Design and Development of New Enantioselective Catalytic Reactions and Progress towards the Total Synthesis of Callipeltoside A

Thesis by

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This thesis is dedicated to David, Mommy, and Da with more love than I can express

Acknowledgements

The MacMillan group has, since its inception, adhered to a level of excellence that can be as powerfully exciting as depressingly backbreaking in its intensity. These standards have been set by my adviser, David MacMillan, and I must thank Dave for being a model to me of the scientific method, of the necessity to strive for perfection in research. But more, Dave holds dear the pursuit of new understandings, and this passion is infused deep within his research group. I cannot thank him enough for helping me both to harness the elements of that drive that are within myself and to use that drive to perform as I have during these five and a half years.

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Abstract

The development of a new enantioselective catalytic *anti* aldol reaction is described. In this Lewis acid-catalyzed process, a chiral metal-ligand enolate complex is accessed through soft-enolization and reacts with an aldehyde to form aldol adducts in good enantioselectivity and *anti* diastereoselection. Mechanistic studies confirm the non-Mukaiyama pathway involving a reactive metal enolate species. Investigations have shown that the choice of amine base has a remarkable effect on the mechanism and outcome of the reaction.

The development of the first enantioselective organocatalytic [1,3]-dipolar cycloaddition reaction is also reported. In this imidazolidinone-catalyzed process, nitrones react with □,□-unsaturated aldehydes to form chiral isoxazolidines in excellent yield, enantioselectivity, and diastereoselection. The scope of this process appears quite general with respect to both the nitrone and aldehyde components of the reaction. A second-generation imidazolidinone catalyst offers improved reaction rates and selectivities and has also facilitated the development of the first *exo* selective organocatalytic [1,3]-dipolar and Diels-Alder cycloaddition reactions.

A synthetic approach towards the marine natural product callipeltoside A is described. The synthesis relies upon rapid construction of the stereochemical backbone through a novel tandem amino-sulfide acyl-Claisen rearrangement. Subsequent elaboration towards the macrolide has involved a highly diastereoselective reductive opening of a spirocyclic intermediate, highly diastereoselective Ireland Claisen rearrangement, and synthesis of the tetrahydropyran moiety through a palladium catalyzed carbonylative cyclization. Completion of the synthesis has yet to be achieved due to difficulties in removal of a benzyl ether protecting group.

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Chapter 1

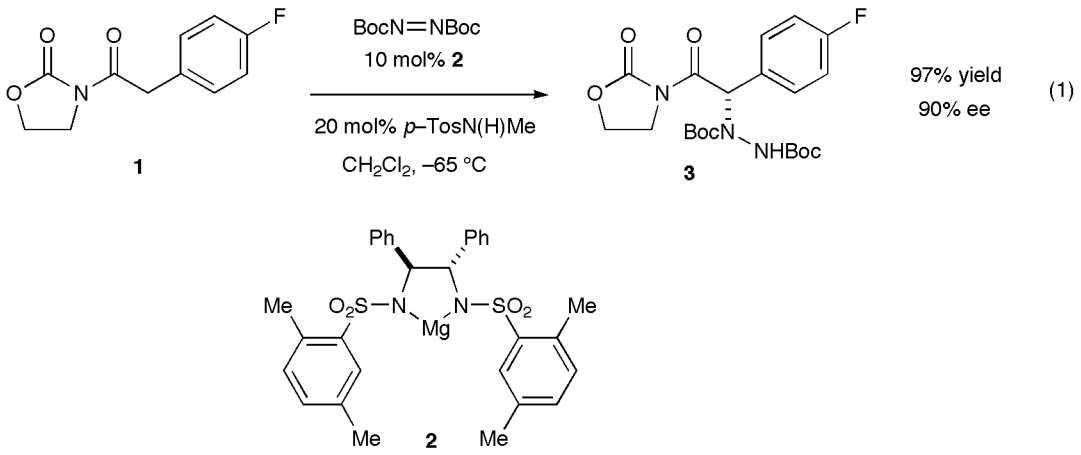
Merging Enolization and Enantioselective Catalysis: Development of a Direct Enantioselective Catalytic *anti* Aldol Reaction

I. Introduction

In recent decades, enantioselective catalytic enolate–electrophile bond formation has received considerable attention from organic chemists.[1] Despite the vast body of research in this area, relatively few reports have detailed enantioselective enolate bond constructions in which the enolization event is included within a catalytic cycle.[2] Stoichiometric enolization protocols typically involve either anionic bases (LDA, LHMDS) or amine bases used in conjunction with Lewis acids (soft-enolization). Enantioselective catalysis traditionally involves Lewis acids bound to chiral ligands, and thus soft-enolization would be the natural choice in seeking to merge enolization with catalysis. Yet, successful implementation of this strategy is contingent upon addressing several potential problems. It has been hypothesized that amine bases complex irreversibly with Lewis acids (such as $TiCl_4$) which are required to activate the carbonyl substrate for enolization, thereby terminating reaction and precluding the development of a catalytic soft–enolization method.[3] In addition, upon reaction of an enolate with an electrophile such as an aldehyde, an anionic heteroatom is typically produced, creating a situation in which the product is tightly bound to the active catalyst, potentially terminating reactivity by inhibiting catalyst turnover.

Among those methods of combining enolization with catalytic bond construction is a particularly elegant report from Evans that overcomes both of these problems.[4]

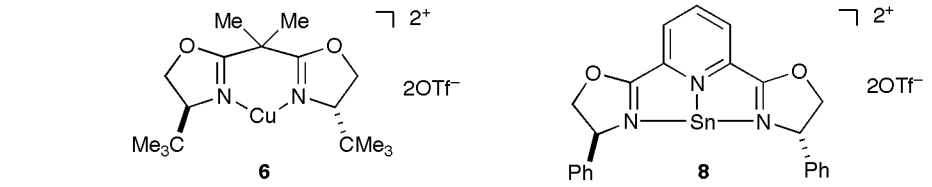
Enantioselective catalytic amination of *N*-acyloxazolidinones such as **1** is effected in the presence of 10 mol% magnesium bis(sulfonamide) catalyst **2** (Equation 1).

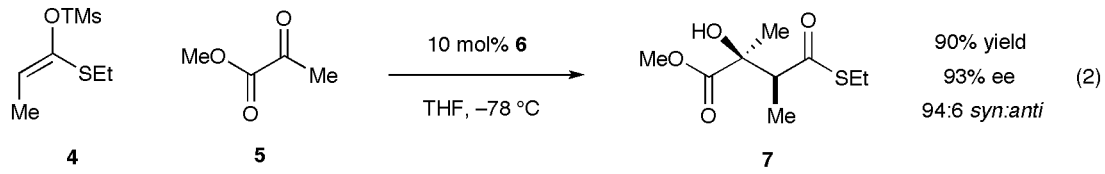


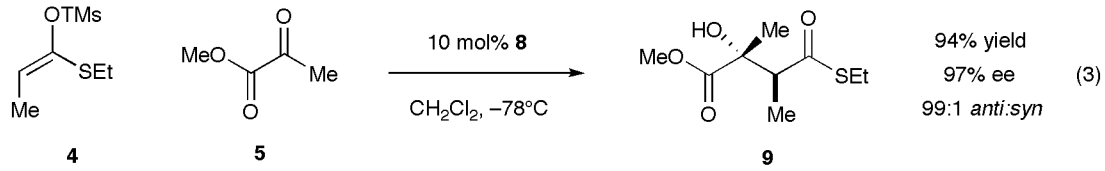
This catalyst system requires 20 mol% N-methyl-*p*-toluenesulfonamide, which is believed to facilitate catalyst turnover by promoting protonation of the intermediate anionic hydrazide species. The □-hydrazido imides **3** are afforded in high yield (> 90%) and good enantiomeric excess (80–90% ee). In this reaction, the catalyst itself is believed to act as the base effecting soft-enolization and thereby allowing catalytic access to a chiral enolate.

The vast majority of catalytic enolate-driven bond constructions reported to date have required the pre-generation of stable enolate surrogates such as silyl ketene acetals.[5] Once isolated, these surrogates then undergo reaction with Lewis acid activated electrophiles. Much of the research involving enolates and enolate equivalents has focused on the aldol reaction, given the important place of this reaction in organic synthesis in both academic and industrial settings. An example are the bis(oxazoline) catalyzed aldol reactions of Evans,[6] in which silyl ketene acetals react with bidentate

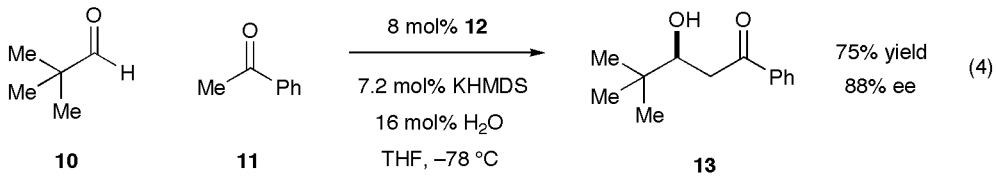
aldehydes in the presence of Cu or Sn bis(oxazoline) complexes **6** and **8**. Importantly, either the *syn* or the *anti* aldol adducts (**7** and **9**, respectively) are accessible, depending upon the choice of metal (Equations 2 and 3).

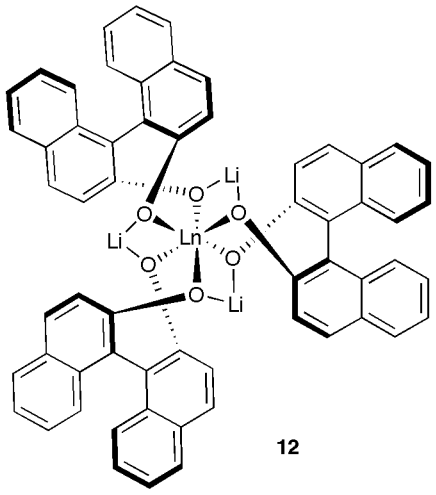




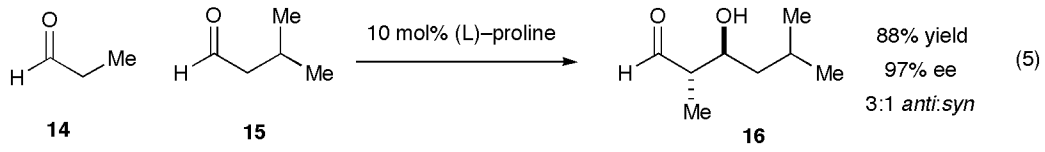


In line with the discussed interest in catalytically accessing chiral enolates, recent developments in aldol technology have sought to effect direct aldol reactions, bypassing the aforementioned enolate surrogates.[7] A notable example is the system designed by Shibasaki[7b] (Equation 4), utilizing the bimetallic catalyst **12** to promote aldol reactions between ketones and a variety of aldehydes.

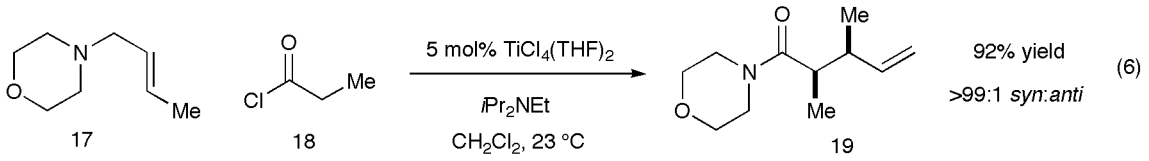




As well, purely organic catalysts including proline have been used in enantioselective production of aldol adducts.[8] One particularly successful approach, reported from these laboratories, has used proline to catalyze the cross-aldol reaction of aldehydes in high yield and enantioselectivity (Equation 5). This reaction proceeds through a proline enamine intermediate. Because this methodology relies upon an organic catalyst, the problems plaguing development of catalytic soft–enolization methods are avoided. Importantly, the products of this aldol reaction are the *anti* diastereomers, a stereochemical relationship that has proven more difficult to achieve than the *syn* variant.[9]



With regard to metal catalyzed soft-enolization, recent reports from these laboratories contradict previous concerns about complexation with and deactivation of Lewis acids by amine bases. Research has shown that sub-stoichiometric quantities of $TiCl_4$ are able to successfully catalyze an acyl-Claisen rearrangement in the presence of stoichiometric *i*Pr_2NEt (Equation 6).[10]

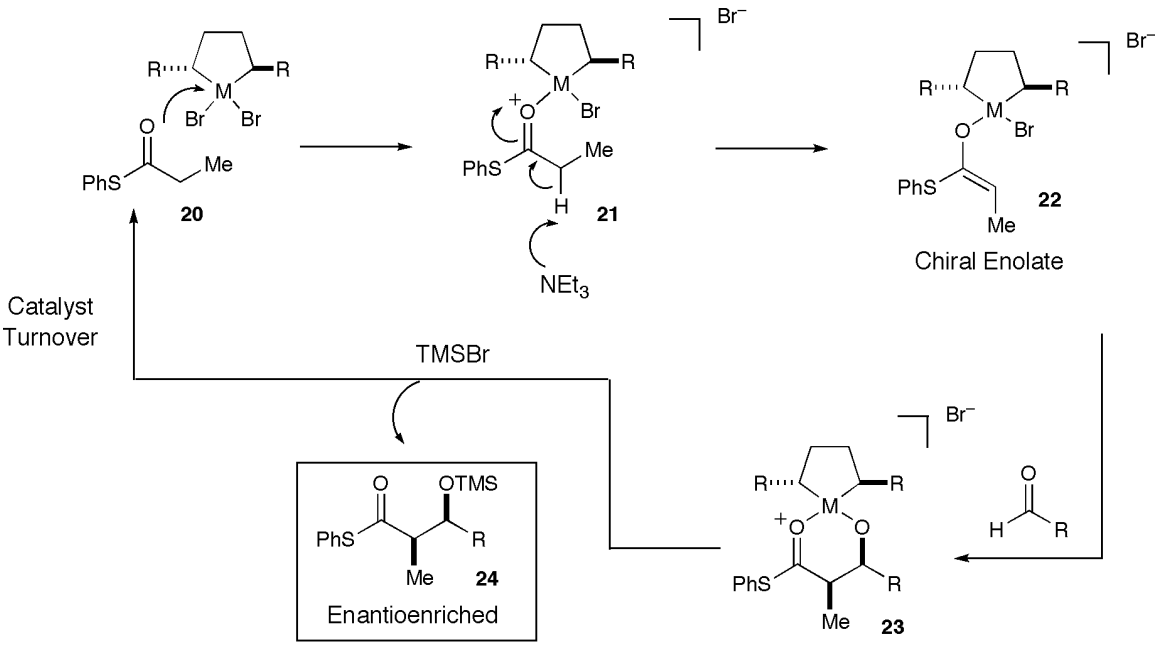


This observation, coupled with the broad interest in and need for new methods of approaching catalytic enantioselective enolate bond constructions, prompted our research group to explore more deeply the ability of Lewis acids to operate under soft-enolization conditions involving amine bases. Given the broad utility of aldol reactions, we sought to develop a platform for enantioselective catalysis through soft-enolization that could be applied to the development of a novel, direct aldol reaction.

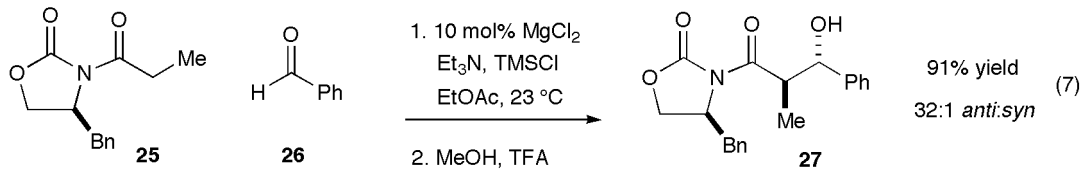
We envisioned a catalytic cycle (Scheme 1) in which a carbonyl compound **20** binds to a Lewis acid-chiral ligand complex, activating it towards soft-enolization. A tertiary amine base would at this point deprotonate the activated carbonyl **21** at the □–position, affording the metal-bound chiral enolate intermediate **22**. We imagined that coordination of the aldehyde electrophile to the metal center would facilitate aldol reaction, in accord with a Zimmerman-Traxler transition state involving aldehyde activation through a closed transition state. To achieve catalyst turnover, disrupting the

chelation of substrate **23** to the metal-ligand complex would be required. We hoped to take advantage of a silyl halide source to silylate metal alkoxide **23** *in situ*, thereby breaking up this chelation.[11] Subsequent dissociation of the metal complex from the monodentate aldol adduct **24** would allow for regeneration of the active catalyst and isolation of the aldol product.

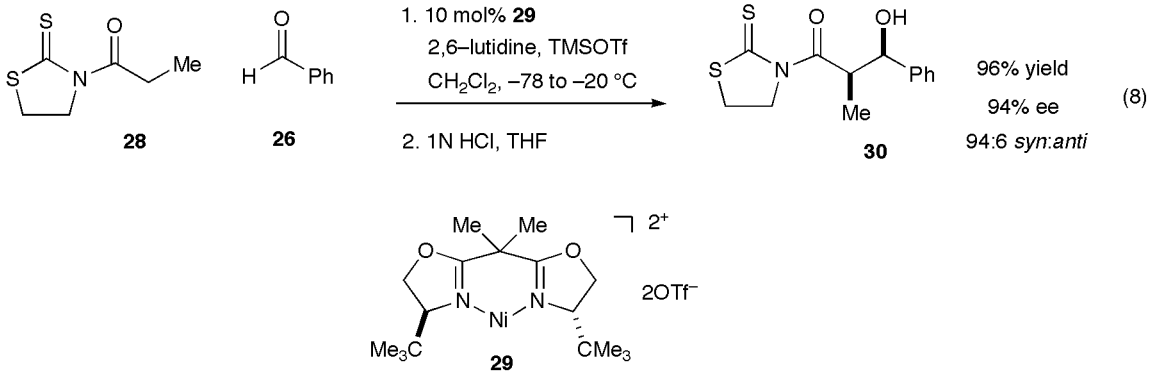
Scheme 1. Proposed catalytic cycle



Subsequent to the completion of the research detailed in this chapter, Evans reported a chiral auxiliary/catalytic achiral Lewis acid–based approach to direct *anti* aldol reactions involving a catalytic cycle similar to our own. Catalytic quantities of achiral magnesium salts and stoichiometric amounts of Et_3N promote soft–enolization of chiral imides such as **25**, and after aldol reaction, silylation of the alkoxide aldol adducts using TMSCl affords catalyst turnover (Equation 7).[12]



As well, Evans has reported a direct enantioselective catalytic *syn* aldol reaction using Ni(II) bis(oxazoline) catalyst **29** to soft-enolize *N*-propionylthiazolidinethiones **28** with 2,6-lutidine and employing silyl triflates to achieve catalyst turnover (Equation 8).[13]

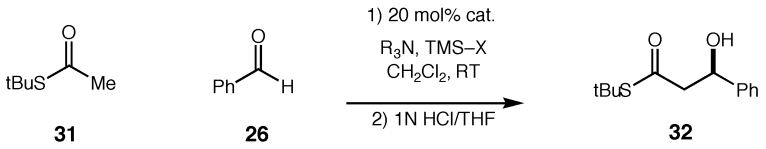


II. Results and Discussion

Acetate ester aldol reaction

Experimentation began by examining the aldol reaction of *tert*-butyl thioacetate **31** with benzaldehyde **26** in the presence of a variety of metal salts and chiral ligands (Table 1).

Table 1. Preliminary results



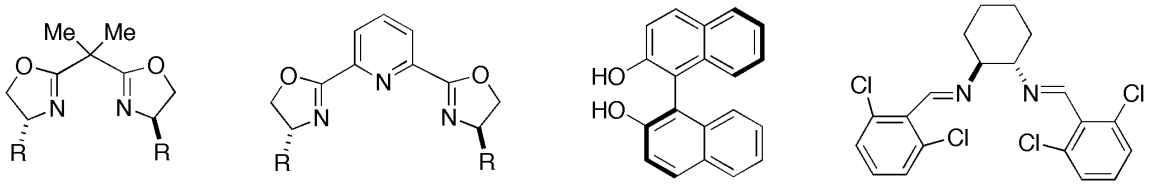
(9)

entry	Lewis Acid	Ligand	R_3N	X	time (h)	% conv[a]	% ee[b]
1	$MgBr_2OEt_2$	**33a**	iPr_2NEt	Cl	76	40	0
2	$ZnBr_2$	**34d**	iPr_2NEt	Cl	76	0	–
3	$SnCl_2$	**34a**	iPr_2NEt	Cl	76	0	–
4	$AlCl_3$	**35**	iPr_2NEt	Cl	5	0	–
5	–	–	iPr_2NEt	Br	36	0	–
6	$MgBr_2OEt_2$	**33a**	iPr_2NEt	Br	47	92	0
7	$MgBr_2OEt_2$	**34d**	iPr_2NEt	Br	68	100	20
8	$MgBr_2OEt_2$	**34b**	Et_3N	Br	30	61	30
9	$MgBr_2OEt_2$	**34d**	Et_3N	Br	24	84	18
10	$MgBr_2OEt_2$	**36**	Et_3N	Br	68	27	0

[a] Conversion to **32** determined by ^1H NMR using an internal bromodecane standard. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralcel OD–H column.

In our hands, magnesium salts were the only Lewis acids able to provide reactivity in this process, and no reaction was observed in the absence of Lewis acid. Bidentate bis(oxazoline) (BOX) ligands **33** and bis(imine) ligands **36** (Figure 1), when bound to the magnesium salt, were unable to impart any enantioselectivity to the catalytic process (for example Table 1, Entries 1, 6, and 10). In contrast, complexes involving magnesium and tridentate pyridinebis(oxazoline) (PyBOX) ligands **34** did afford the aldol adducts with modest enantioselectivity (Table 1, entries 7, 8, and 9).[14]

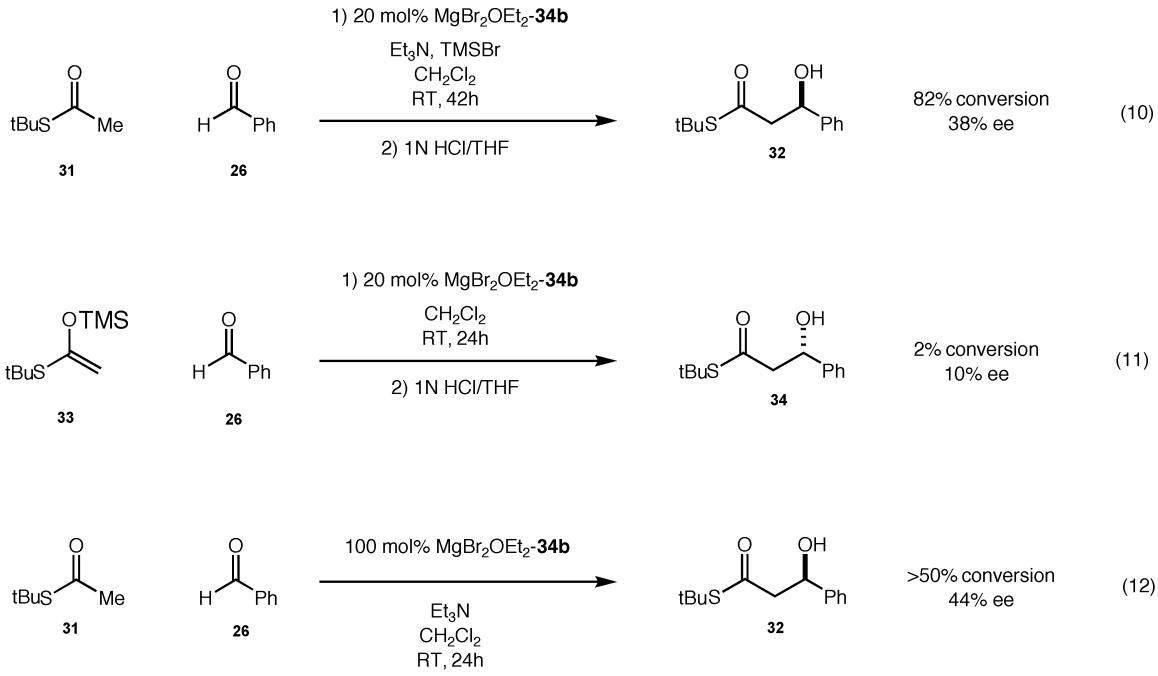
Figure 1. Representative chiral ligands examined in the aldol reaction



33 **34** **35** **36**

a: R = CMe_3; **b:** R = $CHMe_2$; **c:** R = Ph; **d:** R = Bn

Evidence supporting a metal enolate intermediate. At this stage, in an effort to better understand the mechanism of the observed process, we sought to establish whether the reaction was proceeding, as envisioned, *via* a catalytically accessed chiral ligand-metal enolate complex, or if, in fact, the reaction was emulating a traditional Mukaiyama aldol pathway. To explore these mechanistic questions, a series of experiments were conducted. Whereas in the catalytic reaction (Equation 10) the aldol product is formed in 38% ee and 83% conversion, when the silyl ketene acetal is pre-formed and allowed to react with benzaldehyde under the same conditions, the reaction is negligible and produces a product with a slight enrichment of the opposite enantiomer to that observed in the catalytic reaction (Equation 11, 2% conversion, 10% ee favoring the opposite enantiomer). Thus it is unlikely that a Mukaiyama-type reaction manifold could be implicated in the observed outcome of the direct aldol reaction. As further evidence of the intermediacy of an unsilylated metal enolate, the reaction was performed using stoichiometric amounts of the metal–ligand complex with no added silyl halide (Equation 12, >50% conversion, 44% ee), eliminating the possibility of a Mukaiyama aldol pathway. The results of this reaction paralleled the results of our catalytic process (Equation 10, 82% conversion, 38% ee).

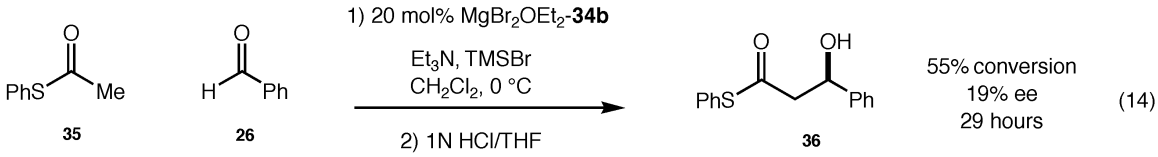


Having provided evidence that this reaction was proceeding through a catalytically accessed chiral ligand-metal enolate complex rather than *via* a Mukaiyama aldol pathway, our attention turned to increasing the rate and selectivity of the process. Due to the low pKa of substrate **31**, imparted by the steric hindrance of the *tert*-butyl group to deprotonation, reactivity remained low despite adjustments to the choice of amine base, solvent, and reagent molarity. In an effort to increase the rate of the soft-enolization step, we sought to alter the nature of the thioester itself; we imagined that more readily enolizable protons □ to the carbonyl might allow for more facile enolization and thus a faster rate of reaction. In turn, a faster reaction would allow for the use of lower reaction temperatures which would accentuate the energetic differences between the two diastereomeric transition states leading to opposite enantiomers of product.

As such, phenyl thioacetate **35** was next investigated as the nucleophilic component of the reaction, under the presumption that the electron withdrawing nature of

the phenyl substituent would activate the substrate toward soft-enolization. In fact, reactions employing this substrate formed product at markedly faster rates, though no significant improvement to the level of enantioselectivity was observed (Equation 13).[15]

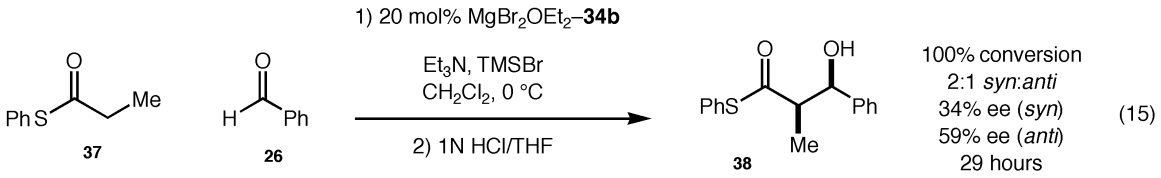
In an effort to increase the enantioselectivity of this process, reactions were performed using phenyl thioacetate at lower temperatures, though this modification to the reaction conditions resulted only in poor reaction efficiency with no concomitant gain in enantioselectivity (Equation 14).[16]



Propionate ester aldol reaction

After establishing that the electronic nature of the thioester was important in achieving reasonable reaction rates yet being unable to improve upon the enantioselectivity of the acetate aldol reactions, we again sought to change the nature of the starting material to increase selectivity. We hypothesized that the terminal position of the enolate, the site of reaction, was relatively small in these acetate aldol reactions; perhaps increasing the steric bulk at the site of bond formation would improve selectivity

by allowing for greater enantiofacial discrimination in the transition state. Accordingly, α-substituted thioesters were chosen for exploration. In particular, phenyl thiopropionate **37** was exposed to benzaldehyde in the presence of a catalytic quantity of a complex of $MgBr_2OEt_2$ and *iso*-propyl PyBOX **34b** (Equation 15) or *tert*-butyl PyBOX **34a** (Equation 16) under the reaction conditions that had proven optimal for the acetate aldol reactions.[17,18,19]



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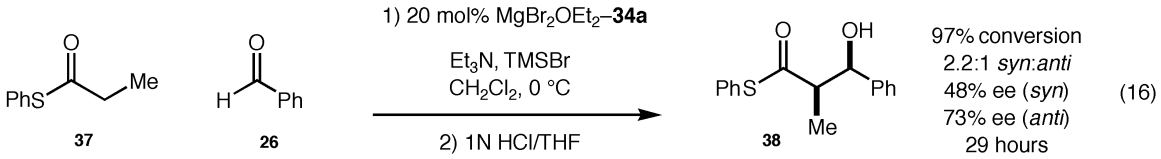
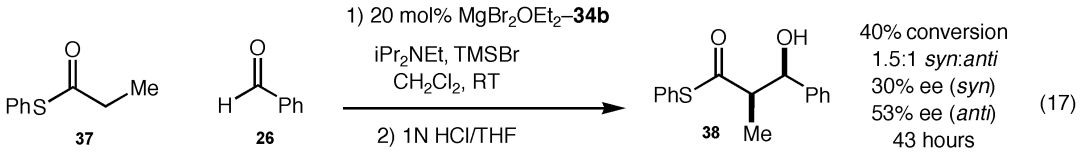


(16)

These reactions each afforded a slight excess of the *syn* diastereomer, and to our delight, the presence of a substituent at the α position resulted in higher levels of enantioselectivity for both the *anti* and *syn* isomers.[20] Unfortunately, the enantiomeric excess of the major, *syn* isomer was significantly lower than that of the minor, *anti* isomer.

Accordingly, we hoped to be able to reverse the sense of diastereoselectivity, such that the diastereomer with higher enantiomeric excess would predominate in the reaction. Given that enolate geometry can control the ratio of *syn* and *anti* products in aldol reactions proceeding through closed transition states, and given that iPr_2NEt and Et_3N

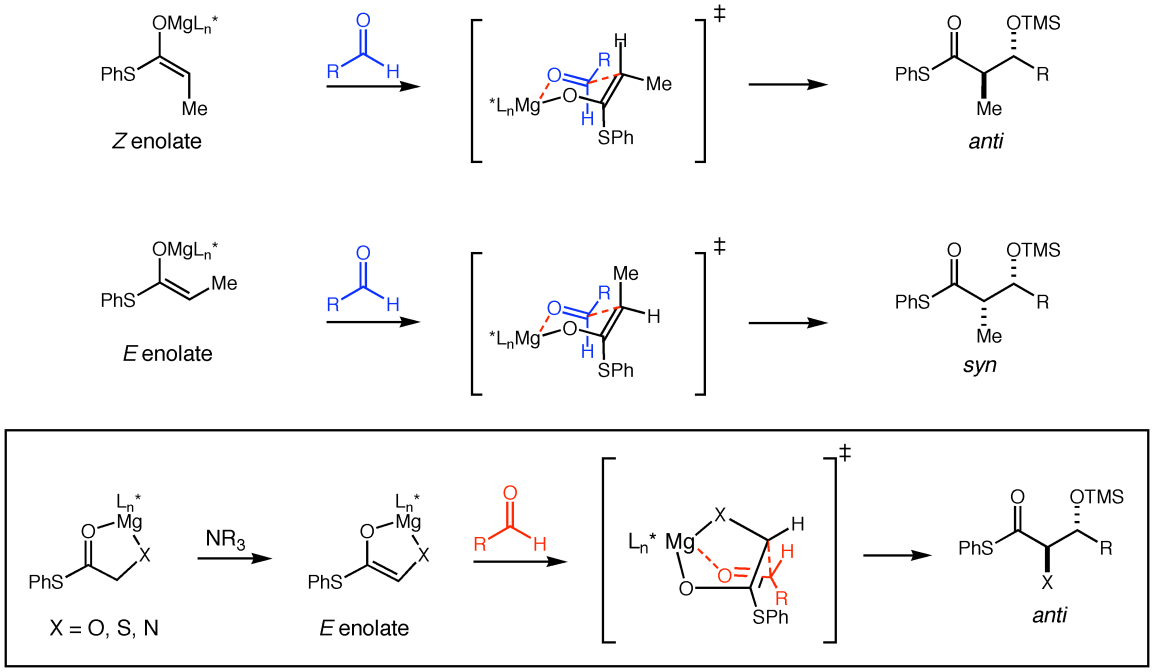
have the potential to afford different enolate geometries when used as soft-enolization bases,[21] it was hoped that employing *i*Pr_2NEt in the reaction would allow for an alteration in diastereoselectivity. In fact, *i*Pr_2NEt was unable to alter the outcome of this reaction (Equation 17).



(17)

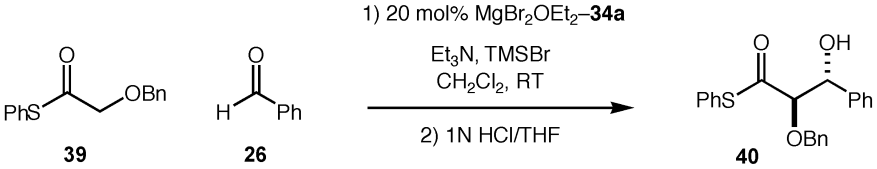
Despite the inability of *i*Pr_2NEt to alter the sense of diastereocontrol in this process through alteration of enolate geometry, we hoped to control the sense of enolate formation through other means to further test this hypothesis. We imagined that use of a substrate bearing heteroatom functionality at the position would allow the substrate to chelate to the metal-ligand complex (Scheme 2). It was hoped that this chelation would enforce exclusive formation of the *E* enolate isomer, which in turn would result in formation of predominantly *anti* aldol adducts. Further, it was imagined that these bidentate chelating substrates would impart overall greater rigidity to the transition state, allowing for greater stereocontrol and thus higher enantioselectivity.[22]

Scheme 2. Enolate geometry and diastereocontrol in the aldol reaction



-Benzyloxy ester aldol reactions

To investigate this hypothesis, -benzyloxy phenylthioacetate **39** was treated with benzaldehyde under the reaction conditions at room temperature (Equation 18, 83% conversion, 2:1 *anti*:*syn*, *anti*: 50% ee). As expected, this new adjustment to the structure of the substrate did result in higher enantioselectivity for the major diastereomer than had been observed with the propionate substrates. At low temperatures (–10 °C), good diastereocontrol as well as moderate levels of enantiomeric excess were observed (78% conversion, 12:1 *anti*:*syn*, *anti*: 73% ee).



83% conversion
2:1 *anti*:*syn*
50% ee (*anti*)
5% ee (*syn*)
105 hours

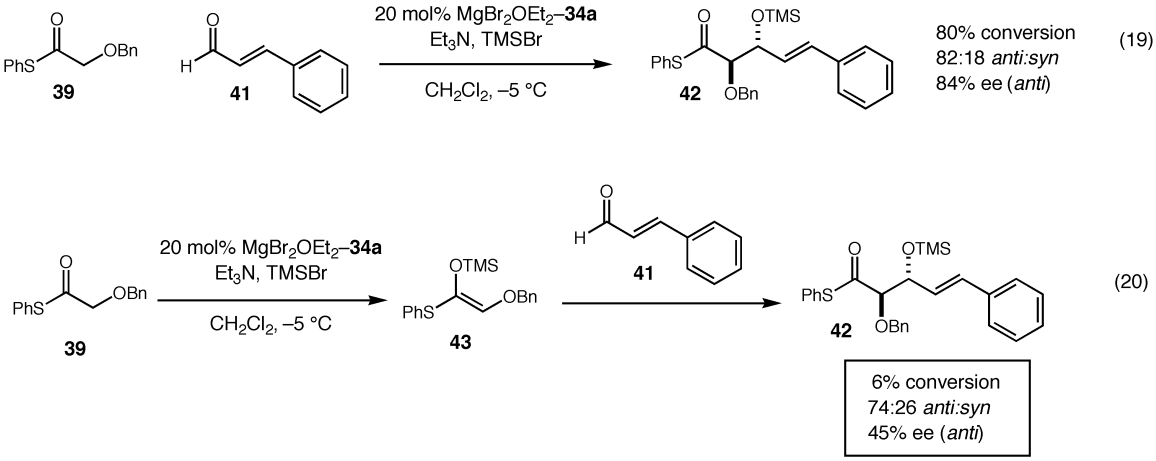
(18)

It was further established that, as had been previously observed, tridentate PyBOX ligands **34** provided superior enantioselectivity than did their bidentate BOX counterparts; of the PyBOX ligands, those bearing *tert*–butyl substituents at the stereogenic positions provided the highest selectivity, presumably for steric reasons. As such, *tert*-butyl PyBOX **34a** was chosen for further reaction optimization. Additional experiments established that cinnamaldehyde was a capable electrophile in this aldol process (Equation 19).

In complete accord with our model (Scheme 2), in which the reaction of the α-oxy thioesters proceeds *via* a closed boat–like transition state involving a 6–coordinate magnesium species[23] with the enolate geometry dictated by chelation, the major observed diastereomer in these α-benzyloxy phenylthioacetate reactions was the *anti* isomer.[24] In an effort to improve upon the reactivity and selectivity of this process we undertook an investigation of the reaction mechanism.

