Investigating Imidazolidinone Catalysts: Enantioselective Organocatalytic Diels–Alder Reactions, Conjugate Additions to Access Non-Natural α-Amino Acids, and Bimodal Catalyst Activation for the Development of Organo-Cascade Reactions

Thesis by

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Abstract

The MacMillan group focuses on the development of new strategies that harness the power of simple organic compounds to catalyze asymmetric reactions. To this end, we have designed amine catalysts which activate α,β-unsaturated aldehydes *via* the reversible formation of chiral iminium ions (in analogy to LUMO-lowering activation by reversible metal-substrate complexation). Kinetic studies highlight the importance of the acid co-catalyst and identified a more reactive imidazolidinone catalyst complex, which improved enantioselectivities and vastly expanded the substrate scope of the first highly enantioselective organocatalytic Diels–Alder reaction. Exploration of the crucial components of catalyst architecture led to the development of the second-generation imidazolidinone that not only catalyzes cycloadditions, but a variety of other reactions of aldehydes with excellent selectivity.

Complementary to the 1,2-addition observed with Lewis acids, the alternative mode of activation offered by iminium catalysis allows for 1,4-addition of heterocycles to α,β-unsaturated aldehydes. Using a chiral amine catalyst, the first asymmetric conjugate addition of oxazoles generates protected quaternary α-amino acids with an adjacent tertiary stereocenter, a widely applicable motif in biology, materials science, and medicine. Finally, having demonstrated that imidazolidinones can activate both electrophiles (LUMO-lowering) and nucleophiles (HOMO-raising), these iminium and enamine catalysis cycles can be linked for tandem nucleophilic addition/electrophilic trapping of enals. In a single synthetic operation, this enantioselective conjugate addition/α-halogenation sequence takes achiral starting materials and selectively connects them, creating multiple stereocenters across the newly formed bonds.

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Chapter 1

Enantioselective Organocatalytic Diels–Alder Reactions

Introduction

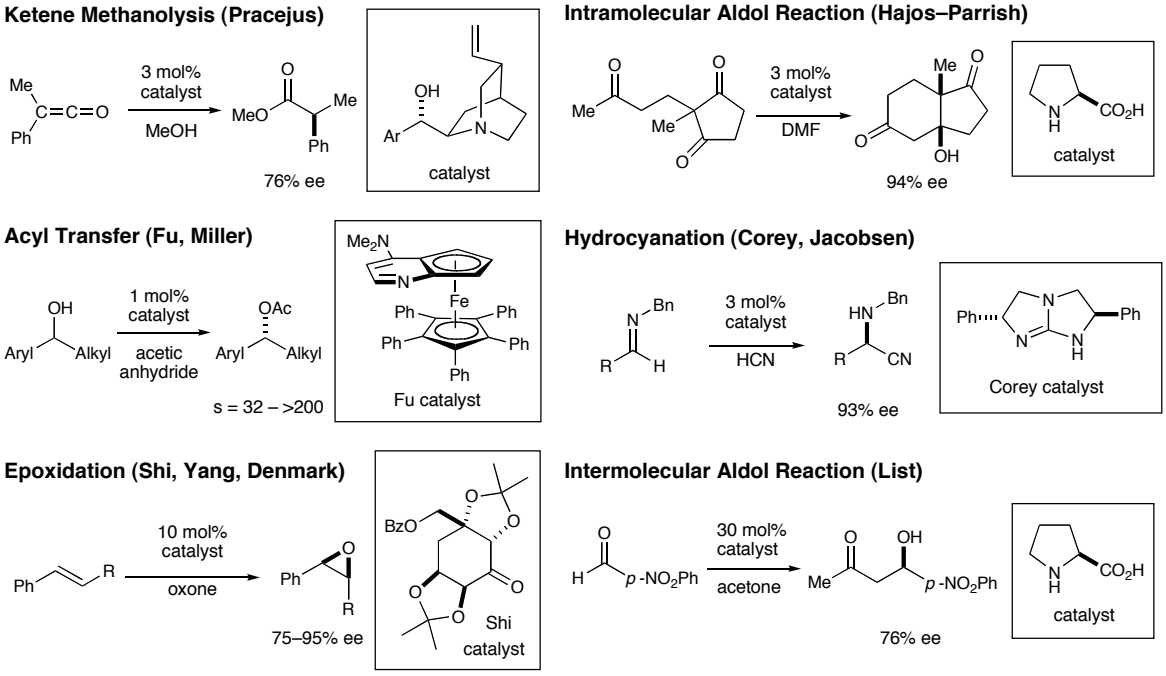
The demand for single enantiomer molecules for academic and industrial applications has propelled asymmetric catalysis to the forefront of investigations in synthetic chemistry. Compared to the field of metal-catalyzed asymmetric transformations, one finds a paucity of reactions catalyzed by organic molecules despite the attendant advantages in cost, operational complexity, time, energy, and elimination of toxic metal wastes. In recent years, there has been a resurgence in the development of enantioselective organocatalytic reactions. A major focus of research in the MacMillan group has become the study of a broadly applicable reaction manifold based upon iminium activation using chiral amine catalysts. This report describes investigations aimed at improving the organocatalytic Diels-Alder reaction developed by our group, a transformation which introduced imidazolidinones as flexible catalysts for the activation of unsaturated carbonyl systems. In order to develop a more reactive imidazolidinone catalyst, the reaction components affecting iminium formation and reactivity were explored. Kinetic studies highlight the importance of the acid co-catalyst and identified a more reactive complex that improves enantioselectivities and vastly expands the substrate scope of this organocatalytic Diels–Alder reaction. Exploration of the catalyst features necessary for reactivity and selectivity led to the development of the second-generation imidazolidinone whose high levels of activity are attributed to the formation of a more reactive iminium intermediate that not only catalyzes cycloadditions, but conjugate additions, hydrogenations, and aldol reactions of aldehydes with excellent selectivity.

Background

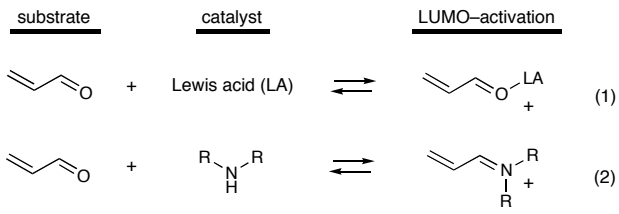
Since the late 1960s, the field of metal based chiral catalysis has amassed an array of enantioselective oxidation, reduction, π-bond activation, and Lewis acid-catalyzed reactions.[1-5] In contrast, until recently, a limited number of asymmetric reactions employed organic molecules as catalysts.[6] Ideally, naturally available enantiopure amino acids, carbohydrates, and hydroxyl acids could be used directly as catalysts. The use of robust organic catalysts would eliminate the need for air- and moisture-free conditions. In addition, the alternative reactivity of organic molecules may allow for catalysis of transformations which are inaccessible via Lewis acid catalysts.

Interestingly, two of the earliest examples of asymmetric catalytic reactions utilize organic systems. In 1960, the pioneering work of Pracejus presented the first enantioselective methanolysis of phenylmethyl ketene using a quinuclidine catalyst (Scheme 1).[7] In the early 1970s, considerable attention was focused on the proline-catalyzed intramolecular aldol commonly termed the Hajos-Parrish reaction (Scheme 1).[8] The reaction was mostly neglected for over a quarter century until List and coworkers demonstrated the first intermolecular variant of this direct aldol protocol.[9] While many successful forays into the field of organocatalysis have been reported in the past few years,[10-12] they highlight a common limitation in organocatalysis. In general, the mechanism of activation in each case is amenable only to a singular type of transformation and thus demands a different catalyst for each specific reaction (Scheme 1).

Scheme 1. Early examples of metal-free catalysis

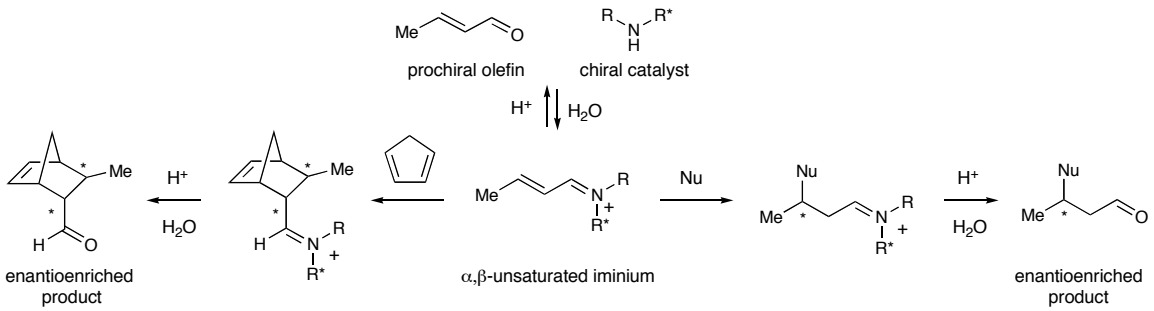


With this is mind we embarked upon the development of a general organocatalytic strategy incorporating design elements from the area of Lewis acid catalysis. Reversible Lewis acid binding forms an equilibrium between an electronically neutral α,β-unsaturated aldehyde and more reactive, charged intermediate (eq. 1). This form of activation lowers the energy of the lowest unoccupied molecular orbital (LUMO), making it closer in energy to the highest occupied molecular orbital (HOMO). As the energy difference between these two reacting partners is decreased, it becomes more facile for them to overcome the energetic barrier that separates them, and consequently, react. As this LUMO-lowering mechanism should apply to any carbogenic system that exists as an equilibrium between a relatively electron-rich and electron-deficient state, we envisioned that the corresponding equilibrium between an α,β-unsaturated aldehyde and the highly reactive α,β-unsaturated iminium ion formed upon condensation with an amine would provide a similarly reactive catalytic system (eq. 2).



Association of chiral ligands to the Lewis acid allows for differentiation of the two prochiral faces of the olefin. We postulated that the analogous equilibrium between a chiral secondary amine and an α,β-unsaturated aldehyde to form a chiral activated iminium ion would provide asymmetric LUMO-lowering catalysis, thereby affording an attractive platform for the development of a new enantioselective organic catalyst that could be utilized for a range of transformations which traditionally employ metal salts (Scheme 1). Furthermore, upon condensation of the chiral amine catalyst and the prochiral olefin, the α,β-unsaturated iminium ion formed can theoretically participate in multiple reaction pathways. For example, Scheme 1 displays the chiral iminium reacting with either cyclopentadiene in a Diels–Alder or with a nucleophile *via* conjugate addition. In both cases, hydrolysis of the catalyst-bound product frees the catalyst to undergo another cycle.

Scheme 2. Versatility of LUMO-lowering iminium catalysis by a chiral amine



To our knowledge this iminium-catalysis cycle had not been documented in the literature prior to our studies. However, some related experiments encouraged us to pursue this organocatalytic strategy. First of all, reductive amination demonstrates the selectivity

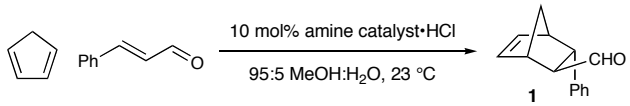
required of LUMO-lowering activation in the rapid reduction of an iminium ion to the corresponding alkyl amine in the presence of the aldehyde starting material.[13] The selectivity of this reaction is key in that only the iminium ion formed from reversible condensation of the aldehyde and amine is sufficiently electron deficient to undergo hydride reduction. Secondly, the work of Jung and co-workers in the late 1980s revealed that α,β-unsaturated iminium ions are significantly more reactive as dienophiles than α,β-unsaturated aldehydes, acid chlorides, ketones, nitriles, or esters.[14,15] In our chiral amine-catalyzed system, the rate acceleration due to the delocalized positive charge would effect the enantioselective bond-forming step. Finally, Grieco and co-workers have clearly demonstrated that iminium ions generated under Mannich conditions will undergo aza-Diels–Alder reactions with electron-rich dienes.[16] While this reaction does incorporate the amine substrate into the Diels–Alder adduct, it provided strong precedent for the supposition that electron-rich substrates will react selectively with an equilibrium concentration of iminium ions in preference to unactivated aldehydes.

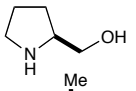
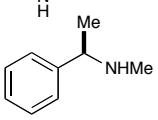
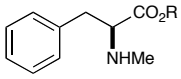
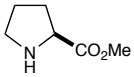
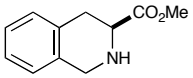
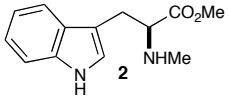
Development of Organocatalyst

To test our iminium-activation strategy, we first examined the capacity of (*S*)-proline methyl ester to enantioselectively catalyze the Diels–Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene to provide bicycle **1**.[17] While exposure of the α,β-unsaturated aldehyde to diene in the absence of the amine resulted only in recovery of starting materials, we were excited to find that the introduction of (*S*)-proline methyl ester•HCl salt in catalytic quantities resulted in formation of bicyclic Diels–Alder adduct **1** in 48% enantioselectivity (ee) and 81% yield (Table 1, entry 4).

Additionally, we were able to demonstrate that this organocatalytic strategy could be accomplished with a variety of amino acids. As revealed in Table 1, amines that incorporate a relatively basic nitrogen component are poor catalysts in terms of both reaction efficiency and enantioselectivity (entries 1 and 2, 5–21% conversion, 0–10% ee). In contrast, amines that are relatively acidic due to a proximal electron withdrawing group (e.g., α-carbonyl as in α–amino acids) provide excellent levels of reaction efficiency (entries 3–6, 100% conversion). In this initial survey of chiral amines, tryptophan-derived catalyst **2** provided the best levels of enantiocontrol (entry 6, 65% ee).

Table 1. Diels–Alder between cinnamaldehyde and cyclopentadiene with representative amine catalysts



entry	catalyst	conv. (%)	ee (%)
1		21	10
2		5	0
3		100	35
4		100	48
5		100	56
6	 **2**	100	65

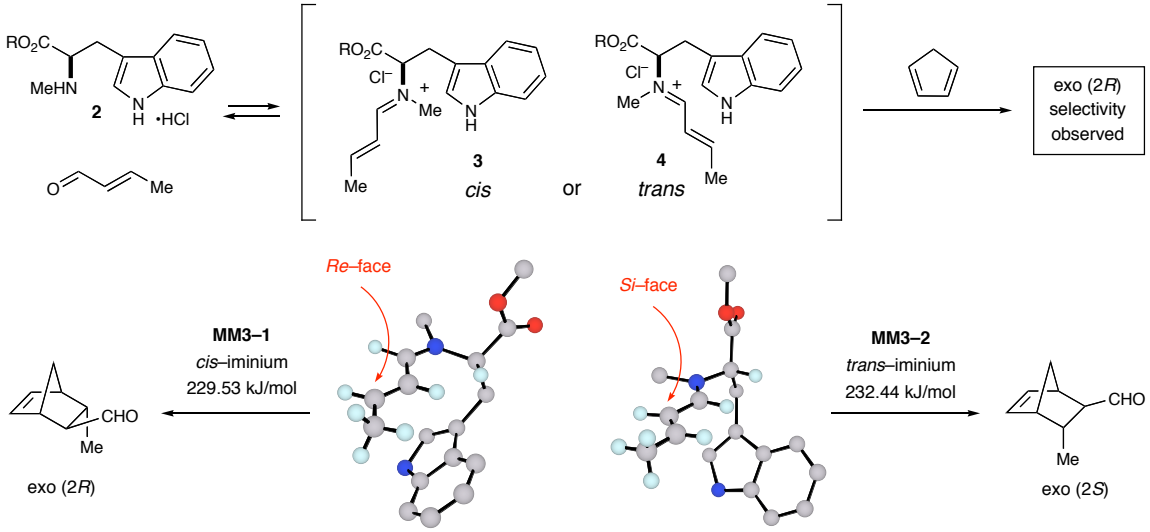
Computational models of iminium ion structures **3** and **4**, which arise from the condensation of catalyst **2** and crotonaldehyde, delineate the structural features from which this selectivity originates (Scheme 2).[18] In the case of the *cis* iminium (**3**), the indole ring of

the catalyst blocks the *Si*-face of the iminium, leaving the *Re*-face open for attack (Scheme 2, **MM3-1**). With the *trans* iminium (**4**), the *Re*-face is blocked such that cycloaddition occurs from the *Si*-face (Scheme 2, **MM3-2**). This dictates that the asymmetric environment associated with each iminium isomer will generate the opposite enantiomeric series. As both *cis* and *trans* iminium ion geometries are operational according to energetic considerations, the 65% enantioselectivity in favor of (*R*)-**1** is due to the presence of an energetic preference for the *cis*-(*R*)–producing iminium over the the *trans*-(*S*)–producing isomer. Therefore, while the indole moiety may confer complete enantiofacial coverage for each geometric isomer, if iminium geometry is not somehow restricted to one isomer, both enantiomers of the product will form. *As such, these models indicate that catalysts that attain poor levels of iminium geometry control will exhibit diminished enantiocontrol.*

Scheme 3. Calculated iminium intermediates of tryptophan-derived catalyst

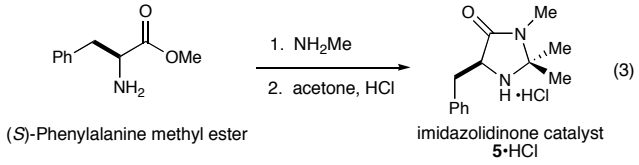
Imidazolidinone Design Elements

Based on the experimental findings summarized in Table 1 and the computational studies outlined in Scheme 2, we have identified four objectives that should be addressed in the development of a highly enantioselective and broadly applicable chiral amine catalyst: i)



efficient reaction rates, ii) iminium ion geometry control, iii) enantiofacial discrimination controlled by catalyst architecture, and iv) ease of preparation and usage.

On the basis of these design criteria, we selected 5-benzyl-2,2-dimethyl imidazolidinone **5** as the target amine catalyst for reaction exploration.[19] From a practical viewpoint, the hydrochloric acid salt of the imidazolidinone (**5**•HCl) is readily accessed as a crystalline bench stable solid in 200-250 gram quantities (Scheme 3). The reaction of phenylalanine methyl ester with *N*-methylamine produces the *N*-methylamide of phenylalanine, which upon condensation with acetone and treatment with hydrochloric acid cleanly provides **5**•HCl.

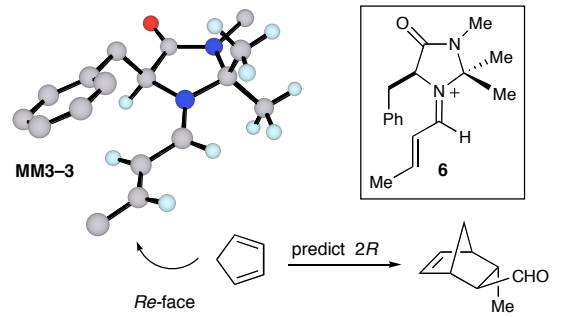


(*S*)-Phenylalanine methyl ester — imidazolidinone catalyst **5**•HCl (3)

This imidazolidinone system (**5**•HCl) was expected to readily condense with an α,β-unsaturated aldehyde such as crotonaldehyde to form iminium **6**. In terms of catalyst architecture, the amide carbonyl acidifies the secondary ammonium of **5**•HCl to allow aldehyde protonation while the five-membered ring enhances the nucleophilicity of the resultant amine for condensation with the protonated aldehyde. As the catalyst is an organic molecule as opposed to an organometallic system, it is straightforward to conduct molecular modeling experiments to determine the most energetically favorable conformation of the chiral iminium (**6**). The expectation for significant levels of asymmetric induction from intermediate **6** was based upon the calculated iminium ion model **MM3-3** (Scheme 3). Inspection of structure **MM3-3** reveals two salient stereocontrol elements: (i) selective formation of the *trans*-iminium isomer to avoid non-bonding interactions between the

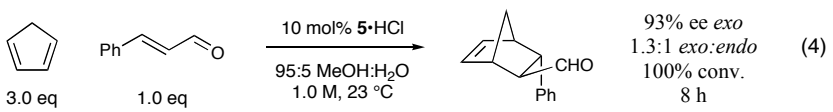
substrate olefin and the geminal methyl substituents and (ii) shielding of the *Si*-face of the dienophile by the benzyl group on the catalyst framework. This leaves the *Re*-face exposed for enantioselective bond formation such that the (2*R*)-cycloadduct is expected in the cycloaddition of cyclopentadiene with iminium **6**.

Figure 1. Calculated iminium intermediates of benzyl imidazolidinone catalyst



i) efficient reaction rates ii) iminium geometry control
iii) enantiofacial discrimination iv) ease of preparation

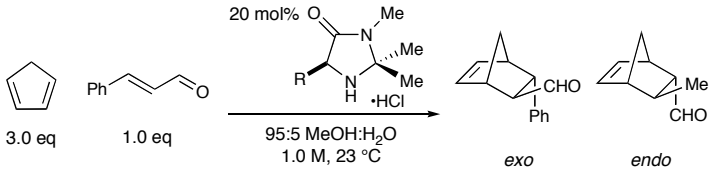
To our great delight, 10 mol% of benzyl imidazolidinone salt **5**•HCl was found to catalyze the cycloaddition of cyclopentadiene and cinnamaldehyde at room temperature (eq. 4). In 8 hours, the aldehyde is completely consumed and provides the cycloadduct in 93% ee![17] In fact, the sense of asymmetric induction observed correlates to that predicted based on the geometrical constraints imposed by catalyst **5** on the formation of the iminium π-system (Figure 1, **MM3-3**). It is notable that this reaction proceeds at room temperature with high enantioselectivity and complete conversion in a relatively concentrated solution of methanol containing 5% water by volume. The fact that this organocatalytic reaction requires no air- or moisture-sensitive techniques means that the crystalline, bench-stable catalyst is simply weighed into a capped vial to which methanol, water, aldehyde, and diene are added.

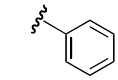
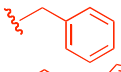
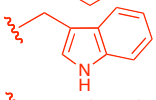
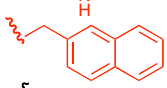
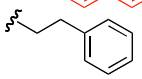


(4)

As the imidazolidinone structure had now proven successful as an asymmetric catalyst for the enantioselective Diels–Alder reaction, the efficacy of catalysts bearing other α-carbonyl substituents needed to be probed (Table 2). These are synthesized in the same sequence as benzyl imidazolidinone catalyst **5**: the *N*-methyl amide of the appropriate amino acid, beaqring the desired R group, is condensed with acetone (as above in eq. 3). Table 2 compares the selectivity imparted by each amine in the Diels–Alder reaction of cyclopentadiene and cinnamaldehyde. The application of catalysts derived from alanine, valine, *tert*-leucine, and phenyl glycine results in a dramatic drop in enantioselectivity (entries 1-4, R = methyl (Me), *iso*-propyl(*i*-Pr), *tert*-butyl (*t*-Bu), and benzyl (Bn)). The most striking change is that from phenyl substitution, 10/30% *exo*/*endo* ee, to benzyl substitution, 93/93% *exo*/*endo* ee (entries 4 and 5). The fact that homologation of the α-amino substituent by a single methylene causes such a drastic improvement in enantioselectivity reinforces the salient features of the molecular model of the iminium formed from benzyl-substituted imidazolidinone **5** (**MM3-3**, Scheme 3 above). Whereas the methylene link between the ring and the phenyl group of **5** allows the benzyl ring to swing over and shield one enantioface of the α,β-unsaturated iminium (**6**), there is almost no shielding in entry 4 as the phenyl ring can only rotate around the bond connecting it directly to the imidazolidinone ring. Furthermore, as shown in entries 5-7 with Ar = phenyl, indole, or napthyl, the identity of the aryl ring of the CH_2Ar moiety is not as critical for high enantioselectivity as the presence of the CH_2Ar itself. Adding another methylene, as in homobenzyl-substituted entry 8, also reduces the shielding ability of the aryl group and leads to poor enantioselectivity (46/61% *exo*/*endo* ee versus 90-93/88-93% *exo*/*endo* ee).

