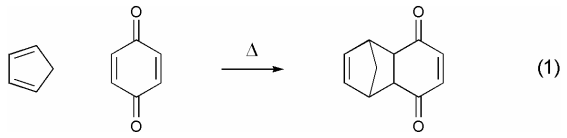
Chapter 2

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.

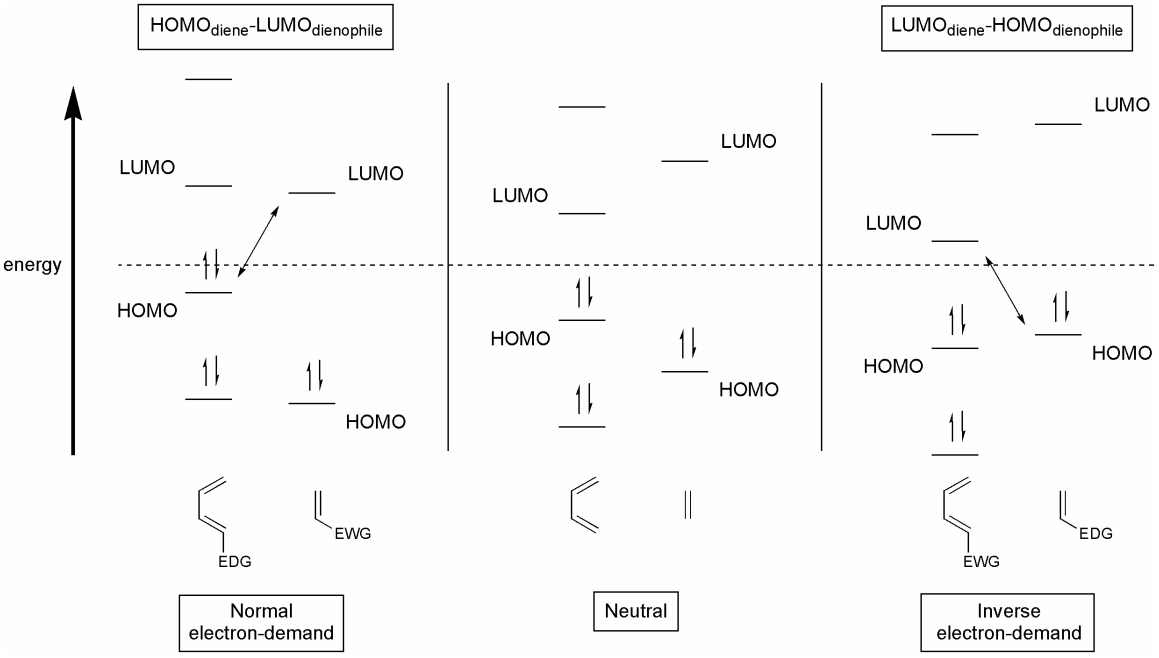


(1)

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]

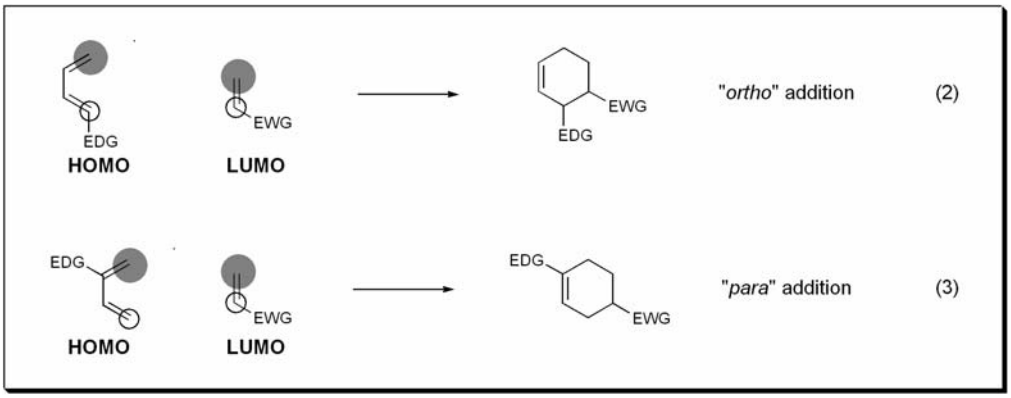
Diels-Alder reactions can be classified and their outcomes predicted based on the HOMO and LUMO involved in the transformation.[6-9] Normal electron-demand Diels-Alder reactions are controlled by the interaction of the $HOMO_{diene}$ and the $LUMO_{dienophile}$; inverse electron-demand Diels-Alder reactions 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.

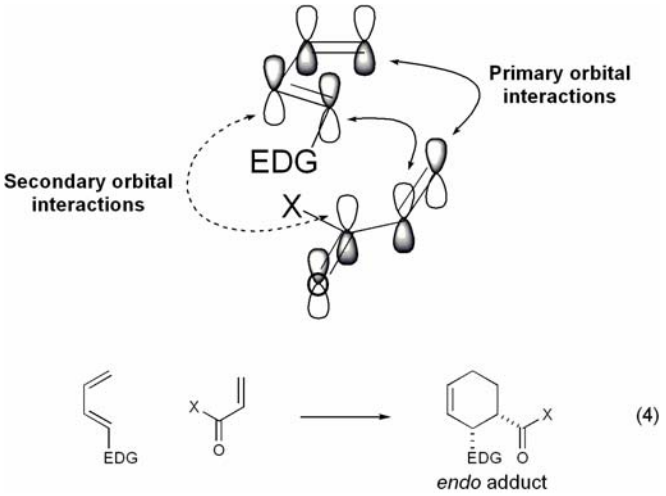


The "*cis* principle" or the *ortho-para* rule, as it is more commonly known, is dictated by the symmetry of the π-orbitals involved in the Diels-Alder cycloaddition.[11,13-15] If the frontier molecular orbitals involved in a normal electron-demand Diels Alder cycloaddition are calculated (the HOMO of 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]