Evidence supporting a metal enolate intermediate and stereochemical rationale. First, we sought to determine whether a chiral enolate intermediate was operational, or if perhaps some other mechanism could be implicated in these α-benzyloxy thioacetate reactions. Using a ReactIR system, α-benzyloxy phenylthioacetate was treated with TMSBr and the catalyst in the absence of any aldehyde (Equation 20). Formation of silyl ketene acetal was monitored until all of the thioester starting material had been consumed. At this stage, cinnamaldehyde was introduced to the reaction vessel, and only negligible amounts of aldol product were observed, in contrast to the comparable standard catalytic reaction (Equation 19, 80% conversion, *anti*: 84% ee).

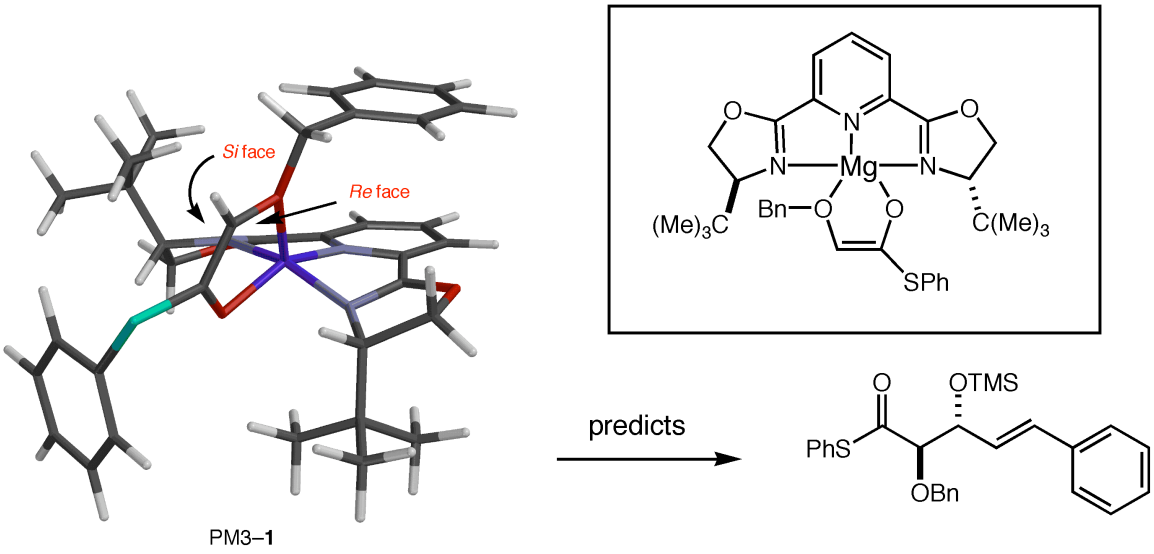
Further, monitoring this catalytic reaction with time showed that silyl ketene acetal **43** is formed as an unreactive byproduct during the course of the reaction, accounting for incomplete conversion to product. Thus it was again concluded that a silyl ketene acetal was not involved in the catalytic aldol reaction, and that a metal enolate species was likely operational.



As further evidence supporting the intermediacy of a catalytically accessed chiral ligand-metal enolate complex, the absolute sense of stereoinduction can be explained by a semiempirical computational model (PM3) of the catalyst–substrate complex (PM3–**1**, Figure 2). In this model the *re* face of the enolate is shielded by the *tert*–butyl substituent of the catalyst, leaving the *si* face open for addition, in accord with the observed stereochemical outcome.[25] Noteworthy is the presence of the benzyl substituent of the thioester near the pyridyl ring of the catalyst, suggesting the potential for a stabilizing cation-π type interaction, which could act as an additional element of structural rigidity in the transition state of the reaction. Further, such an interaction might explain why BOX

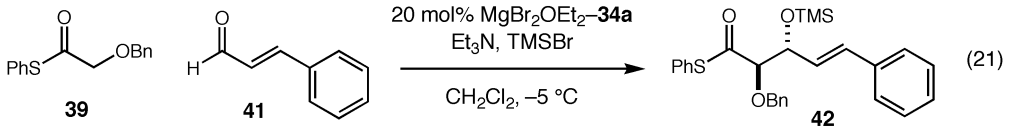
catalysts, which lack this pyridyl ring, catalyzed only racemic reactions using these α-benzyloxy phenylthioacetate substrates.

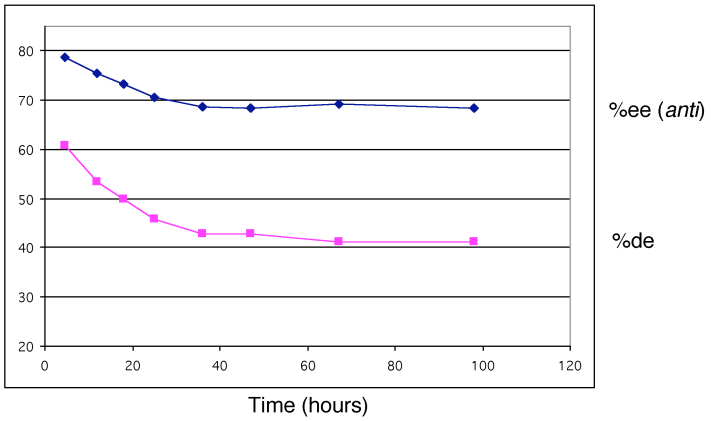
Figure 2. Calculated substrate-catalyst complex



Degradation of selectivity. To further understand this reaction, the process was monitored with time (Scheme 3), and it was noted that the levels of enantio- and diastereoselectivity degrade during the course of the reaction.

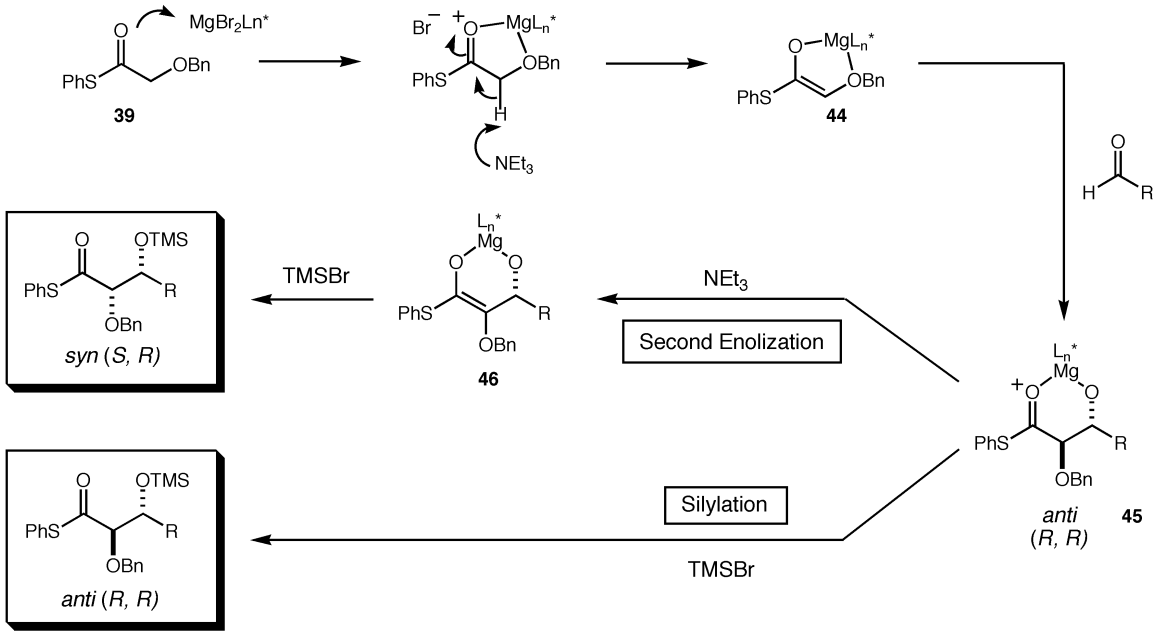
Scheme 3. Degradation of selectivity



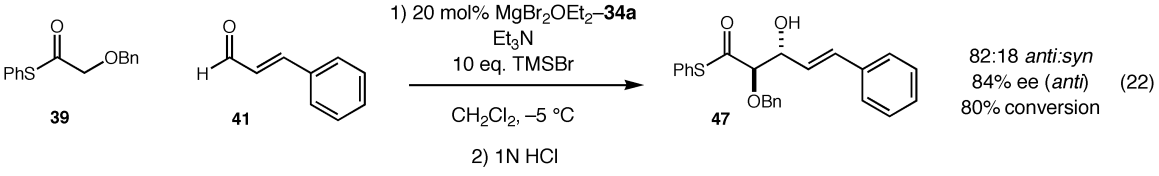


Based on our vision of the implicated catalytic cycle, this degradation was understood as follows (Scheme 4): following aldol reaction, the alkoxide aldol adduct is chelated to the catalyst as complex **45**. This adduct is activated for second soft-enolization at the position □ to the carbonyl to produce enolate **46**. If silylation is slow, then the metal adduct **45** can epimerize, resulting in a degradation of selectivity.

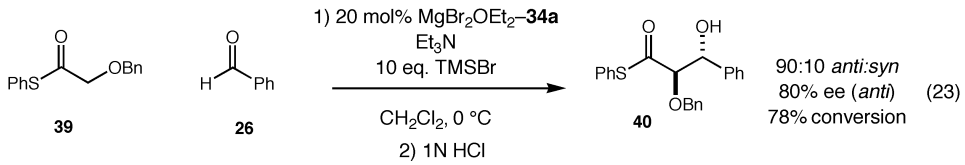
Scheme 4. Proposed rationale for observed degradation of selectivity



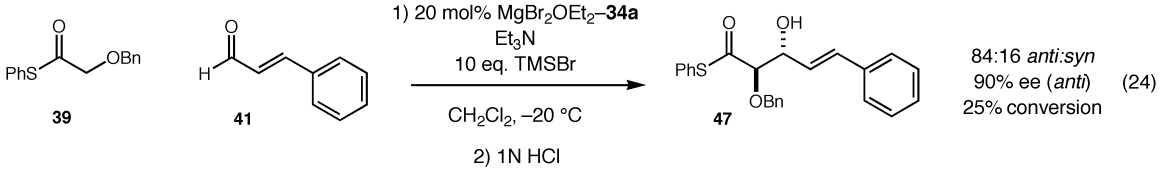
Based on this hypothesis, it was believed that increasing the rate of the silylation step would result in maintenance of enantio- and diastereoselectivity in the process by avoiding the undesired second enolization. Indeed, increasing the amount of TMSBr in the reaction from the standard 2 equivalents to 10 equivalents did result in maintenance in the level of selectivity observed with cinnamaldehyde (Equation 22), supporting our hypothesis concerning the epimerization of an activated product-catalyst complex. Unfortunately, the excess TMSBr did slow the overall rate of the reaction, presumably as a result of increasing the rate of the undesired silyl ketene acetal formation.



Application of these conditions to the aldol reaction with benzaldehyde also resulted in high levels of diastereo- and enantioselectivity (Equation 23).



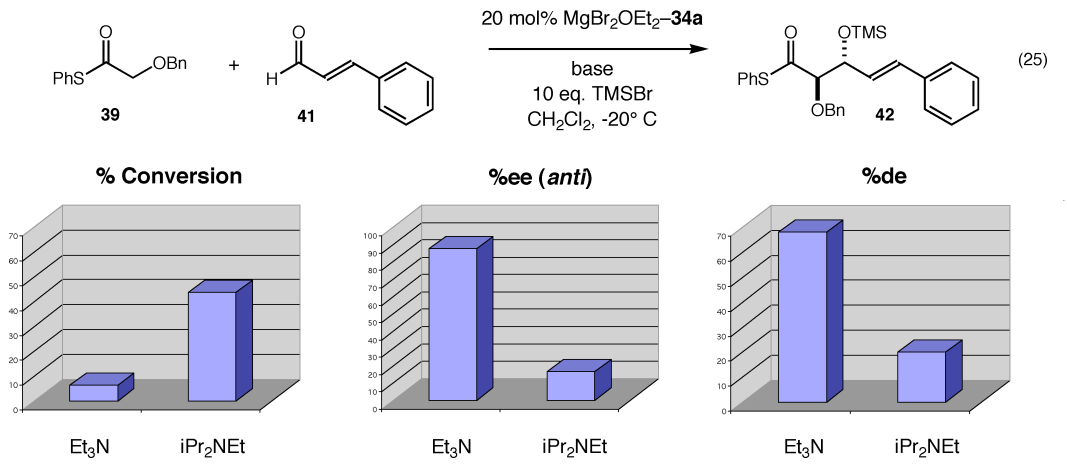
Importantly, the enantioselectivity of the aldol reaction with cinnamaldehyde could be raised to 90% as the temperature of the reaction was lowered to –20 °C, albeit with only modest conversion to product (Equation 24).



Our desire to develop a catalytic system that would be reactive at low temperatures in order to achieve high stereoselectivity led us to investigate whether the nature of the amine base influenced the outcome of the □-benzyloxy phenylthioacetate aldol reactions. We expected that the choice of amine base might be significant, given the hypothesized degradation mechanism involving a second soft-enolization/epimerization event (Scheme 4). In fact, we observed a remarkable effect: whereas the aldol reaction employing Et_3N afforded aldol adduct **42** in 6.4% conversion, 87% ee, and 7:1 *anti*:*syn* selectivity after 47 hours, the analogous reaction involving *i*Pr_2NEt showed 44% conversion,16% ee, and 1.5:1 *anti*:*syn* selectivity after 47 hours

(Figure 3). We expected that investigating this remarkable difference would give insight into the mechanism of the catalytic process.

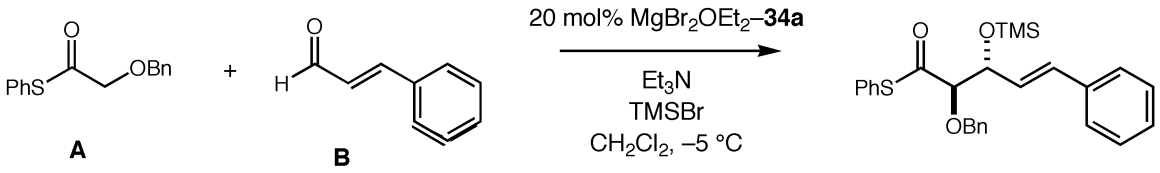
Figure 3. Effect of amine base on the aldol reaction

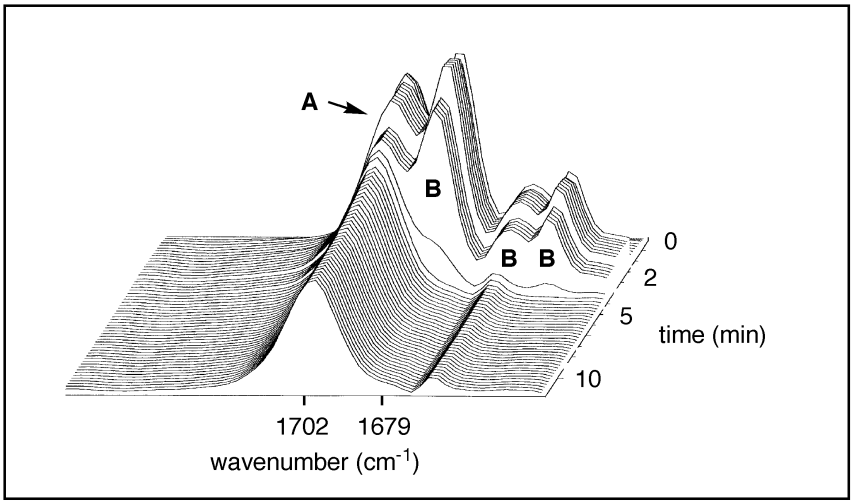


Mechanistic investigations. *In situ* monitoring of the Et_3N experiment with a ReactIR system revealed that upon addition of Et_3N to a reaction mixture containing thioester, cinnamaldehyde, catalyst, and TMSBr, the IR stretches associated with the aldehyde immediately disappeared (Figure 4). Yet, at this stage, no aldol product had formed. Further, over the next 35 hours, aldol adduct did form at the typical rate, and it was therefore concluded that Et_3N was combining reversibly with the aldehyde during the course of the reaction. We hypothesized that the Et_3N was adding as a nucleophile to a silyl activated aldehyde to form a silylated aminol salt **48** (Figure 5), whereas *i*Pr_2NEt, a more sterically encumbered amine, might be unable to add as a nucleophile to cinnamaldehyde and therefore would be unable to form this complex. Thus the two bases might create different reactive intermediates, allowing for starkly different outcomes of

the catalytic reaction. We sought to perform further experiments to reveal the true nature of this complexation.

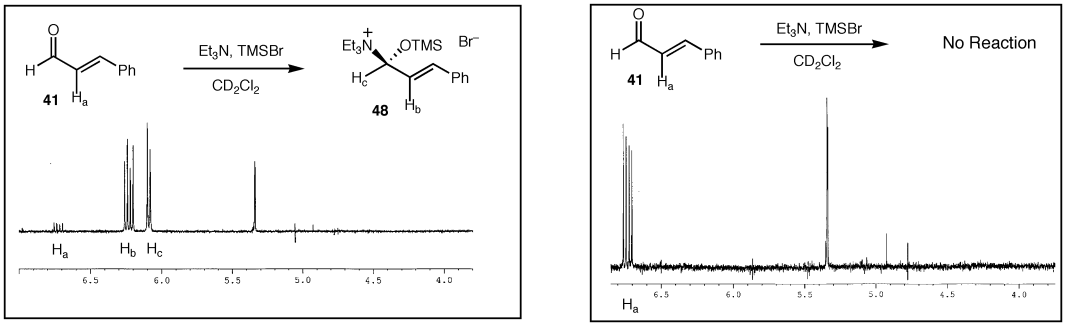
Figure 4. ReactIR investigation reveals aldehyde consumption





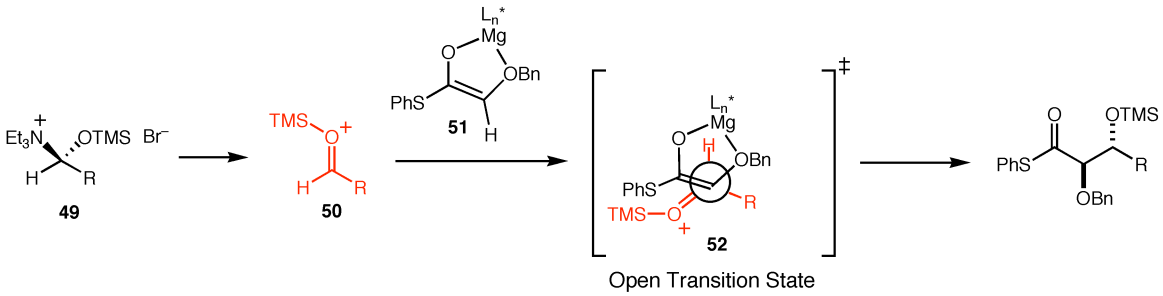
^{1}H NMR studies were employed to investigate further this curious observation. Cinnamaldehyde and TMSBr were combined in CD_2Cl_2, followed by the addition of either Et_3N or *i*Pr_2NEt (Figure 5). In complete accord with our hypothesis, these NMR studies revealed that, in the presence of Et_3N, cinnamaldehyde was immediately converted to silylated aminol **48**. In contrast, in the presence of *i*Pr_2NEt, this silylated aminol species was not formed, and aldehyde remained unaltered.

Figure 5. Detection of silylated aminol by ^{1}H NMR



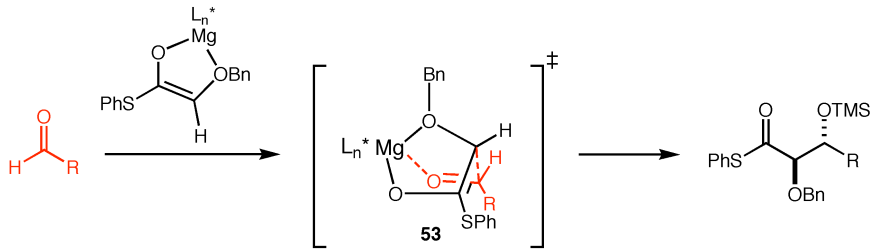
To explain how this difference could account for the observed differences in rate and selectivity of the catalytic reaction, we were required to revise our vision of the catalytic cycle. Based on our new understanding of the intermediates involved in this reaction, we proposed (Scheme 5) that, in the reactions mediated by Et_3N, the resulting silylated aminol **49**, which appears quite stable by ^{1}H NMR, would to some extent break down to form the silyl activated aldehyde **50**, which would then act as a reactive species. Of course, this silylated aldehyde would be required to react *via* an open transition state such as **52**, consistent with the observed *anti* selectivity.

Scheme 5. Silylated aminol intermediate leads to open transition state



In contrast, when *i*Pr_2NEt was employed, no such silylated aminol was formed, and, as a result, a preponderance of free, unsilylated aldehyde remained and could react *via* a closed transition state such as **53** (Scheme 6). Thus, the two different bases lead to the formation of two different reactive intermediates that react through two different transition states, thereby accounting for differences both in reactivity and selectivity. Though the Et_3N-induced complex formation is responsible for high levels of enantioselectivity, this intermediate is also responsible for low reactivity; apparently, the equilibrium between silylated aminol intermediate and silyl-activated aldehyde lies heavily toward the silylated aminol species.

Scheme 6. Free aldehyde leads to closed transition state



Closed Transition State

Importantly, this new understanding of the catalytic system is in complete accord with the maintenance of high selectivity and lower reaction rate observed with increasing the amount of TMSBr in the reaction (*vide supra*). More TMSBr will bias the reaction toward the pathway favoring formation of the relatively stable silylated aminol intermediate, leading to the silyl-activated aldehyde pathway, which is highly enantioselective. In contrast, decreasing the amount of TMSBr allows aldehyde to

remain free and unaltered in solution and to react immediately *via* the faster, less selective path.

Limitations and future directions

Based on these observations and hypotheses, increasing the size of or changing the electronics of the silyl source may have a role in increasing the enantioselectivity of the Et_3N mediated reaction. Given the role of the silyl species in activating the aldehyde after collapse of the aminol intermediate, pre-generation of an activated aldehyde surrogate (for example, an oxocarbenium ion) may be able to promote the aldol reactions while avoiding the thermodynamically stable silylated aminol intermediate, thereby increasing reaction efficiency. As well, other amine bases intermediate in size between *i*Pr_2NEt and Et_3N may allow for formation of a silylated aminol intermediate required for high enantioselectivity but one that might be less stable and more prone to collapsing to the silyl-activated aldehyde species, the reactive component of the highly enantioselective aldol reactions.

Once these investigations have been completed, the scope of this reaction must be expanded to include other thioesters. In particular, other types of chelating heteroatoms β to the carbonyl and the nature of the substituent on these heteroatoms should be explored in an effort to achieve a stronger chelating system. A tighter chelate would be expected to afford a smaller and more rigid catalyst–substrate complex allowing for greater selectivity in the catalytic process. Once good reaction efficency has been obtained with high enantioselectivity (> 90% ee), other aldehydes will be examined to further establish the scope and generality of the process.

III. Conclusion

Our laboratories have shown that $MgBr_2OEt_2$-*tert*-butyl PyBOX complexes are able to catalyze a novel enantioselective *anti* aldol reaction between α–benzyloxy thioesters and a selection of aldehydes with high conversion and good enantioselectivity (up to 90% ee at –20 °C). These reactions rely upon catalytic soft-enolization of the thioester by the catalyst complex and triethylamine, and catalyst turnover is achieved through introduction of trimethylsilyl bromide, which is able to silylate the alkoxide aldol adduct intermediate, thereby freeing the catalyst from the product. This methodology, then, is one of very few processes that are able to include an enolization event in a catalytic cycle. Given the synthetic importance of aldol reactions and of the rare *anti* aldol reaction in particular, the methodology presented herein represents a fundamental contribution to the field. Further, the ability to access chiral ligand–metal enolate complexes in a catalytic fashion, merging enantioselective catalysis with soft–enolization, should allow for development of a range of enantioselective catalytic enolate–based transformations.

IV. Experimental Section

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[26] Non–aqueous reagents were transferred under nitrogen *via* syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Bromotrimethylsilane, methylene chloride, pyridine, diisopropylethylamine, and triethylamine were distilled from calcium hydride. Commercially available (*S*)-(-)-1,1'-bi-2-napthol, aluminium chloride, zinc bromide, tin(II) choride, and magnesium bromide–diethyl etherate were used without further purification. The silylketene acetal derived from *tert*-butyl thioacetate was prepared using LDA and TMSCl.[27] *tert*-Butyl thioacetate, phenyl thiopropionate, and phenylthio α-benzyloxyacetate were prepared from the corresponding thiol and acid chloride in the presence of pyridine and were distilled before use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[28] Thin–layer chromatography (TLC) was performed on EM reagents 0.25 mm silica gel 60-F plates.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-400, AMX-400, and DRX-500 spectrometers, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C are reported in terms of chemical shift. Infrared spectra were recorded on an ASI React–IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained at University of California at Berkeley Mass Spectral laboratory. HPLC analysis was performed on a Hewlett-Packard 1100 series HPLC at 254 nm using the following Daicel Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

Bis(oxazoline) ligands. (*R*,*R*)-Bis(phenyloxazoline), (*R*,*R*)-bis(*tert*-butyloxazoline), (*R*,*R*)-bis(benzyloxazolinyl)pyridine, (*R*,*R*)-bis(isopropyloxazolinyl)pyridine, (*R*,*R*)-bis(*tert*-butyloxazolinyl)pyridine, and bis(imine) **36** were prepared as previously described[29] and were spectroscopically identical in all respects to the reported materials.

General Procedure for the Aldol Addition. To an oven-dried 8 mL vial containing a magnetic stirring bar was added, in an inert atmosphere box, chiral ligand (0.22 mmol) and metal (0.20 mmol). The vial was fitted with a serum cap, removed from the inert atmosphere box, and charged with CH_2Cl_2 (0.9 mL). The resulting suspension was stirred rapidly for 1 to 3 h. The ester (1.0–4.0 mmol) was added by syringe, followed by the sequential addition of the aldehyde (1.0–2.0 mmol), trimethylsilyl bromide (2–10 mmol), and tertiary amine base (1.35–7 mmol). The resulting solution was stirred at room temperature until the aldehyde was consumed, as determined by TLC (1% Et_2O/CH_2Cl_2). The reaction mixture was then partitioned between ph 7 phosphate buffer (5 mL) and Et_2O (5 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford the crude silyl ether which was dissolved in THF (4 mL) and treated with 1N HCl (0.2 mL). After agitation and standing at room temperature for 20 min, this solution was diluted with Et_2O (5 mL) and H_2O (5 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried

over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to give the β-hydroxy esters.

Preparation of (3*R*)-S-*tert*-Butyl-3-hydroxy-3-phenyl-propanethioate (Equation 10). Prepared according to the general procedure using (*R*,*R*)-bis(isopropyloxazolinyl)pyridine (0.20 mmol), magnesium bromide diethyl etherate (46.5 mg, 0.18 mmol), S-*tert*-butyl thioacetate (128 μL, 0.90 mmol), benzaldehyde (180 μL, 1.77 mmol), bromotrimethylsilane (0.90 mmol), and triethylamine (2.25 mmol) in CH_2Cl_2 (3 mL) for 42 h at 23 °C. Analysis of the crude reaction mixture by ^{1}H NMR indicated 82% conversion to the crude trimethylsilyl ether, which was desilylated to the named compound. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexanes:ethanol), 1.0 mL/min; t_r = 11.2 min, 12.9 min; 38% ee. ^{1}H NMR resonances and optical rotation were in complete accord with (3*R*)–S-*tert*-butyl 3-hydroxy-3-phenyl-propanethioate.[30]

Preparation of (3*R*)-S-Phenyl-3-hydroxy-3-phenyl-propanethioate (Equation 13). Prepared according to the general procedure using (*R*,*R*)-bis(isopropyloxazolinyl)pyridine (0.22 mmol), magnesium bromide diethyl etherate (51.7 mg, 0.20 mmol), S-phenyl thioacetate (270 μL, 2.0 mmol), benzaldehyde (100. μL, 1.0 mmol), bromotrimethylsilane (1.0 mmol), and triethylamine (2.5 mmol) in CH_2Cl_2 (1.7 mL) for 4.0 h at 23 °C. Analysis of the crude reaction mixture by ^{1}H NMR indicated a 100% conversion to the crude trimethylsilyl ether, which was desilylated to the named compound. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H

column (90:10 hexanes:ethanol), 1.0 mL/min; t_r = 11.3 min, 13.2 min; 23% ee. ^{13}C NMR resonances were in complete accord with S-phenyl-3-hydroxy-3-phenyl-propanethioate.[31]

Preparation of (2*R* , 3*R*)-S-Phenyl-3-hydroxy-2-methyl-3-phenyl-propanethioate (Equation 16). Prepared according to the general procedure using (*R*,*R*)-bis(*tert*-butyloxazolinyl)pyridine (70.4 mg, 0.22 mmol), magnesium bromide diethyl etherate (51.7 mg, 0.20 mmol), S-phenyl thiopropionate (300. μL, 2.0 mmol), benzaldehyde (100. μL, 1.0 mmol), bromotrimethylsilane (1.0 mmol), and triethylamine (2.5 mmol) in CH_2Cl_2 (0.9 mL) for 29 h at 0 °C. Analysis of the crude reaction mixture by ^1H NMR indicated a 97% conversion to the crude trimethylsilyl ether, which was desilylated to the named compound. Product distribution was determined by HPLC; *anti* diastereomers: Chiralcel OD-H column (94:6 hexanes:ethanol), 1.0 mL/min; t_r = 11.9, 12.8 min, 73% ee (*anti*); *syn* diastereomers: Chiralpak AD column (94:6 hexanes:isopropanol), 1.0 mL/min; t_r = 12.6, 13.9 min, 48% ee (*syn*); 2.2:1 (*syn*:*anti*). ^1H NMR resonances were in complete accord with S-phenyl-3-hydroxy-2-methyl-3-phenyl-propanethioate.[32]

Preparation of (2*R*,3*S*)-S-Phenyl-2-benzyloxy-3-hydroxy-3-cinnamyl-propanethioate (Equation 22). Prepared according to the general procedure using (*R*,*R*)-bis(*tert*-butyloxazolinyl)pyridine (35.2 mg, 0.11 mmol), magnesium bromide diethyl etherate (25.3 mg, 0.10 mmol), S-phenyl thio(α-benzyloxy)acetate (205 μL, 1.0 mmol), cinnamaldehyde (62.5 μL, 0.5 mmol), bromotrimethylsilane (5.0 mmol), and triethylamine (2.5 mmol) in CH_2Cl_2 (0.5 mL) for 35h at –5 °C. Analysis of the crude

reaction mixture by ^{1}H NMR indicated 80% conversion to the crude trimethylsilyl ether, which was desilylated to the named compound. Product distribution was determined by HPLC with a Chiralcel ODH column (97:3 hexanes:ethanol), 1.0 mL/min; *anti* diastereomers t_r = 44.2, 54.8 min, 84% ee (*anti*); *syn* diastereomers t_r = 48.4, 69.9 min; 82:18 (*anti*:*syn*); ***Anti* Diastereomer:** IR (neat) 3439, 1698, 1529, 1351, 1112, 749, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) □ 7.47-7.26 (m, 15H, ArH), 6.66 (d, *J* = 16.2 Hz, 1H, CHC**H**Ph), 6.30 (dd, *J* = 7.3, 15.9 Hz, 1H, C**H**CHPh), 5.30 (d, *J* = 0.6 Hz, 1H, C**H**OH), 5.00 (d, *J* = 11.3 Hz, 1H, OC**H**$_2$Ph), 4.68 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$Ph), 4.22 (d, *J* = 5.0, 1H, C**H**COSPh); ^{13}C NMR (125 MHz, $CDCl_3$) □ 200.2, 136.5, 136.4, 134.7, 133.2, 129.5, 129.2, 129.0, 128.6, 128.5, 128.4, 128.0, 127.9, 126.7, 126.1, 87.3, 74.8, 73.9; HRMS (FAB/$^7Li^+$) exact mass calcd for $(C_{24}H_{22}{}^7LiO_3S)^+$ requires *m*/*z* 397.1450, found *m*/*z* 397.1457.

Preparation of (2*R*,3*S*)-S-Phenyl-2-benzyloxy-3-hydroxy-3-phenyl-propanethioate (Equation 23). Prepared according to the general procedure using (*R*,*R*)-bis(*tert*-butyloxazolinyl)pyridine (70.4 mg, 0.22 mmol) magnesium bromide diethyl etherate (51.7 mg, 0.20 mmol), S-phenyl thio(□-benzyloxy)acetate (410. □L, 2.0 mmol), benzaldehyde (100. □L, 1.0 mmol), bromotrimethylsilane (10.0 mmol), and triethylamine (680. □L, 4.9 mmol) in CH_2Cl_2 (0.9 mL) for 60 h at 0 °C. Analysis of the crude reaction mixture by ^{1}H NMR indicated 78% conversion to the crude trimethylsilyl ether, which was desilylated to the named compound. Product distribution was determined by HPLC with a Chiralcel OD–H column (97.3:2.7 hexanes:ethanol), 1.0 mL/min; *anti* diastereomers t_r = 35.0, 39.9 min, 80% ee (*anti*); *syn* diastereomers t_r =

37.8, 55.0 min; 9:1 (*anti*:*syn*); $[\square]_D^{23}$ = +90.2 (c = 0.76). ^{1}H NMR resonances and optical rotation were in complete accord with (2*R*,3*S*)–S-phenyl-2-benzyloxy-3-hydroxy-3-phenyl-propanethioate.[33]

Procedure for the Mukaiyama Aldol Reaction of Silylketene Acetal 33 with Benzaldehyde (Equation 11). To an oven-dried 8 mL vial containing a magnetic stirring bar was added, in an inert atmosphere box, (*R*,*R*)-bis(isopropyloxazolinyl)pyridine (0.22 mmol) and magnesium bromide-diethyl etherate (0.20 mmol). The vial was fitted with a serum cap, removed from the inert atmosphere box, and charged with CH_2Cl_2 (0.9 mL). The resulting suspension was stirred rapidly for 3 h. The silylketene acetal derived from *tert*-butyl thioacetate (2.0 mmol) was added by syringe, followed by addition of benzaldehyde (1.0 mmol). The resulting solution was stirred at room temperature for 24 hours. The reaction mixture was then partitioned between ph 7 phosphate buffer (5 mL) and Et_2O (5 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford the crude silyl ether which was dissolved in THF (4 mL) and treated with 1N HCl (0.2 mL). After agitation and standing at room temperature for 20 min, this solution was diluted with Et_2O (5 mL) and H_2O (5 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford S-*tert*-butyl-3-hydroxy-3-phenyl-propanethioate in 2% conversion and 10% ee, using the analytical methods described above for S-*tert*-butyl-3-hydroxy-3-phenyl-propanethioate.

^{1}H NMR Observation of Reaction of Cinnamaldehyde with Tertiary Amines. To an oven-dried NMR tube fitted with a serum cap and charged with CD_2Cl_2 (0.5 mL) was added cinnamaldehyde (0.25 mmol) and triethylamine or diisopropylethylamine (1.25 mmol). After 5 min ^{1}H NMR spectra were recorded, indicating consumption of the aldehyde in the case of triethylamine, but no consumption of aldehyde in the case of diisopropylethylamine. After 1 h, ^{1}H NMR spectra indicated no consumption of cinnamaldehyde in the case of diisopropylethylamine.

ReactIR Observation of Cinnamaldehyde Consumption in the Presence of Triethylamine and Degradation of Aldol Reaction Selectivity. To an oven dried 8 mL vial containing a magnetic stirring bar was added, in an inert atmosphere box, (*R*,*R*)-bis(*tert*-butyloxazolinyl)pyridine (0.73 mmol) and magnesium bromide–diethyl etherate (0.66 mmol). The vial was fitted with a serum cap, removed from the inert atmosphere box, and charged with CH_2Cl_2 (3.0 mL). The resulting suspension was stirred rapidly for 45 min, and then cannulated into a schlenk flask. The ReactIR probe was inserted into the flask, and the flask was purged with nitrogen. S-phenyl thio(□-benzyloxy)acetate (6.6 mmol) was added by syringe, and the flask was cooled to –5 °C, followed by addition of cinnamaldehyde (3.3 mmol), triethylamine (16.5 mmol), and trimethylsilyl bromide (6.6 mmol). Immediately upon addition of triethylamine, the cinnamaldehyde IR stretch at 1679 cm^{-1} disappeared. Aqueous workup of an aliquot according to the general procedure after 4.5 h showed 25% conversion, 4.1:1 *anti*:*syn*, and 79% ee (*anti*). The solution was allowed to stir at –5 °C for 67 h. The reaction mixture was then

partitioned between ph 7 phosphate buffer (5 mL) and Et_2O (5 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford the crude silyl ether which was dissolved in THF (4 mL) and treated with 1N HCl (0.2 mL). After agitation and standing at room temperature for 20 min, this solution was diluted with Et_2O (5 mL) and H_2O (5 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford S-phenyl-2-benzyloxy-3-hydroxy-3-cinnamyl-propanethioate in 70% conversion, 2.4:1 *anti*:*syn,* and 69% ee (*anti*), using the analytical methods described above for S-phenyl-2-benzyloxy-3-hydroxy-3-cinnamyl-propanethioate.

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(15) Ethyl thioacetate was also examined, and showed an increased rate of reaction, though no improvement in enantioselectivity. The product of the aldol reaction of ethyl thioacetate and benzaldehyde was fully characterized (^{1}H NMR, ^{13}C NMR, IR, High Resolution MS).

(16) In addition to benzaldehyde, p–nitrobenzaldehyde was employed in this reaction to enhance the rate, though no benefits were observed in either rate or selectivity. The aldol product was fully characterized (^{1}H NMR, ^{13}C NMR, IR, High Resolution MS).

(17) *tert*–Butylthio propionate was examined in the aldol reaction with benzaldehyde as well, though, as expected, it performed sluggishly in the aldol reaction with benzaldehyde. The aldol adduct was fully characterized (^{1}H NMR, ^{13}C NMR, IR, High Resolution MS).

(18) Other aldehydes that did not contain enolizable α protons (furaldehyde and cinnamaldehyde) performed in this reaction as well. These adducts were fully characterized (^{1}H NMR, ^{13}C NMR, IR, High Resolution MS), though they are not discussed here in the interests of brevity.

(19) *tert*–Butylthio α–phenylpropionate and phenylthio α–phenylpropionate were both examined in the aldol reaction with benzaldehyde, though they showed no improvement in rate or selectivity. These adducts were fully characterized (^{1}H NMR, ^{13}C NMR, IR, High Resolution MS).

