# Leveraging the Reactivity of Thioesters in the Development of New Methods for Carbon–Carbon Bond Formation

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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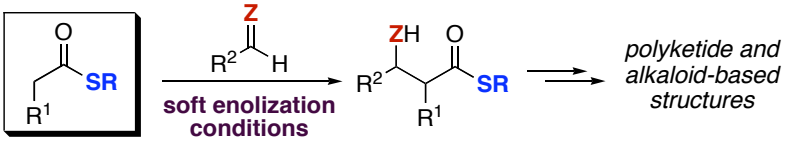
# Abstract




Carbon–carbon bond-forming reactions comprise the most important class of synthetic transformations. The development of improved and simplified approaches to these reactions will make important and useful contributions not only to the field of synthetic organic chemistry, but also to the many other areas of science that rely on it. Enolate based carbon–carbon bond formation is fundamental to synthetic organic chemistry and has provided the foundation for advancement to its present state. Herein, an important aspect of enolate chemistry is explored: the development of *direct* methods for carbon–carbon bond formation based on soft enolization of thioesters. Both metal-mediated and organocatalytic approaches to soft enolization are described.

$MgBr_2 \cdot OEt_2$-promoted soft enolization conditions were developed and successfully applied to the aldol addition and Mannich reactions, resulting in a mild and efficient *direct* reaction that is inexpensive and can be used under atmospheric conditions. A conjugate addition approach to chemoselective deprotonation was also explored and applied to the aldol. In addition, the first organocatalytic Mannich reaction based on proximity-accelerated intramolecular soft enolization of thioesters was developed. Given the advantages of soft enolization, including the inherent operational simplicity, and the accessibility of thioesters, we expect these methods to meet with wide application.

*Dedicated to my loving husband, Matthew.*

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# List of Abbreviations

| | |
|---|---|
| °C | degree(s) Celsius |
| Ac | acetyl, acetate |
| ACP | acyl carrier protein |
| app | apparent |
| aq | aqueous |
| Ar | aromatic group; argon |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| br | broad |
| BuLi | butyllithium |
| ca. | approximately |
| calcd | calculated |
| cat | catalytic |
| $CDCl_3$ | chloroform-d |
| $CH_2Cl_2$ | dichloromethane, methylene chloride |
| $CHCl_3$ | chloroform |
| CoA | Coenzyme A |
| concn | concentration |
| conv | conversion |
| CS | citrate synthase |
| d | doublet; day(s) |
| dq | doublet of quartets |
| d.r. | diastereomeric ratio |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N*′-Dicyclohexylcarbodiimide |
| dd | doublet of doublets |
| ddd | doublet of doublets of doublets |
| DMAP | 4-(dimethylamino)pyridine |

| | |
|---|---|
| DME | 1,2-dimethoxyethane |
| DMF | dimethyl formamide |
| DMSO | dimethyl sulfoxide |
| DPPA | diphenyl phosphoryl azide |
| dt | doublet of triplets |
| e.r. | enantiomeric ratio |
| ea. | each |
| EDCI | *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride |
| ee | enantiomeric excess |
| equiv | equivalent(s) |
| ESI | electrospray ionization |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| $Et_3N$ | triethylamine, TEA |
| $Et_3SiH$ | triethylsilane |
| EtOAc | ethyl acetate |
| EtOH | ethanol, ethyl alcohol |
| FAB | fast atom bombardment |
| g | gram(s) |
| h | hour(s) |
| H/D | proton/deuterium exchange rate |
| HCl | hydrochloric acid |
| HPLC | high performance liquid chromatography |
| Hz | Hertz |
| *i*-$Pr_2NEt$ | *N*,*N*-diisopropylethylamine, Hünig's base |
| *J* | coupling constant |
| KS | ketosynthase |
| L | liter(s) |
| LAH | Lithium aluminum hydride |
| LDA | Lithium diisopropylamide |
| LHMDS | Lithium hexamethyldisilazide, Lithium bis(trimethylsilyl)amide |
| m | milli, multiplet (NMR) |

| | |
|---|---|
| M | moles per liter |
| m/z | mass to charge ratio |
| MAHT(s) | malonic acid half thioester(s) |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| $MgBr_2 \cdot OEt_2$ | magnesium bromide diethyl etherate |
| MHz | Megahertz |
| min | minute(s) |
| mmol | millimole(s) |
| mol | mole(s) |
| mol% | molar percent |
| MS | mass spectrometry |
| N.R. | no reaction |
| *n*-Bu | *n*-butyl |
| NMR | nuclear magnetic resonance |
| OAc | *O*-acetate |
| OTf | *O*-triflate, *O*-trifluoromethanesulfonate |
| *p* | para |
| Ph | phenyl |
| pH | hydrogen ion concentration |
| PhMe | toluene |
| $PPh_3$ | triphenylphosphine |
| ppm | parts per million |
| ppt | precipitate |
| PPTS | pyridinium para-toluenesulfonic acid |
| *p*-TsOH | *para*-toluenesulfonic acid |
| pyr | pyridine |
| q | quartet |
| qd | quartet of doublets |
| rt | room temperature, ambient temperature |

| | |
|---|---|
| s | singlet (NMR) |
| sat | saturated |
| t | triplet |
| $t_{1/2}$ | half-life |
| TBS | *tert*-butyldimethylsilyl |
| *t*-Bu | *tert*-butyl |
| td | triplet of doublets |
| temp | temperature |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N'*,*N'*-tetramethylethylenediamine |
| TMS | trimethylsilyl; tetramethylsilane (NMR standard) |
| TMSOTf | trimethylsilyl triflate, trimethylsilyl trifluoromethanesulfonate |
| Ts | toluenesulfonyl |
| vol | volume |
| δ | chemical shift (ppm) downfield from TMS |
| μ | micro |

# Acknowledgements

I would like to express my deepest gratitude to my mentor, Dr. Don Coltart, for his profound level of support and encouragement throughout my graduate career, and without whom this would not have been possible. Don, thank you for the discussions, the endless supply of new ideas, the vast array of opportunities, and for your advice over the years. I am truly grateful. I would also like to thank my committee members for the letters of recommendation and for all of our conversations.

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I would like to thank my family, especially my parents, without whom I would not be here today. And I would like to thank my husband, Matthew, for all of the late nights in lab, the homemade dinner attempts, the morning wake-up calls, and for the bottomless cups of coffee. More importantly, thank you for your patience and understanding when lab consumed our lives, for the sacrifices that were made to allow both of us to pursue scientific careers, and for your unconditional love and support.

# Leveraging the Reactivity of Thioesters in the Development of New Methods for Carbon–Carbon Bond Formation

**General considerations.** Synthetic organic chemistry is an extremely important and powerful component of science that enables research spanning an unusually broad and diverse portion of the scientific landscape. It has proven vital to many of the most meaningful and socially relevant scientific discoveries that have been made in the past century. Indeed, it is difficult to imagine where we would be as a society were it not for the ability of scientists to probe disease states using small molecules, or to target enzymes responsible for diseases, using synthetic organic chemistry. As a society, we are becoming increasingly reliant on our ability to manipulate molecular architecture to serve our purposes, whether it is for the synthesis of drugs to treat new or existing infectious diseases, or to aid in the development of chemical and biological sensors for a variety of purposes. Despite this, except for the most trivial reactions, synthetic organic chemistry remains exclusive to highly trained and skilled individuals in specially equipped laboratories. Clearly, this is not in keeping with an imminent greater demand for synthetic organic chemistry and the many benefits it has to offer. As such, there is a clear and compelling need to develop improved and simplified approaches to conducting synthetic chemistry, both in the context of new and existing reactions.

Carbon–carbon bond-forming reactions are the most important class of synthetic transformations practiced in the modern pharmaceutical industry and academic laboratories throughout the world. Over the years, numerous noteworthy advances have been made in the area of carbon–carbon bond formation resulting in highly effective procedures that offer considerable structural control over the products produced.[1, 2] Until the recent developments in the area of organocatalysis,[3, 4] most polar

carbon–carbon bond-forming reactions generally involved the use of metals (transition and otherwise) and, to a lesser extent, enzymes. The former typically require rather harsh conditions, such as the use of very strong amide bases, and/or include highly reactive, and/or often toxic metals, along with any number of stringent technical requirements, such as scrupulous exclusion of moisture and air from the reaction environment, along with strict low temperature regulation. At the other end of the spectrum are the enzymatic processes.[5, 6] These are generally only applied to asymmetric reactions and, while they are inherently milder and less toxic in nature, they too can be technically challenging and, in most cases, very modest in scope and applicability.

As such, most of the common and useful methods for carbon–carbon bond formation preclude the possibility of general access and instead restrict their use to trained synthetic chemists in appropriately equipped laboratories. However, even under such circumstances, it is often not possible to carry out such reactions on the large scales that are essential to the mass production of drugs. Clearly, it would be highly beneficial to overcome, or at least diminish, the technical constraints surrounding certain common approaches to carbon–carbon bond formation. This could reasonably be achieved through the development of *direct* methods for conducting reactions – those that are conducted by simply combining appropriate substrates and reagents to form the desired product without additional manipulations, such as prior enolate formation – and/or the development of reactions able to be carried out under atmospheric conditions using readily accessible, relatively innocuous and inexpensive reagents and commercial grade solvents. Furthermore, eliminating the use of certain transition metals and enzymes from the reaction milieu would also be expected to correlate with a lowered cost of production and, in the former case, a diminished environmental impact.[4, 7]

# 1. Enolate-Mediated Carbon–Carbon Bond Formation

Carbon–carbon bond-forming reactions can be categorized using simplified mechanistic criteria as either polar, free-radical, pericyclic or transition metal-mediated reactions. Polar reactions are, by far, the most pervasive, and have provided the foundation for the advancement of synthetic organic chemistry to its present state. The most useful approach to carbon–carbon bond formation via polar intermediates is the reaction of an enolate with a carbon electrophile. Enolate chemistry has been the subject of extensive study over the past several decades and is an indispensable method for carbon bond formation. Indeed, it is not unreasonable to state that enolate chemistry has provided the foundation for the advancement of synthetic organic chemistry to its present state. However, despite its usefulness and wide-spread application, enolate chemistry is inherently complex since multiple reaction pathways, in addition to the desired one, are typically possible for a given transformation. Thus, the majority of work that has gone into developing practically useful enolate reactions has focused on resolving the issues of regio- and chemoselective enolate formation and, where applicable, stereoselectivity of electrophile addition.

The problem of regioselective enolate formation arises in situations where the parent carbonyl is an unsymmetrical ketone, having protons on both the α- and α′-carbons that can be removed to give two regioisomeric enolates (see Figure 1A). A number of procedures have been devised to preferentially form one or the other regioisomeric enolate in such cases, based on the principles of kinetic and thermodynamic deprotonation. Importantly, when a carboxylate derivative serves as the enolate source, there is no issue of regioselective deprotonation (Figure 1A). This imparts great synthetic advantage, especially in acyclic systems. Furthermore, the

carboxyl moiety can serve as a platform for subsequent transformations, including conversion to a ketone, adding even greater benefit (Figure 1A). Chemoselectivity in the context of enolate reactions refers to the fact that the base used to form the enolate might also be capable of reacting with the intended electrophile in undesired ways. In the case of a simple alkylation reaction involving an alkyl halide or related electrophile, this can lead to byproduct formation via substitution and/or elimination mechanisms (see Figure 1B). When the electrophile is itself a carbonyl group and has α-protons, then it too can form an enolate, leading to various byproducts. For example, in the case of a crossed aldol addition[8] this can result in the formation of self addition products of both the aldehyde and thioester, along with the desired crossed product (see Figure 1B).

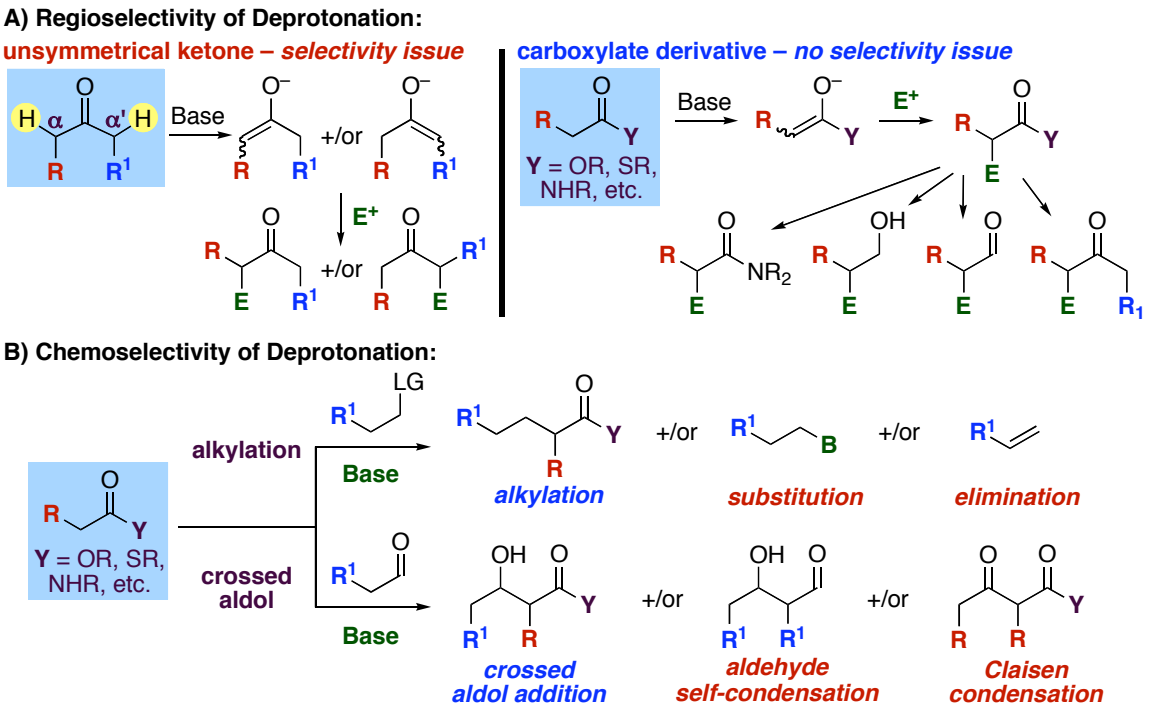


**Figure 1: Regioselectivity and Chemoselectivity Issues of Deprotonation in Selected Enolate Reactions**

The stereoselectivity of addition to an enolate is the final control issue that must be considered. Here, depending on the nature of the reaction, this problem becomes one of absolute and/or relative stereochemistry. Control over absolute stereochemistry is possible through incorporation of a chiral auxiliary into the enolate species, use of chiral metal complexes, and/or the use of chiral electrophiles. In certain cases, such as the Mukaiyama aldol reaction,[9] chiral Lewis acids can be used to both promote and induce asymmetry in the addition reaction. The issue of relative stereochemistry is primarily a concern in aldol addition reactions involving enolates formed from β-substituted acetates such as propanoate and higher carboxyl derivatives, and can often be controlled by, for example, stereoselective (*i.e.*, *E* or *Z*) enolate formation.

## *1.1 Pre-LDA Era of Enolate Formation*

Prior to the middle of the 20$^{th}$ century, strong bases (*e.g.*, LDA, LHMDS, etc.) were unavailable, so enolates were formed using hydroxide or alkoxide bases. Consequently, reactions involving enolates were conducted in a direct sense when mono-carbonyl compounds were used (Figure 2A), or relied on the use of enolate precursors that are considerably more acidic than water or alcohols (β-ketoesters, β-diesters, etc.) to enable prior enolate formation (see Figure 2B). While operationally convenient, direct reactions of mono-carbonyls were limited to systems in which regio- and chemoselective enolate formation, as well as the possibility of side reactions between, for example, the base and electrophile, were not issues. Consequently, the self-coupling reactions were possible (*i.e.*, aldol[8] and Claisen condensations[10]), as well as crossed coupling reactions where there was only a single enolizable carbonyl

compound. However, direct alkylation using, for example, two different enolizable carbonyl species was problematic (*e.g.*, crossed aldol addition).

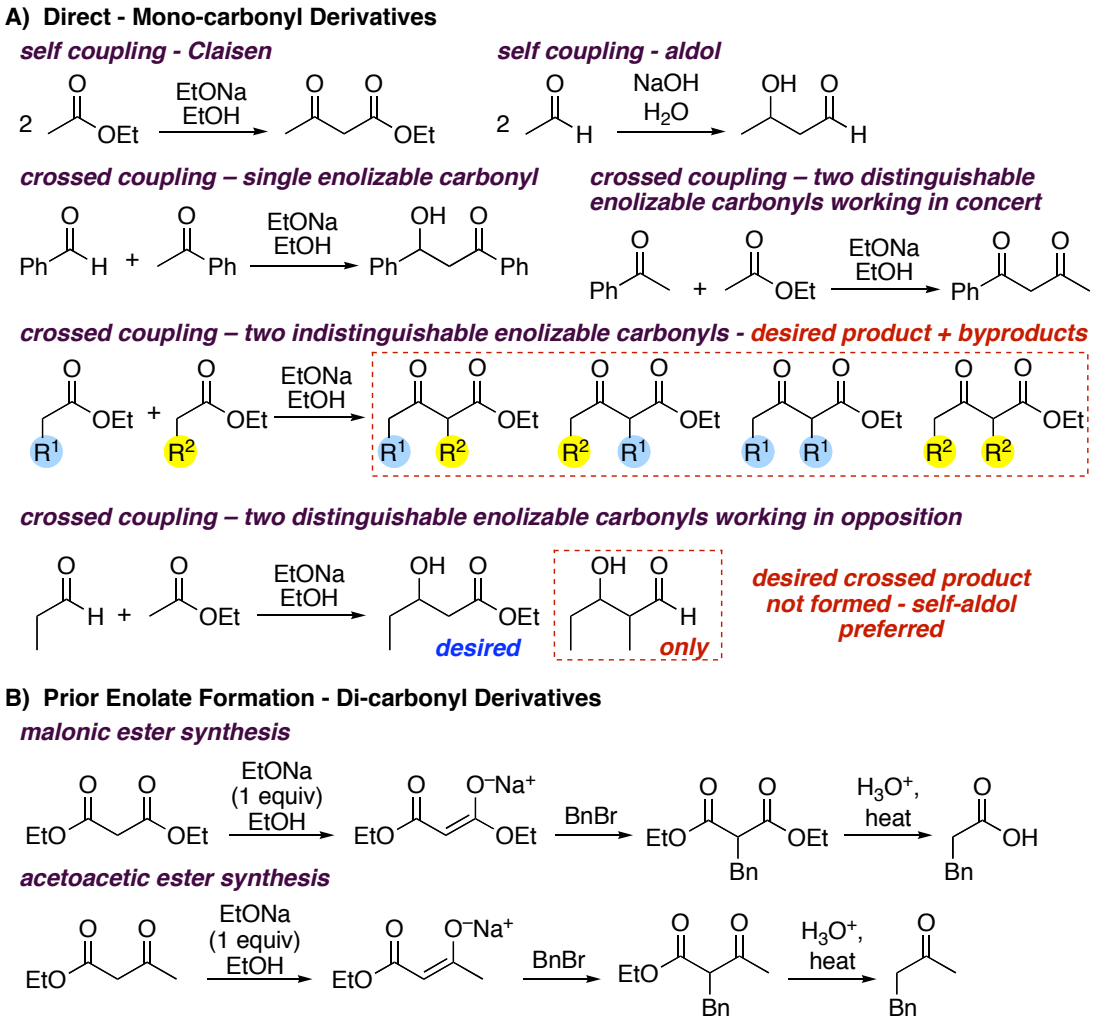


**Figure 2: Pre-LDA Methods for Enolization**

## *1.2 Prior Enolate Formation*

Much of the control that is currently possible in enolate chemistry stems from the use of preformed enolates.[8, 11] Prior enolate formation of mono-carbonyls was first

introduced by Hauser in 1950,[12] and this ushered in a new and highly prolific era of research devoted to the α-functionalization of carbonyl compounds. Hauser demonstrated the formation of the lithium enolates of ethyl acetate and *t*-butyl acetate using $LiNH_2$ in liquid ammonia, which were then treated with aldehydes and ketones, including those possessing α-protons, to furnish the corresponding β-hydroxy esters.[13-16] While highly significant as a pioneering demonstration of the utility of strong bases, the superiority of lithium dialkylamides (*e.g.*, LDA) and disilylamides (*e.g.*, LHMDS) for prior enolate formation was established soon after.[17] The bulky hydrophobic substituents of these bases impart greater solubility in common organic solvents such as $Et_2O$ and THF, while at the same time diminishing their nucleophilicity and suppressing unwanted carbonyl addition byproducts. The importance of strong bases such as LDA cannot be overstated; they have provided the basis for the advancement of enolate chemistry to its present state, and have revolutionized the field of carbon–carbon bond formation.

The basis of prior enolate formation via a strong base (*i.e.*, hard enolization) is straightforward (see Figure 3A). The enolate is first generated in the absence of the electrophile using the base and, once formed, the electrophile is added to the reaction. By conducting the reaction in a stepwise fashion, potential side reactions between the base and electrophile are avoided. For this approach to be effective, however, the enolate must be quantitatively and irreversibly formed prior to addition of the electrophile. This is commonly achieved in one of two ways. In the first, the enolate is generated from a carbonyl compound using a very strong base that ensures complete deprotonation. Alternatively, the enolate intermediate[18] is generated and then trapped as, for example, a silyl ketene acetal[19] or silyl enol ether.[20] Following isolation and purification, as needed, this masked enolate is exposed in a subsequent reaction to the electrophile under conditions that liberate the enolate in situ (*e.g.*, MeLi), thus avoiding

the unwanted side reactions. In both processes a strong base (*e.g.*, LDA) is normally used to access the preformed enolate. While these hard enolization approaches have essentially solved any selectivity issues of deprotonation, they are not without limitations. For example, these stepwise processes can be time consuming, especially if isolation and purification of the trapped intermediate is required. Also, due to the nature of the strong bases used, the processes generally require specific techniques and apparatus to ensure that all steps are conducted at low temperature and to the exclusion of air and moisture.

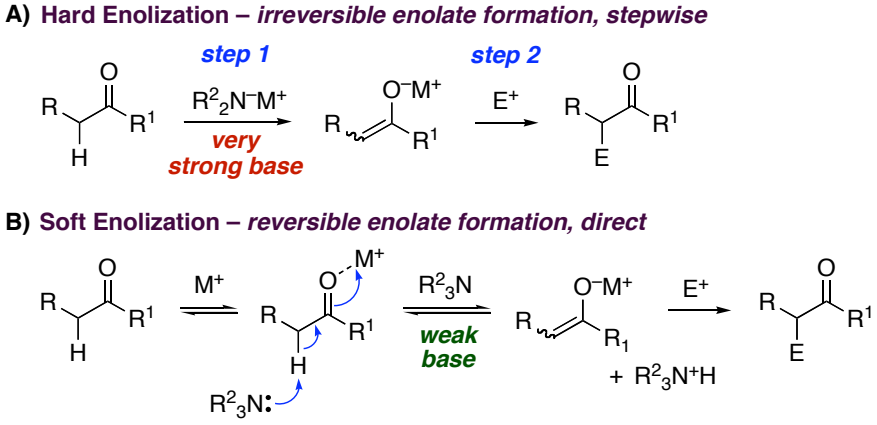


**Figure 3: Methods for Enolate Formation: Hard and Soft Enolization**

## *1.3 Soft Enolization*

An alternative to the use of strong bases for deprotonation is soft enolization (Figure 3B).[21-28] Here, rather than forcing deprotonation irreversibly using a base many orders of magnitude stronger than the resulting enolate, a relatively weak base (*e.g.*, tertiary amine) is used in combination with a Lewis-acid to effect deprotonation *reversibly*. Interaction of the Lewis-acid with the carbonyl polarizes it beyond its normal

state, making the α-protons susceptible to removal by the weak base (Figure 3B). Not only are soft enolization processes easy to carryout given their *direct* nature, but they are also inherently milder and can be conducted under much less stringent conditions (*e.g.*, open to the air, untreated solvent, rt) than are required of hard enolization.

By definition, reactions employing soft enolization are direct processes since enolization must be conducted in the presence of the electrophilic component. Consequently, the fundamental selectivity issues solved through the use of prior enolate formation re-emerge. To be of general use, such direct reactions must possess control elements to ensure regio- and chemoselective enolate formation in a manner that does not affect the electrophile. In some cases, this may be expected to require additional effort early on in the developmental process. However, once these elements are programmed into the system, they may be relied on to provide, ideally, a single product without additional input from the user in the form of, for example, stepwise manipulations. This initial investment may be well worth the effort given the high return gained through simplification of some of the key bond-forming reactions of organic synthesis, and avoidance of protecting groups in total synthesis endeavors, not to mention the potential benefits of reduced cost and environmental impact of such relatively mild and undemanding methods.

## *1.4 Using Thioesters in Soft Enolization*

We were intrigued by the possibility of using thioesters in the context of developing soft enolization methods as they have a number of advantageous properties, compared to other carboxylate derivatives (*e.g.*, oxoester, amide, etc.), that we speculated would make them particularly well-suited to such conditions. Particularly,

the $pK_a$ of the thioester α-proton has been reported to be 2 units less than that of the corresponding oxoester.[29] As will be presented herein, the enhanced acidity of thioesters over other simple carboxylate derivatives served as an advantage for the use of thioesters in the soft enolization methods developed.[24-26]

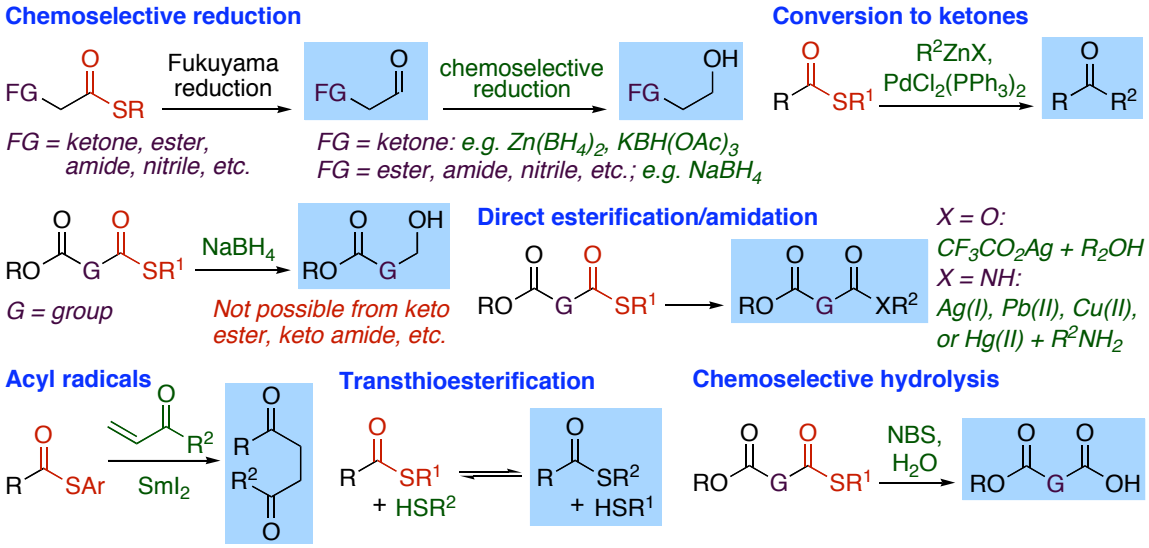


**Figure 4: Chemoselective Transformations of Thioesters**

From a practical point of view, the use of thioesters for *direct* carbon–carbon bond-forming reactions was desirable for a number of other reasons. For instance, they are readily accessible from inexpensive, commercially available thiols, or are themselves commercially available. They are also stable and easily handled. In addition, they provide numerous opportunities for subsequent synthetic manipulations under mild and selective conditions, including reduction to aldehydes or alcohols,[30-35] conversion to ketones,[31, 36, 37] conversion to acyl radical intermediates,[36] transthioesterification,[38] direct esterification/amidation,[39-41] and hydrolysis[42-44] to carboxylic acids (see Figure 4). Thus using established conditions, the organosulfur products could be readily converted into

a variety of structures for use in many different applications (*e.g.*, natural product synthesis, drug development, etc.).

## *1.5 Enolization in Nature*

In terms of developing mild synthetic methods, Nature's repertoire of reactions seemed an ideal source of inspiration given that these reactions are conducted in an aqueous environment and, typically, under aerobic conditions. Years of evolution have led to the refinement of these transformations and much can be learned from the way they are carried out. For instance, thioesters are employed in numerous biosynthetic transformations, such as aldol-based carbon–carbon bond formation. Indeed, when one examines the approaches that Nature takes to carbon–carbon bond formation, it is difficult to overstate the importance of thioesters. There is little doubt that Nature's choice to use thioesters over oxoesters for these reactions is a deliberate one and it is likely due in large part to the greater acidity of the thioester α-protons.

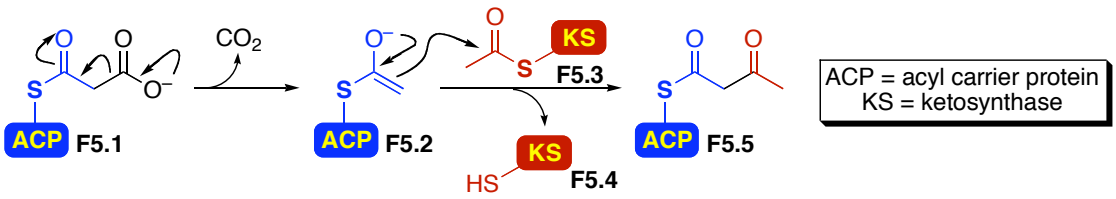


**Figure 5: Fatty Acid Biosynthesis: Nature's Approach to Prior Enolate Formation using Thioesters**

The primary carbon–carbon bond-forming reaction in the biosynthesis of polyketides and fatty acids is a decarboxylative Claisen condensation with malonic acid half thioesters (MAHTs) as ester enolate equivalents (see Figure 5).[45, 46] The acyl

participants in these chemical reactions are bound as thioesters or MAHTs to the set of enzymes used for chain extension. The starting acyl group is attached to a cysteine thiol of ketosynthase (KS, **F5.3**) and the MAHT to the terminus of the acyl carrier protein (ACP, **F5.1**).[45] Condensation extends the chain, forming a β-ketoester bound to ACP (**F5.5**).[45] Thus, Nature uses enzymatic activation of a MAHT to selectively generate a thioester enolate, or its equivalent, in the presence of another thioester, achieving a selective cross-Claisen condensation.[45, 46]

The mild and selective activation of MAHTs in Nature has inspired others to explore their use in metal-catalyzed decarboxylative aldol reactions.[46-48] While chemoselective enolate formation is achieved via decarboxylation of MAHTs in the presence of other electrophiles, the selectivity is due to the orthogonal reactivity of the two components involved. Thus, since the necessary MAHTs have to be synthesized before carrying out the intended reaction, it is not a direct process and can instead be considered as Nature's approach to prior enolate formation using thioesters.

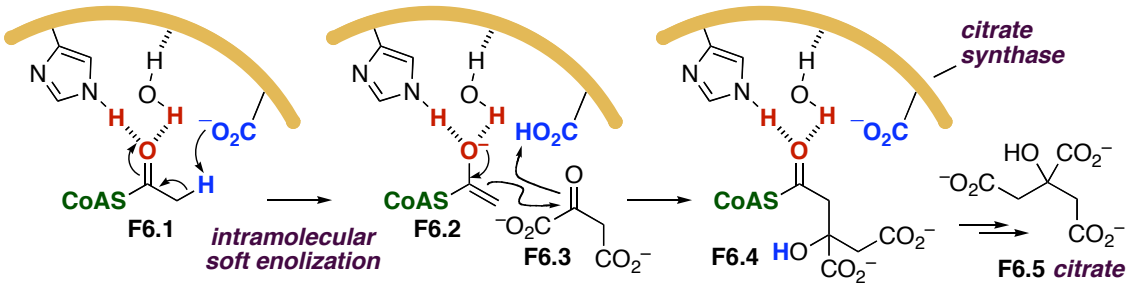


**Figure 6: Citrate Synthase: Nature's Approach to Direct Bond Formation using Thioesters**

An important example of the utility of thioesters in a *direct* biological carbon–carbon bond formation is found with the enzyme citrate synthase (CS) (Figure 6).[49-51] CS catalyzes the first reaction of the Citric Acid Cycle, and is responsible for the

condensation of acetyl coenzyme A (acetyl CoA, **F6.1**) and oxaloacetate (**F6.3**) to give citrate (**F6.5**) (see Figure 6). During catalysis acetyl CoA is situated within the active site in proximity to an imidazole group (His-274), an ordered water molecule (Wat-585), and a carboxylate group (Asp-375). His-274 and Wat-585 interact with the thioester carbonyl of acetyl-CoA via hydrogen bonding interactions, while Asp-375 serves as a base for removal of the α-proton, allowing enolization and subsequent aldol addition to occur.

The underlying factors at work in CS, with regard to the key enolization event, undoubtedly consist of a subtle balance between the proximal orientation of activating functionality to the carbonyl group of the thioester, the acidity of its α-protons, and the availability of a suitable base. The critical nature of the hydrogen bonding interactions to thioester carbonyl activation and, correspondingly the $pK_a$ of the α-protons, has been established by a theoretical study of a related enzyme, acetyl-CoA dehydrogenase.[52] In this system it was found that the hydrogen bonding interactions between the thioester carbonyl of acetyl-CoA and the proximal hydroxyl and amide groups of the enzyme contribute significantly to the overall increase (>9 pH units) in acidity of the thioester α-protons in the bound state. Thus, enolate formation in citrate synthase occurs in a direct manner via soft enolization with no prior manipulations required of the enolate species. Unlike with MAHTs, chemoselective enolization in CS is a result of enzyme specificity, not orthogonal reactivity of the starting components. The ability to mimic this thioester activating/enolization event in non-natural systems served as the basis for our development of novel approaches to organic-promoted reactions.

## *1.6 Organocatalysis*

It is difficult to overstate the importance of metal-facilitated reactions to the field of synthetic organic chemistry. These processes allow a wide array of important carbon–carbon bond-forming and other reactions to be conducted in highly controlled ways. In fact, the use of metals in organic synthesis makes possible transformations that would be impossible using organic molecules alone. Indeed, some of the most important and paradigm shifting contributions to synthetic organic chemistry in relatively recent times, such as Pd-mediated cross coupling reactions, olefin metathesis and C–H bond insertion, would not have been realized without transition metals. Despite their importance, much effort has been invested recently to develop synthetic methods that are facilitated using only organic molecules, to the exclusion of metals. Many of these procedures have been developed to the extent that they can be carried out using catalytic amounts of the organic promoter and these processes have come to be known as organocatalytic reactions.

Organocatalysis is a relatively new field within the domain of enantioselective synthesis. Between 1968 and 1997, there were only a handful of reports that used small organic molecules as catalysts for asymmetric reactions, with the Hajos-Parrish reaction[A, 4] probably being the most famous. However, these early reports were only considered as individual cases, and the field of organocatalysis had not really started to materialize until the late 1990s when individual reports by Shi,[53] Denmark,[54] and Yang[55] demonstrated that enantiomerically pure ketones could be used to promote the enantioselective epoxidation of simple alkenes. Shortly thereafter, Jacobsen[56] and

---

[A] In 1971, two independent papers – one by Zoltan Hajos and David Parrish, and the other by Rudolph Weichert, Gerhard Sauer and Ulrich Eder reported an enantioselective intramolecular aldol reaction catalyzed by proline in the synthesis of the Wieland-Miescher ketone. This was one of the first examples of organocatalysis, even though the underlying mode of activation was not fully exploited for another 30 years.