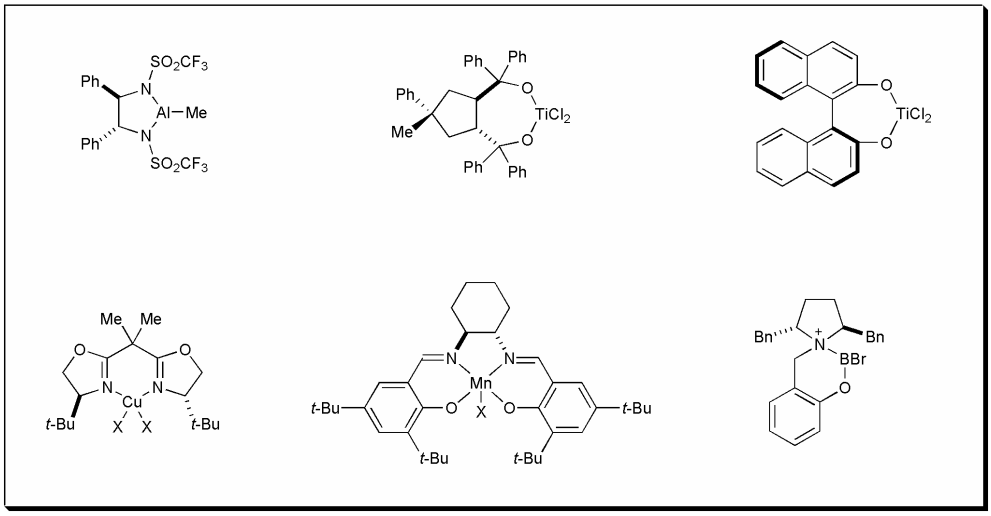
Scheme 3. Orbital interactions in the Diels-Alder cycloaddition.



Enantioselective Catalysis of the Diels-Alder Reaction

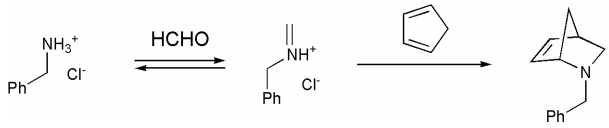
Due to the great utility of this transformation, much research has been devoted to the development of asymmetric catalytic methods.[4,17-19] Effective chrial organometallic catalysts have been developed for the asymmetric Diels-Alder reaction (Figure 1). These catalysts have shown excellent selectivity 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)

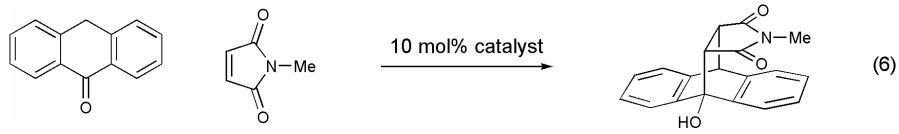
The Diels-Alder reaction need not be Lewis acid catalyzed. The Grieco laboratory has demonstrated that the Diels-Alder reaction will occur under mild conditions when an iminium ion is employed in the transformation as the dienophile

(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]

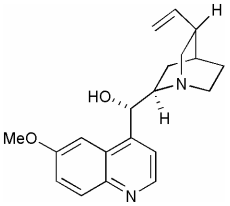
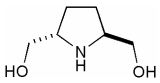
Organocatalysis of the Diels-Alder Reaction

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.

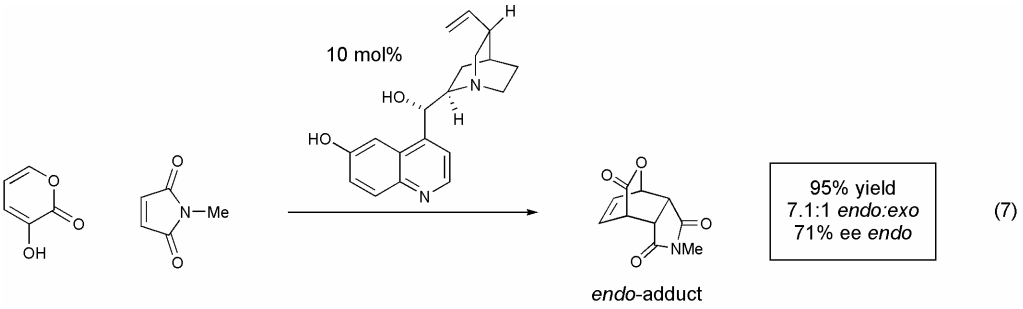


(6)

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)

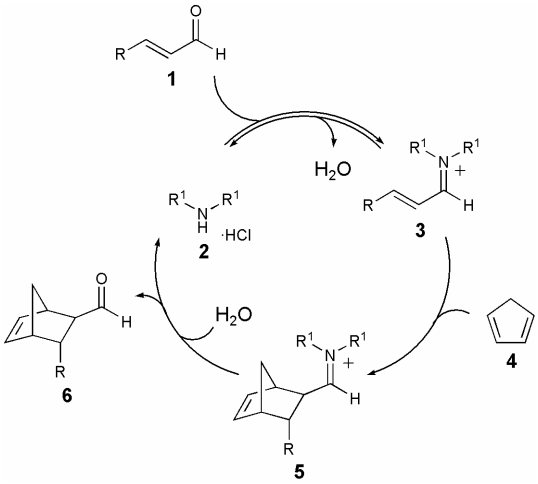
Despite the many examples of organocatalytic Diels-Alder reactions in the literature (catalytic antibodies, cinchona alkaloids, etc.), there has not been a general organocatalytic Diels-Alder strategy reported.