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(24) Absolute and relative stereochemistry were assigned by correlation to known (2*R*,3*S*)–S-phenyl-2-benzyloxy-3-hydroxy-3-phenyl-propanethioate: Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron*, **1997**, *16*, 5909.

(25) Absolute stereochemistry of S-phenyl-2-benzyloxy-3-hydroxy-3-cinnamyl-propanethioate was assigned by analogy to the reaction producing (2*R*,3*S*)–S-phenyl-2-benzyloxy-3-hydroxy-3-phenyl-propanethioate (see endnote 23).

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Chapter 2

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

I. Introduction

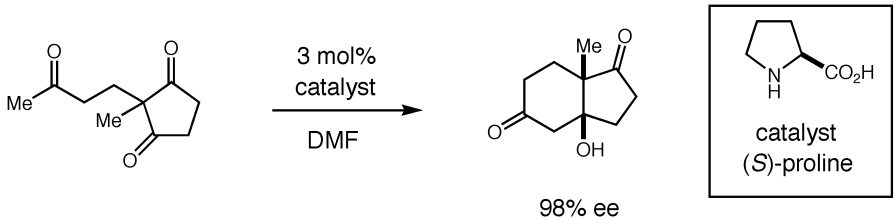
Organocatalysis

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

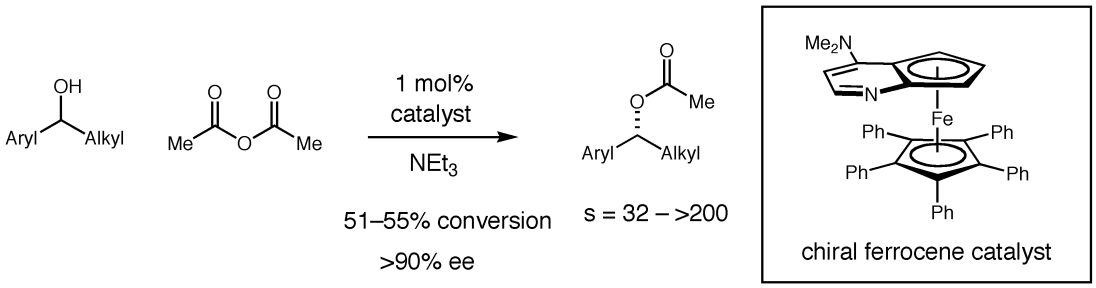
to catalyze new, previously inaccessible reactions and explore novel realms of stereocontrol.

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]



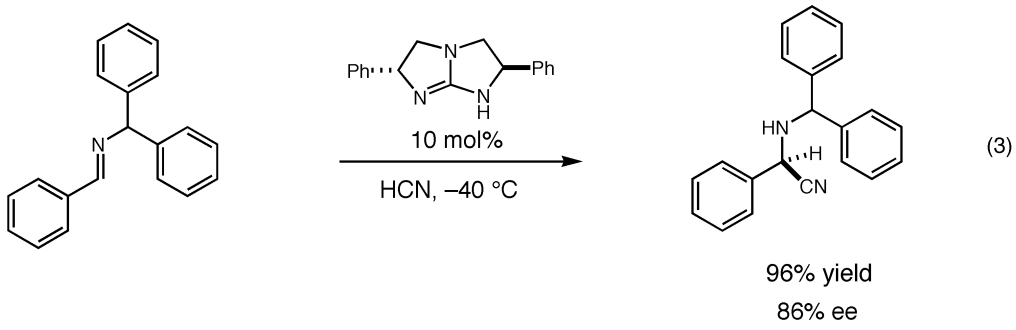
(1)

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.

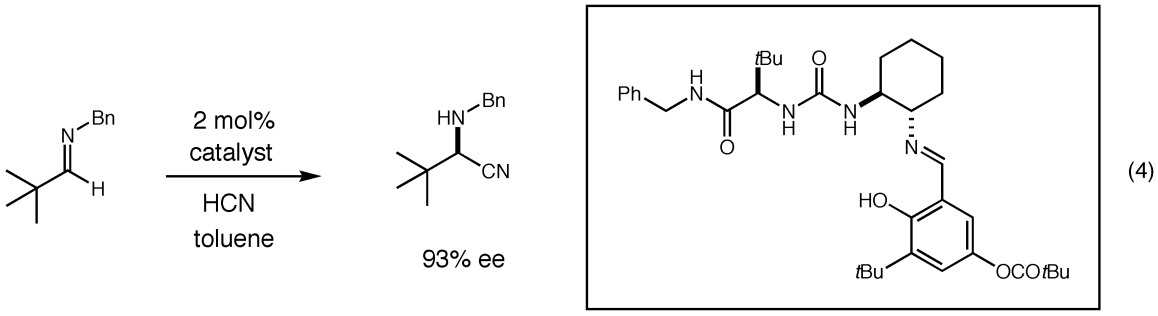


(2)

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]

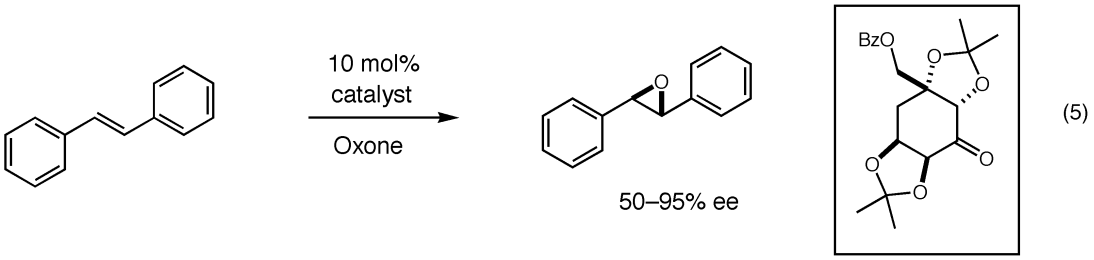


(3)



(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).

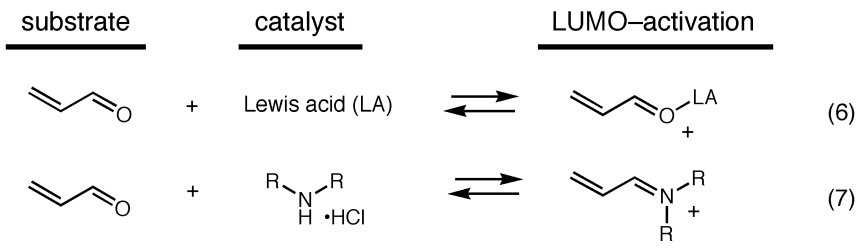


(5)

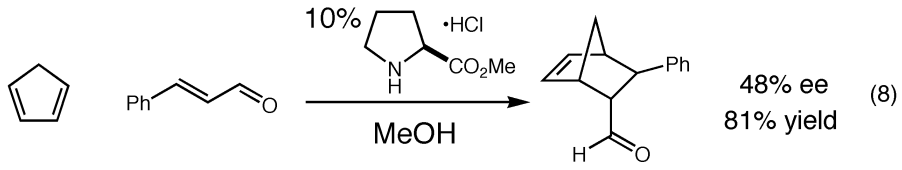
In contrast to these highly effective yet uniquely applicable organic catalysts, the most successful organometallic catalysts are each able to catalyze a broad range of transformations with high enantioselectivity.[8] Thus, the frontier of asymmetric organocatalysis must involve the development of catalytic 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.

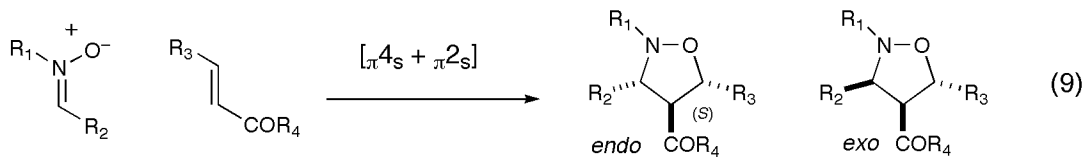


At this stage, it became apparent that our approach to organocatalysis was a reasonable one, and, in concert with the further development of this Diels-Alder reaction,[10] we sought to investigate the ability of this LUMO-lowering activation to be applied to other organic transformations.

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]



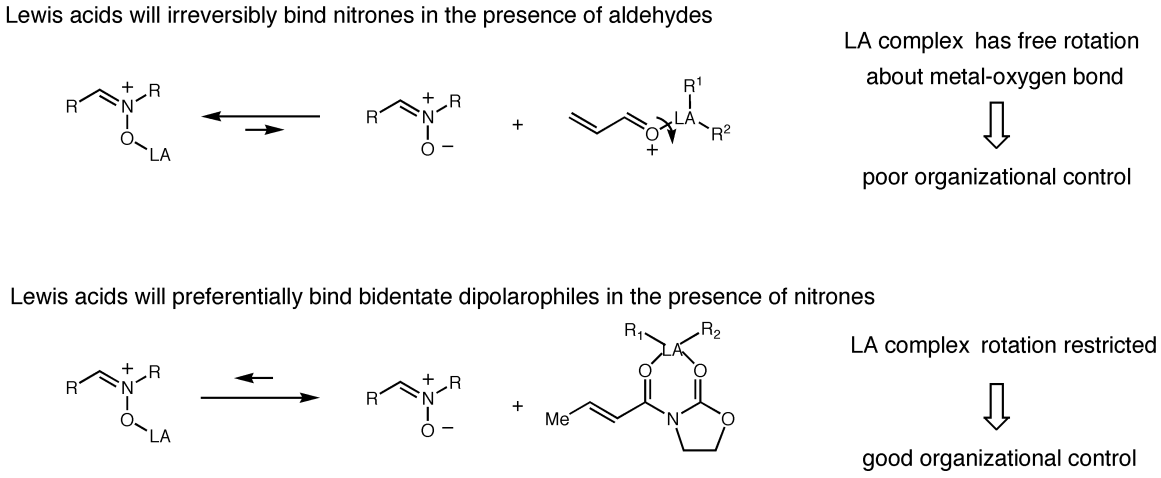
(9)

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.

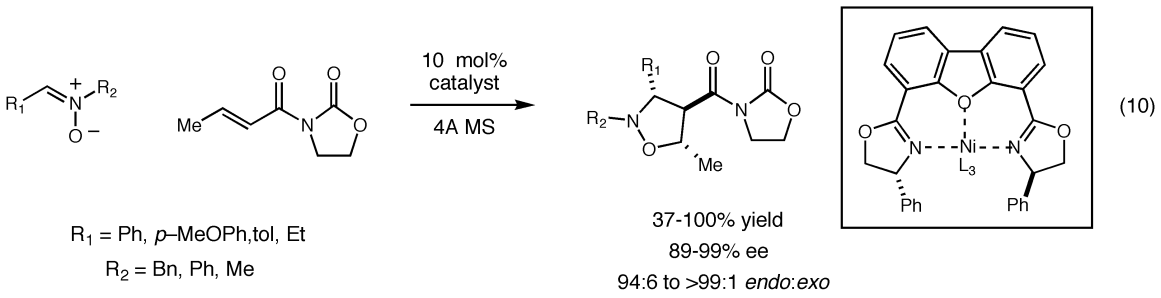
Whereas dipolar cycloaddition reactions are most commonly diastereoselective in nature, involving chiral dipoles and/or chiral dipolarophiles,[12] approaches to the enantioselective catalytic 1,3-dipolar cycloaddition reaction between nitrones and olefins have been more recently, and more infrequently, 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



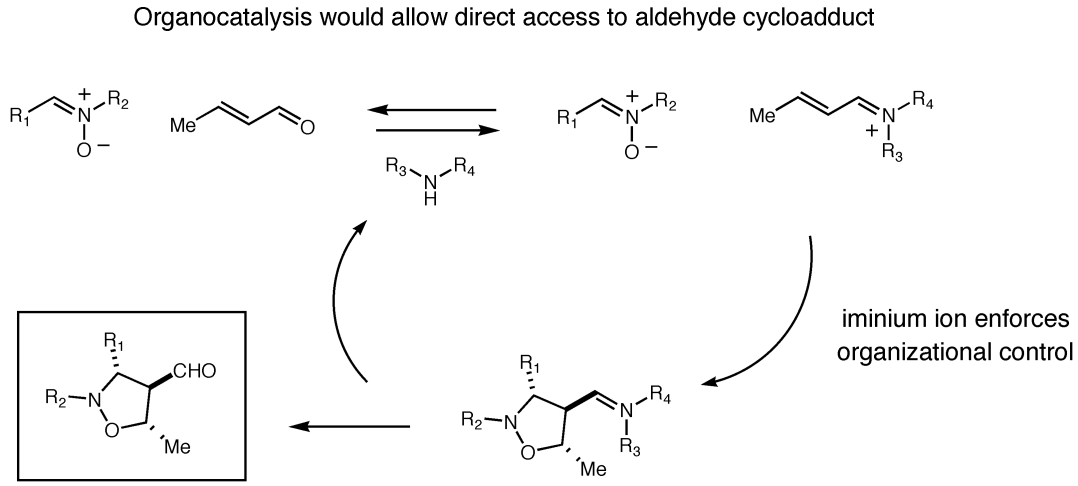
Among these Lewis acid catalyzed cyclizations employing bidentate dipolarophiles is the work of Kanemasa (Equation 10). In these reactions, high levels of enantiocontrol, diastereocontrol, and reaction efficiency are achieved in the reaction of α,β-unsaturated imides with a variety of nitrones bearing 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)

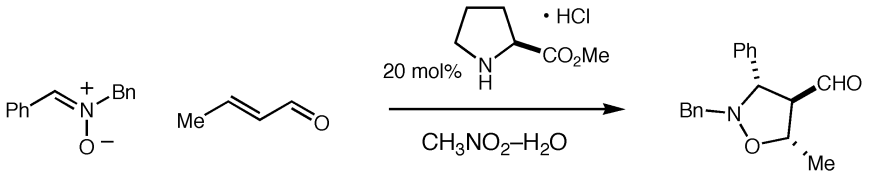
At the time that our laboratories became interested in organocatalytic approaches to the dipolar cycloaddition reaction, all reported enantioselective catalytic methods relied upon bidentate dipolarophiles and were thus unable to utilize aldehydes as substrates. In addition to the practical advantages 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]

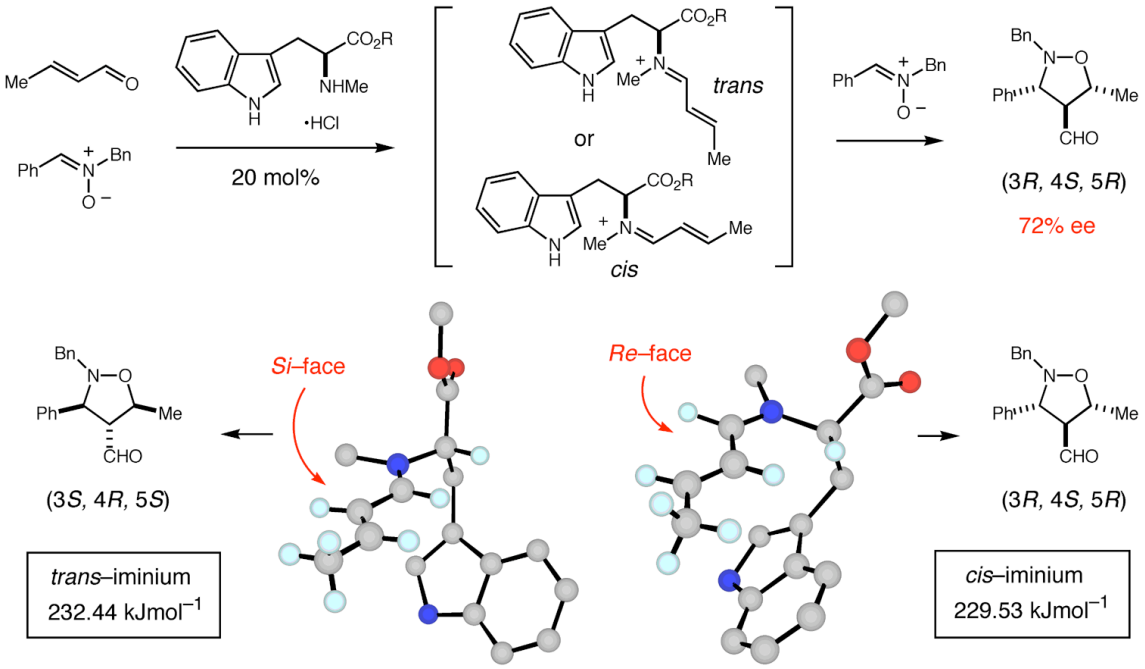
Initial investigations determined that, as with the Diels-Alder reaction, proline methyl ester showed promise as a catalyst for the 1,3-dipolar cycloaddition (Equation 11).



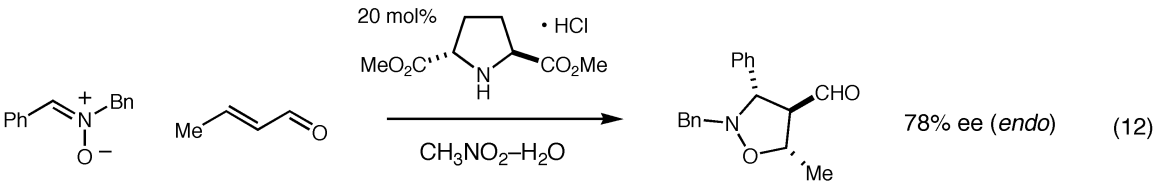
43% ee (*endo*) (11)

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.



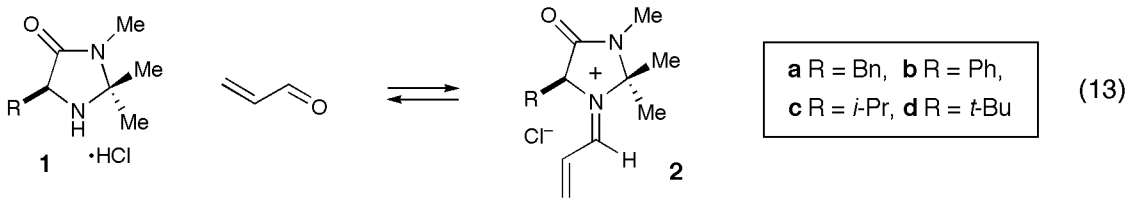
(12)

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).

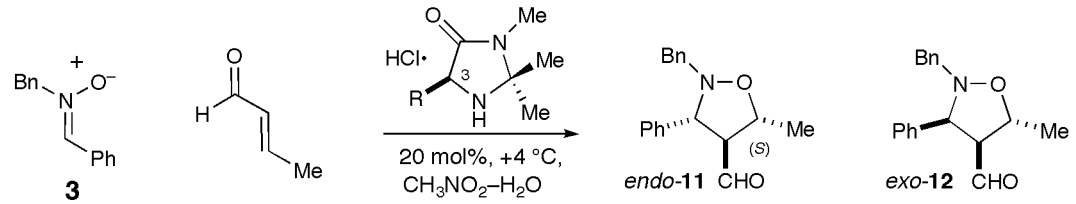


(13)

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.

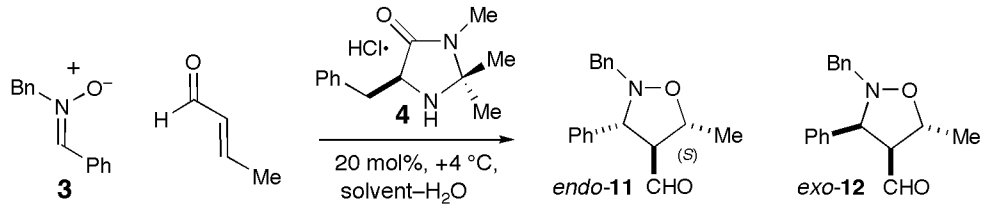
As hoped, this catalyst architecture indeed provided access to highly enantioenriched isoxazolidines **11** and **12**, with a variety of imidazolidinones bearing differing substituents at the stereogenic position successfuly catalyzing the dipolar cycloaddition (Table 1, entries 1–7, 45–77% yield, 20–93 % 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**



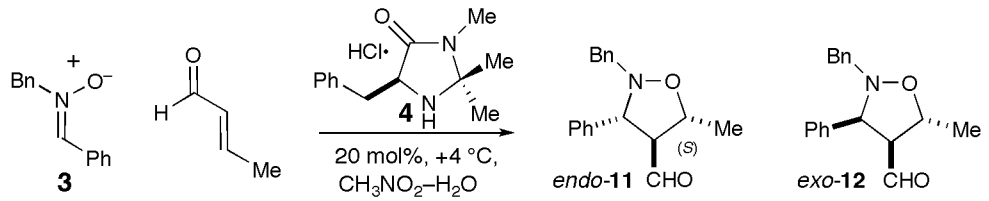
entry	Solvent	Dielectric Constant	Time (h)	% Conversion	*endo*:*exo*[a]
1	toluene	2.4	39	9	50:50
2	EtOAc	6.1	39	30	67:33
3	THF	7.6	39	31	67:33
4	CH_2Cl_2	9.1	39	39	50:50
5	acetone	21.0	39	37	67:33
6	MeOH	32.6	39	--	--
7	CH_3NO_2	36.0	39	70	88:12
8	CH_3CN	37.5	39	60	88:12
9	H_2O	80.1	39	--	--

[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**

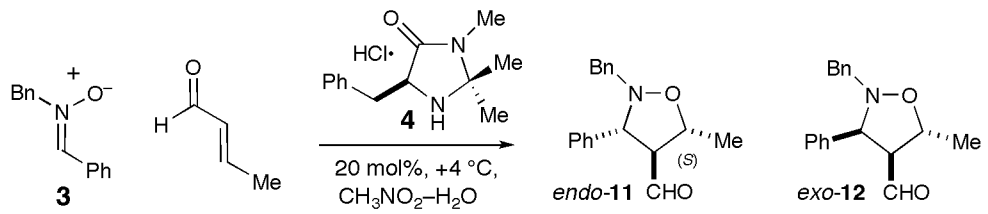


entry	H_2O (equiv.)	Time (h)	% Conversion	*endo*:*exo*[a]
1	0	12	23	93:7
2	1.5	12	48	88:12
3	3	12	70	88:12
4	9	12	74	86:14
5	12	12	73	83:17

[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**



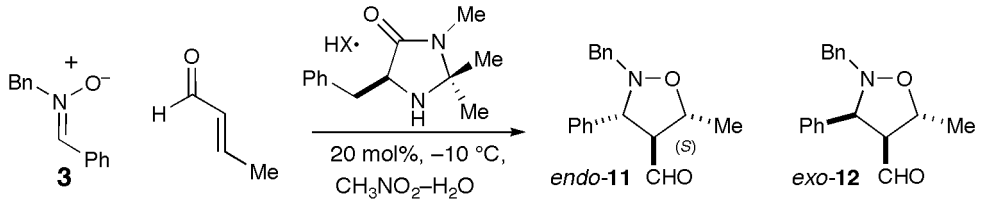
entry	conc (M)	Time (h)	% Conversion	*endo*:*exo*	% ee *(endo)*[a]
1	1.0	39	67	80:20	94
2	0.5	39	75	80:20	94
3	0.3	39	75	83:17	94
4	0.1	39	70	88:12	93
5	0.05	39	16	88:12	83
6	0.01	39	16	90:10	85

[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

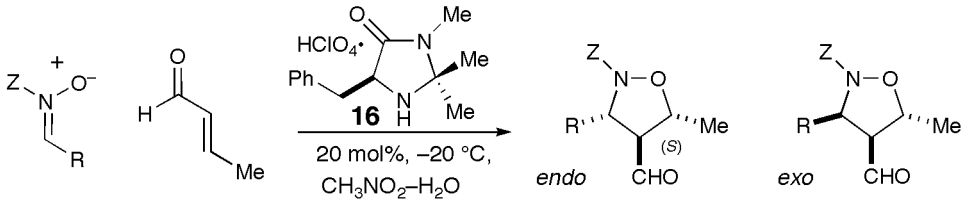
We expected that use of increasingly acidic co-catalysts would allow for faster iminium ion formation and thus that these co-catalysts would mediate faster dipolar cycloaddition reactions. A number of benzyl imidazolidinone acid salts were found to catalyze the formation of isoxazolidine **11** in good 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

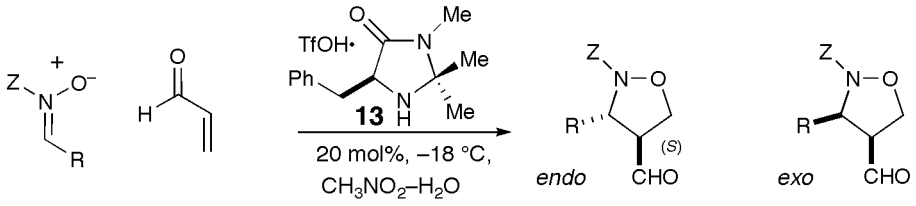


entry	Z	R	% yield	*endo*:*exo*	% ee (*endo*)[a,b]
1	Bn	Ph	98	94:6	94
2[c]	Allyl	Ph	73	93:7	98
3[c]	Me	Ph	66	95:5	99
4	Bn	C_6H_4Cl-4	78	92:8	95
5	Me	C_6H_4Cl-4	76	93:7	94
6	Bn	C_6H_4OMe-4	93	98:2	91
7	Me	C_6H_4Me-4	82	93:7	97
8	Bn	2-naph	98	95:5	93
9	Bn	*c*-hex	63	96:4	99

[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



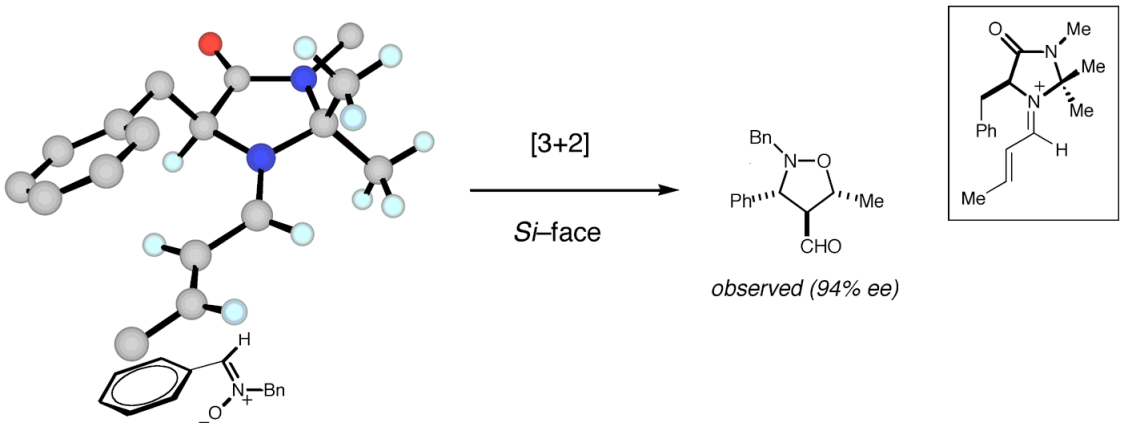
entry[a]	Z	R	% yield	*endo*:*exo*	% ee (*endo*)[b,c]
1[d]	Bn	Ph	72	81:19	90
2	Bn	Ph	80	86:14	92
3	Bn	C_6H_4Me-4	80	85:15	90
4	Bn	C_6H_4Cl-4	80	80:20	91
5	Bn	2-naph	82	81:19	90
6	Bn	C_6H_4OMe-4	83	91:9	90

[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

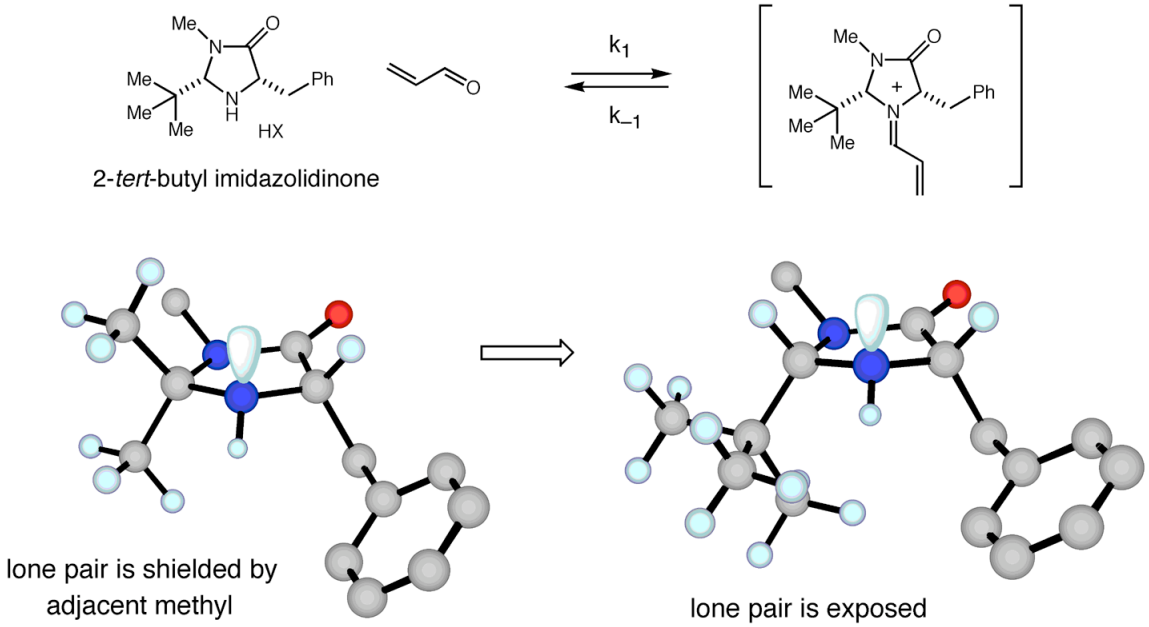
alternatives to this methodology, long reaction times may be of only secondary significance. Still, the relatively low reactivity of this catalyst system was responsible for the relatively limited scope of the cycloaddition with respect to dipolarophile. More sterically encumbered aldehydes (for example, 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.

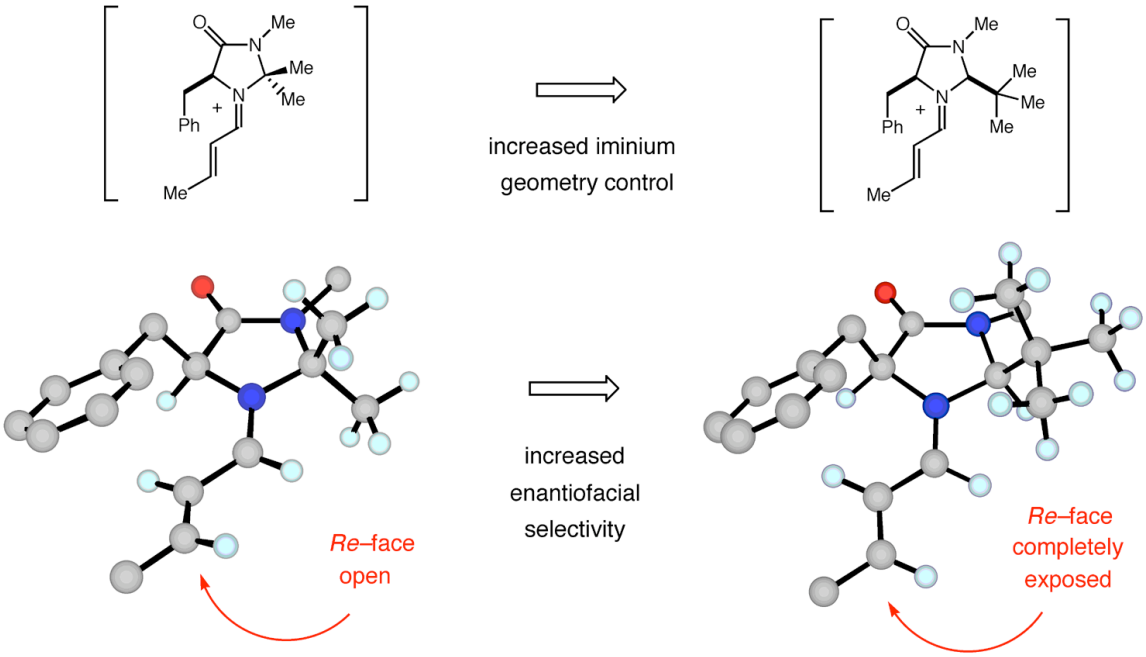
The proposed 2-*tert*-butyl imidazolidione catalyst (Scheme 3) seemed a promising choice toward fulfilling these criteria.[22] As can be seen in Scheme 3, the *cis* relationship between the *tert*-butyl substituent and the benzyl group should allow the nitrogen atom of the catalyst to be more exposed,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

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



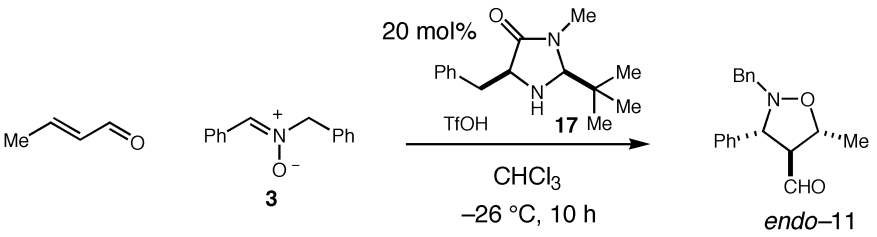
Further, the presence of the *tert*-butyl substituent should effectively enforce iminium ion geometry control (Scheme 4). Moreover, this large substituent should provide enhanced coverage of the undesired enantioface, while the absence of the methyl substituent from first-generation dimethyl imidazolidinone 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



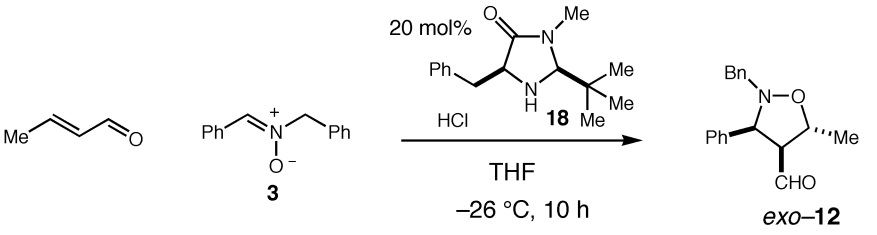
The power of this second-generation catalyst was aptly demonstrated in the context of the 1,3-dipolar cycloaddition of nitrone **3** with crotonaldehyde, catalyzed by 2-*tert*-butyl imidazolidine **17** (Equation 14, 98% ee, 96% yield, >99:1 *endo*:*exo*). Importantly, this reaction is not only higher 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).

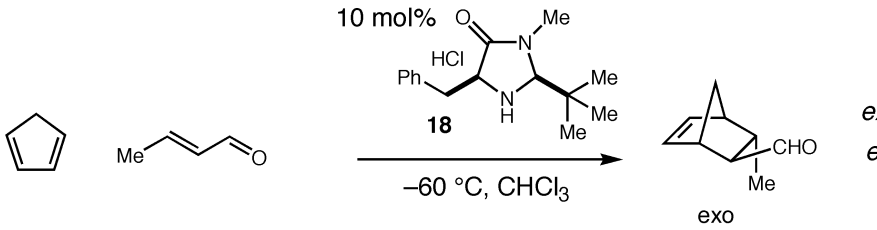


(15)

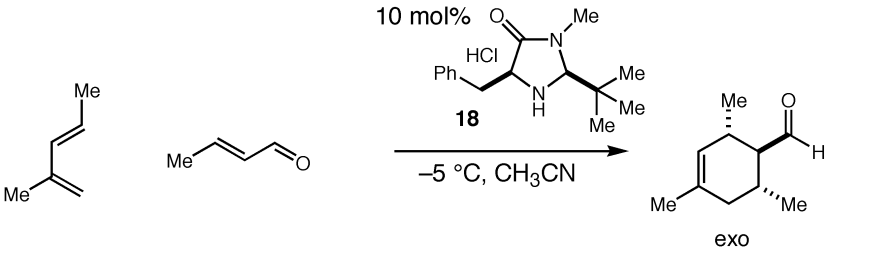
The definitive explanation for this finding will require further experimentation and computational modeling. Specifically, given the crucial role played by the reaction medium (solvent and co-catalyst), it is possible either that solvent effects help to stabilize the *exo* topography of the concerted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

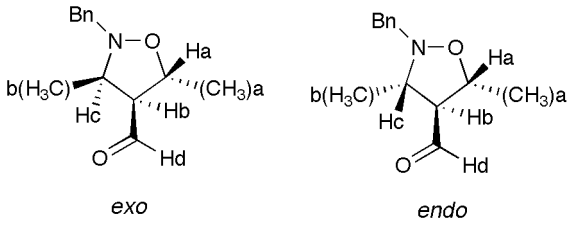
C**H**$_2$C$_6$H$_5$), 3.53 (m, 1H, C**H**CHO); ^{13}C NMR (100 MHz, $CDCl_3$) □ 198.7, 137.1, 135.4, 133.3, 133.2, 128.9, 128.7, 128.2, 127.9, 127.8, 127.7, 127.3, 127.2, 126.4, 126.3, 125.0, 110.4, 70.8, 65.9, 64.2, 59.7; LRMS (CI) *m/z* 317 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{21}H_{19}NO_2$) 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.