Corey[57] each demonstrated the use of hydrogen-bonding catalysis in the asymmetric Strecker reaction (see below) and Miller[58] reported the concept of minimal peptides for the enantioselective kinetic resolution of alcohols. Organocatalysis was launched, and the name coined,[59] in 2000 with the appearance of two papers each reporting a new mode of organocatalytic activation: one by Barbas[60] on enamine catalysis and the other by MacMillan[59] on iminium catalysis. Between 1998 and 2008, over 1500 manuscripts describing the use of organocatalysis were published.[4]

From a primarily practical standpoint, certain advantages can be attributed to metal-free processes. For instance, metal-free systems generally require less stringent reaction conditions (reactions can often be carried out open to the atmosphere and using commercial grade solvents without further purification), and may offer advantages of operational simplicity as well as lower cost and environmental toxicity.[4, 7] Of course, when using metals that are themselves easily manipulated and tolerant of atmospheric conditions, as well as relatively innocuous and inexpensive, these proposed benefits become less compelling. Nonetheless, the arguments are well made in the context of metals that do not meet these criteria and, in such cases, the importance of developing effective synthetic procedures able to be conducted to the exclusion of metals has a significant place in synthetic organic chemistry. It must be noted, however, that organic-promoted reactions should be considered as complementary to metal-based procedures, and vice versa, and it should not be assumed that one or the other of these approaches is *generally* better than the other; each has appropriate applications.

## 1.6.1 Hydrogen-Bonding Organocatalysis

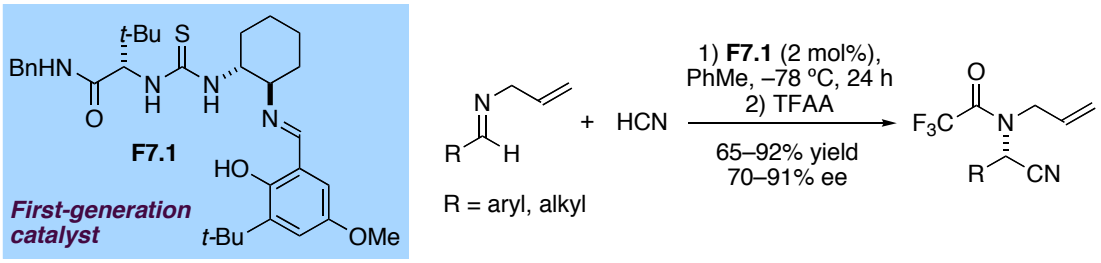


**Figure 7: Chiral Thiourea Catalysis of the Strecker Reaction as Reported by Jacobsen**

Pioneers in the field of hydrogen-bonding organocatalysis reported several catalytic asymmetric processes in the early 1980s proposing that activation of the substrate and organization of the transition state were occurring through well-defined hydrogen-bonding interactions.[4, 61] However, the potential of this new mode of activation was not fully realized until 1998 and 1999 when Jacobsen[56] (see Figure 7) and Corey[57] independently reported an asymmetric version of the Strecker reaction that used well-defined hydrogen-bonding organocatalysts to activate the imine electrophiles. Subsequently, Jacobsen showed that these thiourea catalysts were not limited in scope and could indeed be used for other synthetic reactions,[62] launching the generic use of enantioselective hydrogen-bonding organocatalysis.[4] In the past decade, more than 30 new asymmetric reactions have been developed based on this mode of activation,[4, 61] including the Strecker,[56, 63] Michael addition,[64] Mannich,[65] Aza-Henry (nitro-Mannich),[66] Acyl-Pictet-Spengler,[67] conjugate nitromethane addition,[68] allylation of acylhydrazones,[69] and conjugate amine addition reactions.[70]

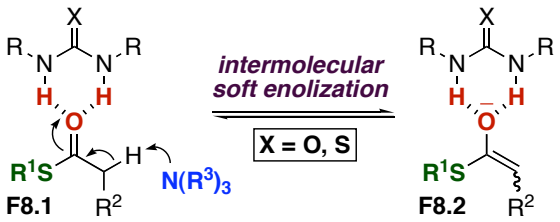


**Figure 8: Bidentate Hydrogen-Bonding Activation of a Carbonyl Compound**

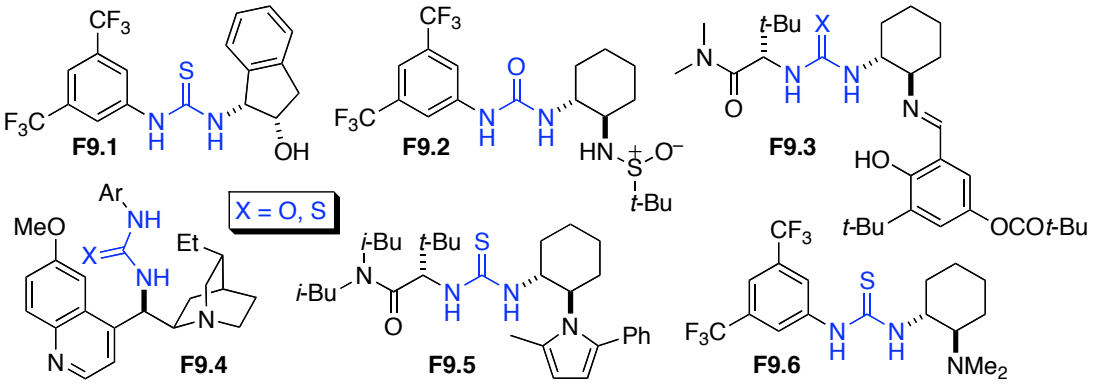


**Figure 9: Selected Examples of Chiral Thioureas and Ureas Used in Hydrogen-Bond Based Catalysis**

To this day, the most widely employed carbonyl-activating hydrogen-bonding systems are the thioureas and ureas (see Figure 9 for selected examples).[71] Since these and related compounds all share the bidentate H-bond donor site, they are all capable of carbonyl activation via hydrogen bonding through a six-membered system (**F8.1**, see Figure 8). The catalysts also all share sites for secondary interaction with the substrate adjacent to the (thio)urea moiety, such as aromatic, weakly basic or acidic, or strongly basic functionality (see Figure 9).[61] Generally, thioureas have been favored over ureas for a number of reasons. First, thioureas are more acidic ($pK_a$ thiourea = 21.0[72]; $pK_a$ urea = 26.9[72]) and are therefore better hydrogen bond donors than ureas.[73] In addition, sulfur is less electronegative than oxygen, decreasing the extent of self-association of the thiourea catalyst (interaction of the N-H group of one molecule with the carbonyl or

thiocarbonyl group of another).[73, 74] Thioureas are also more soluble in organic solvents, and are generally easier to prepare.[74]

## 1.7 Aldol Addition Reaction

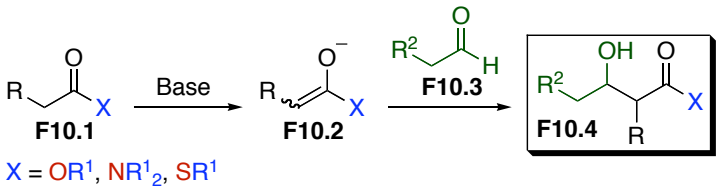


**Figure 10: Base-Mediated Aldol Addition Reaction**

The aldol addition reaction is among the most important chemical reactions known and provides access to some of the most prevalent structural motifs found in natural products and pharmaceuticals.[8] Substantial effort has gone into the development of aldol reactions using enolates derived mainly from ketones or carboxylate derivatives (Figure 10) resulting in a remarkable level of regio-, chemo- and stereochemical control.[8, 11] The most trivial method for controlling regioselectivity of enolate formation is to simply use a carboxylate derivative as the enolate source. This is also beneficial in terms of providing a mechanism for iteration, allowing access to polyketide and related structures (see Figure 11[B]).[75, 76] In such cases the β-hydroxy carboxylate product first undergoes hydroxyl protection and the derivatized carboxyl function is then reduced to an aldehyde, which serves as the electrophile in a subsequent aldol addition.

[B] The ---- lines indicate the carbon–carbon bonds formed using the aldol reaction en route to the polyketide natural products shown.

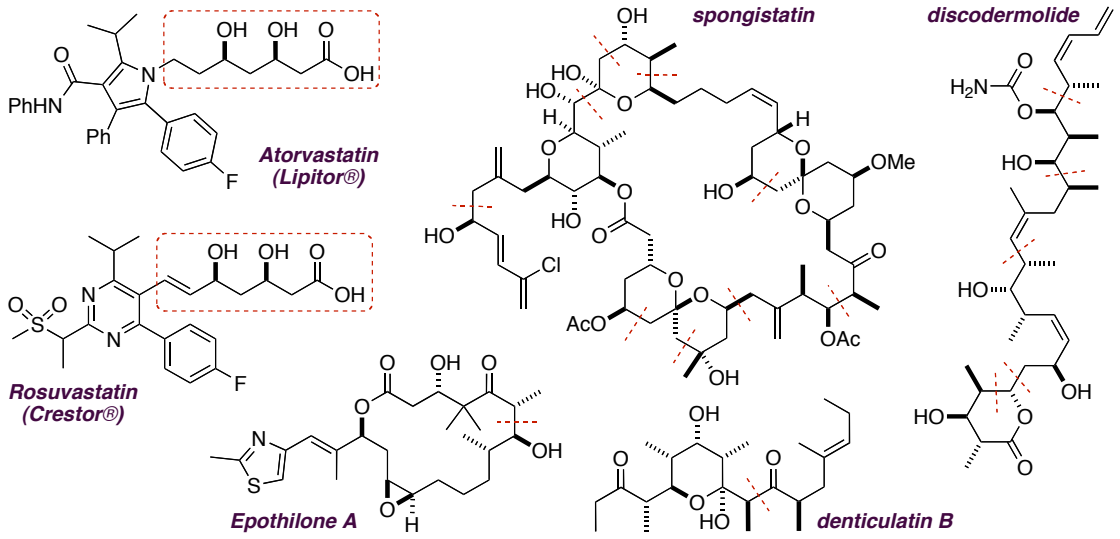


**Figure 11: Selected Examples of Polyketide Natural Products and Drugs Synthesized Using the Aldol Reaction**

Controlling chemoselectivity of deprotonation in the aldol addition is a much less trivial matter. When an aldehyde having one or more α-protons is used as the electrophile in an aldol addition reaction along with a carboxylate derivative as the intended nucleophile, it is not possible to simply add a base to the reaction mixture and obtain the desired addition product – the so called *direct* reaction. Under such conditions, the aldehyde may also form an enolate and so it too has the potential to serve as the nucleophile leading, predominantly, to self-addition byproducts. Indeed, given the significantly lower $pK_a$ of the aldehydic α-proton compared to that of the carboxylate derivative,[77] this reaction manifold would dominate. To avoid this competing reaction, the desired enolate is preformed in the absence of the aldehyde, and this is then added to allow the addition reaction to proceed.

The introduction of preformed enolate technology[8, 11] revolutionized aldol chemistry and advanced it to a level of practicality and control previously unattainable. Yet, as discussed earlier, access to preformed enolates can be a time consuming process

and requires specialized techniques and apparatus to ensure that all manipulations are conducted to the exclusion of moisture. In another approach to controlling chemoselectivity of deprotonation, a latent enolate,[18] typically a trimethylsilyl ketene acetal[19] or trimethylsilyl enol ether,[20] is preformed by trapping the enolate intermediate generated using TMSCl. This species is subsequently isolated and may be purified and is then combined in solution with the aldehyde and an appropriate activator to initiate the addition reaction.

Despite the remarkable achievements made to date in the area of aldol chemistry, there is considerable room for further improvement through the development of milder and operationally-simplified approaches to this important reaction. Indeed, this desire has spawned a renewed interest in the direct aldol reaction,[8] without reliance on preformed enolates. While only a limited number of reports have appeared,[46-48, 60, 78-95] initial investigations into these in situ enolization approaches clearly establish their potential.

## *1.8 Mannich Reaction*

The classic Mannich reaction[96-100] is a three-component amino-methylation from an amine, formaldehyde and an enolizable aldehyde or ketone (see Figure 12A). The reaction results in the formation of β-aminocarbonyl products (*i.e.*, Mannich bases, **F12.4**) which serve as important amino-containing building blocks for the synthesis of α- and β-amino acid derivatives, γ-amino alcohols, *syn* and *anti*-1,2-amino alcohols and β-lactams.[96] As such, the Mannich reaction is a very important carbon–carbon bond-forming reaction in organic chemistry and has been employed as the key step in the

synthesis of numerous alkaloid-derived natural products and pharmaceuticals (see Figure 13).[98, 100-103]

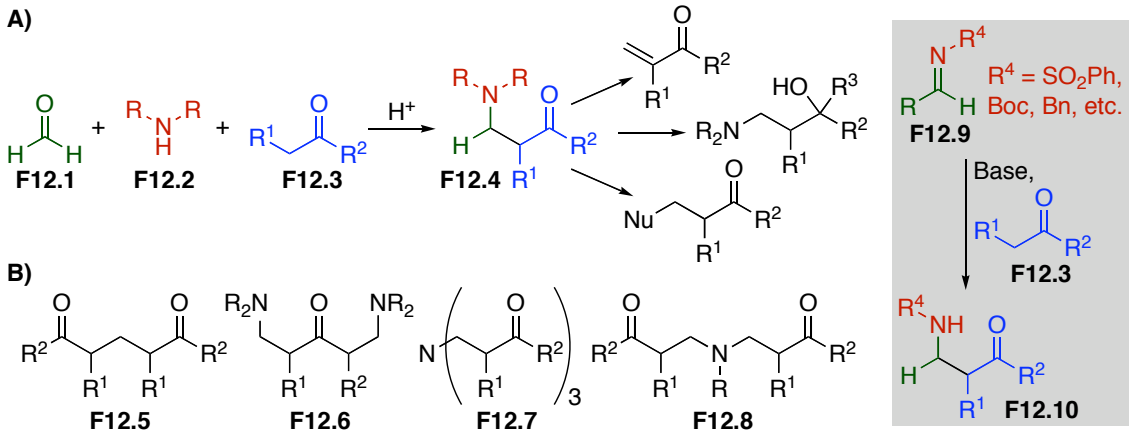


**Figure 12: A) Mannich Reaction and Subsequent Transformations B) Common Byproducts in the Direct Mannich Reaction**

While an important transformation, the direct three-component Mannich reaction suffers from long reaction times, elevated temperatures, and both regioselectivity and chemoselectivity issues leading to the formation of several byproducts (Figure 12B).[100] Specifically, the Mannich base is prone to deamination, which leads to bisketones (**F12.5**). When using ketones, a large excess of the ketone is also generally required to avoid bis-alkylation byproducts (**F12.6**).[100] In addition, ammonia and primary amines react further giving additional byproducts **F12.7** and **F12.8**, thus secondary amines are generally required. The reaction is also limited by the general need to use formaldehyde (**F12.1**) as the electrophile and either an enolizable ketone or aldehyde as the nucleophile, restricting the overall structural diversity in the products.[100] To overcome some of these selectivity limitations, preformed electrophiles (*e.g.*, imines, iminium salts, etc.) or preformed nucleophiles (*e.g.*, enolates, enol ethers, enamines, etc.) have been used.[97, 99, 100] For our studies, we focused on the Mannich

reaction of thioesters and various imines (**F12.9**) to give the analogous products **F12.10** (see Figure 12, inset).

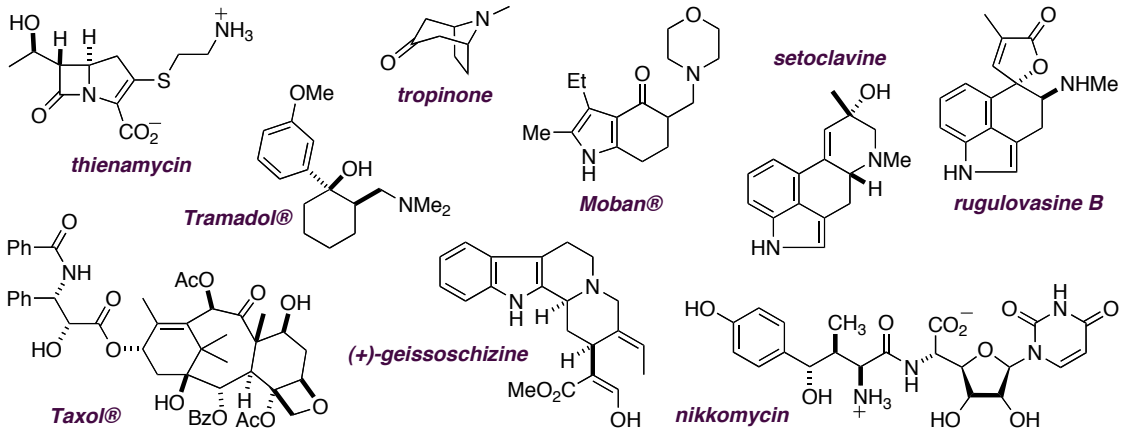


**Figure 13: Selected Examples of Natural Products and Drugs Synthesized Using the Mannich Reaction**

# 2. Results and Discussion

## *2.1 Direct Aldol Addition of Simple Thioesters Employing Soft Enolization*[C]

As indicated above, we were intrigued by the possibility of using simple thioesters in a direct aldol addition reaction employing soft enolization.[24, 25] We began this work by exploring the possibility of using simple thioesters to develop a direct aldol addition reaction by investigating the reaction between *S*-benzyl thioacetate (**T1.1**) and benzaldehyde (**T1.2**) under a variety of conditions using several different metal salts including those based on Zn, Cu, Ni and Mg (Table 1, entries 1–4). Only in the case of the $Mg^{2+}$ salt ($MgCl_2$) was the desired aldol product detected, albeit in low yield (32%) after 24 h. Nonetheless, formation of the desired product was encouraging and prompted us to screen additional $Mg^{2+}$ salts, including $MgBr_2$ and $MgI_2$ (Table 1, entries 5 and 6). Both of these reactions afforded the desired aldol product in good to excellent yield (83% and 95%, respectively), but notably, the reaction using $MgI_2$ as the metal promoter was complete within only 25 min (entry 6). In comparison, the $MgBr_2$ reaction still required up to 24 h (entry 5). Consequently, we initially settled on the use of $MgI_2$, *i*-$Pr_2NEt$ (Hünig's base) and $CH_2Cl_2$ to conduct this reaction. Coincidentally, these conditions had previously been reported to provide moderate to high yields for the direct aldol addition reaction between ketones and aromatic aldehydes, and modest yields (60–72%) with certain oxoesters and benzaldehyde.[82] Significantly, comparison of

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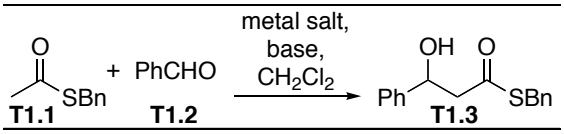
[C] Portions of this section have been reproduced in part with permission from Yost, J. M.; Zhou, G. Z.; Coltart, D. M., A facile and efficient direct aldol addition of simple thioesters. *Org. Lett.* **2006**, *8*, 1503–1506. Copyright 2006 American Chemical Society. [and] Zhou, G. Z.; Yost, J. M.; Coltart, D. M., A direct aldol addition of simple thioesters employing soft enolization. *Synthesis* **2007**, 478–482. Copyright 2007 Georg Thieme Verlag Stuttgart.

our preliminary result to this literature report supported the beneficial reactivity of thioesters in a soft enolization reaction, which was further investigated (see below).

**Table 1: Metal Screen for the Direct Aldol Addition Reaction**




| Entry | Metal Salt | Base | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $ZnCl_2$ | *i*-$Pr_2NEt$ | 24 h | N.R. |
| 2 | $Cu(OAc)_2$ | *i*-$Pr_2NEt$ | 24 h | N.R. |
| 3 | $NiBr_2$ | *i*-$Pr_2NEt$ | 24 h | N.R. |
| 4 | $MgCl_2$ | *i*-$Pr_2NEt$ | 24 h | 32 |
| 5 | $MgBr_2$ | *i*-$Pr_2NEt$ | 24 h | 83 |
| 6 | $MgI_2$ | *i*-$Pr_2NEt$ | 25 min | 95 |
| 7 | $MgI_2$ | – | 48 h | N.R. |
| 8 | – | *i*-$Pr_2NEt$ | 48 h | N.R. |

To establish the nature of this reaction and confirm the enolization event was indeed a result of soft enolization control, two control experiments were conducted. First, an experiment in which *S*-benzyl thioacetate and benzaldehyde were combined in $CH_2Cl_2$ in the presence of *i*-$Pr_2NEt$, but in the absence of any Mg salt, resulted in only detection of starting material after 2 days (Table 1, entry 7). Likewise, the addition reaction was also attempted in the presence of $MgI_2$, but in the absence of base, and again, no desired product was detected after 2 days (entry 8). These reactions are indicative of the necessity of having both the metal promoter and the mild base acting in concert to promote the desired soft enolization event. Eliminating one of these components results in no reaction occurring.

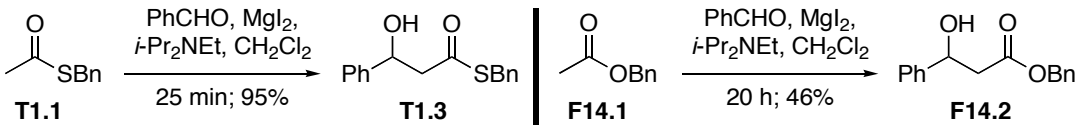



**Figure 14: $MgI_2$-Promoted Direct Aldol Reaction of Thioester T1.1 and Oxoester F14.1 with Benzaldehyde**

After determining that $MgI_2$ was an efficient metal promoter for the direct aldol addition, we investigated whether thioesters were in fact more reactive in this reaction than other simple carboxylate derivatives (*i.e.*, oxoesters and amides). To test this, we first compared the reaction times between *S*-benzyl thioacetate with its oxoester counterpart (see Figure 14). Thus, *S*-benzyl thioacetate (**T1.1**) and *O*-benzyl acetate (**F14.1**) were each combined with benzaldehyde under the established $MgI_2$ conditions as described above. The thioester, as presented in Table 1, afforded the desired aldol product in extremely high yield after only 25 min. The oxoester analogue, however, only gave 46% yield of the desired product after 20 h (see Figure 14). To further study the superior reactivity of thioesters over other simple carboxylate derivatives, a series of competition experiments was conducted. Equimolar amounts of the competing species and benzaldehyde were combined under the standard conditions and allowed to stir for 30 min (see Figure 15). In each case, the β-hydroxy thioester aldol product (**T1.3**) was isolated in excellent yield (91–96%). The competing products derived from oxoester **F14.1** and amides **F15.1** and **F15.2** were not detected, further confirming the superior reactivity of thioesters in this reaction (Figure 15).

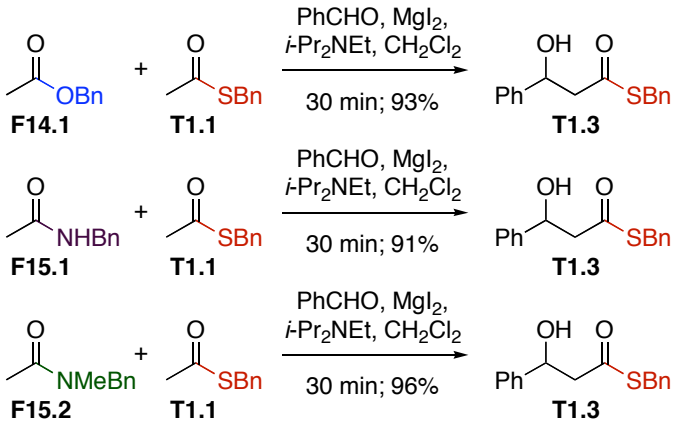
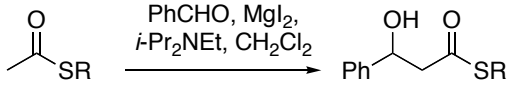



**Figure 15: Competition Experiments to Establish Superior Reactivity of Thioesters over other Carboxylate Derivatives**

We next examined the effect of the thiol component of the thioester on its reactivity (see Table 2). To do this, a range of both electron-rich and electron-poor thioesters were prepared and then subjected to the $MgI_2$ conditions as described above. Remarkably, thioesters **T2.1**, **T2.3**, and **T2.5** provided the desired aldol products in near quantitative yield after only 20 min. These initial results, however, revealed thioester **T2.7**, which contains an electron-withdrawing group, was the slowest to react, taking almost 1 h for complete conversion (entry 5). This result contradicts the initial thought that thioesters are more reactive due to the enhanced acidity of their α-protons, which one would expect an electron-withdrawing group on the thiol component of the thioester to only enhance further. As a result, it was then postulated that the beneficial reactivity observed with thioesters is not just a matter of α-proton acidity but instead a balance between α-proton acidity and the ability of the thioester carbonyl oxygen to coordinate with the metal. However, it was also suggested that a nitro group could potentially complex the metal, slowing the overall reaction, and is therefore not truly representative of an electron-poor thioester. As such, additional investigations into the

effect of the thiol component of the thioester were conducted, as described later (see Table 6).

**Table 2: Investigations of the Effect of the Thiol on Thioester Reactivity in the $MgI_2$-Promoted Direct Aldol Reaction**




| Entry | Thioester | β-Hydroxythioester | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 | AcSBn **T1.1** | Ph, OH, O, SBn **T1.3** | 25 | 95 |
| 2 | AcSPh **T2.1** | Ph, OH, O, SPh **T2.2** | 20 | 94 |
| 3 | AcS, OMe **T2.3** | Ph, OH, O, S, OMe **T2.4** | 20 | 98 |
| 4 | AcS, OMe **T2.5** | Ph, OH, O, S, OMe **T2.6** | 20 | 96 |
| 5 | AcS, $NO_2$ **T2.7** | Ph, OH, O, S, $NO_2$ **T2.8** | 60 | 92 |
| 6 | AcS, O **T2.9** | Ph, OH, O, S, O **T2.10** | 30 | 96 |

Conducted under Ar by combining 1 molar equiv of thioester, 1.2 molar equiv of benzaldehyde, and 1.2 molar equiv of $MgI_2$ in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 1.3 molar equiv of *i*-$Pr_2NEt$.

Given the extremely rapid nature of the reaction in the cases of **T2.1**, **T2.3**, and **T2.5** (Table 2, entries 2–4), a clear preference for either of the thioesters in the aldol addition could not be definitively established. However, a competition experiment

involving equimolar equivalents of **T2.1**, **T2.3**, and **T2.5** with benzaldehyde showed a slight preference for the formation of product **T2.2** over **T2.4** and **T2.6**. On this basis, and the fact that *S*-phenyl thioacetate (**T2.1**) is commercially available, **T2.1** was chosen for subsequent studies. On account of the extremely rapid nature of this reaction when using **T2.1**, it became of interest to compare the reactivity of this simple thioester to the analogous ketone. Thus, a competition experiment was conducted between *S*-phenyl thioacetate (**T2.1**) and acetophenone. Significantly, the competition experiment afforded a 3:1 mixture of the corresponding β-hydroxy ketone to the β-hydroxy thioester aldol product. Although not exclusively the thioester product, this result demonstrated that the reactivity of the simple thioester in the direct aldol reaction is indeed comparable to that of a highly reactive ketone.

Subsequent investigations explored the possibility of conducting the reaction catalytic in the metal promoter. We, like Evans, anticipated the turnover step in the catalytic process would involve ammonium ion protonation of the $Mg^{2+}$ aldolate intermediate, thus returning both the metal halide and the amine base to the reaction pool.[78] To test this, benzaldehyde was combined with each of *S*-phenyl thioacetate (**T2.1**), **T2.5**, and **T2.9** in the presence of *i*-$Pr_2NEt$ and 20 mol% of $MgI_2$. Unfortunately, due to what is presumed to be a thermodynamic preference of $MgI_2$ to interact with the β-hydroxy thioester product over the starting thioester and benzaldehyde, the reactions were unable to be performed catalytically. Even in the cases of **T2.5** and **T2.9**, where there was an additional oxygen atom in the thiol component available for coordination, albeit through a seven-membered ring, there was no indication that the $MgI_2$/β-hydroxy thioester complex exchanged with the starting thioester. Efforts to facilitate this exchange by liberating the metal via in situ silylation of the product through the addition of TMSCl, in a manner analogous to that used by Evans,[78-80] showed no indication of catalysis.

The majority of methods reported recently for effecting the direct aldol addition have employed catalytic amounts of the activating component, be it an organic molecule or a metal.[8, 46, 47, 78-80] When organic molecules or transition metals are used, it is generally desirable to use them catalytically for reasons most commonly associated with cost and toxicity of the metal. For instance, organocatalysts are not generally commercially available and therefore require a great deal of time, effort, and cost to prepare them. For transition metal-mediated processes, cost and toxicity of the metal are the major concerns, along with downstream purification requirements of the products, especially in pharmaceutical applications.

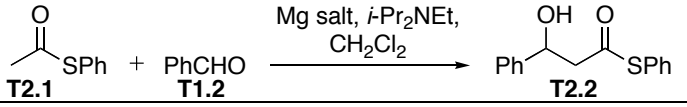
The catalytic requirement of a process is diminished, however, when one uses a promoter this is readily accessible, very inexpensive, and relatively environmentally benign. While $MgI_2$ is commercially available and non-toxic, it is also moisture sensitive so the reactions could only effectively be conducted using anhydrous conditions and an inert atmosphere. As such, given the extremely rapid nature of the reaction with *S*-phenyl thioacetate, we wondered about the possibility of substituting $MgBr_2{\cdot}OEt_2$ for $MgI_2$. $MgBr_2{\cdot}OEt_2$ is less moisture sensitive, is both commercially available and very inexpensive, and, like $MgI_2$, generates no toxic byproducts on aqueous workup. While we speculated the reaction with $MgBr_2{\cdot}OEt_2$ would be slower, we hoped that this would be more than compensated for, not only by the lower cost of the reagent, but also by allowing us to conduct the reactions open to the air using untreated,[D] reagent grade solvent.

To explore this, *S*-phenyl thioaetate (**T2.1**) was combined with benzaldehyde, *i*-$Pr_2NEt$ and $MgBr_2{\cdot}OEt_2$ in $CH_2Cl_2$ (see Table 3, entry 2). We were pleased to find that the desired aldol product was obtained in very good yield (88%) after only 20 min, albeit in

[D] Untreated refers to solvent used directly without any measures taken to dry before use.

slightly lower yield than when $MgI_2$ was used under the same conditions (94%) (entry 1). However, with this promising result in hand, we next attempted to further refine the reaction conditions by carrying out a cursory investigation of the effect of molar equivalents of each of the reactants relative to the thioester. While increasing the amount of aldehyde seemed to have no effect on either reaction yield or time, increasing the amount of $MgBr_2 \cdot OEt_2$ and *i*-$Pr_2NEt$ improved the overall yield without slowing the reaction. Ultimately, we settled on the following conditions: *S*-phenyl thioacetate (1.0 equiv), benzaldehyde (1.2 equiv), $MgBr_2 \cdot OEt_2$ (1.4 equiv), and *i*-$Pr_2NEt$ (2.0 equiv) in $CH_2Cl_2$ (concn 0.2 M). Indeed, these new conditions under anhydrous conditions (entry 3) resulted in both a highly efficient (96% yield) and extremely facile reaction, taking only 30 min to go to completion. Even more significantly, there was no change in yield or reaction time when untreated, reagent grade $CH_2Cl_2$ and atmospheric conditions were employed (Table 3, entry 4).

**Table 3: Simplifying the Direct Aldol Reaction to Employ $MgBr_2 \cdot OEt_2$ Under Atmospheric Conditions**




| Entry | Mg salt | Method | $CH_2Cl_2$ | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|---|
| 1† | $MgI_2$ | A | anhydrous | 20 | 94 |
| 2† | $MgBr_2 \cdot OEt_2$ | A | anhydrous | 20 | 88 |
| 3† | $MgBr_2 \cdot OEt_2$ | B | anhydrous | 30 | 96 |
| 4§ | $MgBr_2 \cdot OEt_2$ | B | untreated, reagent grade | 30 | 96 |

**A)** Conducted by combining 1 molar equiv of **T2.1**, 1.2 molar equiv of **T1.2**, and 1.2 molar equiv of Mg salt in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 1.3 molar equiv of *i*-$Pr_2NEt$. **B)** As in method A, except with 1.4 molar equiv of Mg salt and 2.0 molar equiv of *i*-$Pr_2NEt$. †Argon. §Atmospheric conditions.

During the initial survey of metal salts to promote the direct aldol addition of simple thioesters, a pronounced difference in reactivity was observed between the different Mg salts tested (see Table 1). Afterward, these differences were attributed, in part, to solubility issues of the Mg salt. Consequently, with our modified $MgBr_2 \cdot OEt_2$ conditions in hand, a variety of standard solvents were screened in an attempt to further refine the reaction conditions, including THF, $Et_2O$, ethyl acetate, benzene, toluene, and DMF. No improvement, however, was observed over the initial results obtained with $CH_2Cl_2$.

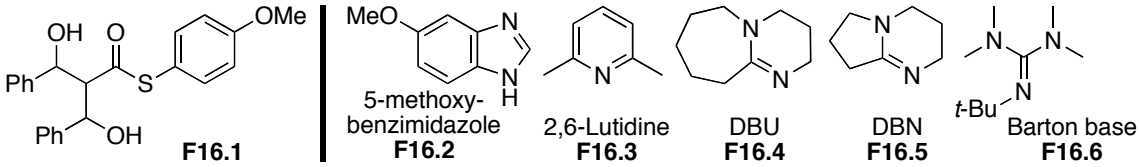
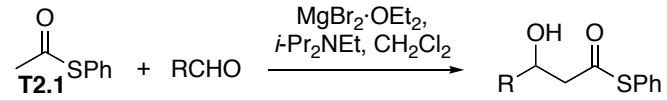
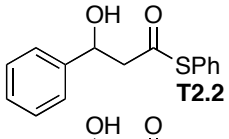
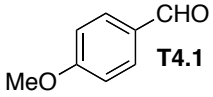
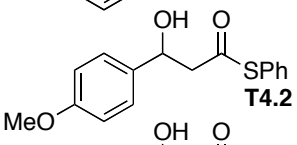
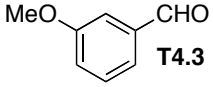
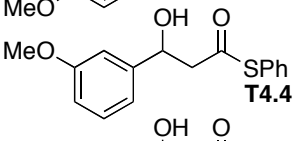
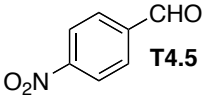
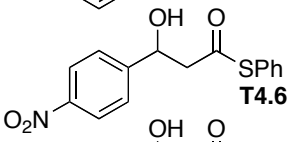
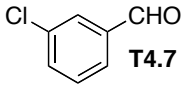
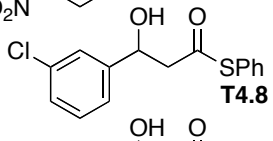
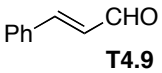
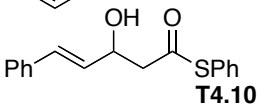
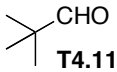
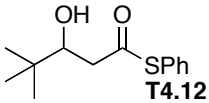
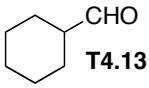
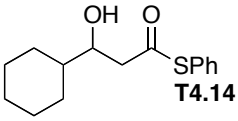



**Figure 16: Bis-alkylated Byproduct and Representative Tertiary Amine Bases Screened**

The effect of the tertiary amine base was also investigated in context of the $MgBr_2 \cdot OEt_2$-promoted reaction using, in this case, *S*-4-methoxyphenyl thioacetate (**T2.3**) and benzaldehyde in $CH_2Cl_2$. Of the bases tested, *i*-$Pr_2NEt$ was again the most effective, affording clean and high-yielding (>90%) reactions after only 30 min. Triethylamine resulted in a lower isolated yield (75%) after 1 h and the additional formation of the bis-alkylated byproduct **F16.1** with extended reaction times (see Figure 16). No desired product formation was detected after 24 h when pyridine or 5-methoxybenzimidazole (**F16.2**) were employed. 2,6-Lutidine (**F16.3**), DBU (**F16.4**), DBN (**F16.5**), and Barton base (**F16.6**) all gave <50% conversion after 1 h, with unwanted byproducts developing over extended periods of time.