Table 2. Effect of α-amino substituent on selectivity of organocatalytic cycloaddition

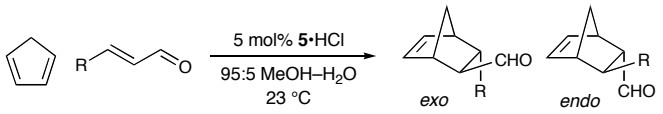


entry	R	*exo*:*endo*[a,b]	*exo* ee (%)	*endo* ee (%)
1	Me	1.5:1.0	30	58
2	*i*-Pr	1.4:1.0	51	67
3	*t*-Bu	1.0:1.3	45	27
4		2.2:1.0	10	30
5		1.3:1.0	93	93
6		1.2:1.0	92	90
7		1.3:1.0	90	88
8		2.0:1.0	46	61

Preliminary Results

As the original benzyl-substituted imidazolidinone catalyst synthesized was found to be the most selective and reactive, the capacity of imidazolidinone **5**•HCl to enantioselectively catalyze the Diels-Alder reaction between a variety of α,β-unsaturated aldehydes and cyclopentadiene was investigated (Table 3).* The amine-catalyzed cycloaddition tolerates a steric range of alkyl-substituted dienophiles (entries 1-3, R = Me, Pr, and *i*-Pr, 75-92% yield, 84-86% *exo* ee, 90-93% *endo* ee). Aromatic-substituted dienophiles provide somewhat higher selectivities (entries 4 and 5). A 50-mmol cycloaddition of cyclopentadiene and cinnamaldehyde was carried out to demonstrate that catalyst **5**•HCl (5 mol%) operates equally well on preparative scale (12 g (*2S*)-**8**, 99% yield, 93% *exo* ee).

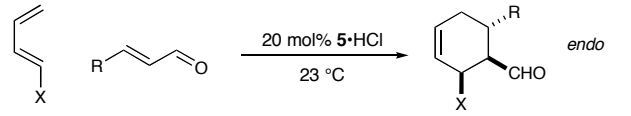
Table 3. Organocatalyzed Diels–Alder reaction between cyclopentadiene and representative dienophiles

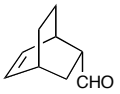
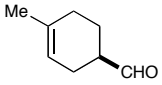
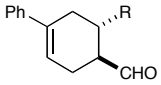
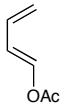
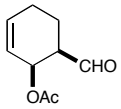


entry	R	time (h)	yield (%)	*exo*:*endo*[a,b]	*exo* ee (%)	*endo* ee (%)
1	Me	16	75	1:1	86 (2*R*)	90 (2*R*)
2	Pr	14	92	1:1	86 (2*R*)	90 (2*R*)
3	*i*-Pr	14	81	1:1	84 (2*S*)	93 (2*S*)
4	Ph	21	99	1.3:1	93 (2*S*)	93 (2*S*)
5	Furyl	24	89	1:1	91 (2*S*)	93 (2*S*)

With less-reactive cyclic and acyclic dienes, acrolein (R = H) provides excellent reactivity without a loss in selectivity in the imidazolidinone-catalyzed reaction (Table 4). Cyclohexadiene reacts efficiently to produce a bicyclic aldehyde in 14:1 *endo:exo* and 94% ee (entry 1). Alkyl-, aryl-, and acetoxy-subsituted cyclohexene aldehydes are produced with high regio- and enantioselectivity (entries 2-5, 72-90% yield, 1:11-1:14 *exo:endo*, 83-90% ee). The fact that these reactions are all performed under an aerobic atmosphere and with wet solvents illustrates the preparative advantages of our inexpensive, bench-stable organic catalyst. In all cases, the sense of stereoinduction is consistent with iminium formation away from the geminal methyl groups and diene addition from the face opposite the benzyl group (predicted by the calculated iminium ion model **MM3-3**).

Table 4. Organocatalyzed Diels–Alder Reaction with Representative Dienes



entry	diene	R	product[a]	yield	*exo*:*endo*	ee(%)[a,b]
1		H		82	1:14	94[d]
2		H		84	--	89
3		H		90	--	83
4		Me		75	--	90
5		H		72	1:11	85

Unfortunately, attempts to expand the utility of the organocatalyzed Diels–Alder reaction with less reactive dienes and substituted dienophiles were unsuccessful due to insufficient activity of the catalyst. For example, while cyclopentadiene is reactive enough to cyclize with a range of alkyl- and aryl-substituted aldehydes under these conditions, 2-phenyl-1,3-butadiene in Table 4 was the only diene to react successfully with a dienophile other than acrolein. While some substrates provide greater than 90% ee, many display selectivities below this standard. In order to develop a more reactive and selective catalyst system, some fundamental questions needed to be answered:

What parameters affect iminium formation and reactivity?

What is the rate-determining step?

Which catalyst features are necessary for reactivity and selectivity?

A. Studies to Determine the Mechanism of the Organocatalytic Diels–Alder

Faced with a fundamental need for greater reactivity to broaden scope and improve enantioselectivity, the effects of each reaction component required examination. The understanding of the origins of the activity of imidazolidinone organocatalyst **5** garnered from these investigations could then be applied to provide greater substrate scope in conjunction with higher enantioselectivities.

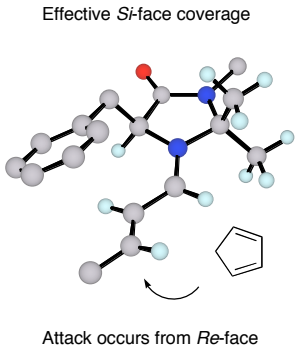
A definitive priority was to answer the question as to whether or not the reaction mechanism operates as postulated. While computations support the proposed iminium intermediate and the *trans*-conformation through which it proceeds, experimental evidence needed to be gathered since the formation of a particular iminium is the cornerstone for not only reactivity but enantioselectivity.

Control of Iminium Geometry is Essential for Enantiocontrol

To reiterate, the first stereocontrol element relies on the rigidity of the iminium framework enforced by the geminal methyl groups at the aminal position of catalyst **5**. The energetic preference to avoid nonbonding interactions with the methyl substituents forces iminium formation over towards the benzyl group on the catalyst framework, resulting in the (*E*)-iminium isomer, as shown in Figure 2. This overriding preference for one iminium isomer is the organocatalytic analogy to bidentate chelation. The restriction of rotation enforced by the π-bond of the iminium ion obviates the need for a second chelating group such as the chiral auxiliaries often necessary in Lewis acid-catalyzed Diels-Alder reactions. The second stereocontrol element involves the shielding of the *Re* face of the dienophile by the benzyl group, which leaves the *Si* face open to undergo a cycloaddition. It is critical to

note that formation of the other iminium isomer would leave the opposite prochiral face of the olefin exposed, leading to an erosion of enantioselectivity.

Figure 2. Formation of one iminium isomer is required for high enantioselectivity

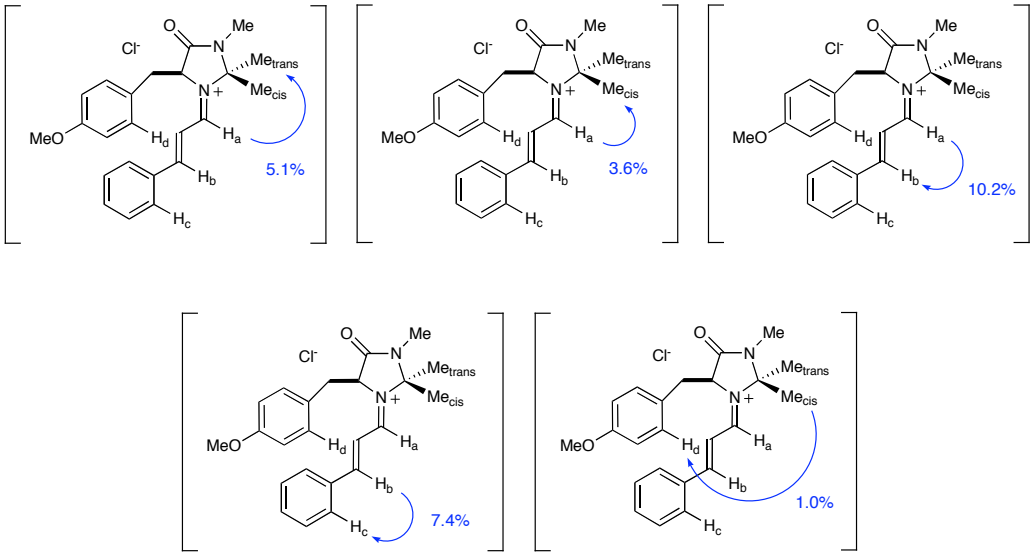


Beginning with the first portion of the catalytic cycle, iminium formation was studied. Despite the multiple functional groups of these molecules, they are extremely amenable to observation by ^{1}H NMR. The geminal methyl groups on the catalyst are diagnostic and shift in the iminium complex, and the product aldehyde and alkene resonances are distinct from those of the starting diene and dienophile.

As this model, relies on the fact that the (*E*)- and (*Z*)-iminium isomers present opposite enantiofaces, the high level of enantiocontrol observed is dependent on the formation of one iminium isomer over the other. Therefore, the geometric structure of the iminium was determined experimentally by measuring nuclear effects (nOe's) between various protons on the iminium ion formed from cinnamaldehyde and *para*-methoxy-**5**•HCl. The catalyst with the *para*-methoxy group on the benzyl substituent was used to better differentiate the numerous phenyl peaks in the spectrum. In addition, the electron-donating ability of the methoxy group stabilizes the positively charged iminium such that it is formed to a greater extent, making it easier to measure these through-space interactions.

Figure 3 shows that the nuclear interactions can be utilized to travel down the left side of the iminium as depicted: from the methyl group *trans* to the benzyl, the *cis* methyl group, H_a from the aldehyde, β-substituent H_b, and to *ortho*-phenyl substituent H_c. The nOe's definitively show that all of these nuclei are on the same side of the iminium ion, confirming that the geminal methyl groups push the iminium ion backbone towards the benzyl substituent and that iminium ion geometry is a key stereocontrol element. The data also substantiate the calculations which depict the shielding of one enantioface of the iminium by the benzyl group as a second stereocontrol element. A 1.0% nOe was measured for the protons on the methyl group *cis* to an aromatic proton *meta* to the methoxy group on the catalyst. There was even a 0.6% nOe between the *cis* methyl group and one of the benzylic catalyst protons, a significant indication of the extent to which the benzyl group is positioned under the iminium ion.

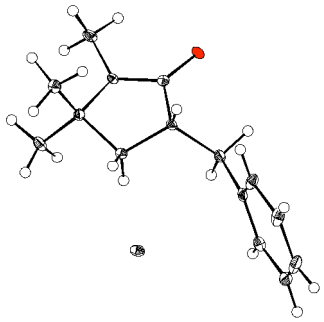
Figure 3. % nOe's for iminium formed from cinnamaldehyde and *para*-methoxy-**5**•HCl



Of course, the most rigorous method of proving the (ground-state) conformation of the chiral iminium ion would be an x-ray crystal structure. Formation of iminium could be

driven to near completion with the addition of drying agents, but attempts to recrystallize these foaming to crystalline solids in the moisture-free environment of a glove box did not yield suitable iminium crystals. However, the solid-state structure of the HCl salt of catalyst **5** was achieved.

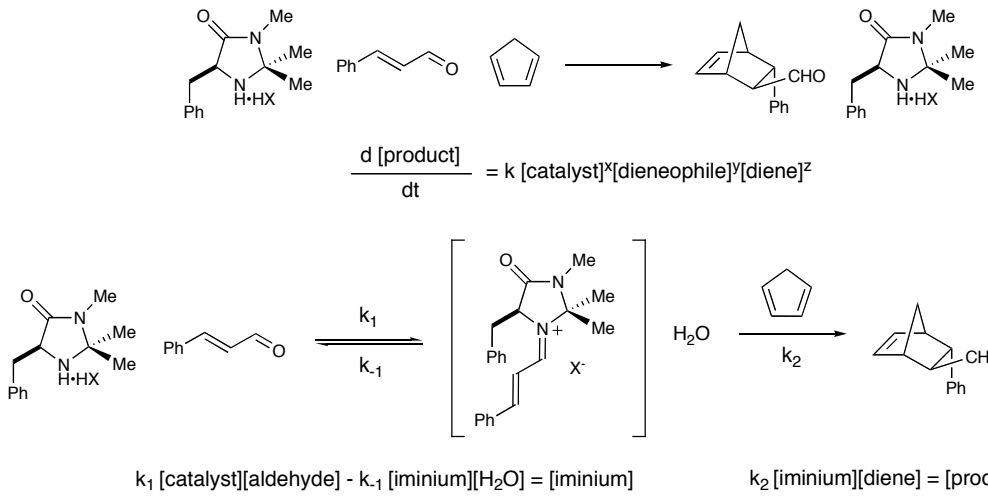
Figure 4. X-ray crystal structure of dimethyl benzyl imidazolidinone catalyst **5**•HCl



Order in Catalyst Complex

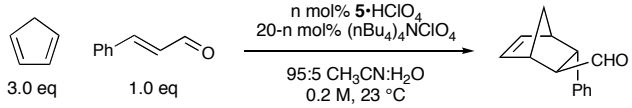
For the overall reaction, the order in each reaction component must be determined. The reaction as designed requires reversible iminium formation followed by cycloaddition of this reactive intermediate (Scheme 4). If iminium formation is the rate-determining step, the reaction would be first order in catalyst and dienophile but zero order in diene (x = y = 1, z = 0) as the cycloaddition would occur after the slow step. However, if cycloaddition is the rate-determining step, then the reaction would be first order in all three components (x = y = z = 1) as the concentration of diene would impact the reaction rate as it adds to the iminium formed from condensation of the catalyst with the dienophile.

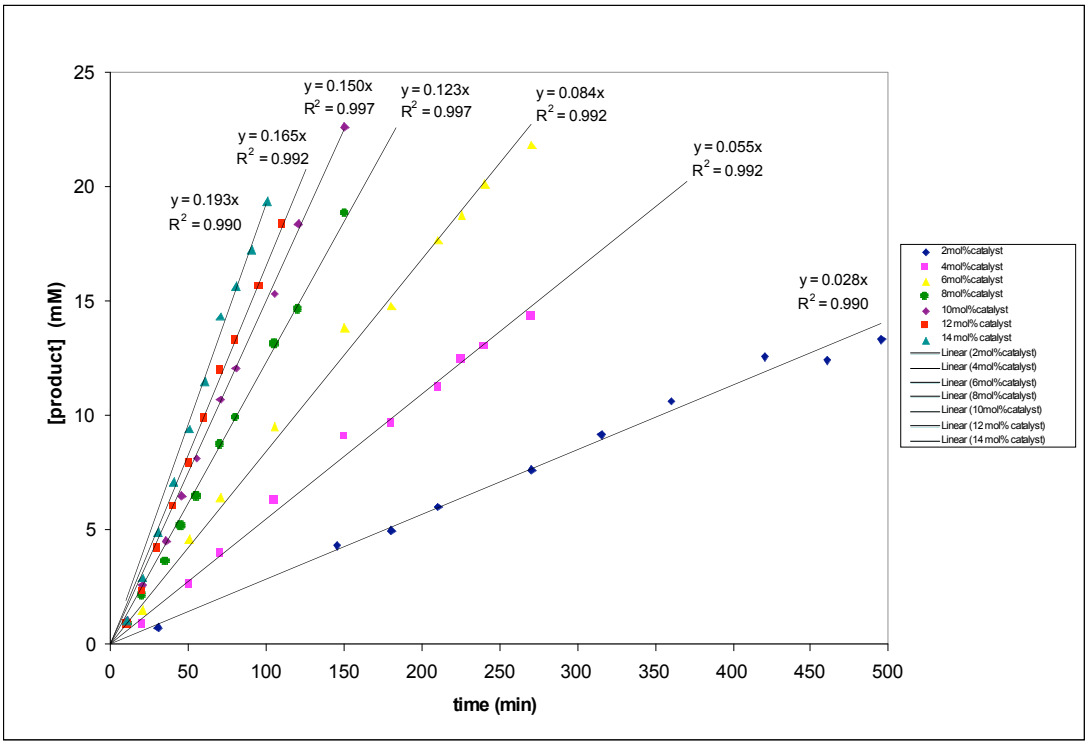
Scheme 4. Relevant rate equations for imidazolidinone-catalyzed Diels–Alder



The order in the acid salt of imidazolidinone **5** was determined by gas chromatography (GLC) analysis of reaction aliquots of the cycloaddition between cinnamaldehyde and cyclopentadiene. Tetra-*n*-butyl ammonium perchlorate was added to correct for any differences in ionic strength of the reaction medium due to the differing molar amounts of the perchloric acid salt of amine catalyst **5**. Benzyl methyl ether was used as the internal standard. A thorough check for background reactions, non-catalyzed and catalyzed by the ammonium perchlorate or standard, showed that they were not significant on the timescale of the reaction. The reactions were run at five times the dilution (0.2 M) of the normal concentration (1.0 M) for the organocatalyzed Diels-Alder reaction between cinnamaldehyde and cyclopentadiene for data consistency and manageable reaction times.[20] CH_3CN was used as the solvent rather than MeOH, which forms acetals with the aldehyde products, complicating the quantification of product formation over time. Ten aliquots were taken over the first 10% conversion of the reaction of (*E*)-cinnamaldehyde and cyclopentadiene for each catalyst loading. The catalyst loading was increased in 2 mol% increments from 2-20 mol% **5**•$HClO_4$ (Figure 5).

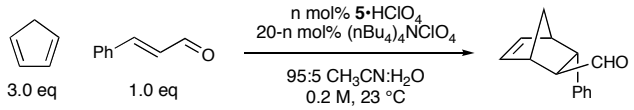
Figure 5. Concentration of cycloadduct over time for 2-14 mol% catalyst

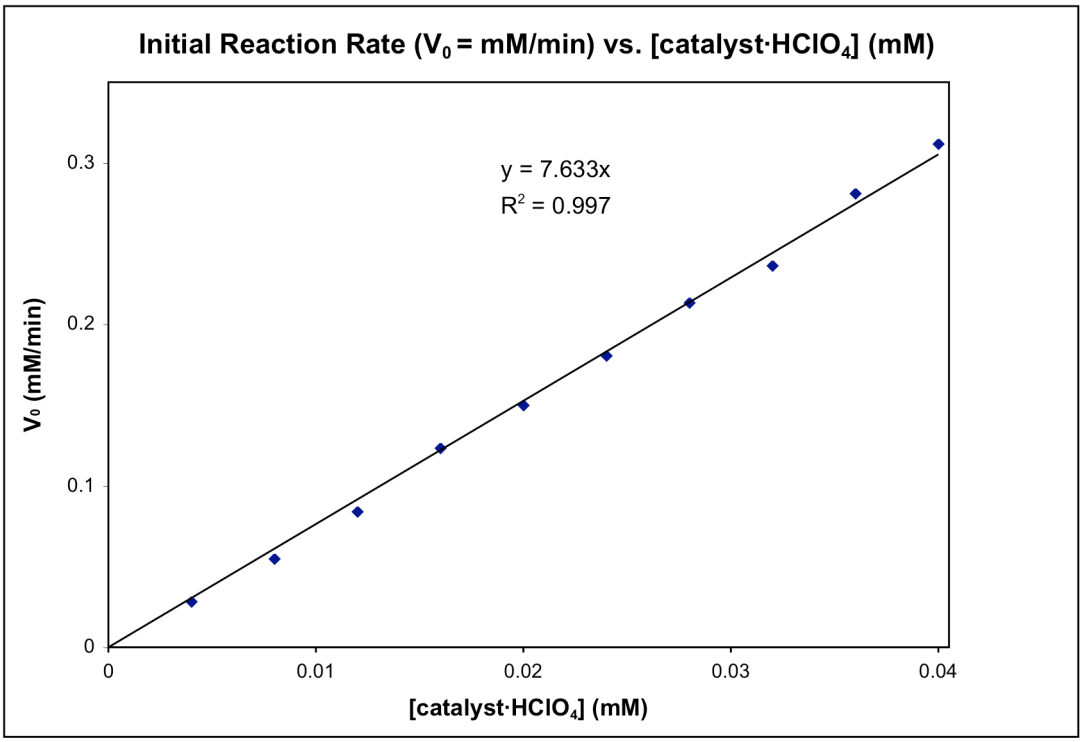




A plot of the initial rates (V_0) of product formation at each of the catalyst loadings corresponds to a linear plot for rate of reaction versus concentration of catalyst (Figure 6). The R^2 value is 0.99, in extremely high agreement with a linear plot of the data. Therefore, the organocatalyzed Diels-Alder reaction is first order in catalyst: doubling the concentration of catalyst doubles the rate of the reaction. It also indicates that the amine and acid portions of the catalyst salt work in concert; the two components operate as a discrete entity in the reaction. This is not surprising as the amine is the most basic species under the reaction conditions, generally with water as a distant second basic species, and the co-catalyst serves to activate the aldehyde for condensation with the chiral amine catalyst.

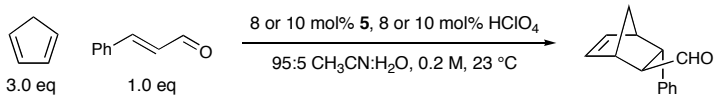
Figure 6. Linear plot of Diels-Alder rates (mM/min) with 2-20 mol% **5**•$HClO_4$

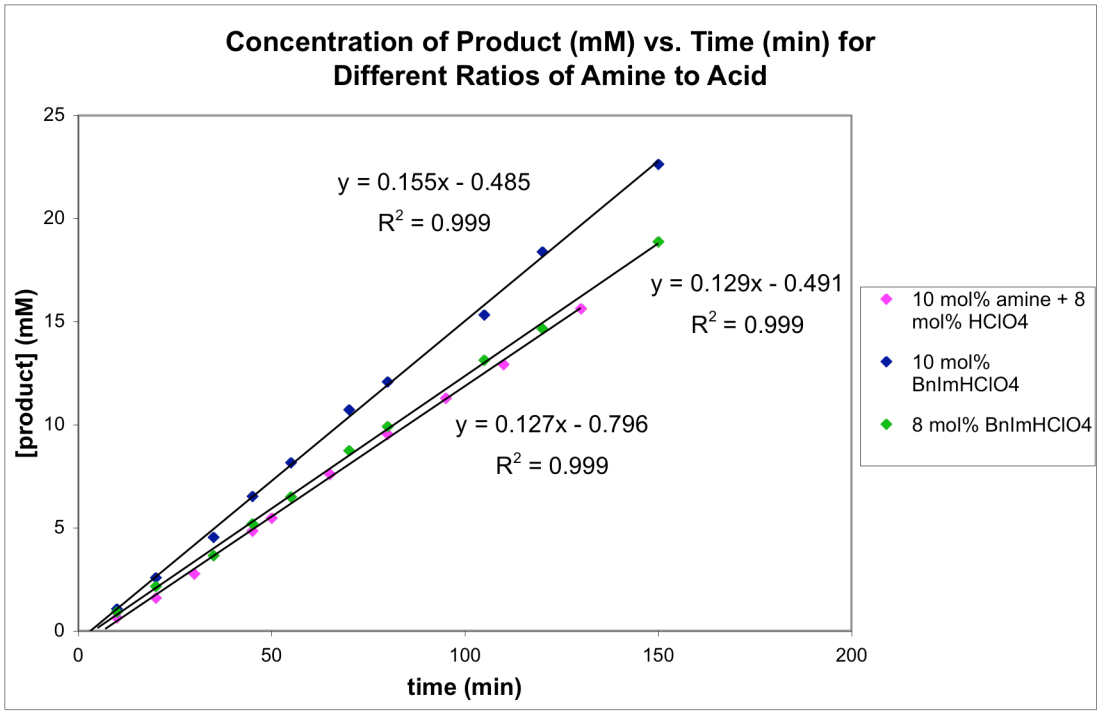




In fact, any alteration from equimolar amounts of amine catalyst and acid co-catalyst causes the reaction to operate at a rate equal to the molarity of limiting catalyst component. For example, in the cycloaddition of cyclopentadiene and cinnamaldehyde, the initial rate of product formation for 10 mol% amine **5** and 8 mol% $HClO_4$ is nearly identical to that of 8 mol% **5**•$HClO_4$, not 10 mol% **5**•$HClO_4$ (Figure 7). So, the fact that there is only 8 mol% acid means that there is only 8 mol% of the catalyst complex in solution with an additional 2 mol% of free amine **5**. The inverse situation in which there is 10 mol% $HClO_4$ and 8 mol% amine **5** again behaves more similarly to 8 mol% **5**•$HClO_4$, but as the extra 2 mol% acid can catalyze the racemic background reaction (whereas 2 mol% of the free amine does not), the alignment of initial rates is not as precise.