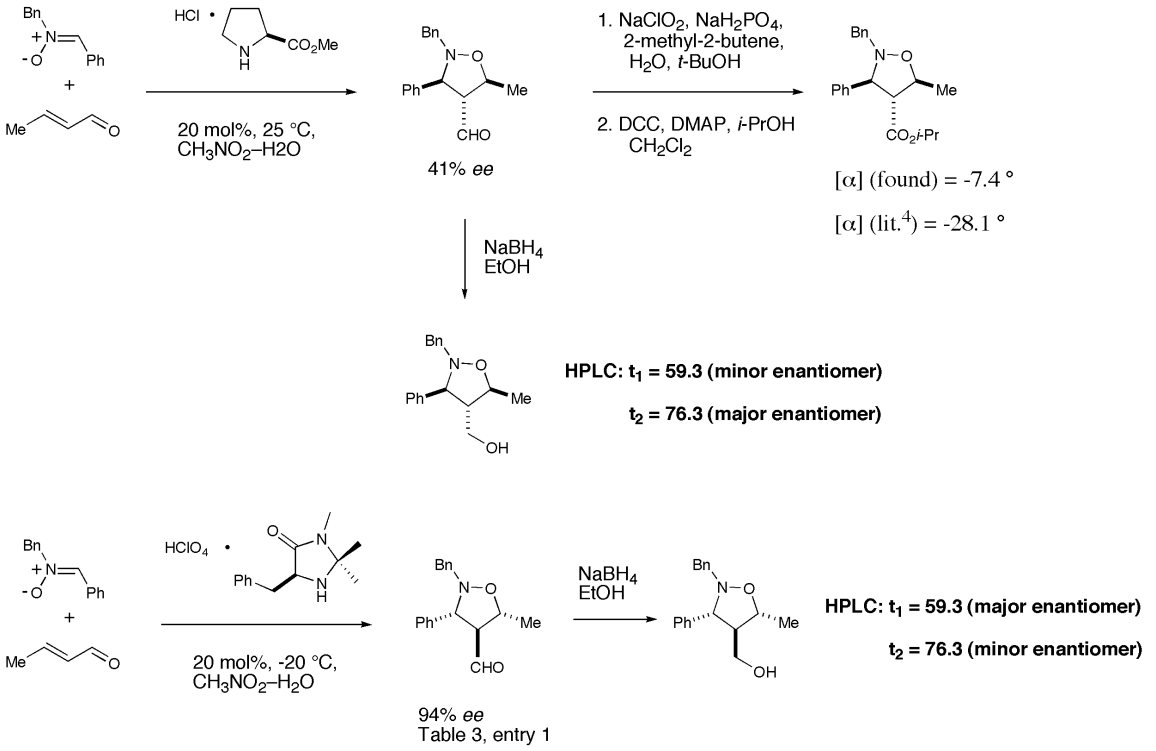
A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (20% EtOAc/hex) for the determination of enantiomeric purity; *exo* 94% ee. Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD 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).

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Chapter 3

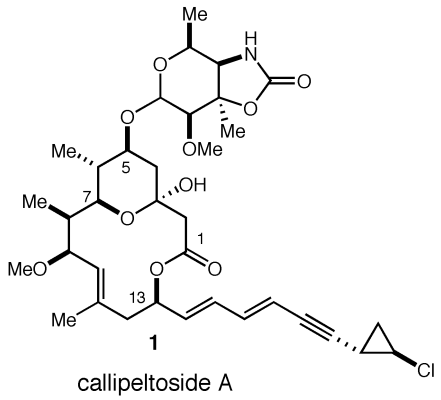
Progress towards the Total Synthesis of Callipeltoside A

I. Introduction

Isolation and biological activity

Minale and co-workers[1] first isolated callipeltoside A **1** (Figure 1) from the lithistid sponge *Callipelta* sp., which grows in the shallow waters off the east coast of New Caledonia. Preliminary *in vitro* biological investigations indicated that this structurally unique macrolide possessed potent cytotoxicity: the compound was found to inhibit the proliferation of P388 cells (IC_{50}: 11.26 μg mL^{-1}), as well as NSCLC-N6 human brochopulmonary nonsmall-cell lung carcinoma cells (IC_{50}: 15.26 μg mL^{-1}). Further results pointed to the fact that this activity was cell-cycle dependent, blocking cell proliferation in the G1 phase and thereby identified the natural product as a putative mechanism-based lead. Small amounts of two structurally related biologically active macrolides, callipeltosides B and C, which differ from callipeltoside A only in their sugar residues, were subsequently isolated from the same source.[2]

Figure 1. Callipeltoside A



1

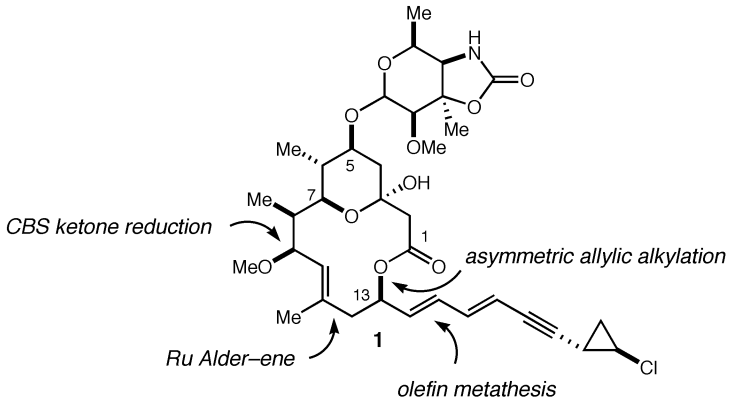
callipeltoside A

Synthetic approaches to callipeltoside A

Callipeltoside A **1** is characterized structurally by a 14-membered macrolide bearing a glycosidic linkage at C5 to a deoxyamino sugar and a dienyne *trans*-chlorocyclopropane sidechain. The macrolide bears a number of intriguing architectural features, including a six-membered hemiacetal ring, a trisubstituted olefin, and a polypropionate backbone consisting of five contiguous stereocenters. Given its unique structure and cytotoxicity, callipeltoside A has been the subject of fervent synthetic work,[3] with total syntheses of the natural product reported recently, subsequent to the commencement of the research detailed in this chapter, by Trost,[4] Evans,[5] and Paterson.[6] These syntheses have, as well, enabled the full stereochemical assignment of callipeltoside A.

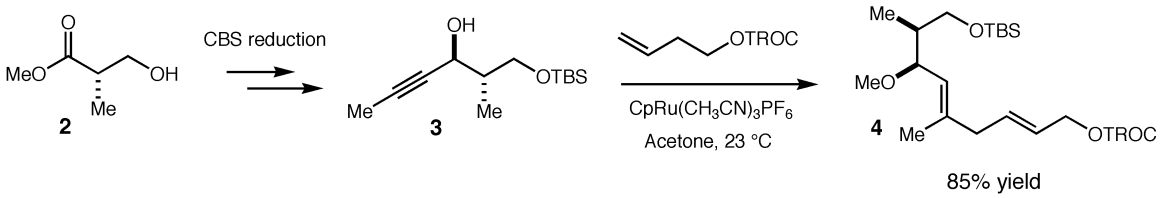
Trost's approach to callipeltoside A (Scheme 1) relies upon olefin metathesis to introduce the *trans*-chlorocyclopropane sidechain, and the deoxyamino sugar, derived from L-rhamnose, is affixed to the core *via* a glycosidic linkage. The 18 linear step construction of the macrolactone core begins with a commercially available chiral starting material, but proceeds to invoke a series of reagent-controlled asymmetric reactions to establish the required configuration of the remaining stereogenic centers. As such, the synthesis of the core utilizes a ruthenium Alder-ene coupling to establish the trisubstituted olefin geometry, a palladium catalyzed asymmetric allylic alkylation reaction, and an asymmetric CBS-oxazaborilidine ketone reduction.

Scheme 1. Trost's retrosynthesis of callipeltoside A



Elaboration of commercially available methyl (*S*)-3-hydroxy-2-methyl propionate **2** to the alkyne **3** over several steps including an asymmetric CBS-oxazaborilidine ketone reduction precedes the ruthenium catalyzed Alder-ene reaction (Figure 2), which affords alkene **4** in 85% yield.

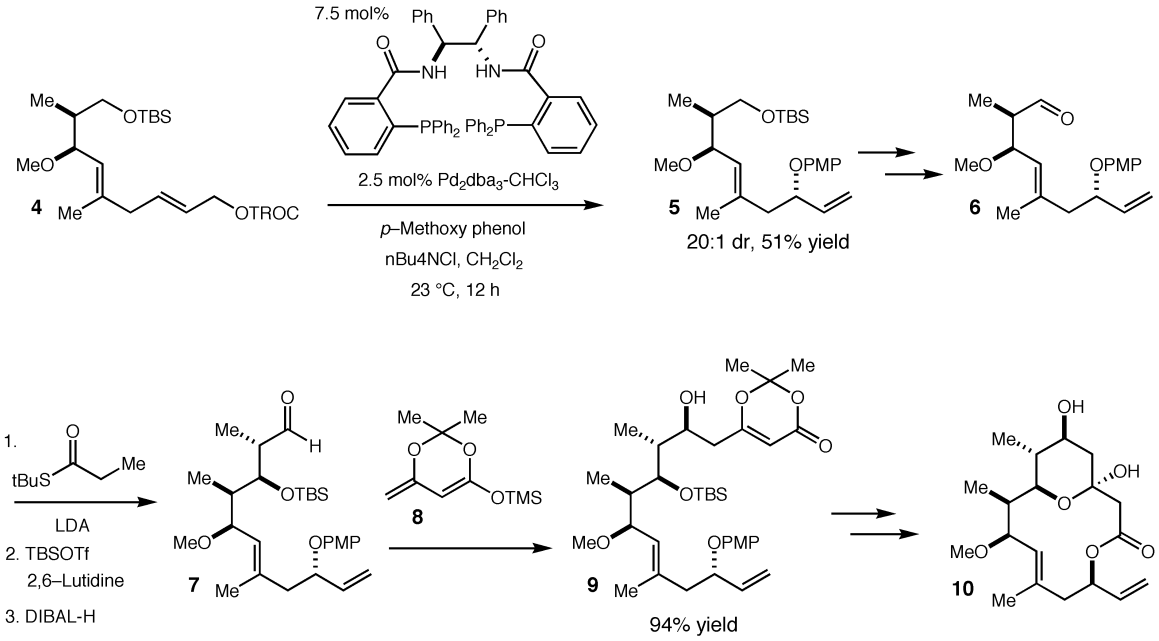
Figure 2. Ruthenium-catalyzed Alder–ene reaction



The palladium-catalyzed asymmetric allylic alkylation reaction of diene **4** proceeds in high diastereoselectivity but modest yield to afford the protected allylic alcohol **5** (Figure 3), which is elaborated to aldehyde **6** over several steps. Aldol addition of a kinetically formed *(E)* lithium enolate of *tert*–butyl thiopropionate to aldehyde **6** is followed by Felkin-Ahn addition of dienyl silyl ether **8** to the resultant aldehyde **7**. Following oxidative removal of the acetonide protecting group from **9**, several steps

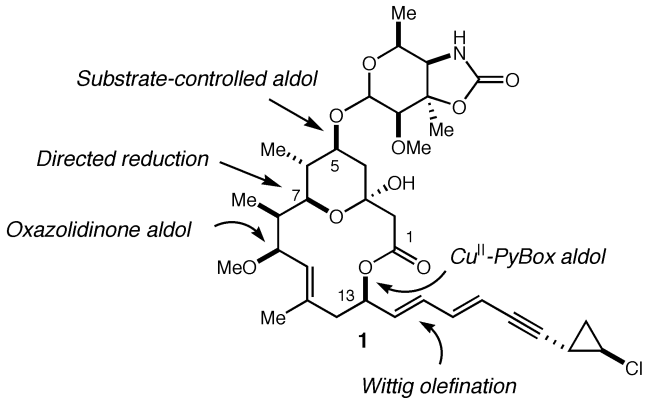
including macrolactonization and intramolecular condensation afford the callipeltoside core **10**.

Figure 3. Trost's synthesis of the callipeltoside core



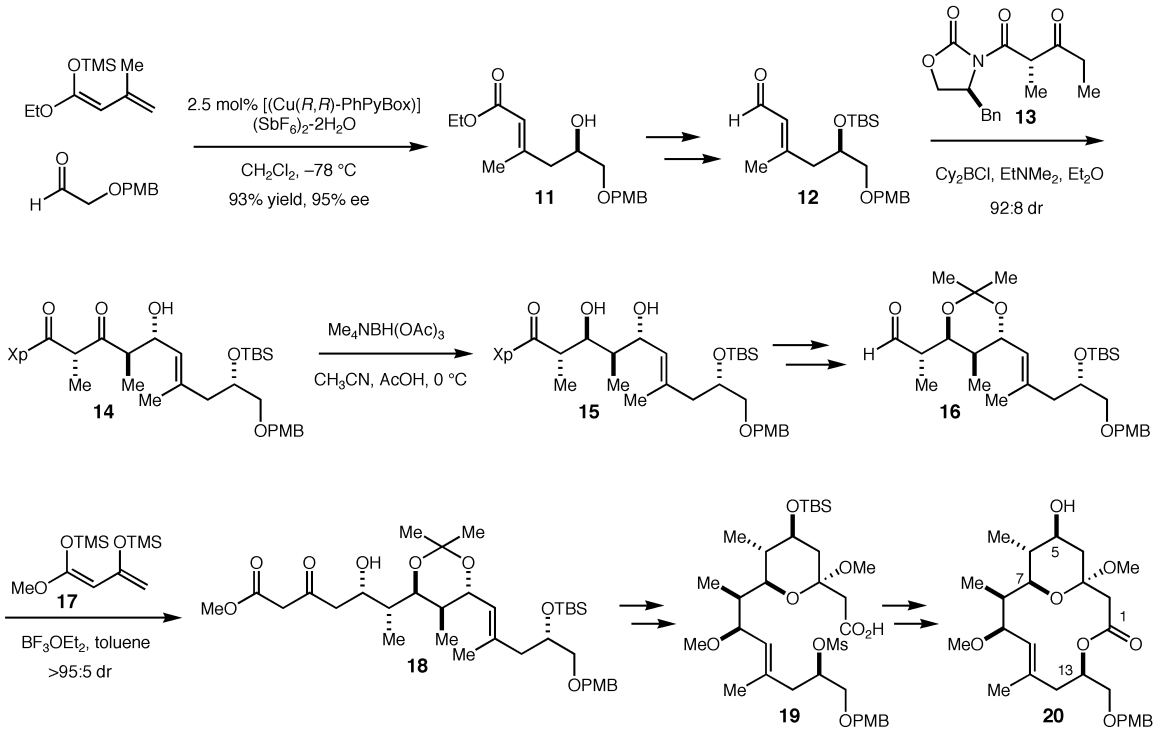
The Evans approach to callipeltoside A (Scheme 2) involves a Wittig olefination to attach the chlorocyclopropane sidechain to the macrolactone core and appends the callipeltose sugar to the core *via* NIS-mediated glycosidation. The 20-step synthesis of the macrolactone involves as key stereochemistry-determining steps an enantioselective catalytic Cu^{II}-PyBOX aldol reaction, diastereoselective chiral oxazolidinone aldol reaction, a directed ketone reduction, and a substrate-controlled aldol addition. Though marginally longer than the Trost approach to the macrolactone, this synthesis utilizes to a greater extent substrate control of stereochemical development.

Scheme 2. Evans' retrosynthesis of callipeltoside A



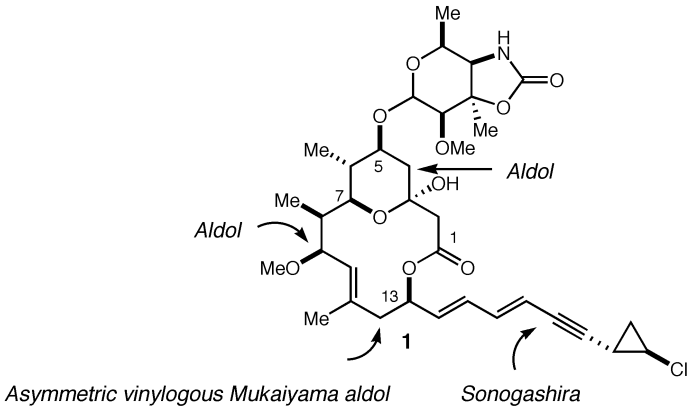
Key ester substrate **11** is prepared from available starting materials through a copper (II) catalyzed enantioselective aldol reaction in 93% yield and 95% ee (Figure 4). After derivatization to the aldehdye **12**, aldol reaction with chiral oxazolidinone **13** affords □-keto imide **14** with 92:8 diastereoselection, which then undergoes directed reduction to afford the alcohol **15**. After further elaboration, the diene **17** is employed in a substrate-controlled aldol reaction to afford □-keto ester **18**. Tetrahydropyran **19** is formed in several steps subsequent to deprotection of acetonide **18**, and the macrolatone **20** is constructed after further elaboration of **19** over multiple steps which include an intramolecular mesylate displacement.

Figure 4. Evans' synthesis of the callipeltoside macrolactone



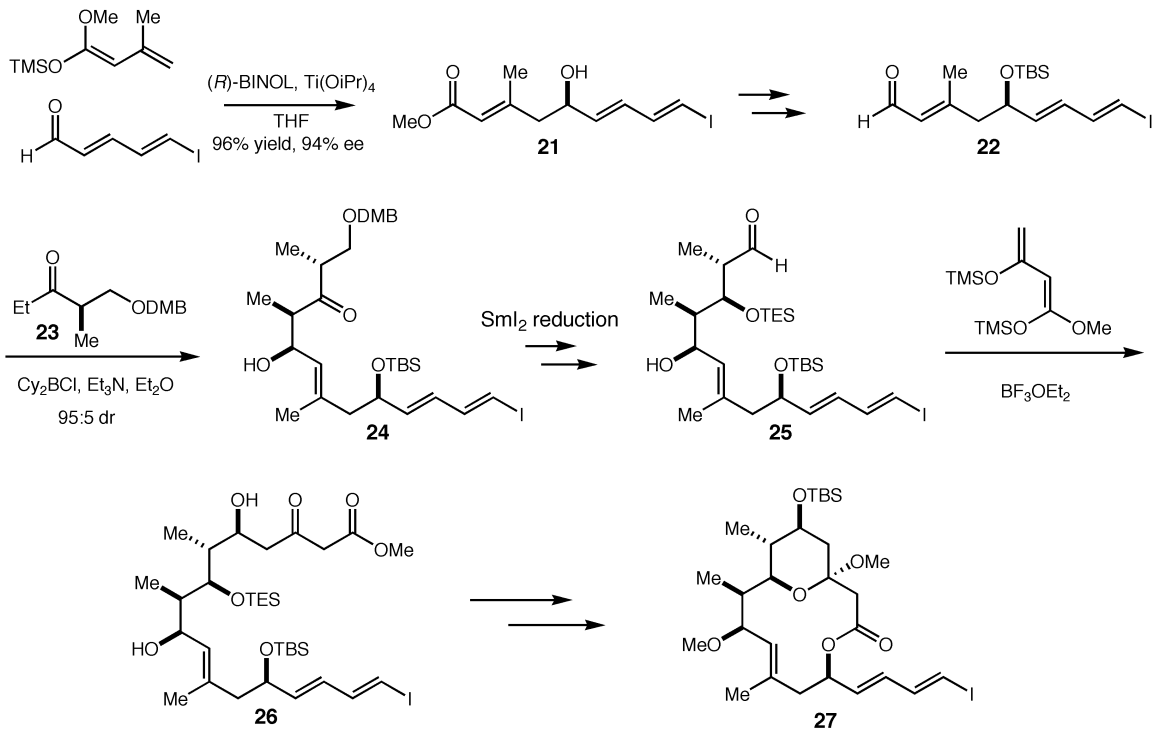
The Paterson approach to callipeltoside A (Scheme 3) employs a Sonogashira coupling to introduce the chlorocyclopropane sidechain and a Schmidt-type glycosidation to affix the L-rhamnose-derived callipeltose sugar onto the macrolactone. The macrolactone itself is constructed in 17 steps and involves coupling of three main chiral fragments. Importantly, after independent asymmetric assembly of two fragments, all further stereocenters are formed using substrate control with achiral reagents.

Scheme 3. Paterson's retrosynthesis of callipeltoside A



Asymmetric vinylogous Mukaiyama aldol reaction affords hydroxy ester **21** in 96% yield and 94% ee. Elaboration of this fragment to the aldehyde **22** precedes aldol coupling to chiral ketone **23** to produce ketone **24** in 95:5 diastereoselection. After substrate-directed SmI_2-mediated ketone reduction of ketone **24** and further elaboration to aldehyde **25**, aldol coupling produces keto-ester **26** in 95:5 diastereoselection. A sequence of steps including acid-catalyzed tetrahydropyran formation and subsequent macrolactonization affords the macrolactone **27**.

Figure 5. Paterson's synthesis of the callipeltoside macrolactone

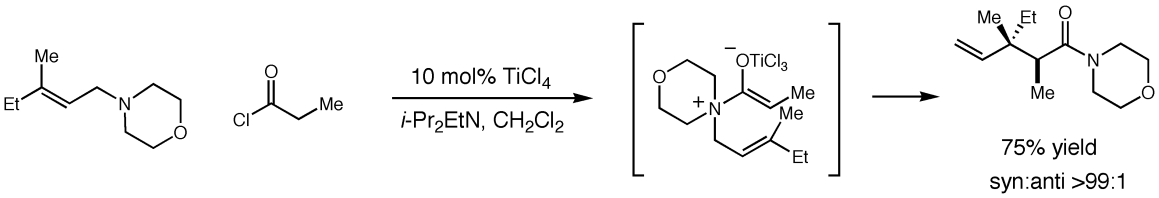


Tandem amino-sulfide acyl-Claisen rearrangement

Prior to the inception of the research detailed below, our research laboratory became interested in utilizing tandem reactions to rapidly develop a high level of molecular complexity. Our goal in the development of tandem reactions has been the application of these reactions to efficient synthesis of complex targets, and it is in the context of a total synthesis of callipeltoside A that we conceived of a new tandem Claisen rearrangement.

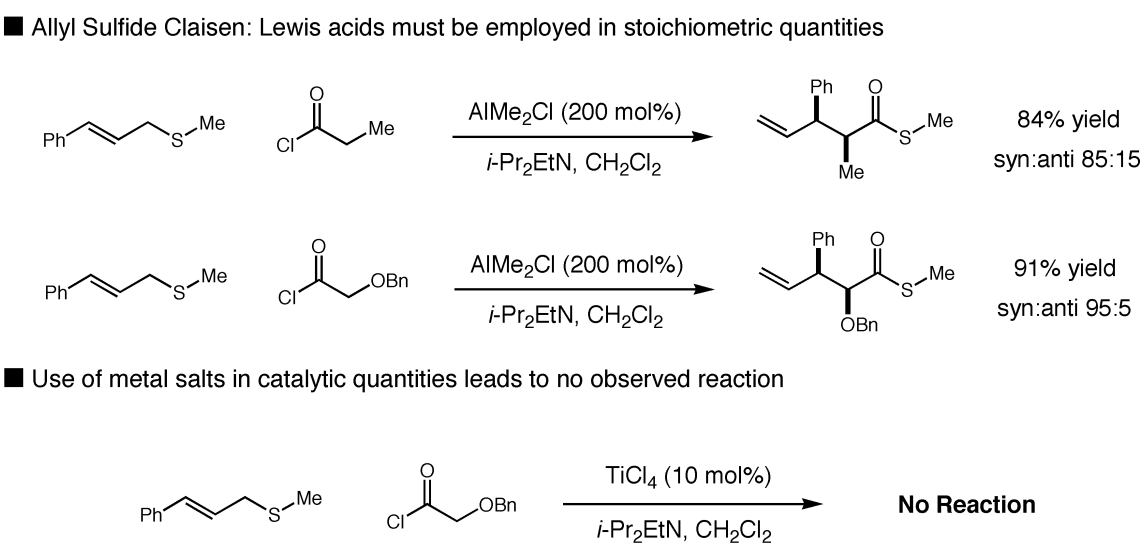
Studies from our laboratory have shown that allylic amines and acid chorides in the presence of a catalytic quantity of $TiCl_4$ will engage in a highly diastereoselective Claisen rearrangement, termed the acyl-Claisen (Figure 6).[7]

Figure 6. Acyl-Claisen rearrangement



Further investigations indicated that the allyl sulfide variant of this process was not possible in the presence of catalytic $TiCl_4$, though rearrangement was facile in the presence of stoichiometric amounts of aluminium Lewis acids (Figure 7).[8]

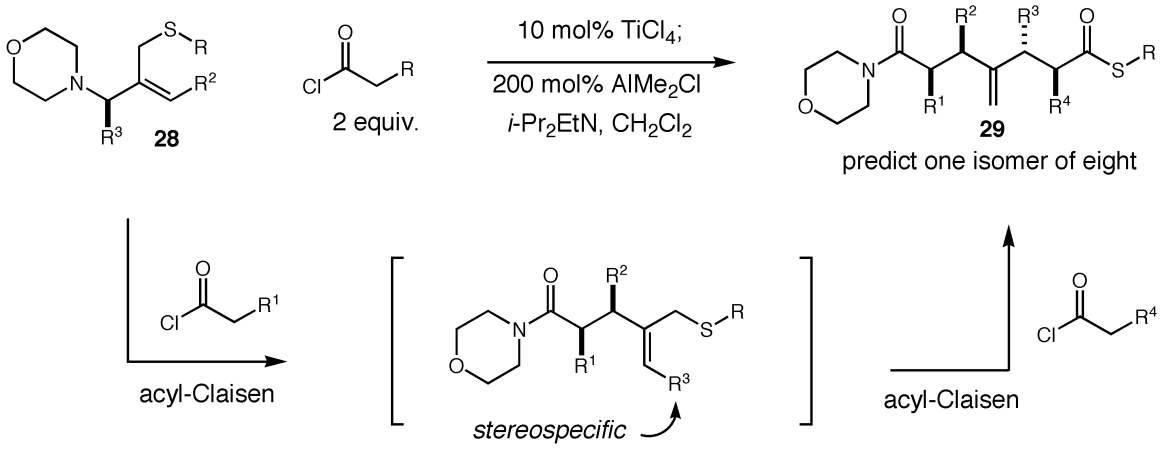
Figure 7. Sulfide acyl-Claisen rearrangement



Given these orthogonal modes of reactivity, we hoped to combine the two processes into a novel tandem reaction (Scheme 4). As such, we envisioned an allylic amino-sulfide **28** which could react first with one acid chloride in the presence of a catalytic quantity of $TiCl_4$. Once the amino sulfide **28** had been completely converted to the product of the amino acyl-Claisen rearrangement, a second acid chloride and a

stoichiometric quantity of Me_2AlCl could be introduced to allow formation of the highly functionalized amide-thioester **29**. Importantly, this product would bear differentially protected carbonyls at each terminus, allowing for facile elaboration.

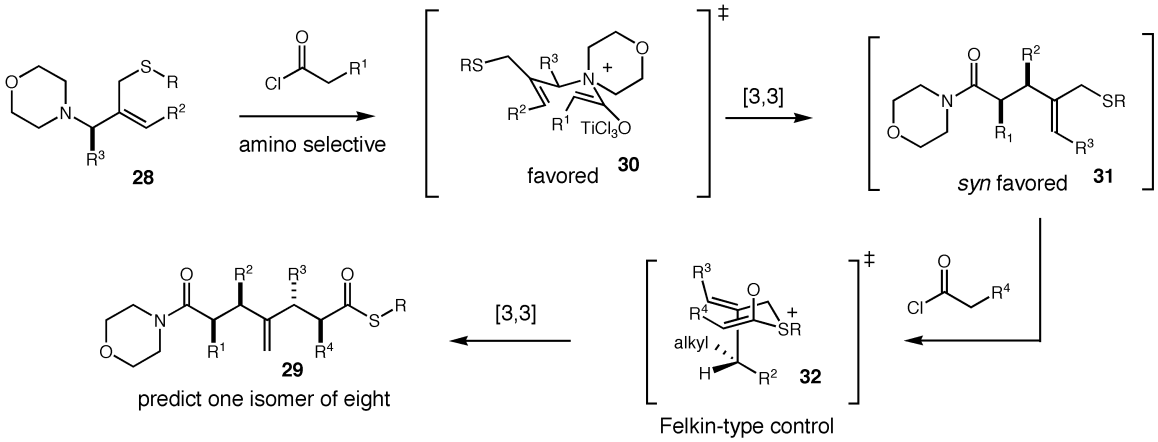
Scheme 4. Proposed tandem amino-sulfide acyl-Claisen rearrangement



Modular control of R^1, R^2, R^3, R^4; orthogonal protection of amide and thioester carbonyls

In this proposed reaction, the chirality of the amino-sulfide **28** would translate into four stereocenters on the product **29**; we believed that stereocontrol would be good based on two considerations (Scheme 5). First, the initial amino acyl-Claisen rearrangement should proceed *via* a highly ordered chair-like transition state **30** to produce products **31** of high *syn* diastereoselectivity, in accord with the high levels of diastereocontrol we had observed with the acyl-Claisen rearrangement discussed above. In the subsequent sulfide acyl-Claisen rearrangement, Felkin-type control in a transition state such as **32** was expected to dominate the selective formation of thioester **29**.[9]

Scheme 5. Stereochemical rationale for the tandem amino-sulfide acyl-Claisen rearrangement



With the appropriate choice of acid chlorides in this tandem process, the produced stereochemical array would map directly onto the backbone of the callipeltoside A macrolactone (Scheme 6). Thus we imagined that development of this novel tandem process might allow the rapid development of the stereochemical core of callipeltoside A and thereby facilitate an efficient total synthesis of this macrolide.

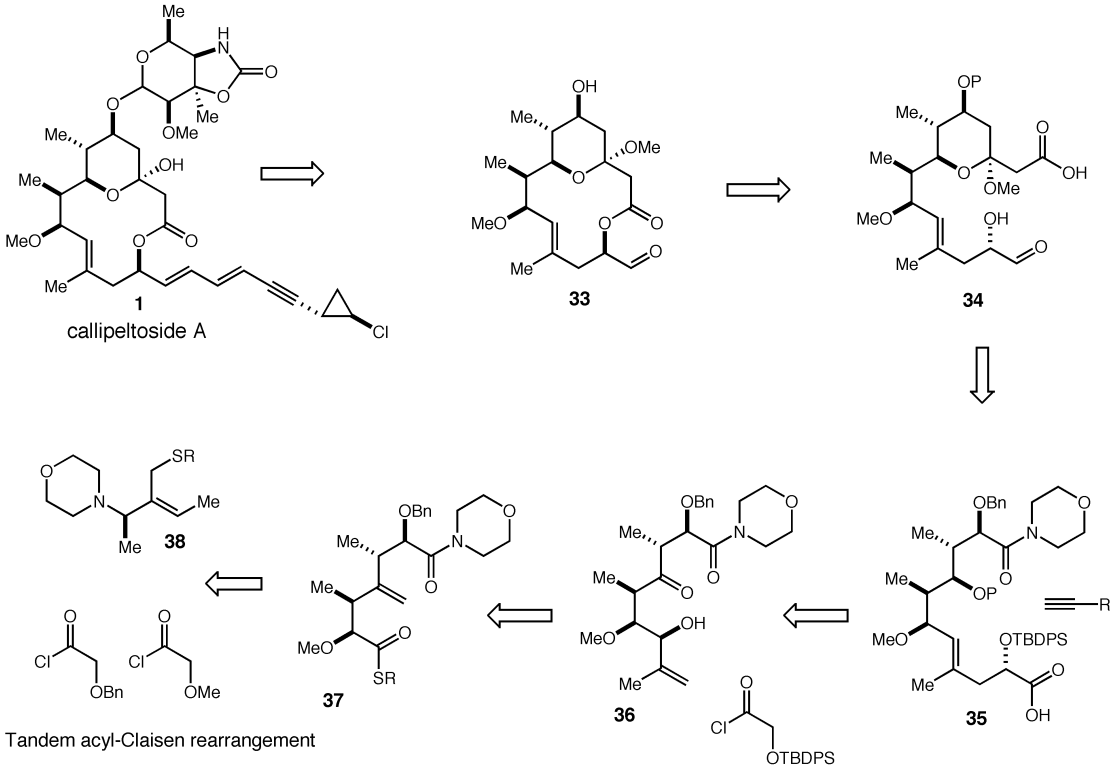
II. Results and Discussion

Retrosynthetic analysis of callipeltoside A

We envisioned that our approach to the total synthesis of callipeltoside A (Scheme 6) would involve synthesis of the macrolactone core **33** of the natural product, which would be coupled to the callipeltose sugar and the chloro cyclopropane side-chain to complete the synthesis. The macrolactone core **33**, itself containing a 6-membered tetrahydropyran ring, would derive from a macrolactonization of the acid **34**. Closure of the tetrahydropyran moiety of acid **34** would arise from intramolecular cyclization of an

alcohol with an appropriately substituted alkyne, either following the precedent of Marshall's palladium catalyzed intramolecular carbonylative cyclization[10] or through nucleophilic heteroconjugate addition. The protected homoallylic alcohol functionality of amide **35** would be installed through an Ireland Claisen rearrangement after acylation of the allylic alcohol and *anti* reduction of the central ketone functionality of compound **36**. Alcohol **36** would in turn derive from thioester **37** after reduction of the thioester and oxidation of the internal alkene to the ketone. Thioester **37** would itself be the product of our proposed tandem amino-sulfide acyl-Claisen rearrangement, utilizing two different acid chlorides and an appropriate amino-sulfide **38**. Importantly, this synthesis would involve establishment of four stereocenters of the macrolactone in a single step, followed by rapid elaboration to the macrolactone, relying on internal substrate control to establish the remaining stereocenters

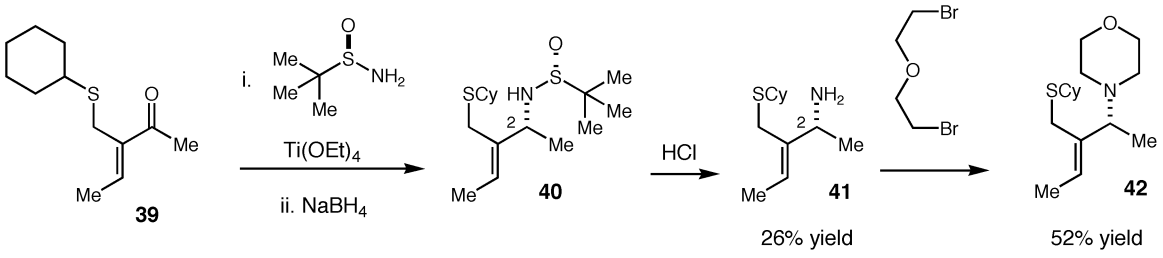
Scheme 6. First–generation retrosynthesis of callipeltoside A



Synthesis of precursor to the tandem amino-sulfide acyl-Claisen rearrangement

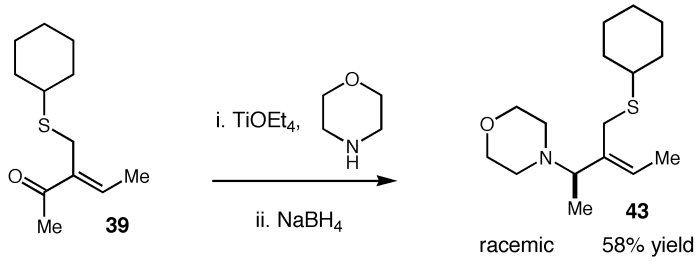
The proposed tandem Claisen rearrangement required the transfer of stereochemistry from the single stereocenter of the amino sulfide starting material **42** into the four stereocenters of the product amide thioester **45**, requiring a synthesis of enantiopure amino sulfide **42** in order to establish an enantioselective synthesis of callipeltoside A. As such, the enantioselective reductive amination technology of Ellman afforded an enantiopure route to amino sulfide **42** (Scheme 7). In the event, □,□-unsaturated ketone **39**[11] was condensed with commercially available (*R*)-*tert*-butanesulfinamide and reduced *in situ* to the sulfinamide **40** with $NaBH_4$ in the presence of $Ti(OEt)_4$, followed by acid-promoted cleavage to the amine **41**.[12] In accord with reported reductions, this reaction sequence afforded the sulfinamide **41** as a single diastereoisomer by ^1H NMR analysis, and, based on the reported stereochemical models, we believed that the (*S)* absolute configuration at C2 was produced during the course of this reaction. Morpholine formation using dibromoethyl ether afforded the desired enantiopure tandem acyl–Claisen precursor **42** in 52% yield.[13]

Scheme 7. Enantioselective synthesis of acyl–Claisen precursor



In addition to enantiopure amino-sulfide **42**, we sought to produce, if possible, large quantities of the racemate through more efficient means to conduct optimization

studies at later stages in the synthesis. As such, we found that a similar reductive amination protocol involving $NaBH_4$ and $Ti(OEt)_4$ could be employed with ketone **39** and morpholine to provide, directly, racemic amino sulfide **43** in 58% yield (Equation 1).[14]

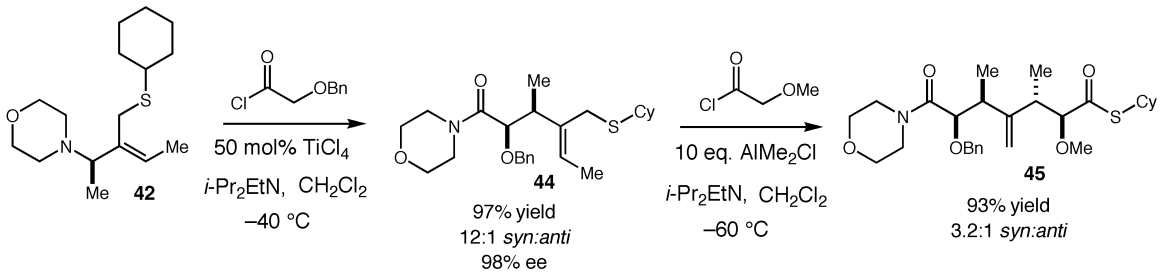


(1)

Tandem amino–sulfide acyl–Claisen rearrangement[15]

With sufficient quantities of amino-sulfide **42** in hand, we next sought to explore the tandem acyl-Claisen rearrangement. In conjunction with Dr. Jeongbeob Seo, it was determined that this transformation afforded the highest levels of reaction efficiency and selectivity when performed as a two-step process (Scheme 8).[16]

Scheme 8

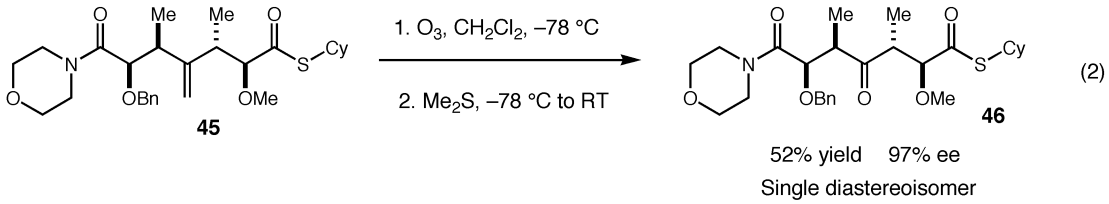


The initial amino acyl-Claisen rearrangement proceeds under conditions essentially identical to those reported previously for the acyl-Claisen rearrangement to afford the amide product **44** in 97% yield as a 12:1 *syn:anti* mixture of diastereoisomers.

