SYNTHETIC STUDIES ON SILYL GYOXIMINES, ALTERNARIC ACID, AND QUATERNARY DONOR SITE CYCLOPROPANES

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ABSTRACT

MICHAEL CHRISTOPHER SLADE: **Synthetic Studies on Silyl Glyoximines, Alternaric Acid, and Quaternary Donor Site Cyclopropanes**

(Under the direction of Professor Jeffrey Scott Johnson)

Silyl glyoxylates were converted to a variety of nitrogenous derivatives and their suitability for three component coupling reactions was investigated. Silyl glyoximines bearing electron-rich or -neutral *N*–aryl groups were suitable electrophiles for addition of sp^3-hybridized alkyllithium nucleophiles. The relatively unstudied [1,2]-aza-Brook rearrangement serves as a key mechanistic feature for the generation of a glycinate enolate for second-stage electrophilic trapping, which could be accomplished with aldehyde, cyanoformate, or anhydride electrophiles. These reactions thus demonstrate the ability of silyl glyoximines to serve as dipolar glycinate linchpins complementary to their silyl glyoxylate parents. To the best of our knowledge, the use of an aza-Brook rearrangement to enable multicomponent coupling is without precedent.

The ability of silyl glyoxylates to serve as effective linchpins for the union of nucleophiles and electrophiles at a glycolic acid junction has been leveraged in synthetic efforts toward the total synthesis of alternaric acid, a biologically active natural product. The second-stage glycolate aldol reaction with the aldehyde that directly affords the aldol subunit in the natural product suffers from poor diastereoselectivity. Efforts to overcome this obstacle demonstrated that a wide variety of substituents are tolerated on the aldehyde electrophile, and exert varying degrees of stereochemical control. Significantly,

a method for generating functionalized vinyl nucleophiles suitable for efficient three component coupling reactions has been established, increasing the convergency of the route and expanding known reactivity patterns of silyl glyoxylates.

A diastereoselective synthesis of pentasubstituted tetrahydrofurans via a Lewis acid catalyzed (3 + 2)-annulation of quaternary donor site cyclopropanes and aldehydes is described. Yields (up to 95%) and diastereoselectivities (up to 99:1) are in some cases competitive with related (3 + 2)-annulation reactions of tertiary donor site cyclopropanes, despite the increased hindrance and reduced steric differentiation between the substituents on the donor site. Chirality transfer studies are consistent with the operation of a similar mechanism for both quaternary and tertiary donor site cyclopropanes, and demonstrate the impact of the stability of carbenium ion character at the cyclopropane donor site on the reaction course. Significantly, it is still possible to obtain highly enantioenriched tetrahydrofuran products from enantioenriched cyclopropane starting materials.

ACKNOWLEDGEMENTS

First and foremost, I must attempt to express my gratitude to my loving and supportive wife Emily Megan. "Attempt" is the operative word, for I know that my words, however well crafted they could ever be, would not due justice to the sincerity and the depth of feeling behind them. These last five years have been a wild ride, and I am so glad to have shared them with you. You have seen me through all the ups and the downs that are summarized on the rest of these pages, even if you don't have the storehouse of technical vocabulary to be fluent in what it all means. I am so proud of the studies you completed at Duke Divinity—even though the formation was hard at times, you have emerged as a thoughtful and capable minister. I am also proud of what you have done these past few years at Macedonia: not only what you have done with the youth, but also for having been the first woman to ever preach there. Most of all, I am so thankful for and proud of the mother you are to Caleb Owen. I do not know how you have done it, but you have single-handedly taken care of both of us over the last few months. I know it has been difficult and no doubt has at least *felt* thankless at times, but I cannot say enough how thankful I am and will always be for the support you have provided. I love you more than you will ever know.

I must also express my gratitude to Jeff, who has been a fantastic mentor over the past five years. Your support, your willingness to let us explore our own ideas, and your patience when these ideas do not always pan out in the hood as they would appear to on paper have meant a great deal to me. I have greatly appreciated the fact that your door

was always open when you were in town, as well your enthusiasm for talking chemistry and thinking through problems at the board or over spectral data. I hope to be more like the chemist and writer I have had the privilege to follow—I have been fortunate to get to learn from the best. As I will soon thank the rest of the group, I will just say that the group is and has always been fantastic, and I think it all starts at the top.

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collaboration and all the chemistry talks were as fruitful for you as they were for me. Two more group members in particular need to be mentioned: Justin Malinowski and Michael Corbett have been quite generous of their time and mass spec training, and I can say with confidence that ≥95 % of the mass spectral data contained herein was obtained by these two. This generosity is characteristic of both these classy individuals in particular, and of the group as a whole. May it always be so.

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2D-NMR	two-dimensional nuclear magnetic resonance
9-BBN	9-borabicyclo[3.3.1]nonane
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetate
Ac_2O	acetic anhydride
AcOH	acetic acid
A–D	asymmetric dihydroxylation
approx.	approximately
Ar	aryl
aq.	aqueous
Bn	benzyl
br	broad
^{i}Bu	*iso*-butyl
^{n}Bu	*normal*-butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-butyl
^{t}BuSal	*tert*-butylsalicylimine
CAM	ceric ammonium molybdate
cat.	catalytic amount or catalyst
CN	cyanide or cyano
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
COD	cyclooctadienyl
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether

CSA	camphorsulfonic acid
d	doublet
D–A	donor–acceptor
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
S-DOSP	1-[[4-alkyl(C_{11}-C_{13})phenyl]sulfonyl]-(2*S*)-pyrrolidinecarboxylate
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
dt	doublet of triplets
DyKAT	dynamic kinetic asymmetric transformation
E	*entgegen*
ee	enantiomeric excess
El^+	electrophile
ent	enantiomer
eq.	equation
equiv.	equivalents

er	enantiomeric ratio
ESI	electrospray ionization
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{n}Hex	*normal*-hexyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
LA	Lewis acid
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile

2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mol	mole
mp	melting point
MS	molecular sieves
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
OMP	*ortho*-methoxyphenyl
^{n}Pent	*normal*-pentyl
Ph	phenyl
Phth	phthalyl
PMP	*para*-methoxyphenyl
PNP	*para*-nitrophenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
PT	1-phenyl-1*H*-tetrazol-5-yl
PTC	phase-transfer catalyst
pybox	pyridine-2,6-bis(oxazoline)
q	quartet
quint	quintuplet

R	alkyl or aryl
R_L	large substituent
R_M	medium-sized substituent
rac or (±)	racemic
rt	room temperature
s	singlet
sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	tetramethylethylenediamine
Tr	triphenylmethyl (trityl)
trig	trigonal
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	anionic ligand or counterion
Z	*zusammen*

δ	chemical shift
Ψ or Ω	hypothetical group whose identity is to be determined

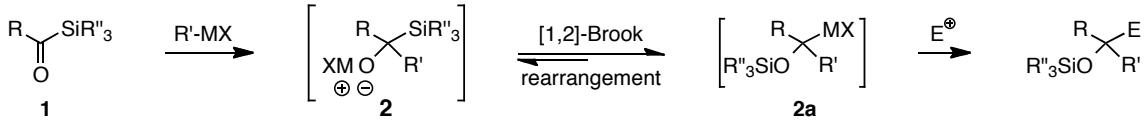
CHAPTER 1

NOVEL DERIVATIVES OF SILYL GLYOXYLATES AND THEIR PARTICIPATION IN MULTICOMPONENT COUPLING REACTIONS

1.1 Introduction

Acylsilanes **1** have received attention as linchpins for multicomponent coupling reactions and tandem bond-forming processes,[1] which are attractive routes for the rapid development of molecular complexity. The reactivity of acylsilanes in these contexts is largely driven by the [1,2]–Brook rearrangement.[2] As demonstrated in **Scheme 1-1**, nucleophilic addition of an organometallic species to an acylsilane results in an alkoxide **2** capable of undergoing a rearrangement in which the silicon is transferred from carbon to oxygen to arrive at a carbanion **2a**. This rearrangement is often favorable due to the greater Si–O bond strength relative to the Si–C bond strength; while it is not an absolute requirement, the rearrangement is greatly facilitated when either R or R' is an electron-withdrawing group (EWG). The resulting carbanion is poised for subsequent trapping with electrophiles in a tandem fashion.

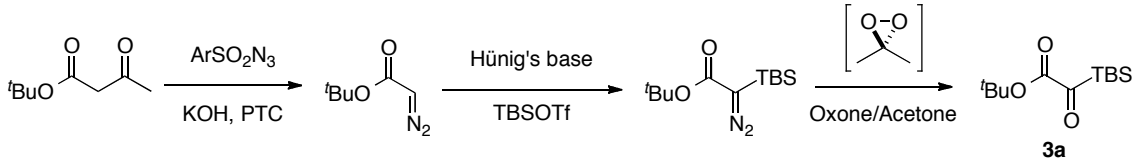
Scheme 1-1. [1,2]-Brook Rearrangement of an Acylsilane



From an acylsilane, there are two possible ways at arriving at an intermediate such as **2**, in which either R or R' is a group that can stabilize the carbanion **2a**: the nucleophile itself (R') could be the EWG, as is the case for cyanide $(CN)^{3-6}$ or phosphite $(P(O)OR"_2)^{7-10}$ nucleophiles, which can be used catalytically in reactions in which **1** serves as an acyl anion equivalent. Another approach is to include the EWG in the original acylsilane; this latter approach was recently developed for use in multicomponent coupling chemistry in our laboratory. The embedded EWG, R, is an

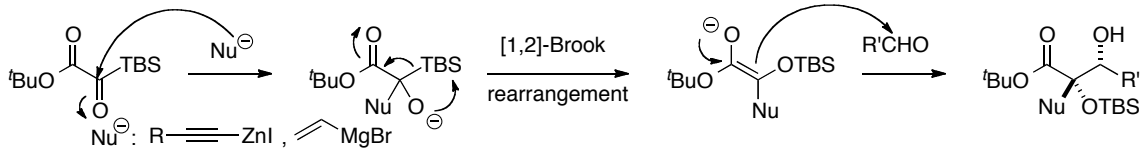
ester: the reagent is therefore known as a silyl glyoxylate.[11,12] This approach is particularly attractive, as it allows for the expansion of the scope of nucleophiles to be used in these reactions beyond those which inherently contain anion-stabilizing capability. Silyl glyoxylates **3** are readily prepared on a large scale in three to four steps in good overall yield (~50%), requiring only one purification at the end of the synthesis (**Scheme 1-2**).[13]

Scheme 1-2. Silyl Glyoxylate Synthesis



Nicewicz demonstrated that silyl glyoxylates are effective as the central linchpin of three component coupling reactions.[12] The transformation is shown in **Scheme 1-3**: nucleophilic addition of an alkynylzinc iodide or vinylmagnesium bromide to the silyl glyoxylate initiates a [1,2]–Brook rearrangement, and the resulting glycolate enolate attacks the terminal electrophile, an aldehyde. One of the key features of this reaction was its high chemoselectivity, as direct nucleophile-terminal electrophile coupling was not observed, although all three components were present simultaneously in the reaction mixture. Another attractive feature of these reactions was the high diastereoselectivity, in which the *syn*-aldol products were obtained with diastereomeric ratios ranging from 83:17 to 92:8.

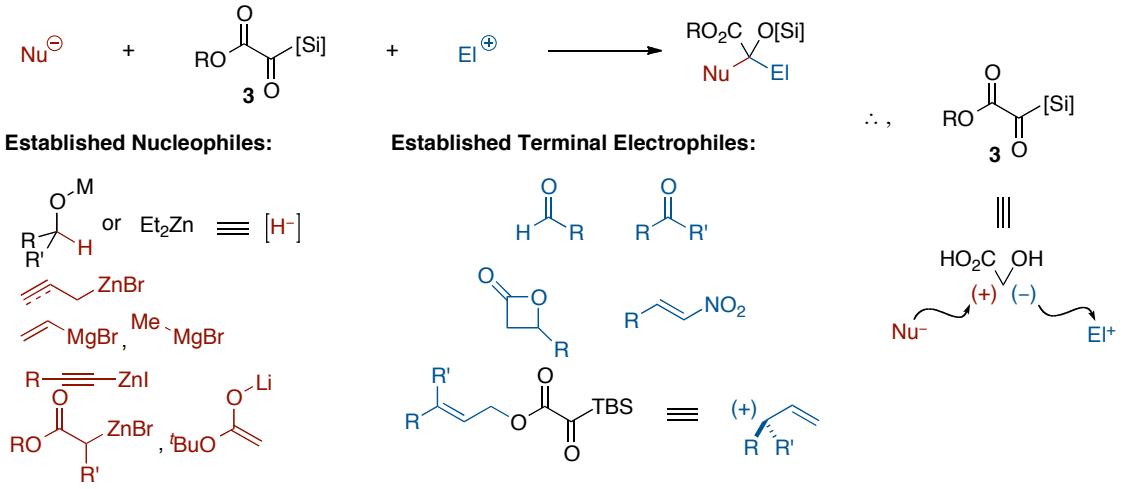
Scheme 1-3. Initial Study of Silyl Glyoxylates in Three Component Couplings



In the intervening period since this initial study of silyl glyoxylate reactivity in three component coupling reactions, additional examples have been developed in our laboratory that serve to highlight the utility of silyl glyoxylates by mixing and matching competent nucleophile/terminal electrophile pairs. In addition to alkynylzincs and vinylmagnesium bromide, hydride nucleophiles (via transfer from metal alkoxides[14,15] or diethylzinc[16]), allyl or propargyl zinc bromides,[16] methylmagnesium bromide,[16] the lithium enolate of *tert*-butyl acetate,[16] and Reformatsky reagents[17] have all been shown to

be efficient promoters of reactions involving silyl glyoxylates (**Scheme 1-4**). While it has been leveraged to great effect in an elegant synthesis of zaragozic acid C,[18] the propensity of the highly electrophilic silyl glyoxylates to undergo oligomerization must often be slowed in these coupling reactions to achieve efficient transformations. In some cases, this has meant either employing a highly reactive nucleophile to rapidly consume the silyl glyoxylate,[16] or judiciously choosing the solvent and temperature such that the timing of the Brook rearrangement can be controlled.[17] The range of terminal electrophiles used as reaction partners has also been expanded to include ketones,[17] nitro olefins,[19] and β-lactones.[20] If the starting silyl glyoxylate **3** bears an allylic ester, a cascade sequence is possible wherein the [1,2]-Brook rearrangement serves to generate an enolate poised to undergo an additional Ireland-Claisen rearrangement.[16] Silyl glyoxylates have thus emerged as highly versatile dipolar synthons for the geminal coupling of nucleophilic and electrophilic components at a glycolic acid junction.

Scheme 1-4. Expanded Nucleophile and Electrophile Scope for Silyl Glyoxylate Three Component Couplings

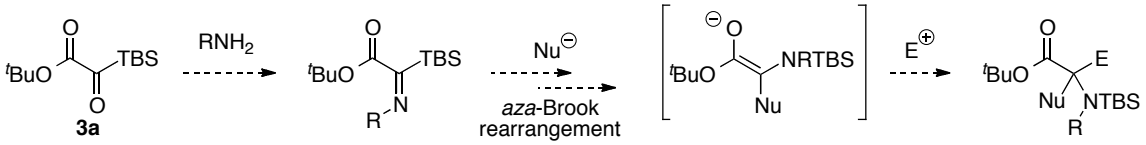


1.2 Background

Given the preponderance of amines in biologically relevant molecules, our research goal was to expand the reaction manifold detailed in section **1.1** to substrates containing nitrogen-bearing functionality. Of the several ways this could potentially be realized, a direct incorporation of nitrogen into the silyl glyoxylate structure would be an interesting entry point. This was envisaged to be feasible through condensation of a variety of amines with the silyl ketone, affording silyl glyoximines (**Scheme 1-5**). The

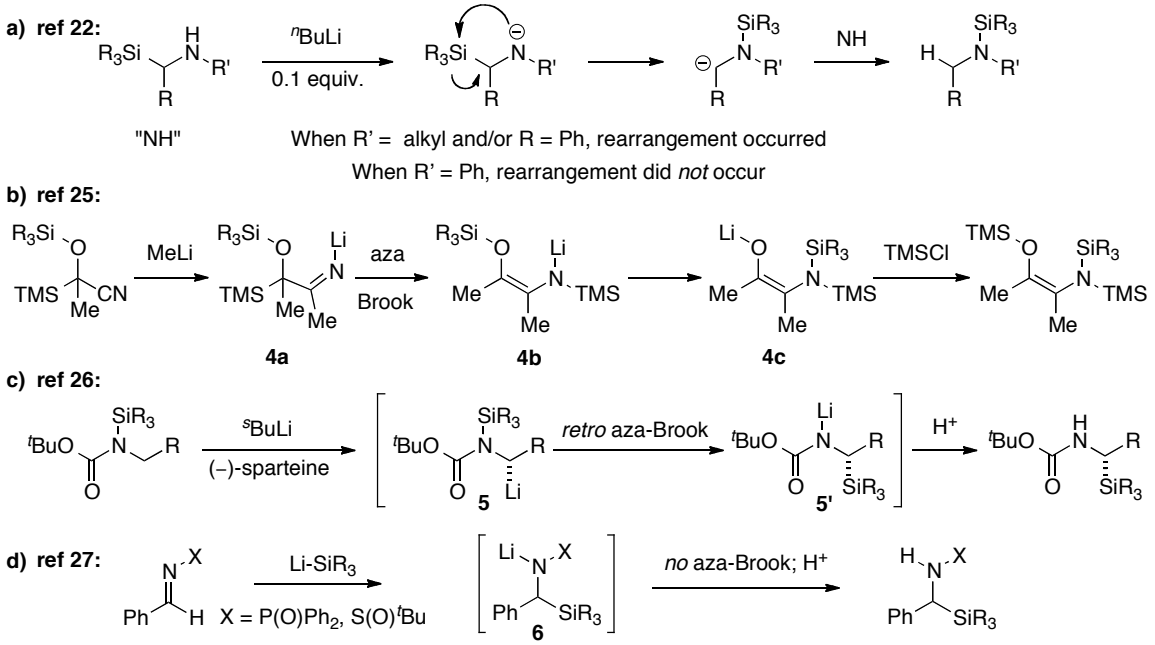
silyl glyoxylate initially employed for derivatization would be *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a**, the optimized reagent for the first-reported three component couplings. From this point, there would be broad flexibility in studying the participation of silyl glyoximines in analogous three component coupling reactions through variation of the nucleophiles and electrophiles used, with a scope potentially as broad as those above.

Scheme 1-5. Proposed Silyl Glyoximine Three Component Couplings



Moreover, this would offer an opportunity to study the known, but far less common, aza-Brook rearrangement.[21,22] The reason for the scarce documentation of this rearrangement is presumably due in part to the reduced driving force of C→N migration of the silicon relative to C→O migration.[1] This may be attributed largely to the relative differences in bond strengths: the energetic benefit in going from a Si–C bond (~88 kcal/mol) to a Si–N bond (~100 kcal/mol) is much lower than in going from a Si–C to a Si–O bond (~128 kcal/mol).[23] In fact, the extant literature on the aza-Brook rearrangement can be broken up into examples in which the C→N migration occurs,[24,25] examples in which the reverse occurs,[26] and examples in which rearrangement is possible but does *not* occur.[27] These data points are summarized in **Scheme 1-6**.

Scheme 1-6. Brief Survey of Literature Studies on the aza-Brook Rearrangement

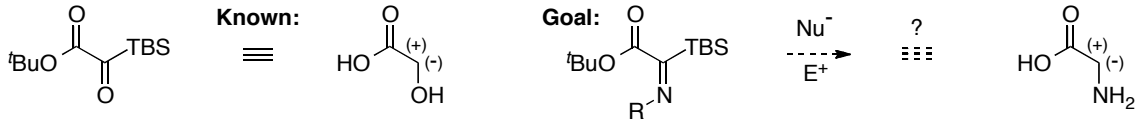


In the absence of the strong driving force of Si–O bond formation, the direction and feasibility of aza-Brook rearrangement appears to involve a delicate balance of the relative stabilities of the anionic species involved. As a particularly interesting example, the reaction in **Scheme 1-6 b)** not only contains a C→N migration (**4a**→**4b**), but also a O→N migration of a silyl group (**4b**→**4c**) despite the fact that the Si–O bond is significantly stronger than the Si–N bond. In this case, the relative stability of the lithium enolate **4c** compared to the lithiated enamine **4b** possibly accounts for the direction of the migration observed. In **Scheme 1-6 c)**, the silicon migrates from nitrogen in **5** to carbon in **5'** likely due to the relative stability of the carbamate anion over the carbanion. In the related intermediates **6** in **Scheme 1-6 d)**, in which the nitrogen atom also bore an electron-withdrawing group, the electron-poor amide anions failed to attack the silicon and initiate the rearrangement.

Thus, depending on the particular nitrogenous derivative of the silyl glyoxylate we were to access, there existed reasonable uncertainty as to whether the aza-Brook rearrangement would even occur as desired. Should the aza-Brook rearrangement in fact occur from our silyl glyoxylate derivatives, and should we be able to realize three component coupling reactions, this would create a useful dipolar glycinate synthon complementary to the glycolate synthon represented by the silyl glyoxylate parent

(**Figure 1-1**). This could potentially provide convenient access to a range of unnatural, α,α,-disubstituted amino acid derivatives, which are targets of interest due to their presence as a subunit in numerous natural products as well as their application toward designer peptides.[28,29]

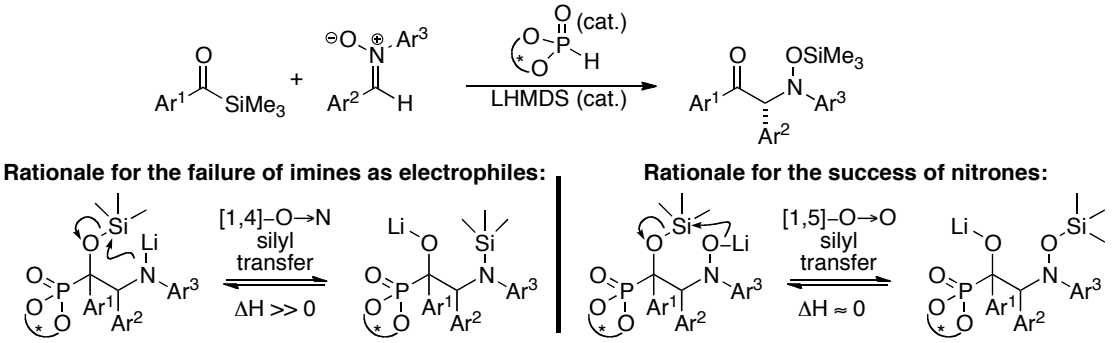
Figure 1-1. Silyl Glyoxylate-Derived Dipolar Synthons



1.3 Results and Discussion: Various Derivatives of the Silyl Glyoxylate

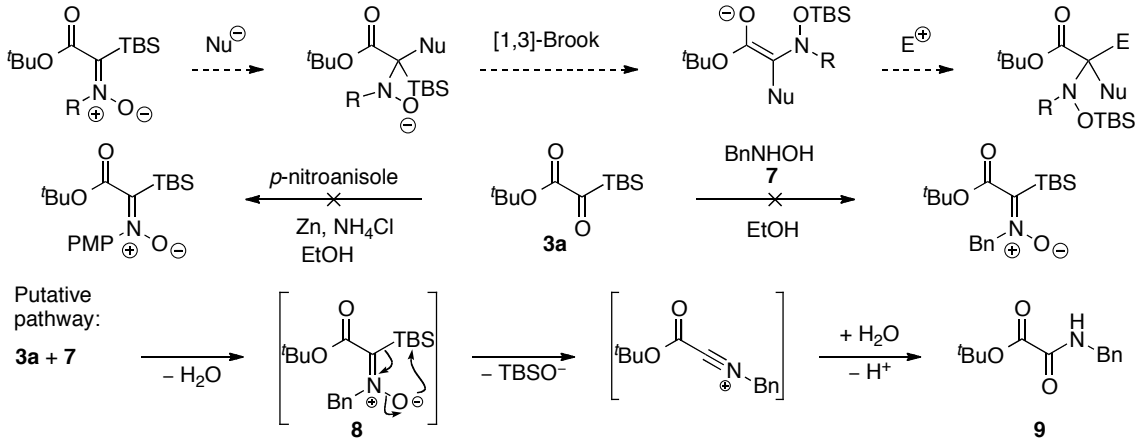
In addition to the above caveats about the potential difficulties in realizing an aza-Brook rearrangement, another potential problem in transferring this chemistry from paper to practice would be the well-known decrease in electrophilicity in going from aldehydes or ketones to imines. As a starting point, it was anticipated that conversion of the silyl glyoxylate to a nitrone would circumvent both of those potential issues. Nitrones are among the most electrophilic of the stable/isolable nitrogenous carbonyl derivatives; if such a species could be synthesized, a silyl glyoxylnitrone would likely retain the strong driving force of C→O Si migration. Extant group precedent in related work with metallophosphite-catalyzed reactions of acylsilanes as acyl anion equivalents attacking azomethine electrophiles demonstrated that, while nitrones were competent reaction partners, imines failed to yield coupling products (**Scheme 1-7**).[30] The rationale for the observed reactivity profile was that imines did not undergo the final silyl transfer to regenerate the starting alkoxide, which in the last step of the mechanism expels the metallophosphite catalyst. This was presumably due to the endothermic nature of O→N Si migration; a thermoneutral O→O migration with nitrones allowed this transfer to occur.

Scheme 1-7. Group Precedent for Nitrones as Successful Electrophiles Where Imines Failed



Initial attempts to convert the silyl glyoxylate **3a** to a nitrogenous derivative thus focused on synthesizing the requisite nitrones, either from an isolated hydroxylamine or from the *in situ* reduction of a nitroarene in the presence of the silyl glyoxylate (**Scheme 1-8**). Perhaps as a testament to the strength of the driving force for C→O migration of the silicon moiety, the only isolable products from such reactions demonstrated that desilylation had occurred *in situ*. In the condensation of the silyl glyoxylate with *N*-benzyl hydroxylamine **7**, for example, instead of forming the desired nitrone we had synthesized the oxamate **9**. This presumably formed through Peterson-type elimination of TBS–O^- from an initially formed nitrone **8**, followed by hydrolysis of the resultant nitrilium ion by the H_2O released during the condensation event. It was not anticipated that changing condensation conditions would eliminate this problem; this necessitated the investigation of other nitrogenous derivatives of silyl glyoxylates.

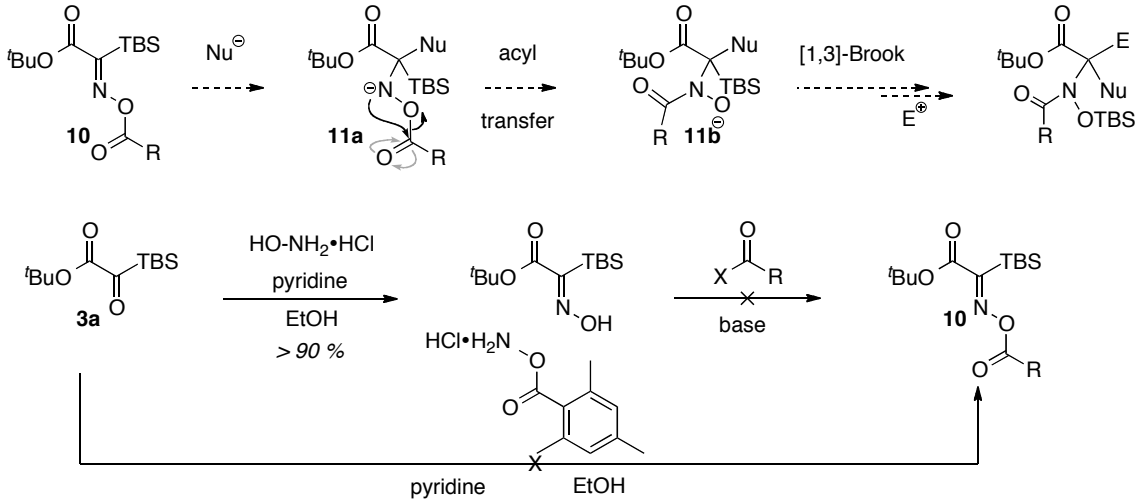
Scheme 1-8. Proposed Silyl Glyoxylnitrones and Attempted Syntheses



Another approach to the proposed chemistry was through attempted derivatization of the silyl glyoxylate to an *O*-acyl oxime. We hypothesized that its participation in a

three component coupling reaction could be as follows: after nucleophilic addition to the oxime carbon in **10**, the resultant amide anion **11a** could attack the acyl group, ultimately resulting in acyl transfer from oxygen to nitrogen. This intermediate **11b** would be closely related to the intermediate envisioned in the nitrone case, and would again undergo a C→O migration of the silicon group (**Scheme 1-9**). However, these desired substrates also proved elusive. While the synthesis of a silyl glyoxime proved straightforward, subsequent *O*-acylation could not be realized without decomposition. This is perhaps due to elimination pathways as above, likely as a consequence of the increased nucleofugality of the *O*-acyl group if formed. As an alternative approach, it was considered that condensation of an *O*-acyl hydroxylamine with the silyl glyoxylate **3a** might furnish the desired derivatives. Attempts to condense *O*-(mesitoyl) hydroxylamine onto the silyl glyoxylate were ultimately unsuccessful as well, using either the HCl salt or the free base.

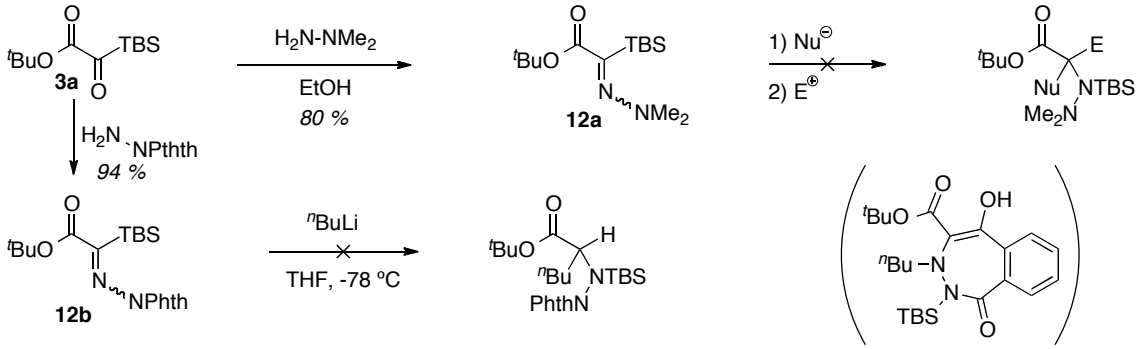
Scheme 1-9. Proposed *O*-Acyl Oxime Couplings and Failed Attempts to Obtain the Required Substrates



We next investigated hydrazones as potential silyl glyoxylate derivatives. There have been numerous reports of the use of chiral hydrazones to stereoselectively direct the addition of organometallic nucleophiles to the azomethine center;[31] in our case, a chiral substituent on the nitrogen of our glycinate enolate might serve as a convenient means to impart absolute stereochemical asymmetry into these reactions. We successfully prepared the dimethyl hydrazone derivative of the silyl glyoxylate (**Scheme 1-10**). However, it was soon found that this substrate **12a** was not sufficiently electrophilic for

the desired reactivity to occur; even powerful nucleophiles such as alkyllithium reagents failed to add to the silyl hydrazone. It was thought that perhaps modification of the hydrazone to contain electron-withdrawing groups on the distal nitrogen would enhance its electrophilicity. Toward that end, a phthalyl hydrazone was synthesized and reacted with butyllithium. While some consumption of the hydrazone starting material **12b** was observed, most was recovered unchanged. The consumed hydrazone had apparently been attacked at nitrogen instead of carbon, leading to the tentatively assigned product in less than 10% yield. The use of more electrophilic derivatives of silyl glyoxylates was subsequently pursued.

Scheme 1-10. Silyl Hydrazones as Unsuccessful Substrates for Three Component Coupling

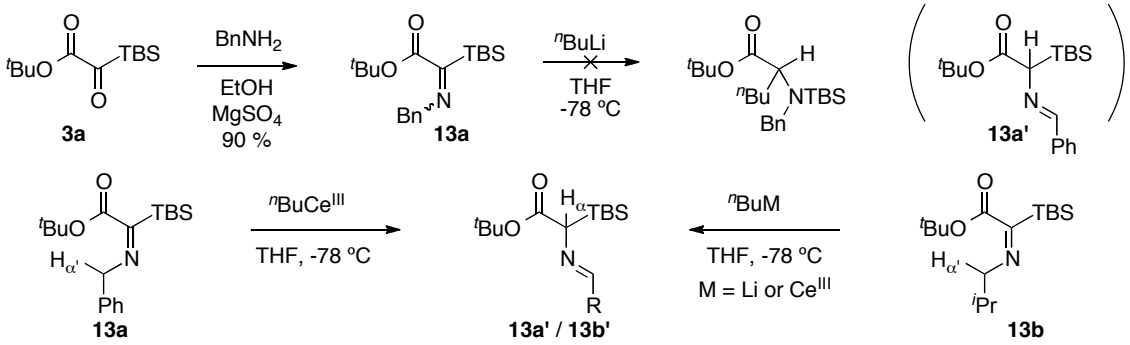


Imines were anticipated to be more electrophilic than hydrazones because they lack the electron-donating second nitrogen atom. The first imine to be synthesized with the hopes of achieving the desired three component coupling reaction was the condensation product of benzylamine with the silyl glyoxylate **3a** (**Scheme 1-11**). The condensation reaction to form the imine **13a** was facile, and the imine could be isolated in pure form as long as the silica gel used for chromatography had been pretreated with triethylamine.

Unfortunately, attempts to promote the three component coupling reaction were again unsuccessful. Instead of nucleophilic addition to the imine moiety, deprotonation at the benzylic position by the organometallic reagent had occurred. The product isolated from this reaction, **13a'**, was an isomer of the silyl glyoximine starting material. It was thought that alkylcerium reagents could potentially be used to effect the desired addition; these reagents have been found to display enhanced nucleophilicity and reduced basicity, affording higher yields of 1,2-addition products into carbonyls which are prone to

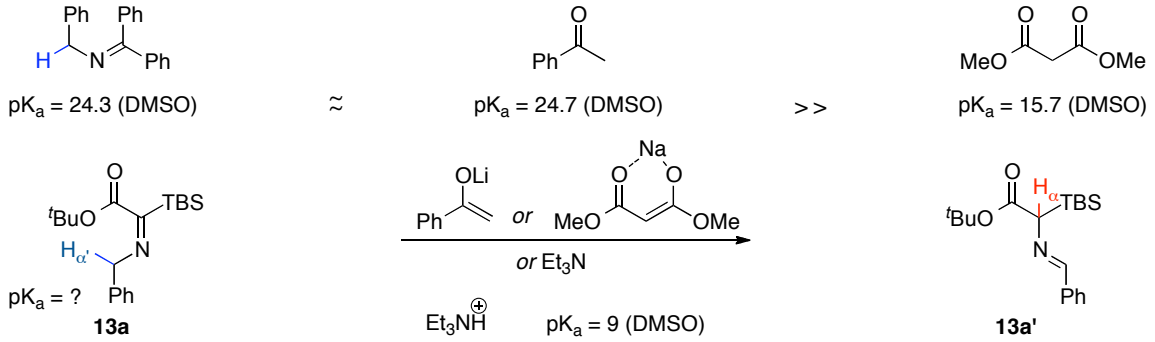
enolize.[32,33] However, this modification to our nucleophiles did not attenuate the deprotonation and isomerization problem. In an attempt to reduce the acidity of the $H_{\alpha'}$ protons adjacent to N, the imine **13b** derived from isobutylamine was prepared. It was anticipated that the isomerization of the proton (α'→α) would be less facile, since it was no longer benzylic. However, this silyl glyoximine yielded the analogous isomer **13b'** when treated with either organometallic species. While the presumed intermediate in these reactions was an enolate which could potentially engage an electrophile, such trapping was not observed upon addition of aldehydes. Attempts to engage the presumed 2-aza-allyl anion with dipolarophiles in a (3+2) reaction were also unsuccessful.

Scheme 1-11. First Silyl Glyoximines and Problematic Isomerization



Another potential avenue for circumventing this problem was inspired by the realization that the benzyl protons of the condensation product of benzylamine with benzophenone are reported to have a pK_a of 24.3 in DMSO.[34] It was postulated that perhaps the use of a nucleophile with a lower pK_a for its conjugate acid, such as acetophenone or dimethyl malonate, would allow for nucleophilic addition to occur in preference to deprotonation (**Scheme 1-12**). Both of these attempts were ultimately unsuccessful, and the isomerized imine was obtained in each. It was ultimately found, accidentally, that a base as weak as triethylamine could effect the isomerization sequence.

Scheme 1-12. Attempts to Lower the Basicity of the Nucleophile and Avoid Isomerization

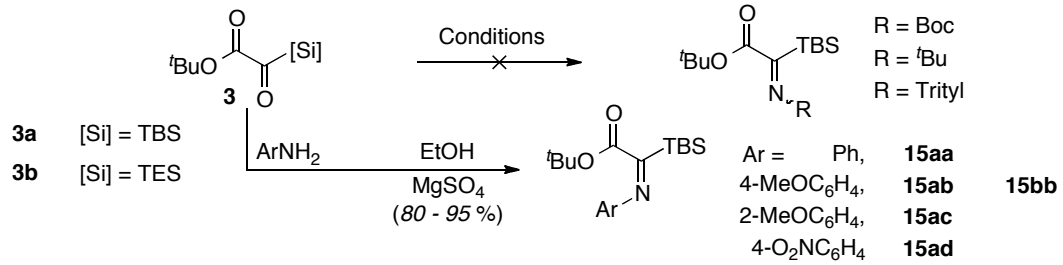


As mentioned above, it was necessary to pretreat the silica gel used for purification of the imine with triethylamine; this was typically done by preparing the slurry for column packing with a 5% Et_3N/hexanes solution. Such a procedure avoided the decomposition of **13a**, while leading to no isomerization to **13a'**. On one occasion, the triethylamine solution was also used to load **13a** onto the column. The product isolated in that instance consisted of a mixture of **13a** and **13a'**. Subsequently, the facility of this isomerization was confirmed by stirring **13a** with triethylamine in ethanol for a few hours, which led to quantitative formation of **13a'**. The reasons for this unexpected, yet evidently quite facile, isomerization are unknown at this time. This fatal discovery led to the abandonment of *N*-alkyl imines bearing protons α to nitrogen, as this isomerization issue presented an insurmountable impasse.

Attempts to synthesize silyl glyoximines without such protons initially focused on making *N*-Boc, *N*-Trityl, and *N*-*tert*-butyl imines (**Scheme 1-13**). Although a variety of reaction conditions were utilized, they were all ultimately unsuccessful. Presumably the failure of these attempts can be attributed to the electronic deactivation and/or the extreme steric hindrance of these amines, limiting their nucleophilicity and thus their ability to condense onto the silyl ketone. The only successful route to the desired class of imines proved to be the facile condensation of anilines **14a-d** with the silyl glyoxylate **3a**. Throughout the course of these studies (*vide infra*), a variety of such imines **15aa-ad** with variable electronic and steric character of the aryl moiety have been synthesized in generally high yields. These substrates were ultimately utilized in studying the proposed three component couplings. The *E*-imine geometry shown has been presumed on the basis of the upfield chemical shift of the *tert*-butyl ester (δ ~1.2 ppm in compounds **15** vs.

1.54 ppm in **3a**), as well as the fact that the use of a smaller triethylsilyl group in the silyl glyoxylate **3b** leads to the imine **15bb** being isolated as a mixture of isomers.

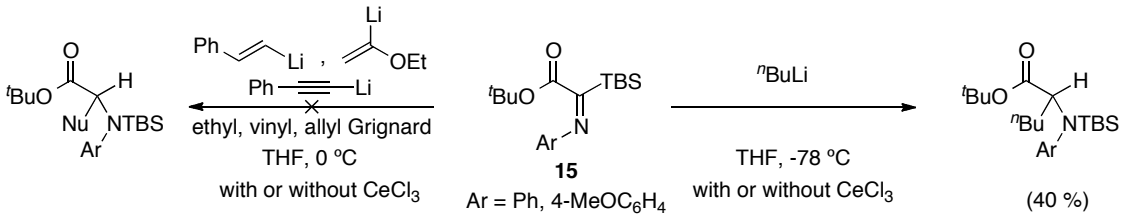
Scheme 1-13. Ultimate Arrival at Silyl Glyoximines Without Protons α to Nitrogen



1.4 Results and Discussion: Silyl Glyoximines in Three Component Coupling Reactions

Initial attempts to engage these imines with nucleophiles involved the reaction of the *N*-(phenyl)-silyl glyoximine **15aa** with a butylcerium reagent[33] (**Scheme 1-14**). These were successful: not only had the desired addition occurred, the aza-Brook rearrangement had occurred as well, and the quenched glycinate enolate had been obtained upon quenching of the reaction mixture with NH_4Cl. With the goal of simplifying the procedure, it was soon discovered that the use of added cerium was not necessary in the reactions with silyl glyoximines **15** when an alkyllithium was used as the parent organometallic species. However, it was also discovered that Grignard reagents, with or without added cerium, did not add to these silyl glyoximines. In addition, sp^2- or sp- hybridized lithium nucleophiles (derived from Li/I exchange of β-iodostyrene, or deprotonation of ethyl vinyl ether or phenylacetylene) were not competent nucleophiles for addition to the silyl glyoximines.

Scheme 1-14. First aza-Brook Rearrangement of Silyl Glyoximines and Nucleophile Comparison

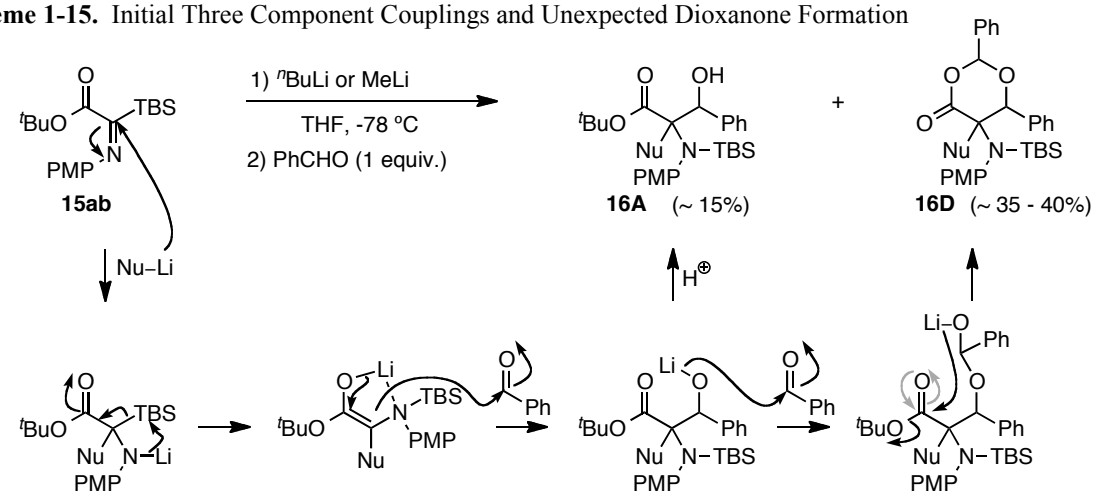


The reduced electrophilicity of silyl glyoximines relative to their oxa parents thus appears to be manifested in the requirement that the nucleophiles used as initiators of

these three component couplings be extremely potent: sp^3-hybridized alkyllithiums. In addition, the reduced electrophilicity of these imines also required the use of a sequential addition approach when moving to the desired three component coupling reactions. Previous silyl glyoxylate couplings had either involved *in situ* generation of the nucleophile in the presence of **3a** and the terminal electrophile, or the addition of a preformed nucleophile to a solution of the other two components. With the imines **15**, it was necessary to add the nucleophile to consume the silyl glyoximine prior to introduction of the terminal electrophile to avoid direct nucleophile/electrophile coupling. While this operationally limited the way the reactions were performed, the benefit to the reduced electrophilicity of the silyl glyoximines was that uncontrolled oligomerization was never an issue. Even if addition/aza-Brook rearrangement were fast enough to occur prior to complete consumption of the imine, the glycinate enolate was not nucleophilic enough to attack the starting imine.

The first three component couplings attempted utilized *N*-(*para*-methoxyphenyl)-silyl glyoximine **15ab**, butyl- or methyl-lithium as the initial nucleophile, and benzaldehyde as the terminal electrophile (**Scheme 1-15**). Interestingly, the reaction afforded something other than the expected simple aldol reaction of the putative glycinate enolate with the aldehyde; the major product isolated no longer contained the *tert*-butyl ester. While the anticipated product **16A** had in fact been formed, its yield was only ~15%. The major product was actually determined to have incorporated two equivalents of the aldehyde, as the ester had been expelled in the formation of the 1,3-dioxan-4-one **16D**. The presumed mechanism for the formation of this product is also shown: after the first aldolization, the intermediate alkoxide attacks another equivalent of benzaldehyde, which ultimately lactonizes with expulsion of the starting ester on the silyl glyoximine.

Scheme 1-15. Initial Three Component Couplings and Unexpected Dioxanone Formation



At the time of these studies, this was the first lactonization of any kind observed in silyl glyoxylate chemistry. This type of product had not been observed in earlier glycolate aldols employing silyl glyoxylates, regardless of the nucleophilic initiator. Subsequent work in our group has shown that an aldol/lactonization pathway is operative when Reformatsky reagents, silyl glyoxylates, and ketones are coupled. In that case, the alkoxide formed from second-stage aldolization of the ketone electrophile spontaneously attacks the ester of the starting Reformatsky reagent to form a γ-butyrolactone.[17] These imine couplings, however, remain the only examples to date in which a dioxanone is formed after aldolization. The reasons for the formation of the dioxanone product **16D** during attempted second-stage aldol reactions with silyl glyoximines are unknown at this time; while this can be impacted by metal counterion (*vide infra*), it appears that this reaction is somehow biased towards this process.

The yields of **16D** in these initial reactions were <40%, but they had only been conducted with one molar equivalent of aldehyde relative to imine. It was anticipated that increasing the amount of aldehyde used should increase the yield of the major product. This proved true, to a point: the yields of each product type marginally increased upon the use of excess aldehyde, although these were still far from optimal (15-20% **16A**, ~50% **16D**). Reactions with methyllithium were especially clean, and it was used as the nucleophile of choice in subsequent experiments. Extensive attempts to optimize the reaction were initiated: these involved the variation of the solvent used, the

reaction stoichiometry, the temperature, the time allowed for the addition/rearrangement to occur prior to addition of benzaldehyde, as well as the concentration.

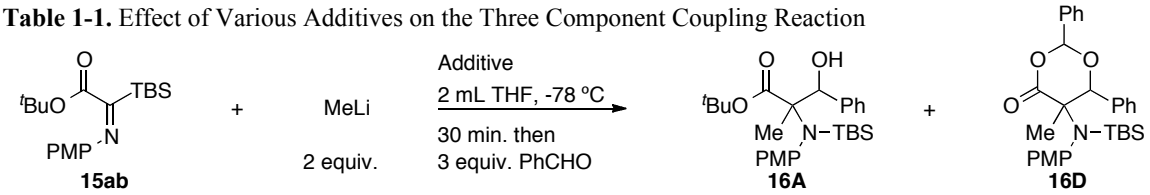
The only significant piece of information gleaned in these studies was that the optimum solvent proved to be THF. Reduced yields were observed in 2-MeTHF, and in both Et_2O and CPME addition of the methyl group to the imine was not observed. This dramatic solvent effect appears to follow the solvents' coordinating ability; it is therefore possible that the presumably looser aggregation states of the methyllithium nucleophile in the more coordinating solvents allows for the addition to the imine to occur. The standard conditions established from these studies were as follows: to one equivalent of silyl glyoximine **15** in THF cooled to -78 ºC were added two equivalents of methyllithium, followed 30 min later by three equivalents of benzaldehyde. The reaction generally afforded the simple aldol product **16A** in ~20% yield (<4:1 dr), and the dioxanone product **16D** in ~50% yield (1.4:1 dr). None of the conditions examined afforded dramatic improvement in either the yield or stereo- and chemo-selectivity.

Other variables were studied in attempts to improve the efficiency and selectivity of the reaction. In light of the demonstrated solvent effect and the apparent impact of the aggregation states of the lithium species present in the reaction, various additives were used to attempt to alter the reaction course (**Table 1-1**). The addition of two equivalents of various LiX salts to the reaction mixture was examined (entries 2-4). Whereas LiF and LiBr had little effect, the addition of LiCl to the reaction mixture led to an alternate product distribution in which the simple aldol product **16A** had become the major product. The yield of **16A** and the selectivity between the two products were still low; variation of the amount of LiCl added to the reaction likewise afforded no significant improvement (entries 5-7).

Polar additives that could chelate to lithium, such as TMEDA, (−)-sparteine, and quinidine, were also employed to attempt to alter the reaction course (**Table 1-1**). It was anticipated that this might increase the nucleophilicity of the various alkoxide species present, perhaps through weakening of the O−Li bond. If successful, **16D** might be more greatly favored due to a more facile attack onto the ester. In practice, the only general effect of these additives was to increase the amount of the 1-phenylethanol byproduct arising from methyl addition to benzaldehyde, while the **16A**/**16D** product distribution

remained essentially unchanged (entries 8-12). It may be noted that the diastereoselectivities for the formation of product **16D** have not been tabulated in **Table 1-1**; this is due in part to very little variation from a typical value of 1.4:1, but also to our current hypothesis that the site of stereoisomerism in **16D** lies at the acetal methine and is relatively fluxional (*vide infra*).

Table 1-1. Effect of Various Additives on the Three Component Coupling Reaction



Entry	Additive	equiv.	**16A** % yield[a] (*dr*)[b]	**16D** % yield[a]
1	none	0	20 (< 4:1)	50 (1.4:1)
2	LiF	2	20 (1.5:1)	41
3	LiCl	2	43 (2.5:1)	29
4	LiBr	2	23 (2.9:1)	46
5	LiCl	0.5	35 (1.1:1)	20
6	LiCl	1	18 (1.1:1)	44
7	LiCl	4	32 (2:1)	9
8	TMEDA	1	21 (1.8:1)	38
9	TMEDA	2	24 (1.7:1)	39
10	TMEDA	4	19 (1.8:1)	46
11	(−)-sparteine	2	20 (2:l)	46
12	quinidine	2	10 (5:1)	36

[a]Determined by ^{1}H NMR versus an internal standard. [b]Determined by ^{1}H NMR.

We then investigated the effect of modifying the silyl glyoximine structure. The modifications involved variation of the ester group, the silyl group, and the *N*-aryl group on the imine. With regard to the modification of the ester, the impetus was two-fold. First, it was conceivable that modification of the ester would alter the steric environment of the enolate with potential effects on the diastereoselectivity in the aldol step. The use of a chiral group on the ester could also serve as a means to imparting stereochemical asymmetry into the reaction via auxiliary control. Additionally, we were cognizant of the fact that *tert*-butoxide is the worst possible alkoxide leaving group: the pK_a of its conjugate acid is several units higher than other aliphatic alcohols.[34] As such, it was anticipated that increasing the nucleofugality of the alkoxide could facilitate the final step

in the presumed mechanism (**Scheme 1-15**, above) and lead to improved yields of product **16D**. The silyl glyoximines used to test these hypotheses bore ethyl and (–)-menthyl groups as their ester functionalities.

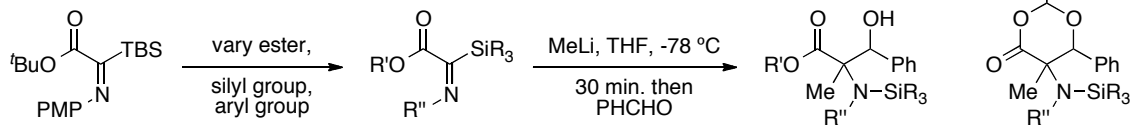
The results from these experiments were mixed (**Table 1-2**). The use of the (–)-menthyl ester generally had no effect on the dr of the products that were obtained or the distribution between products **16A/D**, and the separation of the expelled (–)-menthol byproduct from **16D** was difficult (entry 2). It has since been shown that promising results can be obtained via auxiliary control in silyl glyoxylate three component couplings using other auxiliaries;[35] it is therefore possible that (–)-menthyl was a poor choice, and that other auxiliaries may have served more effectively in this regard. Nevertheless, due to a lack of stereochemical control and the newfound difficulties in purification, use of this silyl glyoximine was soon abandoned. The ethyl silyl glyoximine, on the other hand, had a dramatic effect on the dr of the products obtained (*vide infra*), and the ethanol byproduct was easily removed. However, the yields for reactions with this modified substrate were in general no better than with the original silyl glyoxyimine under a variety of conditions (entry 3).

The next variations on the silyl glyoximine structure involved modification of the steric bulk of the silyl group (**Table 1-2**). Given the proximity of the –N(Ar)(SiR_3) group to the site of the aldol reaction, one might expect some effect on the stereochemical outcome. To this end, formation of a trimethylsilyl glyoximine was attempted. This substrate proved to be unstable and desilylation occurred during the condensation reaction (entry 4). For increased steric bulk, the triisopropylsilyl glyoximine was synthesized, but methyllithium failed to add to the acylimine moiety (entry 5). As a compromise in steric demand between trimethylsilyl and *tert*-butyldimethylsilyl, a triethylsilyl glyoximine was synthesized. However, results with this silyl glyoximine were not a significant improvement over the original substrate (entry 6 vs. entry 1).

The *N*-aryl group on the imine was also varied (**Table 1-2**). Subjecting the *N*-phenyl silyl glyoximine to the standard three component coupling reaction conditions, average results were obtained (19% **14A** (4:1), 48% **14D**; entry 7**)**. With an electron-poor *para*-nitrophenyl (PNP) group, methyllithium addition occurred but the product obtained had not undergone aza-Brook rearrangement, and thus no benzaldehyde was incorporated

(entry 8). This result is not entirely surprising, in light of the literature precedent in which electron-poor amide anions such as **6** (**Scheme 1-6, d**) fail to rearrange.[27] Lastly, using an *ortho*-methoxyphenyl (OMP) group, the reaction was indeed selective for product **16A**, although the yield and stereoselectivity were still lower than desired (36%, 2.3:1; entry 9).

Table 1-2. Summary of the Effects of Modifications of the Silyl Glyoximine Structure

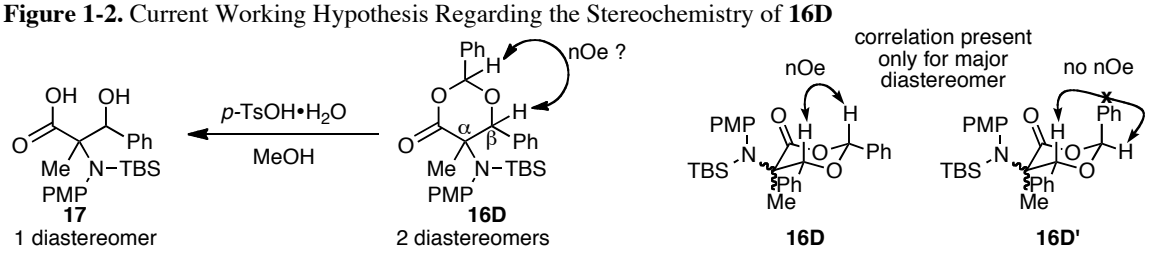


Entry	Ester, R'	Silyl Group, SiR_3	Aryl Group, R''	Result
1	^{t}Bu	TBS	PMP	20% **16A** (< 4:1), 50% **16D** (1.4:1)
2	(–)-menthyl	TBS	PMP	no significant effect on yield, dr, or **16A**/**16D** distribution; (–)-menthol difficult to separate
3	Et	TBS	PMP	crude dr of **16D** ~1:10→variable after chromatography;
4	^{t}Bu	TMS	PMP	yields the same or slightly lower desilylation during condensation; silyl glyoximine never isolated
5	^{t}Bu	TIPS	PMP	MeLi addition never occurred
6	^{t}Bu	TES	PMP	17% **16A** (2:1), 56% **16D** (1:1.4)
7	^{t}Bu	TBS	Ph	19% **16A** (4:1), 48% **16D** (1.6:1)
8	^{t}Bu	TBS	PNP	no aza-Brook rearrangement occurred
9	^{t}Bu	TBS	OMP	36% **16A** (2.3:1)

The effect on the stereochemical outcome of the reaction upon switching from the *tert*-butyl to the ethyl ester is quite pronounced in the formation of product **16D**. Starting with a *tert*-butyl ester, this product is almost invariably isolated as a mixture of two diastereomers in a 1.4:1 ratio. However, when the ethyl silyl glyoximine is used, the product **16D** is obtained with a marked increase in and reversal of the usual stereoselectivity in the crude reaction mixture (1:10). Upon column chromatography, the dr begins to erode and approach the normal ratio. This observation led us to the hypothesis that in the dioxanone **16D**, the relative orientation between the quaternary

center and the first equivalent of aldehyde incorporated is the same in both diastereomers. The isomerism in this product type then lies at the acetal methine, which would likely be the most prone to epimerization in the presence of silica gel. Indeed, when product **16D** is treated with acid, the acetal moiety is cleaved and the product β-hydroxy acid **17** is obtained as a single diastereomer. This evidence supports the hypothesis: elimination of the acetal stereocenter removes the isomerism evident in the product. Further support for the above hypothesis comes from 2-D ^{1}H NMR spectroscopy, in which a nOe enhancement is observed for the methine protons of only one of the diastereomers (assuming an equatorial orientation for the phenyl group of the first aldehyde; **Figure 1-2**). Unfortunately, from this data it was not possible to unambiguously determine relative stereochemistry between the α- and β-stereocenters.

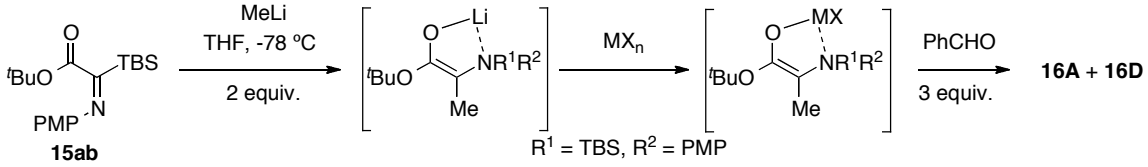
Figure 1-2. Current Working Hypothesis Regarding the Stereochemistry of **16D**



Arising out of this work had been the unexpected formation of product type **16D**, unobserved to date in silyl glyoxylate couplings, as well as the unprecedented requirement for the nucleophiles employed to be as powerful as alkyllithium reagents. Perhaps the reason a product analogous to **16D** had not been observed in prior silyl glyoxylate chemistry was that Grignard reagents and zinc acetylides had been employed as nucleophiles, and the metal counterion for the enolate and alkoxide species generated is what controls the **16A**:**16D** product distribution. To determine if this was in fact the case, the intermediate enolate was transmetallated by the addition of various metal salts prior to addition of benzaldehyde (**Table 1-3**). It was found that the metal counterion did in fact play a key role in determining the ratio of simple aldol to dioxanone products. Some salts seemed to have little to no effect on the reaction, such as CuBr, $MgCl_2$, MgI_2, ZnI_2, or $Zn(OTf)_2$ (entry 2). Other salts such as $MgBr_2$, $ZnCl_2$, and $TiCl_4$ all inhibited the formation of **16D** to varying degrees (entries 3-5). While $MgBr_2$ was most successful in achieving selective formation of **16A** in preference to **16D** (with a promising 10:1 dr), the yield was still below an optimal level.

Although it was not an improvement in the overall reaction, it was clear that the presence of a titanium counterion had strongly affected its course. Further studies to examine this effect were undertaken. The electronic and steric character of the Ti^{IV} species in a given reaction can be conveniently altered simply by mixing $TiCl_4$ and $Ti(O^iPr)_4$ in varying stoichiometric amounts to arrive at species such as $TiCl_n(O^iPr)_{4-n}$.[36] After surveying this series of titanium species (**Table 1-3**, entries 5-9), it was noted that as the chloride content on the titanium increased, so did the suppression of the formation of product **16D**. However, the aldol step was more sluggish: despite increased reaction times, the proton-quenched enolate was isolated in increasing amounts. Again, the stereoselectivity and yield of **16A** remained below that desired for synthetic utility.

Table 1-3. Summary of Metal Counterion Effects



Entry	MX_n	Yield **16A**,%[a] (dr)[b]	Yield **16D**,%[a]
1	none	20 (< 4:1)	50
2	CuBr, $MgCl_2$, MgI_2, ZnI_2, $Zn(OTf)_2$	15 - 20	40 - 50
3	$MgBr_2$	41 (10:1)	trace/none
4	$ZnCl_2$	64 (1.4:1)	20
5	$TiCl_4$	17 (2.8:1)	< 10
6	$Ti(O^iPr)_4$	18 (1.4:1)	49
7	$TiCl(O^iPr)_3$	46 (2:1)	35
8	$TiCl_2(O^iPr)_2$	36 (2.5:1)	13
9	$TiCl_3(O^iPr)$	36 (3:1)	8

[a]Determined by ^1H NMR versus an internal standard. [b]Determined by ^1H NMR.