**Table 4: $MgBr_2 \cdot OEt_2$-Promoted Direct Aldol Addition between *S*-Phenyl Thioacetate and Various Aldehydes using Untreated Solvent under Atmospheric Conditions**




| Entry | Aldehyde | β-Hydroxythioester | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 | PhCHO **T1.2** |  **T2.2** | 30 | 96 |
| 2 |  **T4.1** |  **T4.2** | 30 | 97 |
| 3 |  **T4.3** |  **T4.4** | 30 | 96 |
| 4 |  **T4.5** |  **T4.6** | 60 | 94 |
| 5 |  **T4.7** |  **T4.8** | 60 | 95 |
| 6 |  **T4.9** |  **T4.10** | 60 | 92 |
| 7 |  **T4.11** |  **T4.12** | 60 | 94 |
| 8[a] |  **T4.13** |  **T4.14** | 60 | 83 |

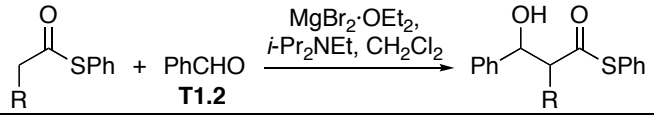
Conducted under atmospheric conditions by combining 1 molar equiv of thioester, 1.2 molar equiv of aldehyde, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent grade $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$. [a] 2.0 molar equiv thioester, relative to aldehyde.

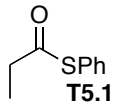
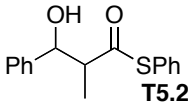
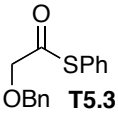
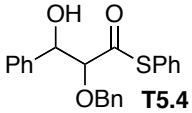
Using the refined $MgBr_2 \cdot OEt_2$-promoted atmospheric conditions, the scope of the direct aldol addition reaction was explored using various aldehydes (see Table 4). Both electron-rich and electron-poor aldehydes in addition to an α,β-unsaturated system and a bulky *t*-butyl aldehyde were screened. In all cases, reaction times were short (30–60

min) and yields were excellent (92–97%). Notably, the reaction could be carried out chemoselectively in the presence of an enolizable aldehyde, cyclohexanecarboxaldehyde (**T4.13**), with only a trace amount (<4%) of the self-addition product detected (Table 4, entry 8). In this case, best results were obtained when 2.0 molar equiv of the thioester was used, relative to the aldehyde.

The effect of α-substitution on the thioester was also examined via the direct aldol addition by combining benzaldehyde and each of *S*-phenyl thiopropionate (**T5.1**) and *S*-phenyl-α-benzyloxythioacetate (**T5.3**) under the $MgBr_2 \cdot OEt_2$-promoted atmospheric conditions (see Table 5). In both cases, the reactions proceeded in excellent yield affording the respective diastereomeric products (**T5.2** and **T5.4**, respectively) in reasonably short reaction times. Additionally, in the case of *S*-phenyl thiopropionate (**T5.1**), a 2:1 *syn*:*anti* ratio was observed.

**Table 5: $MgBr_2 \cdot OEt_2$-Promoted Direct Aldol Reaction of α-Substituted Thioesters with Benzaldehyde**




| Entry | Thioester | Aldol Product | *syn*:*anti* | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|---|
| 1 |  **T5.1** |  **T5.2** | 2:1 | 60 | 90 |
| 2 |  **T5.3** |  **T5.4** | 1:1 | 30 | 97 |

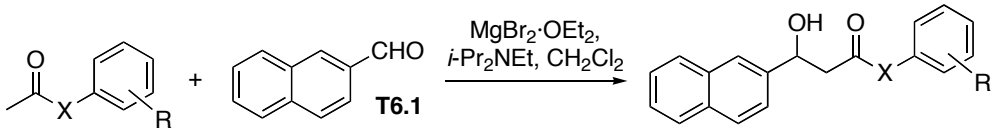
Conducted under atmospheric conditions by combining 1 molar equiv of thioester, 1.2 molar equiv of benzaldehyde, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent grade $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.

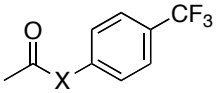
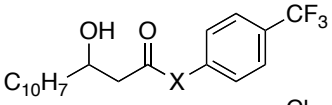
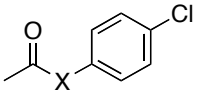
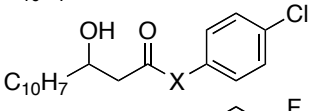
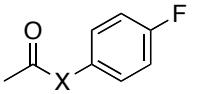
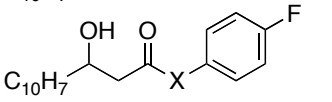
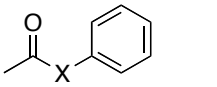
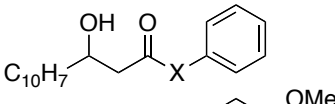
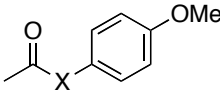
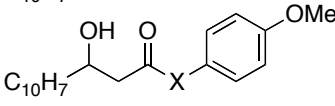
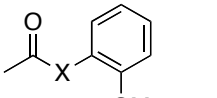
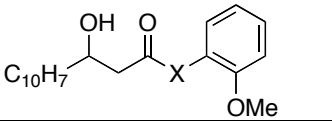
We also probed the issue of reversibility of the $MgBr_2 \cdot OEt_2$-promoted aldol addition reaction. Thus, aldol product **T2.2** was combined with $MgBr_2 \cdot OEt_2$ (1.4 molar equiv), *i*-$Pr_2NEt$ (2.0 molar equiv) and *S*-4-methoxyphenyl thioester **T2.3** (1 molar equiv). A 1:1 mixture of aldol products **T2.2** to **T2.4** was obtained from this experiment, suggesting that the addition process is in fact reversible under these conditions. The corresponding experiment in which *S*-phenyl thioester **T2.1** was added to a mixture containing aldol product **T2.4**, $MgBr_2 \cdot OEt_2$ and *i*-$Pr_2NEt$ was also conducted and afforded the analogous result. These results indicate that, to develop an asymmetric variant of this reaction, it would be necessary to trap the product in a manner similar to that reported by Evans.[78-80] Accordingly, various trimethylsilyl halides were screened, including TMSCl, TMSBr, TMSI, and TMSOTf in the $MgBr_2 \cdot OEt_2$-mediated reaction between *S*-phenyl thioacetate (**T2.1**) and benzaldehyde. Indeed, in the presence of TMSBr and a catalytic amount (20 mol%) of $MgBr_2 \cdot OEt_2$, we were able to trap the desired β-hydroxy thioester in good isolated yield (73%) after 16 h.

Finally, the effect of the thiol component of the thioester on reactivity and comparison to the corresponding oxoesters was reexamined using $MgBr_2 \cdot OEt_2$ (Table 6). Previous experiments had suggested that electron-withdrawing containing thioesters reacted slower than electron-donating ones (see Table 2, entry 5), thus contradicting beliefs that thioesters are more reactive than oxoesters due to the enhanced acidity of their α-protons. As a result, additional electron-withdrawing containing thioesters (*i.e.*, F, Cl, and $CF_3$) were prepared and tested using $MgBr_2 \cdot OEt_2$, and compared directly against the analogous oxoesters (Table 6). Indeed, data from these studies showed that the rate of reaction increases with the electron withdrawing ability of the thiol and, therefore, thioester acidity. Remarkably, the reaction with 4-trifluoromethylphenyl thioester **T6.2** was complete after only 3 min (see Table 6, entry 1). Furthermore, all

thioesters outperformed the corresponding oxoesters, reaffirming that, as hypothesized, they are extremely well-suited to soft enolization.

**Table 6: Reevaluation of the Effect of the Thiol on Reactivity and Comparison to the Corresponding Oxoesters using $MgBr_2 \cdot OEt_2$**




| Entry | Oxo/Thiolate | | Aldol Product | | X | Time (min) | Conversion (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **T6.2** |  | **T6.3** | **S** | 3 | > 95 |
| 2 | | **T6.4** | | **T6.5** | **O** | 180 | > 50 |
| 3 |  | **T6.6** |  | **T6.7** | **S** | 15 | > 95 |
| 4 | | **T6.8** | | **T6.9** | **O** | 180 | > 50 |
| 5 |  | **T6.10** |  | **T6.11** | **S** | 10 | > 95 |
| 6 | | **T6.12** | | **T6.13** | **O** | 180 | > 50 |
| 7 |  | **T2.1** |  | **T6.14** | **S** | 25 | > 95 |
| 8 | | **T6.15** | | **T6.16** | **O** | 180 | < 50 |
| 9 |  | **T2.3** |  | **T6.17** | **S** | 25 | > 95 |
| 10 | | **T6.18** | | **T6.19** | **O** | 180 | < 50 |
| 11 |  | **T2.5** |  | **T6.20** | **S** | 45 | > 95 |
| 12 | | **T6.21** | | **T6.22** | **O** | 180 | < 50 |

Conducted under atmospheric conditions by combining 1 molar equiv of 2-naphthaldehyde, 1.2 molar equiv of (thio)oxoester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent grade $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$. Reactions were monitored by TLC.

In summary, a mild and efficient direct aldol reaction using simple thioesters was developed. The reaction is conducted using inexpensive $MgBr_2 \cdot OEt_2$ in untreated, reagent grade solvent under atmospheric conditions, and the superior reactivity of thioesters over oxoesters in this reaction was established.

## 2.2 Soft Enolization of Thioesters: Direct Mannich Addition Reaction[E]

Having established the ability to conduct the direct aldol addition reaction under soft enolization conditions to afford the desired β-hydroxy carbonyl compounds, we next focused on the possibility of extending our established soft enolization conditions[21-23] to facilitate a direct Mannich addition reaction.[26] The Mannich addition reaction provides a convenient approach to the synthesis of β-amino acid derivatives, which are extremely important compounds to both organic and medicinal chemistry.[96-100, 104, 105]

We first set out to establish that our soft enolization conditions could indeed be used to promote the direct Mannich addition reaction. This was carried out by screening various imines by combining them with commercially available *S*-phenyl thioacetate (**T2.1**) in the presence of $MgBr_2 \cdot OEt_2$ and *i*-$Pr_2NEt$ in $CH_2Cl_2$ (see Figure 17). Of the three imines tested, only the sulfonylimine (**F17.1**) reacted cleanly and with acceptable yield within a very short amount of time (15 min). The Boc-derived imine (**F17.3**) reacted to only a very small extent, affording only 21% of the desired Mannich product after an extended period of time (3 h). Conversely, no Mannich addition product was detected between the benzyl-derived imine (**F17.5**) and *S*-phenyl thioacetate. Instead, *N*-benzylamine, benzaldehyde and starting thioester were detected following acidic workup.

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[E] Portions of this section have been reproduced in part with permission from Yost, J. M.; Garnsey, M. R.; Kohler, M. C.; Coltart, D. M., Direct carbon–carbon bond formation via soft enolization of thioesters: an operationally simple Mannich addition reaction. *Synthesis* **2009**, 56–58. Copyright 2007 Georg Thieme Verlag Stuttgart.

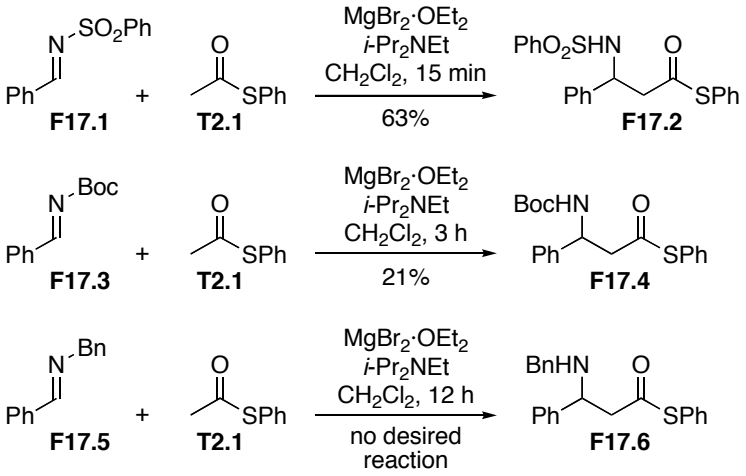
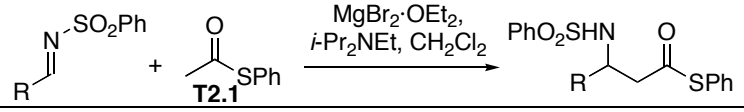
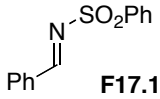
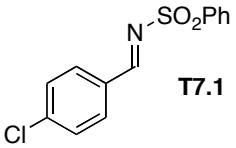
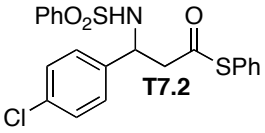
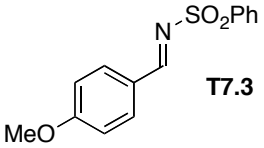
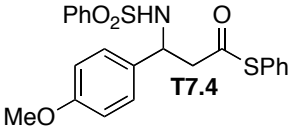
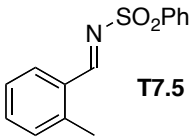
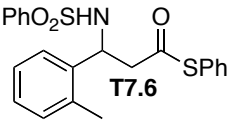
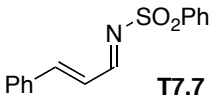
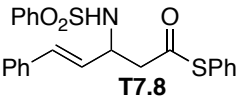



**Figure 17: Model Studies of the $MgBr_2 \cdot OEt_2$-Promoted Mannich Addition Employing Soft Enolization**

Having established the viability of the desired transformation, we next investigated the scope of the Mannich reaction with various sulfonylimines and *S*-phenyl thioacetate (see Table 7). Both electron-rich and electron-poor sulfonylimines in addition to an α,β-unsaturated system were represented. In general, the reactions proceeded in moderate to good yields (57–74%) after relatively short reaction times (<2 h). In addition, a small amount (up to ~10%) of presumably the corresponding β-lactam was detected, and increased with extended reaction times. As such, the reaction times were limited (typically 15–60 min), which may have resulted in lower isolated yields of the desired Mannich product. Modified reaction conditions to potentially suppress the presumed byproduct formation were not investigated.

**Table 7: Scope of the $MgBr_2 \cdot OEt_2$-Promoted Thioester Mannich Addition Reaction Using *S*-Phenyl Thioacetate**




| Entry | Sulfonylimine (R) | Product | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  **F17.1** |  **F17.2** | 15 | 63 |
| 2 |  **T7.1** |  **T7.2** | 30 | 67 |
| 3 |  **T7.3** |  **T7.4** | 60 | 74 |
| 4 |  **T7.5** |  **T7.6** | 120 | 73 |
| 5 |  **T7.7** |  **T7.8** | 30 | 57 |

Conducted under Ar by combining 1 molar equiv of sulfonylimine, 1.2 molar equiv of *S*-phenyl thioacetate, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.

Instead, we turned our attention to the issue of diastereoselectivity using a propionate-derived thioester in the Mannich addition reaction. Thus, *N*-benzylidenebenzenesulfonamide (**F17.1**) was combined with *S*-phenyl thiopropionate (**T2.1**) under the $MgBr_2 \cdot OEt_2$-promoted soft enolization conditions described above (see Table 8, entry 1). While the reaction proceeded rapidly and with very good conversion (92%), no appreciable *syn*:*anti* diastereoselectivity was displayed. As a result, in an attempt to improve the diastereoselectivity, a variety of propionate-derived thioesters were prepared and examined, each of which differed in the steric bulk of the thiol

component.[106, 107] Using a standard open transition state model, it was predicted that as the steric bulk of the thiol component of the thioester increased (R*), greater developing steric strain in the *E*-(*O*)-enolate (**F18.5**) would lead the system to favor formation of the *Z*-(*O*)-enolate (**F18.2**). Reaction with the sulfonylimine via the lower-energy transition state (**F18.3**) would result, then, in greater *syn* selectivity (→ **F18.4**) (see Figure 18).

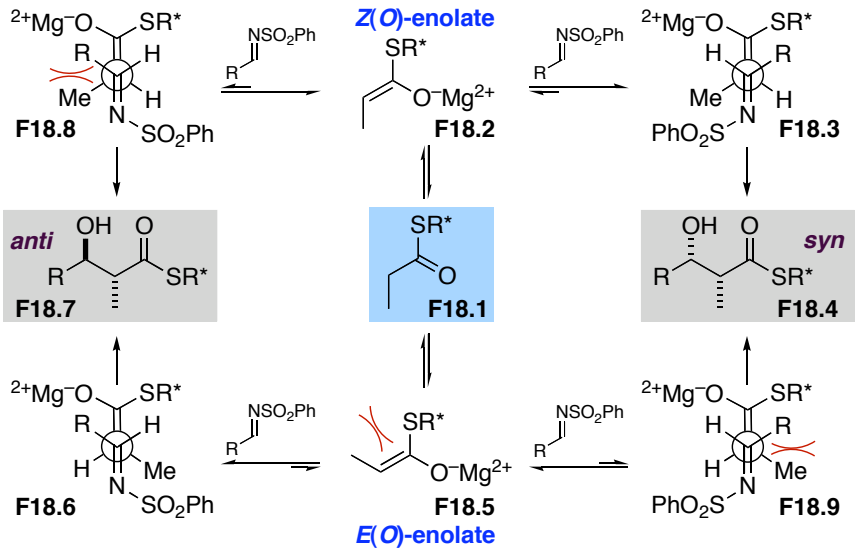
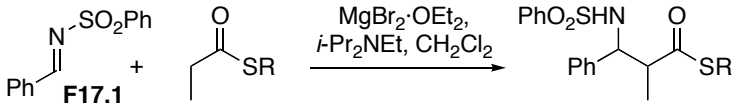
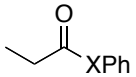
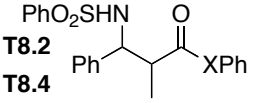
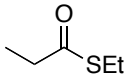
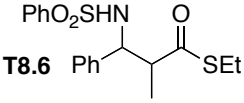
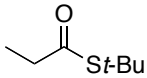
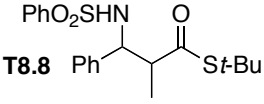
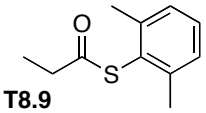
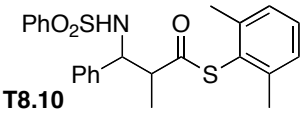
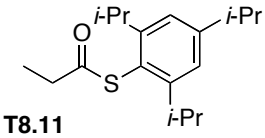
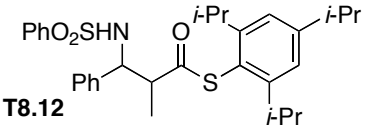



**Figure 18: Stereochemical Model for the $MgBr_2 \cdot OEt_2$-Promoted Mannich Addition Reaction**

**Table 8: Effect of the Thioester on Diastereoselectivity in the $MgBr_2 \cdot OEt_2$-Promoted Mannich Addition Reaction**



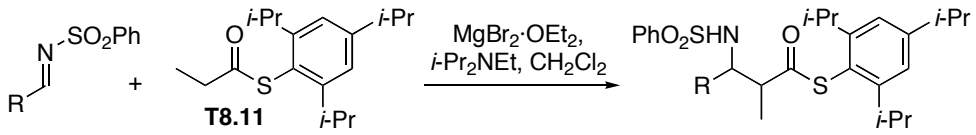

| Entry | Thioester (R) | Product | | *syn*:*anti* | Time (h) | Conversion (%) |
|---|---|---|---|---|---|---|
| 1 | **T8.1**  | **T8.2**  | X = S | 1.1:1 | 2 | 92 |
| 2 | **T8.3** | **T8.4** | X = O | 1.2:1[a] | 24 | 56 |
| 3 | **T8.5**  | **T8.6**  | | 1.1:1 | 3 | 70 |
| 4 | **T8.7**  | **T8.8**  | | 2.2:1 | 3 | 74 |
| 5 |  **T8.9** |  **T8.10** | | 3.1:1 | 6 | 78 |
| 6 |  **T8.11** |  **T8.12** | | 5.2:1 | 6 | 62 |

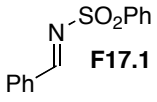
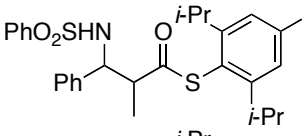
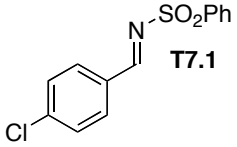
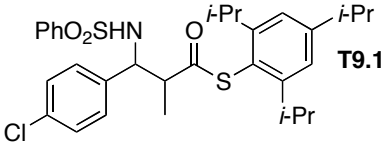
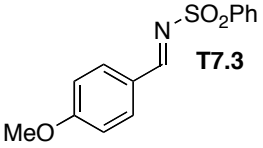
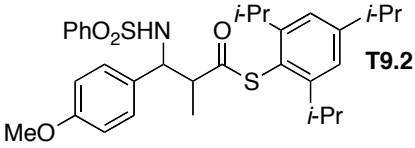
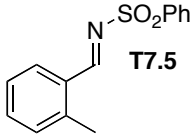
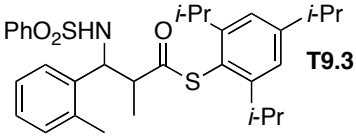
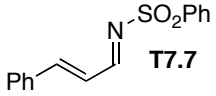
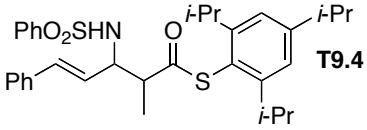
Conducted under Ar by combining 1 molar equiv of *N*-benzylidenebenzenesulfonamide, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$. [a] *syn* and *anti* assignment not determined.

As expected, the *S*-ethyl thioester **T8.5** reacted in an analogous manner to the *S*-phenyl system (**T8.1**), failing to react diastereoselectively (Table 8, entry 3). However, as one increased the bulk of the thiol component, diastereoselectivities generally improved in favor of the *syn* diastereomer. The *S*-*tert*-butyl species **T8.7** led to a 2.2:1 *syn*:*anti* ratio (entry 4) and an even greater amount of the *syn* diastereomer was produced when bulkier thioesters (**T8.9** and **T8.11**) were used (entries 5 and 6). The bulkiest of the thioesters examined, 2,4,6-triisopropylphenyl thioester (**T8.11**), afforded the most pronounced *syn*:*anti* ratio observed of 5.2:1 (Table 8, entry 6). Additionally, the

reactivity of *S*-phenyl thiopropionate (**T8.1**) was compared with the corresponding oxoester, *O*-phenyl propionate (**T8.3**) (Table 8, entries 1 and 2). The oxoester analogue, however, only gave 56% conversion after 24 h, demonstrating the superior reactivity of thioesters in this transformation.

**Table 9: Scope of the $MgBr_2 \cdot OEt_2$-Promoted Thioester Mannich Addition Reaction Using 2,4,6-Triisopropylphenyl Thioester T8.11**




| Entry | Sulfonylimine (R) | Product | *syn*:*anti* | Time (h) | Conversion (%) |
|---|---|---|---|---|---|
| 1 |  **F17.1** |  **T8.12** | 5.3:1 | 12 | 73 |
| 2 |  **T7.1** |  **T9.1** | 2.6:1 | 12 | 80 |
| 3 |  **T7.3** |  **T9.2** | 4.6:1 | 12 | 66 |
| 4 |  **T7.5** |  **T9.3** | 2.4:1 | 12 | 80 |
| 5 |  **T7.7** |  **T9.4** | 2.1:1 | 12 | 61 |

Conducted under Ar by combining 1 molar equiv of sulfonylimine, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.

With the bulky isopropyl propionate-derived thioester (**T8.11**) in hand affording promising diastereoselectivities, we next investigated the scope of the Mannich reaction

with each of the sulfonylimines used previously (see Table 9). Due to the inherent bulky nature of the 2,4,6-triisopropylphenyl thioester being used, longer reaction times were needed and, as such, the reactions were allowed to stir at rt for 12 h without noticeable byproduct formation. In general, good to very good conversions were obtained (61–80%), with moderate to good *syn*:*anti* ratios ranging from 2.1:1 to 5.3:1 (see Table 9).

The relative stereochemistry of the Mannich product was confirmed by obtaining an X-ray crystal structure of the major diastereomer of **T8.12**, which was determined to have the *syn* configuration (see Figure 19). Assignment of the *syn* and *anti* diastereomers of **T9.1**–**T9.3** was made by comparison of their $^{1}$H NMR spectra to that of **T8.12** (see experimental section for details).

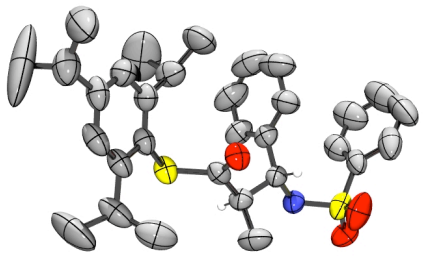


**Figure 19: Crystal structure of Mannich Product T8.12 Showing the Relative *syn* Configuration**

In summary, we developed a simple, direct Mannich addition reaction based on $MgBr_2 \cdot OEt_2$-promoted soft enolization of thioesters. The reaction proceeds readily with a range of sulfonylimines and, in the case of 2,4,6-triisopropyphenyl thiopropionate (**T8.11**), gave moderate to good diastereoselectivity in favor of the *syn* isomer.

## 2.3 Stereoselective Aldol Addition of α-Halogenated Thioesters Employing Soft Enolization

As described, we have developed a $MgBr_2 \cdot OEt_2$-promoted direct aldol addition of simple thioesters via soft enolization and showed it to be a mild, simple, and efficient method. Notably, we demonstrated that we could chemoselectively generate thioester enolates using a bulky amine base in the presence of an aldehyde having a single α-proton, giving the aldol products in high yield with only trace aldehyde self-condensation (see Table 4, entry 8). Nonetheless, obtaining the aldol addition product in the presence of an aldehyde containing two α-protons remained problematic. Instead, the aldehyde self-condensation products were isolated. To circumvent this chemoselectivity issue, we reasoned that by increasing the acidity of the thioester α-proton by adding a useful electron-withdrawing substituent on the α-carbon, such as a halogen, we could potentially control the reaction to favor the formation of the crossed aldol addition over the aldehyde self-condensation product.

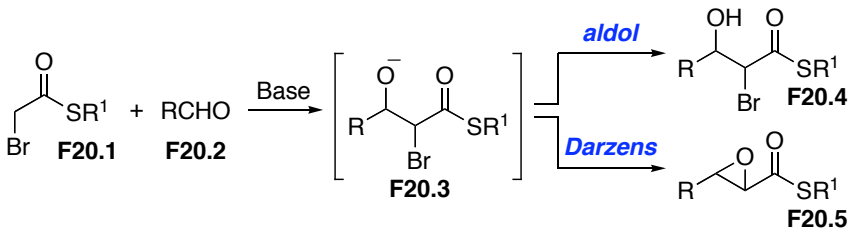



**Figure 20: Aldol Addition and Darzens Condensation of α-Halogenated Thioesters**

A similar reaction, the Darzens condensation, combines an α-halogenated carbonyl compound and an aldehyde or ketone which undergoes an aldol addition reaction to give intermediate **F20.3** followed by an intramolecular cyclization to afford

α,β-epoxy carbonyl compound **F20.5** (Figure 20). Both the aldol intermediate and the Darzens product are versatile synthetic intermediates and can be readily converted into a wide variety of polyfunctionalized compounds.

In our earlier attempts to render the $MgI_2$-promoted aldol addition reaction catalytic in the metal, it was discovered that, presumably, due to the tight coordination of the $Mg^{2+}$ aldolate intermediate, ammonium ion protonation to turn over the metal and base does not occur.[24, 25] Thus, we speculated about the possibility of using our soft enolization conditions to control the reaction between an α-halogenated thioester and an aldehyde to afford the aldol addition product (**F20.4**) exclusively without subsequent conversion to the Darzens epoxide (**F20.5**). This would potentially grant access to a *direct* reaction using highly acidic thioesters that could undergo chemoselective deprotonation in the presence of aldehydes possessing two α-protons.

To explore the possibility of using α-halogenated thioesters under our soft enolization conditions to afford aldol addition products, we first investigated the reaction of *S*-phenyl α-bromothioacetate (**F21.1**) with 2-naphthaldehyde (**T6.1**) in the presence of $MgBr_2{\cdot}OEt_2$ and *i*-$Pr_2NEt$ in $CH_2Cl_2$ (see Figure 21). Indeed, combining an α-bromo thioester and an aldehyde under our direct aldol conditions afforded the α-bromo-β-hydroxy thioester (**F21.2**) almost quantitatively in a very short amount of time (30 min). Significantly, competing Darzen-like epoxide formation was not detected, likely due to the stable $Mg^{2+}$ aldolate intermediate.

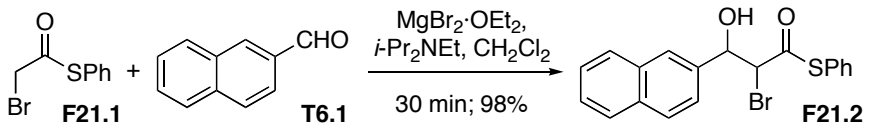
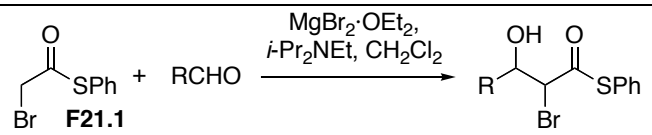
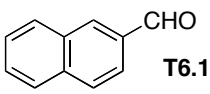
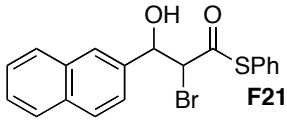
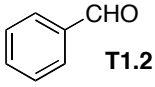
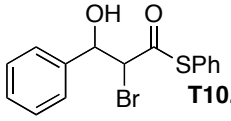
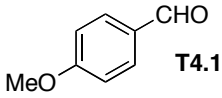
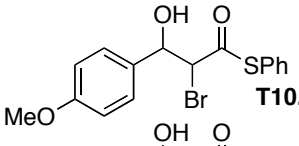
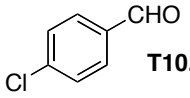
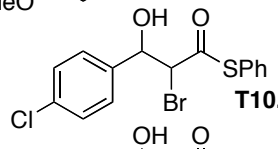
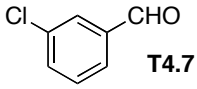
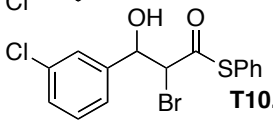
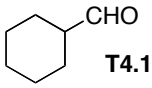
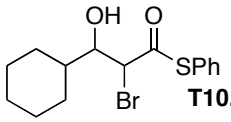
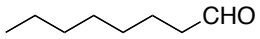
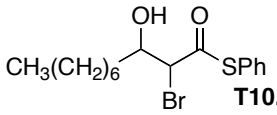



**Figure 21: $MgBr_2{\cdot}OEt_2$-Promoted Direct Aldol Reaction of *S*-Phenyl α-Bromothioacetate with 2-Naphthaldehyde**

**Table 10: Scope of the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction Using *S*-Phenyl α-Bromothioacetate**



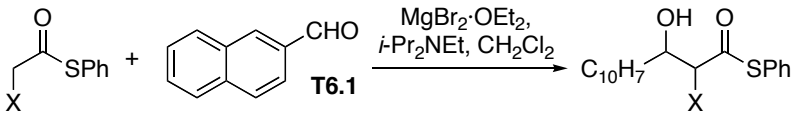

| Entry | Aldehyde (R) | Product | Time (min) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  **T6.1** |  **F21.2** | 30 | 98 |
| 2 |  **T1.2** |  **T10.1** | 30 | 89 |
| 3 |  **T4.1** |  **T10.2** | 30 | 96 |
| 4 |  **T10.3** |  **T10.4** | 60 | 94 |
| 5 |  **T4.7** |  **T10.5** | 60 | 91 |
| 6 |  **T4.13** |  **T10.6** | 60 | 96 |
| 7 |  **T10.7** |  **T10.8** | 60 | 81 |

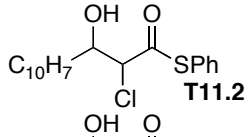
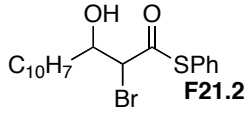
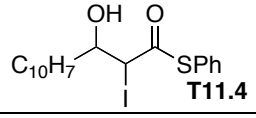
Conducted under atmospheric conditions by combining 1 molar equiv of aldehyde, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent grade $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.

Having established the ability to carry out the aldol addition reaction using α-halogenated thioesters, we next explored the scope of the aldol reaction with various aldehydes and *S*-phenyl α-bromothioacetate (**F21.1**). To test our hypothesis that increasing the acidity with the addition of a halogen would shift the reaction in favor of the crossed aldol addition over competing aldehyde self-condensation, two aliphatic

aldehydes containing acidic α-protons were screened in addition to the standard electron-rich and electron-poor aromatic aldehydes (see Table 10). In all cases, the reactions proceeded in good to excellent yields (81–98%) after short reaction times (< 1 h). Significantly, the reaction was tolerant of aldehydes possessing both one and two α-protons (entries 6–7) without competing aldehyde self-condensation.

**Table 11: Effect of the Halogen on Rate in the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction**




| Entry | Thioester (X) | Product | Time (min) | Conversion (%) |
|---|---|---|---|---|
| 1 | Cl **T11.1** |  **T11.2** | 5 | 95 |
| 2 | Br **F21.1** |  **F21.2** | 5 | 90 |
| 3 | I **T11.3** |  **T11.4** | 5 | 85 |

Conducted under atmospheric conditions by combining 1 molar equiv of 2-naphthaldehyde, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent grade $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.

A cursory investigation of the effect of the halogen on the rate of the reaction was conducted. Thus, the α-chloro, α-bromo, and α-iodo thioesters were prepared and then each combined with 2-naphthaldehyde in the presence of $MgBr_2 \cdot OEt_2$ and *i*-$Pr_2NEt$ in $CH_2Cl_2$ (see Table 11). The reactions were stopped after 5 min. Remarkably, after only 5 min, all three of the reactions showed ≥85% conversion. However, as anticipated, based on the relative electronegativities of the halogens and corresponding α-proton acidities

of the thioesters, the most acidic α-chloro thioester (**T11.1**) provided the aldol product in the highest conversion, nearly quantitatively, after only 5 min. Given the extremely rapid nature of this reaction, α-chloro substituted-thioesters were employed in subsequent studies.

With the aldol addition reaction proceeding nearly quantitatively after only 5 min, we speculated whether the reaction was proceeding under soft enolization control and, specifically, whether the enolization event required the presence of a metal promoter. As such, the negative control experiment excluding $MgBr_2 \cdot OEt_2$ from the reaction was conducted with both α-chloro thioester **T11.1** and α-bromo thioester **F21.1** (Figure 22). Each of the thioesters were combined with 2-naphthaldehyde (**T6.1**) and *i*-$Pr_2NEt$ in $CH_2Cl_2$ and allowed to stir at ambient temperature for 72 h. In the absence of $MgBr_2 \cdot OEt_2$, both reactions failed to react to any appreciable extent. Only the more acidic α-chloro thioester afforded a trace amount (<5%) of the aldol product (**T11.2**) after 72 h, while the α-bromo thioester (**F21.1**) failed to react altogether (Figure 22).

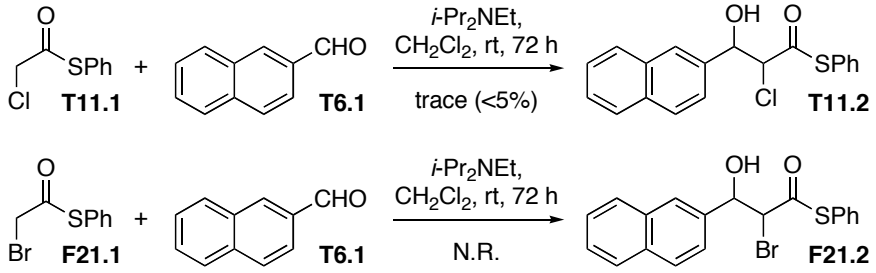



**Figure 22: Negative Control Experiments for the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition using α-Halogenated Thioesters**

We next explored the issue of diastereoselectivity in an attempt to develop a stereoselective variant of the aldol addition reaction using α-halogenated thioesters. To render the reaction diastereoselective, an analogous approach to the $MgBr_2 \cdot OEt_2$-

promoted Mannich addition reaction was applied.[26, 106, 107] Thus, using standard models, it was predicted that as the steric bulk of the thiol component of the thioester increased (R*), greater developing steric strain in the *E*-(*O*)-enolate (**F25.5**) would lead the system to favor formation of the *Z*-(*O*)-enolate (**F23.2**). Reaction, then, with the aldehyde via the lower-energy Zimmerman-Traxler transition state (**F23.3**) would result in greater *syn* selectivity (→ **F23.4**) (see Figure 23).