II. Results and Discussion[28]

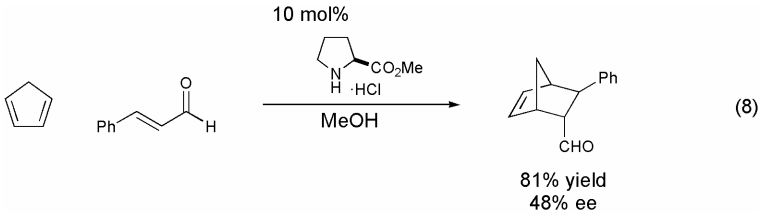
Initial Investigations

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.

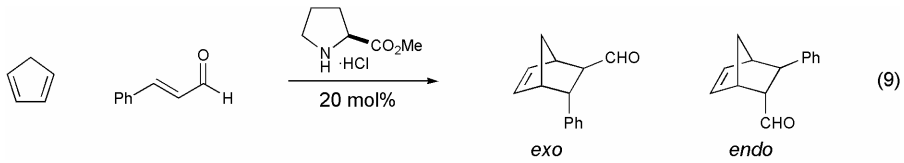


Initial Investigations of Reaction Conditions[30]

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]

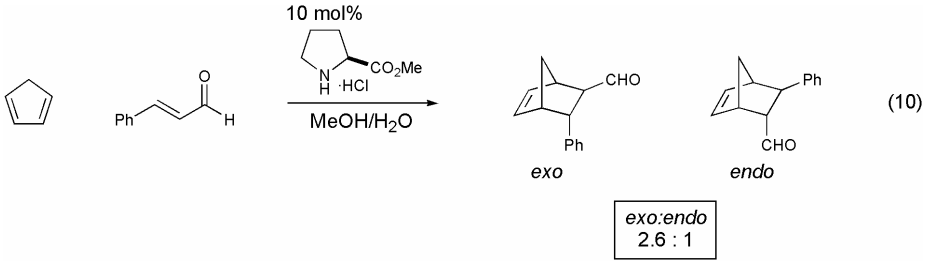


Entry	Solvent	E_T^N	*exo:endo*[b]	% ee (*exo*)[b]
1	THF	0.207	2.3:1	18
2	CH_2Cl_2	0.309	3.3:1	28
3	DMF	0.404	2.4:1	25
4	DMSO	0.444	2.5:1	22
5	CH_3CN	0.460	2.6:1	39
6	CH_3NO_2	0.481	2.7:1	36
7	MeOH	0.762	2.4:1	48

[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.

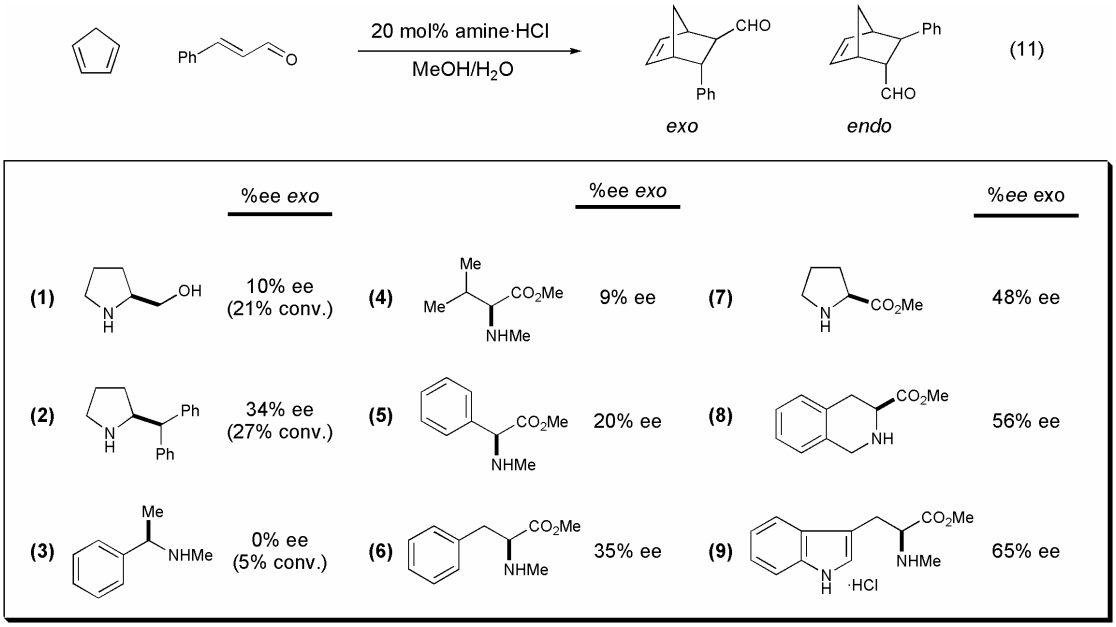
All initial investigations of the organocatalytic Diels-Alder reaction were performed at 1.0 M concentration, based on the limiting reagent. Examination of concentration effects showed that decreased concentrations increased the reaction time without improving selectivity, and increased concentrations 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]



