.7, 156.0, 140.6, 121.1, 111.1, 62.0, 55.4, 48.2, 37.1, 13.9; TLC (20% EtOAc/hexanes) R_f 0.18; **Anal.** Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.62; H, 6.69; N, 4.85.



48 **49**

3-Ethoxy-1-(4-methoxy-phenyl)-pyrrolidine-2,2-dicarboxylic acid diethyl ester (49). A small vial containing $Zn(OTf)_2$ (19.9 mg, 0.0547 mmol, 0.20 equiv) was charged with a solution of the aziridine (80.0 mg, 0.274 mmol, 1.0 equiv) and ethyl vinyl ether (300 mg, 4.16 mmol, 15.2 equiv) in 2 mL of toluene. The mixture was heated to 40 °C with stirring. After 17 hours, 97.5 mg more ethyl vinyl ether was added to the reaction. After an additional 7 h, 195 mg more ethyl vinyl ether was added to the reaction. After 40 h total, the reaction mixture was passed over a small plug of silica gel, eluting with Et_2O, and the solvent was removed with a rotary evaporator. The crude material was purified by flash chromatography with a 10-20% EtOAc/hexanes linear gradient to afford 71 mg (71%) of the product as a yellow oil.

Analytical data for **49**: **IR** (thin film, cm^{-1}) 2980, 2936, 2903, 2873, 2835, 1763, 1730, 1515, 1480, 1465, 1444, 1365, 1352, 1334, 1292, 1247, 1179, 1100, 1074, 1039, 864,

817, 785; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.73 (d, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 9.3 Hz, 2H), 4.51 (dd, *J* = 5.7, 5.7 Hz, 1 H), 4.30-4.04 (m, 4H), 3.76-3.44 (m, 7H), 2.32 (dddd, *J* = 12.6, 7.8, 6.0, 6.0 Hz, 1H), 2.12 (dddd, *J* = 12.6, 7.8, 6.3, 6.3 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 6.9 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 167.6, 152.1, 140.0, 115.5, 113.9, 86.2, 77.1, 66.4, 61.5, 61.3, 55.6, 48.3, 29.9, 15.2, 14.1, 13.9; TLC (20% EtOAc/petroleum ether) R_f 0.27; **Anal.** Calcd. for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.61; H, 7.45; N, 3.81.

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CHAPTER 2

HETEROCYCLE SYNTHESIS VIA [3+2] REACTIONS OF CYCLOPROPANES

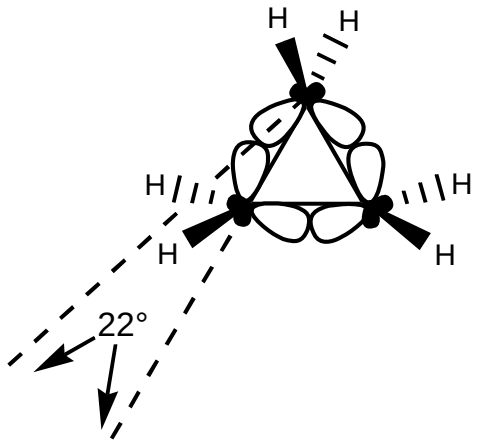
2.1 Introduction

The efficient synthesis of heterocycles constitutes an ongoing objective in synthetic organic chemistry owing to the repetitive occurrence of these structures in biologically important compounds. From a practical standpoint, this underscores the need for stereoselective, one-step fabrication processes of these motifs from relatively simple starting materials. An area that continues to receive attention in this regard is the [3+2] cycloaddition reaction of substituted cyclopropanes.[1,2] The usefulness of these precursors in the synthesis of five-membered heterocycles requires an understanding of their reactivity.[3]

The carbon-carbon σ-bonds of cyclopropane are particularly susceptible to cleavage versus those of other cycloalkanes. This lability has been attributed to the unusual strain energy present in cyclopropane. A significant amount of angular (Bayer) strain is associated with the requisite 60° bond angles of cyclopropane versus those of 109.5° for an unstrained sp^3-hybridized carbon. Additionally, the forced eclipsing of the C-H bonds results in high torsional (Pitzer) strain. As a result, the strain energy of cyclopropane is measured to be 27.5 kcal/mol. The high reactivity of cyclopropane is also considered to be a result of its bonding. The Coulson-Moffitt Model (**Figure 2-1**) describes cyclopropane as being constructed from

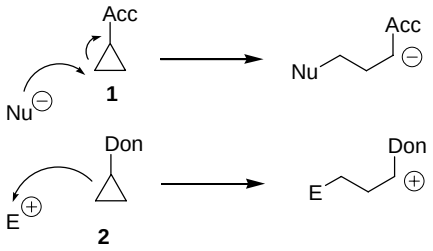
three sp^3 hybridized carbon atoms, hence the lobes involved in bonding are ~22° off of the internuclear axes. This results in about 20% less orbital overlap in a cyclopropane carbon-carbon bond relative to ethane.

Figure 2-1. The Coulson-Moffitt Model for Bonding in Cyclopropane



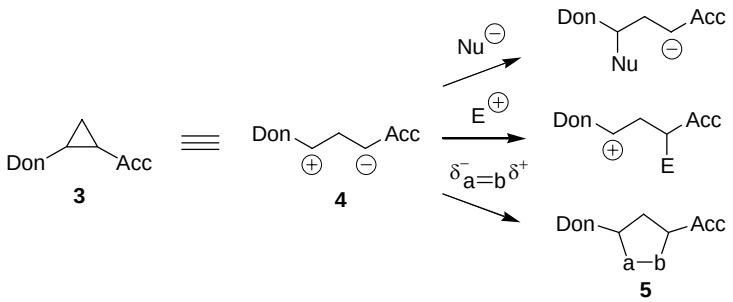
The reactivity of cyclopropanes has been compared to that of alkenes, since depending on their substitution pattern, they show reactivity toward both electrophilic and nucleophilic agents (**Scheme 2-1**). A cyclopropane substituted with an electron-withdrawing group (**1**) is susceptible to ring cleavage by nucleophiles as the acceptor (Acc) group stabilizes the incipient negative charge. Conversely, a cyclopropane substituted with an electron-releasing group (**2**) is labile towards electrophiles, and carbon-carbon bond cleavage occurs leaving a cation α to the donor (Don) group.[2]

Scheme 2-1. Ambiphilic Reactivity of Substituted Cyclopropanes



Donor-acceptor (D-A) substituted cyclopropanes (**3**) are vicinally substituted with electron-releasing and electron-withdrawing groups. This unique class of cyclopropanes shows reactivity towards both nucleophiles and electrophiles. The synergistic relationship between substituents in donor-acceptor cyclopropanes imparts even greater reactivity to these substrates and allows them to serve as a ring-opened three-carbon 1,3-dipolar synthons (**4**) (**Scheme 2-2**). This charge relationship makes D-A cyclopropanes ideal candidates for regioselective cycloaddition reactions with polarized multiple bond systems to prepare five-membered rings (**5**). Although not a prerequisite, a significant number of [3+2] cyclopropane cycloadditions involve the use of donor-acceptor cyclopropanes.[1,4]

Scheme 2-2. Reactivity Patterns of Donor-Accpetor (D-A) Cyclopropanes



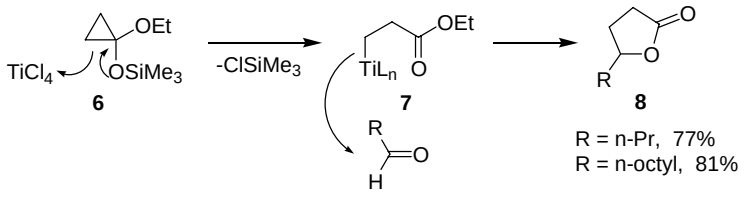
2.2 Synthetic Methods

The synthesis of a five-membered heterocycle from a cyclopropane involves the net addition of a three-carbon fragment derived from the cyclopropane across a heteroatom-containing π-bond. A cyclopropane must be substituted with either an electron-withdrawing and/or electron-donating group in order to exhibit reactivity in this [3+2] cycloaddition manifold. Except for a few examples, the scope of this chapter involves the formation of a stable heterocycle in a single step from a starting cyclopropane. The products of some [3+2] cycloadditions, such as γ-lactols and their open chain tautomers require further manipulation to realize stable heterocycles. Therefore, these reactions will not be discussed.

2.2.1 Lactones and Tetrahydrofurans

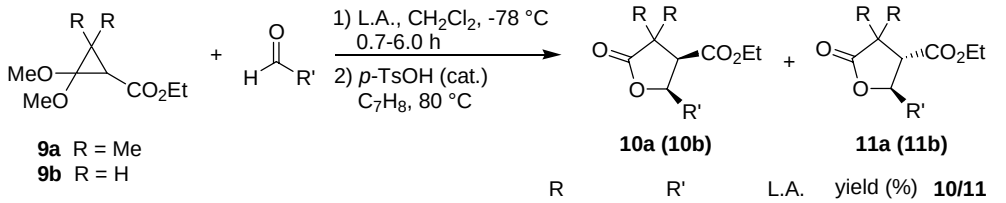
One of the first examples of a productive [3+2] cyclopropane cycloaddition was reported by Kuwajima.[5] This reaction involved the addition of 1-ethoxy-1-trimethylsilyloxycyclopropane **6** to aldehydes in the presence of a stoichiometric amount of $TiCl_4$ (**Scheme 2-3**). The mechanism is believed to involve initial electrophilic attack on the bis(donor) substituted cyclopropane by $TiCl_4$ to afford titanium ester homoenolate **7**, which then adds to the aldehyde affording γ-lactone **8** after ring closure. This one step synthesis of γ-lactones was shown to be effective only for linear aliphatic aldehydes.

Scheme 2-3. $TiCl_4$ Promoted γ-Lactone Formation from Donor Substituted Cyclopropane **6** and Aldehydes



In a series of reports, Saigo demonstrated the facile synthesis of highly substituted γ-lactones through metal promoted [3+2] cyclopropane cycloadditions with carbonyl compounds.[4,6-8] In the presence of a stoichiometric amount of Lewis acid, donor-acceptor cyclopropanes **9** react with aldehydes to produce 3,4-*cis*-substituted γ-lactones (**10**) with good diastereoselectivity (**Scheme 2-4**).[4] With both aliphatic and aromatic aldehydes, $SnBr_4$ and $TiBr_4$ are effective promoters for the cycloaddition; however, with both metals selectivity is generally higher with 3,3-dimethyl substituted cyclopropane **9a** versus 3-unsubstituted analog **9b**. While lactone formation is noted upon aqueous workup, complete lactonization typically requires subsequent heating of the product mixture with TsOH in toluene. The reaction is believed to proceed through ring-opened zwitterion **12** with the enolate being formed in an *E*-geometry (**Scheme 2-5**). Placing the large substituent of the aldehyde in an equatorial position, the aldol reaction with **12** may proceed through a chair-like transition state to afford the observed major stereoisomer.

Scheme 2-4. Metal Bromide Promoted γ-Lactone Formation from D-A Cyclopropane **9** and Aldehydes

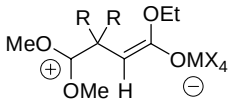


9a R = Me
9b R = H

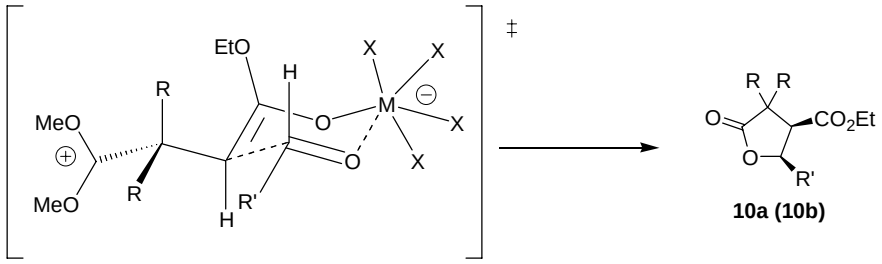
10a (10b) **11a (11b)**

R	R'	L.A.	yield (%)	**10/11**
Me	$PhCH_2CH_2$	$SnBr_4$	50	99:1
H	$PhCH_2CH_2$	$SnBr_4$	61	81:19
Me	$(CH_3)_2CH$	$TiBr_4$	87	95:5
H	$(CH_3)_2CH$	$TiBr_4$	88	82:18
Me	Ph	$TiBr_4$	91	98:2
H	Ph	$TiBr_4$	87	85:15

Scheme 2-5. Proposed Transition State for the Formation of 3,4-*cis*-Substituted γ-Lactones



12

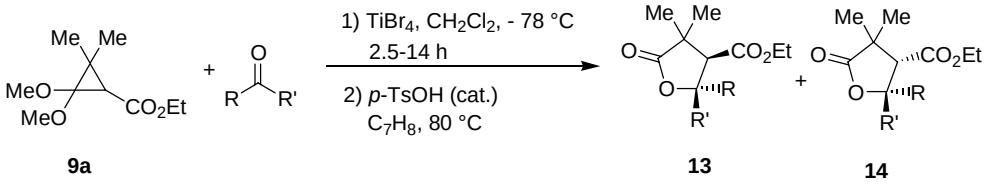


10a (10b)

In a similar manner, unsymmetrical ketones also undergo cycloaddition with D-A cyclopropane **9a** in the presence of a stoichiometric amount of $TiBr_4$ to afford γ-lactones (**13**) in which the carboxyester and large substituent from the ketone are in a *cis*-relationship (**Scheme 2-6**). In general, the cycloadditions are highly stereoselective with ketones that are

either unsaturated or have α-branching, but lose selectivity with simple straight chain aliphatic ketones.

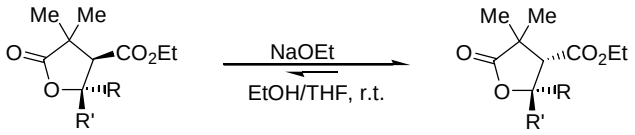
Scheme 2-6. $TiBr_4$ Promoted γ-Lactone Formation from D-A Cyclopropane **9a** and Unsymmetrical Ketones



R	R'	yield (%)	**13/14**
Me	*n*-C_8H_{17}	80	74:26
Me	^{i}Bu	93	91:9
Me	^{i}Pr	82	99:1
Me	$CH{=}CH_2$	70	93:7
Me	$CH{=}CMe_2$	35	99:1

An interesting facet of this chemistry is the ability to stereoselectively convert the primary 3,4-*cis*-adducts from the cycloadditions with aldehyde and ketones to the more thermodynamically stable *trans*-lactones through simple basic equilibration (**Scheme 2-7**). Although the equilibrium mixture generally favors the *trans*-product to a large degree, the exact equilibrium ratio depends on the nature of the substituents and may prove modest.

Scheme 2-7. Basic Equilibration of *cis*-γ-Lactones to *trans*-γ-Lactones

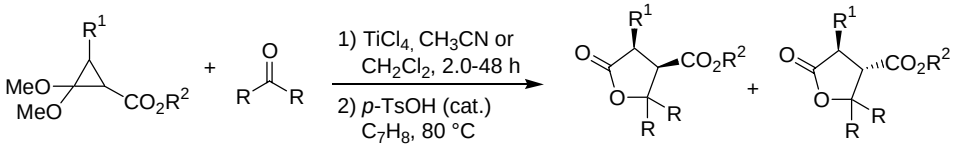


10a or **13** (*cis*) → **11a** or **14** (*trans*)

R	R'	time (h)	yield (%)	*cis*/*trans*
H	$PhCH_2CH_2$	7	86	8:92
H	Ph	3	84	3:97
Me	*n*-C_8H_{17}	42	91	21:79
Me	^{i}Bu	14	quant.	18:82
Me	^{i}Pr	72	91	4:96

With the use of similar D-A cyclopropanes possessing a stereogenic center at the 3-position (**15**), 2,3-*cis*-γ-lactones (**16**) can be formed via a $TiCl_4$ promoted cycloaddition with symmetrical dialkyl ketones in good yields and excellent diastereoselectivities (**Scheme 2-8**).[7] As with the 3,4-*cis*-lactones, these products can be converted to the *trans*-isomers (**17**) with high selectivity through a basic equilibration protocol.

Scheme 2-8. $TiCl_4$ Promoted γ-Lactone Formation From D-A Cyclopropane **15** and Symmetrical Ketones



15 R = alkyl → **16** + **17**

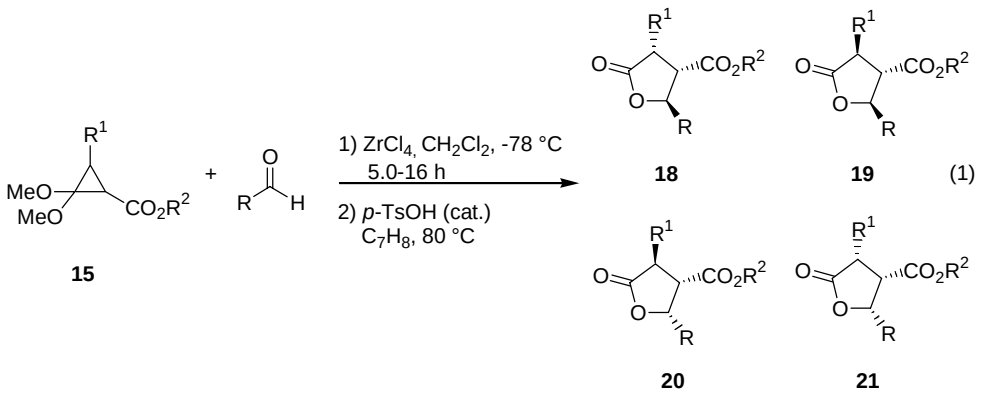
71% (avg.)

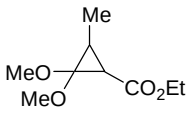
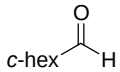
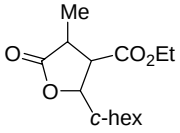
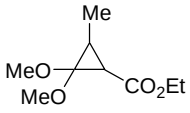
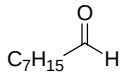
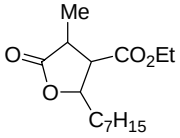
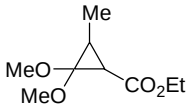
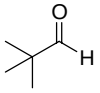
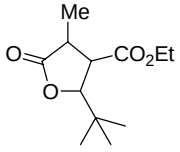
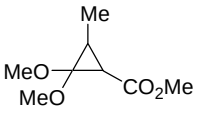
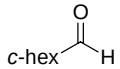
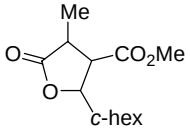
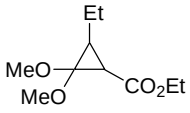
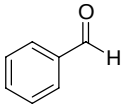
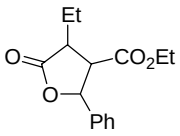
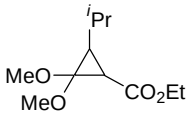
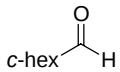
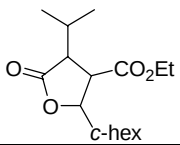
16:17 = 93:7 (avg.)

As far as the rapid construction of stereochemical density is concerned, the highlight of this [3+2] cycloaddition strategy is realized with the reaction of D-A cyclopropanes **15** and

aldehydes (eq 1).[8] In the presence of a stoichiometric amount of $ZrCl_4$ (2α,3α,4β)-trisubstituted γ-lactones (**18**) are produced in good yields and stereoselectivities (**Table 2-1**).

Table 2-1. $ZrCl_4$ Promoted Cycloaddition of D-A Cyclopropane **15** with Aldehydes[a]

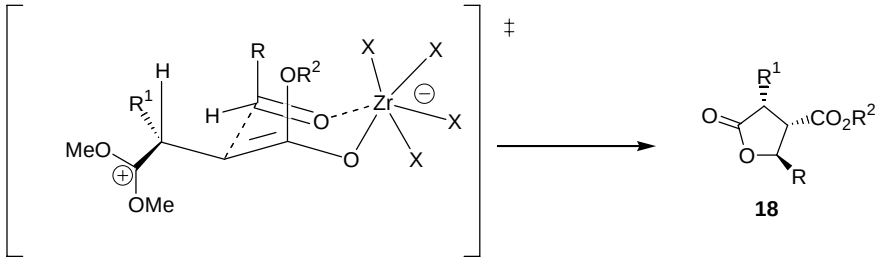


Entry	Cyclopropane	Aldehyde	Product	Yield (%)	18/19/20/21
1				89	81:4:4:11
2				84	68:14:5:13
3				84	86:3:1:10
4				90	81:3:4:12
5				92	74:4:3:19
6				96	90:5:2:3

a) Cyclopropane (1.1 equiv), Aldehyde (1.0 equiv), $ZrCl_4$ (1.1 equiv).

The stereoselectivity observed in this reaction is rationalized by invoking a transition state similar to that shown in **Scheme 2-5**. In this transition state, the hydrogen at the stereogenic center is eclipsed with the enolate double bond to reduce $A^{1,3}$ strain (**Scheme 2-9**). The polarized aldehyde approaches the enolate from the face opposite the cationic substituent due to electrostatic repulsion, affording the *cis*-2,3-selectivity. The *trans*-3,4-selectivity is explained if the aldehyde substituent is situated in an axial position. This would assume that the steric repulsions between R and X, as well as R and OR^2 are less than the repulsion between R and R^1 that would occur if the substituent were equatorial.

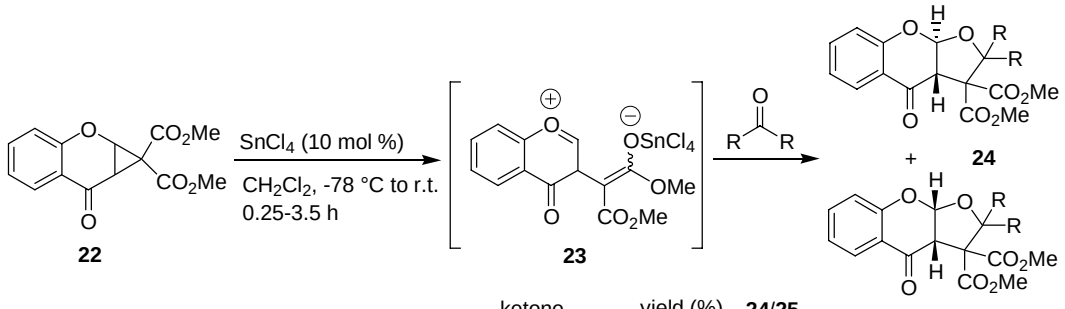
Scheme 2-9. Proposed Transition State For the Formation of (2α,3α,4β)-γ-Lactones



The synthesis of tetrahydrofuro[2,3-*b*][1]benzopyranones from methanochromanone has been described by Sugita.[9] When 2,3-methanochromanone is geminally substituted at the methano-position with two electron-withdrawing groups (**22**) it is susceptible to Lewis acid assisted cyclopropane ring cleavage. The carbon-carbon bond between the methano- and 2-positions undergoes selective heterolysis affording 1,3-zwitterion **23**, which can then be trapped with carbonyl compounds (**Scheme 2-10**). In the presence of catalytic $SnCl_4$ this D-A cyclopropane undergoes facile [3+2] cycloaddition with a variety of symmetrical ketones to afford *trans*-fused tetrahydrofurans (**24**) in excellent yields and diastereoselectivities.

Treatment of the acetone adduct with triethylamine in CH_2Cl_2 at room temperature affords complete conversion to the *cis*-isomer (**25**) in 86% yield.

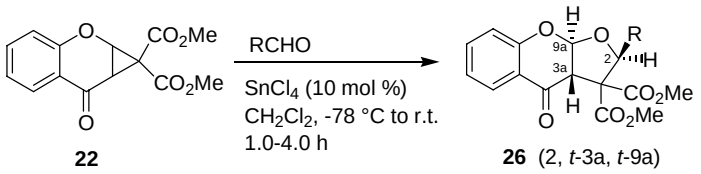
Scheme 2-10. $SnCl_4$ Catalyzed Tetrahydrofuran Synthesis from 2,3-Methanochromanone **22** and Symmetrical Ketones



ketone	yield (%)	**24/25**
acetone	99	>99:1
3-pentanone	70	>99:1
benzophenone	80	>99:1
cyclopentanone	88	>50:1
cyclohexanone	88	>99:1
cycloheptanone	67	>50:1

When conducted with aldehydes, the reaction is also very efficient, with excellent control over the three stereocenters formed in the cyclic acetals.[10] This reaction is effective for aliphatic, aromatic, and unsaturated aldehydes, and in all cases examined the ratio of the (2, *t*-3a, *t*-9a)-isomer (**26**) to all other isomers was greater than 20:1 (**Scheme 2-11**). The *trans*-2,3a selectivity is believed to arise from a transition state similar to that proposed by Saigo for the formation of trisubstituted lactones (see **Scheme 2-9**), where the coordinated aldehyde and enolate assume a chair-like conformation (**Scheme 2-12**). The hydrogen at the stereogenic center eclipses the enolate double bond and the aldehyde approaches from the

Scheme 2-11. $SnCl_4$ Catalyzed Tetrahydrofuran Synthesis from 2,3-Methanochromanone **22** and Aldehydes

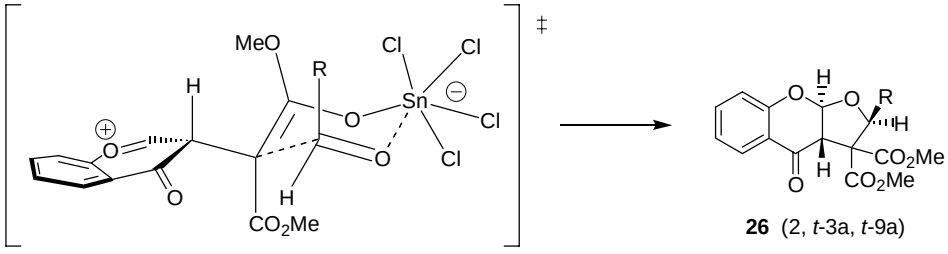


22 **26** (2, *t*-3a, *t*-9a)

R	yield (%)	d.r.
Ph	89	>50:1
p-$MeOC_6H_4$	92	>50:1
MeCH=CH	99	>20:1
PhCH=CH	98	>20:1
$Me(CH_2)_4$	40	>20:1

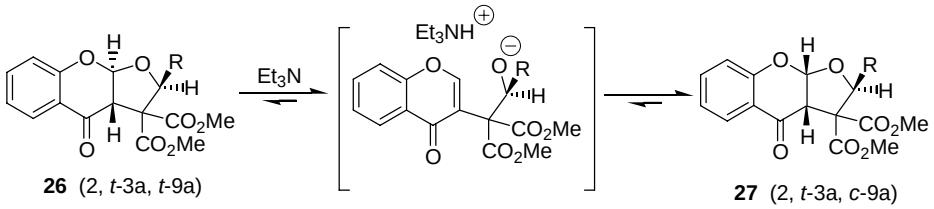
face opposite the oxocarbenium ion. The aldehyde substituent assumes an axial position to avoid unfavorable steric interaction with the benzopyran ring ketone, leading to the observed relative stereochemistry at the 2- and 3a-positions. The source of the diastereoselectivity at the 9a-position is not clearly disseminated by the authors. Under basic conditions (Et_3N, CH_2Cl_2, r.t.) the (2, *t*-3a, *t*-9a)-isomer is converted through a retro-Michael-type/Michael-type addition pathway to the thermodynamically most stable (2, *t*-3a, *c*-9a)-isomer **27** selectively over other possible stereoisomers (**Scheme 2-13**).

Scheme 2-12. Proposed Transition State for the Formation of (2, *t*-3a, *t*-9a)-Tetrahydrofuran **26**



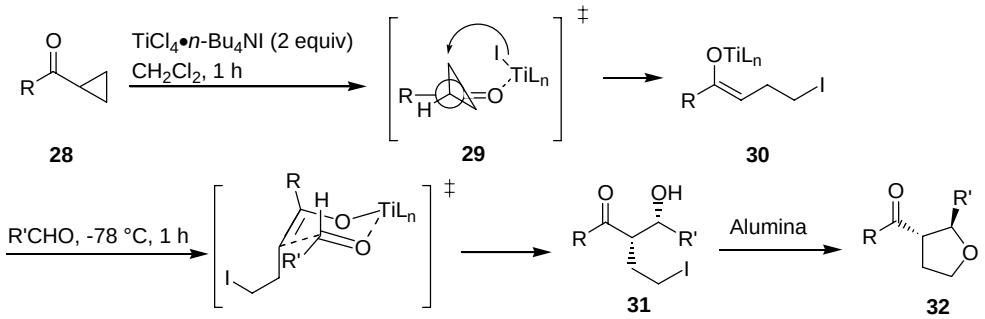
26 (2, *t*-3a, *t*-9a)

Scheme 2-13. Basic Equilibration of the Primary Cycloadduct **26**



The synthesis of *trans*-acyltetrahydrofurans from the [3+2] cycloaddition of cyclopropyl ketones and aldehydes was described by Oshima.[11] Unlike D-A cyclopropanes, the carbon-carbon bond cleavage of a cyclopropane possessing only an acceptor substituent requires the use of a nucleophile in addition to a Lewis acid. Upon carbonyl complexation of cyclopropyl ketone **28** with $TiCl_4$ the carbon-carbon bond of the cyclopropane is significantly weakened and the cyclopropane becomes a homologous Michael-acceptor (**Scheme 2-14**). Iodide serves as an internal nucleophile in species **29**, rupturing the bond, with simultaneous enolate formation. In the preferred conformation, the steric interaction between the cyclopropane ring and the ketone substituent is minimized and the *Z*-titanium enolate **30** is formed. Aldol addition produces *syn*-α-iodoethyl-β-hydroxyketone **31**, and iodide serves as a convenient leaving group in a 5-*exo*-*tet* cyclization. Formation of the *trans*-acyltetrahydrofuran (**32**) may occur spontaneously, or is easily facilitated by treatment with active alumina. The reaction is effective with both aromatic and aliphatic aldehydes and furnishes substituted tetrahydrofurans in good yields with only trace isomeric impurities.

