Chapter 1

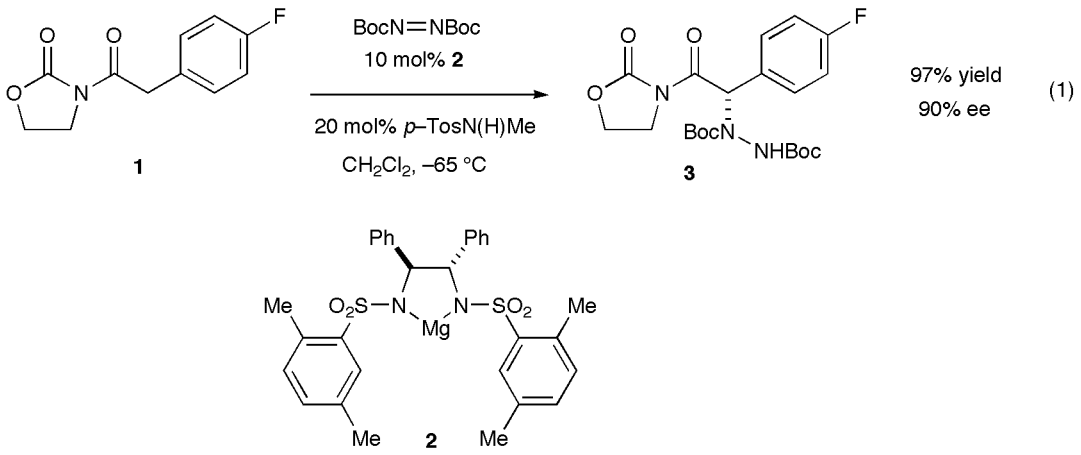
Merging Enolization and Enantioselective Catalysis: Development of a Direct Enantioselective Catalytic *anti* Aldol Reaction

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]

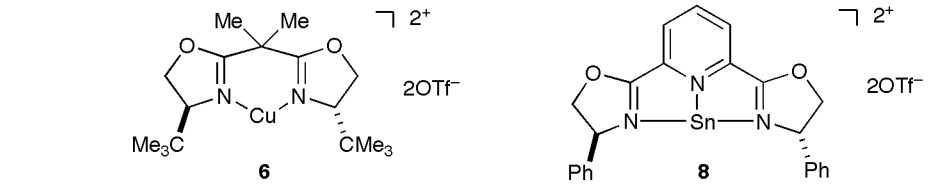
Enantioselective catalytic amination of *N*-acyloxazolidinones such as **1** is effected in the presence of 10 mol% magnesium bis(sulfonamide) catalyst **2** (Equation 1).

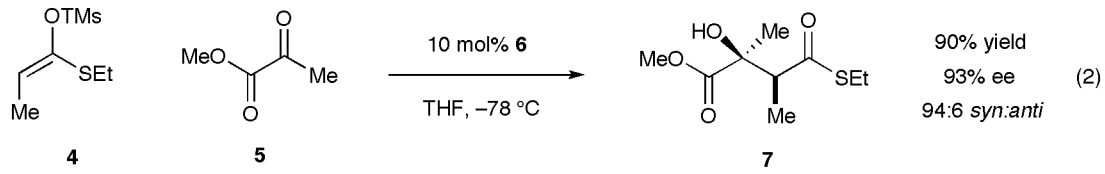


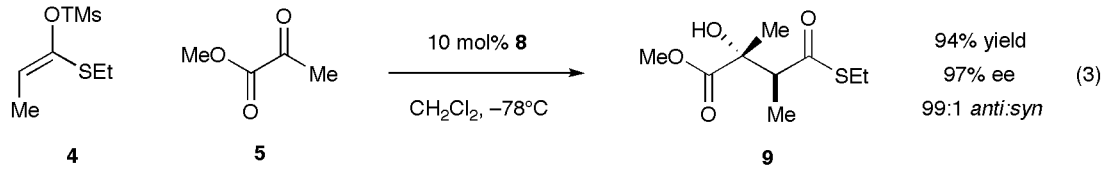
This catalyst system requires 20 mol% N-methyl-*p*-toluenesulfonamide, which is believed to facilitate catalyst turnover by promoting protonation of the intermediate anionic hydrazide species. The □-hydrazido imides **3** are afforded in high yield (> 90%) and good enantiomeric excess (80–90% ee). In 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

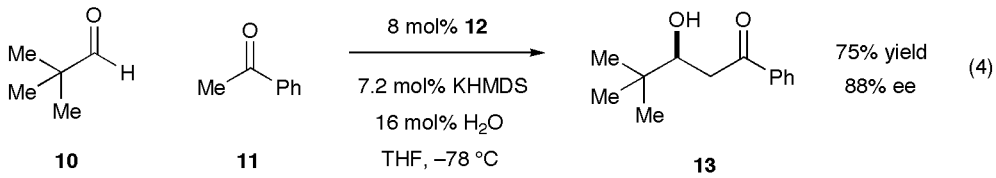
aldehydes in the presence of Cu or Sn bis(oxazoline) complexes **6** and **8**. Importantly, either the *syn* or the *anti* aldol adducts (**7** and **9**, respectively) are accessible, depending upon the choice of metal (Equations 2 and 3).