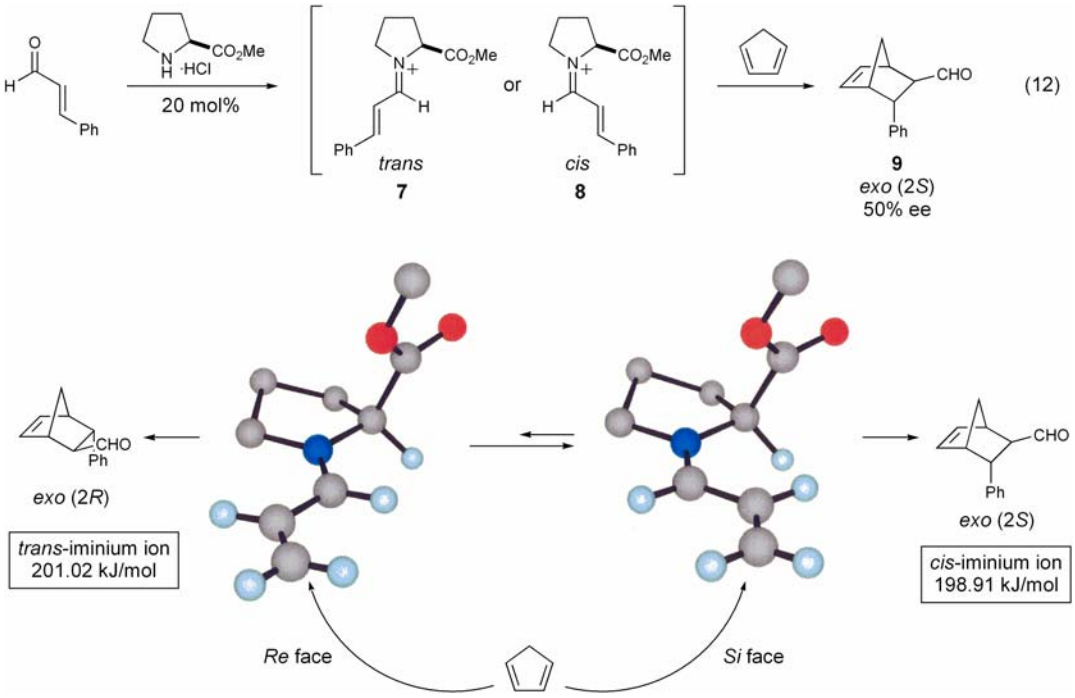
[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); Conversion and enantioselectivity determined by GLC analysis.

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

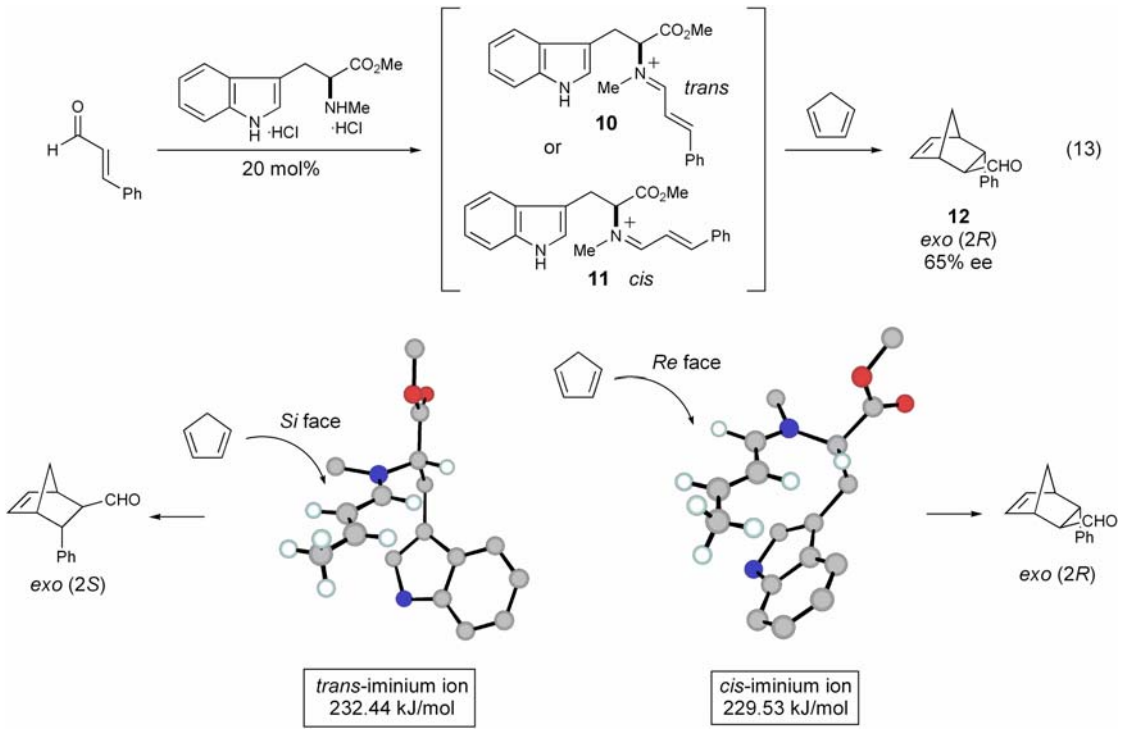
Scheme 5. Calculated iminium ion structures for the iminium ion formed from proline methyl ester.



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.



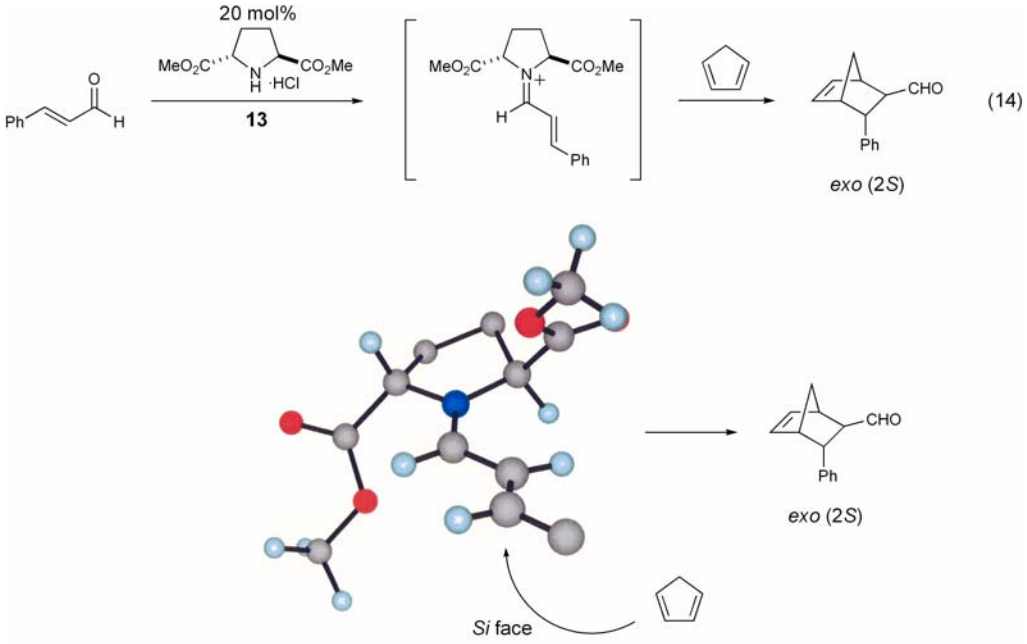
A similar study was conducted with the most selective catalyst discovered, abrine (Scheme 6).[32] An iminium ion formed from an α,β-unsaturated aldehyde and abrine can also form with one of two possible geometries, one with the reactive olefin oriented *trans* to the chiral center of abrine (**10**)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