Scheme 2-14. $TiCl_4$•*n*-Bu_4NI Promoted Cycloaddition of Acylcyclopropanes and Aldehydes

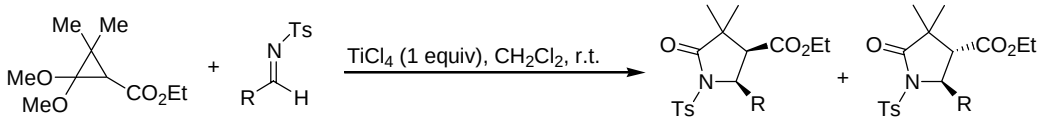


R	R'	yield (%)	d.r.
Ph	Ph	94	>99:1
Ph	*n*-C_9H_{19}	67	>99:1
Ph	^{i}Pr	64	>99:1
Ph	CH_3	78	>99:1
Me	Ph	72	>99:1
Me	*t*-Bu	76	>99:1
Me	CH_3	60	80:20

2.2.2 Lactams, Pyrroles, and Polyhydropyrroles

The [3+2] cycloaddition chemistry developed by Saigo for the stereoselective synthesis of γ-lactones was extended to the synthesis of γ-lactams.[6] It was found that the reaction of D-A cyclopropane **9a** with aromatic *N*-tosyl aldimines under $TiCl_4$ promotion affords *cis*-3,4-γ-lactams (**33**) in good yields and excellent diastereoselectivities (**Scheme 2-15**). It should be noted that only aldimines derived from *p*-toluenesulfonamide display significant stereoselectivity in this reaction. Additionally, unlike the analogous synthesis of γ-lactones, no separate step is needed to ensure complete lactamization.

Scheme 2-15. $TiCl_4$ Promoted γ-Lactam Synthesis from D-A Cyclopropane **9a** and *N*-Tosyl Aldimines

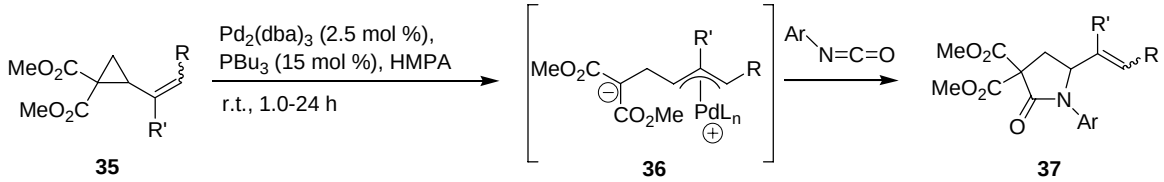


9a **33** **34**

R	yield (%)	**33/34**
Ph	81	98:2
p-$MeOC_6H_4$	73	98:2
p-$NO_2C_6H_4$	91	98:2
2-furyl	83	95:5
E-PhCH=CH	67	96:4

A mechanistically distinct approach to butyrolactam synthesis involves the palladium catalyzed [3+2] cycloaddition of vinyl cyclopropanes and isocyanates.[12] Vinyl cyclopropanes activated with electron-withdrawing groups (**35**) undergo oxidative addition to Pd(0) and subsequent cycloaddition with aromatic isocyanates via π-allyl complex **36** to afford *N*-aryl-γ-lactams (**37**) (**Scheme 2-16**). The intermediate 1,3-zwitterion is not active towards aliphatic isocyanates.

Scheme 2-16. Lactam Synthesis via π-Allylpalladium Complex **36** and Aryl Isocyanates

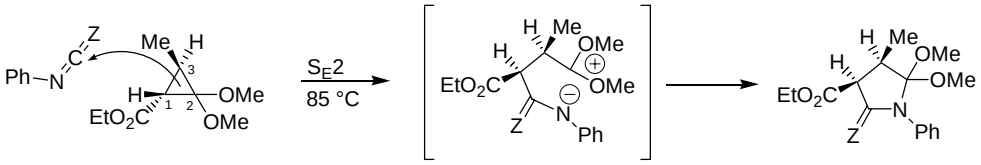


35 **36** **37**

R	R'	Ar	yield (%)
H	H	Ph	87
H	H	*p*-$MeOC_6H_4$	86
H	H	*p*-$NO_2C_6H_4$	69
H	Me	Ph	90
Me	H	Ph	77

Purely thermal [3+2] cycloadditions of D-A cyclopropanes and electron deficient π-systems are known, although the scope of these reactions is not well developed.[13,14] Heating cyclopropane **38** separately in the presence of phenyl isocyanate and phenyl isothiocyanate affords pyrrolidinone **40a** and pyrrolidine-2-thione **40b**, respectively (**Scheme 2-17**). The reaction is believed to take place via an S_E2-type mechanism with inversion occurring at cyclopropane C-1. Due to various side reactions, both products are produced in low isolated yields.

Scheme 2-17. Thermal Cycloaddition Pathway of Cyclopropane **38** and Isocyanates/Isothiocyanates



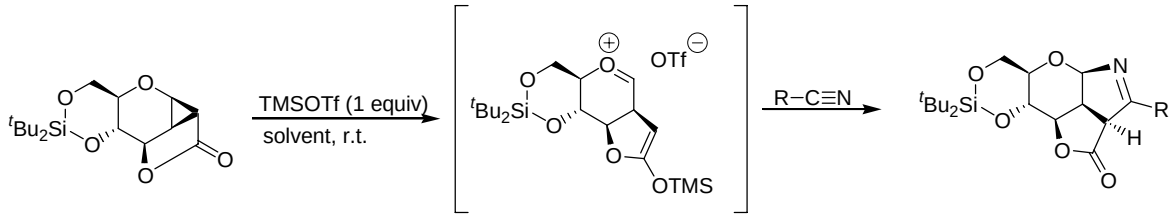
38

39a, Z = O
39b, Z = S

40a, 35%
40b, 35%

Investigations by Pagenkopf into the reactivity of glycal-derived cyclopropane **41** revealed that nitriles could act as dipolarophiles in [3+2] cycloadditions with D-A cyclopropanes to afford 2*H*-3,4-dihydropyrroles.[2,15] In the presence of a stoichiometric amount of TMSOTf, regioselective cyclopropane ring cleavage occurs affording 6-membered oxocarbenium ion intermediate **42** (**Scheme 2-18**). This intermediate can be trapped with aliphatic, aromatic, and α,β-unsaturated nitriles affording highly functionalized optically pure dihydropyrroles (**43**) as single stereoisomers.

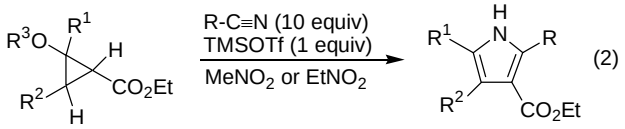
Scheme 2-18. [3+2] Cycloaddition of Glycal-Derived D-A Cyclopropane **41** and Nitriles



41 **42** **43**

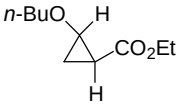
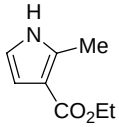
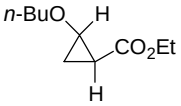
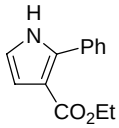
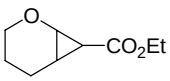
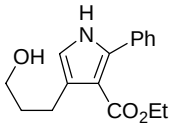
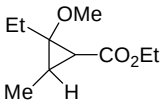
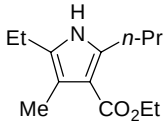
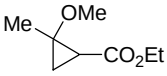
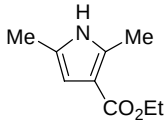
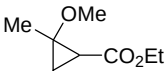
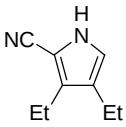
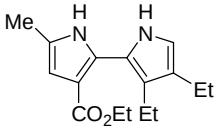
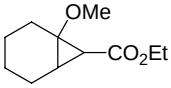
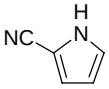
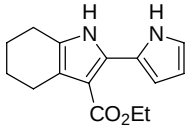
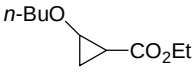
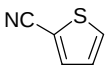
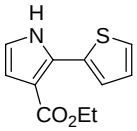
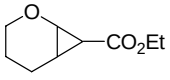
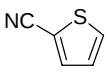
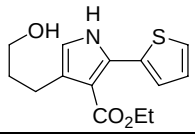
R	solvent	yield (%)
Ph	CH_2Cl_2	81
Me	MeCN	96
^{t}Bu	CH_2Cl_2	79
$Cl(CH_2)_3$	CH_2Cl_2	87
E-PhCH=CH	$MeNO_2$	60

Attempts to extend the generality of this methodology through the use of non-lactonized D-A cyclopropanes (**44**) lead to spontaneous alkoxide elimination and tautomerization, to directly produce pyrroles (**45**) (eq 2).[16,17] Furthermore, no [3+2] cycloaddition is observed unless the reactions are carried out in either nitromethane or nitroethane. However, under these conditions this [3+2] cycloaddition strategy represents an extremely powerful method for the rapid construction of substituted pyrroles with complete regiochemical control (**Table 2-2**). Selective substitutition at the C-4 and C-5 positions of the pyrrole can be controlled through the appropriate cyclopropane substitution pattern. Substitution at both, either, or neither of these positions can readily be accommodated (entries 1-5). Moreover, the use of 2-cyanopyrroles (entries 6 and 7) and 2-cyanothiophenes (entries 8 and 9) allows for the synthesis of diverse 2,2'-bipyrroles and 2,2'-thienylpyrroles, respectively.



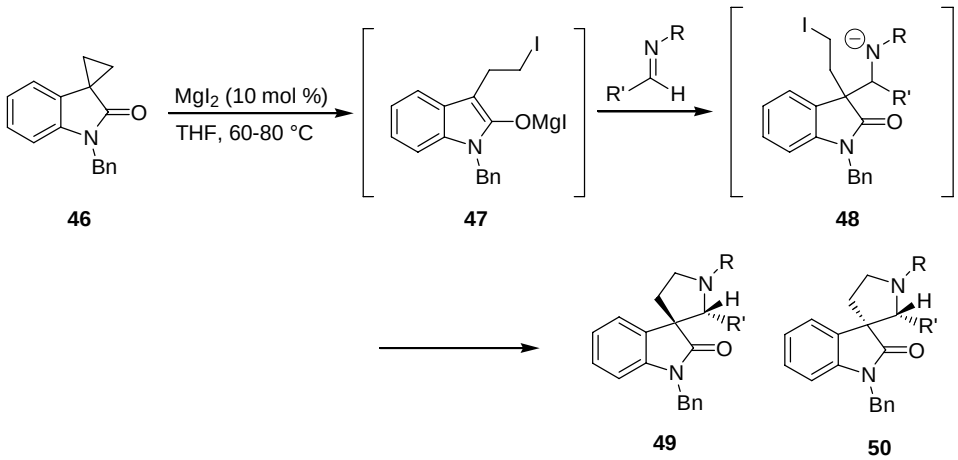
44 **45**

Table 2-2. Scope of Pyrrole Synthesis from D-A Cyclopropanes and Nitriles (Eq 2)

Entry	Cyclopropane	Nitrile	Product	Yield (%)
1		MeCN		80
2		PhCN		35
3		PhCN		58
4		*n*-PrCN		85
5		MeCN		62
6				82
7				62
8				47
9				73

The use of Lewis acids in conjunction with an iodide source for the cleavage of acceptor substituted cyclopropanes (*vide supra*) was initially developed described by Carreira for the synthesis of the spiro[pyrrolidin-3,3'-oxindole] ring system.[18] Due to the facile dissociation of iodide from MgI_2 complexes, this metal salt acts as both a Lewis acid and nucleophile source Thus, in the presence of a catalytic amount of MgI_2, spiro[cyclopropane-1,3'-oxindole] **46** undergoes [3+2] cycloaddition with a variety of aldimines (**Scheme 2-19**). The mechanism is believed to involve initial carbonyl/Mg(II) coordination followed by iodide transfer to produce magnesium enolate **47**, which then undergoes Mannich addition to the aldimine. Iodide displacement from **48** affords the target ring system **49** in good yield with moderate to excellent diastereoselectivity. This methodology was used in the total syntheses of (±)-strychnofoline and spirotryprostatin B.[19,20]

Scheme 2-19. MgI_2 Catalyzed Cycloaddition of Spiro[cyclopropane-1,3'-oxindole] **46** and Aldimines

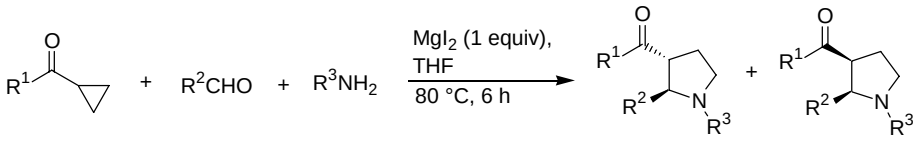


R	R'	yield (%)	**49/50**
$-CH_2CH_2CH_2CH_2-$		68	86:14
Allyl	^{i}Pr	83	80:20
p-$TolSO_2$	Ph	97	91:90
p-$TolSO_2$	Furyl	97	85:15
p-$TolSO_2$	PhCH=CH	62	74:16
p-$TolSO_2$	$^i Pr_3Si{\equiv}C$	77	98:2

After the reports from Carreira and Oshima exhibiting the reactivity of acylcyclopropanes in the presence of a Lewis acid and iodide source, Olsson reported a general one-pot synthesis of 2,3-disubstituted pyrrolidines using this same methodology.[21] At elevated temperature, *trans*-2,3-pyrrolidines (**51**) are formed from the three-component reaction of cyclopropyl ketones, aldehydes and primary amines in the presence of a stoichiometric amount of MgI_2 (**Scheme 2-20**). Aromatic ketones are effective substrates in this reaction, while cyclopropyl methyl ketone shows very poor reactivity. The *trans*-adduct is favored in all cases with good diastereoselectivity, and this selectivity improves upon the use of branched aliphatic aldehydes. The use of linear aliphatic aldehydes, however, results in no product formation. The amine component is shown to have little effect on the selectivity. In addition to MgI_2, these reactions can be promoted with 1.5 equivalents of

Et_2AlI in THF at room temperature. In most cases this variation does not produce significantly different results from MgI_2, except in the case of hexanal. While the three-component reaction of this aldehyde with cyclopropyl phenyl ketone and 4-methyl-benzylamine affords no product with MgI_2, the desired product is produced as a single stereoisomer in 57% yield when treated with Et_2AlI.

Scheme 2-20. MgI_2 Promoted Three-Component Synthesis of Substituted Pyrrolidines



51 **52**

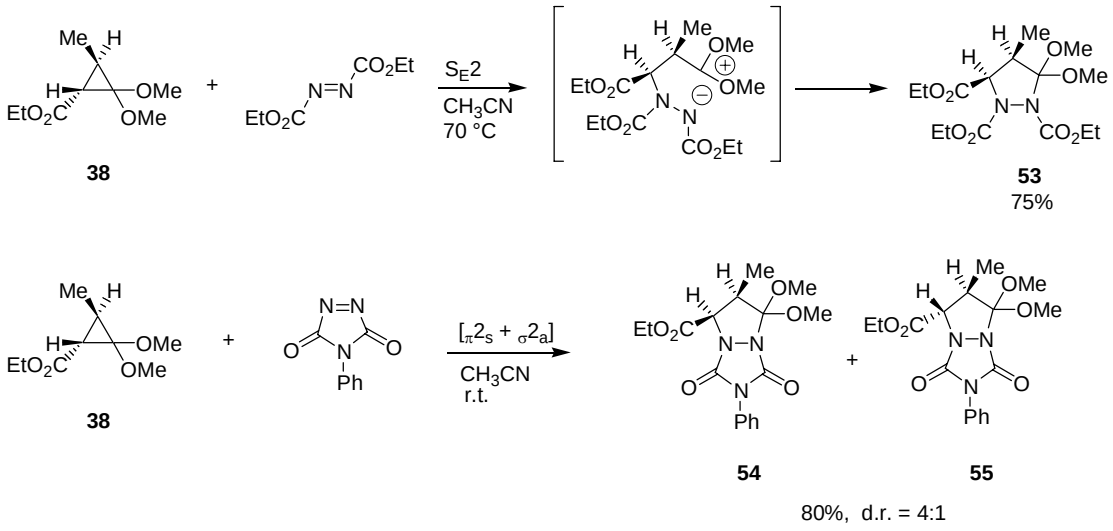
R^1	R^2	R^3	yield (%)	**51/52**
Ph	*p*-FC_6H_4	$CH_3C_6H_4CH_2$	64	82:18
Ph	*p*-$MeOC_6H_4$	$CH_3C_6H_4CH_2$	56	90:10
Ph	$(CH_3)_3CCH_2$	$CH_3C_6H_4CH_2$	73	>99:1
Ph	*p*-FC_6H_4	Allyl	67	95:5
Thienyl	$(CH_3)_3CCH_2$	$CH_3C_6H_4CH_2$	64	>99:1
Me	*p*-$MeOC_6H_4$	*n*-C_5H_{11}	16	93:7

2.2.3 Various Heterocycles

Under thermal conditions D-A cyclopropane **38** undergoes [3+2] cycloadditions with diazenes to afford substituted pyrazolidines.[22] The mechanism by which this transformation occurs has an impact on the stereoselectivity and is believed to vary depending on the electrophilicity of the dipolarophile (**Scheme 2-21**). When diastereomerically pure **38** is treated with diethyl azodicarboxylate (DEAD), a single isomeric pyrazolidine (**53**), which results from an S_E2 attack on the cyclopropane, is produced in 75% yield. When the same cyclopropane is treated with 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) a mixture of diastereomers (**54**/**55**) is produced in 80% yield. The extreme electrophilic nature of PTAD

is assumed to make available a concerted symmetry-allowed [$_{\pi}2_s$ + $_{\sigma}2_a$] process that competes with the ionic process. The concerted process necessitates inversion at one reacting cyclopropane carbon with retention at the other, thus allowing for the formation of isomers.

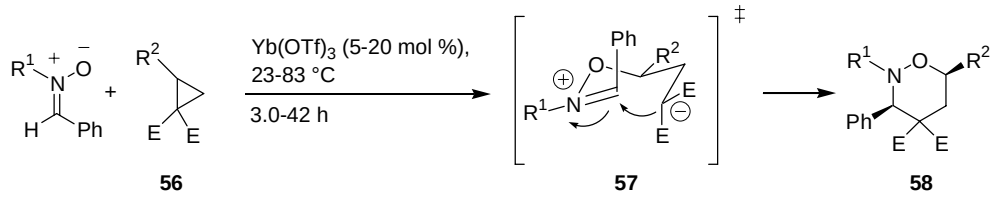
Scheme 2-21. Mechanistic Pathways in the Thermal Synthesis of Pyrazolidines from D-A Cyclopropane **38** and Diazenes



The synthesis of tetrahydro-1,2-oxazines (**58**) through the $Yb(OTf)_3$-catalyzed cycloaddition of 1,1-cyclopropane diesters (**56**) and nitrones was reported by Kerr (**Scheme 2-22**).[23] Although this reaction produces a six-membered ring, the authors have designated it a "homo [3+2] cycloaddition," citing the non-electronic involvement of the cyclopropane methylene unit in the process. Cyclopropanes substituted at the 2-position with unsaturated units display the greatest efficiency in this cycloaddition, though unsubstituted cyclopropanes can be accommodated with increased temperature or higher catalyst loadings. In each case studied, the product was formed solely as the *cis*-isomer with complete regioselectivity. One

possible mechanism that accounts for this selectivity involves initial attack at the cyclopropane tertiary carbon by the nitrone oxygen and subsequent ring closure of the imminium ion species **57** through a chair-like conformation. Subsequent to the initial disclosure of this reaction, a one-pot cycloaddition process in which the nitrone is generated *in situ* from an aldehyde and hydroxylamine was disclosed.[24] The generality of the reagents was also greatly broadened in this report.

Scheme 2-22. $Yb(OTf)_3$ Catalyzed Cycloaddition of 1,1-Cyclopropane Diester **56** and Nitrones



56 **57** **58**

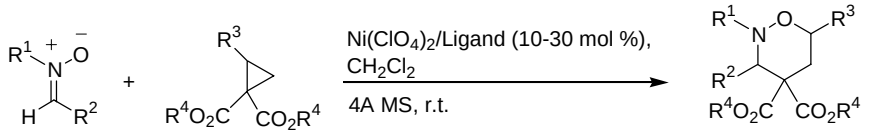
E = CO_2Me or CO_2Et

R^1	R^2	yield (%)
p-Tolyl	H	77
p-Tolyl	Ph	94
p-Tolyl	Vinyl	73
Me	Ph	84
Me	Styryl	74
Me	Vinyl	52

An enantioselective variant of the cyclopropane/nitrone homo [3+2] cycloaddition has been developed by Sibi.[25] A screen of Lewis acids in combination with various chiral ligands lead to the discovery that $Ni(ClO_4)_2$ in conjunction with bisoxazoline **59** is an effective catalyst for the asymmetric formation of tetrahydro-1,2-oxazines (**60**) (**Scheme 2-23**). The conditions are tolerant of a variety of nitrones derived from aromatic aldehydes and aryl or alkyl hydroxylamines. While substitution at the 2-position of the cyclopropane is not required, it is noted that unsubstituted cyclopropanes are very slow to react compared to their

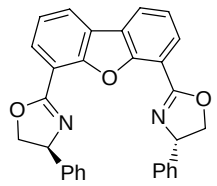
substituted counterparts. The enantioselectivity is excellent in most cases, but diastereoselectivity is almost nonexistent. This is in stark contrast to the racemic reaction reported by Kerr (*vide supra*). In the cases where diastereomers are possible, the enantioselectivity for the formation of both the *cis*- and *trans*-isomers is quite good. This evidence suggests a stepwise mechanism in which the chiral catalyst is only effective in controlling the absolute stereochemical induction at one center.

Scheme 2-23. Catalytic Enantioselective Synthesis Tetrahydro-1,2-oxazines



56 **60**

Ligand =



59

R^1	R^2	R^3	R^4	yield (%)	trans/cis	% ee
Me	Ph	H	Et	99	-	92
Ph	Ph	H	Et	99	-	94
Bn	Ph	H	Et	99	-	93
Me	4-BrPh	Me	Me	99	0.8:1	96 (90)
Me	4-BrPh	Ph	Me	99	1.4:1	95 (90)
Me	Ph	Ph	Me	99	1.4:1	96 (90)

2.3 Conclusions

The reactivity of substituted cyclopropanes has led to the development of number of methods for the rapid stereoselective synthesis of 5-membered heterocycles. The lability of the carbon-carbon σ-bonds of cyclopropanes, allows these structures to serve as convenient 1,3-dipolar synthons that react readily with a number of heterodipolarophiles including aldehydes, ketones, imines, isocyanates, and nitriles. Consequently, current methodology allows convenient access to such ubiquitous structures as γ-lactones, γ-lactams, tetrahydrofurans, pyrroles and pyrrolidines. The enhanced reactivity observed for donor-

acceptor (D-A) cyclopropanes in particular has spurred the extensive use of these cyclopropane derivatives in [3+2] cycloaddition chemistry. Furthermore, the products of these reactions often possess several points for further functionalization. Although thermal and transition metal catalyzed methods exist, Lewis acid promotion/catalysis constitutes the bulk of known procedures involving D-A cyclopropanes. This chemistry is also amendable to asymmetric catalysis, however representation in minimal. Recent developments have shown that dual activation of the cyclopropane is not a prerequisite for successful cycloaddition. This has been exemplified by the use of Lewis acids/iodide sources and acceptor substituted cyclopropanes in the synthesis of acylpyrrolidines. The high reactivity and ease of preparation of substituted cyclopropanes is likely to sustain continued interest in the use of these compounds in [3+2] cycloaddition methodology.

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CHAPTER 3

ENANTIOSPECIFIC AND DIASTEREOSELECTIVE TIN-CATALYZED CYCLOADDITION REACTIONS OF ALDEHYDES AND DONOR-ACCEPTOR CYCLOPROPANES: THE SYNTHESIS OF 2,5-DISUBSTITUTED TETRAHYDROFURANS

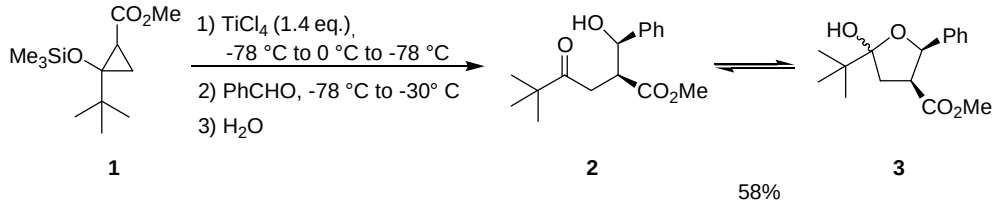
3.1 Introduction

The prevalence of tetrahydrofuran moieties in important natural products makes the straightforward preparation of these structures an important issue in synthetic organic chemistry. Among the methods for the preparation of substituted tetrahydrofurans, the use of cyclopropanes in [3+2] cycloadditions with carbonyl compounds has not been comprehensively explored, but nonetheless represents a powerful and convergent entry into these types of compounds.[1-3] The relative ease with which diverse cyclopropanes can be synthesized combined with their inherent ring strain makes the utilization of these compounds as 3-carbon fragments in the synthesis of 5-membered heterocycles desirable.

Several reports addressing the synthesis of tetrahydrofurans employing cycloaddition methodology have been described. Oshima has shown that tetrahydrofuran formation can occur in a stereoselective manner from cyclopropyl ketones and aldehydes in the presence of 2 equivalents of $TiCl_4$•*n*-Bu_4NI.[4] This methodology is limited to tetrahydrofurans unsubstituted at the 5-position (see **Chapter 2**). Under Lewis acid catalysis, Sugita has

formed acetal tetrahydrofurans via the cycloaddition of an activated methanochromanone with carbonyl compounds.[5,6] Reissig has demonstrated the use of silyloxy-substituted donor-acceptor (D-A) cyclopropanes in a diastereoselective cycloaddition manifold with aldehydes and ketones.[7] The $TiCl_4$ promoted reaction of D-A cyclopropane **1** with benzaldehyde demonstrates this methodology (**Scheme 3-1**). A stoichiometric amount of Lewis acid is necessary to effect ring cleavage and addition to the aldehyde, affording homoaldol product **2** in equilibrium with its tautomeric γ-lactol **3**. In order to "provide preparatively more valuable products," processes were developed to stereoselectively remove

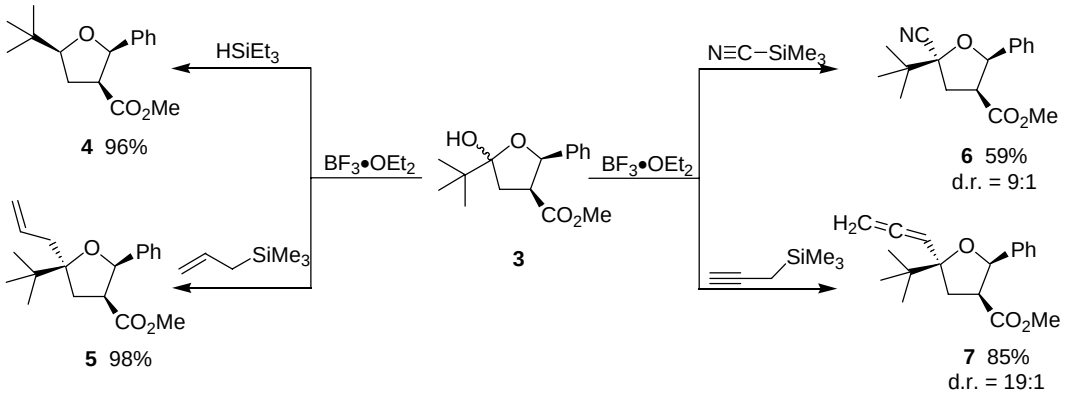
Scheme 3-1. $TiCl_4$ Promoted Cycloaddition of a Silyloxy-Substituted D-A Cyclopropane with Benzaldehyde



the resultant anomeric hydroxyl group. Reduction of γ-lactol **3** with triethylsilane in the presence of $BF_3 \bullet OEt_2$ affords substituted tetrahydrofuran **4** (**Scheme 3-2**). Carbon-carbon bonds can be formed at the anomeric center under the same conditions with the use of various silyl nucleophiles, producing tetrahydrofurans (**5**, **6**, and **7**) containing quaternary centers. While this method is effective for both aldehydes and ketones and represents a particularly reliable route to tetrahydrofuran structures, its multi-step nature detracts from its usefulness. There are no reports in the literature of a catalytic one step synthesis of

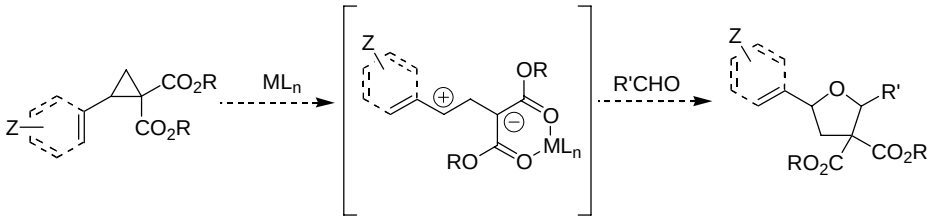
substituted tetrahydrofurans devoid of an anomeric carbon using simple cyclopropane and carbonyl precursors.

