DISSERTATION

APPLICATION OF THE INTRAMOLECULAR ASYMMETRIC STETTER REACTION TO THE SYNTHESIS OF 2,3-, 2,4-, AND 2,5-DISUBSTITUTED CYCLOPENTANONES AND THE DEVELOPMENT OF THE AZOLIUM CARBENE CATALYZED WALLACH REARRANGEMENT WITH AN APPLICATION TO THE ASYMMETRIC SYNTHESIS OF α-CHLOROESTERS

Submitted by

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In partial fulfillment of the requirements

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY NATHAN THOMAS REYNOLDS ENTITLED APPLICATION OF THE INTRAMOLECULAR ASYMMETRIC STETTER REACTION TO THE SYNTHESIS OF 2,3-, 2,4-, AND 2,5-DISUBSTITUTED CYCLOPENTANONES AND THE DEVELOPMENT OF THE AZOLIUM CARBENE CATALYZED WALLACH REARRANGEMENT WITH AN APPLICATION TO THE ASYMMETRIC SYNTHESIS OF α-CHLOROESTERS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS OF THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT OF DISSERTATION

APPLICATION OF THE INTRAMOLECULAR ASYMMETRIC STETTER REACTION TO THE SYNTHESIS OF 2,3-, 2,4-, 2,5-DISUBSTITUTED CYCLOPENTANONES AND THE DEVELOPMENT OF THE AZOLIUM CARBENE CATALYZED WALLACH REARRANGEMENT WITH AN APPLICATION TO THE ASYMMETRIC SYNTHESIS OF α-CHLOROESTERS

A series of disubstituted cyclopentanones has been synthesized by the intramolecular Stetter reaction from racemic substrates containing one chiral center. 2,3- and 2,4-disubstituted cyclopentanones were synthesized as an approximately 1:1 mixture of *cis*- and *trans*-diastereomers with high enantioselectivity. The Stetter reaction of 2,5-disubstituted cyclopentanones proved to be substrate controlled, resulting in the selective formation of the *cis*-diastereomers with low enantiomeric excess.

The conversion of α-haloaldehydes to α-reduced esters, the Wallach rearrangemt, has been catalyzed by azolium carbenes. The scope of the reaction is broad allowing the transformation of a wide variety of α-haloaldehydes into the corresponding esters. Primary and secondary alcohols are efficient nucleophiles for this reaction and the acylation of aniline has been demonstrated. Evidence for the proposed in situ generated acyl azolium species was gained by the demonstration of the kinetic resolution of *racemic*-ethyl lactate and the desymmetrization of hydrobenzoin using a chiral triazolium salt.

An asymmetric synthesis of α-chloroesters has been developed via an asymmetric protonation of the in situ generated chiral enolate. Treatment of α,α-dichloroaldehydes with a chiral triazolium salt in the presence of base and a nucleophilic alcohol provides

the desired α-chloroesters in good yield. The reaction is applicable to the synthesis of phenyl and benzyl α-chloroesters with high enantiomeric excess, with other alcohols providing the desired product with lower enantiomeric excess. The product α-chloroesters are useful intermediates for the synthesis of more complex structures and the conversion of the products to α-chloroalcohols, α-chloroacids, and α-azido and α-thioesters has been demonstrated.

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Summer 2006

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As I submit this thesis and think about all of those people responsible for getting me to where I am today, I am overcome with reverence and gratitude. I would like to first thank my advisor Tomislav Rovis for calling me while I was working at Wasson ECE and encouraging me to come to CSU. I would also like to thank him for helping me become a scientist; a process that I know has been painful for both of us. I am forever indebted to Tom for allowing me this opportunity, Thank You.

I would next like to thank my parents for all of their support and encouragement. You are the best parents that anyone in this world could possibly hope for and as I embark on my own path as a parent, I hope to emulate your example. To my sister, I thank you for all of the lessons that you have taught me and for all of your support.

I am deeply indebted to current and former members of the Rovis group. I want to thank you all for being a part of my graduate career. I also want to thank all of the people inside and outside of the chemistry department who helped me to maintain my sanity by reminding me that there are other things in life besides chemistry.

Lastly, I want to thank my wife, Rebecca. You came into my life during this process and have given me the power to see it through. Words cannot describe what you mean to me. For my girls, Sailor and Mirabai, thank you for teaching me to stop and smell the sunflowers.

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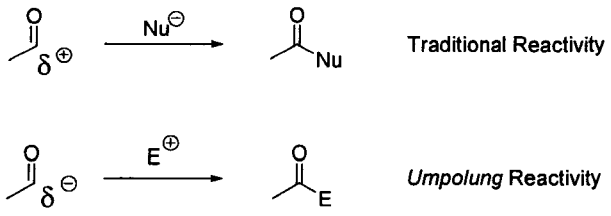
Chapter 1

Umpolung Reactivity of Aldehydes

1.1 Introduction

The development of new methodologies for the asymmetric construction of carbon-carbon bonds is of paramount importance to organic synthesis. In particular, reactions utilizing reactivity *umpolung* of standard functional groups are important because they allow for the use of novel disconnections in complex molecule synthesis.[1] *Umpolung* reactivity occurs when the electron donor and acceptor properties of a functional group are inverted (Figure 1). For example, the carbonyl carbon is traditionally used as an electrophile, but in an *umpolung* reaction this carbon becomes nucleophilic. When *umpolung* reactivity is imparted to aldehydes the intermediates are referred to as acyl anions and organic chemists have devised two methods for there

Figure 1.



generation: indirect and direct. Indirect methods involve the conversion of aldehydes, via chemical methods, to new functional groups that render the previously aldehydic proton, acidic and direct methodologies use catalysts to convert the aldehyde directly to an acyl anion equivalent.

1.2 Indirect Methods for Acyl Anion Generation

Indirect methods for the generation of acyl anion equivalents use the electrophilic nature of aldehydes to temporarily install new functional groups (FG) that allow the formerly aldehydic carbon to be deprotonated with base (Scheme 1). The resultant anion is reacted with an electrophile and removal of the temporary functional group regenerates the desired carbonyl compound. The ideal functional group for this type of strategy

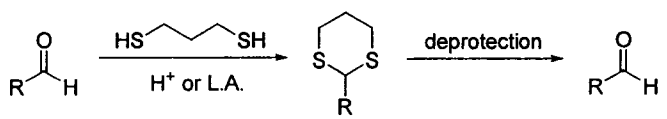
Scheme 1.

would be easily synthesized from the requisite aldehyde and deprotected under mild conditions to regenerate the carbonyl functionality. Dithianes, protected cyanohydrins and α-aminonitriles meet these requirements and have been incorporated into powerful strategies for organic synthesis.

1.2.1 1,3-Dithianes

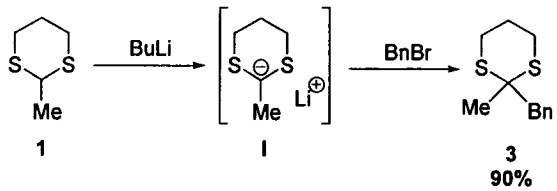
1,3-Dithianes are easily synthesized by treating the corresponding aldehyde with 1,3-propanedithiol in the presence of catalytic amounts of Lewis or Bronsted base and many methods have been developed for their deprotection (Scheme 2).[2] Corey and

Scheme 2.



Seebach pioneered the dithiane approach to acyl anion equivalents in 1965.[3] Treatment of dithiane **1** with *n*-butyllithium generates acyl anion equivalent **I** which is then trapped

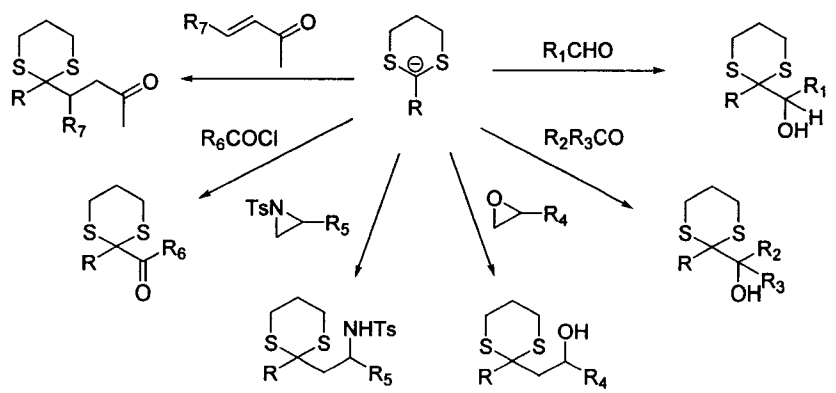
Scheme 3.



1 I 3 90%

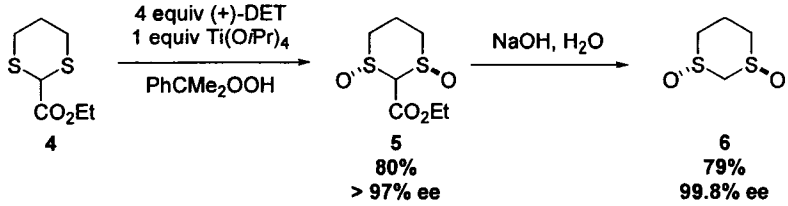
with benzyl bromide to provide dithiane **3** in 90% yield (Scheme 3). Since this initial publication, dithianes have been shown to react with a wide variety of electrophiles and have found many applications in natural product synthesis (Scheme 4).[4]

Scheme 4.



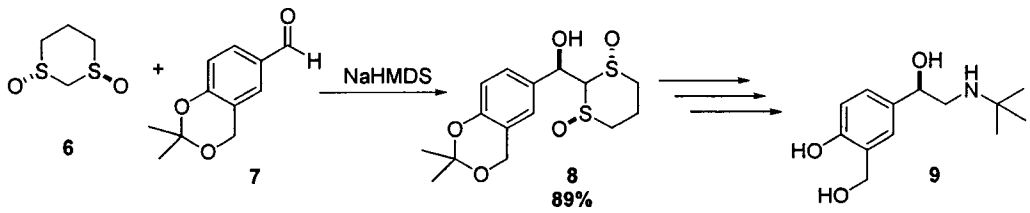
Although dithianes have proven to be extremely useful acyl anion equivalents the development of asymmetric methodologies has been very limited. Aggarwal and co-workers reported the enantioslective synthesis of the C_2 symmetric *trans*-1,3-dithiane-1,3-dioxide **6** in 1992 (Scheme 5).[5] Asymmetric oxidation of 1,3-dithiane **4** using a

Scheme 5.



titanium-diethyl tartrate derived oxidant affords **5** in 80% yield and greater than 97% ee. Removal of the ester from **5** is accomplished with sodium hydroxide in water affording **6** in 79% yield and 99.8% ee. Further studies by Aggarwal demonstrated that the corresponding anion derived from **6** by deprotonation with sodium hexamethyldisilazane adds to aldehydes with high diastereoselectivity.[6] In 2002, Aggarwal and Esquivel-Zamora used this methodology as the key step in their synthesis of (*R*)-salbutamol **9**, which is used for the treatment of asthma (Scheme 6).[7] Treatment of **7** with the anion of

Scheme 6.

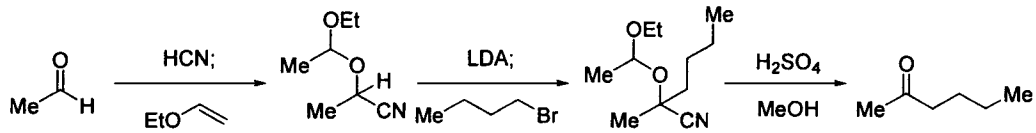


6 generated from sodium hexamethyldisilazane affords **8** as a single diastereomer in 89% yield.

1.2.2 Protected Cyanohydrins

Stork and Maldonado were the first to demonstrate the potential utility of protected cyanohydrins as acyl anion equivalents in 1971.[8] The requisite protected

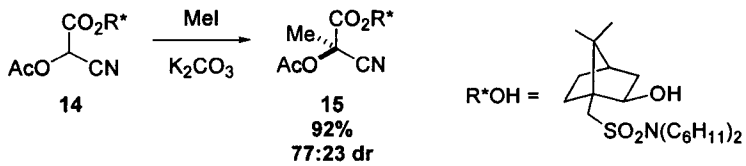
Scheme 7.



cyanohydrins are easily prepared by the treatment of aldehydes with cyanide followed by protection of the cyanohydrin with ethyl vinyl ether. Treatment of protected cyanohydrin **11** with lithium diisopropyl amide followed by the addition of bromobutane affords the alkylated product **12** in 80% yield, which is deprotected with 5% aqueous sulfuric acid affording the desired ketone **13**. Protected are competent nucleophiles for Michael additions and addition to carbonyls.[9]

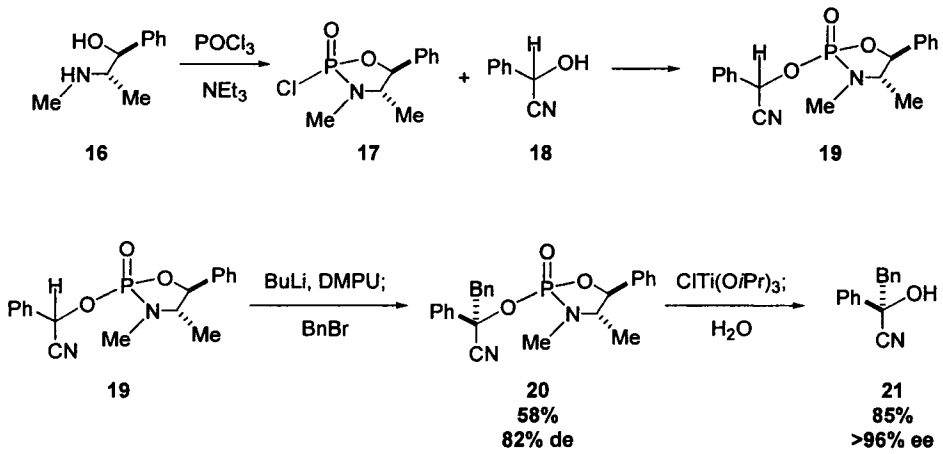
Early attempts to develop asymmetric reactions using protected cyanohydrins focused on the use of chiral auxiliaries. Cativiela *et al.* demonstrated that a camphor derived chiral auxiliary incorporated into the substrate could affect a diastereoselective alkylation of the pendant cyanohydrin (Scheme 8).[10] Treatment of substrate **14** with

Scheme 8.



methyl iodide in the presence of potassium carbonate affords the alkylated product in 92% yield and 77:23 dr. Schrader investigated the use of chiral phosphonamides as auxiliaries in 1997.[11] Treatment of ephedrine derived **16** with phosphoryl chloride affords

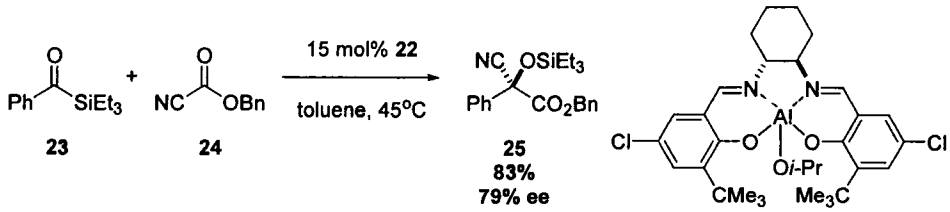
Scheme 9.



17, which was directly treated with cyanohydrin **18** to afford cyanohydrin phosphate **19**. Deprotonation of **19** with butyllithium and trapping of the resultant anion with benzyl bromide affords the alkylated product **20** in 58% yield and 82% de. Separation of the diastereomers by column chromatography and deprotection of the major diastereomer provides **21** in 85% yield and greater than 96% ee.

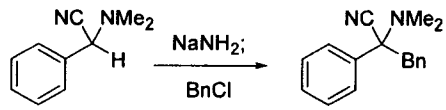
Johnson and co-workers published an elegant approach to the acylation of cyanohydrin derivatives in 2004 based upon the use of acylsilanes as protected cyanohydrin precursors.[12] Their strategy incorporates a catalytic asymmetric cyanation reaction with a Brook rearrangement followed by acylation of the resultant anion and is shown in Scheme 10. Acyl silane **23** and mixed carbonate **24** are reacted in the presence of catalyst **22** for 72h to afford the desired acylated protected cyanohydrin **25** in 83% yield and 79% ee.

Scheme 10.



23 24 25 83% 79% ee 22

Scheme 11.



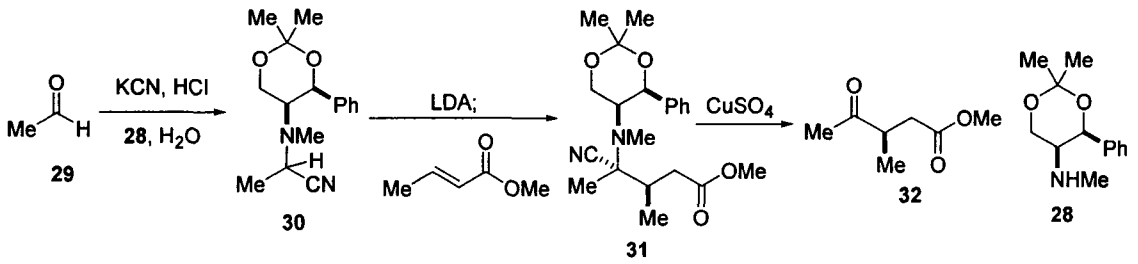
26 27 91%

1.2.3 α-Aminonitriles

The first demonstration of α-aminonitriles as acyl anion equivalents was published in 1959 by Hauser *et al.*[13] α-Aminonitrile **26**, synthesized via the Strecker reaction, was deprotonated with sodium amide and alkylated with benzyl chloride to afford the desired product **27** in 91% yield. The incorporation of a secondary amine into the α-aminonitriles has been an attractive target for the development of chiral auxiliary strategies.

Enders and co-workers were the first to use chiral α-aminonitriles in 1990.[14] Using **28** as a chiral auxiliary they are able to effect the Michael addition of the anion derived from **30** to methyl crotonate with excellent diastereoselectivity to afford **31**. Treatment of **31** with copper sulfate provides 1,4-dicarbonyl **32** in 69% overall yield and 93% ee.

Scheme 12.



Dithianes, protected cyanohydrins and α-aminonitriles have proven to be versatile precursors to acyl anion equivalents. With the exception of Johnson's catalytic methodology (Scheme 10), the development of asymmetric variants of these reactions has been limited to the use of chiral auxiliaries. In addition to this limitation, indirect methods for acyl anion generation suffer from the need to use two additional steps to effect the desired reaction (functional group incorporation and deprotection). A more efficient approach to the use of acyl anions in organic synthesis would focus on the generation of acyl anions directly from aldehydes.

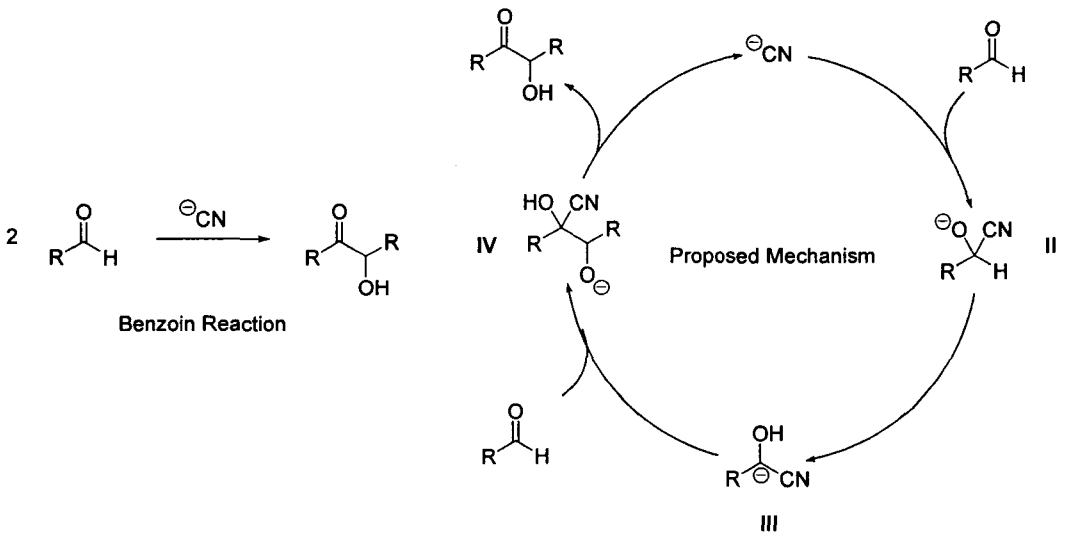
1.3 Direct Methods for Acyl Anion Generation

1.3.1 The Benzoin Reaction

The benzoin reaction, first reported in 1823, is a classic example of direct aldehyde *umpolung* reactivity (Scheme 1). [15] In this reaction two molecules of aldehyde in the presence of a nucleophilic catalyst dimerize to form α-hydroxyketone products. The currently accepted mechanism of this reaction was proposed in 1903 by Lapworth (Scheme 13).[16] In this mechanism the nucleophilic catalyst (cyanide anion) adds to the aldehyde to give the tetrahedral intermediate **II**. Upon proton transfer, an acyl anion equivalent **III** is generated that can react with another equivalent of aldehyde to give

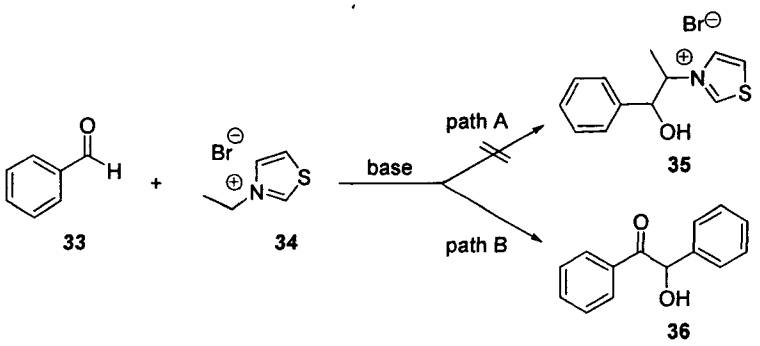
intermediate **IV**. Proton transfer precedes catalyst release, which provides the benzoin product.

Scheme 13.



In 1943 Ukai and co-workers serendipitously discovered a new class of nucleophilic catalyst for the benzoin reaction.[17] During their investigations into nitrogen ylide reactivity they attempted to generate a nitrogen ylide from **34**. Subjecting **34** to base and benzaldehyde **33** they had hoped to observe simple addition to the aldehyde (path A, Scheme 14). Instead of their desired reaction they observed formation of the product benzoin (path B, Sheme 14). The discovery of a new catalyst for the benzoin reaction was very important from a historical perspective, because organic chemist now had a scaffold to which they could append chirality with the goal of transferring stereochemical information into the benzoin products. However, before the development of chiral

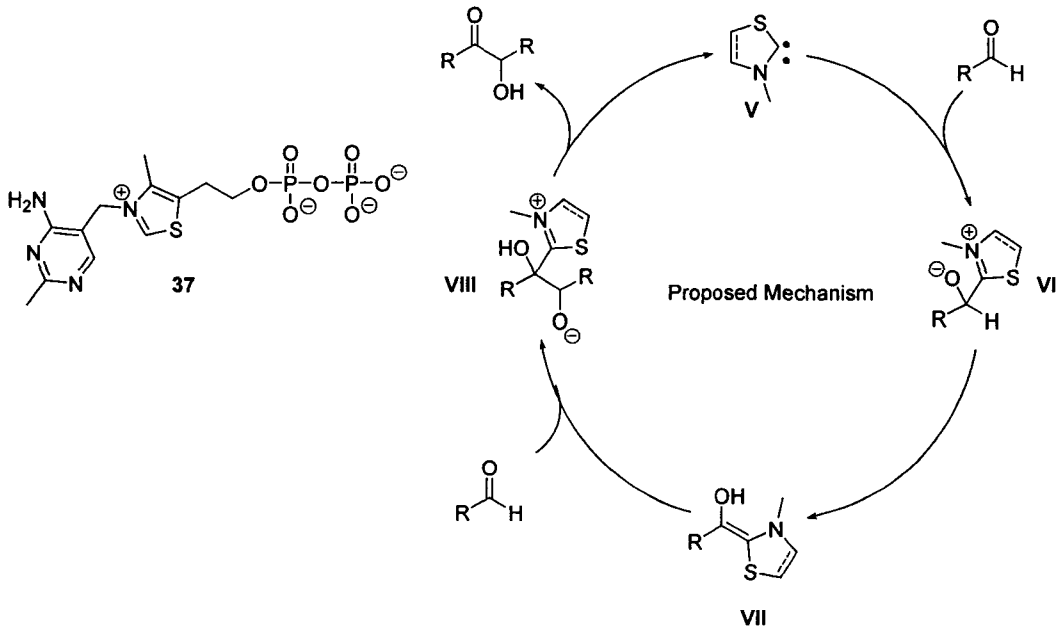
Scheme 14.



catalysts could begin, a clear understanding of the mechanism of thiazolium catalysis was necessary.

By discovering that thiamine was an active catalyst for the benzoin reaction they linked the mechanistic understanding of the benzoin reaction to the mechanism of thiamine diphosphate **37** catalyzed reactions (Scheme 15).[18] Thiamine diphosphate is a coenzyme involved in the metabolism of α-ketoacids, converting them to aldehydes and carbon dioxide. The mechanism of this transformation was believed to involve an acyl carbanion and led to the proposal of a variety of different mechanisms, ultimately leading to the currently accepted mechanism proposed Breslow in 1958.[19] The key mechanistic contribution by Breslow was that the C-2 position of the thiazolium ring was the first to be deprotonated in the presence of base forming the catalytically active species, carbene **V** (Scheme 15). Using the deprotonated C-2 position as a nucleophile, Breslow's proposed mechanism is analogous to that proposed by Lapworth for the cyanide anion catalyzed benzoin reaction.[3] In the thiazolium catalyzed reaction the acyl anion can be drawn as nucleophilic alkene **VII** and this intermediate has become known as the Breslow intermediate. With a clear understanding of the mechanism of the thiazolium salt

Scheme 15.

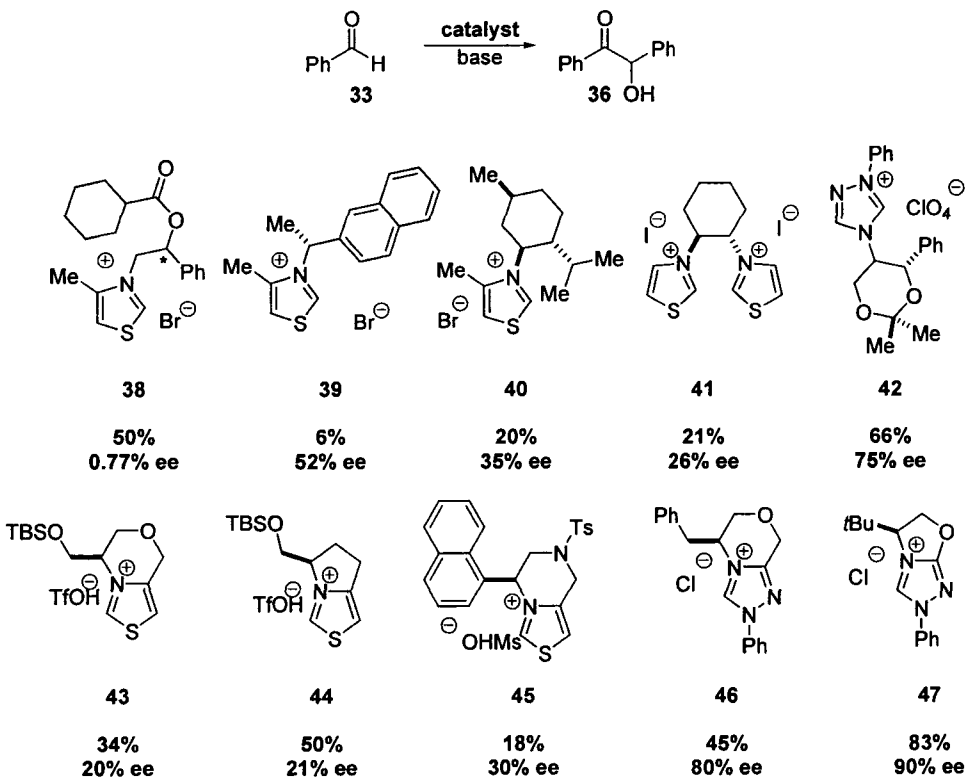


catalyzed benzoin reaction the synthetic community began to pursue the development of asymmetric variants of this reaction.

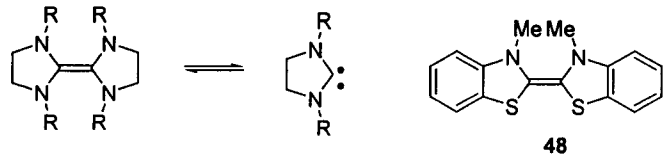
The first attempt to design a chiral azolium salt for the benzoin reaction was published in 1966 by Sheehan and Hunneman (Figure 2).[20] They reported the use of catalyst **38**, obtaining benzoin in 50% yield and 0.77% ee. They were able to increase the ee to 52% by moving the chiral information one carbon closer to the thiazolium ring and using a naphthyl substituent **39** but suffered a dramatic decrease in yield.[21] Tagaki et al. synthesized a menthyl-substituted thiazolium salt **40** and were able to obtain benzoin in 35% ee.[22]

Investigations by Wanzlick and co-workers in the 1960's led to the proposal that diaminocarbenes were in equilibrium with tetraaminoolefins (Scheme 16) and in 1971 on the basis of this equilibrium they were able to show that dimerized thiazolium compound **48** was an active catalyst for the benzoin reaction.[23,24] In 1988 López-Calahorra and co-workers, on the basis of theoretical and experimental results, proposed that the dimerized thiazolium compounds instead of the dissociated carbenes were the active catalysts for

Figure 2.



Scheme 16.



48

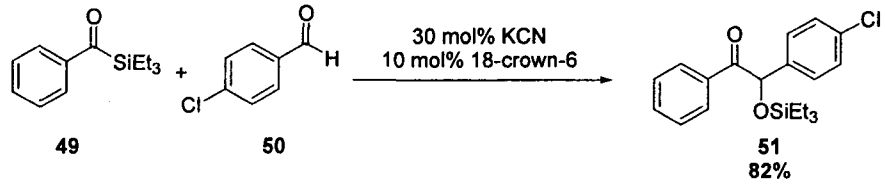
the benzoin reaction, culminating in the report of bis-thiazolium salt **41** in 1993.[25] In 1994 Breslow and Kim refuted this hypothesis by showing that the thiazolium salt catalyzed reaction was first order in thiazolium salt.[26] In 1996 Enders et al. demonstrated that triazolium salts **42** in the presence of base were efficient catalysts for the benzoin reaction.[27]

In 1997 Leeper reported a new concept in azolium salt design.[28] These researchers hypothesized that the ability of the chiral moiety in azolium salts **38-42** to rotate around a carbon nitrogen single bond was leading to low enantioselectivities. They attempted to rectify this problem by synthesizing chiral azolium salts in which the chiral information was incorporated into a rigid bicyclic system (**43-44**); unfortunately low enantioselectivities were still obtained. The following year Rawal and Dvorak reported another chiral bicyclic thiazolium salt **45** obtaining ee's as high as 30%.[29] Leeper and co-workers obtained a significant improvement in the enantiomeric excess of the benzoin products by incoporating the bicyclic design into triazolium salt **46**.[30] Enders and co-workers reported the current state of the art for the benzoin reaction in 2002. Using chiral triazolium salt **47** they were able to obtain benzoin in 83% yield with an ee of 90%.[31]

One limitation of the benzoin reaction is the inability to form mixed benzoin products. Subjection of two different aldehydes to the benzoin reaction leads to a

mixture of the four possible benzoin products with the distribution being determined by the relative stability of the products.[32] Johnson and Linghu published a way to circumvent this limitation in 2003.[33] The authors demonstrated that acyl silanes could be selectively coupled with aldehydes affording the silyl protected cross benzoin products.

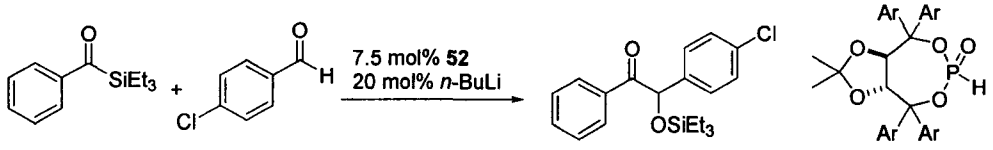
Scheme 17.



49 **50** **51** **82%**

Subjection of a 1:1.1 mixture of **49** and **50** to catalytic amounts of potassium cyanide in the presence of 18-crown-6 affords the silyl protected cross benzoin product **51** in 82% yield. The following year Johnson and co-workers published an asymmetric variant of the cross silyl benzoin reaction (Scheme 18).[34] A metallophosphite catalyst generated in situ from the deprotonation of **52** with butyllithium affords the desired product **51** in 75% yield and 82% ee.

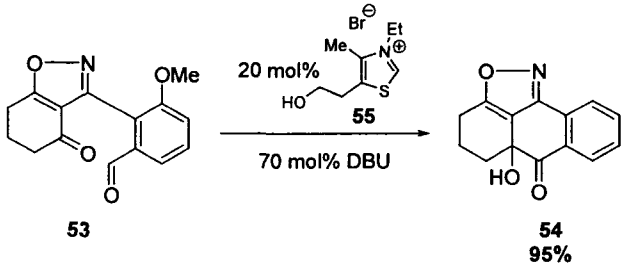
Scheme 18.



49 **50** **51** **75%** **82% ee** Ar = 2-FPh **52**

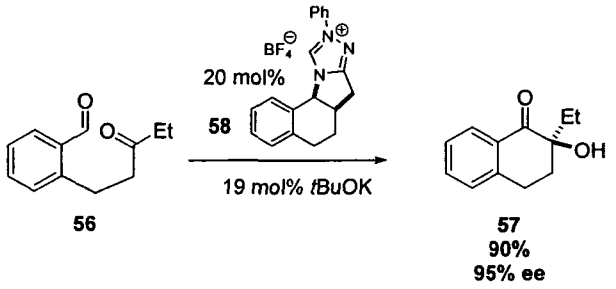
Ketones, which are less electrophilic than aldehydes, have also proven to be competent electrophiles for the acyl anion generated directly from aldehydes and azolium carbenes. Suzuki and co-workers published the first example of this type of reactivity in 2003 (Scheme 19).[35] Treatment of substrate **53** with 20 mol% thiazolium salt **55** and 70

Scheme 19.



mol% DBU afforded the cross aldehyde-ketone benzoin product **54** in 95% yield. Recognizing the potential power of this direct crossed benzoin reaction Enders and co-workers quickly developed an asymmetric variant (Scheme 20).[36] In 2006 they showed

Scheme 20.



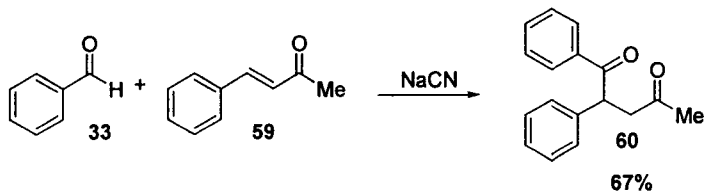
that catalyst **58** in the presence of potassium *tert*-butoxide produces the desired benzoin product **57** in 90% yield and 95% ee.

1.3.2 The Stetter Reaction

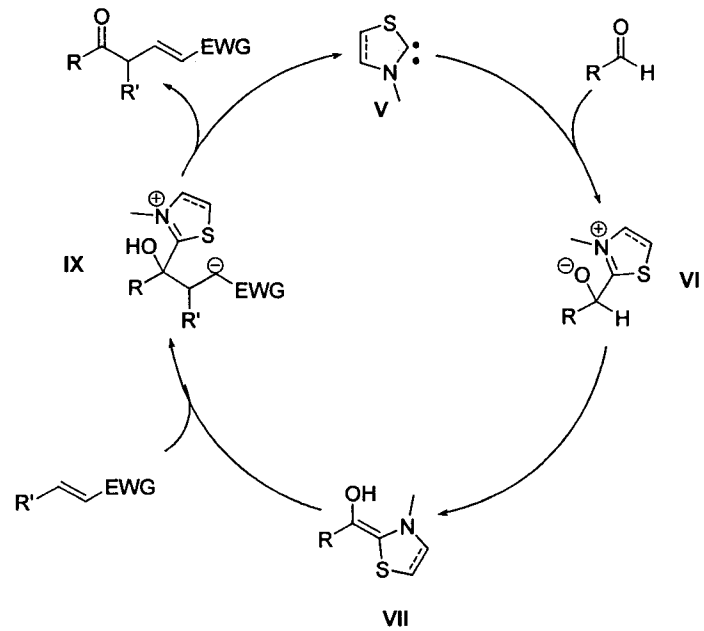
Stetter and Schreckenberg took the nucleophilic catalyst-imparted *umpolung* reactivity of aldehydes in a new direction in 1973 by demonstrating that cyanide anion catalyzed the addition of aldehydes to activated double bonds (Scheme 21).[37] Stetter and Kuhlmann soon demonstrated that thiazolium salts in the presence of base were also efficient catalysts for the reaction and proposed a mechanism that proceeds through the Breslow intermediate **VII** (Scheme 22).[38] Trost and co-workers demonstrated the synthetic utility of the 1,4-diketones generated via the Stetter reaction in 1979 as the key

step in their synthesis of hirsutic acid c (Scheme 23).[39] In the presence of 2.3 equivalents of **63** and 50 equivalents of triethylamine in refluxing 2-propanol they were able to form the congested quaternary center of **62** in 67% yield.

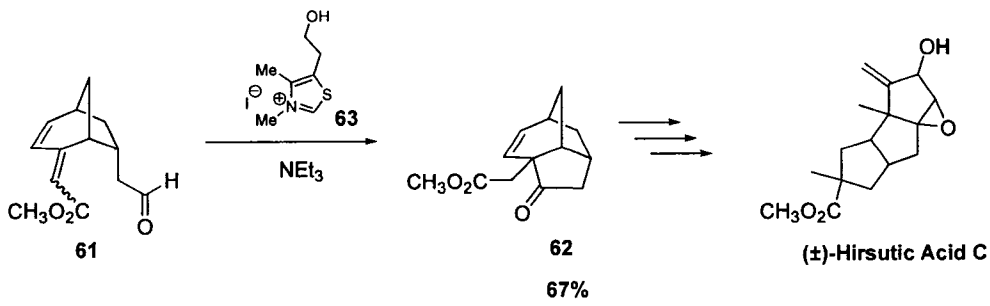
Scheme 21.



Scheme 22.

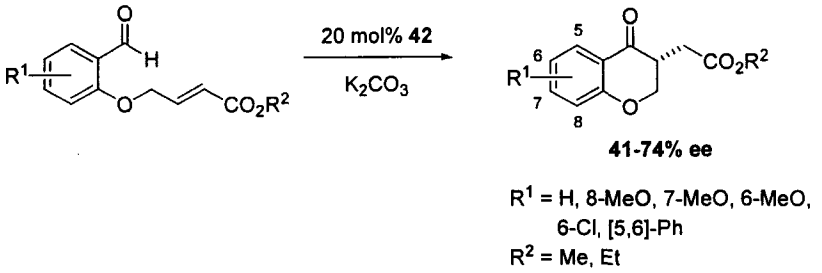


Scheme 23.



Controlling the absolute stereochemistry in the Stetter reaction has proven to be a formidable challenge for organic synthesis. At the time our laboratories began investigating asymmetric catalysis of the intramolecular variant of this reaction there was only one previous report of an asymmetric Stetter reaction (Scheme 24).[40] Using a substrate developed by Ciganek, Enders and co-workers reported the enantioselective synthesis of chromanone derivatives using triazolium salt **42**.[41]

Scheme 24.

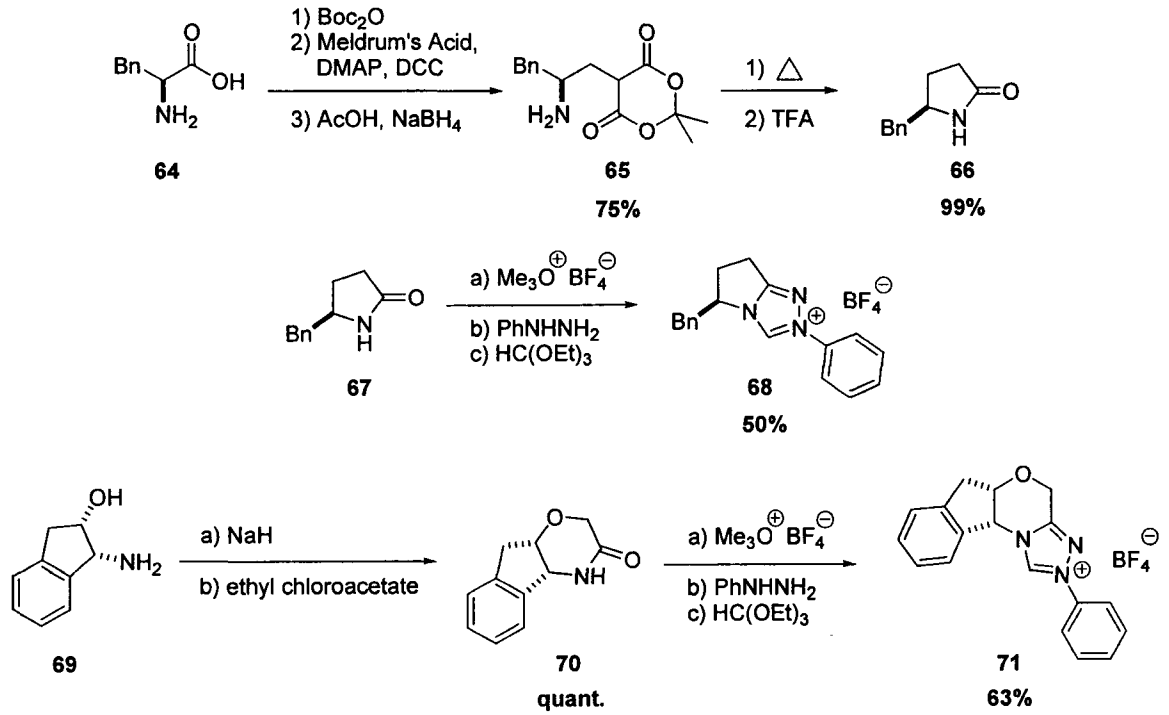


Mark Kerr and Javier Read de Alaniz pioneered the investigations into the asymmetric intramolecular Stetter reaction in our lab. They began with the hypothesis that a chiral bicyclic triazolium salt with stationary chirality would be a good catalyst for the intramolecular Stetter reaction. They focused on the versatile bicyclic triazolium salt design put forth by Leeper and co-workers in 1998.[17] The key points of this catalyst design are: 1) The chiral information is locked into place by the rigid bicyclic design. 2) Chirality is derived from readily available amino acids. 3) The aryl ring may be substituted, changing the electronic and steric nature of the chiral platform. 4) Changing the counter-ion allows one to fine tune the solubility characteristics of the triazolium salt.

Investigations were initially focused on two chiral scaffolds derived from phenylalanine and amino indanol (Scheme 25).[42]

Boc protection of phenylalanine followed by treatment with Meldrum's acid, DMAP, DCC and reduction of the resultant ketone with sodium borohydride in the presence of acetic acid affords **65** in 75% yield. A thermally-induced retro-Diels-Alder reaction generates a ketene which is trapped by the pendant amine, which, after removal of the Boc, group affords **66** in 99% yield. A one-pot three-step sequence involving

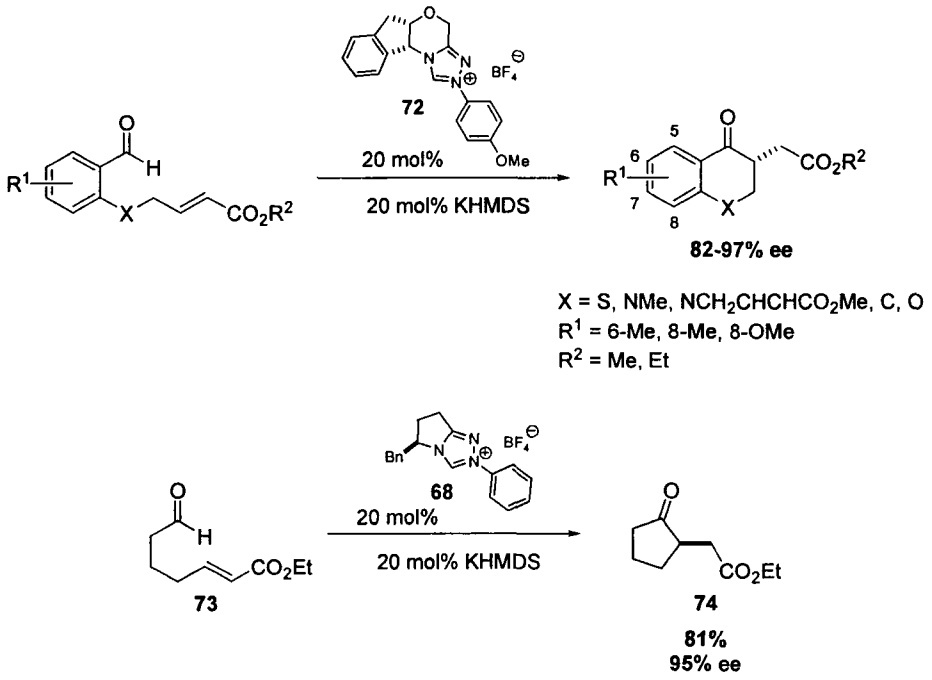
Scheme 25.



amidate formation, methoxy-hydrazine exchange, and cyclization affords triazolium salt **68** in 50% yield. Treatment of amino indanol **69** with sodium hydride and ethyl chloroacetate provides morpholinone **70** in quantitative yield. Using the same one-pot procedure as before provides **71** in 63% yield.

These catalysts have proven highly effective in the intramolecular Stetter reaction. Using the Ciganek substrate and catalyst **72,** a wide range of chromanones was synthesized in excellent yield and ee (Scheme 26).[43] The reaction is also tolerant of heteroatoms other than oxygen in the backbone. Aliphatic substrate **73** also successfully underwent the intramolecular Stetter reaction with catalyst **68** affording the desired cyclopentanone **74** in 81% yield and 95% ee.

Scheme 26.

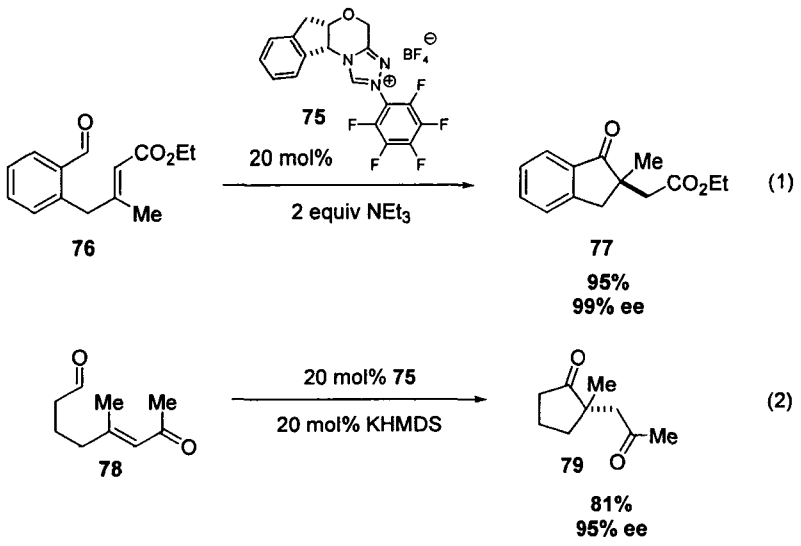


Kerr and Rovis have also found the intramolecular Stetter reaction to be capable of setting quaternary stereocenters.[44] Treatment of **76** with 20 mol% **75** in the presence of 2 equivalents of triethylamine affords **77** in 95% yield and 99% ee (Equation 1, Scheme 27). Aliphatic substrates reacted slowly under the triethylamine conditions resulting in a low yielding reaction giving products with low enantiomeric excess.

However, the use of KHMDS provided the cyclopentanones bearing a quaternary center in excellent yield and ee (Equation 2, Scheme 27).

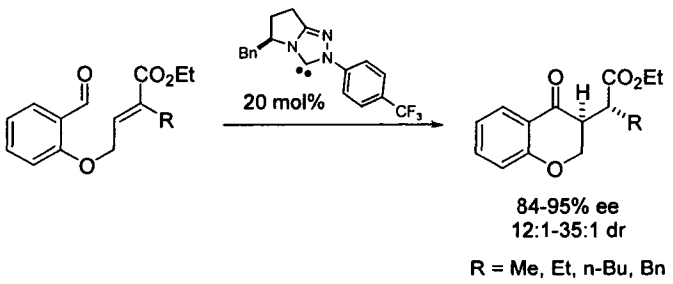
During initial investigations with dueterio-aldehydes Read de Alaniz and Rovis discovered that the deuterium was being selectively incorporated in the products at the α-

Scheme 27.