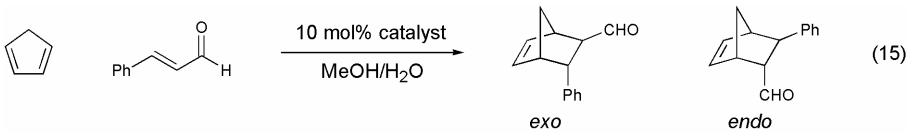
Scheme 7. Calculated iminium ion geometry for the iminium ion formed from a C_2-symmteric catalyst.



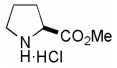
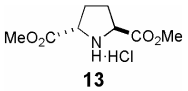
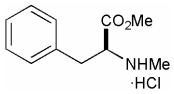
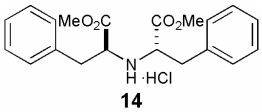
Investigation of C_2-Symmetric Catalysts

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]

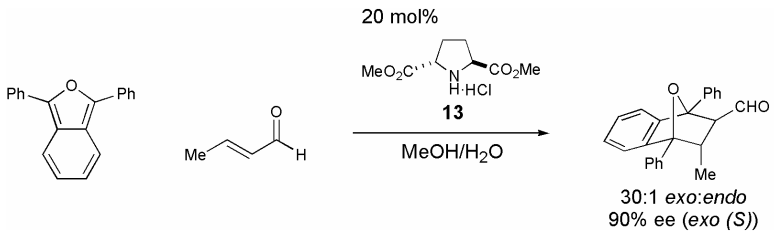


(15)

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]

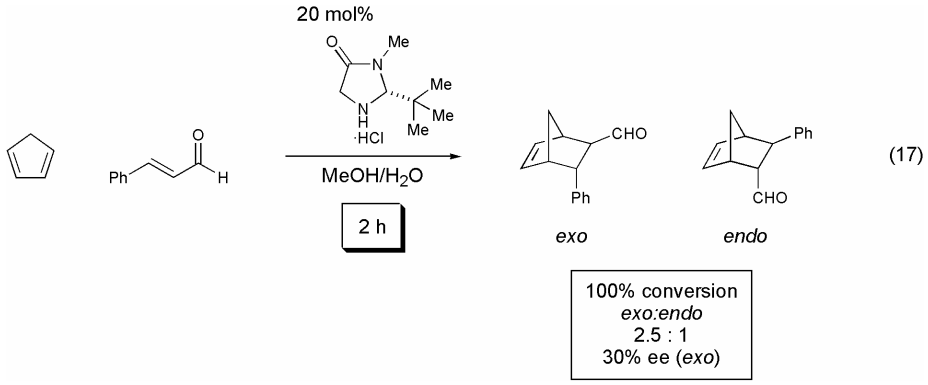


(16)

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.

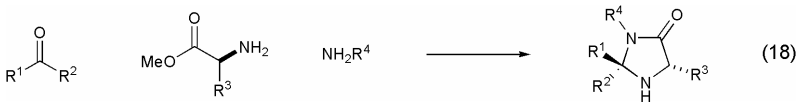
Imidazolidin-4-one catalysts were a particularly promising architecture. This chemotype has been extensively described in the literature, and has been used successfully as a chiral auxiliary.[36-39] Initial results with this catalyst architecture had also shown that this structure exhibits excellent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

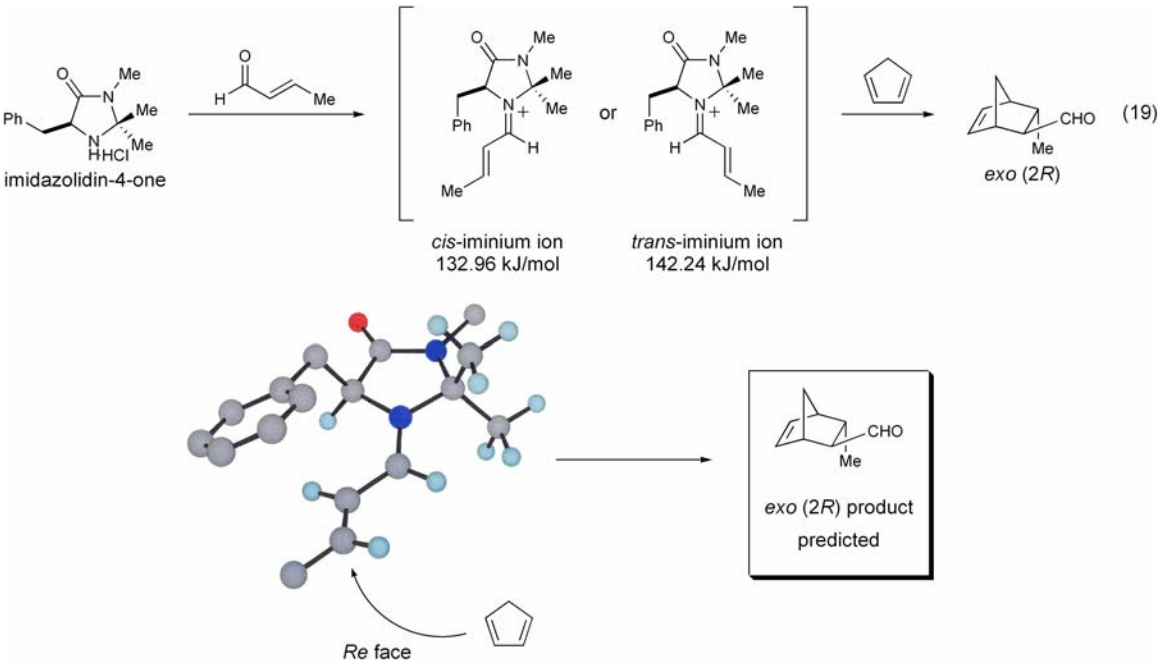
study (Table 4). In addition, the imidazolidin-4-one heterocycle is easily synthesized from an amino acid, ketone or aldehyde, and primary amine, allowing for great structural diversity (equation 18).