Scheme 3-2. Tetrahydrofuran Synthesis via Transformation of Primary Cycloadduct **3**



The "reintroduction" of stereochemistry necessary in the synthesis of tetrahydrofuran derivatives from alkoxy- or silyloxy-substituted D-A cyclopropanes is undesirable (*vide supra*). In lieu of this, we envisioned, in conjunction with a malonyl diester acceptor group, the use of a carbon-based donor on the D-A cyclopropane (**8**). It was hypothesized that this unsaturated donor would, after ring cleavage, stabilize a cationic intermediate (**9**) through resonance, and afford a tetrahydrofuran (**10**) in a single step through cycloaddition with an aldehyde (**Scheme 3-3**). Kerr has successfully employed such cyclopropanes in nucleophilic ring opening/cycloaddition reactions with indoles[8,9] and nitrones.[10,11]

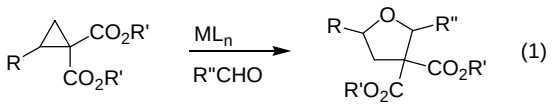
Scheme 3-3. Tetrahydrofuran Synthesis via the Cycloaddition of Carbon-Based D-A Cyclopropanes and Aldehydes



8 **9** **10**

3.2 Racemic Tetrahydrofuran Synthesis: Results and Discussion

This study focused on the Lewis acid-catalyzed cycloaddition reaction of racemic carbon-based D-A cyclopropanes and aldehydes in the synthesis of racemic 2,5-disubstituted tetrahydrofuran derivatives (eq 1).[12] Subsequent to the work reported herein, reports were disclosed describing the analogous use of imines for the synthesis of pyrrolidines.[13,14]



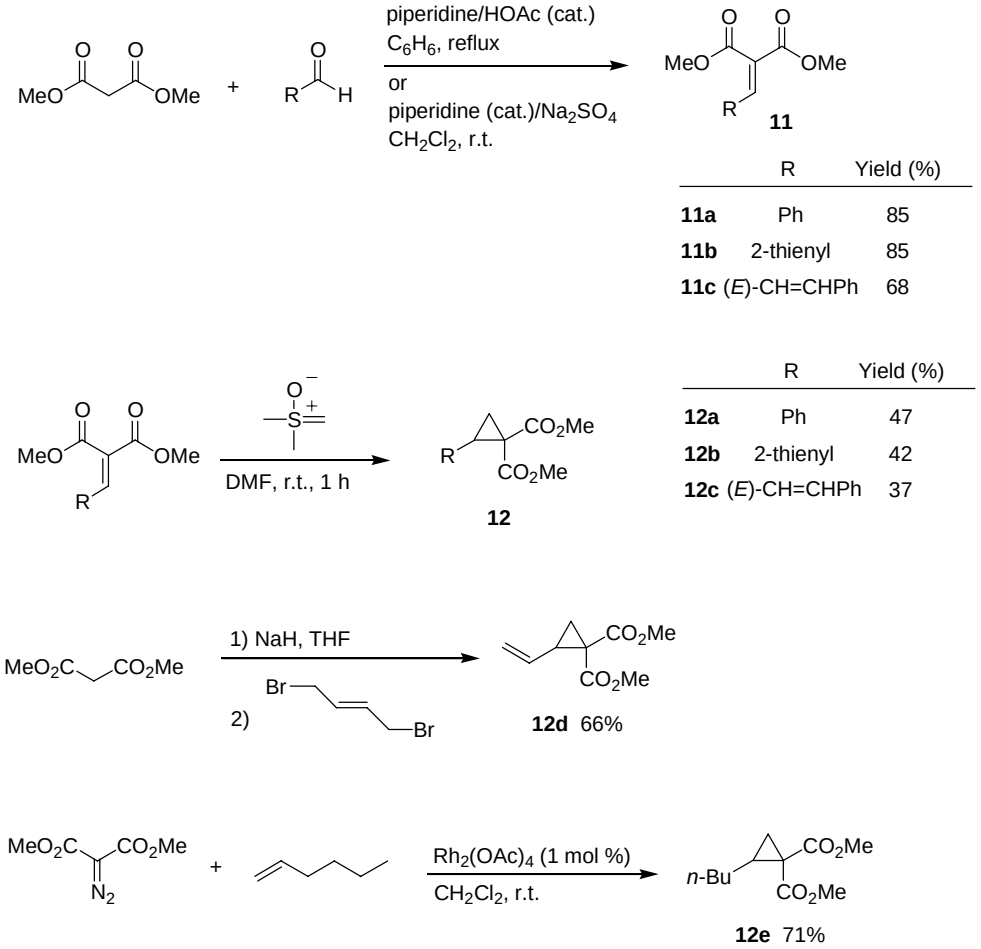
(1)

3.2.1 Substrate Synthesis

The preparation of 2-aryl-cyclopropane-1,1-dicarboxylic acid dimethyl esters (**12a** and **12b**) and the 2-styryl variant (**12c**) were accomplished through the direct cyclopropanation of benzylidene/allylidene malonates with dimethyloxosulfonium methylide (**Scheme 3-4**).[15,16] Benzylidene malonates (**11a** and **11b**) were prepared from the corresponding aldehydes and dimethyl malonate under Knoevenagel condensation conditions employing a catalytic amount of piperidinium acetate with azeotropic removal of water.[15,17] Allylidene malonate **11c** was also prepared via a Knoevenagel condensation with

dehydration by Na_2SO_4 at room temperature.[18] 2-Vinyl cyclopropane **12d** was prepared from the double alkylation of dimethyl malonate with (*E*)-1,4-dibromo-but-2-ene.[19] The preparation of 2-butyl-substituted cyclopropane **12e** was accomplished through the $Rh_2(OAc)_4$-catalyzed decomposition of dimethyl diazomalonate in the presence of 1-hexene.[20]

Scheme 3-4. Synthesis of Racemic D-A Cyclopropanes

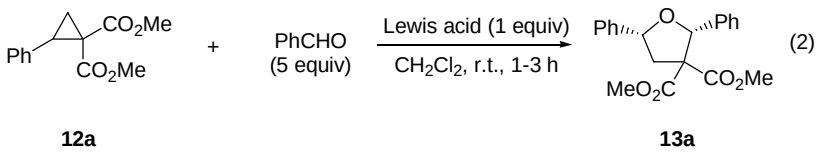


	R	Yield (%)
11a	Ph	85
11b	2-thienyl	85
11c	(*E*)-CH=CHPh	68

	R	Yield (%)
12a	Ph	47
12b	2-thienyl	42
12c	(*E*)-CH=CHPh	37

3.2.2 Reaction Development

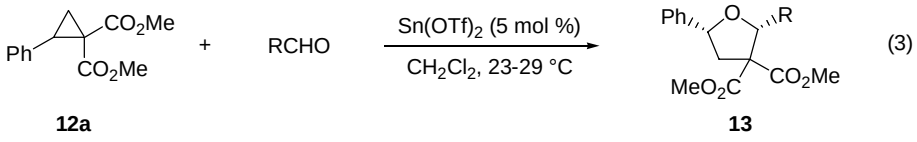
In order to test the viability of the hypothesis depicted in **Scheme 3-3**, a number of Lewis acids were screened for the cycloaddition of phenyl cyclopropane **12a** and benzaldehyde (eq 2), with close attention being paid to conversion, cleanliness and diastereoselectivity. Strong Lewis acids such as $TiCl_4$ and $AlCl_3$ gave significant decomposition of the cyclopropane, while several milder Lewis acids such as $SnCl_2$, $ZnCl_2$, $Mg(OTf)_2$, and $La(OTf)_3$ exhibited no reactivity towards the cyclopropane. $Cu(OTf)_2$ provided clean cycloadduct **13a** in 89% conversion after 3 h with a diastereomer ratio of 59:1. $Sc(OTf)_3$ and $SnCl_4$ cleanly produced **13a** in 100% conversion after 3 h, with diastereomer ratios of 3.1:1 and 31:1, respectively. After 1 h, $Sn(OTf)_2$ afforded the tetrahydrofuran adduct exclusively with 100% conversion and >100:1 *cis*:*trans* selectivity. In light of this, subsequent studies employed $Sn(OTf)_2$ as the Lewis acid catalyst.



12a **13a**

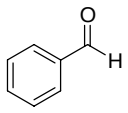
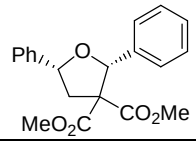
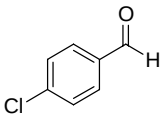
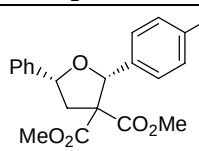
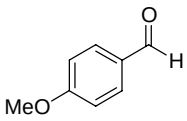
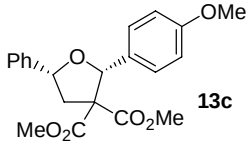
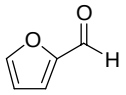
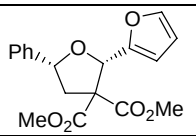
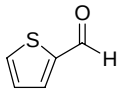
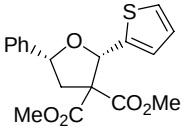
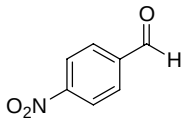
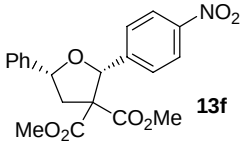
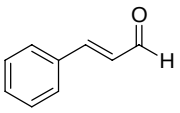
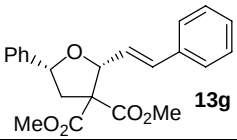
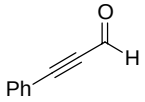
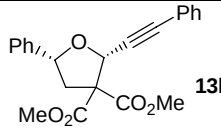
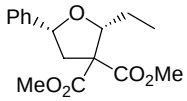
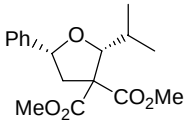
The conditions for the cycloaddition with **12a** were optimized to 5 mol % $Sn(OTf)_2$ and 3 equivalents of aldehyde. Under these conditions, a range of aldehydes was studied to determine the scope of this reaction (eq 3). A number of electronically and sterically diverse 2,5-disubstituted tetrahydrofurans (**13**) were successfully prepared in excellent yields and diastereoselectivities **(Table 3-1**). Electron-rich, -neutral, and slightly electron-poor aldehydes undergo cycloaddition affording the tetrahydrofuran derivatives smoothly in a matter of hours (entries 1-3). The rather electron-poor *p*-nitrobenzaldehyde requires

increased catalyst loading and reaction time, but these conditions gives the product in excellent yield and stereoselectivity (entry 6). The heterocyclic aldehydes furfural and 2-thiophenecarboxaldehyde are suitable substrates for this chemistry (entries 4 and 5); however, 2-pyridinecarboxaldehyde is completely unreactive, presumably due to coordination of $Sn(OTf)_2$ with the Lewis basic nitrogen. α,β-Unsaturated aldehydes in conjugation with an aryl system are effective dipolarophiles (entries 7 and 8). The use of these aldehydes affords a simple means for functionalization of the tetrahydrofuran products. Aliphatic aldehydes are inactive towards cyclopropane **12a** in the presence of $Sn(OTf)_2$, but undergo efficient cycloaddition under $SnCl_4$ catalysis. With the exception of entry 8, in which the diastereomeric ratio is quite low, the 2,5-disubstituted tetrahydrofurans are synthesized in excellent yields and *cis* diastereoselectivity. It is also important to note that all of the cycloadducts are produced as single regioisomers in which the carbonyl oxygen of the aldehyde has formed a bond to the tertiary carbon of the cyclopropane and the carbonyl carbon and the quaternary (malonyl) carbon of the cyclopropane have formed a bond.



12a **13** (3)

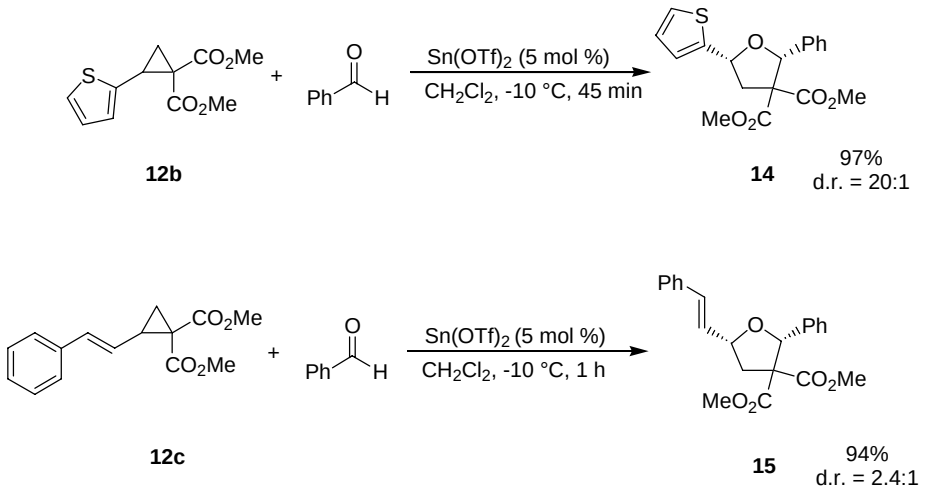
Table 3-1. Aldehyde Scope in the [3+2] Cycloadditon with Cyclopropane **12a** (Eq 3)[a]

Entry	Aldehyde	Product	Time (h)	yield (%)[b]	d.r.[f]
1		 **13a**	2.25	100	>100:1
2		 **13c**	4.75	97	>83:1
3		 **13c**	3.5	99	>84:1
4		 **13d**	3.25	83	24:1
5		 **13e**	3.25	98	>92:1
6[c]		 **13f**	15	91	>52:1
7		 **13g**	3.5	97	17:1
8[d]		 **13h**	6	90	1.6:1
9[e]		 **13i**	1.75	100	>36:1
10[e]		 **13j**	2.5	98	>56:1

a) Cyclopropane (1.0 equiv), aldehyde (3.0 equiv), $Sn(OTf)_2$ (5 mol %), 23-29 °C. b) Isolated yields. c) 20 mol % of $Sn(OTf)_2$ used. d) 10 mol % of $Sn(OTf)_2$ used. e) 5 mol % of $SnCl_4$ used as Lewis acid. f) Determined by ^1H NMR analysis of the crude product mixture.

Simple manipulation of the donor substituent on the cyclopropane ring allows for the formation of a wider range of tetrahydrofuran derivatives. Substituted tetrahydrofurans **14** and **15** are prepared in high yields employing thienyl cyclopropane **12b** and styrenyl cyclopropane **12c** in the $Sn(OTf)_2$-catalyzed cycloaddition with benzaldehyde (**Scheme 3-5**). These adducts are regioisomeric to those synthesized from **12a** using 2-thiophenecarboxaldehyde and (*E*)-cinnamaldehyde (**Table 3-1**, entries 5 and 7). It is interesting to note that these cycloadditions are particularly facile and are complete within one hour at –10 °C. This may be due to the excellent electron-donating ability of the sulfur atom in **12b** and the system of extended conjugation in **12c**.

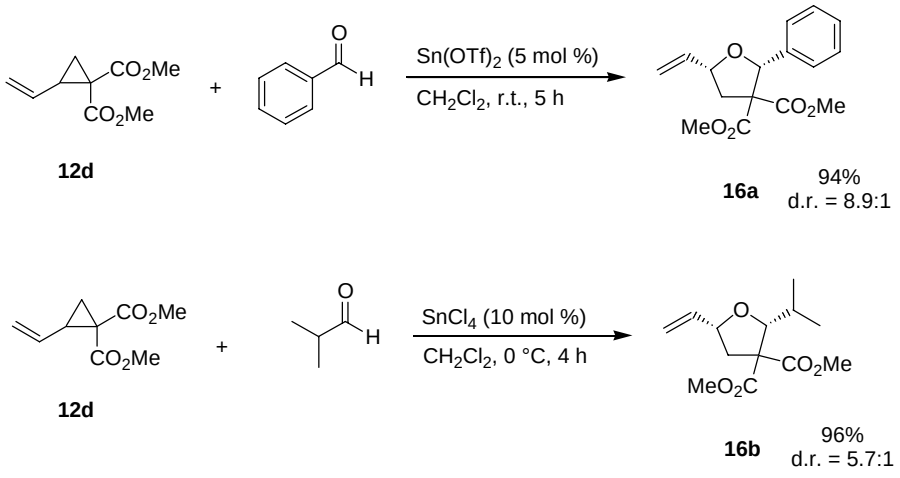
Scheme 3-5. Synthesis of Regiosiomeric Tetrahydrofuran Derivatives via Modification of the Cyclopropane Donor Group



Synthetically more useful 2,5-disubstituted tetrahydrofurans can be prepared from cyclopropanes in which the donor group can easily be manipulated after the [3+2] cycloaddition. In D-A cyclopropane **12d**, a simple vinyl group acts as the donor group. This cyclopropane undergoes facile cycloaddition with both aromatic and aliphatic aldehydes

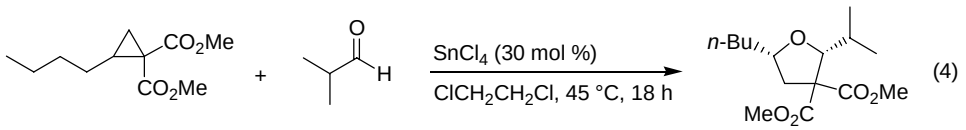
under similar conditions to those with phenyl-substituted cyclopropane **12a**, affording substituted tetrahydrofurans in excellent yields (**Scheme 3-6**). However, unlike the products of the reaction with **12a**, the vinyl group at the 5-position allows straightforward functionali zation of the tetrahydrofuran. Unfortunately, the diastereoselectivities with **12d** are considerably lower with both benzaldehyde and isobutyraldehyde at 8.9:1 and 5.7:1, respectively. While the reactions are somewhat selective, the diastereomers ***cis*-** and ***trans*-16b** are inseparable by flash chromatography.

Scheme 3-6. [3+2] Cycloaddition Reactions with Vinyl Cyclopropane **12d**



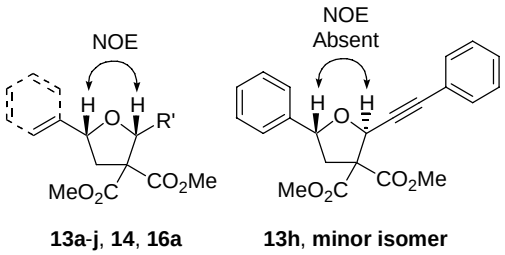
The greatest versatility in this methodology has been achieved with the cycloaddition of *n*-butyl-substituted cyclopropane **12e** with isobutyraldehyde furnishing 2,5-dialkyl tetrahydrofuran **7** (eq 4). The success of this reaction demonstrates not only that a simple alkyl group can function as an electron-donating group in these reactions, but that alkyl aldehydes can serves as viable dipolarophiles. A six-fold increase in catalyst loading relative to phenyl cyclopropane **12a**, as well as a temperature increase of ca. 20 °C is required for efficient cycloaddition, clearly demonstrating the decreased electron-donating ability of a

saturated substituent. While the diastereoselectivity is rather poor, this reaction nonetheless indicates a process where functionalization of the donor group in target-directed synthesis might not be necessary.



The 2,5-relative stereochemistry of the major stereoisomers from each reaction was determined by NOESY analysis. For compounds **13a-j**, **14**, and **16a**, this was invariably shown to be *cis*. The key NOE enhancement that was used in this determination is shown in **Figure 3-1**. It is important to note that the minor diastereomer of **13h** does not show this enhancement. Additionally, the relative stereochemistry of the major isomer of **13b** was shown to be *cis* by single crystal X-ray analysis of a derivative (see **3.3.2.3**). For compounds **15**, **16b**, and **17**, the diastereomers were inseparable, and the major isomer is assumed to be *cis* by analogy.

Figure 3-1. Observed NOE Enhancements in Tetrahydrofuran Products



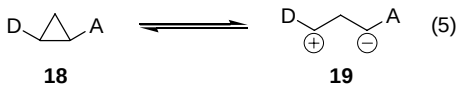
3.3 Enantiospecific Tetrahydrofuran Synthesis

3.3.1 Background

With the discovery and successful development of the racemic Lewis acid-catalyzed [3+2] cycloaddition reaction of carbon-based D-A cyclopropanes and aldehydes, it was then of interest to develop an asymmetric version of this process. However, the exact mechanism of the cycloaddition reaction dictates the approach that must be taken to achieve asymmetric induction.

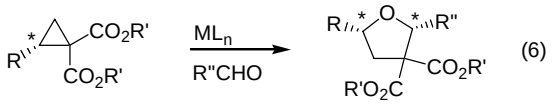
The ambiphilic behavior D-A cyclopropanes (**18**) exhibit toward both electrophiles and nucleophiles suggests the consideration of these compounds as ring-opened 1,3-zwitterionic equivalents (**19**).[1] This view implies loss of chirality concurrent with reaction progress (eq 5). Assuming participation of a species such as **19** in the reaction mechanism, it would be necessary to employ ligand control to effect absolute stereochemical induction. Indeed, Sibi successfully employed this strategy in the cycloaddition of nitrones with cyclopropanes,[21] a reaction discovered and developed by Kerr (see **Chapter 2**).[10,11] On the other hand, if initial bond formation between the reacting species in the cycloaddition occurs while the cyclopropane still possesses chirality, then the use of ligand control in conjunction with racemic starting material becomes a particularly complicated issue. In this case, the use of optically active reagents with achiral Lewis acids is perhaps the best option for the synthesis of enantioenriched tetrahydrofuran derivatives. Insight into the reaction mechanism could be gained by conducting the reaction with *scalemic* starting material in the absence of additional chirality. It was thought that support for cyclopropane ring-opening to

a 1,3-zwitterion would be gained upon the subsequent isolation of *racemic* tetrahydrofuran product.



3.3.2 Results and Discussion

This study focused on the Lewis acid-catalyzed cycloaddition reaction of enantioenriched carbon-based D-A cyclopropanes and aldehydes in the synthesis of enantioenriched 2,5-disubstituted tetrahydrofuran derivatives (eq 6).[22]

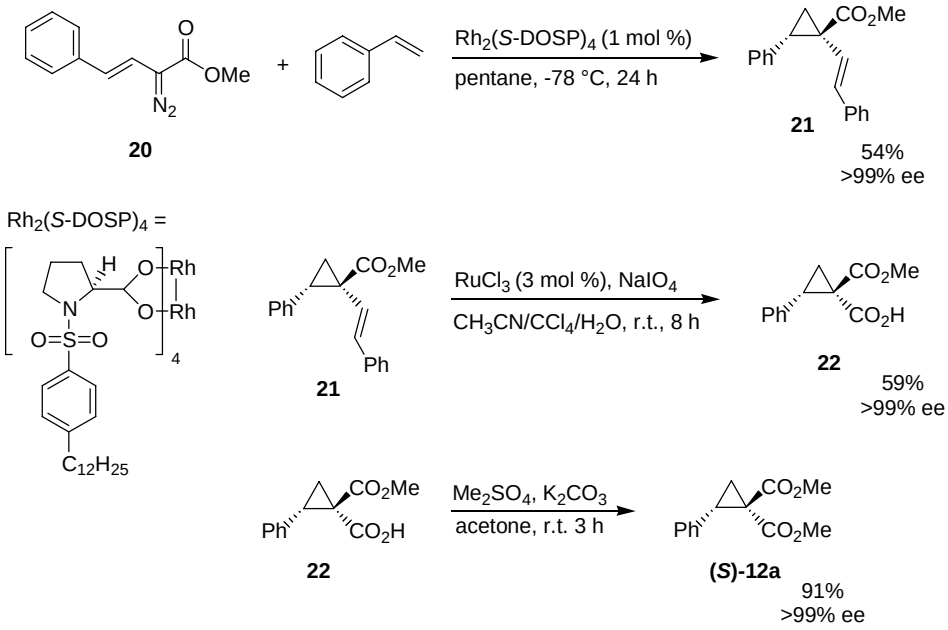


3.3.2.1 Substrate Synthesis

In order to carry out a preliminary mechanistic study on this system it was necessary to synthesize cyclopropanes in enantioenriched form. Due to its wide success in the racemic reaction with various aldehydes, phenyl cyclopropane **12a** was initially chosen for study. The (*S*)-enantiomer of this cyclopropane is easily synthesized in several steps employing an asymmetric cyclopropanation strategy developed by Davies (**Scheme 3-7**).[23] The cyclopropanation between methyl 2-diazo-4-phenylbutenoate (**20**) and styrene catalyzed by chiral rhodium species Rh_2(*S*-DOSP)$_4$ affords (1*S*,2*S*)-cyclopropane **21** in 54% yield and >99% enantiomeric excess after a single recrystallization. Diazoester **20** is accessible in three steps from phenylacetaldehyde,[24,25] and Rh_2(*S*-DOSP)$_4$ is commercially available or

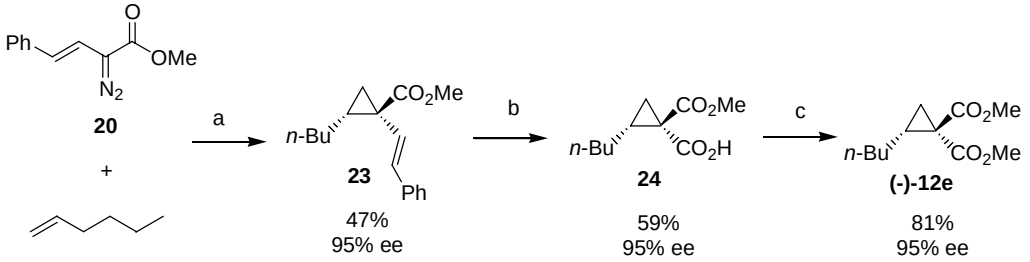
may be prepared in a few steps from L-proline and $Rh_2(OAc)_4$.[23] The styryl-portion of cyclopropane **21** is then oxidatively cleaved through treatment with $RuCl_3$ and $NaIO_4$ giving

Scheme 3-7. Synthesis of Enantioenriched Cyclopropane **(*S*)-12a**



carboxylic acid **22**.[23] Simple esterification with dimethyl sulfate affords the desired enantioenriched cyclopropane **(*S*)-12a** in good yield.[26] In an analogous fashion, **(-)-12e** was synthesized in 95% ee (**Scheme 3-8**). The absolute configuration of the major enantiomer of enantioenriched **12e** is not known but is assumed to be (*R*) by analogy.[23]

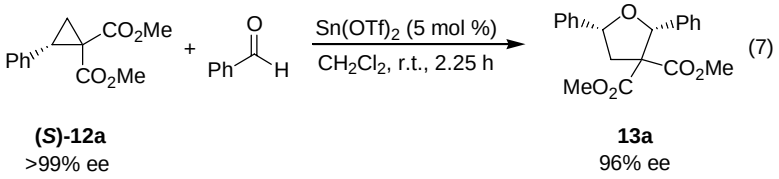
Scheme 3-8. Synthesis of Enantioenriched Cyclopropane **(-)-12e**



Conditions: a) Rh_2(*S*-DOSP)$_4$ (1 mol %), pentane, 25 °C, 19 h
b) $RuCl_3$ (3 mol %), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, r.t., 9 h
c) Me_2SO_4, K_2CO_3, acetone, r.t., 6 h

3.3.2.2 Reaction Development

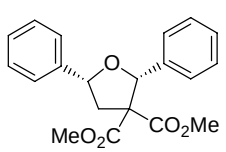
The initial control experiment employing cyclopropane **(*S*)-12a** (>99% ee), benzaldehyde, and $Sn(OTf)_2$ (5 mol %), afforded tetrahydrofuran **13a** in 96% ee (eq 7). This



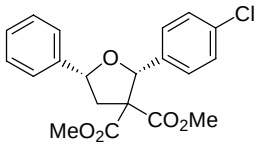
result indicated that the chiral information contained in the cyclopropane was being transferred in the initial bond-forming event, zwitterion **19** was not significant, and that ligand control might not be necessary. To investigate this possibility, the substrate scope was evaluated with a number of aldehydes in the presence of catalytic quantities of $Sn(OTf)_2$ and $SnCl_4$ (**Figure 3-2**). The absolute stereochemical information from the cyclopropane was regularly transferred to the tetrahydrofuran products with high fidelity. Only extremely

electron-poor aldehydes, which require higher catalyst loading and longer reaction times, gave products of <96% enantiomeric excess (**13f** and **13h**).

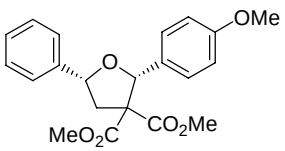
Figure 3-2. Aldehyde Scope in the Lewis Acid-Catalyzed Asymmetric [3+2] Cycloaddition of Cyclopropane **(*S*)-12a**



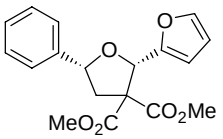
13a
96% ee
5 mol % $Sn(OTf)_2$
2.25 h



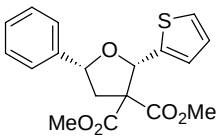
(2*R*,5*R*)-13b
96% ee
5 mol % $Sn(OTf)_2$
4.75 h



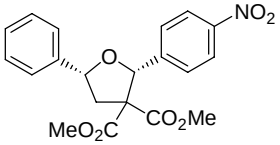
13c
99% ee
5 mol % $Sn(OTf)_2$
3.5 h



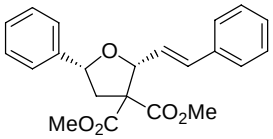
13d
99% ee
5 mol % $Sn(OTf)_2$
3.25 h



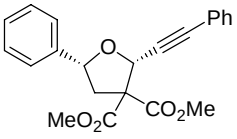
13e
98% ee
5 mol % $Sn(OTf)_2$
3.25 h



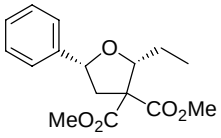
13f
34% ee
20 mol % $Sn(OTf)_2$
15 h



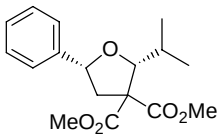
13g
99% ee
5 mol % $Sn(OTf)_2$
3.5 h



13h
88% ee
10 mol % $Sn(OTf)_2$
6 h



13i
96% ee
5 mol % $SnCl_4$
1.75 h



13j
96% ee
5 mol % $SnCl_4$
2.5 h

Several experiments were carried out to probe the erosion of enantiopurity observed with electron-poor aldehydes. First, the reaction conditions used for the synthesis of **13f** were reproduced in the absence of *p*-nitrobenzaldehyde. After quenching the reaction, complete racemization of **(*S*)-12a** was observed. Second, the cycloaddition reactions leading to **13f** and **13h** were reproduced but quenched after only 45 and 30 minutes, respectively. In each case the tetrahydrofuran products were formed in 93% ee. It is apparent with these results that there is noticeable loss of stereochemical integrity of the cyclopropane throughout the course of the reaction with these sluggish dipolarophiles (cf. eq 5).[27] Moreover, in the absence of appreciable cyclopropane racemization, it is likely that the optical purity of the tetrahydrofurans would be as high with these aldehydes as it is with others.

