Investigations in Enantioselective Catalysis. Development of Novel Asymmetric Organocatalytic Reactions.

Thesis by

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For Liz, with more love and gratitude than words can express

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I was fortunate enough to join the MacMillan group at its inception. I'll never forget my first day in a research laboratory at graduate school; I spent it washing glassware that had been scavenged from around the department. The group that first year at Berkeley

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My first interest in chemistry was a gift from my Aunt Mary. The help with grade school science projects and the chemistry books she gave me sparked my strong interest in

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My family has always been there for me. My parents have encouraged me, supported me, and loved me more than anyone has a right to expect. I do not know how to begin to thank you for all that you have given me; I will always be grateful.

She's only been here for the last year, but the wonder and joy my daughter Virginia brings to everything has been an inspiration to me.

Finally, I don't know if I would have been able to do any of this if it weren't for the love and support of my wife, Liz. She has always been supportive of me in all things and in all ways. She's been my harshest critic and my best friend since I met her. Our marriage has been joyous, and I am ecstatic to spend the rest of my life with her.

Abstract

A new strategy for the catalysis of organic transformations using iminium ion activation has been developed. Using this strategy, the first asymmetric organocatalytic Diels-Alder reaction has been developed. This methodology has demonstrated the possibility of an imidazolidinone salt to function as an effective asymmetric catalyst for a wide variety of chemical transformations.

The iminium ion activation strategy has also proved successful for conjugate additions, and an asymmetric organocatalytic Mukaiyama-Michael reaction has been developed using the principles of LUMO-lowering catalysis. A more reactive and selective chiral imidazolidinone catalyst was developed, and this secondary amine has extended the range of transformations possible with iminium ion catalysis.

Progress has been made towards the development of an enantioselective organocatalytic alpha-oxidation of ketones. Proline catalysis has been demonstrated to effectively catalyze the asymmetric alpha-oxidation of cyclohexanone, but extension of this methodology to other ketones has not been successful. These studies have further demonstrated the utility of proline as a catalyst, and provide a platform for the extension of HOMO-raising catalysis to other organic transformations.

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Abbreviations

Cbz: Benzyloxycarbonyl

CI: Chemical Ionization

DBA: DiBromoAcetic acid

DCA: DiChloroAcetic acid

DFA: DiFluoroAcetic acid

DME: 1,2-DiMethoxyEthane

DMSO: DiMethylSulfonyl Oxide

DNBA: 2,4-DiNitroBenzoic Acid

d.r.: Diastereomer Ratio

$\boldsymbol{E_T^N}$: Normalized empirical solvent polarity parameter; derived from the solvatochromism of a standard pyridinium-*N*-phenoxide betaine dye[a]

EDG: Electron-Donating Group

ee: Enantiomeric Excess

EI: Electrospray Ionization

EtOAc: Ethyl acetate

EWG: Electron-Withdrawing Group

FAB: Fast Atom Bombardment ionization

FMO: Frontier Molecular Orbital

GLC: Gas Liquid Chromatography

h: hour

Hex: hexanes

HOAc: Acetic acid

HOAcCN: Cyanoacetic acid

HOMO: Highest Occupied Molecular Orbital

HPLC: High Performance Liquid Chromatography

HRMS: High Resolution Mass Spectroscopy

Hz: Hertz

IR: Infrared

LUMO: Lowest Unoccupied Molecular Orbital

M: Molar

***m*:** *meta*

mg: milligram

min: minute

mL: milliliter

mmol: millimole

MsOH: Methanesulfonic acid

mT: millitorr

NMR: Nuclear Magnetic Resonance spectroscopy

***o*:** *ortho*

organocatalysis: Catalysis of a transformation by a wholly organic catalyst (not by an organometallic catalyst)

organocatalyst: A catalyst of wholly organic composition (not organometallic)

***p*:** *para*

ppm: Parts Per Million

PTSA: *para*-Tolune Sulfonic Acid

TBS: *tert*-ButyldimethylSilyl

TIPS: TriIsopropylSilyl

TMS: TriMethylSilyl

TCA: TriChloroAcetic acid

TFA: TriFluoricAcetic acid

TfOH: Trifluoromethanesulfonic acid

THF: TetraHydroFuran

TLC: Thin Layer Chromatography

XRD: X-Ray Diffraction

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[a] Reichardt, C.; Harbusch-Görnert, E. *Liebigs. Ann. Chem.* **1983**, 721. Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 125. Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 1001.

Chapter 1

Organocatalysis

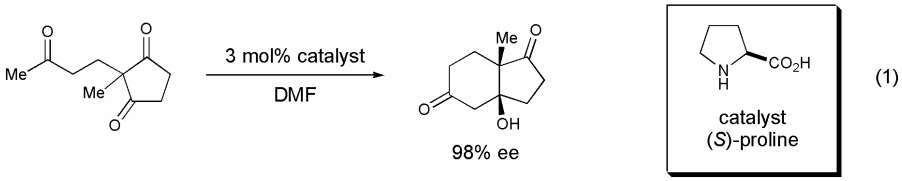
I. Background

Organocatalysis

For the last 40 years, enantioselective catalysis has been in the forefront of research in synthetic organic chemistry. This growth has seen the development of a wide variety of chiral Lewis acidic organometallic catalysts capable of effecting a broad range of transformations.[1-5] These catalysts have proven successful at the enantioselective catalysis of many organic transformations including asymmetric oxidations, reductions, cycloadditions, conjugate additions, and π-bond activation reactions.

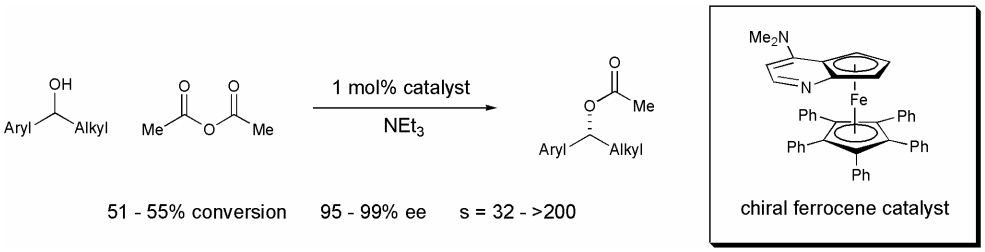
However, relatively few asymmetric transformations have been reported which use wholly organic molecules as catalysts. Since organometallic catalysts typically involve an air- or moisture-sensitive metal as the catalytically active species, moving towards using completely organic molecules would prove beneficial from a variety of perspectives. Organocatalysts have the potential of avoiding the sensitivities of organometallic catalysts, eliminating the need to exclude oxygen or water from reaction conditions. Organocatalysts could possibly be discovered within the great number of naturally occurring enantiopure organic compounds such as carbohydrates, amino acids, nucleic acids, and their oligomers, facilitating access to effective chiral catalysts. Using catalysts that can be accessed more directly from a naturally occurring chiral source would most likely prove more cost-effective and efficient than a corresponding

organometallic catalyst, a catalyst which typically involves a multi-step synthesis from the same naturally occurring chiral starting materials. As such, this field offers a unique opportunity for the development and elucidation of conceptually novel enantioselective transformations.



(1)

The concept of utilizing an organocatalyst for enantioselective transformation has not been lost on the chemical community, and there have been reports of enantioselective organocatalysts as early as 1912.[6] One of the best known early asymmetric organocatalytic reactions is the proline-catalyzed intramolecular aldol reaction, the Hajos-Parrish-Eder-Sauer-Wiechert reaction (equation 1).[7,8] This reaction has been used extensively in natural product synthesis and elsewhere since its development.

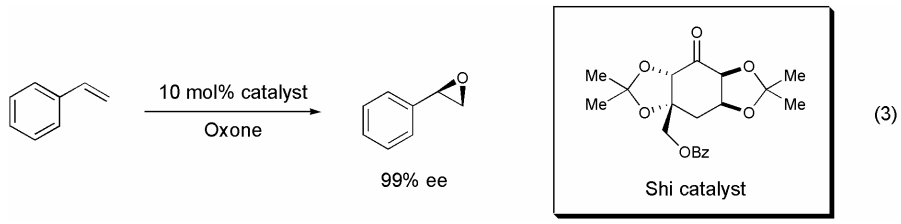


(2)

A variety of chiral nucleophilic amines have been developed as catalysts for kinetic resolutions, cycloadditions, halogenations reactions, Baylis-Hillman reactions, anhydride desymmetrizations, acylations, and cyanation reactions.[9] Cinchona alkaloids

and organocatalysts discovered through rational design, such as the ferrocene-based catalyst of Fu, have been utilized for the kinetic resolution of alcohols by acylation (equation 2).[10]

Several groups have developed chiral ketones that can function effectively as catalysts for the enantioselective epoxidation of olefins.[11-15] These organocatalysts can efficiently epoxidize a wide range of olefins with high yields and selectivities (equation 3).



(3)

Additionally, other chemotypes have proven successful as organocatalysts.[9,16-19] Antibodies have been developed as catalysts for organic transformations.[20] Quaternary ammonium salts have been developed as selective phase-transfer catalysts.[21] Hydrogen bond donors have also functioned as catalysts.[22-24] Even synthetic peptides have been used as catalysts for organic transformations.[16]

Although there have been many reports of organocatalysts, these chiral catalysts differ from successful organometallic catalysts in one significant respect. Organometallic complexes derived from BINOL, BINAP, Salen, and bisoxazoline ligands have been successful at catalyzing a broad range of transformations with excellent selectivity.[25] Catalysts derived from these ligands have been termed “privileged” catalysts by the chemical community, and for good reason. A small number of chiral organometallic

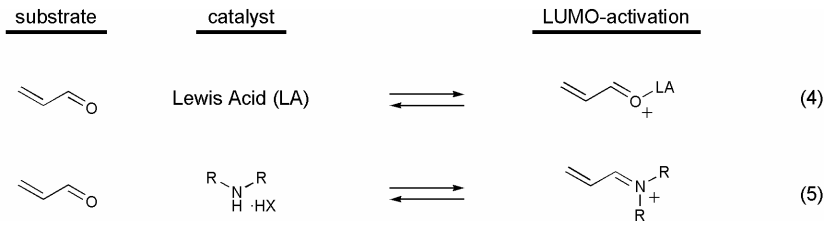
catalysts are able to affect most of the asymmetric transformations that have been realized. These catalysts have been successful because of general nature of Lewis acid-activation and the strong ability of their asymmetric ligands to transmit their chirality. While organometallic catalysts operate through Lewis acid-activation, a means of activation applicable to a wide variety of synthetic transformations, organocatalysts appear to operate through reaction-specific means of activation.

II. Developing a General Approach towards Enantioselective Organocatalysis

LUMO-Lowering Catalysis

We began our research program with the intent of developing a general strategy for organocatalysis based on the most successful aspects of Lewis acid catalysis (Scheme 1). The equilibrium of a Lewis acid catalyst system and the effect of that catalyst on the energy of a substrate's π-orbital system were two features of Lewis acid-activation that we sought to mimic using a wholly organic system. In doing so, we believed we could develop a catalyst capable of affecting the same broad range of transformations possible with Lewis acid-catalysis.

Scheme 1. LUMO-lowering activation of α,β-unsaturated aldehydes by secondary amines.



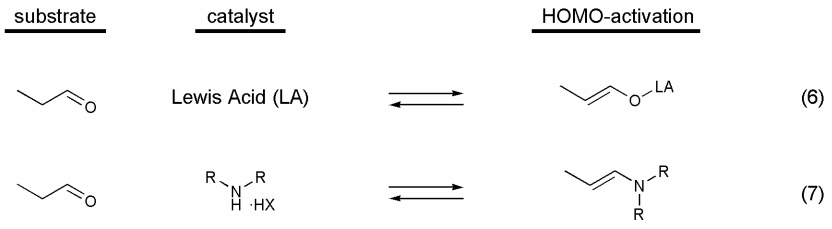
An organic system that exists as a rapid equilibrium between a relatively electron-rich and electron-deficient state should mimic these features of Lewis acid catalysis. The reversible formation of an iminium ion from the corresponding secondary amine and α,β-unsaturated aldehyde was chosen as a platform for the development of a general organocatalytic strategy (Scheme 1, equation 5). The formal cationic charge and electronegative heteroatom should both serve to lower the LUMO of the α,β-unsaturated iminium ion relative to the corresponding α,β-unsaturated aldehyde starting material.

This chemical activation through LUMO-lowering and reversible iminium ion formation is analogous to the Lewis acid catalysis of reactions involving α,β-unsaturated carbonyl compounds (Scheme 1, equation 4). Most significantly, this proposal led to the hypothesis that secondary amines should be able to catalyze the same range of chemical transformations as Lewis acids.

HOMO-Raising Catalysis

Another mechanism of activating a chemical species toward a transformation is HOMO-raising, and this is another avenue for developing a general method of organocatalysis (Scheme 2). This form of organocatalysis accelerates a reaction by increasing the energy of the HOMO of one reacting partner. An enamine can be formed by the condensation of a secondary amine and an aldehyde (Scheme 2, equation 7). The resulting enamine has a higher HOMO than the corresponding aldehyde, and, therefore, is activated towards further transformation. This is analogous to the formation of a nucleophilic enol from a carbonyl compound (Scheme 2, equation 6). Research on proline-catalysis led to the hypothesis that secondary amines should also be able to catalyze a broad range of organic transformations through HOMO-raising catalysis.[7,8,26,27]

Scheme 2. Organocatalytic HOMO-activation.



Efforts towards General Enantioselective Organocatalysis

The following chapters detail efforts towards developing a general organocatalytic methodology. Chapter Two discusses the development of a general strategy for organocatalysis using LUMO-lowering activation and the development of the first enantioselective organocatalytic Diels-Alder reaction. Chapter Three details the development of a second-generation organocatalyst and the extension of organocatalytic methodology to an enantioselective Mukaiyama-Michael reaction. Chapter Four describes investigations into HOMO-raising organocatalysis, the proline-catalyzed α-oxidation of ketones.

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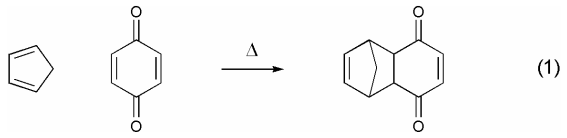
Chapter 2

Development of a New Strategy for Catalysis: The First Enantioselective Organocatalytic Diels-Alder Reaction

I. Introduction

The Diels-Alder Reaction

Examples of the [2+4]-cycloaddition known as the Diels-Alder reaction can be found in the literature as early as the end of the 19th century.[1] The formal elucidation of this reaction did not occur until early in the 20th century when Otto Diels and Kurt Alder correctly deduced the product of the thermal reaction of *p*-benzoquinone and cyclopentadiene (equation 1).[2] This discovery was of such significance to the chemical community that Diels and Alder were awarded the Nobel Prize in 1950.

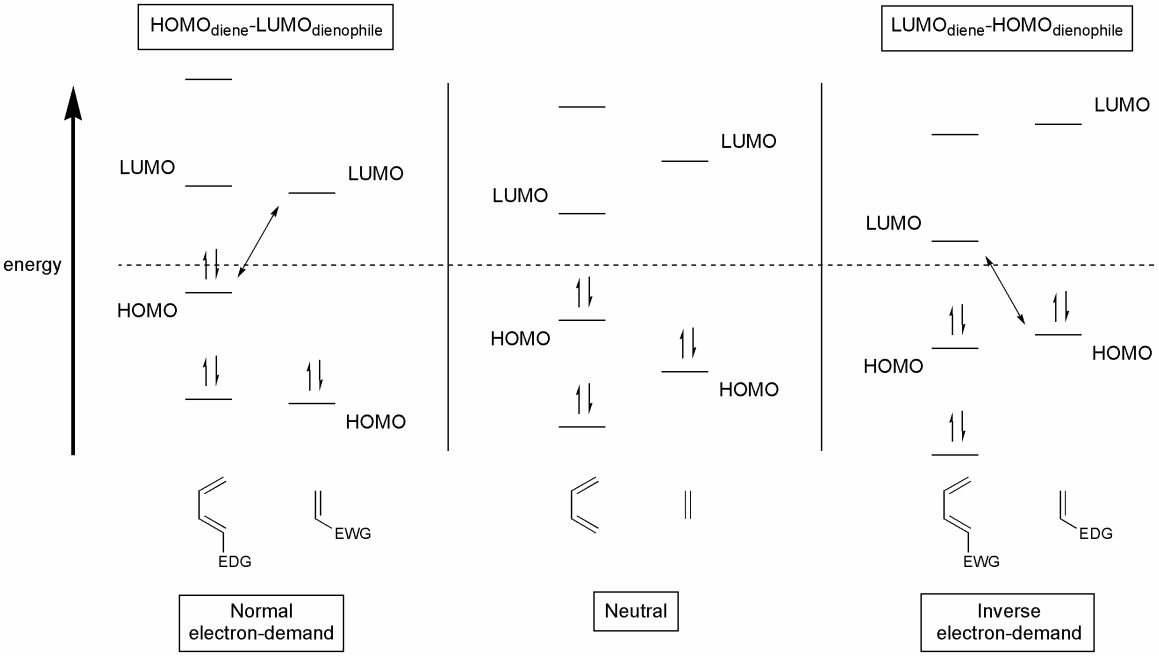


(1)

The Diels-Alder reaction is one of the most frequently used transformations in organic chemistry because of its highly stereoselective nature. The Diels-Alder reaction can regio- and diastereoselectively create six-membered and polycyclic ring systems, and it has the potential to set four contiguous stereogenic centers.[3-5] It has even been referred to as "the single most important reaction in the synthetic chemist's tool box."[5]

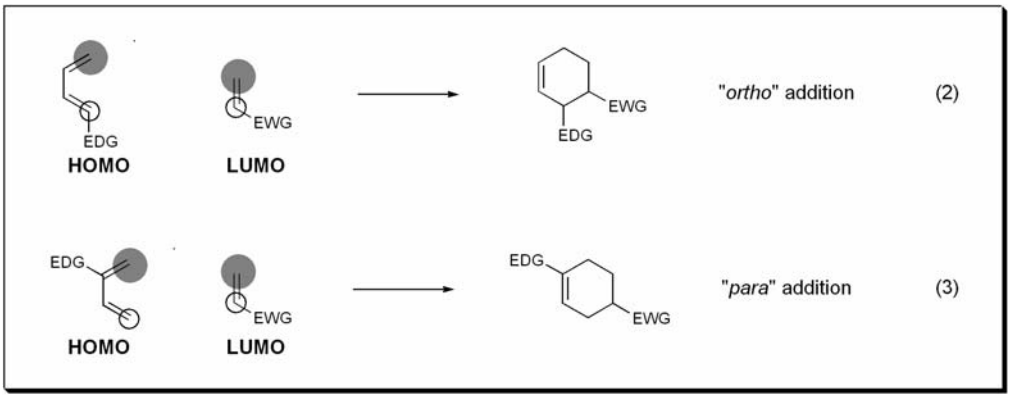
Diels-Alder reactions can be classified and their outcomes predicted based on the HOMO and LUMO involved in the transformation.[6-9] Normal electron-demand Diels-Alder reactions are controlled by the interaction of the $HOMO_{diene}$ and the $LUMO_{dienophile}$; inverse electron-demand Diels-Alder reactions are controlled by the interaction of the $LUMO_{diene}$ and the $HOMO_{dienophile}$; neutral Diels-Alder reactions have no one dominant molecular orbital interaction (Scheme 1). Historically, the normal electron-demand Diels-Alder reaction has been the most studied and utilized.[10]

Scheme 1. Classification of Diels-Alder reactions based on the energy of the frontier molecular orbitals involved.



It is the electronics of the Diels-Alder cycloaddition that dictate the nature of stereocontrol in the reaction and lead to the high selectivities observed in the transformation.[11,12] Two general principles govern the selectivity of Diels-Alder reactions, the "*cis* principle" (as coined by Alder),[13] and secondary orbital interactions.

Scheme 2. FMO theory correctly predicts the regioselectivity of Diels-Alder cycloadditions.

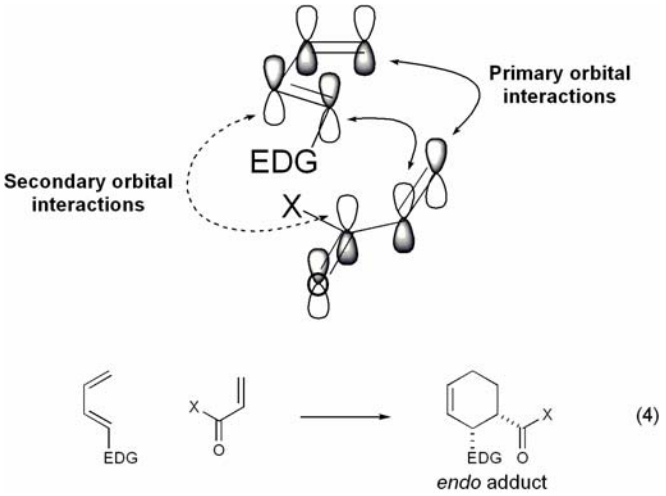


The "*cis* principle" or the *ortho-para* rule, as it is more commonly known, is dictated by the symmetry of the π-orbitals involved in the Diels-Alder cycloaddition.[11,13-15] If the frontier molecular orbitals involved in a normal electron-demand Diels Alder cycloaddition are calculated (the HOMO of the diene and the LUMO of the dienophile in a normal electron-demand Diels-Alder reaction), and orbitals of similar sign and magnitude are allowed to interact, the regiochemistry of the Diels-Alder is correctly predicted (Scheme 2). This results in either a 1,2- or a 1,4-relationship between the electron-donating group on the diene and the electron-withdrawing group on the dienophile.

Diels-Alder reactions typically form *endo* cycloadducts.[11,14] This is due to secondary orbital interactions, interactions between of parts of the frontier molecular orbitals not directly involved in forming new bonds. It is because of these attractive secondary orbital interactions that the *endo* cycloadduct is the more commonly formed product of Diels-Alder reactions, except when steric demands override this interaction (Scheme 3). While frontier molecular orbital theory correctly predicts the formation of

the *endo* Diels-Alder cycloadduct, the existence of secondary orbital interactions has recently been questioned.[12,16]

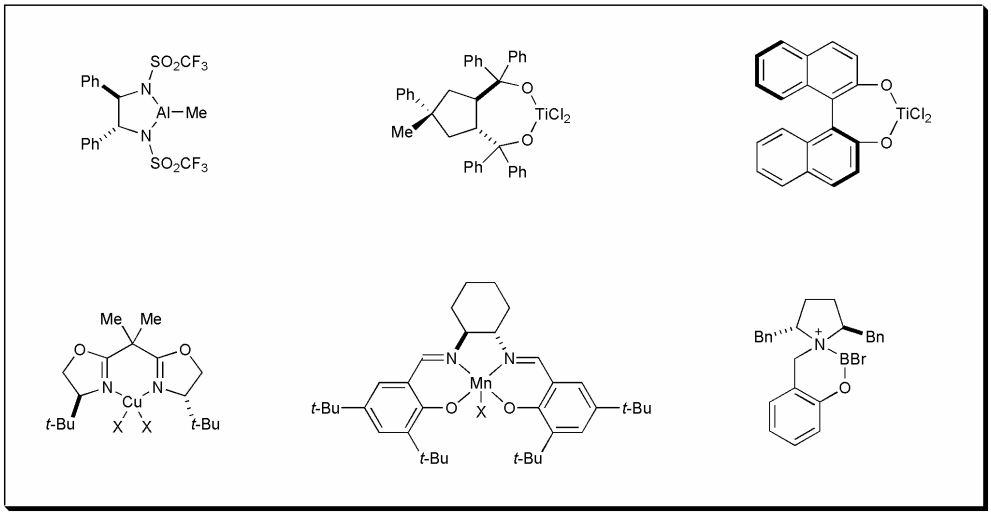
Scheme 3. Orbital interactions in the Diels-Alder cycloaddition.



Enantioselective Catalysis of the Diels-Alder Reaction

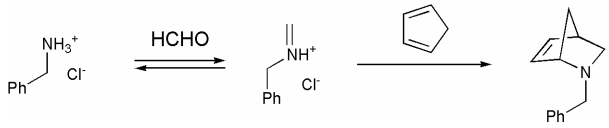
Due to the great utility of this transformation, much research has been devoted to the development of asymmetric catalytic methods.[4,17-19] Effective chrial organometallic catalysts have been developed for the asymmetric Diels-Alder reaction (Figure 1). These catalysts have shown excellent selectivity and reactivity, yielding products in greater than 99% ee in some cases.

Figure 1. Selected chiral organometallic Diels-Alder catalysts.[18,20]



Lewis acid catalysts typically activate α,β-unsaturated carbonyl compounds towards reaction through LUMO-lowering activation by coordination with the carbonyl oxygen.[18] This lowers the activation energy of a normal electron-demand Diels-Alder reaction and enhances the selectivity of the transformation by affecting the FMO's involved.

Iminium Ion Acceleration of the Diels-Alder Reaction



(5)

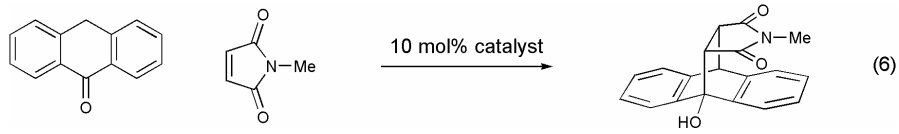
The Diels-Alder reaction need not be Lewis acid catalyzed. The Grieco laboratory has demonstrated that the Diels-Alder reaction will occur under mild conditions when an iminium ion is employed in the transformation as the dienophile

(equation 5).[21,22] Studying the effect of chiral auxiliaries in this transformation, Greico also demonstrated that (-)-α-methylbenzylamine functions as an effective auxiliary, generating Diels-Alder adducts with 4:1 diastereoselectivity.[21]

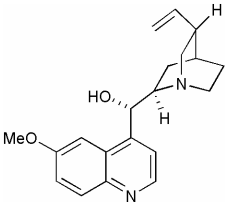
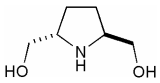
Organocatalysis of the Diels-Alder Reaction

The Diels-Alder reaction has previously been catalyzed by wholly organic molecules.[4,17,23,24] Catalysis of the Diels-Alder reaction has been demonstrated by bovine serum albumin, antibodies, enzymes, and cyclodextrins.

Table 1. Asymmetric base-catalyzed Diels-Alder reactions.

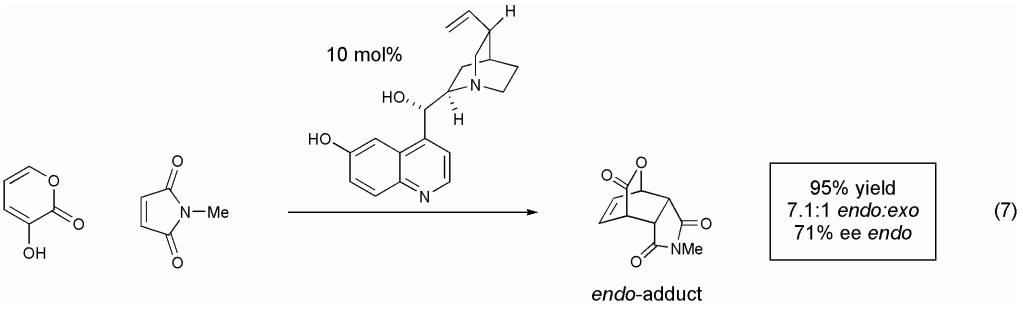


(6)

Entry	Catalyst	% Yield	% ee
1		97	61
2		88	61

Only three examples of small molecule organocatalysis of the Diels-Alder have been reported prior to the study outlined in this thesis. Cinchona alkaloids have been demonstrated to be competent catalysts of the asymmetric Diels-Alder reaction, catalyzing the cycloaddition of anthrone to *N*-methylmaleimide in 97% yield and 61% ee (Table 1, entry 1).[25] Chiral pyrrolidines have also been demonstrated to be effective basic catalysts for this transformation (88% yield, 61% ee, Table 1, entry 2).[26] The Diels-

Alder cycloaddition of 3-hydroxy-2-pyrone and *N*-methylmaleimide has also been effectively catalyzed by cinchona alkaloids.[27] Cinchonine proved to be the most effective catalyst, producing the cycloadduct in 95% yield and 71% ee (equation 7). These transformations are believed to be accelerated by the formation of the enolate of the diene. Asymmetry is believed to result from a tight ion pairing between the diene enolate and the protonated chiral base catalyst.



(7)

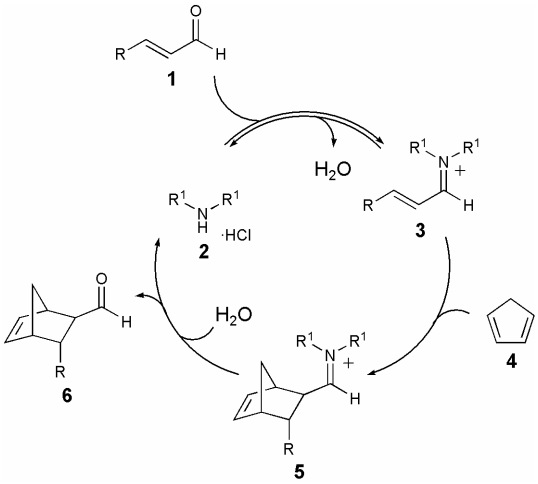
Despite the many examples of organocatalytic Diels-Alder reactions in the literature (catalytic antibodies, cinchona alkaloids, etc.), there has not been a general organocatalytic Diels-Alder strategy reported.

II. Results and Discussion[28]

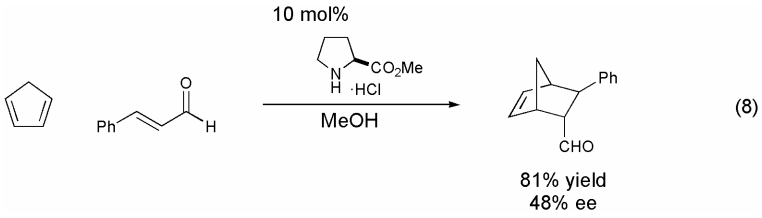
Initial Investigations

We chose the Diels-Alder reaction as a platform for the development of a general organocatalytic strategy, attempting to discover an organocatalyst either directly or easily accessible from the chiral pool, and we hoped that the reaction would provide a good starting point for the extension of organocatalytic methodology to other organic transformations like dipolar cycloadditions and conjugate additions. We hypothesized that a secondary amine should be able to catalyze the same reactions as a Lewis acid through a LUMO-lowering equilibrium with an α,β-unsaturated aldehyde (see Chapter 1). We believed that the iminium ion **3** generated from an α,β-unsaturated aldehyde **1** and a chiral secondary amine **2** would be activated towards cycloaddition with an appropriate diene **4** (Scheme 4). The Diels-Alder reaction with the activated iminium ion **3** would generate an iminium ion cycloadduct **5** which, in the presence of water, would hydrolyze to yield the enantioenriched product **6** and regenerate the chiral secondary amine catalyst **2**.

Scheme 4. Proposed secondary amine-catalyzed Diels-Alder reaction.



Serendipitously, the first reaction studied by Kateri Ahrendt was the proline methyl ester catalyzed reaction between cyclopentadiene and cinnamaldehyde. This reaction afforded cycloaddition product in 81% yield and 48% ee for the *exo* product isomer (equation 8).[29] Importantly, without the proline-derived catalyst present, only a 13% yield of cycloadduct was isolated from similar reaction conditions after 48 h. This demonstrated that the amine-catalyzed Diels-Alder reaction was significantly accelerated relative to the thermal background reaction.

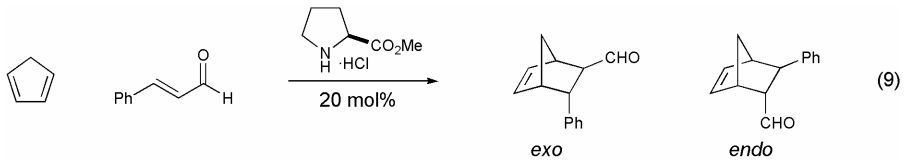


Initial Investigations of Reaction Conditions[30]

Initial studies on the organocatalytic Diels-Alder reaction were conducted with varying ratios of acid to free amine. It was discovered that ratios of acid to amine deviating from unity showed either decreased enantioselectivity (when less acid than amine was used) or no improvement in reaction rate (when more acid than amine was used). It was determined that one equivalent of acid to amine is optimal for the formation of a reactive iminium ion under equilibrium conditions. Condensation of an aldehyde and an amine hydrochloride salt forms an iminium hydrochloride, whereas the condensation of an aldehyde and a free amine under aqueous conditions will form an iminium hydroxide. The formation of an iminium hydroxide is expected to be significantly less favorable than the formation of an iminium chloride, due to the relative stability of the anions, therefore it is believed that a greater concentration of reactive iminium ion is present when an amine acid salt is used as the catalyst. All further studies were conducted using acid salts of the chiral amine catalysts.

An initial investigation into reaction conditions quickly showed methanol to be the best solvent for the amine-catalyzed Diels-Alder reaction between cinnamaldehyde and cyclopentadiene (Table 2). Both the highest reaction rate (not shown) and highest selectivities were obtained in methanol (Table 2, entry 7). It is believed that the polarity of the solvents studied explains the observed trend. The solvent studied with the highest polarity (methanol) is best able to stabilize charged intermediates, thereby increasing the concentration of the reactive iminium ion and increasing both reaction rate and selectivity.

Table 2. Effect of solvent on the proline methyl ester catalyzed Diels-Alder cycloaddition between cyclopentadiene and cinnamaldehyde.[a]

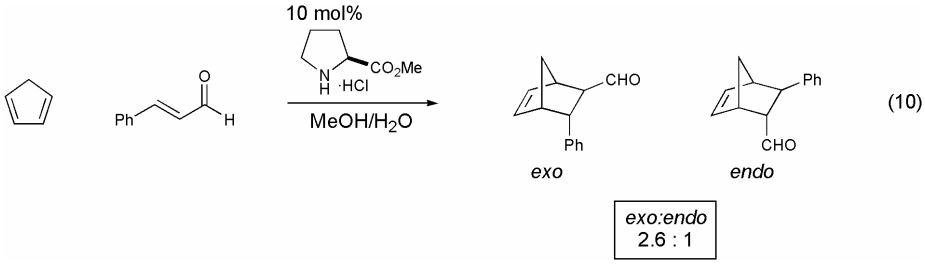


Entry	Solvent	E_T^N	*exo:endo*[b]	% ee (*exo*)[b]
1	THF	0.207	2.3:1	18
2	CH_2Cl_2	0.309	3.3:1	28
3	DMF	0.404	2.4:1	25
4	DMSO	0.444	2.5:1	22
5	CH_3CN	0.460	2.6:1	39
6	CH_3NO_2	0.481	2.7:1	36
7	MeOH	0.762	2.4:1	48

[a] All reactions were performed at room temperature (1.0 M); [b] Product ratios and enantioselectivity determined by GLC analysis.

Because of the strong dependence on the polarity of the reaction medium shown by the organocatalytic Diels-Alder reaction, the effect of water on the reaction was next studied. Since higher polarity solvents produced more favorable results, it was hypothesized that the addition of water to the reaction medium would accelerate the reaction by increasing the solvent's polarity. The best results were obtained when 5% (v/v) water was incorporated into the reaction medium (Table 3, entry 2). As can be seen in Table 3, no water retards the reaction rate and decreases the selectivity, and excess water also impedes reactivity and selectivity. It is believed that a small amount of water facilitates the formation of the reactive iminium ion by increasing the polarity of the reaction medium, while a large amount of water retards the reaction by inhibiting the formation of the iminium ion through hydrolysis.

Table 3. Effect of water concentration on the proline methyl ester catalyzed Diels-Alder cycloaddition between cyclopentadiene and cinnamaldehyde.[a]



Entry	v/v% H_2O	Time (h)	% Conversion[b]	% ee (*exo*)[b]
1	0	4	51	48
2	5	4	70	50
3	10	4	54	46
4	20	4	41	40

[a] All reactions were performed at room temperature (1.0 M); [b] Conversion and enantioselectivity determined by GLC analysis.