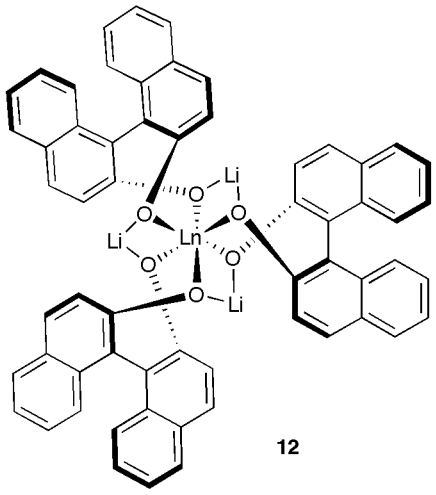




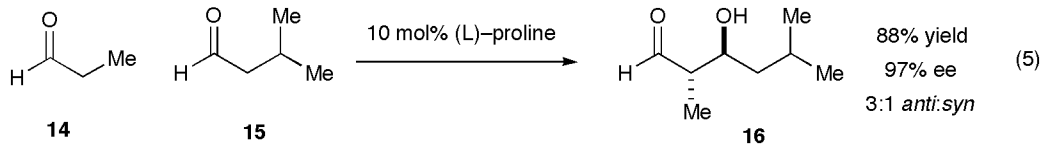


In line with the discussed interest in catalytically accessing chiral enolates, recent developments in aldol technology have sought to effect direct aldol reactions, bypassing the aforementioned enolate surrogates.[7] A notable example is the system designed by Shibasaki[7b] (Equation 4), utilizing the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

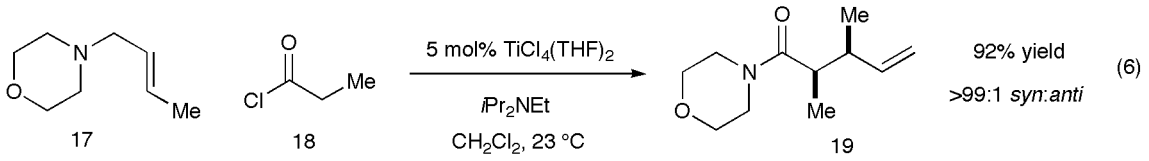




As well, purely organic catalysts including proline have been used in enantioselective production of aldol adducts.[8] One particularly successful approach, reported from these laboratories, has used proline to catalyze the cross-aldol reaction of aldehydes in high yield and enantioselectivity (Equation 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]

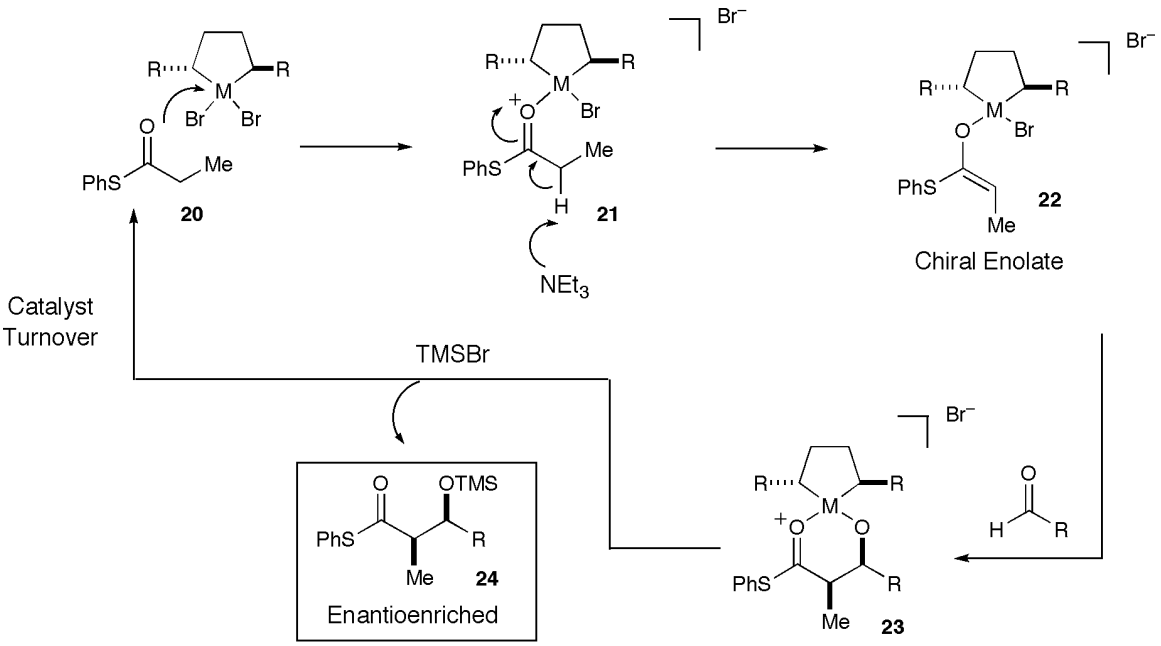


This observation, coupled with the broad interest in and need for new methods of approaching catalytic enantioselective enolate bond constructions, prompted our research group to explore more deeply the ability of Lewis acids to operate under soft-enolization conditions involving amine bases. Given the 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.