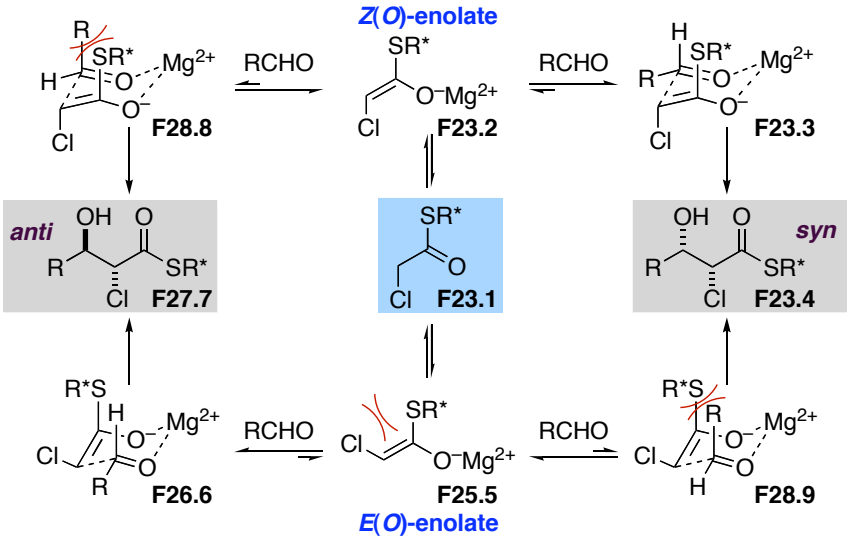



**Figure 23: Stereochemical Model for the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction using α-Halogenated Thioesters**

To begin, a variety of propionate-derived α-halogenated thioesters was prepared and examined, each of which differed in the steric bulk of the thiol component (see Figure 24). α-Chloro thioesters **T11.1**, **F24.3**, **F24.6**, and **F24.9** were readily prepared via acylation of the corresponding thiols with chloroacetyl chloride under standard conditions (see Figure 24). 2,4,6-Triisopropylbenzenethiol (**F24.5**) was prepared by reduction of the commercially available sulfonyl chloride (**F24.4**) with LAH (see Figure 24B). 2,4,6-Tri-*tert*-butylbenzenethiol (**F24.8**) was prepared from aryl bromide **F24.7** via

halogen-lithium exchange followed by addition of elemental sulfur and reduction with LAH (see Figure 24C).

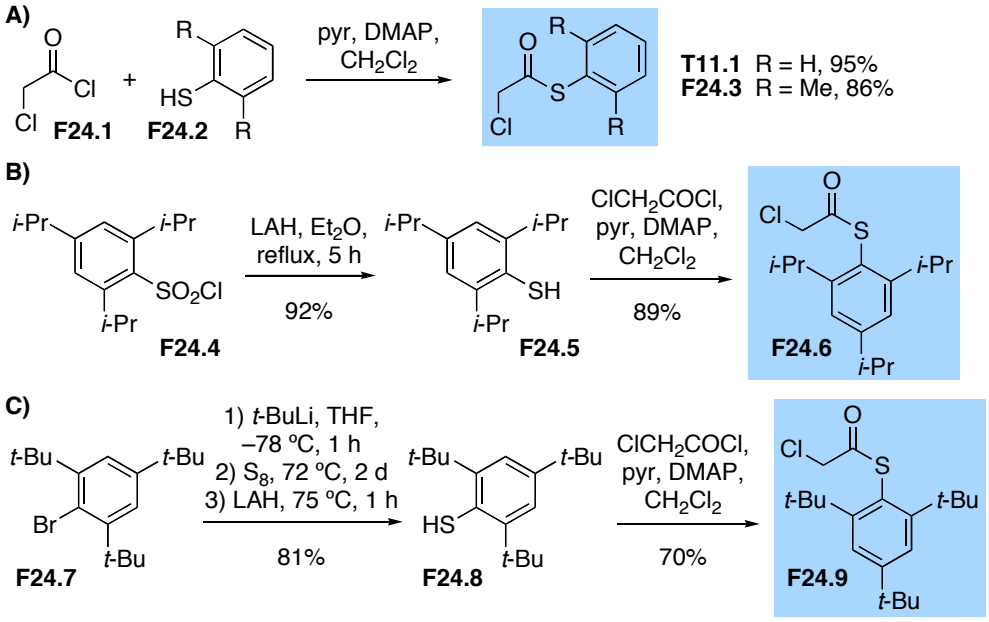


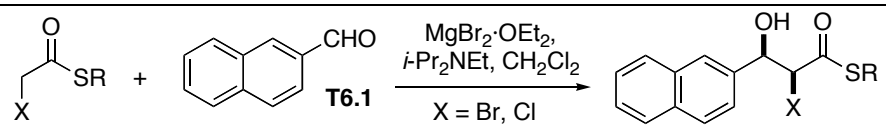

**Figure 24: Synthesis of α-Halogenated Thioesters for the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction**

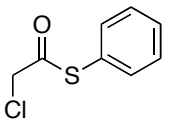
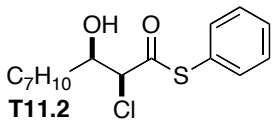
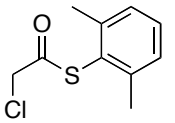
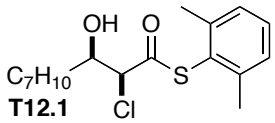
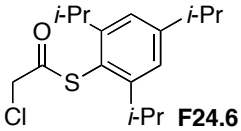
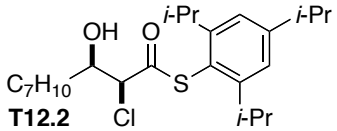
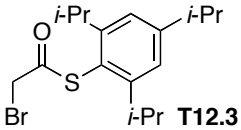
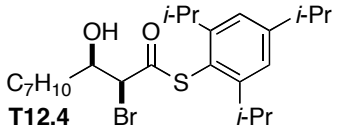
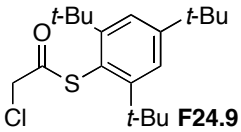
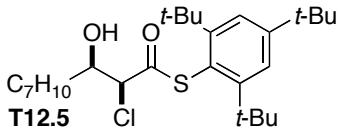
As predicted, when conducted at room temperature, the *S*-phenyl α-chlorothioester **T11.1** did not react diastereoselectively (Table 12, entry 1). However, as the bulk of the thiol component was increased, diastereoselectivity generally improved in favor of the *syn* isomer. The *S*-(2,6-dimethyl)phenyl species **F24.3** led to a 2.5:1 *syn*:*anti* ratio (entry 3) and an even greater amount of the *syn* diastereomer was produced when bulkier thioesters (**F24.6** and **F24.9**) were used (entries 5 and 9). The 2,4,6-triisopropylphenyl thioester (**F24.6**) afforded the most pronounced *syn*:*anti* ratio observed of 5.2:1 (Table 12, entry 5). Interestingly, however, when the reactions were conducted at –78 °C, even greater diastereoselectivities were observed in favor of the *syn* diastereomer. While at room temperature the *S*-phenyl α-chlorothioester (**T11.1**) failed

to react diastereoselectively, at –78 °C, a modest *syn*:*anti* ratio of 1.9:1 was observed (entry 2). The *syn*:*anti* ratio when using the *S*-(2,6-dimethyl)phenyl species **F24.3** at –78 °C increased by more than three-fold to give a d.r. of 8.2:1 (entry 4). Moreover, the diastereoselectivity using 2,4,6-triisopropylphenyl thioester **F24.6** doubled to afford the most pronounced *syn*:*anti* ratio observed at –78 °C of 10.4:1 (Table 12, entry 6). For comparison, 2,4,6-triisopropylphenyl α-bromo-thioester **T12.3** was prepared and tested. However, diastereoselectivities were slightly lower than with the analogous α-chloro thioester (**F24.6**) at both rt and –78 °C (see Table 12, entries 7 and 8). Surprisingly, the bulkiest 2,4,6-tri-*tert*-butylphenyl thioester (**F24.9**) did not afford the highest diastereoselectivities. This could be due to the inherent bulky nature of the *tert*-butyl system and the necessity, then, for longer reaction times or increased molar equivalents of the thioester for comparable conversions.

Having discovered that the diastereoselectivity in the $MgBr_2 \cdot OEt_2$-promoted aldol addition reaction using α-halogenated thioesters varied considerably with reaction temperature, we next examined whether the reaction was operating under thermodynamic or kinetic control at both rt and –78 °C. Based on previous reversibility studies for the $MgBr_2 \cdot OEt_2$-promoted aldol addition reaction using simple thioesters,[24] we speculated that the reaction at rt was under thermodynamic control, and thus the addition reaction was reversible. Correspondingly, due to the dramatic increase in diastereoselectivity when conducted at –78 °C, we predicted the reaction might instead be under kinetic control. To test this, various control experiments were conducted.

**Table 12: Effect of the Thiol Component on Diastereoselectivity in the $MgBr_2 \cdot OEt_2$-Promoted Aldol Addition Reaction using α-Halogenated Thioesters**




| Entry | Thioester | Product | Temp (ºC) | Time (h) | *syn*:*anti* | Conversion (%) |
|---|---|---|---|---|---|---|
| 1 |  **T11.1** |  **T11.2** | rt | 0.5 | 1.2:1 | 98 |
| 2 | | | –78 | 5 | 1.9:1 | 72 |
| 3 |  **F24.3** |  **T12.1** | rt | 0.5 | 2.5:1 | 97 |
| 4 | | | –78 | 5 | 8.2:1 | 65 |
| 5 |  **F24.6** |  **T12.2** | rt | 0.5 | 5.2:1 | 97 |
| 6 | | | –78 | 12 | 10.4:1 | 85 |
| 7 |  **T12.3** |  **T12.4** | rt | 0.5 | 4.8:1 | 96 |
| 8 | | | –78 | 14 | 9:1 | 90 |
| 9 |  **F24.9** |  **T12.5** | rt | 1 | 4.5:1 | 90 |
| 10[a] | | | –78 | 12 | 9:1 | 95 |

Conducted under Ar by combining 1 molar equiv of 2-naphthaldehyde, 1.2 molar equiv of thioester, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in $CH_2Cl_2$ (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-$Pr_2NEt$.
[a] 2.0 molar equiv thioester added.

First, α-chloro thioester **F24.6** was combined with 2-naphthaldehyde (**T6.1**) in the presence of $MgBr_2 \cdot OEt_2$ and *i*-$Pr_2NEt$ in $CH_2Cl_2$ under the standard conditions at rt for 30 min (see Figure 25A). The same reaction was then stirred at –78 ºC for 5 h. The *syn*:*anti* ratios previously determined for the analogous separate reactions were 5.2:1 and 10.4:1 at rt and –78 ºC, respectively (see Table 12, entries 5 and 6). Thus, after 30 min at rt, we would expect a *syn*:*anti* ratio of 5.2:1. When the temperature is lowered to –78 ºC and allowed to stir for an additional 5 h, if under kinetic control, then the reaction would be

irreversible and the *syn*:*anti* ratio would remain ~5.2:1. If however, the reaction was still reversible at –78 °C, then the product distribution would re-equilibrate to ~10.4:1. The resulting *syn*:*anti* ratio was indeed 5:1, indicative of the reaction operating under kinetic control at –78 °C.

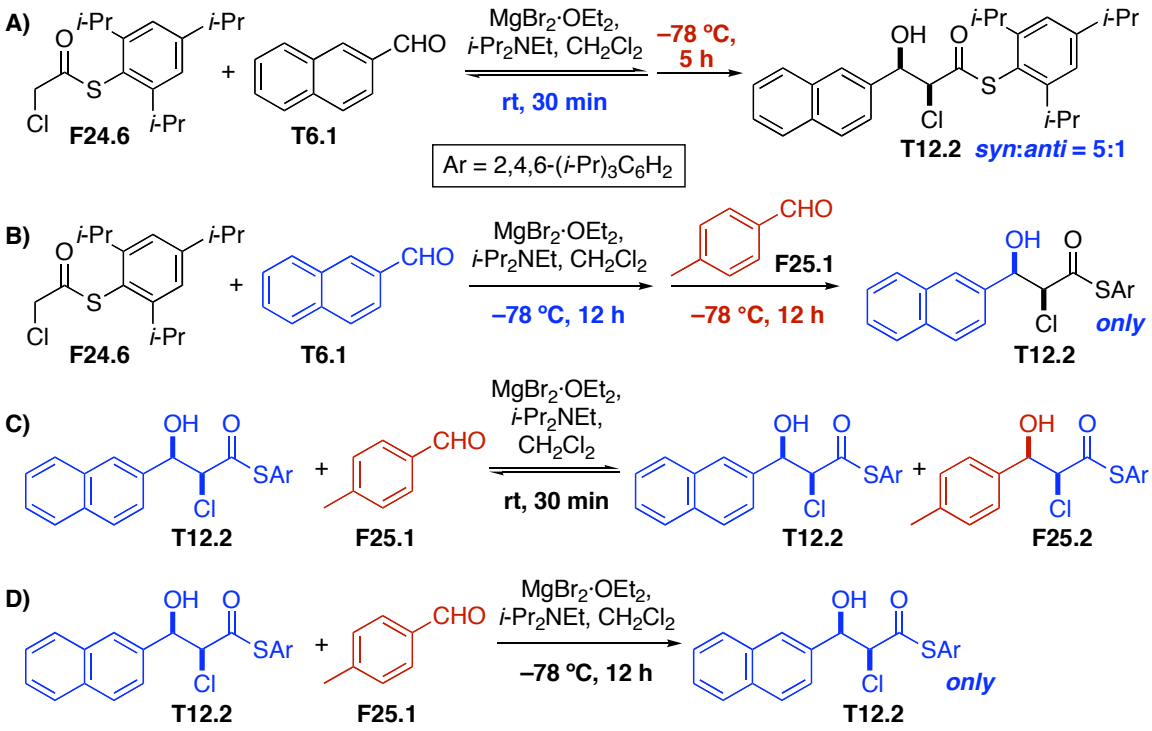



**Figure 25: Reversibility Studies for the $MgBr_2$·$OEt_2$-Mediated Aldol Addition Using α-Halogenated Thioesters**

In a subsequent experiment, equimolar amounts of α-chloro thioester **F24.6** (1.0 molar equiv) and 2-naphthaldehyde (1.0 molar equiv) were combined in the presence of $MgBr_2$·$OEt_2$ (1.4 equiv) and *i*-$Pr_2NEt$ (2.0 molar equiv) in $CH_2Cl_2$ at –78 °C (see Figure 25B). The reaction stirred at –78 °C for 12 h, then, *p*-tolualdehyde (**F25.1**, 1.0 molar equiv) was added to the reaction and was stirred for an additional 12 h at –78 °C. If under kinetic control, then there would be no incorporation of *p*-tolualdehyde since the reaction was previously determined to be complete after the first 12 h and there was no

remaining starting material to react with the second equivalent of aldehyde during the second 12 h unless the retro-aldol occurred. Indeed, the only product formed was the naphthaldehyde-derived product **T12.2**, further supporting the notion of the reaction being under kinetic control at –78 °C.

Additional cross-over experiments were conducted at both rt and –78 °C (see Figure 25C and D). Thus, aldol product **T12.2** was combined with $MgBr_2 \cdot OEt_2$ (1.4 molar equiv), *i*-$Pr_2NEt$ (2.0 molar equiv) and *p*-tolualdehyde (**F25.1**, 1.0 molar equiv) in $CH_2Cl_2$ at rt. Approximately a 3:1 mixture of aldol products **T12.2** to **F25.2** was obtained, suggesting that the addition process is in fact reversible under these conditions at rt (Figure 25C). The corresponding experiment conducted at –78 °C, however, only resulted in the re-isolation of aldol product **T12.2** with no cross-over product **F25.2** detected, indicative of an irreversible reaction at –78 °C (Figure 25D).

In summary, we conducted the direct aldol addition using α-bromo thioesters to give the α-bromo-β-hydroxy thioesters, without competing Darzen-like epoxide formation. The scope of the reaction appears general as we have successfully carried it out with a variety of aldehydes including those containing acidic α-protons without competing aldehyde self-condensation products. Additionally, the reaction was stereoselective affording *syn* products when conducted under kinetic control at –78 °C.

## *2.4 Organocatalytic Asymmetric Mannich Reaction via Soft Enolization of Thioesters*

Efforts in our lab to develop mild and efficient carbon–carbon bond-forming reactions using thioesters was inspired by Nature's approach to soft enolization, specifically in the case of citrate synthase.[49-51] We have defined soft enolization as a mild and operationally

simple approach to enolate formation, in which an amine and Lewis-acid act in concert to effect reversible deprotonation. In Nature's case, however, thioester activation is achieved by hydrogen-bonding rather than Lewis-acid coordination (see Figure 26, left). While a weaker form of carbonyl activation, the interaction is sufficient,[52] allowing deprotonation to occur by a mildly basic carboxylate group in close proximity to the thioester α-protons.[108] We have previously suggested[24, 25, 27] that the use of a thioester in this case likely aides soft enolization given the enhanced acidity of a thioester relative to other simple carboxylate derivatives.[29, 77] Thus, one can postulate enolate formation in citrate synthase to be the result of a combination of two things: the *enhanced acidity* of the thioester and the *appropriate spatial orientation* of the activating hydrogen bonding functionality to the thioester carbonyl and a base to the α-protons, such that intramolecular deprotonation can readily occur.[109-112] Based on this, we were interested in attempting to develop a biomimetic version of citrate synthase that not only incorporates these key attributes but allows for a wide variety of thioesters and electrophiles to be used (see Figure 26, right). For the initial proof of concept, we explored the Mannich addition reaction[98, 113] of thioesters[104, 114-117] and sulfonylimines.

In order to achieve the desired intramolecular hydrogen-bond promoted soft enolization event, the key structural elements of the catalyst (**F26.1**) had to be carefully considered (see Figure 26, right). Ultimately, we focused on a catalyst that contained a (thio)urea moiety, which would provide the activating hydrogen bonding interaction, as well as an amine, connected through an appropriate tether, that would be positioned in proximity to the thioester α-protons, thus enabling intramolecular deprotonation to occur (**F26.3** → **F26.4**). We anticipated the close proximity[110] of the amine to the thioester in **F26.3** would increase the rate of deprotonation, as compared to the situation where deprotonation occurs intermolecularly (*c.f.*, **F27.1** → **F27.2**, Figure 27). An amine was

preferred, in this case, over a carboxylate as it would be both more strongly basic and, following proton transfer, would generate a relatively stable ammonium enolate (**F26.4**, Figure 26).[F, 118] Reaction of the enolate (**F26.4**) with imine **F26.5**, followed by proton transfer, would then liberate the desired addition product (**F26.7**) and regenerate the catalyst (**F26.1**).

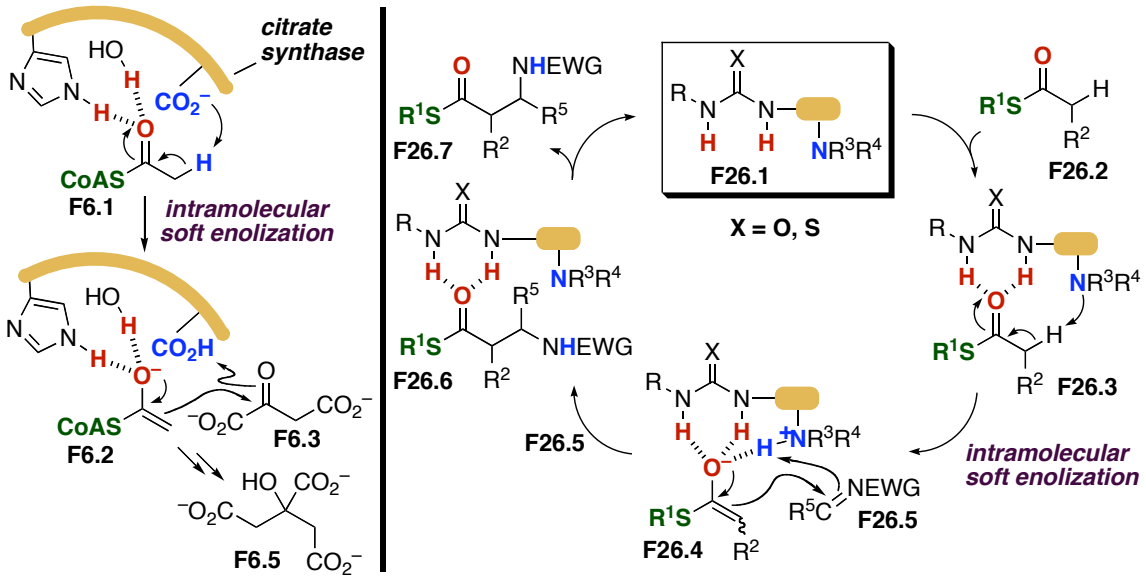



**Figure 26: Citrate Synthase Reaction and Proposed Biomimetic Asymmetric Mannich Reaction**

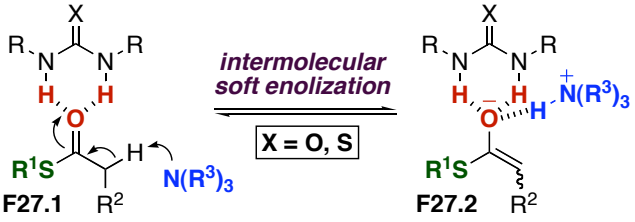
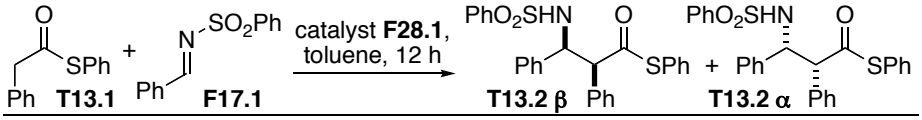



**Figure 27: Intermolecular Hydrogen Bond-Promoted Soft Enolization**

[F] Whether enolate stabilization is the result of a strong hydrogen bond or an ionic bond is uncertain.

To start our investigations for the development of a biomimetic Mannich reaction, we first combined *S*-phenyl phenylthioacetate (**T13.1**) and *N*-benzylidenebenzenesulfonamide (**F17.1**) in toluene in the presence of 10 mol% amino thiourea catalyst **F28.1** (see Table 13, entry 2 and Figure 28).[68, 119] After stirring at rt for 12 h, we were pleased to find that the desired Mannich addition product had in fact formed, giving 86% conversion of starting sulfonylimine to desired product (Table 13).

**Table 13: Survey of Catalyst Loading in the Biomimetic Mannich Reaction**




| Entry | Catalyst Loading (mol %) | *syn*:*anti* | er (β:α) | Conversion (%) |
|---|---|---|---|---|
| 1 | 20 | 93:07 | 45:55 | 85 |
| 2 | 10 | 93:07 | 44:56 | 86 |
| 3 | 5 | 92:08 | 44:56 | 77 |

Conducted under Ar by combining 1.2 molar equiv of *S*-phenyl phenylthioacetate, 1 molar equiv of *N*-Benzylidenebenzenesulfonamide, and catalyst **F28.1** in toluene (concn 0.5 M); stirred at rt for 12 h.

A subsequent investigation found there was no improvement in conversion when the catalyst loading was increased from 10 to 20 mol% (Table 13, entries 1 and 2). More significantly, the catalyst loading could be decreased to as low as 5 mol% without an appreciable erosion in conversion (see Table 13, entry 3). Significantly, the analogous reaction using the oxoester, *O*-phenyl phenylacetate (**F28.2**), and sulfonylimine **F17.1** gave only recovered starting material after 36 h. Unfortunately, while the *syn*:*anti* selectivity was excellent in all cases (d.r. ≥92:8), the reaction exhibited very poor enantioselectivity (see Table 13).

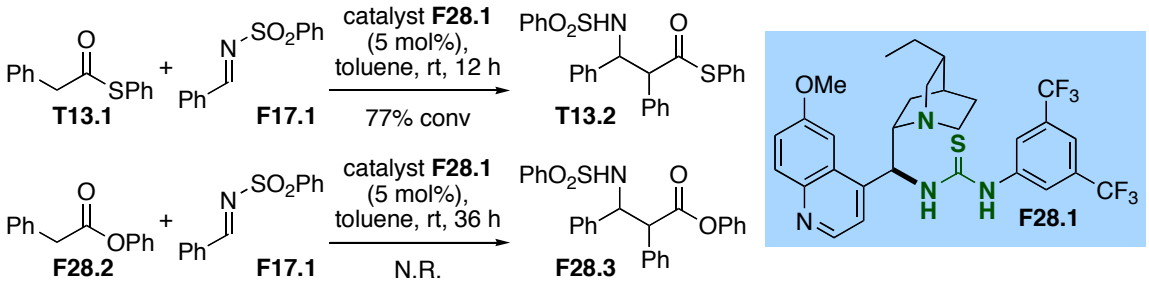
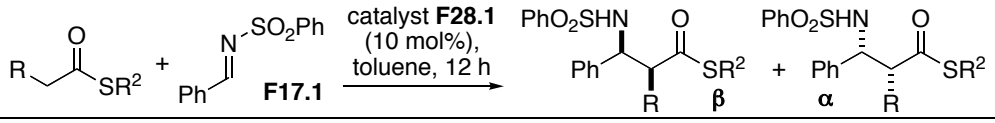
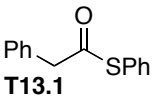
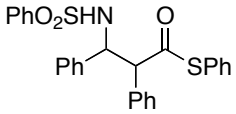
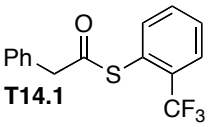
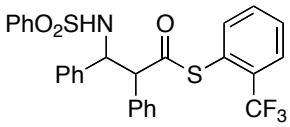
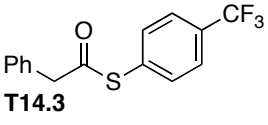
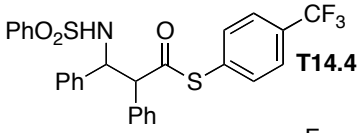
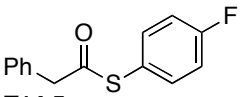
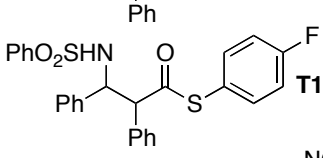
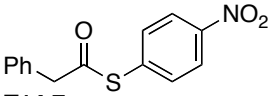
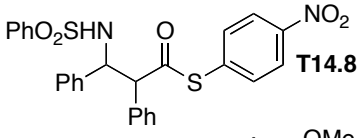
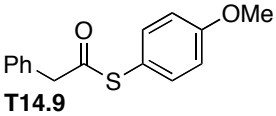
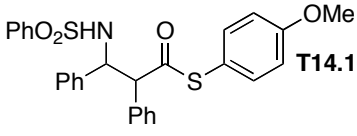
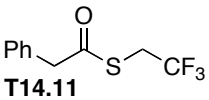
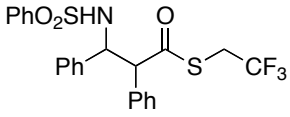
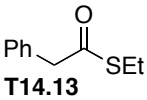
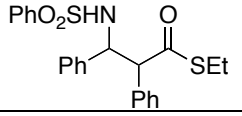



**Figure 28: Initial Survey for the Biomimetic Mannich Addition Reaction**

As a result, we investigated the effect of the thiol component of the thioester on selectivity. A range of electron-rich and electron-poor thioesters was prepared and examined. Variation of the thioester had little impact on the diastereoselectivity (*syn*:*anti* 88:12–95:5), but significantly affected the enantioselectivity (see Table 14). Only the non-aromatic thioesters tested exhibited any appreciable enantioselectivity, albeit modest (entries 7 and 8). Of these, the *S*-2,2,2-trifluoroethyl thioester **T14.11** gave the best conversion (98%, entry 7), while the simple *S*-ethyl thioester **T14.13** afforded the best asymmetric induction (e.r. 78:22, entry 8), although with only 54% conversion. Still, with these promising results in hand, we decided to further investigate the potential of the non-aromatic thioesters by screening various (thio)urea catalysts (see Table 15). For all of the thioesters examined, except for *S*-ethyl thioester **T14.13**, the catalyst screen was conducted with a catalyst loading of 5 mol% and a reaction time of 3 h. In the case of *S*-ethyl thioester **T14.13**, since previous reactions resulted in only modest conversion, reactions were conducted using 10 mol% of the catalyst for 12 h.

**Table 14: Survey of Thioesters for the Biomimetic Mannich Reaction**



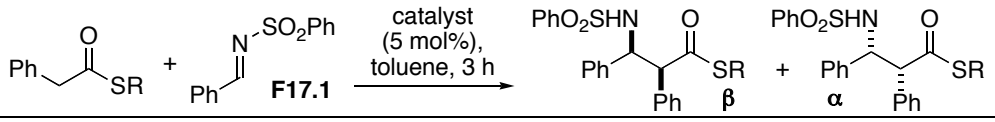

| Entry | Thioester | Mannich Product | | *syn*:*anti* | er (β:α) | Conversion (%) |
|---|---|---|---|---|---|---|
| 1 |  **T13.1** |  | **T13.2** | 93:07 | 44:56 | 86 |
| 2 |  **T14.1** |  | **T14.2** | 92:08 | 44:56 | 82 |
| 3 |  **T14.3** |  | **T14.4** | 92:08 | 47:53 | 81 |
| 4 |  **T14.5** |  | **T14.6** | 88:12 | 45:55 | 78 |
| 5 |  **T14.7** |  | **T14.8** | 95:05 | 45:55 | 74 |
| 6 |  **T14.9** |  | **T14.10** | 93:07 | 50:50 | 71 |
| 7 |  **T14.11** |  | **T14.12** | 94:04 | 65:35 | 98 |
| 8 |  **T14.13** |  | **T14.14** | 91:09 | 78:22 | 54 |

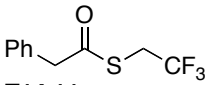
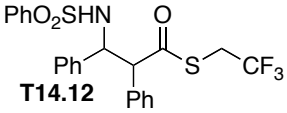
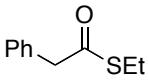
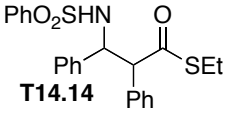
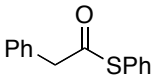
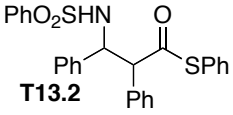
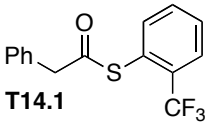
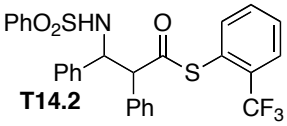
Conducted under Ar by combining 1 molar equiv of *N*-Benzylidenebenzenesulfonamide, 1.2 molar equiv of thioester and 10 mol% of catalyst **F28.1** in toluene (concn 0.5 M); stirred at rt for 12 h.

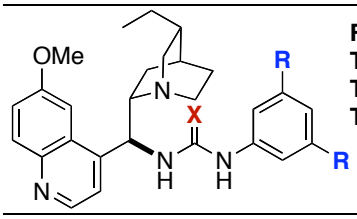
In an effort to improve asymmetric induction, we first examined urea catalyst **T15.1**. We had originally anticipated a urea catalyst to be less effective[61] than the thiourea analogue due to reduced hydrogen-bonding capabilities[120] of the oxygen versus sulfur-analogue. However, in some cases, urea catalysts have also been reported to

possess superior anion stabilizing properties.[121-123] In addition, some have reported greater levels of asymmetric induction with a urea over a thiourea catalyst, including, for example, a recent report on malonic acid half thioester addition to nitroolefins.[116] Indeed, the enantioselectivity of the Mannich reaction between sulfonylimine **F17.1** and both of the non-aromatic thioesters tested, **T14.11** and **T14.13**, improved with the use of the urea catalyst **T15.1** (e.r. 66:34→71:29 and 78:22→82:18, respectively, Table 15, entries 2 and 6). Next, in an attempt to further improve the enantioselectivity, we conducted a cursory investigation of the effect of substitution on the aniline component of the urea catalyst. To do this, we prepared and screened 3,5-dimethyl urea catalyst **T15.2** and phenyl urea catalyst **T15.3**. Interestingly, changing the aniline substituents from the strong electron-withdrawing trifluoromethyl groups to the weak electron-releasing methyl groups (see catalyst **T15.2**) appeared to have no affect on the enantioselectivity, suggesting that the electronic properties of the aniline group were not important to asymmetric induction in this reaction (Table 15, entries 3 and 7). However, when the trifluoromethyl and methyl groups were removed altogether and replaced with hydrogens (see catalyst **T15.3**), the enantioselectivities for both non-aromatic thioesters **T14.11** and **T14.13** improved (e.r. 71:29→81:19 and 82:18→86:14, respectively, Table 15, entries 4 and 8), suggesting that, instead, steric properties of the aniline system were relevant in this particular transformation.

**Table 15: Survey of (Thio)urea Catalysts for the Biomimetic Mannich Reaction**




| Entry | Thioester | Mannich Product | Catalyst | *syn*:*anti* | er (β:α) | Conversion (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | **F28.1** | 96:04 | 66:34 | 95 |
| 2 | | | **T15.1** | 96:04 | 71:29 | 93 |
| 3 | **T14.11** | **T14.12** | **T15.2** | 92:08 | 71:29 | 98 |
| 4 | | | **T15.3** | 97:03 | 81:19 | 88 |
| 5 |  |  | **F28.1** | 91:09 | 78:22 | 54[a] |
| 6 | | | **T15.1** | 92:08 | 82:18 | 48[a] |
| 7 | **T14.13** | **T14.14** | **T15.2** | 91:09 | 81:19 | 49[a] |
| 8 | | | **T15.3** | 92:08 | 86:14 | 51[a] |
| 9 |  |  | **F28.1** | 88:12 | 43:57 | 72 |
| 10 | | | **T15.3** | 93:07 | 61:39 | 81 |
| | **T13.1** | **T13.2** | | | | |
| 11 |  |  | **T15.1** | 93:07 | 49:51 | 70 |
| 12 | | | **T15.2** | 88:12 | 57:43 | 82 |
| 13 | **T14.1** | **T14.2** | **T15.3** | 93:07 | 64:36 | 83 |



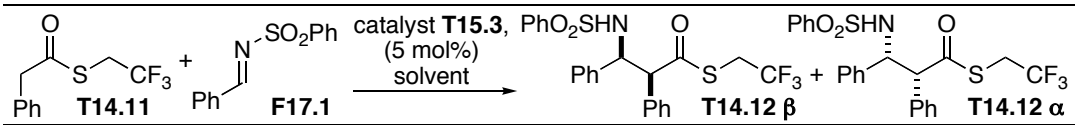

**F28.1** **X** = S, **R** = $CF_3$
**T15.1** **X** = O, **R** = $CF_3$
**T15.2** **X** = O, **R** = Me
**T15.3** **X** = O, **R** = H

Conducted under Ar by combining 1 molar equiv of *N*-Benzylidenebenzenesulfonamide, 1.2 molar equiv of thioester and 5 mol% of catalyst in toluene (concn 0.5 M); stirred at rt for 3 h.
[a] 10 mol% of catalyst; stirred at rt for 12 h.