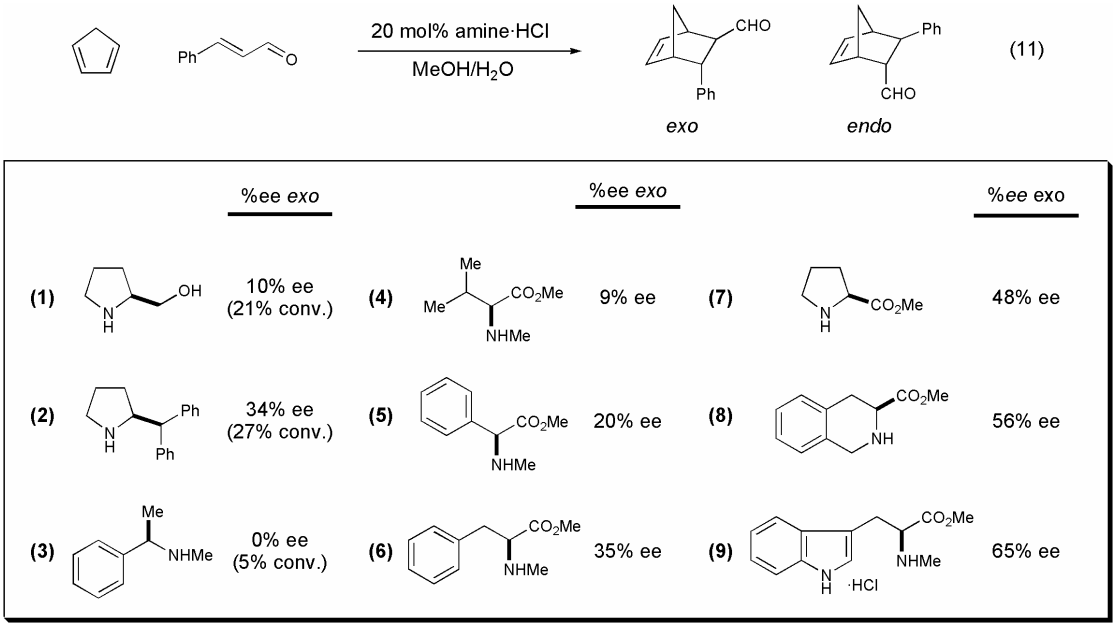
All initial investigations of the organocatalytic Diels-Alder reaction were performed at 1.0 M concentration, based on the limiting reagent. Examination of concentration effects showed that decreased concentrations increased the reaction time without improving selectivity, and increased concentrations eroded the enantioselectivity of the process. As a result of this determination, all subsequent studies were also performed at a concentration of 1.0 M relative to the limiting reagent.

Investigation of Catalyst Architecture

Using the previously developed reaction conditions, a variety of chiral amine salts were examined to assess the chemical and structural requirements of potential catalysts. These initial studies with commercially available chiral amines led to some useful observations. All primary amines studied proved to be poor catalysts of the Diels-Alder reaction, exhibiting both low conversions and selectivities (data not shown). Relatively

basic secondary amines (Table 4, entries 1-3) showed only poor to moderate levels of reactivity and poor selectivity. Less basic secondary amine catalysts, such as those amines containing an α-ester group, all showed good levels of conversion (Table 4, entries 4-9). Among the most selective catalysts were those containing a cyclic secondary amine proximal to an electron withdrawing group (Table 4, entries 7 and 8).

Table 4. Organocatalytic Diels-Alder reaction between cyclopentadiene and cinnamaldehyde with representative amine catalysts.[a]



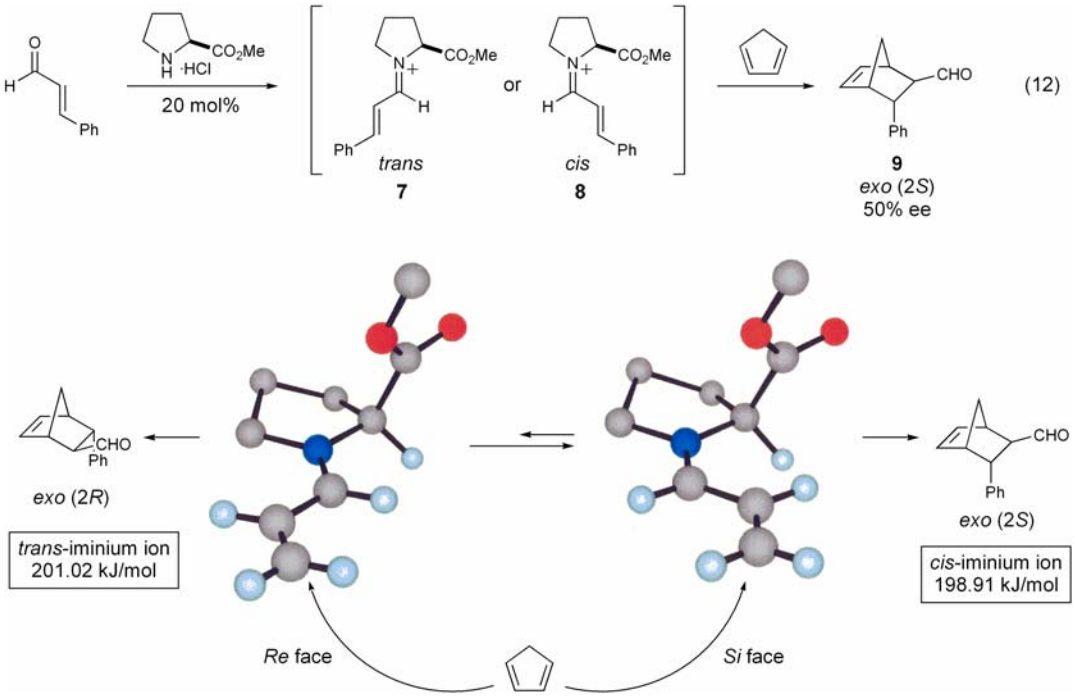
[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); Conversion and enantioselectivity determined by GLC analysis.

This finding is in agreement with the observation that less basic amines more readily form iminium ions with aldehydes.[31] Presumably, the most reactive amine catalysts are nucleophilic enough to form iminium ions at a rate faster than the subsequent cycloaddition reaction, and the iminium ions formed from those catalysts are electron-deficient enough to be activated towards the cycloaddition. It is interesting to note that the most successful catalyst discovered, abrine (Table 4, entry 9), is not a cyclic

secondary amine. This prompted a computational investigation into the organocatalytic Diels-Alder reaction in an effort to understand the important aspects of catalyst architecture.

Molecular Modeling of Amine Catalysts

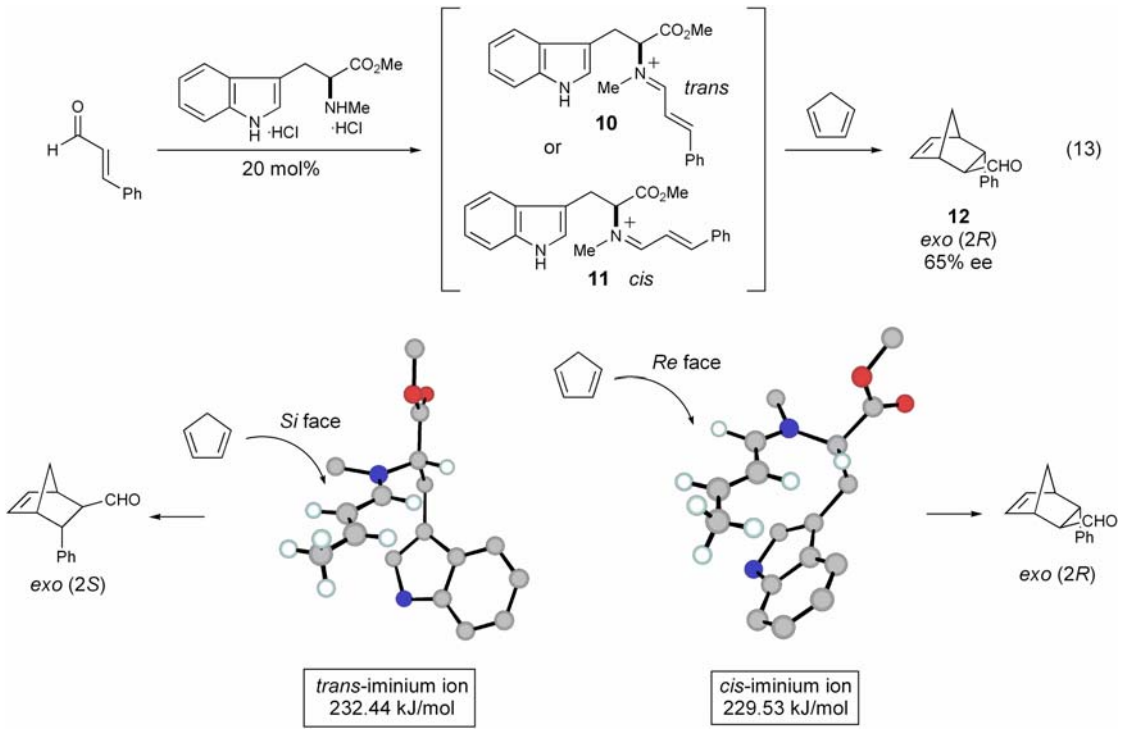
Scheme 5. Calculated iminium ion structures for the iminium ion formed from proline methyl ester.



The first successful amine catalyst for the organocatalytic Diels-Alder reaction, the methyl ester of proline, was the catalyst chosen for the initial computational studies (Scheme 5). The condensation of an α,β-unsaturated aldehyde with the methyl ester of proline can yield one of two possible iminium ions (**7** or **8**), depending on the geometry of the C-N double-bond. The conformation of these two possible iminium ions was calculated, and the geometry and energies of the two ions were compared.[32] The two

iminium ions were calculated to have different heats of formation, therefore different stabilities, and each iminium ion shields a different π-enantioface of the reactive olefin. The geometry of each of the two iminium ions leads to preferential cycloaddition through opposite enantiofaces of the reactive olefin. The iminium ion with the lowest calculated energy (**8**) correctly predicts the observed sense of enantioinduction (**9**), suggesting the geometry of the iminium ion to play an important role.

Scheme 6. Calculated iminium ion structures for the iminium ion formed from proline methyl ester.



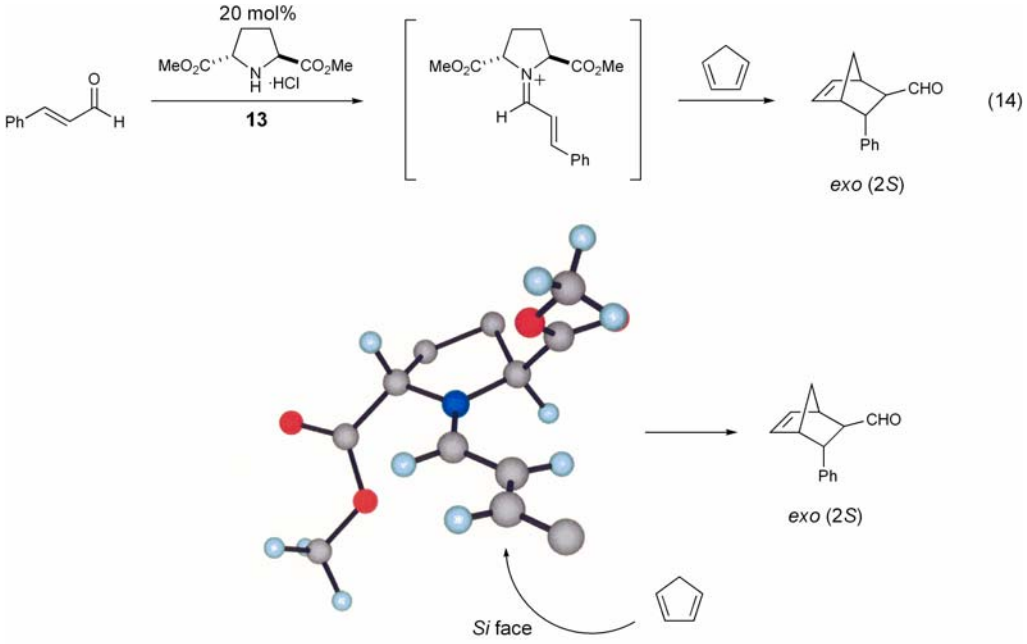
A similar study was conducted with the most selective catalyst discovered, abrine (Scheme 6).[32] An iminium ion formed from an α,β-unsaturated aldehyde and abrine can also form with one of two possible geometries, one with the reactive olefin oriented *trans* to the chiral center of abrine (**10**) and one with the reactive olefin oriented *cis* to the

chiral center of abrine (**11**). These two iminium ions are also calculated to have different heats of formation, and each iminium ion shields a different π-enantioface of the reactive olefin. This leads to the formation of a different product enantiomer from each reactive iminium ion, and the iminium ion with the lowest calculated energy (**11**) correctly predicts the observed sense of enantioinduction (**12**).

These two calculations suggest that the geometry of the reactive iminium ion is the controlling factor in determining the sense of enantioinduction observed in the organocatalytic Diels-Alder reaction. The close energy of the iminium ions calculated in each case (about 2 and 3 $kJ \cdot mol^{-1}$, respectively) suggests that both iminium ion geometries are intermediates in the cycloaddition. In an effort to improve the selectivity of the process, investigations into the control of iminium ion geometry were undertaken.

An obvious method of iminium ion geometry control is through symmetry. If a C_2-symmetric secondary amine were employed as the catalyst, there could be only one possible iminium ion, since the two geometric isomers are degenerate. Macromodel calculations supported this hypothesis, and suggested the same sense of enantioinduction as observed with the proline methyl ester catalyst (Scheme 7).[32]

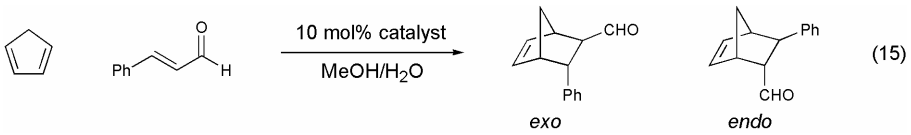
Scheme 7. Calculated iminium ion geometry for the iminium ion formed from a C_2-symmteric catalyst.



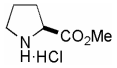
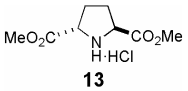
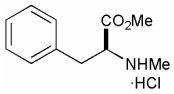
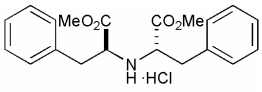
Investigation of C_2-Symmetric Catalysts

C_2-Symmetric catalysts were synthesized to test the importance of iminium ion geometry control as an important element of enantiocontrol. A C_2-symmteric derivative of proline methyl ester **13** was synthesized according to literature procedures,[33,34] and a C_2-symmetric derivative of phenylalanine methyl ester **14** was also synthesized.[35] These catalysts did show an improvement in enantioselectivity relative to their parent structures (Table 5). The phenylalanine-derived catalyst showed a significant improvement in selectivity, but at the cost of an extremely long reaction time (Table 5, entry 4).

Table 5. Examination of C_2-symmetric amine catalysts on the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.[a]

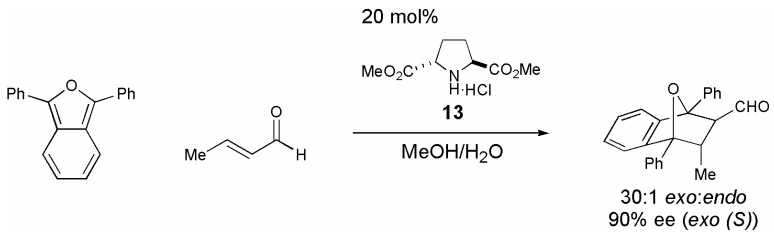


(15)

Entry	Catalyst	Time (h)	% yield	*exo:endo*[b]	% ee *exo*[b]
1		27	81	2.7:1	48
2	 **13**	23	92	2.6:1	57
3		20	80	2.2:1	35
4	 **14**	84	82	3.6:1	74

[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); [b] Product ratios and enantioselectivity determined by GLC analysis.

Further studies with the C_2-symmetric proline derivative **13** showed that this catalyst did provide adequate enantiofacial discrimination with some dienes (equation 16). While the improvement in enantioselectivity with the C_2-symmetric catalysts was significant, these catalysts were not in line with our original goal of developing chiral organocatalysts accessible directly or easily from the chiral pool. The syntheses of the C_2-symmetric catalysts were not simple and involved multiple steps.[33-35]

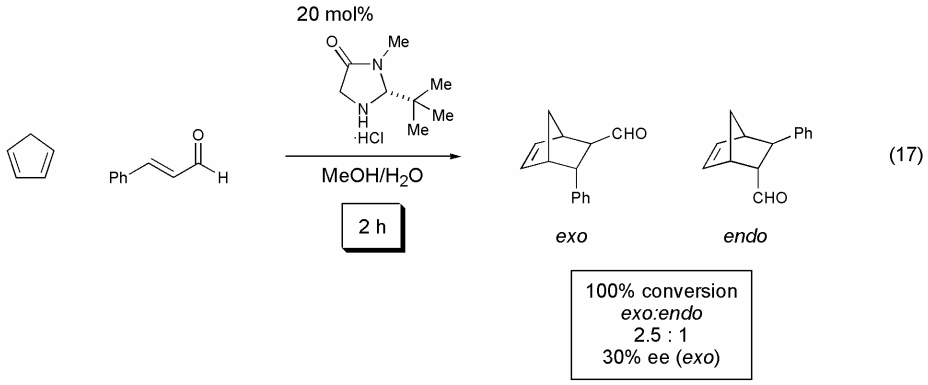


(16)

Investigation of Imidazolidinone Catalysts

The ideal catalyst for use in the organocatalytic Diels-Alder reaction must form only one iminium ion and completely block one π-enantioface of the reactive olefin. This catalyst must form iminium ion quickly, and it must be easily accessible from inexpensive, readily available chiral starting materials. With these design factors in mind, we examined the sterics of catalyst architecture as a means of iminium ion geometry control.

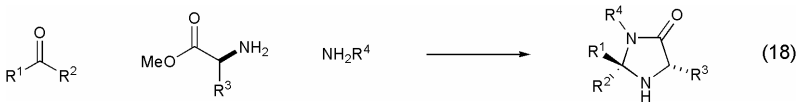
Imidazolidin-4-one catalysts were a particularly promising architecture. This chemotype has been extensively described in the literature, and has been used successfully as a chiral auxiliary.[36-39] Initial results with this catalyst architecture had also shown that this structure exhibits excellent reactivity in the organocatalytic Diels-Alder reaction (equation 17).



(17)

The imidazolidin-4-one heterocycle possesses many features that are desirable in an organocatalyst. The nucleophilic nitrogen is incorporated within a five-membered ring, and the ring contains an α-electron-withdrawing carbonyl moiety. These are both features discovered to be beneficial for organocatalysts in the initial catalyst architecture

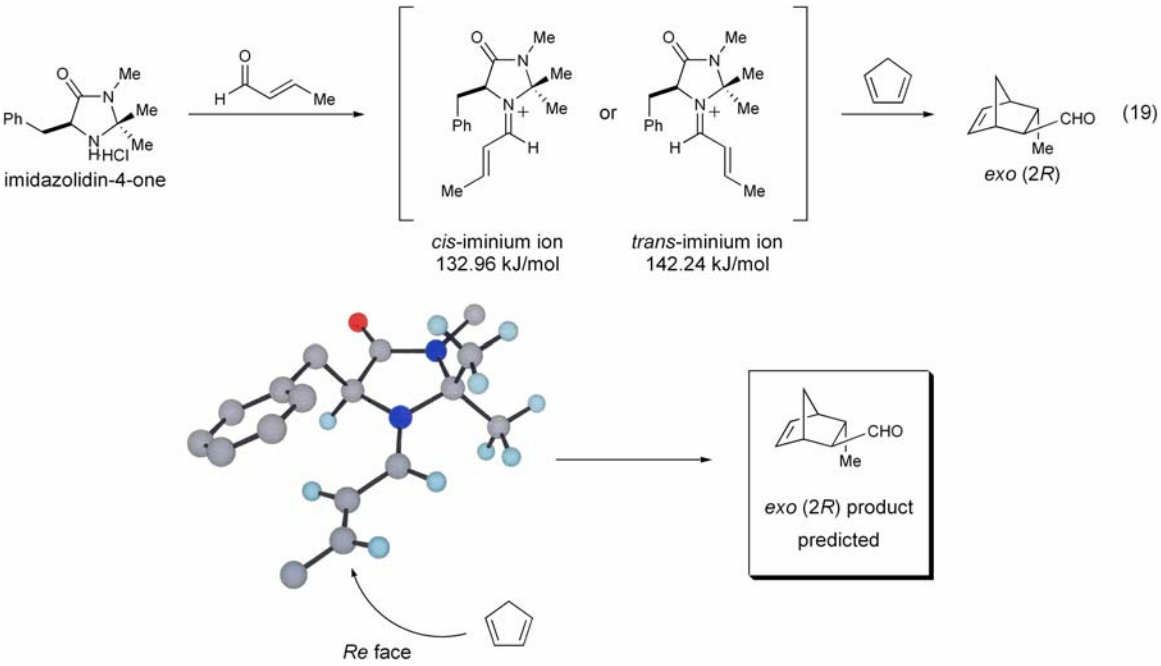
study (Table 4). In addition, the imidazolidin-4-one heterocycle is easily synthesized from an amino acid, ketone or aldehyde, and primary amine, allowing for great structural diversity (equation 18).



(18)

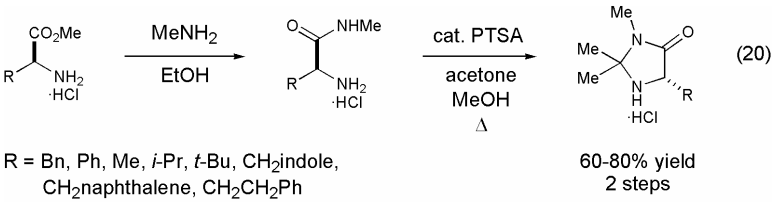
Molecular modeling of this catalyst chemotype showed that it would be possible to select for one iminium ion geometry by taking advantage of steric interactions within the catalyst substrate adduct (Scheme 8).[32] By placing a geminal dimethyl group in the 2-position on the imidazolidin-4-one ring, the reactive olefin is partitioned into one of the two possible iminium ion geometries. The calculated energy difference between the two possible iminium ion geometries is almost 10 $kJ \cdot mol^{-1}$, indicating the significance of this steric interaction. Molecular modeling also suggested a benzyl group in the 5-position would be properly disposed to fully shield one π-enantioface of the reactive olefin.

Scheme 8. MM3 calculations predict 2,2-dimethyl-imidazolidin-4-ones to be effect organocatalysts for the Diels-Alder transformation.



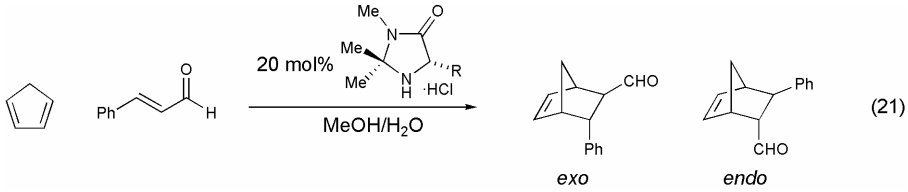
Because of the promising reactivity shown by the 2-*tert*-butyl-imidazolidin-4-one catalyst (equation 17) and because of the promising level of iminium ion geometry control suggested by calculations (Scheme 8), a variety of 2,2-dmethyl-imidazolidin-4-one catalysts were synthesized for examination (Scheme 9). These catalysts were easily accessed via amino amide formation from methyl amine and the corresponding amino methyl ester. The amino amides could be cyclized in refluxing acetone in the presence of a catalytic amount of PTSA. The imidazolidinone catalysts were isolated as HCl salts for examination as organocatalysts of the Diels-Alder reaction.

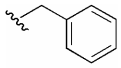
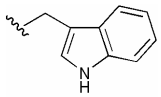
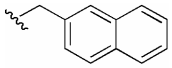
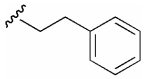
Scheme 9. Synthesis of imidazolidinone catalysts.



The Diels-Alder reaction between cinnamaldehyde and cyclopentadiene was examined using the various imidazolidinones as catalysts (Table 6). The nature of the substituent at the 5-position plays a critical role in the enantioselectivity of the transformation. Catalysts with aliphatic side chains at the 5-position showed poor to modest levels of enantioselectivity (30-67% ee; Table 6, entries 1-3). Consistent with the prediction derived from molecular modeling, the phenylalanine-derived catalyst **19** (Table 6, entry 5) showed very good enantioselectivity (93% ee, *exo*; 93% ee, *endo*). Also consistent with the prediction from the molecular modeling, catalysts possessing a methylene spacer and aromatic group at the 5-position showed excellent enantioselectivity (90-93% ee, *exo*; 88-93% ee, *endo*; Table 6, entries, 5-7). The size of this spacing group is important, for when it is shortened by one carbon unit (Table 6, entry 4) or extended by one carbon (Table 6, entry 8), the enantioselectivity of the reaction suffers significantly (10% ee, *exo* and 46% ee, *exo*, respectively).

Table 6. Effect of imidazolidinone catalyst structure on cinnamaldehyde cyclopentadiene Diels-Alder cycloaddition.[a]

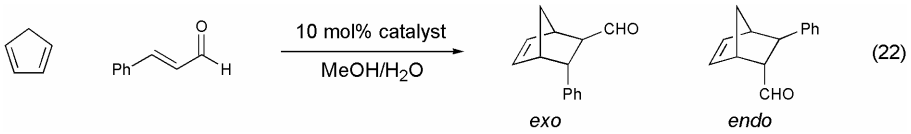


Entry	R	*exo:endo*[b]	%ee *exo*[b]	%ee *endo*[b]
1	Me **15**	1.5:1	30	58
2	*i*-Pr **16**	1.4:1	51	67
3	*t*-Bu **17**	1:1.3	45	27
4	Ph **18**	2.2:1	10	30
5	 **19**	1.3:1	93	93
6	 **20**	1.2:1	92	90
7	 **21**	1.3:1	90	88
8	 **22**	2.0:1	46	61

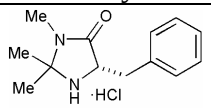
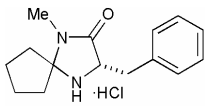
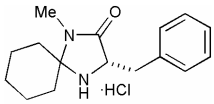
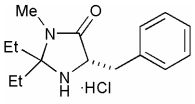
[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); [b] Product ratios and enantioselectivity determined by GLC analysis.

Variants of the benzyl imidazolidinone catalyst **19** were synthesized with different geminal dialkyl substituents in an attempt to improve the *exo:endo* ratios of the organocatalytic Diels-Alder reaction. The cycloaddition between cinnamaldehyde and cyclopentadiene was examined with these catalysts (Table 7). In all cases, no improvement in diastereoselectivity or enantioselectivity was observed.

Table 7. Examination of geminal dialkyl substituents on the benzyl imidazolidinone-catalyzed Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.[a]



(22)

Entry	Catalyst	*exo:endo*[b]	% ee *exo*[b]	% ee *endo*[b]
1	 **19**	1.3:1	93	93
2	 **23**	1:1	89	89
3	 **24**	1:1	79	61
4	 **25**	1:1	53	53

[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); [b] Product ratios and enantioselectivity determined by GLC analysis.

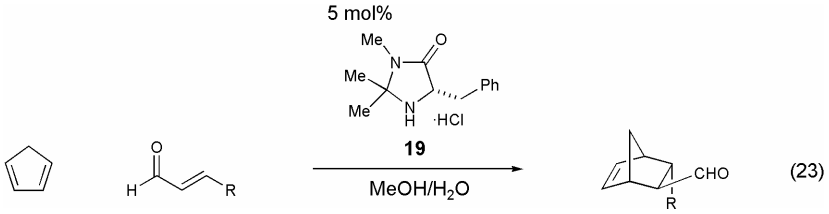
Reaction Scope

With an optimized organocatalyst for the Diels-Alder reaction identified, the ability of imidazolidinone **19** to catalyze a range of cycloadditions was examined. All reactions were performed under a wet, aerobic atmosphere in the presence of added water

and at temperatures no lower than -10 °C. This is in contrast to Lewis acid-catalyzed Diels-Alder reactions, most often performed at -78 °C and always performed under a dry atmosphere.

Variation of the α,β-unsaturated aldehyde component of the Diels-Alder reaction was first examined (Table 8). Changes in steric demand at the β-position of the α,β-unsaturated aldehyde were well-tolerated (Table 8, entries 1-4), and the reaction is also tolerant of aromatic α,β-unsaturated aldehydes (Table 8, entries 4 and 5). All substrates exhibited excellent yields and enantioselectivities.

Table 8. Organocatalytic Diels-Alder reaction between cyclopentadiene and representative α,β-unsaturated aldehydes.[a]



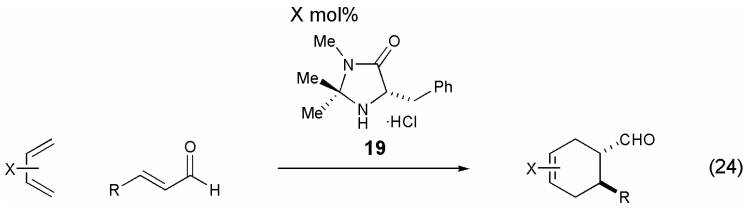
(23)

Entry	R	Time (h)	% yield	*exo*:*endo*[b]	% ee *exo*[b]	% ee *endo*[b]
1	Me	16	75	1:1	86	90
2	*n*-Pr	14	92	1:1	86	90
3	*i*-Pr	14	81	1:1	84	93
4	Ph	21	99	1:1	93	93
5	furyl	24	89	1.3:1	91	93

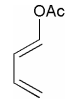
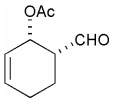
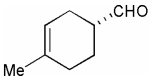
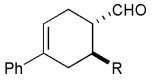
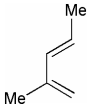
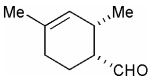
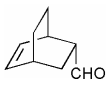
[a] All reactions performed with 5% (v/v) water; [b] Product ratios and enantioselectivity determined by GLC analysis.

The organocatalytic Diels-Alder reaction was also shown to be general with respect to the diene component of the reaction (Table 9). It was shown that less reactive dienes in addition to cyclopentadiene undergo the Diels-Alder cycloaddition with good yields and excellent selectivities (72-90% yield, 83-94% ee). All dienes examined, except cyclopentadiene, showed preference for the *endo* cycloadduct.

Table 9. Organocatalytic Diels-Alder reaction with representative dienes.[a]



(24)

Entry	Diene	R	mol% catalyst	% yield	product	*exo*:*endo*[b]	% ee[b]
1		H	10	72[c]		1:11	85[d]
2		H	20	84		--	89
3		H	10	90		--	83
4		Me	10	75		--	90
5		H	20	75		1:5	90[d]
6		H	5	82		1:14	94[c]

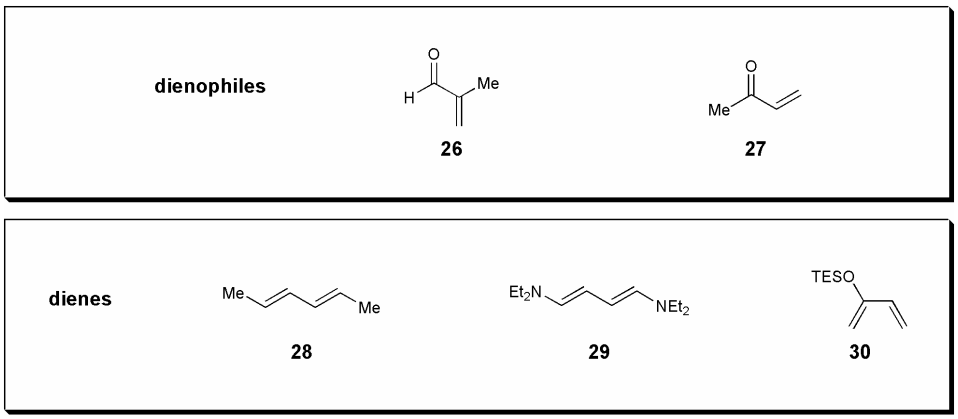
[a] Reactions performed with 5% (v/v) water; [b] Product ratios and enantioselectivity determined by GLC; [c] yield determined by GLC; [d] *endo* ee

Limitations

Unfortunately, not all substrates studied proved to be compatible with the organocatalytic reaction conditions (Figure 2). α,β-Unsaturated aldehydes possessing an α-substituent (**26**) and α,β-unsaturated ketones (**27**) are not amenable to the

organocatalytic Diels-Alder reaction. These substrates react with cyclopentadiene to yield cycloadducts in poor enantioselectivities and significantly increased reaction times. It is believed that these substrates do not form significant concentrations of reaction iminium ion either due to $A^{1,3}$-strain or the lower carbonyl reactivity, respectively.

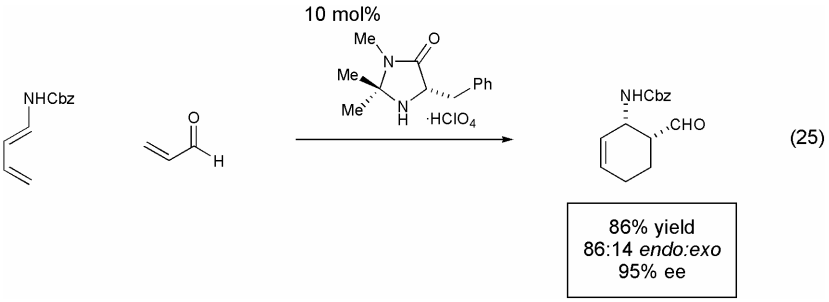
Figure 2. Substrates not able to participate in the organocatalytic Diels-Alder reaction.



Similarly, several dienes studied did not participate in the organocatalytic Diels-Alder reaction (Figure 2). 2,4-Hexadiene (**28**) was found to be of insufficient reactivity to participate in the organocatalytic Diels-Alder reaction with acrolein, the most reactive dienophile examined. At the other end of the spectrum, the 1,4-diamino-diene (**29**) studied proved too reactive for the organocatalytic Diels-Alder reaction conditions, oligomerizing almost instantly when introduced to the acidic reaction medium. Enol silanes also proved to be incompatible substrates for the organocatalytic cycloaddition. Enol silane (**30**) underwent acid catalyzed decomposition to the corresponding carbonyl compound under all reaction conditions examined.

Further studies conducted in the MacMillan lab by Catharine Larsen have demonstrated the benefit of varying the acidity of the co-catalyst used in the

organocatalytic Diels-Alder reaction.[40] By using co-catalyst acids of varying pK_a's, slightly higher selectivities can be achieved in the demonstrated transformations, and amine-containing dienes can be utilized as substrates (equation 25).

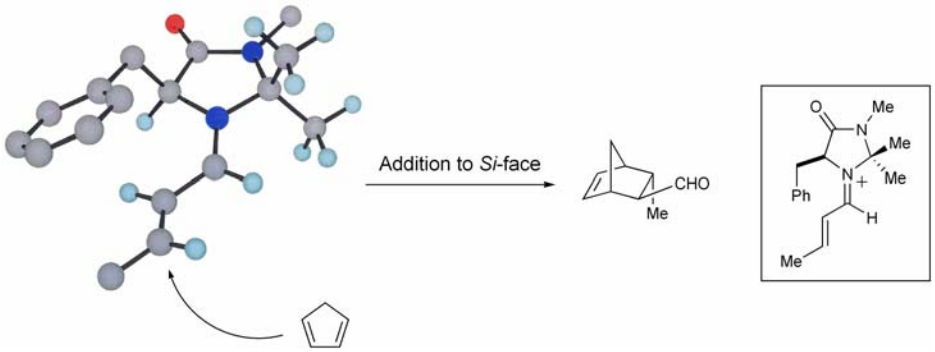


(25)

Stereochemical Rationale

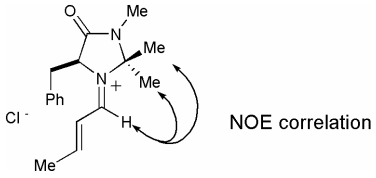
The stereochemistry observed in the organocatalytic Diels-Alder reaction is consistent with the calculated iminium ion (Scheme 10). The (*E*)-iminium ion isomer is enforced by the presence of the geminal dimethyl substitution on the imidazolidinone framework, and this control over the iminium ion geometry disposes the reactive olefin properly to have one enantioface shielded by the benyl group in the 5-position. This combination of control elements effectively shields the *Re*-face of the olefin and allows the cycloaddition to occur on the exposed *Si*-face. It is believed that favorable catalyst-substrate interactions exist between the 5-benzyl group of the imidazolidinone and the activated olefin, but the calculations performed in this study do not take these interactions into account.[32,41]

Scheme 10. The calculated imidazolidinone-derived iminium ion predicts the enantioselectivity of the organocatalytic Diels-Alder reaction.



nOe experiments performed by Kateri Ahrendt support the calculated iminium ion model.[42] Condensation of the imidazolidinone catalyst **19** with a variety of α,β-unsaturated aldehydes in deuterated solvents yields concentrations of a single iminium ion that can be observed by ^{1}H NMR. These iminium ions have been shown to adopt the (*E*)-configuration about the C-N double bond, consistent with the calculated structure (Figure 3).