Importantly, the enantiopurity of the amino-sulfide starting material **42** is preserved throughout the course of this reaction, with the amide product **44** being produced in 98% ee. As well, no evidence of any undesired sulfide acyl-Claisen rearrangement with a second equivalent of benzyloxyacetylchloride was observed, indicating, as expected, that the second rearrangement would require more reactive conditions and providing the requisite opportunity to employ a different acid chloride in the second rearrangement.

The sulfide acyl-Claisen rearrangement in the second step required a stronger Lewis acid, and, after extensive optimization of reaction conditions including solvent, Lewis acid, temperature, and reagent stoichiometry and molarity, it was determined that aluminum Lewis acids performed best and were required in large excess. It is believed this decreased reactivity can be attributed to (1) the *cis* relationship between the sulfide and the alkene alkyl substituent[17] and (2) coordination of the amido sulfide starting material **44**, containing five hetereoatoms, to the Lewis acid used. Utilizing Me_2AlCl and methoxyacetylchloride afforded the thioester product in 93% yield and a 3.2:1 ratio of the desired diastereoisomer **45** to all other isomers.[18] The observed stereochemical outcome of this tandem process is in complete accord with that predicted above.

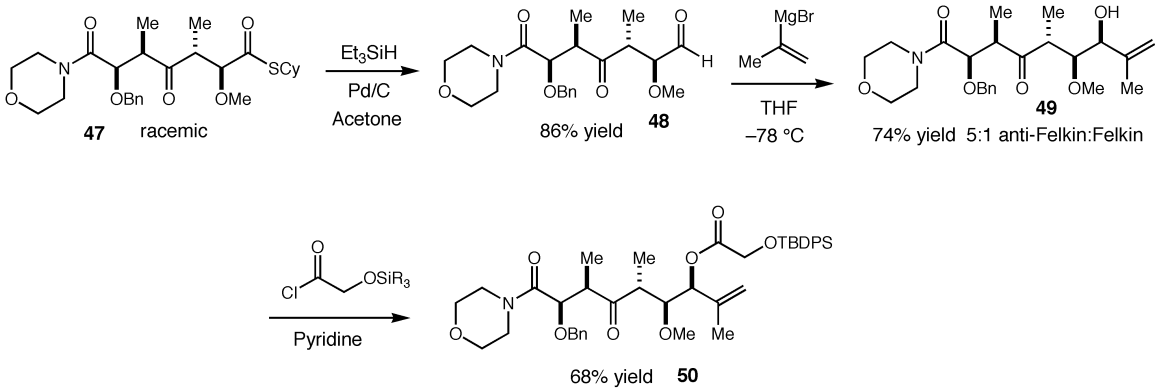
After ozonolytic cleavage of the alkene of amide-thioester **45**, the ketone **46** was separated from the other isomers deriving from the tandem Claisen transformation and isolated in 52% yield with 97% ee, indicating that the enantiopurity of the starting material was preserved through the second acyl-Claisen rearrangement (Equation 2). The relatively low yield of this reaction likely relates to oxidative decomposition of the thioester moiety.



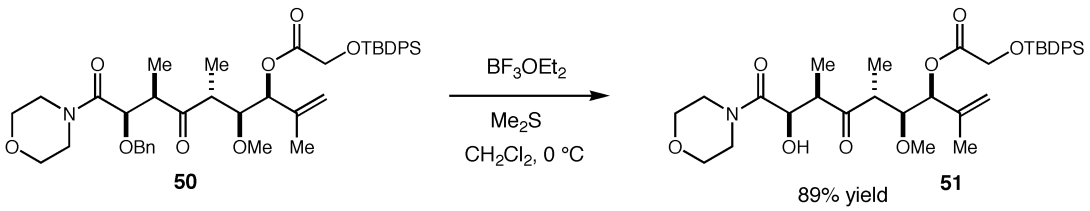
***Anti* reduction of β-hydroxy ketone and Ireland Claisen rearrangement**

Ozonolysis of the tandem amino-sulfide acyl-Claisen rearrangement product afforded the ketone moiety that would be reduced to establish the required 1,3-*anti* diol relationship in callipeltoside A. Prior to attempting this *anti* reduction, we sought to install the β-oxy ester functionality that would facilitate Ireland Claisen rearrangement subsequent to the *anti* reduction (Scheme 9). As such, the thioester **47** was reduced to the corresponding aldehyde **48** in 86% yield under Fukaiyama reduction conditions, demonstrating the ease with which this tandem rearrangement allows for differential functionalization of the termini of the complex products. This aldehyde was readily converted to the allylic alcohol **49** in 74% yield by addition of isopropenyl magnesium bromide. Chelation control governed this addition, affording a 5:1 mixture of the desired anti-Felkin to the undesired Felkin product. Allylic alcohol **49** was then immediately acylated with *tert*-butyldiphenylsilyloxyacetyl chloride in the presence of pyridine to form the ester **50** in 68% yield.

Scheme 9. Installation of β-oxy ester



At this stage, the benzyl protecting group was removed in preparation for an internally directed *anti* reduction. This deprotection was not possible using standard hydrogenation conditions, though the benzyl group was efficiently cleaved using BF_3OEt_2 and Me_2S to afford the alcohol **51** in 89% yield (Equation 3).[19] This reaction operates through coordination of the benzylic oxygen to the Lewis acid followed by nucleophilic displacement by Me_2S.

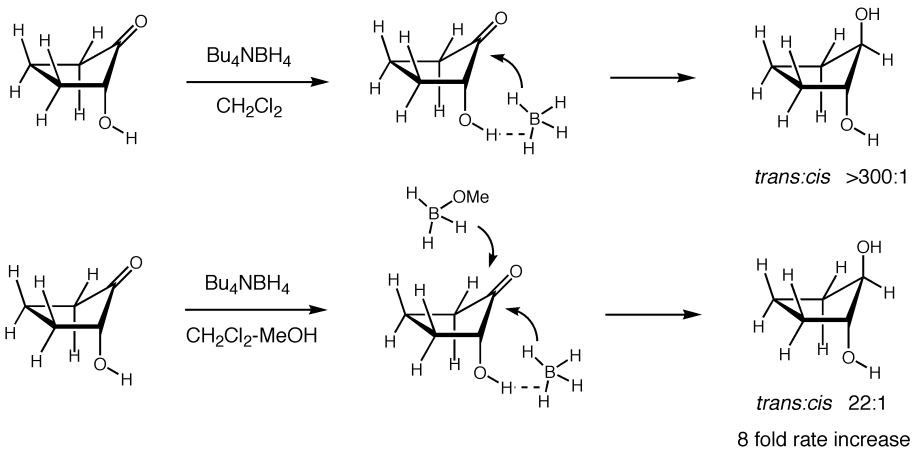


(3)

Selective *anti* reduction of the β–hydroxy ketone **51** proved difficult using standard *anti* reducing conditions such as sodium triacetoxyborohydride and SmI_2, which afforded predominantly the *syn* isomer. A report by Jackson[20] indicated that Bu_4NBH_4, when used with CH_2Cl_2, afforded preferentially the *trans* (*anti)* reduction products of cyclic hydroxy ketones. In contrast, when a solvent mixture of CH_2Cl_2 with a small

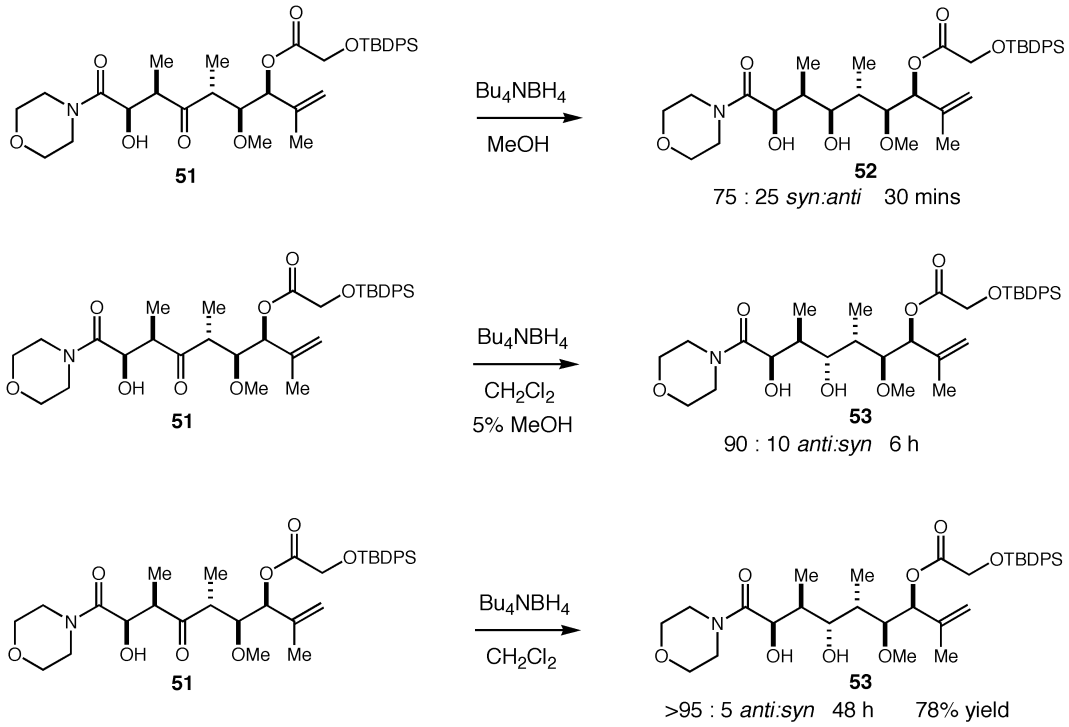
amount of MeOH was used, the reaction was much less *trans* selective and much faster. This difference is believed to result from competitive coordination of MeOH with the reducing agent; in the absence of MeOH, the reducing agent is coordinated only through an intramolecular dihydrogen bond (Scheme 10).

Scheme 10. Jackson's *anti* reduction of cyclic ketones



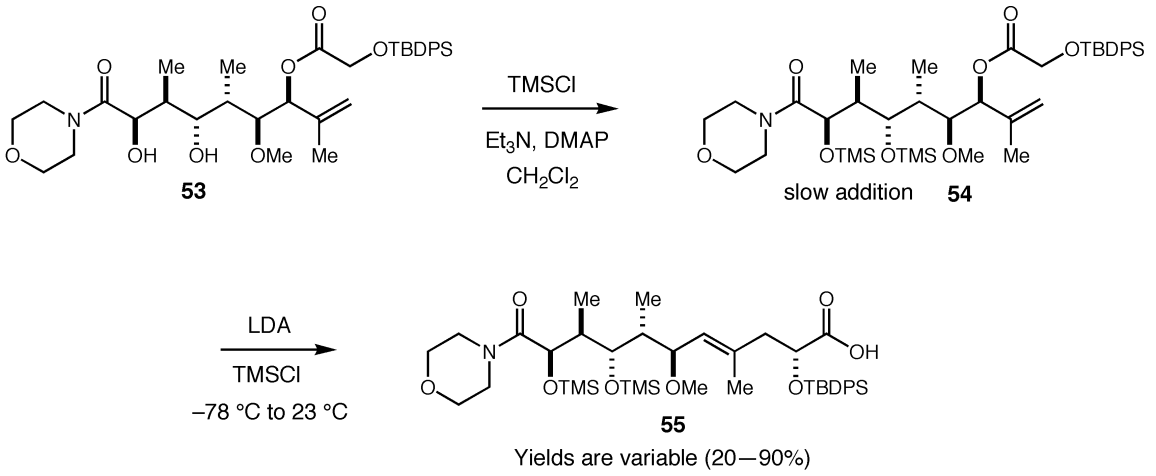
Though no reports have involved Bu_4NBH_4 used in CH_2Cl_2 to perform *anti* reductions of acyclic hydroxy ketones, we proposed that this reagent when used in CH_2Cl_2 might be able to effect the desired *anti* reduction for our system. In fact, when Bu_4NBH_4 was employed in the context of the acyclic □–hydroxy ketone **51**, a similar trend was observed (Scheme 11). Though the *anti* reduction was slow, the desired *anti* diol **53** was isolated in 78% yield after recovery of starting material (>95:5 *anti:syn*).

Scheme 11. Bu_4NBH_4 reduction stereochemistry as a function of solvent



Protection of the diol as the bis-TMS ether was effected in 75% yield, and at this stage Ireland Claisen rearrangement was attempted (Scheme 12). Though Claisen products were isolable, and the diastereoselectivity of the reaction was high, the yield of this reaction was decidedly variable; despite efforts to control the outcome of this reaction, various by-products relating to amide decomposition were frequently observed.

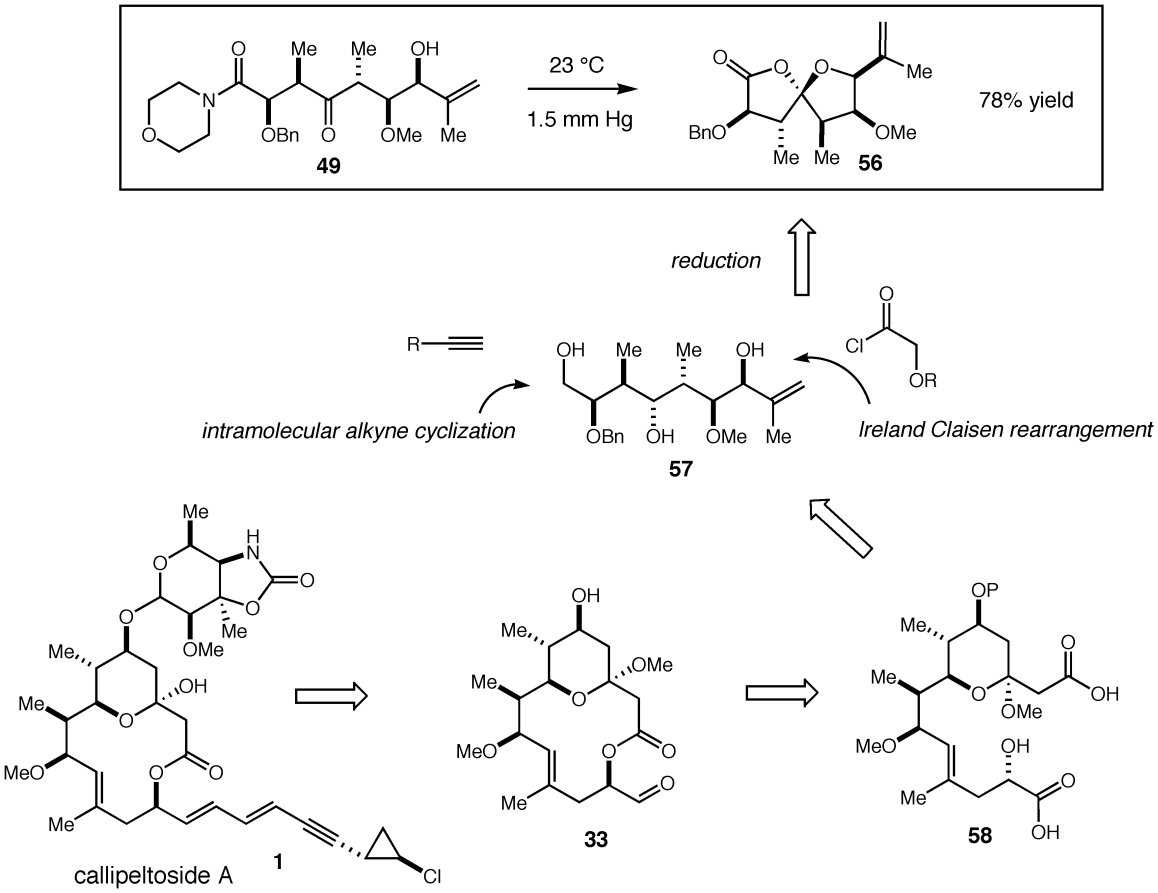
Scheme 12. Ireland Claisen rearrangement



Given the irreproducibility of this reaction and our belief that the presence of the amide was adversely affecting the rearrangement, we sought to revise our synthesis to perform the Ireland Claisen rearrangement subsequent to removal of the amide. Further, we hoped to improve upon the low reactivity observed in the *anti* reduction step.

We had noted that the allylic alcohol **49**, on standing, would spontaneously cyclize to form the spirocycle **56** (Scheme 13), and we had previously sought to avoid this perceived problem by immediately acylating to form Ireland Claisen precursor **50**. Yet, this spirocycle formation became attractive as we sought to revise our synthetic strategy. In the course of the spirocyclization, the amide functionality, so problematic during the Ireland Claisen rearrangement, was removed. Further, this spirocycle held the possibility for a reductive opening that might afford the desired and often elusive 1,3-*anti* diol relationship. Thus we revised our synthesis in an attempt to take advantage of this spontaneous spirocyclization (Scheme 13).

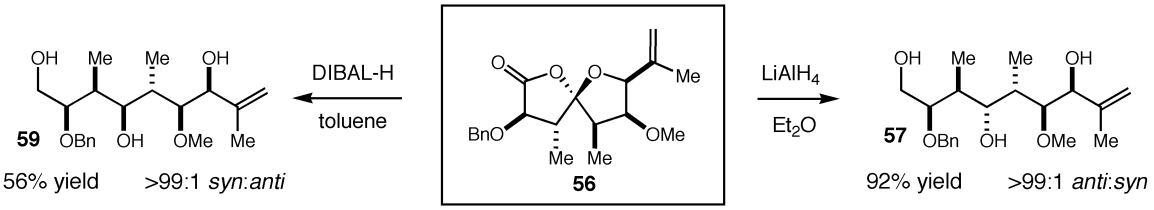
Scheme 13. Spirocyclization leads to revised retrosynthesis



Indeed, the reductive opening of spirocycle **56** was effected in high yield and excellent *anti* selectivity in the presence of $LiAlH_4$ in Et_2O (Scheme 14).[21] In contrast, an analogous reaction involving DIBAL-H as reductant and employing toluene as solvent afforded exclusively the *syn* 1,3 diol relationship. The origins of this selectivity difference will require further investigations, though it is probable that both the solvent and reducing agent are relevant variables. A coordinating solvent such as Et_2O will preclude any internal coordination between substrate and reducing agent, whereas toluene will allow significant coordination, and thus the potential exists for the two solvents to each bias the reaction toward a different transition state. Of course, the nature of the

reducing agent should have an affect as well; in accord with the proposed importance of intramolecular vs. intermolecular coordination of the reducing agent, the different Lewis acidities of $LiAlH_4$ and DIBAL-H would be expected to further differentiate between various transition states. Investigations to probe the differential selectivity should include variation of solvents and, as well, variation in the molar equivalents of reducing agent; presumably, if intramolecular coordination is important in determining the selectivity of one of these reductions, then introduction of additional equivalents of the reducing agent has the potential to introduce a non-coordinated reductant and thereby alter the selectivity of the reaction.

Scheme 14. Reductive opening of spirocycle

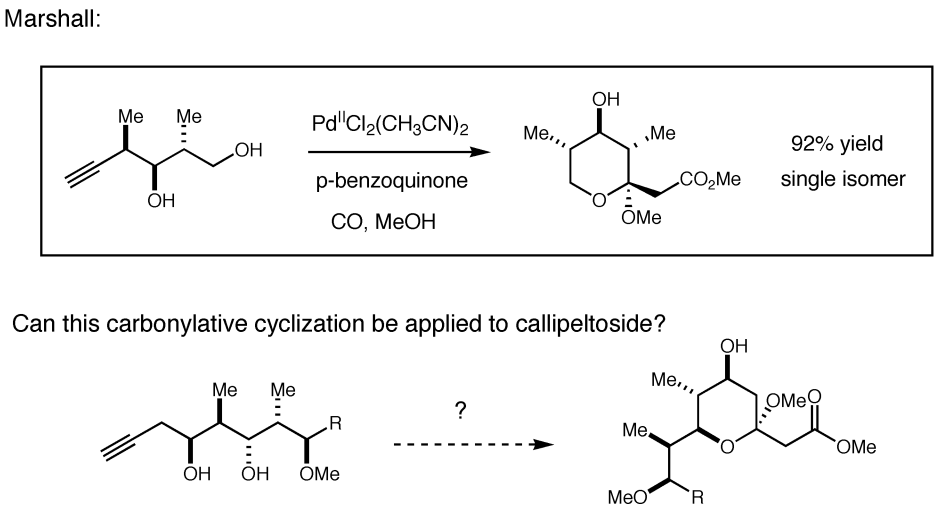


Acetylide opening of epoxide

With the desired *anti* 1,3 diol relationship in place and the amide removed, we turned to elaborating the stereochemical array **57** toward (1) performing the Ireland Claisen rearrangement and (2) introducing the tetrahydropyran moiety.

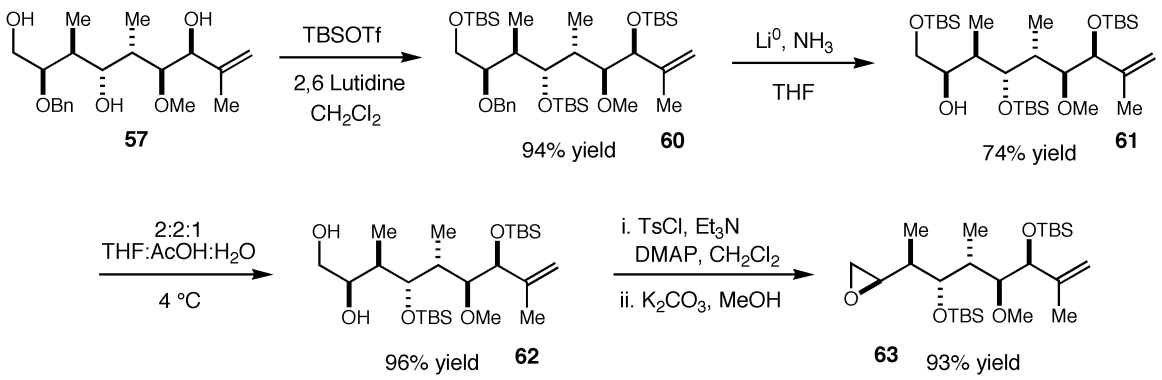
Marshall recently reported that alkynyl alcohols readily undergo a palladium catalyzed carbonylative cyclization to form tetrahydropyrans (Scheme 15).[22] We proposed that analogous conditions might be able to form the tetrahydropyran subunit of callipeltoside A.

Scheme 15. Marshall's carbonylative cyclization



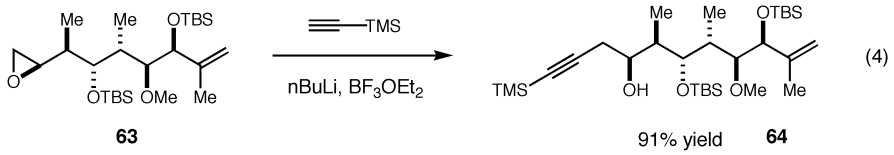
Thus we sought to introduce a protected alkyne into our stereochemical array. We imagined that the terminal 1,2 diol relationship of triol **57** might be readily transformed into an epoxide which could then be opened using an appropriately protected acetylene. As such, the triol **57** was tris-TBS protected in 94% yield and the benzyl protecting group was removed under Birch conditions in 74% yield (Scheme 16). It is noteworthy that hydrogenation conditions failed to cleave the benzyl group, and the BF_3OEt_2 conditions discussed above resulted only in substrate decomposition. Further, when the Birch reduction was performed using sodium metal rather than lithium, complete 1,3-TBS migration was observed, as has been described for other benzyl deprotections.[23] Selective removal of the primary TBS ether proceeded in 96% yield to afford the 1,2 diol **62**. Sequential one-pot treatment of the diol with toluenesulfonyl chloride/Et_3N followed by K_2CO_3 afforded epoxide **63** in 93% yield.

Scheme 16. Formation of terminal epoxide



57 **60** **61** **62** **63**

Treatment of epoxide **63** with the lithium anion of trimethylsilylacetylene in the presence of BF_3OEt_2 at –78 °C[24] effected the desired epoxide opening in 91% yield (Equation 4).



63 **64** (4)

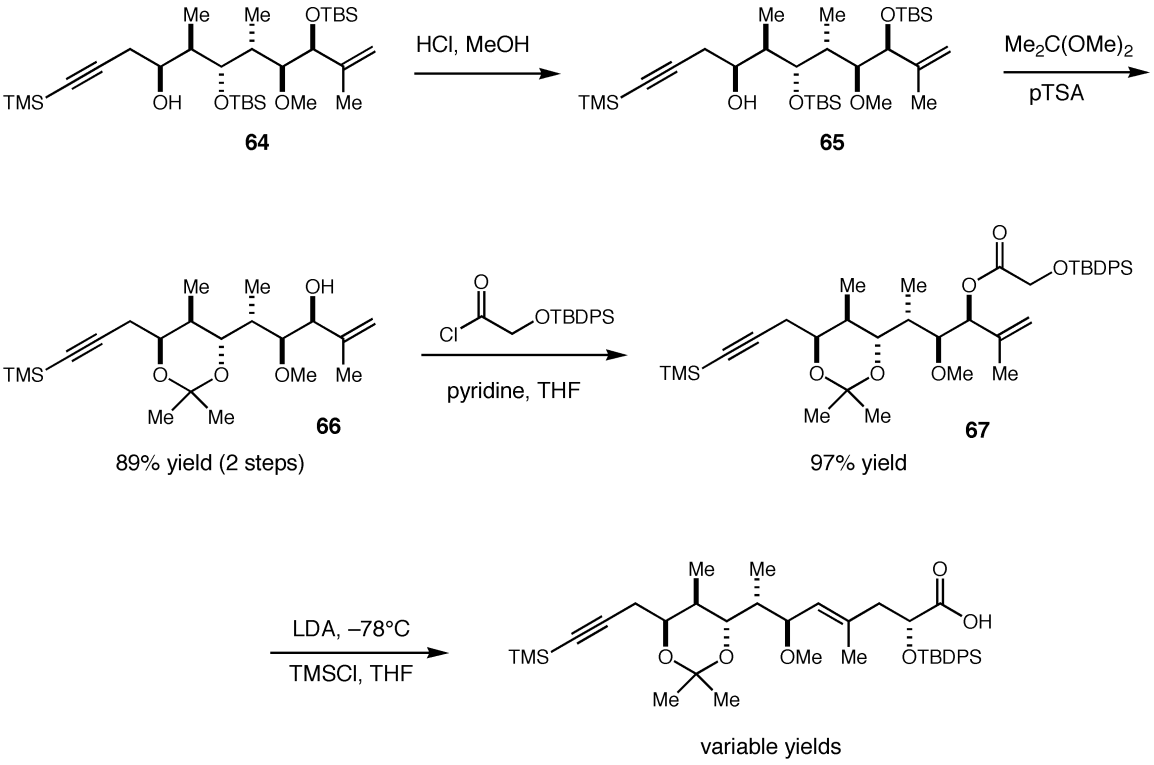
At this stage, prior to attempting the tetrahydropyran formation, we chose to perform the Ireland Claisen rearrangement. Were the THP formation conducted first, we feared that a competitive enolization of the THP-ester during the course of enolization might interfere with the Ireland Claisen rearrangement.

Ireland Claisen Rearrangement

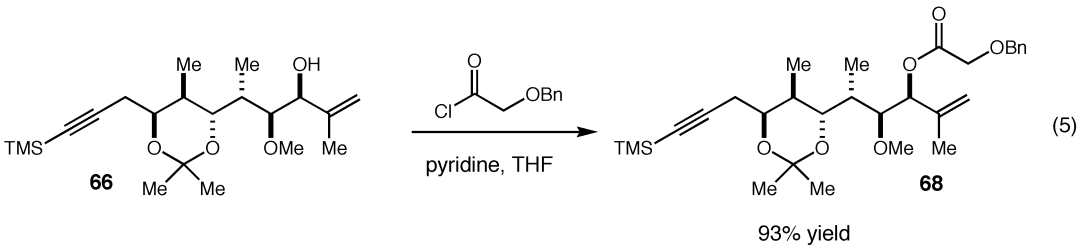
The ester precursor **67** to the Ireland Claisen rearrangement was accessed in high yield from the alkynyl alcohol **64** (Scheme 17). Removal of both TBS protecting groups

using concentrated HCl in MeOH was followed by acetonide protection of the *anti* 1,3 diol in 89% yield over two steps. The alcohol of the acetonide was then acylated with *tert*-butyldiphenylsilylacetyl chloride to afford the ester **67** in 97% yield.

Scheme 17. Synthesis of Ireland Claisen precursor

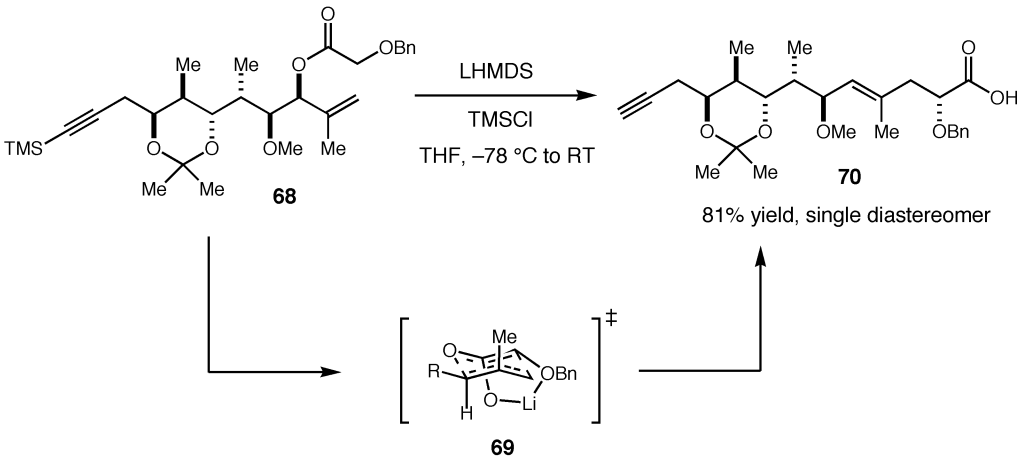


Ester **67** was poised for Ireland Claisen rearrangement, and treatment with LDA followed by TMSCl at –78 °C with subsequent warming to room temperature afforded the Claisen adduct in only variable, irreproducible yields, though again with high levels of diastereoselectivity. We proposed that the β–silyloxy moiety was responsible for the variable yields, with a silyl migration-decomposition pathway potentially in operation. Thus, the analogous β-benzyloxy substrate **68**, available in high yield from allylic alcohol **66** (Equation 5), was employed in the Ireland Claisen rearrangement.



(5)

Ester **68** performed consistently well in the Ireland Claisen rearrangement with LDA, though optimal levels of reaction efficiency were observed when LHMDS was used as the enolization base, to afford the Claisen product **70** in 81% yield as a single diastereoisomer, with concomitant deprotection of silyl-protected alkyne under the basic workup conditions (Equation 6). The high levels of diastereocontrol observed in this reaction are attributable to a chair-like transition state **69**, in accord with other Claisen rearrangements.[25]

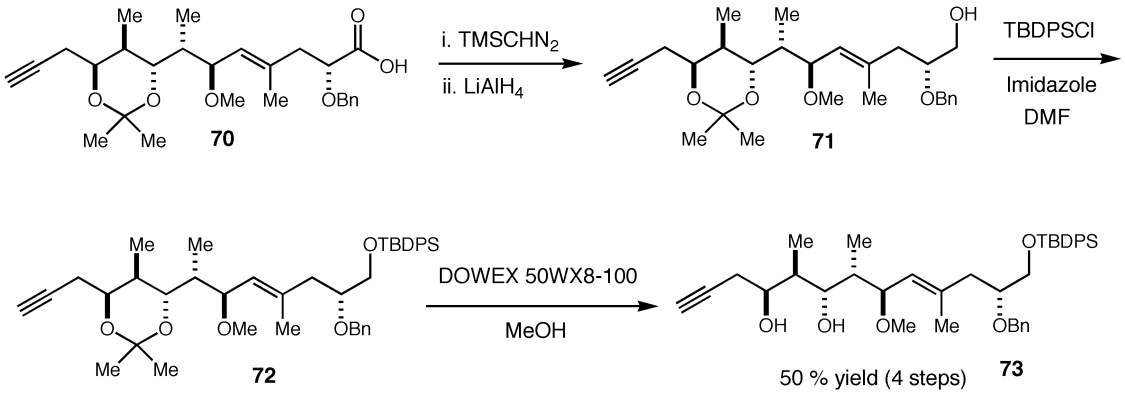


(6)

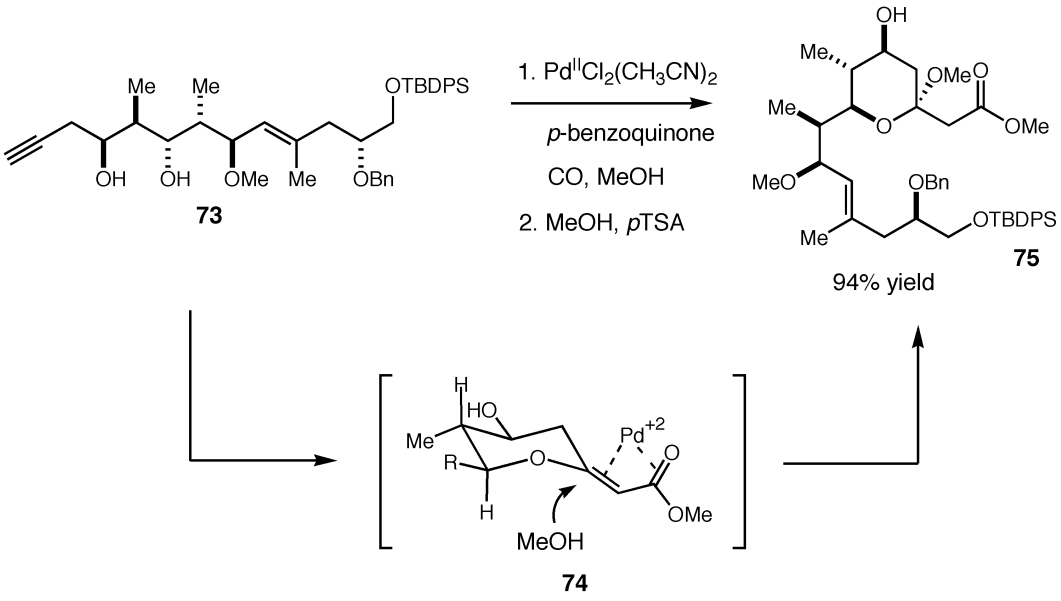
Tetrahydropyran formation

Having installed the internal alkene with the appropriate olefin geometry as well as the C13 stereocenter, we next turned our attention to closure of the tetrahydropyran ring, which would precede completion of the synthesis. Preparation of the precursor to the carbonylative cyclization entailed conversion of the acid functionality of Claisen product **70** to the corresponding methyl ester and immediate reduction to alcohol **71**. Protection of the alcohol as the TBDPS ether and cleavage of the acetonide protecting group using acidic DOWEX resin afforded the diol **73** in 50% overall yield for the rapid four-step sequence (Scheme 18).

Scheme 18. Synthesis of carbonylative cyclization precursor

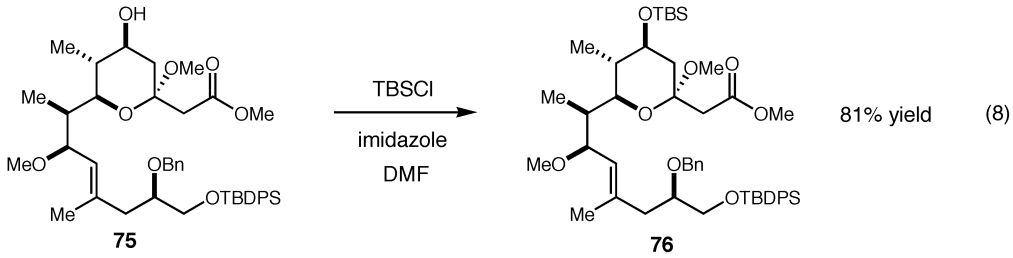


Diol **73** was next subjected to the carbonylative cyclization conditions reported by Marshall, and to our delight the THP derivative **75** was isolated in 94% yield as a single diastereoisomer (Equation 7). This high selectivity is in complete accord with the model proposed by Marshall involving a chair-like transition state.[26]



(7)

After TBS protection of tetrahydropyran **75** in 81% yield (Equation 8), attempts were made to remove the benzyl protecting group at C13 to allow for macrolactonization and completion of the synthesis.



(8)

Unfortunately, a wide variety of known conditions for removal of the benzyl protecting group resulted only in decomposition of the substrate or no reaction whatsoever. The sensitivity of the tetrahydropyran ring of **76** to acidic conditions rendered Brønsted-acid and Lewis-acid dependent deprotections deleterious, while the presence of the olefin precluded hydrogenation as a means to remove the benzyl ether.

Indeed, under various hydrogenation conditions, saturation of the olefin was typically fast, while no benzyl deprotection was observed. Oxidative conditions such as DDQ resulted in neither desired reaction nor decomposition of substrate, and it was thus concluded that a more readily removable protecting group such as a *para*-methoxybenzyl ether would be appropriate. Such a protecting group could be introduced as part of the acid chloride used to acylate allylic alcohol **66** (Equation 5) prior to the Ireland Claisen rearrangement. Following removal of that protecting group after formation of the tetrahydropyran ring, macrolactonization would likely be facile, following the precedent of Paterson, and coupling of the chlorocyclopropane sidechain and the sugar residue would allow access to callipeltoside A.

III. Conclusion

The novel tandem amino-sulfide acyl-Claisen rearrangement has been employed in research directed towards the total synthesis of callipeltoside A. The key rearrangement affords the stereochemical backbone of callipeltoside A with excellent diastereocontrol and retention of enantiopurity from starting material to the product of the Claisen rearrangement. Elaboration after the tandem Claisen has involved reductive opening of a spirocyclic intermediate with excellent stereoselectivity, a highly diastereoslective Ireland Claisen rearrangement, and an intramolecular carbonylative cyclization reaction to form a tetrahydropyran ring system. This synthetic approach relies entirely upon substrate control to establish relative stereochemical relationships subsequent to an initial enantioselective reaction. Future work will include modification of the protecting group strategy in the Ireland Claisen rearrangement which will facilitate

the macrolactonization step and give access to the macrolide core of callipeltoside A, which can then be elaborated to the natural product after coupling to the chlorocyclopropane sidechain and deoxyamino sugar in accord with literature precedent.