Variation of the catalyst had little impact on the diastereoselectivity and, accordingly, the *syn*:*anti* ratios remained excellent for both thioesters **T14.11** and **T14.13** (d.r. 91:9–97:3, Table 15). After finding that the phenyl urea catalyst **T15.3** afforded the highest enantioselectivities, of the catalysts tested, for the non-aromatic thioesters, we reexamined two of the aromatic thioesters for comparison (see Table 15, entries 9–13). Indeed, the aromatic thioesters exhibited modest enantioselectivity with the refined catalyst (**T15.3**), but remained lower than the non-aromatic thioesters (entries 10 and 13).

With phenyl urea catalyst **T15.3** in hand, a variety of standard solvents was screened in an attempt to further refine the reaction conditions and possibly increase selectivity, including THF, $CH_2Cl_2$, $Et_2O$ and MeCN. No improvement in selectivity, however, was observed over the initial results obtained with toluene (see Table 16). Varying the solvent also affected conversions, resulting in lower conversions than with toluene in all cases, except for MeCN. Additionally, lower temperatures were screened (0 °C and –78 °C) with no improvement in selectivity, and often resulting in lower conversions.

**Table 16: Survey of Solvents for the Biomimetic Mannich Reaction**

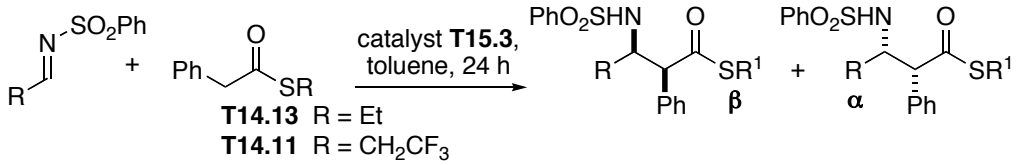


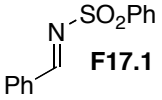
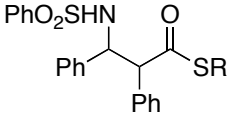
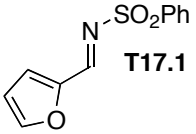
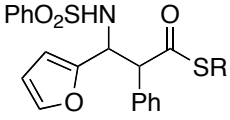
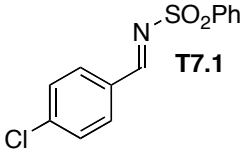
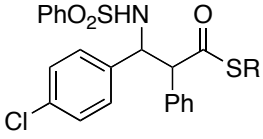
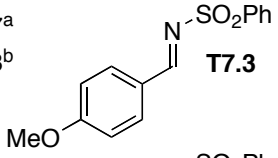
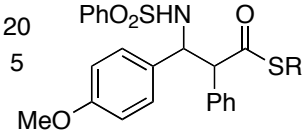
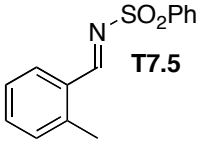
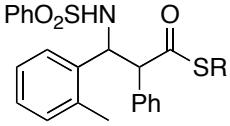

| Entry | Solvent | Time (h) | *syn*:*anti* | er (β:α) | Conversion (%) |
|---|---|---|---|---|---|
| 1 | toluene | 3 | 97:03 | 81:19 | 88 |
| 2 | THF | 6 | 77:23 | 78:22 | 67 |
| 3 | $CH_2Cl_2$ | 6 | 84:16 | 78:22 | 67 |
| 4 | $Et_2O$ | 6 | 85:15 | 79:21 | 84 |
| 5 | MeCN | 6 | 27:73 | 50:50 | 95 |

Conducted under Ar by combining 1 molar equiv of *N*-Benzylidenebenzenesulfonamide, 1.2 molar equiv of *S*-2,2,2-Trifluoroethyl phenylthioacetate, and 5 mol% catalyst **T15.3** in solvent (concn 0.5 M); stirred at rt for 3 or 6 h.

Using phenyl urea catalyst **T15.3**, the scope of the reaction with various sulfonylimines, both electron-rich and electron-poor, was tested (see Table 17). While the reaction with *S*-2,2,2-trifluoroethyl thioester **T14.11** could be conducted using a lower catalyst loading (5 mol% versus 20 mol%) and were consistently more rapid and higher yielding (generally, 85–95%), enantioselective induction was uniformly better with *S*-ethyl thioester **T14.13** (generally, e.r. ≥84:16, see Table 17). Diastereomeric ratios were consistently high in both cases.

**Table 17: Scope of the Biomimetic Mannich Reaction with Various Sulfonylimines**




| Entry | Sulfonylimine | Thioester (R) | mol% T15.3 | Mannich Product | | *syn*:*anti* | er (β:α) | Isolated Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1[a] |  | Et | 20 |  | **T14.14** | 95:05 | 87:13 | 77 |
| 2[b] | **F17.1** | $CH_2CF_3$ | 5 | | **T14.12** | 93:07 | 81:19 | 95 |
| 3[a] |  | Et | 20 |  | **T17.2** | 92:08 | 76:24 | 66 |
| 4[b] | **T17.1** | $CH_2CF_3$ | 5 | | **T17.3** | 92:08 | 73:27 | 94 |
| 5[a] |  | Et | 20 |  | **T17.4** | 93:07 | 85:15 | 73 |
| 6[b] | **T7.1** | $CH_2CF_3$ | 5 | | **T17.5** | 91:09 | 74:26 | 90 |
| 7[a] |  | Et | 20 |  | **T17.6** | 93:07 | 84:16 | 41 |
| 8[b] | **T7.3** | $CH_2CF_3$ | 5 | | **T17.7** | 83:17 | 74:26 | 50 |
| 9[a] |  | Et | 20 |  | **T17.8** | 98:02 | 88:12 | 78 |
| 10[b] | **T7.5** | $CH_2CF_3$ | 5 | | **T17.9** | 97:03 | 66:34 | 85 |

[a] Conducted under Ar by combining 1 molar equiv of sulfonylimine, 3 molar equiv of **T14.13**, 20 mol% of catalyst **T15.3** in toluene (concn 0.2 M); stirred at rt for 24 h. [b] Conducted under Ar by combining 1 molar equiv of sulfonylimine, 1.5 molar equiv of **T14.11**, 5 mol% of catalyst **T15.3** in toluene (concn 0.2 M); stirred at rt for 24 h.

A stereochemical model consistent with the empirical data is shown in Figure 29. We propose that intramolecular deprotonation of the hydrogen bonded thioester gives an *E*-(*O*)-enolate[49, 118] (**F29.2**) which is then stabilized by both the resulting ammonium ion[G] and the urea moiety. Approach to the *si*-face of the enolate is blocked by the

[G] Whether enolate stabilization is the result of a strong hydrogen bond or an ionic bond is uncertain.

quinuclidine moiety and the *re*-face is blocked by the aniline component. As the steric bulk of the aniline substituents decreases (R, *e.g.*, $CF_3$ and $CH_3$ → H), the *re*-face becomes more accessible leading, then, to greater enantioselectivity. Additionally, a reduction in the size of the thiol component of the thioester ($R^1$, *e.g.*, Ph → $CH_2CF_3$ → Et) decreases any unfavorable nonbonding interactions that would exist between it and both the urea moiety and the aromatic group (Ar) of the catalyst, leading to a more closely associated enolate complex, and, consequently, improved facial selectivity during imine addition (**F29.2** → **F29.3** → **F29.4**). The notion of a more closely associated enolate complex leading to improved facial selectivity was suggested based on the known property of ureas to better stabilize an anion,[121-123] and is consistent with the higher level of asymmetric induction observed for the urea catalyst over the thiourea counterpart.

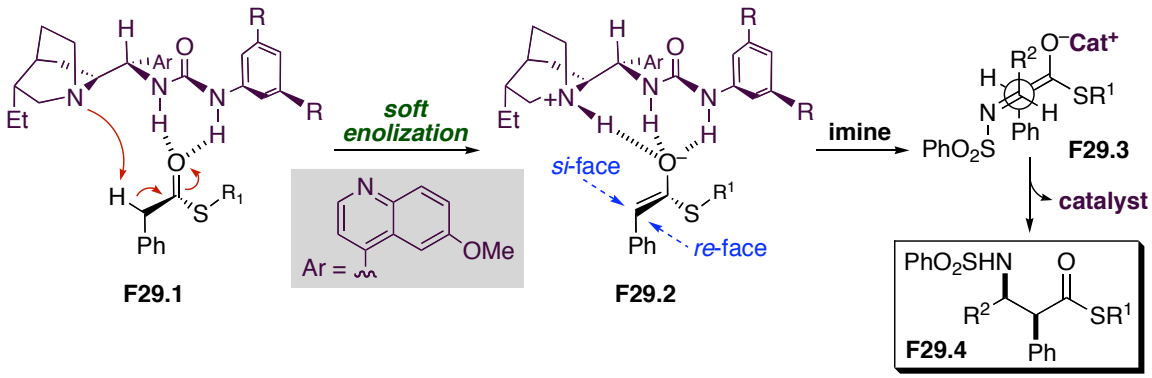



**Figure 29: Stereochemical Model of the Biomimetic Asymmetric Mannich Addition Reaction**

It has been reported that organocatalytic approaches to amine catalysis have a functional $pK_a$ barrier for nucleophile activation between the $pK_a$ values of 16 and 17.[114] Correspondingly, two recent reports describing an intermolecular amine catalyzed approach to thioester deprotonation were restricted by this barrier and needed then to seek appropriate thioesters that were acidic enough to be in the suitable range for

organocatalysis, which led them to the highly acidic *S*-2,2,2-trifluoroethyl α-arylthioesters (*e.g.*, **T14.11**, $pK_a$ <16.9).[114, 115] The slightly less acidic *S*-phenyl thioester **T13.1** ($pK_a$ = 16.9[29]) failed to react under their conditions.[114] Although significant as a demonstration of the feasibility of amine catalyzed deprotonation in organocatalytic method development, the associated functional $pK_a$ barrier precludes this previous report as a general enolization technique. In contrast to this enolization method, the present mode of organocatalysis was designed around intramolecular hydrogen bond-promoted soft enolization. Consequently, the ability to use the much less acidic *S*-ethyl phenylthioacetate (**T14.13**) in place of the *S*-2,2,2-trifluoroethyl α-arylthioesters, alone, ranks this method as a more general mode of enolization-based organocatalysis.

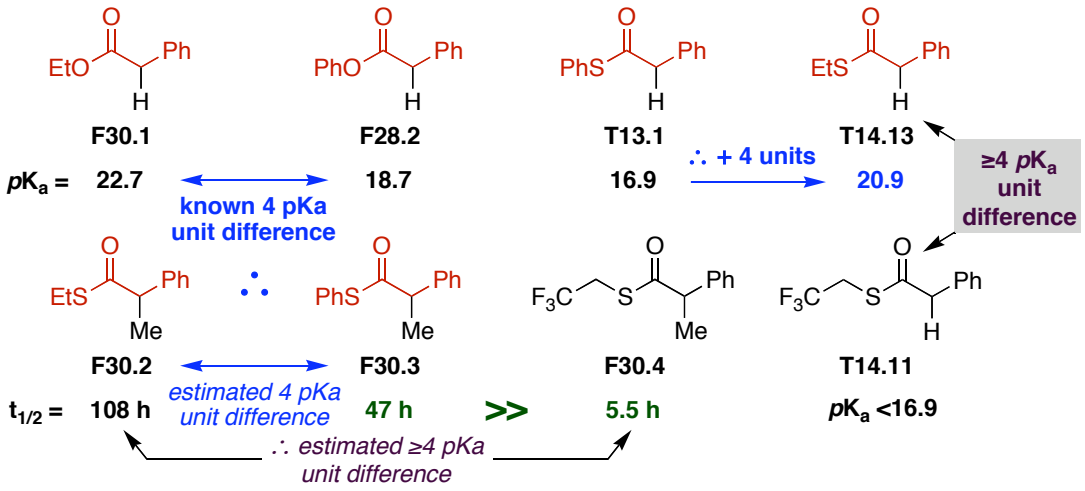



**Figure 30: Acidity and H/D Exchange rates of Various Phenylacetic Acid Derivatives**

While the $pK_a$s of thioesters **T14.13** and **T14.11** have not been reported, their *differential acidity* can be estimated from the known[29, 68, 77, 119] $pK_a$s of **F30.1**, **F28.2**, and **T13.1** (see Figure 30), along with the rate of H/D-exchange ($Et_3N$, $CD_3OD$, toluene-$d_8$) of the related α-phenyl propionate derivatives **F30.2–F30.4**.[124] It is known that *O*-ethyl ester

**F30.1** is less acidic than *O*-phenyl ester **F28.2** by 4 units, thus, by correlation, we can estimate the $pK_a$ difference between **F30.2** and **F30.3** to be approximately 4 units. Furthermore, since the half-life for H/D exchange of *S*-trifluoroethyl ester **F30.4** ($t_{1/2}$ = 5.5 h[124]) is considerably less than that of the corresponding *S*-phenyl thioester (**F30.3**; $t_{1/2}$ = 47 h[124]), we can assume that the $pK_a$ difference between **F30.2** and **F30.4** is at least 4 $pK_a$ units. Correspondingly, the $pK_a$ difference between **T14.13** and **T14.11** must be at least 4 units. In addition, based on the above correlation, we can estimate the $pK_a$ of *S*-ethyl thioester **T14.13** to be 4 units higher than *S*-phenyl thioester **T13.1**, resulting in an approximate $pK_a$ of 20.9. As such, the effective $pK_a$ barrier of our present catalytic method can be estimated to be 21, which is well above that associated with simple intermolecular amine catalyzed enolization (*i.e.*, 16–17).[114, 115] Significantly, this $pK_a$ barrier is not that far beyond the acidity range of simple thioesters (*i.e.*, 22–23[29]).

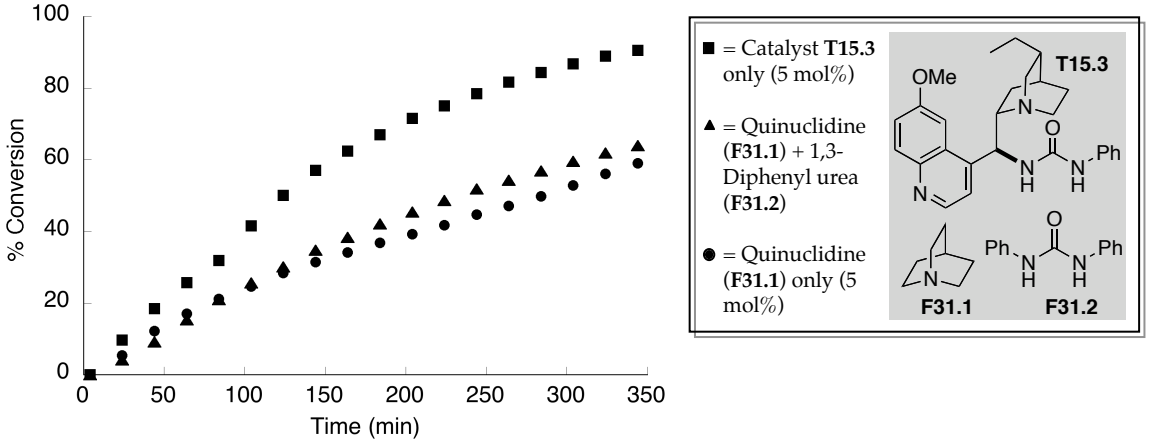



**Figure 31: Evidence of Proximity Accelerated Soft Enolization in the Biomimetic Asymmetric Mannich Addition Reaction**

We believe the intramolecular nature of enolization in this case, specifically, the cooperative stabilization of the hydrogen bonding and ammonium moieties which leads to a thermodynamically more stable enolate, is what permits this form of

organocatalysis to accommodate relatively weakly acidic thioesters. To lend support, we tested this theory regarding the importance of proximity effects in the Mannich addition reaction. To do so, three separate $^1$H NMR spectroscopy experiments were conducted which combined *S*-2,2,2-trifluoroethyl phenylthioacetate (**T14.11**) and sulfonylimine **F17.1** in toluene-$d_8$ along with: 1) quinuclidine (**F31.1**), 2) quinuclidine (**F31.1**) and 1,3-diphenyl urea (**F31.2**), and 3) phenyl urea catalyst **T15.3**. The experiments were monitored by $^1$H NMR (300 MHz) over the course of 6 h at ambient temperature (see Figure 31). Addition of urea **F31.2** only showed a marginal increase in reaction rate over the experiment with quinuclidine alone. However, the rate increased significantly when catalyst **T15.3** was used, supporting the notion of proximity-accelerated deprotonation.

In conclusion, the first organocatalytic Mannich reaction based on proximity-accelerated intramolecular soft enolization of thioesters was developed. Significantly, with a functional $p$K$_a$ barrier associated with this method estimated at 21 units, thioesters over a range of acidity are able to react efficiently. Thus, there is great potential for this cooperative mode of enolization to serve as a general enolization-based organocatalytic strategy applicable to simple monocarboxylic acid derivatives.

## *2.5 Anti-Selective Four-Component Direct Aldol Addition via Chemoselective Thioester Enolate Formation*[H]

As part of our efforts to develop generally applicable direct aldol addition reactions, we were intrigued by the possibility of achieving chemoselective enolate

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[H] Portions of this section have been reproduced in part with permission from Zhou, G. Z.; Yost, J. M.; Sauer, S. J.; Coltart, D. M., A facile and efficient *anti*-selective four-component direct aldol addition via chemoselective thioester enolate formation. *Org. Lett.* **2007**, *9*, 4663–4665. Copyright 2007 American Chemical Society.

formation in the presence of readily enolizable aldehydes by way of a four-component direct aldol addition of thioesters.[35] In such a reaction, the enolates would be generated in situ via an acylation/conjugate addition sequence of a thiolate to acryloyl chloride (**F32.1**). This chemoselective mode of enolate formation would preclude aldehyde enolization and, consequently, undesired self-addition of the aldehyde. Additionally, the organosulfur aldol products could then be readily converted into a variety of polyketide structures using established reduction conditions (see Figure 4).[30-35]

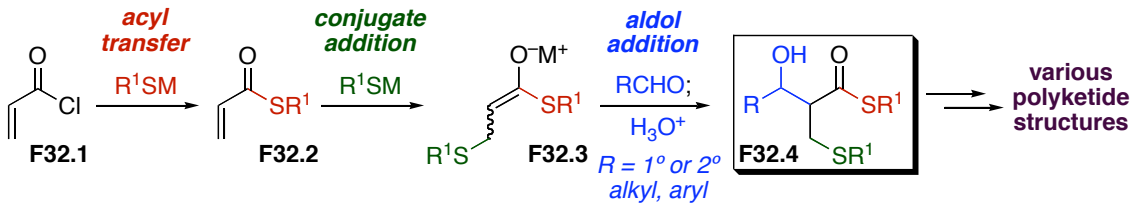



**Figure 32: Four-Component Direct Aldol Addition Reaction**

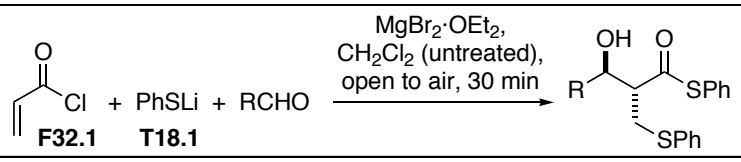
Given that thiols and their derivatives are highly nucleophilic, they have been exploited for the development of a number of important chemoselective reactions. For instance, they can be selectively acylated in the presence of other common nucleophiles[38] (*e.g.*, $H_2O$, alcohol, amine, etc.), or added to α,β-unsaturated carbonyls via conjugate addition.[125-130] Along these lines, we reasoned that the combination of two equivalents of a thiolate, along with one equivalent each of an α,β-unsaturated acid chloride and an aldehyde, would initiate a one-pot four-component cascade sequence leading to a single aldol addition product. The first thiolate equivalent and the acid chloride would rapidly react to generate an α,β-unsaturated thioester (**F32.1** → **F32.2**), followed by formation of a thioester enolate (**F32.3**) via 1,4-addition of the second thiolate equivalent. Once formed, the enolate would then react with the aldehyde to form the desired aldol addition product (**F32.4**). Given the absence of a suitably strong external Brønsted base,

and assuming that the trans-enolization event between the thioester enolate and aldehyde is relatively slow compared with addition to the aldehyde carbonyl, competing self-addition of the aldehyde would not be expected to interfere. Furthermore, since the acylation/Michael addition cascade sequence is initiated by attack of the highly nucleophilic thiolate, background reactions involving trace amounts of moisture in the atmosphere or solvent should not be a factor, thus further simplifying the process. Coincidentally, Michael addition of a thiolate and subsequent aldehyde addition using α,β-unsaturated oxoesters and amides was already known.[125-128]

To test the feasibility of the idea, sodium thiophenolate (PhSNa, 2 equiv) was added to a mixture of acryloyl chloride (**F32.1**, 1 equiv) and benzaldehyde (1 equiv) in $CH_2Cl_2$. However, the aldol product was not detected and, instead, protonated thioester **F32.3** ($R^1$ = Ph) was isolated in 92% yield. Attempts to vary the solvent and counterion of the thiolate source (*e.g.*, $Li^+$, $K^+$, $Cu^+$) also did not result in any desired product formation. On account of our initial success with the $MgBr_2 \cdot OEt_2$-promoted aldol addition,[24, 25] we attempted the reaction with lithium thiophenolate (PhSLi) in the presence of $MgBr_2 \cdot OEt_2$ (1.2 equiv). Under these conditions, the aldol addition product was in fact obtained in 67% yield within only 30 min. Surprisingly, the reaction proved to be highly selective for the *anti* diastereomer, which classically is uncommon in an aldol addition,[8, 131-133] with an *anti*:*syn* ratio of 13:1. Prolonging the reaction time did not improve the yield, nor did it affect the diastereomeric ratio. Thus, we explored the effect of the molar equivalents of each of the reactants relative to the aldehyde. Ultimately, we settled on the following refined conditions: lithium thiophenolate (3.0 equiv), acryloyl chloride (1.5 equiv), $MgBr_2 \cdot OEt_2$ (1.2 equiv), and benzaldehyde (1.0 equiv) in $CH_2Cl_2$ (concn 0.2 M). Indeed, these new equivalencies afforded the desired aldol product in very good yield (88%) and *anti*:*syn* diastereoselectivity (d.r. 13:1, see Table 18, entry 1). As expected, there was no detectable difference in conversion, reaction time, or

diastereoselectivity when reactions were conduced under anhydrous[I] versus atmospheric[J] conditions.

**Table 18: Direct Four-Component Aldol Reaction with Various Aldehydes**




| Entry | Aldehyde | Addition Product (*anti*-shown) | Isolated Yield (%) | *anti*:*syn* |
|---|---|---|---|---|
| 1 | PhCHO **T1.2** | **T18.2** | 88 | 13:1 |
| 2 | CHO **T18.3** | **T18.4** | 71 | 11:1 |
| 3 | CHO **T10.7** | **T18.5** | 68 | 16:1 |
| 4 | Ph CHO **T18.6** | **T18.7** | 71 | 14:1 |
| 5 | CHO **T4.13** | **T18.8** | 81 | >20:1 |
| 6 | CHO **T18.9** | **T18.10** | 76 | >20:1 |

Having established simple and efficient conditions, we next examined the scope of the reaction with a variety of enolizable aldehydes, each containing either one or two

[I] Dry $CH_2Cl_2$; Ar atmosphere.
[J] Untreated Aldrich ACS-grade $CH_2Cl_2$; open to air.

α-protons (see Table 18). In all cases the four-component reaction proceeded efficiently, giving the desired addition products in 68 to 88% yield, with consistently short reaction times (30 min). Notably, in no case was the aldehyde self-addition product observed, thus confirming the compatibility of this method with enolizable aldehydes. Significantly, in each case, the stereochemical outcome of the reaction strongly favored the *anti* product over the more commonly obtained *syn* diastereomer.[8, 131-133]

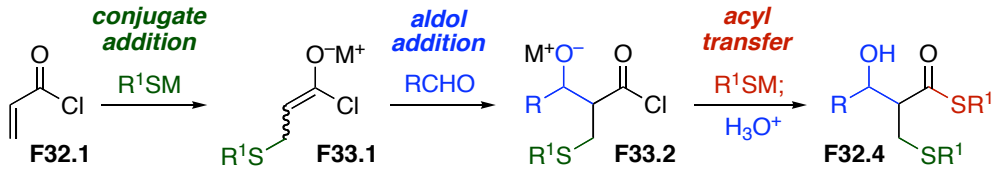



**Figure 33: Alternate Reaction Pathway for the Four-Component Direct Aldol Addition Reaction**

From the beginning we expected that *Cl→S* acyl transfer would precede enolate-forming conjugate addition (see Figure 32), in a manner consistent with kinetic 1,2-addition preference of α,β-unsaturated carbonyl compounds. Nonetheless, an alternate possibility was that conjugate addition occurs first giving an acid chloride enolate (**F33.1**) which would then undergo the aldol addition (Figure 33). Thus, *Cl→S* acyl transfer from **F33.2** would give the observed product (**F32.4**). This alternate pathway was ruled out, however, by conducting a control experiment using only 1.5 molar equiv of lithium thiophenolate – equimolar to acryloyl chloride. Accordingly, lithium thiophenolate (1.5 equiv), acryloyl chloride (1.5 equiv), $MgBr_2 \cdot OEt_2$ (1.2 equiv), and benzaldehyde (1.0 equiv) in $CH_2Cl_2$ reacted to give acrylate thioester **F32.2** ($R^1$ = Ph) in 93% yield, with less than 4% of the aldol product **T18.2**. Hence, since only 1 molar equiv of the thiolate species was available, relative to the α,β-unsaturated acid chloride (**F32.1**), the intermediate species prior to the second addition of thiolate would be trapped upon

workup (**F32.2** or **F33.2**). In this case, the α,β-unsaturated thioester **F32.2** ($R^1$ = Ph) was isolated, corresponding to the initially proposed pathway as shown in Figure 32.

Next, we investigated the origin of the *anti*-selectivity in the reaction. Assuming standard models,[8] the diastereoselectivity would originate either from kinetic addition of the *E*-(*O*)- or *Z*-(*O*)-enolate to the aldehyde or on the basis of the relative thermodynamic stability of the *syn* and *anti* products in a reversible addition. Several attempts to trap either the enolate intermediate or the kinetic addition product under a variety of conditions were not successful.[125] However, we were able to establish that the origin of the diastereoselectivity is likely thermodynamic in nature by demonstrating that the addition reaction is reversible. To do this, the reaction was carried out as usual using benzaldehyde but, after the standard 30 min reaction period, 1 equiv of *p*-tolualdehyde (**F25.1**) was added and the mixture was stirred for an additional 30 min prior to workup (see Figure 34). This resulted in approximately a 1:1 mixture of aldol addition products **T18.2** and **F34.1**, with a 13:1 *anti*:*syn* ratio in each case. Having detected a mixture of both addition products established that the addition reaction was, in fact, reversible.

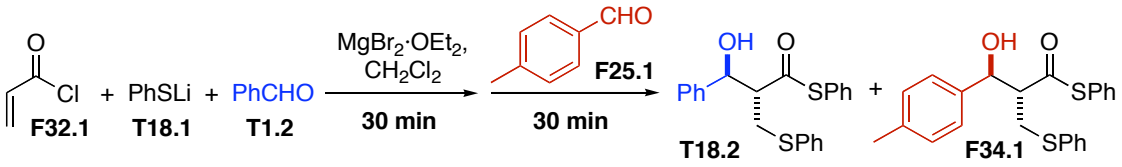


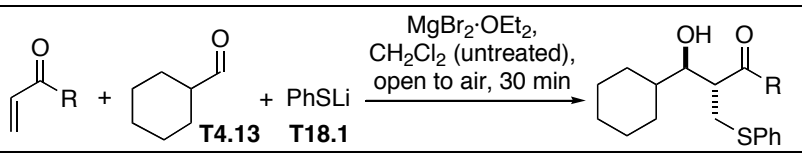

**Figure 34: Reversibility Study for the Four-Component Direct Aldol Addition Reaction**

The inherent thermodynamic preference of the addition products for the *anti* or *syn* configuration, as it relates to acrylate structure, was examined by conducting the reaction with several different acrylate derivatives (Table 19). In each case, the desired

addition product was isolated in good yields (60–82%), but the diastereomeric ratios varied considerably. Nevertheless, with the exception of **T19.6**, the different thioesters examined showed a significant preference for the *anti* product (Table 19, entries 1–3). Interestingly, the oxoesters and the amide that were examined showed either very modest or no *anti*-selectivity (entries 5–7).

Initial results in this study (see above) established the essential role of $Mg^{2+}$ in the addition reaction – the aldol product was only observed after $MgBr_2 \cdot OEt_2$ was included. As such, we wondered if the thiolate $Li^+$ counterion had only a passive role in the transformation and whether omitting $Li^+$ from the reaction mixture would affect the feasibility of the transformation and the stereochemical outcome. To examine this, we attempted the aldol addition using PhSMgBr as the thiolate source, in place of PhSLi. Thus, acryloyl chloride (**F32.1**), cyclohexanecarboxaldehyde (**T14.13**), PhSMgBr and $MgBr_2 \cdot OEt_2$ were combined under the standard conditions. The aldol addition product (**T18.8**) was indeed obtained but, remarkably, with a 2:1 preference for the *syn* product. In addition, when PhSNa was used as the thiolate source, a 2:1 preference for the *syn* product was also observed, thus implicating $Li^+$ as a key factor in achieving *anti*-selectivity. To confirm the importance of $Li^+$ in this regard, the reaction just described using PhSMgBr was repeated but, after the standard 30 min reaction time, PhSLi was added. After an additional 30 min interval, the reaction was worked up as usual. Surprisingly, the selectivity for the aldol product **T18.8** was restored to >20:1 in favor of the *anti* product. Overall, these results show that the stereochemical outcome of the reaction is strongly dependent on the nature of the thiolate counterion.

**Table 19: Effect of Acrylate Structure on Diastereoselectivity in the Direct Four-Component Aldol Reaction**




| Entry | α,β-Unsaturated Carboxyl | Aldol Adduct (*anti*-shown) | Isolated Yield (%) | *anti*:*syn* |
|---|---|---|---|---|
| 1 | SPh **T19.1** | SPh / SPh **T18.8** | 79 | >20:1 |
| 2 | S **T19.2** | S / SPh **T19.3** | 60 | 11:1 |
| 3 | SEt **T19.4** | SEt / SPh **T19.5** | 82 | 4:1 |
| 4 | S*t*-Bu **T19.6** | S*t*-Bu / SPh **T19.7** | 77 | 1.5:1 |
| 5 | OPh **T19.8** | OPh / SPh **T19.9** | 72 | 2:1 |
| 6 | O*t*-Bu **T19.10** | O*t*-Bu / SPh **T19.11** | 78 | 1:1 |
| 7 | NHPh **T19.12** | NHPh / SPh **T19.13** | 64 | 2:1 |

A rationale for this outcome that is consistent with its reversible nature can be made using the model shown in Figure 35. Here, it is assumed that the thioether and thioester sulfur atoms of the addition product coordinate $Li^+$ through a six-membered chelate (Figure 35).[134] In the presence of $Li^+$, then, coordination with sulfur leads to the

*E*-(*O*)-enolate (**F35.1**), which then reacts via the lower-energy Zimmerman-Traxler transition state to give intermediate **F35.2** preferentially over **F35.4** and, consequently, the *anti* product (**F35.3**) over the *syn* (**F35.5**). In the absence of $Li^+$, both the *E*-(*O*)-enolate (**F35.1** without the $Li^+$) and *Z*-(*O*)-enolate (**F35.6**) exist, allowing *syn* product **F35.5** to form via **F35.8**, in addition to **F35.4**. However, when PhSLi is subsequently added to the system prior to workup, the *syn* intermediate **F35.8** is converted to $Li^+$-complexed *E*-(*O*)-enolate **F35.1** via a thermodynamically driven conformational ring inversion of **F35.7** to **F35.9**. Addition from **F35.1** then gives *anti* product **F35.3**, analogously to the first reaction containing only PhSLi (Figure 35).

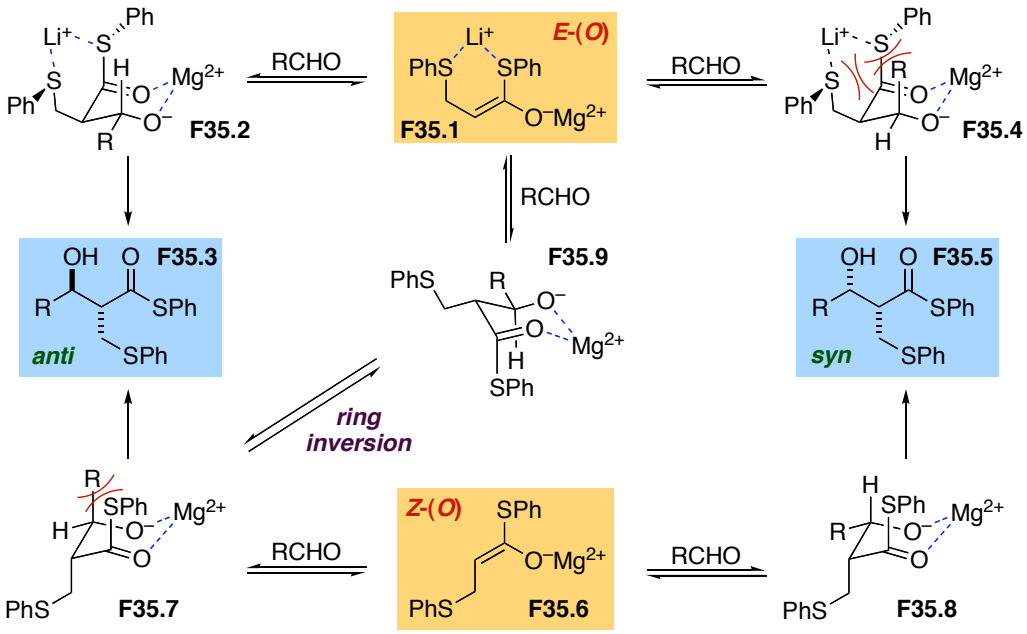



**Figure 35: Stereochemical Model for the Four-Component Direct Aldol Addition**

This model is also consistent with the variation in diastereoselectivity seen for the various acrylate thioesters examined, if it is assumed that tendency of the six-membered sulfur lithium chelate (**F35.1**) to form is dependant on the Lewis-basicity of

the sulfur atoms. In this case, the aromatic thioesters would be expected to be more basic than the alkyl thioesters due to their greater electron donating ability and, therefore, more likely to coordinate $Li^+$ through the six-membered chelate, leading to a greater proportion of *anti* product (see Figure 35). Furthermore, of the two aryl thioesters, the less sterically hindered phenyl thioester would have the greater tendency to coordinate $Li^+$ via the six-membered chelate and, as such, gives a greater proportion of the *anti* isomer than the more bulky 2,6-dimethylphenyl species. Likewise, of the two alkyl thioesters, the less sterically demanding ethyl thioester gave a greater proportion of the *anti* product than the bulky *t*-butyl thioester (see Table 19).

