LEWIS ACID-PROMOTED FRIEDEL-CRAFTS ALKYLATION OF α-KETOPHOSPHATE ELECTROPHILES

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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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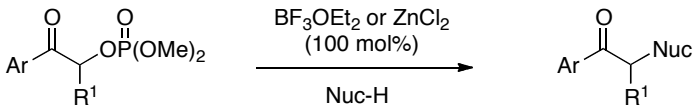
ABSTRACT

AUSTIN GERALD SMITH: Lewis Acid-Promoted Friedel-Crafts Alkylation of α-Ketophosphate Electrophiles
(Under the direction of Professor Jeffrey Scott Johnson)

I. Lewis Acid-Promoted Friedel-Crafts Alkylation of α-Ketophosphate Electrophiles

The α-alkylation of α-ketophosphate electrophiles by electron-rich neutral nucleophiles is described. The reaction is promoted by either $BF_3 \cdot OEt_2$ or $ZnCl_2$. Aromatic, heteroaromatic, heteroatom and nonaromatic nucleophiles are tolerated. Electron-rich α-ketophosphates display the highest reactivity; electron-neutral and electron-poor substrates are also tolerated at elevated temperatures. Enantioenriched α-ketophosphate yields racemic product, lending evidence to an α-acyl carbenium ion intermediate.

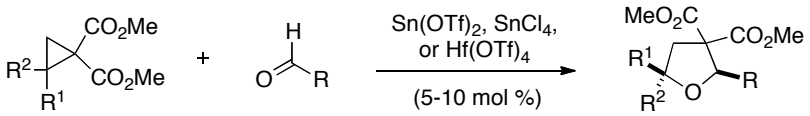


44-84% yield

II. (3+2)-Annulation of Quaternary Donor-Acceptor Cyclopropanes and Aldehydes

The (3+2)-annulation of all-carbon donor site donor-acceptor cyclopropanes and aldehydes is described. Catalytic Sn(II), Sn(IV), or Hf(IV) facilitates the diastereoselective annulation. One-step access to highly substituted *cis*-tetrahydrofurans is possible. The reaction is tolerant of electron-rich and electron poor aromatic aldehydes, as well as alkenyl and aliphatic aldehydes. Mechanistic experiments with optically active cyclopropanes

suggest an aldehyde nucleophilic substitution mechanism is operative and demonstrate that chirality transfer to the tetrahydrofuran products is possible.

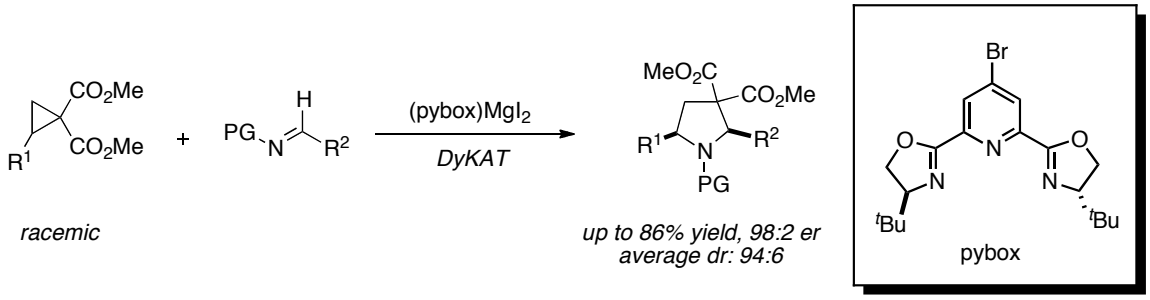


R^1, $R^2 \neq H$

up to 95% yield
up to 99:1 dr

III. Enantioselective Synthesis of of Pyrrolidines From Racemic Cyclopropanes and Aldimines: Reaction Development and Mechanistic Insights

A dynamic kinetic asymmetric (3+2)-annulation of racemic D-A cyclopropanes and *N*-benzyl aromatic aldimines is described. Enantio- and diastereoselective access to 2,5-*cis* pyrrolidines is possible through the use of a (4-Br-^{t}Bu-pybox)MgI_2 catalyst. Results from experiments with cyclically-constrained (*Z*)-aldimine suggest that the major *cis*-isomer in the DyKAT is not a product of a (*Z*)-aldimine pathway.



up to 86% yield, 98:2 er
average dr: 94:6

ACKNOWLEDGEMENTS

I must begin this section by thanking the person most responsible for my intellectual development in graduate school: my advisor, Jeff Johnson. It has been a true privilege working under Jeff's guidance the past five years. Jeff's enthusiasm for chemistry is infectious and is something I find inspiring. Jeff displays an incredible level of patience as an advisor; it is this quality that has allowed me to succeed under his watch. As I matured as a graduate student, Jeff let me explore areas of my projects on my own that I found particularly interesting. I credit him for instilling in me the confidence to propose creative solutions and complex but logical arguments to rationalize data. These solutions were usually poor, and the logic flawed, but Jeff never faulted the effort and always remained constructive in his critique. In five years, Jeff was able to mold an unfocused student into a confident, knowledgeable scientist. It took a lot of persistence, a lot of white-board sessions and a lot of failures (on my end), but Jeff never stopped instructing. The greatest compliment I can give Jeff is that he is a teacher in every sense of the word. I cannot express enough my sincere gratitude.

I thank Professors Erik Alexanian, Dave Nicewicz, and Joe Templeton for serving on my defense committee, and Professor Marcey Waters for serving as the chair of my defense committee. In addition, I owe Professor Nicewicz and Professor Waters a great deal of thanks for providing for me NIH letters of recommendation. The University of North Carolina is a special place to study; if I only knew how lucky a decision I was making five years ago to come to graduate school in Chapel Hill. I'm proud to call myself a Tar Heel.

Working in the Johnson lab has been a real treat. I credit a great group of people for maintaining an entertaining and hardworking environment. Past and present members include: Cory Bausch, Greg Boyce, Matthew Campbell, Michael Corbett, Do Dung, Rebecca Duenes, Steve Greszler, Justin Malinowski, Andrew Parsons, Shanina Sanders, Andy Satterfield, Dan Schmitt, Mike Slade, Kim Steward, and Chris Tarr. Working in Caudill 223 just produced a different breed of chemist; only Cory Bausch, Michael Corbett, Andrew Parsons, Andy Satterfield, and Kim Steward can understand. (Example--Austin does a potentially risky or not well-thought out maneuver: Jeff: "Austin, that's not a recommended strategy." 223: "Smith, what the hell are you doing?"). Both teaching methods got the point across. I will especially miss the coffee club, Friday lunch, 80's Thursday (and Wednesday, and Friday), and dominating this group in Fantasy Football for three straight seasons. For fine friendships, I thank Steve Greszler, Justin Malinowski, Andrew Parsons, Dan Schmitt, and Mike Slade. In addition, I thank Michael Corbett, Justin Malinowski, Dan Schmitt, and Mike Slade for editing portions of this thesis. Any mistakes you find are entirely my own.

I owe Andrew Parsons a special thanks for inviting me on the pyrrolidine project. It was a generous gesture on his part, and I learned an incredible amount of chemistry just following his lead. Andrew had a precise way of doing things that I tried my best to emulate after the project was completed. That project forced me to think much deeper about chemistry than I ever had before. I have him to thank for being an exceptional leader by example.

I thank Mike Slade for the time spent working on the quaternary cyclopropane project with me. Besides his effort, Mike's high aptitude helped advance the project from its early stages. I will truly miss our mechanistic discussions.

I thank Alessa Gambardella, my girlfriend of two years for her love and unwavering support as I trekked through my graduate studies. She has a remarkable way of remaining patient when the hours get longer and the days get worse. There was no better way to turn my mind off a failed day in lab than to sit down and watch an episode of "Dexter" or "The Wire" with her. Trips to Weaver Street on Sunday morning were the highlight of my week. For a chemist who's just trying to get by, having an award-winning scientist by your side every step of the way is pretty awesome.

Support is a special thing; it makes you feel you can accomplish anything. I thank the most important people in my life: my mother, Sally Smith, and my brothers, Tom and Peter Smith. My brothers are the best. I don't think I'll ever get tired of kidding around with them, giving them a hard time and of course, arguing with them. They are two guys I love to see every time I come home, and I'm very proud of their individual academic accomplishments. My mom's fighting spirit is a source of inspiration for me. From an early age, my mom and dad showed me what quality of work was acceptable and what was not. They took time out of their evenings to help me with projects, edit English papers, tackle Calculus problems, and quiz me for exams. They didn't do any of this because they had to; they did it because they wanted to. I lost sight of this along the way, but I'll never forget my mom's words in my second year of graduate school: "Hard work is what got you here." Everything I am today, I have them to thank.

To my dad: It's been a hard seven years. I miss you very much. You're the original reason I studied science. I hope I've made you proud.

To my family
and
In loving memory of my father
Austin Gerald Smith
(1955-2003)

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LIST OF ABBREVIATIONS AND SYMBOLS

A	acceptor
$A^{1,3}$	1,3-allylic strain
Ac	acetate
acac	acetylacetone
acc	acceptor
Ar	aryl
aq	aqueous
atm	atmospheres
BOC	*tert*-butyloxycarbonyl
Bn	benzyl
br	broad
bs	broad singlet
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
C–C	carbon-carbon bond
calcd.	calculated
cat	catalytic amount or catalyst
conv	conversion
d	doublet or days
dd	doublet of doublet

ddt	doublet of doublet of triplet
dq	doublet of quartet
D	donor
D–A	donor-acceptor
don	donor
DCE	dichloroethane
DCM	dichloromethane
DKR	dynamic kinetic resolution
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DOSP	N-(*p*-dodecylphenylsulfonyl)prolinato
dr	diastereomeric ratio
dt	doublet of triplet
DyKAT	dynamic kinetic asymmetric transformation
E	electron withdrawing group
E	*entgegen*
El(+)	electrophile
endo	endocyclic
eq	equation
equiv	equivalents

er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
exo	exocyclic
FID	flame ionization detector
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
k	reaction rate
kcal	kilocalorie
L*	chiral ligand
LA	Lewis acid
LA*	chiral Lewis acid
LRMS	low resolution mass spectroscopy

LUMO	lowest unoccupied molecular orbital
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
n	*normal* or number of atoms or counterions
NBS	*N*-bromosuccinimide
nd	not determined
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
nr	no reaction

Nu(–)	nucleophile
Nuc	nucleophile
o	ortho position
p	para position
PG	protecting group
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
pybox	pyridine-2,6-bis(oxazoline)
q	quartet
qd	quartet of doublet
R	substituent
R_f	retention factor
R_L	large substituent
R_S	small substituent
rac	racemic
RCHO	aldehyde
rt	room temperature
s	singlet
SFC	supercritical fluid chromatography
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution

T	temperature
t	triplet
$t_{1/2}$	half-life
t_r	retention time
TBME	*tert*-butylmethylether
TBS	*tert*-butyldimethylsilyl
td	triplet of doublet
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
TPDPS	*tert*-butyldiphenylsilyl
triflate	trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	anionic ligand, halide, substituent, or number
Z	*zusammen*
Å	Ångstrom
[α]	optical rotation

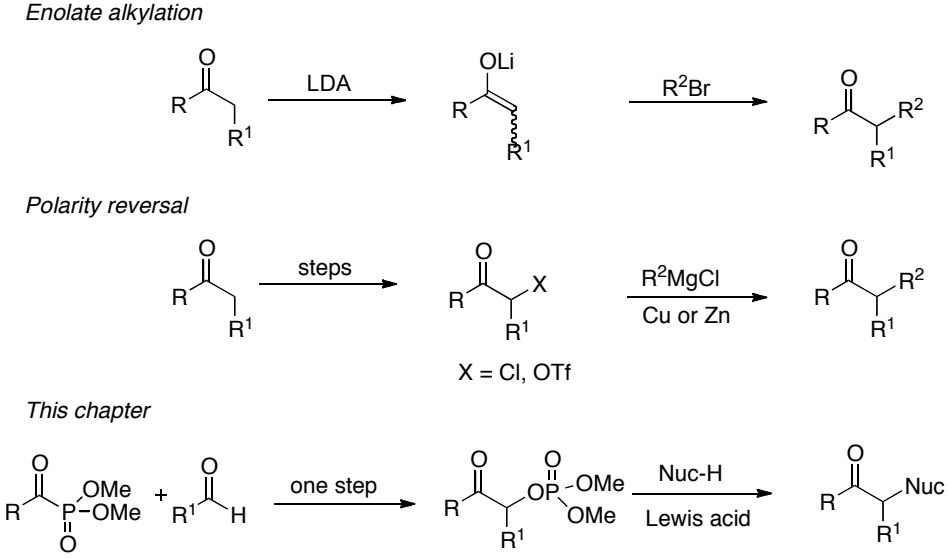
Δ	heat
δ	chemical shift or partial charge
μL	microliter
μm	micrometer

CHAPTER 1
LEWIS ACID-PROMOTED FRIEDEL-CRAFTS ALKYLATION OF α-KETOPHOSPHATE ELECTROPHILES

1.1 Introduction

Enolate alkylation of unhindered alkyl electrophiles is the most powerful method to install sp^3-sp^3 α-C–C bonds.[1] Forming sp^3-sp^2 bonds, however, is a more longstanding problem. The Pd(0)-catalyzed cross-coupling of ketone enolates and aryl or vinyl halides is an elegant solution.[2-5] These reactions exhibit a normal mode of reactivity by harnessing the nucleophilicity of alkali enolates and electrophilicity of electron deficient C-Pd(II)-X species. While less explored, α-alkylation reactions proceeding through reverse polarity (or umpolung) pathways are powerful methods to install sp^3-sp^3 bonds adjacent to carbonyl sites. α-Triflate or α-halocarbonyls can react with premetalated nucleophiles to provide access to sterically encumbered α-alkylated ketones through the use of catalytic copper or zinc.[6,7] Merging α-nucleofuge installation with another productive synthetic operation (e.g. C–C bond formation) would make a polarity reversal strategy increasingly attractive. Using such a strategy to install sp^3-sp^2 bonds (as opposed to sp^3-sp^3 bonds) alpha to carbonyl compounds would add value. In addition, avoiding prefunctionalization of the nucleophilic component would aid in synthetic efficiency (Figure 1-1). This chapter explores the discovery, optimization, and scope of a Lewis acid promoted Friedel–Crafts alkylation of α-ketophosphate electrophiles to arrive at α-alkylated ketones. Studies with enantioenriched α-ketophosphates assist in the mechanistic understanding of this transformation. Attempts to render this reaction enantioselective are also discussed.

Figure 1-1. α-C–C Bond Formation *via* Enolate Alkylation (top), Polarity Reversal (middle) and Work Described in this Chapter



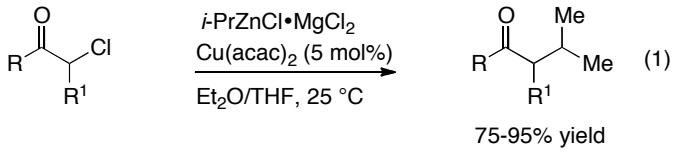
1.2 Background

1.2.1 Known Polarity Reversal Strategies

Polarity reversal methodology is an effective strategy to install sp^3-sp^3 C–C bonds alpha to carbonyl groups, mainly in instances where traditional enolate alkylation attempts fail.[1] In particular, enolate additions to sterically encumbered secondary alkyl electrophiles are known to exhibit slow reaction rates compared to their primary counterparts.[8] Polarity reversal methodology has drawn interest in part because of its mechanistic intrigue: carbon atoms adjacent to carbonyl functionality are traditionally rendered nucleophilic by treatment of a ketone with strong base to generate an alkali enolate. Routes to install nucleophilic carbon fragments at this conventionally nucleophilic carbon atom are therefore not obvious.

Ready has published the cross-coupling of α-chloroketones and alkylzinc halides catalyzed by $Cu(acac)_2$ (eq 1).[6] Transmetallation of the Grignard reagent with $ZnCl_2$ proved

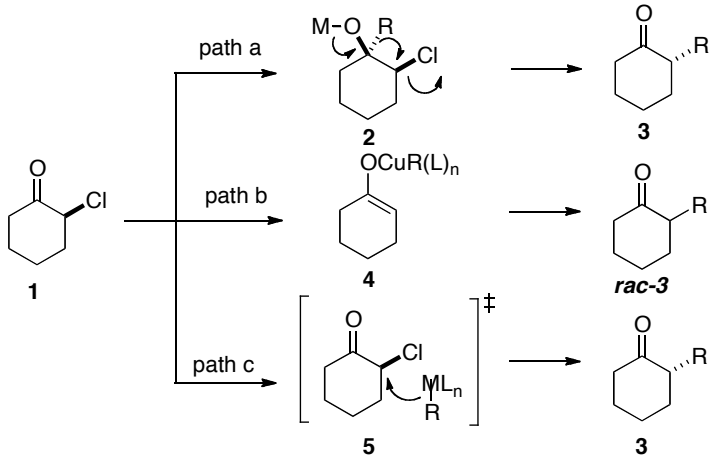
critical; Mg-free diorganozinc nucleophiles gave poor yields and organozinc reagents derived from organolithium nucleophiles gave no desired product.



(1)

Ready identifies three possible mechanistic pathways for the observed cross-coupled product (Scheme 1-1). The first pathway (path a) is the 1,2-addition of the organozinc nucleophile to the ketone **1** to form tetrahedral intermediate **2**, which is followed by collapse of **2** and 1,2-alkide migration to install the C_α–C bond and expel chloride. A second pathway (path b) involves formation of either an O or C bound alkylcopper enolate **4**. Reductive elimination at this stage would yield the substituted ketone product as a racemic mixture (***rac-3***). A third pathway (path c) involves direct nucleophilic substitution of the alkyl chloride by an organometallic nucleophile (M = Cu, Zn, Mg, transition state **5**). Path a and c would result in inversion of stereochemistry at the α-carbon when stereodefined alkyl chlorides are used.

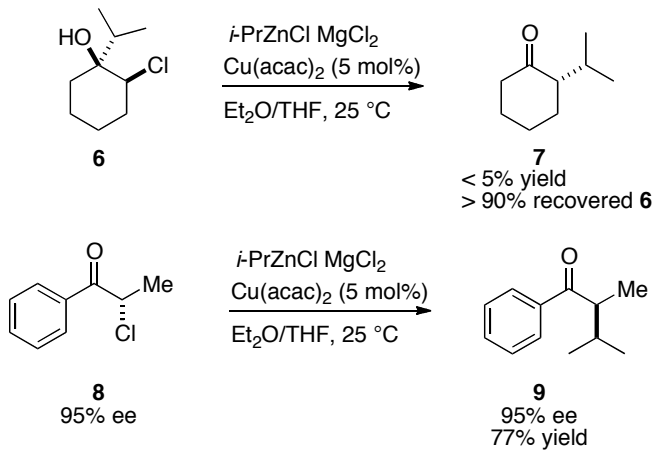
Scheme 1-1. Possible Pathways in Ready's Cross-Coupling of α-Chloroketones



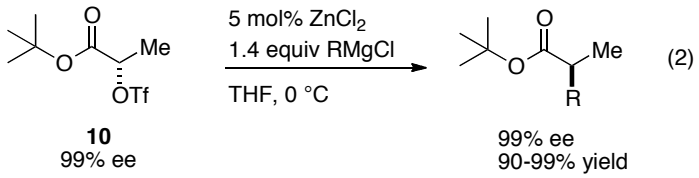
Path a was ruled out based on the results from the first of two experiments (Scheme 1-2). Racemic halohydrin **6** was prepared and treated under the standard cross-coupling conditions.

Halohydrin **6** was recovered in >90% yield with <5% yield of the desired α-alkyl ketone **7**. This result demonstrates the stability of **6** and suggests in all likelihood that it is not a viable intermediate in this reaction. To distinguish between paths b and c, optically active α-chloroketone **8** (95% ee) was prepared and subjected to the reaction conditions. α-Alkylated ketone **9** was isolated in 95% ee with inversion of stereochemical configuration (the absolute configuration was assigned by comparison to an authentic prepared sample). Taken together, these results are most consistent with an S_N2 displacement of an organometallic nucleophile to the α-chloride as described in path c. Thus, path b can be ruled out because reductive elimination of the alkylcopper enolate would yield a racemic product.

Scheme 1-2. Control Experiments Conducted by Ready

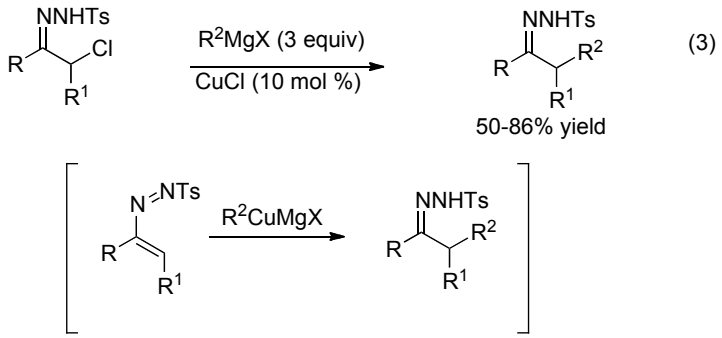


Breit has described an alternative sp^3-sp^3 cross-coupling of organometallic nucleophiles and α-carbon electrophiles using catalytic $ZnCl_2$ (eq 2).[7] Stereodefined α-hydroxy ester triflates of type **10** derived from α-amino acid precursors were used as the electrophilic component.



In the absence of any catalyst, addition of *n*BuMgCl resulted in low yields due to poor conversions and competitive α-addition of chloride. When $Fe(acac)_3$ was used instead of $ZnCl_2$, no desired product was observed and only homocoupled ester was seen. Addition of a copper salt ($Li_2Cu_2Cl_4$) gave yields inferior to $ZnCl_2$ due to competitive reduction of the α-triflate. Interestingly, not only the metal catalyst but the choice of nucleophilic salt proved critical for success: *n*BuLi gave no desired product, and switching from *n*BuMgCl to *n*BuMgBr gave only trace α-alkylation. A variety of primary and secondary alkyl-MgCl nucleophiles and triflate electrophiles were tolerated in outstanding yields. Analogous to Ready's chemistry, the reaction proceeded with complete transfer of stereochemical information and inversion of configuration at the α-carbon. This result is again consistent with a direct nucleophilic displacement of the triflate nucleofuge by either a Zn- or Mg-alkyl nucleophile. Using a polarity reversal strategy thus allows for the synthesis of stereodefined, sterically encumbered α-alkylated esters that would be difficult to access via traditional enolate alkylation methods.

After completion of the work described in this chapter, Coltart published an α-alkylation of *in-situ* generated *N*-sulfonyl azoalkenes catalyzed by CuCl (eq 3).[9] α-Halo *N*-sulfonyl hydrazones are treated with catalytic CuCl and excess Grignard reagent. The Grignard reagent first acts as a Bronsted base to dehalogenate the starting material and generate the *N*-sulfonyl azoalkene *in-situ*.



Transmetalation of a second equivalent of Grignard with the Cu(I) catalyst generates an organocuprate nucleophile, which is capable of conjugate addition to the azoalkene. Primary, secondary, and tertiary alkyl carbon nucleophiles are tolerated in promising yields (50-86%). Coltart is also able to demonstrate a one-pot α-oxidation/α-alkylation protocol, which circumvents the extra step to α-halogenate the hydrazone.

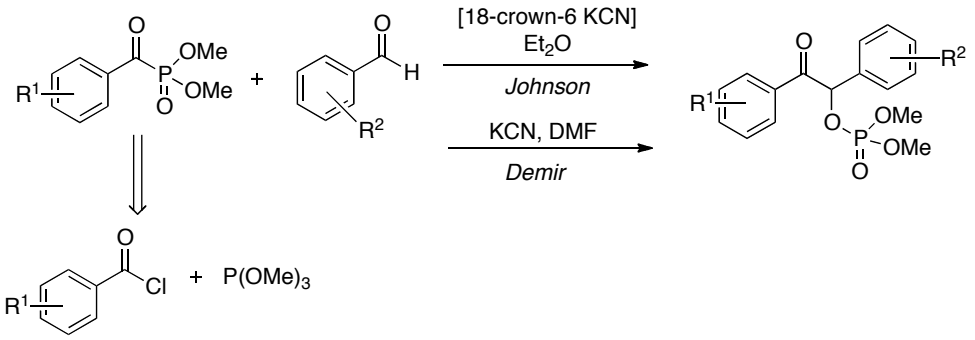
Ready and Breit's methods both require synthetic manipulations from the carbonyl precursor in order to oxidize the α-carbon. Ready treats most of his ketone substrates with *N*-chlorosuccinimide to install the α-halogen; Breit perfoms a diazotization reaction on an α-amino acid to install the α-hydroxy group followed by treatment with sulfonyl chloride to make the triflate. Ready, Breit, and Coltart's methods all require strong nucleophiles; therefore, premetallation of the nucleophilic component is necessary. Finally, while sterically crowded sp^3-sp^3 centers are possible, aryl, alkenyl, and allyl Grignard reagents were generally not suitable in all three methods. These nucleophiles gave only poor to mediocre yields with catalytic $ZnCl_2$ in Breit's reaction; Coltart shows only one example of phenylmagnesium bromide α-addition to an α-chloro *N*-sulfonyl hydrazone.

1.2.2 Connection to previous work

In the context of streamlining the synthetic process, we identified a potential connection to previously published work from our laboratory. Both Demir and our group

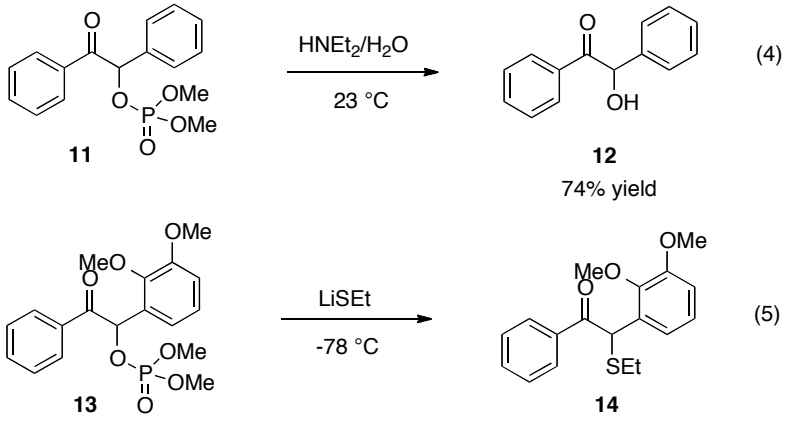
have independently published a cyanide-catalyzed reaction between acyl phosphonates and aldehydes to arrive at α-ketophosphate products (Figure 1-2).[10,11]

Figure 1-2. Demir and Johnson Synthesis of α-Ketophosphates



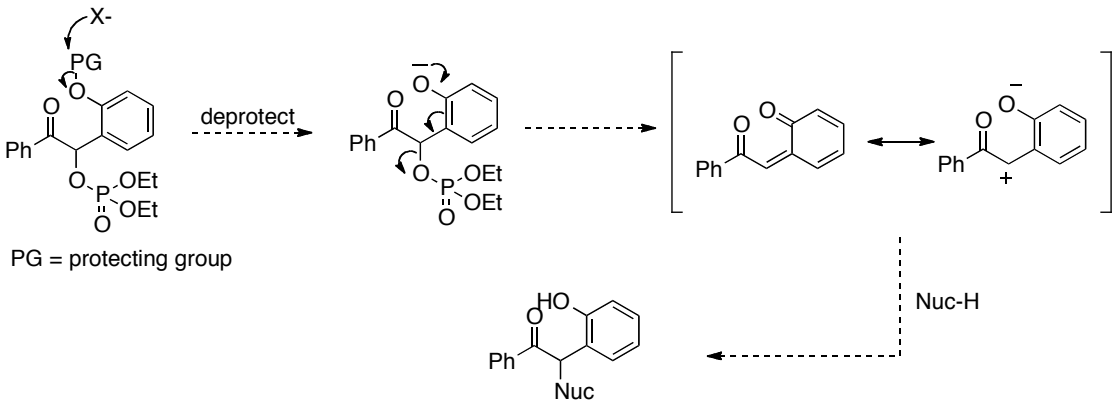
This reaction demonstrates the utility of acylphosphonates as regioselective acyl donors and shows that they can serve as viable alternatives to acylsilanes, dithianes, and benzils in cross-benzoin reactions. Acyl phosphonates can also be easily prepared from the corresponding acyl chloride and trialkylphosphite in one step via the Michaelis-Arbuzov reaction, making them an inexpensive and practical acyl donor.

The resultant α-ketophosphate products can be deprotected to reveal the desired α-hydroxyketone subunit **12** by treatment with an aqueous diethylamine solution. Furthermore, treatment of α-ketophosphate **13** with lithium ethanethiolate at -78 °C provides α-thioether **14** in 84% yield (eq 4 and 5).



Thus, at least in this example, the α-phosphate can serve as a suitable nucleofuge for direct nucleophilic substitution chemistry. More importantly, leaving group installation and C–C bond formation during the phospha-benzoin reaction take place concomitantly. Extraneous steps to install, deprotect, or manipulate functional groups to prepare for downstream α-substitution are avoided. This enhances the synthetic value of this phospha-benzoin reaction and distinguishes it from other cross-benzoin methods involving acyl silanes and benzils.[12,13] The results in equation 5 led us to question whether α-ketophosphates could serve as general electrophilic α-X-carbonyl platforms for neutral nucleophiles. More specifically, we wondered whether deprotection of an *ortho*-phenol could trigger leaving group expulsion and the formation of a highly electrophilic *ortho*-quinone methide intermediate (Figure 1-3).[14]

Figure 1-3. Proposed Route to α,α′-Disubstituted Ketones



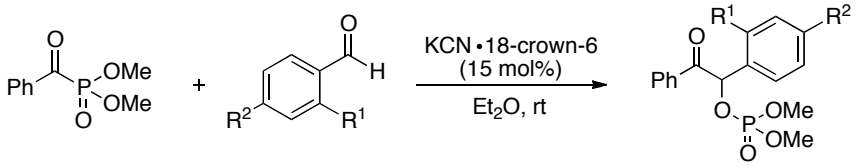
This chapter details the exploration of such strategy and the eventual discovery of a Lewis acid-promoted ionization/Friedel–Crafts alkylation of α-ketophosphate substrates to arrive at α,α′-disubstituted ketones. Subsequent control experiments help to delineate an operative S_N1 mechanism with nucleophilic addition to a resonance stabilized α-acyl carbenium ion.[15] Attempts to control facial selectivity in the Friedel–Crafts addition via a chiral counterion reveal a slight stereofacial preference.

1.3 Results and Discussion

1.3.1 Attempts with Silyl Based Protecting Groups

We initially set out to discover if silyl-protected *ortho*-phenols were competent substrates for this transformation, since established deprotection methods with fluoride sources would yield the desired phenoxide and subsequent quinone methide in the same step.[16] This route presented unforeseen problems. The results of this investigation are outlined in Table 1-1.

Table 1-1. Silyl Protecting Groups in the Phospha-Benzoin Reaction



entry	R^1	R^2	result
1	OTMS	H	salicaldehyde
2	OTES	H	salicaldehyde
3	OTBS	H	salicaldehyde
4	OTBDPS	H	Recovered SM

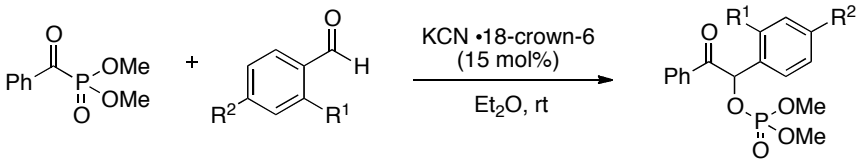
When trimethylsilyl, triethylsilyl, and *tert*-butyldimethylsilyl protecting groups were used, cleavage of the silicon-oxygen bond was observed in the phospha-benzoin reaction with acyl phosphonate and 18-crown-6/KCN catalyst and only salicylaldehyde was recovered as a byproduct (entries 1-3). The bulkier *tert*-butyldiphenylsilyl group prevented silyl cleavage, but this aldehyde was not a viable substrate in the phospha-benzoin reaction and only starting material was recovered (entry 4).

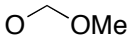
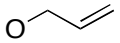
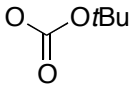
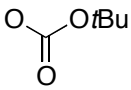
1.3.2 Alternative Carbon Based Protecting Groups

The failures of silyl protecting groups in this reaction led us to explore other possible phenol protecting groups that upon deprotection would result in a free phenol substrate. We

reasoned that exposure of the free phenol to basic conditions could generate the phenoxide and subsequent quinone methide intermediate upon expulsion of phosphate. A protecting group strategy summary is in Table 1-2.

Table 1-2. Carbon-Based Protecting Groups in the Phospha-Benzoin Reaction

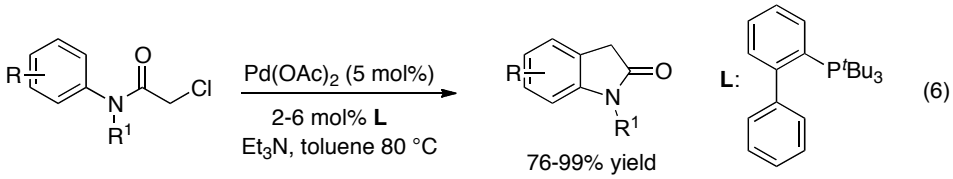


entry	R^1	R^2	result
1		H	α-ketophosphate
2		H	Recovered SM
3		H	Recovered SM
4	H		α-ketophosphate

Methoxymethyl-protected salicylaldehyde was tolerated in the cyanide-catalyzed reaction with acyl phosphonates (entry 1). However, the MOM ether proved to be particularly robust; cleavage under standard deprotection conditions (conc. HCl, TMSCl, NaI) failed to reveal the free phenol.[17] Allyl-protected salicylaldehyde was also tolerated under phospha-benzoin conditions, but deprotection attempts under Pd(0) and Kulinkovich conditions gave only recovered starting material (entry 2).[18,19] *Ortho-tert*-butyloxycarbonyl (BOC) was not tolerated in the phospha-benzoin reaction (entry 3). We suggested a negative steric interaction was preventing this bulky aldehyde substrate from reacting. Our hypothesis proved to be correct when *para-tert*-butyloxycarbonyl ether aldehyde was tolerated (entry 4). However, BOC-deprotection under aqueous trifluoroacetic acid conditions yielded a complex product mixture.

1.3.3. Pd-Catalyzed Cross-Coupling Strategies

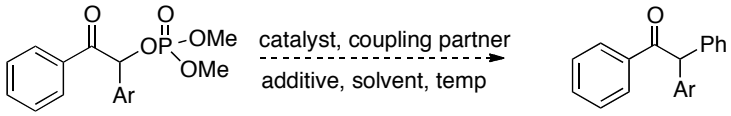
Buchwald has published a Pd-catalyzed method to access various oxindoles from the corresponding α-chloroacetanilide presursor (eq 6).[20] The process is likely initiated by an oxidative addition of the Pd(0) to the α-chloroamide followed by either an electrophilic aromatic substitution/reductive elimination of the Pd(0) species or a carbopalladation/β-hydride elimination event to form the observed C–C bond. In either case, the process can be viewed as an example of polarity reversal catalysis to arrive at the desired oxindoles.



(6)

Inspired by these results, we experimented with cross-coupling strategies using α-ketophosphates, since aryl and benzylic phosphate groups are known to participate in cross-coupling reactions with transition metals.[21,22] The results of these cross-coupling attempts are summarized in Table 1-3. α-Ketophosphate **15a** was not tolerated under Suzuki conditions (entries 1-4). Instead of desired product, deoxybenzoin product was isolated. Kumada conditions with both $Pd(PPh_3)_4$ and $Pd(dba)_2$ gave only trace product that was unable to be isolated (entries 5-8). Under Stille conditions, only starting material was recovered, even after the reaction was heated to reflux for 18 hours (entry 9). This last result strongly suggested that cross-coupling with these phosphate electrophiles using Pd(0) catalysis would be difficult. We were thus forced to look to other methods to promote α-alkylation.

Table 1-3. Pd(0)-Catalyzed Cross-Coupling Efforts

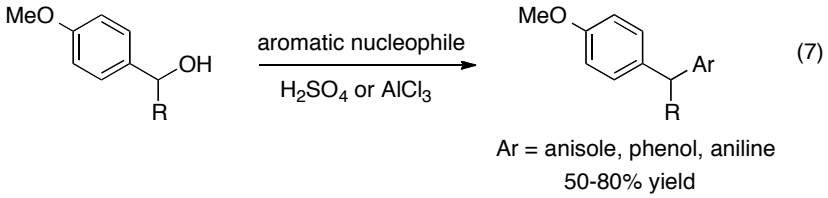


15a
Ar = 2-MeOPh

Entry	catalyst	coupling partner	additive	solvent	temp
1	$Pd(PPh_3)_4$	$PhB(OH)_2$	2 M Na_2CO_3	4:1 toluene/EtOH	70 °C
2	$Pd(dba)_2$	$PhB(OH)_2$	2 M Na_2CO_3	4:1 toluene/EtOH	70 °C
3	$Pd(PPh_3)_4$	$PhB(OH)_2$	2 M K_2CO_3	THF	70 °C
4	$Pd(dba)_2$	$PhB(OH)_2$	2 M K_2CO_3	THF	70 °C
5	$Pd(PPh_3)_4$	PhMgBr	none	THF	-78 ºC
6	$Pd(dba)_2$	PhMgBr	none	THF	-78 ºC
7	$Pd(PPh_3)_4$	PhMgBr	none	Et_2O	-78 ºC
8	$Pd(dba)_2$	PhMgBr	none	Et_2O	-78 ºC
9	$Pd(PPh_3)_4$	$SnPhBu_3$	none	toluene	90 °C

1.3.4 Initial Results with Lewis Acids

Panda has described the synthesis of various trisubstituted methane derivatives upon treatment of the carbinol precursors with either concentrated H_2SO_4 or $AlCl_3$ in the presence of an arene nucleophile (eq 7).[23]

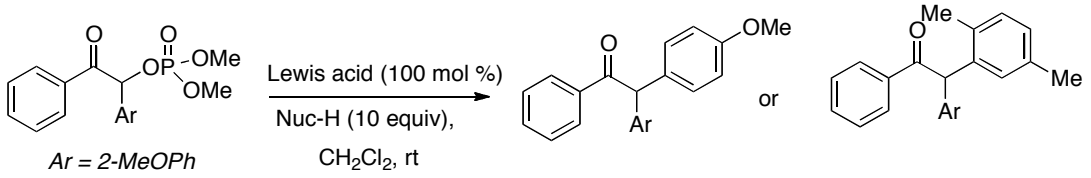


(7)

We hypothesized that α-ketophosphates could behave in a similar manner when subjected to the right Lewis acid. To test this idea, *o*-OMe substituted α-ketophosphate **15a** was prepared and treated with arene nucleophiles (10 equiv) in the presence of several Lewis acids (1.0

equiv) in CH_2Cl_2. We observed the desired α-alkylation under these reaction conditions with complete regioselectivity for *para*-addition when anisole was used. The results of these initial experiments are summarized in Table 1-4. The reaction was independent of Lewis acid promoter with anisole, but $BF_3{\cdot}OEt_2$ gave slightly elevated yields when *p*-xylene was employed.

Table 1-4. Initial Lewis Acid and Nucleophile Screen[a]



Ar = 2-MeOPh

15a **16a** **16b**

entry	Lewis acid	Nuc-H	yield (%)[b]
1	$TiCl_4$	anisole	66%
2	TMSOTf	anisole	66%
3	$ZnCl_2$	anisole	67%
4	$BF_3{\cdot}OEt_2$	anisole	67%
5	$TiCl_4$	*p*-xylene	40%
6	TMSOTf	*p*-xylene	40%
7	$ZnCl_2$	*p*-xylene	40%
8	$BF_3{\cdot}OEt_2$	*p*-xylene	45%

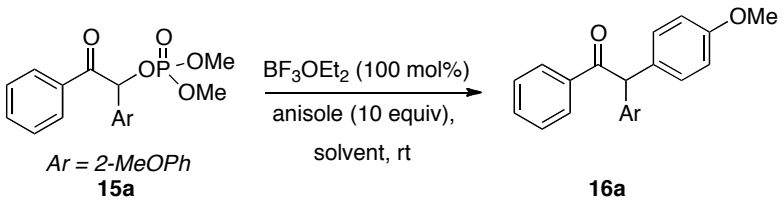
[a]Reaction conditions: **15a** (1.0 equiv), Lewis acid (1.0 equiv), Nuc-H (10 equiv), $[\mathbf{15a}]_0$ = 0.1 M in CH_2Cl_2, 23 °C, 5 h. [b]Refers to isolated yield after column chromatography.

1.3.5 Solvent and Lewis Acid Optimization

With positive results for both anisole and *p*-xylene using $BF_3{\cdot}OEt_2$, we next examined the optimal solvent for this reaction. The alkylation was tolerant of a number of organic

media but gave no desired product in polar aprotic solvents (entries 9-14), presumably due to strong Lewis basic interactions with $BF_3{\cdot}OEt_2$. The best yields using $BF_3{\cdot}OEt_2$ and anisole were observed in 1,2-DCE (entry 2, 99%). The α-aryl ketone **16a** was observed in 80% yield with 0.10 equivalents of $BF_3{\cdot}OEt_2$ (entry 15); however, using catalytic Lewis acid resulted in significantly longer reaction times and diminished yields for a number of different nucleophiles. $BF_3{\cdot}OEt_2$ is an inexpensive reagent; we thus investigated the reaction scope with a full equivalent of Lewis acid (Table 1-6).

Table 1-5. Solvent Screen with Anisole and **15a**[a]



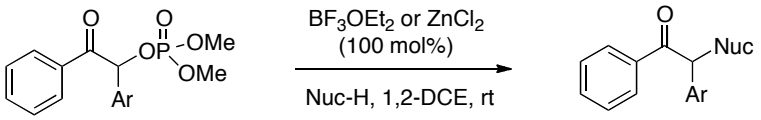
entry	solvent	yield (%)[b]
1	CH_2Cl_2	86
2	1,2-DCE	99
3	CH_3CN	71
4	Toluene	66
5	Benzene	85
6	$CHCl_3$	76
7	CCl_4	80
8	1,2-DME	74
9-14	[c]	0
15	1,2-DCE	80[d]

[a]Reaction conditions: **15a** (1.0 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), anisole (10 equiv), $[\mathbf{15a}]_0$ = 0.1 M in solvent, 23 °C. [b]Calculated by ^1H NMR spectroscopy using a mesitylene internal standard. [c]Et_2O, THF, DMF, DMA, TBME, and acetone all gave no desired product. [d]Reaction performed with 0.10 equiv of $BF_3{\cdot}OEt_2$, 23 °C, 17 h.

1.3.6. Scope of Nucleophile and α-Ketophosphate

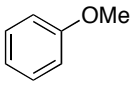
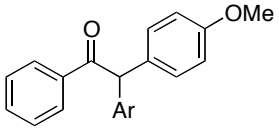
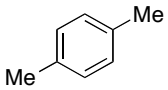
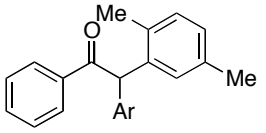
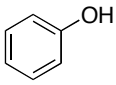
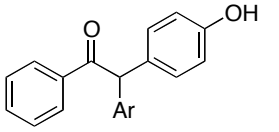
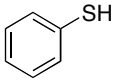
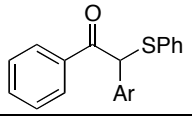
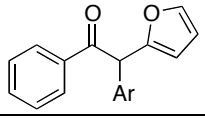
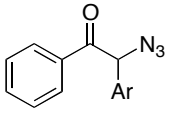
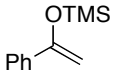
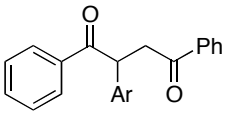
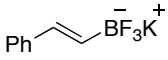
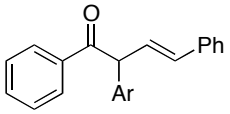
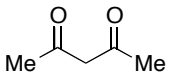
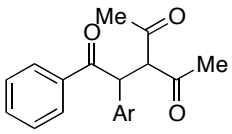
Using *ortho*-methoxy substituted ketone **15a** as the standard electrophile, we investigated the limits of nucleophilic incorporation. The results are summarized in Table 1-6. Both aromatic and heteroaromatic nucleophiles were tolerated with varying reaction times depending on the nucleophile employed (entries 1-5). Both anisole and phenol reacted to give exclusive *para*-addition at 23 °C in very good yields. *p*-Xylene gave diminished yields due to competitive decomposition of the starting ketophosphate. Contrary to phenol, thiophenol reacted through the more nucleophilic sulfur atom to provide the aryl sulfide in 84% yield (entry 4). Furan gave heteroaromatic product in 84% yield (entry 5). Several nonarene nucleophiles performed well in this system (entries 6-9). Molander's potassium trifluoroborate styrenyl salt[24] gave poor conversion in 1,2-DCE due to poor solubility of the nucleophile. Switching to acetonitrile and $ZnCl_2$ as the Lewis acid promoter at 90 °C delivered the *trans* olefin in 60% yield (3 h); identical reaction conditions with $BF_3{\cdot}OEt_2$ gave no desired product. Interestingly, this reaction produced **16h** cleanly with no migration of the olefin into conjugation and no competitive Ritter-type reactivity in CH_3CN. This entry demonstrates the ability to install α-vinyl groups using this chemistry. Trimethylsilylazide was well tolerated upon switching to CH_2Cl_2 at 23 °C, providing the α-azido ketone in 81% yield. Silyl enol ether and acetylacetone addition were also feasible, delivering 1,4-diketone products in promising yields. Silyl enol ether addition was optimized with $ZnCl_2$ at 80 °C; reaction with $BF_3{\cdot}OEt_2$ gave only trace product at elevated temperatures.

Table 1-6. Scope of Nucleophile[a]



Ar = 2-MeOPh
15a

16a-i

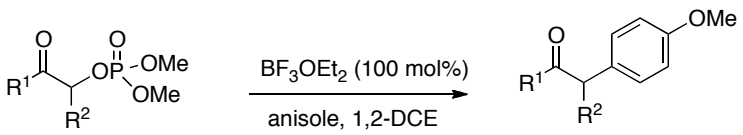
entry	Nuc-H	product	product	yield (%)[b]
1			**16a**	84
2[c]			**16b**	44
3			**16c**	72
4			**16d**	84
5			**16e**	83
6[c]	$TMSN_3$		**16f**	81
7[d]			**16g**	70
8[e]			**16h**	60
9[f]			**16i**	46

[a]Reaction conditions: **15a** (1.0 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), Nuc-H (10 equiv), $[\mathbf{15a}]_0$ = 0.1 M in 1,2-DCE, 23 °C. [b]Refers to isolated yield after column chromatography, average of two trials. [c]Reaction performed in CH_2Cl_2. [d]Reaction perfomed at 80 °C in a Teflon seal-capped vial with 1.0 equiv of $ZnCl_2$. [e]Reaction perfomed at 90 °C in a Teflon seal-capped vial in

CH_3CN with 1.0 equiv of $ZnCl_2$ and 3.0 equiv of Nuc-H. [f]Reaction performed with 5.0 equiv of nucleophile.