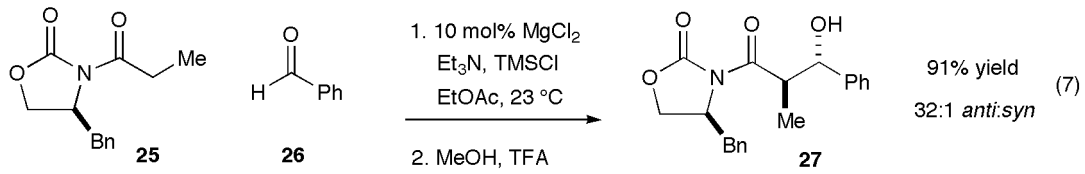
We envisioned a catalytic cycle (Scheme 1) in which a carbonyl compound **20** binds to a Lewis acid-chiral ligand complex, activating it towards soft-enolization. A tertiary amine base would at this point deprotonate the activated carbonyl **21** at the □–position, affording the metal-bound chiral enolate 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.

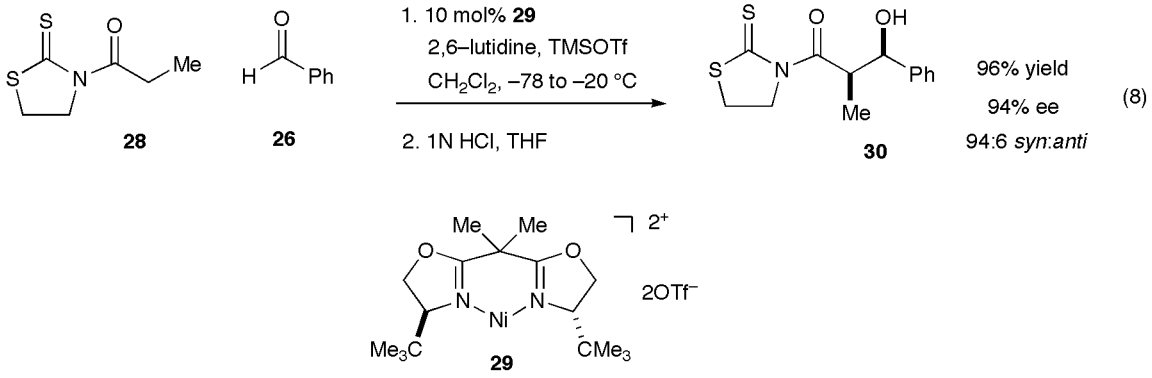
Scheme 1. Proposed catalytic cycle



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]

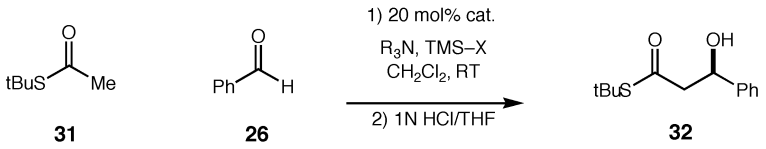


II. Results and Discussion

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



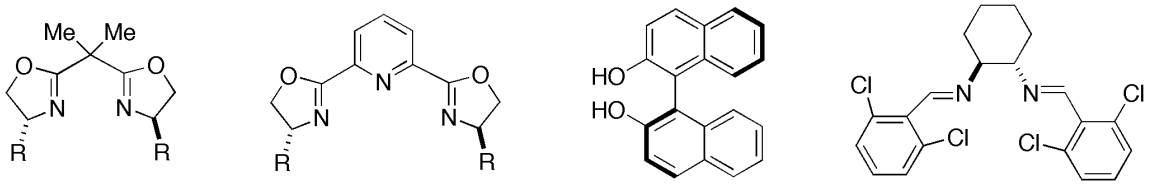
(9)

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]

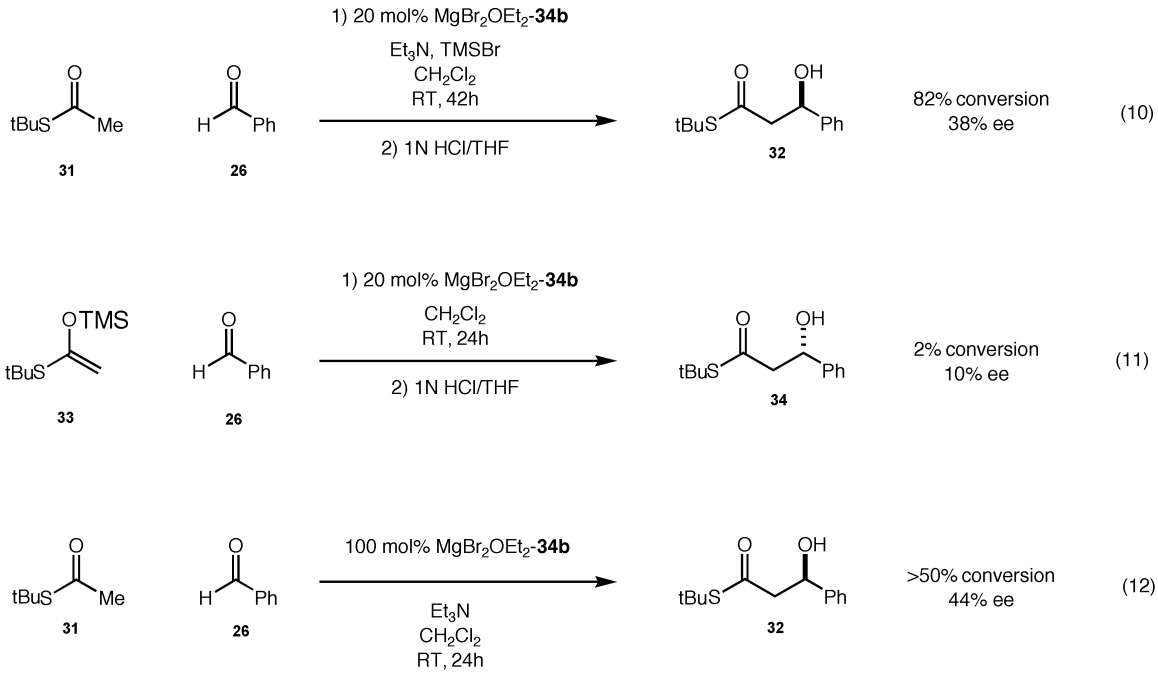
Figure 1. Representative chiral ligands examined in the aldol reaction



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).

