Chapter 2

Development of the First Enantioselective Organocatalytic Dipolar Cycloaddition Reaction and Enantioselective Organocatalytic *Exo*-selective Cycloadditions

I. Introduction

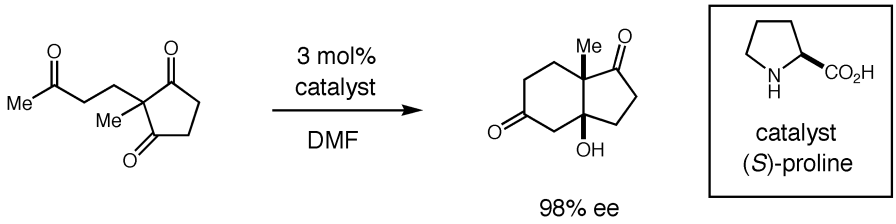
Organocatalysis

Over the last 40 years, the field of organic chemistry has witnessed tremendous growth in the importance of single enantiomer compounds and the development of methodologies for their syntheses. Accordingly, the field of enantioselective catalysis has burgeoned, with practitioners of synthetic chemistry making remarkable advances in the design of organometallic enantioselective catalysts. These catalysts have led to the development of a vast array of asymmetric catalytic transformations, including oxidation, reduction, π-bond activation, and Lewis acid-catalyzed processes.[1]

In contrast to the wealth of research into asymmetric catalytic methods facilitated by these organometallic complexes, relatively few enantioselective processes have been developed which rely upon purely organic reagents as catalysts.[2] As organometallic catalysts typically involve complexation of air- and moisture-sensitive metals to chiral ligands accessible only through multi-step synthesis, it would be desirable to employ the chiral pool directly as reaction catalysts. Indeed, given the large number of naturally occurring enantiopure chemicals, such as carbohydrates and amino acids, it would seem that enantioselective catalytic systems relying on organic molecules as catalysts would be potentially more efficient and cost-effective than their organometallic counterparts. Further, the development of new, organocatalytic protocols would offer the opportunity

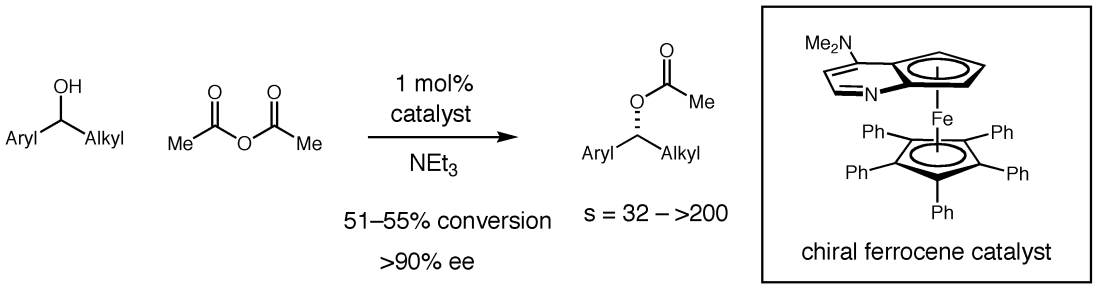
to catalyze new, previously inaccessible reactions and explore novel realms of stereocontrol.

Though purely organic enantioselective catalysts have been reported, they typically represent singular catalysts developed for singular transformations. Among the earliest reactions employing enantioselective organic catalysts are the Hajos-Parrish-Eder-Sauer-Wiechert reaction, utilizing proline to catalyze an intramolecular aldol reaction (Equation 1).[3]



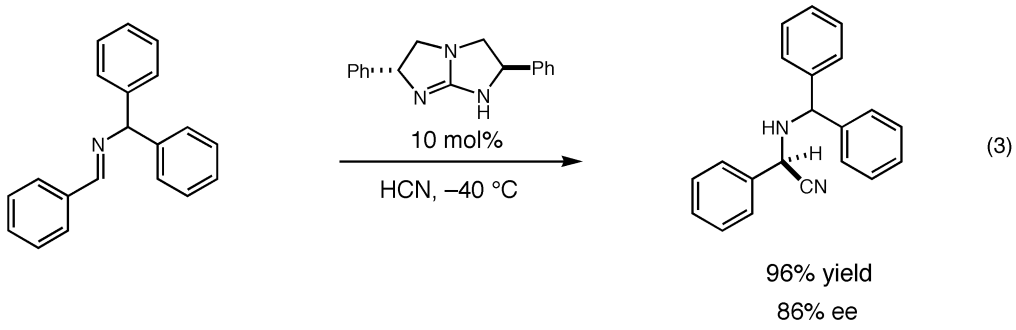
(1)

Fu has accomplished an enantioselective acyl transfer[4] to induce alcohol desymmetrization using a chiral ferrocene catalyst (Equation 2), in which the ferrocene portion of the catalyst is not the reactive site, and thus this can be considered an organic catalyst.

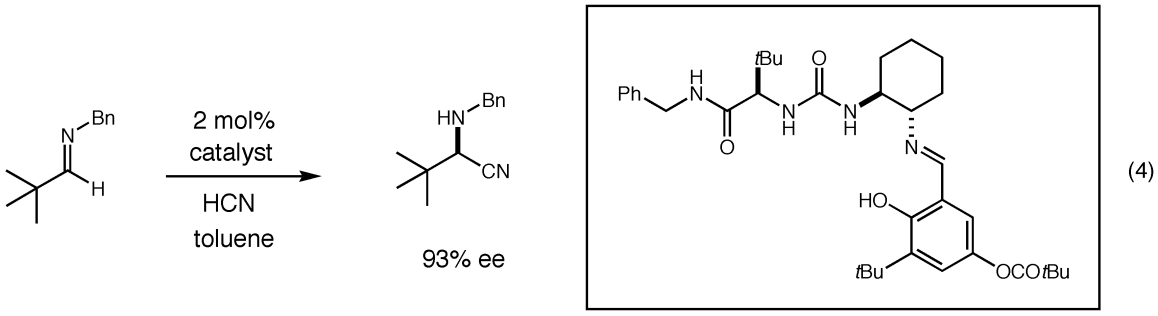


(2)

The valuable Strecker reaction has been accomplished in an enantioselective organocatalytic fashion by Corey, employing a C_2-symmetric guanidine catalyst to induce asymmetry (Equation 3).[5] Jacobsen has developed a peptide-like catalyst that also facilitates an enantioselective Strecker reaction (Equation 4).[6]

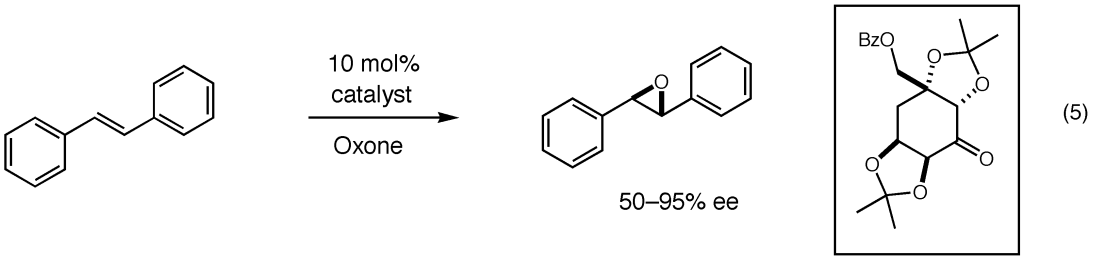


(3)



(4)

One of the most versatile approaches to olefin epoxidation has been provided by the efforts of Shi, Yang, and Denmark.[7] The three researchers have independently offered a variety of chiral ketones capable of epoxidizing a range of olefins with high yield and enantioselectivity (Equation 5).

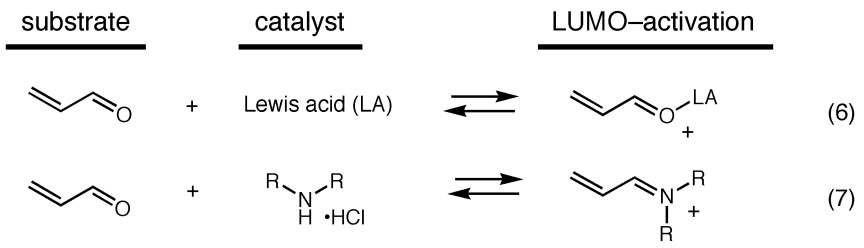


(5)

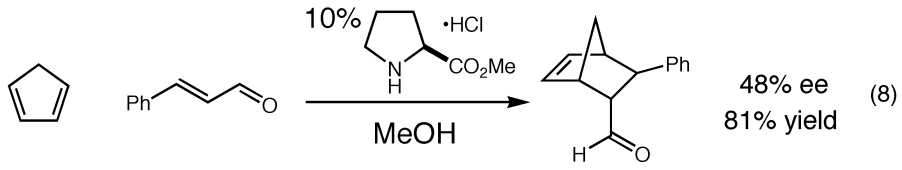
In contrast to these highly effective yet uniquely applicable organic catalysts, the most successful organometallic catalysts are each able to catalyze a broad range of transformations with high enantioselectivity.[8] Thus, the frontier of asymmetric organocatalysis must involve the development of catalytic systems that can have broad utility across a range of chemical transformations. Accordingly, our research group has become interested in developing methods for enantioselective organocatalysis that would be generally applicable across a range of reaction manifolds, both new and existing, and allow for the high levels of asymmetric induction typically observed in organometallic asymmetric catalysis.

LUMO-lowering activation

We conceived of an approach to organocatalysis that would take advantage of several design features of Lewis acid catalysis. Through the reversible formation of iminium ions from secondary amines and aldehydes (Equation 7), we sought to emulate the equilibrium dynamics and π-orbital electronics that render Lewis acid catalysis possible (Equation 6). In particular, this formation of iminium ion should allow for LUMO-lowering activation toward reaction and should afford a vehicle for catalyst turnover through iminium ion formation-hydrolysis equilibrium.



This approach to organocatalysis was first applied in our research laboratories to the development of the first enantioselective organocatalytic Diels-Alder reaction. Initial studies[9] found that proline methyl ester was a promising catalyst for the Diels-Alder cycloaddition (Equation 8), affording the cycloadducts in 48% ee and 81% yield. Importantly, in the absence of amine catalyst, no product formation was observed.

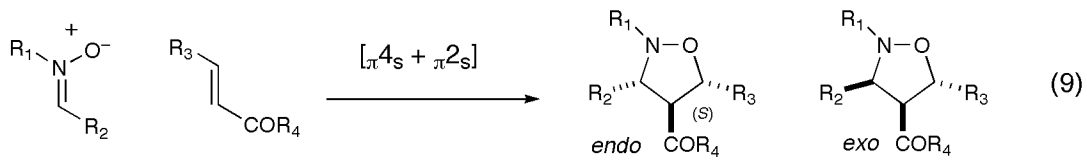


At this stage, it became apparent that our approach to organocatalysis was a reasonable one, and, in concert with the further development of this Diels-Alder reaction,[10] we sought to investigate the ability of this LUMO-lowering activation to be applied to other organic transformations.

1,3-Dipolar cycloadditions between nitrones and olefins

Another cycloadditon reaction of great importance to organic chemistry is the 1,3–dipolar cycloaddition (Equation 9) between nitrones and olefins to provide

isoxazolidines, useful synthons for the construction of biologically important amino acids, β-lactams, amino carbohydrates, and amino alkaloids.[11]



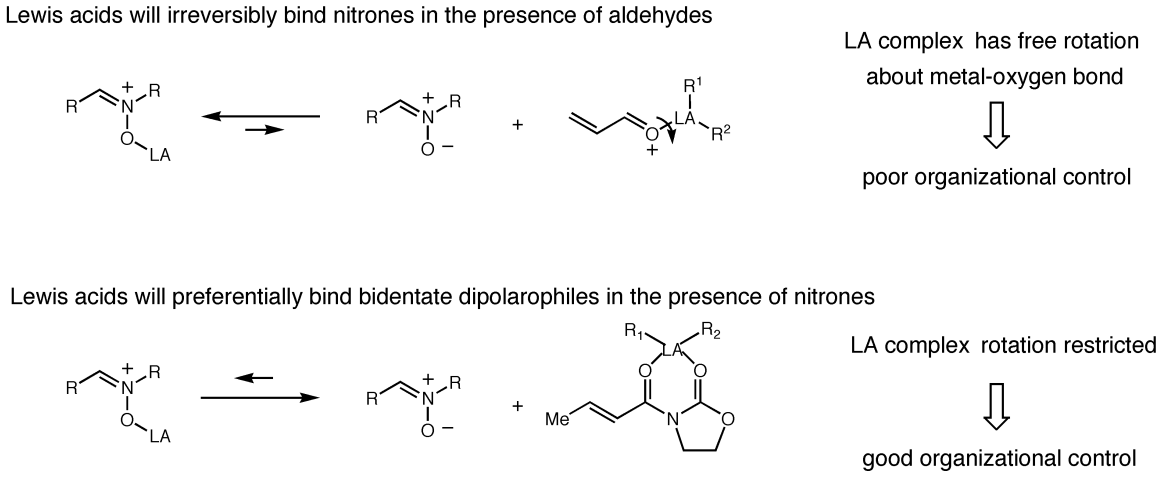
(9)

Generally, these dipolar cycloaddition reactions involve the interaction of the HOMO of a dipole with the LUMO of a dipolarophile, similar to the interaction between a diene HOMO and dienophile LUMO in the Diels-Alder reaction. Regioselectivity in the cycloaddition is controlled through electronics to form preferentially the isoxazolidines bearing the more electron withdrawing substituents of the dipolarophile at the 4-position. As with the Diels-Alder reaction, diastereoselection between *endo* and *exo* topographies is controlled, in part, through secondary orbital interactions, though these factors are relatively less significant in the dipolar cycloaddition reaction; as well, steric features of the reactive substrates and catalysts have a significant role in determining the stereochemical outcome of these cycloadditions.

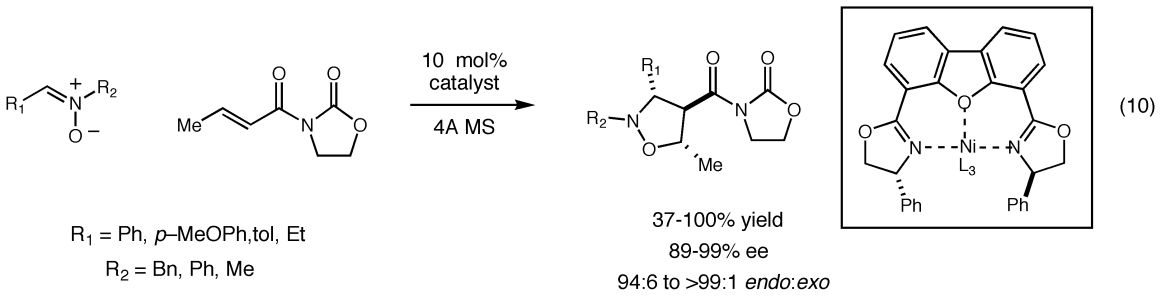
Whereas dipolar cycloaddition reactions are most commonly diastereoselective in nature, involving chiral dipoles and/or chiral dipolarophiles,[12] approaches to the enantioselective catalytic 1,3-dipolar cycloaddition reaction between nitrones and olefins have been more recently, and more infrequently, reported. Typically, these approaches utilize Lewis acids to catalyze cycloadditions between nitrones and bidentate chelating dipolarophiles;[13] the use of aldehydes and other monodentate dipolarophiles has remained an elusive, though desirable, goal. The requirement of bidentate dipolarophiles in Lewis

acid catalyzed processes arises, presumably, due to preferential coordination of Lewis acids to nitrones in the presence of monodentate carbonyls (Figure 1).