Table 1-7 summarizes the scope of the electrophile with anisole as the nucleophile. *Para*-substituted aromatic substrates and heteroaromatic substrates were tolerated (entries 1-2). Substituted aryl ketones reacted cleanly with no decrease in yield (entry 6). Up until this point, all substitution on the aromatic ring adjacent to phosphate (R^2 in Table 1-8, 2-MeOPh in Table 1-7) had been electron releasing. In investigating the tolerance of electron neutral and electron poor aryl donors, we discovered that unsubstituted, *para*-Cl substituted, and naphthyl aromatic substrates gave no desired product at 23 °C, but were acceptable for α-alkylation at elevated temperatures (entries 3-5). We did observe competitive *ortho*-addition of anisole at these temperatures, but the minor product was produced in 7-8% yield and easily separated from the major product by silica gel chromatography.

Table 1-7. Scope of the α-Ketophosphate[a]



15b-g **16j-o**

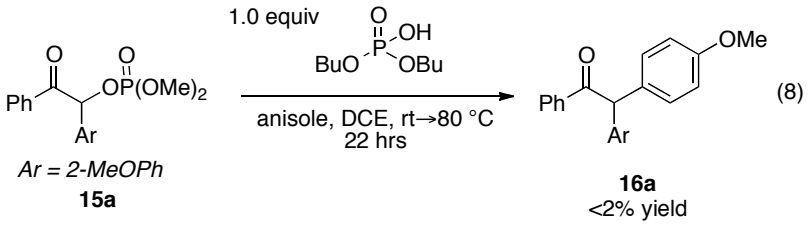
entry	R^1	R^2	temp (°C)	product	yield (%)[b]
1[c]	Ph	4-OMePh	23	**16j**	73
2	Ph	2-thienyl	23	**16k**	48
3[d,e]	Ph	Ph	85	**16l**	54
4[d,e]	Ph	4-ClPh	85	**16m**	51
5[d,f]	Ph	2-naphthyl	85	**16n**	61
6	4-ClPh	4-OMePh	23	**16o**	71

[a]Reaction conditions: **15b-g** (1.0 equiv), $BF_3 \cdot OEt_2$ (1.0 equiv), Nuc-H (10 equiv), $[\mathbf{15b\text{-}g}]_0$ = 0.1 M in 1,2-DCE, 23 °C. [b]Refers to isolated yield after column chromatography, average of two trials. [c]Reaction performed in CH_2Cl_2. [d]Reaction perfomed at 85 °C in a Teflon seal-capped vial. [e]*Ortho*-addition product isolated in 8% yield. [f]*Ortho*-addition product isolated in 7% yield.

1.3.7. Control Experiments

The fact that such a range of Lewis acids promoted Friedel-Crafts alkylation with competitive yields (Table 1-4) led us to question whether the reaction was being promoted by a non-Lewis acidic source. In electrophilic aromatic substitution reactions as described by Olah,[25] attack of the arene nucleophile generates an intermediate bound to both an electrophile and a proton, known as a σ-complex. A final deprotonation of this proton by a weak Brønsted base in order to restore aromaticity is relatively fast. The expelled dimethyl phosphate most likely serves as the Brønsted base in this system. The result of this

deprotonation is a stoichiometric amount of dimethyl phosphoric acid that could promote the next α-phosphate ionization event. In order to test whether the generated Brønsted acid was promoting this transformation, we performed the following control experiment. α-Ketophosphate **15a** was treated with di-*n*-butyl phosphoric acid (1.0 equiv) etc and 10 equivalents of anisole in 1,2-dichloroethane at 23 °C. No desired product was observed after several hours. Forcing conditions (80 °C, 18 hours) led to ketone **16a** in <2% yield (eq 8). Considering the ease with which this particular α-ketophosphate is alkylated with anisole and 1.0 equivalent of $BF_3{\cdot}OEt_2$ at 23 °C, we can conclude that the generated diakyl phosphoric acid does not promote this Friedel-Crafts alkylation.

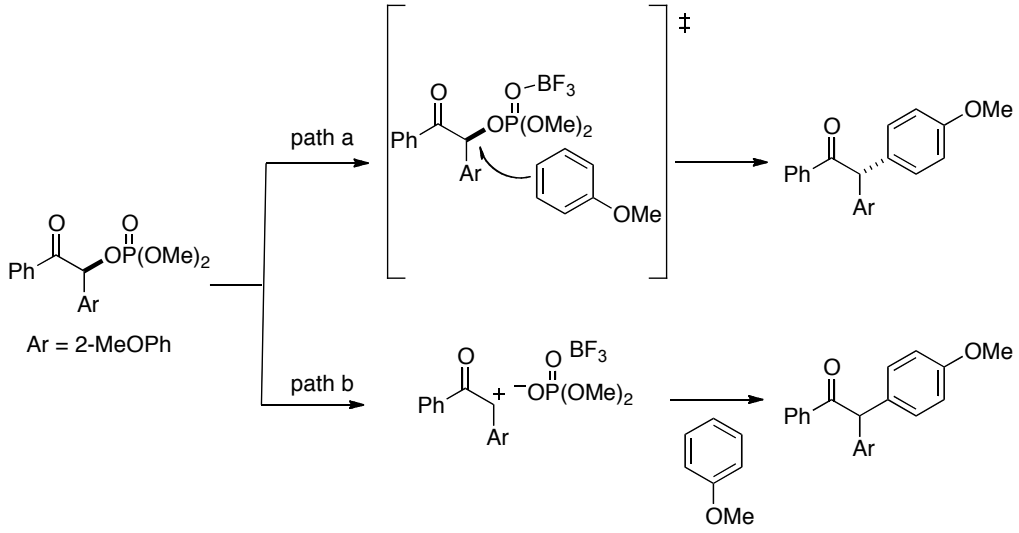


(8)

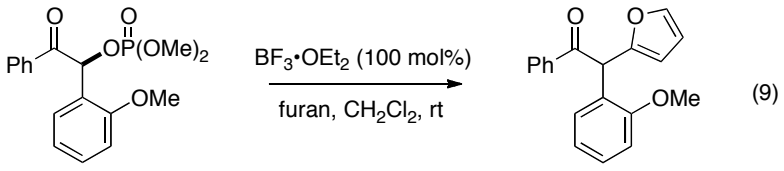
We proposed two possible mechanistic pathways for nucleophilic substitution. The first pathway (Scheme 1-3, path a) would involve a Lewis acid-assisted S_N2 reaction at the α-carbon, analogous to Ready and Breit's polarity reversal strategies with metallated nucleophiles (eq 1 and 2). While the rates of S_N2 reactions at secondary electrophiles are considerably slower compared to primary sites, α-halogenated ketones and esters are known to react through S_N2 pathways due to the facilitation of the rehybridization of the electrophilic carbon atom from sp^3 to sp^2 in the transition state. Electron density at the electrophilic carbon is delocalized into the C=O π* orbital which leads to a transition state energy stabilization.[26] This rate-increasing substituent effect is also observed with benzylic halides. In our system, the phosphate leaving group is both benzylic and adjacent to a

carbonyl. The second pathway (path b) would involve Lewis acid-promoted ionization of the phosphate group to produce an sp^2-hybridized α-acyl carbenium ion followed by Friedel-Crafts addition. If path a is operative, an enantioenriched α-ketophosphate would deliver an α-alkylated ketone product with a transfer of stereochemical information.

Scheme 1-3. Two Possible Pathways for the α-Alkylation of α-Ketophosphates



In order to probe the mechanism, we synthesized optically active α-ketophosphate **(+)-15a** (er 69:31) using previously published methods from our laboratory[27] and treated it under the standard reaction conditions with furan (10 equiv). α-Aryl ketone **16e** was observed in a 50:50 enantiomeric ratio (eq 9). This result is consistent with an S_N1 pathway operating via an α-acyl carbenium ion.



(+)-15a, er 69:31

16e
50%, er 50:50

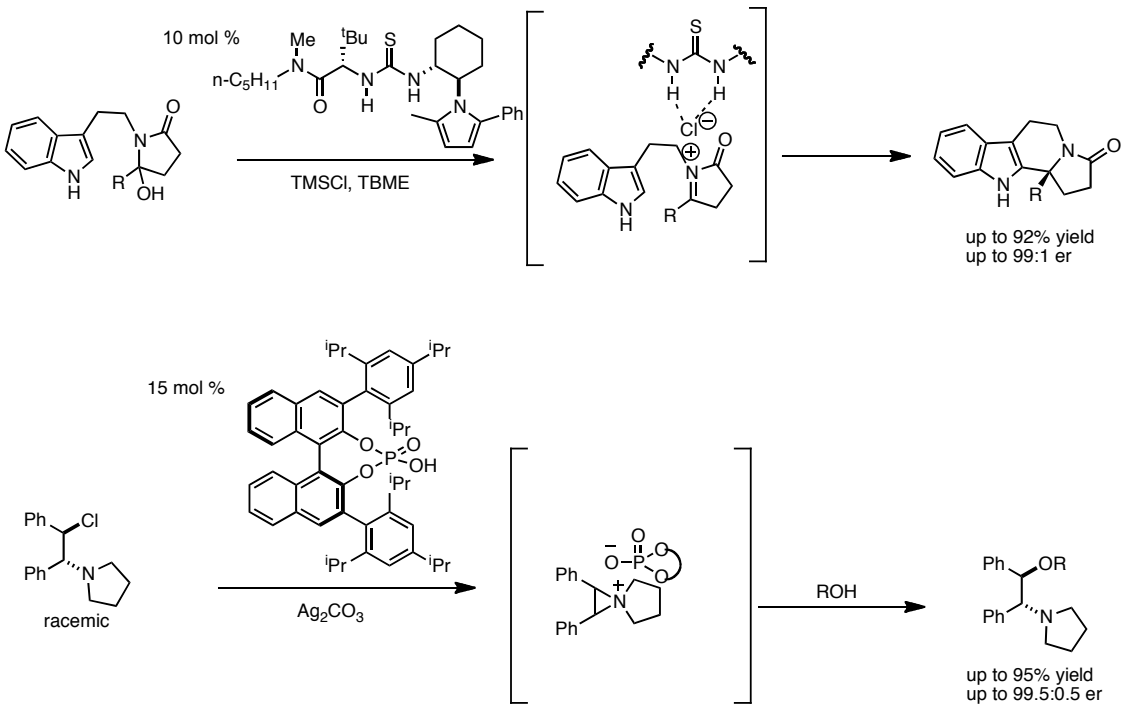
While certainly uncommon, there is literature precedent for α-acyl carbenium ion intermediates. Morize has reported the dehalogenation and subsequent solvolysis of α-bromobenzyl ketones by treatment with $AgSbF_6/SO_2$ at -75 °C.[28] After visible AgBr precipitation, MeOH was added to trap the resultant intermediate. α-Methoxy ketone products were isolated in ~40% yield. NMR experiments designed to probe the dehalogenation step produced NMR signals consistent with an α-acyl carbenium ion. Wadia has reported nucleophilic substitutions with *p*-cresol and various α-chloroketones that lend support to the presence of an α-acyl carbenium ion intermediate.[29] Reaction with *p*-OMe substituted aryl ketones and *p*-cresol gave benzofuran products at 23 °C. Analogous experiments with electron neutral aryl ketones gave only recovered starting material. Taken together, these results indicate the necessity for an electron-releasing aromatic group adjacent to the chloride and are consistent with an α-acyl carbenium ion that is stabilized by resonance donation through the aromatic ring. Reaction rates in our α-ketophosphate system qualitatively correlate with the electron-donating ability of the adjacent aromatic ring, as evidenced by the necessity for elevated temperatures with electron neutral and electron poor α-ketophosphates (entries 4-6, Table 1-7).

1.3.8 Efforts Toward an Asymmetric Variant

Having elucidated the mechanism for this transformation, our efforts turned toward a possible asymmetric variant. Enantioselective S_N1 reactions that proceed through anion binding pathways are quite sparse. This is due to the absence of strongly directional catalyst-substrate interactions in the transition state, making the necessary transfer of chiral information in the enantioselectivity-determining step difficult.[30] Nevertheless, there are

impressive examples of catalytic, enantioselective S_N1 reactions in which stereofacial approach is controlled by a chiral counterion (Scheme 1-4). Jacobsen has described an asymmetric Pictet-Spangler cyclization in which a tethered indole nucleophile adds to an *N*-acyl iminium ion intermediate.[31] Control experiments point toward enantioselectivity being controlled through a chiral thiourea-chloride complex. Toste has reported an asymmetric S_N1 reaction of *meso* aziridinium ions and alcohol nucleophiles using an axially chiral phosphoric acid.[32] Vicinal amino alcohols are produced in up to 99.5:0.5 er. The chiral phosphate is presumed to direct the stereofacial preference of nucleophilic attack through a chiral tight ion pair to the positively charged aziridinium or carbenium ion.

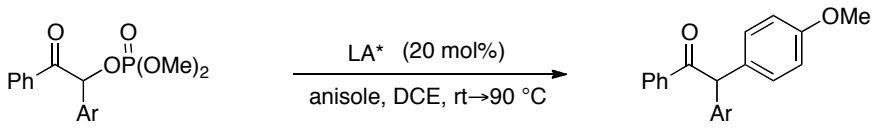
Scheme 1-4. Jacobsen's (top) and Toste's (bottom) Enantioselective S_N1 Examples



We hypothesized that ionization with a chiral Lewis acid would create an ion pair between the α-acyl carbenium ion and the phosphate/chiral Lewis acid complex. Facial selectivity could in turn be controlled by this chiral anion.

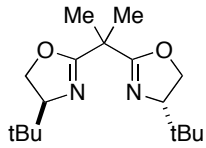
With the results from achiral Lewis acids in mind, we first investigated chiral C_2-symmetric (bis)oxazoline (BOX) ligands in combination with various metal-centered Lewis acids. The results are summarized in Figure 1-4. Experiments at room temperature in 1,2-DCE with **15a** and anisole gave trace product with $ZnCl_2$ and $ZnOTf_2$, regardless of the chiral ligand employed. However, elevating the temperature to 90 °C with these chiral Lewis acid complexes gave desired Friedel-Crafts alkylation in appreciable yields. The majority of Lewis acid/ligand combinations delivered product as a racemic mixture, although very slight stereofacial preference was observed in a few cases, the highest being 57.5:42.5 er with $Zn(OTf)_2$ and BnBOX ligand. We reasoned that in order to promote high levels of enantioinduction, a close association of the carbenium ion and chiral counterion would be necessary. Temperature could play an important role in promoting this close interaction;[33] thus, we examined more active Lewis acid/ligand combinations in order to avoid elevated temperatures. Switching to the stronger Lewis acid $Sc(OTf)_3$, however, gave largely racemic product with both ^{t}BuBOX and BnBOX ligands; highly electron-deficient $Cu(SbF_6)_2$/^{t}BuBOX also gave racemic product. A short solvent screen with the most selective $Zn(OTf)_2$/BnBOX Lewis acid led to a significant increase in yield with toluene, benzene, and $CHCl_3$; however, product was obtained as a racemic mixture in each case.

Figure 1-4. Asymmetric efforts with chiral C_2-symmetric BOX ligands/Lewis acids

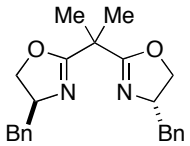


Ar = 2-MeOPh
15a

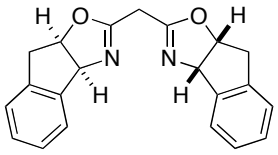
16a



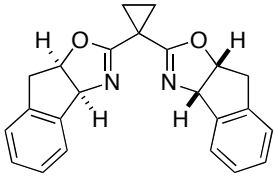
$ZnCl_2$: 60%, er 52:48
$Zn(OTf)_2$: 42%, er 55:45
$Sc(OTf)_3$: 44%, er 50:50
$Cu(SbF_6)_2$: 52%, er 50:50



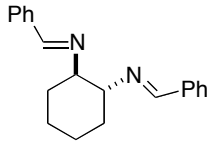
$ZnCl_2$: 45% yield, er 50:50
$Zn(SbF_6)_2$: 58% yield, er 55.5:44.5
$Sc(OTf)_3$: 60% yield, er 52:48
$Zn(OTf)_2$: 24% yield, er 57.5:42.5
in toluene: 50% yield, er 50:50
in benzene: 52% yield, er 50:50
in $CHCl_3$: 54% yield, er 50:50
CCl_4: trace pdt, er 50:50



$Zn(OTf)_2$: 55%, er 55:45



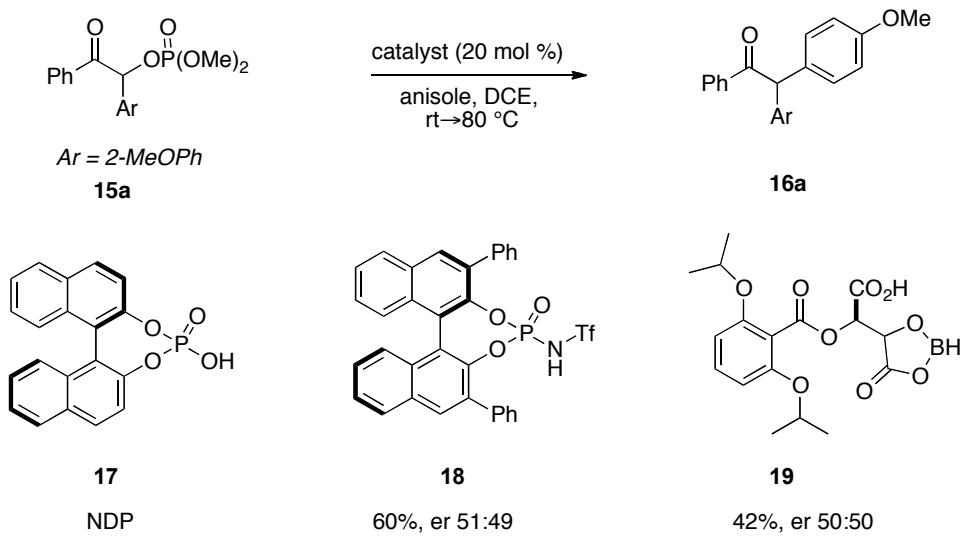
$Zn(OTf)_2$: 71% yield, er 54:46



$ZnCl_2$: 60% yield, er 50:50

Toste's success in directing stereofacial attack at aziridinium ions with an axially chiral phosphate catalyst led us to employ BINOL derived phosphoric acids in our asymmetric efforts. The results are summarized in Figure 1-5.

Figure 1-5. Chiral Brϕnsted Acid Catalysts



Chiral BINOL phosphoric acid **17** gave no desired product even at elevated temperatures for extended time periods. BINOL derived *N*-triflyl phosphoramide **18** gave desired product at elevated temperatures in 60% yield, but as a racemic mixture. The success with $BF_3{\cdot}OEt_2$ in the racemic series led us to try Yamamoto's chiral acyloxyborane complex **19**.[34] Again, product was obtained in promising yields but as a racemic mixture.

1.4 Conclusions

We have developed a Lewis acid promoted α-alkylation of α-ketophosphate electrophiles with electron-rich arene nucleophiles. Reactions generally perform best in 1,2-DCE with either BF_3OEt_2 or $ZnCl_2$ as the Lewis acid promoter. Sp^3-sp^2 bond formation is possible using a polarity reversal strategy; furthermore, C–C bond formation and leaving group installation are parlayed into a single synthetic operation during the phospha-benzoin reaction. Direct nucleophilic α-substitution chemistry is possible on these α-ketophosphate products without any extra steps to install the proper nucleofuge. In addition, the nature of this alkylation method circumvents the need to premetallate the nucleophilic component.

Aryl, hetroaryl, alkenyl, and heteroatom nucleophiles are tolerated; sp^3-sp^3 C–C bonds can also be installed by using silyl enol ether or acetylacetone as the nucleophile. Mechanistic experiments point toward an S_N1 mechanism at a resonance stabilized α-acyl carbenium ion. Asymmetric attempts were largely unsuccessful, but reaction with $Zn(OTf)_2$/BnBOX did promote slight stereofacial preference (er 57.5:42.5), presumably via a chiral counterion.

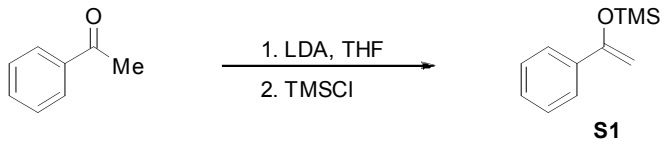
1.5 Experimental

Methods: Infrared (IR) spectra were obtained using a JASCO FT/IR 460-plus spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker model AMX 300 (^{1}H NMR at 300 or 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Silia-P flash silica gel (40-63 μm) purchased from Silacycle. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific

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

Materials. Dichloromethane and THF were dried by passage through a column of neutral alumina under nitrogen prior to use. Chlorotrimethylsilane, diisopropylamine, 1,2-dichloroethane and acetonitrile were freshly distilled from calcium hydride prior to use. All other reagents were obtained from Acros or Sigma-Aldrich and used without further purification.

Preparation of trimethyl(1-phenylvinyloxy)silane (S1).

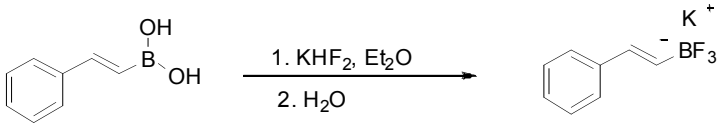


S1

A flame dried 250 mL round-bottom flask equipped with a magnetic stir bar was fitted with a rubber septum and charged with diisopropylamine (6.67 mL, 47.5 mmol) and THF (125 mL). The solution was cooled to 0 ºC under a stream of N_2 and *n*BuLi (30.6 mL, 47.5 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for an additional 10 minutes, then cooled to -78 ºC. Acetophenone (5 mL, 42.8 mmol) was added dropwise over a 5 minute time period, and the reaction mixture was stirred for an additional 20 minutes. After 20 minutes of stirring, chlorotrimethylsilane (5.97 mL, 47.5 mmol) was added via syringe. The reaction mixture was stirred for 5 minutes, then allowed to warm up to room temperature. The solution was transferred to a separatory funnel, diluted with 50 mL of cold pentates, and washed quickly with a 0.5 M solution of acetic acid, saturated aqueous

$NaHCO_3$, distilled H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an orange liquid. ^1H NMR analysis of the unpurified product showed clean trimethyl(1-phenylvinyloxy)silane formation. Spectral data matched those reported for the title compound.[35]

Preparation of potassium (*E*)-trifluoro(styryl)borate (S2).



S2

The title compound was prepared according to Molander's method.[2] A polyethylene screw-capped scintillation vial equipped with a magnetic stir bar was charged with (*E*)-styrylboronic acid (500 mg, 3.38 mmol) and Et_2O (6.75 mL). The solution was stirred at room temperature and KHF_2 was added, followed by syringe pump addition of H_2O (3.0 mL) over a period of 30 minutes. The reaction mixture was stirred for 3 hours, then concentrated in vacuo to remove Et_2O and H_2O. The solid precipitate was dissolved in acetone, then filtered through filter paper to remove excess KHF_2 and concentrated. The resultant solid was recrystallized from hot acetone and Et_2O, and the product was isolated via vacuum filtration as a white crystalline solid. Spectral data matched those reported for the title compound.[24]

General Procedure for the preparation of α-ketophosphates 15a-g. α-Ketophosphate substrates were prepared from acylphosphonates and aldehydes according to previous published methods in our laboratory.[3] A 25-mL round bottom flask equipped with a magnetic stir bar was charged with the appropriate acylphosphonate (1.0 equiv) and aldehyde (1.05 equiv). Et_2O (0.20 M in acylphosphonate) was added followed by KCN/18-crown-6

complex (0.20 equiv). Upon completion of the reaction (TLC analysis), Et_2O was added and the organic layer was washed twice with H_2O. The organic extracts were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography, eluting with the indicated solvent system.

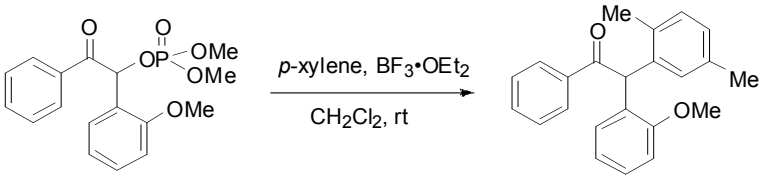
General Procedure (A) for the $BF_3 \cdot OEt_2$ catalyzed addition of nucleophiles to α-ketophosphate substrates. A flame-dried teflon-capped screw-thread vial equipped with a magnetic stir bar was charged with the appropriate α-ketophosphate substrate (1.0 equiv) and anhydrous 1,2-dichloroethane or dichloromethane (10mL/mmol). The vial was sealed with a rubber septum under a stream of N_2, and the appropriate liquid nucleophile (3.0-10.0 equiv) was added to the reaction vial via syringe and then stirred at room temperature for 5 minutes under N_2. Solid nucleophiles (3.0-10.0 equiv) were also added to the reaction vial, followed by purging the vial for several minutes with a stream of N_2 and stirring at room temperature. $BF_3 \cdot OEt_2$ (1.0 equiv) was then added to the reaction mixture via syringe. The vial was screw-capped and stirred at the indicated temperature (either room temperature or 85ºC) for the indicated time period. Upon completion of the reaction, H_2O was added to quench the $BF_3 \cdot OEt_2$. The organic layer was extracted with dichloromethane (3x) and washed with H_2O (2x). The solution was dried over sodium sulfate and concentrated in vacuo. The product was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (B) for the $ZnCl_2$ catalyzed addition of nucleophiles to α-ketophosphate substrates. In a glovebox, a flame-dried teflon-capped screw-thread vial (vial #1) equipped with a magnetic stir bar was charged with $ZnCl_2$ (1.0 equiv). A second flame-dried screw-thread vial (vial #2) out of the glovebox was equipped with a magnetic stir

bar and charged with the appropriate α-ketophosphate substrate (1.0 equiv) and anhydrous acetonitrile or 1,2-dichloroethane (10mL/mmol). Vial #2 was sealed with a rubber septum and purged under a stream of N_2, stirring for 5 minutes. The contents of vial #2 were then transferred via syringe to vial #1. The appropriate liquid nucleophile (3.0-10.0 equiv) was added to vial #1 via syringe. Solid nucleophiles (3.0-10.0 equiv) were also added to vial #l, followed by purging the vial for several minutes with a stream of N_2 and stirring at room temperature. Vial #1 was then screw-capped and heated to the appropriate temperature for the indicated time period. Upon completion of the reaction in 1,2-dichloroethane, H_2O was added to quench the $ZnCl_2$. The organic layer was extracted with dichloromethane (3x) and washed with H_2O (2x). Reactions in acetonitrile were concentrated in vacuo to remove all solvent, then extracted with dichloromethane (3x) and washed with H_2O (2x). The solution was dried over sodium sulfate and concentrated in vacuo. The product was purified via flash chromatography, eluting with the indicated solvent system.

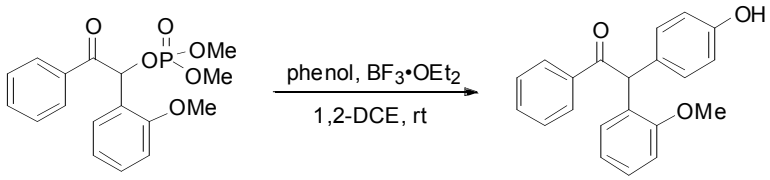
2-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1-phenylethanone (16a). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (100 mg, 0.285 mmol), anisole (311 mg, 312 μL, 2.85 mmol) and $BF_3{\cdot}OEt_2$ (36 μL, 0.285 mmol). After 2 hours at room temperature, 2-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1-phenylethanone **16a** was isolated as a pale yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16a**: **IR**

(thin film, cm^{-1}) 3054, 2986, 2685, 2305, 1685, 1596, 1510, 1490, 1421, 1178, 1107, 1030, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 8 Hz, 2H), 7.28-7.25 (m, 4H), 6.93 (t, *J* = 6.4 Hz, 1H), 6.93-6.88 (m, 3H), 6.29 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.0, 158.8, 156.4, 137.4, 132.4, 130.8, 129.7, 129.6, 129.2, 128.6, 128.4, 128.2, 120.6, 114.2, 110.5, 55.5, 55.2, 52.3; **TLC** (10% EtOAc/hexanes) R_f 0.17; **HRMS** (ESI) Calcd. for $C_{20}H_{20}O_3$+Na 333.1491, Found 333.1497.

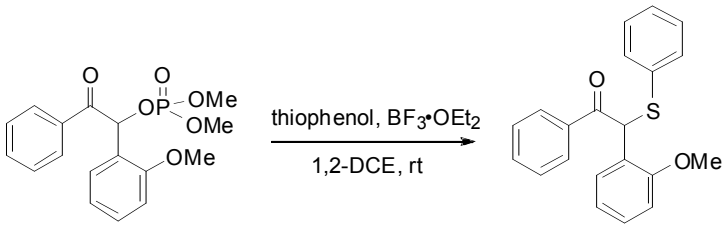


2-(2,5-dimethylphenyl)-2-(2-methoxyphenyl)-1-phenylethanone (16b). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (100 mg, 0.285 mmol), *p*-xylene (302 mg, 349 μL, 2.85 mmol) and $BF_3{\cdot}OEt_2$ (36 μL, 0.285 mmol). After 3.5 hours at room temperature, 2-(2,5-dimethylphenyl)-2-(2-methoxyphenyl)-1-phenylethanone **16b** (38 mg, 0.115 mmol, 41% yield) was isolated as a clear, colorless oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16b**: **IR** (thin film, cm^{-1}) 3053, 2986, 2305, 1685, 1597, 1490, 1463, 1447, 1244, 1206, 1106, 1051, 1029, 1007, 895, 808; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.52 (t, J = 6.8 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.29-7.26 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.93-6.88 (m, 2H), 6.82 (d, *J* = 6.4 Hz, 1H), 6.44 (s, 1H), 3.80 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 156.6, 137.4, 135.9, 135.6, 133.2, 132.5, 130.7, 130.0, 129.8, 128.5,

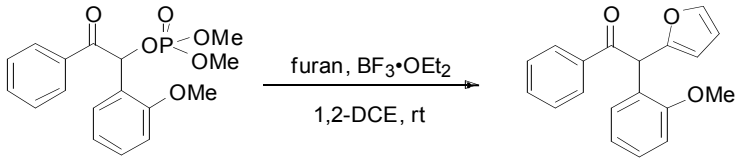
128.4, 128.2, 128.0, 127.7, 120.6, 110.2, 55.5, 49.8, 21.1, 19.3; **TLC** (10% EtOAc/hexanes) R_f 0.31; **HRMS** (ESI) Calcd. for $C_{23}H_{22}O_2$+H 331.1698, Found 331.1703.



2-(4-hydroxyphenyl)-2-(2-methoxyphenyl)-1-phenylethanone (16c). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (100 mg, 0.285 mmol), phenol (268 mg, 2.85 mmol) and $BF_3 \cdot OEt_2$ (36 μL, 0.285 mmol). After 2 hours at room temperature, 2-(4-hydroxyphenyl)-2-(2-methoxyphenyl)-1-phenylethanone **16c** (66 mg, 0.207 mmol, 83% yield) was isolated as a white solid after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **16c**: mp 179 ºC; **IR** (thin film, cm^{-1}) 3584, 3053, 2986, 2685, 2305, 1685, 1596, 1512, 1489, 1421, 1213, 1174, 1107, 1028, 1003, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 6.8 Hz, 2H), 7.29-7.23 (m, 1H), 6.95-6.89 (m, 3H), 6.81 (d, *J* = 6.8 Hz, 2H), 6.28 (s, 1H), 4.99 (s, 1H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 156.3, 154.8, 137.2, 132.6, 131.0, 129.7, 129.5, 129.1, 128.7, 128.4, 128.3, 120.7, 115.7, 110.5, 55.5, 52.4; **TLC** (20% EtOAc/hexanes) R_f 0.14; **HRMS** (ESI) Calcd. for $C_{21}H_{18}O_3$+H 319.1334, Found 319.1343.

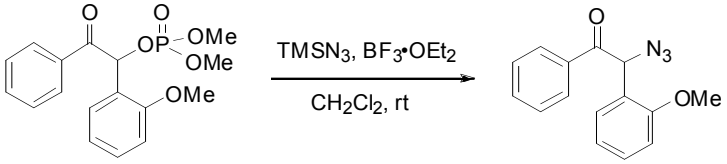


2-(2-methoxyphenyl)-1-phenyl-2-(phenylthio)ethanone (16d). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (75 mg, 0.214 mmol), thiophenol (235 mg, 219 μL, 2.14 mmol) and $BF_3 \cdot OEt_2$ (25 μL, 0.214 mmol). After 5.5 hours at room temperature, 2-(2-methoxyphenyl)-1-phenyl-2-(phenylthio)ethanone **16d** (60 mg, 0.179 mmol, 84% yield) was isolated as a yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16d**: **IR** (thin film, cm^{-1}) 3053, 2986, 2685, 2305, 1682, 1596, 1490, 1438, 1421, 1100, 1025, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8 Hz, 2H), 7.51-7.45 (m, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.36-7.31 (m, 2H), 7.22-7.19 (m, 4H), 6.93 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 3.73 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.2, 155.9, 135.8, 134.6, 133.0, 132.5, 129.7, 129.2, 128.7, 128.6, 128.5, 127.3, 125.2, 121.2, 110.9, 55.6, 52.7; **TLC** (10% EtOAc/hexanes) R_f 0.21; **HRMS** (ESI) Calcd. for $C_{21}H_{18}O_2S$+H 335.1106, Found 335.1109.



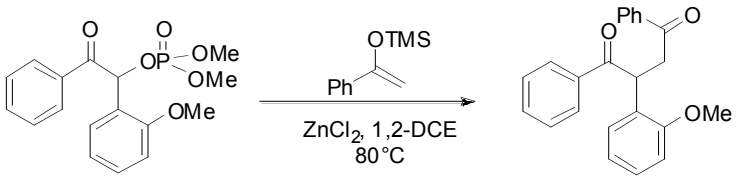
2-(furan-2-yl)-2-(2-methoxyphenyl)-1-phenylethanone (16e). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (100 mg, 0.285 mmol), furan (194 mg, 0.207 mL, 2.85 mmol) and

$BF_3{\cdot}OEt_2$ (36 μL, 0.285 mmol). After 36 hours at room temperature, 2-(furan-2-yl)-2-(2-methoxyphenyl)-1-phenylethanone **16e** (70 mg, 0.236 mmol, 83% yield) was isolated as a brown oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16e**: **IR** (thin film cm^{-1}) 3054, 2986, 2685, 2305, 1691, 1598, 1492, 1421, 1161, 1106, 1051, 1027, 895; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 6.9 Hz, 1H), 7.49-7.38 (m, 3H), 7.26-7.24 (m, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.94-6.89 (m, 2H), 6.46 (s, 1H), 6.33 (s, 1H), 6.14 (s, 1H), 3.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.2, 156.1, 151.7, 142.3, 136.5, 132.8, 129.6, 128.8, 128.6, 128.4, 125.7, 120.8, 110.7, 110.5, 109.0, 55.5, 46.5; **TLC** (10% EtOAc/hexanes) R_f 0.25; **HRMS** (ESI) Calcd. for $C_{19}H_{16}O_3$+H 293.1178, Found 293.1182.

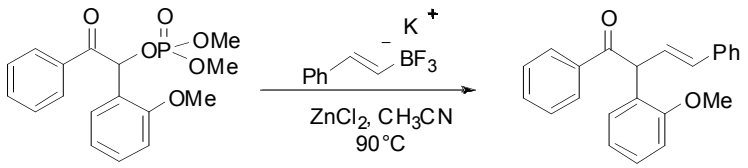


2-azido-2-(2-methoxyphenyl)-1-phenylethanone (16f). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (100 mg, 0.285 mmol), azidotrimethylsilane (328 mg, 374 μL, 2.85 mmol) and $BF_3{\cdot}OEt_2$ (36 μL, 0.285 mmol). After 2 hours at room temperature, 2-azido-2-(2-methoxyphenyl)-1-phenylethanone **16f** (63 mg, 0.265 mmol, 82% yield) was isolated as a clear, colorless oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16f**: **IR** (thin film, cm^{-1}) 3054, 2986, 2685, 2305, 2101, 1694, 1598, 1492, 1438, 1421, 1213, 1104, 1027, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 8.0, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.94 (t, 7.6 Hz, 1H), 6.23 (s, 1H), 3.96 (s, 3H); **^{13}C NMR** (100

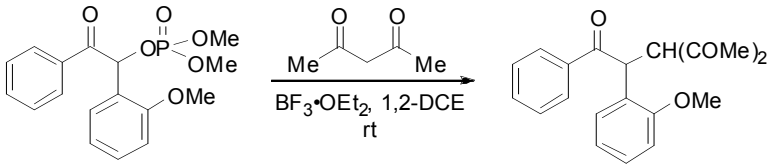
MHz, $CDCl_3$) δ 194.5, 156.3, 134.4, 133.4, 130.6, 128.6, 128.5, 128.4, 122.5, 121.1, 111.4, 61.3, 55.7; **TLC** (15% EtOAc/hexanes) R_f 0.29; **HRMS** (ESI) Calcd. for $C_{15}H_{13}N_3O_2$+Na 290.0905, Found 290.0903.



2-(2-methoxyphenyl)-1,4-diphenylbutane-1,4-dione (16g). The title compound was prepared according to General Procedure **B** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (99 mg, 0.283 mmol), trimethyl(1-phenylvinyloxy)silane (544 mg, 2.83 mmol) and $ZnCl_2$ (38.5 mg, 0.283 mmol) in dry 1,2-dichloroethane (2.83 mL). After 16 hours at 80ºC, 2-(2-methoxyphenyl)-1,4-diphenylbutane-1,4-dione **16g** (69 mg, 0.200 mmol, 71% yield) was isolated as a yellow oil after flash chromatography with 5% ethyl acetate/hexanes. Analytical data for **16g**: **IR** (thin film, cm^{-1}) 3054, 2986, 2305, 1681, 1597, 1493, 1448, 1203, 1181, 1105, 1028, 1001, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 2H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.51-7.45 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.26-7.18 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.79 (dd, *J* = 10.0 Hz, 3.2 Hz, 1H), 4.14 (dd, *J* = 17.6, 10.4 Hz, 1H), 3.93 (s, 3H), 3.23 (dd, *J* = 17.6, 3.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 198.3, 156.0, 136.7, 136.4, 132.9, 132.6, 128.7, 128.4, 128.2, 128.0, 127.1, 121.0, 110.9, 55.4, 42.1, 41.4; **TLC** (10% EtOAc/hexanes) R_f 0.16; **HRMS** (ESI) Calcd. for $C_{23}H_{20}O_3$+H 345.1491, Found 345.1489.

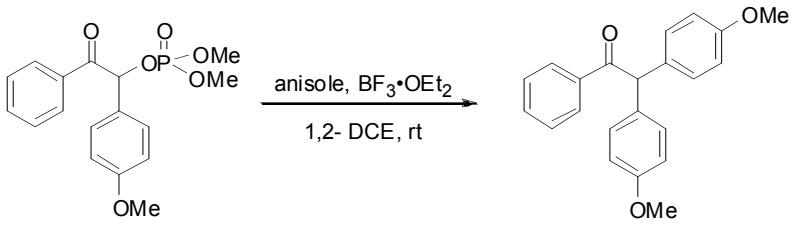


(*E*)-2-(2-methoxyphenyl)-1,4-diphenylbut-3-en-1-one (16h). The title compound was prepared according to General Procedure **B** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (80 mg, 0.228 mmol), potassium (*E*)-trifluoro(styryl)borate (144 mg, 0.685 mmol) and $ZnCl_2$ (31 mg, 0.228 mmol) in dry acetonitrile (2.28 mL). After 3 hours at 90ºC, (*E*)-2-(2-methoxyphenyl)-1,4-diphenylbut-3-en-1-one **16h** (45 mg, 0.137 mmol, 60% yield) was isolated as a white solid after flash chromatography with 5% ethyl acetate/hexanes. Analytical data for **16h**: mp 109 ºC; **IR** (thin film, cm^{-1}) 3054, 2986, 2360, 1682, 1596, 1491, 1448, 1421, 1117, 1027, 967, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.32-7.22 (m, 5H), 6.97-6.91 (m, 2H), 6.71 (dd, *J* = 16, 8.4 Hz, 1H), 6.51 (d, *J* = 16 Hz, 1H), 5.89 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.3, 156.1, 137.2, 136.8, 132.7, 132.6, 129.0, 128.6, 128.4, 127.8, 127.5, 126.5, 121.1, 111.0, 55.6, 50.0; **TLC** (10% EtOAc/hexanes) R_f 0.26; **HRMS** (ESI) Calcd. for $C_{23}H_{20}O_2$+H 329.1542, Found 329.1543.

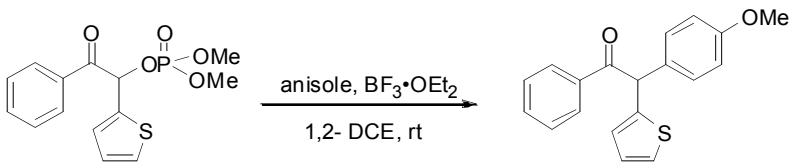


3-acetyl-2-(2-methoxyphenyl)-1-phenylpentane-1,4-dione (16i). The title compound was prepared according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl

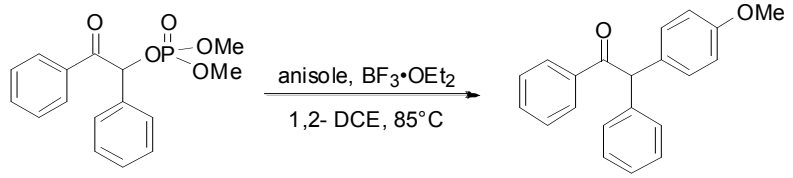
dimethyl phosphate **15a** (100 mg, 0.285 mmol), acetylacetone (143 mg, 147 μL, 1.43 mmol) and $BF_3 \cdot OEt_2$ (36 μL, 0.285 mmol). After 1 hour at room temperature, 3-acetyl-2-(2-methoxyphenyl)-1-phenylpentane-1,4-dione **16i** (43 mg, 0.132 mmol, 46% yield) was isolated as a clear, colorless oil after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **16i**: **IR** (thin film, cm^{-1}) 3054, 2986, 2685, 2305, 1731, 1698, 1682, 1597, 1492, 1421, 1358, 1161, 1026, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.18-7.15 (m, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 8.0 Hz, 1H) 5.87 (d, *J* = 11.2 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 3.87 (s, 3H), 2.32 (s, 3H), 1.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.0, 202.5, 198.1, 156.1, 135.8, 133.0, 129.4, 128.7, 128.3, 123.5, 121.5, 111.5, 71.2, 55.5, 46.4, 30.2, 29.6; **TLC** (10% EtOAc/hexanes) R_f 0.19; **HRMS** (ESI) Calcd. for $C_{20}H_{20}O_4$+H 325.1440, Found 325.1443.



2,2-bis(4-methoxyphenyl)-1-phenylethanone (16j). The title compound was prepared according to General Procedure **A** using 1-(4-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15b** (100 mg, 0.285 mmol), anisole (311 mg, 312 μL, 2.85 mmol) and $BF_3 \cdot OEt_2$ (36 μL, 0.285 mmol). After 5 hours at room temperature, 2,2-bis(4-methoxyphenyl)-1-phenylethanone **16j** (73 mg, 0.220 mmol, 78% yield) was isolated as a yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16j** matched previously reported.[36]

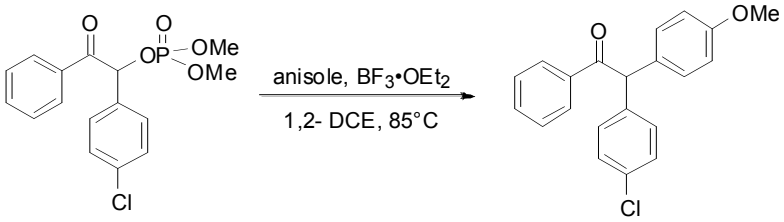


2-(4-methoxyphenyl)-1-phenyl-2-(thiophen-2-yl)ethanone (16k). The title compound was prepared according to General Procedure **A** using dimethyl 2-oxo-2-phenyl-1-(thiophen-2-yl)ethyl phosphate **15c** (50 mg, 0.153 mmol), anisole (167 mg, 168 μL, 1.53 mmol) and $BF_3 \cdot OEt_2$ (19 μL, 0.153 mmol). After 1.5 hours at room temperature, 2-(4-methoxyphenyl)-1-phenyl-2-(thiophen-2-yl)ethanone **16k** (23 mg, 0.073 mmol, 48% yield) was isolated as a yellow oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for **16k**: **IR** (thin film, cm^{-1}) 3054, 2986, 2685, 2305, 1685, 1652, 1595, 1540, 1509, 1421, 1179, 1033, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 6.8, Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 5.2 Hz, 1H), 6.95 (t, *J* = 3.6 Hz, 1H), 6.90 (d, *J* = 3.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.19 (s, 1H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.0, 159.0, 142.3, 136.4, 133.1, 131.0, 129.7, 128.9, 128.6, 126.6, 126.2, 125.4, 114.4, 55.2, 53.4; **TLC** (10% EtOAc/hexanes) R_f 0.21; **HRMS** (ESI) Calcd. for $C_{19}H_{16}O_2S$+H 309.0949, Found 309.0951.



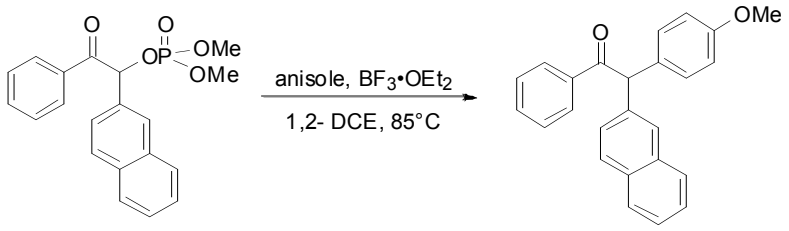
2-(4-methoxyphenyl)-1,2-diphenylethanone (16l). The title compound was prepared according to General Procedure **A** using dimethyl 2-oxo-1,2-diphenylethyl phosphate **15d** (100 mg, 0.313 mmol), anisole (341 mg, 342 μL, 3.13 mmol) and $BF_3 \cdot OEt_2$ (39 μL, 0.313

mmol). After 17 hours at 85ºC, 2-(4-methoxyphenyl)-1,2-diphenylethanone (55 mg, 0.182 mmol, 58% yield) **16l** was isolated as a clear, colorless oil after flash chromatography with 2.5% ethyl acetate/hexanes. Analytical data for **16l**: **IR** (thin film cm^{-1}) 3054, 2986, 2305, 1686, 1609, 1510, 1447, 1421, 1209, 1178, 1032, 895; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 8 Hz, 2H), 7.38-7.34 (m, 2H), 7.31-7.28 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.90 (d, 8.8 Hz, 2H), 6.03 (s, 1H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.5, 158.8, 139.6, 137.0, 132.9, 131.3, 130.2, 129.1, 128.9, 128.7, 128.6, 127.0, 114.3, 58.6, 55.2; **TLC** (10% EtOAc/hexanes) R_f 0.21; **HRMS** (ESI) Calcd. for $C_{21}H_{18}O_2$+H 303.1385, Found 303.1385.