Figure 7. Varying molar ratio of imidazolidinone catalyst to acid co-catalyst



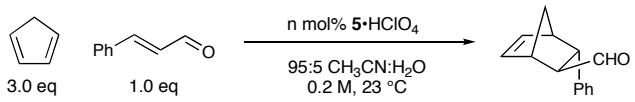


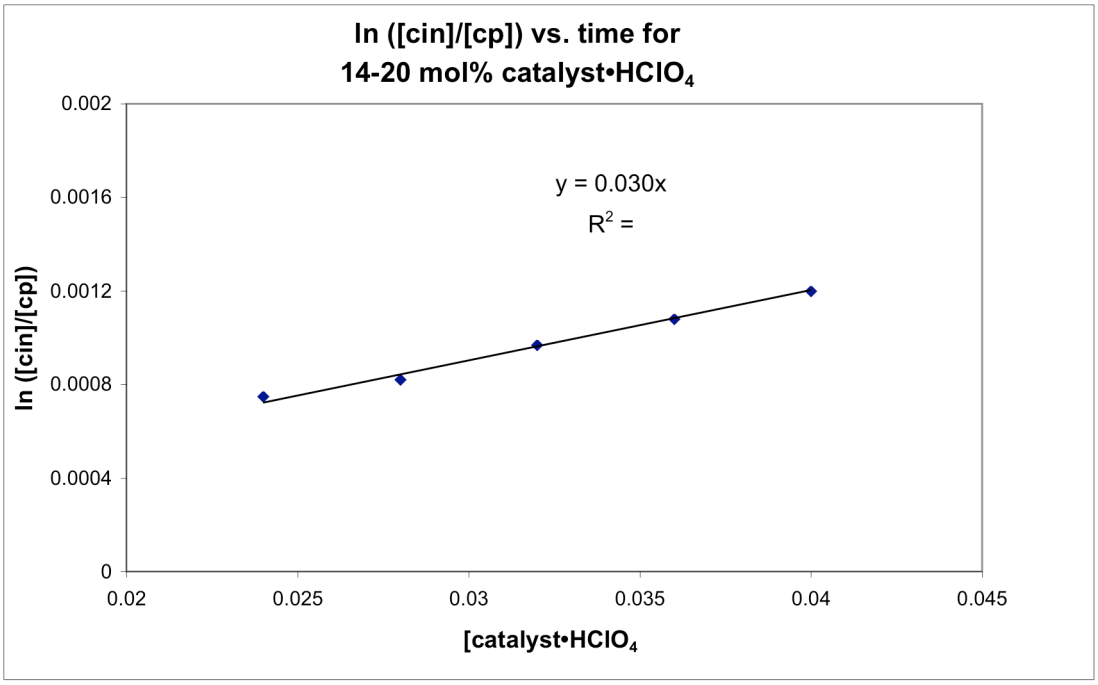
Order in Dienophile and Diene

A single study allows the determination of the order in both the α,β-unsaturated aldehyde and the diene. If the reaction is first-order in each component, then the concentration of the dienophile and of the diene should experience exponential decay. In such a case, the natural log of the ratio of the concentrations of cinnamaldehyde and cyclopentadiene over time should give a straight line if plotted at various catalyst loadings. Figure 8 plots a line with $R^2 = 0.99$, indicating that the reaction is first order in both diene and dienophile. Thus, this organocatalyzed Diels–Alder reaction is first order in catalyst,

dienophile, and diene, and the rate-determining step is the cycloaddition of the diene with the iminium formed from aldehyde and catalyst.

Figure 8. First order in cinnamaldehyde and cyclopentadiene



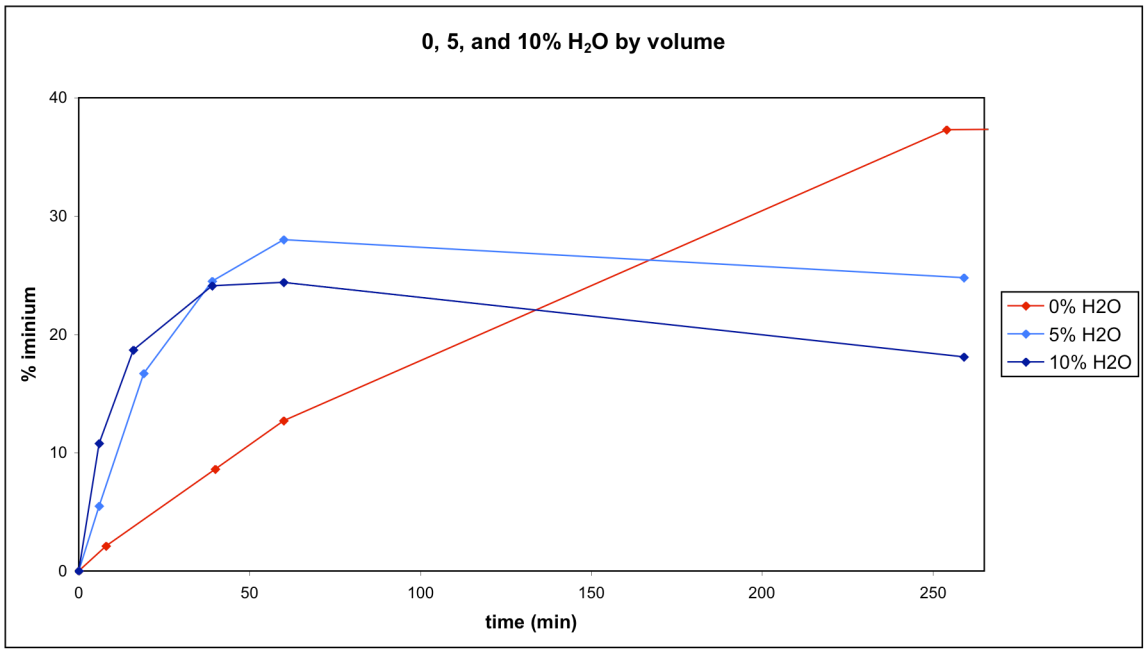


Water

As it is a product of iminium formation, and by the same token, an agent for iminium hydrolysis, the effect of water is not as straightforward to quantify. Quantifying the percent of iminium (% iminium) is straightforward by ^{1}H NMR as the peaks corresponding to free and iminium-bound catalyst are easily distinguishable. Without water, the formation of iminium over time proceeds at a nearly constant rate. At just over 4 hours, 37% iminium compared to 62% catalyst is observed, and this concentration holds nearly steady with 40% at 24 hours (Figure 9). With the addition of 5% water by volume, the initial rate of product

formation is twice as fast and even faster with 10% water. However, as the addition of water shifts the equilibrium position of iminium ion formation more towards iminium hydrolysis, the maximum % iminium observed is 28% at 60 minutes for 5% water and 24% at about 40 minutes for 10% water.

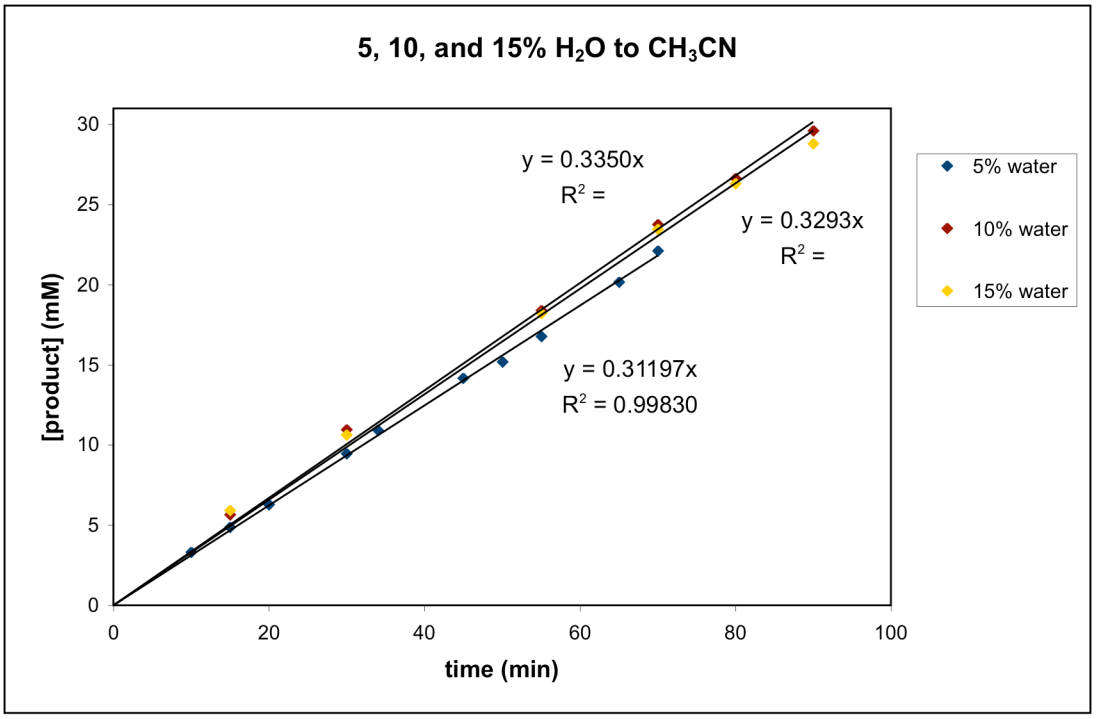
Figure 9. Percent of catalyst converted to iminium is based on amount of water added



In the imidazolidinone-catalyzed cycloaddition of cyclopentadiene and cinnamaldehyde, there is a rate increase with the addition of 5-15% water/CH_3CN, and at 20% water by volume, the rate begins to drop off. Without any water added to the reaction mixture, the reactivity is about half of that observed with water added. In fact, as observed by GLC analysis of the organocatalyzed cycloaddition of cyclopentadiene and cinnamaldehyde, while there is a 10% increase in rate from 5% to 10% water, the rates of 10% and 15% water are nearly identical (Figure 10). As for stereoselectivity with added water, the enantioselectivity drops only 1% moving from 5% to 10% water. This would align with the

statement that at lower concentrations of water, catalyst turnover is aided while at higher concentrations of water, the equilibrium is pushed away from iminium formation, towards free catalyst and aldehyde, such that there is a smaller amount of iminium which can undergo cycloaddition.

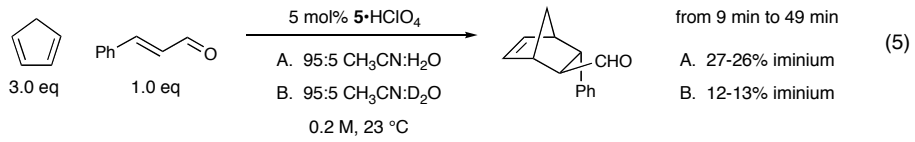
Figure 10. Rate of Diels–Alder reaction with 5%, 10%, and 15% water added



Again, the cycloaddition rate increase with the addition of water in the Diels-Alder reaction is mirrored with a greater initial rate of iminium formation. However, analyzing iminium formation in the absence of cyclopentadiene does not give information about the effect of water on iminium formation under actual reaction conditions. While observing solely iminium formation by ^{1}H NMR, water increases the rate of iminium formation but lowers the equilibrium concentration of iminium that is reached over time. However, under reaction conditions, a steady-state iminium concentration is reached in less than 10 minutes

as demonstrated by ^{1}H NMR analysis of the reaction of cyclopentadiene and cinnamaldehyde catalyzed by **5**•$HClO_4$ in CD_3CN:H_2O (eq. 5).

Interestingly, substituting D_2O for H_2O decreases the rate of reaction. The Diels–Alder reaction between cyclopentadiene and cinnamaldehyde was carried out with either 5% H_2O or 5% D_2O in CD_3CN in side-by-side round-bottom flasks. The half-life of the organocatalyzed cycloaddition was determined by GLC analysis of reaction aliquots and increased from $t_{1/2}$ = 3.8 h with 5% H_2O to $t_{1/2}$ = 10.4 h with 5% D_2O. Observation of the same reaction by ^{1}H NMR showed the same halving of reaction of rate but also allowed the percent of catalyst bound as iminium to be quantified as 26-27% for water and 12-13% for deuterium oxide (eq. 5). Under reaction conditions identical except for the 5% H_2O or 5% D_2O, the iminium concentration and correspondingly the rate of the reaction with H_2O are double those of D_2O. Therefore, a proton transfer is involved in the rate determining-step, and the choice of acid co-catalyst should have a marked effect on the rate of product formation.



(5)

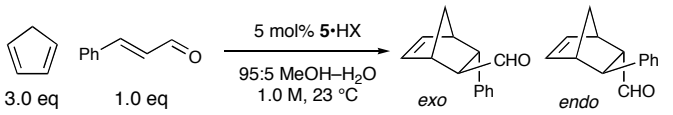
B. Identity of Acid Co-catalyst Drastically Affects Reaction Rate

Using cyclopentadiene and cinnamaldehyde as a model system, the acid co-catalyst is found to be the key factor affecting the rate of the imidazolidinone-catalyzed Diels-Alder. Both the rate cycloaddition and extent of iminium formation are impacted.

More Acidic Co-catalysts Increase Rate of Product Formation

One of the interesting features of this reaction is the striking increase in reactivity with increased acidity of the co-catalyst. To quantify the magnitude of the rate differences in terms of reaction half-life, reactions with a range of **5**•HX were conducted under standard conditions and monitored by GLC analysis of aliquots with benzyl methyl ether as the internal standard. In both MeOH and CH_3CN, the reactions repeat the observed rate increase going from HCl to TfOH and $HClO_4$, which is in accordance with the pKa trend in organic media (entries 1-3, Table 5). The enantioselectivity of the reactions in Table 5 remained in the previously-obtained range of 90-94% ee, ensuring that the rate measured was due to the imidazolidinone-catalyzed reaction and not from the racemic background reaction.[16] As this preliminary kinetic data highlights the acid co-catalyst as a key determinant of reactivity and selectivity, the exact mechanism by which the acid co-catalyst accelerates the reaction needed to be determined.

Table 5. Half-life for reactions of cyclopentadiene and cinnamaldehyde with **5**•HX

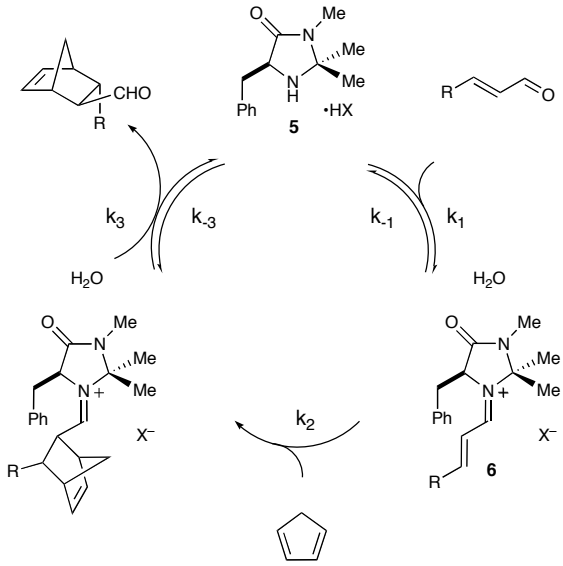


entry	HX	pKa (H_2O)	pKa (CH_3CN)	$t_{1/2}$ (h) MeOH	$t_{1/2}$ (h) CH_3CN
1	$HClO_4$	> -10	1.6	3.0	4.2
2	TfOH	> -10	2.6	3.8	4.6
3	HCl	-7	10.4	4.5	6.9

There are three main components of the reaction mechanism which may be the origins of the acid-dependence of reaction rate: 1) iminium formation upon protonation of the enal, 2) cycloaddition of the diene with the unsaturated iminium, 3) hydrolysis of iminium-bound product to liberate catalyst (Figure 11). It is duly noted that there are numerous minor acid-base and addition equilibria embedded in this view of the key steps of the reaction of

cyclopentadiene and cinnamaldehyde, but this treatment simplifies the kinetic discussion at hand. And in fact, as the concentration of iminium can be quantified by ^{1}H NMR, the concentration that is measured takes into account the components of the reaction mechanism which contribute to iminium formation, such as the proton transfers which activate the aldehyde for attack by the amine catalyst and which contribute to the extrusion of water.

Figure 11. Iminium catalysis cycle for Diels–Alder reaction of cinnamaldehyde and cyclopentadiene

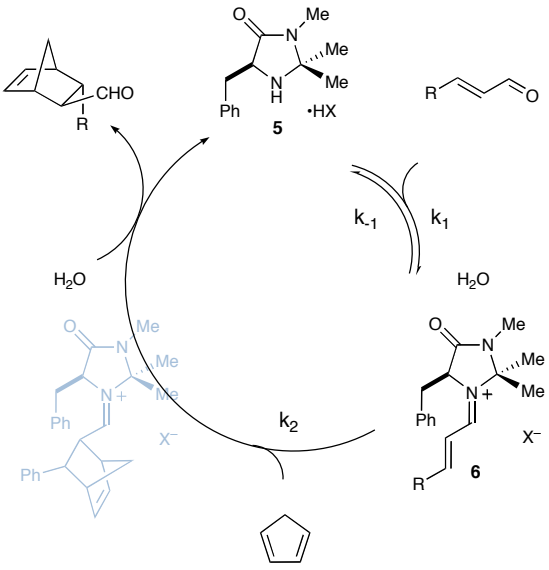


Lack of product inhibition

In addition, although iminium formation (k_1/k_{-1}) and the cycloaddition between iminium and diene (k_2) are discussed, catalyst turnover (k_3/k_{-3}) is not considered (Fig. 12). One reason is that the product-bound catalyst has not been observed for any Diels-Alder adduct. The lack of spectroscopic evidence for the product iminium is attributed to the steric congestion, which is related to the fact that that catalyst **5** does not function with α-

substituted α,β-unsaturated aldehydes. This is likely due to an unfavorable steric interaction in the iminium between the α-substituent and adjacent benzyl and methyl groups on the catalyst. As the cycloaddition product possesses substitution at that position, hydrolysis to regenerate amine **5** is proposed to be extremely fast. As product hydrolysis occurs after the rate determining cycloaddition step, it does not impact the reaction rate. For the general reaction of cinnamaldehyde and cyclopentadiene catalyzed by **5**•HX, iminium formation is reversible and maintains a steady state under reaction conditions (k_1/k_{-1}), and the cycloaddition is rate-limiting and irreversible (k_2).

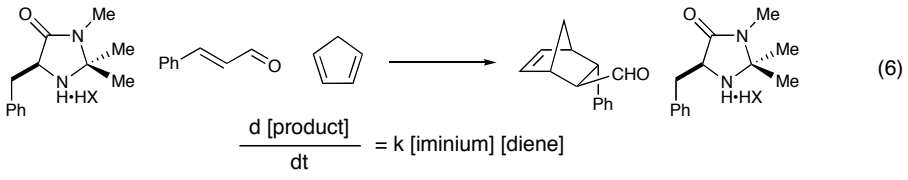
Figure 12. Components of iminium reaction mechanism affecting rate



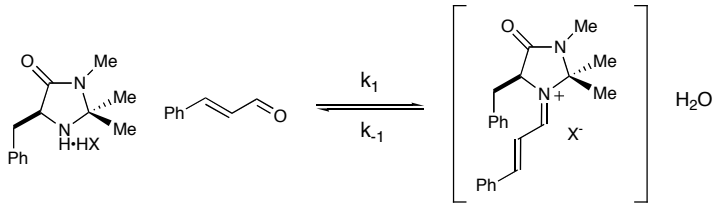
Origins of the Rate Increase with Highly Acidic Co-catalysts

For the purposes of determining the respective contributions of iminium formation and of cycloaddition to the co-catalyst dependent rate acceleration, the individual steps can be separated into their individual equations. For the overall reaction in equation 6, the observed reaction rate is affected by both iminium formation (eq. 7) and attack by the diene on the iminium formed from condensation of the catalyst and the aldehyde (eq. 8). In other

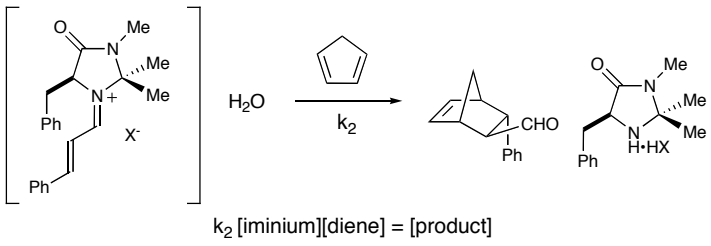
words, the reaction has been shown to be first order in catalyst, dienophile, and diene (Chapter I-A), and as the catalyst and dienophile condense to form the reactive iminium intermediate, the rate of product formation should correspond to equation 6.



$$\frac{d\,[\text{product}]}{dt} = k\,[\text{iminium}]\,[\text{diene}] \qquad (6)$$



$$k_1\,[\text{catalyst}][\text{aldehyde}] - k_{-1}\,[\text{iminium}][H_2O] = [\text{iminium}] \qquad (7)$$

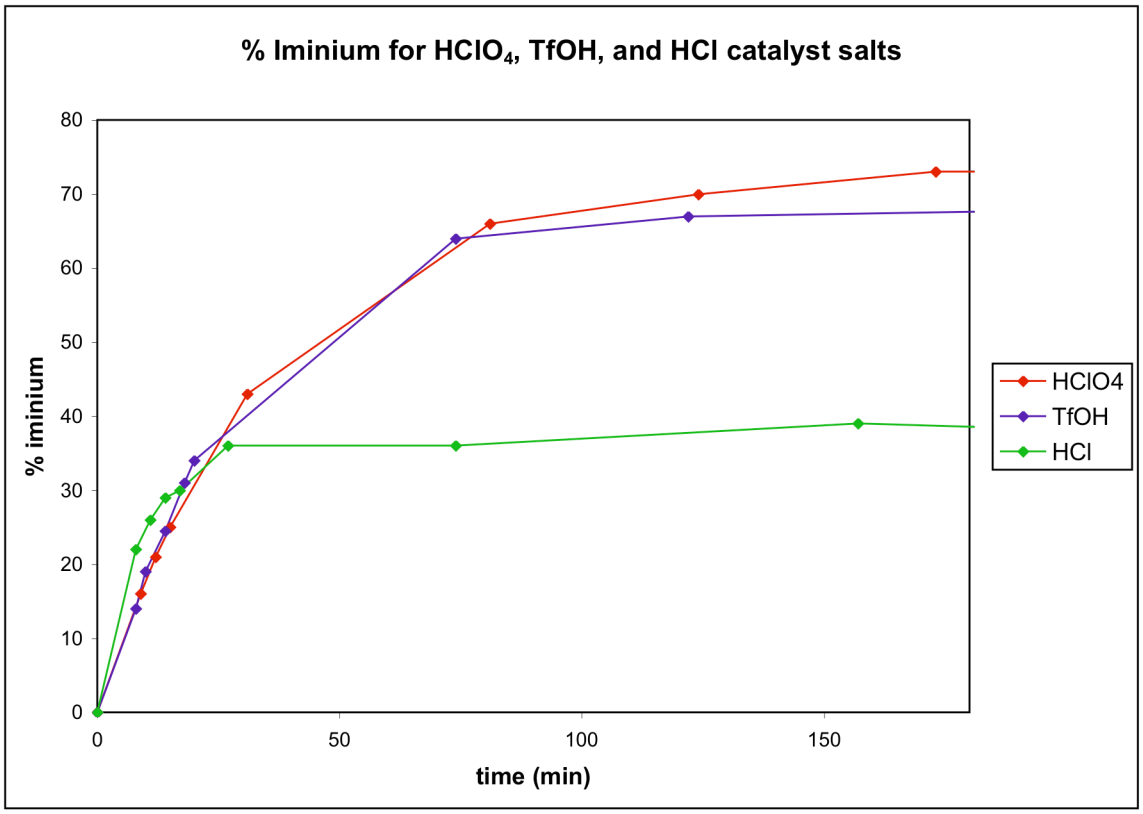


$$k_2\,[\text{iminium}][\text{diene}] = [\text{product}] \qquad (8)$$

Analysis of the origins of the rate increase with more acidic co-catalysts begins with iminium formation based on the individual equilibrium of which it is composed (eq. 7). As rate of the reaction is directly proportional to the concentration of iminium, the extent of iminium formation for representative **5**•HX in the absence of diene was quantified by ^{1}H NMR studies of the catalyst-aldehyde iminium complex (Figure 13). As determined by integration of catalyst methyl peaks compared to iminium methyl peaks, the less reactive co-catalysts form iminium to a lesser extent but reach their equilibrium position faster. $HClO_4$ forms a maximum of 73% iminium in 280 minutes, TfOH reaches 68% iminium in 220 minutes, and HCl only yields 39% iminium in 160 minutes. The results of these

experiments correlate acid co-catalysts that provide a faster reaction with a higher iminium concentration.