Figure 1. Lewis acid binding to nitrones



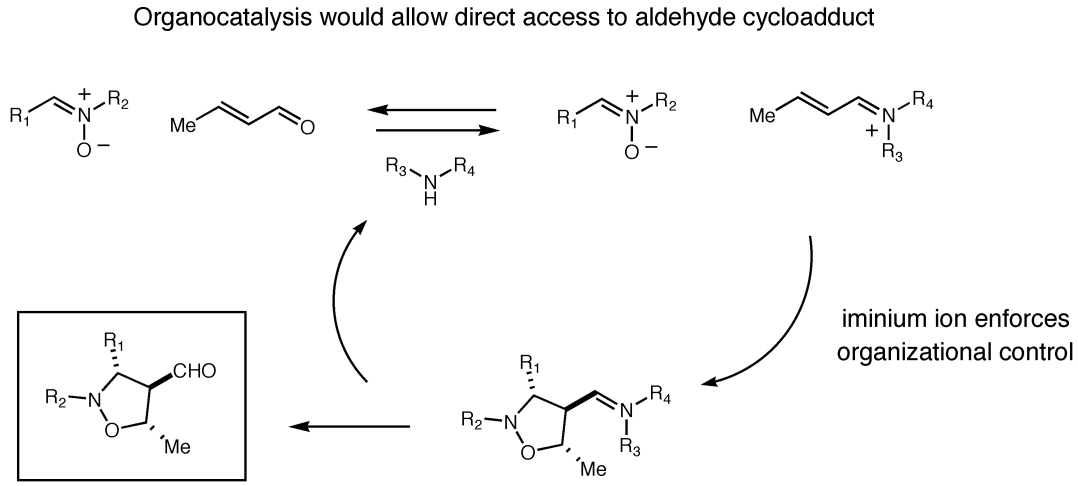
Among these Lewis acid catalyzed cyclizations employing bidentate dipolarophiles is the work of Kanemasa (Equation 10). In these reactions, high levels of enantiocontrol, diastereocontrol, and reaction efficiency are achieved in the reaction of α,β-unsaturated imides with a variety of nitrones bearing aryl and alkyl substituents, catalyzed by the aqua complex of 4,6-dibenzofurandiyl-2,2'bis(4-phenyl-oxazoline)-nickel(II) perchlorate (DBFOX/Ni) complexes. Through bidentate binding, preferential coordination of the Lewis acid to the dipolarophile rather than the nitrone is achieved.



(10)

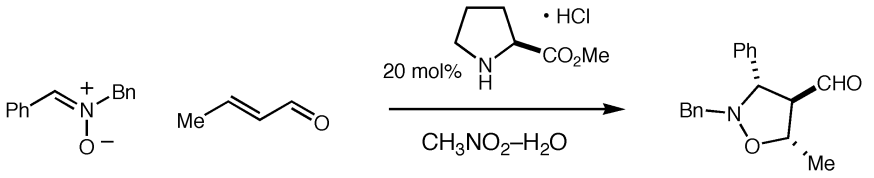
At the time that our laboratories became interested in organocatalytic approaches to the dipolar cycloaddition reaction, all reported enantioselective catalytic methods relied upon bidentate dipolarophiles and were thus unable to utilize aldehydes as substrates. In addition to the practical advantages of an organocatalytic protocol discussed above, we believed that our LUMO-lowering approach to amine catalysis would offer the ability to use monodentate carbonyls directly in a dipolar cycloaddition reaction, given that the amine catalysts should have no tendency to associate with nitrones. Further, we proposed that the reactive iminium ion intermediate should possess sufficient conformational rigidity to allow for excellent organizational control in the transition state leading to the isoxazolidine products (Scheme 1).[14,15]

Scheme 1. Proposed catalytic cycle for organocatalytic dipolar cycloaddition



Initial optimization of the enantioselective organocatalytic dipolar cycloaddition[16]

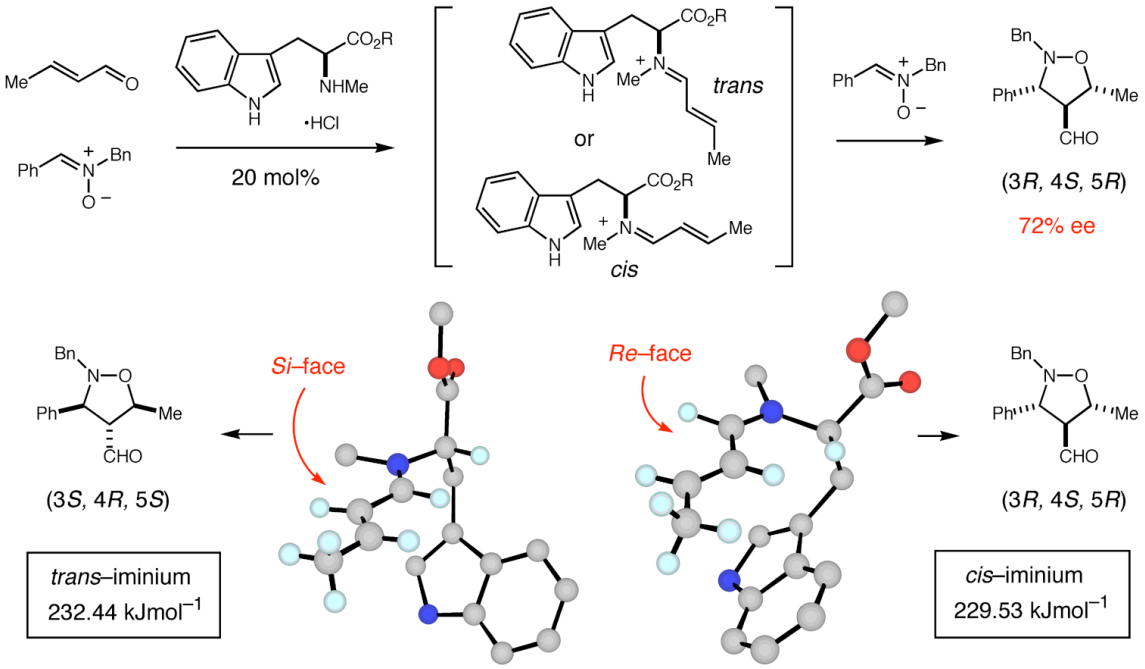
Initial investigations determined that, as with the Diels-Alder reaction, proline methyl ester showed promise as a catalyst for the 1,3-dipolar cycloaddition (Equation 11).



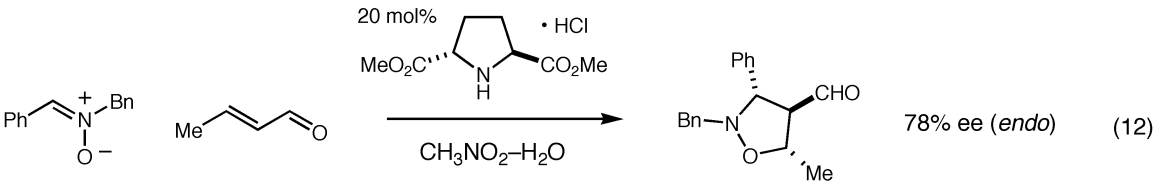
43% ee (*endo*) (11)

Further optimization determined that the ability of the amine catalyst to impart control over iminium ion geometry was crucial to achieving high levels of enantiocontrol,[17] and established that the tryptohan-serived catalyst in Figure 2 performed better than proline in these reactions. Semi-empirical calculations[18] indicated that only a small energetic difference could be expected between the two iminium ion isomers using this tryptophan-derived catalyst and, further, that these iminium ion isomers each led to formation of a different isoxazolidine enantiomer (Figure 2).

Figure 2. Iminium ion geometry control affects enantioselectivity



In an effort to control iminium ion geometry and thereby enforce greater enantiocontrol, a C_2-symmetric proline derivative was utilized (Equation 12). This catalyst, which precluded the issue of iminium ion geometry, afforded markedly better levels of enantioselectivity than did the proline methyl ester (Equation 11), indicating that control of iminium ion geometry was an important feature in an amine catalyst.



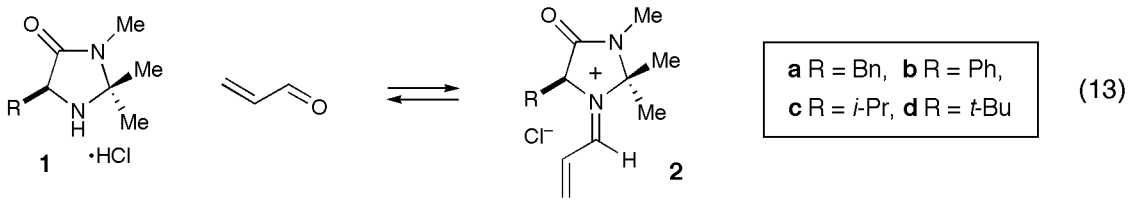
(12)

Still, stereocontrol remained less than optimal, and so at this stage it became apparent that a new catalyst system was required, one that would seek to control iminium ion geometry produced during the course of the reaction in an effort to enforce high levels of enantiocontrol in the reaction. As well, an improved catalyst system would be more readily available from the chiral pool, in keeping with the practical goals of developing an organocatalytic system.

II. Results and Discussion

Catalyst design and reaction optimization

To achieve better iminium geometry control and increase the enantioselectivity of the organocatalytic [3+2] addition, our laboratory became interested in the imidazolidinone catalysts **1**.[19] We believed that these cyclic secondary amines would have the advantage of enforcing strict iminium ion geometry control through the presence of the geminal–dimethyl moiety with the substituent R creating suitable enantiofacial bias (Equation 13).

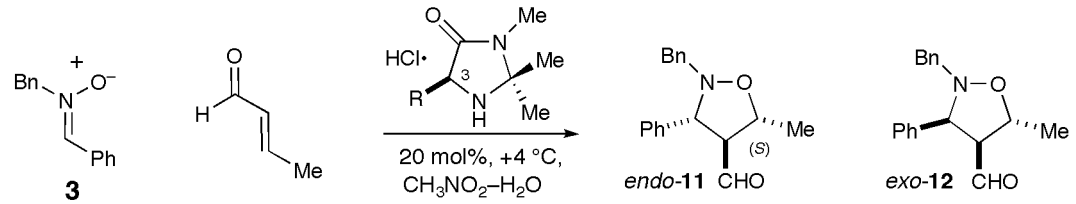


(13)

In tandem with the development in our group of the first enantioselective organocatalytic Diels-Alder reaction through use of this imidazolidinone framework we sought to apply this catalyst to the organocatalytic enantioselective dipolar cycloaddition

reaction. To this end, our amine-catalysis strategy was evaluated using *N*-benzylidenebenzylamine *N*-oxide **3** with (*E*)–crotonaldehyde and a series of chiral imidazolidinone-HCl salts (**4**–**10**) (Table 1).

Table 1. Effect of catalyst structure on the dipolar cycloaddition between crotonaldehyde and nitrone **3**[c]



entry	R–(catalyst)	Time (h)	% yield	*endo*:*exo*	% ee (*endo*)[a,b]
1	CH_2Ph (**4**)	72	70	88:12	93
2	Ph (**5**)	70	73	78:22	44
3	*i*-Pr (**6**)	60	68	58:32	42
4	*t*-Bu (**7**)	70	45	33:66	20
5	CH_2-2-napthyl (**8**)	48	62	78:22	86
6	$CH_2C_6H_4OMe$-4 (**9**)	48	77	79:21	89
7	CH_2CH_2Ph (**10**)	48	72	50:50	69

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$.
[b] Absolute and relative configurations assigned by chemical correlation or by analogy (Experimental Section).
[c] Research conducted with Wendy S. Jen.

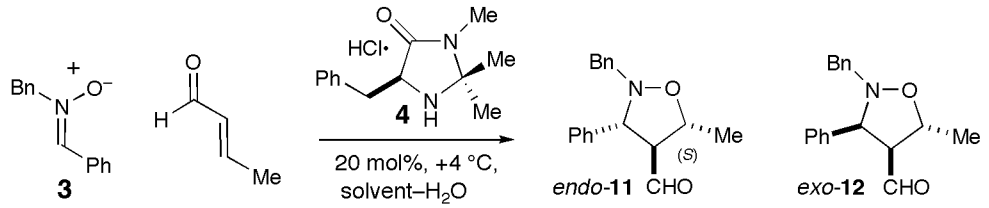
As hoped, this catalyst architecture indeed provided access to highly enantioenriched isoxazolidines **11** and **12**, with a variety of imidazolidinones bearing differing substituents at the stereogenic position successfuly catalyzing the dipolar cycloaddition (Table 1, entries 1–7, 45–77% yield, 20–93 % ee), in CH_3NO_2-H_2O at +4 °C. From this investigation it was determined that those catalysts incorporating benzylic substituents at the C(3) position of the catalyst framework provide the highest levels of enantiocontrol. (**4**, R = CH_2Ph, 93% ee; **8**, R = CH_2-2-naphthyl, 86% ee; **9**, R = $CH_2C_6H_4OMe$-4, 89% ee). In contrast, the homobenzylic and phenyl-substituted

catalysts, as well as the non-aromatic catalyst afforded much lower enantioselectivity (**10**, R = CH_2CH_2Ph, 69% ee; **5**, R = Ph, 44% ee; **6**, R = *i*Pr, 42% ee, **7**, R = *t*Bu, 20% ee), indicating not only that an aromatic substituent is required, but, in particular, one that is benzylic, an observation in accord with our proposed stereochemical rationale for these and other organocatalytic LUMO-lowering methodologies (*vide infra*).

Having established that the phenylalanine-derived imidazolidinone **4** afforded the highest levels of diastereo- and enantiocontrol in this dipolar cycloaddition reaction, we next sought to investigate the influence of various reaction parameters (solvent, reagent molarity, co-catalyst) on the outcome of this reaction.

A survey of solvents quickly established that nitromethane afforded the highest levels of both reactivity and diastereoselectivity when employed in the reaction of *N*-benzylidenebenzylamine *N*-oxide **3** with (*E*)-crotonaldehyde in the presence of the benzyl imidazolidinone-HCl salt **4** (Table 2).

Table 2. Effect of solvent on the dipolar cycloaddition reaction between crotonaldehyde and nitrone **3**



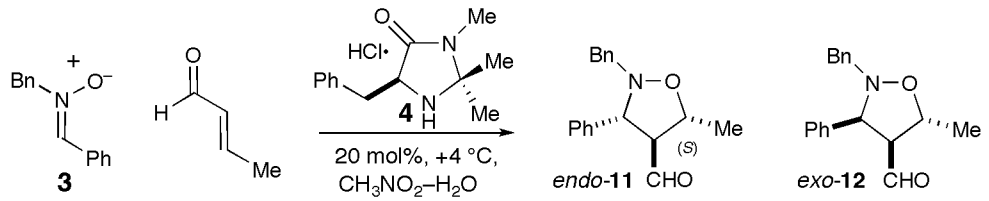
entry	Solvent	Dielectric Constant	Time (h)	% Conversion	*endo*:*exo*[a]
1	toluene	2.4	39	9	50:50
2	EtOAc	6.1	39	30	67:33
3	THF	7.6	39	31	67:33
4	CH_2Cl_2	9.1	39	39	50:50
5	acetone	21.0	39	37	67:33
6	MeOH	32.6	39	--	--
7	CH_3NO_2	36.0	39	70	88:12
8	CH_3CN	37.5	39	60	88:12
9	H_2O	80.1	39	--	--

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$.