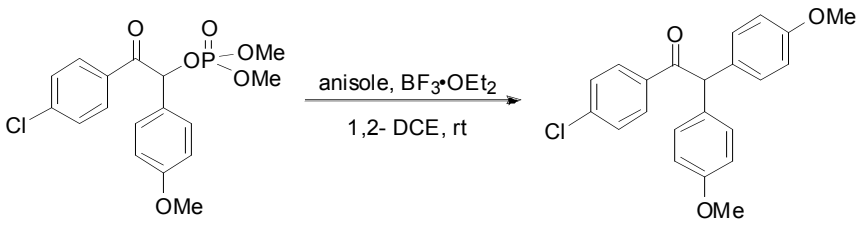


2-(4-chlorophenyl)-2-(4-methoxyphenyl)-1-phenylethanone (16m). The title compound was prepared according to General Procedure **A** using 1-(4-chlorophenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15e** (100 mg, 0.282 mmol), anisole (307 mg, 309 μL, 2.82 mmol) and $BF_3{\cdot}OEt_2$ (35 μL, 0.282 mmol). After 17 hours at 85ºC, 2-(4-chlorophenyl)-2-(4-methoxyphenyl)-1-phenylethanone **16m** (52 mg, 0.146 mmol, 52% yield) was isolated as a clear, colorless oil after flash chromatography with 2.5% ethyl acetate/hexanes. Analytical data for **16m**: **IR** (thin film, cm^{-1}) 3054, 2986, 2926, 2305, 1685, 1594, 1510, 1489, 1447, 1421, 1177, 1092, 1033, 895, 806; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz,

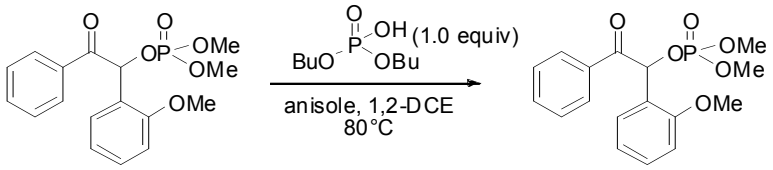
4H), 6.87 (d, J = 8.4 Hz, 2H), 5.96 (s, 1H), 3.79 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 198.1, 158.9, 138.1, 136.7, 133.1, 130.7, 130.4, 130.1, 128.9, 128.8, 128.7, 114.4, 57.9, 55.2; **TLC** (10% EtOAc/hexanes) R_f 0.18; **HRMS** (ESI) Calcd. for $C_{21}H_{17}ClO_2$+H 337.0995, Found 337.1005.



2-(4-methoxyphenyl)-2-(naphthalen-2-yl)-1-phenylethanone (16n). The title compound was prepared according to General Procedure **A** using dimethyl 1-(naphthalen-2-yl)-2-oxo-2-phenylethyl phosphate **15f** (100 mg, 0.270 mmol), anisole (295 mg, 296 µL, 2.70 mmol) and $BF_3{\cdot}OEt_2$ (34 µL, 0.270 mmol). After 3.5 hours at 85ºC, 2-(4-methoxyphenyl)-2-(naphthalen-2-yl)-1-phenylethanone **16n** (55 mg, 0.156 mmol, 58% yield) was isolated as a clear, colorless oil after flash chromatography with 2.5% ethyl acetate/hexanes. Analytical data for **16n**: **IR** (thin film, cm^{-1}) 3056, 2931, 2835, 1683, 1595, 1509, 1447, 1302, 1250, 1209, 1178, 1110, 1032, 1002, 813, 750, 690, 670; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.86-7.78 (m, 3H), 7.71 (s, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.49-7.42 (m, 5H), 7.27 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.19 (s, 1H), 3.81 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 198.4, 158.7, 137.0, 136.9, 133.4, 132.9, 132.4, 131.0, 130.2, 128.9, 128.5, 128.3, 127.8, 127.5, 127.3, 126.0, 125.8, 114.1, 58.6, 55.1; **TLC** (10% EtOAc/hexanes) R_f 0.19; **HRMS** (ESI) Calcd. for $C_{25}H_{20}O_2$+H 353.1542, Found 353.1538.

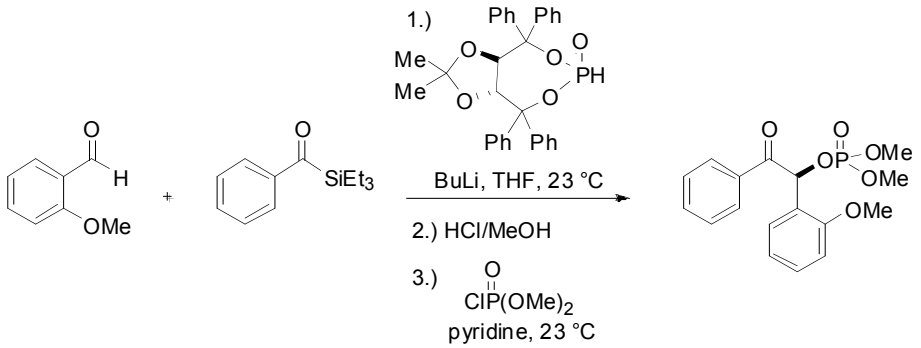


1-(4-chlorophenyl)-2,2-bis(4-methoxyphenyl)ethanone (16o). The title compound was prepared according to General Procedure **A** using 2-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate **15g** (78 mg, 0.202 mmol), anisole (220 mg, 221 μL, 2.02 mmol) and $BF_3{\cdot}OEt_2$ (25 μL, 0.202 mmol). After 30 min at room temperature, 1-(4-chlorophenyl)-2,2-bis(4-methoxyphenyl)ethanone **16o** (53 mg, 0.144 mmol, 71% yield) was isolated as a yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **16o**: **IR** (thin film, cm^{-1}) 3053, 2986, 2838, 2305, 1684, 1608, 1587, 1509, 1464, 1441, 1421, 1302, 1207, 1178, 1093, 1033, 1000, 895, 814; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 4H), 6.87 (d, *J* = 8.8 Hz, 4H), 5.88 (s, 1H), 3.79 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.5, 158.8, 139.3, 135.3, 131.2, 130.3, 130.0, 128.9, 114.2, 57.9, 55.2; **TLC** (10% EtOAc/hexanes) R_f 0.15; **HRMS** (ESI) Calcd. for $C_{22}H_{19}ClO_3$+H 367.1101, Found 367.1109.

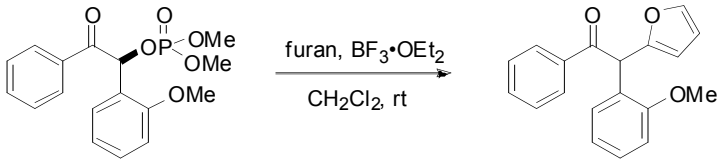


The preceding control experiment was performed according to General Procedure **A** using 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** (20 mg, 0.057 mmol), anisole (62 mg, 62 μL, 0.57 mmol) and dibutyl phosphoric acid (12 mg, 0.057 mmol) in lieu

of $BF_3 \cdot OEt_2$. After 22 hours at 80 ºC, the reaction mixture was concentrated in vacuo and 1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate **15a** was isolated in >98% recovery.



(*S*)-1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate ((+)-15a). The title compound was prepared according to previous published methods in our laboratory.[27] **(+)-15a** was isolated as a colorless oil in 40% yield from phenyl(triethylsilyl)methanone after flash chromatography with 40% ethyl acetate/hexanes and 69:31 e.r. as determined by chiral SFC analysis ((*S,S*)-Whelk-O1, 5.0% MeOH, 2.0 ml/min, 200 bar, 27ºC, 240 nm, $t_{r\text{-major}}$ 10.101 min, $t_{r\text{-minor}}$ 8.835 min). Analytical data for **(+)-15a** matched those previously reported.[3]



2-(furan-2-yl)-2-(2-methoxyphenyl)-1-phenylethanone (16e). The title compound was prepared according to General Procedure **A** using (*S*)-1-(2-methoxyphenyl)-2-oxo-2-phenylethyl dimethyl phosphate (+)-**15a** (100 mg, 0.285 mmol, e.r. 69:31), furan (194 mg, 0.207 mL, 2.85 mmol) and $BF_3 \cdot OEt_2$ (36 µL, 0.285 mmol) in CH_2Cl_2. After 10 hours at

room temperature, 2-(furan-2-yl)-2-(2-methoxyphenyl)-1-phenylethanone **16e** was isolated as a brown oil in 36% yield after flash chromatography with 10% ethyl acetate/hexanes and 50:50 e.r. as determined by chiral SFC analysis ((*S,S*)-Whelk-O1, 3.0% MeOH, 2.0 ml/min, 200 bar, 27ºC, 240 nm, $t_{r\text{-major}}$ 8.101 min, $t_{r\text{-minor}}$ 9.729 min).

1.6 References

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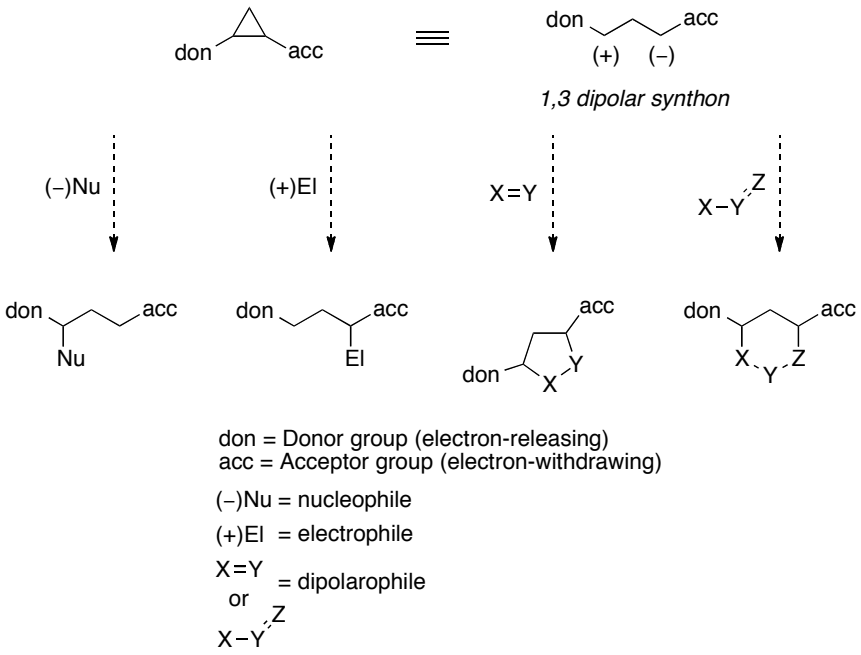
CHAPTER TWO
(3+2)-ANNULATION OF QUATERNARY DONOR-ACCEPTOR CYCLOPROPANES AND ALDEHYDES

2.1 Introduction

The synthesis of substituted heterocycles lies at the heart of organic chemistry. Heterocycles comprise the core of countless bioactive natural products and pharmaceutical targets; consequently, methods to their stereoselective preparation continue to attract the attention of research groups. Accessing heterocyclic building blocks in a stereodefined, one-step manner from readily available starting materials is a highly desirable synthetic goal. To this end, several laboratories have employed donor-acceptor (D-A) cyclopropanes in ring expansion reactions with various dipolarophiles.[3-6] Cyclopropanes are the simplest and most highly strained class of cycloalkanes. This inherent ring strain accounts for their high degree of reactivity. D-A cyclopropanes are a highly reactive subset of cyclopropane molecules capable of stabilizing both positive and negative charges upon heterolytic ring cleavage due to the presence of vicinal electron-donating and electron-withdrawing functional groups on the cyclopropane molecule. The D-A cyclopropane is thus viewed as a synthetic equivalent to an all-carbon 1,3-dipolar synthon capable of reacting with a nucleophiles, electrophiles, and dipolarophiles (Scheme 2.1).[7]

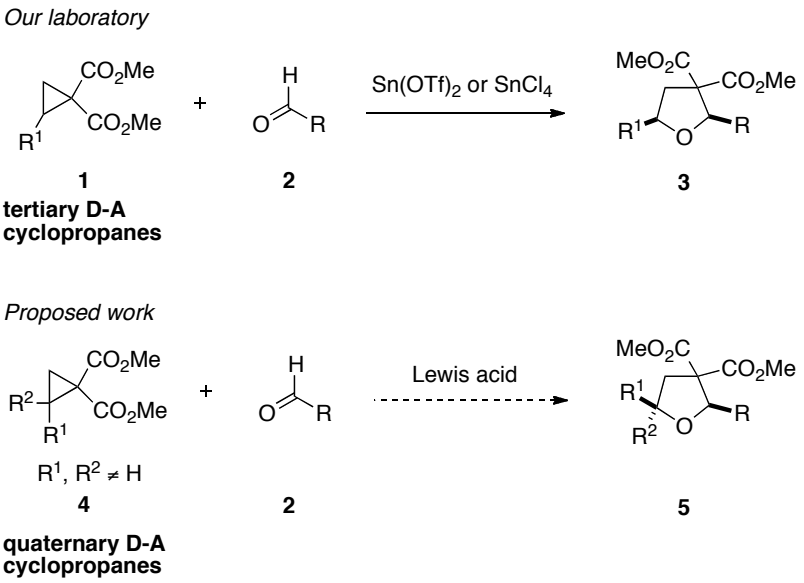
Scheme 2-1. D-A Cyclopropanes as 1,3-Dipolar Synthons



Our laboratory has published a highly diastereoselective synthesis of *cis*-2,5-dialkyl tetrahydrofurans *via* the Lewis acid-catalyzed (3+2)-annulation of D-A cyclopropanes and aldehyde dipolarophiles.[8] Reaction rates correlated with aldehyde nucleophilicity and the electronic stability of the carbenium ion at the donor site.[9] Accumulated experimental data were consistent with an unusual substitution mechanism in which the aldehyde acts as a nucleophile toward a configurationally stable intimate ion pair. The increased reaction rates observed with more electron-rich monosubstituted donor site cyclopropanes prompted us to investigate aldehydes and D-A cyclopropanes containing full substitution at the donor site. A second carbon substituent could serve to better stabilize the incipient carbenium ion generated under Lewis acidic conditions. Furthermore, whereas monosubstituted donor site D-A cyclopropanes **1** (tertiary D-A cyclopropanes) have been extensively studied in various annulation and substitution reactions, disubstituted donor site D-A cyclopropanes **4** (quaternary D-A cyclopropanes) have not been investigated to nearly the same degree.

Reactions with D-A cyclopropanes of this type and aldehydes could allow access to tetrahydrofuran building blocks of type **5** possessing a fully substituted stereocenter (Scheme 2-2). This chapter discusses the discovery and development of a Lewis acid-catalyzed diastereoselective (3+2)-annulation of quaternary D-A cyclopropanes and aldehydes. Results collected from chirality transfer experiments provide evidence for the same aldehyde nucleophilic attack mechanism that is observed with tertiary D-A cyclopropanes and aldehydes.

Scheme 2-2. (3+2)-Annulation with Tertiary D-A Cyclopropanes (top) and Proposal with Quaternary D-A Cyclopropanes (bottom)



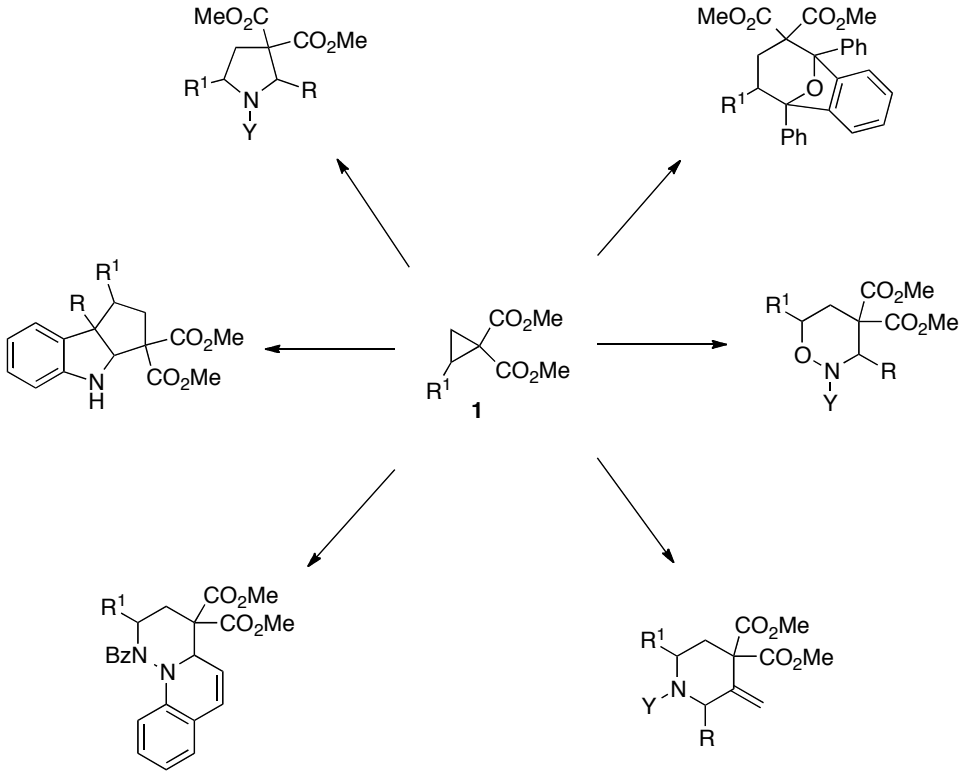
2.2 Background

2.2.1 Initial Discovery

The seminal work involving D-A cyclopropanes by Cram and Danishefsky harnessed the thermal instability of cyclopropane molecules to promote substitution reactions at the donor site by alcohol and amine nucleophiles, respectively.[10,11] Since these early studies, research groups have focused on using Lewis acids to activate D-A cyclopropanes. Lewis

acid activation of the acceptor groups allows for significantly lower temperatures to promote reactivity and renders D-A cyclopropanes electrophilic at the donor carbon and nucleophilic at the acceptor carbon. Kerr was the first to demonstrate the feasibility of this strategy in the synthesis of fused 5-membered carbocycles derived from D-A cyclopropanes and indole dipolarophiles.[12] Since this work, a number of research groups have utilized malonate-derived D-A cyclopropanes of type **1** as generic reagents for the synthesis of substituted carbocycles and heterocycles of varying size with Lewis acids (Scheme 2-3).[13-17]

Scheme 2-3. Some Reported Annulations with Type **1** D-A Cyclopropanes



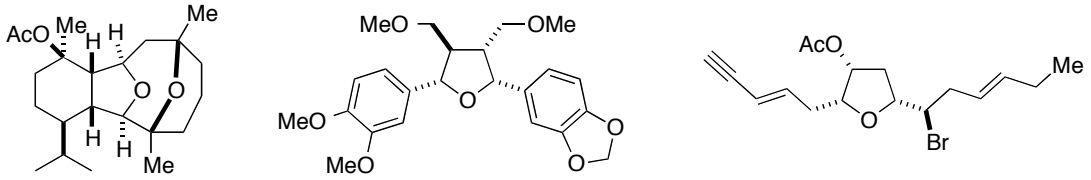
Malonate-derived D-A cyclopropanes are intriguing due to their ease of preparation, benchtop stability, and geminal diester functionality, which provides a source of two-point binding for Lewis acid activation and a functional handle for downstream synthetic manipulation. Knoevenagel condensation of dimethyl malonate and an aldehyde, followed

by Corey-Chaykovsky cyclopropanation with a sulfoxonium ylide provides the racemic cyclopropane 1,1-diester.[18]

2.2.2 Access to Tetrahydrofurans *via* D-A Cyclopropanes

Tetrahydrofurans are a targeted building block in synthesis due to their appearance in a number of natural products and medicinally relevant compounds (Figure 2-1).[1]

Figure 2-1. THF-Containing Natural Products

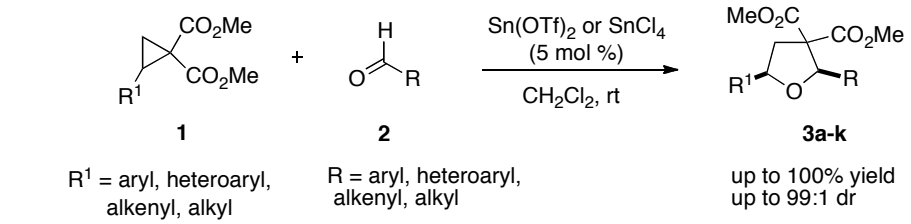


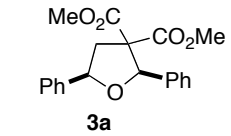
(+)-polyanthellin A (+)-virgatusin *trans*-kumausyne

As a consequence of their bioactivity, routes to stereodefined tetrahydrofurans have commanded the interest of a number of different research groups.[2] In this context, D-A cyclopropanes have served as an attractive class of reagents for the synthesis of substituted tetrahydrofuran (THF) derivatives, as shown by Reissig, Oshima, and Sugita.[19-21] These routes, however, display certain limitations. Reissig's method requires stoichiometric $TiCl_4$ to promote cyclopropyl ring cleavage and is limited to cyclopropanes bearing an oxygen atom at the donor site. Oshima's route requires a $TiCl_4/^nBu_4NI$ reaction promoter and an oxygen donor atom. Sugita has described the $SnCl_4$-catalyzed (3+2)-annulation of aldehydes and D-A cyclopropanes; again, this method requires a donor site oxygen atom. Extraneous steps to install the desired carbon substituent at the donor carbon after annulation *via* ionization/carbenium ion formation are necessary. Our laboratory saw a need for a one-step catalytic route to stereodefined tetrahydrofurans from simple aldehydes and malonate-derived D-A cyclopropanes containing carbon-based donor groups. Kerr had previously

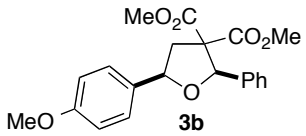
demonstrated that carbon-based donor groups were satisfactory donors in Lewis acid-catalyzed ring opening/cycloaddition reactions with indole and nitrone dipolarophiles.[12,13] Based on this precedent, our group evaluated malonate-derived D-A cyclopropanes of type **1** possessing carbon-based donor groups and aldehyde dipolarophiles in an effort to access 2,5-dialkyl tetrahydrofurans **3a-3k**. The results are summarized in Scheme 2-4.

Scheme 2-4. Results from the (3+2)-Annulation of Tertiary D-A Cyclopropanes and Aldehydes

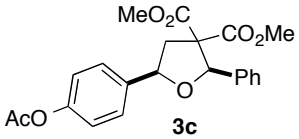




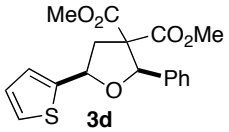
3a
100% yield
99:1 dr
(2.25 h)



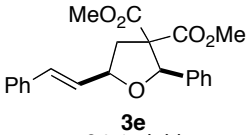
3b
85% yield
98:2 dr
(< 20 min)



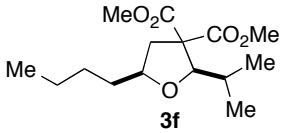
3c
91% yield
99:1 dr



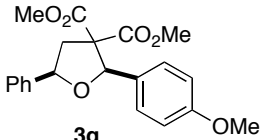
3d
97% yield
96:4 dr



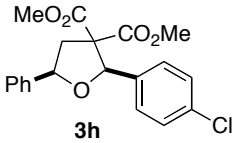
3e
94% yield
70:30 dr



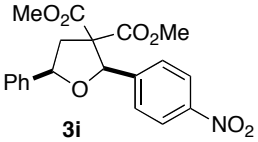
3f
77% yield
82:18 dr (30 mol % $SnCl_4$)



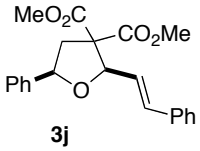
3g
99% yield
99:1 dr



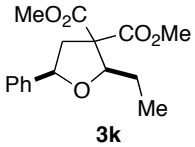
3h
97% yield
99:1 dr



3i
89% yield
95:5 dr (20 mol % $SnOTf_2$)



3j
97% yield
94:6 dr



3k
100% yield
97:3 dr (5 mol % $SnCl_4$)

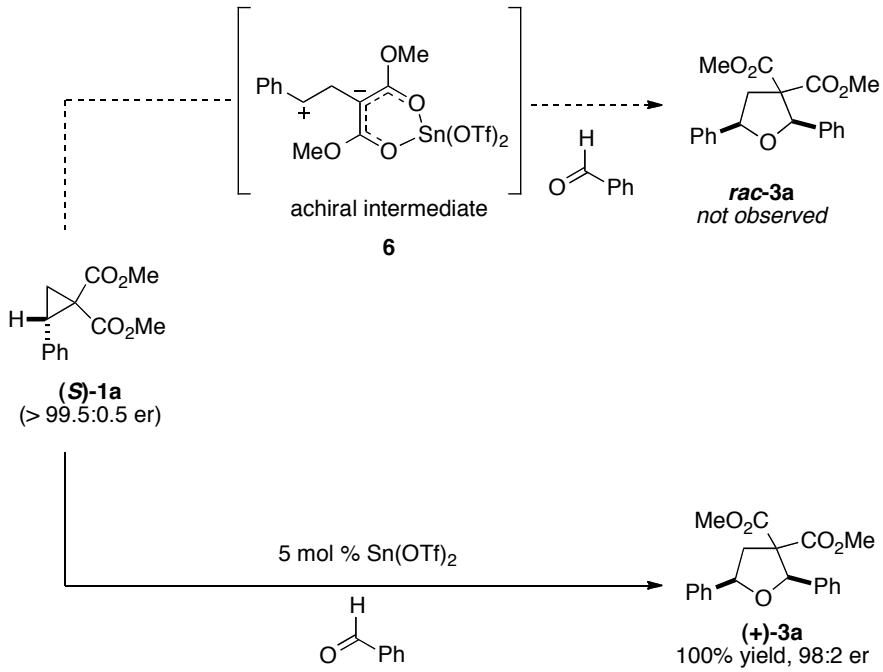
A number of Lewis acids were successful in catalyzing this transformation; $Sn(OTf)_2$ was optimal with regard to yield and *cis*-diastereoselectivity. The cyclopropane donor site was tolerant of aryl, heteroaryl, and alkenyl donor groups. Alkyl D-A cyclopropanes could also participate at higher temperatures and catalyst loadings, but lower yields and dr's were observed. A variety of aldehyde dipolarophiles were tolerated; yields were generally above 90% and products were in most cases isolated as a single diastereomer. Aliphatic aldehydes generally worked best by switching to $SnCl_4$ as the catalyst.[9]

2.2.3 Mechanistic Experiments with D-A Cyclopropanes

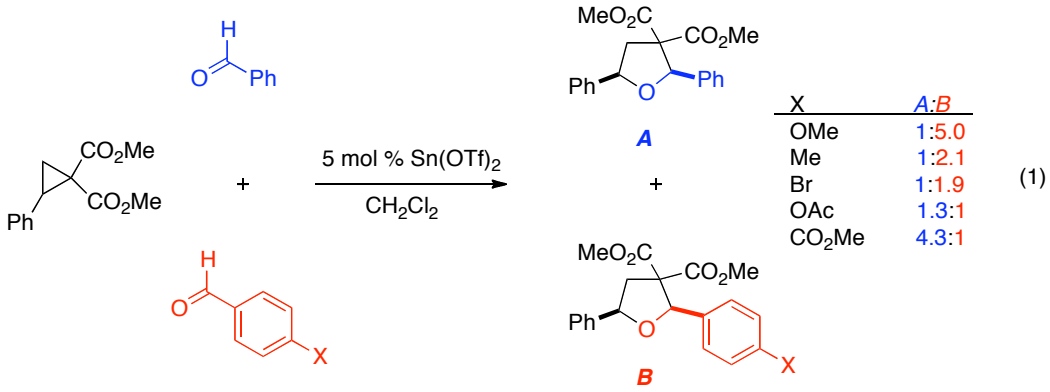
Reaction rates in the aldehyde/cyclopropane (3+2)-annulation correlated with the electron-releasing character of R^1 on D-A cyclopropane **1**. For example, when R^1 = phenyl, annulation with benzaldehyde was complete in 2.25 hours (**3a**); however, when R^1 = *p*-$OMeC_6H_4$, reaction with benzaldehyde was complete in under 20 minutes (**3b**). Based on these results, the authors envisioned the reaction proceeding through a ring-opened achiral 1,3-zwitterion (**6**, Scheme 2-5). Lewis acid activation of the diester would trigger vicinal C–C cyclopropane bond cleavage. Formal [3+2]-cycloaddition with an aldehyde at this juncture would reveal the 2,5-disubstituted tetrahydrofuran **3a** as a mixture of stereoisomers when optically active cyclopropane **(*S*)-1a** was used. Chirality transfer experiments proved this assumption incorrect. When enantioenriched **(*S*)-1a** (> 99.5:0.5 er) reacted with benzaldehyde under the standard conditions, the tetrahydrofuran product **(+)-3a** was isolated in 98:2 er. In order to help elucidate the mechanism of this process, determining the absolute configuration of the THF products **3** was necessary. The enantiospecific (3+2)-annulation was thus performed with **(*S*)-1a** and 4-Cl-benzaldehyde. THF product (+)-**3h** was isolated in 97% yield and 98:2 er. Single crystal X-ray diffraction analysis of a barbituric acid

derivative of **3h** revealed the product to be of (2*R*, 5*R*) absolute stereochemistry, indicating an inversion event had occurred at the donor site. The authors inferred from this set of results that any reaction through achiral 1,3-zwitterionic intermediate **6** was not significant.

Scheme 2-5. Experiments with Enantioenriched **(*S*)-1a** and Benzaldehyde



Competition experiments with electronically-diverse aldehydes revealed faster reaction rates when more electron-rich aldehydes were used. Conversely, when electron-neutral benzaldehyde was used in competition with more electron-poor aldehydes, product ratios favored tetrahydrofuran product derived from benzaldehyde (eq 1).

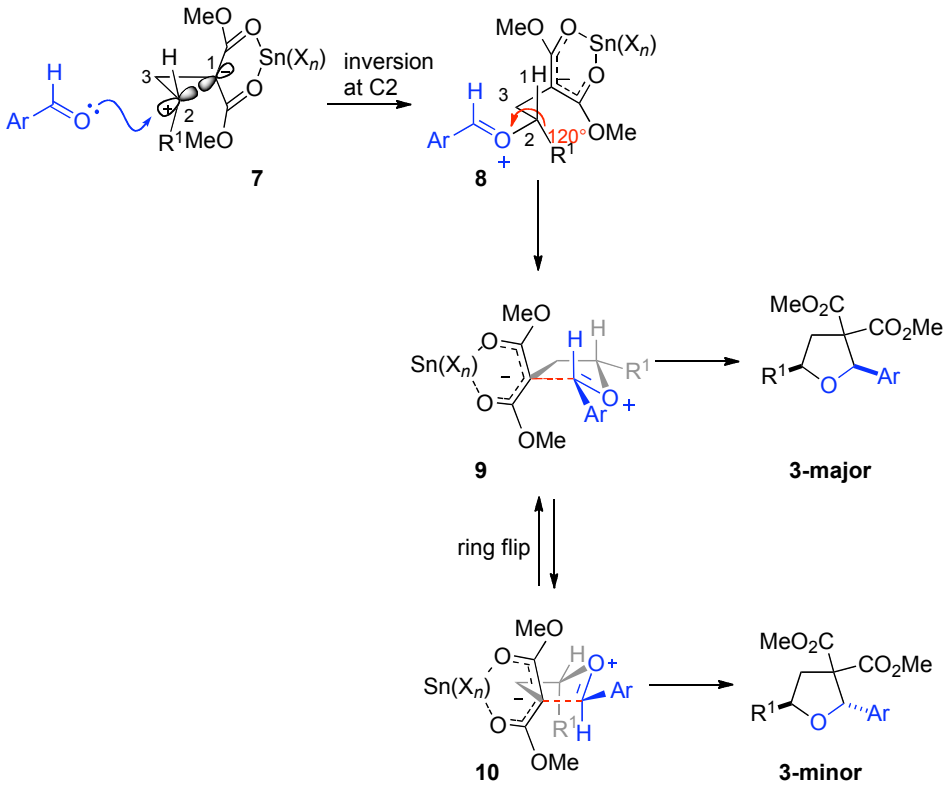


X	*A*:*B*
OMe	1:5.0
Me	1:2.1
Br	1:1.9
OAc	1.3:1
CO_2Me	4.3:1

(1)

Taken together, these data were consistent with an unusual substitution mechanism in which the aldehyde acts as a nucleophile toward a configurationally stable intimate ion pair (**7**, Scheme 2-6). A similar configurationally stable intimate ion pair has been proposed by Cram to account for the observed stereochemistry in the methanolysis of optically active cyano-ester cyclopropanes.[10] Attack by the more accessible *trans* aldehyde oxygen lone pair results in inversion of stereochemistry at C2 and (*E*)-oxocarbenium ion **8**. 120° Bond rotation provides envelope **9**, in which Ar and R^1 are positioned pseudoequatorially. Diastereoselective ring closure at this juncture provides the *cis*-THF product **3-major**. Ring-flip isomerization from envelope **9** to envelope **10**, which places R^1 in a pseudoaxial conformation with respect to Ar, presumably accounts for the minor *trans* diastereomer **3-minor**.

Scheme 2-6. Proposed Mechanism for (3+2)-Annulation with Aldehydes

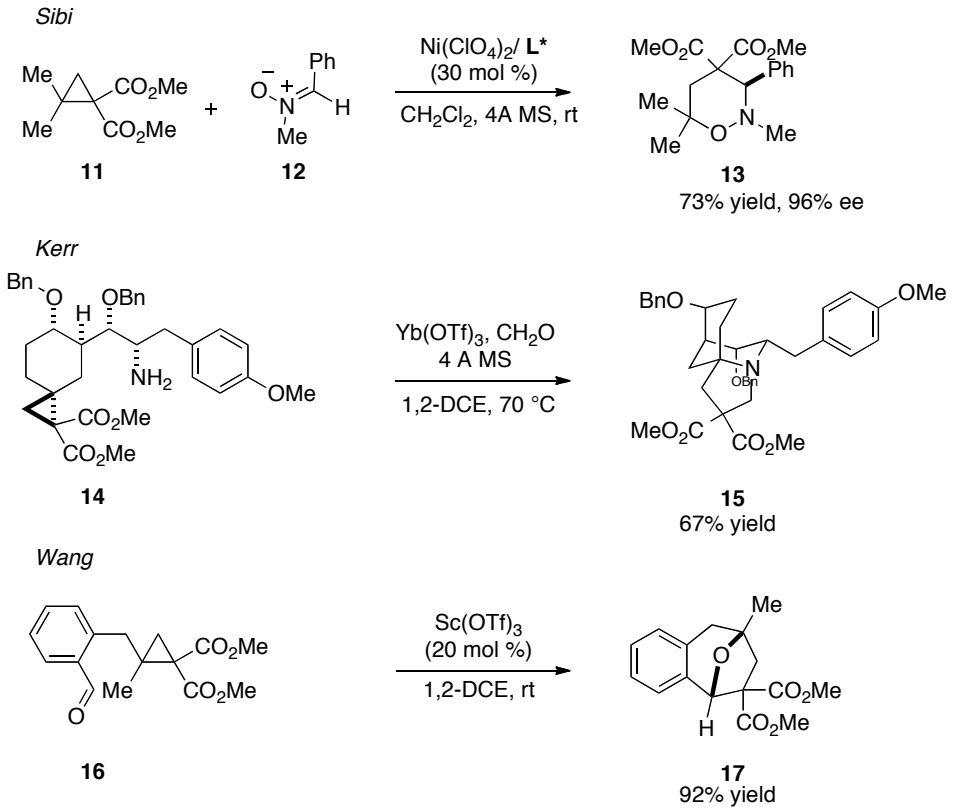


2.2.4 Extension to Quaternary Cyclopropanes

Aldehyde/D-A cyclopropane annulations worked best when the carbon-based donor group was aryl or alkenyl, but even alkyl donors were tolerated in promising yields and good diastereoselectivities (Scheme 2-4). Reaction rates correlated with electronic stability of the resultant carbenium ion at the donor site. Based on these results, we hypothesized that D-A cyclopropanes with full substitution at the donor site (quaternary cyclopropanes) would behave similarly in (3+2)-annulations with aldehydes. A second carbon substitutent should assist in carbenium ion stability. Aldehyde/quaternary D-A cyclopropane annulations would provide one-step access to 2,2,5-trialkyl tetrahydrofurans such as **5**. THF building blocks of this type are the core structures of a number of natural product scaffolds.[1] Furthermore, where tertiary D-A cyclopropanes **1** have been extensively studied in annulation reactions

with a myriad of dipolarophiles, annulations with quaternary D-A cyclopropanes of type **4** are limited to three independent examples (Scheme 2-7). Sibi has described the enantioselective (3+3)-annulation of D-A cyclopropanes and nitrone dipolarophiles using a chiral $Ni(ClO_4)_2$ catalyst.[22] Dimethylcyclopropane-1,1,-diester **11** reacted under the standard conditions to provide 1,2-oxazine **13** in 73% yield and 96% ee. Kerr has reported an intramolecular imine/D-A cyclopropane (3+2)-annulation as a key step in the total synthesis of the immunosuppressive alkaloid FR901483.[23] *In-situ* amine condensation onto formaldehyde and subsequent (3+2)-annulation with quaternary cyclopropane **14** proceeded in 67% yield. Wang has recently reported an intramolecular (3+2)-annulation of aldehydes and imines with D-A cyclopropanes.[24] Quaternary D-A cyclopropane **16**, upon treatment with 20 mol % $Sc(OTf)_3$, reacted to give cyclic ether **17** in 92% yield. Despite these independent reports, we contended that an extensive study of quaternary cyclopropanes was warranted.

Scheme 2-7. Previously Reported Annulations with Quaternary D-A Cyclopropanes



Increased reaction rates with quaternary D-A cyclopropanes and aldehydes would expand the scope of the (3+2)-annulation to more electronically diverse aldehydes and would provide access to more complex tetrahydofurans. However, we tempered our expectations by acknowledging three realistic reaction possibilities: 1) Increased steric hindrance at the donor site could counteract increased electronic stability with quaternary D-A cyclopropanes and slow the rates of aldehyde addition or change the mechanism of annulation entirely. 2) Changing the second substituent on the donor site from H to Me (or a larger *C*-donor group) could significantly curb levels of diastereoselection. The rationale for the high *cis*-diastereoselectivity in aldehyde annulations with tertiary D-A cyclopropanes is consistent with a lower energy (*E*)-carbenium ion **8** generated after aldehyde attack. A ring flip prior to an intramolecular aldol event presumably accounts for the minor diastereomer (Scheme 2-6).

A larger substituent could minimize the energy difference between envelopes **9** and **10** and accelerate equilibration. 3) Increased electronic stability at the donor site could accelerate C–C bond cleavage and lead to an erosion of enantiointegrity when optically active quaternary D-A cyclopropanes are used. This could make the transfer of stereochemical information in the (3+2)-annulation difficult.

This chapter discusses the Lewis acid-catalyzed (3+2)-annulation of quaternary D-A cyclopropanes and aldehyde dipolarophiles.[25] The cyclopropane and dipolarophile scope are both investigated. Experiments with enantioenriched quaternary D-A cyclopropanes help elucidate the mechanism for this transformation and demonstrate that chirality transfer from cyclopropane to THF product is possible when optically active quaternary D-A cyclopropanes are used.

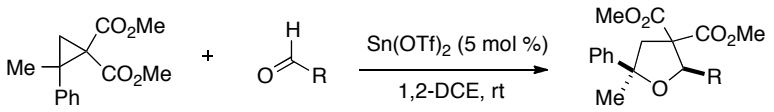
2.3 Results and Discussion

2.3.1 Initial Discovery and Aldehyde Scope

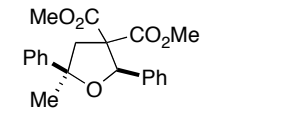
$Sn(OTf)_2$ gave outstanding yields and diastereoselectivities in the (3+2)-annulation of tertiary D-A cyclopropanes **1** and a variety of aldehydes of type **2**. Naturally, we began our investigations with this Lewis acid. Treating racemic dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate **4a** and benzaldehyde with $Sn(OTf)_2$ in 1,2-dichloroethane at 23 °C provided tetrahydrofuran **5a** in 91% yield and 97:3 diastereoselection; the illustrated diastereomer with the C2-and C5-phenyl groups in a *cis* orientation was preferred (Scheme 2-8). Cyclopropane **4a** was easily accessed *via* the $Rh_2(OAc)_4$-catalyzed cyclopropanation of α-methylstyrene and dimethylmalonate-derived iodonium ylide.[26] We next investigated different aldehydes in (3+2)-annulations with **4a**.

The reactions were tolerant of a range of electronically diverse aromatic aldehydes, with yields from 82 to 95%. Heteroaromatic (**5g**), α,β-unsaturated (**5h**), aliphatic (**5i**), and branched aliphatic aldehydes (**5j**) also performed well under identical reaction conditions. In addition to the high yields, we observed high levels of *cis*-diastereoselection that were competitive with the dr's found in the (3+2)-annulation of aldehydes and tertiary D-A cyclopropanes **1**, despite the steric difference between H and Me. Dr's were generally at or above 95:5 and as high as 99:1. As a solvent comparison, reaction with **4a** and 4-chlorobenzaldehyde was performed in both 1,2-DCE and CH_2Cl_2. The reaction worked well in both solvents but showed slightly superior yields in 1,2-DCE (91% compared to 85%). We thus proceeded to investigate the scope of this (3+2)-annulation in 1,2-DCE.

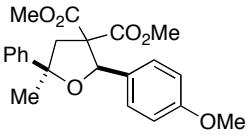
Scheme 2-8. Scope of Aldehydes in the (3+2)-Annulation with D-A Cyclopropane **4a**[a]



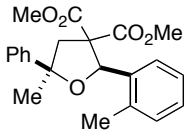
4a **2** **5a-j**



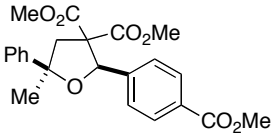
5a
91% yield,[b] 97:3 dr[c]



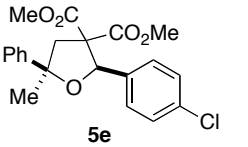
5b
95% yield, 96:4 dr



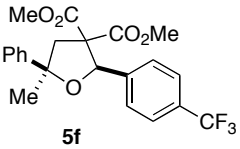
5c
94% yield, 97:3 dr



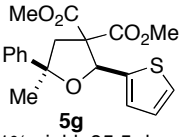
5d
93% yield, 99:1 dr



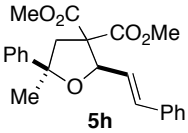
5e
91% yield, 95:5 dr (in 1,2-DCE)
85% yield, 95:5 dr (in CH_2Cl_2)



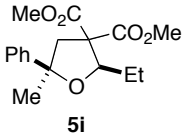
5f
82% yield, 99:1 dr



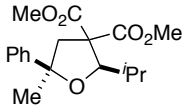
5g
91% yield, 95:5 dr



5h
87% yield, 92:8 dr



5i
83% yield, 96:4 dr



5j
82% yield, 96:4 dr

[a]Reaction conditions: **4a** (1.0 equiv), **2** (3.0 equiv), $Sn(OTf)_2$ (5 mol %), $[\mathbf{4a}]_0$ = 0.3 M in 1,2-DCE, 23 °C. [b]Refers to isolated yield after column chromatography. [c]Ratio was determined by NMR analysis of crude material.