Figure 13. Effect of acid co-catalyst on percentage of catalyst condensed to form iminium over time



As the inherent reactivity of each catalyst complex could also be affecting reaction rate, the actual cycloaddition step was studied next (eq. 8). The reaction operates under pre-equilibrium conditions that result in a steady state of iminium, and the cycloaddition is treated as irreversible and rate-determining. From equation 3 with the concentration of iminium as [im] and the concentration of cyclopentadiene as [cp], the initial rate (V_0) of the reaction can be equated as shown in equation 9.

$$V_0 = k_2 [im][cp] \qquad (9)$$

This equation takes into account the steps preceding the cycloaddition in the term for concentration of iminium. Therefore, the rate differences for the two catalysts would be reflected in k_2. In other words, we needed to measure k_2 (as defined by eq 3) for the rate-determining cycloaddition as shown in equation 10 to compare acid co-catalysts $HClO_4$, TfOH, and HCl.

$$k_2 = \frac{V_0}{[im][cp]} \qquad (10)$$

Fortunately, each of these variables is easily quantified by ^1H NMR under reaction conditions. To simplify the treatment of the kinetics further, the reaction was carried out with 10 equivalents of cyclopentadiene such that its concentration was considered constant over the first 10% conversion. With the reaction running pseudo-zero order in cyclopentadiene, the concentration of iminium and products formed were measured over the initial course of the reaction.[19] Comparing the values of k_2 under equivalent conditions apart from the identity of the acid co-catalyst, the rate constant for the cycloaddition with $HClO_4$ = 0.0775, TfOH = 0.0752, HCl = 0.0727, and TFA = 0.0560 $(mmol \cdot min)^{-1}$. (27-21%im) Therefore, more acidic co-catalysts provide a faster rate and greater reaction scope by forming greater quantities of a more reactive iminium. Again, only one iminium conformation is observed throughout these experiments in complete agreement with the structural results of molecular modeling studies.

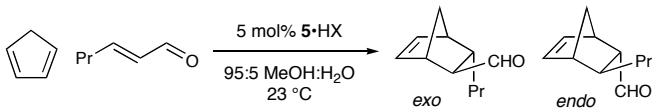
C. Improved Enantioselectivity and Expanded Substrate Scope Using More Acidic Co-catalysts in the Imidazolidinone-Catalyzed Diels–Alder Reaction

The catalyst systems discovered from these investigations provide greater substrate scope in conjunction with higher enantioselectivities in the organocatalyzed Diels–Alder.

Increase in Reactivity Translates to Higher Enantioselectivities

In determining whether the greater reactivity imparted by more acidic co-catalysts is delivered in conjunction with higher enantioselectivity for the entire range of substrates, the organocatalytic addition of cyclopentadiene to hexenal was reexamined first. Table 6 demonstrates that the more acidic $HClO_4$ and TfOH acid co-catalysts raise enantioselectivity and slightly augment diastereoselectivity in the formation of the cycloadduct compared to HCl. Less acidic co-catalysts such as TFA provide even poorer reactivity and lower enantiomeric ratios. Therefore, the ability of the acid co-catalyst to increase reactivity also confers increased enantioselectivity of amine-catalyzed reactions.

Table 6. Co-catalyst effects on the cycloaddition of (E)-hex-2-enal and cyclopentadiene



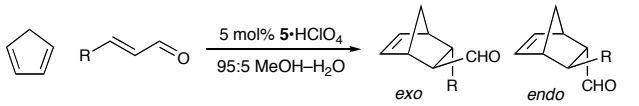
entry	HX	*endo:exo*	*exo* ee (%)	*endo* ee (%)
1	$HClO_4$	1.3:1	88	93
2	TfOH	1.1:1	87	94
3	HCl	1.0:1	86	90

Increased Range of Dienes and Dienophiles

The superior activity of $HClO_4$- and TfOH-derived amine salts marked these catalysts for further study. Table 7 shows that the Diels-Alder reaction of a range of dienophiles with cyclopentadiene was improved to 90-93% *exo* ee and 94-96% *endo* ee (entries 1-6, from 84-93% *exo* ee and 90-93% *endo* ee with HCl). Interestingly, aromatic α,β-unsaturated

aldehydes were not as improved by the more acidic co-catalysts as the aliphatic α,β-unsaturated aldehydes were (entry 4, R = Ph from 91% *exo* ee, 93% *endo* ee; entry 5, R = furyl from 93% *exo* ee, 93% *endo* ee). The similar ee's with $HClO_4$, TfOH, and HCl may be due to the lesser tendency of a more conjugated phenyl- or furyl-substituted α,β-unsaturated aldehyde to participate in a racemic background reaction to begin with. The available functionality in the Diels-Alder reaction with cyclopentadiene was expanded with (2*E*)-4-oxobut-2-enyl benzoate (entry 6). This benzoyloxy-substituted crotonaldehyde is less prone to decomposition and produces a bicycle with similar selectivities as those observed with crotonaldehyde (95/91% ee versus 95/92% ee for crotonaldehyde, entry 1) but with a protected-oxygen substituent.

Table 7. Diels-Alder of alkyl- and aromatic-substituted aldehydes and cyclopentadiene

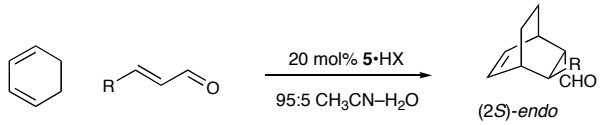


entry	R	temp (°C)	time (h)	yield (%)	*endo*:*exo*[a,b]	*exo* ee (%)	*endo* ee (%)
1	Me	4	16	83	1.2:1	92	95
2	Pr	4	25	73	1.1:1	91	94
3	*i*-Pr	4	23	90	1.0:1	90	96
4	Ph	23	28	92	1.1:1	92	94
5	Furyl	23	18	93	1:1.3	93	94
6	CH_2OBz[c]	4	11	89	1:1.3	91	95

While cyclopentadiene exhibits broad dienophile scope, attempts to use dieneophiles other than acrolein with less reactive dienes were generally not successful. In fact, the observed increase in reaction time between cyclopentadiene and hexenal as opposed to crotonaldehyde suggests that sterics play a role in governing the feasibility of these reactions (Table 7, entries 1-3). Unfortunately, the benzoyloxy aldehyde which performed so well with cyclopentadiene (Table 7, entry 6) is not sufficiently more reactive than crotonaldehyde

to react well with cyclohexadiene. As an ester group at the β-position is sterically smaller than a methyl group, and the electron-withdrawing effect of the ester group should result in a more reactive iminium ion, it was proposed that an ester-substituted aldehyde would provide the desired reactivity. Indeed, the reaction of cyclohexadiene with (*E*)-methyl-4-oxobutenoate proceeded similarly to the reaction with acrolein and provided β-ester aldehyde **9** in 97% ee, 5:1 *endo*:*exo*, and 92% yield (Table 8, entries 1 and 2). These examples demonstrate that the low diastereoselectivity is a function of cyclopentadiene itself and not the catalyst system

Table 8. Organocatalyzed Diels-Alder with cyclohexadiene

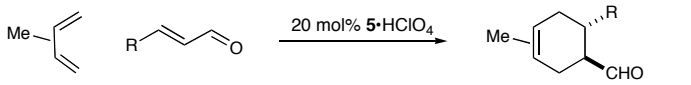


entry	R	HX	temp (°C)	time (h)	yield (%)	*endo:exo*	ee (%)[a,b]
1	H	$HClO_4$	–10	24	93	16:1	96
2	CO_2Me	TfOH	4	23	92	5:1	97

Acyclic, methyl-substituted dienes were examined next. These aliphatic dienes continue to exhibit better enantioselectivity and conversion with $HClO_4$ and TFOH as co-catalysts than with HCl as a co-catalyst at these lower temperatures. For example, the Diels-Alder reaction between isoprene and acrolein does not proceed to complete conversion at –10 ºC with HCl. However, $HClO_4$ as the co-catalyst provides a 92% ee and 94% yield (Table 9, entry 1). The effect of additional substitution on the diene was examined with 2,3-dimethylbutadiene which exhibits similar reactivity to isoprene, producing tetrasubstituted cyclohexenes in 91% ee, 92% yield (entry 3). 2-Methyl-1,3-pentadiene exhibited similar reactivity to other alkyl-substituted dienes with acrolein (88% ee, 84% yield, entry 5). The high enantioselectivity for and excellent conversion to β-ester aldehyde cycloadducts was

extremely encouraging, demonstrating that the butenoate aldehyde reacts with as great a variety of dienes as acrolein. Furthermore, the butenoate aldehyde allows for an expanded number of substrates that possess an additional functional handle with defined stereochemistry.

Table 9. Methyl-substituted dienes with acrolein or butenoate aldehyde

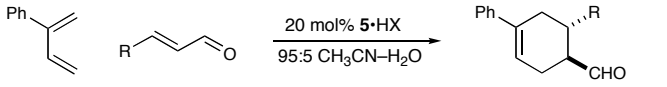


entry	diene	R	temp (°C)	time (h)	yield (%)	ee (%)[a,b]
1	2-methylbutadiene	H	–10	11	94	92
2	2-methylbutadiene	CO_2Me	–10	23	81	95
3	2,3-dimethylbutadiene	H	–20	15	92	91
4	2,3-dimethylbutadiene	CO_2Me	–20	23	88	95
5	2-methyl-1,3-pentadiene	H	–20	26	84[c]	88

Aldehydes bearing a styrenyl moiety are accessed by a Diels-Alder reaction between 2-phenyl-1,3-butadiene and a variety of α,β-unsaturated aldehydes (Table 10). Acrolein proves problematic due to its propensity to polymerize. Conditions were found that emulated previous results for the reaction of acrolein and 2-phenyl-1,3-butadiene (entry 1, 83% ee, 87% yield).[17] 2-Phenyl-1,3-butadiene was the only diene with the exception of cyclopentadiene which had been shown in our original communication react cleanly with (*E*)-crotonaldehyde.[17] Due to the high propensity of crotonaldehyde to polymerize, the equivalencies of diene to aldehyde were varied, demonstrating that excess aldehyde provides better conversion than excess diene in this case. Careful GLC monitoring of the reaction of 1 equivalent of 2-phenylbutadiene to 3 equivalents of crotonaldehyde and **5**•TfOH demonstrates that conversion reached a maximum then decreased after 18 hours, an indication of product decomposition. This cycloaddition to form a β-methyl aldehyde reaches 91% ee and 70% yield in 16 hours (entry 2). In entry 3, the butenoate aldehyde

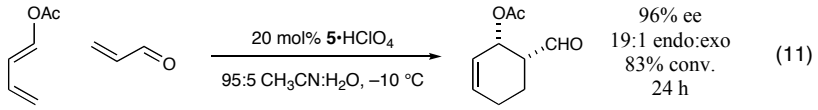
reacts to provide a β-ester aldehyde cycloadduct in 90% ee and 86% yield. As the reaction of 2-phenylbutadiene proceeds smoothly with crotonaldehyde, it seems reasonable that this diene would cyclize efficiently with the benzoyloxy aldehyde as these aldehydes exhibit similar reactivity. The benzoyloxy aldehyde continues to be more reactive than crotonaldehyde at 4 °C, delivering 91% ee in 86% yield in 13 hours (as compared to 90% ee in 16 hours for crotonaldehyde, entry 4 versus 2).

Table 10. 2-Phenyl-1,3-butadiene with substituted α,β-unsaturated aldehydes



entry	R	R	temp (°C)	time (h)	yield (%)	ee (%)[b,c]
1	H	TfOH	–10	7	87	83
2	Me	$HClO_4$	4	16	70	91
3	CO_2Me	$HClO_4$	–20	24	87	90
4	CH_2OBz	TfOH	4	13	86	90

1-Acetoxybutadiene represents the first heteroatom-substituted diene in this study. Initial studies have shown that the reaction with acrolein provides the desired cycloadduct in 85% ee in room temperature trifluoroethanol.[17] Lowering the temperature and changing the solvent to CH_3CN yielded an significant increase to 96% ee and a higher *endo*:*exo* ratio (eq. 11).



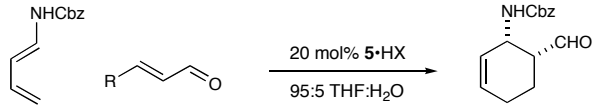
(11)

Having extended the functional handles available on the dienophile, the utility of dienes with additional functionality was examined next. For example, if the oxygen in 1-acetoxy butadiene is replaced with nitrogen, this organocatalytic Diels-Alder reaction can potentially deliver enantiopure β-amino acid precursors, which are valuable architectures in asymmetric

synthesis. Surprisingly, 1-carbamate-substituted dienes of the Oppolzer-Overman type have been known for decades, and yet, they have only recently been utilized in enantioselective Diels-Alder reactions. In fact, the first example of an enantioselective Lewis acid-catalyzed Diels-Alder reaction of a simple amine-substituted diene was by Evans *et al.* in 1999.[4d]

Solvent studies showed that the imidazolidinone-catalyzed reaction of N-Cbz-amino-1,3-butadiene with acrolein is far less solvent dependent than previous cycloaddition partners. CH_3CN, acetone, isopropanol, dioxane, diethyl ether, and tetrahydrofuran (THF) exhibit 90-93% ee at 4 ºC. Lowering the temperature to –20 ºC, the reaction proceeded in 95% ee and 86% yield in THF (Table 12, entry 1). For crotonaldehyde and N-Cbz-amino-1,3-butadiene, **5**•$HClO_4$ provides 97% ee and 4:1 *endo*:*exo* (entry 2). Once again, the methyl ester-substituted α,β-unsaturated aldehyde exhibits similar reactivity to acrolein at –20 ºC. However, whereas acrolein is highly enantioselective in CH_3CN, the butenoate aldehyde is poorly selective in CH_3CN (43% ee, 60% conv., 17h). However, substituting THF for CH_3CN provides 93% ee and 79% yield with only the *endo* isomer visible by ^1H NMR (entry 3). Note that this imidazolidinone-catalyzed Diels-Alder reaction creates a single, enantioenriched isomer of a β-amino acid precursor, which possesses three functionally-differentiated heteroatomic handles (carbamate, aldehyde, and butenoate) on a cyclohexene ring (entry 3). Finally, the benzoyloxy-substituted α,β-unsaturated aldehyde affords the highest enantioselectivity seen in the organocatalyzed Diels-Alder reaction, 99% ee in 83% yield with 10:1 diastereoselectivity at –20 ºC (entry 4).

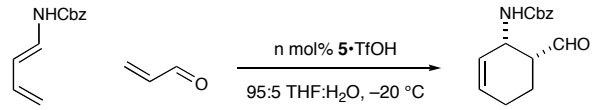
Table 11. Cycloadducts of N-Cbz-amino-1,3-butadiene



entry	R	HX	temp (°C)	time (h)	yield (%)	*endo:exo*	ee (%)
1	H	TfOH	–20	6	86	6:1	95
2	Me	$HClO_4$	–10	9	71	4:1	97[a]
3	CO_2Me	TfOH	–20	14	79	>20:1	93
4	CH_2OBz	$HClO_4$	–10	17	83	10:1	99

The excellent reactivity of *N*-Cbz-diene with acrolein (95% ee in 6 h at –20 ºC) prompted a catalyst loading study (Table 12). Entry 4 shows that the catalyst loading can be decreased to 2% (below even the 5% loading for cyclopentadiene reactions) while maintaining a 90% ee. This is an especially reactive diene, and the fact that there is a decrease in enantioselectivity with lower catalyst loadings is probably due to the background reaction, which can now compete at longer reaction times.

Table 12. Catalyst loading study for amino diene and acrolein



entry	mol% **5**•TfOH	time (h)	yield (%)	*endo:exo*	ee (%)
1	20	6	86	6:1	95
2	10	11	84	6:1	93
3	5	25	82	6:1	91
4	2	52	79	6:1	90

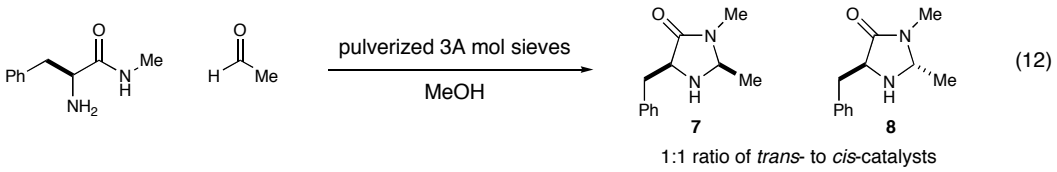
These studies have demonstrated that a key component to the successful optimization of organocatalytic cycloadditions has been the use of perchloric and triflic acid derived amine catalysts. The general strategy of taking advantage of the increased reaction rates with more acidic co-catalysts to lower reaction temperature, and thereby providing higher enantioselectivities, was applied to a range of new substrates. The number of chiral building blocks available through an imidazolidinone-catalyzed Diels-Alder reaction was doubled by

expanding the types and number of substituents both on the dienes and the α,β-unsaturated aldehyde dienophiles. Additional Diels-Alder adducts were synthesized in 90-99% ee, and except for one, none of these products had been previously synthesized asymmetrically. These adducts display a range of substitution on the product alkene and adjacent to the aldehyde, including alkyls, aryls, esters, amines, and an acetate. These multiple functional handles make the products of the imidazolidinone-catalyzed Diels-Alder extremely useful chiral building blocks.

D. Origins of the Effect of Catalyst Structure on Reactivity and Enantioselectivity

Whereas the use of more acidic co-catalysts vastly improved the reactivity, selectivity, and scope of the imidazolidinone-catalyzed Diels–Alder reaction, it became clear that modifications to the catalyst architecure would be necessary to improve other methodologies under development in the MacMillan group. The key is to modify the catalyst structure without losing the iminium geometry control exhibited by the first-generation dimethyl imidazolidinone catalyst. Only one iminium isomer is observed in the ^{1}H NMR studies with catalyst **5** because the steric bulk of the geminal methyl groups forces the iminium geometry towards the benzyl substituent. However, the methyl group *trans* to the benzyl projects up and partially blocks the hemisphere from which the nucleophile attacks according to our model. It was postulated that removal of this methyl group would allow for greater reactivity. The effect of the each individual methyl groups was probed by synthesizing *trans*- and *cis*-monomethyl imidazolidinone catalysts (eq. 12). The *N*-methyl amide of phenylalanine is now condensed with acetaldehyde (rather than acetone as with catalyst **5**). The reaction is conducted with the slightly acidic hydroscopic molecular sieves rather than

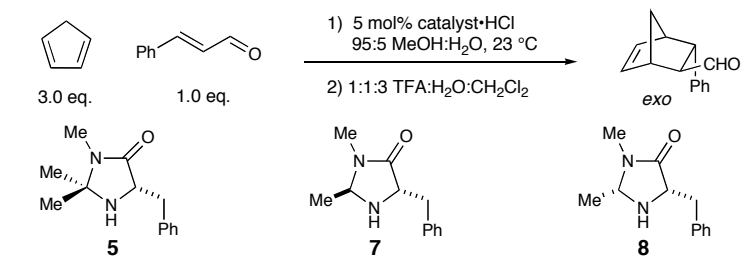
adding any other acid source, and it produces a 1:1 ratio of diastereomeric monomethyl catalysts separable by preparatory HPLC.



(12)

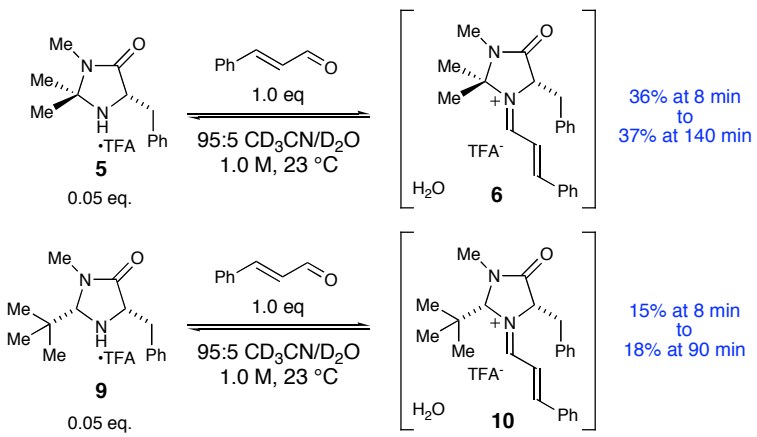
The reactivity and selectivity of these catalysts was assessed through the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene monitored by GLC (Scheme 5, catalysts **7** and **8**). *Trans*-catalyst **7** exhibits poor enantioselection and a 50% slower rate than **5**. As expected, the *cis*-catalyst (**8**) is nearly twice as reactive as the dimethyl benzyl imidazolidinone (**5**) and provides increased *exo* selectivity but extremely low enantioselectivity. ^{1}H NMR observation of iminium formation between cinnamaldehyde (1 eq.) and *trans*-3-methyl imidazolidinone·HCl (**7**•HCl, 1 eq.) displays a 3:1 ratio of iminium geometries. In short, although removing the *trans* methyl substituent does nearly double the rate of reaction, the monomethyl catalysts do not possess the steric bulk necessary for the control of iminium ion geometry required for high levels of enantioselectivity. The simple solution is to create a *cis*-imidazolidinone catalyst with a sterically demanding group at the aminal position.

Scheme 5. Effects of 3-methyl substitution on catalyst reactivity and selectivity



Cis-3-*tert*-butyl-5-benzyl imidazolidinone (**9**) exhibits high reactivity, catalyzing reactions that are not efficient with **5**.[20] Furthermore, the high enantioselectivities afforded by this second-generation catalyst dictate that a single *tert*-butyl group is of adequate size to control iminium geometry; the singularity of iminium ion geometry was confirmed when reactions were monitored by ^{1}H NMR. In comparing the extent of iminium formation for catalysts **5** and **9**, it was expected that more reactive catalyst **9** would produce a higher equilibrium concentration of the reactive iminium intermediate (as with more acidic co-catalysts). Surprisingly, the concentration of iminium **10** was half that of **6** (Scheme 6).

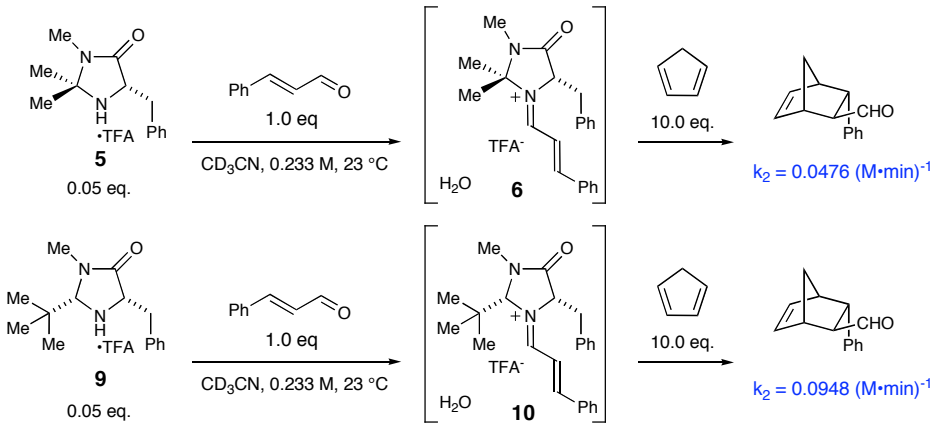
Scheme 6. Percent of catalyst forming reactive iminium ion



If the extent of iminium formation (k_1/k_{-1}) is not the origin of the greater reactivity of catalyst **9**, then it must be the inherent reactivity of the corresponding iminium intermediate **10** (k_2). Again setting k_2 equal to $V_0/([im][cp])$ for each catalyst, the concentration of iminium ion and cycloadduct formed were measured over the initial 10% of the reaction by ^{1}H NMR. Conducting the organocatalytic cycloaddition with a large, near constant [cp], the concentration of iminium was steady over the first half of the reaction, 44% for first-generation catalyst **5** and 32% for second-generation catalyst **9**. The rate constant for the

cycloaddition with *cis*-*t*-butyl catalyst **9** is twice that of dimethyl catalyst **5** (Scheme 7). Therefore, *the second-generation catalyst provides a faster rate and greater reaction scope by forming a much more reactive iminium ion, albeit at a lower concentration than the iminium formed from the first-generation catalyst*.

Scheme 7. Comparison of reactivity of 1st- and 2nd-generation catalyst iminium ions



The imidazolidinone-catalyzed Diels–Alder reaction developed in the MacMillan Grouop activates enal substrates *via* a reversible condensation to form a chiral α,β-unsaturated iminium ion upon which the rate-determining cycloaddition occurs. Kinetic studies highlight the importance of the acid co-catalyst and identified a more reactive catalyst complex, significantly improving enantioselectivities and vastly expanding the substrate scope of the first highly enantioselective organocatalytic Diels–Alder reaction. Exploration of the crucial components of catalyst architecture led to the development of a second-generation *tert*-butyl imidazolidinone scaffold that not only catalyzes cycloadditions, but conjugate additions, hydrogenations, and tandem reactions of aldehydes with excellent selectivity.

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Supporting Information

General Information. All solvents were used as obtained from commercial suppliers unless otherwise indicated. Other commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Thin layer chromatograms (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 chromatograms on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2]

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz and 75 MHz, respectively) instrument, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as 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 as chemical shift. IR spectra were recorded on Perkin-Elmer Paragon 1000 spectrometer as thin films and reported in terms of frequency of absporption. Mass spectra were obtained from the California Institute of Technology facility. GLC was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex β-DM (30 m × 0.25 mm), Bodman Chiraldex Γ-TA (30 m × 0.25 mm), and C&C Column Technologies CC-1701 (30 m × 0.25 mm). High

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[2] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

performance liquid chromatograms (HPLC) analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254 nm, using a Chiralcel OD-H column (1.6 × 25 cm) and Chiralcel OD guard (1.6 × 5 cm).