(18)

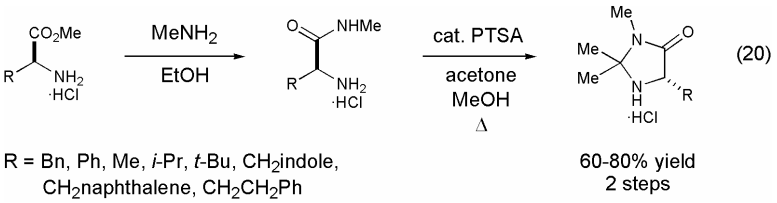
Molecular modeling of this catalyst chemotype showed that it would be possible to select for one iminium ion geometry by taking advantage of steric interactions within the catalyst substrate adduct (Scheme 8).[32] By placing a geminal dimethyl group in the 2-position on the imidazolidin-4-one ring, the 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.



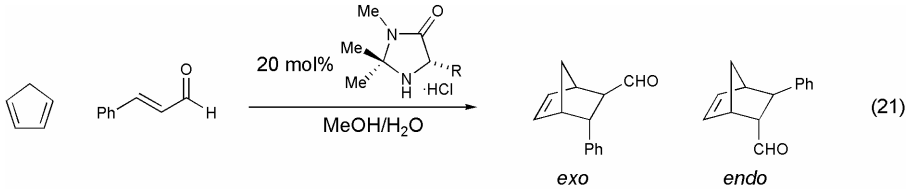
Because of the promising reactivity shown by the 2-*tert*-butyl-imidazolidin-4-one catalyst (equation 17) and because of the promising level of iminium ion geometry control suggested by calculations (Scheme 8), a variety of 2,2-dmethyl-imidazolidin-4-one catalysts were synthesized for examination (Scheme 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.

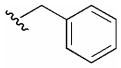
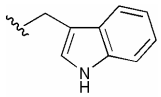
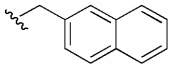
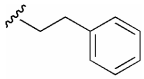
Scheme 9. Synthesis of imidazolidinone catalysts.



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]

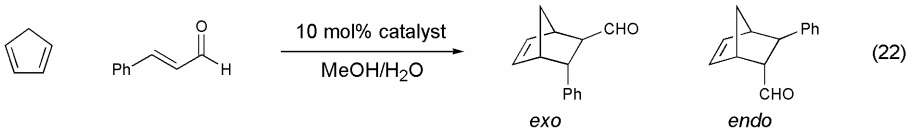


Entry	R	*exo:endo*[b]	%ee *exo*[b]	%ee *endo*[b]
1	Me **15**	1.5:1	30	58
2	*i*-Pr **16**	1.4:1	51	67
3	*t*-Bu **17**	1:1.3	45	27
4	Ph **18**	2.2:1	10	30
5	 **19**	1.3:1	93	93
6	 **20**	1.2:1	92	90
7	 **21**	1.3:1	90	88
8	 **22**	2.0:1	46	61

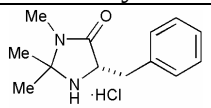
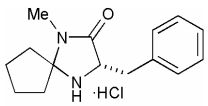
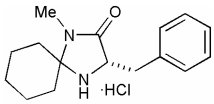
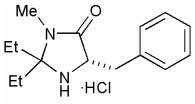
[a] All reactions were performed at room temperature with 5% (v/v) added water (1.0 M); [b] Product ratios and enantioselectivity determined by GLC analysis.

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.

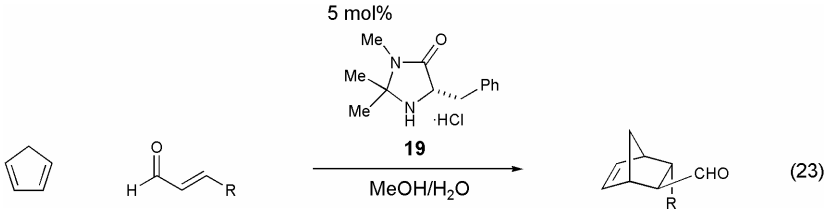
Reaction Scope

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]



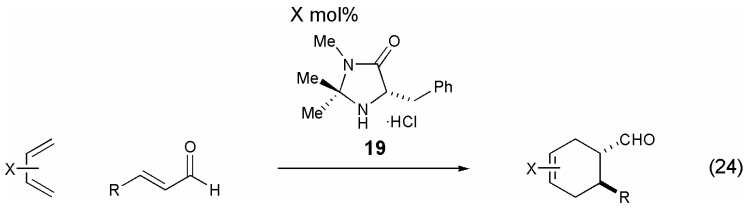
(23)

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

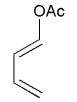
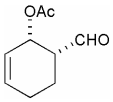
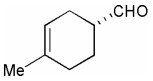
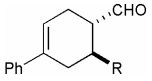
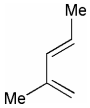
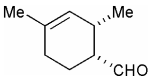
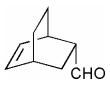
[a] All reactions performed with 5% (v/v) water; [b] Product ratios and enantioselectivity determined by GLC analysis.

