Stereoselective Carbon-Carbon Bond Forming Reactions:

Improving the Stereoselectivity of a Catalytic Homoaldol Reaction

and

The Development of a General Method to Access the α-Quaternary Carbon β-Hydroxy Carbonyl Motif

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FOOTPRINTS IN THE SAND
By Mary Stevenson

One night I dreamed I was walking
Along the beach with the Lord.

Many scenes from my life flashed across the sky.
In each scene I noticed footprints in the sand.

Sometimes there were two sets of footprints.
Other times there were one set of footprints.

This bothered me because I noticed that
During the low periods of my life when I was

Suffering from anguish, sorrow, or defeat,
I could see only one set of footprints,

So I said to the Lord, "You promised me,
Lord, that if I followed You,
You would walk with me always.

But I noticed that during the most trying periods
Of my life there have only been
One set of prints in the sand.

Why, When I have needed You most,
You have not been there for me?"

The Lord replied,
"The times when you have seen only one set of footprints
Is when I carried you."

ABSTRACT

The following thesis describes two stereoselective carbon-carbon bond forming processes – the aldol reaction and its one-carbon homologue, the homoaldol reaction. The first chapter describes our efforts to increase the stereoselectivity of a catalytic homoaldol reaction. This methodology features a second generation Binol titanium (IV) fluoride catalyst capable of opening a silyloxycyclopropane ring to form discrete homoenolates. These homoenolates react with a variety of aldehydes to form 1,4-hydroxy carbonyl compounds. The catalyst was prepared by a literature method and has improved the stereoselectivity of this reaction compared to the first generation Binol titanium (IV) triflate catalyst. A variety of substituted Binol ligands were studied to determine the effect of steric and electronic modifications on reaction selectivity.

In the second chapter, a general method for the asymmetric synthesis of α,α-disubstituted-β-hydroxy carbonyl compounds is described. This methodology relies on the stereoselective formation of acyclic α,α-disubstituted amide enolates. These enolates were prepared using methodology developed in the Gleason laboratory. Transmetallation of the initially formed lithium enolate was necessary to achieve high relative and absolute product stereocontrol. The *E*- and *Z*-enolate isomers were investigated. The *Z*-enolate reacted with high stereocontrol, whereas the *E*- enolate was not able to provide the *anti* isomer selectively. An X-ray crystal structure confirmed the absolute configuration of the product.

RÉSUMÉ

Deux procédés de formation stéréosélective de lien carbone-carbone seront présentés dans cette thèse, soient la condensation aldolique et son homologue mono-carboné, l'homoaldol. Le premier chapitre présente les efforts déployés afin d'améliorer la stéréosélectivité de la réaction de condensation aldolique homologuée catalytique. La méthodologie utilisée implique un catalyseur Binol-titane(IV) fluoré de seconde génération qui permet d'effectuer l'ouverture d'un anneau silyloxycyclopropane afin de former des composés homoénolates discrets. Lors de leur mise en présence d'une variété d'aldéhydes, ces derniers permettront l'obtention de composés 1,4-hydroxycarbonylés. Préparé selon une méthode connue de la littérature, le catalyseur fluoré a permis d'obtenir de meilleurs résultats que le catalyseur de première génération utilisant le Binol-titane(IV) triflate en ce qui a trait à la stéréosélectivité de la réaction. Une variété de substitutions sur les ligands Binols fut étudiée afin de déterminer les effets de modifications stériques et électroniques sur la sélectivité de la réaction.

La deuxième partie consiste en la description d'une synthèse asymétrique de composés α,α-disubstitués-β-hydroxycarbonylés. Le principe de cette méthodologie repose sur la formation d'énolates d'amides acycliques α,α-disubstitués préparés selon un protocole dont la mise au point fut développée dans le laboratoire Gleason. Une transmétallation de l'énolate de lithium initialement formé s'est avérée nécessaire afin de contrôler les stéréochimies relatives et absolues des produits obtenus. Les deux isomères d'énolates ont été étudiés. Bien qu'un haut contrôle ait été observé quant à la stéréosélectivité l'énolate *Z*, il n'en fut pas de même avec l'énolate de conformation *E*.

Un rayon-X de la structure cristalline du produit a permis de confirmer la configuration absolue.

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TABLE OF CONTENTS

ABBREVIATIONS

$A^{1,3}$	1,3 allylic
Ar	aryl
Anal.	Analysis
aux	auxiliary
(*R*)-Binol	(*R*)-2,2'-dihydroxy-1,1'-dinaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bs	broad singlet
Bu	butyl
Calcd	calculated
cat.	catalyst/catalytic
*c*Hx or Cy	cyclohexyl
Cp	cyclopentadienyl
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
de	diastereomeric excess
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethyl amino pyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio

ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
Et_2O	diethyl ether
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
HREIMS	high resolution electron impact mass spectrometry
Hz	Hertz
J	coupling constant
L	liter
LAB	lithium amidotrihydroborate
LDA	lithium diisopropylamide
LDBB	lithium 4,4'-di-*tert*-butylbiphenylide
m	milli, multiplet
M	moles per liter, metal
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
mL	milliliter(s)
mmol	millimole(s)

MOM	methoxymethyl
Ms	methanesulfonyl
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
O*i*Pr	isopropoxide
OTf	triflate
Ph	phenyl
Pr	propyl
*p*TSA	*p*-toluenesulfonic acid
R_t	retention time
rt	room temperature
s	singlet
t	tertiary
t	triplet
TBSOTf	*tert*-butyldimethylsilyl triflate
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

General Introduction

Modern organic synthesis demands the development of efficient, stereospecific carbon-carbon bond forming reactions. While the aldol reaction features prominently in this category, the homoaldol reaction is a lesser-known contributor. The aldol reaction has enjoyed considerable development as a reliable carbon-carbon bond forming reaction over the past twenty years, with many asymmetric and catalytic, asymmetric variants available. By comparison, the homoaldol reaction, a one-carbon homologue, has not developed as quickly due to complications with homoenolate formation.

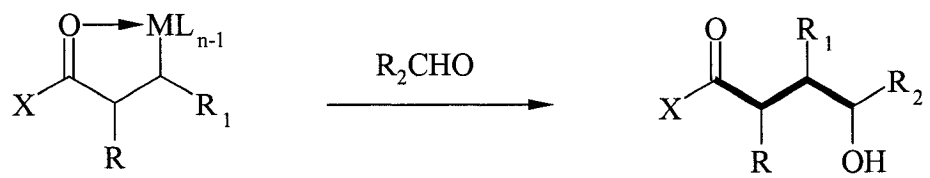
The following two chapters will outline our contributions to these carbon-carbon bond-forming reactions. Chapter one will focus on our attempts to increase the enantioselectivity of a catalytic homoaldol reaction using an alkoxytitanium(IV) fluoride catalyst. This process involves a discrete homoenolate that is formed by ring opening of a silyloxyalkoxycyclopropane with the aforementioned Lewis acid catalyst.

Chapter two will outline our contributions to the development of a general stereospecific method to access α,α-disubstituted-β-hydroxy carbonyl compounds *via* an aldol reaction. This methodology relies on the stereospecific generation of α,α-disubstituted amide enolates.

Chapter One

1.1 An Introduction to the Homoaldol Reaction

The homoaldol reaction is the addition of a β-metalated carbonyl unit to an aldehyde or ketone to form 1,4-oxygenated subunits (**Figure 1-1**).[1]



X = hydrogen, alkyl, aryl or ester

M = Ti, Zn, Ce, Sm

Figure 1-1. The homoaldol reaction.

Homoenolates are unique carbanionic units. They are formally umpolung synthons[2] as the β-position of carbonyl compounds is normally an electrophilic site, reserved for nucleophilic additions (i.e. Michael acceptors). In comparison to the aldol reaction, the chemistry of homoenolates is considerably less developed due to complications with homoenolate tautomerization and the difficulties associated with direct β-deprotonation. Unlike enolates, which can be easily formed by base deprotonation of esters, amides, ketones and aldehydes (pKa at C_α-proton 20-25) using mild amide bases, the homoenolate cannot be formed in such a direct manner due to the higher pKa of the β-proton. Direct deprotonation is possible with an activating group at the β-position (*vide infra*).

The development of homoenolate chemistry has been complicated by isomer tautomerization between the oxyanionic and carbanionic forms (**Figure 1-2**). This rapid and irreversible cyclization of the carbanionic tautomer to the oxanionic isomer prevents the homoenolate from acting as a carbon centered nucleophile.[1] Methods have been developed to overcome this problem. These will be discussed in the following sections.

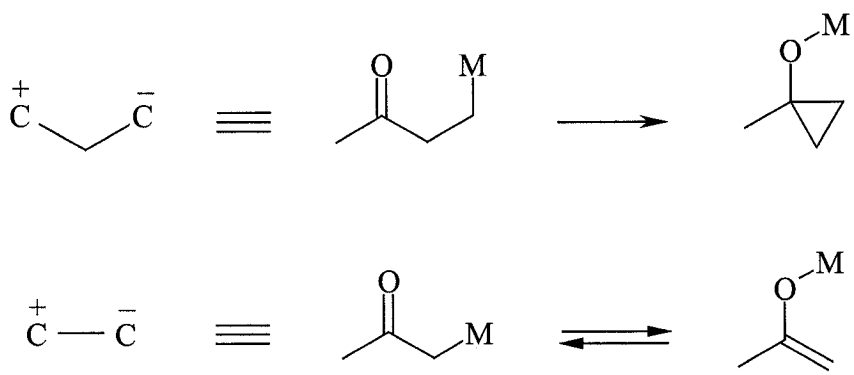


Figure 1-2. Homoaldol and aldol tautomers.

1.1.2 Homoenolate Equivalents

The homoenolate synthon is an inherently unstable species since it possesses sites of nucleophilic and electrophilic behavior in close proximity. To make the homoaldol reaction viable, several approaches have been taken to address this fundamental problem. The two main strategies that have been employed involved masking of the carbonyl functionality as (i) a heterovinyl reagent (offensive strategy) or as (ii) an acetal like structure (defensive strategy).[3] Both approaches are amenable to the introduction of chiral auxiliaries (**Figure 1-3**).

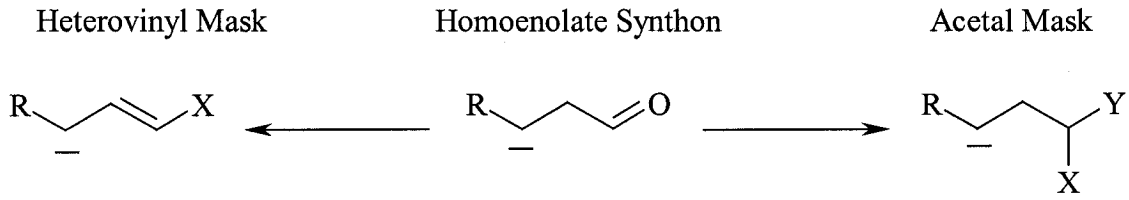
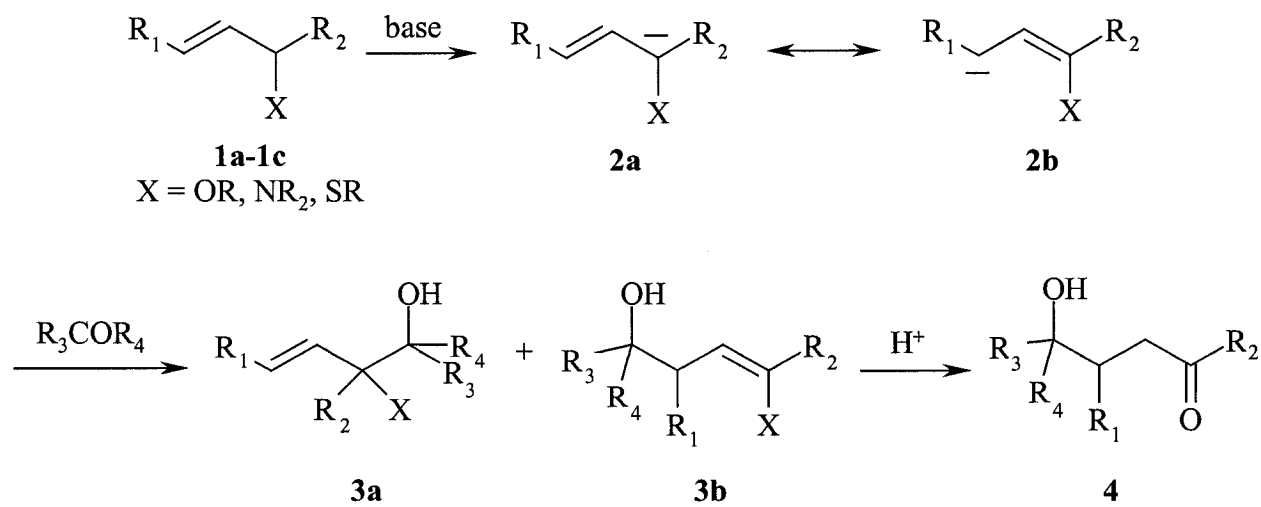


Figure 1-3. Homoenolate synthons.

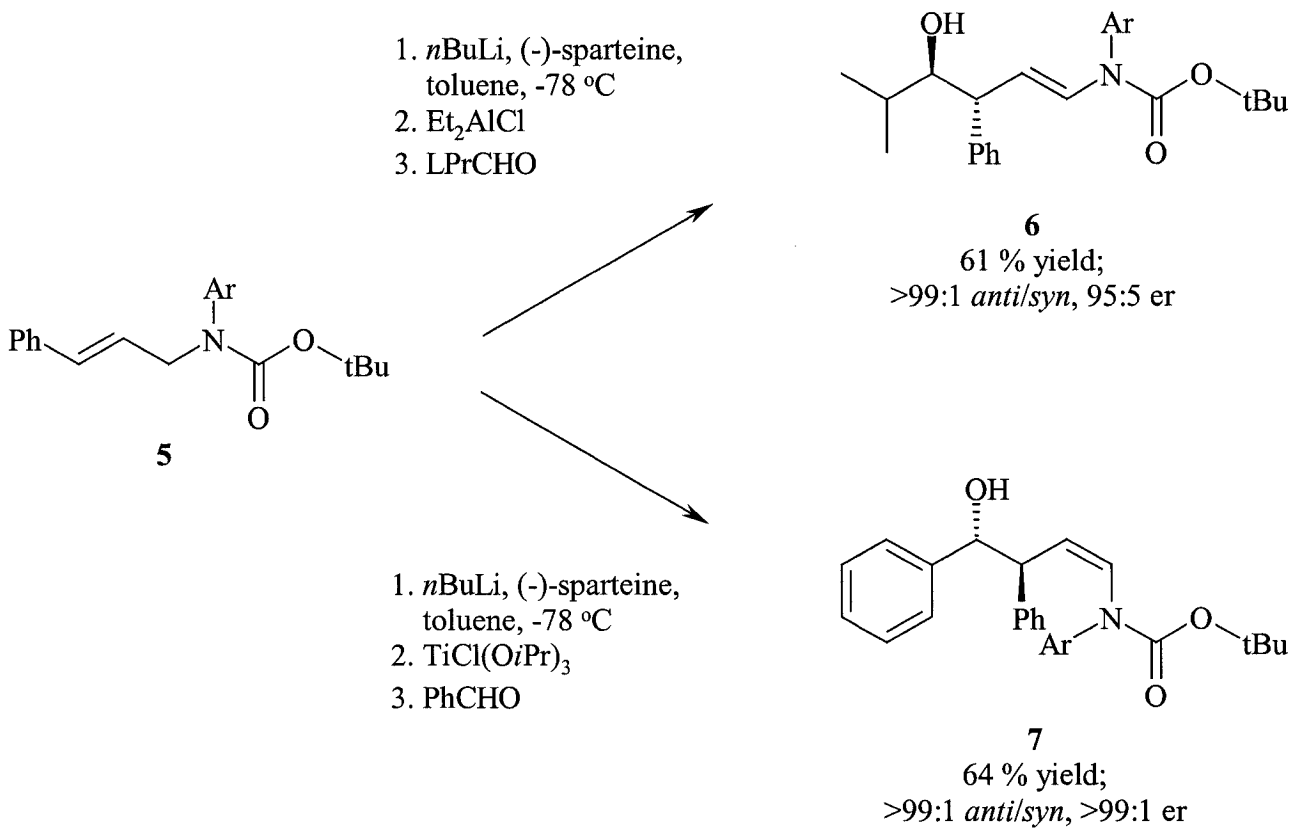
1.1.2.1 The Heterovinyl Offensive Approach

The heterovinyl approach encompasses a wide variety of substrates, including 1-aminoallyl, 1-oxyallyl and 1-thioallyl organometallic reagents. These reagents **1a-1c** are deprotonated to form heteroallyl-stabilized anions, which undergo additions to carbonyl compounds (**Scheme 1-1**). A mixture of regioisomers **3a and 3b** usually results, but hydrolysis of **3b** (X = OR, NR_2 or SR) provides the desired homoaldol product **4**. This approach is problematic as increasing alkyl substitution at the α- and γ- positions makes formation of the allyl anion more difficult and increases the instability of the reagent.[4]



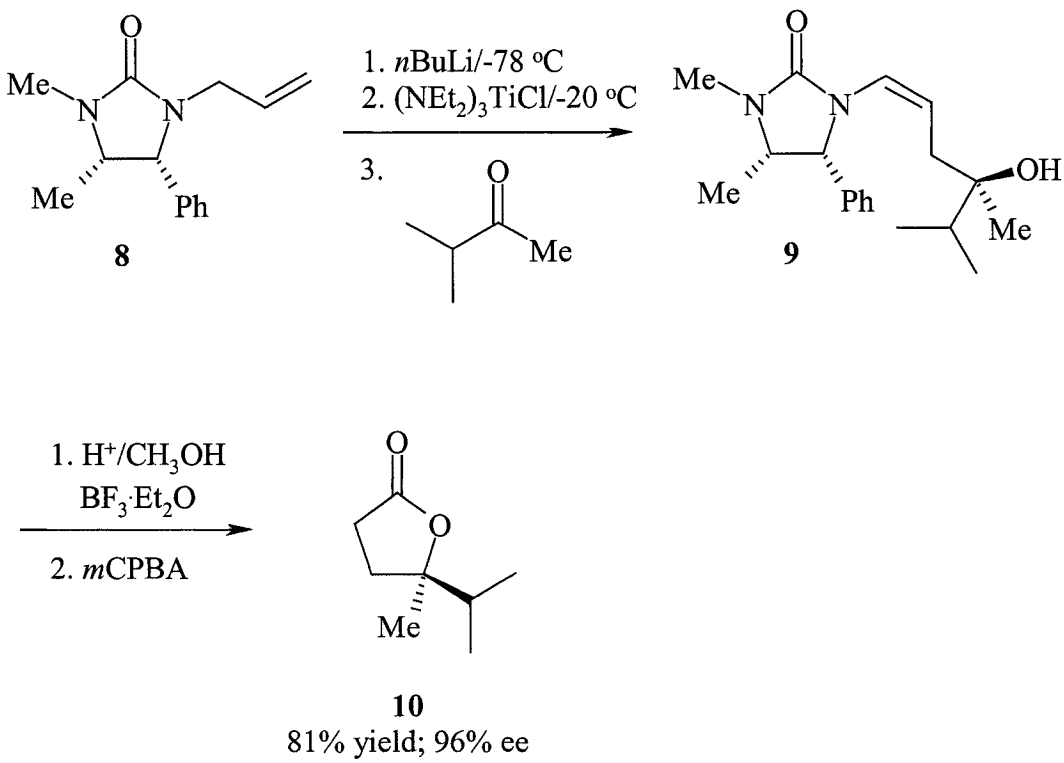
Scheme 1-1. Heterovinyl offensive approach to homoaldol adducts.

Allylcarbamates offer a viable solution to the problems cited above. The carbamate carbonyl group is able to direct the lithiations to the α-position through chelation, which improves the regiochemistry of the addition reaction.[4] Beak and coworkers have employed this approach to form the *anti* homoaldol products **6** and **7** enantioselectively from a (-)-sparteine-mediated lithiation/transmetallation of *N*-allyl carbamate **5** (**Scheme 1-2**).[5] Hydrolysis provides the desired homoaldol adducts.



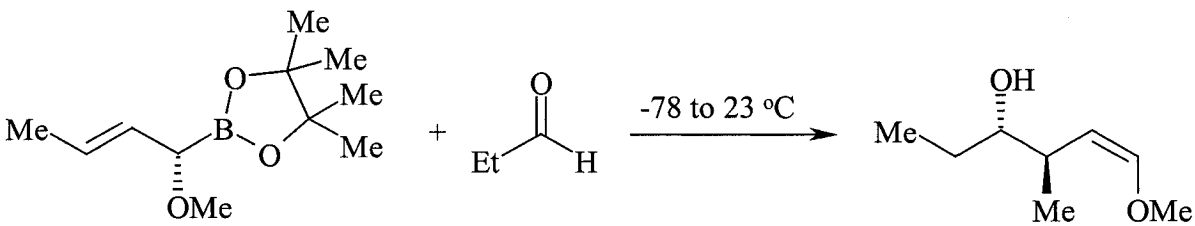
Scheme 1-2. Stereoselective induction using (-)-sparteine and homoenolate equivalent allylcarbamate.

Stereoselectivity is also easily introduced through the use of chiral auxiliaries, albeit with a high degree of variability. Lithium to titanium transmetallation is often necessary to improve the product diastereoselectivity. Helmchen and coworkers have utilized chiral allyl urea **8** as a homoenolate equivalent (**Scheme 1-3**).[6] Deprotonation of **8** with *n*-butyllithium and transmetallation with bis(diethylamino)titanium chloride provides an aminoallyl titanium reagent. This reagent reacts efficiently with aldehydes to provide the addition product **9** with high diastereoselectivity. Enantiopure lactones **10** are obtained after hydrolysis and oxidation.



Scheme 1-3. Improved asymmetric induction through lithium-titanium transmetallation.

Like their nitrogen analogues, oxyallylhomoenolate equivalents suffer from regioselectivity issues during the homoaldol addition if an alkali metal counterion is employed. These reagents can be made synthetically useful if another metal is utilized. Oxyallyl-boron and tin reagents have been used successfully as homoenolate equivalents as well as titanium (after lithium-titanium transmetallation).[3] In the case of allylboron reagents, excellent simple as well as induced diastereoselectivity have been achieved (**Scheme 1-4**). (*S*)-(*E*)-1-methoxybut-2-enylboronate reagent **11** reacts with various aldehydes to provide the (*Z*)-homoallyl alcohols **12** with excellent levels of diastero- and enantiocontrol.[7]



11

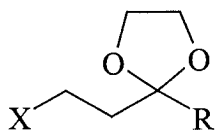
12
81 % yield;
> 98:2 dr; 90 % ee

Scheme 1-4. *E*-Crotylboron reagents as masked homoenolates.

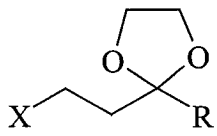
1.1.2.2 The Acetal Defensive Approach

In order for this approach to be successful, activating substituents must be employed for deprotonation or other methods used such as reductive lithiation or lithium-halogen exchange. Activating groups for deprotonation include phenylsulfonyl, nitro,

phosphonium and phosphane oxide, while halide substituents are necessary for lithium exchange or Grignard formation (**Figure 1-4**).[4]



13a. X = MgBr
13b. X = Li

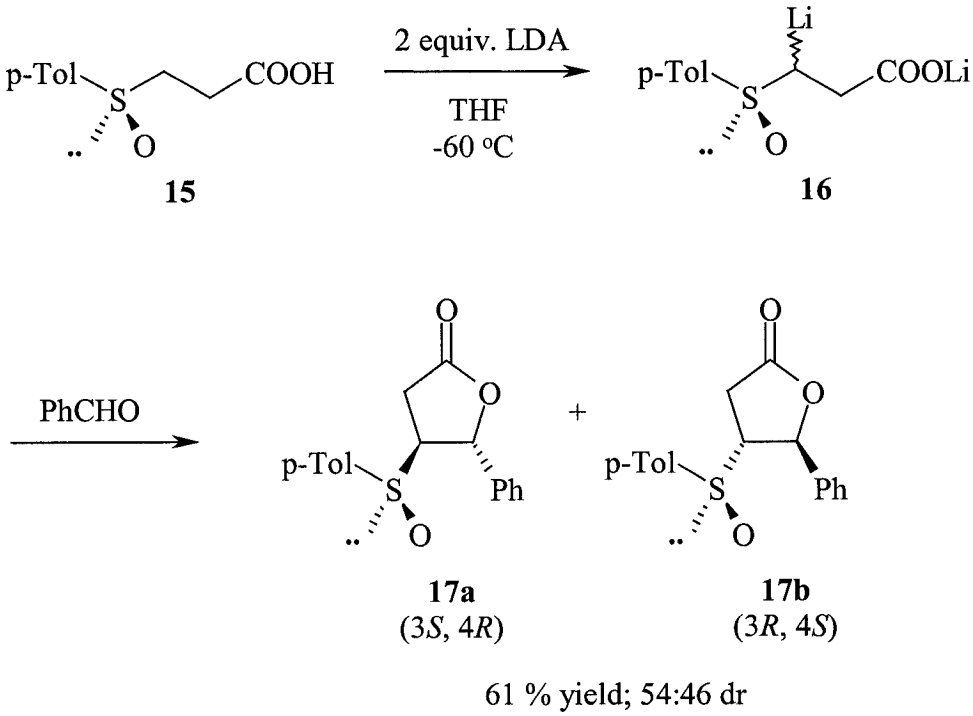


14a. X = $PhSO_2$
14b. X = NO_2
14c. X = Ph_3P
14d. X = $Ph_3P(O)$

Figure 1-4. Homoenolate equivalents derived from carbonyl-protected compounds.

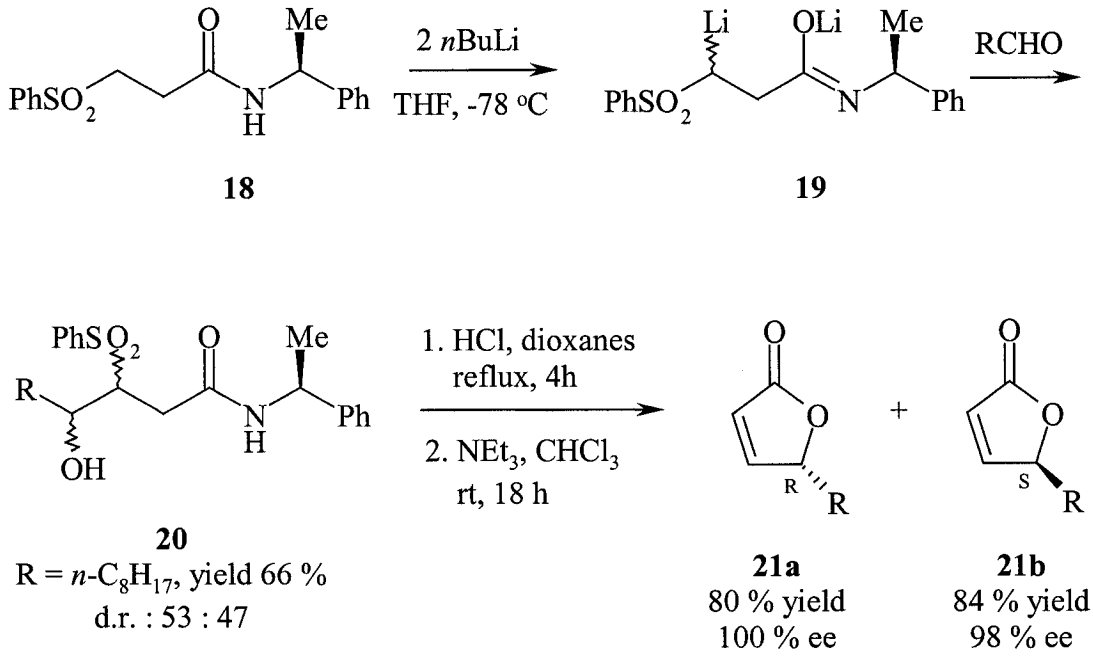
1.1.3 Direct Generation of Homoenolates

This approach involves generation of the homoenolate without direct protection of the carbonyl functionality. To achieve this, the reactivity of the carbon-metal bond and/or the carbonyl carbon must be reduced to avoid undesired intra- or intermolecular side reactions.[3] The *in situ* protection of the carbonyl group of β-activated carboxylic acids and amides may be accomplished through dilithiation. Bravo has shown that the dianion of (+)-(*R*)-3-[(4-methylphenyl)sulphinyl]propionic acid **15** adds to aldehydes to afford two main diasteroisomeric β-sulphinyl-γ-lactones **17a** and **17b** (**Scheme 1-5**).



Scheme 1-5. Bismetallated carboxylic acids.

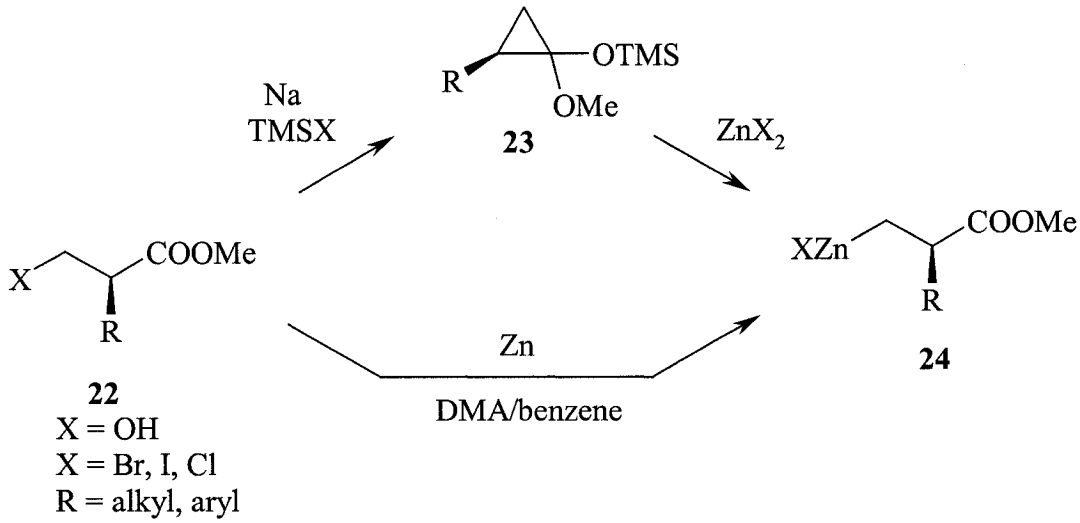
Tanaka and coworkers have demonstrated the utility of the dianions of chiral *N*-monosubstituted-3-(phenylsulfonyl)propanamides **18** for the preparation of optically active γ-furanones (**Scheme 1-6**).[8] Addition of dianion **19** to nonanal provides the 1,4-hydroxy amide **20**. Treatment of **20** with dilute acid, followed by triethylamine, yields the 2(5*H*)-furanones **21a** and **21b**.



Scheme 1-6. Bismetallated carboxylic amides.

1.1.4 Cyclopropane Ring Cleavage to Form Discrete Homoenolates

Discrete homoenolates can be prepared directly *via* ring opening of silyloxyalkoxycyclopropanes, or by halogen-metal exchange with 3-halo esters (**Scheme 1-7**).[3,9] The pioneering work in this area was accomplished by Nakamura and Kuwajima when they demonstrated that 1-alkoxy-1-(trimethylsilyloxy)cyclopropanes could be opened using titanium tetrachloride.[9] The cleavage is proposed to occur through initial σ-coordination of the metal to one of the carbon-carbon bonds, followed by bond cleavage to form a stabilized homoenolate due to internal chelation of the carbonyl unit to the metal.[10]

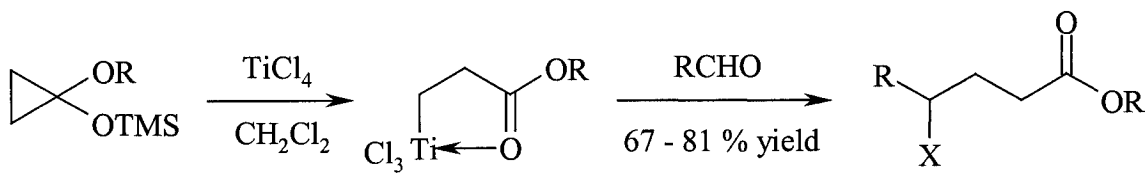


Scheme 1-7. Preparation of discrete homoenolates by halogen-metal exchange and ring opening.

In order to form these discrete homoenolate species, a delicate balance between homoenolate reactivity and stability must be achieved. This balance is most often dictated by the nature of the counterion. If the homoenolate is too reactive, cyclization to the oxyanionic form dominates and the homoaldol reaction does not take place. This is observed with alkali metal counterions such as lithium and sodium. However, if the carbon-metal bond is not reactive enough, addition to the electrophilic reagent does not occur. While many metals have been demonstrated to open silyloxycyclopropanes to form discrete homoenolates (M = Fe, Hg, Zn, Cu, Pb, Sn, Ag, Ce, Sm),[11] titanium and zinc homoenolates are the most widely known participants in the homoaldol reaction.

1.1.4.1 Titanium Homoenolates

Titanium tetrachloride derived homoenolates are formed by reaction of the silyloxycyclopropane unit with $TiCl_4$ in CH_2Cl_2. The nature of the titanium homoenolate was deduced by ^1H- and ^{13}C–NMR analysis, which showed two nonequivalent methylene signals as well as a low field signal characteristic of a carbon-metal bond in the ^{13}C NMR spectrum. In addition, an IR spectrum showed a carbonyl stretch at 1600 cm^{-1}, supporting the proposal of internal chelation to account for the observed thermal stability of the homoenolate (**Structure 26, Scheme 1-8**). The titanium-bound homoenolate was crystallized from hexanes and was shown to contain only one homoenolate per titanium center.[9,10]



25a. R = Me
25b. R = Et
25c. R = *i*Pr

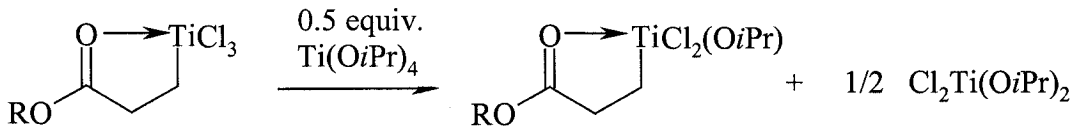
26

27a. X = OH
27b. X = Cl

Scheme 1-8. Ring opening with titanium tetrachloride to form a discrete homoenolate.

Titanium tetrachloride derived homoenolates are limited to additions to reactive species such as aldehydes, and the acetals of aldehydes and ketones. No external Lewis acid activation of the carbonyl group is necessary for the addition to occur. Chlorination products are often observed, however, when aromatic and α,β-unsaturated aldehydes are used, due to ionization of the initial homoaldol product (**Scheme 1-8**).[10] The introduction

of alkoxide-based ligands increases the nucleophilicity of the titanium homoenolate and removes the problem of undesired chloride by-product formation. This has been accomplished by ligand exchange with 0.5 equivalents of $Ti(OiPr)_4$ or $Ti(OtBu)_4$ (**Scheme 1-9**). The introduction of alkoxide-based ligands opens the possibility of introducing chirality through the use of chiral alkoxide ligands such as Binol or TADDOL (*vide infra*).

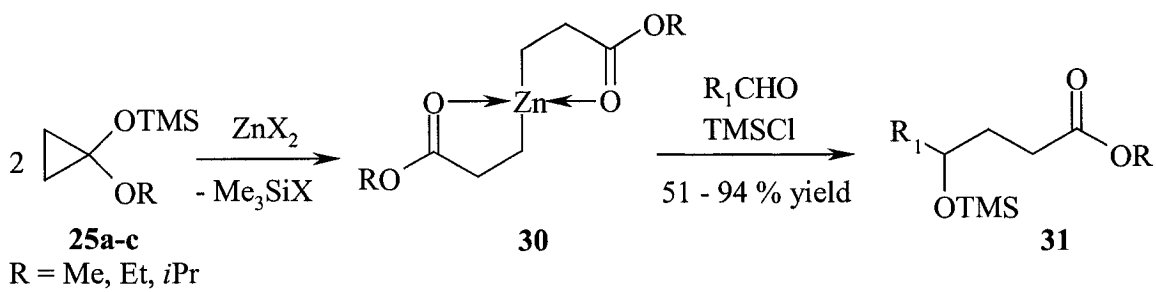


28 **29**

Scheme 1-9. Formation of alkoxide titanium homoenolates *via* ligand exchange.

1.1.4.2 Zinc Homoenolates

Discrete zinc homoenolates are versatile three carbon building blocks that possess a stability and chemical versatility that is rare among most homoenolates. Nakamura and Kuwajima have shown that the treatment of 1-silyloxy-1-alkoxycyclopropane with $ZnCl_2$ in diethyl ether results in the formation of zinc homoenolate **30** containing two homoenolate moieties per metal center (**Scheme 1-10**).[12]



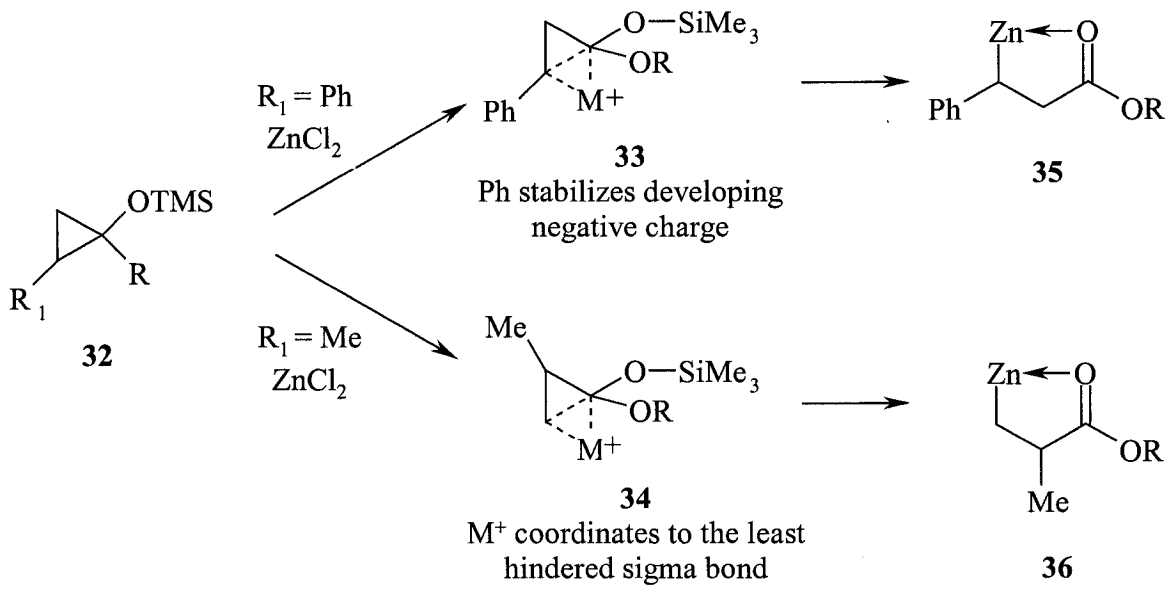
25a-c
R = Me, Et, *i*Pr

30

31

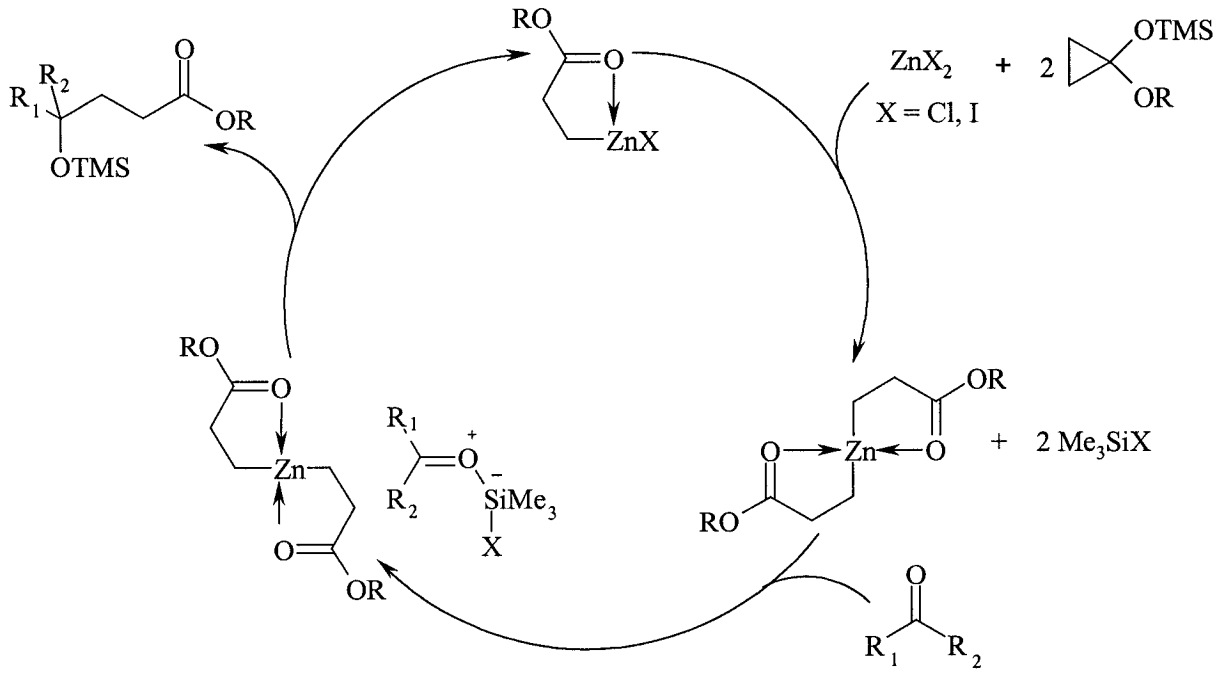
Scheme 1-10. Ring opening with zinc halide salts to form discrete homoenolates.

Substituted silyloxycyclopropanes can be regioselectively opened in the presence of $ZnCl_2$ (**Scheme 1-11**). If the R group is capable of anionic stabilization, then the opening will occur preferentially at the most substituted position. If R is alkyl, however, the cleavage occurs at the least substituted position for steric reasons. Cleavage of substituted silyloxycyclopropanes does not occur as regioselectively with $TiCl_4$.[12]



Scheme 1-11. Regioselective silyloxycyclopropane ring opening by $ZnCl_2$.

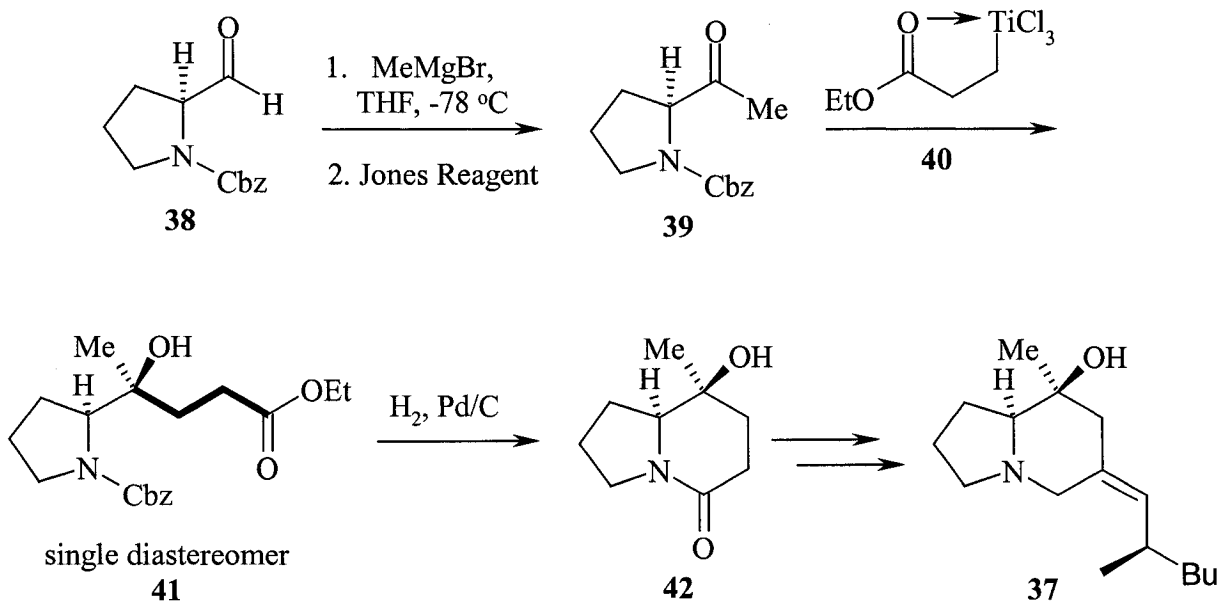
The zinc homoenolate participates in a variety of addition reactions, including conjugate addition in the presence of Cu(I), HMPA; addition to acyl chloride; S_N2' displacement of allylic halides; palladium coupling, and the homoaldol reaction.[13] In dichloromethane, the homoaldol reaction can be made catalytic in zinc (no reaction in diethyl ether). The addition reaction does require, however, the presence of a Lewis acidic species such as trimethylsilyl chloride or $BF_3{\cdot}OEt_2$. The desired γ-silyloxyester can be formed in good yield by treatment of a silyloxycyclopropane with aldehydes in the presence of 2 mol % $ZnCl_2$ or ZnI_2 in CH_2Cl_2 at 25 °C. Benzaldehyde dimethyl acetal also reacts, but ketones are unreactive (except for acetophenone). The following catalytic cycle has been proposed to account for the accelerating effect of TMSX (**Scheme 1-12**). Activation of the carbonyl group is believed to be its main function. ZnI_2 is often used, as the TMSI byproduct is a stronger Lewis acid than TMSCl.[9,12]



Scheme 1-12. Proposed catalytic cycle for the ZnX_2 mediated homoaldol reaction.

1.1.5 Synthetic Applications

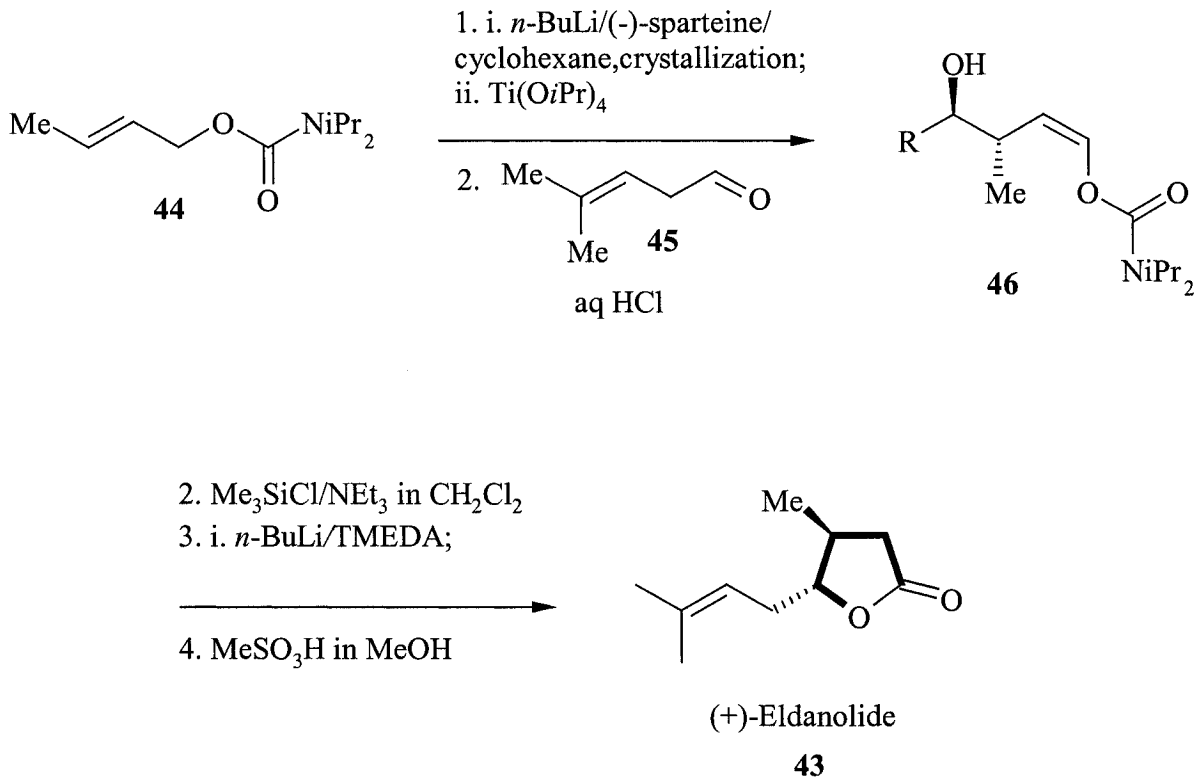
The homoaldol reaction has tremendous synthetic potential as the 1,4-oxygenated motif is often found in natural products. Barrett and Damiani reported the formal synthesis of Pumiliotoxin 251D **37**, *via* the addition of alkoxytitanium homoenolate **40** to *L*-Proline derivative **39** (**Scheme 1-13**).[14] The addition occurs stereospecifically, as only diastereomer **41** is obtained.