Progress of the Diels–Alder reaction was typically monitored by TLC analysis or by GLC analysis of reaction aliquots.

General Procedure for Amine-Catalyzed Diels–Alder Reaction: To a 1-dram vial equipped with a magnetic stir bar and charged with an acid salt of (2S, 5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one was added solvent/H_2O (95:5 v/v), and an α,β-unsaturated aldehyde. After stirring for 5 minutes in the appropriate temperature bath, the diene was added in one portion, and the resulting solution was stirred at constant temperature. Upon consumption of the limiting reagent (determined by TLC or by GLC conversion assay on parallel reaction with benzyl methyl ether as standard), the reaction mixture was then directly purified by silica gel chromatograms and fractions concentrated *in vacuo* (with ice bath for volatile substrates) to provide the title compounds.

General Procedure for Amine-Catalyzed Diels–Alder Reaction in MeOH: To a 1-dram vial equipped with a magnetic stir bar and charged with an acid salt of (2S, 5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one in CH_3OH/H_2O (95/5 v/v, 1.0 M) was added the α,β-unsaturated aldehyde. After stirring for 5 minutes in the appropriate temperature bath, the diene was added in one portion, and the resulting solution was stirred at constant temperature. Upon consumption of the limiting reagent (determined by TLC or by GLC conversion assay on parallel reaction with benzyl methyl ether as standard), the reaction

mixture was diluted with Et_2O and washed successively with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA:H_2O:CH_2Cl_2 (1:1:3) for 2 h at room temperature, followed by neutralization with sat. aq. $NaHCO_3$ and extraction with Et_2O. Purification of the Diels–Alder adduct was accomplished by silica gel (solvents noted) and fractions concentrated *in vacuo* to provide the title compounds.

Enantioselectivity was determined by chiral GLC or HPLC analysis of the title compound or its derivative. Absolute configurations were determined by comparison to literature optical rotation values where indicated. Other absolute configurations were assigned by chemical correlation.

(1*S*, 2*R*, 3*S*, 4*R*)-3-Propyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1*R*, 2*R*, 3*S*, 4*S*)-3-Propyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde. Prepared according to the general procedure with (*E*)-hex-2-enal (142 μL, 1.22 mmol), cyclopentadiene (302 μL, 3.66 mmol), and **7** (16 mg, 0.061 mmol) to provide the title compound as a colorless oil in 91% yield (184 mg, 1.12 mmol) after silica gel chromatograms (10% EtOAc/hex); 1.1:1.0 *endo:exo*; *endo* 94% ee; *exo* 91% ee. Product ratios were determined by GLC (Bodman Γ-TA column, 102 °C isotherm, 23 psi); *exo* isomers t_r = 20.1 min and 21.1 min, *endo* isomers t_r = 20.7 min and 22.5 min. ^{1}H NMR for the *endo* isomer was consistent with previously

reported values.[3] ^{1}H NMR for the *exo* isomer was consistent with previously reported values.[4]

(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. Prepared according to the general procedure with (*E*)-crotonaldehyde (871 μL, 10.0 mmol), cyclopentadiene (2.50 mL, 30.0 mmol), and **7** (109 mg, 0.50 mmol) to afford the title compound as a colorless oil in 83% yield (1.02 g, 7.5 mmol) after silica gel chromatograms (3% EtOAc/hex); 1.2/1.0 *endo*:*exo*, *endo* 95% ee, *exo* 92% ee. Product ratios were determined by GLC (Bodman β-DM column, 60 ^{o}C, 40 min; 5 ^{o}C/min gradient, 23 psi); (1*S*, 2*R*, 3*S*, 4*R*) *endo* isomer t_r = 41.5 min, (1*R*, 2*S*, 3*R*, 4*S*) *endo* isomer t_r = 45.1 min, 42.4 min; *endo* isomers t_r = 38.6 min and 42.4 min. ^{1}H NMR data for the *endo* isomer is consistent with previously reported values.[5] ^{1}H NMR data for the *exo* isomer is consistent with previously reported values.[4]

(1*S*, 2*S*, 3*S*, 4*R*)-3-Isopropyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-Isopropyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde. Prepared according to the general procedure with (*E*)-4-methyl-pent-2-enal (142 μL, 1.22 mmol), cyclopentadiene (302 μL, 3.66 mmol), and **7** (16 mg, 0.061 mmol) to afford the title compound as a colorless oil in 92% yield (162 mg, 0.99 mmol) after silica gel chromatograms (10% EtOAc/hex); 1.0:1.0 *endo:exo*; *endo* 96% ee; *exo* 90% ee. Product ratios were determined by GLC (Bodman β-DM column, 85 °C isotherm, 1 ml/min); *endo*

[3] Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.

[4] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.

isomers t_r = 43.5 min and 44.4 min, *exo* isomers t_r = 42.1 min and 46.2 min. ^{1}H NMR data for the *endo* and *exo* isomer are consistent with previously reported values.[4]

(1*S*, 2*S*, 3*S*, 4*R*)-3-Furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1*R*, 2*S*, 3*S*, 4*S*)-3-Furan-2-yl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde. Prepared according to the general procedure with (*E*)-3-furyl-acrolein (166 mg, 1.36 mmol), cyclopentadiene (329 μL, 3.99 mmol) and **1**·$HClO_4$ (34 mg, 0.13 mmol) to afford the title compound as a colorless oil as a mixture of acetal and aldehyde in 89% yield (5.7:1, 270 mg) after silica gel chromatography (10% EtOAc/hex); 1.1:1.0 *endo:exo*; *endo* 94% ee; *exo* *92*% ee. Product ratios were determined by GLC (Bodman β-DM column, 140 °C isotherm, 1 ml/min); *exo* isomers t_r = 11.2 min and 12.0 min, *endo* isomers t_r = 11.6 min and 12.3 min. ^{1}H NMR data are consistent with previously reported values.[4]

(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. Prepared according to the general MeOH procedure with (*E*)-cinnamaldehyde (6.36 mL, 50.4 mmol), cyclopentadiene (12.5 mL, 151 mmol), and **1**·TfOH (640 mg, 2.5 mmol) to afford the title compound as a colorless oil in 93% yield (12.2 g, 50.0 mmol) after silica gel chromatography (10% EtOAc/hex); 1.0/1.3 *endo*:*exo*, *endo* 94% ee, *exo* 93% ee. Product ratios were determined by GLC (Bodman B-DM column, 140 ^{o}C isotherm, 23 psi); *endo* isomers t_r = 31.2 min and

33.5 min, *exo* isomers t_r = 29.7 min and 32.5 min. ^{1}H NMR data are consistent with previously reported values.[5]

(1*R*, 2*S*)-2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde. To a –20 °C solution of **1**·$HClO_4$ (27 mg, 0.11 mmol) in THF/H_2O (95/5 v/v, 1.0 M) was added acrolein (102 μL, 1.53 mmol), and 2-methyl-1,3-pentadiene (60 μL, 0.51 mmol). The solution was stirred for 26 h then directly purified by silica gel chromatography (10% EtOAc/hex) affording the **7** as a colorless oil in 84% yield (85 mg, 12 mmol); 10:1 *endo:exo;* 88% ee. Product ratios were determined by GLC (Bodman β-DM column, 90 °C initial temp, 30 psi); *endo* isomers t_r = 9.4 min and 10.0 min, *exo* isomers t_r = 5.4 min and 7.2 min. ^{1}H NMR data are consistent with previously published spectra.[5]

(1*R*)-4-methyl-3-cyclohexene-1-carboxaldehyde. To a –10 ^{o}C solution of **1**·$HClO_4$ (32 mg, 0.12 mmol) in CH_3NO_2/H_2O (95/5 v/v, 1.0 M) was added acrolein (1.0 mL, 15 mmol), and isoprene (0.50 mL, 5 mmol). The solution was stirred at -10 ^{o}C for 11 hr, then directly placed onto a silica gel column and eluted with 3% Et_2O/pentane, affording the title compound as a colorless oil in 94% yield (745 mg, 92% ee). Product ratios were determined by GLC (Bodman Γ-TA column, 30 ^{o}C isotherm 40 min, 0.5 ^{o}C/min gradient, 30 psi) t_r = 74.6 min, 75.8 min. ^{1}H NMR data are consistent with previously reported values. [5]

(1*R*, 2*S*)-Acetic acid 6-formyl-cyclohex-2-enyl ester. To a solution of **1**·$HClO_4$ (27 mg, 0.11 mmol) and benzylmethyl ether (50 mg, 0.36 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0

[5] Ishihara, K.; Kurihara, H.; Matsumoto, M; Yamamoto, H. *J. Am. Chem. Soc*., **1998**, 120, 6920.

M) was added acrolein (214 μL, 3.21 mmol) followed by 1-acetoxybutadiene (127 μL, 1.07 mmol). The resulting solution was stirred until the diene was consumed (GLC analysis, CC-1701 column, 50 °C isotherm for 10 min, then 40 °C/min to 280 °C isotherm, 23 psi); *cis*-1-acetoxybutadiene t_r = 10.3 min, *trans*-1-acetoxybutadiene t_r = 9.9 min, benzylmethyl ether t_r = 13.5 min, *trans*-acetic acid 6-formyl-cyclohex-2-enyl ester t_r = 14.2 min, *cis*-acetic acid 6-formyl-cyclohex-2-enyl ester t_r = 16.4 min. A GLC yield of 83% was determined by comparison of the peak areas of acetic acid 6-formyl-cyclohex-2-enyl ester and benzylmethyl ether; 96% ee, 19:1 *endo:exo*. Enantiomeric excess was determined by GLC analysis using a Bodman Γ-TA column (90 °C isotherm 78 min, ramp 3 ºC/min to 108 ºC, 23 psi) t_r = 47.7 min and 80.0 min. ^{1}H NMR data are consistent with previously reported values.[6]

(2*R*)-Bicyclo[2.2.2]oct-5-ene-2-carboxaldehyde. To a –10 ºC solution of **1**·$HClO_4$ (32 mg, 0.12 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added acrolein (501 μL, 7.5 mmol), and cyclohexadiene (238 μL, 2.5 mmol). The solution was stirred for 24 h, after which time the reaction mixture was applied directly to a silica gel column and eluted with (5% ether/pentane) to afford the title compound as a colorless oil in 93% yield (280 mg, 2.06 mmol); 16:1 *endo:exo;* 96% ee. Product ratios were determined by GLC (Bodman β-DM column, 120 °C isotherm, 1 ml/min) t_r = 31.9 min and 34.8 min. ^{1}H NMR data were consistent with previously reported values.[5]

[6] Gouesnard, J.P.; Martin, G.J. *Tetrahedron* **1974**, *30*, 151.

(1*R*)-4-Phenyl-3-cyclohexene-1-carbaldehyde. To a –10 °C solution of 2-phenyl-1,3-butadiene[7] (89 mg, 0.68 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added **1**·TfOH (29.8 mg, 0.14 mmol) and acrolein (135 μL, 2.1 mmol). The solution was stirred at -10 °C for 7 hr, then directly placed onto a silica gel column and eluted with 5% EtOAc/hex affording the title compound as a colorless oil in 87% yield (114 mg, 0.61 mmol, 83% ee). Product ratios were determined by GLC (Bodman β-DM column, 120 °C isotherm, 23 psi) t_r = 86.8 min and 87.8 min. ^{1}H NMR data are consistent with previously reported values.[4]

(1*R, 6S*)-6-Methyl-4-phenylcyclohex-3-ene-1-carbaldehyde. To a 4 °C solution of 2-phenyl-1,3-butadiene[7] (89 mg, 0.68 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added **1**·$HClO_4$ (29.8 mg, 0.14 mmol) and (E)-crotonaldehyde (135 μL, 2.1 mmol). The solution was stirred at +4 °C for 16 hr, then directly placed onto a silica gel column and eluted with 5% EtOAc/hex affording the title compound as a colorless oil in 70% yield (114 mg, 0.61 mmol, 91% ee). Product ratios were determined by GLC (Bodman β-DM column, 165 °C isotherm, 23 psi) t_r = 46.9 min and 49.4 min. ^{1}H NMR data are consistent with previously reported values.[4]

(1R)-3,4-dimethylcyclohex-3-ene-1-carbaldehyde. To a –10 °C solution of **1**·$HClO_4$ (32 mg, 0.12 mmol) in CH_3NO_2/H_2O (95/5 v/v, 1.0 M) was added acrolein (1.0 mL, 15 mmol), and 2,3-dimethylbutadiene (0.50 mL, 5 mmol). The solution was stirred at -10 °C for 11 hr, then directly placed onto a silica gel column and eluted with 3% Et_2O/pentane, affording the title compound as a colorless oil in 94% yield (745 mg, 92%

[7] Marvel, C. S.; Woolford, R. G. *J. Org. Chem.* **1958**, *23*, 1658.

ee). Product ratios were determined by GLC (Bodman β-DM column, 80 ^{o}C isotherm 40 23 psi) t_r = 16.2 min, 16.7 min. IR (CH_2Cl_2) 2926, 2837, 2714, 1722, 1494, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.40-7.23 (m, 5H, ArH), 6.16-6.12 (m, 1H, PhC=C**H**), 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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 186.1045, found *m/z* 186.1041. ^{1}H NMR data are consistent with previously reported values. [5]

Methyl (1S, 6S)-6-formyl-3,4-dimethylcyclohex-3-ene-1-carboxylate. To a -20 °C solution of **1**·$HClO_4$ (29.8 mg, 0.14 mmol) and (E)-methyl-4-oxo-butenoate (135 μL, 2.1 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added 2,3-dimethylbutadiene (89 mg, 0.68 mmol). The solution was stirred at -20 ^{o}C for 23 hr, then directly isolated by flash chromatography in 5% ether/pentane to afford the title compound as a colorless oil in 88% yield (114 mg, 0.61 mmol, 95% ee). Enantiomeric excess was determined by GLC (Bodman β-DM column, 95 ºC isotherm, 23 psi) t_r = 61.5 min and 62.9 min. IR (CH_2Cl_2) 2926, 2837, 2714, 1722, 1494, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.40-7.23 (m, 5H, ArH), 6.16-6.12 (m, 1H, PhC=C**H**), 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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 186.1045, found *m/z* 186.1041. (1*R*)-4-phenyl-3-cyclohexene-1-ol: IR (CH_2Cl_2) 3374, 3289, 2918, 2860, 1444 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.39 (d, *J* = 7.6 Hz, 2H, *o*-ArH), 7.34-7.31 (t, *J* = 7.7 Hz, 2H, *m*-ArH), 7.26-7.22 (m, 1H, *p*-ArH), 6.13 (br, 1H, PhC=C**H**), 3.66-3.58 (m, 2H, C**H**$_2$OH), 2.58-2.41 (m, 2H), 2.40-2.31 (m, 1H), 2.05-

1.83 (m, 3H), 1.72-1.68 (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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 188.1201, found *m/z* 188.1203.

Methyl (1S,6S)-6-formyl-3-methylcyclohex-3-ene-1-carboxylate. To a –10 °C solution of **1**·$HClO_4$ (29.8 mg, 0.14 mmol) and (E)-methyl-4-oxo-butenoate (135 μL, 2.1 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added isoprene (89 mg, 0.68 mmol). The solution was stirred at -10 ^{o}C for 23 hr, then directly isolated by flash chromatography in 5% ether/pentane to afford the title compound as a colorless oil in 81% yield (114 mg, 0.61 mmol, 95% ee). Enantiomeric excess was determined by GLC (Bodman β-DM column, 90 ºC isotherm, 23 psi) t_r = 43.3 min and 45.4 min. IR (CH_2Cl_2) 2926, 2837, 2714, 1722, 1494, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.40-7.23 (m, 5H, ArH), 6.16-6.12 (m, 1H, PhC=C**H**), 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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 186.1045, found *m/z* 186.1041. (1*R*)-4-phenyl-3-cyclohexene-1-ol: IR (CH_2Cl_2) 3374, 3289, 2918, 2860, 1444 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.39 (d, *J* = 7.6 Hz, 2H, *o*-ArH), 7.34-7.31 (t, *J* = 7.7 Hz, 2H, *m*-ArH), 7.26-7.22 (m, 1H, *p*-ArH), 6.13 (br, 1H, PhC=C**H**), 3.66-3.58 (m, 2H, C**H**$_2$OH), 2.58-2.41 (m, 2H), 2.40-2.31 (m, 1H), 2.05-1.83 (m, 3H), 1.72-1.68 (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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 188.1201, found *m/z* 188.1203.

Methyl (2S,3S)-3-formylbicyclo[2.2.2]oct-5-ene-2-carboxylate. To a 4 ºC solution of **1**·TfOH (32 mg, 0.12 mmol) and (*E*)-methyl-4-oxo-butenoate (135 μL, 2.1 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added cyclohexadiene (238 μL, 2.5 mmol). The solution was stirred for 23 h, after which time the reaction mixture was applied directly to a silica gel column and eluted with (5% ether/pentane) to afford the title compound as a colorless oil in 92% yield (280 mg, 2.06 mmol); 5:1 *endo:exo;* 97% ee. Product ratios were determined by GLC (Bodman β-DM column, 90 °C isotherm 5 min, ramp 10ºC/min to 110 ºC, 23 psi) *endo* isomers t_r = 32.2 min and 33.5 min, *exo* isomers t_r = 32.9 min and 35.4 min. 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, PhC=C**H**), 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 (CI) exact mass calcd for ($C_{13}H_{19}N_2OCl$) requires *m/z* 186.1045, found *m/z* 186.1041.

[(2*S*, 3*S*)-3-Formylbicyclo[2.2.1]hept-5-en-2-yl]-methyl benzoate and [(2*S*, 3*S*)-3-Formylbicyclo[2.2.1]hept-5-en-2-yl]-methyl benzoate. Prepared according to the general procedure with **1**•$HClO_4$ (34 mg, 0.13 mmol) and (*E*)-4-benzyloxy-but-2-enal (166 mg, 1.36 mmol) in THF/H_2O (95/5 v/v, 1.0 M) at +4 °C. Reaction was complete 11 h after addition of cyclopentadiene (329 μL, 3.99 mmol). Direct isolation by silica gel chromatography (10% EtOAc/hex) gave **17** as a colorless oil in 89% yield (1.0:1.3 *endo:exo*; *endo* 95% ee; *exo 91*% ee). Product ratios were determined by GLC (Bodman β-DM column, 170 °C, 23 psi); *exo* isomers t_r = 34.6 min and 35.7 min, *endo* isomers t_r = 37.8 min and 38.8 min. ^1H NMR data are consistent with reported values.[4]

Methyl (1S,6S)-6-formyl-3-phenylcyclohex-3-ene-1-carboxylate. Prepared according to the general procedure with **1**·$HClO_4$ (34 mg, 0.13 mmol) and (E)-methyl-4-oxo-butenoate (166 mg, 1.36 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) at -20 °C. Reaction was complete 24 h after addition of 2-phenyl-1,3-butadiene.[8] Direct isolation by silica gel chromatography (10% EtOAc/hex) gave **18** as a colorless oil in 87% yield ((89 mg, 0.68 mmol, 90% ee). Product ratios were determined by GLC (Bodman β-DM column, 135 °C, 40 psi); t_r = 94.5 min and 96.9 min. ^{1}H NMR data are consistent with reported values.[4]

[(1S,6S)-6-formyl-3-phenylcyclohex-3-en-1-yl]methyl benzoate. To a +4 °C solution of **1**·TfOH (29.8 mg, 0.14 mmol) and (*E*)-4-benzyloxy-but-2-enal (135 mg, 2.1 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) at +4 °C. The solution was stirred at +4 ^{o}C for 12 hr, then directly placed onto a silica gel column and eluted with 5% EtOAc/hex affording the title compound as a colorless oil in 86% yield (114 mg, 0.61 mmol, 90% ee). Product ratios were determined by HPLC analysis of of alcohol, obtained by $NaBH_4$ reduction of the aldehyde using Chiracel OD-H column (1.6 × 25 cm) and Chiralcel OD guard (1.6 × 5 cm); 2% ethanol in hexanes, 1.0 mL/min; t_r = 46.3 min and 54.7 min. ^{1}H NMR data are consistent with previously reported values.[4]

Benzyl (1S,6R)-6-formylcyclohex-2-en-1-ylcarbamate. To a -20 °C solution of **1**·TfOH (27 mg, 0.11 mmol) in THF/H_2O (95/5 v/v, 1.0 M) was added acrolein (102 μL, 1.53 mmol), and N-Cbz-amino-1,3-butadiene (60 mg, 0.51 mmol). The solution was stirred

[8] Marvel, C. S.; Woolford, R. G. *J. Org. Chem.* **1958**, *23*, 1658.

for 6 h then directly purified by silica gel chromatography (10% EtOAc/hex) affording the **20** as a white solid in 86% yield (85 mg, 12 mmol); 6:1 *endo:exo;* 95% ee. Product ratios were determined by GLC (Bodman β-DM column, 160 °C initial temp, 30 psi); *endo* isomers t_r = 103.0 min and 106.2 min, *exo* isomers t_r = 94.0 min and 96.1 min. ^{1}H NMR data are consistent with previously published spectra.[5]

Benzyl (1S,5S,6R)-6-formyl-5-methylcyclohex-2-en-1-ylcarbamate (21). To a -10 °C solution of **1**·$HClO_4$ (29.8 mg, 0.14 mmol) and (E)-crotonaldehyde (135 μL, 2.1 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added N-Cbz-amino-1,3-butadiene (89 mg, 0.68 mmol). The solution was stirred at -10 ^oC for 9 hr, then directly placed onto a silica gel column and eluted with 5% EtOAc/hex affording the title compound as a colorless oil in 70% yield (114 mg, 0.61 mmol, 91% ee). Product ratios were determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde using Chiracel OD-H column (1.6 × 25 cm) and Chiralcel OD guard (1.6 × 5 cm); 2% ethanol in hexanes, 1.0 mL/min; t_r = 25.5 min and 28.3 min. ^{1}H NMR data are consistent with reported values.[4]

Benzyl (1S,6R)-6-formylcyclohex-2-en-1-ylcarbamate. To a -20 °C solution of **1**·$HClO_4$ (27 mg, 0.11 mmol) in CH_3CN/H_2O (95/5 v/v, 1.0 M) was added (*E*)-methyl-4-oxo-butenoate (102 mg, 1.53 mmol) and N-Cbz-amino-1,3-butadiene (260 mg, 1.71 mmol). The solution was stirred for 9 h then directly purified by silica gel chromatography (10% EtOAc/hex) affording **22** as a white solid in 71% yield (85 mg, 1.2 mmol); 4:1 *endo:exo;* 97% ee. Product ratios were determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde using Chiracel AD column (1.6 × 25 cm) and Chiralcel

AD guard (1.6 × 5 cm); 7% isopropanol in hexanes, 1.0 mL/min; t_r = 30.3 min and 34.3 min. ^{1}H NMR data are consistent with published spectra.[5]

Benzyl (1S,5S,6R)-6-formyl-5-methylcyclohex-2-en-1-ylcarbamate. To a -10 °C solution of **1**·$HClO_4$ (29.8 mg, 0.14 mmol) and (*E*)-4-benzyloxy-but-2-enal (135 mg, 2.1 mmol) in THF/H_2O (95/5 v/v, 1.0 M) was added N-Cbz-amino-1,3-butadiene (89 mg, 0.68 mmol). The solution was stirred at -10 ^oC for 17 hr, then directly placed onto a silica gel column and eluted with 5% EtOAc/hex affording the title compound as a colorless oil in 83% yield (114 mg, 0.61 mmol 10:1 *endo:exo*, 99% ee). Product ratios were determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde using Chiracel OD-H column (1.6 × 25 cm) and Chiralcel OD guard (1.6 × 5 cm); 7% isopropanol in hexanes, 1.0 mL/min; *endo* t_r = 36.6 min and 52.9 min and *exo* t_r = 41.2 min and 63.9 min). ^{1}H NMR data are consistent with previously reported values.[4]

Chapter 2

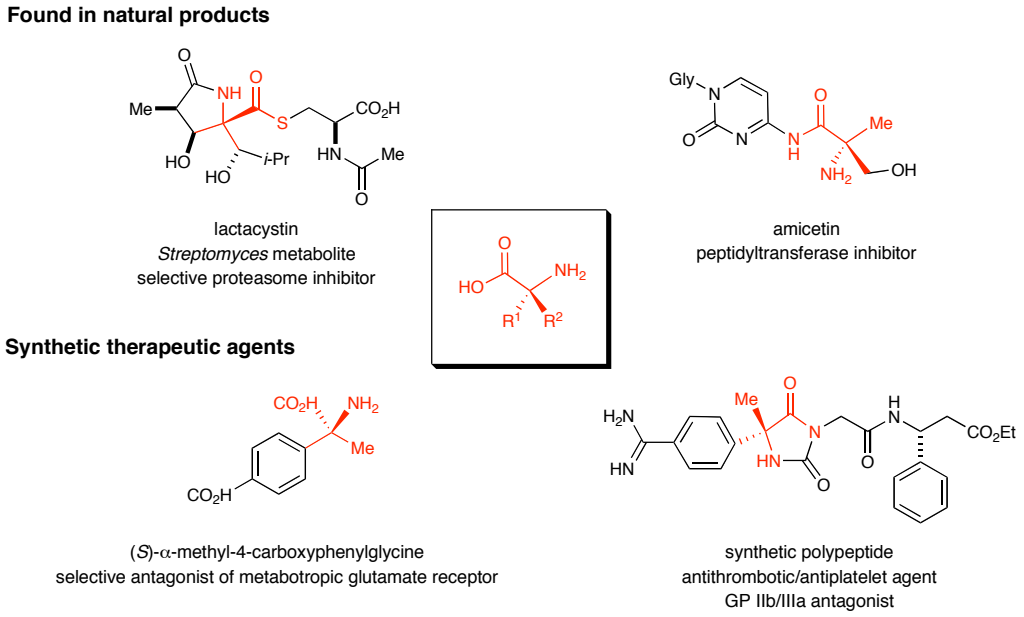
Access to α-Alkylated α-Amino Acids *via* Asymmetric Organocatalysis

Introduction

α-Alkylated α-amino acids are particularly valuable as components of natural products,[1] pharmaceutical targets,[2] and probes of peptide conformation and enzyme activity.[3] While the applications of these non-natural amino acids continue to expand in biology, medicine, materials science, and chemical synthesis, there are limited catalytic asymmetric methods to produce fully-substituted α-amino acids.[4,5] Using LUMO-lowering iminium catalysis, conjugate addition of silanyloxy oxazoles to α,β-unsaturated aldehydes provides an asymmetric catalytic method by which to access these acids.