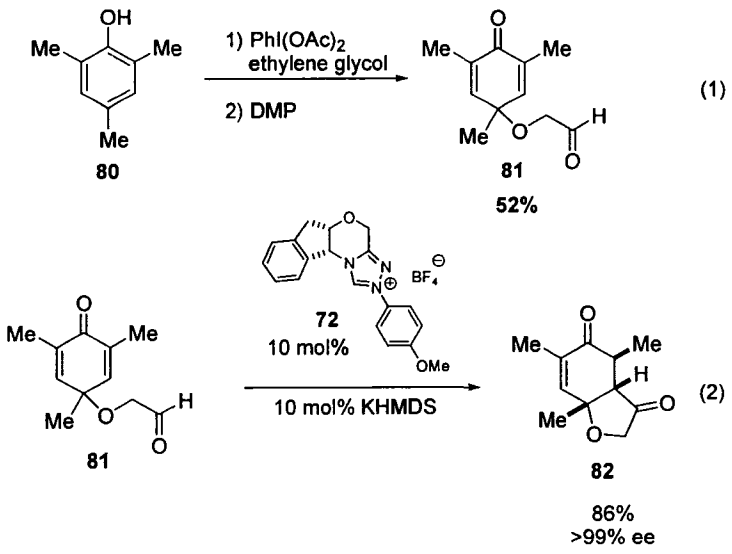
position of the Michael acceptor.[45] Further experimentation revealed that higher diastereoselectivities could be obtained if the HMDS generated upon deprotonation of the triazolium salt was removed before addition of the substrate. Aliphatic and aromatic substrates both undergo a diastereoselective proton transfer resulting in the synthesis of two contiguous centers with diastereoselectivities ranging from 12:1 to 150:1 and ee's from 83-99% (Scheme 28).

Scheme 28.



The asymmetric intramolecular Stetter reaction has also proven to be ideal for the synthesis of hydrobenzofuranones with the required substrates easily synthesized from commercially available phenols. [46] Phenol **80** was subjected to oxidative ether formation followed by oxidation to provide **81** in 52% overall yield. Treatment of **81** with 10 mol% **72** provided hydrobenzofuranone **82** in 86% yield and 99% ee establishing 3 contiguous stereocenters in a single transformation.

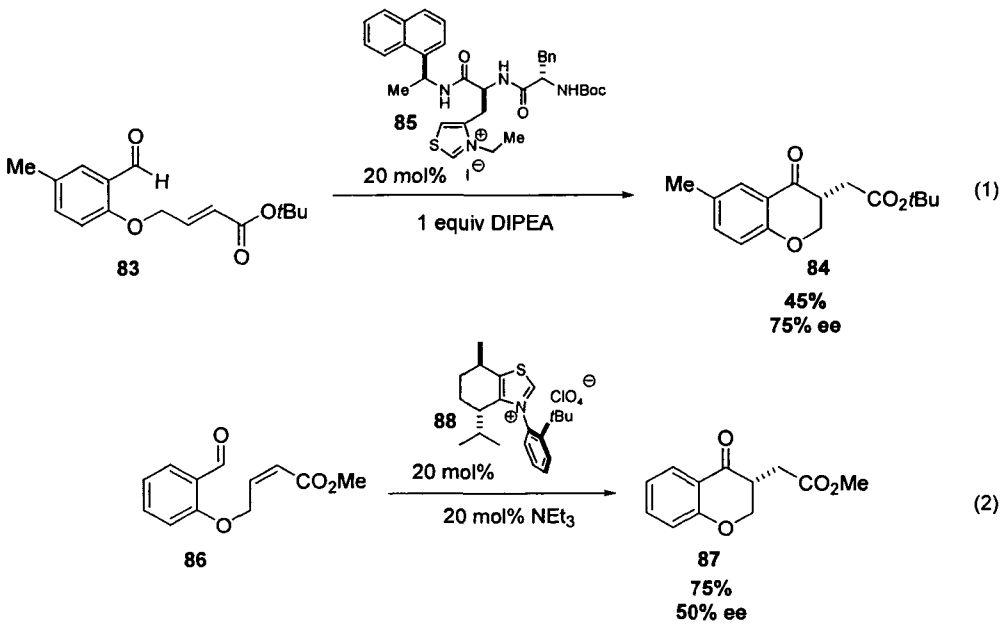
Scheme 29.



During studies on the intramolecular Stetter reaction, two unique catalyst designs were tested for their efficiency in the reaction. Miller and co-workers reported that the

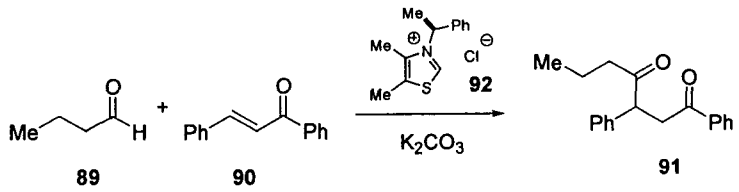
peptide-derived thiazolium salt **85** was a competent catalyst for the intramolecular Stetter, reaction generating chromanone **84** in 45% yield and 75% ee (Equation 1, Scheme 30).[47] Bach and co-workers reported the use of axially chiral thiazolium salt **88** obtaining the desired chromanone **87** in 75% yield and 50% ee (Equation 2, Scheme 30).[48]

Scheme 30.



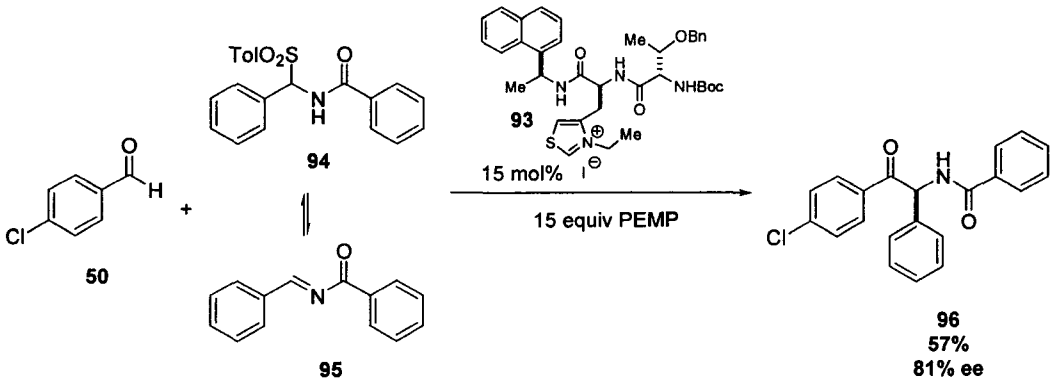
The development of an asymmetric intermolecular Stetter reaction has proven to be a more difficult endeavor than the intramolecular variant. The first example using aldehydes directly appeared in 1994 (Scheme 29).[49] Treatment of a mixture of **89** and **90**

Scheme 31.



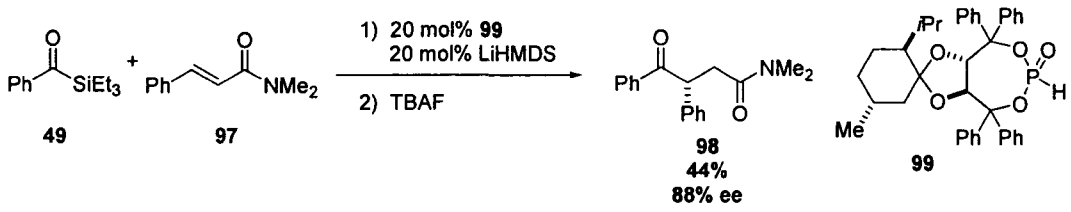
with thiazolium salt **92** in the presence of potassium carbonate afforded a 4% yield of the desired Stetter product **91** in 39% ee. In 2001, a research group at Merck demonstrated that acylimines dervied from tosylamides were competent acceptors for the in situ generated acyl anion derived from aldehydes and thiazolium carbenes.[50] Miller and co-workers were able to render this reaction asymmetric using their peptide derived thiazolium salts in 2005 (Scheme 32).[51] Treatment of a mixture of **50** and **94** (which is in

Scheme 32.



equilibrium with acyl imine **95**) with catalyst **93** in the presence of pentamethylpiperdine affords a 57% yield of **96** in 81% ee. Capitalizing on the success in the cross benzoin reaction, Johnson and co-workers have recently disclosed an asymmetric intermolecular variant of the Stetter reaction using acyl silanes as aldehyde equivalents (Scheme 33).[52] Using the metallophosphite generated from **99** and lithium hexamethyldisilazane, **49** and **97** combine to give, after removal of the α-silyl group, **98** in 44% yield and 88% ee.

Scheme 33.



In this thesis, investigations into the nucleophilic carbene-imparted *umpolung* reactivity of aldehydes are described. The focus of the first investigation is to determine the effect pre-existing stereocenters have on the stereochemical outcome of the intramolecular asymmetric Stetter reaction and an application to the synthesis of 2,3-, 2,4-, and 2,5-disubstituted cylopentanones is discussed. The focus of the second investigation is the Wallach rearrangement, a reaction that converts α-haloaldehydes to α-reduced esters, and azolium carbenes are shown to be efficient catalysts for the reaction. The last chapter of the thesis details the use of chiral carbenes in the Wallach rearrangement to affect an enantioselective protonation at the α-position of the newly formed esters and its application to the synthesis of α-haloesters.

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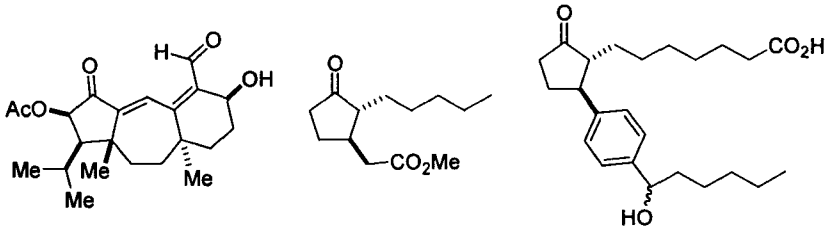
Chapter 2

The Asymmetric Intramolecular Stetter Reaction: Application to the Synthesis of Di-Substituted Cyclopentanones

2.1 Introduction

Substituted cyclopentanone subunits are found in a wide variety of natural and unnatural products with significant biological activities and as useful intermediates for the synthesis of more complex structures (Scheme 1).[1] Guanacastepene A is a

Scheme 1.



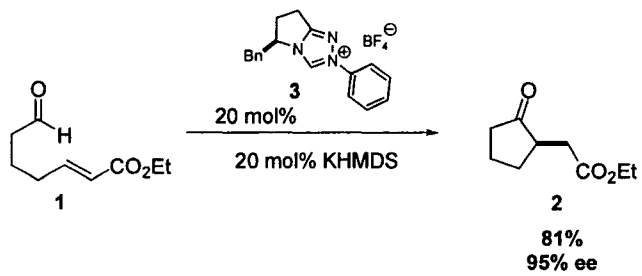
Guanacastepene A **Hedione** **AH13205**

structurally interesting natural product, isolated from fungal extracts, that possesses antiobiotic properties.[2] Hedione is a dihydro derivative of the jasmonate family of natural products and has provided the fragrance industry with a jasmine scent.[3] AH13205 is an analogue of the prostaglandin family of natural products and lowers intraocular pressure.[4]

Kerr, Read de Alaniz and Rovis demonstrated the use of the intramolecular asymmetric Stetter reaction to synthesize mono-substituted cyclopentanones (Scheme 2). In light of this result and the prevalence of the cyclopentanone architecture investigations to determine the effect of pre-existing stereocenters on the stereochemical outcome of the intramolecular asymmetric Stetter reaction were initiated (Scheme 3). Investigation focused on the cyclization of substrates containing one pre-existing

stereocenter in order to determine the effect of substitution at each position of the substrate, providing access to 2,3, 2,4, and 2,5 di-substituted cyclopentanones.

Scheme 2.

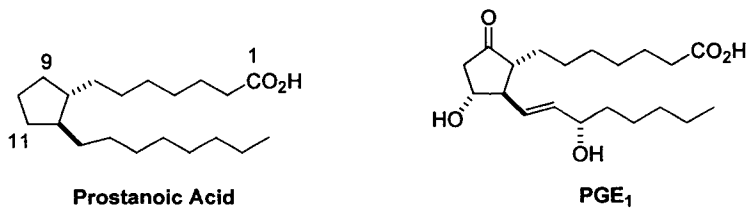


Scheme 3.

2.2 Synthesis of Substituted Cyclopentanones

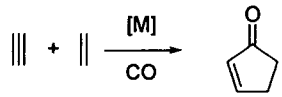
The isolation and structural elucidation of the prostaglandins in the 1960's by Bergström and co-workers led to an explosion in interest in the synthesis of substituted cyclopentanones.[5] The basic structural unit of the prostaglandins is shown in Scheme 4 and is called prostanoic acid.[6] The prostaglandins are typically oxygenated at the 9 and 11 positions and a represantative example, **PGE_1**, is shown in Scheme 4.

Scheme 4.



A classical approach to the cyclopentanone scaffold is the Pauson-Khand reaction, which combines an alkyne, alkene, and carbon monoxide in the presence of a metal complex to form cyclopentenones (Scheme 5).[7] Reduction of the double bond

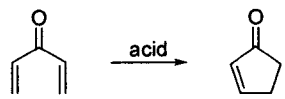
Scheme 5.



affords the desired cyclopentanones and this route has been used in the synthesis of natural products.[8] However, one significant limitation of the Pauson-Khand reaction is the need for the use of strained olefins in the intermolecular variant and this has limited the synthetic utility of the Pauson-Khand reaction to the synthesis of multi-cyclic systems.[7]

Another approach widely used for the synthesis of cyclopentanones is the Nazarov cyclization.[9] In this reaction divinyl ketones are cyclized to cyclopentenones

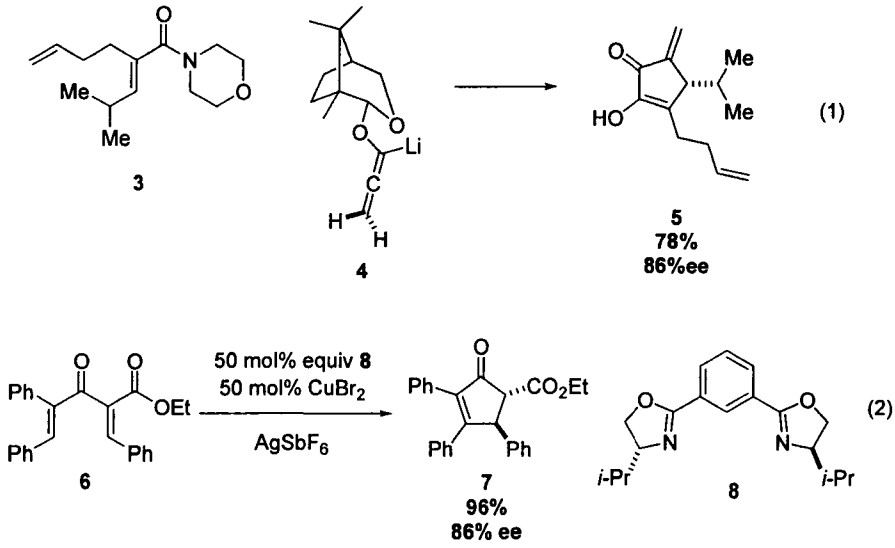
Scheme 6.



under acid catalysis (Scheme 6). In contrast to the Pauson-Khand, reaction the Nazarov cyclization has proven more applicable to the asymmetric synthesis of mono-cyclic cyclopentanones.

Pridgen et al. first demonstrated the use of chiral auxiliaries in the Nazarov cyclization in 1999.[10] Two years later, Tius and co-workers extended this work and applied the concept of a chiral auxiliary-controlled Nazarov cyclization to the synthesis of roseophilin (Equation 1, Scheme 7).[11] Treatment of amide **3** with enantiopure allene **4**

Scheme 7.



leads to the cyclopentenone **5** in 78% yield and 86% ee. Aggarwal and Belfield have developed a catalytic asymmetric variant of the Nazarov reaction (Equation 2, Scheme 7).[12,13] Treatment of substrate **6** with 50 mol% of a copper oxazoline complex prepared from **8** and copper (II) bromide affords the desired cyclopentenone **7** in 96% yield and 86% ee.

The Pauson-Khand and Nazarov reactions are elegant methodologies for the synthesis of substituted cyclopentenones and further research in both reaction manifolds will continue to lead to new and improved methods for the asymmetric synthesis of cyclopentenones. However, these methodologies have not been applied to asymmetric synthesis of simple disubstituted cyclopentanones.

Many creative methodologies have been developed for the direct synthesis of 2,3, 2,4, and 2,5 disubstituted cyclopentanone scaffolds.[14] Two general approaches have been utilized for their synthesis: 1) construction of the cyclopentanone ring as the key step, and

2) addition of substituents to a preformed cyclopentanone scaffold. Some of the highlights from these investigations will be discussed below.

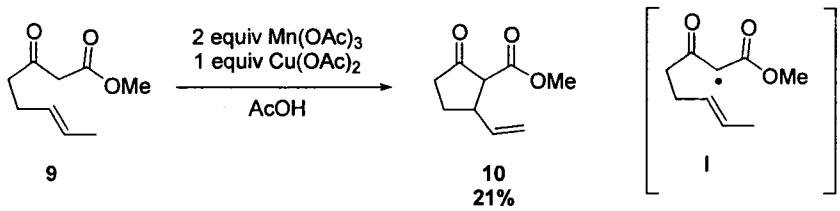
2.2.1 Strategies Utiliizing Cyclopentanone Ring Formation as the Key Step

The most commonly used methods for the direct construction of cyclopentanone architectures are radical, hydroacylation, C-H insertion, ring contraction-expansion-cycloaddition processes, and anionic reactions. The unifying factor, with the exception of C-H insertion reactions, in these different reaction manifolds is that the key bond formation is an acyl-carbon bond.

2.2.1.1 Radical Cyclizations

In 1984 Snider and co-workers published a manganese(III)-based oxidative free radical cyclization approach to 2,3-disubstituted cyclopentanones (Scheme 8).[15] Treatment of β-ketosubstrate **9** with a mixture of Mn(III) and Cu(II) affords **10** in 21% yield, presumably through intermediate enol radical **I**.

Scheme 8.

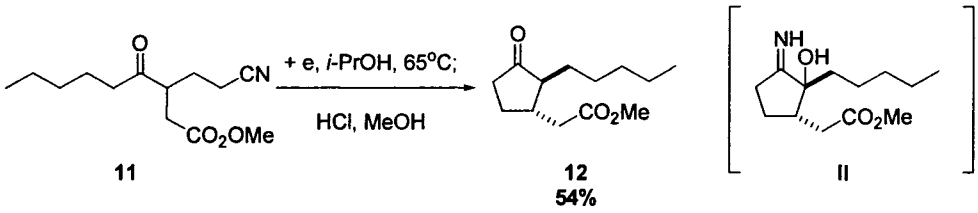


9 **10** **21%** **I**

A more common approach to the radical cyclization reaction utilizes an acyl radical followed by addition to an alkene and three approaches to these species have been demonstrated in the synthesis of disubstituted cyclopentanones: electrochemical, chemical, and free-radical carbonylation reactions. Shono and co-workers demonstrated that ketones and nitriles could be effectively coupled by electroreduction (Scheme 9).[16]

The reaction presumably proceeds through intermediate **II**, which can be isolated at lower temperatures and, after in situ dehydration and double bond reduction, affords

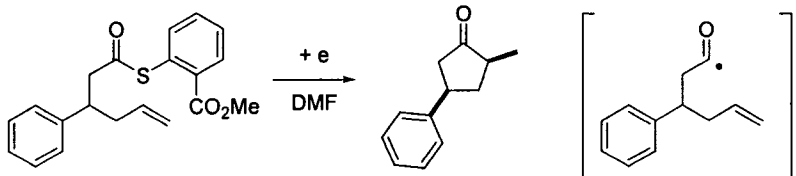
Scheme 9.



11 **12** **54%** **II**

methyl dihydrojasmonate **12** in 54% yield. The electrochemical reduction of thiolesters has also proven amenable to the synthesis of cyclopentanes (Scheme 10).[17] Reduction of substrate **13** in DMF provides a 31% yield of **14** as a 3.2:1 mixture of *cis* and *trans* isomers, presumably via acyl radical **III**.

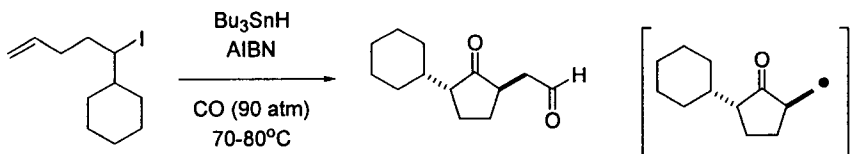
Scheme 10.



13 **14** **31%** **3.2:1 dr** **III**

Ryu et al. have pioneered the development of free-radical carbonylation reactions.[18] In 1996 Ryu and co-workers published a double carbonylative variant of their methodology and its application to the synthesis of cyclopentanones (Scheme 11).[19]

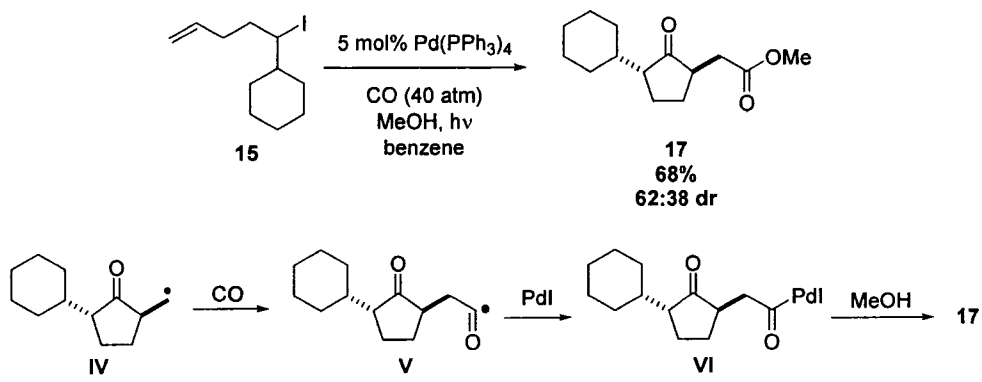
Scheme 11.



15 **16** **47%** **62:38 dr** **IV**

Treatment of alkenyl iodide **15** with tributyltin hydride and AIBN under an atmosphere of carbon monoxide affords the ketone-aldehyde product **16** in 47% yield with a 62:38 diastereoselectivity. The authors propose that radical **IV,** generated after the cyclization event, reacts with carbon monoxide to generate an acyl radical that is quenched via hydrogen transfer. The same group has also published a variant of this reaction using palladium (0) as a catalyst and light as a radical initiator (Scheme 12).[20] In this reaction the authors propose that **V**, generated from carbonylation of **IV**, reacts with palladium (I) iodide (from the reaction of palladium (0) with iodine radical) to form acyl palladium species **VI**, which acylates methanol to afford **17** in 68% yield and 62:38 diastereoselectivity.

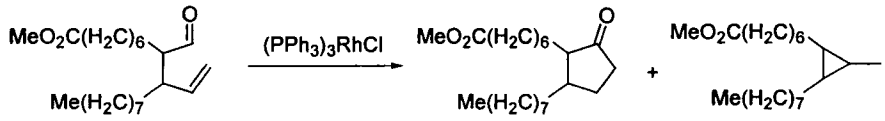
Scheme 12.



2.2.1.2 Hydroacylation

The hydroacylation of alkenes was first reported in 1972.[21] In their communication Sakai et al. reported that 4-pentenals cyclized to the corresponding cyclopentanones in the presence of 1 equivalent of Wilkinson's catalyst (Scheme 13). In

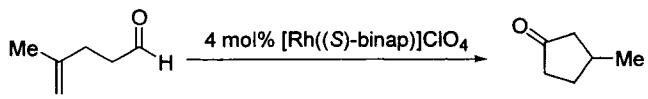
Scheme 13.



18 19 30% 20 30%

addition to the desired cyclopentanone **19** the product was accompanied by cyclopropane **20** that presumably arises through decarbonylation of the intermediate acyl rhodium species. Lochow and Miller reported a catalytic version of this reaction in 1976, and obtained exclusively the cyclopentanone products by conducting the reaction in chloroform solutions saturated with ethylene.[22] Although this reaction has not been used for the synthesis 2,3-, 2,4-, or 2,5-disubstituted cyclopentanones since it was originally reported, asymmetric variants have been developed for the synthesis mono-substituted cyclopentanones (Scheme 14).[23]

Scheme 14.

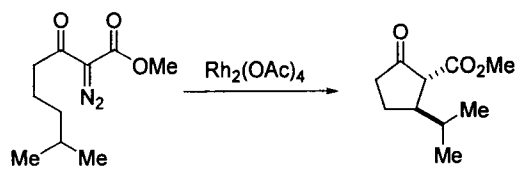


21 22 78% ee

2.2.1.3 C-H Insertion Reactions

Metal catalyzed C-H insertion reactions of α-diazocarbonyl compounds have provided a powerful method for the synthesis of cyclopentanone ring structures.[24] Taber

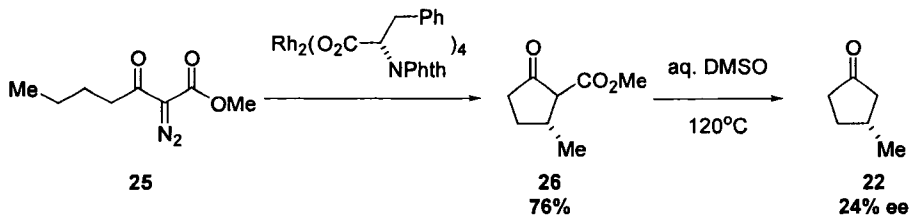
Scheme 20.



23 24 55%

and Petty demonstrated the synthesis of cyclopentanones from α-diazocarbonyl compounds in 1982 (Scheme 20).[25] Treatment of **23** with catalytic amounts of rhodium (II) acetate provided **24** in 55% yield. In 1990 Ikegami and co-workers reported the asymmetric synthesis of 3-substituted cyclopentanones by using a chiral rhodium complex to affect an enantioselective C-H insertion reaction (Scheme 21).[26] Subjection of

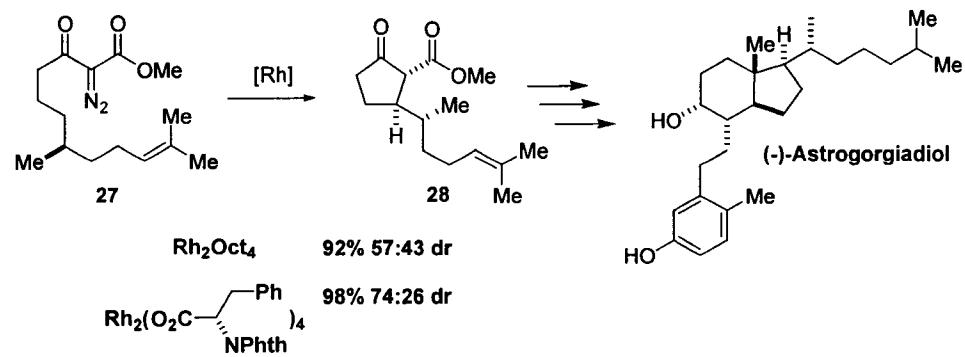
Scheme 21.



25 to 5 mol% of a chiral rhodium complex affords a 76% yield of the disubstituted cyclopentanone **26** that exists as a mixture of keto and enol forms. In order to determine the enantioselectivity of the newly formed center **26** was subjected to decarboxylation, by heating in aqueous dimethyl sulfoxide, to affod **22** in 24% ee.

Taber and Malcolm used the rhodium catalyzed C-H insertion reaction as a key-step in their total synthesis of (-)-Astrogorgiadiol (Scheme 22).[27] Hoping to observe a diastereoselective C-H insertion reaction, substrate **27** was treated with rhodium

Scheme 22.

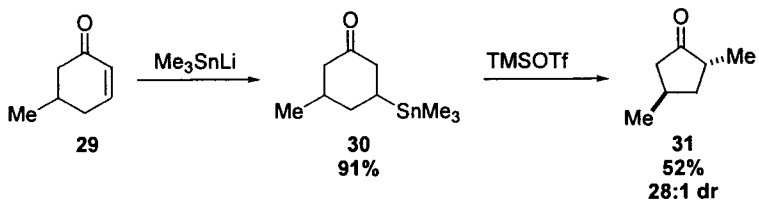


octanoate (0.6 mol%) to afford a 92% yield of the desired cyclopentanone **28** in only 57:43 diastereselectivity. Hoping to increase the diastereoselectivity of the reaction, chiral rhodium catalysts were screened. The use of chiral rhodium catalysts on an enantiopure substrate will lead to the formation of diastereomeric transition states, which may have different energies, leading to an enrichment of one diastereomer of product over the other. After screening various chiral catalysts they discovered that the chiral rhodium complex reported by Ikegami and co-workers (Scheme 21), favored the formation of the desired *trans*-cyclopentanone **28**, with approximately 3:1 diastereoselectivity. The *trans-cis* ratio of **28** was further improved by a kinetic resolution, that selectively reduced the ketone of the *cis*-diastereomer of **28**, ultimately affording the desired cyclopentanone **28** with a diastereoselectivity of greater than 10:1.

2.2.1.4 Ring Contraction-Expansion-Cycloaddition Processes

The first examples of ring contraction strategies for the synthesis of disubstituted cyclopentanones appeared in 1989. Building on their strategy utilizing rearrangements of β-trimethylstannyl ketones, Sato et al. published a ring contraction reaction of cyclohexenones (Scheme 15).[28] Treating the β-trimethylstannyl ketone **30**, derived from treatment of **29** with trimethylstannyl-lithium, with trimethylsilyl trifluoromethane sulphonate provided **31** in a 52% yield and 28:1 diastereoselectivity.

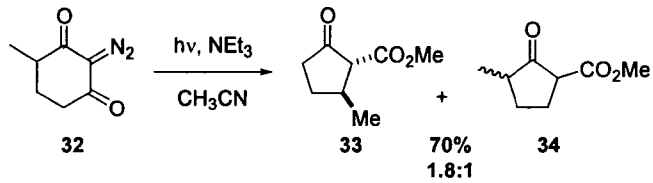
Scheme 15.



29 **30** **91%** **31** **52%** **28:1 dr**

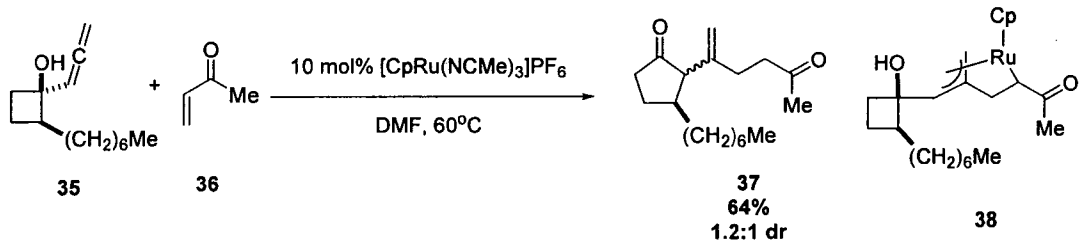
Cossy reported the application of the photo-initiated Wolff rearrangement of α-diazo-β-diketones to the synthesis 2,3- and 2,5-disubstituted cyclopentanones (Scheme 16).[29] Exposure of **32** to light led to a 1.8:1 mixture of regioisomers **33** and **34** in a yield of 70%.

Scheme 16.



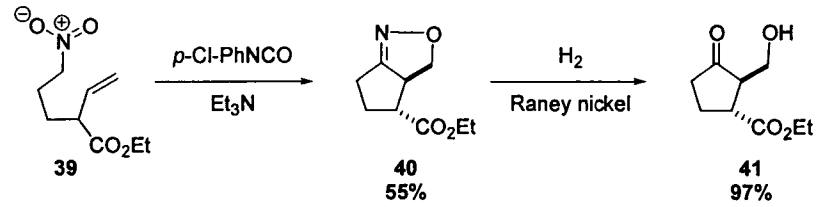
Building on precedent from the Trost group, who reported the interception of ruthenium allyl intermediates generated from an allenyl-alkene dimerization reaction with pendant nucleophiles, Ihara and co-workers reported the ruthenium-catalyzed ring expansion of allenylclobutanols (Scheme 17).[30] The combination of allenylcyclobutanol **35** and methylvinylketone **36** in the presence of ruthenium affords a 64% yield of **37** with a diastereoselectivity of 1.2:1. The authors propose the initial formation of ruthenium allyl species **38**, which triggers a ring expansion leading to the desired product.

Scheme 17.



Kozikowski and Stein reported the application of the intramolecular nitrile oxide cycloaddition reaction to the synthesis of 2,3-disubstituted cyclopentanones as part of their formal synthesis of sarkomycin in 1982 (Scheme 18).[31] Treatment of nitroalkene **39** with *para*-chloroisocyanate in the presence of triethylamine affords isoxazoline **40** in

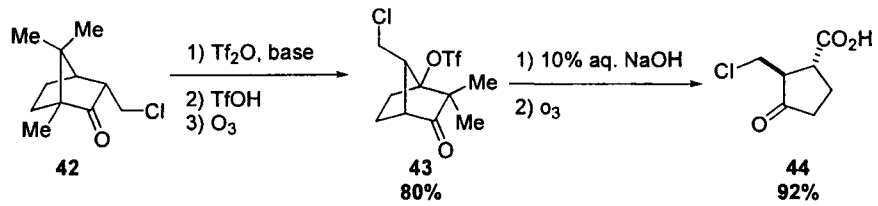
Scheme 18.



55% yield as a single diastereomer. Reduction with hydrogen over Raney nickel affords **41** in 97% yield.

Martínez et al. disclosed an elegant stereocontrolled approach to the enantiopure synthesis of 2,3-disubstituted cyclopentanones utilizing a ring opening strategy in 2001.[32] Starting from **42**, which is available from (1*R*)-camphor in 3-steps, **43** was synthesized

Scheme 19.

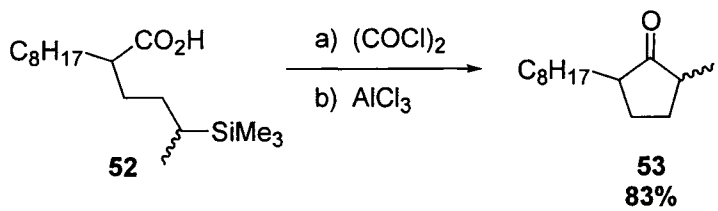


via a Wagner-Meerwein rearrangement followed by ozonolysis. Treatment of **43** with 10% aqeous sodium hydroxide induces a fragmentation reaction that affords a methylene cyclopentane, which following ozonlysis produces cyclopentanone **44** in 92% yield.

2.2.1.5 Anionic Reactions

Urabe and Kuwajima explored the use of an intramolecular acylation of alkyl silanes as an approach to cyclopentanones (Scheme 20).[33] In situ conversion of **52** to the

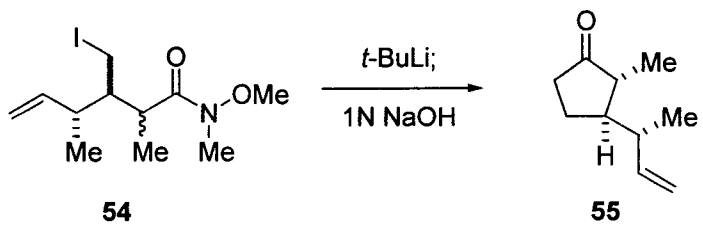
Scheme 20.



corresponding acyl chloride, followed by treatment with aluminum trichloride affords the 2,5-disubstituted cyclopentanone in 83% yield. The authors note that the methyl ketone that could potentially be obtained by transfer of a methyl group, as opposed to the alkyl substituent, from the trimethylsilyl group is not observed.

Sato and co-workers reported the synthesis of (2*R*, 3*R*)-2-methyl-3-[(1*R*)-1-methylprop-2-enyl]cyclopentanone utilizing a Weinreb amide for intramolecular ketone formation in 2003 (Scheme 21).[34] Iodoamide **54** was treated with 2.4 equivalents of *tert*-butyl lithium and the corresponding alkyl lithium compound cyclized smoothly at –78°C to give **55.**

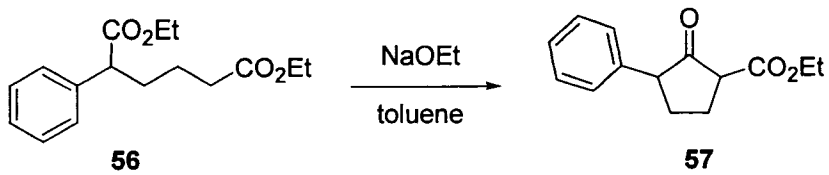
Scheme 21.



54 **55**

A classical anionic approach to the synthesis of cyclopentanones is the Dieckman cyclization of alkyl adipates.[35] In 2000, Pederson and co-workers used this strategy for the synthesis 2,5-disubstituted cyclopentanone **57** (Scheme 22).[36] Treatment of **56** with

Scheme 22.

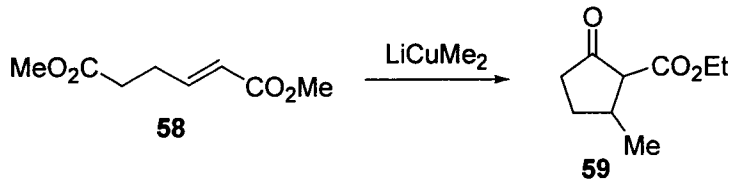


56 **57**

sodium ethoxide in toluene afforded the desired cyclopentanone **57.** An extension of the Dieckmann cyclization approach was reported in 1982 by Nugent and Hobbs Jr..[37] The

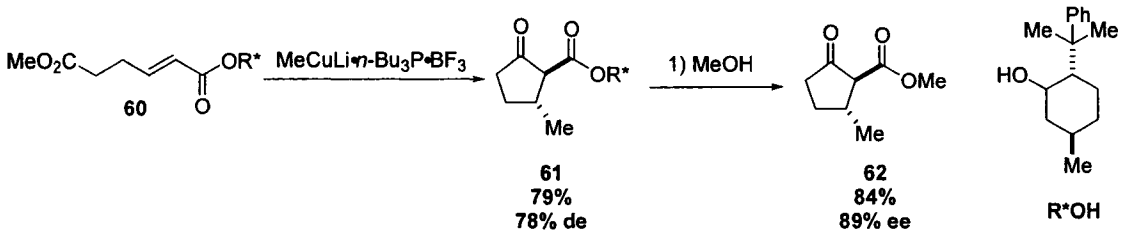
authors reported that conjugate addition reactions to appropriately functionalized substrates could result in the trapping of the resultant enolates by pendant esters giving rise to 2,3-disubstituted cyclopentanones of type **59** (Scheme 23).

Scheme 23.



Recognizing that an asymmetric conjugate addition might result in an asymmetric synthesis of substituted cyclopentanones Groth et al. used a chiral auxiliary on the Michael acceptor to control the stereochemistry of the conjugate addition (Scheme 24).[38] Addition of methylcuprate to **60**, followed by cyclization of the resulting anion, afforded

Scheme 24.



61 in 79% yield with 78% diastereomeric excess. Methanolysis of the product allows the chiral auxiliary to be recovered. The methanolysis of the *trans*-diastereomer of **61** occurs faster than that of the *cis*-diastereomer and allowed **62** to be isolated as a single diastereomer in 84% ee.

2.2.2 Addition of Substituents to Preformed Cyclopentanone Rings

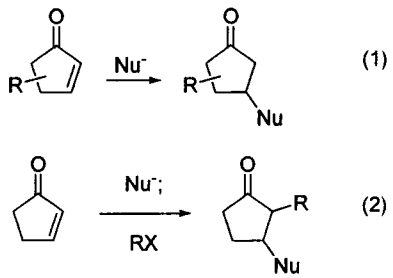
The use of enolate alkylation reactions for the formation of substituted cyclopentanones, although an attractive strategy, has not been widely used. Successful

approaches to 2,5-disubstituted cyclopentanones have been developed using the related enamine methodology developed by Stork and in some cases alkylation of 2-substituted cyclopentanones has been achieved by the use of strong, bulky bases (i.e. LDA).[39] To the best of our knowledge, enolate approaches to the selective synthesis of 2,3 and 2,4-disubstituted cyclopentanones have not been reported, presumably due to issues of regioselectivity in enolate formation.[40] A much more successful strategy for the synthesis of disubstituted cyclopentanones has been the addition of nucleophiles to α,β-unsaturated cyclopentanones.

2.2.2.1 Conjugate Addition Reactions

Two approaches have been used in the synthesis of cyclopentanones via conjugate addition. The first involves conjugate addition to a mono-substituted cyclopentanone (Equation 1, Scheme 25) and the second involves an addition-enolate alkylation strategy that forms a disubstituted cyclopentanone in a single operation (Equation 2, Scheme 25).

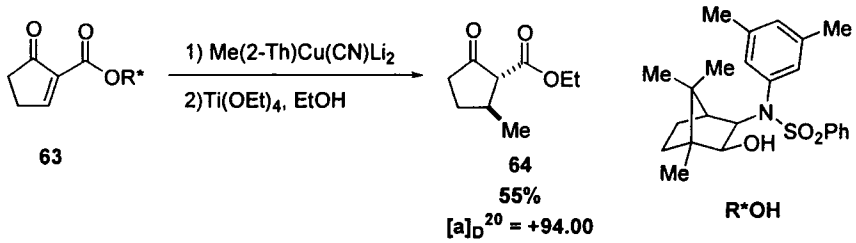
Scheme 25.



Asymmetric reactions have been developed using both strategies and some of these will be discussed below.

In 1996 Urban et al. reported the asymmetric synthesis of 2,3-disubstituted cyclopentanones using a chiral auxiliary appended to the cyclopentenone (Scheme 26).[41]

Scheme 26.

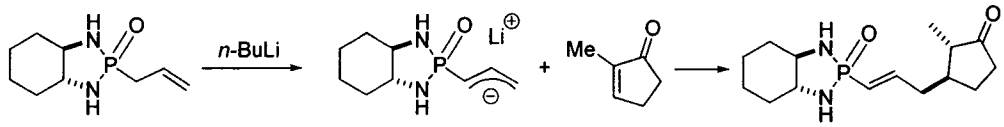


63 64 55% $[a]_D^{20}$ = +94.00 R*OH

Using a camphor-derived chiral auxiliary they reported the selective addition of methyl cuprate to cyclopentenone **63**. After removal of the chiral auxiliary, the enantioenriched ethyl ester **64** was obtained in 55% yield.

The addition of chiral phosphorus-stabilized allyl anions to cyclic enones has proven to be a powerful method for the asymmetric synthesis of cyclic ketones.[42] Hanessian and co-workers reported a highly selective synthesis of substituted cyclopentanones using this strategy in 2000 (Scheme 27).[43] Formation of allyllithium **66**

Scheme 27.



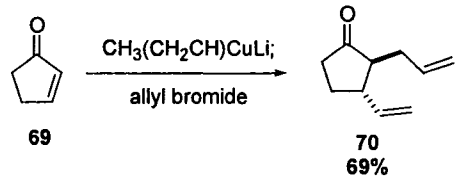
65 66 67 68 80% 93:7 dr

by treating **65** with butyllithium, followed by addition of cyclopentenone **67** affords the desired disubstituted cyclopentanone **68** in 80% yield with a diastereoselectivity of 93:7.

2.2.2.2 Conjugate Addition-Enolate Trapping Strategies

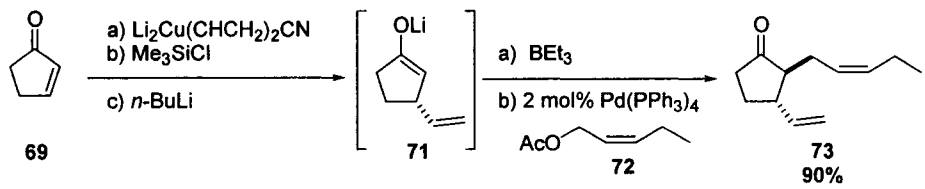
In 1974 Posner et al. reported the regioselective generation of cyclopentanone enolates, via a conjugate addition reaction of organocopper reagents, and their trapping with allylic halides (Scheme 28).[44] Treatment of **69** with lithium methyl(vinyl)cuprate followed by trapping of the resultant enolate with allyl bromide affords **70** in 69% yield.

Scheme 28.



The extension of this chemistry to other allylic reagents has proven problematic with the main problems being loss of enolate regiospecificity, loss of allyl stereochemistry and the need for a large excess of allyl halide.[45] Luo and Negishi addressed this problem by combining their laboratories methodology for palladium-catalyzed allylation of lithium enolates with regioselective enolate generation via cuprate conjugate additions.[46] Treatment of **69** with vinyl cuprate followed by enolate trapping with trimethylsilyl chloride and lithium enolate formation presumably gives **71**. **71** is treated with 2 equivalents of triethylborane followed by trapping with the allylic palladium species generated from palladium (0) tetrakistriphenylphophine and allyl acetate **72** to give **73** in 90% yield.

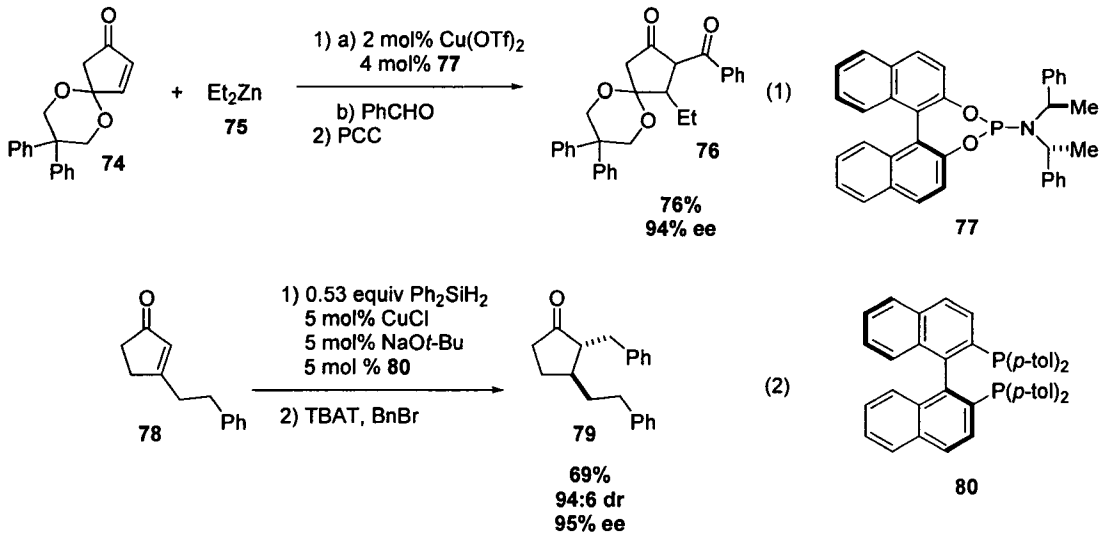
Scheme 29.



The main limitation of the conjugate addition-enolate trapping approach to the asymmetric synthesis of 2,3-disubstituted cyclopentanones is the limited scope of nucleophiles that participate in the asymmetric conjugate addition to cyclopentenones.[47] In light of this limitation, Feringa and co-workers reported the asymmetric synthesis of 2,3-disubstituted cyclopentanone **76** in 2001 (Equation 1, Scheme 30).[48] In order to

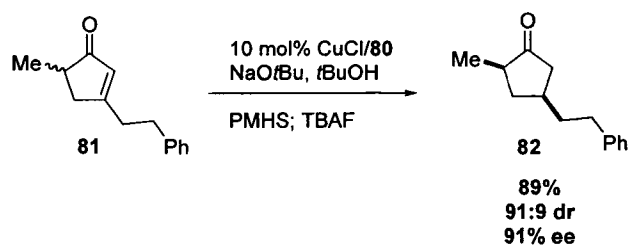
address the limited nucleophile scope available to asymmetric conjugate addition reactions to cyclopentanones, Yun and Buchwald reported a complimentary approach to 2,3-disubstituted cyclopentanones involving copper catalyzed hydride addition to 3-substituted cyclopentenones followed by alkylation of the resultant enolate (Equation 2, Scheme 30).[49]

Scheme 30.



As an extension of their conjugate hydride addition-enolate trapping sequence, Jurkauskas and Buchwald reported the dynamic kinetic resolution of substrate **16** when subjected to their developed copper catalyzed conjugate reduction chemistry in the presence of *tert*-butoxide providing **17** in 89% yield as a 91:9 mixture of diastereomers with the major diastereomer having an ee of 91% (Scheme 31).[50]

Scheme 31.