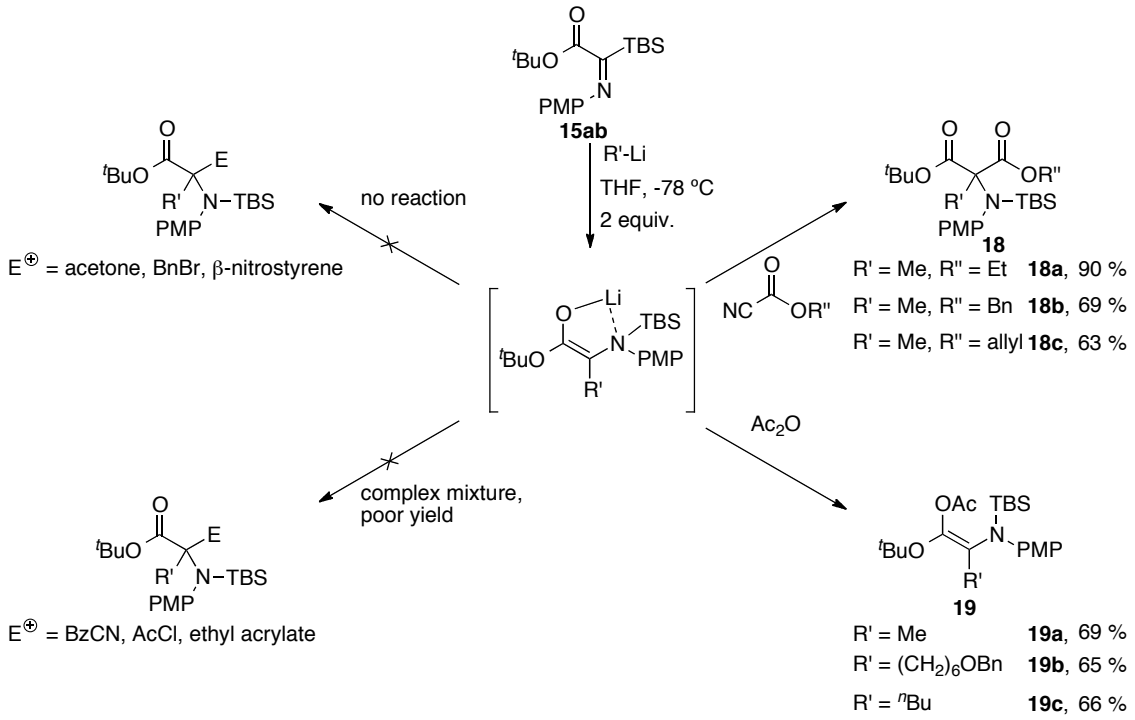
At this point, a thorough examination of ways to potentially optimize the initially planned three component coupling reaction had been conducted. The total conversion of the silyl glyoximine into three component coupling products was acceptable—usually >65% of the starting material could be accounted for in the two products, which would be enough for a synthetically useful methodology, given the complexity built up in a single

step. The real issue was that none of the reaction conditions examined were able to bias the mixture of **16A** and **16D** into a synthetically useful combination of yield and stereoselectivity. Exploratory attempts with other aldehydes revealed that this issue seemed to be general for a second-stage aldol process, and not unique to benzaldehyde. With no clear breakthroughs apparent in the aldol reaction, different classes of electrophiles were then studied for reactivity with the intermediate lithium enolate.

As summarized in **Scheme 1-16**, no desired products were obtained from attempts to react the enolate with acetone, benzyl bromide, or β-nitrostyrene; the proton-quenched enolate was recovered in all cases. Complex mixtures were obtained upon reaction with benzoyl cyanide, acetyl chloride, and ethyl acrylate, from which little or no desired product was isolated. Successful reactions were achieved when the third component was either a cyanoformate or an anhydride. Consistent with significant precedent, the lithium enolate could be *C*-acylated upon reaction with cyanoformates to give products **18a-c**,[37] whereas acetic anhydride gave exclusive *O*-acylation to give products **19a-c**.[38]

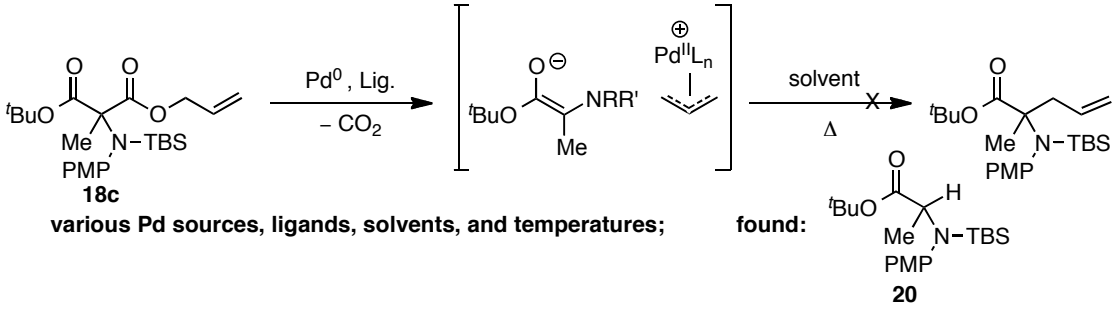
A few additional alkyllithium reagents were used as initiators of these *O*-acylation reactions to demonstrate that these reactions were limited only by the availability of the sp^3-hybridized alkyllithium nucleophile. These included butyllithium as well as a non-commercially available reagent derived from lithium-halogen exchange, and the yields of these products were consistently good regardless of the nucleophilic initiator. The double bond geometry assigned was based on a 2-D NOESY analysis of product **19a**; it is consistent with a (*Z*)-glycinate enolate geometry. This was expected to be favored due to the opportunity for chelation to the metal counterion. Although it had not yet been firmly established at the time of the studies in this chapter, it is also consistent with the favored enolate geometry of the parent glycolate enolate accessed by nucleophilic addition to silyl glyoxylates.[16]

Scheme 1-16. Summary of the Use of Other Nucleophiles and Electrophiles



While these acylation reactions were in fact successful in providing single products in synthetically useful yields, the products themselves were deemed less interesting. It was thus desirable to explore a few derivatizations of these products to increase their synthetic utility. For example, the allyl cyanoformate-derived **18c** was expected to be a viable substrate for decarboxylative allylation chemistry.[39] To realize this goal, several conditions were explored to react this substrate with Pd^0. As summarized in **Scheme 1-17**, we were unable to successfully achieve the reunion of the fragments formed upon extrusion of CO_2 from our substrate. Although heating to 100 ºC enabled the decarboxylation, no return of the allyl fragment was evident: the product isolated was simply the proton-quenched enolate **20**.

Scheme 1-17. Attempts to Demonstrate Utility of Acylation Product via Decarboxylative Allylation



1.5 Conclusions

This chapter has described attempts made to derivatize the silyl glyoxylate from a dipolar glycolate synthon for the geminal coupling of nucleophilic and electrophilic components to an analogous glycinate synthon. Several derivatives were explored, and the syntheses of these intermediates were often straightforward. However, for potential application to the envisioned three component coupling chemistry, several limitations were encountered. The first limitation discovered was the unexpected and ultimately quite facile isomerization of *N*-alkyl silyl glyoximines with protons adjacent to the nitrogen atom. The reasons for the facility of this isomerization are unknown, but it was evident that no modifications of nucleophile and/or reaction conditions would overcome this problem. Thus, a simple solution was found by synthesizing silyl glyoximines bearing *N*-aryl groups, which could in fact be used in the desired three component coupling chemistry.

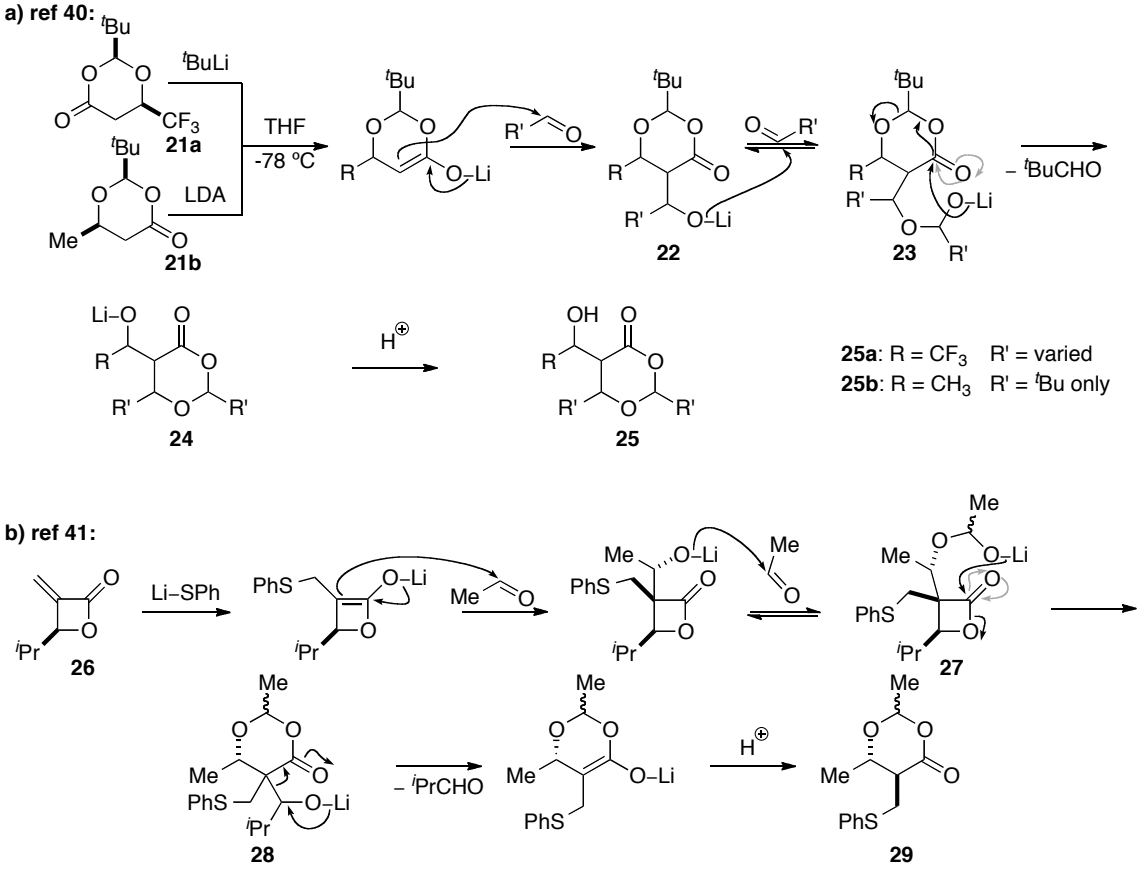
Further limitations were uncovered. The first and perhaps most significant was the fact that only extremely potent, sp^3-hybridized alkyllithium nucleophiles could engage these imines due to a markedly reduced electrophilicity. A second consequence of the reduced electrophilicity of these imines was that the three component coupling reactions had to be performed under sequential addition conditions. Another substrate limitation was the electronic character of the *N*-aryl group, which had to be at least electron-neutral in order for the aza-Brook rearrangement to occur. While the putative glycinate enolate formed in these reactions could engage aldehyde electrophiles, the reaction followed competitive pathways for formation of a mixture of products **16A** and **16D**. While these pathways could be impacted in various ways, no conditions were

found to bias the reaction sufficiently to achieve a synthetically useful transformation. Other electrophiles were examined, but these were either unsuccessful reaction partners, or the products obtained were less interesting and lacked synthetic utility.

The major drawback to the chemistry described herein was the relatively unselective **16A**/**16D** product distribution in attempted aldol reactions with the glycinate enolate. To the best of our knowledge, there are only two examples of such unexpected dioxanone formation during aldol reactions. These are summarized in **Scheme 1-18**, and in both of these cases, there appears to be a strong driving force for dioxanone formation. With substrate **21a** in **Scheme 1-18 a)**,[40] deprotonation of the starting dioxanone **21** is followed by aldol reaction with an aldehyde. Alkoxide **22** attacks another equivalent of aldehyde to afford **23**. Attack of the dioxanone carbonyl leads to the rearranged dioxanone **24** with loss of pivaldehyde. The alkoxide **24a** is strongly inductively stabilized (R = CF_3). The authors cite the difference in pK_a between CF_3CH_2OH (12.4) and CH_3CH_2OH (15.5) as a rationale for the α-CF_3 alkoxide **24a** acting as a "sink" for the reaction prior to quenching.

With respect to substrate **21b** in **Scheme 1-18 a)**, which lacks the trifluoromethyl group, the authors noted that only pivaldehyde reacted in an analogous fashion to afford **25b**. This stood in contrast to reactions with **21a**, which proceeded to the rearranged dioxanone **25a** with a variety of aldehydes. The authors propose that with substrate **21b**, dioxanone reorganization must be controlled by conformational biases of the intermediates because it was only with the extreme steric demands of the pivaldehyde electrophile that this pathway was observed.

Scheme 1-18. Literature Examples of Unexpected Dioxanone Formation in Aldol Reactions



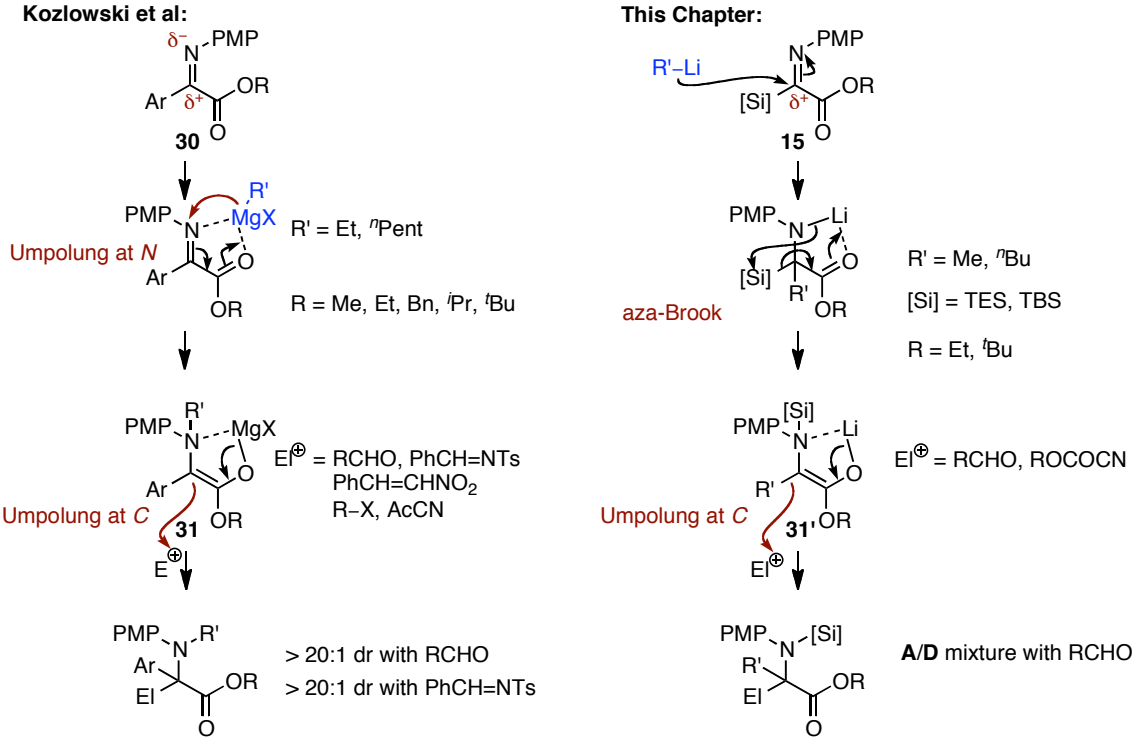
The other extant literature example of unexpected dioxanone formation is shown in **Scheme 1-18 b)**,[41] in the transformation of the β-lactone **26** to the dioxanone **29**. In the presumed reaction pathway, the lithium enolate of β-lactone **26** is generated via the conjugate addition of a lithium thiolate. The resultant enolate undergoes an aldol reaction with acetaldehyde, followed again by incorporation of a second equivalent of acetaldehyde to afford **27**. The alkoxide **27** then attacks the β-lactone, forming dioxanone **28** which undergoes a retro-aldol fragmentation and loss of isobutyraldehyde prior to workup. In this reaction, it is likely that the relief of ring strain in opening the β-lactone serves as a key driving force for the overall transformation; this presumably also limits the reversibility of the dioxanone-forming step (**27**→**28**).

A few features of this precedent are worth noting and comparing to the chemistry described in this chapter. In both examples in **Scheme 1-18**, the alkoxide counterion is lithium and the solvent used is THF, as it was for much our chemistry. In addition, the major product in these studies was typically the dioxanones **25** and **29**, even when only

one equivalent of aldehyde was used. The simple aldol product was also formed to an appreciable extent in these studies. Last, the products **25** and **29** were confirmed to favor either a twist-boat or a boat conformation to minimize steric interactions. Especially since **25b** was only formed when pivaldehyde was used as the electrophile, it appears as though conformational biases in these reactions may play a key role in directing them towards dioxanone formation. It is therefore possible that the steric demands inherent to our system are what predisposed it to such a pathway, and that is why modification of the counterion could only avoid this to a limited extent. Likewise, **16D** may also reside in a boat or twist-boat conformation, complicating the analysis of its relative configuration.

Shortly after the conclusion of the studies described in this chapter, a paper entitled "*Three Component Coupling of α-Iminoesters via Umpolung Addition of Organometals: Synthesis of α,α-Disubstituted α-Amino Acids*" emerged from the Kozlowski laboratory.[42] Given that a strikingly similar title could have been given to much of the work discussed in this chapter, a brief examination of the Kozlowski findings may be instructive here. As summarized in **Scheme 1-19**, the key similarities are that the thrust of the work focused on achieving three component coupling reactions of α-imino esters with organometallic reagents and terminal electrophiles through the intermediacy of glycinate enolates. Fully α-substituted glycinate derivatives were generated in both reactions, which featured the achievement of umpolung reactivity.

Scheme 1-19. Comparison of Methods for Three Component Coupling of α-Imino Esters



The chief differences in the two studies are the particular iminoesters studied, the site of the reactivity umpolung, and the organometallic reagents employed. The Kozlowski α-imino esters **30** also bore a *N*-PMP group, but they bore aryl groups instead of silyl groups at the imine carbon as in our substrates **15**. In the Kozlowski study, polarity reversal was achieved at nitrogen *and* at carbon, due to the site of original attack: an aza-Brook rearrangement was not necessary to generate the second-stage glycinate enolate nucleophile **31** as it was for **31'**. The identity of the organometallic nucleophile employed played a crucial role in determining the site-selectivity of initial attack in the Kozlowski report: organozinc and Grignard nucleophiles added at nitrogen, whereas alkyllithiums attacked at carbon. In our study of imines **15**, we never observed any reactivity with Grignard reagents—no addition occurred, regardless of whether it was at nitrogen or carbon.

Exact reasons for the differences in reactivities observed are only speculative at this point, but two key factors are possibly responsible for the success of the Kozlowski system, and the lack thereof in ours. It is likely that these disparities stem from both the identity of the metal counterion as well as the substituents on nitrogen in the intermediate

enolates. Perhaps the most important divergence in reactivity between the two systems was that Kozlowski and co-workers observed excellent diastereoselectivities when the terminal electrophiles were aldehydes and imines (>20:1 dr); this contrasts sharply with what we observed in our system. Enolates **31** could also be alkylated with alkyl halide electrophiles, whereas enolates **31'** were unreactive toward such secondary electrophiles. The extreme steric bulk of the silyl group in **31'** (as compared to the linear alkyl groups in **31**) may be responsible for imparting significant conformational biases that impacted both the stereoselectivity and the ability to engage weaker electrophiles. Certainly, if conformational factors are central to the reactivities observed in **Scheme 1-18**, they are likely to have been at play in directing our system toward dioxanone formation due to the extreme steric demands of a fully substituted center in which one of the substituents is an exceedingly large amine moiety.

While the work described in this chapter was ultimately less successful than desired for publication as a synthetically useful method, we had accomplished a number of the goals we had set out for ourselves. We were in fact able to explore a variety of nitrogenous derivatives of silyl glyoxylates and gain insights into their chemical behavior. We were able to demonstrate the ability of the aza-Brook rearrangement to serve as a key mechanistic step in three component coupling reactions, which to the best of our knowledge was without precedent. Lastly, we were able to thus demonstrate the ability of these silyl glyoximines to serve as the glycinate complement to the demonstrated utility of silyl glyoxylates as geminal dipolar glycolate synthons, even if their inherent limitations created some challenges to success.

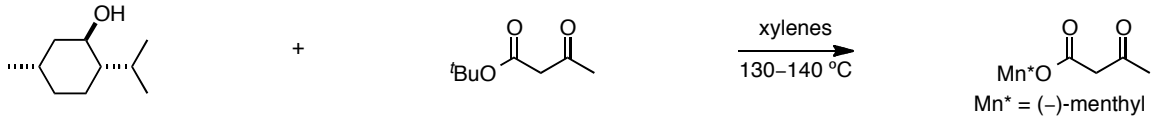
1.6 Experimental

Materials and Methods: General. 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 300, Avance 400, DRX 400, or 600 MHz (^{1}H NMR at 300, 400, or 600 MHz and ^{13}C NMR at 100 or 150

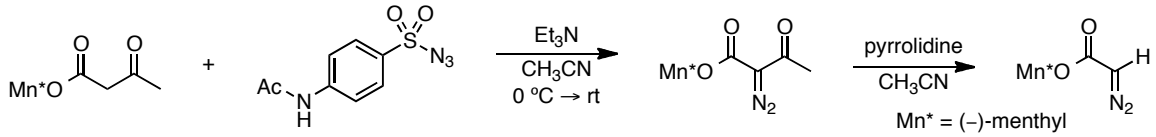
MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, 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 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 column 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. The diastereomer ratios reported are for crude reaction mixtures. Reactions were performed in oven- or flame-dried glassware equipped with Teflon coated stir bars in solvents that had been dried by passage through a column of neutral alumina under nitrogen prior to use, unless otherwise stated. Benzaldehyde and acetic anhydride were purified and dried according to the established method.[43] The LiX salts used in General Procedure C had been dried at ~120 ºC in an oven for >12 h prior to use. TMEDA was distilled from calcium hydride prior to use. The following reagents were prepared according to literature methods: ethyl diazoacetate,[44] *N*-benzyl hydroxylamine,[45] *N*-aminophthalimide,[46] *p*-acetamidobenzensulfonamide (*p*-ABSA),[47] allyl cyanoformate,[48] 6-iodo-1-benzyloxy-hexane.[49] All other reagents and solvents were obtained from commercial sources and used without further purification unless otherwise noted.

Synthesis of Novel Silyl Glyoxylates:

(–)-menthyl *tert*-butyldimethylsilyl glyoxylate (3c):



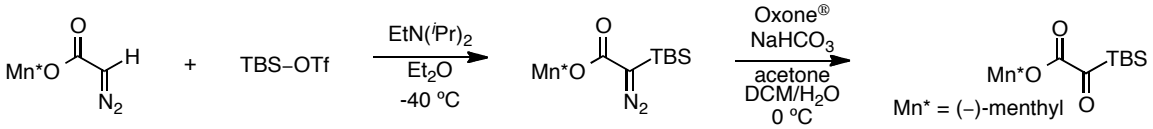
(–)-Menthyl acetoacetate (E-1). This compound was prepared analogously to the literature procedure.[50] A solution of (–)-menthol (1.88 g, 12.07 mmol, 1.0 equiv.) and *tert*-butyl acetoacetate (2 mL, 1.91 g, 12.07 mmol, 1.0 equiv.) in xylenes (~10 mL) was prepared in a 50 mL Erlenmeyer flask equipped with a stir bar. The solution was stirred while being heated on a hot plate, with a thermometer was placed just below the opening of the flask. The reaction began to boil, the *tert*-butanol (bp 82 ºC) was driven off, and the reaction temperature was allowed to proceed approx. 5 min past when the vapor temperature reached the boiling point of xylenes (130-140 ºC). The reaction was cooled to room temperature and concentrated with heating on a rotary evaporator to a clear oil which required no purification (2.88 g, quant. yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.70 (dt, *J* = 10.8, 4.2 Hz, 1H), 3.39 (s, 2H), 2.22 (s, 3H), 2.05-1.95 (m, 1H), 1.90-1.78 (m, 1H), 1.68-1.58 (m, 2H), 1.50-1.30 (m, 2H), 1.10-0.90 (m, 2H), 0.95-0.80 (m, 1H), 0.85 (m, 6H), 0.72 (d, *J* = 6.6 Hz, 3H). Peaks for the enol tautomer were also evident.



(–)-Menthyl diazoacetate (E-2). The standard two-step diazo transfer/retro-Claisen protocol was followed,[17] without drying solvents or reagents and without inert atmosphere. To a stirred suspension of **E-1** (2.88 g, 12 mmol, 1.0 equiv.) and *p*-ABSA (3.19 g, 13.2 mmol, 1.1 equiv.) in acetonitrile (20 mL) at 0 ºC was added triethylamine (5

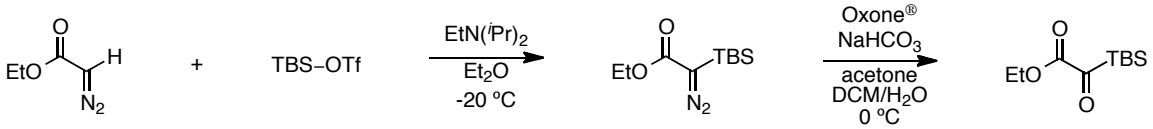
mL, 3.66 g, 36.2 mmol, 3 equiv.). The reaction was allowed to warm to room temperature and monitored by periodic removal of aliquots for NMR analysis. When complete, the mixture was filtered, concentrated, and the residue was taken up in Et_2O/H_2O (1:1, ~50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated to a yellow oil.

The crude diazoacetoacetate was dissolved in CH_3CN (20 mL) and pyrrolidine (2 mL, 1.7g, 24 mmol, 2 equiv.) was added. The reaction was stirred at room temperature and monitored by periodic removal of aliquots for NMR analysis. Upon completion, the reaction was concentrated *in vacuo* and the residue was redissolved in Et_2O (~50 mL). The solution was washed with 2M NaOH (2 x 20 mL), H_2O (2 x 20 mL), brine (30 mL), dried over $MgSO_4$, and concentrated to a yellow oil. **^{1}H NMR**: δ 4.76 (dt, *J* = 11.1, 4.5 Hz, 1H), 4.71 (br s, 1H), 2.08-1.98 (m, 1H), 1.90-1.78 (m, 1H), 1.68-1.58 (m, 2H), 1.50-1.30 (m, 2H), 1.10-0.90 (m, 2H), 0.95-0.80 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H). This material was carried through without purification.

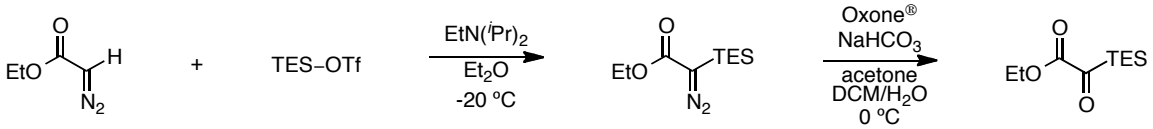


(–)-Menthyl *tert*-butyldimethylsilyl glyoxylate (3c). The silylation and oxidation steps were performed according to the standard protocol.[13] The title compound was purified using a hexanes flush followed by elution with 2.5% EtOAc/hexanes, collecting the bright yellow band. The yield over the five steps from *tert*-butyl acetoacetate was ~55%. Analytical data for **3c**: **IR** (thin film, cm^{-1}): 2956, 2930, 2860, 1740, 1712, 1658, 1464,

1389, 1367, 1259, 1181, 995, 948, 909, 843, 785; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.81 (dt, *J* = 10.8, 7.2 Hz, 1H) 2.00 (m, 1H), 1.87-1.82 (m, 1H), 1.70-1.68 (m, 2H), 1.50-1.46 (m, 2H), 1.12-1.04 (m, 2H), 0.95 (s, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (m, 1H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.27 (s, 3H), 0.26 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 232.3, 163.0, 76.1, 46.8, 40.6, 34.0, 31.5, 26.4, 26.0, 23.2, 21.9, 20.7, 17.0, 16.0, -6.8, -6.9; **TLC** (5% EtOAc/hexanes): R_f 0.45 (UV/CAM; also visible to naked eye); **LRMS** (ESI): Calcd. for $C_{18}H_{34}O_3Si$+Na: 349.22; Found: 349.22; Calcd. for $C_{18}H_{34}O_3Si$+Cs: 449.13; Found: 449.14

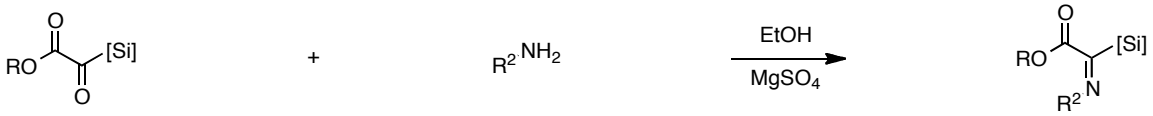


Ethyl *tert*-butyldimethylsilyl glyoxylate (3d). The silylation and oxidation steps were performed according to the standard protocol.[13] Purification was effected via flash column chromatography, eluting with 5% Et_2O/hexanes, collecting the bright yellow band. The two-step yield from ethyldiazoacetate was 65% (29 mmol scale afforded 4 g, 18.7 mmol of the desired product over the two steps). Analytical data for **3d**: **IR** (thin film, cm^{-1}): 2956, 2932, 2861, 1741, 1719, 1658, 1466, 1365, 1254, 1096, 1028, 842, 784; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.28 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.94 (s, 9H), 0.26 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 232.0, 162.8, 61.6, 26.4, 16.9, 14.0, -6.9; **TLC** (5% EtOAc/hexanes): R_f 0.28 (UV/CAM; also visible to naked eye); **LRMS** (ESI): Calcd. for $C_{10}H_{20}O_3Si$+Na: 239.11; Found: 239.12



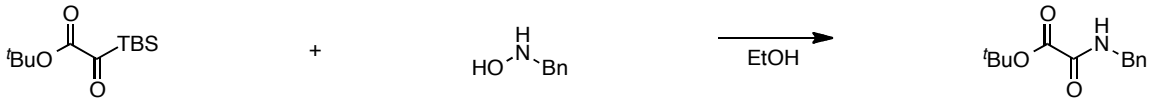
Ethyl triethylsilyl glyoxylate (3e). The silylation and oxidation steps were performed according to the standard protocol,[13] with slight deviations in the final oxidation step due to a propensity of this substrate to undergo overoxidation/decomposition. The oxidation was performed according to a slight modification of the standard protocol: instead of a standard 0 ºC bath, an ice/NaCl/brine bath was used to maintain the reaction temperature ≤0 ºC to avoid overoxidation. A solution of the crude silyl diazoacetate (~12 mmol) in DCM (20 mL) was added to a mechanically stirred suspension of Oxone® (15 g, 24 mmol, 2 equiv.), sodium bicarbonate (8.2 g, 98 mmol, ~8 equiv.) in an acetone/H_2O (1:1.5) solvent system (90 mL total) which was cooled in the cold bath. As the reaction proceeded, the pale yellow color of the silyl diazoacetate typically became a deeper yellow-gold, indicative of silyl glyoxylate formation. The reaction was monitored by TLC analysis, and additional Oxone/bicarbonate and acetone/H_2O were added periodically (~2 h intervals) as needed. Upon completion of the reaction, the workup was performed as quickly as possible to avoid decomposition. The layers of the biphasic reaction mixture were separated, and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The mixture was filtered and carefully concentrated to a yellow oil, and purification via column chromatography with 5% Et_2O/pentanes as eluent afforded the silyl glyoxylate as a bright yellow oil (1 g, 4 mmol, 33% yield over the two steps). Analytical data for **3e**: **IR** (thin film, cm^{-1}): 2958, 2913, 2878, 1747, 1717, 1662, 1466, 1415, 1265, 1021; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.30 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.83 (q, J = 7.8 Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 232.6, 162.4, 61.6, 14.1, 7.1, 2.1; **TLC** (5% EtOAc/hexanes): R_f 0.31

(UV/CAM; also visible to naked eye); **LRMS** (ESI): Calcd. for $C_{10}H_{20}O_3Si$+Na: 239.11; Found: 239.12



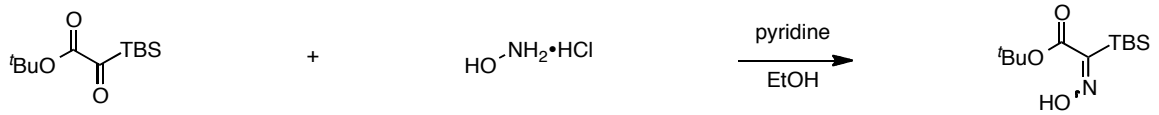
General Procedure A: Synthesis of silyl glyoxylate derivatives

To a stirred solution of the particular silyl glyoxylate (1 equiv.) in EtOH was added a generous spatula tip of $MgSO_4$. To the resulting bright yellow suspension was added the particular amine (1.2 equiv.), followed by additional EtOH. The reaction was stirred at room temperature open to air until it was judged complete by TLC analysis (or aliquot removal for NMR analysis, if no change in R_f was observed), at which point the mixture was filtered through a 3 cm Celite plug to remove the $MgSO_4$. The plug was rinsed thoroughly with Et_2O and concentrated. The residue was loaded onto a silica gel column that had been packed using a 5% Et_3N/hexanes solution (hereafter referred to as a "pretreated column"), and eluted with a hexanes flush followed by the indicated solvent system.



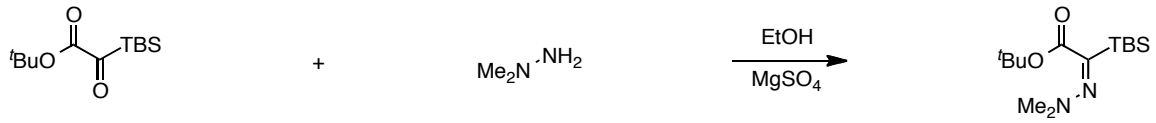
***tert*-butyl 2-(benzylamino)-2-oxoacetate (9).** The title compound was prepared by the addition of silyl glyoxylate **3a** (100 mg, 0.409 mmol, 1.0 equiv.) to a solution of benzyl hydroxylamine (50 mg, 0.409 mmol, 1.0 equiv.) in EtOH (2 mL), with an additional 1.5 mL EtOH used to rinse the pipette used for transfer. Within 15 minutes, the bright yellow color from the silyl glyoxylate had dissipated, at which point TLC analysis indicated that the reaction was complete. The reaction was concentrated and loaded directly onto a pretreated silica gel column, which was flushed with hexanes followed

and eluted with 15% EtOAc/hexanes. The undesired product **9** was isolated in 93% yield (88 mg, 0.380 mmol) as a waxy white solid. Analytical data for **9**: **IR** (thin film, cm^{-1}): 3317, 2981, 2935, 1730, 1687, 1524, 1455, 1370, 1314, 1249, 1223, 1157, 842; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40 (br s, 1H), 7.34 (app t, J = 8.4 Hz, 2 H), 7.29 (app d, J = 6 Hz, 3H), 4.49 (d, J = 6 Hz, 2H), 1.55 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 159.6, 157.3, 136.9, 128.8, 128.0, 127.8, 84.5, 43.8, 27.7; **TLC** (20% EtOAc/hexanes): R_f 0.21 (UV only); **LRMS** (ESI): Calcd. for $C_{13}H_{17}NO_3$+Na: 258.11, Found: 258.11; Calcd. for $C_{13}H_{17}NO_3$+Cs: 368.03, Found: 368.02

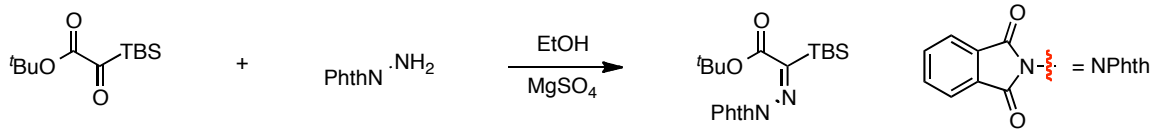


***tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-(hydroxyimino)acetate (E-3).** A solution of hydroxylamine hydrochloride (34 mg, 0.494 mmol, 1.05 equiv.) and pyridine (41 mg, 0.518 mmol, 1.1 equiv.) in EtOH (2mL) was prepared and stirred at ambient temperature open to the air. The silyl glyoxylate **3a** (115 mg, 0.471 mmol, 1.0 equiv.) was added, rinsing through with EtOH (1.5 mL) to complete the transfer. The reaction was stirred for ~30 min, by which point the bright yellow color had dissipated. The solution was poured into 1:4 Et_2O:H_2O (50 mL total), and the layers were shaken and separated. The aqueous layer was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude yield of **E-3** was 92% (111 mg, 0.454 mmol) as a white solid which required no further purification. Analytical data for **E-3**: **IR** (thin film, cm^{-1}): 3437, 2960, 2931, 2960, 1724, 1472, 1393, 1369, 1254, 1160, 1063, 840; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 1.53 (s, 9H), 0.95 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.0, 158.1, 83.1, 28.2, 26.4, 17.3, -6.3; **TLC** (10% EtOAc/hexanes, pre-

treated plate): R_f 0.22 (UV/CAM; faint in CAM); **LRMS** (ESI): Calcd. for $C_{12}H_{25}NO_3Si$+Na: 282.1; Found: 282.1

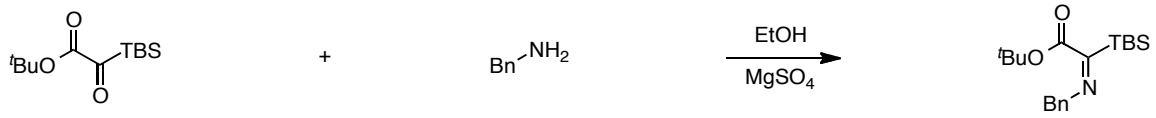


(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-(2,2-dimethylhydrazono)acetate (12a). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (204 mg, 0.834 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *N*,*N*-dimethylhydrazine (60 mg, 1 mmol), followed by additional EtOH (3 mL). The yellow reaction mixture was stirred until it was judged complete by NMR analysis of an aliquot (approx. 1 h), at which point the mixture was filtered and concentrated to a yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes to afford the desired product in 79% yield (189 mg, 0.742 mmol) as a pale yellow oil. Analytical data for **12a**: **IR** (thin film, cm^{-1}): 2955, 2929, 2857, 1698, 1471, 1367, 1248, 1227, 1155, 836, 825; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.95 (s, 6H), 1.49 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.8, 141.2, 80.7, 46.4, 28.1, 26.7, 17.6, -5.7; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.42 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{14}H_{30}N_2O_2Si$+Na: 309.2; Found: 309.2



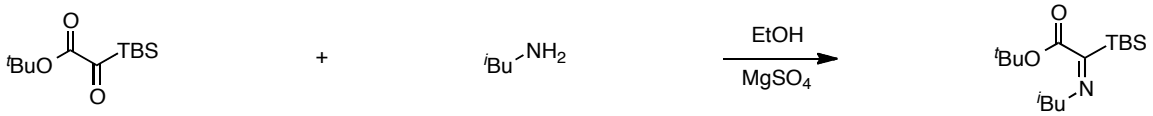
***tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((1,3-dioxoisoindolin-2-yl)imino)acetate (12b).** The title compound was prepared according to a slight modification of General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (114 mg, 0.466 mmol) in EtOH

(3 mL), and *N*-aminophthalimide (76 mg, 0.466 mmol), followed by additional EtOH (3 mL). The mixture was heated to reflux for 2 h, and then cooled to room temperature and concentrated *in vacuo* to afford a 94% yield (170 mg, 0.438 mmol) of product as a white solid. Analytical data for **12b**: **IR** (thin film, cm^{-1}): 2931, 2859, 1728, 1469, 1369, 1303, 1250, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.71 (m, 2H), 1.45 (s, 9H), 1.04 (s, 9H), 0.33 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.0, 163.2, 162.2, 134.3, 131.0, 123.6, 83.2, 28.0, 26.6, 17.4, -5.9; **TLC** (10% EtOAc/hexanes, pre-treated plate): R_f 0.47 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{20}H_{28}N_2O_4Si$+Cs: 521.1; Found: 521.1

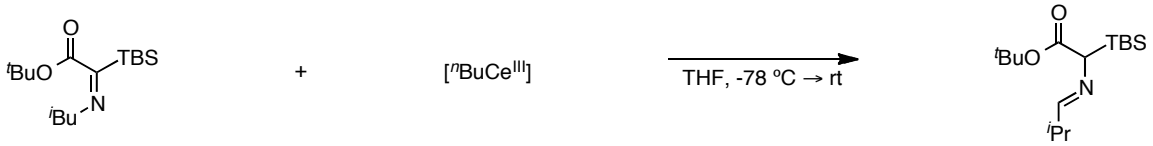


(*E*)-*tert*-butyl 2-(benzylimino)-2-(*tert*-butyldimethylsilyl)acetate (13a). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (126 mg, 0.515 mmol, 1.0 equiv.) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and benzylamine (66 mg, 0.619 mmol, 1.2 equiv.), followed by additional EtOH (3 mL). The yellow reaction mixture became slightly paler, and was stirred until it was judged complete by NMR analysis of an aliquot (~1 h), at which point the mixture was filtered and concentrated to a yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes to afford the desired product in 93% yield (160 mg, 0.478 mmol) as a yellow oil. Analytical data for **13a**: **IR** (thin film, cm^{-1}): 2957, 2930, 2858, 1714, 1471, 1463, 1369, 1248, 1155, 840; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34-7.30 (m, 4H), 7.26-7.20 (m, 1H), 4.69 (s, 2H) 1.54 (s, 9H), 0.98 (s, 9H), 0.21 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.6, 167.3, 139.3, 128.2, 127.8, 126.7, 82.8, 61.0, 28.3, 26.5, 17.4, -6.4;

TLC (10% EtOAc/hexanes, pre-treated plate): R_f 0.74 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{31}NO_2Si$+Na: 356.2; Found: 356.2

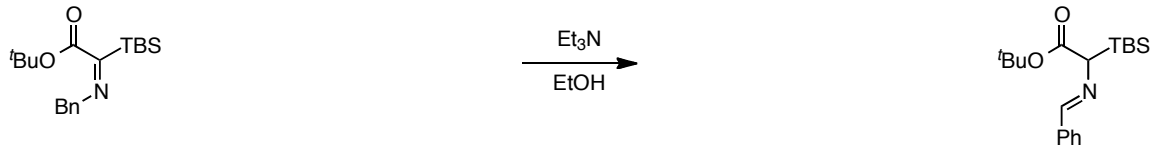


(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-(isobutylimino)acetate (13b). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (122 mg, 0.500 mmol, 1.0 equiv.) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and isobutylamine (44 mg, 0.600 mmol, 1.2 equiv.), followed by additional EtOH (3 mL). The yellow reaction mixture was stirred until it was judged complete by NMR analysis of an aliquot (approx. 1 h), at which point the mixture was filtered and concentrated to a yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes to afford the desired product in 85% yield (127 mg, 0.425 mmol) as a pale yellow oil. Analytical data for **13b**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.28 (d, J = 4.8 Hz, 2H), 1.98 (m, 1H), 1.50 (s, 9H), 0.95 (s, 9H), 0.90 (d, J = 5.1 Hz, 6H), 0.15 (s, 6H)



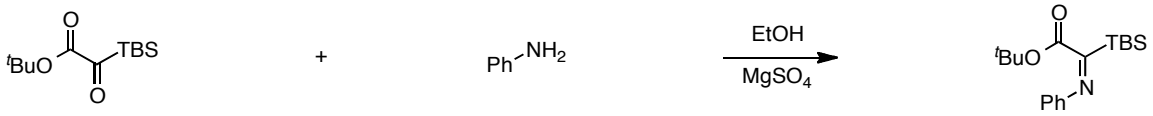
(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((2-methylpropylidene)amino)acetate (13b'). The following procedure is representative of the reactions involving organocerium nucleophiles, which were generated using Imamoto's method.[33] A round-bottomed flask was charged with a stir bar and cerium (III) chloride heptahydrate (85 mg, 0.228 mmol, 1.3 equiv.) and heated for 2 h under high vacuum at a bath temp of 140 ºC. The flask was

cooled to room temperature under N_2, and 5 mL dry THF were added. The white suspension was stirred for 2 h and then cooled to -78 ºC. *n*-Butyllithium (1.5 M in hexanes, 0.14 mL, 0.228 mmol, 1.3 equiv.) was added, and the mixture was stirred 1 h at this temperature (generally the suspension took on a slightly yellow/brown hue) prior to the addition of a solution of **13b** (50 mg, 0.175 mmol, 1.0 equiv.) in THF (2 mL). The reaction was stirred at -78 ºC for 1 h and then warmed to room temperature and stirred an additional 1 h. The reaction was quenched with 10% (v/v) aq. AcOH (30 mL; other workup solutions typically led to cerium emulsions), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed successively with H_2O (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), and dried over $MgSO_4$. ^{1}H NMR analysis of this mixture indicated that the nucleophile had not added, and isomerization to **13b'** had occurred. Analytical data for **13b'**: **^{1}H NMR** (300 MHz, $CDCl_3$) for **13b':** 7.39 (d, J = 3.9 Hz, 1H), 3.91 (s, 1H), 2.55-2.48 (m, 1H), 1.43 (s, 9H), 1.07 (d, J = 5.1 Hz, 6 H), 0.91 (s, 9H), 0.06 (s, 6H)

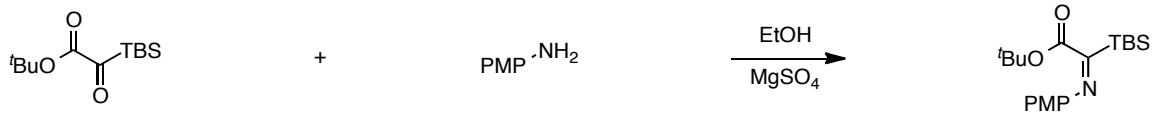


(*E*)-*tert*-butyl 2-(benzylideneamino)-2-(*tert*-butyldimethylsilyl)acetate (13a'). The title compound was prepared by dissolving (*E*)-*tert*-butyl 2-(benzylimino)-2-(*tert*-butyldimethylsilyl)acetate **13a** (41 mg, 0.123 mmol) in EtOH (1 mL) in a shell vial, and adding 1 mL triethylamine (large excess). The reaction was stirred at room temperature until NMR analysis of an aliquot showed complete consumption of the starting material (~3 h), at which point the reaction was concentrated and flashed through a pretreated

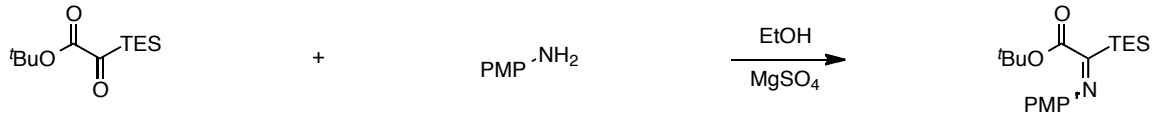
silica plug. The product was thus obtained in 95% yield (39 mg, 0.117 mmol) as a colorless oil. Analytical data for **13a'**: **IR** (thin film, cm^{-1}): 2973, 2930, 2558, 1731, 1708, 1635, 1367, 1251, 1146, 840, 826; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.75 (m, 2H), 7.38 (m, 3H), 4.24 (s, 1H) 1.49 (s, 9H), 0.97 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.5, 158.6, 136.5, 130.2, 128.4, 128.1, 80.6, 68.0, 28.3, 26.9, 17.9, -6.2, -6.5; **TLC** (10% EtOAc/hexanes, pre-treated plate): R_f 0.59 (UV only); **LRMS** (ESI): Calcd. for $C_{19}H_{31}NO_2Si$+Na: 356.2; Found: 356.2



(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-(phenylimino)acetate (15aa). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (100 mg, 0.409 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and aniline (46 mg, 0.491 mmol), followed by additional EtOH (3 mL). The pale yellow reaction mixture was stirred until it was judged complete by TLC analysis (< 1 h), at which point the mixture was filtered and concentrated to a pale yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, to afford the desired product in 95% yield (125 mg, 0.391 mmol) as a yellow oil. Analytical data for **15aa**: **IR** (thin film, cm^{-1}): 2956, 2930, 2859, 1714, 1483, 1369, 1252, 1158, 1021, 840, 822; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (t, J = 7.6 Hz, 2H), 7.06 (t, J = 7.6Hz, 1H), 1.20 (s, 9H), 1.04 (s, 9H), 0.28 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 181.4, 166.5, 153.0, 128.4, 124.3, 119.1, 82.5, 27.8, 26.6, 17.4, -6.6; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.59 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{18}H_{29}NO_2Si$+Na: 342.2; Found: 342.2

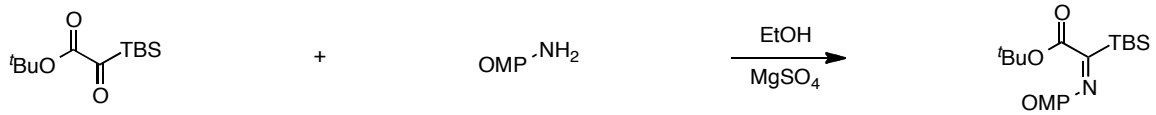


(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((4-methoxyphenyl)imino)acetate (15ab). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (122 mg, 0.500 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-anisidine (74 mg, 0.600 mmol), followed by additional EtOH (3 mL). The brownish reaction mixture was stirred until it was judged complete by TLC analysis (approx. 1 h), at which point the mixture was filtered and concentrated to a yellow-brown oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes. The bright yellow fractions were collected and concentrated to afford the desired product in 95% yield (166 mg, 0.475 mmol) as a bright yellow oil. Analytical data for **15ab**: **IR** (thin film, cm^{-1}): 2956, 2930, 2858, 1714, 1604, 1502, 1465, 1368, 1248 1156, 1038, 838; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.80 (s, 4H), 3.77 (s, 3H) 1.26 (s, 9H), 1.021 (s, 9H), 0.26 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.7, 167.1, 156.9, 146.2, 120.7, 113.6, 82.4, 55.4, 27.9, 26.6, 17.5, -6.6 ; **TLC** (10% EtOAc/hexanes, pre-treated plate): R_f 0.63 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{19}H_{31}NO_3Si$+Cs: 482.1; Found: 482.1



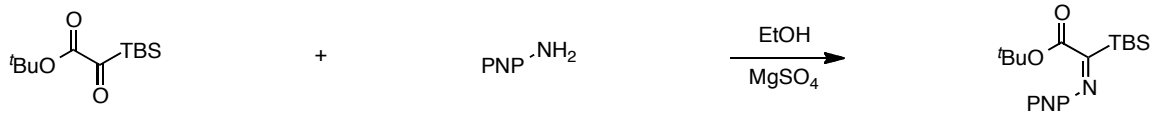
***tert*-butyl 2-((4-methoxyphenyl)imino)-2-(triethylsilyl)acetate (15bb).** The title compound was prepared according to General Procedure **A** using *tert*-butyl triethylsilyl glyoxylate **3b** (48 mg, 0.196 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-anisidine (30 mg, 0.235 mmol), followed by additional EtOH (3 mL). The yellow

reaction mixture was stirred until it was judged complete by TLC analysis (< 1 h), at which point the mixture was filtered and concentrated to a brown-yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 70% yield (48 mg, 0.137 mmol) as a bright yellow oil. This compound exists as a approx. 5:1 mixture of imine isomers. Analytical data for **15bb**: **IR** (thin film, cm^{-1}): 2955, 2876, 1712, 1501, 1368, 1245, 1156, 842; **^{1}H NMR** (400 MHz, $CDCl_3$): *major isomer:* δ 6.80 (s, 4H), 3.78 (s, 3H), 1.28 (s, 9H), 1.04 (t, *J* = 8 Hz, 9H) 0.86 (q, *J* = 8 Hz, 6H); *minor isomer:* δ 6.80 (m, 4H), 3.81 (s, 3H), 1.58 (s, 9H), 0.88 (t, *J* = 8 Hz, 9H), 0.48 (q, *J* = 8 Hz, 6H) ; **^{13}C NMR** (150 MHz, $CDCl_3$): *major isomer:* δ 180.6, 167.2, 157.0, 146.3, 120.8, 113.6, 82.3, 55.4, 27.9, 7.2, 2.6; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.30 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{19}H_{31}NO_3Si$+Na: 372.2; Found: 372.2.



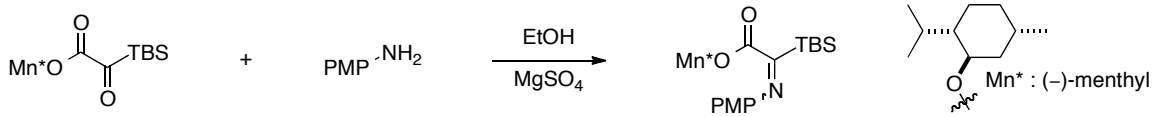
(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((2-methoxyphenyl)imino)acetate (15ac). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (93 mg, 0.381 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *o*-anisidine (56 mg, 0.457 mmol), followed by additional EtOH (3 mL). The yellow reaction mixture was stirred until it was judged complete by TLC analysis (~3 h), at which point the mixture was filtered and concentrated to a yellow-orange oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to

afford the desired product in 84% yield (113 mg, 0.323) as a bright yellow oil. Analytical data for **15ac**: **IR** (thin film, cm^{-1}): 3062, 2955, 2930, 2858, 1714, 1592, 1489, 1465, 1368, 1248, 1158, 1112, 1046, 1026, 841; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (t, *J* = 7.2 Hz, 1H), 6.82 (m, 2H), 6.64 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 1.18 (s, 9H), 1.04 (s, 9H), 0.28 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 182.2, 165.8, 149.1, 142.8, 125.0, 120.3, 119.3, 111.2, 82.0, 55.6, 27.7, 26.5, 17.4, -6.6; **TLC** (2.5% EtOAc/hexanes, pre-treated plate): R_f 0.49 (UV/CAM; orange when dipped→blue when developed); **LRMS** (ESI): Calcd. for $C_{19}H_{31}NO_3Si$+Na: 372.2; Found: 372.2

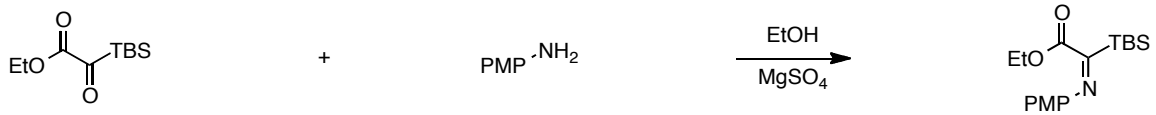


(*E*)-*tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((4-nitrophenyl)imino)acetate (15ad). The title compound was prepared according to General Procedure **A** using *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **3a** (104 mg, 0.427 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-nitroaniline (71 mg, 0.512 mmol), followed by additional EtOH (3 mL). The yellow reaction mixture was stirred until it was judged complete by TLC analysis (>48 h), at which point the mixture was filtered and concentrated to a yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 77% yield (120 mg, 0.329 mmol) as a bright yellow oil. Analytical data for **15ad**: **IR** (thin film, cm^{-1}): 2956, 2931, 2859, 1716, 1588, 1518, 1369, 1343, 1252, 1155; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 12 Hz, 2H), 6.86 (d, *J* = 12 Hz, 2H), 1.22 (s, 9H), 1.03 (s, 9H), 0.28 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 183.5, 165.1, 158.5, 144.3, 124.4, 119.2, 83.6, 27.9, 26.5, 17.4, -6.7; **TLC** (5%

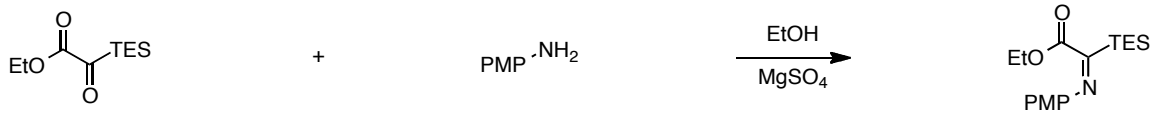
EtOAc/hexanes, pre-treated plate): R_f 0.39 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{18}H_{28}N_2O_4Si$+Na: 387.2; Found: 387.2.



(*E*)-(−)-menthyl 2-(*tert*-butyldimethylsilyl)-2-((4-methoxyphenyl)imino)acetate 15cb. The title compound was prepared according to General Procedure **A** using (–)-menthyl *tert*-butyldimethylsilyl glyoxylate **3c** (115 mg, 0.352 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-anisidine (52 mg, 0.422 mmol), followed by additional EtOH (3 mL). The yellow-brown reaction mixture was stirred until it was judged complete by TLC analysis (< 1 h), at which point the mixture was filtered and concentrated to a brown-yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 90% yield (137 mg, 0.317 mmol) as a bright yellow oil. Analytical data for **15cb**: **IR** (thin film, cm^{-1}): 2955, 2929, 2859, 1713, 1501, 1465, 1245, 1027, 837; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.78 (s, 4H), 4.56 (dt, *J* = 10.8, 4.4 Hz, 1H), 3.76 (s, 3H), 1.72 (m, 1H), 1.58 (m, 2H), 1.53-1.40 (m, 1H), 1.35 (m, 3H), 1.03 (s, 9H), 0.93-0.80 (m, 2H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.85-0.6 (m, 2H), 0.69 (d, *J* = 7.2 Hz, 3H), 0.51 (d, *J* = 7.2 Hz, 3H), 0.25 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.5, 167.8, 157.1, 146.3, 120.6, 113.8, 75.0, 55.3, 46.5, 40.4, 33.9, 31.3, 26.6, 24.9, 22.6, 21.9, 20.8, 17.6, 15.6, -6.5, -6.6; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.41 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{25}H_{41}NO_3Si$+Na: 454.3; Found: 454.3

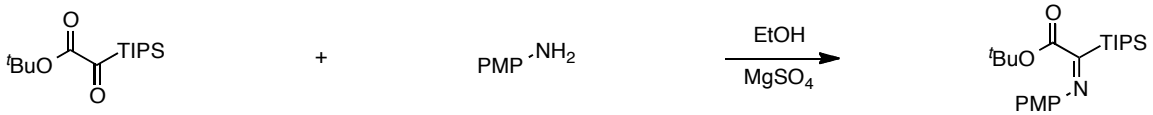


(*E*)-ethyl 2-(*tert*-butyldimethylsilyl)-2-((4-methoxyphenyl)imino)acetate (15db). The title compound was prepared according to General Procedure **A** using ethyl *tert*-butyldimethylsilyl glyoxylate **3d** (235 mg, 1.09 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-anisidine (161 mg, 1.31 mmol), followed by additional EtOH (3 mL). The yellow-brown reaction mixture was stirred until it was judged complete by TLC analysis (< 1 h), at which point the mixture was filtered and concentrated to a brown-yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 32% yield (111 mg, 0.348 mmol) as a bright yellow oil. Analytical data for **15db**: **IR** (thin film, cm^{-1}): 2956, 2930, 2858, 1717, 1604, 1501, 1465, 1247, 1036, 837; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.80 (s, 4H), 4.04 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H), 1.02 (s, 9H), 0.26 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.8, 168.0, 157.2, 146.0, 120.7, 113.8, 60.4, 55.4, 26.5, 17.5, 14.0, -6.7; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.30 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{17}H_{27}NO_3Si$+Na: 344.2; Found: 344.2



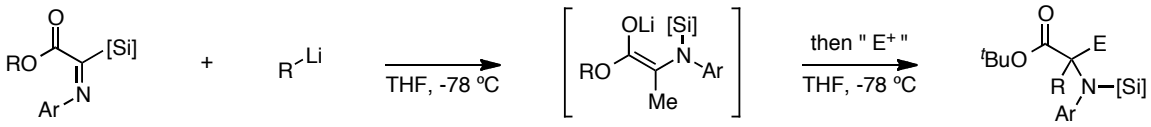
Ethyl 2-((4-methoxyphenyl)imino)-2-(triethylsilyl)acetate (15eb). The title compound was prepared according to General Procedure **A** using ethyl triethylsilyl glyoxylate **3e** (137 mg, 0.633 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$,

and *p*-anisidine (94 mg, 0.760 mmol), followed by additional EtOH (3 mL). The yellow-brown reaction mixture was stirred until it was judged complete by TLC analysis (< 1 h), at which point the mixture was filtered and concentrated to a brown-yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 50% yield (102 mg, 0.315 mmol) as a bright yellow oil. This compound exists as a approx. 3:1 mixture of imine isomers. Analytical data for **15eb**: **IR** (thin film, cm^{-1}): 2955, 2876, 1716, 1501, 1244, 1036, 736; **^{1}H NMR** (400 MHz, $CDCl_3$): *major isomer:* δ 6.79 (s, 4H), 4.05 (q, *J* = 7.2 Hz, 2), 3.77 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 8 Hz, 9H), 0.85 (q, *J* = 8Hz, 6H); *minor isomer:* δ 6.83-6.77 (m, 4H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 8 Hz, 9H), 0.50 (q, *J* = 8Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): *major isomer:* δ 170.7, 168.0, 157.2, 146.1, 120.8, 113.8, 60.4, 55.4, 14.0, 7.1, 2.6; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.29 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{17}H_{27}NO_3Si$+Na: 344.2; Found: 344.2



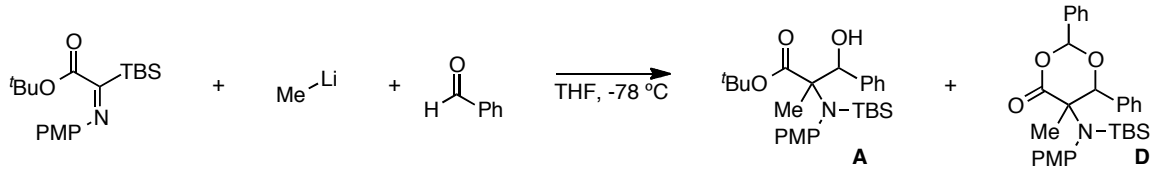
(*E*)-*tert*-butyl 2-((4-methoxyphenyl)imino)-2-(triisopropylsilyl)acetate (15fb). The title compound was prepared according to General Procedure **A** using *tert*-butyl triisopropylsilyl glyoxylate **3f** (108 mg, 0.377 mmol) in EtOH (3 mL), a generous spatula tip of $MgSO_4$, and *p*-anisidine (56 mg, 0.452 mmol), followed by additional EtOH (3 mL). The yellow-brown reaction mixture was stirred until it was judged complete by TLC analysis (~24 h), at which point the mixture was filtered and concentrated to a

brown-yellow oil. The residue was purified on a pretreated column using a hexanes flush followed by elution with 5% EtOAc/hexanes, collecting the bright yellow band, to afford the desired product in 88% yield (130 mg, 0.331 mmol) as a bright yellow oil. Analytical data for **15fb**: **IR** (thin film, cm^{-1}): 2945, 2867, 1714, 1501, 1465, 1368, 1245, 1156, 1038, 883; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.80 (d, *J* = 8.8 Hz, 2H), 6.76 (*J* = 8.8 Hz, 2H), 3.77 (s, 3H), 1.37 (m, 3H), 1.26 (s, 9H), 1.17 (d, *J* = 7.6 Hz, 18H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.1, 167.2, 156.8, 146.4, 120.5, 113.6, 82.3, 55.5, 27.8, 18.5, 11.3; **TLC** (5% EtOAc/hexanes, pre-treated plate): R_f 0.50 (UV/CAM; purple when dipped → blue after developing); **LRMS** (ESI): Calcd. for $C_{22}H_{37}NO_3Si$+Na: 414.2; Found: 414.2



General Procedure B: Three-Component Couplings

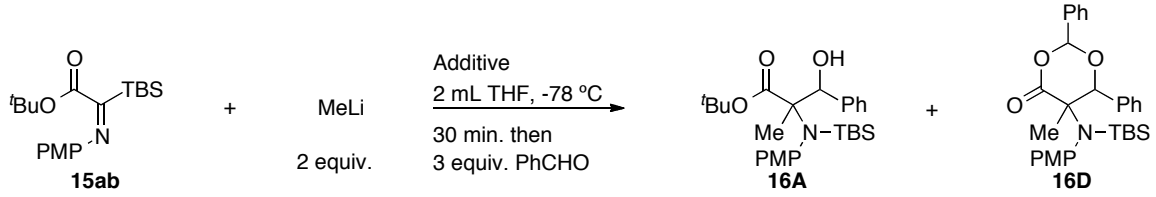
The silyl glyoximine (1 equiv.) was dissolved in 2 mL dry THF in an oven-dried shell vial equipped with a magnetic stirrer and capped and placed under N_2. This bright yellow solution ([**15ab**]$_0$ = 0.05M) was cooled to -78 ºC for 15 min prior to the dropwise addition of the solution of alkyllithium nucleophile (2 equiv.), at which point the solution lost its characteristic yellow color. After 30 min of stirring at -78 ºC, the terminal electrophile (2-3 equiv.) was added dropwise. The reaction was stirred for 30 min and then quenched with a solution of sat. aq. NH_4Cl. The biphasic mixture was diluted with Et_2O (5 mL) and H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with additional Et_2O (3x 5 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified via flash column chromatography using the indicated solvent system.