Scheme 1-13. Formal synthesis of Pumiliotoxin 251D *via* homoenolate methodology.

Hoppe and Paulsen provided an example of the usefulness of homoenolate equivalents in their concise synthesis of the insect pheromone (+)-Eldanolide **43** (**Scheme 1-14**).[15] A (-)-sparteine-directed lithiation/transmetallation of *N*-allyl carbamate **44** provides a titanium allylcarbamate anion, which adds selectively to β,γ-unsaturated

aldehyde **45**. *Anti* vinyl carbamate **46** is obtained with >98 % ds and 92 % ee. Subsequent hydrolysis of **46** provides (+)-Eldanolide **43**.



Scheme 1-14. (+)-Eldanolide synthesis *via* homoenolate methodology.

Titanium homoenolates have also been employed in the preparation of hydroxyethylene isosteres of peptides, i.e. the formation of peptidomimetics.[16] The main thrust of this work is the synthesis of structural mimics, units that are capable of binding to enzyme active sites but lack a scissile amide bond linkage.[17] This amide bond linkage is replaced with another less labile functional group such as a hydroxyethylene unit (**Figure 1-5**). The peptide isostere binds to the protease active site, but does not suffer from hydrolysis, thus inhibiting normal protease function.

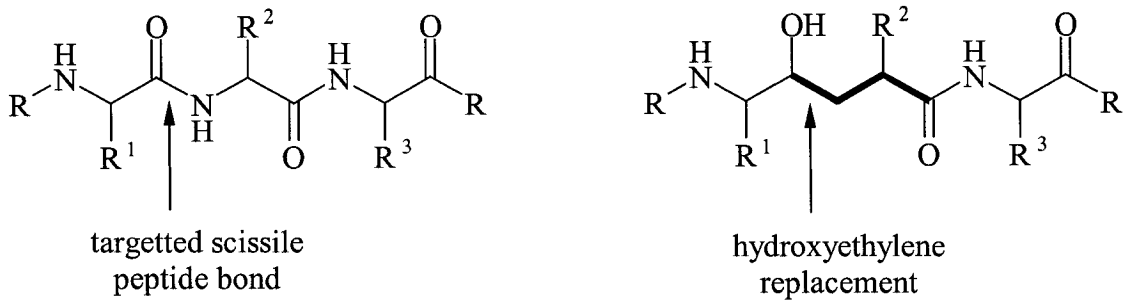
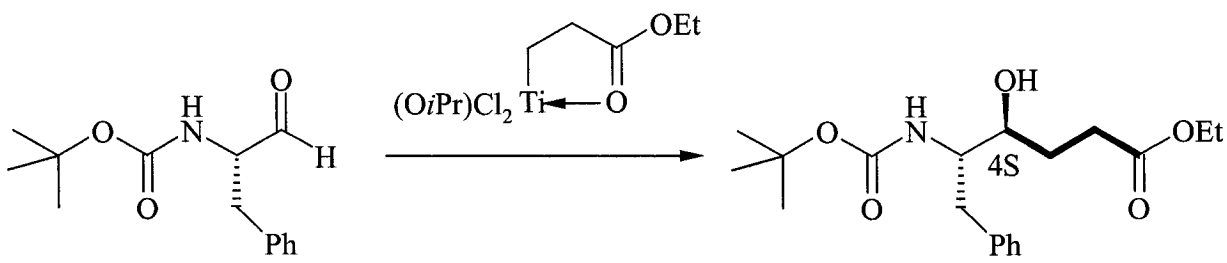


Figure 1-5. Design of peptidomimetics.

The homoaldol reaction could potentially be employed to develop these peptide isosteres as the 1,4-dioxygenated unit could arise from the addition of an amide homoenolate to an appropriately functionalized aldehyde or the condensation of a homoenolate with an α-amino aldehyde.[18] DeCamp and coworkers have demonstrated the utility of this method in the synthesis of the hydroxyester **48** from chiral α-amino aldehyde **47** (**Scheme 1-15**).[19] The selectivity of the reaction (4*S*:4*R* ratio) is dependent upon the titanium:ligand ratio, the presence of ZnX_2 salts, and the number of equivalents of homoenolate anion relative to aldehyde.

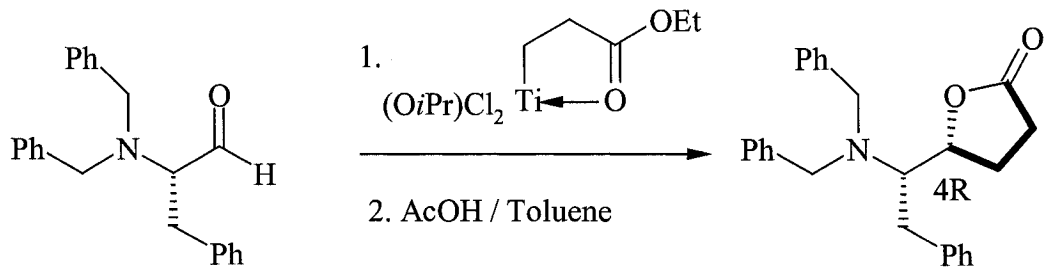


47

48
82 % yield;
16:1 4*S*:4*R*

Scheme 1-15. Synthesis of peptide mimics.

The type of nitrogen protecting group on the α-amino aldehyde influences the diastereoselectivity of the homoenolate addition (chelation *vs.* nonchelation control). This is illustrated in **Scheme 1-16** as the titanium homoenolate adds to the benzyl protected aldehyde **49** with Felkin-Ahn control to form the undesired C4 epimeric homoaldol adduct **50**.[19]

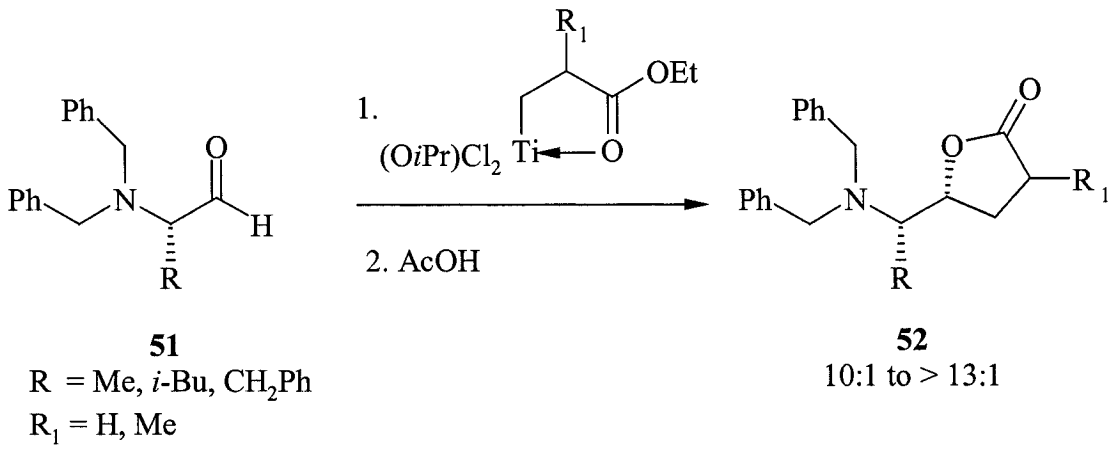


49 **50**
$4R{:}4S > 20{:}1$

Scheme 1-16. Influence of *N*-protecting group on reaction selectivity.

1.1.6 Stereoselective Homoaldol Reactions

Compared to the aldol reaction, there are relatively few known stereoselective homoaldol reactions involving discrete homoenolates. In addition, to date there exists only two reported cases of catalytic, stereoselective homoaldol reactions involving discrete homoenolates.[20] An example of substrate control in a homoaldol reaction was provided by Shibuya and coworkers. This group reported the addition of dichloroisopropoxy titanium ester homoenolates to (S)-α-dibenzylamino aldehydes **51** to afford γ-aminoalkyl-γ-lactones **52** with *erytho:threo* selectivity ranging from 10:1 to 13:1 (**Scheme 1-17**).[21]

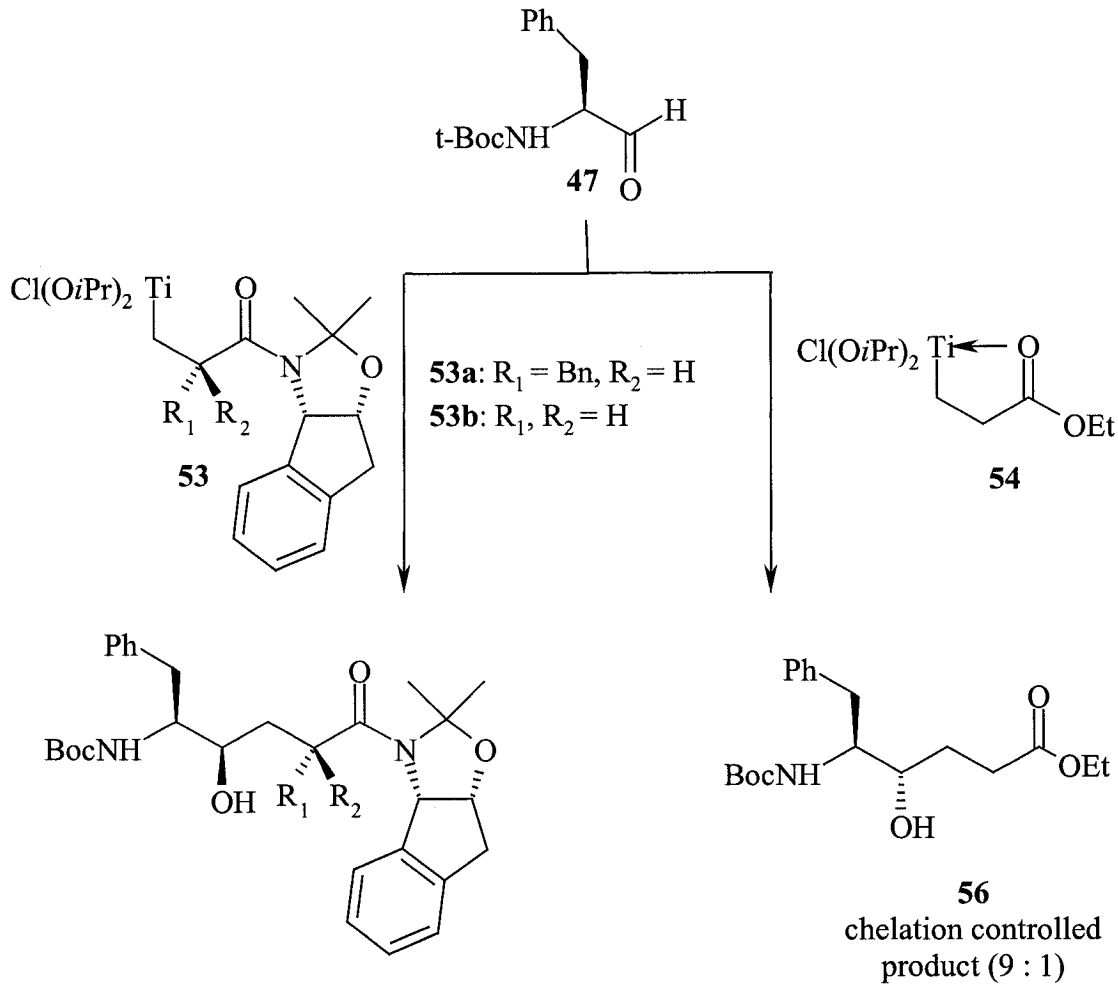


51
R = Me, *i*-Bu, CH_2Ph
R_1 = H, Me

52
10:1 to > 13:1

Scheme 1-17. Substrate control using discrete homoenolates.

Armstrong and coworkers reported an interesting example of reagent control through the addition of chiral indanolamide homoenolates to *t*-Boc-(S)-phenylalaninal **47**.[22] The homoaldol reaction with the α-benzylindanolamide titanium homoenolate **53a** produces the desired product **55a** *via* a non-chelation pathway, presumably due to steric blocking of the α-face of the homoenolate by the benzyl group. Reagent control was demonstrated by comparing the products formed using the indanolamide homoenolate **53b** to that of the simple ester homoenolate **54**. In the case of the unsubstituted indanolamide homoenolate, only one diastereomeric product **55b** is formed through a non-chelation pathway (**Scheme 1-18**). This occurs by attack of the homoenolate from its least hindered β-face. The ester titanium homoenolate, however, provides a mixture of products with the chelation controlled product **56** being the major isomer formed (9:1).

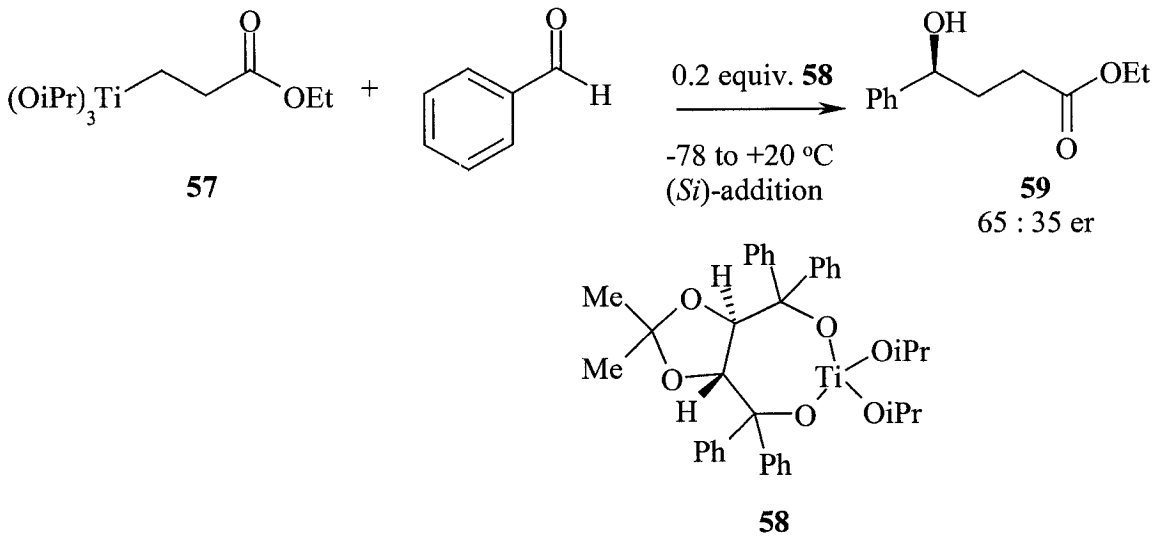


Scheme 1-18. Reagent controlled homoenolate addition.

1.1.7 Catalytic Homoaldol Reactions

Examples of catalytic homoaldol reactions are relatively rare in the literature. Seebach reported the addition of a discrete triisopropoxytitanium homoenolate to benzaldehyde in the presence of titanium TADDOLate catalyst **58** (**Scheme 1-19**).[23] The

reaction does not generate the homoenolate catalytically and the resultant 1,4-hydroxy carbonyl product **59** is obtained with a poor enantiomeric ratio of 65:35.



57 **59** 65 : 35 er

58

Scheme 1-19. Addition of discrete homoenolate to benzaldehyde in the presence of a chiral titanium TADDOLate complex.

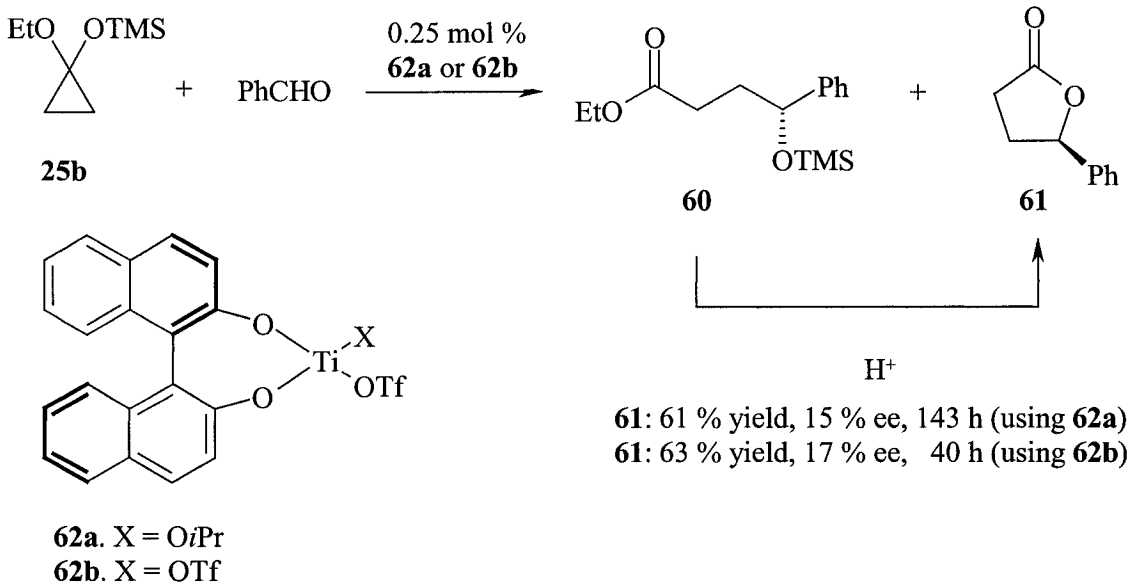
More recently, work from the Gleason laboratory has provided a second example of a titanium catalyzed homoaldol reaction.[24] Fundamentally, the homoaldol reaction differs from the aldol reaction due to the need to form a discrete metal alkyl bond prior to aldehyde addition. This makes the development of a catalytic process difficult. Nakamura and Kuwajima had shown that while both $TiCl_4$ and ZnX_2 were capable of silyloxycyclopropane ring opening, only ZnX_2 could be used in substoichiometric amounts. Martins initially investigated the zinc catalyzed homoaldol reaction using a variety of coordinating ligands such as β-amino alcohols and bis-oxazolines, but without success.[25] Consequently, this route was abandoned in favour of a catalytic process

involving an alkoxide coordinated titanium homoenolate derived from silyloxycyclopropane ring opening.

Before these alkoxide-based titanium homoenolates could be formed, two main concerns regarding their suitability needed to be addressed. First, although $TiCl_4$ is Lewis acidic enough to induce ring opening, would an alkoxide substituted titanium(IV) species of reduced Lewis acidity be capable of the same? Secondly, a catalytic cycle requires the regeneration of the alkoxytitanium(IV) species. This necessitates silylation of the intermediate titanium homoaldolate complex. A catalytic cycle with $TiCl_4$ is precluded because cleavage of the intermediate Ti-O homoaldolate bond to regenerate the active titanium species is thermodynamically unfavourable. The Ti-O bond is stronger than the Ti-Cl bond by ≈12 kcal/mol, which impedes catalysis.[24] To circumvent these problems, an alkoxide titanium(IV) triflate was deemed to be a suitable catalyst, since both problems sited above would be addressed. With regards to catalyst Lewis acidity, it was anticipated that the triflate counterion would offset the electron donation abilities of the alkoxide ligands, thus permitting ring opening to occur. In addition, it was assumed that the difference in bond energy between a Ti-O bond in titanium(IV) triflate and titanium(IV) alkoxide would be smaller and comparable to the difference found between a Si-O bond in silicon-triflate and silicon-alkoxide. This would favour silylation of the titanium-bound homoaldolate product and thus regeneration of the catalyst. Based on these assumptions, a variety of chiral alkoxide titanium(IV) triflate catalysts were explored.

Initial experiments with this system explored the mono- and ditriflate-(*R*)-Binol titanium(IV) catalysts **62a** and **62b** respectively. The ditriflate catalyst was prepared by

treatment of (*R*)-Binol $TiCl_2$ with silver triflate in toluene,[26] while the monotriflate was prepared analogously from (*R*)-Binol TiCl(O*i*Pr).[25] Modest catalysis was obtained with both titanium complexes (**Scheme 1-20**).

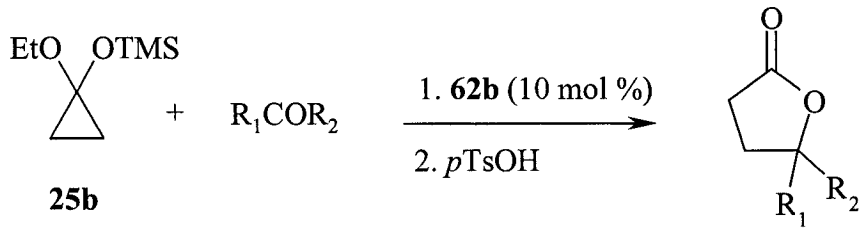


Scheme 1-20. Homoaldol reaction with mono- and ditriflate-(*R*)-Binol titanium(IV) catalyst.

The reaction rate was improved (143 h *vs.* 20 h) when the monotriflate catalyst was prepared by addition of trimethylsilyl triflate to (*R*)-Binol $Ti(OiPr)_2$.[27] The optimized reaction conditions utilized 10 mol % of the monotriflate-(*R*)-Binol titanium catalyst, and 1.5 equivalents of the cyclopropane in a 3:1 $CD_3CN/CDCl_3$ solvent system. The above protocol was amenable to a variety of aldehyde substrates (aromatic and unsaturated aldehydes). The catalyst was also capable of reacting with less reactive substrates such as acetophenone and pivaldehyde at elevated temperatures, which indicates its thermal

stability. This system however, was not applicable to aliphatic aldehydes with enolizable α-protons (**Table 1-1**). Low levels of enantioselectivity were observed in all cases.

Table 1-1. Homoaldol reaction mediated by Binol Ti(O*i*Pr)(OTf).



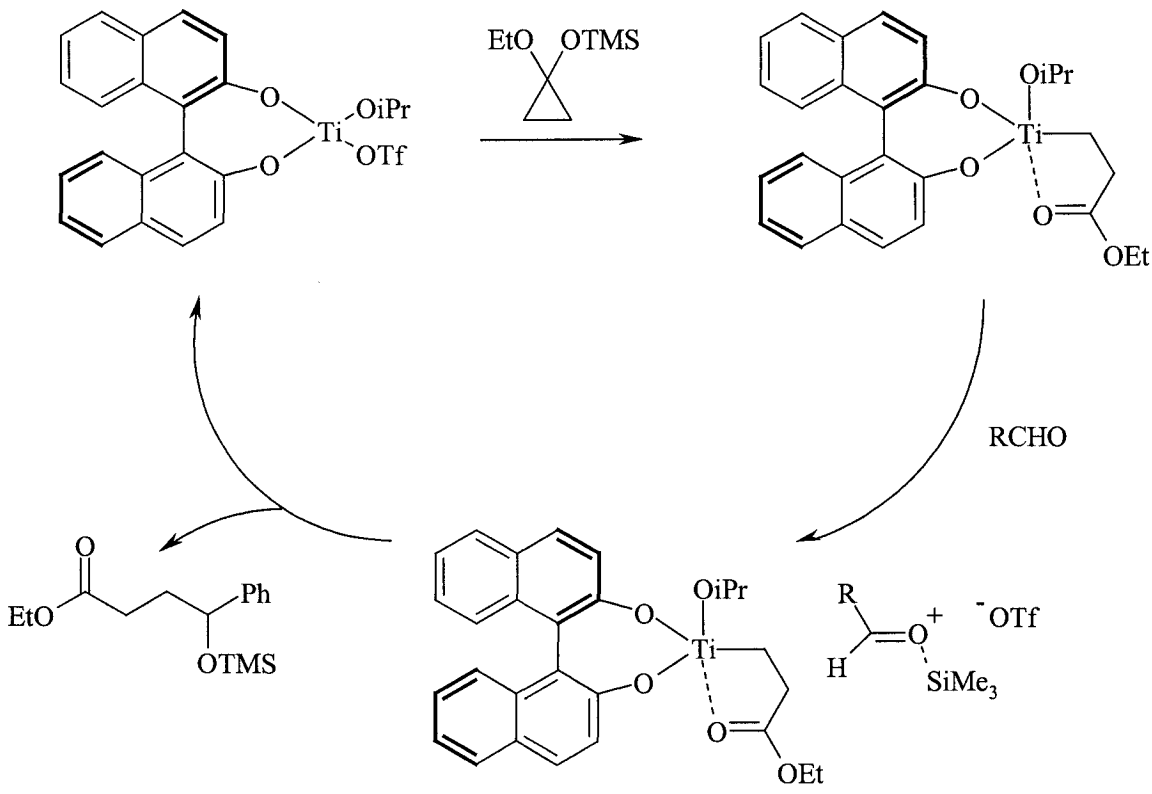
25b

Entry	substrate	conditions [a]	yield (%)
1.	PhCHO	0 °C, 24 h	99
2.	PhC≡CCHO	0 °C, 36 h	76
3.	TMSC≡CCHO	0 °C, 36 h	82
4.	*p*ClPhCHO	0 °C, 80 h	84
5.	*t*BuCHO	45-50 °C, 54 h[b]	52
6.	PhCOMe	45-50 °C, 60 h[b]	78

[a] All reactions were performed in $CD_3CN/CDCl_3$ (3:1) using 1.5 equiv. of **25b**, except where noted. [b] Reaction conducted using 2 equiv. of **25b**

The catalytic cycle had initially been envisioned to proceed with silyloxycyclopropane ring opening to form a chiral titanium homoenolate, followed by nucleophilic addition to an aldehyde to form a titanium coordinated homoaldolate. Silylation of the homoaldolate product would regenerate the titanium catalyst. In light of the low product stereoselectivity levels, an alternative cycle involving activation of the aldehyde with the TMSOTf liberated during the catalyst preparation was put forward

(**Scheme 1-21**). An open transition state would now seem plausible, and without aldehyde coordination to the chiral titanium center, the transfer of chirality is reduced.



Scheme 1-21. Proposed catalytic cycle.

1.1.8 Project Overview

The homoaldol reaction has the potential to be a reliable and concise approach to the synthesis of 1,4-oxygenated units found in many natural products and peptidomimetics. However, this reaction is still underdeveloped because of its many inherent difficulties.

In light of the progress previously reported by Martins in the development of a catalytic homoaldol reaction using a chiral bidentate titanium(IV) homoenolate, we felt that there was potential to develop a synthetically useful process. One of the key problems to be addressed was the low chirality transfer from the chiral catalyst to the homoaldol product. Two solutions were presented: change the catalyst counteranion from triflate to fluoride, and modify the steric and/or electronic properties of the Binol ligand. The following sections outline our attempts to improve the stereoselectivity of this reaction to a synthetically useful level.

1.2 Improving the Selectivity of a Catalytic Homoaldol Reaction - The Development of a Second Generation Catalyst

The original catalytic homoaldol reaction reported by Martins and Gleason utilized an alkoxide titanium(IV) monotriflate catalyst to induce silyloxyalkoxycyclopropane ring opening.[24] While this complex was able to effect a catalytic cycle, it failed to induce significant stereoselectivity into the reaction. Silicon coordination to the carbonyl unit prevented its coordination to the chiral titanium complex, which resulted in a competing open transition state (**Scheme 1-21**). If this homoaldol process were to be made synthetically useful, this problem needed to be addressed. A new catalyst was therefore required.

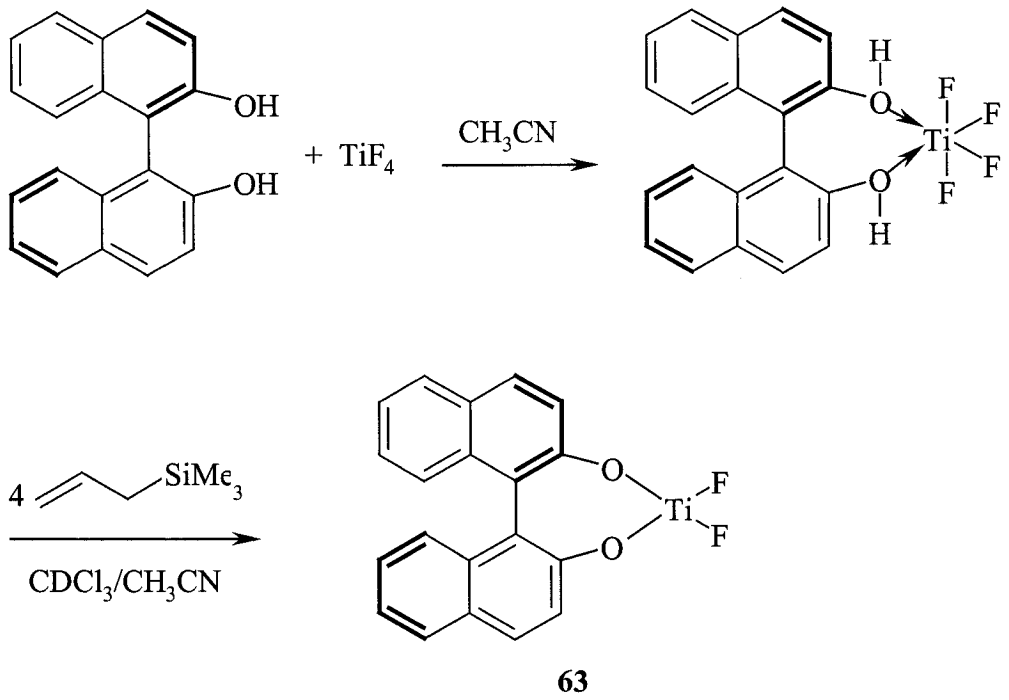
The catalytic cycle requires the ring opening of a silyloxycyclopropane unit to generate a discrete titanium homoenolate. It is this process that releases the cationic alkylsilyl group and makes it available for coordination to the carbonyl unit. To reduce this problem, we sought to develop a second generation catalyst that would trap the trimethylsilyl group, but retain the high reaction rate and stability of the original catalyst. This goal was achieved (*vide infra*) by changing the catalyst counteranion from triflate to fluoride. The catalyst change resulted in the formation of a trimethylsilyl fluoride species of lower Lewis acidity than the trimethylsilyl triflate species released with the original catalyst. As a result, the undesired silicon co-catalysis pathway was impeded. The development of this catalyst and its use in the homoaldol reaction will now be described.

1.2.2 Stereoselective Nucleophilic Additions to Carbonyl Compounds Mediated by Alkoxytitanium(IV) Fluoride Complexes

Titanium(IV) complexes have enjoyed much success as catalysts in the stereoselective addition of allyl- or methallyltin reagents to carbonyl compounds.[28] In an attempt to develop the chemistry of the corresponding inexpensive and nontoxic, but less reactive allyltrimethylsilanes, Carreira and coworkers have utilized a novel, reactive Binol titanium(IV) catalyst derived from TiF_4.[29] The development of an enantioselective, catalytic allylTMS addition reaction had been impeded by the absence of a Lewis acid reactive enough to activate carbonyl compounds towards the addition of the relatively unreactive allyltrimethylsilane. It was assumed that the Binol and TiF_4-derived complex would be capable of satisfying this requirement for two reasons: (i) the increased electronegativity of fluorine in comparison with the chlorine and bromine derivatives makes the TiF_4 derived complex a stronger Lewis acid and (ii) the strong Ti-F bond would permit a catalytic cycle by disfavouring product desilylation to form TMSF (i.e. the allylTMS reagent and resulting TMS-ether are stable under the reaction conditions).

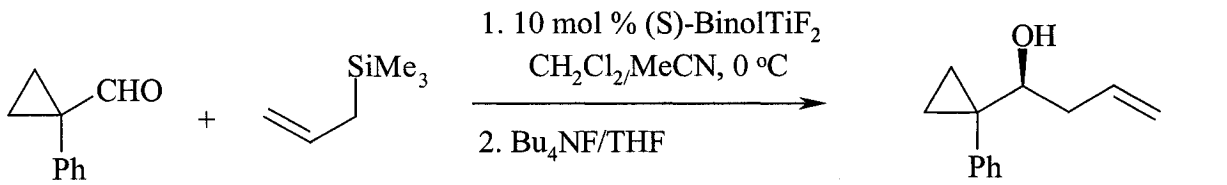
The titanium catalyst was prepared by combining (*S*)-2,2'-binaphthol (20 mol %) with a solution of titanium(IV) fluoride (10 mol %) in acetonitrile, which produced a deep red solution (polymeric TiF_4 is available as an inexpensive solid, and with the exception of acetonitrile, is insoluble in common aprotic organic solvents). Allyltrimethysilane (2 equiv.), which functions as a base or proton scavenger by consuming two equivalents of HF to give propene and TMSF, was then added. Evaporation under reduced pressure yielded the active catalyst as a red-brown solid (**Scheme 1-22**). The Binol titanium(IV) fluoride derived complex proved to be amenable to the allylation reaction and provides

TMS protected homoallyl alcohols with enantioselectivities ranging from 60 – 94 % and yields from 69 – 93 % (**Scheme 1-23**).[29]



63

Scheme 1-22. Preparation of Binol titanium(IV) fluoride catalyst.



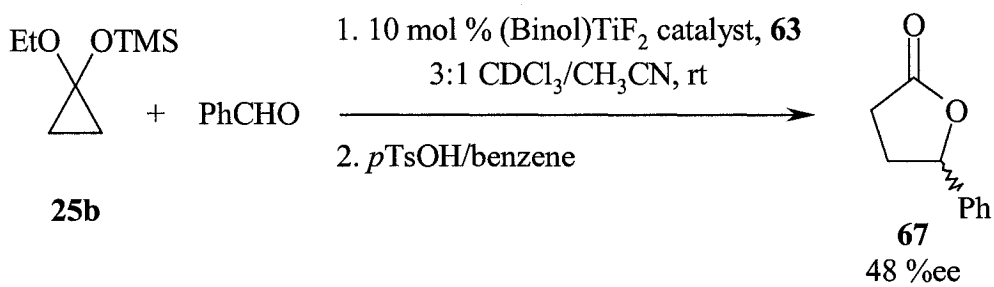
64 **65**

66
92 % yield, 93 % ee, 20 h

Scheme 1-23. Enantioselective allyltrimethylsilane additions to aldehydes.

1.2.3 Homoaldol Reactions Using a Binol Titanium(IV) Fluoride Catalyst

It was proposed that the stereoselectivity of the catalytic homoaldol reaction developed by Martins could be augmented by the use of the Carreira alkoxytitanium(IV) fluoride complex.[29] Ngiap Kie Lim, a research assistant in the Gleason laboratory, conducted the initial investigations with the second generation catalyst. A general experimental procedure was followed for the formation of lactone **67**. The catalyst was prepared as outlined in **Scheme 1-22** and dissolved in a 3:1 chloroform/acetonitrile solvent mixture. 1-Ethoxy-1-(trimethylsilyloxy)cyclopropane was added to this catalyst solution, followed by addition of benzaldehyde. The reaction was quenched with 1M HCl(aq). Lactonization was accomplished with *p*TSOH (cat) in benzene. The homoaldol lactone **67** was obtained with 48 % ee compared to the 10 % ee obtained with the Binol titanium(IV) monotriflate catalyst (**Scheme 1-24**).[24] To improve the reaction stereoselectivity to a synthetically useful level, ligand modifications were now investigated. These studies were conducted to determine if electronic and/or steric modifications to the Binol ligand would influence the product enantioselectivity. Ngiap Kie Lim began these initial studies, which I completed.



25b **67** 48 %ee

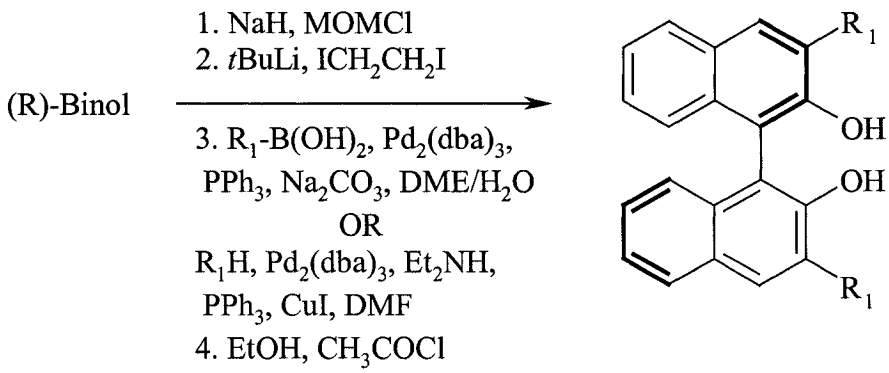
Scheme 1-24. Stereoselective homoaldol reaction catalyzed by Binol Ti(IV) fluoride.

1.2.4 Ligand Modifications

Steric and/or electronic modifications at the 3,3'- and 6,6'- positions of Binol ligand are easily accomplished. It was proposed that the introduction of substituents would influence the Lewis acidity of the titanium catalyst, which would effect the rate of silyloxycyclopropane ring opening. More importantly, these substituents would modify the steric environment at the chiral titanium center. It was anticipated that the increased congestion would provide a smaller chiral pocket, thus leading to improved reaction selectivity. The following section describes the various 3,3'- and 6,6'-Binol ligands synthesized.

The reaction sequence above **Table 1-2** showed the synthesis of some selected 3,3'-disubstituted Binol ligands. The alkoxide groups were protected with methoxymethyl chloride followed by directed *ortho*-lithiation to install the 3,3'-iodo substituents.[30] Compounds **68-71** were synthesized *via* a standard Suzuki coupling,[31] while a Sonogashira coupling allowed access to compound **72**.[32] This was followed by deprotection under mild acid conditions. Compound **73** was obtained by directed *ortho*-lithiation of the (R)-2,2'-dimethoxymethoxy-1,1'-binaphthyl ligand with *t*-BuLi, followed by the addition of excess methyl iodide.[33] Deprotection was accomplished as indicated above.

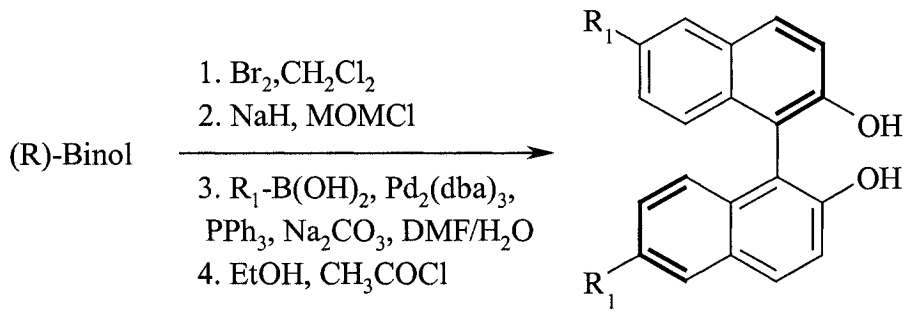
Table 1-2. Synthesis of 3,3'-disubstituted Binol ligands.



Entry	Compound	R_1	Yield (%)
1.	**68**	Ph	82
2.	**69**	3,5-$(CF_3)_2$Ph	98
3.	**70**	2-MeOPh	80
4.	**71**	2,4-MeOPh	76
5.	**72**	PhC≡C	69
6.	**73**	Me	60

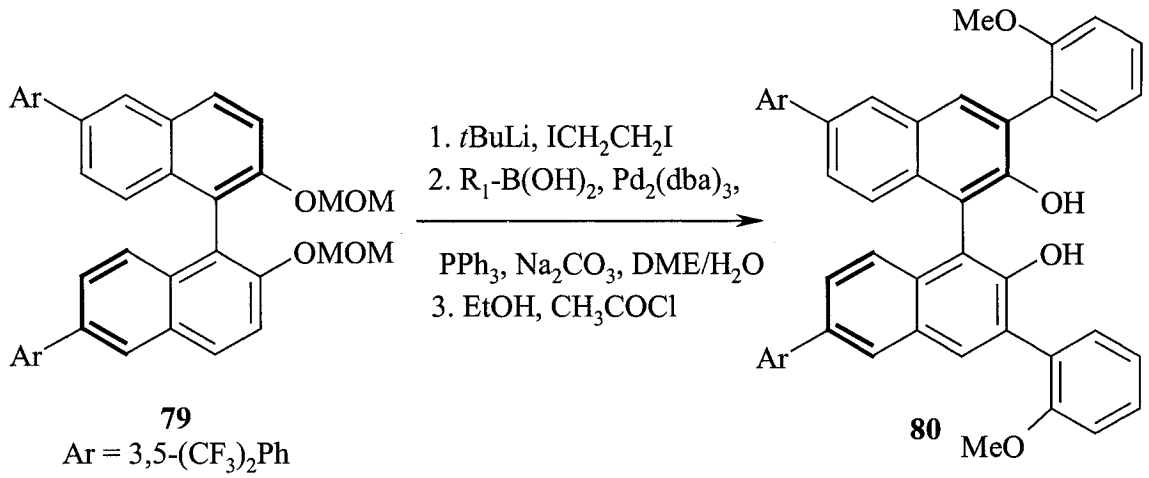
The reaction sequence above **Table 1-3** outlines the synthesis of selected 6,6'-disubstituted Binol ligands **74-77**. Bromination of unprotected Binol with bromine in dichloromethane provided known compound 6,6'-dibromo-2,2'-dihydroxy-1,1'-binaphthyl.[34] Alcohol protection was again accomplished with methoxymethyl chloride. A standard Suzuki coupling permitted the introduction of a variety of 6,6'-Binol substituents. Mild acid hydrolysis furnished the desired modified Binol ligands.

Table 1-3. Synthesis of 6,6'-disubstituted Binol ligands.



Entry	Compound	R_1	Yield (%)
1.	**74**	4-F-2-MeOPh	42
2.	**75**	3,5-$(CF_3)_2$Ph	85
3.	**76**	2-MeOPh	92
4.	**77**	4-F-3-MePh	64
5.	**78**	2,6-$(MeO)_2$Ph	40

Ligand **80** was also synthesized in an analogous manner (**Scheme 1-25**). The methoxymethyl-protected ligand **75** was subjected to the directed *ortho* lithiation/iodination conditions, followed by Suzuki coupling with 2-methoxyboronic acid. Hydrolysis was accomplished with acetyl chloride in ethanol.



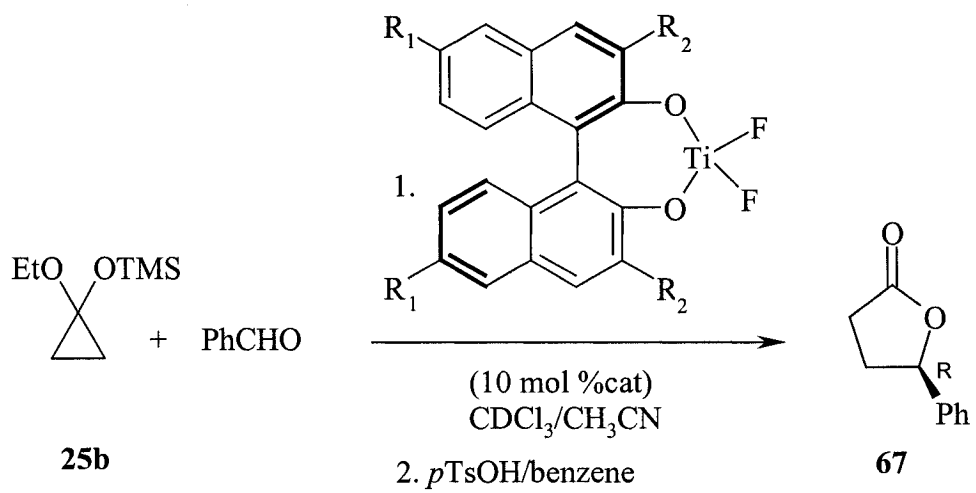
79
Ar = 3,5-$(CF_3)_2$Ph

80

Scheme 1-25. Synthesis of tetrasubstituted ligand **80**.

To assess the substituent effect on selectivity, each modified ligand was used in the homoaldol reaction. **Table 1-4** indicates how the substituent influenced the product enantioselectivity in comparison to unsubstituted Binol. Electron-donating substituents in the 3-position had a positive effect on the reaction selectivity (**entries 4, 5** *vs.* **1**) while electron-withdrawing groups did not (**entry 3**). Electron-withdrawing groups in the 6-position failed to appreciably improve the selectivity (**entry 9** *vs.* **1**), while electron-donating groups were detrimental to reaction selectivity (**entries 10, 12**). Other substituents such as Br, I, simple alkyl groups (**entry 7**), esters, acetylenic groups (**entry 11**) placed in the 3-position failed to improve the selectivity above the level of unsubstituted Binol. 3,3',6,6'-tetrasubstituted Binol ligand **80** (**entry 13**) also failed to improve the product enantioselectivity. Despite the many structural changes to Binol, the reaction selectivity could not be raised to synthetically useful levels.

Table 1-4. Effect of ligand substituents on homoaldol reaction selectivity.



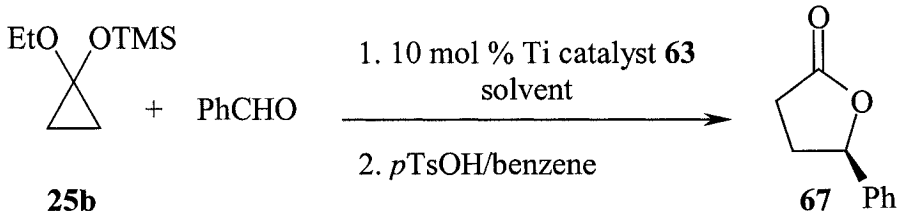
Entry	R_1	R_2	% ee [a]
1.	H	H	48
2.	H	Ph	46
3.	H	3,5-$(CF_3)_2$Ph	39
4.	H	2-MeOPh	61
5.	H	2,4-$(MeO)_2$Ph	65
6.	H	C≡CPh	22
7.	H	Me	41
8.	4-F-2-MeOPh	H	40
9.	3,5-$(CF_3)_2$Ph	H	48
10.	2-MeOPh	H	25
11.	3-F-2-MePh	H	58
12.	2,6-$(MeO)_2$Ph	H	0
13.	3,5-$(CF_3)_2$Ph	2-MeOPh	57

[a] Absolute stereochemistry was established by comparison of the optical rotation of product **67** product with literature values.[35]

1.2.5 Reaction Optimization Using Binol

It was later discovered that the solvent system influenced the product enantioselectivity. A solvent study was conducted using unmodified (*R*)-Binol as the chiral ligand. The results are shown in **Table 1-5**.

Table 1-5. Effect of solvent on the stereoselectivity of the homoaldol reaction.



25b **67**

Entry	Solvent [a]	% ee [b]
1.	3:1 $CDCl_3/CH_3CN$	48
2.	$CDCl_3$	0
3.	**CH_3CN**	**69**
4.	PhCN	35
5.	Et_2O	17
6.	THF	5
7.	CH_3NO_2	7
8.	DMF	8
9.	C_6H_6	0

[a] All reactions were carried out using 10 mol % catalyst **63** and 1.0 equiv. silyloxycyclopropane in the indicated solvent. [b] Determined by chiral GC analysis (Chirasil-dex column).