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]

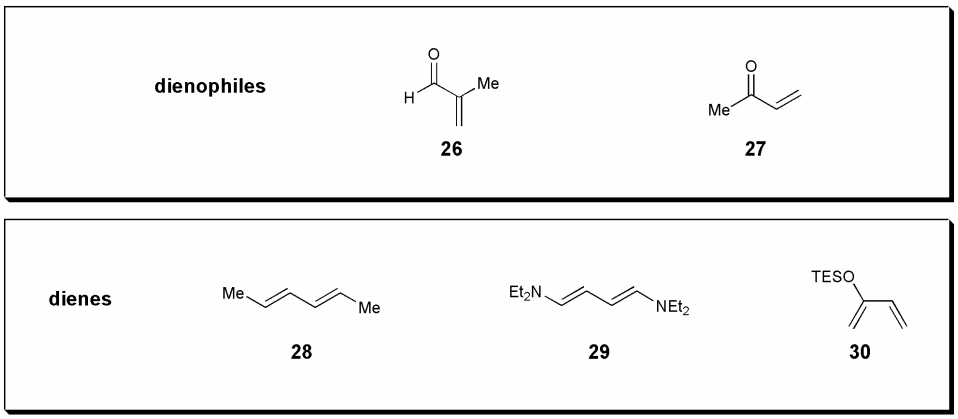
[a] Reactions performed with 5% (v/v) water; [b] Product ratios and enantioselectivity determined by GLC; [c] yield determined by GLC; [d] *endo* ee

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.

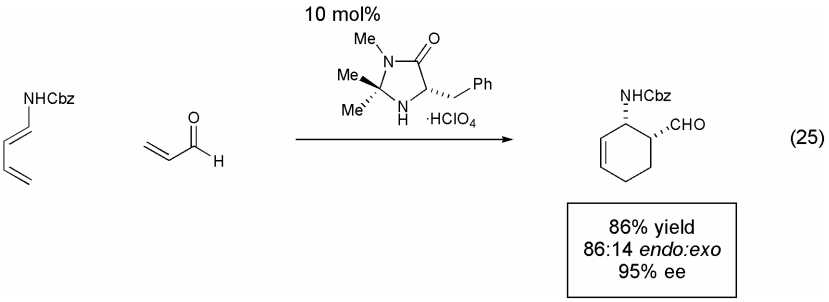
Figure 2. Substrates not able to participate in the organocatalytic Diels-Alder reaction.



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).

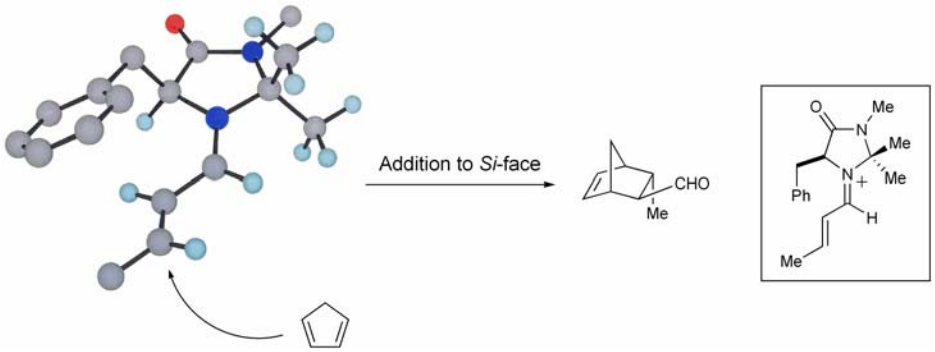


(25)

Stereochemical Rationale

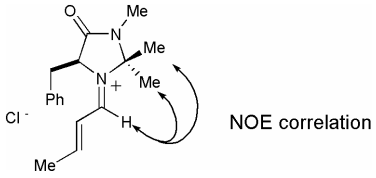
The stereochemistry observed in the organocatalytic Diels-Alder reaction is consistent with the calculated iminium ion (Scheme 10). The (*E*)-iminium ion isomer is enforced by the presence of the geminal dimethyl substitution on the imidazolidinone framework, and this control over the iminium ion geometry 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.

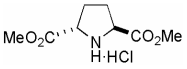
IV. Experimental Section

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]

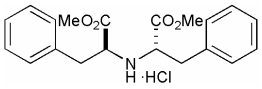
^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHZ and 125 MHz, respectively), AM-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H are reported as follows: chemical shift (δ 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).

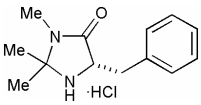
Progress of the Diels-Alder reaction was typically monitored by TLC analysis, or in cases where necessary, ^{1}H NMR analysis of the reaction *in situ* in deuterated solvent or by GLC analysis of reaction aliquots.



(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.

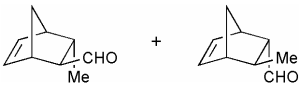


(5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (19). A solution of phenylalanine methyl ester hydrochloride (26.0 g, 121 mmol) and ethanolic $MeNH_2$ (8.0 M, 60 mL) was stirred at room temperature until the amino ester was consumed as determined by TLC (20 hr). After removal of the organic solvents *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.

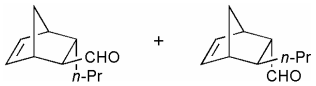
General Procedure for the Organocatalytic Diels-Alder Reaction: To a solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** in wet methanol (5% water) was added the α,β-unsaturated aldehyde (1M). After stirring for 1-2 minutes, diene was added to the solution. Upon consumption 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.