Figure 3. Solution phase conformation of the imidazolidinone (**19**)-derived iminium ion as determined by ^{1}H NOE.



III. Conclusion

The first asymmetric organocatalytic Diels-Alder reaction has been described herein. Using a chiral imidazolidinone salt, Diels-Alder cycloadducts of α,β-unsaturated aldehydes and dienes can be accessed in good yields and high selectivities. The developed methodology has demonstrated the utility of a secondary chiral amine to function as a catalyst in a manner similar to Lewis acid catalysts, namely, through LUMO-lowering catalysis. This discovery demonstrates that organocatalysis should be possible for a wide variety of chemical transformations, including transformations not possible using Lewis acid catalysis.

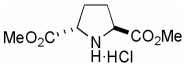
IV. Experimental Section

General Information. All solvents were used as obtained from commercial suppliers unless otherwise indicated. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[43] Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, $KMnO_4$ stain, or *para*-anisaldehyde stain. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[44]

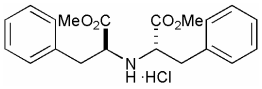
^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHZ and 125 MHz, respectively), AM-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ^{13}C are reported in terms of chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the University of California, Berkeley Microanalytical Services facility. Gas chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm), Bodman Chiraldex β-PH (30 m x 0.25 mm), and C&C Column Technologies CC-1701 (30 m x 0.25 mm).

HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254 nm, using a Chiracel OD-H (25 cm) column and Chiralcel OD guard column (5 cm).

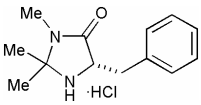
Progress of the Diels-Alder reaction was typically monitored by TLC analysis, or in cases where necessary, ^{1}H NMR analysis of the reaction *in situ* in deuterated solvent or by GLC analysis of reaction aliquots.



(2*S*, 5*S*)-pyrrolidine-2,5-dicarboxylic acid dimethyl ester hydrochloride (13). The title compound was prepared as described in the literature.[33,34] All spectra were in agreement with those previously reported.



(2*S*)-2-((1*S*)-1-Methoxycarbonyl-2-phenyl-ethylamino)-3-phenyl-propionic acid methyl ester hydrochloride (14). The title compound was prepared as described in the literature.[35] All spectra were in agreement with those previously reported.

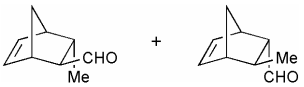


(5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (19). A solution of phenylalanine methyl ester hydrochloride (26.0 g, 121 mmol) and ethanolic $MeNH_2$ (8.0 M, 60 mL) was stirred at room temperature until the amino ester was consumed as determined by TLC (20 hr). After removal of the organic solvents *in vacuo*, the residue was suspended in Et_2O and then concentrated. This procedure was repeated twice to provide solid (*S*)-phenylalanine N-methyl amide hydrochloride. The amide hydrochloride was then treated with sat. $NaHCO_3$ and the free amine was extracted

with $CHCl_3$ (3x), dried (Na_2SO_4), filtered, and concentrated. To the residue was added MeOH (240 mL), acetone (45 mL, 605 mmol), and pTSA (230 mg, 1.2 mmol). The solution was heated to reflux for 18 hr, cooled to room temperature, and then concentrated *in vacuo*. The residue was dissolved in Et_2O, and a solution of HCl in dioxane (4.0 M) was added to precipitate (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride. The precipitate was recrystallized from isopropanol to provide colorless crystals of the title compound in a 59% overall yield from phenylalanine methyl ester hydrochloride (18.1 g, 71 mmol). IR (CH_2Cl_2) 3366, 1722, 1644 cm^{-1}; ^1H NMR: (400 MHz, d_6-DMSO) δ 7.47-7.49 (d, *J* = 7.2 Hz, 2H, Ph**H**), 7.32-7.36 (m, 2H, Ph**H**), 7.25-7.29 (m, 1H, Ph**H**), 4.59-4.57 (br d, *J* = 7.6 Hz, 1H, COCH), 3.35-3.42 (dd, *J* = 15.0, 10.2 Hz, 1H, PhC**H**H), 3.22-3.26 (dd, *J* = 15.0, 3.6 Hz, 1H, PhCH**H**), 2.76 (s, 3H, NCH_3), 1.70 (s, 3H, CHC**H**$_3$$CH_3$), 1.50 (s, 3H, $CHCH_3$C**H**$_3$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.9, 136.8, 129.7, 128.8, 127.2, 77.1, 57.7, 33.2, 25.2, 23.9, 22.2. HRMS (EI) exact mass calcd for ($C_{13}H_{19}N_2O$) requires *m/z* 219.1497, found *m/z* 219.1487. The enantiopurity was confirmed (>99% ee) by HPLC analysis of the free amine (OD-H and OD guard, 6% isopropanol in hexanes, 1 mL/min); (*S*)-enantiomer t_r = 14.1 min, (*R*)-enantiomer t_r = 16.6 min.

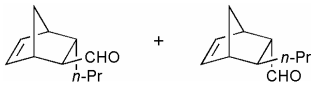
General Procedure for the Organocatalytic Diels-Alder Reaction: To a solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** in wet methanol (5% water) was added the α,β-unsaturated aldehyde (1M). After stirring for 1-2 minutes, diene was added to the solution. Upon consumption of the limiting reagent, as judged by TLC, ^1H NMR, or GLC analysis, the reaction mixture was diluted into ether (10 mL) and

washed successively with water (10 mL) and brine (10 mL). The aqueous layer was extracted twice with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting concentrate was then rapidly stirred in TFA:H_2O:$CHCl_3$ (1:1:2, 4 mL) for 2 hr at room temperature followed by neutralization with saturated aqueous $NaHCO_3$ and extraction with ether. Purification of the Diels-Alder adduct was performed using silica gel chromatography.



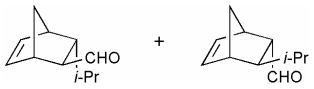
(1*S*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde and (1*R*, 2*R*, 3*S*, 4*S*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Table 8, entry 1). Prepared according to general procedure A from crotonaldehyde (871 μL, 10.0 mmol) and cyclopentadiene (2.5 mL, 30.0 mmol), using 5 mol% (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (109 mg, 0.5 mmol). Hydrolysis of the crude product mixture after 16 h followed by silica gel chromatography (3% EtOAc/Hex) afforded the title compound in 75% yield (1.02 g, 7.5 mmol) as a 1.0/1.0 mixture of *endo* (90% ee) and *exo* (86% ee) isomers. The ee's and exo/endo ratio were determined by GLC with a Bodman Γ-TA column (50 ^{o}C, 2 ^{o}C/min gradient, 23 psi); (1*S*, 2*S*, 3*S*, 4*R*) *endo* adduct t_r = 24.7 min, (1*R*, 2*R*, 3*R*, 4*S*) *endo* adduct t_r = 25.0 min, *exo* adducts t_r = 22.4 min, 22.9 min. Characterization data for the endo adduct were consistent with those reported in the literature.[45] The absolute configuration of the *endo* adduct was established by reduction to the alcohol (4 equiv $NaBH_4$ in MeOH) and comparison of the optical rotation with reported data.[46] *Exo* isomer: IR (CH_2Cl_2) 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 2.8 Hz, 1H, CHO), 6.23-6.25 (dd, *J* = 5.7, 3.1 Hz, 1H,

C**H**=CH), 6.15-6.17 (dd, *J* = 5.7, 3.0 Hz, 1H, CH=C**H**), 3.02 (br s, 1H, C**H**CH=CH), 2.79 (br s, 1H, CHCH=C**H**), 2.37-2.45 (m, 1H, C**H**CHO), 1.70-1.73 (m, 1H, C**H**CH_3), 1.44-1.48 (m, 2H, C**H**H), 0.89-0.91 (d, *J* = 6.9 Hz, CHC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 136.3, 135.9, 60.0, 47.5, 47.4, 45.3, 35.7, 18.8; LRMS (EI) *m/z* 136 $(M)^+$; HRMS (EI) exact mass calcd for ($C_9H_{12}O$) requires *m/z* 136.0888, found *m/z* 136.0892.



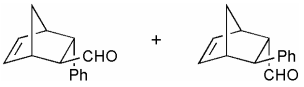
(1*S*, 2*R*, 3*S*, 4*R*)-3-Propyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*R*, 3*S*, 4*S*)-3-propyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 2). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride (16 mg, 0.061 mmol), *trans*-hex-2-enal (142 μL, 1.22 mmol), and cyclopentadiene (302 μL, 3.66 mmol). The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the product in 92% yield (184 mg, 1.12 mmol) as a colorless oil; 1:1 *exo:endo*; *Exo* 86% ee; *Endo* 90% ee. *Exo* isomer: IR (CH_2Cl_2) 3060, 2960, 2924, 2872, 2710, 1719, 1466, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.7 Hz, 1H, C**H**O), 6.19 (dd, *J* = 5.6, 3.2 Hz, 1H, vinyl), 6.11 (dd, *J* = 5.6, 2.9 Hz, 1H, vinyl), 3.00 (br s, 1H, allyl), 2.85 (br s, 1H, allyl), 2.23-2.30 (m, 1H, methylene), 1.72-1.76 (m, 1H, CHOC**H**), 1.00-1.47 (m, 6H, methylene, C**H**C**H**$_2$C**H**$_2$$CH_3$), 0.86 (t, *J* = 7.2 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 136.0, 135.9, 58.7, 47.0, 45.7, 44.8, 41.6, 36.4, 21.6, 14.1; LRMS (EI) *m/z* 164 $(M)^+$; HRMS (EI) exact mass calcd for ($C_{11}H_{16}O$) requires *m/z* 164.1201, found *m/z* 164.1200; $[\alpha]_D$ = + 89.4 °. The e*ndo* isomer exhibited spectral data identical in all respects to those reported.[45] Diastereomer ratios were determined by ^{1}H NMR analysis.

Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (100 °C isotherm, 23 psi); *exo* adduct t_r = 25.6 min and 26.7 min, *endo* adduct t_r = 30.1 min and 30.1 min.

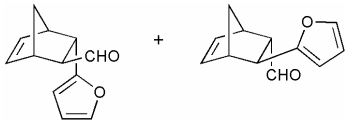


(1*S*, 2*S*, 3*S*, 4*R*)-3-Isopropyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-isopropyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 3). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (16 mg, 0.061 mmol), 4-methyl-pent-2-enal (142 μL, 1.22 mmol), and cyclopentadiene (302 μL, 3.66 mmol). The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product in 81% yield (162 mg, 0.99 mmol) as a colorless oil; 1.3:1 *exo:endo*; *Exo* 84% ee; *Endo* 93% ee. *Exo* isomer: IR (CH_2Cl_2) 3061, 2957, 2871, 2809, 2711, 1719, 1465, 1386, 1368, 1336 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 2.6 Hz, 1H, C**H**O), 6.19 (dd, *J* = 5.6, 3.1 Hz, 1H, vinyl), 6.15 (dd, *J* = 5.6, 2.8 Hz, 1H, vinyl), 3.02 (br s, 1H, allyl), 2.96 (br s, 1H, allyl), 1.84-1.92 (m, 2H, CHOC**H** and methylene), 1.38-1.47 (m, 2H, C**H***i*Pr, and methylene), 0.97-1.08 (m, 1H, C**H**$(CH_3)_2$), 0.94 (d, *J* = 6.2, 3H, CH(C**H**$_3$)(CH_3)), 0.84 (d, *J* = 6.4, 3H, CH(CH_3)(C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 136.2, 135.7, 57.9, 50.2, 46.9, 45.0, 44.9, 32.4, 22.0, 21.5; LRMS (EI) *m/z* 164 $(M)^+$; HRMS (EI) exact mass calcd for ($C_{11}H_{16}O$) requires *m/z* 164.1201, found *m/z* 164.1202; $[\alpha]_D$ = + 98.6 °. *Endo* isomer: IR (CH_2Cl_2) 3060, 2956, 2873, 2808, 2715, 1719, 1469, 1456, 1387, 1368, 1333 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 3.4 Hz, 1H, C**H**O), 6.26 (dd, *J* = 5.7, 3.2 Hz, 1H, vinyl), 6.06 (dd, *J* = 5.7, 2.8 Hz, 1H, vinyl),

3.11 (m, 1H, allyl), 2.85 (m, 1H, allyl), 2.49 (m, 1H, C**H**CHO), 1.41-1.52 (m, 3H, C**H***i*Pr and methylene), 1.29-1.35 (m, 1H, C**H**$(CH_3)_2$), 1.01 (d, J = 6.5 Hz, 3H, CH(C**H**$_3$)(CH_3)), 0.91 (d, J = 6.6 Hz, 3H, CH(CH_3)(C**H**$_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 138.9, 133.0, 58.6, 50.0, 46.5, 45.2, 45.1, 32.8, 21.9, 21.8; LRMS (EI) *m/z* 164 $(M)^+$; HRMS (EI) exact mass calcd for ($C_{11}H_{16}O$) requires *m/z* 164.1201, found *m/z* 164.1198; $[\alpha]_D$ = + 47 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (100 °C isotherm, 23 psi); *exo* adduct t_r = 25.5 min and 27.2 min, *endo* adduct t_r = 29.7 min and 30.5 min.

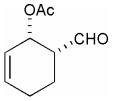


(1*S*, 2*S*, 3*S*, 4*R*)-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Table 8, entry 4). Prepared according to the general procedure from cinnamaldehyde (252 μL, 2.0 mmol) and cyclopentadiene (495 μL, 6.0 mmol), using 5 mol% (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (21.8 mg, 0.1 mmol). Hydrolysis of the crude product mixture after 21 h followed by silica gel chromatography (10% EtOAc/Hex) afforded the title compound in 89% yield (294 mg, 1.8 mmol) as a 1.0/1.3 mixture of *endo* (91% ee) and *exo* (92% ee) isomers. The ee's and exo/endo ratio were determined by GLC with a Bodman B-PH column (60 ^{o}C, 1.5 ^{o}C/min gradient, 23 psi); *endo* adducts t_r = 53.1 min, 53.4 min, *exo* adducts t_r = 52.2 min, 52.7 min. All spectra obtained were in agreement with those previously published.[45]

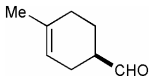


(1*S*, 2*S*, 3*S*, 4*R*)-3-Furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 5). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (34 mg, 0.13 mmol), 3-furyl-acrolein (166 mg, 1.36 mmol), and cyclopentadiene (329 μL, 3.99 mmol). The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the product as a mixture of acetal and aldehyde (5.7:1, 270 mg) as a colorless oil in 88% yield; 1:1.1 *exo:endo*; *Exo 91*% ee; *Endo* 93% ee. A sample of aldehyde was purified by preparatory HPLC for characterization. *Exo* isomer: IR (CH_2Cl_2) 2974, 2878, 2827, 2724, 1717, 1506, 1456, 1334 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.90 (d, *J* = 1.7 Hz, 1H, C**H**O), 6.29 (dd, *J* = 5.6, 3.2 Hz, 1H, vinyl), 6.23 (dd, *J* = 3.1, 1.9 Hz, 1H, furyl), 6.05 (dd, *J* = 5.6,2.9 Hz, 1H, vinyl), 5.89 (d, *J* = 3.2, 1H, furyl), 3.70 (t, *J* = 4.3 Hz, 1H), 3.26 (br s, 1H), 3.20 (br s, 1H), 2.50 (d, *J* = 5.1 Hz, 1H), 1.57 (br s, 1H), 1.55-1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 156.9, 141.1, 136.6, 136.2, 110.0, 105.0, 58.2, 46.9, 46.9, 44.9, 39.1; HRMS (EI) exact mass calcd for ($C_{12}H_{12}O_2$) requires *m/z* 188.0837, found *m/z* 188.0838; $[\alpha]_D$ = + 230 °. *Endo* isomer: IR (CH_2Cl_2) 2981, 2872, 2824, 2717, 1718, 1506, 1332 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, *J* = 1.9 Hz, 1H, C**H**O), 7.32 (d, *J* = 1.0, 1H, furyl), 6.35 (dd, *J* = 5.6, 3.1 Hz, 1H, vinyl), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H, furyl), 6.13 (dd, *J* = 5.6, 2.7 Hz, 1H, vinyl), 6.07 (d, *J* = 3.2 Hz, 1H, furyl), 3.33 (br s, 1H), 3.13-3.09 (m, 1H), 3.08-3.04 (m, 2H), 1.78 (br d, *J* = 8.7, 1H), 1.59-1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 157.0, 141.3, 138.1, 133.7, 110.1, 105.0, 58.3, 48.5, 47.4, 44.6, 39.7; HRMS (EI) exact mass calcd for ($C_{12}H_{12}O_2$) requires *m/z*

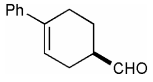
188.0837, found *m/z* 188.0838; $[\alpha]_D$ = + 169 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (70 °C initial temp, 5 °C/min, 23 psi); *exo* adduct t_r = 17.4 min and 17.7 min, *endo* adduct t_r = 17.9 min and 18.1 min.



(1*S*, 6*R*)-Acetic acid 6-formyl-cyclohex-2-enyl ester (Table 9, entry 1). To a solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (27 mg, 0.11 mmol) and 1,4-dimethoxybenzene (50 mg, 0.36 mmol) in wet trifluoroethanol (5% water) was added acrolein (214 μL, 3.21 mmol). After stirring 1 minute, 1-acetoxybutadiene (127 μL, 1.07 mmol) was added to the solution. The solution was stirred until the diene was judged to be completely consumed by GLC analysis on a CC-1701 column (50 °C isotherm for 10 min, then 50 °C/min to 240 °C isotherm, 25 psi); *cis*-1-acetoxybutadiene t_r = 4.5 min, *trans*-1-acetoxybutadiene t_r = 4.7 min, cyclohexa-1,3-dienecarbaldehyde t_r = 12.0 min, 1,4-dimethoxybenzene t_r = 13.0 min, *trans*-acetic acid 6-formyl-cyclohex-2-enyl ester t_r = 13.7 min, *cis*-acetic acid 6-formyl-cyclohex-2-enyl ester t_r = 13.8 min. A yield of 72% was determined by comparison of the peak areas of acetic acid 6-formyl-cyclohex-2-enyl ester and 1,4-dimethoxybenzene; 85% ee. The product exhibited spectral data identical in all respects to those reported for acetic acid 6-formyl-cyclohex-2-enyl ester.[47] Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (100 °C, 1 mL/min) t_r = 34.0 min and 47.9 min.

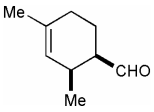


(1*R*)-4-methyl-3-cyclohexene-1-carboxaldehyde (Table 9, entry 2). To a 0 °C solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (32 mg, 0.12 mmol) in wet nitromethane (5% v/v water, 1.0 M) was added acrolein (1.0 mL, 15 mmol), and isoprene (0.50 mL, 5.0 mmol). The solution was stirred at 0 °C for 7 h, then directly placed onto a silica gel column (3% Et_2O/pentane), affording the title compound in 70% yield (621 mg, 3.5 mmol); 87% ee. Spectral data were identical in all respects to those previously reported.[45] Product ratios were determined by GLC analysis (Bodman Γ-TA column, 35 °C, 0.25 °C/min gradient, 23 psi) t_r = 84.1 min and 85.3 min. The absolute configuration of the title compound was determined after xidation to 4-methyl-3-cyclohexene-1-carboxylic acid and correlation of the optical rotation to the reported value. To the aldehyde (260 mg, 2.0 mmol) was added a solution of isobutylene in THF (2.0 M, 30 mL), followed by *t*-BuOH/H_2O (5:1 v/v, 20 mL), KH_2PO_4 (840 mg, 6 mmol), and $NaClO_2$ (540 mg, 6.0 mmol). The mixture was stirred for 4 h, then partitioned between EtOAc and H_2O. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The white solid was purified by silica gel chromatography (20% EtOAc/hexanes) to afford (*R*)-4-methyl-3-cyclohexene-1-carboxylic acid as a white solid in 48% yield (138 mg, 0.98 mmol); $[\alpha]_D$ = + 89 °. Reported specific rotation for (*S*)-4-methyl-3-cyclohexene-1-carboxylic acid; $[\alpha]_D$ = - 107 °.[48]



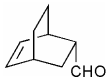
(1*R*)-4-Phenyl-3-cyclohexene-1-carboxaldehyde (Table 9, entry 3). To a 0 °C solution of 2-phenyl-1,3-butadiene[49] (89 mg, 0.68 mmol) in wet nitromethane (5% v/v water, 1.0 M) was added (5*S*)-5-benzyl-2,2,3-

trimethylimidazolidin-4-one hydrochloride (30 mg, 0.14 mmol) and acrolein (135 μL, 2.1 mmol). The solution was stirred at 0 °C for 7 h, then directly placed onto a silica gel column (5% EtOAc/hexanes) affording the title compound as a colorless oil in 89% yield (114 mg, 0.61 mmol, 83% ee). Product ratios were determined by HPLC analysis after conversion to the corresponding alcohol (Chiralcel OD-H column, 6% isopropanol in hexanes, 1 mL/min); t_r = 16.2 and 20.4 min. (1*R*)-4-Phenyl-3-cyclohexene-1-carboxaldehyde: IR (CH_2Cl_2) 2926, 2837, 2714, 1722, 1494, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.40-7.23 (m, 5H, ArH), 6.16-6.12 (m, 1H, vinyl), 2.64-2.50 (m, 5H), 2.23-2.15 (m, 1H), 1.90-1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 141.6, 136.8, 128.2, 126.9, 125.0, 122.0, 45.7, 26.0, 25.0, 22.6; HRMS (EI) exact mass calcd for ($C_{13}H_{14}O$) requires *m/z* 186.1045, found *m/z* 186.1041. Conversion of the aldehyde to the corresponding alcohol was accomplished with excess $NaBH_4$ in MeOH. (1*R*)-4-phenyl-3-cyclohexene-1-ol: IR (CH_2Cl_2) 3374, 3289, 2918, 2860, 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.26-7.22 (m, 1H), 6.13 (br s, 1H), 3.66-3.58 (m, 2H), 2.58-2.41 (m, 2H), 2.40-2.31 (m, 1H), 2.05-1.83 (m, 3H), 1.70 (s, 1H), 1.50-1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 136.5, 128.2, 126.6, 124.9, 123.3, 67.6, 35.9, 28.8, 26.8, 25.7; HRMS (EI) exact mass calcd for ($C_{13}H_{16}O$) requires *m/z* 118.1201, found *m/z* 118.1203.



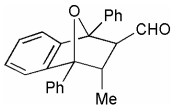
(1*R*, 2*S*)-2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde (Table 9, entry 5). To a -10 °C solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (27 mg, 0.11 mmol) in wet acetonitrile (5% v/v water, 1.0 M) was added acrolein (102 μL, 1.53 mmol). After stirring 1 minute, 2-methyl-1,3-pentadiene

(60 μL, 0.51 mmol) was added to the solution. The solution was stirred for 31 h and then passed through a silica plug (1.5") with 3 mL methylene chloride. To the crude solution of *cis*-2,4-dimethyl-cyclohex-3-enecarbaldehyde in methylene chloride was added (R,R)-2,4-pentanediol (160 mg, 1.54 mmol) and a single crystal of PTSA. The solution was allowed to stand 10 h. The solution was then concentrated and purified by silica chromatography (10% EtOAc/Hexanes) to provide 85 mg of the (R,R)-2,4-pentanediol acetal as a colorless oil (75% yield); 5:1 *endo:exo; endo* adduct 88% ee. The product exhibited spectral data identical in all respects to those previously reported.[45] Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (70 °C initial temp, 3 °C/min gradient, 23 psi) t_r = 24.0 min and 24.9 min.



(2*R*)-Bicyclo[2.2.2]oct-5-ene-2-carbaldehyde (Table 9, entry 6). To a solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (32 mg, 0.12 mmol) in wet acetonitrile (5% v/v water) was added acrolein (501 μL, 7.5 mmol). After stirring 1 minute, cyclohexadiene (238 μL, 2.5 mmol) was added to the solution. The solution was stirred until the diene was judged to be completely consumed by TLC analysis. The reaction mixture was diluted into ether (10 mL) and washed with water (10 mL). The aqueous layer was extracted twice with ether (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by distilling away the ether. The resulting residue was purified by silica gel chromatography (10% ether/pentane) to provide the pure product in 82% yield (280 mg, 2.06 mmol) as a colorless oil; 14:1 *endo:exo; endo* adduct 94% ee. The product exhibited spectral data identical in all respects to those reported for bicyclo[2.2.2]oct-5-ene-2-carbaldehyde.[45]

Enantiomeric excess was determined by GLC alaysis on a Bodman Γ-TA column (75 °C isotherm, 23 psi); *exo* adduct t_r = 51.0 min and 54.4 min.



(1*S*, 8*R*, 9*S*, 10*S*)-1,8-Diphenyl-10-methyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-9-carbaldehyde (equation 16). To a 10 °C solution of (2*S*, 5*S*)-pyrrolidine-2,5-dicarboxylic acid dimethyl ester hydrochloride **13** (13 mg, 0.058 mmol), 1,3-diphenylisobenzofuran (162 mg, 0.60 mmol), and methanol (12 μL, 0.30 mmol) in wet N,N-dimethylformamide (0.5 mL, 5% v/v water) was added crotonaldehyde (25 μL, 0.30 mmol). The solution was stirred at 10 °C until the aldehyde was judged to be completely consumed by TLC analysis (24 h). The reaction mixture was diluted into ether (10 mL) and washed with water (10 mL). The aqueous layer was extracted twice with ether (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel chromatography (7% EtOAc/Hex) to provide the title compound as a yellow solid in 75% yield (76 mg, 0.22 mmol); 35:1 *exo:endo*; *Exo* 96% ee. *Exo* isomer: IR (CH_2Cl_2) 3066, 3041, 2828, 2729, 1722, 1603, 1499, 1457, 1448, 1381, 1355, 1309 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (d, *J* = 5.8 Hz, 1H, C**H**O), 7.73-7.78 (m, 2H, aryl), 7.43-7.57 (m, 7H, aryl), 7.35-7.40 (m, 1H, aryl), 7.16-7.26 (m, 3H, aryl), 7.04-7.08 (m, 1H, aryl), 3.08 (dq, *J* = 6.9, 4.1 Hz, 1H, C**H**CH_3), 2.56 (dd, *J* = 5.8, 4.2 Hz, 1H, C**H**CHO), 0.96 (d, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz) δ 201.9, 147.4, 145.0, 145.0, 136.6, 135.7, 135.5, 128.8, 128.6, 128.0, 127.4, 127.3, 127.0, 126.0, 125.5, 121.7, 118.5, 91.4, 89.2, 66.0, 43.0, 34.2, 30.3, 16.5; HRMS (EI) exact mass clacd for ($C_{24}H_{20}O_2$) requires *m/z* 341.1542, found *m/z* 341.1542; $[\alpha]_D$ = - 82.4 °. Enantiomeric excess was determined,

after reduction of a small portion of the product to the corresponding alcohol (4 eq $NaBH_4$ in EtOH (0.1 M)), by HPLC analysis (Chiralcel OD-H column, 3% ethyl acetate in hexanes, 1.0 mL/min); *exo* isomers t_r = 14.1 and 15.3 min, *endo* isomers t_r = 16.2 and 20.4 min.

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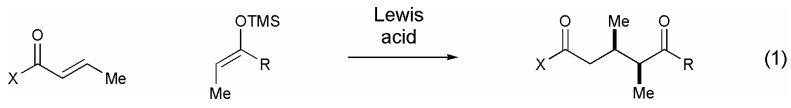
Chapter 3

Development of a General Enantioselective Organocatalytic Mukaiyama-Michael Reaction: Development of a Second-Generation Organocatalyst

I. Introduction

The Mukaiyama-Michael Reaction

The first report of the conjugate addition of silyl enol ethers to α,β-unsaturated carbonyl compounds was made by Mukaiyama in 1974.[1] Since that first report, the conjugate addition of latent enolate equivalents to α,β-unsaturated carbonyl compounds has been termed the Mukaiyama-Michael reaction (equation 1). This reaction is an effective method for the establishment of stereochemical relationships in an acyclic framework.[2] The conjugate addition of latent enolate equivalents to α,β-unsaturated carbonyl compounds is possible under milder conditions and with superior regioselectivity (1,2- vs. 1,4-addition) than metalloenolate conjugate additions.[3-8] There have been many examples of diastereoselective Mukaiyama-Michael reactions, particularly those employing chiral Michael acceptors, but catalytic enantioselective reactions present a greater synthetic challenge and are the ultimate goal of asymmetric Mukaiyama-Michael technology.

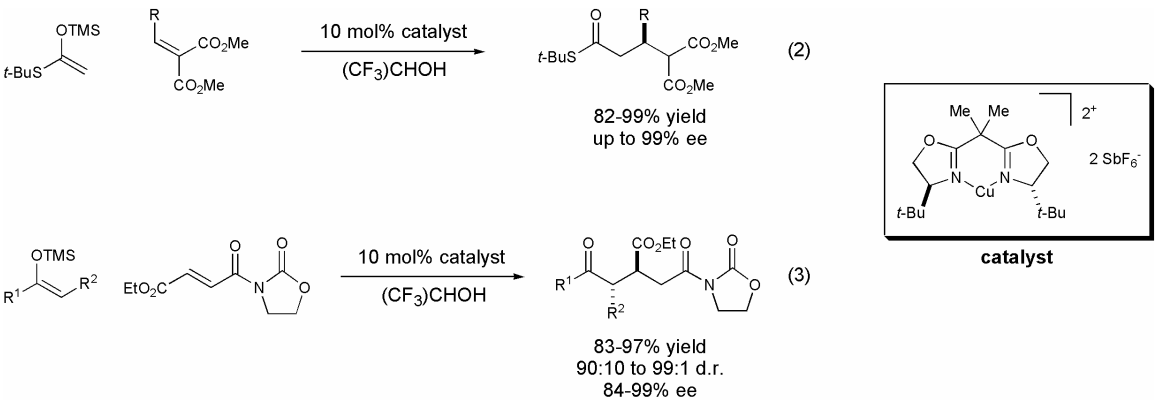


(1)

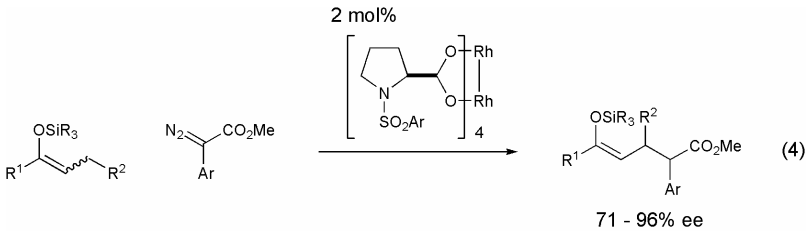
Enantioselective Catalysis of the Mukaiyama-Michael Reaction

There have been many reports of chiral Lewis acid promoted and catalyzed asymmetric Mukaiyama-Michael reactions.[9-25] The most general chiral Lewis acid catalyzed systems have been developed by the Evans laboratory (Scheme 1).[19,20] Using a copper(II) bis(oxazoline) catalyst, an enantioselective Mukaiyama-Michael reaction has been demonstrated with alkylidene malonates as Michael acceptors, and a formal Mukaiyama-Michael reaction has been demonstrated with unsaturated acyl oxazolidinones as Michael acceptors (Scheme 1, equations 2 and 3). The formal Mukaiyama-Michael reaction of acyl oxazolidinones has been shown to proceed through a hetero Diels-Alder/hydrolysis pathway rather than the expected conjugate addition manifold.

Scheme 1. Copper-bis(oxazoline)-catalyzed Mukaiyama-Michael reactions.

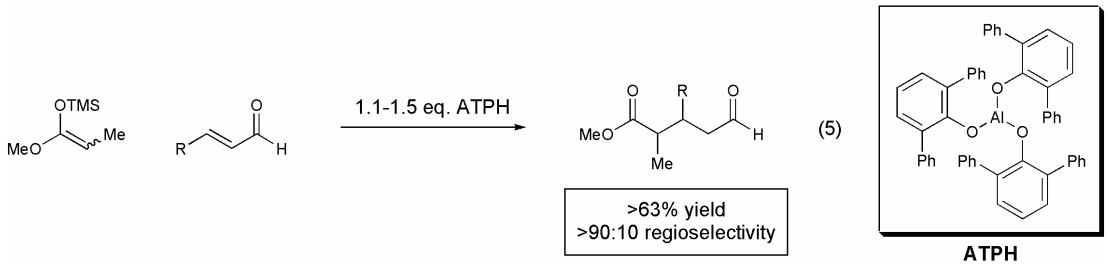


There have been other approaches to the development of an asymmetric Mukaiyama-Michael reaction. The Davies group has reported a formal asymmetric Mukaiyama-Michael reaction that proceeds through the catalytic C-H activation of silyl enol ethers with enantioselectivities as high as 96% (equation 4).[26]



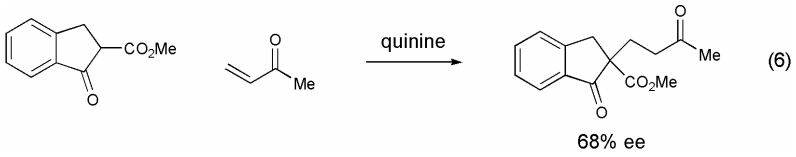
Mukaiyama-Michael Reactions with α,β-Unsaturated Aldehydes

When a Mukaiyama-Michael reaction is attempted between an α,β-unsaturated aldehyde and a latent enolate equivalent, 1,2-addition of the nucleophile to the aldehyde occurs, resulting in a Mukaiyama-aldol reaction. [5-8,27-29] The only example of a Lewis acid catalyzed Mukaiyama-Michael reaction involving α,β-unsaturated aldehydes as Michael-acceptors was reported by the Yamamoto group.[30] An aluminum Lewis acid was developed that completely shields the carbonyl carbon of an α,β-unsaturated aldehyde from nucleophilic attack by a variety of nucleophiles, including silyl ketene acetals (equation 5).

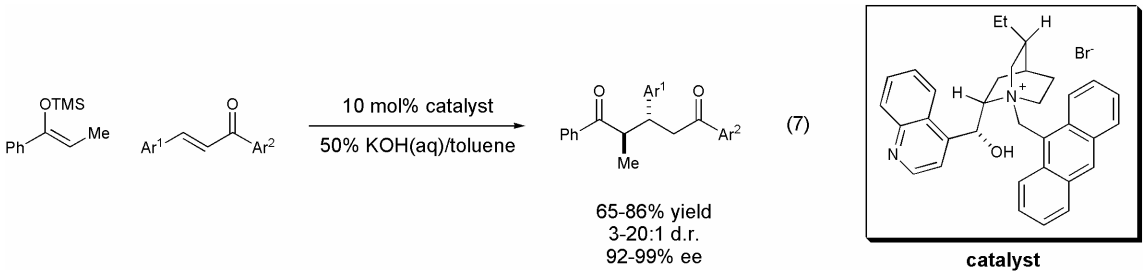


Organocatalysis of the Michael Reaction

The first organocatalytic enantioselective Michael reaction was reported in 1975 (equation 6).[31] Since the initial report, a variety of cinchona alkaloids have been used as catalysts for the Michael addition reaction.[32]



Phase-transfer agents have been used to catalyze the Mukaiyama-Michael reaction.[33,34] The Corey laboratory has demonstrated that chiral quaternary ammonium salts derived from cinchona alkaloids can catalyze the addition of silyl enol ethers to chalcones with excellent selectivity (equation 7).