Upon changing from the first generation alkoxytitanium(IV) monotriflate catalyst to the alkoxytitanium(IV) fluoride catalyst, the $CDCl_3/CH_3CN$ solvent mixture was maintained. Unfortunately, this was not the optimal solvent system for the new catalyst (**Table 1-5, entry 1**). The polar noncoordinating solvent chloroform gave racemic material (**entry 2**), while the weakly coordinating polar solvent acetonitrile afforded the highest product stereoselectivity (**entry 3**).[36] The results in **Table 1-5** indicated that the polar coordinating solvents ether, tetrahydrofuran, nitromethane, *N,N*-dimethylformamide (**entries 5-8**) and the non-coordinating solvents chloroform and benzene were detrimental to achieving high product selectivity (**entry 9**). Compared to the strong donor ligand

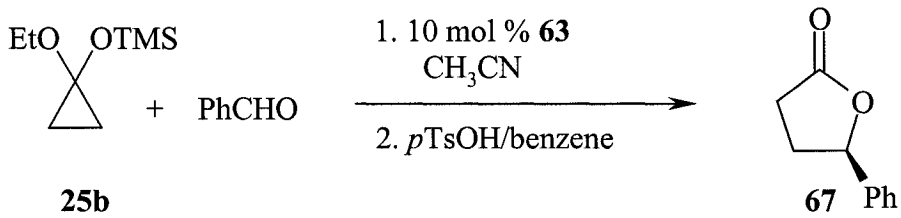
N,*N*-dimethylformamide, acetonitrile is a weak ligand, easily displaced by another ligand in solution. Consequently, ligand exchange between a titanium-bound acetonitrile ligand and Binol (or the aldehyde) is facilitated. In addition, in acetonitrile the catalyst may adopt an aggregation state that is capable of directing the addition of the homoenolate to a titanium-coordinated aldehyde. In the presence of strongly polar solvents, the titanium center may favour the formation of a non-selective monomeric catalyst structure. Aldehyde coordination to the chiral catalyst may also be prohibited, thereby reducing the transfer of chiral information during the addition of the homoenolate.[37] The catalyst aggregation state in non-coordinating solvents may also not be suitable for a stereoselective process. Acetonitrile, therefore, provides a balance between strongly coordinating and non-coordinating solvents.

The discovery that the reaction solvent system played a crucial role in determining the reaction stereoselectivity occurred after a variety of modified Binol ligands were examined. One modified Binol ligand was investigated, however, under the new reaction conditions (acetonitrile as solvent). Substituted Binol ligand **70** (3,3'-2-methoxyphenyl) provided the desired homoaldol lactone with 61% ee in the original solvent system employed for the reaction (**Table 1-4, entry 4**). When this ligand was used in the homoaldol reaction with acetonitrile as the solvent, the homoaldol product was obtained with a disappointing 41 % ee. As previously discussed, each modified ligand usually required a minimum of four steps to prepare. While some of these ligands enhanced the stereoselectivity, it was decided that the search for optimized reaction conditions would utilize the unmodified Binol ligand. If this reaction sequence were to be a viable

synthetic strategy for the organic chemist, quick access to the chiral ligand would be an attractive feature. Subsequent studies therefore focused on the effects of reaction temperature, cyclopropane to aldehyde ratio, and reaction concentration on product enantioselectivity using Binol as the source of chirality.

A reaction optimization study was conducted and the results are reported in **Table 1-6**. A temperature study indicated that the highest enantioselectivities were observed at room temperature (**entries 3, 5-8**). Reactions conducted at temperatures above (50 °C) or below (0°C or -30°C) room temperature reduced the product selectivity (**entries 1, 2, 4**). In addition, two equivalents of Binol were necessary to achieve good levels of product enantioselectivity (**entries 5** *vs.* **6**). Several experiments were conducted at room temperature to optimize the reaction yield and selectivity. When a one to one ratio of silyloxycyclopropane to benzaldehyde was employed, the product was obtained with 69 % ee, but with only a modest 36 % yield (**entry 3**). The yield was increased by employing a slight excess of cyclopropane and by running the reaction at higher concentrations (**entries 7 and 8**). The reaction conditions described for **entry 8** were chosen as the optimal reaction conditions. Although the product enantioselectivity was slightly lower than **entry 7** (65 *vs.* 72 % ee), the reaction yield was at an acceptable level (80 *vs.* 66 % yield).

Table 1-6. Optimization of reaction temperature and concentration conditions.[a]



25b **67**

Entry	T (°C)	**25b**:PhCHO	[PhCHO] (M)	ee [b] (%)	yield (%)
1.	-30	1 : 1	0.55	0	ND
2.	0	1 : 1	0.55	31	ND
3.	25	1 : 1	0.55	69	36
4.	50	1 : 1	0.55	57	ND
5.[c]	25	1.5 : 1	0.37	43	ND
6.	25	1.5 : 1	0.37	66	54
7.[d]	25	1.5 : 1	0.52	72	66 [e]
8.	25	1.5 : 1	0.69	65	80 [e]

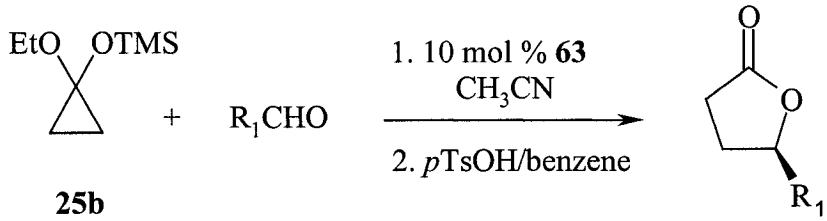
[a] Reactions were conducted over a 24 h period with a catalyst aging time of 1 h prior to addition of **25b** and PhCHO, except as noted. [b] Determined by chiral GC analysis (Chirasil-dex column). [c] The catalyst was prepared using 1.0 equivalent of Binol. [d] The catalyst was aged for three hours rather than one hour prior to addition of **25b** and PhCHO. [e] Reaction time 3 days.

1.2.6 Investigating the Reaction Scope

To determine the general applicability of this reaction sequence, a series of aromatic and acetylenic aldehydes were surveyed using the optimized reaction conditions. **Table 1-7** indicates that good yields and modest selectivities were observed with acetylenic, simple aromatic and aromatic aldehydes containing electron-withdrawing groups at the 4-position (**entries 1-6 and 9**). Electron-donating groups at the 4-position, however, significantly reduced the enantioselectivity of the reaction (**entries 7 and 8**).

Aliphatic and α,β-unsaturated aldehydes were not useful substrates for this reaction. Similar results were observed with the titanium(IV) triflate catalysts employed by Martins.[24]

Table 1-7. Homoaldol reactions of aromatic and acetylenic aldehydes.[a]



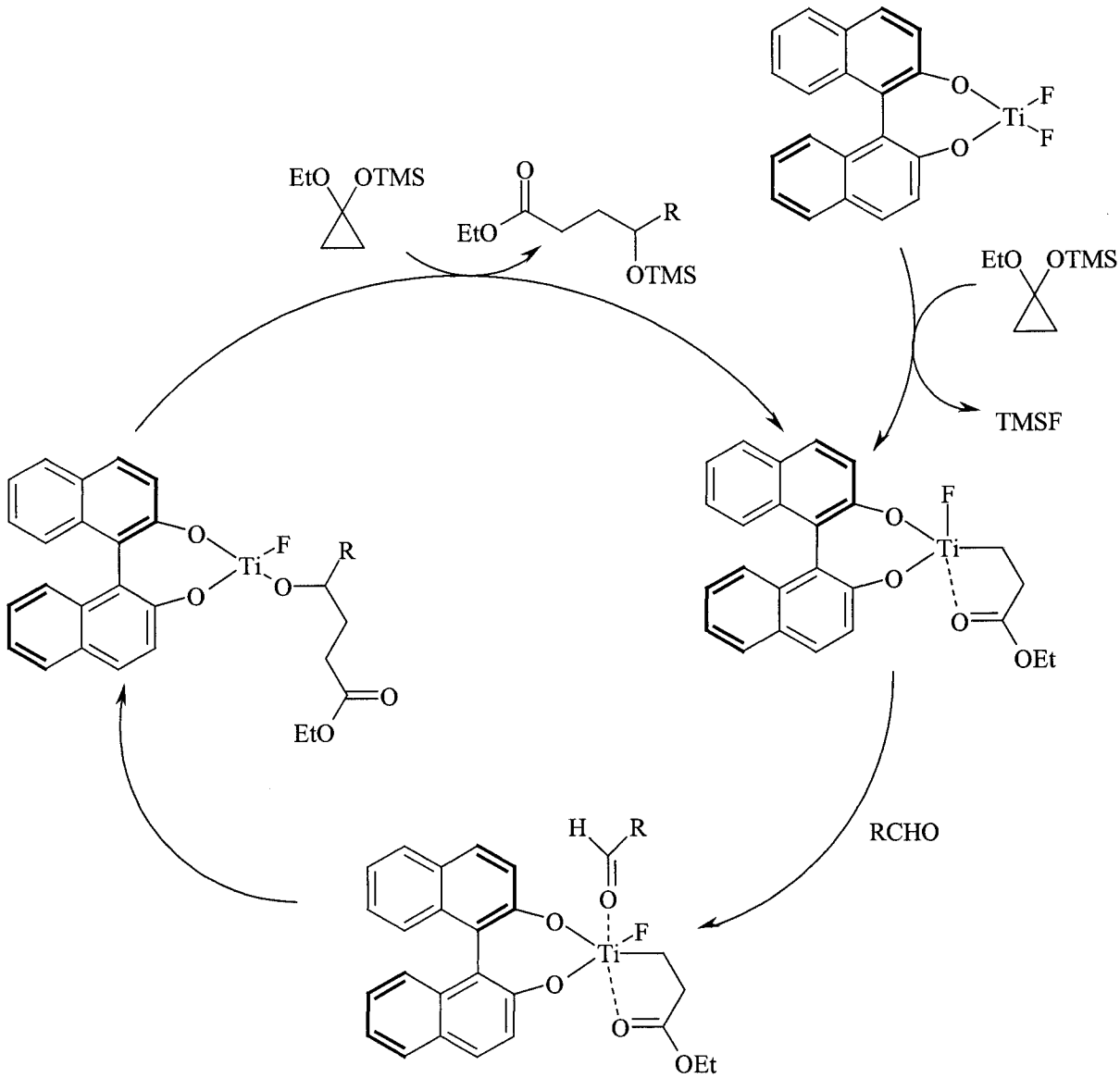
25b

Entry	Compound	R_1	ee [b] (%)	yield (%)
1.	**67**	C_6H_5-	65	80
2.	**81**	1-$C_{10}H_9$-	55	59[c]
3.	**82**	2-$C_{10}H_9$- [d]	61[e]	85
4.	**83**	4-ClC_6H_4-	45	62
5.	**84**	4-BrC_6H_4-	43	69[c]
6.	**85**	4-$CF_3C_6H_4$-	40	59
7.	**86**	4-$CH_3C_6H_4$-	18	59
8.	**87**	4-$CH_3OC_6H_4$-	0	ND
9.	**88**	$C_6H_5C\equiv C$-	61[e]	41

[a] Reactions were allowed to proceed under conditions cited in **Table 1-6, Entry 8** over a period of 168 h. [b] Determined by chiral GC analysis (Chirasil-dex column). [c] Based on recovered starting material. [d] The catalyst was aged for 2.5 h for this example. [e]Determined by chiral HPLC analysis (Pirkle covalent(*S*,*S*) Whelk-OD).

1.2.7 Possible Reaction Mechanisms

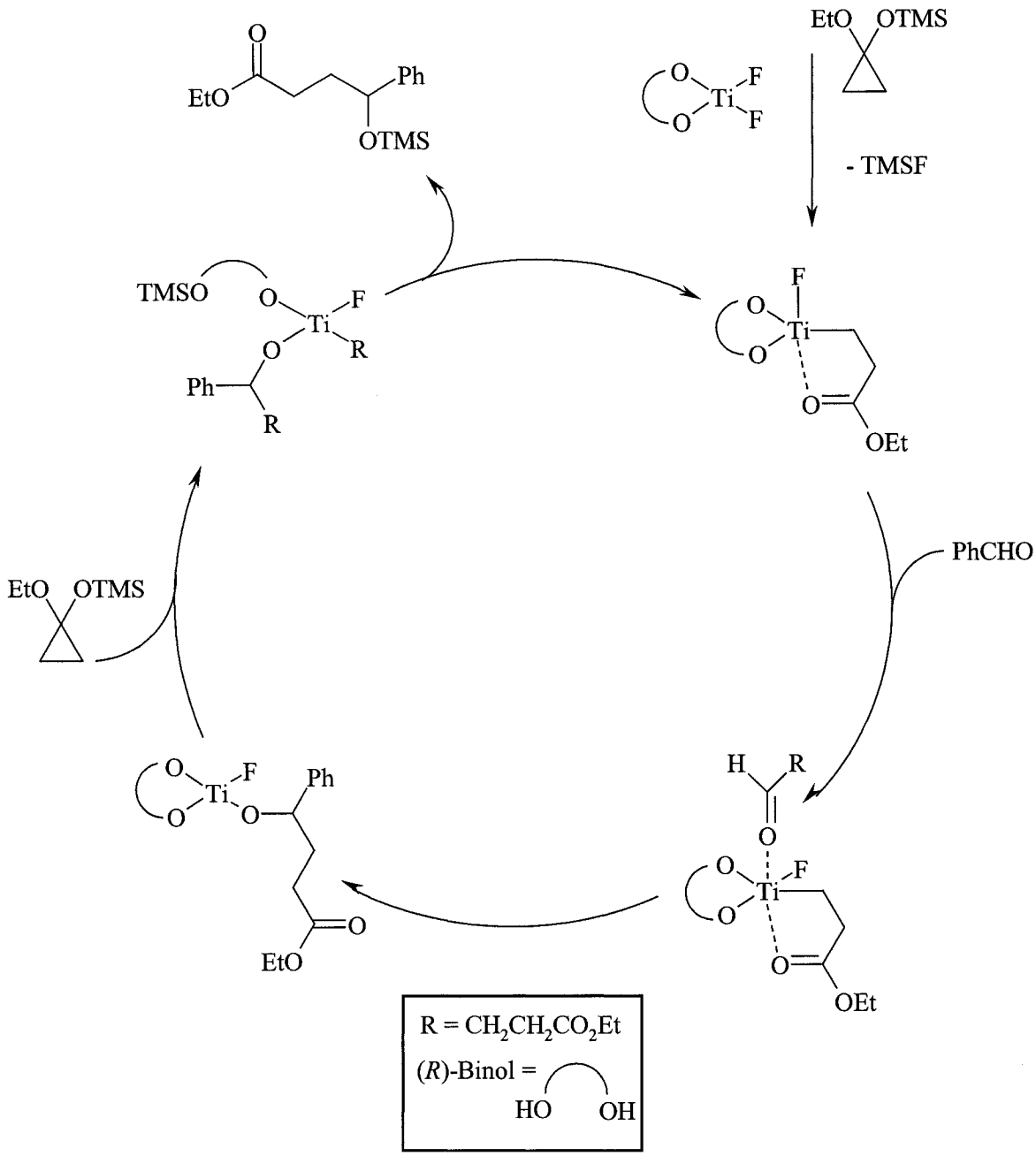
Although the intermediacy of a metal homoenolate seems likely, as with the titanium(IV) triflate catalyzed reaction, it was not possible to observe homoenolate formation by ^{1}H-NMR. The products were invariably isolated as the trimethylsilyl ethers. Given the low probability of silylation by trimethylsilyl fluoride, two plausible mechanisms to account for homoaldolate silylation are possible. The first would be direct silicon transfer during the ring opening of the cyclopropane by a product homoenolate titanium complex, simultaneously forming the silylated homoaldolate product and a new homoenolate (**Scheme 1-26**).



Scheme 1-26. Proposed catalytic cycle for Binol titanium(IV) fluoride catalyzed homoaldol reaction.

A second mechanism invokes the binaphthol ligand to play the role of a silicon shuttle (**Scheme 1-27**). As illustrated in **Table 1-6** (**entry 5** *vs.* **6**), a 2:1 ratio of 2,2'-binaphthol/TiF_4 was necessary to achieve good product yields and selectivity. This result

indicates that silicon transfer may be problematic if the 2,2'-binaphthol to TiF_4 ratio is lower than 2:1.

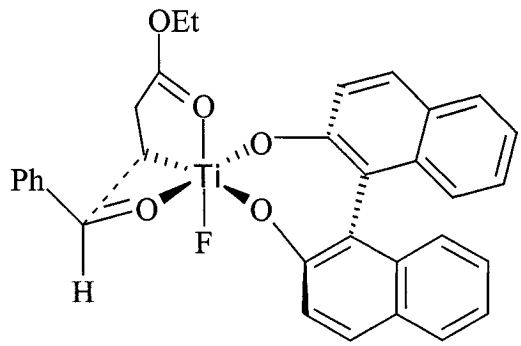


Scheme 1-27. Alternative catalytic cycle for homoaldol reaction catalyzed by Binol $Ti(IV)F_2$.

The low Lewis acidity of the released TMSF species makes the possibility of a silicon co-catalyzed open transition state unlikely. Yet, the homoenolate addition is not able to successfully discriminate between the aldehyde faces to achieve high reaction stereoselectivity. This suggests that either (i) the addition is occurring without prior coordination of the aldehyde to the chiral titanium center, i.e. an open transition state is competing (literature precedent has shown that titanium additions to carbonyl compounds do not require prior Lewis acid activation)[9]; or (ii) even with aldehyde coordination, the chiral environment surrounding the titanium center is not sufficient to permit the homoaldol addition to occur selectively. This latter situation may arise for two reasons. The absence of an α-substituent on the homoenolate removes the directing influence of steric interactions between the homoenolate and the aldehyde. Normally, these interactions would direct the addition to one aldehyde face in preference to the other (i.e. simple diastereoselection). Evans and coworkers have observed a similar effect with *N*-acetyl imides. They have shown that α–unsubstituted acetate enolates are unselective in the aldol reaction, giving approximately equal amounts of the two aldol diastereomers.[38] Secondly, the chiral sphere of the Binol ligand may not be close enough to the reacting centers to sufficiently direct the addition. The homoaldol reaction involves a seven-membered ring cyclic transition state, unlike the tight six-membered cyclic transition state of the aldol reaction, and the ensuing increase in flexibility means that steric factors can be accommodated more easily.

A closed transition state, which may account for the observed product stereochemistry, is shown in **Figure 1-6**. Steric interactions between the homoenolate, aldehyde and chiral Binol ligand are minimized in this configuration. The homoenolate

preferentially adds to the *re*-face of a titanium-coordinated aldehyde to provide the (*R*)-configured 1,4-trimethylsilyl protected homoaldolate product. As discussed earlier (**Table 1-4**), extending the chiral sphere by the introduction of bulky aryl substituents at the 3- and 3'-positions of Binol did not increase the reaction stereoselectivity appreciably. The proposed transition state shows that the subsitutents are directed away from the reacting centers, which reduces their influence on the reaction selectivity.



89

Figure 1-6. Potential transition state for homoenolate addition to benzaldehyde.

The mechanistic schemes outlined above (**Schemes 1-26** and **1-27**) have illustrated the titanium catalyst as a monomeric species. This is a simplified representation, as it is well known that coordinatively unsaturated titanium complexes often exist as dimers, trimers and other aggregates in solution.[39] It has been demonstrated that the homoaldol reaction selectivity is sensitive to reaction concentration, ligand ratio, temperature, and solvent (**Tables 1-5** and **1-6**). Varying these parameters may influence the formation of different chiral titanium complexes. The absence of a well-defined Binol titanium(IV) fluoride catalyst has made it difficult to logically modify the system so as to

improve the product stereoselectivity (ligand modification effects, **Table 1-4**). This may ultimately explain why the reaction selectivity could not be increased to synthetically useful levels.

1.2.8 Conclusions

A catalytic asymmetric homoaldol reaction, which utilizes an alkoxytitanium(IV) fluoride catalyst to generate discrete homoenolates *via* silyloxyalkoxycyclopropane ring opening, has been described. The enantioselectivities, while modest, are the highest reported to date for this class of reaction. The reaction selectivity is sensitive to solvent, the ratio of silyloxycyclopropane reagent to aldehyde, reaction concentration and substituents on Binol.

The reaction tolerates aromatic and acetylenic aldehydes and gives the highest enantioselectivities for aromatic aldehydes bearing electron-neutral and electron-poor substituents.

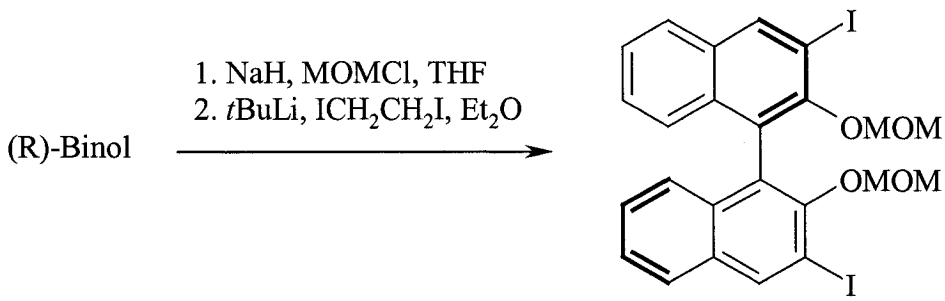
1.3 Experimental Section

General Experimental. All reagents were commercial materials and were used without further purification with the following exceptions. Preparation of catalysts and homoaldol reactions were carried out in Schlenk flasks using distilled reagents. Gas-tight syringes were used for transferring reagents for the homoaldol reactions. Tetrahydrofuran was distilled from sodium benzophenone ketyl, while toluene and other solvents used in the solvent study were distilled from calcium hydride. Deuterated chloroform was distilled over phosphorus pentoxide and stored over molecular sieves prior to use. Benzaldehyde and all remaining aldehydes used in the homoaldol reaction were distilled over calcium hydride and stored over molecular sieves in a fridge.

Thin-layer chromatography was performed on silica gel glass plates (250 μm) and viewed by exposure to UV light and/or immersing in a staining solution of phosphomolybdic acid, followed by heating. Flash chromatography was performed using Silicycle silica gel, 230-400 mesh silica gel, using the eluent specified.

NMR spectra were recorded at 300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C. ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, integration constants (J values) are given in Hertz (Hz) and the spin multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet) and m (multiplet), q (quartet), bs (broad singlet). Data for GC analyses were conducted on a CP Chiralsil-dex column (25 m x 0.25 mm) using He (14 psi) as carrier gas. HPLC analyses were conducted on a Chiracel OD Column.

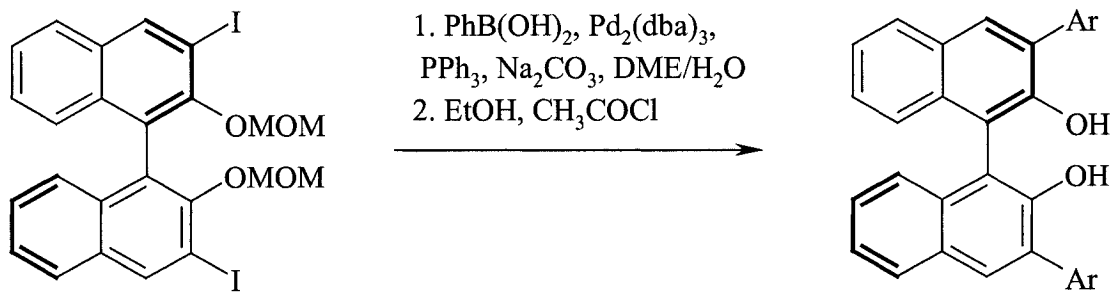
Sample procedure for formation of (*R*)-3,3'-Diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl:



(*R*)-2,2'-dihydroxy-1,1'-dinaphthyl (BINOL) (3.0 g, 10.5 mmol, 1.1 equiv.) was dissolved in dry THF (150 mL) and the solution was cooled to 0°C. After 15 minutes, a sodium hydride suspension was added (60 % w/w in hexanes, 1.26, 52.4 mmol, 5.1 equiv.). The mixture was stirred at 0 °C for 45 minutes. Methoxymethyl chloride (1.79 mL, 23.6 mmol, 2.25 equiv.) was added dropwise *via* syringe. The reaction was warmed to 23 °C and stirred overnight. Distilled water (15 mL) was slowed added to quench any unreacted sodium hydride. The solution was then concentrated under reduced pressure. The organic material was extracted with dichloromethane (3x75 mL). The organic layer was then washed with distilled water (1x50 mL) and brine (1x50mL), followed by drying over sodium sulfate. The residue was purified by chromatography on silica gel eluting with 40-70 % dichloromethane and hexanes to afford (*R*)-2,2'-dimethoxymethoxy-1,1'-dinaphthyl as a white solid (3.45 g, 88 % yield). ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.37-7.13 (m, 6H), 5.08 (d, J = 6.6 Hz, 2H), 4.97 (d, J = 6.6 Hz, 2H), 3.14 (s, 6H). (R)-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (3.0 g, 8.02 mmol, 1.1 equiv.) was dissolved in dry ether (90 mL) and the solution was cooled to 0 °C. After 15 minutes, a solution of *t*-BuLi in hexanes (1.68M in hexanes, 13.4 mL, 2.8 equiv.) was slowly added *via* syringe. The mixture was stirred at 0

°C for 45 minutes. 1,2-Diiodoethane (19.3 mmol, 5.43 g, 2.4 equiv.) was dissolved in dry diethyl ether (10 mL) and cannulated into the above mixture. The solution was warmed to 23 °C and stirred overnight. Distilled water (15 mL) was slowed added to quench any unreacted sodium hydride. The solution was then concentrated under reduced pressure. The organic material was extracted with diethyl ether (3x75 mL). The organic layer was then washed with a saturated sodium thiosulfate solution until all of the excess iodine was extracted. The organic layer was then washed with brine (1x50mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes to afford 3,3'-diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl as a yellow solid (43 % yield). ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 9.6 Hz, 2H), 7.36-7.23 (m, 2H), 7.14 (d, J = 7.7 Hz, 2H), 4.80 (d, J = 6.4 Hz, 2H), 4.69 (d, J = 6.4 Hz, 2H), 2.58 (s, 6H).

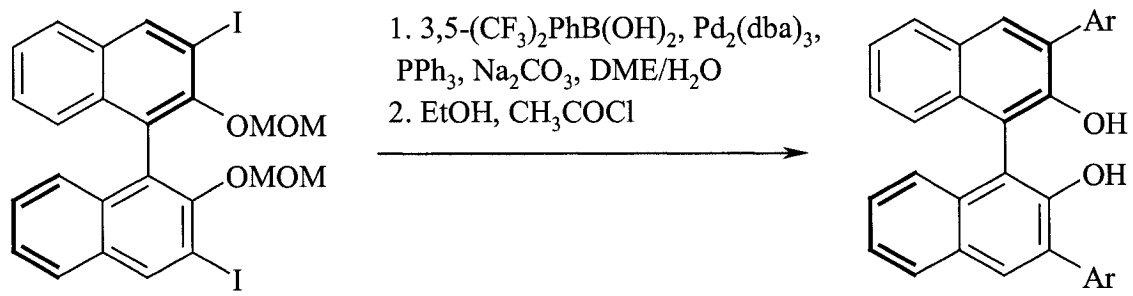
(*R*)-3,3'-Diphenyl-2,2'-dihydroxy-1,1'-dinaphthyl (68):



(*R*)-3,3'-Diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.160 mmol, 1.1 equiv.), palladium dibenzylidene acetone (0.013 mmol, 0.08 equiv.), sodium carbonate (0.416 mmol, 2.6 equiv.), triphenyl phosphine (0.048 mmol, 0.3 equiv.) and phenyl boronic acid (0.383 mmol, 2.4 equiv.) were dissolved in dimethoxyethane (8 mL) and distilled water (1.5 mL). The mixture was then degassed (x4). The solution was warmed to 80 °C and

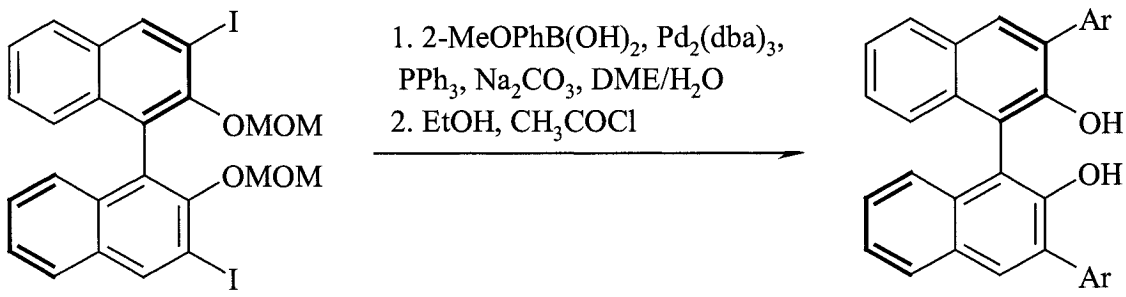
stirred overnight under an argon atmosphere. The reaction was monitored by TLC. Upon completion, the mixture was filtered through celite and the solvent removed under reduced pressure. The organic material was extracted with ethyl acetate (3x15 mL). The organic layer was then washed with distilled water (1x15 mL) followed by brine (1x15mL). The ethyl acetate layer was then dried over sodium sulfate. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes to afford (*R*)-3,3'-diphenyl-2,2'-dimethoxymethoxy-1,1'-dinaphthyl as a yellow oil (104 mg, 82 % yield). The crude material was immediately subjected to methoxymethyl hydrolysis conditions. 3,3'-diphenyl-1,1'-methoxymethyl-Binol (0.346 mmol, 1.0 equiv.) was dissolved in a diethyl ether (2 mL)/95 %ethanol (10 mL) solvent mixture. Acetyl chloride (6.91 mmol, 20 equiv.) was then added dropwise at room temperature. The resulting solution was stirred overnight. The reaction was quenched by the slow addition of distilled water (1 mL). The reaction was then concentrated under reduced pressure. The organic material was extracted with ethyl acetate (3x10 mL). The organic layer was then washed with brine (1x10mL), followed by drying over sodium sulfate. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes. The desired product was isolated as a yellow solid (154 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H), 7.93 (d, J = 7.96 Hz, 2H), 7.74 (d, J = 7.35 Hz, 4H), 7.50 (t, J = 7.34 Hz, 4H), 7.43-7.38 (q, J = 7.34 Hz, 2H), 7.33 (t, J = 7.35, 2H), 7.24 (d, J = 8.89 Hz, 2H) 5.38 (s, 2H, OH).

(*R*)-3,3'-Di[3,5-Bis(trifluoromethyl)phenyl]-2,2'-dihydroxy-1,1'-dinaphthyl (69):



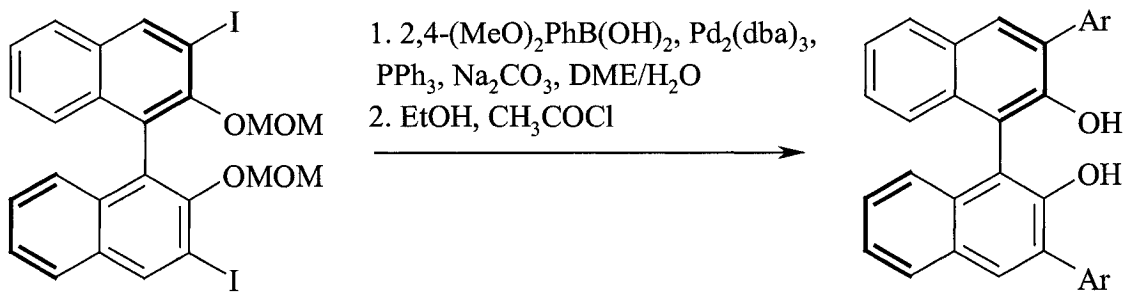
The coupling was carried out at 80 °C over 24 h using 3,5-(ditrifluoromethyl)phenyl boronic acid (0.383 mmol, 2.4 equiv.), (*R*)-3,3'-diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.160 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.013 mmol, 0.08 equiv.), sodium carbonate (0.42 mmol, 2.6 equiv.), triphenyl phosphine (0.048 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired product as a yellow solid (125 mg, 98 % yield). The hydrolysis was accomplished by dissolving the starting material (0.415 mmol, 1.0 equiv.) in a diethyl ether (5 mL)/95 % ethanol (10 mL) solvent mixture, followed by addition of acetyl chloride (12.4 mmol, 30 equiv.). The reaction was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired product as a yellow solid (262 mg, 98 % yield). ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 4H) 8.11 (s, 2H), 8.00 (d, J = 8.19 Hz, 2H), 7.91-7.40 (m, 4H) 7.26-7.22 (m, 2H), 5.36 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 149.7, 139.3, 133.1, 132.3, 131.7, 131.2, 129.7, 129.3, 128.8, 128.6, 127.6, 125.1, 123.9, 121.2, 111.6.

(*R*)-3,3'-Di(2-methoxyphenyl)-2,2'-dihydroxy-1,1'-dinaphthyl (70):



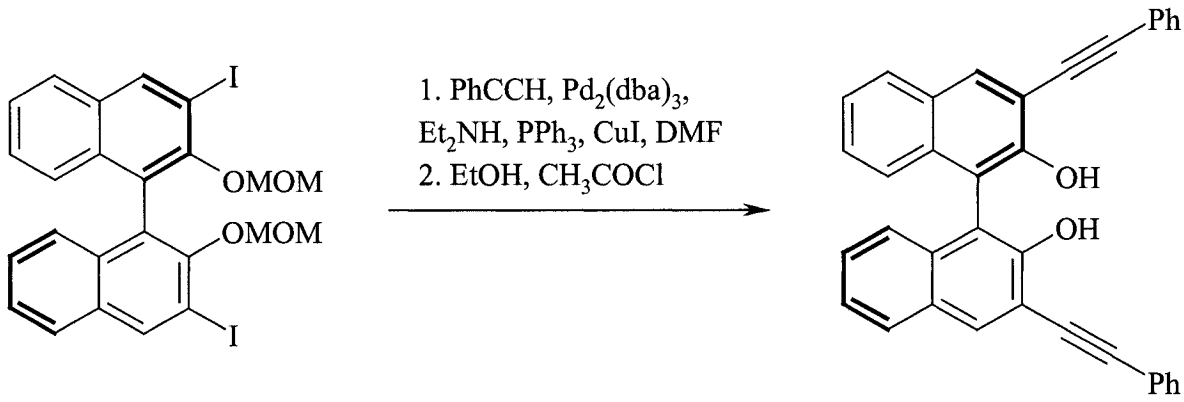
The coupling was carried out at 80 °C over 24 h using 2-methoxyphenyl boronic acid (2.4 equiv., 0.809 mmol), (*R*)-3,3'-diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.337 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.027 mmol, 0.08 equiv.), sodium carbonate (0.88 mmol, 2.6 equiv.), triphenyl phosphine (0.10 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired product as a yellow oil (294 mg, 80 % yield). The hydrolysis was accomplished by dissolving the starting material (0.378 mmol, 1.0 equiv.) in a diethyl ether (5 mL)/95 % ethanol (30 mL) solvent mixture, followed by addition of acetyl chloride (7.57 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 10 % ethyl acetate in hexanes to afford the desired product as a yellow solid (199 mg, 98 % yield). ^{1}H NMR ($CDCl_3$) δ7.91-7.86 (m, 4H) 7.52-7.25 (m, 10H), 7.13 (t, J = 7.54 Hz, 2H), 7.03 (d, 2H, J = 8.34 Hz, 2H), 5.74 (s 2H), 3.83 (s, 6H).

(*R*)-3,3'-Bis(2,4-dimethoxy phenyl)-2,2'-dihydroxy-1,1'-dinaphthyl (71):



The coupling was carried out at 80 °C over 24 h using 2,4-dimethoxyphenyl boronic acid (0.621 mmol, 2.4 equiv.), (*R*)-3,3'-diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.259 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.021 mmol, 0.08 equiv.), sodium carbonate (0.68 mmol, 2.6 equiv.), triphenyl phosphine (0.079 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as an orange oil (127 mg, 76 % yield). The hydrolysis was accomplished by dissolving the starting material (0.461 mmol, 1.0 equiv.) in a diethyl ether (5 mL)/95 % ethanol (10 mL) solvent mixture, followed by addition of acetyl chloride (9.22 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 25 % ethyl acetate in hexanes to afford the desired product as a yellow powder (209 mg, 81 % yield). ^{1}H NMR ($CDCl_3$) δ7.89-7.86 (m, 4H) 7.44-7.25 (m, 8H), 6.68-6.60 (m, 4H), 5.72 (s 2H), 3.88 (s, 6H), 3.81 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 160.7, 157.4, 133.0, 132.3, 131.0, 129.0, 128.0, 127.9, 126.3, 124.6, 123.5, 119.4, 114.4, 105.1, 98.8, 55.8, 55.3.

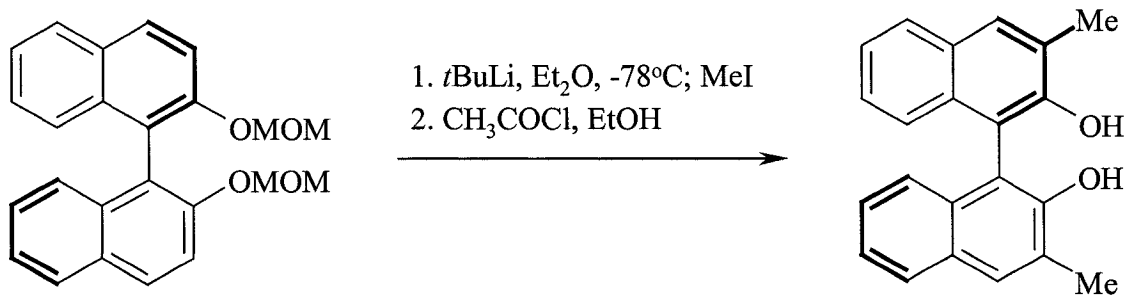
(*R*)-3,3'-Diphenylacetylene-2,2'-dihydroxy-1,1'-dinaphthyl (72):



(*R*)-3,3'-Diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.297 mmol, 1.1 equiv.), palladium dibenzylidene acetone (0.018 mmol, 0.06 equiv.), diethyl amine (0.743 mmol, 2.5 equiv.), triphenyl phosphine (0.071 mmol, 0.24 equiv.) and phenyl acetylene (0.832 mmol, 2.8 equiv.) were dissolved in dimethylformamide (4 mL). The mixture was then degassed (x4). The solution was warmed to 60 °C and stirred overnight under an argon atmosphere. The reaction was monitored by TLC. Upon completion, the mixture was filtered through celite and the solvent removed under reduced pressure. The organic material was extracted with ethyl acetate (3x15 mL). The organic layer was then washed with distilled water (3x15 mL) followed by brine (1x15mL). The ethyl acetate layer was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes to afford 3the desired product as a yellow solid (104 mg, 82 % yield). The crude material was immediately subjected to methoxymethyl hydrolysis conditions. 3,3'-diphenylacetylene-2,2'-methyloxymethyl-1,1'-dinaphthyl (0.573 mmol, 1.0 equiv.) was dissolved in a diethyl ether (3 mL)/95 % ethanol (5 mL) solvent mixture. Acetyl chloride (11.5 mmol, 20 equiv.) was then added dropwise at room temperature. The resulting solution was stirred overnight. The reaction

was quenched by the slow addition of distilled water (1 mL) followed by concentration under reduced pressure. The organic material was extracted with ethyl acetate (3x10 mL). The organic layer was then washed with brine (1x10mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes. The desired product was isolated as a yellow solid (234 mg, 84 %) ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 2H), 7.87-7.85 (d, J = 8.16 Hz, 2H), 7.58-7.56 (m, 4H), 7.38-7.17 (m, 12H), 5.83 (2, 2H); ^{13}C NMR ($CDCl_3$) δ 150.6, 133.6, 133.1, 131.5, 128.7, 128.5, 128.3, 128.1, 127.7, 124.5, 124.2, 122.2, 113.3, 112.1, 96.1, 83.8.

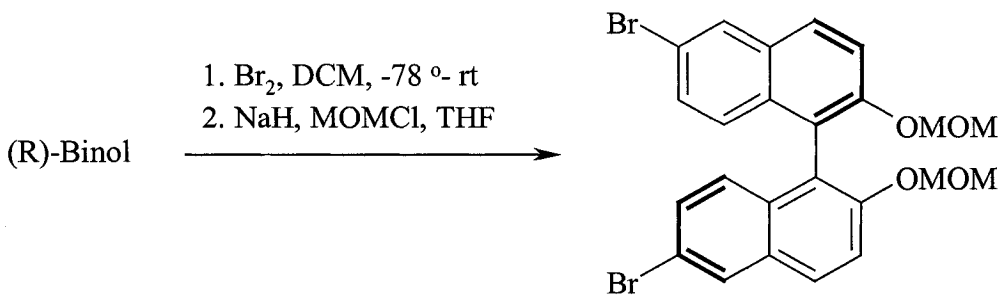
(*R*)-3,3'-Dimethyl-2,2'-dihydroxy-1,1'-binaphthyl (73):



(*R*)-3,3'-Diiodo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl (0.476 mmol, 1.1 equiv.) was dissolved in dry ether (6 mL) and the solution was cooled to 0 °C. After 15 minutes, a solution of *t*-BuLi (1.68M in hexanes, 1.14 mmol, 2.4 equiv.) was slowly added *via* syringe. The mixture was stirred at 0 °C for 45 minutes. Methyl iodide (10 equiv., 4.76 mmol) was then added dropwise *via* syringe. The solution was stirred for 1.5 h at 0 °C. TLC indicated that starting material was still present. The reaction was then warmed to 23 °C and stirred overnight. Distilled water (3 mL) was slowed added to quench any unreacted *t*-butyl lithium. The organic material was extracted with ethyl acetate (3x20 mL). The organic layer was then washed with brine (1x50mL), dried over sodium sulfate

and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes to afford the desired methylated material as a yellow precipitate (129 mg, 67 % yield). The crude material was immediately subjected to methoxymethyl hydrolysis conditions. 3,3'-dimethyl-2,2'-methoxymethyl-1,1'-dinaphthyl (0.320 mmol, 1.0 equiv.) was dissolved in 95 % ethanol (15 mL). Acetyl chloride (6.40 mmol, 20 equiv.) was then added dropwise at room temperature. The resulting solution was stirred overnight. The reaction was quenched by the slow addition of distilled water (1 mL). The reaction was then concentrated under reduced pressure. The organic material was extracted with ethyl acetate (3x10 mL). The organic layer was then washed with brine (1x10mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 30 % dichloromethane and hexanes. The desired product was isolated as a while solid (89 mg, 88 %). ^{1}H NMR ($CDCl_3$) δ 8.14-8.06 9m, 4H0 7.84 9s, 4H) 7.56-7.43 (m, 4H) 7.17 (t, J = 7.34 Hz, 4H) 7.08 (d, J = 8.26, 4H), 6.04 (s, 2H), 3.88 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 151.9, 149.7, 132.0, 130.6, 129.3, 127.4, 126.9, 126.3, 124.0, 123.8, 17.1.

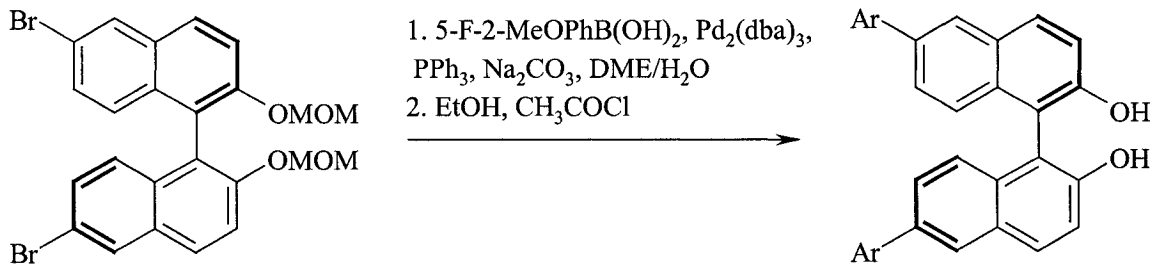
Sample procedure for formation of (*R*)-6,6'-Dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl:



(*R*)-2,2'-dihydroxy-1,1'-dinaphthyl (8.73 mmol, 1.1 equiv.) was dissolved in dry dichloromethane (50 mL) and the solution was cooled to –78 °C. After 15 minutes, bromine (24.4 mmol, 2.8 equiv.) was slowly added *via* syringe over a 20 minute period. The mixture was stirred at -78 °C for 2 hours and then warmed to 23 °C and stirred an additional 2 hours. The reaction was quenched with a 10 % aqueous solution of sodium bisulfite (1x80 mL). The organic material was extracted with dichloromethane (1x100 mL). The organic layer was then washed with distilled water (1x50 mL) and brine (1x50mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 40-70 % dichloromethane and hexanes to afford (R)-6,6'-dibromo-2,2'-dihydroxy-1,1'-binaphthyl as an orange oil (3.88, 99 % yield). ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 2 Hz, 2H), 7.90 (d, J = 2 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.24 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 5.07 (s, 2H). (*R*)-6,6'-Dibromo-2,2'-dihydroxy-1,1'-binaphthyl (8.74 mmol, 1.1 equiv.) was dissolved in dry THF (150 mL) and the solution was cooled to 0 °C. After 15 minutes, a sodium hydride suspension was added (26.2 mmol, 3.1 equiv.). The mixture was stirred at 0 °C for 45 minutes. Methoxymethyl chloride (19.2 mmol, 2.25 equiv.) was added dropwise *via* syringe. The reaction was warmed to 23 °C and stirred overnight. Distilled water (15 mL) was slowed added to quench any unreacted sodium hydride. The solution was then concentrated under reduced pressure. The organic material was extracted with ethyl acetate (3x75 mL). The organic layer was then washed with distilled water (1x50 mL) and brine (1x50mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate and hexanes to afford 6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-dinaphthyl as a yellow solid

(3.50g, 80 % yield). ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J = 1.8 Hz, 2H), 7.87 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.29 (dd, J_1 = 2.2, J_2 = 9.1 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 5.09 (d, J = 6.8 Hz, 2H), 4.98 (d, J = 6.8 Hz, 2H), 3.16 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.9, 132.4, 130.8, 129.9, 129.7, 128.7, 127.1, 120.7, 118.0, 95.0, 55.9.

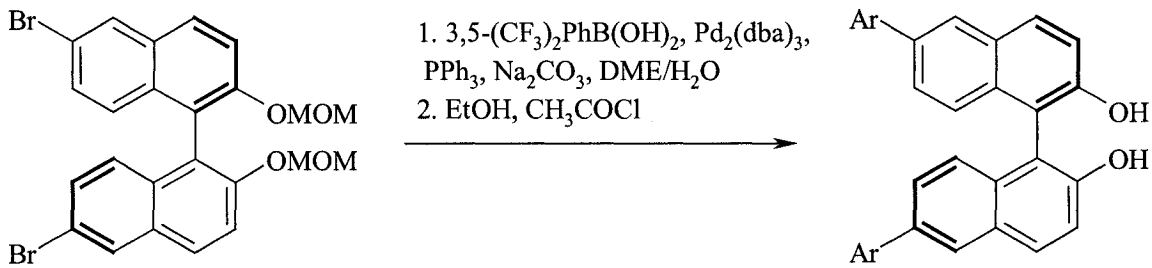
(*R*)-6,6'-Di(5-Fluoro-2-methoxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (74):



The coupling was carried out at 80 °C over 24 h using 5-fluoro-2-methoxyphenyl boronic acid (1.37 mmol, 2.4 equiv.), (*R*)-6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.571 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.046 mmol, 0.08 equiv.), sodium carbonate (1.48 mmol, 2.6 equiv.), triphenyl phosphine (0.171 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 10 % ethyl acetate in hexanes to afford the desired product as a yellow solid (232 mg, 65 % yield). ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 4H), 7.62 (d, J = 9.27, 2H), 7.46-7.42 (dd, J_1 = 8.78, J_2 = 1.46, 2H), 7.25-7.22 (m, 2H), 7.17-7.13 (dd, J_1 = 9.02 Hz, J_2 = 3.17 Hz, 2H), 7.03-6.97 (dt, J_1 = 8.17 Hz, J_2 = 2.93 Hz, 4H), 6.93-6.89 (m, 4H), 5.12 (d, J = 6.58 Hz, 2H), 5.04 (d, J = 6.58 Hz, 2H), 3.78 (s, 6H), 3.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.1, 155.9, 153.3, 153.1$_3$, 153.1, 133.5 132.2 (d, J = 29.4 Hz), 130.1, 128.5 (d, J = 39.9 Hz), 125.5, 121.3, 118.0, 117.7, 117.6, 114.6 (d, J = 89.7 Hz), 112.6 (d, J = 33.0 Hz), 95.4, 56.4, 56.2. The hydrolysis was accomplished by dissolving the starting material (0.337 mmol, 1.0 equiv.,) in a

diethyl ether (10 mL)/95 % ethanol (30 mL) solvent mixture, followed by addition of acetyl chloride (6.75 mmol, 20 equiv.,). The reaction was purified by chromatography on silica gel eluting with 15-30 % ethyl acetate in hexanes to afford the desired product as a white solid (179 mg, 99 % yield).