***tert*-butyl 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-3- hydroxy-2-methyl-3-phenylpropanoate (16A).** This product was formed from the ^{t}Bu/TBS/PMP silyl glyoximine **15ab** (105 mg, 0.302 mmol, 1.0 equiv.), methyllithium (1.6M in Et_2O, 0.38 mL, 0.604 mmol, 2 equiv.), and benzaldehyde (96 mg, 0.906 mmol, 3 equiv.) according to General Procedure **B**. In this iteration, 23 mg (0.0488 mmol, 16% yield) of the product **16A** were isolated. It was typically formed in ~15-20% yield, with a dr of < 3:1 as a mixture of diastereomers inseparable by flash column chromatography. Analytical data for **16A**: **IR** (thin film, cm^{-1}): 3382, 2953, 2930, 2735, 1723, 1598, 1512, 1367, 1250, 1166, 1095, 1067, 838; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer:* δ 7.45-7.35 (m, 2H), 7.30-7.26 (m, 3H), 4.86 (s, 1H), 4.34 (br s, 1H) 3.73 (s, 3H), 1.43 (s, 3H), 1.31 (s, 9H), 0.93 (s, 9H), 0.08 (s, 3H), -0.32 (s, 3H); *minor diastereomer:* δ 7.45-7.35 (m, 2H), 7.30-7.26 (m, 3H), 4.93 (s, 1H), 4.24 (br s, 1H) 3.73 (s, 3H), 1.37 (s, 9H), 1.24 (s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), -0.31 (s, 3H; **^{13}C NMR** (150 MHz, $CDCl_3$): *all resolved peaks, cannot distinguish major/minor*: δ 173.5, 172.8, 153.5, 153.4, 139.8, 139.6, 128.7, 128.5, 127.9, 127.5, 127.4, 120.4, 120.0, 114.1, 114.0, 81.4, 81.3, 80.2, 80.1, 67.2, 66.8, 55.6, 27.9, 27.8, 25.8, 19.6, 18.1, 17.6, -4.4, -4.5, -5.2, -5.3 (six coincident resonances); **TLC** (10% EtOAc/hexanes): R_f 0.47 (UV/CAM;); **LRMS** (ESI): Calcd. for $C_{27}H_{41}NO_4Si$+Na: 494.3; Found: 494.3

5-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-5-methyl-2,6-diphenyl-1,3-dioxan-4-one (16D). This particular reaction (amounts above) afforded 36 mg (0.0717

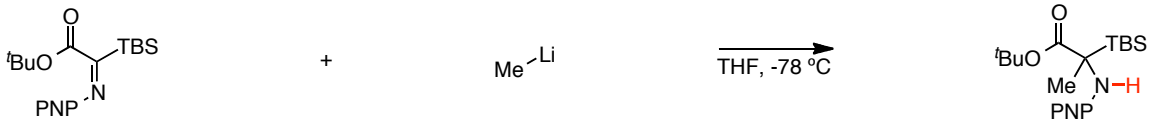
mmol, 40% yield) of **16D** as a white solid. It was typically formed in ~40-50% yield, with a dr of 1.4:1. These isomers were inseparable by flash column chromatography. Analytical data for **16D**: **IR** (thin film, cm^{-1}): 2954, 2930, 2858, 1786, 1514, 1457, 1250, 1068, 837; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer:* δ 7.30-7.25 (m, 7H), 7.19 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz), 6.10 (s, 1H), 5.35 (s, 1H), 3.74 (s, 3H), 1.53 (s, 3H), 1.01 (s, 9H), 0.19 (s, 3H), -0.14 (s, 3H); *minor diastereomer:* δ: 7.5-7.25 (m, 10H), 6.92 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H), 5.06 (s, 1H), 3.75 (s, 3H), 1.63 (s, 3H), 0.92 (s, 9H), -0.18 (s, 3H), -0.56 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): *all 44 peaks, cannot distinguish minor/major*: δ 175.3, 173.8, 154.4, 154.3, 140.6, 139.6, 136.5, 136.0, 135.7, 134.7, 129.8, 129.4, 128.7, 128.4, 128.31, 128.29, 128.27, 127.8, 127.74, 127.67, 127.5, 127.4, 121.3, 121.0, 114.3, 113.9, 91.6, 91.4, 80.3, 77.7, 70.8, 69.4, 55.4, 55.3, 25.90, 25.87, 25.78, 18.2, 17.9, 17.6, -4.3, -4.7, -5.0, -5.4; **TLC** (10% EtOAc/hexanes): R_f 0.37 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{30}H_{37}NO_4Si$+Na: 526.2; Found: 526.2



General Procedure C: Screen of Additives (Table 1-2)

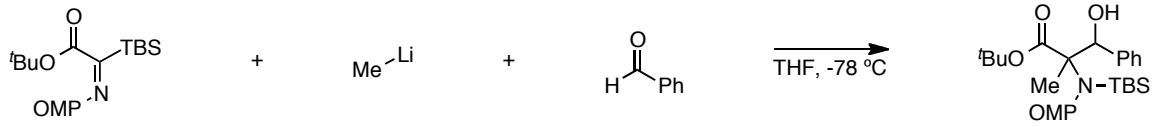
This procedure was followed for the results summarized in **Table 1-2**, and represents only a slight modification from General Procedure B. The silyl glyoximine **15ab** (1 equiv.) was dissolved in dry THF (2 mL) in an oven-dried vial equipped with a magnetic stirrer and placed under N_2. If the additive was a LiX salt, it was charged into the dry vial with the silyl glyoximine from the beginning. This bright yellow solution was

cooled to -78 ºC for 15 min prior to the dropwise addition of the solution of methyllithium (2 equiv.), at which point the solution lost its characteristic yellow color. In the case of the (–)-sparteine, TMEDA, and quinidine additives, these were precomplexed with the methyllithium for 15 min at -78 ºC in a separate dry vial containing said additive and THF (1mL), and then transferred to the cooled silyl glyoximine solution via cannula. In the case of the quinidine additive, four equiv. methyllithium were used (two equiv. were consumed by the hydroxyl protons of two equiv. quinidine). After 30 min of stirring at -78 ºC, benzaldehyde (3 equiv.) was added dropwise. The reaction was stirred for 30 min and then quenched with a solution of sat. aq. NH_4Cl. The biphasic mixture was diluted with Et_2O (5 mL) and H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with additional Et_2O (3x 5 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and concentrated. A carefully weighed sample of mesitylene was added to the residue for determination of the **16A**/**16D** yields and diastereomer ratios by ^1H NMR. Isolated yields were generally in good agreement (within ~5%).



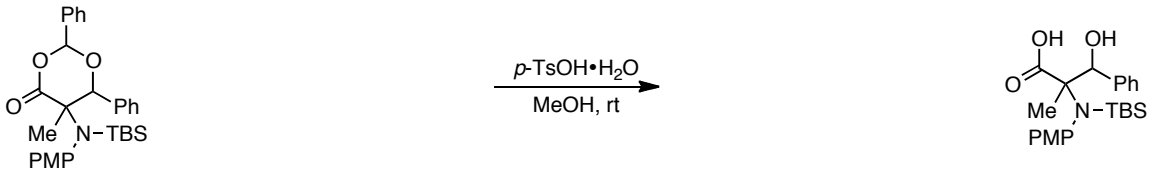
***tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-((4-methoxyphenyl)amino)propanoate (E-4).** The title compound was prepared according to General Procedure **B**, as an attempted three-component coupling with benzaldehyde. The reaction was conducted with *p*-nitrophenyl silyl glyoximine **15ad** (59 mg, 0.164 mmol), methyllithium (0.21 mL, 0.33 mmol), and benzaldehyde (52 mg, 0.49 mmol). The reaction instantly became reddish upon addition of methyllithium, and was a deep reddish black by the end of addition.

Purification of the residue after workup via flash column chromatogaphy using a short hexanes flush followed by elution with 5% EtOAc/hexanes to afford the undesired, non-aza-Brook rearranged addition product. The yield was not determined, but this was the only silyl glyoximine-derived product isolated. Analytical data for **E-4**: **IR** (thin film, cm^{-1}): 3420, 2973, 2933, 2861, 1712, 1598, 1505, 1477, 1324, 1310, 1112, 837; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 9.2 Hz, 2H), 6.43 (d, *J* = 9.2 Hz, 2H), 4.88 (br s, 1H), 1.69 (s, 3H), 1.39 (s, 9H), 1.06 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.5, 152.3, 138.3, 125.8, 113.0, 81.8, 54.9, 28.0, 27.7, 19.2, 19.1, -7.3, -7.5; **TLC** (10% EtOAc/hexanes): R_f 0.29 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{23}H_{33}NO_4Si$+Na: 403.2; Found: 403.2

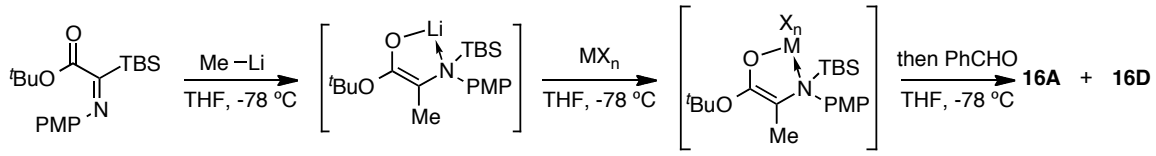


***tert*-butyl 2-((*tert*-butyldimethylsilyl)(2-methoxyphenyl)amino)-3-hydroxy-2- methyl-3-phenylpropanoate (E-5).** The title compound was prepared according to General Procedure **B** using silyl glyoximine **15ac** (38 mg, 0.109 mmol), methyllithium (1.6M in Et_2O, 0.14 mL, 0.22 mmol), and benzaldehyde (35 mg, 0.33 mmol). The average yield of two trials was 36% (18 mg, 0.388 mmol), and the dr was 2.3:1. Analytical data for **E-5**: **IR** (thin film, cm^{-1}): 3399, 2954, 2930, 2857, 1729, 1602, 1513, 1456, 1367, 1252, 1225, 1067, 1032, 839 **^{1}H NMR** (400 MHz, $CDCl_3$): *major diastereomer:* δ 7.42-7.37 (m, 2H), 7.30-7.26 (m, 3H), 6.80-6.70 (m, 2H), 6.65-6.60 (m, 2H), 5.46 (br s, 1H), 4.91 (s, 1H), 3.82 (s, 3H), 1.56 (s, 3H), 1.25 (s, 9H), 0.93 (s, 9H), 0.09 (s, 3H), -0.34 (s, 3H); *minor diastereomer:* δ 7.37-7.30 (m, 2H), 7.30-7.26 (m, 3H), 6.80-6.70 (m, 2H), 6.65-6.55 (m, 1H), 6.5 (d, 1H), 5.35 (br s, 1H), 5.03 (s, 1H), 3.83 (s, 3H), 1.38 (s, 3H), 1.32 (s, 9H),

0.95 (s, 9H), 0.16 (s, 3H), -0.30 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): *all resolved peaks, cannot distinguish major/minor*: δ: 172.9, 172.4, 148.1, 147.9, 139.9, 139.5, 136.1, 136.0, 128.6, 128.0, 127.53, 127.51, 120.5, 120.4, 116.9, 116.8, 113.5, 112.7, 109.6, 109.5, 81.5, 81.2, 80.2, 80.1, 66.2, 65.8, 55.3, 55.1, 27.8, 27.1, 25.73, 25.67, 19.7, 18.1, 15.9, -4.52, -4.54, -5.35, -5.44 (three coincident resonances); **TLC** (10% EtOAc/hexanes): R_f 0.32 (UV/CAM; red/orange when dipped→blue when developed); **LRMS** (ESI): Calcd. for $C_{27}H_{41}NO_4Si$+Na: 494.3; Found: 494.3

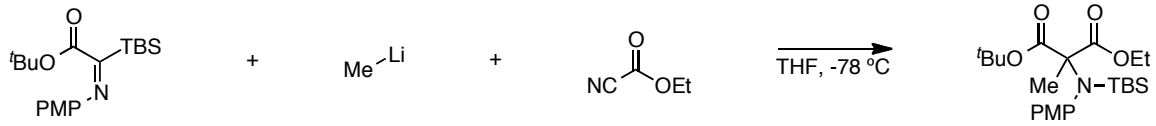


2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-3-hydroxy-2-methyl-3-phenylpropanoic acid (17). The title compound was prepared by charging a vial equipped with a stir bar with three-component-coupling product **16D** (50 mg, 0.1 mmol, 1.0 equiv.), *p*-toluenesulfonic acid monohydrate (25 mg, 0.13 mmol, 1.3 equiv.), and methanol (2mL). The reaction mixture was initially a heterogeneous, milky white suspension which gradually cleared as the reaction progressed. Upon consumption of the starting material by TLC, the reaction was concentrated. ^{1}H NMR analysis of the crude mixture indicated the presence of the sulfonic acid, benzaldehyde, and the product as a single diastereomer. Purification could not be achieved via flash column chromatography due to the instability of this compound. Analytical data for **17**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.42 (m, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.19-1.14 (m, 3H), 6.72 (d, J = 8.8 Hz, 2H), 5.22 (s, 1H), 3.73 (s, 3H), 3.36 (br s, 1H), 1.34 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), -0.28 (s, 3H); **LRMS** (ESI): Calcd. for $C_{23}H_{33}NO_4Si$+Na: 438.21, Found: 438.19; Calcd. for $C_{23}H_{33}NO_4Si$+Cs: 548.12, Found: 548.11



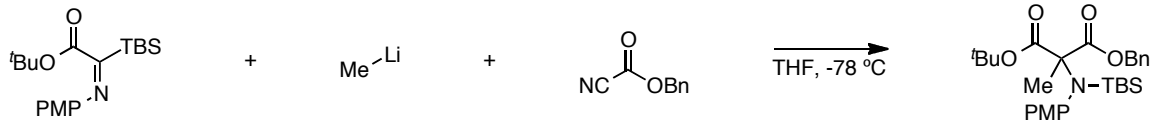
General Procedure D: Screen of Metal Salt/Counterion Effects (Table 1-3).

This procedure was used to generate the results summarized in **Table 1-3**. A solution of ^{t}Bu/TBS/PMP silyl glyoximine **15ab** (35 mg, 0.1 mmol, 1.0 equiv.) in dry THF (2 mL) was cooled to -78 ºC for at least 10 min and then a solution of methyllithium (1.6M in Et_2O, 0.13 mL, 0.200 mmol, 2 equiv.) was added dropwise; the bright yellow color of the imine dissipated. After 30 min, a solution of the metal salt (0.16 mmol, 1.6 equiv.) in THF (1 mL) was added. After 30 min, benzaldehyde (32 mg, 0.30 mmol, 3 equiv.) was added neat, dropwise to the solution. After 30 min, the reaction was quenched with sat. NH_4Cl solution (2 mL) and warmed to room temperature. The mixture was diluted with Et_2O/H_2O (approx. 5/30 mL, respectively), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. To the crude residue was added a carefully weighed sample of mesitylene as an NMR standard, followed by $CDCl_3$ for NMR analysis. The **16A**/**16D** yields and diastereomer ratios were calculated from the crude mixture. Isolated yields were generally in good agreement (within ~5%).

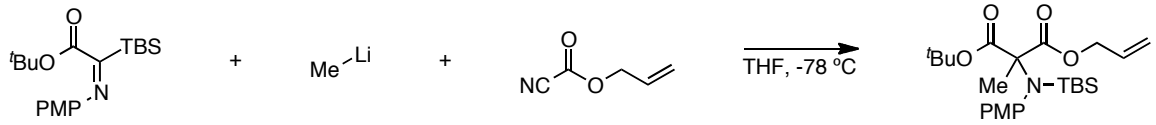


1-*tert*-butyl 3-ethyl 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-2-methylmalonate (18a). The title compound was prepared according to General Procedure **B** using silyl glyoximine **15ab** (39 mg, 0.112 mmol), methyllithium (0.14 mL, 0.22 mmol), and ethyl cyanoformate (33 mg, 0.333 mmol). Purification was effected

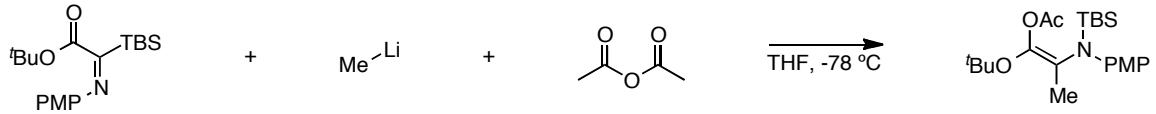
using 5% EtOAc/hexanes on a pretreated column to afford 94% (46 mg, 0.105 mmol) of the product as a clear, colorless oil. Analytical data for **18a**: **IR** (thin film, cm^{-1}): 2977, 2935, 2856, 1731, 1506, 1470, 1368, 1247, 1223, 1140, 1038, 900, 835; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.09 (br s, 2H), 6.72 (d, *J* = 8.4 Hz), 4.12 (m, 2H), 3.76 (s, 3H), 1.40 (s, 9H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.70 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H) ; **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.1, 171.4, 157.5, 138.2, 133.8, 113.1, 81.7, 71.9, 61.2, 55.3, 27.7, 27.5, 25.7, 19.9, 14.0, -1.7, -2.0; **TLC** (5% EtOAc/hexanes): R_f 0.22 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{23}H_{39}NO_5Si$+Na: 460.2; Found: 460.2



1-benzyl 3-*tert*-butyl 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-2-methylmalonate (18b). The title compound was prepared according to General Procedure **B**. Accordingly, silyl glyoximine **15ab** (39 mg, 0.112 mmol), methyllithium (0.14 mL, 0.22 mmol), and benzyl cyanoformate (36 mg, 0.22 mmol) were employed in the reaction, which was purified via flash column chromatography using a pretreated column and eluting with 5% EtOAc/hexanes. The product was isolated as a clear, colorless oil: 40 mg (0.0806 mmol, 72% yield). Analytical data for **18b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (m, 5H), 7.09 (br s, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.16 (d, *J* = 12 Hz, 1H), 5.04 (d, *J* = 12 Hz, 1H), 3.76 (s, 3H), 1.42 (s, 3H), 1.33 (s, 9H), 0.71 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); **TLC** (5% EtOAc/hexanes): R_f 0.22 (UV/CAM; purple when dipped→blue when developed).

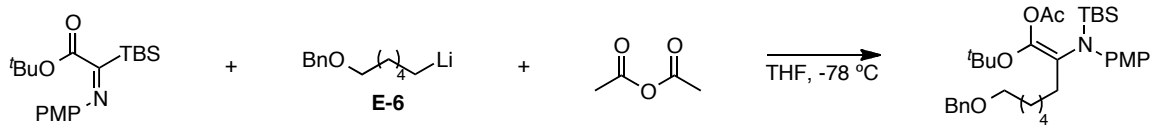


1-allyl 3-*tert*-butyl 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)-2-methyl-malonate (18c). The title compound was prepared according to General Procedure **B**. Accordingly, silyl glyoximine **15ab** (35 mg, 0.100 mmol), methyllithium (0.13 mL, 0.200 mmol), and benzyl cyanoformate (22 mg, 0.200 mmol) were employed in the reaction, which was purified via flash column chromatography using a pretreated column and eluting with 5% EtOAc/hexanes. The product was isolated as a clear, colorless oil: 28 mg (0.062 mmol, 62% yield). Analytical data for **18c**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.10 (br s, 2H), 6.72 (d, *J* = 9 Hz, 2H), 6.0-5.80 (m, 1H), 5.33 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.65-4.47 (m, 2H), 3.76 (s, 3H), 1.39 (s, 3H), 1.39 (s, 9H), 0.70 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); **TLC** (10% EtOAc/hexanes, pretreated plate), R_f 0.45 (UV/CAM ; purple when dipped→blue when developed).

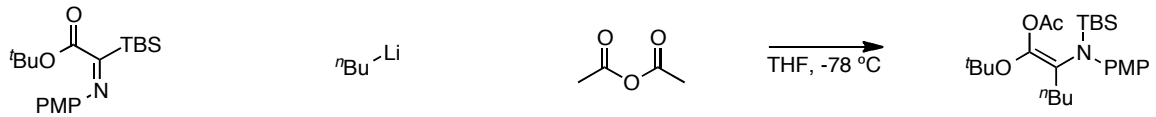


(*Z*)-1-(*tert*-butoxy)-2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)prop-1-en-1-yl acetate (19a). The title compound was prepared according to General Procedure **B**. Thus, silyl glyoximine **15ab** (70 mg, 0.200 mmol), methyllithium (0.25 mL, 0.400 mmol), and acetic anhydride (41 mg, 0.200 mmol) were employed in the reaction, which afforded 56 mg (0.139 mmol, 70% yield) of the product as a clear oil after purification via flash column chromatography using 5% EtOAc/hexanes as eluent. Analytical data for **19a**: **IR** (thin film, cm^{-1}): 2954, 2931, 2856, 1771, 1691, 1507, 1368, 1262, 1240, 1195, 1146, 1075, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.93 (d, *J* = 9.2 Hz, 2H), 6.72 (d, *J* = 9.2 Hz, 2H), 3.75 (s, 3H), 2.14 (s, 3H), 1.77 (s, 3H), 1.13 (s, 9H), 0.88 (s, 9H), 0.34 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.0, 153.0, 147.9, 143.6, 121.4, 116.8, 113.6,

80.4, 55.4, 29.0, 28.0, 21.0, 19.8, 18.8, -2.4; **TLC** (5% EtOAc/hexanes): R_f 0.16 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{37}NO_4Si$+Na: 430.2; Found: 430.2



(*Z*)-8-(benzyloxy)-1-(*tert*-butoxy)-2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl) amino)oct-1-en-1-yl acetate (19b). The title compound was prepared according to General Procedure **B** using 2.0 equiv. of the terminal electrophile. The alkyllithium reagent **E-6** was prepared using a typical protocol for Li/I exchange: to a -78 ºC solution of *tert*-butyllithium (1.7M in pentanes, 0.24 mL, 0.41 mmol, 2 equiv. relative to the alkyl iodide) in 1 mL THF was added the corresponding alkyl iodide (64 mg, 0.20 mmol, 2 equiv.). The solution was stirred at this temperature for 5 min, and then a solution of the silyl glyoximine **15ab** (35 mg, 0.100 mmol) in 1 mL THF was added, followed 30 min later by acetic anhydride (20 mg, 0.200 mmol). Purification of the crude residue was effected by flash column chromatography with 5% EtOAc/hexanes as eluent to afford 39 mg (0.066 mmol, 66% yield) of the product as a clear, colorless oil. Analytical data for **19b**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.50-7.26 (m, 5H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 9 Hz, 2H), 4.49 (s, 2H), 3.75 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 2.12 (s, 3H), 2.02-1.93 (m, 2H), 1.60-1.26 (m, 8 H), 1.21 (s, 9H), 0.85 (s, 9H), 0.33 (s, 6H); **TLC** (10% EtOAc/hexanes, pretreated plate): R_f 0.34 (UV/CAM).



(*Z*)-1-(*tert*-butoxy)-2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)amino)hex-1-en-1-yl acetate (19c). The title compound was prepared according to General Procedure **B**

using 2.0 equiv. of the terminal electrophile. Thus, silyl glyoximine **15ab** (61 mg, 0.175 mmol), *n*-butyllithium (1.5M in hexanes, 0.23 mL, 0.35 mmol), and acetic anhydride (36 mg, 0.35 mmol) were employed in the reaction, which afforded 51 mg (0.115 mmol, 66% yield) of the product as a clear, colorless oil after purification via flash column chromatography using 5% EtOAc/hexanes as eluent. Analytical data for **19c**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.01 (d, *J* = 7.2 Hz, 2H), 6.73 (d, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 2.14 (s, 3H), 2.03-1.95 (m, 2H), 1.50-1.38 (m, 2H), 1.32-1.20 (m, 2H), 1.21 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 2H), 0.85 (s, 9H), 0.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.6, 154.0, 146.9, 142.8, 124.2, 120.3, 113.4, 80.3, 55.4, 32.4, 29.6, 29.2, 28.2, 23.2, 21.2, 19.9, 13.9, -2.1; **TLC** (10% EtOAc/hexanes, pretreated plate): R_f 0.53 (UV/CAM).

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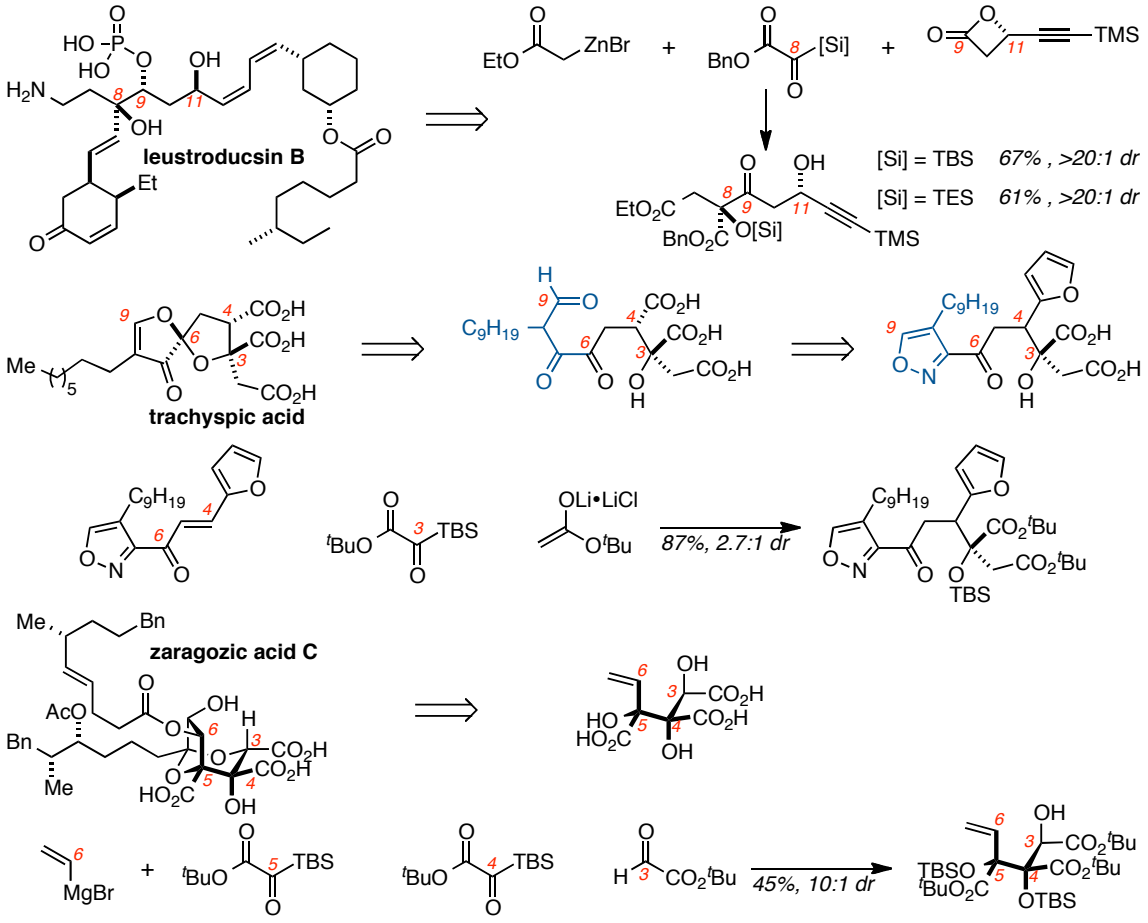
CHAPTER 2

EFFORTS TOWARD THE TOTAL SYNTHESIS OF ALTERNARIC ACID

2.1 Introduction

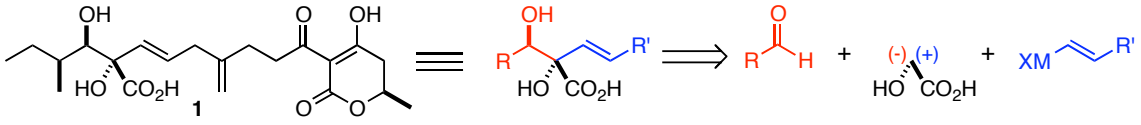
Silyl glyoxylates have emerged as powerful conjunctive reagents for the coupling of nucleophilic and electrophilic reaction partners to forge a fully substituted glycolic acid, a subunit embedded in several natural products of interest. The successful expansion of silyl glyoxylate reactivity to incorporate a variety of coupling partners has demonstrated that, in principle, a variety of nucleophile/electrophile pairings can be made to achieve synthetically useful reactions for target-directed synthesis (see **Section 1.1** and **Scheme 1-4**). Within the context of total synthesis, silyl glyoxylates have been used as tools in the construction of leustroducsin B,[1] trachyspic acid,[2] and zaragozic acid C.[3] **Scheme 2-1** summarizes the key retrosynthetic steps in each, as well as the associated multicomponent couplings in the forward sense. In the leustroducsin B and zaragozic acid C syntheses, the multicomponent coupling is the first step. These couplings highlight the utility of silyl glyoxylates to rapidly generate molecular complexity with a high degree of stereoselectivity in a single step from readily available starting materials.

Scheme 2-1. Demonstrated Silyl Glyoxylate Utility in the Context of Total Synthesis



This chapter will describe efforts to apply silyl glyoxylates to the total synthesis of alternaric acid (**1**), which relies on the ability of silyl glyoxylates to undergo glycolate aldol reactions of the latent enolate formed after nucleophilic addition/[1,2]-Brook rearrangement **(Scheme 2-2)**. These efforts have yet to yield the natural product, but significant progress has been made which features the expansion of silyl glyoxylate reactivity to more highly functionalized reaction partners. Like the trachyspic acid synthesis, it has been demonstrated herein that the key multicomponent coupling reaction can be moved to a later stage in the route, which highlights the versatility of silyl glyoxylates to forge crucial C–C bonds in a synthesis.

Scheme 2-2. Alternaric Acid **1** as an Application of Silyl Glyoxylates



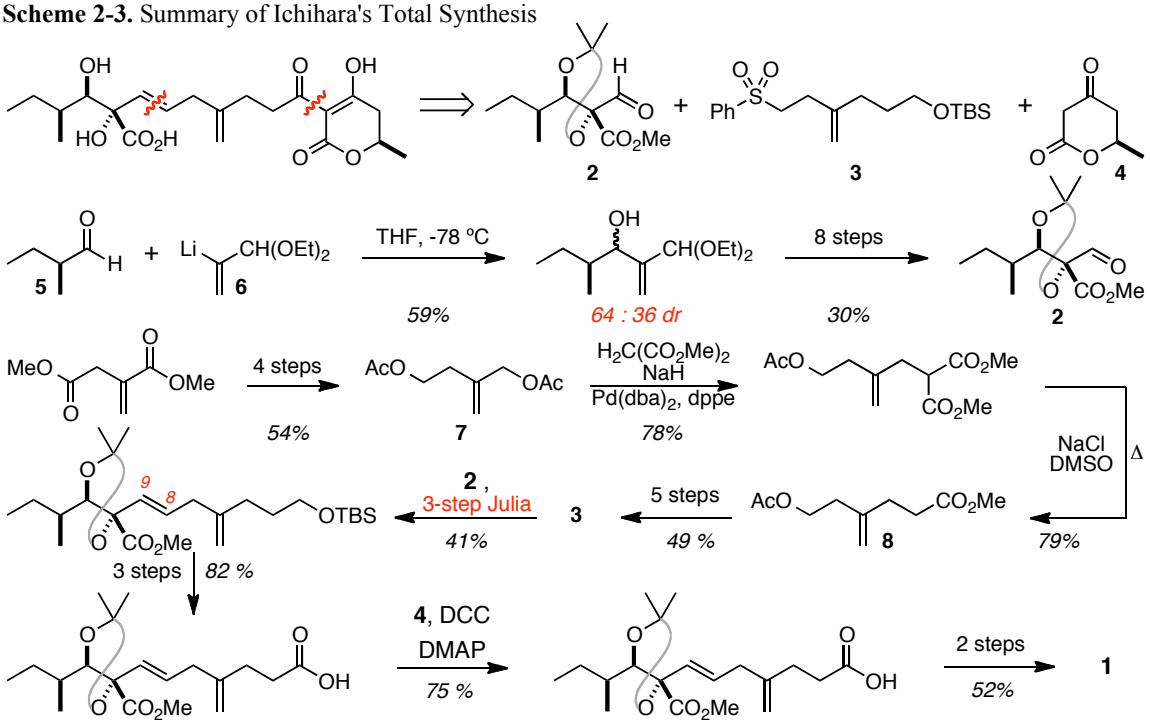
2.2 Background: Previous Synthetic Efforts

Alternaric acid was isolated in 1949 from the fungus *Alternaria solani*, which is a fungus responsible for early blight disease in tomato and potato plants.[4] In addition to this biological activity, alternaric acid was also linked to specific antifungal activity.[5] The gross structure was elucidated in 1960 using classical chemical degradation methods,[6] although the stereochemistry was not established until a total synthesis by Ichihara and co-workers in 1994.[7] Ichihara's route allowed for the preparation of several diastereomers of key intermediates, which could be compared to products isolated from degradation studies. A few years later, a formal synthesis by Trost that utilized ruthenium-catalyzed Alder-ene reaction methodology,[8] provided significant precedent as to how one might approach the synthesis of alternaric acid. We were attracted to this natural product due to the glycolic acid subunit embedded in the more stereochemically and functionally dense core of the molecule, which we anticipated would be conveniently accessed via silyl glyoxylate methodology.

The Ichihara synthesis was not only significant for establishing the stereochemistry of the natural product, but also for an important methodological development and an attractive synthesis of a key fragment.[7] The synthesis is summarized in **Scheme 2-3**. Addition of vinyllithium **6** to (*S*)-2-methylbutanal **5** proceeded in moderate yield with poor diastereoselectivity; this lack of stereoselectivity was acceptable for a synthesis in which the desired stereochemistry of the natural product was

unknown. Through an eight step sequence, including chromatographic separation of the initially formed diastereomeric mixture, the first key fragment **2** was accessed. Sulfone **3** was prepared in 11 steps from dimethyl itaconate. One of the key carbon chain elongation sequences for fragment **3** involved the reaction of a catalytically generated Pd-π-allyl electrophile from derived from allylic acetate **7** with dimethyl malonate, followed by decarboxylation (**7** → **8**). The union of aldehyde **2** and sulfone **3** involved the three-step classical Julia olefination sequence, which forged the C8-C9 alkene with excellent *E*-selectivity. Functional group manipulation allowed for elaboration of the protected primary alcohol to a carboxylic acid, which was coupled to the third key fragment, pyrone **4**, via a DCC coupling/*in situ* Fries rearrangement reaction. Hydrolysis of the ester and deprotection of the acetonide furnished the natural product, which was complete in 29 total steps and less than 0.001% yield. The synthesis of the third key fragment **4** was particularly attractive and concise, but a synthesis which could significantly shorten the syntheses of fragments **2** and **3**, or demonstrate a new fragment union, would be a significant contribution to this arena.

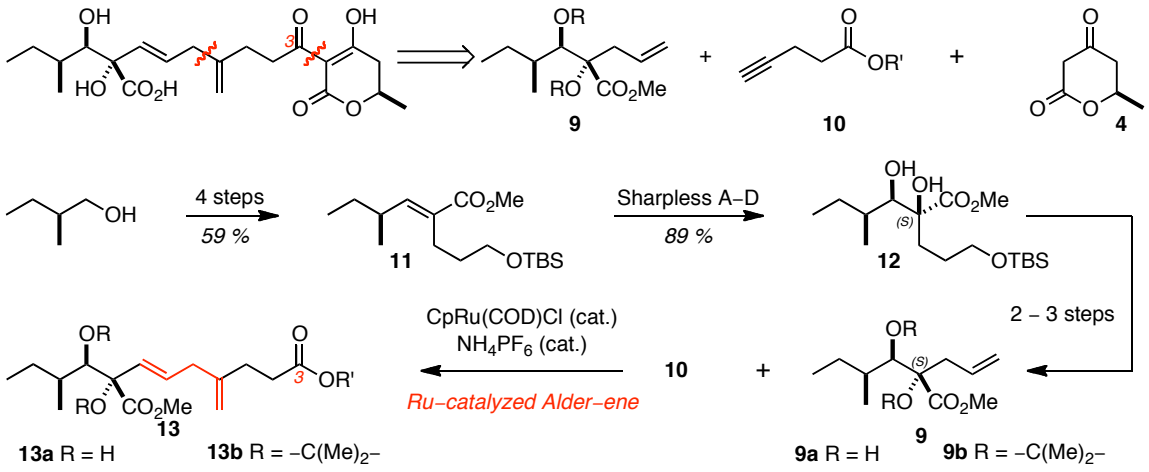
Scheme 2-3. Summary of Ichihara's Total Synthesis



The Trost formal synthesis reported four years later was significantly more concise due in part to the development of the ruthenium-catalyzed Alder-ene reaction. In this synthesis, the allyl group in the key fragment **9** was to serve as the precursor to the 1,4-diene segment of the molecule **(Scheme 2-4)**. This synthesis also relied on (*S*)-2-methylbutanal **5** as an early intermediate, which was converted through three additional steps to the trisubstituted alkene **11**. A completely catalyst-controlled Sharpless asymmetric dihydroxylation of enoate **11** provided diol **12.** The Sharpless dihydroxylation step is an attractive way to establish the stereochemistry of the target fragment **9** with exquisite control; this will prove important in the context of the work presented in this chapter (*vide infra*). Diol **12** could be converted to terminal olefin in **9** via a Grieco elimination of the primary alcohol after its deprotection; this directly afforded **9a**, and in an additional step, acetonide formation afforded **9b**. The key Alder-ene reaction then proceeded to afford the 1,4-diene, and was tolerant to both coupling

partners **9a**/**9b**, as well as variation of the ester group in **10**. Deprotection of the C3 ester in **13b** revealed the carboxylic acid, intercepting an intermediate from Ichihara's synthesis. This could be converted to the natural product in three additional steps.

Scheme 2-4. Summary of Trost's Formal Synthesis

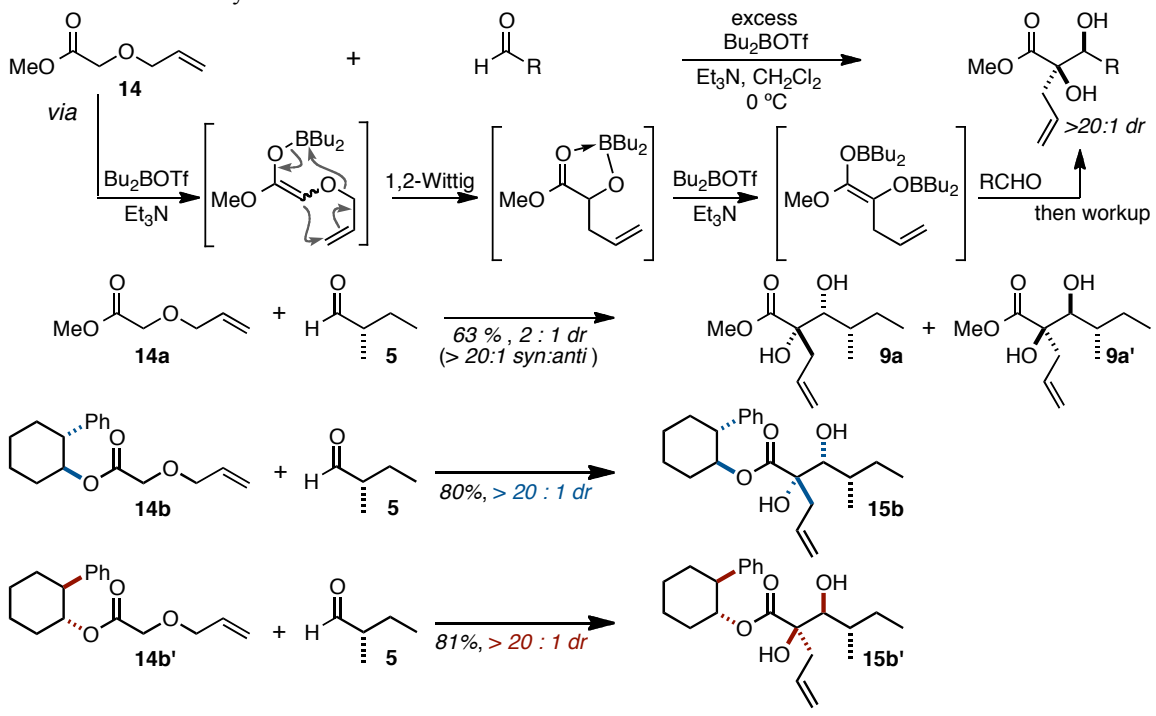


Key contributions from this synthesis were the demonstration that an allyl group could serve as the precursor to the 1,4-diene, as well as the establishment of a concise and efficient method for fragment union via the Alder-ene reaction using fragments such as **9** and **10**. Thus, a novel synthesis in this arena should demonstrate a concise method for the synthesis of the key fragment **9** or a closely related analog thereof, due to the demonstrated latitude of functionality tolerated in the Alder-ene reaction. Such a synthesis should also adequately control the stereochemistry of the three adjacent stereocenters in a fragment analogous to **9**.

Wolfe and co-workers presented an elegant approach to meeting both of the above criteria while the studies presented in this chapter were ongoing.[9] This work is summarized in **Scheme 2-5**: starting from an *O*-allyl glycolate such as **14**, exposure to excess dibutylboron triflate and triethylamine leads to enolization and 1,2-Wittig rearrangement to the *C*-allyl glycolate. A second deprotonation reveals another glycolate

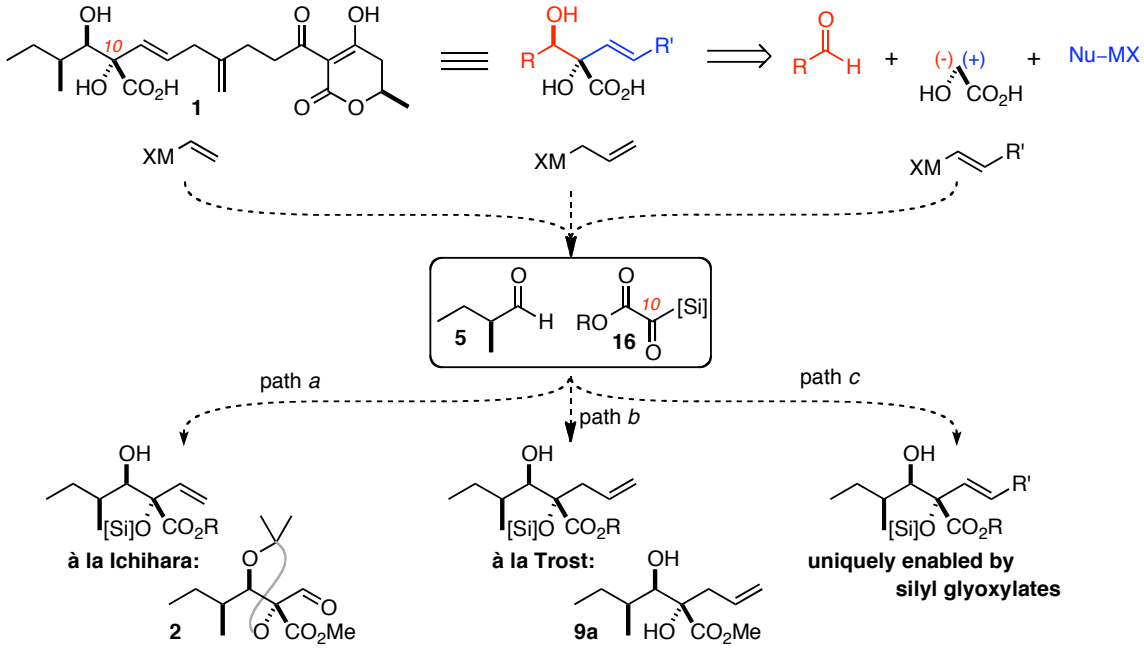
enolate, which undergoes aldol reactions with a variety of aldehydes with a high degree of *syn*-diastereoselectivity. The reaction could be rendered asymmetric by the use of a 2-phenylcyclohexanol auxiliary. To highlight this glycolate aldol construction, the reaction was attempted with glycolate **14a** and **5** to directly access **9a**, which Trost accessed in seven steps; the reaction proceeded with only moderate facial selectivity, leading to a mixture of diastereomers (2:1 **9a**:**9a'**). On the other hand, the 2-phenylcyclohexanol auxiliary in each glycolate **14** was able to override the substrate bias from the aldehyde, and either diastereomer **15b** / **15b'** could be accessed simply by judicious selection of the auxiliary antipode **14b** / **14b'**. Thus, the diastereomeric mixture **9** and the diastereomerically pure analogs **15** were available in three steps from commercially available materials. Although not demonstrated for these particular substrates **15**, cleavage of the auxiliary could be conducted either via acetonide formation followed by basic methanolysis, or by reduction.

Scheme 2-5. Summary of Wolfe's Contribution



The synthetic work by Ichihara and Trost, extant at the time these studies were begun, was able to directly inform our approach to this natural product. Silyl glyoxylates, by virtue of their versatility as glycolic acid synthons (see **Section 1.1** and **Scheme 1-4**),[10-16] offer an interesting approach to this molecule: any one of several bond disconnections could be envisioned as potential routes to the target **(Scheme 2-6)**. The glycolate aldol subunit present at C10 in alternaric acid intimates that the combination of an aldehyde (such as **5**), a silyl glyoxylate **16**, and an appropriate nucleophile could serve as a key step. The early success of three component coupling reactions with silyl glyoxylates, vinylmagnesium bromide, and aldehydes would allow access to an intermediate such as Ichihara's fragment **2** in short order (path *a*). Alternatively, the Trost synthesis revealed that an allyl group could serve as the precursor to the 1,4 diene portion of the molecule: thus an allyl nucleophile could allow rapid access to an intermediate analogous to **9** (path *b*). Lastly, the use of a functionalized nucleophile would potentially allow unique access to the natural product, which would represent a significant contribution both to silyl glyoxylate reactivity and to the synthesis of this molecule (path *c*). Key to the attractiveness of such an approach would be how much of the carbon skeleton of the natural product could conceivably be combined in a single step.

Scheme 2-6. Silyl Glyoxylates Offer a Versatile Approach to Alternaric Acid



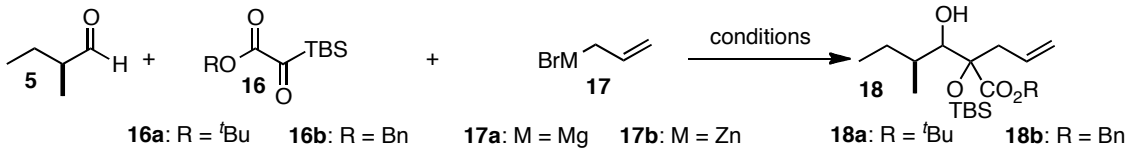
2.3 Results and Discussion

2.3.1 An Allyl Nucleophile-Based Approach

The success of Trost's Alder-ene reaction, as well as the direct access to analogs of **9** via three component coupling, provided the impetus to examine the combination of an allyl nucleophile, silyl glyoxylates, and (*S*)-2-methylbutanal **5**. Preliminary results with such couplings had given us cause to anticipate that such a reaction held significant promise for this synthesis,[17] as it was believed to proceed with high *syn*-/*anti*-diastereoselectivity. Initial studies employed the silyl glyoxylates **16a**/**16b** and allylmagnesium bromide **17a (Table 2-1)**. These reactions gave complex mixtures regardless of the silyl glyoxylate employed or the temperature of the reaction; after several attempts at purification, the product was still judged impure. We quickly modified the conditions to employ allylzinc bromide **17b** and the benzyl silyl glyoxylate

16b since these conditions led to much cleaner reactions. Under these conditions, we believed we were achieving ~50% yield of product **9c** with a ~3.6:1 diastereomer ratio; importantly, these diastereomers were separable.

Table 2-1. Initial Exploration of Allyl Three Component Couplings



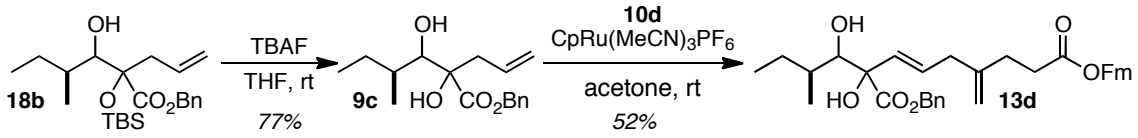
16a: R = ^{t}Bu **16b**: R = Bn **17a**: M = Mg **17b**: M = Zn **18a**: R = ^{t}Bu **18b**: R = Bn

Entry	Silyl Glyoxylate	Nucleophile	Conditions (solvent, temp)	Result
1	**16a**	**17a**	THF, -78 ºC	Complex mixture
2	**16b**	**17a**	THF, -78 ºC	Complex mixture
3	**16a**	**17a**	THF, -100 ºC	Complex mixture
4	**16b**	**17a**	THF, -100 ºC	20%[a] of major diast. of **18b**
5	**16b**	**17b**	THF, -78 ºC → rt	45% total **18b**, [a] 3.6:1 dr[b]
6	**16b**	**17b**	THF, 0 ºC → rt	50% total **18b**, [a] 3.6:1 dr[b]

[a]Isolated yield. [b]Determined after isolation of the diastereomers and mixed fractions via chromatography.

Eager to intercept a Trost-type intermediate, we proceeded to explore deprotection strategies which would allow for a successful Alder-ene reaction. Fluoride-promoted deprotection of the silyl group led directly to a benzyl analog **9c** of one of Trost's successful Alder-ene substrates **(Scheme 2-7)**. With this substrate in hand, the Alder-ene reaction was attempted and was indeed successful. However, at this point, close examination of the spectral data revealed the presence of an additional diastereomer of the product; this surprising discovery was ultimately traced back to the original three component coupling reaction.

Scheme 2-7. Successful Implementation of the Alder-Ene Reaction

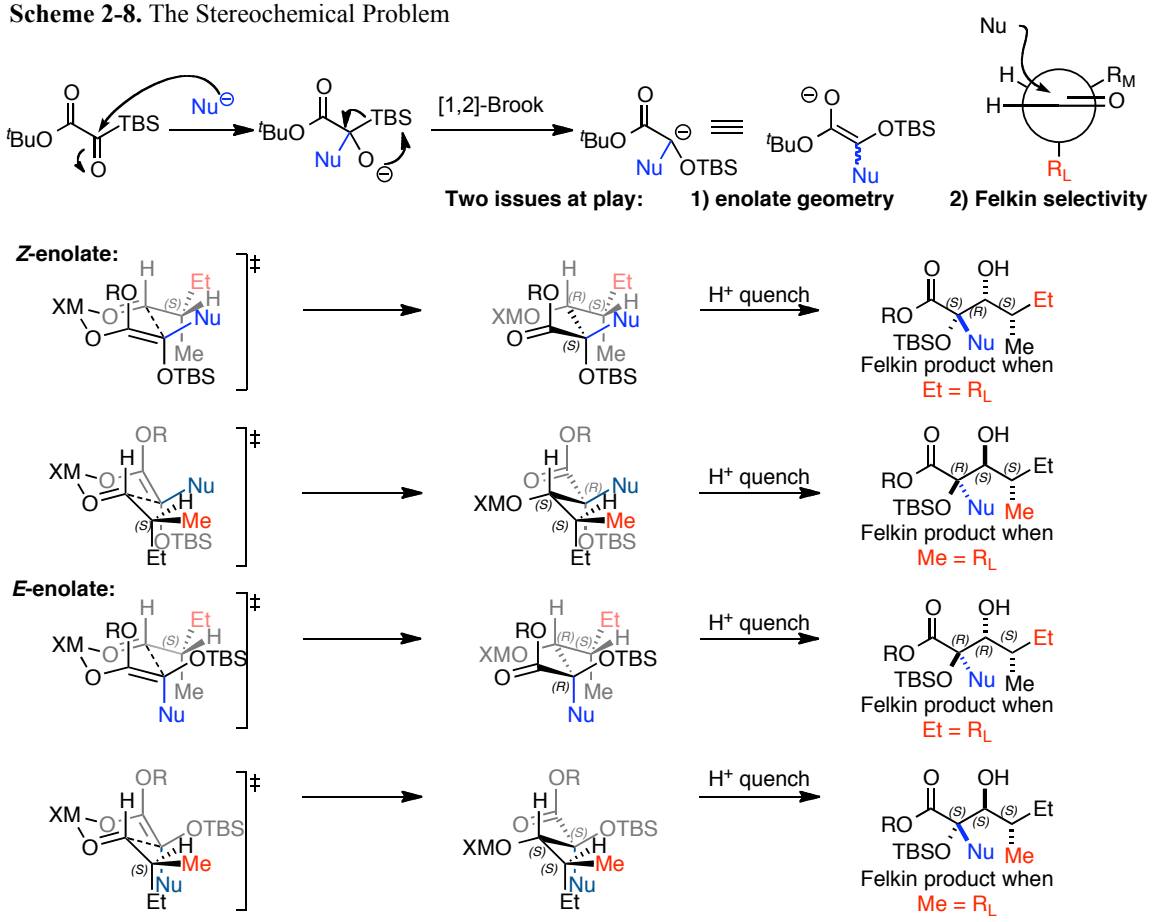


The perceived "cleanliness" of the reaction with the benzyl silyl glyoxylate **16b** was rather a consequence of coincident signals in the ^{1}H NMR spectrum of product **18b**: it was not the *reaction* was so much cleaner, but rather the *spectrum of the product*. In fact, the reaction had produced 50% yield of a 3.6:1 mixture of separable *syn*-/*anti*-diastereomers; each *syn*-/*anti*- "diastereomer" was actually a *set* of diastereomers, in a ~1.7:1 ratio, resulting from the facial selectivity due to the use of the chiral aldehyde **5**. Reexamination of the reactions of the *tert*-butyl silyl glyoxylate **16a** revealed a similar pattern, and the initially perceived "complex mixtures" actually contained all four diastereomers of the product **18a**, with more of the signals resolved. With this discovery, the use of allyl nucleophiles as an entry into the synthesis of alternaric acid was soon abandoned.

The issue at play is common to all aldol reactions of an achiral enolate with a chiral aldehyde. The enolate geometry is typically responsible for the determination of the *syn*-/*anti*- selectivity of a given aldol reaction; the facial selectivity of approach of the enolate to a chiral aldehyde is typically governed by the substrate bias of the aldehyde, as predicted by the Felkin-Anh model. In the case of this particular reaction, the picture is as summarized in **Scheme 2-8**: four diastereomers are possible, given two possible enolate geometries and two possible approaches to the aldehyde. The desired product in the three component coupling reaction results from a *syn*-aldol reaction (from a *Z*-enolate) that proceeds with Felkin selectivity with respect to the aldehyde. Both of these

are expected, and in fact are favored, but the selectivity for each (3.6:1 and 1.7:1, respectively) is rather poor. In order to solve this problem, the enolate geometry and the facial selectivity would have to be better controlled. With respect to the control of enolate geometry, precedent from the work of other former group members provided a route forward.[10,18]

Scheme 2-8. The Stereochemical Problem

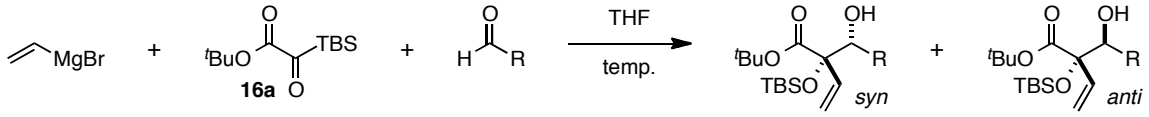


2.3.2 A Vinyl Nucleophile-Based Approach

The potential partial solution to this problem would rely on a change in nucleophile. Initial reaction development with vinylmagnesium bromide as a nucleophile in silyl glyoxylate aldols was conducted by Xin Linghu, who found a striking temperature dependence of the diastereoselectivity **(Table 2-2)**. If the reaction was run at -78 ºC, the

three component adduct was isolated with moderate diastereoselectivity for the *anti* aldol (entries 5 and 6). If the reaction was allowed to warm to room temperature prior to quenching and workup, the *syn*-aldol product was observed with excellent diastereoselectivity (entries 1-4). The rationale for this observation was that, with a vinyl group on the intermediate glycolate enolate, the initial aldol reaction with the aldehyde was reversible and that equilibration could occur upon warming the reaction prior to quenching. This equilibration led to the observed *syn*-diastereoselectivity.

Table 2-2. Switchable Diastereoselectivity in Glycolate Aldols Initiated by Vinylmagnesium Bromide[a]



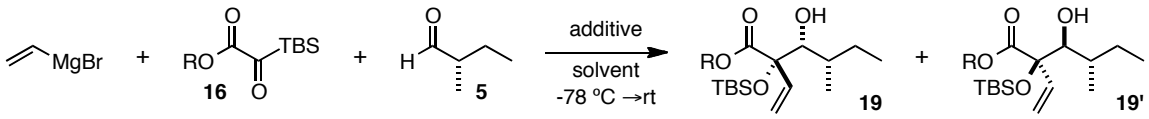
Entry	Aldehyde R	Temperature	Yield (%)	*syn:anti*
1	$^{c}C_6H_{11}$	-78 to 23 ºC	76	>95:5
2	$^{n}C_6H_{13}$	-78 to 23 ºC	72	>95:5
3	Ph	-78 to 23 ºC	74	>95:5
4	(*S*)-CHMeEt	-78 to 23 ºC	74	>95:5[b]
5	$^{c}C_6H_{11}$	-78 ºC	60	20:80
6	(*S*)-CHMeEt	-78 ºC	86	9:91[b]

[a]Xin Linghu, unpublished results. [b]The facial selectivity was still poor: < 2:1.

Initial explorations of this three component coupling reaction for this synthesis in our hands aimed to reproduce and confirm this result; these results are contained in **Table 2-3**, below. The key finding from these reactions was that the reaction with vinylmagnesium bromide could indeed be highly *syn*-selective if warmed to room temperature prior to quenching. The use of toluene as solvent proved superior to the use of THF, giving slightly higher yields (entry 2 vs. entry 1). Moreover, the use of (–)-sparteine as an additive improved the diastereoselectivity: without it, the reaction

produced appreciable amounts of the third and fourth diastereomers (entries 3-4). The exact role for the (−)-sparteine is not definitively known, but it is possible that chelation of the Lewis basic nitrogen atoms to the magnesium center is responsible for a more facile enolate equilibration, leading to better *syn*-/*anti*- diastereoselectivity. The *tert*-butyl silyl glyoxylate **16a** was superior to the benzyl silyl glyoxylate **16b** under similar conditions (entry 2 vs. entry 6). Unfortunately, in none of the many iterations of this reaction were the diastereomers separable via flash column chromatography or HPLC.