Since it was observed that longer reaction times and high catalyst loadings facilitated racemization of cyclopropane **(*S*)-12a**, it was postulated that the much more vigorous conditions required for the reactivity of 2-alkyl-substituted cyclopropane **12e** (eq 4) would lead to racemic product. However, upon subjecting **(-)-12e** (95% ee) to the optimized reaction conditions with isobutyraldehyde, tetrahydrofuran **17** was produced in 93% ee. Thus, in this system, racemization of the cyclopropane is significantly slower than reaction with the aldehyde. The poorer ability of an alkyl group versus a phenyl group in stabilizing the positive charge of a ring-opened zwitterion is the most likely cause of this result.

The practicality of this cycloaddition strategy for the synthesis of useful chiral building blocks hinges in part on the ability to manipulate the tetrahydrofuran products. Upon treatment with NaCN in wet DMSO, tetrahydrofuran **13a** undergoes decarboxylation in a stereoselective manner, without undesired ring opening, to afford monoester **25** in good yield (eq 8).[28] This facile process should allow simple functionalization of the ring 3-

position. The *trans*-relationship between the carbomethoxy and phenyl groups and retention of the *cis*-relationship between the 2,5-phenyl groups is confirmed by NOESY analysis (**Figure 3-3**).

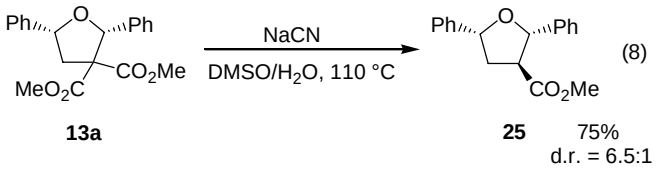
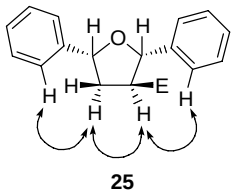


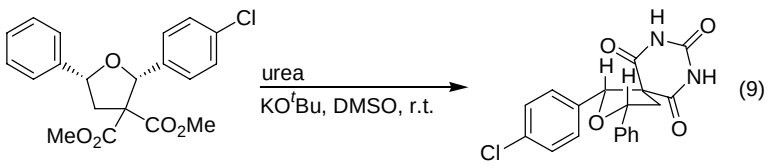
Figure 3-3. Observed NOE Enhancements in Decarboxylation Product **25**



25

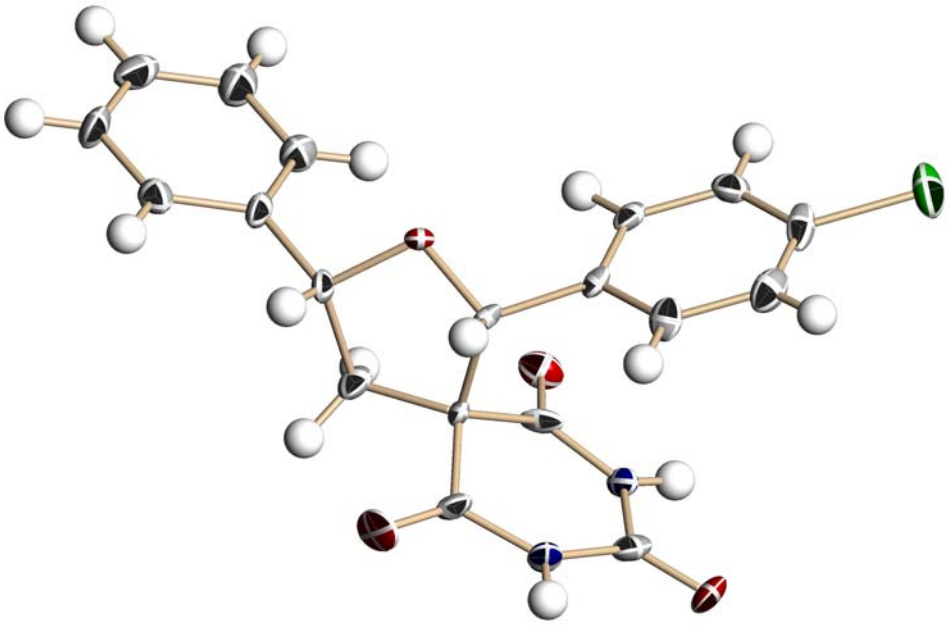
3.3.2.3 Mechanistic Analysis

With the discovery of efficient absolute stereochemical transfer from scalemic D-A cyclopropanes to substituted tetrahydrofuran derivatives, it was then of interest to investigate the mechanism of the reaction and elucidate the origin of this transfer. Central to this goal was the determination of the absolute stereochemistry of the major enantiomer of the tetrahydrofuran products. To this end, the cycloadduct of **(*S*)-12a** with *p*-chlorobenzaldeyde was converted to its derived barbituric acid (**26**) (eq 9).[29] The absolute stereochemistry was determined by single crystal X-ray diffraction to be (2*R*,5*R*) as shown in **Figure 3-4**.



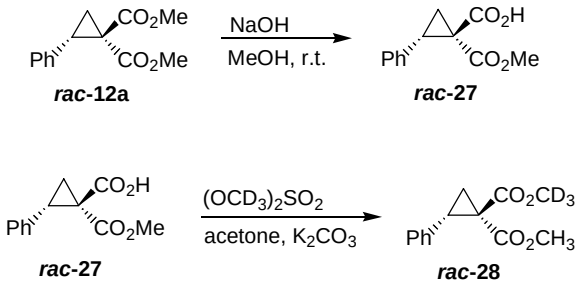
13b **26**

Figure 3-4. ORTEP of **26**

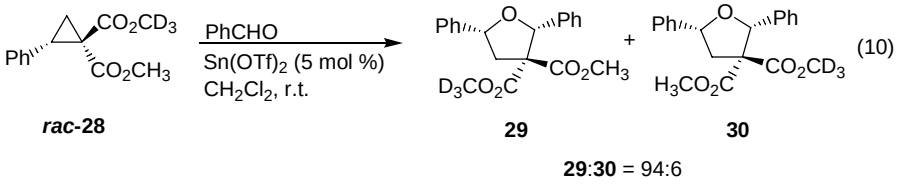


Next, a labeling study was conducted with deuterated cyclopropane ***rac*-28**. In this compound, one of the diastereotopic carbomethoxy groups of cyclopropane ***rac*-12a** is selectively labeled. Cyclopropane ***rac*-28** was prepared via the monosaponification of ***rac*-12a**, hydrolyzing the ester group *trans* to the phenyl substituent exclusively,[23] and subsequent reesterification with perdeuterated dimethyl sulfate (**Scheme 3-9**).[26] After subjecting the

Scheme 3-9. Synthesis of Deuterium Labeled Cyclopropane ***rac*-28**



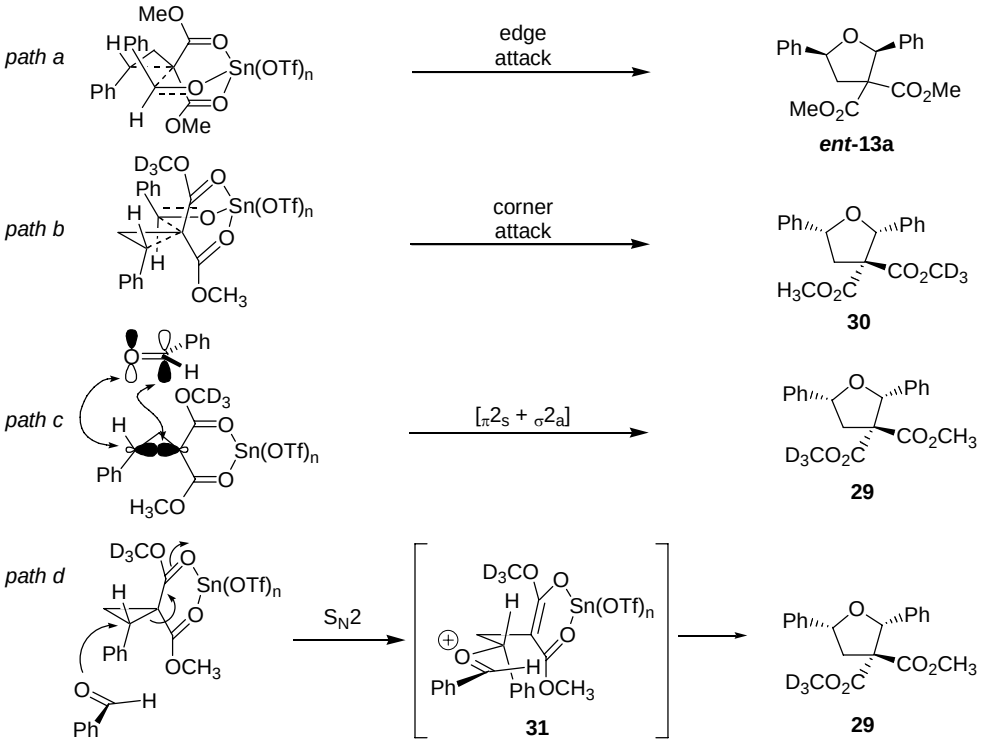
labeled cyclopropane to the optimum reaction conditions with benzaldehyde, 94% of the label was found *cis* to the phenyl groups in the tetrahydrofuran as determined by ^{1}H NMR analysis (eq 10). The assignment of the relative stereochemistry of **29** is based on the fact that each tetrahydrofuran derivative with a 2-aryl substituent shows one downfield resonance (~3.7 ppm) and one upfield resonance (~3.2 ppm) for the two diastereotopic carbomethoxy groups in the ^{1}H NMR spectra. The downfield resonance arises from the ester group *trans* to the aryl ring. The unusual upfield resonance for a typical carbomethoxy group arises from the ester group *cis* to the aryl ring. This artifact presumably results from an anisotropic effect and has not gone unnoticed by others.[7,30] The fact that this reaction (eq 10) was performed with racemic material is of no consequence, since the results were analyzed using ^{1}H NMR spectroscopy.



Four reasonable mechanisms for the cyclopropane/aldehyde cycloaddition can be evaluated in the context of the experimental observations (**Scheme 3-10**). An S_E2-process in which the cyclopropane undergoes "edge" attack by the aldehyde would occur with retention of configuration at the 1-position (**path a**).[7] Placing the large group of the aldehyde away from the phenyl group on the cyclopropane would lead to the incorrect absolute stereochemistry (***ent*-13a**). An S_E2-process occurring by a "corner" attack mechanism would proceed with inversion at the cyclopropane 1-position and afford tetrahydrofuran **30** (**path b**);[31-34] however, this is the minor diastereomer observed from the labeling experiment. If a concerted mechanism is considered, the reaction would need to occur via a symmetry allowed [$_{\pi}2_s + {}_{\sigma}2_a$] pathway.[35-37] There is only one coplanar orientation of reactants that is consistent with the observed relative and absolute stereochemistry and would not suffer from large unfavorable steric interactions (**path c**). Lastly, an unusual S_N2 process where the aldehyde acts as a nucleophile inverting the stereochemistry at the activated C-2 carbon of the cyclopropane is entirely consistent with all experimental evidence (**path d**).[38] This substitution mechanism has been observed for the methanolysis and aminolysis of diactivated cyclopropanes at elevated temperatures.[39,40] An S_N2 pathway has also been noted in a Hg(II)-assisted cyclopropane cleavage reaction, where a tethered carboxyester serves as the nucleophile.[41] In the mechanism described in **path d** little rotation occurs about the enolate carbon-methylene carbon σ-bond in intermediate **31** before the oxocarbenium ion is internally quenched to form the heterocycle. Since the reaction of **(*S*)-12a** affords **13a** in 96% ee, 2% of the scrambling in the labeling study reaction (eq 10) can be assumed to arise from racemization. Thus, only 4% of intermediate **31** undergoes bond rotation before ring closure. The results of this experiment suggest the possible rapid synthesis of optically

active substituted tetrahydrofurans containing one quaternary and two tertiary stereogenic centers, through the use of differentiated ester groups.

Scheme 3-10. Mechanistic Analysis of the Cyclopropane/Aldehyde [3+2] Cycloaddition

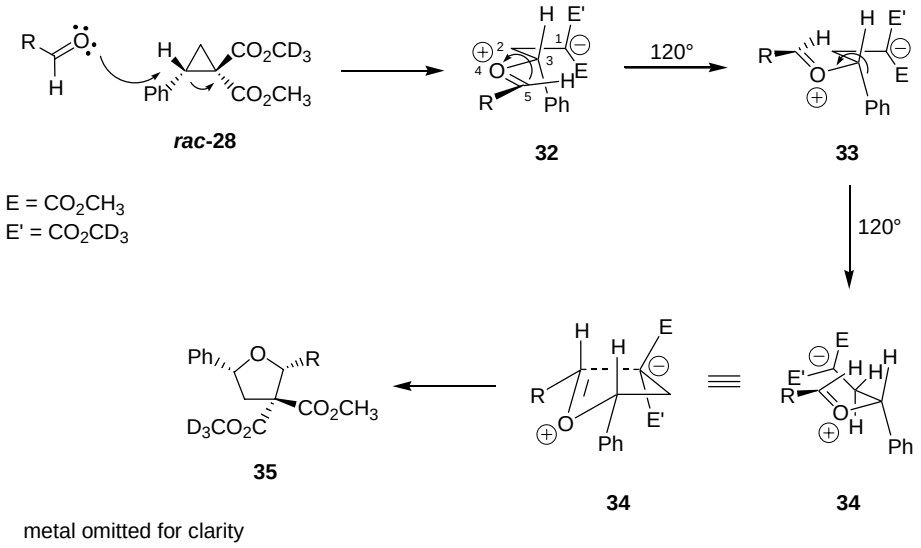


With respect to the two possible mechanisms that correctly predict the observed product, an S_N2 displacement is favored over a concerted reaction pathway. First, in the concerted reaction, the primary orbital interaction is between the HOMO of the cyclopropane and LUMO of the aldehyde. This is not congruent with the sluggish reactivity of electron-poor aldehydes, which have lower LUMO energies and should therefore react faster if such a mechanism were operative. Secondly, every dipolarophile studied affords the product in very similar enantiomeric excess regardless of the size of the aldehyde substituent (except for

very electron-poor dipolarophiles, which has been shown is not a steric effect), a fact that is more consistent with an enantiospecific reaction than an enantioselective reaction.

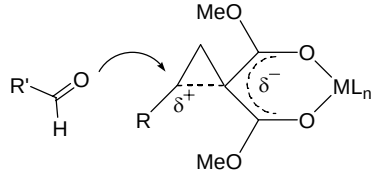
The origin of diastereoselectivity in these cycloaddition reactions can be analyzed in the context of the proposed mechanism. The more accessible *tran*s lone pair on the carbonyl oxygen most likely attacks the cyclopropane, ***rac*-28** for example, in the initial S_N2 reaction (**Scheme 3-11**). This would produce (*E*)-oxocarbenium ion **32**. From the staggered conformation, a 120° rotation about the C3-O4 σ-bond followed by a 120° rotation about the C2-C3 σ-bond would place the zwitterion in an envelope conformation (**34**). The substituents from the cyclopropane and aldehyde occupy pseudoequatorial positions in this conformation, and ring closure affords the *cis*-tetrahydrofuran. Little bond rotation about the C1-C2 σ-bond occurs during this process, affording tetrahydrofuran **35** with the labeled carbomethoxy group *cis* to the 2- and 5-substituents. This retention of configuration is conceivable considering that scrambling at this position would require a 180° bond rotation to be faster than simultaneous 120° bond rotations. Additionally, this 180° rotation would involve an eclipsing butane interaction between C3 and one carboxyester group, while neither of the 120° rotations would suffer similar torsional strain.

Scheme 3-11. Origin of *cis*-2,5-Disasteroselectivity in [3+2] Cycloaddition Reactions



Finally, the issue of regioselectivity should be addressed. As noted before, all of the cycloaddition reactions studied produce substituted tetrahydrofurans as single regioisomers in which the oxygen atom of the aldehyde has become bonded to the tertiary carbon of the cyclopropane and the carbonyl carbon atom has become bonded to the quaternary carbon of the cyclopropane. This results from nucleophilic attack by the aldehyde at the more substituted position of the cyclopropane ring. Coordination of the Lewis acid to the cyclopropane ester groups is expected to create a partial charge separation with the simultaneous weakening of a cyclopropane σ-bond (**Scheme 3-12**).[8,10] The presence of an electron-releasing group stabilizes the partial positive charge, and hence, the bond between the substituted carbon and the quaternary carbon is weakened to the greatest degree. This paradigm also explains why the successful cycloaddition of a simple alkyl-substituted cyclopropane requires more vigorous conditions than reactions of cyclopropanes having unsaturated substitution.

Scheme 3-12. Model for Regioselectivity in [3+2] Cycloaddition Reactions



3.4 Conclusions

A Lewis acid-catalyzed [3+2] cycloaddition reaction of carbon-based D-A cyclopropanes and aldehydes has been developed. This methodology achieves the rapid synthesis of 2,5-disubstituted tetrahydrofurans from readily available starting materials. This practical one step synthesis is effective for both alkyl and aryl aldehydes of varying electronics and typically produces tetrahydrofurans in very high yields with excellent *cis*-diastereoselectivities. Furthermore, both unsaturated and aliphatic substituents on the D-A cyclopropane provide the necessary stabilization for successful reactivity, allowing access to a diverse array of tetrahydrofuran derivatives.

Mechanistic studies have shown that this [3+2] cyclopropane/aldehyde cycloaddition occurs via an unusual S_N2 mechanism in which the aldehyde acts as a nucleophile toward the activated cyclopropane. The enantiospecificity of this reaction mechanism mediates the efficient transfer of absolute stereochemical information from both aryl- and alkyl-substituted cyclopropanes to the products, allowing the facile synthesis of optically active 2,5-*cis*-disubstituted tetrahydrofurans from enantioenriched cyclopropanes. With the exception of extremely electron-poor aldehydes, almost complete conservation of stereochemical integrity is observed in these cycloadditions, suggesting that racemization is overall not a significant problem in this methodology. Furthermore, effective decarboxylation of a tetrahydrofuran

derivative has demonstrated that the products realized from this cycloaddition strategy are amendable to further functionalization. Lastly, mechanistic results have suggested the application of this process to the facile synthesis of substituted tetrahydrofurans containing an even greater degree of stereochemical density.

3.5 Experimental

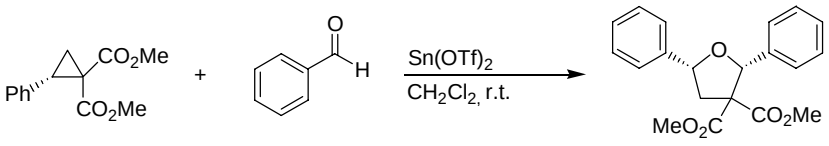
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with tetramethylsilane (TMS) or DMSO solvent resonance as the internal standard for ^{1}H NMR at 0.00 ppm and 2.50 ppm, respectively, and $CDCl_3$ or DMSO solvent resonance as the internal standard for ^{13}C NMR at 77.16 ppm and 39.52 ppm, respectively. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Structural assignments were made using a combination of COSY and NOESY experiments. Enantiomeric excesses were obtained using a Berger Supercritical Fluid Chromatograph model FCM 1100/1200 equipped with an Agilent 1100 series UV-Vis detector using one of the following chiral HPLC columns: Chiralcel Chiralpak AD or OD column. Samples were eluted with SFC grade CO_2 and the indicated percentage of MeOH. Enantiomeric excesses were alternatively obtained using an Agilent 6890N Network Gas Chromatograph System equipped with a Chiraldex G-TA column (30 m x 0.25

mm, oven = 100 °C, pressure = 80 kPa, detector = FID, 250 °C) with helium gas as carrier. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 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 Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables and equations, which are averages of at least two experiments. Methylene chloride and THF were dried by passage through a column of neutral alumina under nitrogen prior to use. DMSO and dichloroethane were distilled from CaH_2 under Ar prior to use. Acetone was distilled from $CaSO_4$ prior to use. Pyridine was distilled from KOH prior to use. Solid aldehydes, 4-nitrobenzaldehyde and 4-chlorobenzaldehyde were purified by sublimation prior to use. All other aldehydes were distilled from $CaSO_4$ prior to use. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification.

General Procedure (A) for the Lewis Acid-Catalyzed Cycloaddition. In an inert atmosphere glovebox, a flame-dried vial was charged with 0.017 mmol of $Sn(OTf)_2$ (0.050 equiv), 0.34 mmol of the cyclopropane (1.0 equiv), and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere and charged with 0.5 mL of CH_2Cl_2 followed by 1.0 mmol of the aldehyde (3.0 equiv). The reaction was stirred at room

temp (23 °C - 29 °C) until the disappearance of starting material was confirmed by TLC. The reaction mixture was then passed over a plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) overnight. The product was purified by flash chromatography, eluting with the indicated solvent system to afford the pure tetrahydrofuran.

General Procedure (B) for the Lewis Acid-Catalyzed Cycloaddition. In an inert atmosphere glovebox, a flame-dried vial was charged with 0.34 mmol of the cyclopropane (1.0 equiv) and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere and charged with a solution of 0.017 mmol of $SnCl_4$ (0.050 equiv) in 0.5 mL of CH_2Cl_2 followed by 1.0 mmol of the aldehyde (3.0 equiv). The reaction was stirred at room temp (23 °C - 29 °C) until the disappearance of starting material was confirmed by TLC. The reaction mixture was then passed over a plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) for a short time to remove excess aldehyde affording the pure tetrahydrofuran.

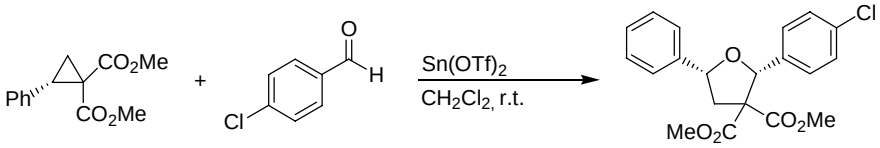


13a

2,5-Diphenyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13a). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 80.0

mg of the cyclopropane (>99% ee), and 110 mg of the aldehyde. After 2.25 h at room temperature and workup, ^{1}H NMR analysis of the unpurified product (δ 5.79 vs. δ 5.98) gave the diastereomeric ratio: >100:1. The crude product was purified by flash chromatography with 7.5% EtOAc/petroleum ether to afford 117 mg (100%) of the product as a colorless oil in 96% ee as determined by chiral SFC analysis (Chiralpak AD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 4.1 min, $t_{r\text{-minor}}$ 5.1 min).

Analytical data for **13a**: $[\alpha]_D^{25}$ +95.6 (c = 1.01, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3064, 2953, 1732, 1606, 1497, 1456, 1435, 1360, 1271, 1232, 1209, 1176, 1093, 1064, 1028, 943, 902, 812, 750, 700; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58-7.47 (m, 4H), 7.44-7.23 (m, 6H), 5.79 (s, 1H), 4.95 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.82 (s, 3H), 3.09 (s, 3H), 3.00 (dd, *J* = 13.5, 10.8 Hz, 1H), 2.73 (dd, *J* = 13.2, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 169.3, 140.0, 137.8, 128.6, 128.22, 128.17, 127.9, 127.1, 126.6, 84.6, 80.0, 66.5, 53.0, 52.2, 42.9; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.34; **Anal.** Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.64; H, 6.00.

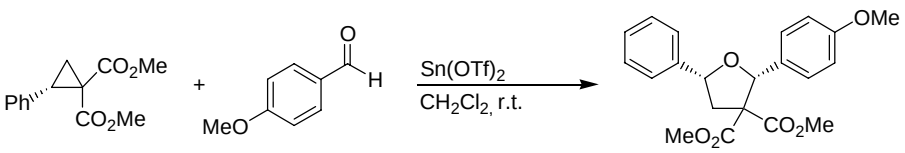


13b

(2*R*,5*R*)-2-(4-Chlorophenyl)-5-phenyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13b). In an inert atmosphere glovebox, a flame-dried vial was charged with $Sn(OTf)_2$ (7.1 mg, 0.017 mmol, 0.050 equiv), the cyclopropane (80.0 mg, 0.34 mmol, 1.0 equiv, >99% ee), and a stir bar. Outside of the glovebox, the vial was placed under argon and charged

with the aldehyde (144 mg, 1.0 mmol, 3.0 equiv) in 0.5 mL of CH_2Cl_2. The reaction was stirred at room temperature. After 4.75 h the reaction was passed over a small plug of silica gel, eluting with 50 mL of Et_2O, and the solvent was removed by rotary evaporation. ^1H NMR analysis of the unpurified product (δ 5.73 vs. δ 3.70) gave the diastereomeric ratio: >71:1. The crude product was purified by flash chromatography with a 2.5% to 5% acetone/petroleum ether gradient to afford 128 mg (99%) of the product as a slightly yellow oil in 95% ee as determined by chiral SFC analysis (Chiralpak OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 6.8 min, $t_{r\text{-minor}}$ 7.9 min).

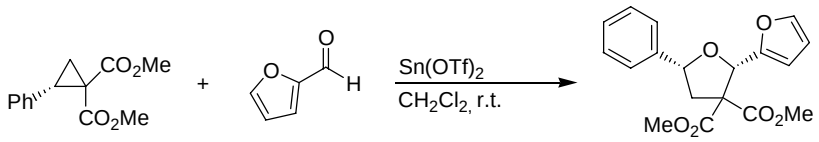
Analytical data for **13b**: $[\alpha]_D^{22}$ +81.4 (c = 1.00, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3034, 2953, 2883, 1732, 1599, 1491, 1435, 1385, 1348, 1271, 1232, 1209, 1198, 1176, 1089, 1057, 1028, 1015, 941, 906, 843, 800, 760, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.36-7.25 (m, 3H), 5.74 (s, 1H), 4.94 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.81 (s, 3H), 3.16 (s, 3H), 2.97 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 169.2, 139.8, 136.3, 134.0, 128.64, 128.55, 128.3, 128.1, 126.6, 83.9, 80.1, 66.3, 53.1, 52.4, 42.8; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.56; **Anal.** Calcd. for $C_{20}H_{19}ClO_5$: C, 64.09; H, 5.11. Found: C, 64.20; H, 5.16.



13c

2-(4-Methoxyphenyl)-5-phenyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13c). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 80.0 mg of the cyclopropane (>99% ee), and 140 mg of the aldehyde. After 3.5 h at room temperature and workup, ^{1}H NMR analysis of the unpurified product (δ 5.75 vs. δ 3.65) gave the diastereomeric ratio: >71:1. The crude product was purified by flash chromatography with a 5% to 10% acetone/petroleum ether gradient to afford 126 mg (100%) of the product as a slightly yellow oil in 99% ee as determined by chiral SFC analysis (Chiralpak AD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 8.6 min, $t_{r\text{-minor}}$ 9.7 min).

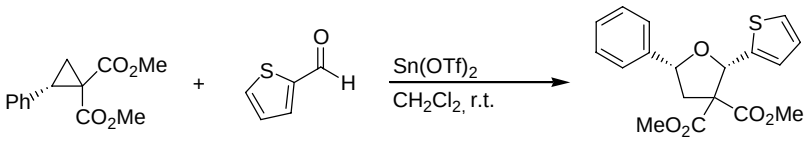
Analytical data for **13c**: $[\alpha]_D^{25}$ +78.4 (c = 1.02, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3003, 2953, 2839, 1732, 1614, 1585, 1514, 1435, 1387, 1358, 1273, 1250, 1211, 1174, 1092, 1057, 1032, 939, 904, 841, 804, 760, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.48-7.29 (m, 5H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.74 (s, 1H), 4.93 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.15 (s, 3H), 2.98 (dd, *J* = 13.2, 10.8 Hz, 1H), 2.72 (dd, *J* = 13.6, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 169.4, 159.6, 140.1, 129.8, 128.6, 128.4, 128.1, 126.5, 113.3, 84.4, 79.8, 66.3, 55.3, 52.9, 52.3, 42.8; TLC (20% EtOAc/petroleum ether) R_f 0.37; **Anal.** Calcd. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.07; H, 5.94.



13d

5-Phenyl-1,2,3,4-tetrahydro[2,2']bifuryl-3,3-dicarboxylic acid dimethyl ester (13d). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 80.0 mg of the cyclopropane (>99% ee), and 99 mg of the aldehyde. After 3.25 h at room temperature and workup, ^{1}H NMR analysis of the unpurified product (δ 4.93 vs. δ 3.67) gave the diastereomeric ratio: 23.3:1. The crude product was purified by flash chromatography with 5% acetone/petroleum ether to afford 97 mg (86%) of the product as a colorless oil in 98% ee as determined by chiral SFC analysis (Chiralpak OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 6.5 min, $t_{r\text{-minor}}$ 7.6 min).

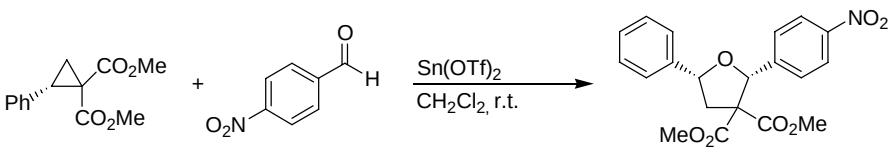
Analytical data for **13d**: $[\alpha]_D^{28}$ +91.1 (c = 1.06, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2954, 2359, 2343, 1736, 1497, 1450, 1435, 1333, 1273, 1232, 1209, 1173, 1151, 1093, 1051, 1011, 945, 895, 808, 746, 700, 669; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2H), 7.43-7.27 (m, 4H), 6.38 (d, *J* = 3.1 Hz, 1H), 6.35-6.29 (m, 1H), 5.85 (s, 1H), 4.93 (dd, *J* = 11.2, 5.6 Hz, 1 H), 3.83 (s, 3H), 3.44 (s, 3H), 3.04 (dd, *J* = 13.2, 11.6 Hz, 1H), 2.72 (dd, *J* = 13.6, 5.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 168.3, 151.5, 142.8, 139.9, 128.5, 128.1, 126.5, 110.4, 109.1, 80.2, 78.1, 65.2, 53.3, 52.8, 41.9; TLC (5% acetone/petroleum ether) R_f 0.11; **Anal.** Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.73; H, 5.56.