As shown in Table 2, the rate of this reaction generally increases as a function of the dielectric constant of the solvent used. We therefore hypothesized that the rate of formation of iminium ion is important to the overall rate of this process and that solvents with higher dielectric constants are more able to stabilize charged intermediates, thereby facilitating formation of iminium ion. It is for these reasons that we expected that the presence of water in the reaction medium might aid in increasing the rate of the reaction by increasing the overall dielectric constant of the solvent medium. Indeed, as revealed in Table 3, the reaction of *N*-benzylidenebenzylamine *N*-oxide **3** with (*E*)-crotonaldehyde in the presence of the benzyl imidazolidinone-HCl salt **4** in CH_3NO_2 performs best when three equivalents of water are added to the reaction mixture. Notably, large excesses of

water, while not further improving the reaction efficiency, do result in a degradation of diastereoselectivity, and in the limiting case of running the reaction in water, no product formation is observed (Table 2, entry 9).

Table 3. Effect of amount of water on the dipolar cycloaddition of crotonaldehyde with nitrone **3**

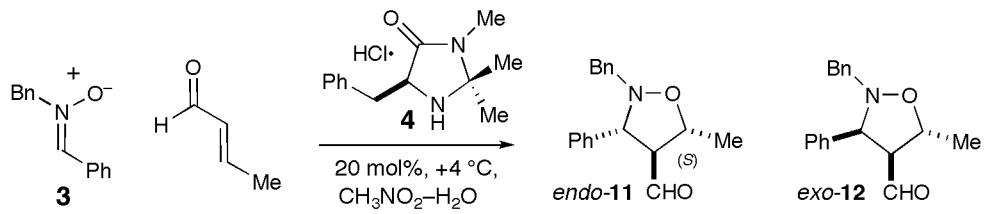


entry	H_2O (equiv.)	Time (h)	% Conversion	*endo*:*exo*[a]
1	0	12	23	93:7
2	1.5	12	48	88:12
3	3	12	70	88:12
4	9	12	74	86:14
5	12	12	73	83:17

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$.

In an effort to increase the rate of this organocatalyzed process, an investigation into the importance of molarity in the reaction of *N*-benzylidenebenzylamine *N*-oxide **3** with (*E*)-crotonaldehyde in the presence of the benzyl imidazolidinone-HCl salt **4** in CH_3NO_2-H_2O at +4 °C was conducted (Table 4).

Table 4. Effect of reagent molarity on the dipolar cycloaddition of crotonaldehyde with nitrone **3**



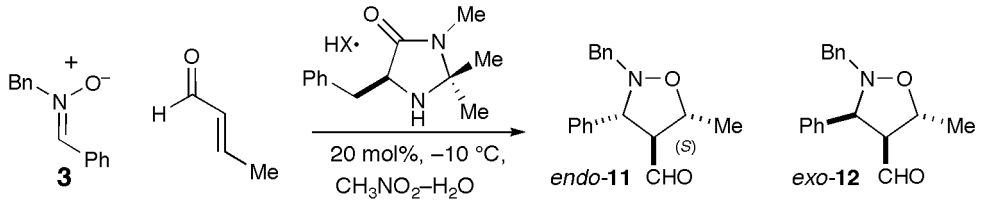
entry	conc (M)	Time (h)	% Conversion	*endo*:*exo*	% ee *(endo)*[a]
1	1.0	39	67	80:20	94
2	0.5	39	75	80:20	94
3	0.3	39	75	83:17	94
4	0.1	39	70	88:12	93
5	0.05	39	16	88:12	83
6	0.01	39	16	90:10	85

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$.

As expected, the efficiency of the transformation increased with increasing concentration relative to nitrone **3**. However, at molarities above 0.5M, the level of conversion declines, due to undesired decomposition of nitrone **3** that was also observed at higher temperatures. Further, optimal diastereo- and enantioselectivity were observed at 0.1M, and this molarity was employed in further investigations into the importance of the co-catalyst.

As discussed, our optimization studies indicated that accelerating the rate of iminium ion formation affected the rate of the overall cycloaddition. At this stage, given that the cycloaddition, though highly stereoeselective, formed product at a relatively low rate, variation in the Brønsted acid component of the benzyl imidazolidinone catalyst was examined (Table 5).

Table 5. Effect of the Brønsted acid co–catalyst on the dipolar cycloaddition between crotonaldehyde and nitrone **3**



entry	HX co-catalyst	Time (h)	% yield	*endo*:*exo*	% ee (*endo*)[a]
1	HCl (**4**)	108	70	88:12	95
2	TfOH (**13**)	101	88	89:11	90
3	TFA (**14**)	80	65	72:28	86
4	HBr (**15**)	80	77	94:6	93
5	$HClO_4$ (**16**)	80	86	94:6	90
6	$HClO_4$ (**16**)	100	98	94:6	94[b]

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$. [b] Reaction performed at –20 °C

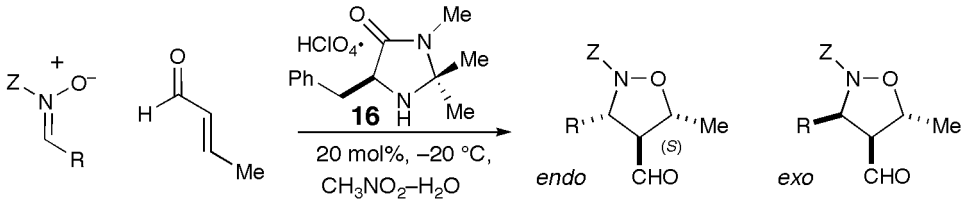
We expected that use of increasingly acidic co-catalysts would allow for faster iminium ion formation and thus that these co-catalysts would mediate faster dipolar cycloaddition reactions. A number of benzyl imidazolidinone acid salts were found to catalyze the formation of isoxazolidine **11** in good yield and in greater than 86% ee (entries 1–6). An enantioselectivity/temperature profile documents that optimal stereocontrol and reaction efficiency are achieved at –10 °C with catalysts **4**, **13**–**15** (entries 1–4), while the benzyl imidazolidinone-$HClO_4$ salt **16** is most effective at –20 °C (entry 6). In accord with our hypothesis, we believe that the observed variation in enantioselectivity as a function of co-catalyst can be attributed to the increased rate of iminium formation in the presence of the more acidic co-catalysts; with higher reactivity and greater reaction efficiency, the salts involving the more acidic Brønsted acid component can be used at lower temperatures, affording higher enantioselectivity as well

as decreased nitrone decomposition (*vide supra*), thereby providing higher isolated yields of the isoxazolidines. The superior levels of asymmetric induction and diastereocontrol exhibited by the $HClO_4$ salt **16** to afford isoxazolidine **11** in 94% ee, 94:6 dr, and 98% yield (20 mol% catalyst, –20 °C) prompted us to select this catalyst for exploration of the scope of the dipolar cycloaddition.

Substrate scope

With these optimized conditions, the scope of the organocatalytic enantioselective 1,3-dipolar cycloaddition reaction with respect to the nitrone component was investigated. As revealed in Table 6, the reaction appears quite general with regard to the nitrone structure (entries 1–9, 63–98% yield, 92:8 to 98:2 *endo*:*exo*, 91–99% ee). Variation in the *N*-alkyl group (R = Me, Bn, allyl, entries 1–3) is possible without loss in enantioselectivity (*endo* 94–99% ee). As revealed with 4-chlorophenyl- and 4-methoxy-substituted nitrones (entries 4–6), the reaction is tolerant to a range of aromatic substituents on the dipole (76–93% yield, 92:8 to 98:2 *endo*:*exo*, 91–95% ee). Moreover, excellent levels of diastereo- and enantioselectivity can be achieved with alkyl–substituted nitrones (entry 9, 96:4 *endo*:*exo*, 99% ee). To demonstrate the preparative utility of this process, the addition of nitrone **3** to crotonaldehyde was performed on a 25 mmol scale with catalyst **16** to provide the isoxazolidine product in high yield and enantioselectivity (entry 1, 94% ee, 98% yield).

Table 6. Organocatalyzed dipolar cycloadditions between representative nitrones and crotonaldehyde

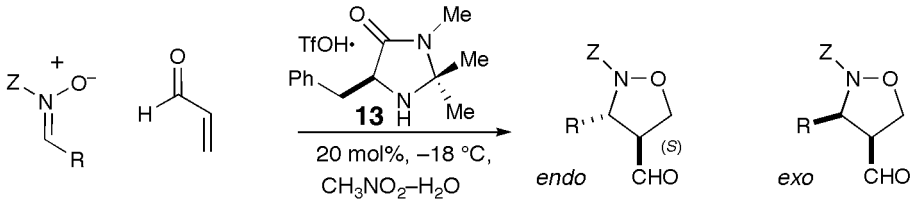


entry	Z	R	% yield	*endo*:*exo*	% ee (*endo*)[a,b]
1	Bn	Ph	98	94:6	94
2[c]	Allyl	Ph	73	93:7	98
3[c]	Me	Ph	66	95:5	99
4	Bn	C_6H_4Cl-4	78	92:8	95
5	Me	C_6H_4Cl-4	76	93:7	94
6	Bn	C_6H_4OMe-4	93	98:2	91
7	Me	C_6H_4Me-4	82	93:7	97
8	Bn	2-naph	98	95:5	93
9	Bn	*c*-hex	63	96:4	99

[a] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$. [b] Absolute and relative configurations assigned by chemical correlation or by analogy (Experimental section). [c] Reaction conducted by Wendy S. Jen.

A simple extension of the scope of the organocatalytic 1,3-dipolar cycloaddition involved variation of the dipolarophile component of the reaction, with representative nitrones reacting with acrolein to afford the isoxazolidine products under the previously optimized reaction conditions (Table 7), further establishing the generality of this process.[20]

Table 7. Organocatalyzed dipolar cycloadditions between representative nitrones and acrolein



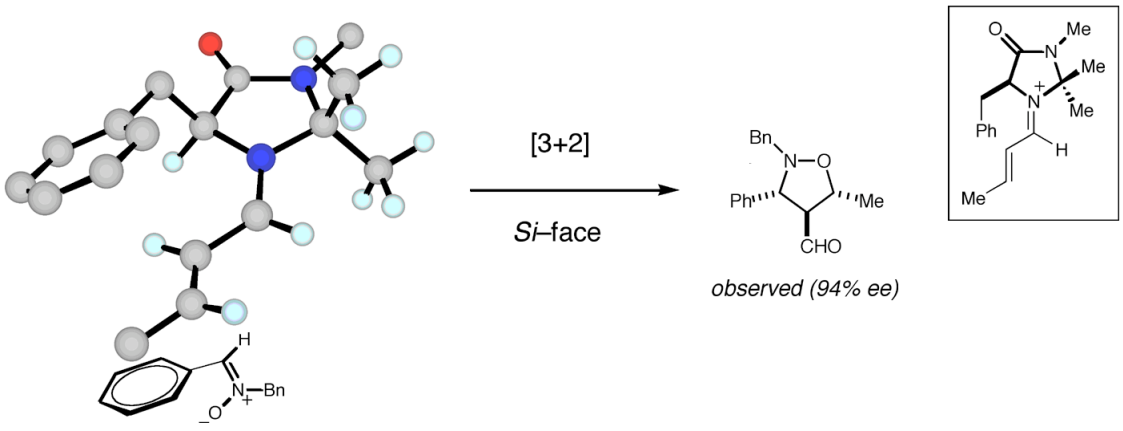
entry[a]	Z	R	% yield	*endo*:*exo*	% ee (*endo*)[b,c]
1[d]	Bn	Ph	72	81:19	90
2	Bn	Ph	80	86:14	92
3	Bn	C_6H_4Me-4	80	85:15	90
4	Bn	C_6H_4Cl-4	80	80:20	91
5	Bn	2-naph	82	81:19	90
6	Bn	C_6H_4OMe-4	83	91:9	90

[a] Reactions conducted by Wendy S. Jen. [b] Product ratios determined by HPLC using a Chiralcel OD–H column after reduction of the formyl group with $NaBH_4$. [c] Absolute and relative configurations assigned by chemical correlation or by analogy (Experimental section). [d] Reaction donducted with catalyst 16.

Stereochemical rationale

In keeping with the thermondynamics of dipolar cycloadditions, all products of these cyclizations were the *endo* isomers. Further, the (3*R*, 4*S*, 5*R*) enantiomer was observed with the crotonaldehyde reactions. Importantly, this sense of asymmetric induction and diastereoselectivity are consistent with the presence of an (*E*)-iminium isomer (Scheme 2).

Scheme 2. Calculated (MM3)[21] iminium isomer predicts stereochemistry of cycloaddition



As predicted, the formation of the (*E*)-iminium isomer and the position of the benzyl group on the catalyst framework effectively promote cycloaddition from the *si*-face of the dipolarophile. Indeed, the proximity of the benzyl group to the olefin of the iminium ion indicates the potential for an attractive cation-π interaction, allowing for close association of the aromatic substituent with the olefin, effectively shielding the *re*-face of the iminium ion. Furthermore, cycloaddition through the *endo* topography effectively alleviates nonbonding interactions between the nitrone phenyl group and the neopentyl methyl substituent on the catalyst.

Limitations

Despite the generality of this catalyst system with respect to nitrone architecture and, to a lesser extent, with regard to the nature of the dipolarophile in promoting the dipolar cyloaddition, these reactions were plagued by one central limitation: long reaction times. Of course, given the high selectivity of these reactions and the lack of reported

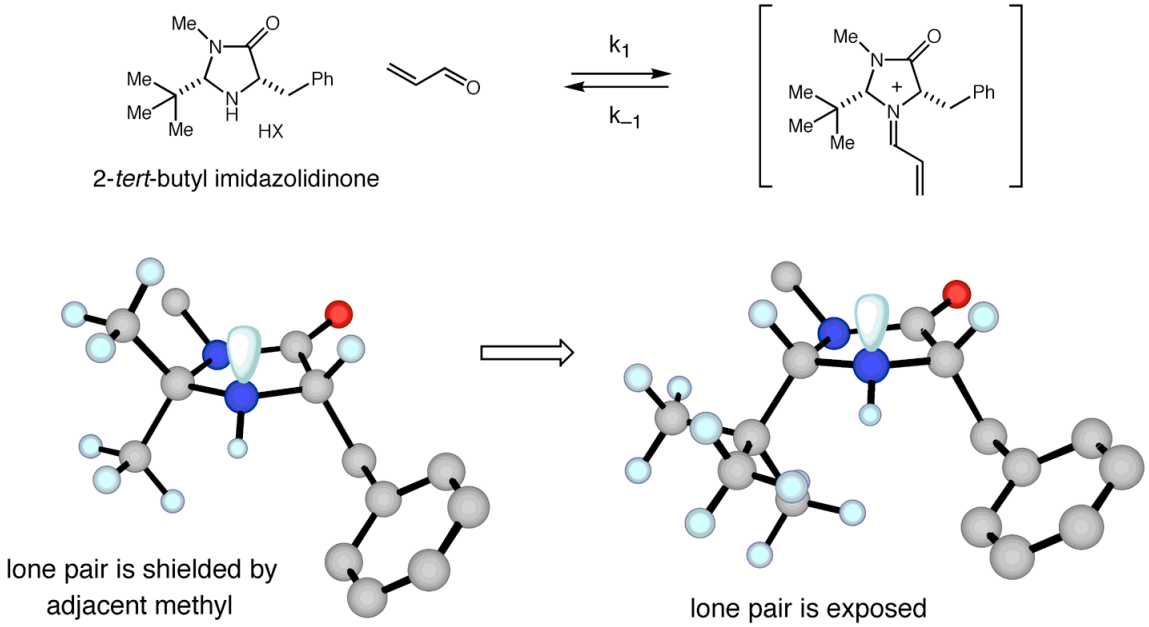
alternatives to this methodology, long reaction times may be of only secondary significance. Still, the relatively low reactivity of this catalyst system was responsible for the relatively limited scope of the cycloaddition with respect to dipolarophile. More sterically encumbered aldehydes (for example, hexenal) proved unreactive in this process, presumably due to the nonbonding interactions created by their presence as part of a catalyst-substrate iminium complex, and the concordant difficulty in formation of this complex.