Table 2-3. Exploration of the Vinyl Three Component Coupling



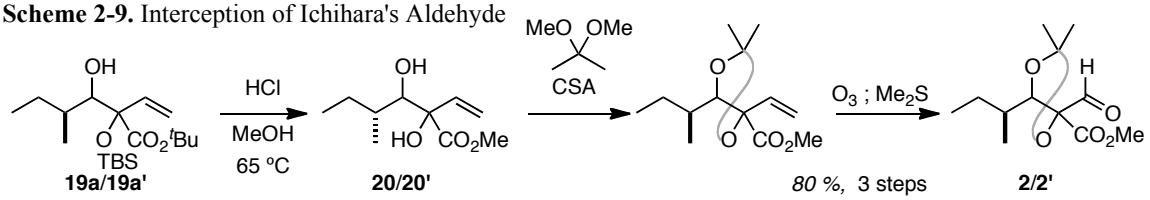
Entry	Silyl Glyoxylate	Solvent	Additive	Yield (%)[a]	dr
1	**16a**; R = ^{t}Bu	THF	(−)-sparteine	40	1.4:1
2	**16a**	Toluene	(−)-sparteine	65	1.7:1
3	**16a**	THF	---	42	1.3:1[b]
4	**16a**	Toluene	---	< 40	1.4:1[b]
5	**16b**; R = Bn	Toluene	(−)-sparteine	39	1.6:1

[a]Isolated yield after chromatography. [b]The 3rd and 4th diastereomers formed appreciably.

Nevertheless, we proceeded to advance this approach in the hope that the diastereomers may prove separable at some intermediate stage, as they had in the Ichihara synthesis. Various derivatizations of the three component coupling product **19a** (as a mixture with diastereomer **19a'**) were investigated with the ultimate goal of advancement to an aldehyde substrate for a modified Julia olefination—without necessarily aiming to intercept Ichihara's intermediate **(Scheme 2-9)**. Ozonolytic cleavage of the vinyl group to the aldehyde was typically much more efficient when both hydroxyl groups and the

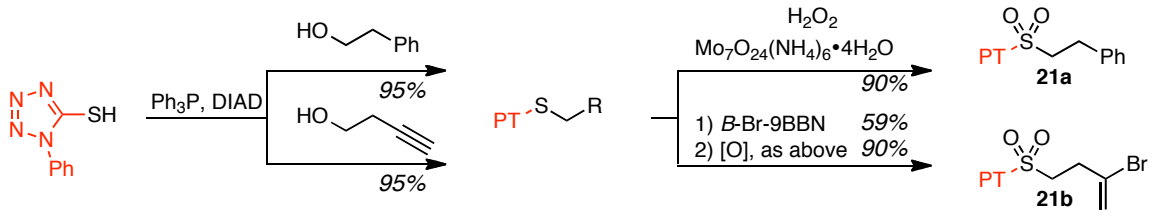
carboxylic acid were protected in some way. Ultimately, the most efficient set of transformations led to an interception of Ichihara's aldehyde **2**: treatment of the three component coupling product with HCl in methanol led to clean transesterification and silyl deprotection, affording the diols **20/20'**. Acetonide formation and ozonolysis were then performed to arrive at the mixture of aldehydes **2/2'**; the three step yield for this short sequence was quite good, at 80%. The reactions were exceptionally clean, and the majority of the mass loss was attributed to volatility of the intermediates.

Scheme 2-9. Interception of Ichihara's Aldehyde



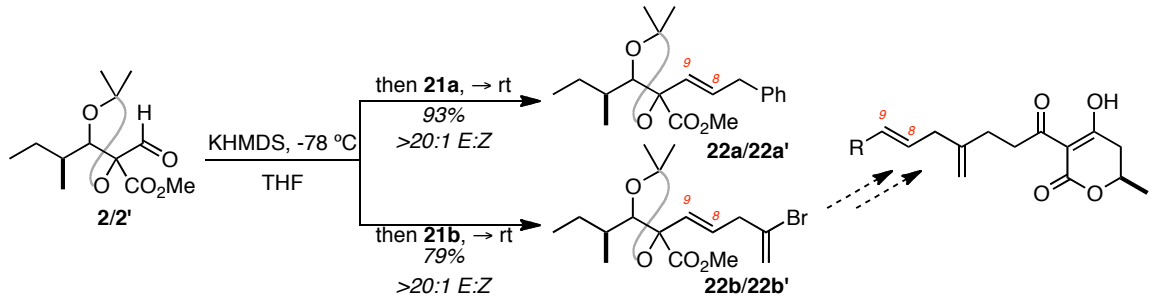
With aldehyde **2** secured, attention was turned to establishing the success of a modified Julia olefination.[19] Whereas Ichihara demonstrated a successful classical Julia olefination, a one-step version would increase the step efficiency of this synthesis. It remained to be established which variant of the modified Julia olefination would be most successful—in short, which of the potential heteroaromatic sulfones to employ for optimal *E*/*Z* selectivity in the olefination. Due to the availability of the phenyltetrazole (PT) thiol precursor, as well as several precedents which show this heteroaromatic core to be successful for highly *E*-selective olefinations,[19] a few sulfones were prepared according to **Scheme 2-10**. The sulfide linkage could be formed in high yield via a Mitsunobu reaction from the corresponding alcohol.[20] Oxidation to the sulfones proceeded without event to afford test substrates **21** for the olefination.

Scheme 2-10. Sulfones Prepared to Test the Modified Julia Olefination



The modified Julia olefinations attempted using typical conditions were quite successful **(Scheme 2-11)**. Deprotonation of the sulfone at -78 ºC in THF with KHMDS, followed by addition of the aldehyde **2** and warming to room temperature led to high yields of the olefination product **22** with complete *E*-selectivity in each case. Thus, a modified Julia olefination would be a viable, step-efficient means for forging the C8–C9 olefin stereoselectively. It should be noted that product **22a** established the proof of concept with this approach; there would be no need to investigate other heteroaromatic sulfones, given the high yield and stereoselectivity observed. The reaction to give **22b** provided a substrate with a vinyl bromide functional handle for further elaboration if desired. For example, this handle could potentially be used to append the rest of the alternaric acid carbon skeleton via conjugate addition to an acrylate followed by ester hydrolysis and coupling to the pyrone fragment **4**.

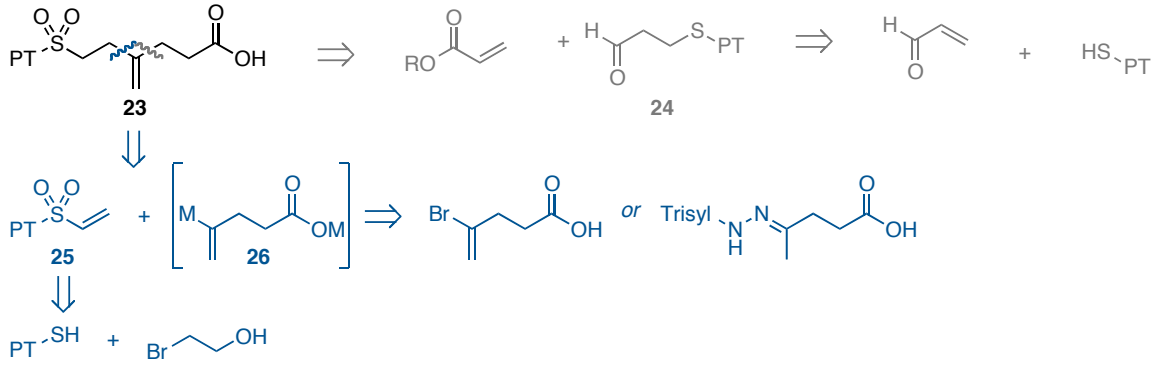
Scheme 2-11. Successful Demonstration of the Modified Julia Olefination



A more convergent approach was desired, as an attractive feature of our approach to aldehyde **2** was the brevity of the sequence. If the bulk of the remaining carbon

skeleton could be introduced in the olefination step, the step count to the natural product could compare favorably to Trost's eight-step sequence to fragment **9**. This goal served as the guiding framework for many of the strategic decisions that followed. We thus targeted a sulfone such as **23 (Scheme 2-12)**, as it was anticipated that the use of excess base would allow for dianion formation. The resultant carboxylate salt would hopefully be a non-complicating factor in the olefination reaction. The first attempt to synthesize this intermediate target focused on a Stetter-type reaction of **24** and an acrylate. It proved trivial to prepare **24** from the corresponding thiol and acrolein, but the Stetter reaction with the acrylate was unsuccessful. Under a few of the original Stetter conditions,[21] retro-Michael of the thiol from acrolein followed by Michael addition into the acrylate occurred. Although β-thiomethyl and β-dithianyl aldehydes have been shown to participate in Rh-catalyzed Stetter reactions,[22] attempts with the β-heteroarylsulfide **24** were unsuccessful. As chelation from the sulfur is necessary to stabilize the Rh complex after insertion into the formyl C–H bond, it is possible that the electron-withdrawing nature of the tetrazole prevented the requisite coordination by lowering the Lewis basicity of the sulfur atom in **24**.

Scheme 2-12. New Sulfone Target and 1st and 2nd Generation Retrosyntheses

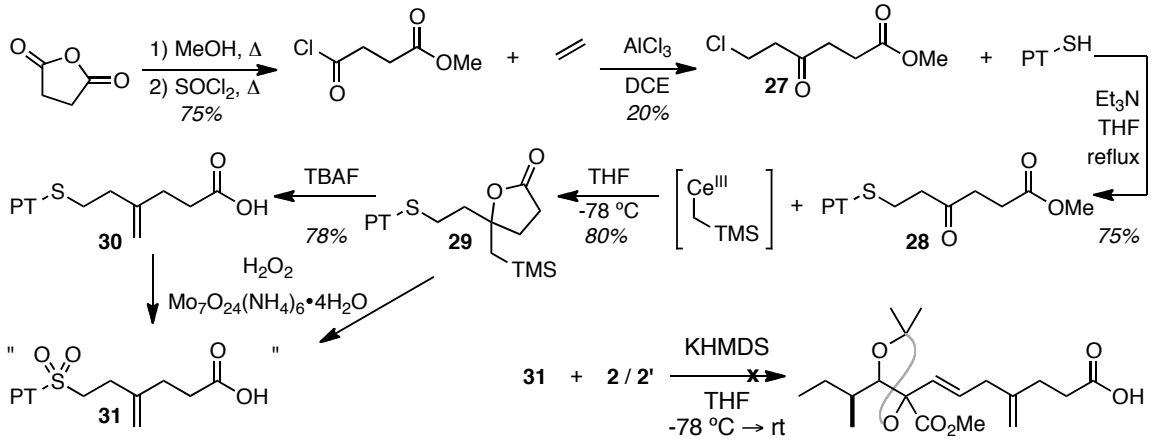


Other attempts to make **23** essentially "umpoled" the approach. Instead of conjugate addition into an acrylate, conjugate addition of an organometallic such as **26** into vinyl sulfone **25** was attempted; while these fragments were easily accessed, their union was unsuccessful. The dianion **26** could be generated from either of two precursors: via Li/Br exchange from the vinyl bromide, or via Shapiro reaction from the hydrazone.[23] Although its proton-quenched product was isolated from these failed attempts, no fragment union was ever observed. While this particular reaction may have been ambitious, model studies with conjugate addition of simple nucleophiles to **25** using a variety of copper sources were ultimately unsuccessful as well. Vinyl sulfones have been known to undergo conjugate additions,[24] but to the best of our knowledge this would have been the first example of a PT-sulfone being synthesized in such a manner.

The route that came closest to successful completion of sulfone fragment **23** is shown in **Scheme 2-13**. It began with conversion of succinic anhydride to its half-ester/half-acid chloride, followed by a Friedel-Crafts type acylation of ethylene to the β-chloroketone **27**. The poor yield in that step was attributed to premature termination of the reaction. It could thus likely have been improved upon in subsequent runs, but advancement of the available material precluded this necessity (*vide infra*). The sulfide linkage could be forged by alkylation of the PT thiol with **27**. Several methylenations of the ketone **28** were investigated next; this transformation required non-basic conditions to avoid elimination of the sensitive β-sulfide. While the Lombardo[25] and Tebbe[26] reagents displayed some promise, the cerium-modified Peterson reagent[27] had the added benefit of concomitant lactonization onto the ester to give **29**. It was anticipated that an elimination process here would expel the carboxylate, ultimately shortening the route to the desired

carboxylic acid by one step. Fluoride-induced elimination to **30** was successful, but the oxidation of the sulfide to the sulfone could not be achieved without complication. An exact structure for the compound isolated (**31**) was not established; while the spectral data bore many similarities to what one would expect for the desired sulfone **23**, it was not in fact consistent with **23**. Interestingly, **29** could be converted directly to the compound **31** using the standard oxidation conditions employed for conversion of the sulfide to the sulfone. A sampling of other oxidation conditions afforded the same unidentified product. We believe some form of over-oxidation is occurring, perhaps due to the unique structural features in **29**. Unsurprisingly, attempted Julia olefinations with **31** were unsuccessful.

Scheme 2-13. Closest Route to Completion of the Desired Sulfone



The Julia olefination route retained promise despite the difficulties encountered in synthesizing the target sulfone. A different configuration of the functionality in the sulfone, perhaps requiring a lengthier post-Julia endgame, might have been "safer" and successful in the end. Nevertheless, we had firmly established that the modified Julia olefination was a viable approach, and would increase the step efficiency over the Ichihara precedent. Concurrently, we were still aware of the fact that we had yet to

resolve the stereochemical issue in the three component coupling reaction, and for the time being our attention shifted to address this issue.

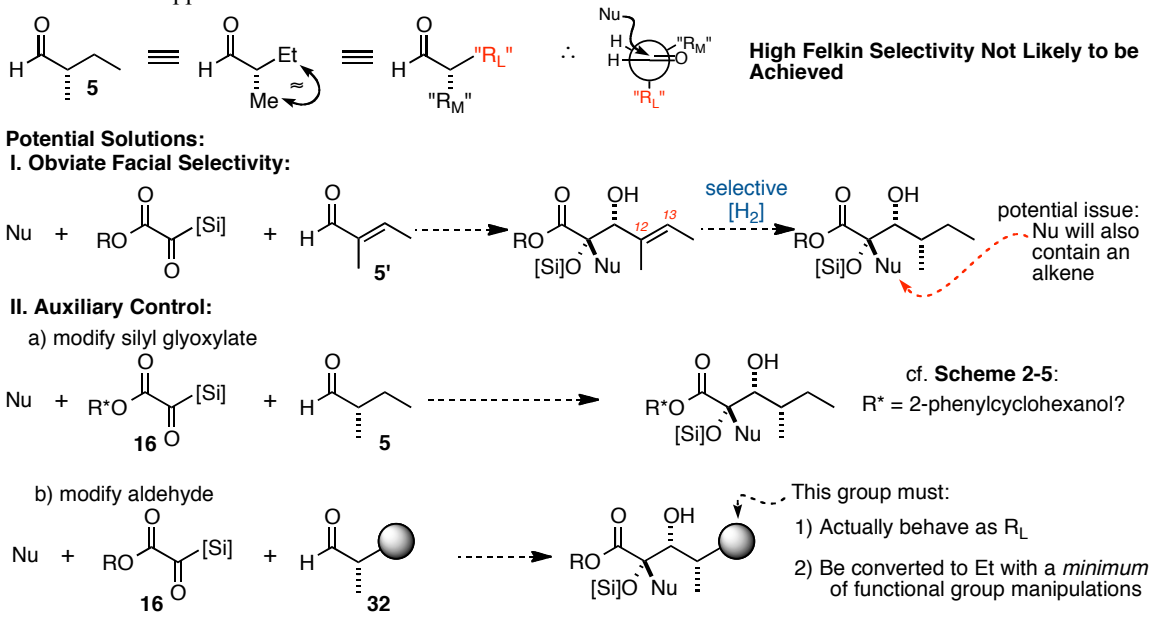
2.3.3 Attempts to Improve the Stereoselectivity of the Glycolate Aldol

The stereochemical problem with the three component coupling reactions thus far was significant. Whether the allyl or vinyl nucleophile was employed, the facial selectivity in the three component coupling with (*S*)-2-methylbutanal **5** was ~1.7:1, or ~63:37. Placed in the context of Ichihara's initial vinyllithium addition to **5** (64:36 dr), as well as Wolfe's glycolate aldol with **5** (2:1, or ~67:33), it is clear that the limitation is due to the aldehyde. Attempts to achieve Felkin selectivity in additions to this aldehyde with a variety of nucleophiles are thus limited by the insufficient steric differentiation of the methyl and ethyl groups on the aldehyde.[28] While the use of **5** directly affords the structural motif in the natural product, it is clear that the difference between "R_M" and "R_L" in this case is, as a practical matter, insignificant. Compounding the issue was the inability to separate the diastereomers at any intermediates yet synthesized; the synthesis of alternaric acid as a mixture with *ent*-(12-*epi*)-alternaric acid was looming.

There are a few possible approaches we considered to solve this problem, as summarized in **Scheme 2-14**. First, it might be possible to use tiglic aldehyde **5'**, which would eliminate the facial selectivity issues in the three component coupling (approach **I**). A subsequent hydrogenation would be required to establish the C12 stereocenter. Given the potential chemoselectivity issues with hydrogenation of a C12–C13 olefin in preference to the C8–C9 and the C6–C19 olefin, as well as preliminary results revealing such difficulties,[17] such an approach was not pursued. An alternative approach would be to use auxiliary control (approach **II**), which was envisioned through either of two

modifications. First, it might be possible to employ an auxiliary on the silyl glyoxylate (approach **II** a)). Wolfe and co-workers demonstrated that the 2-phenylcyclohexanol auxiliary in their glycolate aldol was able to override the modest substrate bias from the aldehyde. Another potential solution would be to modify the aldehyde: It may be possible to use an aldehyde **32** with a larger R_L—although the group would have to meet the additional requirement that it could serve as the surrogate for the ethyl group with a minimum number of functional group manipulations.

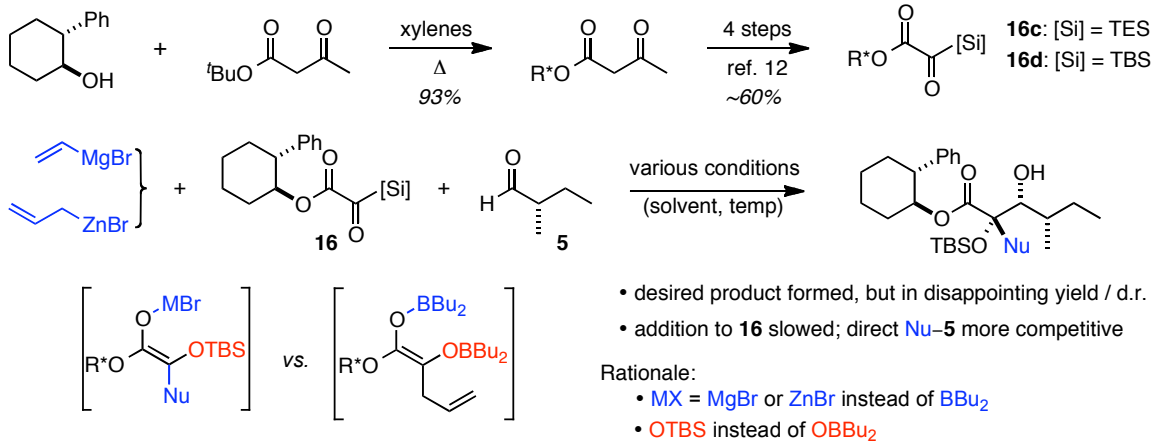
Scheme 2-14. Approaches Considered to Address the Stereochemical Issue



The Wolfe report surfaced during the course of these synthetic efforts and naturally caught our attention. In order to test such an approach, the corresponding silyl glyoxylates **16c** and **16d** were prepared **(Scheme 2-15)**: heating a mixture of (1*S*,2*R*)-2-phenylcyclohexanol[29] and *tert*-butyl acetoacetate in xylenes[30] afforded the corresponding chiral acetoacetate, which could be converted to the silyl glyoxylates via the standard protocol.[12] Unfortunately, attempts to use these silyl glyoxylates in three component coupling reactions with vinyl or allyl nucleophiles and (*S*)-2-methylbutanal **5** were less

successful than desired. The chemoselectivity typically observed in these reactions, wherein the nucleophile preferentially attacks the silyl glyoxylate over the terminal electrophile (although introduced to a solution of both), was not observed: direct nucleophile-electrophile coupling and decomposition of the silyl glyoxylates were evident.

Scheme 2-15. Auxiliary Control via Silyl Glyoxylate

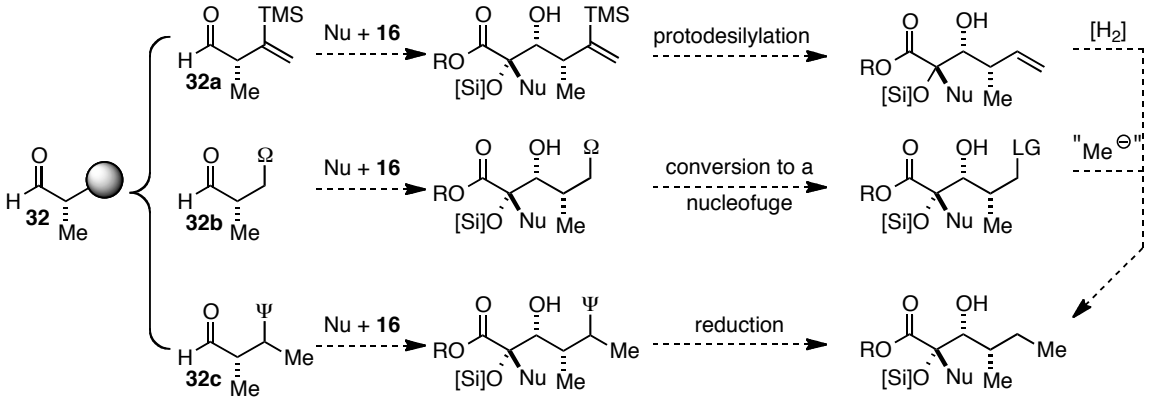


In reactions employing vinylmagnesium bromide as the nucleophile, attempts to use a sequential addition approach to solve this problem were unsuccessful: complex mixtures and silyl glyoxylate oligomerization were observed. Using allylzinc bromide and sequential addition in Et_2O, the oligomerization issue was curtailed by controlling the timing of Brook rearrangement.[12] Promising diastereoselectivity (5:1) was observed with benzaldehyde as the terminal electrophile under these conditions. It seemed plausible at this point that the diastereomers were the result of an *E*-/*Z*- enolate mixture, while the facial selectivity was high. However, three component coupling attempts with **5** were less successful: again, a mixture of four diastereomers was observed. This was attributed to incomplete control over the enolate geometry, coupled with an inability of the auxiliary to override the facial bias from the aldehyde. This could perhaps be due to the

differences highlighted in **Scheme 2-15** above. First, the presence of the bulky silyl group instead of the dibutylboron on the glycolate α-*O* atom may play a role due to increased steric demand. Second, boron enolates typically display increased diastereoselectivities relative to enolates of other metals due to the smaller ionic radius of boron, which leads to tighter transition states. Thus, the presence of a zinc or magnesium counterion in these three component couplings is also a likely factor in reducing the diastereoselectivity.

The alternate approach, wherein the aldehyde was to be modified to contain an actual R_L, was subsequently explored. Several different aldehydes were synthesized and utilized in this three component coupling chemistry with varying degrees of success. The aldehydes envisioned, and potential manipulations of the directing groups thereof, are summarized in **Scheme 2-16**. The aldehyde **32a**,[31] if successful in controlling the stereoselectivity, would require a protodesilylation followed by a chemoselective hydrogenation of the least-hindered, terminal olefin. Alternatively, an aldehyde such as **32b** would require conversion of Ω to a suitable leaving group, followed by displacement with a methide equivalent. An aldehyde such as **32c** would require Ψ to be an easily reducible group for the synthesis of the alkane as in the natural product.

Scheme 2-16. Auxiliary Control via a Bulky Aldehyde and Projected Post-Coupling Manipulation

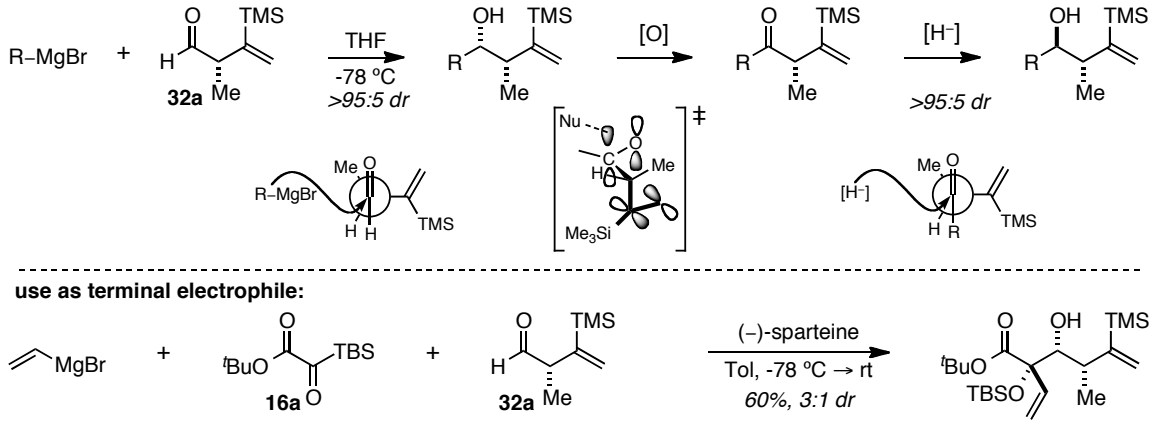


The aldehyde **32a** developed by Sato and co-workers has been shown to undergo highly selective additions of a variety of nucleophiles, including Grignard reagents,[32] hydrides (to the derived ketone),[33] enolates,[34] and dithianes,[35] to name a few **(Scheme 2-17)**. This is attributed to the preference for the β-γ unsaturated system to align itself perpendicularly to the C=O π system such that a $\pi^*_{C=O}$–$\pi^*_{C=C}$ interaction is present in the transition state for nucleophilic addition.[31] This kinetic effect is operative at the low temperatures at which these reactions have been conducted, and leads to a high degree of *syn*-selectivity between the resultant hydroxyl group and the extant methyl group. Subsequent oxidation to the ketone followed by hydride addition can afford the *anti*-relationship with equally high diastereoselectivity due to a preference for the same sense of addition.

When aldehyde **32a** was utilized in the three component coupling reaction with silyl glyoxylate **16a** and vinylmagnesium bromide, the results were disappointing: approximately 3:1 diastereoselectivity was observed. A potential reason for the relative lack of selectivity in our system is the need to warm our three component coupling reactions to room temperature to allow thermodynamic equilibration to occur in order to

observe good *syn*-selectivity with respect to the aldol stereocenters. This conflicts with the need to maintain cryogenic temperatures to maintain the kinetic directing effect of this particular aldehyde and observe the *syn*- selectivity with respect to the extant methyl stereocenter.

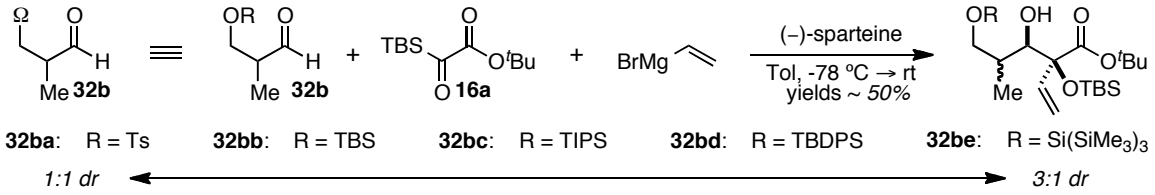
Scheme 2-17. Nucleophile Additions to Aldehyde **32a** and Application to Three Component Couplings



The class of aldehydes represented by **32b**, with a group Ω that would need to be replaced by a methyl group, were also only moderately successful at controlling the diastereoselectivity of the three component coupling **(Scheme 2-18)**. The aldehydes investigated all bore a β-oxygenated function, due to the ease of synthesis (two steps from 2-methyl-1,3-propanediol) and anticipated post-coupling manipulation. The β-tosyl aldehyde **32ba**, was investigated due to the direct access to a coupling product bearing a leaving group which could potentially be displaced by a methyl cuprate.[36] This aldehyde actually performed worse than **5**, giving a 1:1 dr. A series of silyloxy aldehydes, varying in bulk from *tert*-butyldimethylsilyl to tris-(trimethylsilyl), was also explored and found wanting in their ability to direct the facial selectivity. The lack of adequate stereocontrol even with **32be**, despite the extreme steric bulk of the supersilyl group, was attributed to

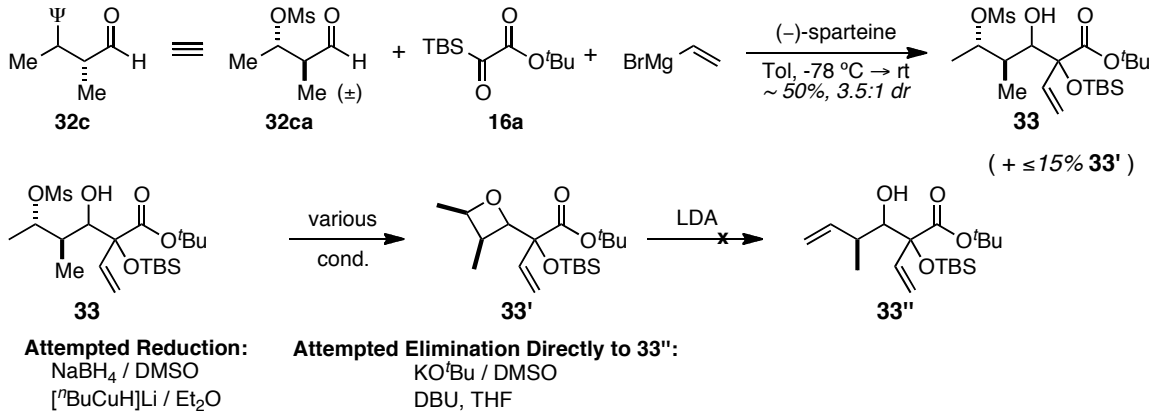
the need for an additional branch in the carbon backbone: aldehydes of type **32c** were subsequently explored.

Scheme 2-18. Three Component Couplings With Aldehydes of Type **32b**



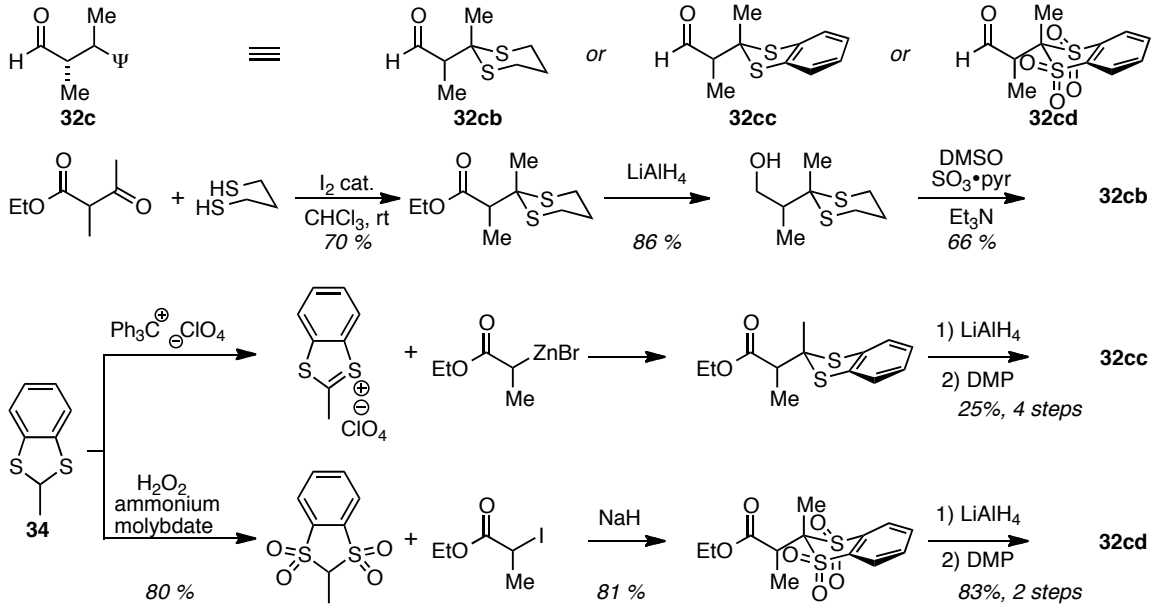
These aldehydes already had the full carbon skeleton in place: the requirement for this class was that Ψ should be easily reduced to the alkane. For example, the β-mesyloxy group of **32ca** could potentially be displaced by a hydride source **(Scheme 2-19)**. This aldehyde was moderately successful in the three component coupling: despite the relatively small size of the mesylate, the diastereoselectivity of the reaction was moderately controlled (~3.5:1 dr). Attempts to effect a displacement of the mesylate in **33** with hydride were unsuccessful: oxetane formation to give **33'** was the dominant pathway under a variety of conditions. Attempts to open oxetane **33'** to olefin **33"** were unsuccessful, as were attempts to access this olefin directly from **33**. The dominance of this pathway under various conditions is particularly interesting, given the relatively small contribution (≤15%) of such a process in the three component coupling. While protection of the free hydroxyl group in **33** could potentially have avoided these complications, such a solution would necessarily add an additional one to two refunctionalization steps (over the already conceded step(s) envisioned for auxiliary removal); for a group which did not completely control the diastereoselectivity of the three component coupling, this was rapidly departing from our requirement set forth for the R_L surrogate to require minimal functional group manipulation.

Scheme 2-19. An Aldehyde With a Reducible Group Ψ



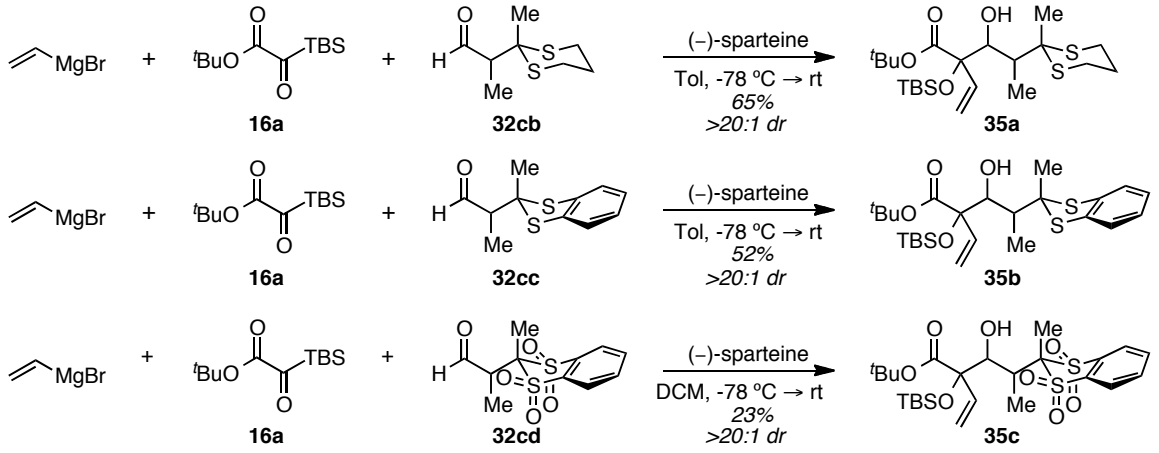
Thus, an aldehyde wherein Ψ was a sulfur-bearing group, such as a dithiane **32cb (Scheme 2-20)**, was attractive due not only to its large size but also the wealth of precedent for single-step desulfurization from various substrates. Aldehydes **32cc** and **3cd** were also prepared due to the body of precedent for desulfurization of aryl sulfones (as in the classical Julia olefination). In these reactions, the aryl group presumably facilitates the reduction by serving as an "antenna" to capture the electrons from the reductant (typically $1e^-$ donors). The dithiane aldehyde **32cb** was prepared in straightforward manner from ethyl (2-methyl)-acetoacetate by dithiane formation and a reduction-oxidation sequence. Aldehydes **32cc** and **32cd** were prepared from **34**, itself prepared in two steps from anthranilic acid.[37,38]

Scheme 2-20. Synthesis of Aldehydes Containing Sulfur-Based Functionality as the Reducible Group Ψ



These aldehydes were much more successful at controlling the diastereoselectivity of the three component coupling reaction. **Scheme 2-21** reveals that all three aldehydes of type **32c** were capable of completely controlling the stereochemistry of the three component coupling reaction, as the product **35** in each case was isolated as a single diastereomer. The dithiane aldehyde **32cb** proved superior to all other aldehydes examined, as the yield of product **35a** was the highest at 65%. The use of dichloromethane for the reaction with aldehyde **32cd** was necessary due to the insolubility of the aldehyde in toluene; this unoptimized yield could perhaps be improved upon with additional solvent screening, but this was deemed unnecessary due to the success with aldehyde **32cb**.

Scheme 2-21. Performance of Aldehydes **32c** as Stereocontrolling Elements



The control of diastereoselectivity in these three component coupling reactions was particularly gratifying, and provided the impetus for exploration of a new approach to silyl glyoxylate three component couplings: the use of a functionalized nucleophile. This approach would maintain the convergence of the synthesis, especially as the aldehyde synthesis was becoming more involved and would necessitate one or more additional steps for the removal of the directing group. Efforts to synthesize aldehyde **32cb** asymmetrically would be pursued pending demonstration that the relative stereochemistry was controlled in the desired sense, and that the dithiane could in fact be successfully removed.

2.3.4 Functionalized Nucleophiles in Three Component Couplings

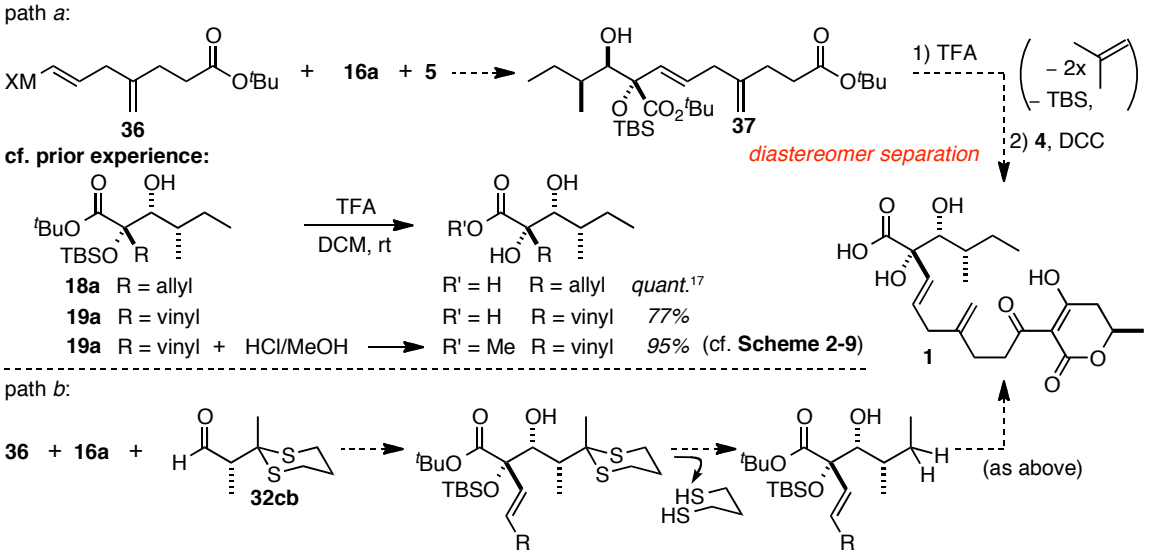
Most of the three component coupling reactions developed with silyl glyoxylates to date have involved the pairings of relatively simple nucleophiles and electrophiles. As mentioned above, the zaragozic acid C and leustroducsin B syntheses have utilized a silyl glyoxylate multicomponent reaction as the first key step. This is due at least in part to the attractiveness of the rapid build-up of molecular complexity afforded by such reactions, which serves as a reasonable starting point for synthetic design. The trachyspic acid

synthesis developed during the course of these efforts is an example where significant synthetic effort has gone into making the terminal electrophile for the key step;[2] it was now becoming apparent that the aldehyde used for the key step toward alternaric acid would also require multiple steps (and require concession steps for auxiliary removal). To maintain a convergent approach, the use of a functionalized nucleophile would be highly desirable; given the elegant precedents by Trost (and by this point, Wolfe) in the context of alternaric acid, it was deemed of utmost importance to demonstrate the unique abilities of silyl glyoxylates to have a meaningful contribution in this arena. Thus, the demonstration that *both* reaction partners with silyl glyoxylates in a given coupling reaction could be highly functionalized, and that their union could be highly efficient, became a primary goal.

The limitation to such an approach is of course the functional-group compatibility issues that affect typical organometallic reagents. We envisioned the use of a nucleophile such as **36**, which could potentially minimize the post-coupling effort required to reach **1** **(Scheme 2-22)**. Coupling of **36**, **16a**, and **5** should yield **37**, from which alternaric acid could be potentially as few as two steps away (path *a*, top). This was based on the demonstration that products **18** and **19** (derived from the coupling of **16a**, **5**, and allylzinc bromide or vinylmagnesium bromide, respectively) could undergo efficient dual deprotection of both the *tert*-butyl ester and silyl group upon treatment with TFA in DCM. Alternatively, we have also demonstrated that the *tert*-butyl ester and silyl group in **19** can be cleaved to the methyl ester diol (**20**, cf. **Scheme 2-9** above). Coupling of pyrone **4** with the least-hindered carboxylic acid should provide **1**. Choosing this path, and performing the three component coupling with **5** as a terminal electrophile would

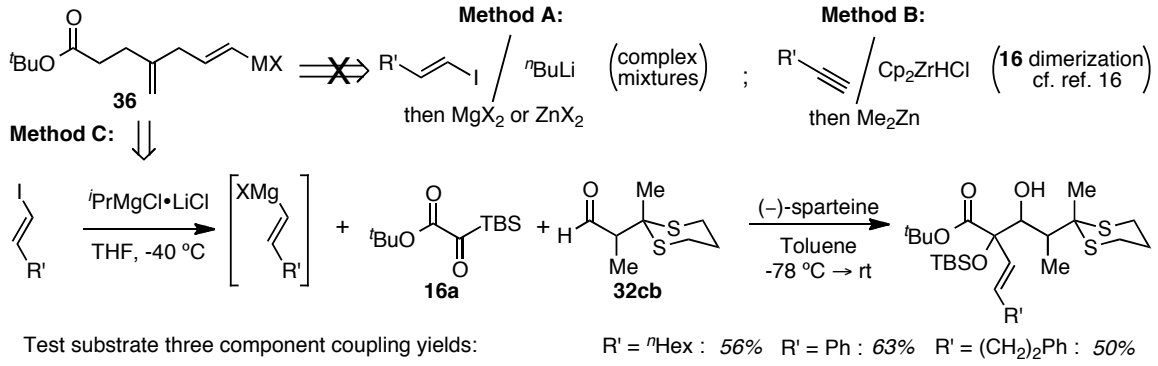
require diastereomer separation at some point. Since that has yet to be accomplished, the alternative path *b* would employ an aldehyde **32** for control of stereochemistry, but would require conversion of the R_L to the ethyl group.

Scheme 2-22. Functionalized Nucleophile Envisioned and Proposed Endgame



The desire for our nucleophile to contain the *tert*-butyl ester as in **36** meant that the vinyl nucleophile generated should be compatible with such functionality **(Scheme 2-23)**. Precedent exists for low-temperature Li/I exchanges that are compatible with esters;[39] transmetallation to either Mg or Zn could also be anticipated to provide competent nucleophiles for this chemistry (method A). Alternatively, one could envision a hydrometallation from an alkyne to give **36** (method B),[40,41] or direct Mg/I exchange using ^{i}PrMgCl•LiCl (method C).[42] We thus prepared a few vinyl iodides and an alkyne to test as precursors to the nucleophilic component in three component coupling reactions.

Scheme 2-23. Potential Methods of Generating the Vinyl Nucleophile and Three Component Coupling

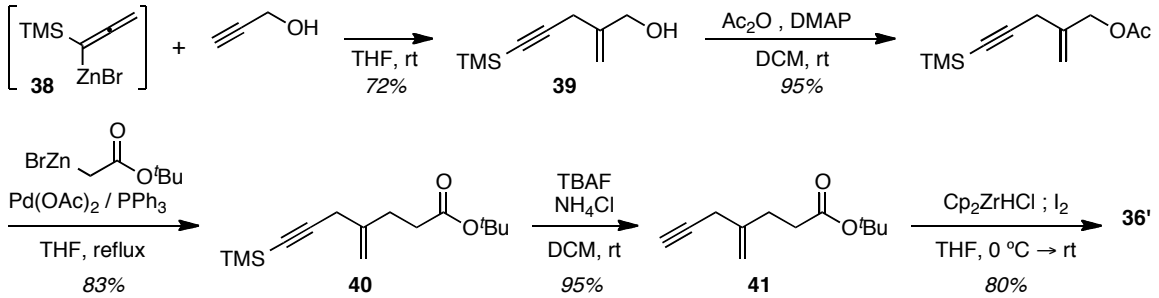


Of these methods, the direct Mg/I exchange developed by Knochel (method C) was the only acceptable method for nucleophile generation for three component coupling. The Li/I exchange (method A), whether followed by transmetallation or not, led to intractable product mixtures. Silyl glyoxylate oligomerization was predominant using this method of nucleophile generation. The alkyne hydrometallation/transmetallation to zinc (method B) led to a fairly weak nucleophile, and silyl glyoxylate dimerization/elimination to a tetrasubstituted olefin occurred.[16] Employing a ligand to accelerate the addition[41] of the vinylzinc to the silyl glyoxylate did not improve the three component coupling. Using the Knochel method for direct Mg/I exchange, the biggest competing side reaction involved hydride addition to the silyl glyoxylate and isolation of the analogous three component coupling product. This byproduct formation was not usually a significant problem, and the desired product was typically isolated in 50–63% yields, which was comparable to the three component coupling reactions with vinylmagnesium bromide. It should be noted again that the dithiane aldehyde **32cb** was capable of completely controlling the stereoselectivity of the three component coupling reaction in all cases. With these vinyl iodides and three component couplings as

successful as proof-of-concept, we next targeted a vinyl iodide precursor for generation of fully functionalized nucleophile **36**.

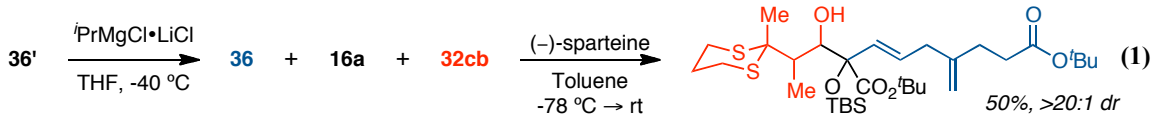
The route that we developed for this goal is summarized in **Scheme 2-24**. This route relies on the known addition of the allenylzinc reagent **38** to propargyl alcohol,[43] leading to the allylic alcohol **39**. The alcohol was activated by conversion to the acetate, and reacted as a catalytically generated Pd-π-allyl electrophile with the Reformatsky reagent generated from *tert*-butyl bromoacetate to give **40**. This underdeveloped reaction was successful when the reaction of the lithium enolate of *tert*-butyl acetate failed: Claisen condensation onto the acetate with expulsion of **39** was predominant with the more reactive lithium enolate. Additionally, this was more step-economical than the more common sequence of reacting a π-allyl electrophile with a malonate followed by decarboxylation, as employed by Ichihara (**7→8**) in the synthesis of the sulfone fragment **3**. Removal of the TMS group from the alkyne could be effected using buffered TBAF, which was necessary to avoid allene formation. Conversion to the vinyl iodide via hydrozirconation/iodination of **41** using Schwartz's reagent[44] led to the fully functionalized vinyl iodide **36'**. With this vinyl iodide in hand, the three component coupling reaction and potentially short endgame to the natural product could be investigated.

Scheme 2-24. Synthesis of the Desired Fully Functionalized Vinyl Iodide for Conversion to **36**



2.3.5 Attempts to Complete the Natural Product

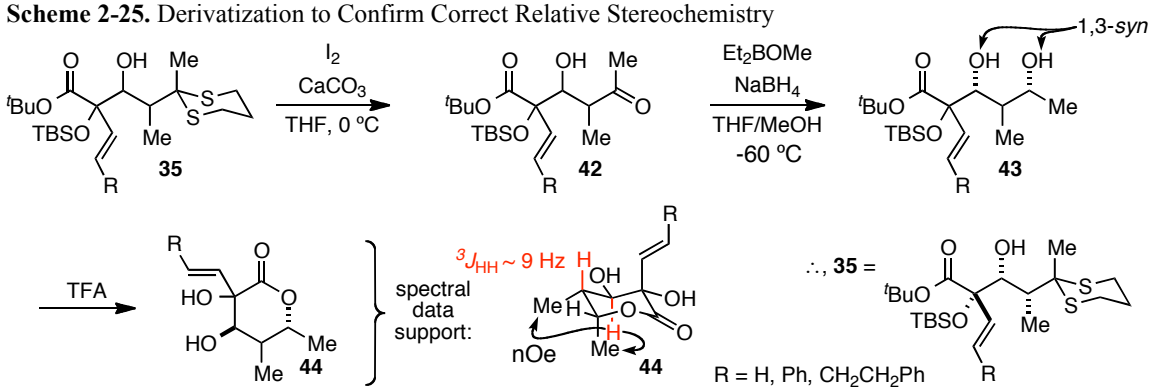
With a reliable synthesis of a vinyl iodide which would allow for the rapid assembly of the alternaric acid carbon skeleton in a three component coupling, as well as a means of controlling the stereochemistry of the reaction in the form of dithiane aldehyde **32cb**, efforts thus focused on the union of these fragments. Gratifyingly, the standard reaction conditions for generation of the nucleophile followed by standard three component coupling reaction conditions were successful in generating the desired coupling product in acceptable yield and with complete diastereoselectivity (eq. 1).



(1)

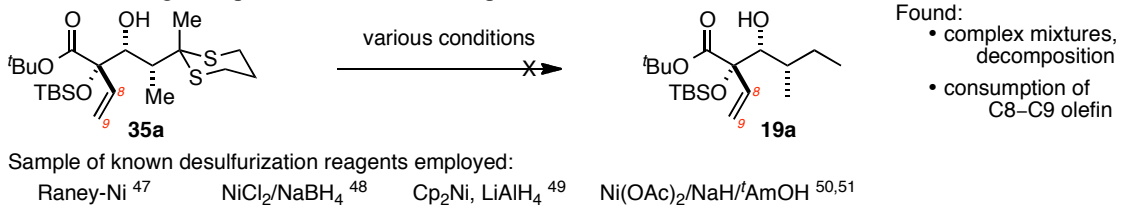
With this satisfactory result, attention shifted to confirmation that the dithiane was serving its two-fold purpose: 1) that it was controlling the stereochemistry in the correct relative sense; and 2) that it could in fact be readily reduced to the alkane. To verify the first goal, we carried out the following derivatizations as summarized in **Scheme 2-25**: deprotection of the dithiane to the ketone **42**,[45] followed by 1,3-*syn*-selective reduction[46] to the diol **43** and lactonization led to **44**. Analysis of the coupling constant and 2-D NOESY data for these compounds supported the correct relative orientation between the aldol stereocenter and the methyl group on the aldehyde. This data was thus consistent with our expectation that the bulky dithiane group was serving as an R_L, and that the three component coupling was thus proceeding with *syn*-aldol and Felkin facial selectivity.

Scheme 2-25. Derivatization to Confirm Correct Relative Stereochemistry



With this confirmation, attention thus focused on dithiane removal to the alkane. Due to the ready availability of the three component coupling product **35a** wherein vinylmagnesium bromide was used as the nucleophile, efforts focused on this substrate. Unfortunately, these attempts were entirely unsuccessful **(Scheme 2-25)**. Despite the precedent for clean desulfurization of a variety of substrates with Raney nickel,[47] nickel boride,[48] and others,[49-51] these studies were uniformly unsuccessful in formation of even traces of the desired product. In all cases, the vinyl group was conspicuously absent from the reaction products, regardless of whether the reactions were relatively clean or whether complex mixtures were obtained. It was presumed at this stage that the alkene had been saturated by hydrogenation by the adsorbed/complexed hydrogen in these nickel reagents.

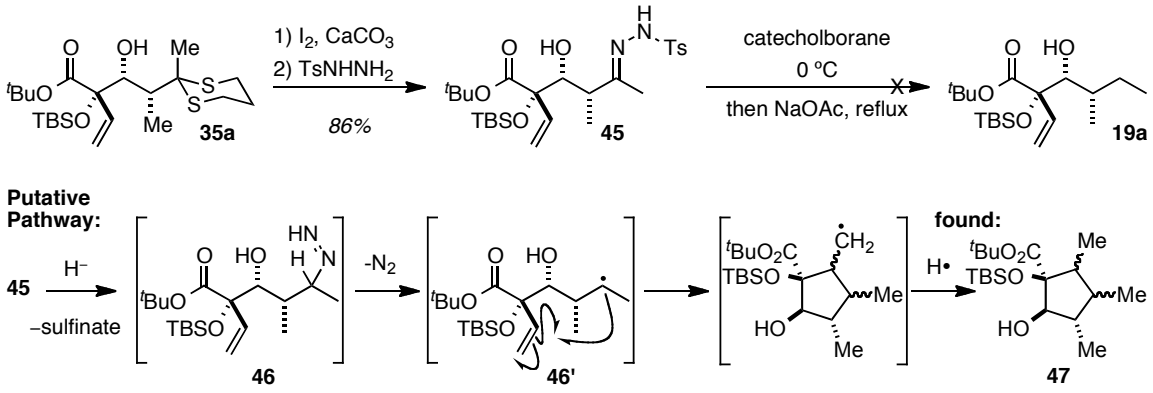
Scheme 2-26. Single-Step Desulfurization Attempts



Despite getting further from the ideal single-step reduction, a more stepwise route was considered. Ultimately, this approach provided some potential insight into what may

have been a dominant pathway in the desulfurization attempts above. Again, deprotection of the dithiane led to the ketone **42a** which was now converted to the tosylhydrazone **45 (Scheme 2-27)**. There have been numerous reports of the reduction of tosylhydrazones to alkanes,[52-56] which is a milder means of conducting a Wolff-Kishner reduction.[57] Reduction of the tosylhydrazone with catecholborane, followed by the addition of sodium acetate and heating to reflux,[52] led to a remarkably clean reaction—but unfortunately the alkene had again been consumed. The product obtained was determined to be the fully substituted cyclopentanol **47**; this presumably formed *via* a 5-*exo*-trig radical cyclization from the monoalkyl diazene **46**. This putative intermediate would have been formed from hydride reduction of the tosylhydrazone followed by elimination of the catecholboronate and the sulfinate.

Scheme 2-27. More Stepwise Reduction Attempts Reveal a Dominant Pathway



Although monoalkyl diazenes are excellent H• donors, with a donor ability surpassing tributyltin hydride,[58] it was conceivable that the concentration of such a donor was too low to quench the secondary radical **46'** prior to cyclization. Thus, addition of >20 equivalents of strong H• donors such as *tert*-butyl mercaptan, tributyltin hydride, and tris-(trimethylsilyl)silane prior to the second stage of the above reaction was attempted with the goal of attenuating this cyclization process. These H• donors were ineffective in

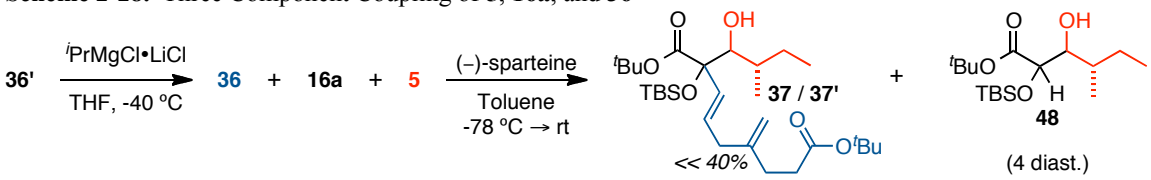
shutting down the 5-*exo*-trig cyclization: at best, a 1:5 ratio of **19a**:**47** was obtained with *tert*-butyl mercaptan. Evidently the 5-*exo*-trig intramolecular cyclization, perhaps in part due to the Thorpe-Ingold compression of this substrate, is much more rapid than intermolecular quenching of **46'**.

The prospects for the success of this approach were looking more and more bleak. These results, while valuable for the insight they provided, spelled disaster for several potential approaches to the solution to the stereochemical problem. The aldehyde class represented by **32c** with an "easily reducible" Ψ-group now had to be reducible via ionic/polar methods: radical methods were evidently untenable due to the operation of this pathway. This meant that continued study with aldehydes **32cc** and **32cd** was likely to be fruitless, as would any approach where Ψ-reduction would involve a Barton deoxygenation. While the mechanisms of action of each of the variety of nickel desulfurization reagents employed are not all established, single-electron-transfer processes may well be involved.[50,51] Thus, it is possible that the production of **47** (as four possible diastereomers) is at least partly responsible for the complex mixtures obtained in many of the desulfurization attempts.

Nevertheless, the development of the vinyl iodide **36'** and the demonstration of effective nucleophile generation/three component coupling thereof meant that the natural product could be accessed in as few as two additional steps, if (*S*)-2-methylbutanal **5** were used as the terminal electrophile in the three component coupling. The coupling reaction of these components was thus investigated **(Scheme 2-28)**. Unfortunately, with this set of components, the coupling is not only much less efficient but it is also complicated by the presence of a ubiquitous byproduct that is formed in almost all of the

silyl glyoxylate aldol reactions studied to date. Namely, silyl glyoxylates are known to undergo facile hydride addition, either from organometallics such as diethylzinc[16] or metal alkoxides.[11,13] The resultant glycolate enolate can engage additional silyl glyoxylate and oligomerize, or it can engage the terminal electrophile and lead to three component coupling products. In this particular reaction, the byproduct **48** is formed as a mixture of four diastereomers, which happen to coelute with the two diastereomers of desired product **37**. Typically, multiple repetitions of standard flash column chromatography as well as HPLC attempts are required to achieve even a poor level of purity (~2:1 **37**:**48**).

Scheme 2-28. Three Component Coupling of **5**, **16a**, and **36**

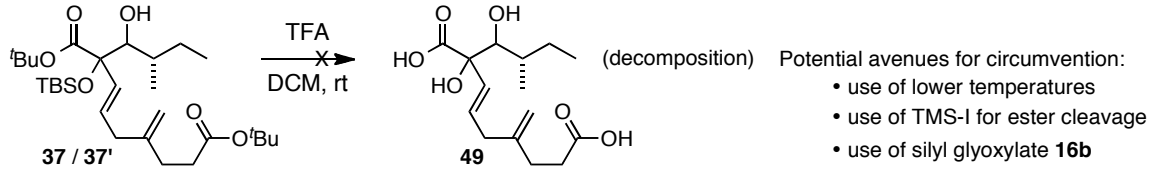


In these three component coupling reactions, there are multiple sources of hydride: any leftover ^{i}PrMgCl•LiCl, alkoxides present in its THF solution, or the alkoxides generated in the reaction (from desired product, direct nucleophile-electrophile pairing, or even hydride reduction of the aldehyde). It should be noted that H^- addition/three component coupling products analogous to **48** had been observed before, but they had previously been easily separated from the desired product. Here, the separation is laborious, and has yet to be successfully accomplished.

Nevertheless, given that the natural product is potentially only two steps (and diastereomer separation) away at this point, efforts to reach the end are currently underway. The plan has been to use acidic conditions to cleave the *tert*-butyl esters and the silyl group (outlined in **Scheme 2-21**, above) in **37**, revealing a diacid. It has been

anticipated that DCC coupling of pyrone **4** with such a diacid would be selective for the least-hindered site, and lead to the natural product. Work with other intermediates such as **18** and **19** has shown that they can undergo an ester/silyl deprotection upon treatment with TFA in dichloromethane without event. Despite those promising results, this particular substrate **37** displays appreciable sensitivity to acid, leading to decomposition under identical conditions **(Scheme 2-29)**. Preliminary results indicate that reduced temperatures and/or reaction times may be inroads to address this issue. Alternatively, ester cleavage may be effected via a hard Lewis acid/soft Lewis base reagent like TMS–I.[59] Another potential approach would be to use different esters which may be more prone to cleavage under non-acidic conditions (such as Et or Bn).[60] Such a modification would also highlight the versatility of the silyl glyoxylates in the approach to alternaric acid: judicious choice of coupling partners (for example, exchanging **16b** for **16a**) would allow for tuning the functionalities in the three component coupling product and their ability to be manipulated orthogonally.