13e

5-Phenyl-2-(2-thienyl)tetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13e). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 80.0 mg of the cyclopropane (>99% ee), and 115 mg of the aldehyde. After 3.25 h at room temperature and workup, ^{1}H NMR analysis of the unpurified product (δ 6.07 vs. δ 3.68) gave the diastereomeric ratio: >100:1. The crude product was purified by flash chromatography with 7.5% acetone/petroleum ether to afford 117 mg (99%) of the product as a colorless oil in 99% ee as determined by chiral SFC analysis (Chiralpak AD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 12.0 min, $t_{r\text{-minor}}$ 14.2 min).

Analytical data for **13e**: $[\alpha]_D^{26}$ +123 (c = 1.10, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3068, 3034, 3007, 2953, 2359, 1732, 1498, 1439, 1367, 1321, 1273, 1236, 1213, 1198, 1174, 1092, 1072, 1051, 1024, 943, 899, 858, 841, 825, 806, 758, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.38 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.34-7.28 (m, 1H), 7.24 (d, *J* = 4.8 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.95 (dd, *J* = 4.6, 3.7 Hz, 1H), 6.06 (s, 1H), 4.94 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.83 (s, 3H), 3.32 (s, 3H), 2.96 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 168.8, 141.0, 139.7, 128.5, 128.2, 126.5, 126.4, 125.7, 125.3, 81.1, 80.1, 66.5, 53.2, 52.6, 42.1; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.37; **Anal.** Calcd. for $C_{18}H_{18}O_5S$: C, 62.41; H, 5.24. Found: C, 62.20; H, 5.28.

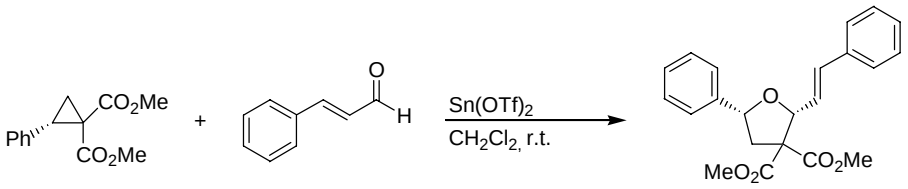


13f

2-(4-Nitrophenyl)-5-phenyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13f). In an inert atmosphere glovebox, a flame-dried vial was charged with $Sn(OTf)_2$ (28.5 mg, 0.068 mmol, 0.20 equiv), the cyclopropane (80.0 mg, 0.34 mmol, 1.0 equiv, >99% ee), and a stir bar. Outside of the glovebox, the vial was placed under argon and charged with the aldehyde (155 mg, 1.0 mmol, 3.0 equiv) in 1.0 mL of CH_2Cl_2. The reaction was stirred at room temperature. After 15 h the reaction was passed over a small plug of silica gel, eluting with 50 mL of Et_2O, and the solvent was removed by rotary evaporation. ^{1}H NMR analysis of the unpurified product (δ 5.83 vs. δ 3.82) gave the diastereomeric ratio: >52:1. The crude product was purified by flash chromatography with a 40% to 50% to 60% to 100% CH_2Cl_2/petroleum ether gradient to afford 127 mg (96%) of the product as a white semi-solid in 34% ee as determined by chiral SFC analysis (Chiralpak OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 11.1 min, $t_{r\text{-minor}}$ 12.8 min).

Analytical data for **13f**: $[\alpha]_D^{27}$ +27.7 (c = 1.42, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2954, 1732, 1606, 1524, 1495, 1435, 1387, 1348, 1313, 1273, 1232, 1209, 1176, 1109, 1092, 1059, 1030, 1016, 941, 862, 845, 806, 762, 746, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.42 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.39-7.31 (m, 1H), 5.82 (s, 1H), 4.99 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.85 (s, 3H), 3.15 (s, 3H), 3.00 (dd, *J* = 13.2, 10.8 Hz, 1H), 2.81 (dd, *J* = 13.2, 6.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 169.0, 147.8, 145.0, 139.3, 128.7, 128.5, 128.1, 126.6, 123.0, 83.5, 80.4,

66.4, 53.3, 52.5, 42.9; TLC (20% EtOAc/petroleum ether) R_f 0.36; **Anal**. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.05; H, 4.96; N, 3.65.

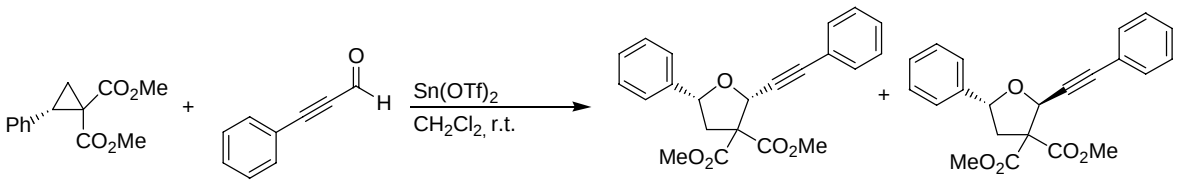


13g

5-Phenyl-2-styryltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (13g). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 80.0 mg of the cyclopropane (>99% ee), and 137 mg of the aldehyde. After 3.75 h at room temperature and workup, ^{1}H NMR analysis of the unpurified product (δ 4.91 vs. δ 3.69) gave the diastereomeric ratio: 17.5:1. The isomers were separated and purified by flash chromatography with a 3% to 5% acetone/petroleum ether gradient to afford 126 mg (100%) of the products as yellow oils with the major diastereomer in 99% ee as determined by chiral SFC analysis (Chiralpak OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 9.8 min, $t_{r\text{-minor}}$ 11.7 min).

Analytical data for **13g**: $[\alpha]_D^{25}$ +105.6 (c = 1.00, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3084, 3057, 3030, 3003, 2953, 2927, 2848, 1732, 1657, 1601, 1578, 1497, 1450, 1435, 1387, 1354, 1335, 1273, 1225, 1198, 1176, 1140, 1090, 1086, 1043, 1005, 970, 945, 914, 845, 818, 796, 760, 748, 696; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H), 7.40-7.20 (m, 8H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.23 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.28 (dd, *J* = 7.0, 1.0 Hz, 1H), 4.91 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 2.85 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.77 (dd, *J* = 13.5, 6.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.0, 169.4, 140.2, 136.5, 133.1, 128.7,

128.6, 128.2, 128.0, 126.8, 126.6, 125.0, 83.2, 80.2, 65.3, 53.2, 52.9, 42.3; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.38; **Anal.** Calcd. for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.25; H, 6.20.



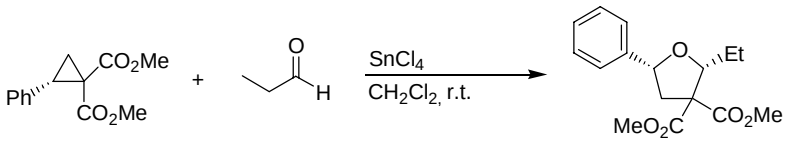
***cis*-13h** ***trans*-13h**

***cis*-5-Phenyl-2-phenylethynyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (*cis*-13h).** In an inert atmosphere glovebox, a flame-dried vial was charged with $Sn(OTf)_2$ (14.2 mg, 0.034 mmol, 0.10 equiv), the cyclopropane (80.0 mg, 0.34 mmol, 1.0 equiv, >99% ee), and a stir bar. Outside of the glovebox, the vial was placed under argon and charged with 0.5 mL of CH_2Cl_2 and the aldehyde (133 mg, 1.0 mmol, 3.0 equiv). The reaction was stirred at room temperature. After 6 h the reaction was passed over a small plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed by rotary evaporation, and the residue placed under vacuum (<0.1 torr) overnight. ^{1}H NMR analysis of the unpurified product (δ 5.67 vs. δ 5.93) gave the diastereomeric ratio: 1.6:1. The isomers were separated and purified by flash chromatography with a 7.5% to 10% acetone/petroleum ether gradient to afford 106 mg (85%) of the products as yellow oils with the major diastereomer formed in 88% ee as determined by chiral SFC analysis (Chiralpak OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 254 nm, $t_{r\text{-major}}$ 9.4, $t_{r\text{-minor}}$ 11.7 min).

Analytical data for ***cis*-13h**: $[\alpha]_D^{26}$ +82.4 (c = 0.690, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3064, 3032, 3005, 2953, 2231, 1738, 1599, 1574, 1491, 1435, 1383, 1354, 1327, 1273, 1228,

1196, 1173, 1092, 1070 1049, 1028, 1001, 989, 955, 914, 887, 843, 804, 758, 692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.23 (m, 10H), 5.66 (s, 1H), 4.96 (dd, *J* = 10.8, 6.0 Hz, 1 H), 3.86 (s, 3H), 3.77 (s, 3H), 2.93 (dd, *J* = 13.2, 10.8 Hz, 1H), 2.82 (dd, *J* = 13.2, 5.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 168.0, 140.3, 131.8, 128.8, 128.6, 128.4, 128.1, 126.5, 122.2, 87.8, 85.2, 81.1, 73.0, 66.6, 53.5, 53.1, 41.5; TLC (10% acetone/petroleum ether) R_f 0.17; **Anal.** Calcd. for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.79; H, 5.48.

Analytical data for ***trans*-5-phenyl-2-phenylethynyltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (*trans*-13h)**: **IR** (thin film, cm^{-1}) 3064, 3034, 3003, 2953, 2850, 2227, 1740, 1599, 1491, 1435, 1331, 1269, 1228, 1198, 1171, 1109, 1049, 1001, 987, 970, 939, 916, 889, 758, 692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.24 (m, 10H), 5.91 (s, 1H), 5.41(dd, *J* = 7.6, 7.6 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.40 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.23 (dd, *J* = 13.6, 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.1, 168.4, 140.5, 132.0, 128.9, 128.6, 128.4, 128.0, 126.0, 122.2, 87.8, 84.6, 80.4, 73.3, 66.6, 53.3 (two overlapping signals), 41.5; TLC (10% acetone/petroleum ether) R_f 0.24; **Anal.** Calcd. for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.63; H, 5.49.

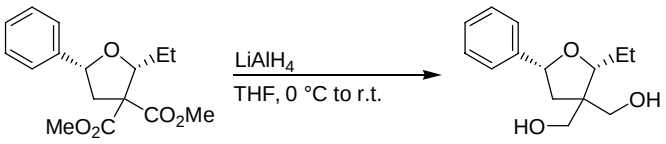


13i

2-Ethyl-5-phenyl-tetrahydro-furan-3,3-dicarboxylic acid dimethyl ester (13i). The title compound was prepared according to General Procedure **B** using 4.5 mg of $SnCl_4$, 80.0 mg of the cyclopropane (>99% ee), and 60 mg of the aldehyde. After 1.75 h at room temperature

and workup, ^{1}H NMR analysis of the product (δ 4.79 vs. δ 3.68) gave the diastereomeric ratio: >37:1. The pure product was obtained as 100 mg (100%) of a slightly yellow oil. This product was converted to **36**, which was determined to be 96% ee by chiral SFC analysis.

Analytical data for **13i**: $[\alpha]_D^{27}$ +101.9 (c = 1.02, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3032, 2954, 2879, 1734, 1497, 1456, 1435, 1269, 1232, 1198, 1176, 1132, 1093, 1068, 1028, 993, 758, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 4.79 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.43 (dd, *J* = 10, 3.0 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 2.71 (d, *J* = 8.5 Hz, 2H), 1.78-1.67 (m, 1H), 1.59-1.45 (m, 1H), 1.09 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.2, 170.1, 140.6, 128.4, 127.9, 126.4, 84.5, 79.6, 63.8, 52.9, 52.6, 42.8, 25.0, 11.4; TLC (10% EtOAc/petroleum ether) R_f 0.23; **Anal.** Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.66; H, 6.88.

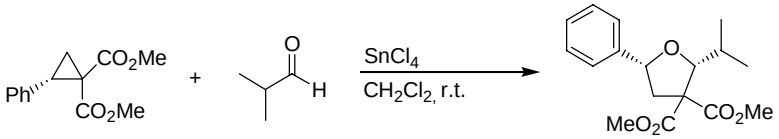


13i **36**

(2-Ethyl-3-hydroxymethyl-5-phenyl-tetrahydro-furan-3-yl)-methanol (36). A stirring suspension of $LiAlH_4$ (50.2 mg, 1.32 mmol, 5.0 equiv) in 1.5 mL of THF at 0 °C was treated with a solution of **13i** (77.3 mg, 0.264 mmol, 1.0 equiv) in 1.5 mL of THF via syringe. After addition, the reaction was allowed to warm to room temperature with stirring. After 1.5 h the reaction was quenched with 50 μL H_2O, 50 μL of a 15% NaOH (aq.) solution, and 150 μL of H_2O. The mixture was filtered through a Büchner funnel and the filter cake was washed with several portions of Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated by

rotary evaporation affording a white solid. The crude product was purified by flash chromatography with 60% EtOAc/petroleum ether to afford 54 mg (87%) of the product as a white solid in 96% ee as determined by chiral SFC analysis (Chiralpak AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 225 nm, $t_{r\text{-major}}$ 9.2 min, $t_{r\text{-minor}}$ 6.9 min).

Analytical data for **36**: $[\alpha]_D^{27}$ +69.0 (c = 1.03, CH_2Cl_2); mp 82-84 °C; **IR** (Nujol mull, cm^{-1}) 3298, 1128, 1059, 1024, 987, 957, 762, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 4.88 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 2H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.66 (dd, *J* = 10.0, 3.2 Hz, 1H), 2.29 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.08 (br s, 2H), 1.76 (dd, *J* = 12.8, 9.2 Hz, 1H), 1.78-1.54 (m, 2H), 1.10 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5, 128.5, 127.5, 125.9, 85.7, 79.0, 67.8, 66.0, 50.9, 41.1, 24.1, 12.0; TLC (40% EtOAc/petroleum ether) R_f 0.07; **Anal.** Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.21; H, 8.62.

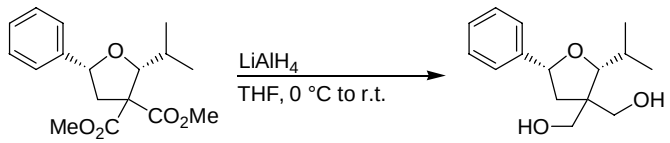


13j

2-Isopropyl-5-phenyl-tetrahydro-furan-3,3-dicarboxylic acid dimethyl ester (13j). The title compound was prepared according to General Procedure **B** using 4.5 mg of $SnCl_4$, 80.0 mg of the cyclopropane (>99% ee), and 74 mg of the aldehyde. After 2.5 h at room temperature and workup, ^{1}H NMR analysis of the product (δ 4.76 vs. δ 3.84) gave the diastereomeric ratio: >100:1. The pure product was obtained as 100 mg (96%) of a colorless

oil. This product was converted to **37**, which was determined to be 95% ee by chiral SFC analysis.

Analytical data for **13j**: $[\alpha]_D^{26}$ +94.4 (c = 1.01, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3066, 3030, 2954, 2873, 1732, 1498, 1450, 1435, 1385, 1369, 1348, 1313, 1269, 1232, 1198, 1176, 1099, 1061, 1022, 760, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.0 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 4.76 (dd, *J* = 9.5, 7.5 Hz, 1H), 4.31 (d, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.77-2.66 (m, 2H), 2.03-1.93 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.7, 170.5, 140.6, 128.4, 127.8, 126.4, 88.4, 78.9, 63.2, 52.9, 52.6, 44.4, 30.1, 20.6, 19.1; TLC (20% EtOAc/petroleum ether) R_f 0.48; **Anal.** Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.85; H, 7.11.

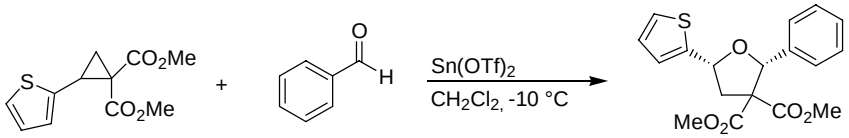


13j **37**

(3-Hydroxymethyl-2-isopropyl-5-phenyl-tetrahydro-furan-3-yl)-methanol (37). A stirring suspension of $LiAlH_4$ (42.4 mg, 1.12 mmol, 5.0 equiv) in 1.5 mL of THF at 0 °C was treated with a solution of **13j** (68.5 mg, 0.224 mmol, 1.0 equiv) in 1.5 mL of THF via syringe. After addition the reaction was allowed to warm to room temperature with stirring. After 1.5 h the reaction was quenched with 40 μL H_2O, 40 μL of a 15% NaOH (aq.) solution, and 120 μL of H_2O. The mixture was filtered through a Büchner funnel and the filter cake was washed with several portions of Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation affording a white solid. The crude product was purified

by flash chromatography with 50% EtOAc/petroleum ether to afford 51 mg (91%) of the product as a white solid in 95% ee as determined by chiral SFC analysis (Chiralpak AD, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 225 nm, $t_{r\text{-major}}$ 7.9 min, $t_{r\text{-minor}}$ 6.7 min).

Analytical data for **37**: $[\alpha]_D^{26}$ +54.3 (c = 1.03, CH_2Cl_2); mp 78.5-80 °C; **IR** (Nujol mull, cm^{-1}) 3255, 1134, 1097, 1063, 1045, 1012, 760, 702; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.20 (m, 5H), 4.79 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.88 (d, *J* = 10.5 Hz, 1 H), 3.82 (d, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 10.2 Hz, 1H), 3.60 (d, *J* = 10.5 Hz, 1H), 3.38 (br s, 2H), 3.22 (d, *J* = 7.8 Hz, 1H), 2.38 (dd, *J* = 12.9, 7.2 Hz, 1H), 1.96-1.75 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.4, 128.4, 127.4, 125.8, 89.0, 78.2, 69.0, 66.6, 51.1, 41.8, 28.7, 20.8 (two overlapping resonances); TLC (60% EtOAc/petroleum ether) R_f 0.37; **Anal.** Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.93.

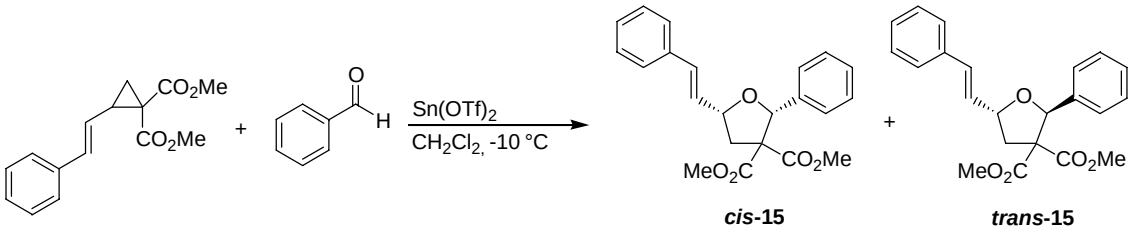


14

2-Phenyl-5-(2-thienyl)tetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (14). In an inert atmosphere glovebox, a flame-dried vial was charged with $Sn(OTf)_2$ (7.1 mg, 0.017 mmol, 0.050 equiv) and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere, charged with 0.5 mL of CH_2Cl_2 and cooled to –10 °C with stirring. After 5 min, the stirring suspension was charged with the cyclopropane (81.5 mg, 0.34 mmol, 1.0 equiv) via syringe, followed by the aldehyde (110 mg, 1.0 mmol, 3.0 equiv). The reaction was stirred at –10 °C for 45 min. The reaction mixture was then passed over a

plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) overnight. ^{1}H NMR analysis of the unpurified product (δ 5.22 vs. δ 2.58) gave the diastereomeric ratio: 21.7:1. The crude product was purified by flash chromatography with 10% acetone/petroleum ether to afford 113.5 mg (97%) of the product as a slightly yellow oil.

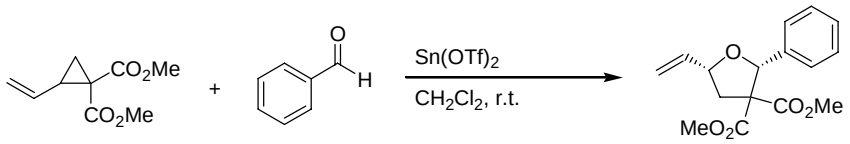
Analytical data for **14**: **IR** (thin film, cm^{-1}) 2953, 1732, 1497, 1456, 1435, 1387, 1365, 1327, 1273, 1232, 1207, 1174, 1107, 1076, 1053, 1028, 1022, 933, 922, 897, 852, 833, 814, 752, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 2H), 7.37-7.23 (m, 4H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.00 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.79 (s, 1H), 5.22 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.81 (s, 3H), 3.15-3.09 (m, 4H), 2.76 (dd, *J* = 13.6, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 168.9, 142.7, 137.6, 128.3, 127.9, 127.1, 126.7, 125.7, 125.5, 84.5, 75.8, 66.4, 53.1, 52.3, 42.9; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.43; **Anal.** Calcd. for $C_{18}H_{18}O_5S$: C, 62.41; H, 5.24. Found: C, 62.32; H, 5.23.



***cis*-2-Phenyl-5-styryltetrahydrofuran-3,3-dicarboxylic acid dimethyl ester (*cis*-15)**. In an inert atmosphere glovebox, a flame-dried vial was charged with $Sn(OTf)_2$ (7.1 mg, 0.017 mmol, 0.050 equiv) and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere, charged with 0.5 mL of CH_2Cl_2 and cooled to –10 °C with stirring. After 5 min, the stirring suspension was charged with the cyclopropane (89.0 mg,

0.34 mmol, 1.0 equiv) via syringe, followed by the aldehyde (110 mg, 1.0 mmol, 3.0 equiv). The reaction was stirred at –10 °C for 1h. The reaction mixture was then passed over a plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) overnight. ^{1}H NMR analysis of the unpurified product (δ 5.73 vs. δ 5.87) gave the diastereomeric ratio: 2.4:1. The crude product was purified by flash chromatography with a 5% to 10% acetone/petroleum ether gradient to afford 123.1 mg (98%) of the product (inseparable diastereomers) as a colorless oil.

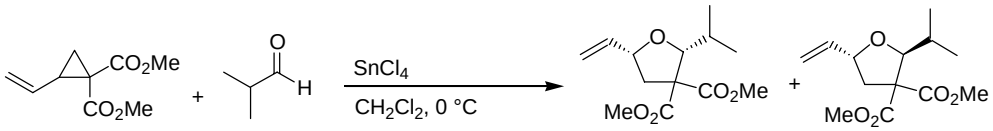
Analytical data for combined ***cis*-15/*trans*-15**: **IR** (thin film, cm^{-1}) 3082, 3062, 3001, 2953, 1732, 1601, 1578, 1497, 1452, 1435, 1360, 1335, 1269, 1228, 1207, 1174, 1109, 1090, 1070, 1049, 1028, 968, 916, 881, 845, 825, 814, 752, 698; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54-7.18 (m, 20H, major/minor), 6.72 (d, *J* = 15.9 Hz, 1H, major), 6.68 (d, *J* = 15.6 Hz, 1H, minor), 6.44 (dd, *J* = 15.9, 6.9 Hz, 1H, major), 6.25 (dd, *J* = 15.9, 6.6 Hz, 1H, minor), 5.87 (s, 1H, minor), 5.73 (s, 1H, major), 5.27 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H, minor), 4.59 (ddd, *J* = 9.9, 6.6, 6.6 Hz, 1H, major), 3.80 (s, 3H, major), 3.74 (s, 3H, minor), 3.17 (s, 3H, minor), 3.11 (s, 3H, major), 3.08 (dd, *J* = 13.2, 6.9 Hz, 1H, minor), 2.87 (dd, *J* = 13.2, 10.2 Hz, 1H, major), 2.55 (dd, *J* = 13.5, 6.0 Hz, 1H, major), 2.28 (dd, *J* = 13.2, 7.5 Hz, 1H, minor); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2, 170.4, 169.2, 169.1, 138.3, 137.8, 136.5, 136.4, 133.0, 131.5, 129.4, 128.6, 128.2, 128.1, 128.03, 127.95, 127.89, 127.86, 127.6, 127.0, 126.8, 126.62, 126.55, 84.3, 83.6, 79.9, 79.2, 66.29, 66.26, 53.0, 52.9, 52.3, 52.2, 41.1, 40.7 (2 overlapping sp^2 signals); TLC (80% CH_2Cl_2/petroleum ether) R_f 0.43; **Anal.** Calcd. for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.40; H, 6.15.



16a

2-Phenyl-5-vinyl-tetrahydro-furan-3,3-dicarboxylic acid dimethyl ester (16a). The title compound was prepared according to General Procedure **A** using 7.1 mg of $Sn(OTf)_2$, 63.0 mg of the cyclopropane, and 110 mg of the aldehyde. After 5 h at room temperature, passage over a plug of silica gel, and solvent removal, the residue was placed under vacuum (<0.1 torr) for 45 min **only**. ^{1}H NMR analysis of the unpurified product (δ 6.10 vs. δ 5.91) gave the diastereomeric ratio: 8.9:1. The isomers were separated and purified by flash chromatography with 7.5% EtOAc/petroleum ether to afford 93.4 mg (94%) of the products as colorless oils.

Analytical data for **16a**: **IR** (thin film, cm^{-1}) 2954, 2922, 2852, 1734, 1495, 1456, 1435, 1271, 1230, 1207, 1157, 1092, 1055, 1028, 928, 912, 814, 752, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.38 (m, 2H), 7.37-7.21 (m, 3H), 6.10 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.69 (s, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.48-4.38 (m, 1H), 3.81 (s, 3H), 3.11 (s, 3H), 2.77 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.50 (dd, *J* = 13.2, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 169.1, 138.0, 136.7, 128.2, 127.9, 127.1, 117.7, 84.4, 79.4, 66.4, 53.1, 52.3, 40.6; TLC (10% EtOAc/petroleum ether) R_f 0.18; **Anal.** Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.05; H, 6.20.

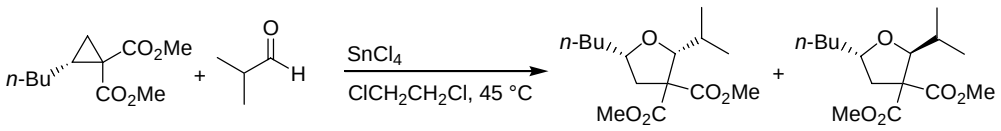


***cis*-16b** ***trans*-16b**

***cis*-2-Isopropyl-5-vinyl-tetrahydro-furan-3,3-dicarboxylic acid dimethyl ester (*cis*-16b).** In an inert atmosphere glovebox, a flame-dried vial was charged with the cyclopropane (63.0 mg, 0.34 mmol, 1.0 equiv) and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere, charged with 0.4 mL of CH_2Cl_2, and cooled to 0 °C. A solution of $SnCl_4$ (8.9 mg, 0.034 mmol, 0.10 equiv) in 0.1 mL of CH_2Cl_2 was added to the chilled mixture followed by the aldehyde (74 mg, 1.0 mmol, 3.0 equiv). The reaction was stirred at 0 °C for 4 h. The reaction mixture was then passed over a plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) for 20 min **only** to remove excess aldehyde. ^{1}H NMR analysis of the unpurified product (δ 2.51 vs. δ 2.90) gave the diastereomeric ratio: 5.7:1. The crude product was purified by flash chromatography with 15% Et_2O/petroleum ether to afford 84.2 mg (96%) of the product (inseparable diastereomers) as a colorless oil.

Analytical data for combined ***cis*-16b/*trans*-16b**: **IR** (thin film, cm^{-1}) 3084, 2987, 2956, 2875, 1736, 1647, 1471, 1435, 1394, 1367, 1342, 1265, 1232, 1205, 1157, 1093, 1066, 1053, 1024, 989, 930, 806; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H, major), 5.79 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H, minor), 5.30-5.19 (m, 2H, major/minor), 5.14 (d, *J* = 10.4 Hz, 1H, major), 5.07 (d, *J* = 10.4 Hz, 1H, minor), 4.66-4.60 (m, 1H, minor), 4.25-4.13 (m, 3H, major/minor), 3.74 (s, 3H, major), 3.73-3.70 (m, 9H, major/minor), 2.90 (dd, *J* = 12.8, 7.2 Hz, 1H, minor), 2.51 (dd, *J* = 13.2, 8.8 Hz, 1H, major), 2.42 (dd, *J* = 13.2,

7.2 Hz, 1H, major), 2.05 (dd, J = 12.8, 7.2 Hz, 1H, minor), 1.87-1.75 (m, 2H, major/minor), 0.97 (d, J = 6.8 Hz, 3H, minor), 0.96-0.91 (m, 9H, major/minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5 (major), 170.9 (minor), 170.2 (major), 169.9 (minor), 138.8 (minor), 137.3 (major), 117.1 (major), 115.2 (minor), 88.2 (major), 87.8 (minor), 78.3 (major), 78.0 (minor), 63.2 (major), 63.1 (minor), 52.8 (major), 52.7 (minor), 52.54 (major), 52.51 (minor), 42.2 (minor), 41.9 (major), 30.5 (minor), 30.2 (major), 20.5 (major), 20.1 (minor), 19.7 (minor), 19.0 (major); TLC (15% Et_2O/petroleum ether) R_f 0.20; **Anal.** Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.09; H, 7.98.