Second-generation imidazolidinone catalyst design and implementation

To this end, and because other methodologies being concurrently developed in our research group displayed a similarly limited reactivity with the dimethyl imidazolidinone catalysts such as **4**, we sought to design a more reactive second-generation catalyst. Among the goals of a second–generation catalyst were (1) to increase reaction rates by allowing for more rapid iminium ion formation, (2) to increase iminium ion geometry control, given the apparent role of iminium ion geometry in determining enantiofacial bias, and (3) to further increase coverage of the blocked enantioface or decrease coverage of the reactive iminium enantioface.

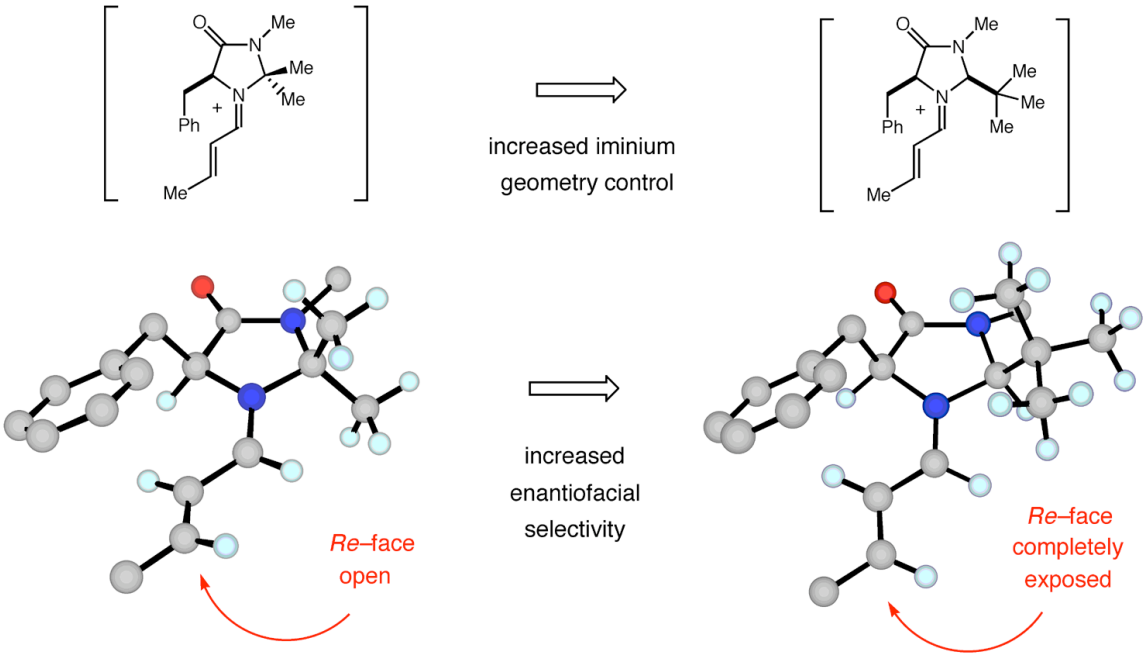
The proposed 2-*tert*-butyl imidazolidione catalyst (Scheme 3) seemed a promising choice toward fulfilling these criteria.[22] As can be seen in Scheme 3, the *cis* relationship between the *tert*-butyl substituent and the benzyl group should allow the nitrogen atom of the catalyst to be more exposed, thereby potentially allowing a faster rate of iminium formation.

Scheme 3. Second-generation catalyst should afford higher reaction rates



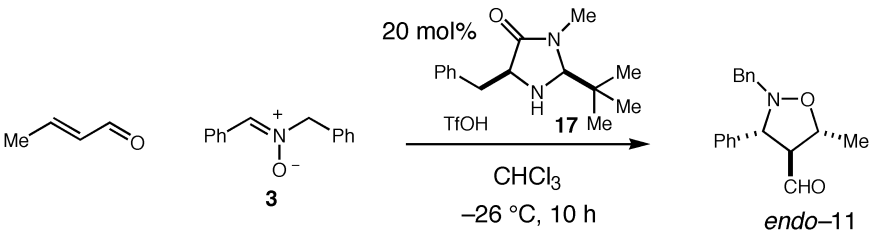
Further, the presence of the *tert*-butyl substituent should effectively enforce iminium ion geometry control (Scheme 4). Moreover, this large substituent should provide enhanced coverage of the undesired enantioface, while the absence of the methyl substituent from first-generation dimethyl imidazolidinone catalyst should allow greater exposure of the reactive enantioface, increasing enantioselectivity and also increasing the rate of the cycloaddition step.

Scheme 4. Second-generation catalyst should afford increased enantioselectivity



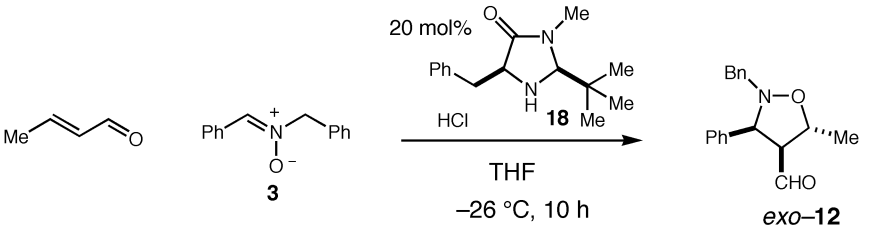
The power of this second-generation catalyst was aptly demonstrated in the context of the 1,3-dipolar cycloaddition of nitrone **3** with crotonaldehyde, catalyzed by 2-*tert*-butyl imidazolidine **17** (Equation 14, 98% ee, 96% yield, >99:1 *endo*:*exo*). Importantly, this reaction is not only higher yielding and more enantio- and diastereoselective than the analogous reaction performed using the first generation benzyl imidazolidinone **16** (Table 5, entry 6), in complete accord with our predictions, but reaction times have been reduced from 100 hours to 10 hours, making the process one that can be truly useful in both academic and industrial settings. With this new catalyst system, extension of the scope of the enantioselective organocatalytic dipolar

cycloaddition reaction to more sterically encumbered dipolarophiles and nitrones should be possible.



(14)

During the course of investigations using this second–generation catalyst, it became apparent that a simple alteration to the reaction medium could result in a turnover in diastereoselectivity to afford, selectively, the *exo* isomer, an unprecedented result for 1,3-dipolar cycladditions employing nitrones. In particular, when the reaction is performed using THF as solvent and the HCl co-catalyst, the *exo* isoxazolidine **12** is produced (Equation 15, 97% yield, 80:20 *exo*:*endo*, *exo*: 94% ee).

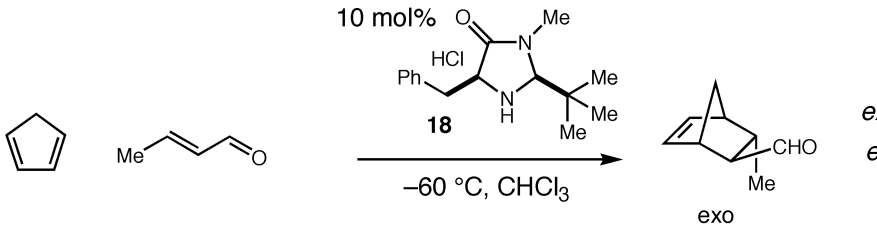


(15)

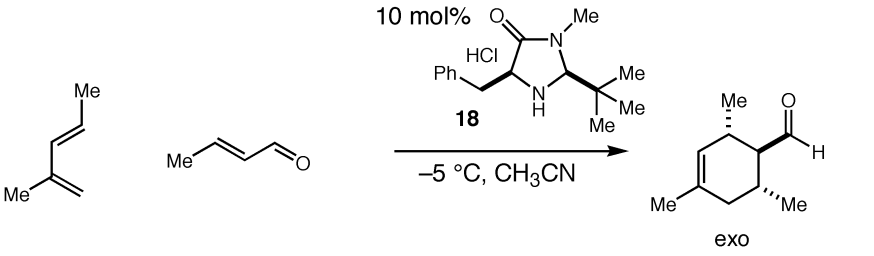
The definitive explanation for this finding will require further experimentation and computational modeling. Specifically, given the crucial role played by the reaction medium (solvent and co-catalyst), it is possible either that solvent effects help to stabilize the *exo* topography of the concerted cycloaddition transition state or that alteration of

solvent leads to a completely different reaction mechanism. If both diastereomers arise from concerted dipolar cycloaddition mechanisms, then calculations including solvent effects that model the *endo* and *exo* transition states should display high energetic differences for the two topographies. In contrast, should those calculations not show a large difference, the possibility that an entirely different reaction manifold is responsible for formation of the *exo* isomers must be examined. A possible alternative mechanism could involve stepwise heteroconjugate addition of the nitrone oxygen to the iminium ion, followed by intramolecular trapping of the resultant enol to complete formation of the isoxazolidine.[23]

To evaluate the extent to which these extraordinary findings could be applied toward other cycloadditons, the Diels-Alder reaction was investigated, as the development of a general *exo*-selective Diels-Alder reaction would not only be the first of its kind but also allow rapid access to a host of natural product and pharmaceutical architectures previously accessible only by other, less efficient means. We were delighted to see that the second-generation catalyst indeed allowed access to the *exo* Diels-Alder adducts deriving both from cyclopentadiene (Equation 16) and from an acyclic diene as well (Equation 17). A simple modification of the catalyst has enabled the development of a general strategy toward the enantioselective organocatalytic *exo*-selective Diels-Alder reaction,[24] and, as with the *exo*-selective dipolar cycloaddition reaction, full mechanistic understanding of this process will require further calculations and experimentation.



(16)



(17)

III. Conclusion

The principles of LUMO-lowering organocatalysis have enabled the development of the first enantioselective catalytic 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated aldehydes. Optimization studies revealed that imidazolidinone catalysts, used in conjunction with highly acidic Brønsted acid co–catalysts, can effect the dipolar cycloaddition to afford isoxazolidines in high yield, enantioselectivity, and diastereoselectivity. Further, a range of nitrones are amenable to the cyclization, and both substituted and unsubstituted aldehydes perform well in the reaction. Development of a second-generation imidazolidinone catalyst has been reported, and this amine effectively catalyzes the *endo*-selective dipolar cycloaddition with higher yield and stereoselectivity than the first-generation catalyst. Additionally, under modified conditions, the second-generation imidazolidinone is able to catalyze *exo*-selective dipolar cycloaddition reactions and *exo*-selective Diels-Alder reactions with high levels of asymmetric induction.

IV. Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[25] Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[26] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by florescence quenching or $KMnO_4$ stain.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 (400 MHz and 100 MHz, respectively), Bruker DRX-500 (500 MHz and 125 MHz, respectively), Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported with chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical Rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25°C). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Gas Chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex -TA (30 m x 0.25 mm) column. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at

254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt (13). Prepared from the hydrochloride salt **4**[27] by treatment with saturated aq. $NaHCO_3$ (100 mL) and extraction of the free amine with $CHCl_3$ (3 x 100 mL). The solution was dried over Na_2SO_4, filtered, and concentrated. The residue was taken up in Et_2O and trifluoromethanesulfonic acid was added to precipitate **13**. The precipitate was recrystallized from 2-propanol to provide the title compound as colorless crystals. IR (CH_2Cl_2) 2363, 1730, 1290, 1182 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 10.35 (br s, 1H, $^+NH_2$), 9.27 (br s, 1H, $^+NH_2$), 7.19–7.38 (m, 5H, C_6H_5), 4.67 (br d, J = 8.6 Hz, 1H, COCH), 3.30 (dd, J = 3.3, 15.4 Hz, 1H, $CH_2C_6H_5$), 2.93 (dd, J = 11.0, 15.4 Hz, 1H, $CH_2C_6H_5$), 2.79 (s, 3H, CH_3NCO), 1.62 (s, 3H, CH_3), 1.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.6, 129.7, 129.3, 127.8, 77.5, 57.9, 34.4, 25.7, 24.6, 22.5; LRMS (CI) *m/z* 219 $(MH)^+$; HRMS (CI) exact mass calcd for $(C_{17}H_{19}N_2O)^+$ requires *m/z* 219.1497, found *m/z* 219.1497; $[\alpha]_D$ = –58.8° (c = 1.0, CH_3OH).

(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one trifluoroacetic acid salt (14). Prepared from the hydrochloride salt **4** by treatment with saturated aq. $NaHCO_3$ (100 mL) and extraction of the free amine with $CHCl_3$ (3 x 100 mL). The solution was dried over Na_2SO_4, filtered, and concentrated. The residue was taken up in Et_2O and trifluoroacetic acid was added to precipitate the title compound as white crystals. IR (film) 3437, 2920, 2742, 2518, 2418, 1722, 1653, 1491, 1429, 1398, 1274, 1182, 1074, 834, 695 cm^{-1}; ^1H

NMR (300 MHz, d_6-DMSO) □ 9.97 (br s, 1H, $^{+}$N**H**$_2$), 7.22–7.37 (m, 5H, C$_6$**H**$_5$), 4.53 (br d, J = 7.1 Hz, 1H, COC**H**), 3.27 (dd, J = 3.3, 14.8 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.00 (dd, J = 10.2, 14.8 Hz, 1H, C**H**$_2$C$_6$H$_5$), 2.76 (s, 3H, C**H**$_3$NCO), 1.59 (s, 3H, C**H**$_3$), 1.46 (s, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 167.6, 136.9, 129.8, 129.1, 127.5, 77.2, 58.0, 34.7, 25.6, 24.7, 22.8; LRMS (EI) m/z 218 $(M)^+$; HRMS (EI) exact mass calcd for $(C_{17}H_{19}N_2O)^+$ requires m/z 219.1497, found m/z 219.1494; $[□]_D$ = –63.2° (c = 1.0, $CHCl_3$).

(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrobromide (15). Prepared from the hydrochloride salt **4** by treatment with saturated aq. $NaHCO_3$ (100 mL) and extraction of the free amine with $CHCl_3$ (3 x 100 mL). The solution was dried over Na_2SO_4, filtered, and concentrated. The residue was taken up in Et_2O and 48% hydrobromic acid was added to precipitate the title compound as white crystals. IR (film) 3414, 2912, 2711, 2557, 1707, 1607, 1390, 1274, 1197, 1159, 1058, 989, 703 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) □ 10.41 (brs, 1H, $^{+}$N**H**$_2$), 9.69 (br s, 1H, $^{+}$N**H**$_2$), 7.24–7.43 (m, 5H, C$_6$**H**$_5$), 4.69 (br d, J = 7.1 Hz, 1H, COC**H**), 3.28 (dd, J = 3.0, 15.1 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.15 (dd, J = 10.4, 14.8 Hz, 1H, C**H**$_2$C$_6$H$_5$), 2.77 (s, 3H, C**H**$_3$NCO), 1.67 (s, 3H, C**H**$_3$), 1.49 (s, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 166.8, 136.7, 129.9, 129.2, 127.7, 77.6, 58.1, 33.9, 25.8, 24.5, 22.6; LRMS (EI) m/z 218 $(M)^+$; HRMS (EI) exact mass calcd for $(C_{17}H_{18}N_2O)^+$ requires m/z 218.1419, found m/z 218.1420; $[□]_D$ = –21.3 (c = 1.0, $CHCl_3$).