Scheme 2-29. Attempted Completion of Alternaric Acid



2.4 Conclusion

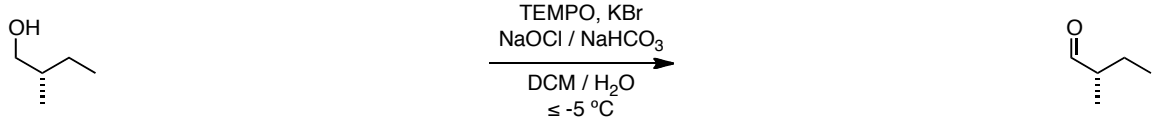
Efforts aimed toward the total synthesis of alternaric acid, an antifungal/phytotoxic natural product, have been described. These efforts were initiated as a demonstration of the unique ability of silyl glyoxylates **16** to forge fully substituted glycolic acid subunits by three component coupling with nucleophiles and terminal

electrophiles. At its current stage, this chapter has demonstrated that ability in a variety of unanticipated ways. The initially planned use of (*S*)-2-methylbutanal as the terminal electrophile was fraught with a problematic lack of stereoselectivity, as well as an inability to separate the diastereomers of the product formed. The attempts to address these issues have demonstrated that there is significant latitude with respect to substituents tolerated on the reaction partners in these three component couplings, as well as the degree to which these can exert stereochemical control. Another significant finding in this chapter has been a method to utilize functionalized vinyl iodides as precursors to effective nucleophiles, which will go a long way toward streamlining this particular synthesis as well as increasing the demonstrated utility of silyl glyoxylates. While the natural product has yet to succumb to total synthesis, the work herein has provided significant insights as to how to achieve such a goal using silyl glyoxylates.

2.5 Experimental

Materials and Methods: General. 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 300, Avance 400, DRX 400, or 600 MHz (^{1}H NMR at 300, 400, 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 (app = apparent, s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet),

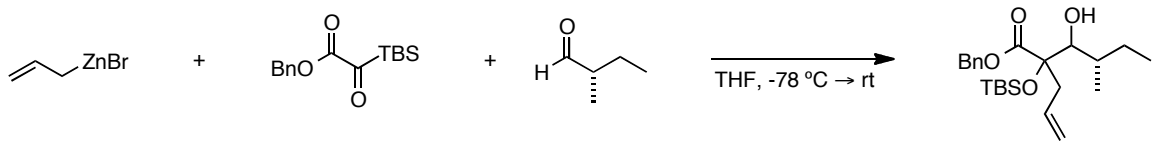
coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution ($KMnO_4$), or aqueous ceric ammonium molybdate solution (CAM) followed by heating. Flash column 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 chapter's tables and schemes. The diastereomer ratios reported are for crude reaction mixtures. Reactions were performed in oven- or flame-dried glassware equipped with Teflon coated stir bars in solvents that had been dried by passage through a column of neutral alumina under nitrogen prior to use, unless otherwise stated. When reagents that are not commercially available were employed, a reference for the compound has been provided in the procedure. All other reagents were obtained from commercial sources and used as received, unless otherwise noted.



(*S*)-2-methylbutanal (5). This reaction was performed according to the reported procedure,[61] with slight modifications. To a solution of (*S*)-2-methylbutanol (5 mL,

4.095 g, 46.5 mmol, 1.0 equiv.) in DCM (15 mL) was added TEMPO (73 mg, 0.465 mmol, 0.01 equiv.). A solution of potassium bromide (553 mg, 4.65 mmol, 0.10 equiv.) in H_2O (approx. 2 mL) was added, and the resulting biphasic mixture was cooled in an ice/salt/brine bath for 15 min. Sodium bicarbonate (840 mg) was added to buffer the commercial aqueous solution of sodium hypochlorite (0.7M, 73 mL, 51.1 mmol, 1.1 equiv.), which was placed in a pressure-equalizing addition funnel. The buffered oxidant solution was added dropwise to the reaction mixture such that the total time for addition was 15-20 min (approx. 1 drop/sec). After 5 additional min, the reaction was allowed to warm to room temperature, and after an additional 5 min the layers were separated. The aqueous layer was extracted with additional DCM (3 x 25 mL), and the combined organic extracts were washed with 1M HCl (30 mL) to which KI (approx. 300 mg) had been added (this treatment caused the organic layer to become deep red). The organic layer was subsequently washed with H_2O (30 mL), sat. aq. $Na_2S_2O_3$ (30 mL), H_2O (30 mL), sat. $NaHCO_3$ (30 mL), H_2O (30 mL), brine (30 mL), and dried over Na_2SO_4. The mixture was filtered, and the bulk of the solvent was distilled at atmospheric pressure until the vapor temperature began to rise past 40 ºC. At this point, the dilute solution of aldehyde in DCM was stored in the freezer until ready for use. Prior to use, a portion of the stock aldehyde solution was distilled further using a microscale Hickman distillation tube; the desired aldehyde was distilled from the less volatile acid (from overoxidation) and aldehyde decomposition byproducts. The residual DCM content was quantified by NMR, and the aldehyde was typically used as a concentrated solution. This treatment led to aldehyde loss (early portions of its azeotrope with DCM were discarded), but it

avoided the total decomposition of the aldehyde, which has an exceedingly short shelf-life when highly concentrated (~1 week in the glovebox freezer).

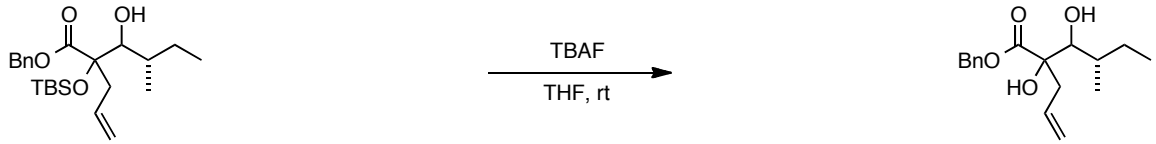


(4*S*)-benzyl 2-allyl-2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methylhexanoate (18b). Allylzinc bromide was prepared analogously to a reported procedure.[62] The zinc dust could be activated either with 1,2-dibromoethane/TMSCl[62] or using Br_2. A typical preparation using the latter method will be described: a dry flask with stir bar was charged with Zn dust (~330 mg, approx. 5 mmol, 1.2 equiv.) in the glovebox, sealed with a septum, and brought out of the glovebox. THF (4 mL) was added, and the vigorously stirred suspension was cooled to 0 ºC for 5 min and Br_2 (0.03 mL, 0.5 mmol, 0.10 equiv relative to Zn^0) was added dropwise. The Br_2 color quickly dissipated, and after an additional 5 min allyl bromide (0.35 mL, 4 mmol, 1.0 equiv.) was added dropwise. The suspension was stirred at 0 ºC for 1 h, at which point stirring was stopped and the excess of Zn dust was allowed to settle. The solution of allylzinc bromide thus prepared was assumed to be 1.0 M.

The appropriate amount of such a solution (in this case: 0.30 mL, 0.30 mmol, 1.5 equiv.) was added to a stirred solution of Bn/TBS silyl glyoxylate **16b** (56 mg, 0.20 mmol, 1.0 equiv.) and (*S*)-2-methylbutanal **5** (0.30 mmol, 1.5 equiv.) in 3 mL THF, which had been cooled to -78 ºC for ≥15 min. The bright yellow gold color due to **16b** dissipated, and 15 min later the reaction was warmed to rt for 3 h and quenched with sat. NH_4Cl (5 mL).

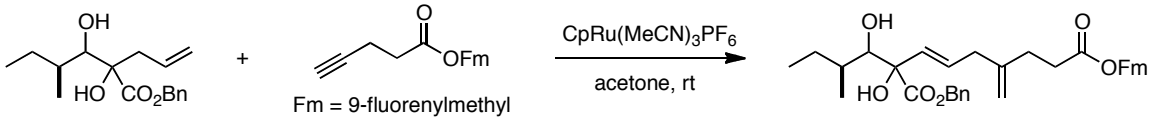
The mixture was diluted with H_2O (30 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated *in vacuo*, and the residue was purified via flash column chromatography eluting with 2.5% Et_2O/hexanes. "Diastereomers A" eluted first, followed by "diastereomers B" (typically with mixed fractions in between), and the combined yield in this run was 48 mg (0.118 mmol, 60% yield) of approx. 1:2.4 "diastereomers A":"diastereomers B". **^{1}H NMR** for **18b**, "diastereomers A": (400 MHz, $CDCl_3$): *major diastereomer*: δ 5.76-5.60 (m, 1H), 5.70-5.60 (m, 2H), 5.60-4.48 (m, 2H), 3.67 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.72-2.62 (m, 1H), 2.62-2.52 (m, 1H), 2.0 (d, *J* = 10.8, 1H), 1.45-1.35 (m, 2H), 1.20-1.08 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 3H), 0.19 (s, 3H), 0.15 (s, 3H); *resolved signals for minor diastereomer*: δ 3.59 (dd, *J* = 10.4, 6.6 Hz, 1H), 1.80 (d, *J* = 10.4 Hz, 1H), 1.70-1.60 (m, 1H), 1.55-1.45 (m, 1H), 0.95-0.88 (m, 1H), 0.88 (s, 9H), 0.83-0.77 (m, 6H), 0.17 (s, 3H), 0.16 (s, 3H); **TLC** (5% EtOAc/hexanes) R_f 0.27 (CAM). Analytical data for **18b**, "diastereomers B": **IR** (thin film, cm^{-1}): 3464, 3078, 2957, 2930, 2857, 1750, 1641, 1462, 1388, 1254, 1215, 1139, 919, 837, 778; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer*: δ 7.5 (br s, 5H), 5.78-5.75 (m, 1H), 5.15 (d, *J* = 12 Hz, 1H), 5.12 (d, *J* =12 Hz, 1 H), 5.06 (app d, *J* = 12 Hz, 2H), 3.66 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.66 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.53 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.36 (d, *J* = 10.8 Hz, 1H), 1.70-1.60 (m, 1H), 1.45-1.39 (m, 1H), 1.30-1.24 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.15 (s, 3H), 0.12 (s, 3H); *resolved signals for minor diastereomer*: δ 3.56 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.30 (d, *J* = 9.6 Hz, 1H), 0.93 (d, *J* = 7.2

Hz, 3H), 0.83 (t, J = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers* δ 174.0, 173.8, 134.94, 134.90, 132.8, 132.6, 128.9, 128.8, 128.61, 128.59, 128.57, 119.0, 118.9, 83.0, 82.7, 80.3, 78.1, 67.34, 67.27, 42.3, 41.9, 35.1, 34.4, 28.7, 26.2, 26.1, 23.0, 19.0, 17.6, 12.9, 11.9, 11.6, -2.0, -2.2, -2.46, -2.54 (two coincident resonances); **TLC** (5% EtOAc/hexanes), R_f 0.18 (CAM); **LRMS** (ESI): Calcd. for $C_{23}H_{38}O_4$+Na: 429.24, Found: 429.25.



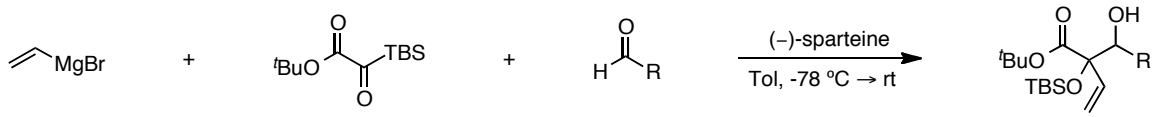
(4*S*)-benzyl 2-allyl-2,3-dihydroxy-4-methylhexanoate (9c). Three component coupling product **18b** (180 mg, 0.443 mmol, 1.0 equiv.) was dissolved in 2 mL THF and then TBAF (1M in THF, 2.2 mL, 2.2 mmol, 5 equiv.) was added and the reaction was stirred at room temperature for 1.5 h. The reaction was poured into H_2O (50 mL), and the layers were shaken and separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), then dried over $MgSO_4$. Purification of the residue via flash column chromatography using 15% EtOAc/hexanes afforded 100 mg of the product as a clear oil (0.342 mmol, 77% yield). Analytical data for **9c**: **^{1}H NMR** (400 MHz, $CDCl_3$): *major diastereomer*: δ 7. 37 (br s, 5H), 5.75-5.48 (m, 1H), 5.23 (d, J = 12 Hz, 1H), 5.17 (d, J = 12 Hz, 1H), 5.05-4.98 (m, 2H), 3.83 (dd, J = 10.8, 1.6 Hz, 1H), 3.49 (s, 1H), 2.49-2.40 (m, 2H), 2.13 (d, J = 10.8 Hz, 1H), 1.78-1.55 (m, 1H), 1.50-1.39 (m, 1H), 1.37-1.28 (m, 1H), 0.95-0.85 (m, 6H); *resolved signals for the minor diastereomer*: δ 3.71 (dd, J = 11.2,

2.8 Hz, 1H), 3.49 (s, 1H), 2.12 (d, J = 11.2 Hz, 1H), 1.01 (d, J = 7.2 Hz, 3H); **TLC** (15% EtOAc/hexanes), R_f 0.44 (CAM)

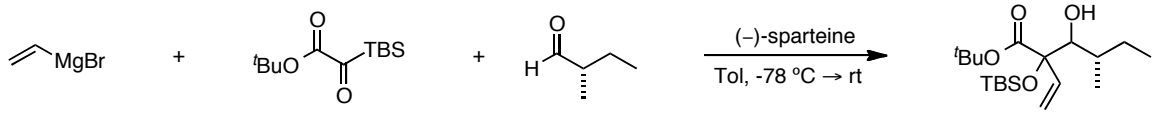


(*E*)-9-(9-fluorenylmethyl) 1-benzyl 2-hydroxy-2-((2*S*)-1-hydroxy-2-methylbutyl)-6-methylenenon-3-enedioate (13d). A vial was charged with cyclopentadienylruthenium (tris-acetonitrile) hexafluorophosphate (3 mg, 0.0075 mmol, 0.10 equiv.) and a stir bar. A solution of **9c** (22 mg, 0.075 mmol, 1.0 equiv.) and (9-fluorenylmethyl)-4-pentynoate **10d** (21 mg, 0.075 mmol, 1.0 equiv.) in 0.80 mL acetone was added and the reaction was stirred overnight (~18 h), and then poured into H_2O (10 mL). The cloudy mixture was extracted with Et_2O (3 x 5 mL), and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Purification of the residue via flash column chromatography using 15% EtOAc/hexanes as eluent afforded 22 mg of the product as a clear oil (0.0387 mmol, 52% yield). Analytical data for **13d**: **^{1}H NMR** (400 MHz, $CDCl_3$): *major diastereomer*: δ 7.77 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.45-7.28 (m, 9H), 6.05-5.95 (m, 1H), 5.58 (d, J = 15.2 Hz, 1H), 5.28 (d, J = 9 Hz, 1H), 5.22 (d, J = 9 Hz, 1H), 4.75 (s, 1H), 4.73 (s, 1H), 4.39 (d, J = 7.2 Hz, 2H), 4.20 (t, J = 7.2 Hz, 1H), 3.98 (m, 1H), 3.62 (s, 1H), 2.76 (m, 2H), 2.51 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.10 (d, J = 10.2 Hz, 1H), 1.78-1.55 (m, 1H), 1.50-1.39 (m, 1H), 1.37-1.28 (m, 1H), 0.95-0.85 (m, 6H); *resolved signals for the minor diastereomer*: δ 7.53 (d, J = 7.6 Hz, 2H), 3.85 (m, 1H), 3.66 (s, 1H), 0.95 (d, J = 6.8 Hz, 3H) **TLC** (20% EtOAc/hexanes) R_f 0.29 (CAM).

General Procedure A: Three Component Coupling Reactions With Vinyl Grignard

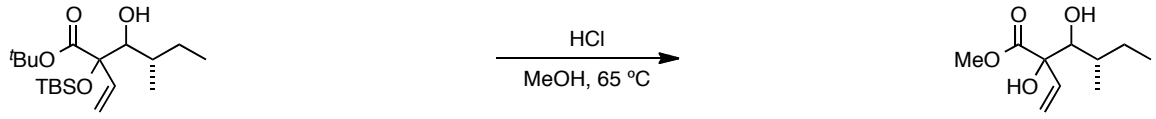


To a solution of (–)-sparteine (1.5 equiv.) in dry toluene at -78 ºC under N_2 was added a solution of vinylmagnesium bromide (solution in THF, 1.5 equiv.). A solution of silyl glyoxylate **16** (1.0 equiv.) and an aldehyde (1.5 equiv.) in dry toluene was prepared and cooled to -78 ºC for ≥15 min, at which point the (–)-sparteine/Grignard solution was transferred into the reaction via cannula. After an additional 15 min, the solution was warmed to room temperature and stirred for ≥1.5 h before quenching with 10% aq. AcOH (v/v). The reaction was diluted with H_2O, the layers were separated, and the aqueous layer was extracted with Et_2O three times. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via flash column chromatography using the indicated solvent system. This procedure was used to investigate the three component coupling reactions with all aldehydes of type **32**, although particular details for all of these will not be reproduced here.



(4*S*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methyl-2-vinylhexanoate (19). This reaction was conducted according to General Procedure A, using vinylmagnesium bromide (0.7M in THF, 7.6 mL, 5.31 mmol, 2 equiv.) complexed with (–)-sparteine (1.24 g, 5.31 mmol, 2 equiv.) in 20 mL toluene, which was added to a solution

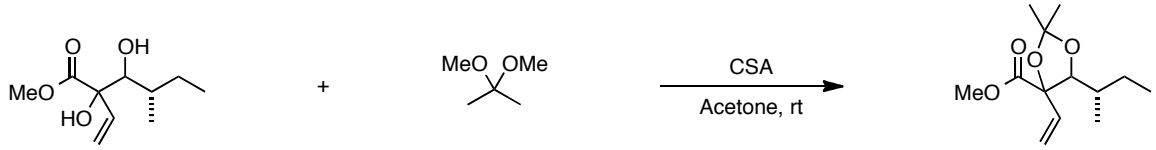
of ^{t}Bu/TBS silyl glyoxylate **16a** (650 mg, 2.65 mmol, 1.0 equiv.), and (*S*)-2-methylbutanal **5** (5.31 mmol, 2 equiv.) in 40 mL dry toluene. In this particular run, the yield was 610 mg of product as a clear, slightly yellow oil (1.7 mmol, 64% yield). The dr was > 20:1 *syn*:*anti*, ≤1.7:1 facial selectivity (**19a**:**19a'**). Over many iterations of this reaction, the isolated yield was generally 50–65% depending on the phases of the moon. Analytical data for **19a**/**19a'**: **IR** (thin film, cm^{-1}): 3582, 3480, 2959, 2931, 2858, 1747, 1639, 1472, 1463, 1393, 1369, 1253, 1156, 1056, 1005, 926, 838, 780; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* **19a**: δ 5.95 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.40 (d, *J* = 17.4 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 3.72 (dd, *J* = 10.8, 3 Hz, 1H), 2.41 (d, *J* = 10.8 Hz, 1H), 1.75-1.65 (m, 2H), 1.49 (s, 9H), 1.28-1.22 (m, 1H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.20 (s, 3H), 0.11 (s, 3H); *resolved signals for minor diastereomer* **19a'**: δ 5.39 (d, *J* = 17.4 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 3.60 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.22 (d, *J* = 10.8 Hz, 1H), 0.12 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers*: δ 171.8, 171.6, 138.4, 138.3, 116.1, 115.8, 84.3, 83.8, 82.4, 82.3, 80.7, 78.8, 36.3, 35.3, 28.6, 27.97, 27.96, 26.37, 26.33, 24.0, 19.18, 19.14, 17.7, 13.6, 11.7, 11.4, -2.26, -2.29, -2.38 (two coincident resonances); **TLC** (5% EtOAc/hexanes), R_f 0.26 (CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{38}O_4$+Na: 381.24, Found: 381.25.



(4*S*)-methyl 2,3-dihydroxy-4-methyl-2-vinylhexanoate (20/20'). The title compound was prepared using a solution of methanolic HCl, generated as follows: to a long test tube containing methanol (~10 mL) was carefully added acetyl chloride (0.21 mL, 0.231 g, 3 mmol, 3 equiv.) slowly, dropwise (audible popping sound). This solution was used to

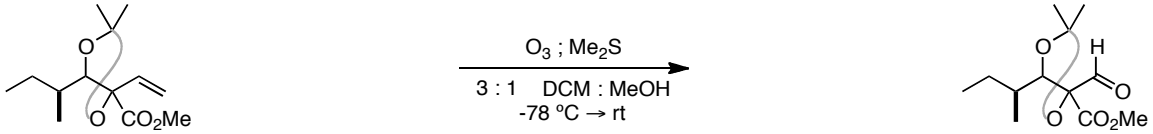
dissolve the starting material **19a/19a'** (359 mg, 1.0 mmol, 1.0 equiv.) and transfer it to a 50 mL round bottomed flask equipped with a stir bar, to which was subsequently affixed a reflux condenser. Another 3 mL of methanol was used to ensure complete transfer of the starting material to the reaction flask. The reaction was heated to reflux, open to air, until it was judged complete by TLC analysis (a compound of intermediate R_f, isolated once and determined to be the desilylated *tert*-butyl ester, appears *en route* to the desired product of lower R_f). Upon completion, the reaction was poured into a separatory funnel containing H_2O (~75 mL), and Et_2O (~10 mL) was added to form two layers, which were shaken and separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), and dried over $MgSO_4$. Filtration and careful concentration *in vacuo* afforded 200 mg (~1 mmol, quant. yield) of the title compound **20/20'** as a clear oil, which required no further purification. Purification in an attempt to separate the diastereomers at this stage was unsuccessful. Analytical data for **20/20'**: **IR** (thin film, cm^{-1}): 3499, 2960, 2934, 2877, 1738, 1638, 1462, 1439, 1402, 1245, 1170, 1004, 932, 789; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* **20**: δ 5.91 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.59 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.25 (d, *J* = 10.8, 1.2 Hz, 1H), 3.95 (d, *J* = 1.8 Hz, 1H), 3.81 (s, 3H), 3.6 (br s, 1H), 2.1 (br s, 1H), 1.70-1.60 (m, 1H), 1.45-1.38 (m, 1H), 1.30-1.20 (m, 1H), 0.90-0.85 (m, 6H); *resolved signals for minor diastereomer* **20'**: δ 5.94 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.57 (d, *J* = 17.4, 1.2 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.80 (s, 3H), 1.75-1.65 (m, 2H), 1.10-1.00 (m, 1H), 0.95 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers*: δ 175.1, 175.0, 135.6, 135.2, 116.1, 115.9, 81.9, 81.8, 78.2, 75.8, 53.50,

53.47, 36.0, 35.3, 28.2, 22.8, 17.4, 12.8, 11.8, 11.5; **TLC** (20% EtOAc/hexanes), R_f 0.21 (CAM only); **LRMS** (ESI): Calcd. for $C_{10}H_{18}O_4$+Na: 225.11, Found: 225.12.



Methyl 5-((*S*)-*sec*-butyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane-4-carboxylate (E-1). To a solution of **20/20'** (200 mg, approx. 1 mmol, 1.0 equiv.) and 2,2-dimethoxy propane (5 mL) in acetone (5 mL) was added (±)-camphorsulfonic acid (46 mg, 0.2 mmol, 0.2 equiv.). The reaction was stirred at room temperature without rigorous exclusion of air and moisture until TLC analysis indicated complete consumption of **20/20'**. The reaction was quenched with 5% Et_3N/hexanes (2mL) and concentrated *in vacuo*. The residue was purified via flash column chromatography using 15% Et_2O/hexanes as eluent to afford 204 mg (0.84 mmol, 84% in the two steps from the three component coupling) of **E-1** as a clear oil. Attempted diastereomer separation at this stage was also unsuccessful. Analytical data for **E-1**: **IR** (thin film, cm^{-1}): 2965, 2878, 1737, 1638, 1381, 1261, 1218, 1119, 1039, 929, 891; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer*: δ 6.04 (dd, *J* = 16.8, 13.2 Hz, 1H), 5.54 (d, *J* = 16.8 Hz, 1H), 5.33 (d, *J* = 13.2 Hz, 1H), 4.13 (d, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 1.72-1.60 (m, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.15-1.10 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); *resolved signals for minor diastereomer*: δ 6.08 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 4.09 (d, *J* = 9.6 Hz, 1H), 1.46 (s, 3H), 1.28-1.20 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers*: δ 172.97, 172.93, 133.8, 133.5, 117.3, 117.1, 109.2, 86.0, 85.5, 85.2, 85.0, 52.7, 35.0, 34.5, 27.24, 27.20, 26.1, 25.9, 25.1, 25.0, 15.6, 14.8, 11.1, 10.2 (two

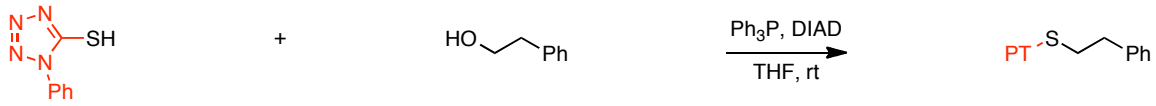
coincident resonances, likely 109.2 and 52.7); **TLC** (20% EtOAc/hexanes), R_f 0.55 (CAM only); **LRMS** (ESI): Calcd. for $C_{13}H_{22}O_4$+Na: 265.14, Found: 265.14



Methyl 5-((*S*)-*sec*-butyl)-4-formyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2/2'). A solution of **E-1** (41 mg, 0.169 mmol, 1.0 equiv.) in 4 mL DCM:MeOH (3:1) was cooled to -78 ºC and sparged with N_2 for 5 min. Ozone was subsequently passed through the solution until the characteristic blue color of ozone saturation was achieved (~10 min). TLC analysis indicated complete consumption of **E-1**, and the solution was sparged with N_2 until colorless again. Dimethyl sulfide (0.06 mL, 53 mg, 5.0 equiv.) was added, and the reaction was allowed to warm to room temperature and stirred overnight (12 h). TLC analysis to ensure the absence of peroxides was performed, and the reaction mixture was poured into H_2O (50 mL). The layers were separated, the aqueous layer was extracted with 1:1 Et_2O/pentanes (3 x 10 mL), and the combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), and dried over $MgSO_4$. Filtration and careful concentration *in vacuo* afforded the crude aldehyde which was purified on a silica column that had been packed with 5% Et_3N/hexanes and flushed with pentanes. Elution with 10% Et_2O/pentanes afforded 36 mg (0.147 mmol, 87% yield) of the desired product **2/2'** as a clear oil. Analytical data for **2/2'**: **IR** (thin film, cm^{-1}): 2967, 2938, 2879, 1754, 1737, 1637, 1459, 1438, 1384, 1261, 1221, 1095, 1071, 881; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer*: δ 9.69 (s, 1H), 4.39 (*d, J* = 7.8 Hz, 1H), 3.83 (s, 3H), 1.78-1.70 (m, 1H), 1.66 (s, 3H), 1.63-1.55 (m, 1H), 1.43 (s, 3H), 1.25-1.15 (m, 1H), 0.97 (d, *J*

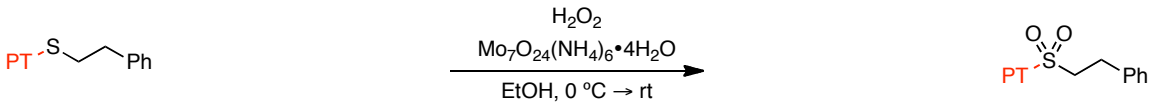
= 6.6 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); *resolved signals for minor diastereomer*: δ 9.68 (s, 1H), 4.33 (d, *J* = 9.6 Hz, 1H), 1.70-1.66 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers*: δ 196.8, 196.5, 111.5, 111.4, 87.8, 87.3, 86.5, 86.3, 53.2, 53.1, 34.2, 33.9, 30.3, 27.02, 26.99, 26.4, 25.9, 25.0, 15.8, 14.7, 11.1, 10.2 (two coincident resonances); **TLC** (10% EtOAc/hexanes, pretreated plate), R_f 0.19 (CAM only); **LRMS** (ESI): Calcd. for $C_{12}H_{20}O_5$+Na: 267.12, Found: 265.12

Preparation of Sulfones for and Execution of Modified Julia Olefination:

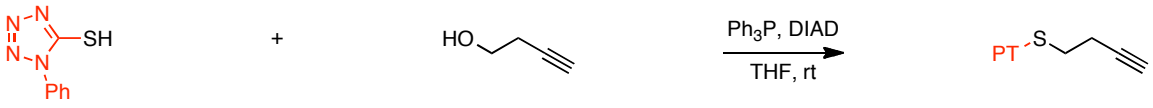


5-(phenethylthio)-1-phenyl-1*H*-tetrazole (E-2). This procedure is representative of another Mitsunobu reaction with this thiol (*vide infra*). To a solution of triphenylphosphine (1.062 g, 4.05 mmol, 1.53 equiv.), 1-phenyl-1*H*-tetrazole-5-thiol (0.943 g, 5.29 mmol, 2 equiv.), and 2-phenylethanol (0.32 mL, 0.323 g, 2.65 mmol, 1.0 equiv.) in THF (25 mL) at 0 ºC was added diisopropylazodicarboxylate (1 mL, 0.974 g, 4.815 mmol, 1.82 equiv.), which caused the solution to turn bright yellow. The reaction allowed to warm to room temperature and stirred overnight (16 h) until it was poured into a solution of 80 mL brine and 20 mL H_2O. The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined extracts were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to a sticky yellow semisolid. Purification was effected using a dry-loaded silica gel column, eluting with 10% EtOAc/hexanes to afford 700 mg (2.6 mmol, 98% yield) of the desired product as a thick oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56 (br s, 4H), 7.35-7.25 (m,

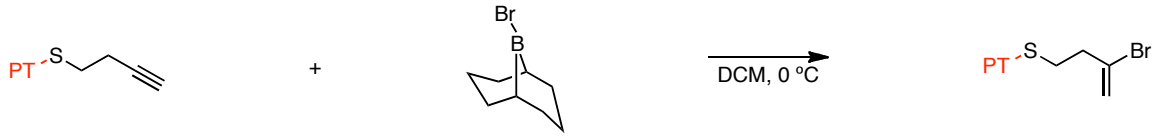
6H), 3.64 (d, J = 7.2 Hz, 2 H), 3.16 (d, J = 7.2 Hz, 2 H); **TLC** (20% EtOAc/hexanes) R_f 0.45 (UV/CAM).



5-(phenethylsulfonyl)-1-phenyl-1*H*-tetrazole (21a). This procedure is representative of the oxidation of a sulfide to a sulfone, and was quite general for a variety of substrates. A solution of the sulfide (700 mg, 2.6 mmol, 1.0 equiv.) in EtOH (25 mL) was cooled to 0 ºC while a solution of ammonium molybdate tetrahydrate in 30% aq. H_2O_2 (240 mg/mL) was prepared. This bright yellow solution (3 mL) was added to the solution of the substrate in EtOH, and allowed to warm to room temperature with stirring overnight open to air. The reaction was poured into 100 mL H_2O and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to a solid which required no further purification (735 mg, 90% yield). Analytical data for **21a**: **IR** (thin film, cm^{-1}): 3065, 3030, 2920, 1595, 1498, 1456, 1342, 1238, 1154, 1076, 916, 764; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (m, 2H), 7.66-7.60 (m, 3H), 7.36 (m, 2H), 7.30-7.26 (m, 3H), 4.01 (m, 2H), 3.28 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): 153.3, 136.3, 132.9, 131.5, 129.7, 129.0, 128.5, 127.4, 125.0, 57.2, 28.4; **TLC** (20% EtOAc/hexanes), R_f 0.22 (UV; faint in CAM); **LRMS** (ESI): Calcd. for $C_{15}H_{14}N_4O_2S$+Na: 337.07, Found: 337.07; Calcd. for $C_{15}H_{14}N_4O_2S$+Cs: 446.99, Found: 446.99

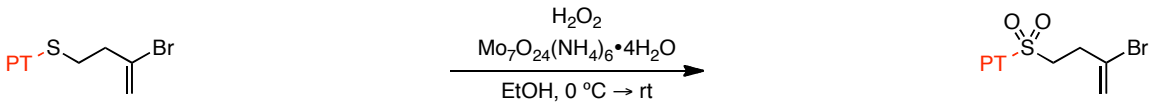


5-(but-3-yn-1-ylthio)-1-phenyl-1*H*-tetrazole (E-3). This reaction was performed according to the Mitsunobu procedure detailed above, using triphenylphosphine (2.24 g, 8.54 mmol, 1.53 equiv.), 1-phenyl-1*H*-tetrazole-5-thiol (2 g, 11.2 mmol, 2 equiv.), and 3-butyn-1-ol (0.42 mL, 0.391 g, 5.58 mmol, 1.0 equiv.), THF (50 mL), and diisopropylazodicarboxylate (2 mL, 2.054 g, 10.2 mmol, 1.82 equiv.) Partial purification was achieved using flash column chromatography, eluting with 20% EtOAc/hexanes. The isolated material was contaminated by the starting thiol, which could be conveniently removed via basic extraction to afford the desired product **E-3** 1.2 g (5.2 mmol, 93% yield) as a thick semisolid. Analytical data for **E-3**: **IR** (thin film, cm^{-1}): 3293, 3064, 2934, 2118, 1597, 1499, 1462, 1414, 1388, 1281, 1243, 1091, 1015, 762; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.58-7.50 (m, 5H), 3.53 (t, J = 7.2 Hz, 2H), 2.80 (dt, J = 6.6, 2.4 Hz, 2H), 2.05 (t, J = 2.4 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): 153.6, 133.5, 130.2, 129.8, 123.7, 81.1, 70.6, 32.0, 19.2; **TLC** (20% EtOAc/hexanes), R_f 0.25 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{11}H_{11}N_4S$+Na: 253.05, Found: 253.06; Calcd. for $C_{11}H_{10}N_4S$+Cs: 362.97, Found: 362.97



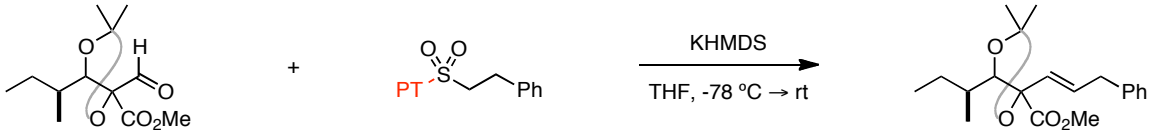
5-((3-bromobut-3-en-1-yl)thio)-1-phenyl-1*H*-tetrazole (E-4). This procedure was performed analogously to a literature procedure.[63] A cloudy suspension of sulfide **E-3** (1.2 g, 5.2 mmol, 1.0 equiv.) in dry DCM (50 mL) was cooled to 0 °C under N_2. A solution of 9-Br-9-BBN (1M in DCM, 6.25 mL, 6.25 mmol, 1.2 equiv.) was added, and the mixture gradually cleared noticeably and became a pale yellow solution as the reaction

was stirred for 3 h at 0 ºC. Glacial acetic acid (~4 mL) was added neat, dropwise to the reaction, followed 1 h later by 3M NaOH (25 mL) and 30% aq. H_2O_2 (10 mL). The biphasic mixture was stirred vigorously for 30 min, and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL), and the combined organic extracts were washed with brine (20 mL) and dried over Na_2SO_4. Concentration *in vacuo* and analysis of the crude mixture revealed that only approx. 33% conversion had occurred. Purification via flash column chromatography with 15% EtOAc/hexanes as eluent afforded 336 mg (1.08 mmol, 59% yield brsm) of the product as a clear oil. Analytical data for **E-4**: **IR** (thin film, cm^{-1}): 3101, 3064, 2927, 1628, 1597, 1499, 1412, 1387, 1244, 1188, 1090, 1015, 896, 761; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.57-7.50 (m, 5H), 5.67 (d, *J* = 1.8 Hz, 1H), 5.51 (d, *J* = 1.8 Hz, 1H), 3.59 (d, *J* = 7.2 Hz, 2H), 3.00 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): 153.7, 133.5, 130.4, 130.2, 129.8, 123.7, 119.5, 40.4, 31.4; **TLC** (20% EtOAc/hexanes), R_f 0.32 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{11}H_{11}BrN_4S$+Na: 332.98, Found: 332.98; Calcd. for $C_{11}H_{11}BrN_4S$+Cs: 442.89, Found: 442.90



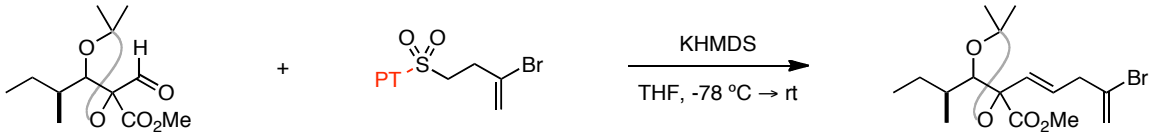
5-((3-bromobut-3-en-1-yl)sulfonyl)-1-phenyl-1*H*-tetrazole (21b). This oxidation was performed analogously to the oxidation above, using **E-4** (335 mg, 1.075 mmol, 1 equiv.), and of the ammonium molybdate/aq. H_2O_2 solution (240 mg/mL; 1.2 mL). Purification was effected using flash column chromatography using 20% EtOAc/hexanes as eluent to afford 330 mg (0.962 mmol, 89% yield) of the product **21b** as a white solid. Analytical

data for **21b**: **IR** (thin film, cm^{-1}): 2988, 2923, 1631, 1497, 1348, 1151, 903, 763, 688; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.65-7.60 (m, 3H), 5.81 (s, 1H), 5.56 (s, 1H), 3.99 (m, 2H), 3.11 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): 153.2, 132.8, 131.6, 129.8, 127.5, 125.0, 120.4, 54.6, 34.4; **TLC** (20% EtOAc/hexanes), R_f 0.24 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{11}H_{11}BrN_4O_2S$+Na: 364.97, Found: 364.97



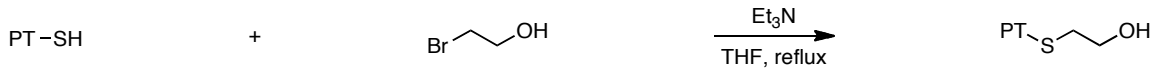
Methyl 5-((*S*)-*sec*-butyl)-2,2-dimethyl-4-((*E*)-3-phenylprop-1-en-1-yl)-1,3-dioxolane-4-carboxylate (22a/22a'). To a stirred solution of **21a** (33 mg, 0.104 mmol, 1.1 equiv.) in dry THF (1 mL) under N_2 and cooled to -78 ºC was added a solution of potassium hexamethyldisilazide (0.5M in toluene, 0.28 mL, 0.141 mmol, 1.5 equiv.), and the clear solution became yellow. After 15 min at this temperature, a solution of aldehyde **2** (23 mg, 0.094 mmol, 1.0 equiv.) in THF (1 mL) was added via syringe, followed by a THF rinse to ensure complete transfer (0.5 mL). The reaction was allowed to warm slowly to room temperature overnight (12 h), by which point the yellow color had faded and the reaction had become cloudy due to precipitate formation. TLC analysis indicated complete consumption of the aldehyde **2**, and the reaction was quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with Et_2O (5 mL) and H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified via flash column chromatography using 5% EtOAc/hexanes to afford 29 mg (0.087 mmol, 93% yield) of **22a/22a'** as a clear oil.

Analytical data for **22a/22a'**: **^{1}H NMR** (300 MHz, $CDCl_3$): *major diastereomer*: δ 7.30-7.26 (m, 2H), 7.22- 7.15 (m, 3H), 6.12-6.02 (m, 1H), 5.63 (d, *J* = 15.3 Hz, 1H), 4.11 (d, *J* = 5.1 Hz, 1H), 3.77 (s, 3H), 3.48-3.40 (m, 2H), 1.75-1.60 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.30-1.00 (m, 2H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); *resolved signals for minor diastereomer*: δ 5.72 (d, *J* = 15.3 Hz, 1H), 4.09 (d, *J* = 5.1 Hz, 1H), 1.43 (s, 3H); **TLC** (20% EtOAc/hexanes) R_f 0.51 (CAM).

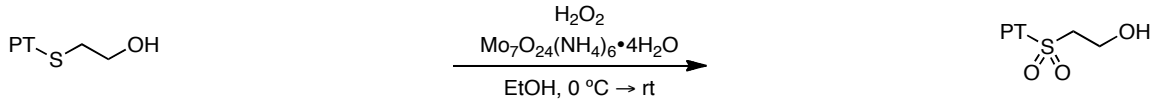


Methyl 4-((*E*)-4-bromopenta-1,4-dien-1-yl)-5-((*S*)-*sec*-butyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (22b/22b'). The reaction was performed according to the Julia olefination procedure above, using **21b** (42 mg, 0.123 mmol, 1.0 equiv.), KHMDS (0.5M in toluene, 0.37 mL, 0.184 mmol, 1.5 equiv.), and aldehyde **2/2'** (30 mg, 0.123 mmol, 1.0 equiv.) and the same volumes of THF. Purification was effected via flash column chromatography using 10%EtOAc/hexanes as eluent, to afford 35 mg (0.097 mmol, 79% yield) as a clear oil. Analytical data for **22b/22b'**: **IR** (thin film, cm^{-1}): 2964, 2936, 2877, 1738, 1630, 1460, 1435, 1381, 1371, 1259, 1216, 1117, 1065, 1033, 976, 893; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer*: δ 5.96-5.88 (m, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 5.6 (s, 1H), 5.45 (s, 1H), 4.11 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.23 (m, 2H), 1.72-1.65 (m, 2H), 1.53 (s, 3H), 1.44 (s, 3H), 1.43 (m, 1H), 0.87 (m, 6H); *resolved signals for minor diastereomer*: δ 5.82 (d, *J* = 15.6 Hz, 1H), 4.07 (d, *J* = 9.6 Hz, 1H), 1.445 (s, 3H), 1.25-1.15 (m, 1H), 1.15-1.05 (m, 1H), 0.97 (d, *J* = 6.6 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): *both diastereomers*: δ 172.92, 172.89, 131.7, 131.5, 129.3, 129.2, 128.2, 128.1,

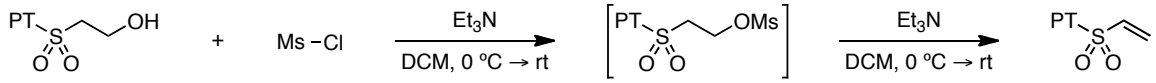
117.42, 117.38, 109.2, 86.1, 85.6, 84.8, 84.6, 52.7, 44.1, 35.0, 34.5, 27.29, 27.26, 26.1, 25.9, 25.0, 24.9, 15.6, 14.9, 11.1, 10.3 (three coincident resonances: likely 109.2, 52.7, and 44.1); **TLC** (10% EtOAc/hexanes, pretreated plate), R_f 0.38 (CAM only); **LRMS** (ESI): Calcd. for $C_{16}H_{25}BrO_4$+Na: 383.08, Found: 383.08; Calcd. for $C_{16}H_{25}BrO_4$+Cs: 493.00, Found: 493.00



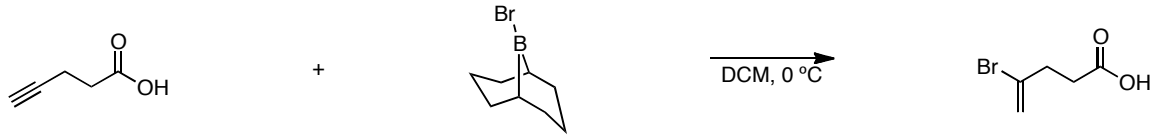
2-((1-Phenyl-1*H*-tetrazol-5-yl)thio)ethanol (E-5). To a solution of 2-bromoethanol (1.13 mL, 2 g, 16 mmol, 1 equiv.) and 1-phenyl-1*H*-tetrazole-5-thiol (2.85 g, 16 mmol, 1 equiv.) in THF (~100 mL) was added triethylamine (6.7 mL, 4.86 g, 48 mmol, 3 equiv.) and the solution was heated to reflux overnight (12 h). During this time, the reaction became cloudy with precipitated ammonium salts, which were filtered away. The mixture was concentrated *in vacuo* to an off-white residue, which was triturated with hexanes to remove residual THF to afford 3.45 g (15.5 mmol, 97% crude yield) of the desired sulfide **E-5** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60-7.55 (m, 5 H), 4.06 (d, J = 7.2 Hz, 2H), 3.57 (d, J = 7.2 Hz, 2H), 2.62 (br s, 1H).



2-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethanol (E-6) The crude sulfide **E-5** (3.4 g, 15.3 mmol) was oxidized according to the procedure described above using the ammonium molybdate/aq. H_2O_2 solution (240 mg/mL, 17.3 mL) in 200 mL EtOH. The crude product **E-6** was obtained as a white solid 3.35 g (13.1 mmol, 86% crude yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72-7.58 (m, 5H), 4.24 (m, 2H), 3.95 (m, 2H), 2.59 (br s, 1 H).

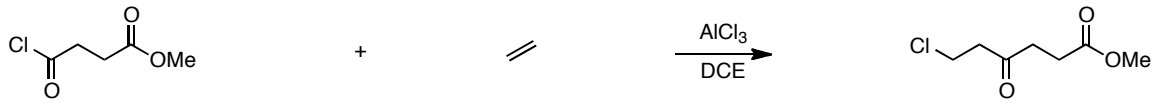


1-phenyl-5-(vinylsulfonyl)-1*H*-tetrazole (25). To a solution of the crude sulfone **E-6** (3 g, 11.8 mmol, 1.0 equiv.) and triethylamine (4.94 mL, 3.58 g, 35.4 mmol, 3 equiv.) in DCM (50 mL) at 0 ºC was added methanesulfonyl chloride (1.37 mL, 2.03 g, 17.7 mmol, 1.5 equiv.), dropwise. The reaction was allowed to warm slowly to rt over 3 h, then poured into H_2O (150 mL) and the layers were shaken and separated. The organic layer was extracted with DCM (3 x 30 mL), and the combined organic extracts were washed with H_2O (40 mL), brine (40 mL), and dried over Na_2SO_4. Concentration *in vacuo* and purification via flash column chromatography using 30% EtOAc/hexanes as eluent afforded 560 mg (2.37 mmol, 20% yield) of the desired product **25** as a white solid. Analytical data for **25**: IR (thin film, cm^{-1}): 3109, 3068, 1749, 1606, 1594, 1498, 1462, 1386, 1347, 1153, 1108, 1049, 1015, 989, 947, 916, 765, 747, 690, 661; **^{1}H NMR** (600 MHz, $CDCl_3$): 7.68-7.59 (m, 5H), 7.12 (dd, J = 17.8, 10.8 Hz, 1H), 6.65 (d, J = 17.8 Hz, 1H), 6.48 (d, J = 10.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): 154.0, 135.1, 134.7, 132.9, 131.5, 129.7, 125.1; **TLC** (30% EtOAc/hexanes) R_f 0.26 (UV/CAM); **LRMS** (ESI): Calcd. for: $C_9H_8N_4O_2S$+Na: 259.03; Found: 259.04.



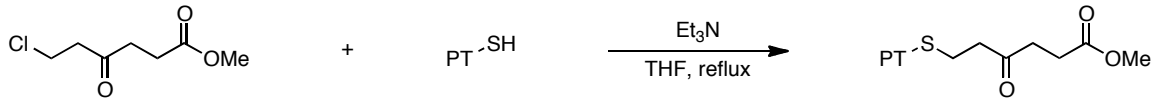
4-Bromopent-4-enoic acid (26'). To a solution of 4-pentynoic acid (196 mg, 2.0 mmol, 1 equiv.) in dry DCM (10 mL) under N_2 at 0 ºC was added 9-Br-9-BBN (1M in DCM, 4.4 mL, 4.4 mmol, 2.2 equiv.) and the clear pale yellow solution was stirred 3 h under N_2

at this temperature. Glacial acetic acid (1 mL) was added after this time, followed 1 h later by 3M NaOH (20 mL) and of 30% aq. H_2O_2 (3 mL), and the biphasic mixture was raised to room temperature and stirred vigorously for 30 min. The layers were separated, the aqueous layer was acidified to pH 1 with conc. HCl, and extracted with EtOAc (3 x 15 mL). The combined extracts were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified using 30% EtOAc/hexanes (to which ~1% v/v AcOH had been added) as eluent, affording 264 mg (1.48 mmol, 74% yield) of the desired product **26'** as a white solid. Analytical data for **26'**: IR (thin film, cm^{-1}): 3100, 3044, 2924, 2668, 1712, 1631, 1432, 1296, 1216, 1193, 1119, 893; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.50 (br s, 1H), 5.66 (d, *J* = 1.8 Hz, 1H), 5.45 (d, *J* = 1.8 Hz, 1H), 2.76 (t, *J* = 7.2 Hz, 1H), 2.64 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): 178.4, 131.7, 118.0, 36.3, 32.7; **TLC** (30% EtOAc/hexanes) R_f 0.25 (CAM).



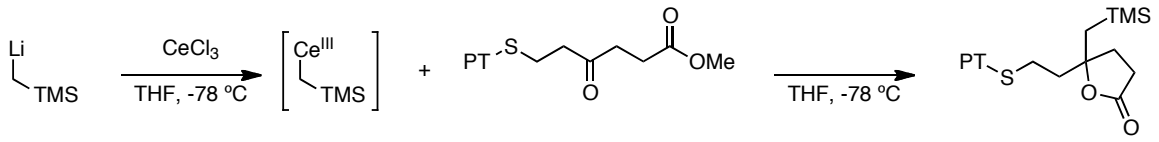
Methyl 6-chloro-4-oxohexanoate (27). This reaction was attempted according to a literature procedure.[64] To a suspension of aluminum chloride (11.9 g, 89.3 mmol, 1.2 equiv.) in dry 1,2-dichloroethane (50 mL) under N_2 was added methyl 4-chloro-4-oxobutanoate[64] (11.2 g, 74.4 mmol, 1.0 equiv.) dropwise via syringe. The suspension soon cleared and the resultant dark red-orange solution was placed in a 40 ºC heating bath. A stream of ethylene was bubbled gently through the solution for 75 min and then the reaction was poured onto icy 1M HCl, and the biphasic mixture was stirred vigorously

for 30 min before the layers were separated. The organic layer was dried over Na_2SO_4, and then a distillation from solid Na_2CO_3 was attempted, at which point it became evident that the reaction had been terminated prematurely: copious gas evolution and the precipitation of salts was observed. These salts were triturated with Et_2O, and 3 g (16.8 mmol, 22%) of **27** were obtained as a clear yellow oil. Analytical data for **27**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.75 (t, *J* = 6.8 Hz, 2H), 3.68 (s, 3H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H); this material was mixed with ~20% of the enone from elimination of the β-chloride: *resolved signals*: δ 6.38 (dt, *J* = 18, 10.4 Hz, 1H), 6.26 (dd, *J* = 18, 1.2 Hz, 1H), 5.88 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.70 (s, 3H), **TLC** (20% EtOAc/hexanes) R_f 0.30 (CAM only).



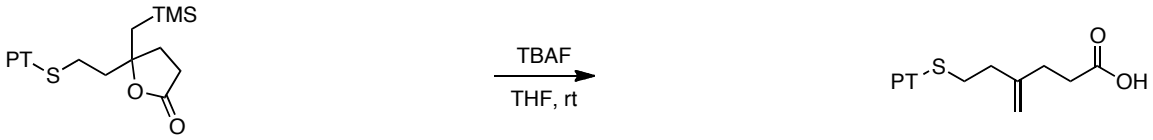
Methyl 4-oxo-6-((1-phenyl-1*H*-tetrazol-5-yl)thio)hexanoate (28). To a solution of **27** (1.33 g, 6.4 mmol, 1.0 equiv.) and 1-phenyl-1*H*-tetrazole-5-thiol (1.714 g, 9.62 mmol, 1.5 equiv.) in THF (~60 mL) was added triethylamine (2.70 mL, 1.95 g, 19.24 mmol, 3 equiv.) and the solution was heated to reflux overnight (12 h). The reaction had become cloudy due to precipitation of ammonium salts, and the mixture was cooled to room temperature then to 0 ºC. A solution of 1:1 Et_2O/hexanes (approx. 50 mL) was added to precipitate additional salts, which were removed by filtration. The filter cake was washed with Et_2O, and the filtrate was concentrated *in vacuo*. The crude residue was purified via flash column chromatography using 30% EtOAc/hexanes as eluent to afford 1.935 g (6.04 mmol, 94% yield) of the product **28** as a waxy solid. Analytical data for **28**: **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8 Hz, 2H), 7.58-7.47 (m, 3H), 4.64 (t, *J* = 6.8 Hz, 2H), 3.68 (s, 3H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H); **TLC** (30% EtOAc/hexanes) R_f 0.24 (UV/CAM)



5-(2-((1-phenyl-1*H*-tetrazol-5-yl)thio)ethyl)-5-((trimethylsilyl)methyl)dihydro-furan-2(3*H*)-one (29). This procedure was adapted from a literature procedure.[27] Cerium (III) chloride heptahydrate (652 mg, 1.75 mmol, 1.75 equiv.), was dried under vacuum at ~120 ºC for 2 h, and then cooled to room temperature under N_2. Dry THF (5 mL) was added, and the white suspension was stirred 2 h at room temperature before being cooled to -78 ºC. (Trimethylsilyl)methyllithium (0.7 M in THF, 2.14 mL, 1.5 mmol, 1.5 equiv.) was added and the slightly brownish suspension was stirred 30 min at -78 ºC prior to the addition of ketone **28** (320 mg, 1.0 mmol, 1.0 equiv.) as a solution in THF (1 mL). The reaction was stirred 4 h at -78 ºC, and then TMEDA (1 mL) was added. After 30 min the suspension was poured into sat. aq. $NaHCO_3$ (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined extracts were washed with 10% (v/v) aq. AcOH (10 mL) to break up the cerium emulsion, H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The mixture was concentrated *in vacuo* and the residue was purified via flash column chromatography using 30% EtOAc/hexanes as eluent to afford 265 mg (0.70 mmol, 70% yield) of the desired product **29** as a sticky semisolid. Analytical data for **29**: **IR** (thin film, cm^{-1}):

3066, 2952, 2898, 1770, 1596, 1498, 1415, 1369, 1251, 1167, 914, 847, 761; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.60-7.48 (m, 3H), 4.52 (m, 2H), 2.70-2.58 (m, 2H), 2.45-2.25 (m, 3H), 2.15-2.05 (m, 1H), 1.34 (d, *J* = 10.8 Hz, 1H), 1.23 (d, *J* = 10.8 Hz, 1H), 0.15 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 175.7, 163.1, 134.6, 129.6, 129.2, 123.7, 87.7, 43.8, 38.0, 33.8, 28.81, 28.79, 0.05; **TLC** (20% EtOAc/hexanes), R_f 0.22 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{17}H_{24}N_4O_2SSi$+Na: 399.13, Found: 399.12; Calcd. for $C_{17}H_{24}N_4O_2SSi$+Cs: 509.04, Found: 509.04

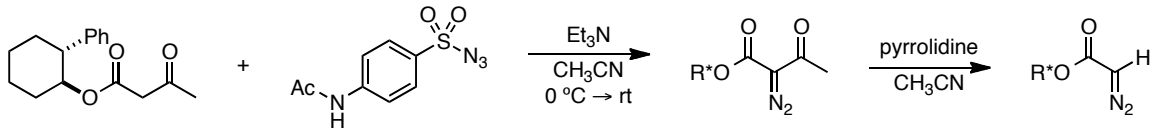


4-methylene-6-((1-phenyl-1*H*-tetrazol-5-yl)thio)hexanoic acid (30). To a solution of **29** (80 mg, 0.213 mmol, 1.0 equiv.) in THF (6 mL) was added tetrabutylammonium fluoride (1M in THF, 0.43 mL, 0.43 mmol, 2 equiv.). The reaction was stirred until TLC analysis indicated complete consumption of **29**, and the reaction was poured into 1M HCl (30 mL). The layers were shaken and separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue via flash column chromatography using 30% EtOAc/hexanes (to which ~1% v/v AcOH had been added) afforded 59 mg (0.168 mmol, 74% yield) of the product **30**. Analytical data for **30**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8 Hz, 2H), 7.60-7.45 (m, 3H), 4.89 (br s, 2H), 4.50 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.47 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 179.2, 163.2, 142.6,

134.8, 129.6, 129.3, 123.7, 113.0, 46.4, 34.0, 32.2, 30.2; **TLC** (50% EtOAc/hexanes + 1% AcOH) R_f 0.42 (UV/CAM)

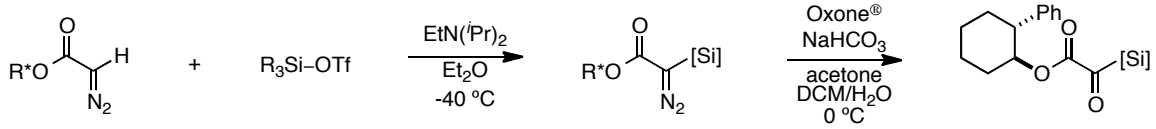
Synthesis of the 2-phenylcyclohexanol silyl glyoxylates:

(1*S*,2*R*)-2-phenylcyclohexyl acetoacetate (E-7): The title compound was prepared analogously to a literature procedure.[30] A solution of (1*S*,2*R*)-2-phenylcyclohexanol[29] (3.79 g, 21.5 mmol, 1.0 equiv.) and *tert*-butyl acetoacetate (3.56 mL, 3.4 g, 21.5 mmol, 1.0 equiv.) in xylenes (~30 mL) was prepared in a 125 mL Erlenmeyer flask equipped with a stir bar. The solution was stirred while being heated on a hot plate, with a thermometer was placed just below the opening of the flask. The reaction began to boil, the *tert*-butanol (bp 82 ºC) was driven off, and the reaction temperature was allowed to proceed approx. 5 min past when the vapor temperature reached the boiling point of xylenes (130-140 ºC). The reaction was cooled to room temperature and concentrated with heating on a rotary evaporator to a clear oil which required no further purification. Analytical data for **E-7**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.02 (m, 1H), 3.14 (s, 2H), 2.68 (m, 1H), 2.20-2.10 (m, 1H), 2.00-1.80 (m, 3H), 1.78 (s, 3H), 1.52-1.22 (m, 5H). **TLC** (30% EtOAc/hexanes) R_f 0.42



(1*S*,2*R*)-2-phenylcyclohexyl diazoacetate (E-8). The standard two-step diazo-tranfer and retro Claisen sequence was followed.[12] The crude yield over the two steps was 91% (20 mmol of acetoacetate yielded 18.2 mmol of diazoacetate). For the diazoacetoacetate:

^{1}H NMR (400 MHz, $CDCl_3$): 7.30-7.25 (m, 2H), 7.23-7.13 (m, 3H), 5.01 (m, 1H), 2.68 (m, 1H), 2.29 (s, 3H), 2.00-1.90 (m, 2H), 1.88-1.78 (m, 1H), 1.70-1.33 (m, 5H). **TLC** (30% EtOAc/hexanes) R_f 0.82. Analytical data for the diazoacetate **E-8**: **IR** (thin film, cm^{-1}): 3109, 3029, 2935, 2859, 2110, 1689, 1603, 1494, 1449, 1384, 1354, 1243, 1190, 1034, 757, 739, 700; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.22-7.15 (m, 3H), 5.01 (dt, J = 10.8, 4.2 Hz, 1H), 4.46 (br s, 1H), 2.66 (dt, J = 12.6, 3.6 Hz, 1H), 2.24-2.17 (m, 1H), 1.97-1.91 (m, 1H), 1.89-1.84 (m, 1H), 1.82-1.77 (m, 1H), 1.62-1.32 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 166.0, 142.9, 128.2, 127.4, 126.4, 76.6, 49.7, 45.9, 33.8, 32.6, 25.7, 24.7; **TLC** (20% EtOAc/hexanes) R_f 0.40 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{14}H_{16}N_2O_2$+Na: 267.11; Found: 267.12.



(1*S*,2*R*)-2-phenylcyclohexyl silyl glyoxylates (16c and **16d).** The standard protocol was followed for both silyl glyoxylates,[65] using the corresponding silyl triflate in the silylation step. The TES silyl glyoxylate was obtained in 70% yield over the two steps (8.8 mmol of the diazoacetate **E-8** afforded ~2.2 g product **16c**, 6.3 mmol). The TBS silyl glyoxylate was obtained in 76% yield (9.4 mmol of the diazoacetate **E-8** afforded ~2.5 g product **16d**, 7.2 mmol) over the two steps.

For the TES silyl diazoacetate: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.22-7.15 (m, 3H), 5.08 (m, 1H), 2.65 (m, 1H), 2.24-2.17 (m, 1H), 1.97-1.91 (m, 1H), 1.89-1.84 (m, 1H), 1.82-1.77 (m, 1H), 1.62-1.32 (m, 4H), 0.80 (t, J = 8 Hz, 9H), 0.53 (q, J = 8 Hz, 6H); **TLC** (20% EtOAc/hexanes): R_f 0.68.

For the TES silyl glyoxylate **16c**: **IR** (thin film, cm^{-1}): 3062, 3030, 2937, 2876, 1741, 1712, 1662, 1495, 1451, 1414, 1267, 1212, 1125, 1007, 751, 699; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.26-7.22 (m, 2H), 7.20-7.12 (m, 3H), 5.16 (dt, *J* = 10.2, 4.2 Hz, 1H), 2.77 (dt, *J* = 12.6, 4.2 Hz, 1H), 2.19-2.13 (m, 1H), 1.97-1.92 (m, 1H), 1.90-1.84 (m, 1H), 1.82-1.77 (m, 1H), 1.62-1.45 (m, 3H), 1.42-1.32 (m, 1H), 0.79 (t, *J* = 7.8 Hz, 9H), 0.55 (t, *J* = 7.8 Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 232.6, 161.8, 142.4, 128.4, 127.4, 126.6, 77.5, 49.6, 34.3, 32.1, 25.6, 24.7, 6.9, 1.8; **TLC** (5% EtOAc/hexanes) R_f 0.31 (UV/CAM; also visible to naked eye); **LRMS** (ESI): Calcd. for $C_{20}H_{30}O_3Si$+Na: 369.19; Found: 369.23; Calcd. for $C_{20}H_{30}O_3Si$+Cs: 479.10; Found: 479.15

For the TBS silyl diazoacetate: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.22-7.15 (m, 3H), 5.06 (m, 1H), 2.64 (m, 1H), 2.24-2.17 (m, 1H), 1.97-1.91 (m, 1H), 1.89-1.84 (m, 1H), 1.82-1.77 (m, 1H), 1.62-1.32 (m, 4H), 0.77 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **TLC** (20% EtOAc/hexanes): R_f 0.68.