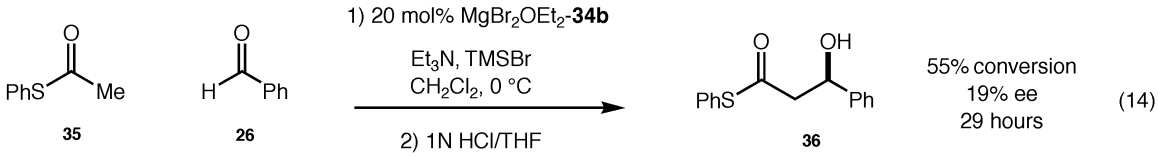


Having provided evidence that this reaction was proceeding through a catalytically accessed chiral ligand-metal enolate complex rather than *via* a Mukaiyama aldol pathway, our attention turned to increasing the rate and selectivity of the process. Due to the low pKa of substrate **31**, imparted by 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]

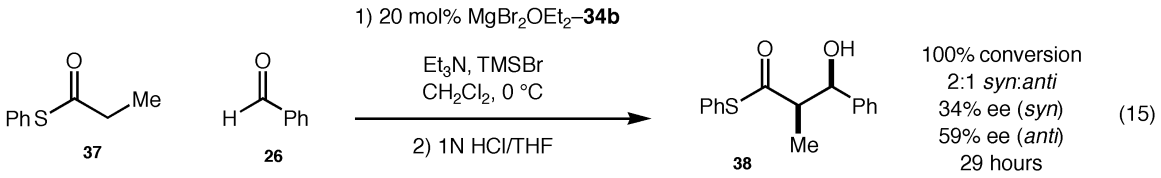
In an effort to increase the enantioselectivity of this process, reactions were performed using phenyl thioacetate at lower temperatures, though this modification to the reaction conditions resulted only in poor reaction efficiency with no concomitant gain in enantioselectivity (Equation 14).[16]



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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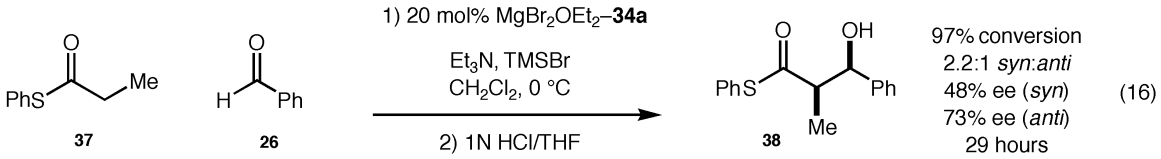
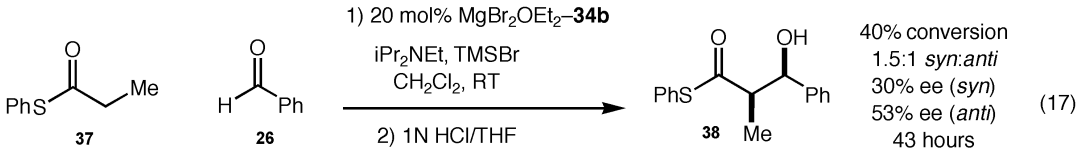


(16)

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

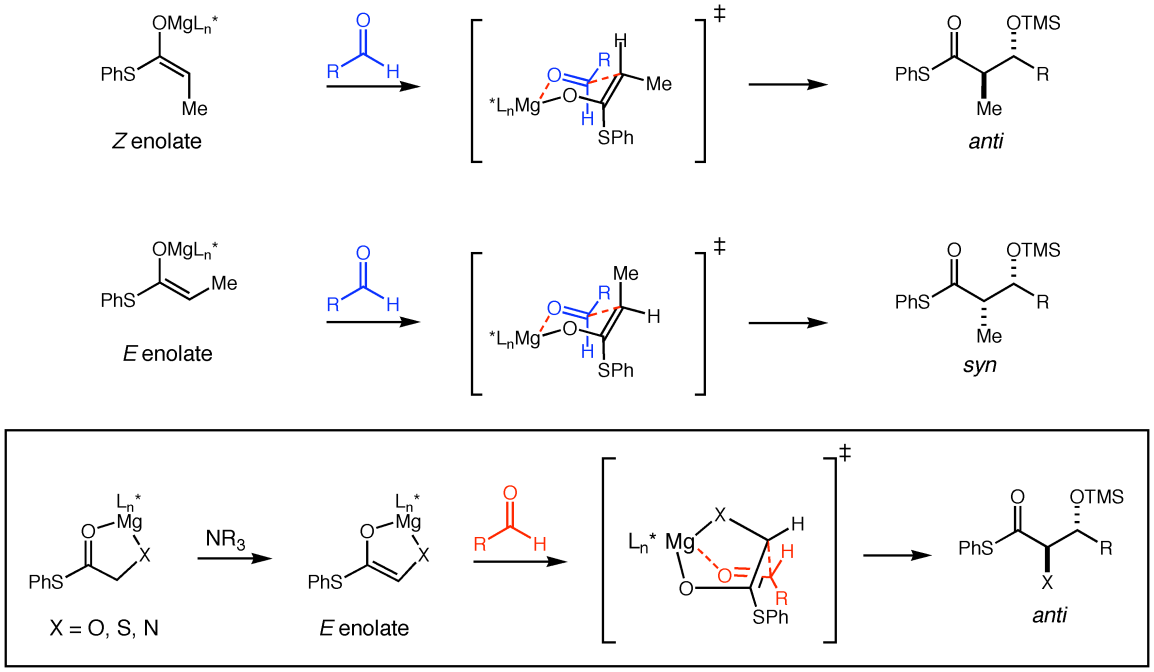
have the potential to afford different enolate geometries when used as soft-enolization bases,[21] it was hoped that employing *i*Pr_2NEt in the reaction would allow for an alteration in diastereoselectivity. In fact, *i*Pr_2NEt was unable to alter the outcome of this reaction (Equation 17).