(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (16). Prepared from the hydrochloride salt **4** by treatment with saturated aq. $NaHCO_3$ (100 mL)

and extraction of the free amine with $CHCl_3$ (3 x 100 mL). The solution was dried over Na_2SO_4, filtered, and concentrated. The residue was taken up in Et_2O and perchloric acid was added to precipitate the title compound as white crystals. IR (film) 3514, 3059, 2927, 2850, 1707, 1607, 1398, 1267, 1097, 927. 703 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 10.37 (br s, 1H, $^+NH_2$), 9.25 (br s, 1H, $^+NH_2$), 7.26–7.43 (m, 5H, C_6H_5), 4.66 (br d, J = 8.8 Hz, 1H, COCH), 3.33 (dd, J = 3.3, 15.1 Hz, 1H, $CH_2C_6H_5$), 2.94 (dd, J = 10.7, 15.1 Hz, 1H, $CH_2C_6H_5$), 2.78 (s, 3H, CH_3NCO), 1.62 (s, 3H, CH_3), 1.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.5, 129.7, 129.3, 127.8, 77.6, 58.0, 34.4, 25.7, 24.6, 22.5; LRMS (EI) m/z 218 $(M)^+$; HRMS (CI) exact mass calcd for $(C_{17}H_{18}NO_2)^+$ requires m/z 218.1419, found m/z 218.1428; $[\alpha]_D$ = –61.1 (c = 1.0, CH_3NO_2).

General Procedure A. A flask containing nitrone and imidizolidinone catalyst was charged with CH_3NO_2, then treated with the appropriate amount of H_2O. After cooling the solution to the desired temperature, α,β unsaturated aldehyde was added dropwise to the flask. After the appropriate reaction time, the resulting solution was passed through a silica gel column with ethyl acetate. Removal of volatiles resulted in an oily residue, which was purified by silica gel chromatography to afford the title compounds.

General Procedure B. A flask containing nitrone and imidizolidinone catalyst was charged with CH_3NO_2, then treated with the appropriate amount of H_2O. After cooling the solution to the desired temperature, α,β-unsaturated aldehyde was added

dropwise to the flask. Additional aldehyde was added to the reaction mixture at 24 h intervals until the specified reaction time was reached. The resulting solution was passed through a silica gel column with ethyl acetate. Removal of volatiles resulted in an oily residue, which was purified by silica gel chromatography to afford the title compounds.

General Procedure C: The Reduction of Isoxazolidine Products. To a solution of the isoxazolidine aldehyde in absolute ethanol (1ml) were added 3 equivalents of $NaBH_4$. After 0.5 hours, the reaction mixture was quenched with H_2O, and extracted with 2 x 10mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the resultant residue by silica gel chromatography provided the corresponding primary alcohol.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 6, entry 1). Prepared according to general procedure B from (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (5.28 g, 25.0 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (1.59 g, 5.00 mmol), crotonaldehyde (8.28 mL, 100.0 mmol followed by 5 x 6.21 mL, 75.0 mmol over 24 h intervals) and H_2O (1.35 mL, 75.0 mmol) in CH_3NO_2 (250.0 ml) at –20 ˚C over the course of 144 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 98% yield (6.85 g); 94:6 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2853, 1722, 1494, 1455, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.81 (d, J = 2.4 Hz, 1H, C**H**O), 7.24–7.58 (m, 10H, $C_6\mathbf{H_5}$ and $CH_2C_6\mathbf{H_5}$), 4.57 (dq, J = 6.1, 12.2 Hz, 1H, C**H**CH_3), 4.21 (d, J = 7.8 Hz, 1H, C**H**C_6H_5), 4.02 (d, J = 14.4 Hz, 1H, C**H**$_2C_6H_5$), 3.84 (d, J = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.15

(m, 1H, C**H**CHO), 1.52 (d, *J* = 6.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.5, 138.4, 137.3, 129.0, 128.6, 128.3, 128.2, 127.5, 127.1, 73.4, 71.5, 71.1, 59.5, 21.2; LRMS (CI) *m*/*z* 281 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{19}NO_2$) requires *m*/*z* 281.1418, found *m*/*z* 281.1413 $(M)^+$; $[\square]_D$ = +82.5 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 94% ee. ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.22–7.47 (m, 10H, Ar**H**), 4.22-4.24 (m, 1H, C**H**ON), 4.00 (d, *J* = 14.6 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.81 (d, *J* = 14.6 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.74-3.75 (m, 2H, C**H**$_2$OH), 3.65 (d, *J* = 8.3 Hz, 1H, C**H**C$_6$H$_5$), 2.36-2.42 (m, 1H, C**H**CH$_2$OH), 1.46 (d, *J* = 6.4 Hz, 3H, C**H**$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (2.5% *i*PrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 59.3 min (major enantiomer) and 76.3 min (minor enantiomer).

(3*R*,4*S*,5*R*)-2-Allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 6, entry 2).[28] Prepared according to general procedure B from (*Z*)-*N*-benzylideneallylamine *N*-oxide (63 mg, 0.30 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (19 mg, 0.08 mmol), crotonaldehyde (133 □L, 1.6 mmol followed by 5 x 75 □L, 1.2 mmol over 24 h intervals) and H_2O (22 □L, 1.2 mmol) in CH_3NO_2 (4.0 ml) at –20 ˚C over the course of 132 h to provide the title compound as a colorless oil in 73% yield (68 mg); 93:7 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2981, 2842, 1722, 1645, 1498, 1376 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 9.77 (d, *J* = 2.2 Hz, 1H, C**H**O), 7.14–7.24 (m, 5H, C$_6$**H**$_5$), 5.84–5.98 (m, 1H, CH$_2$=C**H**CH$_2$), 5.06–5.28 (m, 2H, C**H**$_2$=CH), 4.51 (dq, *J* = 6.0,

6.0 Hz, 1H, C**H**CH_3), 4.10 (d, *J* = 7.7 Hz, 1H, C**H**C_6H_5), 3.46 (dd, *J* = 5.5, 14.3 Hz, 1H, CH_2=CHC**H**$_2$N), 3.31 (dd, *J* = 6.6, 14.3 Hz, 1H, CH2=CHC**H**$_2$N), 3.09 (ddd, *J* = 2.5, 5.8, 8.0 Hz, 1H, C**H**CHO), 1.50 (d, *J* = 6.0 Hz, 3H, C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.7, 138.6, 133.9, 129.1, 128.4, 127.8, 118.1, 73.7, 71.9, 71.3, 59.1, 21.3; LRMS (CI) *m*/*z* 231 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{14}H_{17}NO_2$) requires *m*/*z* 231.1259, found *m*/*z* 231.1256 $(M)^+$; [□]$_D$ = +63.8 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 98% ee. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.13–7.41 (m, 5H, C_6**H$_5$**), 5.83–5.97 (m, 1H, CH_2=C**H**CH_2), 5.08–5.22 (m, 2H, C**H$_2$**=CH), 4.21 (dq, *J* = 6.4, 6.4 Hz, 1H, C**H**CH_3), 3.64–3.83 (br s, 2H, C**H$_2$**OH), 3.57 (d, *J* = 8.0 Hz, 1H, C**H**C_6H_5), 3.44 (dd, *J* = 5.2, 14.3 Hz, 1H, CH2=CHC**H**$_2$N), 3.28 (dd, *J* = 6.6, 14.3 Hz, 1H, CH2=CHC**H**$_2$N), 2.34 (m, 1H, C**H**CH_2OH), 1.44 (d, *J* = 6.1 Hz, 3H, C**H$_3$**). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (3% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 18.2 min and 24.2 min.

(3*R*,4*S*,5*R*)-2,5-Dimethyl-4-formyl-3-phenylisoxazolidine (Table 6, entry 3).[28] Prepared according to general procedure B from (*Z*)-*N*-benzylidenemethylamine *N*-oxide (54.1 mg, 0.40 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (26 mg, 0.08 mmol), crotonaldehyde (133 □L, 1.6 mmol followed by 5 x 100 □L, 1.2 mmol, over 24 h intervals) and H_2O (22 □L, 1.2 mmol) in CH_3NO_2 (4.0 ml) at –20 °C over the course of 132 h to provide the title compound as a colorless oil in 66% yield (54

mg); 95:5 *endo:exo*. *Endo* >99% ee *Endo* isomer: IR (CH_2Cl_2) 2974, 2873, 1722, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.74 (d, *J* = 2.5 Hz, 1H, C**H**O), 7.26–7.39 (m, 5H, $C_6\mathbf{H_5}$), 4.54 (dq, *J* = 6.0, 12.3 Hz, 1H, C**H**CH_3), 3.83 (br s, 1H, C**H**C_6H_5), 3.09 (m, 1H, C**H**CHO), 2.60 (s, 3H, NC$\mathbf{H_3}$), 1.50 (d, *J* = 6.3 Hz, 3H, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 198.6, 137.8, 129.1, 128.5, 127.8, 73.5, 72.2, 66.3, 43.6, 21.9; LRMS (CI) *m/z* 205 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{12}H_{15}NO_2$) requires *m/z* 205.1103, found *m/z* 205.1100 $(M)^+$; $[□]_D$ = +77.2° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. Enantiomeric ratios were determined by GLC with a Bodman □-PH column (100 °C, 23 psi); *endo* isomers t_r = 38.0 min and 39.8 min.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine (Table 6, entry 4). Prepared according to general procedure B from (*Z*)-*N*-*para*-chlorobenzylidenebenzylamine *N*-oxide (74 mg, 0.30 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (19 mg, 0.06 mmol), crotonaldehyde (100 □L, 1.2 mmol followed by 7 x 75 □L, 0.90 mmol, over 24 h intervals) and H_2O (16 □L, 0.90 mmol) in CH_3NO_2 (3.0 ml) at –20 °C over the course of 160 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 78% yield (74 mg); 92:8 *endo:exo*. *Endo* isomer: IR (film) 3429, 3066, 2981, 2873, 2835, 2726, 1722, 1599, 1491, 1452, 1375, 1089, 1020, 819, 734, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.79 (d, *J* = 2.2 Hz, 1H, C**H**O), 7.24–7.38 (m, 9H, $C_6\mathbf{H}_4Cl$ and $CH_2C_6\mathbf{H_5}$), 4.55 (m, 1H, C**H**CH_3), 4.16 (d, *J* = 7.7 Hz, 1H, C**H**C_6H_4Cl), 3.97 (d, *J* = 14.0 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.84 (d, *J* = 14.3 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.06 (ddd, *J* = 7.4, 5.5, 2.2 Hz, 1H, C**H**CHO), 1.50 (d, *J* = 6.0 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) □

198.6, 137.5, 137.2, 134.1, 129.8, 129.6, 129.4, 129.1, 128.8, 128.6, 127.6, 21.3; LRMS (CI) *m/z* 315 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{18}NClO_2$) requires *m/z* 315.1026, found *m/z* 315.1023 $(M)^+$; $[\alpha]_D$ = +69.8 (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 95% ee. ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.39 (m, 9H, Ar**H**), 4.23 (m, 1H, C**H**ON), 3.97 (d, *J* = 14.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.84 (d, *J* = 14.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.73-3.81 (m, 2H, C**H**$_2$OH), 3.67 (d, *J* = 7.8 Hz, 1H, C**H**C$_6$H$_4$Cl), 2.31-2.33 (m, 1H, C**H**CH$_2$OH), 1.44 (d, *J* = 6.4 Hz, 3H, C**H**$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (2.4% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 47.7 min and 83.6 min.

(3*R*,4*S*,5*R*)-2,5-Dimethyl-4-formyl-3-(4-chlorophenyl) isoxazolidine (Table 6, entry 5). Prepared according to general procedure B from (*Z*)-*N*-*para*-chlorobenzylidenemethylamine *N*-oxide (68 mg, 0.40 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (26 mg, 0.08 mmol), crotonaldehyde (133 μL, 1.6 mmol followed by 8 x 100 μL, 1.20 mmol, over 24 h intervals) and H_2O (22 μL, 1.20 mmol) in CH_3NO_2 (4.0 ml) at –20 °C over the course of 160 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 76% yield (73 mg); 93:7 *endo:exo*. *Endo* isomer: IR (film) 3429, 2974, 2927, 2850, 2781, 2734, 1908, 1722, 1599, 1490, 1460, 1375, 1344, 1298, 1205, 1089, 1020, 911.4, 818.7, 679.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 2.3 Hz,

1H, C**H**O), 7.25-7.33 (m, 4H, Ar**H**), 4.51 (dq, J_d = 5.9, J_q = 6.1 Hz, 1H, C**H**CH_3), 3.82-4.01 (m, 1H, C**H**C_6H_4Cl), 3.02 (ddd, J = 8.0, 5.5, 2.3 Hz, 1H, C**H**CHO), 2.59 (s, 3H, NC**H**$_3$), 1.55 (d, J = 6.2 Hz, 3H, CHC**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) □ 198.3, 136.7, 134.3, 129.6, 129.5, 129.3, 129.1, 73.5, 73.1, 72.2; LRMS (FAB) *m/z* 239 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{12}H_{14}ClNO_2$) requires *m/z* 239.0713, found *m/z* 239.0707 $(M)^+$; $[□]_D$ = +64.1 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the determination of enantiomeric purity; *endo* 94% ee. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.24-7.38 (m, 4H, Ar**H**), 4.20 (dq, J_d = 6.2, J_q = 6.0, 1H, C**H**ON), 3.66-3.75 (m, 2H, C**H**$_2$OH), 3.35 (d, J = 8.52 Hz, 1H, C**H**C_6H_4Cl), 2.28-2.34 (m, 1H, C**H**CH_2OH), 1.43 (d, J = 6.3 Hz, 3H, C**H$_3$**). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (3.0% iPrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 29.0 min and 45.3 min.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-(4-methoxyphenyl) isoxazolidine (Table 6, entry 6). Prepared according to general procedure B (*Z*)-*N*-*para*-methoxybenzylidenebenzylamine *N*-oxide (72 mg, 0.30 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (19 mg, 0.06 mmol), crotonaldehyde (100 □L, 1.2 mmol followed by 5 x 75 □L, 0.90 mmol, over 24 h intervals) and H_2O (16 □L, 0.90 mmol) in CH_3NO_2 (3.0 ml) at –20 ˚C over the course of 136 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 93% yield (86 mg); 98:2 *endo:exo*. *Endo* isomer: IR (film) 3429,

3035, 2974, 2935, 2835, 2726, 1722, 1614, 1514, 1452, 1375, 1298, 1251, 1174, 1035, 826, 734, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.76 (d, *J* = 2.5 Hz, 1H, C**H**O), 7.23–7.38 (m, 7H, Ar**H**), 6.87-6.91 (m, 2H, Ar**H**), 4.52 (m, 1H, C**H**CH_3), 4.06 (d, *J* = 8.2 Hz, 1H, C**H**$C_6H_4OCH_3$), 3.99 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.80 (s, 3H, OC**H**$_3$), 3.76 (d, *J* = 14.6 Hz, 1H, C**H**$_2C_6H_5$), 3.08 (ddd, *J* = 8.0, 5.5, 2.5 Hz, 1H, C**H**CHO), 1.50 (d, *J* = 6.3 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 199.1, 159.8, 137.7, 130.1, 129.1, 128.7, 128.5, 137.4, 114.6, 73.6, 71.8, 71.2, 59.5, 55.6, 21.5; LRMS (CI) *m*/*z* 311 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{19}H_{21}NO_3$) requires *m*/*z* 311.1521, found *m*/*z* 311.1514 $(M)^+$; $[□]_D$ = +71.8 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 91% ee. ^1H NMR (500 MHz, $CDCl_3$) □ 7.17–7.41 (m, 7H, Ar**H**), 6.86-6.93 (m, 2H, Ar**H**), 4.17 (dq, J_d = 5.9, J_q = 6.0, 1H, C**H**ON), 3.96 (d, *J* = 14.6 Hz, 1H, C**H**$_2C_6H_5$), 3.80 (s, 3H, OC**H**$_3$), 3.73 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.69-3.73 (m, 2H, C**H**$_2$OH), 3.56 (d, *J* = 8.5 Hz, 1H, C**H**$C_6H_4OCH_3$), 2.29-2.38 (m, 1H, C**H**CH_2OH), 1.43 (d, *J* = 6.0 Hz, 3H, C**H**$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (3.0% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 37.7 min and 69.5 min.