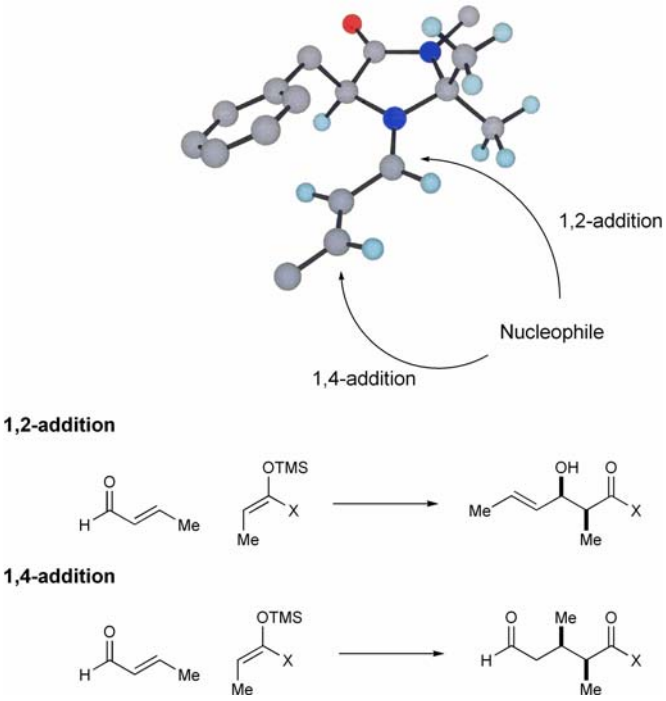


Imidazolidinone-Catalyzed Conjugate Addition

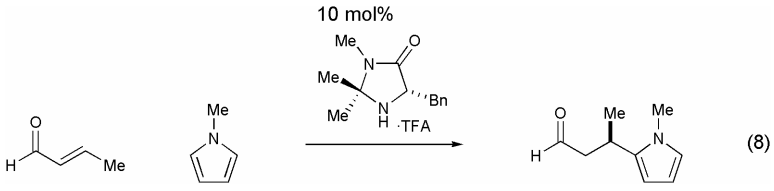
The chemoselectivity of the addition of a silyl ketene acetal to an α,β-unsaturated aldehyde was one of the known challenges to developing an organocatalytic Mukaiyama-Michael reaction. If the proposed reaction was to be successful, the imidazolidinone catalyst developed in the context of the Diels-Alder cycloaddition would need to provide

enough shielding of the iminium carbon to prevent 1,2-addition of silyl ketene acetals to the catalyst-aldehyde adduct (Scheme 2).

Scheme 2. 1,2- versus 1,4-addition to the imidazolidinone-aldehyde adduct.

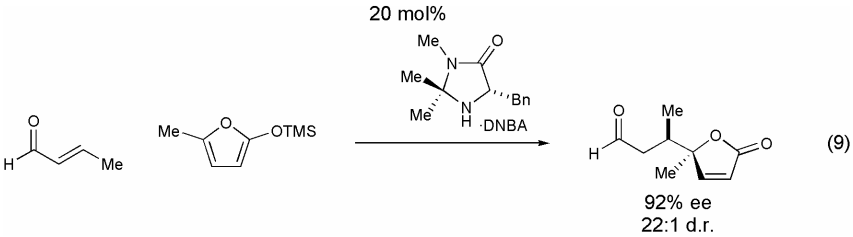


Previous research in the MacMillan laboratory had shown that the imidazolidinone catalyst is effective at promoting 1,4- over 1,2-additon of pyrroles to α,β-unsaturated aldehydes (equation 8).[35] Therefore, it was believed that the success of the organocatalytic Mukaiyama-Michael was probable.



(8)

During the course of this research, organocatalysis of the Mukaiyama-Michael reaction was achieved within the context of butenolide synthesis.[36] The conjugate addition of siloxy furans to α,β-unsaturated aldehydes was demonstrated with enantioselectivities up to 98% (equation 9).

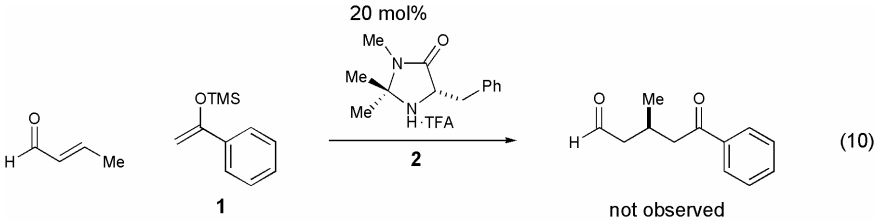


(9)

II. Results and Discussion

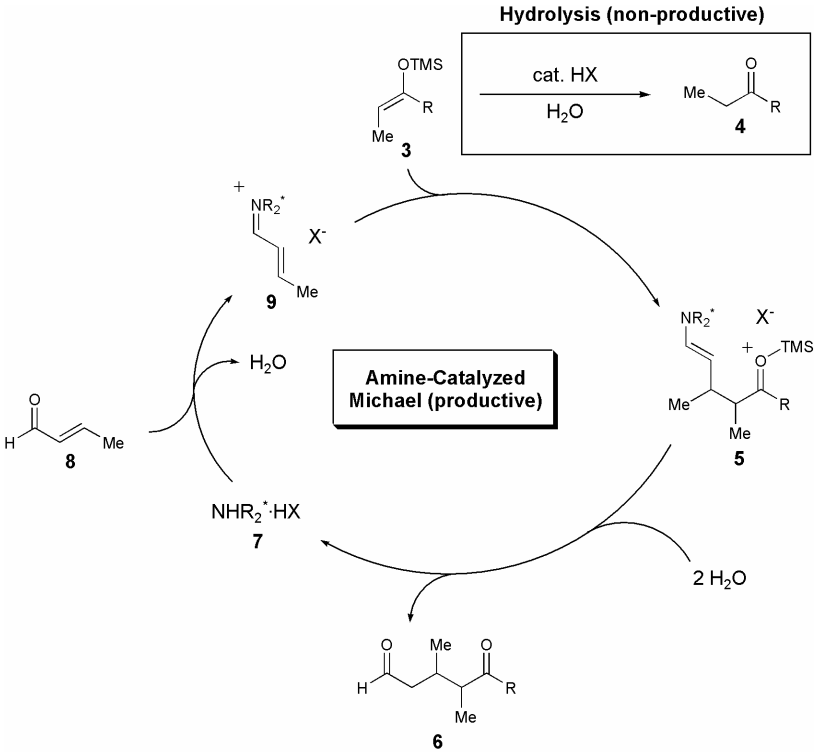
Initial Investigations

The first attempt at developing an organocatalytic Mukaiyama-Michael reaction in the MacMillan laboratory was unsuccessful (equation 10).[37] The only chemical species observed in this reaction were unmodified α,β-unsaturated aldehyde and the ketone derived from hydrolysis of **1**.



Under organocatalytic reaction conditions, two pathways are possible for the nucleophilic silyl enol ether **3** (Scheme 3). The acid catalyzed hydrolysis of silyl enol ether **3** can occur, consuming the reagent and leading to the non-productive formation of the carbonyl compound **4**. Or the silyl enol ether **3** can productively react with the iminium ion **9** formed from the organocatalyst **7** and α,β-unsaturated aldehyde **8**, leading to product adduct **6** regenerating the organocatalyst **7** after hydrolysis.

Scheme 3. Proposed organocatalytic Mukaiyama-Michael catalytic cycle.

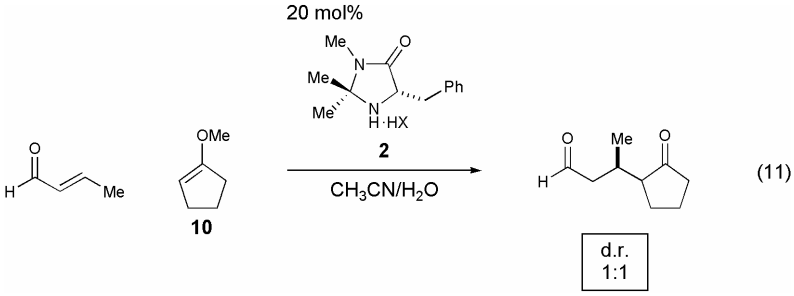


Investigations with Alkyl Enol Ethers

Subsequent study of the organocatalytic Mukaiyama-Michael reaction took this into account. A nucleophile that would be robust enough to survive the acidic, aqueous conditions needed for organocatalysis must be used. Non-aromatic alkyl enol ethers were chosen for study.

Initial studies of the organocatalytic Mukaiyama-Michael reaction examined the conjugate addition of the methyl enol ether **10** with crotonaldehyde. The hydrolysis of the nucleophile **10** plays a significant role in achieving reasonable chemical yields, therefore the effect of the acid co-catalyst was examined.

Table 1. Effect of acid co-catalyst on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the methyl enol ether of cyclopentanone (**10**).[a]

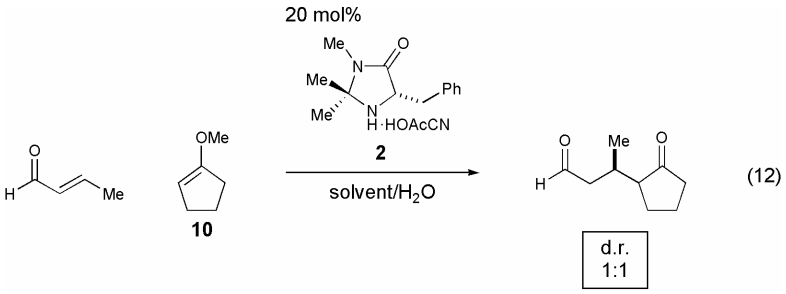


Entry	HX	pK_a (H_2O)	% Conversion[b]	% ee[b]
1	HOAcCN	2.47	55	50
2	DCA	1.35	49	49
3	TFA	0.52	18	49
4	TCA	0.51	14	50
5	PTSA	-1.34	2	--
6	MsOH	-2.6	15	49
7	H_2SO_4	-3.0	7	49
8	HCl	-6.1	10	48
9	HNO_3	-8	8	49
10	$HClO_4$	-10	4	--
11	TfOH	-14	2	--

[a] All reactions performed at -20 °C; [b] Conversion, diastereoselectivity, and enantioselectivity determined by GLC analysis.

The acidity of the Brønsted acid co-catalyst plays a significant role in the reactivity of the silyl ketene acetal nucleophile (Table 1). Only the most weakly acidic co-catalysts examined produced product in moderate yields (49-55%, Table 1, entries 1, 2). All other acid co-catalysts examined proved to be too acidic, hydrolyzing the alkyl enol ether nucleophile **10** rather than catalyzing conjugate addition. Interestingly, the selectivity of the transformation does not appear to be dependent upon the co-catalyst pK_a. All reaction conditions examined resulted in the same diastereoselectivity (1:1), and very similar enantioselectivities (48-50% ee).

Table 2. Effect of solvent on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the methyl enol ether of cyclopentanone (**10**).[a]



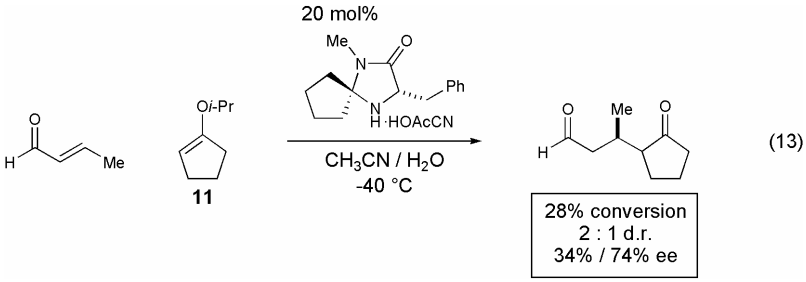
Entry	Solvent	E_T^N	% Conversion[b]	% ee[b]
1	MeOH	0.762	<5	--
2	EtOH	0.654	<5	--
3	*n*-BuOH	0.602	<5	--
4	*i*-PrOH	0.546	8	45
5	CH_3NO_2	0.481	26	49
6	CH_3CN	0.460	33	53
7	DMSO	0.444	<5	--
8	DMF	0.404	<5	--
9	acetone	0.355	9	51
10	CH_2Cl_2	0.309	8	33
11	$CHCl_3$	0.259	5	5
12	DME	0.231	<5	--
13	EtOAc	0.228	<5	--
14	THF	0.207	<5	--
15	1,4-dioxane	0.164	5	39
16	ether	0.117	<5	--
17	toluene	0.099	<5	--
18	hexanes	0.009	<5	--

[a] All reactions performed at -30 °C; [b] Conversion, diastereoselectivity, and enantioselectivity determined by GLC analysis on a Bodman Chiraldex Γ-TA column

A survey of solvents demonstrated that polar aprotic solvents afforded the highest conversions for the conjugate addition of alkyl enol ether **10** to crotonaldehyde (Table 2). Polar protic solvents produced almost no product, instead hydrolyzing the alkyl enol ether (Table 2, entries 1-4). Less polar solvents, while not rapidly hydrolyzing the acid sensitive nucleophile **10**, did not allow sufficient formation of reactive iminium ion intermediate. The lack of significant quantities of iminium ion allowed the relatively

slow alkyl enol ether hydrolysis to dominate under these reaction conditions. Because of its superior performance, yielding product in 53% ee, further studies with alkyl enol ether **10** were performed in acetonitrile (Table 2, entry 6).

Variation in the alkyl group of the alkyl enol ether was examined, and it was quickly determined that those alkyl enol ethers possessing the largest alkyl substituent performed the best under organocatalytic conditions. Imidazolidinone architectures surveyed in the development of the organocatalytic Diels-Alder reaction (Chapter 2, Tables 6 and 7) were studied as catalysts for the organocatalytic Mukaiyama-Michael reaction. Through these studies and others, reaction conditions were optimized to yield product from alkyl enol ether **11** and crotonaldehyde with good enantioselectivity for the minor diastereomer (equation 13, 2:1 d.r., 74% ee, minor diastereomer).

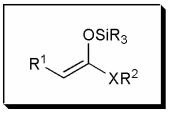


(13)

Investigations with Silyl Ketene Acetals

In an effort to increase the yield and selectivity of the organocatalytic Mukaiyama-Michael reaction, a different class of nucleophile was examined. Silyl ketene acetals were chosen because they are common nucleophiles for Mukaiyama-Michael reactions, and they allow access to a large variety of architectures (Figure 1).[5]

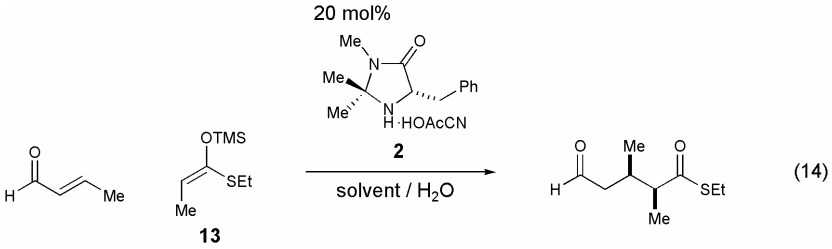
Figure 1. Silyl ketene acetals are potential nucleophiles for the organocatalytic Mukaiyama-Michael reaction.



SiR_3 = TMS, TES, TBS, TPS, TBDPS, TIPS
R^1 = H, alkyl, aryl, OR
X = O, S
R^2 = Me, Et, Ph, *i*-Pr, *t*-Bu

Silyl ketene acetals derived from thioesters were first examined. Initial studies were performed with the trimethylsilyl ketene acetal derived from *S*-ethyl thiopropionate (**13**) and crotonaldehyde. It was quickly discovered that Mukaiyama-Michael reactions with this class of substrates do not occur at temperatures above -30 °C. All subsequent studies were performed at cryogenic temperatures.

Table 3. Effect of solvent on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the silyl ketene acetal **13**.[a]



Entry	Solvent	E_t^N	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	*i*-PrOH	0.546	86	1:1.3	17
2	CH_3NO_2	0.481	81	3.3:1	60
3	CH_3CN	0.460	79	1.6:1	54
4	DMSO	0.444	23	1:1.8	21
5	DMF	0.404	36	1:1.9	19
6	acetone	0.355	80	2.1:1	56
7	CH_2Cl_2	0.309	85	3.5:1	62
8	$CHCl_3$	0.259	58	1.3:1	61
9	DME	0.231	67	1:1.2	23
10	EtOAc	0.228	81	3.0:1	53
11	THF	0.207	64	3.4:1	54
12	1,4-dioxane	0.164	69	2.9:1	53
13	ether	0.117	74	4.1:1	55
14	toluene	0.099	59	1.4:1	52
15	hexanes	0.009	64	1.3:1	53

[a] All reactions performed at -50 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The conjugate addition of silyl ketene acetal **13** to crotonaldehyde was examined in a variety of solvents (Table 3). It quickly became apparent that, with few exceptions, the organocatalytic Mukaiyama-Michael reaction between silyl ketene acetal **13** and crotonaldehyde shows little solvent dependence. The combination of the highest conversion and selectivities was observed in methylene chloride, a solvent of intermediate polarity (85% conversion, 3.5:1 *syn:anti*, 62% ee, Table 3, entry 7). Acetone, chloroform, and ether did not perform significantly worse (Table 3, entries 6, 8,

13). Further experimentation revealed that the solvent of choice may vary for different substrate combinations.

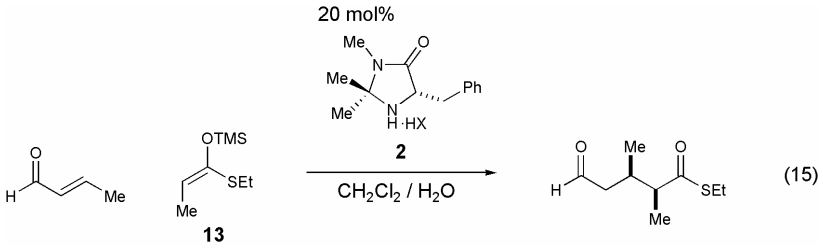
The effect of concentration on the organocatalytic Mukaiyama-Michael was examined. Conversion and selectivity of the conjugate addition increased with concentration up to 2.0 M, relative to the limiting reagent. At concentrations higher than 2.0 M, the conversion and selectivity of the process sharply decreased.

The effect of the co-catalyst acid on the addition of silyl ketene acetal **13** to crotonaldehyde was carefully examined because of the known silyl ketene hydrolysis side reaction and the known acid catalyzed nature of this hydrolysis (Table 4). A strong dependence on co-catalyst pK_a became immediately evident. Weakly acidic co-catalysts with pK_a's greater than 3 (Table 4, entries 1 and 2) did not yield product under reaction conditions. It is believed that the reaction medium is not acidic enough to form sufficient quantities of reactive iminium ion. Therefore, without a competent electrophile (iminium ion), the silyl ketene acetal **13** can only hydrolyze under the reaction conditions. Strongly acidic co-catalysts with pK_a's less than 0 (Table 4, entries 8-15) did not yield product either. These co-catalysts present the opposite problem. While the acid co-catalysts are acidic enough for the formation of significant quantities of reactive iminium ion, the strong acids also significantly promote the hydrolysis of the silyl ketene acetal **13**.

It is only when acid co-catalysts with intermediate acidities are used (Table 4, entries 3-7) that moderate quantities of Mukaiyama-Michael adduct are detected. These catalysts are acidic enough to form sufficient quantities of reactive iminium ion but not acidic enough to significantly promote the hydrolysis of silyl ketene acetal **13**. It was discovered through additional experimentation that the optimal co-catalyst can vary with

different substrate combinations. In general, at lower the reaction temperatures, more acidic co-catalysts were more effective.

Table 4. The effect of co-catalyst pK_a on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13**.[a]



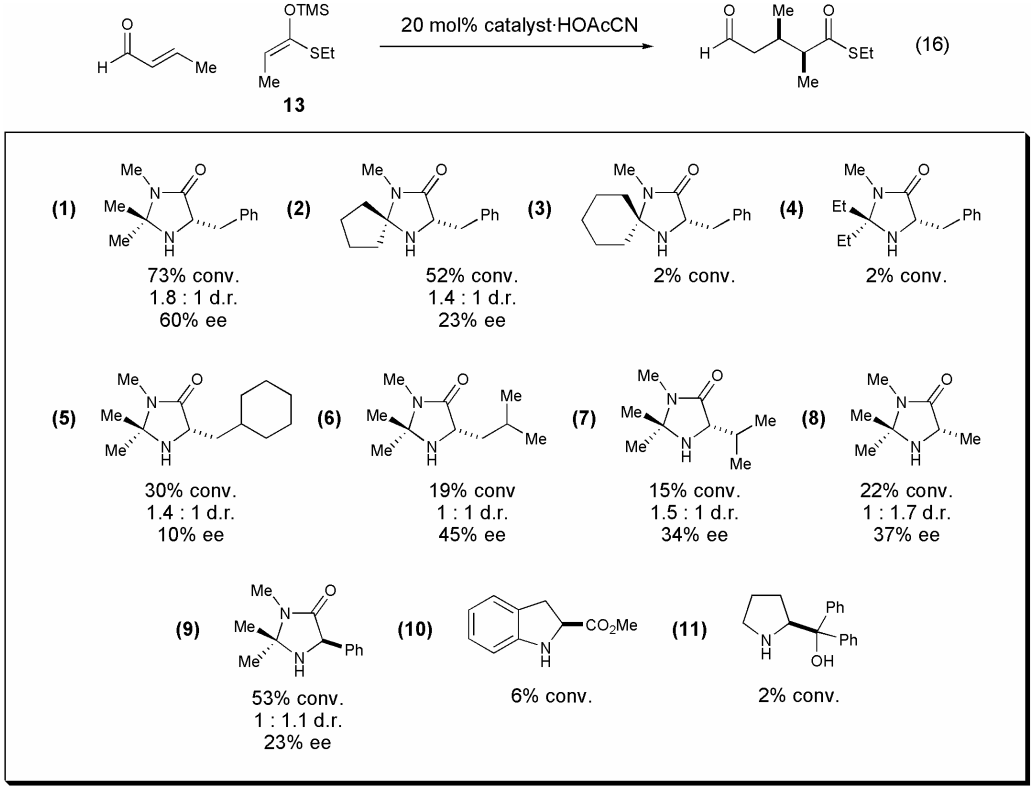
Entry	HX	$pK_a(H_2)$	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	HOAc	4.76	0	--	--
2	HF	3.18	1	--	--
3	HOAcCN	2.47	54	2.6:1	66
4	DBA	1.48	34	2.2:1	72
5	DCA	1.35	31	2.5:1	66
6	DFA	1.34	42	2.5:1	62
7	TCA	0.51	14	2.6:1	66
8	PTSA	- 1.34	3	--	--
9	HNO_3	- 1.44	0	--	--
10	MsOH	- 2.6	3	--	--
11	H_2SO_4	- 3.0	5	--	--
12	HCl	- 6.1	2	--	--
13	HBr	- 9.0	5	--	--
14	$HClO_4$	- 10	0	--	--
15	TfOH	- 14	11	--	--

[a] All reactions performed at -50 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

A variety of chiral secondary amines were surveyed as potential catalysts to assess the reactivity and selectivity of various structural architectures (Table 5). Catalysts that had promoted the organocatalytic Diels-Alder reaction with good yield (Table 5, entry 10) did not catalyze the Mukaiyama-Michael reaction, and catalyst architectures that failed to catalyze the organocatalytic Diels-Alder reaction also failed to

catalyze the Mukaiyama-Michael reaction (Table 5, entry 11). Imidazolidinone catalysts were the only structural framework to yield product in significant quantities. Increasing the steric demand of the imidazolidin-4-one framework proved detrimental to the transformation. As the steric demand of the geminal substituents at the 2-position of the imidazolidin-4-one ring was increased (Table 5, entries 1-4), the conversion of the Mukaiyama-Michael reaction was reduced from 73% to trace amounts. An increase in steric demand at the 5-position of the imidazolidin-4-one ring also produced unfavorable results. When the size of the 5-substituent was increased (Table 5, entries 5-8) the conversion also decreased from 73% to 15-53%.

Table 5. Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13** with representative amine catalysts.[a]



[a] All reactions performed at -50 °C; Conversion determined by GLC analysis; Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; Enantioselectivity reported for major diastereomer.

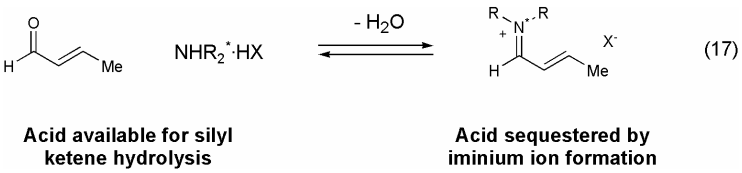
In an attempt to increase the chemical yield of the process, varying ratios of amine and acid co-catalyst were examined. In the end, it was determined that a ratio of unity between the amine and Brønsted acid was most favorable. When fewer equivalents of acid than amine were used, the reaction proceeded more slowly, but approached the same overall yield. That is, both conjugate addition and silyl ketene acetal hydrolysis appeared to be retarded equally. When more equivalents of acid were used than amine, greater hydrolysis of the nucleophile was observed, and chemical yields decreased.

Formation of iminium ion was attempted without Brønsted acid co-catalyst, using the bis-sulfonamide developed by the Crabtree laboratory to promote iminium ion formation between the α,β-unsaturated aldehyde and the free base of imidazolidinone **2** in the absence of protic acid.[38] Unfortunately, iminium ion formation using this hydrogen-bonding catalyst did not occur below -20 °C, and rapid hydrolysis of the silyl ketene acetals occurred above this temperature.

After a through investigation into reaction conditions and catalyst architecture, the most reactive and selective catalyst examined for the Mukaiyama-Michael reaction was benzyl imidazolidinone **2** (73% conversion, 1.8:1 *syn:anti*, 60% ee, *syn* isomer). It became apparent that the imidazolidinone catalyst developed for the organocatalytic Diels-Alder reaction would not effectively catalyze a Mukaiyama-Michael reaction.

Development of a Second-Generation Organocatalyst

A more reactive and selective organocatalyst was needed for the organocatalytic Mukaiyama-Michael reaction. Two design features were necessary to accomplish this goal: (1) an increase in reaction rate and (2) increased enantiofacial discrimination.

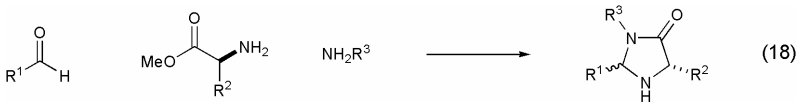


It was hypothesized that increasing the nucleophilicity of the catalyst nitrogen would increase the rate of iminium ion formation and, therefore, increase the reaction rate. By increasing the rate of iminium ion formation, the time the catalyst exists as an acid salt under reaction conditions is also reduced, thereby decreasing the rate of silyl ketene acetal hydrolysis (equation 17). This should effectively favor conjugate addition of the silyl ketene acetal over hydrolysis, increasing the conversion of the transformation (Scheme 3).

To develop a useful organocatalytic Mukaiyama-Michael reaction, the new catalyst must also show an increase in enantioselectivity. This could be accomplished by two different methods. The reactivity of the catalyst could be increased, thereby allowing the organocatalytic Mukaiyama-Michael reaction to be performed at lower temperatures, increasing the observed enantioselectivity, or the steric demand of the portion of the catalyst architecture that shields one π-enantioface of the reactive olefin could be increased. This would increase the enantioselectivity of the process without the need for a decrease in temperature. Ideally, the new organocatalyst should both show increased reaction rates and an increase in enantioselectivity relative to the first-generation imidazolidinone **2**.

The modular nature of the imidazolidinone catalyst lent itself well to these investigations (equation 18). It was believed that modification at the 2-position of the

imidazolidin-4-one catalyst would realize the design goals for the new organocatalyst.[39] Synthesizing an imidazolidinone catalyst using an aldehyde rather than a ketone removes steric congestion from the fully substituted 2-position of the imidazolidinone by introducing a hydrogen atom at that position. This decrease in steric congestion on the imidazolidinone ring should increase the nucleophilicity of the catalyst, fulfilling the first design goal. Prudent choice of the aldehyde could also increase the coverage of the blocked enantioface, meeting the requirements of the second design goal.

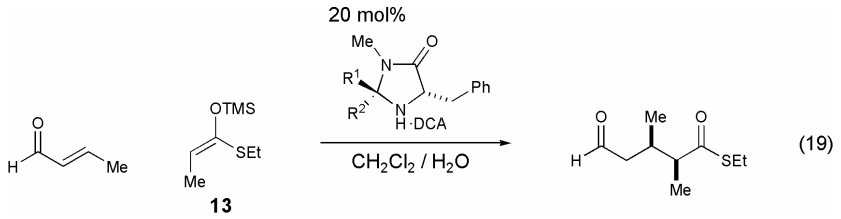


(18)

To this end, several different imidazolidinone catalysts were synthesized with differing substitution at the 2-position of the imidazolidin-4-one catalyst, and the Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13** was used to evaluate the new catalysts (Table 6). All catalysts synthesized with a *cis* relationship between the 2- and 5-substituents showed higher selectivities and conversions than the original *gem*-dimethyl imidazolidinone catalyst **2** (Table 6, entries 1, 3, 5, 7). Those catalysts synthesized with a *trans* relationship showed either no significant change in reactivity or a decrease in reactivity relative to imidazolidinone catalyst **2** (Table 6, entries 1, 2, 4, 6). The best performing catalyst examined, imidazolidinone catalyst **19** ((2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one) increased conversion from 40% to 53% and, more significantly, increased enantioselectivity from 58% to 83% ee (Table 6, entries 1 and 7). In addition, the reaction catalyzed by imidazolidinone **19** showed complete consumption of silyl ketene

acetal **13** in 12 h, a considerably faster reaction time than was previously observed under similar reaction conditions using catalyst **2** (24 h).

Table 6. Effect of imidazolidinone structure on the Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13**.[a]



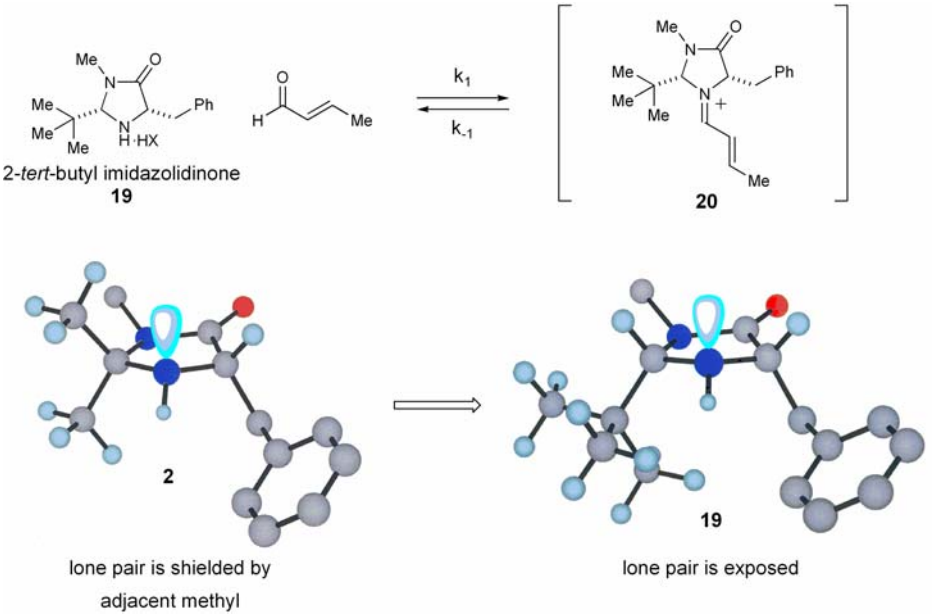
Entry	Catalyst	R^1	R^2	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	**2**	Me	Me	40	1.2:1	58
2	**14**	*i*-Pr	H	47	2.7:1	42
3	**15**	H	*i*-Pr	54	2.4:1	68
4	**16**	Ph	H	36	1.5:1	47
5	**17**	H	Ph	52	1:1.4	61
6	**18**	*t*-Bu	H	17	2.4:1	61
7	**19**	H	*t*-Bu	53	2.3:1	83

[a] All reactions performed at -40 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The *cis*-relationship between the *tert*-butyl and benzyl substitutents on imidazolidinone catalyst **19** allows the increase in reactivity over catalyst **2**. Computational studies of the two catalysts show the decrease in steric congestion around the nucleophilic nitrogen on the new catalyst **19** (Figure 2).[40] The first catalyst developed (**2**) has an eclipsing interaction between the nucleophilic nitrogen lone pair and a methyl group at the 2-position. This reduces the overall nucleophilicity of the nitrogen atom and impedes the reaction rate. By removing the methyl group and replacing it with hydrogen, as in catalyst **19**, the nitrogen lone pair is unencumbered on one side of the imidazolidinone ring and, therefore, is more nucleophilic. This increases the rate of iminium ion formation, increasing the overall rate of the Mukaiyama-Michael reaction.

This also decreases the amount of free acid present in the reaction medium, reducing hydrolysis of the silyl ketene acetal, and increasing conversion.

Figure 2. The second-generation imidazolidinone catalyst **19** increases reaction rates.

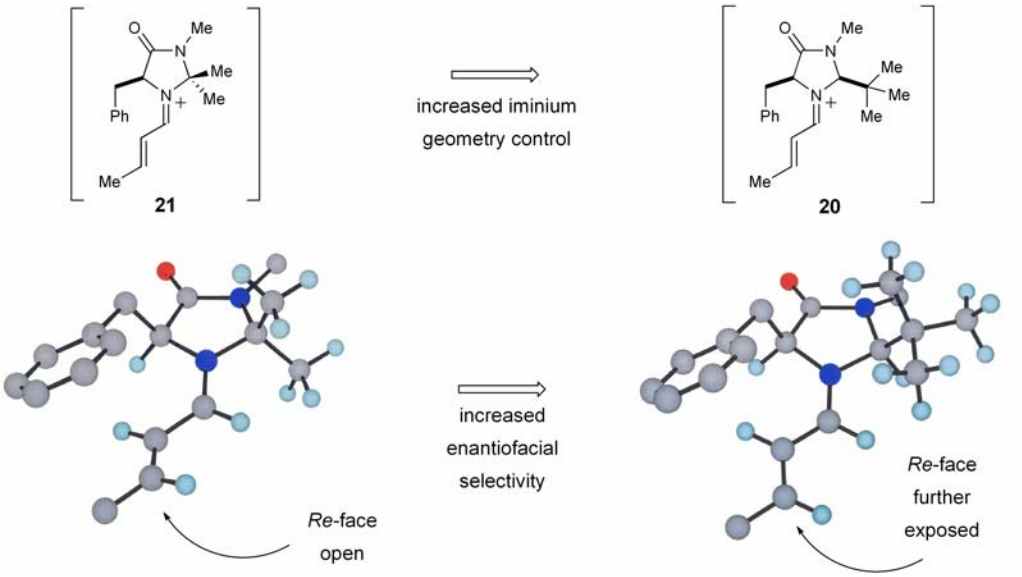


The increase in enantioselectivity is also apparent from the computational study (Figure 3).[40] The steric bulk of the 2-*tert*-butyl group effectively controls the iminium ion geometry. The calculated energy difference between the two iminium ions possible from condensation of catalyst **19** with an α,β-unsaturated aldehyde is 9 kJ·mol^{-1}, favoring the (*Z*)-iminium ion shown. The magnitude of this number supports the conclusion that the Mukaiyama-Michael reaction occurs primarily through only one iminium ion geometry.