2.3.2 Quaternary D-A Cyclopropane Synthesis and Scope

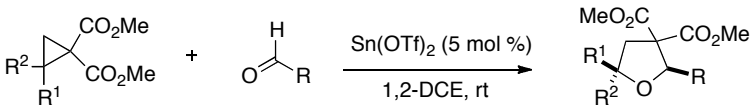
With the promising results observed with a broad selection of aldehydes and cyclopropane **4a**, we turned our attention to more sterically demanding and functionally useful cyclopropanes. Counter to the malonate-derived tertiary D-A cyclopropanes **1**, which were accessed *via* Corey-Chaykovsky cyclopropanation of the requisite alkylidene malonate, each quaternary D-A cyclopropane in the substrate scope was derived from a Rh(II)-

catalyzed cyclopropanation with either dimethyl diazomalonate or dimethylmalonate-derived iodonium ylide and the necessary 1,1-disubstituted alkene precursor. With the exception of phenyl-methyl cyclopropane **4a** and isopropenyl-methyl cyclopropane **4b**, the 1,1-disubstituted alkene precursors were not commercially available. The requisite alkenes were synthesized according to previously published methods.[27-29]

Quaternary D-A cyclopropanes **4b-4f** were examined under the annulation conditions with benzaldehyde, 4-chlorobenzaldehyde, and propanal as representative dipolarophiles. The results are summarized in Scheme 2-9. Annulations with isopropenyl-methyl cyclopropane **4b** proceeded with exceptionally high levels of *cis*-diastereoselection with each aldehyde employed. Slight modifications to the reaction conditions were necessary when propanal was used in conjunction with **4b**: 5 mol % $Hf(OTf)_4$ at -50 °C in CH_2Cl_2 provided **5m** in 64% yield and 99:1 dr. Reactions with phenyl-allyl cyclopropane **4c** proceeded in high yield and moderate dr with both benzaldehyde and 4-chlorobenzaldehyde (**5n**, **5o**). Again, diminished yields were observed with propanal (**5p**, 32%, dr 90:10), but more sterically hindered isobutyraldehyde provided desired THF product **5q** in 63% yield and 90:10 dr. We observed moderate diastereoselectivities in the (3+2)-annulation even when R^1 and R^2 were similar in size. Reactions with phenyl-benzyl cyclopropane **4d** proceeded in yields as high as 87% and roughly 80:20 dr with each aldehyde dipolarophile. Switching to 10 mol % $SnCl_4$ in toluene provided the optimal result for the reaction with propanal and **4d**. 4-CNC_6H_4-methyl cyclopropane **4e** was an excellent substrate for annulation, despite the electron-withdrawing nature of the para-cyano group. Yields were up to 90% and diastereoselectivities were at or above 95:5. These results demonstrate the broad electronic tolerance of the donor site on the quaternary cyclopropane. Electron-donating 4-$MeOC_6H_4$-

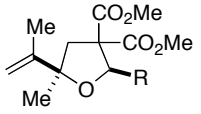
methyl cyclopropane **4f** was a particularly fast-reacting substrate in this study. Reactions with representative dipolarophiles proceeded in promising to high yields and high diastereoselection and were complete within 20 minutes (**5x-5z**). In the annulation with **4f** and benzaldehyde, the product diastereomer ratio eroded with extended reaction times. The dr was 96:4 after 20 minutes, 83:17 after 3.5 hours, and 1:1 after 24 hours. We attributed this stereochemical erosion to Lewis acid-catalyzed ring opening of the product tetrahydrofuran **5x**. Increased electronic stability at the donor site presumably allows for THF-ring opening in the presence of $Sn(OTf)_2$ (Scheme 2-10). Similar acid-catalyzed THF isomerizations have been observed by our group in the total synthesis of (+)-virgatusin.[30]

Scheme 2-9. Scope of Quaternary D-A Cyclopropanes with Representative Aldehydes[a]

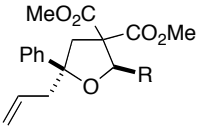


4b-4f **2** **5k-z**

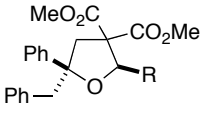
R^1 = isopropenyl, R^2 = Me (**4b**)
R^1 = Ph, R^2 = allyl (**4c**)
R^1 = Ph, R^2 = CH_2Ph (**4d**)
R^1 = 4-CNC_6H_4, R^2 = Me (**4e**)
R^1 = 4-$MeOC_6H_4$, R^2 = Me (**4f**)



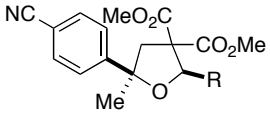
with **4b**
R = Ph (**5k**): 79% yield,[b] 96:4 dr[c]
R = 4-ClC_6H_4 (**5l**): 79% yield, 99:1 dr
R = Et (**5m**): 64% yield, 99:1 dr[d]



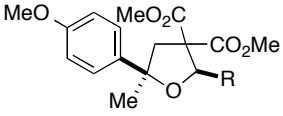
with **4c**
R = Ph (**5n**): 79% yield, 83:17 dr
R = 4-ClC_6H_4 (**5o**): 85% yield, 83:17 dr
R = Et (**5p**): 32% yield, 90:10 dr[e]
R = ^{i}Pr (**5q**): 63% yield, 90:10 dr



with **4d**
R = Ph (**5r**): 87% yield, 80:20 dr
R = 4-ClC_6H_4 (**5s**): 85% yield, 80:20 dr
R = Et (**5t**): 78% yield, 81:19 dr[e]



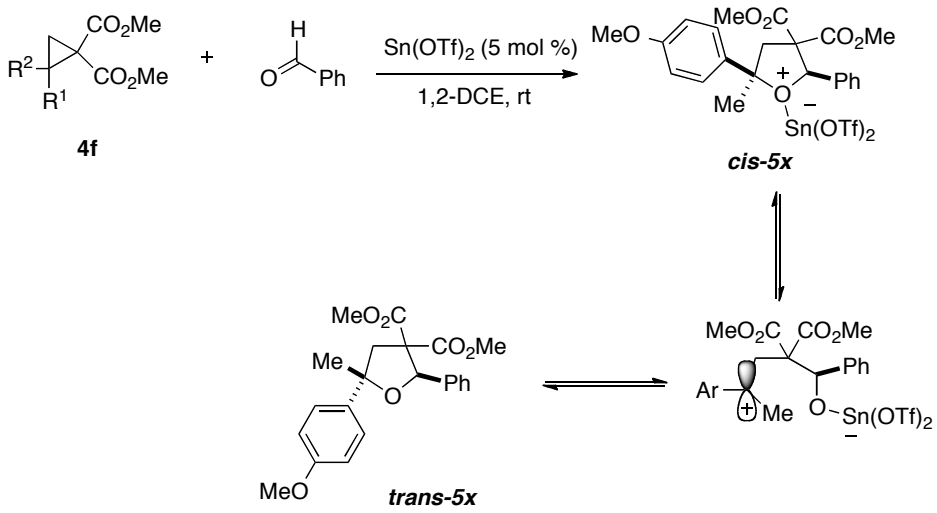
with **4e**
R = Ph (**5u**): 90% yield, 95:5 dr
R = 4-ClC_6H_4 (**5v**): 90% yield, 95:5 dr
R = Et (**5w**): 59% yield, 96:4 dr[e]



with **4f**
R = Ph (**5x**): 91% yield, 96:4 dr
R = 4-ClC_6H_4 (**5y**): 87% yield, 97:3 dr
R = Et (**5z**): 74% yield, 90:10 dr

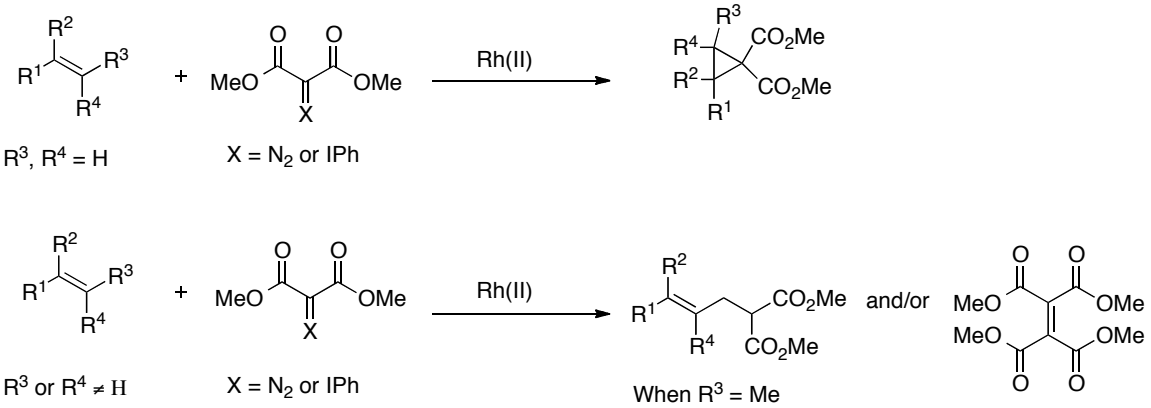
[a]Reaction conditions: **4b-f** (1.0 equiv), **2** (3.0 equiv), $Sn(OTf)_2$ (5 mol %), [**4b-f**]$_0$ = 0.3 M in 1,2-DCE, 23 °C. [b]Refers to isolated yield after column chromatography. [c]Ratio was determined by NMR analysis of crude material. [d]Reaction performed with 5 mol % $Hf(OTf)_4$ at -50 °C in CH_2Cl_2. [e]Reaction performed with 10 mol % $SnCl_4$ at 23 °C in toluene.

Scheme 2-10. Rationale for Stereochemical Erosion with **5x**



Accessing pentasubstituted D-A cyclopropanes proved to be a difficult challenge. Whereas intermolecular Rh(II)-catalyzed cyclopropanations with dimethyldiazomalonate or dimethyl malonate-derived iodonium ylide and 1,1-disubstituted alkenes proceeded in a straightforward manner, intermolecular cyclopropanations with more sterically hindered trisubstituted alkenes resulted in either no reaction, competitive C–H insertion, or malonate dimerization (Figure 2-2).

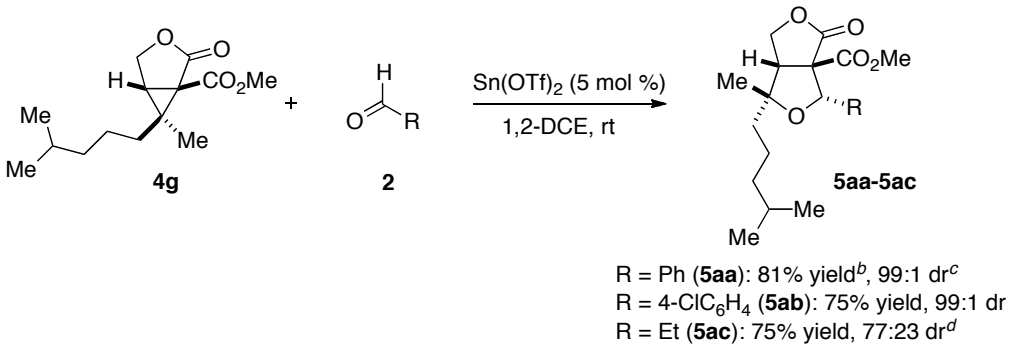
Figure 2-2. Intermolecular Cyclopropanations



A highly substituted cyclopropane was obtained, however, *via* intramolecular cyclopropanation of a trisubstituted alkene.[31] Geraniol-derived alkyl-alkyl lactone

cyclopropane **4g** emerged as an effective candidate for (3+2)-annulation. High yields and diastereoselectivities as high as 99:1 were observed with aromatic aldehydes, favoring the *endo* product. Diminished diastereocontrol was observed with propanal using 10 mol % $SnCl_4$ in 1,2-DCE; THF **5ac** was isolated in 75% yield and 77:23 dr. The diastereomers in **5ac** were separable by silica gel chromatography. This (3+2)-annulation can thus be extended to cyclopropanes of higher substitution and moderate donor ability (Scheme 2-11).

Scheme 2-11. Alkyl/Alkyl D-A Cyclopropane **4g** in the (3+2)-Annulation with Aldehydes

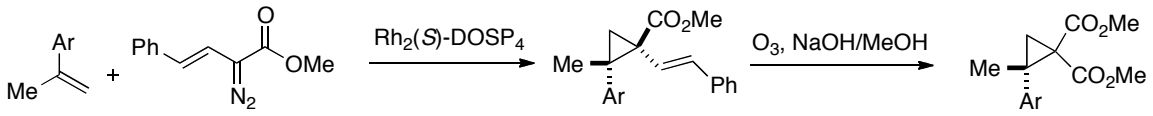


[a]Reaction conditions: **4g** (1.0 equiv), **2** (3.0 equiv), $Sn(OTf)_2$ (5 mol %), $[\mathbf{4g}]_0$ = 0.3 M in 1,2-DCE, 23 °C. [b]Refers to isolated yield after column chromatography. [c]Ratio was determined by NMR analysis of crude material. [d]Reaction performed with 10 mol % $SnCl_4$ at 23 °C in 1,2-DCE, diastereomers separable by column chromatography.

2.3.3 Chirality Transfer Experiments

In an effort to better understand the mechanism of this annulation, we synthesized optically active cyclopropane **(−)-4a** for chirality transfer studies. **(−)-4a** was accessed *via* a slightly modified Davies protocol.[32] The synthesis of **(−)-4a** is outlined in Scheme 2-12. α-Methylstyrene was treated with styryldiazoacetate and Rh_2(*S*)-$DOSP_4$ catalyst at -40 °C in pentanes. After 16 hours, phenyl-methyl styrylcyclopropane was isolated in 65% yield and 4:1 dr. Ozonolysis with NaOH/MeOH directly gave **(−)-4a** in 76:24 er as determined by SFC analysis.

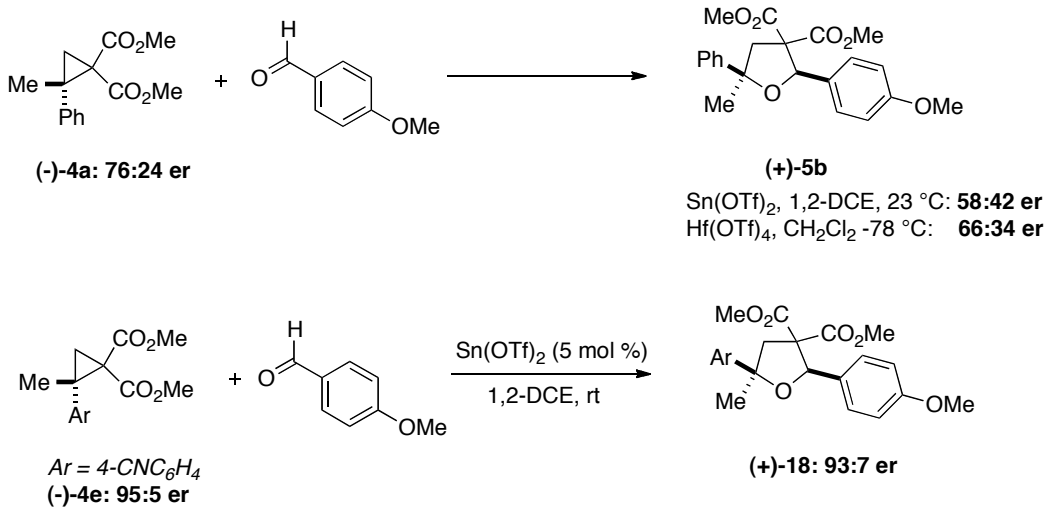
Scheme 2-12. Synthesis of Optically Active D-A Cyclopropanes **(–)-4a** and **(–)-4e**



(–)-4a: Ar = Ph: 42% yield over 2 steps, **76:24 er**
(–)-4e: Ar = 4-CNC_6H_4: 39% yield over 2 steps, **95:5 er**

(3+2)-annulation with **(–)-4a** and *p*-anisaldehyde under the standard reaction conditions outlined in Scheme 2-8 gave anisaldehyde-derived THF **(+)-5b** in 58:42 er. This result demonstrates that chirality transfer is possible in these annulations, but racemization of the starting cyclopropane is apparently competitive with alkylation at room temperature. Fortunately, lowering the reaction temperature to -78 °C and switching to the stronger Lewis acid $Hf(OTf)_4$ allowed for better transfer of stereochemical information. Under these conditions, THF **(+)-5b** was isolated in 66:34 er in less than 2 hours. The short reaction time at these low temperatures is a testament to the potent reactivity of quaternary D-A cyclopropanes. Using the more electron-withdrawing 4-CNC_6H_4-methyl cyclopropane **(–)-4e** in chirality transfer studies, complete transfer of stereochemical information was possible. **(–)-4e** was synthesized using the same modified Davies protocol. After ozonolysis of the styrylcyclopropane and treatment with NaOH/MeOH, **(–)-4e** was isolated in 39% yield over two steps and 95:5 er. Exposing **(–)-4e** to the standard reaction conditions $(SnOTf)_2$, 1,2-DCE, 23 °C) with anisaldehyde gave THF product **(+)-18** in 93:7 er (Scheme 2-13).

Scheme 2-13. Chirality Transfer Studies



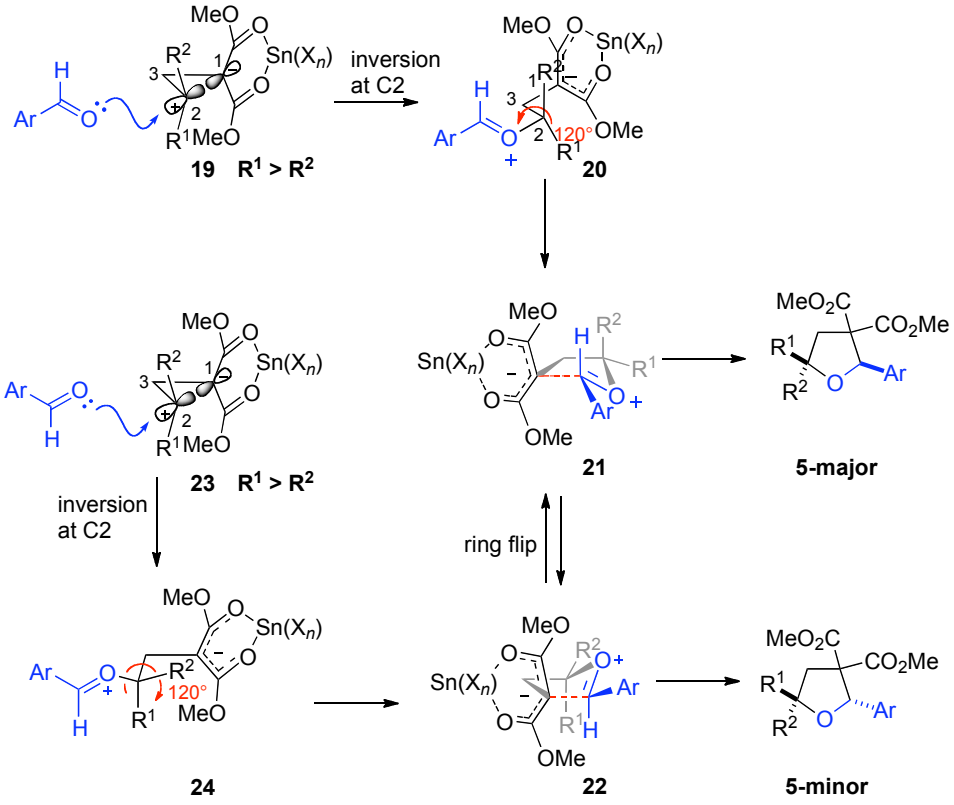
2.3.4 Mechanistic Rationale

Taken together, the results from the chirality transfer experiments are consistent with the same stereospecific nucleophilic substitution mechanism at a stabilized carbenium ion that is used to rationalize results in the (3+2)-annulation of type **1** D-A cyclopropanes and aldehydes. More electron-releasing donor site cyclopropanes can still participate with a partial transfer of stereochemical information but low temperatures are required to curb cyclopropane racemization.

A similar model to those previously proposed for this reaction family can be used to rationalize the observed diastereoselectivity in this reaction. Initial nucleophilic attack by an aldehyde results in inversion of stereochemical configuration at the donor site and a ring-opened zwitterionic species (**20**, Scheme 2-14). The aldehyde presumably attacks through the more accessible *trans* lone pair to form a lower energy (*E*)-oxocarbenium ion in which $A_{1,3}$strain is minimized. 120° bond rotation about the C2-C3 bond places the zwitterion in an envelope transition state in which the Ar group in the aldehyde and the larger R^1 group on the cyclopropane are positioned pseudoequatorially. Intramolecular aldolization at this stage

provides the *cis*-tetrahydrofuran product **5-major**. A ring flip prior to intramolecular aldol addition, which places the larger R^1 group in a pseudoaxial position on the envelope (**22**), presumably accounts for the minor *trans*-diastereomer and is consistent with experimental observations. As R^1 and R^2 grow similar in size (cyclopropanes **4c** and **4e**), the energy difference between envelope **21** and envelope **22** decreases and ring flip becomes more facile. An alternative but equally plausible mechanism involves a 180 °C reversal in aldehyde approach in the first step. Attack at the stabilized donor site would provide (*E*)-oxocarbenium ion **24**. 120° Bond rotation would provide a direct route to envelope **22**.

Scheme 2-14. Mechanistic Rationale for the (3+2)-Annulation with Type **4** D-A Cyclopropanes



2.3.5 Reflections on Results

Having observed the behavior of quaternary D-A cyclopropanes in (3+2)-annulations with aldehydes, we looked back to the three plausible reaction outcomes that were raised before this study began (Section 2.2.4). The first prediction was that steric crowding at the donor site might counteract increased electronic stability and slow the rate of annulation or change the mechanism of annulation entirely. This hypothesis was proven false. We observed very high yields with cyclopropanes **4a-4g** and the majority of aldehydes. Results from chirality transfer experiments with optically active **(−)-4a** and **(−)-4e** were consistent with the same aldehyde nucleophilic substitution mechanism. The second prediction was that the diastereoselectivity in the (3+2)-annulation would decrease as the donor site substituents grew more similar in size. This hypothesis was correct but dependent on the cyclopropane in question. We observed only moderate diastereoselectivities with phenyl-allyl cyclopropane **4c** and phenyl-benzyl cyclopropane **4d**. Remarkably, however, aryl/methyl D-A cyclopropanes **4a**, **4e**, and **4f** and isopropenyl-methyl D-A cyclopropane **4b** exhibited very high diasteroselectivities that were competitive with the dr's recorded for tertiary D-A cyclopropane/aldehyde annulations. The third prediction was that increased electronic stability at the donor site would accelerate C–C bond cleavage and make chirality transfer in the (3+2)-annulation with optically active D-A cyclopropanes difficult. This hypothesis was proven true. Optically active phenyl-methyl cyclopropane **(−)-4a** reacted with an unsatisfactory transfer of stereochemical information under the standard reaction conditions with anisaldehyde. Lowering the temperature to -78 °C and switching to a more reactive $Hf(OTf)_4$ catalyst improved this result, but complete chirality transfer still did not occur. However, when the more electron-deficient 4-CNC_6H_4-methyl cyclopropane **(−)-4e**

was employed with anisaldehyde, nearly complete transfer of stereochemical information was possible under the standard reaction conditions. This result is consistent with a slower rate of cyclopropane equilibration due to the electron-withdrawing nature of the *para*-cyano group.

2.4 Conclusions

We have investigated D-A cyclopropanes with full substitution at the donor site in annulation reactions with aldehyde dipolarophiles. Quaternary D-A cyclopropanes **4** display excellent reactivity with aldehydes under conditions nearly identical to those developed for the (3+2)-annulation with tertiary D-A cyclopropanes. Yields are generally above 80% and diastereoselectivities range from moderate to very high depending on the identity of the donor substituents. The reaction displays broad aldehyde tolerance; aliphatic aldehydes generally require a switch from the standard $Sn(OTf)_2$/1,2-DCE system to a $SnCl_4$/toluene system to minimize aldehyde decomposition. Aryl/alkyl, alkenyl/alkyl, and alkyl/alkyl donor site combinations are tolerated on the cyclopropane. Chirality transfer studies demonstrate that a transfer of stereochemical information in the annulation is possible when optically active D-A cyclopropanes are used. Results lend further support for a stereospecific aldehyde nucleophilic attack mechanism at the electronically stabilized donor site to be operative.

2.5 Experimental

Methods. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and

^{13}C NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 100 or 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralcel WO and Chiralpak AD column. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical chiral stationary phase HPLC was performed on an Agilent Technologies 1200 System equipped with a Chiralpak IA column at constant flow (1.00 mL/min). Preparative HPLC was performed on a Varian ProStar LC instrument equipped with a Berger Instruments Cyano 60A 6u column, 150x21.2 mm. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution ($KMnO_4$), or aqueous ceric ammonium molybdate solution (CAM) followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63 μm) purchased from Silicycle. Ozonolyses were performed with O_3 produced by a Yanco Industries Ozone Services model OL80B ozonator. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomer ratios (dr's) are reported herein for a specific experiment and as a result may differ slightly from those found in the manuscript's tables, which are averages of at least two experiments. The diastereomer ratios reported are for crude reaction mixtures, and may differ slightly from the attached

spectra. Melting points were determined on a Thomas Hoover uni-melt apparatus, and are uncorrected.

Materials. Dichloromethane (DCM) and tetrahydrofuran (THF) were dried by passage through a column of neutral alumina under nitrogen prior to use, and 1,2-dichloroethane (DCE) and acetonitrile were distilled from calcium hydride under N_2 prior to use. The following compounds were prepared according to literature procedures: Bis(methoxycarbonyl)(phenyliodinio) methanide,[33] dimethyldiazomalonate,[34] 4-methoxy-α-methylstyrene,[27] 4-isopropenyl benzonitrile,[28] α-allylstyrene,[29] methyl malonyl chloride,[35] *p*-acetamidobenzenesulfonyl azide (*p*ABSA),[36] copper(II) bis(*t*-butyl-salicylimine),[31] and methyl styryldiazoacetate.[37] Aldehydes used in annulation reactions had been distilled and were stored in an inert atmosphere glovebox. All other reagents and solvents were obtained from commercial sources and used without further purification unless otherwise noted.

Preparation of Cyclopropanes, General Procedure A:

The cyclopropane dicarboxylates were prepared by carbene transfer via $Rh_2(OAc)_4$-catalyzed decomposition of the iodonium ylide- / diazo-malonate precursor. In reactions using dimethyldiazomalonate, precautions were taken to vent the pressure built up from N_2 evolution.

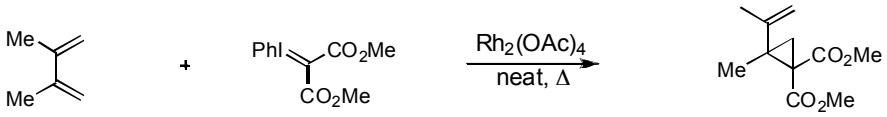
A fine suspension of $Rh_2(OAc)_4$ (0.012 g, 0.0277 mmol, 0.01 equiv.), alkene (1.0 g, 6.93 mmol, 2.5 equiv) and dimethyldiazomalonate (0.439 g, 2.77 mmol, 1.0 equiv) was made in a flame dried reaction tube in toluene (2 mL) and placed under a stream of nitrogen. A large-

bore needle was inserted through the septum to vent the vigorous evolution of nitrogen. The reaction was placed in a 120 ºC sand bath and stirred. After the evolution of nitrogen slowed, the mixture was stirred for an additional 30 min, then cooled to room temperature and filtered through a Monstr-Pette plug of Celite (3 cm), rinsing with Et_2O. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography using an hexanes flush followed by the indicated eluent system.

Dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (4a).

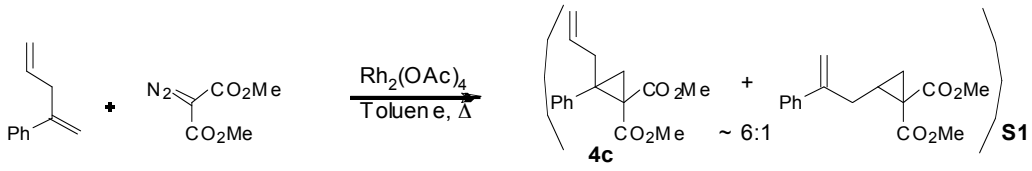
The title compound was prepared according to literature procedure.[26] The spectral data were in accordance with those reported.

Dimethyl 2-methyl-2-(prop-1-en-2-yl)cyclopropane-1,1-dicarboxylate (4b).



The title compound was prepared according to literature procedure.[26] The spectral data were in accordance with those reported.

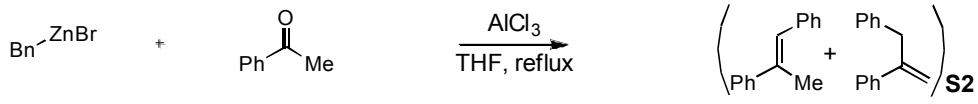
Dimethyl 2-allyl-2-phenylcyclopropane-1,1-dicarboxylate (4c).



The title compound was prepared according to General Procedure A using $Rh_2(OAc)_4$ (0.012 g, 0.0277 mmol, 0.01 equiv.), α-allylstyrene (1.0 g, 6.93 mmol, 2.5 equiv),

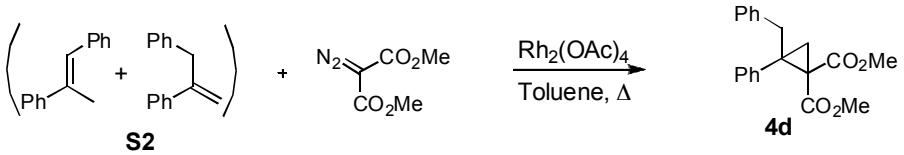
dimethyldiazomalonate (0.439 g, 2.77 mmol, 1.0 equiv) and 2 mL of toluene. After workup, the residue was purified by flash chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.537 g (70%) of **S1** as a colorless oil in an 86:14 inseparable mixture of desired cyclopropane **4c** to undesired isomer. The mixture **S1** was used in annulation reactions as such, with no apparent deleterious effects. Analytical data for **4c**: **IR** (thin film, cm^{-1}): 3027, 2952, 2359, 1736, 1436, 1275, 1224, 1126; **^{1}H NMR** (600 MHz, $CDCl_3$): major isomer **4c**: δ 7.31 - 7.22 (m, 5H), 5.65 - 5.58 (ddt, *J* = 17, 10.2, 6.6 Hz, 1H), 4.94 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.91 (dd, *J* = 17, 1.2 Hz, 1H), 3.86 (s, 3H), 3.50 (s, 3H), 2.82 (dd *J* = 14.4, 6.6 Hz, 1H), 2.22 (d, 5.4 Hz, 1H), 2.20 (dd *J* = 14.4, 6.6 Hz, 1H), 1.75 (d, *J* = 5.4 Hz, 1H); minor isomer: δ 7.40 (d, *J* = 7.2 Hz, 1H), 7.35 (t *J* = 7.2 Hz, 1H), 7. 22 (t *J* = 7.2 Hz, 1H), 5.36 (s, 1H), 5.20 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2. 75 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.39 (dd, *J* = 16.2, 8.0 Hz, 1H), 2. 15 (m, 1H), 1.51 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.48 (dd, *J* = 9.0, 4.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): major isomer **4c**: δ 168.7, 167.7, 138.7, 134.2, 129.2, 127.9, 127.1, 117.4, 52.7, 52.1, 41.8, 41.4, 40.4, 23.5; minor isomer: δ 170.5, 168.6, 146.1, 140.9, 128.3, 127.5, 126.0, 113.1, 52.7, 52.1, 33.8, 33.7, 26.9, 21.3; **TLC** (20 % EtOAc/hexanes), R_f 0.33 (CAM); **LRMS** (ESI): Calcd. for $C_{16}H_{18}O_4$+Cs: 407.0, Found: 407.0.

Dimethyl 2-benzyl-2-phenylcyclopropane-1,1-dicarboxylate (4d).



The reaction of benzylzinc bromide with acetophenone was carried out via a modification of the literature procedure.[38] In a glove box, a dry 50 mL round-bottomed flask was charged with Zn dust (1.96 g, 30 mmol, 3.0 equiv) and placed under nitrogen. Dry THF was added

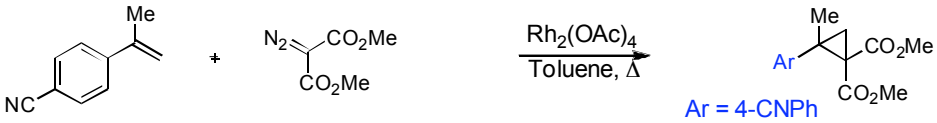
(10 mL) and the suspension was cooled to 0 ºC with vigorous stirring. The Zn dust was activated by a dropwise addition of Br_2 (0.15 mL, 3 mmol, 0.10 equiv). Once the brown color of the solution had dissipated, benzyl bromide (1.78 mL, 15 mmol, 1.5 equiv) was added dropwise and the reaction was stirred for 1 h at 0 ºC. The reaction mixture was warmed to room temperature and allowed to stand for 30 min. The benzylzinc bromide solution was then transferred to a 0 ºC suspension of $AlCl_3$ (4.0 g, 30 mmol, 3.0 equiv) and acetophenone (1.17 mL, 10 mmol, 1.0 equiv) in THF (30 mL) via cannula. After the transfer was complete, the reaction was heated at reflux overnight (12 h). The reaction was then cooled to room temperature and quenched with saturated aqueous NH_4Cl solution , followed by dilution with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl solution, dried with $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash chromatography (100% hexanes) to afford 1.81 g (93%) of **S2** as a white solid in a 2:1 mixture of *trans*-(α-methyl)-stilbene and α-benzylstyrene. The mixture **S2** was used in cyclopropanation reactions with no apparent deleterious effects.



The title compound **4d** was prepared according to General Procedure A using mixture **S2** (1.81 g, 9.3 mmol, 2.5 equiv), dimethyldiazomalonate (0.589 g, 3.73 mmol, 1.0 equiv), and $Rh_2(OAc)_4$ (0.016 g, 0.0373 mmol, 0.01 equiv) in 2 mL toluene. The trisubstituted olefin was completely unreactive and easily separated from the product cyclopropane by flash chromatography (hexanes flush followed by 10 % EtOAc/hexanes). Purification afforded

480 mg (48% based on amount of α-benzylstyrene in the starting mixture) of cyclopropane **4d** as waxy solid. Analytical data for **4d**: **IR** (thin film, cm^{-1}): 3029, 2952, 2844, 1731, 1604, 1496, 1435, 1226, 1125, 896, 753, 703; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.17 - 7.05 (m, 8H), 6.81 (m, 2H), 3.90 (s, 3H), 3.36 (d, *J* = 13.2 Hz), 3.33 (s, 3H), 2.75 (d, *J* = 13.2 Hz, 1H), 2.22 (d, *J* = 4.8 Hz, 1H), 1.99 (d, *J* = 4.8 Hz, 1H) ; **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.8, 167.6, 138.4, 137.9, 129.4, 129.3, 127.8, 127.7, 127.0, 126.3, 52.7, 52.1, 43.3, 42.6, 40.5, 23.6; **TLC** (20 % EtOAc/hexanes), R_f 0.31 (CAM); **LRMS** (ESI): Calcd. for $C_{20}H_{20}O_4$+Cs: 457.0, Found: 457.0.

Dimethyl 2-(4-cyanophenyl)-2-methylcyclopropane-1,1-dicarboxylate (4e).



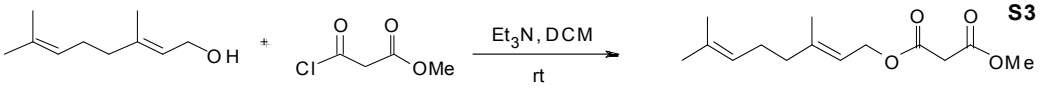
The title compound was prepared according to General Procedure A using 4-isopropenylbenzonitrile (0.695 g, 4.85 mmol, 2.5 equiv), dimethyldiazomalonate (0.307 g, 1.94 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.009 g, 0.0194 mmol, 0.01 equiv) in 2 mL toluene. After workup, the residue was purified by flash chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.243 g (45%) of cyclopropane **4e** as a pale yellow oil. Analytical data for **4e**: **IR** (thin film, cm^{-1}): 3004, 2954, 2846, 2228, 1731, 1608, 1508, 1436, 1269, 1234, 1128, 1103, 898, 844, 736; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 3.41 (s, 3H), 2.15 (d, *J* = 5.2 Hz), 1.75 (d, *J* = 5.2 Hz, 1H), 1.48 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.1, 167.8, 146.6, 132.1, 129.1, 118.7, 111.0, 52.8, 52.4, 40.3, 37.2, 24.9, 24.1; **TLC** (20 % EtOAc/hexanes), R_f 0.30 (UV; CAM when highly concentrated); **LRMS** (ESI): Calcd. for $C_{15}H_{15}NO_4$+Na: 296.1, Found: 296.1.

Dimethyl 2-(4-methoxyphenyl)-2-methylcyclopropane-1,1-dicarboxylate (4f).

The title compound was prepared according to General Procedure A using 4-methoxy-α-methylstyrene (1.5 g, 10 mmol, 2.5 equiv), dimethyldiazomalonate (0.632 g, 4 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.018 g, 0.40 mmol, 0.01 equiv) in 2 mL toluene. After workup, the residue was purified by flash chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.600 g (54%) of cyclopropane **4f** as a colorless oil. Analytical data for **4f**: **IR** (thin film, cm^{-1}): 3002, 2954, 2839, 1733, 1613, 1517, 1436, 1249, 1179, 1128, 1103, 1033, 896, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.36 (s, 3H), 2.19 (d, *J* = 5.2 Hz, 1H), 1.68 (d, *J* = 5.2 Hz, 1H), 1.50 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.9, 168.0, 158.4, 133.0, 129.3, 113.5, 55.1, 52.6, 52.1, 40.5, 37.6, 24.9, 24.2; **TLC** (20 % EtOAc/hexanes), R_f 0.22 (CAM); **LRMS** (ESI): Calcd. for $C_{15}H_{18}O_5$+Na: 301.1, Found: 301.1.

Preparation of methyl 6-methyl-6-(4-methylpentyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (4g):

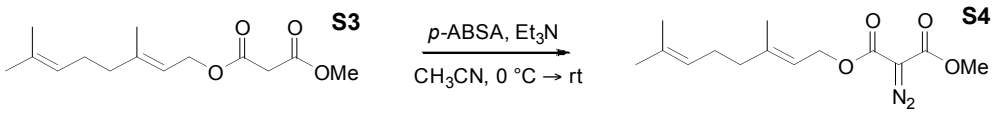
Methyl geranyl malonate (S3).



To a 0 ºC solution of geraniol (0.250 g, 1.62 mmol, 1.0 equiv) and methyl malonyl chloride (0.221 g, 1.70 mmol, 1.05 equiv) in dichloromethane (6 mL) under nitrogen was added triethylamine (0.172 g, 0.24 mL, 1.70 mmol, 1.05 equiv) over 5 min. The reaction was allowed to warm to room temperature and stirred overnight (12 h). Upon complete

consumption of starting material as indicated by TLC analysis, the reaction was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2x). The combined organic layers were washed with water (2x) and saturated aqueous NaCl solution, then combined, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford 0.360 g (83%) of **S3** as a yellow oil. Analytical data for **S3**: **IR** (thin film, cm^{-1}): 2955, 2923, 2857, 1737, 1670, 1438, 1412, 1378, 1331, 1275, 1200, 1149, 979; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.33 (t, J = 6.8 Hz, 1H), 5.06 (t, J = 6.0 Hz, 1H), 4.65 (d, J = 7.2 Hz, 2H), 3.73 (s, 3H), 3.37 (s, 3H), 2.09-2.03 (m, 4H), 1.69 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.9, 166.4, 142.9, 131.7, 123.7, 117.7, 62.3, 52.3, 41.3, 39.5, 26.2, 25.6, 17.6, 16.4; **TLC** (20 % EtOAc/hexanes), R_f 0.48; **LRMS** (ESI): Calcd. for $C_{14}H_{22}O_4$+Cs: 387.1 , found: 387.1.

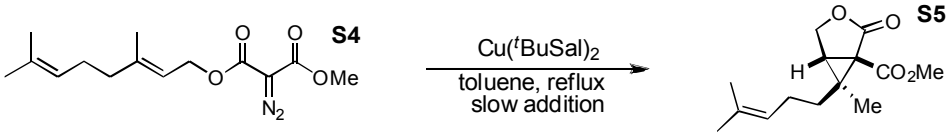
Methyl geranyl diazomalonate (S4).



To a 0 ºC solution of **S3** (0.360 g, 1.42 mmol, 1.0 equiv) in dry acetonitrile (14 mL) was added *p*-ABSA (0.389 g, 1.49 mmol, 1.05 equiv). Triethylamine (0.287 g, 0.40 mL, 2.83 mmol, 2.0 equiv) was added, and the reaction was allowed to warm to room temperature while stirring overnight. Upon complete consumption of starting material as indicated by TLC analysis, the reaction was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2x) The combined organic layers were washed with water (2x) and saturated aqueous NaCl solution, then combined, dried with $MgSO_4$ and concentrated *in vacuo*. The residue

was purified by flash chromatography (10 % EtOAc/hexanes) to afford 0.364 g (91%) of **S4** as a yellow oil. Analytical data for **S4**: **IR** (thin film, cm^{-1}): 2921, 2136, 1763, 1739, 1694, 1438, 1322, 1180, 1079, 761; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.34 (t, *J* = 6.4 Hz, 1H), 5.05 (t, *J* = 6.4 Hz, 1H), 4.73 (d, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 2.09-2.02 (m, 4H), 1.70 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.5, 160.7, 143.1, 131.7, 123.6, 117.8, 62.3, 53.5, 52.3, 39.5, 26.2, 25.5, 17.5, 16.4; **TLC** (10 % EtOAc/hexanes), R_f 0.20; **LRMS** (ESI): Calcd. for $C_{14}H_{20}N_2O_4$+Cs: 413.0 , found: 413.0.

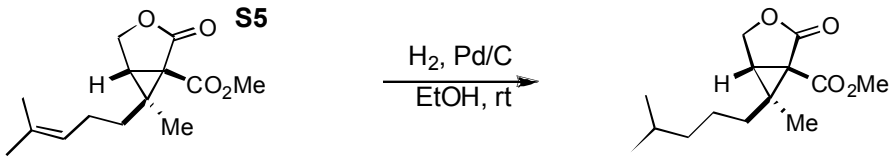
Methyl 6-methyl-6-(4-methylpent-3-en-1-yl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (S5).



To a refluxing solution of copper(II) bis(*t*-butyl-salicylimine) (0.057 g, 0.137 mmol, 0.05 equiv) in toluene (68 mL) was added a solution of **S4** (0.770 g, 2.74 mmol, 1.0 equiv) in toluene (25 mL) over 20 hours via syringe pump. Upon completion of addition, the reaction was heated at reflux for an additional 2 hours, at which point TLC analysis indicated complete consumption of **S4**. The reaction was concentrated *in vacuo* and the residue was purified via flash chromatography (20 % EtOAc/hexanes) to afford 0.555 g (80%) of cyclopropane **S5** as a yellow solid. Analytical data for **S5:** mp 39-40 ºC; **IR** (thin film, cm^{-1}): 2869, 2256, 1771, 1439, 1391, 1366, 1228, 1084, 1063, 800, 625; **^{1}H NMR** (400 MHz, $CDCl_3$): δ5.00 (t, *J* = 6.8 Hz, 1H), 4.39 (dd, *J* = 10 Hz, *J* = 5.6 Hz, 1H), 4.09 (d, *J* = 10 Hz, 1H), 3.79 (s, 3H), 2.57 (d, *J* = 5.2 Hz, 1H), 2.11-1.96 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.54-1.49 (m, 2H), 1.25 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.9, 166.5, 132.4, 122.9, 64.7, 52.6, 40.9, 35.7, 34.6, 34.5, 25.6, 24.9, 17.7, 12.9; **TLC** (20 % EtOAc/hexanes), R_f

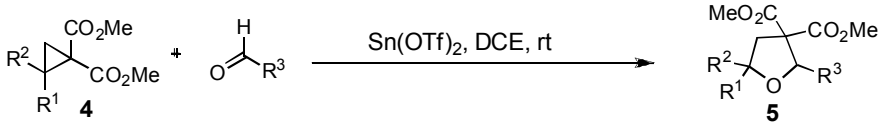
0.19; **LRMS** (ESI): Calcd. for $C_{14}H_{20}O_4$+Cs: 385.0 , found: 385.0.

Methyl 6-methyl-6-(4-methylpentyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (4g).



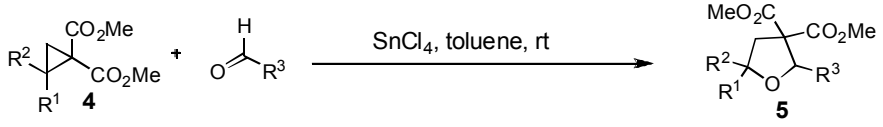
A flame-dried round bottomed flask was charged with 10 % Pd/C (0.030 g, 0.0276 mmol Pd, 0.01 equiv Pd) and placed under a stream of nitrogen. **S5** (0.698 g, 2.76 mmol, 1.0 equiv) and ethanol (7 mL) were added. The suspension was stirred vigorously and the vessel was purged twice with a stream of hydrogen by affixing a balloon to the vessel and inserting a vent needle through the septum. A third balloon of hydrogen was affixed to the vessel with no vent needle, and the reaction was stirred at room temperature for 2 h. Upon complete consumption of the starting material as indicated by TLC analysis, the system was purged with a stream of nitrogen for 5 min then filtered through a Celite plug, rinsing with EtOH. The solution was concentrated *in vacuo* and purified via flash chromatography (10 % EtOAc/hexanes) to afford 0.450 g (64 %) of the cyclopropane **4g** as a white solid. Analytical data for **4g**: mp 49-50 ºC; **IR** (thin film, cm^{-1}): 3064, 2954, 1774, 1728, 1465, 1311, 1133, 1018, 800, 648, 577; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.37 (dd, *J* = 10.0 Hz, 5.2 Hz, 1H), 4.08 (d, *J* = 10 Hz, 1H), 3.77 (s, 3H), 2.55 (d, *J* = 5.2 Hz, 1H), 1.50-1.35 (m, 4H), 1.30-1.22 (m, 1H), 1.21 (s, 3H), 1.11-1.05 (m, 2H), 0.82 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.9, 166.4, 64.5, 52.8, 40.7, 38.8, 36.2, 34.7, 27.8, 24.0, 22.4, 22.4, 12.9; **TLC** (20 % EtOAc/hexanes), R_f 0.24; **LRMS** (ESI): Calcd. for $C_{14}H_{22}O_4$+Cs: 387.1, found: 387.1.

Cyclopropane-Aldehyde Annulation Reactions: General Procedure B



In a glovebox, a dry Teflon screw-cap vial (vial A) containing a magnetic stir bar was charged with $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv). In a separate vial (vial B), a solution of cyclopropane dicarboxylate **4** (0.080 g, 0.322 mmol, 1.0 equiv) and aldehyde (0.103 g, 0.967 mmol, 3.0 equiv) was prepared in 1,2-dichloroethane (0.800 mL). This solution was transferred via pipette to vial A, followed by a 0.200 mL 1,2-dichloroethane rinse of vial B to ensure complete transfer ($[\mathbf{4}]_0$ = 0.3 mmol/mL). The reaction mixture was then brought out of the glovebox and stirred at room temperature until TLC analysis indicated complete consumption of cyclopropane **4**. The reaction mixture was filtered through a Monstr-Pette plug of silica (~3 cm) and rinsed thoroughly with Et_2O. The solution was concentrated *in vacuo*, and the diastereomer ratio was determined by ^{1}H NMR analysis of the unpurified mixture. The residue was purified via flash chromatography using an hexanes flush followed by the indicated eluent system.

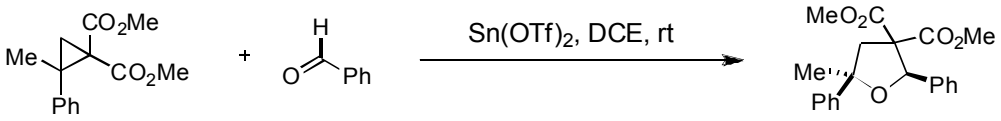
Cyclopropane-Aldehyde Annulation Reactions: General Procedure C



In a glovebox, a dry Teflon screw-cap vial (vial A) containing a magnetic stir bar was charged with cyclopropane dicarboxylate **4** (0.040 g, 0.123 mmol, 1.0 equiv), aldehyde (0.021 g, 0.370 mmol, 3.0 equiv) and 0.410 mL dry toluene ($[\mathbf{4}]_0$ = 0.3 mmol/mL). The vial was capped with a septum, the mixture was brought out of the glovebox, placed under

nitrogen, and stirred at room temperature. $SnCl_4$ (0.020 mL, 0.10 equiv) was added from a [0.6]M stock solution and the reaction was allowed to stir at room temperature until TLC analysis indicated complete consumption of cyclopropane **4**. The reaction mixture was filtered through a Monstr-Pette plug of silica (~3 cm) and rinsed thoroughly with Et_2O. The solution was concentrated *in vacuo*, and the diastereomer ratio was determined by ^{1}H NMR analysis of the unpurified mixture. The residue was purified via flash chromatography using an hexanes flush followed by the indicated eluent system.