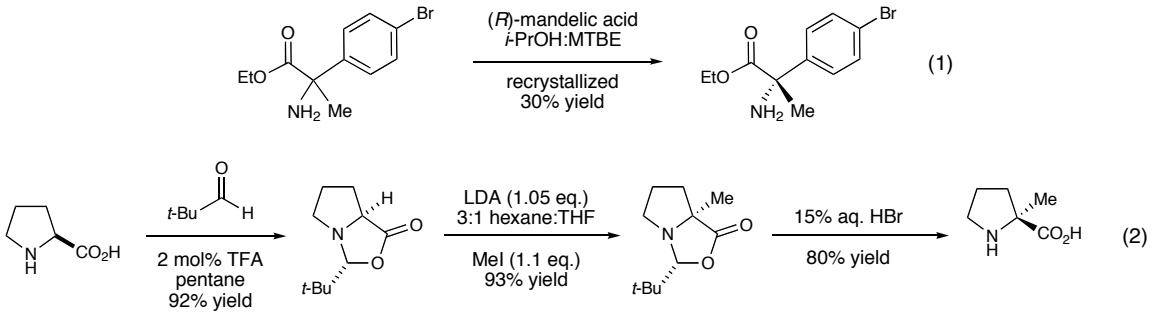
The utility of non-natural amino acids has been demonstrated in biological systems as their incorporation into peptides and pharmaceutical agents alters activity and allows scientists to probe enzymes. Promising as catalysts, they are implicated in the evolution of homochirality required for life on earth. The added substitution at the α-carbonyl position compared to naturally occurring amino acids blocks the epimerization at that center commonly observed when an enolizable hydrogen is present. The greater stability of these compounds extends to include increased rigidity when they are incorporated into peptides and other biological polymers and oligomers.[3] In drug targets, the fully-substituted amino acid exhibits better metabolic stability such that more of the treatment reaches its target.

Figure 1. Sampling of biologically active compounds with fully-substituted amino motif

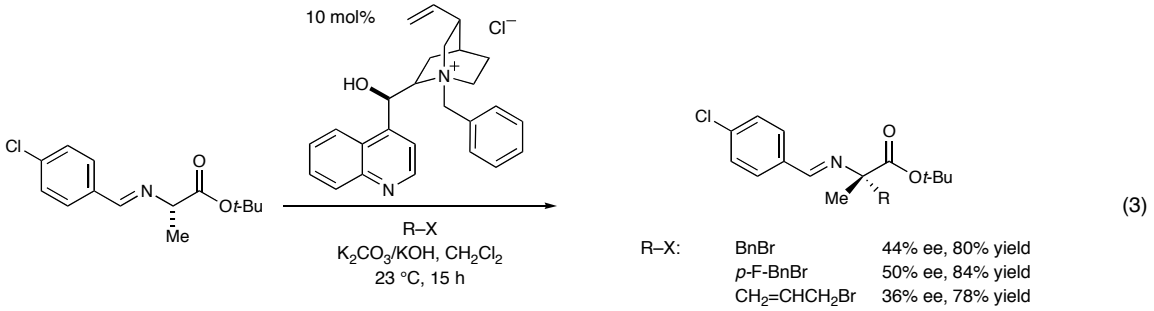


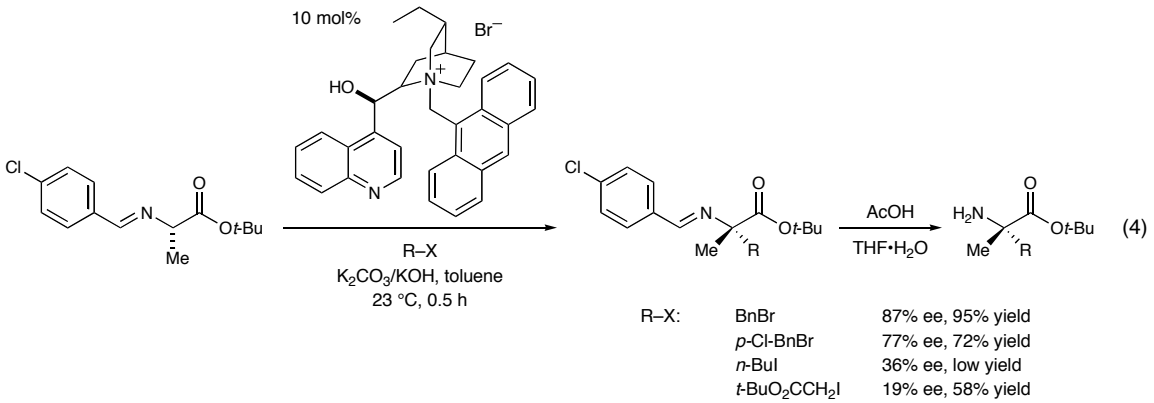
Background

To date, classical resolution of a racemate is still one of the simplest methods to produce the enantiopure amino compound on large scale, despite the maximum 50% yield.[6] In the example shown in equation 1, (*R*)-mandelic acid yields (*S*)-ethyl 2-amino-2-(4-bromophenyl)propanoate after recrystallization. Another common route of access to desired unnatural amino acids is the diastereoselective alkylation of auxiliary-derived intermediates.[7] Again, a stoichiometric amount of an enantiopure compound is required to differentiate enantiomers by the formation of energetically distinct diastereomeric complexes. In the widely applicable synthetic sequence developed by Seebach and coworkers, the enantiopure trisubstituted amino acid is condensed with bulky trimethylacetaldehyde, and the bicyclic oxazolidone is alkylated in what is termed self-reproducing chirality (eq. 2). Then, the desired diastereomer is purified away from the undesired minor product and then liberated by acid hydrolysis of the N,O-acetal.



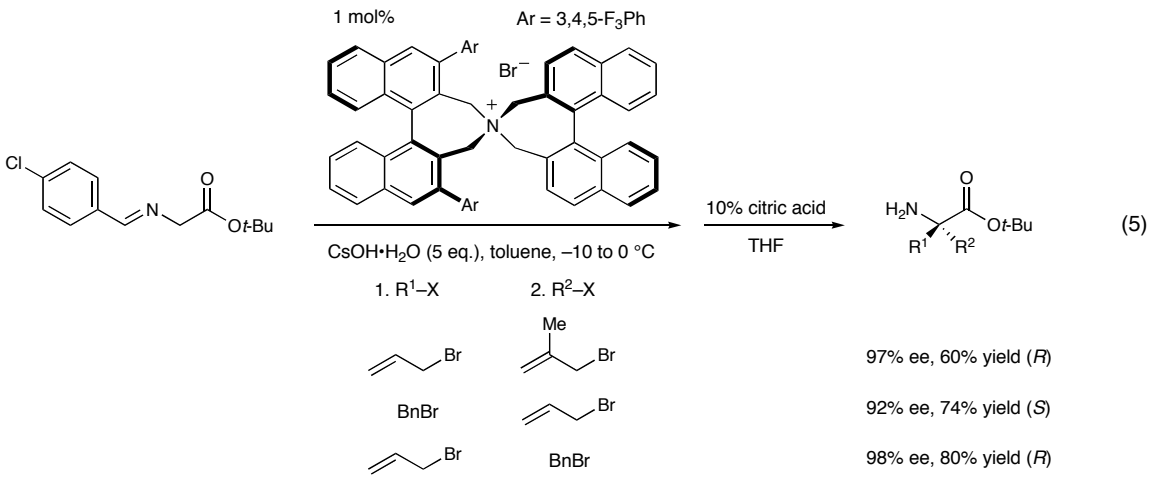
A large number of groups have explored chiral phase transfer catalysis to access α-alkylated amino acids.[8] While successful in the enantioselective synthesis of monoalkylated glycine derivatives, the alkylation of tertiary centers to produce quaternary α-amino acids is not as selective or high-yielding.[9] In 1989, O'Donnell reported the asymmetric phase-transfer alkylation of Schiff bases using cinchona alkaloid-derived quaternary ammonium salts and extended the methodology a few years later from glycine-derived imines to alanine-derived imines to yield quaternary amino acids (eq. 3).[10] One of the best examples uses the same imine reported by O'Donnell, but modifying the catalyst from *N*-benzyl to *N*-anthracenyl-methyl and switching the solvent from dichloromethane to toluene raises the selectivity of alkylation with benzyl bromide from 44% ee to 87% ee.[11]





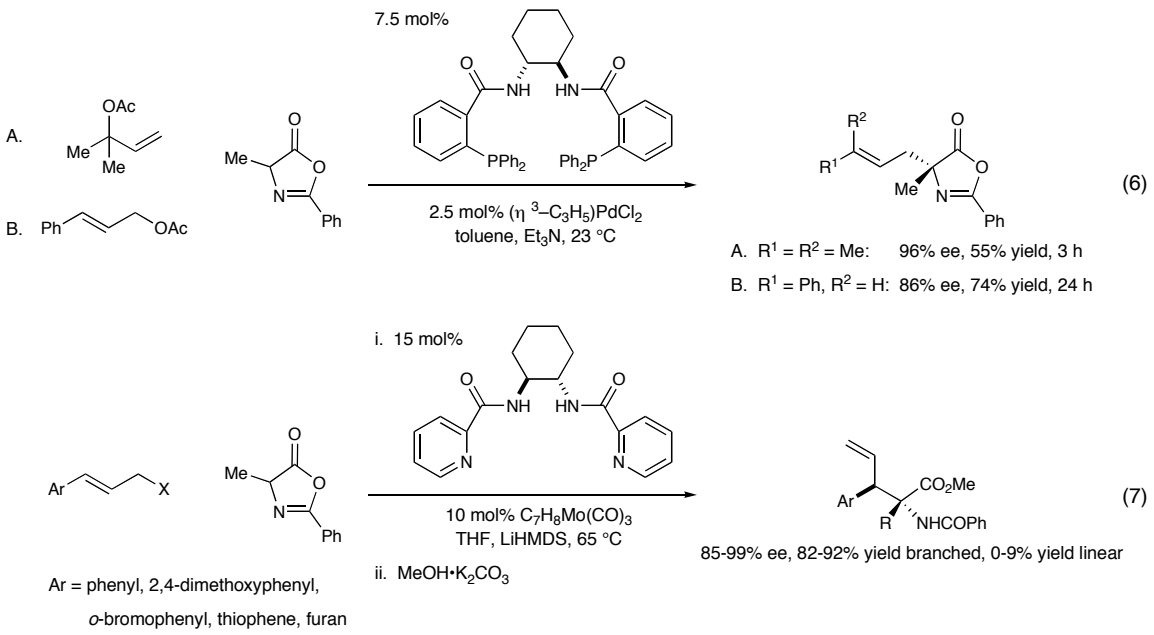
(4)

Faced with a maximum enantioselectivity which is still less than 90% for an already limited substrate scope, the best way to develop a method which would allow modulation of both R groups is to add each one separately. Using a C_2-symmetric binapthyl-based quaternary ammonium salt designed for the monoalkylation of a glycine ketimine, Maruoka and coworkers demonstrated that high enantioselectivities and good yields could be achieved in the phase-transfer catalyzed sequential bis-alkylation of glycine aldimines (eq. 5).[12] As the order of addition of the allyl or benzyl bromide alters the enantiomeric series of the product, it is likely that a chiral ammonium enolate is formed after the first alkylation, and that intermediate then attacks the second alkylating agent with high enantioselectivity. This methodology forms a single quaternary stereocenter in high enantioselectivity, but the groups that can be added are limited to accessible alkylating agents.



(5)

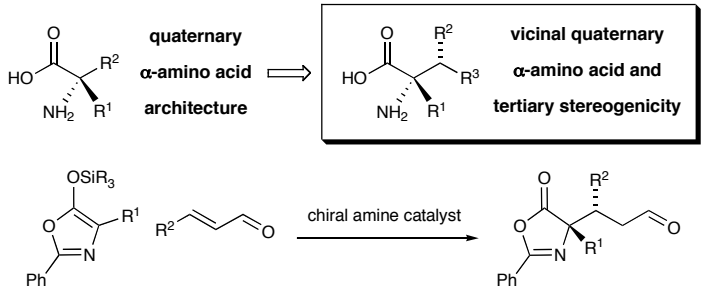
Another catalytic asymmetric method to form α-alkylated-α-amino acids is asymmetric allylic alkylation.[5,6] In 1999, Trost and Azria reported the alkylation of 4-substituted-2-phenyloxazolones with allylic esters using the bis-2-diphenylphosphino-benzamide of (*R,R*)-1,2-diaminocyclohexane as the palladium ligand (eq. 6). While some of the branched product bearing a stereocenter adjacent to the quaternary center is observed, the best enantioselectivity with this palladium-based catalytic system is only 40%. Switching to a molybdenum-based system with an acylpyridine of 1,2-diaminocyclohexane as the ligand allows for optimization to yield the branched amino acid as the major product (eq. 7). In fact, the benzoyl-protected quaternary amino acid is synthesized directly *via* a one-pot procedure in good enantioselectivity and excellent yield as potassium carbonate in methanol can simply be added to the crude reaction mixture to affect hydrolysis of the oxazolone. However, even with extensive optimization, this asymmetric alkylation reaction is not completely regioselective and requires an aryl moiety on the allylating agent to operate successfully.



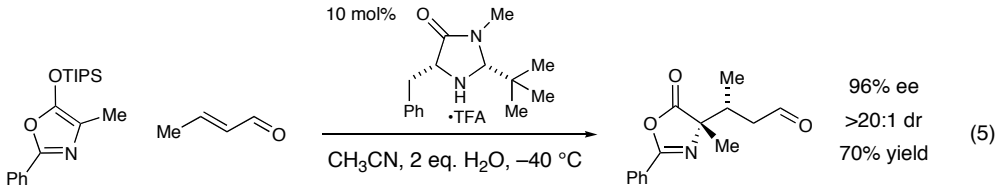
Preliminary Results

Our laboratory has designed amine catalysts which activate α,β-unsaturated carbonyls *via* the reversible formation of chiral iminium ions.[13] Based upon this LUMO-lowering mode of electrophile activation, we envisioned that protected quaternary α-amino acids could be accessed by an organocatalytic conjugate addition of silanyloxy oxazoles to α,β-unsaturated aldehydes (eq. 1). The added utility of this 1,4-addition manifold is the regioselective creation of a tertiary stereocenter vicinal to the quaternary amino center.[6]

Scheme 1. Quaternary amino acids *via* organocatalytic conjugate addition of oxazoles



Increasing the reactivity of the nucleophile by using the known 4-methyl-2-phenyl silanyloxy oxazole, Sean Brown found that 10 mol% of the second-generation *t*-butyl benzyl imidazolidinone catalyst provided excellent enantioselectivity in the formation of the protected quaternary α-amino acid as a single diastereomer (eq. 5). However, these adducts are highly sensitive to acid, and the trace acid in silica gel is enough to decompose a significant portion of the product during column chromatography. From alumina to base-treated silica as the immobile phase, the maximum yield observed is 70%. Furthermore, despite trying a large number of enals, oxazoles, and other heteroaromatic nucleophiles, the selectivity of the product from only one other aldehyde with only the 4-methyl oxzaole could be determined as assay development proved extremely difficult. For adducts with a molecular weight too high to attempt a GLC assay, using the HPLC was attempted, but sodium borohydride ($NaBH_4$) reduction of these aldehyde-bearing protected amino acids in methanol produced an unusable mix of undetermined products. Faced with these difficulties, the project was put on hold.



(5)

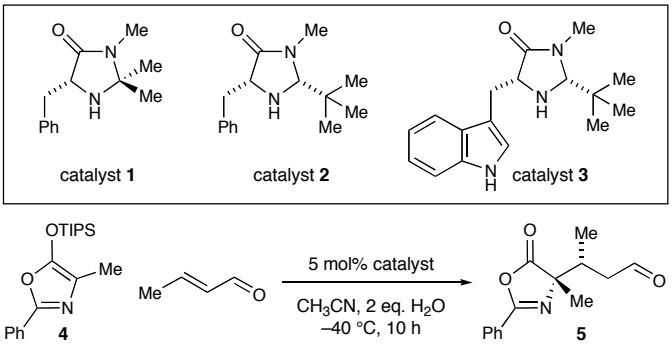
A. Asymmetric Conjugate Additions of Oxazoles to α,β-Unsaturated Aldehydes

One of the first studies conducted upon taking up this project was the reevaluation of reaction efficiency and selectivity with amines **1-3**. In the conjugate addition of 4-methyl silanyloxy oxazole **4** to (*E*)-crotonaldehyde, proline exhibits poor selectivity for latent amino acid **5** (Table 1, entry 1, 32% ee). Although dimethyl imidazolidinone **1**•TFA

significantly improves enantioselectivity (entry 2, 65% ee), both catalysts affect substantial hydrolysis of the starting oxazole to the less-reactive oxazolone. As there is a marked increase in reactivity and selectivity between first-generation catalyst **1** and second-generation catalyst **2** due to the fact that imidazolidinone catalyst **2** forms a more reactive iminium ion intermediate (see section I-C), it is not surprising that *tert*-butyl benzyl catalyst **2**•TFA[13,14] provides synthetically useful levels of enantioenriched aldehyde (entry 3, 83% yield, 93% ee).

In the conjugate addition of silanyloxy oxazole **4** to (*E*)-crotonaldehyde, tryptophan-derived **3** is the optimal imidazolidinone catalyst for the generation of aldehyde-bearing quaternary α-amino acid **5** (Table 1). The higher enantioselectivity imparted by catalyst **3** is attributed to the greater ability of indole versus benzyl to participate in a cation–π interaction with the α,β-unsaturated iminium. Proline exhibits poor activity and selectivity for the formation of protected amino acids (entry 4, 5% yield, 23% ee). There is no detectable background reaction in the absence of catalyst (entry 5).

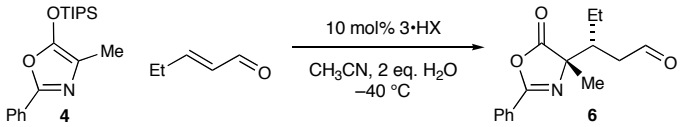
Table 1. Choice of Amine Catalyst is Critical



entry	catalyst	hydrolysis (%)	yield (%)	*syn:anti*	ee (%)
1	D-proline	38	14	5:1	32
2	**1**•TFA	39	26	20:1	65
3	**2**•TFA	2	68	>20:1	95
4	**3**•TFA	2	73	>20:1	97

Whereas only one diastereomer (**5**) is observed in the conjugate addition of 4-methyl silanyloxy furan **4** to (*E*)-crotonaldehyde with either trifluoroacetic acid (TFA) as co-catalyst, the diastereoselectivity of other α,β-unsaturated aldehydes showed a marked dependence on the identity of the acid co-catalyst (Table 2). In the organocatalyzed addition of **4** to *trans*-2-pentenal, high diastereoselection in the formation of **6** is achieved with acids with the largest conjugate bases (entry 2, trichloroacetic acid (TCA), >20:1; entry 4, dibromoacetic acid (DBA), 16:1), while none is observed with diminutive cyanoacetic acid (entry 5, 1:1). Intimate association of the negatively charged conjugate base with the positively charged iminium ion may account for the variation in the facial selectivity with co-catalyst size rather than acidity, but there is no data as yet which pinpoints the location of the conjugate base of the iminium ion. Interestingly, while the diastereoselectivity ranges from 1:1 to greater than 20:1 and the yield from 16-52% for the oxazole addition into 2-pentenal, the enantioselectivities are all 97% for a variety of less-acidic co-catalysts, with the exception of poorly reactive cyanoacetic acid.

Table 2. Effect of the Acid Co-catalyst on Diastereoselectivity

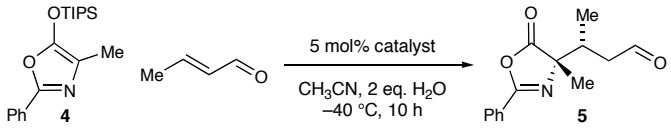


entry	HX	yield (%)	dr	ee (%)
1	TFA	22	4:1	97
2	TCA	52	>20:1	97
3	DCA	25	5:1	97
4	DBA	28	16:1	97
5	cyanoacetic acid	16	1:1	93

As careful selection of both the chiral amine and acid co-catalyst is required for the diastereoselective as well as enantioselective generation of quaternary α-amino acids, the

effect of the acid co-catalyst on the original conjugate addition of oxazole **4** to crotonaldehyde was reassessed (Table 3). Increasing the acidity of the co-catalyst to TfOH causes hydrolysis and diminished yield and selectivity for protected amino acid **5** (entry 5, 16% hydrolysis, 83% ee, 34% yield). TFA and 2,4-dinitrobenzoic acid (2,4-DNBA) maintain greater than 90% ee but result in slower conversion to product (entries 6 and 7, 65% and 12% yield). Not only is the rate of reaction much slower with TFA than TCA, the enantioselectivity is higher. Note that there is no detectable background reaction in the absence of catalyst.

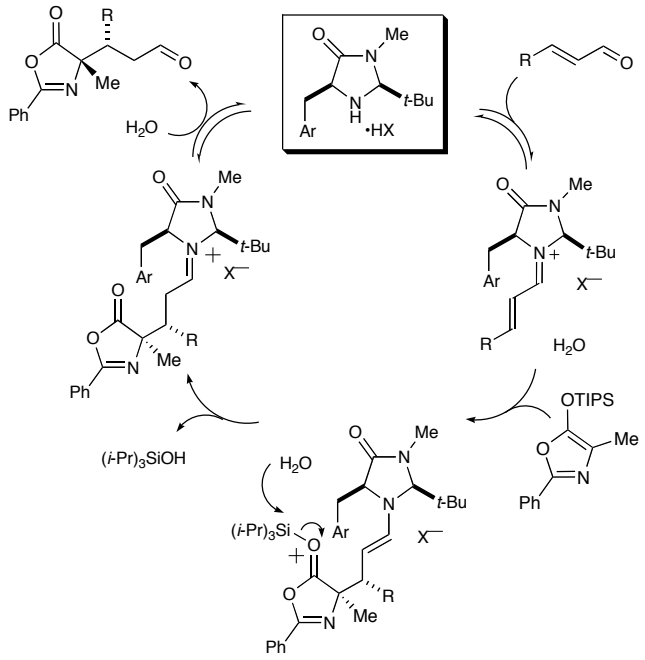
Table 3. High selectivities with TCA transfer to original addition with crotonaldehyde



entry	catalyst	hydrolysis (%)	yield (%)	*syn:anti*	ee (%)
1	**3**•TfOH	16	34	>20:1	83
2	**3**•TFA	1	65	>20:1	97
3	**3**•TCA	2	96	>20:1	98
4	**3**•2,4-DNBA	1	12	>20:1	94
5	none	0	0	ND	ND

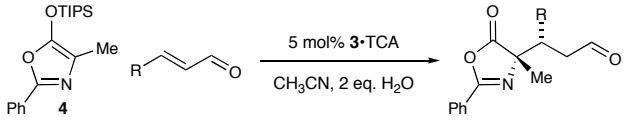
It is important to note that each reaction component is essential for optimum results. Although the omission of H_2O only lowers the enantioselectivity by 1%, conversion is severely decreased when comparing 2 eq. H_2O (100% conv.), 1 eq. H_2O (81% conv.), and 0 eq H_2O (41% conv.). This addition of 2 eq. H_2O is required as the water formed from condensation of the amine catalyst with the aldehyde substrate becomes trapped as TIPSOH upon desilylation of the oxazolone after the rate-determining conjugate addition.[14c] In this form, the water is unavailable to hydrolyze product-bound catalyst as shown by the catalytic cycle shown in Figure 2.