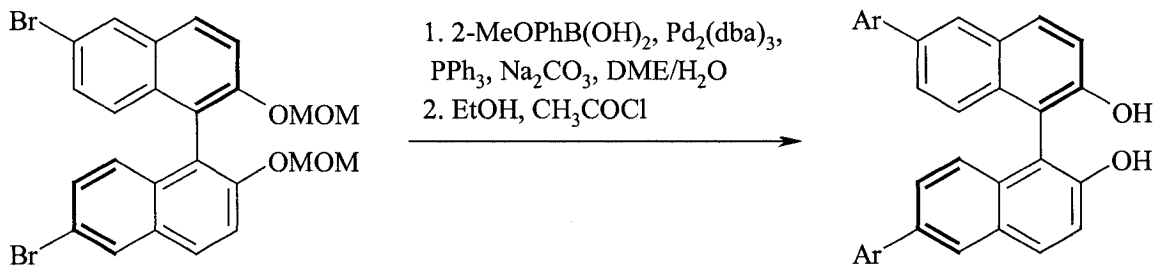
(*R*)-6,6'-Di[3,5-Bis(trifluoromethyl)phenyl]-2,2'-dihydroxy-1,1'-binaphthyl (75):



The coupling was carried out at 80 °C over 24 h using 3,3-di(trifluoromethylphenyl) boronic acid (0.685 mmol, 2.4 equiv.), (*R*)-6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.564 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.023 mmol, 0.08 equiv.), sodium carbonate (0.744 mmol, 2.6 equiv.), triphenyl phosphine (0.086 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired product as a yellow oil (165 mg, 57% yield). ^{1}H NMR ($CDCl_3$) δ 8.13-8.06 (m, 6H), 7.84 (s, 2H), 7.74 (d, J = 9.24 Hz, 2H), 7.48 (d, J = 8.75, 2H), 7.29 (d, J = 8.75 Hz, 4H), 5.15 (d, J = 6.81 Hz, 2H), 5.06 (d, J = 6.81 Hz, 2H), 3.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.4, 143.0, 133.7, 133.6, 132.0 (q, J = 131.7 Hz), 130.1, 129.8, 128.9, 128.4, 127.1, 126.6, 125.2, 120.6, 117.9, 95.0, 56.0. The hydrolysis was accomplished by dissolving the starting material (0.176 mmol, 1.0 equiv.) in a diethyl ether (4 mL)/95 % ethanol (25 mL) solvent mixture, followed by addition of acetyl chloride (5.28 mmol, 30 equiv.). The reaction was purified by chromatography on

silica gel eluting with 10-20 % ethyl acetate in hexanes to afford the desired product as a yellow solid (120 mg, 74 % yield). ^{1}H NMR ($CDCl_3$) δ 8.20-8.05 (m, 6H), 7.90 (s, 2H), 7.57 (d, J = 6.8 Hz, 2H), 7.50 (d, J = 6.7 Hz, 2H), 7.30 (d, J = 6.3 Hz, 4H).

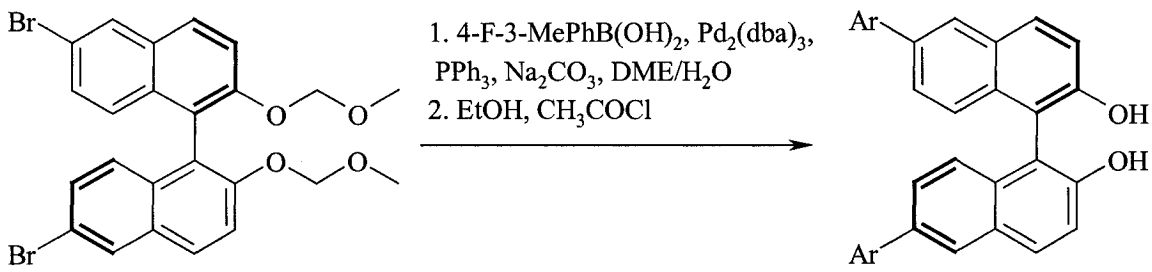
(*R*)-6,6'-Di(2-methoxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (76):



The coupling was carried out at 80 °C over 24 h using 2-methoxyphenyl boronic acid (1.13 mmol, 2.4 equiv.), (*R*)-6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.470 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.038 mmol, 0.08 equiv.), sodium carbonate (1.22 mmol, 2.6 equiv.), triphenyl phosphine (0.141 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a yellow solid (454 mg, 96 % yield). ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 2H), 8.06 (d, J = 8.3 Hz, 4H), 7.67 (d, J = 8.82 Hz, 2H), 7.56 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 2H), 7.48 (dd, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 2H), 7.40-7.28 (m, 4H), 7.12 (t, J = 7.2 Hz, 2H), 7.12 (d, J = 7.24 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 156.9, 153.1, 134.6, 133.4, 131.4, 130.9, 130.2, 129.9, 128.9, 128.8, 128.4, 125.4, 121.4, 121.2, 117.6, 111.5, 95.5, 56.2, 55.8. The hydrolysis was accomplished by dissolving the starting material (0.597 mmol, 1.0 equiv.) in a diethyl ether (3 mL)/95 % ethanol (10 mL) solvent mixture, followed by addition of acetyl chloride (11.9 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 10 % ethyl acetate in hexanes to afford the

desired product as a yellow powder (284 mg, 96 % yield). ^{1}H NMR ($CDCl_3$) δ 8.02-7.99 (m, 4H), 7.53-5.49 (dd, J_1 = 8.46 Hz, J_2 = 1.69 Hz, 2H), 7.41 (d, J = 9.02 Hz, 2H), 7.25-7.21 (m, 2H), 7.15-7.11 (dd, J_1 = 9.02 Hz, J_2 = 3.10 Hz, 2H), 7.05-6.98 (dt, J_1= 8.74 Hz, J_2 = 3.10 Hz, 2H), 6.94-6.89 (m, 2H), 5.14 (s, 2H), 3.79 (s, 6H)

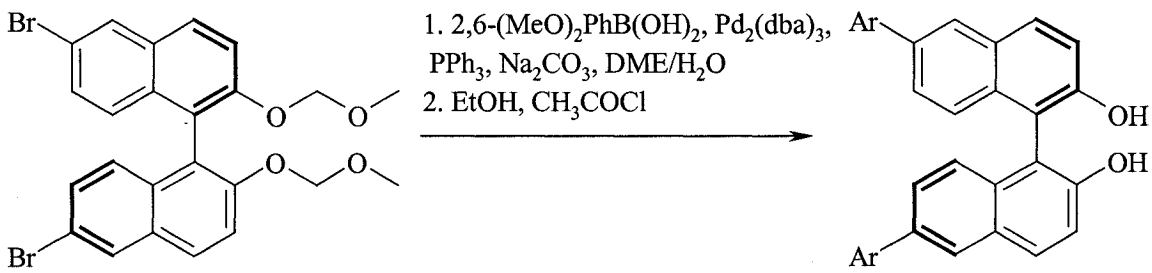
(*R*)-6,6'-Di(4-Fluoro-3-methylphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (77):



The coupling was carried out at 80 °C over 24 h using 4-Fluoro-3-methylphenyl boronic acid (1.39 mmol, 2.4 equiv.), (*R*)-6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.579 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.046 mmol, 0.08 equiv.), sodium carbonate (1.51 mmol, 2.6 equiv.), triphenyl phosphine (0.174 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a yellow solid (253 mg, 74 % yield). ^{1}H NMR ($CDCl_3$) δ 8.82-7.98 (m, 4H), 7.62 (d, J = 8.67 Hz, 2H), 7.46-7.11 (m, 8H), 7.06 (t, J = 8.85 Hz, 2H), 5.11 (d, J = 6.77, 2H), 5.01 (d, J = 6.77 Hz, 2H), 3.19 (s, 6H), 2.35 (s, 6H). The hydrolysis was accomplished by dissolving the starting material (0.363 mmol, 1.0 equiv.) in a diethyl ether (5 mL)/95 % ethanol (30 mL) solvent mixture, followed by addition of acetyl chloride (7.25 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a grey solid (159 mg, 87 % yield). ^{1}H NMR ($CDCl_3$) δ 8.06-7.93 (m,

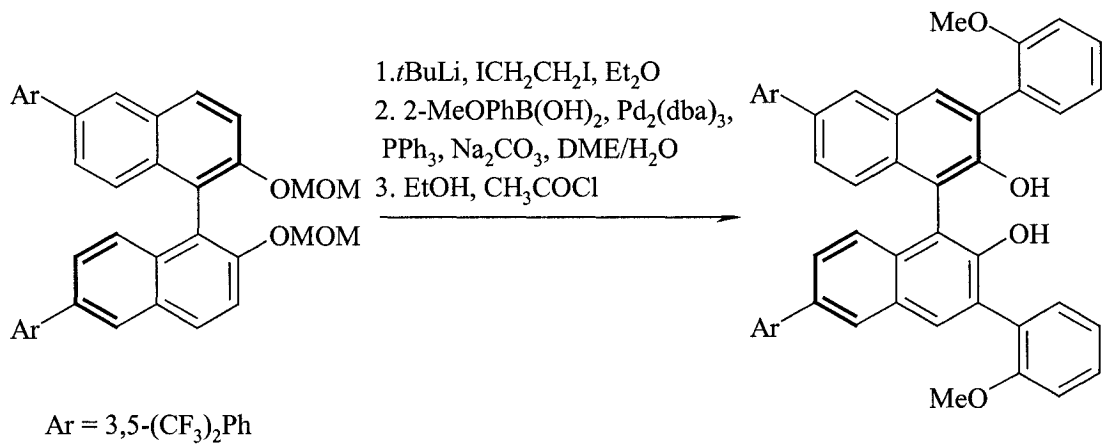
4H), 7.56-7.34 (m, 8H), 7.24 (d, J = 8.6 Hz, 2H), 7.09 (t, J = 9.71 Hz, 2H), 5.31 (s, 2H), 2.36 (s, 6H).

(*R*)-6,6'-Bis(2,6-dimethoxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (78):



The coupling was carried out at 80 °C over 24 h using 2,6-dimethoxyphenyl boronic acid (0.977 mmol, 2.4 equiv.), (*R*)-6,6'-dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.376 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.033 mmol, 0.08 equiv.), sodium carbonate (1.05 mmol, 2.6 equiv.), triphenyl phosphine (0.12 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a yellow solid (119 mg, 49 % yield). The hydrolysis was accomplished by dissolving the starting material (0.315 mmol, 1.0 equiv.) in a diethyl ether (5 mL)/95 % ethanol (10 mL) solvent mixture, followed by addition of acetyl chloride (6.31 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 10 % ethyl acetate in hexanes to afford the desired product as a yellow powder (145 mg, 82 % yield). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 3.10 Hz, 2H), 7.89 (s, 2H), 7.37-7.24 (m, 8H), 6.68 (d, J = 8.45, 4H), 5.09 (s, 2H), 3.74 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.6, 152.5, 149.6, 132.2, 131.5, 130.8, 130.1, 129.5, 129.2, 128.6, 123.4, 118.8, 117.2, 110.7, 104.0, 55.9.

(*R*)-6,6'-Di[3,5-bis(trifluoromethyl)phenyl]-3,3'-di(2-methoxyphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (80):



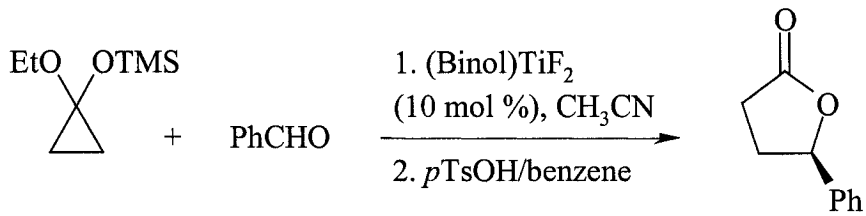
Ar = 3,5-$(CF_3)_2$Ph

The iodination was carried out as described above. The coupling was carried out at 80 °C over 24 h using 2-methoxyphenyl boronic acid (1.35 mmol, 2.4 equiv.), (*R*)-6,6'-[3,5-bis(trifluoromethyl)phenyl]-3,3'-diiodo-2,2'-dimethoxymethoxy-1,1'-binaphthyl (0.564 mmol, 1.0 equiv.), palladium dibenzylidene acetone (0.045 mmol, 0.08 equiv.), sodium carbonate (1.47 mmol, 2.6 equiv.), triphenyl phosphine (0.169 mmol, 0.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired product as a yellow solid (369 mg, 82 % yield). The hydrolysis was accomplished by dissolving the starting material (2.13 mmol, 1.0 equiv.) in a diethyl ether (10 mL)/95 % ethanol (50 mL) solvent mixture, followed by addition of acetyl chloride (7.25 mmol, 20 equiv.). The reaction was purified by chromatography on silica gel eluting with 30 % dichloromethane in hexanes to afford the desired product as a yellow solid (116 mg, 77 % yield). ^{1}H NMR ($CDCl_3$) δ 8.14-8.06 (m, 4H), 7.84 (s, 2H), 7.56-7.43 (m, 8H), 7.19-7.14 (t, J = 7.38 Hz, 4H), 7.09-7.06 (d, J = 8.13 Hz, 4H), 6.04 (s 2H), 3.88 (s, 6H).

Catalyst Preparation:

In a flame dried Schlenk flask was added (*R*)-2,2'-dihydroxy-1,1'-binaphthyl (56 mg, 0.195 mmol, 0.2 equivalents). This was washed with 2 x 2 mL dry toluene. The solvent was then removed *in vacuo* to remove any traces of water. The ligand was then dried over night *in vacuo*. In a glove box, an acetonitrile solution (~ 1.5 mL) of Titanium (IV) fluoride (12 mg, 0.095 mmol, 0.1 equiv.) was added at room temp to an acetonitrile solution of the Binol ligand (~1.5 mL). Immediate formation of a red solution was observed. The reaction mixture was stirred for 1 hour at room temperature. The solvent was then removed *in vacuo* and dried for ~ 10 minutes. The red oil was then redissolved in an appropriate quantity of dry acetonitrile. To this red solution was added allyltrimethylsilane (62 μL, 0.392 mmol, 0.4 equivalents) and the solution was allowed to stir for an appropriate period of time. Precipitate formation was observed.

General Homoaldol Procedure:

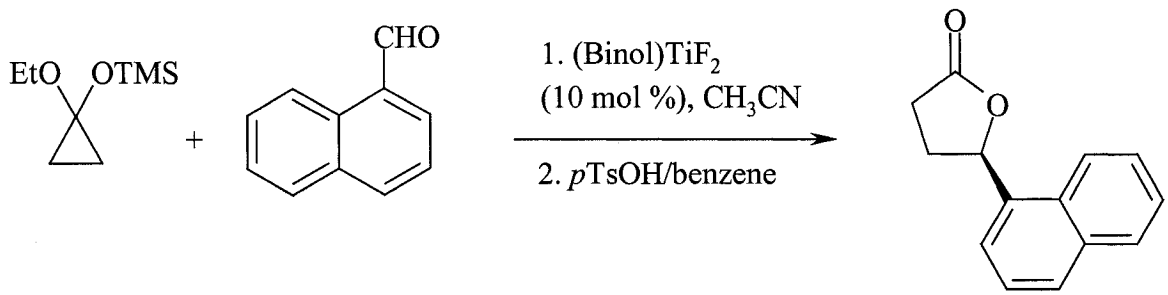


67

To the catalyst solution prepared above was now added 1-ethoxy-1-(trimethylsilyloxy)cyclopropane (300 μL, 1.50 mmol, 1.5 equivalents), followed by addition of benzaldehyde (100 μL, 0.99 mmol, 1.0 equivalents) after ~10 minutes of stirring. This final solution was continuously stirred over the entire reaction time period. After 7 days, the reaction was quenched by addition of 1 M HCl (30 mL) and the products were extracted into ethyl acetate (2 x 30 mL). The organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was dissolved in benzene (6 mL) to which ρTSOH (cat) was added. The reaction mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the products extracted into ethyl acetate (2 x 30 mL). The organic layer was washed once with brine (30 mL), dried over Na_2CO_3, filtered and concentrated. Purification of the residue by column chromatography on silica gel, using 30 % hexanes in methylene chloride as eluent, afforded 128.0 mg of the lactone (80.2 % yield). The product was determined to have a 65 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C, R_t = 20.1 minutes (minor enantiomer) and R_t = 21.3 minutes (major enantiomer)). ^{1}H NMR ($CDCl_3$) δ 7.24–7.39 (m, 5H), 5.46 (dd, J = 7.9, 6.2Hz, 1H), 2.54–2.67 (m, 3H), 2.04–2.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.8, 139.2, 128.5, 125.1, 81.0, 30.7, 28.7. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C,

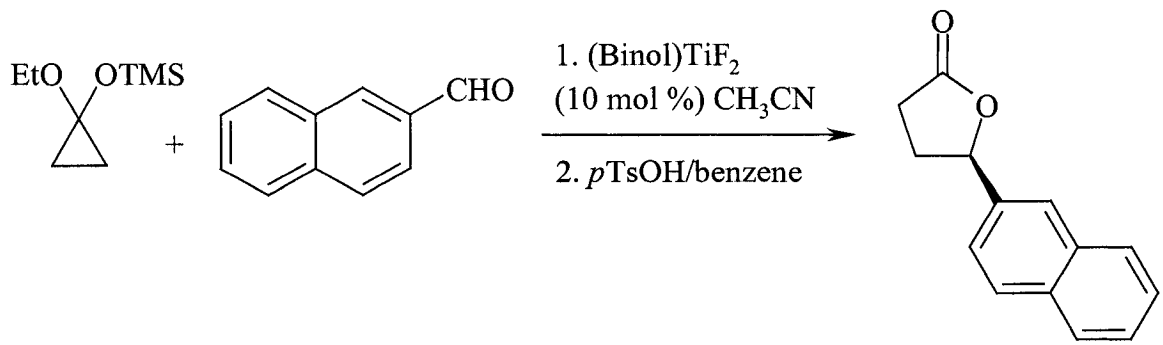
73.73; H, 6.02. $[\alpha]^{rt}_D$ (72 % ee) = +12.96° (c = 0.0301, CH_2Cl_2); Literature[35]: $[\alpha]^{rt}_D$ = + 31.0° (c = 0.675, CH_2Cl_2).

Homoaldol aldol adduct of 1-naphthaldehyde (81).



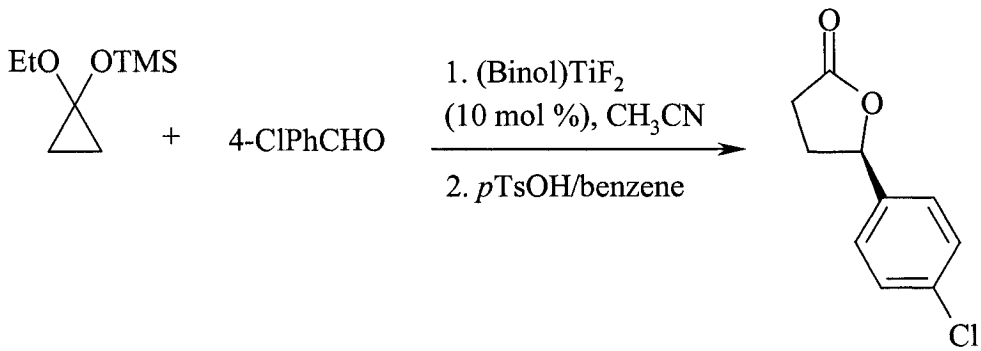
The product was determined to have a 55 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C). ^{1}H NMR ($CDCl_3$), δ 7.89-7.91 (m, 1H), 7.82-7.85 (m, 2H), 7.46-7.58 (m, 4H), 6.26 (t_{obs}, J_{obs} = 6.93 Hz, 1H), 2.85-2.92 (m, 1H), 2.61-2.76 (m, 2H), 2.25-2.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177.2, 135.2, 133.9, 129.6, 129.3, 128.9, 126.7, 126.1, 125.6, 122.6, 121.8, 78.9, 30.4, 28.7. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.82; H, 5.57.

Homoaldol aldol adduct of 2-naphthaldehyde (82).



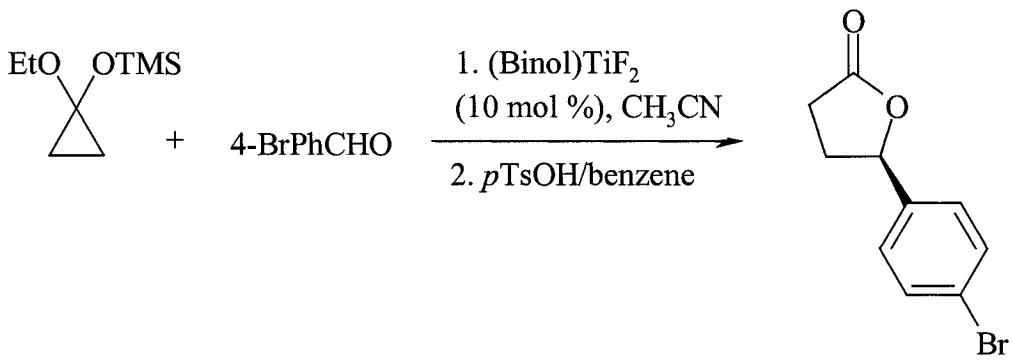
The product was determined to have a 61 % ee by HPLC analysis (chiral Pirkle covalent (S,S) Whelk-OD column, 1 % *i*PrOH/hexanes). ^{1}H NMR ($CDCl_3$) δ 7.80-7.88 (m, 4H), 7.48-7.52 (m, 2H), 7.39 (dd, J = 1.71 Hz, 1H), 5.65-5.69 (m, 1H), 2.67-2.78 (m, 3H), 2.21-2.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177.0, 136.8, 133.3, 133.2, 129.0, 128.2, 127.9, 126.8, 126.6, 124.4, 123.0, 81.6, 31.3, 29.3. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.93; H, 5.64.

Homoaldol aldol adduct of *p*-ClPhCHO (83).



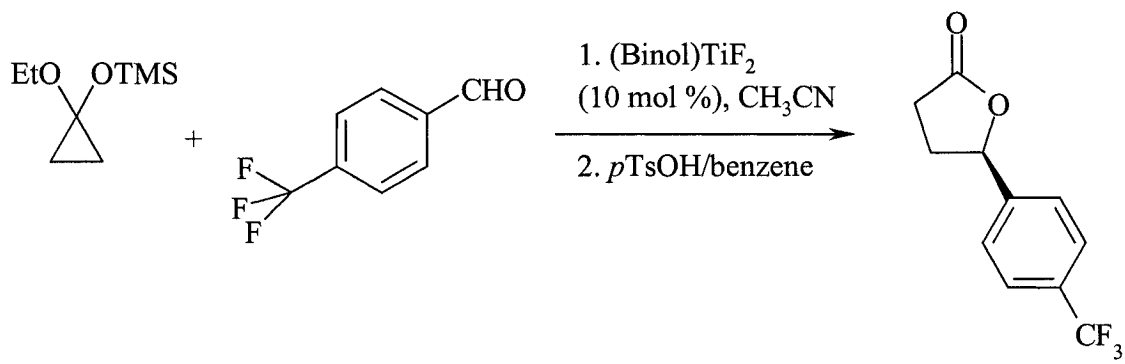
The product was determined to have a 45 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.30 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 5.41 (dd, J = 5.9 Hz, 6.4 Hz, 1H), 2.52–2.67 (m, 3H), 2.00–2.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.4, 137.8, 134.0, 128.7, 126.6, 80.3, 30.7, 28.7; Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.34; H, 4.72.

Homoaldol aldol adduct of *p*-BrPhCHO (84).



The product was determined to have a 43 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C). ^{1}H NMR ($CDCl_3$), δ 7.50 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 5.45 (t_{obs}, J_{obs} = 1.6 Hz, 1H), 2.59-2.70 (m, 3H), 2.08-2.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.6, 138.5, 132.0, 127.1, 122.5, 80.7, 31.3, 29.3. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 50.12; H, 3.74. Found: $[\alpha]^{rt}_D$ (43 % ee) = +8.32° (c = 0.0226, CH_2Cl_2); Literature[35]: $[\alpha]^{rt}_D$ = + 14.4° (c = 1.30, CH_2Cl_2).

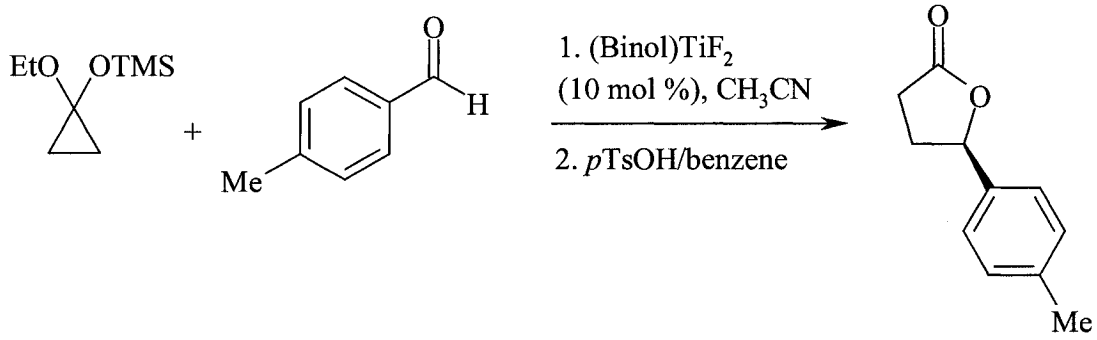
Homoaldol aldol adduct of 4-(CF_3)PhCHO (85).



The product was determined to have a 40 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C). ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 8.35 Hz, 2H), 7.42 (d, J = 8.35 Hz, 2H), 5.53 (t_{obs}, J_{obs} = 7.23 Hz, 1H), 2.62-2.75 (m, 3H), 2.08-

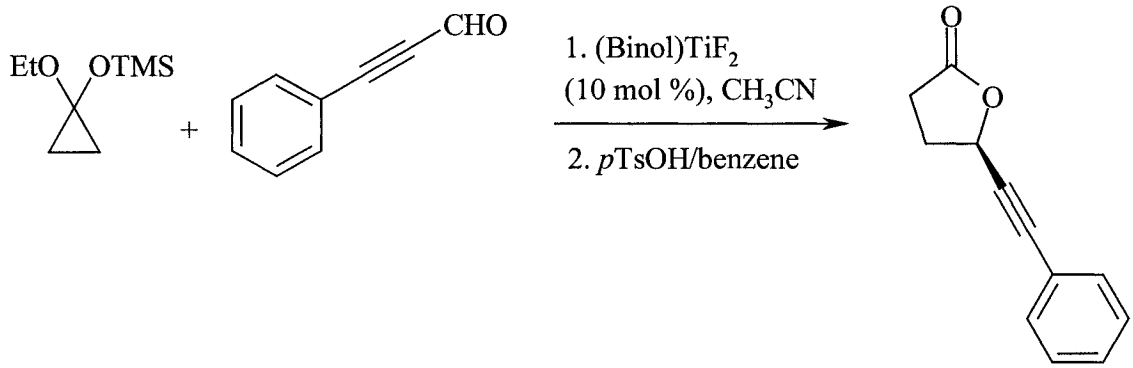
2.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.6, 143.6, 130.6 (q, J = 32.81), 128.1, 125.9 (q, J = 3.82), 125.7, 125.4, 80.5, 31.3, 29.1. Anal. Calcd for $C_{11}H_9F_3O_2$: C, 77.40; H, 5.41. Found: C, 57.50; H, 3.87.

Homoaldol aldol adduct of 4-CH_3PhCHO (86).



The product was determined to have 18 % ee by GC analysis (Chirasil-dex column, He carrier gas, 14 psi, oven temperature = 140 °C). ^{1}H NMR ($CDCl_3$) δ 7.25-7.17 (m, 4H), 5.48-5.44 (m, 1H), 2.66-2.58 (m, 3H), 2.36 (s, 3H), 2.23-2.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.6, 137.9, 136.0, 129.0, 125.1, 81.1, 30.7, 28.8, 20.9.

Homoaldol aldol adduct of PhC≡CCHO (88).



The product was determined to have a 61 % ee by HPLC analysis (chiral Pirkle covalent (S,S) Whelk-OD column, 1 % *i*PrOH/hexanes). ^{1}H NMR ($CDCl_3$) δ 7.42-7.44 (m, 2H), 7.28-7.34 (m, 3H), 5.35 (dd, J = 5.60 Hz, 1H), 2.51-2.75 (m, 1H), 2.37-3.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.2, 131.9, 129.3, 128.6, 121.7, 87.5, 85.4, 69.9, 30.2, 28.3. HRMS: calculated for $C_{12}H_{10}O_2$: 186.0681; observed: 186.0676 ± 0.0005.

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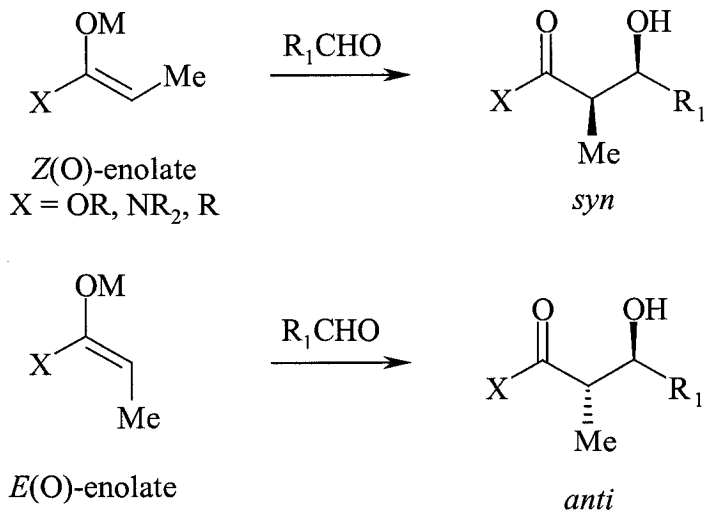
Chapter Two

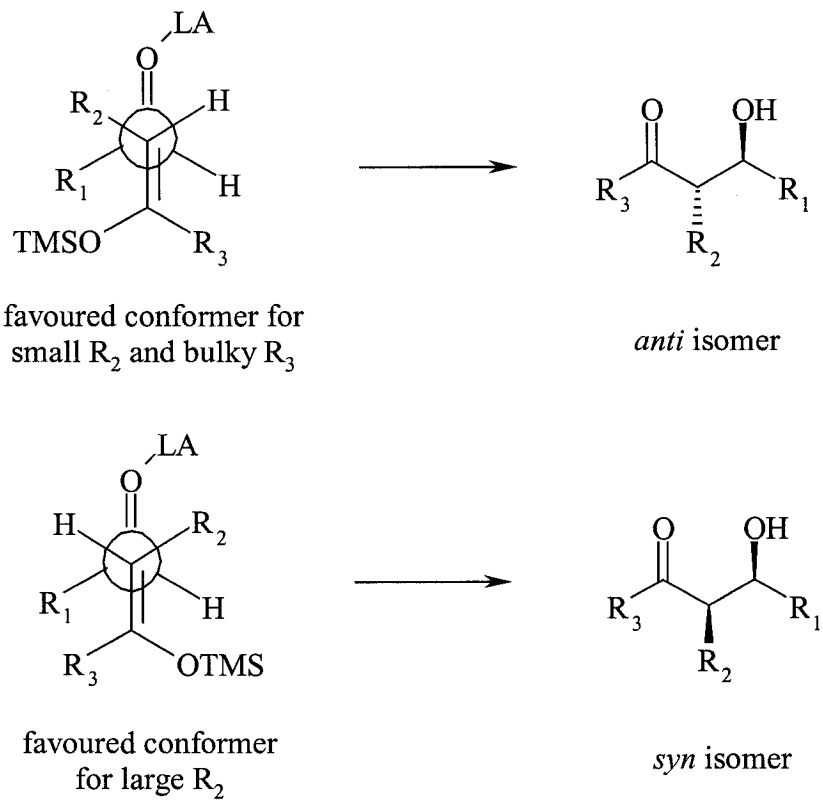
2.1 An Introduction to the Aldol Reaction

The aldol reaction is of primary importance to organic chemistry. Over the years, it has developed into a reliable method for the stereoselective construction of carbon-carbon bonds. Many asymmetric versions have been developed, including the Evans chiral oxazolidinone auxiliary-mediated aldol additions, chiral Lewis acid-mediated Mukaiyama aldol reactions, and chiral Lewis base catalyzed reactions of trichlorosilyl enolates to carbonyl compounds.[1] Most of these methods access the β-hydroxy carbonyl- or α-alkyl-β-hydroxy carbonyl motif with the *syn/anti* product stereochemistry predetermined based upon enolate geometry (*Z*-enolate→*syn*, *E*-enolate→*anti*) (**Scheme 2-1**). The high stereoselectivity arises because the reaction proceeds through the highly ordered, closed six-membered ring Zimmerman-Traxler transition state (*vide infra*).[2]



Scheme 2-1. General aldol reaction.

An alternative strategy involves the addition of an enolate (chiral or achiral) to a carbonyl compound in the presence of an external Lewis acid. The proposed mechanism for this approach is an open transition state assembly (**Scheme 2-2**).[3] The Mukaiyama aldol reaction (the addition of a silylenol ether to a carbonyl compound in the presence of a Lewis acid) proceeds *via* this mechanism.[4] The main advantage of this approach is the independence of the *syn/anti* product selectivity on the *E/Z* geometry of the reacting enolate.



Scheme 2-2. Transition state assembly for Lewis acid-mediated aldol reactions.

In contrast, the stereoselective formation of α,α-disubstituted-β-hydroxy carbonyl compounds using the aldol reaction is a relatively underdeveloped field. This is due to

the difficulty associated with the stereoselective formation of α,α-disubstituted enolates (*E vs. Z* geometry).[5] Nakamura has shown that reactions of disubstituted enolates proceed, in general, *via* the Zimmerman-Traxler six-membered ring transition state (**Section 2.1.4**).[6] Consequently, enolates of high *E*/*Z* purity are essential if high product stereocontrol is to be achieved. Other groups have contributed to this area and their results will be presented in **Sections 2.1.4-2.1.5**.

The aldol reaction has been successfully carried out with many metal countercations.[7] Magnesium, boron, lithium, titanium, zirconium, and tin are but a few examples of metals capable of mediating this reaction. The choice of metal countercation plays a crucial role in the stereochemical outcome of the aldol reaction as it influences the type of transition state interactions (open versus closed). In the case of a closed transition state, the chelation abilities of the metal determine the severity of the 1,3-diaxial interactions, which are necessary to favour one transition state over another. Boron enolates, in comparison to other metal and metaloide enolates, are at the forefront of asymmetric aldol chemistry. One of the key attributes of boron enolate chemistry is the short boron-oxygen bond (1.36-1.47 Å), which leads to a tight, six-membered cyclic transition state upon addition of an aldehyde and consequently, to high stereoselectivity. In addition, boron enolate chemistry enjoys great flexibility with regard to the type and steric demands of its ligands (alkyl and alkoxy), which permits discrimination between competing transition states.[1]

2.1.2 Controlling Reaction Selectivity with Boron Enolates

The aldol reaction results in the formation of either one or two new stereogenic centers. In order for the reaction to be synthetically useful, control over the relative and absolute product stereochemistry is essential. Relative stereochemistry, (*anti* versus *syn*) in the case of boron enolates, is usually governed by the Zimmerman-Traxler six-member ring transition state where (*Z*)-enolates provide the *syn* products and the (*E*)-enolates provide the *anti* products. The avoidance of severe 1,3-diaxial interactions in the cyclic transition states (**TS 1** *vs.* **TS 2** and **TS 3** *vs.* **TS 4**) controls the relative stereochemistry of these reactions (**Figure 2-1**).

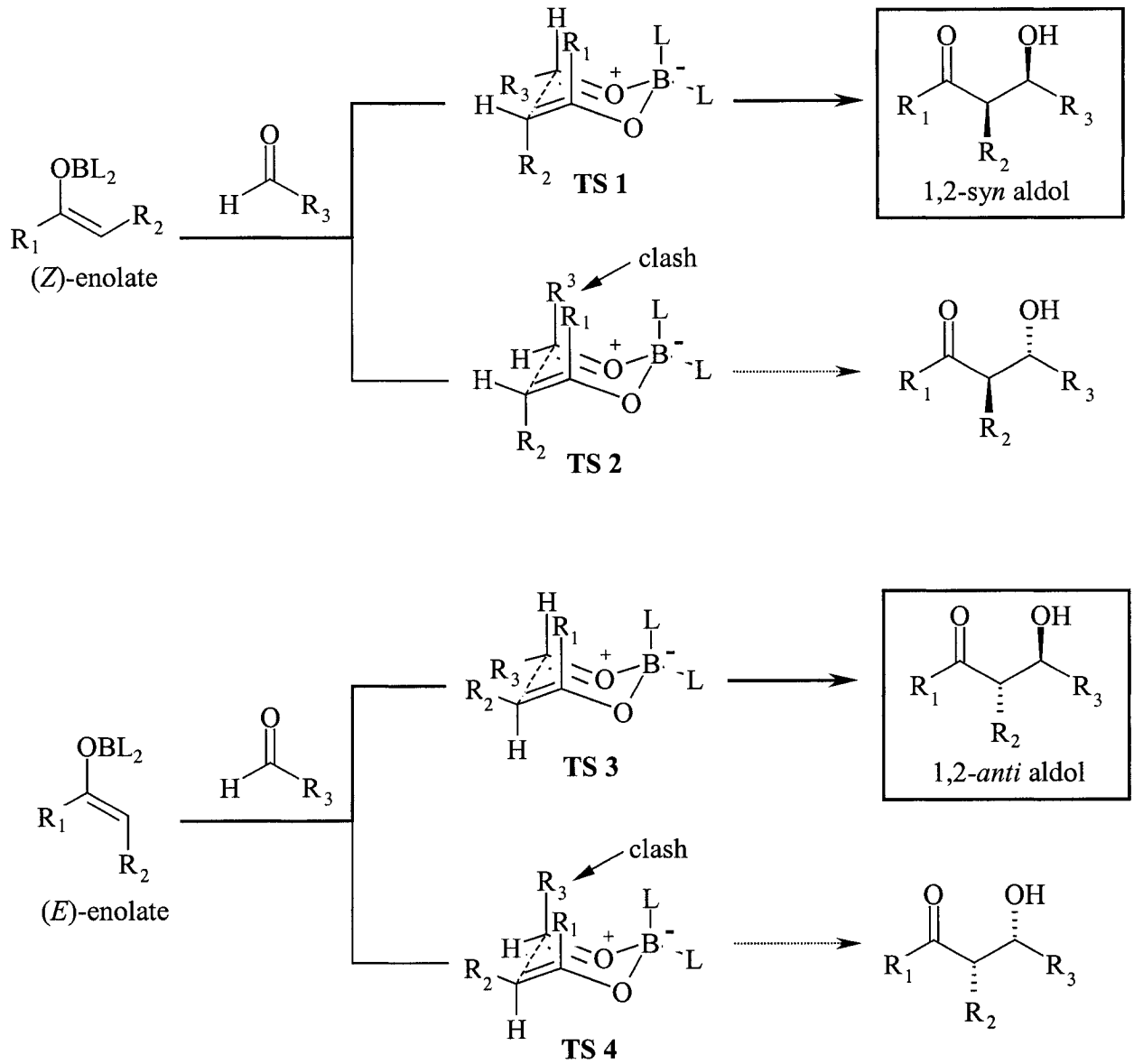


Figure 2-1. Zimmerman-Traxler transition states for boron aldols.

As illustrated in **Figure 2-1**, the favoured **TS 1** pathway provides the two enantiomeric *syn* products, while favoured **TS 3** pathway leads to two enantiomeric *anti* products. The aldol reaction proceeds with absolute stereocontrol if the enolate adds

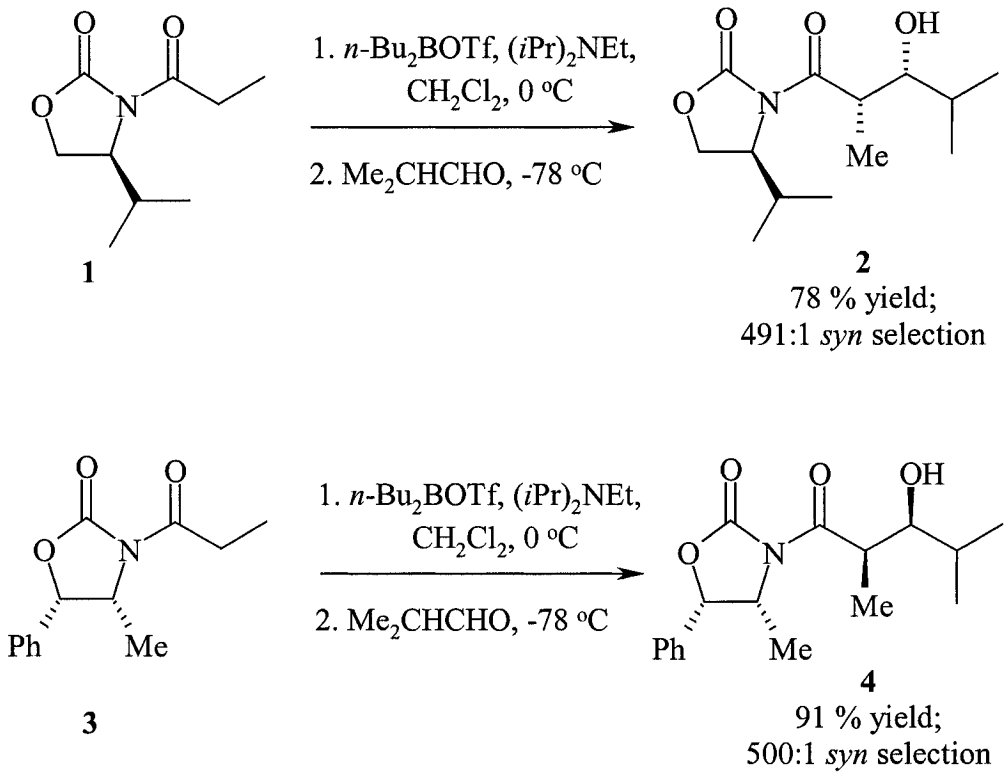
selectively to either the *re*- or *si*-carbonyl face. This would allow access to only one *syn* enantiomer (or one *anti* enantiomer). This can be achieved through one of the following strategies: reagent control with chiral ligands on boron enolates leading to enantiomerically enriched adducts; the addition of boron enolates to chiral aldehydes; substrate control from a chiral boron enolate; or auxiliary control.[1]

2.1.3 Chiral Auxiliary Methodologies to Access Monosubstituted Aldol Products

A complete literature review of all aldol reactions is beyond the scope of this thesis. As a result, this thesis focuses on chiral auxiliary based methods. Because of the breadth of even this field, only the practical and illustrative auxiliaries of Evans[8] and Masamune[9] are discussed. The auxiliaries developed by these researchers are easily and cheaply available and versatile. They provide the desired products in high yield and with excellent levels of diastereo- and enantiocontrol thereby allowing access to more than one of the four possible product diastereomers. Their strategies rely on the manipulation of the steric environment of the auxiliary or on the changing of the metal counterion. Moreover, these methodologies are amenable to large scale syntheses. All of these features make these chiral auxiliaries attractive to the synthetic chemist.

The Evans oxazolidinones have been firmly established as excellent chiral auxiliaries for the stereoselective formation of α-alkyl-β-hydroxy carbonyl compounds.[8] The oxazolidinone systems are highly selective for the formation of the (*Z*)-enolate, provide remarkable levels of *syn* diastereoface selection, allow access to both *syn* aldol isomers, and the auxiliaries are readily removed from the aldol product and recycled without racemization of the substrate. An important modification in the aldol procedure,

which provided high levels of stereocontrol, was the use of boron as the counterion instead of traditional lithium (**Scheme 2-3**). The *Z*-boron enolate of oxazolidinone **1**, derived from valinol, adds to isobutyraldehyde to provide the *syn* aldol adduct **2** with excellent selectivity. Likewise, oxazolidinone **3**, derived from norephedrine, adds selectively to isobutyraldehyde to provide the other *syn* adduct **4**. Aromatic, aliphatic and bulky aldehydes are all tolerated. Additionally, auxiliary removal is facile and can be readily achieved by hydrolysis to the corresponding carboxylic acids with lithium peroxide in methanol or esterification with sodium methoxide in anhydrous methanol.

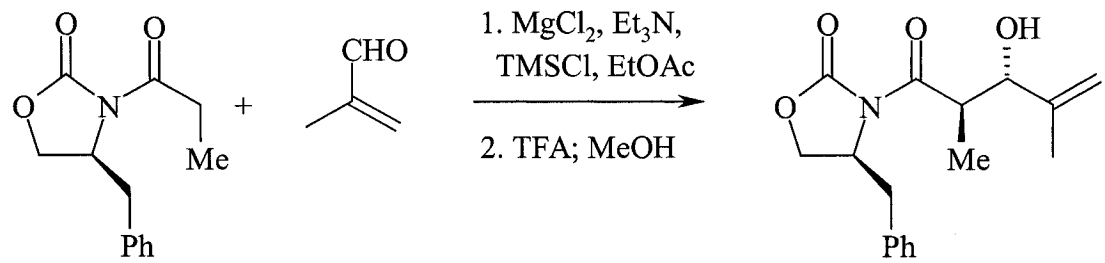


1 → **2**: 78 % yield; 491:1 *syn* selection

3 → **4**: 91 % yield; 500:1 *syn* selection

Scheme 2-3. Evans oxazolidinone auxiliaries access both *syn* aldol isomers.

Evans recently developed a magnesium halide catalyzed aldol reaction using a phenylalanine-derived oxazolidinone auxiliary **5** to access the *anti* isomer **6** (**Scheme 2-4**).[10] A boat transition state, in which the enolate, aldehyde and auxiliary carbonyl oxygens are all coordinated to the magnesium, has been proposed to account for the observed stereochemistry.[11] A variety of groups are tolerated at the α-position, including alkyl, allyl and benzyl substituents. The reaction also performs well with aromatic and unsaturated aldehydes, with selectivities for the isomer shown in **Scheme 2-4** ranging from 6:1 to 32:1.



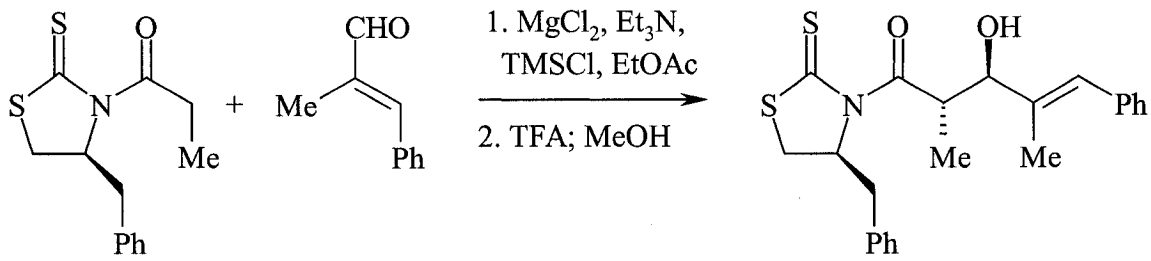
5

6
77 % yield;
16:1 (major *anti* : sum of other diastereomers)

Scheme 2-4. Magnesium chloride catalyzed *anti* aldol.