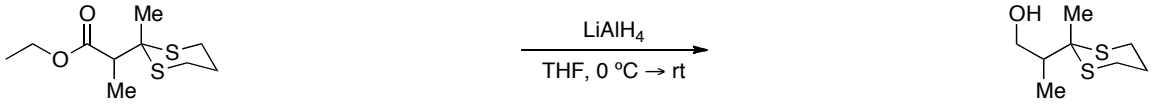
Analytical data for the TBS silyl glyoxylate **16d**: **IR** (thin film, cm^{-1}): 3031, 2932, 2859,1736, 1714, 1658, 1494, 1464, 1450, 1364, 1258, 1005, 842, 785, 755, 699; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.22-7.15 (m, 3H), 5.14 (dt, *J* = 10.2, 4.2 Hz, 1H), 2.76 (dt, *J* = 12, 3.6 Hz, 1H), 2.19-2.13 (m, 1H), 1.97-1.92 (m, 1H), 1.90-1.84 (m, 1H), 1.82-1.77 (m, 1H), 1.62-1.45 (m, 3H), 1.42-1.32 (m, 1H), 0.78 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 231.9, 162.4, 142.4, 128.4, 127.5, 126.7, 77.6, 49.5, 34.1, 32.1, 26.2, 25.6, 24.7, 16.8, -7.2, -7.3; **TLC** (10% EtOAc/hexanes) R_f 0.5 (UV/CAM; also visible to naked eye); **LRMS** (ESI): Calcd. for

$C_{20}H_{30}O_3Si$+Na: 369.19; Found: 369.19; Calcd. for $C_{20}H_{30}O_3Si$+Cs: 479.10; Found: 479.11.

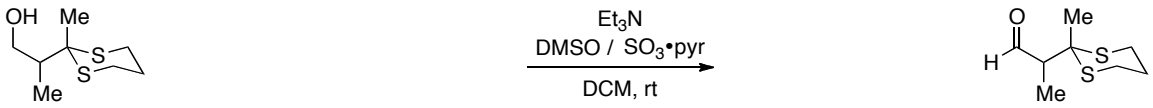
Synthesis of Dithiane Aldehyde 32cb:

Ethyl 2-(2-methyl-1,3-dithian-2-yl)propanoate (E-9). This procedure was conducted analogously to a literature procedure.[66] To a solution of ethyl 2-methylacetoacetate[67] (5 g, 34.68 mmol, 1 equiv.) and 1,3-propanedithiol (4.2 mL, 4.5 g, 41.6 mmol, 1.2 equiv.) in chloroform (125 mL) was added iodine (880 mg, 3.47 mmol, 0.1 equiv.) and the resultant deep red solution was stirred at room temperature without the need for an N_2 atmosphere overnight (12 h). The reaction was worked up by pouring into 10% aq. (w/w) KOH (75 mL) and sat. aq. $Na_2S_2O_3$ (75 mL) and shaking vigorously until the I_2 color had dissipated. The layers were separated, and the aqueous layer was extracted with additional chloroform (2 x 10 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude yellow oil obtained (8 g, 34.1 mmol, 98% crude yield) required no further purification. Analytical data for **E-9**: **IR** (thin film, cm-1): 2977, 2935, 2904, 2830, 1731, 1641, 1446, 1423, 1372, 1335, 1254, 1184, 1111, 1070, 1043, 1020, 906, 866; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.22-4.08 (m, 2H), 3.35 (q, *J* = 7.2 Hz, 1H), 3.20-3.10 (m, 1H), 3.0-2.90 (m, 1H), 2.68-2.60 (m, 2H), 2.10-2.03 (m, 1H), 1.80-1.70 (m, 1H), 1.59 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.2, 60.4, 49.2, 45.6,

26.5, 26.4, 24.5, 23.1, 14.1, 13.5; **TLC** (20 % EtOAc/hexanes) R_f 0.47 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{10}H_{18}O_2S_2$+Na: 257.06; Found: 257.09

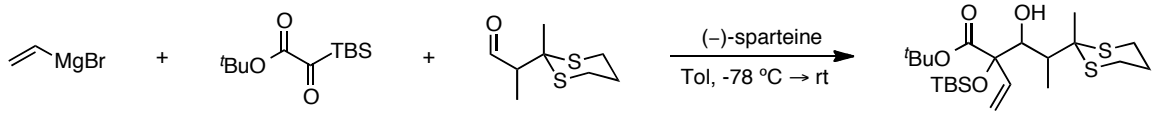


2-(2-Methyl-1,3-dithian-2-yl)propan-1-ol (E-10). To a solution of dithiane ester **E-9** (5.7 g, 24 mmol, 1 equiv.) in dry THF (100 mL) under N_2 at 0 ºC was added a solution of lithium aluminum hydride (1M in THF, 18 mL, 18 mmol, 0.75 equiv.). The reaction was allowed to warm to room temperature, and upon completion, the solution was cooled again to 0 ºC. A sat. aq. solution of Rochelle's salt (Na/K tartrate) was added carefully until the mixture no longer effervesced. Once the reaction mixture was thus quenched, additional Rochelle's salt solution (~200 mL) was added and the mixture was stirred vigorously until the two layers cleanly separated when stirring was stopped (1-2 h). The aqueous layer was extracted with Et_2O (3 x 50 mL), and the combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The material thus obtained required no further purification, and its spectral properties matched those reported in the literature.[68]



2-(2-methyl-1,3-dithian-2-yl)propanal (32cb). This reaction has been reported in a footnote, but no experimental details were given in the text or supporting information.[69] To a solution of alcohol **E-10** (1 g, 5.2 mmol, 1 equiv.) in DCM (20 mL) were added dimethylsulfoxide (3.6 mL, 3.94 g, 50.4 mmol, 9.7 equiv.), triethylamine (7.25 mL, 5.26 g,

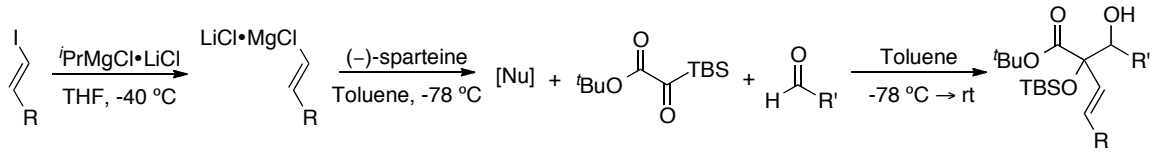
52 mmol, 10.4 equiv.), and the sulfur trioxide•pyridine complex (4.3 g, 27 mmol, 5.2 equiv.). The reaction was stirred 1 h at room temperature then the reaction mixture was poured into H_2O (150 mL). The layers were shaken and separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified via flash column chromatography using 20% Et_2O/hexanes to afford 660 mg (66% yield) of the product **32cb** as a colorless oil. Analytical data for **32cb**: IR (thin film, cm-1): 2973, 2934, 2907, 2830, 2731, 1715, 1446, 1422, 1375, 1277, 1239, 1135, 1110, 1077, 906; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.81 (d, *J* = 3.6 Hz, 1H), 3.03-2.98 (m, 1H), 2.97-2.90 (m, 1H), 2.89-2.85 (m, 1H), 2.80-2.70 (m, 2H), 2.10-2.00 (m, 1H), 1.97-1.89 (m, 1H), 1.59 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 201.3, 51.1 48.5, 26.3, 25.7, 24.4, 24.3, 10.5; **TLC** (10% EtOAc/hexanes) R_f 0.20 (UV/CAM); **LRMS** (ESI): Calcd. for $C_8H_{14}OS_2$+Na: 213.04, Found: 213.05



***tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-(2-methyl-1,3-dithian-2-yl)-2-vinylpentanoate (35a).** The title compound was prepared according to General Procedure A using vinylmagnesium bromide (0.7M in THF, 4.3 mL, 3 mmol), ^{t}Bu/TBS silyl glyoxylate **16a** (489 mg, 2 mmol, 1.0 equiv.), dithiane aldehyde **32cb** (571 mg, 3 mmol, 1.5 equiv.), and (–)-sparteine (703 mg, 3 mmol, 1.5 equiv.). The total volume of the (–)-sparteine/Grignard solution was 20 mL dry toluene, and the silyl glyoxylate/aldehyde solution was 40 mL. Analysis of the crude ^{1}H NMR indicated

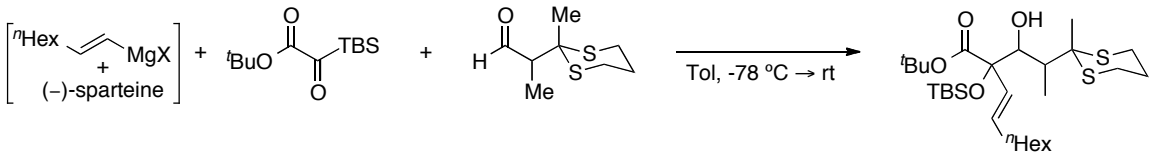
formation of a single diastereomer, which was purified and isolated via flash column chromatography using 2.5% Et_2O/hexanes to afford **35a** 590 mg (1.28 mmol, 64% yield) as a white solid. Analytical data for **35a**: **IR** (thin film, cm^{-1}): 3573, 2930, 2903, 2857, 1746, 1640, 1472, 1393, 1369, 1253, 1157, 995, 917, 842; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.00 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.52 (d, *J* = 17.4, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 2.85-2.80 (m, 1H), 2.75-2.65 (m, 3H), 2.44 (q, *J* = 7.2 Hz, 1H), 2.29 (d, *J* = 10.8 Hz, 1H), 1.95-1.85 (m, 2 H), 1.54 (s, 3H), 1.50 (s, 9H), 0.25 (s, 3H) 0.12 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.2, 138.1, 116.5, 85.9, 82.3, 74.4, 54.3, 38.5, 28.0, 26.8, 26.4, 26.3, 25.0, 23.9, 19.4, 9.5, -1.9, -2.1 (one coincident resonance); **TLC** (20% EtOAc/hexanes), R_f 0.53 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{22}H_{42}O_4S_2Si$+Na: 485.22, Found: 485.21; Calcd. for $C_{22}H_{42}O_4S_2Si$+Cs: 595.13, Found: 595.13

General Procedure B: Three Component Coupling Reactions With Substituted Vinyl Nucleophiles Generated by Mg/I Exchange



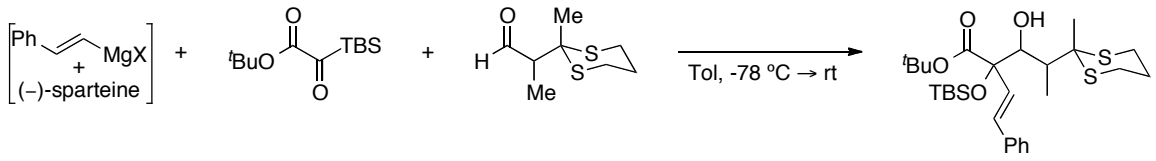
The procedure for the generation of the nucleophile was analogous to the literature procedure.[42] To a solution of the vinyl iodide (1.5 equiv.) in a minimal amount of dry THF (≤ 0.20 mL) cooled to -78 ºC under N_2 was added a solution of ^{i}PrMgCl•LiCl (1.65 equiv.), and the reaction was stirred overnight (12 h) in a cryocool set to -40 ºC. The solution of the vinyl nucleophile thus generated was cooled to -78 ºC, and a solution of (–)-sparteine (1.5 equiv.) in toluene was added, and the solution was stirred at -78 ºC. Meanwhile, a separate solution of the silyl glyoxylate **16** (1.0 equiv.) and the aldehyde (**5**

or **32**; 1.5 equiv.) in dry toluene was prepared and cooled to -78 ºC for 15 min. The nucleophile/sparteine solution was transferred to the silyl glyoxylate/aldehyde solution via cannula, and the reaction mixture was stirred at -78 ºC for an additional 15 min followed by warming to room temperature for 1.5 h. The reaction was quenched with 10% (v/v) aq. AcOH and diluted with H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via flash column chromatography using the indicated eluent system.

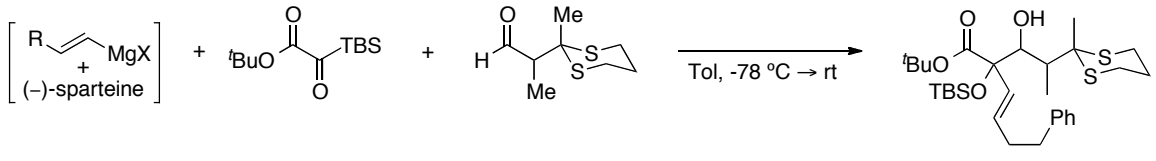


(*E*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-2-(1-hydroxy-2-(2-methyl-1,3-dithian-2-yl)propyl)dec-3-enoate (35b). The title compound was prepared according to General Procedure B using (*E*)-1-iodooct-1-ene[41] (54 mg, 0.225 mmol, 1.5 equiv.) in THF (0.200 mL), and ^{i}PrMgCl•LiCl (1.5M in THF, 0.16 mL, 0.248 mmol, 1.65 equiv.). After overnight nucleophile generation, (–)-sparteine (53 mg, 0.225 mmol, 1.5 equiv.) in toluene (1 mL) was used to complex the Grignard. The silyl glyoxylate **16a** (37 mg, 0.150 mmol, 1.0 equiv.) and dithiane aldehyde **32cb** (43 mg, 0.225 mmol, 1.5 equiv.) solution was prepared in toluene (2 mL). Purification was effected using 5% Et_2O/hexanes to afford 46 mg (0.0841 mmol, 56% yield) of the desired product as a clear oil. Analytical data for **35b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.56 (d, J = 16 Hz, 1H), 4.54 (d, J = 10.8 Hz, 1H), 2.75-2.55 (m, 4H), 2.50 (q, J = 7.2 Hz, 1H), 2.40 (d, J = 10.8 Hz, 1H),

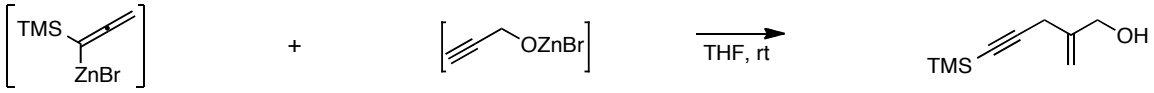
2.10-2.00 (m, 2H), 1.98-1.88 (m, 2H), 1.54 (s, 3H), 1.50 (s, 9H), 1.40-1.25 (m, 8H), 1.12 (d, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H), 0.22 (s, 3H), 0.11 (s, 3H); **TLC** (5% EtOAc/hexanes) R_f 0.22



(*E*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-(2-methyl-1,3-dithian-2-yl)-2-styrylpentanoate (35c). The title compound was prepared according to General Procedure B using β-iodostyrene[70] (78 mg, 0.338 mmol, 1.5 equiv.) in THF (0.200 mL), and ^{i}PrMgCl•LiCl (1.5M in THF, 0.25 mL, 0.370 mmol, 1.65 equiv.). After overnight nucleophile generation, (–)-sparteine (79 mg, 0.338 mmol, 1.5 equiv.) in toluene (1 mL) was used to complex the Grignard. The silyl glyoxylate **16a** (55 mg, 0.225 mmol, 1.0 equiv.) and dithiane aldehyde **32cb** (64 mg, 0.338 mmol, 1.5 equiv.) solution was prepared in toluene (3 mL). Purification was effected using 5% Et_2O/hexanes to afford 76 mg (0.141 mmol, 63% yield) of the desired product as a clear oil. Analytical data for **35c**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H), 6.83 (d, J = 16.2 Hz, 1H), 6.34 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 11.1 Hz, 1H), 2.75-2.55 (m, 3H), 2.55-2.45 (m, 2H), 2.29 (d, J = 11.1 Hz, 1H), 1.85-1.75 (m, 2H), 1.54 (s, 9H), 1.54 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.02 (s, 9H), 0.29 (s, 3H), 0.17 (s, 3H); **TLC** (10% EtOAc/hexanes) R_f 0.35

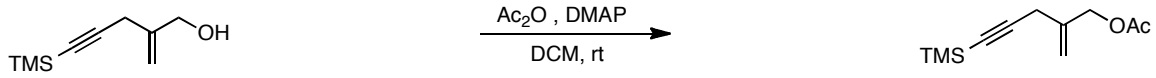


(*E*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-2-(1-hydroxy-2-(2-methyl-1,3-dithian-2-yl)propyl)-6-phenylhex-3-enoate (35d). The title compound was prepared according to General Procedure B using (*E*)-(4-iodobut-3-en-1-yl)benzene[71] (52 mg, 0.200 mmol, 1.5 equiv.) in THF (0.200 mL), and ^{i}PrMgCl•LiCl (1.3M in THF, 0.17 mL, 0.220 mmol, 1.65 equiv.). After overnight nucleophile generation, (–)-sparteine (47 mg, 0.200 mmol, 1.5 equiv.) in toluene (1 mL) was used to complex the Grignard. The silyl glyoxylate **16a** (33 mg, 0.133 mmol, 1.0 equiv.) and dithiane aldehyde **32cb** (38 mg, 0.200 mmol, 1.5 equiv.) solution was prepared in toluene (2 mL). Purification was effected using 5% Et_2O/hexanes to afford 37 mg (0.0653 mmol, 49% yield) of the desired product as a clear oil. Analytical data for **35d**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-2.22 (m, 2H), 7.20-7.13 (m, 3H), 5.89 (m, 1H), 5.63 (d, *J* = 15.6 Hz, 1H), 4.52 (d, *J* = 10.5 Hz, 1H), 2.80-2.65 (m, 6H), 2.50-2.38 (m, 3H), 2.39 (d, *J* = 10.5 Hz, 1H), 1.98-1.89 (m, 2H), 1.56 (s, 3H), 1.47 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H).

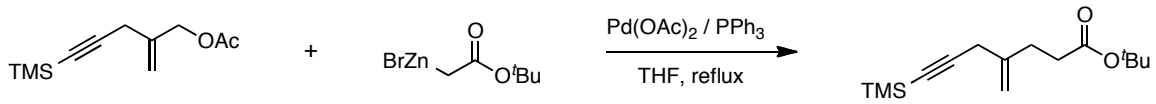


2-methylene-5-(trimethylsilyl)pent-4-yn-1-ol (39). This procedure is based on a literature precedent for which a detailed procedure is lacking.[43] The allenylzinc reagent is generated from trimethylsilyl propargyl bromide[72] as follows: to a suspension of Zn^0 (6.29g, 96 mmol, 2.0 equiv.) in dry THF (100mL) under N_2 is slowly added Br_2 (0.49 mL, 1.53g, 9.6 mmol, 10 mol% relative to Zn^0) to activate the metal surface. The suspension is refluxed for 15 min and then cooled to room temperature, at which point the TMS propargyl bromide (9.2 g, 48 mmol, 1.0 equiv.) is added dropwise. The mixture was

stirred overnight (12 h) under N_2, and then stirring was stopped to allow the excess Zn^0 to settle. The solution is titrated with I_2,[73] and the amount of active allenylzinc is calculated: in this case, it was 29.6 mmol active reagent (62% yield; typically approx. 60% yield of active reagent was observed over several runs). Based on the calculation, 1.0 equiv. of propargyl alcohol (1.72 mL, 1.66 g, 29.6 mmol) was added to a separate dry flask containing THF 60 mL, which was cooled to -78 ºC. A solution of *n*-butyllithium (1.5 M in hexanes, 21.7 mL, 32.5 mmol, 1.1 equiv.) is added, and the solution is warmed to room temperature for 30 min, after which it is cooled again to -78 ºC. A solution of $ZnBr_2$ (7.33 g, 32.5 mmol, 1.1 equiv.) in THF (40 mL) is transferred to the lithium alkoxide, which is warmed again to room temperature for 30 min. The allenylzinc solution is transferred to the solution of zinc alkoxide via cannula, and the reaction is stirred overnight (12 h). The reaction is quenched with a solution of NH_4Cl (50 mL), and diluted with H_2O (500 mL). The layers are separated, and the aqueous layer is extracted with Et_2O (3 x 75 mL). The combined organic extracts are washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via flash column chromatography using 10% EtOAc/hexanes to afford 2.64 g (15.7 mmol, 53% yield) of the product **39** as a colorless oil (reported: 80% yield; best run in our hands: 72% yield). **39** is a known compound, but its ^1H NMR has not been reported in $CDCl_3$ before: **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 5.21 (s, 1H), 5.15 (s, 1H), 4.15 (d, J = 6.3 Hz, 2H), 3.06 (s, 2H), 1.50 (d, J = 6.3 Hz, 1H), 0.17 (s, 9H); **TLC** (20% EtOAc/hexanes) 0.28 ($KMnO_4$/CAM).

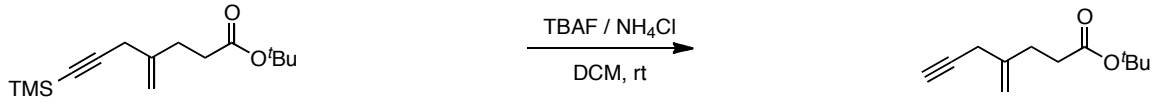


2-methylene-5-(trimethylsilyl)pent-4-yn-1-yl acetate (E-11). To a solution of **39** (185 mg, 1.1 mmol, 1.0 equiv.), *N*,*N*-dimethylamino pyridine (27 mg, 0.22 mmol, 0.20 equiv.), and triethylamine (278 mg, 2.75 mmol, 2.5 equiv.) at 0 ºC in DCM (12 mL) was added acetic anhydride (224 mg, 2.2 mmol, 2 equiv.) neat, dropwise. Dry solvent and N_2 atmosphere were not necessary. The solution was stirred until TLC analysis indicated consumption of **39** (≤ 1 h), at which point the solution was carefully concentrated *in vacuo*. The crude oil was purified via flash column chromatography, eluting with 10% Et_2O/pentanes to afford 220 mg (1.045 mmol, 95% yield) of **E-11** as a clear, colorless oil. Analytical data for **E-11**: **IR** (thin film, cm^{-1}): 3090, 2960, 2899, 2179, 1744, 1658, 1419, 1373, 1249, 1233, 1030, 913, 844, 761; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (5.32 (s, 1H), 5.18 (s, 1H), 4.58 (s, 2H), 3.03 (s, 2H), 2.08 (s, 3H), 0.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.6, 138.5, 114.9, 102.4, 87.9, 66.3, 24.5, 20.9, 0.01; **TLC** (20% EtOAc/hexanes), R_f 0.62 ($KMnO_4$/CAM); **LRMS** (ESI): Calcd. for $C_{11}H_{18}O_2Si$+Na: 233.16 Found: 233.10.

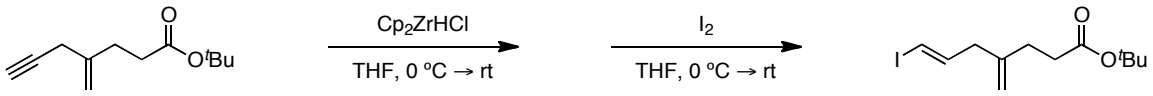


***tert*-butyl 4-methylene-7-(trimethylsilyl)hept-6-ynoate (40).** To a suspension of Zn^0 (3.92 g, 60 mmol, 2 equiv.) in THF (60 mL) under N_2 was added Br_2 (0.31 mL, 0.967 g, 6 mmol, 0.1 equiv. relative to Zn^0) to activate the metal surface. The suspension was heated to reflux, and *tert*-butyl bromoacetate (4.43 mL, 5.85g, 30 mmol, 1 equiv.) was added slowly over 15 min via syringe pump. The reaction mixture was heated at reflux

for 1h, and then heating and stirring were stopped to allow the solution to cool and the excess Zn^0 to settle. The Reformatsky reagent thus generated was titrated with I_2,[73] on this occasion, it was 0.45M (90% yield of active reagent; this was typical). In a separate flask, palladium acetate (107 mg, 0.475 mmol, 0.05 equiv.), triphenylphosphine (249 mg, 0.95 mmol, 0.10 equiv.), and the allylic acetate **E-11** (2 g, 9.5 mmol, 1.0 equiv.) were mixed in THF (60 mL). To this mixture was added the Reformatsky reagent (31.7 mL, 14.3 mmol, 1.5 equiv.), and the resulting solution was heated to reflux overnight (12 h). TLC analysis indicated consumption of the acetate **E-11**, and the reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with H_2O (250 mL). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue via flash column chromatography using 2.5% EtOAc/hexanes afforded 2.1 g (7.88 mmol, 83% yield) of **40** as a clear, slightly pale yellow oil. Analytical data for **40**: **IR** (thin film, cm^{-1}): 3084, 2963, 2900, 2177, 1732, 1652, 1367, 1251, 1148, 1033, 900, 844, 760; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.85 (s, 1H), 2.97 (s, 2H), 2.40-2.35 (m, 4H), 1.43 (s, 9H), 0.15 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.3, 142.5, 111.3, 103.6, 87.3, 80.3, 33.7, 30.7, 28.1, 27.3, 0.0; **TLC** (5% EtOAc/hexanes), R_f 0.41 ($KMnO_4$/CAM); **LRMS** (ESI): Calcd. for $C_{15}H_{26}O_2Si$+Na: 289.16 Found: 289.17.

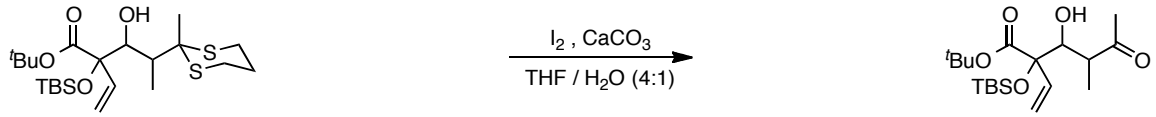


***tert*-butyl 4-methylenehept-6-ynoate (41).** To a solution of protected alkyne **40** (138 mg, 0.518 mmol, 1.0 equiv.) in DCM (10 mL) was added NH_4Cl (138 mg, 2.6 mmol, 5 equiv.), to make a fine suspension. To this mixture was added tetrabutylammonium fluoride (1M in THF, 1.55 mL, 1.55 mmol, 3 equiv.), and the reaction was monitored by removal of aliquots for NMR analysis. Upon completion, the reaction mixture was filtered and carefully concentrated *in vacuo*. The crude oil was purified via flash column chromatography using 5% Et_2O/pentanes to afford 95 mg (0.489 mmol, 95% yield) of the free alkyne **41** as a clear, pale yellow oil. Similar results were obtained on a larger scale (approx. 2 g). Analytical data for **41**: **IR** (thin film, cm^{-1}): 3086, 2979, 2931, 2121, 1730, 1654, 1368, 1255, 1148, 901, 847; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.85 (s, 1H), 2.92 (br s, 2H), 2.40-2.35 (m, 4H), 2.11 (t, J = 2.4 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.2, 142.3, 111.4, 81.1, 80.3, 70.8, 33.6, 30.6, 28.1, 25.9; **TLC** (10% EtOAc/hexanes), R_f 0.50 ($KMnO_4$/CAM); **LRMS** (ESI): Calcd. for $C_{12}H_{18}O_2$+Na: 217.12 Found: 217.13.



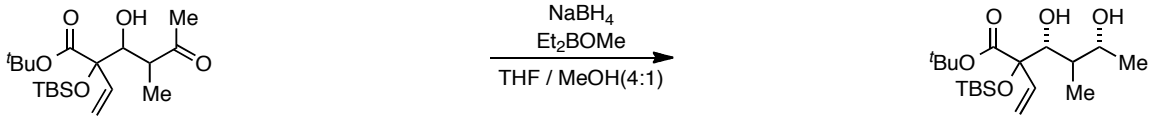
(*E*)-*tert*-butyl 7-iodo-4-methylenehept-6-enoate (36'). To a suspension of zirconocene hydrochloride (520 mg, 2 mmol, 1.4 equiv.) in THF (10 mL) under N_2 at 0 ºC was added a solution of the free alkyne **41** (280 mg, 1.44 mmol, 1 equiv.) in THF (1.5 mL). The suspension was warmed to room temperature and stirred 30 min past when the suspension had cleared (approx. 1.5 h total), at which point the solution was cooled once again to 0 ºC. A solution of iodine (585 mg, 2.3 mmol, 1.6 equiv.) in THF (5 mL) was

added to the reaction mixture, and the reddish color eventually persisted. The reaction was stirred 30 min then poured into 100 mL of 1:1 sat. aq. $NaHCO_3$: sat. aq. $Na_2S_2O_3$, and stirred vigorously until the I_2 color had dissipated. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified via flash column chromatography using 5% EtOAc/hexanes to afford 400 mg (1.24 mmol, 86% yield) of the vinyl iodide **36'** as a clear, pale yellow oil. Analytical data for **36'**: **IR** (thin film, cm^{-1}): 3080, 3050, 2978, 2930, 1730, 1649, 1604, 1434, 1391, 1367, 1252, 1150, 953, 898, 845; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.50 (m, 1H), 6.07 (d, *J* = 14.4 Hz, 1H), 4.80 (s, 2H), 2.75 (d, *J* = 6.8 Hz), 2.35 (m, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.3, 144.9, 143.5, 111.3, 80.4, 76.4, 42.8, 33.6, 30.8, 28.1; **TLC** (5% EtOAc/hexanes), R_f 0.53 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{12}H_{19}IO_2$+Na: 345.03 Found: 345.04



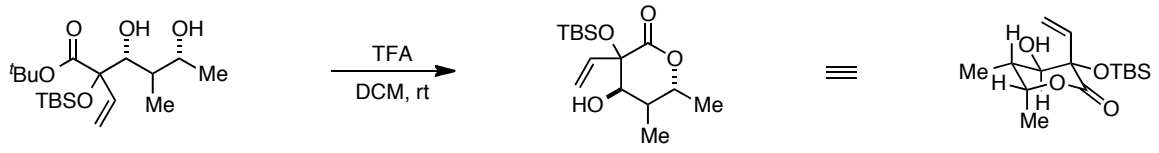
***tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methyl-5-oxo-2-vinylhexa-noate (42a).** Three component coupling product **35a** (149 mg, 0.321 mmol, 1.0 equiv.) was dissolved in 4:1 THF:H_2O (5 mL tot) and the mixture was cooled to 0 ºC. Calcium carbonate (32 mg, 0.321 mmol, 1.0 equiv.) was added, and 5 min later iodine (244 mg, 0.963 mmol, 3 equiv.) was added and the solution became dark red-brown. The reaction was stirred at 0 ºC open to air until judged complete by TLC analysis; this was typically checked by NMR analysis of an aliquot because on more than one occasion the reaction

was terminated prematurely due to misleading TLC appearance. When complete, the reaction was worked up by pouring into half-saturated aq. $Na_2S_2O_3$ and shaking vigorously until the I_2 color had dissipated. The layers were separated, the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the ketone **42a** (which typically required no further purification as long as the reaction had gone to completion). An analytical sample was purified using flash column chromatography, eluting with 7.5% EtOAc/hexanes to afford 100 mg (0.268 mmol, 83% yield) of the desired product as a white solid. Analytical data for **35a**: **IR** (thin film, cm^{-1}): 3485, 2955, 2931, 2856, 1747, 1713, 1460, 1369, 1253, 1161, 1056, 841; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.45 (d, *J* = 17.4, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.31 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.85 (quint, *J* = 7.2 Hz, 1H), 2.16 (d, *J* = 10.8 Hz, 1H), 2.11 (s, 3H), 1.49 (s, 9H), 1.11 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.22 (s, 3H) 0.16 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 211.3, 170.9, 137.3, 116.4, 84.4, 82.7, 47.5, 29.4, 27.9, 26.51, 26.48, 19.4, 13.6, -2.2, -2.6; **TLC** (20% EtOAc/hexanes), R_f 0.45 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{36}O_5Si$+Na: 395.22, Found: 395.22; Calcd. for $C_{19}H_{36}O_5Si$+Cs: 505.14, Found: 505.13



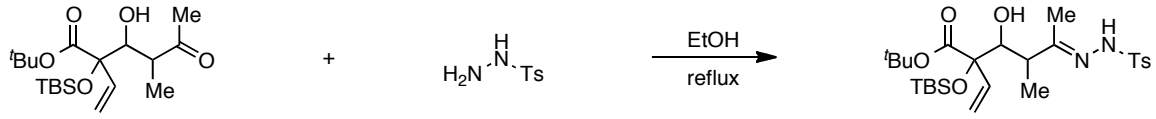
(3*R,5*R**)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3,5-dihydroxy-4-methyl-2-vinylhexanoate (43a).** A solution of **42a** in (60 mg, 0.161 mmol) 4:1 THF:MeOH (2 mL) was cooled to -78 ºC and a solution of diethylmethoxyborane (1M in THF, 0.21 mL,

0.21 mmol, 1.3 equiv.) was added, and the solution was stirred for 45 min prior to the addition of sodium borohydride (18 mg, 0.483 mmol, 3 equiv.). The reaction was moved to a cryocool, set to -70 ºC, and stirred at this temperature until judged complete by TLC analysis. The reaction was quenched by pouring into MeOH (10 mL) and carefully adding glacial acetic acid to the mixture, which effervesced. The reaction was concentrated *in vacuo*, redissolved in MeOH, and concentrated again (3x). The crude residue was triturated and filtered with Et_2O and concentrated to a clear oil. The residue was purified via flash column chromatography, using 15% EtOAc/hexanes as eluent to afford 50 mg (0.133 mmol, 83% yield) of **43a** as a clear colorless oil. Analytical data for **43a**: **IR** (thin film, cm^{-1}): 3438, 2974, 2930, 2857, 1747, 1472, 1462, 1370, 1252, 1153, 927, 840, 779; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.94 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.42 (d, *J* = 17.4, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.00 (m, 2H), 3.22 (d, *J* = 10.2 Hz, 1H), 3.04 (br s, 1H), 1.86-1.80 (m, 1H), 1.52 (s, 9H), 1.22 (d, *J* = 6 Hz, 3H), 0.91 (s, 9H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.20 (s, 3H) 0.12 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.8, 138.0, 117.0, 83.2, 82.5, 81.0, 72.3, 38.8, 28.0, 26.3, 20.3, 19.0, 5.9, -2.2, -2.3; **TLC** (20% EtOAc/hexanes), R_f 0.26 (CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{38}O_5Si$+Na: 397.24, Found: 397.23; Calcd. for $C_{19}H_{38}O_5Si$+Cs: 507.15, Found: 507.15



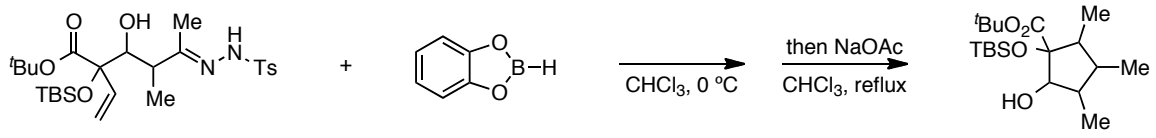
(4*R*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5,6-dimethyl-3-vinyltetrahydro-2*H*-pyran-2-one (44a). To a solution of **43a** (30 mg, 0.800 mmol, 1 equiv.) in DCM (0.67 mL) was added trifluoroacetic acid (0.33 mL). The reaction was stirred at room

temperature until TLC analysis indicated consumption of the starting material **43a**. The reaction was concentrated *in vacuo*, redissolved in $CHCl_3$, and concentrated again (repeated twice more to remove the TFA). The residue was purified via flash column chromatography using 10% EtOAc/hexanes to afford 10 mg (0.033 mmol, 41% yield) of **44a** as a clear oil. Analytical data for **44a**: **IR** (thin film, cm^{-1}): 3461, 2929, 2856, 2359, 1747, 1633, 1463, 1250, 1159, 1056, 839, 781; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.12 (dd, J = 17.4, 10.8 Hz, 1H), 5.42 (d, J = 10.8, 1H), 5.38 (d, J = 17.4 Hz, 1H), 4.69 (quint, J = 6.6 Hz, 1H), 3.74 (d, J = 10.2 Hz, 1H), 2.24-2.19 (m, 1H), 2.19 (s, 1H), 1.30 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.18 (s, 3H) 0.16 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.0, 134.2, 119.8, 81.2, 76.5, 35.6, 26.0, 18.6, 17.2, 13.2, -2.8, -3.0 (one coincident resonance); **TLC** (10% EtOAc/hexanes), R_f 0.11 (CAM); **LRMS** (ESI): Calcd. for $C_{15}H_{28}O_4Si$+Na: 323.17, Found: 323.16



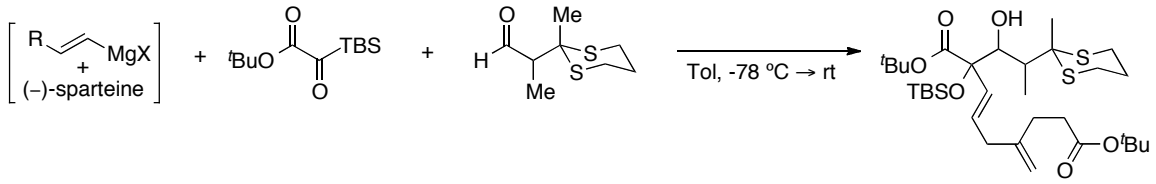
(*E*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methyl-5-(2-tosylhydrazono)-2-vinylhexanoate (45). To a solution of ketone **42a** (100 mg, 0.268 mmol, 1.0 equiv.) in EtOH (5 mL) was added *p*-toluenesulfonyl hydrazide (50 mg, 0.268 mmol, 1.0 equiv.). The mixture was heated to reflux for 10 min and cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography using a 10 → 20% EtOAc/hexanes gradient to afford 123 mg (0.227 mmol, 85% yield) of the tosylhydrazone **45** as a white foam. Analytical data for **45**: **IR** (thin film, cm^{-1}): 3327, 2956, 2930, 2856, 2253, 1744, 1708, 1640, 1460, 1369, 1252, 1166, 916, 840; **^{1}H NMR**

(600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 5.54 (dd, *J* = 17.4, 11.4 Hz, 1H), 5.22 (d, *J* = 17.4, 1H), 4. 90 (d, *J* = 11.4, 1H), 4.04 (d, *J* = 7.2 Hz, 1H), 2.64 (app quint, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 1.67 (s, 3H), 1.47 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.9, 160.7, 143.8, 137.7, 135.6, 129.4, 128.1, 114.9, 84.3, 82.5, 76.7, 42.8, 27.9, 26.4, 21.6, 19.3, 15.1, 14.6, -2.3, -2.6; **TLC** (20% EtOAc/hexanes), R_f 0.21 (UV/CAM).



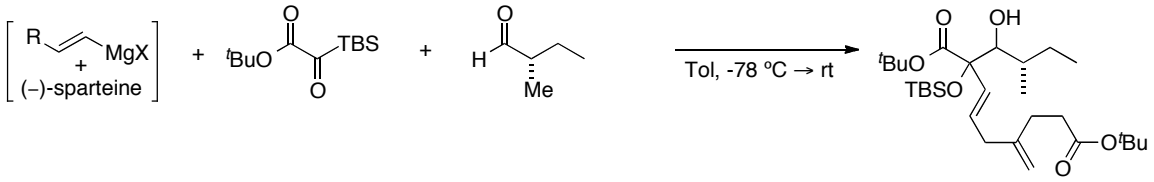
***tert*-butyl 1-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-3,4,5-trimethylcyclopentane-carboxylate (47).** This reaction was performed analogously to a literature procedure. To a solution of **45** (12 mg, 0.0222 mmol, 1.0 equiv.) in dry $CHCl_3$ (3 mL) under N_2 at 0 ºC was added a solution of catecholborane (1M in THF, 0.05 mL, 0.05 mmol, 2.3 equiv.). The mixture was stirred at 0 ºC until TLC analysis indicated consumption of **45**, at which point NaOAc•$3H_2O$ (21 mg, 0.153 mmol, 6.9 equiv.) was added to the flask, which was affixed with a reflux condenser. The reaction was heated under reflux for 1h. TLC analysis indicated consumption of the intermediate and formation of the product, and the cloudy reaction mixture was cooled to room temperature. The mixture was filtered through Celite and concentrated *in vacuo*. Purification via flash column chromatography using 2.5% EtOAc/hexanes afforded the product as as a mixture of diastereomers. The yield was not determined, but **47** was the sole product obtained and none of the desired reduction product **19a** was obtained. Preparative HPLC using 2.5% EtOAc/hexanes afforded a single diastereomer, which was characterized as follows: analytical data for **47**:

IR (thin film, cm^{-1}): 3458, 2956, 2929, 2856, 2090, 1737, 1696, 1645, 1461, 1369, 1251, 1157, 1048, 839, 779; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.83 (t, *J* = 10.2 Hz, 1H), 2.36-2.30 (m, 1H), 1.66 (d, *J* = 10.2 Hz, 1H), 1.67-1.59 (m, 1H), 1.56-1.45 (m, 1H), 1.47 (s, 9H), 1.09 (d, *J* = 6.6 Hz, 1H), 0.92 (d, *J* = 7.2 Hz, H), 0.92 (s, 9H), 0.84 (d, *J* = 7.2 Hz, 1H), 0.22 (s, 3H) 0.15 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.9, 87.4, 82.9, 81.4, 47.3, 41.0, 39.2, 28.0, 26.5, 19.6, 16.9, 16.0, 9.5, -2.2, -2.7; **TLC** (5% EtOAc/hexanes), R_f 0.27 (CAM); **LRMS** (ESI): Calcd. for $C_{19}H_{38}O_4Si$+Na: 381.24, Found: 381.24; Calcd. for $C_{19}H_{38}O_4Si$+Cs: 491.16, Found: 491.15



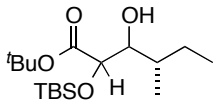
(*E*)-di-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-2-(1-hydroxy-2-(2-methyl-1,3-dithian-2-yl)propyl)-6-methylenenon-3-enedioate (35e). The title compound was prepared according to General Procedure B using **36'** (74 mg, 0.230 mmol, 1.5 equiv.) in THF (0.200 mL), and ^{i}PrMgCl•LiCl (1.3M in THF, 0.19 mL, 0.253 mmol, 1.65 equiv.). After overnight nucleophile generation, (–)-sparteine (54 mg, 0.230 mmol, 1.5 equiv.) in toluene (1 mL) was used to complex the Grignard. The silyl glyoxylate **16a** (37 mg, 0.153 mmol, 1.0 equiv.) and dithiane aldehyde **32cb** (44 mg, 0.230 mmol, 1.5 equiv.) solution was prepared in toluene (3 mL). Purification was effected using 2.5% Et_2O/hexanes to afford 53 mg (0.0840 mmol, 55% yield) of the desired product as a clear oil. Analytical data for **35e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.90 (m, 1H), 5.62 (d, *J* = 15.6 Hz, 1H), 4.77 (s, 1H), 4.75 (s, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 2.78 (d, *J* = 8.4 Hz, 1H), 2.80-2.65

(m, 4H), 2.47 (q, J = 7.2 Hz, 1H), 2.37-2.30 (m, 3H), 2.30-2.25 (m, 2H), 1.95-1.85 (m, 2H), 1.53 (s, 3H), 1.49 (s, 9H), 1.43 (s, 9H), 1.13 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.23 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.3, 171.5, 146.3, 131.9, 129.6, 110.5, 85.1, 82.3, 80.2, 74.7, 54.3, 39.4, 33.7, 31.2, 28.1, 28.0, 26.8, 26.3, 26.2, 25.7, 24.9, 23.9, 19.3, 9.5, -1.99, -2.00; **TLC** (5% EtOAc/hexanes) R_f 0.18 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{32}H_{58}O_6S_2Si$+Na: 653.33, Found: 653.33; Calcd. for $C_{32}H_{58}O_6S_2Si$+Cs: 753.25, Found: 763.24.



(*E*)-di-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-2-((2*S*)-1-hydroxy-2-methylbutyl)-6-methylenenon-3-enedioate (37). The title compound was prepared according to General Procedure B using **36'** (193 mg, 0.600 mmol, 1.5 equiv.) in THF (0.200 mL), and ^{i}PrMgCl•LiCl (1.3M in THF, 0.51 mL, 0.660 mmol, 1.65 equiv.). After overnight nucleophile generation, (–)-sparteine (147 mg, 0.600 mmol, 1.5 equiv.) in toluene (1 mL) was used to complex the Grignard. The silyl glyoxylate **16a** (98 mg, 0.400 mmol, 1 equiv.) and dithiane aldehyde **32cb** (52 mg, 0.600 mmol, 1.5 equiv.) solution was prepared in toluene (5 mL). Purification was effected using 2.5% Et_2O/hexanes to afford 77 mg (which would be 0.146 mmol, 37% yield, if pure, although this is far from true) of **37** contaminated by **48** as a clear oil. Preparative HPLC (2.5% EtOAc/hexanes, hexanes→ 5% EtOAc hexanes gradient, and others) only marginally improved product purity. Analytical data for **37**: **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer*: δ 5.82-5.75

(m, 1H), 5.59 (d, *J* = 15.6 Hz, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.69 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.76 (d, *J* = 6.6 Hz, 2H), 2.47 (d, *J* = 10.2 Hz, 1H), 2.36 (m, 2H), 2.28 (m, 2H), 1.75-1.65 (m, 1H), 1.49 (s, 9H), 1.49-1.40 (m, 1H), 1.43 (s, 9H), 1.28-1.20 (m, 1H), 0.90 (s, 9H), 0.89-0.84 (m, 6H), 0.18 (s, 3H), 0.10 (s, 3H); *resolved signals for minor diastereomer*: δ 5.58 (d, *J* = 15.6 Hz, 1H), 3.57 (dd, *J* = 10.2, 5.4 Hz, 1H), 0.182 (s, 3H), 0.11 (s, 3H); *resolved signals for two diastereomers of* **48**: δ 4.17 (d, *J* = 2.4 Hz, 1H; 1 diastereomer), 4.13 (d, *J* = 4.2 Hz, 1H), 3.55-3.50 (m, 1H), 3.45-3.40 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **TLC** (5% EtOAc/hexanes) R_f 0.15 (CAM); **LRMS** (ESI): Calcd. for $C_{29}H_{54}O_6Si$+Na: 549.36; Found: 549.41; Calcd. for $C_{29}H_{54}O_6Si$+Cs: 659.27; Found: 659.33



(4*S*)-*tert*-butyl 2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methylhexanoate (48). This byproduct is formed appreciably in all the three component couplings with silyl glyoxylates **16** and (*S*)-2-methylbutanal **5**. It can be prepared via the MPV/aldol reaction of the silyl glyoxylate **16** and the magnesium alkoxide derived from (S)-2-methyl butanol,[11] from addition of ^{i}PrMgCl•LiCl to a solution of the silyl glyoxylate **16** and **5** (relatively little ^{i}Pr addition occurs), or addition of Et_2Zn to a solution of **16** and **5** (no Et addition occurs). It is usually formed as a mixture of all four possible diastereomers, and it is particularly difficult to remove from **37**. This has yet to be successfully accomplished. Diagnostic signals for the other two diastereomers not reported above will be reported here: **^{1}H NMR** (400 MHz, $CDCl_3$): *major:* δ 4.10 (d, *J* = 4.0 Hz, 1H), 3.66

(dd, J = 6.8, 4.0 Hz, 1H), 2.26 (d, J = 4.0 Hz, 1H), 1.62-1.57 (m, 1H), 1.53-1.45 (m, 1H), 1.48 (s, 9H), 1.30-1.20 (m, 1H), 0.92-0.88 (m, 6H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); *minor:* δ 4.15 (d, J = 2.8 Hz, 1H), 3.53-3.48 (m, 1H), 2.40 (d, J = 3.2 Hz, 1H), 1.76-1.68 (m, 1H), 1.63-1.56 (m, 1H), 1.48 (s, 9H), 1.21-1.12 (m, 1H), 0.95 (d, J = 4.8 Hz, 3H), 0.91 (s, 9H), 0.92-0.88 (m, 3H); **LRMS** (ESI): Calcd. for $C_{17}H_{36}O_4Si$+Na: 355.23; found: 355.27; Calcd. for $C_{17}H_{36}O_4Si$+Cs:465.14; found: 465.19

2.6 References

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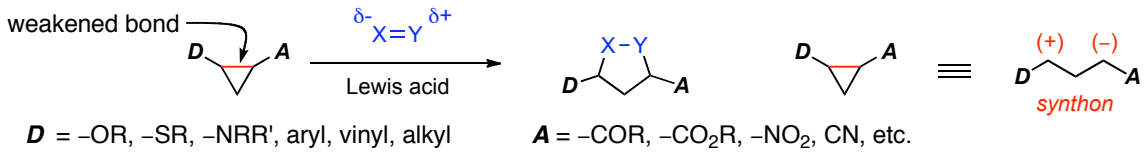
CHAPTER 3

CYCLOPROPANE – ALDEHYDE (3+2) ANNULATIONS AT QUATERNARY DONOR SITES

3.1 Introduction

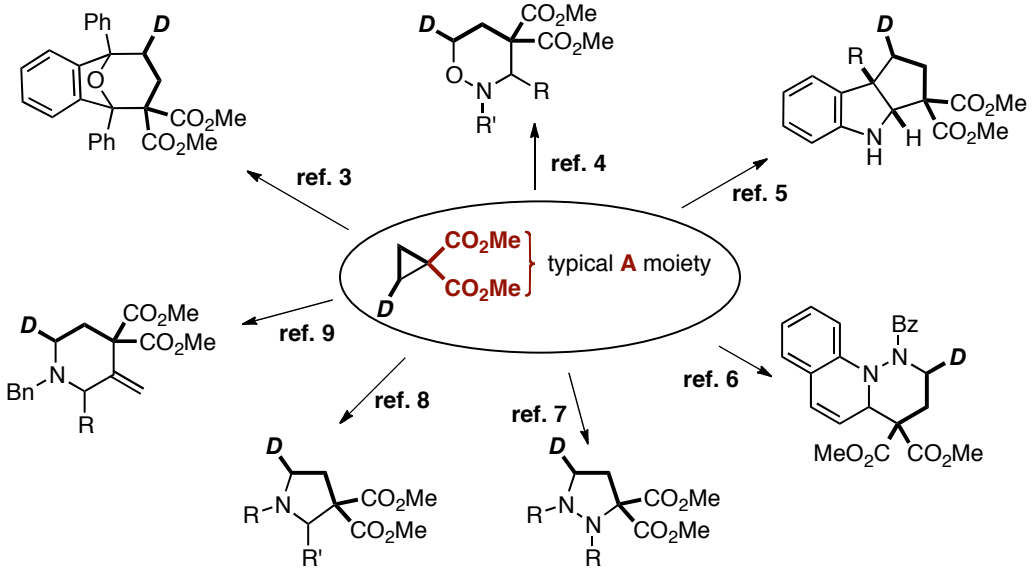
The study of the reactions of donor–acceptor (D–A) cyclopropanes has been a fruitful area of research for a number of research groups in recent years. The success of these reactions to afford a variety of different products is remarkable and stems directly from the versatility of cyclopropanes in synthesis.[1] The inherent ring strain of cyclopropanes (approx. 27.4 kcal/mol)[2] provides a strong thermodynamic driving force for any reaction which will open the ring. The adornment of the ring with certain substituents can provide kinetic handles with which to promote such reactions by lowering the energy barrier to ring opening. In particular, placement of electron-releasing "Donor" (D) groups vicinally to electron-withdrawing "Acceptor" (A) groups serves to further weaken the connecting bond, thus allowing site-specific cleavage of the cyclopropane in a highly predictable manner. Such cyclopropanes can therefore be envisioned as synthetic equivalents to 3-carbon dipoles, wherein the D & A groups serve to stabilize the respective charges of the ring-opened zwitterionic form of the cyclopropane upon heterolytic bond cleavage **(Figure 3-1)**. This heterolysis can be promoted by activation of either the donor or the acceptor groups; a common means of activating the acceptor group is via coordination to a Lewis acid.

Figure 3-1. Donor–Acceptor Cyclopropanes as 1,3-Dipolar Carbon Synthons



Typical donor groups that have been widely employed in this type of reactivity are heteroatomic moieties (–OR, –SR, –NRR', etc.) and unsaturated (aryl, vinyl) carbon-based donors. These groups are able to stabilize the positive charge of the ring-opened cyclopropane by resonance; simple alkyl groups which do not offer such resonance stabilization are less common, but they can still be employed in ring opening reactions of D–A cyclopropanes under more vigorous conditions. The acceptor groups that have been used in this ring-opening chemistry include anion-stabilizing functionalities (–COR, $-CO_2R$, $-NO_2$, –CN etc.); perhaps the most common is a geminal diester. **Scheme 3-1** presents a few pertinent examples of reactions of various X=Y dipoles with D–A cyclopropanes as reported by other research groups.[3-9] Our laboratory has also been interested in reactions of D–A cyclopropanes for some time, and has demonstrated that they can undergo (3+2) annulation reactions with C=X dipoles such as aldehydes and aldimines. The work presented in this chapter builds upon this wealth of successful precedent.

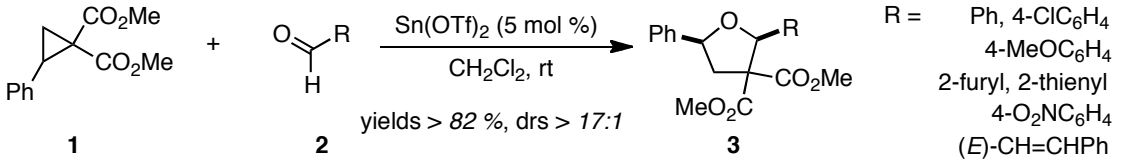
Scheme 3-1. Brief Survey of D–A Cyclopropane Reactivity With Dipolarophiles



3.2 Background

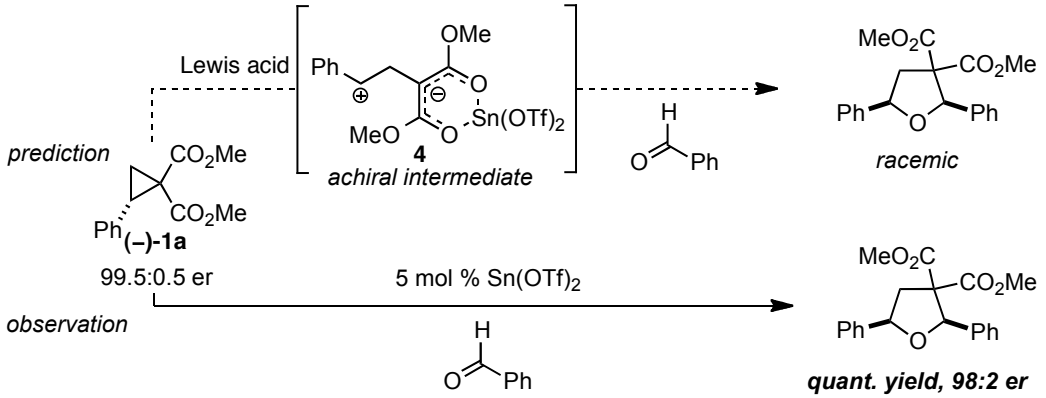
The (3+2) annulations of D–A cyclopropanes **1** with aldehydes **2** were initially developed in our laboratory by Patrick Pohlhaus.[10] As summarized in **Scheme 3-2**, the initial reaction was highly successful for electronically diverse aromatic and α,β-unsaturated aldehydes; the transformation was not only efficient, but also highly diastereoselective. The reaction could be promoted by various Lewis acids, but 5 mol% of $Sn(OTf)_2$ at room temperature in dichloromethane provided optimal results. The aldehyde scope under these conditions was limited to aryl and α,β-unsaturated aldehydes. Alkyl aldehydes displayed poor reactivity, leading to low conversions and significant byproduct formation. This methodology provides access to 2,5-*cis*-tetrahydrofurans **3**, a subunit found in numerous biologically relevant natural products.[11]

Scheme 3-2. Initial (3+2) Reaction Between D–A Cyclopropanes and Aldehydes



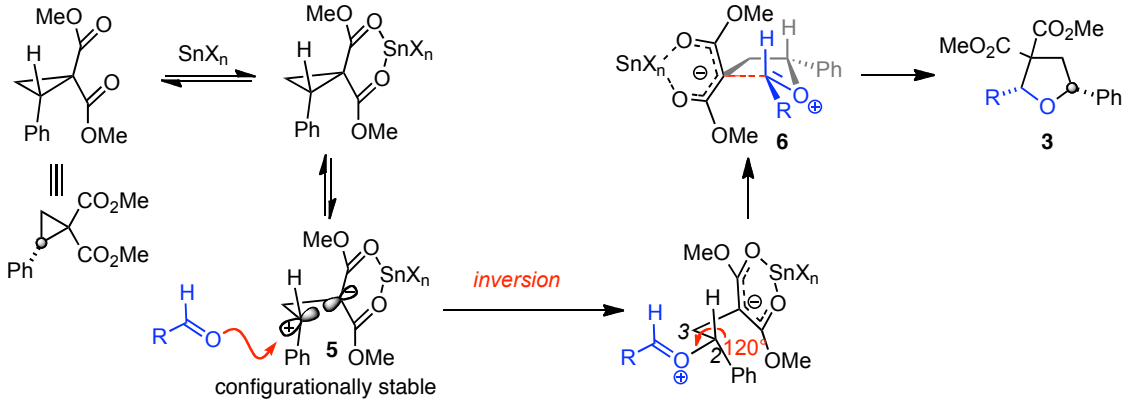
Continued reaction development afforded a surprising mechanistic result **(Scheme 3-3)**. [12] If one envisions the D–A cyclopropane as the functional equivalent of a ring-opened, zwitterionic 1,3–dipole such as **4**, one would reasonably expect racemic product formation during the course of this reaction if one were to start with a highly enantioenriched cyclopropane. However, the data that emerged were in complete opposition to this expectation; in fact, there is almost complete transfer of chirality from D–A cyclopropane **(–)-1a** to product during the course of the reaction. Thus, not only does this methodology allow access to highly diastereoselective chemistry, but the discovery of chirality transfer also demonstrated that highly enantioenriched THF products could be accessed from this reaction. Further enhancing the utility of this methodology, it was discovered that the use of a different Lewis acid, $SnCl_4$, allowed for successful incorporation of alkyl aldehydes as dipolarophiles without the complications observed under the originally established conditions using $Sn(OTf)_2$.

Scheme 3-3. A Mechanistic Surprise: Efficient Transfer of Chirality is Possible



Tracing the stereochemical course of the reaction revealed that the cyclopropane donor site had undergone an enantiospecific inversion of configuration during the reaction. The mechanistic picture of these (3+2) reactions that has emerged as a consequence of these preceding studies is summarized in **Scheme 3-4**.[13] Chelation of the Lewis acid to the diester serves to open the cyclopropane to the intimate ion pair **5**. Due to the constraints of the methylene linker, this ion pair has a high degree of configurational stability; thus, the "separated" zwitterionic form (**4**, above in **Scheme 3-3**) does not appear to predominate in the presence of a competent dipolarophile. In an unusual fashion, the aldehyde attacks ion pair **5** as a nucleophile. After 120º bond rotation about the C_2–C_3 axis, the envelope **6** is accessed in which the bulkier R group from the aldehyde and the donor group from the cyclopropane are placed in pseudoequatorial positions. Ring closure of the malonate onto the oxocarbenium ion at this stage provides the observed 2,5-*cis* THF products **3**.

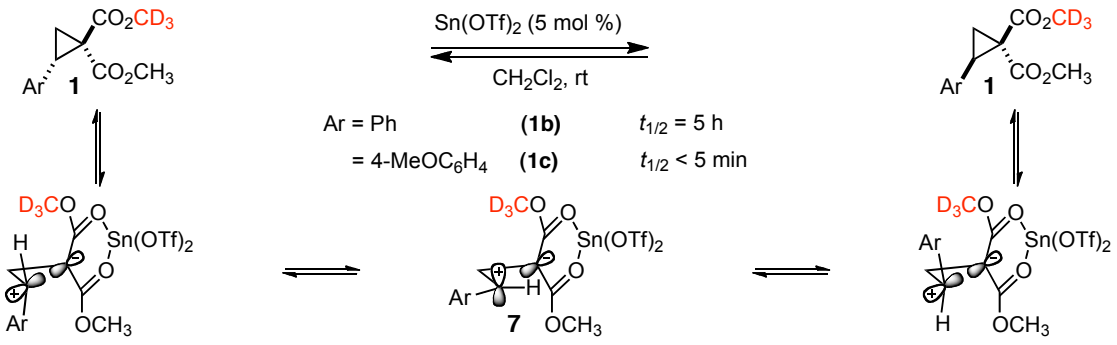
Scheme 3-4. Proposed Mechanism Includes an Intimate Ion Pair to Rationalize Chirality Transfer With Inversion of Configuration at the Donor Site



Given the highly efficient and diastereoselective nature of these (3+2)-annulations, the additional discovery of chirality transfer from the cyclopropanes to the THF products revealed one of the few limitations to this chemistry. Namely, it was the

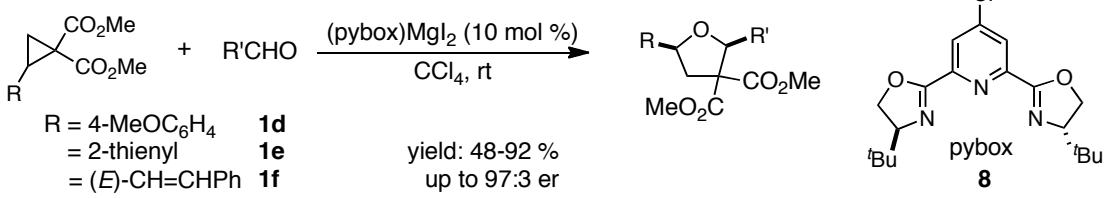
need to access highly enantioenriched D–A cyclopropane starting materials to arrive at enantioenriched THFs. Indeed, the first iterations of this process in our group involved a relatively lengthy approach to the enantioenriched starting materials. In some cases, the approach involved simple resolution of cyclopropane dicarboxylic acids with chiral amines followed by repeated crystallizations.[13] A more desirable solution to this limitation would be the development of a dynamic process that would allow the easily–accessed racemic D–A cyclopropanes to be converted to highly enantioenriched THF products. The development of this chemistry was successfully accomplished by Parsons, who made use of a key result from earlier work by Pohlhaus and Sanders as a starting point: the behavior of a more electron-rich group at the donor site of the cyclopropane shows a greatly increased rate of epimerization when treated with a Lewis acid in the absence of an aldehyde dipolarophile **(Scheme 3-5)**.[13] The rate at which **1c** scrambles the labeled methyl group is dramatically increased relative to the electron-neutral **1b**. This behavior is directly linked to the electronic nature of the donor group and its ability to stabilize the carbenium ion character of the ring-opened form. Thus, as the nascent carbenium ion character at the cyclopropane donor site becomes more highly stabilized, the intimacy of the ion pair may be disrupted (as in **7** below, or **4**, above).