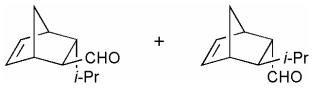
(1*S*, 2*R*, 3*S*, 4*R*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde and (1*R*, 2*R*, 3*S*, 4*S*)-3-Methylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Table 8, entry 1). Prepared according to general procedure A from crotonaldehyde (871 μL, 10.0 mmol) and cyclopentadiene (2.5 mL, 30.0 mmol), using 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.



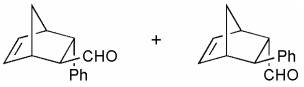
(1*S*, 2*R*, 3*S*, 4*R*)-3-Propyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*R*, 3*S*, 4*S*)-3-propyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 2). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride (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.

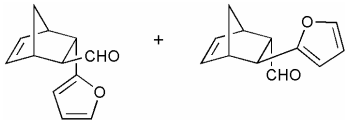


(1*S*, 2*S*, 3*S*, 4*R*)-3-Isopropyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-isopropyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 3). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **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.

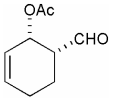


(1*S*, 2*S*, 3*S*, 4*R*)-3-Phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde (Table 8, entry 4). Prepared according to the general procedure from cinnamaldehyde (252 μL, 2.0 mmol) and cyclopentadiene (495 μL, 6.0 mmol), using 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]

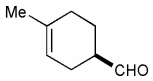


(1*S*, 2*S*, 3*S*, 4*R*)-3-Furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 8, entry 5). The title compound was prepared according to the general procedure from (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one 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*

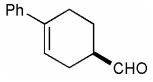
188.0837, found *m/z* 188.0838; $[\alpha]_D$ = + 169 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by GLC analysis on a Bodman Γ-TA column (70 °C initial temp, 5 °C/min, 23 psi); *exo* adduct t_r = 17.4 min and 17.7 min, *endo* adduct t_r = 17.9 min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

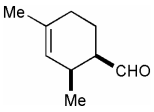


(1*R*)-4-methyl-3-cyclohexene-1-carboxaldehyde (Table 9, entry 2). To a 0 °C solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (32 mg, 0.12 mmol) in wet nitromethane (5% v/v water, 1.0 M) was added acrolein (1.0 mL, 15 mmol), and isoprene (0.50 mL, 5.0 mmol). The solution 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]



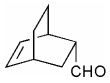
(1*R*)-4-Phenyl-3-cyclohexene-1-carboxaldehyde (Table 9, entry 3). To a 0 °C solution of 2-phenyl-1,3-butadiene[49] (89 mg, 0.68 mmol) in wet nitromethane (5% v/v water, 1.0 M) was added (5*S*)-5-benzyl-2,2,3-

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.



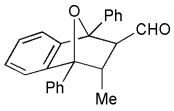
(1*R*, 2*S*)-2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde (Table 9, entry 5). To a -10 °C solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **19** (27 mg, 0.11 mmol) in wet acetonitrile (5% v/v water, 1.0 M) was added acrolein (102 μL, 1.53 mmol). After stirring 1 minute, 2-methyl-1,3-pentadiene

(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.

V. References

(1) Zincke, T.; Guenther, H. *Liebigs Ann. Chem.* **1893**, *272*, 243.

(2) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98.

(3) Whiting, A. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall: London, 1996, pp 126-145.

(4) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

(5) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001**, *12*, 597.

(6) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.

(7) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

(8) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(9) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.

(10) Boger, D. L. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 451.

(11) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976.

(12) Coxon, J. M.; Froese, R. D. J.; Ganguly, B.; Marchand, A. P.; Morokuma, K. *Synlett* **1999**, 1681.

(13) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

(14) Woodward, R. B.; Hoffman, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(15) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(16) García, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658.

(17) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(18) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.

(19) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439.

(20) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465.

(21) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(22) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron* **1986**, *27*, 1975.

(23) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

(24) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

(25) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403.

(26) Tokioka, K.; Masuda, S.; Fujii, T.; Hata, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 101.

(27) Okamura, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Chem. Lett.* **1996**, 193.

(28) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(29) Ahrendt, K. A., Initial studies with cinnamaldehyde and cyclopentadiene.

(30) All subsequent organocatalytic Diels-Alder studies were conducted in collaboration with Kateri A. Ahrendt, graduate student.

(31) Lamchen, M.; Pugh, W.; Stephen, A. M. *J. Chem. Soc.* **1954**, 4418.

(32) Monte Carlo simulation performed with the MM3 force field; Macromodel V6.5.

(33) Buchman, E. R.; Reims, A. O.; Skei, T.; Schlatter, M. J. *J. Am. Chem. Soc.* **1942**, *64*, 2696.

(34) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298.

(35) Effenberger, F.; Burkard, U. *Liebigs Ann. Chem.* **1986**, 334.

(36) Bezencon, O.; Seebach, D. *Liebigs Ann. Chem.* **1996**, 1259.

(37) Seebach, D.; Maetzke, T.; Petter, W.; Klotzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781.

(38) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622.

(39) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.

(40) Larsen, C. H., unpublished results.

(41) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(42) Ahrendt, K. A. In *Chemistry*; University of California, Berkeley: Berkeley, CA, 2003.

(43) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Fourth ed.; Butterworth-Heinemann: Oxford, 1996.

(44) Still, W. C. *J. Org. Chem.* **1978**, *43*, 2923.

(45) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.

(46) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.

(47) Gouesnard, J. P.; Martin, G. J. *Tetrahedron* **1974**, *30*, 151.

(48) Poll, T.; Sobczak, A.; Hartman, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *36*, 3095.

(49) Marvel; Woolford *J. Org. Chem.* **1958**, *23*, 1658.