Access to the other *anti* isomer **8** is possible through the use of chiral *N*-acylthiazolidinethione **7** in the presence of magnesium bromide etherate, triethylamine and trimethylsilylchloride (**Scheme 2-5**).[11] A boat transition state is again used to account for the observed *anti* stereochemistry. The C=S moiety, however, does not coordinate to the magnesium. As a result, the observed facial selectivity reversal arises from a

minimization of the C=O and C=S dipole interactions in the transition state. A variety of α-substituents are tolerated (selectivities ranged from 8:1 to 19:1 for the *anti* isomer shown) as well as aromatic and unsaturated aldehydes (selectivities ranged from 7:1 to 19:1).



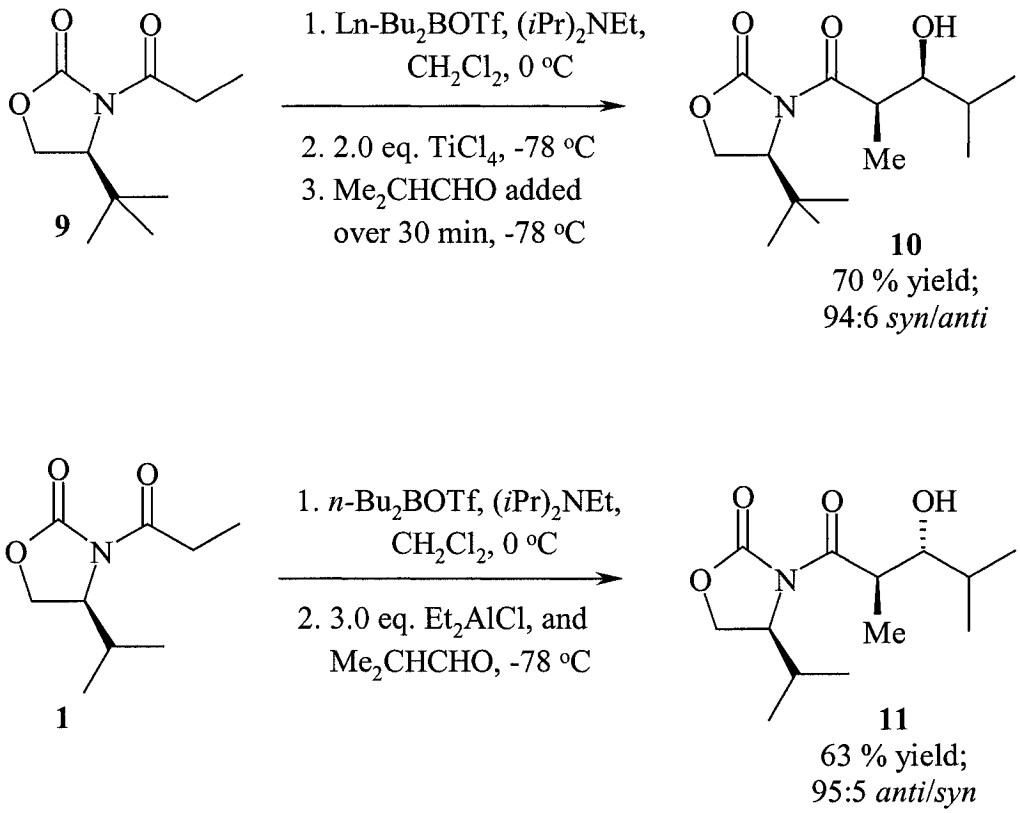
7

8
90 % yield;
19:1 (major *anti:* sum of other diastereomers)

Scheme 2-5. Magnesium halide catalyzed *anti* aldol with *N*-acylthiazolidinethiones.

Heathcock and Walker have extended the scope of the original Evans oxazolidinone auxiliaries.[12] They demonstrated that enolates derived from imides **9** react with aldehydes under Lewis acid catalysis to give *anti* and non-Evans *syn* aldols, depending on the reaction conditions (**Scheme 2-6**). The boron enolates of the Evans reagent are reacted with carbonyl compounds that are complexed to Lewis acids. Consequently, the normal Zimmerman-Traxler closed transition state is precluded and the reaction now proceeds *via* an open transition state. The π-facial approach of the aldehyde (*re vs. si*) to the enolate is determined by the relative size of the complexing Lewis acid. Heathcock showed that small Lewis acids (e.g. $TiCl_4$) provide the non-Evans *syn* aldol

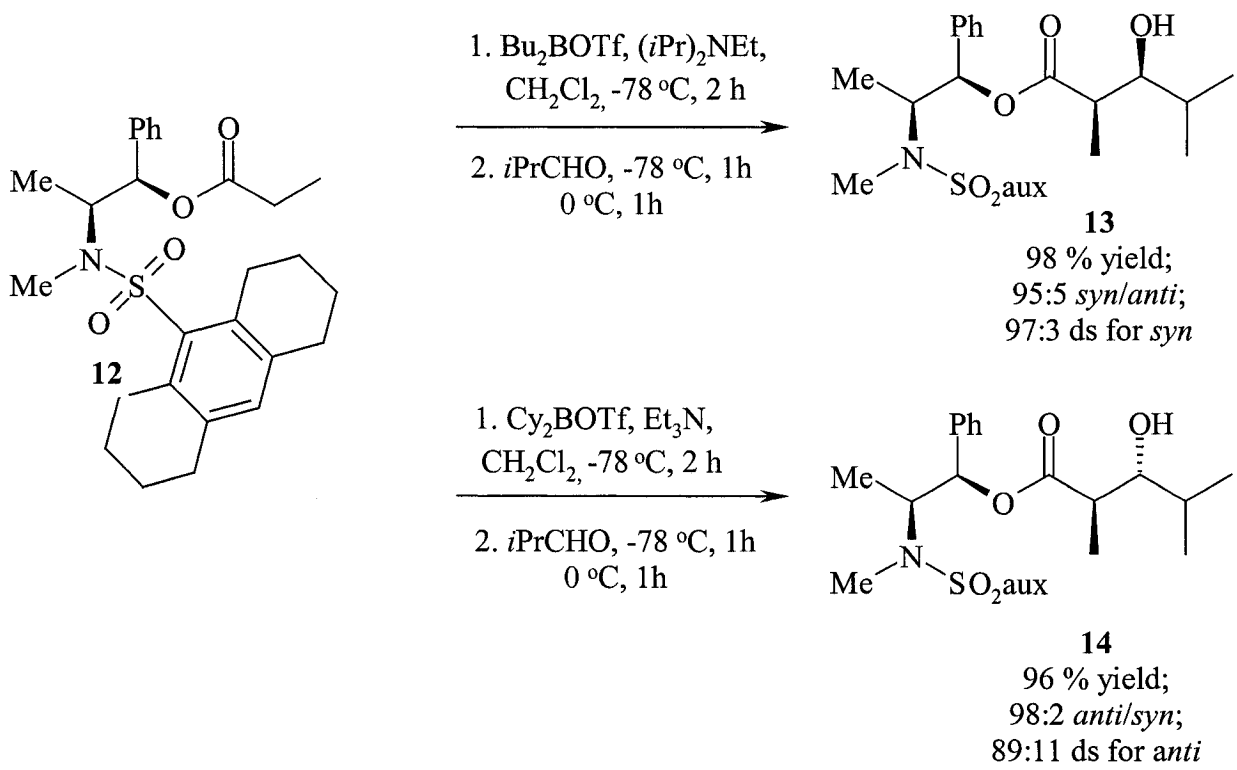
adducts **10**, while larger Lewis acids (e.g. Et_2AlCl) lead to the *anti* aldol adducts **11**. Lower selectivities are observed with this Lewis acid methodology compared to the selectivities obtained by Evans. The products, however, are usually crystalline and can be purified by chromatography.



Scheme 2-6. Lewis acid catalyzed *anti* and non-Evans *syn* aldols.

Abiko and Masamune described the development of an ephedrine derived chiral auxiliary **12** capable of producing both *syn* and *anti* aldol adducts depending on reaction conditions.[9] The auxiliary was highly *syn* selective under the enolization conditions of dibutylboron triflate/diisopropylethylamine. Addition of the boron enolate to

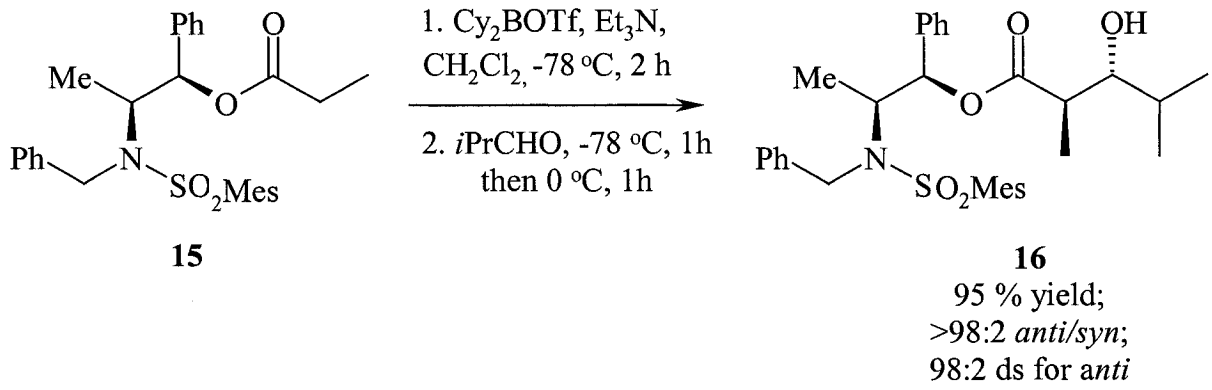
isobutyraldehyde provided the *syn* isomer **13** with excellent *syn/anti* and *syn* diasterocontrol. This auxiliary works well with aliphatic, aromatic and unsaturated aldehydes (**Scheme 2-7**). Auxiliary **12** also provides excellent *anti/syn* selectivity under the enolization conditions of dicyclohexylboron triflate/triethylamine. The *anti* adduct **14** was formed with slightly lower diastereoselectivity. The auxiliary is readily removed and recovered by mild saponification or reductive cleavage of the aldol products.



Scheme 2-7. *Syn* and *anti* aldol products using an ephedrine derived auxiliary.

Abiko was able to improve the *anti* diastereoselectivity by changing the substituents on the ephedrine nitrogen (**Scheme 2-8**).[13] The more sterically hindered auxiliary **15** was able to provide the *anti* aldol adduct **16** with an excellent *anti/syn* ratio

and *anti* diastereocontrol. Aliphatic, heteroatom-containing aliphatic, aromatic and unsaturated aldehydes are all tolerated (*anti* diastereoselectivities ranged from 95:5 to >99:1).



15

16
95 % yield;
>98:2 *anti/syn*;
98:2 ds for a*nti*

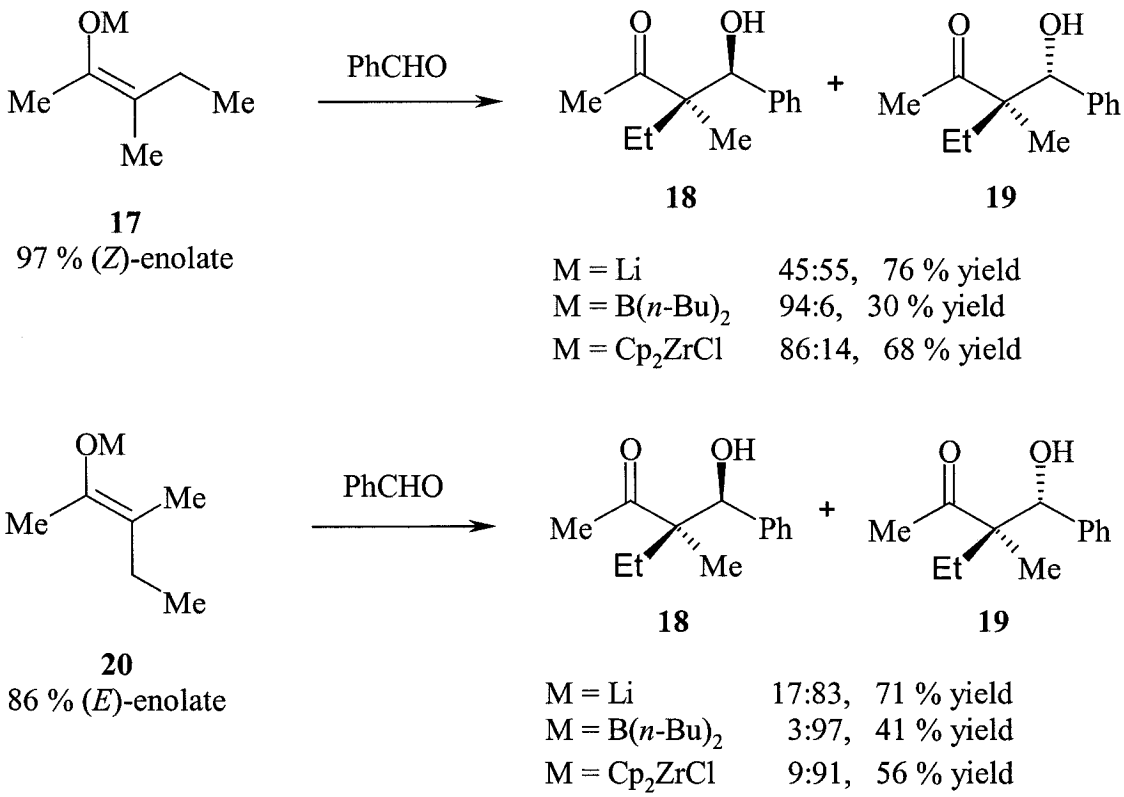
Scheme 2-8. *Anti* selective aldol reactions.

2.1.4 Aldol Reactions Which Access the α,α-Disubstituted-β-Hydroxy Carbonyl Motif

A literature review indicated that several groups have reported access to the α,α-disubstituted-β-hydroxy carbonyl motif through the aldol reaction. However, to the best of our knowledge, no general method is currently available to access these types of compounds with high levels of enantio- and diasterocontrol.

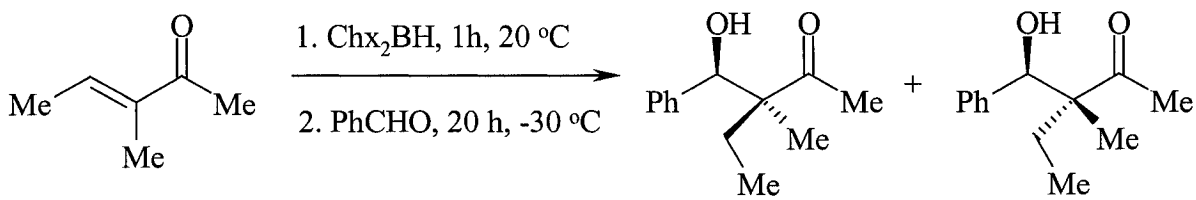
In 1991, Nakamura and coworkers reported a detailed investigation of the simple diastereoselectivity in the aldol reaction of persubstituted cyclic and acyclic enolates with a variety of metals.[6] Several types of enolate countercations were examined in the aldol reaction including lithium, borinate, borate, trialkoxytitanium, trichlorotitanium and zirconium. Additionally, silyl enol ethers under high pressure, fluoride catalysis and

Lewis acid catalysis conditions were investigated. **Scheme 2-9** illustrates that high levels of simple diastereoselectivity (*syn vs. anti*) can be achieved using the sterically unbiased tetrasubstituted enolates **17** and **20**. Nakamura concluded that all of the reactive metal tetrasubstituted enolates examined conformed to the Zimmerman-Traxler transition state model regardless of the nature of the metal. The fluoride-catalyzed and Lewis acid catalyzed reactions of the silyl enolates, however, exhibited less defined stereochemical behavior.



Scheme 2-9. Persubstituted enolates in aldol reactions with a variety of metal countercations.

Trombini and coworkers developed a novel one-pot, two-step procedure for the regio- and stereocontrolled aldol reaction through the conjugate addition of dialkylboranes to α,β-unsaturated ketones (**Scheme 2-10**).[14] The overall process is valuable because it provides aldol adducts from unsymmetrical ketones regioselectively. The initial addition proceeds with selective conjugate reduction of (*E*)-3-methyl-3-penten-2-one **21**, possibly through a pericyclic mechanism, to give a (*Z*)-(vinyloxy)borane in high stereochemical purity. Aldehyde addition yielded the *syn* aldol product **22** as the major isomer.

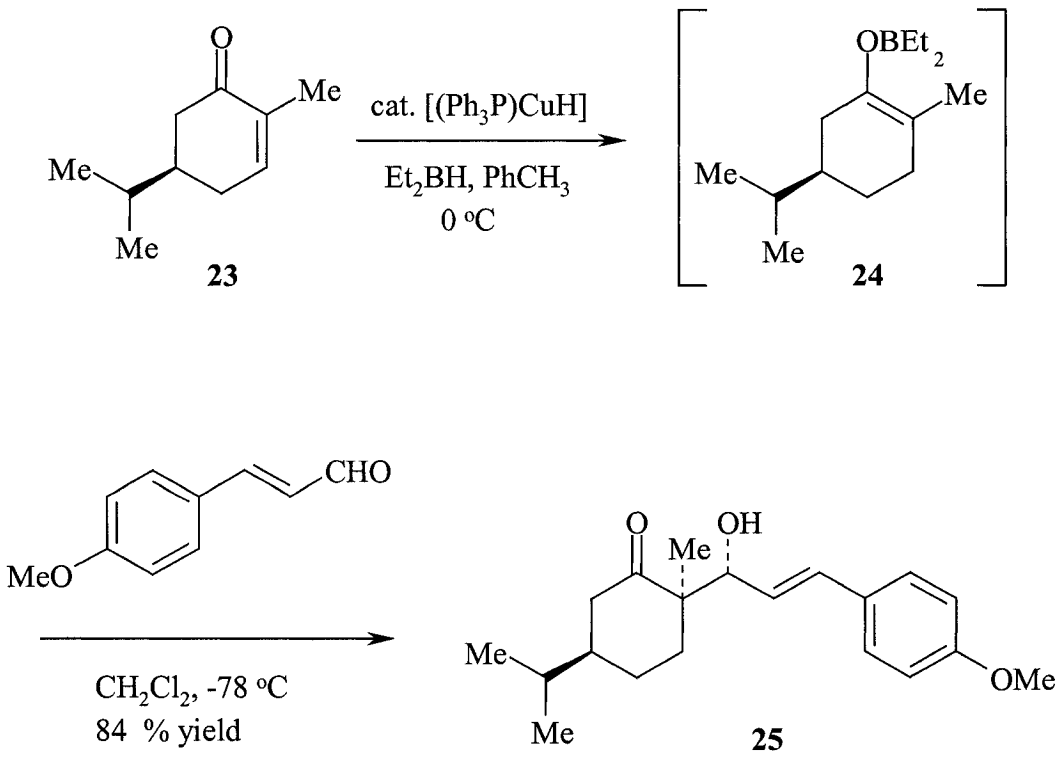


21 **22** **19**

de 2:1

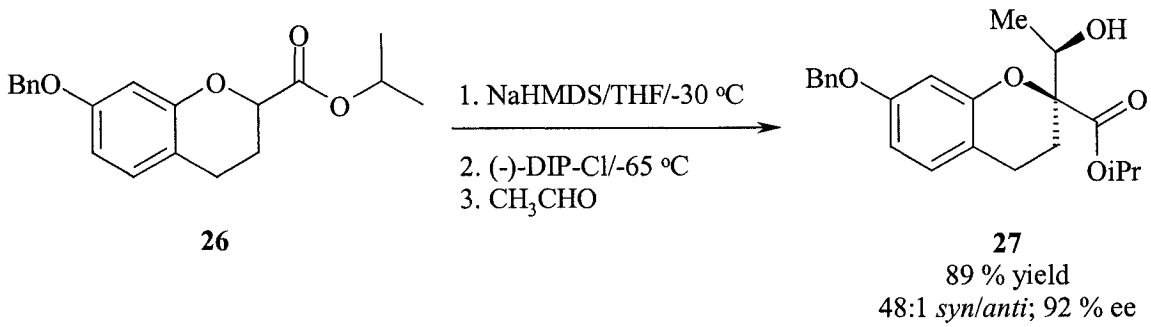
Scheme 2-10. Conjugate addition/aldol reaction to form aldol products with an α- quaternary center.

Using a similar approach, Lipshutz recently reported a 1,4-reduction of a cyclic enone dihydrocarvone **23** with Stryker's reagent, $(Ph_3P)CuH$, followed by a novel copper-boron transmetallation with Et_2BH to generate boron enolate **24**.[15] *Anti* aldol adduct **25** bearing an α-quaternary center was then obtained after aldehyde addition (**Scheme 2-11**).



Scheme 2-11. 1,4-Reduction/transmetallation/aldol reaction of dihydrocarvone.

Lang and coworkers have reported a stereoselective aldol reaction using diisopinocampheyl boron enolates derived from chromane carboxylate ester **26** to generate the aldol motif with an α,α-disubstituted center.[16] Initial investigations with the sodium enolate generated using sodium hexamethyldisilazide, resulted in a mixture of four isomers in a 1:3 *anti/syn* ratio. Trapping of the sodium enolate with triethylsilylchloride indicated only (*Z*)-enolate formation. The reaction selectivity was improved by transmetallation to boron at –65 °C. *Syn* aldol adduct **27** was subsequently obtained with high diasteroselectivity (**Scheme 2-12**).



26

27
89 % yield
48:1 *syn/anti*; 92 % ee

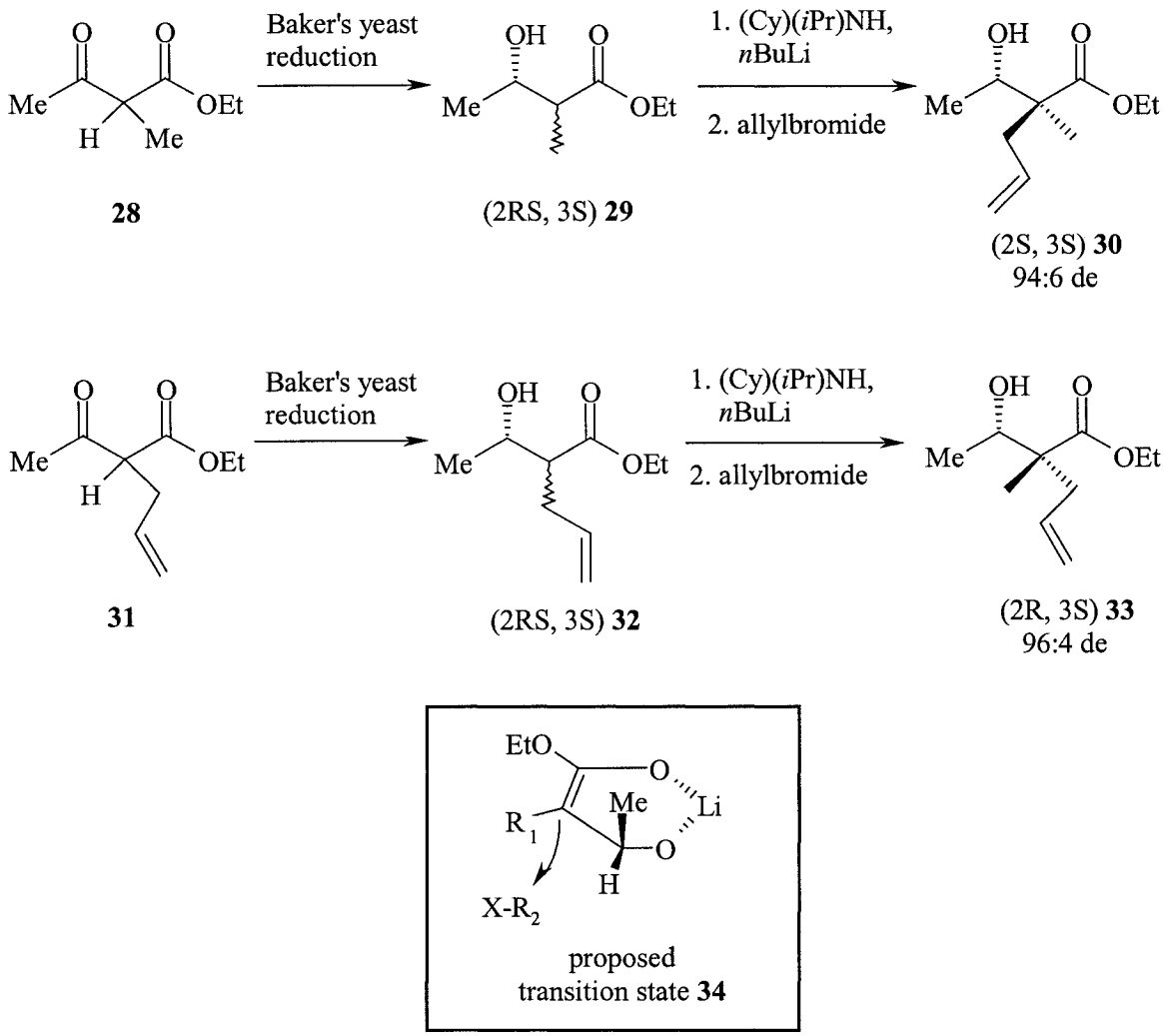
Scheme 2-12. Generation of a quaternary carbon center using boron chromane enolates.

2.1.5 Alternative Approaches to α,α-Disubstituted-β-Hydroxy Carbonyl Compounds

2.1.5.1 Alkylation of α-Monoalkylated-β-Hydroxy Carbonyl Compounds

Frater and coworkers had initially reported the α-alkylation of dianions derived from chiral β-hydroxy esters with high stereoselectivity.[17] The *anti* products are formed with high selectivity as a result of lithium cation chelation through the two O-anions, which allows formation of a rigid cyclic structure (**Structure 34, Scheme 2-13**). As an extension of this methodology, the group investigated the utility of applying the dianion strategy to produce α,α-disubstituted aldol products stereoselectively. The feasibility of the reaction was determined by reacting ethyl propionate with acetaldehyde to form the aldol adduct (mixture of four isomers). Dianion alkylation of the isomer mixture with allylbromide provided the racemic *anti* material in 96:4 ratio. Based on these results, stereoselective α-substituted aldol adducts **29** and **32** were prepared using β-keto ester enzyme reduction methodology. α-Deprotonation of the epimeric C2 center in **29** and **32**

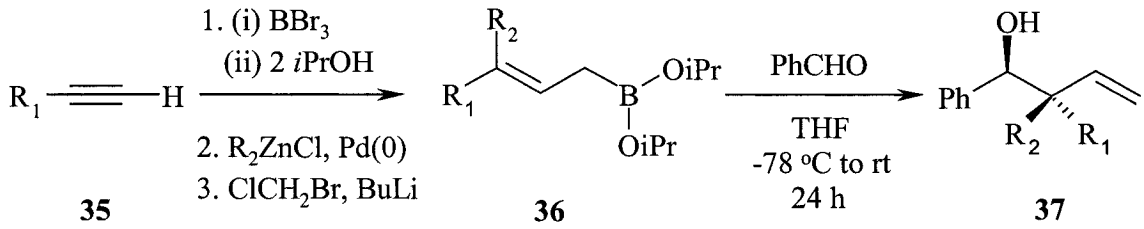
and alkylation with allyl bromide and methyl iodide respectively, provided the diastereomeric aldol adducts **30** and **33**.



Scheme 2-13. Frater's dianion approach to α,α-disubstituted-β-hydroxy carbonyl compounds.

2.1.5.2 Allyl Metal Reagents

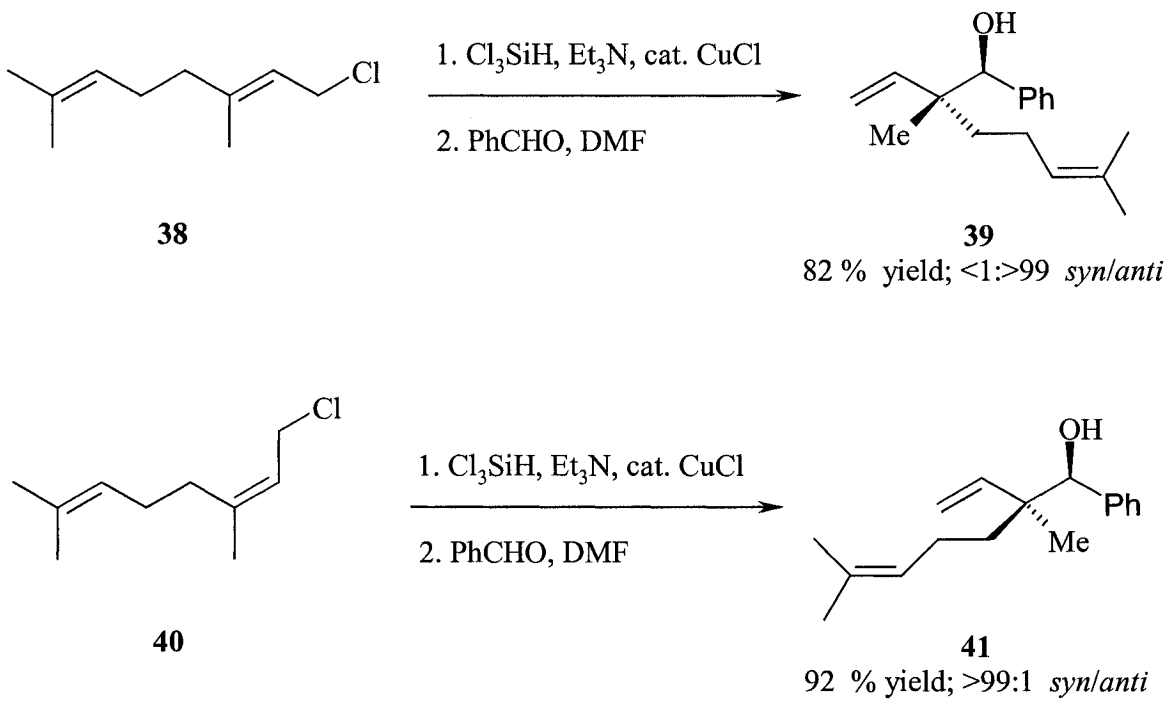
The addition of 3,3-disubstituted allylmetal reagents to aldehydes is an efficient method of synthesizing homoallylic alcohols possessing an α-quaternary carbon center. Formation of geometrically pure (*E*)- and (*Z*)- 3,3-disubstituted allylmetal reagents has been the limiting factor in this methodology. Several groups, however, have developed excellent strategies for accessing these reagents. Suzuki has reported the stereoselective synthesis of 3,3-disubstituted allylboranes **36** through the haloboration/coupling/homologation of alkynes (**Scheme 2-14**).[18] Subsequent addition of these borane reagents to aldehydes yields the α,α-disubstituted homoallylic alcohols **37** diastereospecifically (*Z*→*syn* and *E*→*anti* homoallylic isomers). This methodology is versatile as aromatic, α,β-unsaturated and saturated aldehydes are amenable to the reaction conditions; the 3,3-substituents can also be varied without affecting the reaction diastereoselectivity.



R_1 = Me, R_2 = *n*Bu 97:3 ratio at C2; 95 % yield
R_1 = *n*Bu, R_2 = Me 12:88 ratio at C2; 96 % yield

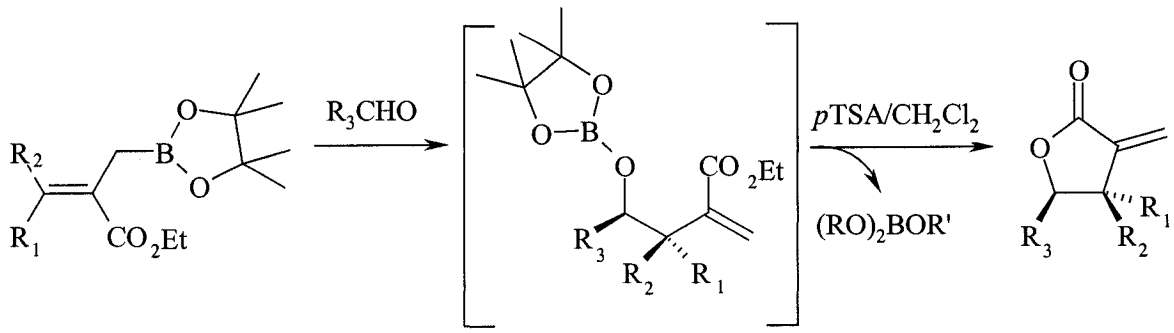
Scheme 2-14. Diastereoselective addition of 3,3-disubstituted allylboranes.

Kobayashi and Nishio reported the regio- and stereospecific addition of 3,3-disubstituted allyltrichlorosilanes to aldehydes, in the presence of DMF and without the aid of a catalyst, to afford the corresponding diastereomeric homoallylic alcohols **39** and **41** in high yield (**Scheme 2-15**).[19] The *E*- and *Z*-allylsilanes are generated *in situ* from the corresponding allylchlorides **38** and **40**. A hypervalent silicate species, formed by DMF coordination, is believed to promote the reaction. Demark and Fu extended this methodology by developing a catalytic and stereoselective variant of this reaction using a tethered chiral 2,2'-bispyrrolidine-based phosphoramide.[20]



Scheme 2-15. Allylsilane additions to aldehydes in the presence of DMF.

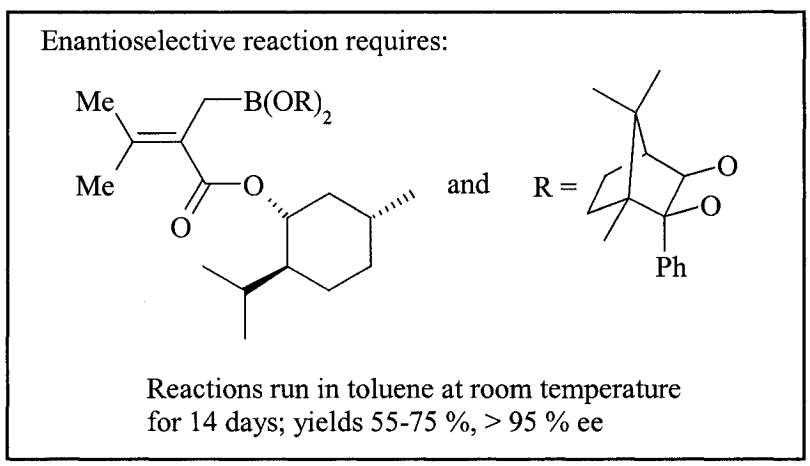
Hall and Kennedy have recently shown that isomerically pure tetrasubstituted allylboronates **42** can be prepared and reacted with aldehydes to form aldol-like adducts with high levels of diastereocontrol.[21] Their novel method of preparing the tetrasubstituted allylboronates involved trapping a 1-alkoxycarbonyl vinylcopper (I) intermediate with iodomethylboronate. Additionally, both *cis* and *trans* isomers are available through temperature control. These allylboronates added in a highly diastereoselective manner to afford α-exomethylene γ-lactones **43** with a stereogenic quaternary β-carbon center (**Scheme 2-16**). Preliminary results with chiral 3,3-dimethyl allylboronates have indicated that the lactones could be obtained selectively if a dual auxiliary approach is used (i.e. chiral boron alkoxy ligands and chiral ester unit).



42
> 95 % yield
>20:1 cis:trans addition

43

	% yield	dr
R_1 = Bu, R_2 = Me, R_3 = 4-$NO_2C_6H_4$	76	> 20:1
R_1 = Me, R_2 = Bu, R_3 = 4-$NO_2C_6H_4$	67	> 20:1

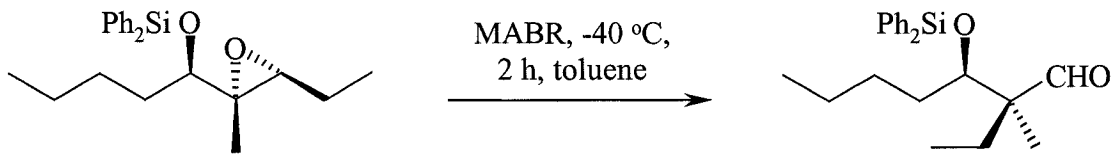


Scheme 2-16. The synthesis of quaternary carbon containing γ-lactones using allylboronate methodology.

2.1.5.3 Epoxy Rearrangements

The rearrangement of epoxy silyl ethers or 2,3-epoxy alcohols has developed into an efficient method for the direct formation of aldol adducts. Several groups have investigated the stereoselective generation of quaternary carbon centers using this methodology.[22] In 1991, Yamamoto and coworkers investigated the asymmetric synthesis of *erythro* and *threo* aldols based on the Lewis acid promoted rearrangement of

optically active epoxy silyl ethers, which were easily obtained by Sharpless asymmetric epoxidation of allylic alcohols followed by silylation.[23] The rearrangement of epoxy silyl ether **44** proceeded with *anti* migration of the ethyl group to form the protected aldol adduct **45** stereoselectively (**Scheme 2-17**).



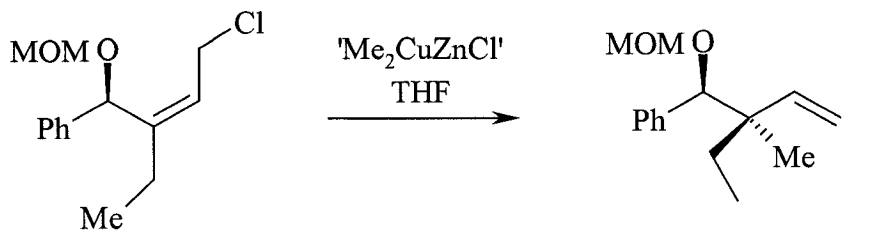
44
MABR = methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide)

45
64 % yield;
200:1 *syn/anti*

Scheme 2-17. Epoxy silyl ether rearrangement.

2.1.5.4 S_N2' allylations

Nakamura reported in 1989 the S_N2' allylation of organocopper reagents to form protected homoallylic alcohols possessing a quaternary carbon center.[24] The reaction proceeds with virtually complete diastereofacial selectivity (**Scheme 2-18**). Dimethyl zinc cuprate adds to the *Z*-allylic chloride **46** with good S_N2' selectivity, despite the steric congestion at the alkylated center, to form protected homoallylic alcohol **47** diastereoselectively. The selectivity was proposed to arise from a combination of Felkin-Ahn considerations plus d-π^* complexation of the copper reagent and the allyl system.



46 **47**

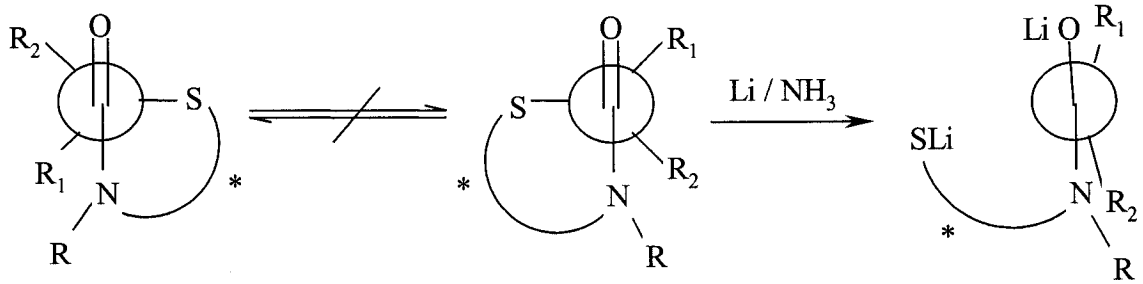
89 % yield;
70 % S_N2', 100 % de

Scheme 2-18. S_N2' allylation of organocopper reagents.

2.1.6 A General Method for the Stereospecific Synthesis of α,α-Disubstituted Enolates

The development of a general and stereospecific method to access α,α-disubstituted-β-hydroxy carbonyl compounds requires the generation of geometrically pure disubstituted *E*- and *Z*-enolates. This criterion arises because, in general, the purity of the enolate geometry is reflected in the product stereochemistry.

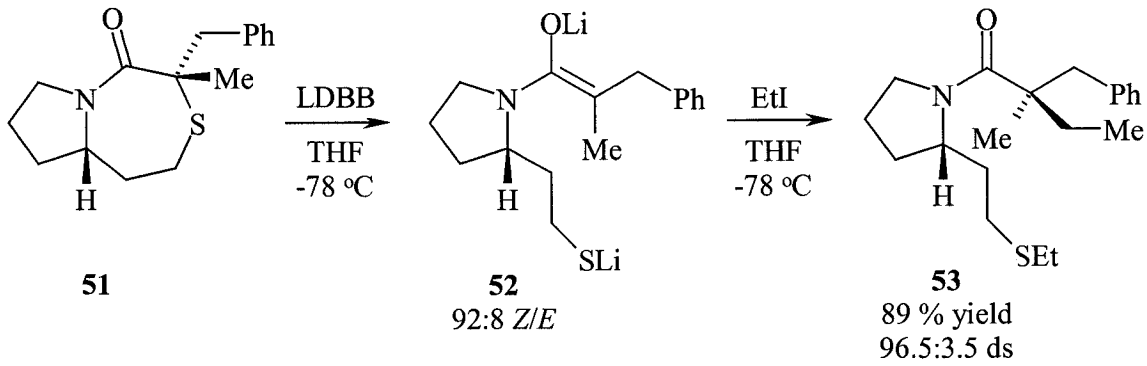
The Gleason research group has had a longstanding interest in the stereospecific generation of α,α-disubstituted enolates. Jeffery Manthorpe from the Gleason group recently developed a chiral 5,7-bicyclic thioglycolate lactam auxiliary that provided stereoselective access to *E*- and *Z*- α,α-disubstituted enolates.[25] The chiral auxiliary was designed to meet the following criteria (**Figure 2-2**): (i) stereoselective installation of the alkyl groups R_1 and R_2 at the α-position; (ii) an O-C-C-S dihedral angle approximating 90°; (iii) prevention of significant bond rotation about the carbonyl-carbon/α-carbon bond during the two-electron reduction process and (iv) utilization of the bicyclic residue to introduce chirality in subsequent addition reactions to the α,α-disubstituted enolate.



Ideal conformation
for reduction: S-C-C-O dihedral = 90°

Figure 2-2. Model for reductive enolization of thioglycolate lactams.

A 5,7-bicyclic framework proved to be successful for the stereospecific generation of α,α-disubstituted amide enolates. It provided sufficient rigidity to the system so that equilibration between conformer **48** and **49** was not possible. This prevented an inversion of the stereochemical information introduced during the initial alkylation. Upon reductive enolization, the R_1 and R_2 alkyl groups maintain their relative proximities to the amide oxygen and nitrogen respectively. As a result, the stereochemical information at the α-carbon of the starting lactam was effectively transferred to the enolate **50**. Access to the other enolate geometrical isomer was possible by inverting the positions of R_1 and R_2 during the initial alkylation. The usefulness of this auxiliary was successfully demonstrated by the stereoselective formation of quaternary carbon centers *via* enolate alkylation (**Scheme 2-19**).[26] Reductive enolization of bicyclic thioglycolate lactam **51** provided the *Z*(O) amide enolate **52** with 92:8 *Z*/*E* stereocontrol. Alkylation of **52** with ethyl iodide formed quaternary carbon product **53** with excellent stereoselectivity.

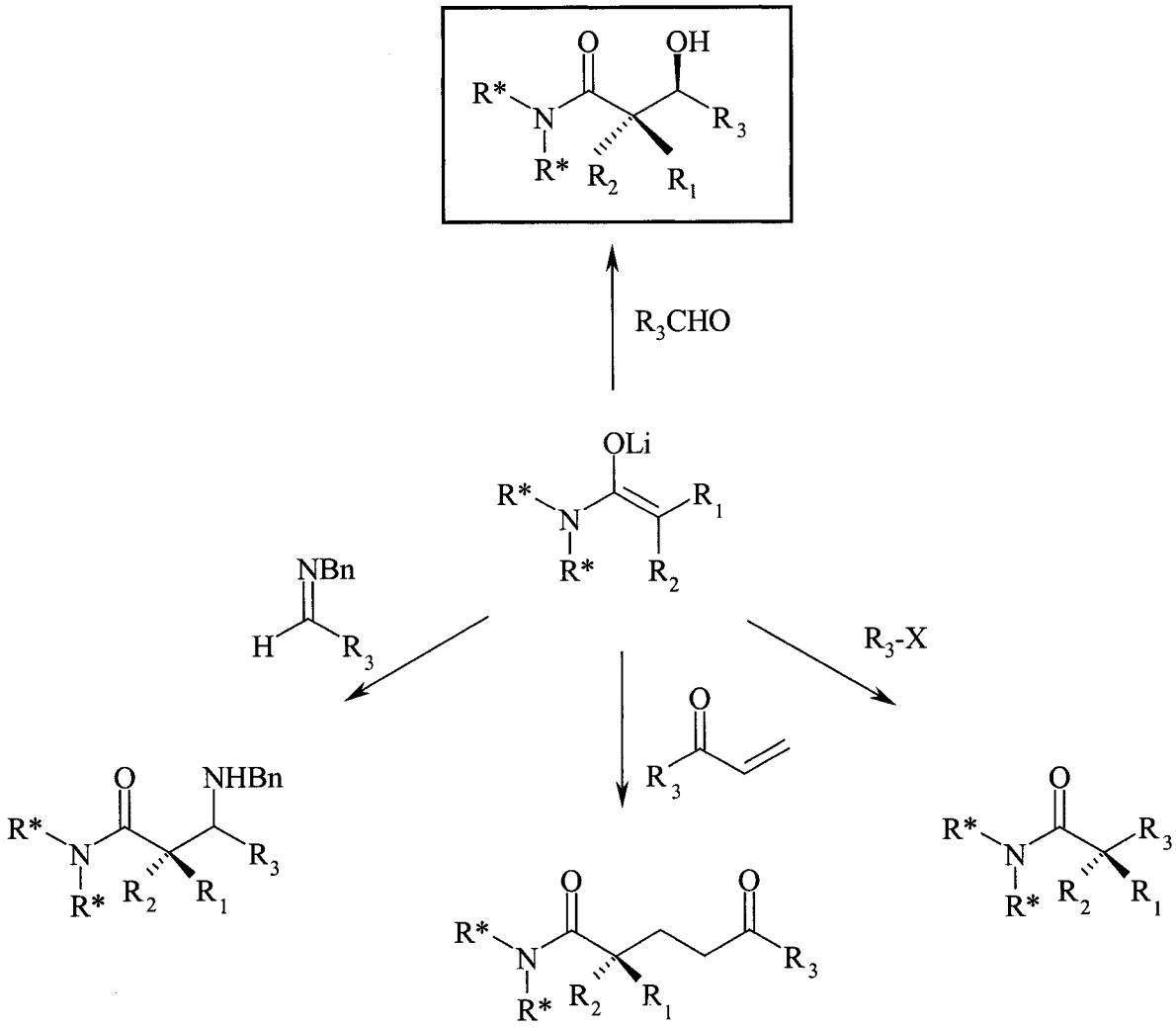


51 **52** 92:8 *Z/E* **53** 89 % yield 96.5:3.5 ds

Scheme 2-19. 5,7-Bicylic lactam for the stereoselective formation of *Z*(O)-amide enolates.

2.1.7 Potential Synthetic Applications

This methodology could potentially be extended to a variety of other carbon-carbon bond forming reactions (**Scheme 2-20**). The aldol reaction features prominently in many organic syntheses and as no general method is currently available for the synthesis of α,α-disubstituted-β-hydroxy carbonyl compounds, it was decided to apply this methodology to this particular problem. The results will be discussed in the following sections.



Scheme 2-20. Potential synthetic applications of α,α-disubstituted amide enolates.