Additionally, the large *tert*-butyl substituent provides greater coverage of the blocked π-enantioface relative to the first generation imidazolidinone catalyst adduct **21** (Figure 3). The exposed π-enantioface of the second-generation catalyst adduct **20** is also

more accessible relative to the first generation catalyst adduct **21** due to the lack of a methyl substituent on the exposed face of the imidazolidinone ring. The strong control of iminium ion geometry and the increased coverage one π-enantioface of the catalyst substrate adduct **20** both serve to increase the enantioselectivity of the Mukaiyama-Michael conjugate addition, meeting the second catalyst design goal.

Figure 3. The second-generation imidazolidinone catalyst **19** increases enantioselectivity.

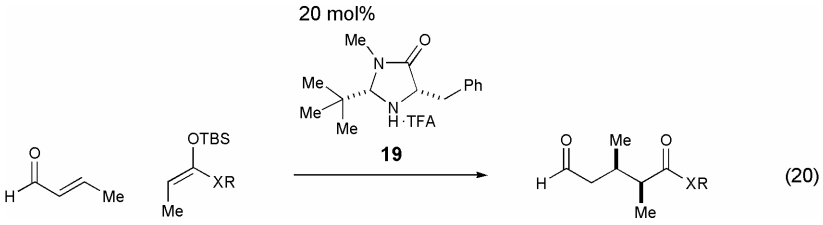


Investigations with the Second-Generation Organocatalyst

With the second generation imidazolidinone catalyst **19** identified, the nature of the silyl group on the silyl ketene acetal nucleophile was then examined. Silyl ketene acetals were generated from *S*-ethyl propionate with a variety of silyl groups. It became evident that *tert*-butyldimethylsilyl ketene acetals were the substrate of choice for the organocatalytic Mukaiyama-Michael reaction. Silyl groups of less steric bulk and less stability towards acid (trimethylsilyl, triethylsilyl, and triphenylsilyl) yielded products in

lower conversion and selectivity.[41] Silyl ketene acetals synthesized with triisopropylsilyl groups, a silyl group showing greater stability towards acid than *tert*-butyldimethylsilyl, proved too stable and did not yield product in higher selectivities than *tert*-butyldimethylsilyl ketene acetals.

Table 7. Effect of silyl ketene acetal alkyl group variation on the Mukaiyama-Michael reaction of crotonaldehyde and representative silyl ketene acetals.[a]



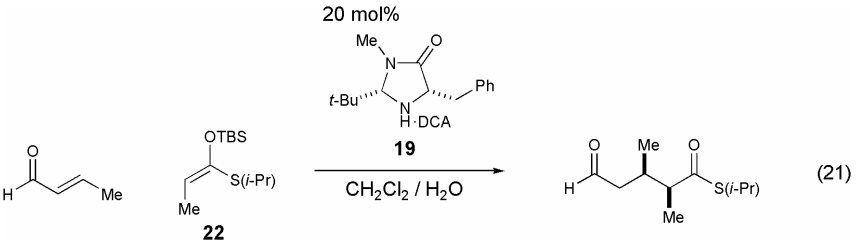
Entry	XR	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	O(*t*-Bu)	0	--	--
2	SPh	0	--	--
3	SMe	38	3.2:1	91
4	SEt	43	2.6:1	86
5	S(*i*-Pr)	70	5.8:1	90
6	S(*t*-Bu)	38	5.4:1	86
7	1-pyrrole	90	1:8	78

[a] All reactions performed in CH_2Cl_2 at -78 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The effect of varying the alkyl component of the silyl ketene acetal was examined (Table 7). It was expected that an increase in the steric demand of this portion of the nucleophile's architecture would increase the selectivity of the transformation. This was true, but to a defined limit. Ester-derived silyl ketene acetals (Table 7, entry 1) and *S*-phenyl silyl ketene acetals (Table 7, entry 2) were easily hydrolyzed under reaction conditions and did not yield product. As the *S*-alkyl substituent increased in size from methyl to isopropyl (Table 7, entries 3-5), the conversion and selectivity of the organocatalytic Mukaiyama-Michael increased to 70% conversion, 5.8:1 d.r., and 90%

ee. Increasing the size of the *S*-alkyl substituent to *tert*-butyl decreased the selectivity and significantly decreased the conversion of the transformation (Table 7, entry 6). Examination of silyl ketene acetals derived from 1-acyl pyrroles yielded conjugate addition products in excellent yields and selectivities (90% yield, 1:8 d.r., 78% ee, Table 7, entry 7), but with a diastereoselectivity opposite that of products synthesized from thioester-derived silyl ketene acetals.

Table 8. Effect of the amount of water on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **22**.[a]



Entry	Eq. H_2O	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	0	61	7.3:1	91
2	1	85	5.0:1	90
3	2	85	5.4:1	89
4	4	67	6.8:1	90

[a] All reactions performed at -55 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

In the course of the conjugate addition of a silyl ketene acetal to an α,β-unsaturated aldehyde, one equivalent of a protic species must be consumed to protonate the conjugate addition adduct and scavenge the silyl group. Water had been used as the protic species of choice, and the stoichiometry of this reagent was examined (Table 8). The addition of one equivalent of water to the reaction was determined to be the optimum condition for the organocatalytic Mukaiyama-Michael reaction (85% conversion, 5.0:1 *syn:anti*, 90% ee *syn*, Table 8, entry 2). When no water was added to the reaction

mixture, lower conversion to product was observed (61% conversion, Table 8, entry 1). The conversion of the transformation is not adversely affected until four equivalents of water are used (67% conversion, 6.8:1 *syn:anti*, 90% ee *syn*, Table 8, entry 4).

Other protic agents were also examined as silyl scavengers. A variety of alkyl alcohols, fluorinated alcohols and phenols were examined, but no reagent performed better than water. Therefore, one equivalent of water was used as the silyl scavenger in all subsequent organocatalytic Mukaiyama-Michael reactions.

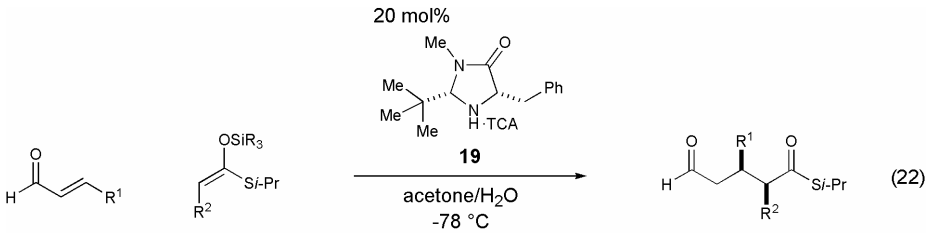
The stoichiometry of the transformation was also examined. It was believed that an excess of aldehyde produced favorable reaction conditions for the conjugate addition of silyl ketene acetals by sequestering most of the catalyst salt as iminium ion. This hypothesis held under experimental examination. Reactions performed with the silyl ketene acetal as the limiting reagent and an excess of α,β-unsaturated aldehyde showed higher conversions and yields than reactions performed with excess silyl ketene acetal and a limiting amount of α,β-unsaturated aldehyde.

Substrate Scope

With an optimized second generation organocatalyst identified and reaction conditions thoroughly examined, the ability of imidazolidinone **19** to catalyze a variety of conjugate additions was examined. All reactions were performed under a wet, aerobic atmosphere, in contrast with Lewis acid catalyzed Mukaiyama-Michael reactions. The organocatalytic reaction also utilizes α,β-unsaturated aldehydes directly as substrates unlike asymmetric Lewis acid catalyzed Mukaiyama-Michael reactions.

The synthesis of *syn*-Mukaiyama-Michael products was first examined (Table 9). The reaction is quite general with respect to the α,β-unsaturated aldehyde structure; variation of the β-substituent of the α,β-unsaturated aldehyde is possible without loss in enantioselectivity (≥4:1 *syn:anti*, 90-91% ee *syn*, Table 9, entries 1-4). The conjugate addition is also tolerant of varying substitution on the nucleophilic silyl ketene acetal, tolerating extended alkyl chains (R^2 = Et, 76% yield, 4:1 *syn:anti*, 94% ee *syn*, Table 9, entry 5) and oxygenation (R^2 = OBn, 82% yield, >20:1 *syn:anti*, 90% ee *syn*, Table 9, entry 6).

Table 9. Organocatalytic synthesis of *syn*-Mukaiyama-Michael products.[a]



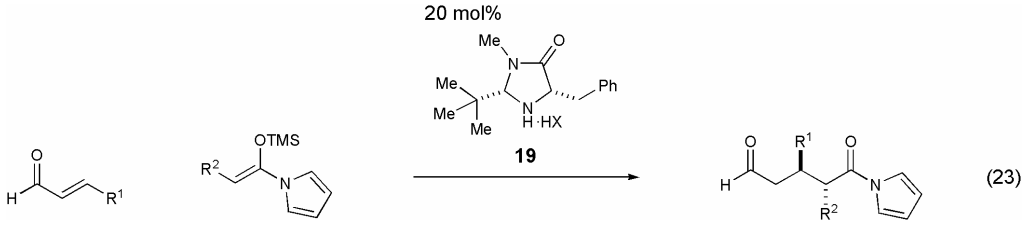
Entry	R^1	R^2	SiR_3	% Yield	*syn:anti*[e]	% ee[f,g]
1	Me	Me	TBS	76	10:1	90
2	*n*-Pr	Me	TBS	62	6:1	90
3[b]	Ph	Me	TMS	50	20:1	90[h]
4	CO_2Me	Me	TMS	73	4:1	91
5[c]	Me	Et	TBS	76	4:1	94
6[d]	Me	OBn	TBS	82	>20:1	90

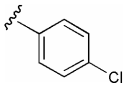
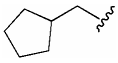
[a] All reactions performed at 2 M with one equivalent of H_2O; [b] Reaction performed with 7% (v/v) cyclohexane; [c] Reaction performed in ether; [d] Reaction performed in methylene chloride with TFA co-catalyst; [e] Determined by ^1H NMR analysis; [f] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [g] Enantioselectivity reported for major diastereomer; [h] Absolute configuration assigned by derivitization and XRD analysis.

Examination of the reaction conditions employed for the various Mukaiyama-Michael reactions with thioester derived silyl ketene acetals reveals that one reaction condition is not appropriate for all substrates examined. This due to the varying reactivity of the aldehydes and silyl ketene acetals examined. α,β-Unsaturated aldehydes

that form more stable iminium ions (R^1 = Ph, Table 9, entry 3) or more reactive iminium ions (R^1 = CO_2Me, Table 9, entry 4) require more reactive silyl ketene acetals to yield reasonable amounts of product (SiR_3 = TMS, Table 9, entries 3, 4). In one case (Table 9, entry 6), a different acid co-catalyst was determined to be optimal, and half of the substrates examined (Table 9, entries 3, 5, 6) proved to require different solvent systems for optimal performance.

Table 10. Organocatalytic synthesis of *anti*-Mukaiyama-Michael products.[a]



Entry[b]	R^1	R^2	HX	% Yield	*syn:anti*[c]	% ee[d,e]
1	Me	Me	TCA	92	1:17	83[f]
2	*n*-Pr	Me	DNBA	56	1:4	93
3		Me	TFA	74	1:3	98
4	Me	OBn	TBA	69	1:>20	93[f]
5	Me		TBA	68	1:10	88
6	Me	Ph	TfOH	78	1:3	87

[a] All reactions performed at 2 M with one equivalent of H_2O; [b] See experimental section for solvent and temperature; [c] Determined by ^{1}H NMR analysis; [d] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [e] Enantioselectivity reported for major diastereomer; [f] Absolute configuration assigned by derivitization to a known compound.

The synthesis of *anti*-Mukaiyama-Michael products was then examined (Table 10). These products can be accessed by simply using a silyl ketene acetal with the opposite olefin geometry; silyl ketene acetals derived from 1-acyl pyrroles were chosen for this purpose. The reaction is quite general with respect to the α,β-unsaturated aldehyde structure; variation of the β-substituent of the α,β-unsaturated aldehyde is

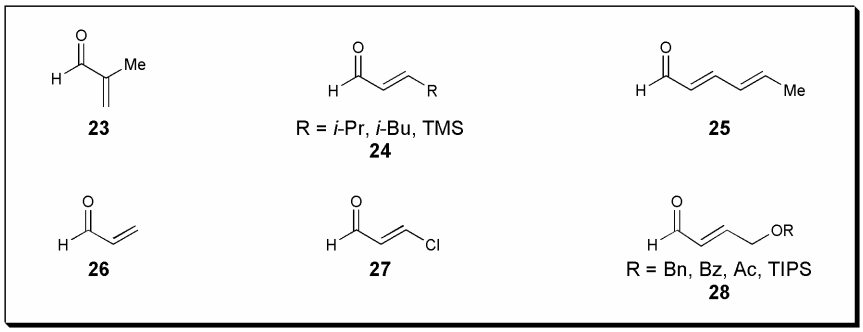
possible while retaining good to excellent enantioselectivity (1:≥3 *syn:anti*, 83-98% ee *anti*, Table 10, entries 1-3). The conjugate addition is also tolerant of varying substitution on the nucleophilic silyl ketene acetal, tolerating oxygenation (R^2 = OBn, 69% yield, 1:>20 *syn:anti*, 93% ee *anti*, Table 10, entry 4), extended alkyl chains (R^2 = CH_2Cp, 68% yield, 1:10 *syn:anti*, 88% ee *anti*, Table 10, entry 5), and aromatic substitution (R^2 = Ph, 78% yield, 1:3 *syn:anti*, 87% ee *anti*, Table 10, entry 6).

As was the case for the Mukaiyama-Michael reactions involving silyl ketene acetals derived from thioesters, the reaction conditions for different substrate combinations varies. Each set of substrates examined has its own optimum solvent or solvent combination, and most reactions use different acid co-catalysts. Acyl pyrrole-derived silyl ketene acetal nucleophiles appear to be much more sensitive to reaction conditions than thioester-derived silyl ketene acetals.

Limitations

While the organocatalytic Mukaiyama-Michael reaction is possible with a variety of structurally diverse substrates, there are certain substrate architectures that are not compatible with these reaction conditions. α,β-Unsaturated aldehydes possessing an α-substituent (**23**) are not competent substrates (Figure 4). It is believed that these substrates do not form significant concentrations of reactive iminium ion. This class of aldehydes has yet to prove competent for any secondary amine-catalyzed LUMO-lowering process.

Figure 4. α,β-Unsaturated aldehydes unable to participate in the organocatalytic Mukaiyama-Michael reaction.

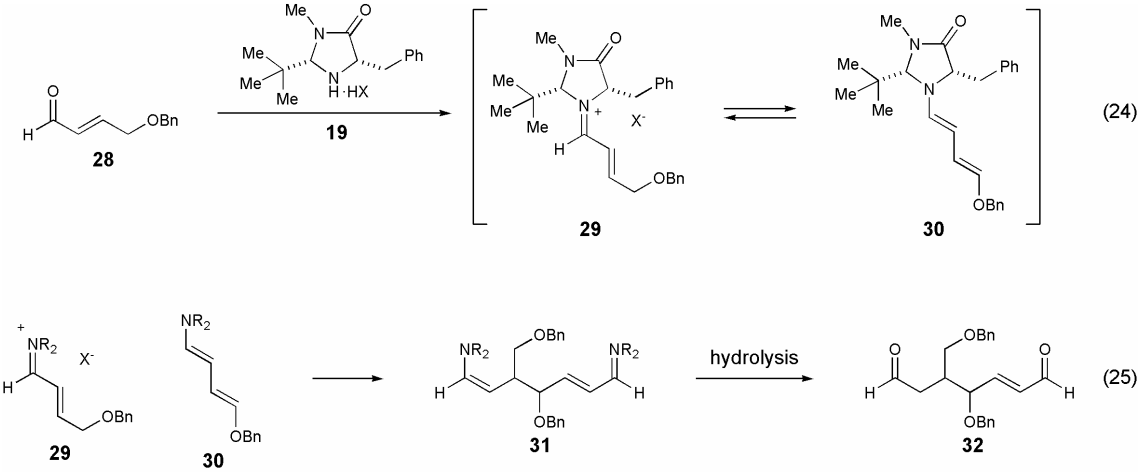


α,β-Unsaturated aldehydes with large β-substituents (**24**) also are not compatible with the organocatalytic Mukaiyama-Michael reaction (Figure 4). Large substituents at the β-position of α,β-unsaturated aldehydes are believed to retard the conjugate addition of the silyl ketene acetal through unfavorable steric interactions. This results in the acid catalyzed hydrolysis of the silyl ketene acetal becoming a much more competitive reaction pathway, thereby diminishing or obliterating yields. The α,β,γ,δ-unsaturated aldehyde **25** did not yield product, presumably due in part to this effect, and due in part to the greater stability and lesser reactivity of the iminium ion formed with the imidazolidinone catalyst **19**. Acrolein (**26**) and β-chloro acrolein (**27**) also do not participate in the organocatalytic Mukaiyama-Michael reaction.

Aldehydes with γ-oxygen substitution (**28**) also do not participate in the organocatalytic Mukaiyama-Michael reaction (Scheme 4). The acidity of the γ-hydrogens of the intermediate iminium ion **29** is high enough to allow the formation of a nucleophilic dienamine **30** (equation 24). The nucleophilic species **30** can then add to iminium ion **29** resulting in an overall dimerization of the starting aldehyde (**32**) after

hydrolysis of the intermediate **31** (equation 25). This process out competes the conjugate addition of the silyl ketene acetal yielding dimer of the starting aldehyde (**32**) and the thioester resulting from hydrolysis of the starting silyl ketene acetal.

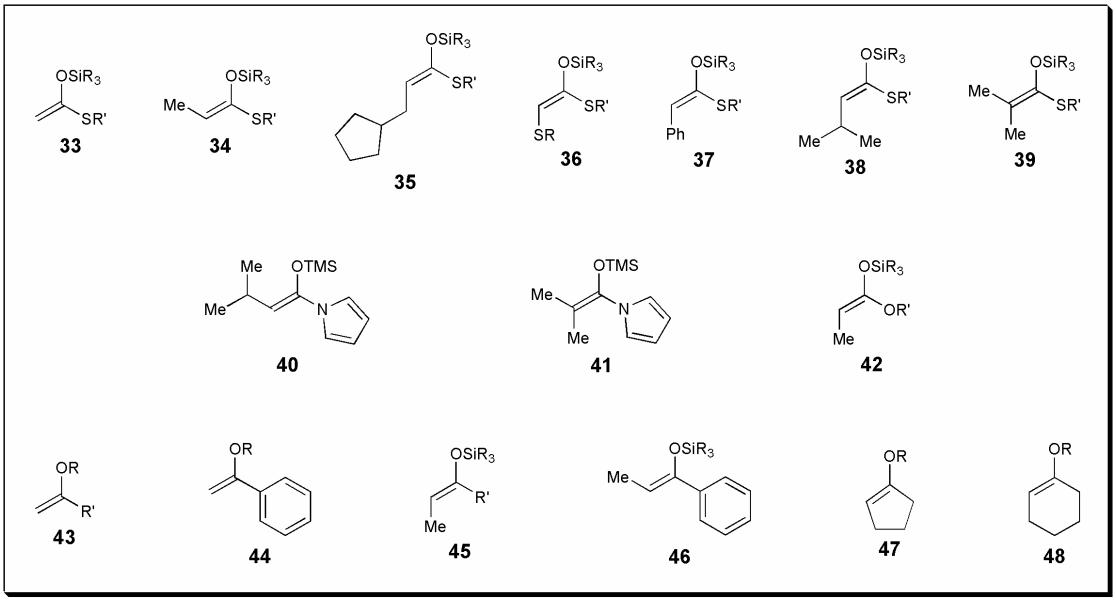
Scheme 4. Side reaction of γ-oxygenated α,β-unsaturated aldehydes under organocatalytic Mukaiyama-Michael reaction conditions.



While both *syn*- and *anti*-Mukaiyama-Michael products can be accessed based upon the proper choice of silyl ketene acetal, many latent enolate equivalents examined were not competent substrates for this transformation (Figure 5). Silyl ketene acetals derived from thioacetates (**33**) and *E*-silyl ketene acetals derived from thiopropionates (**34**) are less nucleophilic than the corresponding *Z*-thiopropionate silyl ketene acetals.[42] These substrates did not prove nucleophilic enough to participate in the conjugate addition, and yielded primarily hydrolysis products under organocatalytic reaction conditions. Increasing the steric bulk on thioester-derived silyl ketene acetals (compounds **35**-**39**) diminished their nucleophilicity enough to inhibit conjugate addition under organocatalytic conditions.

A similar effect was observed with pyrrole-derived silyl ketene acetals (Figure 5). Increased steric bulk at the α-position of the acyl pyrrole-derived latent enolate equivalent (compounds **40** and **41**) decreases its nucleophilicity enough to inhibit the conjugate addition.

Figure 5. Latent enolate equivalents not able to participate in the organocatalytic Mukaiyama-Michael reaction.

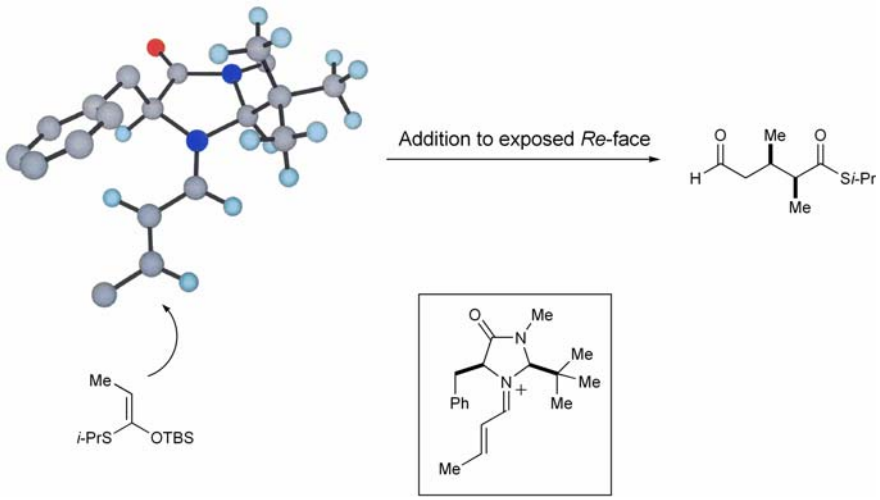


No ester-derived silyl ketene acetals (**42**) ever afforded conjugate addition product, and alkyl enol ethers and silyl enol ethers (**43**-**48**) were not competent substrates (Figure 5). Only latent enolate equivalents **46** and **47** yielded Mukaiyama-Michael adducts in significant yields, but these were in poor diastereo- and enantioselectivity.

Stereochemical Rationale

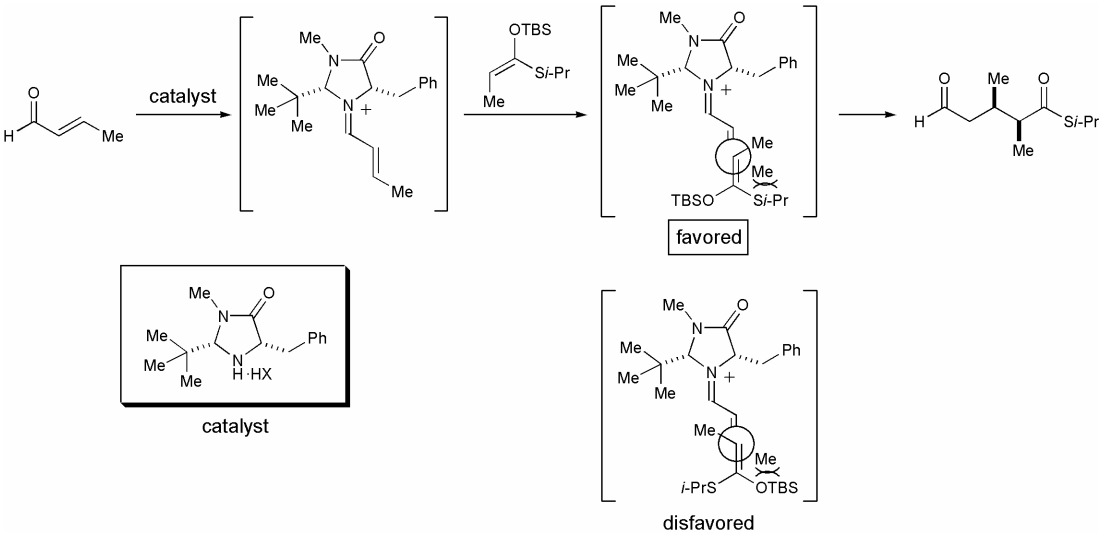
One of the great benefits of organocatalytic methodology is the ease with which it can be modeled using relatively simple computational methods. This simplicity in the calculation of intermediates allows accurate prediction of the selectivity of an organocatalytic process. The sense of enantioinduction observed in all cases is consistent with the conformation of a calculated iminium ion formed from imidazolidinone catalyst **19** and an α,β-unsaturated aldehyde (Scheme 5).[40] The steric bulk of the catalyst's *t*-butyl substituent controls the geometry of the iminium ion. The *E*-iminium ion and the position of the benzyl group combine to effectively shield the *Si*-face of the reactive olefin, and only allows conjugate addition to occur from the exposed *Re*-face. The *cis*-disposition of the *t*-butyl group relative to the benzyl group serves to reinforce this selectivity.

Scheme 5. Stereochemical rationale for the observed sense of enantioinduction.



The organocatalytic Mukaiyama-Michael reaction sets two stereocenters, so diastereoselectivity as well as enantioselectivity must be considered. The diastereoselectivity of the conjugate addition switches with the geometry of the nucleophile (Tables 9 and 10). The diastereoselectivity observed with each geometry of latent enolate equivalent is consistent with what has been observed in the literature for Lewis acid-catalyzed Mukaiyama-Michael reactions.[43]

Scheme 6. Stereochemical rationale for the observed diastereoselectivity with thioester-derived silyl ketene acetals.

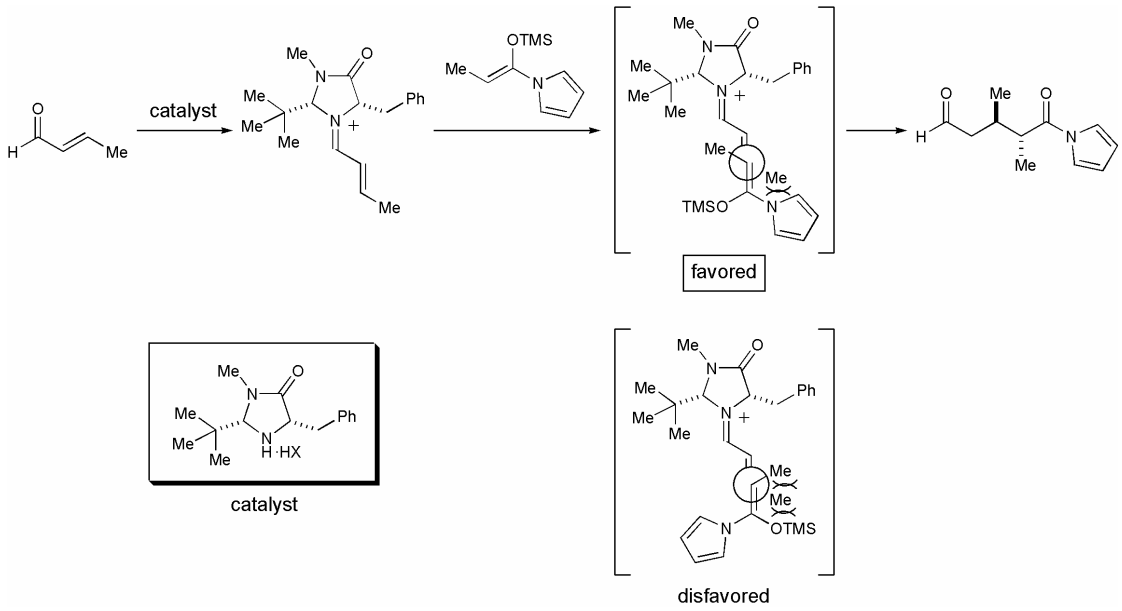


Organocatalytic Mukaiyama-Michael reactions between α,β-unsaturated aldehydes and *Z*-silyl ketene acetals derived from thioesters yield *syn*-products (Scheme 6). It is assumed that the conjugate addition of the latent enolate equivalent will occur through an open transition state. This is the case for Lewis acid catalyzed Mukaiyama-Michael reactions, and the same reasoning applies under organocatalytic conditions.[43] In an open transition state, approach of the nucleophilic olefin occurs anti-periplanar to the electrophilic olefin. Once the proper orientation between the reacting

olefins is established, minimization of steric interactions results in the prediction of the *syn*-product. In the favored transition state, the β-methyl substituent of the iminium ion is involved in two gauche interactions, one with the methyl group of the silyl ketene acetal, and one with the thioether of the silyl ketene acetal. There is also a weak gauche interaction between the *S*-isopropyl group of the silyl ketene acetal and the β-substituent of the aldehyde. In the disfavored transition state the methyl group of the silyl ketene acetal is involved in a gauche interaction with the iminium ion, and the large silyl group is involved in a gauche interaction with the β-methyl substituent of the iminium ion. The interaction between the silyl group and the β-methyl substituent is the dominating interaction, and it is of sufficient magnitude to favor the former transition state.

Organocatalytic Mukaiyama-Michael reactions between α,β-unsaturated aldehydes and *Z*-silyl ketene acetals derived from acyl pyrroles yield *anti*-products (Scheme 7). The olefin geometry for the silyl ketene acetal is designated (*Z*) for both thioester- and acyl pyrrole-derived silyl ketene acetals, but the relative configurations are opposite. Again, it is assumed that the conjugate addition of the latent enolate equivalent will occur through an open transition state.[43] In an open transition state, approach of the nucleophilic olefin occurs anti-periplanar to the electrophilic olefin. Once the proper orientation between the reacting olefins is established, minimization of steric interactions results in the prediction of the *anti*-product. In the favored transition state, the β-methyl substituent of the iminium ion is involved in only one gauche interaction with the relatively small, planar pyrrole ring. In the disfavored transition state, the same β-methyl substituent is involved in a gauche interaction with the large silyl group and the methyl group of the latent enolate equivalent.

Scheme 7. Stereochemical rationale for the observed diastereoselectivity with acyl pyrrole-derived silyl ketene acetals.



III. Conclusion

An asymmetric organocatalytic Mukaiyama-Michael reaction has been described herein. Using a chiral imidazolidinone salt, Mukaiyama-Michael adducts of α,β-unsaturated aldehydes and latent enolate equivalents can be accessed in good yields and selectivities. The organocatalytic Mukaiyama-Michael reaction has led to the development of a second generation imidazolidinone catalyst that demonstrates higher reactivity and selectivity than the catalyst developed for the organocatalytic Diels-Alder reaction. This new catalyst should allow the development of a greater number of organocatalytic transformations than possible with the original imidazolidinone catalyst.

IV. Experimental Section

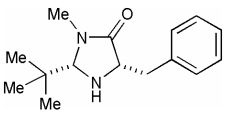
General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[44] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of prducts was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[45] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed be fluorescence quenching, *p*-anisaldehyde stain, or $KMnO_4$ stain.

^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively) or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported with chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) , integration, and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C, $CHCl_3$). Mass spectra were obtained from the California Institute of Technology Mass Spectrometer Facility. Gas chromatography was performed on Agilent 5890A and Hewlett-Packard 6890 Series gas chromatographs equipped with a split/splitless capillary injection system and flame ionization detectors using the following columns: J&C industries DB-1701 (30 m x 0.25 mm), Bodman Chiraldex Γ-

TA (30 m x 0.25 mm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254 nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

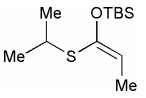
General procedure for the organocatalytic Mukaiyama-Michael reaction. A 1-dram vial with a magnetic stirrer was charged with the appropriate (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one salt (**19**), the appropriate solvent, H_2O, and α,β-unsaturated aldehyde. The solution was then stirred at room temperature for 5 min before being cooled to the desired temperature. The solution was stirred for 5 min before the appropriate silyl ketene acetal was added. The resulting mixture was maintained at the desired temperature until consumption of the silyl ketene acetal as determined by TLC. The reaction was then quenched by cold filtration through silica and purified by silica gel chromatography.

General procedure for the preparation of acyl oxazolidinone derivatives. An analytical quantity (approximately 10 mg) of the purified Mukaiyama-Michael adduct was oxidized to the corresponding acid according to the procedure previously described in the literature.[46] The crude acid was then coupled to 2-oxazolidinone according to the procedure previously described in the literature.[20] The resulting product was purified by silica gel chromatography (20-35% EtOAC/Hex).

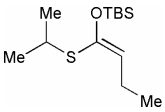


(2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (19). The title compound was prepared as previously described in the

literature.[47] All spectral data were in agreement with those previously reported. $[\alpha]_D$ = - 71.8 ° (free base).

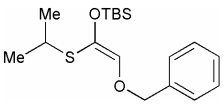


***tert*-Butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane.** The title compound was prepared from thiopropionic acid *S*-isopropyl ester according to the procedure described in the literature.[20] bp = 43 °C (160 mT); IR (CH_2Cl_2) 2960, 2930, 2860, 1634, 1473, 1463, 1364, 1256, 1152, 1110, 946, 853, 840, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (q, *J* = 6.8 Hz, 1H, vinyl), 3.30 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 1.68 (d, *J* = 6.8 Hz, 3H, methyl), 1.26 (d, *J* = 6.9 Hz, 6H, SCH(C**H**$_3)_2$), 0.93 (s, 9H, Si$(CH_3)_2$C(C**H**$_3)_3$), 0.17 (s, 6H, Si(C**H**$_3)_2$C$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 110.2, 35.0, 25.9, 25.7, 23.2, 18.1, 13.7, -4.7; HRMS (FAB peg) exact mass calcd for M+H ($C_{12}H_{27}OSiS$) requires *m/z* 247.1552, found *m/z* 247.1540.

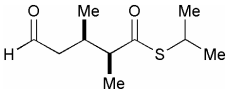


***tert*-Butyl-(1-isopropylsulfanyl-but-1-enyloxy)-dimethyl-silane.** The title compound was prepared from thiobutyric acid *S*-isopropyl ester according to the procedure described in the literature.[20] The title compound was purified by removing all volatiles from the crude product by distillation (15 mT, 100 °C bath). IR (CH_2Cl_2) 2960, 2931, 2896, 2860, 1627, 1472, 1463, 1363, 1256, 1151, 1130, 1112, 1063, 1006, 840, 781, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, *J* = 7.5 Hz, 1H, vinyl-H), 3.30 (septet, *J* = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 2.13 (app pentet, *J* = 7.7 Hz, 2H, C**H**$_2CH_3$), 1.51 (d, *J* = 6.9 Hz, 6H, SCH(C**H**$_3)_2$), 0.96-0.90 (m, 12H, SiC(C**H**$_3)_3$ and CH_2C**H**$_3$), 0.18 (s, 6H, Si(*t*-Bu)(C**H**$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 117.9, 34.8, 25.7, 23.2, 21.9, 18.1, 14.7, -4.7; HRMS (EI) exact mass calcd for ($C_{13}H_{28}OSiS$) requires

m/z 260.1630, found *m/z* 260.1625.

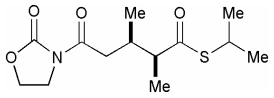


Z-(2-Benzyloxy-1-isopropylsulfanyl-vinyloxy)-*tert*-butyl-dimethylsilane. The title compound was prepared from benzyloxy-thioacetic acid *S*-isopropyl ester according to the procedure described in the literature.[20] The title product was isolated from the crude reaction mixture by filtration through triethylamine-treated silica (5% TEA/hexanes). IR (CH_2Cl_2) 2958, 2929, 2859, 1252, 1153, 839, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H, ArH), 6.18 (s, 1H, vinyl-H), 4.70 (s, 2H, CH_2Ph), 3.19 (septet, J = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 1.19 (d, J = 6.6, 6H, SCH(C**H**$_3)_2$), 0.81 (s, 9H, Si(C(C**H**$_3)_3)(CH_3)_2$), 0.01 (s, 6H, Si(C$(CH_3)_3)$(C**H**$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.4, 133.0, 128.5, 128.0, 127.9, 74.4, 35.6, 25.9, 23.4, 18.3, -4.4; HRMS (FAB) exact mass calcd for ($C_{18}H_{30}O_2SiS$) requires *m/z* 338.1736, found *m/z* 338.1747.