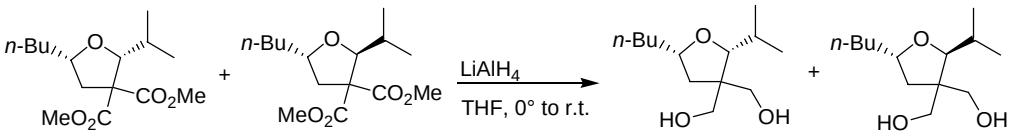


***cis*-17** ***trans*-17**

***cis*-5-Butyl-2-isopropyl-tetrahydro-furan-3,3-dicarboxylic acid dimethyl ester (*cis*-17).** In an inert atmosphere glovebox, a flame-dried vial was charged with the cyclopropane (150 mg, 0.70 mmol, 1.0 equiv, 95% ee) and a magnetic stir bar. Outside of the glove box, the vial was placed under an argon atmosphere and charged with a solution of $SnCl_4$ (56 mg, 0.21 mmol, 0.31 equiv) in 1.0 mL of dichloroethane followed by the aldehyde (151 mg, 2.1 mmol, 3.0 equiv). The reaction was stirred at 45 °C for 19 h. The reaction mixture was then passed over a plug of silica gel, eluting with 50 mL of Et_2O. The solvent was removed with a rotary evaporator, and the residue placed under vacuum (<0.1 torr) for a short time to remove excess aldehyde. ^{1}H NMR analysis of the unpurified product (δ 2.40-2.34 vs. δ 2.85) gave the diastereomeric ratio: 5.2:1. The crude product was purified by flash

chromatography with a 5% to 7.5% EtOAc/petroleum ether gradient to afford 154 mg (77%) of the product (inseparable diastereomers) as a colorless oil. This product was converted to **39**, and the major diastereomer was determined to be 93% ee by chiral SFC analysis.

Analytical data for combined ***cis*-17/*trans*-17**: **IR** (thin film, cm^{-1}) 2957, 2932, 2873, 1734, 1469, 1453, 1436, 1389, 1367, 1265, 1234, 1197, 1179, 1147, 1120, 1097, 1078, 1061, 1012, 983, 958, 937, 897, 806, 730, 623; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.21-4.13 (m, 1H, minor), 4.13-4.05 (m, 2H, major/minor), 3.80-3.68 (m, 13H, major/minor), 2.85 (dd, J = 12.7, 7.0 Hz, 1H, minor), 2.40-2.34 (m, 2H, major), 1.91 (dd, J = 12.9, 7.6 Hz, 1H, minor), 1.85-1.64 (m, major/minor), 1.61-1.48 (m, major/minor), 1.45-1.15 (m, major/minor), 1.0-0.85 (m, 18H, major/minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8 (major), 171.3 (minor), 170.6 (major), 170.1 (minor), 88.0 (major), 87.2 (minor), 77.44 (major), 77.36 (minor), 63.0 (minor), 62.9 (major), 52.7 (major), 52.6 (minor), 52.5 (major, 1 minor resonance overlapping), 42.5 (minor), 41.8 (major), 36.0 (minor), 34.5 (major), 30.4 (minor), 30.2 (major), 28.4 (major), 28.2 (minor), 22.8 (major), 22.7 (minor), 20.3 (major), 20.0 (minor), 19.9 (minor), 19.3 (major), 14.1 (major, 1 minor resonance overlapping); TLC (20% EtOAc/petroleum ether) R_f 0.57; **Anal.** Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.80; H, 9.15.

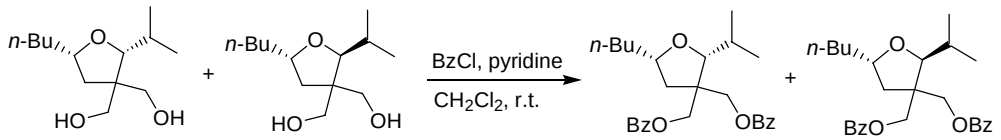


***cis*-17** ***trans*-17** ***cis*-38** ***trans*-38**

***cis*-(5-Butyl-3-hydroxymethyl-2-isopropyl-tetrahydro-furan-3-yl)-methanol (*cis*-38).** A stirring suspension of $LiAlH_4$ (92 mg, 2.4 mmol, 5.0 equiv) in 3.5 mL of THF at 0 °C was treated with a solution of ***cis*-17/*trans*-17** (139 mg, 0.49 mmol, 1.0 equiv, d.r. = 4.5:1) in 2.5 mL of THF via cannula (1 mL THF rinse). After addition the reaction was allowed to warm to room temperature with stirring. After 45 min, the reaction was quenched with 95 μL H_2O, 95 μL of a 15% NaOH (aq.) solution, and 285 μL of H_2O. The mixture was filtered through a Büchner funnel and the filter cake was washed with several portions of Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford 111 mg (99%) of the pure product (inseparable diastereomers) as a slightly yellow oil. This product was converted to **39**, and the major diastereomer was determined to be 93% ee by chiral SFC analysis.

Analytical data for combined ***cis*-38/*trans*-38**: **IR** (thin film, cm^{-1}) 3363, 2957, 2928, 2873, 2860, 1468, 1386, 1149, 1029; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.05-3.30 (m, major/minor), 3.22 (d, *J* = 8.8 Hz, 1H, minor), 3.07 (d, *J* = 8.1 Hz, 1H, major), 2.39 (dd, *J* = 12.8, 6.9 Hz, 1H, minor), 2.10 (dd, *J* = 12.7, 6.9 Hz, 1H, major), 1.87-1.15 (m, major/minor), 1.05-0.79 (m, 18H, major/minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 88.4 (major), 87.4 (minor), 77.2 (major), 76.2 (minor), 69.7 (minor), 68.9 (major), 66.7 (major), 65.0 (minor), 51.6 (minor), 50.9 (major), 39.3 (major), 39.2 (minor), 36.6 (minor), 35.7 (major), 28.9 (minor), 28.7 (major), 28.6 (major), 28.4 (minor), 22.9 (major), 22.8 (minor), 21.2 (minor),

20.9 (major), 20.7 (major), 19.9 (minor), 14.2 (major, 1 minor resonance overlapping); TLC (50% EtOAc/petroleum ether) R_f 0.24; **Anal.** Calcd. for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.84; H, 11.38.

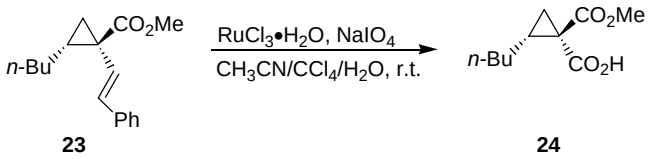


***cis*-38** ***trans*-38** ***cis*-39** ***trans*-39**

***cis*-Benzoic acid 5-butyl-2-isopropyl-3-benzoyloxymethyl-tetrahydro-furan-3-ylmethyl ester (*cis*-39).** A solution of ***cis*-38/*trans*-38** (101 mg, 0.438 mmol, 1.0 equiv, d.r. = 4.4:1) in 4.7 mL of CH_2Cl_2 was treated with benzoyl chloride (135 mg, 0.963 mmol, 2.2 equiv) and pyridine (349 mg, 4.41 mmol, 10 equiv). The reaction was stirred at 23 °C for 22 h. The mixture was partitioned between 10 mL of CH_2Cl_2 and 5 mL of H_2O. After separation, the aqueous layer was extracted with 10 mL of CH_2Cl_2. The combined organic extracts were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude product was purified by flash chromatography with 5% EtOAc/petroleum ether to afford 153 mg (80%) of the product (inseparable diastereomers) as a slightly yellow oil with the major diastereomer in 93% ee as determined by chiral SFC analysis (Chiralpak OD, 1.8% MeOH, 2.0 mL/min, 200 bar, 40 °C, 240 nm, $t_{r\text{-major}}$ 12.3 min, $t_{r\text{-minor}}$ 16.6 min).

Analytical data for combined ***cis*-39/*trans*-39**: **IR** (thin film, cm^{-1}) 3068, 2957, 2930, 2872, 2859, 1722, 1603, 1584, 1468, 1451, 1379, 1314, 1269, 1176, 1110, 1070, 1027, 989, 972, 711, 687; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05-7.97 (m, major/minor), 7.60-7.51 (m, major/minor), 7.46-7.37 (m, major/minor), 4.63-4.48 (m, 5H, major/minor), 4.46-4.38 (m,

3H, major/minor), 4.08 (dddd, J = 6.8, 6.8, 6.8, 6.8 Hz, 1H, minor) 3.85 (dddd, J = 8.2, 6.5, 6.5, 6.5 Hz, 1H, major), 3.56 (d, J = 8.8 Hz, 1H, minor), 3.44 (d, J = 8.0 Hz, 1H, major), 2.34 (dd, J = 13.1, 7.2 Hz, 1H, minor), 2.22 (dd, J = 13.1, 7.0 Hz, 1H, major), 2.05-1.88 (m, 2H, major/minor), 1.77 (dd, J = 13.1, 8.0 Hz, 1H, minor), 1.74-1.56 (m, major/minor), 1.55-1.17 (m, major/minor), 1.09-1.00 (m, 12H, major/minor), 0.93-0.85 (m, 6H, major/minor); **^{13}C NMR** (***cis*-39** only) (100 MHz, $CDCl_3$) δ 166.54, 166.46, 133.22, 133.17, 130.0, 129.9, 129.69, 129.66, 128.54, 128.51, 88.1, 76.8, 67.3, 66.1, 48.8, 40.6, 35.7, 28.8, 28.5, 22.8, 20.9, 20.8, 14.1; TLC (20% EtOAc/petroleum ether) R_f 0.69; **Anal.** Calcd. for $C_{27}H_{34}O_5$: C, 73.94; H, 7.81. Found: C, 74.02; H, 7.86.

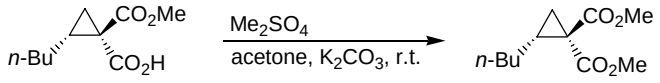


23 **24**

2-Butyl-cyclopropane-1,1-dicarboxylic acid methyl ester (24). Enantioenriched cyclopropane **23** (905 mg, 3.50 mmol, 1.0 equiv) was dissolved in a solution consisting of 7 mL of CH_3CN, 7 mL of CCl_4, and 10.5 mL of H_2O. $NaIO_4$ (6.0 g, 28.1 mmol, 8.0 equiv) was added and the mixture was stirred to a uniform suspension. $RuCl_3•H_2O$ (21.8 mg, 0.105 mmol, 0.030 equiv) was then added and the mixture was stirred for 8 h at 23 °C. The reaction was quenched with 50 mL of 2 N HCl (aq.) and the mixture was extracted with four 25 mL portions of EtOAc. The combined organic extracts were filtered through a charcoal/celite cake. The filtrate was dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude material was purified by flash chromatography with a 10% to 20% EtOAc/petroleum ether gradient to afford 413 mg (59%) of the product as a colorless

oil. This product was converted to **(-)-12e**, which was determined to be 95% ee by chiral GC analysis.

Analytical data for **24**: $[\alpha]_D^{21}$ +40.4 (c = 0.985, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3016, 2959, 2929, 2873, 2861, 1760, 1733, 1701, 1676, 1438, 1350, 1282, 1252, 1221, 1202, 1149, 1073, 990, 914, 878, 847, 806, 740, 677; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 2.08-1.99 (m, 1H), 1.95 (dd, *J* = 9.2, 3.9 Hz, 1H), 1.87 (dd, *J* = 8.6, 3.9 Hz, 1H), 1.75-1.60 (m, 2H), 1.41-1.25 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 168.5, 53.5, 38.2, 31.4, 30.8, 26.5, 24.6, 22.4, 14.1; TLC (20% EtOAc/petroleum ether) R_f 0.19; **Anal.** Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.02; H, 8.09.

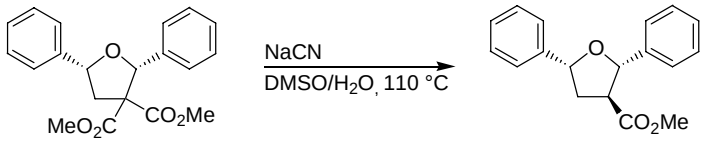


24 **(-)-12e**

(-)-2-Butyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester ((-)-12e). A stirring suspension of enantioenriched carboxylic acid **24** (323 mg, 1.61 mmol, 1.0 equiv) and K_2CO_3 (227 mg, 1.80 mmol, 1.1 equiv) in 30 mL of acetone was treated with Me_2SO_4 (245 mg, 1.77 mmol, 1.1 equiv). The reaction was stirred at 23 °C for 6 h. The mixture was partitioned between 75 mL of Et_2O and 50 mL of H_2O. After separation, the aqueous layer was extracted with two 50 mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude material was purified by flash chromatography with 10% EtOAc/petroleum ether to afford 281 mg (81%) of the product as a colorless oil in 95% ee as determined by chiral GC analysis (Chiraldex G-

TA column (30 m x 0.25 mm), oven = 100 °C, pressure = 80 kPa, detector = FID, 250 °C, $t_{r\text{-}major}$ 34.7 min, $t_{r\text{-}minor}$ 39.8 min).

Analytical data for **(-)-12e**: The spectral data for this compound was identical to that reported for the racemic cyclopropane.[20] $[\alpha]_D^{21}$ –46.7 (c = 1.04, CH_2Cl_2).

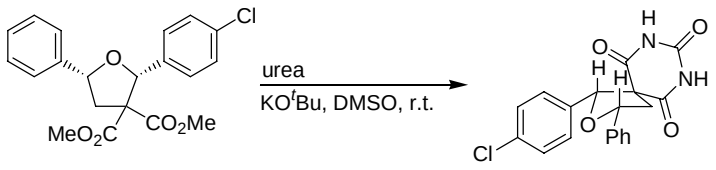


13a **25**

2,5-Diphenyl-tetrahydro-furan-3-carboxylic acid methyl ester (25). A 10-mL round bottomed flask was charged with **13a** (80.0 mg, 0.235 mmol, 1.0 equiv), NaCN (21.0 mg, 0.428 mmol, 1.8 equiv), 2 mL of DMSO, and H_2O (20.0 mg, 1.11 mmol, 4.7 equiv). The flask was affixed with a reflux condenser and the reaction was heated to 110 °C with stirring. After 20 h, the reaction was cooled to room temperature and partitioned between 20 mL of Et_2O and 20 mL of water. After separation the aqueous layer was extracted with three 20 mL portions of Et_2O. The combined organic extracts were washed with three 20 mL portions of water and 20 mL of brine, dried over $MgSO_4$, and concentrated by rotary evaporation affording a colorless oil. ^{1}H NMR analysis of the unpurified product (δ 2.72 vs. δ 5.28) gave the diastereomeric ratio: 6.7:1. The isomers were separated and purified by flash chromatography with 5% EtOAc/petroleum ether to afford 53 mg (80%) of the products as a colorless oil (major diastereomer) and a white solid (minor diastereomer).

Analytical data for **25**: When performed with 97% ee **13a**; $[\alpha]_D^{26}$ +50.8 (c = 1.04, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3089, 3064, 3032, 2951, 1736, 1605, 1497, 1452, 1435, 1358,

1308, 1263, 1196, 1171, 1086, 1059, 1026, 756, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.22 (m, 10H), 5.20 (d, *J* = 7.2 Hz, 1 H), 5.16 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.75 (s, 3H), 3.13 (ddd, *J* = 10.4, 7.2, 5.2 Hz, 1H), 2.72 (ddd, *J* = 12.8, 6.8, 5.2 Hz, 1H), 2.23 (ddd, *J* = 12.8, 9.2, 9.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 141.5, 141.1, 128.6, 128.0, 127.8, 126.2, 126.1, 83.8, 80.9, 52.3, 52.2, 38.9 (two overlapping sp^2 resonances); TLC (5% EtOAc/petroleum ether) R_f 0.18; **Anal.** Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.39; H, 6.36.



13b **26**

(1*R*,3*R*)-1-(4-Chlorophenyl)-3-phenyl-2-oxa-7,9-diaza-spiro[4.5]decane-6,8,10-trione (26). A solution of **13b** (114.3 mg, 0.305 mmol, 1.0 equiv, 96% ee) in 0.6 mL DMSO was treated with urea (108.0 mg, 1.80 mmol, 5.9 equiv) and KO^{t}Bu (75.3 mg, 0.671 mmol, 2.2 equiv). After stirring for 1 h, the reaction was diluted with 15 mL of EtOAc and washed with 20 mL of a 0.1 N HCl (aq.) solution. The aqueous phase was extracted with three 20 mL portions of EtOAc. The combined organic extracts were washed with two 20 mL portions of water and 25 mL of brine, dried over $MgSO_4$, and concentrated by rotary evaporation affording a white solid. The crude product was purified by flash chromatography with a 30% to 40% EtOAc/petroluem ether gradient to afford 58 mg (51%) of the product as a white solid. A portion of this material was dissolved in a small amount of THF and recrystallized (for X-ray analysis) by slow diffusion of petroleum ether vapor into the solution.

Analytical data for **26**: $[\alpha]_D^{26}$ +71.0 (c = 1.00, THF); mp 263-265 °C; **IR** (Nujol mull, cm^{-1}) 3236, 1759, 1728, 1705, 1194, 843, 762; **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.43 (s, 1H), 10.78 (s, 1H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.50-7.25 (m, 7H), 5.12 (dd, *J* = 9.0, 9.0 Hz, 1H), 5.07 (s, 1H), 2.93 (dd, *J* = 12.9, 7.2 Hz, 1H), 2.55 (dd, *J* = 12.9, 9.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 171.8, 170.3, 150.1, 140.5, 134.5, 133.4, 128.4, 128.3, 128.1, 128.0, 126.7, 89.3, 81.1, 63.7, 42.8; TLC (40% EtOAc/petroleum ether) R_f 0.30; **Anal.** Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; N, 7.56. Found: C, 61.58; H, 4.11; N, 7.49.

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CHAPTER 4

APPLICATION OF THE TIN-CATALYZED CYCLOPROPANE/ALDEHYDE CYCLOADDITION REACTION: PROGRESS TOWARDS THE 2-OXABICYCLO[4.3.0]NONANE CORE OF THE CLADIELLIN DITERPENES

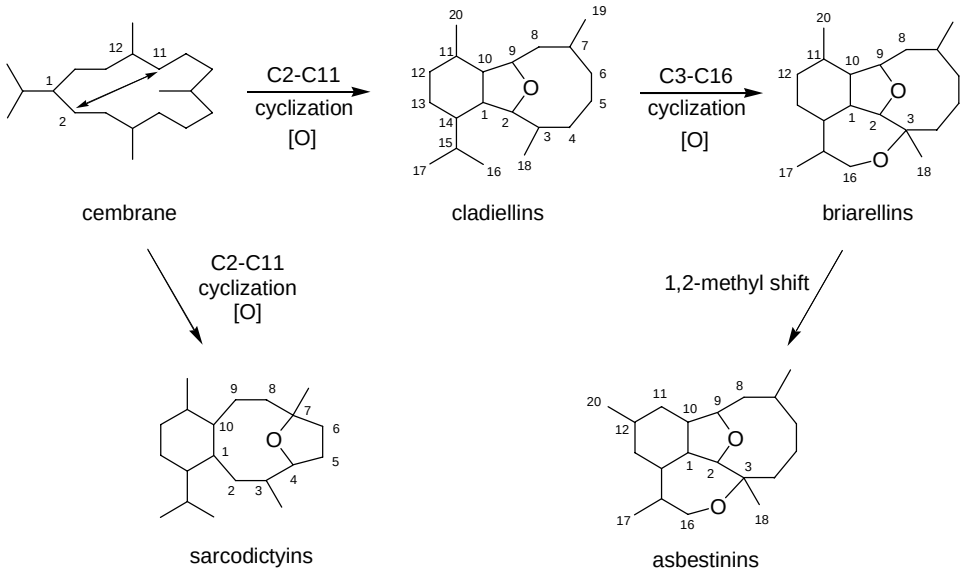
4.1 Introduction

4.1.1 Cladiellin Diterpene Chemistry

Since the late 1960's a considerable number of structurally intriguing oxacyclic diterpenes have been isolated from octocorals inhabiting various coastal marine habitats.[1] One large family consists of structures containing an [8.4.0]tetradecane ring system formally derived from the intramolecular cyclization of a cembrane. The members of this family have been further classified into four categories based on differences in both carbon skeleton and the presence/position of ethereal linkages: the cladiellins, briarellins, asbestinins, and sarcodictyins. The biosynthesis of each of these secondary metabolites has been proposed to originate from C2-C11 bond formation in the cembranoid precursor (**Scheme 4-1**). Ether formation between C4 and C7 of the resulting bicyclo[8.4.0] system affords the sarcodictyins, while ether formation bridging C2 and C9 produces the cladiellins. The briarellins are formed through the formation of an additional ether linkage between C3 and

C16 of the cladiellin structure. A methyl shift from C11 to C12 is believed to convert the briarellins to the asbestinins.

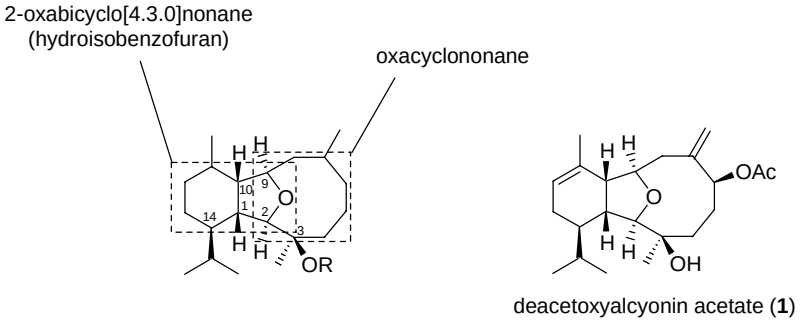
Scheme 4-1. Proposed Biosynthesis of Polycyclic Ethers from Cembrane Precursors



The most abundant and widely studied of these polycyclic ethers are the cladiellins (eunicellins). The majority of these diterpenes have been isolated from octocorals of the orders Alcyonacea and Gorgonacea. Although the natural function of these compounds is believed to be predatory deterrence, several cladiellins are known to have antiinflammatory and antitumor activity, making them ideal synthetic targets. All cladiellin diterpenes have several common structural features. The tricyclic ring system is composed of 2-oxabicyclo[4.3.0]nonane and oxacyclononane subunits (**Figure 4-1**).[2] Cladiellins have at least six stereocenters at C1, C2, C3, C9, C10, and C14. The configurations of these six stereocenters have the absolute sense indicated below, even though the formal assignment may change with differing substitution. Carbon 3 is invariably an oxygenated quaternary

center. Although the carbon skeleton of the cladiellins remains unchanged, the individual species differ in additional heteroatom substitution and carbon oxidation states (except for the aformentioned six stereocenters). As a consequence, cladiellins may contain additional stereochemistry. Deacetoxyalcyonin acetate is a representative cladiellin diterpene and the first 2,11-cyclized cembranoid to be synthetically prepared.[3]

Figure 4-1. Common Structural Features of the Cladiellin Ditepenes

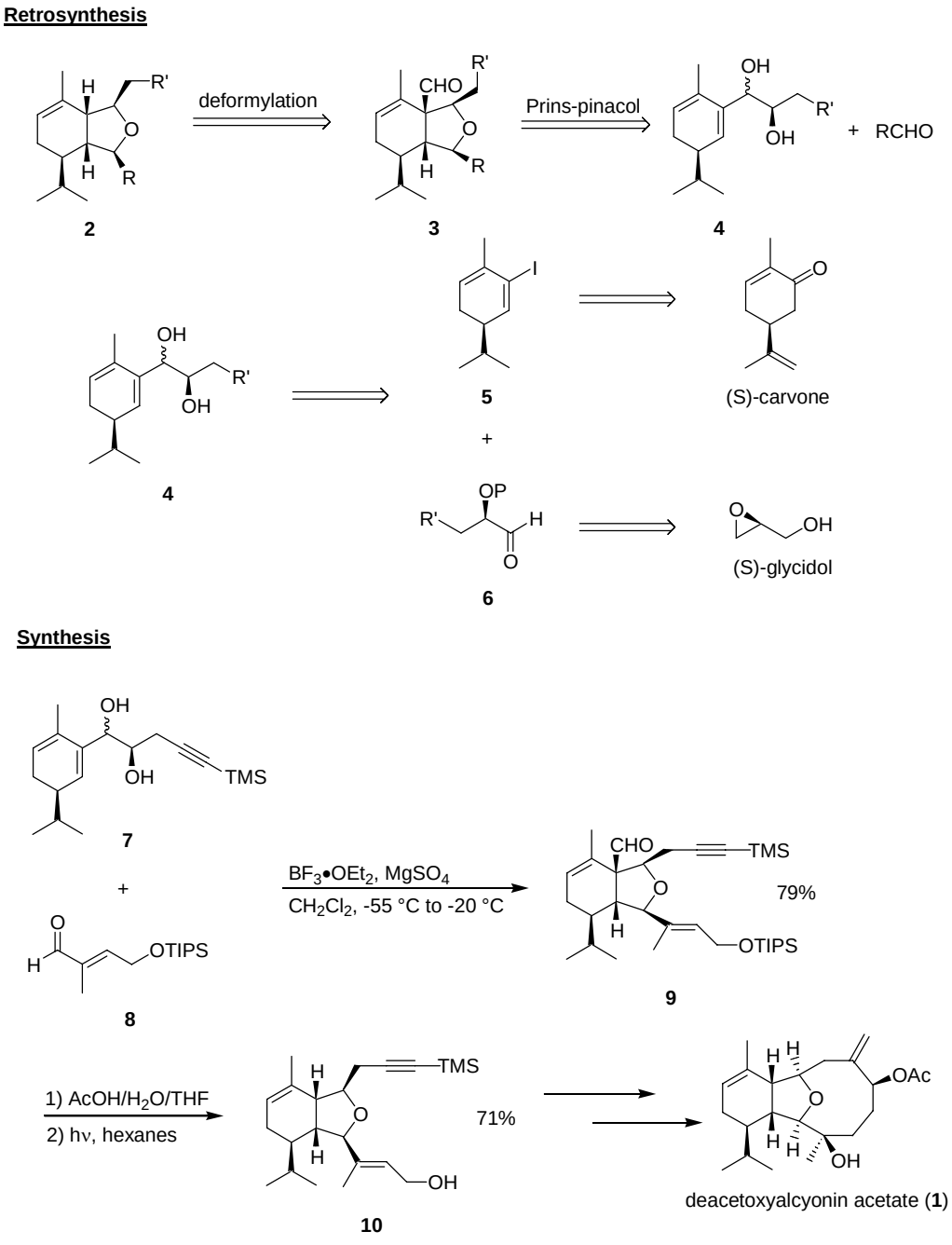


Inspection of the oxatricyclic ring system of the cladiellin diterpenes reveals that the greatest invariability is found in the hydroisobenzofuran core. Thus, a sensible synthetic strategy would be the rapid preparation of this rather intricate subunit. The achievement of such a goal would install two of the three rings and five of the six requisite stereocenters found in each of the known cladiellins. Divergent synthetic operations after this point would then allow access to the entire class of diterpenes from a common complex intermediate. To date, three groups have efficiently approached the synthesis of cladiellin diterpenes by initially targeting the hydroisobenzofuran core.[2,4,5]

In 1995, Overman reported the synthesis of deacetoxyalcyonin acetate (**1**), which constituted the first synthesis of a cladiellin diterpene.[3] The key steps in the retrosynthetic

analysis are a Prins-pinacol reaction between enantiopure dienyl diol **4** and an aldehyde, and a stereospecific deformylation of the primary product (**3**) to produce the cladiellin hydroisobenzofuran core (**2**) (**Scheme 4-2**). Cyclic diene **4** is easily prepared from commercially available (*S*)-carvone and (*S*)-glycidol. The $BF_3 \bullet OEt_2$-mediated Prins-pinacol reaction of dienyl diol **7** and enal **8** followed by photochemical deformylation afforded the requisite 2-oxabicyclo[4.3.0]nonane system (**10**) as a single stereoisomer in good yield. This product was subsequently converted to deacetoxyalcyonin acetate (**1**), and the above methodology has since been applied to the synthesis of a number of additional cladiellin diterpenes.[2]

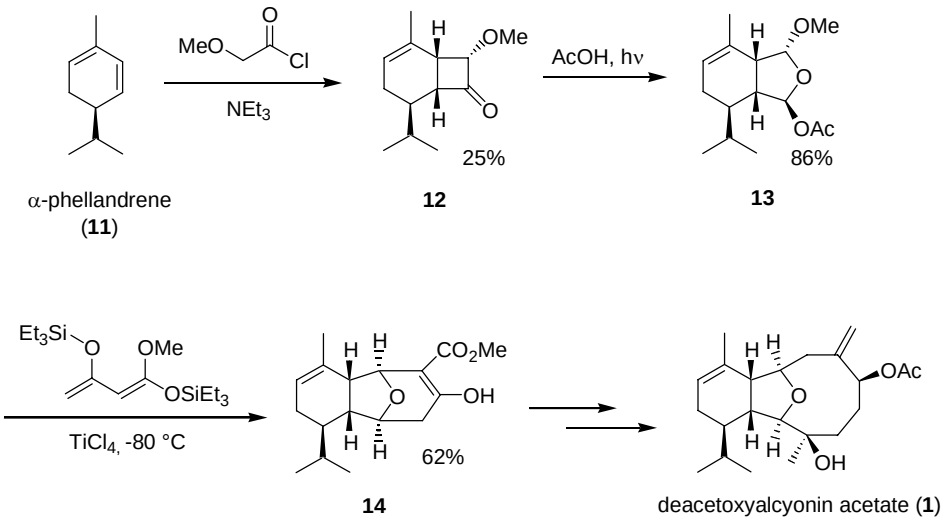
Scheme 4-2. Synthesis of the Cladiellin Hydroisobenzofuran Core via a Prins-Pinacol Rearrangement and Application to the Total Synthesis of Deacetoxyalcyonin Acetate (**1**)



The cladiellin hydroisobenzofuran core was also expeditiously synthesized by Molander, employing a novel Lewis acid-promoted [4+3] annulation strategy (**Scheme 4-**

3).[4,6] The three-step sequence begins with the thermal [2+2] cycloaddition of α-phellandrene (**11**) and methoxy ketene affording cyclobutanone **12**. Under photochemical conditions, **12** undergoes rearrangement to give mixed bis-acetal **13**. Upon treatment with $TiCl_4$, this compound undergoes acetate ionization to produce an oxocarbenium ion regioselectively, followed by addition of the nucleophilic diene to the convex face of the bicyclic system. A second ionization, followed by ring closure affords the 2-oxabicyclo[4.3.0]nonane structure **14** as a single regio- and stereoisomer. Although the first step of this sequence is rather low yielding, the rapid increase in molecular complexity is nonetheless impressive. Polycyclic ether **14** was later converted to deacetoxyalcyonin acetate (**1**) through a series of structural elaborations and eventual ring expansion/opening to the oxacyclononane.