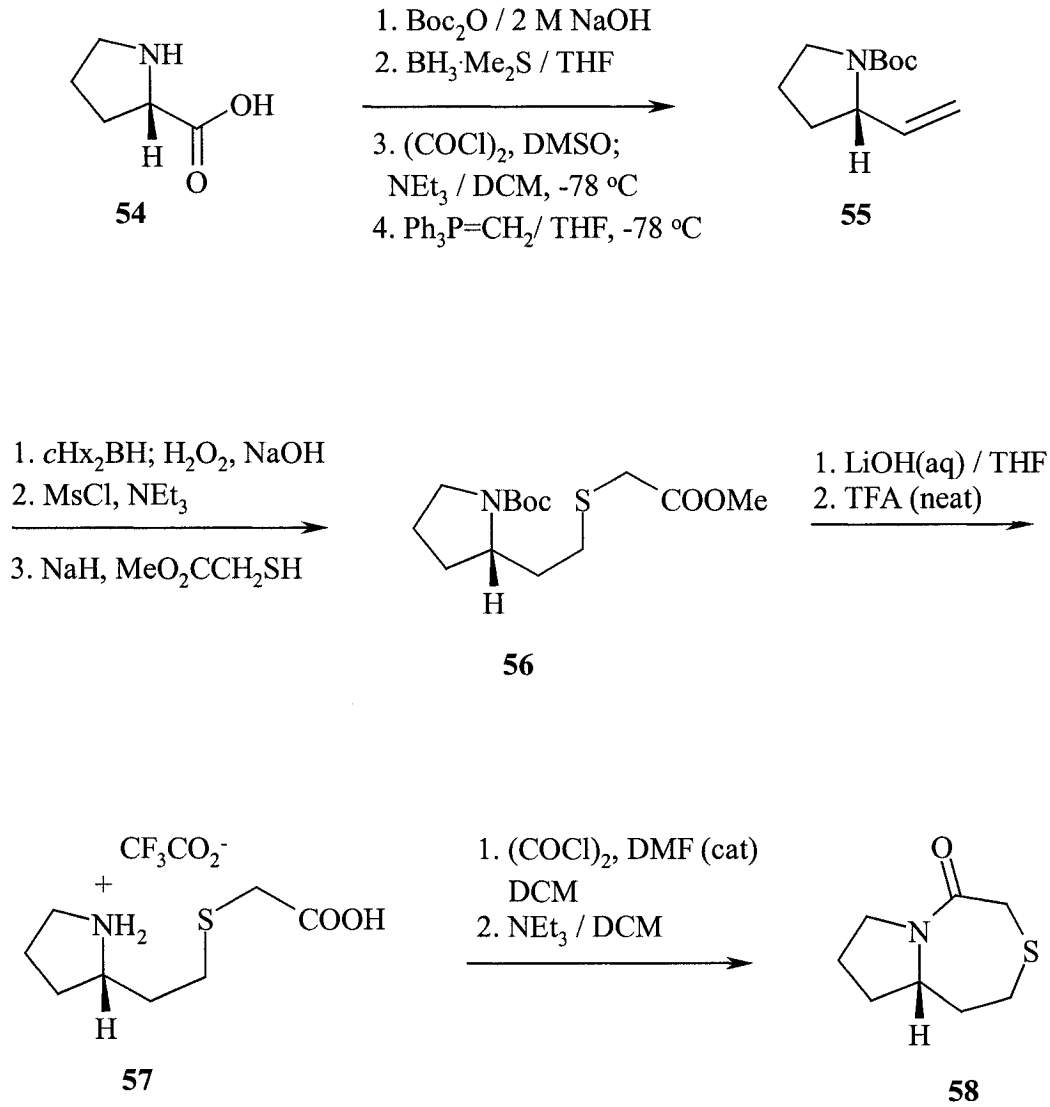
2.1.8 Project Overview

A general approach to the stereoselective synthesis of α,α-disubstituted-β-hydroxy carbonyl compounds is not yet available to the organic chemist. Most of the methodologies previously described have limited versatility, are substrate specific or require additional transformations to form the aldol adduct.

As previously described, the Gleason research group had reported an efficient and stereoselective method of accessing α,α-disubstituted amide enolates through the reductive enolization of a 5,7-thioglycolate lactam.[25] We now propose to develop a versatile and efficient method for generating these α-quaternary carbon aldol products by extending the utility of these disubstituted amide enolates. We began this study by investigating the effect of the metal counterion on product stereoselectivity.

2.2 A General Method for the Synthesis of α,α-Disubstituted-β-Hydroxy Carbonyl Compounds

The 5,7-thioglycolate lactam auxiliary required for our investigations was synthesized from (S)-proline according to a procedure developed by Jeff Manthorpe (**Scheme 2-21**).[25] The N-terminus of proline was Boc-protected and the carboxylic acid was reduced with borane. Subsequent Swern oxidation of the primary alcohol to the aldehyde and Wittig methylenation resulted in alkene **55**. Hydroboration/oxidation with dicyclohexylborane furnished the homologated alcohol, *N*-Boc-2-(2-pyrrolidine)ethanol. Mesylation followed by displacement with the thiolate ion derived from methylthioglycolate provided the sulfide **56**. Ester saponification was followed by Boc group cleavage with TFA. The amino acid trifluoroacetate salt **57** was converted to an acid chloride with oxalyl chloride and catalytic DMF in dichloromethane at room temperature without affecting the protonated amine moiety. Slow addition of triethylamine to a solution of the acid chloride provided the desired lactam **58**.

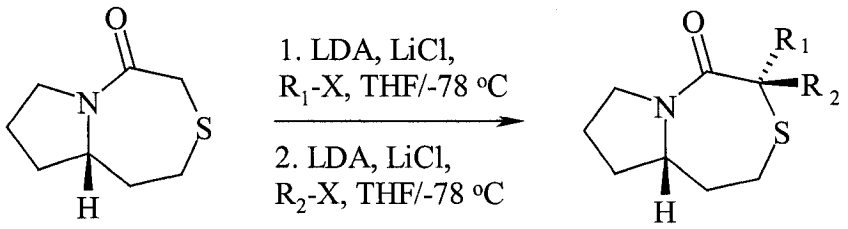


54 **55** **56** **57** **58**

Scheme 2-21. The synthesis of bicyclic thioglycolate lactam **58**.

The α-substituents were then installed *via* alkylation chemistry. The results are provided in **Table 2-1**.[25] The lactam was alkylated to access both the *E*- and *Z*-enolate isomer precursors **59-62**.

Table 2-1. Alkylation of bicyclic lactam.



58

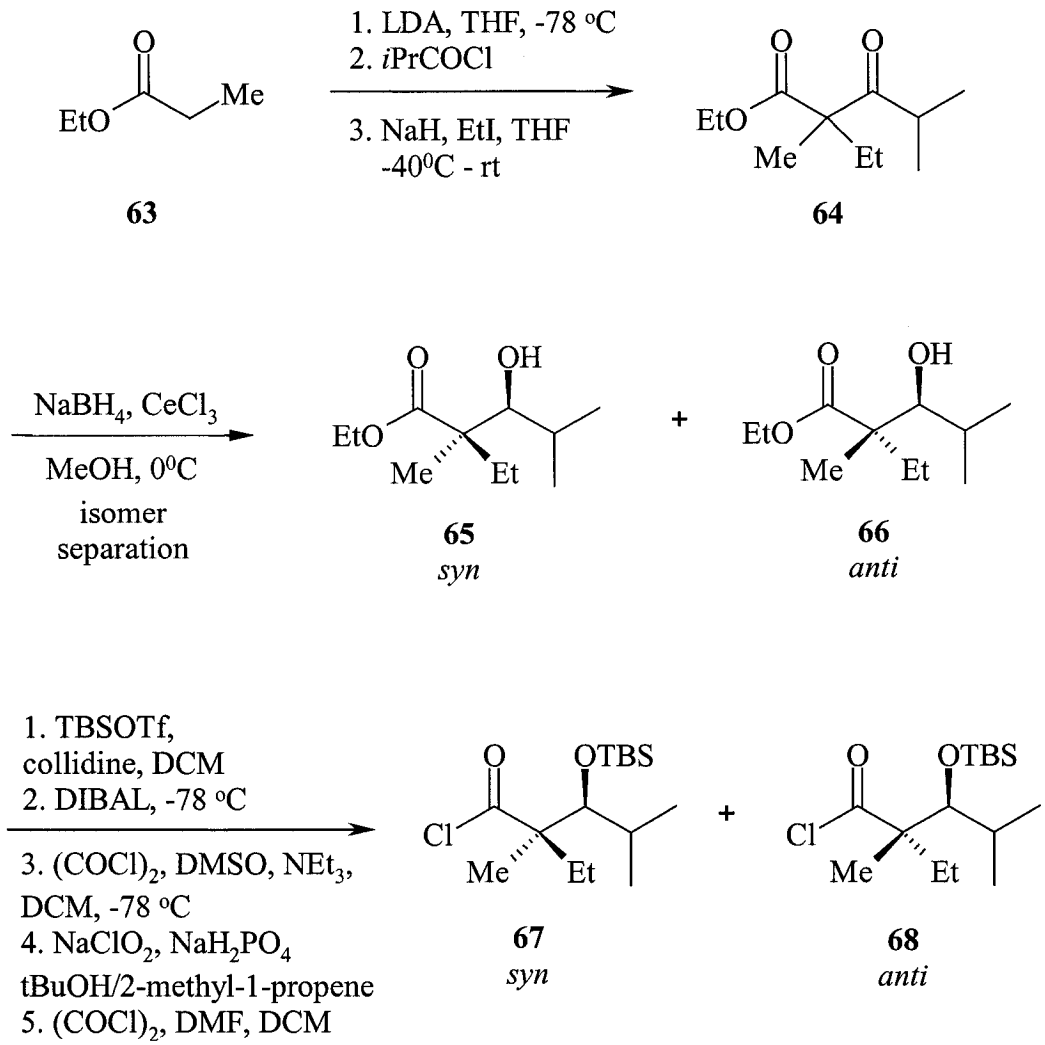
Entry	Compound	R_1-X	yield (%)	R_2-X	yield (%)	de [a] (%)
1.	**59**	MeI	86	EtI	72	>99 [b]
2.	**60**	EtI	88	MeI	85	>99 [b]
3.	**61**	allylBr	85	MeI	80	95
4.	**51**	BnBr	96	MeI	88	>99
5.	**62**	MeI	86	BnBr	91	>99

[a] Determined by capillary gas chromatography on a Chiralsil Dex of 5 % cross-linked phenyl, methyl siloxane column. [b] Separated out minor diastereomer *via* column chromatography.

2.2.2 Transmetallation Experiments with (*Z*)- and (*E*)-α,α-Disubstituted Enolates

Initial experiments with the Me/Et alkylated auxiliary **60** (*Z*-enolate precursor) were performed with isobutyraldehyde as the electrophile. Product standards had been independently prepared and analyzed by ^{1}H NMR and HLPC to provide authentic spectra for comparison purposes (**Scheme 2-22**). Ethyl propionate **63** was acylated with isopropanoyl chloride at –78 °C. The resulting β-keto ester was then deprotonated with sodium hydride and alkylated with ethyl iodide to introduce the α-quaternary carbon center (**64**).[27] Reduction of the keto functionality with sodium borohydride in the presence of cerium trichloride provided a racemic α,α-disubstituted-β-hydroxy carbonyl compound. Separation of the racemic *syn* and *anti* isomers **65** and **66** respectively, was

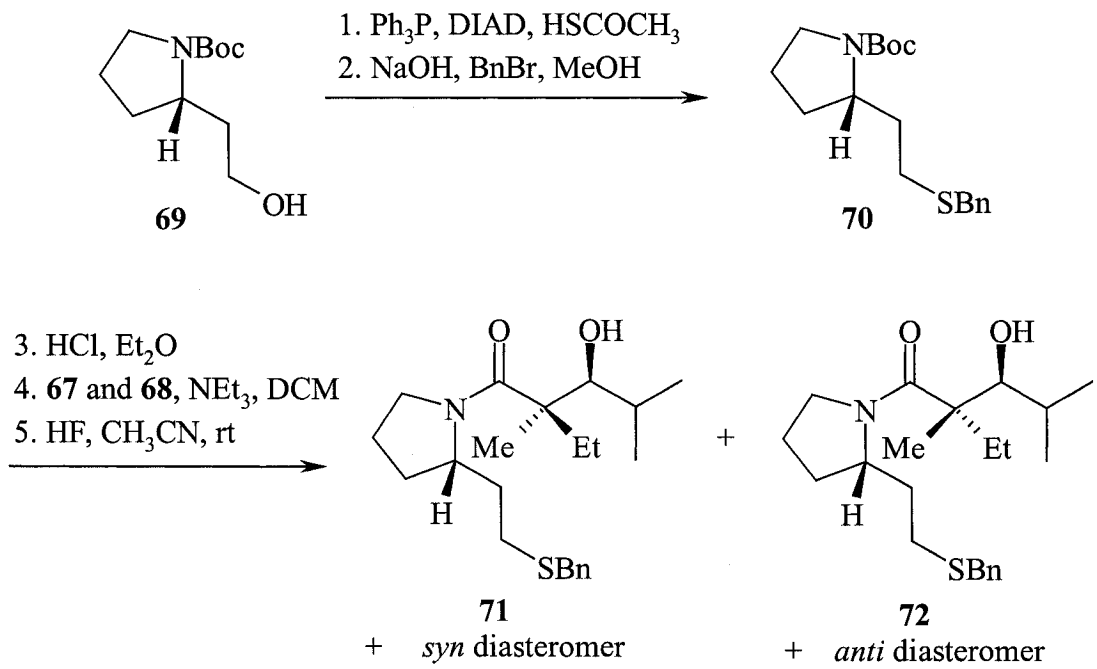
possible *via* careful column chromatography. The *syn/anti* stereochemistry was assigned by reduction of the ester functionality followed by protection of the resulting 1,3-diols as acetonides. NOE studies were then used to make the assignment (*vide infra*). The hydroxyl functionality of isomers **65** and **66** was then protected with TBSOTf, followed by reduction at –78 °C with DIBAL in toluene. Protection of the hydroxyl functionality was necessary as any attempt to form the desired carboxylic acid directly by ethyl ester saponification caused the molecule to undergo an undesired retroaldol reaction. The primary alcohols were then oxidized to aldehydes with oxalyl chloride and dimethyl sulfoxide. Further oxidation to the carboxylic acids was accomplished with sodium chlorite and sodium dihydrogen phosphate. The acid chloride coupling partners **67** and **68** were obtained by reacting the carboxylic acids with oxalyl chloride and catalytic *N,N*-dimethylformamide in dichloromethane.



Scheme 2-22. Preparation of coupling partners **67** and **68**.

The pyrrolidine-based amino acid component **70** was derived from the homologated primary alcohol **69** used in the auxiliary synthesis (**Scheme 2-23**). Displacement of the hydroxyl functionality was accomplished with Ph_3P, DIAD and thioacetic acid. *In situ* thioester saponification and benzylation proceeded easily with NaOH and benzyl bromide in methanol. Removal of the *tert*-butyloxycarbonyl nitrogen protecting group was accomplished with HCl (g) in dry diethyl ether. The intermediate

protonated amino acid was then coupled with acid chlorides **67** and **68** in the presence of triethylamine to furnish the protected aldol adducts. The TBS protecting group was removed with HF in acetonitrile at room temperature to furnish compounds **71** and **72**. The ^{1}H NMR and MS confirmed the formation of the desired aldol standards. These compounds were then used to identify the products obtained from the aldol reaction of the enolate of the α,α-methyl/ethyl 5,7-thioglycolate lactam **60** with isobutyraldehyde.



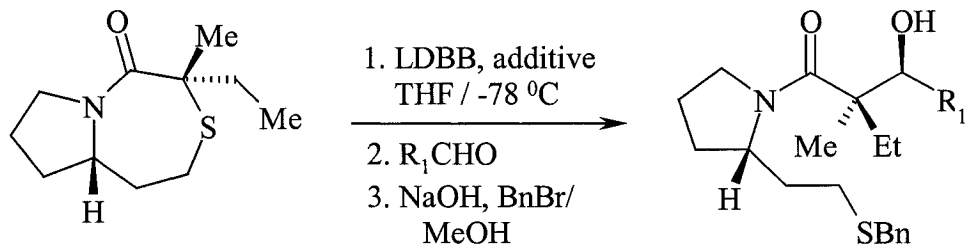
Scheme 2-23. Preparation of aldol standards.

A general experimental procedure was followed for the formation of the aldol adducts. The thioglycolate lactam **60** was reduced at -78°C with LDBB. The metal additive was immediately added dropwise *via* syringe (*via* cannula in the case of $ZnCl_2$ and Cp_2ZrCl_2, 0.5 M THF solution). The solution was allowed to stir for 30 minutes at

–78 °C before dropwise addition of the aldehyde (neat). The reaction was stirred for 2 hours at –78 °C before quenching with a saturated solution of aqueous ammonium chloride. The organic material was extracted with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated. When dialkylboron triflate and halide sources were employed, dechelation was accomplished with 4.0 equivalents of diethanolamine in dry diethyl ether at room temperature for 2 hours. The crude material was analyzed by HPLC using a chiral column. This analysis was aided by benzylation of the thiol group with benzyl bromide and sodium hydroxide in methanol at room temperature for 1 hour.

It was expected that the lithium enolates generated by the reductive enolization of the α,α-disubstituted thioglycolate amide auxiliary with LDBB would not provide high stereocontrol in the aldol reaction as compared to the alkylation chemistry.[1,8] This was indeed observed (**Table 2-2, entry 1**). In an effort to improve the reaction selectivity, transmetallation of the lithium enolate became necessary.[28] A variety of metals (Ti, Zr, Zn) were surveyed for an aliphatic and an aromatic aldehyde, isobutyraldehyde and benzaldehyde respectively. The results are provided in **Table 2-2**.

Table 2-2. Transmetallation effects on aldol stereoselectivity with the (*Z*)-enolate.



60

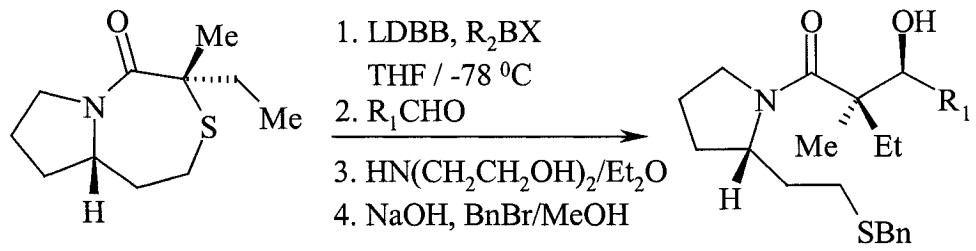
Entry	R_1	Additive	Equivalents	*syn/anti*	de (*syn*) [a] (%)
1.	*i*Pr	none	-	54:46	40
2.		$TiCl_4$	3.3	74:26	56
3.		$ZnCl_2$	2.1	68:32	-
4.		Cp_2ZrCl_2	2.1	-	-
5.	Ph	none	-	52:48	23
6.		$TiCl_4$	1.1	45:55	20
7.		$ZnCl_2$	2.0	61:39	48
8.		Cp_2ZrCl_2	2.0	71:29	52

[a] Determined by HPLC using Chiracel OD Column.

Three metals were explored ($TiCl_4$, Cp_2ZrCl_2, $ZnCl_2$) in addition to the lithium enolate. Modest *syn/anti* selectivity was observed in the aldol reaction of isobutyraldehyde with the enolates derived from $TiCl_4$ and $ZnCl_2$ (**entries 2** and **3**). The dicyclopentadienyl zirconium dichloride derived enolate did not provide the desired aldol product (**entry 4**). Entries **5-8** in **Table 2-2** highlight the results for the aldol reaction using benzaldehyde. Only the zirconium enolate (**entry 8**) was able to improve the *syn/anti* selectivity of the aldol reaction (71:29), but the *syn* diastereoselectivity remained low (52 %). As is evident from the results above, synthetically useful levels of product stereocontrol were not observed from these metal enolates.

As stated previously, there are countless examples of stereoselective boron-mediated aldol reactions in the literature. It was therefore decided to explore boron enolates in an attempt to improve the reaction selectivity. The results for isobutyraldehyde and benzaldehyde are provided in **Table 2-3**.

Table 2-3. Aldol reaction with (*Z*)-boron enolate.



60

Entry	R_1	Additive	Equivalents	*syn/anti*	de (*syn*) (%)	yield (%)
1.	Ph	none	-	52:48	23	71
2.		Bu_2BOTf	2.2	79:21	95	48
3.		Bu_2BOTf	3.0	83:17	92	39
4.		Cy_2BOTf	2.2	69:31	30	46
5.		Cy_2BOTf	3.3	91:9	93	53
6.		Bu_2BCl	2.1	75:25	81	63
7.		Cy_2BCl	1.1	73:27	50	ND
8.		Cy_2BCl	2.1	92:8	96	31
9.		Cy_2BCl	3.0	74:26	77	29
10.		Cy_2BBr	1.1	55:45	93	ND
11.		**Cy_2BBr**	**2.1**	**91:9**	**94**	**80**
12.	*i*Pr	none	-	54:46	40	ND
13.		Cy_2BOTf	1.9	52:48	99	ND
14.		Cy_2BOTf	3.3	-	-	ND
15.		Bu_2BCl	1.1	70:30	82	ND
16.		Cy_2BCl	1.1	52:48	99	ND
17.		Cy_2BCl	2.1	76:24	99	ND
18.		Cy_2BBr	1.1	46:54	93	ND

[a] Determined by HPLC using Chiracel OD Column.

As can be seen from **Table 2-3**, transmetallation of the lithium enolate of **60** with a variety of boron sources (Bu_2BOTf, Bu_2BCl, Cy_2BOTf, Cy_2BCl, Cy_2BBr) prior to benzaldehyde condensation improved the *syn/anti* ratio considerably in comparison to the lithium enolate reaction (**entries 2-11**). The first boron source investigated, dibutylboron triflate (**entries 2** and **3**), provided similar *syn/anti* control as zirconium. The *syn* diastereoselectivity, however, improved dramatically (2.2 equiv. Bu_2BOTf - 95 % de, 3.0 equiv. Bu_2BOTf - 92 % de *vs.* 2.0 equiv. Cp_2ZrCl_2 - 52% de). In an attempt to improve the *syn/anti* selectivity, *syn* diastereoselectivity and reaction yield, several other boron sources were investigated. Switching to the more sterically demanding dicyclohexylboron triflate provided a mixture of results. If 2.2 equivalents were employed, low *syn/anti* and *syn* diastereoselectivities were obtained (**entry 4**). Transmetallation with 3.0 equivalents of this reagent prior to aldehyde addition, however, yielded a 91:9 *syn/anti* ratio and 93 % de for the *syn* isomer (**entry 5**), albeit in modest yield. The *syn/anti* selectivity in this reaction was very close to the *Z/E* ratio of the intermediate enolate, 94:6 *Z/E*. Further investigation revealed that while both dicyclohexylboron chloride and dicyclohexylboron bromide afforded similar selectivity as the triflate version, the reaction yield was greatly improved with the bromide reagent. In addition, only two equivalents of the reagent were required to achieve optimum stereoselectivity (**entry 11**).

A variety of boron source were also investigated with isobutyraldehyde (**entries 12-18**). High levels of *syn* diastereoselectivity were observed (82-99 % de), but the *syn/anti* stereocontrol could not be raised to a synthetically useful level (varied from 76: 24 to 46:54). The reaction also suffered from low product yields (HPLC trace showed

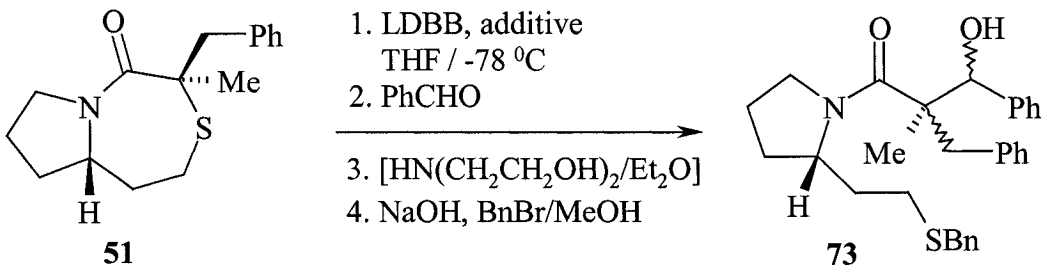
large amounts of quenched enolate and other side reaction products). Isobutyraldehyde is more sterically demanding than benzaldehyde. In order to reduce steric interactions in the transition state, a boat conformation could be adopted which would compete with the favoured chair conformation (*vide infra* **Figure 2-5, 90a**). This would lead to the observed mixture of *syn* and *anti* aldol adducts. Consequently, the optimized reaction conditions (**Table 2-3, entry 11**) developed for benzaldehyde were used to determine reaction scope with the *Z*-enolate (*vide infra*). Benzaldehyde was also chosen as the aldehyde for the *E*-enolate study (**Table 2-4**).

The improved product selectivity was not surprising since boron enolates traditionally offer some of the highest levels of *syn/anti* control reported in the literature.[1] Compared to lithium, for example, the shorter boron-oxygen bond in boron enolates leads to a tighter cyclic transition state upon aldehyde addition, resulting in highly stereoselective carbon-carbon bond formation. What was particularly interesting, however, was the lithium to boron transmetallation. Boron enolates are usually formed directly by enolboration (R_2BX and an amine base) of acidic carbonyl substrates such as ketones, imides, *N*-acyl isoxazolidines and thioesters.[29] There are only a few examples involving direct transmetallation to form boron enolates in the literature and the *syn/anti* stereoselectivity of subsequent aldol reactions is often quite variable.[30] In our system, lithium to boron transmetallation occurred easily.

The *E*-enolate was also investigated to access the *anti* stereoisomer. As **Table 2-3** illustrates, varying the number of metal equivalents greatly affected the reaction

stereoselectivity. It was therefore hoped that optimized reaction conditions for the *E*-enolate could be found by varying the metal source and its number of equivalents. The results are provided in **Table 2-4**. The methyl/benzyl *E*-enolate was chosen as the model for this study because of the high selectivity for its formation (12:88 *Z*/*E*).[25] The methyl/ethyl *E*-enolate was not chosen as the model due to the low selectivity for its formation (1:2 *Z*/*E*, determined by enolate trapping experiment). A preliminary experiment with the Me/Et lactam precursor, using 2.0 equivalents of dicyclohexylboron bromide, found that the poor enolate ratio was reflected in the *syn*/*anti* aldol product distribution (34:66 *syn*/*anti*).

Table 2-4. Transmetallation effects on aldol stereoselectivity with the (*E*)-enolate.



51 **73**

Entry	Additive	Equivalents	*syn*/*anti* ratio	de (*anti*)[a] (%)
1.	None	-	38:62	48
2.	$TiCl_4$	2.1	72:28	21
3.	$TiCl_4$	3.1	76:24	41
4.	Cp_2ZrCl_2	2.1	17:83	77
5.	Cp_2ZrCl_2	3.1	20:80	74
6.	Bu_2BCl	1.1	17:83	70
7.	Bu_2BCl	2.1	22:78	97
8.	Bu_2BCl	3.1	23:77	98
9.	Cy_2BBr	1.1	15:85	60
10.	Cy_2BBr	2.1	25:75	65
11.	Cy_2BBr	3.1	56:44	86

[a] Determined by HPLC using Chiracel OD Column.

From the results in **Table 2-4**, it is evident that the methyl/benzyl *E*-enolate reacts quite variably. The highest levels of *anti/syn* stereocontrol were achieved using Cp_2ZrCl_2, Bu_2BCl and Cy_2BBr (**entries 4-9**). While high levels of *anti* diastereoselectivity were obtainable with Bu_2BCl (2.1 and 3.1 equivalents, **entries 7** and **8**), the modest *anti/syn* ratio (78:22 and 77:23 respectively) reduced the usefulness of these results. When the reaction was conducted with 1.1 equivalents of Cy_2BBr (**entry 9**), the 85:15 *anti/syn* product ratio obtained closely reflected the *E/Z* enolate ratio (88:12). The reaction proceeded, however, with low *anti* diastereocontrol (60 % de). Increasing the number of boron equivalents eroded the *anti/syn* control (**entries 10** and **11**), but improved the *anti* diastereoselectivity. The reduced stereocontrol observed with the *E*-enolate may arise because of the absence of a favoured transition state. Increased steric interactions between the large benzyl group and the aldehyde may prevent the system from adopting a chair transition state (*vide infra*) and instead lead to competing twisted chair or boat conformations.

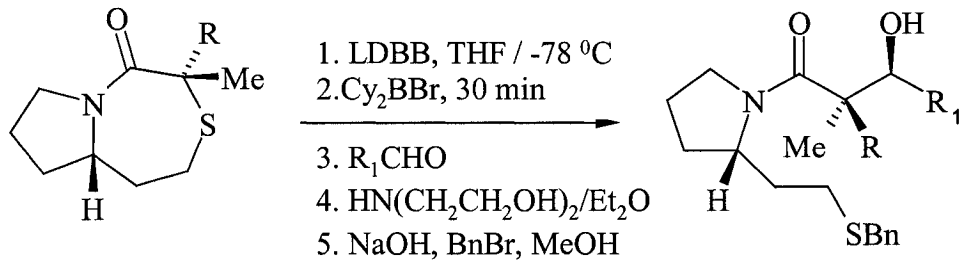
As access to the diastereomeric aldol product relies on the *E*-enolate reacting stereoselectively, the inability of the *E*-enolate to react selectively is currently the primary limitation of this methodology. Similar limitations were also observed in the alkylation chemistry.

2.2.3. Investigating the Reaction Scope

The reaction scope was determined by surveying a variety of aldehydes using the optimized reaction conditions (2.1 equiv. Cy_2BBr). High selectivity and yields could be achieved with both aromatic and α,β-unsaturated aldehydes. The results are provided in

Table 2-5. Finally, examination of other α,α-substituents showed that the reaction extends beyond the simple methyl/ethyl enolate substitution pattern (**Table 2-5, entries 7** and **8**, allyl/methyl and benzyl/methyl respectively).

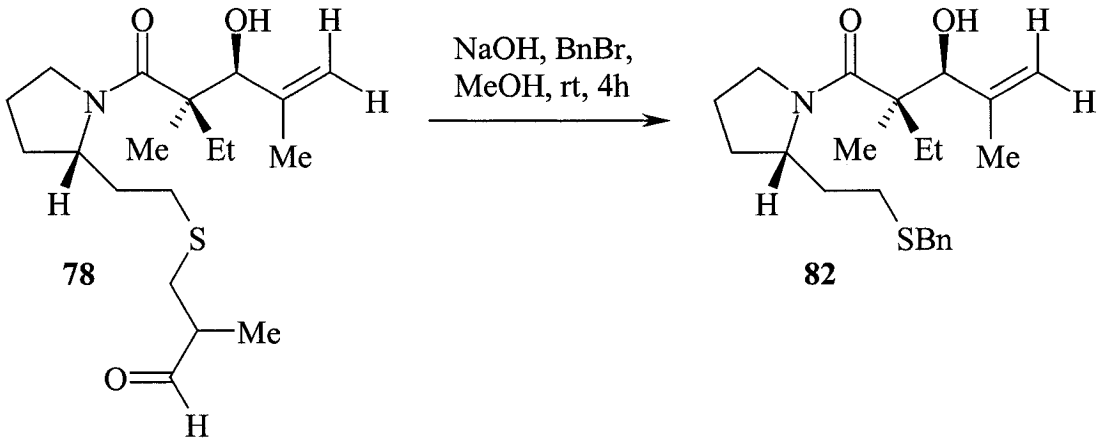
Table 2-5. Aldol reactions with aromatic and α,β-unsaturated aldehydes.



Entry	R	Compound	R_1	*syn/anti* ratio	de (*syn*)[a] (%)	yield (%)
1.	Et	**74**	Ph	91:9	94	80
2.	Et	**75**	4-MeOPh	91:9	98	83
3.	Et	**76**	4-BrPh	93:7	99	81
4.	Et	**77**	(*E*)-PhCH=CH	91:9	99	63
5.	Et	**78**	CH_2=C(Me)	98:2	95	44
6.	Et	**79**	(*E*)-MeCH=C(Me)	91:9	91	95
7.	allyl	**80**	Ph	92:8	91	71
8.	Bn	**81**	Ph	91:9	99	91

[a] Determined by HPLC using Chiracel OD Column.

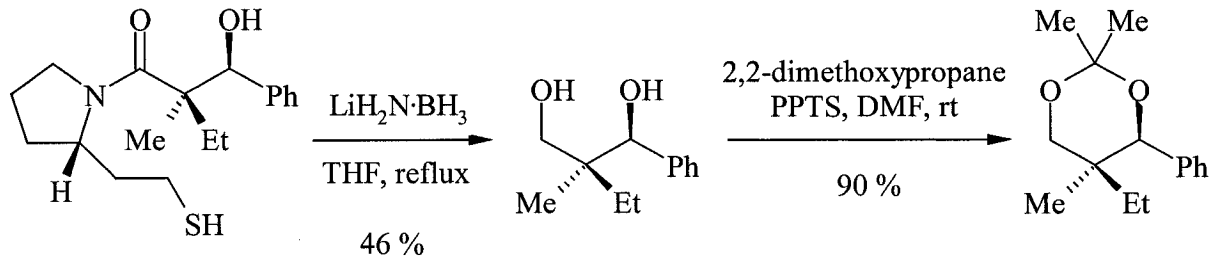
In the case of α,β-unsaturated aldehydes, conjugate addition of the thiolate to a second equivalent of the aldehyde was observed (**Scheme 2-24**). The addition products reverted under the S-benzylation conditions, through a β-elimination pathway, to give the desired final products. As previously mentioned, aliphatic aldehydes were not amenable to this reaction system, but the α,β-unsaturated aldehydes may potentially provide access to these substrates through hydrogenation.



Scheme 2-24. Reversal of thiol addition to α,β-unsaturated aldehydes under benzylation conditions.

2.2.4 Isolation of Quaternary Carbon Adducts *via* Reductive Amide Cleavage

The aldol condensation product **83** (free thiol) was removed from the auxiliary by amide cleavage with lithium amidoborohydride (LAB).[31] This cleavage provides a 1,3-diol **84**, which was then protected as an acetonide using 2,2-dimethoxypropane and PPTS in DMF (**Scheme 2-25**). The LAB reagent, a metal amide-borane complex, is prepared by deprotonation of the commercially available borane-ammonia complex with LDA at 0 °C. The thiol group may be playing a role in the reduction reaction since the reaction fails when the -SBn and -OH aldol adduct material is used. Its role is unclear at this stage because -SBn and O-silylated material can also be cleaved from the auxiliary using the amide reductive cleavage conditions. While silyl based protecting groups did work, they were difficult to introduce due to the steric environment surrounding the hydroxyl group. In both instances, the retro-aldol reaction was the major competing process.



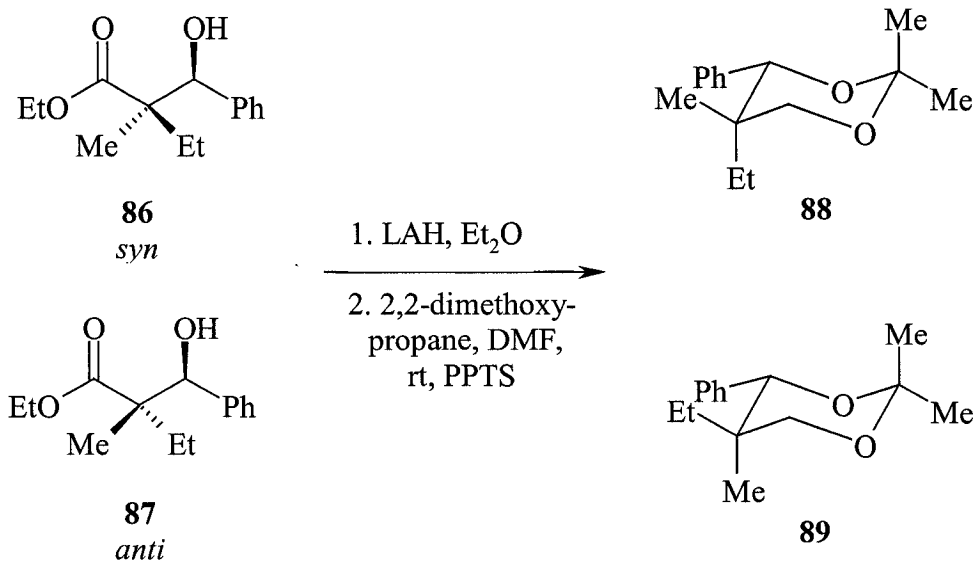
83 **84** **85**

Scheme 2-25. Auxiliary cleavage with lithium amidotrihydroborate.

2.2.5 Product Stereochemical Assignment

2.2.5.1 Relative Stereochemistry

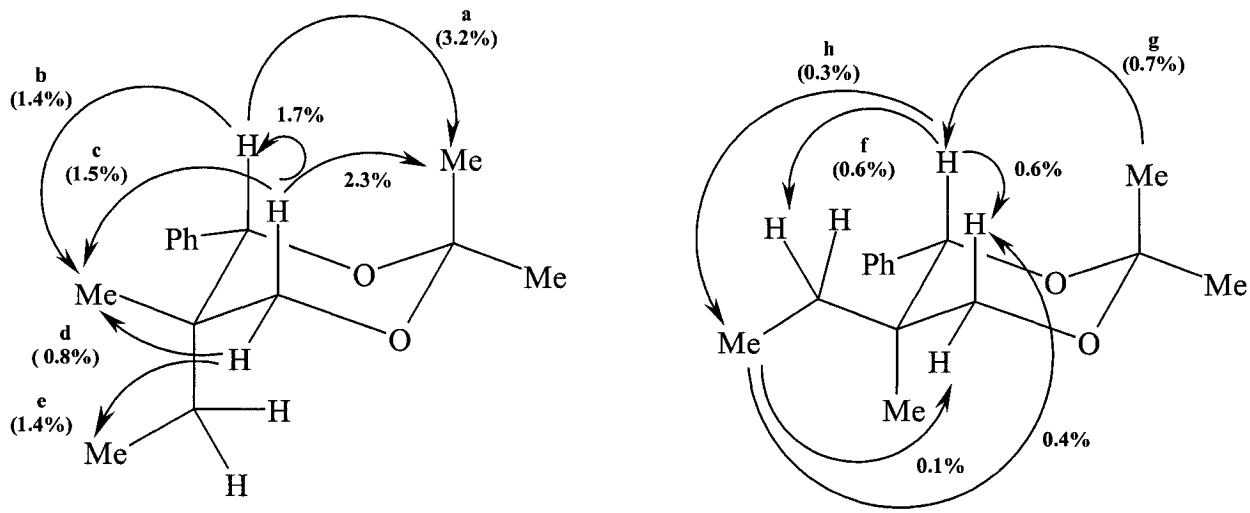
It was now important to make the stereochemical assignment of the newly formed stereogenic centers. This would provide insight into a possible transition state assembly. The relative stereochemical assignment (i.e. *syn* verses *anti*) of the condensation products was initially determined by comparing the ^{1}H and ^{13}C NMR spectra of acetonide aldol material **85** to racemic material synthesized *via* the route outlined in **Scheme 2-26**. *Syn* and *anti* isomers **86** and **87** were obtained in a manner analogous to isomers **65** and **66** previously described in **Scheme 2-22**. Reduction of the isomers **86** and **87** was accomplished with lithium aluminum hydride. The 1,3-diols were converted to the acetonides **88** and **89** with 2,2-dimethoxypropane in DMF.



Scheme 2-26. Formation of acetonides **88** and **89**.

The assignment of the relative stereochemistry was accomplished using NOESY experiments of the acetonides **88** and **89** (chair conformations were assumed). The observed enhancements are shown in **Figure 2-3**. Strong NOE enhancements were observed in **88** between the axial acetonide methyl group and the benzyl proton (arrow **a**). Likewise, the α-methyl group showed strong signals with the benzyl proton and the axial methylene proton (arrows **b**, **c**). In addition, NOE signals were observed between the equatorial methylene proton and the α-methyl group (arrow **d**) and the methyl group of the α-ethyl substitutent (arrow **e**). Based on these NOESY enhancements, acetonide **88** was assigned to be *syn*. In a similar manner, the other acetonide isomer was analyzed. Structure **89** showed strong NOE enhancements between the α-ethyl methylene protons and the benzyl proton (arrow **f**), between the axial acetonide methyl group and the benzyl proton (arrow **g**) and between the benzyl proton and the methyl group of the α-ethyl

substituent (arrow **h**). Structure **89** was thus assigned to be the *anti* isomer. Other NOE signals are shown in **Figure 2-3**.



88
syn configuration

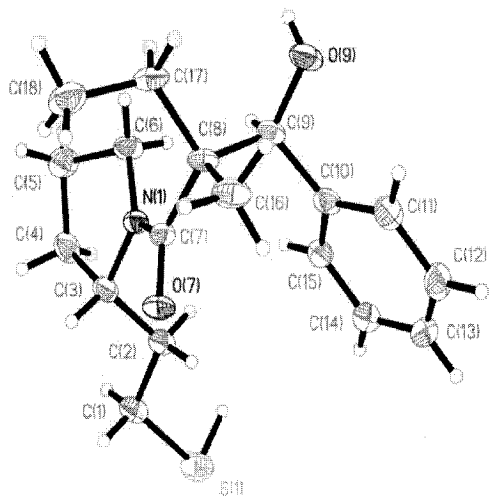
89
anti configuration

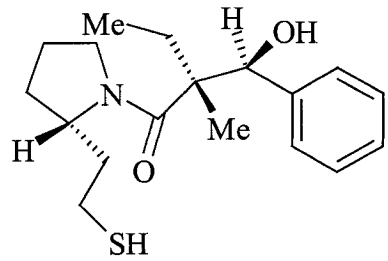
Figure 2-3. NOESY analyses of acetonide isomers.

Comparison of the ^{1}H-NMR spectra from the authentic acetonide materials **88** and **89** and the reduced aldol condensation product **85** revealed that the major isomer was the *syn* isomer. This provides preliminary proof that the reaction may be proceeding through a closed transition state.

2.2.5.2 Absolute Stereochemistry

This relative *syn* stereochemical assignment was confirmed by an X-ray crystal structure of product **83**. It also provided the absolute stereochemistry as (2R, 3S) at the newly formed stereogenic centers (**Figure 2-4**).



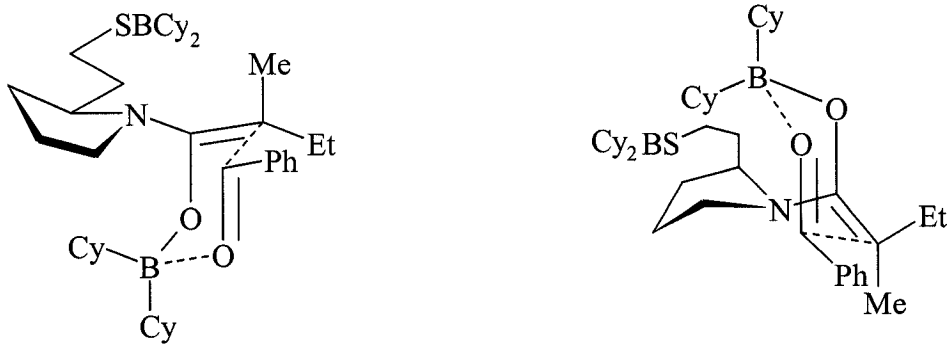


83

Figure 2-4. X-ray crystal structure of **83**.

The *syn* product stereochemistry is consistent with a chairlike transition state expected for boron-mediated aldol reactions. Two possible closed transition state assemblies may be considered (**Figure 2-5**). Both structures **90a** and **90b** invoke a loss of conjugation of the nitrogen lone pair with the π-system of the amide enolate.[32] Furthermore, the proposed twisted geometry minimizes the potential $A^{1,3}$- strain between the nitrogen substituents and the groups at the α-position on the enolate. **90a** and **90b** illustrate two possible envelope conformations of the pyrrolidine ring, each of which hold

the enolate in a pseudoequatorial position to minimize steric interactions. Transition state **90b** is disfavoured due to significant *syn* pentane interactions between the enolate oxygen and the pseudoaxial thioethylene chain.



90a
Favoured

90b
Disfavoured

Figure 2-5. Potential transition state assemblies.

An open transition state was also considered. This transition state would require the formation of an eight-membered ring involving one of the boron equivalents linking the sulfur and oxygen atoms, with the second boron equivalent activating the aldehyde towars addition. The high flexibility associated with this ring, the low driving force for its formation, and the increased steric interactions near the reacting centers would make such a transition state unfavourable.

The closed transition state structures proposed in **Figure 2-5** require the use of two equivalents of boron reagent, with transmetallation occuring at two sites - oxygen and sulfur. When fewer equivalents of reagent are employed, other transition state assemblies

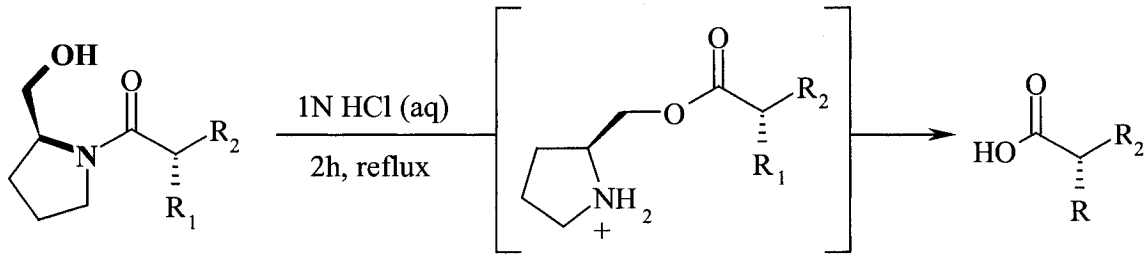
would have to be considered since the overall steric bulk of the system is reduced, and a mixture of boron metallated species may exist in solution. When the boron reagent is used in excess, open transition state assemblies must be considered.[12] The presence of competing transition states would account for the reduction in *syn/anti* stereocontrol previously observed with less than or greater than two equivalents of boron reagent (**Table 2-3** and **2-4**).

2.2.6 Second Generation Auxiliary

A chiral auxiliary is considered successful if it is synthesized cheaply and easily, performs the desired reaction selectively, and is easily removed and recovered. While the auxiliary presented in the preceding sections permits the stereoselective formation of the α-quaternary carbon β-hydroxy carbonyl compound, it requires 11 steps to synthesize, is difficult to remove and is not recoverable. In an attempt to overcome these shortcomings, a second generation chiral auxiliary has been developed in the Gleason group by Jeffery Manthorpe and Azélie Arpin (*vide infra*).

An auxiliary cleavage protocol based on N→O acyl transfer hydrolysis was deemed to be an effective and a mild method for auxiliary removal. This methodology has been utilized with prolinol and pseudoephedrine amide auxiliaries.[33] Prolinol amide auxiliary **91** (**Scheme 2-27**) was shown by Evans to undergo facile acid catalyzed hydrolysis. This protocol requires the incorporation of an ethanolamine moiety (bold) into the auxiliary. This unit allows an acid-promoted N→O acyl shift to proceed *via* a five-membered ring transition state, resulting in the formation of an ester and an amine.