(17)

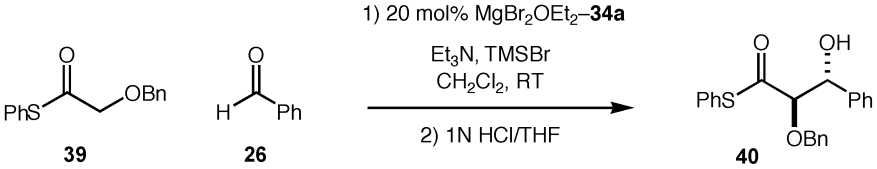
Despite the inability of *i*Pr_2NEt to alter the sense of diastereocontrol in this process through alteration of enolate geometry, we hoped to control the sense of enolate formation through other means to further test this hypothesis. We imagined that use of a substrate bearing heteroatom functionality 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

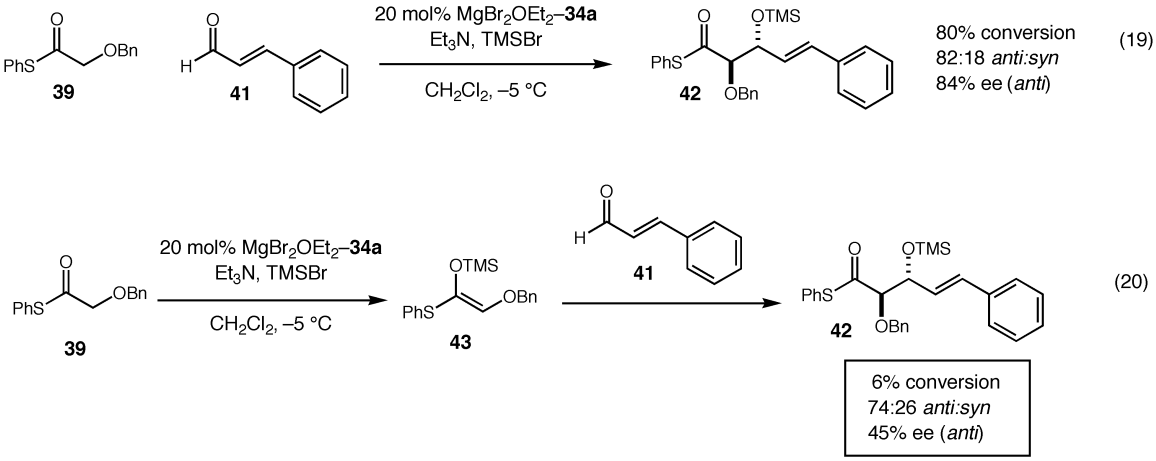
(18)

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).

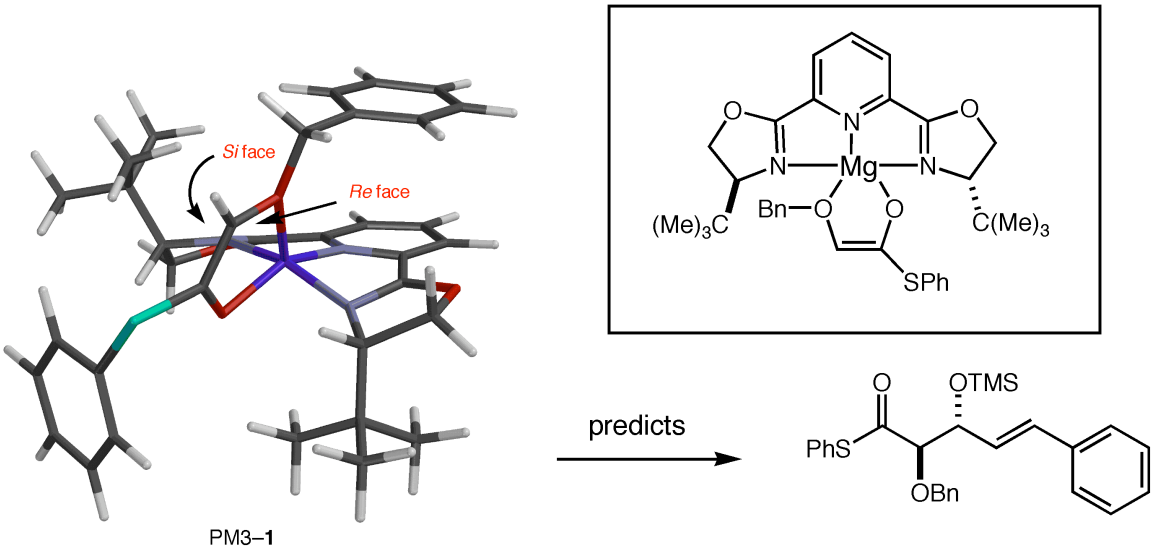
Further, monitoring this catalytic reaction with time showed that silyl ketene acetal **43** is formed as an unreactive byproduct during the course of the reaction, accounting for incomplete conversion to product. Thus it was again concluded that a silyl ketene acetal was not involved in the catalytic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