Scheme 3-5. Substituent Effects Dramatically Affect Rate of Isomerization



One could anticipate that the reactivity profile of the cyclopropanes would also be dramatically affected in the presence of a dipolarophile in annulation reactions. The greatly increased rate of racemization of **1c** relative to **1b** suggested that **1c** could potentially be a candidate for the envisioned dynamic process: if the rate of racemization were faster than the rate of (3+2) annulation, one could arrive at highly enantioenriched products from racemic starting materials. This proved to be the case for the dynamic kinetic asymmetric transformation (DyKAT) that Parsons developed. In this process **(Scheme 3-6)**,[14] the Lewis acid MgI_2 ligated by 4-Cl-^{t}BuPybox **8** served as a catalyst for both the interconversion of the cyclopropane enantiomers as well as the annulation reaction with aldehydes to give highly enantioenriched products in excellent yields and diastereoselectivities. In addition to the electron-rich PMP cyclopropane **1d**, the donor group could also be an electron-rich heteroaromatic (**1e**) or styryl (**1f**) moiety. Electron-neutral substrates such as **1a** were candidates for simple kinetic resolution under these conditions, as the annulation reaction was faster than racemization.

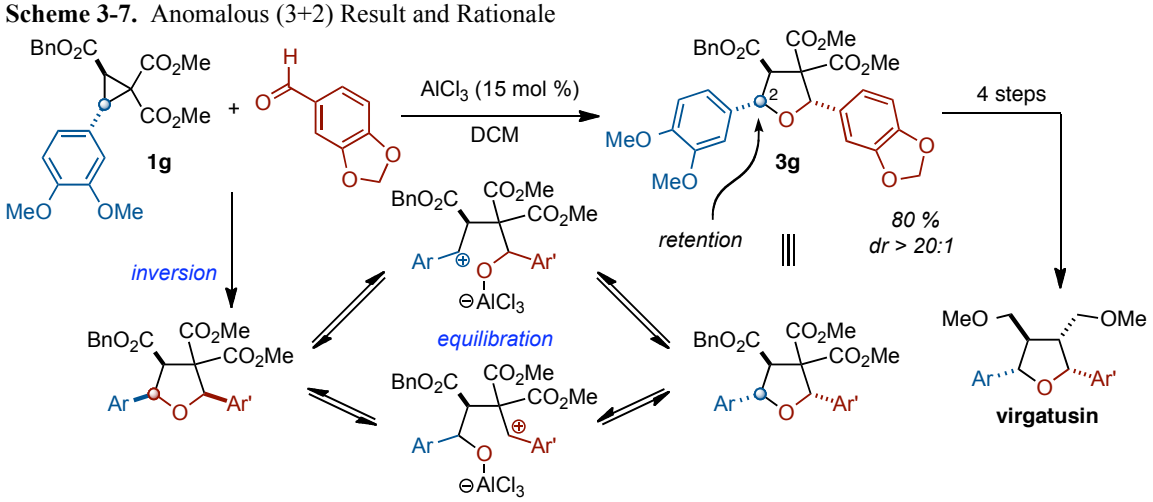
Scheme 3-6. DyKAT with Electron-Rich Donor Groups and Aldehydes



Other relevant group precedent for the work in this chapter comes from an elegant, concise total synthesis of virgatusin completed by Sanders.[15] The (3+2)-annulation chemistry with aldehydes maps directly onto the core of the natural product: it was anticipated that judicious choice of cyclopropane and aldehyde starting materials would yield a core THF structure that could be elaborated to the natural product with

minimal post-annulation effort. Thus, the annulation reaction would require the use of a doubly activated aryl ring at the donor site, as well as the use of a highly electron-rich aldehyde. As shown in **Scheme 3-7**, these efforts afforded yet another surprise: instead of the expected inversion at the donor site of **1g**, the THF **3g** obtained had retained the stereochemistry at C_2. It was subsequently determined through independent synthesis of the expected isomer of the product that the reaction had presumably followed the expected inversion pathway; **3g** was the result of subsequent Lewis acid catalyzed equilibration of the stereoisomers. It was fortuitous that the thermodynamic ratio of isomers in that case was so favorable in the direction of the desired isomer.

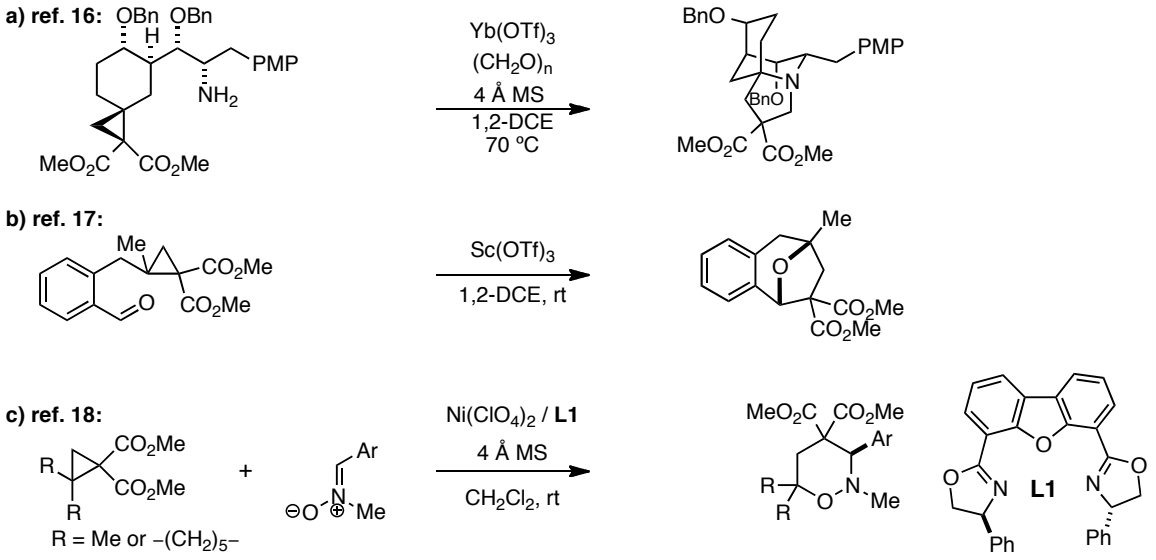
Scheme 3-7. Anomalous (3+2) Result and Rationale



It is within the context of these related studies that the genesis of the current chapter arose. Both the Parsons and Sanders precedent demonstrated the profound impact that carbenium ion stability at the cyclopropane donor site would have for the overall course of the (3+2) reaction. It thus became of interest to determine what would be the outcome of reactions with cyclopropanes fully substituted at the donor site; whereas our group and others have extensively studied the reactions of tertiary donor site

cyclopropanes, there have only been a few scattered examples of the use of quaternary donor site cyclopropanes in annulation reactions **(Scheme 3-8)**.[16-18]

Scheme 3-8. Extant examples of Quaternary Donor Site Cyclopropanes in Annulation Reactions



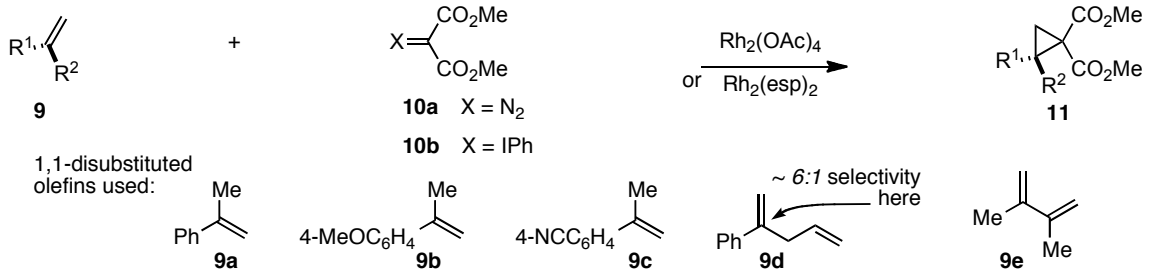
The reactions above were either in the context of a total synthesis, or isolated examples in a substrate scope. In these examples, the annulation reaction was either intramolecular (as in **Scheme 3-8 a)** and **b)**), or the donor site was symmetrical (as in **Scheme 3-8 c)**). The issue of whether there could be any diastereoselectivity in a broader study of annulation reactions with quaternary donor site cyclopropanes was thus unanswered: it could be attributed to the conformational biases of the substrates in the intramolecular cases or was nonexistent due to the symmetrical donor site in the intermolecular case. While our group has established that highly diastereoselective intermolecular reactions with aldehydes can be achieved when the substituents on the cyclopropane donor site are as differentiated as aryl–/vinyl–/alkyl– vs. H, it remained to be established what would happen as these groups approach each other in size.

Additionally, it should be noted that while acetone was a competent dipolarophile with our group's (3+2) reactions, attempts to use acetophenone were unsuccessful.[13] Thus, application of monosubstituted D–A cyclopropanes in combination with ketones did not appear to be a broadly applicable means of accessing 2,2,5-trisubstitued THFs, which is another motif found in a number of natural products.[19] The desire to explore the reactivity of quaternary donor site cyclopropanes in annulation reactions naturally flowed out of the above motives.

3.3 Results and Discussion: Access to the Cyclopropane Substrates

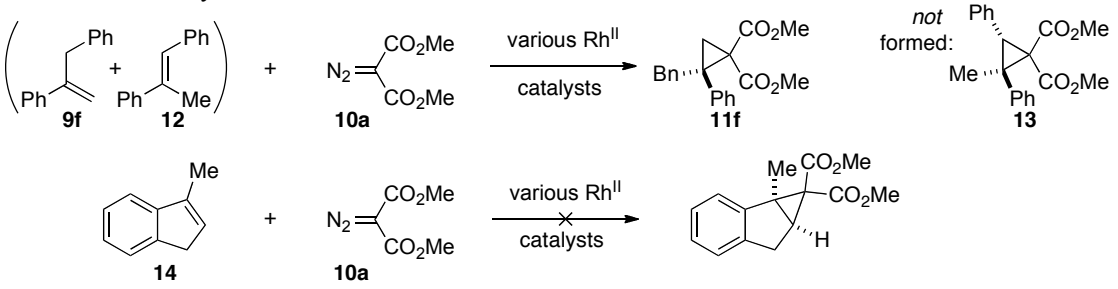
This study was initiated with the synthesis of a variety of the requisite fully donor-substituted cyclopropanes, for which direct literature methods are surprisingly sparse. As shown in **Scheme 3-9**, the most straightforward route to these substrates **11a-e** was soon found to be the Rh^{II}-catalyzed carbene decomposition of either a phenyliodonium[20] or diazo malonate[21] precursor **10** in the presence of a 1,1-disubstituted alkene **9** (see section **3.6** for further details). This proved to be general for a variety of electronically diverse α-methylstyrene derivatives **9a-c**, as well as 2,3-dimethyl-1,3-butadiene **9e**, and the cyclopropanes were typically isolated in ~50% yield (unoptimized). This method also proved applicable to α-allylstyrene **9d**; it should be noted that the terminal olefin in **9d** could also undergo cyclopropanation. This did in fact occur, although the desired selectivity for the more electron-rich 1,1-disubstituted olefin was moderate (6:1). The two isomers proved to be inseparable via standard flash column chromatography as well as by HPLC. Fortunately, the isomeric mixture could be used in annulation reactions with no apparent deleterious effects due to the presence of the undesired isomer.

Scheme 3-9. Access to Quaternary Donor Site Cyclopropanes via Carbene Transfer



In attempts to synthesize more highly substituted cyclopropanes, we discovered that intermolecular carbenoid transfer of such malonate-derived carbenes was ineffective. This is evident in **Scheme 3-10**: in attempted cyclopropanation of a mixture of α-benzylstyrene **9f** and *trans*-(α-methyl)-stilbene **12**, we saw exclusive reaction with the styrene to afford cyclopropane **11f**. No reaction was observed with **12**; upon recovery of this unreacted olefin, further attempts to effect cyclopropanation with different Rh catalysts and reaction conditions still afforded no desired product. In these reactions, **12** was recovered unchanged while **10a** dimerized. The same was true for attempts to cyclopropanate 3-methyl indene **14**, which had been anticipated to be sterically more accessible to reaction with the carbenoid. Thus, to arrive at more highly substituted cyclopropanes, another method would be required.

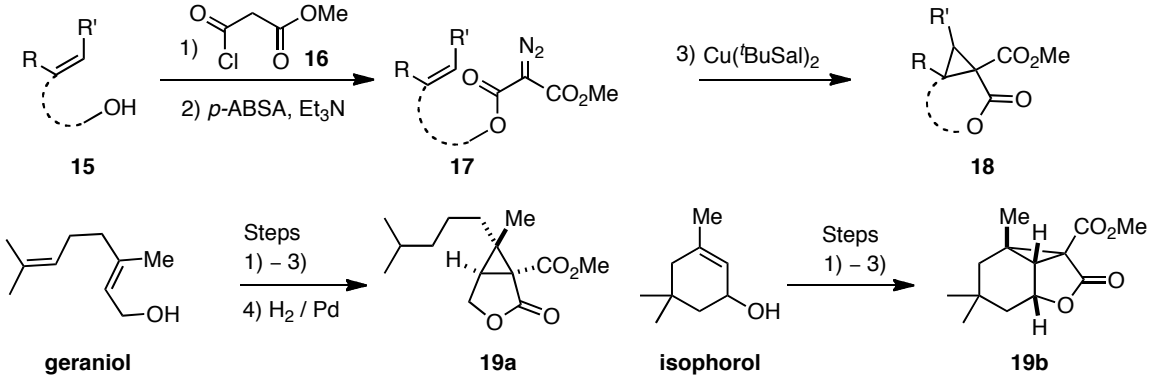
Scheme 3-10. Inability to Transfer the Malonate Carbene to Trisubstitued Olefins



To accomplish this task, we resorted to the use of Corey's Cu(^{t}BuSal)$_2$ catalyst for intramolecular cyclopropanation of trisubstituted olefins.[22] Two highly substituted

cyclopropanes were accessed as shown in **Scheme 3-11**: the acylation of commercially available allylic alcohols **15** with methyl malonyl chloride **16** followed by diazo transfer afforded substrates for intramolecular cyclopropanation. Slow addition of the diazo alkene **17** to a refluxing solution of the cyclopropanation catalyst in the appropriate solvent afforded the cyclopropanes (see section **3.6** for more details). The remaining olefin in the geraniol-derived cyclopropane was subsequently hydrogenated to avoid issues in the annulation reactions (*vide infra*) to afford **19a**, while the isophorol derived cyclopropane **19b** required no further modification. Another route to such 1,1,2,2,3-pentasubstituted cyclopropanes was projected to be six steps (including starting material synthesis), and was never pursued.[23]

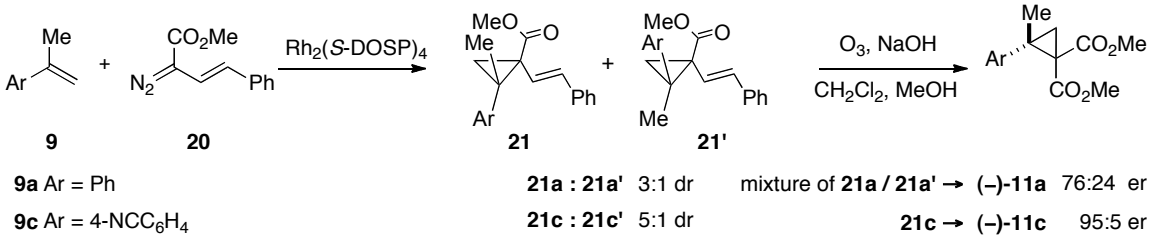
Scheme 3-11. Intramolecular Cyclopropanation of Trisubstited Olefins



It was also necessary to synthesize optically active cyclopropanes for use in chirality transfer studies. We targeted aryl-methyl cyclopropanes and followed the Davies route established for styrenes, which also included a single example of cyclopropanation of a 1,1-disubstituted olefin.[24] While this example proceeded with high enantioselectivity, the alkene was symmetrical and there were thus no additional issues with respect to diastereoselectivity which could conceivably impact the utility of this approach. We attempted the asymmetric cyclopropanation of α-methylstyrene **9a** and 4-

isopropenylbenzonitrile **9c** with methyl styryldiazoacetate **20** catalyzed by Rh_2(*S*-DOSP)$_4$ as shown in **Scheme 3-12**. The diastereoselectivity of this reaction proved to be moderate (3:1 or 5:1, respectively), but the enantioselectivity for the formation of the major diastereomer of **21** in both cases was excellent (95:5 er). With a deviation from the Davies precedent, the use of ozonolysis conditions for the direct conversion of the styryl moiety to the methyl ester shortened the route to enantioenriched diester cyclopropanes by one step.[25]

Scheme 3-12. Access to Enantiomerically Enriched D–A Cyclopropanes



9 **20** **21** **21'**

9a Ar = Ph

9c Ar = 4-NCC$_6$H$_4$

21a : 21a' 3:1 dr

21c : 21c' 5:1 dr

mixture of **21a / 21a'** → **(–)-11a** 76:24 er

21c → **(–)-11c** 95:5 er

The lower enantiomer ratio for the cyclopropane **(–)-11a** annulation substrate is a consequence of the fact that the diastereomers of **21a** from the cyclopropanation were inseparable. The diastereomers **21c/21c'** of the intermediate cyclopropane were separable when starting from **9c**, and the major diastereomer was carried through to the oxidative cleavage of the styryl moiety to give the cyclopropane **(–)-11c**. Thus, this modification of the Davies approach should be applicable to obtaining highly enantioenriched diester cyclopropanes from a variety of 1,1-disubstituted olefins as long as the diastereomers of the intermediate styryl cyclopropanes are separable. It is apparent that the catalyst is able to exert a high degree of control over the facial selectivity with respect to the carbenoid, but the facial selectivity with respect to the olefin is only moderately controlled. These enantioenriched substrates completed a small library of quaternary donor-site

cyclopropanes (**11a-f**, **19a-b, (−)-11a**, and **(−)-11c**), which were investigated in (3+2) annulation reactions with aldehydes.

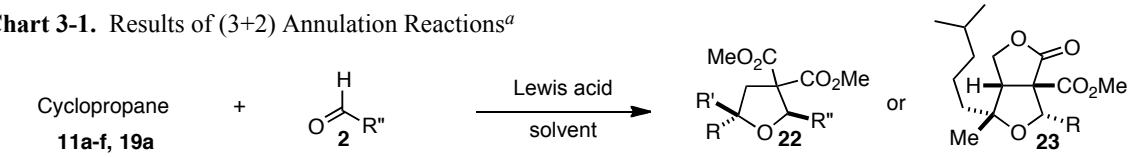
3.4 Results and Discussion: (3+2) Annulation Reactions

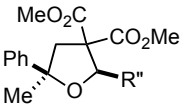
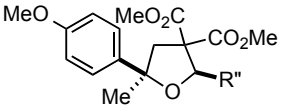
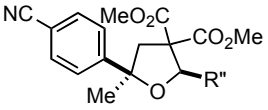
The initial results obtained with the Ph/Me cyclopropane **11a** and benzaldehyde were promising, and required limited deviation from the optimal conditions established in the initial D−A cyclopropane/aldehyde annulation. The only deviation was a change in solvent from dichloromethane to 1,2-dichloroethane. This change was made based on the NMR yield in a few preliminary trials being slightly higher in dichloroethane relative to dichloromethane, although the reaction was still successful in the latter solvent. In fact, these (3+2) reactions appear to be fairly tolerant to changes in the identity of the Lewis acid and solvent employed. Throughout the course of these studies (*vide infra*), $Hf(OTf)_4$ and $SnCl_4$ have been employed in certain cases, as has a change in solvent to dichloromethane or toluene. These modifications were made on an empirical basis with reactions that were initially less successful under the standard conditions.

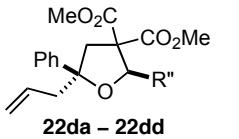
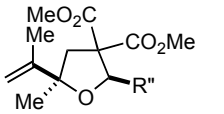
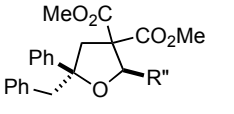
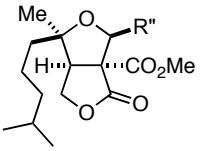
The results of a broad aldehyde screen with cyclopropane **11a** with a wide variety of aldehydes were promising, as summarized in **Chart 3-1**. Across the board, the yields and diastereoselectivities were excellent. The yields were slightly reduced with aliphatic aldehydes, but α-branching was well-tolerated. Other cyclopropane substrates were investigated with a smaller sampling of aldehydes, as the primary goal of the study was to investigate the reactivity of these novel quaternary donor site cyclopropanes. We believe the results obtained with these other cyclopropanes could be generalized to a broader aldehyde scope if desired; the smaller scope of aldehydes with the different cyclopropanes was enough to establish a few general trends for each cyclopropane

investigated. The isopropenyl/Me cyclopropane **11e**, for example, reacted with uniformly high yields and diastereoselectivities to afford products **22ea-ec**.

Chart 3-1. Results of (3+2) Annulation Reactions[a]



THF Product:	R	yield[b] (%)	dr[c]
 **22aa – 22aj**	Ph	91	97 : 3
	4-ClC$_6$H$_4$	91	95 : 5
	Et	83	96 : 4
	^{i}Pr	82	96 : 4
	4-MeO$_2$CMeC$_6$H$_4$	93	99 : 1
	2-MeC$_6$H$_4$	94	97 : 3
	4-CF$_3$C$_6$H$_4$	82	99 : 1
	4-MeOC$_6$H$_4$	95	96 : 4
	(*E*)-CH=CHPh	87	92 : 8
	2-thienyl	91	95 : 5
 **22ba – 22bc**	Ph	91	96 : 4
	4-ClC$_6$H$_4$	87	97 : 3
	Et	74	90 : 10
 **22ca – 22ch**	Ph	90	95 : 5
	4-ClC$_6$H$_4$	90	95 : 5
	Et	59[d]	96 : 4
	4-MeOC$_6$H$_4$	89	95 : 5

THF Product:	R	yield[b] (%)	dr[c]
 **22da – 22dd**	Ph	91	83 : 17
	4-ClC$_6$H$_4$	85	83 : 17
	Et	32[d]	90 : 10
	^{i}Pr	63	90 : 10
 **22ea – 22ec**	Ph	79	96 : 4
	4-ClC$_6$H$_4$	79	99 : 1
	Et	64[e]	99 : 1
 **22fa – 22fc**	Ph	87	80 : 20
	4-ClC$_6$H$_4$	85	80 : 20
	Et	78[d]	81 : 19
 **23aa – 23ac**	Ph	81	99 : 1
	4-ClC$_6$H$_4$	75	99 : 1
	Et	75[f]	77 : 23

[a]Reactions conducted with 5 mol % Sn(OTf)$_2$ with 1.0 equiv. **11** or **19** and 3.0 equiv **2** in 1,2-DCE ([**cyclopropane**]$_0$ = 0.3 M) at room temperature unless stated otherwise. [b]Isolated yield after column chromatography, average of at least two trials. [c]Determined by ^{1}H NMR of crude mixture. [d]Reaction performed with 10 mol % SnCl$_4$ in toluene. [e]Reaction performed with 5 mol % Hf(OTf)$_4$ at -50 ºC. [f]Reaction performed with 10 mol % SnCl$_4$ in 1,2-DCE.

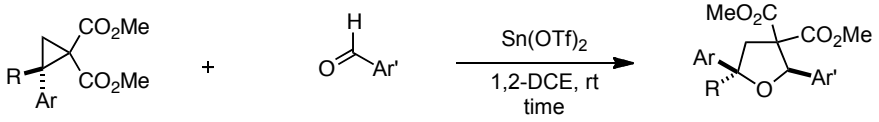
With respect to the cyclopropanes **11b** and **11c** derived from electronically modified α-methylstyrenes, results were comparable to the electron-neutral cyclopropane **11a**. The diastereoselectivity remained just as high as with **11a**, as could be expected on steric grounds. However, there were notable differences with respect to the reaction rates with these substrates. The electron-poor benzonitrile cyclopropane **11c** exhibited lower reaction rates; this was not a problem with aromatic aldehydes, which still gave excellent yields in addition to the high diastereoselectivities (**Chart 3-1**). With aliphatic

aldehydes, the reduced rate of reaction with this cyclopropane meant that slight modifications to the standard procedure had to be made. Under the standard reaction conditions, aliphatic aldehydes decomposed (presumably via enolization/aldol pathways), which led to incomplete consumption of the starting material **11c**. Changing from 5 mol% $Sn(OTf)_2$ in 1,2-DCE to 10 mol% $SnCl_4$ in toluene alleviated this problem, allowing for complete consumption of the cyclopropane.

The electron-rich PMP cyclopropane **11b**, on the other hand, was a fast-reacting substrate. While the reactions may have been complete within seconds of dissolution of all components, in practice they were at most allowed to run for 20 min. This was necessary to observe the high diastereoselectivities summarized in **Chart 3-1**. If the reactions with this substrate were allowed to proceed longer prior to quenching, the diastereoselectivity began to erode, as summarized in **Scheme 3-13**. The reaction of electron-neutral cyclopropane **11a** could be allowed to proceed without quenching the Lewis acid for a full 24 h without any erosion of the initially high dr of product **22aa**. Product **22ba**, derived from the electron-rich cyclopropane **11b**, began to lose its stereochemical integrity within a few hours, and within 24 h it consisted of a 1:1 ratio of diastereomers. It is interesting to note that earlier results from our group with the electron-rich PMP/H cyclopropane **1d** also showed that extended reaction times led to such equilibration. In that case, the diastereomer ratio of the product **3dh** after 3.75 h was still ~92:8,[13] whereas in a similar time frame the PMP/Me product ratio **22ba** had eroded much more significantly to 80:20. The lack of stereochemical erosion of **22aa**, in light of the result with **3dh**, points to the electronic nature of the aryl ring being the determining factor in this process: despite the increased stabilization of a 3º over a 2º

benzylic site, the product maintains its stereochemical integrity throughout the course of an extended reaction.

Scheme 3-13. Experiments Regarding the Erosion of Diastereoselectivity



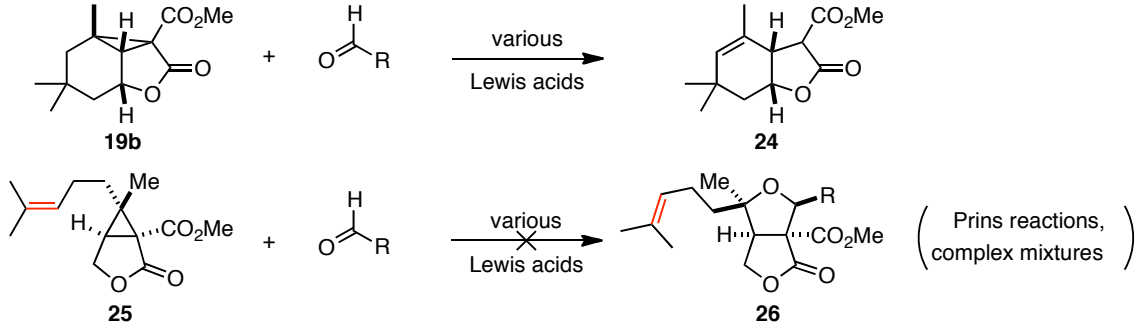
11a	Ar = Ph, R = Me	**2a**	Ar' = Ph	**22aa**	2 h =	*97 : 3 dr*
				Ar = Ph, R = Me	24 h =	*97 : 3 dr*
11b	Ar = PMP, R = Me	**2a**	Ar' = Ph	**22ba**	0.3 h =	*97 : 3 dr*
				Ar = PMP, R = Me	3.5 h =	*80 : 20 dr*
					24 h =	*50 : 50 dr*
ref. 12:						
1d	Ar = PMP, R = H	**2h**	Ar' = PMP	**3dh**	0.1 h =	*> 100 : 1 dr*
				Ar = PMP, R = H	3.75 h =	*92 : 8 dr*

Moving to cyclopropanes **11d (**Ph/allyl) and **11f** (Ph/Bn), with donor sites that are less sterically differentiated (vs. Ar/H or Ar/Me), it was still possible to achieve synthetically useful results, as summarized in **Chart 3-1**. High yields of the products were still obtained with these substrates, although the diastereoselectivity of these reactions was noticeably reduced: approximately 83:17 and 80:20 drs were observed for reactions with **11d** and **11f**, respectively. The yields reported in **Chart 3-1** for products **22da-dc** derived from cyclopropane **11d** are corrected for the amount of the quaternary donor site isomer present in the starting mixture. There were no problems with purification of products **22da-dc** due to the presence of the other isomer; no products derived from the undesired isomer of the starting material were ever isolated. Cyclopropane **11f**, the most sterically demanding substrate investigated, displayed sluggish reactivity in addition to the reduced diastereoselectivity. However, given the above finding with product **22aa** in **Scheme 3-12**, we do not believe that the reduced diastereoselectivity is a result of the increased reaction times leading to product equilibration. Rather, the reduced diastereoselectivity may be due to a few factors in the

transition state for ring closure (*vide infra*). In addition, as a result of the sluggish reactivity, the same modification had to be made for complete conversion of **11f** with aliphatic aldehydes as was made for **11c**—a change to $SnCl_4$ in toluene allowed the reaction to proceed to complete conversion of the cyclopropane.

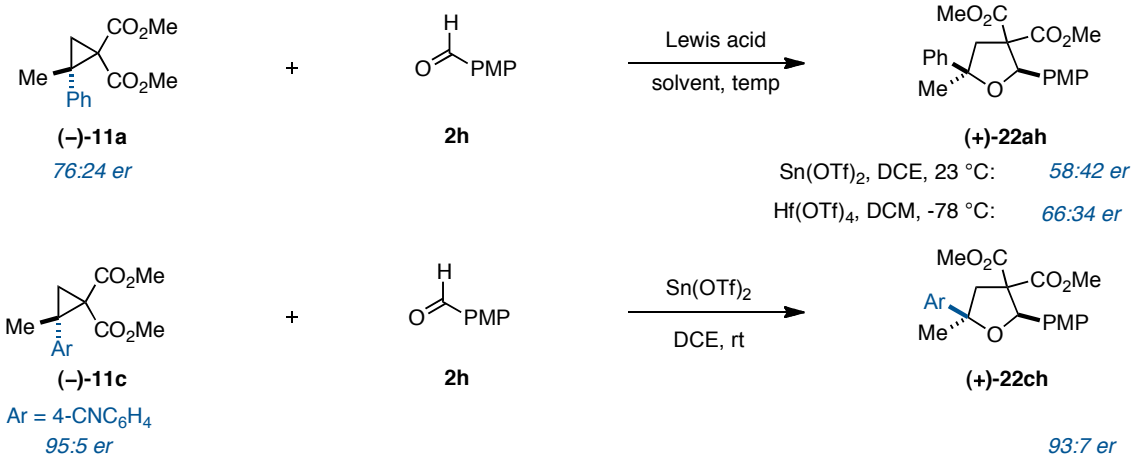
The more highly substituted cyclopropanes synthesized were less broadly successful. The cyclopropane **19b** derived from isophorol was an unsuccessful reaction partner under several different conditions screened. As shown in **Scheme 3-14**, the preferred pathway for this substrate involved elimination to the cyclohexene **24**. It is possible that the geometric constraints of the existing bicyclic ring system were too great, and that subsequent formation of the tricycle was disfavored. The geraniol-derived cyclopropane also gave disappointing results at first: the presence of the tethered alkene in the initial cyclopropane **25** led to apparent Prins-type reactivity and intractable product mixtures. However, simply saturating the alkene by hydrogenation afforded the cyclopropane **19a**, which ultimately was a highly successful reaction partner in (3+2) annulation reactions to give the bicyclic lactone/THF products **23aa-ac** as shown in **Chart 3-1**. This substrate demonstrates the ability of a weaker donor site (alkyl–alkyl) to still allow for the reaction to occur under mild conditions with a reasonable reaction rate. It may therefore be possible to generalize this annulation to other highly substituted cyclopropanes without severe geometric and conformational restraints. An earlier example from our laboratory of a cyclopropane bearing a single alkyl donor required the use of higher catalyst loadings, extended reaction times, and higher temperature.[13]

Scheme 3-14. Initial Annulation Attempts With More Highly Substituted Cyclopropanes



The substrates used for chirality transfer studies were **(–)-11a** and **(–)-11c**, and these results are summarized in **Scheme 3-15**. When the electron-neutral Ph/Me cyclopropane **(–)-11a** was employed using the standard reaction conditions of 5 mol% $Sn(OTf)_2$ at room temperature, the enantioenrichment eroded significantly from 76:24 to 58:42 er in the product **(+)-22ah**. Upon changing to $Hf(OTf)_4$ at -78 ºC in dichloromethane, the erosion of enantioenrichment was attenuated significantly, and the product was isolated with a 66:34 er. Thus, by lowering the temperature of the reaction, the rate of racemization was reduced and the rate of annulation became competitive. By using an electron-poor donor group on the cyclopropane, as in **(–)-11c**, the rate of racemization was almost completely attenuated: even upon subjection to the standard reaction conditions at room temperature, the enantioenrichment of the product only eroded slightly, and **(+)-22ch** was isolated with 93:7 er. These results are consistent with the fact that the ability of the groups at the donor site to stabilize carbenium ion character is directly linked to the rate of racemization, and that in some cases the rate of the (3+2) annulation reaction can exceed the rate of racemization to allow for effective chirality transfer.

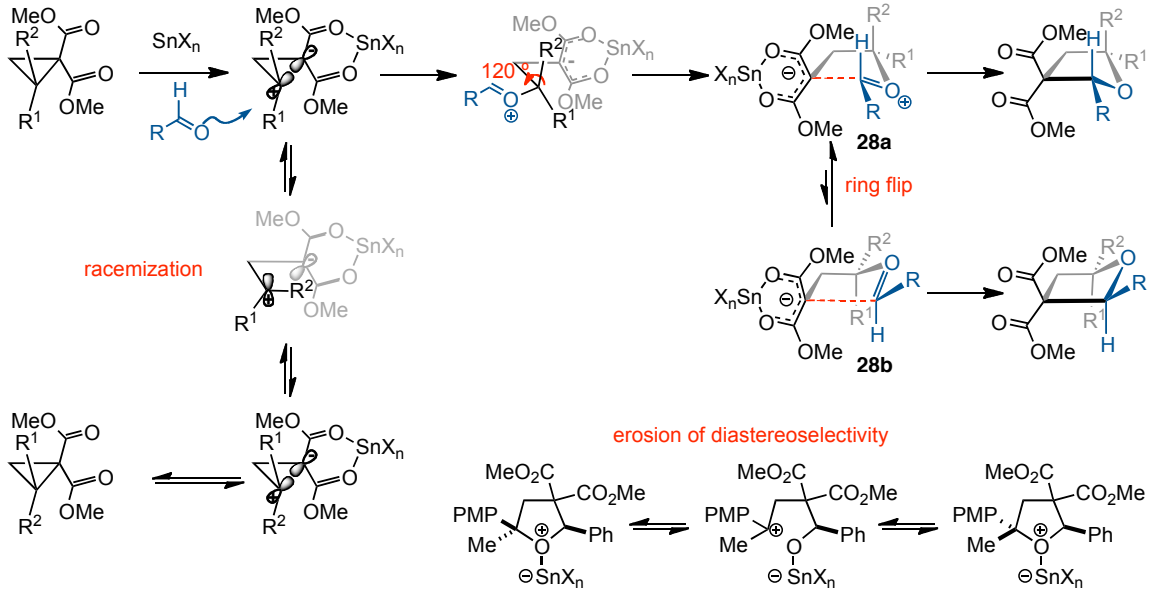
Scheme 3-15. Chirality Transfer Studies With Enantioenriched Starting Materials



The results of the studies outlined in this chapter are internally consistent with the information gained about D–A cyclopropane/aldehyde annulation reactions in all prior studies. The picture can be summarized in **Scheme 3-16**, with particular attention being given to a few processes that are more significant in quaternary donor-site cyclopropanes. Namely, these appear to be racemization, ring flip, and erosion of initially high diastereoselectivity. The chirality transfer studies in this chapter support and extend the link between rate of cyclopropane racemization and carbenium ion stability at the donor site. The reduced diastereoselectivity observed as the substituents on the donor site become less sterically differentiated (Ph/allyl or Ph/Bn vs. Ar/H or Ar/Me) may be attributed to an increased propensity to ring-flip prior to closure; as R and R' approach each other in size, there is a less-distinct preference for placing the larger group pseudoequatorially (**28a** vs. **28b**). A slower rate of ring closure thus likely allows the ring-flipped conformation to be accessed, and the diastereoselectivity erodes. In addition to the increased rate of racemization, increased carbenium ion stability at the donor site is likely responsible for the erosion of diastereoselectivity of the products over time. Here, the increased stabilization in going from a 2º to a 3º benzylic site may be responsible for

allowing this process to occur much more quickly than in the earlier studies involving tertiary donor-site cyclopropanes. The added stabilization is still not enough for electron-neutral aryl donors to lose their stereochemical integrity, and for most of the reactions studied this process posed no threat to the utility of the reactions or their products.

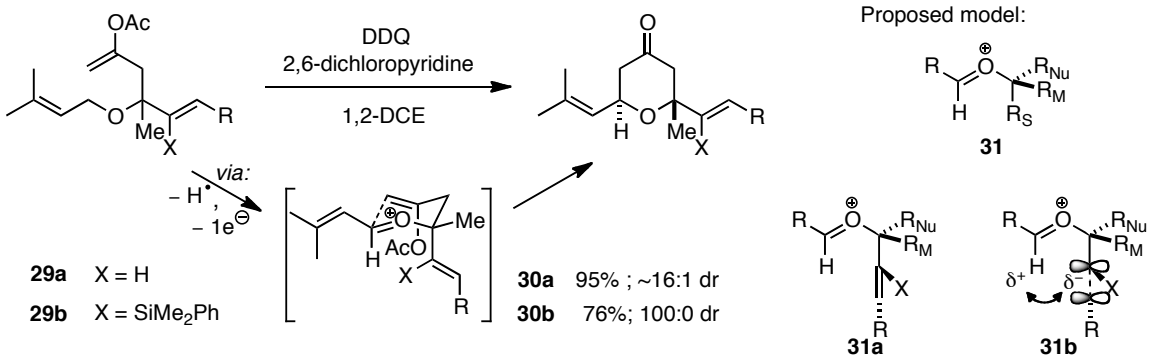
Scheme 3-16. A Similar Mechanism is Operative, While Several Processes are More Significant With Quaternary Donor Site Cyclopropanes



The arguments above are predicated on the assumption that steric size is the dominant factor in determining the envelope conformation preferred in the transition state for ring closure. Moreover, it assumes that the steric size follows the order Ar > CH_2R > CH_3 > H. Floreancig and co-workers have proposed a potentially conflicting model for diastereoselectivity in the formation of 6-membered rings by ring closure of enol acetate nucleophiles onto oxidatively generated oxocarbenium ions.[26] Although generated differently, the oxocarbenium ions accessed in these two studies are similar in that the oxygen atom is flanked on one side by a fully substituted carbon. Two substrates from their study (**29a,b)** are shown in **Scheme 3-17**, leading to the pyranone products **30a,b** via nucleophilic attack of the enol acetate. In their model **31**, R_{Nu} is the tethered

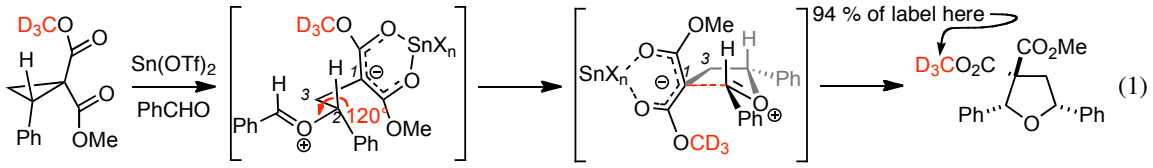
nucleophile, while R_S and R_M denote the relative size of the remaining groups as small and medium, respectively. They propose that a group with a π-system will behave as R_S because it can orient itself perpendicularly and thus present a flat side to minimize unfavorable eclipsing interactions with the formyl proton (**31a**). In addition, they propose that an electrostatic attraction between the electron-deficient formyl proton and the electron-rich π-system would stabilize such a conformation (**31b**). This model, while intriguing, does not rationalize the bulk of our results: applied to our case, it would lead to the 2,5-*trans* relationship between the aryl groups in our THF products. Our 2-D NOESY data, on the other hand, uniformly supports a *cis* relationship between these substituents (see section **3.6** for further details).

Scheme 3-17. A Potentially Conflicting Stereochemical Model in a Related System



The key differences between the two reactions are the ring size of the products being formed, and the potency of the nucleophiles attacking the intermediate oxocarbenium ion to form the products. It should be noted that in the Floreancig system, with substrates that were initially showing poor diastereoselectivity, a change in solvent to nitroethane afforded better results. This improvement was attributed to a slowing of the rate of ring closure in the more polar solvent, thus allowing the reaction to proceed under more thermodynamic control. It is therefore likely that in our case, the greatly

increased nucleophilicity of the malonate (relative to the enol acetate in the Floreancig system) is responsible for a much stricter adherence to kinetic control. Since the rate of ring closure in our case is evidently much more rapid, the initially accessed envelope conformation (**28a**, **Scheme 3-16**) will likely dictate the observed product. Equation 1 reveals the rapidity of ring closure in the cyclopropane annulation: 120º rotation about C2–C3 and closure is significantly faster than rotation about the C1–C3 bond, such that 94% of the isolated product contains the labeled methyl group in a *cis* orientation relative to the phenyl groups.[13]

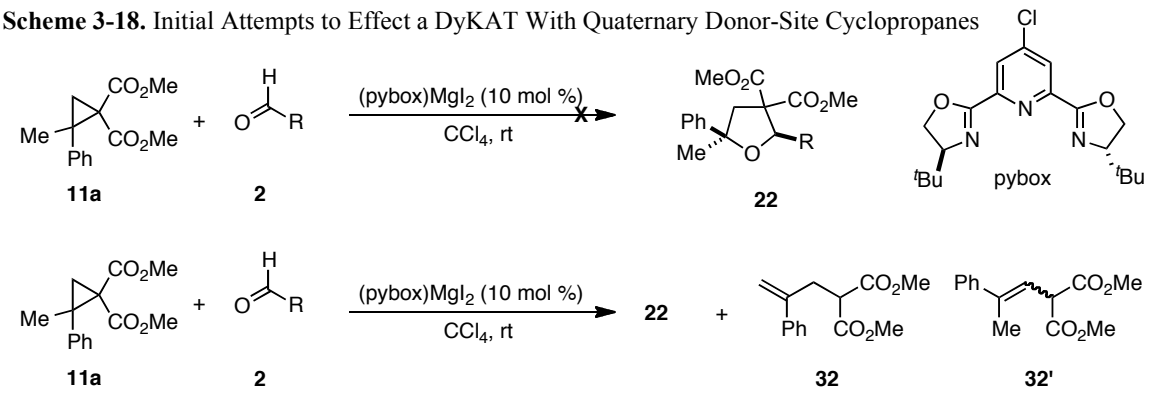


(1)

A potential rationale for reduced the diastereoselectivity with the Ph/allyl and Ph/Bn cyclopropanes in our case that is consistent with Floreancig's model is as follows: a slower rate of ring closure allows for slightly more thermodynamic control, and that in fact the phenyl group would be thermodynamically favored to be the R_S group (placed pseudoaxially as in **28b**). This would serve as the driving force that makes the ring flip (**28a** → **28b**) favorable when ring closure is slow enough that it occurs when the envelope conformation is under slightly more thermodynamic control. The stereochemical erosion observed in (3+2) reactions with electron-rich donor groups is potentially consistent with the idea that these reactions are normally dominated by kinetic control: thermodynamic equilibration leads to different diastereoselectivity. Therefore, the observed stereoselectivity in this chapter may actually support Floreancig's model if it is assumed that the model is operative for reactions which proceed under thermodynamic control. The (3+2)-annulations that our group has developed are primarily under kinetic control.

Given the increased rate of racemization of the quaternary-donor site cyclopropanes studied, it therefore seems likely that a DyKAT may be realized for these substrates as well. Preliminary results along these lines have indicated that while such a process may still be developed, extensive tuning of the catalyst and reaction conditions may be required. Attempts to apply the MgI_2/Pybox system established for the tertiary donor site D–A cyclopropanes have thus far been unsuccessful with quaternary donor site substrates: as shown in **Scheme 3-18**, they demonstrate an increased propensity to eliminate to products **32** and **32'**. This is the biggest competing process at this time, and whether the iodide counterion from the catalyst is participating in this pathway is an open question. It remains likely that further work to optimize this reaction may be successful in the future.

Scheme 3-18. Initial Attempts to Effect a DyKAT With Quaternary Donor-Site Cyclopropanes



3.5 Conclusion

The results discussed in this chapter have expanded some of our group's most successful chemistry in a meaningful way. The expansion of substrate scope from tertiary donor site cyclopropanes to quaternary donor site cyclopropanes has led to a broadly successful solution to an earlier limitation in scope for the synthesis of 2,2,5-trisubstituted THFs. Whereas ketone dipolarophiles lacked generality with earlier D–A

cyclopropanes, here the use of aldehyde dipolarophiles overcomes the inefficiency and byproduct-formation issues which plagued the former approach while giving complementary regioselectivity. The experimental results obtained herein are consistent with the knowledge gained from the earlier studies, and provide further support for our current understanding of these reactions. The continued development of these new quaternary donor site cyclopropanes may thus follow a similar trajectory, and the creation of a dynamic process for them may be still be successful with continued efforts. If not, we have demonstrated that there remains the possibility to access highly enantioenriched THF products from this reaction as long as the donor strength of the fully substituted donor site is attenuated.

3.6 Experimental

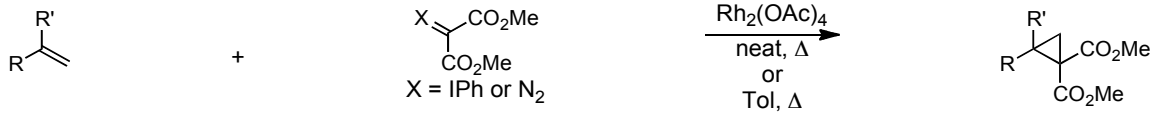
Methods. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 100 or 150 MHz) 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, br s = 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 column 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 chapter's charts and schemes, which are averages of at least two experiments. The diastereomer ratios reported are for crude reaction mixtures. 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,[27] dimethyldiazomalonate,[28] 4-

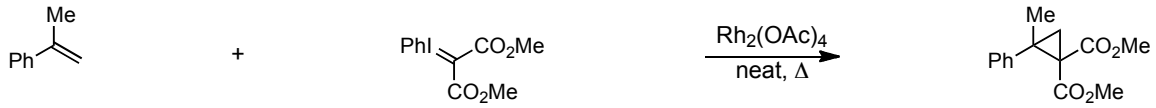
methoxy-α-methylstyrene,[29] 4-isopropenyl benzonitrile,[30] α-allylstyrene,[31] methyl malonyl chloride,[32] *p*-acetamidobenzenesulfonyl azide (*p*-ABSA),[33] copper(II) bis(*t*-butyl-salicylimine),[22] and methyl styryldiazoacetate.[34] Aldehydes used in annulation reactions had been distilled and 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:

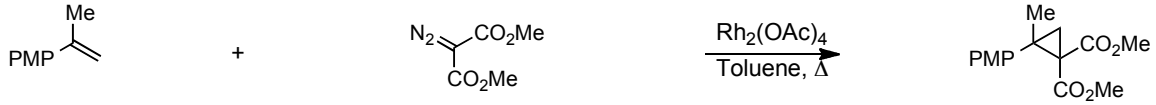


The cyclopropane dicarboxylates were prepared by carbene transfer via $Rh_2(OAc)_4$-catalyzed decomposition of the iodonium ylide- / diazo-malonate precursor. In reactions using dimethyldiazomalonate, precautions were taken to vent the pressure built up from N_2 evolution.

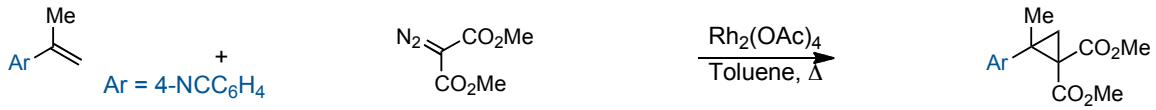
A fine suspension of $Rh_2(OAc)_4$ (0.012 g, 0.0277 mmol, 0.01 equiv.), alkene (1.0 g, 6.93 mmol, 2.5 equiv.) and dimethyldiazomalonate (0.439 g, 2.77 mmol, 1.0 equiv.) was made in a flame dried reaction tube in toluene (2 mL) and placed under a stream of nitrogen. A large-bore needle was inserted through 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 column chromatography using an hexanes flush followed by the indicated eluent system.



Dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (11a). The title compound was prepared according to the literature procedure using α-methylstyrene **9a** and the iodonium ylide **10b**.[20] The spectral data were in accordance with those reported.

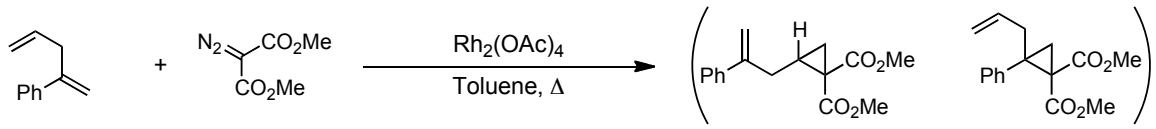


Dimethyl 2-(4-methoxyphenyl)-2-methylcyclopropane-1,1-dicarboxylate (11b). The title compound was prepared according to General Procedure A using 4-methoxy-α-methylstyrene **9b** (1.5 g, 10 mmol, 2.5 equiv.), dimethyldiazomalonate **10a** (0.632 g, 4 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (0.018 g, 0.40 mmol, 0.01 equiv.) in 2 mL toluene. After workup, the residue was purified by flash column chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.600 g (54%) of cyclopropane **11b** as a colorless oil. Analytical data for **11b**: **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.



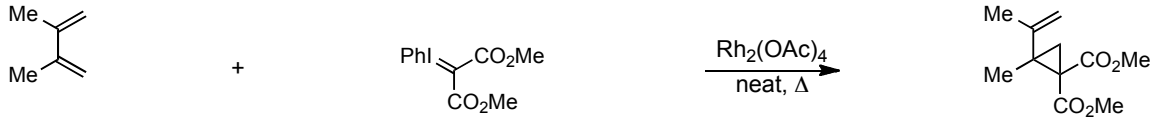
Dimethyl 2-(4-cyanophenyl)-2-methylcyclopropane-1,1-dicarboxylate (11c). The title compound was prepared according to General Procedure A using 4-

isopropenylbenzonitrile **9c** (0.695 g, 4.85 mmol, 2.5 equiv.), dimethyldiazomalonate **10a** (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 column chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.243 g (45%) of cyclopropane **11c** as a pale yellow oil. Analytical data for **11c**: **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 $C_{15}H_{15}O_4$+Na: 296.1, Found: 296.1.



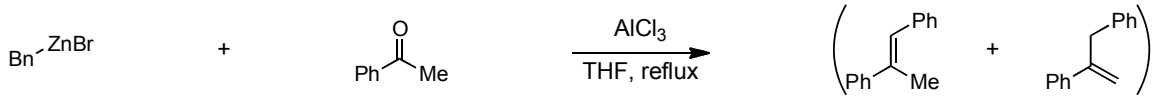
Dimethyl 2-allyl-2-phenylcyclopropane-1,1-dicarboxylate (11d). The title compound was prepared according to General Procedure A using $Rh_2(OAc)_4$ (0.012 g, 0.0277 mmol, 0.01 equiv.), α-allylstyrene **9d** (1.0 g, 6.93 mmol, 2.5 equiv.), dimethyldiazomalonate **10a** (0.439 g, 2.77 mmol, 1.0 equiv.) and 2 mL of toluene. After workup, the residue was purified by flash column chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.537 g (70%) of as a colorless oil in an 86:14 inseparable mixture of desired cyclopropane **11d** to the undesired isomer **11d'**. Attempted separation via HPLC was also unsuccessful. The mixture **11d**/**11d'** was used in annulation reactions as such, with no apparent deleterious effects. Analytical data for **11d**/**11d'**: **IR** (thin film, cm^{-1}): 3027, 2952, 2359, 1736, 1436, 1275, 1224, 1126; **^{1}H NMR** (600 MHz, $CDCl_3$): **11d**: 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); **11d'**: 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, $CDCl_3$): **11d**: 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; **11d'**: 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.



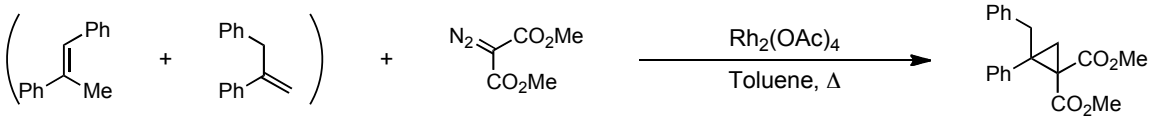
Dimethyl 2-methyl-2-(prop-1-en-2-yl)cyclopropane-1,1-dicarboxylate (11e). The title compound was prepared according to the literature procedure using 2,3-dimethylbutadiene **9e** and the iodonium ylide **10b**.[20] The spectral data were in accordance with those reported.

Dimethyl 2-benzyl-2-phenylcyclopropane-1,1-dicarboxylate (11f).



The reaction of benzylzinc bromide with acetophenone was carried out via a modification of the literature procedure.[35] 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 cooled to room temperature and quenched with sat. aq. 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 brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (100% hexanes) to afford 1.81 g (93%) of a white solid which consisted of a 2:1 mixture of *trans*-(α-methyl)-stilbene **12** and α-benzylstyrene **9f**.

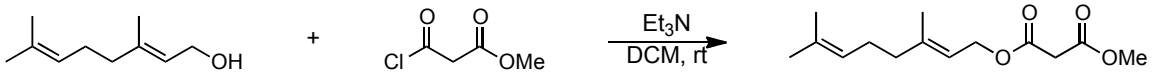


Dimethyl 2-benzyl-2-phenylcyclopropane-1,1-dicarboxylate (11f). The title compound **11f** was prepared according to General Procedure A using the **9f/12** mixture(1.81 g, 9.3 mmol, 2.5 equiv.), dimethyldiazomalonate **10a** (0.589 g, 3.73 mmol, 1.0 equiv.), and $Rh_2(OAc)_4$ (0.016 g, 0.0373 mmol, 0.01 equiv.) in 2 mL toluene. The trisubstituted olefin **12** was completely unreactive and easily separated from the product cyclopropane by flash column 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 **11f** as a waxy solid. Analytical

data for **11f**: **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.

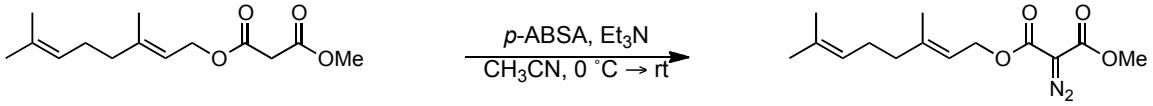
Attempted cyclopropanation of the **9f**/**12** mixture revealed that the 1,1-disubstituted olefin **9f** reacted and the trisubstituted olefin **12** did not. Subsequent attempts with different Rh catalysts (Rh_2esp_2, $Rh_2(OTFA)_4$) and solvents (DCM) also yielded no cyclopropane from carbene transfer to the trisubstituted olefin.

Preparation of methyl 6-methyl-6-(4-methylpentyl)-2-oxo-3-oxabicyclo[3.1.0] hexane-1-carboxylate (19a):



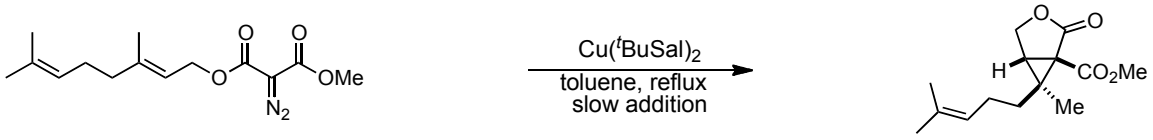
Methyl geranyl malonate (E-1). To a 0 ºC solution of geraniol (0.250 g, 1.62 mmol, 1.0 equiv.) and methyl malonyl chloride (0.221 g, 1.70 mmol, 1.05 equiv.) in dichloromethane (6 mL) under nitrogen was added triethylamine (0.172 g, 0.24 mL, 1.70 mmol, 1.05 equiv.) over 5 min. The reaction was allowed 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 sat. aq. 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 extracts were washed with H_2O (2x) and brine, then combined, dried over $MgSO_4$, and concentrated *in vacuo*. The residue

was purified by flash column chromatography (10% EtOAc/hexanes) to afford 0.360 g (83%) of **E-1** as a yellow oil. Analytical data for **E-1**: **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.

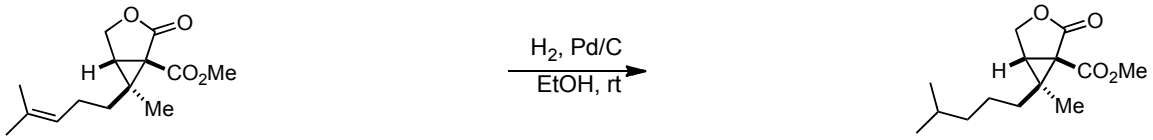


Methyl geranyl diazomalonate (E-2). To a 0 ºC solution of **E-1** (0.360 g, 1.42 mmol, 1.0 equiv.) in dry acetonitrile (14 mL) was added *p*-ABSA (0.389 g, 1.49 mmol, 1.05 equiv.). Triethylamine (0.287 g, 0.40 mL, 2.83 mmol, 2.0 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring overnight. Upon complete consumption of starting material as indicated by TLC analysis, the reaction was quenched with sat. aq. 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 extracts were washed with H_2O (2x) and brine, then combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 0.364 g (91%) of **E-2** as a yellow oil. Analytical data for **E-2**: **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.

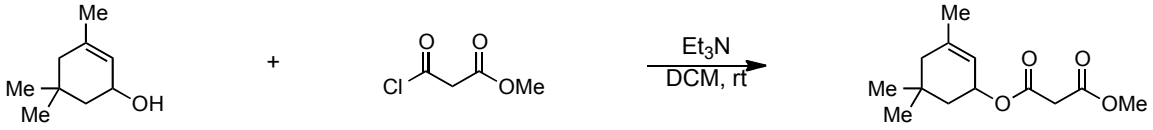


Methyl 6-methyl-6-(4-methylpent-3-en-1-yl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (E-3). To a refluxing solution of copper(II) bis(*t*-butyl-salicylimine) (0.057 g, 0.137 mmol, 0.05 equiv.) in toluene (68 mL) was added a solution of **E-2** (0.770 g, 2.74 mmol, 1.0 equiv.) in toluene (25 mL) over 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 **E-2**. The reaction was concentrated *in vacuo* and the residue was purified via flash column chromatography (20% EtOAc/hexanes) to afford 0.555 g (80%) of cyclopropane **E-3** as a yellow solid. Analytical data for **E-3**: 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.



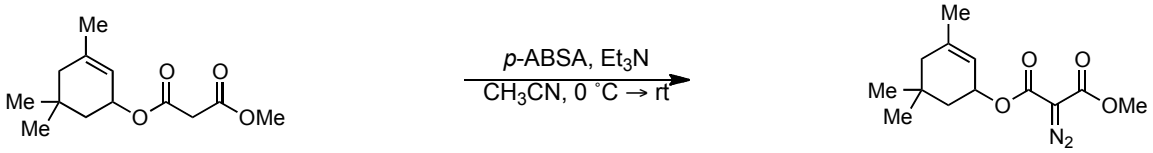
Methyl 6-methyl-6-(4-methylpentyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (19a). A flame-dried round bottomed flask was charged with 10% Pd/C (0.030 g, 0.0276

mmol Pd, 0.01 equiv Pd) and placed under a stream of nitrogen. **E-3** (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 column chromatography (10% EtOAc/hexanes) to afford 0.450 g (64%) of the cyclopropane **19a** as a white solid. Analytical data for **19a**: 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.