(3*R*,4*S*,5*R*)-2,5-Dimethyl-4-formyl-3-(4-tolyl) isoxazolidine (Table 6, entry 7). Prepared according to general procedure B from (*Z*)-*N*-*para*-

methylbenzylidenemethylamine *N*-oxide (60 mg, 0.40 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (26 mg, 0.08 mmol), crotonaldehyde (133 μL, 1.6 mmol followed by 7 x 100 μL, 1.20 mmol, over 24 h intervals) and H_2O (22 μL, 1.20 mmol) in CH_3NO_2 (4.0 ml) at –20 ˚C over the course of 160 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 82% yield (72 mg); 93:7 *endo:exo*. *Endo* isomer: IR (film) 3429, 2974, 2927, 2873, 2726, 1722, 1514, 1452, 1375, 1344, 1112, 1066, 911, 811, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, J = 2.5 Hz, 1H, C**H**O), 7.12-7.26 (m, 4H, Ar**H**), 4.53 (dq, J_d = 5.9, J_q = 6.3 Hz, 1H, C**H**CH_3), 3.78 (bs, 1H, C**H**$C_6H_4CH_3$), 3.09 (ddd, J = 8.4, 5.4, 2.5 Hz, 1H, C**H**CHO), 2.59 (s, 3H, NC**H**$_3$), 2.34 (s, 3H, C_6H_4C**H**$_3$), 1.51 (d, J = 6.3 Hz, 3H, CHC**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 138.3, 134.5, 130.0, 129.6, 128.0, 127.5, 73.6, 72.2, 43.7, 21.6; LRMS (CI) m/z 219 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{13}H_{17}NO_2$) requires m/z 219.1259, found m/z 219.1262 $(M)^+$; $[\alpha]_D$ = +67.9 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 97% ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.13-7.26 (m, 4H, Ar**H**), 4.20 (dq, J_d = 6.2, J_q = 6.0 Hz, 1H, C**H**ON), 3.63-3.71 (m, 2H, C**H**$_2$OH), 3.29 (d, J = 7.7 Hz, 1H, C**H**$C_6H_4CH_3$), 2.55 (s, 3H, NC**H**$_3$), 2.33 (s, 3H, C_6H_4C**H**$_3$), 2.31-2.39 (m, 1H, C**H**CH_2OH), 1.44 (d, J = 6.0 Hz, 3H, CHC**H$_3$**). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (3.0% iPrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 40.2 min and 47.6 min.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-(2-napthyl) isoxazolidine (Table 6, entry 8). Prepared according to general procedure B from (*Z*)-*N*-2-napthylidenebenzylamine *N*-oxide (78 mg, 0.30 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (19 mg, 0.06 mmol), crotonaldehyde (100 μL, 1.2 mmol followed by 5 x 75 μL, 0.90 mmol, over 24 h intervals) and H_2O (16 μL, 0.90 mmol) in CH_3NO_2 (3.0 ml) at –20 °C over the course of 138 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide the title compound as an oil in 98% yield (97 mg); 95:5 *endo:exo*. *Endo* isomer: IR (film) 3429, 3059, 2981, 2927, 2866, 2726, 1954, 1722, 1607, 1498, 1452, 1375, 1313, 1120, 819, 742, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 2.3 Hz, 1H, C**H**O), 7.84-7.89 (m, 5H, Ar**H**), 7.61 (dd, *J* = 1.6 Hz, 1H, Ar**H**), 7.49-7.52 (m, 2H, Ar**H**), 7.24–7.38 (m, 2H, Ar**H**), 4.61 (dq, J_d = 5.9, J_q = 6.1 Hz, 1H, C**H**CH_3), 4.35 (d, *J* = 7.7 Hz, 1H, C**H**Napth), 4.06 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.89 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 2.20 (ddd, *J* = 7.8, 5.5, 2.3 Hz, 1H, C**H**CHO), 1.55 (d, *J* = 6.2 Hz, 3H, CHC**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 137.5, 136.0, 133.5, 133.4, 129.1, 128.7, 128.4, 128.1, 127.9, 137.4, 127.1, 126.6, 126.5, 125.1, 73.8, 71.6, 71.5, 59.8, 21.3; LRMS (CI) *m/z* 331 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{22}H_{21}NO_2$) requires *m/z* 331.1572, found *m/z* 331.1567 $(M)^+$; $[\alpha]_D$ = +53.1 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 93% ee. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.86 (m, 4H, Ar**H**), 7.66-7.67 (m, 1H, Ar**H**), 7.48-7.52 (m, 2H,

Ar**H**), 7.20-7.40 (m, 5H, Ar**H**), 4.28 (dq, J_d = 6.1, J_q = 5.9, 1H, C**H**ON), 4.04 (d, J = 14.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.75-3.87 (m, 4H, C**H**$_2$C$_6$H$_5$, C**H**$_2$OH, C**H**Napth), 2.46-2.51 (m, 1H, C**H**CH$_2$OH), 1.50 (d, J = 5.9 Hz, 3H, C**H**$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (2.5% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 57.7 min and 107.6 min.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-cyclohexyl isoxazolidine (Table 6, entry 9). Prepared according to general procedure A from (*Z*)-*N*-cyclohexylmethylidenebenzylamine *N*-oxide (65 mg, 0.30 mmol), (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt **16** (19 mg, 0.06 mmol), crotonaldehyde (200 μL) and H_2O (16 μL, 0.90 mmol) in CH_3CN (3.0 ml) at –40 °C over the course of 96 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 and purified by silica gel chromatography (8% EtOAc/Hex) to provide the title compound as an oil in 69% yield (59 mg); 99:1 *endo:exo*. *Endo* isomer: IR (film) 2927, 2858, 2719, 1722, 1498, 1452, 1383, 1328, 1074, 1027, 973, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J = 3.0 Hz, 1H, C**H**O), 7.23-7.40 (m, 5H, Ar**H**), 4.57-4.64 (dq, J_d = 7.7, J_q = 6.1 Hz, 1H, C**H**ON), 4.08 (d, J = 13.5 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.82 (d, J = 13.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.05 (dd, J = 7.7, 5.5 Hz, 1H, C**H**-chex), 2.86-2.91 (m, 1H, C**H**CHO), 1.35 (d, J = 6.1 Hz, 3H, CHC**H**$_3$), 0.70-2.03 (m, 11H, *c*hex-**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.6, 72.8, 67.2, 62.0, 42.6, 30.9, 29.8, 26.7, 26.3, 26.2, 18.1; LRMS (EI) *m*/*z* 287 (M)$^+$; HRMS (EI) exact mass calcd for ($C_{18}H_{25}NO_2$) requires *m*/*z* 287.1885, found *m*/*z* 287.1881 (M)$^+$; $[\alpha]_D$ = +48.6 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding

primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 99% ee. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.32-7.41 (m, 5H, Ar**H**), 4.32-4.34 (m, 1H, C**H**ON), 4.14 (d, *J* = 12.7 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.88 (d, *J* = 13.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.73-3.84 (m, 2H, C**H**$_2$OH), 2.58 (dd, J = 6.1, 5.4 Hz, 1H, C**H**-chex), 2.14-2.18 (m, 1H, C**H**CH$_2$OH), 1.34 (d, *J* = 6.4 Hz, 3H, CHC**H$_3$**), 0.82-1.74 (m, 11H, *c*hex-**H**). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (3.0% iPrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 22.9 min and 26.7 min.

(3*R*,4*S*)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 2).[28] Prepared according to general procedure A from (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (63 mg, 0.30 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt **13** (22 mg, 0.06 mmol), acrolein (71 □L, 1.2 mmol) and H_2O (16 □L, 0.90 mmol) in CH_3NO_2 (3.0 ml) at –18 °C over the course of 120 h to provide the title compound as a colorless oil in 80% yield (63 mg); 86:14 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2873, 1722, 1498, 1452, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.80 (d, *J* = 2.1 Hz, 1H, C**H**O), 7.27–7.51 (m, 10H, C$_6$**H$_5$** and CH$_2$C$_6$**H$_5$**), 4.27–4.30 (m, 2H, C**H$_2$**ON), 4.07 (d, *J* = 7.1 Hz, 1H, C**H**C$_6$H$_5$), 3.99 (d, *J* = 14.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.78 (d, *J* = 14.2 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.44 (m, 1H, C**H**CHO); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.4, 138.1, 137.1, 128.9, 128.6, 128.3, 128.2, 127.8, 127.3, 70.6, 65.8, 64.3, 59.6; LRMS (CI) *m*/*z* 267 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{17}H_{17}NO_2$) requires *m*/*z* 267.1259, found *m*/*z* 267.1268; $[□]_D$ = +43.4 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^{1}H NMR analysis. A portion of the title

compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 92% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.51 (m, 10H, $C_6\mathbf{H_5}$ and $CH_2C_6\mathbf{H_5}$), 4.19 (dd, *J* = 8.2, 8.2 Hz, 1H, C**H**$_2$ON), 3.94 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.88–3.92 (dd, *J* = 4.4, 8.2 Hz, 1H, C**H**$_2$ON), 3.65–3.83 (m, 2H, CH_2OH), 3.70 (d, *J* = 14.0 Hz, 1H, C**H**$_2C_6H_5$), 3.47 (d, *J* = 7.7 Hz, 1H, C**H**C_6H_5), 2.72–2.83 (m, 1H, C**H**CH_2OH). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column (4% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 15.8 min and 20.4 min.

(3*R*,4*S*)-2-Benzyl-4-formyl-3-(4-methylphenyl)isoxazolidine (Table 7, entry 3).[28] Prepared according to general procedure B from (*Z*)-*N*-*para*-methylbenzylidenebenzylamine *N*-oxide (72 mg, 0.30 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt **13** (22 mg, 0.06 mmol), acrolein (71 μL, 1.2 mmol followed by 4 x 36 μL, 0.60 mmol, over 24 h intervals), H_2O (16 μL, 0.90 mmol), and in CH_3NO_2 (3.0 ml) at –18 °C over the course of 112 h to provide the title compound as a colorless oil in 80% yield (66 mg) after silica gel chromatography (17% EtOAc/hex); 85:15 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2873, 1722, 1514, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.2 Hz, 1H, C**H**O), 7.19–7.47 (m, 7H, $C_6\mathbf{H}_4CH_3$ and $CH_2C_6\mathbf{H_5}$), 4.24–4.28 (m, 2H, C**H$_2$**ON), 3.97–4.02 (m, 2H, C**H**NO and C**H**$_2C_6H_5$), 3.75 (d, *J* = 14.0 Hz, 1H, C**H**$_2C_6H_5$), 3.38–3.46 (m, 1H, C**H**CHO), 2.39 (s, 3H, $C_6H_4C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 138.4, 137.5, 135.0, 129.9, 128.9, 128.5, 128.0, 127.5, 70.9, 66.2, 64.6, 59.9, 21.6; LRMS (CI) *m*/*z* 281 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{19}NO_2$) requires *m*/*z* 281.1416, found

m/z 281.1415; $[\alpha]_D$ = +39.8 ° (c = 1.0, $CHCl_3$). Diastereomeric ratio was determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 90% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.37 (m, 9H, $C_6\mathbf{H_4}CH_3$ and $CH_2C_6\mathbf{H_5}$), 4.18 (dd, *J* = 8.2, 8.2 Hz, 1H, C**H**$_2$ON), 3.94 (d, *J* = 14.8 Hz, 1H, C**H**$_2C_6H_5$), 3.87-3.91 (dd, *J* = 4.3, 8.1 Hz, 1H, C**H**$_2$ON), 3.67–3.82 (m, 2H, C**H**$_2$OH), 3.65 (d, *J* = 14.3 Hz, 1H, C**H**$_2C_6H_5$), 3.44 (d, *J* = 7.7 Hz, 1H, C**H**$C_6H_4CH_3$), 2.70–2.81 (m, 1H, C**H**CH_2OH), 2.35 (s, 3H, $C_6H_4C\mathbf{H_3}$). Enantiomeric ratios were determined by HPLC with Chiralcel AD column and AD guard column (10% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 9.1 min and 10.0 min.

(3*R*,4*S*)-2-Benzyl-4-formyl-3-(4-chlorophenyl)isoxazolidine (Table 7, entry 4).[28] Prepared according to general procedure B from (*Z*)-*N*-*para*-chlorobenzylidenebenzylamine *N*-oxide (74 mg, 0.30 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt **13** (22 mg, 0.06 mmol), acrolein (71 μL, 1.2 mmol followed by 3 x 36 μL, 0.60 mmol, over 24 h intervals) and H_2O (16 μL, 0.90 mmol) in CH_3NO_2 (3.0 ml) at –18 °C over the course of 96 h to provide the title compound as a colorless oil in 80% yield (70 mg) after silica gel chromatography (20% EtOAc/hex); 80:20 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2881, 1722, 1599, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 2.0 Hz, 1H, C**H**O), 7.26–7.44 (m, 9H, $C_6\mathbf{H_4}$Cl and $CH_2C_6\mathbf{H_5}$), 4.27–4.29 (m, 2H, C**H**$_2$ON), 4.08 (d, *J* = 7.0 Hz, 1H, C**H**C_6H_4Cl), 3.96 (d, *J* = 14.0 Hz, 1H, C**H**$_2C_6H_5$), 3.80 (d, *J* = 14.2 Hz, 1H, C**H**$_2C_6H_5$), 3.34–3.40 (m, 1H, C**H**CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 136.8, 134.0, 136.7, 129.1, 128.7,

128.2, 127.4, 129.1, 69.6, 65.8, 64.3, 59.7; LRMS (CI) *m/z* (M); HRMS (CI) exact mass calcd for ($C_{17}H_{16}ClNO_2$) requires *m/z* 301.0870 $(M)^+$, found *m/z* 301.0862; $[\alpha]_D$ = +36.5 ° (c = 1.0, $CHCl_3$). Diastereomeric ratios were determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the determination of enantiomeric purity; *endo* 91% ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.04–7.42 (m, 9H, $C_6\mathbf{H_4}Cl$ and $CH_2C_6\mathbf{H_5}$), 4.17 (dd, *J* = 8.2, 8.2 Hz, 1H, $C\mathbf{H}_2ON$), 3.91 (d, *J* = 14.0 Hz, 1H, $C\mathbf{H}_2C_6H_5$), 3.86–3.90 (dd, *J* = 4.7, 8.2 Hz, 1H, $C\mathbf{H}_2ON$), 3.72–3.78 (m, 2H, $C\mathbf{H_2}OH$), 3.72 (d, *J* = 14.0 Hz, 1H, $C\mathbf{H}_2C_6H_5$), 3.49 (d, *J* = 7.7 Hz, 1H, $C\mathbf{H}C_6H_4Cl$), 2.68–2.76 (m, 1H, $C\mathbf{H}CH_2OH$). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (5% *i*PrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 20.7 min and 23.5 min.