2.3 Results

After Kerr, Read de Alaniz, and Rovis' initial publication in 2002, we became curious as to what effect pre-existing stereocenters would have on the course of the asymmetric intramolecular stetter reaction. In particular, we were interested in derivatives of aliphatic substrate **1** that upon cyclization could potentially provide an asymmetric route to disubstituted cyclopentanones (Scheme 32). At the outset of the investigation we were intrigued by the potential to observe a kinetic resolution. However, we were also curious to see how chiral carbenes behaved in the presence of pre-existing stereocenters envisioning the future application of the asymmetric intramolecular Stetter reaction to complex molecule synthesis.

Scheme 32.

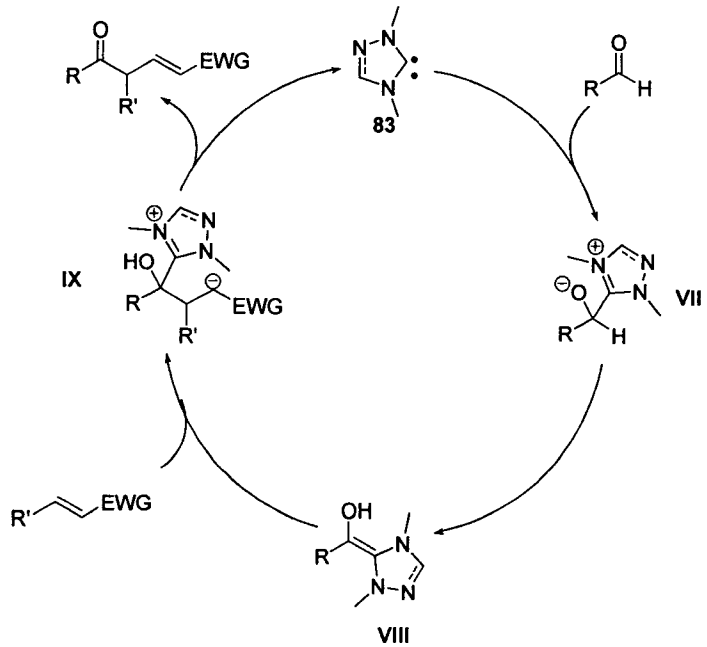
The application of chiral catalysts to racemic substrates offers the opportunity to observe a kinetic resolution.[51] Kinetic resolutions by non-enzymatic systems have become increasingly valuable. Traditional kinetic resolution occurs when one enantiomer of substrate reacts at a faster rate than the other allowing for the synthesis of enantiopure product with a maximum yield of 50%. Dynamic kinetic resolution occurs when the pre-existing stereocenter is racemized faster than the desired enantioselective process, offering the potential to synthesize single enantiomer products in high yields from racemic material. Parallel kinetic resolution occurs when different products are formed from each substrate enantiomer.[52] In this context, we became interested in assessing the

impact of substitution at every position between the aldehydes and the Michael acceptor on rate and enantioselectivity of the intramolecular asymmetric Stetter reaction.

The working hypothesis for the mechanism of the Stetter Reaction is shown in Scheme 33.[53] Triazolium salt **83** first interacts with an aldehyde to provide tetrahedral intermediate **VII**. A proton transfer event then affords Breslow intermediate **VIII** that can then combine with a Michael acceptor to form intermediate **IX**. A second proton transfer event provides the desired product and returns the carbene to the catalytic cycle.

In order for a kinetic resolution to be observed in the catalytic intramolecular asymmetric Stetter reaction and still obtain high yields of products, one of two things must be true: 1) the catalyst selectively interacts with one enantiomer of substrate over the other, or 2) the catalyst interacts with both enantiomers of substrate but the formed diastereomeric intermediates have different energies, thus leading to different rates of product formation. In the case of substrates that contain pre-existing stereocenters on carbon atoms not prone to epimerization another requirement implied is that the formation of the diastereomeric transition states is reversible, allowing the catalyst to return to the catalytic cycle. Therefore, the observation of kinetic resolution would provide insight into the mechanism of the Stetter reaction.

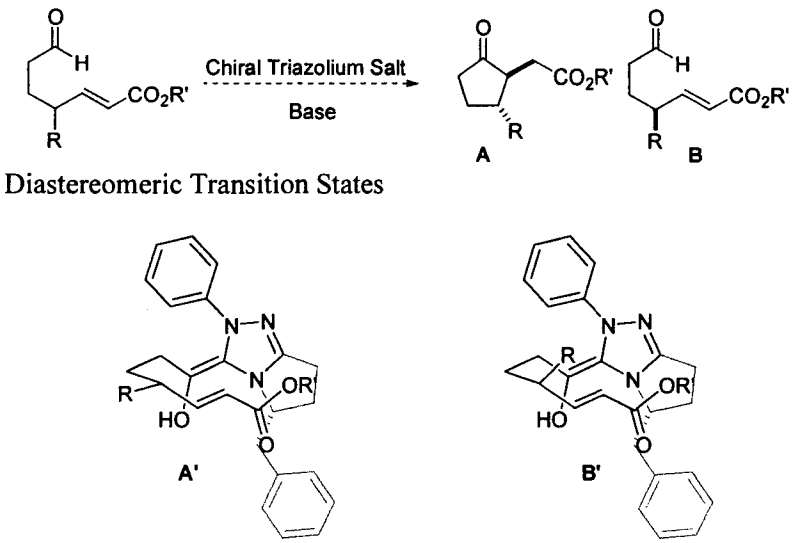
Scheme 33.



2.3.1 Synthesis of 2,3-Disubstituted Cyclopentanones

With a substituent in close proximity to the Michael acceptor we were intrigued by the possibility of observing a kinetic resolution (Scheme 34). In the perfect kinetic resolution, a 50% yield of enantiopure **A** would be obtained, and unreacted substrate **B** would be recovered enantiopure in 50% yield. In order for a kinetic resolution to be observed formation of Breslow intermediates **A'** and **B'** or the tetrahedral intermediate (**VII**, Scheme 33) leading to the Breslow intermediates would need to be reversible and the amount of kinetic resolution observed would depend upon the energy difference between these intermediates. We hypothesized that steric interactions between the R-substituent and the catalyst in the proposed Breslow inermediate **B'** would make **A'** the lower energy pathway providing **A** as the major product.

Scheme 34.

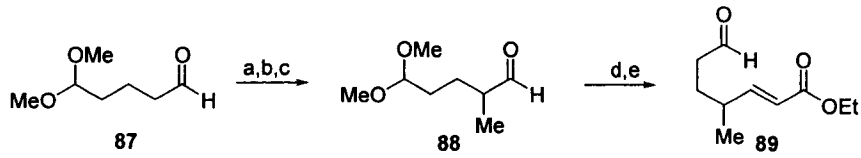


2.3.1.1 Substrate Synthesis

Two different routes to the required substrates **89** and **92** were developed. The synthesis of **89** began with the differentially protected dialdehyde **87** from the Schreiber ozonolysis of cyclopentene.[54] The hydrazone, formed by treatment with *N,N*-dimethyl hydrazine, was alkylated with iodomethane. Removal of the hydrazone afforded the intermediate aldehyde **88**.[55] The aldehyde was treated with (carboethoxymethylene)triphenyl-phosphorane, followed by triflouroacetic acid to afford **89** (Scheme 35).

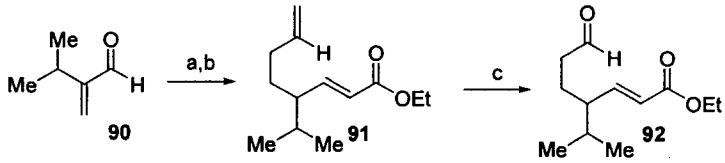
The synthesis of **92** began with the addition of allylmagnesium chloride to isopropylacrolein. The secondary alcohol then underwent an anionic oxy-Cope rearrangement by treatment with potassium hydride in refluxing dioxane.[56] Treatment of the resulting aldehyde with (carboethoxymethylene)triphenyl-phosphorane, followed by a two-step Lemieux oxidation afforded **92** (Scheme 36).[57]

Scheme 35.



Reagents: a) *N,N*-dimethylhydrazine, b) LDA, iodomethane (85%), c) $NaIO_4$ (34%), d) (carboethoxymetylene)tri-phenyl-phosphorane (81%), e) trifloroacetic acid (72%).

Scheme 36.

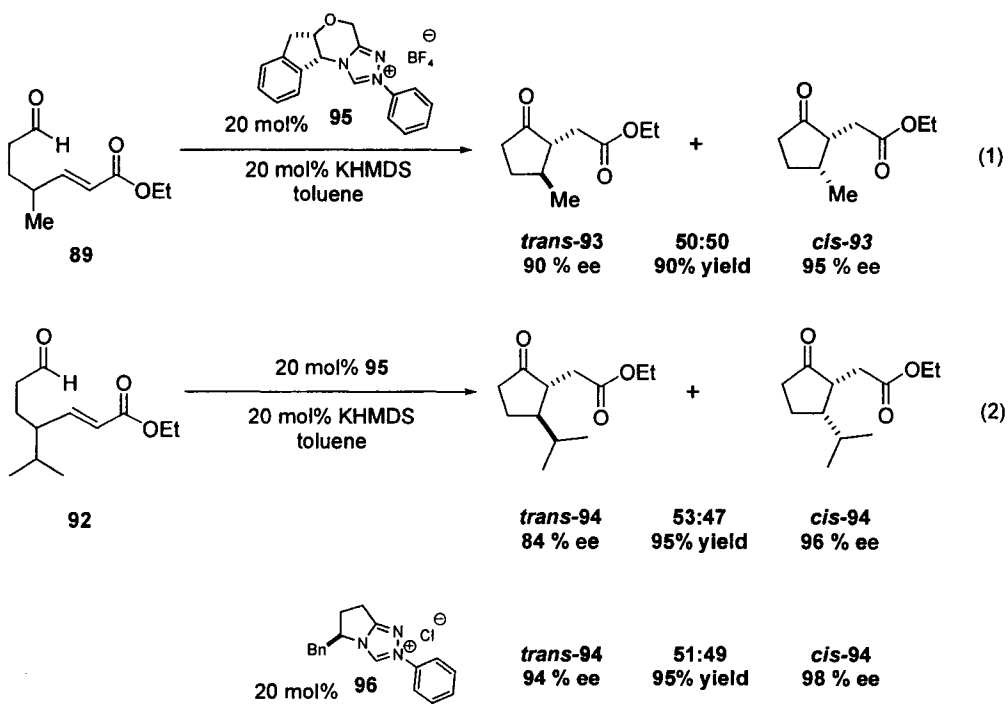


Reagents: a) allyl-MgCl (84%), b) KH, reflux; (carboethoxymethylene)triphenyl-phosphorane (41%), c) osmium tetroxid; lead tetraacetate (34%)

2.3.1.2 Intramolecular Stetter Results

The results for the cyclization of **89** and **92** are shown in Scheme 37. Upon treatment with **95**, **89** cyclizes smoothly to afford a 1:1 mixture of ***trans*-93** and ***cis*-93** in 90% yield with enantioselectivities of 90% and 95% respectively. Subjection of **92** to **95** afforded a 53:47 mixture of ***trans*-94** and ***cis*-94** in 95% yield with 84% and 96% ee respectively. The enantioselectivities were improved by the use of sterically smaller catalyst **96**. The results indicate that substitution α to the Michael acceptor has little effect on the stereochemical outcome of the Stetter reaction.

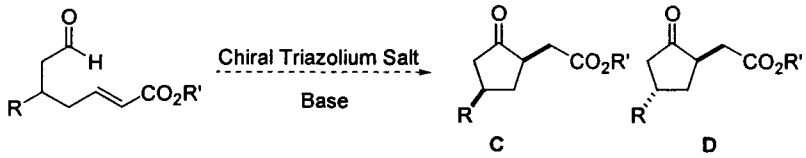
Scheme 37.



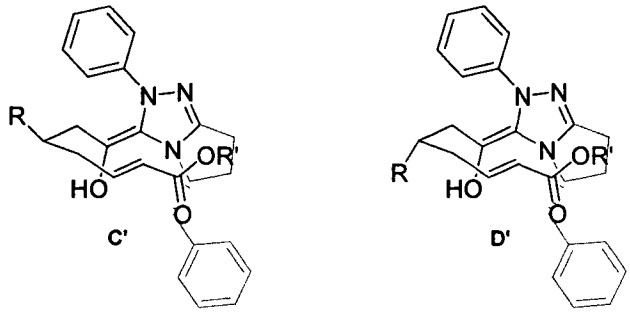
2.3.2 2,4-Disubstituted Cyclopentanones

The substrates required for the intermolecular Stetter reaction are shown in Scheme 38. Examination of the proposed transition states **C'** and **D'** suggested that their would be little interaction between the catalyst and the pre-existing stereocenter, which might allow for the synthesis of both diastereomers of the product.

Scheme 38.



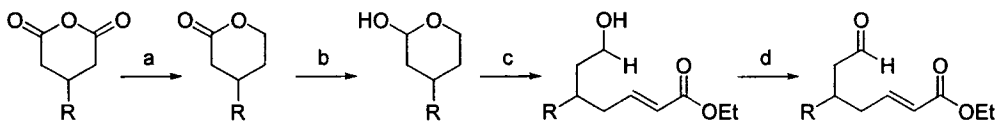
Diastereomeric Transition States



2.3.2.1 Substrate Synthesis

Substrate synthesis commenced with the appropriate 3-substituted glutaric anhydride **97** and **98**. Reduction with sodium borohydride provided the 3-substituted lactone. Further reduction with Dibal-H affords the lactol that was treated with (carboethoxymethylene)triphenyl-phosphorane to install the Michael acceptor. Swern oxidation of the resultant primary alcohol completed a four step unoptimized synthesis of **105** and **106** (Scheme 39).

Scheme 39.

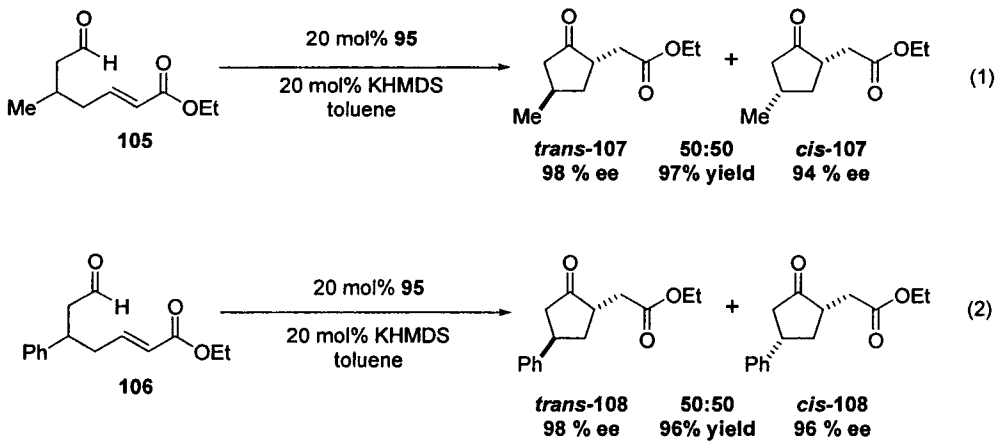


Reagents: a) $NaBH_4$; TFA, b) Dibal-H, c) (carboethoxymethylene)triphenyl-phosphorane, d) Swern.

2.3.2.2 Intramolecular Stetter Results

The results for the cyclization of **105** and **106** are shown in Scheme 40. Substrate **105** cyclizes to provide ***trans*-107** and ***cis*-107** as a 1:1 mixture in 97% yield, with 98% and 94% ee respectively. Substrate **106** cyclizes to provide ***trans*-108** and ***cis*-108** in 96% yield, with 98% and 96% ee respectively. Once again the outcome appears to be independent of steric bulk suggesting that the pre-existing stereocenters at the 5-position have no effect on the intramolecular Stetter reaction.

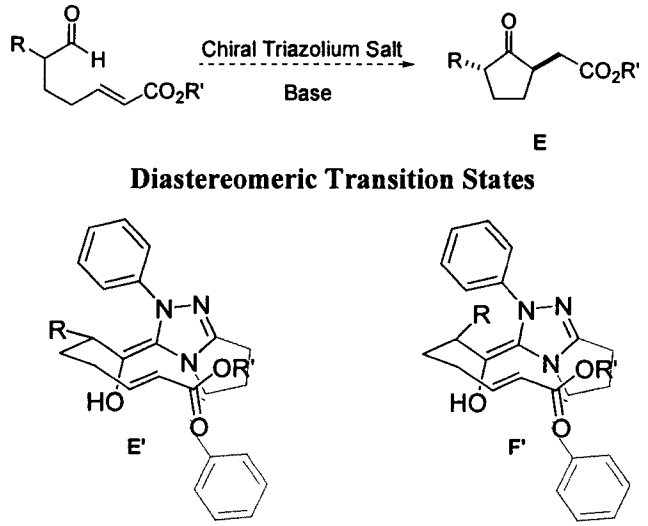
Scheme 40.



2.3.3 2,5-Disubstituted Cyclopentanones

To the best of our knowledge there are no examples of the asymmetric synthesis of 2,5-disbustituted cyclopentanones. Therefore we were excited about the potential of the Stetter reaction to fill this gap in the literature. Also intriguing was the possibility of observing a dynamic kinetic resolution (Scheme 41). If the formation of Breslow intermediates **A'** and **B'** is reversible and the pre-existing stereocenter next to the aldehydes was epimerized under the reaction conditions, the formation of one diastereomer of product in high yield and ee could potentially be observed. Analysis of the proposed transition state suggested that transition state **E'** leading to product **E** would

Scheme 41.

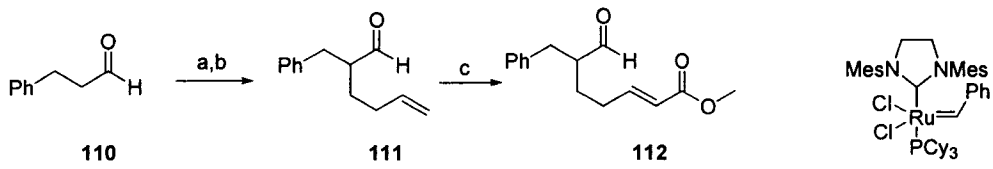


be lower in energy than **F'** due to the apparent interaction between the R-substituent and the catalyst.

2.3.3.1 Substrate Synthesis

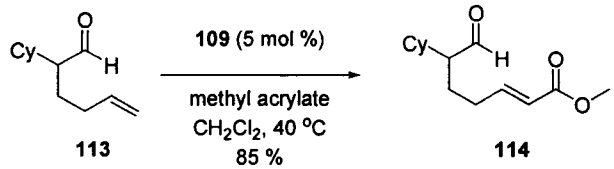
The synthesis of substrate **112** began with alkylation of hydrocinnamaldehyde *N,N*-dimethyl hydrazone with 4-bromobutene.[58] After hydrazone cleavage, the aldehyde was subjected to cross metathesis with methyl acrylate, providing **112** (Scheme 42).[59] Substrate **114** was made by cross metathesis of 5-cyclohexyl-hex-5-enal **113** with methyl acrylate (Scheme 43). The enal **113** was prepared in direct analogy to the precursor to **91**.

Scheme 42.



Reagents: a) *N,N*-dimethyhydrazine, b) LDA, 4-bromobutene; Ambelyst-15, (19 %) c) **109** (5 mol %), methyl acrylate (67 %)

Scheme 43.

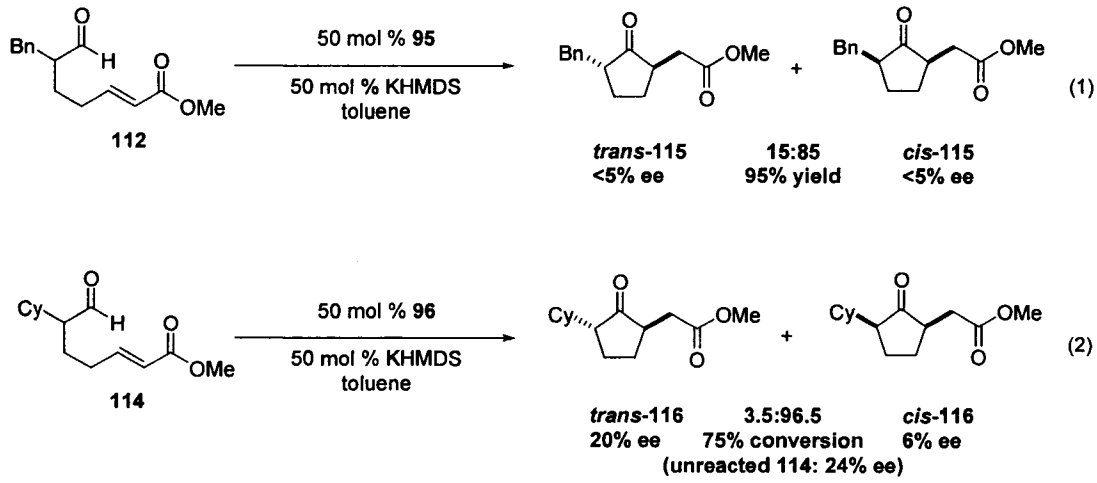


2.3.3.2 Intramolecular Stetter Results

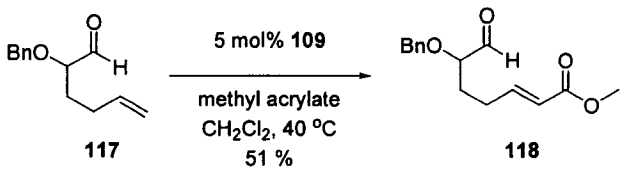
The results for the cyclization of **112** and **114** are shown in Scheme 44. Under the conditions used for the previous substrates (20 mol% catalyst), **112** fails to give reproducible results, a situation that was rectified upon increasing the catalyst loading to 50 mol%. Cyclization of **112** affords a 95% yield of product, with 85:15 selectivity favoring the *cis* diastereomer, formed as a racemate. Cyclization of **114** fails in the presence of catalyst **95**, but occurs with the sterically smaller catalyst **96** to afford ***cis*-116** in low ee but excellent selectivity over its *trans* isomer, validating the fact that the alpha stereocenters have a dramatic effect on the intramolecular Stetter reaction. Interestingly, the unreacted starting material from this reaction was modestly enantioenriched.

In light of this result sterically smaller substituents were examined using the benzyloxy substituted substrate **118**.[60] The required substrate **118,** was prepared from the known aldehyde **117** by cross-metathesis with methyl acrylate (Scheme 45).[61] Subjection of **118** to 50 mol% **95** affords a nearly 1:1 mixture of ***cis*-119** and ***trans*-119** in 54 and 14% ee respectively. Concerned that the carbinol position was being epimerized under our reaction conditions, we were curious to see if the removal of HMDS from the reaction solution would afford a more selective reaction. Subjection of **118** to 50 mol% **95** in the absence of HMDS affords a 95% yield of **119** as a 59:41 mixture of diastereomers in 70% and 42% ee respectively.

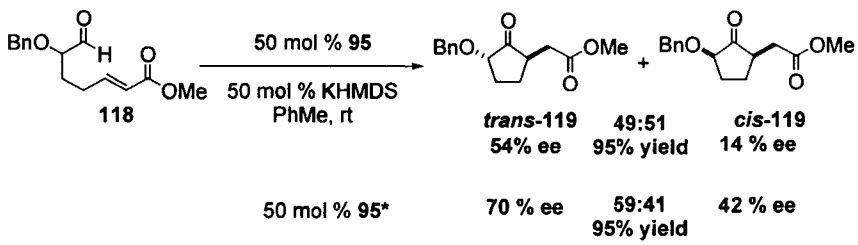
Scheme 44.



Scheme 45.



Scheme 46.



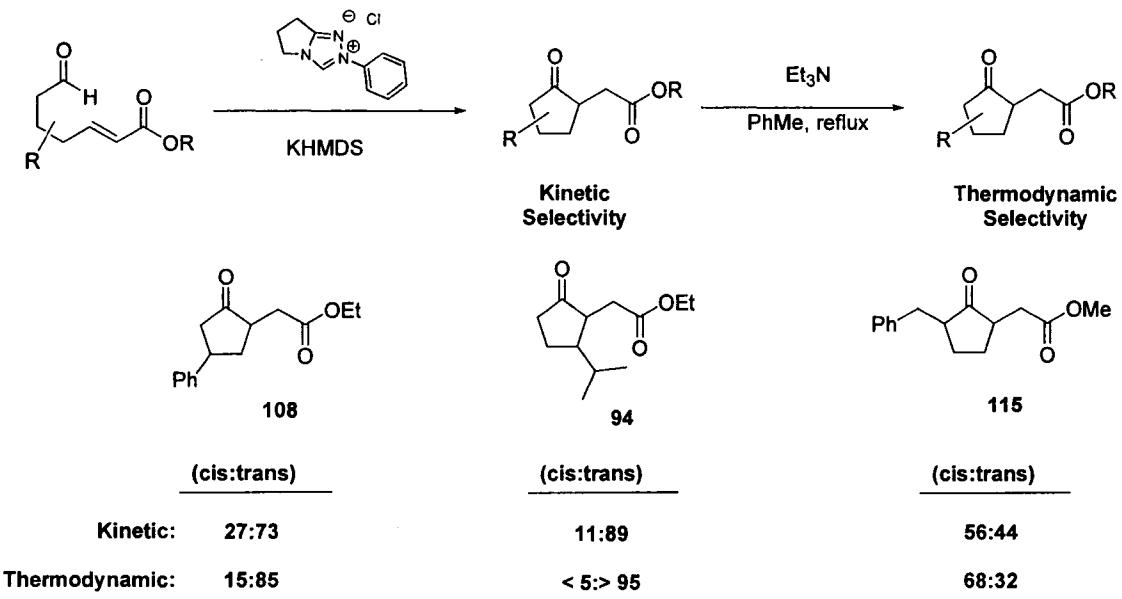
* HMDS was removed before substrate was added.

2.4 Kinetic and Thermodynamic Selectivities

In order to help analyze the above results, the kinetic and thermodynamic ratios for the disubstituted cyclopentanones **108**, **94**, and **115** were examined. Kinetic ratios were determined by cyclization with 1 equivalent of achiral triazolium salt and the thermodynamic ratios were determined by heating the substrates in toluene in the presence of excess triethylamine (Scheme 31). It is intriguing to note that the achiral

catalyst provides low selectivity in the formation of **115**. This is in sharp contrast to the ability of chiral triazolium salts to form the *cis* product in high diastereoselectivity, a situation ascribed to the large steric differences between the achiral and chiral triazolium salts.

Scheme 47.

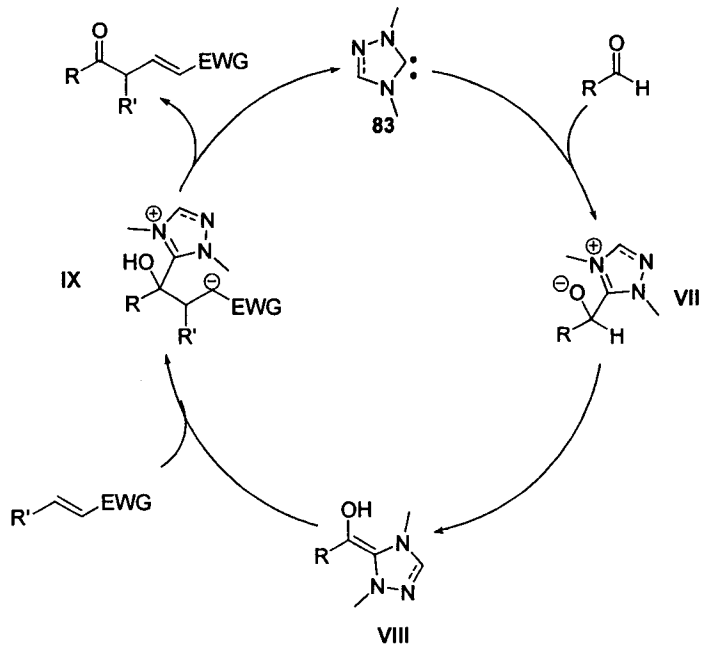


2.5 Discussion

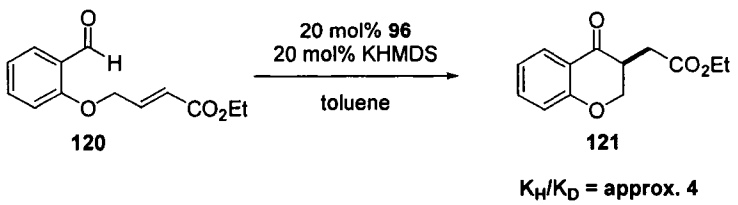
Concurrently with our investigation into the effect of pre-existing stereocenters in the intramolecular asymmetric Stetter reaction, Javier Read de Alaniz has carried out investigations into the reaction mechanism.[62] In the proposed reaction mechanism there are two proton transfer events (**VII** to **VIII**, **IX** to release product and return **83** to the catalytic cycle) and one carbon-carbon bond-forming event (**VII** to **IX**) (Scheme 48). In order to elucidate whether a proton transfer event or the carbon-carbon bond-forming event was the rate determining step, the rate differences between protio- and duetereoaldehydes were investigated, resulting in the observation that there is a kinetic

isotope effect of approximately 2 for the intramolecular Stetter reaction shown in Scheme 49.[63] This value is consistent with a primary isotope effect indicating that a proton

Scheme 48.



Scheme 49.



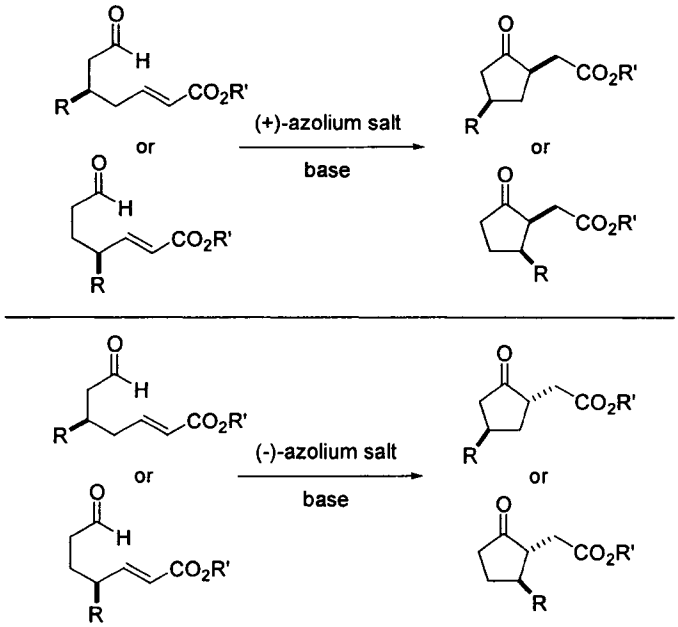
transfer event is the rate limiting step.

Since there are two proton transfer events in the proposed reaction mechansim, Javier collaborated with the laboratories of Dan Singleton to gain further insight.[61] The Singleton group has developed a method that allows for the determination of ^{13}C isotope effects at natural abundance.[64] The methodology involves the execution of a reaction to greater than 80% completion followed by isolation of the starting material. ^{13}C NMR is

then used to determine if any carbon atoms have been isotopically enriched by comparing them to a carbon atom in the molecule, not involved in the reaction. That is chosen as an internal standard. Javier conducted the experiment in Scheme 49 and sent samples from the reaction to the Singleton laboratories. Jackie Besinaiz of the Singleton group analyzed the samples and discovered that the aldehydic carbon of **120** had been isotopically enriched indicating that the aldehyde is involved in the first irreversible step. The implication for the mechanistic proposal is that either addition of the carbene to the aldehyde to form **VI** or proton transfer to form the Breslow intermediate (**VI** to **VII**) is the rate-determining step. Taken together, the deuterium isotope effect and the ^{13}C isotope effect, suggest the rate-determining step is the transformation of the tetrahedral intermediate **VI** to the Breslow intermediate **VII.**

The results from investigations into the effects of pre-existing stereocenters on the Stetter reaction are in accord with the above mechanistic investigations. In all substitution patterns examined both enantiomers of starting material were cyclized to the desired product, indicating that once formed the Breslow intermediate proceeds to product. In the case of 2,3- and 2,4-disubstituted cyclopentanones the pre-existing stereocenter had no effect on the stereochemical outcome of the intramolecular asymmetric Stetter reaction. The implication of this is that the Stetter reaction may find potential uses for the synthesis of enantiopure *trans* or *cis* diastereomers of these cyclopentanones. Either diastereomer may be obtained from the same enantiomer of substrate, depending the antipode of the chiral catalyst used (Scheme 50). Although the

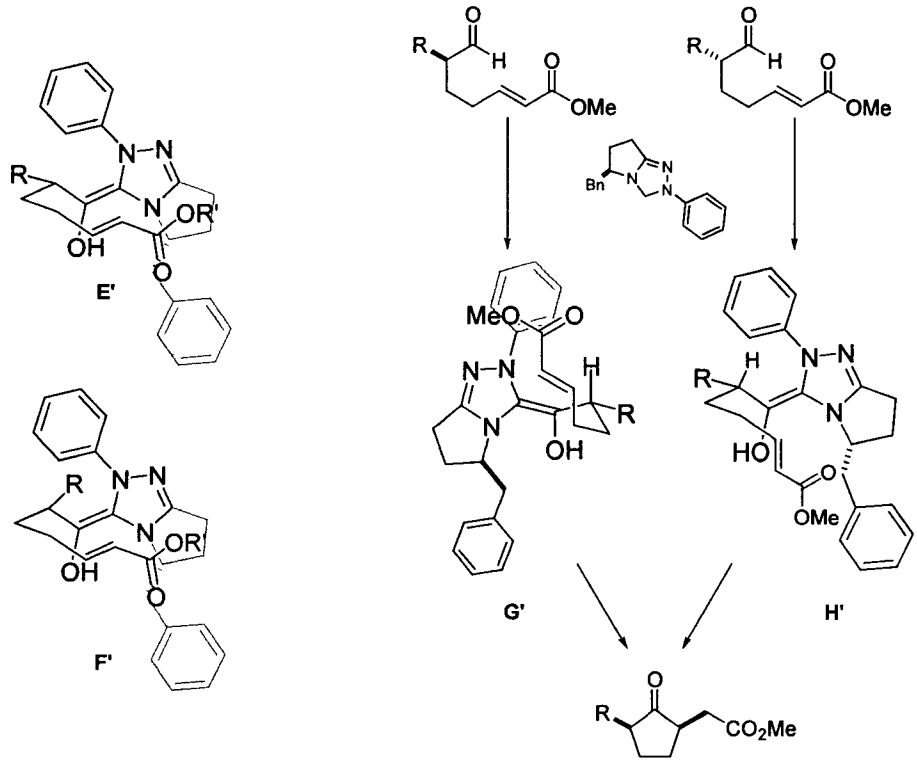
Scheme 50.



use of a chiral catalyst on a chiral substrate is not desirable, the dearth of catalytic asymmetric methodologies for the synthesis of these types of cyclopentanones may make the strategy attractive.

The effect of stereocenters α to aldehydes is more difficult to interpret. The intramolecular Stetter reaction using chiral triazolium salts formed the *cis*-diastereomers as racemic mixtures. In the proposed transition states (Scheme 51), the *cis*-diastereomer would presumably arise via what appears to be the more sterically hindered transition state **F'**. The results have led us to reexamine the proposed transition state. Our current hypothesis is that the pre-existing stereocenter determines the facial selectivity of attack on the Michael acceptor by the Breslow intermediate. This may be due to a significant interaction between a psuedo-axial substituent α to the nucleophilic alkene and the aryl ring of the catalyst.

Scheme 51.



Taking this proposed steric interaction into account, and also the diastereoselective outcome of the reaction, two new diastereomeric transition states **G'** and **H'** are proposed (Scheme 51). In these models it is proposed that the substituent resides in the psuedoaxial position to minimize the potential $A_{1,3}$ strain. The orientation of the pre-existing substituent then dictates which face of the chiral carbene, the Michael acceptor occupies, leading to the obtained *cis* stereochemistry. The results obtained with the α-benzyloxy substituents are not readily explained by the models **G'** and **H'**, but may be explained by our original models **E'** and **F'**. Due to steric and electronic factors, the smaller A-value for alkoxy substituents (-OMe = 0.6) compared to alkyl substituents (-Et = 1.8) may lead to less of an energetic preference for the psueodo-equatorial postion

versus the psuedo-axial position. If this is indeed the case proposed transition state **E'** would lead to the *trans*-2,5-disubstituted cyclopentanone in moderate enantioselectivity, as we observed. Under this assumption, transition state **F'** may also be operational allowing for the formation of the *cis*-diastereomer, but an interaction between the benzyloxy substituent and the aryl ring may force the Michael acceptor to reside in two different positions, leading to the low enantioselectivity that we observed. A mathematical treatment of the results obtained for the cyclization of benzyloxy substrate **118** reveals that the product ratios obtained for the cyclization in the absence of HMDS could only be obtained if the racemic substrate had become enantioenriched, favoring the (*S*)-enantiomer, during the course of the reaction.

2.6 Conclusion

The Stetter reaction is a viable option for the synthesis of disubstituted cyclopentanones. 2,3- and 2,4-disubstituted cyclopentanones are synthesized via a parallel kinetic resolution providing both *trans* and *cis* diastereomers in high ee. There appears to be little effect of steric bulk at the 4- and 5-positions of the substrates indicating that there is very little interaction with the catalyst. Substituents next to the aldehydes seem to override catalyst control and dictate the course of the reaction to selectively form the 2,5-*cis* disubstituted cyclopentanones in good yield.

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Chapter 3

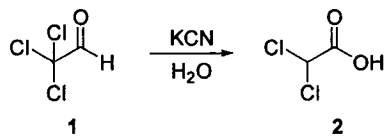
Catalysis of the Wallach Rearrangement by Triazolium Carbenes

3.1 Introduction

Esters are a ubiquitous functional group in organic synthesis and there have been many methods developed for their synthesis. Most of these methodologies rely on stoichiometric amounts of coupling reagents or activated carboxylates.[1] Due to cost and environmental concerns, the use of stoichiometric reactions is generally not as desireable their catalytic counterparts. Therefore, the development of catalytic processes for the synthesis of esters is desirable for the organic chemist. In conjunction with efforts to extend the utility of chiral triazolium salts, the triazolium carbene catalyzed Wallach rearrangement is reported herein.

In 1873 Wallach reported the conversion of chloral to dichloroacetic acid in the presence of aqeous potassium cyanide (Scheme 1).[2] This simultaneous reduction-oxidation reaction inspired lively mechanistic discussions in the literature.

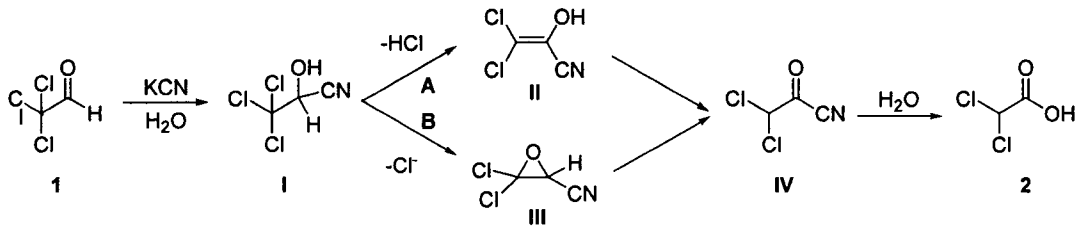
Scheme 1.



1 2

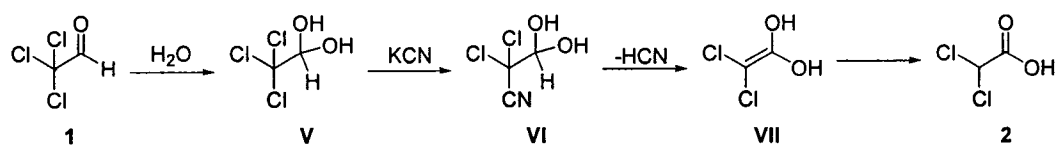
Kötz contributed the first mechanistic proposal in 1913, suggesting two possible pathways for the formation of **2** (Scheme 2).[3] The first step is the addition of cyanide anion to **1** to form cynohydrin **I**. In path **A** the authors propose the loss of HCl to give

Scheme 2.



intermediate **II** which then tautomerizes to give **IV**. In path **B** the authors propose the formation of epoxide **III** which then rearranges perhaps via a 1,2-hydride shift to give **IV**. The last step of the mechanism involves the hydrolysis of the acyl cyanide to give product **2**. The authors presented evidence for the formation of cyanohydrin **I** and the lability of acylcyanide **IV** but were unable to distinguish between the two intermediates **II** and **III**. Chattaway and Irving rebutted this mechanistic proposal in 1929, suggesting that cyanohydrin formation was not necessary for product formation (Scheme 3).[4] They proposed that cyanide anion first displaces a chloride anion on chloral hydrate **V** to give **VI** followed by loss of HCN to generate intermediate **VII**, which then tautomerizes to product **2**. Lapworth and co-workers criticized this rebuttal in 1931 based on their previous investigations into the cyanide catalyzed Benzoin reaction and they extended their support for intermediate **II**.[5]

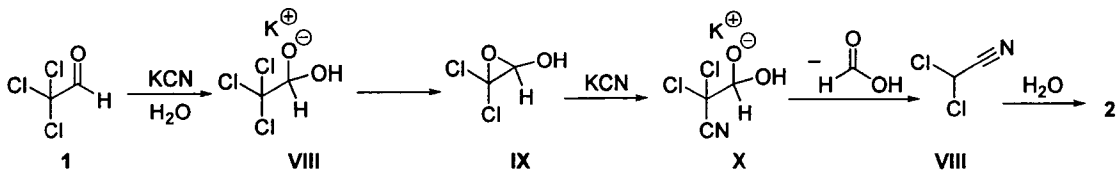
Scheme 3.



Cram and Hammond speculatively put forth an interesting proposal in an organic chemistry textbook published in 1958 (Scheme 4).[6] The authors suggested that

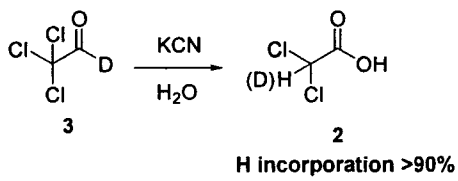
intermediate epoxide **IX** was formed by an intramolecular chloride displacement. The epoxide is then opened by cyanide ion to generate intermediate **X**, which then diproportionates into formic acid and dichloroacetonitrile with the latter being hydrolyzed into the observed product **2**. Rosenblum et al. were able to discount this mechanism by using C^{14} labeled potassium cyanide, showing that the product **2** contained only negligible amounts of radioactivity.[7]

Scheme 4.



In the Pinner-Kötz mechanistic proposal (Scheme 2) intermediate **III** may rearrange into **IV** via a 1,2 hydride shift. Fodor and Katritzky were able to rule out a 1,2-hydride shift by using deuterium-labeling studies in 1961 (Scheme 5).[8] By subjecting deuterium labeled chloral **3** to potassium cyanide in water they observed greater than 90% proton incorporation at the α-position suggesting a hydride shift mechanism is not operative.

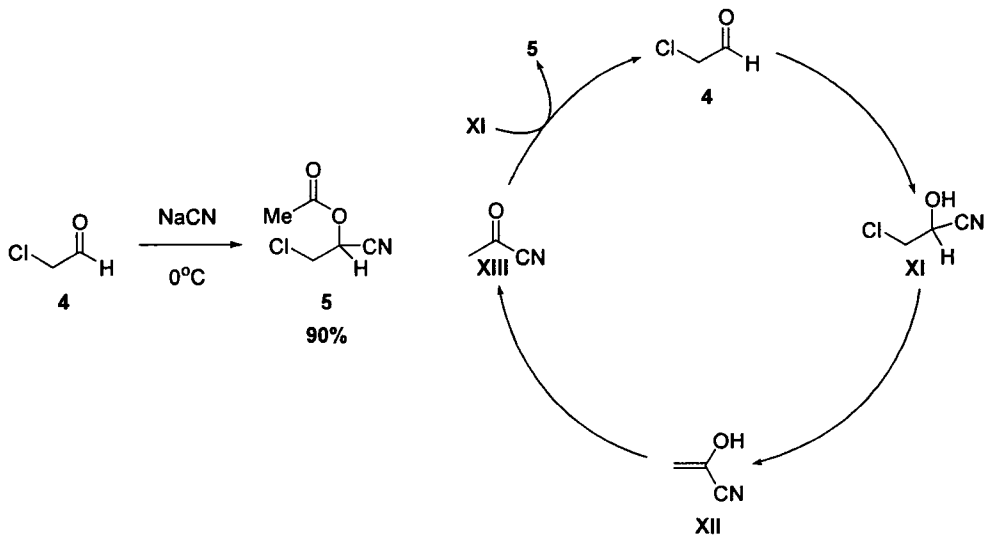
Scheme 5.



In 1963 Nowak reported the conversion of chloroacetaldehyde **4** to 2-chloro-1-cyanoethyl acetate **5** in the presence of aqueous sodium cyanide at 0°C (Scheme 6).[9] His

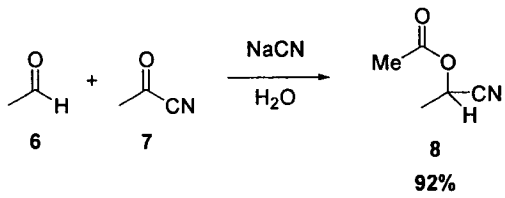
proposed mechanism is analogous to that proposed by Pinner and Kötz (Path A, Scheme 2) with **5** being formed by reaction of cyanohydrin **XI** with acyl cyanide **XIII**. To test

Scheme 6.

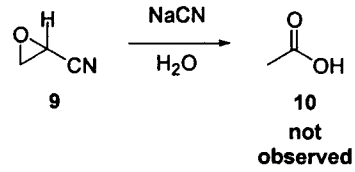


whether or not acyl cyanide was an intermediate in the reaction mechanism Nowak slowly added cyanoacetate to an aqueous mixture of acetaldehyde and sodium cyanide (Scheme 7). The major product of this reaction was 1-cyanoethyl acetate, stongly implicating **7** as an intermediate in the reaction mechanism. In order to distinguish

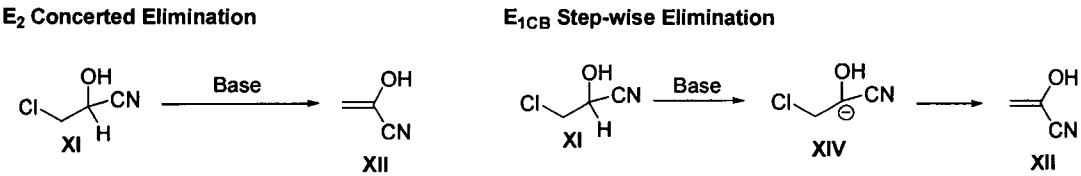
Scheme 7.



Scheme 8.

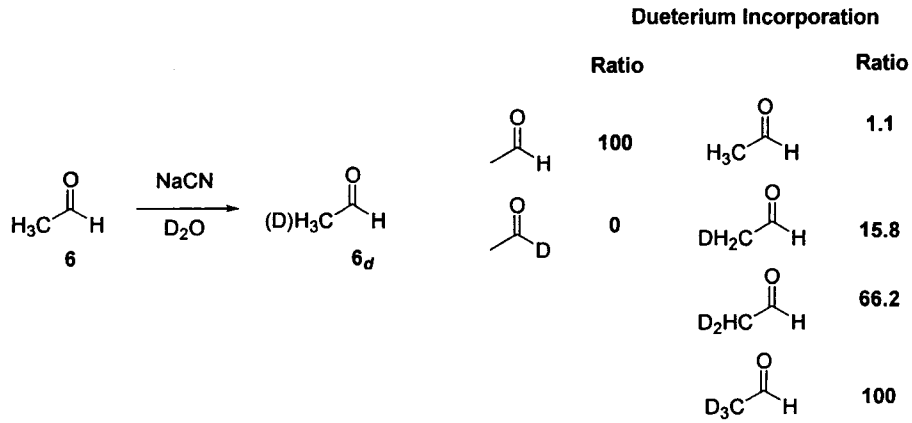


Scheme 9.



between path **A** and **B** in the Pinner-Kötz, mechanism glycidonitrile **9** was subjected to the reaction conditions (Scheme 8). Acetic acid **10** was not isolated from this reaction indicating that an epoxide intermediate is unlikely. Nowak then became concerned with the mechanism of HCl elimination, trying to discern whether an E_{1CB} or an E_2 mechanism was operative (Scheme 9). In order to determine which mechanism was operative acetaldehyde was subjected to sodium cyanide in D_2O (Scheme 10). As expected the enolizable protons at the α-position underwent significant amounts of deuterium exchange. However no deuterium was incorporated at the aldehydic position suggesting that anion **XIV** is not formed and an E_{1CB} mechanism is not operative. These mechanistic

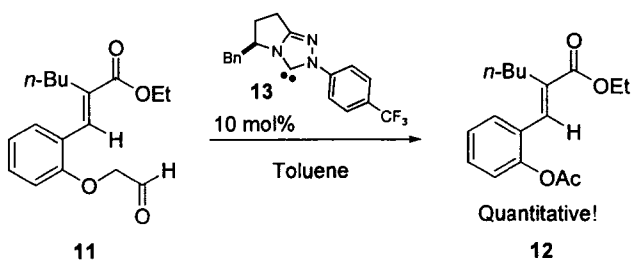
Scheme 10.