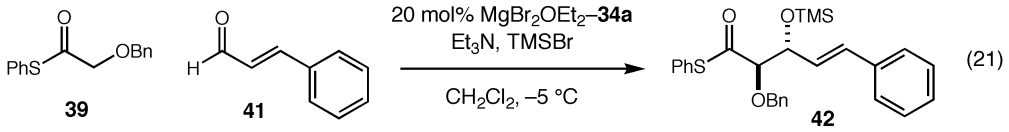
catalysts, which lack this pyridyl ring, catalyzed only racemic reactions using these α-benzyloxy phenylthioacetate substrates.

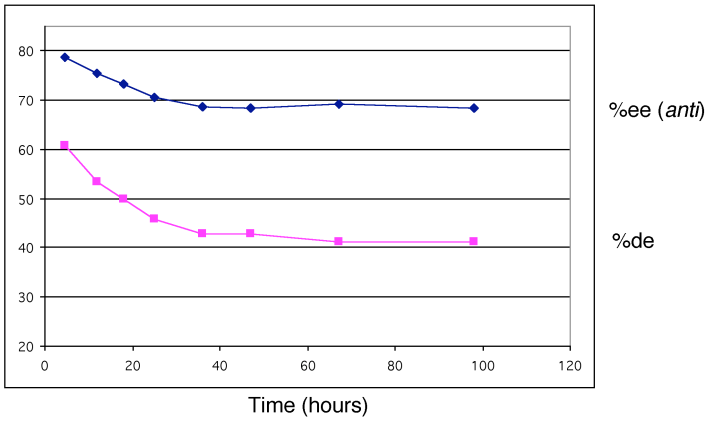
Figure 2. Calculated substrate-catalyst complex



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.