(3*R*,4*S*)-2-Benzyl-4-formyl-3-napthylisoxazolidine (Table 7, entry 5).[28] Prepared according to general procedure A from (*Z*)-*N*-2-napthylidenebenzylamine *N*-oxide (78 mg, 0.30 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt **13** (22 mg, 0.06 mmol), acrolein (71 μL, 1.2 mmol), H_2O (16 μL, 0.90 mmol), and in CH_3NO_2 (3.0 ml) at –18 ˚C over the course of 112 h to provide the title compound as a colorless oil in 82% yield (75 mg) after silica gel chromatography (25% EtOAc/hex); 81:19 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 3059, 2835, 1722, 1498, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 2.0 Hz, 1H, $C\mathbf{H}O$), 7.27–7.95 (m, 12H, $C_{10}\mathbf{H_7}$ and $CH_2C_6\mathbf{H_5}$), 4.32–4.36 (m, 2H, $C\mathbf{H_2}ON$), 4.28 (d, *J* = 7.0 Hz, 1H, $C\mathbf{H}C_{10}H_7$), 4.01 (d, *J* = 14.1 Hz, 1H, $C\mathbf{H}_2C_6H_5$), 3.85 (d, *J* = 14.2 Hz, 1H,

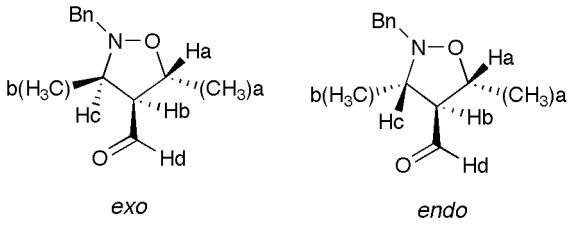
C**H**$_2$C$_6$H$_5$), 3.53 (m, 1H, C**H**CHO); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.7, 137.1, 135.4, 133.3, 133.2, 128.9, 128.7, 128.2, 127.9, 127.8, 127.7, 127.3, 127.2, 126.4, 126.3, 125.0, 110.4, 70.8, 65.9, 64.2, 59.7; LRMS (CI) *m/z* 317 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{21}H_{19}NO_2$) requires *m/z* 317.1416, found *m/z* 317.1416; $[□]_D$ = +20.3 ° (c = 1.0, $CHCl_3$). Diastereomeric ratio was determined by ^{1}H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 89% ee. ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.21–7.89 (m, 12H, C$_{10}$**H$_7$** and CH$_2$C$_6$**H$_5$**), 4.26 (dd, *J* = 8.2, 8.2 Hz, 1H, C**H**$_2$ON), 3.98 (d, *J* = 14.0 Hz, 1H, C**H**$_2$C$_6$H$_5$), 3.93–3.98 (dd, *J* = 4.6, 8.2 Hz, 1H, C**H**$_2$ON), 3.75 (d, *J* = 14.0, 1H, C**H**$_2$C$_6$H$_5$), 3.72–3.83 (m, 2H, CH_2OH), 3.67 (d, *J* = 7.7 Hz, 1H, C**H**C$_{10}$H$_7$), 2.82–2.93 (m, 1H, C**H**CH_2OH). Enantiomeric ratios were determined by HPLC with Chiralcel AD column and AD guard column (10% EtOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 12.7 min and 17.5 min.

(3*R*,4*S*)-2-Benzyl-4-formyl-3-(4-methoxyphenyl)isoxazolidine (Table 7, entry 6).[28] Prepared according to general procedure B from (*Z*)-*N*-*para*-methoxybenzylidenebenzylamine *N*-oxide (72 mg, 0.30 mmol), (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt **13** (22 mg, 0.06 mmol), acrolein (71 □L, 1.2 mmol followed by 3 x 36 □L, 0.60 mmol, over 24 h intervals), H_2O (16 □L, 0.90 mmol), and in CH_3NO_2 (3.0 ml) at –18 °C over the course of 87 h to provide the title compound as a colorless oil in 83% yield (73 mg) after silica gel chromatography (30% EtOAc/hex); 91:9 *endo:exo*. *Endo* isomer: IR (CH_2Cl_2) 2935,

1722, 1614, 1514, 1460, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □ 9.77 (d, *J* = 2.1 Hz, 1H, C**H**O), 7.26–7.42 (m, 7H, $C_6\mathbf{H}_4OCH_3$ and $CH_2C_6\mathbf{H_5}$), 6.94 (d, *J* = 8.7 Hz, 2H, ortho $C_6\mathbf{H}_4OCH_3$), 4.22–4.28 (m, 2H, C$\mathbf{H_2}$ON), 3.96–4.00 (m, 2H, C**H**NO and C$\mathbf{H}_2C_6H_5$), 3.82 (s, 3H, OC$\mathbf{H}_3$), 3.73 (d, *J* = 14.2 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.40 (m, 1H, C**H**CHO); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.9, 159.6, 137.3, 129.6, 129.0, 128.6, 128.2, 127.2, 114.3, 70.3, 65.8, 64.1, 59.4, 55.2; LRMS (CI) *m*/*z* 297 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{19}NO_3$) requires *m*/*z* 297.1365, found *m*/*z* 297.1361. $[□]_D$ = +31.9 ° (c = 1.0, $CHCl_3$) Diastereomeric ratio was determined by ^1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the determination of enantiomeric purity; *endo* 90% ee. ^1H NMR (300 MHz, $CDCl_3$) □ 7.19–7.40 (m, 7H, $C_6\mathbf{H_4}OCH_3$ and $CH_2C_6\mathbf{H_5}$), 6.92 (d, *J* = 1.9 Hz, 2H, $C_6\mathbf{H_4}OCH_3$), 4.16 (dd, *J* = 8.2, 8.2 Hz, 1H, C$\mathbf{H}_2$ON), 3.90 (d, *J* = 14.3 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.87 (dd, *J* = 4.4, 8.2 Hz, 1H, C$\mathbf{H}_2$ON), 3.81 (s, 3H, $C_6H_4OC\mathbf{H_3}$), 3.66–3.79 (m, 2H, C$\mathbf{H_2}$OH), 3.65 (d, *J* = 14.3 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.42 (d, *J* = 7.6 Hz, 1H, C$\mathbf{H}C_6H_5OCH_3$), 2.69–2.80 (m, 1H, C$\mathbf{H}CH_2OH$). Enantiomeric ratios were determined by HPLC with Chiralcel AD column and AD guard column (8% *i*PrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 15.4 min and 17.0 min.

(3*S*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine (Equation 15). To a solution of (2*S*,5*S*,)-5-benzyl,-2-*tert*-butyl-3-methylimidazolidin-4-one (6.7 mg, 0.027 mmol) and (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (28.5 mg, 0.135 mmol) in THF (1.35 mL) in a 2 dram vial was added 4M HCl in dioxane (6.75 □L, 0.027 mmol HCl). The stirring solution was cooled to –20 °C and crotonaldehyde (44.7 □L, 0.846 mmol) was

added in one portion. The reaction was stirred at –20 ° C for 10 hours, at which time the reaction was flushed through a silica gel column with EtOAc. Concentration afforded an oil which was purified to provide the title compound as a colorless oil in 97% yield (36.8 mg) after silica gel chromatography (CH_2Cl_2); 80:20 *exo*:*endo*. *Exo* stereochemical relationship was determined by nOe analysis of this product and of the *endo* product (*vida supra*): Irradiation of Hb (*exo*) resulted in interaction with Hd, Hc, and (CH_3)a. Similar irradiation of Hb (*endo*) resulted only in interaction with Hd, (CH_3)b, and (CH3)a.



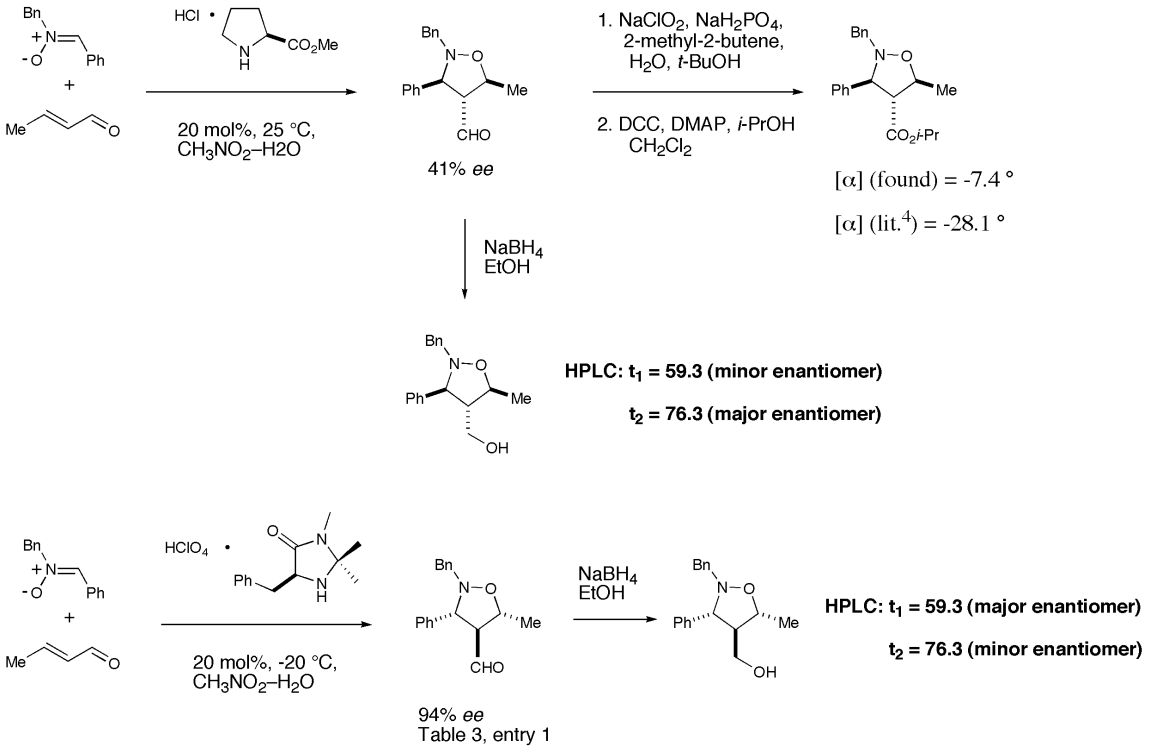
A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (20% EtOAc/hex) for the determination of enantiomeric purity; *exo* 94% ee. Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (2.0% *i*PrOH/hex, 1 mL/min flow rate); *exo* isomers t_r = 21.7 min (major enantiomer) and 23.8 min (minor enantiomer).

(1*R*,2*R*,3*S*,4*S*)–3–methylbicyclo[2.2.1]hex–5–ene–2–carboxaldehyde

(Equation 16). To a solution of (2S,5S,)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (4.9 mg, 0.02 mmol) in $CHCl_3$ (0.2 mL) in a 2-dram vial was added 4M HCl in

dioxane (5 μL, 0.02 mmol HCl) followed by crotonaldehyde (16.6 μL, 0.2 mmol). The yellow solution was stirred for 5 minutes at room temperature and cooled to –60 °C. Cyclopentadiene (67 μL, 0.6 mmol) was pre–cooled to –60 °C and then added to the stirring solution in one portion. The reaction was stirred at –60 °C for 63.5 hours, at which time the solution was passed through a silica gel column with 3% Et_2O/pentane. Analysis of the reaction mixture GLC (Bodman β–TA column, 50 °C, 2°C/min gradient, 23 psi) indicated an 80% conversion to product relative to an internal standard; (1*S*, 2*R*,3*S*,4*R*) *endo* isomer t_r = 24.7 min, (1*R*,2*S*,3*R*,4*S*) *endo* isomer t_r = 25.0 min, exo isomers t_r = 22.4, 22.9 min; 83:17 *exo*:*endo*; *exo*: 93% ee. All spectral data were in complete accord with previously reported values.[27]

Determination of the Absolute Configuration of (3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 6, entry 1) by Correlation with (3*R*,4*S*,5*R*)-2-benzyl-5-methyl-3-phenylisoxazolidine-4-carboxylic acid isopropyl ester.[28]



(3*S*,4*R*,5*S*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine was prepared according to general procedure B from (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (105.6 mg, 0.50 mmol), (2*S*)-proline methyl ester hydrochloric acid salt (20.3 mg, 0.10 mmol), crotonaldehyde (0.13 mL, 1.50 mmol) and H_2O (5.0 μL, 0.09 mmol) in CH_3NO_2 (5.0 mL) over the course of 24 h. The resulting solution was passed through a silica gel column with CH_2Cl_2 to provide an oil. A portion of the product was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 41% ee. Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (2.5% *i*PrOH/hex, 1 mL/min flow rate); *endo* isomers t_r = 59.3 min (minor enantiomer) and 76.3 min (major enantiomer). The remainder of the product (59.4 mg, 0.21 mmol) was dissolved in t*ert*-butanol (4.4 mL). To this solution was added 2-methyl-2-butene (1

mL, 90 mmol) and, dropwise, a solution of $NaClO_2$ (175 mg, 1.93 mmol) and NaH_2PO_4 (203 mg, 1.47 mmol) in H_2O (1.8 mL). The biphasic solution was stirred for 11h. The reaction was concentrated, diluted with H_2O, and washed with hexanes. The aqueous layer was acidified with 1N HCl to pH 2, and extracted twice with Et_2O. The combined organic layers were washed with cold H_2O, dried (Na_2SO_4), and concentrated. To this oil was added CH_2Cl_2 (0.75 mL), 4-dimethylamino-pyridine (1.0 mg, 0.008 mmol), and 2-propanol (0.023 mL, 0.3 mmol). This solution was added to dicyclohexylcarbodiimide (19.3 mg, 0.09 mmol) and the reaction was stirred for 2 h at which time it was filtered, concentrated, dissolved in CH_2Cl_2, and filtered. The filtrate was washed sequentially with 0.5M HCl and sat. aq. $NaHCO_3$, dried (Na_2SO_4), and concentrated. The resulting oil was purified by silica gel chromatography (10% EtOAc/hex) to afford an oil with spectral data identical to those reported for (3*S*,4*R*,5*S*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine isopropyl ester;[29] $[\alpha]_D$ (literature) = -28.1 ° (c = 1.0, $CHCl_3$); $[\alpha]_D$ (found) = -7.4 ° (c = 1.0, $CHCl_3$).

Determination of the Absolute Configuration of (3*R*,4*S*,5*R*)-2-allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 6, entry 2) by Correlation with (2*R*)-[1-((*R*)-allyl-benzyl-amino)-phenyl-methyl]-butane-1,(3*R*)-diol.