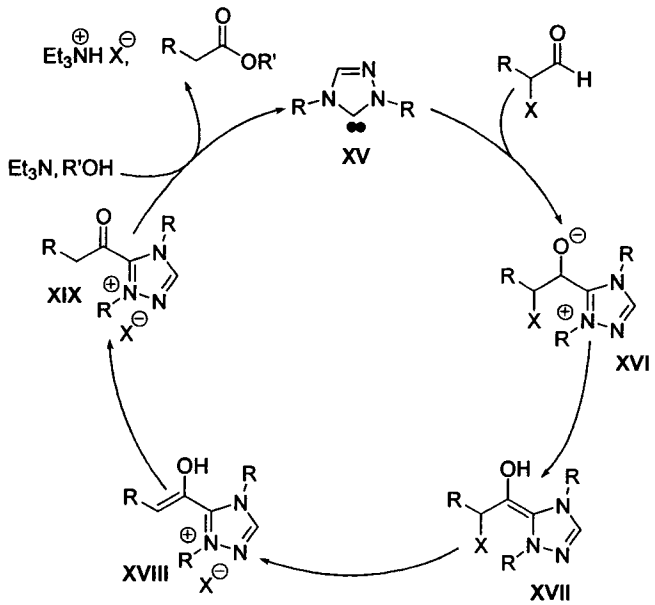
investigations set the stage for our investigations into the azolium carbene catalyzed Wallach rearrangement.

More than 40 years after Nowak's publication our interest was drawn to the Wallach rearrangement by a serendipitous discovery made by my colleague Javier Read de Alaniz (Scheme 11).[10] In conjunction with his studies on the diastereoselective proton transfer in the Stetter reaction he subjected α-phenoxyaldehyde **11** to free carbene **13**. Instead of the desired Stetter cyclization he recovered a quantitative yield of the acetylated phenol **12**. This result was rationalized by proposing a reaction mechanism similar to the accepted mechanism for the Wallach rearrangement (Scheme 12) and herein results concerning the development of a general strategy for the catalytic synthesis of esters from α-haloaldehydes are reported.

Scheme 11.



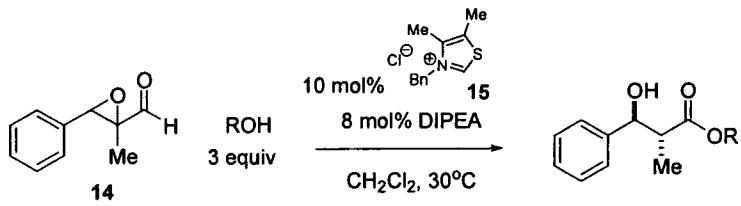
Scheme 12.



3.2 Recent Developments

Concurrent with our investigations into this new mode of reactivity available to azolium catalysis, Bode and Chow reported a related transformation that converts α,β-epoxyaldehydes into esters by reducing the α-carbon-oxygen bond catalyzed by thiazolium salts in the presence of base (Table 1).[11] The authors found that primary and secondary alcohols provided the desired esters in good yield and diastereoselectivity with no mention of the reactions of tertiary alcohols. One potential drawback of this methodology is the requirement for the use of 3 equivalents of alcohol due to the competitive acylation of the product hydroxyl groups.

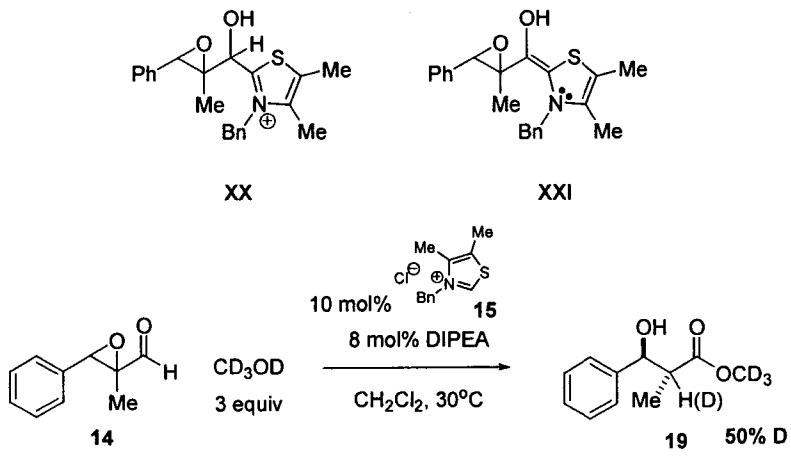
Table 1.



R	Product	Yield	dr
EtOH	**16**	89	13:1
BnOH	**17**	89	>10:1
*i*PrOH	**18**	79	>10:1

The authors propose a mechanism identical to the proposed mechanism in Scheme 12 with the exception that the carbon-halogen bond cleaved on going from intermediate **XVII** to **XVIII** is replaced with a carbon oxygen bond. In order to address the mechanism of elimination (E_2 vs E_{1CB}) and the viability of a 1,2-hydride shift, the authors reported a deuterium labeling study of substrate **14** (Scheme 13). Upon

Scheme 13.

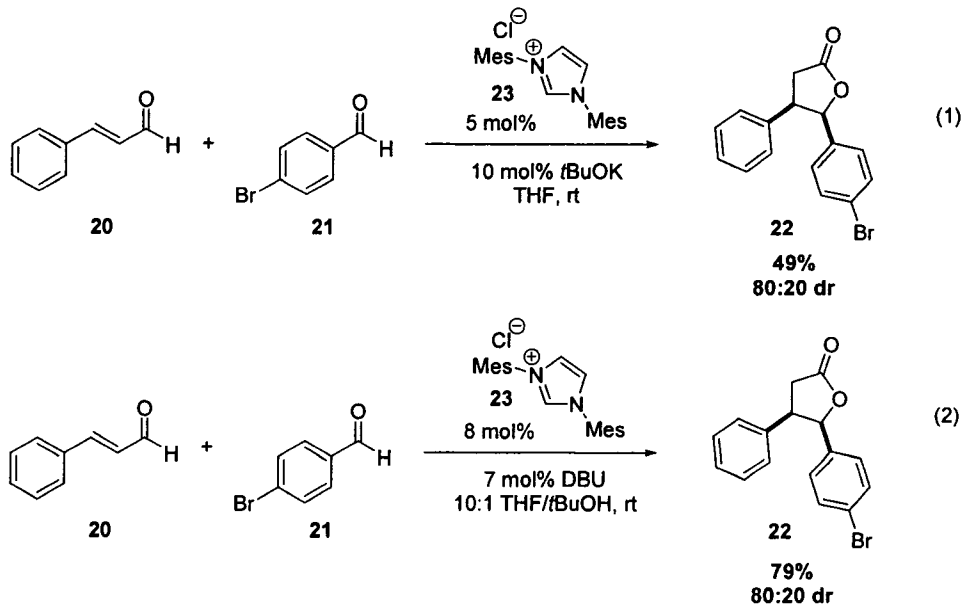


subjecting **14** to the reaction conditions using deuterium labeled methanol as a nucleophile and stopping the reaction at approx 50% conversion, they recovered the

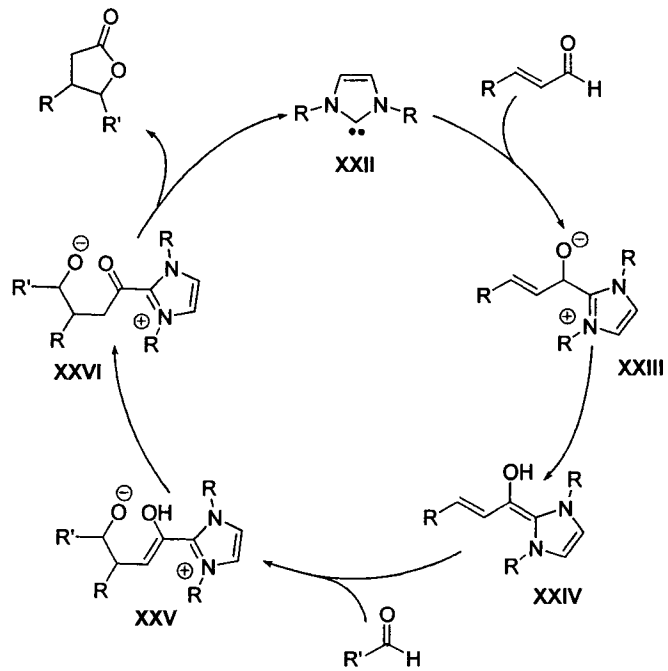
desired ester **19** with approximately 50% deuterium incorporation, suggesting that a hydride shift mechanism is not the dominant reaction pathway. In order to determine if the epoxide was opened in an E_2 fashion by deprotonation of **XX** or first undergoes deprotonation to generate intermediate **XXI** followed by epoxide ring opening by the enamine, the authors analyzed the recovered starting material looking for deuterium incorporation at the aldehydic position. If intermediate **XXI** is generated during the course of the reaction and its' formation is reversible, deuterium incorporation would be expected. However ^2H NMR indicated no deuterium incorporation in the recovered starting material lending support for an E_2 elimination of the carbon-oxygen bond or irreversible addition to the aldehyde.

An extension of this chemistry was reported later in 2004 independently by the groups of Glorius and Bode. Both groups found that by treating enals with bis-mesityl imidazolium chloride **23** in the presence of base and aldehyde they were able to obtain γ-butyrolactones in good yield (Scheme 14).[12] Burstein and Glorius discovered that 5 mol% **23** and 10 mol% *t*BuOK in THF at room temperature are the ideal conditions for coupling 1 equivalent of aldehyde and 1 equivalent of enal providing the desired product **22** in 49% yield with a diastereoselectivity of 80:20 (Equation 1). Bode and co-workers reported an almost identical system utilizing 8 mol% **23**, 7 mol% DBU, and 2 equivalents of nucleophilic aldehyde to get the desired product **22** in 79% yield with a diastereoselectivity of 80:20 (Equation 2). Interestingly *t*-BuOH, which is present in the

Scheme 14.



Scheme 15.

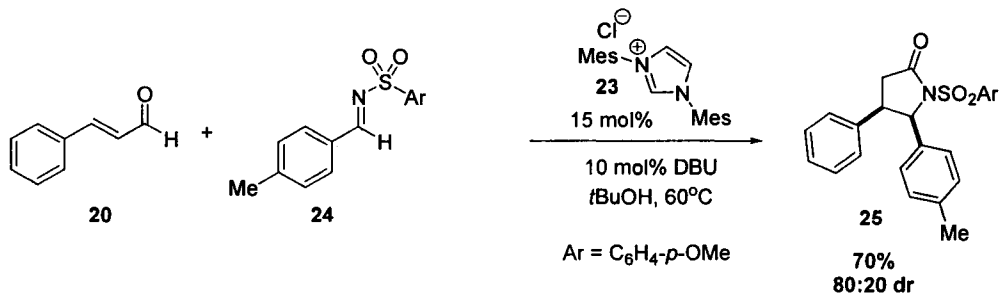


Glorius system as the conjugate acid of potassium *tert*-butoxide, was required as a co-solvent in Bode's system to provide increased yields.

Both researchers proposed the same mechanism for the transformation (Scheme 15). Interaction of carbene **XXII** with enal provides the tetrahedral intermediate **XXIII**, which upon proton transfer generates homoenolate equivalent **XXIV**. Nucleophilic attack by the β-position of **XXIV** on the aldehyde provides intermediate **XXV**, which after tautomerization and intramolecular displacement of the carbene provides the desired lactone.

In 2005 He and Bode extended the homoenolate chemistry to include the synthesis of lactams (Scheme 25).[13] Treatment of **20** with 1 equivalent of **24** in the presence of 15 mol% **23** and 10 mol% DBU in *t*BuOH at 60°C provides a 70% yield of the desired lactam **25** with a diastereoselectivity of 80:20.

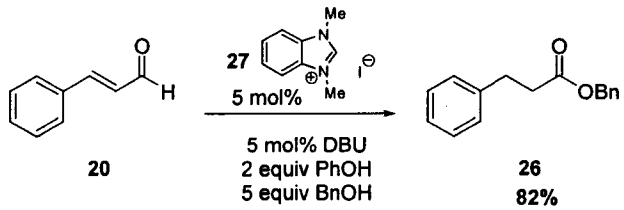
Scheme 16.



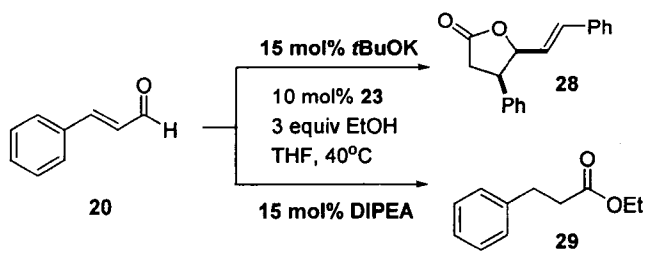
In 2005 Scheidt and co-workers reported the reduction of enals by trapping the intermediate homoenolate with a proton (Scheme 17).[14] Treatment of **20** with 5 mol% imidazolium salt **27** and 5 mol% DBU in the presence of benzyl alcohol provides the desired ester **26** in 82% yield. Phenol had to be present in the reaction mixture to afford good yields of product presumably to serve as a proton source for the *in situ* generated homo-enolate. Bode and co-workers reported this same transformation in 2005 but reported an interesting product-determining role for the base used in the reaction (Scheme

18).[15] Treatment of **20** with 10 mol% **23** in the presence of 3 equivalents of ethanol in THF at 40 °C provided two different products depending on the base used. The use of potassium *tert*-butoxide provided lactone **28** as the major product, wherein the use of the weaker base di-*iso*propyl ethyl amine afforded the product of double bond reduction **29** as the major product, indicating that the conjugate acid of the tertiary amine base is able to protonate the *in situ* generated homoenolate, a pathway not available when using potassium *tert*-butoxide.

Scheme 17.

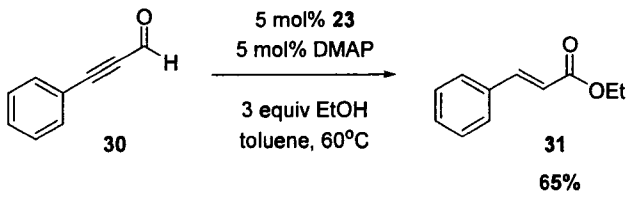


Scheme 18.



This reaction was also found to be suitable for the synthesis of α,β-unsaturated aldehydes (Scheme 19).[16] Zeitler found that treatment of propargyl aldehyde **30** with 5 mol% catalyst **23**, 5 mol% DMAP, and 3 equivalents of ethanol in toluene at 60°C afforded the desired ester **31** in 65% yield and greater than 95:5 selectivity for the E isomer.

Scheme 19.

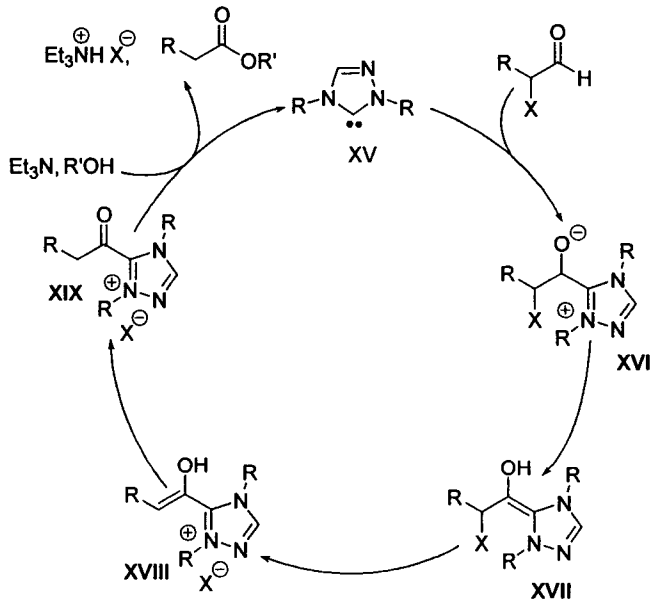


3.3 Results

Hoping to develop a general methodology for the *in situ* generation of an acylating agent from aldehydes possessing α-leaving groups via triazolium carbene catalysis, investigations using readily available α-haloaldehydes were initiated. The goal was to develop an efficient procedure that allowed one equivalent of nucleophile to be coupled with one equivalent of α-haloaldehyde in the presence of a mild base, hopefully making the methodology attractive for use in complex molecule synthesis.

The mechanistic hypothesis is shown in Scheme 20. Combination of triazolium carbene **XV** with α-haloaldehyde provides tetrahedral intermediate **XVI** which after proton transfer provides Breslow intermediate **XVII**. In contrast to the Benzoin and Stetter reactions, the nucleophilic alkene then displaces the α-halide providing enol **XVIII** which after tautomerization affords acyl azolium intermediate **XIX**. Nucleophile acylation provides the acylated nucleophile and returns the carbene to the catalytic cycle.

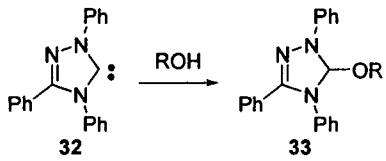
Scheme 20.



Similar to Kötz's mechanistic proposal in 1913, the first and last steps of the proposed catalytic cycle have literature precedent. The formation of Breslow intermediate intermediate **XVII** is part of the currently accepted mechanistic pathways in the Benzoin and Stetter reactions.[17] Intermediate **XIX** has been implicated in transesterification reactions catalyzed by nucleophilic carbenes.[18]

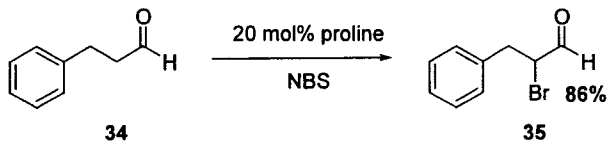
A challenge in the development of this methodology would be inhibiting the reaction of nucleophile with the *in situ* generated carbenes, based on the reported insertion of triazolium carbenes into heteroatom-hydrogen bonds as reported by Enders and co-workers (Scheme 21).[19]

Scheme 21.

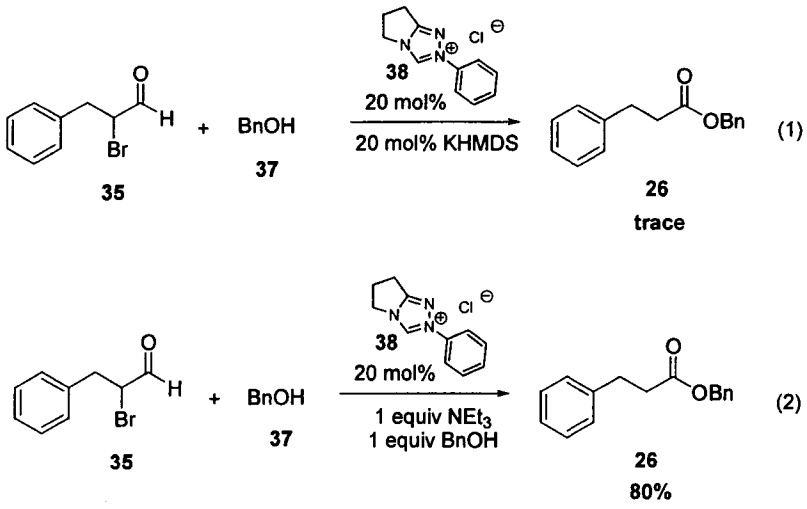


In initial studies α-bromohydrocinnamaldehyde **35** was used, obtained by treating hydrocinnamaldehyde with NBS in the presence of proline (Scheme 22).[20] Subjection of **35** to standard Stetter reaction conditions (20 mol% triazolium salt **38**, 20 mol% KHMDS, toluene) in the presence of 1 equivalent of benzyl alcohol provided only trace amounts of the desired benzyl ester **26** (Equation 1, Scheme 23). Suspecting that the HCl generated during the course of the reaction was shutting down the catalytic cycle the KHMDS was replaced with one equivalent of triethylamine (Eqaution 2, Scheme 23). Under these conditions the reaction proceeded to completion in 4h and provided 80% of the desired benzyl ester **26**.

Scheme 22.

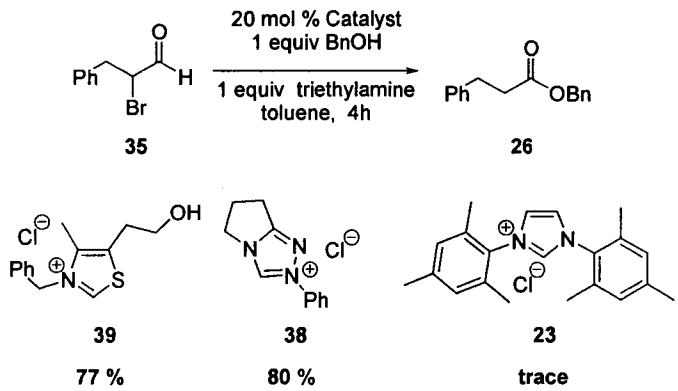


Scheme 23.



With this initial result the effect catalyst precursor on reactivity was determined (Scheme 24). Thiazolium salt **39** is an efficient catalyst precursor giving the desired product in 77% yield while imidazolium salt **23** provided only trace amounts of the desired product. Due to the ready availability of triazolium salts, these catalyst precursors were chosen for reaction development.

Scheme 24.

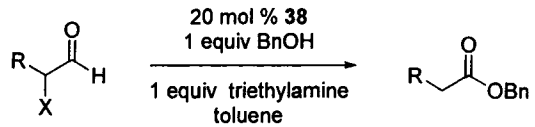


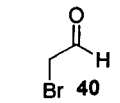
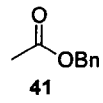
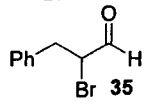
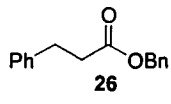
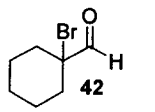
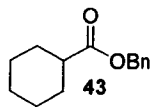
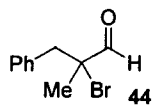
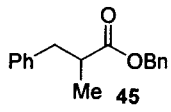
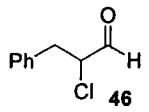
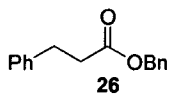
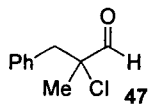
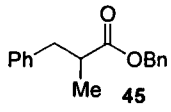
3.3.1 Aldehyde Scope

A variety of α-haloaldehydes were then screened to determine the effects of aldehyde structure on the reaction (Table 2). α-Bromoacetaldehyde **40** provided the desired product **41** in 60% yield (Entry 1). Sterically congested α-bromocyclohexanecarboxaldehyde **42** required a 24-hour reaction time but provided a 99% yield of the desired product **43**. In stark contrast to this result the α-dialkyl-α-bromoaldehyde **44** provided none of the desired product. Assuming that the aldehyde in **44** was too sterically hindered to interact with the carbene we examined α-dialkyl-α-chloroaldehyde **31,** which also failed to react, where as the parent α-chloroaldehyde **46** provided a 65% yield of the desired product.

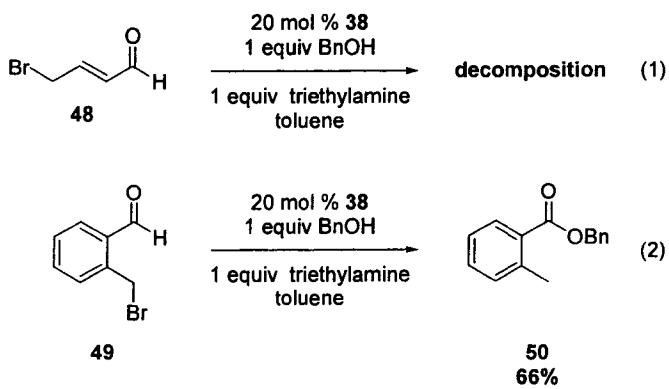
γ-Bromo-α,β-unsaturated aldehydes such as **32** were also examined (Scheme **18**). However, none of the desired product was obtained and control experiments revealed that the starting material **32** decomposed rapidly in the presence of triethylamine. α-Bromomethylbenzaldehyde **33** proved to be stable to our reaction conditions and provided the desired product in 66% yield.

Table 2.



Entry	Aldehyde	Time (h)	Product	Yield (%)
1	 **40**	4	 **41**	60
2	 **35**	4	 **26**	80
3	 **42**	24	 **43**	99
4	 **44**	24	 **45**	0
5	 **46**	4	 **26**	65
6	 **47**	24	 **45**	0

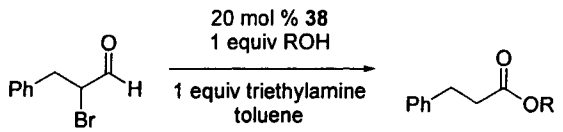
Scheme 25.



3.3.2 Nucleophile Scope

Having successfully demonstrated the triazolium carbene catalyzed Wallach rearrangement with benzyl alcohol as a nucleophile the effect of alcohol structure on the course of the reaction was addressed (Table 3). Other primary alcohols furnish the desired esters in yields similar to that for benzyl alcohol (Entries 1-3). Secondary alcohols required a longer reaction time (24h) in order to obtain a desirable yield (Entries

Table 3.

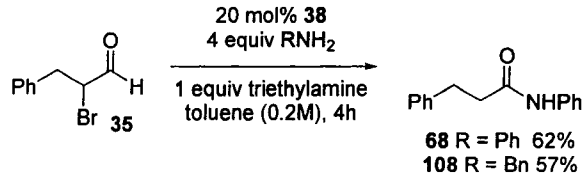


Entry	Alcohol	Time (h)	Product	Yield (%)
1	MeOH **51**	4	**52**	78
2	EtOH **53**	4	**29**	78
3	**54**	4	**55**	73
4	**56**	24	**57**	66
5	**58**	24	**59**	66
6	**60**	24	**61**	65
7	**62**	24	**63**	55
8	**64**	24	**65**	65
9	99% ee **66**	24	94% ee **67**	56

4-6 & 8-9) and tertiary alcohols failed to provide the desired product. Even the much less nucleophilic phenol provided the desired phenolic ester in 55% yield. In order to demonstrate the mildness of the reaction conditions (*S*)-ethyl lactate of 99% ee was subjected to the reaction conditions and the desired ester **67** was obtained in 94% ee indicating minimal epimerization under the reaction conditions

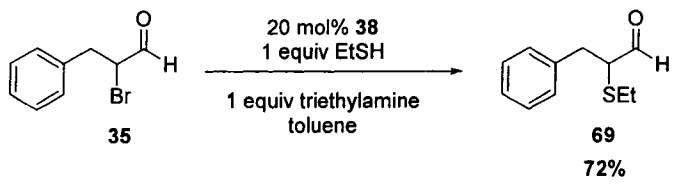
The synthesis of amides was studied next. Of a wide variety of nitrogen nucleophiles surveyed only primary amines provided the desired amides in good yield, under slightly more dilute conditions (Scheme 26).

Scheme 26.



The synthesis of thioesters was examined by using thiols as nucleophiles. Treatment of **35** with ethane thiol under optimized reaction conditions provided exclusively the product of direct halide displacement **69** in 72% yield (Scheme 27). To slow down the rate of direct halide substitution, substrate **42,** possessing a tertiary halide was used (Table 4). Under standard reaction conditions a 48% yield of **71** was obtained

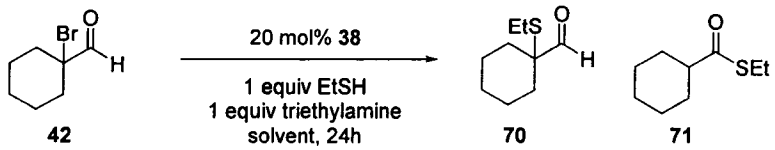
Scheme 27.



accompanied by an inseparable 36% of **70**, the product of direct halide displacement (Entry 1). The more polar solvent methylene chloride provided a 79% yield of **70** (Entry

2). Since the direct displacement of a tertiary halide was unexpected we thought involvement of the carbene was possible. Subjecting **42** to triethylamine and ethane thiol in methylene chloride with no triazolium salt present afforded an 80% yield of the direct displacement product **70** (Entry 3). A search of the literature revealed that the direct displacement of tertiary bromides with thiols is well precedented.[21]

Table 4.



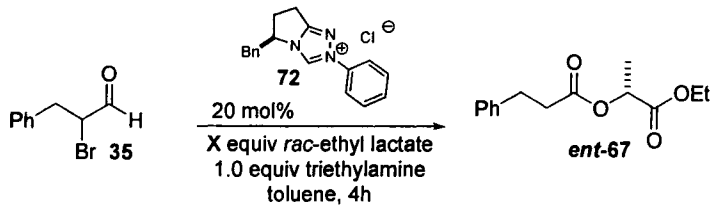
42 **70** **71**

Entry	solvent	**70**	yield (%) **71**
1	toluene	36	48
2	methylene chloride	79	trace
3	methylene chloride (No Catalyst)	80	0

3.3.3 Kinetic Resolution

One of the more exciting aspects of this project was the development of a new reaction manifold that could be used to develop asymmetric reactions catalyzed by chiral triazolium salts. In the proposed reaction mechanism, the reaction proceeds through an acyl azolium species **XIX**, Scheme 20. The use of a chiral triazolium salt should produce a chiral acylating agent that may be able to discriminate between the two enantiomers of a chiral nucleophile. Of particular interest was the kinetic resolution of secondary alcohols.[22]

Scheme 28.

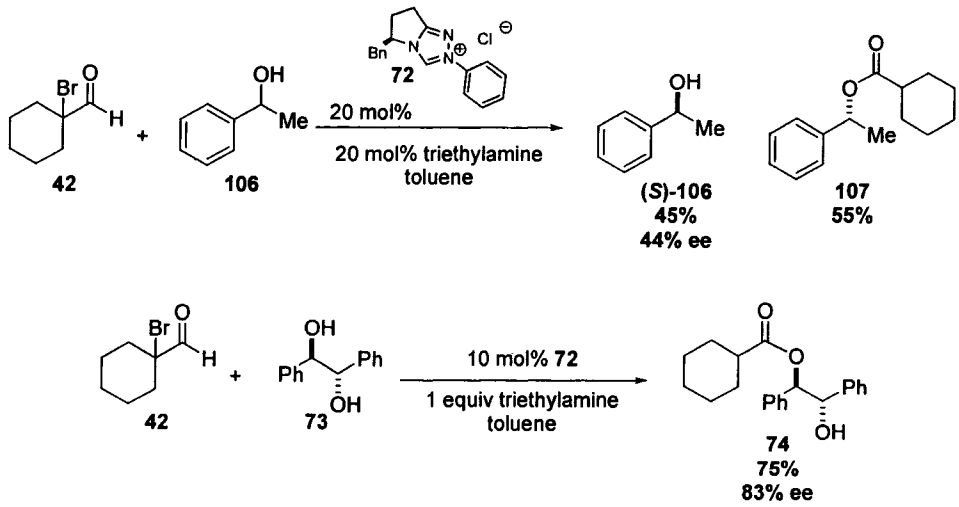


Entry	X	Yield(%)	ee(%)
1	1	41	20
2	2	71	32

In order to investigate the possibility of using a chiral triazolium carbene for the resolution of secondary alcohols, the desymmetrization of *rac*-ethyl lactate by the chiral acylating agent generated from the interaction of chiral triazolium salt with triethylamine and α-bromoaldehyde **35** was investigated (Scheme 28). The desired ester ***ent*-67** was produced in 41% yield and 20% ee when using 1 equivalent of *rac*-ethyl lactate. The use of 2 equivalents of *rac*-ethyl lactate afforded a 71% yield of ***ent*-67** with 32% ee. Although these results are not proof of the existence of intermediate **XIX** (scheme 20), they are evidence that the carbene is intimately involved in the bond-forming event.

In addition to the above examples of kinetic resolution, Javier Read de Alaniz has also investigated the ability of the in situ generated chiral acylating agent to resolve secondary alcohols and desymmetrize meso-diols (Scheme 29).[10] He discovered that α-methylbenzylalcohol **106** could be enriched to 44% ee, when using the chiral acylating agent generated from **42** and chiral triazolium salt **72**, corresponding to an S value of 5.0. Subjection of a mixture of α-bromoaldehyde **42** and hydrobenzoin **73**, to 10 mol% **72** in

Scheme 29.

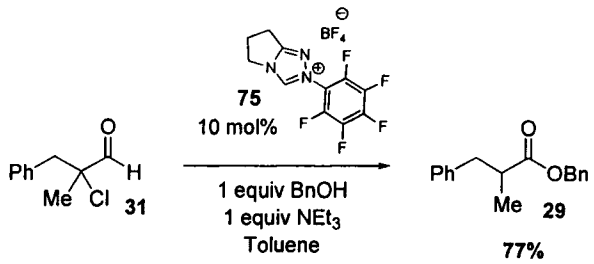


the presence of 1 equivalent of triethylamine afforded the mono-acylated diol **74** in 75% yield and 83% ee.

3.4 Second Generation Triazolium Carbene Catalyzed Wallach Rearrangement

Since the initial publication of the triazolium carbene catalyzed Wallach rearrangement, these laboratories have developed a new family of triazolium salts having a pentafluorophenyl group as a substituent on the triazole ring and these catalysts have shown superior reactivity in our investigations into the Stetter reaction. [23] With an interest in expanding the substrate scope of the Wallach rearrangement to include α-alkyl-α-haloaldehydes, the reaction of α-chloro-α-methylhydrocinnamaldehyde **47** using 10 mol% **75** was reexamined. The desired benzyl ester **45** was obtained in 77% yield (Scheme 30). With this discovery, the reaction conditions for the triazolium carbene catalyzed Wallach rearrangement using catalyst **72** were optimized.

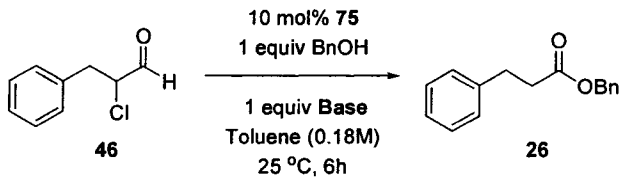
Scheme 30.



3.4.1 Reaction Optimization

Investigations began with substrate **46** which had only provided a 65% yield of the desired product using catalyst **38**, and began by examining the effect of base on the yield of the reaction (Table 5). Strong bases such as *t*-BuOK and DBU provide only trace amounts of the desired product (Entries 1 & 2). Triethylamine provides the

Table 5.

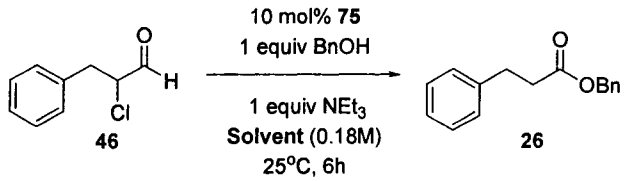


Entry	Base	Yield(%)
1	*t*-BuOK	trace
2	DBU	trace
3	NEt_3	84
4	DMAP	55
5	imidazole	69
6	$NaHCO_3$	9
7	Na_2CO_3	8
8	$KHCO_3$	65
9	K_2CO_3	trace
10	KH_2PO_4	0
11	K_2HPO_4	trace

best yield of **26** (Entry 3). Suprisingly, the weak bases DMAP, imidazole, and potassium bicarbonate provide moderate amounts of the desired product (Entries 4-5, 8). Other carbonate bases and phosphate derived bases provided only small amounts of the desired product.

The effect of solvent on the reaction was next addressed (Table 6). Non-polar solvents are the best for this reaction providing yields greater than 70%, with best yield being obtained by using toluene (Entries 1-3). Etherel solvents also provide acceptable yields with the exception of tetrahydrofuran (Entries 4-6). Interestingly, the very polar solvents dimethyl formamide and dimethylsulfoxide provide only trace amounts of product, where as acetonitrile provides the desired product in good yield (Entry 9). The best yield was obtained when using benzyl alcohol as the solvent (Entry 11).

Table 6.

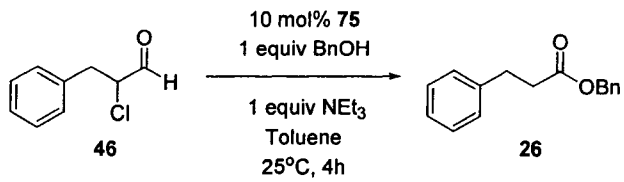


Entry	Solvent	Yield(%)
1	hexanes	73
2	heptane	76
3	toluene	84
4	diethyl ether	71
5	methyl *t*-butylether	52
6	tetrahydrofuran	24
7	methylene chloride	66
8	dimethyl formamide	trace
9	acetonitrile	57
10	dimethylsulfoxide	trace
11	benzyl alcohol	92
12	*t*-BuOH	23
13	*t*-BuOH:toluene 1:1	23

However, this may be attributed to increasing the rate of the acylation, due to the excess nucleophile present, and not solvent characteristics, as the use of *t*BuOH provides only 23% yield of the desired product.

The effect of concentration was next examined (Table 7). High concentrations of reaction mixtures provide lower yields of the desired product. The best yield of desired product was obtained at 0.13 M and this concentration was chosen for further reactions.

Table 7.



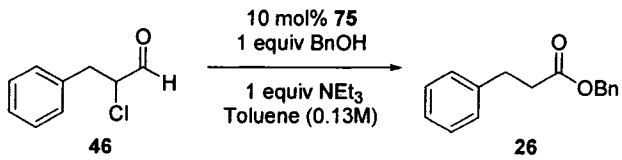
Entry	[M]	Yield(%)
1	0.063	83
2	0.13	90
3	0.25	79
4	0.50	65
5	1.00	67

The concentration screen was conducted with a four hour reaction time but further investigations revealed that good yields of the desired product can be obtained in as little as one hour (Table 8).

Up to this point, reactions had been run in an analogous manner to the Stetter reactions, with the substrate being added last. In order to determine if this was the ideal way to run the Wallach reactions and to determine the effect of increasing temperature on the reaction, three different reactions adding a different reagent as the last reagent were run. To determine if there was a competing side reaction occurring when only three of the reagents were in solution, the initial reagents were allowed to stir for 30 minutes at the indicated temperature followed by addition of the fourth reagent (Table 9). When the

reaction is run at either 25°C or 75°C, it appears there is little dependence on the order of addition of the reagents. However, the reactions run at 75°C give an approximately 10% lower yield (Entries 4-6) irrespective of the order of addition.

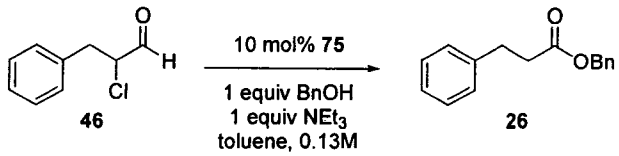
Table 8.



46 26

Entry	Time (h)	Yield(%)
1	1	75
2	2	73
3	3	82
4	4	90

Table 9.



46 26

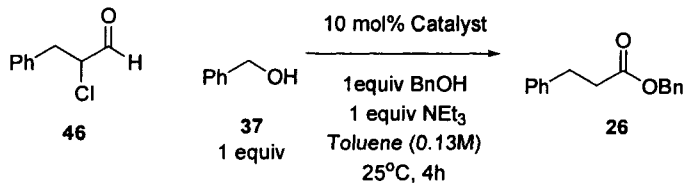
Entry	4th reagent	Temp. (°C)	Yield(%)
1	aldehyde	25	82
2	base	25	87
3	alcohol	25	75
4	aldehyde	75	73
5	base	75	72
6	alcohol	75	67

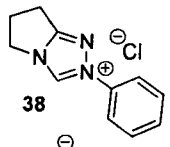
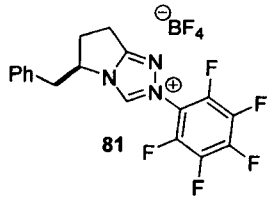
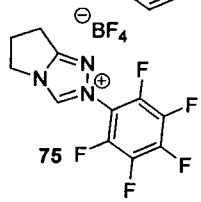
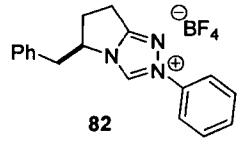
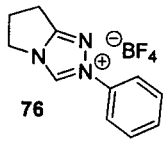
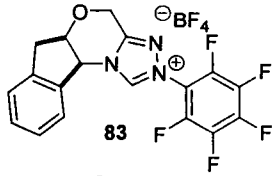
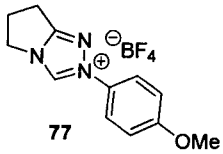
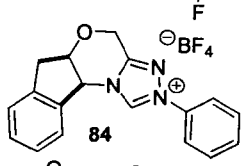
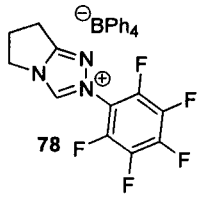
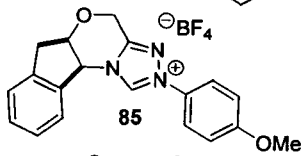
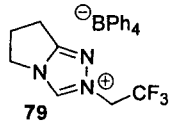
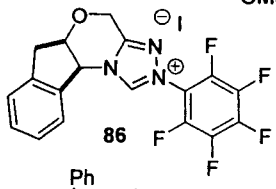
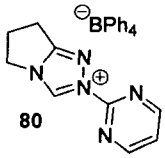
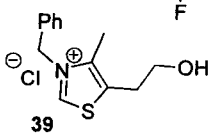
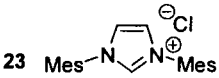
Combine 3 out of 4 reagents stir at temp. for 30min.
then add 4th reagent stir 2h at temp.

After optimizing the reaction for catalyst **75**, other catalysts were examined under the optimized conditions (Table 10). All of the triazolium catalysts screened, except for the pyrimidine derived catalyst **80**, provided the desired product in acceptable yields.

Thiazolium salt **39** was also an efficient catalyst, while imidazolium salt **23** afforded none of the desired product.

Table 10.

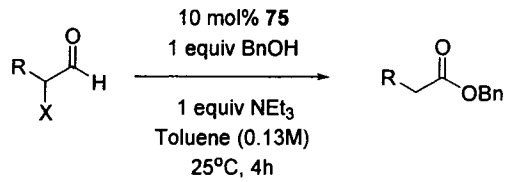


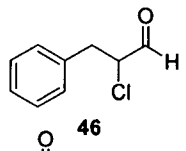
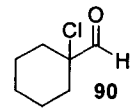
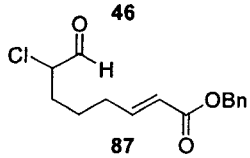
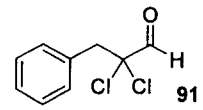
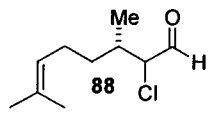
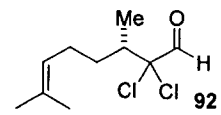
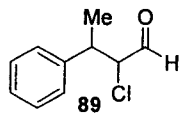
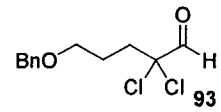
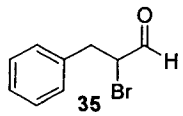
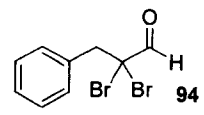
Entry	Catalyst	Yield (%)	Entry	Catalyst	Yield (%)
1	 **38**	60	8	 **81**	83
2	 **75**	90	9	 **82**	76
3	 **76**	70	10	 **83**	60
4	 **77**	61	11	 **84**	68
5	 **78**	70	12	 **85**	60
6	 **79**	82	13	 **86**	80
7	 **80**	trace	14	 **39**	61
			15	 **23**	0

3.4.2 Substrate Scope

Having successfully optimized the reaction using catalyst precursor **75,** the scope of aldehydes that would participate in the reaction was next addressed (Table 11). In contrast to the first generation reaction conditions, substrates **46** and **35** underwent the rearranagement in nearly identical yields (Entries 1 & 5). Substrate **87** provided the desired ester in 71% yield, an interesting result considering that the pendant Michael acceptor could have allowed for a competing Stetter reaction or addition reaction of the intermediate enol. Substrate **90** which failed to give the desired product using catalyst precursor **38,** gave a 61% yield of the desired product under the new conditions.

Table 11.

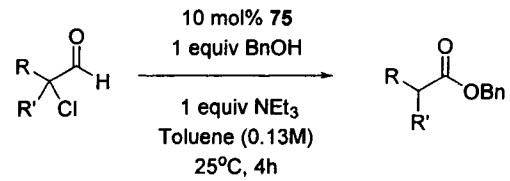


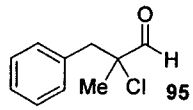
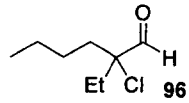
Entry	Substrate	Yield(%)	Entry	Substrate	Yield(%)
1	 **46**	90	6	 **90**	61
2	 **87**	71	7	 **91**	82
3	 **88**	81	8	 **92**	97[a]
4	 **89**	90	9	 **93**	90
5	 **35**	91	10	 **94**	87

[a] Product was isolated as a 1:1 mixture of diastereomers.

α,α-Dichloro and α,α-dibromoaldehydes were also competent substrates under our new reaction conditions. Substrate **92** provided the desired ester in 97% yield with a diastereoselectivity of 1:1.

Table 12.



Entry	Substrate	Time (h)	Yield (%)	Entry	Substrate	Time (h)	Yield (%)
1		4	40	2		24	61
		24	79			48	79

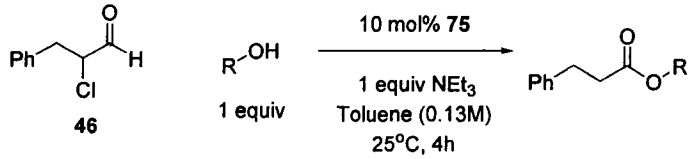
α-Alkyl-α-halo aldehydes are successfully converted to the desired esters under the new conditions, albeit with longer reaction times (Table 12). Subjecting substrate **95** to our standard reaction conditions provided the desired ester in only 40% yield (Entry 1). Increasing the reaction time to 24 hours provided a 79% yield of the desired ester. Substrate **96** provided a 61% yield of the desired ester in 24h. Increasing the reaction time to 48h provided the desired ester in 79% yield.

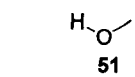
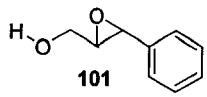
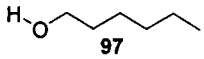
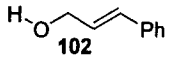
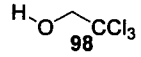
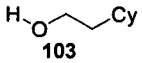
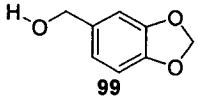
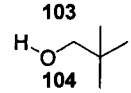
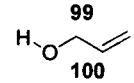
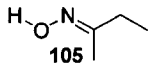
3.4.3 Nucleophile Scope

As with the first generation triazolium carbene catalyzed Wallach rearrangement, primary alcohols are excellent nucleophiles in the second generation reaction (Table 13). Alkyl alcohols provide the desired product in good yields (Entries 1 & 2). Trichloroethanol and allyl alcohol are competent nucleophiles providing easily deprotected trichloro and allylic esters (Entries 3, 5).[24] Of note are the sterically bulky

alcohols, 2-cyclohexylethanol and pivaloyl alcohol, providing the desired esters in acceptable yields. Oximes are also competent nucleophiles (Entry 10).

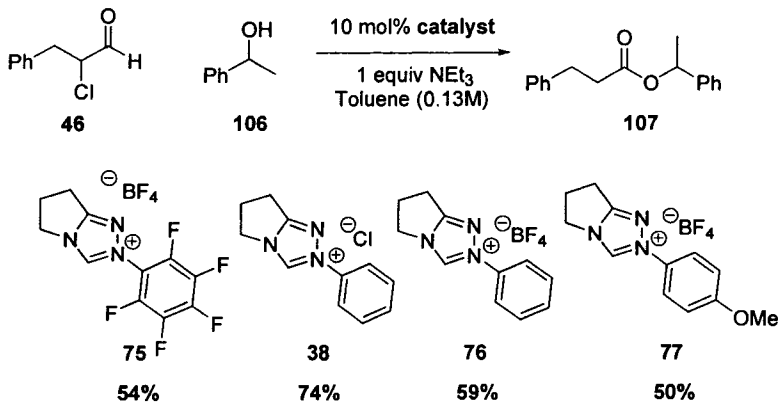
Table 13.



Entry	ROH	Yield	Entry	ROH	Yield
1	 **51**	80	6	 **101**	81
2	 **97**	87	7	 **102**	89
3	 **98**	74	8	 **103**	88
4	 **99**	80	9	 **104**	61
5	 **100**	69	10	 **105**	41

Preliminary results with secondary alcohols indicate the catalyst precursor **75** is not as effective for this transformation as the originally-reported catalyst **38** (Scheme 30).

Scheme 30.



3.5 Conclusion

We have demonstrated that triazolium carbenes are efficient catalysts for the Wallach rearrangement. The highlights of this transformation are the need for only one equivalent of nucleophile and the mild conditions. In addition, the in situ generated acyl azolium species has allowed for the development of a kinetic resolution using chiral triazolium salts.