Figure 2. Catalytic cycle of silanyloxy oxazole conjugate addition to enals



Examination of aldehyde scope of the conjugate addition of 4-methyl oxazole **4** demonstrates that the **3**•TCA organocatalytic system tolerates considerable steric variation at the enal β-position (Table 4, entries 1-4, R = Me, Et, *i*-Pr, Me_2 96-98% ee, 15 to >20:1 dr). For aldehydes that form more conjugated, stable iminium intermediates, complete conversion requires higher reaction temperature (entry 5, R = Ph, 92% ee, –20 °C), and reversal of diastereoselectivity is observed.[14c] As this is result is not observed for the sterically similar *i*Pr-substituted enal, it is likely that there is a π-π interaction with the Ph of the enal which disrupts a similar interaction with the Ph of the approaching silanyloxy oxazole. In entry 6, organocatalyzed addition produces a quaternary α-amino acid with a vicinal tertiary center bearing a protected alcohol and a pendant aldehyde in 94% ee, 10:1 dr, and 85% yield. Acetonitrile (CH_3CN) is the only solvent that combines complete conversion with enantioselectivities greater than 90% for all these substrates.

Table 4. Organocatalyzed oxazole conjugate addition to representative α,β-unsaturated aldehydes



entry	R	temp (°C)	time (h)	% yield	*syn:anti*	% ee[a]
1	Me	–40	10	90	>20:1	98[b]
2	Et	–40	13	84	>20:1	96
3	*i*-Pr	–30	13	75	15:1	96
4	*gem*-Me_2	–40	15	82	NA	97[c]
5	Ph	–20	23	93	1:12	92[c,d]
6	CH_2OBz	–30	9	85	10:1	94

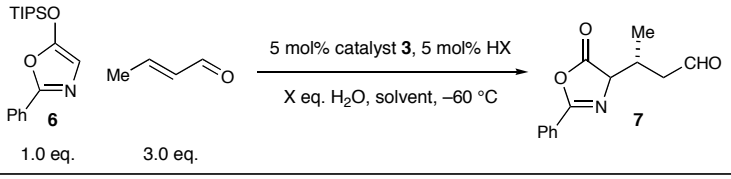
[a]Product ratios by chiral GC or HPLC. [b]Absolute and relative configuration assigned by single-crystal X-ray analysis of derivative (SPB). [c]Absolute and relative configuration assigned by chemical correlation to a known compound. [d]5 mol% TFA as co-catalyst.

Although the main impetus of this methodology is to provide access to quaternary α-amino acids, in order to achieve the broadest substrate scope, the ability to couple a 4-hydrogen substituted glycine-derived silanyloxy oxazole would form a tertiary α-amino center (or a secondary amino stereocenter). Of course, a concern with the formation of such products is that this α-carbonyl hydrogen is acidic and makes this stereocenter prone to epimerization. Different silyl groups were tested in order to ascertain whether triisopropylsilyl (TIPS) still provides the best combination of reactivity and selectivity compared to *tert*-butyldimethylsilyl (TBS) or triethylsilyl (TES) protecting groups for these 5-oxy oxazoles. After 12 hours at –40 °C, TIPS protection leads to the highest conversion (67%) with TBS and TES providing 39% and 13% conversion, respectively. The maximum diastereoselectivity observed is 4:1 with either TCA or TFA as the acid co-catalyst.

Unfortunately, there is a significant amount of hydrolysis of even the TIPS oxazole to the less reactive oxazolone at this temperature. This is likely caused by the fact that unsubstituted oxazole (**5**) is significantly less soluble at low temperatures than the

corresponding 4-methyl triisopropyl silanyloxy oxazole (**4**). In comparing other solvents to CH_3CN, conducting the conjugate addition of **5** to crotonaldehyde in acetone greatly increases conversion without as significantly decreasing enantioselectivity of aldehyde **7**. Comparing 2:1 and 1:1 mixtures of CH_3CN:acetone along with TCA versus TFA and 1 or 2 equivalents water at –60 °C shows that the best overall conversion and enantioselectivity is achieved with the greater ratio of CH_3CN, TCA, and 1 equivalent water (Table 5, entry 7). However, on large scale the yield reaction in acetone does contain the hydrolyzed oxazolone of **5** according to the crude ^{1}H NMR, something that is not observed with oxazole **4**, and the large scale reaction in CH_3CN alone operates more efficiently on large scale.

Table 5. Optimization of reaction conditions for unsubstituted silanyloxy oxazole

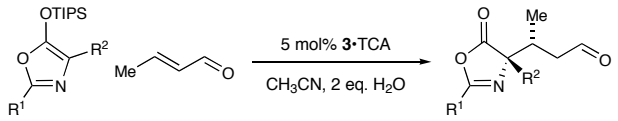


entry	HX	eq. H_2O	solvent	conv. (%) 4h	conv. (%) 20h	conv. (%) 29h	ee (%)
1	TCA	2	MeCN:acetone	43	85	88	95/94
2	TFA	2	(1:1, 0.25 M)	58	73	75	91/88
3	TCA	2	MeCN:acetone	47	85	82	96/94
4	TFA	2	(2:1, 0.33 M)	53	69	73	91/90
5	TCA	1	MeCN:acetone	28	85	96	95/93
6	TFA	1	(1:1, 0.25 M)	53	93	--	95/91
7	TCA	1	MeCN:acetone	31	92	--	97/95
8	TFA	1	(2:1, 0.33 M)	55	93	--	96/94

More extensive variation on the oxazole component further expands the synthetic utility of this organocatalytic transformation (Table 6). When R^2 is isopropyl, a single enantiopure protected amino acid is produced (entry 2, >99% ee, >20:1 dr, 90% yield). Both 4-phenyl and 4-benzyl substituted oxazoles add with excellent selectivities (entry 3, R=Ph, 96% ee, 10:1 dr, 85% yield; entry 4, R=Bn, 97% ee, >20:1 dr, 96% yield). Exchange of the 2-phenyl

for a 2-trifluoromethyl (CF_3) group at R^1 does not diminish the enantioselectivity observed with 4-benzyl oxazoles (entries 4 and 5, 97% ee). The conjugate addition of the 4-hydrogen substituted silanyloxy oxazole provides 96% ee, 89% yield, and a crude 9:1 dr; however, as the tertiary α-amino center epimerizes upon chromatography, the isolated dr is only 3:1 (entry 6). It is important to note that no 1,2-addition products are observed for the organocatalyzed conjugate addition of any aldehyde or oxazole substrates,[13c,14] and all adducts are formed in greater than 90% enantioselectivity.

Table 6. Various substituents on oxazole nucleophile provide high enantioselectivities



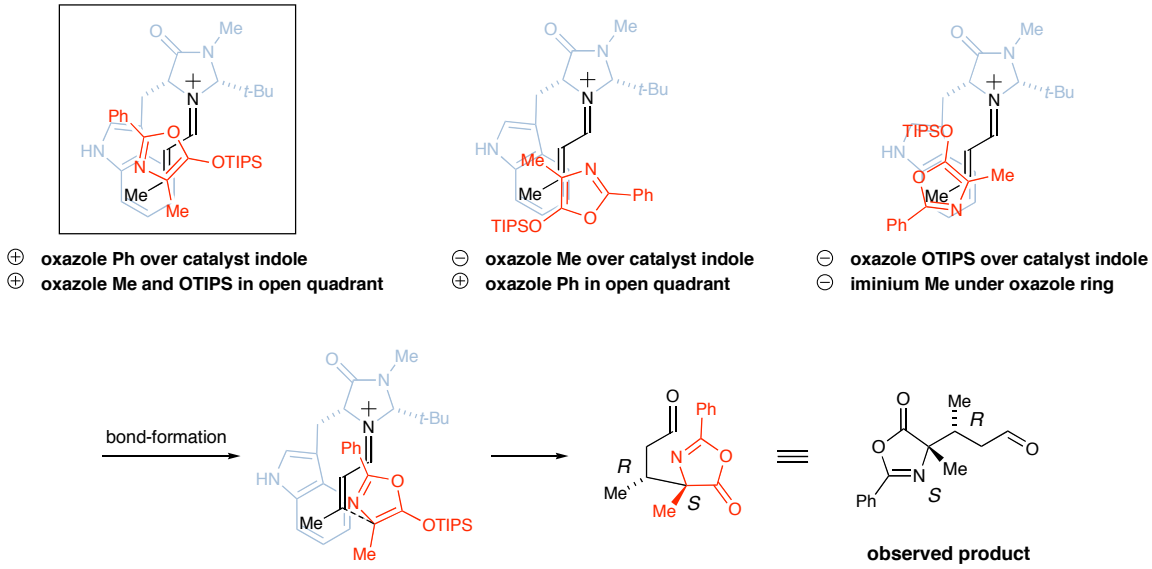
entry	oxazole R^1 =	R^2 =	temp (°C)	time (h)	% yield	*syn:anti*	% ee[a]
1	Ph	Me	–40	10	90	>20:1	98
2	Ph	*i*-Pr	–20	2	90	>20:1	>99
3	Ph	Ph	–30	23	85	10:1	96
4	Ph	Bn	–40	13	96	>20:1	97
5	CF_3	Bn	–40	8	78	9:1	97
6	Ph	H	–40	7	89	3:1[b]	96

[a]Product ratios determined by chiral GC or HPLC. [b]Crude dr = 9:1.

Considering the possible trajectories of oxazole addition shows that a combination of energetically favorable interactions leads to the observed diastereoselectivity (Fig. 3). The lowest energy approach places the methyl (Me) and silanyloxy (OTIPS) moieties of the oxazole in the open quadrant of the iminium C–C double bond and accesses a stabilizing π-π interaction between the indole of the catalyst and the phenyl (Ph) of the oxazole. In the middle of Fig. 3, this favorable interaction with the indole is replaced by steric repulsion of the oxazole methyl and a possible gauche interaction with the iminium methyl. The worst trajectory clashes the iminium methyl with the oxazole ring itself. Unraveling the lowest

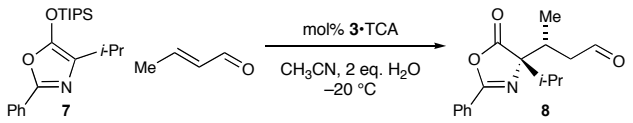
energy conjugate addition adduct leads to the observed stereochemistry as proven by x-ray crystallography.

Figure 3. Proposed transition state leading to observed diastereoselectivity



While 5 mol% of imidazolidinone **3**•TCA is routinely employed in this investigation, catalyst loading as low as 0.5 mol% maintains >99.5% ee, >20:1 dr, and 76% yield of **8** (Table 7). Hydrolysis of the silanyloxy oxazole to the less-reactive oxazolone at longer reaction times accounts for the reduction in yield between 1 and 0.5 mol% amine catalyst **3** (entries 4 and 5, 87% yield and 76% yield). Conjugate addition of the unsilylated 4-methyl oxazolone results in a 93% ee compared to 98% ee with 4-methyl silanyloxy oxazole **4**. In addition, these studies reveal that the observed change in reaction rate as a function of catalyst loading is consistent with first-order kinetics in the catalyst•TCA component.

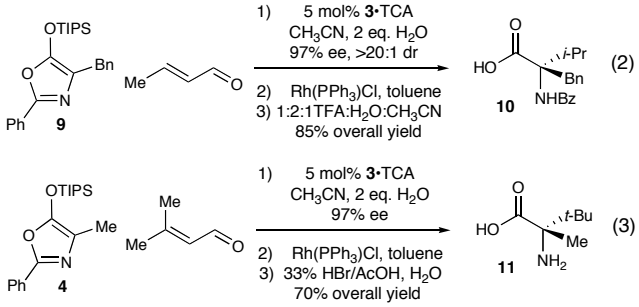
Table 7. Effect of catalyst loading on organocatalyzed alkylations



entry	mol% **3**•TCA	time (h)	% yield	dr	% ee[a]
1	10	1	92	>20:1	>99.5
2	5	2	90	>20:1	>99.5
3	2	5	89	>20:1	>99.5
4	1	9	87	>20:1	>99.5
5	0.5	19	76	>20:1	>99.5

[a]Product ratios determined by chiral HPLC.

Furthermore, a sequence for unmasking these unnatural α-amino acids was developed. If the pendant aldehyde is not desired, decarbonylation of the conjugate addition product of **9** and (*E*)-crotonaldehyde with Wilkinson's catalyst followed by acidic hydrolysis cleanly provides *N*-benzoyl amino acid **10** in 85% overall yield (eq. 2).[18] As shown in equation 3, treatment of the adduct of **4** and 3-methyl-2-butenal with Wilkinson's catalyst followed by strong acid provides fully-deprotected quaternary amino acid **11** in 70% yield over 3 steps.[18] The only other reported synthesis of enantioenriched α-methyl-*tert*-leucine proceeds in only 2% overall yield.[3]



In summary, iminium catalysis is a valuable platform for the development of practical enantioselective processes for the formation of quaternary stereocenters. This work establishes the first asymmetric addition of silanyloxy oxazoles to enals to generate aldehydes bearing vicinal quaternary *α*-amino acid and tertiary carbon stereocenters in high selectivity and yield. The dense functionality and defined stereochemistry of these products

marks them as highly useful synthetic amino acid building blocks. It is also important to note that the sense of asymmetric induction observed in all cases is predicted by our previously described model.[13,14] Moreover, these unnatural *α*-amino acid adducts, which are not currently accessible *via* Lewis acid catalysis, are produced under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst.

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[9] While these are technically tertiary amino compounds, the literature describing the methods for their formation refers to them as "quaternary" despite a non-carbon substituent.

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[17] X-ray crystal structure of derivative formed by reductive amination, and hydrolyze was obtained by Sean P. Brown.

[18] This method was used to prove stereochemistry by chemical correlation.

Supporting Information

General Information. All solvents were used as obtained from commercial suppliers unless otherwise indicated. Other commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[9] Thin layer chromatograms (TLC) was performed on EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and $KMnO_4$ 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 chromatograms on Iatrobeads or Fisher 200-425 mesh Davisil (grade 643, type 150A) according to the method of Still.[10]

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz) instrument, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as 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 as chemical shift. IR spectra were recorded on Perkin-Elmer Paragon 1000 spectrometer as thin films and reported in terms of frequency of absorption. Mass spectra were obtained from the California Institute of Technology Microanalytical Services facility. GLC was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex β-DM (30 m × 0.25 mm) and Bodman Chiraldex

[9] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Fourth ed.; Butterworth-Heinemann: Oxford, 1996.
[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Γ-TA (30 m × 0.25 mm). High performance liquid chromatograms (HPLC) analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254 nm, using a Chiralcel OD-H column (1.6 × 25 cm) and Chiralcel OD guard (1.6 × 5 cm).

Progress of silanyloxy oxazole conjugate addition was typically monitored by TLC analysis or by GLC analysis of reaction aliquots.

General Procedure for Amine-Catalyzed Oxazole Conjugate Addition Reaction: To a 2-dram vial equipped with a magnetic stir bar and charged with (2*R*, 5*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one, acid co-catalyst in CH_3CN and 2 eq. H_2O are added. Upon addition of an α,β-unsaturated aldehyde, reaction is cooled immediately. After stirring for 5 minutes in the appropriate temperature bath, the silanyloxyoxazole was added dropwise, and the resulting solution was stirred at constant temperature. Upon consumption of the oxazole (determined by TLC or by GLC conversion assay on parallel reaction with benzyl methyl ether as standard), the reaction mixture was then directly purified by chromatography in iatrobeads and fractions concentrated *in vacuo* to provide the title compounds.

Enantioselectivity was determined by chiral GLC or HPLC analysis of the title compound or its derivative. Absolute configurations were assigned by chemical correlation to the corresponding α-amino acid or by x-ray crystallography of a derivative.

(3*R*, 4*S*)-3-(4-Methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-butyraldehyde. Prepared according to the general procedure with (*E*)-crotonaldehyde (124 μL, 1.5 mmol),

4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol), and **4** (14.3 mg, 0.05 mmol) to afford the title compound as a colorless oil in 95% yield (0.117 g, 0.48 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 98% ee. Product ratios were determined by GLC (Bodman β-DM column, 60 ^{o}C, 40 min; 5 ^{o}C/min gradient, 23 psi); (3*S*, 4*S*) *syn* isomer t_r = 41.5 min. IR (film) 3064, 2971, 1821, 1725, 1655, 1004 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (dd, *J* = 1.1, 2.2 Hz, 1H, CHO), 7.96 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.46 (m, 2H, ArH), 2.71 (m, 1H, C**H**$_2$CHO), 2.63 (m, 1H, C**H**CH_3), 2.40 (ddd, *J* = 2.2, 8.8, 17.1 Hz, 1H, C**H**$_2$CHO), 1.48 (s, 3H, CH_3), 0.99 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 180.1, 160.6, 133.1, 129.0, 128.2, 125.7, 71.8, 45.6, 35.0, 22.0, 15.2; HRMS (FAB) exact mass calcd for ($C_{14}H_{15}NO_3$) requires *m/z* 246.1130, found *m/z* 246.1122; $[\alpha_D]$ = -12.5 (c = 1.0, $CHCl_3$).

(3*R*, 4*S*)- 3-(4-Methyl-5-oxo-2-phenyl-4,5- dihydro-oxazol-4-yl)-pentanal. Prepared according to the general procedure with **3** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), *trans*-2-pentenal (124 μL, 1.5 mmol), and 4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) to afford the title compound as a colorless oil in 95% yield (0.117 g, 0.48 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 98% ee. Product ratios were determined by GLC (Bodman β-DM column, 60 ^{o}C, 40 min; 5 ^{o}C/min gradient, 23 psi); (3*S*, 4*S*) *syn* isomer t_r = 41.5 min. IR (film) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (t, *J* = 1.9 Hz, 1H, CHO), 7.97 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.48 (m, 2H, ArH), 2.76 (m, 1H, C**H**$_2$CHO), 2.56-2.43 (m, 2H, C**H**C**H**$_2$CHO), 1.48 (s, 3H, CH_3), 1.25 (m, 2H, C**H**$_2$$CH_3$) 0.99 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$). ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.2, 180.5, 160.4, 133.1, 129.0, 128.2, 125.8, 72.4, 43.4,

41.7, 23.3, 12.3; HRMS (FAB) exact mass calcd for ($C_{15}H_{17}NO_3$) requires *m/z* 260.1287, found *m/z* 260.1289; [α_D] = -3.2 (c = 1.0, $CHCl_3$).

(3*R*,4*S*)-4-Methyl-3-(4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-pentanal. Prepared according to the general procedure with **3** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), *trans*-4-methyl-2-pentenal (124 μL, 1.5 mmol), and 4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) to afford the title compound as a colorless oil in 75% yield (0.38 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 96% ee. Product ratios were determined by GLC. IR (film) 3065, 2962, 1820, 1725, 1655, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.90 (dd, *J* = 1.4,1.9 Hz, 1H, CHO), 7.98 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.50 (m, 2H, ArH), 2.85 (ddd, *J* = 1.9, 6.3, 17.7 Hz, 1H, C**H**$_2$CHO), 2.65 (m, 1H, C**H**CH$(CH_3)_2$), 2.54 (ddd, *J* = 1.4, 4.4, 17.7 Hz, 1H, C**H**$_2$CHO), 1.48 (s, 3H, CH_3), 0.99 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$). ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.5, 180.7, 160.1, 133.0, 129.0, 128.1, 126.0, 73.2, 44.2, 40.2, 29.5, 23.9, 23.5, 18.0; HRMS (FAB) exact mass calcd for ($C_{16}H_{20}NO_3$) requires *m/z* 274.1443, found *m/z* 274.1456; [α_D] = -41.1 (c = 1.0, $CHCl_3$).

(4*S*)-3-Methyl-3-(4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-butyraldehyde. Prepared according to the general procedure with **3** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), *trans*-3-methyl-2-butenal (124 μL, 1.5 mmol), and 4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) to afford the title compound as a colorless oil in 82% yield (0.41 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); 97% ee. Product ratios were determined by GLC. IR (film) 3063, 2975, 1818,

1716, 1657, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (dd, *J* = 2.7, 3.3 Hz, 1H, CHO), 7.99 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.49 (m, 2H, ArH), 2.63 (dd, *J* = 3.3, 14.9 Hz, 1H, C**H**$_2$CHO), 2.43 (dd, *J* = 2.5, 14.9 Hz, 1H, C**H**$_2$CHO), 1.51 (s, 3H, CH_3), 1.30 (s, 3H, $CH_3CC\mathbf{H}_3$), 1.19 (s, 3H, $CH_3CC\mathbf{H}_3$). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.6, 179.7, 160.4, 133.1, 129.0, 128.2, 125.7, 74.4, 50.9, 39.9, 22.7, 22.5, 19.5; HRMS (CI) exact mass calcd for ($C_{15}H_{17}NO_3$) requires *m/z* 259.1208, found *m/z* 259.1205; $[\alpha_D]$ = -28.0 (c = 0.9, $CHCl_3$).

(3*S*,4*S*)-3-(4-Methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-3-phenyl-propionaldehyde. Prepared according to the general procedure with **3** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), *trans*-cinnamaldehyde (1.5 mmol), and 4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) to afford the title compound as a colorless oil in 93% yield (0.47 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 92% ee. Product ratios were determined by GLC. IR (film) 3033, 2934, 1822, 1725, 1655, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 1.5 Hz, 1H, CHO), 7.88 (m, 2H, ArH), 7.56 (m, 1H, ArH), 7.46 (m, 2H, ArH), 7.17 (m, 5H, ArH), 3.79 (t, *J* = 7.2 Hz,), 3.16 (dd, *J* = 1.4, 7.4 Hz, 2H, C**H**$_2$CHO), 1.58 (s, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.4, 179.4, 160.8, 137.4, 129.2, 129.0, 128.6, 128.2, 128.1, 125.8, 72.8, 46.2, 22.6; HRMS (FAB) exact mass calcd for ($C_{19}H_{18}NO_3$) requires *m/z* 308.1287, found *m/z* 308.1272; $[\alpha_D]$ = -154.1 (c = 2.6, $CHCl_3$).

(3*R*,4*S*)-Benzoic acid 2-(4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-4-oxo-butyl ester. Prepared according to the general procedure with **4** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), (*E*)-3-formylallyl benzoate (190 mg, 1.0 mmol), and 4-methyl-2-phenyl-

5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) to afford the title compound as a colorless oil in 85% yield (0.117 g, 0.48 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); 10:1 *syn:anti*, 94% ee. Product ratios were determined by GLC. IR (film) 3065, 2979, 1823, 1723, 1653, 1006, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (t, *J* = 1.2 Hz, 1H, CHO), 7.91 (m, 4H, ArH), 7.55 (m, 1H, ArH), 7.42 (m, 4H, ArH), 4.35 (d, *J* = 1.7 Hz,), 4.33 (d, *J* = 2.5 Hz,), 3.17 (ddd, *J* = 4.7, 7.1, 13.5 Hz, 1H, C**H**CH_2), 2.96 (m, 1H, CH_2CHO), 2.69 (ddd, *J* = 1.7, 7.4, 18.2 Hz, 1H, C**H**$_2$CHO), 1.55 (s, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.5, 179.9, 166.2, 161.1, 133.4, 133.1, 129.8, 129.4, 129.0, 128.6, 128.2, 125.6, 69.5, 64.1, 41.6, 38.8, 22.8; HRMS (FAB) exact mass calcd for ($C_{21}H_{20}NO_5$) requires *m/z* 366.1341, found *m/z* 366.1343; $[\alpha_D]$ = -67.9 (c = 1.5, $CHCl_3$).