(2*R*)-[(*R*)-Benzylamino-phenyl-methyl]-butane-1-(3*R*)-diol, of known absolute configuration (*vida infra*) (23.0 mg, 0.08 mmol), and K_2CO_3 (44.8 mg, 0.32 mmol) were dissolved in 1 : 1 H_2O : CH_3CN (0.5 mL : 0.5 mL). To the solution was added allyl bromide (0.05 mL, 0.32 mmol) and the reaction was stirred for 63 h. The reaction was extracted with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated. The

resulting oil was purified by silica gel chromatography (40% EtOAc/hex) to afford (2*R*)-[1-((*R*)-allyl-benzyl-amino)-phenyl-methyl]-butane-1-(3*R*)-diol: ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.45–7.21 (m, 10H, $C_6\mathbf{H_5}$), 5.93–5.87 (m, 1H, CH_2=C**H**CH_2), 5.25–5.21 (m, 2H, C$\mathbf{H_2}$=CH), 4.17-4.10 (m, 1H, C**H**CH_3), 4.07 (d, *J* = 11.2 Hz, 1H, NC**H**C_6H_5), 4.02 (d, *J* = 13.7 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 3.55-3.49 (m, 2H, C$\mathbf{H}_2$OH, CH_2=CHC$\mathbf{H}_2$N), 3.31 (dd, *J* = 3.4, 11.3 Hz, 1H, C$\mathbf{H}_2$OH), 2.95 (d, *J* = 13.7 Hz, 1H, C$\mathbf{H}_2C_6H_5$), 2.55 (dd, *J* = 8.8, 13.2 Hz, 1H, CH_2=CHC$\mathbf{H}_2$N), 2.26-2.22 (m, 1H, C**H**CH_2OH), 1.33 (d, *J* = 6.3 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 138.5, 135.7, 133.9, 130.1, 129.4, 128.9, 128.5, 128.0, 127.6, 119.1, 70.2, 65.0, 61.8, 54.4, 53.1, 46.1, 21.2; $[\square]_D$ = +74.3 ° (c = 1.0, $CHCl_3$).

A solution of (3*R*,4*S*,5*R*)-2-allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 6, entry 2), (51.0 mg, 0.22 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil (24.8 mg, 0.11 mmol) was dissolved in EtOH (3.5 mL) and heated to reflux. Sodium metal (150 mg, 6.52 mmol) was added in 25 mg portions to the solution. After 3 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH_4Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the resulting oil by silica gel chromatography (4% Et_3N/EtOAc) afforded a white solid**.** The solid (5.4 mg, 0.023 mmol) was dissolved in CH_3CN (1.0 mL). To the stirring solution was added benzyl bromide (3.0 □L, 0.025 mmol) and K_2CO_3 (5.7 mg, 0.041 mmol). The reaction was heated to reflux for 12 h. The solution was filtered and concentrated. The resulting oil was purified by silica gel chromatography (50% EtOAc/hex) to afford a clear oil with ^{1}H and ^{13}C NMR spectra

identical to those of (2*R*)-[1-((*R*)-allyl-benzyl-amino)-phenyl-methyl]-butane-1-(3*R*)-diol above; $[\alpha]_D$ = +72.1° (c = 1.0, $CHCl_3$).

Determination of the Absolute Configuration of (3*R*,4*S*,5*R*)-2,5-dimethyl-4-formyl-3-phenylisoxazolidine (Table 6, entry 3) by Correlation with (2*R*)-[1-((*R*)-benzyl-methyl-amino)-phenyl-methyl]-butane-1,(3*R*)-diol.

(2*R*)-[(*R*)-Benzylamino-phenyl-methyl]-butane-1-(3*R*)-diol, of known absolute configuration (*vida infra*) (26.8 mg, 0.09 mmol), and K_2CO_3 (52.0 mg, 0.38 mmol) were suspended in CH_3CN (1.5 mL). To the suspension was added iodomethane (5.8 μL, 0.09 mmol) and the reaction was stirred for 48 h. The reaction was diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated. The resulting oil was purified by silica gel chromatography (50% EtOAc/hex) to afford (2*R*)-[1-((*R*)-benzyl-methyl-amino)-phenyl-methyl]-butane-1-(3*R*)-diol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.22 (m, 10H, $C_6\mathbf{H_5}$), 4.24 (dq, *J* = 2.4, 6.4 Hz, 1H, C**H**CH_3), 4.14 (d, *J* = 11.2 Hz, 1H, NC**H**C_6H_5), 3.61 (dd, *J* = 2.4, 11.8 Hz, 1H, C**H**$_2$OH), 3.48 (m, 2H, NC**H**$_2C_6H_5$), 3.37 (dd, *J* = 3.9, 11.7 Hz, 1H, C**H**$_2$OH), 2.20-2.13 (m, 1H, C**H**CH_2OH), 2.12 (s, 3H, NC**H**$_3$), 1.38 (d, *J* = 6.4 Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 133.5, 130.1, 129.3, 128.9, 128.5, 128.1, 127.7, 70.3, 69.9, 61.7, 60.0, 45.9, 37.0, 21.9; $[\alpha]_D$ = -10.3 ° (c = 1.0, $CHCl_3$).

A solution of (3*R*,4*S*,5*R*)-2,5-dimethyl-4-formyl-3-phenylisoxazolidine (Table 6, entry 3), (51.0 mg, 0.25 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (5.0 mL) and heated to reflux. Sodium metal (180

mg, 7.83 mmol) was added in 25 mg portions to the solution. After 4 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH_4Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the resulting oil by silica gel chromatography (10% Et_3N/EtOAc) afforded a white solid**.** The solid (9.1 mg, 0.047 mmol) was dissolved in CH_3CN (1.0 mL). To the stirring solution was added benzyl bromide (5.8 μL, 0.048 mmol) and K_2CO_3 (12.0 mg, 0.086 mmol). The reaction was heated to reflux for 14h hours . The solution was filtered and concentrated. The resulting oil was purified by silica gel chromatography (65% EtOAc/hex) to afford a clear oil with ^1H and ^{13}C NMR spectra identical to those of (2*R*)-[1-((*R*)-benzyl-methyl-amino)-phenyl-methyl]-butane-1,(3*R*)-diol above; $[\alpha]_D$ = -8.4 ° (c = 1.0, $CHCl_3$).

Determination of the Absolute Configuration of (3*R*,4*S*,5*R*)-2-benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine (Table 6, entry 4) by Correlation with (2*R*)-[(*R*)-benzylamino-phenyl-methyl]-butane-1,(3*R*)-diol.

(3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine, of known absolute configuration (Table 6, entry 1) (25.0 mg, 0.09 mmol), was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (1.2 mL) and heated to reflux. Sodium metal (180 mg, 7.83 mmol) was added in 25 mg portions to the solution. After 2.5 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with

EtOAc, washed with NH_4Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the resulting oil by silica gel chromatography (2.5% Et_3N/EtOAc) afforded (2*R*)-[(*R*)-benzylamino-phenyl-methyl]-butane-1-(3*R*)-diol as a white solid**:** ^1H NMR (300 MHz, $CDCl_3$) □ 7.42–7.20 (m, 10H, $C_6\mathbf{H_5}$), 4.07 (dq, J = 2.2, 6.0 Hz, 1H, C**H**CH_3), 3.99 (d, *J* = 9.3 Hz, 1H, NC**H**C_6H_5), 3.60 (d, *J* = 12.6 Hz, 1H, C**H**$_2C_6H_5$), 3.54 (d, *J* = 12.6 Hz, 1H, C**H**$_2C_6H_5$), 3.52 (dd, J = 3.9, 11.3 Hz, 1H, C**H**$_2$OH), 3.19 (dd, *J* = 3.3, 11.3 Hz, 1H, C**H**$_2$OH), 1.74-1.66 (m, 1H, C**H**CH_2OH), 1.25 (d, *J* = 6.3 Hz, 3H, C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) □ 141.4, 139.0, 129.1, 128.8, 127.9, 127.6, 127.5, 69.6, 64.9, 61.6, 51.9, 51.7, 22.3; $[□]_D$ = +41.5 ° (c = 1.0, $CHCl_3$).

A solution of (3*R* , 4*S*,5*R*)-2-benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine, (25.0 mg, 0.08 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (1.2 mL) and heated to reflux. Sodium metal (180 mg, 7.82 mmol) was added in 25 mg portions to the solution. After 2 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH_4Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the resulting oil by silica gel chromatography (2.5% Et_3N/EtOAc) afforded a white solid oil with ^1H and ^{13}C NMR spectra identical to those of (2*R*)-[(*R*)-benzylamino-phenyl-methyl]-butane-1-(3*R*)-diol above; $[□]_D$ = +35.5 ° (c = 1.0, $CHCl_3$).

Determination of the Absolute Configuration of (3*R*,4*S*)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 2) by Correlation with (*S*)-3-Benzylamino-3-phenyl-propan-1-ol. To Wilkinson's catalyst (72.2 mg, 0.078 mmol) was added a solution of (3*R*,4*S*)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 2) (20.4 mg, 0.078 mmol) in degassed benzene (3.5 mL). The stirring solution was heated to reflux under a nitrogen atmosphere. After 20h, the reaction was cooled to room temperature and H_2O was added. The mixture was extracted with Et_2O, dried (Na_2SO_4), and concentrated to give a red oil which was purified by silica gel chromatography (10% EtOAc/hex). The resulting oil was dissolved in EtOH (2 mL) and heated to reflux. Sodium metal (120 mg, 5.22 mmol) was added in 25 mg portions to the solution. After 4 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH_4Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the resulting oil by silica gel chromatography (EtOAc) afforded an oil with ^1H and ^{13}C NMR spectra identical to those reported for (*S*)-3-Benzylamino-3-phenyl-propan-1-ol;[30] $[\alpha]_D$ (literature) = -28.1 ° (c = 1.0, $CHCl_3$); $[\alpha]_D$ (found) = +26.2 ° (c = 1.0, $CHCl_3$).

Determination of the Relative Configuration of (3*R*,4*S*)-2-Benzyl-4-formyl-3-napthylisoxazolidine (Table 7, entry 5) by X-ray Crystallography.[28] 2-Benzyl-4-formyl-3-napthylisoxazolidine (54 mg, 0.18 mmol) was dissolved in t*ert*-butanol (3.9 mL). To this solution was added 2-methyl-2-butene (1 mL, 90 mmol) and, dropwise, a solution of $NaClO_2$ (152 mg, 1.69 mmol) and NaH_2PO_4 (178 mg, 1.29 mmol) in H_2O (1.7

mL). The biphasic solution was stirred for 12 h. The reaction was then concentrated, diluted with H_2O and EtOAc and extracted twice with EtOAc. The combined organic layers were washed with cold H_2O, dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (40% EtOAc/hex). The resulting yellow oil was subsequently taken up in methanol (0.5 mL) and cooled to 0 °C. A solution of KOH (5 mg) in methanol (53 μL) was added to the reaction mixture. After stirring for 3 h, the solution was concentrated and the resulting yellow solid was recrystallized from ethanol/THF to afford crystals suitable for single crystal X-ray diffraction (see Appendix 1 for X-ray data).

V. References

(1) For leading references, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed; Wiley: New York, 1994. (c) *Asymmetric Synthesis*; Ojima, I., Ed; VCH: New York, 1993.

(2) Ref #2 from Borths and Ahrendt

(3) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.

(4) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.

(5) Corey, E. J.; Grogan, M. *J. Org. Lett.* **1999**, *1*, 157.

(6) Vachal, P. Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.

(7) (a) Yand, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (b) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (c) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (d) Tian, H. Q.; She, X. G.; Shu, L. H.; Yu, H. W.; Shi, Y. J. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (e) Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847.

(8) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(9) These initial studies were conducted in our laboratories by Kateri A. Ahrendt.

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

(11) For leading references, see: (a) Fredrickson, M. *Tetrahedron*, **1997**, *53*, 403. (b) Dirrat, O.; Kouklovsky, C.; Mauduit, M.; Langlois, Y. *Pure Appl. Chem.* **2000**, *72*, 1721.

(12) For leading references, see: (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Gothelf, K. V.; Jorgensen, K. A. In *Synthetic Applications of 1,3 Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Ed; Wiley: New York, 2002. (c) Gothelf, K. V. *In Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds; Wiley–VCH Verlag: Weinham, 2002.

(13) Chiral Lewis acid mediated [3+ 2] cycloadditions involving bidentate chelating dipolarophiles have been reported: (a) Gothelf, K. V.; Jorgensen, K. A.; *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. V.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**,

79, 1710. (c) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett*. **1996**, *37*, 5947. (d) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett*. **1997**, 547. (e) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem*. **1997**, *62*, 2471. (f) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc*. **1998**, *120*, 5840. (g) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc*. **1998**, *120,* 12355. (h) Gothelf, K. V.; Thomsen, I.; Jorgensen, K. A. *J. Am. Chem. Soc*. **1996**, *118*, 59. (i) Jensen, K. B.; Gothelf, K. V.; Jorgensen, K. A. *Helv. Chim. Acta* **1997**, *80*, 2039. (j) Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem*. **1998**, *63*, 5483. (k) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett*. **1997**, 1039. (l) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 3213.

(14) Subsequent to the publication of the studies detailed in this chapter, other laboratories have reported methods of Lewis acid–based catalysis of 1,3–dipolar cycloadditions between monodentate aldehyde dipolarophiles and nitrones: (a) Viton, F.; Bernardelli, G.; Kundig, E. P. *J. Am. Chem. Soc*. **2002**, *124*, 4968. (b) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett*. **2002**, *4*, 2457. (c) Kanemasa, S.; Naohisa, U.; Shirahase, M. *Tetrahedron Lett*. **2002**, *43*, 657. (d) Kanemasa, S. In *Cycloaddition reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A. Eds; Wiley–VCH Verlag: Weinham, 2002.

(15) The research reported in this chapter has been published as a communication: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 9874.

(16) Initial investigations into the enantioselective catalytic dipolar cycloaddition reaction were conducted by Wendy S. Jen.

(17) Jen, W. S. Doctoral Thesis, California Institute of Technology, 2003.

(18) A Monte Carlo simulation using the MM3 force–field; Macromodel V6.5.

(19) This catalyst was first synthesized (2 steps from the respective amino acids – see Experimental Section) in our laboratories by Kateri A. Ahrendt and applied to the enatioselective organocatalytic Diels Alder reaction: Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.

(20) The optimized conditions were applied to these substrates by Wendy S. Jen.

(21) A Monte Carlo simulation using the MM3 force–field; Macromodel V6.5.

(22) This catalyst was first proposed by Joel F. Austin and Christopher J. Borths.

(23) Such a stepwise mechanism has been proposed for other dipolar cycloaddition reactions: Kanemasa, S.; Naohisa, U.; Shirahase, M. *Tetrahedron Lett*. **2002**, *43*, 657.

(24) Dr. Yong Huang has extended the scope of the *exo* Diels–Alder reaction through simple modification to the reaction conditions reported by the author of this thesis.

(25) Perrin, D. D.; Armarego, W.L.F. *Purification of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

(26) Still, W.C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

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

(28) Reaction performed by Wendy S. Jen

(29) Gothelf, K. V., Thomsen, I., Jørgensen, K. A., *J. Am. Chem. Soc.* **1996**, *118*, 59.

(30) Shimizu, M.; Maruyama, S.; Suzuki, Y.; Fujisawa, T. *Heterocycles* **1997**, *45*, 1883.