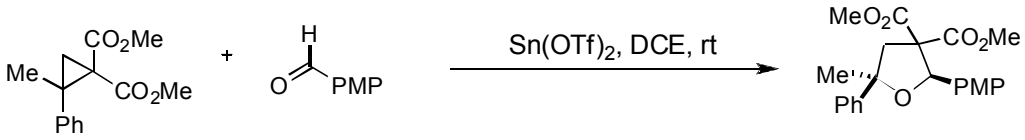
Dimethyl 5-methyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (5a).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), benzaldehyde (0.103 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.100 g (88%) of the product **5a** as a white solid in 97:3 dr. Analytical data for **5a**: mp 91-93 ºC; **IR** (thin film, cm^{-1}): 3060, 3027, 3001, 2953, 2839, 1731, 1614, 1585, 1514, 1496, 1435, 1378, 1251 1209, 1174, 1125, 1065, 1032, 962, 841, 804, 766, 737, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.32 - 7.26 (m, 4H), 6.06 (s, 1H), 3.85 (s, 3H), 3.23 (d, J = 13.6 Hz, 1H), 3.04 (s, 3H), 2.72 (d, J = 13.6 Hz, 1 H), 1.61 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.7, 169.1, 146.9, 137.8, 128.2, 128.0, 127.8, 127.0, 126.8, 124.6, 83.5, 82.6, 66.6, 53.0, 52.1, 47.5, 27.8; **TLC** (30 % EtOAc/hexanes), R_f 0.48 (UV / CAM); **HRMS**

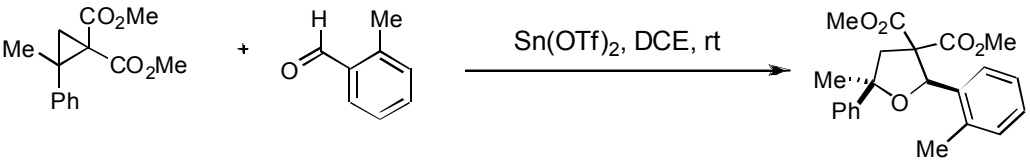
(ESI): Calcd. for $C_{21}H_{22}O_5$+Na: 377.1365, Found: 377.1366.

Dimethyl 2-(4-methoxyphenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5b).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), *p*-anisaldehyde (0.132 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.117 g (95%) of the product **5b** as a colorless oil in 96:4 dr. Analytical data for **5b**: **IR** (thin film, cm^{-1}): 3060, 3027, 3001, 2953, 2839, 1731, 1614, 1514, 1435, 1251, 1209, 1125, 1065, 1032, 962, 841, 766, 737, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.43 - 7.38 (m, 4H) 7. 291 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.01 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.21 (d, *J* = 13.6 Hz, 1H), 3.11 (s, 3H), 2.71 (d, *J* = 13.6, 1H), 1.59 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.8, 169.2, 159.4, 147.1, 129.9, 128.4, 128.2, 126.8, 124.6, 113.2, 83.4, 82.4, 66.5, 55.2, 53.0, 52.3, 47.5, 27.9; **TLC** (30 % EtOAc/hexanes), R_f 0.41 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{24}O_6$+Cs: 517.0, Found: 517.0.

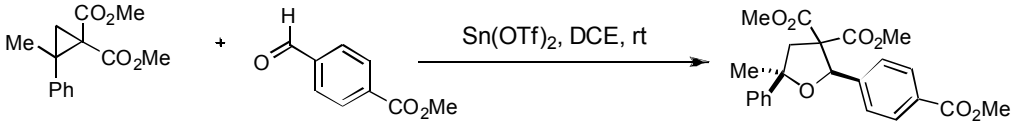
Dimethyl 5-methyl-5-phenyl-2-(o-tolyl)dihydrofuran-3,3(2H)-dicarboxylate (5c).



The title compound was prepared according to General Procedure B using cyclopropane **4a**

(0.080 g, 0.322 mmol, 1.0 equiv), *o*-tolualdehyde (0.116 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.110 g (93%) of the product **5c** as a white solid in 97:3 dr. Analytical data for **5c**: mp 100-102 ºC; **IR** (thin film, cm^{-1}): 3059, 3028, 2952, 1733, 1495, 1435, 1377, 1265, 1232, 1203, 1129, 756, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.2 Hz, 2 H), 7.41 - 7.37 (m, 3H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.15 - 7.10 (m, 3H), 6.43 (s, 1H), 3.85 (s, 3H), 3.28 (d, *J* = 13.6 Hz, 1H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.47 (s, 3H), 1.57 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.1, 168.8, 147.0, 136.7, 136.4, 129.8, 128.3, 127.8, 127.5, 126.8, 125.5, 124.4, 83.9, 79.4, 66.6, 53.1, 52.1, 47.0, 27.5, 19.8; **TLC** (30 % EtOAc/hexanes), R_f 0.51 (UV / CAM); **HRMS** (ESI): Calcd. for $C_{22}H_{24}O_5$+Na: 391.1522, Found: 391.1533.

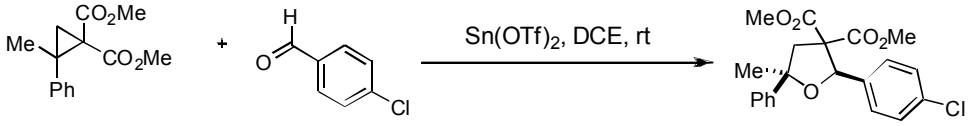
Dimethyl 2-(4-(methoxycarbonyl)phenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5d).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), methyl-4-formylbenzoate (0.159 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.123 g (93%) of the product **5d** as a white solid in 99:1 dr. Analytical data for **5d**: mp 124-126 ºC; **IR** (thin film, cm^{-1}): 3060, 3028, 2953, 2844, 1731, 1614, 1435, 1280, 1209, 1113, 1071, 962, 864, 763, 737, 702; **^{1}H NMR** (400 MHz, $CDCl_3$):

δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 7.6 Hz), 7.41 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.07 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.21 (d, *J* = 13.2 Hz, 1H), 3.04 (s, 3H), 2.74 (d, *J* = 13.2 Hz, 1H), 1.60 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.5, 168.9, 166.9, 146.6, 143.1, 129.8, 129.1, 128.3, 127.1, 127.0, 124.6, 83.9, 82.2, 66.7, 53.2, 52.3, 52.1, 47.5, 27.9; **TLC** (30 % EtOAc/hexanes), R_f 0.37 (UV / CAM) ; **LRMS** (ESI): Calcd. for $C_{23}H_{24}O_7$+Cs: 545.0, Found: 545.0.

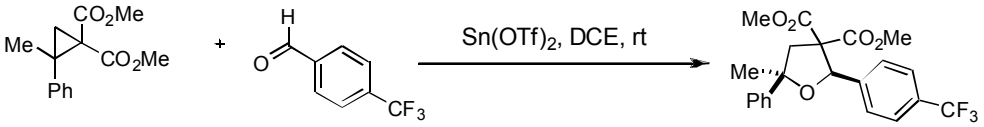
Dimethyl 2-(4-chlorophenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5e).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.136 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.110 g (88%) of the product **5e** as a colorless oil in 96:4 dr. Analytical data for **5e**: **IR** (thin film, cm^{-1}): 3055, 2983, 2954, 2305, 1732, 1491, 1436, 1266, 1125, 1015, 909, 739; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8 Hz, 2 H), 7.49 (d, *J* = 8 Hz, 2H); 7.43 (t, *J* = 7.6 Hz, 2 H) 7.34 - 7.30 (m, 3H), 6.04 (s, 1H), 3.87 (s, 3H), 3.24 (d, *J* = 13.6 Hz, 1H), 3.14 (s, 1H), 2.76 (d, *J* = 13.6 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 168.9, 146.8, 136.5, 133.8, 128.6, 128.3, 128.0, 127.0, 124.6, 83.8, 82.0, 66.6, 53.0, 52.3, 47.5, 27.9; **TLC** (20 % EtOAc/hexanes), R_f 0.42; **LRMS** (ESI): Calcd. for $C_{21}H_{21}ClO_5$+Na: 411.1, Found: 411.1.

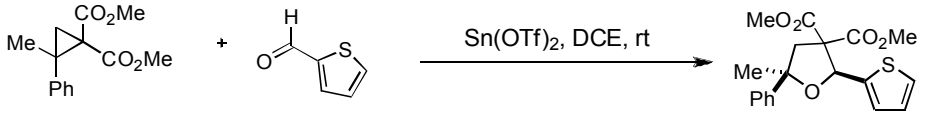
Dimethyl 5-methyl-5-phenyl-2-(4-(trifluoromethyl)phenyl)dihydrofuran-3,3(2*H*)-

dicarboxylate (5f).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.115 g (85%) of the product **5f** as a colorless oil in 99:1 dr. Analytical data for **5f**: **IR** (thin film, cm^{-1}): 3060, 3030, 2954, 2844, 1734, 1621, 1436, 1326, 1125, 1067, 852, 739, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2 H) 7.44 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.11 (s, 1H), 3.89 (s, 3H), 3.26 (d, J = 13.6 Hz, 1H), 3.08 (s, 3H), 2.78 (d, J = 13.6 Hz, 1H), 1.64 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.4, 168.8, 146.7, 142.1, 130.4, 130.1, 128.3, 127.5, 127.0, 124.7, 124.7, 124.6, 84.0, 82.0, 66.7, 53.1, 52.2, 47.6, 28.0; **TLC** (20 % EtOAc/hexanes), R_f 0.44; **LRMS** (ESI): Calcd. for $C_{21}H_{21}F_3O_5$+Cs: 555.0, Found: 555.0.

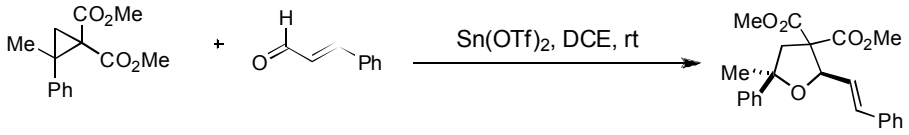
Dimethyl 5-methyl-5-phenyl-2-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (5g).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), thiophene-2-carboxaldehyde (0.108 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.105 g (90%) of the product **5g** as a yellow oil in 96:4 dr.

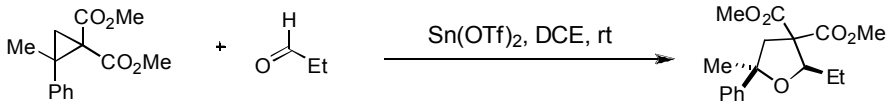
Analytical data for **5g**: **IR** (thin film, cm^{-1}): 3058, 3029, 2953, 1733, 1436, 1266, 1236, 1208, 1123, 738, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.33 - 7.25 (m, 2H), 7.15 (d, *J* = 2.8 Hz, 1H), 6.99 (t, *J* = 2.8 Hz, 1H), 6.31 (s, 1H), 3.88 (s, 3H), 3.28 (s, 3H), 3.26 (d, *J* = 13.6 Hz, 1H), 2.77 (d, *J* = 13.6 Hz, 1H), 1.61 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.2, 168.7, 147.0, 141.0, 128.2, 126.8, 126.4, 125.6, 125.1, 124.6, 84.0, 79.8, 66.6, 53.1, 52.5, 47.1, 28.5; **TLC** (20 % EtOAc/hexanes), R_f 0.34; **LRMS** (ESI): Calcd. for $C_{19}H_{20}O_5S$+Cs: 493.0, Found: 493.0.

Dimethyl 5-methyl-5-phenyl-2-((*E*)-styryl)dihydrofuran-3,3(2*H*)-dicarboxylate (5h).



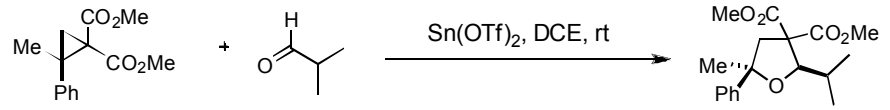
The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), cinnamaldehyde (0.128 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.113 g (92%) of the product **5h** as a colorless oil in 92.5:7.5 dr. Analytical data for **5h**: **IR** (thin film, cm^{-1}): 3056, 2984, 2954, 2305, 1735, 1437, 1265, 738, 703; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.6 Hz, 2 H), 7.40 - 7.24 (m, 8H), 6.79 (d, *J* = 16 Hz, 1H), 6.20 (dd, *J* = 16, 7.2 Hz, 1H), 5.51 (d, *J* = 7.2 Hz), 3.86 (s, 3H), 3.53 (s, 3H), 3.18 (d, *J* = 13.6 Hz, 1H), 2.81 (d, *J* = 13.6 Hz, 1H), 1.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.0, 168.8, 147.8, 136.6, 132.9, 128.5, 128.1, 127.9, 126.7, 126.7, 125.4, 124.6, 84.0, 82.3, 65.6, 53.0, 52.6, 46.9, 29.5; **TLC** (20 % EtOAc/hexanes), R_f 0.41; **LRMS** (ESI): Calcd. for $C_{23}H_{24}O_5$+Cs: 513.0, Found: 513.0.

Dimethyl 2-ethyl-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5i).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), propanal (0.056 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.081 g (82%) of the product **5i** as a colorless oil in 96:4 dr. Analytical data for **5i**: **IR** (thin film, cm^{-1}): 3087, 3060, 3027, 2971, 2879, 1732, 1495, 1435, 1374, 1264, 1121, 1030, 991, 955, 765, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.6 Hz, 2 H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 4.69 (dd, *J* = 10, 3.2 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.06 (d, *J* = 13.2 Hz, 1H), 2.70 (d, *J* = 13.2 Hz, 1H), 1.58 - 1.48 (m, 1H), 1.45 (s, 3H), 1.45 - 1.35 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.4, 169.5, 148.3, 128.0, 126.5, 124.4, 82.9, 82.9, 64.2, 52.9, 52.5, 46.9, 29.9, 24.9, 11.3; **TLC** (30 % EtOAc/hexanes), R_f 0.52 (UV / CAM); **HRMS** (ESI): Calcd. for $C_{17}H_{22}O_5$+Cs: 439.0522 , Found: 439.0536.

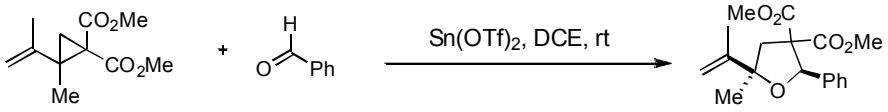
Dimethyl 2-isopropyl-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5j).



The title compound was prepared according to General Procedure B using cyclopropane **4a** (0.080 g, 0.322 mmol, 1.0 equiv), isobutyraldehyde (0.070 g, 0.967 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5%

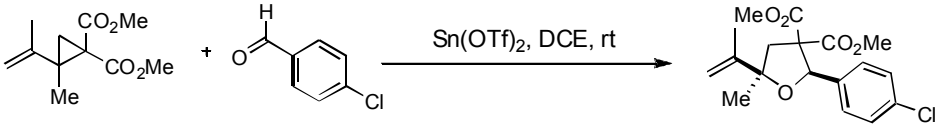
EtOAc/hexanes) to afford 0.085 g (82%) of the product **5j** as a colorless oil in 96:4 dr. Analytical data for **5j**: **IR** (thin film, cm^{-1}): 3028, 2954, 2874, 1734, 1436, 1236, 1069, 1030, 910; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.6 Hz, 2 H), 7.32 (t, *J* = 8.8 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 1H), 4.31 (d, *J* = 7.6 Hz, 1H), 3.78 (s, 3H), 3.53 (s, 3H), 3.06 (d, *J* = 13.2 Hz, 1H), 2.66 (d, *J* = 13.2 Hz, 1H), 2.05 (m, 1H), 1.50 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3 H), 1.01 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.7, 169.8, 147.8, 127.9, 126.4, 124.5, 87.2, 82.0, 63.3, 52.7, 52.1, 49.4, 30.1, 29.2, 20.0, 19.8; **TLC** (20 % EtOAc/hexanes), R_f 0.47; **LRMS** (ESI): Calcd. for $C_{18}H_{24}O_5$+Cs: 453.1, Found: 453.1.

Dimethyl 5-methyl-2-phenyl-5-(prop-1-en-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (5k).



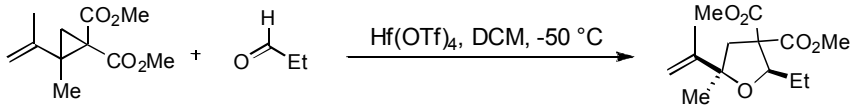
The title compound was prepared according to General Procedure B using cyclopropane **4b** (0.040 g, 0.188 mmol, 1.0 equiv), benzaldehyde (0.060 g, 0.565 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv) in 0.63 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.046 g (77%) of the product **5k** as a colorless oil in 96:4 dr. Analytical data for **5k**: **IR** (thin film, cm^{-1}): 3055, 2984, 2953, 2305, 1732, 1436, 1266, 1237, 1209, 1122, 898, 740, 703; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, J = 7.6 Hz, 2H), 7.33 - 7.25 (m, 3H), 5.94 (s, 1H), 5.16 (s, 1H), 4.92 (s, 1H), 3.83 (s, 3H), 3.10 (d, J = 13.6 Hz, 1H), 3.07 (s, 3H), 2.37 (d, J = 13.6 Hz, 1H), 1.97 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 177.8, 169.2, 149.0, 138.1, 127.9, 127.7, 127.1, 109.5, 84.3, 82.6, 66.4, 52.9, 52.1, 45.3, 24.8, 19.3; **TLC** (20 % EtOAc/hexanes), R_f 0.52; **LRMS** (ESI): Calcd. for $C_{18}H_{22}O_5$+Cs: 451.1, Found: 451.1.

Dimethyl 2-(4-chlorophenyl)-5-methyl-5-(prop-1-en-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (5l).



The title compound was prepared according to General Procedure B using cyclopropane **4b** (0.040 g, 0.188 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.079 g, 0.565 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv) in 0.63 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.050 g (75%) of the product **5l** as a colorless oil in 99:1 dr. Analytical data for **5l**: **IR** (thin film, cm^{-1}): 3056, 2953, 1733, 1597, 1491, 1436, 1379, 1122, 1015, 842, 739, 704; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 5.89 (s, 1H), 5.13 (s, 1H), 4.91 (s, 1H), 3.83 (s, 3H), 3.14 (s, 3H), 3.07 (d, *J* = 13.2 Hz, 1H), 2.37 (d, 13.6 Hz, 1H), 1.95 (s, 3H), 1.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 169.0, 148.8, 136.7, 133.7, 128.5, 127.9, 109.6, 84.5, 81.9, 66.3, 52.9, 52.2, 45.2, 24.8, 19.3; **TLC** (20 % EtOAc/hexanes), R_f 0.48; **LRMS** (ESI): Calcd. for $C_{18}H_{21}ClO_5$+Na: 375.1, Found: 375.1.

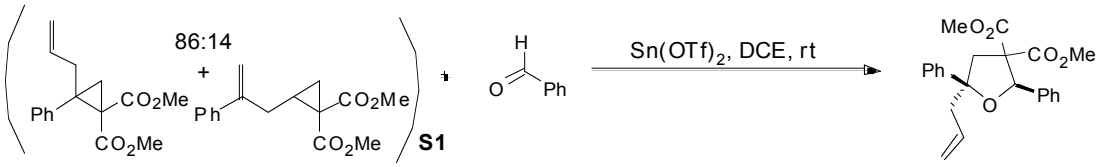
Dimethyl 2-ethyl-5-methyl-5-(prop-1-en-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (5m).



The title compound was prepared analogously to General Procedure B, but modified as follows: A solution of cyclopropane **4b** (0.040 g, 0.188 mmol, 1.0 equiv), propanal (0.033 g, 0.565 mmol, 3.0 equiv) in 0.63 mL dichloromethane was cooled to -50 ºC. This solution was

subsequently transferred to a reaction vial containing a stir bar and $Hf(OTf)_4$ (0.007 g, 0.009 mmol, 0.05 equiv), which had also been cooled to -50 ºC. The reaction was stirred at this temperature in a cryocool until TLC analysis indicated complete consumption of **4b**. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.033 g (65%) of the product **5m** as a colorless oil in 99:1 dr. Analytical data for **5m**: **IR** (thin film, cm^{-1}): 2954, 2879, 1648, 1436, 1372, 1206, 1144, 1118, 1144, 1118, 1073, 991, 903; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.03 (s, 1H), 4.77 (s, 1H), 4.59 (dd, *J* = 9.6 Hz, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.90 (d, *J* = 13.6 Hz, 1H), 2.36 (d, J = 13.2 Hz, 1H), 1.82 (s, 3H), 1.51-1.43 (m, 2H), 1.27 (s, 3H), 1.04 (t, 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.5, 169.6, 108.7, 83.7, 82.7, 64.0, 52.7, 52.4, 44.5, 26.2, 25.0, 19.2, 11.2; **TLC** (20 % EtOAc/hexanes), R_f 0.47; **LRMS** (ESI): Calcd. for $C_{14}H_{22}O_5$+Na: 293.1, Found: 293.1.

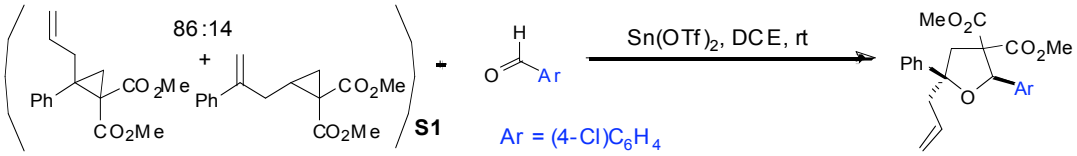
Dimethyl 5-allyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (5n).



The title compound was prepared according to General Procedure B using cyclopropane mixture **S1** (0.050 g, 1.0 equiv), benzaldehyde (0.058 g, 0.555 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv) in 0.60 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (91% based on the amount of quaternary cyclopropane in **S1**) of the product **5n** as a white solid in 83:17 dr. Analytical data for **5n**: mp 104-114 ºC; **IR** (thin film, cm^{-1}): 3064, 3032, 2952, 2843, 1734, 1435, 1267, 1117, 1060, 752, 700; **^{1}H NMR**

(400 MHz, $CDCl_3$): major diastereomer: δ 7.48 (d, *J* = 7.2 Hz, 4H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.27 (m, 4H), 6.02 (s, 1H), 5.60 - 5.50 (m, 1H), 5.00 - 4.90 (m, 2H), 3.85 (s, 3H), 3.21 (d, *J* = 13.6 Hz, 1H), 3.02 (s, 3H), 2.82 (d, *J* = 13.6 Hz, 1H), 2.68 (dd, *J* = 14, 6.8 Hz, 1H), 2.59 (dd, *J* = 14, 6.8 Hz, 1H); resolved signals for the minor diastereomer: 5.80 - 5.70 (m, 1H), 5.72 (m, 1H), 5.15 - 5.05 (m, 2H), 3.50 (s, 3H), 3.08 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): major diastereomer: δ 171.6, 168.9, 144.9, 137.8, 133.1, 128.0, 128.0, 127.8, 127.1, 126.7, 125.2, 118.2, 85.7, 82.8, 66.5, 53.0, 52.1, 45.6, 44.9; minor diastereomer: δ 170.5, 169.1, 143.4, 137.9, 133.2, 128.1, 127.8, 127.1, 127.0, 125.5, 118.4, 86.2, 82.5, 66.6, 52.8, 52.6, 47.4, 43.8; **TLC** (30 % EtOAc/hexanes), R_f 0.52; **LRMS** (ESI): Calcd. for $C_{23}H_{24}O_5$+Cs: 513.1, Found: 513.1.

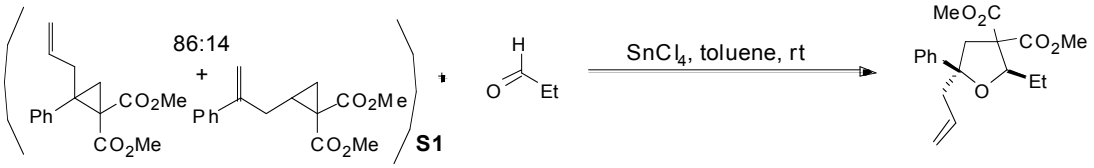
Dimethyl 5-allyl-2-(4-chlorophenyl)-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5o).



The title compound was prepared according to General Procedure B using cyclopropane mixture **S1** (0.050 g, 1.0 equiv), 4-chlorobenzaldehyde (0.078 g, 0.555 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv) in 0.60 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.054 g (85% based on the amount of quaternary cyclopropane in **S1**) of the product **5o** as a colorless oil in 83:17 dr. Analytical data for **5o**: **IR** (thin film, cm^{-1}): 2952, 1734, 1491, 1435, 1065, 1015, 842, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 - 7.35 (m, 6H), 7.30 - 7.26 (m, 3H), 5.97 (s, 1H), 5.60 - 5.50 (m, 1H), 5.00 - 4.90 (m, 2H), 3.85 (s, 3H), 3.18 (d, *J* = 13.6 Hz), 3.08 (s, 3H), 2.82 (d, *J* = 13.6 Hz, 1H), 2.65 (dd, *J* = 14.4, 6.8

Hz), 2.58 (dd, *J* = 14.4, 7.2 Hz); resolved signals for minor diastereomer: δ 5.85 - 5.75 (m, 1H), 5.66 (s, 1H), 5.15 - 5.05 (m, 2H), 3.51 (s, 3H), 3.15 (s, 3H), 2.99 (d, *J* = 13.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): major diastereomer: δ 171.4, 168.8, 144.7, 136.3, 133.8, 132.9, 128.5, 128.0, 127.9, 126.9, 125.1, 118.4, 85.9, 82.1, 66.4, 53.1, 52.3, 45.5, 45.0; minor diastereomer: δ 170.4, 169.0, 143.2, 136.4, 133.7, 133.1, 128.4, 128.2, 128.2, 127.2, 125.4, 118.5, 86.4, 81.8, 66.5, 52.9, 52.7, 47.3, 43.9; **TLC** (30 % EtOAc/hexanes), R_f 0.51 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{23}H_{23}ClO_5$+Cs: 547.0, Found: 547.0.

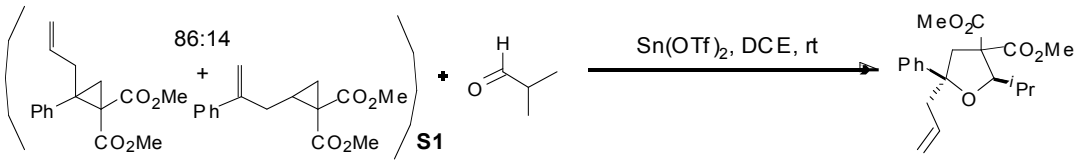
Dimethyl 5-allyl-2-ethyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5p).



The title compound was prepared according to General Procedure C using cyclopropane mixture **S1** (0.050 g, 1.0 equiv), propanal (0.032 g, 0.555 mmol, 3.0 equiv) and 0.03 mL of a [0.6 M] $SnCl_4$ stock solution (0.018 mmol, 0.10 equiv) in 0.60 mL toluene. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.017 g (33% based on the amount of quaternary cyclopropane in **S1**) of the product **5p** as a colorless oil in 90:10 dr. Analytical data for **5p**: **IR** (thin film, cm^{-1}): 2953, 1737, 1435, 1263, 1110, 1026, 703; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.57 - 5.46 (m, 1H), 4.97 - 4.89 (m, 2H), 4.63 (dd, *J* = 10, 3.2 Hz, 1H), 3.80 (s, 3H), 3.59 (s, 3H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.76 (d, *J* = 13.2 Hz, 1H), 2.50 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.43 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.60 - 1.50 (m, 1H), 1.45 - 1.35 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.2, 169.4, 146.3, 133.4, 127.7, 126.5, 125.1, 118.0, 84.8, 83.1, 64.0, 52.8, 52.5,

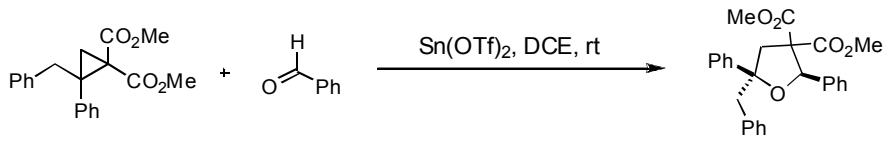
46.7, 44.9, 24.8, 11.3; **TLC** (20 % EtOAc/hexanes), R_f 0.47 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{24}O_5$+Na: 355.2, Found: 355.2.

Dimethyl 5-allyl-2-isopropyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5q).



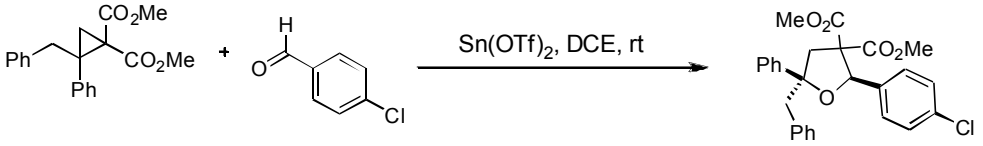
The title compound was prepared according to General Procedure B using cyclopropane mixture **S1** (0.050 g, 1.0 equiv), isobutyraldehyde (0.039 g, 0.555 mol, 3.0 equiv) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv) in 0.60 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.036 g (67% based on the amount of quaternary cyclopropane in **S1**) of the product **5q** as a colorless oil in 90:10 dr. Analytical data for **5q**: **IR** (thin film, cm^{-1}): 2953, 1735, 1447, 1435, 1262, 1060, 918, 703; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 - 7.26 (m = 4H), 7.21 - 7.19 (m, 1H), 5.60 - 5.50 (m, 1H), 5.0 - 4.90 (m, 2H), 4.32 (d, *J* = 8 Hz, 1H), 3.76 (s, 3H), 3.44 (s, 3H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.70 (d, *J* = 13.2 Hz, 1H), 2.58 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.49 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.10 - 2.00 (m, 1H), 1.05 (d, *J* = 6.4 Hz. 3H), 0.97 (d, *J* = 6.4 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.5, 169.6, 145.8, 133.4, 127.6, 126.3, 125.1, 118.0, 87.8, 83.8, 62.7, 52.8, 52.1, 47.9, 46.0, 30.2, 20.1, 19.7; **TLC** (30 % EtOAc/hexanes), R_f 0.57 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{20}H_{26}O_5$+Cs: 479.0835, Found: 479.0827.

Dimethyl 5-benzyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (5r).



The title compound was prepared according to General Procedure B using cyclopropane **4d** (0.040 g, 0.123 mmol, 1.0 equiv), benzaldehyde (0.039 g, 0.370 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.006 mmol, 0.05 equiv) in 0.41 mL 1,2-dichloroethane. After workup, the product was purified by preparative HPLC, eluting with 5% EtOAc/hexanes to afford 0.045 g (85%) of the product **5r** as a white solid in 80:20 dr. Analytical data for **5r**: mp 127-128 ºC; **IR** (thin film, cm^{-1}): 3061, 3030, 2951, 2359, 1733, 1496, 1454, 1435, 1267, 1232, 1209, 1060, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 - 7.43 (m, 2H), 7.32 - 7.20 (m, 8H), 6.76 (dd, *J* = 7.2, 1.2 Hz), 6.10 (s, 1H) 3.88 (s, 3H), 3.29 (d, *J* = 13.6 Hz, 1H), 3.19 (d, *J* = 13.6 Hz, 1H), 3.02 (s, 3H), 3.00 (d, *J* = 13.6 Hz, 1H), 2.95 (d, *J* = 13.6 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.6, 168.9, 144.9, 137.9, 136.3, 130.4, 128.0, 127.8, 127.7, 127.5, 127.1, 126.6, 126.2, 125.5, 86.7, 83.0, 66.6, 53.1, 52.2, 47.0, 45.6; **TLC** (30 % EtOAc/hexanes), R_f 0.44 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{27}H_{26}O_5$+Cs: 563.1, Found: 563.1.

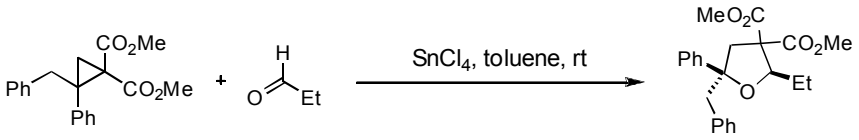
Dimethyl 5-benzyl-2-(4-chlorophenyl)-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5s).



The title compound was prepared according to General Procedure B using cyclopropane **4d** (0.040 g, 0.123 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.052 g, 0.370 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.006 mmol, 0.05 equiv) in 0.41 mL 1,2-dichloroethane. After

workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.050 g (87%) of the product **5s** as a white solid in 80:20 dr. Analytical data for **5s**: mp 131-132 ºC; Analytical data for **5s**: **IR** (thin film, cm^{-1}): 3029, 2951, 1734, 1491, 1435, 1268, 1232, 1209, 1065, 842, 737, 700; **^{1}H NMR** (600 MHz, $CDCl_3$): major diastereomer: δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.30 - 7.15 (m, 7H), 7.15 - 7.05 (m, 3H), 6.75 (d, *J* = 7.2 Hz, 2H), 6.02 (s, 1H), 3.88 (s, 3H), 3.27 (d, *J* = 13.8 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.08 (s, 3H), 3.00 (d, *J* = 13.8 Hz, 1H), 2.95 (d, *J* = 13.8 Hz, 1H); resolved signals for minor diastereomer: 6.98 (m, 2H), 5.63 (s, 1H), 3.46 (s, 3H), 3.11 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) major diastereomer (isolated via preparative HPLC): δ 171.4, 168.7, 144.8, 136.4, 136.2, 133.8, 130.4, 128.5, 127.9, 127.7, 127.6, 126.7, 126.3, 125.4, 86.8, 82.4, 66.4, 53.1, 52.3, 47.1, 45.6; **TLC** (30 % EtOAc/hexanes), R_f 0.50 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{27}H_{25}ClO_5$+Cs: 597.0, Found: 597.0.

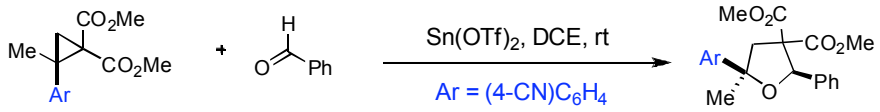
Dimethyl 5-benzyl-2-ethyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5t).



The title compound was prepared according to General Procedure C using cyclopropane **4d** (0.040 g, 0.123 mmol, 1.0 equiv), propanal (0.021 g, 0.370 mmol, 3.0 equiv) and 0.021 mL of a [0.6 M] $SnCl_4$ stock solution (0.012 mmol, 0.10 equiv) in 0.41 mL toluene. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.036 g (76%) of the product **5t** as a colorless oil in 81:19 dr. Analytical data for **5t**: **IR** (thin film, cm^{-1}): 3029, 2952, 1737, 1453, 1435, 1262, 1093, 1075, 1026, 771, 701; **^{1}H NMR** (400 MHz, $CDCl_3$): major diastereomer: δ 7.25 - 7.05 (m, 8H), 6.78 (dd, *J* = 6.8, 1.6 Hz), 4.58 (dd, *J* = 10.4, 3.2 Hz), 3.81 (s, 3H), 3.55 (s, 3H), 3.11 (d, *J* =

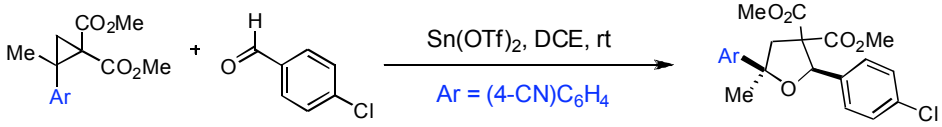
13.6 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 2.89 (d, J = 13.6 Hz, 1H), 2.88 (d, J = 13.6 Hz, 1H), 1.62 - 1.52 (m, 1H), 1.45 - 1.35 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H); resolved signals for minor diastereomer: δ 6.90 - 6.85 (m, 2H), 4.33 (dd, J = 10, 2.8 Hz, 1H), 3.72 (s, 3H), 3.42 (s, 3H), 2.84 (d, J = 13.6 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): major diastereomer: δ 171.1, 169.3, 146.1, 136.6, 130.6, 127.4, 126.3, 126.2, 125.3, 85.4, 83.2, 63.8, 52.9, 52.4, 48.5, 45.2, 24.8, 11.5; **TLC** (20% EtOAc/hexanes), R_f 0.50 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{23}H_{26}O_5$+Na: 405.2, Found: 405.2.

Dimethyl 5-(4-cyanophenyl)-5-methyl-2-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5u).



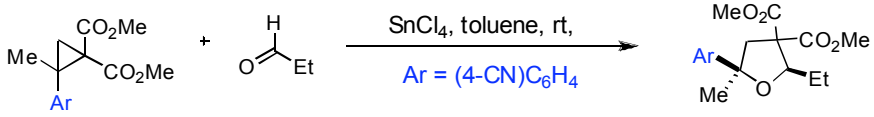
The title compound was prepared according to General Procedure B using cyclopropane **4e** (0.040 g, 0.146 mmol, 1.0 equiv), benzaldehyde (0.046 g, 0.439 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.050 g (87%) of the product **5u** as a white solid in 95:5 dr. Analytical data for **5u**: mp 154-156 ºC; **IR** (thin film, cm^{-1}): 2953, 2228, 1733, 1609, 1435, 1268, 1210, 1108, 1060, 963, 841, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 6.8 Hz, 2H), 7.35 - 7.28 (m, 3H), 6.00 (s, 1H), 3.83 (s, 3H), 3.17 (d, J = 13.6 Hz, 1H), 3.04 (s, 3H), 2.69 (d, J = 13.6 Hz, 1H), 1.60 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.1, 168.7, 152.2, 137.2, 132.2, 128.4, 128.0, 126.9, 125.5, 118.9, 110.8, 83.0, 82.7, 66.3, 53.1, 52.3, 47.4, 28.2; **TLC** (30 % EtOAc/hexanes), R_f 0.31 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{21}NO_5$+Cs: 512.1, Found: 512.1.

Dimethyl 2-(4-chlorophenyl)-5-(4-cyanophenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (5v).



The title compound was prepared according to General Procedure B using cyclopropane **4e** (0.040 g, 0.146 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.061 g, 0.439 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.054 g (90%) of the product **5v** as a colorless oil in 95:5 dr. Analytical data for **5v**: **IR** (thin film, cm^{-1}): 2953, 2228, 1732, 1491, 1435, 1270, 1210, 1088, 1015, 840, 738; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.95 (s, 1H), 3.83 (s, 3H), 3.15 (d, J = 13.6 Hz), 3.10 (s, 3H), 2.69 (d, J = 13.6 Hz, 1H), 1.59 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.9, 168.7, 151.9, 135.7, 134.1, 132.2, 128.3, 128.1, 125.4, 118.8, 110.8, 83.1, 82.0, 66.1, 53.1, 52.4, 47.3, 28.3; **TLC** (30 % EtOAc/hexanes), R_f 0.29 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{20}ClO_5$+Cs: 546.0, Found: 546.0.

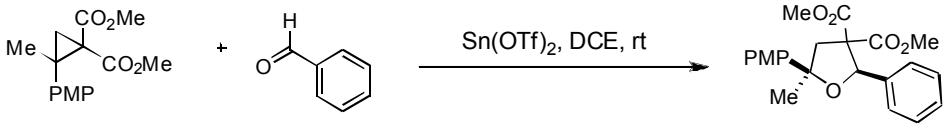
Dimethyl 5-(4-cyanophenyl)-2-ethyl-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (5w).



The title compound was prepared according to General Procedure C using cyclopropane **4d** (0.040 g, 0.146 mmol, 1.0 equiv), propanal (0.025 g, 0.439 mmol, 3.0 equiv) and 0.024 mL of a [0.6 M] $SnCl_4$ stock solution (0.015 mmol, 0.10 equiv) in 0.490 mL toluene. After workup, the product was purified by flash chromatography (hexanes flush followed by 10%

EtOAc/hexanes) to afford 0.025 g (57%) of the product **5w** as a colorless oil in 98:2 dr. Analytical data for **5w**: **IR** (thin film, cm^{-1}): 2973, 2360, 2228, 1736, 1436, 1265, 1206, 1100, 992, 842; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.62 (dd, *J* = 10, 3.2 Hz), 3.79 (s, 3H), 3.61 (s, 3H), 2.98 (d, *J* = 13.6 Hz, 1H), 2.65 (d, *J* = 13.6 Hz), 1.70 - 1.60 (m, 1H), 1.46 (s, 3H), 1.40 - 1.30 (m, 1H), 1.08 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.8, 169.3, 153.4, 131.9, 125.3, 119.0, 110.4, 83.0, 82.4, 63.8, 53.0, 52.6, 47.1, 29.7, 24.8, 11.3; **TLC** (20 % EtOAc/hexanes), R_f 0.31 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{18}H_{21}NO_5$+Na: 354.1, Found: 354.1.

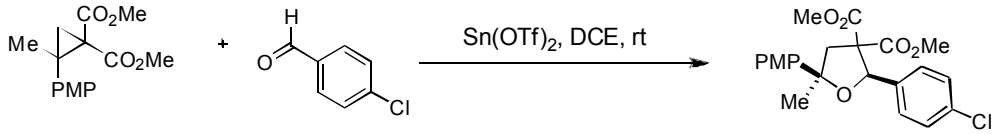
Dimethyl 5-(4-methoxyphenyl)-5-methyl-2-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (5x).



The title compound was prepared according to General Procedure B using cyclopropane **4f** (0.040 g, 0.144 mmol, 1.0 equiv), benzaldehyde (0.046 g, 0.431 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.48 mL 1,2-dichloroethane. After workup (20 min reaction time), the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (95%) of the product **5x** as a colorless oil in 96:4 dr (83:17 dr after 3.5 hr, 1:1 dr after 24 h). Analytical data for **5x**: **IR** (thin film, cm^{-1}): 2952, 2838, 1732, 1613, 1515, 1435, 1250, 1108, 1032, 962, 833, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 - 7.48 (m, 4H), 7.35 - 7.25 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H) 6.03 (s, 1H), 3.84 (s, 3H), 3.83, (s, 3H), 3.20 (d, *J* = 13.2 Hz, 1H), 3.04 (s, 3H), 2.67 (d, *J* = 13.2 Hz, 1H), 1.59 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.7, 169.2, 158.4, 139.1, 137.8, 128.0,

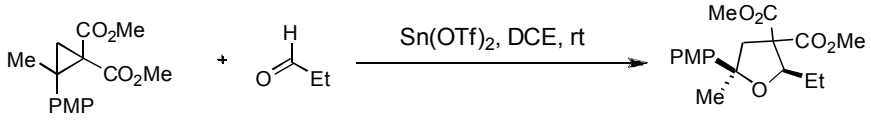
127.8, 127.0, 125.9, 113.5, 66.7, 55.2, 53.0, 52.2, 47.7, 27.5; **TLC** (30 % EtOAc/hexanes), R_f 0.44 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{24}O_6$+Cs: 517.0, Found: 517.0.

Dimethyl 2-(4-chlorophenyl)-5-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (5y).



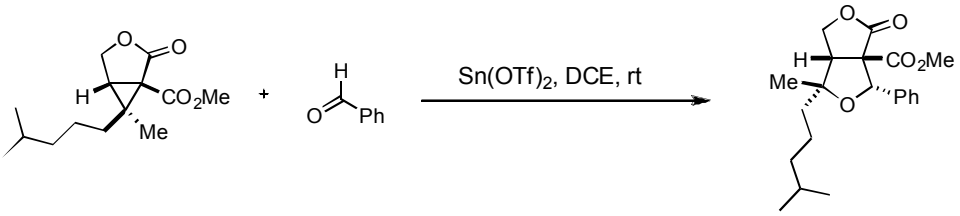
The title compound was prepared according to General Procedure B using cyclopropane **4f** (0.040 g, 0.144 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.061 g, 0.431 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.48 mL 1,2-dichloroethane. After workup (20 min reaction time), the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (88%) of the product **5y** as a colorless oil in 97:3 dr. Analytical data for **5y**: **IR** (thin film, cm^{-1}): 2953, 2838, 1732, 1612, 1515, 1435, 1250, 1089, 962, 833, 737; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.98 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.18 (d, *J* = 13.2 Hz, 1H), 3.11 (s, 3H), 2.67 (d, *J* = 13.2 Hz, 1H), 1.57 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.6, 169.0, 158.5, 138.8, 136.4, 133.7, 128.4, 127.9, 125.8, 113.5, 83.4, 81.9, 66.6, 55.2, 53.1, 52.3, 47.7, 27.6; **TLC** (30 % EtOAc/hexanes), R_f 0.41 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{23}ClO_6$+Cs: 551.0, Found: 551.0.

Dimethyl 2-ethyl-5-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (5z).



The title compound was prepared according to General Procedure B using cyclopropane **4f** (0.040 g, 0.144 mmol, 1.0 equiv), propanal (0.025 g, 0.431 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.48 mL 1,2-dichloroethane. After workup (20 min reaction time), the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.035 g (72%) of the product **5z** as a colorless oil in 93:7 dr. Analytical data for **5z**: **IR** (thin film, cm^{-1}): 2954, 2879, 2838, 1736, 1612, 1514, 1435, 1248, 1098, 1035, 990, 833; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.66 (dd, *J* = 10, 3.2 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.02 (d, *J* = 13.2 Hz, 1H), 2.65 (d, *J* = 13.2 Hz, 1H) 1.60 - 1.50 (m, 1H) 1.43 (s, 3H), 1.45 - 1.35 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.4, 169.5, 158.1, 150.5, 125.6, 113.3, 82.8, 82.6, 64.2, 55.2, 52.9, 52.5, 47.1, 29.6, 24.8; **TLC** (20 % EtOAc/hexanes), R_f 0.29 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{18}H_{24}O_6$+Na: 359.1, Found: 359.1.

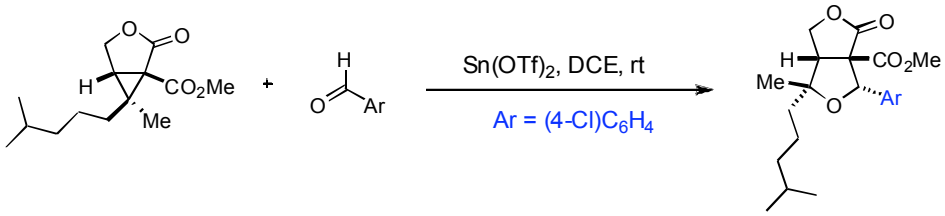
Methyl 1-isopentyl-1-methyl-4-oxo-3-phenylhexahydrofuro[3,4-*c*]furan-3a-carboxylate (5aa).