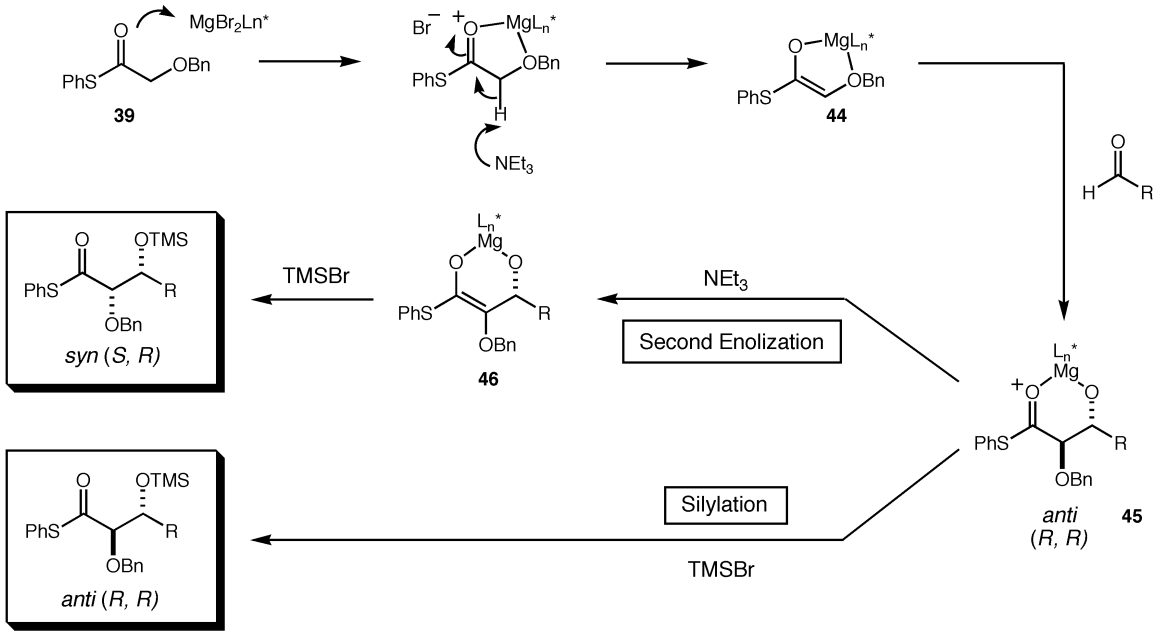
Scheme 3. Degradation of selectivity



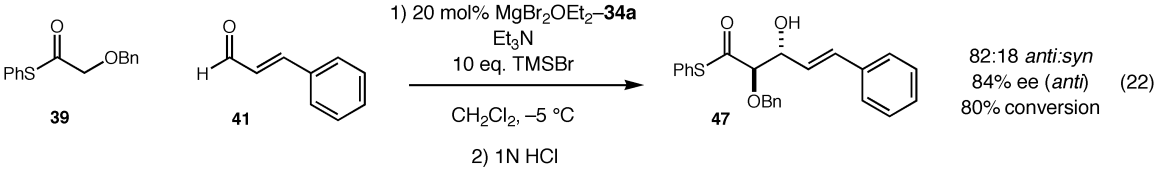


Based on our vision of the implicated catalytic cycle, this degradation was understood as follows (Scheme 4): following aldol reaction, the alkoxide aldol adduct is chelated to the catalyst as complex **45**. This adduct is activated for second soft-enolization at the position □ to the carbonyl to produce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

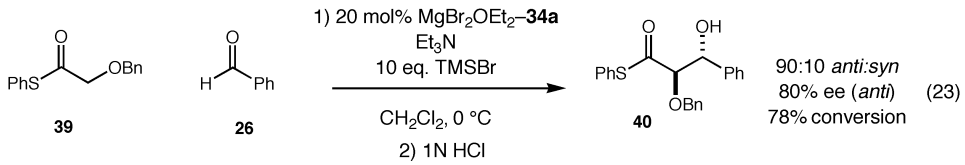
Scheme 4. Proposed rationale for observed degradation of selectivity



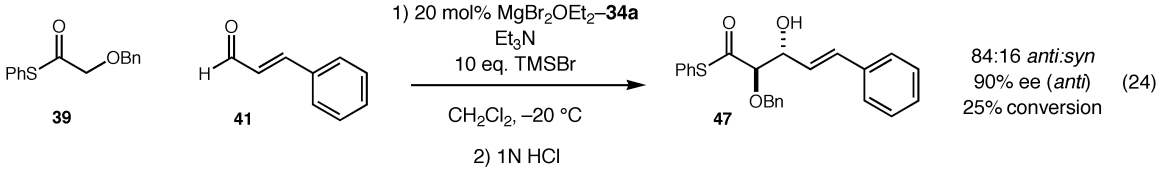
Based on this hypothesis, it was believed that increasing the rate of the silylation step would result in maintenance of enantio- and diastereoselectivity in the process by avoiding the undesired second enolization. Indeed, increasing the amount of TMSBr in the reaction from the standard 2 equivalents 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).



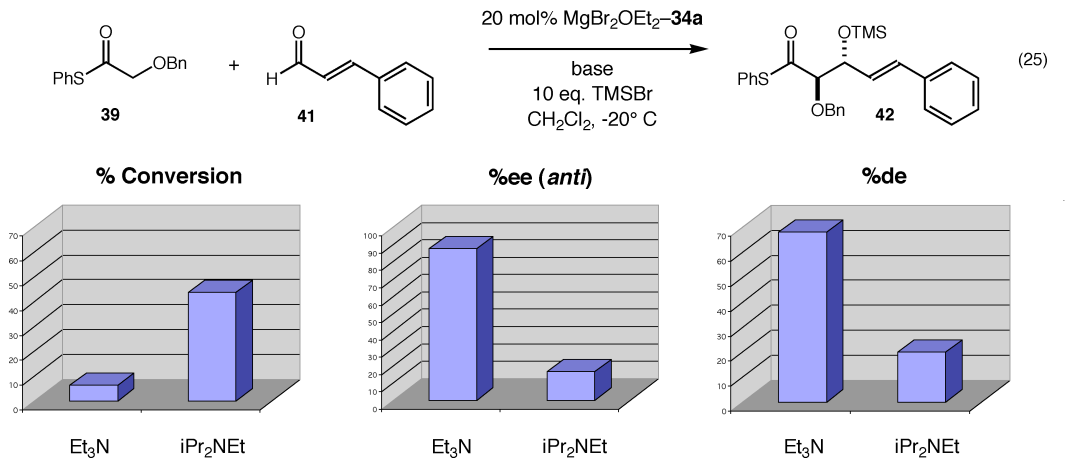
Importantly, the enantioselectivity of the aldol reaction with cinnamaldehyde could be raised to 90% as the temperature of the reaction was lowered to –20 °C, albeit with only modest conversion to product (Equation 24).



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.

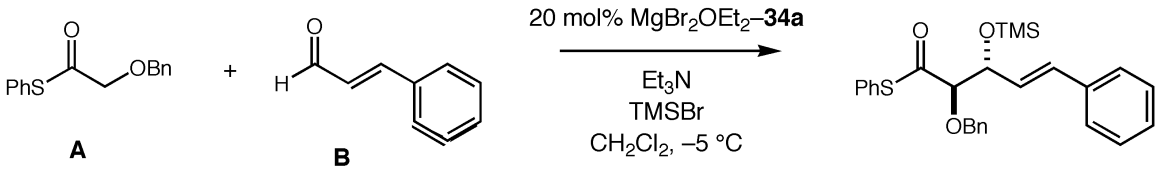
Figure 3. Effect of amine base on the aldol reaction