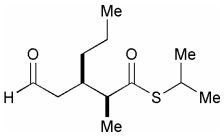


(2*S*, 3*R*)-2,3-Dimethyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 1). The title compound was prepared according to the general procedure from crotonaldehyde (124 μL, 1.5 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (0.14 mL, 0.50 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (41 mg, 0.10 mmol) in acetone (0.25 mL) and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 23 h. The resulting residue was purified by silica gel chromatography (10% ether/pentane) to provide the pure product as a colorless oil in 76% yield (77 mg, 0.38 mmol). 10:1 *syn*:*anti*, *Syn* isomer: IR (CH_2Cl_2) 2968, 1725, 1681, 1455, 1384, 1369, 1246, 965, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

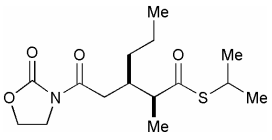
9.72 (dd, *J* = 2.5, 1.7 Hz, 1H, CHO), 3.62 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 2.58-2.38 (m, 2H, CHOC**H**$_2$), 2.34-2.22 (m, 1H, COC**H**(CH_3)C), 1.32-1.24 (m, 7H, CC**H**(CH_3)C and SCH(C**H**$_3)_2$), 1.14 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)), 0.96 (d, *J* = 6.6 Hz, 3H, CCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 201.7, 53.1, 48.8, 34.9, 31.3, 23.3, 23.2, 17.2, 14.5; HRMS (EI) exact mass calcd for M+H ($C_{10}H_{19}O_2S$) requires *m/z* 203.1106, found *m/z* 203.1106. $[\alpha]_D$ = + 34.1 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



(2*S*, 3*R*)-2,3-Dimethyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2970, 1780, 1697, 1685, 1388, 1219, 965 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, *J* = 8.0 Hz, 2H, OC**H**$_2$CH$_2$N), 4.01 (t, *J* = 8.2 Hz, 2H, OCH$_2$C**H**$_2$N), 3.61 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 3.16-2.36 (m, 4H, COC**H**$_2$C**H**(CH_3)C**H**(CH_3)CO), 1.29 (d, *J* = 1.9 Hz, 3H, SCH(C**H**$_3)(CH_3)$), 1.27 (d, *J* = 1.9 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 1.12 (d, *J* = 7.2 Hz, 3H, COCH(C**H**$_3$)C), 0.95 (d, *J* = 6.9 Hz, 3H, COCH$_2$CH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 172.3, 153.7, 62.2, 52.4, 42.7, 39.9, 34.7, 34.5, 32.4, 23.2, 16.2, 13.1; HRMS (FAB) exact mass calcd for ($C_{13}H_{22}NO_4S$) requires *m/z* 288.1270, found *m/z* 288.1264. $[\alpha]_D$ = + 37.1 °. Enantiomeric excess was determined by HPLC analysis(ODH and ODH guard, 3% isopropanol in hexanes, 1 mL/min); (2*R*, 3*S*) isomer t_r = 89.3 min and (2*S*, 3*R*) isomer t_r = 100.0 min.

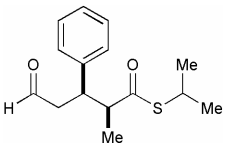


(2*S*, 3*R*)-2-Methyl-3-(2-oxo-ethyl)hexanethioic acid *S*-isopropyl ester (Table 9, entry 2). The title compound was prepared according to the general procedure from 2-hexenal (157 μL, 1.35 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (0.13 mL, 0.45 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (37 mg, 0.090 mmol) in acetone (0.225 mL) and H_2O (8.1 μL, 0.45 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (3% EtOAc/Hex) to provide the pure product as a colorless oil in 62% yield (64 mg, 0.28 mmol). 6:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2961, 2931, 1725, 1680, 1463, 1367, 965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.0 Hz, 1H, CHO), 3.62 (septet, *J* = 6.8 Hz, 1H, SC**H**$(CH_3)_2$), 2.72-2.64 (m, 1H, COC**H**(CH_3)C), 2.52 (ddd, *J* = 17.1, 5.4, 2.0 Hz, 1H, CH**H**CHO), 2.43-2.32 (m, 2H, C**H**(*n*-Pr)C**H**HCHO), 1.43-1.22 (m, 10H), 1.14 (d, *J* = 6.8 Hz, 3H, COCH(C**H**$_3$)C), 0.89 (t, *J* = 6.8, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 202.1, 51.0, 46.2, 36.1, 34.9, 33.8, 23.3, 23.1, 20.1, 14.9, 14.5; HRMS (EI) exact mass calcd for ($C_{12}H_{22}O_2S$) requires *m/z* 230.1341, found *m/z* 230.1341. $[\alpha]_D$ = + 29.5 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



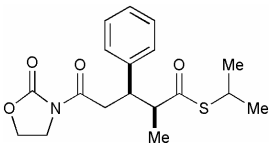
(2*S*, 3*R*)-2-Methyl-3-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-hexanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2962, 1782, 1697, 1684, 1387, 1223, 1197, 958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, *J* = 7.2 Hz, 2H, OC**H**$_2$CH$_2$N), 4.02 (t, *J* = 7.7 Hz, 2H, OCH$_2$C**H**$_2$N), 3.61 (septet, *J* =

6.9 Hz, 1H, SC**H**$(CH_3)_2$), 3.12-2.70 (m, 3H COC$\mathbf{H}_2$CH(*n*-Pr)C**H**(CH_3)CO), 2.52-2.40 (m, 1H, CCH(*n*-Pr)C), 1.40-1.20 (m, 10H, SCH(C$\mathbf{H}_3)_2$ and C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 1.11 (d, *J* = 6.9 Hz, 3H, CH(C$\mathbf{H}_3$)CO), 0.87 (t, *J* = 6.6 Hz, 3H, CH_2C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 172.8, 153.7, 62.2, 50.6, 42.8, 37.1, 37.0, 34.6, 32.9, 23.3, 23.1, 20.3, 14.4, 13.1; HRMS (FAB) exact mass calcd for ($C_{15}H_{26}NO_4S$) requires *m/z* 316.1583, found *m/z* 316.1581. $[\alpha]_D$ = + 30.3 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 3% isopropanol in hexanes, 1 mL/min); (2*S*, 3*R*) isomer t_r = 25.3 min and (2*R*, 3*S*) isomer t_r = 27.0 min; *Anti* diastereomers t_r = 30.2 and 33.5 min.

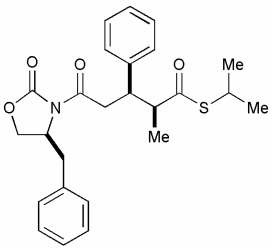


(2*S*, 3*R*)-2-Methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester (Table 9, entry 3). The title compound was prepared according to the general procedure from cinnamaldehyde (76 μL, 0.60 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (95 μL, 0.40 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (33 mg, 0.080 mmol) in acetone (0.20 mL), cyclohexane (14 μL), and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (5% EtOAc/Hex) to provide the pure product as a colorless oil in 50% yield (52 mg, 0.20 mmol). 20:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2967, 1725, 1677, 1453, 963, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (t, *J* = 2.2 Hz, 1H, CHO), 7.34-7.14 (m, 5H, ArH), 3.67 (septet, *J* = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 3.44 (dt, *J* = 10.4, 7.1 Hz, 1H CHPh), 2.86-2.78 (m, 1H, COC**H**(CH_3)C), 2.77 (dd, *J* = 7.1, 1.7 Hz, 2H, CHOC$\mathbf{H}_2$), 1.33 (d, *J* = 6.7 Hz, 3H, SCH(C$\mathbf{H}_3$)(CH_3)), 1.31 (d, *J* = 6.0 Hz, 3H, SCH(CH_3)(C$\mathbf{H}_3$)), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 200.8, 140.8, 128.9, 128.2, 127.4, 54.0, 48.3,

43.6, 35.1, 23.3, 23.2, 17.2; HRMS (EI) exact mass calcd for ($C_{15}H_{20}O_2S$) requires *m/z* 264.1184, found *m/z* 264.1182. $[\alpha]_D$ = + 49.6 °. Diastereomer ratios were determined by GLC analysis (Γ-TA column, 130 °C isotherm, 1 mL/min); *syn* diastereomer t_r = 33.1 min and *anti* diastereomer t_r = 36.6 min. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

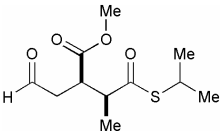


(2*S*, 3*R*)-2-Methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-3-phenyl-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2968, 2929, 1780, 1699, 1678, 1455, 1388, 1272, 1224, 1041, 968, 760, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H, ArH), 4.35-4.15 (m, 2H, OC**H**$_2$CH$_2$N), 3.95-3.45 (m, 5H), 3.10 (app dd, *J* = 16.2, 3.0 Hz, 1H, COC**H**HCH(Ph)), 2.88 (ddd, *J* = 17.1, 9.9, 7.2 Hz, 1H, COCH**H**CH(Ph)), 1.33 (d, *J* = 6.9 Hz, 3H, SCH(C**H**$_3$)(CH$_3$)), 1.30 (d, *J* = 7.2 Hz, 3H, SCH(CH$_3$)(C**H**$_3$)), 0.93 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 171.2, 153.4, 141.2, 128.4, 128.3, 126.9, 61.9, 53.3, 44.4, 42.4, 39.4, 34.7, 23.0, 22.9, 17.0; HRMS (FAB) exact mass calcd for M+H ($C_{18}H_{24}NO_4S$) requires *m/z* 350.1426, found *m/z* 350.1421. $[\alpha]_D$ = + 34.7 °. Enantiomeric excess was determined by HPLC analysis (ODH and ODH guard, 6% isopropanol in hexanes, 1 mL/min); (2*S*, 3*R*) isomer t_r =47.6 min and (2*R*, 3*S*) isomer t_r = 54.3 min.



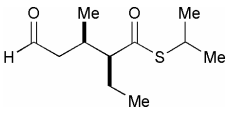
(2*S*, 3*R*)-5-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure.

IR (CH_2Cl_2) 2971, 2928, 1782, 1702, 1674, 1454, 1388, 1355, 1213, 954, 761, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.03 (m, 10H, ArH), 4.38-4.26 (m, 1H, OCH_2C**H(**Bn)N), 3.95 (dd, *J* = 9.0, 2.7 Hz, OC**H**HCH(Bn)N), 3.90-3.36 (m, 4H), 3.13-3.00 (m, 2H, CH_2Ph), 2.90-2.76 (m, 1H, COC**H**HCH(Ph)), 2.55 (dd, *J* = 13.4, 9.8 Hz, 1H, COCH**H**CH(Ph)), 1.29 (d, *J* = 6.9 Hz, 3H, SCH(C**H**$_3$)(CH_3)), 1.25 (d, *J* = 6.9 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 0.88 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 171.1, 153.3, 141.1, 135.3, 129.4, 128.9, 128.5, 128.4, 127.2, 127.0, 66.0, 55.1, 53.5, 44.7, 39.7, 37.7, 34.7, 31.2, 23.0, 22.9, 17.0; HRMS (FAB) exact mass calcd for M+H ($C_{25}H_{30}NO_4S$) requires *m/z* 440.1896, found *m/z* 440.1882. $[\alpha]_D$ = + 64.5 °. The title compound was recrystallized (THF/hexanes) to afford x-ray quality crystals for XRD analysis (see Appendix 1).



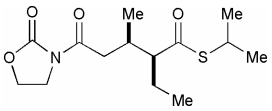
(2*S*, 3*R*)-3-Isopropylsulfanylcarbonyl-2-(2-oxo-ethyl)-butyric acid methyl ester (Table 9, entry 4). The title compound was prepared according to the general procedure from 4-oxo-but-2-enoic acid methyl ester (43 mg, 0.38 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (59 μL, 0.25 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (20 mg, 0.050 mmol) in acetone (0.125 mL) and H_2O (4.5 μL, 0.25 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (CH_2Cl_2) to provide the pure product as a colorless oil in 73% yield (45 mg, 0.18 mmol). 4:1 *syn*:*anti*, *Syn* 91% ee. *Syn* isomer: IR (CH_2Cl_2) ; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (app s, 1H, CHO), 3.71 (s, 3H, CO_2CH_3), 3.64 (septet, *J* = 6.9 Hz, 1H, SC**H**(CH_3)$_2$), 3.19 (qd, *J* = 7.7, 3.7 Hz, 1H COC**H**(CH_3)C), 3.01-2.87 (m, 2H, $COCH_2C$), 2.64 (td, *J* = 3.2, 0.5 Hz, 1H,

$(CH_2)(CH)C\mathbf{H}CO_2CH_3$), 2.60 (d, *J* = 6.9 Hz, 6H, $SCH(C\mathbf{H}_3)_2$), 1.20 (d, *J* = 6.9 Hz, 3H, $COCH(C\mathbf{H}_3)C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 199.4, 173.3, 52.1, 48.2, 43.2, 41.0, 34.9, 22.9, 22.8, 15.8; HRMS (EI) exact mass calcd for M+H ($C_{11}H_{19}O_4S$) requires *m/z* 247.1004, found *m/z* 247.1015. $[\alpha]_D$ = + 0.74 °. Diastereomer ratios and enantiomeric excess were determined by GLC analysis (Γ-TA column, 130 °C isotherm, 1 mL/min); (2*S*, 3*R*) isomer t_r =29.1 min, (2*R*, 3*S*) isomer t_r = 30.4 min, and *anti* isomer t_r = 33.0 min.

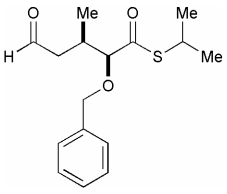


(2*S*, 3*R*)-2-Ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 5). The title compound was prepared according to the general procedure from crotonaldehyde (25 μL, 0.30 mmol), *tert*-Butyl-(1-isopropylsulfanyl-but-1-enyloxy)-dimethyl-silane (29 μL, 0.10 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (8.0 mg, 0.020 mmol) in diethyl ether (0.050 mL), benzyl methyl ether (5.0 μL), and H_2O (1.8 μL, 0.10 mmol) at -78 °C. The solution was stirred until the reaction was judged to be complete by GLC analysis (DB-1701 column, 70 °C, 25 °C/min gradient, 1 mL/min); benzyl methyl ether t_r = 3.75 min, 2-ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester t_r = 6.40 min. A yield of 76% was determined by comparison of the peak areas of benzyl methyl ether and 2-ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester. 4:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2968, 1727, 1678, 1461 990, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 2.4, 1.3 Hz, 1H, CHO), 3.66 (septet, *J* = 6.9 Hz, 1H, $SC\mathbf{H}(CH_3)_2$), 2.62-2.20 (m, 3H, $CHOC\mathbf{H}_2CH(CH_3)C\mathbf{H}(Et)COS(i\text{-}Pr)$), 1.77-1.46 (m, 3H, $CH_2C\mathbf{H}(CH_3)C$ and $C\mathbf{H}_2CH_3$), 1.30 (d, *J* = 6.9 Hz, 6H, $SCH(C\mathbf{H}_3)_2$), 0.99 (d, *J* = 6.1 Hz, 3H, $CH_2CH(C\mathbf{H}_3)C$), 0.91 (t, *J* = 7.5 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6,

201.8, 60.5, 48.3, 48.2, 34.7, 30.3, 23.0, 22.9, 17.9, 11.8; HRMS (EI) exact mass calcd for M-H ($C_{11}H_{19}O_2S$) requires *m/z* 215.1106, found *m/z* 215.1114. $[\alpha]_D$ = + 2.0 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

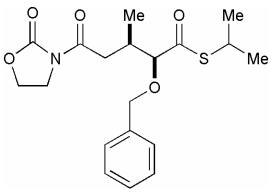


(2*S*, 3*R*)-2-Ethyl-3-methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 94% ee. *Syn* isomer: IR (CH_2Cl_2) 2966, 1779, 1682, 1456, 1386, 1223, 1109, 1042, 990, 827, 761, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.2 Hz, 2H, OC**H$_2$**CH$_2$N), 4.02 (t, *J* = 7.4 Hz, 2H, OCH$_2$C**H$_2$**N), 3.65 (septet, *J* = 6.9 Hz, 1H, SC**H**(CH$_3$)$_2$), 3.03-2.85 (m, 1H, CHCOS(*i*-Pr)), 2.53-2.36 (m, 2H, COCH$_2$), 1.80-1.40 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 6H, SCH(C**H$_3$**)$_2$), 0.99 (d, *J* = 6.6 Hz, 3H, CHC**H$_3$**), 0.90 (t, *J* = 7.2 Hz, 3H, CH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 172.3, 153.4, 62.0, 60.0, 42.5, 39.6, 34.6, 31.8, 26.3, 22.9, 21.8, 17.1, 12.0; HRMS (EI) exact mass calcd for M + H ($C_{14}H_{24}NO_4S$) requires *m/z* 302.1426, found *m/z* 302.1440. $[\alpha]_D$ = + 20.7 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 1% ethanol in hexanes, 1 mL/min); *syn* isomers t_r = 54.2 and 68.4 min and *anti* isomers t_r = 48.6 and 49.8 min.



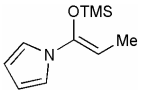
(2*S*, 3*R*)-2-Benzyloxy-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 6). The title compound was prepared according to the general procedure from crotonaldehyde (85 μL, 1.0 mmol), *Z*-(2-benzyloxy-1-isopropylsulfanyl-vinyloxy)-*tert*-butyl-dimethylsilane (0.12

mL, 0.34 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TFA **19** (25 mg, 0.068 mmol) in CH_2Cl_2 (0.17 mL) and H_2O (6.1 μL, 0.34 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as a colorless oil in 82% yield (82 mg, 0.28 mmol). >20:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2966, 1724, 1676, 1456, 1124, 1087, 1059, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (t, *J* = 2.2 Hz, 1H, CHO), 7.40-7.28 (m, 5H, ArH), 4.81 (d, *J* = 11.5 Hz, 1H, PhC**H**HO), 4.35 (d, *J* = 11.5 Hz, 1H, PhCH**H**O), 3.86 (d, *J* = 4.4 Hz, 1H, COCH(OBn)C), 3.65, (septet, *J* = 7.1 Hz, 1H, SC**H**$(CH_3)_2$), 2.66-2.45 (m, 2H, CHOCH**H**C**H**(CH_3)C), 2.31 (ddd, *J* = 16.5, 6.6, 1.6 Hz, 1H, CHOC**H**HC), 1.34 (d, *J* = 3.3 Hz, 3H, SCH(C**H**$_3$)(CH_3)), 1.32 (d, *J* = 3.3 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 0.98 (d, *J* = 7.1 Hz, 3H, CHOCH$_2$CH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 201.2, 137.1, 128.6, 128.4, 128.2, 86.8, 73.9, 47.4, 32.3, 25.9, 23.3, 23.2, 15.0; HRMS (FAB) exact mass calcd for M+H ($C_{16}H_{23}O_3S$) requires *m/z* 295.1368, found *m/z* 295.1376. $[\alpha]_D$ = + 77.1 °. Diastereomer ratios were determined by ^1H NMR or GLC analysis (DB-1701 column, 70 °C, 25 °C/min gradient to 280 °C isotherm, constant flow 1 mL/min); *syn* isomer t_r = 9.02 min and *anti* isomer t_r = 9.38 min. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

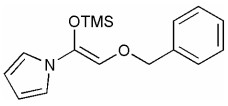


(2*S*, 3*R*)-2-Benzyloxy-3-methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentantthioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2968, 2929, 2869, 1782, 1697, 1677, 1479, 1455, 1388, 1312, 1223, 1102, 1042, 755, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H, ArH), 4.86

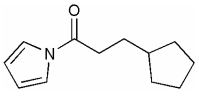
(d, *J* = 11.5 Hz, 1H, OC**H**HCH$_2$N), 4.35 (d, *J* = 8.2 Hz, 2H, CH$_2$Ph), 4.32 (d, *J* = 5.0 Hz, 1H, OCH**H**CH$_2$N), 4.00 (d, *J* = 3.9 Hz, 1H, COCH(OBn)C), 3.97-3.71 (m, 2H, OCH$_2$C**H$_2$**N), 3.65 (septet, *J* = 7.1 Hz, 1H, SCH(Me)$_2$), 2.94 (dd, *J* = 17.6, 8.2 Hz, 1H, COC**H**HC), 2.79 (dd, *J* = 17.6, 5.5 Hz, 1H, COCH**H**C), 2.63-2.52 (m, 1H, CHMe), 1.34 (d, *J* = 2.2 Hz, 3H, SCH(C**H$_3$**)(CH$_3$)), 1.32 (d, *J* = 2.8 Hz, 3H, SCH(CH$_3$)(C**H$_3$**)), 0.98 (d, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.2, 171.8, 155, 137.5, 128.7, 128.5, 127.9, 85.9, 73.9, 62.1, 42.5, 38.5, 34.1, 33.4, 23.3, 23.3, 14.6; HRMS (EI) exact mass calcd for ($C_{19}H_{27}NO_5S$) requires *m/z* 380.1532, found *m/z* 380.1537. $[\alpha]_D$ = +63.6 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 10% isopropanol in hexanes, 1 mL/min); *syn* isomers t_r = 25.1 and 31.9 min.



1-(1-Trimethylsilanyloxy-propenyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[48] All spectral data were in agreement with those previously reported.

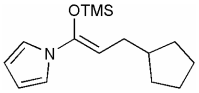


1-(2-Benzyloxy-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[20] All spectra data were in agreement with those previously reported.

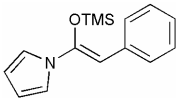


3-Cyclopentyl-1-pyrrol-1-yl-propan-1-one. The title compound was prepared from pyrrole and 3-cyclopentyl-propionyl chloride according to the procedure described in the literature.[48] Analytical data: bp = 125-130 °C (2 mm Hg); IR (CH_2Cl_2) 2948, 2866, 1717, 1469, 1331, 1277, 1118, 1071, 921, 740 cm^{-1}; ^{1}H

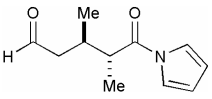
NMR (300 MHz, $CDCl_3$) δ 7.32 (t, *J* = 2.2 Hz, 2H, ArH), 6.28 (t, *J* = 2.2 Hz, 2H, ArH), 2.82 (dd *J* = 8.5, 7.4 Hz, 2H, $COCH_2$), 1.90-1.40 (m, 9H), 1.25-1.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 119.0, 113.0, 39.6, 33.9, 32.5, 32.4, 30.9, 25.6, 25.2; HRMS (EI) exact mass calcd for ($C_{12}H_{27}NO$) requires *m/z* 191.1310, found *m/z* 191.1310.



1-(3-Cyclopentyl-1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole. The title compound was prepared from 3-cyclopentyl-1-pyrrol-1-yl-propan-1-one (X) according to the procedure described in the literature.[48] IR (CH_2Cl_2) 2953, 2869, 1723, 1682, 1470, 1312, 1254, 1200, 1087, 921, 847, 801, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (t, *J* = 2.4 Hz, 2H, ArH), 6.17 (t, *J* = 2.4 Hz, 2H, ArH), 4.71 (t, *J* = 7.4 Hz, 1H, vinyl), 2.88-2.62 (m, 1H), 2.49-2.31 (m, 1H), 1.95-1.35 (m, 7H), 1.30-1.00 (m, 2H), 0.35 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.7, 119.0, 108.8, 107.5, 40.2, 32.9, 32.7, 32.4, 25.2, 25.0, 2.1; HRMS (EI) exact mass calcd for M + H ($C_{15}H_{26}NOSi$) requires *m/z* 264.1784, found *m/z* 264.1772.

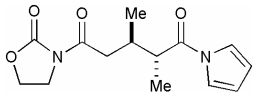


1-(2-Phenyl-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[20] All spectral data were in agreement with those previously reported.

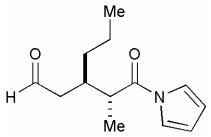


(3*R*, 4*R*)-Dimethyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 1). The title compound was prepared according to the general procedure from crotonaldehyde (124 μL, 1.5 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (0.104 mL, 0.50 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-

one·TCA **19** (41 mg, 0.10 mmol) in toluene (1.0 mL) and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 21 h. The resulting residue was purified by silica gel chromatography (30% ether/pentane) to provide the pure product as an oil in 92% yield (89 mg, 0.46 mmol). 1:17 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 2971, 1717, 1468, 1369, 1272, 1104, 1074, 909, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 2.4, 1.1 Hz, 1H, CHO), 7.30 (t, *J* = 2.4 Hz, 2H, ArH), 6.29 (t, *J* = 2.1 Hz, 2H, ArH), 3.13 (app pentet, *J* = 6.4, 1H, COC**H**(CH_3)C), 2.69-2.48 (m, 2H, CHOC**H**HC**H**(CH_3)C), 2.31 (ddd, *J* = 16.8, 8.2, 2.1 Hz, 1H, CHOCH**H**C), 1.23 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)), 1.08 (d, *J* = 6.9 Hz, 3H, CCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 173.3,119.0, 113.3, 46.7, 42.4, 30.8, 18.5, 14.1; HRMS (EI) exact mass calcd for ($C_{11}H_{15}NO_2$) requires *m/z* 193.1103, found *m/z* 193.1101. $[\alpha]_D$ = - 36.6 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

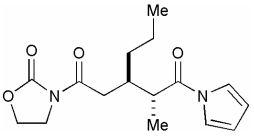


(2*R* 3*R*)-2,3-Dimethyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 83% ee. All spectral data were consistent with those reported in the literature.[20]



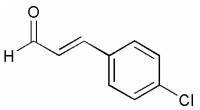
(3*R*)-3-((1*R*)-1-Methyl-2-oxo-2-pyrrol-1-yl-ethyl)-hexanal (Table 10, entry 2). The title compound was prepared according to the general procedure from 2-hexenal (157 μL, 1.35 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole **X** (94 μL, 0.45 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-

imidazolidin-4-one·DNBA (41 mg, 0.090 mmol) in DME (0.225 mL) and H_2O (8.1 μL, 0.45 mmol) at -40 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 56% yield (55 mg, 0.25 mmol). 1:4 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 2959, 1715, 1469, 1273, 1103, 1073, 910, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.3 Hz, 1H, CHO), 7.46 (t, *J* = 2.4 Hz, 2H, ArH), 6.31 (t, *J* = 2.4 Hz, 2H, ArH), 3.33 (septet, *J* = 5.3 Hz, 1H, SC**H**$(CH_3)_2$), 2.71-2.32 (m, 4H, CHOC**H**$_2$C**H**(*n*-Pr)C**H**(CH_3)), 1.46-1.10 (m, 7H, C**H**$_2$C**H**$_2CH_3$ and CHC**H**$_3$), 0.85 (t, *J* = 6.9 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 173.5, 119.3, 113.2, 45.8, 40.4, 35.1, 32.1, 20.1, 14.0, 13.2; HRMS (EI) exact mass calcd for ($C_{13}H_{19}NO_2$) requires *m/z* 221.1416, found *m/z* 221.1419. $[\alpha]_D$ = + 0.42 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

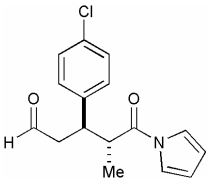


(2*R*, 3*R*)-2-Methyl-5-(2-oxo-oxazolidin-3-yl)-3-propyl-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 93% ee. *Anti* isomer: IR (CH_2Cl_2) 2959, 1785, 1700, 1685, 1467, 1391, 1334, 1311, 1265, 1225, 1119, 1100, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 2.6, 2.2 Hz, 2H, ArH), 6.30 (dd, *J* = 2.6, 2.2 Hz, 2H, ArH), 4.43 (t, *J* = 8.4 Hz, 2H, OC**H**$_2CH_2$N), 4.03 (t, *J* = 8.4 Hz, 2H, OCH_2C**H**$_2$N), 3.43 (qd, *J* = 6.6, 4.4 Hz, 1H, COC**H**(Me)C), 3.13 (dd, *J* = 18.5, 9.2 Hz, 1H, COC**H**HC), 3.00 (dd, *J* = 18.0, 4.4 Hz, 1H, COCH**H**C), 2.55-2.43 (m, 1H, CCCH(*n*-Pr)), 1.47-1.21 (m, 4H, C**H**$_2$C**H**$_2CH_3$), 1.18 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 0.82 (t, *J* = 6.6 Hz, 3H, CH_2C**H**$_3$); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 173.7, 173.0, 153.7, 119.7, 113.2, 62.3, 42.8, 40.6, 37.0, 36.6, 31.5, 20.5, 14.2, 11.7; HRMS (FAB) exact mass calcd for ($C_{16}H_{23}N_2O_4$) requires *m/z* 307.1658, found *m/z* 307.1653; $[\alpha]_D$ = -18.5 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 6% isopropanol in hexanes, 1 mL/min); (2*S*, 3*S*) isomer t_r = 38.6 min and (2*R*, 3*R*) isomer t_r = 41.6 min; *syn* isomers t_r = 29.4 and 35.4 min.



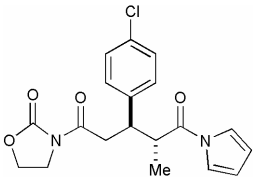
3-(4-Chlorophenyl)-propenal. The title compound was prepared as described in the literature.[49] All spectral data were in agreement with those previously reported.



(3*R*, 4*R*)-3-(4-Chlorophenyl)-4-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 3). The title compound was prepared according to the general procedure from 3-(4-chlorophenyl)-propenal (117 mg, 0.70 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (73 μL, 0.35 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TFA **19** (25 mg, 0.070 mmol) in THF (0.70 mL), cyclohexane (49 μL), and H_2O (6.3 μL, 0.35 mmol) at -60 °C for 23 h. The resulting residue was purified by silica gel chromatography (20% EtOAc/Hex) to provide the pure product as an oil in 74% yield (75 mg, 0.26 mmol). 1:3 *syn:anti*. *Anti* isomer: IR (CH_2Cl_2) 1718, 1492, 1468, 1411, 1368, 1325, 1298, 1271, 1111, 1092, 1074, 1014, 917, 894, 827, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (t, *J* = 1.8 Hz, 1H, CHO), 7.36 (br s, 2H, ArH), 7.30 (d, *J* = 8.5 Hz, 2H, ArH), 7.14 (d, *J* = 8.5 Hz, 2H, ArH), 6.34 (t, *J* = 2.1 Hz, 2H, ArH), 3.66 (td, *J* = 9.1, 5.3 Hz, 1H, CHAr), 3.42-3.32 (m, 1H,

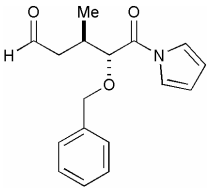
$CHCONR_2$), 2.89-2.71 (m, 2H, C**H**$_2$CHO), 1.33 (d, *J* = 7.0, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 172.9, 138.8, 133.2, 129.5, 129.0, 119.0, 113.8, 47.7, 43.3, 42.2, 16.7; HRMS (EI) exact mass calcd for ($C_{16}H_{17}NO_2Cl$) requires *m/z* 290.0948, found *m/z* 290.0951; $[\alpha]_D$ = -28.0 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

Syn isomer: IR (CH_2Cl_2) 2976, 1720, 1710, 1492, 1467, 1409, 1366, 1323, 1275, 1094, 1074, 1014, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (dd, *J* = 2.1, 1.2 Hz, 1H, CHO), 7.26-7.13 (m, 6H, ArH), 6.25 (t, *J* = 2.4 Hz, 2H, ArH), 3.74 (ddd, *J* = 9.7, 8.2, 5.0 Hz, 1H, CHAr), 3.43 (dt, *J* = 15.2, 7.0 Hz, 1H, $CHCONR_2$), 2.98 (ddd, *J* = 17.3, 4.7, 1.2, 1H, C**H**HCHO), 2.85 (ddd, *J* = 17.3, 9.7, 2.1, 1H, CH**H**CHO), 1.33 (d, *J* = 7.0, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 172.7, 140.1, 133.3, 129.5, 129.2, 119.1, 113.8, 45.7, 43.9, 41.7, 15.6; HRMS (EI) exact mass calcd for ($C_{16}H_{17}NO_2Cl$) requires *m/z* 290.0948, found *m/z* 290.0945; $[\alpha]_D$ = +16.2 °.



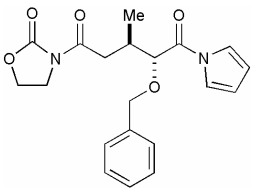
(2*R*, 3*R*)-3-(4-Chloro-phenyl)-2-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 98% ee. *Anti* isomer: IR (CH_2Cl_2) 1777, 1703, 1468, 1389, 1271, 1225, 1092, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 2.1 Hz, 2H, ArH), 7.29 (d, *J* = 8.4 Hz, 2H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 6.34 (t, *J* = 2.1 Hz, 2H, ArH), 4.31 (t, *J* = 8.4 Hz, 2H, OC**H**$_2$CH$_2$), 3.94-3.72 (m, 3H, CH_2C**H**$_2$N and CHAr), 3.57-3.37 (m, 2H, COC**H**(CH_3)C and COC**H**HC), 3.16 (dd, *J* = 17.3, 5.1 Hz, 1H, COCH**H**C), 1.06 (d, *J* = 7.2 Hz, 3H, CH_3);

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 170.9, 153.5, 139.3, 132.9, 129.8, 128.8, 119.1, 113.7, 62.1, 43.3, 43.0, 42.2, 39.5, 16.8; HRMS (FAB) exact mass calcd for M+H ($C_{19}H_{20}N_2O_4Cl$) requires *m/z* 375.1112, found *m/z* 375.1110. $[\alpha]_D$ = - 12.4 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 15% isopropanol in hexanes, 1 mL/min); (2*R*, 3*R*) isomer t_r = 30.4 min and (2*S*, 2*S*) isomer t_r = 34.7 min.

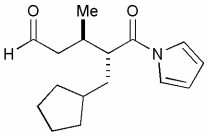


(3*R*, 4*R*)-4-Benzyloxy-3-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 4). The title compound was prepared according to the general procedure from crotonaldehyde (87 μL, 1.05 mmol), 1-(2-benzyloxy-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole (97 μL, 0.35 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TBA **19** (38 mg, 0.070 mmol) in THF (0.175 mL) and H_2O (6.3 μL, 0.35 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 69% yield (69 mg, 0.24 mmol). 1:42 *syn*:*anti*. A*nti* isomer: IR (CH_2Cl_2) 1720, 1469, 1318, 1295, 1099, 1076, 745, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (t, *J* = 1.6 Hz, 1H, CHO), 7.43-7.05 (m, 7H, ArH), 6.20-6.05 (m, 2H, ArH), 4.48 (d, *J* = 11.4 Hz, 1H, OC**H**HPh), 4.22 (d, *J* = 11.4 Hz, 1H, OCH**H**Ph), 4.05 (d, *J* = 7.7 Hz, 1H, COCH(OBn)C), 2.62-2.41 (m, 2H, CHOC**H**$_2$), 2.28 (td, *J* = 8.5, 1.6 Hz, 1H, CH_2C**H**(CH_3)CH), 0.85 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 169.5, 136.3, 128.5, 128.3, 128.3, 119.5, 113.5, 83.9, 72.6, 47.3, 32.3, 16.8; HRMS (EI) exact mass calcd for ($C_{17}H_{19}NO_3$) requires *m/z* 285.1365, found *m/z* 285.1358.

$[\alpha]_D$ = - 39.8 °. Diastereomer ratios and enantiomeric excess were determined by HPLC analysis of the corresponding acyl oxazolidinone.

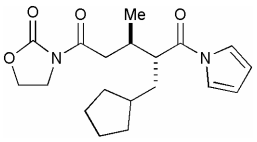


(2*R*, 3*R*)-2-Benzyloxy-3-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure.[20] All spectral data were in agreement with those previously reported.