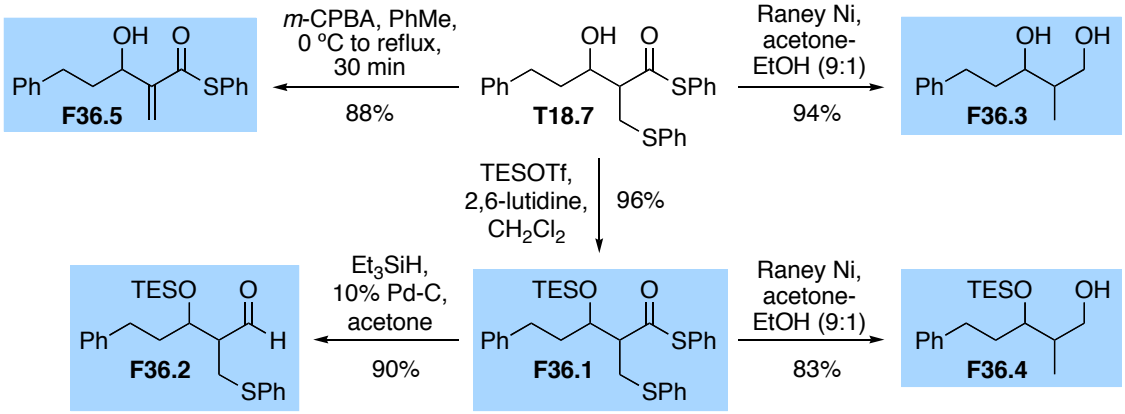



**Figure 36: Representative Transformations of Four-Component Aldol Product T18.7**

As mentioned previously, one of the compelling reasons for using thiol derivatives in organic synthesis is the numerous possibilities for subsequent transformations, often under very mild conditions (see Figure 4). As an initial demonstration of the utility of organosulfur products and the potential for them to lead to a variety of polyketide structures, **T18.7** was first silylated (→ **F36.1**) and then treated under Fukuyama reduction conditions to afford the aldehyde **F36.2** in high yield.[135] Furthermore, diols **F36.3** and **F36.4** were readily prepared from **T18.7** and **F36.1**,

respectively, by simple treatment with Raney nickel. Additionally, subsequent studies in our lab have shown the feasibility of converting the four-component aldol products into Baylis-Hillman derivatives through a one-pot oxidative-elimination sequence upon treatment with *m*-CPBA and heat (*e.g.*, **T18.7 → F36.5**).[136]

In summary, we developed a facile and efficient *anti*-selective four-component direct aldol addition of thioester enolates that is fully compatible with enolizable aldehydes. Chemoselective deprotonation was achieved by generating the thioester enolates in situ via an acylation/conjugate addition sequence, and the resulting organosulfur products were easily reduced to demonstrate the potential to form various polyketide-based structures.

# 3. Conclusion

$MgBr_2 \cdot OEt_2$-promoted soft enolization conditions were developed and successfully applied to the aldol addition reaction, resulting in a mild and efficient direct reaction that is inexpensive and can be used under atmospheric conditions. Competition experiments established the superior reactivity of thioesters over oxoesters under these soft enolization conditions. The conditions were also used successfully in promoting the Mannich reaction. The reaction proceeded readily with a range of sulfonylimines and gave moderate to good diastereoselectivity in favor of the *syn* isomer. When α-halogenated thioesters were employed in the direct aldol, the addition products were isolated without competing Darzen-like epoxide formation or aldehyde self-condensation products. Indeed, the addition of the halogen allowed for chemoselective deprotonation to occur. Additionally, the aldol reaction was stereoselective affording high levels of the *syn* product when conducted under kinetic control.

In addition, the first organocatalytic Mannich reaction based on proximity-accelerated intramolecular soft enolization of thioesters was developed. Significantly, thioesters over a range of acidity were able to react efficiently. Thus, there is great potential for this cooperative mode of enolization to serve as a general enolization-based organocatalytic strategy applicable to simple monocarboxylic acid derivatives.

Alternative modes of achieving chemoselective deprotonation were also considered, which led to the development of a facile and efficient $MgBr_2 \cdot OEt_2$-promoted *anti*-selective four-component direct aldol addition of thioester enolates formed in situ via an acylation/conjugate addition sequence. The resulting organosulfur products

were easily reduced to demonstrate the potential to form various polyketide-based structures.

Given the advantages of soft enolization including the inherent operational simplicity of all of the reactions described, and the accessibility of thioesters, we expect these methods to meet with wide application.

# 4. Experimental Section

**General Considerations:** Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, $Et_2O$, $CH_2Cl_2$, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Sigma-Aldrich. Commercial grade solvents were used for routine purposes without further purification. $Et_3N$, pyridine, *i*-$Pr_2NEt$, 2,6-lutidine, *i*-$Pr_2NH$, and TMEDA were distilled from $CaH_2$ under a $N_2$ atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (32-63μ). $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian spectrometer (400 MHz and 100 MHz, respectively) at ambient temperature. All $^1H$ chemical shifts are reported in ppm (δ) relative to TMS (0.00); $^{13}C$ shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16).

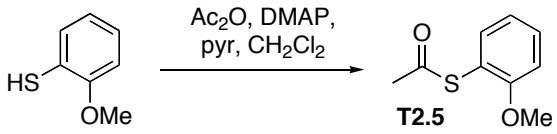
## 4.1 Direct Aldol Addition of Simple Thioesters Employing Soft Enolization

**General Considerations.** Diastereomeric ratios were determined by $^1$H NMR analysis of the crude materials.

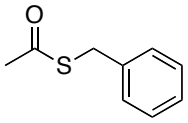
### *Thioester and Oxoester Preparation*

*S*-Phenyl thioacetate (**T2.1**), *S*-furfuryl thioacetate (**T2.9**), and phenyl acetate (**T6.15**) were purchased from Sigma Aldrich. *S*-(4-Nitrophenyl) thioacetate (**T2.7**) (Cat. No. S888524) and *S*-phenyl thiopropionate (**T5.1**) (Cat. No. 376809) were originally purchased from Sigma-Aldrich but are no longer readily available. As such, *S*-(4-nitrophenyl) thioacetate (**T2.7**) was also prepared from the commercially available (Sigma-Aldrich) thiol and acetic anhydride under standard conditions (see below). *S*-Phenyl thiopropionate (**T5.1**) was prepared from the commercially available (Sigma-Aldrich) thiol and propionyl chloride or propionic acid under standard conditions.[24] Spectroscopic data for *S*-phenyl thiopropionate (**T5.1**) was identical to that reported previously.[137] *S*-Phenyl benzyloxythioacetate (**T5.3**) was prepared from the commercially available (Sigma-Aldrich) thiol and benzyloxyacetic acid under standard EDCI-mediated coupling conditions (see below). All other thioesters and oxoesters were prepared via acylation of the corresponding commercially available (Sigma-Aldrich) thiols or phenols, respectively, as described below.

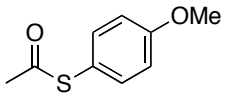
***The following is representative of the synthesis of thioesters and oxoesters used in Tables 1, 2, and 6:***



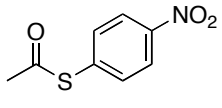

***S*-(2-Methoxy)phenyl thioacetate (T2.5).** Acetic anhydride (1.86 mL, 19.68 mmol) was added via syringe to a stirred solution of the thiol (2.00 mL, 16.43 mmol), DMAP (0.0464 g, 0.38 mmol), pyridine (1 mL) and $CH_2Cl_2$ (19 mL). The mixture was allowed to stir for 12 h and then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic phase was washed with water, brine, dried ($MgSO_4$), and evaporated to give a pure, colorless oil. Flash chromatography over silica gel, using 6:94 EtOAc-hexanes gave **T2.5** (2.755 g; 92%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.48–7.34 (m, 2H), 7.04–6.92 (m, 2H), 3.86 (s, 3H), 2.41 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 193.5, 159.2, 136.8, 131.8, 121.2, 116.2, 111.6, 56.0, 30.1; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_9H_{10}NaO_2S$: 205.0, found: 204.8.



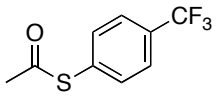

***S*-Benzyl thioacetate (T1.1).** Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave **T1.1** (1.664 g; 87%) as a pure, colorless liquid. Spectroscopic data was identical to that reported previously.[138]



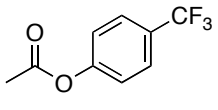

***S*-(4-Methoxy)phenyl thioacetate (T2.3).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T2.3** (2.114 g; 93%) as a pure, light yellow oil. Spectroscopic data was identical to that reported previously.[138]



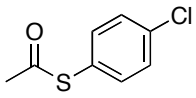

***S*-(4-Nitro)phenyl thioacetate (T2.7).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T2.7** (0.800 g; 81%) as a pure, light yellow solid. Spectroscopic data was identical to that reported previously.[139, 140]



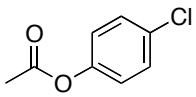

***S*-4-(Trifluoromethyl)phenyl thioacetate (T6.2).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T6.2** (0.985 g; 91%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (d, $J$ = 8.8 Hz, 2H), 7.54 (d, $J$ = 8.8 Hz, 2H), 2.45 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 192.6, 134.6, 132.7 (app q, $J$ = 1.5 Hz), 131.4 (q, $J$ = 32.7 Hz), 126.1 (q, $J$ = 3.7 Hz), 123.9 (q, $J$ = 271.0 Hz), 30.5; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_9H_7F_3NaOS$: 243.0, found: 242.9.



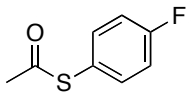

**4-Trifluoromethylphenyl acetate (T6.4).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T6.4** (0.924 g; 92%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.65 (d, $J$ = 8.4 Hz, 2H), 7.22 (d, $J$ = 8.4 Hz, 2H), 2.32 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.0, 153.3, 128.2 (q, $J$ = 32.6 Hz), 126.9 (q, $J$ = 3.7 Hz), 124.0 (q, $J$ = 270.3 Hz), 122.2, 21.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_9H_7F_3NaO_2$: 227.0, found: 226.9.



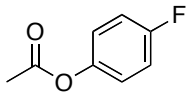

***S*-(4-Chloro)phenyl thioacetate (T6.6).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T6.6** (2.560 g; 80%) as a pure, colorless liquid. Spectroscopic data was identical to that reported previously.[141]



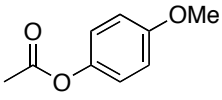

**4-Chlorophenyl acetate (T6.8).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T6.8** (1.264 g; 95%) as a pure, colorless liquid. Spectroscopic data was identical to that reported previously.[142]



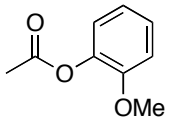

***S*-(4-Fluoro)phenyl thioacetate (T6.10).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T6.10** (1.094 g; 92%) as a pure, colorless liquid. Spectroscopic data was identical to that reported previously.[143, 144]



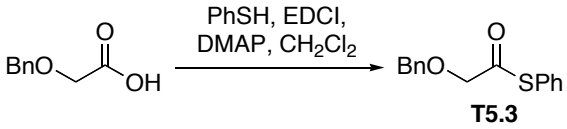

**4-Fluorophenyl acetate (T6.12).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T6.12** (1.205 g; 88%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.06–7.01 (m, 4H), 2.27 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.6, 160.3 (d, $J$ = 242.3 Hz), 146.6 (d, $J$ = 3.0 Hz), 123.1 (d, $J$ = 8.8 Hz), 116.2 (d, $J$ = 22.7 Hz), 21.1; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_9H_7FNaO_2$: 177.0, found: 176.9.




**4-Methoxyphenyl acetate (T6.18).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T6.18** (1.191 g; 89%) as a pure, colorless solid. Spectroscopic data was identical to that reported previously.[145, 146]

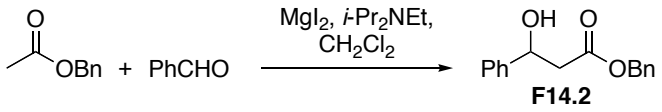



**2-Methoxyphenyl acetate (T6.21).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T6.21** (1.374 g; 91%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.[147]




**T5.3**

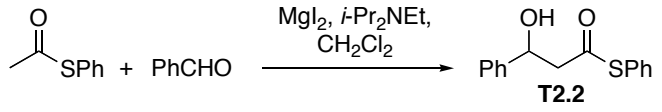
***S*-Phenyl benzyloxythioacetate (T5.3).** EDCI (1.3073 g, 6.82 mmol) and DMAP (0.0731 g; 0.60 mmol) were added to a stirred solution of benzyloxyacetic acid (1.0323g, 6.21 mmol) and benzenethiol (0.95 mL; 9.29 mmol) in $CH_2Cl_2$ (30 mL). The mixture was allowed to stir for 3 h and was partitioned between EtOAc and water. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T5.3** (1.5081 g; 94%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.48–7.29 (m, 10H), 4.73 (s, 2H), 4.27 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 198.2, 136.9, 134.9, 129.6, 129.3, 128.7, 128.3, 128.1, 75.0, 74.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_2S$: 281.1, found: 280.8.




**F14.2**

**β-Hydroxy oxoester (F14.2).** $MgI_2$ (0.167 g, 0.6 mmol) was added to a stirred solution of *O*-benzyl acetate (**F14.1**) (0.075 g, 0.5 mmol) and benzaldehyde (61 $\mu$L, 0.6 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2$NEt (0.11 mL, 0.65 mmol). Stirring was continued for 20 h and EtOAc (2.5 mL) and 10% (v/v) aqueous HCl (2.5 mL) were added. Stirring was continued for 15 min and the mixture was partitioned between EtOAc (15 mL) and $H_2O$ (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **F14.2** (0.0593 g; 46%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.[148]

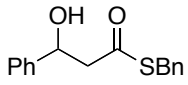
***The following reaction is representative of those depicted in Table 2:***



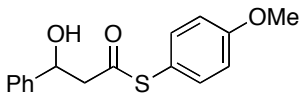

**T2.2**

**β-Hydroxy thioester (T2.2).** $MgI_2$ (0.167 g, 0.6 mmol) was added to a stirred solution of thioester **T2.1** (0.076 g, 0.5 mmol) and benzaldehyde (61 $\mu$L, 0.6 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2$NEt (0.11 mL, 0.65 mmol). Stirring was continued for 30 min and EtOAc (2.5 mL) and 10% (v/v) aqueous HCl (2.5 mL) were added. Stirring was continued for 15 min and the mixture was partitioned between EtOAc (15 mL) and $H_2O$ (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the

combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T2.2** (0.121 g; 94%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.50–7.26 (m, 10H), 5.21 (X of an ABX system, app td, $J$ = 3.4, 8.7 Hz, 1H), 3.12 (A of an ABX system, app dd, $J$ = 8.8, 16.0 Hz, 1H), 3.03 (B of an ABX system, app dd, $J$ = 3.8, 16.0 Hz, 1H), 2.97 (d, $J$ = 3.3 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.4, 142.3, 134.6, 129.8, 129.4, 128.8, 128.1, 127.2, 125.8, 70.9, 52.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_2S$: 281.1, found: 280.8.

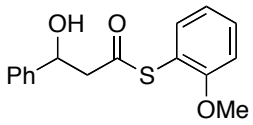



**β-Hydroxy thioester (T1.3).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T1.3** (0.1294 g; 95%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.42–7.18 (m, 10H), 5.20 (X of an ABX system, app td, $J$ = 3.6, 8.7 Hz, 1H), 4.17 and 4.15 (AB q, $\Delta\nu_{AB}$ = 6.6 Hz, $J$ = 13.8 Hz, 2H), 3.08–2.88 [m, 3H, including A of an ABX system, app dd, at δ 3.02 ($J$ = 9.0, 15.9 Hz, 1H) and B of an ABX system, app dd, at δ 2.93 ($J$ = 3.9, 15.9 Hz, 1H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 198.2, 142.4, 137.2, 129.0, 128.82, 128.75, 128.1, 127.5, 125.8, 71.0, 52.4, 33.4; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_2S$: 295.1, found: 294.9.

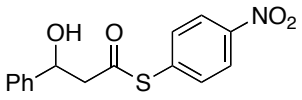



**β-Hydroxy thioester (T2.4).** Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **T2.4** (0.1413 g; 98%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz):

δ 7.39–7.20 (m, 7H), 7.00–6.90 (m, 2H), 5.20 (X of an ABX system, app td, $J$ = 3.3, 8.7 Hz, 1H), 3.83 (s, 3H), 3.14–2.97 [m, 3H, including A of an ABX system, app dd, at δ 3.09 ($J$ = 8.7, 15.9 Hz, 1H), a d at δ 3.04 ($J$ = 4.2 Hz), and B of an ABX system, app dd, at δ 2.99 ($J$ = 3.3, 15.9 Hz, 1H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 198.7, 161.0, 142.3, 136.2, 128.8, 128.1, 125.8, 117.8, 115.1, 70.9, 55.5, 51.9; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_3S$: 311.1, found: 310.9.

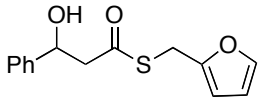



**β-Hydroxy thioester (T2.6).** Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **T2.6** (0.1384 g; 96%) as a pure, light-yellow solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.45–7.20 (m, 7H), 7.06–6.97 (m, 2H), 5.20 (X of an ABX system, app dd, $J$ = 8.1, 4.5 Hz, 1H), 3.85 (s, 3H), 3.24–2.96 [m, 3H, including A of an ABX system, app dd, at δ 3.15 ($J$ = 5.4, 15.9 Hz, 1H), and B of an ABX system, app dd, at δ 3.05 ($J$ = 4.2, 15.9 Hz, 1H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.0, 159.2, 142.3, 136.8, 132.1, 128.7, 128.0, 125.8, 121.3, 115.4, 111.8, 71.0, 56.1, 52.1; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_3S$: 311.1, found: 310.9.




**β-Hydroxy thioester (T2.8).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T2.8** (0.1395 g; 92%) as a pure, light-yellow solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.30–8.20 (m, 2H), 7.70–7.55 (m, 2H), 7.50–7.22 (m, 5H), 5.26 (X of an ABX

system, app td, $J$ = 3.6, 9.0 Hz, 1H), 3.25–3.00 [m, 2H, including A of an ABX system, app dd, at δ 3.19 ($J$ = 9.0, 15.9 Hz, 1H), and B of an ABX system, app dd, at δ 3.06 ($J$ = 3.6, 15.9 Hz, 1H)], 2.64 (d, $J$ = 3.6 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 194.5, 148.4, 142.1, 135.7, 134.9, 128.9, 128.4, 125.8, 124.2, 70.9, 52.8; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO_4S$: 326.0, found: 325.9.

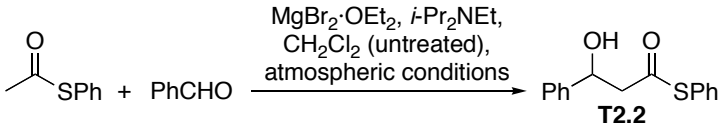



**β-Hydroxy thioester (T2.10).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T2.10** (0.1259 g; 96%) as a pure, light-yellow oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.41–7.23 (m, 6H), 6.33–6.18 (m, 2H), 5.20 (X of an ABX system, br app td, ($J$ = 2.7, 8.7 Hz, 1 H) 4.20 and 4.17 (AB q, $\Delta\nu_{AB}$ = 10.4 Hz, $J$ = 15.3 Hz, 2H), 3.09–2.88 [m, 3H, including A of an ABX system, app dd, at δ 3.03 ($J$ = 8.8, 15.8 Hz), B of an ABX system, app dd, at δ 2.93 ($J$ = 3.9, 15.8 Hz), overlapping a br d at δ 2.92 ($J$ = 2.4 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.5, 150.1, 142.4, 142.3, 128.7, 128.0, 125.7, 110.7, 108.2, 70.8, 52.4, 25.8; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{14}H_{14}NaO_3S$: 285.1, found: 284.8.

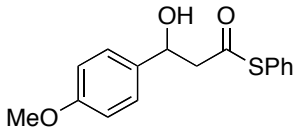
***The following reaction is representative of those depicted in Tables 4 and 5:***

*The following reactions were conducted using untreated $CH_2Cl_2$,[K] open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*

[K] Sigma-Aldrich. ACS reagent grade, ≥99.5%.

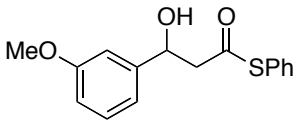



**β-Hydroxy thioester (T2.2).** $MgBr_2 \cdot OEt_2$ (0.181 g, 0.7 mmol) was added to a stirred solution of thioester **T1.2** (0.076 g, 0.5 mmol) and benzaldehyde (61 $\mu$L, 0.6 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2NEt$ (0.17 mL, 1.0 mmol). The reaction flask was capped to prevent evaporation. Stirring was continued for 30 min and then EtOAc (2.5 mL) and 10% (v/v) aqueous HCl (2.5 mL) were added. Stirring was continued for 20 min and the mixture was partitioned between EtOAc (30 mL) and $H_2O$ (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T2.2** (0.1240 g; 96%) as a pure, colorless solid. Spectroscopic data was identical to that reported above.

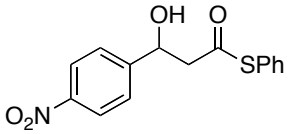



**β-Hydroxy thioester (T4.2).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T4.2** (0.1399 g; 97%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.44–6.84 [m, 9H, including app d at δ 7.30 (*J* = 8.8 Hz), and app d at δ 6.89 (*J* = 8.8 Hz)], 5.16 (X of an ABX system, br app d (*J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.11 (A of an ABX system, app dd, *J* = 8.7, 15.9 Hz, 1H), 3.00 (B of an ABX system, app dd, *J* = 3.6, 15.9 Hz, 1H), 2.90 (br app s, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.1, 159.3, 134.53, 134.50, 129.7,

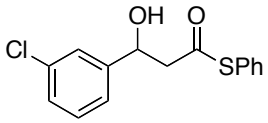
129.3, 127.2, 127.0, 114.0, 70.4, 55.3, 52.2; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{16}NaO_3S$: 311.1, found: 310.8.



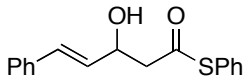

**β-Hydroxy thioester (T4.4).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T4.4** (0.1384 g; 96%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.50–7.22 (m, 6H), 6.98-6.78 (m, 3H), 5.19 (X of an ABX system, app overlapping td, $J$ = 3.6, 8.5 Hz, 1H), 3.81 (s, 3H), 3.17–2.92 [m, 3H, including A of an ABX system, app dd, at δ 3.10 ($J$ = 8.5, 16.0 Hz), B of an ABX system, app dd, at δ 3.02 ($J$ = 3.6, 16.0 Hz), and a d at δ 2.97 ($J$ = 3.6 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz, 2 overlapping peaks): δ 197.0, 159.8, 144.0, 134.5, 129.7, 129.3, 127.2, 118.0, 113.6, 111.1, 70.6, 55.3, 52.2; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{16}NaO_3S$: 311.1, found: 310.8.



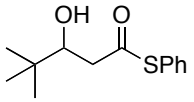

β-**Hydroxy thioester (T4.6).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T4.6** (0.1355 g; 94%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.22 (app d, $J$ = 8.7 Hz, 2H), 7.56 (app d, $J$ = 8.7 Hz, 2H), 7.48–7.34 (m, 5H), 5.32 (dt, $J$ = 3.6, 6.3 Hz, 1H), 3.30 (d, $J$ = 3.6 Hz, 1H), 3.08 (d, $J$ = 6.3 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz, 2 overlapping peaks): δ 197.3, 149.4, 147.7, 134.6, 130.1, 129.6, 126.7, 124.0, 69.9, 51.6; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{13}NNaO_4S$: 326.0, found: 325.8.



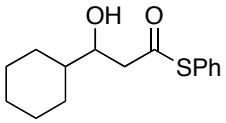

**β-Hydroxy thioester (T4.8).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T4.8** (0.1420 g; 95%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.46–7.36 (m, 6H), 7.34–7.20 (m, 3H), 5.18 (X of an ABX system, app overlapping td, $J$ = 3.9, 7.8 Hz, 1H), 3.14–2.96 [m, 3H, including A of an ABX system, app dd, at δ 3.08 ($J$ = 7.8, 15.9 Hz), overlapping a d at δ 3.08 ($J$ = 3.3 Hz), and B of an ABX system, app dd, at δ 3.01 ($J$ = 4.4, 15.9 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz, 2 overlapping peaks): δ 197.2, 144.3, 134.6, 130.0, 129.8, 129.4, 128.1, 126.9, 126.0, 123.9, 70.1, 51.9; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{13}ClNaO_2S$: 315.0, found: 314.8.



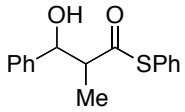

**β-Hydroxy thioester (T4.10).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T4.10** (0.1307 g; 92% with trace impurities) as a colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.46–7.20 (m, 10H), 6.68 (d, $J$ = 15.8 Hz, 1H), 6.23 (dd, $J$ = 6.0, 15.8 Hz, 1H), 4.87–4.76 (m, 1H), 3.00 (app d, $J$ = 6.6 Hz, 2H), 2.74 (d, $J$ = 4.2 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.1, 136.4, 134.6, 131.2, 129.8, 129.6, 129.4, 128.7, 128.0, 127.2, 126.7, 69.5, 50.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{17}H_{16}NaO_2S$: 307.1, found: 306.9.



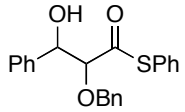

**β-Hydroxy thioester (T4.12).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T4.12** (0.1120 g; 94%) as a pure, light-yellow oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.44–7.40 (m, 5H), 3.78 (X of an ABX system, app d, $J$ = 10.2 Hz, 1H), 2.94–2.58 [m, 3H, including A of an ABX system, app dd, at δ 2.88 ($J$ = 2.0, 15.8 Hz), B of an ABX system, app dd, at δ 2.71 ($J$ = 10.2, 15.8 Hz), and a d at δ 2.62 ($J$ = 3.3 Hz)], 0.93 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 198.8, 134.6, 129.7, 129.4, 127.4, 76.0, 45.9, 34.8, 25.7; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_2S$: 261.1, found: 260.9.




**β-Hydroxy thioester (T4.14).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T4.14** (0.1084 g; 83%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.43–7.37 (m, 5H), 3.92–3.78 (X of an ABX system, m, 1H), 2.90–2.64 [m, 3H, including A of an ABX system, app dd, at δ 2.86 ($J$ = 3.3, 15.9 Hz), B of an ABX system, app dd, at δ 2.77 ($J$ = 8.7, 15.9 Hz), and a d at δ 2.68 ($J$ = 3.9 Hz)], 1.94-0.88 (m, 11H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 198.3, 134.5, 129.6, 129.3, 127.4, 72.7, 47.8, 43.2, 28.9, 28.1, 26.4, 26.2, 26.1; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_2S$: 287.1, found: 286.9.




**α-Methyl-β-Hydroxy thioester (T5.2).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T5.2** (0.1226 g; 90%) as a pure, colorless oil comprised of a 2:1 (*syn:anti*) mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz, 2:1 mixture of diastereomers): δ 7.52–7.22 (m, 10H), 5.20–4.78 [m, 1H, including a dd at δ 5.13 ($J$ = 2.7, 4.2 Hz) and a dd at δ 4.84 ($J$ = 4.4, 8.2 Hz), 3.20–2.98 (m, 1H), 2.82–2.67 (m, 1H, including a m from δ 2.82–2.75 and a m from δ 2.73–2.67), 1.32–1.06 [m, 3H, including a d at δ 1.30 ($J$ = 7.2 Hz) and a d at δ 1.10 ($J$ = 7.2 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz, 2:1 mixture of diastereomers): δ 201.8, 201.6, 141.6, 141.2, 134.52, 134.50, 129.6, 129.5, 129.25, 129.23, 128.6, 128.3, 128.2, 127.7, 127.5, 127.2, 126.7, 126.2, 76.6, 74.0, 55.3, 55.1, 15.4, 11.9; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{16}NaO_2S$: 295.1, found: 294.8.




**α-Benzyloxy-β-hydroxy thioester (T5.4).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T5.4** (0.1768 g; 97%) as a pure, colorless solid comprised of a 1:1 (*syn:anti*) mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz, 1:1 mixture of diastereomers): δ 7.48–7.16 (m, 15H), 5.13–4.92 [m, 1H, including a dd at δ 5.07 ($J$ = 4.2, 6.6 Hz), and a dd at δ 4.95 ($J$ = 3.9, 6.6 Hz)], 4.80–4.25 [m, 2H, including an AB q at δ 4.75 and 4.70 ($\Delta\nu_{AB}$ = 16.0 Hz, $J$ = 11.1 Hz) and an AB q at δ 4.43 and 4.26 ($\Delta\nu_{AB}$ = 24.6 Hz, $J$ = 11.1 Hz)], 4.22–4.12 [m, 1H, including a d at δ 4.19 ($J$ = 4.2 Hz) and a d at δ 4.17 ($J$ = 6.6 Hz)], 3.30–2.90 [m, 1H, including a dd at δ 3.10 ($J$ = 1.2, 3.9 Hz) and a dd at δ 2.94 ($J$ = 1.5,

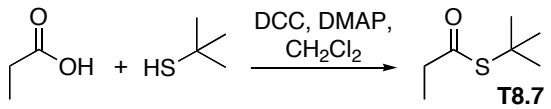
6.6 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz, 1:1 mixture of diastereomers, contains some overlapping peaks): δ 201.0, 199.5, 139.4, 139.1, 136.5, 136.2, 134.62, 134.56, 129.43, 129.40, 129.2, 128.45, 128.42, 128.3, 128.23, 128.16, 128.1, 128.0, 127.4, 127.09, 127.06, 126.4, 88.3, 87.4, 74.9, 74.6, 74.5; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{20}NaO_3S$: 387.1, found: 386.8.

## *4.2 Soft Enolization of Thioesters: Direct Mannich Addition Reaction*

**General Considerations.** Diastereomeric ratios and percent conversions were determined by $^1$H NMR analysis of the crude materials. The *syn* and *anti* diastereomers were each isolated and characterized separately.

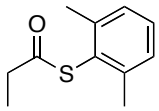
### *Thioester Preparation*

*S*-Ethyl thiopropionate (**T8.5**) was purchased from Alfa Aesar (Cat. No. B24918). Phenyl propionate (**T8.3**) was purchased from TCI America (Cat. No. P0509). *S*-Phenyl thiopropionate (**T8.1**) was originally purchased from Sigma-Aldrich (Cat. No. 376809) but has since been discontinued. *S*-Phenyl thiopropionate (**T8.1**), *S*-*t*-butyl thiopropionate (**T8.7**), and *S*-(2,6-dimethyl)phenyl thiopropionate (**T8.9**) were prepared from the commercially available (Sigma-Aldrich) thiols and propionyl chloride or propionic acid under standard conditions.[24] Spectroscopic data for *S*-phenyl thiopropionate (**T8.1**) was identical to that reported previously.[137] The thiol used in the synthesis of *S*-(2,4,6-triisopropyl)phenyl thiopropionate (**T8.11**) was prepared according to ref. 149 (see below for adapted procedure).

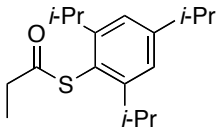



**T8.7**

***S*-*t*-Butyl thiopropionate (T8.7).** DCC (6.130 g, 29.7 mmol) was added to a stirred solution of propionic acid (2.02 mL, 27.0 mmol), *t*-butyl thiol (3.65 mL, 32.4 mmol), and DMAP (0.330 g, 2.70 mmol) in $CH_2Cl_2$ (135 mL) at 0 °C. The mixture was allowed to warm to rt and stirred overnight. Reaction filtered over celite and ppt washed with $CH_2Cl_2$. Organic phase washed with saturated aqueous $NaHCO_3$, $dH_2O$, brine, dried ($MgSO_4$) and evaporated to give a colorless liquid. Purification by vacuum distillation (57 °C at 24 torr) gave **T8.7** (0.9513 g, 24%) as a pure, colorless liquid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.47 (q, *J* = 7.6 Hz, 2H), 1.46 (s, 9H), 1.13 (t, *J* = 7.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz)[150]: δ 201.3, 47.8, 38.0, 30.0, 9.7; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_7H_{14}NaOS$: 169.1, found: 169.0.




***S*-(2,6-Dimethyl)phenyl thiopropionate (T8.9).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T8.9** (1.308 g; 90%) as a pure, colorless oil**: $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.24–7.11 (m, 3H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.34 (s, 6H), 1.23 (t, *J* = 7.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.5, 142.8, 129.8, 128.3, 127.3, 37.3, 21.8, 10.0; **ESI-MS** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}OS$: 195.1, found: 195.0.

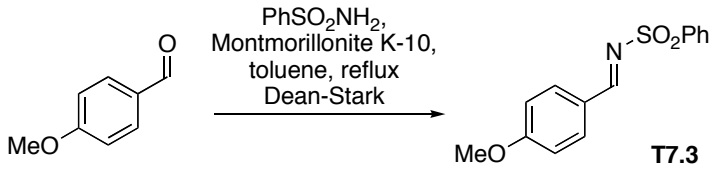



***S*-(2,4,6-Triisopropyl)phenyl thiopropionate (T8.11).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T8.11** (2.348 g; 95%) as a pure, light yellow oil: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.10–7.06 (m, 2H), 3.41 (sept, *J* = 6.8 Hz, 2H), 2.90 (sept, *J* = 6.8 Hz, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 12H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.1, 152.5, 151.1, 122.1, 122.0, 37.1, 34.5, 32.0, 24.4, 24.0, 23.6, 10.2; **ESI-MS** *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}OS$: 293.2, found: 293.2.

### *Imine Preparation*

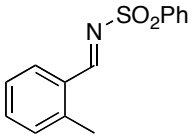
All sulfonylimines, with the exception of commercially available (Sigma-Aldrich) *N*-Benzylidenebenzenesulfonamide (**F17.1**), were prepared by condensation of the corresponding aldehyde and benzenesulfonamide according to ref. 151 (see below for representative procedure). Spectroscopic data for *N*-(4-chlorobenzylidene)benzene-sulfonamide[152] (**T7.1**) and *N*-(3-phenylallylidene)benzenesulfonamide[153] (**T7.7**) were identical to that reported previously. *N*-Boc imine **F17.3** was prepared according to ref. 62. Spectroscopic data for **F17.3** was identical to that reported previously.[62] *N*-Benzyl imine **F17.5** was purchased from Sigma-Aldrich.

***The following reaction represents the general procedure for the preparation of sulfonylimines T7.1, T7.3, T7.5, and T7.7:***




**T7.3**

**General procedure. *N*-(4-Methoxybenzylidene)benzenesulfonamide (T7.3).** A mixture of 4-methoxybenzaldehyde (0.89 mL, 7.35 mmol), benzenesulfonamide (1.16 g, 7.35 mmol) and activated Montmorillonite K-10[L] (0.650 g, 9 wt%) in toluene (38 mL) was heated to reflux (138 °C) in a Dean Stark apparatus. The reaction was stirred at reflux overnight, then cooled to rt, filtered, and evaporated to give a white solid. Recrystallization with EtOAc/hexanes gave **T7.3** (1.63 g, 81%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.97 (s, 1H), 8.03–7.85 (m, 4H), 7.64–7.48 (m, 3H), 7.00–6.94 (m, 2H), 3.88 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.8, 165.5, 138.9, 133.9, 133.4, 129.2, 127.9, 125.2, 114.8, 55.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_3S$: 298.0, found: 298.0. For additional spectral data, see ref. 154.




***N*-(2-Methylbenzylidene)benzenesulfonamide (T7.5).** Recrystallization with EtOAc/hexanes gave **FX.X** (1.22 g, 57%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.36 (s, 1H), 8.05–7.98 (m, 3H), 7.66–7.44 (m, 4H), 7.32–7.23 (m, 2H), 2.61 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.2, 142.5, 138.5, 134.8, 133.6, 131.7, 130.8, 130.4, 129.2, 128.0, 126.7, 19.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_2S$: 282.1, found: 282.0.

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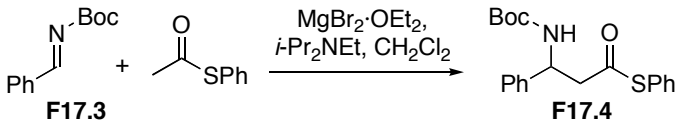
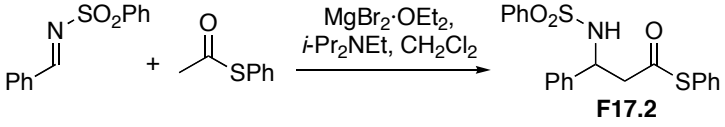
[L] Montmorillonite K-10 was activated in an oven (120 °C) overnight (>12 h) prior to use.