The title compound was prepared according to General Procedure B using cyclopropane **4g** (0.040 g, 0.157 mmol, 1.0 equiv), benzaldehyde (0.050 g, 0.471 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.008 mmol, 0.05 equiv) in 0.52 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.044 g (78%) of the product **5aa** as a colorless oil in 99:1 dr. Analytical data for **5aa**: **IR** (thin film, cm^{-1}): 2955, 2871, 1783, 1739, 1492, 1437, 1382,

1174, 1036, 1014, 840, 704; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.33-7.29 (m, 1H), 5.86 (s, 1H), 4.84-4.37 (m, 2H), 3.89 (s, 3H), 3.52 (t, *J* = 8.4 Hz, 1H), 1.80-1.49 (m, 4H), 1.35 (s, 3H), 1.28-1.27 (m, 3H), 0.93 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.4, 169.7, 136.3, 128.5, 128.4, 126.3, 84.4, 82.1, 67.1, 66.9, 55.2, 53.6, 39.4, 37.0, 27.8, 23.3, 22.8, 22.5; **TLC** (20 % EtOAc/hexanes), R_f 0.31; **LRMS** (ESI): Calcd. for $C_{21}H_{28}O_5$+Cs: 493.1, Found: 493.1.

Methyl 3-(4-chlorophenyl)-1-isopentyl-1-methyl-4-oxohexahydrofuro[3,4-*c*]furan-3a-carboxylate (5ab).



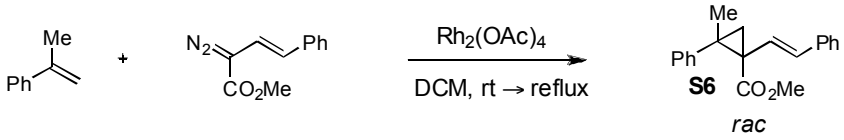
The title compound was prepared according to General Procedure B using cyclopropane **4g** (0.040 g, 0.157 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.066 g, 0.471 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.008 mmol, 0.05 equiv) in 0.52 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.047 g (75%) of the product **5ab** as a colorless oil in 99:1 dr. Analytical data for **5ab**: **IR** (thin film, cm^{-1}): 2955, 2871, 1783, 1738, 1456, 1382, 1176, 935, 739, 701; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.81, (s, 1H), 4.56 (t, *J* = 9.2 Hz, 1H), 4.38-4.34 (m, 1H), 3.89 (s, 3H), 3.50 (dd, *J* = 8.8 Hz, 7.2 Hz, 1H), 1.78-1.46 (m, 5H), 1.38 (s, 3H), 1.29-1.23 (m, 2H), 0.92 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.2, 169.5, 134.9, 134.3, 128.6, 127.8, 84.6, 81.4, 66.9, 55.1, 53.6, 39.4, 37.0, 27.8, 23.4, 22.7, 22.5; **TLC** (20 % EtOAc/hexanes), R_f 0.29; **LRMS** (ESI): Calcd. for $C_{21}H_{27}ClO_5$+Cs: 527.1, Found: 527.1.

Methyl 3-ethyl-1-isopentyl-1-methyl-4-oxohexahydrofuro[3,4-*c*]furan-3a-carboxylate (5ac).

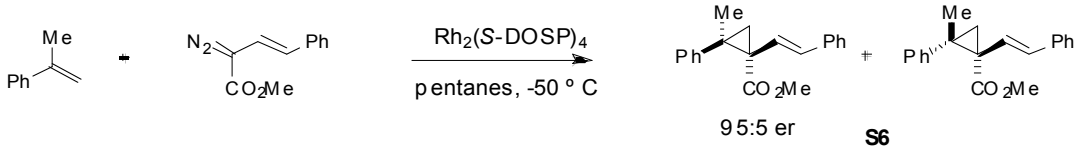
The title compound was prepared according to General Procedure C using cyclopropane **4g** (0.040 g, 0.157 mmol, 1.0 equiv), propanal (0.027 g, 0.472 mmol, 3.0 equiv) and 0.026 mL of a [0.6]M $SnCl_4$ solution (0.0157 mmol, 0.10 equiv) in 0.52 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.056 g (75%) of the product **5ac** as a colorless oil in 77:23 dr. Analytical data for **5ac**: Major diastereomer: **IR** (thin film, cm^{-1}): 3055, 2956, 2871, 2305, 1778, 1740, 1437, 1384, 1195, 1029, 897, 739; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.48 (dd, *J* = 9.2 Hz, *J* = 4 Hz, 1H), 4.39 (t, *J* = 9.2 Hz, 1H), 4.24 (dd, *J* = 9.2 Hz, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 3.35 (dd, *J* = 8.8 Hz, *J* = 6.8 Hz, 1H), 1.91-1.85 (m, 1H), 1.85-1.41 (m, 6H), 1.20-1.15 (m, 5H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.5, 169.6, 83.4, 81.4, 67.1, 64.7, 55.2, 53.3, 48.8, 39.3, 37.2, 27.7, 25.4, 23.3, 22.6, 22.5, 11.1; **TLC** (20 % EtOAc/hexanes), R_f: 0.39; **LRMS** (ESI): Calcd. for $C_{17}H_{28}O_5$+Cs: 445.1, Found: 445.1. Minor diasteromer: **IR** (thin film, cm^{-1}): 3055, 2956, 2871, 2305, 1778, 1740, 1437, 1384, 1195, 1029, 897, 739; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.38-4.31 (m, 2H), 4.12 (dd, *J* = 9.2 Hz, *J* = 4 Hz, 1H), 3.83 (s, 3H), 3.36 (d, *J* = 6 Hz, 1H), 1.78-1.72 (m, 1H), 1.59-1.50 (m, 4H), 1.41-1.38 (m, 5H), 1.21-1.18 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.1, 167.5, 83.8, 83.2, 66.5, 66.0, 56.3, 53.0, 39.3, 33.3, 27.8, 26.0, 25.2, 22.5, 22.4, 20.9, 10.6; **TLC** (20 % EtOAc/hexanes), R_f 0.29; **LRMS** (ESI): Calcd. for $C_{17}H_{28}O_5$+Na: 335.2, Found: 335.2.

Preparation of Enantioenriched Cyclopropanes for Chirality Transfer Studies:

(*E*)-methyl 2-methyl-2-phenyl-1-styrylcyclopropanecarboxylate (S6).



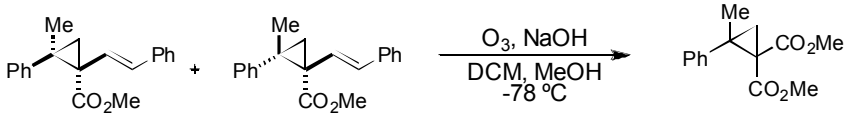
The racemic reaction was conducted as follows: To a solution of $Rh_2(OAc)_4$ (0.002 g, 0.00494 mmol, 0.01 equiv) and α-methylstyrene (0.228 mL, 2.47 mmol, 5.0 equiv) in dichloromethane (4.94 mL) was added a solution of methyl styryldiazoacetate (0.100 g, 0.494 mmol, 1.0 equiv) in DCM (2.5 mL) over 10 min. The reaction was stirred overnight at room temperature, then heated to reflux for 24 hours. Upon complete consumption of styryldiazoacetate as indicated by TLC analysis, the reaction was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes flush followed by 10 % EtOAc/hexanes) to afford 0.090 g (63%) of product *rac*-**S6** as a yellow solid in 75:25 dr.



The enantioselective reaction was performed according a modified literature method.[32] To a -50 ºC solution of Rh_2(*S*-DOSP)$_4$ (0.040 g, 0.021 mmol, 0.01 equiv) and α-methylstyrene (1.38 mL, 10.6 mmol, 5.0 equiv) in pentanes (35 mL) was added a solution of methyl styryldiazoacetate (0.430 g, 2.12 mmol, 1.0 equiv) dissolved in a minimum amount of pentanes (3 mL). The reaction was stirred at -50 ºC for 12 h in a cryocool, at which point the red color of the diazoacetate was discharged. The reaction was warmed to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.404 g (65%) of product **S6** in 75:25 dr and

95:5 er for the major diastereomer as determined by chiral HPLC (column IA, 5 % ^{i}PrOH/hexanes, 1 mL/min, 220 nm) $t_{r\text{-}major}$ 4.2 min, $t_{r\text{-}minor}$ 4.5 min. Analytical data for **S6**: **IR** (thin film, cm^{-1}): 3059, 3026, 2951, 2872, 1727, 1602, 1496, 1435, 1239, 1123, 964, 744, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 7.32-7.23 (m, 5H), 7.20 (d, 6.8 Hz, 2H), 7.18-7.12 (m, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.15 (d, *J* = 16 Hz, 1H), 6.04 (d, *J* = 16 Hz, 1H), 3.84 (s, 3H), 1.90 (d, *J* = 5.6 Hz, 1H), 1.81 (d, *J* = 5.6 Hz, 1H), 1.54 (s, 3H); minor diasteromer: δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.39-7.33 (m, 3H), 7.33-7.28 (m, 2H), 7.26-7.18 (m, 3H), 6.96 (d, *J* = 16 Hz, 1H), 6.52 (d, *J* = 16.4 Hz, 1H), 3.29 (s, 3H), 2.31 (d, 5.2 Hz, 1H), 1.49 (d, *J* = 5.6 Hz, 1H), 1.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.1, 141.8, 137.4, 130.2, 129.0, 128.6, 128.4, 128.2, 128.1, 127.7, 127.0, 126.6, 126.4, 126.0, 52.1, 38.1, 37.0, 23.0, 22.9; **TLC** (10 % EtOAc/hexanes), R_f 0.41; **LRMS** (ESI): Calcd. for $C_{20}H_{20}O_2$+Na: 315.1, found: 315.1.

Preparation of enantioenriched dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (-)-4a.



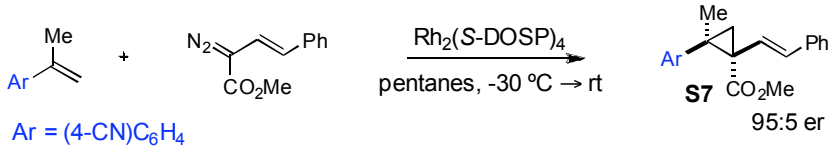
S6 77:23 er

The cyclopropane dicarboxylate was prepared according to a modified literature method.[39] To a solution of **S6** (0.290 g, 0.993 mmol, 1.0 equiv) in dry dichloromethane (16 mL) at -78 ºC under nitrogen was added 4 mL of a 2.5 M solution of NaOH in MeOH (10.0 equiv). The solution was stirred at -78 ºC for 10 min, at which point O_3 was bubbled through the reaction mixture. After 1.5 h, TLC analysis indicated complete consumption of **S6.** The solution was purged by sparging with nitrogen for 5 minutes until colorless and then warming to room

temperature. The reaction was poured into water, the layers were separated and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with water and saturated aqueous NaCl solution, then dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.160 g (65%) of cyclopropane **(-)-4a** as a colorless oil in 77:23 er as determined by chiral SFC analysis (Chiralcel WO, 0.6% MeOH, 1.2 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 9.4 min, $t_{r\text{-minor}}$ 10.8 min; $[\alpha]_D^{28} = -42.0$ (*c* = 0.440, $CHCl_3$); The spectral data were consistent with racemic material.

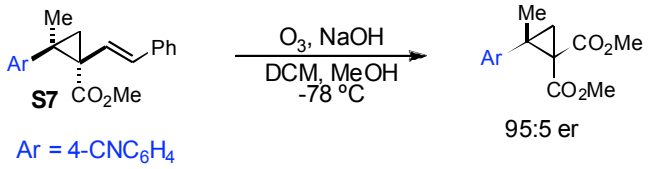
(*E*)-methyl 2-(4-cyanophenyl)-2-methyl-1-styrylcyclopropanecarboxylate (S7).

The racemic reaction was conducted according to a literature procedure.[40] To a 0 ºC solution of $Rh_2(esp)_2$ (0.001 g, 0.0006 mmol, 0.001 equiv) and 4-isopropenylbenzonitrile (0.087 g, 0.609 mmol, 1.0 equiv) in dry dichloromethane (1.5 mL) under a stream of nitrogen was added a solution of methyl styryldiazoacetate (0.160 g, 0.791 mmol, 1.3 equiv) in dichloromethane (3 mL) over 10 min. The red color was quickly consumed, at which point the reaction was warmed to room temperature. TLC analysis indicated complete consumption of 4-isopropenylbenzonitrile, and the reaction was concentrated *in vacuo*. The residue was purified by flash chromatography (10 % EtOAc/hexanes) to afford 0.135 g (70%) of product *rac*-**S7** as a white foam in 85:15 dr. The diastereomers were separable by preparative HPLC (10% EtOAc/hexanes).



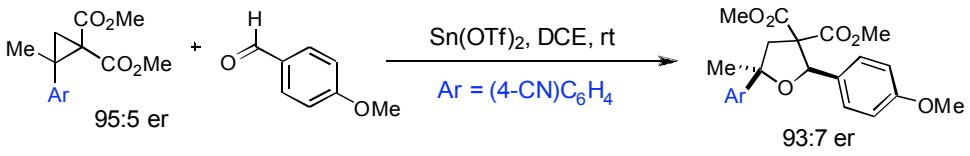
The enantioselective reaction was performed according to a modified literature method.[32] To a -30 ºC solution of Rh_2(*S*-DOSP)$_4$ (0.025 g, 0.0133 mmol, 0.01 equiv) and 4-isopropenylbenzonitrile (0.230 g, 1.60 mmol, 1.2 equiv) in pentanes (30 mL) was added a solution of methyl styryldiazoacetate (0.270 g, 1.33 mmol, 1.0 equiv) in a minimum amount of pentanes (5 mL) The reaction was stirred for 24 h at -30 ºC in a cryocool and then allowed to warm slowly to room temperature over 5 h, at which point the red color of the styryldiazoacetate was consumed. The reaction was concentrated *in vacuo*, and the product was purified by flash chromatography (10 % EtOAc/hexanes) followed by preparative HPLC (10 % EtOAc/hexanes) to afford 0.200 g (47 %) of product **S7** in 83:17 dr and 95:5 er for the major diastereomer as determined by HPLC analysis (column IA, 5 % ^{i}PrOH/hexanes, 1 mL/min, 220 nm) $t_{r\text{-major}}$ 7.2 min, $t_{r\text{-minor}}$ 8.2 min. Analytical data for **S7**: **IR** (thin film, cm^{-1}): 3026, 2592, 2228, 1727, 1607, 1436, 1241, 1123, 1071, 967, 841, 747, 695; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8 Hz, 2 H), 7.35 (d, *J* = 8 Hz, 2H), 7.22 - 7.15 (m, 3 H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.12 (d, *J* = 16 Hz, 1H), 6.03 (d, *J* = 16 Hz, 1H), 3.82 (s, 3H), 1.92 (d, *J* = 6 Hz, 1H), 1.82 (d, *J* = 6 Hz, 1H), 1.52 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.4, 147.3, 136.5, 132.0, 131.0, 129.8, 128.4, 127.4, 126.1, 125.9, 118.7, 110.4, 52.3, 38.0, 36.5, 22.3, 22.2; **TLC** (20 % EtOAc/hexanes), R_f 0.27 (UV / CAM / $KMnO_4$); **LRMS** (ESI): Calcd. for $C_{21}H_{19}NO_2$+Na: 340.1, Found: 340.1; $[\alpha]_D^{28}$ = -133.18 (*c* = 1.00, $CHCl_3$).

Preparation of enantioenriched dimethyl 2-(4-cyanophenyl)-2-methylcyclopropane-1,1-dicarboxylate dicarboxylate ((-)-4e).



The cyclopropane dicarboxylate was prepared according to a modified literature method.[39] To a solution of **S7** (0.053 g, 0.167 mmol, 1.0 equiv) in dry dichloromethane (2.7 mL) at -78 ºC under nitrogen was added 0.67 mL of a 2.5 M solution of NaOH in MeOH (10.0 equiv). The solution was stirred at -78 ºC for 10 min at which point O_3 was bubbled through the reaction mixture. After 1.5 h, TLC analysis indicated complete consumption of **S7.** The solution was purged by sparging with nitrogen for 5 minutes until colorless and then warming to room temperature. The reaction was poured into water, the layers were separated and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with water and saturated aqueous NaCl solution, then dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes flush followed by 30 % EtOAc/hexanes) to afford 0.038 g (83%) of product **(-)-4e** as a colorless oil in 95:5 er as determined by SFC analysis (Chiralcel WO column, 1.2 mL/min flow rate, 0.6 % MeOH modifier, 200 bar, 220nm) $t_{r\text{-major}}$ 15.6 min, $t_{r\text{-major}}$ 18. 9 min; $[\alpha]_D^{27} = -77.884$ (*c* = 0.750, $CHCl_3$). Spectral data were consistent with racemic material.

Dimethyl 5-(4-cyanophenyl)-2-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate ((+)-18).

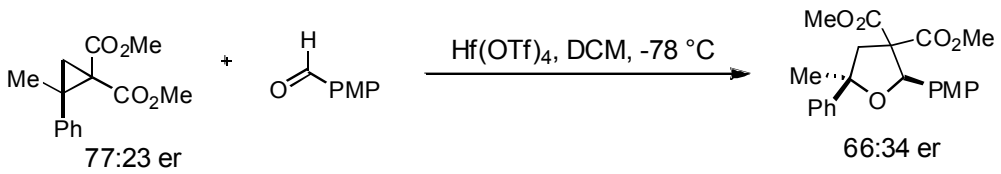


The title compound was prepared in racemic fashion according to General Procedure B using cyclopropane **4e** (0.040 g, 0.146 mmol, 1.0 equiv), *p*-anisaldehyde (0.060 g, 0.441 mmol, 3.0 equiv) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv) in 0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.056 g (94%) of product ***rac*-18** as a white solid in 95:5 dr.

A chirality transfer experiment was performed according to General Procedure B using enantioenriched cyclopropane **(-)-4e** (0.021 g, 1.0 equiv, 95:5 er), *p*-anisaldehyde (0.031 g, 3.0 equiv) and $Sn(OTf)_2$ (0.001 g, 0.05 equiv) in 0.30 mL 1,2-dichloroethane. After workup, the product was purified by flash chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.028 g of product **(+)-18** (90 %) as a white solid in 95:5 dr and 93:7 er as determined by chiral SFC analysis (Chiralcel, AD, 2.5 % MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-}minor}$ 12.4 min, $t_{r\text{-}major}$ 14.1 min.

Analytical data for **(+)-18**: mp 135-137 ºC; **IR** (thin film, cm^{-1}): 2953, 2839, 2228, 1732, 1613, 1514, 1436, 1251, 1127, 1108, 1064, 841; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8 Hz, 2H) 7.38 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.95 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.15 (d, *J* = 13.2 Hz, 1H), 3.10 (s, 3H), 2.68 (d, *J* = 13.2 Hz, 1H), 1.58 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.1, 169.0, 159.5, 152.3, 132.2, 129.1, 128.1, 125.4, 118.9, 113.3, 110.7, 82.7, 82.5, 66.1, 55.2, 53.0, 52.4, 28.3; **TLC** (30 % EtOAc/hexanes), R_f 0.25; **LRMS** (ESI): Calcd. for $C_{23}H_{23}NO_6$+Cs: 542.0, Found: 542.0; $[\alpha]_D^{28}$ = +34.34 (*c* = 0.750, $CHCl_3$).

Dimethyl 2-(4-methoxyphenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate ((+)-5b).



In a glovebox, a flame-dried round bottomed flask (flask 1) was charged with a magnetic stir bar and $Hf(OTf)_4$ (0.008 g, 0.01 mmol, 0.05 equiv). A separate round bottomed flask (flask 2) was charged with **(-)-4a** (0.050 g, 0.201 mmol, 1.0 equiv, 77:23 er), anisaldehyde (0.080 g, 0.604 mmol, 3.0 equiv), and 0.67 mL of dichloromethane. Both flasks were cooled to -78 ºC bath for 20 min under a stream of N_2. The contents of flask 2 were then transferred to flask 1 via cannula. The reaction was stirred for 4 hours at -78 ºC, at which point TLC analysis confirmed complete consumption of **(-)-4a**. The reaction mixture was filtered through a Monstr-Pette plug of silica (3 cm) and rinsed thoroughly with Et_2O. Purification by flash chromatography (hexanes followed by 5% EtOAc/hexanes) afforded 0.050 g (65%) of product **(+)-5b** as a colorless oil in 98:2 dr and 66:34 er as determined by SFC analysis (Chiralcel, OD, 3% MeOH, 2 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 10.7 min, $t_{r\text{-minor}}$ 13.0 min; $[\alpha]_D^{28} = +17.8$ ($c = 0.800$, $CHCl_3$); the spectral data were consistent with racemic material**.**

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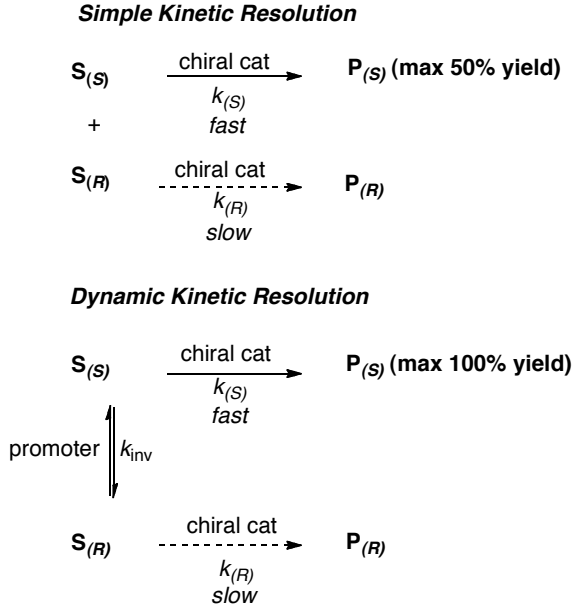
CHAPTER 3
ENANTIOSELECTIVE SYNTHESIS OF PYRROLIDINES FROM RACEMIC CYCLOPROPANES AND ALDIMINES: REACTION DEVELOPMENT AND MECHANISTIC INSIGHTS

3.1 Introduction

Developing methods to access enantiopure compounds is an important goal in organic synthesis. The kinetic resolution of racemates is a classical method to achieve this task and is still widely used in industrial settings.[1] In a perfect kinetic resolution, one enantiomer of the racemic mixture reacts at a significantly faster rate than the other enantiomer through the use of a chiral promoter or catalyst. The "fast" enantiomer reacts to form product, while the "slow" enantiomer is inert. The end result is isolable enantiopure product and enantiopure starting material. While effective and particularly useful if both enantiopure product and starting material are desired, a kinetic resolution has limitations; namely, the process has a maximum theoretical product yield of 50%. To overcome this key limitation, chemists have developed dynamic kinetic resolutions (DKRs).[2] In a DKR, the same concept of a "fast" reacting enantiomer vs. a "slow" reacting enantiomer is applied. However, a DKR employs an additional reaction promoter or catalyst to conduct a racemization or interconversion event between the two enantiomers of starting material. In a system in which racemization is spontaneous, an additional promoter or catalyst is unnecessary for an effective DKR.

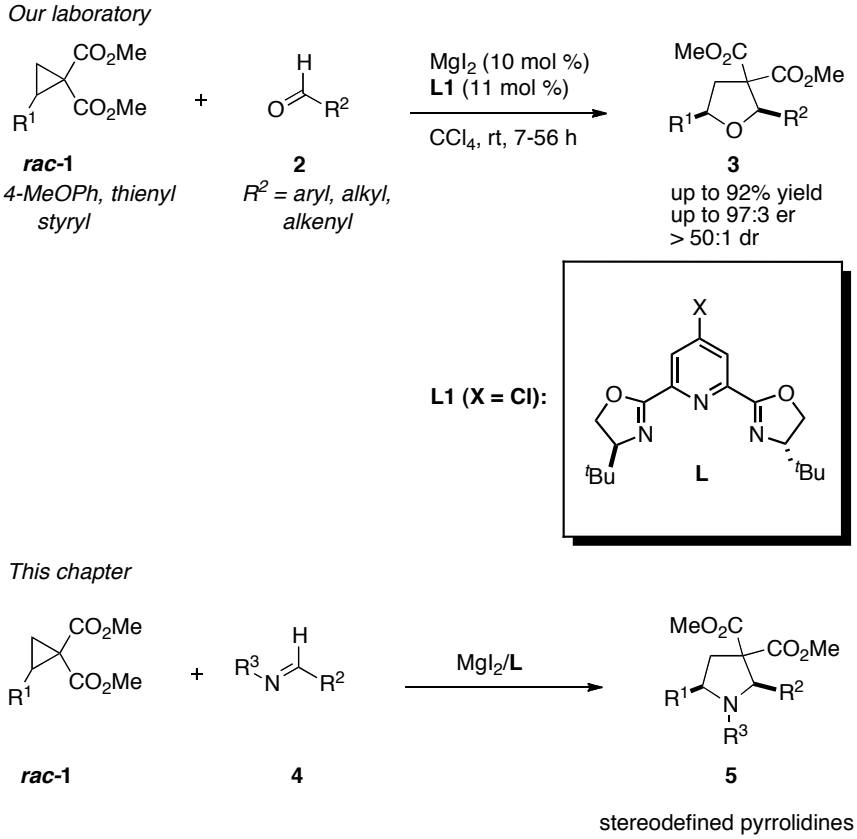
Figure 3-1. Simple and Dynamic Kinetic Resolution



The "slow" reacting enantiomer can thus be converted to the "fast" reacting enantiomer and eventually be transformed into desired enantiopure product. Unlike a kinetic resolution, a DKR has a maximum theoretical yield of 100%. A dynamic kinetic asymmetric transformation (DyKAT) is another technique used to access high yields of enantioenriched product from a mixture of racemates.[3] A DyKAT distinguishes itself from a DKR in that one chiral catalyst bears the dual responsibility of interconverting the substrate enantiomers and catalyzing the desired transformation. Our laboratory has published an enantioselective synthesis of substituted tetrahydrofurans *via* a DyKAT of racemic D-A cyclopropanes (***rac*-1**).[4] The reaction utilizes a (pybox)MgI_2 complex to catalyze both the interconversion of the starting cyclopropane enantiomers and the stereoselective (3+2)-annulation with aldehyde dipolarophiles. The end result is highly diastereo- and enantioenriched *cis*-2,5-dialkyl tetrahydrofurans. With the success of the (pybox)MgI_2 catalyst in the cyclopropane/aldehyde DyKAT, we were interested in observing its effect on other dipolarophiles known to participate in (3+*n*)-annulations with D-A cyclopropanes.[5] Specifically, we wanted to test *N*-

alkyl aldimine dipolarophiles of type **4**; an enantioselective (3+2)-annulation with racemic D-A cyclopropanes and aldimines would provide access to optically active 2,5-dialkyl pyrrolidines **5**. Substituted pyrrolidines are ubiquitous in nature and are an important heterocyclic subunit in myriad bioactive compounds. Consequently, routes to their synthesis have commanded the interest of several research groups. This chapter details the development and scope of a DyKAT of ***rac*-1** D-A cyclopropanes *via* (pybox)MgI_2-catalyzed (3+2)-annulation with (*E*)-aldimine dipolarophiles. Experiments with geometrically-constrained (*Z*)-aldimines help probe the mechanism of this transformation and lend support for an unusual 2,5-diaxial transition state that accounts for the observed *cis*-diastereoselectivity in **5**.

Scheme 3-1. Published DyKAT with D-A Cyclopropanes and Aldehydes (top) and Proposed Work with (*E*)-Aldimines (bottom)



3.2 Background

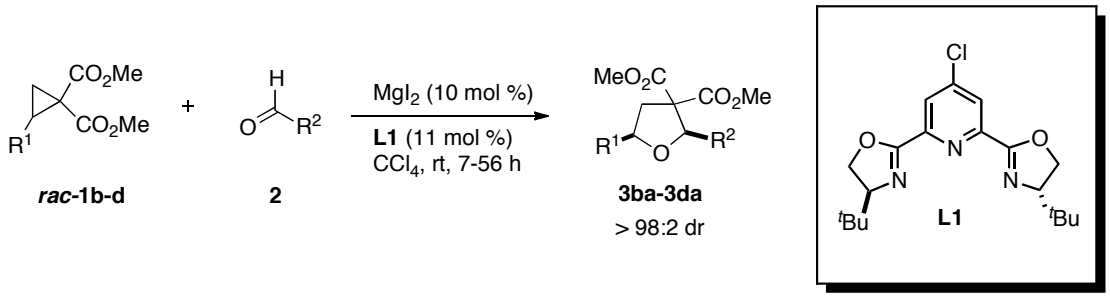
3.2.1 Early Work: Cyclopropane/Aldehyde DyKAT

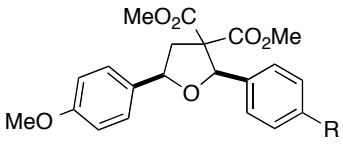
As detailed in Chapter 2, our laboratory has developed chemistry that allows access to optically active tetrahydrofurans in one step *via* (3+2)-annulation of D-A cyclopropanes and aldehydes.[7-9] A requirement of this method, however, is the use of nonracemic D-A cyclopropane starting materials. Routes to enantioenriched cyclopropanes are well established but often require multiple synthetic operations to arrive at the desired substrate. Indeed, published routes to type **1** D-A cyclopropanes require five synthetic steps and harsh oxidative conditions to install the desired diester;[10] alternatively, accessing racemic type **1** cyclopropanes can be achieved in two steps from inexpensive starting materials.[11] A route to enantioenriched THFs from racemic D-A cyclopropanes and aldehydes via a DyKAT would be significantly more attractive from a cost and utility standpoint. In order to achieve this difficult task, developing a catalyst effective at interconverting the starting cyclopropane enantiomers was required.

Our laboratory began its initial efforts with D-A cyclopropanes bearing electron-rich groups at the donor site, as previous mechanistic experiments suggested the rate of cyclopropane racemization with catalytic Lewis acid was dependent on donor-site carbenium ion stability.[8] While substrate racemization was undesired in the stereospecific (3+2)-annulation with optically active D-A cyclopropanes, our laboratory recognized these electron-rich cyclopropanes as potential platforms for the development of a dynamic kinetic asymmetric transformation; fast racemization of substrate is a requirement for a successful DyKAT.[3] Through extensive optimization of the Lewis acid, chiral ligand, solvent and reaction concentration, our laboratory developed a DyKAT of ***rac*-1** D-A cyclopropanes with

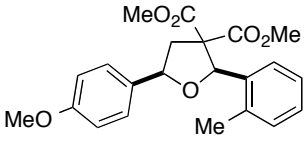
aldehydes.[4,12] The reaction is catalyzed by a (pybox)MgI_2 complex. Ligand optimization revealed ^{t}Bu-pybox ligands to be critical for high enantioselectivity. In addition, moderately electron-deficient groups in the 4-position on the pyridine ligand provided the highest yields, with 4-Cl-pybox being optimal. The best balance between stereoselectivity and yield was observed in CCl_4. The results from the DyKAT substrate scope are summarized in Scheme 3-2.

Scheme 3-2. Substrate Scope for the (pybox)MgI_2-Catalyzed DyKAT of D-A Cyclopropanes **1b-d** and Aldehydes

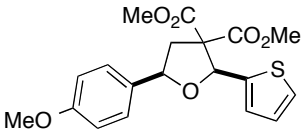




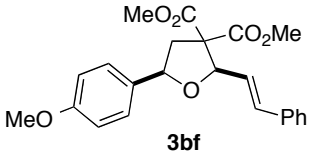
R = 4-MeO **(3ba)** 88% yield, 95:5 er
= 4-Cl **(3bb)** 65% yield, 94:6 er
= 4-F_3C **(3bc)** 48% yield, 91.5:8.5 er



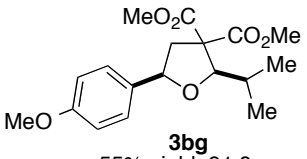
3bd
81% yield, 96.5:3.5 er



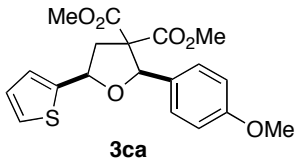
3be
84% yield, 95.5:4.5 er



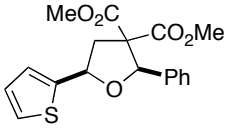
3bf
92% yield, 94:6 er



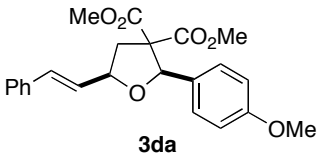
3bg
55% yield, 91:9 er



3ca
91% yield, 97:3 er



3ch
64% yield, 96.5:3.5 er

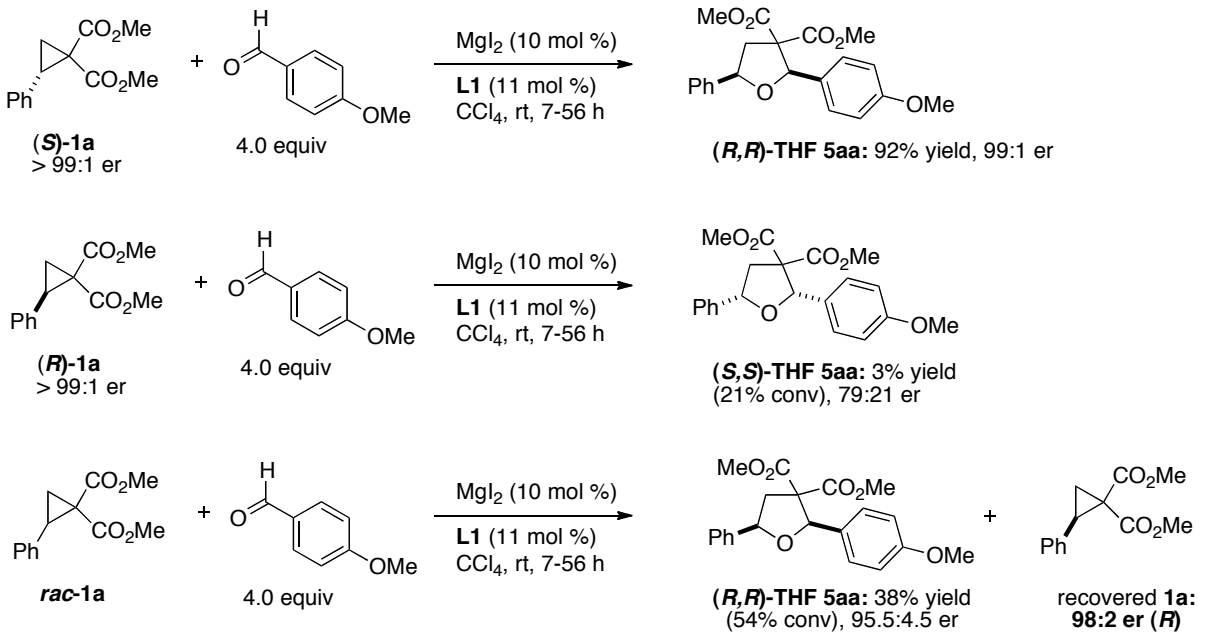


3da
75% yield, 95:5 er

The reaction was tolerant of both electron-rich and electron-poor aromatic aldehydes but yields decreased significantly in the latter cases. Heteroaromatic, alkenyl, and aliphatic aldehydes all provided desired THF product in promising to high yield and enantioselectivities above 91:9. The main limitation arose from the R^1 group on the cyclopropane starting material. Only 4-MeOPh, thienyl, and styryl-substituted cyclopropanes were effective substrates in this dynamic system due to their increased rate of racemization.

Cyclopropane ***rac*-1a** (R^1 = Ph) was unable to participate in the dynamic system presumably due to a slow rate of racemization but did exhibit excellent substrate selectivity with MgI_2/**L1**; **1a** was thus a substrate for a simple kinetic resolution. Control experiments with **1a** provided useful pieces of mechanistic information (Scheme 3-3).[4] When cyclopropane **(*S*)-1a** (>99:1 er) was subjected to the standard DyKAT conditions with 4.0 equivalents of anisaldehyde, **(*R*,*R*)-THF-5aa** was isolated in 92% yield and >99:1 er. A comparison of the optical rotation data to previously reported data for **5aa** allowed for the absolute stereochemical assignment.[8] Conducting a similar experiment with **(*R*)-1a** resulted in low conversion to the desired product; **(*S*,*S*)-THF-5aa** was isolated in 3% yield (21% conversion) and 79:21 er. An analogous experiment with ***rac*-1a** produced **(*R*,*R*)-THF-5aa** in 38% yield (54% conversion) and 95.5:4.5 er. Analysis of unreacted **1a** by gas chromatography and comparison to previously reported data for **1a** showed the sample to be highly enriched in the (*R*)-enantiomer (98:2 er).[10]

Scheme 3-3. Mechanistic Experiments with Cyclopropane **1a**



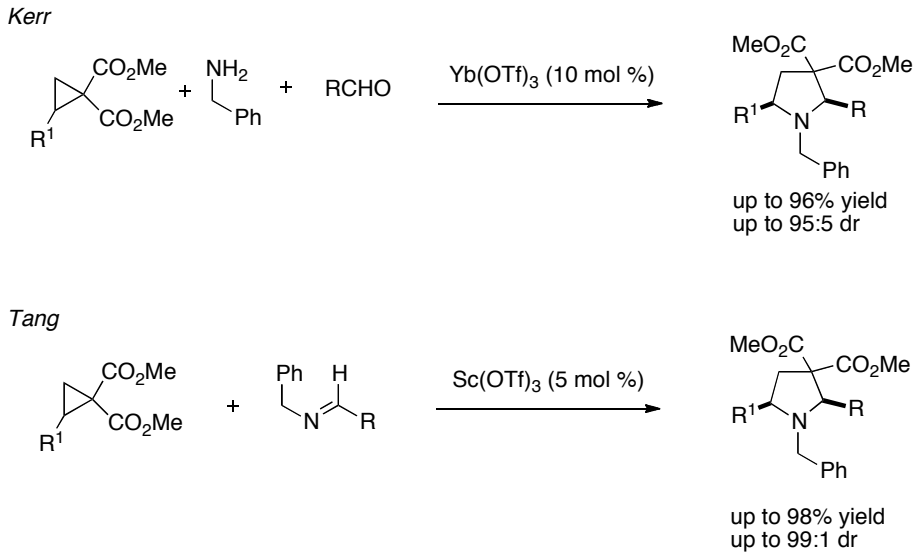
These experimental results suggest the (**L1**)MgI_2-complex directs aldehyde annulation with enantiomer **(*S*)-1a** preferentially. The slow reaction rate with enantioenriched **(*R*)-1a**, the absolute stereochemical assignment of **(*R,R*)-THF-5aa** in the reaction with ***rac*-1a**, and the stereochemical analysis of recovered **1a** in the experiment with ***rac*-1a** support this conclusion. Also, the results from the reactions with **(*S*)-1a** and **(*R*)-1a** provide evidence that a stereospecific nucleophilic substitution mechanism is operative.

3.2.2 Extension of DyKAT to Aldimine Dipolarophiles

Finding success with aldehydes in the (pybox)MgI_2-DyKAT of racemic cyclopropanes **1b-1d**, we were curious if other dipolarophiles known to participate in reactions with D-A cyclopropanes under Lewis acid catalysis could undergo annulation in a dynamic process. Kerr and Tang have independently reported highly diastereoselective, racemic syntheses of *cis*-2,5-dialkyl pyrrolidines *via* (3+2)-annulation of D-A cyclopropanes

and *N*-benzyl (*E*)-aldimines.[13,14] $Yb(OTf)_3$ and $Sc(OTf)_3$ both catalyzed this transformation in excellent yields and dr's up to 95:5 and 99:1, respectively (Scheme 3-4).

Scheme 3-4. Kerr and Tang's Published (3+2)-Annulations with D-A Cyclopropanes and Aldimines

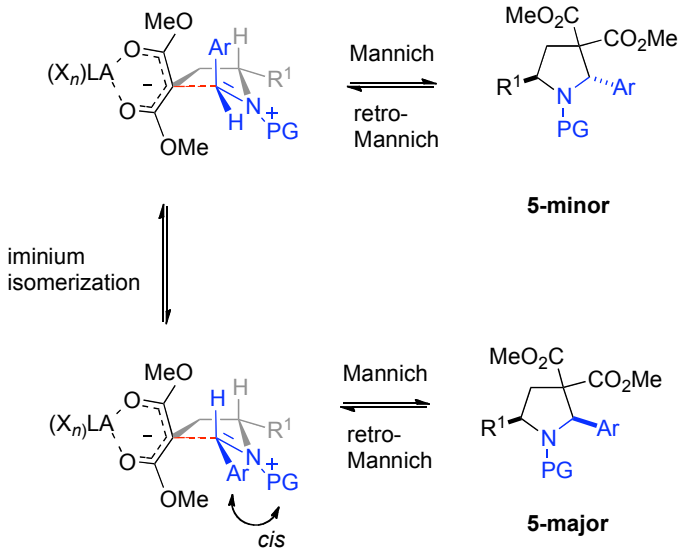


Pyrrolidines are prevalent substructures in many bioactive natural products.[15] Furthermore, optically active pyrrolidines and proline derivatives have found important use as organocatalysts in a variety of enantioselective processes.[16] A route to enantioenriched pyrrolidines in one step from racemic, easily accessible starting materials would therefore be of high synthetic value.

Models proposed by Kerr to account for the observed *cis*-diastereoselectivity in the (3+2)-annulation with aldimine dipolarophiles hinge on the fluxional *E*/*Z* geometry of aldimines.[13] After *N*-alkylation, Mannich-type ring closure onto an (*E*)-iminium ion through an envelope transition state would place the R^1 group on the cyclopropane in a pseudoequatorial position and the Ar group on the aldimine in a pseudoaxial position. This transition state would provide access to the minor-*trans* product. Kerr postulates that a retro-Mannich reaction of this *trans*-cycloadduct followed by iminium isomerization to the (*Z*)-

isomer occurs. This isomerization would place both Ar and R^1 in a pseudoequatorial arrangement in an envelope transition state; Mannich-type ring closure at this juncture would lead to the major *cis*-product (Scheme 3-5). Kerr also suggests the major *cis*-isomer could arise from an (*E*)/(*Z*)-aldimine isomerization prior to alkylation. However, he does not perform any additional experiments to probe either of these mechanistic pathways.

Scheme 3-5. Kerr's Mechanistic Proposal for Observed *Cis*-Diastereoselectivity



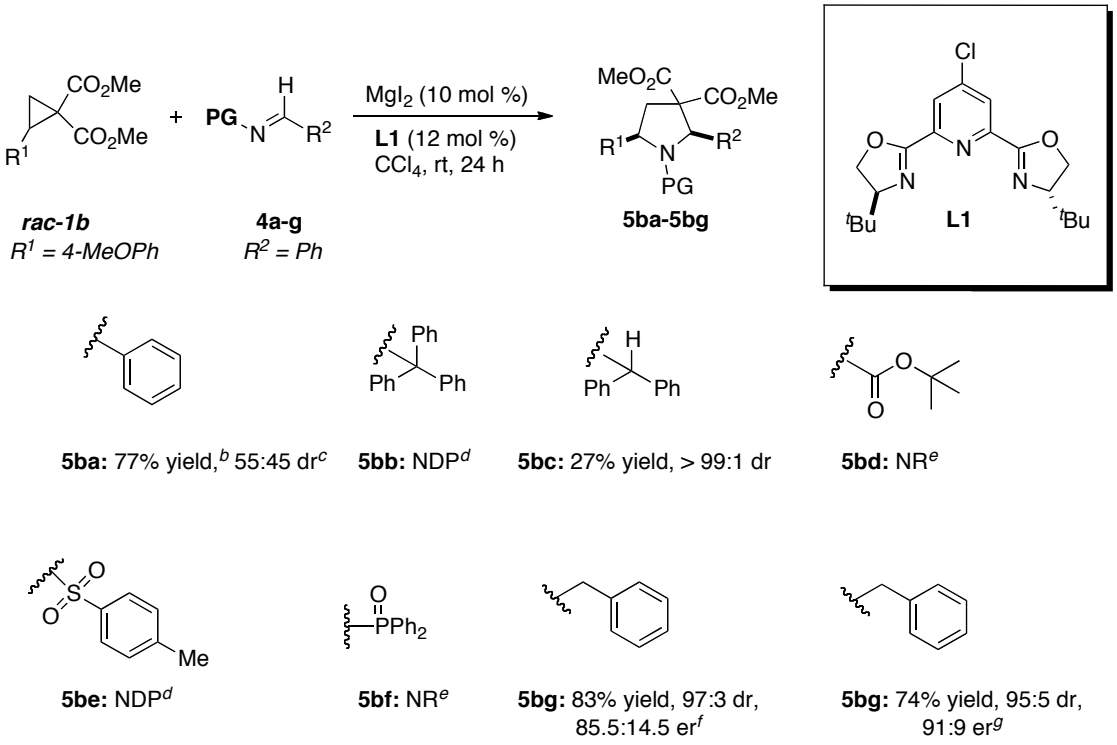
This chapter details the development and scope of a (pybox)MgI_2-catalyzed DyKAT of type **1** D-A cyclopropanes with (*E*)-aldimines.[17] Single crystal X-ray diffraction analysis of a derivative of one of the enantioenriched pyrrolidine cycloadducts confirms the product to be of (*R,R*)-absolute stereochemistry. Studies with a cyclically-constrained (*Z*)-aldimine strongly suggest an (*E*)-aldimine reaction pathway accounts for the major *cis*-isomer, counter to Kerr's mechanistic proposal.

3.3 Results and Discussion

3.3.1 Reaction Optimization

Both Kerr and Tang observed an effect on diastereoselectivity with different protecting groups on nitrogen in their racemic cyclopropane/aldimine annulations.[13,14] Therefore, we began our studies by screening a variety of *N*-protecting groups in the (pybox)MgI_2 system. Reactions were performed with benzaldehyde-derived aldimine and the optimal 4-Cl-^{t}BuPybox/MgI_2 catalyst that was identified in the cyclopropane/aldehyde DyKAT. The results are summarized in Scheme 3-6.

Scheme 3-6. Protecting Group Screen[a]

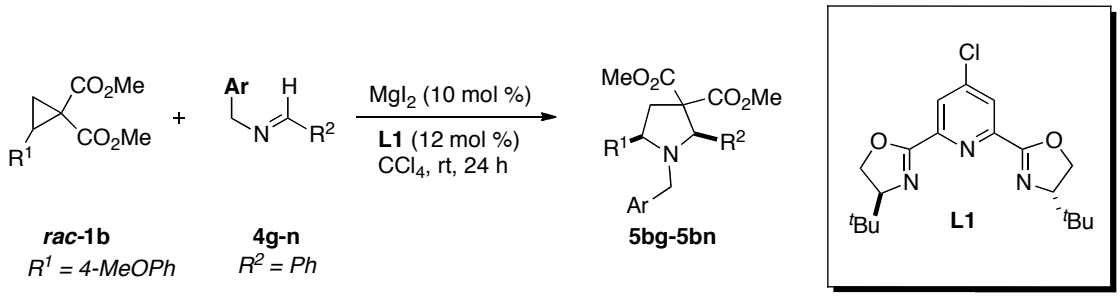


[a]Reaction conditions: **1b** (1.0 equiv), **4a-g** (2.0 equiv), MgI_2 (0.10 equiv), **L1** (0.12 equiv), $[\mathbf{1b}]_0$ = 0.050 M in CCl_4, rt, 24 h. [b]Yield determined by 1H NMR spectroscopy using a mesitylene internal standard. [c]Ratio determined by 1H NMR analysis of crude material. [d]No desired product observed. [e]No reaction. [f]Ratio determined by chiral SFC analysis. [g]Reaction performed with 1.1 equiv of **4g**.