IV. Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[27] All non–aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Non-aqueous reagents were transferred under nitrogen *via* syringe or cannula. Solvents were purified using an alumina column. 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.[28] 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 $KMnO_4$, CAM, or anisaldehyde stain.

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{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 a Perkin-Elmer infrared 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 Caltech Mass Spectral Facility. 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).

3-Cyclohexylsulfanylmethyl-pent-3-en-2-one (39). A solution of methyl magnesium iodide (1.0 M THF, 100 mL, 0.3 mol) in 300 mL dry diethyl ether in a flame dried 5 L round bottom flask under an atmosphere of argon was cooled to 0 °C. Cyclohexyl thiol (36.6 mL, 0.3 mol) in 300 mL dry diethyl ether was added via an addition funnel over 30 min to the stirring solution. A solution of methyl vinyl ketone (25 mL, 0.3 mol) and acetaldehyde (16.8 mL, 0.3 mol) in 300 mL dry diethyl ether was added to the 0 °C solution. The reaction was stirred at 0 °C for 3 h at which time it was quenched with sat. aq. NH_4Cl. The organic layer was removed and washed twice with 10% NaOH (200 mL) and once with sat. aq. NaCl (200 mL), dried over $MgSO_4$, filtered through a cotton plug, and concentrated. The oil was taken up in 245 mL dry diethyl ether in a dry 5 L round bottom flask, which was then purged with argon. Methanesulfonyl chloride (20 mL, 0.264 mol) was added *via* syringe, and the solution was cooled to 0 °C. Et_3N (34 mL, 0.264 mol) was added, and the reaction was stirred at 0 °C for 30 min at which time the mixture was filtered through a cotton plug and concentrated. The resulting oil was dissolved in 333 mL dry THF in a dry 5 L round bottom flask which was then purged with argon. DBU (50 mL, 0.333 mol) was added *via* syringe over 10 min during which time the solution became cloudy. After addition was

complete, 300 mL Et_2O was added and mixture was washed twice with H_2O (300 mL), twice with sat. aq. $CuSO_4$ (200 mL), once with sat. aq. NaCl (200 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a yellow oil in 25% yield (16 g). IR (film) 2928, 2851, 1717, 1675, 1669, 1657, 1448, 1385, 1341. 1277, 1162, 999, 954, 829, 742, 609, 580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.77 (q, J = 6.5 Hz, 1H, $H_3CC\mathbf{H}$), 3.42 (s, 3H, $COC\mathbf{H}_3$), 2.62-2.58 (m, 2H, $SC\mathbf{H}_2$), 1.92 (d, J = 6.5 Hz, 3H, $CHC\mathbf{H}_3$), 1.57-1.55 (m, 1H, SC**H**), 1.31-1.18 (m, 10H, Cy-**H**); ^{13}C NMR (125 MHz, $CDCl_3$) 198.1, 140.7, 140.4, 44.5, 33.8, 26.3, 26.1, 25.8, 24.0, 15.2; LRMS (FAB) m/z 211 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{12}H_{19}OS$) requires m/z 211.1150, found m/z 211.1157.

(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enylamine (41).[29] 3-Cyclohexylsulfanylmethyl-pent-3-en-2-one **39** (1.58 g, 7.5 mmol) and (*R*)-(-)-2-methyl-2-propanesulfinamide (1.00 g, 8.25 mmol, 97% ee) were dissolved in 15.0 mL dry THF in a dry 100 mL round bottom flask under argon. $Ti(OEt_4)$ (6.13 mL, 22.5 mmol) was added via syringe, and the solution was stirred at 75 °C for 16.5 h. After cooling the reaction vessel to –78 °C, the mixture was added to a –60 °C suspension of $NaBH_4$ (1.13 g, 30.0 mmol) in 15 mL dry THF, and stirred at –60 °C for 23 h. The reaction was quenched slowly by addition of MeOH (30 mL) with stirring. Sat. aq. NaCl (30 mL) was added and the mixture was extracted once with EtOAc (40 mL). The organic layer was washed once with sat. aq. NaCl (30 mL). The combined aqueous layers were extracted three times with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4,

filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided a yellow oil which was immediately dissolved in 1.33 mL MeOH. A solution of HCl in dioxane (4.0 M, 1.33 mL, 5.33 mmol) was added and the solution was stirred for 15 min. 15 mL CH_2Cl_2 was added and the solution was extracted three times with 1N aq. $KHSO_4$. 10% aq. NaOH was added to the combined aqueous layers to pH >7. The aqueous phase was then extracted five times with CH_2Cl_2, dried over Na_2SO_4, filtered through a cotton plug, and concentrated to afford the title compound as an oil in 26% yield (423.3 mg). IR (film) 2926, 2851, 1575, 1557, 1447, 1368, 1262, 1199, 1100, 999, 885, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.61 (q, *J* = 7.0 Hz, 1H, C**H**), 3.61 (q, *J* = 7.0 Hz, 1H, (vinylC)**H**NH_2), 3.35 (d, *J* = 12.0 Hz, 1H, N**H**H), 2.65-2.60 (m, 2H, C**H**$_2$S), 1.71 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 1.64-1.62 (m, 1H, SC**H**), 1.40-1.25 (m, 10H, Cy-**H**), 1.21 (d, *J* = 7.0 Hz, 3H, CNH_2C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 121.3, 51.8, 44.4, 33.9, 27.8, 26.4, 26.1, 23.4, 17.1, 13.6; LRMS (FAB) *m*/*z* 214 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{12}H_{24}NS$) requires *m*/*z* 214.1630, found *m*/*z* 214.1629.

4-[(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine (42). To (1*S*)-2-cyclohexylsulfanylmethyl-1-methyl-but-2-enylamine **41** (354.7 mg, 1.66 mmol) in 2.6 mL dry CH_3CN in a dry 20 mL vial under argon was added K_2CO_3 followed by dropwise addition of bis(2–bromoethyl)ether (0.209 mL, 1.66 mmol). The vial was flushed with argon, sealed, and heated to 80 °C for 12.5 h. The reaction was then cooled to ambient temperature, and Na_2SO_4 (50 mg) was added. The mixture was filtered through a cotton plug and concentrated. Purification of the resulting oil by silica gel

chromatography (10% EtOAc/hex) provided the title compound as an oil in 52% yield (246.3 mg). IR (film) 2928, 2851, 2805, 2760, 1448, 1372, 1308, 1263, 1201, 1177, 1140, 1119, 1069, 999, 947, 918, 864, 855, 837, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (q, *J* = 7.0 Hz, 1H, vinylC**H**), 3.71-3.64 (m, 4H, NC$\mathbf{H}_2$C$\mathbf{H}_2$), 3.01 (q, *J* = 7.0 Hz, 1H, C**H**NR_2), 2.63-2.58 (m, 2H, SC$\mathbf{H}_2$), 2.48-2.39 (m, 4H, OC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.71 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 1.63-1.60 (m, 1H, SC**H**), 1.38-1.23 (m, 10H, Cy-**H**), 1.12 (d, *J* = 7.0 Hz, $CHNH_2C\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 123.9, 67.7, 64.3, 50.4, 44.5, 33.9, 27.9, 26.4, 26.1, 14.8, 13.7; LRMS (FAB) *m/z* 282 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{16}H_{28}NOS$) requires *m/z* 282.1898, found *m/z* 282.1892.

4-(2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine (43). 3-Cyclohexylsulfanylmethyl-pent-3-en-2-one **39** (7.16 g, 33.88 mmol) and morpholine (8.86 mL, 101.63 mmol) were dissolved in 67.8 mL dry THF in a 250 mL round bottom flask. $Ti(OEt_4)$ (27.71 mL, 101.63 mmol) was added via syringe, and the solution was stirred at reflux for 14 h. After cooling the reaction vessel to –78 °C, the mixture was added to a –50 °C suspension of $NaBH_4$ (5.13 g, 135.52 mmol) in 68 mL dry THF, and stirred at –50 °C for 23 h. The reaction was quenched slowly by addition of MeOH (150 mL) with stirring. Sat. aq. NaCl (150 mL) was added and the mixture was extracted once with EtOAc (200 mL). The organic layer was washed once with sat. aq. NaCl (150 mL). The combined aqueous layers were extracted three times with EtOAc (250 mL). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as an oil in 58% yield (5.58 g). All spectral

data were in complete accord with 4-(2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine **3** (*vida supra*).

(2*S*,3*S*)-2-Benzyloxy-4-cyclohexylsulfanylmethyl-3-methyl-1-morpholin-4-yl-hex-4-en-1-one (44). 4-[(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine **(42)** (3.00 g, 10.6 mmol) was dissolved in 15 mL CH_2Cl_2 in a dry 500 mL round bottom flask under argon. A solution of $TiCl_4(THF)_2$ (2.65 g, 7.8 mmol) in 250 mL CH_2Cl_2 was added *via* cannula, and iPr_2NEt (3.69 mL, 21.2 mmol) was then added *via* syringe. The stirring solution was cooled to –40 °C, and 21.2 mL of a 1 M solution in CH_2Cl_2 of freshly distilled benzyloxyacetylchloride (3.34 mL, 21.2 mmol) was added *via* syringe pump over 17 h. After addition, the reaction was poured into 1N aq. NaOH (200 mL) and extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting red oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 97% yield (4.41 g), 12:1 *syn* diastereomer: other diastereoisomers, *syn* 98% ee. IR (film) 3035, 2927, 2858, 1645, 1444, 1367, 1305, 1267, 1112, 1027, 966, 919, 842, 734, 703, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.36-7.23 m, 5H, Ar-**H**), 5.51 (q, *J* = 7.2 Hz, 1H, vinylC**H**), 4.63 (d, *J* = 12.0 Hz, 1H, OC**H**H), 4.38 (d, *J* = 12.0 Hz, 1H, OCH**H**), 4.11 (d, *J* = 7.2Hz, 1H, C**H**OBn), 3.74-3.44 (m, 8H, morph-**H**), 3.29 (d, *J* = 12.3 Hz, 1H, SC**H**H), 3.01 (d, *J* = 12.3, 1H, SCH**H**), 2.72 (dq, *J* = 7.2, 7.2, 1H, CHOBnC**H**CH_3), 1.66 (d, *J* = 7.2, 3H, vinylCHC**H**$_3$), 1.62-1.59 (m, 1H, SC**H**), 1.36-1.24 (m, 10H, Cy-**H**), 1.20 (d, *J* = 7.2, 3H, CHOBnCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.8, 137.0, 128.6, 128.1, 124.6, 82.5, 72.1, 67.4, 67.1, 46.1, 44.2, 42.7, 42.0, 34.0, 30.0,

26.5, 26.2, 16.9, 14.1; LRMS (FAB) *m/z* 432 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{38}NO_3S$) requires *m/z* 432.2566, found *m/z* 432.2572. Enantiomeric ratio was determined by HPLC with Chiralcel AD column and AD guard column (4% *i*PrOH/hex, 1 mL/min flow rate); t_r = 17.1 min (major) and 19.9 min (minor).

(2*S*,3*R*)-4-[(1*S*,2*S*)-2-Benzyloxy-1-methyl-3-morpholin-4-yl-3-oxo-propyl]-2-methoxy-3-methyl-pent-4-enethioic acid *S*-cyclohexyl ester (45). (2*S*,3*S*)-2-Benzyloxy-4-cyclohexylsulfanylmethyl-3-methyl-1-morpholin-4-yl-hex-4-en-1-one **44** (12.1 g, 28.07 mmol) was dissolved in 280.7 mL CH_2Cl_2 in a dry 1 L round bottom flask under argon. Me_2AlCl (26.07 mL, 280.7 mmol) was added *via* syringe, and iPr_2NEt (34.2 mL, 196.5 mmol) was then added *via* syringe. The stirring solution was cooled to –60 °C, and 20.16 mL of a 9.7 M solution in CH_2Cl_2 of freshly distilled methoxyacetylchloride (17.96 mL, 196.49 mmol) was added *via* syringe pump over 20 h. The reaction was then stirred at –60 °C for 10 d, at which time it was quenched with 1N aq. NaOH (200 mL) and sat. aq. NaCl (100 mL). The mixture was extracted three times with Et_2O, and the combined organic extracts were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 93% yield (13.07 g) as a 3.2:1 mixture of diastereomers. IR (film) 2935, 2858, 2248, 1645, 1452, 1359, 1305, 1267, 1236, 1112, 973, 911, 850, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.36-7.25 (m, 5H, Ar-**H**), 5.05 (d, *J* = 10.8 Hz, 2H, vinylC**H**$_2$), 4.61 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.40 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.09 (d, *J* = 7.2 Hz, 1H, C**H**OBn), 3.69-3.53 (m, 8H, morph-**H**), 3.49 (d, *J* = 7.2 Hz, 1H, C**H**OMe), 3.35 (s, 3H, OC**H**$_3$),

2.63 (dq, *J* = 7.2 Hz, 7.2 Hz, 1H, NC**H**CH_3), 2.46 (dq, *J* = 7.2 Hz, 7.2 Hz, SC**H**CH_3), 1.92-1.34 (m, 11H, Cy-**H**), 1.20 (d, *J* = 7.2 Hz, 3H, NCHC**H**$_3$), 0.97 (d, *J* = 7.2 Hz, 3H, SCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 169.8, 152.0, 128.6, 128.1, 128.0, 112.5, 92.4, 81.7, 71.8, 67.4, 67.0, 59.6, 46.2, 43.3, 42.9, 41.6, 33.5, 33.3, 26.3, 25.9, 16.9, 16.5; LRMS (FAB) *m*/*z* 504 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{28}H_{42}NO_5S$) requires *m*/*z* 504.2762, found *m*/*z* 504.2784.

(2*S*,3*R*,5*S*,6*S*)-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanethioic acid *S*-cyclohexyl ester (46). (2*S*,3*R*)-4-[(1*S*,2*S*)-2-Benzyloxy-1-methyl-3-morpholin-4-yl-3-oxo-propyl]-2-methoxy-3-methyl-pent-4-enethioic acid *S*-cyclohexyl ester 4**5** (12.9 g, 25.6 mmol) was dissolved in 128 mL dry CH_2Cl_2 in a dry 1 L 3-neck round bottom flask under argon. The stirring solution was cooled to –78 °C, and oxygen was bubbled through the solution for 10 min, after which time a stream of ozone was passed through the solution for one hour until a faint blue color appeared. The ozone stream was removed and oxygen was again bubbled through the stirring solution for 5 min, at which time dimethyl sulfide (2.8 mL, 38.4 mmol) was added and the mixture was stirred at –78 °C for 10 min and then at ambient temperature for 10 h. The reaction was then concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 52% yield (6.68 g) as a single diastereoisomer, 97% ee. IR (film) 2935, 2858, 2248, 1962, 1715, 1645, 1452, 1383, 1305, 1267, 1236, 1112, 1012, 966, 911, 857, 819, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.37-7.25 (m, 5H, Ar-**H**), 4.54 (d, *J* = 9.6 Hz, 1H, C**H**OBn), 4.52 (d, *J* = 11.6 Hz, 1H, C**H**HAr), 4.30 (d, *J* = 11.6 Hz, 1H, CH**H**Ar), 3.81 (d, *J* = 9.3 Hz, 1H, C**H**OMe), 3.66-

3.40 (m, 9H, morph-**H**, CHOBnC**H**Me), 3.30 (s, 3H, OC**H**$_3$), 3.04 (dq, *J* = 9.6 Hz, 7.2 Hz, 1H, CHOMeC**H**Me), 1.94-1.35 (m, 11H, Cy-**H**), 1.26 (d, *J* = 7.2 Hz, 3H, CHOBnCHC**H**$_3$), 1.00 (d, *J* = 7.2 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 212.7, 201.5, 168.8, 137.5, 128.0, 88.5, 75.9, 69.4, 67.0, 59.2, 49.0, 47.0, 46.4, 42.6, 41.7, 33.5, 33.3, 26.3, 25.9, 13.2, 13.0; LRMS (FAB) *m/z* 506 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{40}NO_6S$) requires *m/z* 506.2567, found *m/z* 506.2576. Enantiomeric ratio was determined by HPLC with Chiralcel AD column and AD guard column (6% *i*PrOH/hex, 1 mL/min flow rate); t_r = 22.5 min (major) and 26.1 min (minor).

***(2S*,3R*,5S*,6S*)*-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal (48).** To a dry 100 mL round bottom flask containing 10% Pd/C (1.87 g, 1.76 mmol Pd) under a nitrogen atmosphere was added *via* cannula a solution of (2*S**,3*R**,5*S**,6*S**)-6-benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanethioic acid *S*-cyclohexyl ester **47** (5.54 g, 10.97 mmol) in freshly distilled acetone (21.4 mmol). The stirring mixture was cooled to +4 °C, and freshly distilled Et_3SiH (8.76 mL, 54.85 mmol) which had been pre–cooled to +4 °C was added slowly *via* syringe. The reaction was monitored by TLC (50% EtOAc/hex) and upon consumption of starting material after 70 min, the reaction mixture was flushed through a pad of celite with EtOAc. The solution was concentrated. Purification of the resulting oil by silica gel chromatography (60% EtOAc/hex) provided the title compound as a colorless oil in 86% yield (3.7 g). IR (film) 3441, 2934, 2858, 1730, 1710, 1645, 1455, 1379, 1301, 1271, 1235, 1114, 1017, 967, 855, 742, 699, 578 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.71 (d, *J* = 2.5 Hz, CO**H**), 7.39-7.31 (m, 5H, Ar-**H**), 4.59 (d, *J* = 9.5 Hz, 1H, C**H**OBn), 4.55 (d, *J* =

12, 1H, C**H**HAr), 4.34 (d, *J* = 12 Hz, 1H, CH**H**Ar), 4.14 (dd, *J* = 7.5 Hz, 6.5 Hz, C**H**OMe), 3.70-3.46 (m, 9H, morph-**H**, CHOBnC**H**Me), 3.39 (s, 3H, OC**H**$_3$), 3.18 (dq, *J* = 6.5 Hz, 8.0 Hz, 1H, CHOMeC**H**Me), 1.29 (d, *J* = 7.5 Hz, 3H, CHOBnCHC**H**$_3$), 1.16 (d, *J* = 7.5 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 212.4, 202.7, 168.8, 137.4, 128.7, 128.0, 86.6, 76.0, 69.2, 67.0, 59.4, 46.8, 46.4, 46.3, 42.7, 13.3, 12.8; LRMS (FAB) *m*/*z* 392 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{21}H_{30}NO_6$) requires *m*/*z* 392.2059, found *m*/*z* 392.2073.

(3*S,4*S**,7*S**,8*S**,9*R**)-3-Benzyloxy-7-isopropenyl-8-methoxy-4,9-dimethyl-1,6-dioxa-spiro[4.4]nonan-2-one (56).** *(*2*S**,3*R**,5*S**,6*S**)-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal **48** (1.56 g, 3.99 mmol) was dissolved in 64.3 mL dry THF in a 250 mL round bottom flask, and the stirring solution was cooled to –78 °C. Isopropenyl magnesium bromide (0.5M in THF, 9.6 mL, 4.79 mmol) was added *via* syringe pump over 45 min. Stirring was continued for 1.5 h after addition was complete, at which time the reaction was quenched with sat. aq. NH_4Cl and extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the intermediate allylic alcohol product as a colorless oil in 74% yield (1.28 g). A portion of this oil (0.937 g) was immediately placed under high vacuum (1.5 mm Hg) for 32 d, after which time TLC analysis indicated formation of the title compound. Purification of the oil by silica gel chromatography (30% EtOAc/hex to 60% EtOAc/hex) provided recovery of 20% of the starting allylic alcohol (237.8 mg) and isolation of the title compound as a colorless oil in

58% yield (437.2 mg) from the allylic alcohol (78% yield based on recovered starting material). IR (film) 2970, 2936, 1784, 1717, 1645, 1497, 1456, 1352, 1250, 1205, 1141, 1113, 1072, 1010, 911, 742, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.41-7.29 (m, 5H, Ar-**H**), 5.14 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 5.05 (s, 1H, vinylC**H**), 4.99 (s, 1H, vinylC**H**), 4.76 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.41 (d, *J* = 3.9 Hz, 1H, allylicC**H**), 4.09 (d, *J* = 10.8 Hz, 1H, C**H**OBn), 3.73 (ss, *J* = 4.8 Hz, 4.8 Hz, 1H, C**H**OMe), 3.39 (s, 3H, OC$\mathbf{H}_3$), 2.44 (dq, *J* = 6.9 Hz, 10.5 Hz, 1H, CHOBnC**H**Me), 2.28 (dq, *J* = 6.9 Hz, 5.4 Hz, 1H, CHOMeC**H**Me), 1.80 (s, 3H, vinylC$\mathbf{H}_3$), 1.14 (d, *J* = 6.9 Hz, 1H, CHOBnCHC$\mathbf{H}_3$), 1.08 (d, *J* = 6.6 Hz, 1H, CHOMeCHC$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 174.4, 140.9, 137.2, 128.4, 128.1, 127.9, 113.5, 113.0, 87.5, 83.7, 77.8, 72.8, 60.7, 43.4, 42.3, 19.5, 10.7, 7.7; LRMS (FAB) *m/z* 347 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{20}H_{27}O_5$) requires *m/z* 347.1846, found *m/z* 347.1858.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol (57).** (3*S**,4*S**,7*S**,8*S**,9*R**)-3-Benzyloxy-7-isopropenyl-8-methoxy-4,9-dimethyl-1,6-dioxa-spiro[4.4]nonan-2-one **56** (76.0 mg, 0.219 mmol) was dissolved in 4.38 mL dry Et_2O in a dry 50 mL round bottom flask under argon, and the stirring solution was cooled to 0 °C. $LiAlH_4$ (33.3 mg, 0.877 mmol) was added and the flask was flushed with argon. The reaction was stirred at ambient temperature for 24 h at which time it was quenched slowly with sat. aq. Rochelle's salt solution (30 mL) and stirred for 4 d. The mixture was extracted four times with EtOAc (40 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless

oil in 92% yield (70.8 mg). IR (film) 3424, 3033, 2973, 2939, 1646, 1497, 1455, 1380, 1211, 1092, 1028, 979, 902, 736, 699, 540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35-7.28 (m, 5H, Ar-**H**), 5.00 (s, 1H, vinylC**H**), 4.92 (s, 1H, vinylC**H**), 4.71-4.66 (m, 2H, C**H**$_2$Ar), 4.10 (bs, 1H, allylic**H**), 3.96-3.29 (m, 5H, C**H**2OH, C**H**OBn, C**H**OMe, C**H**OH), 3.52 (s, 3H, OC**H**$_3$), 2.15-1.78 (m, 2H, C**H**Me, C**H**Me), 1.76, (s, 3H, vinylC**H**$_3$), 0.96 (d, *J* = 7.5 Hz, 3H, CHOBnCHC**H**$_3$), 0.77 (d, *J* = 6.5 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 145.3, 128.7, 128.1, 128.0, 127.9, 113.2, 86.5, 82.2, 75.9, 73.4, 71.8, 63.0, 62.3, 37.7, 35.7, 18.5, 11.8, 10.3; LRMS (FAB) *m/z* 353 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{20}H_{33}O_5$) requires *m/z* 353.2339, found *m/z* 353.2328.

[(1*S,2*S**,3*R**,4*R**,5*S**,6*S**)-3,6-Bis(*tert*-butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-methoxy-2,4,7-trimethyl-oct-7-enyloxymethyl]-benzene (60).** (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **57** (363 mg, 1.03 mmol) was dissolved in 32 mL dry CH_2Cl_2 in a 100 mL round bottom flask under argon. The solution was cooled to 0 °C and freshly distilled TBSOTf (2.37 mL, 10.3 mmol) was added, followed by freshly distilled 2,6–lutidine (1.2 mL, 10.3 mmol). The reaction was allowed to warm to ambient temperature and was then stirred for 3.5 h at which time it was quenched with sat. aq. NH_4Cl (30 mL) and extracted four times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a colorless oil in 94% yield (673.5 mg). IR (film) 2927, 2855, 1653, 1472, 1252, 1093, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.37-7.24 (m, 5H, Ar-**H**), 5.09 (s, 1H, vinylC**H**), 4.91 (s,

1H, vinylC**H**), 4.78 (d, *J* = 11.7 Hz, 1H, C**H**HAr), 4.56 (d, *J* = 12.0 Hz, 1H, CH**H**Ar), 4.22 (bs, 1H, allylicC**H**), 4.14 (d, *J* = 7.2 Hz, 1H, $(CHMe)_2$C**H**OTBS), 3.78 (dd, *J* = 10.5 Hz, 5.7 Hz, 1H, C**H**HOH), 3.69 (dd, *J* = 10.5 Hz, 4.2 Hz, 1H, CH**H**OH), 3.59 (ddd, *J* = 5.1 Hz, 4.8 Hz, 5.0 Hz, 1H, C**H**OBn), 3.42 (s, 3H, OC$\mathbf{H}_3$), 3.16 (dd, *J* = 3.0 Hz, 10.2 Hz, 1H, C**H**OMe), 2.00-1.89 (m, 2H, C**H**Me, C**H**Me), 1.74 (s, 3H, vinylC$\mathbf{H}_3$), 0.95-0.86 (m, 33H, $(SitBu)_3$, $(CHMe)_2$), 0.13-0.01 (m, 18H, $(SiMe_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 139.8, 128.3, 127.4, 127.3, 112.1, 83.7, 81.1, 75.4, 72.8, 72.1, 64.3, 57.5, 41.1, 35.7, 26.6, 26.3, 26.1, 20.5, 19.0, 18.6, 11.0, 10.9, -2.5, -3.3, -3.5, -3.9, -4.7, -4.9, -5.0; LRMS (FAB) *m*/*z* 695 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{38}H_{75}O_5Si_3$) requires *m*/*z* 695.4897, found *m*/*z* 695.4922.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-1,4,7-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-2-ol (61).**[30] A dry 50 mL 3-neck round bottom flask under argon with a condensing aparatus attached was cooled to –78 °C and 10 mL NH_3 was condensed into the flask. Lithium metal (8 mg) was added, and the mixture was stirred until a deep blue color persisted. A solution of [(1*S**,2*S**,3*R**,4*R**,5*S**,6*S**)-3,6-bis(*tert*-butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-methoxy-2,4,7-trimethyl-oct-7-enyloxymethyl]-benzene **60** (17.5 mg, 0.025 mmol) in 1 mL dry THF was added, and the reaction was stirred for two minutes, at which time solid NH_4Cl (30 mg) was added, and the blue color disappeared. The mixture was allowed to warm to ambient temperature, and the mixture was stirred until the NH_3 had evaporated. Water (30 mL) was added, and the mixture was extracted three times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the

resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a colorless oil in 74% yield (11.3 mg). IR (film) 3442, 2956, 2930, 2886, 2858, 2096, 1644, 1472, 1463, 1388, 1361, 1253, 1089, 1044, 1005, 940, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.00 (s, 1H, vinylC**H**), 4.90 (s, 1H, vinylC**H**), 4.16 (d, *J* = 4.5 Hz, 1H, allylicC**H**), 4.03 (dd, *J* = 2.0 Hz, 4.0 Hz), 3.95 (m, 1H, C**H**OH), 3.55 (dd, *J* = 9.5Hz, 6.0 Hz, 1H, C**H**HOTBS), 3.51 (dd, *J* = 6.5 Hz, 9.5 Hz, 1H, CH**H**OTBS), 3.44 (s, 3H, OC$\mathbf{H}_3$), 3.23 (s, 1H, O**H**), 3.08 (dd, *J* = 4.5 Hz, 7.5 Hz, 1H, C**H**OMe), 1.95 (ddq, *J* – 7.0 Hz, 7.0 Hz, 2.0 Hz, 1H, CHOMeC**H**Me), 1.70-1.67 (m, 1H, CHOHC**H**Me), 1.56 (s, 3H, vinylC$\mathbf{H}_3$), 0.953 (d, *J* = 7.5 Hz, 1H, C**H**Me), 0.946 (d, *J* = 7.5 Hz, 1H, C**H**Me), 0.93-0.89 (m, 27H, $(SitBu)_3$), 0.11-0.02 (m, 18H, $(SiMe_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.4, 113.0, 86.0, 76.5, 75.4, 71.7, 65.1, 60.6, 59.1, 40.6, 37.5, 26.5, 26.1, 19.4, 18.8, 18.5, 18.4, 14.4, 12.9, 10.9, -3.6, -4.3, -4.8, -5.1, -5.2; LRMS (FAB) *m/z* 605 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{31}H_{69}O_5Si_3$) requires *m/z* 605.4447, found *m/z* 605.4453.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-4,7-Bis-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-1,2-diol (62).** To a solution of (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-1,4,7-tris-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-2-ol **61** (56.4 mg, 0.093 mmol) in a 100 mL round bottom flask was added 32 mL of a solution of THF:AcOH:H_2O (2:2:1 v:v:v) that had been pre–cooled to +4 °C. The reaction was stirred at +4 °C for 2.5 d at which time it was quenched with $NaHCO_3$ (30 mL), extracted four times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel

chromatography (30% EtOAc/hex) provided the title compound as a colorless oil in 96% yield (44.0 mg). IR (film) 3418, 2953, 2927, 2855, 1652, 1472, 1387, 1250, 1092, 1005, 941, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H, vinylC**H**), 4.93 (s, 1H, vinylC**H**), 4.15 (d, *J* = 4.5 Hz, 1H, allylicC**H**), 4.10 (m, 1H, $(CHMe)_2$C**H**OTBS), 4.00 (m, 1H, C**H**OHCH_2OH), 3.66-3.62 (m, 2H, C$\mathbf{H}_2$OH), 3.48 (s, 3H, OC$\mathbf{H}_3$), 3.07 (dd, *J* = 7.5 Hz, 5.5 Hz, 1H, C**H**OMe), 1.98-1.94 (m, 1H, CHOMeC**H**Me), 1.8-1.75 (m, 1H, CHOHC**H**Me), 1.57 (s, 3H, vinylC$\mathbf{H}_3$), 1.000 (d, *J* = 7.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.996 (d, *J* = 7.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.94 (s, 9H, tBu), 0.93 (s, 9H, tBu), 0.15 (s, 3H, SiMe), 0.14 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.05 (s, 3H, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 113.3, 87.1, 76.6, 76.5, 72.5, 66.1, 60.1, 42.0, 38.3, 26.5, 26.2, 19.4, 18.8, 18.6, 13.9, 11.8, -3.4, -4.1, -4.2, -4.6; LRMS (FAB) *m/z* 491 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{55}O_5Si_2$) requires *m/z* 491.3605, found *m/z* 491.3588.

(2*S)-2-[(1*S**,2*R**,3*R**,4*S**,5*S**)-2,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-1,3,6-trimethyl-hept-6-enyl]-oxirane (63).** To (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-4,7-bis-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-1,2-diol **62** (61.6 mg, 0.126 mmol), toluenesolfonyl chloride (127 mg, 0.665 mmol), and DMAP (5 mg) in a 25 mL round bottom flask under argon was added 9.0 mL CH_2Cl_2. Et_3N was added (0.28 mL, 2.01 mmol), and the reaction was allowed to stir for 2.5 h, at which time the mixture was concentrated. 11.4 mL MeOH was added, followed by K_2CO_3 (257 mg), and the reaction was stirred at ambient temperature for three hours. The reaction was quenched with sat. aq. NH_4Cl (10 mL), extracted four times with EtOAc (20 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the

resulting oil by silica gel chromatography (10% EtOAc/hex) provided the title compound as a colorless oil in 93% yield (55.2 mg). IR (film) 3413, 2955, 228, 2894, 2857, 1652. 1473, 1463, 1405, 1387, 1360, 1251, 1190, 1158, 1095, 1043, 1005, 939, 899, 862, 835, 792, 774, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.06 (s, 1H, vinylC**H**), 4.95 (s, 1H, vinylC**H**), 4.22 (s, 1H, allylicC**H**), 4.01 (d, *J* = 6.0 Hz, 1H, $(CHMe)_2$C**H**OTBS), 3.44 (s, 3H, OC$\mathbf{H}_3$), 3.14 (dd, *J* = 8.5 Hz, 3.5 Hz, 1H, C**H**OMe), 2.89-2.87 (m, 1H, C**H**OCH_2), 2.81 (dd, *J* = 5.0 Hz, 5.0 Hz, 1H, C**H**HO), 2.6 (dd, *J* = 5.0 Hz, 3.0 Hz, 1H, CH**H**O), 1.95-1.91 (m, 1H, C**H**Me), 1.64-1.60 (m, 1H, C**H**Me), 1.57 (s, 3H, vinylC$\mathbf{H}_3$), 1.06 (d, *J* = 6.5 Hz, CHC$\mathbf{H}_3$), 0.93-0.91 (m, 21H, $(tBu)_2$, CHC$\mathbf{H}_3$), 0.11 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.05 (s, 3H, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.5, 112.6, 84.3, 75.9, 73.2, 58.0, 55.1, 48.8, 43.6, 37.5, 29.9, 26.4, 26.1, 19.8, 18.8, 18.5, 14.6, 11.8, -3.5, -3.9, -4.2; LRMS (FAB) *m/z* 473 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{53}O_4Si_2$) requires *m/z* 473.3480, found *m/z* 473.3482.

(4*S,5*S**,6*R**,7*R**,8*S**,9*S**)-6,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-1-(trimethyl-silanyl)-undec-10-en-1-yn-4-ol (64).**[31] To trimethylsilyl acetylene (0.132 mL, 0.934 mmol) in 2.72 mL dry THF in a dry 10 mL round bottom flask under argon at –78 °C was added nBuLi (2.36M in THF, 0.396 mL, 0.934 mmol). The reaction was stirred at –78 °C for 1 h. BF_3OEt_2 was added at –78 °C, and the reaction was stirred at –78 °C for 30 min. (2*S**)-2-[(1*S**,2*R**,3*R**,4*S**,5*S**)-2,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-1,3,6-trimethyl-hept-6-enyl]-oxirane **63** (55.2 mg, 0.117 mmol) was added as a solution in 1.8 mL dry THF *via* syringe, and the syringe rinsed twice with 0.9 mL dry THF. After 1 h, the reaction was quenched with

sat. aq. NH_4Cl (10 mL) and extracted four times with Et_2O (15 mL). The combined organic layers were washed once with sat. aq. NaCl (15 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (10% EtOAc/hex) provided the title compound as a colorless oil in 91% yield (60.7 mg). IR (film) 3477, 2956, 2921, 2857, 2176, 1653, 1473, 1463, 1388, 1361, 1249, 1099, 1005, 939, 903, 839, 774, 675, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.01 (s, 1H, vinylC**H**), 4.93 (s, 1H, vinylC**H**), 4.18-4.14 (m, 2H, allylicC**H**, C**H**OH), 4.05-4.03 (m, 1H, $(CHMe)_2$C**H**OTBS), 3.56 (d, *J* = 1.5 Hz, 1H, O**H**), 3.47 (s, 3H, OC$\mathbf{H}_3$), 3.09 (dd, *J* = 6 Hz, 6 Hz, 1H, C**H**OMe), 2.51 (dd, *J* = 6.0 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.36 (dd, *J* = 8.5Hz, 16.5 Hz, 1H, TMSCCH**H**), 1.99 (ddq, *J* = 3 Hz, 6.5 Hz, 6.5 Hz, 1H, CHOMeC**H**Me), 1.81-1.72 (m, 4H, vinylC$\mathbf{H}_3$, CHOHC**H**Me), 1.003 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 0.995 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 0.93 (s, 9H, tBu), 0.92 (s, 9H, tBu), 0.17-0.05 (m, 21H, $SiMe_3$, $(SiMe_2)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.4, 113.3, 104.1, 86.4, 76.7, 76.6, 70.3, 59.5, 41.9, 38.0, 29.9, 26.5, 26.2, 26.1, 19.2, 18.8, 18.5, 13.3, 10.5, 0.4, -3.6, -4.2, -4.5, -4.7; LRMS (FAB) *m/z* 571 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{30}H_{63}O_4Si_3$) requires *m/z* 571.4030, found *m/z* 571.4034.

(3*S,4*S**,5*R**,6*R**,7*S**,8*S**)-4-Methoxy-2,5,7-trimethyl-11-(trimethyl-silanyl)-undec-1-en-10-yne-3,6,8-triol (65).** To (4*S**,5*S**,6*R**,7*R**,8*S**,9*S**)-6,9-bis-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-1-(trimethyl-silanyl)-undec-10-en-1-yn-4-ol **64** (45.0 mg, 0.079 mmol) in 5 mL MeOH in a 25 mL round bottom flask was added conc. HCl (33 drops) and the reaction was allowed to stire at room temperature for 6 h, at which time sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was extracted

five times with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless oil in 91% yield (56.2 mg). IR (film) 3422, 2963, 2937, 2173, 1464, 1248, 1090, 1064, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.04 (s, 1H, vinylC**H**), 4.95 (s, 1H, vinylC**H**), 4.21 (dd, *J* = 4.8 Hz, 6.3 Hz, 1H, allylicC**H**), 4.06-3.98 (m, 2H, (C**H**OH)$_2$), 3.62 (d, *J* = 1.5 Hz, O**H**), 3.59 (s, 3H, OC**H**$_3$), 3.31 (dd, *J* = 3.9 Hz, 6.6 Hz, 1H, C**H**OMe), 3.08 (d, *J* = 6.0 Hz, 1H, O**H**), 2.54 (dd, *J* = 8.1 Hz, 16.8 Hz, 1H, C**H**HCTMS), 2.43 (dd, *J* = 5.4 Hz, 16.5 Hz, 1H, CH**H**CTMS), 2.38 (d, *J* = 4.5 Hz, 1H, allylicO**H**), 1.99-1.86 (m, 1H, C**H**Me), 1.76-1.70 (m, 4H, vinylC**H**$_3$, C**H**Me), 1.04 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$), 0.75 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$), 0.14 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 161.3, 144.6, 114.4, 104.6, 88.1, 86.9, 72.7, 62.8, 39.7, 35.7, 25.2, 18.1, 12.0, 11.4, 0.5; LRMS (FAB) *m/z* 343 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{18}H_{35}O_4Si$) requires *m/z* 343.2303, found *m/z* 343.2305.