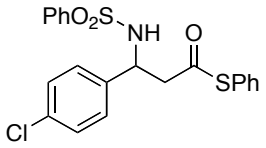

**β-amino thioester F17.4.** (Figure 17) $MgBr_2 \cdot OEt_2$ (0.090 g, 0.35 mmol) was added to a stirred solution of *S*-phenyl thioacetate (0.034 mL, 0.25 mmol) and *N*-Boc-imine (**F17.3**) (0.062 g, 0.30 mmol) in $CH_2Cl_2$ (1.25 mL), followed by the addition of *i*-$Pr_2NEt$ (0.087 mL, 0.50 mmol). Stirring was continued for 3 h and then EtOAc (1.25 mL) and 10% (v/v) aq. HCl (1.25 mL) were added. Stirring was continued for 5 min and the mixture was diluted in EtOAc (30 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **F17.4** (0.023 g; 21%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.44–7.21 (m, 10H), 5.47 (app br s, 1H), 5.15 (app br s, 1H), 3.30–3.02 (m, 2H), 1.41 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.8, 155.1, 140.8, 134.6, 129.7, 129.3, 128.8, 127.8, 127.3, 126.4, 79.9, 52.2, 49.3, 28.5; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_3S$: 380.1, found: 380.1.

***The following reaction is representative of those depicted in Table 7:***

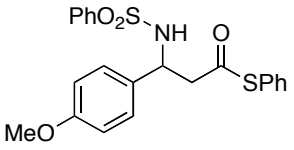



**General procedure. β-amino thioester F17.2.** (Table 7, entry 1) $MgBr_2 \cdot OEt_2$ (0.181 g, 0.70 mmol) was added to a stirred solution of *S*-phenyl thioacetate (0.081 mL, 0.60 mmol) and *N*-benzylidenebenzenesulfonamide (0.123 g, 0.50 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2NEt$ (0.17 mL, 1.0 mmol). Stirring was continued for 15 min and then

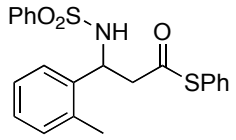
EtOAc (2.5 mL) and 10% (v/v) aq. HCl (2.5 mL) were added. Stirring was continued for 5 min and the mixture was diluted in EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **F17.2** (0.126 g; 63%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.73–7.64 (m, 2H), 7.51–7.02 (m, 13H), 5.75 (d, $J$ = 7.6 Hz, 1H), 4.82 (q, $J$ = 6.8 Hz, 1H), 3.16 and 3.06 (d AB q, $\Delta\nu_{AB}$ = 40.7 Hz, $J$ = 6.4, 15.6 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.7, 140.3, 138.8, 134.5, 132.6, 129.8, 129.4, 129.0, 128.7, 128.1, 127.2, 126.9, 126.6, 55.2, 49.6; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO_3S_2$: 420.1, found: 420.1.



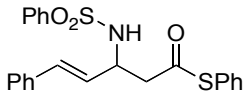

**β-amino thioester T7.2.** (Table 7, entry 2) Flash chromatography over silica gel, using a gradient of 15:85→25:75 EtOAc-hexanes gave **T7.2** (0.144 g; 67%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70–7.65 (m, 2H), 7.52–6.99 (m, 12H), 5.84 (d, $J$ = 7.6 Hz, 1H), 4.79 (q, $J$ = 6.0 Hz, 1H), 3.12 and 3.04 (d AB q, $\Delta\nu_{AB}$ = 34.3 Hz, $J$ = 6.0, 15.8 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.7, 140.3, 137.4, 134.5, 133.9, 132.7, 130.0, 129.4, 129.0, 128.8, 128.1, 127.1, 126.6, 54.6, 49.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{21}H_{18}ClNNaO_3S_2$: 454.0, found: 454.1.




**β-amino thioester T7.4.** (Table 7, entry 3) Flash chromatography over silica gel, using a gradient of 15:85→25:75 EtOAc-hexanes gave **T7.4** (0.158 g; 74%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.71–7.67 (m, 2H), 7.49–7.31 (m, 6H), 7.27–7.22 (m, 2H), 7.01–6.96 (m, 2H), 6.72–6.67 (m, 2H), 5.72 (d, $J$ = 7.2 Hz, 1H), 4.76 (q, $J$ = 6.8 Hz, 1H), 3.73 (s, 3H), 3.16 and 3.04 (d AB q, $\Delta\nu_{AB}$ = 45.5 Hz, $J$ = 6.4, 15.4 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.6, 159.3, 140.4, 134.4, 132.5, 130.9, 129.8, 129.3, 128.9, 127.9, 127.2, 127.0, 114.0, 55.4, 54.7, 49.7; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_4S_2$: 450.1, found: 450.2.

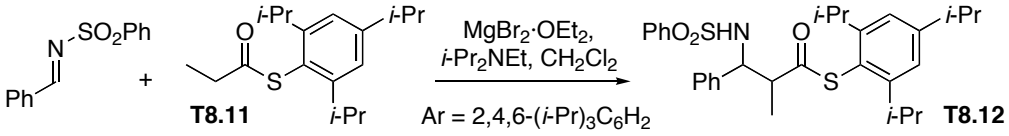



**β-amino thioester T7.6.** (Table 7, entry 4) Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **T7.6** (0.149 g; 73%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69–7.62 (m, 2H), 7.44–7.19 (m, 8H), 7.12–6.95 (m, 4H), 5.88 (d, $J$ = 7.2 Hz, 1H), 5.08 (q, $J$ = 6.8 Hz, 1H), 3.16 and 3.04 (d AB q, $\Delta\nu_{AB}$ = 44.5 Hz, $J$ = 6.4, 15.3 Hz, 2H), 2.14 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.1, 140.1, 136.9, 135.0, 134.4, 132.5, 130.6, 129.7, 129.3, 128.8, 127.9, 127.02, 127.01, 126.5, 126.1, 51.1, 49.3, 19.0; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_3S_2$: 434.1, found: 434.2.




**β-amino thioester T7.8.** (Table 7, entry 5) Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave **T7.8** (0.121 g; 57%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.86–7.81 (m, 2H), 7.51–7.11 (m, 13H), 6.33 (d, *J* = 16.0 Hz, 1H), 5.92 (dd, *J* = 7.2, 16.0 Hz, 1H), 5.42 (d, *J* = 8.4 Hz, 1H), 4.44–4.34 (m, 1H), 3.02 (d, *J* = 5.2 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ195.9, 140.8, 135.8, 134.5, 132.6, 129.8, 129.4, 129.1, 128.6, 128.1, 127.2, 126.8, 126.6, 126.5 (2 overlapping peaks), 53.5, 48.4; **ESI-MS** *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}NNaO_3S_2$: 446.1, found: 446.2.

***The following reaction is representative of those depicted in Table 9:***

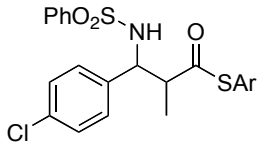



**General procedure. β-amino thioester T8.12.** (Table 9, entry 1) $MgBr_2{\cdot}OEt_2$ (0.181 g, 0.70 mmol) was added to a stirred solution of thioester **T8.11** (0.175 g, 0.60 mmol) and *N*-benzylidenebenzenesulfonamide (F**17.1**) (0.123 g, 0.50 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2NEt$ (0.17 mL, 1.0 mmol). Stirring was continued for 12 h and then EtOAc (2.5 mL) and 10% (v/v) aq. HCl (2.5 mL) were added. Stirring was continued for 5 min and the mixture was diluted in EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a light yellow oil. Flash

chromatography over silica gel, using a gradient of 10:90→15:85 EtOAc-hexanes gave **T8.12** (*syn*) (0.130 g; 48%) and **T8.12** (*anti*) (0.025 g; 9%) as pure, colorless solids.

**T8.12 (*syn*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.61–7.56 (m, 2H), 7.41–6.90 (m, 10H), 5.67 (d, *J* = 9.2 Hz, 1H), 4.46 (app t, *J* = 9.2 Hz, 1H), 3.32–3.14 [m, 2H, including a qd at δ 3.27 (*J* = 6.8, 9.2 Hz)], 2.83 (sept, *J* = 6.8 Hz, 1H), 2.43–2.27 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.13–1.03 (m, 6H), 0.88–0.75 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.6, 152.6, 152.1, 151.2, 140.5, 138.4, 132.4, 128.8, 128.5, 127.8, 127.4, 127.2, 122.0 (2 overlapping peaks), 120.9, 60.6, 54.0, 34.4, 31.8, 31.5, 24.5, 24.2, 23.94, 23.91, 23.6, 23.2, 16.4; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{39}NNaO_3S_2$: 560.2, found: 560.3.

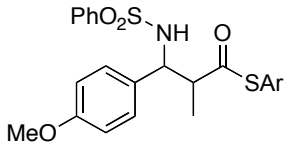
**T8.12 (*anti*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.61–7.56 (m, 2H), 7.40–6.97 (m, 10H), 6.23 (d, *J* = 9.2 Hz, 1H), 4.67 (dd, *J* = 4.4, 9.6 Hz, 1H), 3.36–3.22 [m, 2H, including a dq at δ 3.30 (*J* = 4.4, 6.8 Hz)], 2.87 (sept, *J* = 6.8 Hz, 1H), 2.69–2.57 (m, 1H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.18–1.09 (m, 6H), 1.02–0.85 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 152.7, 152.1, 151.6, 141.2, 138.9, 132.2, 128.7, 128.4, 127.4, 126.8, 126.4, 122.2 (2 overlapping peaks), 120.7, 60.6, 53.1, 34.5, 32.0, 31.6, 24.6, 24.2, 24.0, 23.9, 23.7, 23.4, 17.2; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{39}NNaO_3S_2$: 560.2, found: 560.3.




**β-amino thioester T9.1.** (Table 9, entry 2) Flash chromatography over silica gel, using a gradient of 10:90→15:85 EtOAc-hexanes gave **T9.1** (*syn*) (0.150 g; 52%) and **T9.1** (*anti*) (0.053 g; 19%) as pure, colorless solids.

**T9.1 (*syn*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.62–7.24 (m, 5H), 7.08–6.86 (m, 6H), 5.69 (d, *J* = 8.8 Hz, 1H), 4.44 (app t, *J* = 9.2 Hz, 1H), 3.28–3.12 [m, 2H, including a qd at δ 3.22 (*J* = 6.8, 9.4 Hz)], 2.84 (sept, *J* = 6.8 Hz, 1H), 2.39–2.25 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.14–1.03 (m, 6H), 0.93–0.80 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.5, 152.6, 152.1, 151.4, 140.3, 136.9, 133.8, 132.6, 129.0, 128.9, 128.6, 127.2, 122.1 (2 overlapping peaks), 120.6, 60.0, 53.8, 34.4, 31.9, 31.7, 24.5, 24.1, 23.93, 23.91, 23.6, 23.1, 16.3; **ESI-MS** *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{38}ClNNaO_3S_2$: 594.2, found: 594.3.

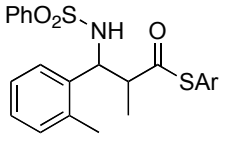
**T9.1 (*anti*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.64–7.24 (m, 5H), 7.15–6.94 (m, 6H), 6.21 (d, *J* = 9.2 Hz, 1H), 4.65 (dd, *J* = 4.4, 8.8 Hz, 1H), 3.36–3.18 [m, 2H, including a dq at δ 3.27 (*J* = 4.4, 7.2 Hz)], 2.87 (sept, *J* = 6.8 Hz, 1H), 2.61–2.47 (m, 1H), 1.39 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 6H), 1.19–1.07 (m, 6H), 1.03–0.87 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 152.5, 152.1, 151.7, 141.2, 137.6, 133.4, 132.4, 128.9, 128.6, 127.9, 126.8, 122.2 (2 overlapping peaks), 120.4, 59.9, 52.9, 34.5, 32.0, 31.8, 24.6, 24.2, 23.9 (2 overlapping peaks), 23.7, 23.2, 17.1; **ESI-MS** *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{38}ClNNaO_3S_2$: 594.2, found: 594.3.




**β-amino thioester T9.2.** (Table 9, entry 3) Flash chromatography over silica gel, using a gradient of 15:85→20:80 EtOAc-hexanes gave **T9.2** (*syn*) (0.153 g; 54%) and **T9.2** (*anti*) (0.030 g; 11%) as pure, colorless solids.

**T9.2 (*syn*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.64–7.57 (m, 2H), 7.44–6.89 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 8.4 Hz, 2H), 5.68 (d, *J* = 9.2 Hz, 1H), 4.40 (app t, *J* = 9.4 Hz, 1H), 3.72 (s, 3H), 3.33–3.13 [m, 2H, including a qd at δ 3.25 (*J* = 6.8, 10.0 Hz)], 2.83 (sept, *J* = 6.8 Hz, 1H), 2.42–2.25 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 6H), 1.14–1.03 (m, 6H), 0.89–0.76 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.5, 159.1, 152.6, 152.1, 151.2, 140.6, 132.3, 130.6, 128.8, 128.6, 127.2, 122.0 (2 overlapping peaks), 120.9, 113.7, 60.1, 55.2, 54.1, 34.4, 31.8, 31.4, 24.5, 24.1, 23.91, 23.90, 23.6, 23.1, 16.4; **ESI-MS** $m/z$ $[M + NH_4]^+$ calcd for $C_{32}H_{45}N_2O_4S_2$: 585.3, found: 585.2.

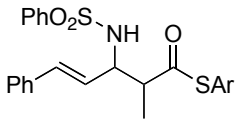
**T9.2 (*anti*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.61–7.55 (m, 2H), 7.40–6.97 (m, 5H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.15 (d, *J* = 9.2 Hz, 1H), 4.62 (dd, *J* = 4.8, 9.2 Hz, 1H), 3.74 (s, 3H), 3.36–3.20 [m, 2H, including a dq at δ 3.26 (*J* = 4.6, 7.0 Hz)], 2.87 (sept, *J* = 6.8 Hz, 1H), 2.77–2.64 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.19–1.07 (m, 6H), 1.06–0.98 (m, 3H), 0.97–0.88 (m, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 202.7, 158.9, 152.6, 152.1, 151.6, 141.3, 132.1, 131.0, 128.7, 127.6, 126.9, 122.2 (2 overlapping peaks), 120.7, 113.8, 60.1, 55.4, 53.3, 34.5, 32.0, 31.7, 24.6, 24.2, 23.95, 23.93, 23.7, 23.4, 17.1; **ESI-MS** $m/z$ $[M + NH_4]^+$ calcd for $C_{32}H_{45}N_2O_4S_2$: 585.3, found: 585.3.




**β-amino thioester T9.3.** (Table 9, entry 4) Flash chromatography over silica gel, using a gradient of 10:90→15:85 EtOAc-hexanes gave **T9.3** (*syn*) (0.126 g; 46%) and **T9.3** (*anti*) (0.031 g; 11%) as pure, colorless solids.

**T9.3 (*syn*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.56 (app d, *J* = 7.6 Hz, 2H), 7.36 (app t, *J* = 7.2 Hz, 1H), 7.26–7.15 (m, 3H), 7.09–6.79 (m, 5H), 6.06 (d, *J* = 9.2 Hz, 1H), 4.77 (app t, *J* = 9.8 Hz, 1H), 3.38–3.22 [m, 2H, including a qd at δ 3.30 (*J* = 6.8, 10.0 Hz)], 2.81 (sept, *J* = 6.8 Hz, 1H), 2.07–1.97 (m, 4H, including a s at δ 2.04), 1.46 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.16–1.02 (m, 6H), 0.81–0.69 (m, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.0, 152.8, 151.9, 151.1, 140.5, 137.3, 135.9, 132.3, 130.4, 128.6, 127.7, 126.8, 126.5, 126.3, 122.0, 121.8, 121.0, 55.5, 54.3, 34.4, 31.9, 31.2, 24.6, 23.90 (2 overlapping peaks), 23.87, 23.7, 22.9, 19.3, 16.5; **ESI-MS** *m*/*z* $[M + NH_4]^+$ calcd for $C_{32}H_{45}N_2O_3S_2$: 569.3, found: 569.3.

**T9.3 (*anti*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.51–7.45 (m, 2H), 7.33–7.13 (m, 3H), 7.08–6.96 (m, 4H), 6.81–6.73 (m, 2H), 6.29 (d, *J* = 8.8 Hz, 1H), 4.86 (dd, *J* = 4.4, 9.2 Hz, 1H), 3.37–3.24 (m, 1H), 3.14 (dq, *J* = 4.6, 7.0 Hz, 1H), 2.95–2.76 [m, 2H, including a sept at δ 2.88 (*J* = 6.8 Hz)], 2.34 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.19–1.06 (m, 9H), 0.96–0.89 (m, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 152.7, 152.1, 151.6, 141.0, 136.7, 134.3, 132.0, 130.6, 128.5, 127.3, 126.7, 126.1, 126.0, 122.2 (2 overlapping peaks), 120.7, 56.9, 51.5, 34.5, 32.0, 31.7, 24.6, 24.2, 24.0, 23.9, 23.7, 23.6, 19.4, 17.4; **ESI-MS** *m*/*z* $[M + NH_4]^+$ calcd for $C_{32}H_{45}N_2O_3S_2$: 569.3, found: 569.3.




**β-amino thioester T9.4.** (Table 9, entry 5) Flash chromatography over silica gel, using a gradient of 10:90→15:85 EtOAc-hexanes gave **T9.4** (*syn*) (0.094 g; 33%) and **T9.4** (*anti*) (0.046 g; 16%) as pure, colorless solids.

**T9.4 (*syn*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.84–7.78 (m, 2H), 7.45–7.00 (m, 10H), 6.17 (d, *J* = 16.0 Hz, 1H), 5.82 (dd, *J* = 8.4, 16.0 Hz, 1H), 5.35 (d, *J* = 8.8 Hz, 1H), 4.08 (app q, *J* = 7.6 Hz, 1H), 3.34–3.05 [m, 3H, including an app pent at δ 3.10 (*J* = 6.8 Hz)], 2.88 (sept, *J* = 7.2 Hz, 1H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.24 (d, 7.2 Hz, 6H), 1.16–0.96 (m, 12H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 201.1, 152.6, 152.2, 151.5, 141.0, 135.9, 134.2, 132.6, 129.0, 128.5, 128.2, 127.4, 126.6, 124.7, 122.2 (2 overlapping peaks), 120.8, 59.4, 52.6, 34.4, 32.0, 24.4, 24.2, 23.9, 23.6, 23.5, 15.6; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{41}NNaO_3S_2$: 586.2, found: 586.4.

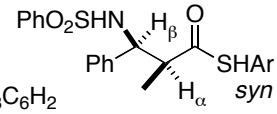
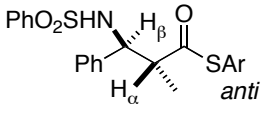
**T9.4 (*anti*). $^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.83–7.77 (m, 2H), 7.46–6.98 (m, 10H), 6.26 (d, *J* = 16.0 Hz, 1H), 5.85 (dd, *J* = 6.6, 16.0 Hz, 1H), 5.75 (d, *J* = 9.2 Hz, 1H), 4.28–4.19 (m, 1H), 3.40–3.02 [m, 3H, including a dq at δ 3.19 (*J* = 4.0, 7.0 Hz)], 2.88 (sept, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.30–0.84 [m, 18H, including a d at δ 1.24 (*J* = 6.8 Hz)]; **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 202.7, 152.6, 152.2, 151.6, 141.7, 135.9, 132.4 (2 overlapping peaks), 129.0, 128.5, 128.1, 127.1, 126.7, 126.5, 122.2, 120.7, 58.8, 51.5, 34.5, 32.0, 24.3, 24.2, 24.0, 23.9, 23.7, 23.4, 16.2 (2 peaks overlapping); **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{41}NNaO_3S_2$: 586.2, found: 586.4.

### *Assignment of syn and anti Configuration*

A crystal structure was obtained for the major diastereomer of **T8.12**,[M] which was determined to have the *syn* configuration (see Figure 19). Assignment of the *syn* and *anti* diastereomers of **T9.1**–**T9.3** was done by analogy of their $^1$H NMR spectra to that of **T8.12**. In each case, the major (*syn*) isomer showed an apparent $H_\beta$ triplet, whereas the minor (*anti*) isomer showed a $H_\beta$ double of doublets (see Table 20).

[M] Needle-like crystals of the major isomer of **T8.12** were obtained after slow evaporation from MeOH.

**Table 20: Selected $^1$H NMR Shifts and Coupling Constants for Mannich Products T8.12, T9.1–T9.3**

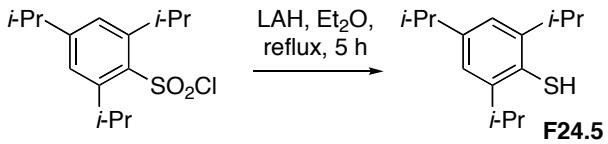
| Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ |  *syn* |  *anti* |
|---|---|---|
| **Compd** | ***syn* $H_\beta$ (δ)** | ***anti* $H_\beta$ (δ)** |
| **T8.12** | 4.46 (app t, *J* = 9.2 Hz) | 4.67 (dd, *J* = 4.4, 9.6 Hz) |
| **T9.1** | 4.44 (app t, *J* = 9.2 Hz) | 4.65 (dd, *J* = 4.4, 8.8 Hz) |
| **T9.2** | 4.40 (app t, *J* = 9.4 Hz) | 4.62 (dd, *J* = 4.8, 9.2 Hz) |
| **T9.3** | 4.77 (app t, *J* = 9.8 Hz) | 4.86 (dd, *J* = 4.4, 9.2 Hz) |

## *4.3 Stereoselective Aldol Addition of α-Halogenated Thioesters Employing Soft Enolization*

**General Considerations.** Diastereomeric ratios and percent conversions were determined by $^1$H NMR analysis of the crude materials.

### *Thiol Preparation*

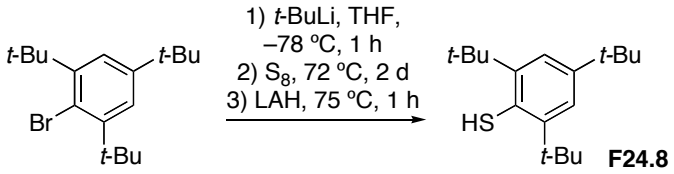
2,4,6-Triisopropylbenzenethiol (**F24.5**) was prepared according to ref. 149 (see below for adapted procedure). 2,4,6-Tri-*tert*-butylbenzene-thiol (**F24.8**) was prepared according to ref. 155 (see below for adapted procedure).



**F24.5**

**2,4,6-Triisopropylbenzenethiol (F24.5).** To a suspension of LAH (1.52 g, 40.0 mmol) in $Et_2O$ (30 mL) at 0 °C was added *slowly* a solution of 2,4,6-triisopropylbenzenesulfonyl

chloride (4.0 g, 13.2 mmol) in $Et_2O$ (20 mL) via cannula. The reaction was heated to reflux and stirred for 5.5 h. Reaction cooled to 0 °C, quenched by the *dropwise* addition of 10% aq. HCl (20 mL), diluted in $Et_2O$, and filtered over celite to remove the heavy grey ppt. Aq. phase extracted with $Et_2O$ (3 x 30 mL), organic phases combined, washed with brine, dried ($MgSO_4$) and evaporated to give **F24.5** (2.86 g; 92%) as a light yellow oil, which was used without any further purification. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.00 (s, 2H), 3.50 (sept, $J$ = 6.8 Hz, 2H), 3.07 (s, 1H), 2.86 (sept, $J$ = 6.8 Hz, 1H), 1.26 (d, $J$ = 7.2 Hz, 12H), 1.24 (d, $J$ = 7.2 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 148.2, 147.2, 124.4, 121.5, 34.3, 31.9, 24.2, 23.4; **ESI-MS** $m/z$ [M – H] calcd for $C_{15}H_{24}NaS$: 235.2, found: 235.1.



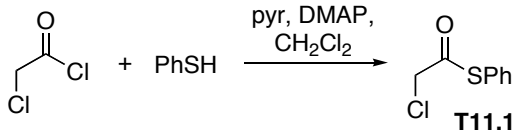
**F24.8**

**2,4,6-Tri-*tert*-butylbenzenethiol (F24.8).** A solution of *t*-BuLi (1.7 M in pentane, 4.4 mL, 7.50 mmol) was added dropwise to a stirred solution of 1-bromo-2,4,6-tri-*t*-butylbenzene (1.65 g, 5.07 mmol) in THF (24 mL) at –78 °C. Reaction stirred at –78 °C for 1 h, then warmed to rt. Sulfur (0.246 g, 7.61 mmol) was added to the reaction followed by THF (2 mL) to rinse, heated to reflux (72 °C), and stirred for 2 d. Reaction cooled to rt and an excess of LAH (1.0 g, 26.4 mmol) was added followed by THF (5 mL) to rinse, heated to reflux (75 °C), and stirred for 1 h. Reaction cooled to 0 °C, followed by *careful dropwise* addition of $dH_2O$ until gas release ceased (~ 5 mL). Resulting precipitate was dissolved in 10% aq. $H_2SO_4$ (40 mL) at 0 °C. Benzene (20 mL) was added, stirred rapidly for 20 min at 0 °C, then warmed to rt. Additional benzene (20 mL) was added, stirred rapidly for 2 min, then diluted in EtOAc (100 mL), aq. phase extracted with EtOAc (3 x 50 mL),

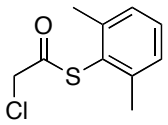
organics combined and washed with $dH_2O$ (2 x 10 mL), brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 100% hexanes gave a 77:23 mixture of **F24.8** to 1,3,5-tri-*tert*-butylbenzene (1.148 g; 81%) as a colorless solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.42 (s, 2H), 3.57 (s, 1H), 1.60 (s, 18H), 1.31 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 150.7, 148.1, 122.8, 119.6, 37.6, 35.1, 31.54, 31.53; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{18}H_{30}NaS$: 301.2, found: 301.2. For additional spectral data, see refs. 155-157.

### *Thioester Preparation*

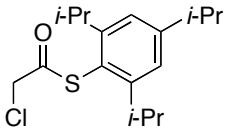
***The following reaction represents a general procedure for the preparation of α-chloro thioesters T11.1, F24.3, F24.6, and F24.9:***



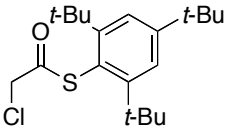

**General procedure. *S*-Phenyl α-chlorothioacetate (T11.1).** Pyridine (2.5 mL, 5 vol%) was added dropwise to a stirred solution of chloroacetyl chloride (1.80 mL, 22.6 mmol), benzenethiol (2.0 mL, 19.5 mmol) and DMAP (0.243 g, 1.99 mmol) in $CH_2Cl_2$ (48 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min, then warmed to rt and allowed to stir overnight. Reaction quenched by the addition of saturated aqueous $NH_4Cl$ (15 mL), diluted in EtOAc (200 mL), $dH_2O$ added to just dissolve the formed ppt (5 mL), organic phase washed with $dH_2O$ (2 x 10 mL), brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T11.1** (3.452 g; 95%) as a pure, colorless solid. Spectroscopic data was identical to that reported previously.[158, 159]




***S*-(2,6-Dimethyl)phenyl α-chlorothioacetate (F24.3).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **F24.3** (0.640 g; 86%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.28–7.21 (m, 1H), 7.19–7.13 (m, 2H), 4.26 (s, 2H), 2.35 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 191.3, 143.0, 130.4, 128.6, 125.8, 48.0, 21.7; **ESI-MS** $m/z$ [M + H]$^+$ calcd for $C_{10}H_{12}ClOS$: 215.0, found: 214.9.



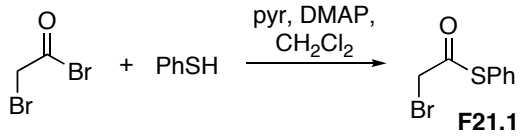

***S*-(2,4,6-Triisopropyl)phenyl α-chlorothioacetate (F24.6).** Flash chromatography over silica gel, using 3:97 EtOAc-hexanes gave **F24.6** (0.353 g; 89%) as a pure, light yellow solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.10 (s, 2H), 4.28 (s, 2H), 3.35 (sept, $J$ = 6.8 Hz, 2H), 2.92 (sept, $J$ = 6.8 Hz, 1H), 1.27 (d, $J$ = 6.8 Hz, 6H), 1.19 (d, $J$ = 6.8 Hz, 12H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 192.8, 152.7, 151.8, 122.4, 120.4, 48.0, 34.5, 32.1, 24.5, 24.0, 23.6; **ESI-MS** $m/z$ [M + $NH_4$]$^+$ calcd for $C_{17}H_{29}ClNOS$: 330.2, found: 330.2.




***S*-(2,4,6-Tri-*tert*-butyl)phenyl α-chlorothioacetate (F24.9).** Flash chromatography over silica gel, using 2.5:97.5 EtOAc-hexanes gave **F24.9** (0.449 g; 70%) as a pure, colorless

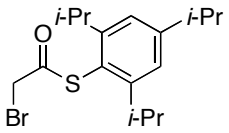
solid: **$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ 7.50 (s, 2H), 4.17 (br s, 2H), 1.45 (s, 18H), 1.34 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 193.3 (br s), 154.8, 152.4 (br s), 123.5, 121.5 (br s), 47.8, 38.0, 35.4, 32.1, 31.4; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{31}ClNaOS$: 377.2, found: 377.2.

***The following reaction represents a general procedure for the preparation of α-bromo thioesters F21.1 and T12.3:***

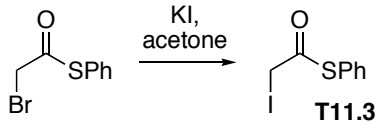



**F21.1**

**General procedure. *S*-Phenyl α-bromothioacetate (F21.1).** Pyridine (0.93 mL, 11.5 mmol) was added dropwise to a stirred solution of bromoacetyl bromide (1.09 mL, 12.5 mmol), benzenethiol (1.12 mL, 10.9 mmol) and DMAP (0.136 g, 1.11 mmol) in $CH_2Cl_2$ (50 mL) at 0 ºC. The mixture was stirred at 0 ºC for 10 min, then warmed to rt and allowed to stir overnight. Reaction quenched by the addition of saturated aqueous $NH_4Cl$ (15 mL), diluted in EtOAc (200 mL), $dH_2O$ added to just dissolve the formed precipitate (5 mL), organic phase washed with $dH_2O$ (2 x 10 mL), brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **F21.1** (2.365 g; 94%) as a pure, colorless solid. Spectroscopic data was identical to that reported previously.[160, 161]



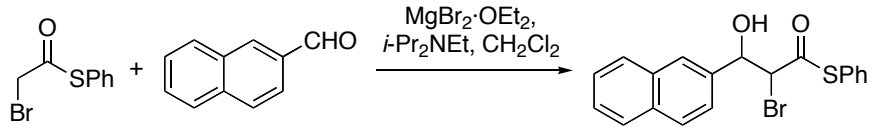

***S*-(2,4,6-Triisopropyl)phenyl α-bromothioacetate (T12.3).** Flash chromatography over silica gel, using 2.5:97.5 EtOAc-hexanes gave **T12.3** (0.696 g; 92%) as a pure, colorless solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.10 (s, 2H), 4.12 (s, 2H), 3.38 (sept, $J$ = 6.8 Hz, 2H), 2.91 (sept, $J$ = 6.8 Hz, 1H), 1.27 (d, $J$ = 7.2 Hz, 6H), 1.19 (d, $J$ = 7.2 Hz, 12H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 191.6, 152.7, 151.8, 122.4, 120.8, 34.5, 33.1, 32.1, 24.5, 24.0, 23.7; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{17}H_{25}BrNaOS$: 379.1, found: 379.2.




***S*-Phenyl α-iodothioacetate (T11.3).** NaI (1.69 g, 11.3 mmol) was added to a stirred solution of *S*-phenyl α-bromothioacetate (**F21.1**) (1.31 g, 5.67 mmol) in acetone (50 mL). The reaction was covered to exclude the light and allowed to stir overnight. The mixture was concentrated and then dissolved in $Et_2O$. Organic phase washed with $dH_2O$, brine, dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T11.3** (1.545 g; 98%) as a yellow light-sensitive solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.43 (app s, 5H), 4.08 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 191.2, 134.5, 130.0, 129.5, 127.2, 3.6; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_8H_7INaOS$: 300.9, found: 300.9.

***The following reaction is representative of those depicted in Figure 21 and Table 10:***

*The reactions were conducted using untreated $CH_2Cl_2$,[N] open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*




**General Procedure. α-Bromo-β-Hydroxy thioester (F21.2).** $MgBr_2{\cdot}OEt_2$ (0.181 g, 0.7 mmol) was added to a stirred solution of *S*-phenyl α-bromothioacetate (**F21.1**) (0.139 g, 0.6 mmol) and 2-naphthaldehyde (0.078 g, 0.5 mmol) in $CH_2Cl_2$ (2.5 mL), followed by the addition of *i*-$Pr_2NEt$ (0.17 mL, 1.0 mmol). The reaction flask was capped to prevent evaporation. Stirring was continued for 30 min at rt and then EtOAc (2.5 mL) and 10% (v/v) aqueous HCl (2.5 mL) were added. Stirring was continued for 10 min and the mixture was partitioned between EtOAc (30 mL) and $H_2O$ (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

## *4.4 Organocatalytic Asymmetric Mannich Reaction via Soft Enolization of Thioesters*

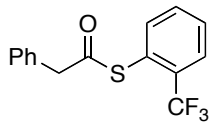
**General considerations.** Diastereomeric ratios were determined by either $^1H$ NMR or HPLC analysis of the crude materials. Percent conversions were determined by $^1H$ NMR analysis of the crude materials. Only NMR data of the major (*syn*)

[N] Sigma-Aldrich. ACS reagent grade, ≥99.5%.

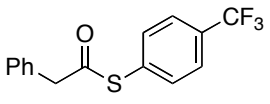
diastereomer is reported below. Enantiomeric ratios (e.r.) were based on the major diastereomer and determined by chiral-phase HPLC using a Hewlett-Packard 1090 Series instrument.

### *Thioester Preparation*

Thioesters were prepared from the corresponding commercially available (Sigma-Aldrich) thiols and phenylacetic acid under typical DCC or EDCI-mediated coupling conditions (see, for example, refs. 24, 115, 162). Spectroscopic data for thioesters *S*-phenyl phenylthioacetate[163] (**T 1 3 . 1**) and *S*-2,2,2-trifluoroethyl phenylthioacetate[115] (**T14.11**) were identical to that reported previously.

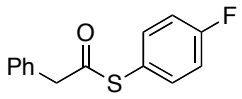



***S*-(2-Trifluoromethylphenyl) phenylthioacetate** (**T14.1**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.75 (app d, $J$ = 7.2 Hz, 1H), 7.58–7.46 (m, 3H), 7.39–7.26 (m, 5H), 3.94 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 194.2, 139.0, 133.2 (q, $J$ = 32.8 Hz), 133.0, 132.3, 130.0, 129.8, 128.9, 127.8, 127.2 (q, $J$ = 5.3 Hz), 126.6, 123.3 (q, $J$ = 273.9 Hz), 50.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{11}F_3NaOS$: 319.0, found: 319.0.

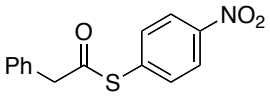



***S*-(4-Trifluoromethylphenyl) phenylthioacetate** (**T14.3**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.65–7.60 (m, 2H), 7.53–7.47 (m, 2H), 7.40–7.30 (m, 5H), 3.94 (s, 2H); **$^{13}$C NMR** ($CDCl_3$,

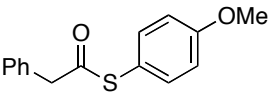
100 MHz): δ 194.3, 134.6, 132.9, 132.6 (br signal), 131.4 (q, $J$ = 32.9 Hz), 129.8, 129.0, 127.9, 126.0 (q, $J$ = 3.7 Hz), 123.9 (q, $J$ = 272.3 Hz), 50.5; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{11}F_3NaOS$: 319.0, found: 319.0.




***S*-(4-Fluorophenyl) phenylthioacetate** (**T14.5**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.39–7.27 (m, 7H), 7.11–7.02 (m, 2H), 3.90 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 195.5, 163.6 (d, $J$ = 249.8 Hz), 136.6 (d, $J$ = 8.3 Hz), 133.2, 129.8, 128.9, 127.7, 123.2 (d, $J$ = 3.4 Hz), 116.5 (d, $J$ = 22.1 Hz), 50.1; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{14}H_{11}FNaOS$: 269.0, found: 269.0.