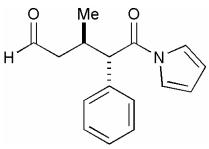


(3*R*, 4*R*)-4-Cyclopentylmethyl-3-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 5). The title compound was prepared according to the general procedure from crotonaldehyde (99 μL, 1.2 mmol), 1-(3-cyclopentyl-1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (0.11 mL, 0.40 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TBA **19** (43 mg, 0.080 mmol) in CH_2Cl_2 (0.10 mL), toluene (0.10 mL), and H_2O (7.2 μL, 0.40 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as a yellow oil in 68% yield (71 mg, 0.27 mmol). 1:10 *syn*:*anti*. A*nti* isomer: IR (CH_2Cl_2) 2951, 1709, 1467, 1273, 1073, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.5 Hz, 1H, CHO), 7.34 (br s, 2H, ArH), 6.35-6.15 (m, 2H ArH), 3.34-2.92 (m, 1H), 2.7-1.8 (m, 3H), 1.78-1.36 (m, 9H), 1.16-0.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 173.2, 119.1, 113.5, 47.4, 47.3, 38.2, 35.5, 33.3, 33.1, 32.3, 31.0, 25.1, 18.0; HRMS (EI) exact mass calcd for ($C_{16}H_{23}NO_2$) requires *m/z* 261.1729, found *m/z* 261.1724. $[\alpha]_D$ = - 14.8 °. Diastereomer ratios were determined by ^1H NMR

analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

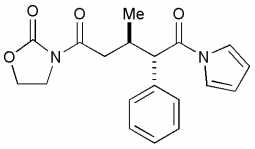


(2*R*, 3*R*)-2-Cyclopentylmethyl-3-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. A*nti* 88% ee. *Anti* isomer: IR (CH_2Cl_2) 2950, 2868, 1780, 1703, 1467, 1388, 1270, 1222, 1112, 1073, 1041, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (br s, 2H, ArH), 6.30 (t, *J* = 2.1 Hz, 2H, ArH), 4.39 (t, *J* = 8.0 Hz, 2H, OC**H**$_2$CH$_2$N), 3.99 (t, *J* = 8.2 Hz, 2H, OCH$_2$C**H**$_2$N), 3.23 (ddd, *J* = 10.4, 5.9, 3.7 Hz, 1H, COC**H**(CH$_2$*c*-penyl)CH), 3.12 (dd, *J* = 17.0, 5.1 Hz, 1H, COC**H**HCH(CH$_3$)C), 2.80 (dd, *J* = 17.3, 8.0 Hz, 1H, COCH**H**CH(CH$_3$)C), 2.58-2.42 (m, 1H, CH$_2$C**H**(CH$_3$)C), 2.10-0.84 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.1, 153.4, 119.2, 113.2, 62.0, 47.1, 42.5, 38.6, 38.3, 35.8, 33.3, 32.6, 32.4, 25.2, 25.1, 17.8; HRMS (EI) exact mass calcd for ($C_{19}H_{26}N_2O_4$) requires *m/z* 346.1893, found *m/z* 346.1894. $[\alpha]_D$ = -8.0 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 15% ethanol in hexanes, 1 mL/min); *anti* isomers t_r = 10.8 and 15.2 min.



(3*R*, 4*S*)-3-Methyl-5-oxo-4-phenyl-5-pyrrol-1-yl-pentanal (Table 10, entry 6). The title compound was prepared according to the general procedure from crotonaldehyde (97 μL, 1.2 mmol), 1-(2-phenyl-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole **X** (99 μL, 0.39 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TfOH (31 mg, 0.078 mmol) in $CHCl_3$ (0.195 mL) and H_2O (7.0 μL, 0.39 mmol) at -65 °C for 24 h. The resulting residue was purified by silica gel

chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 78% yield (78 mg, 0.31 mmol). 1:3 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 1709, 1470, 1288, 914, 474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (app br s, 1H, CHO), 7.40-7.20 (m, 7H, ArH), 6.25-6.20 (m, 2H, ArH), 4.12 (d, *J* = 9.3 Hz, 1H, CHPh), 3.10-2.88 (m, 1H, $CH_2C\mathbf{H}(CH_3)C$), 2.67 (app dd *J* = 16.5, 3.3 Hz, 1H, CHOC**H**HC), 2.49-2.35 (m, 1H, CHOCH**H**C), 0.85 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 201.2, 136.5, 129.2, 128.4, 128.1, 119.4, 113.5, 56.2, 49.2, 32.2, 17.9; HRMS (FAB) exact mass calcd for M+H ($C_{16}H_{18}NO_2$) requires *m/z* 256.1338, found *m/z* 256.1349. $[\alpha]_D$ = - 0.51 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



(2*S*, 3*R*)-3-Methyl-5-(2-oxo-oxazolidin-3-yl)-2-phenyl-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 87% ee. *Anti* isomer: IR (CH_2Cl_2) 1778, 1705, 1469, 1388, 1270, 1116, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.18 (m, 7H, ArH), 6.25-6.15 (m, 2H, ArH), 4.45-3.70 (m, 5H), 3.02-2.90 (m, 1H, COC**H**HC), 2.67 (dd, *J* = 17.0, 7.5 Hz, 1H, COCH**H**C), 1.29-1.18 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 170.4, 136.8, 129.0, 128.7, 127.9, 119.3, 113.2, 62.0, 56.2, 42.4, 40.2, 33.0, 19.1; HRMS (EI) exact mass calcd for ($C_{19}H_{20}N_2O_4$) requires *m/z* 340.1423, found *m/z* 340.1434. $[\alpha]_D$ = + 0.76 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 10% ethanol in hexanes, 1 mL/min); *anti* isomers t_r = 20.1 and 37.0 min and *syn* isomers t_r = 23.2 and 28.5 min.

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Chapter 4

Progress towards the Development of an Enantioselective Organocatalytic Ketone α-Oxidation

I. Introduction

α-Oxidation of Carbonyl Compounds

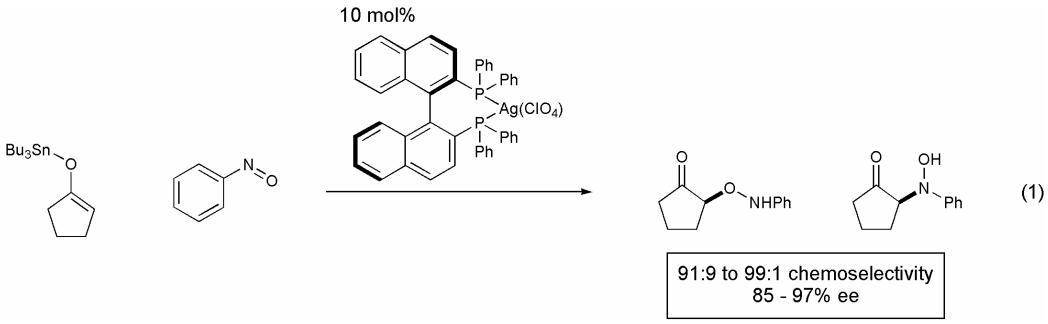
The synthesis of the α-hydroxy carbonyl structural motif is of great importance due to its prevalence in a wide variety of biologically active compounds such as sugars, antibiotics, pheromones, terpenes, and alkaloids.[1] The asymmetric construction of this structural motif is important as an end in itself, and it is useful as a directing group for the synthesis of other enantioenriched structures.[2-4]

One of the most common methods for introducing α-oxygenation to a carbonyl compound is through aprotic oxidation of the corresponding enolate[5]. These procedures typically involve the formation of an enolate from the carbonyl compound and subsequent oxidation by a molybdenum peroxo complex or *N*-solfonyloxaziridines.[6] Diastereoselective and reagent-controlled asymmetric α-oxidations based upon these two reagents have been developed by a number of groups.[1,5]

Catalytic Enantioselective α-Oxidation of Carbonyl Compounds

The development of a practical and highly selective system for asymmetric α-oxidation of carbonyl compounds is the ultimate goal of research in this field. The first report of a general enantioselective Lewis acid catalyzed α-oxidation of carbonyl

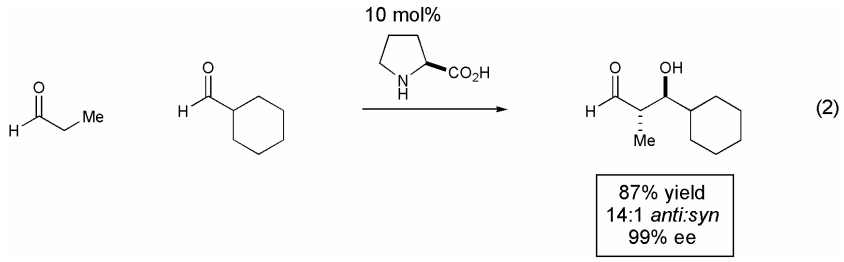
compounds was made by the Yamamoto laboratory (equation 1).[7] The oxidation of tin enolates by nitrosobenzene was catalyzed by a silver-BINAP catalyst with good yields and selectivities. This is possible because of the ambiphilic nature of the N-O double bond of nitroso compounds.[8-10] The tin enolates preferentially add to the nitroso group at the oxygen resulting in an enantioenriched α-hydroxy ketone after subsequent deprotection of the aryl hydroxy amine.



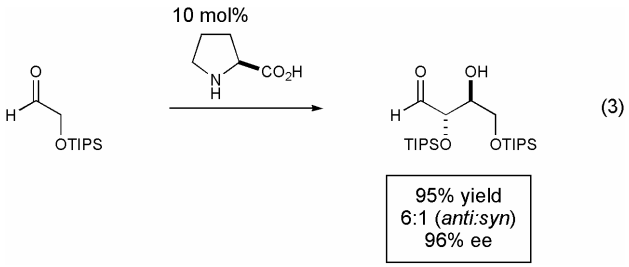
(1)

Proline Catalyzed Aldol Reactions

Research in the MacMillan lab has increased the utility of proline as a catalyst for the intermolecular aldol reaction by developing the first direct cross-aldol reaction between aldehydes (equation 2).[11] This methodology was demonstrated to be an effective procedure for coupling aldehydes of differing steric demand.



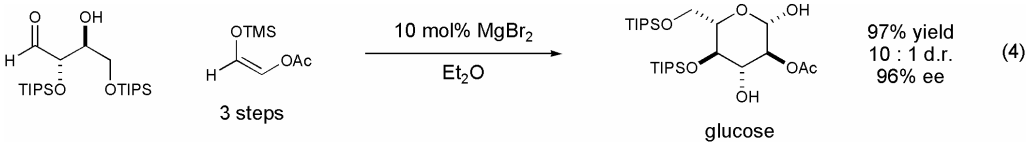
(2)



(3)

Research in the MacMillan lab has extended proline catalyzed aldol methodology to the asymmetric synthesis of highly oxygenated substrates, forming products with a high density of stereochemical information (equation 3).[12] The utility of this chemistry was demonstrated through a four-step synthesis of differentially protected hexoses (equation 4).[13]

The first report of a synthesis of a hexose from non-sugar starting materials was made by Emil Fischer in 1890.[14] Since then, there has been a great deal of research into the synthesis of monosaccharides from non-sugars, including Sharpless's elegant iterative synthesis of all eight *L*-hexoses.[15,16] The shortest synthesis of a differentially protected hexose previously reported was eight steps.[17]

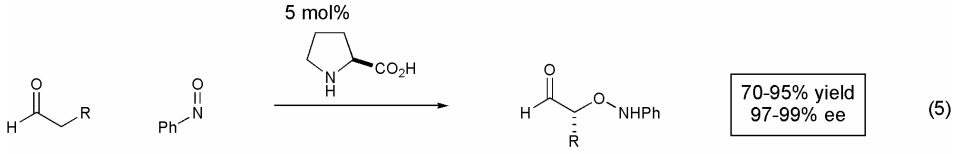


(4)

Asymmetric Organocatalytic α-Oxidation of Aldehydes

An interest in sugar synthesis led naturally to an interest in asymmetric α-oxidation chemistry. Development of the proper asymmetric α-oxidation and aldol chemistry would allow synthetic access to any monosaccharide desired from non-sugar starting materials.

The chemistry of the Yamamoto group inspired investigations into proline catalyzed α-oxidation of carbonyl compounds in the MacMillan laboratory. Under Lewis acid catalyzed conditions, latent enolate equivalents were demonstrated to preferentially add to the oxygen of nitrosobenzene.[7] Proline has been repeatedly shown to form nucleophilic enolates from carbonyl compounds, and these enolates have demonstrated the ability to participate in subsequent organic transformations.[18,19] Based on the mechanistic similarity between the Lewis acid catalyzed α-oxidation of enolates with nitrosobenzene and proline catalyzed reactions, investigations into an organocatalytic α-oxidation of carbonyl compounds were began in the MacMillan laboratory.



R = Me, *n*-Pr, *i*-Pr, allyl, Bn, Ph, $(CH_2)_3OTIPS$, CH_2-(3'-*N*-methyl-indole)

The first proline catalyzed α-oxidation of aldehydes was reported by the MacMillan laboratory (equation 5).[20] This work demonstrated a variety of structurally diverse aldehydes to be competent substrates for the proline catalyzed α-oxidation with

nitrosobenzene. Similar results were independently reported by other research groups shortly after the initial literature account.[21-23]

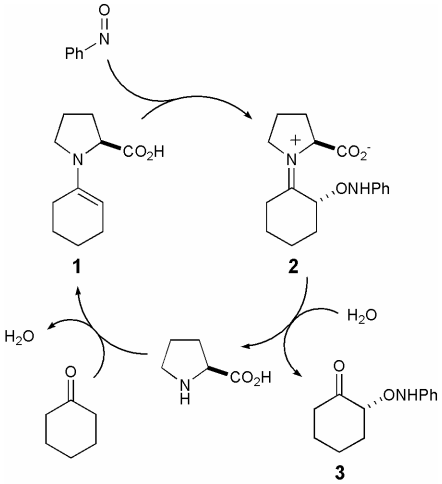
II. Results and Discussion

Initial Investigations

Initial studies in the MacMillan laboratory on the proline catalyzed α-oxidation of aldehydes had demonstrated the transformation to be possible with ketones, and it was with this knowledge that research was begun in earnest.[24]

The proposed catalytic cycle for the proline catalyzed α-oxidation of ketones with nitrosobenzene is shown in Scheme 1. Condensation of proline with a ketone and subsequent tautomerization of the iminium ion to a nucleophilic enamine results in the formation of **1**. The addition of **1** to nitrosobenzene formally oxidizes the alpha position of the carbonyl compound, and hydrolysis of the resulting iminium ion **2** regenerates the proline catalyst and frees the oxidized ketone product **3**, thereby completing the catalytic cycle.

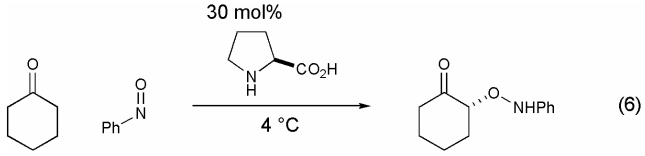
Scheme 1. Proposed proline catalyzed α-oxidation of ketones.



Concentration studies indicated that better chemical yields were possible at higher concentrations. Therefore, all initial studies were carried out at a concentration of 2.0 M relative to the limiting reagent.

Proline Catalyzed α-Oxidation of Cyclohexanone

Table 1. Effect of solvent on the proline catalyzed oxidation of cyclohexanone with nitrosobenzene.[a]



Entry	Solvent	E_T^N	% Conversion[b]	% ee[c]
1	MeOH	0.762	49	98
2	*i*-PrOH	0.546	9	93
3	CH_3NO_2	0.481	18	82
4	CH_3CN	0.460	9	99
5	DMSO	0.444	58	94
6	DMF	0.404	15	95
7	DMPU	0.352	7	94
8	CH_2Cl_2	0.309	8	96
9	$CHCl_3$	0.259	6	78
10	EtOAc	0.228	3	--
11	THF	0.207	4	--
12	Et_2O	0.117	6	--
13	Toluene	0.099	5	--

[a] All reactions performed at 2.0 M; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis.

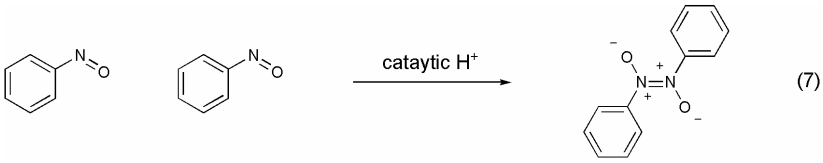
Examination of the proline-catalyzed α-oxidation of cyclohexanone was preformed in various solvents with a wide range of polarities (Table 1). This survey demonstrated that highly polar solvents like methanol and DMSO were most effective at promoting the desired oxidation reaction (Table 1, entries 1 and 5). Interestingly, other highly polar solvents were not as effective at promoting the desired transformation.

Nitromethane and DMF were noticeably better performers than other solvents studied (Table 1, entries 3 and 6), but the yields in these solvents were unsatisfactory. These results can be understood by considering the catalytic cycle proposed in Scheme 1. Those solvents most effective at promoting the formation of the nucleophilic enamine intermediate are the solvents which are most effective at promoting the oxidation reaction. DMSO and DMF are known to be effective solvents for the promotion of proline catalyzed aldol reactions, and methanol is by far the most polar solvent examined and, therefore, most able to promote the formation of enamine from iminium ion.[18] The enantioselectivity of the process appears to be quite good and relatively insensitive to solvent (78-99% ee, Table 1, entries 1-9).

The effect of temperature on the proline catalyzed oxidation of cyclohexanone in DMSO was then examined. While good yields and selectivities were observed at room temperature, the optimum temperature for the transformation was 4 °C. Yield and enantioselectivity peaked at this temperature, and reduction of temperature beyond this point only served to diminish both.

Initially, the oxidation was performed with an excess of cyclohexanone and a limiting amount of nitrosobenzene oxidant. These ratios were varied in an attempt to increase the yield of the process, and it was discovered that lower conversion occurred when excess oxidant was used. This led to the observation that a side reaction was occurring with the nitrosobenzene oxidant.

In the proline catalyzed oxidation of ketones, nitrosobenzene must exist in acidic conditions. Under these conditions, nitrosobenzene is known to dimerize (equation 7).[9,10,25] This side reaction was decreasing the overall yield of the desired transformation. Isolation of the nitrosobenzene dimer from a proline catalyzed oxidation reaction confirmed the existence of this undesired process.



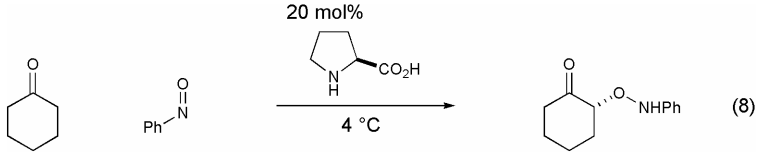
(7)

To limit the exposure of nitrosobenzene to acidic reaction conditions, an engineering solution was attempted. By adding nitrosobenzene via syringe pump to a solution of ketone and proline, the instantaneous concentration of nitrosobenzene should be low at all times during the reaction. Because the dimerization of the nitrosobenzene involves two molecules of nitrosobenzene, it is second order. The α-oxidation of ketones is only first order in nitrosobenzene. Reducing the instantaneous concentration of nitrosobenzene through syringe pump addition should therefore retard the unwanted dimerization side reaction more than the desired oxidation.

Initial studies were attempted using DMSO as the solvent, but at the optimum temperature (4 °C) syringe pump addition of a nitrosobenzene solution was not possible due to the relatively high freezing point of DMSO. Protic solvents are known to increase the rate of nitrosobenzene dimerization, so methanol was not used for further studies.[9,10,25] Subsequent investigations revealed DMF as the solvent of choice for the syringe pump additions.

As is shown in Table 2, syringe pump addition greatly increased the yield of the organocatalytic oxidation of cyclohexanone with nitrosobenzene. Slow addition of the oxidant significantly reduced the dimerization of the nitrosobenzene, thereby allowing the α-oxidation to occur in good yield.

Table 2. Reducing the rate of addition of nitrosobenzene significantly improves the organocatalytic oxidation of cyclohexanone.



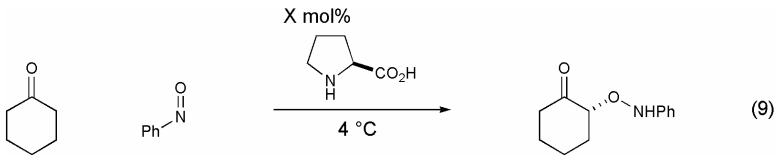
Entry	Solvent	Rate of addition of nitrosobenzene	% Converison[b]	% ee[c]
1	DMSO	Added as one portion	58	94
2	DMF	Added as one portion	31	95
3	DMSO	Syringe pump addition (4h)[d]	--	--
4	DMF	Syringe pump addition (4h)	>90	98

[a] All reactions performed at final concentration of 0.67 M; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis; [d] Syringe pump addition using DMSO at 4 °C was not possible due to the freezing point of the solvent.

The amount of proline catalyst required for the organocatalytic α-oxidation of cyclohexanone was examined. The oxidation appeared quite efficient when monitored by TLC. The nitrosobenzene was being consumed as quickly as it was being added to the reaction mixture, making a reduction in catalyst loading possible. This study demonstrated that 5 mol% catalyst was the ideal catalyst loading for the organocatalytic oxidation of cyclohexanone (>90% conversion, 99% ee, Table 3, entry 3). The selectivity was slightly higher than 20 mol% catalyst loading (>90% conversion, 98% ee, Table 3, entry 1) and the same as 10 mol% catalyst loading (>90% conversion, 99% ee, Table 3, entry 2). Reducing the amount of catalyst present in the reaction mixture to 2

mol% began to have deleterious effects on the conversion to product (70% conversion, 98% ee, Table 3, entry 4).

Table 3. Effect of catalyst loading on the proline catalyzed oxidation of cyclohexanone with nitrosobenzene.[a]

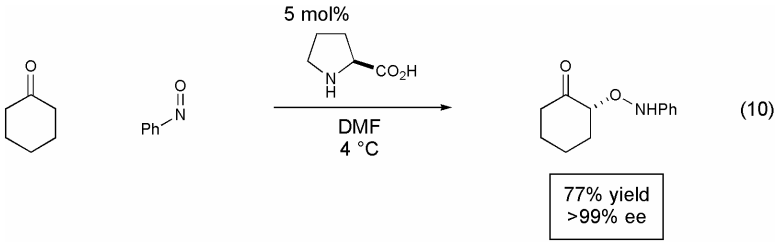


Entry	mol% proline	% Conversion[b]	% ee[c]
1	20	>90	98
2	10	>90	99
3	5	>90	99
4	2	70	98

[a] All reactions performed at a final concentration of 0.67 M in DMF; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis

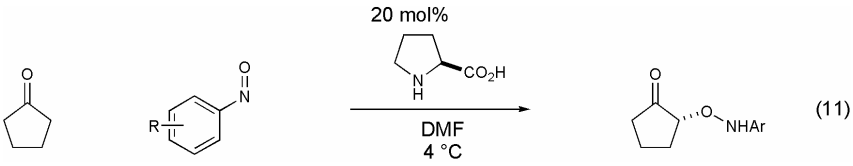
Substrate Scope

With optimized conditions for the proline catalyzed oxidation of cyclohexanone with nitrosobenzene identified, the scope of this transformation was examined. The elucidated conditions performed admirably for the organocatalytic oxidation of cyclohexanone, resulting in the isolation of oxidized product in 77% yield and >99% ee (equation 10).



Extension of this methodology to other ketones did not prove simple. Initial attempts at the organocatalytic oxidation of 3-pentanone, cyclopentanone and cycloheptanone with nitrosobenzene yielded only trace amounts of oxidized product and almost stoichiometric amounts of the nitrosobenzene dimer.

Table 4. Effect of nitrosoarene variation on the organocatalytic α-oxidation of cyclopentanone.[a]



Entry	R	% Conversion[b]	% ee[c]
1	H	<5	--
2	2-Me	<5	--
3	2-Et	18	--
4	2-(*i*-Pr)	25	69
5	2-(*t*-Bu)	0	--
6	2,6-diMe	0	--
7[d]	4-NO_2	0	--

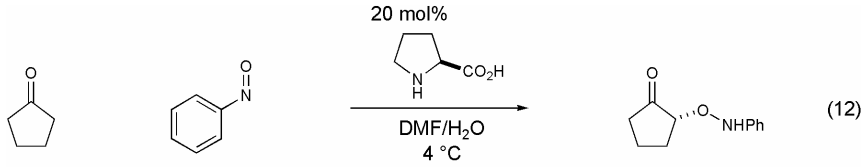
[a] All reactions performed at a final concentration of 0.67 M; nitrosoarene added via syringe pump over 4h; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis; [d] 4-nitronitrosobenzene added in one portion.

Variation of the nitrosoarene oxidant was examined to improve the proline catalyzed oxidation of cyclopentanone (Table 4). The steric demand of the nitrosoarene oxidant was increased in an attempt to inhibit the dimerization side reaction. This strategy did improve the yield of the α-oxidation. Only trace product was observed when nitrosobenzene and 2-nitrosotoluene were used as oxidants (Table 4, entries 1 and 2). Increasing the bulk of the 2-substituent on the nitrosobenzene ring served to increase the conversion (2-ethylnitosobenzene, 18% yield, Table 4, entry 3 and 2-isopropylnitrosobenzene, 25% yield, 69% ee, Table 4, entry 4), but once a certain steric demand is reached, both conversion to product and dimerization of the nitrosoarene halt

(Table 4, entries 5 and 6). Electron deficient nitrosobenzenes are less prone to undergo dimerization, and 4-nitronitrosobenzene is known to be particularly stable to dimerization while able to undergo other chemical transformations such as ene and Diels-Alder reactions.[25] 4-Nitronitrosobenzene was examined as an oxidant for the proline catalyzed α-oxidation of ketones, and was unreactive (Table 4, entry 7).

Tautomerization between an iminium ion and an enamine is strongly dependent on the structure of the carbonyl compound and amine involved.[26] Increasing the polarity of the reaction medium can promote enamine formation, so the effect of water on the organocatalytic α-oxidation was studied.[27] It is known that the addition of a small amount of water can have a dramatic effect on a solution's polarity and, therefore, on organocatalytic reactions (see Chapter 2, Table 3).

Table 5. Effect of added water on the proline-catalyzed α-oxidation of cyclopentanone with nitrosobenzene.[a]



(12)

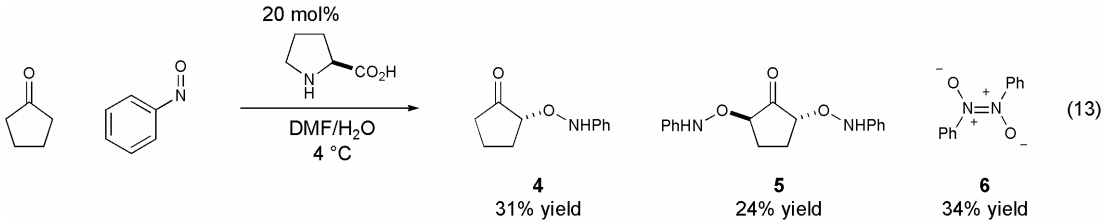
Entry	Equivalents of H_2O	% Conversion[b]
1	0	trace
2	1	68
3	2	70
4	4	80
5	6	71
6	8	53
7	10	32

[a] All reactions performed at a final concentration of 0.67 M; nitrosobenzene added via syringe pump over 8 h; [b] Conversion determined by ^{1}H NMR analysis.

As can be seen in Table 5, the addition of water to the reaction medium had a dramatic effect. When no added water is present, only trace oxidation occurs, and the

dimerization of nitrosobenzene is the dominant reaction (Table 5 entry 1). With increasing amounts of water, the conversion of the oxidation reaction increases (Table 5 entries 1-4) until the concentration of water reaches a point where the dimerization of the nitrosobenzene is again favored over oxidation of the ketone (Table 5 entries 5-7).

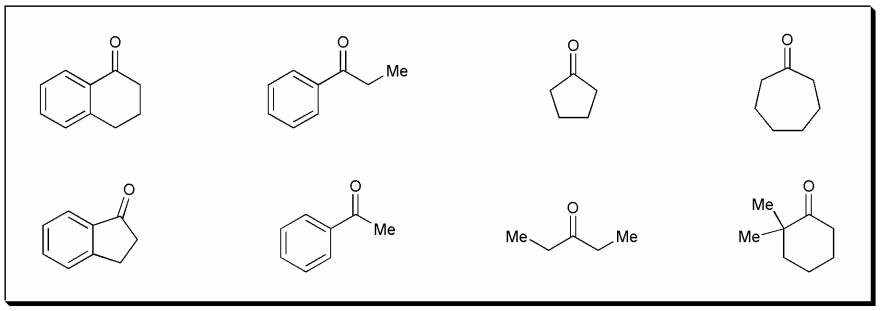
Unfortunately, the reaction conditions developed for cyclopentanone are not optimal. While the majority of nitrosobenzene is oxidizing the cyclopentanone under organocatalytic reaction conditions, dimerization is still occurring. Oxidation of the cyclopentanone is also occurring at both α-carbons (equation 13). This double oxidation (**5**) accounts for the previously observed levels of conversion (Table 5, entry 4), and results in a reduced yield of the cyclopentanone oxidation product **4**.



Limitations

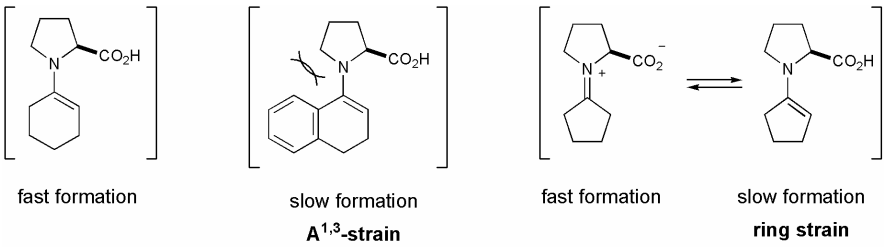
Unfortunately, most ketones studied did not prove to be competent substrates for the proline catalyzed α-oxidation (Figure 1). Of the ketones studied, only cyclohexanone produced oxidation product in reasonable yield. Aryl ketones, cyclic ketones of different sizes, acyclic ketones and sterically encumbered ketones all failed to yield oxidized products.

Figure 1. Ketones not able to participate in the proline catalyzed α-oxidation reaction.



Failure of these ketones to participate in the organocatalytic oxidation can be explained by their failure to form sufficient quantities of reactive enamine quickly (Scheme 2). Aryl ketones do not form significant amounts of enamine or iminium ions due to $A^{1,3}$-strain between the aromatic group and the substituents on the secondary amine. Cyclopentanone failed as a substrate under organocatalytic conditions because it did not form enamine quickly enough. Formation of iminium ions by proline and cyclopentanone occurs quickly and reversibly, allowing facile catalyst turnover, but the subsequent enamine formation is retarded by the ring strain inherent in the formation of a cyclopentene ring and occurs too slowly to allow an efficient α-oxidation.[28]

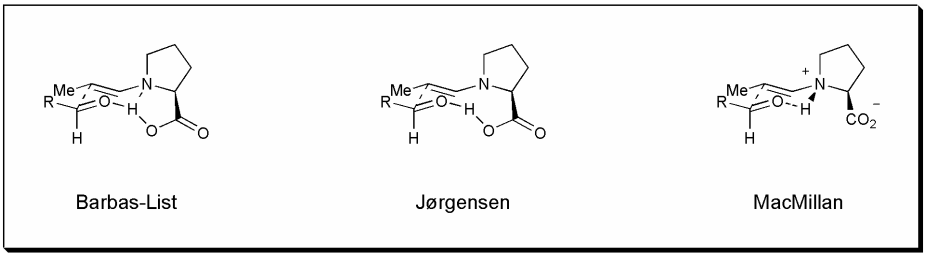
Scheme 2. Proposed rationale for substrate limitations in the organocatalytic α-oxidation reaction.



Stereochemical Rationale

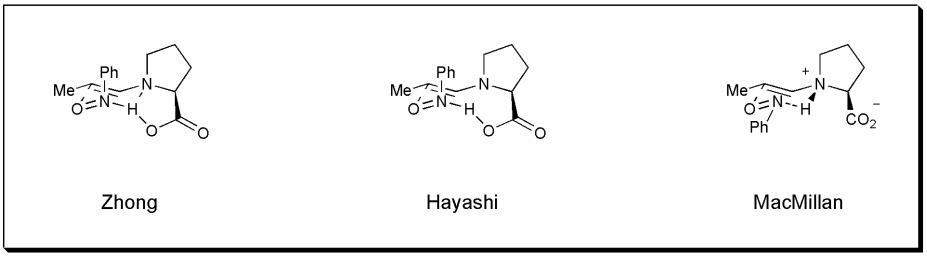
Several models have been proposed to explain the stereochemical outcome of proline catalyzed transformations (Figure 2).[11,20,21,29-31] The three models proposed in the literature correctly predict the stereochemistry resulting from a proline catalyzed aldol reaction. Computational studies appear to support the 9-membered ring transition state.[32,33] These quantum mechanical calculations suggest a pseudo-chair conformation for the closed transition state and indicate an intramolecular transfer of the hydrogen atom from the carboxylic acid of proline to the developing alkoxide in the aldol transition state. The distance between the nitrogen of the enamine and the transferring hydrogen atom was not indicative of hydrogen bonding, supporting the plausibility of a 9-membered ring transition state.

Figure 2. Proposed proline catalyzed aldol transition states.



Possible transition states for the proline catalyzed α-oxidation of aldehydes using nitrosobenzene have also been proposed (Figure 3).[20-23] All the transition states correctly predict the stereochemical course of the organocatalytic oxidation. Based on the computational studies performed on enamine aldol reactions, the 9-membered ring transition state seems most probable.[32,33]

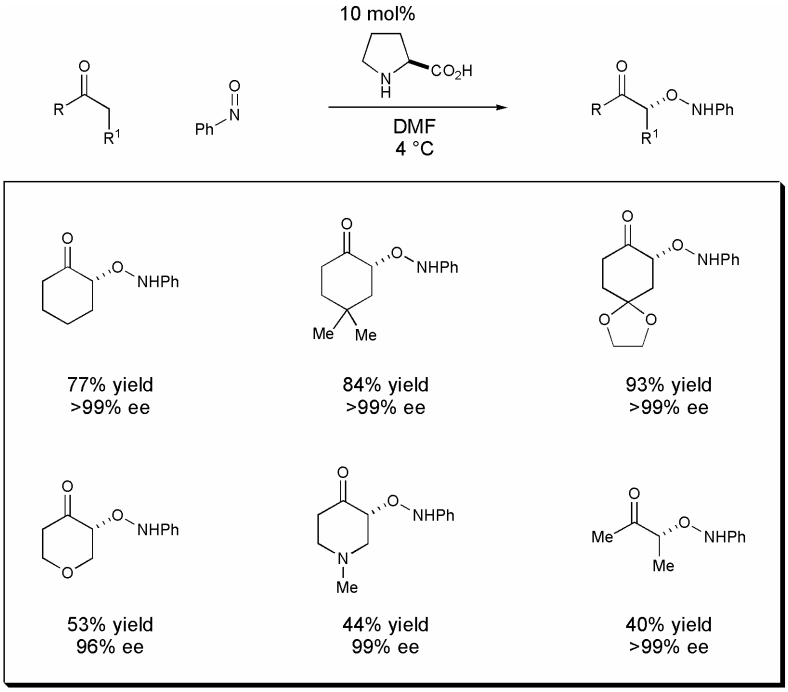
Figure 3. Proposed proline catalyzed aldehyde α-oxidation transition states.