(3*S,4*S**,5*R**)-4-Methoxy-2-methyl-5-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-hex-1-en-3-ol (66).** To (3*S**,4*S**,5*R**,6*R**,7*S**,8*S**)-4-methoxy-2,5,7-trimethyl-11-(trimethyl-silanyl)-undec-1-en-10-yne-3,6,8-triol **65** (31.4 mg, 0.092 mmol) in a 25 mL round bottom flask was added freshly distilled 2,2-dimethoxy-propane (8 mL, 0.065 mol), followed by *para*–toluenesulfonic acid (5 mg). The reaction was stirred for 20 min and then quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was extracted five times with EtOAc (15 mL), and the combined organic layers were dried over Na_2SO_4, filtered

through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as a colorless oil in 98% yield (34.4 mg). IR (film) 3480, 3059, 2996, 2360, 2342, 2178, 1456, 1380, 1249, 1226, 1170, 1135, 1076, 1035, 1016, 993, 953, 887, 843, 761, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (s, 1H, vinylC**H**), 4.98 (s, 1H, vinylC**H**), 4.02 (d, *J* = 8.5 Hz, 1H, allylic**CH**), 4.00-3.96 (m, 1H, $(CHMe)_2$**CH**), 3.63 (d, *J* = 8.0 Hz, 1H, $TMSCCH_2$**CH**O), 3.42 (s, 3H, O**CH**$_3$), 3.26 (d, *J* = 9.0 Hz, 1H, **CH**OMe), 2.51 (d, *J* = 9.0 Hz, 1H, O**H**), 2.40 (dd, *J* = 7.0 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.32 (dd, *J* = 7.0 Hz, 16.5 Hz, 1H, TMSCCH**H**), 1.97-1.91 (m, 1H, C**H**Me), 1.84-1.80 (m 1H, C**H**Me), 1.38 (s, 3H, CC**H**$_3$C**H**$_3$), 1.36 (s, 3H, CC**H**$_3$C**H**$_3$), 0.98 (d, *J* = 6.5 Hz, 3H, CHC**H**$_3$), 0.88 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 0.16 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 119.4, 110.9, 104.0, 100.9, 82.6, 73.7, 73.3, 68.8, 61.3, 38.5, 36.0, 25.5, 24.1, 22.7, 19.9, 11.7, 10.7, 0.3; LRMS (FAB) *m/z* 383 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{21}H_{39}O_4Si$) requires *m/z* 383.2600, found *m/z* 383.2618.

Benzyloxy-acetic acid (1S*)-1-((1*S,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester (68).** To (3*S**, 4*S**,5*R**)-4-methoxy-2-methyl-5-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-hex-1-en-3-ol **66** (17.5 mg, 0.0457 mmol) in 0.3 mL dry THF under argon in a 2-dram vial was added pyridine (18.5 uL, 0.229 mmol) and the stirring solution was cooled to 0 °C. Benzyloxyacetylchloride (28.4 uL, 0.183 mmol) was added slowly, and the reaction was allowed to warm to ambient temperature. After 5 h, the reaction was quenched with sat.

aq. $NaHCO_3$ (2 mL) and extracted three times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as a colorless oil in 93% yield (22.5 mg). IR (film) 2921, 2178, 1756, 1456, 1380, 1250, 1226, 1195, 1134, 1017, 844, 760, 700, 558 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 7.39-7.28 (m, 5H, Ar-**H**), 5.35 (s, 1H, vinylC**H**), 5.04 (s, 1H, vinylC**H**), 5.00 (s, 1H, vinylC**H**), 4.69 (d, *J* = 12.0 Hz, 1H, C**H**HAr), 4.65 (d, *J* = 12.0 Hz, 1H, CH**H**Ar), 4.24 (d, *J* = 16.5 Hz, 1H, C**H**HOBn), 4.19 (d, *J* = 16.5 Hz, 1H, CH**H**OBn), 3.96 (m, 1H, $(CHMe)_2C$**H**OH), 3.64 (d, *J* = 8.0 Hz, 1H, $TMSCCH_2C$**H**O), 3.44 (s, 3H, O**C**H_3), 3.35 (d, *J* = 9.0 Hz, 1H, C**H**OMe), 2.40 (dd, *J* = 7.0 Hz, 17.0 Hz, 1H, TMSCC**H**H), 2.31 (dd, *J* = 8.0 Hz, 17.0 Hz, 1H, TMSCCH**H**), 1.94-1.87 (m, 1H, C**H**Me), 1.67-1.58 (m, 4H, C**H**CH_3, vinylCH_3), 1.37 (s, 3H, CCH_3CH_3), 1.35 (s, 3H, CCH_3CH_3), 0.90 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.85 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.16 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) □ 169.8, 141.6, 137.3, 128.7, 128.4, 112.4, 103.9, 100.9, 86.1, 82.5, 76.3, 73.5, 73.1, 68.8, 67.1, 61.2, 38.6, 35.9, 29.9, 25.4, 24.1, 22.7, 20.5, 11.7, 10.1, 0.3; LRMS (FAB) *m/z* 531 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{30}H_{47}O_6Si$) requires *m/z* 531.3149, found *m/z* 531.3142.

(2*R,6*S**,7*R**)-2-Benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-enoic acid (70).[32]** To a flame dried 2-dram vial under argon containing 0.38 mL dry THF was added LHMDS (1.0 M in THF) and the solution was cooled to –78 °C. A solution of benzyloxy-acetic acid (1S*)-1-((1*S**,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-

ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester **68** which had been concentrated three times from benzene (13.4 mg, 0.025 mmol) in 0.58 mL dry THF was added over 6 min. *via* syringe, and then syringe was rinsed with 0.58 mL THF which was added over 6 min. The reaction was stirred at –78 °C for 42 min at which time freshly distilled TMSCl (8 uL, 0.063 mmol) was added *via* syringe. After 70 min the reaction was warmed to 0 °C and stirred for 25 min. The 0 °C bath was then removed and after 10 min the reaction was quenched with 2 mL of 1N aq. NaOH, and the mixture was stirred for 1 hour. The mixture was then poured into EtOAc (3 mL), and 1N aq. HCl was added to pH = 7. The aqueous layer was removed and acidified to pH = 1 with 1N aq. HCl. The aqueous layer was then extracted seven times with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex to 15 drops AcOH in 50 mL of 50% EtOAc/hex) provided the title compound as a colorless oil in 73% yield (8.4 mg). IR (film) 3402, 3296, 2920, 2851, 2363, 1734, 1456, 1382, 1227, 1171, 1126, 1100, 1054, 1018, 991, 939, 883, 737, 699, 635, 561 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.38-7.26 (m, 5H, Ar-**H**), 5.09 (d, *J* = 9.6 Hz, 1H, vinylC**H**), 4.68 (d, *J* = 11.0 Hz, 1H, C**H**HAr), 4.52 (d, *J* = 11.0 Hz, 1H, CH**H**Ar), 4.17 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H, C**H**OBn), 4.00-3.93 (m, 1H, $(CHMe)_2$C**H**O), 3.78-3.70 (m, 2H, C**H**OMe, $HCCH_2$C**H**O), 3.18 (s, 3H, OC$\mathbf{H}_3$), 2.61-2.54 (m, 2H, C$\mathbf{H}_2$CHOBn), 2.41-2.22 (m, 2H, HCC$\mathbf{H}_2$), 1.99-1.92 (m, 1H, **H**CCH_2), 1.73 (d, *J* = 1.2 Hz, 3H, vinylC$\mathbf{H}_3$), 1.53-1.48 (m, 2H, $(C\mathbf{H}CH_3)_2$), 1.34 (s, 6H, CC$\mathbf{H}_3$C$\mathbf{H}_3$), 0.84 (d, *J* = 6.6 Hz, CHC$\mathbf{H}_3$), 0.77 (d, *J* = 7.2 Hz, CHC$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 175.3, 136.9, 135.3, 129.7, 128.8, 128.5, 128.4, 101.0, 81.4, 78.1, 73.0, 72.1, 69.5, 68.7, 56.2, 43.0, 40.3, 35.5, 30.0, 25.2, 23.7, 21.3, 17.4, 11.4, 9.8;

LRMS (FAB) *m/z* 459 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{39}O_6$) requires *m/z* 459.2746, found *m/z* 459.2747.

(2*R,6*S**,7*R**)-2-Benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-en-1-ol (71).** To (2*R**,6*S**,7*R**)-2-benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-enoic acid **70** (7.8 mg, 0.017 mmol) in 1.1 mL of a 10:1 (v:v) solution of MeOH:CH_2Cl_2 under argon in a 2-dram vial was added $TMSCHN_2$ (2.0 M solution in hexanes, 50 uL). After 5 min the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL), and extracted four times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated to afford a white film which was used immediately. As such, the white film was dissolved in 1.0 mL dry Et_2O in a 2-dram vial under argon. A solution of $LiAlH_4$ (1.0 M, Et_2O, 86.0 uL) was added via syringe, and the reaction was stirred for 15 min before being quenched slowly with sat. aq. Rochelle's salt (3 mL). EtOAc was added (3 mL) and the mixture was stirred for 10 h. Sat. aq. NaCl (2 mL) was added and the mixture was extracted four times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless oil in quantitative yield (6.9 mg). IR (film) 3420, 2917, 2850, 1652, 1456, 1381, 1227, 1171, 1088, 1054, 1018, 991, 940, 883, 737, 698, 634, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.39-7.26 (m, 5H, Ar-**H**), 5.05 (d, *J* = 9.9 Hz, 1H, vinylC**H**), 4.68 (d, *J* = 11.2 Hz, 1H, C**H**HAr), 4.55 (d, *J* = 11.2 Hz, 1H, CH**H**Ar), 4.00-3.93 (m, 1H,

(CHMe)$_2$C**H**O), 3.79-3.67 (m, 5H, HCCH$_2$C**H**O, C**H**OBn, C**H**OMe, C**H**$_2$OH), 3.19 (s, 3H, OC**H**$_3$), 2.50-2.21 (m, 4H, HCC**H**$_2$, C**H**$_2$CHOBn), 1.99-1.93 (m, 1H, **H**CCH$_2$), 1.75 (d, *J* = 1.2 Hz, 3H, vinylC**H**$_3$), 1.34 (s, 3H, CC**H**$_3$CH$_3$), 1.33 (s, 3H, CCH$_3$C**H**$_3$), 0.84 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.77 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) 138.5, 136.7, 128.9, 128.8, 128.0, 101.0, 81.5, 78.5, 78.1, 72.2, 71.8, 69.5, 68.7, 64.6, 56.3, 41.5, 40.5, 35.6, 29.9, 25.2, 23.7, 21.3, 17.8, 11.4, 9.8; LRMS (FAB) *m*/*z* 445 (M)$^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{41}O_5$) requires *m*/*z* 445.2963, found *m*/*z* 445.2954.

(4*S,5*S**,6*R**,7*R**,8*S**,12*R**)-12-Benzyloxy-13-(*tert*-butyl-diphenyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-tridec-9-en-1-yne-4,6-diol (73).** To (2*R**,6*S**,7*R**)-2-benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-en-1-ol **71** (6.9 mg, 0.016 mmol) in 0.7 mL dry DMF in dry 2-dram vial under argon was added imidazole (3.2 mg, 0.047 mmol) and the vial was purged with argon. TBDPSCl (11.9 uL, 0.0465 mmol) was added and the reaction was stirred at ambient temperature for 2 h. The mixture was then poured into sat. aq. NaHCO$_3$ (1 mL) and sat. aq. NaCl (1 mL) was added. The mixture was extracted four times with EtOAc (2 mL), and the combined organic layers were washed once with H$_2$O (2 mL), once with sat. aq. NaCl (2 mL), dried over Na$_2$SO$_4$, filtered through a plug of cotton, and concentrated. The oil was then dissolved in 2 mL MeOH in a 25 mL round bottom flask, and DOWEX 50WX8-100 resin (washed with MeOH and air-dried before use) was added. The mixture was stirred vigorously for 48 h and then filtered through a glass frit, washing the resin with MeOH. To the combined MeOH washings was added

0.4 mL Et_3N, and the volatiles were removed by concentration. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a colorless oil in 50% yield (5.0 mg). IR (film) 3433, 3308, 3070, 2930, 2858, 1664, 1589, 1462, 1428, 1389, 1361, 1188, 1112, 1084, 978, 824, 740, 702, 614, 504, 457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 7.49-7.22 (m, 12H, Ar-**H**), 5.23 (d, *J* = 9.0 Hz, 1H, vinylC**H**), 4.66 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.53 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.08-4.00 (m, 1H, $(CHMe)_2$C**H**OH), 3.93-3.89 (m, 2H, $HCCH_2$C**H**OH, C**H**OMe), 3.79-3.76 (m, 1H, C**H**OBn), 3.70-3.64 (m, 2H, C$\mathbf{H}_2$OTBDPS), 3.11 (s, 3H, OC$\mathbf{H}_3$), 2.50 (ddd, *J* = 8.0 Hz, 3.0 Hz, 16.5 Hz, 1H, C**H**HCHOBn), 2.41-2.30 (m, 3H, CH**H**CHOBn, HCC$\mathbf{H}_2$CHOH), 2.03 (m, 1H, **H**CCH_2), 1.95-1.92 (m, 1H, MeOCHC**H**Me), 1.69-1.63 (m, 4H, vinylC$\mathbf{H}_3$, C**H**Me$(CHOH)_2$), 1.09 (s, 9H, tBu), 0.91 (d, *J* = 6.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.75 (d, *J* = 6.5 Hz, 3H, CHC$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 139.0, 138.1, 135.9, 133.7, 129.9, 128.5, 127.9, 127.8, 127.7, 127.0, 126.9, 88.7, 82.5, 81.4, 78.4, 73.6, 72.9, 72.2, 70.0, 69.9, 66.2, 56.4, 42.4, 40.2, 39.1, 29.9, 27.1, 23.6, 19.5, 17.4, 12.2, 10.3; LRMS (FAB) *m/z* 642, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{40}H_{54}O_5NaSi$) requires *m/z* 665.3641, found *m/z* 665.3638.

{(2*S,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-Benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-hydroxy-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester (75).**[33] (4*S**,5*S**,6*R**,7*R**,8*S**,12*R**)-12-Benzyloxy-13-(*tert*-butyl-diphenyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-tridec-9-en-1-yne-4,6-diol **73** (4.3 mg, 0.0067 mmol) was dissolved in 0.91 mL dry MeOH in dry 5 mL round bottom flask. The flask was sealed and purged with CO and CO was

bubbled through the solution for 1 min., followed by passing a stream of CO over the solution for an additional 30 seconds. After stirring for 8 min, a solution of $PdCl_2(CH_3CN)_2$ (0.29 mg, 0.0011 mmol) and *p*–benzoquinone (1.6 mg, 0.015 mmol) in 0.34 mL dry MeOH was added *via* syringe. After 45 min the reaction was concentrated and then diluted with EtOAc (1 mL). The solution was washed twice with sat. aq. $NaHCO_3$ (2 mL), once with sat. aq. NaCl (2 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. The oil was then dissolved in 1.2 mL MeOH and 15 mg *p*TSA was added and the reaction allowed to stir for 25 min. The solution was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted four times with EtOAc (2 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% MeOH/CH_2Cl_2) provided the title compound as a colorless oil in 94% yield (4.6 mg). This unstable intermediate was stored in frozen benzene. IR (film) 3452, 2928, 2856, 1739, 1455, 1428, 1379, 1319, 1260, 1222, 1112, 1027, 933, 799, 740, 702, 614, 505, 458 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) 7.80-7.77 (m, 2H, Ar-**H**), 7.34-7.07 (m, 13H, Ar-**H**), 5.10 (d, *J* = 10.0 Hz, 1H, vinylC**H**), 4.61 (d, *J* = 11.7 Hz, 1H, C**H**HAr), 4.45 (d, *J* = 11.7 Hz, 1H, CH**H**Ar), 4.03-3.99 (m, 2H, C**H**OH, C**H**OCOMe), 3.90-3.76 (m, 2H, C**H**$_2$OTBPDS), 3.72-3.64 (m, 2H, C**H**$_2$OTBDPS), 3.34 (s, 3H, CO2C**H**$_3$), 3.29 (s, 3H, HCOCOC**H**$_3$), 3.04 (s, 3H, CHOC**H**$_3$), 2.64 (d, *J* = 13.5 Hz, 1H, C**H**HCO_2Me), 2.57 (d, *J* = 13.5 Hz, 1H, CH**H**CO_2Me), 2.41-2.38 (m, 2H, C**H**$_2$CHOBn), 2.22-2.04 (m, 2H, C**H**$_2$CHOH), 1.82-1.68 (m, 2H, (C**H**Me)$_2$), 1.65 (s, 3H, vinylC**H**$_3$), 1.18 (s, 9H, tBu), 0.85 (d, *J* = 6.0 Hz, CHC**H**$_3$), 0.77 (d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 170.1, 139.1, 138.0, 135.9, 133.7, 129.9, 128.5, 127.9, 127.6, 122.4, 99.0, 79.2, 78.8, 72.3, 71.9, 70.5, 70.3, 66.4, 55.5, 51.9, 43.1, 42.3, 42.2,

40.0, 38.6, 29.9, 27.1, 27.0, 19.5, 17.6, 14.3, 12.2, 8.9, 5.3, 1.3; LRMS (FAB) *m/z* 732, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{43}H_{60}O_8NaSi$) requires *m/z* 755.3941, found *m/z* 755.3955.

{(2*S,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-Benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester (76).** To {(2*S**,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-hydroxy-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester **75** (4.7 mg, 0.008 mmol) in 1.0 mL dry DMF in a dry 2-dram vial under argon was added imidazole (30.1 mg, 0.443 mmol) and TBSCl (55.8 mg, 0.370 mmol). The reaction was stirred for 2 h and then quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted five times with EtOAc (2 mL). The combined organic layers were washed once with H_2O (5 mL) and once with sat. aq. NaCl (5 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex to 10% EtOAc/hex) provided the title compound as a colorless oil in 81% yield (4.4 mg). This unstable intermediate was stored in frozen benzene. IR (film) 2929, 2857, 2875, 1743, 1453, 1428, 1381, 1315, 1257, 1221, 1112, 1081, 1029, 1006, 932, 836, 776, 740, 702, 611, 505, 488 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) □ 7.81-7.79 (m, 3H, Ar-**H**), 7.34-7.07 (m, 12H, Ar-**H**), 5.11 (d, *J* = 10.0 Hz, 1H, vinylC**H**), 4.61 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.45 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.11 (dd, *J* = 2.0 Hz, 10.5 Hz, C**H**OTBS), 4.03 (dd, *J* = 10.0 Hz, 10.0 Hz, C**H**OCOMe), 3.95 (ddd, *J* = 4.5 Hz, 11.0 Hz, 11.0 Hz, C**H**OBn), 3.84 (dd, *J* = 5.5 Hz,

10.7 Hz, CH**H**OTBDPS), 3.78 (dd, *J* = 4.5 Hz, 10.7 Hz, C**H**HOTBDPS), 3.69-3.64 (m, 1H, C**H**OMe), 3.34 (s, 3H, $CO_2C\mathbf{H}_3$), 3.31 (s, 3H, $H_2CCOC\mathbf{H}_3$), 3.06 (s, 3H, $CHOC\mathbf{H}_3$), 2.66 (d, *J* = 13.7 Hz, C**H**HCO_2Me), 2.60 (d, *J* = 13.7 Hz, CH**H**CO_2Me), 2.52 (dd, *J* = 5.0 Hz, 13.0 Hz, C**H**HCHOTBS), 2.38 (d, *J* = 6.0 Hz, 2H, $C\mathbf{H}_2$CHOBn), 1.97 (dd, *J* = 10.0 Hz, 5.0 Hz, 13.0 Hz, CH**H**CHOTBS), 1.86-1.80 (m, 1H, C**H**CH_3), 1.70-1.59 (m, 4H, vinyl$C\mathbf{H}_3$, C**H**CH_3), 1.18 (s, 9H, tBu), 0.98 (s, 9H, tBu), 0.93 (d, *J* = 6.0 Hz, 3H, $CHC\mathbf{H}_3$), 0.78 (d, *J* = 7.0 Hz, 3H, $CHC\mathbf{H}_3$), 0.12 (s, 3H, SiMe), 0.07 (s, 3H, SiMe); ^{13}C NMR (125 MHz, C_6D_6) □ 196.7, 169.2, 139.3, 137.6, 136.0, 133.8, 129.9, 129.1, 128.3, 127.5, 107.6, 99.2, 90.8, 78.8, 77.5, 72.1, 71.9, 71.3, 66.3, 55.0, 51.0, 47.8, 44.1, 42.2, 42.1, 40.4, 39.0, 30.1, 27.0, 26.0, 25.7, 19.4, 18.2, 17.5, 12.5, 8.8, 2.6, -4.0, -4.7; LRMS (FAB) *m*/*z* 845, $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{49}H_{73}O_8Si_2$) requires *m*/*z* 845.4850, found *m*/*z* 845.4844.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-benzyloxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester (50).** *(2S*,3R*,5S*,6S*)*-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal **48** (1.56 g, 3.99 mmol) was dissolved in 64.3 mL dry THF in a 250 mL round bottom flask, and the stirring solution was cooled to –78 °C. Isopropenyl magnesium bromide (0.5M in THF, 9.6 mL, 4.79 mmol) was added *via* syringe pump over 45 min. Stirring was continued for 1.5 h after addition was complete, at which time the reaction was quenched with sat. aq. NH_4Cl and extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50%

EtOAc/hex) provided the intermediate allylic alcohol product **49** as a colorless oil in 74% yield (1.28 g), and this oil was immediately dissolved in 9.6 mL dry THF in a 100 mL round bottom flask. Freshly distilled pyridine (0.232 mL, 4.10 mmol) was added and the flask was purged with argon and cooled to 0 °C. *tert*–Butyldiphenylsilyloxyacetyl chloride (1.08 mL, 2.38 mmol) was added slowly *via* syringe, and the reaction was stirred for 30 min. at 0 °C before being warmed to ambient temperature. After 48 h at room temperature, the reaction was quenched with NH_4Cl/NH_4OH (pH = 8) solution (20 mL) and extracted three times with EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (40% EtOAc/hex) provided the ester as a colorless oil in 68% yield (406 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.62 (m, 6H, Ar-**H**), 7.46-7.25 (m, 9H, Ar-**H**), 5.21 (s, 1H, allylic**H**), 4.93 (bs, 2H, vinylC**H**, vinylC**H**), 4.58-4.51 (m, 2H, C**H**HAr, C**H**HOTBDPS), 4.38-4.22 (m, 4H, CH**H**Ar, CH**H**OTBDPS, C**H**OBn, C**H**OMe), 3.67-3.29 (m, 9H, morph-**H**,C**H**Me), 3.24 (s, 3H, OC**H**$_3$), 3.03-2.84 (m, 1H, C**H**CH_3), 1.82 (s, 3H, vinylC**H**$_3$), 1.22 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$), 1.11 (s, 9H, tBu), 0.98 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 163.4, 141.6, 135.8, 135.6, 135.0, 130.1, 129.9, 128.0, 127.9, 112.2, 103.9, 100.9, 86.0, 82.4, 76.1, 73.1, 68.8, 62.4, 61.1, 38.5, 35.8, 26.9, 26.8, 25.4, 24.1, 22.7, 20.4, 19.5, 11.7, 10.2, 0.3.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-hydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester (51).** To (1*S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-

5-benzyloxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester **50** (383.0 mg, 0.525 mmol) in 10.5 mL dry CH_2Cl_2 at 0 °C in a 100 mL round bottom flask under argon was added BF_3OEt_2 (0.332 mL, 2.623 moml) followed immediately by Me_2S (0.539 mL, 7.345 mmol), and the reaction was stirred for 1 h, at which time at was quenched with NH_4Cl/NH_4OH (pH = 8) (20 mL). The mixture was extracted four times with EtOAc (20 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the ester as a colorless oil in 89% yield (299 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H, Ar-**H**), 7.47-7.34 (m, 6H, Ar-**H**), 5.24 (s, 1H, allylic**CH**), 4.94 (s, 1H, vinyl**CH**), 4.92 (s 1H, vinyl**CH**), 4.66 (bs, 1H, **CH**OH), 4.36-4.26 (m, 3H, **CH**$_2$OTBDPS, **CH**OMe), 3.74-3.36 (m, 8H, morph-**H**), 3.23 (s, 3H, O**CH**$_3$), 2.96-2.86 (m, 1H, CH**CH**$_3$), 2.78-2.70 (m, 1H, **CH**CH$_3$), 1.82 (s, 3H, vinyl**CH**$_3$), 1.09 (s, 9H, tBu), 1.05 (d, *J* = 6.9 Hz, 3H, CH**CH**$_3$), 0.93 (d, *J* = 6.9 Hz, 3H, CH**CH**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 171.1, 170.0, 140.2, 135.3, 132.5, 132.4, 129.9, 127.9, 127.7, 112.6, 82.9, 74.9, 67.6, 66.6, 66.4, 62.0, 60.9, 50.9, 46.1, 45.9, 42.8, 26.6, 20.1, 19.3, 13.6, 10.5.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((1*S**,2*R**,3*R**,4*S**,5*S**)-3,5-dihydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-hexyl)-2-methyl-allyl ester (53).**[34,35] To (1 *S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-hydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester **51** (1.04 g, 1.63 mmol) in 84 mL dry CH_2Cl_2 under argon at 0 °C in a dry 1 L round bottom flask was added Bu_4NBH_4 (376 mg, 1.46 mmol) in 26.1 mL

dry CH_2Cl_2 *via* cannula, and the cannula was rinsed into the reaction vessel with 26.1 mL dry CH_2Cl_2. The reaction was allowed to warm to ambient temperature, and after 63 h the reaction was quenched with H_2O (150 mL) and poured into sat. aq. $NaHCO_3$ (100 mL). The mixture was extracted four times with CH_2Cl_2 (200 mL) and once with EtOAc (200 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (67% EtOAc/hex) provided the starting material as an oil (603.8 mg) and the title compound as a white solid in 33% yield (406 mg) (78% yield based on recovered starting material), >95:5 *anti*:*syn* (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.75-7.65 (m, 4H, Ar-**H**), 7.50-7.34 (m, 6H, Ar-**H**), 5.58 (d, 1H, allylicC**H**), 5.15 (s, 1H, vinylC**H**), 5.02 (s, 1H, vinylC**H**), 4.93 (d, 1H, $R_2NCOC\mathbf{H}OH$), 4.33-4.19 (m, 2H, $C\mathbf{H}_2$OTBDPS), 4.02 (d, 1H, $(CHMe)_2C\mathbf{H}OH$), 3.80-3.43 (m, 9H, morph-**H**, C**H**OMe), 3.40 (s, 3H, $OC\mathbf{H}_3$), 1.71-1.53 (m, 4H, vinyl$C\mathbf{H}_3$, $R_2NCHOHC\mathbf{H}Me$), 1.07 (s, 9H, tBu), 0.99 (d, 3H, $CHC\mathbf{H}_3$), 0.87-0.79 (m, 1H, $C\mathbf{H}CH_3$), 0.58 (d, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 173.2, 169.8, 145.9, 139.6, 135.4, 135.3, 132.6, 132.5, 129.8, 127.7, 117.4, 87.2, 79.7, 70.7, 66.9, 66.5, 62.4, 54.1, 45.5, 42.8, 39.7, 33.8, 26.7, 19.3, 18.0, 10.9, 8.5.

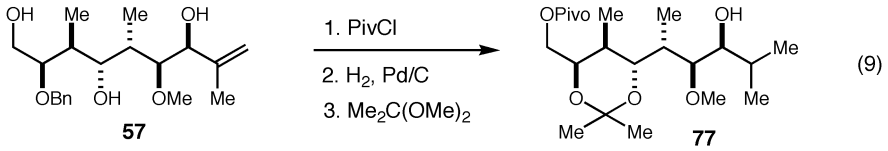
(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-[(1*S**,2*R**,3*R**,4*S**,5*S**)-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-3,5-bis-(trimethyl-silanyloxy)-hexyl]-2-methyl-allyl ester (54).** To (1*S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((1*S**,2*R**,3*R**,4*S**,5*S**)-3,5-dihydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-hexyl)-2-methyl-allyl ester **53** (341 mg, 0.531 mmol) and DMAP (154 mg) in 26.6 mL dry CH_2Cl_2 under argon in a dry 500 mL round bottom flask was added TMSCl

(0.674 mL, 5.31 mmol) and the flask was cooled to 0 °C. Et_3N (0.740 mL, 5.31 mmol) was added and the reaction was stirred for 17 h before being quenched with pH 7 phosphate buffer and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as an oil in 75% yield (314.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H, Ar-**H**), 7.45-7.34 (m, 6H, Ar-**H**), 5.33 (s, 1H, allylicC**H**), 4.92 (s, 1H, vinylC**H**), 4.85 (s, 1H, vinylC**H**), 4.78 (s, 1H, R_2NCOC**H**OTMS), 4.32 (bs, 2H, C**H**$_2$OTBDPS), 3.91 (d, *J* = 8.7 Hz, 1H, $(CHMe)_2$C**H**OTMS), 3.76-3.37 (m, 8H, morph-**H**), 3.33 (s, 3H, OC**H**$_3$), 1.90-1.61 (m, 5H, vinylC**H**$_3$, C**H**CH_3, C**H**CH_3), 1.08 (s, 9H, tBu), 0.71 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.69 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.15-0.12 (m, 18H, $(TMS)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.4, 141.2, 135.7, 132.9, 132.8, 130.1, 128.0, 112.0, 79.7, 76.8, 73.4, 70.8, 67.5, 67.0, 62.4, 60.0, 46.2, 42.8, 42.7, 41.3, 35.0, 27.0, 20.3, 19.6, 10.5, 9.6, 1.7, 1.5.

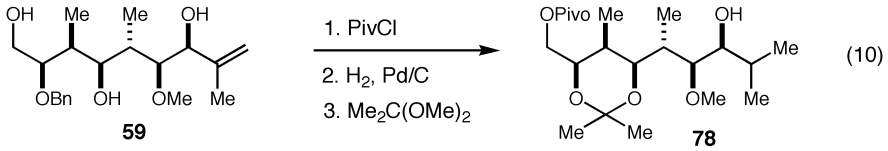
(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid (1*S**)-1-((1*S**,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester (67).** To (3*S**,4*S**,5*R**)-4-methoxy-2-methyl-5-{(5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[(1*R**)-1,3]dioxan-4-yl}-hex-1-en-3-ol **66** (6.2 mg, 0.0162 mmol) in 0.3 mL dry THF under argon in a dry 2-dram vial was added pyridine (6.6 uL, 0.081 mmol) and the reaction was cooled to 0 °C. *tert*-Butyldiphenylsilyloxyacetyl chloride (20.3 uL, 0.0648 mmol) was added slowly and the reaction was allowed to warm to ambient temperature. After 22 h,

the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted four times with EtOAc (2 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex to 10% EtOAc/hex) provided the title compound as an oil in 97% yield (10.7 mg). IR (film) 3447, 2929, 2856, 2359, 2178, 1762, 1653, 1472, 1428, 1380, 1249, 1225, 1136, 1113, 1016, 842, 821, 740, 702, 668, 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.73-7.63 (m, 4H, Ar-**H**), 7.44-7.33 (m, 6H, Ar-**H**), 5.24 (s 1H, allylic C**H**), 4.92 (s, 1H, vinylC**H**), 4.90 (s, 1H, vinylC**H**), 4.34 (bs, 2H, C**H**$_2$OTBDPS), 3.94 (ddd, *J* = 4.5 Hz, 7.8 Hz, 7.8 Hz, 1H, TMSCCH$_2$C**H**O), 3.57 (d, *J* = 7.2 Hz, 1H, (CHMe)$_2$C**H**O), 3.38 (s, 3H, OC**H**$_3$), 3.28 (dd, *J* = 9.9 Hz, 1.5 Hz, 1H, C**H**OMe), 2.39 (dd, *J* = 7.2 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.29 (dd, *J* = 16.5 Hz, 7.8 Hz, 1H, TMSCH**H**), 1.90-1.81 (m, 4H, C**H**CH$_3$, vinylC**H**$_3$), 1.55-1.47 (m, 1H, C**H**CH$_3$), 1.34 (s, 3H, CC**H**$_3$CH$_3$), 1.33 (s, 3H, CCH$_3$C**H**$_3$), 1.09 (s, 9H, tBu), 0.80 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.79 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.15 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) □ 135.7, 135.0, 130.1, 129.6, 128.0, 127.5, 112.3, 100.2, 77.9, 77.5, 68.8, 62.3, 60.7, 56.9, 38.6, 35.9, 32.1, 30.1, 27.0, 26.9, 25.6, 24.2, 22.8, 21.5, 20.6, 14.6, 10.4, 7.0, 5.0, 0.5, -7.8; LRMS (FAB) *m*/*z* 679, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{39}H_{59}O_6Si_2$) requires *m*/*z* 679.3849, found *m*/*z* 679.3850.

Proof of *anti* relative stereochemistry of (2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol 57[36]**



(9)



(10)

2,2-Dimethyl-propionic acid (4*S,5*S**,6*R**)-6-((1*R**,2*S**,3*S**)-3-hydroxy-2-methoxy-1,4-dimethyl-pentyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (77).** (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **57** (27.7 mg, 0.079 mmol) and DMAP (2.7 mg, 0.039 mmol) were dissolved in 1.58 mL freshly distilled pyridine in a dry 25 mL round bottom flask under argon, and to the stirring solution was added pivaloyl chloride (29.1 uL, 0.236 mmol). After stirring for 3.5 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), extracted four times with EtOAc (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the pivaloate ester as a colorless oil in 77% yield (28.7 mg). The ester (11.4 mg, 0.024 mmol) was dissolved in 1.0 mL dry THF and10% Pd/C (10.2 mg, 0.0096 mmol) was added. The flask was purged with H_2 and pressurized to 50 PSI. After 53 h, the mixture was flushed through a pad of celite with EtOAc and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the triol as a colorless oil in 80% yield (6.7 mg). To the triol (6.0 mg, 0.017 mmol) was added freshly distilled 2,2-dimethoxy-propane (1.5 mL) and *p*TSA (5 mg) in a 10 mL round bottom flask, and the reaction was stirred for 3 h, at

which time sat. aq. $NaHCO_3$ (5 mL) was added. Extraction four times with EtOAc (5 mL) and combination of the organic layers was followed by drying over Na_2SO_4. The solution was filtered through a plug of cotton and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the acetonide as a colorless oil in 60% yield (3.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 3.5 Hz, 10 Hz, 1H, C**H**HOPiv), 4.06-3.99 (m, 2H, C**H**HOPiv, PivOCH_2C**H**O), 3.60 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H, (CHMe)$_2$C**H**O), 3.52 (s, 3H, OC**H**$_3$), 3.23 (d, *J* = 9.0 Hz, 1H, C**H**OH), 3.14 (dd, *J* = 9.5 Hz, 9.5 Hz, C**H**OMe), 2.07 (d, *J* = 10.0 Hz, 1H, O**H**), 1.93-1.89 (m, 1H, C**H**Me), 1.83-1.74 (m, 2H, C**H**Me, C**H**Me$_2$), 1.60 (bs, 6H, $O_2C(C\mathbf{H}_3)_2$), 1.40 (s, 3H, CHC**H**$_3$CH$_3$), 1.34 (s, 3H, CHCH$_3$C**H**$_3$), 1.22 (s, 9H, tBu), 1.06 (d, *J* = 6.5 Hz, 3H, C**H**$_3$), 0.96 (d, *J* = 7.0 Hz, 3H, C**H**$_3$), 0.92 (d, *J* = 7.0 Hz, 3H, C**H**$_3$), 0.88 (d, *J* = 7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 100.8, 81.9, 77.4, 73.4, 67.8, 64.1, 61.0, 39.0, 38.3, 35.4, 32.1, 27.4, 25.4, 24.2, 19.9, 19.8, 12.1, 10.4.

2,2-Dimethyl-propionic acid (4*S,5*S**,6*S**)-6-((1*R**,2*S**,3*S**)-3-hydroxy-2-methoxy-1,4-dimethyl-pentyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (78).** (2*S**,3*S**,4*S**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **59** (15.8 mg, 0.045 mmol) and DMAP (4.5 mg, 0.066 mmol) were dissolved in 0.9 mL freshly distilled pyridine in a dry 10 mL round bottom flask under argon, and to the stirring solution was added pivaloyl chloride (33.0 μL, 0.268 mmol). After stirring for 12 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), extracted four times with EtOAc (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel

chromatography (20% EtOAc/hex) provided the pivaloate ester as a colorless oil in 41% yield (8.7 mg). The ester (9.5 mg, 0.020 mmol) was dissolved in 0.8 mL dry THF and 10% Pd/C (8.5 mg, 0.008 mmol) was added. The flask was purged with H_2 and pressurized to 50 PSI. After 96 h, the mixture was flushed through a pad of celite with EtOAc and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the triol as a colorless oil in 47% yield (3.3 mg). To the triol (3.3 mg, 0.0095 mmol) was added freshly distilled 2,2-dimethoxy-propane (0.8 mL) and *p*TSA (5 mg) in a 10 mL round bottom flask, and the reaction was stirred for 20 min, at which time sat. aq. $NaHCO_3$ (5 mL) was added. Extraction four times with EtOAc (5 mL) and combination of the organic layers was followed by drying over Na_2SO_4. The solution was filtered through a plug of cotton and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the acetonide as a colorless oil in 82% yield (3.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15-4.06 (m, 3H, C**H**$_2$OPiv, PivOCH$_2$C**H**O), 3.78 (d, *J* = 10.0 Hz, 1H, (CHMe)$_2$C**H**O), 3.49-3.42 (m, 4H, 4H, OC**H**$_3$, C**H**OH), 3.31-3.28 (m, 1H, C**H**OMe), 2.46 (d, *J* = 8.0 Hz, 1H, O**H**), 2.11-2.07 (m, 1H, C**H**Me), 1.79-1.74 (m, 2H, C**H**Me, C**H**Me$_2$), 1.41 (s, 3H, O$_2$CC**H**$_3$CH$_3$), 1.40 (s, 3H, O$_2$CCH$_3$C**H**$_3$), 1.23 (s, 9H, tBu), 0.97-0.90 (m, 12H, (CHC**H**$_3$)$_4$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 99.3, 80.1, 75.4, 73.9, 71.9, 65.2, 58.3, 39.0, 35.3, 32.6, 31.1, 30.0, 29.9, 27.4, 19.7, 18.2, 10.7, 5.1.

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(13) Synthesis of the enantiopure amino sulfide was conducted with James R. Falsey.

(14) This reaction was first observed by James R. Falsey

(15) Concurrent with but separate from the research reported here, James R. Falsey explored the optimal conditions for and scope of the tandem amino thio acyl–Claisen rearrangement.