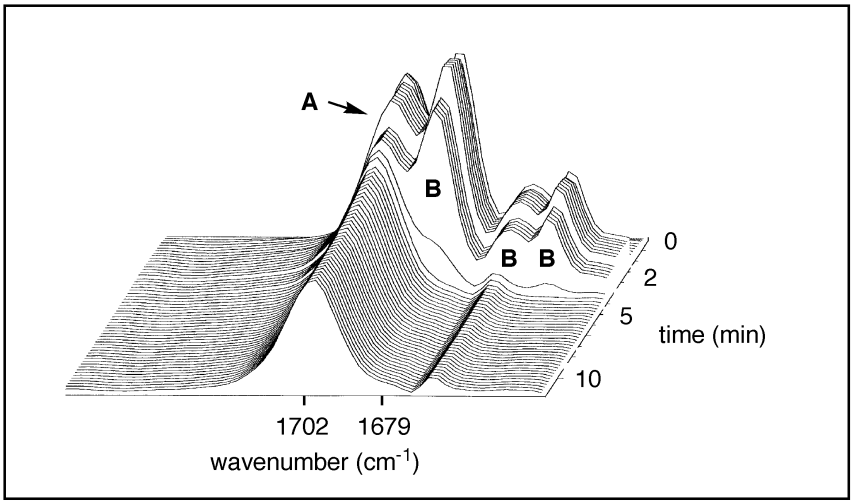


Mechanistic investigations. *In situ* monitoring of the Et_3N experiment with a ReactIR system revealed that upon addition of Et_3N to a reaction mixture containing thioester, cinnamaldehyde, catalyst, and TMSBr, the IR stretches associated with the aldehyde immediately disappeared (Figure 4). Yet, at 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.

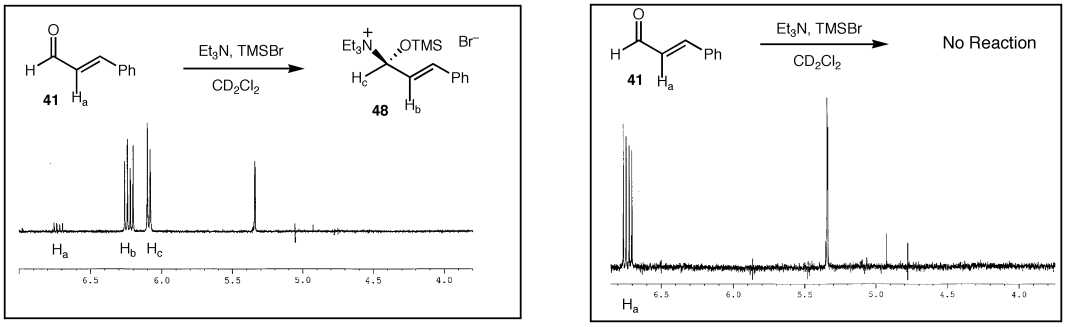
Figure 4. ReactIR investigation reveals aldehyde consumption





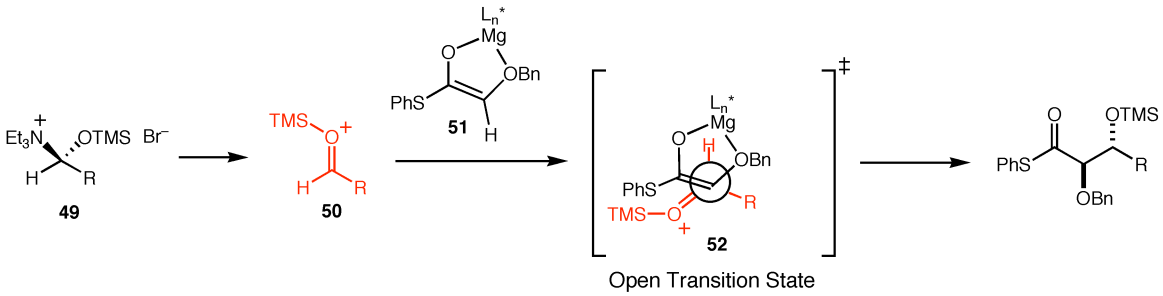
^{1}H NMR studies were employed to investigate further this curious observation. Cinnamaldehyde and TMSBr were combined in CD_2Cl_2, followed by the addition of either Et_3N or *i*Pr_2NEt (Figure 5). In complete accord with our hypothesis, these NMR studies revealed that, in the presence of Et_3N, cinnamaldehyde 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



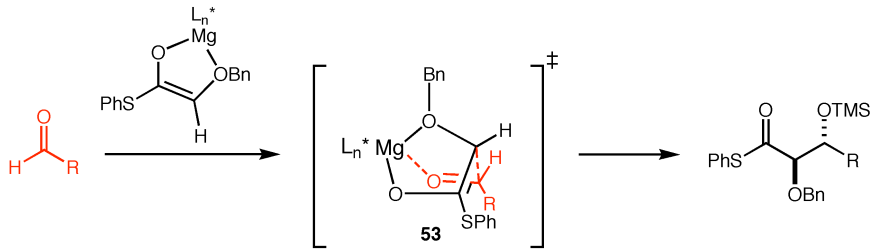
To explain how this difference could account for the observed differences in rate and selectivity of the catalytic reaction, we were required to revise our vision of the catalytic cycle. Based on our new understanding of the intermediates involved in this reaction, we proposed (Scheme 5) that, in the 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.

V. References

(1) For general reviews, see: (a) Sauamura, M.; Ito, Y. Asymmetric Aldol Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (c) Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095. (d) Spino, C. *Org. Prep. Proced. Int.* **2003**, *35*, 3.

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(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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