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Chapter 4

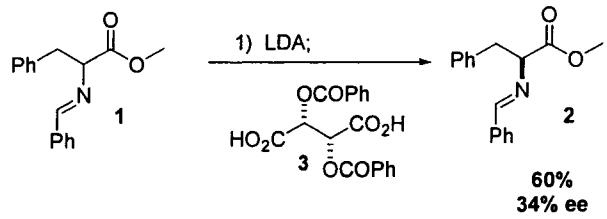
In Situ Generation of Chiral Enolates: Asymmetric Protonation in the Wallach Rearrangement

4.1 Introduction

The control of stereochemistry α to carbonyl compounds is a long-standing problem in organic synthesis with a host of solutions based on chiral auxiliary chemistry.[1] More recently, a number of catalytic asymmetric methods have appeared, taking advantage of in situ generated nucleophiles.[2] In general, these approaches rely on carbon-carbon bond formation for stereocenter generation. Another strategy for setting stereocenters next to carbonyls involves carbon-hydrogen bond formation via an enantioselective protonation.[3] Two approaches have been utilized in these reactions: the first involves the protonation of a prochiral enolate with a chiral acid and the second involves the in situ generation of a chiral enolate followed by protonation with an achiral acid.

The protonation of prochiral enolates with chiral acids appeared as early as 1975.[4] Duhamel and Plaquevent published the first thorough study of the effect of acid structure

Scheme 1.



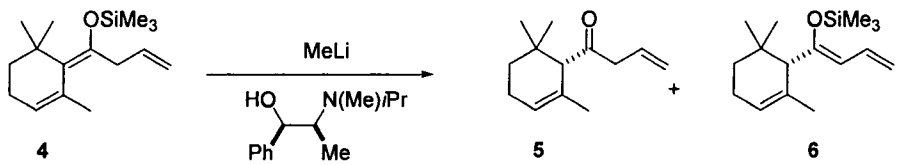
on the protonation event in 1978, in their synthesis of α-amino esters (Scheme 1).[5] Deprotonation of α-iminoester **1** with LDA at –70°C and protonation of the resultant enolate with 3.0 equivalents of tartaric acid derived **3** affords a 60% yield of the desired

ester in 34% ee. Although these reactions required superstoichiometric amounts of chiral reagents, the groundwork was laid for an important concept.

A serendipitous discovery by Fehr and Galindo in 1994, demonstrated that the asymmetric protonation of prochiral enolates with chiral acids could be performed with catalytic amounts of chiral acid (Scheme 2).[6] Treatment of **4** with methyllithium generates a lithium enolate that, when treated with **7**, affords **5** in 95% ee. In order to determine if enolate protonation was more selective at lower conversions the authors ran the same reaction using only 0.5 equivalents of **7** followed by trapping with TMS-Cl hoping to isolate **5** in 50% yield. They isolated an equal mixture of **5** and **6** both in 94% ee, demonstrating that the enantioselective protonation was catalytic in **7**, presumably via regeneration of **7** by the allylic protons in **5**.

Vedejs and coworkers investigated the synthesis of α-chiral amides using catalytic amounts of chiral amine **10** and discovered that properly matching the pK_a of

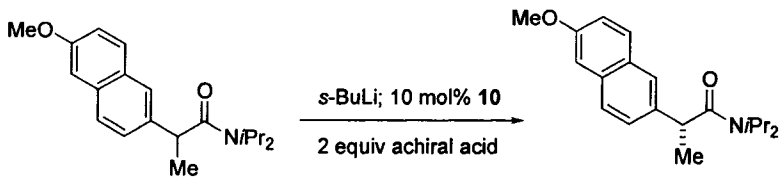
Scheme 2.

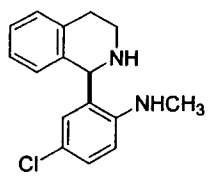


the achiral acid additive could have a dramatic affect on the products ee (Scheme 3).[7] Treating the lithium enolate of **8** with 10mol% **10** followed by slow addition of an achiral proton source, enantioenriched **9** was obtained. In order to induce enantioselectivity in this reaction **10** (pK_a = 27.7), has to be regenerated by the achiral acid faster than the enolate is protonated. With this premise in mind a series of carbon acids was screened to determine the optimum structure of the achiral acid. They proposed that acetonitrile

(which gives the product in 0% ee) is not competent for regenerating the chiral acid and that methyl phenylacetate reacts preferentially with the

Scheme 3.





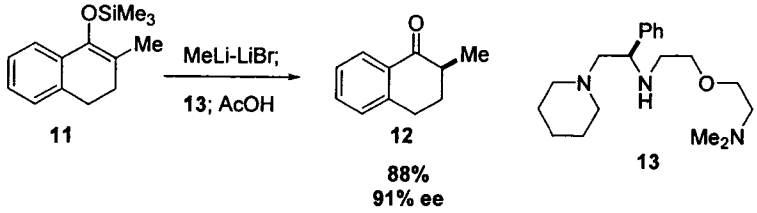
10

achiral acid	pK_a	ee%
CH_3CN	31	0
CH_3CO_2tBu	30	35
$PhCH_2CO_2tBu$	23.6	94
$PhCH_2CO_2Et$	22.7	92
$PhCH_2CO_2Me$	20	6

lithium enolate, affording the desired product in 6% ee. Optimal ee's were obtained when using esters with a pK_a around 23 with the best result obtained using *tert*-butyl phenylacetate.

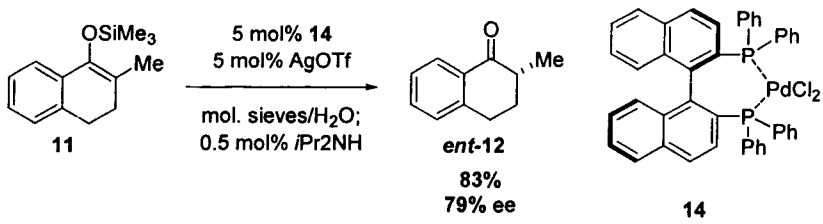
In contrast to Vedejs' approach of using chiral amines as proton sources Koga and co-workers have pursued the use of chiral amines as ligands to form chiral lithium enolates (Scheme 4).[8] Treatment of silyl-enol ether **11** with methyllithium and lithium bromide followed by addition of 1 equivalent of **13** and quenching with acetic acid affords the desired product **12** in 88% yield and 91% ee. More recently Koga and co-workers have developed a two phase system using catalytic amounts of a derivative of **13** and 1,4-di-(dimethylamino)-butane as an achiral additive that allows for water to be used as the proton source, affording the desired products in good yields and enantioselectivities.

Scheme 4.



In 1995 Shibasaki and co-workers used chiral cationic palladium complexes to effect an enantioselective Mukiyama-Michael reaction.[9] Based on NMR experiments they proposed that the reaction proceeds through a chiral palladium enolate and in 1997 Sugiura and Nakai demonstrated that the in situ generated chiral enolates could be

Scheme 5.

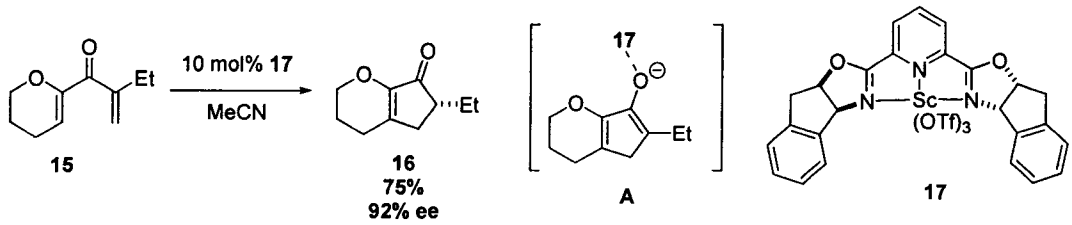


efficiently protonated to afford α-chiral ketones (Scheme 5).[10] Pre-formation of the palladium catalyst by treating **14** with silver triflate, molecular sieves, and water followed by addition of diisopropyl amine generates a catalyst that effects the enantioselective protonation of **11** affording ***ent*-12** in 83% yield and 79% ee. Although the work of Koga and Nakai demonstrated the ability to form chiral enolates in situ, a potential drawback is the need to first generate the silyl-enol ether. A more efficient strategy would form the desired enolate in situ from unprotected functional groups.

Liang and Trauner used this strategy for the asymmetric synthesis of cyclopentenones via the Nazarov reaction. Treatment of divinylketone **15** with 10 mol%

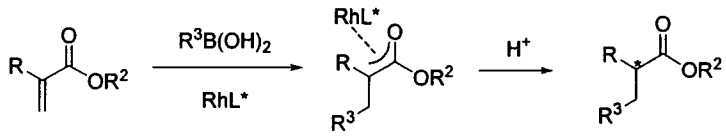
17 afforded a 75% yield of cyclopentanone **16** in 92% ee (Scheme 6). The enantioselectivity is proposed to arise via protonation of chiral lewis acid complexed enolate **A**.

Scheme 6.

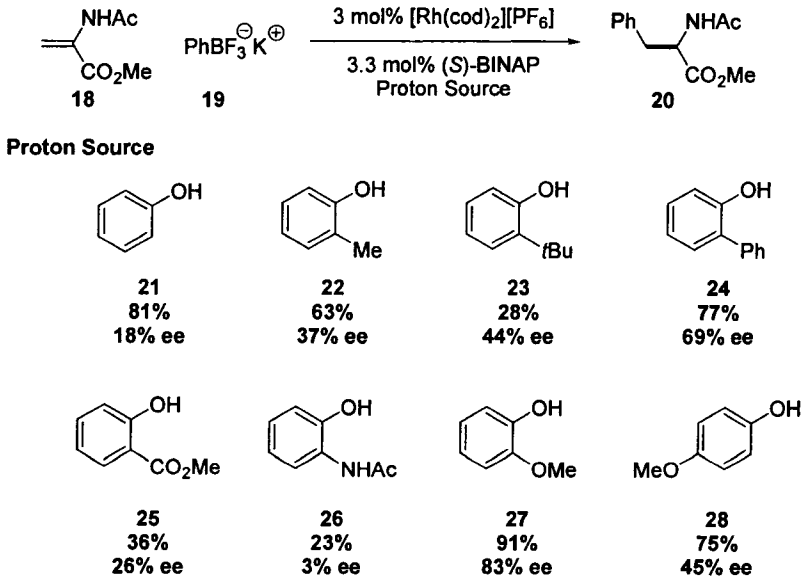


One strategy that has been successfully employed for the enantioselective protonation of esters is the rhodium catalyzed conjugate addtion of boronic acids to form a chiral enolate in situ followed by protonation with an achiral proton source (Scheme 7). Genet and co-workers adapted this strategy to the synthesis of α-amino esters in 2004 (Scheme 8).[11] Treatment of **18** with potassium trifluoro(phenyl)borate **19** in the presence

Scheme 7.



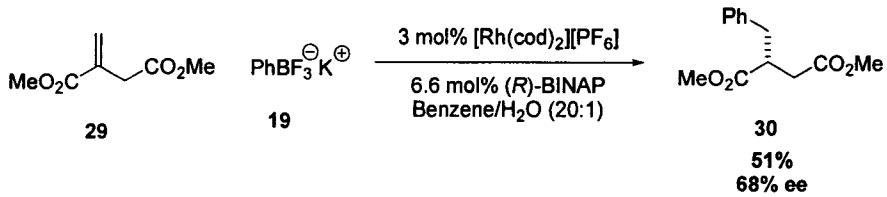
Scheme 8.



of 3 mol% rhodium and (*S*)-BINAP affords the enantioenriched amino ester **20**. Initial attempts using water as a proton source gave excellent yields but poor selectivity and the use of acids resulted in none of the desired product. However, phenol **21** provided the desired product in 81% yield and 18% ee. Increasing steric bulk at the ortho position resulted in increasing selectivities **21-24**. Coordinating substituents at the ortho position were then investigated revealing that guaiacol **27** provided the desired product in 91% yield and 83% ee.

In 2004 Frost and co-workers reported a very similar system for the synthesis of succinic esters (Scheme 9).[12] Treating **29** and **19** with catalytic amounts of rhodium in the presence of BINAP the authors were able to synthesize the desired succinic ester **30** in 51% yield and 68% ee. Interestingly in this system water serves as the proton source, giving higher enantioselectivities than phenolic derivatives. In addition to the Genet and

Scheme 9.

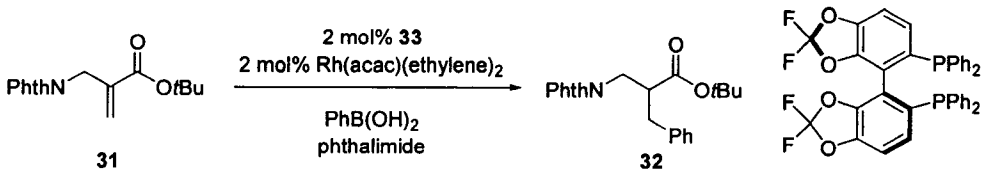


29 19 30

51%

68% ee

Scheme 10.



31 32 33

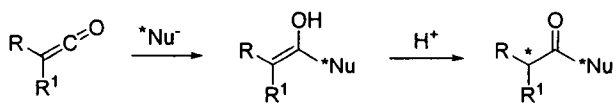
91%

88% ee

Frost methodologies, Sibi and co-workers have used this concept to develop a system for the asymmetric synthesis of β-amino esters (Scheme 10).[13]

Another approach for the in situ formation of chiral enolates is the esterification of ketenes (Scheme 11).[14] In this reaction a ketene is treated with a chiral nucleophile that adds to the ketene to form a chiral enolate which is then protonated by an achiral proton source. Weiss first attempted the implementation of this strategy in 1919 but an unfortunate choice of substrate led to a 1:1 mixture of diastereomers.[15] Ugi and co-workers published the first successful demonstration of this concept in 1973 when they were able to obtain diastereoselectivities of up to 53% using chiral secondary alcohols.[16] In 1989, Larsen et al. studied the effect of alcohol structure

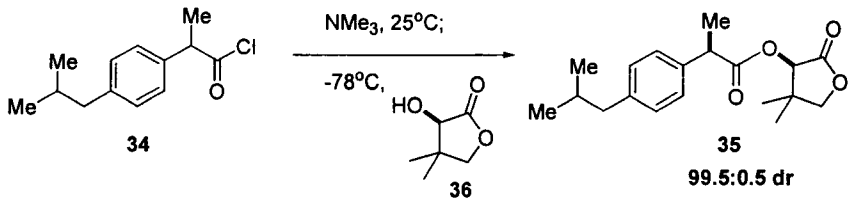
Scheme 11.



on the protonation event.[17] Surveying a series of naturally occurring chiral α-hydroxy esters they discovered that (*R*)-pantolactone **36** gave almost exclusively 1 diastereomer of

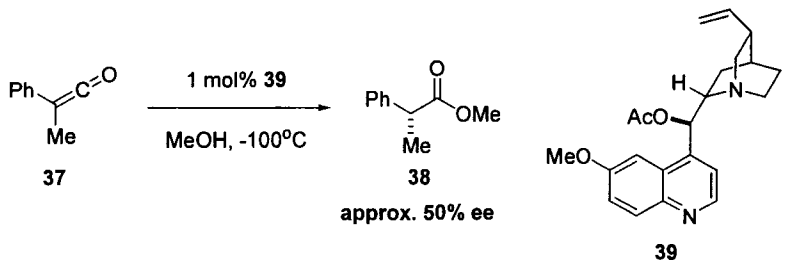
the desired 2-arylpropionic acid **35** (Scheme 12). One potential drawback to this methodology is that the chirality required for the transformation is incorporated into the product. An alternative approach to the esterification of ketenes would involve the use of a chiral catalyst to form the chiral enolate, which upon protonation would also form an activated ester allowing for displacement of the chiral catalyst by a nucleophilic alcohol.

Scheme 12.



Pracejus and co-workers reported the first examples of the catalytic esterification of ketenes in the 1960's (Scheme 13).[18] Treatment of ketene **37** in methanol at –100°C with 1 mol% of acetylated quinine **39** afforded the desired methyl ester in approx 50% ee. The authors propose that **39** reacts with ketene **37** to afford a chiral enolate that is then protonated by methanol, forming an activated ester that then acylates the formed methoxide.

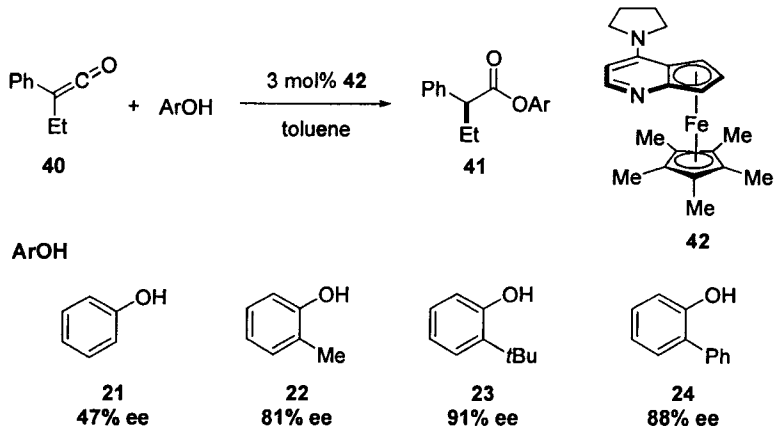
Scheme 13.



In a program to develop chiral DMAP derivatives as nucleophilic catalysts, Fu and co-workers have recently investigated the catalytic esterification of ketenes (Scheme

14).[19] Addition of ketene **40** to a solution of phenol **21** and 3 mol% of **42** in toluene at room temperature afforded the desired ester in 41% ee. Upon screening a range of phenols it was discovered that ortho-substitution provided the best improvement in enantioselectivity. In particular, *o*-*t*Bu-phenol **23** provided the desired *o*-*t*Bu-phenolic ester in 91% ee.

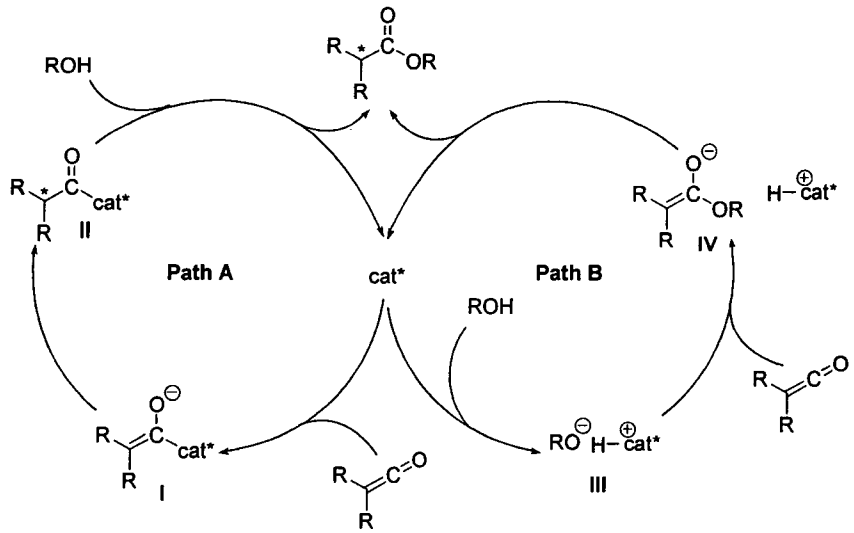
Scheme 14.



At the outset of the development of this reaction the authors proposed that the reaction proceedes via the in situ generated chiral enolate **I** (Path A, Scheme 15) which undergoes a diastereoselective protonation producing activated ester **II** which then acylates the requisite alcohol. Investigations into the interaction of phenols and catalyst **39** have revealed that **39** is quantitatively protonated in the presence of phenol and that the addition of ketene to this mixture produces enantioenriched aryl esters. With this evidence the authors now support Path B as the mechanistic course for the reaction. Interaction of alcohol and catalyst produce ion pair **III**. The anionic oxygen in **III** then attacks the ketene to afford ion pair **IV**, protonation of **IV** by the chiral Bronsted base then produces the desired ester and returns the catalyst to the catalytic cycle. Although in

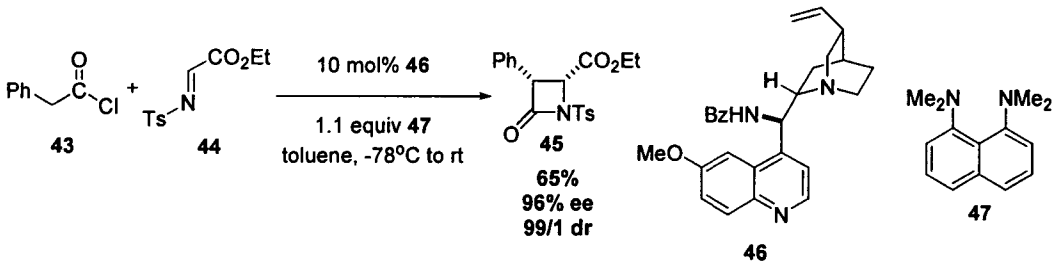
situ generated chiral enolate **I** is apparently not involved in this transformation, the Letcka and Fu groups have been able to develop reactions demonstrating the potential power of the in situ generated enolate **I**.

Scheme 15.

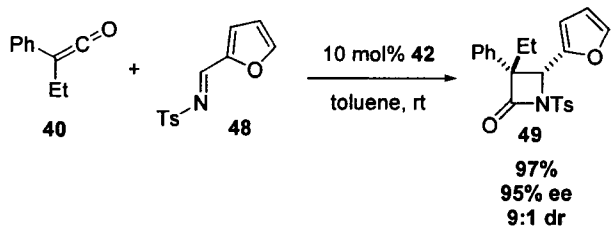


In 2000, Letcka and co-workers reported the synthesis of β-lactams from ketenes and imines by a quinuclidine catalyst (Scheme 16).[20] In situ generation of the ketene by the action of **46** and **47** affords a chiral enolate that reacts with the electron-deficient imine **44** to provide the desired product **45** in 65% yield and 96% ee. Two years later Hodous and Fu published this same transformation with preformed ketenes and a wider imine scope, using chiral DMAP catalyst **42** (Scheme 17).[21] Wilson and Fu have also demonstrated that the in situ generated chiral enolate can be trapped with aldehydes to afford lactone products **52** in good yield and enantioselectivity.[22]

Scheme 16.

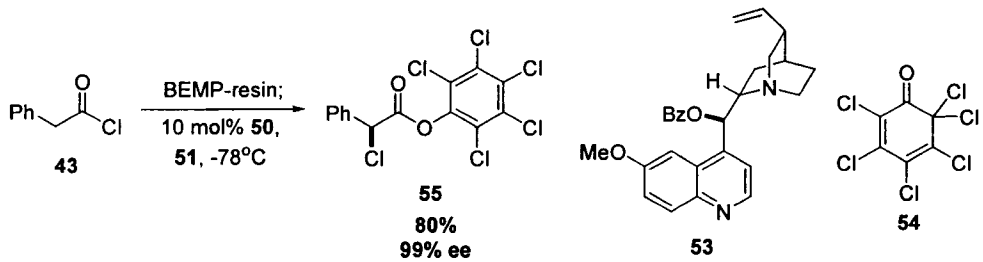


Scheme 17.



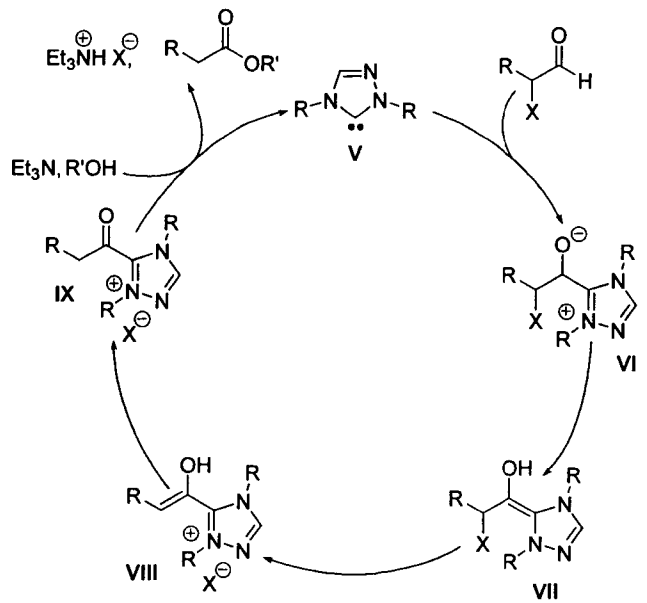
The traditional syntheses of enantioenriched α-haloesters have relied on the use of chiral auxilaries, a strategy pioneered by Evans.[23,24] In 2001 Letcka and co-workers reported a catalytic halogenation reaction via their in situ generated chiral enolate (Scheme 18).[25] Passing a solution of acid chloride **43** through a column of BEMP-resin (immobilized triaminophosphonamide imine), forms the requisite ketene, which is then treated with catalyst **53** and chlorinating agent **54** to afford the desired pentachlorophenyl α-chloroester in 80% yield and 99% ee.

Scheme 18.



In conjuction with our efforts to develop the triazolium carbene catalyzed Wallach rearrangement, reactions based on proposed in situ generated enol **VIII** were investigated (Scheme 19). The deveolopment of an asymmetric protonation reaction was the starting point, and the results of these studies are reported below.

Scheme 19.

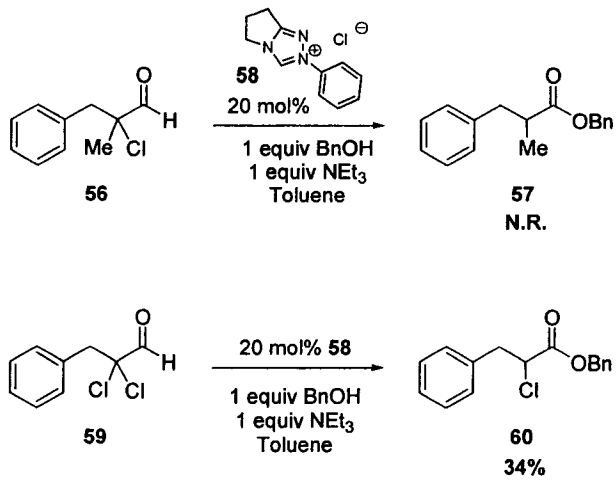


4.2 Reaction Development

Investigations into an asymmetric variant of the Wallach rearrangement were begun by subjecting α-chloro-α-methyl hydrocinnamaldehyde **56** to the originally reported conditions. Unfortunately, no reaction took place and the starting material was recovered unchanged (Equation 1, Scheme 20). Initially it was assumed that the starting

material was too sterically hindered to interact with the carbene. Based on this hypothesis attention turned to α,α-dichloro aldehyde **59**. The desired benzyl α-chloroester **60** was produced in 34% yield (Equation 2, Scheme 20). The exchange of a chlorine for a methyl group may not seem likely to afford a less sterically encumbered aldehyde based on size alone as the radius of chlorine (1.75Å) is only slightly smaller than that of a methyl group (2.0Å); however,

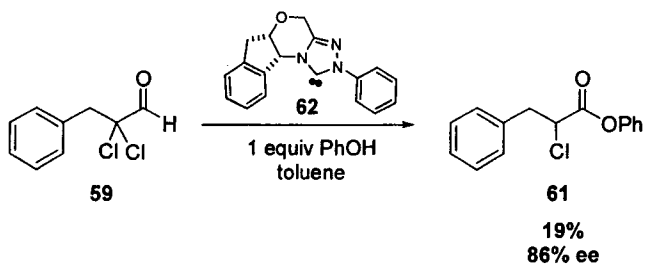
Scheme 20.



despite this small difference in size, there is a substanial difference in the A-values for the two groups, with methyl having an A value of 1.8 versus 0.53 for chlorine.[26] Eliel and Haber have suggested that chlorine is effectively smaller because the chlorine-carbon bond length (1.77Å) is longer than that of the carbon-carbon bond (1.54Å).[27] Having successfully generated an ester with an alpha substituent attention turned to the use of a chiral catalyst, to produce enantioenriched product. The first successful asymmetric protonation is shown in Scheme 22. Treatment of **59** with one equivalent of the free carbene **62** afforded **61** in 19% yield and 86% ee. With this result in hand, optimization of the process was studied.

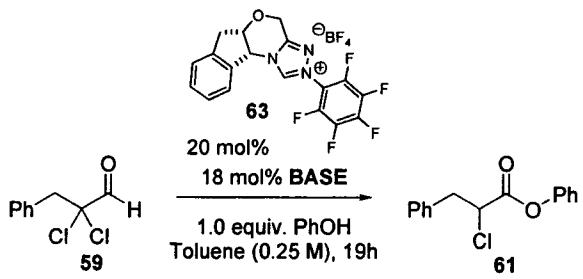
Initial studies focused on the chiral triazolium salt **63** and the effect of base on the reaction (Table 1). To prevent excess base in solution from epimerizing the product, 0.9 equivalents of base relative to triazolium salt was used. The strong base potassium hexamethyldisilazane (KHMDS) provided the desired product in only 4% ee (Entry 1).

Scheme 22.



Generating the carbene with KHMDS and removing the produced hexamethyldisilazane before adding the phenol and substrate provided the desired product in 56% ee (entry 2) indicating that perhaps the hexamethyldisilazane present in Entry 1 epimerized the product. Amine bases provided the desired product with good enantioselectivity, as did potassium *tert*-butoxide. In order to investigate if low yields were obtained because the

Table 1.

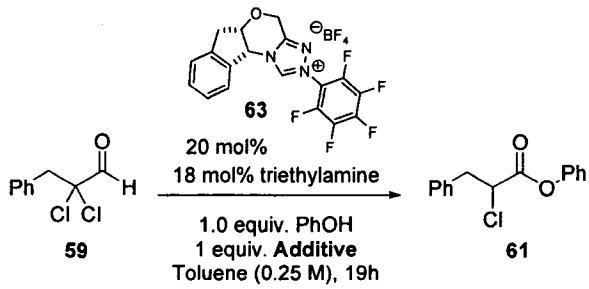


Entry	Base	Yield	*ee*
1	KHMDS	22	4
2	KHMDS (Free Carbene)	5	56
3	triethylamine	16	84
4	diisopropylethylamine	8	82
5	DBU	14	76
6	*t*-BuOK	9	76

generated HCl was shutting down the catalytic cycle and attention turned to adding bases to the reaction that could sequester the generated HCl without epimerizing the product.

Using 1.18 equivalents of diisopropylamine provided the desired product in 41% yield and 56% ee (Entry 1, Table 2). Pyridine was not an effective HCl sink as the yield obtained was the same as the reaction in its absence (Entry 2). Proton sponge provided a comparable yield of product with a slightly decreased enantioselectivity (Entry 3). Sodium bicarbonate provided the desired product in 27% yield and 82% ee (Entry 4). Potassium phenoxide generated in situ from potassium hydride and phenol provided the desired product 38% and 78% ee (Entry 5).

Table 2.

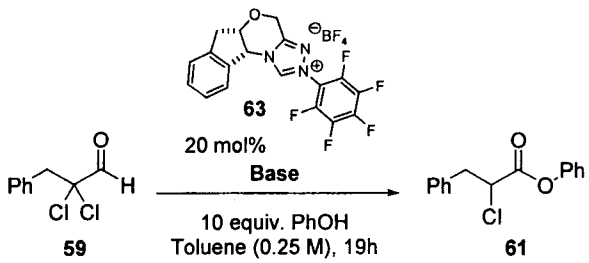


Entry	Additive	Yield	*ee*
1[a]	diisopropylethylamine	56	52
2	pyridine	17	58
3	proton sponge	36	50
4	sodium bicarbonate	27	82
5[b]	potassium hydride*	38	78

[a] 1.2 equiv. Additive, no triethylamine
[b] 1.15 equiv. KH, 1.2 equiv. phenol, no triethylamine

In order to increase the rate of the acylation event, Entries 1,4, and 5 from Table 2 were repeated in the presence 10 equivalents of phenol (Table 3). In all three reactions

Table 3.



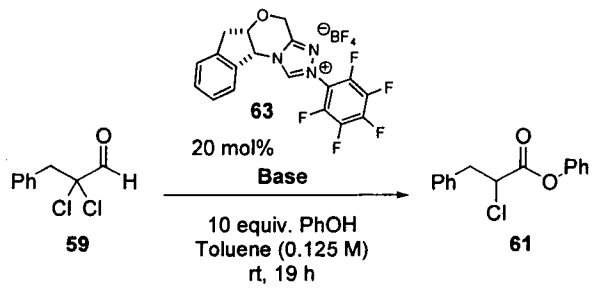
Entry	Base	Yield (%)	ee (%)
1	1.2 equiv *i*-Pr_2NEt	88	74
2	0.18 equiv Et_3N, 1.0 equiv $NaHCO_3$	61	88
3	1.15 equiv potassium phenoxide	75	84

an increase in yield was observed. Potassium phenoxide was chosen for further development as it provided the best combination of yield and enantioselectivity.

At the 0.25M concentration used in the previous studies, potassium phenoxide provides a viscous solution; therefore, the reaction was diluted to 0.125M and the desired product obtained in 91% yield and 88% ee (Entry 1, Table 4). Sodium and lithium phenoxide were competent bases for the reaction although they provided the product in lower yields than potassium phenoxide.

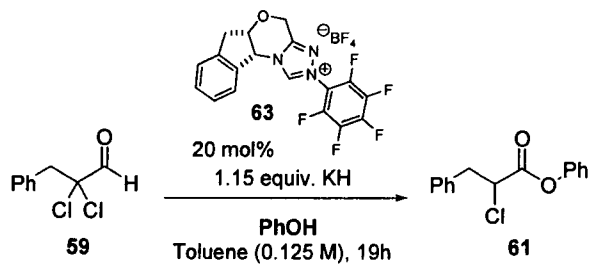
The effect of increasing or decreasing the amount of phenol in the reaction was next examined (Table 5). The use of ten equivalents of phenol provided the product with the highest enantiomeric excess. The excess phenol may be recovered at the end of the reaction by simply washing the filtered reaction solution with 0.1M NaOH. Having optimized our reaction conditions we turned our attention to determining the scope of aldehydes that participate in our asymmetric variant of the Wallach reaction.

Table 4.



Entry	Base	Yield	ee
1	KH	91	88
2	NaH	70	72
3	BuLi	59	86

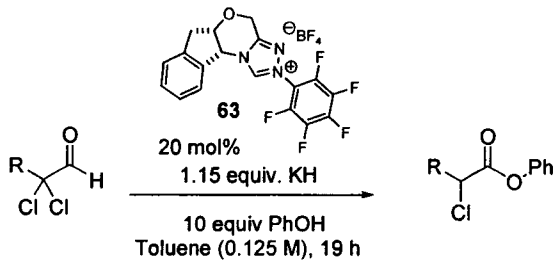
Table 5.

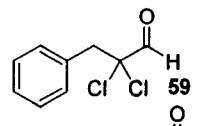
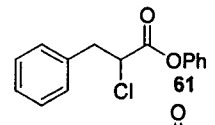
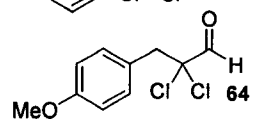
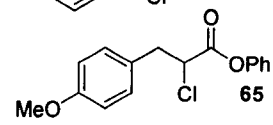
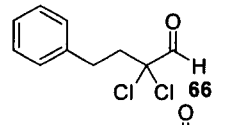
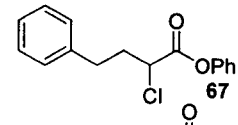
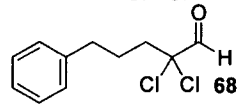
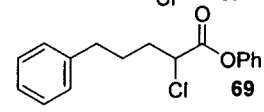
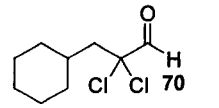
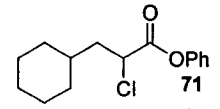
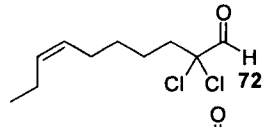
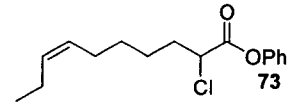
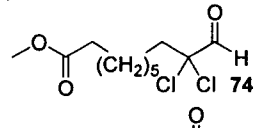
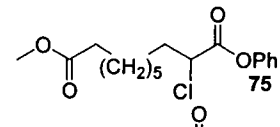
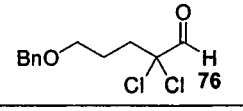
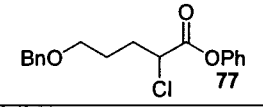


Equiv. Phenol	Yield	*ee*
2.5	39	66
5	66	88
7.5	67	86
10	89	90
12.5	66	86
20	61	84

The first substrate screen reveled that the reaction is general providing the desired α-chloroesters in 51-90% yield and 78-90% ee (Table 6). The conditions are also tolerant of esters (Entry 7) and ethers (Entry 8). Substrates possessing substitution at the β-position, exemplified by **78**, failed to give appreciable yields of the desired products (Table 7). Under our optimized conditions **78** provides a 25:75 mixture of the desired

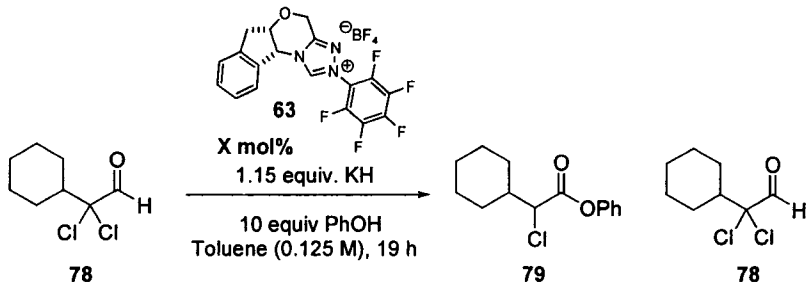
Table 6.



Entry	Substrate	Product	Yield	*ee*
1	 59	 61	89	90
2	 64	 65	76	86
3	 66	 67	51	78
4	 68	 69	58	82
5	 70	 71	50	80
6	 72	 73	70	82
7	 74	 75	59	82
8	 76	 77	90	80

ester **79** and returned starting material (Entry 1). Increasing the catalyst loading provided a greater percentage of the desired ester, but the reaction still failed to go to completion (Entries 2 & 3).

Table 7.

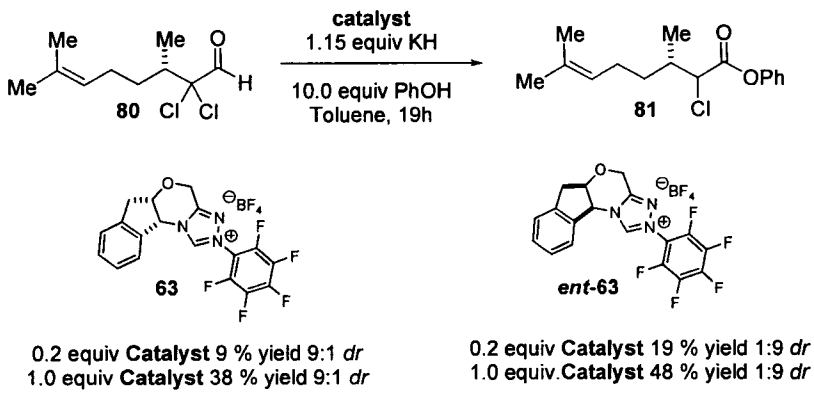


Entry	X mol%	79:78[a]	79(ee%)
1	20	30:70	80
2	50	71:29	82
3	100	62:38	82

[a] Determined by analysis of the crude NMR spectra.

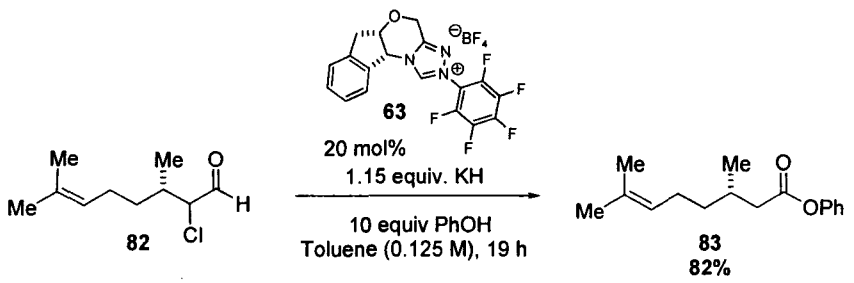
In order to determine if there was an interaction between the β-substituent and the catalyst, (*S*)-citronellal derived substrate **80** was subjected to the optimized reaction conditions (Scheme 23). Subjection of enantiopure **80** to our reaction conditions using catalyst **63** affords a 9% yield of the desired product **81** with a 87:13 diastereomeric ratio. When ***ent*-63** was used as the catalyst the desired product was obtained in 19% yield with

Scheme 23.

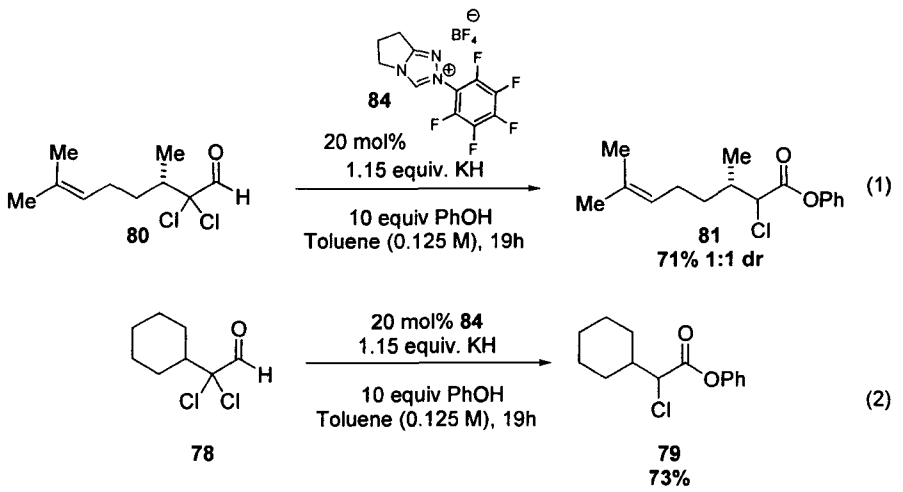


a 13:87 diastereomeric ratio. The observed increase in yield when using ***ent*-59** as the catalyst might be due to a better match between substrate and catalyst chirality, providing evidence for a steric interaction between the catalyst and the β-substituents. Interestingly, the products from **63** and ***ent*-63** are obtained as opposite diastereomers in identical ratios indicating that the pre-existing chirality on the substrate did not interfere with the asymmetric protonation event. Subjection of α-chloroaldehyde **82** to the same reaction conditions using catalyst **63** afforded the desired ester **83** in 82% yield providing further evidence for a steric interaction and demonstrating that β-substituents only pose a problem with α,α-dichloroaldehydes (Scheme 24). The use of achiral catalyst **84** also affords the desired products in good yield (Scheme 25).

Scheme 24.

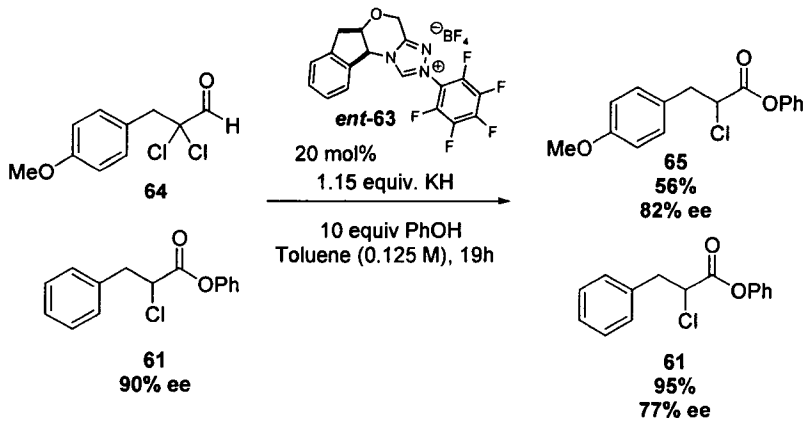


Scheme 25.



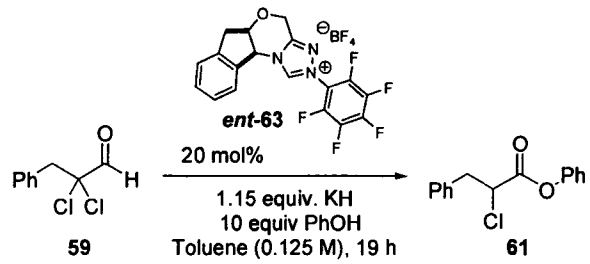
Under the optimized conditions enantioselectivities tended to vary slightly from run to run, perhaps due to a small amount of background epimeriztion. In order to test this hypothesis **64** was subjected to the reaction conditions in the presence of **61** of 90% ee. The α-haloester **65** was obtained in 56% yield and 82% ee, while **61** was recovered in 95% yield with only 77% enantiomeric excess, having undergone a modest amount of epimerization. Having verified that epimerization was taking place under our reaction conditions, attention turned to possible ways to prevent the epimerization.

Scheme 26.



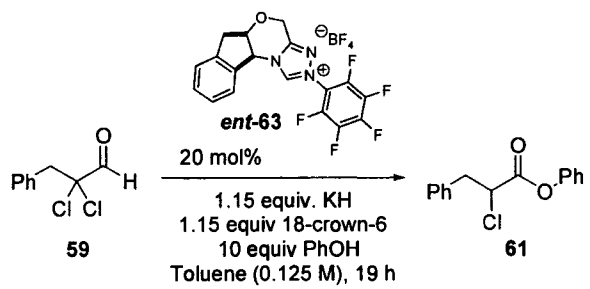
The heterogeneity of the reaction solution, due to the insolubility of potassium phenoxide, was next addressed. In order to address this issue 18-crown-6 was added to the reaction and a more homogenous solution was obtained (Scheme 27). No decrease in yield was observed in the presence of 18-crown-6 although **61** was produced with a slightly lower enantioselectivity. After the discovery that 18-crown-6 afforded a

Scheme 27.



homogeneous reaction the issue of epimerization was addressed. Investigations began by examing the effect of cooling and dilution on the selectivity of the reaction (Scheme 28). The reaction did not proceed at 0°C but upon warming the solution to room temperature and allowing it to stir for 1h the crude NMR indicated a 40:60 mixture of product to starting material, with the product being produced in 92% ee. Decreasing the reaction concentration from 0.125M to 0.063M the desired product was provided in 86% ee.

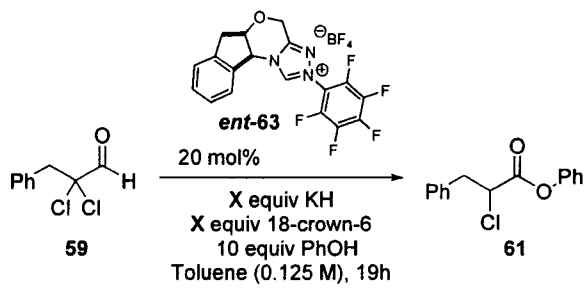
Scheme 28.



Entry	Conditions	Crude NMR Prod:SM	ee
1	rt, 3 hour	85:15	84
2	0°C 2 hour, rt 1 hour	40:60	92
3	rt, 0.063 M, 3 hour	70:30	86

The previously developed reaction conditions used 1.15 equivalents of base in order to allow the base to deprotonate the triazolium salt and react with the generated HCl. In order to determine if excess base was indeed required the reaction was conducted in the presence of different amounts of KH and 18-crown-6 (Scheme 29). Decreasing the amount of base present from 1.15 equivalents to 1.00 equivalent afforded the product with an 8% increase in enantioselectivity and no further increases were obtained on decreasing the amount of base further.

Scheme 29.



Entry	X	Crude NMR Prod:SM	ee
1	1.15	95:5	76
2	1.0	95:5	84
3	0.8	95:5	84
4	0.6	94:6	84

At the beginning of the reaction development we recognized the potential need for four reagents in this transformation (Scheme 30):

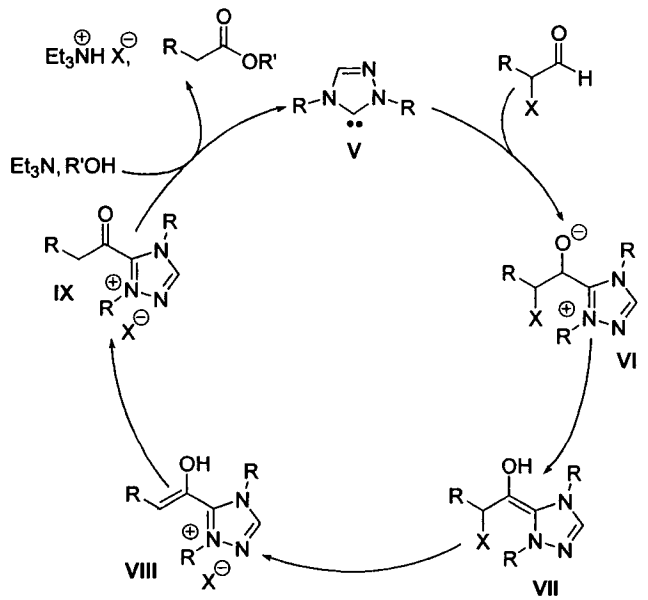
1) Base to deprotonate the triazolium salt, forming the active catalyst.