(16) Investigations with regard to sulfide substituent, solvent, temperature, Lewis acid, and reagent molarity and stoichiometry were conducted to arrive at optimal reaction conditions for both the amino- and sulfide- acyl-Claisen steps.

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(31) (a) Deng, Y.; Salomon, R. G. *J. Org. Chem.* **2000**, *65*, 6660. (b) Kobayashi, Y.; Nakayama, Y.; Yoshida, S. *Tetrahedron Lett.* **2000**, *41*, 1465.

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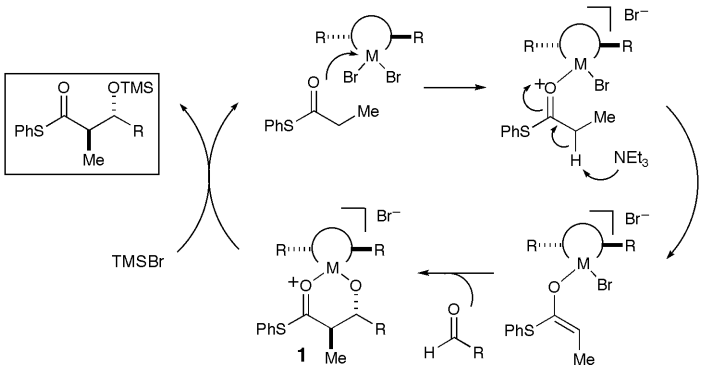
Chapter 4

Summary of Doctoral Research

I. Design of a Conceptually Novel Lewis Acid-Catalyzed Enantioselective *Anti* Aldol Reaction

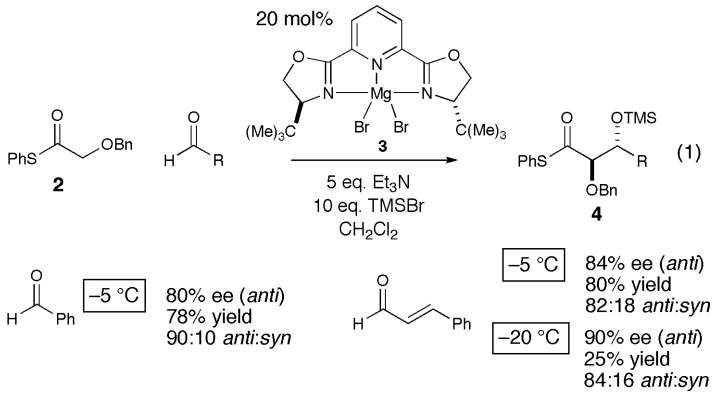
Our group has sought to develop a platform for enantioselective catalysis involving Lewis acid activation of unmodified carbonyls. In the context of a direct aldol reaction, we envisioned that catalyst turnover might be achieved *via* silylation of covalently bound catalyst-aldolate adduct **1** using an appropriate silyl halide source (Scheme 1).

Scheme 1. Proposed catalytic cycle for novel aldol reaction



After extensive optimization, we found that tridentate magnesium PyBOX complex **3** was a suitable catalyst for the formation of enantioenriched aldol adducts **4** from thioester **2** (Figure 1). Most notably, *anti* reaction diastereoselection was observed (82:18 to 90:10 *anti*:*syn*), a reaction manifold that has traditionally been difficult to access.

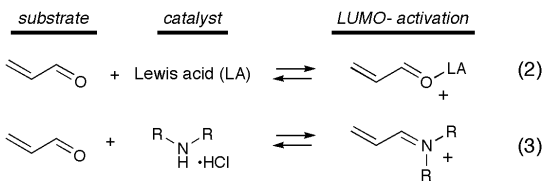
Figure 1. Direct *Anti* Aldol Reaction



Mechanistic studies indicate that the reaction proceeds *via* an open transition state involving silyl activation of the aldehyde electrophile and subsequent addition of a catalytically generated chiral enolate; this mechanism operates in contrast to the traditional Mukaiyama aldol pathway. Significantly, this new reaction technology represents the first direct method for *anti*-aldol catalysis using metal salts.

II. Enantioselective Organocatalytic [1,3]-Dipolar Cycloaddition and *Exo* Selective Cycloaddition Reactions

A major focus of our research has been the development of a general strategy for enantioselective organocatalysis. We have found that chiral secondary amines act as LUMO-lowering catalysts *via* the reversible formation of iminium ions from □,□-unsaturated aldehydes (Equation 3).

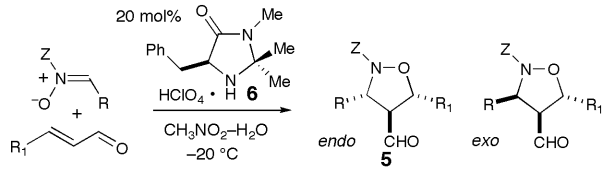


As part of these studies, we have extended our LUMO-lowering organocatalysis strategy to [3+2] cycloadditions between nitrones and α,β-unsaturated aldehydes to provide isoxazolidines **5**, useful synthons for the construction of amino acids, β-lactams, amino carbohydrates, and alkaloids.

It has been established that α,β-unsaturated aldehydes are generally poor substrates for metal-catalyzed nitrone cycloadditions, presumably due to the preferential coordination of Lewis acids to nitrone oxides in the presence of monodentate carbonyls. In contrast, we expected amine catalysts to be inert to nitrone association, thereby enabling α,β-unsaturated aldehydes to participate in iminium activation and subsequent [3+2] cycloaddition. Importantly, this methodology would allow, for the first time, simple aldehydes to function as dipolarophiles in a nitrone cycloaddition.

After investigating the effects of solvent and co-catalyst, it became apparent that LUMO-lowering organocatalysis could be successfully applied to the [3+2] cycloaddition.[1] A range of nitrones are compatible with a variety of aldehyde dipolarophiles in the presence of a catalytic quantity of chiral imidazolidinone **6** (70–98% yield, 81:19 to 99:1 *endo*:*exo*, 90–99% ee) (Table 1).

Table 1. Organocatalyzed dipolar cycloadditions between representative nitrones and dipolarophiles

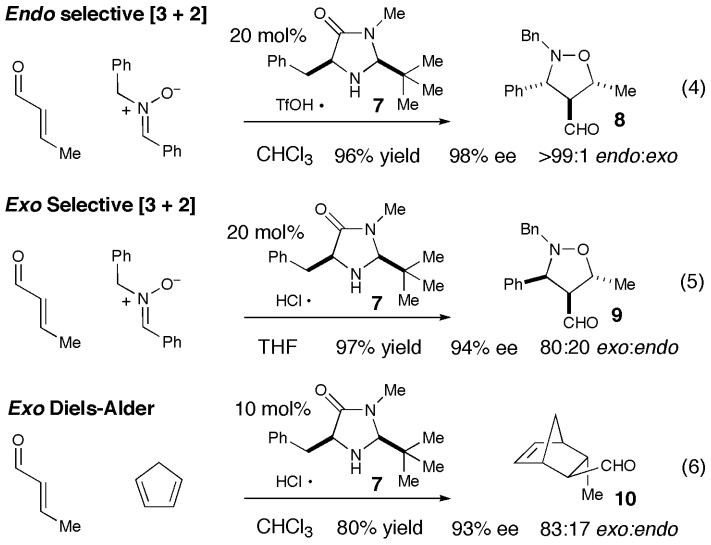


entry	Z	R	R_1	*endo*:*exo*	yield	% ee (*endo*)
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92
12	Bn	C_6H_4Me-4	H	85:15	80	90
13	Bn	C_6H_4Cl-4	H	80:20	80	91
14	Bn	2-naph	H	81:19	82	90
15	Bn	C_6H_4OMe-4	H	91:9	83	90

As an extension of this methodology, we investigated the catalytic activity of *tert*-butyl substituted imidazolidinone **7** (Equation 4). Catalyst **7** afforded isoxazolidinone **8** in 96% yield with 98% ee and >99:1 *endo*:*exo* selectivity after ten hours. These findings represent a marked improvement in reaction rate as well as enantio- and diastereoselectivity for the [3+2] cycloaddition.

The choice of solvent and co-catalyst had a remarkable effect on the [3+2] cycloaddition using catalyst **7**. When THF was employed as solvent with HCl as co-catalyst, the *exo* cycloaddition adduct **9** was preferentially formed (80:20 *exo*:*endo*) (Equation 5). Imidazolidinone **7** was found to catalyze an *exo* selective organocatalytic Diels-Alder cycloaddition as well (Equation 6). To our knowledge, this is the first

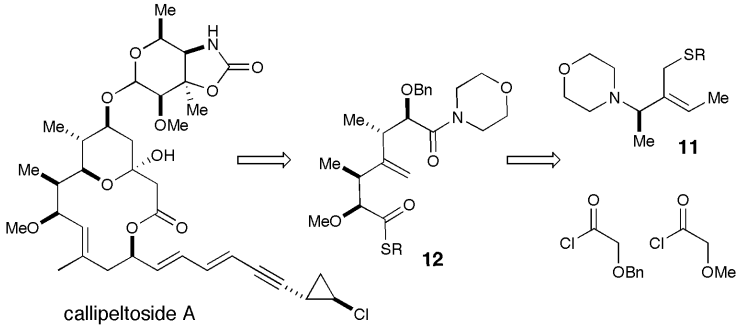
example of an *exo* selective, enantioselective catalytic Diels-Alder reaction. We are currently exploring the origins and scope of these *exo* selective processes.



III. Progress towards the Total Synthesis of Callipeltoside A

Callipeltoside A (Scheme 3), an architecturally complex natural product isolated from the lithistid sponge *Callipelta* sp., is known to protect cells infected with HIV and to inhibit *in vitro* proliferation of NSCLC-N6 and P388 cells.

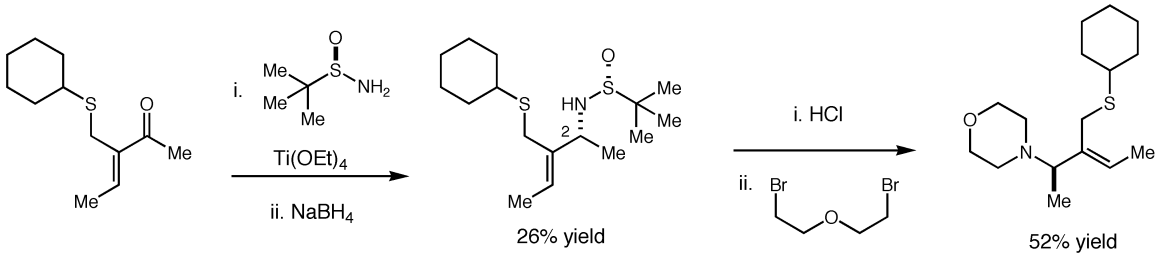
Scheme 2. Tandem Claisen provides access to callipeltoside A



We envisioned that a synthetic approach to callipeltoside A might be established around the tandem amino-sulfide acyl-Claisen rearrangement, a new cascade technology developed in our laboratories.[2] More specifically, we envisioned that treatment of **11** with two discreet acid chlorides would afford the acyclic stereochemical core **12** of callipeltoside A (Scheme 3).

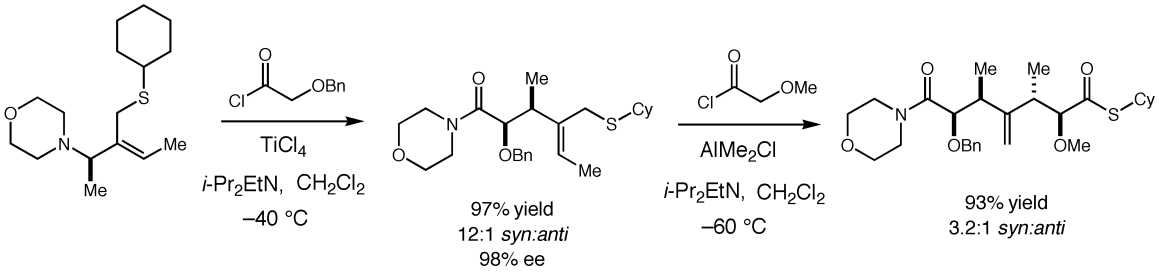
The allylic amino-sulfide precursor to the Claisen rearrangement (Scheme 4) is readily available in enantioenriched form from methyl vinyl ketone using Ellman's sulfinimine technology.

Scheme 3. Preparation of enantiopure allylic amino-sulfide



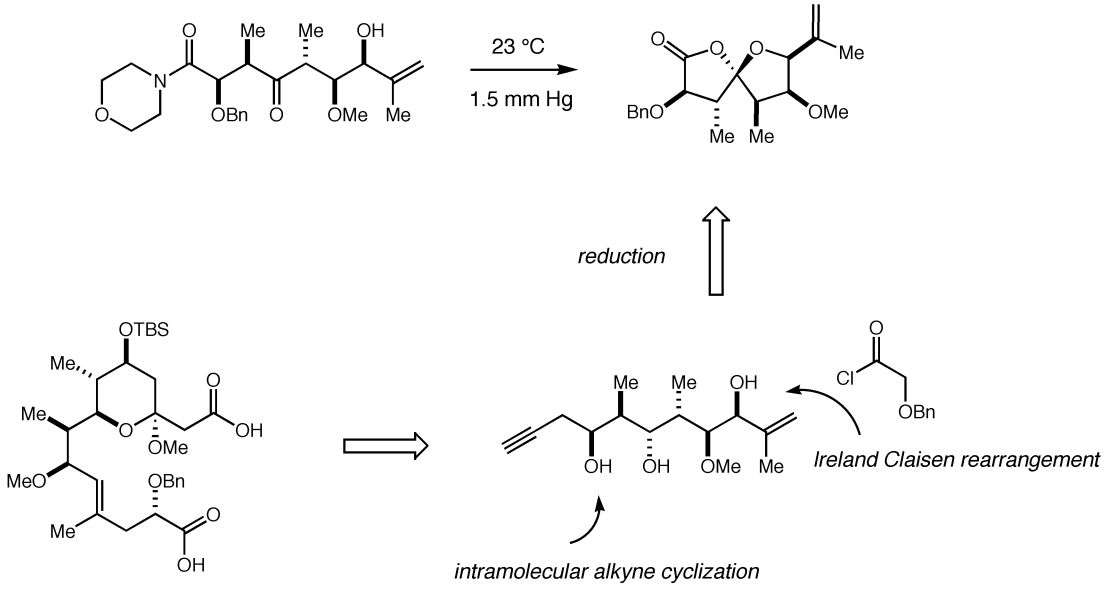
The key tandem Claisen rearrangement was accomplished as a two-step sequence, using catalytic $TiCl_4$ followed by stoichiometric $AlMe_2Cl$ to afford the acyclic stereochemical array in high yield and stereoselectivity (Scheme 5).

Scheme 4. Tandem amino-sulfide acyl-Claisen rearrangement



Key steps in the synthesis subsequent to the tandem acyl-Claisen rearrangement (Scheme 5) include reductive opening of a spirocycle, Ireland Claisen rearrangement, and formation of the tetrahydropyran moiety through an intramolecular carbonylative cyclization reaction. Synthesis of the macrolactone core was not achieved due to difficulties removing a benzyl protecting group; alteration of the protecting strategy should allow for facile completion of the total synthesis.

Scheme 5. Synthetic route subsequent to tandem acyl-Claisen rearrangement



IV. References

(1) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

(2) Seo, J.; Falsey, J. R.; Wiener, J. J. M.; MacMillan D. W. C., unpublished results.

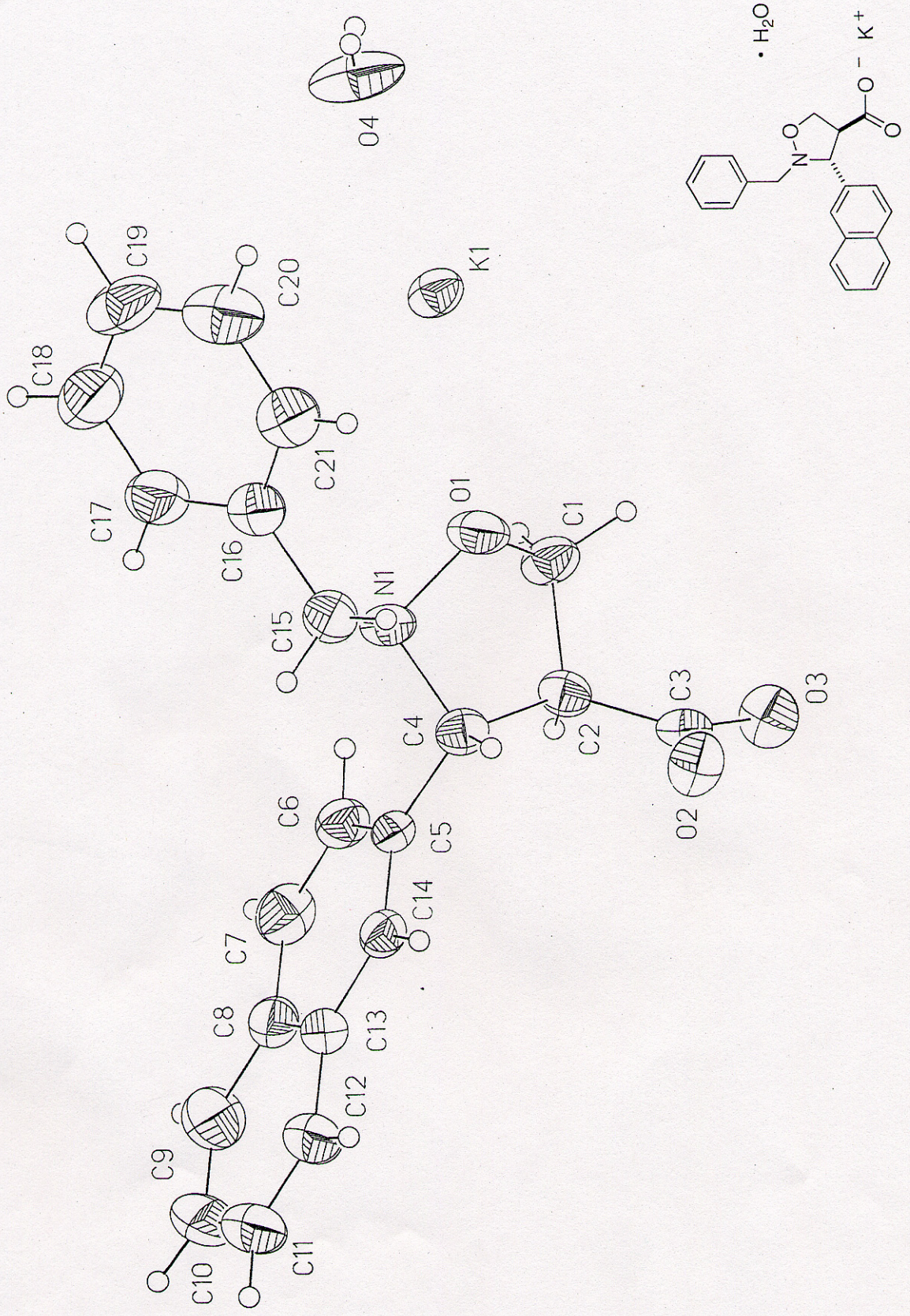

O4
K1
C19
C20
C18
C21
C17
C16
O1
C1
C15
N1
C4
C2
C3
O3
O2
C6
C5
C14
C7
C8
C13
C12
C9
C11
C10
• H2O
O
N
O
O
K+

Table 1. Crystal data and structure refinement for WSJ01.

Empirical formula	$[C_{21}H_{18}NO_3]^- K^+ H_2O$
Formula weight	389.48
Crystallization Solvent	Ethanol/THF
Crystal Habit	Blade
Crystal size	0.31 x 0.25 x 0.11 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	CCD area detector
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 7998 reflections used in lattice determination	2.50 to 25.50°
Unit cell dimensions	a = 6.7539(13) Å b = 8.2935(16) Å β= 91.678(3)° c = 34.251(7) Å
Volume	1917.7(6) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.349 Mg/m^3
F(000)	816
Data collection program	Bruker SMART
θ range for data collection	2.38 to 28.67°
Completeness to θ = 28.67°	92.4 %
Index ranges	$-8 \le h \le 9, -10 \le k \le 10, -45 \le l \le 44$
Data collection scan type	ω scans at 7 ϕ settings
Data reduction program	Bruker SAINT v6.1
Reflections collected	33077
Independent reflections	4566 [R_{int}= 0.1032]
Absorption coefficient	0.303 mm^{-1}
Absorption correction	None
Max. and min. transmission (theory)	0.9671 and 0.9105

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4566 / 0 / 324
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.798
Final R indices [$I>2\sigma(I)$, 3026 reflections]	R1 = 0.0733, *w*R2 = 0.0929
R indices (all data)	R1 = 0.1131, *w*R2 = 0.0960
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.605 and -0.385 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for WSJ01. U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
K(1)	9902(1)	7017(1)	9649(1)	39(1)
O(1)	6333(3)	5665(2)	9377(1)	46(1)
O(2)	1388(3)	4094(2)	9634(1)	45(1)
O(3)	3030(2)	1983(2)	9870(1)	46(1)
O(4)	13167(4)	8714(3)	9781(1)	72(1)
N(1)	5728(3)	5485(3)	8958(1)	36(1)
C(1)	6302(4)	4064(4)	9509(1)	42(1)
C(2)	4406(4)	3321(3)	9330(1)	34(1)
C(3)	2798(4)	3142(3)	9630(1)	33(1)
C(4)	3909(4)	4476(3)	8992(1)	34(1)
C(5)	3433(4)	3665(3)	8609(1)	30(1)
C(6)	4816(4)	2617(3)	8443(1)	39(1)
C(7)	4389(5)	1804(4)	8110(1)	48(1)
C(8)	2529(4)	1988(4)	7911(1)	43(1)
C(9)	2041(6)	1171(5)	7562(1)	63(1)
C(10)	240(6)	1381(5)	7379(1)	75(1)
C(11)	-1143(5)	2419(6)	7541(1)	70(1)
C(12)	-736(4)	3218(5)	7878(1)	52(1)
C(13)	1128(4)	3038(4)	8076(1)	37(1)
C(14)	1639(4)	3859(3)	8424(1)	33(1)
C(15)	5256(4)	7128(4)	8838(1)	43(1)
C(16)	7090(4)	8137(3)	8809(1)	40(1)
C(17)	8462(5)	7830(4)	8522(1)	52(1)
C(18)	10192(5)	8717(5)	8506(1)	64(1)
C(19)	10583(6)	9911(5)	8772(1)	65(1)
C(20)	9263(6)	10220(4)	9058(1)	64(1)
C(21)	7510(5)	9346(4)	9074(1)	49(1)

Table 4. Bond lengths [Å] and angles [°] for WSJ01.

K(1)-O(2)#1	2.625(2)	C(15)-H(15B)	0.96(3)
K(1)-O(4)	2.644(2)	C(16)-C(21)	1.377(4)
K(1)-O(3)#2	2.743(2)	C(16)-C(17)	1.392(4)
K(1)-O(2)#2	2.789(2)	C(17)-C(18)	1.383(5)
K(1)-O(1)	2.7932(18)	C(17)-H(17)	0.95(4)
K(1)-C(3)#2	3.117(3)	C(18)-C(19)	1.366(5)
K(1)-C(21)	3.167(3)	C(18)-H(18)	1.02(3)
K(1)-C(20)	3.359(4)	C(19)-C(20)	1.368(6)
K(1)-C(1)	3.475(3)	C(19)-H(19)	0.98(3)
K(1)-C(16)	3.525(3)	C(20)-C(21)	1.391(5)
K(1)-K(1)#3	4.1212(14)	C(20)-H(20)	0.90(4)
O(1)-C(1)	1.403(3)	C(21)-H(21)	0.83(2)
O(1)-N(1)	1.486(3)		
O(2)-C(3)	1.237(3)	O(2)#1-K(1)-O(4)	100.22(8)
O(2)-K(1)#4	2.625(2)	O(2)#1-K(1)-O(3)#2	125.05(6)
O(2)-K(1)#2	2.789(2)	O(4)-K(1)-O(3)#2	110.44(8)
O(3)-C(3)	1.271(3)	O(2)#1-K(1)-O(2)#2	80.89(7)
O(3)-K(1)#2	2.743(2)	O(4)-K(1)-O(2)#2	107.79(8)
O(4)-H(4AA)	0.92(4)	O(3)#2-K(1)-O(2)#2	47.15(6)
O(4)-H(44B)	0.73(3)	O(2)#1-K(1)-O(1)	87.11(6)
N(1)-C(15)	1.457(4)	O(4)-K(1)-O(1)	167.96(7)
N(1)-C(4)	1.493(3)	O(3)#2-K(1)-O(1)	71.99(6)
C(1)-C(2)	1.531(4)	O(2)#2-K(1)-O(1)	82.67(6)
C(1)-H(1A)	0.96(2)	O(2)#1-K(1)-C(3)#2	102.09(7)
C(1)-H(1B)	1.05(3)	O(4)-K(1)-C(3)#2	113.03(8)
C(2)-C(3)	1.523(4)	O(3)#2-K(1)-C(3)#2	23.98(6)
C(2)-C(4)	1.534(4)	O(2)#2-K(1)-C(3)#2	23.35(6)
C(2)-H(2A)	1.03(3)	O(1)-K(1)-C(3)#2	74.22(6)
C(3)-K(1)#2	3.117(3)	O(2)#1-K(1)-C(21)	137.69(9)
C(4)-C(5)	1.500(4)	O(4)-K(1)-C(21)	100.92(9)
C(4)-H(4A)	0.99(2)	O(3)#2-K(1)-C(21)	79.94(9)
C(5)-C(14)	1.360(3)	O(2)#2-K(1)-C(21)	125.63(9)
C(5)-C(6)	1.408(4)	O(1)-K(1)-C(21)	67.55(7)
C(6)-C(7)	1.348(4)	C(3)#2-K(1)-C(21)	102.65(10)
C(6)-H(6)	0.97(2)	O(2)#1-K(1)-C(20)	139.56(10)
C(7)-C(8)	1.420(4)	O(4)-K(1)-C(20)	76.92(9)
C(7)-H(7)	0.95(3)	O(3)#2-K(1)-C(20)	92.34(10)
C(8)-C(9)	1.405(4)	O(2)#2-K(1)-C(20)	138.95(10)
C(8)-C(13)	1.415(4)	O(1)-K(1)-C(20)	91.29(7)
C(9)-C(10)	1.364(5)	C(3)#2-K(1)-C(20)	116.30(11)
C(9)-H(9)	0.96(3)	C(21)-K(1)-C(20)	24.38(9)
C(10)-C(11)	1.397(5)	O(2)#1-K(1)-C(1)	67.22(7)
C(10)-H(10)	0.95(4)	O(4)-K(1)-C(1)	167.33(8)
C(11)-C(12)	1.352(5)	O(3)#2-K(1)-C(1)	77.39(8)
C(11)-H(11)	0.93(3)	O(2)#2-K(1)-C(1)	69.73(7)
C(12)-C(13)	1.420(4)	O(1)-K(1)-C(1)	22.71(6)
C(12)-H(12)	1.02(3)	C(3)#2-K(1)-C(1)	69.90(8)
C(13)-C(14)	1.409(4)	C(21)-K(1)-C(1)	90.11(8)
C(14)-H(14)	0.88(2)	C(20)-K(1)-C(1)	113.42(8)
C(15)-C(16)	1.501(4)	O(2)#1-K(1)-C(16)	115.12(7)
C(15)-H(15A)	0.90(3)	O(4)-K(1)-C(16)	115.23(8)

O(3)#2-K(1)-C(16)	91.73(7)	C(5)-C(4)-C(2)	114.6(2)
O(2)#2-K(1)-C(16)	129.18(7)	N(1)-C(4)-H(4A)	106.9(12)
O(1)-K(1)-C(16)	52.75(6)	C(5)-C(4)-H(4A)	112.2(12)
C(3)#2-K(1)-C(16)	110.15(7)	C(2)-C(4)-H(4A)	108.4(13)
C(21)-K(1)-C(16)	22.96(8)	C(14)-C(5)-C(6)	118.5(3)
C(20)-K(1)-C(16)	40.86(8)	C(14)-C(5)-C(4)	121.3(3)
C(1)-K(1)-C(16)	73.44(7)	C(6)-C(5)-C(4)	120.2(2)
O(2)#1-K(1)-K(1)#3	41.93(4)	C(7)-C(6)-C(5)	121.5(3)
O(4)-K(1)-K(1)#3	108.65(6)	C(7)-C(6)-H(6)	120.4(16)
O(3)#2-K(1)-K(1)#3	84.58(5)	C(5)-C(6)-H(6)	117.9(16)
O(2)#2-K(1)-K(1)#3	38.96(4)	C(6)-C(7)-C(8)	121.1(3)
O(1)-K(1)-K(1)#3	83.20(4)	C(6)-C(7)-H(7)	121.3(17)
C(3)#2-K(1)-K(1)#3	60.80(6)	C(8)-C(7)-H(7)	117.6(17)
C(21)-K(1)-K(1)#3	149.91(7)	C(7)-C(8)-C(9)	122.6(3)
C(20)-K(1)-K(1)#3	174.29(7)	C(7)-C(8)-C(13)	117.9(3)
C(1)-K(1)-K(1)#3	61.24(5)	C(9)-C(8)-C(13)	119.5(3)
C(16)-K(1)-K(1)#3	134.26(5)	C(10)-C(9)-C(8)	120.9(4)
C(1)-O(1)-N(1)	102.03(19)	C(10)-C(9)-H(9)	119.2(17)
C(1)-O(1)-K(1)	107.07(14)	C(8)-C(9)-H(9)	119.8(17)
N(1)-O(1)-K(1)	124.89(14)	C(9)-C(10)-C(11)	119.6(4)
C(3)-O(2)-K(1)#4	152.17(17)	C(9)-C(10)-H(10)	119(2)
C(3)-O(2)-K(1)#2	93.37(16)	C(11)-C(10)-H(10)	121(2)
K(1)#4-O(2)-K(1)#2	99.11(6)	C(12)-C(11)-C(10)	121.3(3)
C(3)-O(3)-K(1)#2	94.74(16)	C(12)-C(11)-H(11)	117(2)
K(1)-O(4)-H(4AA)	117(2)	C(10)-C(11)-H(11)	121.7(19)
K(1)-O(4)-H(44B)	135(3)	C(11)-C(12)-C(13)	120.7(4)
H(4AA)-O(4)-H(44B)	104(3)	C(11)-C(12)-H(12)	126.3(15)
C(15)-N(1)-O(1)	103.4(2)	C(13)-C(12)-H(12)	112.9(15)
C(15)-N(1)-C(4)	111.8(2)	C(14)-C(13)-C(8)	119.0(2)
O(1)-N(1)-C(4)	100.70(19)	C(14)-C(13)-C(12)	123.0(3)
O(1)-C(1)-C(2)	105.8(2)	C(8)-C(13)-C(12)	118.0(3)
O(1)-C(1)-K(1)	50.22(11)	C(5)-C(14)-C(13)	122.0(3)
C(2)-C(1)-K(1)	155.79(19)	C(5)-C(14)-H(14)	118.4(13)
O(1)-C(1)-H(1A)	111.1(15)	C(13)-C(14)-H(14)	119.4(13)
C(2)-C(1)-H(1A)	113.9(14)	N(1)-C(15)-C(16)	111.5(2)
K(1)-C(1)-H(1A)	77.7(14)	N(1)-C(15)-H(15A)	105(2)
O(1)-C(1)-H(1B)	105.2(17)	C(16)-C(15)-H(15A)	111.2(18)
C(2)-C(1)-H(1B)	116.2(16)	N(1)-C(15)-H(15B)	109.8(16)
K(1)-C(1)-H(1B)	78.6(17)	C(16)-C(15)-H(15B)	111.5(15)
H(1A)-C(1)-H(1B)	104(2)	H(15A)-C(15)-H(15B)	107(2)
C(1)-C(2)-C(3)	112.1(2)	C(21)-C(16)-C(17)	118.0(3)
C(1)-C(2)-C(4)	102.2(2)	C(21)-C(16)-C(15)	121.1(3)
C(3)-C(2)-C(4)	115.2(2)	C(17)-C(16)-C(15)	120.8(3)
C(1)-C(2)-H(2A)	109.9(13)	C(21)-C(16)-K(1)	63.76(15)
C(3)-C(2)-H(2A)	108.7(15)	C(17)-C(16)-K(1)	99.94(17)
C(4)-C(2)-H(2A)	108.5(14)	C(15)-C(16)-K(1)	103.01(17)
O(2)-C(3)-O(3)	123.8(3)	C(18)-C(17)-C(16)	120.8(4)
O(2)-C(3)-C(2)	120.6(2)	C(18)-C(17)-H(17)	120(2)
O(3)-C(3)-C(2)	115.6(2)	C(16)-C(17)-H(17)	119(2)
O(2)-C(3)-K(1)#2	63.28(14)	C(19)-C(18)-C(17)	120.3(4)
O(3)-C(3)-K(1)#2	61.28(14)	C(19)-C(18)-H(18)	124.6(18)
C(2)-C(3)-K(1)#2	169.60(15)	C(17)-C(18)-H(18)	115.0(18)
N(1)-C(4)-C(5)	109.9(2)	C(18)-C(19)-C(20)	119.8(4)
N(1)-C(4)-C(2)	104.23(19)	C(18)-C(19)-H(19)	120.3(19)

C(20)-C(19)-H(19)	119.9(19)	C(20)-C(21)-C(16)	120.9(4)
C(21)-C(20)-C(19)	120.2(4)	C(20)-C(21)-K(1)	85.54(18)
C(21)-C(20)-K(1)	70.07(18)	C(16)-C(21)-K(1)	93.29(18)
C(19)-C(20)-K(1)	102.0(2)	C(20)-C(21)-H(21)	119.8(18)
C(21)-C(20)-H(20)	119(2)	C(16)-C(21)-H(21)	119.3(18)
C(19)-C(20)-H(20)	121(2)	K(1)-C(21)-H(21)	91.0(17)
K(1)-C(20)-H(20)	98(2)		

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z
#2 -x+1,-y+1,-z+2
#3 -x+2,-y+1,-z+2
#4 x-1,y,z

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for WSJ01. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
K(1)	298(3)	364(3)	490(4)	71(3)	-36(3)	-18(3)
O(1)	451(12)	431(13)	483(13)	54(10)	-191(10)	-98(10)
O(2)	347(10)	452(12)	548(13)	134(10)	66(9)	138(10)
O(3)	472(11)	368(11)	527(12)	73(11)	12(9)	88(10)
O(4)	414(14)	412(15)	1310(30)	64(15)	-340(16)	-46(12)
N(1)	313(12)	328(13)	429(15)	15(11)	-91(11)	-55(10)
C(1)	276(16)	442(19)	530(20)	80(16)	-59(15)	-18(14)
C(2)	315(15)	353(18)	344(16)	7(13)	-65(12)	32(12)
C(3)	290(14)	312(15)	382(16)	-44(14)	-77(12)	-45(13)
C(4)	271(14)	344(16)	397(18)	-27(14)	-8(13)	20(13)
C(5)	277(14)	313(15)	298(15)	30(12)	-12(12)	-73(12)
C(6)	296(15)	442(19)	434(18)	-20(14)	17(14)	-9(13)
C(7)	447(18)	454(19)	540(20)	-89(18)	122(16)	13(16)
C(8)	463(16)	481(18)	358(17)	-70(16)	66(14)	-147(16)
C(9)	650(20)	760(30)	490(20)	-200(20)	108(19)	-100(20)
C(10)	720(30)	1100(40)	420(20)	-260(20)	-20(20)	-320(20)
C(11)	480(20)	1130(40)	470(20)	-80(20)	-100(19)	-190(20)
C(12)	417(18)	700(20)	420(19)	-19(19)	-73(15)	-58(18)
C(13)	354(15)	438(17)	320(15)	3(15)	-10(12)	-94(15)
C(14)	273(15)	363(16)	347(17)	18(14)	30(13)	-12(13)
C(15)	350(16)	510(20)	421(19)	96(17)	-63(15)	23(16)
C(16)	415(16)	306(15)	457(18)	79(15)	-77(14)	41(14)
C(17)	500(20)	560(20)	510(20)	40(20)	-89(17)	-51(18)
C(18)	510(20)	680(30)	730(30)	180(20)	10(20)	-100(20)
C(19)	480(20)	530(20)	920(30)	320(20)	-170(20)	-170(20)
C(20)	740(30)	330(20)	820(30)	50(20)	-270(20)	-25(19)
C(21)	470(20)	430(20)	570(20)	77(18)	-46(19)	62(17)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for WSJ01.

	x	y	z	U_{iso}
H(1A)	7490(40)	3500(30)	9442(7)	31(7)
H(1B)	6380(40)	4140(40)	9815(10)	64(10)
H(2A)	4710(30)	2200(40)	9216(7)	48(8)
H(4A)	2830(30)	5210(30)	9073(6)	17(6)
H(6)	6130(40)	2550(30)	8565(7)	47(8)
H(7)	5300(40)	1070(40)	8005(8)	54(9)
H(9)	2960(40)	420(40)	7456(9)	53(10)
H(10)	-10(50)	870(50)	7134(12)	99(13)
H(11)	-2380(40)	2590(40)	7423(9)	58(9)
H(12)	-1630(40)	4020(30)	8009(8)	43(8)
H(14)	740(30)	4460(30)	8538(6)	10(6)
H(15A)	4620(40)	7040(40)	8604(8)	49(8)
H(15B)	4340(40)	7590(30)	9014(7)	36(8)
H(17)	8190(40)	7000(40)	8337(10)	79(12)
H(18)	11090(40)	8420(40)	8283(10)	65(10)
H(19)	11810(40)	10540(40)	8760(9)	65(10)
H(20)	9510(50)	11000(40)	9238(10)	73(12)
H(21)	6700(30)	9550(30)	9246(7)	20(8)
H(4AA)	13020(50)	9790(50)	9838(11)	95(15)
H(44B)	14180(50)	8520(40)	9846(10)	69(13)

Table 7. Hydrogen bonds for WSJ01 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(4AA)...O(3)#5	0.92(4)	1.82(4)	2.730(3)	169(4)
O(4)-H(44B)...O(3)#3	0.73(3)	2.14(3)	2.861(3)	171(4)

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z
#2 -x+1,-y+1,-z+2
#3 -x+2,-y+1,-z+2
#4 x-1,y,z
#5 x+1,y+1,z