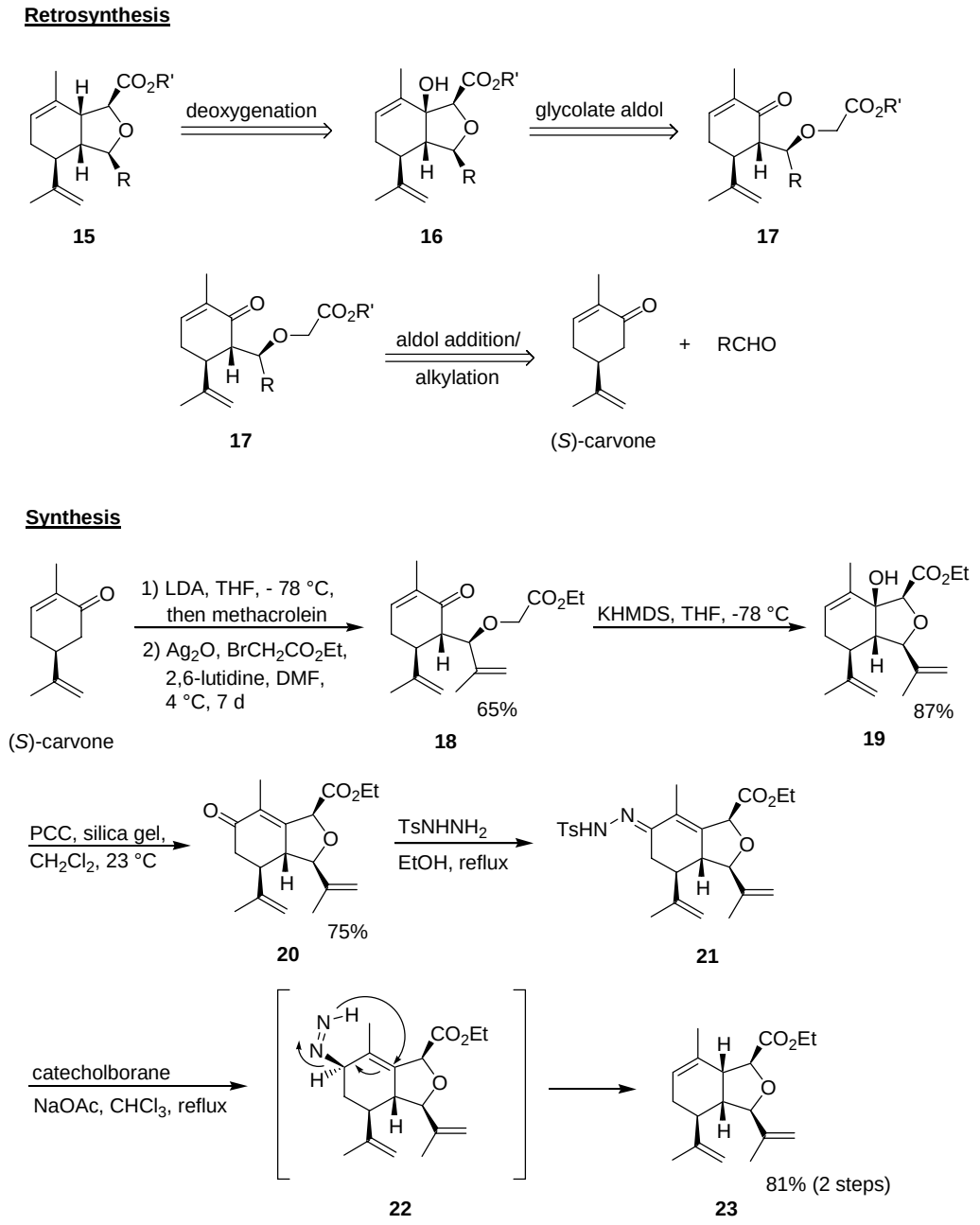
Scheme 4-3. Synthesis of the Cladiellin Hydroisobenzofuran Core via a [4+3] Annulation and Application to the Total Synthesis of Deacetoxyalcyonin Acetate (**1**)



McIntosh reported a third efficient approach to the cladiellin hydroisobenzofuran core (**15**).[5] Retrosynthetic analysis reveals the key steps in this sequence (**Scheme 4-4**). One

central transformation is the intramolecular glycolate aldol reaction of ketoester **17** to furnish bicyclic system **16**, possessing the overall diterpene carbon skeleton. In a similar fashion to Overman's sequence, the allylic carbon at the ring junction of the hydroisobenzofuran is in the incorrect oxidation state. Thus, a second key step is the stereoselective deoxygenation of this aldol product. Finally, ketoglycolate **17** may be formed from an aldol addition of (*S*)-carvone to an appropriate aldehyde followed by *O*-alkylation. The synthetic sequence begins with addition of the lithium enolate of (*S*)-carvone to methacrolein, selectively producing the anti-aldol adduct. Alkylation of the secondary hydroxyl group with ethyl bromoacetate in the presence of Ag(I) affords ketoglycolate **18**. Treatment of this ketoester with KHMDS induces an intramolecular glycolate aldol addition onto the cyclohexenone in excellent yield. The only isomer produced in this cyclization is the *cis*-fused adduct (**19**). The requisite deoxygenation of this product is a three step process. Oxidative rearrangment of hydroisobenzofuran **19** with PCC on silica gel produces enone **20**, which is then converted to tosylhydrazone **21**. Subsequent hydride reduction from the α-face with catecholborane forms an intermediate allylic diazene (**22**), which undergoes a suprafacial rearrangement affording the cladiellin hydroisobenzofuran unit (**23**) in good yield.

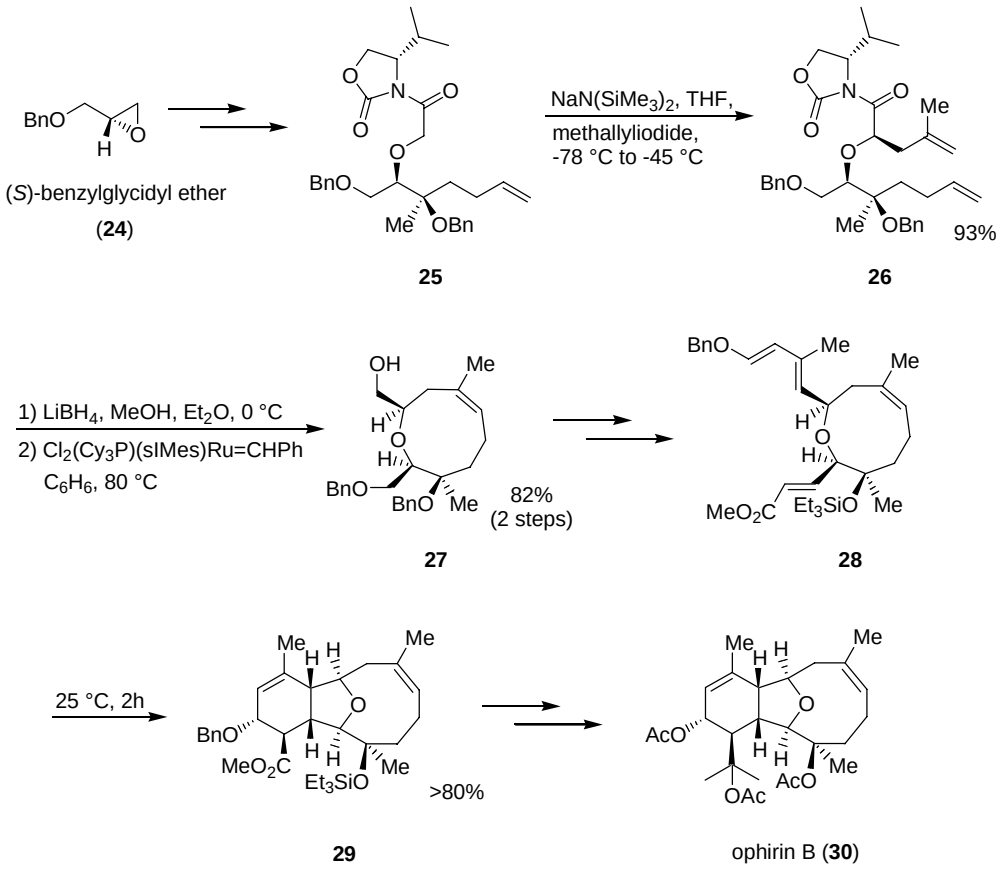
Scheme 4-4. Synthesis of the Cladiellin Hydroisobenzofuran Core via an Intramolecular Glycolate Aldol Addition



A rather unique approach to the synthesis of cladiellin diterpenes was reported by Crimmins in 2004.[7] Unlike previous methods which focused on the construction of the 2-oxabicyclo[4.3.0]nonane segment first and fabricated the oxacyclononane portion at a later

stage in the synthesis (*vida supra*), this approach tackles initial formation of the nine-membered ether and assembles the hydroisobenzofuran unit last. A few of the central synthetic transformations in the total synthesis of ophirin B are shown in **Scheme 4-5**. Absolute stereochemistry is introduced in the first step of the synthesis through the functionalization of commercially available (*S*)-benzylglycidyl ether (**24**). Advanced intermediate *N*-acyloxazolidinone **25** is asymmetrically alkylated with methallyliodide affording diene **26**. Following reductive removal of the auxiliary, this species undergoes ring-closing metathesis, to furnish oxacyclononene **27**. A series of synthetic operations are performed in the elaboration of the side chains, ultimately producing tetraene **28**. Intramolecular Diels-Alder cycloaddition of this compound ensues spontaneously at room temperature, giving oxatricyclic compound **29** containing the hydroisobenzofuran moiety. Minor manipulations to this product result in the eventual formation of ophirin B (**30**). This RCM/Diels-Alder methodology was also employed by the Crimmins group in the total synthesis of astrogorgin.[8]

Scheme 4-5. Overview of the Total Synthesis of Ophirin B



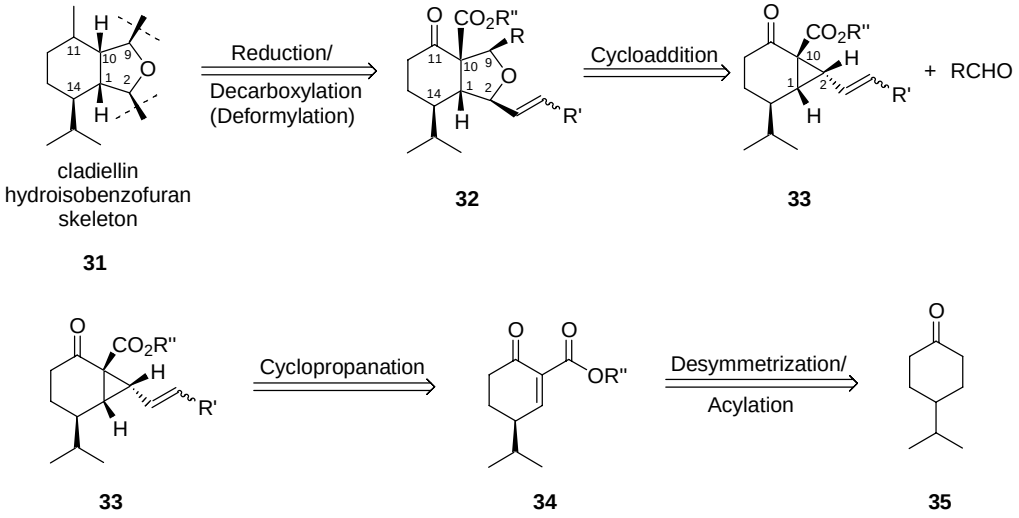
4.1.2 Retrosynthetic Analysis of the Cladiellin 2-Oxabicyclo[4.3.0]nonane Core

With the successful development of the enantiospecific tin-catalyzed aldehyde/cyclopropane cycloaddition reaction (**Chapter 3**), an interest emerged in testing the performance of this chemistry under more demanding conditions. Specifically, the application of this novel reaction to the synthesis of a natural product containing a substituted tetrahydrofuran seemed appropriate. This process would not only probe the nature of the cycloaddition in the presence of greater functionality, but if successful, would constitute a significant advance in the overall scope of this reaction. In light of the highly substituted tetrahydrofuran ring present in the cladiellin diterpenes and continued the interest in this

intriguing class of marine compounds, the 2-oxabicyclo[4.3.0]nonane core of these natural products seemed a worthy target.

The proposed retrosynthesis of the cladiellin 2-oxabicyclo[4.3.0]nonane core (**30**) is shown in **Scheme 4-6**. The primary target, bicyclic ether **32**, is envisioned to arise from the tin-catalyzed cycloaddition protocol employing vinyl cyclopropane **33** and an appropriate aldehyde. The β-ketoester functionality in cyclopropane **33** should serve as a viable coordination site for the Lewis acid, while the vinyl group should be an effective donor substituent. Moreover, the unsaturation will be an important functional handle, should the core be elaborated to a natural product. Based on mechanistic results, the requisite relative stereochemistry at C1 and C10 in **32** should be transferred from **33** by inversion at the donor position and retention at the acceptor position, while the stereochemistry at C9 should result from the preferential formation of *cis*-2,5-disubstituted tetrahydrofurans. D-A cyclopropane **33** is expected to be available from the cyclopropantion of enone **34**, which is readily synthesized from 4-isopropylcyclohexanone (**35**). The introduction of absolute stereochemistry into the system may be possible at this point through the asymmetric enolization of **35** followed by acylation.[9-12] After the formation of bicyclic ether **32**, the required carbon at C11 of **31** can be placed through reduction of the ketone moiety and the unwanted carboxyester group at C10 removed through a decarboxylation or through the stereospecific deformylation protocol used by Overman.[13]

Scheme 4-6. Proposed Retrosynthesis of the Cladiellin Hydroisobenzofuran Core

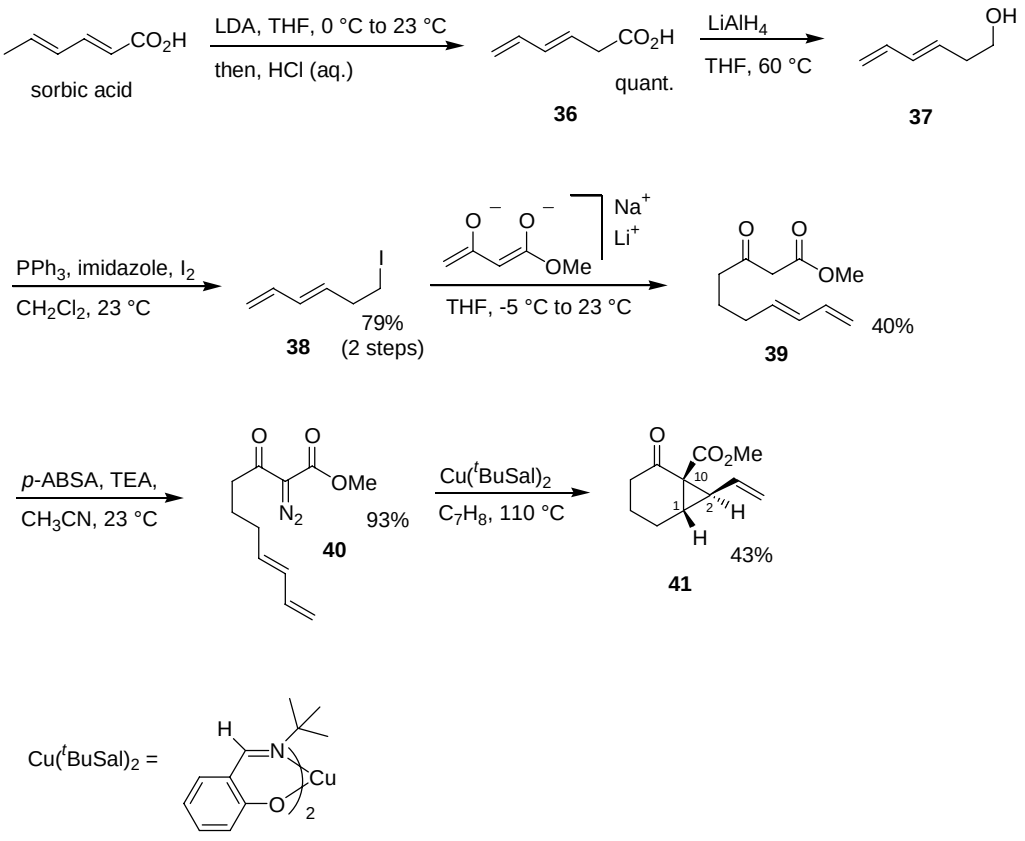


4.2 Results and Discussion

Prior to synthesizing an advanced intermediate suitable for the construction of the 2-oxabicyclo[4.3.0]nonane core of the cladiellin diterpenes, a relatively simple model system was constructed to explore reactivity and stereochemical issues. This was especially important since it was not known whether β-ketoesters were suitable substrates in the tin-catalyzed cycloaddition. Additionally, the inclusion of an invariable resident stereocenter (C1) in the cyclopropane may provide further evidence for the proposed S_N2 mechanism. Previously described vinyl cyclopropane **41** was chosen as the test substrate since it was easily accessible in six steps from commercially available starting material following a procedure disclosed by Stoltz (**Scheme 4-7**).[14,15] Deconjugation of sorbic acid was accomplished through kinetic quenching of the derived lithium enolate affording diene **36** in quantitative yield. Reduction to the primary alcohol followed by iodination furnished dienyl iodide **38**. Alkylation of the dianion of methyl acetoacetate produced β-ketoester **39**, which was converted to diazoester **40** through treatment with *p*-acetamidobenzenesulfonyl azide.

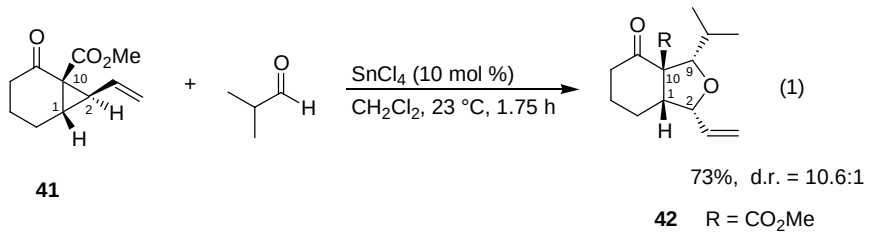
The desired vinyl cyclopropane (**41**) was then obtained via a copper carbenoid intramolecular cyclopropanation. Although this substrate has the undesired relative stereochemistry at the allylic carbon (β vs. α) for the synthesis of the cladiellin core, it should still disclose important information regarding the general reactivity of the system.

Scheme 4-7. Synthesis of Cyclopropane Test Substrate **41**



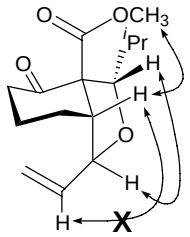
In order to test the feasibility of the new methodology for the synthesis of the cladiellin diterpene core, cyclopropane **41** was subjected to cycloaddition conditions employing isobutyraldehyde in the presence of a catalytic amount of $SnCl_4$. As anticipated, bicyclic ether **42** was formed in good yield and diastereoselectivity (eq 1). Additionally,

NOESY analysis indicated that the relative stereochemistry of the major diastereomer was in accordance with the proposed reaction mechanism (**Figure 4-2**). The stereochemistry of



invariant C1 relative to C2 (cladiellin numbering system) shows that an inversion has in fact occurred at the latter center. This not only lends support to the proposed aldehyde S_N2 mechanism but also shows that the required stereochemistry at C2 for the cladiellin diterpene core should be readily accessible through preparation of the C2-epimer of **41**. The major product also possesses a *cis*-ring fusion, which is a necessary feature if the primary adduct is to be stereospecifically deformylated. This stereochemical outcome may be a result of retention at the C10 center due to rapid quenching of the initially formed oxocarbenium ion (see **3.3.2.3**), or may simply be a consequence of the existing stereochemistry in the molecule. Finally, the *cis*-relationship between the substituents at the C2- and C9-positions is in agreement with precedence in these cycloaddition reactions. It should be noted, however, that no previous substrate studied possessed additional stereochemistry, and thus the influence of the C1 and C10-positions is not known. If the stereochemical outcome at C9 is driven primarily by the stereochemistry at C2, then the C2-epimeric substrate should give the desired 2,9-*cis* product. There is some concern that a *cis*-relationship between the aldehyde substituent at C9 and the carbomethoxy substituent at C10 may not be favored. This can only be determined experimentally.

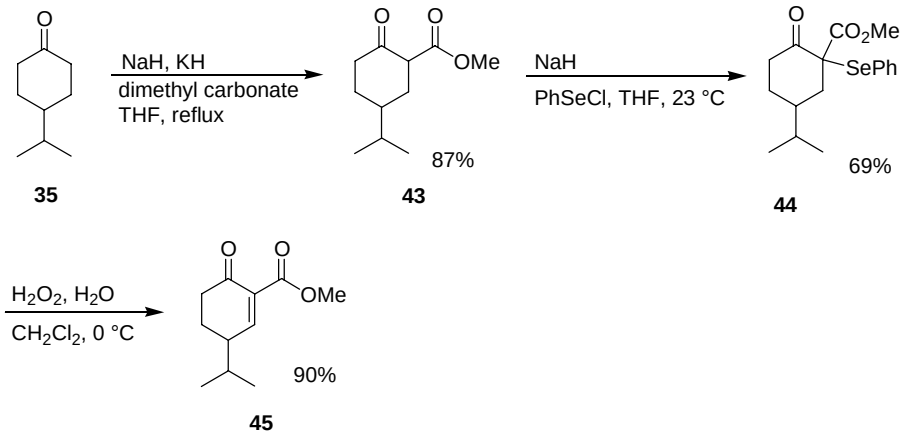
Figure 4-2. Observed NOE Enhancements in Cycloadduct **42**



42

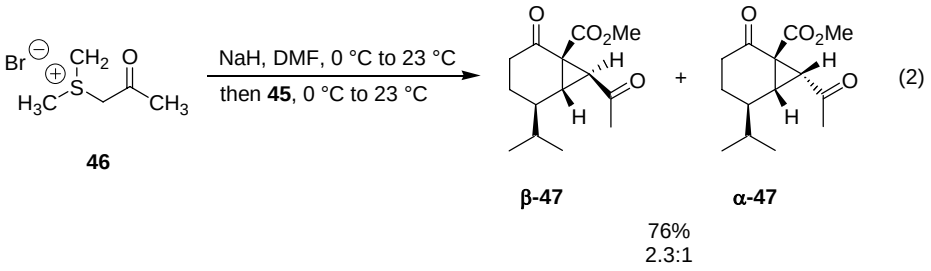
Owing to the successful cycloaddition of test substrate **41**, focus turned to the synthesis of a vinyl cyclopropane resembling **33**, containing all of the elements necessary for the construction of the cladiellin hydroisobenzofuran core. In the interest of time, an initial racemic synthesis was planned. Following the retrosynthetic plan outlined in **Scheme 4-6**, enone **45** was synthesized according to a procedure reported by Danishefsky (**Scheme 4-8**).[16] The enolate of commercially available 4-isopropylcyclohexanone (**35**) was acylated with dimethyl carbonate affording β-ketoester **43** in excellent yield. Selenation of this species followed by mild oxidation produced the desired Michael acceptor.

Scheme 4-8. Synthesis of Cyclopropane Precursor **45**



35 **43** **44** **45**

The synthesis of acylcyclopropanes from α,β-unsaturated carbonyl compounds can be accomplished via Corey-Chaykovsky-type reactions with β-carbonyl sulfonium ylides.[17-19] Use of this methodology, followed by a chemoselective olefination, was initially investigated en route to the desired vinyl cyclopropane. The treatment of **45** with the dimethylsulfonium ylide derived from bromoacetone (**46**) afforded acetyl cyclopropane **47** as a 2.3:1 mixture of separable β- and α-isomers (eq 2). The relative stereochemistry of these



(2)

46

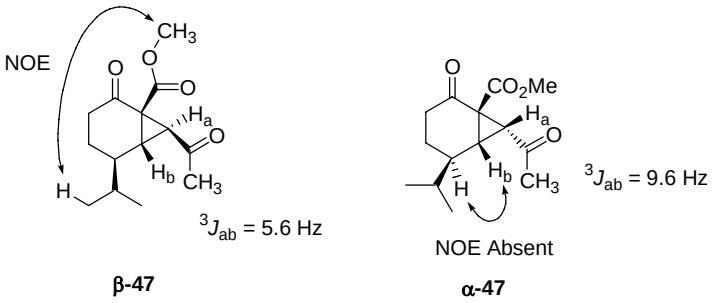
β-47 **α-47**

76%
2.3:1

products was determined through cyclopropyl ^{1}H NMR coupling constant values and NOESY analysis (**Figure 4-3**). For cyclopropanes, *trans* coupling constants are typically 3-5 Hz, while *cis* coupling constants are in the range of 6-10 Hz.[20] Epimerization of **β-47** to **α-47** was unsuccessful. Kinetic quenching of the thermodynamic enolate of **47** was expected to afford desired isomer **α-47** from convex (β) face protonation. However, treatment of **β-47** with LDA and subsequent treatment with dilute HCl resulted in decomposition, presumably via a retro-Michael ring opening of the cyclopropyl anion. Noting the inability to epimerize the undesired diastereomer, several attempts were made to convert the minor diastereomer (**α-47**) directly to the vinyl cyclopropane. Wittig olefination conditions with triphenylphosphonium methylide afforded only decomposition, most likely due to deprotonation of the cyclopane ring α to the ketone. In an attempt to avoid complications

observed with the use of basic reagents, methylenation was attempted with the Tebbe reagent.[21] Unfortunately, decomposition was noted with no desired product formation. The inability to further functionalize this cyclopropyl ketone, warranted a different synthetic approach to the vinyl cyclopropane.

Figure 4-3. Relative Stereochemical Determination of Acetyl Cyclopropanes **β-47** and **α-47**



Based on the fact that vinyl cyclopropanes can successfully be constructed from intramolecular S_N2' reactions, another approach to this synthetic problem was to construct a substrate capable of undergoing a 3-*exo*-*trig* cyclization.[22-24] Enol phosphate **52** was targeted for this purpose, in the anticipation that under basic conditions the phosphate group would be cleaved simultaneously forming an enloate capable of attacking the (*E*)-alkene (**Scheme 4-9**). Preparation of this compound began with the treatment of enone **45** with vinyl cuprate **48**, affording protected allyl alcohol **49**. The 3,4-stereochemstry of the cyclohexanone ring is assumed to be *trans* based on an analogous cuprate addition.[16] Due to instability, the crude product was directly protected by treatment of the enolate with diethyl chlorophosphate. Removal of the TBS group from **50** was accomplished with HF•pyridine affording allyl alcohol **51** in excellent yield. Iodination of this compound furnished cyclopropane precursor **52**. As expected, exposure of the allyl iodide to NaOMe afforded vinyl cyclopropane **53** (the

reaction was not optimized). Only a single diastereomer was formed, and NOESY analysis showed the presence of correlations between two vinyl protons and the angular proton, revealing that the stereochemistry at the allylic carbon was β and thus opposite of what was required for the intended use of this substrate (**Figure 4-4**).