The protecting group identity had a dramatic effect on reaction results. Consistent with Kerr and Tang's work, the best results were observed with benzyl protecting groups. Pyrrolidine **5bg** was synthesized in 83% yield with 97:3 dr for the 2,5-*cis*-dialkyl isomer and 85.5:14.5 er with *N*-benzyl aldimine **4g**. Interestingly, lowering the equivalents of **4g** from 2.0 to 1.1 led to a significant increase in enantioselectivity (91:9 er) with only a modest drop in yield and diastereoselection (74%, 95:5 dr). Encouraged by this result, and in anticipation of being able to easily deprotect the *N*-benzyl pyrrolidine under hydrogenolysis conditions, we examined the remaining parameters of this transformation with 1.1 equivalents of *N*-benzyl aldimine.

We next explored the effect of substitution patterns on the protecting group aromatic ring. The results are found in Scheme 3-7.

Scheme 3-7. An Examination of Benzyl Protecting Group Substitution Patterns[a]

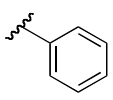


***rac*-1b**
R^1 = *4-MeOPh*

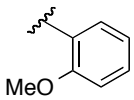
4g-n
R^2 = *Ph*

5bg-5bn

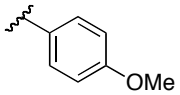
Ar:



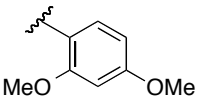
5bg: 74% yield,[b] 95:5 dr[c] 91:9 er[d]



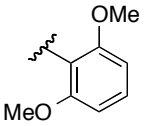
5bh: 71% yield, 96:4 dr, 95:5 er



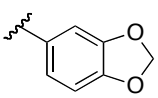
5bi: 77% yield, 95:5 dr 90.5:9.5 er



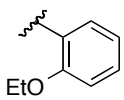
5bj: 75% yield, 96:4 dr 93:7 er



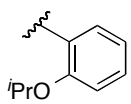
5bk: 69% yield, 99:1 dr, 90.5: 10.5 er



5bl: 68% yield, 80:20 dr 92:8 er



5bm: 76% yield, 95:5 dr, 94:6 er



5bn: 75% yield, 94:6 dr, 96:4 er

[a]Reaction conditions: **1b** (1.0 equiv), **4g-4n** (1.1 equiv), MgI_2 (0.10 equiv), **L1** (0.12 equiv), $[\mathbf{1b}]_0$ = 0.050 M in CCl_4, rt, 24h. [b]Yield determined by ^1H NMR spectroscopy using a

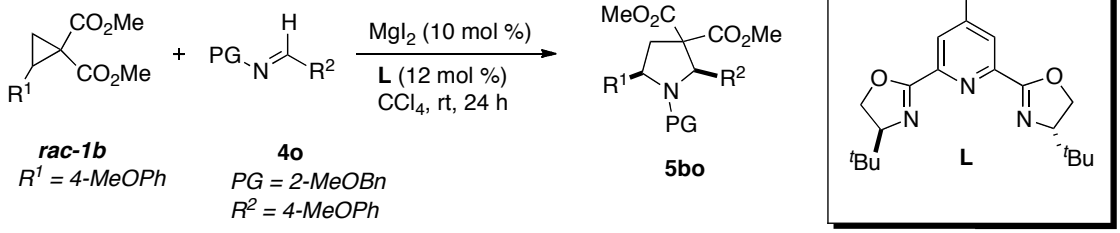
mesitylene internal standard. [c]Ratio determined by ^{1}H NMR analysis of crude material. [d]Ratio determined by chiral SFC analysis.

Changes to the benzyl protecting group led to slightly varied results. While yields were roughly the same throughout, higher levels of enantioselectivity were seen with 2-alkoxy substituted aldimines. 2-methoxy- (**5bh**), 2-ethoxy- (**5bm**), and 2-isopropoxybenzyl protecting groups (**5bn)** all provided the highest combination of yield, dr and er; however, of these parent amines, only the 2-methoxybenzylamine was commercially available. The high selectivity obtained with 2-methoxybenzyl aldimine and its ready availability led us to proceed with this protecting group for the remainder of our studies.

With the optimal *N*-protecting group identified, we next investigated the effect of the chiral ligand in this transformation. In the aldehyde/cyclopropane DyKAT, ^{t}BuPybox ligands proved critical for high levels of enantioselectivity.[12] In addition, electron-deficient pybox ligands provided significant increases in yield compared to unsubstituted and electron-rich pybox ligands. With this latter set of results in mind, we examined the optimal pybox ligand for the aldimine/cyclopropane DyKAT. We chose to conduct this study with anisaldehyde-derived aldimine **4o** due to its tendency to give lower enantioselectivities in preliminary experiments (data not shown). We inferred that this aldimine would better allow us to distinguish the subtleties of ligand effects. The results of this study are summarized in Table 3-1. Unsubstituted ^{t}BuPybox ligand (X = H) gave incomplete conversion after 24 hours (entry 3). Consistent with results obtained from the cyclopropane/aldehyde DyKAT, electron-deficient ligands provided complete conversions and the highest yields of desired pyrroldine (entries 1-2, 4). We observed the highest yield overall with 4-Br-^{t}BuPybox ligand (79%, entry 3). In addition, we noted a slight increase in enantioselectivity with the 4-Br-

^{t}BuPybox ligand (93:7 er) compared to the previously optimal 4-Cl-^{t}BuPybox in the cyclopropane/aldehyde DyKAT (89.5:10.5 er).

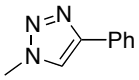
Table 3-1. Ligand Optimization



rac-1b
R^1 = 4-MeOPh

4o
PG = 2-MeOBn
R^2 = 4-MeOPh

5bo

entry	X	conversion (%)[b]	yield (%)[b]	dr[c]	er[d]
1	Cl	100	66	96:4	89.5:10.5
2	Br	100	79	97:3	93:7
3	H	44	39	84:16	74:26
4	CF_3	100	69	96:4	92:8
5	Ph	93	63	94.5:5.5	83:17
6	Mes	64	56	91:9	89:11
7		100	76	94.5:5.5	80:20

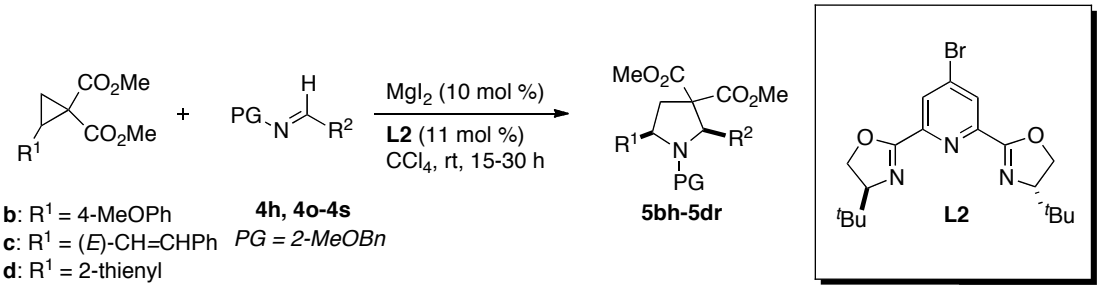
[a]Reaction conditions: **1b** (1.0 equiv), **4o** (1.1 equiv), MgI_2 (0.10 equiv), **L** (0.12 equiv), $[\mathbf{1b}]_0$ = 0.050 M in CCl_4, rt, 24 h. [b]Determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. [c]Ratio determined by ^{1}H NMR analysis of crude material. [d]Ratio determined by chiral SFC analysis.

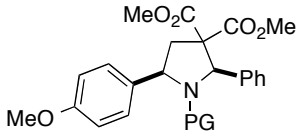
3.3.2 Substrate Scope and Deprotection Scheme

We next investigated the substrate scope for this transformation. As was observed in the cyclopropane/aldehyde DyKAT, only electron-rich donor site cyclopropanes were dynamic in the (pybox)MgI_2 system (R^1 = *p*-OMePh, (*E*)-CH=CHPh, 2-thienyl). Electron-rich, electron-poor aromatic and heteroaromatic (*E*)-aldimines were all tolerated in this transformation. Yields of the desired pyrrolidine product ranged from 66-86%, with enantioselectivies at or above 95.5:4.5 er and products generally isolated as a single

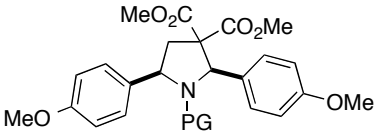
diastereomer. The substrate scope for this reaction was more limited than the cyclopropane/aldehyde DyKAT. In the seminal work, aliphatic aldehydes were tolerated in the (pybox)MgI_2 system with dynamic cyclopropanes. However, in the cyclopropane/aldimine DyKAT, aliphatic (*E*)-aldimines led to significant decomposition. This was not unexpected, as aliphatic aldimines were not tolerated in either Kerr or Tang's racemic systems. The results from the cyclopropane/aldimine DyKAT are summarized in Scheme 3-8.

Scheme 3-8. Substrate Scope for Cyclopropane/Aldimine DyKAT[a]

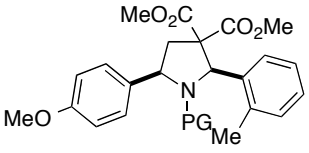




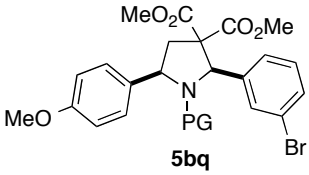
5bh
70% yield,[b] 97:3 dr,[c] 96.5:3.5 er[d]



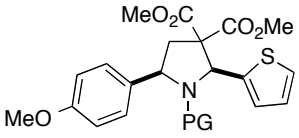
5bo
79% yield, 96:4 dr
93:7 er



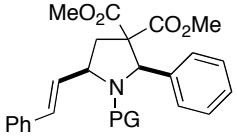
5bp
86% yield, 98:2 dr,
94.5:5.5 er



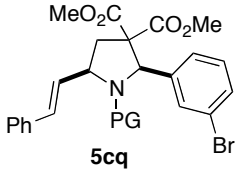
5bq
67% yield, 97:3 dr,
er 96:4 er



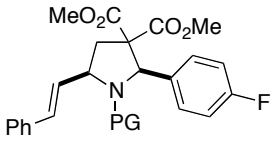
5bs
83% yield, 93:7 dr,
97.5:2.5 er



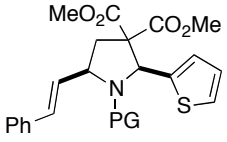
5ch
73% yield, 91:9 dr,
98:2 er



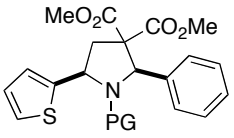
5cq
67% yield, 93:7 dr,
97:3 er



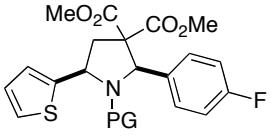
5cr
73% yield, 92:8 dr,
97:3 er



5cs
85% yield, 87:13 dr,
97:3 er



5dh
66% yield, 92:8 dr,
95.5:4.5 er



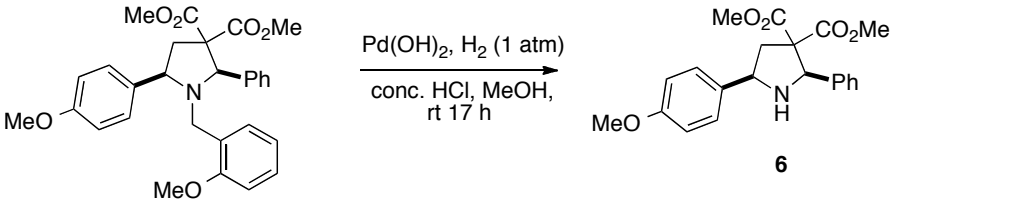
5dr
69% yield, 96:4 dr,
95.5:4.5 er

[a]Reaction conditions: **1b-d** (1.0 equiv), **4h, 4o-4s** (1.1 equiv), MgI_2 (0.10 equiv), **L2** (0.11 equiv), [**1b-d**]$_0$ = 0.050 M in CCl_4, rt, 15-30 h. [b]Isolated yield, average of two trials. [c]Ratio determined by ^{1}H NMR analysis of crude material. [d]Ratio determined by chiral SFC analysis.

The asymmetric (3+2)-annulation of D-A cyclopropanes and aldimines presented an added challenge that did not exist in the cyclopropane/aldehyde DyKAT. The isolated *N*-

alkyl pyrrolidine adducts needed to be deprotected to reveal the desired free pyrrolidine. Hydrogenolysis conditions using catalytic $Pd(OH)_2$ proved effective for this task.[18] Deprotection results showed a correlation between Pd-catalyst loading and racemization of the enantioenriched pyrrolidine adduct. When 2-methoxybenzyl pyrrolidine **5bh** (96.5:3.5 er) was treated with 10 mol% $Pd(OH)_2$ and concentrated HCl in 1 atm H_2, free pyrrolidine **6** was isolated in 86% yield and only a slight loss in enantioenrichment (95:5 er, Scheme 3-9).

Scheme 3-9. Deprotection of *N*-Benzyl Pyrrolidines



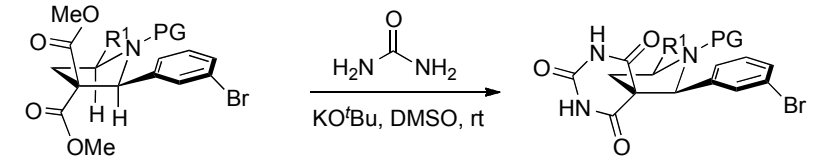
5bh, 96.5:3.5 er

20 mol% $Pd(OH)_2$: 94% yield, 93.5:6.5 er
10 mol% $Pd(OH)_2$: 86% yield, 95:5 er
5 mol% $Pd(OH)_2$: 74% yield, 95.5:4.5 er

3.3.3 Stereochemical Analysis and Mechanistic Rationale

Key mechanistic experiments with aldehyde dipolarophiles and ***rac*-1a** demonstrated an aldehyde reactivity preference for the (***S*)-1a** enantiomer when treated under the DyKAT conditions. Reactions with enantioenriched **1a** and aldehydes provided evidence for a stereospecific reaction mechanism to be operative (Section 3.2.1). To determine whether aldimine dipolarophiles displayed similar reactivity in the DyKAT, we synthesized the barbituric acid derivative of pyrrolidine adduct **5bq** (96:4 er). Single crystal X-ray diffraction analysis confirmed the (***R,R***) absolute stereochemical configuration in **7** (Scheme 3-10). The absolute configuration was identical to that observed with the THFs in the cyclopropane/aldehyde DyKAT. At least with respect to enantiopreference, this data suggested aldimine dipolarophiles reacted identically to aldehydes in the DyKAT.

Scheme 3-10. Absolute Stereochemical Determination through Single Crystal X-Ray Diffraction Analysis of Barbituric Acid Derivative **7**

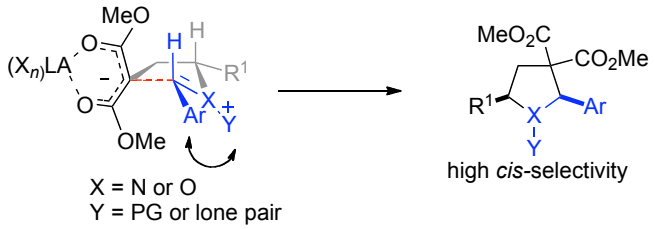


5bq: 96:4 er
R^1 = 4-MeOPh, PG = 2-MeOBn

***(R,R)*-7**: 52% yield (X-ray)

Kerr's proposal of an (*E*)/(*Z*)-aldimine or iminium ion isomerization to account for the observed *cis*-diastereoselectivity in the racemic pyrrolidine synthesis is consistent with known cyclopropane/aldehyde *cis*-selectivity models, in which Ar and R^1 are positioned pseudoequatorially in an envelope transition state (Figure 3-2).[8]

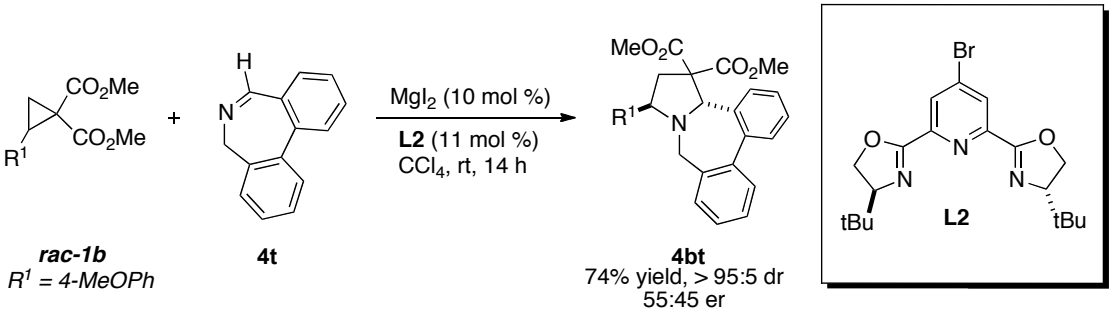
Figure 3-2. Kerr's Postulated Model Based on Aldehydes



In order to probe the geometry of the reactive aldimine in this system, we synthesized cyclically-constrained (*Z*)-aldimine **4t** and tested it under the DyKAT conditions with ***rac*-1b**.[19] We collected a series of fascinating results. When (*Z*)-aldimine **4t** was treated under the standard conditions with ***rac*-1b**, pyrrolidine **4bt** was produced in 74% yield as the 2,5-*trans*-disasteromer in slight enantioenrichment (55:45 er, Scheme 3-11). The pyrrolidine existed as a 2:1 mixture of fluxional atropisomers by ^{1}H NMR. The trans-stereochemistry was initially assigned from 2D-NOESY data by converting **4bt** to the trifluoroacetic acid salt, which favored one atropisomer. The stereochemistry was later confirmed *via* single crystal X-ray diffraction analysis. These data strongly suggest that the major *cis*-diastereomer in the

cyclopropane/aldimine DyKAT is not a product of a (*Z*)-aldimine or (*Z*)-iminium ion pathway, since aldimine and iminium isomerization with aldimine **4t** is precluded.

Scheme 3-11. Results with (*Z*)-Aldimine **4t** and **rac-1b** Under (pybox)MgI_2 Conditions



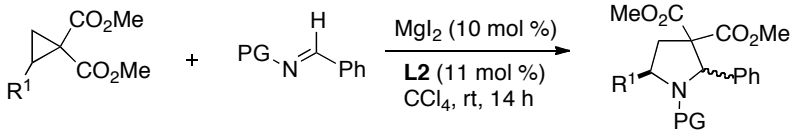
rac-1b
R^1 = 4-MeOPh

4t

4bt
74% yield, > 95:5 dr
55:45 er

The results with the (*Z*)-aldimine also came in contrast to results collected for the minor *trans*-isomer in the substrate scope with (*E*)-aldimines. The *cis* and *trans*-isomers of **5ch,** obtained *via* annulation of **1c** and (*E*)-aldimine **4h**, were both found to have an er of 98:2 as determined by SFC analysis (Scheme 3-12). Taken together, these data suggest that the minor *trans*-diastereomer in the cyclopropane/(*E*)-aldimine DyKAT is not a product of a (*Z*)-aldimine reaction pathway. One would expect this minor *trans*-cycloadduct to be in poor enantioenrichment if that was the case. These results led us to re-examine our rationale for the observed diastereoselectivity in the aldimine/cyclopropane DyKAT.

Scheme 3-12. Results from Annulation of ***rac*-1c** with **4h**



rac-1c
R^1 = CH=CHPh

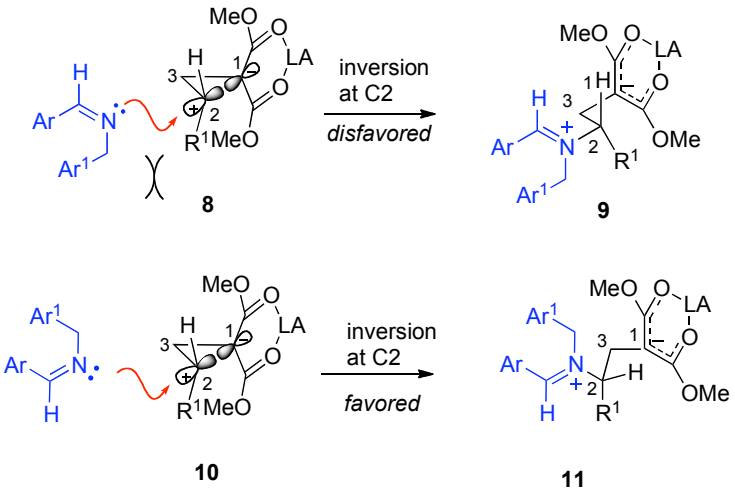
4h
PG = 2-MeOBn

5ch
73% yield, 91:9 *cis/trans*
98:2 er *cis* = er *trans*

(*Z*)-Aldimines are geometrically similar to aldehydes, so the resultant *trans*-pyrrolidines come unexpectedly, especially when one considers that aldimines react with high stereoselectivity in the (pybox)MgI_2 DyKAT with virtually no deviation from the

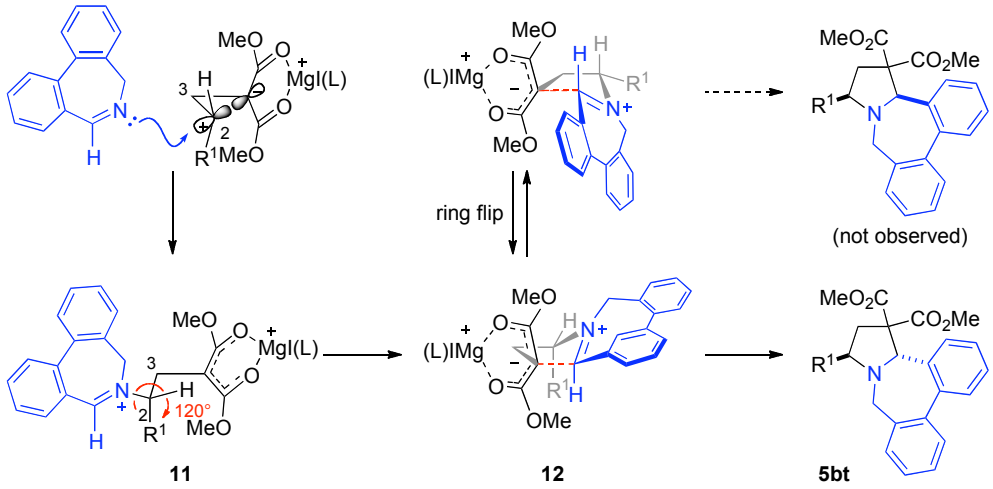
reaction conditions optimized for aldehydes. (*Z*)-Aldimines do differ from aldehydes, however, in the presence of a heteroatom substituent. If one considers this feature in the context of dipolarophile approach to the cyclopropane-MgI_2 complex, the benzyl protecting group on the (*Z*)-aldimine could be responsible for the switch in diastereoselectivity. This concept is illustrated in Figure 3-3. A negative steric interaction in **8** between the benzyl protecting group on the aldimine and R^1 on the cyclopropane could disfavor an approach that mimics the one observed for aldehyde dipolarophiles (cf. Chapter 2). Alleviating this steric penalty *via* 180° rotation (about the N-C2 internuclear axis) in aldimine approach could promote an interaction similar to **10**. Alkylation at C2 from **10** would result in an iminium ion **11** with increased $A^{1,3}$ strain between R^1 and H compared to iminium ion **9**; however, deuterium labeling studies in the (3+2)-annulation between cyclopropanes and aldehydes suggest 120° bond rotation about the C2-C3 bond and subsequent ring closure after alkylation at C2 are fast.[20] It is reasonable to assume the same mechanistic feature holds true in this system. If the steric interaction in **8** is significant enough compared to **10**, then any preference for iminium ion **9** over **11** becomes inconsequential.

Figure 3-3. Considering the (*Z*)-Aldimine Approach



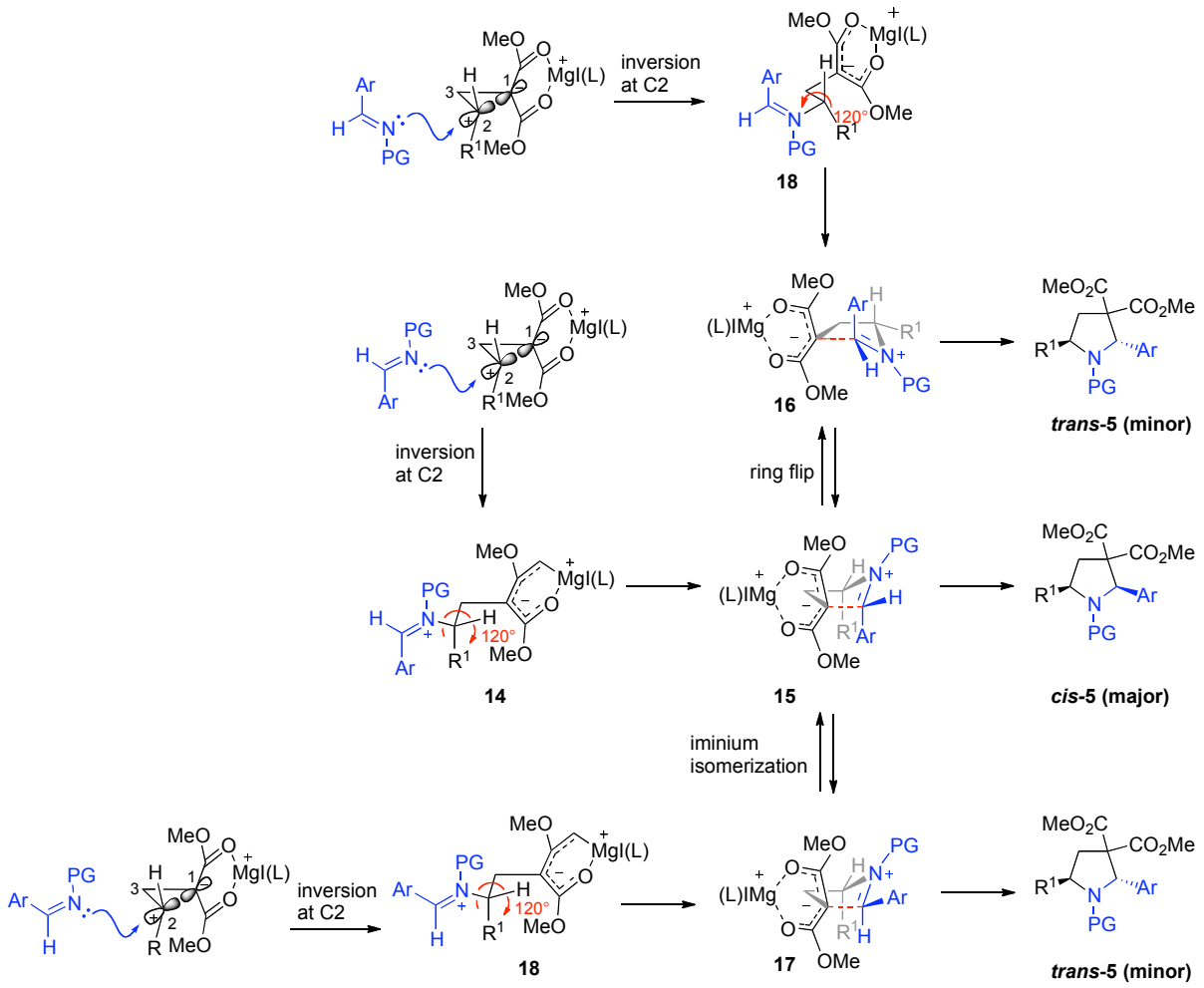
With this consideration of the (*Z*)-aldimine approach, we postulated a mechanism that accounts for the observed *trans*-diastereoselectivity with cyclically-constrained **5t** (Scheme 3-13). Avoiding a negative steric interaction between the benzyl group and R^1 leads to *N*-alkylation and inversion of stereochemical configuration at C2. Least motion 120° bond rotation about the C2-C3 bond in iminium ion **11** leads to envelope **12**, in which R^1 and the aldimine H are pseudoaxial. Diastereoselective ring closure provides exclusive formation of *trans*-pyrrolidine **5bt**.

Scheme 3-13. Mechanistic Rationale for the *Trans*-Pyrrolidine Product Derived from Aldimine **2t**



A similar analysis can be applied to the (3+2)-annulation of D-A cyclopropanes and (*E*)-aldimines (Scheme 3-14). Minimizing the steric penalty between the benzyl protecting group and R^1 on the cyclopropane leads to iminium ion **14** after *N*-alkylation. Least motion 120° bond rotation about C2-C3 leads to envelope **15**, in which R^1 and Ar are both positioned pseudoaxially. Placing these groups in a pseudoaxial orientation presumably minimizes $A^{1,3}$ strain between R^1 and PG in **16** and Ar and PG in **17**. This rationale is precedented by related *N*-acyl iminium ion cyclizations.[21] Ring closure from **15** provides the *cis*-pyrrolidine **5-major**. We have identified several possible pathways that can account for the minor *trans*-diastereomer: 1) ring flip from **15** to envelope **16** followed by Mannich ring closure; 2) iminium isomerization from **15** to the (*Z*)-iminium ion **17** followed by ring closure; 3) 180° reversal in (*E*)-aldimine approach prior to *N*-alkylation, which would lead to envelope **16** directly; and, 4) *E*/*Z* aldimine isomerization prior to *N*-alkylation.

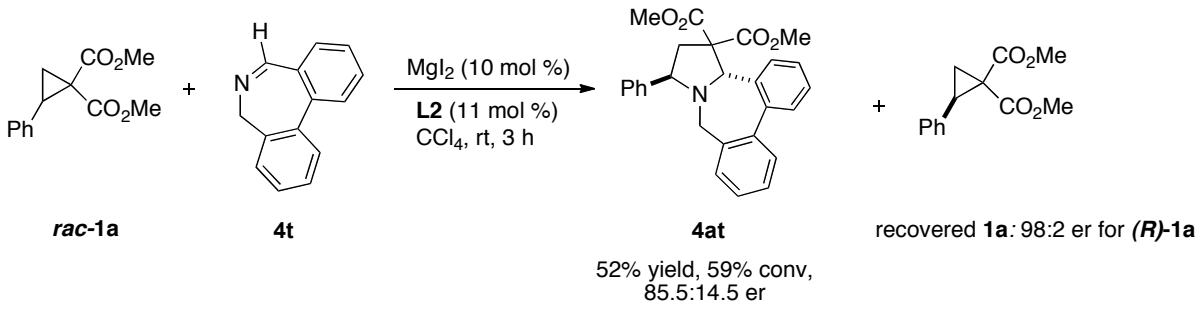
Scheme 3-14. Proposed Mechanism for (pybox)MgI_2-Catalyzed (3+2)-Annulation of (*E*)-Aldimines and D-A Cyclopropanes



At first glance, pathway 4 seems unlikely; we observed high er for the minor *trans*-adduct **5ch** and very poor enantioenrichment when (*Z*)-aldimine **4t** was used in conjunction with ***rac*-1b**. However, if *E*/*Z* aldimine isomerization were slow under DyKAT conditions, it would keep the effective concentration of the more nucleophilic (*Z*)-aldimine in low amounts. This could significantly slow the rate of *N*-alkylation with the (*Z*)-aldimine as compared to the experiments with cyclically-constrained (*Z*)-aldimine **5t**, which is unable to isomerize and is therefore always present in high concentration. If *N*-alkylation is slow, cyclopropane racemization could outcompete alkylation and promote an effective DyKAT.

The low er for the *trans*-pyrrolidine derived from cyclically-constrained (*Z*)-aldimine **4t** was a either a product of poor enantiomer discrimination or a product of *N*-alkylation simply outcompeting racemization. If the latter was true, then pathway 4 was feasible. To test this, we performed an experiment to partial conversion with ***rac*-1a** and (*Z*)-aldimine **5t** under the optimized (**L2**)MgI_2 conditions (Scheme 3-15). After three hours, *trans*-pyrrolidine **4at** was isolated in 52% yield (59% conversion) and 85.5:14.5 er as determined by SFC analysis. Recovered **1a** was found to be highly enriched in the *R*-enantiomer by gas chromatography (98:2 er).[10] These results indicate that (*Z*)-aldimine **4t** does have a preference in the DyKAT for reaction with the *S*-enantiomer of cyclopropane. The low enantioenrichment observed with the more nucleophilic **4t** in the DyKAT is thus a product of noncompetitive cyclopropane racemization. Pathway 4 as a rationale for the minor *trans*-cycloadduct in the DyKAT with (*E*)-aldimines is sound.

Scheme 3-15. Control Experiment with ***rac*-1a** and **4t**



3.4 Conclusions

We have discovered the (pybox)MgI_2 complex developed for the DyKAT of D-A cyclopropanes with aldehydes is also compatible with aldimine dipolarophiles. Aromatic 2-methoxybenzyl-protected (*E*)-aldimines and electron-rich D-A cyclopropanes **1b-d** capable of fast racemization at room temperature react to form *cis*-2,5-dialkyl pyrrolidines in high

diastereo- and enantioenrichment. The 2-methoxybenzyl-protected cycloadducts can be deprotected to reveal the free pyrrolidine with a negligible loss in enantioenrichment. The (2*R,5R)* absolute stereochemical assignment of the pyrrolidine products has been proven *via* single crystal X-ray analysis, indicating the (*E*)-aldimine dipolarophiles display the same enantiopreference for the *S*-enantiomer of cyclopropane as aldehydes. Control experiments with cyclically-constrained (*Z*)-aldimine **2t** and cyclopropane **1b** under (pybox)MgI_2 conditions provide the *trans*-pyrrolidine exclusively; these results strongly disfavor the previously-proposed aldimine or iminium ion isomerization to the (*Z*)-isomer as the likely rationale for the *cis*-selectivity. We propose an unusual diaxial transition state **15** to account for the observed 2,5-*cis*-selectivity, with the aldimine reacting as the (*E*)-isomer.

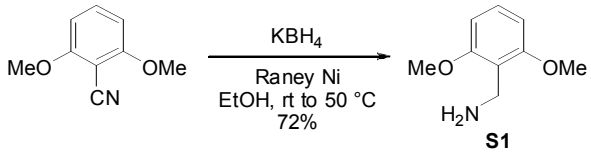
3.5 Experimental

Methods. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 500 (^{1}H NMR at 400 MHz or 500 MHz and ^{13}C NMR at 100 or 125 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, DMSO-d6 at 2.54 ppm, CD_2Cl_2 at 5.32 ppm, and C_6D_6 at 7.15 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, DMSO-d6 at 40.45 ppm, CD_2Cl_2 at 54.0 ppm, and C_6D_6 at 128.6 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector

= FID, 250 ºC) with helium gas as carrier. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralpack WO column (modifier = 2.0% MeOH, flow = 2.0 mL/min, pressure = 200 bar, detector = UV, 210 nm). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63 μm) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

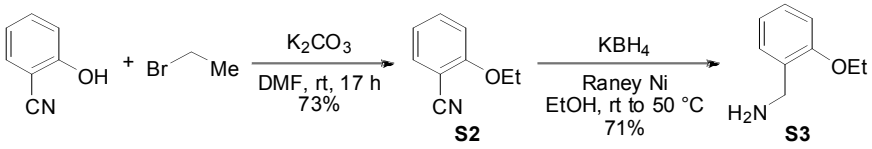
Materials. Dichloromethane was dried by passage through a column of neutral alumina under nitrogen prior to use. Dichloroethane was distilled from calcium hydride under N_2 and stored in a Schlenk flask. Carbon tetrachloride was purified by distillation from phosphorous pentoxide under N_2. Pybox ligands **L1-L7** were synthesized according to previously published work.[4] All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

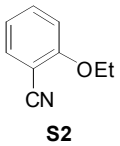
Preparation of (2,6-dimethoxyphenyl)methanamine (S1).



A 100-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (36 mL), potassium borohydride (2.65 g, 49.0 mmol, 4.0 equiv), Raney Ni (1.8 mL of a 50% suspension in H_2O, approx. 1.0 equiv), and 2,6-dimethoxybenzonitrile (2.0 g, 12.26 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 1.5 h at room temperature. The reaction was warmed to 50 °C and stirred for 5.5 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (75 mL), washed with H_2O (3 x 75 mL), dried over magnesium sulfate, and concentrated to afford **S1** (1.48 g, 7.03 mmol, 72% yield) as a clear colorless oil. Analytical data for **S1: IR** (thin film, cm^{-1}) 2940, 2837, 1593, 1476, 1316, 1256, 1155, 1091, 882, 799, 778, 587; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 2H), 3.85 (s, 6H), 1.49 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 127.8, 120.1, 103.7, 55.6, 34.6; **LRMS** (ESI) Calcd. for $C_9H_{13}NO_2$+H: 168.1, Found: 168.1.

Prepararation of (2-ethoxyphenyl)methanamine (S3).

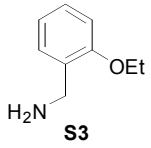




S2

Preparation of 2-ethoxybenzonitrile (S2). A 100-mL round bottomed flask containing a magnetic stir bar was charged with *N,N*-dimethylformamide (DMF, 15 mL), potassium carbonate (2.32 g, 16.8 mmol, 2.0 equiv), 2-hydroxybenzonitrile (1.0 g, 8.40 mmol, 1.0 equiv), and bromoethane (0.915 g, 0.622 mL,

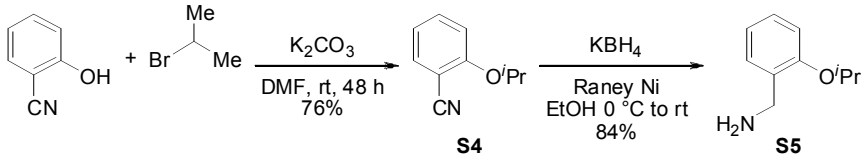
8.40 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 17 h, at which point H_2O (30 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were then washed with H_2O (30 mL), dried over magnesium sulfate, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded **S2** (0.90 g, 6.12 mmol, 73% yield) as a clear yellow oil. Analytical data for **S2** has been previously reported.[22]



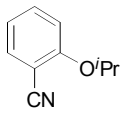
S3

Preparation of (2-ethoxyphenyl)methanamine (S3). A 100-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (18 mL), potassium borohydride (1.32 g, 24.5 mmol, 4.0 equiv), Raney Ni (0.90 mL of a 50% suspension in H_2O, approx. 1.0 equiv), and 2-ethoxybenzonitrile (**S2**, 0.90 g, 6.12 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 0.5 h at room temperature. The reaction was warmed to 50 °C and stirred for 3 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (40 mL), washed with H_2O (3 x 40 mL), dried over magnesium sulfate, and concentrated to afford **S3** (0.658 g, 4.35 mmol, 71% yield) as a clear colorless oil. Analytical data for **S3: IR** (thin film, cm^{-1}) 3376, 2979, 2928, 1600, 1588, 1493, 1454, 1118, 1046, 928, 753, 462; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (t, J = 6.8 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.82 (s, 2H), 1.60 (s, 2H), 1.43 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.7, 132.0, 128.4, 127.9, 120.3, 111.1, 63.3, 42.8, 14.9; **LRMS** (ESI) Calcd. for $C_9H_{13}NO$+H: 152.1, Found: 152.1.

Preparation of (2-isopropoxyphenyl)methanamine (S5).

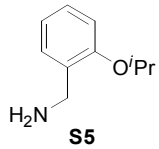


S4 **S5**



S4

Preparation of 2-isopropoxybenzonitrile (S4). A 250-mL round bottomed flask containing a magnetic stir bar was charged with *N,N*-dimethylformamide (DMF, 30 mL), potassium carbonate (4.64 g, 33.6 mmol, 2.0 equiv), 2-hydroxybenzonitrile (2.0 g, 16.80 mmol, 1.0 equiv), and 2-bromopropane (2.01 g, 1.58 mL, 16.80 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 17 h, at which point H_2O (60 mL) was added. The aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then washed with H_2O (60 mL), dried over magnesium sulfate, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded **S4** (2.049 g, 12.71 mmol, 76% yield) as a clear colorless oil. Analytical data for **S4** has been previously reported.[22]

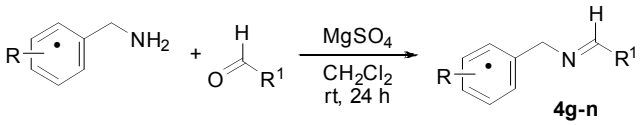


S5

Preparation of (2-isopropoxyphenyl)methanamine (S5). A 250-mL round bottomed flask containing a magnetic stir bar was charged with ethanol (37 mL), potassium borohydride (2.71 g, 24.5 mmol, 4.0 equiv), Raney Ni (1.90 mL of a 50% suspension in H_2O, approx. 1.0 equiv), and 2-isopropoxybenzonitrile (**S4**, 2.025 g, 12.56 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and was allowed to stir for 0.5 h at room temperature. The reaction was warmed to 50 °C and stirred for 2 h. Concentration by rotary evaporation provided a residue which was dissolved in ethyl acetate (75 mL), washed with H_2O (3 x 75 mL), dried over magnesium sulfate, and concentrated to afford **S5** (1.748 g, 10.58 mmol, 84% yield) as a clear colorless oil. Analytical data for **S5: IR** (thin film, cm^{-1}) 3377, 2977, 2931, 1599, 1488, 1455, 1286, 1237, 1119, 957, 751; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 11.8, 4.4 Hz, 2H), 6.87 (dd, J = 12.2, 4.6 Hz, 2H), 4.65 – 4.54 (m, 1H), 3.79 (s, 2H), 1.56 (s, 2H), 1.36 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (100

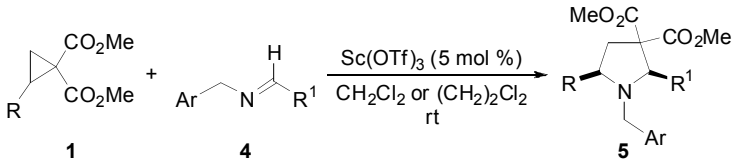
MHz, $CDCl_3$) δ 155.7, 132.9, 128.6, 127.8, 120.2, 112.6, 69.7, 42.9, 22.1; **LRMS** (ESI) Calcd. for $C_5H_{15}NO$+H: 166.1, Found: 166.1.

General Procedure A for the preparation of aldimines 4g-n.



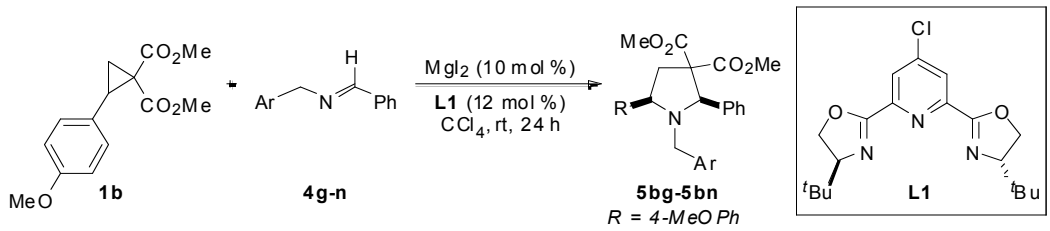
A flame-dried flask was charged with the amine (1.0 equiv), magnesium sulfate (1.5 equiv), and dichloromethane (0.20 – 0.46 M in the amine, concentration is inconsequential). The suspension was stirred for 5 min, at which time the aldehyde (1.0 equiv) was added. The reaction was stirred for 24 h and was then filtered through celite and concentrated to afford aldimines **4g-n** of sufficient purity for subsequent transformations.

General Procedure B for the preparation of racemic pyrrolidines of type 5.



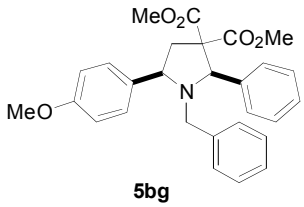
In an inert atmosphere glove box, a 1-dram vial was charged with scandium triflate (0.05 equiv) followed by a solution of cyclopropane **1** and aldimine **4** in dichloromethane or dichloroethane [0.60 M in **1**, CH_2Cl_2 and $(CH_2)_2Cl_2$ can be used interchangeably]. The vial was removed from the glove box and the reaction was allowed to stir until disappearance of **1** is confirmed by thin-layer chromatography (25% EtOAc/hexanes or dichloromethane as the mobile phase) and was quenched by filtration through a 1-inch Monstr-Pette plug of silica with CH_2Cl_2. Concentration *in vacuo* affords pyrrolidine **5**, which is purified by flash chromatography using the indicated solvent systems (*vide infra*).

General Procedure C for the enantioselective MgI_2•L1-catalyzed annulation of cyclopropane 1b and aldimines 4g-n to afford pyrrolidines 5bg-5bn.



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar is charged with MgI_2 (0.0021 g, 0.0076 mmol, 0.10 equiv), **L1** (0.0033 g, 0.0091 mmol, 0.12 equiv), and tetrachloromethane (0.10 mL). The resulting suspension was allowed to stir vigorously for 1 h, at which point a solution of cyclopropane **1b** (0.020 g, 0.0760 mmol, 1.0 equiv) and aldimine **4** (0.0840 mmol, 1.10 equiv) in carbon tetrachloride (1.40 mL) was added. The vial was removed from the glove box and allowed to stir at room temperature. Upon disappearance of **1b** as confirmed by thin-layer chromatography, the reaction was filtered through a 1-inch Monstr-Pette plug of silica with CH_2Cl_2 (approx 10 mL) and concentrated. Yields were determined by ^{1}H NMR using a mesitylene internal standard. Analytically pure material was obtained by purification using flash chromatography.