2) Base to deprotonate tetrahedral intermediate **VI**, leading to enolate **VIII.**

3) Proton source to generate the activated carboxylate **IX**.

4) A nucleophile to be acylated, returning the carbene to the catalytic cycle.

In the first generation of the asymmetric protonation we were pleased that the phenol/phenoxide combination had fulfilled all four roles. However, desiring further increases in enantioselectivity in the presence of 18-crown-6 the use of different bases in the reaction was investigated. Since phenol had been so effective in this transformation ***Scheme 30.***



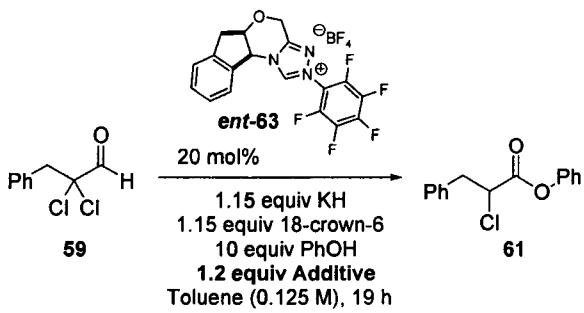
studies focused on the use of different phenolic bases. The added phenol would ideally meet two requirements:

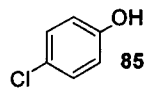
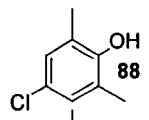
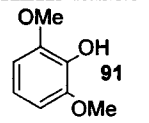
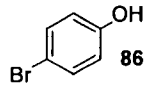
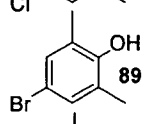
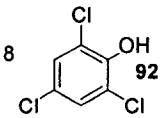
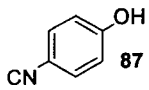
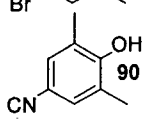
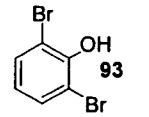
1) A lower pK_a than phenol ensuring deprotonation under thermodynamic conditions

2) Steric bulk, to avoid competing with phenol in the acylation process.

Investigations were conducted by adding 1.20 equivalents of electron deficient and sterically hindered phenols to the standard reaction conditions in the presence of 18-crown-6 (Table 8). The use of a more electron deficient phenol without steric bulk at the

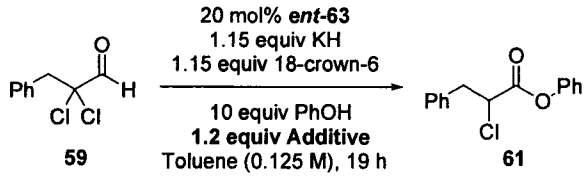
Table 8.

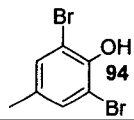


Entry	Additive	ee	Entry	Additive	ee	Entry	Additive	ee
1	 **85**	80	4	 **88**	76	7	 **91**	78
2	 **86**	78	5	 **89**	80	8	 **92**	86
3	 **87**	72	6	 **90**	80	9	 **93**	88

orho-position had little effect on the outcome of the reaction (Entries 1-3). Bisorthoalkyl-substituted phenols also gave little increase in the enantioselectivity of the reaction and bisorthomethoxy phenol was also ineffective (Entries 4-8). Bishalo-substitution at the ortho position afforded the desired product in 10-12% higher ee than the reaction run in its absence (Entry 1, Scheme 29 vs Entries 8 & 9, Table 8). 2,6-Dibromophenol was chosen for further development.

A problem with using 2,6-dibromophenol **89** as base for the reaction is that it cost $15.60 per gram. One of our goals was to develop a practical scalable methodology and the cost of **89** was not in line with our aim. Related 2,6-dibromo-4-methylphenol **94** cost only $2.12 per gram and it provided the desired product in 70% yield and 86% ee (Table 9). Capitalizing on the results from the previous investigations into the asymmetric protonation in the absence of 18-crown-6 and added phenol a further improvement in ***Table 9.***



Entry	$ / gram[a]	Additive	Yield%	ee%
1	15.60	 **93**	62	86
2	2.12	 **94**	70	86

[a] According to the Aldrich online catalogoue May 2, 2006.

yield and enantioselectivity was achieved by decreasing the concentration to 0.06M and the amount of KH/18-crown-6 to 1.00 equivalent in the presence of only 10 mol% catalyst (Scheme 31). Due to the significant cost of 18-crown-6 ($4.26 per gram, Aldrich online catalogue May 3, 2006) the possibility of decreasing the amount of 18-crown-6 in the reaction was investigated (Table 10). The reaction proceeded efficiently in the presence of only 5 mol% 18-crown-6 and provided the desired product in 93% ee.

Scheme 31.

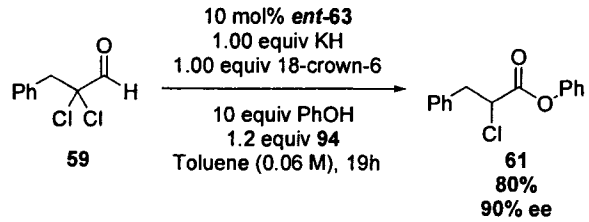
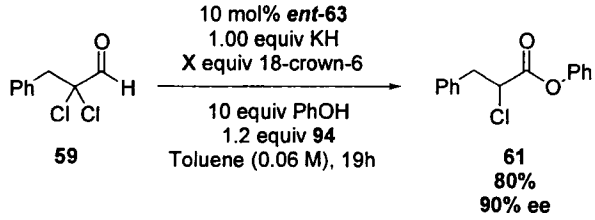


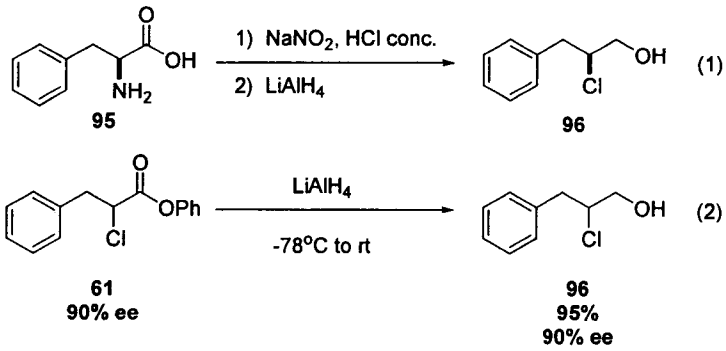
Table 10.



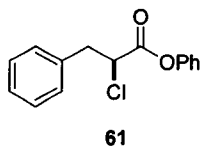
Entry	X	Yield%	ee%
1	1.0	80	90
2	0.5	79	93
3	0.0	75	88

After successful reoptimiztion of the reaction attention turned to determining the absolute stereochemistry of the products. This was accomplished by treating L-phenylalanine **95** with sodium nitrite in the presence of concentrated HCl, followed by reduction of the interemediate α-chloroacid with lithium aluminum hydride to afford α-chloroalcohol **96** in greater than 90% ee (Scheme 32).[28] Comparison of the HPLC trace of **96** obtained in this manner with that of **96** obtained by reduction of **61** with lithium aluminum hydride indicated that they both had the same major enantiomer. Thus, under our optimized conditions using ***ent*-63** the products are obtained as the *S* enantiomer (Scheme 33).

Scheme 32.

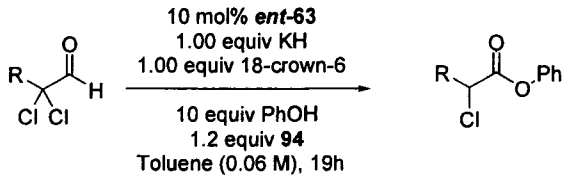


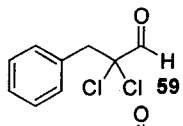
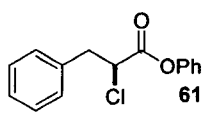
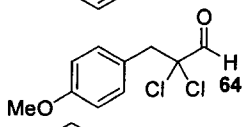
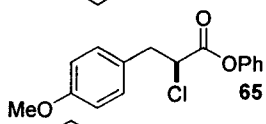
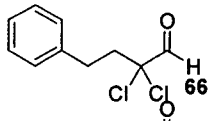
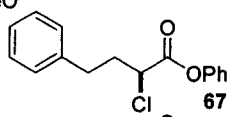
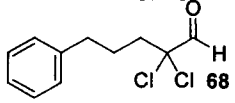
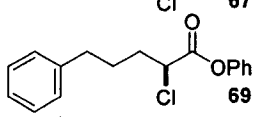
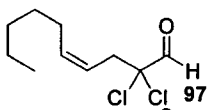
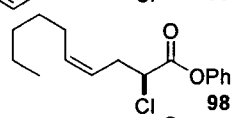
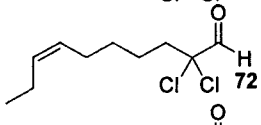
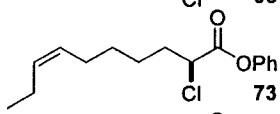
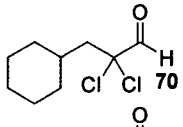
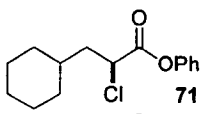
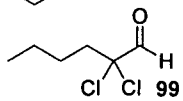
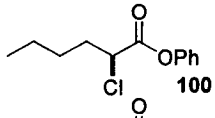
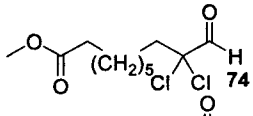
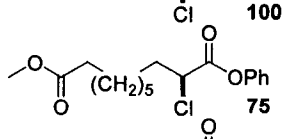
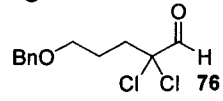
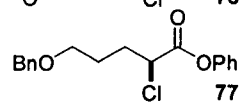
Scheme 33.



The optimized conditions are applicable to a wide variety of α,α-dichloroaldehydes (Table 11). Compared to the first generation conditions the products are obtained in more uniform yields (65-79%) and the enantioselectivities are generally 4-5% higher than in the absence of the added base **94**. Similar to our previous substrate screen substrates possessing β-substitution still fail to participate in the reaction.

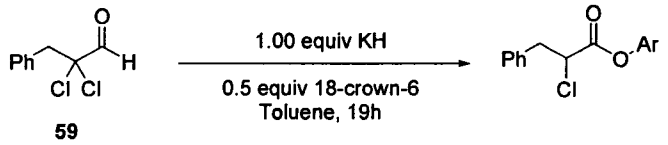
Table 11.



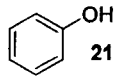
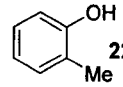
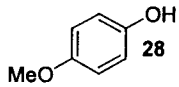
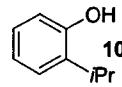
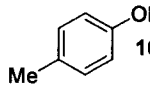
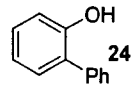
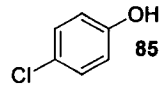
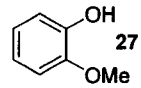
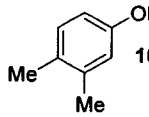
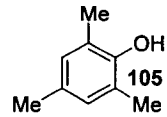
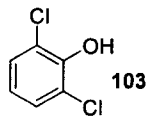
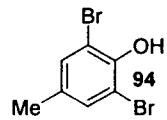
Entry[a]	Substrate	Product	Yield%	ee%
1	 59	 61	79	93
2	 64	 65	76	90
3	 66	 67	73	85
4	 68	 69	68	89
5	 97	 98	74	90
6	 72	 73	71	88
7	 70	 71	65	93
8	 99	 100	65	89
9	 74	 75	75	84
10	 76	 77	71	84

The reaction is also amenable to the synthesis of substituted phenolic esters (Table 12). In order to ascertain the effect of substitution on the participating phenol, 3 different conditions for the synthesis of the desired phenolic esters were screened.

Table 12.



Conditions		
A	B	C
20 mol% **80** 10 equiv ArOH	10 mol% ***ent*-63** 10 equiv ArOH	10 mol% ***ent*-63** 10 equiv ArOH 1.2 equiv **94**

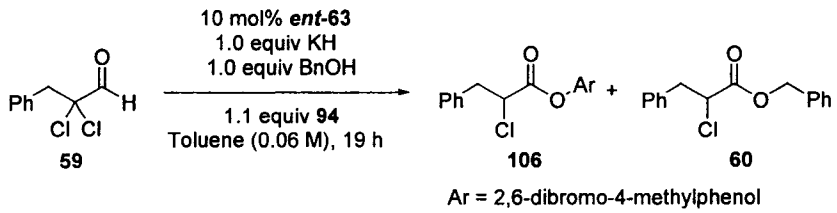
Entry	ArOH	A	B	C	Entry	ArOH	A	B	C
1	 **21**	63%	75% 88% ee	79% 93% ee	7	 **22**	83%	15% 42% ee	62%[a] 90% ee
2	 **28**	71%	68% 89% ee	71% 91% ee	8	 **104**	51%	0%	27%[b] 76% ee
3	 **101**	73%	64% 86% ee	71% 89% ee	9	 **24**	74%	42% 37% ee	53%[c] 85% ee
4	 **85**	64%	63% 81% ee	63% 83% ee	10	 **27**	74%	34% 62% ee	60% 87% ee
5	 **102**	70%	65% 90% ee	80% 89% ee	11	 **105**	30%	0%	0%
6	 **103**	30%	62% 83% ee	65% 82% ee	12	 **94**	40%	85% 76% ee	--

[a] Along with 12% acylated **94**. [b]Along with 19% acylated **94**. [c] Along with 6% acylated **94**.

Condition A used one equivalent of the substituted phenol and 20 mol% of achiral catalyst **84**. Condition B used 10 equivalents substituted phenol and 10 mol% ***ent*-63**. Condition C was the same as condition B except that 1.2 equivalents of **94** was added. Phenol electronics appear to play a minor role on the reaction outcome, with electron deficient phenols **85** and **94** giving slightly lower enantioselectivity (Entries 1-4, 12). Phenols possessing ortho-halosubstitution participate well in the reaction (Entries 6 & 12). In contrast to the success of ortho-halosubstituted phenols ortho-alkylsubstitution

has a more dramatic effect on the reaction (Entries 7-11). Orthomethyl-phenol **23** provided an 83% yield of the desired ester in the presence of achiral catalyst **84**, but only a 15% yield of the desired ester was obtained in the presence of chiral catalyst ***ent*-63**. In the presence of **94** the yield is increased to 62% and the product is produced in 90% ee along with 12% of acylated **94**, indicating that our exogenous base now successfully competes for the activated carboxylate. In the case of more sterically hindered **104** the effect is even more dramatic with 0% yield of the desired product being obtained using condition B (Entry 8). However the use of condition C enables the desired product to be obtained in 27% yield and 76% ee. Taken together, these results suggest that steric bulk at the ortho-position interferes with the ability of the phenol to participate as a base (**VI** to **VII**, Scheme 30) or a proton source (**VIII** to **IX**, Scheme 30) in the proposed mechanism, a role that is filled by **94** allowing the reactions to proceed in increased yield. The use of **94** as a base provides for the synthesis of a wide-range of phenolic esters, but fails when other alcohols are used (Scheme 34). Subjecting 1.0 equivalent of benzyl alcohol to the asymmetric protonation reaction with 1.0 equivalent of the potassium salt of **94** as the base we recovered a mixture of esters **106** and **60** in 59:41 ratio as determined by the crude NMR.

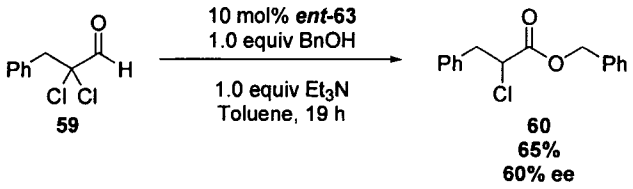
Scheme 34.



Investigations to expand the scope of the asymmetric protonation to other alcohols began with the reaction shown in Scheme 34, which was reinvestigated using

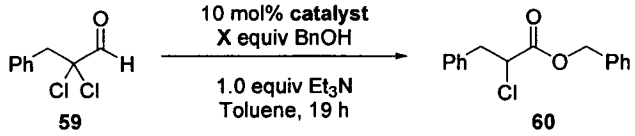
triethylamine as the base (Scheme 35). To our gratification, the desired product **60** was obtained in 65% yield and 60% ee.

Scheme 35.

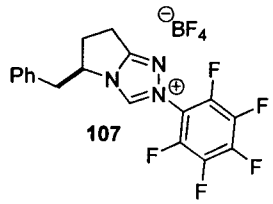


In order to improve the yield of the reaction the use of increasing amounts of benzyl alcohol was examined. 10 equivalents of benzyl alcohol provided the desired ester in 28% yield and 88% ee (Table 13). The use of benzyl alcohol as solvent provided no desired product. This result is an interesting contrast to the achiral version of the triazolium carbene catalyzed Wallach rearrangement, where the use of benzyl alcohol as solvent provided the desired product in 92% yield (Entry 11, Table 6, Chapter 2). A screen of other chiral triazolium salts revealed that **107** was also a competent catalyst for

Table 13.



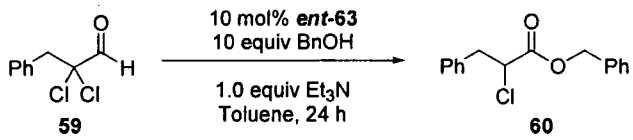
Entry	Catalyst	X	Yield%	ee%
1	*ent*-63	1	65	60
2	*ent*-63	10	28	88
3	*ent*-63	solvent	0	0
4	107	1	83	52
5	107	10	79	72
6	107	solvent	28	91



this reaction providing the desired product **60** in 83% yield and 52% ee in the presence of 1 equivalent of benzyl alcohol (Entry 4, Table 13). This catalyst appears to be less susceptible to deactivation than ***ent*-63** providing the desired product in 28% yield and 91% ee when benzyl alcohol was used as the solvent. With both catalysts an increase in the concentration of benzyl alcohol results in decreased yields but increased enantioselectivity.

The above results suggest that an intermolecular event between the alcohol (or an impurity in the alcohol) and some intermediate in the catalytic cycle was responsible for the decreasing yields therefore the effect of dilution on the reaction was examined (Table 14). Investigations using ***ent*-63** and 10 equivalents of benzyl alcohol revealed that the yield of the reaction did

Table 14.

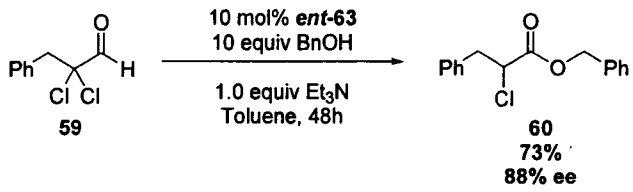


Entry	[M]	Yield%(ee)
1	0.03	38(94)
2	0.02	53(94)
3	0.01	60(88)

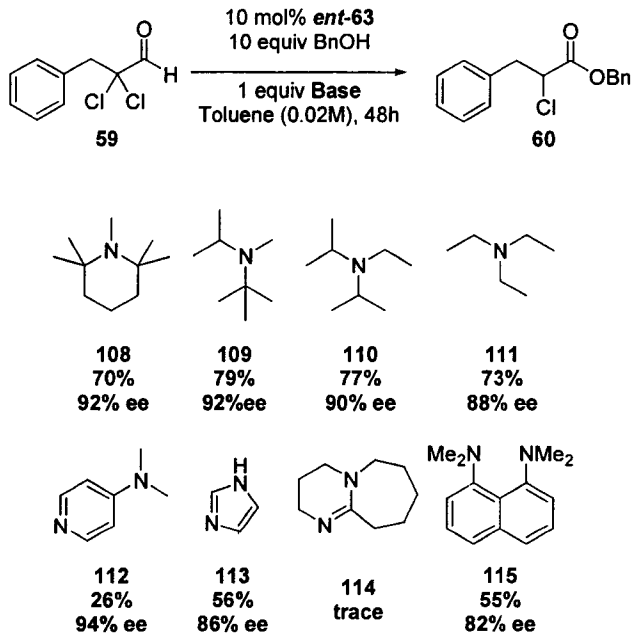
increase with decreasing concentration. A concentration of 0.02M was chosen for further study. Suspecting that the low yield may be due to a decrease in the rate of nucleophile acylation due to the increase in dilution the reaction was allowed to proceed for 48h, which provided the desired ester **60** in 73% yield and 88% ee (Scheme 36).

The effect of amine base structure on the stereoselectivity was next examined. Sterically hindered tertiary amines afforded the best combination of yield and

Scheme 36.



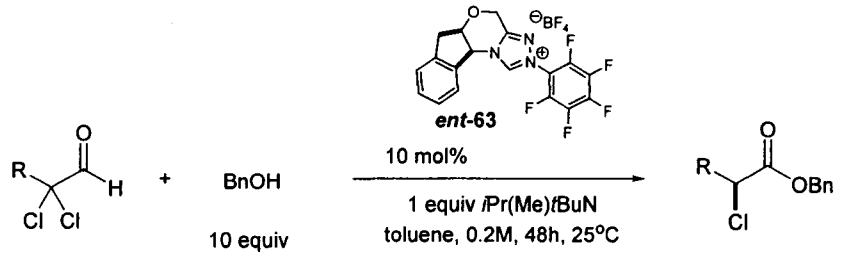
Scheme 37.

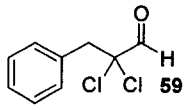
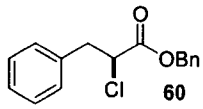
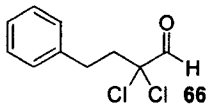
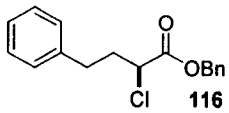
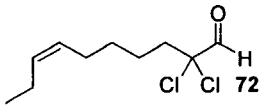
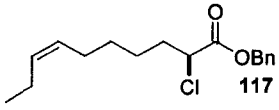
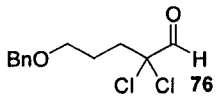
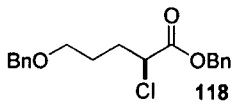


enantioselectivity (Scheme 37). Methyl-*iso*-propyl-tertbutylamine **109** provided the desired product in 79% yield and 92% ee and was chosen for the substrate screen.

The reaction appears to be general with respect to the participating aldehyde providing the desired products with enantioselectivities between 86 and 92% (Table 15). After optimizing the reaction for the synthesis of benzyl α-chloroesters other alcohols were screened (Table 16). The reaction provides only trace amounts of the desired

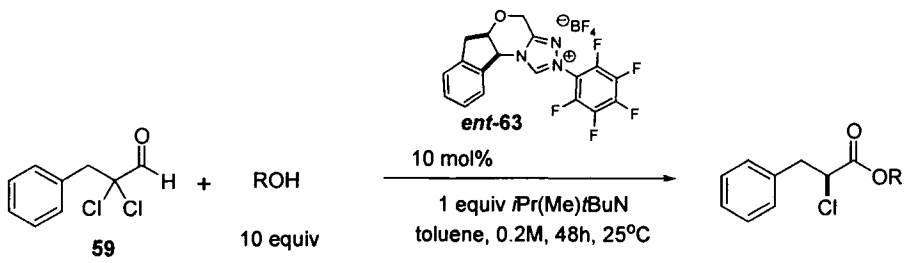
Table 15.



Entry[a]	Substrate	Product	Yield %	ee %
1	 59	 60	79	92
2	 66	 116	92	88
3	 72	 117	76	88
4	 76	 118	49	86

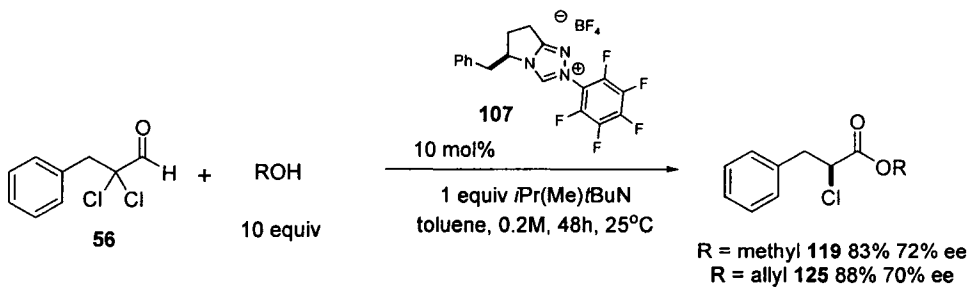
product when using methanol, allyl alcohol, or neopentyl alcohol as a nucleophile. Trichloroethanol and phenol provided the desired esters, but in much lower yield. In the case of phenol, ester **57** was produced in 88% ee but only 47% yield. The slightly more nucleophilic trichloroethanol provided the desired product in 27% yield and only 70% ee. Increasing the equivalents of phenol or trichloroethanol up to 100 equivalents offered little increase in the yield of these reactions.

Table 16.



Entry	ROH	Product	Yield %	ee %
1	benzyl alcohol	**60**	79	92
2	methanol	**119**	trace	--
3	phenol	**61**	47	88
4	trichloroethanol	**120**	27	70

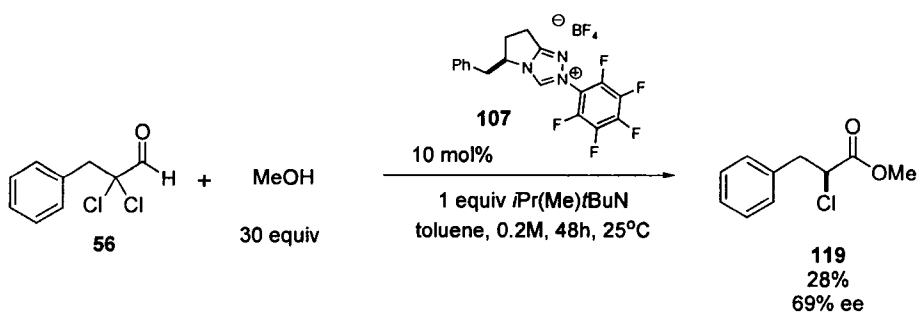
Scheme 38.



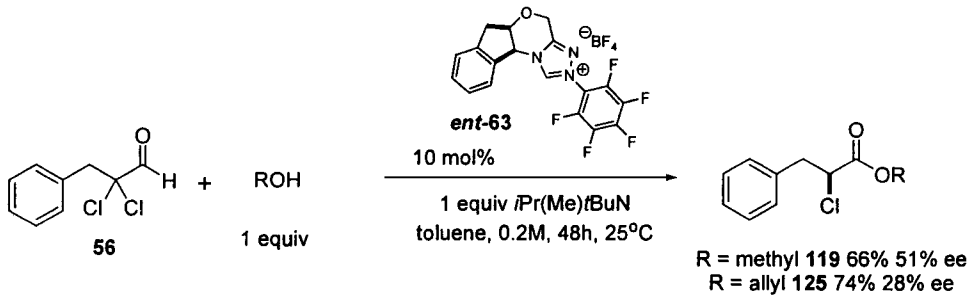
Intrigued by the failure of methanol and allyl alcohol to provide significant amounts of product under the optimized conditions we examined the use of **107** as catalyst, and obtained the desired esters **119** and **125** in 83% yield, 72% ee and 88% yield, 70% ee respectively (Scheme 38). The use of 30 equivalents of methanol in the reaction resulted in a decrease in yield and no increase in the observed enantioselectivity (Scheme 39). The observed decrease in yield upon increasing concentration of methanol is similar to what was observed in the case of benzyl alcohol (Table 13), although the reaction appears to be more sensitive to increasing concentrations of methanol. To test

this hypothesis we reinvestigated the use of ***ent*-63** as catalyst for the reaction using only one equivalent of either methanol or allyl alcohol (Scheme 40). The desired products **119** or **125** are obtained in similar yields to those of benzyl alcohol (Table 13) under these conditions, although with lower enantiomeric excess.

Scheme 39.



Scheme 40.

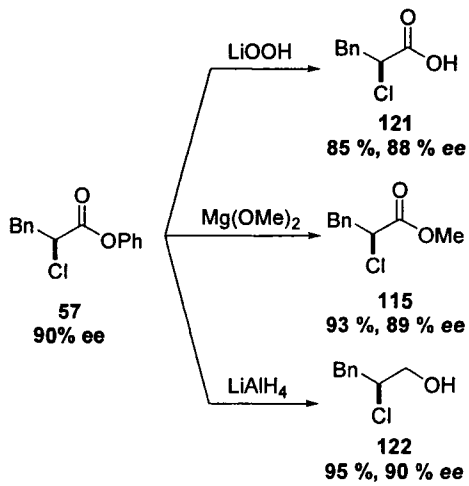


4.3 Reactions of α-Chloroesters

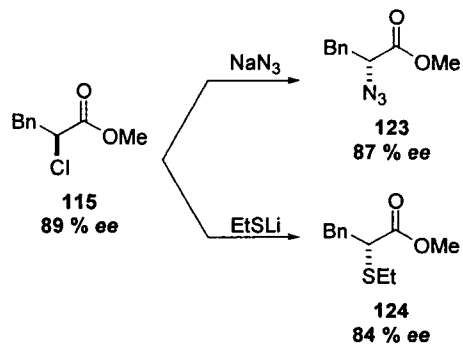
The product α-chloroesters produced in our reactions have found interesting applications in organic synthesis due to their possession of vicinal electrophilic sites. Phenyl α-chloroesters exemplified by **57** undergo reactions typical of esters (hydrolysis, transesterification, reduction) with minimal loss of enantioselectivity (Scheme 41). We attempted to displace the chlorine atom directly on the phenyl α-chloroesters, however complex mixtures were obtained due to competitive reaction of the nucleophile with the

ester functionality. Subjection of our alkyl α-chloroesters to nucleophiles resulted in the S_N2 displacement of the chloride with minimal loss of enantioselectivity (Scheme 42).

Scheme 41.



Scheme 42.



4.4 Conclusion

We have developed an asymmetric variant of the Wallach rearrangement that relies on the protonation of in situ generated chiral enolates to afford enantioenriched α-chloro esters. This reaction is applicable to the synthesis of a wide-range of phenyl or benzyl α-chloroesters lacking substitution at the β-position. More importantly the ability

to trap the in situ generated chiral enolate with an electrophile may find a wider utility in organic synthesis.

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Chapter 2 Experimental

The Asymmetric Intramolecular Stetter Reaction: Application to the Disubstituted Cyclopentanones

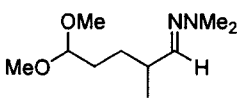
General Methods. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gell (230-400 mesh). Thin layer chromatography was performed on EM Science silica gel 60 (230-400 mesh). Visualization was accomplished with UV light, $KmnO_4$, aqueous ceric ammonium molybdate, or anisaldehyde dips followed by heating.

All chemicals were purchased from Aldrich and used as received. Triazolium salts were prepared according to literature procedures.[1]

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ,ppm) from an internal standard [tetramethylsilane (TMS)] or deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 300, 400, or 500 MHz spectrometer at 75 MHz, 100 MHz, or 125 MHz at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated.

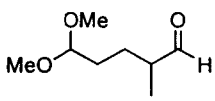
Gas chromatography was performed on a Varian CP 3800 gas chromatograph equipped with a flame ionization detector using Chiraldex chiral columns as indicated.

General Procedure for the Intramolecular Asymmetric Stetter Reaction. To a flame dried round bottom flask was added 0.2 equivalents of catalyst. Toluene (5mL) was then added followed by KHMDS (0.5M in THF). The solution was stirred for 10 minutes followed by the addition of substrate. After 24 hours the reaction mixture was filtered through a short plug of silica gel eluting with diethyl ether. Column chromatography (9:1 hexane/ethyl acetate) afforded analytically pure material.

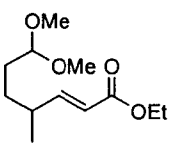


5,5-Dimethoxy-2-methyl-pentanal (88). To 5,5 dimethoxy-pentanal (21.05 g, 144.0 mmol) stirred at 0 °C was added *N,N*-dimethyl hydrazine (13.12 mL, 172.0 mmol) with continued stirring for 30 minutes. 50 mL water and 50 mL diethyl ether were added followed by removal of the aqueous layer. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* affording 23.36 g of product that was used without purification. To a solution of diisopropyl amine (4.78 g, 47.2 mmol) in 50 mL THF at –78 °C was added 1.5 M n-butyllithium (31.9 mL, 47.2 mmol). The mixture was warmed to 0 °C over 5 minutes and then cooled to –78 °C. *N*'-(5,5-dimethoxy-pentylidene)-*N*-*N*-dimethyl-hydrazone (5.08 g, 27.0 mmol) in 50 mL THF was then added and the mixture was stirred at 0 °C for 2 hours, then cooled to –78°C. Methyl iodide (5.75 g, 40.5 mmol) was then added and the solution stirred for 1 hour at this temperature. The solution was then warmed to room temperature and stirred for 1 hour. The solution was poured into 200 mL of a 2:1 solution of H_2O/methylene chloride. 50 mL saturated sodium bicarbonate solution was added and the layers

separated. The aqeous layer was washed with 50 mL (x2) methylene chloride. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford 4.65 g of product (27.0 mmol, 85 %). Rf = 0.10 (3:1 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, 1H, J = 6.4 Hz), 4.30 (t, 1H, J = 5.5 Hz), 3.24 (d, 6H, J = 1 Hz), 2.64 (s, 6H), 2.23-2.30 (m, 1H), 1.51-1.60 (m, 2H), 1.33-1.46 (m, 2H), 1.00 (d, 3H, J = 6.8 Hz) ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.3, 104.4, 52.6, 52.5, 43.2, 36.8, 30.1, 30.0, 19.0.



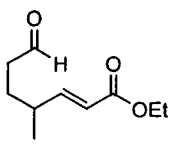
N'-(5,5-Dimethoxy-2-methyl-pentylidene)-*N,N*-dimethyl-hydrazine (1.50 g, 7.4 mmol) was dissolved in 100 mL THF and 100 mL 0.1 M pH = 7 phosphate buffer (95 mL H_2O, 2.85 mL 1M Na_2HPO_4, 2.12 mL 1M NaH_2PO_4). Sodium periodate (8.5 g, 40.0 mmol) was added and the mixture stirred overnight. The solution was then diluted with 100 mL diethyl ether and the layers separated. The aqeous layer was then extracted with 100 mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:1 hexane/diethyl Ether) afforded 0.4 g of product as a clear oil (2.5 mmol, 34 %). Rf = 0.38 (3:1 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 4.29 (t, 1H, J = 5.5 Hz), 3.25 (s, 6H), 2.25-2.33 (m, 1H), 1.66-1.75 (m, 1H), 1.51-1.60 (m, 1H), 1.31-1.40 (m, 1H), 1.04 (d, 3H, J = 7.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.5, 104.1, 52.7, 45.8, 29.7, 25.2, 13.3.



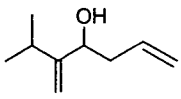
4-Methyl-7-oxo-hept-2-enoic acid ethyl ester (89).

(Carboethoxymethylene)triphenyl-phosphorane (0.98 g, 2.8 mmol) was dissolved in 20 mL THF and 60 (0.37 g, 2.3 mmol) was added. The reaction was stirred

overnight. The reaction was concentrated and subjected directly to column chromatography (4:1 hexane/ethyl acetate) to afford 0.43 g of product as a clear oil (1.9 mmol, 81%). Rf = 0.59 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, 1H, *J* = 7.9, 12.7 Hz), 5.76 (d, 1H, *J* = 15.8 Hz), 4.31 (t, 1H, *J* = 5.3 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.28 (s, 6H), 2.24-2.33 (m, 1H), 1.52-1.60 (m, 2H), 1.37-1.44 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.04 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.7, 153.8, 120.0, 104.4, 60.1, 52.8, 52.7, 36.3, 30.7, 30.2, 19.4, 14.2.

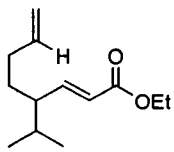


7,7-Dimethoxy-4-methyl-hept-2-enoic acid ethyl ester (0.53 g, 2.3 mmol) was dissolved in 10 mL dichloromethane. H_2O (1 mL), triflouroacetic acid (0.5 mL) were added and the solution stirred overnight. Aqueous sodium bicarbonate (20 mL) was added and the layers separated. The aqueous layer was extracted with 10 mL diethyl ether. The combined organics were dried over $MgSO_4$, concentrated *in vacuo*, and subjected to column chromatography (95:5 hexane/ethyl acetate) affording 0.31 grams of product as a clear oil (1.7 mmol, 72 %). Rf = 0.36 (9:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.76 (dd, 1H, *J* = 15.8, 8.1 Hz), 5.76 (d, 1H, *J* = 15.8 Hz), 4.15 (q, 2H, *J* = 7.0 Hz), 2.41 (t, 2H, *J* = 8.1 Hz), 2.23-2.37 (m, 1H), 1.60-1.76 (m, 2H), 1.25 (t, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.6, 166.5, 152.7, 120.7, 60.2, 41.4, 35.8, 27.7, 19.3, 14.1; IR (NaCl, neat) 1719, 1270, 1179 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 185.1177. Found 185.1179.

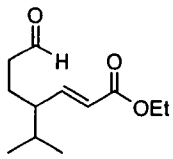


4-Isopropyl-octa-2,7-dienoic acid ethyl ester (91) Isopropylacrolein (4.00 g, 40.8 mmol) was dissolved in 100 mL THF and chilled to –78 °C.

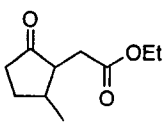
Allyl magnesium chloride (20.3 mL, 40.8 mmol, 2.0 M solution in THF) was then added and the solution stirred for one hour at –78 °C. 10 mL of 10 % v/v HCl was then added and the solution warmed to room temperature. The layers were separated and the aqueous layer was extracted with 20 mL Et_2O, dried with $MgSO_4$ and concentrated *in vacuo*. Column chromatography afforded 4.80 grams of product as a colorless oil (34.2 mmol, 84 %). Rf = 0.54 (3:1 hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.85 (m, 1H), 5.12-5.15 (m, 2H), 5.05 (dd, 1H, J = 1.1, 1.1 Hz), 4.91 (s, 1H), 4.10-4.14 (m, 1H), 2.36-2.43 (m, 1H), 2.20-2.29 (m, 2H), 1.64 (d, 1H, J = 4.0 Hz), 1.06 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 7.0 Hz) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.1, 134.8, 118.1, 107.1, 72.9, 40.9, 30.4, 23.1, 22.5.



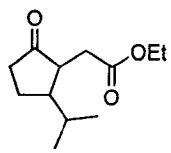
Potassium hydride (1.16 g, 29 mmol) was dissolved in 50 mL dioxane and 6-methyl-5-methylene-hept-1-en-5-ol (2.0 g, 14.0 mmol) in 50 mL dioxane was added. The solution was heated at 100 °C overnight. 50 mL of 10 % v/v HCl and 100 mL Et_2O were then added. The layers were separated, the organics dried over $MgSO_4$, and concentrated to approx. 100 mL. (carboethoxymethylene)triphenyl-phosphorane (5.0 g, 14.4 mmol) was added and the solution stirred overnight. Silica gel (15 g) was added and the mixture concentrated and subjected to column chromatography affording 1.20 g of the desired product (5.7 mmol, 41 %). Rf = 0.56 (9:1 hexane/ethyl acetate) ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (dd, 1H, J = 9.9, 15.8 Hz), 5.69-5.82 (m, 2H), 4.92-5.01 (m, 2H), 4.81 (q, 2H, J = 7.3 Hz), 1.83-2.10 (m, 3H), 1.61-1.73 (m, 1H), 1.52-1.60 (m, 1H), 1.33-1.47 (m, 1H), 1.29 (t, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.4, 151.2, 138.3, 122.3, 114.6, 60.2, 48.6, 31.7, 31.7, 30.7, 20.7, 19.2, 14.4.



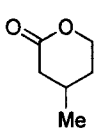
4-Isopropyl-7-oxo-hept-2-enoic acid ethyl ester (92) 64 (0.50 g, 2.4 mmol), was dissolved in 8 mL *t*-BuOH and 2 mL H_2O followed by the addition of trimethylamine *N*-oxide dihydrate (0.20 g, 2.6 mmol), pyridine (0.19 g, 2.4 mmol), OsO_4 (1.45 mL, 0.24 mmol, 4 wt % solution in H_2O) and stirred at 80 °C overnight. Et_2O (50 mL) was added and the layers separated. The organics were dried over $MgSO_4$, concentrated *in vacuo* and dissolved in 50 mL toluene. Lead tetraacetate (1.37 g, 3.1 mmol) was then added followed by stirring for two hours. Silica gel (2.0 grams) was then added followed by concentrating *in vacuo*. Column chromatography afforded 0.17 grams of the desired product (0.80 mmol, 34 %). Rf = 0.20 (3:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.67 (dd, 1H, *J* = 15.7, 9.9 Hz), 6.74 (d, 1H, *J* = 15.7 Hz), 4.16 (q, 2H, *J* = 7.0 Hz), 2.26-2.46 (m, 2H), 1.82-1.96 (m, 2H), 1.50-1.73 (m, 2H), 1.26 (t, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.5, 166.0, 150.0, 123.0, 60.3, 48.6, 42.0, 31.8, 23.7, 20.5, 19.2, 14.3; IR (NaCl, neat) 1719, 1254, 1164 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{20}O_3$, 213.1491. Found 213.1498.



(2-Methyl-5-oxo-cyclopentyl)-acetic acid ethyl ester (93). According to the general procedure, 12 (0.020 g, 0.11 mmol), catalyst 33 (0.008 g, 0.022 mmol), and KHMDS (0.044 mL, 0.022 mmol, 0.5 M in THF), provided the known ester **66** (18.0mg, 90%) as a 51:49 mixture of inseparable diastereomers.[2] GC analysis (G-TA, 90°C, 2.5 mL/min; trans (tr (minor) = 44.8 min., tr (major) = 43.3 min.), cis (tr (minor) = 48.9 min., tr (major) = 49.6 min.)) gave the enantiomeric composition of the trans product: (90 % ee), and the cis product: (95 % ee).

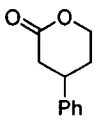


(2-Isopropyl-5-oxo-cyclopentyl)-acetic acid ethyl ester (94). According to the general procedure, 14 (0.020 g, 0.094 mmol), catalyst 33 (0.007 g, 0.019 mmol), and KHMDS (0.036 mL, 0.018 mmol, 0.5 M in THF), produced the product as a 53:47 mixture of inseparable diastereomers. Purification by column chromatography (95:5 hexane/diethyl ether) afforded 16 (19.0 mg, 95 %). Rf = 0.49 (3:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06-4.15 (m, 4H), 2.78 (q, 1H, J = 7.2 Hz), 2.60-2.66 (m, 2H), 2.53-2.59 (m, 1H), 2.33-2.41 (m, 2H), 2.15-2.24 (m, 5H), 1.97-2.1 (m, 2H), 1.85-1.93 (m, 1H), 1.72-1.83 (m, 2H), 1.62-1.70 (m, 1H), 1.46-1.57 (m, 1H), 1.22 (q, 6H, J = 7.0 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.8 Hz), 0.73 (d, 3H, J = 6.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 219.4, 219.3, 172.3, 172.0, 60.7, 60.6, 48.8, 48.4, 47.5, 44.9, 37.2, 36.6, 33.4, 30.5, 29.5, 27.8, 22.4, 22.3, 21.9, 21.2, 18.9, 17.5, 14.1; IR (NaCl, neat) 1736, 1372, 1252, 1183 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{20}O_3$, 213.1494. Found 213.1491. GC analysis (G-TA, 90°C, 2.0 mL/min; trans (tr (minor) = 123.1 min., tr (major) = 116.0 min.), cis (tr (minor) = 151.8 min., tr (major) = 141.8 min.)) gave the enantiomeric composition of the trans product: (84 % ee), and the cis product: (96 % ee).



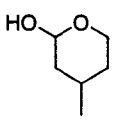
4-Methyl-tetrahydropyran-2-one (99). To a stirred solution of 3-methylglutaric anhydride (1.0 g, 7.8 mmol) in 30 mL THF was added sodium borohydride (0.59 g, 15.6 mmol). After stirring overnight, 10 mL of 10% v/v HCl was slowly added. The solution was then placed in a separatory funnel and extracted with diethyl ether (3x). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The yellow oil was then dissolved in 5mL methylene chloride and 0.3 mL trifluoroacetic acid was added followed by stirring overnight. To the mixture was

then added 50 mL diethyl ether and the solution placed in a separatory funnel, followed by washing with sat. aq. $NaHCO_3$ (3x), and brine (1x). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was then purified by column chromatography eluting with (9:1 hexane/diethyl Ether) to afford 0.260g of the known product **99** (2.28 mmol, 29%).[3]

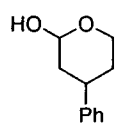


4-Phenyl-tetrahydro-pyran-2-one (100). A flame dried flask was charged with 3-phenylglutaric acid (2.00 g, 9.6 mmol) and 30 mL methylene chloride. The solution was cooled to 0 °C and triflouroacetic anhydride (4.0 mL, 28.8 mmol) was added. The mixture was stirred for 2 hours at this temperature, then concentrated *in vacuo*. The solution was placed under vacuum (1 mmHg) overnight. The white solid was then dissolved in 50 mL THF and sodium borohydride was added (0.73 g, 19.2 mmol), followed by stirring for 24 hours. 20 mL 10 % v/v HCl was then slowly added, followed by 20 mL diethyl ether; the layers were separated and the aqueous layer was extracted with 20 mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* affording an oil. The oil was dissolved in 50 mL methylene chloride and 1 mL triflouroacetic acid was added, followed by stirring for 16 hours. 50 mL sat'd. aq. sodium bicarbonate was slowly added and the layers separated. The organic layer was extracted with 20 mL methylene chloride (2x). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The clear oil was purified by column chromatography (3:1 hexane/ethyl acetate) affording 1.01 g product as a colorless oil (5.7 mmol, 60 %). Rf = 0.13 (3:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.30 (m, 5H), 4.39-4.44 (m, 1H), 4.30 (ddd, 1H, J = 11.2, 10.7, 3.6 Hz), 3.11-3.19 (m, 1H), 2.82 (ddd, 1H, J = 1.5, 6.0, 17.7 Hz), 2.54 (dd, 1H, J = 10.7, 17.7

Hz), 2.05-2.11 (m, 1H), 1.89-1.99 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.5, 142.7, 128.8, 127.0, 126.3, 68.5, 37.4, 37.2, 30.1.

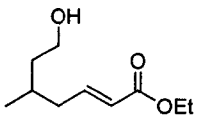


4-Methyl-tetrahydro-pyran-2-ol (101). To a stirred solution of 73 (0.260g, 2.28 mmol) in 10 mL toluene at –78 °C was added Dibal-H (3.0 mL, 3.00 mmol, 1M in hexane). The mixture was stirred for 2 hours at which time 10 mL of a sat'd aqueous solution of Rochelle's Salt was added. The solution was allowed to warm to room temperature and stirred overnight. 10 mL of a sat'd aqueous solution of sodium bicarbonate was added and the organic layer was separated. The aqueous layer was then extracted 3x with 10 mL diethyl ether. The organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. This afforded 0.203 g of pure product as a mixture of diastereomers (1.75 mmol, 77%). Rf = 0.17 (3:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.65 (d, 1H, J = 9.2 Hz), 3.95-4.03 (m, 2H), 3.59-3.65 (m, 1H), 3.48 (ddd, 1H, J = 12.1, 11.9, 2.2 Hz), 3.41 (s, 1H), 2.83 (s, 1H), 1.94-2.05 (m, 1H), 1.85-1.92 (m, 1H), 1.46-1.77 (m, 4H), 1.15-1.34 (m, 3H), 0.99-1.04 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.1, 91.5, 65.6, 59.7, 41.6, 38.7, 34.1, 33.5, 29.4, 23.6, 22.1, 21.9; IR (NaCl, neat) 3386, 2952, 2928, 1068, 1026, 988 cm^{-1}.