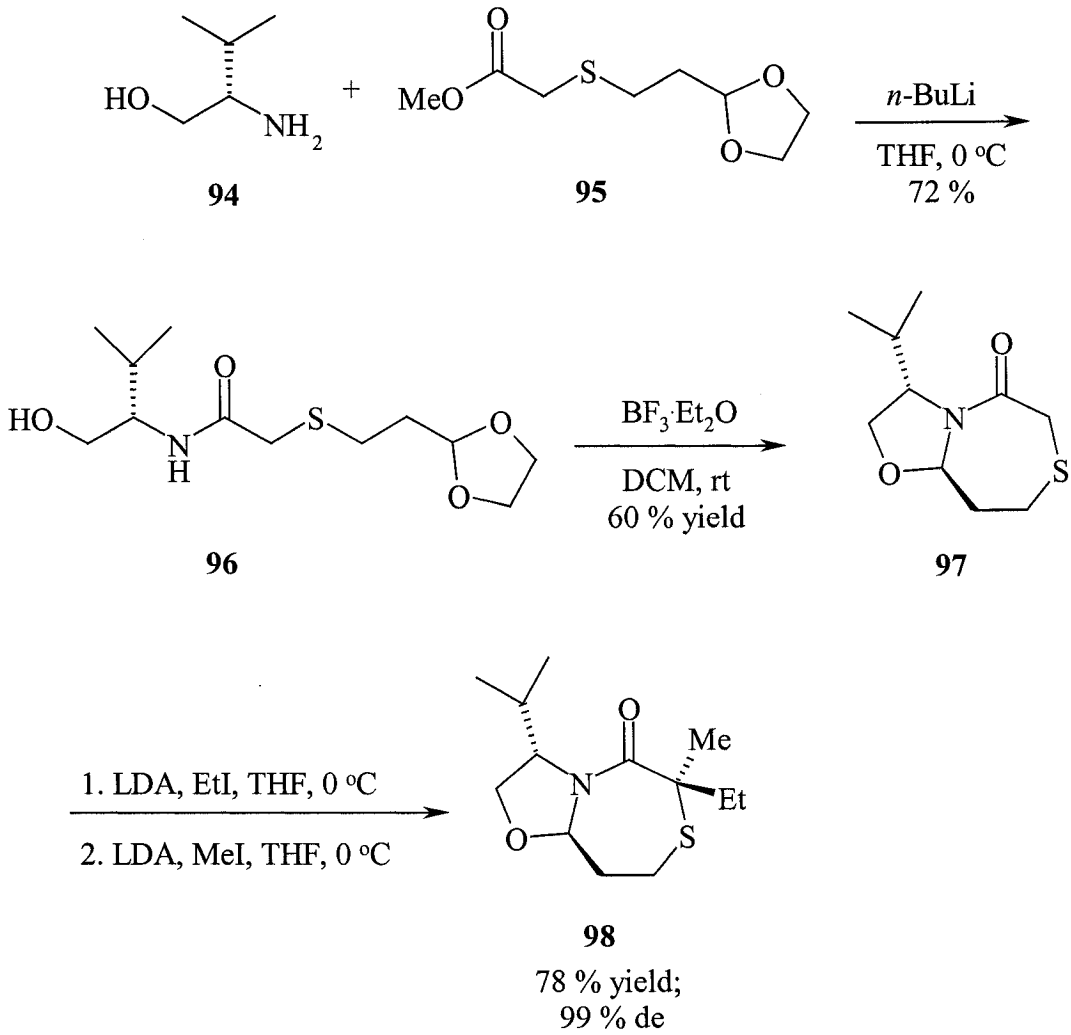
Under these acidic conditions, the resulting amine **92** is protonated, thus making the process irreversible. The increased susceptibility of the ester unit to hydrolysis (compared to an amide) allows the auxiliary cleavage to proceed at an accelerated rate and under milder conditions.



91 **92** **93**

Scheme 2-27. Evans prolinol auxiliary cleavage using N→O assisted hydrolysis.

The second generation auxiliary was also designed to maintain the essential 5,7-bicyclic ring system of the original auxiliary.[25] As **Scheme 2-28** illustrates, aminal auxiliary **97** is synthesized in two steps from cheaply available starting materials. Most importantly, the initial α,α-alkyl substituents are installed with the same high levels of selectivity observed with the 5,7-thioglycolate amide auxiliary.

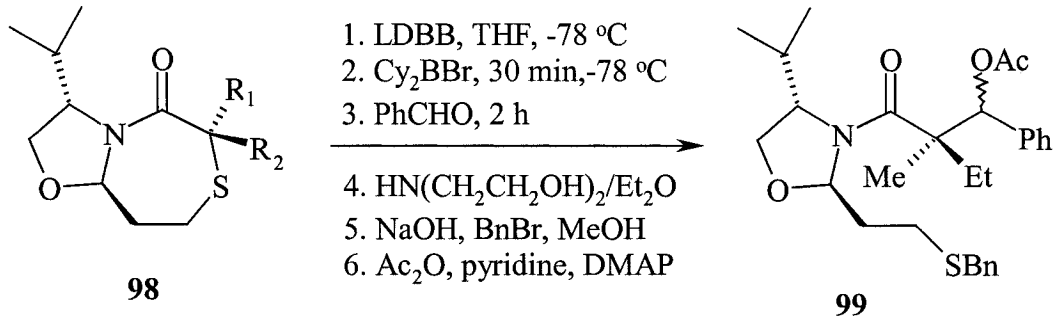


Scheme 2-28. Synthesis and α-alkylation of second generation auxiliary.

A preliminary aldol study has been conducted with this aminal-based auxiliary. As with the first generation auxiliary, the lithium enolate failed to provide sufficient levels of stereocontrol in the reaction. From the results, however, HPLC conditions were developed and ^{1}H NMR and MS data were collected on these new aldol adducts. Dicyclohexylboron bromide was chosen as the boron source since it had been successful with the first generation auxiliary. The aldol stereochemistry has not been definitively

assigned. It was assumed that the *Z*-enolate (**entries 1-4**) would provide the *syn*-adduct and the *E*-enolate (**entry 5**) would provide the *anti*-adduct as the major isomer, as per the 5,7-bicyclic thioglycolate lactam system. The results are presented in **Table 2-6**.

Table 2-6. Preliminary results for the aldol reaction with the second generation auxiliary.



98 **99**

Entry	R_1	R_2	additive	No. equivalents	*syn/anti*	% de [a]
1.	Me	Et	None	-	50:50	91[b]
2.	Me	Et	Cy_2BBr	1.1	92:8	91[b]
3.	Me	Et	Cy_2BBr	2.1	73:27	86[b]
4.	Me	Et	Cy_2BBr	3.1	-	-
5.	Et	Me	Cy_2BBr	1.1	18:82	80[c]

[a] Determined by HPLC using Chiracel OD Column.
[b] *syn* isomer. [c] *anti* isomer.

The reaction was conducted as per the first generation auxiliary. Protection of the hydroxyl functionality as the acetate was necessary to improve the HPLC trace and ^1H NMR spectrum. Although high levels of *syn/anti* diasterocontrol and diastereoselectivity were achieved with 1.1 equivalents of Cy_2BBr (**entries 2** and **5**), the reaction was not clean. Many side products were observed by TLC, ^1H NMR and HPLC. The detrimental effect of excess boron reagent may be attributed to its Lewis acidic nature. Boron coordination to the aminal ring during the transmetallation step could lead to undesired

ring cleavage. This would explain the presence of the many side reaction products observed and the absence of aldol product when three equivalents dicyclohexylboron bromide were used in the transmetallation step (**entry 4**).

This preliminary work has demonstrated that the second generation auxiliary can be used in the aldol reaction to provide the α,α-disubstituted aldol adducts with high selectivity. Azélie Arpin will continue this work by investigating the reaction scope, developing hydrolysis conditions to remove the auxiliary and assigning the product stereochemistry.

2.2.7 Conclusions

A general, diastereoselective method for the formation of quaternary carbon centers *via* a boron-enolate aldol process has been developed. High *syn/anti* selectivity and *syn* diastereoselectivity are observed with the *Z*-enolate. Aromatic and α,β-unsaturated aldehydes can be used with the latter serving as potential substrate surrogates for aliphatic aldehydes.

Two main problems with this first generation auxiliary are: the harsh auxiliary cleavage conditions induce an undesired retro-aldol process (this problem could potentially be solved with the second generation auxiliary) and the *E*-enolates do not provide the *anti* aldol adducts selectively. To address these issues, a second generation auxiliary has been developed *via* an expedient route from readily available starting materials. Preliminary studies have shown that the *Z*-enolate reacts with high selectivity in the presence of only one equivalent of dicyclohexylboron bromide. Hydrolysis conditions remain to be developed.

NOESY data and an X-ray crystal structure determined the aldol product stereochemistry to be the *syn* isomer. This is in agreement with the chairlike transition state model established for boron monosubstituted enolate chemistry and the work conducted by Nakamura.[6]

2.3 Experimental Section

General Experimental. All reagents were commercially available materials and were used without further purification with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, while toluene was distilled from calcium hydride. Alkylation and reductive enolization/trapping substrates were dried *via* azeotropic distillation of water using dry toluene. All aldehydes used were distilled neat and stored over 4 Å molecular sieves. All Schlenk flasks and lithium chloride were flamed-dried under vacuum. Alkyl halides were passed over basic alumina prior to addition. All dialkylboron halides and triflates were distilled upon preparation. Chromatography was conducted using 230-400 mesh silica gel. NMR spectra were recorded at 300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C. GC analyses were conducted on a CP Chiralsil-dex column (25 m x 0.25 mm) using He (14 psi) as the carrier gas. HPLC analyses were conducted on a Chiracel OD Column. Dr. Gaston Boulay at the Université de Sherbrooke, QC, CANADA, performed high resolution mass spectrometry. Dr. Francine Bélanger-Gariépy resolved the X-ray structure at the Université de Montréal, QC, Canada.

Preparation of Lithium di-*tert*-butylbiphenylide (LDBB).

Lithium (1.1 equiv.) was pressed into thin sheets, rinsed sequentially in hexanes, tetrahydrofuran, methanol and tetrahydrofuran and then added to a solution of di-*tert*-butyl biphenyl (1.0 eq) in tetrahydrofuran (50.0 mL) at 0 °C. The resulting solution was stirred for 5 hours before use. The reagent can be stored at 0 ^{0}C for 1 week. Stirring increases the lifetime of the reagent to 2 weeks at 0 °C.

Synthesis of dibutylboron triflate.[34]

To tributylborane (1.0 equiv. 41.0 mmol, 10.0 mL) under argon was slowly added 1 mL of freshly opened trifluoromethanesulfonic acid (1.0 equiv. 41.0 mmol, 3.63 mL). The reaction was warmed to ca. 50 °C until butane evolution was observed. The remaining acid was added dropwise while maintaining the reaction temperature between 25-50 °C. After stirring for 30 min (25 °C), the boryl triflate was isolated *via* short-path distillation (bp 60 °C at 2.0 mm Hg).

Synthesis of dibutylboron chloride.[35]

A cold finger apparatus was used to liquefy butene and introduce it to a flame-dried 3-N round bottom flask, which was cooled to 0 °C. Diethyl ether (67 mL) was then slowly added followed by monochloroborane·dimethylsulfide. The reaction was stirred at 0 °C for 2 h, at room temperature for 2 h and then allowed to stand overnight at room temperature. The ether was removed by distillation followed by distillation of the product (bp = 47-48 °C at 7 mm Hg).

Synthesis of dicyclohexylboron chloride.[36]

Cyclohexene (14.3 mL, 141.0 mmol, 2.1 equiv.) and diethyl ether (50 mL) were added *via* syringe to a flame dried round bottom flask and cooled to 0 °C. To this solution was slowly added a 1.0 M methylene chloride solution of monochloroborane·dimethyl sulfide complex. The resulting solution was stirred at 0 °C for 2 h. The ether was removed by distillation at 760 mm Hg followed by product distillation (bp = 105 °C at 0.5 mm Hg). The clear, colourless oil was stored under argon in the fridge.

Synthesis of dicyclohexylboron triflate.[37]

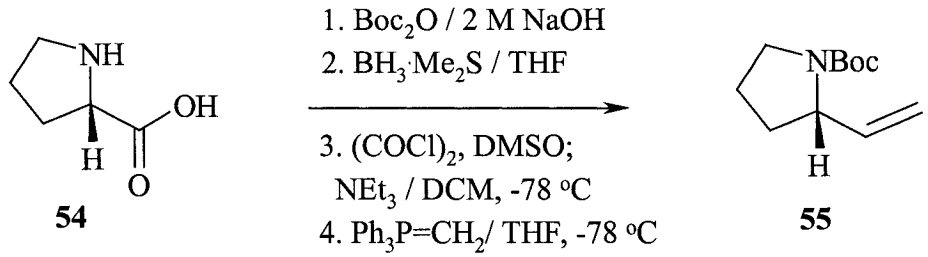
Cyclohexene (11.0 mL, 109.0 mmol, 2.1 equiv.) and diethyl ether (33 mL) were added *via* syringe to a flame dried round bottom flask and cooled to 0 °C. Borane·dimethyl sulfide was then carefully added with vigorous stirring, which continued for 3 h at 0 °C. The reaction was allowed to stand and the ether layer was removed via glass syringe. The solid material was then dried under vacuum for 5 minutes. Dry hexane was added via syringe (52.7 mL) at room temperature. Freshly opened triflic acid was then slowly added over a period of 20 minutes. The resultant orange solution was stirred for 1 h and then allowed to stand at room temperature for 2 h. The top layer was then cannulated into a pre-weighed flame-dried Schlenk fitted with stir bar. Dicyclohexylboron triflate was recrystallized from the oil at –20 °C for 12 h. Additional solvent was removed using a glass syringe and the solid product dried under vacuum for 15 min. The weighed material was then redissolved in dry hexanes to form a 1 M solution, which was stored in the fridge.

Synthesis of dicyclohexylboron bromide.[38]

A 1.0 M solution of monobromoborane·dimethyl sulfide complex (67.6 mL, 1.0 equiv.) in methylene chloride was added to a solution of cyclohexene (8.0 mL, 2.19 equiv.) in methylene chloride (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 h. The reaction was then allowed to stand overnight at room temperature. The methylene chloride was then carefully removed using a vacuum pump. The remaining solid was recrystallized using dry hexanes and the material was allowed to stand overnight under argon. Excess hexanes was removed using a glass syringe. The remaining solid material

was melted and then distilled under vacuum (bp = 108 °C at 1 mm Hg) to provide the desired product as a clear, colourless liquid, which was then stored under argon in the fridge.

Sample procedure for formation of the lactam starting material (7*S*)-1-aza-4-thiabicyclo[5.3.0]-2-decanone (58).[25]



Di-*tert*-butyldicarbonate (20.9 g, 95.5 mmol, 1.1 equiv.) was added in several portions to a stirred solution of (S)-proline (10.0 g, 86.9 mmol, 1.0 equiv.) in *p*-dioxane (300 mL) and aqueous sodium hydroxide (2M, 175 mL) at 23 °C. After 1 h, the solution was concentrate in vacuo to approximately 200 mL, then acidified to pH 1 using aqueous hydrochloric acid solution (6M). The mixture was extracted with dichloromethane (3 x200 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The desired material was obtained as a white solid (17.5 g, 95 %).

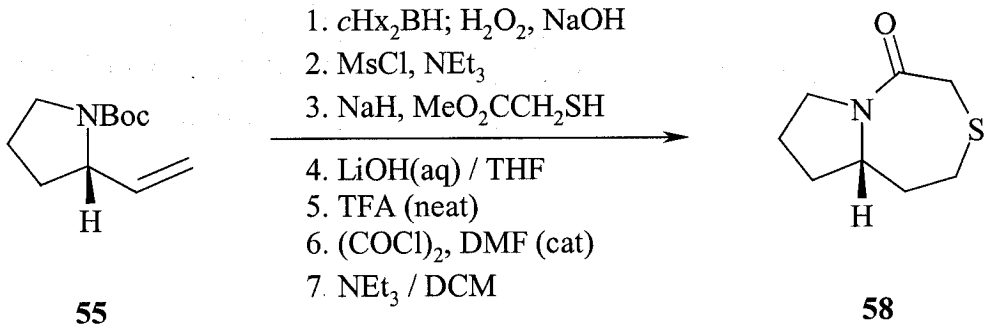
Borane·THF complex (1.0 M in THF, 96.6 mmol, 1.5 equiv.) was added to a stirred solution of the protected amino acid (13.9 g, 64.4 mmol, 1.0 equiv) prepared above in THF (200 mL) at 0 °C. The reaction was warmed to 23 °C and stirred for 3 h then cooled to 0 °C. 20 mL of distilled water was added *via* pipette and the resulting solution stirred overnight. The aqueous phase was then extracted with diethyl ether (3x150 mL).

The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The material was used without purification.

Dimethyl sulfoxide (78 μL, 1.09 mmol, 2.2 equiv.) in dry methylene chloride (200 μL) was added to a stirred solution of oxalyl chloride (53 μL, 0.596 mmol, 1.2 equiv.) in methylene chloride (5 mL) at –78 °C. After 20 minutes, the alcohol prepared above was added *via* cannula as a methylene chloride solution (2 mL). After stirring for 1.5 h at –78 °C, dry triethylamine (277 μL, 2.0 mmol, 4.0 equiv.) was added and the reaction was allowed to warm to 23 °C. The mixture was extracted with dichloromethane (3x10 mL) and washed with aqueous hydrochloric acid solution (1M, 2x2 mL), distilled water (2x3 mL) and brine (1x10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The aldehyde was obtained as a yellow oil (96.0 mg, 97 %).

A solution of *n*BuLi (2.27 M in hexanes, 297 μL, 0.675 mmol, 1.4 equiv.) was slowly added at –78 °C to a stirred suspension of methyl triphenylphosphonium bromide (258 mg, 0.723 mmol, 1.5 equiv.) in dry THF (7 mL). After 30 minutes, the mixture was warmed to 0 °C, stirred for 30 minutes, then recooled to –78 °C. A solution of the aldehyde (96 mg, 0.482 mmol, 1.0 equiv.) prepared above in THF (2 mL) was added *via* cannula. After 1 h, the mixture was warmed to 23 °C, stirred for 1 h, and then diluted with distilled water (1x2mL) and diethyl ether (5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether. The combine organic phases were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford the desired alkene (2S)-N-tert-butoxycarbonyl-2-ethenylpyrrollidine as a colourless oil (45 mg, 48 %). ^{1}H NMR ($C_6D_5CD_3$) δ 5.61 (m, 1H), 4.97-4.84 (m, 2H), 4.13 (m, 1H), 3.21-

3.26 (m, 2H), 1.75-1.11 (m, 4H), 1.36 (s, 9H); ^{13}C NMR ($C_6D_5CD_3$) δ 153.6, 139.5, 112.8, 78.0, 58.8, 46.1, 31.5, 28.2, 22.9.



55 **58**

Borane·Me_2S complex (782 μL, 8.24 mmol, 1.3 equiv.) was added to a stirred solution of dry cyclohexene (1.73 mL, 17.1 mmol, 2.7 equiv.) in dry THF (14 mL) at 0 °C. After 1.5 h, a solution of the alkene (1.25 g, 6.34 mmol, 1.0 equiv.) was added as a THF solution *via* cannula. After 10 minutes, the reaction was warmed to 23 °C and stirred for 1 h. The solution was recooled to 0 °C. A solution of aqueous sodium hydroxide solution (3M, 5.5 mL) and aqueous hydrogen peroxide (30 % solution, 5.5 mL) were added *via* pipette and the reaction was heated to 35 °C for 2 h. After cooling to 23 °C, the mixture was saturated with solid sodium chloride. The organic material was then extracted with diethyl ether (3x20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 25 % ethyl acetate in hexanes to afford the known compound (2S)-2-(2-(*N-tert*-butoxycarbonyl)pyrrolidine)ethanol as a colourless oil (0.76 g, 56 %).

Methanesulfonyl chloride (76 μL, 1.48 mmol, 1.4 equiv.) was added dropwise to a stirred solution of the homologated alcohol (150 mg, 0.697 mmol, 1.0 equiv.) and triethylamine

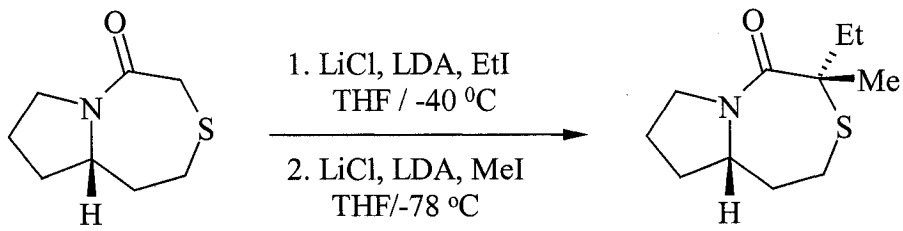
(175 μL, 1.25 mmol, 1.8 equiv.) in dry dichloromethane (7 mL) at 0 °C. After 2 h, the reaction was quenched with saturated ammonium chloride solution (2 mL). The organic material was extracted with dichloromethane (2x10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated.

Methyl thioglycolate (131 μL, 1.46 mmol, 2.1 equiv.) was added to a slurry of sodium hydride (60 % w/w in mineral oil, 55 mg, 1.39 mmol, 2.0 equiv.) in *N*, *N*-dimethylformamide (3 mL) at 23 °C. After 10 minutes, the mesylate (0.697 mmol, 1.0 equiv.) prepared above was added *via* cannula as a solution in DMF (2 mL). After 3.5 h at room temperature, the reaction was quenched by the addition of distilled water (1x2 mL) and sodium hydroxide (2M, 300 μL). The mixture was then concentrated. The residue was partitioned between water (2 mL) and 2:1 diethyl ether:hexanes (4 mL). The layers were separated and the aqueous layer was extracted with 2:1 diethyl ether:hexanes (3x5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 20 % ethyl acetate in hexanes to afford the desired compound (176 mg, 83 %).

The methyl ester (500 mg, 1.65 mmol, 1.0 equiv.) was then saponified with lithium hydroxide monohydrate (82 mg, 1.98 mmol, 1.2 equiv.) in THF (10 mL) and distilled water (6 mL) at 23 °C. After stirring for 5.5 h, the mixture was concentrated. The aqueous phase was extracted with dichloromethane (3x60 mL). The combined aqueous layers were acidified to pH 2 by addition of aqueous hydrochloric acid solution (6M) and the resulting solution was extracted with ethyl acetate (3x50 mL). The combined organic

layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was then immediately dissolved in neat trifluoroacetic acid (2 mL) at 23 °C. After stirring for 30 minutes, the mixture was concentrated. The amino acid trifluoroacetate salt (1.07 mmol, 1.0 equiv.) prepared above was dissolved in dry dichloromethane (5 mL) followed by addition of DMF (10% v/v in methylene chloride, 17 μL, 0.021 mmol, 0.02 equiv.). Oxalyl chloride (131 μL, 1.50 mmol, 1.4 equiv.) was then slowly added to the above solution. Gas evolution was observed. The mixture was stirred at room temperature for 3.5 h and then concentrated. The residue prepared above was dissolved in dry dichloromethane (4 mL). Triethylamine (447 μL, 3.2 mmol, 3.0 equiv.) was added over a 5 minute period *via* syringe. The mixture was stirred overnight at 23 °C. The reaction was quenched by the addition of aqueous hydrochloric acid (1M, 3 mL). The organic material was then extracted with dichloromethane (3x10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 50-90 % ethyl acetate in hexanes to afford the desired compound (7S)-1-aza-4-thiabicyclo[5.3.0]-2-decanone **62** (92 mg, 50 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 1H), 3.65 (m, 1H), 3.40-3.48 (m, 2H), 3.15 (dd, 1H, J_1 = 1.8, J_2 = 14.7 Hz), 2.92 (m, 1H), 2.78 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.67–1.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.2, 58.6, 47.0, 36.5, 36.0, 34.8, 33.1, 23.1.

Sample procedure for formation of dialkylated lactam starting material (3*S*, 7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (60).

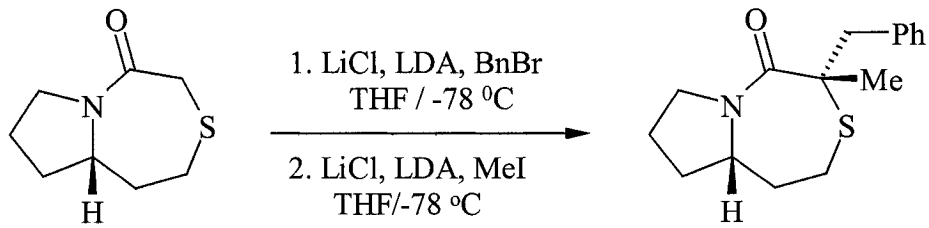


58 **60**

A 2.67M solution of n-butyllithium in hexanes (544 μL, 1.1 equiv.) was added to slurry of diisopropylamine (213 μL, 1.15 equiv.) and lithium chloride (279 mg, 5.0 equiv.) in THF at –78 °C. After 30 minutes, a solution of (7S)-1-aza-4-thiabicyclo[5.3.0]-2-decanone (226 mg, 1.0 equiv.) in THF was added via cannula. The resulting mixture was stirred for 30 minutes, at which time ethyl iodide (116 μL, 1.05 equiv.) was added dropwise. The solution was warmed to –40 °C and stirring was continued for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3R, 7S)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 80 % yield. The second alkylation was performed as follows – a solution of 2.67 M n-butyllithium in hexanes (441 μL, 1.1 equiv.) was added to slurry of diisopropylamine (172 μL, 1.15 equiv.) and lithium chloride (227 mg, 5.0 equiv.) in THF at –78 °C. After 30 minutes, a solution of (3R, 7S)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone (214 mg, 1.0 equiv.) in THF was added via cannula. The resulting mixture was stirred for 30 minutes, at which time methyl iodide

(133 μL, 2.0 equiv.) was added dropwise. Stirring was continued for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3S, 7S)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanoneas a colourless oil in 89 % yield. ^{1}H NMR ($CDCl_3$) δ 4.52 (m, 1H), 3.44-3.59 (m, 2H), 2.84 (m, 1H), 2.63 (m, 1H), 2.08-2.17 (m, 2H), 1.73-1.83 (m, 4H), 1.58-1.71 (m, 2H), 1.48 (s, 3H), 1.02 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 55.7, 53.2, 48.4, 35.8, 33.9, 32.6, 28.3, 25.8, 21.5, 9.5. The product was determined to have > 99 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 15.7 minutes (minor diastereomer), 16.3 minutes (major diastereomer)).

Synthesis of (3*S*, 7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (51).

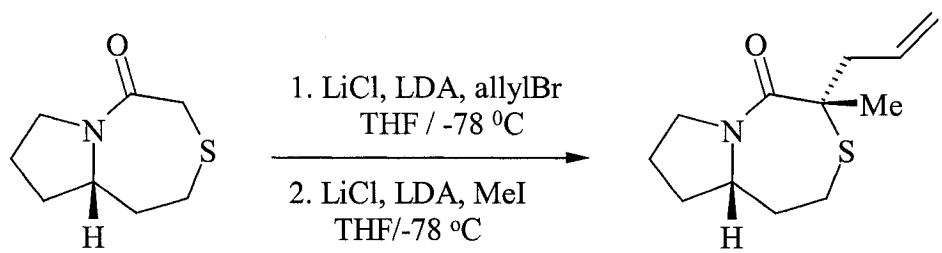


58 **51**

The alkylation was carried out at –78 °C over 3 h using benzyl bromide (156 μL, 1.1 equiv.). The reaction was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3*R*, 7*S*)-1-aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone as a white solid in 90 % yield. The second alkylation was also carried out at –78 °C over 3 h using methyl iodide (73 μL, 1.3 equiv.). The reaction was purified by

chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3*S*, 7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.35-7.38 (m, 2H), 7.10-7.21 (m, 3H), 4.53 (m, 1H), 3.57 (d, 1H, J = 13.2 Hz), 3.40-3.53 (m, 2H), 2.82 (d, 1H, J = 13.2 Hz), 2.45 (m, 1H), 1.93-2.05 (m, 2H), 1.38-1.77 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 171.7, 138.1, 132.0, 127.6, 126.5, 55.8, 54.2, 49.1, 48.0, 33.8, 32.8, 28.0, 26.7, 21.7. Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.64; N, 5.06. The product was determined to have >99 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 18.9 minutes (minor diastereomer), 19.7 minutes (major diastereomer)).

Synthesis of (3*S*, 7*S*)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (61).

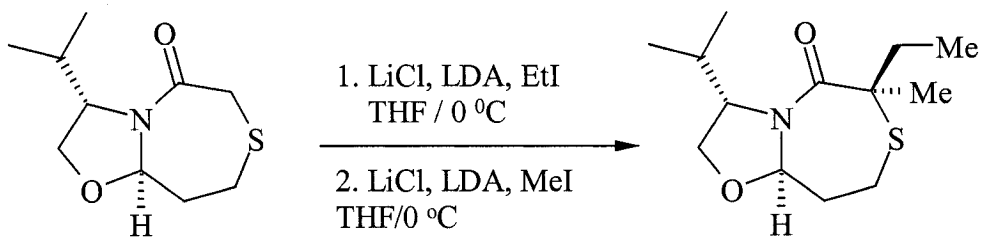


58 **61**

The alkylation was carried out at –78 °C over 3 h using allyl bromide (121 μL, 1.1 equiv.). The reaction was purified by chromatography on silica gel eluting with 40 % ethyl acetate in hexanes to afford (3R, 7S)-1-aza-3-allyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 86 % yield. The second alkylation was also carried out at –78 °C over 3 h using methyl iodide (90 μL, 1.5 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford (3S, 7S)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 85 % yield. ^{1}H NMR ($CDCl_3$) δ 5.95 (m, 1H), 5.04-5.13 (m, 2H), 4.43 (m, 1H), 3.48-3.54 (m,

2H), 2.78-2.87 (m, 2H), 2.63 (m, 1H), 2.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 13.1 Hz), 2.12 (m, 1H), 1.61-1.86 (m, 5H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 135.2, 118.4, 56.2, 51.8, 49.0, 47.0, 34.7, 33.5, 28.4, 25.1, 21.8. Anal. Calcd. for $C_{12}H_{19}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.64; N, 5.06. The product was determined to have >95 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 14.7 minutes (minor diastereomer), 15.5 minutes (major diastereomer)).

Synthesis of (7R, 10S)-3-ethyl-3-methyl-10-isopropyl-1-aza-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98).



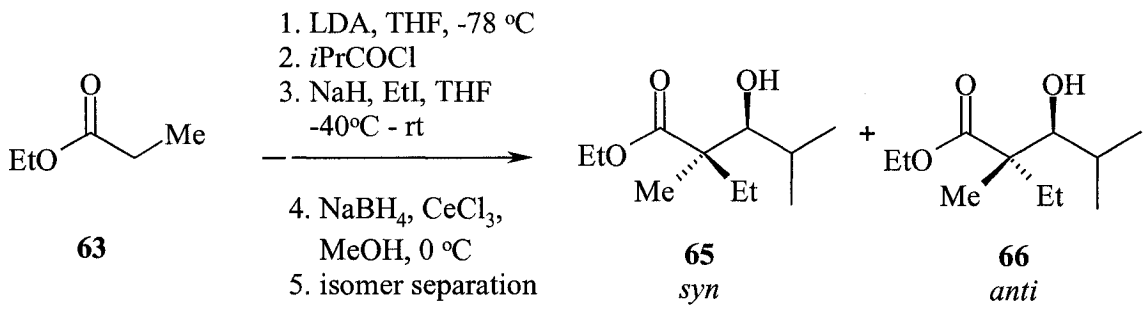
97 **98**

The alkylation was carried out at 0 °C over 24 h using ethyl iodide (382 μL, 2.0 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a white solid (525.0 mg, 90 % yield). The second alkylation was also carried out at 0 °C over 24 h using methyl iodide (175 μL, 1.3 equiv.). The reaction was purified by chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to afford the desired product as a white solid (586 mg, 87 % yield). ^{1}H NMR ($CDCl_3$) δ 5.62 (dd, 1H, J_1 = 2.19 Hz, J_2 = 9.87 Hz), 4.25-4.29 (m, 1H), 3.88-3.92 (m, 1H), 3.80-3.83 (m, 1H), 2.76-2.84 (m, 1H), 2.66-2.72 (m, 1H), 2.34-2.42 (m, 1H), 2.23-2.30 (m, 1H), 1.57-2.00 (m, 3H), 1.49 (s, 3H), 1.05 (t, 3H, J = 7.31 Hz),

0.86 (d, 3H, J = 6.95 Hz), 0.83 (d, 3H, J = 6.95 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 88.5, 63.9, 62.5, 52.2, 34.2, 32.8, 27.4, 24.4, 24.2, 19.1, 15.9, 9.0. The product was determined to have >99 % de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 150 °C, R_t = 27.3 minutes (major diastereomer), 28.9 minutes (minor diastereomer)).

Preparation of isoButyraldehyde Aldol Adduct Standards.

Acylation and Alkylation:



63 **65** *syn* **66** *anti*

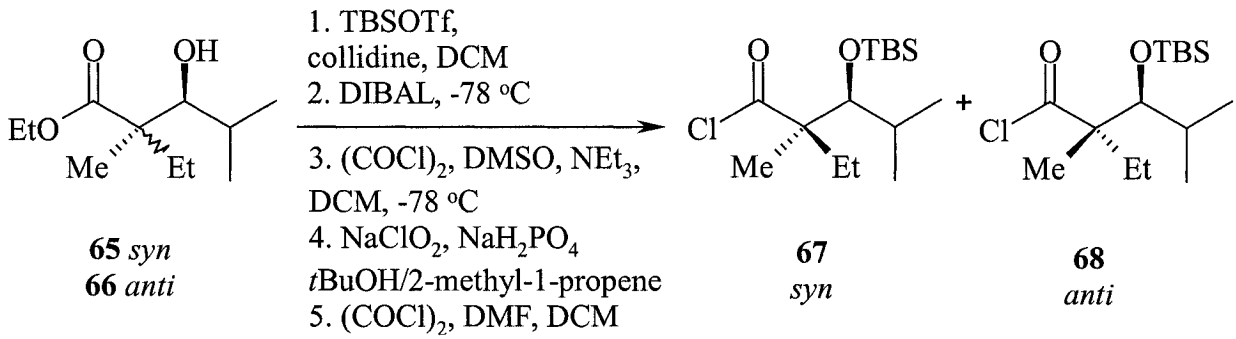
n-Butyl lithium (2.69 M solution in hexanes, 19.9 mL, 2.3 equiv.) was added to diisopropylamine (7.84 mL, 2.4 equiv.) in THF at –78 °C. After 30 minutes, ethyl propionate (5.31 mL, 2.1 equiv.) was added *via* cannula. The resulting mixture was stirred for 30 minutes, at which time isopropanoyl chloride (2.71 mL, 1.05 equiv.) was added dropwise. The solution was stirred at –78 °C for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (15 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford a colourless oil in 62 % yield. This material was then immediately alkylated. Sodium hydride (60 %w/w in hexanes, 1.05g, 1.5 equiv.) was

suspended in THF (330 mL) at room temperature. This slurry was cooled to -40 °C. The starting material (3.0 g, 17.4 mmol, 1.0 equiv.) was added as a solution in THF (20 mL) *via* cannula. This resulting mixture was stirred for 1 h at -40 °C. A solution of ethyl iodide (1.53 mL, 29.2 mmol, 1.2 equiv.) in THF (10 mL) was then added and the reaction stirred for 1 h at –40 °C followed by stirring overnight at room temperature. Saturated aqueous ammonium chloride (15 mL) was added to quench the reaction followed by extraction with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford a colourless oil in 43 % yield. ^{1}H NMR ($CDCl_3$) δ 4.11-4.16 (q, J = 7.2 Hz, 2H), 2.76-2.86 (septet, J = 6.60 Hz, 1H), 1. 88-1.97 (m, 1H), 1.68-1.77 (m, 1H), 1.28(s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 1.6 Hz, 3H), 1.01 (d, J = 1.6 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.2, 172.8, 61.1, 60.4, 37.0, 27.4, 20.7, 20.2, 18.1, 14.2, 8.7.

The α,α-disubstituted-β-keto ester (0.75g, 3.74 mmol, 1.0 equiv.) was dissolved in methanol (37 mL) at room temperature. A catalytic amount of cerium trichloride heptahydrate was then added. This solution was cooled to 0 °C. Sodium borohydride (212 mg, 5.61 mmol, 1.5 equiv.) was then added. The reaction was monitored by TLC. The reaction was quenched with acetone and allowed to warm to room temperature. The solution was concentrated using a rotary evaporator followed by extraction of the product with ethyl acetate (3x50 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 3 to 5 % ethyl acetate in hexanes, which permitted separation of the

isomers. The two products were obtained as colourless oil in a 63 % overall yield. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 4.10-4.13 (q, J = 7.0 Hz, 2H), 3.50 (d, J = 4.5 Hz, 1H), 2.25 (bs, 1H), 1.71-1.79 (m, 2H), 1.51-1.58 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.14 (s, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H) 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.8, 80.3, 60.4, 50.0, 30.7, 29.7, 21.2, 17.7, 16.6, 16.5, 14.1, 8.7. ^{1}H NMR ($CDCl_3$) δ (*anti* isomer) 4.16-4.11 (q, J = 7.25 Hz, 2H), 3.33 (bs, 2H), 2.06-1.98 (m, 1H), 1.91-1.86 (m, 1H), 1.53-1.46 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.07 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 80.6, 60.7, 49.4, 31.2, 29.4, 22.2, 17.7, 15.3, 15.1, 14.2, 8.6.

Reduction and Formation of Acid Chlorides:



65 *syn*
66 *anti*

67
syn

68
anti

The α,α-disubstituted-β-hydroxy ester isomer (300mg, 1.48 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (5 mL). 2,4,6-collidine (528 μL, 0.917 mmol, 2.7 equiv.) was then added, followed by TBSOTf (681 μL, 2.97 mmol, 2.0 equiv.). The reaction was stirred at 23 °C for 5 h. The reaction was quenched by the addition of a saturated sodium bicarbonate solution (aq) followed by the addition of hexanes (3 mL). The mixture was stirred for 20 minutes. The organic material was extracted with ethyl acetate (3x10mL) and washed with brine solution (2x5 mL). The residue was purified by

column chromatography on silica gel by eluting with 3-5 % ethyl acetate in hexanes. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 4.08-4.12 (q, J = 7.0 Hz, 2H), 3.70 (d, J = 1.5 Hz, 1H), 1.48-1.63 (m, 3H), 1.23 (t, J = 7.25, 3H), 1.05 (s, 3H), 0.90 (m, 12H), 0.85 (d, J = 7.0 Hz, 3H), 0.74 (t, J = 7.5 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.3, 83.8, 81.4, 60.4, 54.2, 32.1, 31.8, 26.6, 23.7, 18.4, 14.7, 14.1, 9.36, -2.48, -3.62. ^{1}H NMR ($CDCl_3$) δ (*anti* isomer) 4.10 (q, J = 7.3 Hz, 2H), 3.82 (s_{obs}, 1H), 1.86 (septet, J = 7.3 Hz, 1H), 1.72-1.65 (m, 1H), 1.40-1.32 (m, 1H), 1.23 (t, J = 7.3 Hz, 3H), 1.11 (s, 3H), 0.95 (d, J = 3.6 Hz, 3H), 0.87 (s, 9H), 0.84 (d, J = 3.6 Hz, 3H), 0.78 (t, J = 4.0 Hz, 3H), 0.06 (s, 3H), -0.03 (s, 3H); 176.1, 81.1, 60.1, 53.4, 29.0, 28.8, 26.2, 23.9, 18.7, 17.3, 16.5, 14.3, 9.2, -3.1, -4.5.

The TBS protected material (232 mg, 0.733 mmol, 1.0 equiv.) was then dissolved in dry toluene (5 mL) and cooled to –78 °C. DIBAL (1.5 M solution in hexanes, 2.44 mL, 5.0 equiv.) was then added *via* syringe and the mixture was stirred for 2 h. The reaction was quenched with an aqueous solution of Rochelle's salt (36.6 mmol, 10 equiv.) followed by warming to room temperature and stirring for 2 h. The organic material was extracted with diethyl ether (3x20 mL), washed with brine (1x10 mL), dried over sodium sulfate, filtered and concentrated. It was used without further purification. Oxidation of the primary alcohol was accomplished by adding a solution of dimethyl sulfoxide (304 μL, 4.29 mmol, 2.2 equiv.) in dichloromethane (1 mL) *via* syringe to a stirring solution of oxalyl chloride (204 μL, 2.34 mmol, 1.2 equiv.) in dichloromethane (10 mL) at –78 °C. The mixture was stirred for 20 minutes at –78 °C before addition of the alcohol (536 mg, 1.95 mmol, 1.0 equiv) in dichloromethane (2 mL). After stirring for 1.5 h at –78 °C, dry

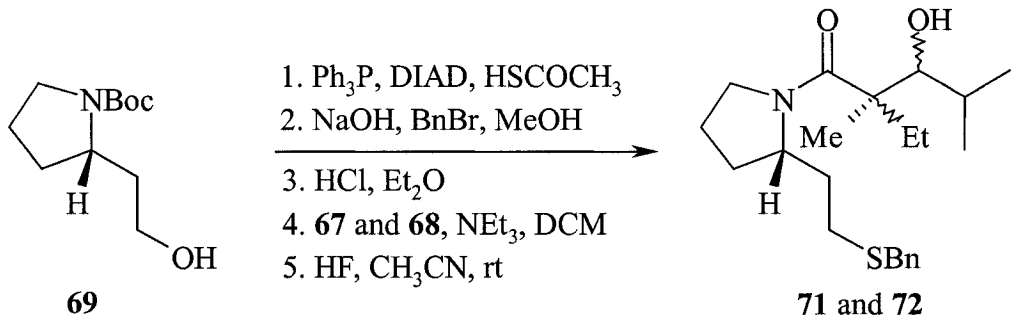
triethylamine (1.08 mL, 7.80 mmol, 4.0 equiv.) was added and the reaction was allowed to warm to 23 °C. The mixture was extracted with aqueous hydrochloric acid solution (1M), distilled water (1x10 mL), and brine (1x10mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 3.60 (d, J = 2.0 Hz, 1H), 1.77-1.85 (doublet of septet, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 1.67-1.76 (m, 1H), 1.46-1.55 (m, 1H), 1.02 (s, 3M), 0.92 (d, J = 7.2 Hz, 3H), 0.90 (s, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.78 (t, J = 7.80 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.0, 81.3, 55.1, 30.5, 26.3, 25.7, 23.0, 18.8, 17.3, 15.8, 8.4, -2.9, -3.8. ^{1}H NMR ($CDCl_3$) δ (*anti* isomer) 9.57 (s, 1H), 1.89-1.81 (septet, J = 6.8 Hz, 1H), 1.67-1.60 (m, 1H), 1.45-1.37 (m, 1H), 0.93 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.84 (s, 3H), 0.77 (d, J = 7.7, 3H), 0.71 (t, J = 7.8 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.1, 80.6, 55.0, 29.6, 26.5, 26.2, 23.0, 18.7, 16.7, 14.1, 8.2, -3.2, -3.9.

The aldehyde (523 mg, 1.92 mmol, 1.0 equiv.), sodium chlorite (521 mg, 5.76 mmol, 3.0 equiv.) and sodium dihydrogen phosphate monohydrate (1.59 g, 11.5 mmol, 6.0 equiv) were dissolved in *tert*-butanol (20 mL) and water/2-methyl-1-propene (7.8 mL and 7.8mL). The solution was stirred overnight at 23 °C. The reaction was diluted with distilled water and the organic material extracted with ethyl acetate (3x20 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. The carboxylic acid was used without further purification. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 3.69 (d, J = 1.8 Hz, 1H), 1.60-1.76 (m, 2H), 1.58-1.49 (m, 1H), 1.24 (s, 3H), 0.93 (d, J = 8.5 Hz, 3H), 0.90 (s, 9 H), 0.86 (d, J = 8.5 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.9, 81.2, 53.1, 31.5, 31.0, 30.5, 26.3, 23.2, 18.7,

17.8, 15.1, 8.8, -2.9, -4.0. ^{1}H NMR (C_6D_6) δ (*anti* isomer) 3.74 (s, 1H), 1.96-1.90 (m, 1H), 1.77-1.70 (m, 1H), 1.42-1.35 (m, 1H), 1.09 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.90-0.83 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 180.5, 82.2, 52.0, 30.3, 29.7, 26.2, 22.9, 18.6, 16.9, 16.6, 8.7, -3.2, -4.2.

The acid chloride coupling partner was formed by dissolving the carboxylic acid (100 mg, 0.347 mmol, 1.0 equiv.) in dichloromethane (3.5 mL) and N,N-dimethylformamide (10 %v/v in dichloromethane, 0.069 mmol, 0.02 equiv.). Oxalyl chloride (42 μL, 0.485 mmol, 1.4 equiv.) was slowly added. Gas evolution was observed. The reaction was stirred for 3.5 h at 23 °C. The solution was concentrated and used without purification.

Coupling:



69 **71** and **72**

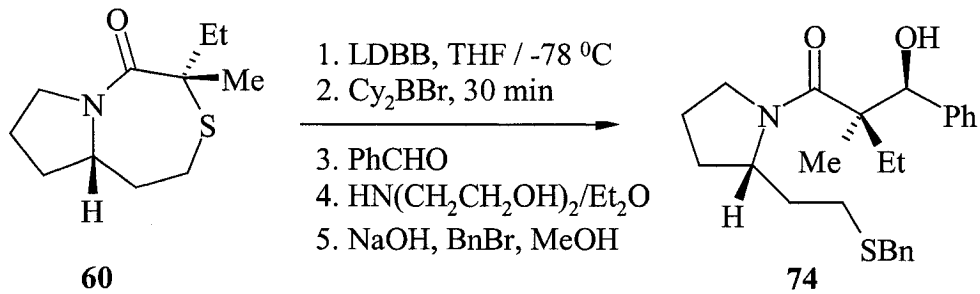
Triphenylphosphine (1.83 g, 6.97 mmol, 2.0 equiv.) was dissolved in dry tetrahydrofuran (20 mL) and cooled to 0 °C. DIAD (1.37 mL, 6.97 mmol, 2.0 equiv.) was added to the above, vigorously stirring solution. After 45 minutes of stirring at 0 °C, a solution of the homologated alcohol **69** (750 mg, 3.48 mmol, 1.0 equiv.), thioacetic acid (498 μL, 6.97 mmol, 2.0 equiv.) in tetrahydrofuran (6 mL) was added via cannula. The reaction was stirred for 1.5 h at 0 °C, followed by warming to 23 °C and stirring an additional hour.

The reaction was concentrated. The residue was purified by column chromatography on silica gel by eluting with 20-100 % ethyl acetate in hexanes. The thioester (26 mg, 0.095 mmol, 1.0 equiv.) was placed under an argon atmosphere. Methanol (1 mL) was added *via* syringe, followed by benzyl bromide (56 μL, 0.475 mmol, 5.0 equiv.) and sodium hydroxide (2M, 95 μL, 2.0 equiv.). The solution was stirred overnight at 23 °C. The reaction was quenched by the addition of saturated ammonium chloride (aq). The organic material was extracted with ethyl acetate (3x5 mL). The combined organic layers were washed with brine (1x5 mL), dried over sodium sulfate, filtered and concentrated. ^{1}H NMR ($CDCl_3$) δ 7.18-7.32 (m, 5H), 3.77-3.85 (m, 1H), 3.72 (s_{obs}, 2H), 3.22-3.39 (m, 2H), 2.39 (bs, 2H), 1.75-2.05 (m, 4H), 1.49-1.63 (m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.5, 138.3, 128.7, 128.4, 126.8, 79.2, 56.5, 46.2, 36.3, 34.2, 30.4, 28.6, 28.1, 23,4. LRAPCIMS *m/z* (M+H) 322.49 $C_{18}H_{28}NO_2S^+$ requires 322.18.

tert-Butyloxycarbonyl deprotection was accomplished by dissolving the starting material (115 mg, 0.358 mmol, 1.0 equiv.) in diethyl ether (2 mL). This solution was then added to a solution of diethyl ether (30 mL) purged with HCl (g). The reaction was stirred for 1.5 h followed by concentration. The protonated material was used without purification. It was immediately dissolved in dry dichloromethane (1.0 mL). The acid chloride prepared above (0.347 mmol, 1.0 equiv.) in dry dichloromethane (1.5 mL) was added *via* cannula. Triethylamine (50 μL, 0.347 mmol, 4.0 equiv.) was then slowly added to the vigorously stirring solution, which was then stirred overnight at 23 °C. The reaction was quenched by the addition of aqueous hydrochloric acid (1M, 3x500 μL). The organic material was extracted with dichloromethane (3x5 mL), dried over sodium sulfate,

filtered and concentrated. The *tert*-butyldimethylsilyl protecting group was then removed from the coupled product by dissolving the starting material (20 mg, 1.0 equiv.) in acetonitrile (100 μL) and adding hydrofluoric acid (30 % solution in acetonitrile, 200 μL). The reaction was complete in 3 h at 23 °C and was quenched by the addition of saturated solution of calcium chloride (2 mL). This mixture was stirred overnight. The organic material was extracted with dichloromethane (3x5 mL), washed with brine (1x5 mL), dried over sodium sulfate, filtered and concentrated. ^{1}H NMR ($CDCl_3$) δ 7.19-7.36 (m, 5H), 4.13-4.29 (m, 1H), 3.59-3.74 (m, 4H), 3.42-3.55 (m, 2H), 2.31-2.44 (m, 2H), 2.06-2.20 (m, 1H), 1.74-1.89 (m, 4H), 1.46-1.60 (m, 4H), 1.18-1.26 (m, 4H), 0.73-1.10 (m, 9H); LREIMS *m/z* (M^+) 377.59 $C_{22}H_{35}NO_2S^+$ requires 377.3.

Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (74).

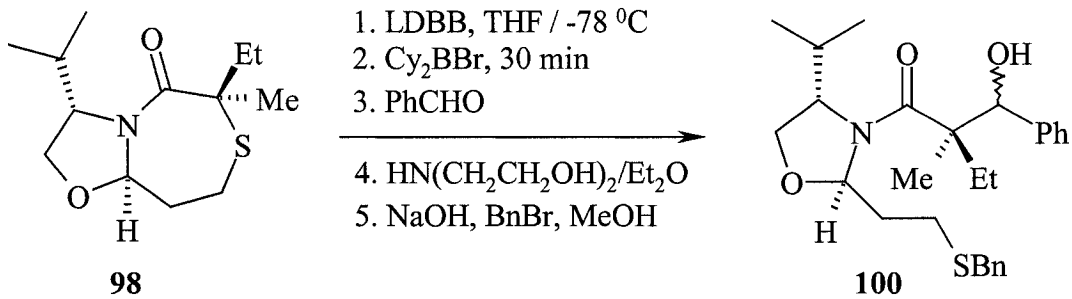


60 **74**

A solution of LDBB in THF was added dropwise via gas syringe to a solution of lactam (99.3 mg, 1.0 equiv.) in THF in a Schlenk flask at –78 °C until the green colour persisted of LDBB persisted. Dicyclohexylboron bromide (203 μL, 2.0 equiv.) was then immediately added dropwise *via* syringe. The solution colour changed from green to red and this solution was stirred for 30 min at –78 °C. Benzaldehyde (95 μL, 2.0 equiv.) was then added dropwise and the resulting mixture was stirred for 2 h at –78 °C, at which

point a saturated solution of ammonium chloride was added to quench the reaction. The product was extracted using ethyl acetate (3 x 20 mL) and the organic layer was dried with anhydrous sodium sulfate. Boron decomplexation was accomplished by stirring the crude product with diethanolamine (196 μL, 4.4 equiv.) in diethyl ether (10 mL) for 2 h at room temperature. The organic layer was then extracted from the solid material using a pipette and the ether was removed using the rotary evaporator. The solid crude material was suspended in reagent grade methanol (15 mL). Benzyl bromide (68 μL, 1.2 equiv.) and 2 M NaOH (349 μL, 1.5 equiv.) were added and the reaction was stirred for 45 min at room temperature. The reaction was quenched with saturated ammonium chloride solution and the material extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with distilled water (1 x 30 mL) and dried over anhydrous sodium sulfate. The material was purified by column chromatography by elution with 10-20 % ethyl actetate/hexanes to afford 154 mg of product (81 % yield). ^{1}H NMR ($CDCl_3$, 23°C) δ 7.22-7.37 (m, 10 H), 4.96 (m, 1H), 4.27 (m, 1H), 3.94 (m, 1H), 3.74 (m, 2H), 3.28 (m, 2H), 2.38-2.42 (t_{obs}, 2H, J_{obs} = 7.7 Hz), 2.19 (m, 1H), 1.88-2.07 (m, 1H, J = 7.2 Hz), 1.4 – 1.84 (m, 6H), 1.13 (s, 3H), 0.89-0.93 (t_{obs}, 3H, J_{obs} = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 174.8, 140.4, 138.2, 128.7, 128.4, 128.0, 127.5, 127.4, 126.8, 79.9, 59.1, 52.3, 47.4, 47.2, 36.2, 29.8, 28.3, 28.2, 25.2, 21.2, 19.5, 10.1; HREIMS *m/z* ($M^{+\cdot}$) 411.2232 $C_{25}H_{33}NO_2S^{+}$ requires 411.2224. The product was determined to have >94 % de (*syn* isomer) and *syn*:*anti* isomer as determined by HPLC by elution with 4 % *i*PrOH/hexanes. Retention times were 19.2 min, 21.6 min, 26.9 min, 48.7 min.

Synthesis of (2R, 5S)-*N*-(2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-5-isopropyloxazolidine (100).

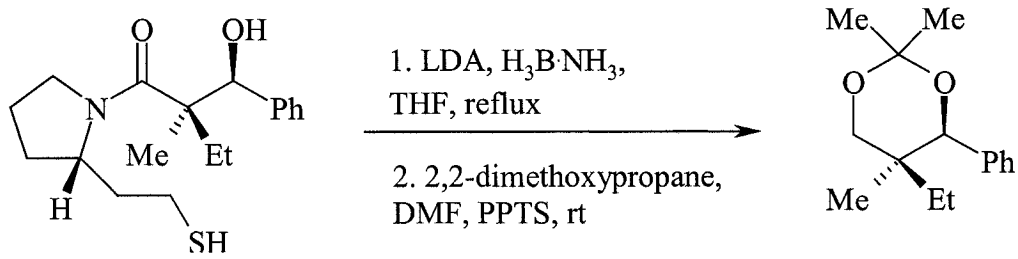


98 **100**

A solution of LDBB in THF was added dropwise via gas syringe to a solution of lactam (53.3 mg, 1.0 equiv.) in THF in a Schlenk flask at –78 °C until the green colour persisted of LDBB persisted. Dicyclohexylboron bromide (47.3 μL, 1.1 equiv.) was then immediately added dropwise *via* syringe and this solution was stirred for 30 min at –78 °C. Benzaldehyde (44 μL, 2.0 equiv.) was then added dropwise and the resulting mixture was stirred for 2 h at –78 °C, at which point a saturated solution of ammonium chloride was added to quench the reaction. The product was extracted using ethyl acetate (3 x 10 mL) and the organic layer was dried with anhydrous sodium sulfate. Boron decomplexation was accomplished by stirring the crude product with diethanolamine (96 μL, 4.4 equiv.) in diethyl ether (5 mL) for 2 h at room temperature. The organic layer was then extracted from the solid material using a pipette and the ether was removed using the rotary evaporator. The solid crude material was suspended in reagent grade methanol (15 mL). Benzyl bromide (42 μL, 1.2 equiv.) and 2 M NaOH (155 μL, 1.5 equiv.) were added and the reaction was stirred for 45 min at room temperature. The reaction was quenched with saturated ammonium chloride solution and the material extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with distilled water (1 x 5 mL) and dried over anhydrous sodium sulfate. The material was purified by

column chromatography by elution with 10-20 % ethyl acetate/hexanes (54 mg, 58 % yield). The product (54 mg, 1.0 equiv.) was acylated with acetic anhydride (51 μL, 4.5 equiv.), pyridine (48 μL, 5.0 equiv.) and catalytic DMAP in dichloromethane. The clear, yellow solution was stirred overnight at 23 °C. The reaction was quenched with saturated ammonium chloride solution and the material extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with distilled water (1 x 5 mL) and dried over anhydrous sodium sulfate. ^{1}H NMR (C_6D_6, 23 °C) δ 7.42 (d, 2H, J = 7.2 Hz), 7.25 (d, 2H, *J* = 7.2 Hz), 7.00-7.11 (m, 6H), 6.77 (s, 1H), 5.61 (d, 1H, *J* = 8.7 Hz), 3.49-3.60 (m, 3H), 3.43 (d, 1H, *J* = 9.3 Hz), 3.16-3.21 (m, 1H), 2.25-2.43 (m, 2H), 2.02-2.09 (m, 2H), 1.68 (s, 3H), 1.24-1.66 (m, 3H), 1.20 (s, 3H), 1.07 (t, 3H, *J* = 7.5 Hz), 0.61 (d, 3H, *J* = 6.9 Hz), 0.51 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 171.6, 169.3, 138.1, 137.5, 128.7, 128.3, 127.6, 126.8 83.5, 79.3, 79.2, 60.8, 52.5, 36.4, 30.3, 27.4, 27.0, 21.3, 19.6, 18.0, 15.6, 9.5. The product was determined to have >99 % de (*syn* isomer) and *syn*:*anti* isomer of 91:9 as determined by HPLC by elution with 5 % *i*PrOH/hexanes. Retention times were 11.6 min, 15.2 min, 16.6 min, 18.1 min.

Synthesis of the acetonide of (2R, 3S)-2-ethyl-2-methyl-1,3-hydrocinnamyl diol (85).

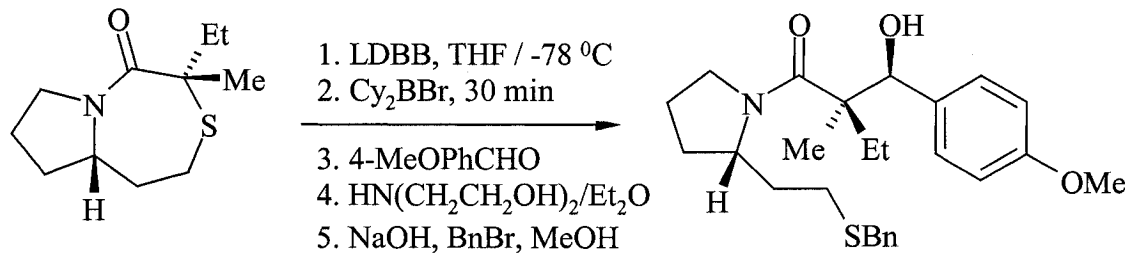


83 **85**

A 2.57 M solution of *n*-butylithium in hexanes (544 μL, 5.8 equiv.) was slowly added to a stirred solution of diisopropylamine (210 μL, 6.2 equiv.) in 1.0 mL tetrahydrofuran at 0 °C. After stirring for 10 minutes, borane-ammonia complex (45 mg, 6.0 equiv., 90 % tech. grade) was added in one portion. After stirring for 15 minutes at 0 °C, the mixture was warmed to 23 °C and a solution of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (78 mg, 1.0 equiv.) in 2.0 mL tetrahydrofuran was added *via* cannula. The mixture was heated to reflux for 24 hours, then cooled to 0 °C and quenched with aqueous hydrochloric acid (3 M, 3 mL). The resulting mixture was warmed to 23 °C and stirred for 30 minutes, at which point aqueous sodium hydroxide (3M, 6 mL) was added. The mixture was stirred at 23 °C for 30 minutes and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography using 10-20 % ethyl acetate/hexanes afforded 20 mg of diol (42 % yield). This material was then converted to the acetonide by stirring in 2,2-dimethoxypropane/DMF (3:2, 3 mL) with a catalytic amount of pyridium *p*-toluenesulfonate at room temperature for 12 h. The mixture was quenched by addition of saturated aqueous sodium bicarbonate and the product was extracted with 2:1 hexanes/ether. The combined organic layers were washed with water (2 x 10 mL), dried over sodium sulfate and concentrated in vacuo. Column

chromatography on silica gel eluting 5 % ethyl acetate/hexanes afforded 22 mg of the desired acetonide (90 % yield). Isomer mixture: ^{1}H NMR (C_6D_6) δ (*syn* isomer) 7.29_3-7.29_7 (d, 2H, J = 1.6 Hz), 7.05-7.15 (m, 3H), 4.57 (s, 1H), 3.56-3.59 (d, 1H, J = 11.6 Hz), 3.35-3.59 (dd, 1H, J_1 = 11.6 Hz, J_2 = 1.2 Hz), 2.13-2.22 (dq, 1H, J = 7.2 Hz), 1.57 (s, 3H), 1.31 (s, 3H), 0.76-0.85 (ddq, 1H, J_1 = 1.2 Hz, J_2 = 7.2 Hz), 0.63-0.66 (t_{obs}, 3H, J_{obs} = 7.2 Hz), 0.41 (s, 3H); ^{13}C NMR (C_6D_6) δ 138.8, 128.3, 127.6, 127.4, 98.9, 81.0, 67.0, 36.7, 30.3, 22.0, 19.1, 18.7, 7.9; (*anti* isomer) 7.295-7.298 (d, 2H, J = 1.53 Hz), 7.04-7.15 (m, 3H), 4.55 (s, 1H), 3.56-3.59 (d, 1H, J = 11.5 Hz), 3.44-3.47 (d, 1H, J = 11.5 Hz), 1.58 (s, 3H), 1.31 (s, 3H), 0.92- 0.98 (m, 5H), 0.45-0.51 (t_{obs}, 3H, J_{obs} = 7.3 Hz); ^{13}C NMR (C_6D_6) δ 139.1, 128.4, 127.6, 127.5, 98.9, 79.7, 69.9, 36.8, 30.2, 28.8, 19.2, 15.9, 7.1; HRCIMS *m/z* (M+H) 235.1698 $C_{15}H_{23}O_2^+$ requires 235.1702.

Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-3-(4-methoxyphenyl)-propanoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (75).

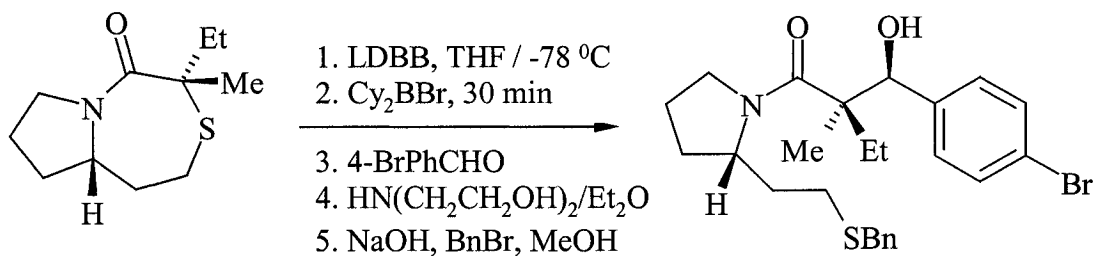


60 **75**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (198 μL, 2.0 equiv.) and 4-methoxybenzaldehyde (110 μL, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 164 mg of product (83 % yield). The product was determined to have a 91:9 *syn*/*anti* ratio with 98

% de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 30.9 min, 38.7 min, 40.1 min, 54.1 min. ^{1}H NMR ($CDCl_3$, 23 °C) δ 7.22-7.31 (m, 7H), 6.82-6.84 (d, 2H, J = 8.4 Hz), 4.91 (s, 1H), 4.17-4.26 (m, 1H), 3.94 (m, 1H), 3.61- 3.79 (m, 5H), 3.32-3.48 (m, 2H), 2.38-2.42 (t_{obs}, 2H, J_{obs} = 7.3 Hz), 2.13-2.27 (m, 1H), 1.96-2.04 (m, 1H, J_{obs} = 6.9 Hz), 1.68-1.86 (m, 3H), 1.11 (s, 3H), 0.88-0.92 (t_{obs}, 3H, J_{obs} = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 175.0, 158.7, 138.2, 132.6, 129.0, 128.7, 128.3, 126.8, 112.9, 79.4, 59.0, 55.2, 52.3, 47.2, 36.1, 32.7, 28.3, 28.1, 25.2, 19.5, 10.1; HREIMS *m/z* ($M^{+\cdot}$) 441.2337 $C_{26}H_{35}NO_3S^+$ requires 441.2348.

Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-3-(4-bromophenyl)-propanoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (76).

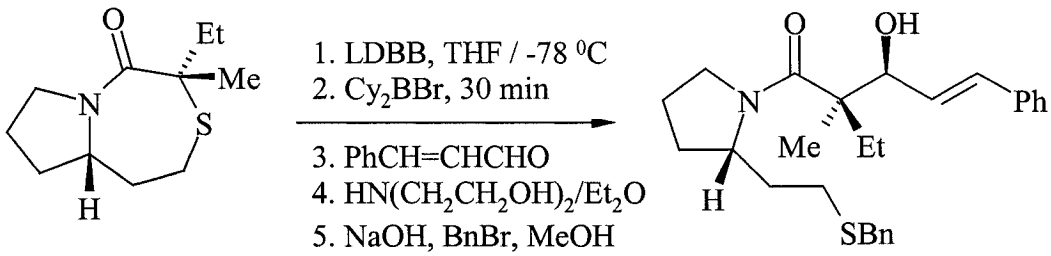


60 **76**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (201 μL, 2.0 equiv.) and 4-bromobenzaldehyde (171 mg, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 184 mg of product (81 % yield). The product was determined to have a 93:7 *syn/anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 21.1 min, 23.1 min 27.3 min. 31.9 min. ^{1}H NMR ($CDCl_3$, 23 °C) δ 7.42-7.44 (d_{obs}, 2 H, J_{obs} = 8.6 Hz), 7.30-7.31 (m, 3 H), 7.23-7.25 (m, 4H), 4.93 (s, 1H),

4.09- 4.29 (m, 2 H), 3.75 (s, 2H), 3.34-3.37 (t_{obs}, 2H, J_{obs} = 5.8 Hz), 2.39-2.43 (t_{obs}, 2H, J_{obs} = 7.4 Hz), 2.18-2.21 (m, 1H), 1.72-1.97 (m, 4H), 1.40-1.53 (m, 3H), 1.10 (s, 3H), 0.89-0.92 (t_{obs}, 3H, J_{obs} = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 174.7, 139.6, 138.3, 130.6, 130.4, 129.8, 128.8, 128.4, 128.1, 126.8, 121.3, 79.4, 59.1, 52.0, 47.3, 36.3, 32.8, 28.3, 28.2, 28.0, 25.2, 19.7, 14.3, 10.1; HREIMS *m/z* ($M^{+\cdot}$) 489.1337 $C_{25}H_{32}BrNO_2S^+$ requires 489.1346.

Synthesis of (2*S*)-*N*-(*trans*-(2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-5-phenyl-pent-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (77).

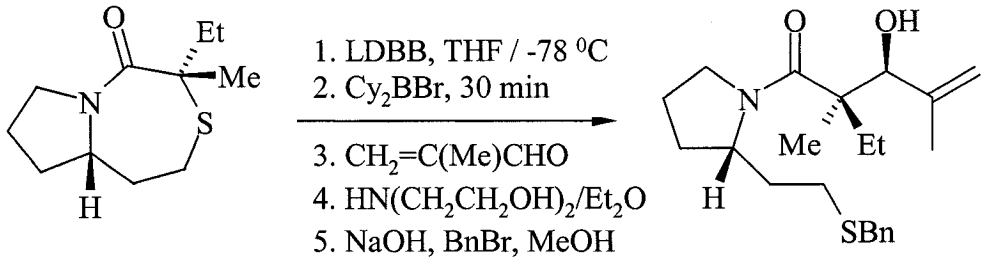


60 **77**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (198 μL, 2.0 equiv.) and *trans*-cinnimaldehyde (115 μL, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 126 mg of product (63 % yield). The product was determined to have a 91:9 *syn*/*anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 39.6 min., 59.0 min., 60.0 min., 65.0 min. ^{1}H NMR ($CDCl_3$, 60 °C) δ 7.19-8.30 (m, 10 H), 6.63-6.67 (m, 1H, J = 15.9 Hz), 6.33-6.39 (dd, 1H, J_{trans} =15.9 Hz, J = 6.7 Hz), 4.41-4.42 (d, 1H, J = 5.9 Hz), 4.27-4.34 (m, 1H), 3.64-3.76 (m, 3 H), 3.43-3.55 (m, 1H), 2.42-2.46 (t_{obs}, 2H, J_{obs} = 7.5 Hz), 2.12-2.20 (m, 1H), 1.25–1.99 (m, 8H),

0.93-0.97 (t_{obs}, 3H, J_{obs} = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 175.0, 138.2, 136.9, 132.0, 128.8, 128.6, 128.4, 128.35, 127.4, 126.8, 126.4, 79.0, 58.7, 50.9, 47.2, 36.1, 32.8, 28.3, 28.1, 27.6, 25.4, 9.9; HREIMS *m/z* ($M^{+\cdot}$) 437.2388 $C_{27}H_{35}NO_2S^+$ requires 437.2397.

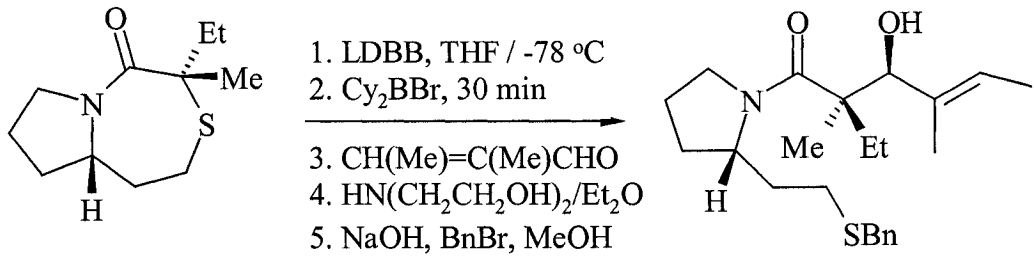
Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-4-methyl-pent-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (78).



60 **78**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (208 μL, 2.0 equiv.) and methacrolein (120 μL, 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 89 mg of product (49 % yield). The product was determined to have a 98:2 *syn/anti* ratio with 95 % de (*syn* isomer) by HPLC analysis by eluting with 2 % 2-propanol/hexanes. The retention times were: 17.0 min., 21.4 min., 22.7 min., 23.8 min. ^{1}H NMR ($CDCl_3$, 23 °C) δ 7.20-7.35 (m, 5H), 4.98 (s, 2H), 4.22-4.27 (m, 2H), 3.62-3.77 (m, 2H), 3.45-3.51 (m, 1H), 2.38-2.42 (t_{obs}, 2H, J_{obs} = 7.3 Hz), 1.71-2.18 (m, 8H), 1.42-1.59 (m, 3H), 1.19-1.39 (m, 4H), 0.88-0.91 (t_{obs}, 3H, J_{obs} = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 175.0, 145.1, 138.3, 128.8, 128.3, 126.8, 114.5, 80.9, 58.9, 51.0, 47.4, 36.1, 32.7, 28.6, 28.4, 28.1, 25.4, 20.8, 20.1, 9.8; HREIMS *m/z* ($M^{+\cdot}$) 375.2232 $C_{22}H_{34}NO_2S^+$ requires 375.2239.

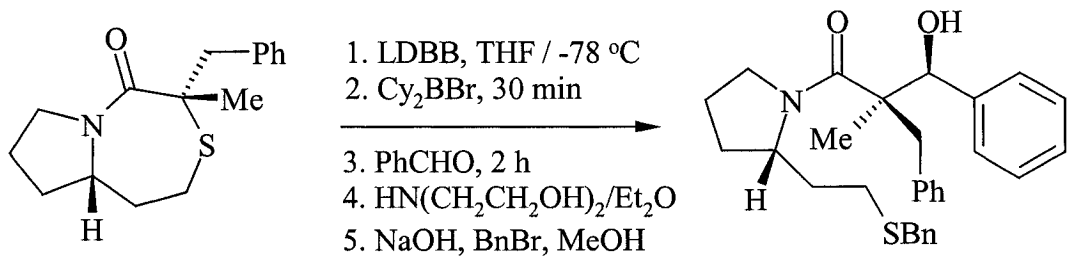
Synthesis of (2*S*)-*N*-(*trans*-(2*R*, 3*S*)-2-ethyl-2-methyl-3-hydroxy-4-methyl-hex-4-enoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (79).



60 **79**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (350 μL, 2.0 equiv.) and 2.0 equiv. of tiglic aldehyde (233 μL, 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford the product in 95 % yield. The product was determined to have a 91:9 *syn/anti* ratio with 91 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 11.2 min., 12.8 min., 14.4 min., 15.7 min.. ^{1}H NMR ($CDCl_3$, 23 °C) δ 7.18- 7.51 (m, 5H), 5.46-5.51 (q_{obs}, 1H, J_{obs} = 6.4 Hz), 4.18-4.34 (m, 2H), 6.65-3.79 (m, 3H), 3.43-3.59 (m, 1H), 2.40-2.44 (t_{obs}, 2H, J_{obs} = 7.73 Hz), 2.09-2.17 (m, 1H), 1.98-2.07 (m, 1H, J = 7.3 Hz), 1.77-1.93 (m, 3H), 1.61-1.67 (m, 6H), 1.43-1.59 (m, 3H), 1.18 (s, 3H), 0.85-0.88 (t_{obs}, 3H, J_{obs} = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ 175.1, 138.2, 135.3, 128.7, 128.3, 126.5, 123.6, 82.7, 58.9, 51.6, 47.4, 36.1, 32.7, 28.7, 28.4, 28.1, 25.4, 20.3, 14.1, 13.3, 9.8; HRCIMS *m/z* (M+H) 390.2467 $C_{23}H_{36}NO_2S^+$ requires 390.2471.

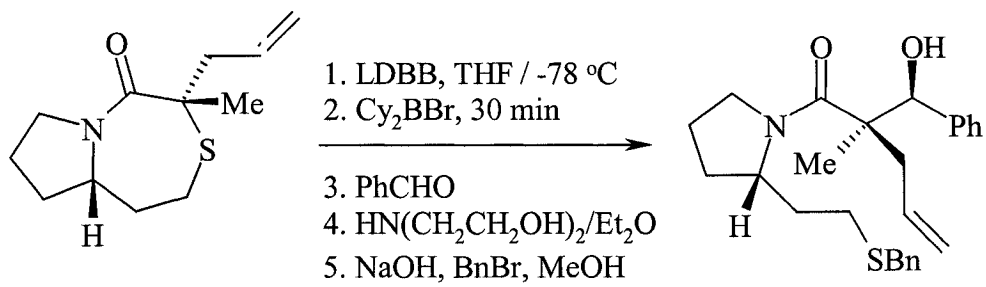
Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-benzyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (80).



51 **80**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (159 μL, 2.0 equiv.) and benzaldehyde (74 μL, 2.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 158 mg of product (91 % yield). The product was determined to have a 91:9 *syn/anti* ratio with 99 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 24.2 min., 28.2 min., 31.5 min., 38.2 min. ^{1}H NMR ($CDCl_3$, 23 °C) δ 7.12-7.51 (m, 15H), 5.07 (s, 1H), 4.11-4.30 (m, 2H), 3.62-3.84 (m, 3H), 2.58-2.81 (m, 3H), 2.13-2.38 (m, 3H), 1.02-1.76 (m, 9H); ^{13}C NMR ($CDCl_3$, 23 °C) δ 174.2, 140.6, 138.3, 138.1, 130.7, 128.8, 128.3, 127.9, 127.7, 127.6, 127.5, 126.8, 126.1, 79.2, 59.5, 53.7, 47.3, 42.5, 36.0, 31.9, 28.0, 27.7, 24.8, 18.2; HRCIMS *m/z* (M+H) 474.2467 $C_{30}H_{36}NO_2S^+$ requires 474.2460.

Synthesis of (2*S*)-*N*-((2*R*, 3*S*)-2-allyl-2-methyl-3-hydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine (81).

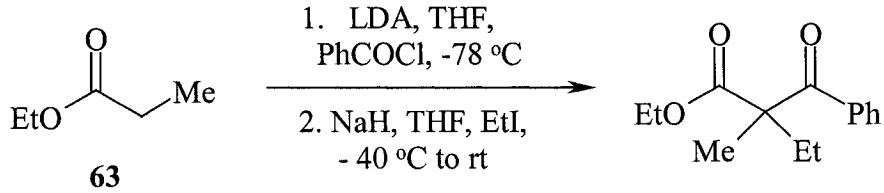


61 **81**

The aldol reaction was carried out at –78 °C over 2 h using Cy_2BBr (196 μL, 2.0 equiv.) and benzaldehyde (137 μL, 3.0 equiv.). The reaction was purified by column chromatography on silica gel eluting with 5-15 % ethyl acetate/hexanes to afford 136 mg of product (71 % yield). The product was determined to have a 92:8 *syn*/*anti* ratio with 91 % de (*syn* isomer) by HPLC analysis by eluting with 4 % 2-propanol/hexanes. The retention times were: 18.5 min., 21.0 min., 24.5 min., 40.9 min. ^{1}H NMR ($CDCl_3$, 23 °C) 7.10-7.37 (m, 10H), 5.75-5.85 (m, 1H), 4.98-5.05 (m, 3H), 4.25 (s_{obs}, 1H), 3.98 (s_{obs}, 1H), 3.75 (s_{obs}, 2H), δ 3.28-3.34 (m, 1H), 3.05-3.14 (m, 1H), 2.84-2.89 (dd, 1H, J_1 = 4.3 Hz, J_2 = 6.0 Hz) 2.37-2.2.41 (t_{obs}, 2H, J_{obs} = 7.5 Hz), 2.05-2.22 (m, 2H), 1.18-1.15 (m, 7H), ^{13}C NMR ($CDCl_3$, 23 °C) δ 174.4, 140.3, 138.3, 135.2, 128.7, 128.3, 128.0, 127.6, 127.4, 126.8, 117.0, 79.3, 59.0, 51.9, 47.3, 40.6, 36.2, 32.7, 28.3, 28.1, 25.1, 19.2; HRCIMS *m/z* (M+H) 424.2310 $C_{26}H_{34}NO_2S^+$ requires 424.2314.

Preparation of Acetonide Standards.

Acylation and Alkylation.

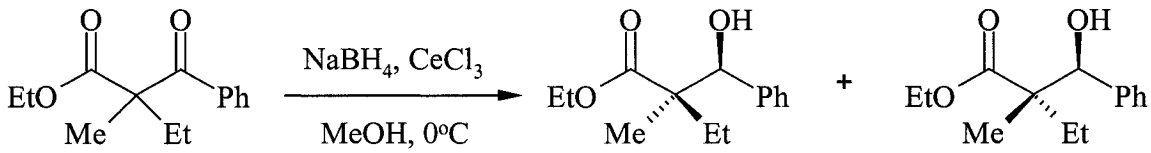


63

A 2.69 M solution of *n*-butyllithium in hexanes (19.9 mL, 2.3 equiv.) was added to diisopropylamine (7.84 mL, 2.4 equiv.) in THF at –78 °C. After 30 minutes, ethyl propionate (5.31 mL, 2.1 equiv.) was added *via* cannula. The resulting mixture was stirred for 30 minutes, at which time benzoyl chloride (2.71 mL, 1.05 equiv.) was added dropwise. The solution was stirred at –78 °C for 3 h, until TLC showed no reaction progress. Saturated aqueous ammonium chloride (15 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford a colourless oil in 62 % yield. This material was then immediately alkylated. Sodium hydride (3.0 g, 1.0 equiv.) was suspended in THF (250 mL) at room temperature. This slurry was cooled to -40 °C. The starting material (3.0 g, 1.0 equiv.) was added as a solution in THF (20 mL) *via* cannula. This resulting mixture was stirred for 1 h at -40 °C. A solution of ethyl iodide (3.42 mL, 1.2 equiv.) in THF (10 mL) was then added and the reaction stirred for 1 h at –40 ^{0}C followed by stirring overnight at room temperature. Saturated aqueous ammonium chloride (15 mL) was added to quench the reaction followed by extraction with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and

concentrated. The residue was purified by chromatography on silica gel eluting with 5 % ethyl acetate in hexanes to afford a colourless oil in 43 % yield. ^{1}H NMR ($CDCl_3$) δ 7.79-7.81 (d, 2H, J = 9.6 Hz), 7.45-7.50 (m, 1H), 7.34-7.40 (m, 2H), 4.05-4.12 (q, 2H, J = 9.2 Hz), 2.02-2.09 (q, 2H, J = 10.0 Hz), 1.49 (s, 3H), 1.01-1.06 (t, 3H, J = 9.2 Hz), 0.79-0.84 (t, 3H, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$) δ197.5, 174.2, 135.6, 132.4, 128.3, 128.2, 61.2, 57.3, 29.3, 20.5, 13.9, 8.3.

Reduction and Separation.



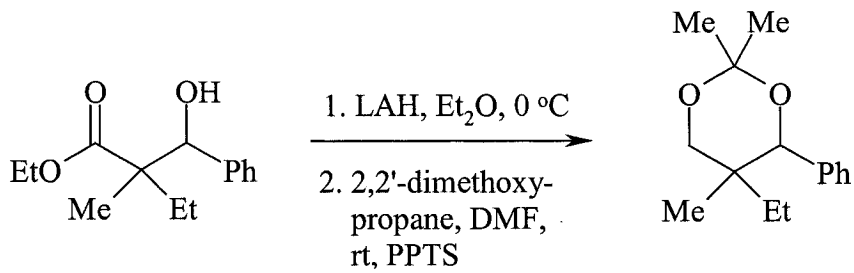
86
syn isomer

87
anti isomer

The α,α-disubstituted-β-keto ester (300 mg, 1.0 equiv.) was dissolved in methanol (1.5 mL) at room temperature. A catalytic amount of cerium trichloride heptahydrate was then added. This solution was cooled to 0 °C. Sodium borohydride (72.6 mg, 1.5 equiv.) was then added. The reaction was monitored by TLC. The reaction was quenched with acetone and allowed to warm to room temperature. The solution was concentrated using a rotary evaporator followed by extraction of the product with ethyl acetate (3x10 mL).The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel eluting with 3 to 5 % ethyl acetate in hexanes, which permitted separation of the isomers. The two products were obtained as colourless oil in a 63 % overall yield. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 7.25-7.30 (m, 5H), 4.87$_5$-4.88 (d, 1H, J = 3.6 Hz), 4.11-4.17 (q, 2H, J = 7.2

Hz), 3.10-3.11 (d, 1H, J = 3.6 Hz), 1.93-2.02 (m, 1H, J = 7.2 Hz), 1.44-1.53 (m, 1H, J = 7.2 Hz), 1.23-1.27 (t_{obs}, 3H, J_{obs} = 7.2 Hz), 1.01 (s, 3H), 0.86-0.90 (t, 3H, J = 7.6 Hz); ^{1}H NMR ($CDCl_3$) δ (*anti* isomer) 7.25-7.32 (m, 5H), 4.88 (s, 1H), 4.17-4.23 (dq, 2H, J_1 = 1.60 Hz, J_2 = 1.80 Hz), 3.1 (s, 1H), 1.76-1.85 (m, 1H, J = 7.20 Hz), 1.25-1.31 (m, 4H), 1.05 (s, 3H), 0.83-0.87 (t, 3H, J = 7.60 Hz); ^{13}C NMR ($CDCl_3$) δ 176.6, 140.2, 127.6, 127.5, 127.4, 76.7, 60.8, 52.1, 30.0, 15.6, 14.4, 9.0.

Reduction and Formation of Acetonides.



86 and **87** **88** and **89**

The *syn* α,α-disubstituted-β-hydroxy ester isomer (35 mg, 1.0 equiv.) was dissolved in diethyl ether (1.5 mL). The solution was cooled to 0 °C. Lithium aluminum hydride (16.8 mg, 3.0 equiv.) was then added. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of distilled water (35 μL), 15 % NaOH (35 μL) and distilled water (105 μL). The mixture was allowed to stir for 30 minutes at room temperature. Anhydrous magnesium sulfate was then added and the resulting slurry was stirred for an additional 30 minutes. Filtration through a frit funnel containing celite separated the solid and liquid phases. The solvent was removed and the isolated material was used without further purification. The colourless oil was obtained in a 72 % yield. ^{1}H NMR ($CDCl_3$) δ (*syn* isomer) 7.24-7.35 (m, 5H), 4.65-4.66 (d, 1H, J = 2.5 Hz), 3.60-3.64 (dd, 1H, J_1 = 5.4 Hz, J_2 = 10.8 Hz),

3.53-3.54 (d, 1H, J = 1.6 Hz), 3.44-3.45 (dd, 1H, J_1 = 4.0 Hz, J_2 = 11.0 Hz, 3.31-3.32 (d, 1H, J = 4.6 Hz), 1.53-1.62 (m, 1H, J = 7.5 Hz), 1.01-1.10 (m, 1H, J = 7.5 Hz), 0.80-0.84 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.2, 127.6, 127.5, 127.4, 82.9, 69.1, 41.4, 23.4, 18.8, 7.7.

The *syn* α,α-disubstituted-1,3-diol (21 mg, 1.0 equiv.) was then dissolved in a 3:2 mixture of 2,2-dimethoxypropane (500 μL) and dry dimethylformamide (350 μL). A catalytic amount of pyridinium *p*-toluene sulfonate was then added. The solution was stirred overnight at room temperature. The reaction was quenched with excess aqueous sodium bicarbonate saturated solution. The material was extracted with 2:1 hexanes/diethyl ether and the organic layer was extensively washed with distilled water. The organic layer was then dried over sodium sulfate followed by concentration using the rotary evaporator. The material was obtained as a white powder in 90 % yield and analyzed without purification: ^{1}H NMR (C_6D_6) δ (*syn* isomer) 7.29-7.30 (d, 2H, J = 1.6 Hz), 7.05-7.15 (m, 3H), 4.57 (s, 1H), 3.56-3.59 (d, 1H, J = 11.6 Hz), 3.35-3.59 (dd, 1H, J_1 = 11.6 Hz, J_2 = 1.2 Hz), 2.13-2.22 (dq, 1H, J = 7.2 Hz), 1.57 (s, 3H), 1.31 (s, 3H), 0.76-0.85 (ddq, 1H, J_1 = 1.2 Hz, J_2 = 7.2 Hz), 0.63- 0.66 (t_{obs}, 3H, J_{obs} = 7.2 Hz), 0.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 128.3, 127.6, 127.4, 98.9, 81.0, 67.0, 36.7, 30.3, 22.0, 19.1, 18.7, 7.9

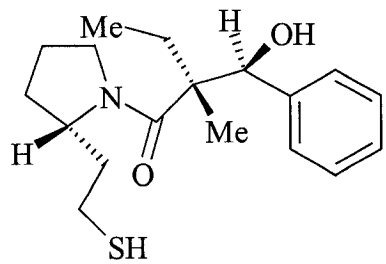
The *anti* α,α-disubstituted-β-hydroxy ester isomer (73 mg, 1.0 equiv.) was reduced with lithium alumium hydride (35.3 mg, 3.0 equiv.) in a similar manner. The colourless oil was obtained in a 63 % yield. ^{1}H NMR ($CDCl_3$) δ (*anti* isomer) 7.2-7.3 (m, 5H), 4.60-4.61 (d, 1H, J = 3.2 Hz), 3.90-3.91 (d, 1H, J = 4.0 Hz), 3.58-3.64 (m, 1H), 3.36-3.39 (dd, 1H, J_1 = 4.4 Hz, J_2 = 10.5 Hz), 1.40-1.59 (m, 2H), 0.87-0.91 (t, 3H, J = 7.3 Hz), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.2, 127.5$_4$, 127.5, 127.2, 81.2, 68.1, 41.1, 27.5, 17.0, 7.9.

The *anti* α,α-disubstituted-1,3-diol isomer (38 mg, 1.0 equiv.) was then dissolved in a 3:2 mixture of 2,2-dimethoxypropane (500 μL) and dry dimethylformamide (350 μL). A catalytic amount of pyridinium *p*-toluene sulfonate was then added. The solution was stirred overnight at room temperature. The reaction was worked up as previously described. The material was obtained as a white powder in 92 % yield and analyzed without purification. (*anti* isomer) 7.30-7.29$_8$ (d, 2H, J = 1.5 Hz), 7.04- 7.15 (m, 3H), 4.55 (s, 1H), 3.56-3.59 (d, 1H, J = 11.5 Hz), 3.44-3.47 (d, 1H, J = 11.5 Hz), 1.58 (s, 3H), 1.31 (s, 3H), 0.92- 0.98 (m, 5H), 0.45-0.51 (t_{obs}, 3H, J_{obs} = 7.3 Hz); ^{13}C NMR (C_6D_6) δ 139.1, 128.4, 127.6, 127.5, 98.9, 79.7, 69.9, 36.8, 30.2, 28.8, 19.2, 15.9, 7.1; HRCIMS *m/z* (M+H) 235.1698 $C_{15}H_{23}O_2^+$ requires 235.1702.

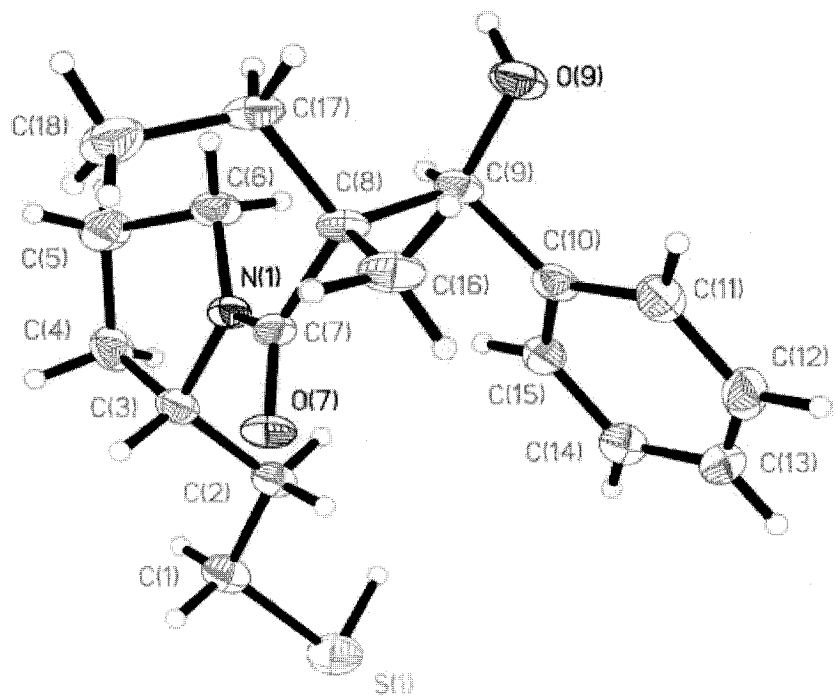
2.4 APPENDIX

X-ray Crystal Structure:

(2*S*)-*N*-((2*R*, 3*S*)-2-ethyl-2-methyl-3-hydrocinnamoyl)-2-(3-propylthiol)-pyrrolidine



83



Crystal Structure Data

Table 2-6. Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$).

$$Ueq=(1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

atom	*x*	*y*	*z*	*Ueq*
S1	0.91379(7)	-0.02434(6)	0.95922(6)	0.0619(2)
H1	0.888(3)	0.059(3)	1.006(2)	0.094(11)
C1	0.9049(2)	0.0473(2)	0.84323(18)	0.0505(6)
H1A	0.9799	0.0942	0.8348	0.061
H1B	0.9043	-0.0092	0.7913	0.061
C2	0.7891(2)	0.12100(17)	0.83425(17)	0.0408(5)
H2A	0.7905	0.1783	0.8855	0.049
H2B	0.7142	0.0743	0.8438	0.049
C3	0.7804(2)	0.17956(17)	0.73636(17)	0.0396(5)
H3	0.7856	0.1228	0.6838	0.048
C4	0.8826(2)	0.26991(19)	0.7221(2)	0.0508(6)
H4A	0.9245	0.2868	0.7836	0.061
H4B	0.9456	0.2441	0.6754	0.061
C5	0.8142(2)	0.3734(2)	0.6841(2)	0.0585(7)
H5A	0.8577	0.4429	0.7032	0.070
H5B	0.8072	0.3712	0.6134	0.070
C6	0.6872(2)	0.36600(17)	0.73105(19)	0.0458(6)
H6A	0.6895	0.3941	0.7978	0.055
H6B	0.6244	0.4086	0.6944	0.055
N1	0.66119(16)	0.24371(13)	0.72815(13)	0.0361(4)
C7	0.55258(19)	0.18827(15)	0.71348(14)	0.0336(4)
O7	0.55311(14)	0.08422(10)	0.70525(11)	0.0413(4)
C8	0.42658(19)	0.25360(15)	0.71139(15)	0.0364(5)
C9	0.40574(19)	0.31279(15)	81189(16)	.0365(4)
H9	0.4798	0.3607	0.8253	0.044
O9	0.29829(14)	0.38409(11)	0.80803(14)	0.0501(4)
H9A	0.3208	0.4504	0.7991	0.075
C10	0.3925(2)	0.22921(16)	0.89411(16)	0.0387(5)
C11	0.2771(2)	0.18188(19)	0.9187(2)	0.0486(6)
H11	0.2040	0.2051	0.8863	0.058
C12	0.2698(3)	0.1004(2)	0.9912(2)	0.0582(7)
H12	0.1918	0.0679	1.0064	0.070
C13	0.3750(3)	0.0670(2)	1.0404(2)	0.0587(7)
H13	0.3692	0.0113	1.0888	0.070
C14	0.4892(3)	0.1151(2)	1.01896(19)	0.0554(6)
H14	0.5615	0.0931	1.0532	0.067

C15	0.4976(2)	0.19657(18)	0.94629(18)	0.0439(5)
H15	0.5756	0.2299	0.9325	0.053
C16	0.3215(2)	0.16771(17)	0.6921(2)	0.0487(6)
H16A	0.3309	0.1369	0.6274	0.073
H16B	0.2407	0.2049	0.6975	0.073
H16C	0.3265	0.1071	0.7392	0.073
C17	0.4185(2)	0.34362(16)	0.62942(17)	0.0461(5)
H17A	0.3300	0.3620	0.6183	0.055
H17B	0.4604	0.4127	0.6515	0.055
C18	0.4763(3)	0.3076(2)	0.5346(2)	0.0700(9)
H18A	0.5663	0.2999	0.5425	0.105
H18B	0.4588	0.3640	0.4855	0.105
H18C	0.4410	0.2357	0.5149	0.105

Table 2-7. Anistropic Displacement Factors.

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	0.0620(4)	0.0564(4)	0.0674(4)	0.0068(3)	-0.0130(3)	0.0141(3)
C1	0.0435(13)	0.0489(12)	0.0590(15)	-0.0011(11)	-0.0008(11)	0.0120(10)
C2	0.0366(11)	0.0353(10)	0.0505(13)	-0.0031(9)	0.0007(10)	0.0041(8)
C3	0.0386(11)	0.0316(10)	0.0486(13)	-0.0040(9)	0.0062(10)	0.0038(9)
C4	0.0385(13)	0.0498(13)	0.0640(16)	-0.0032(11)	0.0120(11)	-0.0007(10)
C5	0.0518(15)	0.0442(12)	0.0795(19)	0.0116(13)	0.0113(14)	-0.0063(10)
C6	0.0474(13)	0.0254(9)	0.0646(15)	0.0003(10)	0.0028(11)	-0.0051(8)
N1	0.0402(10)	0.0237(7)	0.0443(10)	0.0002(7)	0.0030(8)	0.0009(7)
C7	0.0453(12)	0.0235(8)	0.0320(10)	-0.0008(7)	-0.0007(9)	0.0010(8)
O7	0.0504(9)	0.0218(6)	0.0516(9)	-0.0041(6)	-0.0068(7)	0.0025(6)
C8	0.0407(11)	0.0231(8)	0.0454(12)	-0.0010(8)	-0.0088(9)	0.0012(8)
C9	0.0342(10)	0.0254(8)	0.0499(12)	-0.0049(9)	-0.0016(10)	0.0004(7)
O9	0.0455(9)	0.0301(7)	0.0749(12)	-0.0018(8)	0.0024(8)	0.0075(6)
C10	0.0430(12)	0.0265(9)	0.0464(12)	-0.0072(8)	0.0057(9)	-0.0008(8)
C11	0.0416(12)	0.0417(12)	0.0626(15)	-0.0089(11)	0.0082(11)	-0.0071(10)
C12	0.0622(16)	0.0446(13)	0.0679(18)	-0.0093(12)	0.0247(14)	-0.0168(12)
C13	0.0805(19)	0.0376(12)	0.0579(15)	0.0056(11)	0.0231(15)	0.0025(11)
C14	0.0638(16)	0.0512(14)	0.0513(15)	0.0054(11)	0.0089(12)	0.0118(11)
C15	0.0399(12)	0.0401(11)	0.0517(14)	0.0002(10)	0.0067(10)	0.0037(9)
C16	0.0471(13)	0.0318(10)	0.0671(16)	-0.0056(10)	-0.0158(12)	-0.0011(9)
C17	0.0620(14)	0.0262(10)	0.0501(13)	-0.0003(9)	-0.0161(12)	0.0050(9)
C18	0.126(3)	0.0402(13)	0.0441(14)	0.0017(11)	-0.0070(16)	0.0044(15)

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