Scheme 4-9. Attempted Synthesis of Vinyl Cyclopropane **α-53**

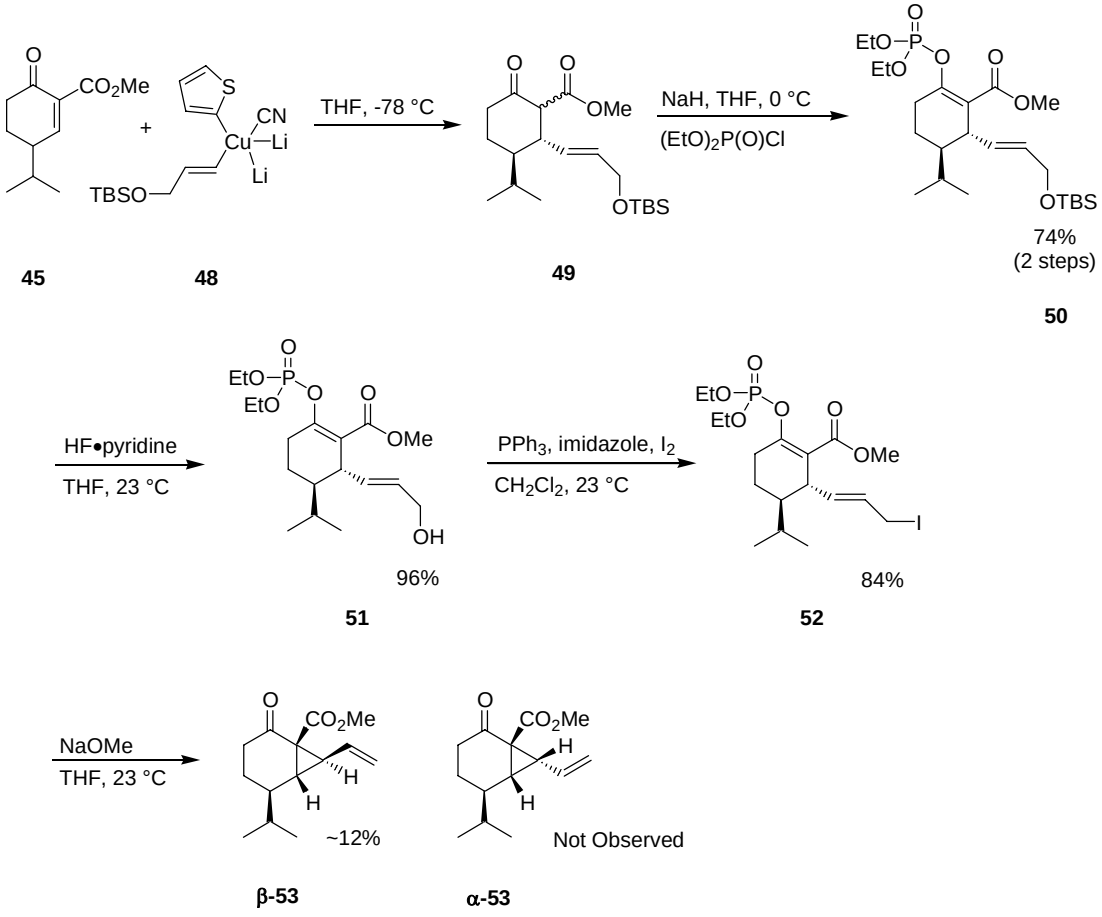
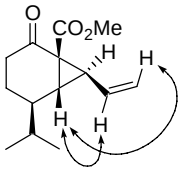


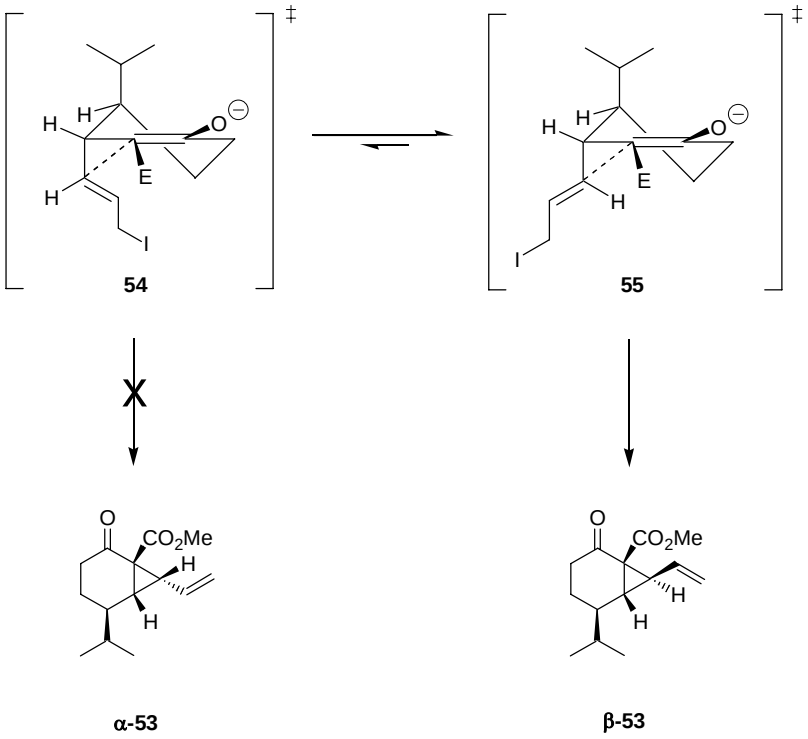
Figure 4-4. Observed NOE Enhancements in Cyclopropane **β-53**



β-53

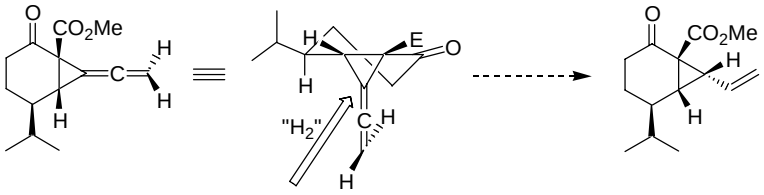
Conformational analysis lends support to the formation of the β-epimer (**Scheme 4-10**). Assuming the enolate resulting from phosphate cleavage adopts a half-chair conformation, the substituents would likely need to occupy pseudo-axial positions for proper orbital overlap. Transition state **54** leading to the α-isomer requires placing the olefin in the cavity of the developing bicyclic system. Rotation about the sp^2-sp^3 bond in transition state **55** alleviates this unfavorable steric interaction and leads to the observed β-epimer. It seemed clear that there was no straightforward way to make this vinyl cuprate addition/cyclization strategy amendable to the synthesis of the α-epimer.

Scheme 4-10. Conformational Analysis of Vinyl Cyclopropane **53** Formation



The large steric crowding observed near the concave face of the desired fused cyclopropane system prompted reevaluation of the means for installing the requisite stereochemistry at the allylic carbon. It seems reasonable that the stereocenter may effectively be set through introduction of the hydrogen atom from the more accessible convex face. The problem can then be simplified to the reduction of an exocyclic olefin from the β-face of the system. A report on the monohydrogenation of a substituted vinylidene cyclopropane suggested that this approach might be feasible for the one step synthesis of **α-53** from allene **56** (**Scheme 4-11**).[25]

Scheme 4-11. Proposed Hydrogenation Route to **α-53**



56 **α-53**

Vinylidene cyclopropanes can conveniently be prepared from the direct reaction of vinylidene carbenes and olefins.[26-29] Due to the electrophilic nature of vinylidene carbenes however, successful cyclopropanation requires the use of either an electon-rich or electron-neutral alkene. Since the desired cyclopropane (**56**) is doubly substituted with electron-withdrawing groups, this methodology could not be used. Instead, cyclopropane **56** was prepared in an analogous fashion to **53**, although employing a novel 3-*exo*-*dig* cyclization (**Scheme 4-12**). This is apparently the first reported example of this cyclization mode and represents a violation of Baldwin's Rules for ring closure.[30] Silyl enol ether **58** was prepared as a single diastereomer via a TBSOTf promoted conjugate addition of lithium acetylidoaluminate **57** to enone **45**.[31] This reaction was not optimized and appears to be the first example of a conjugate addition of an acetylide derived from a propargyl halide. The relative stereochemistry of this addition product was determined by NOESY analysis of vinylidene cyclopropane **56** (**Figure 4-5**).

Scheme 4-12. Synthesis of Vinylidene cyclopropane **56**

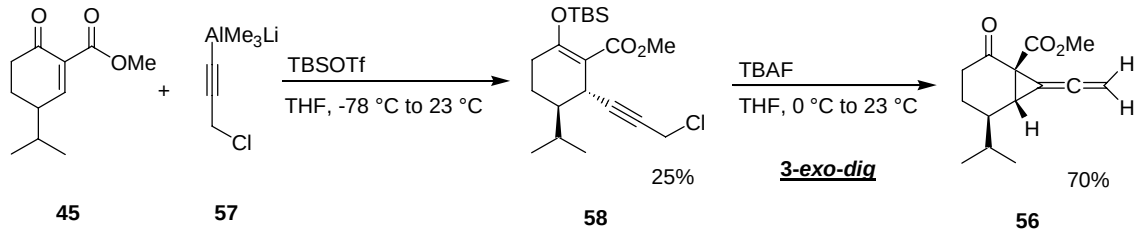
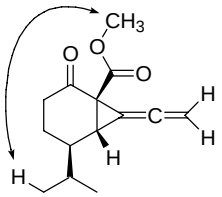
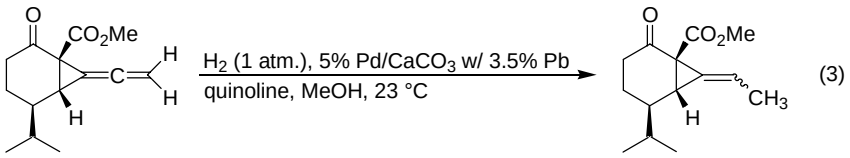


Figure 4-5. Diagnostic NOE Enhancement in Vinylidene Cyclopropane **56**



56

According to the synthetic plan in **Scheme 4-11**, allene **56** was then subjected to heterogeneous hydrogenation (eq 3). Unfortunately, none of the desired vinyl cyclopropane was observed. Along with significant decomposition products, alkylidene cyclopropane **59** was formed in the reaction. This species results from selective hydrogenation of the terminal double bond in **56** and suggests that the internal double bond may be too congested to interact with the catalyst surface; however, it has been noted that both vinyl and alkylidene cyclopropanes are susceptible to hydrogenolysis of the 3-membered ring during catalytic hydrogenation via ring opening of an anionic species.[32] This is particularly prevalent with cyclopropanes bearing two carbonyl substituents. Therefore, the internal unit of unsaturation may be reacting but not ultimately undergoing 1,2-addition of hydrogen.



(3)

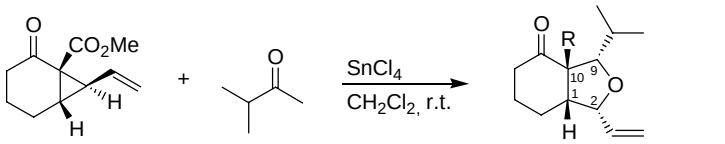
56 **59**

4.3 Conclusions

Significant progress has been made in the application of the tin-catalyzed cyclopropane/aldehyde cycloaddition reaction to the synthesis of the 2-oxabicyclo[4.3.0]nonane core of the cladiellin diterpenes. Cycloaddition with a simple bicyclic vinyl cyclopropane model system has proven successful. This result not only expands the scope of this reaction to a new level, but also gives promise to the accessibility of the hydroisobenzofuran core of the natural products. The stereochemical outcome of this test reaction agrees with prior findings on the mechanistic course of this reaction. In light of the excellent support for an initial S_N2 mechanism, efforts have been devoted to the preparation of the bicyclic vinyl cyclopropane possessing the necessary stereochemistry for the diterpene core. In the course this process, a successful 3-*exo*-*dig* cyclization mode has been discovered. This violation of Balwin's Rules may have general application in the synthesis of electron-poor alkenylidene cyclopropanes, substrates that are not accessible via carbene methodology.

4.4 Experimental

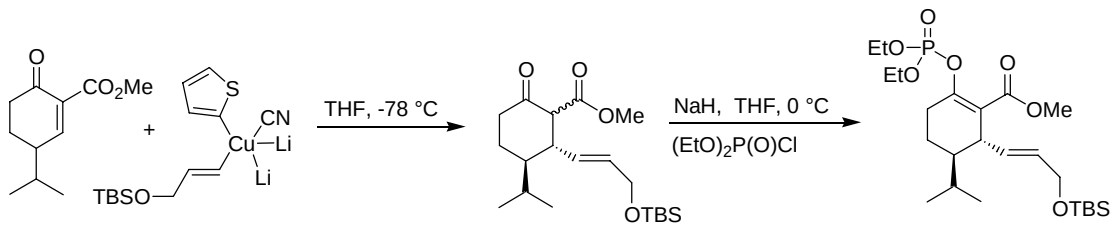
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with tetramethylsilane (TMS), chloroform solvent resonance, or benzene solvent resonance as the internal standard for ^{1}H NMR at 0.00 ppm, 7.26 ppm, and 7.16 ppm, respectively, and $CDCl_3$ solvent resonance as the internal standard for ^{13}C NMR at 77.16 ppm. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Structural assignments were made using a combination of COSY and NOESY experiments. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 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 Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Methylene chloride, THF, and Et_2O were dried by passage through a column of neutral alumina under nitrogen prior to use. Isobutyraldehyde was distilled from $CaSO_4$ prior to use. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification.



41 **42** R = CO_2Me

3-Isopropyl-4-oxo-1-vinyl-hexahydro-isobenzofuran-3a-carboxylic acid methyl ester (42). A flame-dried vial containing cyclopropane **41**[14] (40.0 mg, 0.206 mmol, 1.0 equiv) was charged with a solution of $SnCl_4$ (5.3 mg, 0.021 mmol, 0.10 equiv) in 250 μL of CH_2CH_2 followed by the aldehyde (44 mg, 0.62 mmol, 3.0 equiv), and the reaction was stirred at room temperature. After 1.75 h the reaction was passed over a small plug of silica gel, eluting with 50 mL of Et_2O, and the solvent was removed by rotary evaporation. ^{1}H NMR analysis of the unpurified product (δ 5.37 vs. δ 4.47) gave the diastereomeric ratio: 10.6:1. The isomers were separated and purified by flash chromatography with 10% EtOAc/petroleum ether to afford 40.3 mg (73%) of the products as colorless oils.

Analytical data for **42**: **IR** (thin film, cm^{-1}) 2953, 2871, 1741, 1701, 1646, 1614, 1451, 1434, 1394, 1314, 1226, 1141, 1120, 1076, 1020, 927; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 16.8, 10.6, 5.9, 1H), 5.37 (ddd, *J* = 17.2, 1.3, 1.3 Hz, 1H), 5.26 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.26 (d, *J* = 8.4 Hz, 1H), 4.20 (dddd, *J* = 5.7, 5.7, 1.3, 1.3 Hz, 1 H), 3.76 (s, 3H), 2.95 (ddd, *J* = 9.3, 5.7, 5.7 Hz, 1H), 2.58 (ddd, *J* = 16.6, 4.9, 4.9 Hz, 1 H), 2.36 (ddd, *J* = 16.5, 9.9, 6.4 Hz, 1H), 2.11-1.89 (m, 2H), 1.81-1.57 (m, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.2, 173.1, 134.0, 117.7, 88.5, 80.8, 69.4, 53.9, 51.3, 41.5, 30.3, 23.0, 22.3, 20.3, 19.9; TLC (20% EtOAc/petroleum ether) R_f 0.48; **Anal.** Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.36; H, 8.49.



45 **48** **49** **50**

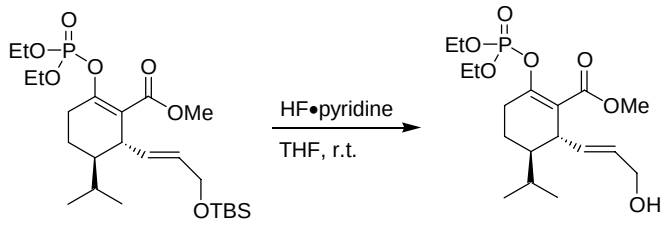
6-[3-(*tert*-Butyl-dimethylsilanyloxy)-propenyl]-2-(diethoxyphosphoryloxy)-5-isopropyl-cyclohex-1-enecarboxylic acid methyl ester (50). A 1.7 M solution of *tert*-butyllithium in pentane (2.8 mL, 4.8 mmol, 2.7 equiv) was added dropwise to a solution of *trans*-(3-bromo-allyloxy)-*tert*-butyl-dimethylsilane (613 mg, 2.44 mmol, 1.4 equiv) in 9.3 mL of Et_2O at –78 °C. The resulting solution was stirred at –78 °C for 20 min. Separately, a solution of 2-thienylcyanocopperlithium was prepared in the following manner: To a solution of thiophene (211 mg, 2.51 mmol, 1.4 equiv) in 7 mL of THF at –78 °C was added a 1.6 M solution of *n*-BuLi in hexanes (1.5 mL, 2.4 mmol, 1.4 equiv). The resulting solution was warmed to 0 °C, stirred at this temperature for 30 min, then transferred via cannula (rinsing with 4.8 mL of THF) to a suspension of CuCN (219 mg, 2.44 mmol, 1.4 equiv) in 7 mL of THF at –78 °C. This suspension was warmed to 0 °C until a light tan homogeneous solution was observed, then was cooled back to –78 °C. To this solution of 2-thienylcyanocopperlithium at –78 °C was added the –78 °C solution of the vinyllithium via cannula over a 10 min period (rinsing with 3 mL of Et_2O). The solution of **48** was stirred at –78 °C for 1 h then charged dropwise with a solution of **45** (342 mg, 1.74 mmol, 1.0 equiv) in 3 mL of THF (rinsing with 1 mL of THF). The reaction mixture was stirred at –78 °C for 2 h and then quenched by the addition of 30 mL of a 20% (w/v) aqueous NH_4Cl solution buffered to pH 8 with concentrated NH_4OH (aq.). Et_2O (10 mL) was added to the mixture

and it was stirred until it reached room temperature, and then stirred for an additional 30 min. The mixture was partitioned between 60 mL of Et_2O and 30 mL of H_2O. After separation, the aqueous layer was extracted with two 40 mL portions of Et_2O. The combined organic extracts were washed with 50 mL of H_2O, 30 mL of brine, dried over $MgSO_4$, and concentrated by rotary evaporation affording a brown oil (**49**).

Crude **49** was dissolved in 3 mL of THF and transferred dropwise to a stirring suspension of NaH (50% dispersion, 125 mg, 2.6 mmol, 1.5 equiv) in 6 mL of THF at 0 °C (rinsing with 1 mL of THF). The mixture was allowed to warm to room temperature with stirring over 30 min. The mixture was then cooled back to 0 °C and diethyl chlorophosphate (358 mg, 2.08 mmol, 1.2 equiv) was added, and the reaction was stirred for 2.5 h at 0 °C. The solution was allowed to warm to ca. 10 °C and quenched by the slow addition of 15 mL of saturated aqueous $NaHCO_3$. Et_2O (30 mL) was added followed by just enough H_2O to dissolve all solid material. After separation, the aqueous layer was extracted with 30 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation affording a brown oil. The crude product was purified by flash chromatography with a 20% to 40% EtOAc/petroluem ether gradient to afford 647 mg (74%) of the product as a yellow oil.

Analytical data for **50**: **IR** (thin film, cm^{-1}) 2956, 2929, 2896, 2857, 1727, 1673, 1472, 1464, 1435, 1389, 1369, 1361, 1290, 1261, 1157, 1122, 1100, 1033, 968, 906, 837, 816, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.50 (ddd, *J* = 15.2, 4.4, 4.4 Hz, 1H), 5.43 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.20-4.00 (m, 6H), 3.64 (s, 3H), 3.29 (br s, 1H), 2.48-2.22 (m, 2H), 1.75-1.59 (m, 2H), 1.53 (dddd, *J* = 13.6, 6.4, 6.4, 6.4 Hz, 1H), 1.31 (dt, *J* = 6.8, 0.8 Hz, 3H), 1.29 (dt, *J* = 6.8, 0.8 Hz, 3H), 1.22-1.12 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.82 (d, *J*

= 6.8 Hz, 3H), -0.01 (s, 6H); **^{13}C NMR** (^{31}P coupling makes chemical shift determination ambiguous; therefore, a peak listing is provided) (100 MHz, $CDCl_3$) δ 166.88, 166.86, 151.6, 151.5, 131.82, 131.81, 131.7, 117.9, 117.8, 64.54, 64.51, 64.48, 64.4, 63.5, 51.5, 43.7, 41.4, 26.8, 26.7, 26.0, 21.6, 20.0, 18.8, 18.4, 16.2, 16.1, -5.1, -5.2; TLC (30% EtOAc/petroleum ether) R_f 0.21; **Anal.** Calcd. for $C_{24}H_{45}O_7PSi$: C, 57.12; H, 8.99. Found: C, 57.34; H, 8.97.

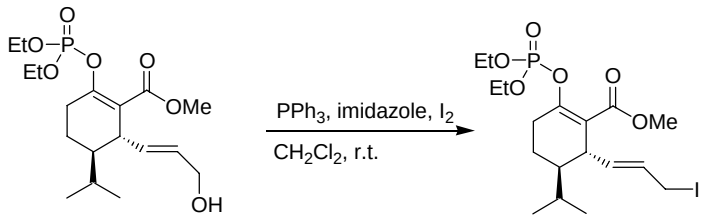


50 **51**

2-(Diethoxyphosphoryloxy)-6-(3-hydroxypropenyl)-5-isopropyl-cyclohex-1-enecarboxylic acid methyl ester (51). A solution of HF•pyridine (900 μL of a 70% HF/30% pyridine solution purchased from Sigma-Aldrich) in 13 mL of THF in a polypropylene bottle was treated with a solution of silyl ether **50** (300 mg, 0.594 mmol, 1.0 equiv) in 2 mL of THF. The solution was stirred for 45 min at room temperature then carefully quenched by the addition of 75 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with three 75 mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation affording a slightly yellow oil. The crude product was purified by flash chromatography with 100% EtOAc to afford 223 mg (96%) of the product as a slightly yellow oil.

Analytical data for **51**: **IR** (thin film, cm^{-1}) 3427, 2958, 2873, 1724, 1618, 1464, 1435, 1388, 1369, 1267, 1156, 1033, 971, 909, 849, 820; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54

(ddd, J = 15.6, 5.2, 5.2 Hz, 1H), 5.44 (dd, J = 15.6, 7.2 Hz, 1H), 4.16-4.01 (m, 4H), 3.97 (d, J = 5.2 Hz, 2H), 3.61 (s, 3H), 3.26 (br s, 1H), 2.52 (br s, 1H), 2.43-2.19 (m, 2H), 1.73-1.40 (m, 3H), 1.27 (t, J = 6.8 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.18-1.10 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (^{31}P coupling makes chemical shift determination ambiguous; therefore, a peak listing is provided) (100 MHz, $CDCl_3$) δ 166.88, 166.86, 151.7, 151.6, 133.14, 133.12, 131.5, 117.6, 117.5, 64.50, 64.49, 64.4, 62.9, 51.5, 43.5, 41.2, 26.7, 26.5, 21.5, 19.8, 18.8, 16.04, 15.97; TLC (100% EtOAc) R_f 0.28; **Anal.** Calcd. for $C_{18}H_{31}O_7P$: C, 55.38; H, 8.00. Found: C, 55.25; H, 8.06.

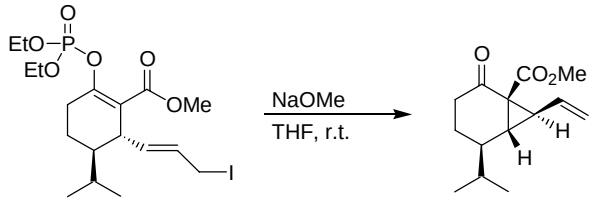


51 **52**

2-(Diethoxyphosphoryloxy)-6-(3-iodopropenyl)-5-isopropyl-cyclohex-1-enecarboxylic acid methyl ester (52). To 5 mL of CH_2Cl_2 were sequentially added PPh_3 (158 mg, 0.602 mmol, 1.4 equiv), imidazole (41.0 mg, 0.602 mmol, 1.4 equiv), and I_2 (153 mg, 0.603 mmol, 1.4 equiv). The mixture was stirred for 5 min at room temperature then charged with a solution of **51** (168 mg, 0.430 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2. After stirring for 50 min at room temperature, the mixture was diluted with 20 mL of CH_2Cl_2 and quenched with 20 mL of 10% aqueous Na_2SO_3. After separation, the aqueous layer was extracted with two 10 mL portions of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation affording a yellow oil. The crude material was purified

by flash chromatography with 40% EtOAc/petroleum ether to afford 182 mg (85%) of the product as a yellow/orange oil.

Analytical data for **52**: **IR** (thin film, cm^{-1}) 2958, 2873, 1725, 1671, 1464, 1434, 1389, 1369, 1280, 1156, 1033, 985, 965, 906, 821; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.66 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 5.46 (dd, *J* = 15.0, 7.5 Hz, 1H), 4.16-4.05 (m, 4H), 3.76 (d, *J* = 7.5 Hz, 2H), 3.65 (s, 3H), 3.24 (br s, 1H), 2.44-2.25 (m, 2H), 1.69-1.55 (m, 2H), 1.50 (dddd, *J* = 13.0, 6.0, 6.0, 6.0 Hz, 1H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.19-1.10 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (^{31}P coupling makes chemical shift determination ambiguous; therefore, a peak listing is provided) (125 MHz, $CDCl_3$) δ 166.47, 166.45, 152.0, 151.9, 135.76, 135.75, 130.1, 117.0, 116.9, 64.47, 64.46, 64.43, 64.41, 51.6, 43.5, 41.1, 26.8, 26.7, 21.5, 20.0, 18.5, 16.08, 16.05, 16.02, 16.00, 5.5; TLC (70% EtOAc/petroleum ether) R_f 0.47; **Anal.** Not sufficiently stable for combustion analysis.

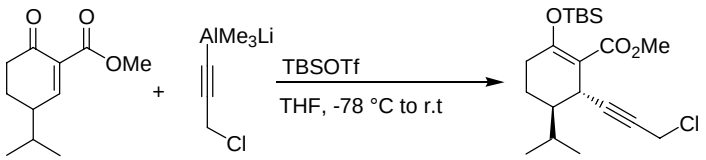


52 **β-53**

5-Isopropyl-2-oxo-7-vinyl-bicyclo[4.1.0]heptane-1-carboxylic acid methyl ester (β-53). A solution of allyl iodide **52** (182 mg, 0.364 mmol, 1.0 equiv) in 12.5 mL of THF was treated with NaOMe (21.6 mg, 0.400 mmol, 1.1 equiv) and the resulting suspension was vigorously stirred at room temperature in the dark. After 17 h, 21.6 mg more NaOMe was added and the

mixture was stirred for an additional 23 h. The reaction was quenched by the addition of 20 mL of saturated aqueous NH_4Cl. The mixture was extracted with 20 mL of Et_2O and then with three 10 mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation affording a yellow oil. The crude product was purified by flash chromatography with 15% EtOAc/petroleum ether to afford ca. 9.9 mg (12%) of the product as a slightly yellow oil.

Analytical data for **β-53**: **^{1}H NMR** (500 MHz, C_6D_6) δ 5.59 (ddd, J = 17.5, 10.5, 9.0 Hz, 1H), 5.11 (d, J = 17.0 Hz, 1H), 5.00 (dd, J = 10.5, 1.5 Hz, 1H), 3.44 (s, 3H), 2.10 (dd, J = 6.5, 2.5 Hz, 1H), 2.08-2.00 (m, 2H), 1.72 (ddd, J = 17.0, 9.5, 6.0 Hz, 1H), 1.41-1.06 (m, 4H), 0.84 (d, J = 6.5 Hz, 3H), 0.70 (d, J = 6.5 Hz, 3H); TLC (20% EtOAc/petroleum ether) R_f 0.29.

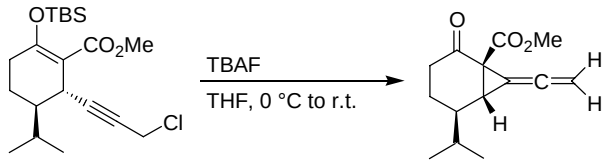


45 **58**

2-(*tert*-Butyl-dimethylsilanyloxy)-6-(3-chloro-prop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylic acid methyl ester (58). A solution of propargyl chloride (314 mg, 4.22 mmol, 1.7 equiv) in 35 mL of THF at –78 °C was treated with a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.8 mmol, 1.5 equiv) over a 10 min period. The resulting solution was stirred at –78 °C for 30 min then treated with a 2.0 M solution of $AlMe_3$ in toluene (1.9 mL, 3.8 mmol, 1.5 equiv) over a 10 min period. The resulting solution was stirred at –78 °C for 1 h. A solution of **45** (500 mg, 2.55 mmol, 1.0 equiv) in 3 mL of THF was introduced into the

aluminate solution at –78 °C by cannula addition down the wall of the chilled flask. TBSOTf (806 mg, 3.05 mmol, 1.2 equiv) was slowly added and the mixture was stirred at –78 °C. After 1.5 h the solution was allowed to warm just to room temperature and then carefully quenched by the addition of 40 mL of saturated aqueous Na_2CO_3. The mixture was extracted with three 100 mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation affording an orange oil. The crude product was purified by flash chromatography with 2.5% EtOAc/petroleum ether to afford 256 mg (26%) of the product as an off-white solid.

Analytical data for **58**: mp 43-45 °C; **IR** (thin film, cm^{-1}) 2956, 2933, 2898, 2859, 2228, 1723, 1693, 1627, 1472, 1464, 1435, 1377, 1292, 1259, 1209, 1136, 1078, 1062, 1010, 943, 899, 841, 814, 782, 693; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.08 (d, *J* = 2.0 Hz, 2H), 3.74 (s, 3H), 3.64 (br s, 1H), 2.18-2.06 (m, 2H), 1.93 (dddd, *J* = 13.5, 7.5, 7.5, 3.0 Hz, 1H), 1.74-1.64 (m, 1H), 1.57 (dddd, *J* = 12.5, 6.0, 6.0, 6.0 Hz, 1H), 1.52-1.45 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.5, 159.3, 108.6, 90.1, 75.1, 51.3, 44.7, 31.4, 31.3, 29.6, 27.1, 25.7, 21.6, 21.2, 19.1, 18.4, -3.6, -3.8; TLC (2.5% EtOAc/petroleum ether) R_f 0.15; **Anal.** Calcd. for $C_{20}H_{33}ClO_3Si$: C, 62.39; H, 8.64. Found: C, 62.68; H, 8.72.



58 **56**

5-Isopropyl-2-oxo-7-vinylidene-bicyclo[4.1.0]heptane-1-carboxylic acid methyl ester (56). A solution of silyl enol ether **58** (200 mg, 0.519 mmol, 1.0 equiv) in 10 mL of THF at 0 °C was treated dropwise with a 1.0 M solution of TBAF in THF (570 μL, 0.570 mmol, 1.1 equiv). The reaction was allowed to warm to room temperature with stirring. After 23 h, 20 mL of saturated aqueous NH_4Cl was added to the reaction followed by 20 mL of H_2O. The mixture was extracted with two 40 mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation affording a yellow oil. The crude product was purified by flash chromatography with 10% EtOAc/petroleum ether to afford 85.7 mg (70%) of the product as a colorless oil.

Analytical data for **56**: **IR** (thin film, cm^{-1}) 2958, 2875, 2021, 1742, 1698, 1463, 1451, 1435, 1389, 1369, 1347, 1328, 1307, 1273, 1232, 1200, 1178, 1137, 1065, 1025, 981, 942, 853, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.16 (dd, J = 11.2, 4.4 Hz, 1H), 5.10 (dd, J = 10.8, 4.4 Hz, 1H), 3.70 (s, 3H), 2.94 (br s, 1H), 2.37-2.10 (m, 2H), 1.97-1.55 (m, 4H), 1.02 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 193.7, 167.7, 85.6, 82.5, 52.7, 43.1, 39.2, 35.1, 34.3, 29.9, 22.7, 20.68, 20.67; TLC (10% EtOAc/petroleum ether) R_f 0.16; **Anal.** Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.96; H, 7.67.

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