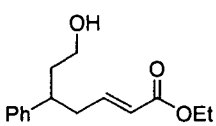


4-Phenyl-tetrahydro-pyran-2-ol (102). **74** (0.50 g, 2.8 mmol) was dissolved in 20 mL Toluene and chilled to –78 °C. Dibal-H (0.54 mL, 3.0 mmol) was then added and the reaction stirred for 2 hours at –78 °C. Methanol (1 mL) was then added and the solution warmed to room temperature. Diethyl ether 20 mL and Rochelle's Salt (sat'd. aq. 20 mL) were then added. The solution was stirred until the

layers separated. The layers were separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organics were dried over $MgSO_4$, and concentrated *in vacuo*. Column chromatography (3:1 hexane/diethyl ether) afforded 0.370 g product as a white solid (mixture of diastereomers) (2.1 mmol, 75 %). Rf = 0.15 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.30 (m, 10H), 5.41 (s, 1H), 4.80 (s, 1H), 4.11-4.19 (m, 2H), 3.72-3.75 (m, 1H), 3.60-3.67 (m, 1H), 3.16-3.24 (m, 2H), 2.78-2.86 (m, 1H), 2.67 (s, 1H), 2.10-2.13 (m, 1H), 1.95-1.98 (m, 1H), 1.69-1.84 (m, 5H), 1.52-1.60 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 145.5, 144.5, 128.6, 128.5, 127.4, 126.8, 126.7, 126.6, 126.3, 96.3, 91.7, 65.8, 59.8, 40.6, 40.3, 37.5, 34.5, 33.0, 32.8

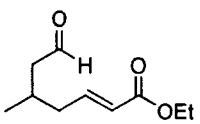


7-Hydroxy-5-methyl-hept-2-enoic acid ethyl ester (103). To a stirred solution of 75 (0.083 g, 0.714 mmol) in 5 mL THF was added (carboethoxymethylene)triphenyl-phosphorane (0.497 g, 1.4 mmol). The solution was heated to 40 °C and stirred overnight. The solution was concentrated *in vacuo* and subjected to column chromotagraphy (3:1 hexane/ethyl acetate) affording 0.107 g product as a clear oil (0.62 mmol, 87%). Rf = 0.06 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92–7.02 (m, 1H), 5.82 (d, 1H, J = 15.7 Hz), 4.18 (q, 2H, J = 7.1 Hz), 3.69 (t, 2H, J = 6.2 Hz), 2.27-2.35 (m, 2H), 1.69-1.78 (m, 2H), 1.42 (bs, 1H), 1.28 (t, 3H, J = 7.1 Hz), 0.94 (d, 3H, J = 6.6 Hz).

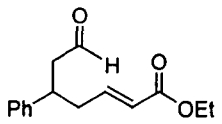


7-Hydroxy-5-phenyl-hept-2-enoic acid ethyl ester (104). To a flame dried flask was added (carboethoxymethylene)triphenyl-phosphorane (4.5 g, 12.9 mmol) and 20 mL THF, followed by addition of 76 (1.25 g, 10.8 mmol). The mixture was stirred overnight and subjected directly to column chromatography (4:1 hexane/ethyl acetate), affording 0.82 g of product (3.3 mmol, 31 %). Rf = 0.20 (3:1

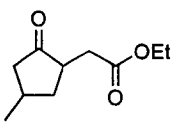
hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.30 (m, 5H), 6.76-6.84 (m, 1H), 6.75 (d, 1H, J = 15.6 Hz), 4.12 (q, 2H, J = 7.0 Hz), 3.40-3.56 (m, 1H), 2.86-2.93 (m, 1H), 2.51 (ddd, 2H, J = 7.4, 7.4, 1.2 Hz), 1.92-2.02 (m, 1H), 1.76-1.85 (m, 1H), 1.23 (t, 3H, J = 7.2 Hz), 1.13 (bs, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.4, 146.8, 143.5, 128.7, 128.5, 147.5, 126.7, 122.9, 60.7, 60.2, 41.6, 39.6, 38.6, 14.2.



5-Methyl-7-oxo-hept-2-enoic acid ethyl ester (105) Oxalyl chloride (0.628 g, 4.95 mmol) and 10 mL methylene chloride was added to a flask and chilled to -78 °C. DMSO (0.773 g, 9.90 mmol) was added and the solution stirred for 5 minutes, then 77 (0.84 g, 4.50 mmol) in 10 mL methylene chloride was added. After 15 minutes triethylamine (2.29 g, 22.50 mmol) was added, the mixture was stirred for 5 min at –78 °C, then allowed to warm to room temperature and stirred overnight. 20 mL water was added and the organic layer separated. The aqeous layer was extracted 2x with 10 mL methylene chloride. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The oil was subjected to column chromatography (4:1 hexane/ethyl acetate), affording 0.400 g (2.17 mmol, 48%) of product as a clear oil. Rf = 0.13 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, 1H, J = 1.5 Hz), 6.85-6.93 (m, 1H), 5.83 (d, 1H, J = 15.6 Hz), 4.18 (q, 2H, J = 7.2 Hz), 2.41-2.47 (m, 1H), 2.13-2.33 (m, 4H), 1.28 (t, 3H, J = 7.3 Hz), 1.00 (d, 3H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 166.3, 146.2, 123.5, 60.3, 50.2, 39.1, 27.5, 19.9, 14.2; IR (NaCl, neat) 1721, 1654, 1270, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 184.1099. Found 184.1099.

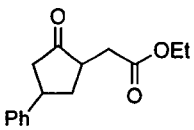


7-Oxo-5-phenyl-hept-2-enoic acid ethyl ester (106). To a flamed dried flask was added 10 mL methylene chloride and oxalyl chloride (0.29 mL, 3.34 mmol). The solution was cooled to –78 °C and DMSO (0.47 mL, 6.60 mmol) was added. After 5 minutes 78 (0.75 g, 3.0 mmol) was added. The solution was stirred for 15 minutes, followed by addition of triethylamine (1.52 g, 15 mmol). After 5 minutes the solution was warmed to room temperature and stirred overnight. Water (50 mL) was added and the layers separated, followed by extraction with methylene chloride. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo.* The oil was subjected to column chromatography (4:1 hexane/ethyl acetate) affording 0.45 g of product as a yellow oil (1.8 mmol, 60 %). Rf = 0.17 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, 1H, J = 1.5 Hz), 7.17-7.34 (m, 5H), 6.74-6.84 (m, 1H), 5.79 (dd, 1H, J = 37.1, 1.1 Hz), 4.15 (q, 2H, J = 7.0 Hz), 3.34-3.44 (m, 1H), 2.78 (d, 2H, J = 7.3 Hz), 2.55 (t, 2H, J = 7.0 Hz) 1.26 (t, 3H, J = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 166.1, 145.5, 142.4, 128.8, 127.3, 127.0, 123.6, 60.3, 49.4, 39.0, 14.2; IR (NaCl, neat) 1721, 1660, 1276, 1204 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1335.

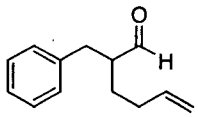


(4-Methyl-2-oxo-cyclopentyl)-acetic acid ethyl ester (107). According to the general procedure, 79 (0.035 g, 0.19 mmol), catalyst 33 (0.014 g, 0.038 mmol), and KHMDS (0.076 mL, 0.038 mmol, 0.5 M in THF), produced the product as a 1:1 mixture of inseparable diastereomers. Purification by column chromatography (95:5 hexane/diethyl ether) afforded 9 (34.0 mg, 97 %). Rf = 0.44 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, 4H, J = 7.3 Hz), 2.64-2.74 (m, 3H), 2.33-2.54 (m, 7H), 2.13-2.24 (m, 1H), 1.78-2.03 (m, 4H), 1.25 (t, 6H, J = 7.2

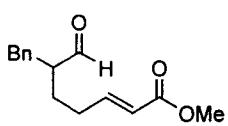
Hz), 1.14 (d, 3H, J = 6.4 Hz), 1.09 (d, 3H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.7, 218.7, 172.1, 172.0, 60.6, 47.2, 46.0, 45.9, 42.7, 38.0, 36.1, 34.6, 34.0, 29.6, 27.8, 20.9, 20.2, 14.2; IR (NaCl, neat) 1721, 1654, 1270, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_3$, 184.1099. Found 184.1092. GC analysis (G-TA, 100°C, 3.0 mL/min; trans (tr (minor) = 32.4 min., tr (major) = 28.7 min.), cis (tr (minor) = 29.7 min., tr (major) = 33.8 min.)) gave the enantiomeric composition of the trans product: 98 % ee, and the cis product: 94 % ee.



(2-Oxo-4-phenyl-cyclopentyl-acetic acid ethyl ester (108). According to the general procedure, 8 (25.0 mg, 0.10 mmol), catalyst 33 (7.5 mg, 0.02 mmol), and KHMDS (0.040 mL, 0.02 mmol, 0.5 M in THF), produced the product as a 55:45 mixture of inseparable diastereomers. Purification by column chromatography (95:5 hexane/diethyl Ether) afforded 9 (24.0 mg, 96 %). Rf = 0.25 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.34 (m, 10H), 4.09-4.15 (m, 4H), 3.57-3.61 (m, 1H, trans), 3.33-3.38 (m, 1H, cis), 2.30-2.80 (m, 12H), 2.18-2.25 (m, 1H), 1.76-1.86 (m, 1H), 1.23 (ddd, 6H, J = 7.1, 7.1, 2.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 218.7, 217.2, 171.9, 171.8, 143.8, 142.8, 128.7, 126.8, 126.7, 126.6, 60.7, 46.9, 45.2, 44.7, 42.9, 40.1, 38.3, 37.2, 36.4, 34.6, 33.8, 14.2; IR (NaCl, neat) 1734, 1180 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1322. GC analysis (G-TA, 140°C, 3.0 mL/min; trans (tr (minor) = 78.9 min., tr (major) = 76.2 min.), cis (tr (minor) = 84.5 min., tr (major) = 90.6 min.)) gave the enantiomeric composition of the trans product: 98 % ee, and the cis product: 96 % ee.

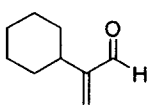


2-Benzyl-hex-5-enal (111). To hydrocinnamaldehyde (8.80 g, 65.6 mmol) stirred at 0 °C was added *N,N*-dimethyl hydrazine (4.73 mL, 78.7 mmol) with continued stirring for 30 minutes. 50 mL water and 50 mL diethyl ether were added followed by removal of the aqueous layer. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* affording 10.00 g of product that was used without purification. To a solution of LDA (12.5 mmol) in 30 mL of THF at 0 °C was added hydrocinnamaldehyde *N,N*-dimethylhydrazone (2.00 g, 11.3 mmol) in 10 mL of THF. The resulting suspension was allowed to stir for 2h at 0 °C, at which time 4-bromo-1-butene (1.69 g, 12.5 mmol) was added. After warming to room temperature the reaction mixture was stirred for an additional 12h. Aqueous workup afforded the crude alkylated hydrazone. The hydrazone was dissolved in 50 mL acetone and 10 mL water, and 12 g of amberlyst-15 was added. The mixture was stirred overnight. Solution was then filtered and subject to column chromatography (95:5 hexane/ethyl acetate) To afford 0.41 g of pure product (2.2 mmol, 19 %). Rf = 0.42 (9:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, 1H, J = 2.2 Hz), 7.15-7.32 (m, 5H), 5.67-5.79 (m, 1H), 4.97-5.05 (m, 2H), 2.89-3.04 (m, 1H), 2.63-2.78 (m, 2H), 2.03-2.15 (m, 2H), 1.72-1.84 (m, 1H), 1.51-1.63 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.4, 138.6, 137.5, 128.9, 128.5, 126.4, 115.5, 52.6, 35.0, 30.1, 27.6; IR (NaCl, neat) 3064, 3028, 3977, 2926, 2855, 2715, 1728, 1641, 1603, 1497, 1454.

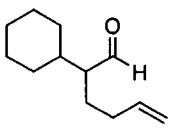


6-Benzyl-7-oxo-hept-2-enoic acid methyl ester (112). To [1,3-bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)dichloro (phenylmethylene)-(tricyclohexyl phosphine)ruthenium] (0.045 g, 0.053 mmol) in 10 mL methylene chloride was added methyl acrylate (0.915 g, 10.6 mmol) and 85 (0.200 g,

1.06 mmol). The solution was heated to 40 °C and stirred overnight. Silica gel (1 g) was then added and the solvent removed *in vacuo*. Column chromatography (9:1 hexane/ethyl acetate) yielded 0.176 g product (0.72 mmol, 67 %). Rf = 0.40 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, 1H, J = 1.8 Hz), 7.14-7.32 (m, 5H), 6.83-6.93 (m, 1H), 5.79 (d, 1H, J = 15.4 Hz), 3.72 (s, 3H), 2.99-3.06 (m, 1H), 2.63-2.77 (m, 2H), 2.13-2.31 (m, 2H), 1.77-1.89 (m, 1H), 1.55-1.66 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.7, 166.8, 147.8, 138.1, 128.9, 128.7, 126.6, 121.7, 52.5, 51.5, 35.1, 29.5, 26.6; IR (NaCl, neat) 1724, 1657, 1436, 1274, 1208 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1327.

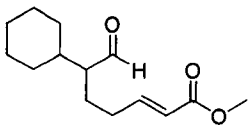


2-Cyclohexyl-hex-5-enal (113). 2-Cyclohexyl-ethanal (5.50 g, 43.6 mmol), formaldehyde (4.40 mL, 47.9 mmol, 30 % in H_2O), piperidine (0.22 mL, 2.2 mmol), and concentrated HCl (0.087 mL, 1.1 mmol) were added to a flask equipped with a reflux condenser. The solution was heated overnight at 80 °C. Steam distillation followed by extraction with diethyl ether and standard aqueous workup afforded 4.0 g of product (29.0 mmol, 66 %).[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 6.17 (s, 1H), 5.90 (s, 1H), 2.38-2.47 (m, 1H), 1.65-1.74 (m, 5H), 1.25-1.39 (m, 2H), 1.03-1.19 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.3, 155.3, 132.5, 35.8, 32.0, 26.4, 26.2.

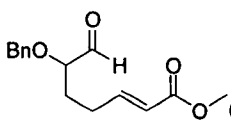


A flame dried flask was charged with cyclohexylacrolein (0.77 g, 5.6 mmol) and 10 mL by THF followed by cooling to –78 °C. Allyl magnesium chloride (3.1 mL, 6.1 mmol, 2M in THF) was added and the reaction stirred for 1 hour. The reaction was quenched 10 % HCl and extracted with ether. The organics were dried over $MgSO_4$, and concentrated *in vacuo*. The crude alcohol in 5 mL dioxane was then added to potassium hydride (0.45 g, 11.1 mmol) in 50 mL dioxane and heated

overnight at 110 °C. Standard aqueous workup and column chromatography (95:5 hexane/diethyl ether) afforded the 0.55 g product as a clear oil (3.1 mmol, 55 %). Rf = 0.63 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (d, 1H, J = 3.3 Hz), 5.65-5.79 (m, 1H), 4.92-5.01 (m, 2H), 1.86-2.13 (m, 3H), 1.53-1.76 (m, 8H), 1.00-1.28 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.4, 137.7, 115.1, 57.0, 38.3, 31.7, 30.8, 30.1, 26.5, 26.3, 25.1.

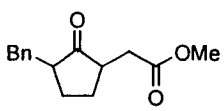


6-Cyclohexyl-7-oxo-hept-2-enoic acid methyl ester (114). A flame dried flask was charged with [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexyl phosphine)ruthenium] (0.049 g, 0.055 mmol) and 5 mL dichloromethane. 87 (0.20 g, 1.1 mmol) and methyl acrylate (1.0 mL, 11.1 mmol) were added and the solution was heated to 40 °C for 72 hours. Silica gel (1 g) was then added and the solvent removed *in vacuo*. Column chromatography (9:1 hexane/ethyl acetate) yielded 0.225 g product (0.95 mmol, 85 %). Rf = 0.36 (3:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, 1H, J = 3.3 Hz), 6.84-6.94 (m, 1H), 5.80 (d, 1H, J = 15.4 Hz), 3.70 (s, 1H), 2.03-2.60 (m, 3H), 1.54-1.84 (m, 8H), 1.02-1.30 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.7, 166.7, 148.1, 121.4, 56.9, 51.4, 38.3, 30.8, 30.2, 30.1, 26.4, 26.3, 24.1; IR (NaCl, neat) 1724, 1658, 1448; HRMS (FAB+) calcd for $C_{14}H_{23}O_3$, 239.1647. Found 239.1646.



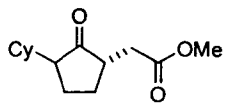
6-Benzyloxy-7-oxo-hept-2-enoic acid methyl ester (118). To [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexyl phosphine)ruthenium] (0.020 g, 0.053 mmol) in 10 ml methylene chloride was added methyl acrylate (0.420 g, 4.9 mmol) and 2-benzyloxy-hex-5-enal[5] (0.100 g, .49 mmol).

The solution was heated to 40 °C and stirred for 72 hours. Silica gel (1 g) was then added and the mixture rotovaped. Column chromatography (9:1 Hexane/EtOAc) yielded 0.065 g product (0.25 mmol, 51 % yield). Rf = 0.15 (3:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.39-7.31 (m, 5H), 6.94-6.86 (m, 1H), 5.80 (d, 1H, *J* = 15.7 Hz), 4.61 (dd, 2H, *J* = 61.6, 11.5, 11.5 Hz), 3.77 (t, 1H, *J* = 6.4, 6.4 Hz), 3.72 (s, 3H), 2.37-2.30 (m, 2H), 1.83 (q, 2H, *J* = 7.5, 6.6, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 166.7, 147.5, 136.9, 128.6, 128.2, 128.1, 121.9, 82.3, 72.7, 51.4, 28.4, 27.4; IR (NaCl, neat) 1725, 1658, 1436, 1275, 1207 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O_4$, 263.1283. Found 263.1282.

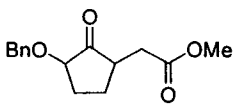


(3-Benzyl-2-oxo-cyclopentyl)-acetic acid methyl ester (115). According to the general procedure, 86 (0.010 g, 0.043 mmol), catalyst 33 (0.008 g, 0.022 mmol), and KHMDS (0.043 mL, 0.022 mmol, 0.5 M in THF), produced the product as a 95:5 mixture of inseparable diastereomers. Purification by column chromatography (95:5 hexane/diethyl ether) afforded 22 (9.5 mg, 95 %). Rf = 0.40 (3:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.28 (m, 10H), 3.66 (s, 3H), 3.65 (s, 3H), 3.15 (dd, 1H, *J* = 13.8, 4.0 Hz, trans), 3.04 (q, 1H, *J* = 9.2, Hz, cis), 2.42-2.76 (m, 8H), 2.27-2.35 (m, 2H), 2.03-2.18 (m, 3H), 1.90-1.96 (m, 1H), 1.69-1.77 (m, 1H), 1.40-1.55 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 219.5, 219.2, 172.5, 172.5, 139.7, 129.0, 128.9, 128.4, 126.3, 126.2, 51.8, 51.8, 50.7, 49.0, 46.0, 45.0, 36.0, 35.9, 34.1, 34.0, 27.2, 26.5, 25.6; IR (NaCl, neat) 1735, 1437, 1261, 1196, 1175 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}O_3$, 247.1334. Found 247.1332. HPLC analysis (AS, 99:1 Hex/*i*PrOH, 0.2 mL/min; trans (tr (minor) = 130.8 min, tr (major) = 82.2 min.), cis (tr

(minor) = 104.4 min, tr (major) = 111.7 min.)) gave the enantiomeric composition of the trans product: < 5 % ee, and the cis product: < 5 % ee.



(3-Cyclohexyl-2-oxo-cyclopentyl)-acetic acid methyl ester (90). According to the general procedure, 88 (0.020 g, 0.084 mmol), catalyst 68 (0.005 g, 0.017 mmol), and KHMDS (0.034 mL, 0.017 mmol, 0.5 M in THF), provided the known compound **90** (14.6mg, 73%) as a 3.5*cis*:96.5*trans* mixture of inseparable diastereomers.[6] GC analysis (BDM, 150°C, 3.0 mL/min; trans (tr (minor) = 53.8 min, tr (major) = 51.5 min.), cis (tr (minor) = 49.7 min, tr (major) = 47.8 min.)) gave the enantiomeric composition of the trans product: 20 % ee, and the cis product: 6 % ee.



(3-Benzyloxy-2-oxo-cyclopentyl)-acetic acid methyl ester (93). According to the general procedure, 92 (0.010 g, 0.038 mmol), catalyst 33 (0.007 g, 0.019 mmol), and KHMDS (0.038 mL, 0.019 mmol, 0.5 M in THF), produced the product as a 51:49 mixture of inseparable diastereomers. Purification by column chromatography (95:5 hexane/diethyl ether) afforded 93 (9.5 mg, 95 %). Rf = 0.43 (3:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.40 (m, 10H), 4.80 (dd, 2H, J = 11.9, 11.9, 43.6 Hz, Major), 4.72 (dd, 2H J = 12.1, 11.9, 38.5 Hz, Minor), 3.87-3.99 (m, 2H), 3.69 (s, 3H, Minor), 3.66 (s, 3H, Major), 2.73-2.82 (m, 1H), 2.56-2.68 (m, 3H), 2.42-2.51 (m, 1H), 2.30-2.40 (m, 2H), 2.13-2.26 (m, 2H), 1.92-2.11 (m, 1H), 1.68-1.84 (m, 2H), 1.43-1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 215.3, 172.4, 172.1, 137.7, 137.6, 128.4, 128.0, 127.8, 80.1, 78.3, 72.3, 71.7, 51.9, 51.8, 43.3, 42.5, 34.8, 34.0, 28.0, 27.8, 25.1, 23.3; IR (NaCl, neat) 1734, 1453, 1436, 1197 cm^{-1}; HRMS (FAB+)

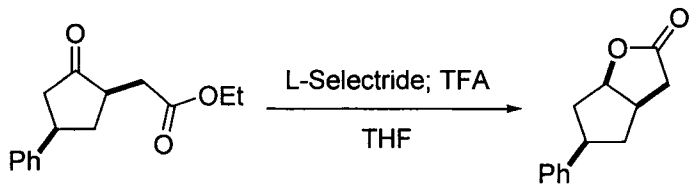
calcd for $C_{15}H_{19}O_4$, 263.1285. Found 263.1284. HPLC analysis (OD-H, 99:1 Hex/*i*PrOH, 0.2 ml/min; trans (tr (minor) = 127.8 min, tr (major) = 181.5 min.), cis (tr (minor) = 157.8 min, tr (major) = 148.5 min.)) gave the enantiomeric composition of the trans product: 54 % ee, and the cis product: 14 % ee.

Determination of Relative Stereochemistry.

2,3-Disubstituted Cyclopentanones

The configuration of **66** was determined by comparison of the H^1 NMR spectra with literature values.[1]

2,4-Disubstituted Cyclopentanones.



82
70:30 dr

E1
70:30 dr

To a solution of 82 (0.068g, 0.28mmol) in 2 mL tetrahydrofuran at –78°C was added L-selectride (1.0 M in THF, 0.33mL, 0.33mmol) after 2.5 hours 0.5mL trifluoroacetic acid was added and the solution allowed to warm to room temperature followed by stirring overnight. Standard aqueous work up and column chromatography afforded a 65% yield of E1 (0.036g, 0.18mmol). The configuration of **E1** was determined by comparison of the H^1 NMR spectra with literature values.[7]

2,5-Disubstituted Cyclopentanones.

The configuration of **90** was determined by comparison of the H^1 NMR spectra with literature values.[8]

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Chapter 3 Experimental

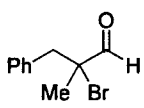
Catalysis of the Wallach Rearrangement by Triazolium Carbenes

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

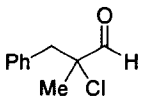
Cyclohexanol was used as purchased from Mallinckrodt. All other alcohols were purchased from Aldrich Chemical Co. and used without further purification. **40** and **48** were prepared according to literature procedures.[1] α–Halo-aldehydes were prepared by literature procedures.[2] Previously synthesized α–halo-aldehydes: **35**[3], **42**[4], **46**[5], **89**[6], **90**[7], **91**[8], matched reported spectra and new aldehydes are characterized below. Thiazolium salt **39** was purchased from TCI and used as received. Imidazolium salt **23** was prepared according to literature procedure.[9] Triazolium salts were prepared according to literature procedure or were generously donated by Mark Kerr.[10]

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ,ppm) from an internal standard [tetramethylsilane (TMS)] or deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet),

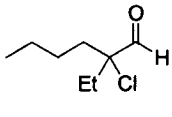
integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 300, 400, or 500 MHz spectrometer at 75, 100, of 125 MHz at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Gas chromatography was performed on a Varian CP 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM capillary column.



2-Bromo-2-methyl-3-phenyl-propionaldehyde (44). Rf = 0.52 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.20-7.31 (m, 5H), 3.35 (q, 2H, J = 14 Hz), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 134.9, 130.5, 128.4, 127.5, 68.1, 44.9, 23.6; IR (NaCl, neat) 1726, 1495, 1454, 1058 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{11}BrO$, 225.9993. Found 225.9987.

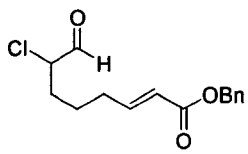


2-Chloro-2-methyl-3-phenyl-propionaldehyde (47). Rf = 0.63 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.2-7.32 (m, 5H), 3.20 (q, 2H, J = 14.4, 14.4 Hz), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 134.2, 130.7, 128.3, 127.4, 72.7, 44.5, 23.5; IR (NaCl, neat) 1733, 1496, 1454, 1083 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{11}ClO$, 182.0498. Found 182.0498.

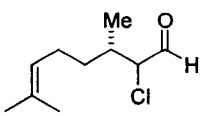


2-Chloro-2-ethyl-hexanal (96). ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 1.84-2.01 (m, 5H), 1.31-1.37 (m, 4H), 0.98 (t, 3H, J = 7.4 Hz), 0.91

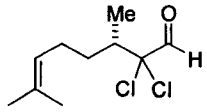
(t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 78.7, 36.2, 29.7, 26.2, 22.8, 13.8, 8.5; IR (NaCl, neat) 1735, 1461, 1382, 1119; HRMS (EI+) calcd for $C_8H_{15}ClO$, 162.0811. Found 162.0810.



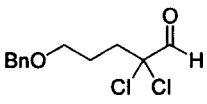
7-Chloro-8-oxo-oct-2-enoic acid benzyl ester (87). Rf = 0.27 (3:1 hexane:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, 1H, J = 2.1 Hz), 7.30-7.38 (m, 5H), 6.98 (ddd, 1H, J = 6.9, 6.9, 15.6 Hz), 5.90 (ddd, 1H, J = 1.6, 1.6, 15.7 Hz), 5.18 (s, 2H), 4.17 (ddd, 1H, J = 2.1, 5.2, 8.4 Hz), 2.23-2.31 (m, 2H), 1.96-2.06 (m, 1H), 1.60-1.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 166.2, 148.1, 136.0, 128.5, 128.2, 121.9, 66.2, 63.5, 31.4, 31.3, 24.0; IR (NaCl, neat) 1720, 1655, 1266, 1183, 1151 cm^{-1}; HRMS (EI+) calcd for $C_{15}H_{17}ClO_3$, 280.0866. Found 280.0869.



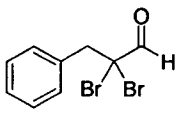
2-Chloro-3,7-dimethyl-oct-6-enal (88). Characterized as a mixture of diastereomers. Rf = 0.69 (3:1 hexane:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (d, 1H, J = 2.3 Hz), 9.50 (d, 1H, J = 2.9 Hz), 5.03-5.11 (m, 2H), 4.20 (dd, 1H, J = 2.2, 4.2 Hz), 4.07 (dd, 1H, J = 2.9, 5.4 Hz), 2.14-2.31 (m, 2H), 1.88-2.09 (m, 4H), 1.68 (s, 6H), 1.60 (s, 6H), 1.47-1.57 (m, 2H), 1.30-1.43 (m, 2H), 1.07 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 196.1, 132.5, 132.4, 123.4, 123.2, 69.7, 69.4, 35.6, 34.9, 33.6, 32.1, 25.7, 25.2, 25.1, 17.7, 14.7; IR (NaCl, neat) 1732, 1455, 1382 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{18}ClO$, 189.1046. Found 189.1054.



2,2-Dichloro-3,7-dimethyl-oct-6-enal (92). Rf = 0.40 (3:1 hexane:ethyl acetate); $[\alpha]_D^{24}$ = -22.5 (c = 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 5.04-5.10 (m, 1H), 2.32-2.38 (m, 1H), 2.08-2.19 (m, 1H), 1.93-2.06 (m, 1H), 1.66-1.76 (m, 4H), 1.61 (s, 3H), 1.28-1.40 (m, 1H), 1.16 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6, 132.8, 123.1, 94.5, 41.7, 31.8, 25.7, 25.3, 17.7, 14.5; IR (NaCl, neat) 1747, 1453, 1382 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}Cl_2O$, 223.0656. Found 223.0668.



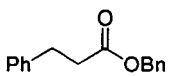
5-Benzyloxy-2,2-dichloro-pentanal (93). Rf = 0.40 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.25-7.36 (m, 5H), 4.51 (s, 2H), 3.56 (t, 2H, J = 6.0 Hz), 2.40-2.44 (m, 2H), 1.93-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.67, 138.1, 128.4, 127.8, 127.6, 88.6, 72.8, 68.8, 37.6, 24.9; IR (NaCl, neat) 1745, 1454, 1361, 1100, 1027 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{15}Cl_2O_2$, 261.0454. Found 261.0449.



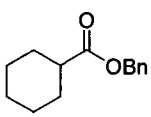
2,2-Dibromo-3-phenyl-propionaldehyde (94). Rf = 0.53 (3:1 hexane:ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.34-7.39 (m, 5H), 3.79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 184.0, 134.3, 131.4, 128.3, 128.2, 127.9, 70.2, 47.1; IR (NaCl, neat) 1729, 1496, 1454, 1422, 1111 cm^{-1}; HRMS (EI+) calcd for $C_9H_8Br_2O$, 289.8942. Found 289.8940.

General procedure for the first generation reaction of α–halo-aldehydes: A flame-dried round bottom was charged with azolium salt (0.2 eq). Toluene (0.15M), triethylamine (1.0 eq), and alcohol (1.0 eq) were added via syringe and the solution was stirred at ambient temperature for 10 minutes. α–Halo-aldehyde was then added via syringe and the reaction was stirred at room temperature for the time indicated. The reaction mixture was then subjected directly to column chromatography eluting with 99:1 hexane/Et_2O affording the pure product.

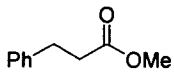
Acetic acid benzyl ester (41). According to the general procedure, 15.0mg (0.068mmol) of **38**, 47μL (0.34mml) of triethylamine, 35μL (0.34mmol) of benzyl alcohol, and 0.246mL (0.34mmol) of a 1.38M solution of **41** afforded 0.031g (60%) of the known ester **41**.[11]



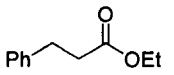
3-Phenyl-propionic acid benzyl ester (26). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 33μL (0.328mmol) of benzyl alcohol, and 0.070g (0.328mmol) of **35** afforded 0.063g (80%) of the known ester **26**.[12]



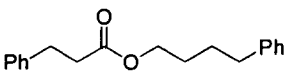
Cyclohexanecarboxylic acid benzyl ester (43). According to the general procedure, 15.0mg (0.068mmol) of **38**, 47μL (0.34mmol) of triethylamine, 35μL (0.34mmol) of benzyl alcohol, and 0.065g (0.34mmol) of **42** afforded 0.074g (quant.) of the known ester **43**.[13]



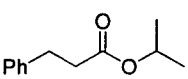
3-Phenyl-propionic acid methyl ester (52). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 13μL (0.328mmol) of methanol, and 0.070g (0.328mmol) of **35** afforded 0.045g (78%) of the known ester **52**.[14]



3-Phenyl-propionic acid ethyl ester (29). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 19μL (0.328mmol) of ethanol, and 0.070g (0.328mmol) of **35** afforded 0.045g (77%) of the known ester **29**.[15]

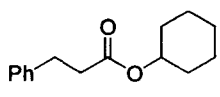


3-Phenyl-propionic acid 4-phenyl-butyl ester (55). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 50μL (0.328mmol) of 4-phenylbutanol, and 0.070g (0.328mmol) of **35** afforded 0.068g (73%) of **55** as a colorless oil. Rf = 0.40 (9:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.36 (m, 10H), 4.12-4.16 (m, 2H), 3.00 (t, 2H, J = 7.7, 8.1 Hz), 2.67 (t, 4H, J = 8.1, 7.3 Hz), 1.67-1.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 141.9, 140.4, 128.4, 128.3, 128.2, 128.1, 126.1, 125.7, 65.8, 64.3, 36.0, 35.5, 31.0, 28.3, 27.7; IR (NaCl, neat) 1733, 1496, 1454, 1162cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{22}O_2$, 283.1698. Found 283.1699.

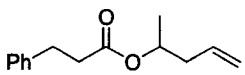


3-Phenyl-propionic acid isopropyl ester (57). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of

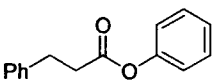
triethylamine, 25μL (0.328mmol) of isopropanol, and 0.070g (0.328mmol) of **35** afforded 0.042g (66%) of the known ester **57**.[16]



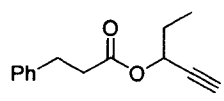
3-Phenyl-propionic acid cyclohexyl ester (59). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 34μL (0.328mmol) of cyclohexanol, and 0.070g (0.328mmol) of **35** afforded 0.050g (66%) of the known ester **59**.[17]



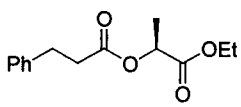
3-Phenyl-propionic acid 1-methyl-but-3-enyl ester (61). According to the general procedure, 14.5mg (0.066mmol) of **21**, 46μL (0.328mmol) of triethylamine, 34μL (0.328mmol) of 1-methyl-3-butenol, and 0.070g (0.328mmol) of **18** afforded 0.047g (65%) of **43** as a colorless oil. Rf = 0.43 (9:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.30 (m, 5H), 5.65-5.75 (m, 1H), 5.03-5.08 (m, 2H), 4.93-5.00 (m, 1H), 2.94 (t, 2H, J = 7.7 Hz), 2.60 (t, 2H, J = 7.9 Hz), 2.24-2.32 (m, 2H), 1.19 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 133.7, 128.4, 128.3, 126.2, 117.7, 70.1, 40.2, 36.1, 31.0, 19.4; IR (NaCl, neat), 1732, 1454, 1375, 1180 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O_2$, 219.1385. Found 219.1391.



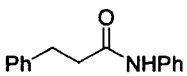
3-Phenyl-propionic acid phenyl ester (63). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 29μL (0.328mmol) of phenol, and 0.070g (0.328mmol) of **35** afforded 0.041g (55%) of the known ester **63**.[18]



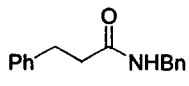
3-Phenyl-propionic acid 1-ethyl-prop-2-ynyl ester (65). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 28μL (0.328mmol) of 1-ethyl-2-propynol, and 0.070g (0.328mmol) of **35** afforded 0.050g (70%) of **65** as a colorless oil. Rf = 0.45 (9:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.33 (m, 5H), 5.36 (td, 1H, J = 6.4, 6.5, 2.2, 2.2, 2.0 Hz), 3.01 (t, 2H, J = 7.7, 7.9 Hz), 2.68-2.74 (m, 2H), 2.48 (d, 1H, J = 2.2 Hz), 1.76-1.86 (m, 2H), 1.02 (t, 3H, J = 7.3, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 140.3, 128.5, 128.3, 126.3, 81.0, 73.5, 64.9, 35.8, 30.8, 27.8, 9.2; IR (NaCl, neat), 1739, 1455, 1159 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_2$, 217.1229. Found 217.1230.



3-Phenyl-propionic acid 1-ethoxycarbonyl-ethyl ester (67). According to the general procedure, 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 38μL (0.328mmol) of (*S*)-ethyl lactate, and 0.070g (0.328mmol) of **35** afforded 0.046g (56%) of the known ester **67**.[19] GC analysis (Chiraldex BDM, 130°C, 3 mL/min, tr(minor) = 93.2 min., tr(major) = 97.0 min.) gave the isomeric composition of the product: 94% ee.

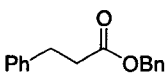


3-*N*-Diphenyl-propionamide (68). According to the general procedure with the exception of a more dilute solution (0.2M), 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 120μL (1.3mmol) of aniline, and 0.070g (0.328mmol) of **35** afforded 0.046g (62%) of the known amide **68**.[20]

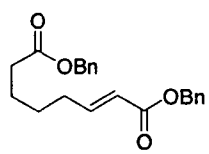


***N*-benzyl-3-phenyl-propionamide (108).** According to the general procedure with the exception of a more dilute solution (0.2M), 14.5mg (0.066mmol) of **38**, 46μL (0.328mmol) of triethylamine, 144μL (1.3mmol) of benzyl amine, and 0.070g (0.328mmol) of **35** afforded 0.045g (57%) of the known amide **108**.[21]

General procedure for the second generation reaction of α–halo-aldehydes: A flame-dried round bottom was charged with azolium salt (0.1 eq). Toluene (0.13M), triethylamine (1.0 eq), and alcohol (1.0 eq) were added via syringe and the solution was stirred at ambient temperature for 10 minutes. α–Halo-aldehyde was then added via syringe and the reaction was stirred at room temperature for the time indicated. The reaction mixture was then subjected directly to column chromatography eluting with 99:1 hexane/Et_2O affording the pure product.

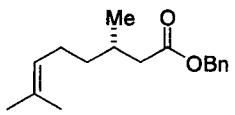


3-Phenyl-propionic acid benzyl ester (26). According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.042g (0.25mmol) of **46** afforded 0.054g (90%) of the known ester **26**.

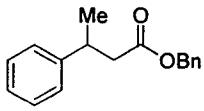


Oct-2-enedioic acid dibenzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.070g (0.25mmol) of **87** afforded 0.067g (91%) of the deired ester as a colorless oil. Rf = 0.42 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.39 (m, 10H),

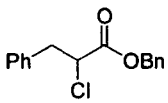
6.99 (ddd, 1H, J = 6.9, 6.9, 15.6 Hz), 5.68 (ddd, 1H, J = 1.6, 1.6, 15.6 Hz), 5.18 (s, 2H), 5.12 (s, 2H), 2.38 (t, 2H, J = 7.3 Hz), 2.22 (ddd, 2H, J = 1.5, 7.1, 14.8 Hz), 1.63-1.71 (m, 2H), 1.45-1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 166.3, 149.2, 136.1, 136.0, 128.5, 128.2, 121.3, 66.2, 66.0, 33.9, 31.8, 27.4, 24.4; IR (NaCl, neat) 1721, 1654, 1264, 1168; HRMS (FAB+) calcd for $C_{22}H_{25}O_4$, 353.1753. Found 353.1741.



3,7-Dimethyl-oct-6-enoic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.047g (0.25mmol) of **88** afforded 0.053g (81%) of the known ester.[22]

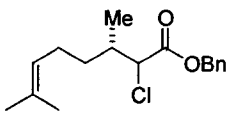


3-Phenyl-butyric acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.046g (0.25mmol) of **89** afforded 0.058g (90%) of the known ester.[23]

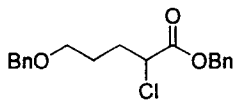


2-Chloro-3-phenyl-propionic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.051g (0.25mmol) of **91** afforded 0.056g (82%) of the desired ester as a colorless oil. Rf = 0.63 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.37 (m, 3H), 7.24-7.30 (m, 5H), 7.17-7.20 (m, 2H), 5.16 (s, 2H), 4.50 (t, 1H, J = 7.5 Hz), 3.37 (dd, 1H, J = 7.5, 14.0 Hz), 3.19 (dd, 1H, J = 7.5, 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 135.7, 134.9, 129.3, 128.6,

128.5, 128.3, 127.3, 67.6, 57.3, 41.1; IR (NaCl, neat) 1747, 1497, 1455, 1268, 1162 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClO_2$, 275.0839. Found 275.0833.

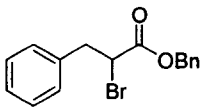


2-Chloro-3,7-dimethyl-oct-6-enoic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.056g (0.25mmol) of **92** afforded 0.071g (97%) of the desired ester as a 1:1 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 10H), 5.24 (s, 4H), 5.00-5.09 (m, 2H), 4.36 (d, 1H, J = 5.1 Hz), 4.24 (d, 1H, J = 6.4 Hz), 2.13-2.23 (m, 2H), 1.88-2.04 (m, 4H), 1.68 (s, 6H), 1.59 (s, 6H), 1.40-1.52 (m, 1H), 1.24-1.36 (m, 3H), 1.00 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.2, 135.1, 132.2, 132.0, 128.6, 128.5, 128.4, 128.3, 123.6, 123.4, 67.5, 67.5, 63.3, 63.2, 37.0, 36.6, 33.6, 32.1, 25.7, 25.2, 24.9, 17.6, 16.3, 14.8; IR (NaCl, neat) 1752, 1456, 1380, 1266, 1160 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{24}ClO_2$, 295.1465. Found 295.1462.

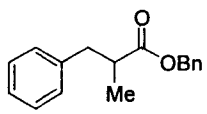


5-Benzyloxy-2-chloro-pentanoic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.065g (0.25mmol) of **93** afforded 0.075g (90%) of the desired ester as a colorless oil. Rf = 0.74 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.36 (m, 5H), 5.20 (s, 2H), 4.48 (s, 2H), 4.37 (dd, 1H, J = 6.4, 6.4 Hz), 3.49 (t, 2H, J = 6.0 Hz), 2.13-2.24 (m, 1H), 1.98-2.10 (m, 1H), 1.66-1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.3, 135.1, 128.6, 128.5, 128.4, 128.2, 127.6, 72.9, 69.0, 67.6, 57.2, 31.9, 26.2; IR (NaCl,

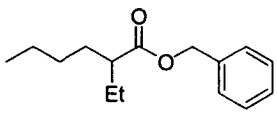
neat) 1746, 1454, 1269, 1165, 1102 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{21}ClO_3$, 332.1179. Found 332.1187.



2-Bromo-3-phenyl-propionic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.072g (0.25mmol) of **94** afforded 0.069g (97%) of ethe desired ester as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.41 (m, 3H), 7.27-7.31 (m, 5H), 7.18-7.20 (m, 2H), 5.16 (s, 2H), 4.47 (dd, 1H, J = 6.9, 8.6 Hz), 3.49 (dd, 1H, J = 8.6, 14.1 Hz), 3.27 (dd, 1H, J = 6.9, 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 136.6, 135.0, 129.2, 128.6, 128.6, 128.4, 128.2, 127.3, 67.6, 45.2, 41.1; IR (NaCl, neat) 1741, 1218, 1144 cm^{-1};

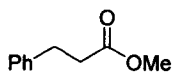


2-Methyl-3-phenyl-propionic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.046g (0.25mmol) of **95** afforded 0.050g (79%) of the known ester.[24]

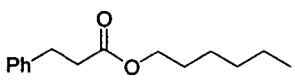


2-Ethyl-hexanoic acid benzyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of benzyl alcohol, and 0.041g (0.25mmol) of **96** afforded 0.046g (79%) of the desired ester as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.37 (m, 5H), 5.13 (s, 2H), 2.33 (dddd, 1H, J = 5.4, 5.4, 8.8, 8.8 Hz), 1.59-1.70 (m, 2H), 1.43-1.58 (m, 2H), 1.18-1.32 (m, 4H), 0.87 (m, 6H); ^{13}C

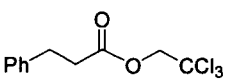
NMR (100 MHz, $CDCl_3$) δ 176.3, 136.3, 128.5, 128.1, 128.0, 65.8, 47.3, 31.8, 29.6, 25.5, 22.6, 13.9, 11.8; IR (NaCl, neat) 1734, 1457, 1213, 1167, 1141 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{23}O_2$, 235.1698. Found 235.1687.



3-Phenyl-propionic acid methyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 10μL (0.25mmol) of methanol, and 0.042g (0.25mmol) of **46** afforded 0.033g (80%) of the known ester.[14]

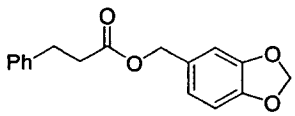


3-Phenyl-propionic acid hexyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 31μL (0.25mmol) of hexyl alcohol, and 0.042g (0.25mmol) of **46** afforded 0.051g (87%) of the desired ester as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.31 (m, 2H), 7.19-7.22 (m, 3H), 4.07 (t, 2H, J = 6.8 Hz), 2.96 (t, 2H, J = 7.7 Hz), 2.64 (t, 2H, J = 8.1 Hz), 1.56-1.62 (m, 2H), 1.27-1.35 (m, 6H), 0.90 (t, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 140.5, 128.4, 128.2, 126.2, 64.6, 35.9, 31.4, 31.0, 28.5, 25.5, 22.5, 14.0; IR (NaCl, neat) 1735, 1497, 1454, 1291, 1240, 1162 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{23}O_2$, 235.1698. Found 235.1698.

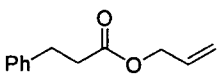


3-Phenyl-propionic acid 2,2,2-trichloro-ethyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 24μL (0.25mmol) of trichloroethanol, and 0.042g (0.25mmol) of **46** afforded 0.052g (74%) of the desired ester as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$)

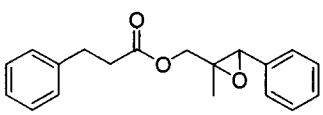
δ 7.21-7.33 (m, 5H), 4.75 (s, 2H), 3.03 (t, 2H, J = 7.6 Hz), 2.81 (t, 2H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.8, 128.5, 128.3, 126.4, 94.9, 73.9, 35.4, 30.6; IR (NaCl, neat) 1756, 1496, 1454, 1379, 1138 cm^{-1}; HRMS (EI+) calcd for $C_{11}H_{11}Cl_3O_2$, 279.9825. Found 279.9816.



3-Phenyl-propionic acid benzo[1,3]dioxol-5-ylmethyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 38mg (0.25mmol) of benzo[1,3]dioxol-5-yl-methanol, and 0.042g (0.25mmol) of **46** afforded 0.057g (80%) of the desired ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.31 (m, 5H), 6.77-6.82 (m, 3H), 5.97 (s, 2H), 5.01 (s, 2H), 2.97 (t, 2H, J = 7.6 Hz), 2.67 (t, 2H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 147.7, 147.5, 140.3, 129.6, 128.5, 128.4, 128.2, 126.2, 122.2, 109.0, 108.2, 101.1, 66.2, 35.9, 30.9; IR (NaCl, neat) 1733, 1503, 1492, 1446, 1252; HRMS (EI+) calcd for $C_{17}H_{16}O_4$, 284.1049. Found 284.1055.

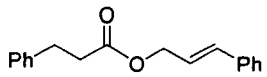


3-Phenyl-propionic acid allyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 17μL (0.25mmol) of allyl alcohol, and 0.042g (0.25mmol) of **46** afforded 0.032g (69%) of the known ester.[25]

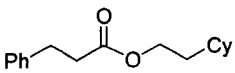


3-Phenyl-propionic acid 3-phenyl-oxiranylmethyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 38mg (0.25mmol) of (3-Phenyl-

oxiranyl)-methanol, and 0.042g (0.25mmol) of **46** afforded 0.057g (81%) of the desired ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.40 (m, 10H), 4.36 (d, 1H, *J* = 11.9 Hz), 4.12 (d, 1H, *J* = 11.9 Hz), 4.01 (s, 1H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 140.2, 135.0, 128.5, 128.3, 128.1, 127.7, 126.4, 126.3, 67.9, 61.6, 61.0, 35.7, 30.9, 13.6; IR (NaCl, neat) 1739, 1497, 1454, 1159; HRMS (FAB+) calcd for $C_{19}H_{21}O_3$, 297.1491. Found 297.1491.

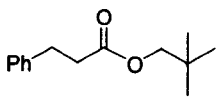


3-Phenyl-propionic acid 3-phenyl-allyl ester. According to the 2nd generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 32μL (0.25mmol) of cinnamyl alcohol, and 0.042g (0.25mmol) of **46** afforded 0.059g (89%) of the desired ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.44 (m, 10H), 6.64 (d, 1H, *J* = 15.9 Hz), 6.27 (ddd, 1H, *J* = 6.4, 6.4, 15.9 Hz), 4.76 (dd, 2H, *J* = 1.2, 6.5 Hz), 3.01 (t, 2H, *J* = 7.6 Hz), 2.70 (t, 2H, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.4, 136.1, 134.1, 128.5, 128.5, 128.3, 128.0, 126.6, 126.2, 123.1, 65.0, 35.9, 30.9; IR (NaCl, neat) 1733, 1496, 1454, 1160; HRMS (EI+) calcd for $C_{18}H_{18}O_2$, 266.1307. Found 266.1314.

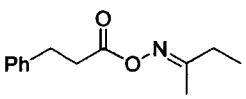


3-Phenyl-propionic acid 2-cyclohexyl-ethyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 35μL (0.25mmol) of 2-cyclohexylethanol, and 0.042g (0.25mmol) of **46** afforded 0.059g (89%) of the desired ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.31 (m, 2H), 7.19-7.22 (m, 3H), 4.11 (t, 2H, *J* = 6.8 Hz), 2.96 (t, 2H, *J* = 7.5 Hz), 2.63 (t, 2H, *J* = 8.3 Hz), 1.64-1.71 (m, 5H), 1.49 (dd, 2H, *J* = 6.8, 13.6 Hz), 1.13-1.36 (m,

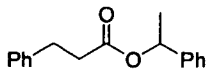
4H), 0.87-0.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 140.6, 128.4, 128.3, 126.2, 62.7, 35.9, 34.5, 33.1, 31.0, 26.4, 26.2; IR (NaCl, neat) 1735, 1449, 1291, 1163 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{25}O_2$, 261.1855. Found 261.1861.