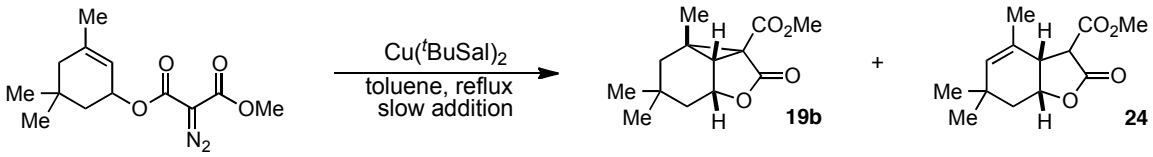
Methyl isophoryl malonate (E-4). To a solution of isophorol (1.2 mL, 1.1 g, 7.85 mmol), *N*,*N*-dimethylamino pyridine (0.192 g, 1.57 mmol, 0.2 equiv.), and triethylamine (2.2 mL, 1.59 g, 15.7 mmol), in dry dichloromethane (30 mL) under N_2 at 0 ºC was added a solution of methyl malonyl chloride (1.5 g, 11 mmol, 1.4 equiv.) in 10 mL dichloromethane via cannula. The reaction was allowed to warm to room temperature

overnight (12 h), by which point triethylammonium salts had precipitated and these were filtered. The mixture was concentrated in vacuo, and the product was triturated out and filtered away from the ammonium salts using 1:1 Et_2O/hexanes. The mixture was concentrated, and the crude red-orange oil was purified via column chromatography using 10% EtOAc/hexanes to afford 1.28 g (5.3 mmol, 68%) of the product as a clear, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ: 5.39 (br s, 2H), 3.74 (s, 3H), 3.69 (s, 2H), 1.86 (d, J = 17.2 Hz), 1.75 (dd, J = 12.8, 5.6 Hz), 1.69 (s, 3H), 1.67 (d, J = 17.2 Hz), 1.42 (dd, J = 12.8, 8.0 Hz), 0.99 (s, 3H), 0.94 (s, 3H).



Methyl isophoryl diazomalonate (E-5). To a stirred suspension of **E-4** (1.27 g, 5.28 mmol, 1.0 equiv.) and *p*-ABSA (1.65 g, 6.87 mmol, 1.3 equiv.) in acetonitrile (20 mL) at 0 ºC was added triethylamine (1.5 mL, 1.07g, 10.6 mmol, 2 equiv.). The reaction was covered in foil and allowed to gradually warm to room temperature as it stirred for 2.5 d. After this time, 1:1 Et_2O/hexanes (approx. 50 mL) were added to precipitate more of the sulfonamide byproduct. The reaction was filtered and concentrated, and the remaining sulfonamide byproduct was removed by trituration and filtration using additional 1:1 Et_2O/hexanes, and the mixture was concentrated to a crude oil which was purified via column chromatography using 10% EtOAc/hexanes to afford 1.34g (95%) of the product as a pale yellow oil. Analytical data for **E-5**: **IR** (thin film, cm^{-1}): 2954, 2869, 2135, 1761, 1731, 1692, 1434, 1368, 1332, 1272, 1181, 1081, 930, 761; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.46 (br s, 1H) 5.43 (br s, 1H), 3.83 (s, 3H), 1.84 (d, 17.4 Hz, 1H), 1.76 (dd, J = 13.2, 7.2 Hz, 1H), 1.70 (d, J = 17.4 Hz, 1H), 1.68 (s, 3H), 1.47 (dd, J = 13.2, 7.2 Hz,

1H), 0.98 (s, 3H), 0.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.8, 160.6, 139.3, 118.5, 71.5, 52.4, 43.9, 40.5, 30.4, 29.7, 27.7, 27.6, 23.7; **TLC** (20% EtOAc/hexanes), R_f 0.38 (UV/CAM); **LRMS** (ESI): Calcd. for $C_{13}H_{18}N_2O_4$+Na: 289.12; found: 289.12; Calcd. for $C_{13}H_{18}N_2O_4$+Cs: 399.03; found: 399.04

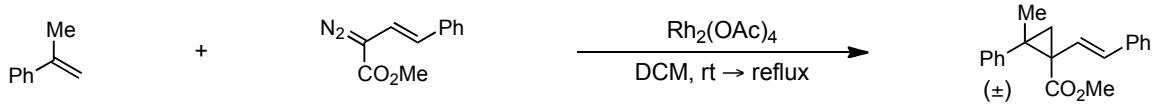


Methyl 2b,4,4-trimethyl-2-oxooctahydrocyclopropa[cd]benzofuran-2a-carboxylate (19b). To a refluxing solution of copper(II) bis(*t*-butyl-salicylimine) (0.011 g, 0.026 mmol, 0.04 equiv.) in toluene (5 mL) was added a solution of **E-5** (0.180 g, 0.65 mmol, 1.0 equiv.) in toluene (5 mL) over 20 hours 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 **E-5**. The reaction was concentrated *in vacuo* and the residue was purified via flash column chromatography (15% EtOAc/hexanes) to afford 0.060 g (38%) of cyclopropane **19b** as a clear oil. Analytical data for **19b**: **IR** (thin film, cm^{-1}): 2955, 2871, 1771, 1731, 1438, 1348, 1313, 1231, 1156, 1096, 1064, 1048, 1008, 977; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.87 (app t, *J* = 5.4 Hz, 1H), 3.83 (s, 3H), 2.62 (d, *J* = 5.4 Hz, 1H), 1.74 (d, *J* = 15.6 Hz, 1H), 1.64 (d, *J* = 15.6 Hz, 1H), 1.48 (dd, *J* = 15.6, 4.8 Hz, 1H), 1.42 (d, *J* = 15.6 Hz, 1H), 1.37 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): 169.7, 166.2, 74.0, 52.9, 43.0, 39.1, 38.1, 32.61, 32.55, 32.0, 31.7, 28.9, 21.5; **TLC** (20% EtOAc/hexanes), R_f 0.20 (CAM only); **LRMS** (ESI): Calcd. for $C_{13}H_{18}O_4$+Na: 261.11, found: 261.12; Calcd. for $C_{13}H_{18}O_4$+Cs: 371.03, found: 371.03

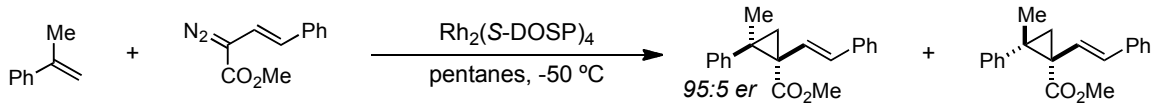
Analysis of the crude reaction mixture indicated a ~1:1 ratio of desired product **19b** to the

tentatively assigned cyclohexene **24**, which was subsequently observed to be the exclusive product formed during attempted (3+2) annulation reactions. **^{1}H NMR** (400 MHz, $CDCl_3$) for **24**: δ 5.36 (s, 1H), 4.93-4.88 (m, 1H), 3.84 (s, 3H), 3.40-3.37 (m, 2H), 1.91 (dd, J = 12.8, 4 Hz, 1H), 1.62 (d, J = 12.8 Hz, 1H), 1.01 (s, 3H), 0.96 (s, 3H).

Preparation of Enantioenriched Cyclopropanes for Chirality Transfer Studies:

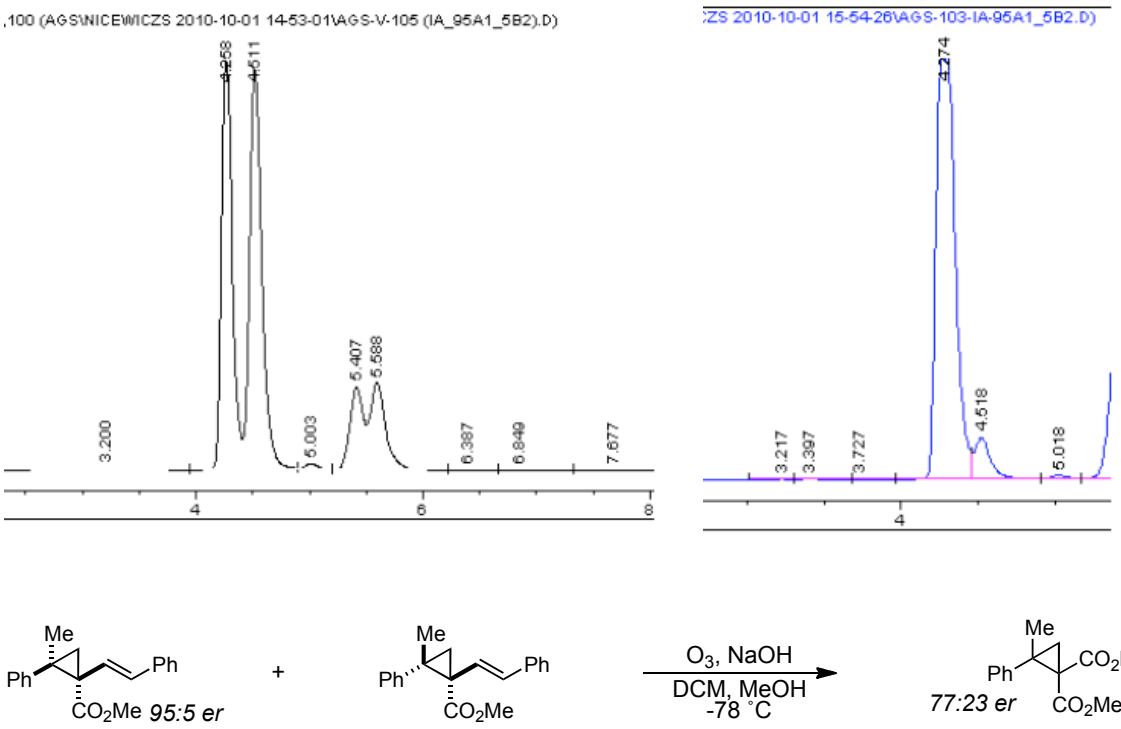


(*E*)-methyl 2-methyl-2-phenyl-1-styrylcyclopropanecarboxylate (21a/21a'). The racemic reaction was conducted as follows: To a solution of $Rh_2(OAc)_4$ (0.002 g, 0.00494 mmol, 0.01 equiv.) and α-methylstyrene **9a** (0.228 mL, 2.47 mmol, 5.0 equiv.) in dichloromethane (4.94 mL) was added a solution of methyl styryldiazoacetate **20** (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 the styryldiazoacetate **20** as indicated by TLC analysis, the reaction was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.090 g (63%) of product *rac*-**21a**/**21a'** as a yellow solid in 75:25 dr.



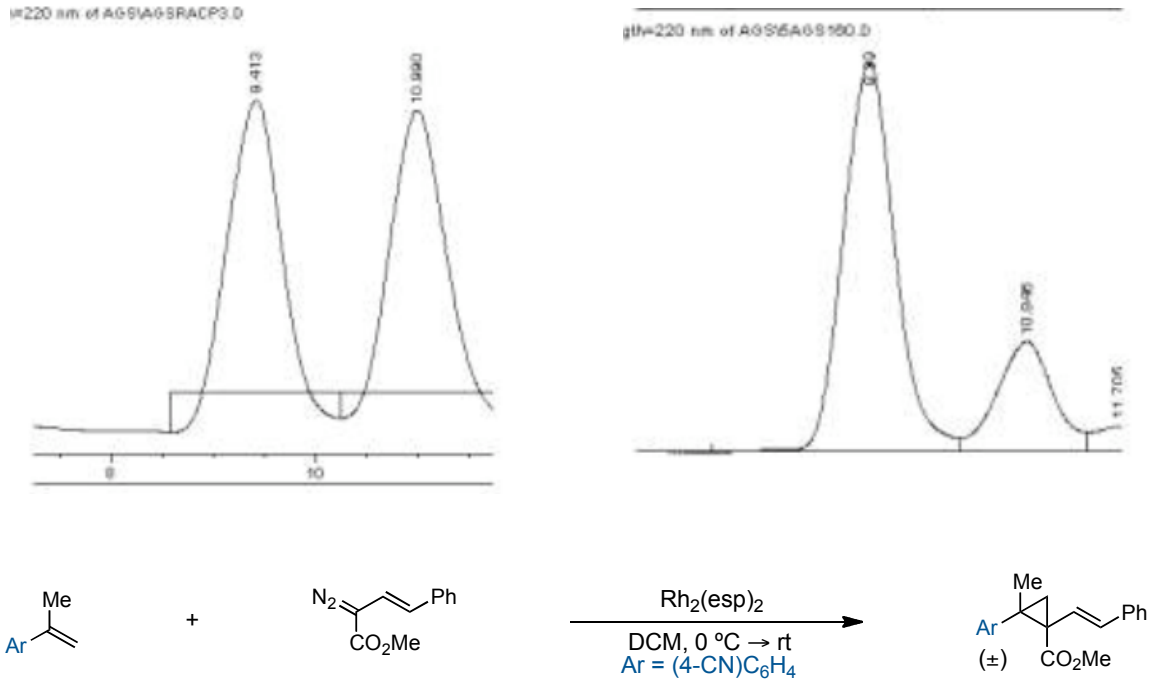
The enantioselective reaction was performed according a modified literature method.[24] To a -50 ºC solution of Rh_2(*S*-DOSP)$_4$ (0.040 g, 0.021 mmol, 0.01 equiv.) and α-methylstyrene **9a** (1.38 mL, 10.6 mmol, 5.0 equiv.) in pentanes (35 mL) was added a solution of methyl styryldiazoacetate **20** (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 **20** was discharged. The reaction was warmed to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.404 g (65%) of product **21a**/**21a'** 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 **21a**/**21a'**: **IR** (thin film, cm^{-1}): 3059, 3026, 2951, 2872, 1727, 1602, 1496, 1435, 1239, 1123, 964, 744, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) **21a**: 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); **21a'**: 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.



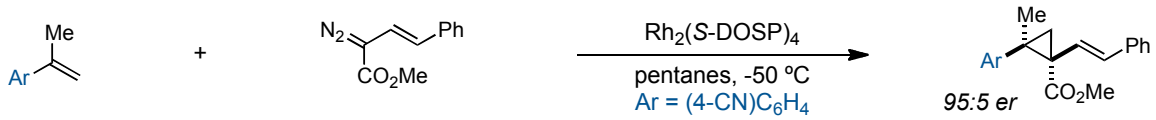
Enantioenriched dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (–)-11a. The cyclopropane dicarboxylate was prepared according to a modified literature method.[25] To a solution of **21a**/**21a'** (0.290 g, 0.993 mmol, 1.0 equiv.) in dry dichloromethane (16 mL) at -78 ºC under nitrogen was 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 **21a**/**21a'.** The solution was purged by sparging with nitrogen for 5 minutes until colorless and then warming to room temperature. The reaction was poured into H_2O, the layers were separated and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with H_2O and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes flush followed by 20% EtOAc/hexanes) to afford 0.160 g (65%) of cyclopropane **(–)-11a** 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.

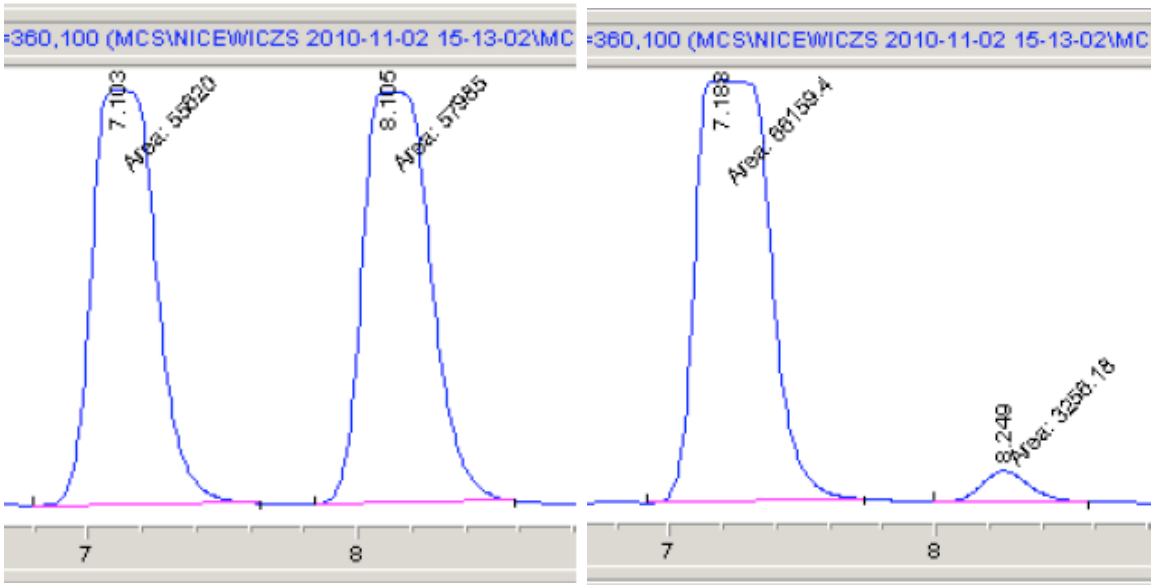


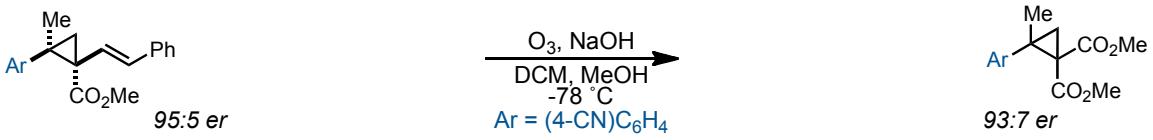
(*E*)-methyl 2-(4-cyanophenyl)-2-methyl-1-styrylcyclopropanecarboxylate (21c). The racemic reaction was conducted according to a literature procedure.[36] To a 0 ºC solution of $Rh_2(esp)_2$ (0.001 g, 0.0006 mmol, 0.001 equiv.) and 4-isopropenylbenzonitrile **9c** (0.087 g, 0.609 mmol, 1.0 equiv.) in dry dichloromethane (1.5 mL) under a stream of nitrogen was added a solution of methyl styryldiazoacetate **20** (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 **9c**, and the reaction was concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 0.135 g (70%) of product *rac*-**21c**/**21c'** as a white foam in 85:15 dr. The diastereomers were separable by careful flash column chromatography, or

more conveniently by preparative HPLC (10% EtOAc/hexanes).



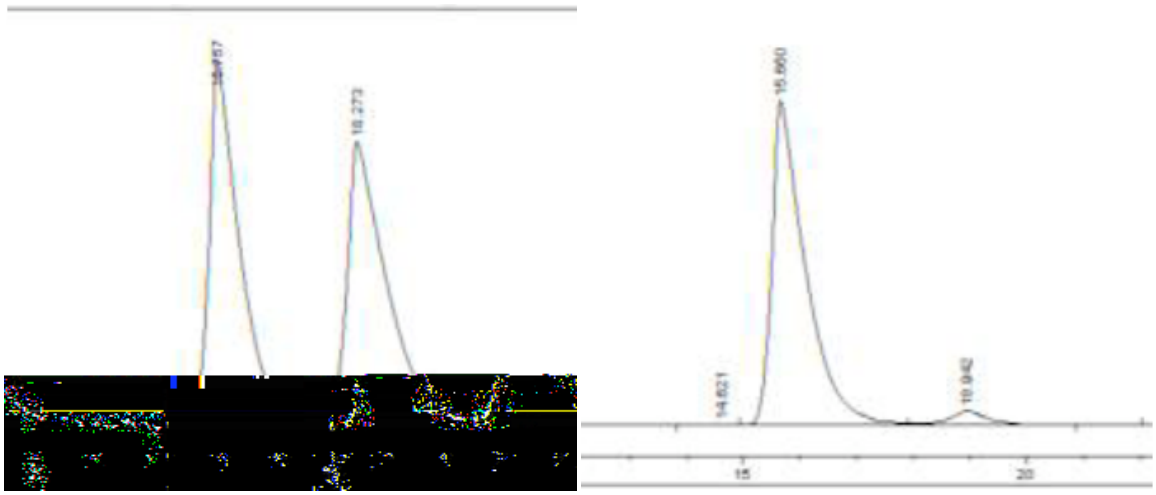
The enantioselective reaction was performed according to a modified literature method.[24] To a -30 ºC solution of Rh_2(*S*-DOSP)$_4$ (0.025 g, 0.0133 mmol, 0.01 equiv.) and 4-isopropenylbenzonitrile **9c** (0.230 g, 1.60 mmol, 1.2 equiv.) in pentanes (30 mL) was added a solution of methyl styryldiazoacetate **20** (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 column chromatography (10% EtOAc/hexanes) followed by preparative HPLC (10% EtOAc/hexanes) to afford 0.200 g (47%) of product diastereomer **21c** in 95:5 er as determined by chiral stationary phase 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 **21c**: **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, $CHCl_3$).

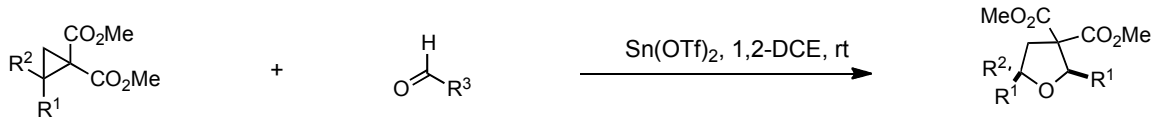




Enantioenriched dimethyl 2-(4-cyanophenyl)-2-methylcyclo-propane-1,1-dicarboxylate dicarboxylate ((–)-11c). The cyclopropane dicarboxylate was prepared according to a modified literature method.[25] To a solution of **21c** (0.053 g, 0.167 mmol, 1.0 equiv.) in dry dichloromethane (2.7 mL) at -78 ºC under 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 **21c.** The solution was purged by sparging with nitrogen for 5 minutes until colorless and then warming to room temperature. The reaction was poured into H_2O, the layers were separated and the aqueous layer was extracted 3x with Et_2O. The combined organic extracts were washed with H_2O and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes flush followed by 30% EtOAc/hexanes) to afford

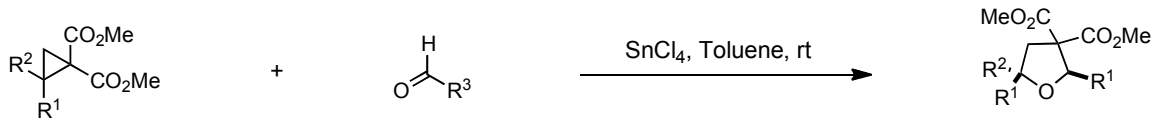
0.038 g (83%) of product **(–)-11c** as a colorless oil in 93:7 er as determined by SFC analysis (Chiralcel WO column, 1.2 mL/min flow rate, 0.6% MeOH modifier, 200 bar, 220nm) $t_{r\text{-major}}$ 15.6 min, $t_{r\text{-major}}$ 18.9 min; $[\alpha]_D^{27}$ = -77.884 (*c* = 0.750, $CHCl_3$). Spectral data were consistent with racemic material.



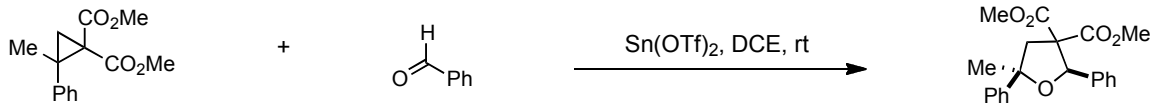


Cyclopropane-Aldehyde Annulation Reactions: General Procedure B: In a glovebox, a dry Teflon screw-cap vial (vial A) containing a magnetic stir bar was charged with $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.). In a separate vial (vial B), a solution of cyclopropane dicarboxylate **11** or **19** (1.0 equiv.) and aldehyde **2**(3.0 equiv.) was prepared in 1,2-dichloroethane (X mL). This solution was transferred via pipette to vial A, followed by a X mL 1,2-dichloroethane rinse of vial B to ensure complete transfer ([**cyclopropane**]$_0$ = 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 **11** or **19**. 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 column chromatography using an hexanes flush followed by the indicated eluent system.



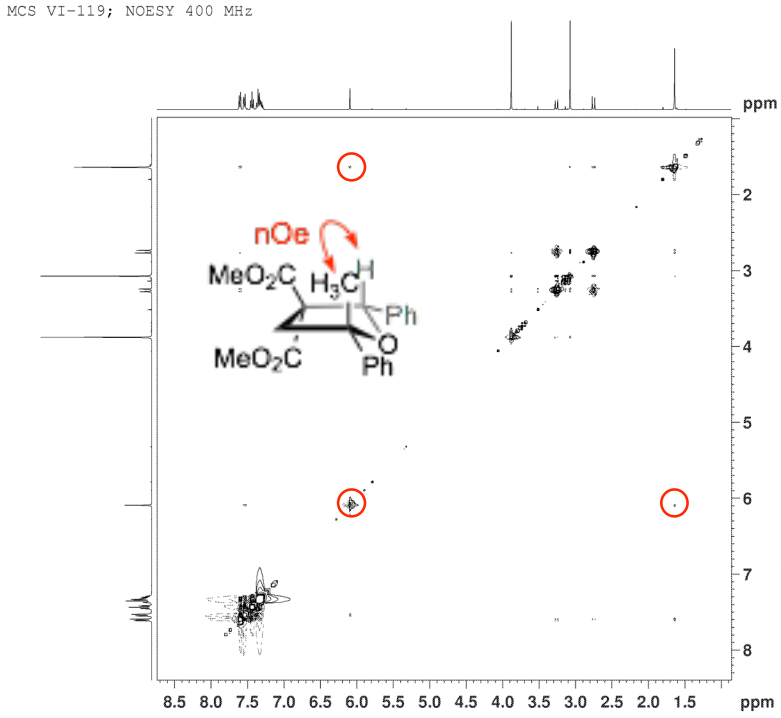
Cyclopropane-Aldehyde Annulation Reactions: General Procedure C: In a glovebox, a dry Teflon screw-cap vial (vial A) containing a magnetic stir bar was charged with cyclopropane dicarboxylate **11** (1.0 equiv.), aldehyde **2** (3.0 equiv.) and X mL dry toluene ([**cyclopropane**]$_0$ = 0.3 mmol/mL). The vial was capped with a septum, the mixture was brought out of the glovebox, placed under nitrogen, and stirred at room temperature. $SnCl_4$ (0.10 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 **11** or **19**. 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 column chromatography using an hexanes flush followed by the indicated eluent system.

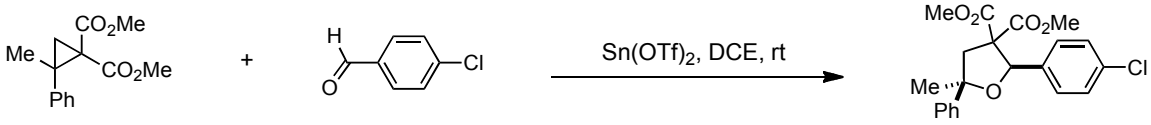


Dimethyl 5-methyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (22aa). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), benzaldehyde **2a** (0.103 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After

workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.100 g (88%) of the product **22aa** as a white solid in 97:3 dr. Analytical data for **22aa**: 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.

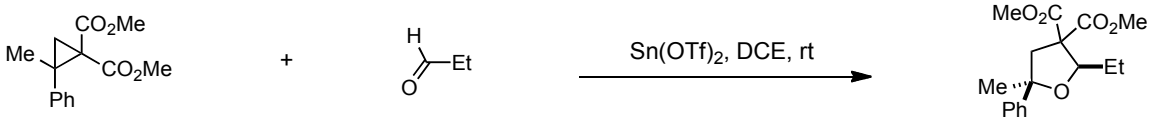
The following is an example of the 2-D NOESY data gathered for each of the THF products in this chapter, which demonstrates the *cis*-relationship between the aryl group on the donor site of cyclopropanes **11** and the incoming R group from the aldehyde **2** (in this case, Ph). The nOe between the donor methyl (or methylene, as appropriate) and the C2 methine proton is diagnostic.



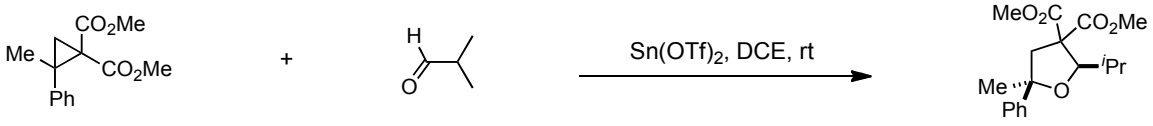


Dimethyl 2-(4-chlorophenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)dicarboxylate (22ab). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), 4-chlorobenzaldehyde (0.136 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.110 g (88%) of the product **22ab** as a colorless oil in 96:4 dr. Analytical data for **22ab**: **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

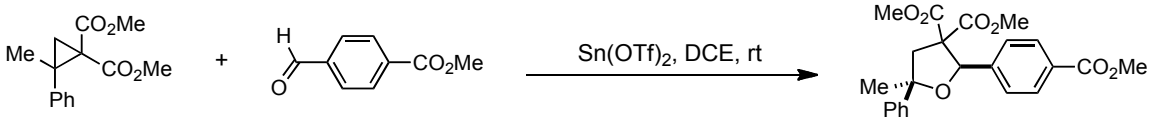
= 13.6 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 168.9, 146.8, 136.5, 133.8, 128.6, 128.3, 128.0, 127.0, 124.6, 83.8, 82.0, 66.6, 53.0, 52.3, 47.5, 27.9; **TLC** (20% EtOAc/hexanes), R_f 0.42 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{21}H_{21}ClO_5$+Na: 411.1, Found: 411.1.



Dimethyl 2-ethyl-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22ac). The title compound was prepared according to General Procedure B using cyclopropane **11a** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.081 g (82%) of the product **22ac** as a colorless oil in 96:4 dr. Analytical data for **22ac**: **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.

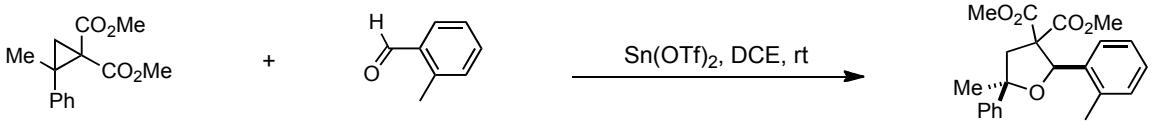


Dimethyl 2-isopropyl-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22ad). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), isobutyraldehyde (0.070 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.085 g (82%) of the product **22ad** as a colorless oil in 96:4 dr. Analytical data for **22ad**: **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 (UV / CAM); **LRMS** (ESI): Calcd. for $C_{18}H_{24}O_5$+Cs: 453.1, Found: 453.1.



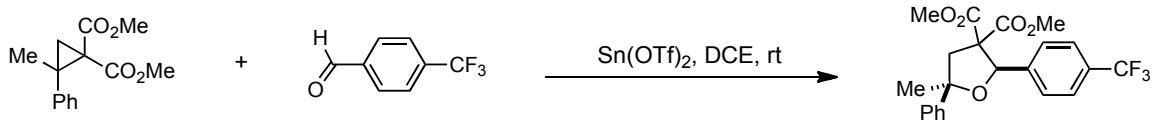
Dimethyl 2-(4-(methoxycarbonyl)phenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22ae). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), methyl-4-formylbenzoate (0.159 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.123 g (93%) of the product **22ae** as a white solid in 99:1 dr. Analytical data for **22ae**: 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.

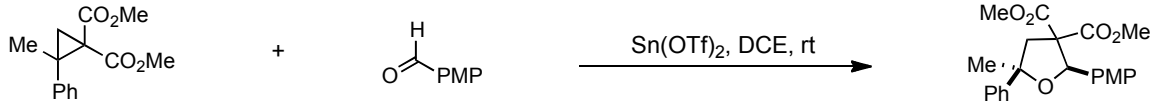


Dimethyl 5-methyl-5-phenyl-2-(o-tolyl)dihydrofuran-3,3(2H)-dicarboxylate (22af). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), *o*-tolualdehyde (0.116 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.110 g (93%) of the product **22af** as a white solid in 97:3 dr. Analytical data for **22af**: 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.

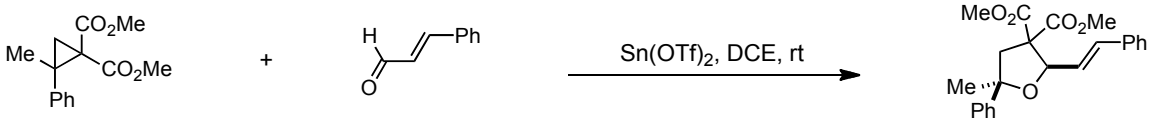


Dimethyl 5-methyl-5-phenyl-2-(4-(trifluoromethyl)phenyl)dihydrofuran-3,3(2*H*)-dicarboxylate (22ag). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.115 g (85%) of the product **22ag** as a colorless oil in 99:1 dr. Analytical data for **22ag**: **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.



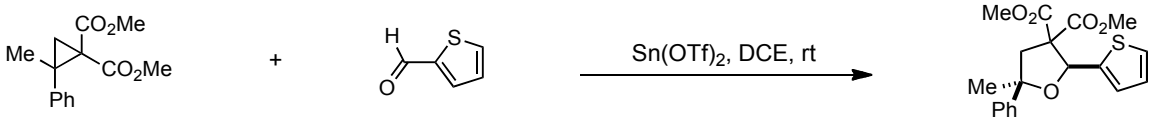
Dimethyl 2-(4-methoxyphenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22ah). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), *p*-anisaldehyde (0.132 g,

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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.117 g (95%) of the product **22ah** as a colorless oil in 96:4 dr. Analytical data for **22ah**: **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.

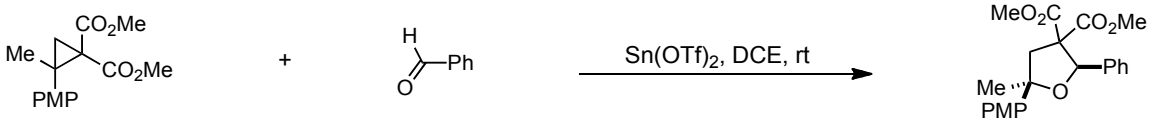


Dimethyl 5-methyl-5-phenyl-2-((*E*)-styryl)dihydrofuran-3,3(2*H*)-dicarboxylate (22ai). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), cinnamaldehyde (0.128 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.113 g (92%) of the product **22ai** as a colorless oil in 92.5:7.5 dr. Analytical data for **22ai**: **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.

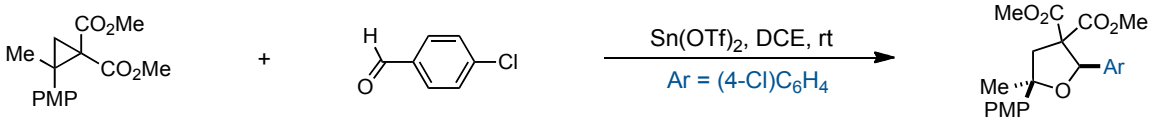


Dimethyl 5-methyl-5-phenyl-2-(thiophen-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (22aj). The title compound was prepared according to General Procedure B using cyclopropane **11a** (0.080 g, 0.322 mmol, 1.0 equiv.), thiophene-2-carboxaldehyde (0.108 g, 0.967 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.007 g, 0.016 mmol, 0.05 equiv.) in 1.0 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.105 g (90%) of the product **22aj** as a yellow oil in 96:4 dr. Analytical data for **22aj**: **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 $C_{19}H_{20}O_5$+Cs: 493.0, Found: 493.0.



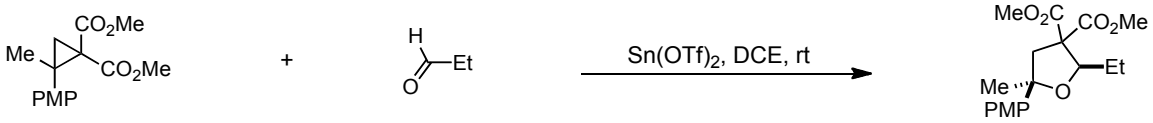
Dimethyl 5-(4-methoxyphenyl)-5-methyl-2-phenyldihydrofuran-3,3(2*H*)- dicar-

boxylate (22ba). The title compound was prepared according to General Procedure B using cyclopropane **11b** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (95%) of the product **22ba** as a colorless oil in 96:4 dr. If this reaction was allowed to proceed longer, the dr eroded significantly: 80:20 dr after 3.5h, 50:50 dr after 24 h. Analytical data for **22ba**: **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.



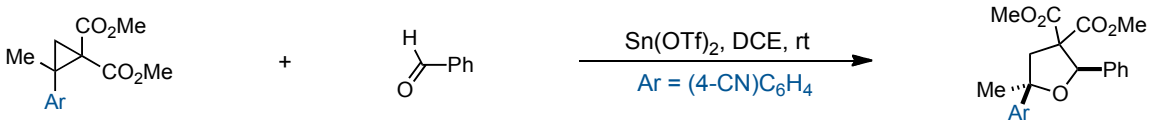
Dimethyl 2-(4-chlorophenyl)-5-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (22bb). The title compound was prepared according to General Procedure B using cyclopropane **11b** (0.040 g, 0.144 mmol, 1.0 equiv.), 4-chlorobenzaldehyde (0.061 g, 0.431 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (88%) of the product **22bb** as a colorless oil in 97:3 dr.

Analytical data for **22bb**: **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.

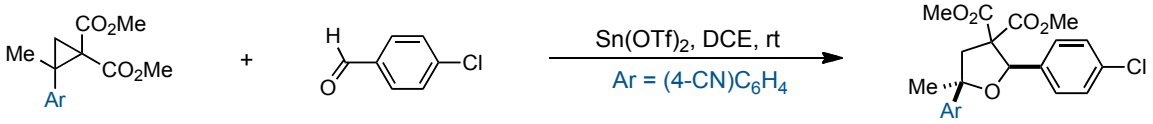


Dimethyl 2-ethyl-5-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (22bc). The title compound was prepared according to General Procedure B using cyclopropane **11b** (0.040 g, 0.144 mmol, 1.0 equiv.), propanal (0.025 g, 0.431 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv.) in 0.48 mL 1,2-dichloroethane. After workup (20 min reaction time), the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.035 g (72%) of the product **22bc** as a colorless oil in 93:7 dr. Analytical data for **22bc**: **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.

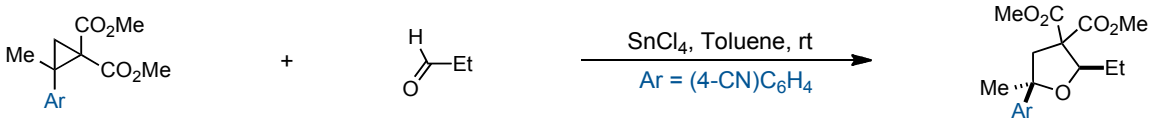


Dimethyl 5-(4-cyanophenyl)-5-methyl-2-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22ca). The title compound was prepared according to General Procedure B using cyclopropane **11c** (0.040 g, 0.146 mmol, 1.0 equiv.), benzaldehyde (0.046 g, 0.439 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv.) in 0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.050 g (87%) of the product **22ca** as a white solid in 95:5 dr. Analytical data for **22ca**: 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.



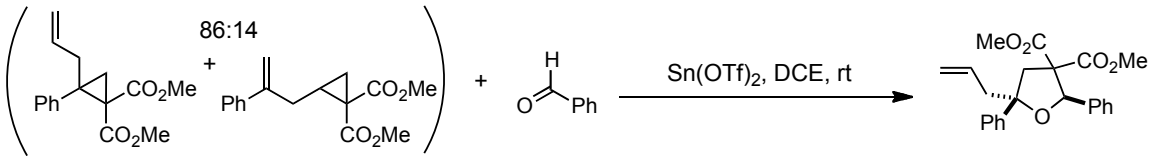
Dimethyl 2-(4-chlorophenyl)-5-(4-cyanophenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (22cb). The title compound was prepared according to General Procedure B using cyclopropane **11c** (0.040 g, 0.146 mmol, 1.0 equiv.), 4-chlorobenzaldehyde (0.061 g, 0.439 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv.) in

0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.054 g (90%) of the product **22cb** as a colorless oil in 95:5 dr. Analytical data for **22cb**: **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.



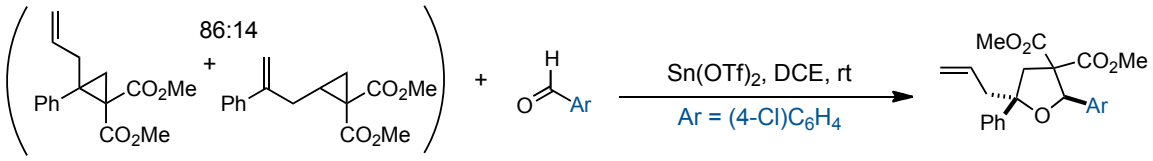
Dimethyl 5-(4-cyanophenyl)-2-ethyl-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate (22cc). The title compound was prepared according to General Procedure C using cyclopropane **11c** (0.040 g, 0.146 mmol, 1.0 equiv.), propanal (0.025 g, 0.439 mmol, 3.0 equiv.) and 0.024 mL of a [0.6 M] $SnCl_4$ stock solution (0.015 mmol, 0.10 equiv.) in 0.490 mL toluene. After workup, the product was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.025 g (57%) of the product **22cc** as a colorless oil in 98:2 dr. Analytical data for **22cc**: **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.

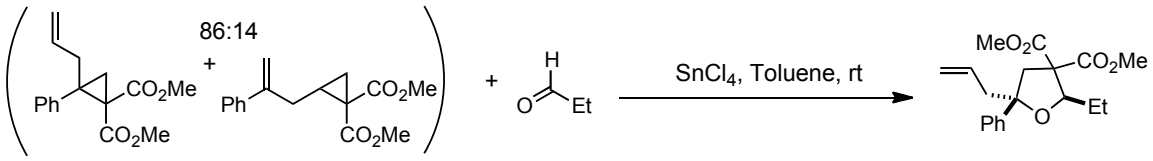


Dimethyl 5-allyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (22da). The title compound was prepared according to General Procedure B using cyclopropane mixture **11d**/**11d'** (0.050 g, 1.0 equiv.), benzaldehyde (0.058 g, 0.555 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv.) in 0.60 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.053 g (91% based on the amount of quaternary cyclopropane **11d**) of the product **22da** as a white solid in 83:17 dr. Analytical data for **22da**: 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

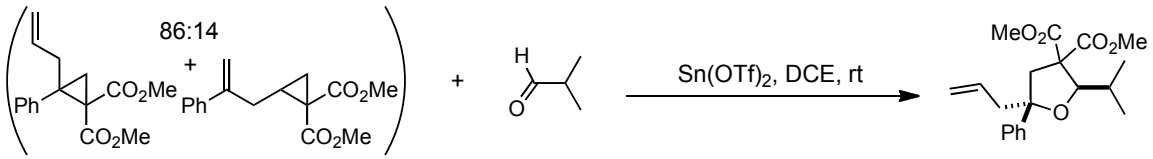
$C_{23}H_{24}O_5$+Cs: 513.1, Found: 513.1.



Dimethyl 5-allyl-2-(4-chlorophenyl)-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22da). The title compound was prepared according to General Procedure B using cyclopropane mixture **11d**/**11d'** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.054 g (85% based on the amount of quaternary cyclopropane **11d**) of the product **22db** as a colorless oil in 83:17 dr. Analytical data for **22db**: **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.

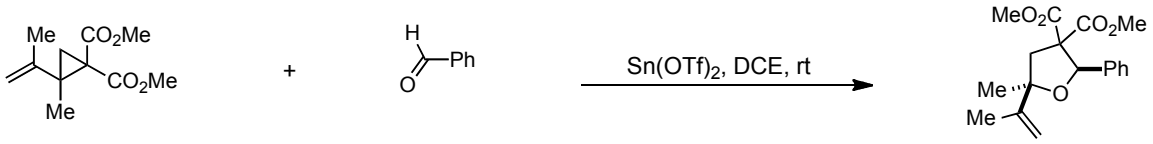


Dimethyl 5-allyl-2-ethyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22dc). The title compound was prepared according to General Procedure C using cyclopropane mixture **11d**/**11d'** (0.050 g, 1.0 equiv.), propanal (0.032 g, 0.555 mmol, 3.0 equiv.) and 0.03 mL of a [0.6 M] $SnCl_4$ stock solution (0.018 mmol, 0.10 equiv.) in 0.60 mL toluene. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.017 g (33% based on the amount of quaternary cyclopropane **11d**) of the product **22dc** as a colorless oil in 90:10 dr. Analytical data for **22dc**: **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.



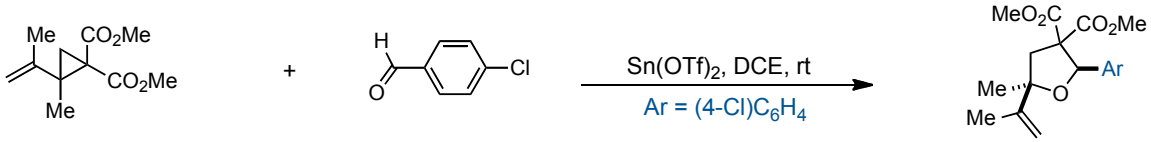
Dimethyl 5-allyl-2-isopropyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22dd). The title compound was prepared according to General Procedure B using cyclopropane

mixture **11d**/**11d'** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.036 g (67% based on the amount of quaternary cyclopropane **11d**) of the product **22dd** as a colorless oil in 90:10 dr. Analytical data for **22dd**: **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); **HRMS** (ESI): Calcd. for $C_{20}H_{26}O_5$+Cs: 479.0835, Found: 479.0827.

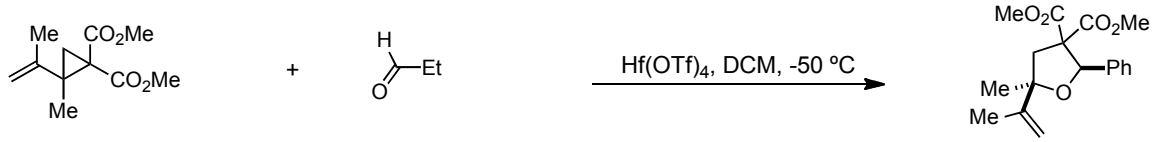


Dimethyl 5-methyl-2-phenyl-5-(prop-1-en-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (22ea). The title compound was prepared according to General Procedure B using cyclopropane **11e** (0.040 g, 0.188 mmol, 1.0 equiv.), benzaldehyde (0.060 g, 0.565 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.004 g, 0.009 mmol, 0.05 equiv.) in 0.63 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.046 g (77%) of the product **22ea** as a colorless oil in 96:4 dr. Analytical data for **22ea**: **IR** (thin film, cm^{-1}): 3055, 2984, 2953, 2305, 1732, 1436, 1266, 1237, 1209, 1122, 898, 740, 703; **^{1}H NMR** (400

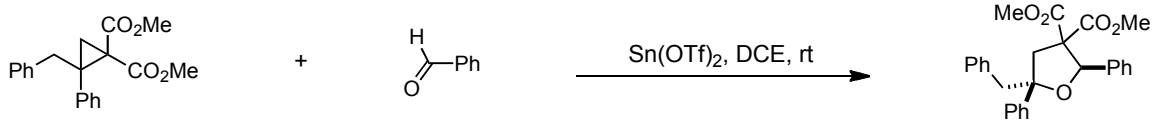
MHz, $CDCl_3$): δ 7.46 (d, J = 7.6 Hz, 2H), 7.33 - 7.25 (m, 3H), 5.94 (s, 1H), 5.16 (s, 1H), 4.92 (s, 1H), 3.83 (s, 3H), 3.10 (d, J = 13.6 Hz, 1H), 3.07 (s, 3H), 2.37 (d, J = 13.6 Hz, 1H), 1.97 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 177.8, 169.2, 149.0, 138.1, 127.9, 127.7, 127.1, 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 (22eb). The title compound was prepared according to General Procedure B using cyclopropane **11e** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.050 g (75%) of the product **22eb** as a colorless oil in 99:1 dr. Analytical data for **22eb**: **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.

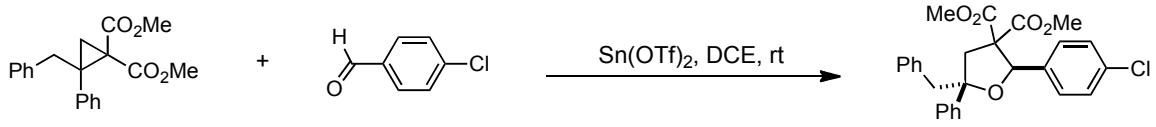


Dimethyl 2-ethyl-5-methyl-5-(prop-1-en-2-yl)dihydrofuran-3,3(2*H*)-dicarboxylate (22ec). The title compound was prepared analogously to General Procedure B, but modified as follows: A solution of cyclopropane **11e** (0.040 g, 0.188 mmol, 1.0 equiv.), propanal (0.033 g, 0.565 mmol, 3.0 equiv.) in 0.63 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 **11e**. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.033 g (65%) of the product **22ec** as a colorless oil in 99:1 dr. Analytical data for **22ec**: **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.



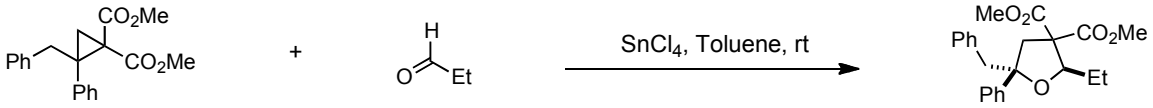
Dimethyl 5-benzyl-2,5-diphenyldihydrofuran-3,3(2*H*)-dicarboxylate (22fa). The title compound was prepared according to General Procedure B using cyclopropane **11f**

(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 **22fa** as a white solid in 80:20 dr. Analytical data for **22fa**: 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.



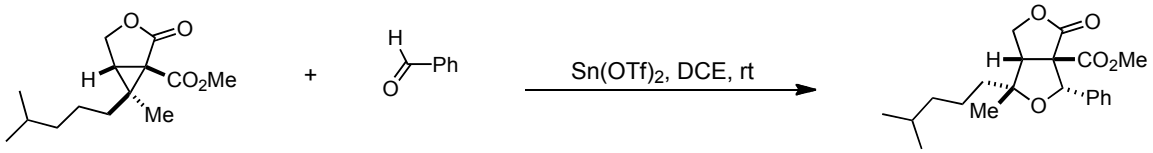
Dimethyl 5-benzyl-2-(4-chlorophenyl)-5-phenyldihydrofuran-3,3(2*H*)-dicar-boxylate (22fb). The title compound was prepared according to General Procedure B using cyclopropane **11f** (0.040 g, 0.123 mmol, 1.0 equiv.), 4-chlorobenzaldehyde (0.052 g, 0.370 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.006 mmol, 0.05 equiv.) in 0.41 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.050 g (87%) of the product **22fb** as a white solid in 80:20 dr. Analytical data for **22fb**: mp 131-132 ºC; **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.

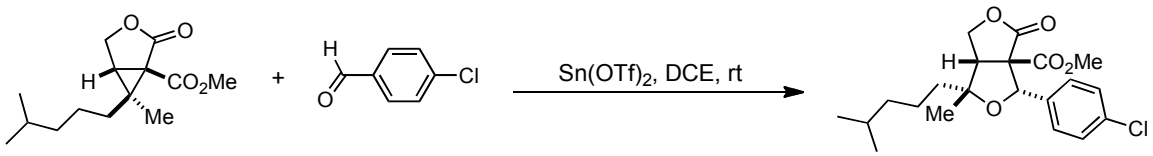


Dimethyl 5-benzyl-2-ethyl-5-phenyldihydrofuran-3,3(2*H*)-dicarboxylate (22fc). The title compound was prepared according to General Procedure C using cyclopropane **11f** (0.040 g, 0.123 mmol, 1.0 equiv.), propanal (0.021 g, 0.370 mmol, 3.0 equiv.) and 0.021 mL of a [0.6 M] $SnCl_4$ stock solution (0.012 mmol, 0.10 equiv.) in 0.41 mL toluene. After workup, the product was purified by flash column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.036 g (76%) of the product **22fc** as a colorless oil in 81:19 dr. Analytical data for **22fc**: **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.

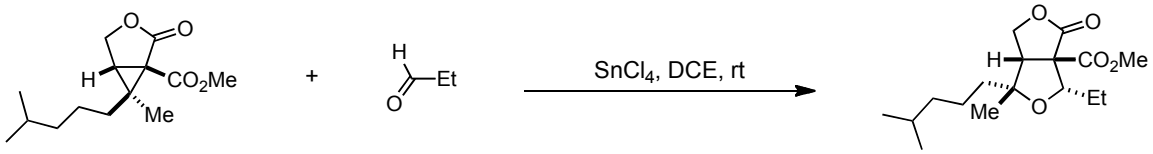


Methyl 1-isopentyl-1-methyl-4-oxo-3-phenylhexahydrofuro[3,4-*c*]furan-3a-carboxylate (23aa). The title compound was prepared according to General Procedure B using cyclopropane **19a** (0.040 g, 0.157 mmol, 1.0 equiv.), benzaldehyde (0.050 g, 0.471 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.008 mmol, 0.05 equiv.) in 0.52 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.044 g (78%) of the product **23aa** as a colorless oil in 99:1 dr. Analytical data for **23aa**: **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-

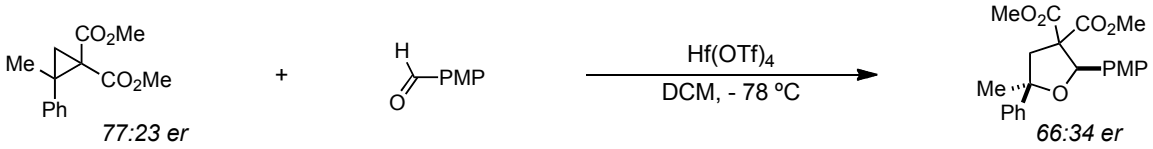
3a- carboxylate (23ab). The title compound was prepared according to General Procedure B using cyclopropane **19a** (0.040 g, 0.157 mmol, 1.0 equiv.), 4-chlorobenzaldehyde (0.066 g, 0.471 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.008 mmol, 0.05 equiv.) in 0.52 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 10% EtOAc/hexanes) to afford 0.047 g (75%) of the product **23ab** as a colorless oil in 99:1 dr. Analytical data for **23ab**: **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 (23ac). The title compound was prepared according to General Procedure C using cyclopropane **19a** (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 column chromatography (hexanes flush followed by 5% EtOAc/hexanes) to afford 0.056 g (75%) of the product **23ac** as a colorless oil in 77:23 dr. Analytical data for **23ac**: Major diastereomer: **IR** (thin film, cm^{-1}): 3055, 2956, 2871, 2305, 1778, 1740, 1437, 1384,

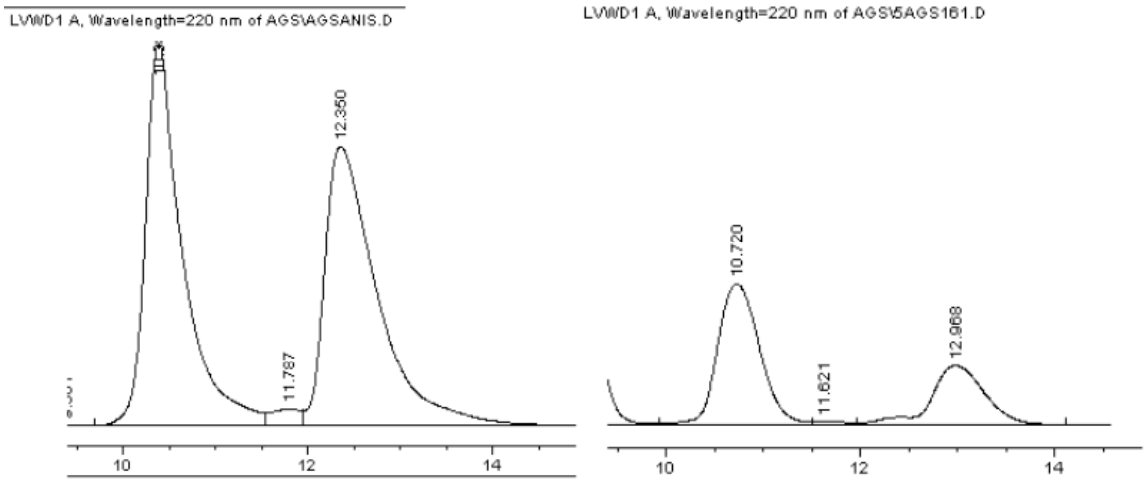
1195, 1029, 897, 739; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.48 (dd, *J* = 9.2 Hz, *J* = 4 Hz, 1H), 4.39 (t, *J* = 9.2 Hz, 1H), 4.24 (dd, *J* = 9.2 Hz, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 3.35 (dd, *J* = 8.8 Hz, *J* = 6.8 Hz, 1H), 1.91-1.85 (m, 1H), 1.85-1.41 (m, 6H), 1.20-1.15 (m, 5H), 1.06 (t, *J* = 7.6 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.

Chirality Transfer Studies:

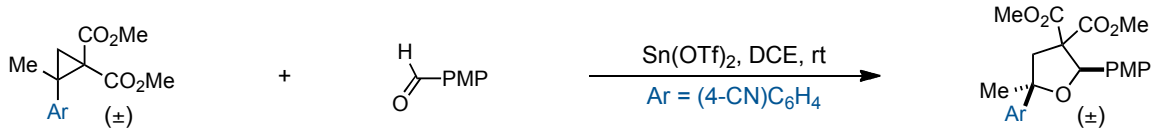


Dimethyl 2-(4-methoxyphenyl)-5-methyl-5-phenyldihydrofuran-3,3(2*H*)- dicarboxylate ((+)-22ah). In a glovebox, a flame-dried round bottomed flask (flask 1) was charged with a magnetic stir bar and $Hf(OTf)_4$ (0.008 g, 0.01 mmol, 0.05 equiv.). A separate round bottomed flask (flask 2) was charged with **(–)-11a** (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 **(–)-11a**. The reaction mixture was filtered through a Monstr-Pette plug of silica (3 cm) and rinsed thoroughly with Et_2O. Purification by flash column chromatography (hexanes followed by 5% EtOAc/hexanes) afforded 0.050 g (65%) of product **(+)-22ah** 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**.** A reaction with **(–)-11a** conducted under the standard conditions (5 mol% $Sn(OTf)_2$ in 1,2-DCE at rt) afforded product **(+)-22ah** in 58:42 er as determined by SFC analysis.

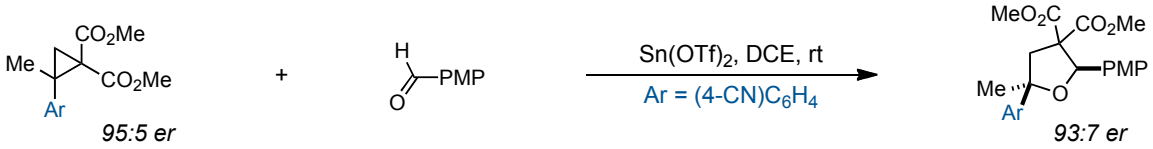


Dimethyl 5-(4-cyanophenyl)-2-(4-methoxyphenyl)-5-methyldihydrofuran-3,3(2*H*)-dicarboxylate ((+)-22ch).



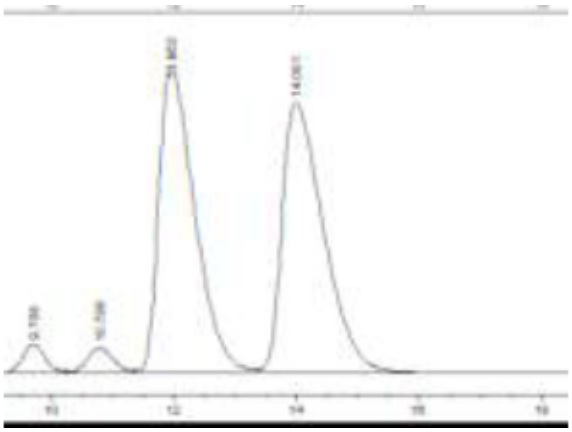
The title compound was prepared in racemic fashion according to General Procedure B using cyclopropane **11c** (0.040 g, 0.146 mmol, 1.0 equiv.), *p*-anisaldehyde (0.060 g,

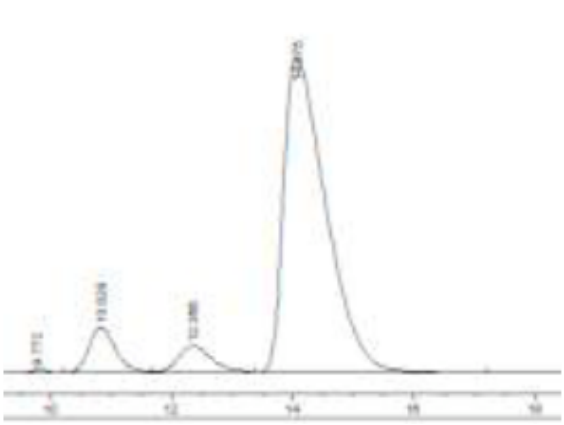
0.441 mmol, 3.0 equiv.) and $Sn(OTf)_2$ (0.003 g, 0.007 mmol, 0.05 equiv.) in 0.49 mL 1,2-dichloroethane. After workup, the product was purified by flash column chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.056 g (94%) of product ***rac*-22ch** as a white solid in 95:5 dr.



A chirality transfer experiment was performed according to General Procedure B using enantioenriched cyclopropane **(–)-11c** (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 column chromatography (hexanes flush followed by 15% EtOAc/hexanes) to afford 0.028 g of product **(+)-22ch** (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 **(+)-22ch**: 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, $CHCl_3$).





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