Reports of Proline Catalyzed α-Oxidation of Ketones

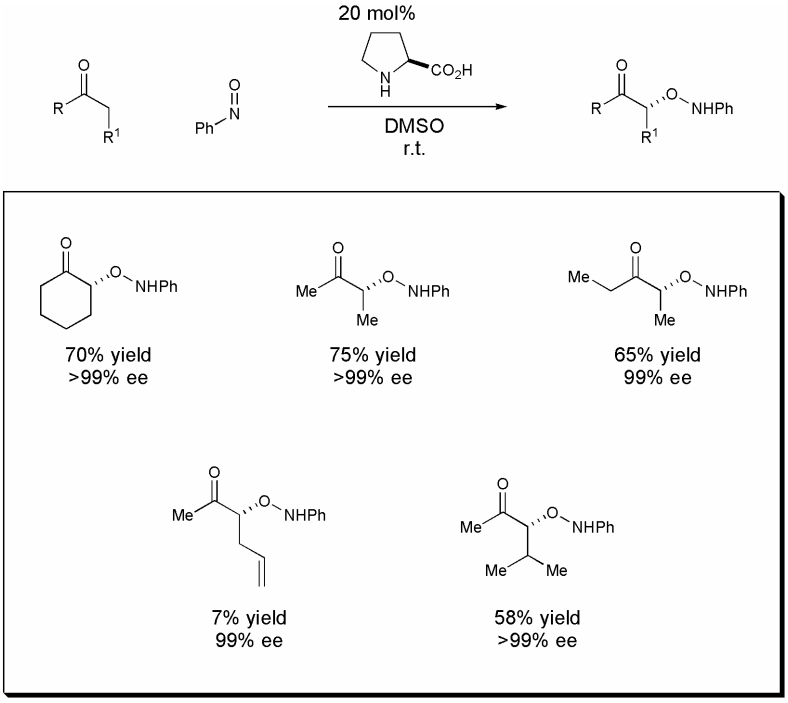
While studies aimed at extending the scope of the proline catalyzed α-oxidation beyond cyclohexanone were underway, two reports regarding this chemistry appeared.[34,35] The research outlined in this chapter is in accord with these reports.

Scheme 3. The proline catalyzed α-oxidation of ketones by the Hayashi laboratory.[35]



The Hayashi laboratory reported almost the exact same experimental conditions as elucidated in this research (DMF, 0 °C, 2 equiv. ketone, slow addition of nitrosobenzene), and found cyclohexanone and some derivatives of cyclohexanone to be competent substrates for the proline catalyzed α-oxidation reaction (Scheme 3).[35] The one alkyl ketone reported in their study only oxidized in moderate yield under forcing reaction conditions (10 equivalents ketone, r.t.).

Scheme 4. The proline catalyzed α-oxidation of ketones by the Córdova laboratory.[34]

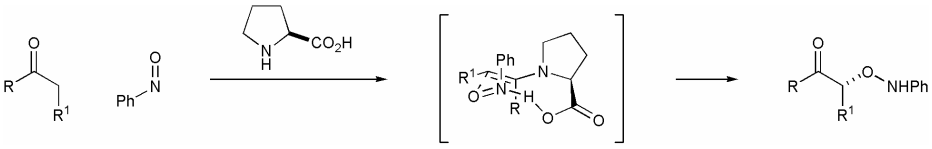


The Córdova laboratory reported different conditions for the proline-catalyzed α-oxidation of ketones than were found in this research or reported by the Hayashi laboratory (DMSO, r.t., 10 equiv. ketone, Scheme 4).[34,35] Not surprisingly, cyclohexanone oxidized with good yield and enantioselectivity under these conditions.

Asymmetric organocatalytic α-oxidation of alkyl ketones appears to be highly substrate dependent, producing enantioenriched product in variable yields (7-75% yield) but excellent enantioselectivity (99->99% ee).

Both literature reports of proline catalyzed α-oxidation of ketones propose a closed 9-membered transition state for the α-oxidation of ketones (Scheme 5).[34,35]

Scheme 5. Reported proline catalyzed ketone α-oxidation transition state.



III. Conclusion

Progress towards the development of an asymmetric, proline catalyzed α-oxidation of ketones has been described herein. Using *L*-proline, cyclohexanone can be α-oxidized in high yield and selectivity. Extension of this methodology to other ketones was not possible with acceptable yields, although all observed selectivities were high. These studies have further demonstrated the utility of proline as a general HOMO-raising catalyst, and provide a platform for the development of subsequent HOMO-raising organocatalytic methods.

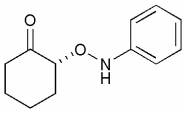
IV. Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[36] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[37] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed be fluorescence quenching, *p*-anisaldehyde stain, or $KMnO_4$ stain.

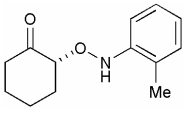
^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively) or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported with chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) , integration, and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C, $CHCl_3$). Mass spectra were obtained from the California Institute of Technology Mass Spectrometer Facility. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254 nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

Progress of the α-oxidation was typically monitored by TLC analysis, or in cases where necessary, ^{1}H NMR analysis of the reaction *in situ* in deuterated solvent.

General procedure for the proline catalyzed α-oxidation of ketones. A 2 dram vial equipped with a magnetic stir bar was charged with the appropriate ketone (1.5 mmol), *L*-proline (5.8 mg, 0.050 mmol), and DMF (0.25 mL). The mixture was stirred at room temperature for 5 min and then cooled to 4 °C with continued stirring. A solution of nitrosobenzene (54 mg, 0.50 mmol) in DMF (0.50 mL) was slowly added to the stirring solution over 4 h. The solution was then stirred for an additional 30 min and quenched with brine (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated.



(2*R*)-2-(*N*-Phenyl-aminooxy)-cyclohexanone (equation 10). The title compound was prepared from cyclohexanone (155 μL, 1.5 mmol) according to the general procedure. The resulting residue was purified by silica gel chromatography (5% EtOAc/Hex) to yield 79 mg (77% yield, 0.38 mmol) of pure product. >99% ee. All spectra were in agreement with those previously reported.[7]



(2*R*)-2-(*N*-*ortho*-Tolylaminooxy)-cyclohexanone. A 2 dram vial equipped with a magnetic stir bar was charged with cyclohexanone (147 mg, 1.5 mmol), *L*-proline (12 mg, 0.10 mmol) and DMSO (0.25 mL). The mixture was stirred at room temperature for 5 min and then cooled to 4 °C with continued stirring. 2-Nitrosotoluene (61 mg, 0.50 mmol) was then added to the stirring solution. Upon

consumption of the nitrosotoluene (1.5 h), as judged by TLC, the reaction was then quenched with brine (5 mL) and extracted with ethyl acetate (3 x 5 mL). The resulting residue was purified by flash chromatography (5% EtOAc/Hex) to yield 63 mg (0.57 mmol, 57% yield) of pure product. 98% ee. IR (CH_2Cl_2) 2942, 2865, 1721, 1607, 1586, 1487, 1450, 1309, 1133, 1098, 1072, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H, NH), 7.21-7.04 (m, 3H, ArH), 6.92-6.85 (m, 1H, ArH), 4.40 (ddd, *J* = 11.7, 6.1, 1.1 Hz, 1H, COCH(OR)C), 2.56-2.30 (m, 3H, cyclohexyl-H), 2.13 (s, 3H, CH_3), 2.11-1.98 (m, 2H, cyclohexyl-H), 1.89-1.58 (m, 3H, cyclohexyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 145.8, 130.2, 126.7, 123.5, 121.9, 114.5, 86.1, 40.9, 32.6, 27.4, 23.8, 17.0; HRMS (FAB) exact mass calcd for ($C_{13}H_{17}NO_2$) requires *m/z* 219.1259, found *m/z* 219.1252. $[\alpha]_D$ = +108.8 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 3% isopropanol in hexanes, 1 mL/min); (*S*) isomer t_r = 14.9 min and (*R*) isomer t_r = 20.9 min.

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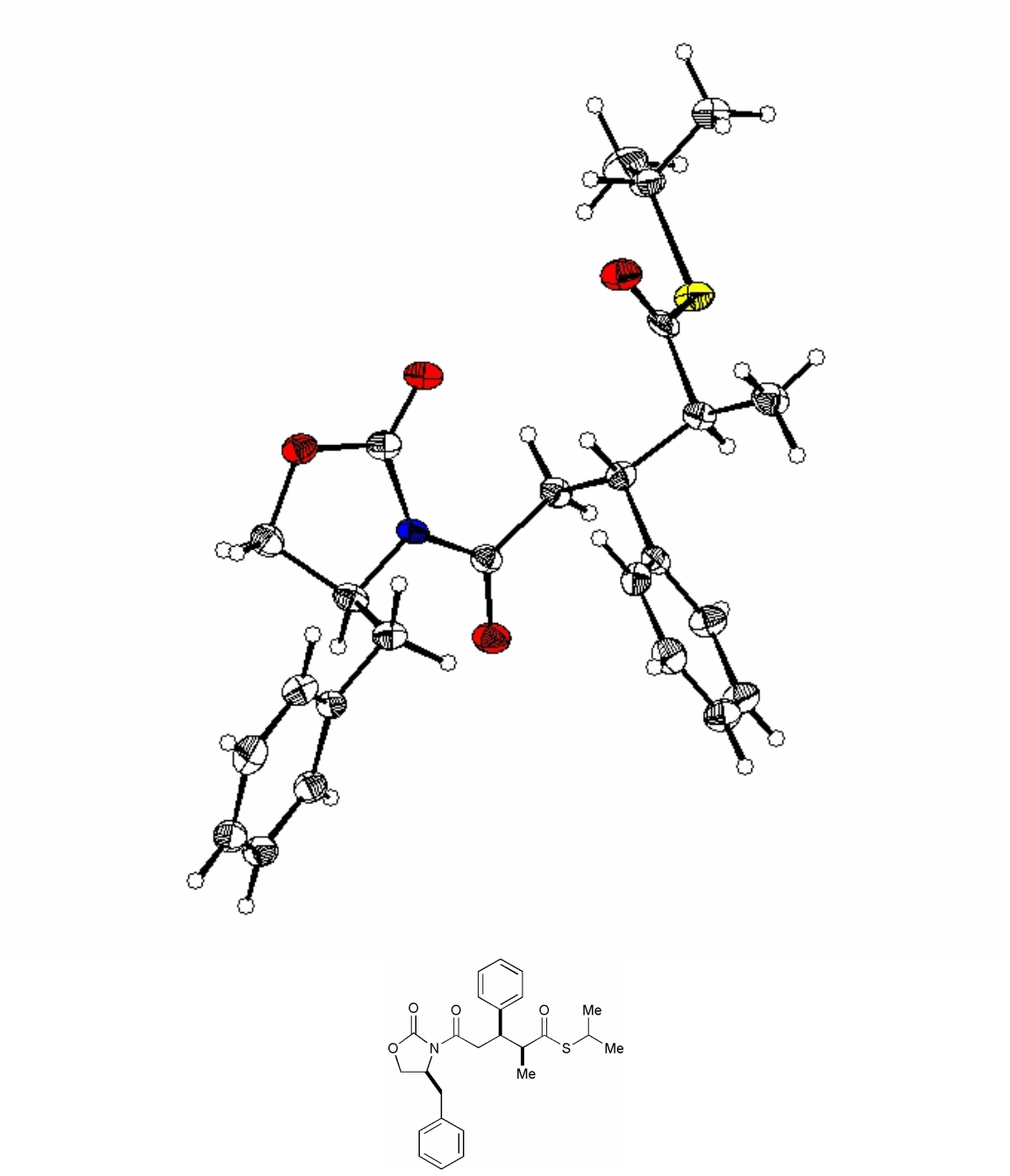
Appendix 1.

X-Ray Crystallographic Data for (2*S*, 3*R*)-5-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester



CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Date 27 June 2004

Crystal Structure Analysis of:

(2*S*, 3*R*)-5-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester (CJB12)

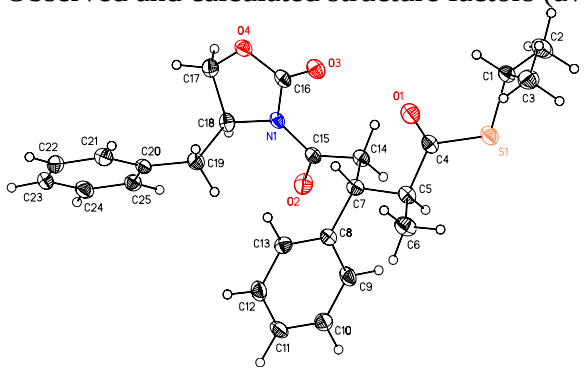
(shown below)

For Investigator: Chris Borths

Advisor: D. W. C. MacMillan

By Michael W. Day

Contents



CJB12

Note: Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 239502.

Table 1. Crystal data and structure refinement for CJB12 (CCDC 239502).

Empirical formula	$C_{25}H_{29}NO_4S$
Formula weight	439.55
Crystallization Solvent	THF/hexanes
Crystal Habit	Column
Crystal size	0.48 x 0.17 x 0.13 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 5769 reflections used in lattice determination	2.86 to 27.99°
Unit cell dimensions	a = 12.701(3) Å b = 6.4520(13) Å β= 107.706(3)° c = 14.854(3) Å
Volume	1159.5(4) $Å^3$
Z	2
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.259 Mg/m^3
F(000)	468
Data collection program	Bruker SMART v5.054
θ range for data collection	1.68 to 27.99°
Completeness to θ = 27.99°	93.5 %
Index ranges	$-16 \le h \le 16, -8 \le k \le 8, -19 \le l \le 19$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.45
Reflections collected	13847
Independent reflections	5068 [R_{int}= 0.0709]
Absorption coefficient	0.170 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9782 and 0.9227

Table 1 (cont.)

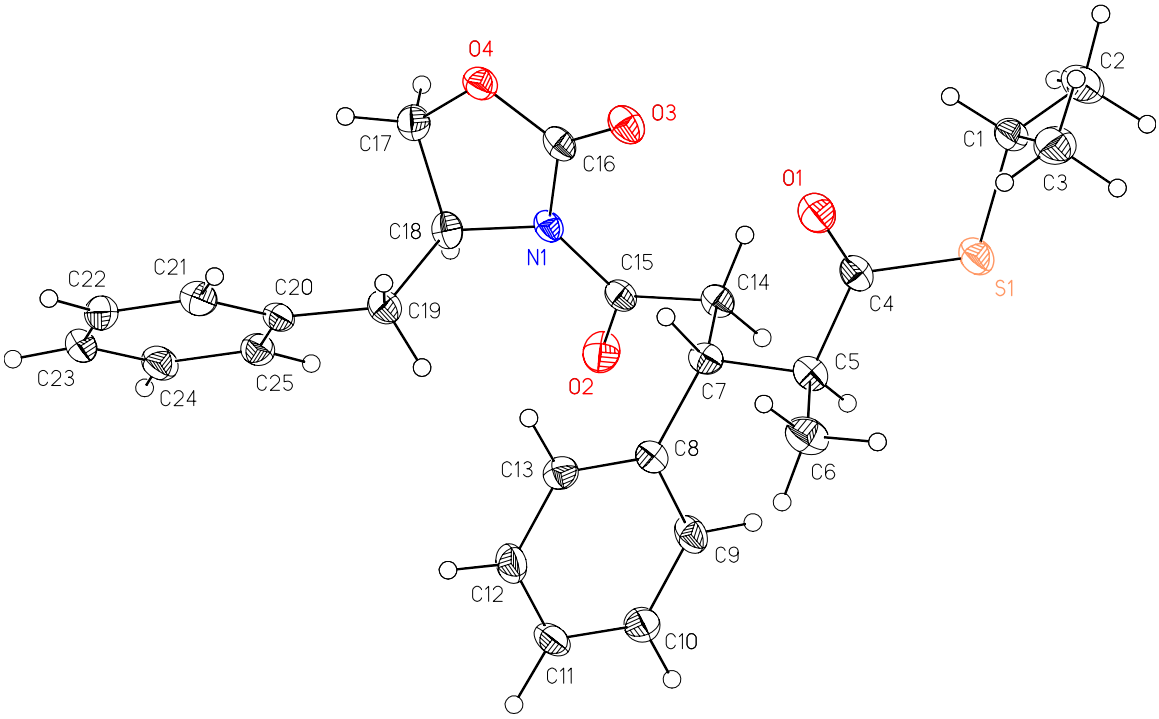
Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5068 / 1 / 396
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.097
Final R indices [$I>2\sigma(I)$, 3973 reflections]	R1 = 0.0415, *w*R2 = 0.0648
R indices (all data)	R1 = 0.0569, *w*R2 = 0.0677
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.03(6)
Largest diff. peak and hole	0.347 and -0.260 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.


O4
O3
C17
C16
C18
N1
C15
C14
O1
C4
S1
C2
C1
C3
C22
C21
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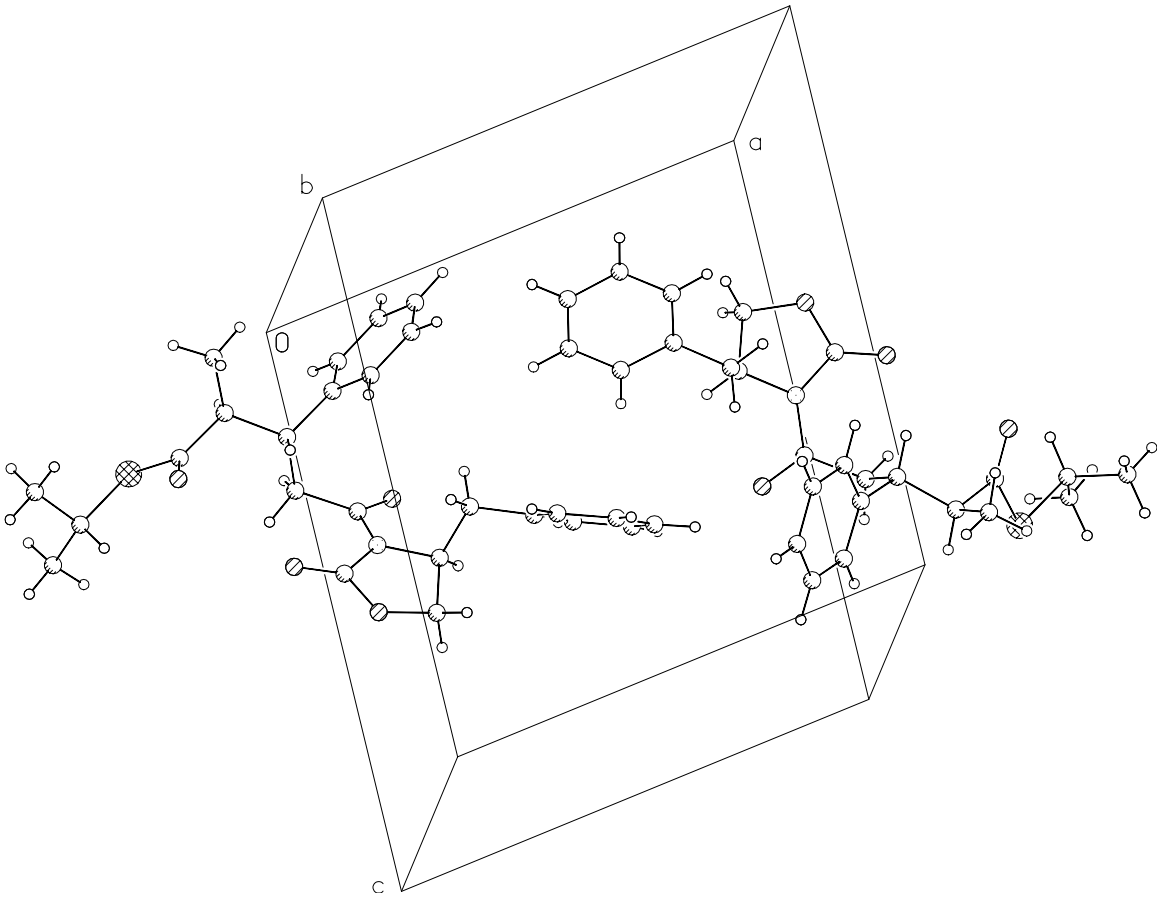
C6
C9
C12
C10
C11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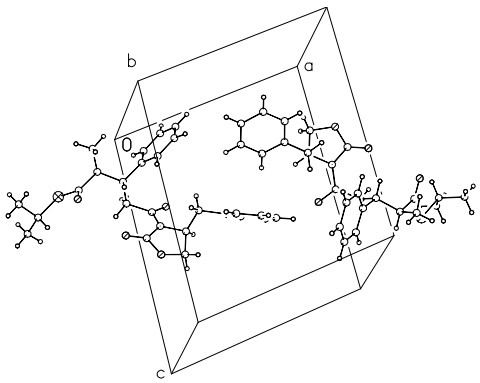
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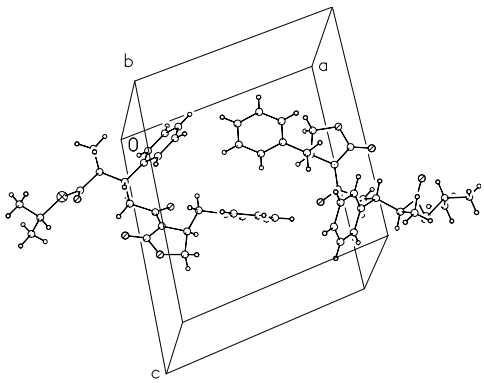
b
a
O
c

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for CJB12 (CCDC 239502). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	-3118(1)	5719(1)	6145(1)	26(1)
O(1)	-2767(1)	9144(2)	7180(1)	28(1)
O(2)	1801(1)	6260(2)	8408(1)	28(1)
O(3)	-837(1)	8606(2)	9285(1)	25(1)
O(4)	553(1)	8885(2)	10641(1)	22(1)
N(1)	1006(1)	7921(3)	9364(1)	17(1)
C(1)	-4286(2)	5646(4)	6632(2)	24(1)
C(2)	-4612(2)	3383(4)	6699(2)	35(1)
C(3)	-5239(2)	6959(5)	6040(2)	33(1)
C(4)	-2452(2)	8061(3)	6650(2)	20(1)
C(5)	-1460(2)	8592(4)	6318(2)	21(1)
C(6)	-1754(2)	10534(4)	5691(2)	30(1)
C(7)	-414(2)	8901(3)	7183(2)	19(1)
C(8)	548(2)	9739(3)	6884(1)	18(1)
C(9)	969(2)	8683(4)	6248(2)	24(1)
C(10)	1829(2)	9494(4)	5962(2)	28(1)
C(11)	2280(2)	11414(4)	6305(2)	26(1)
C(12)	1884(2)	12480(4)	6944(2)	26(1)
C(13)	1027(2)	11643(3)	7231(2)	22(1)
C(14)	-144(2)	6838(3)	7733(2)	19(1)
C(15)	948(2)	6944(3)	8509(1)	19(1)
C(16)	139(2)	8475(3)	9708(2)	19(1)
C(17)	1745(2)	8513(4)	10971(2)	23(1)
C(18)	2083(2)	8361(3)	10067(1)	20(1)
C(19)	2566(2)	10381(4)	9804(2)	21(1)
C(20)	3669(2)	11005(3)	10481(1)	19(1)
C(21)	3796(2)	12904(3)	10956(2)	23(1)
C(22)	4822(2)	13528(4)	11540(2)	27(1)
C(23)	5746(2)	12277(4)	11669(2)	27(1)
C(24)	5629(2)	10374(4)	11214(2)	25(1)
C(25)	4603(2)	9743(4)	10621(2)	21(1)

Table 3. Bond lengths [Å] and angles [°] for CJB12 (CCDC 239502).

S(1)-C(4)	1.782(2)	C(20)-C(21)	1.398(3)
S(1)-C(1)	1.838(2)	C(20)-C(25)	1.402(3)
O(1)-C(4)	1.208(2)	C(21)-C(22)	1.388(3)
O(2)-C(15)	1.220(2)	C(21)-H(21)	0.95(2)
O(3)-C(16)	1.210(2)	C(22)-C(23)	1.388(3)
O(4)-C(16)	1.351(2)	C(22)-H(22)	0.93(2)
O(4)-C(17)	1.462(2)	C(23)-C(24)	1.388(3)
N(1)-C(16)	1.394(2)	C(23)-H(23)	0.97(2)
N(1)-C(15)	1.400(3)	C(24)-C(25)	1.393(3)
N(1)-C(18)	1.474(3)	C(24)-H(24)	0.95(2)
C(1)-C(3)	1.518(3)	C(25)-H(25)	0.93(3)
C(1)-C(2)	1.529(4)		
C(1)-H(1)	0.97(2)	C(4)-S(1)-C(1)	101.09(11)
C(2)-H(2A)	1.02(3)	C(16)-O(4)-C(17)	110.60(15)
C(2)-H(2B)	1.01(3)	C(16)-N(1)-C(15)	128.21(16)
C(2)-H(2C)	1.02(3)	C(16)-N(1)-C(18)	110.95(17)
C(3)-H(3A)	1.02(2)	C(15)-N(1)-C(18)	120.71(16)
C(3)-H(3B)	1.04(3)	C(3)-C(1)-C(2)	112.8(2)
C(3)-H(3C)	1.00(2)	C(3)-C(1)-S(1)	110.79(17)
C(4)-C(5)	1.526(3)	C(2)-C(1)-S(1)	108.47(17)
C(5)-C(6)	1.537(3)	C(3)-C(1)-H(1)	113.1(12)
C(5)-C(7)	1.555(3)	C(2)-C(1)-H(1)	106.6(12)
C(5)-H(5)	0.91(2)	S(1)-C(1)-H(1)	104.6(10)
C(6)-H(6A)	1.04(2)	C(1)-C(2)-H(2A)	112.7(15)
C(6)-H(6B)	0.99(2)	C(1)-C(2)-H(2B)	112.7(15)
C(6)-H(6C)	0.99(3)	H(2A)-C(2)-H(2B)	107(2)
C(7)-C(8)	1.520(3)	C(1)-C(2)-H(2C)	105.8(16)
C(7)-C(14)	1.545(3)	H(2A)-C(2)-H(2C)	106.0(19)
C(7)-H(7)	1.012(19)	H(2B)-C(2)-H(2C)	113(2)
C(8)-C(9)	1.397(3)	C(1)-C(3)-H(3A)	110.8(13)
C(8)-C(13)	1.399(3)	C(1)-C(3)-H(3B)	109.5(15)
C(9)-C(10)	1.388(3)	H(3A)-C(3)-H(3B)	106(2)
C(9)-H(9)	0.95(2)	C(1)-C(3)-H(3C)	110.1(13)
C(10)-C(11)	1.394(3)	H(3A)-C(3)-H(3C)	106.0(17)
C(10)-H(10)	0.97(2)	H(3B)-C(3)-H(3C)	114(2)
C(11)-C(12)	1.384(3)	O(1)-C(4)-C(5)	123.4(2)
C(11)-H(11)	1.02(2)	O(1)-C(4)-S(1)	123.78(16)
C(12)-C(13)	1.393(3)	C(5)-C(4)-S(1)	112.75(16)
C(12)-H(12)	0.97(2)	C(4)-C(5)-C(6)	107.83(18)
C(13)-H(13)	0.99(2)	C(4)-C(5)-C(7)	110.07(17)
C(14)-C(15)	1.512(3)	C(6)-C(5)-C(7)	112.63(18)
C(14)-H(14A)	0.974(19)	C(4)-C(5)-H(5)	109.3(14)
C(14)-H(14B)	0.94(2)	C(6)-C(5)-H(5)	111.9(15)
C(17)-C(18)	1.531(3)	C(7)-C(5)-H(5)	105.1(14)
C(17)-H(17A)	0.95(2)	C(5)-C(6)-H(6A)	110.8(14)
C(17)-H(17B)	0.96(2)	C(5)-C(6)-H(6B)	107.0(14)
C(18)-C(19)	1.541(3)	H(6A)-C(6)-H(6B)	109.8(17)
C(18)-H(18)	0.974(19)	C(5)-C(6)-H(6C)	110.8(14)
C(19)-C(20)	1.509(3)	H(6A)-C(6)-H(6C)	106.9(19)
C(19)-H(19A)	0.96(2)	H(6B)-C(6)-H(6C)	111(2)
C(19)-H(19B)	0.97(2)	C(8)-C(7)-C(14)	113.07(17)

C(8)-C(7)-C(5)	111.40(16)	O(4)-C(17)-H(17A)	108.8(13)
C(14)-C(7)-C(5)	108.83(17)	C(18)-C(17)-H(17A)	111.4(12)
C(8)-C(7)-H(7)	107.4(10)	O(4)-C(17)-H(17B)	111.0(11)
C(14)-C(7)-H(7)	109.0(11)	C(18)-C(17)-H(17B)	113.8(11)
C(5)-C(7)-H(7)	106.9(11)	H(17A)-C(17)-H(17B)	106.9(16)
C(9)-C(8)-C(13)	117.7(2)	N(1)-C(18)-C(17)	100.71(16)
C(9)-C(8)-C(7)	122.11(19)	N(1)-C(18)-C(19)	109.79(17)
C(13)-C(8)-C(7)	120.21(19)	C(17)-C(18)-C(19)	114.05(19)
C(10)-C(9)-C(8)	121.4(2)	N(1)-C(18)-H(18)	110.0(11)
C(10)-C(9)-H(9)	121.6(13)	C(17)-C(18)-H(18)	113.6(11)
C(8)-C(9)-H(9)	117.0(13)	C(19)-C(18)-H(18)	108.5(11)
C(9)-C(10)-C(11)	119.8(2)	C(20)-C(19)-C(18)	114.64(18)
C(9)-C(10)-H(10)	120.4(14)	C(20)-C(19)-H(19A)	114.0(11)
C(11)-C(10)-H(10)	119.7(14)	C(18)-C(19)-H(19A)	105.5(12)
C(12)-C(11)-C(10)	119.8(2)	C(20)-C(19)-H(19B)	109.0(12)
C(12)-C(11)-H(11)	119.8(12)	C(18)-C(19)-H(19B)	104.7(11)
C(10)-C(11)-H(11)	120.2(12)	H(19A)-C(19)-H(19B)	108.5(16)
C(11)-C(12)-C(13)	119.9(2)	C(21)-C(20)-C(25)	118.12(19)
C(11)-C(12)-H(12)	122.4(12)	C(21)-C(20)-C(19)	120.75(19)
C(13)-C(12)-H(12)	117.7(12)	C(25)-C(20)-C(19)	121.1(2)
C(12)-C(13)-C(8)	121.4(2)	C(22)-C(21)-C(20)	120.8(2)
C(12)-C(13)-H(13)	119.0(12)	C(22)-C(21)-H(21)	122.7(13)
C(8)-C(13)-H(13)	119.5(12)	C(20)-C(21)-H(21)	116.6(13)
C(15)-C(14)-C(7)	111.66(18)	C(23)-C(22)-C(21)	120.8(2)
C(15)-C(14)-H(14A)	110.9(10)	C(23)-C(22)-H(22)	119.5(13)
C(7)-C(14)-H(14A)	111.4(12)	C(21)-C(22)-H(22)	119.7(13)
C(15)-C(14)-H(14B)	106.6(11)	C(22)-C(23)-C(24)	119.1(2)
C(7)-C(14)-H(14B)	106.7(12)	C(22)-C(23)-H(23)	119.3(12)
H(14A)-C(14)-H(14B)	109.4(17)	C(24)-C(23)-H(23)	121.6(12)
O(2)-C(15)-N(1)	118.10(18)	C(23)-C(24)-C(25)	120.5(2)
O(2)-C(15)-C(14)	122.17(19)	C(23)-C(24)-H(24)	117.8(12)
N(1)-C(15)-C(14)	119.68(18)	C(25)-C(24)-H(24)	121.6(12)
O(3)-C(16)-O(4)	122.53(18)	C(24)-C(25)-C(20)	120.7(2)
O(3)-C(16)-N(1)	128.7(2)	C(24)-C(25)-H(25)	121.6(14)
O(4)-C(16)-N(1)	108.74(16)	C(20)-C(25)-H(25)	117.6(14)
O(4)-C(17)-C(18)	104.77(16)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for CJB12 (CCDC 239502). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	226(3)	252(3)	343(3)	-70(3)	131(2)	-41(3)
O(1)	262(8)	237(9)	360(10)	-68(7)	133(7)	-12(7)
O(2)	214(8)	303(10)	309(9)	-80(7)	81(7)	46(7)
O(3)	184(8)	228(9)	344(9)	-18(7)	97(7)	7(7)
O(4)	211(7)	223(9)	262(9)	-21(7)	107(6)	-19(7)
N(1)	128(8)	171(10)	220(10)	-16(7)	58(7)	-6(7)
C(1)	215(11)	274(13)	270(12)	-46(12)	115(10)	-51(12)
C(2)	347(15)	326(16)	439(17)	-32(13)	207(13)	-88(13)
C(3)	221(13)	489(19)	298(15)	1(13)	92(11)	17(13)
C(4)	149(10)	192(12)	248(12)	46(10)	31(9)	18(9)
C(5)	183(11)	180(12)	266(12)	15(11)	75(9)	15(10)
C(6)	249(12)	306(15)	332(14)	99(13)	88(11)	24(13)
C(7)	201(11)	152(12)	240(12)	-10(10)	104(9)	23(9)
C(8)	159(11)	165(11)	214(12)	25(9)	54(9)	19(9)
C(9)	239(12)	163(12)	335(13)	-59(11)	115(10)	-43(10)
C(10)	278(13)	297(15)	294(14)	-83(11)	145(11)	-50(11)
C(11)	220(11)	266(14)	299(13)	22(10)	110(10)	-68(10)
C(12)	266(13)	209(14)	286(14)	-32(11)	58(11)	-72(10)
C(13)	253(12)	195(12)	210(12)	1(10)	83(9)	10(10)
C(14)	205(12)	127(12)	239(13)	16(10)	77(10)	7(9)
C(15)	198(11)	149(11)	229(12)	13(9)	75(9)	-22(9)
C(16)	204(11)	90(11)	285(12)	5(10)	91(9)	-7(9)
C(17)	217(12)	231(13)	227(13)	-5(11)	48(10)	-13(11)
C(18)	190(11)	160(12)	239(12)	-4(10)	38(9)	7(10)
C(19)	186(11)	203(13)	248(13)	3(10)	72(9)	7(10)
C(20)	176(10)	211(13)	191(11)	21(9)	68(8)	-33(9)
C(21)	253(13)	191(12)	280(13)	-5(10)	116(11)	9(11)
C(22)	345(13)	241(13)	247(13)	-60(11)	127(11)	-94(12)
C(23)	221(12)	359(15)	229(13)	-14(11)	63(10)	-105(11)
C(24)	190(11)	297(15)	276(13)	16(11)	86(10)	-13(11)
C(25)	230(12)	199(13)	228(12)	-5(10)	92(10)	-16(10)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for CJB12 (CCDC 239502).

	x	y	z	U_{iso}
H(1)	-3984(15)	6140(30)	7273(14)	16(5)
H(2A)	-5220(20)	3220(40)	7012(16)	43(7)
H(2B)	-3970(20)	2490(40)	7070(19)	53(8)
H(2C)	-4950(20)	2890(40)	6019(19)	43(7)
H(3A)	-5515(16)	6420(40)	5367(16)	35(7)
H(3B)	-4960(20)	8460(50)	5996(19)	60(9)
H(3C)	-5881(19)	6860(40)	6297(15)	33(6)
H(5)	-1300(18)	7500(40)	5999(15)	31(7)
H(6A)	-2474(19)	10300(40)	5135(16)	40(7)
H(6B)	-1131(18)	10800(40)	5442(14)	35(6)
H(6C)	-1890(18)	11730(40)	6057(16)	34(7)
H(7)	-607(14)	9980(30)	7600(13)	14(5)
H(9)	641(17)	7380(40)	6020(15)	29(6)
H(10)	2089(17)	8770(40)	5494(15)	32(6)
H(11)	2939(16)	11990(30)	6123(14)	22(6)
H(12)	2189(16)	13800(40)	7213(14)	26(6)
H(13)	782(16)	12380(30)	7716(15)	23(6)
H(14A)	-737(15)	6430(30)	7985(12)	15(5)
H(14B)	-62(14)	5830(40)	7300(13)	15(5)
H(17A)	1882(16)	7250(40)	11317(15)	26(6)
H(17B)	2120(14)	9590(30)	11394(13)	10(5)
H(18)	2598(15)	7240(30)	10078(13)	12(5)
H(19A)	2572(14)	10190(30)	9165(15)	20(6)
H(19B)	2024(16)	11440(30)	9809(13)	13(5)
H(21)	3151(16)	13730(40)	10852(13)	19(5)
H(22)	4888(16)	14780(30)	11864(15)	21(6)
H(23)	6462(17)	12780(30)	12050(14)	20(6)
H(24)	6276(17)	9560(30)	11293(13)	23(6)
H(25)	4517(17)	8500(40)	10289(15)	34(7)