3-Phenyl-propionic acid 2,2-dimethyl-propyl ester. According to the second generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 22mg (0.25mmol) of pivalcohol, and 0.042g (0.25mmol) of **46** afforded 0.034g (61%) of the desired ester as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.32 (m, 5H), 3.78 (d, 2H, J = 0.6 Hz), 2.98 (t, 2H, J = 7.6 Hz), 2.67 (t, 2H, J = 7.9 Hz), 0.92 (d, 9H, J = 0.7 Hz); HRMS (EI+) calcd for $C_{14}H_{20}O_2$, 220.1463. Found 220.1464.



3-Phenyl-propionic acid 2-butanone-oximyl ester. According to the seocond generation general procedure, 9.0mg (0.025mmol) of **75**, 35μL (0.25mmol) of triethylamine, 26μL (0.25mmol) of 2-butanoneoxime, and 0.042g (0.25mmol) of **46** afforded 0.023g (41%) as an 88:12 mixture of oxime isomers. ^1H NMR (400MHz, $CDCl_3$) δ 7.19-7.31 (m, 10H), 3.02 (major, t, 2H, J = 7.6 Hz), 2.97 (minor, t, 2H, J = 7.7 Hz), 2.74 (major, t, 2H, J = 8.2 Hz), 2.69 (minor, t, 2H, J = 8.1 Hz), 2.35 (major, q, 2H, J = 7.5 Hz), 2.34 (minor, q, 2H, J = 7.6 Hz), 2.01 (minor, s, 3H), 1.90 (major, s, 3H), 1.14 (major, t, 3H, J = 7.5 Hz), 1.05 (minor, t, 3H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 168.4, 167.7, 140.3. 128.5, 128.3, 126.3, 35.2, 34.7, 30.9, 30.6, 29.2, 23.8, 19.5, 14.9, 10.8, 10.1; IR (NaCl, neat) 1759, 1454, 1128, 1075; HRMS (FAB+) calcd for $C_{13}H_{18}NO_2$, 220.1338. Found 220.1335.



3-Phenyl-propionic acid 1-phenyl-ethyl ester. According to the 2nd generation general procedure, 9.0mg (0.025mmol) of **65**, 35μL (0.25mmol) of triethylamine, 30μL (0.25mmol) of α-methylbenzyl alcohol, and 0.042g (0.25mmol) of **30** afforded 0.034g (54%) of the known ester **107**.[26]

References

[1] **40**: Kraus, G. A.; Gottschalk, P. *J. Org. Chem.* **1983**, *48*, 2111-2112. **48**: Kinoshita, M.; Takami, H.; Taniguchi, M; Tamai, T. *Bull. Chem. Soc. Japan* **1987**, *60*, 2151-2161.

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Chapter 4 Experimental

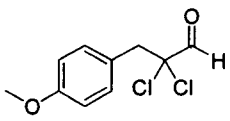
In Situ Generation of Chiral Enolates Asymmetric Protonation in the Wallach Rearrangement

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

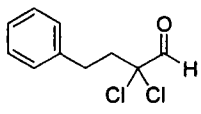
Alcohols were purchased from Aldrich Chemical Co. and used after azeotropic drying with toluene. Aldehydes were obtained from Aldrich Chemical Co. or synthesized from the corresponding alcohol. α,α-Dihaloaldehydes were prepared by the literature procedure.[1] Previously synthesized α,α–dihalo-aldehyde **56**[2] matched reported spectra and new α,α–dihalo-aldehydes are characterized below.

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ,ppm) from an internal standard [tetramethylsilane (TMS)] or deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 300, 400, or 500 MHz spectrometer at 75, 100, of 125 MHz at ambient temperature. Chemical

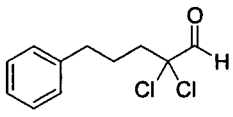
shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Gas chromatography was performed on a Varian CP 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM capillary column.



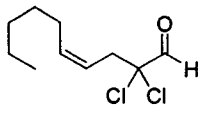
2,2-Dichloro-3-(4-methoxy-phenyl)-propionaldehyde (64). ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.23 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.7 Hz), 3.78 (s, 3H), 3.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 159.3, 132.5, 124.5, 113.6, 113.5, 87.6, 55.2, 45.4; IR (NaCl, neat) 1741, 1611, 1514, 1253, 1180 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{10}Cl_2O$, 232.0058. Found 232.0054.



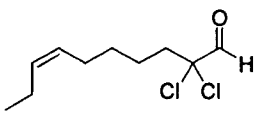
2,2-Dichloro-4-phenyl-butyraldehyde (66) Rf = 0.36 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.28-7.40 (m, 5H), 3.00-3.07 (m, 2H), 2.63-2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 139.4, 128.6, 128.4, 128.4, 126.5, 87.8, 42.3, 30.7; IR (NaCl, neat) 1745, 1497, 1455, 1139, 1017 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}Cl_2O$, 216.0109. Found 216.0098.



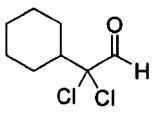
2,2-Dichloro-5-phenyl-pentanal (68). Rf = 0.40 (3:1 hexane:ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.20-7.31 (m, 5H), 2.72 (t, 2H, J = 7.2 Hz), 2.29-2.33 (m, 2H), 1.98-2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 140.9, 128.5, 128.3, 126.2, 88.4, 39.9, 35.0, 26.0; IR (NaCl, neat) 1745, 1496, 1454, 1084 cm^{-1}; HRMS (EI+) calcd for $C_{11}H_{12}Cl_2O$, 230.0265. Found 230.0260.



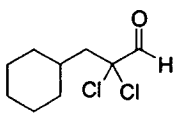
2,2-Dichloro-dec-4-enal (97). Rf = 0.19 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 5.68-5.75 (m, 1H), 5.46-5.52 (m, 1H), 3.06 (dd, 2H, J = 0.8, 7.1 Hz), 2.07 (ddd, 2H, J = 14.9, 7.5, 0.9 Hz), 1.35-1.42 (m, 2H), 1.25-1.33 (m, 4H), 0.89 (t, 3H, J = 6.98 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 136.3, 119.9, 39.0, 31.5, 28.9, 27.7, 22.5, 14.0; IR (NaCl, neat) 1746, 1466, 1422, 1367, 1128 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{16}Cl_2O$, 222.0578. Found 222.0583.



2,2-Dichloro-dec-7-enal (72). Rf = 0.56 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 5.36-5.42 (m, 1H), 5.27-5.33 (m, 1H), 2.25-2.29 (m, 2H), 1.99-2.10 (m, 4H), 1.59-1.67 (m, 2H), 1.40-1.47 (m, 2H), 0.95 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 132.3, 128.1, 88.6, 40.4, 29.0, 26.6, 24.0, 20.5, 14.3; IR (NaCl, neat) 2962, 2934, 1746, 1462 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{16}Cl_2O$, 222.0578. Found 222.0579.

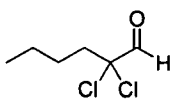


Dichloro-cyclohexyl-acetaldehyde (78). Rf = 0.76 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, 1H, J = 0.6 Hz), 2.11-2.17 (m, 1H), 1.79-1.89 (m, 4H), 1.65-1.68 (m, 1H), 1.09-1.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 93.6, 46.7, 27.5, 25.7, 25.5; IR (NaCl, neat) 1748, 1452, 1123 cm^{-1}; HRMS (EI+) calcd for $C_8H_{12}Cl_2O$, 194.0265. Found 194.0260.

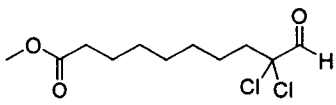


2,2-Dichloro-3-cyclohexyl-propionaldehyde (70). Rf = 0.66 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 2.24 (d,

2H, J = 5.3 Hz), 1.61-1.81 (m, 6H), 0.99-1.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 88.5, 47.4, 34.8, 34.0, 26.2, 26.0, 25.9; IR (NaCl, neat) 1746, 1448 cm^{-1}; HRMS (EI+) calcd for $C_9H_{14}Cl_2O$, 208.0422. Found 208.0418.



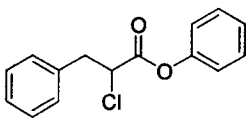
2,2-Dichloro-hexanal (99). Rf = 0.66 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 2.24-2.29 (m, 2H), 1.55-1.65 (m, 2H), 1.34-1.47 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 88.7, 40.3, 26.5, 22.2, 13.8



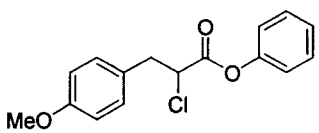
9,9-Dichloro-10-oxo-decanoic acid methyl ester (74). Rf = 0.44 (3:1 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 3.66 (s, 3H), 2.24-2.32 (m, 4H), 1.56-1.68 (m, 4H), 1.29-1.42 (m, 6H); ^{13}C NMR (100 MHz) δ 184.9, 174.2, 88.6, 51.5, 40.4, 34.0, 28.9, 28.8, 24.8, 24.3; IR (NaCl, neat) 1741, 1436, 1198, 1170 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}Cl_2O_3$, 269.0711. Found 269.0705.

General procedure A: Synthesis of phenyl α–halo-esters: A flame-dried round bottom was charged with potassium hydride (1.0 equiv) and 18-crown-6 (0.5 equiv). Toluene (0.062 M), 2,6-dibromo-4-methylphenol (1.2 equiv), and phenol (10.0 equiv) were added via syringe and the solution was stirred at ambient temperature for 5 minutes. Triazolium salt (0.10 equiv) was added and the solution stirred for an additional 5 minutes. α-α-dihaloaldehyde was then added via syringe and the reaction was stirred at room temperature for 19 hours. The reaction mixture was then filtered through a pad of silica gel, eluting with diethyl ether. After washing with 1 M NaOH (2x), brine (1x), and

drying over $MgSO_4$, the solution was concentrated onto silica gel. Flash column chromatography (97:3 hexane:ethyl ether) afforded the desired product.

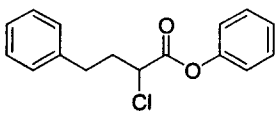


2-Chloro-3-phenyl-propionic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 50.0mg (0.25mmol) of **59** afforded 50.4mg (79%) of the desired ester **61**. Rf = 0.58 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 38.8 (c = 2.4, $CHCl_3$); HPLC analysis – Chiracel OB-H column 97:3 hexanes : isopropanol 0.3 mL / min. Major: 38.0 minutes; Minor: 42.7 minutes gave the isomeric composition of the product: 93% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.39 (m, 8H), 6.97 (d, 2H, *J* = 7.7 Hz), 4.68 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.49 (dd, 1H, *J* = 7.9, 13.9 Hz), 3.33 (dd, 1H, *J* = 7.2, 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 150.2, 135.5, 129.5, 129.4, 128.7, 127.6, 126.3, 121.0, 57.0, 41.1: IR (NaCl, neat), 1766, 1592, 1493, 1456, 1192 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{13}ClO_2$, 261.0682. Found 261.0688.

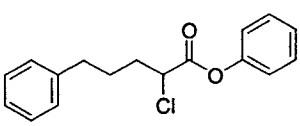


2-Chloro-3-(4-methoxy-phenyl)-propionic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 57.3mg (0.25mmol) of **64** afforded 54.1mg (76%) of the desired ester **65**. Rf = 0.48 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 27.3 (c = 5.5, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99 :1 hexanes : isopropanol 0.3 mL / min. Major: 39.0 minutes, Minor:

35.7 minutes gave the isomeric compostition of the product: 90% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.21-7.27 (m, 3H), 7.00 (d, 2H, *J* = 7.5 Hz), 6.90 (d, 2H, *J* = 8.7 Hz), 4.63 (dd, 1H, *J* = 7.0, 7.9 Hz), 3.82 (s, 3H), 3.44 (dd, 1H, *J* = 7.9, 14.1 Hz), 3.28 (dd, 1H, *J* = 7.0, 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.0, 150.2, 130.5, 129.5, 127.5, 126.3, 121.0, 114.1, 57.2, 55.2, 40.3; IR (NaCl, neat), 1766, 1612, 1514, 1250, 1191 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClO_3$, 291.0788. Found 291.0778.

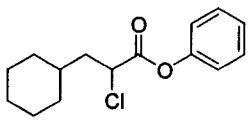


2-Chloro-4-phenyl-butyric acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 54.0mg (0.25mmol) of **66** afforded 49.3mg (73%) of the desired ester **67**. Rf = 0.56 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 6.1 (c = 4.1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 97 : 3 hexanes : isopropanol 1.0 mL / min. Major: 7.7 minutes, Minor: 8.6 minutes gave the isomeric composition of the product: 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.44 (m, 8H), 7.12 (d, 2H, *J* = 7.7 Hz), 4.47 (dd, 1H, *J* = 5.5, 8.4 Hz), 2.83-3.00 (m, 2H), 2.34-2.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 150.2, 139.6, 129.4, 128.6, 128.5, 126.4, 126.2, 121.0, 56.4, 36.3, 32.1; IR (NaCl, neat), 1765, 1592, 1493, 1192, 1163 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClO_2$, 275.0839. Found 275.0826.

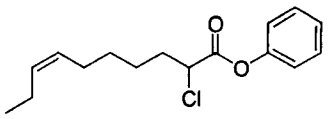


2-Chloro-5-phenyl-pentanoic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg

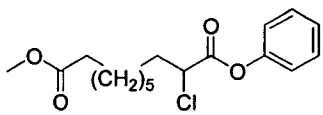
(0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 57.0mg (0.25mmol) of **68** afforded 48.0mg (68%) of the desired ester **69**. Rf = 0.58 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 3.4 (c = 4.8, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 90 : 10 hexanes : isopropanol 1.0 mL / min. Major: 32.2 minutes, Minor: 20.2 minutes gave the isomeric composition of the product: 89% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 2H, *J* = 7.7 Hz), 7.21-7.34 (m, 6H), 7.11 (d, 2H, *J* = 7.9 Hz), 4.51 (dd, 1H, *J* = 6.2, 7.9 Hz), 2.73 (ddd, 2H, *J* = 1.9, 8.5, 8.5 Hz), 2.07-2.29 (m, 2H), 1.81-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 150.3, 141.2, 129.5, 128.5, 128.4, 126.3, 126.1, 121.1, 57.0, 35.0, 34.2, 27.7; IR (NaCl, neat) 1764, 1493, 1192, 1163, 1135 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{18}ClO_2$, 289.0995. Found 289.0986.



2-Chloro-3-cyclohexyl-propionic acid phenyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 108μL (1.2mmol) of phenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 26.0mg (0.12mmol) of **70** afforded 21.3mg (65%) of the desired ester **71**. Rf = 0.64 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 13.6 (c = 1.6, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 10.5 minutes, Minor: 8.4 minutes gave the isomeric composition of the product: 93% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 2H, *J* = 7.7, 7.7 Hz), 7.26 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.12 (d, 2H, *J* = 7.7 Hz), 4.57 (dd, 1H, *J* = 6.4, 8.5 Hz), 1.93-2.06 (m, 2H), 1.67-1.82 (m, 5H), 1.58-1.63 (m, 1H), 1.13-1.34 (m, 3H), 0.87-1.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.65, 150.4, 129.5, 126.3, 121.1, 55.2, 42.1, 34.5, 33.3, 32.2, 26.3, 26.1, 25.9; IR (NaCl, neat) 1767, 1493, 1192, 1163, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{20}ClO$, 267.1152. Found 267.1139.

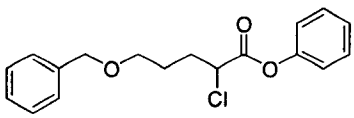


2-Chloro-dec-7-enoic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 55.0mg (0.25mmol) of **72** afforded 49.0mg (71%) of the desired ester **73**. Rf = 0.67 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 8.0 (c = 2.5, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 11.4 minutes, Minor: 8.3 minutes gave the isomeric composition of the product: 88% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.25-7.29 (m, 1H), 7.12 (dd, 2H, *J* = 1.1, 8.7 Hz), 5.37-5.44 (m, 1H), 5.29-5.36 (m, 1H), 4.49 (dd, 1H, *J* = 6.2, 8.2 Hz), 2.14-2.23 (m, 1H), 2.01-2.12 (m, 5H), 1.50-1.63 (m, 2H), 1.41-1.49 (m, 2H), 0.97 (t, 3H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 150.4, 132.2, 129.5, 128.4, 126.3, 121.1, 57.1, 34.7, 28.9, 26.7, 25.6, 20.5, 14.3; IR (NaCl, neat) 1768, 1493, 1458, 1193, 1163 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}ClO_2$, 281.1308. Found 281.1307.

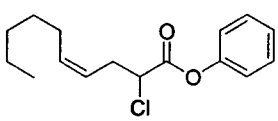


2-Chloro-decanedioic acid 10-methyl ester 1-phenyl ester. According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 66.0mg (0.25mmol) of **74** afforded 60.3mg (75%) of the desired ester **75**. Rf = 0.36 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 5.2 (c = 5.8, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 8.7 minutes, Minor: 8.2 minutes gave the isomeric compostion of the product: 84% ee. ^1H NMR (400 MHz,

$CDCl_3$) δ 7.38 (dd, 2H, J = 7.7, 7.7 Hz), 7.24 (dd, 1H, J = 7.5, 7.5 Hz), 7.10 (d, 2H, J = 7.7 Hz), 4.46 (dd, 1H, J = 6.2, 8.1 Hz), 3.64 (s, 3H), 2.29 (t, 2H, J = 7.5 Hz), 2.09-2.18 (m, 1H), 1.98-2.07 (m, 1H), 1.42-1.64 (m, 4H), 1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 168.3, 150.3, 129.5, 126.3, 121.1, 57.1, 51.5, 34.7, 34.0, 28.9, 28.6, 25.9, 24.8; IR (NaCl, neat) 1766, 1737, 1493, 1193, 1163 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{24}ClO_4$, 327.13630. Found 327.1346.

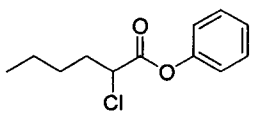


5-Benzyloxy-2-chloro-pentanoic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 64.0mg (0.25mmol) of **76** afforded 55.0mg (71%) of the desired ester **77**. Rf = 0.54 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 6.3 (c = 3.8, $CHCl_3$); HPLC analysis – Chiracel OD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 12.0 minutes, Minor: 13.8 minutes gave the isomeric composition of the product: 84% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, 2H, J = 7.7, 7.7 Hz), 7.33-7.34 (m, 4H), 7.23-7.31 (m, 2H), 7.1 (dd, 2H, J = 8.1, 8.1 Hz), 4.54 (dd, 1H, J = 5.8, 8.1 Hz), 4.51 (s, 2H), 3.55 (t, 2H, J = 6.2 Hz), 2.28-2.36 (m, 1H), 2.11-2.20 (m, 1H), 1.79-1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 150.3, 138.2, 129.5, 128.4, 127.6, 126.3, 121.1, 72.9, 69.0, 57.0, 31.8, 26.2; IR (NaCl, neat) 1765, 1493, 1193, 1163, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{20}ClO_3$, 319.1101. Found 319.1095.



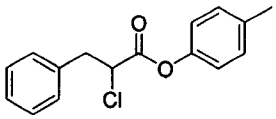
2-Chloro-dec-4-enoic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of

phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 54.9mg (0.25mmol) of **97** afforded 51.0mg (74%) of the desired ester **98**. Rf = 0.70 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = -6.6 (c = 3.9, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 7.7 minutes, Minor: 6.6 minutes gave the isomeric composition of the product: 90% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 2H, *J* = 7.9, 7.9 Hz), 7.26 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.12 (dd, 2H, *J* = 1.1, 8.7 Hz), 5.63-5.69 (m, 1H), 5.42-5.48 (m, 1H), 4.49 (dd, 1H, *J* = 7.0, 7.0 Hz), 2.94 (ddd, 1H, *J* = 14.3, 7.0, 7.6 Hz), 2.83 (ddd, 1H, *J* = 14.4, 7.2, 7.6 Hz), 2.10 (ddd, 2H, *J* = 7.6, 7.2, 7.2 Hz), 1.27-1.42 (m, 6H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 150.4, 135.1, 129.5, 126.3, 122.2, 121.1, 56.3, 32.9, 31.4, 29.1, 27.5, 22.5, 14.0; IR (NaCl, neat) 1768, 1493, 1193, 1163, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}ClO_2$, 281.1308. Found 281.1297.

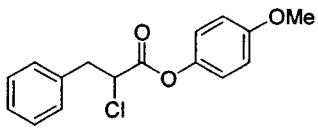


2-Chloro-hexanoic acid phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 216μL (2.5mmol) of phenol, 78.5mg (0.30mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 42.0mg (0.25mmol) of **99** afforded 36.1mg (65%) of the desired ester **100**. Rf = 0.64 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = -11.4 (c = 2.6, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 13.3 minutes, Minor: 9.8 minutes gave the isomeric composition of the product: 89% ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.43 (m, 2H), 7.24-7.29 (m, 1H), 7.11-7.15 (m, 2H), 4.49 (dd, 1H, *J* = 6.3, 7.8 Hz), 2.01-2.24 (m, 2H), 1.36-1.62 (m, 4H), 0.96 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 150.4,

129.5, 126.3, 121.1, 57.2, 34.5, 28.1, 22.0, 13.8; IR (NaCl, neat) 1768, 1493, 1193, 1163, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}ClO_2$, 227.0839. Found 227.0834.

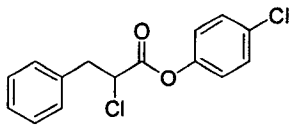


2-Chloro-3-phenyl-propionic acid *p*-tolyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 129μL (1.2mmol) of 4-methylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 24.0mg (71%) of the desired ester. Rf = 0.59 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 28.9 (c = 2.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 24.8 minutes, Minor: 23.3 minutes gave the enantiomeric composition of the product: 89% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.39 (m, 5H), 7.15-7.17 (m, 2H), 6.85-6.88 (m, 2H), 4.67 (dd, 1H, *J* = 7.6, 7.6 Hz), 3.49 (dd, 1H, *J* = 8.0, 14.0 Hz), 3.33 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 148.0, 136.0, 135.6, 130.0, 129.5, 128.7, 127.5, 121.2, 120.7, 57.1, 41.1, 20.8; IR (NaCl, neat) 1763, 1507, 1195, 1166, 1138 cm^{-1}; HRMS (EI+) calcd for $C_{16}H_{15}ClO_2$, 274.0761. Found 274.0760.

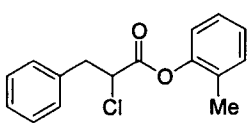


2-Chloro-3-phenyl-propionic acid 4-methoxy-phenyl ester. According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 153mg (1.2mmol) of 4-methoxyphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 25.5mg (71%) of the desired ester Rf = 0.48 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 23.4 (c = 2.8, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 11.6 minutes, Minor: 10.8

minutes gave the isomeric composition of the product: 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.39 (m, 6H), 6.86-6.91 (m, 3H), 4.66 (dd, 1H, J = 8.1, 8.1 Hz), 3.79 (s, 3H), 3.48 (dd, 1H, J = 7.9, 13.8 Hz), 3.32 (dd, 1H, J = 7.2, 13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 157.6, 143.7, 135.6, 129.5, 128.7, 127.5, 121.8, 114.5, 57.0, 55.6, 41.2; IR (NaCl, neat) 1763, 1505, 1248, 1191, 1139 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{15}ClO_3$, 290.0710. Found 290.0718.

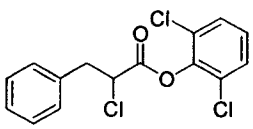


2-Chloro-3-phenyl-propionic acid 4-chloro-phenyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 121μL (1.2mmol) of 4-methylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 23.0mg (63%) of the desired esterRf = 0.85 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 35.1 (c = 1.6, $CHCl_3$); HPLC analysis – Chiracel OD-H column 99 : 1 hexanes : isopropanol 0.3 mL / min. Major: 32.1 minutes, Minor: 34.2 minutes gave the isomeric composition of the product: 83% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.38 (m, 7H), 7.18-7.20 (m, 1H), 6.89-6.92 (m, 2H), 4.67 (ddd, 1H, J = 0.6, 7.2, 7.2 Hz), 3.47 (dd, 1H, J = 8.4, 14.0 Hz), 3.37 (dd, 1H, J = 7.2, 14 Hz), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 148.6, 135.4, 131.8, 129.6, 129.4, 128.8, 127.6, 122.5, 56.8, 41.1; IR (NaCl, neat) 1764, 1486, 1197, 1136, 1090 cm^{-1}; HRMS (EI+) calcd for $C_{15}H_{12}Cl_2O_2$, 294.0214. Found 294.0220.



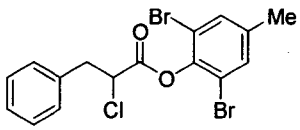
2-Chloro-3-phenyl-propionic acid *o*-tolyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 127μL (1.2mmol) of 2-methylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol,

5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 19.2mg (57%) of the desired ester Rf = 0.61 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 13.5 (c = 2.1, $CHCl_3$); HPLC analysis – Chiracel OB-H column 99 : 1 hexanes : isopropanol 0.3 mL / min. Major: 39.9 minutes, Minor: 42.4 minutes gave the isomeric composition of the product: 90% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 5H), 7.13-7.22 (m, 5H), 6.86 (dd, 1H, *J* = 1.7, 7.5 Hz), 4.7 (dd, 1H, *J* = 7.2, 7.9 Hz), 3.52 (dd, 1H, *J* = 8.1, 14.1 Hz), 3.33 (dd, 1H, *J* = 7.3, 13.9 Hz), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 148.8, 135.6, 131.3, 130.0, 129.5, 128.7, 127.5, 126.9, 126.5, 121.3, 56.8, 41.0, 15.8; IR (NaCl, neat) 1765, 1490, 1222, 1171, 1141, 1109 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}O_2Cl$, 275.0838. Found 275.0830.

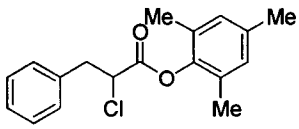


2-Chloro-3-phenyl-propionic acid 2,6-dichloro-phenyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 200mg (1.2mmol) of 2,6-dichlorophenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 26.2mg (65%) of the desired ester. Rf = 0.58 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 1.0 (c = 2.2, $CHCl_3$); HPLC analysis performed on corresponding alcohol provided by LAH reduction – Chiracel ASH 90 : 10 hexanes : isopropanol 0.5 mL / min. Major: 13.0 minutes, Minor: 14.8 minutes gave the isomeric composition of the product: 82% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.40 (m, 7H), 7.14-7.18 (m, 1H), 4.83 (dd, 1H, *J* = 6.8, 8.4 Hz), 3.65 (dd, 1H, *J* = 6.8, 14.4 Hz), 3.35 (dd, 1H, *J* = 8.0, 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 143.2, 135.4, 129.5,

128.7, 128.6, 127.6, 127.4, 56.5, 40.8; IR (NaCl, neat) 1773, 1445, 1227, 1127 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{12}Cl_3O_2$, 328.9903. Found 328.9906.

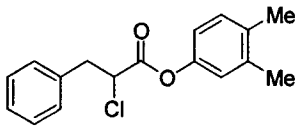


2-Chloro-3-phenyl-propionic acid 2,6-dibromo-4-methyl-phenyl ester: According to general procedure A, 11.5mg (0.025mmol) of ***ent*-63**, 0.65g (2.5mmol) of 2,6-dibromo-4-methylphenol, 9.9mg (0.25mmol) of potassium hydride, 33.0mg (0.13mmol) of 18-crown-6, and 50.0mg (0.25mmol) of **59** afforded 90mg (85%) of the desired ester. Rf = 0.68 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = - 2.8 (c = 3.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 6.2 minutes, Minor: 7.3 minutes gave the isomeric composition of the product: 76% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.33 (m, 7H), 4.76 (dd, 1H, *J* = 7.0 Hz), 3.62 (dd, 1H, *J* = 6.4, 14.1 Hz), 3.29 (dd, 1H, *J* = 8.7, 14.1 Hz), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 143.1, 139.2, 135.6, 132.9, 129.6, 128.7, 127.4, 116.7, 56.8, 40.8, 20.4; IR (NaCl, neat) 1782, 1457, 1243, 1196, 1124 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{13}ClO_2Br_2$, 429.8971. Found 429.8968.

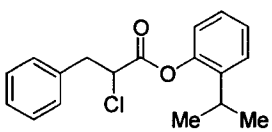


2-Chloro-3-phenyl-propionic acid 2,4,6-trimethyl-phenyl ester: According to general procedure A, 8.9mg (0.024mmol) of **80**, 168mg (1.2mmol) of 2,4,6-trimethylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 11.2mg (30%) of the desired ester. Rf = 0.61 (3:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 5H), 6.85-6.87 (m, 2H), 4.75 (dd, 1H, *J* = 7.2, 8.4 Hz), 3.55 (dd, 1H, *J* = 8.4, 14.0 Hz), 3.33 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.27 (s, 3H), 1.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 145.3, 135.8, 135.7, 131.1, 129.5, 129.3, 128.7, 127.4, 56.4, 40.8,

20.7, 15.8; IR (NaCl, neat) 1760, 1191, 1144 cm^{-1}; HRMS (EI+) calcd for $C_{18}H_{19}ClO_2$, 302.1074. Found 302.1076.

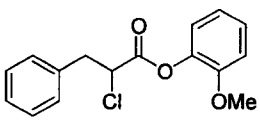


2-Chloro-3-phenyl-propionic acid 3,4-dimethyl-phenyl ester: According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 150mg (1.2mmol) of 3,4-dimethylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 28.3mg (80%) of the desired ester. Rf = 0.70 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 21.6 (c = 2.9, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 6.5 minutes, Minor: 6.0 minutes gave the isomeric composition of the product: 89% ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.38 (m, 5H), 7.12 (d, 1H, *J* = 8.1 Hz), 6.70-6.75 (m, 2H), 4.67 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.50 (dd, 1H, *J* = 7.7, 13.9 Hz), 3.33 (dd, 1H, *J* = 7.3, 13.9 Hz), 2.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 148.0, 137.9, 135.5, 134.5, 130.2, 129.4, 128.6, 127.4, 121.8, 118.0, 57.1, 41.2, 19.9, 19.3; IR (NaCl, neat) 1763, 1497, 1454, 1241, 1155 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{17}ClO_2$, 288.0917. Found 288.0924.

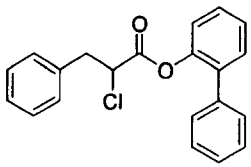


2-Chloro-3-phenyl-propionic acid 2-isopropyl-phenyl ester. According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 163mg (1.2mmol) of 2-isopropylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 20mg of an inseparable mixture of the desired ester along with the 2,6-dibromo-4-methylphenyl ester in a 60:40 ratio as determined by ^1H NMR. Rf = 0.70 (3:1 Hex/EtOAc); HPLC analysis – Chiracel AD-H

column 97 : 3 hexanes : isopropanol 0.3 mL / min. Major: 16.3 minutes, Minor: 15.6 minutes gave the isomeric composition of the product: 76% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.40 (m, 8H), 6.82-6.85 (m, 1H), 4.71 (dd, 1H, J = 7.0, 8.3 Hz), 3.52 (dd, 1H, J = 8.2, 13.9 Hz), 3.34 (dd, 1H, J = 7.0, 13.9 Hz), 2.82 (m, 1H), 1.13 (dd, 6H, J = 2.1, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 147.6, 140.1, 135.6, 129.4, 128.7, 127.5, 126.7, 126.7, 121.6, 56.8, 41.0, 26.9, 22.9, 22.8; IR (NaCl, neat) 1765, 1488, 1217, 1174, 1139; HRMS (EI+) calcd for $C_{18}H_{19}ClO_2$, 302.1074. Found 302.1069.

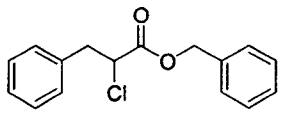


2-Chloro-3-phenyl-propionic acid 2-methoxy-phenyl ester. According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 149mg (1.2mmol) of 2-methoxyphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 21.4mg (60%) of the desired ester. Rf = 0.50 (3:1 Hex/EtOAc); HPLC analysis – Chiracel AD-H column 99 : 1 hexanes : isopropanol 0.15 mL / min. Major: 75.3 minutes, Minor: 73.2 minutes gave the isomeric composition of the product: 87% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.40 (m, 5H), 7.20-7.24 (m, 1H), 6.93-6.98 (m, 3H), 4.72 (dd, 1H, J = 6.9, 7.8 Hz), 3.78 (s, 3H), 3.57 (dd, 1H, J = 6.9, 14.1 Hz), 3.30 (dd, 1H, J = 7.8, 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 150.9, 139.3, 135.9, 129.5, 128.6, 127.4, 122.3, 120.7, 112.5, 57.2, 55.8, 41.1; IR (NaCl, neat) 1768, 1500, 1259, 1138; HRMS (EI+) calcd for $C_{16}H_{15}ClO_3$, 290.0710. Found 290.0722.

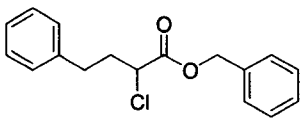


2-Chloro-3-phenyl-propionic acid biphenyl-2-yl ester. According to general procedure A, 5.8mg (0.012mmol) of ***ent*-63**, 209mg (1.2mmol) of 2-phenylphenol, 33.0mg (0.15mmol) of 2,6-dibromo-4-methylphenol, 5.0mg (0.12mmol) of potassium hydride, 16.5mg (0.06mmol) of 18-crown-6, and 25.0mg (0.12mmol) of **59** afforded 24.8mg of an inseparable mixture of the desired ester and the 2,6-dibromo-4-methylphenyl ester in a 90:10 ratio as determined by ^{1}H NMR. Rf = 0.61 (3:1 Hex/EtOAc); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1.0 mL / min. Major: 7.6 minutes, Minor: 7.2 minutes gave the enantiomeric composition of the product: 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.45 (m, 11H), 7.14-7.17 (m, 2H), 7.02-7.05 (m, 1H), 4.48 (ddd, 1H, J = 0.4, 6.8, 8.0 Hz), 3.21 (dd, 1H, J = 6.8, 14.1 Hz), 3.05 (dd, 1H, J = 8.0, 14.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 147.2, 136.8, 135.6, 134.8, 131.0, 129.3, 129.0, 128.6, 128.3, 127.7, 127.4, 126.8, 122.2, 57.1, 40.6; IR (NaCl, neat) 1765, 1478, 1434, 1185, 1139; HRMS (EI+) calcd for $C_{21}H_{17}ClO_2$, 336.0917. Found 336.0919.

General procedure B: Synthesis of alkyl α–halo-esters: A flame-dried round bottom was charged with triazolium salt (0.10 equiv), followed by addition of toluene (0.2M). *N*-Isopropyl-*N*-methyl-*tert*-butylamine (1.0 equiv) and alcohol (10.0 equiv) were then added. α-α-Dihaloaldehyde was added via syringe and the reaction was stirred at 25°C for 48 hours. The reaction mixture was then filtered through a pad of silica gel, eluting with diethyl ether. Flash column chromatography (97:3 hexane:ethyl ether) afforded the desired product.

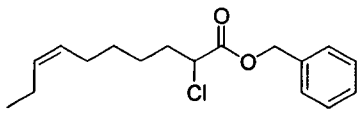


2-Chloro-3-phenyl-propionic acid benzyl ester. According to general procedure B, 12mg (0.026mmol) of ***ent*-63**, 260μL (2.5mmol) of benzyl alcohol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 50.0mg (0.25mmol) of **59** afforded 53.5mg (79%) of the desired ester. $[\alpha]_D^{24}$ = + 8.9 (c = 1.8, $CHCl_3$) HPLC analysis – Chiracel AD-H column 99 : 1 hexanes : isopropanol 0.15 mL / min to 0.244 mL / min over 50 minutes. Major: 46.6 minutes, Minor: 43.5 minutes gave the enantiomeric composition of the product: 92% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.36 (m, 3H), 7.26-7.29 (m, 5H), 7.17-7.20 (m, 2H), 5.16 (s, 2H), 4.50 (t, 1H, *J* = 7.5 Hz), 3.37 (dd, 1H, *J* = 7.5, 14 Hz), 3.19 (dd, 1H, *J* = 7.5, 14 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1, 57.3, 67.6, 127.3, 128.3, 128.5, 128.6, 129.3, 134.9, 135.7, 169.1; IR (NaCl, neat) 1747, 1497, 1455, 1268, 1162 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClO_2$, 275.0839. Found 275.0833.

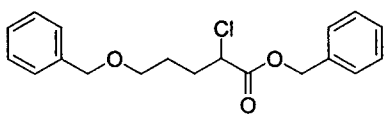


2-Chloro-3-phenyl-propionic acid benzyl ester. According to general procedure B, 216mg (0.463mmol) of ***ent*-63**, 4.79mL (46.3mmol) of benzyl alcohol, 780μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 1.00g (4.63mmol) of **66** afforded 1.23g (92%) of the desired ester. $[\alpha]_D^{24}$ = -16.2 (c = 2.9, $CHCl_3$) HPLC analysis – Chiracel OJ-H column 90 : 10 hexanes : isopropanol 1.0 mL / min. Major: 14.6 minutes, Minor: 17.7 minutes gave the isomeric composition of the product: 88% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.43 (m, 10H), 5.24 (s, 2H), 4.33 (dd, 1H, *J* = 5.5, 8.4 Hz), 2.75-2.88 (m, 2H), 2.26-2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 139.7, 135.0, 128.6, 128.5, 128.5, 128.2, 126.3, 77.2,

67.5, 56.5, 36.2, 31.8; IR (NaCl, neat) 1745, 1497, 1455, 1270, 1161 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{17}ClO_2$, 288.0917. Found 288.0909.

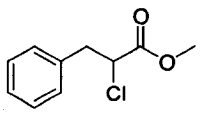


2-Chloro-dec-7-enoic acid benzyl ester. According to general procedure B, 12mg (0.026mmol) of ***ent*-63**, 260μL (2.5mmol) of benzyl alcohol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 55.0mg (0.25mmol) of **72** afforded 55.5mg (76%) of the desired ester. $[\alpha]_D^{24}$ = -7.9 (c = 1.9, $CHCl_3$) HPLC analysis – Chiracel OB-H column 99 : 1 hexanes : isopropanol 0.3 mL / min. Major: 21.6 minutes, Minor: 28.1 minutes gave the isomeric composition of the product: 88% ee. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.38 (m, 5H), 5.34-5.40 (m, 1H), 5.24-5.31 (m, 1H), 5.21 (s, 2H), 4.31 (dd, 1H, *J* = 6.1, 7.9 Hz), 1.89-2.09 (m, 6H), 1.31-1.51 (m, 4H), 0.95 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.1, 132.1, 128.6, 128.5, 128.4, 128.3, 67.5, 57.3, 34.8, 28.9, 26.7, 25.5, 20.5, 14.3; IR (NaCl, neat) 1748, 1456, 1271, 1160 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{23}ClO_2$, 294.1387. Found 294.1374.

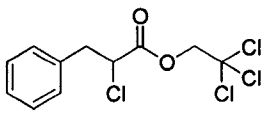


5-Benzyloxy-2-chloro-pentanoic acid benzyl ester. According to general procedure B, 12mg (0.026mmol) of ***ent*-63**, 260μL (2.5mmol) of benzyl alcohol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 65.0mg (0.25mmol) of **76** afforded 40.5mg (49%) of the desired ester. $[\alpha]_D^{24}$ = -6.1 (c = 3.5, $CHCl_3$) HPLC analysis – Chiracel OD-H column 97 : 3 hexanes : isopropanol 0.5 mL / min. Major: 22.7 minutes, Minor: 24.3 minutes gave the isomeric composition of the product: 86% ee. Rf = 0.74 (3:1 Hex/EtOAc); ^1H NMR (400

MHz, $CDCl_3$) δ 7.28-7.36 (m, 5H), 5.20 (s, 2H), 4.48 (s, 2H), 4.37 (dd, 1H, J = 6.4, 6.4 Hz), 3.49 (t, 2H, J = 6.0 Hz), 2.13-2.24 (m, 1H), 1.98-2.10 (m, 1H), 1.66-1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.3, 135.1, 128.6, 128.5, 128.4, 128.2, 127.6, 72.9, 69.0, 67.6, 57.2, 31.9, 26.2; IR (NaCl, neat) 1746, 1454, 1269, 1165, 1102 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{21}ClO_3$, 332.1179. Found 332.1187.

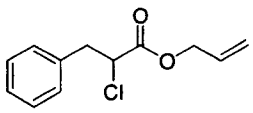


2-Chloro-3-phenyl-propionic acid methyl ester. According to general procedure B, 11.3mg (0.026mmol) of **107**, 101μL (2.5mmol) of methanol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 50.0mg (0.25mmol) of **59** afforded 40.6mg (83%) of the known ester.[3] $[\alpha]_D^{24}$ = + 3.8 (c = 0.8, $CHCl_3$) HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 0.5 mL / min. Major: 36.7 minutes, Minor: 26.6 minutes gave the isomeric composition of the product: 72% ee.

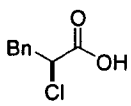


2-Chloro-3-phenyl-propionic acid 2,2,2-trichloro-ethyl ester. According to general procedure B, 12mg (0.026mmol) of ***ent*-63**, 240μL (2.5mmol) of trichloroethanol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 50.0mg (0.25mmol) of **59** afforded 21.0mg (27%) of the desired ester. Rf = 0.66 (3:1 Hex/EtOAc); $[\alpha]_D^{24}$ = + 4.3 (c = 1.1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 97 : 3 hexanes : isopropanol 1 mL / min. Major: 6.2 minutes, Minor: 7.3 minutes gave the isomeric composition of the product: 76% ee. Rf = 0.74 (3:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.32 (m, 5H), 4.76 (s, 2H), 4.59 (dd, 1H, J = 7.3, 7.3 Hz), 3.44 (dd, 1H, J = 7.9, 14.3 Hz), 3.24 (dd, 1H, J = 7.5, 13.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.8, 135.3, 129.3, 128.7, 127.5, 94.1, 74.7, 56.7, 40.9; IR

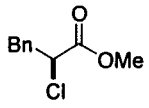
(NaCl, neat) 1764, 1277, 1223, 1148 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{11}Cl_4O_2$, 314.9513. Found 314.9515.



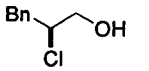
2-Chloro-3-phenyl-propionic acid allyl ester. According to general procedure B, 11.3mg (0.026mmol) of **107**, 170μL (2.5mmol) of allyl alcohol, 42μL (0.25mmol) of *N-iso*-propyl-*N*-methyl-*tert*-butylamine, and 50.0mg (0.25mmol) of **59** afforded 40.6mg (83%) of the desired ester. $[\alpha]_D^{24} = +7.1$ (c = 2.7, $CHCl_3$) HPLC analysis – Chiracel OB-H column 97 : 3 hexanes : isopropanol 0.3 mL / min. Major: 24.6 minutes, Minor: 21.4 minutes gave the isomeric composition of the product: 70% ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.35 (m, 5H), 5.79-5.92 (m, 1H), 5.23-5.32 (m, 2H), 4.62 (d, 2H, J = 5.7 Hz), 4.47 (t, 1H, J = 7.5 Hz), 3.38 (dd, 1H, J = 7.3, 14.0 Hz), 3.19 (dd, 1H, J = 7.6, 14.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 135.8, 131.1, 129.3, 128.6, 127.3, 119.1, 66.4, 57.3, 41.1; IR (NaCl, neat) 1746, 1273, 1164.



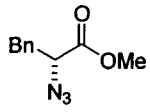
2-Chloro-3-phenyl-propionic acid. 2-Chloro-3-phenyl-propionic acid phenyl ester (0.50g, 1.92mmol) was dissolved in tetrahydrofuran (5mL) and water (2mL) and placed in an ice-water bath. Hydrogen peroxide (0.87mL, 7.67mmol, 30% solution) was added followed by lithium hydroxide (50.5mg, 2.11mmol) in 1mL water. The reaction was stirred in the ice-bath for 1hour and quenched with sodium bisulfite. Standard acid-base workup afforded 300mg (85%) of the known acid.[3] The product acid was converted to the corresponding methyl ester for determination of enantiomeric excess. HPLC analysis. HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 0.5 mL / min. Major: 36.7 minutes, Minor: 26.6 minutes gave the isomeric composition of the product: 88% ee.



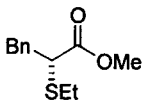
2-Chloro-3-phenyl-propionic acid methyl ester. 2-Chloro-3-phenyl-propionic acid phenyl ester (0.50g, 1.92mmol) was dissolved in methylene chloride (15mL) and methanol (15mL) and placed in a ice-water bath. Magnesium methoxide solution (2.87mL, 2.11mmol, 6-10 wt%) was then added and the solution stirred for 30 minutes at which time the reaction was quenched with ammonium chloride. Standard aqueous workup afforded 353mg (93%) of the known methyl ester. HPLC analysis – Chiracel OJ-H column 97 : 3 hexanes : isopropanol 0.5 mL / min. Major: 36.7 minutes, Minor: 26.6 minutes gave the isomeric composition of the product: 89% ee.



2-Chloro-3-phenyl-propan-1-ol. 2-Chloro-3-phenyl-propionic acid phenyl ester (50.0mg, 0.192mmol) was dissolved in ethyl ether (5mL). After cooling to –78°C with a dry-ice-acetone bath, lithium aluminum hydride (0.011g, 0.288mmol) was added and the solution stirred for 30 minutes. The reaction was then placed in an ice-water bath and stirred for 30 minutes, followed by warming to room temperature. The solution was quenched by addition of water (10μL), 15% aqueous sodium hydroxide (10μL), then water (30μL) followed by addition of $MgSO_4$ and filtration through celite eluting with ethyl ether. The solution was then washed with sodium hydroxide (2 X 20mL), dried over $MgSO_4$, filtered and concentrated to afford 31mg (95%) of the desired alcohol. ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.36 (m, 5H), 4.19-4.27 (m, 1H), 3.66-3.83 (m, 2H), 3.02-3.18 (m, 2H), 2.08 (bs, 1H) HPLC analysis – Chiracel AS-H column 95 : 5 hexanes : isopropanol 1.0 mL / min. Major: 9.6 minutes, Minor: 11.4 minutes gave the isomeric composition of the product: 90% ee.

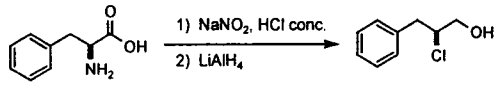


2-Azido-3-phenyl-propionic acid methyl ester. 2-Chloro-3-phenyl-propionic acid methyl ester (20.0mg, 0.100mmol) was treated with sodium azide (0.13g, 0.201mmol) according to the procedure of Halland et al. to afford 20.0mg (97%) of the known α-azidoester.[4] HPLC analysis – Chiracel OD-H column 99 : 1 hexanes : isopropanol 0.3 mL / min. Major: 30.3 minutes, Minor: 37.2 minutes gave the isomeric composition of the product: 87% ee.



2-Ethylsulfanyl-3-phenyl-propionic acid methyl ester. To a flame dried flask was added ethane thiol and tetrahydrofuran (2mL). The solution was cooled to -78°C with a dry-ice-acetone bath and butyl lithium (67μL, 0.100mmol, 1.6M in hexanes) was added followed by stirring for 5 minutes. 2-Chloro-3-phenyl-propionic acid methyl ester (20.0mg, 0.100mmol) was added and the solution was allowed to warm slowly to room temperature. Standard aqueous workup afforded 20.4mg (90%) of the desired α-thioester. $[\alpha]_D^{24}$ = + 20.4 (c = 1.3, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 99 : 1 hexanes : isopropanol 1.0 mL / min. Major: 26.2 minutes, Minor: 16.2 minutes gave the isomeric composition of the product: 84% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.31 (m, 5H), 3.68 (s, 3H), 3.55 (dd, 1H, J = 6.3, 9.2 Hz), 3.21 (dd, 1H, J = 9.3, 13.8 Hz), 2.97 (dd, 1H, J = 6.4, 13.8 Hz), 2.64 (q, 2H, J = 7.3 Hz), 1.23 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 138.0, 128.9, 128.5, 126.8, 52.2, 47.9, 37.8, 25.7, 14.3; IR (NaCl, neat) 1733, 1262, 1151; HRMS (FAB+) calcd for $C_{12}H_{17}O_2S$, 225.0949. Found 225.0941.

Determination of absolute configuration:



L-Phenylalanine was converted to (S)-2-chloro-3-phenyl-propanol according to literature procedures.[2] The HPLC trace of (S)-2-chloro-3-phenyl-propanol provided the same major enantiomer as the alcohol derived from 2-Chloro-3-phenyl-propionic acid 2,6-dichloro-phenyl ester.

References

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[2] Bellesia, F.; De Buyck, L.; Ghelfi, F.; Libertini, E.; Pagnoni, U. M.; Roncaglia, F. *Tetrahedron* **2000**, *56*, 7507-7511.

[3] Tan, E. W.; Chan, B.; Blackman, A. G. J. Am. Chem. Soc. 2002, 124, 2078-2079.

[4] Procedure: Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790-4791. Characterization: Fan, Q. –H. Ni, N. –T.; Li, Q.; Zhang, L. –H.; Ye, X. –S. *Org. Lett.* **2006**, *8*, 1007-1009.