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

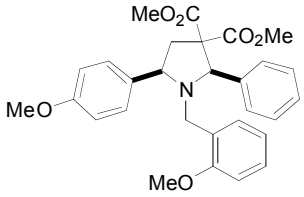


5bg

IR (thin film, cm^{-1}) 3027, 2950, 2836, 1732, 1511, 1455, 1283, 1243, 1172, 1032, 832; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.08 (m, 6H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.22 (s, 1H), 3.93 – 3.78 (m, 3H), 3.49 (s, 3H), 3.38 (s, 3H), 3.33 (d, *J* = 10.8 Hz, 1H), 2.95 (s, 3H), 2.59 (dd, *J* = 13.3, 6.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.0, 169.8, 159.0, 139.2, 134,7, 133.5, 130.2,

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

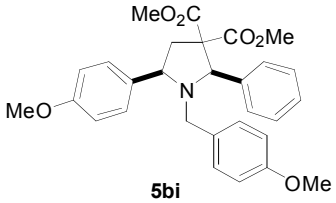
Analytical data for (2*R*,5*R*)-dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (5bh).



5bh

IR (thin film, cm^{-1}) 2952, 2836, 1731, 1511, 1435, 1282, 1243, 1173, 1032, 832; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.06 (dt, *J* = 11.1, 4.8 Hz, 2H), 7.00 – 6.93 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.40 (t, *J* = 8.8 Hz, 1H), 5.29 (s, 1H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.97 – 3.85 (m, 2H), 3.38 (s, 3H), 3.28 (s, 3H), 3.22 (s, 3H), 3.19 (m, 1H), 2.83 (s, 3H), 2.57 (dd, *J* = 13.2, 6.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 170.0, 140.4, 134.3, 132.3, 128.9, 128.8, 128.2, 127.3, 127.1, 124.5, 119.4, 113.6, 109.8, 69.7, 64.2, 55.3, 54.5, 52.7, 51.8, 47.3, 42.5; **TLC** (15% EtOAc/hexanes) R_f 0.17; **LRMS** (ESI) Calcd. for $C_{29}H_{31}NO_6$+H: 490.2, Found: 490.2. SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 95:5 er, $t_{r\text{-}major}$ 7.41 min, $t_{r\text{-}minor}$ 8.14 min; $[\alpha]_D^{29}$ = +60.4 (*c* = 0.580, $CHCl_3$).

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

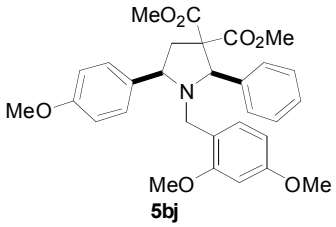


5bi

IR (thin film, cm^{-1}) 2951, 2835, 1731, 1611, 1510, 1455, 1434, 1246, 1175, 1034, 830; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.79 (t, *J* = 12.7 Hz, 2H), 7.58 (t, *J* = 10.1 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H),

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

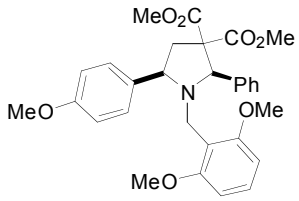
Analytical data for (2*R*,5*R*)-dimethyl 1-(2,4-dimethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (5bj).



5bj

IR (thin film, cm^{-1}) 3001, 2952, 2836, 1732, 1611, 1509, 1291, 1245, 1209, 1172, 1038, 832, 701; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.39 (s, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 5.43 (s, 1H), 4.12 (d, *J* = 13.9 Hz, 1H), 4.06 (dd, *J* = 10.8, 6.3 Hz, 1H), 4.00 (d, *J* = 13.9 Hz, 1H), 3.51 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 3.36 (d, *J* = 13.2 Hz, 1H), 3.31 (s, 3H), 2.95 (s, 3H), 2.71 (dd, *J* = 13.2, 6.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 169.8, 158.7, 140.3, 134.4, 132.8, 128.9, 128.8, 127.3, 127.1, 116.9, 113.6, 103.1, 97.7, 69.5, 64.1, 63.8, 55.2, 55.2, 54.5, 52.7, 51.8, 46.5, 42.5; **TLC** (20% EtOAc/hexanes) R_f 0.27; **LRMS** (ESI) Calcd. for $C_{30}H_{33}NO_7$+H: 520.2, Found: 520.2. SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 93:7 er, $t_{r\text{-major}}$ 8.79 min, $t_{r\text{-minor}}$ 9.56 min; $[\alpha]_D^{28}$ = +57.6 (*c* = 0.610, $CHCl_3$).

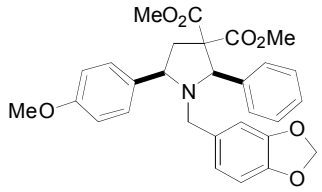
Analytical data for (2*R*,5*R*)-dimethyl 1-(2,6-dimethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (5bk).



5bk

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

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

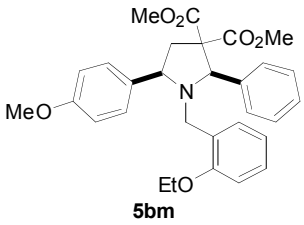


5bl

mp 58-60 °C; **IR** (thin film, cm^{-1}) 2952, 2891, 2837, 1731, 1511, 1488, 1440, 1243, 1039, 930, 833, 737, 702; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.29 (t, *J* = 6.0 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.74 (s, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.38 (dd, *J* = 9.4, 1.2 Hz, 2H), 5.22 (s, 1H), 3.92 (dd, *J* = 10.7, 6.5 Hz, 1H), 3.82 – 3.71 (m, 2H), 3.48 (s, 3H), 3.40 (s, 3H), 3.37 – 3.31 (m, 1H), 2.94 (s, 3H), 2.61 (dd, *J* = 13.3, 6.5 Hz, 1H); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ 172.1, 169.7, 159.1, 147.0, 146.3, 139.4, 133.6, 129.0, 127.8, 127.5, 123.3, 114.0, 110.5, 107.4, 100.6, 69.6, 63.9, 63.7, 55.3, 52.6, 52.3, 51.8, 42.2; **TLC** (20% EtOAc/hexanes) R_f 0.27; **LRMS** (ESI) Calcd. for $C_{29}H_{29}NO_7$+H: 504.2, Found: 504.2. SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 92:8 er, $t_{r\text{-major}}$ 7.29 min, $t_{r\text{-minor}}$ 7.84 min; $[\alpha]_D^{27}$ = +45.0 (*c* = 0.280, $CHCl_3$).

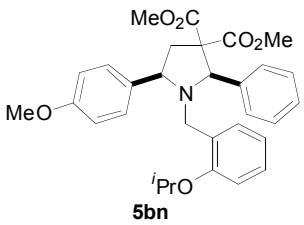
Analytical data for (2*R*,5*R*)-dimethyl 1-(2-ethoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (5bm).



5bm

IR (thin film, cm^{-1}) 3027, 2950, 2837, 1732, 1511, 1493, 1455, 1289, 1241, 1172, 1049, 831; **^{1}H NMR** (500 MHz, C_6D_6) δ 7.70 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.17 – 7.15 (m, 1H), 7.12 – 7.09 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.93 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.35 (d, *J* = 8.2 Hz, 1H), 5.47 (s, 1H), 4.07 (d, *J* = 13.3 Hz, 1H), 3.98 – 3.93 (m, 2H), 3.52 – 3.42 (m, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 3.22 (dd, *J* = 13.1, 11.4 Hz, 1H), 2.82 (s, 3H), 2.62 (dd, *J* = 13.2, 5.9 Hz, 1H), 1.11 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 169.5, 158.8, 157.2, 140.6, 134.2, 132.1, 128.8, 128.7, 128.0, 127.1, 126.9, 125.4, 119.2, 113.6, 110.6, 70.2, 65.2, 64.4, 63.0, 55.3, 52.8, 51.8, 48.8, 42.5, 14.8; **TLC** (15% EtOAc/hexanes) R_f 0.23; **LRMS** (ESI) Calcd. for $C_{30}H_{33}NO_6$+H: 504.2, Found: 504.2; SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 94:6 er, $t_{r\text{-major}}$ 7.43 min, $t_{r\text{-minor}}$ 8.11 min; $[\alpha]_D^{28}$ = +58.3 (*c* = 0.260, $CHCl_3$).

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

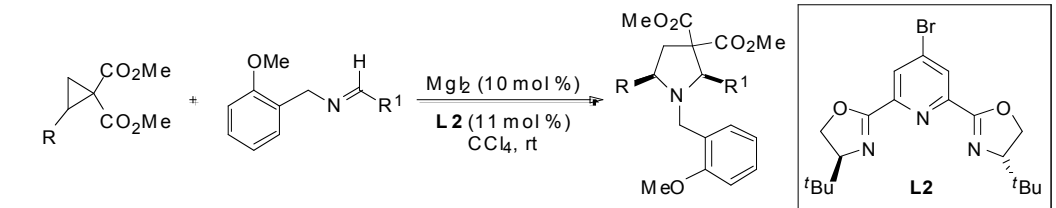


5bn

IR (thin film, cm^{-1}) 2951, 2837, 1734, 1512, 1490, 1455, 1286, 1243, 1173, 957, 831; **^{1}H NMR** (500 MHz, C_6D_6) δ 7.73 (d, *J* = 7.4

Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 5.39 (s, 1H), 4.06 (d, *J* = 13.4 Hz, 1H), 4.02 (dd, *J* = 13.2, 6.4 Hz, 1H), 3.97 (d, *J* = 13.7 Hz, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 3.25 – 3.18 (m, 1H), 2.82 (s, 3H), 2.62 (dd, *J* = 13.2, 5.9 Hz, 1H), 1.10 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 169.5, 158.7, 156.4, 140.6, 134.2, 132.4, 128.8, 128.7, 127.9, 127.1, 126.9, 126.1, 119.2, 113.7, 112.6, 70.2, 69.8, 64.8, 64.4, 55.3, 52.8, 51.8, 48.5, 42.4, 22.1, 22.0; **TLC** (15% EtOAc/hexanes) R_f 0.22; **LRMS** (ESI) Calcd. for $C_{31}H_{35}NO_6$+H: 518.2, Found: 518.3; SFC analysis (Chiralpack, OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 94:6 er, $t_{r\text{-major}}$ 8.82 min, $t_{r\text{-minor}}$ 9.79 min; $[\alpha]_D^{27}$ = +53.0 (*c* = 0.230, $CHCl_3$).

General Procedure D for the enantioselective MgI_2•L2-catalyzed annulation of cyclopropanes 1a-c and aldimines 2c, i-m to afford pyrrolidines 5bh-5dr.



R = *4-MeOPh* (**1b**) = *(E)-CH=CHPh* (**1c**) = *2-thienyl* (**1d**)

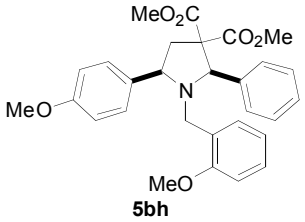
4h, 4o-s

5bh-5dr

In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with MgI_2 (0.0042 g, 0.0151 mmol, 0.10 equiv), **L2** (0.0068 g, 0.0166 mmol, 0.11 equiv), and carbon tetrachloride (0.20 mL). The vial was sealed with a PTFE-lined screw cap and the suspension was stirred vigorously until a pale yellow complex is formed (approx. 1 h) at which point a solution of cyclopropane (0.151 mmol, 1.0 equiv) and aldimine (0.166 mmol, 1.10 equiv) in tetrachloromethane (2.80 mL) was added. The vial was recapped, removed from the box, and allowed to stir. When disappearance of the cyclopropane was confirmed by

thin layer chromatography, the contents of the vial were filtered through a 1-inch Monstr-Pette plug of silica gel with CH_2Cl_2 (10 mL). The resulting solution was concentrated and purified by flash chromatography using the indicated solvent system.

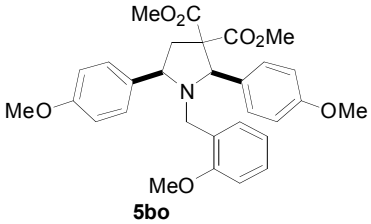
(2*R*,5*R*)-dimethyl 1-(2-methoxybenzyl)-5-(4-methoxyphenyl)-2-phenylpyrrolidine-3,3-dicarboxylate (5bh).



5bh

The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**4h**, 0.038 g, 0.166 mmol, 1.10 equiv). After 15 h, the reaction was worked up and **5bh** was obtained in 97:3 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided **3ac** (0.052 g, 0.106 mmol, 70% yield) as a waxy white solid in 96.5:3.5 er as determined by SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-}major}$ 7.41 min, $t_{r\text{-}minor}$ 8.14 min; $[\alpha]_D^{26} = +76.6$ ($c = 0.280$, $CHCl_3$).

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

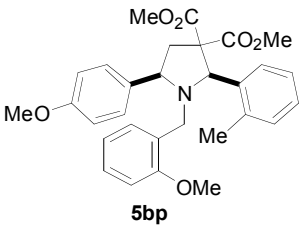


5bo

The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(4-methoxybenzylidene)-1-(2-methoxyphenyl)methanamine (**4o**, 0.042 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **5bo** was obtained in 96:4 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5bo** (0.063 g, 0.121 mmol, 80% yield) as a white solid in 92.5:7.5 er as determined by SFC analysis

(Chiralpack, OD, 10.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 5.7 min, $t_{r\text{-minor}}$ 6.3 min. Analytical data for **5bo: mp** 50-52 °C; **IR** (thin film, cm^{-1}) 2953, 2837, 1732, 1510, 1273, 1245, 1172, 1034, 831, 759; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.14 – 7.08 (m, 1H), 6.99 (dd, *J* = 11.1, 4.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.74 (dd, *J* = 13.9, 6.6 Hz, 1H), 6.42 (d, *J* = 8.1 Hz, 1H), 5.26 (s, 1H), 4.04 (d, *J* = 13.8 Hz, 1H), 3.94 (d, *J* = 13.4 Hz, 1H), 3.92 (dd, *J* = 10.4, 6.7 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 3.23 – 3.17 (m, 1H), 2.90 (s, 3H), 2.58 (dd, *J* = 13.2, 6.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 169.8, 158.7, 158.6, 157.9, 134.3, 132.3, 132.3, 129.9, 128.7, 128.2, 124.5, 119.4, 113.6, 112.7, 109.8, 69.2, 64.0, 64.0, 55.2, 55.1, 54.5, 52.7, 51.9, 47.0, 42.4; **TLC** (15% EtOAc/hexanes) R_f 0.14; **LRMS** (ESI) Calcd. for $C_{30}H_{33}NO_7$+H: 520.2, Found: 520.2; $[\alpha]_D^{26}$ = +38.8 (*c* = 0.370, $CHCl_3$).

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

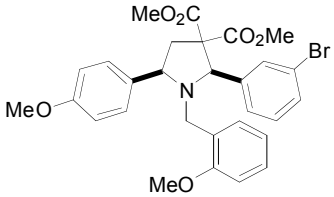


5bp

The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(2-methylbenzylidene)-1-(2-methoxyphenyl)methanamine (**4p**, 0.040 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **5bp** was obtained in 98:2 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5bp** (0.067 g, 0.134 mmol, 89% yield) as a white solid in 94.5:5.5 er as determined by SFC analysis (Chiralpack, OD, 6.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 7.6 min, $t_{r\text{-minor}}$ 8.2 min. Analytical data for **5bp: IR** (thin film, cm^{-1}) 2952, 1731, 1512, 1266, 1246, 1173, 1034, 832, 738, 704; **^{1}H NMR** (500 MHz, C_6D_6) δ 8.16

(d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 7.07 (d, J = 7.3 Hz, 1H), 6.99 (t, J = 7.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.68 (t, J = 7.4 Hz, 1H), 6.32 (d, J = 8.2 Hz, 1H), 5.60 (s, 1H), 4.06 (dd, J = 11.8, 5.0 Hz, 1H), 4.01 (d, J = 13.4 Hz, 1H), 3.90 (d, J = 13.4 Hz, 1H), 3.37 (s, 3H), 3.33 (d, J = 12.6 Hz, 1H), 3.29 (s, 3H), 3.21 (s, 3H), 2.80 (s, 3H), 2.62 (dd, J = 13.1, 5.1 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.3, 169.4, 158.9, 157.7, 138.9, 137.0, 134.0, 131.8, 129.1, 128.8, 128.7, 128.2, 126.6, 125.3, 124.9, 119.4, 113.6, 109.5, 65.1, 65.0, 64.0, 55.3, 54.5, 52.9, 51.6, 48.8, 43.4, 19.5; **TLC** (15% EtOAc/hexanes) R_f 0.20; **LRMS** (ESI) Calcd. for $C_{30}H_{33}NO_6$+H: 504.3, Found: 504.3; $[\alpha]_D^{27}$ = +76.9 (c = 0.300, $CHCl_3$).

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

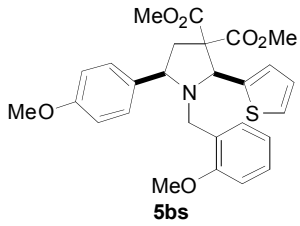


5bq

The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(3-bromobenzylidene)-1-(2-methoxyphenyl)methanamine (**4q**, 0.050 g, 0.166 mmol, 1.10 equiv). After 24 h, the reaction was worked up and **5bq** was obtained in 98:2 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **5bq** (0.055 g, 0.097 mmol, 64% yield) as a white solid in 96:4 er as determined by SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 12.1 min, $t_{r\text{-minor}}$ 13.2 min. Analytical data for **5bq: mp** 48-51 °C; **IR** (thin film, cm^{-1}) 2952, 2835, 1733, 1511, 1465, 1434, 1247, 1174, 1033, 832, 737; **^{1}H NMR** (400 MHz, C_6D_6) δ 8.05 (s, 1H), 7.70 – 7.60 (m, 3H), 7.28 (d, J = 7.0 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.06 (dd, J = 10.7, 4.9 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.94 – 6.86 (m, 1H), 6.80 (t, J =

7.4 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.29 (s, 1H), 4.09 (d, *J* = 13.3 Hz, 1H), 3.95 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.30 – 3.21 (m, 1H), 2.96 (s, 3H), 2.63 (dd, *J* = 13.3, 6.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 169.3, 159.0, 157.9, 143.1, 133.8, 132.1, 131.9, 130.0, 128.8, 128.7, 128.5, 127.4, 124.6, 121.2, 119.5, 113.8, 69.7, 64.8, 64.3, 55.3, 54.6, 52.8, 51.9, 48.3, 42.3; **TLC** (10% EtOAc/hexanes) R_f 0.16; **LRMS** (ESI) Calcd. for $C_{29}H_{30}NO_6$+Cs: 700.1, Found: 700.0; $[\alpha]_D^{26}$ = +35.7 (*c* = 0.280, $CHCl_3$).

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

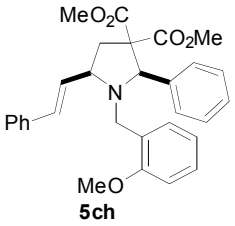


5bs

The title compound was prepared according to General Procedure D using dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) and (*E*)-1-(2-methoxyphenyl)-*N*-(thiophen-2-ylmethylene)methanamine (**4s**, 0.038 g, 0.166 mmol, 1.10 equiv). After 22 h, the reaction was worked up and **5bs** was obtained in 93:7 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (20% EtOAc/hexanes) provided pure **5bs** (0.063 g, 0.127 mmol, 84% yield) as a white solid in 98:2 er as determined by SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 12.9 min, $t_{r\text{-minor}}$ 14.4 min. Analytical data for **5bs: mp** 44-47 °C; **IR** (thin film, cm^{-1}) 2953, 2837, 1733, 1512, 1272, 1245, 1173, 1034, 832, 703; **^{1}H NMR** (500 MHz, C_6D_6) δ 7.60 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.16 (m, 1H), 7.04 – 6.98 (m, 2H), 6.92 (d, *J* = 5.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.79 – 6.72 (m, 2H), 6.47 (d, *J* = 8.1 Hz, 1H), 5.73 (s, 1H), 4.23 (d, *J* = 13.7 Hz, 1H), 4.00 (d, *J* = 13.8 Hz, 1H), 3.96 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 3.26 (s, 3H), 3.24 – 3.18 (m, 1H), 3.04 (s, 3H), 2.61 (dd, *J* = 13.0, 5.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.9, 158.9, 158.0, 147.3, 133.7, 132.2, 128.8, 128.4, 126.0, 124.8, 124.6, 119.5, 113.6, 109.9, 64.6, 64.6, 64.0, 55.2, 54.7, 52.9, 52.2, 47.6, 41.8; **TLC** (20% EtOAc/hexanes) R_f 0.20; **LRMS** (ESI) Calcd. for $C_{27}H_{29}NO_6S$+H: 496.2, Found: 496.3; $[\alpha]_D^{28}$ = +82.3 (*c* = 0.470, $CHCl_3$).

(2*R*,5*R*)-dimethyl 1-(2-methoxybenzyl)-2-phenyl-5-styrylpyrrolidine-3,3-dicarboxylate (5ch).

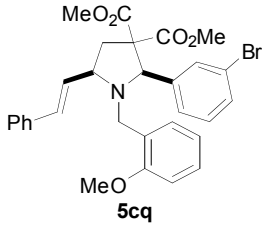


5ch

The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**4h**, 0.038 g, 0.166 mmol, 1.10 equiv). After 26 h, the reaction was worked up and **5ch** was obtained in 91:9 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5ch** (0.054 g, 0.112 mmol, 74% yield) as a clear colorless oil with both diastereomers enriched to 98:2 er as determined by SFC analysis (Chiralpack, OD, 2.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ (*cis*) 24.8 min, $t_{r\text{-minor}}$ (*cis*) 27.3 min, $t_{r\text{-major}}$ (*trans*) 21.7 min, $t_{r\text{-minor}}$ (*trans*) 22.9 min. Analytical data for **5ch: IR** (thin film, cm^{-1}) 3028, 2951, 2836, 1733, 1493, 1435, 1268, 1246, 966, 753, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 4.0 Hz, 4H), 7.15 (dd, *J* = 9.5, 4.8 Hz, 3H), 7.11 – 7.06 (m, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.09 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.70 (s, 1H), 3.76 – 3.66 (m, 2H), 3.64 (s, 3H), 3.56 (s, 3H), 3.34 (dt, *J* = 10.4, 7.1 Hz, 1H), 2.97 (s, 3H), 2.70 (dd, *J* = 13.1, 10.9 Hz, 1H), 2.19 (dd, *J* = 13.2, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 169.5, 157.7, 140.2, 137.3, 132.2, 131.7, 131.1, 128.8, 128.4, 128.0, 127.4, 127.2, 126.3, 126.2, 119.7, 110.0, 71.3, 64.7, 64.4, 54.9, 52.7, 51.8, 48.7,

39.5; **TLC** (15% EtOAc/hexanes) R_f 0.22; **LRMS** (ESI) Calcd. for $C_{30}H_{31}NO_5$+H: 486.2, Found: 486.2; $[\alpha]_D^{28}$ = +125.4 (*c* = 0.430, $CHCl_3$).

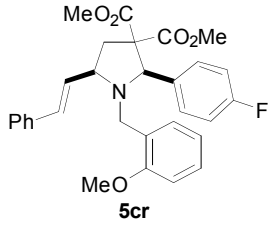
(2*R*,5*R*)-dimethyl 2-(3-bromophenyl)-1-(2-methoxybenzyl)-5-styrylpyrrolidine-3,3-dicarboxylate (5cq).



5cq

The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(3-bromobenzylidene)-1-(2-methoxyphenyl)methanamine (**4q**, 0.050 g, 0.166 mmol, 1.10 equiv). After 39 h, the reaction was worked up and **5cq** was obtained in 93:7 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **5cq** (0.060 g, 0.106 mmol, 70% yield) as a white solid in 96.5:3.5 er as determined by SFC analysis (Chiralpack, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 19.7 min, $t_{r\text{-minor}}$ 21.8 min. Analytical data for **5cq: mp** 41-44 °C; **IR** (thin film, cm^{-1}) 2952, 1733, 1493, 1435, 1266, 1198, 1174, 1070, 967, 737, 695; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 14.5, 7.2 Hz, 3H), 7.31 – 7.24 (m, 2H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.66 (s, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.76 (s, 1H), 3.87 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.71 (d, *J* = 10.5 Hz, 1H), 3.69 (s, 3H), 3.44 (dt, *J* = 10.2, 7.6 Hz, 1H), 3.16 (s, 3H), 2.76 (dd, *J* = 13.0, 11.1 Hz, 1H), 2.31 (dd, *J* = 13.3, 6.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.8, 169.2, 157.7, 142.8, 137.0, 131.8, 131.7, 131.6, 130.1, 128.8, 128.5, 128.3, 127.4, 127.3, 126.3, 125.5, 121.4, 119.6, 109.8, 70.3, 64.3, 64.3, 54.8, 52.9, 52.0, 48.9, 39.2; **TLC** (10% EtOAc/hexanes) R_f 0.18; **LRMS** (ESI) Calcd. for $C_{30}H_{30}BrNO_5$+Cs: 696.1, Found: 696.0; $[\alpha]_D^{28}$ = +124.6 (*c* = 0.290, $CHCl_3$).

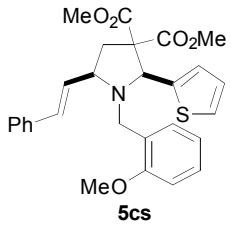
(2*R*,5*R*)-dimethyl 2-(2-fluorophenyl)-1-(2-methoxybenzyl)-5-styrylpyrrolidine-3,3-dicarboxylate (5cr).



5cr

The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(2-fluorobenzylidene)-1-(2-methoxyphenyl)methanamine (**4r**, 0.050 g, 0.166 mmol, 1.10 equiv). After 39 h, the reaction was worked up and **5cr** was obtained in 93:7 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (10% EtOAc/hexanes) provided pure **5cr** (0.055 g, 0.109 mmol, 73% yield) as a waxy slightly yellow solid in 97.5:2.5 er as determined by SFC analysis (Chiralpack, OD, 1.5% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-}major}$ 33.6 min, $t_{r\text{-}minor}$ 38.6 min. Analytical data for **5cr: IR** (thin film, cm^{-1}) 2952, 2837, 1733, 1602, 1507, 1278, 1245, 1222, 966, 850, 692; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 4H), 7.23 (t, *J* = 6.4 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 8.7 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.18 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.76 (s, 1H), 3.80 (d, J = 13.8 Hz, 1H), 3.73 (s, 3H), 3.71 (d, J = 13.8 Hz, 1H), 3.65 (s, 3H), 3.42 (dt, *J* = 10.4, 7.9 Hz, 1H), 3.12 (s, 3H), 2.75 (dd, *J* = 13.2, 10.9 Hz, 1H), 2.28 (dd, *J* = 13.3, 6.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.0, 169.5, 163.0, 161.1, 157.6, 137.1, 135.8, 131.9, 131.7, 131.4, 130.3, 130.2, 128.4, 128.1, 127.4, 126.3, 125.8, 119.7, 114.2, 114.0, 109.9, 70.4, 64.6, 64.2, 54.8, 52.9, 52.0, 48.7, 39.3; **TLC** (10% EtOAc/hexanes) R_f 0.10; **LRMS** (ESI) Calcd. for $C_{30}H_{30}FNO_5$+H: 504.2, Found: 504.2; $[\alpha]_D^{29}$ = +107.8 (*c* = 0.400, $CHCl_3$).

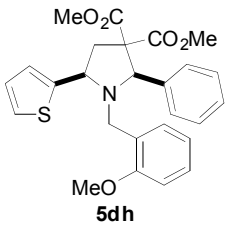
(2*S*,5*R*)-dimethyl 1-(2-methoxybenzyl)-5-styryl-2-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (5cs).



5cs

The title compound was prepared according to General Procedure D using (*E*)-dimethyl 2-styrylcyclopropane-1,1-dicarboxylate (**1c**, 0.039 g, 0.151 mmol, 1.0 equiv) and (*E*)-1-(2-methoxyphenyl)-*N*-(thiophen-2-ylmethylene)methanamine (**4s**, 0.038 g, 0.166 mmol, 1.10 equiv). After 18 h, the reaction was worked up and **5cs** was obtained in 87:13 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5cs** (0.061 g, 0.124 mmol, 82% yield) as a waxy slightly yellow solid in 97.5:2.5 er as determined by SFC analysis (Chiralpack, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 33.6 min, $t_{r\text{-minor}}$ 38.6 min. Analytical data for **5cs: IR** (thin film, cm^{-1}) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.26 – 7.24 (m, 1H), 7.24 – 7.20 (m, 1H), 7.17 – 7.15 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 3.6 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.0 Hz, 1H), 5.15 (s, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.85 (d, *J* = 13.9 Hz, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.45 – 3.38 (m, 1H), 3.32 (s, 3H), 2.77 (dd, *J* = 12.9, 11.2 Hz, 1H), 2.29 (dd, *J* = 13.2, 5.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.6, 169.0, 157.7, 146.4, 137.1, 131.8, 131.7, 131.2, 128.4, 128.1, 127.3, 126.3, 126.1, 126.0, 125.0, 124.8, 119.7, 110.0, 66.0, 64.5, 64.2, 54.9, 52.9, 52.3, 48.6, 38.8; **TLC** (15% EtOAc/hexanes) R_f 0.14; **LRMS** (ESI) Calcd. for $C_{28}H_{29}NO_5S$+H: 492.2, Found: 492.2; $[\alpha]_D^{28}$ = +126.7 (*c* = 0.370, $CHCl_3$).

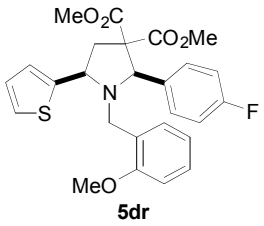
(2*R*,5*R*)-dimethyl 1-(2-methoxybenzyl)-2-phenyl-5-(thiophen-2-yl)pyrrolidine-3,3-dicarboxylate (5dh).



5dh

The title compound was prepared according to General Procedure D using dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (**1d**, 0.036 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-benzylidene-1-(2-methoxyphenyl)methanamine (**4h**, 0.038 g, 0.166 mmol, 1.10 equiv). After 24 h, the reaction was worked up and **3cc** was obtained in 87:13 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5dh** (0.046 g, 0.100 mmol, 66% yield) as a clear slightly yellow oil with the major (*cis*) diastereomer in 97.5:2.5 er as determined by SFC analysis (Chiralpack, OD, 4.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 9.5 min, $t_{r\text{-minor}}$ 10.3 min. Analytical data for **5dh: IR** (thin film, cm^{-1}) 2952, 2837, 1733, 1493, 1436, 1274, 1245, 967, 757, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 4.5 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.17 – 7.08 (m, 2H), 7.04 – 6.94 (m, 2H), 6.80 – 6.72 (m, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.91 (s, 1H), 4.19 (dd, *J* = 10.7, 6.0 Hz, 1H), 3.82 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.06 (s, 3H), 2.93 (dd, *J* = 13.3, 10.9 Hz, 1H), 2.48 (dd, *J* = 13.3, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 169.0, 158.0, 147.8, 140.4, 132.3, 128.8, 128.3, 127.2, 126.1, 124.7, 124.4, 119.5, 110.0, 69.5, 64.4, 60.6, 54.6, 52.7, 51.8, 47.7, 42.9; **TLC** (15% EtOAc/hexanes) R_f 0.25; **LRMS** (ESI) Calcd. for $C_{26}H_{27}NO_5S$+H: 466.2, Found: 466.2; $[\alpha]_D^{26}$ = +80.9 (*c* = 0.400, $CHCl_3$).

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

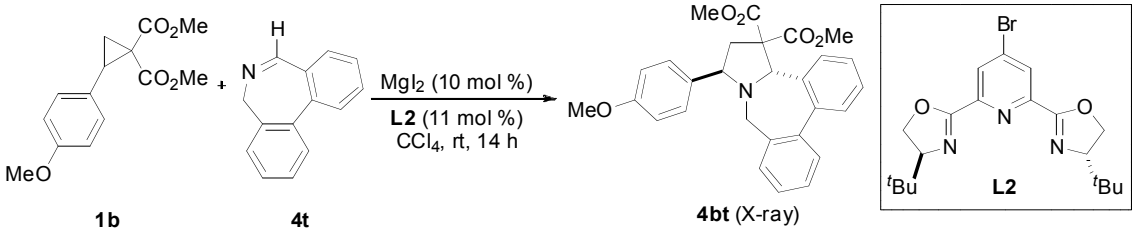


5dr

The title compound was prepared according to General Procedure D using (*E*)-dimethyl dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-

dicarboxylate (**1d**, 0.036 g, 0.151 mmol, 1.0 equiv) and (*E*)-*N*-(2-fluorobenzylidene)-1-(2-methoxyphenyl)methanamine (**4r**, 0.050 g, 0.166 mmol, 1.10 equiv). After 30 h, the reaction was worked up and **5dr** was obtained in 97:3 dr as determined by ^{1}H NMR spectroscopy. Flash chromatography (15% EtOAc/hexanes) provided pure **5dr** (0.050 g, 0.103 mmol, 68% yield) as a clear slightly yellow oil with the major (*cis*) diastereomer in 95.5:4.5 er as determined by SFC analysis (Chiralpack, OD, 3.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-}major}$ 8.9 min, $t_{r\text{-}minor}$ 9.8 min. Analytical data for **5dr: IR** (thin film, cm^{-1}) 3070, 3001, 2952, 2837, 1734, 1602, 1507, 1281, 1244, 849, 823, 517; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.31 (d, *J* = 4.9 Hz, 1H), 7.15 – 7.07 (m, 2H), 6.99 (dt, *J* = 6.3, 3.1 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 8.7 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.87 (s, 1H), 4.16 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.78 (d, *J* = 6.1 Hz, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.11 (s, 3H), 2.90 (dd, *J* = 13.3, 10.9 Hz, 1H), 2.48 (dd, *J* = 13.4, 6.0 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 169.0, 163.3, 160.8, 157.9, 147.5, 136.1, 132.2, 130.4, 130.3, 128.4, 126.2, 124.9, 124.7, 124.5, 119.6, 114.1, 113.9, 110.0, 69.0, 64.3, 60.8, 54.7, 52.8, 51.9, 48.0, 42.7; **TLC** (15% EtOAc/hexanes) R_f 0.18; **LRMS** (ESI) Calcd. for $C_{26}H_{26}FNO_5S$+Na: 506.2, Found: 506.2; $[\alpha]_D^{29}$ = +46.7 (*c* = 0.400, $CHCl_3$).

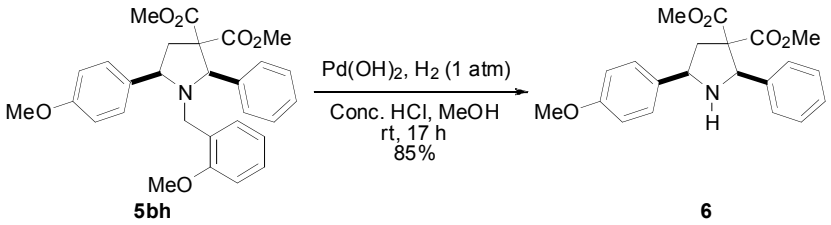
Preparation of (dimethyl 7-(4-methoxyphenyl)-6,7-dihydro-4b*H*-dibenzo[c,e]pyrrolo[1,2-a]azepine-5,5(9H)-dicarboxylate (4bt).



The title compound was prepared according to General Procedure D using 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1b**, 0.040 g, 0.151 mmol, 1.0 equiv) (**1a**, 0.020 g, 0.076 mmol, 1.0 equiv) and 5*H*-dibenzo[c,e]azepine (**4t**, 0.016 g, 0.083 mmol, 1.10 equiv). After 14 h, the reaction was worked up and **4bt** was obtained as a single diastereomer in a 2:1 mixture of conformers in 71% yield as determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. Flash chromatography (20% EtOAc/hexanes) provided pure **3an** as a white solid in 55.5:44.5 er as determined by SFC analysis (Chiralpack, OD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 13.6 min, $t_{r\text{-minor}}$ 11.7 min. Analytical data for **4bt: mp** 83-84 °C; **IR** (thin film, cm^{-1}) 2848, 2685, 2305, 1694, 1597, 1439, 1197, 825, 741; [Note: ^{1}H and ^{13}C NMR spectra were obtained by analyzing the trifluoroacetic acid (TFA) salt of **3an**, prepared by adding 1.0 equiv of neat TFA to a chloroform solution of **3an**] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2, 1H), 7.66 – 7.65 (m, 2H), 7.59 – 7.52 (m, 4H), 7.49 – 7.44 (m, 2H), 7.00 – 6.98 (m, 2H), 6.62 (s, 1H), 4.66 (dd, *J* = 12.0, 6.8 Hz), 4.25 (d, *J* = 14.0 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.85 (s, 3H), 3.25 (s, 3H), 2.79 – 2.68 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 167.9, 161.1, 140.3, 138.3, 134.0, 131.7, 131.0, 130.7, 130.6, 130.3, 129.5, 128.8, 128.6, 114.8, 71.3, 66.3, 62.7, 55.4, 53.3, 52.9, 50.4, 39.2; **TLC** (20% EtOAc/hexanes) R_f 0.20; **LRMS** (ESI) Calcd. for

$C_{28}H_{27}NO_5$+H: 458.2, Found: 458.2; $[\alpha]_D^{26} = -1.95$ (c = 0.25, $CHCl_3$). X-ray quality crystals were obtained by slow evaporation of methanol.

Pd(OH)$_2$-catalyzed reductive debenzylation of pyrrolidine 5bh to provide pyrrolidine 6.

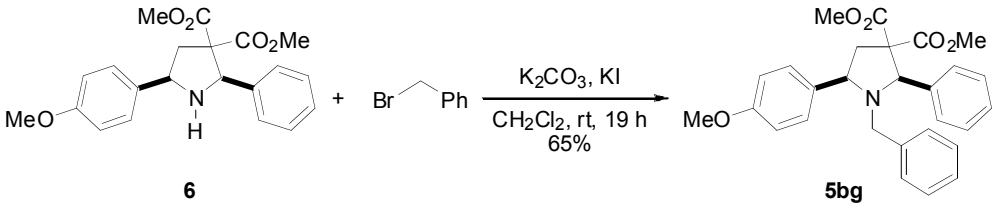


5bh **6**

A flame-dried 5-mL round bottomed flask containing a magnetic stir bar was purged with N_2 and charged with a solution of pyrrolidine **5bh** (0.025 g, 0.051 mmol, 1.0 equiv) in methanol (0.50 mL) containing 1 drop of concentrated hydrochloric acid. To this solution was added $Pd(OH)_2$ (0.0036 g, 0.0051 mmol, 0.10 equiv). The flask was purged with a balloon of H_2 and was placed under a balloon atmosphere of H_2. The reaction was allowed to stir for 17 h and was filtered through a 1-cm Monstr-Pette plug of silica with methanol (10 mL). The solution was concentrated *in vacuo* and the resulting residue taken up in saturated aq. $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (3 x 5 mL), dried over magnesium sulfate and concentrated to provide **6** (0.016 g, 0.043 mmol, 85% yield) as a clear colorless oil. Analytical data for **6: IR** (thin film, cm^{-1}) 3054, 2987, 2305, 1730, 1612, 1512, 1421, 1265, 895, 744; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (t, J = 7.4 Hz, 4H), 7.39 – 7.22 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 5.22 (s, 1H), 4.25 (dd, J = 10.5, 6.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.12 (s, 3H), 2.86 (dd, J = 13.3, 10.7 Hz, 1H), 2.54 (dd, J = 13.4, 6.5 Hz, 1H), 2.30 (s, 1H).; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 170.0, 159.2, 139.9, 134.3, 128.2, 127.9, 127.8, 127.7, 114.0, 67.0, 65.7, 60.3, 55.3, 52.7, 51.9, 42.9; **LRMS** (ESI) Calcd. for $C_{21}H_{23}NO_5$+H:

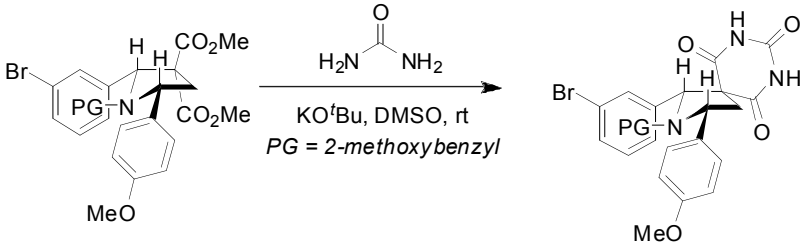
370.2, Found: 370.2; Enantiomeric ratio [determined by converting to the *N*-benzyl derivative (**6a**), *vide infra*] 95.5:4.5 er; $[\alpha]_D^{25}$ = +33.5 (*c* = 0.350, $CHCl_3$).

Preparation of 5bg by *N*-benzylation of 6.



A flame-dried 1-dram vial containing a magnetic stir bar was charged with a solution of **6** (0.017 g, 0.046 mmol, 1.0 equiv) in dichloromethane (0.230 mL). To this solution was added potassium carbonate (0.061 g, 0.437 mmol, 9.5 equiv), benzylbromide (0.024 g, 0.017 mL, 0.138 mmol, 3.0 equiv), and potassium iodide (0.0017 g, 0.010 mmol, 0.22 equiv). The vial was sealed with a PTFE-lined screw cap and was allowed to stir for 19 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography provided **5bg** (0.0137 g, 0.029 mmol, 65%). SFC analysis (Chiralpack, AD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) 95.5:4.5 er, $t_{r\text{-major}}$ 4.7 min, $t_{r\text{-minor}}$ 5.2 min.

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



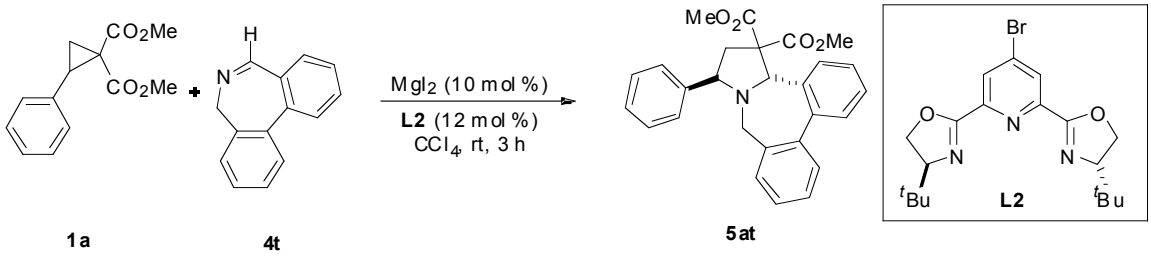
5bq: 96:4 er

(*R*,*R*)-7: 52% (X-ray)

A solution of **5bq** (0.094 g, 0.165 mmol, 1.0 equiv, 96:4 er) in 0.8 mL DMSO was treated with urea (0.060 g, 0.992 mmol, 6.0 equiv) and KO^{t}Bu (0.041 g, 0.364 mmol, 2.2 equiv). After stirring for 1 h, the reaction was diluted with 15 mL of EtOAc and washed with 20 mL of a 0.1 N HCl (aq.) solution. The aqueous phase was extracted with three 20 mL portions of EtOAc. The combined organic extracts were washed with two 20 mL portions of water and 25 mL of brine, dried over MgSO4, and concentrated by rotary evaporation affording a white solid. Flash chromatography (40% EtOAc/hexanes) provided pure **7** (0.048 g, 0.085 mmol, 52%) as a white solid. This material was dissolved in a small amount of THF and recrystallized by slow diffusion of petroleum ether vapor into the solution. The initial batch of crystals was discarded and this process was repeated. A third crystallization provided a single crystal suitable for X-ray analysis. Analytical data for **7: mp** 200 °C (dec); **IR** (thin film, cm^{-1}) 3369, 3214, 3055, 2986, 2961, 2937, 2838, 2305, 1729, 1512, 1422, 1353, 1246, 1173, 1033; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.51 (s, 1H), 7.83 (bs, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.76 – 6.72 (m, 2H), 6.66 (d, 8.0 Hz, 1H), 4.03 (s, 1H), 3.99 (t, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.68 (d, *J* = 14.0 Hz, 2H), 3.54 – 3.51 (m, 2H), 3.51 (s 3H), 2.67 (dd, *J* = 13.0,

8.0 Hz, 1H), 2.50 (dd, J = 13.0, 9.5 Hz, 1H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 172.5, 169.9, 159.7, 158.4, 148.8, 139.7, 134.5, 132.9, 132.2, 131.8, 129.8, 129.4, 127.6, 123.4, 120.1, 114.3, 110.5, 78.8, 68.2, 62.1, 55.8, 55.0, 40.6, 26.1; **TLC** (40% EtOAc/hexanes) R_f 0.18; **LRMS** (ESI) Calcd. for $C_{28}H_{26}BrN_3O_5$+H: 564.1, Found: 564.1; $[\alpha]_D^{28}$ = +38.1 (c = 0.305, THF).

Preparation of (dimethyl 7-phenyl-6,7-dihydro-4bH-dibenzo[c,e]pyrrolo[1,2-a]azepine-5,5(9H)-dicarboxylate (5at).



1a **4t** **5at**

The title compound was prepared according to General Procedure E using dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**, 0.020 g, 0.085 mmol, 1.0 equiv) and 5*H*-dibenzo[c,e]azepine (**4t**, 0.018 g, 0.094 mmol, 1.10 equiv). After 3 h, the reaction was worked up and **5at** was obtained as a single diastereomer in a 2:1 mixture of conformers in 55% yield (64% conversion of **1a**) as determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. Flash chromatography (20% EtOAc/hexanes) provided pure **5at** as a white solid in 77:23 er as determined by SFC analysis (Chiralcel, OD, 8.0% MeOH, 2.0 mL/min, 200 bar, 220 nm) $t_{r\text{-major}}$ 9.75 min, $t_{r\text{-minor}}$ 8.99 min. **1a** was recovered in 98:2 er as determined by GC analysis. Analytical data for **5at: mp** 85-86 °C; **IR** (thin film, cm^{-1}) 2952, 2799, 1736, 1451, 1433, 1277, 1227, 1057, 949, 761, 701; [Note: ^{1}H and ^{13}C NMR spectra were obtained by analyzing the trifluoroacetic acid (TFA) salt of **5at**, prepared by adding 1.0 equiv of neat TFA to a chloroform solution of **5at**] **^{1}H NMR** (400 MHz, $CDCl_3$) δ

7.90 (d, J = 7.2, 1H), 7.66 – 7.65 (m, 2H), 7.59 – 7.52 (m, 4H), 7.49 – 7.44 (m, 2H), 7.00 – 6.98 (m, 2H), 6.62 (s, 1H), 4.66 (dd, J = 12.0, 6.8 Hz), 4.25 (d, J = 14.0 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.85 (s, 3H), 3.25 (s, 3H), 2.79 – 2.68 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 167.6, 140.3, 138.3, 134.0, 132.0, 131.1, 131.0, 130.7, 130.3, 129.6, 129.0, 127.6, 71.9, 67.0, 62.7, 53.4, 53.1, 51.0, 38.9; **TLC** (20% EtOAc/hexanes) R_f 0.21; **LRMS** (ESI) Calcd. for $C_{28}H_{27}NO_5$+H: 458.2, Found: 458.2; $[\alpha]_D^{26}$ = −1.95 (c = 0.25, $CHCl_3$).

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