(3*R*,4*S*)- 3-(4-Isopropyl-5-oxo-2-phenyl-4,5- dihydro-oxazol-4-yl)-butyraldehyde. Prepared according to the general procedure with **4** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), (*E*)-crotonaldehyde (124 μL, 1.5 mmol), and 4-isopropyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.180 g, 0.50 mmol) to afford the title compound as a colorless oil in 90% yield (0.45 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 99% ee. Product ratios were determined by GLC. IR (film) *3065, 2962, 1820, 1725, 1655, 1003* cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (dd, *J* = 1.4, 2.2 Hz, 1H, CHO), 8.00 (m, 2H, ArH), 7.59 (m, 1H, ArH), 7.49 (m, 2H, ArH), 2.87 (m, 1H, C**H**$(CH_3)_2$), 2.47 (dd, *J* = 0.8, 4.0 Hz, 1H, C**H**$_2$CHO), 2.40-2.29 (m, 2H, C**H**$_2$CHO and C**H**CH_3), 1.01 (sept, *J* = 7.0 Hz, 3H, CH(C**H**$_3$)). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 179.1, 161.0, 133.0, 129.0 (2C), 128.2 (2C), 125.7, 78.7, 45.8, 32.0, 31.9, 16.9, 16.6, 14.4 ;

HRMS (EI) exact mass calcd for ($C_{16}H_{19}NO_3$) requires *m/z* 273.1365, found *m/z* 273.1356; [α_D] = (c = 1.0, $CHCl_3$).

(3*R*,4*S*)- 3-(4-Benzyl-5-oxo-2-phenyl-4,5- dihydro-oxazol-4-yl)-butyraldehyde. Prepared according to the general procedure with **4** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), (*E*)-crotonaldehyde (124 μL, 1.5 mmol), and 4-benzyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.204 g, 0.50 mmol) to afford the title compound as a colorless oil in 96% yield (0.45 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); >20:1 *syn:anti*, 97% ee. Product ratios were determined by GLC. IR (film) 3032, 2970, 1815, 1725, 1656, 970, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 1.2, 2.1 Hz, 1H, CHO), 7.81 (m, 2H, ArH), 7.53 (m, 1H, ArH), 7.42 (m, 2H, ArH), 7.17 (m, 5H, CH_2Ar**H**), 3.19 (q, *J* = 12.3 Hz, 2H, C**H**$_2$Ar), 2.82 (m, 2H, C**H**$_2$CHO), 2.52 (ddd, *J* = 2.2, 9.4, 17.9 Hz, 1H, C**H**CH_3), 1.11 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.7, 178.8, 160.6, 134.1, 132.9, 130.4 (2C), 128.9 (2C), 128.3 (2C), 128.0 (2C), 127.5, 125.5, 77.3, 46.1, 41.5, 34.7, 15.5; HRMS (EI) exact mass calcd for ($C_{20}H_{19}NO_3$) requires *m/z* 321.1365, found *m/z* 321.1377; [α_D] = 149.8 (c = 1.6, $CHCl_3$).

(*R*)-3-((*S*)-4-benzyl-2-(trifluoromethyl)-4,5-dihydro-5-oxooxazol-4-yl)butanal. Prepared according to the general procedure with **4** (14.3 mg, 0.05 mmol), TCA (0.05 mmol), (*E*)-crotonaldehyde (124 μL, 1.5 mmol), and 4-benzyl-2-trifluoromethyl-5-triisopropylsilanyloxy-oxazole (0.200 g, 0.50 mmol) to afford the title compound as a colorless oil in 78% yield (0.39 mmol) after chromatography on iatrobeads (2-5-8% EtOAc/hex); 9:1 *syn:anti*, 97% ee. Product ratios were determined by GLC. IR (film) 3032,

2970, 1815, 1725, 1656, 970, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 1.2, 2.1 Hz, 1H, CHO), 7.81 (m, 2H, ArH), 7.53 (m, 1H, ArH), 7.42 (m, 2H, ArH), 7.17 (m, 5H, CH_2Ar**H**), 3.19 (q, *J* = 12.3 Hz, 2H, C**H**$_2$Ar), 2.82 (m, 2H, C**H**$_2$CHO), 2.52 (ddd, *J* = 2.2, 9.4, 17.9 Hz, 1H, C**H**CH_3), 1.11 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.7, 178.8, 160.6, 134.1, 132.9, 130.4 (2C), 128.9 (2C), 128.3 (2C), 128.0 (2C), 127.5, 125.5, 77.3, 46.1, 41.5, 34.7, 15.5; HRMS (EI) exact mass calcd for ($C_{20}H_{19}NO_3$) requires *m/z* 321.1365, found *m/z* 321.1377; $[\alpha_D]$ = 149.8 (c = 1.6, $CHCl_3$).

Chapter 3

Enantioselective Organo-Cascade Catalysis: Electrophilic and Nucleophilic Activation by One Amine Catalyst

Introduction

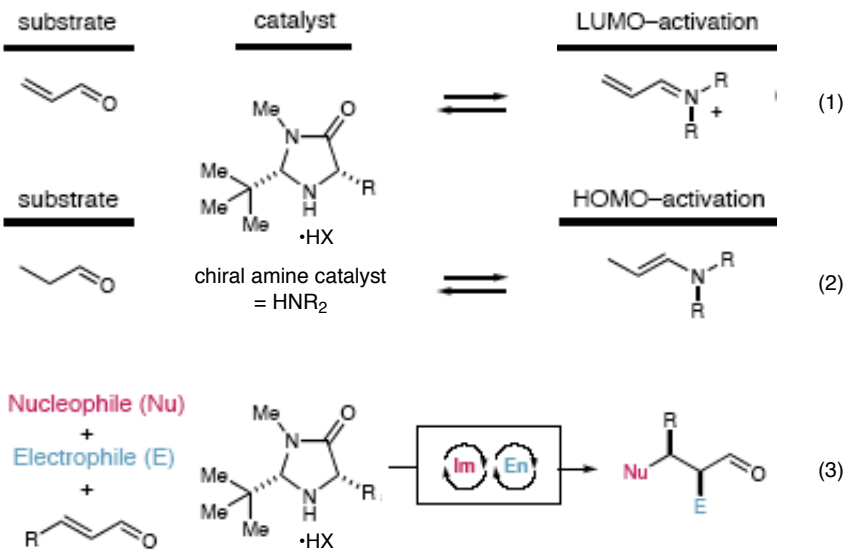
Traditionally, a complex target is synthesized step-by-step, using a different combination of reagents and catalysts for each transformation. An idealized synthesis would involve combining all achiral building blocks at the beginning, adding a single compound that could catalyze every reaction, and isolating a single isomer of pure product. Much effort has been channeled recently into the development of so-called "domino," "cascade," and "tandem" reactions. Herein is described the use of a single imidazolidinone which participates in both nucleophilic iminium catalysis and electrophilic enamine catalysis.[1,2] This chiral amine catalyzes the enantioselective reaction of achiral starting materials to selectively connect multiple stereocenters across the newly formed bonds.

In biological systems, various enzymes will catalyze a string of reactions to build molecular complexity. Rather than the traditional reaction by reaction mode of chemical synthesis, it seemed possible that the appropriate chiral catalysts could be found which could co-exist in the same environment without reacting with each other but which would react rapidly and selectively with their particular substrates in analogy to these enzymatic systems.

A. Concurrent Tandem Reactions with Chiral Imidazolidinone Catalysts

The organocatalytic mechanism heretofore described (Chapters I and II) has been the LUMO-lowering activation of an α,β-unsaturated aldehyde electrophile towards nucleophilic attack (Scheme 1, eq. 1).[1] We have also shown that the first-generation imidazolidinone catalyst is also capable of the HOMO-raising activation of a saturated aldehyde to react as a nucleophile towards an electrophile (Scheme 1, eq. 2).[2e] Considering the fact that nucleophilic attack on an unsaturated aldehyde produces a saturated aldehyde, it should be feasible to start with an α-β-unsaturated aldehyde and add a nucleophile at the β-position and an electrophile at the α-position by joining together these two modes of activation.

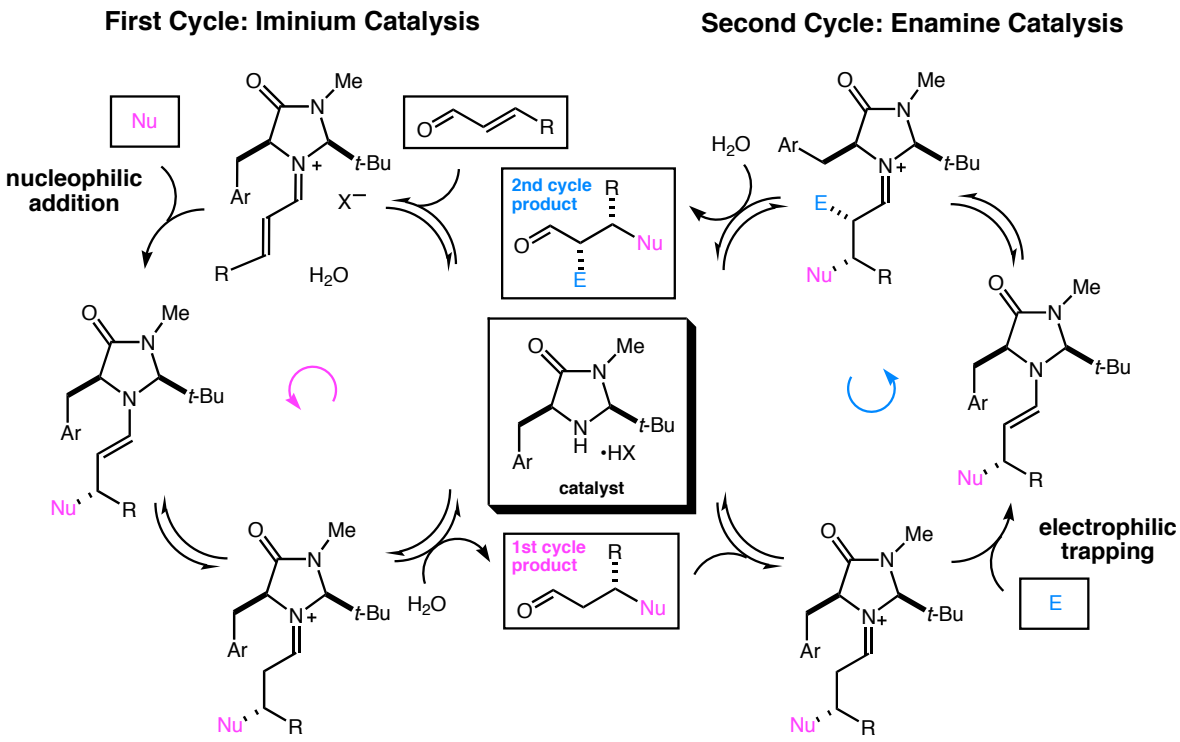
Scheme 1. Linking iminium (Im) and enamine (En) organocatalysis



The proposed linking of two separate catalytic cycles to carry out these transformations is shown in Figure 1. The single catalyst at the center of the figure operates through both cycles. In the first cycle, condensation with the unsaturated aldehyde forms an α,β-

unsaturated iminium, which the nucleophile (Nu) attacks. After tautomerization, hydrolysis liberates the saturated aldehyde bearing the pendant nucleophile. In the second cycle, this saturated aldehyde condenses to again form an iminium, which tautomerizes to the enamine that traps the electrophile (E). The iminium formed upon electrophilic attack is hydrolyzed to yield the desired tandem product and regenerate the chiral amine catalyst.

Figure 1. Merging LUMO-lowering and HOMO-raising iminium and enamine catalysis



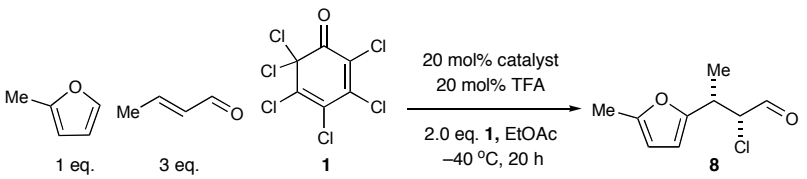
It is important to note that upon iminium formation in the first cycle, the R group on the achiral enal is positioned away from the *tert*-butyl group and under the aryl moiety of the imidazolidinone catalyst. Thus, the catalyst forces the nucleophile to approach from the bottom face, opposite the shielding aryl group. In the second cycle, the stereochemical bias due to the chiral center now at the γ-position of the enamine could run contrary to the

selectivity imposed by the catalyst. Therefore, the selectivity of such a tandem reaction requires that the catalyst control in the second cycle eclipse by far any substrate effects.

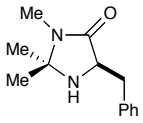
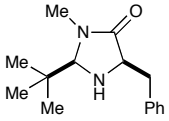
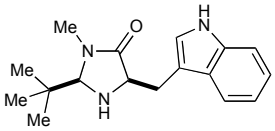
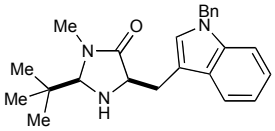
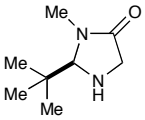
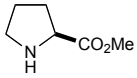
A variety of heterocycles have proved successful in the LUMO-lowering catalyzed conjugate addition to enals, including furans, indoles, and thiophenes.[1] α-Chlorination was chosen as the second step as perchlorinated quinone **1** was expected to be compatible with the entire range of nucleophiles utilized in enantioselective carbon-carbon bond forming conjugate addition reactions.[2e] Exposure of the chiral, activated nucleophile formed upon heterocycle addition with an electrophile such as chlorinating agent **1**,[13] would provide an α-chloroaldehyde with a vicinal tertiary carbon stereocenter in one step.

Catalyst structure is critical to the success of this 3-component coupling (Table 1). Whereas amine catalyst **2** was our original catalyst reported for the organocatalytic α-chlorination of aldehydes, it provides only trace amounts of desired tandem product (**8**). *Tert*-butyl imidazolidinone catalysts **3**-**5** efficiently catalyze the tandem addition/chlorination to form furyl α-chloroaldehyde **8** (entries 2-4, 97-98% ee, 78-79% conv.), with amine **5** inducing a high 11:1 dr. Glycine-derived imidazolidinone **6**[1c] performs poorly for these substrates but outperforms the *N*-benzyl indole catalyst (**4**) for certain non-aromatic tandem products (entry 5, 89% ee, 10% conv.). Although successful for numerous reactions involving enamine catalysis, proline (**7**) does not provide any tandem product (entry 6).[2b,c]

Table 1. Catalyst dependence of tandem conjugate addition/α-chlorination



1 eq. 3 eq. **1** **8**

entry	chiral amine	catalyst #	conv (%)[a]	*syn:anti*[a]	% ee[a]
1		**2**	3	1:1.4	88
2		**3**	79	8.7:1	97
3		**4**	78	8.1:1	97
4		**5**	78	11.0:1	98
5		**6**	10	4.7:1	89
6		**7**	0	ND	ND

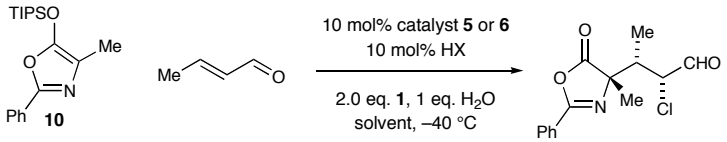
[a]Product ratios determined by chiral GLC with internal standard.

Dr. Yong Huang explored the scope of this tandem addition/chlorination process with aromatic nucleophiles and found that the conjugate addition of indoles, furans, and thiophenes in tandem with chlorination was highly selective for a range of α,β-unsaturated aldehydes (99% ee, 67-87% yield, 9:1-22:1 *syn:anti* dr).

The focus herein is on substrates in which a stereocenter is also formed on the nucleophile. One of the first nucleophiles analyzed was 4-methyl silanyloxy oxazole **10** (II-A). Interestingly, indole substituted catalyst (4), which is the optimal catalyst for the conjugate addition of **10** to α,β-unsaturated aldehydes, was not found to be efficient in the

tandem addition/chlorination reaction. While *tert*-butyl *N*-benzyl indole imidazolidinone catalyst **5** provides high enantioselectivity under a range of conditions (93-97% ee), only the reaction conducted in ethyl acetate (EtOAc) provided useful levels of tandem product in less than a day (Table 2, entry 5). On the other hand, catalyst **6** provides good conversion with both TCA and TFA as co-catalysts and with CH_3CN and acetone as solvents in 99% enantioselectivity in 8 hours at –40 °C (entries 9, 10, 12, and 13).

Table 2. Optimization of reaction conditions for oxazole addition/chlorination

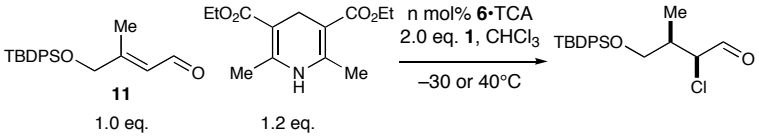


entry	catalyst	HX	solvent	conv. (%)	time (h)	dr	ee (%)
1	**5**	TCA	EtOAc	11	7	9:1	95
2	**5**		CH_3CN	7	7	9:1	93
3	**5**		acetone	15	7	8:1	94
4	**5**	TFA	EtOAc	56	7	6:1	97
5	**5**		EtOAc	74	22	10:1	96
6	**5**		CH_3CN	13	7	8:1	96
7	**5**		acetone	7	7	7:1	96
8	**6**	TCA	EtOAc	48	8	10:1	99
9	**6**		CH_3CN	100	8	9:1	>99.5
10	**6**		acetone	79	8	9:1	98
11	**6**	TFA	EtOAc	55	8	6:1	98
12	**6**		CH_3CN	98	8	7:1	99
13	**6**		acetone	83	8	7:1	99

One of the few β,β-disubstituted enals that provides desired product in the tandem hydrogen transfer/chlorination reaction is γ-silyloxy substituted enal **11**. The reduction is carried out with as little as 1.2 equivalents of the Hantzsch reducing agent, but in accordance with our earlier report[1c] of the catalytic asymmetric hydrogenation of enals, the use of imidazolidinone catalyst **6** is also required. One of the main issues with this reaction is the presence of two byproducts, the diester substituted pyridine from the Hantzsch and

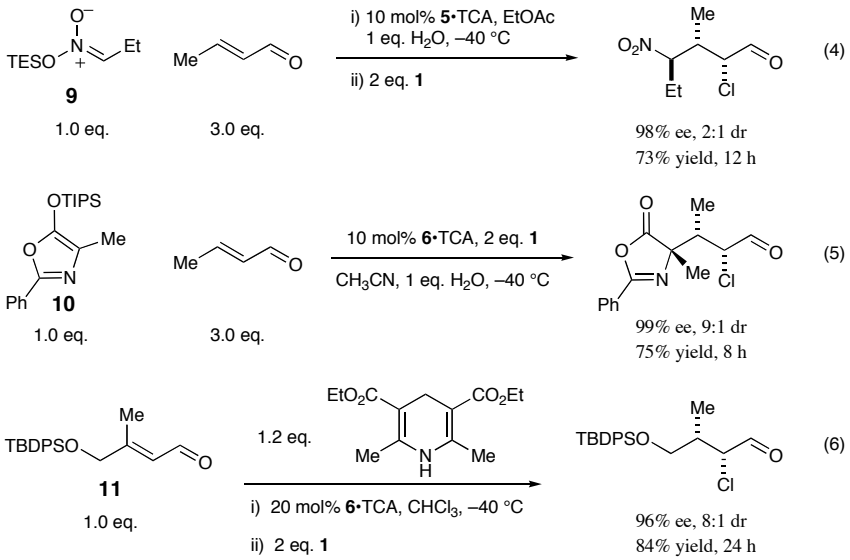
the chlorinated phenol from perchlorinated quinone **1**. In fact, with 10 mol% **6**•TCA at –40 °C, the reaction does not go to completion and becomes messy enough that an accurate conversion could not be gathered, and these reactions take a full 24 h even with 20 mol% imidazolidinone **6**•TCA (Table 3).

Table 3. Higher catalyst loading required for tandem hydrogenation/chlorination



entry	mol% **6**•TCA	temp (°C)	conv. (%)	ee (%)
1	10	–30	76	96
2	10	–40	incomplete	ND
3	20	–30	86	95
4	20	–40	84	96

Equation 4 shows that the tandem addition/chlorination of silylnitronate **9** and crotonaldehyde proceeds in 98% ee, but the major isomer and 3 minor diastereomers are formed in a 2:1 ratio and 73% GC yield. Whereas amine **5** does not efficiently catalyze the tandem process for silanyloxy oxazole **10** (81% conv., 22 h, 96% ee, 10:1 dr), amine **6** provides complete conversion in 8 h with 99% ee, 9:1 dr, and 75% yield of the hydrate upon purification with iatrobeads (Equation 5). *Tert*-butyl catalyst **6** also affects the tandem hydrogenation[1c] and chlorination of aldehyde **11** in 96% ee, 8:1 dr, and 84% yield (Equation 6).



These α-chloroaldehydes are incredibly useful in that they can transmit the stereochemistry at chlorine to the formation of enantioenriched derivatives such as epoxides, aziridines, amino acids, and other important structural motifs.[2e] Coupled with the utility of the nucleophile-derived component of the product, this asymmetric organocatalytic process provides swift access to novel organic scaffolds with multiple functional handles in high selectivity and yield. There are catalysts which can be applied to multiple reactions, but these imidazolidinone catalysts are also capable of operating *via* opposing mechanisms, activation of an electrophile towards nucleophilic addition followed by the activation of that adduct as a nucleophile to attack an electrophile. Our particular interest in new reaction manifolds has led us to new avenues of reactivity in the pursuit of small molecules with significant application in the synthesis of natural products and drug therapies.

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[2] Enamine catalysis: (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152. (c) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722. (d) Brown, S. P.; Brochu, M. P.; Sinz, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (e) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2004**, *126*, 4108. (f) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

[3] Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C., accepted *J. Am. Chem. Soc.* Sept. 2005.

Supporting Information

General Information. All solvents were used as obtained from commercial suppliers unless otherwise indicated. Other commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[11] Thin layer chromatograms (TLC) was performed on EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and $KMnO_4$ 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 chromatograms on Iatrobeads or Fisher 200-425 mesh Davisil (grade 643, type 150A) according to the method of Still.[12]

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz) instrument, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as 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 as chemical shift. IR spectra were recorded on Perkin-Elmer Paragon 1000 spectrometer as thin films and reported in terms of frequency of absorption. Mass spectra were obtained from the California Institute of Technology Microanalytical Services facility. GLC was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-TA (30 m × 0.25 mm) column.

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[11] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Fourth ed.; Butterworth-Heinemann: Oxford, 1996.
[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

(2*R*,3*S*)-2-chloro-3-((*S*)-4,5-dihydro-4-methyl-5-oxo-2-phenyloxazol-4-yl)butanal. To a 1-dram vial equipped with a magnetic stir bar and charged with (2*R*)-2-*tert*-butyl-3-methyl-imidazolidin-4-one TCA salt (16 mg, 0.05 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (300 mg, 1.0 mmol), acetonitrile (1.0 mL) and H_2O (9 μL, 0.5 mmol) were added. The vial was cooled immediately to –40 °C. After 3 minutes, crotonaldehyde (124 μL, 1.5 mmol) and 5-triisopropylsilanyloxy-4-methyl-2-phenyloxazole (166 mg, 0.5 mmol) were added *via* syringe. After 4 h, the reaction was flushed though an Iatrobeads plug with Et_2O and concentrated. The title compound was isolated as the hydrate in 75% yield (0.1123 g, 0.38 mmol) after chromatography on Iatrobeads (0-2-4-7% Et_2O/hex to 4:11:85 to 4:13:83 EtOAc/Et_2O/hex); 9:1 *syn:anti*, 99% ee. Product ratios were determined by GLC (Bodman Γ-TA column, 140 °C, 20 min; 1 °C/min gradient, 145 °C, 20 min; 1 °C/min gradient, 150 °C, 20 min 23 psi); (2*R*, 3*S*) *syn* isomer t_r = 59.9 min, (2*S*, 3*R*) *syn* isomer t_r = 62.7 min, *anti* isomers t = 64.0 min. IR (film) 3045, 2939, 1822, 1724, 1654, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 2H, ArH), 7.43 (m, 3H, ArH), 5.26 (d, *J* = 4.1 Hz, 1H, C**H**$(OH)_2$, 4.34 (dd, *J* = 4.1, 9.2 Hz, 1H, C**H**Cl), 2.77 (m, 1H, C**H**CH_3), 2.06 (s, 3H, CH_3), 1.40 (d, *J* = 7.2 Hz, 3H, CHC**H$_3$**). ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.8, 182.7, 163.6, 135.0, 131.2, 128.5, 128.0, 82.1, 70.2, 62.4, 48.3, 23.3, 11.2; HRMS (FAB) exact mass calcd for ($C_{14}H_{15}ClNO_3$) requires *m/z* 280.0744, found *m/z* 280.0744; $[\alpha_D]$ = –2.1 (c = 1.0, $CHCl_3$).