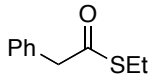



***S*-(4-Nitrophenyl) phenylthioacetate** (**T14.7**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.25–8.16 (m, 2H), 7.60–7.52 (m, 2H), 7.43–7.28 (m, 5H), 3.96 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 193.4, 148.2, 136.4, 134.8, 132.6, 129.9, 129.0, 128.0, 124.0, 50.6; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{14}H_{11}NNaO_3S$: 296.0, found: 296.0.




***S*-(4-Methoxyphenyl) phenylthioacetate** (**T14.9**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.40–7.22 (m, 7H), 6.93–6.87 (m, 2H), 3.88 (s, 2H), 3.78 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100

MHz): δ 196.4, 160.8, 136.2, 133.5, 129.8, 128.8, 127.6, 118.6, 114.9, 55.4, 50.0; **ESI-MS** *m* / *z* $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_2S$: 281.1, found: 281.0.




***S*-Ethyl phenylthioacetate** (**T14.13**). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.38–7.22 (m, 5H), 3.80 (s, 2H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.6, 133.9, 129.7, 128.7, 127.5, 50.6, 23.8, 14.6; **ESI-MS** *m* / *z* $[M + Na]^+$ calcd for $C_{10}H_{12}NaOS$: 203.0, found: 203.0.

### *Catalyst Preparation*

Catalysts **F28.1** and **T15.1–T15.1** were prepared according to literature procedures (see below for representative procedure).[68] Spectroscopic data for 3,5-(bistrifluoromethyl)phenyl thiourea catalyst **F28.1**[68, 164] and 3,5-(bistrifluoromethyl)phenyl urea catalyst **T15.1**[164] were identical to that reported previously. 1,3-Diphenyurea (**F31.2**) was purchased from Sigma-Aldrich.

***The following reactions represent the general procedure for the preparation of thio(urea) catalysts F28.1 and T15.1–T15.3:***

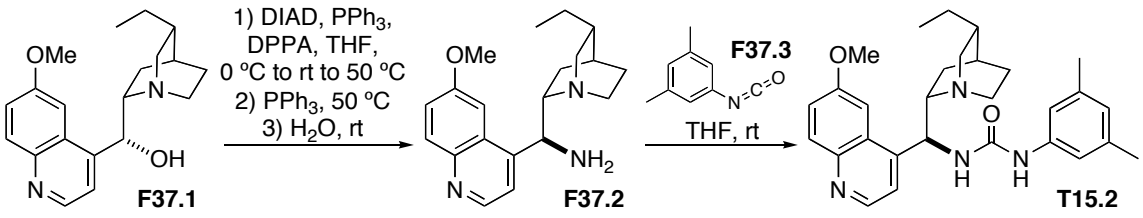


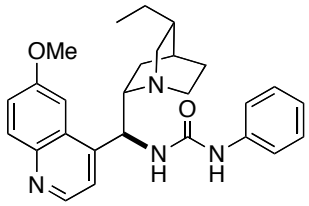

**Figure 37: Representative Synthesis of the Thio(urea) Catalysts**

**General procedure. 3,5-Dimethylphenyl Urea catalyst T15.2.** Hydroquinine (**F37.1**) (0.979 g, 2.0 mmol) and triphenylphosphine (0.944 g, 3.6 mmol) were dissolved in THF (10 mL), and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD, 0.71 mL, 3.6 mmol) was added all at once. Then, a solution of diphenyl phosphoryl azide (DPPA, 0.78 mL, 3.6 mmol) in THF (5 mL) was added dropwise at 0 °C. The mixture was warmed to rt, stirred at rt for 15 h, heated to 50 °C and stirred for an additional 2 h. Triphenylphosphine (1.03 g, 3.9 mmol) was added and heating was maintained until gas evolution had ceased (2 h). The solution was cooled to rt, d$H_2O$ (0.5 mL) was added and stirred for 3 h. Solvents were evaporated and the residue was dissolved in $CH_2Cl_2$ and 10% v/v aq. HCl (1:1, 25 mL). The aq. phase was made alkaline with excess aq. $NH_4OH$ and extracted with $CH_2Cl_2$ (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to yield a light orange viscous oil. Flash chromatography over silica gel, using 49.5:49.5:1 MeOH:EtOAc:aq. $NH_4OH$ gave amine **F37.2** (0.790 g; 80%) as a pure, yellow viscous oil. Spectroscopic data was identical to that reported previously.[68]

3,5-Dimethylphenylisocyanate (**F37.3**) (0.14 mL, 0.98 mmol) was added to a stirred solution of amine **F37.2** (0.319 g, 0.98 mmol) in THF (5 mL) at rt. Reaction stirred at rt for 24 h, then evaporated to give a foam-like solid. Flash chromatography over silica gel, using a gradient of 5:95→10:90 MeOH-$CH_2Cl_2$ + 0.3% aq. $NH_4OH$ gave **T15.2** (0.371 g; 80%) as a pure, foam-like colorless solid[O]: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.75 (d, *J* = 4.8 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.46 (br s, 1H), 7.41–7.34 (m, 2H), 6.84 (s, 2H), 6.68–6.56 [m, 2H, including a d at δ 6.34 (*J* = 4.0 Hz) and a s at δ 6.59], 3.99 (s,

[O] In any case where a manageable foam-like solid was not obtained, and instead the product dried as a glassy solid, the compound was redissolved in $CH_2Cl_2$ and then dried first by removing the solvent under a stream of $N_2$ and then by placing the wet solid on the high vac. The process was repeated, if necessary.

3H), 3.44–3.30 (m, 1H), 3.23–3.10 (m, 1H), 2.95 (dd, $J$ = 10.0, 13.2 Hz, 1H), 2.67–2.54 (m, 1H), 2.30–2.00 (m, 8H, including a s at δ 2.18), 1.71–1.58 (m, 2H), 1.55–1.31 (m, 3H), 1.22–1.07 (m, 2H), 0.92 (dd, $J$ = 6.0, 13.2 Hz, 1H), 0.72 (t, $J$ = 7.4 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz, contains 2 overlapping peaks): δ158.2, 155.7, 147.6, 145.4, 145.0, 138.8, 138.5, 131.8, 128.6, 124.8, 122.1, 119.2 (br s), 117.7, 102.2, 59.7, 57.2, 55.9, 41.4, 36.8, 28.0, 27.3, 26.3, 25.1, 21.4, 12.0; **ESI-MS** $m/z$ $[M + H]^+$ calcd for $C_{29}H_{37}N_4O_2$: 473.3, found: 473.4.

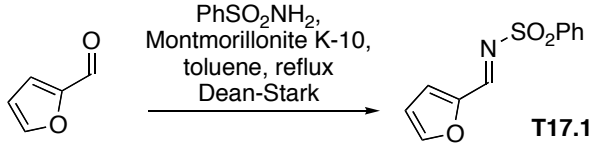



**Phenyl Urea catalyst T15.3.** Flash chromatography over silica gel, using a gradient of 7:92.5→10:90 MeOH-$CH_2Cl_2$ + 0.3% aq. $NH_4OH$ gave **T15.3** (0.341 g; 78%) as a pure, foam-like colorless solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.77 (d, $J$ = 4.4 Hz, 1H), 8.03 (d, $J$ = 9.2 Hz, 1H), 7.78 (d, $J$ = 2.4 Hz, 1H), 7.63 (br s, 1H), 7.42–7.34 [m, 2H, including a dd at δ 7.39 ($J$ = 2.4, 9.2 Hz) and a d at δ 7.36 ($J$ = 4.8 Hz)], 7.24–7.10 (m, 4H), 6.92 (t, $J$ = 7.2 Hz, 1H), 6.50 (d, $J$ = 4.8 Hz, 1H), 3.99 (s, 3H), 3.57–3.34 (m, 2H), 3.27–3.15 (m, 1H), 3.00 (dd, $J$ = 10.4, 13.6 Hz, 1H), 2.71–2.59 (m, 1H), 2.18–2.08 (m, 1H), 1.72–1.59 (m, 2H), 1.57–1.34 (m, 3H), 1.24–1.08 (m, 2H), 0.97–0.88 (m, 1H), 0.73 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz, contains 2 sets of overlapping peaks): δ 158.3, 155.6, 147.5, 145.0, 139.1, 131.8, 128.9, 128.6, 122.8, 122.2, 119.7, 119.1 (br signal), 102.1, 59.7 (br signal), 57.2, 55.9, 41.5, 36.7, 27.9, 27.3, 26.4, 25.1, 11.9; **ESI-MS** $m/z$ $[M + H]^+$ calcd for $C_{27}H_{33}N_4O_2$: 445.3, found: 445.4.

***Imine Preparation***

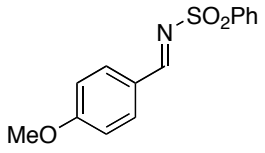
All sulfonylimines, with the exception of commercially available (Sigma-Aldrich) *N*-benzylidenebenzenesulfonamide (**F17.1**), were prepared by condensation of the corresponding aldehyde and benzenesulfonamide according to ref. 151 (see below for representative procedure). Spectroscopic data for *N*-(4-chlorobenzylidene)benzene-sulfonamide (**T7.1**) was identical to that reported previously.[152]

***The following reaction represents the general procedure for the preparation of sulfonylimines T17.1, T7.1, T7.3, and T7.5:***

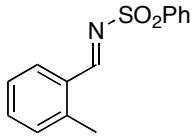



**General procedure. *N*-(Furan-2-ylmethylene)benzenesulfonamide (T17.1).** A mixture of 2-furaldehyde (0.90 mL, 10.9 mmol), benzenesulfonamide (1.715 g, 10.9 mmol) and activated Montmorillonite K-10[p] (985 mg, 9 wt%), in toluene (50 mL) was heated to reflux (138 °C) in a Dean Stark apparatus. The reaction was stirred at reflux for 12 h, then cooled to rt, filtered, and evaporated to give a white solid. Recrystallization with EtOAc/hexanes gave **T17.1** (1.51 g, 59%) as a pure, white solid: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.84 (s, 1H), 8.03–7.97 (m, 2H), 7.78–7.74 (m, 1H), 7.67–7.50 (m, 3H), 7.37 (d, $J$ = 4.0 Hz, 1H), 6.66 (dd, $J$ = 1.6, 4.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 156.1, 150.0, 149.1, 138.3, 133.6, 129.2, 128.1, 125.2, 113.9; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{11}H_9NNaO_3S$: 258.0, found: 258.0.

[p] Montmorillonite K-10 was activated in an oven (120 °C) overnight (>12 h) prior to use.

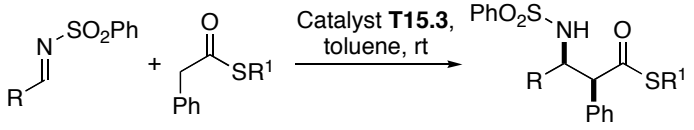



***N*-(4-Methoxybenzylidene)benzenesulfonamide (T7.3).** Recrystallization with EtOAc/hexanes gave **T7.3** (1.63 g, 81%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.97 (s, 1H), 8.03–7.85 (m, 4H), 7.64–7.50 (m, 3H), 7.00–6.94 (m, 2H), 3.88 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.8, 165.5, 138.9, 133.9, 133.4, 129.2, 127.9, 125.2, 114.8, 55.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_3S$: 298.0, found: 298.0. For additional spectral data, see ref. 154.

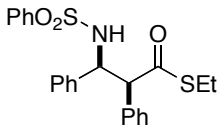



***N*-(2-Methylbenzylidene)benzenesulfonamide (T7.5).** Recrystallization with EtOAc/hexanes gave **T7.5** (1.22 g, 57%): **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.36 (s, 1H), 8.05–7.98 (m, 3H), 7.66–7.44 (m, 4H), 7.32–7.23 (m, 2H), 2.61 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 169.2, 142.5, 138.5, 134.8, 133.6, 131.7, 130.8, 130.4, 129.2, 128.0, 126.7, 19.8; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_2S$: 282.1, found: 282.0.

***Biomimetic Mannich Reaction with Various Sulfonylimines***

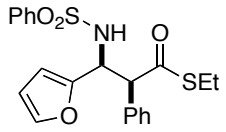



***General procedure for the Mannich Reaction with Thioester T14.13 ($R^1$ = Et).***

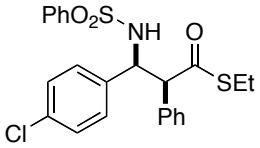



**β-Amino thioester (T14.14).** (Table 17, entry 1) Urea catalyst **T15.3** (0.044 g, 0.10 mmol) was added to a stirred solution of *N*-benzylidenebenzenesulfonamide (**F17.1**) (0.123 g, 0.50 mmol) and *S*-Ethyl phenylthioacetate (**T14.13**) (0.270 g, 1.50 mmol) in toluene (1.0 mL) at rt. Stirring was continued for 24 h, then concentrated and dried under reduced pressure to give a white solid. Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T14.14** (0.165 g; 77%) as a pure, white solid, comprised of a 95:5 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.50–6.97 (m, 15H), 4.92 (dd, $J$ = 4.8, 10.2 Hz, 1H), 4.80 (d, $J$ = 4.8 Hz, 1H), 3.96 (d, $J$ = 10.4 Hz, 1H), 2.62 and 2.51 (q AB q, $\Delta\nu_{AB}$ = 46.1 Hz, $J$ = 7.4, 13.7 Hz, 2H), 0.91 (t, $J$ = 7.4 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.2, 139.7, 138.1, 133.9, 132.4, 129.3, 128.9, 128.8, 128.7, 128.3, 128.1, 128.0, 127.3, 66.5, 60.0, 23.7, 14.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{23}NNaO_3S_2$: 448.1, found: 448.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 27.3 min (*syn*, major enantiomer), 46.0 min (*syn*, minor

enantiomer), 30.2 min (*anti*, major enantiomer), 49.4 min (*anti*, minor enantiomer). e.r. (*syn)* = 87:13.

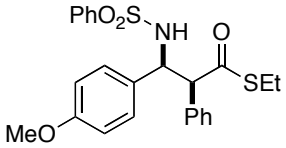



**β-Amino thioester (T17.2).** (Table 17, entry 3) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.2** (0.141 g; 66%) as a pure, off-white solid, comprised of a 92:8 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.62–7.08 (m, 11H), 6.14–6.02 (m, 2H), 5.11 (dd, *J* = 8.0, 10.0 Hz, 1H), 4.85 (app d, *J* = 8.0 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 2.79–2.58 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.5, 150.3, 142.3, 140.1, 133.9, 132.3, 129.1, 129.0, 128.8, 128.6, 127.0, 110.3, 109.3, 63.8, 53.4, 23.7, 14.4; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{21}NNaO_4S_2$: 438.1, found: 438.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 27.6 min (*syn*, major enantiomer), 30.1 min (*syn*, minor enantiomer), 26.6 min (*anti*, major enantiomer), 32.9 min (*anti*, minor enantiomer). e.r. (*syn)* = 76:24.

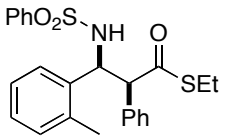



**β-Amino thioester (T17.4).** (Table 17, entry 5) Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T17.4** (0.184 g; 73%) as a pure, white solid, comprised of a 93:7 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.52–7.03 (m,

14H), 4.87 (dd, $J$ = 4.2, 10.2 Hz, 1H), 4.73 (d, $J$ = 4.0 Hz, 1H), 3.91 (d, $J$ = 10.4 Hz, 1H), 2.64 and 2.55 (q AB q, $\Delta\nu_{AB}$ = 34.8 Hz, $J$ = 7.2, 13.6 Hz, 2H), 0.95 (t, $J$ = 7.4 HZ, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ197.1, 139.4, 136.7, 133.9, 133.5, 132.6, 129.6, 129.5, 128.9, 128.85, 128.82, 128.5, 127.3, 66.2, 59.4, 23.8, 14.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{22}ClNNaO_3S_2$: 482.1, found: 482.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 88/12, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 15.6 min (*syn*, major enantiomer), 28.0 min (*syn*, minor enantiomer), 21.7 min (*anti*, major enantiomer), 43.8 min (*anti*, minor enantiomer). e.r. (*syn)* = 85:15.

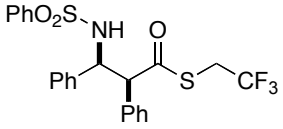



**β-Amino thioester (T17.6).** (Table 17, entry 7) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.6** (0.096 g; 41%) as a pure, white solid, comprised of a 93:7 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.48–7.02 [m, 12H, including a d at δ 7.08 ($J$ = 8.8 Hz)], 6.68 (d, $J$ = 8.8 Hz, 2H), 4.87 (dd, $J$ = 4.2, 10.2 Hz, 1H), 4.59 (d, $J$ = 3.6 Hz, 1H), 3.95 (d, $J$ = 10.0 Hz, 1H), 3.76 (s, 3H), 2.70–2.48 (m, 2H), 0.94 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.3, 159.3, 139.7, 134.0, 132.3, 130.1, 129.35, 129.31, 128.9, 128.8, 128.7, 127.3, 113.7, 66.5, 59.5, 55.4, 23.7, 14.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{24}H_5NNaO_4S_2$: 478.1, found: 478.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 22.7 min (*syn*, major enantiomer), 32.4 min (*syn*, minor enantiomer), 28.2 min (*anti*, major enantiomer), 42.7 min (*anti*, minor enantiomer). e.r. (*syn)* = 84:16.



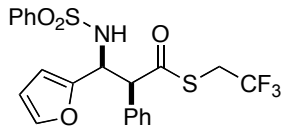

**β-Amino thioester (T17.8).** (Table 17, entry 9) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.8** (0.176 g; 78%) as a pure, white solid, comprised of a 98:2 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.40–6.92 (m, 14H), 5.27 (dd, $J$ = 5.4, 9.8 Hz, 1H), 4.82–4.68 (m, 1H), 4.06 (d, $J$ = 10.0 Hz, 1H), 2.62 and 2.50 (q AB q, $\Delta\nu_{AB}$ = 47.3 Hz, $J$ = 7.2, 13.9 Hz, 2H), 2.36 (s, 3H), 0.89 (t, $J$ = 7.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 197.0, 140.0, 136.41, 136.38, 134.2, 132.1, 130.4, 129.1, 129.0, 128.6, 128.53, 128.51, 127.8, 126.9, 126.2, 65.9, 55.3 (br signal), 23.6, 19.4, 14.2; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{24}H_{25}NNaO_3S_2$: 462.1, found: 462.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 24.9 min (*syn*, major enantiomer), 30.6 min (*syn*, minor enantiomer), 23.2 min (*anti*, major enantiomer), 34.4 min (*anti*, minor enantiomer). e.r. (*syn)* = 88:12.

***General procedure for the Mannich Reaction with Thioester T14.11 ($R^1$ = $CH_2CF_3$).***



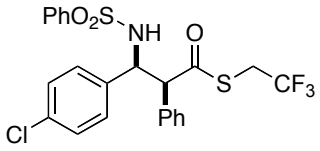

**β-Amino thioester (T14.12).** (Table 17, entry 2) Urea catalyst **T15.3** (0.011 g, 0.025 mmol) was added to a stirred solution of *N*-benzylidenebenzenesulfonamide (**F17.1**) (0.123 g, 0.50 mmol) and *S*-trifluoroethyl phenylthioacetate (**T14.11**) (0.176 g, 0.75 mmol) in toluene (2.5 mL) at rt. Stirring was continued for 24 h, then concentrated and dried

under reduced pressure to give a white solid. Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T14.12** (0.227 g; 95%) as a pure, white solid, comprised of a 93:7 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.45–7.06 (m, 15H), 4.97 (dd, $J$ = 5.2, 10.2 Hz, 1H), 4.78–4.72 (m, 1H), 4.05 (d, $J$ = 10.0 Hz, 1H), 3.34 and 3.31 (q AB q, $\Delta\nu_{AB}$ = 31.2 Hz, $J$ = 10.0, 15.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ193.8, 139.7, 137.5, 132.8, 132.4, 129.5, 129.2, 129.1, 128.8, 128.5, 128.3, 127.8, 127.2, 124.3 (q, $J$ = 275.8 Hz), 66.5, 59.8, 30.8 (q, $J$ = 34.4 Hz); **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{20}F_3NNaO_3S_2$: 502.1, found: 502.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 25.6 min (*syn*, major enantiomer), 46.6 min (*syn*, minor enantiomer), 24.9 min (*anti*, major enantiomer), 27.6 min (*anti*, minor enantiomer). e.r. (*syn)* = 81:19.

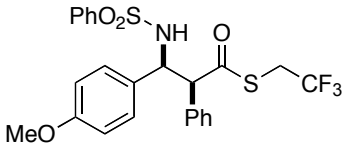



**β-Amino thioester (T17.3).** (Table 17, entry 4) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.3** (0.220 g; 94%) as a pure, white solid, comprised of a 92:8 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.55–7.07 (m, 11H), 6.13–6.07 (m, 1H), 6.01 (d, $J$ = 3.2 Hz, 1H), 5.14 (app t, $J$ = 9.2 Hz, 1H), 5.00–4.91 (m, 1H), 4.30 (d, $J$ = 9.6 Hz, 1H), 3.47 and 3.34 (q AB q, $\Delta\nu_{AB}$ = 50.1 Hz, $J$ = 10.0, 15.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 194.1, 149.8, 142.5, 140.0, 132.8, 132.4, 129.24, 129.19, 129.0, 128.8, 127.0, 124.4 (q, $J$ = 275.8 Hz), 110.4, 109.4, 63.8, 53.3, 30.8 (q, $J$ = 34.3 Hz); **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{21}H_{18}F_3NNaO_4S_2$: 492.1, found: 492.1; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$

24.6 min (*syn*, major enantiomer), 27.8 min (*syn*, minor enantiomer), 21.4 min (*anti*, major enantiomer), 23.5 min (*anti*, minor enantiomer). e.r. (*syn)* = 73:27.

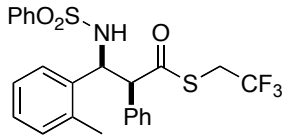



**β-Amino thioester (T17.5).** (Table 17, entry 6) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.5** (0.232 g; 90%) as a pure, white solid, comprised of a 91:9 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.50–7.01 (m, 14H), 4.92 (dd, *J* = 5.0, 10.2 Hz, 1H), 4.87–4.78 [m, 1H, including an app d at δ 4.82 (*J* = 4.8 Hz)], 4.00 (d, *J* = 10.0 Hz, 1H), 3.42–3.21 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ193.7, 139.5, 136.1, 134.2, 132.6, 132.5, 129.7, 129.41, 129.39, 129.0, 128.9, 128.7, 127.2, 124.2 (q, *J* = 276.0 Hz), 66.2, 59.2, 30.9 (q, *J* = 34.7 Hz); **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{19}ClF_3NNaO_3S_2$: 536.0, found: 536.1; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 30.4 min (*syn*, major enantiomer), 69.9 min (*syn*, minor enantiomer), 43.6 min (*anti*, major enantiomer), 33.0 min (*anti*, minor enantiomer). e.r. (*syn)* = 74:26.




**β-Amino thioester (T17.7).** (Table 17, entry 8) Flash chromatography over silica gel, using 25:75 EtOAc-hexanes gave **T17.7** (0.127 g; 50%) as a pure, white solid, comprised of a 83:17 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz, both

diastereomers reported): δ 7.56–7.08 (m, 10H), 7.07–6.82 [m, 2H, including a d at δ 7.03 ($J$ = 8.6 Hz, *syn*) and a d at δ 6.85 ($J$ = 8.0 Hz, *anti*)], 6.73–6.56 [m, 2H, including a d at δ 6.66 ($J$ = 8.6 Hz, *syn*) and a d at δ 6.58 ($J$ = 8.0 Hz, *anti*)], 5.72–4.67 [m, 2H, including a d at δ 5.69 ($J$ = 8.4 Hz, *anti*), a dd at δ 4.91 ($J$ = 5.4, 9.8 Hz, *syn*), and an app d at δ 4.73 ($J$ = 4.8 Hz, *syn*)], 4.17–4.00 [m, 1H, including a d at δ 4.15 ($J$ = 7.2 Hz, *anti*) and a d at δ 4.04 ($J$ = 10.0 Hz, *syn*)], 3.79–3.68 [m, 3H, including a s at δ 3.75 (*syn*) and a s at δ 3.70 (*anti*)], 3.41–3.21 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 193.9, 159.5, 139.8, 132.9, 132.4, 129.5, 129.12, 129.06, 129.0, 128.7, 128.2, 127.3, 124.3 (q, $J$ = 276.2 Hz), 113.9, 66.6, 59.4, 55.4, 30.9 (q, $J$ = 34.7 Hz); **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{24}H_{22}F_3NNaO_4S_2$: 532.1, found: 532.2; **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 38.1 min (*syn*, major enantiomer), 63.8 min (*syn*, minor enantiomer), 40.6 min (*anti*, major enantiomer), 38.2 min (*anti*, minor enantiomer). e.r. (*syn)* = 74:26.

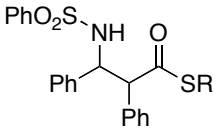
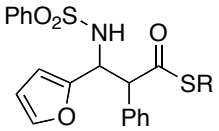
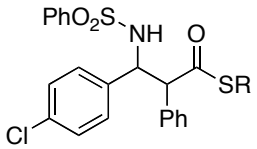
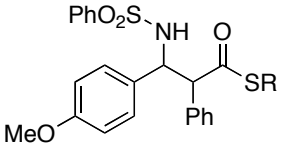
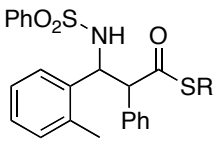



**β-Amino thioester (T17.9).** (Table 17, entry 10) Flash chromatography over silica gel, using 22.5:77.5 EtOAc-hexanes gave **T17.9** (0.209 g; 85%) as a pure, white solid, comprised of a 97:3 (*syn*:*anti*) mixture of diastereomers. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.40–7.24 (m, 8H), 7.21–7.14 (m, 2H), 7.08–6.91 (m, 4H), 5.30 (dd, $J$ = 6.0, 9.6 Hz, 1H), 5.04–4.89 (m, 1H), 4.13 (d, $J$ = 10.0 Hz, 1H), 3.32 and 3.24 (q AB q, $\Delta\nu_{AB}$ = 30.4 Hz, $J$ = 10.0, 15.0 Hz, 2H), 2.30 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz, contains 2 overlapping peaks): δ 193.7, 140.0, 136.4, 135.6, 133.1, 132.2, 130.7, 129.4, 129.2, 129.1, 128.9, 128.6, 128.4, 128.1, 126.9, 126.3, 124.3 (q, $J$ = 276.2 Hz), 66.0, 55.3 (br signal), 30.9 (q, $J$ = 34.3 Hz), 19.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{24}H_{22}F_3NNaO_3S_2$: 516.1, found: 516.2; **HPLC** (Daicel

Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 24.3 min (*syn*, major enantiomer), 33.4 min (*syn*, minor enantiomer), 22.4 min (*anti*, major enantiomer), 21.7 min (*anti*, minor enantiomer). e.r. (*syn)* = 66:34.

### *Synthesis of the Chiral HPLC Control Racemates*

**Table 21: HPLC Retention Times of the Racemic Controls for the Organocatalytic Mannich Addition Reaction**

| Mannich Product | R = Et | | | R = $CH_2CF_3$ | | |
|---|---|---|---|---|---|---|
| | hexanes/ *i*-PrOH | *syn* ee 0% (min) | *anti* ee 0% (min) | hexanes/ *i*-PrOH | *syn* ee 0% (min) | *anti* ee 0% (min) |
|  | 94/6 | 27.3<br>45.6 | 30.1<br>49.2 | 94/6 | 25.9<br>47.7 | 25.0<br>28.2 |
|  | 94/6 | 27.9<br>30.3 | 26.7<br>33.2 | 94/6 | 24.7<br>27.8 | 21.4<br>23.4 |
|  | 88/12 | 15.5<br>27.8 | 21.7<br>44.4 | 94/6 | 30.4<br>71.1 | 33.2<br>45.4 |
|  | 90/10 | 22.8<br>32.4 | 28.2<br>42.7 | 94/6 | 38.1<br>63.8 | 38.2<br>40.6 |
|  | 94/6 | 24.8<br>30.2 | 23.0<br>33.9 | 94/6 | 24.3<br>33.4 | 21.4<br>22.4 |

Each of the Mannich products reported in Table 17 were also synthesized by our previously developed $MgBr_2 \cdot OEt_2$-promoted conditions[24-26] at rt to give racemic mixtures consisting of all 4 isomers. This control mixture was then used to develop HPLC

conditions to assure proper identification and separation of all 4 potential isomers. The HPLC retention times for each of the racemic controls are listed in Table 21.

### *Determination of Absolute Stereochemistry of Mannich Product T14.14*

Despite efforts, the Mannich product derived from *S*-ethyl thioester **T14.13** never afforded single crystals suitable for X-ray analysis. Thus, the absolute stereochemistry was determined by comparing the HPLC retention times of the amino alcohol derived from **T14.14** to the same amino alcohol synthesized by an alternate known enantioselective method.[165]

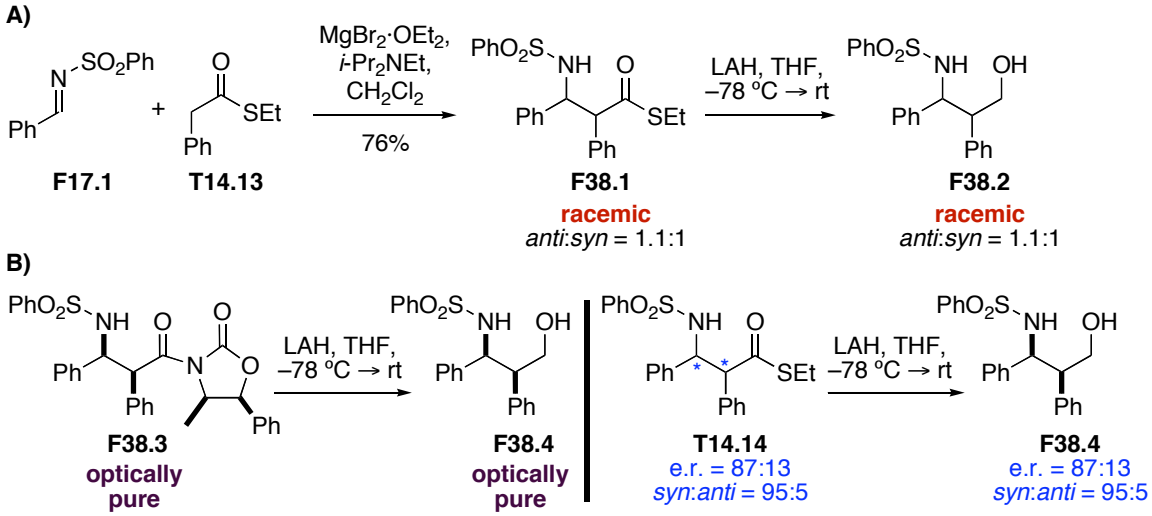
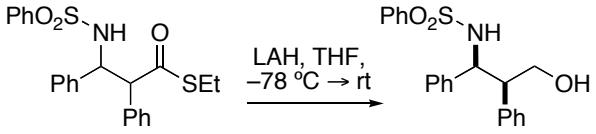



**Figure 38: Determination of the Absolute Stereochemistry of Mannich Product T14.14**

Racemic Mannich product **F38.1** was prepared from sulfonylimine **F17.1** and *S*-ethyl thioester **T14.13** using a modified version of a known procedure,[24, 25] and was then reduced to amino alcohol **F38.2** upon treatment with LAH (see Figure 38A). Compound **F38.2** was analyzed via chiral HPLC under conditions that gave baseline resolution of

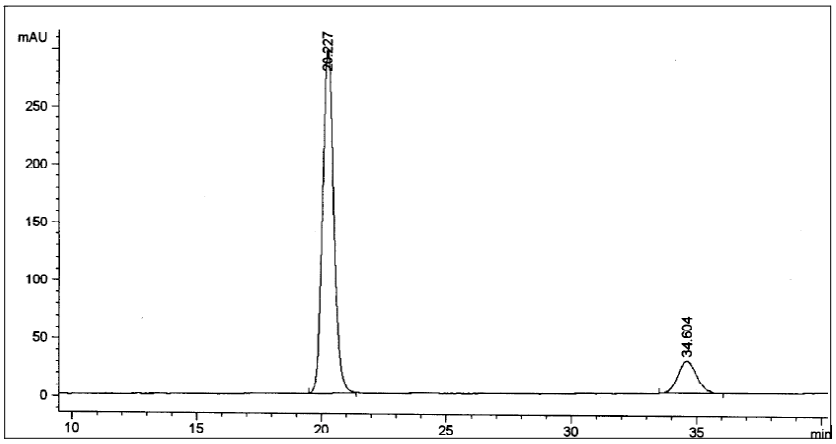
the four stereoisomers. Optically pure **F38.3**[165] was converted to optically pure amino alcohol **F38.4** (see Figure 38B, left). Compound **F38.4** was then analyzed by chiral HPLC and compared to the HPLC data for racemic **F38.2**. Mannich product **T14.14**, prepared according to the present procedure, was converted to amino alcohol **F38.4** upon treatment with LAH. The reduction product was analyzed by chiral HPLC and compared to the HPLC data for racemic **F38.2** and optically pure **F38.4** (obtained from **F38.3**) and the major isomer was found to have the same structure as the latter.



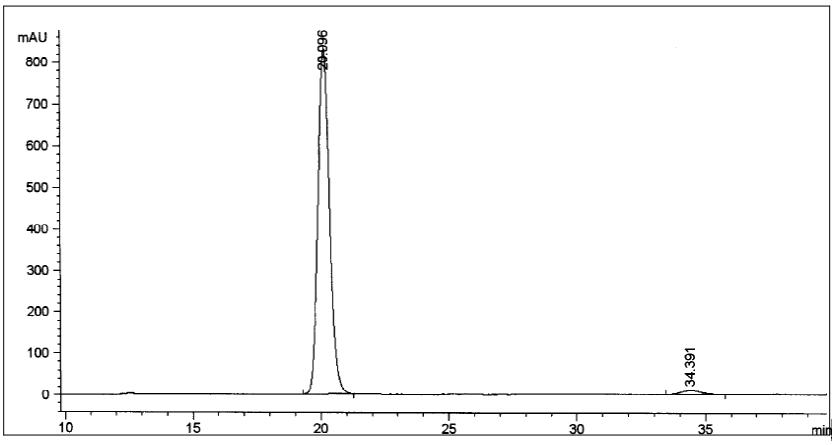

**T14.14** **F38.4**

**General procedure. Amino alcohol F38.4.** LAH (1.0 M in THF, 0.75 mL, 0.75 mmol) was added dropwise to a stirred solution of **T14.14** (0.064 g, 0.15 mmol) in THF (2 mL) at –78 °C . The reaction stirred at –78 °C for 5 min, warmed to 0 °C, stirred for 1 h, and then slowly warmed to rt over the course of 1 h. Reaction quenched by careful addition of 10% aq. $H_2SO_4$ at 0 °C, diluted in $Et_2O$ (30 mL), washed with $H_2O$ (1 x 5 mL), brine, dried ($MgSO_4$) and evaporated to give a colorless solid. Flash chromatography over silica gel, using 30:70 EtOAc-hexanes gave **F38.4** (0.034 g; 62%) as a pure, white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.55–7.50 (m, 2H), 7.41–7.35 (m, 1H), 7.29–7.19 (m, 5H), 7.13–7.03 (m, 3H), 6.96–6.90 (m, 2H), 6.82–6.77 (m, 2H), 5.14 (d, $J$ = 8.0 Hz, 1H), 4.80 (dd, $J$ = 6.2, 8.0 Hz, 1H), 3.94 (ddd, $J$ = 6.2, 8.0, 11.0 Hz, 1H), 3.68 (td, $J$ = 5.6, 11.2 Hz, 1H), 3.08 (td, $J$ = 5.8, 8.4 Hz, 1H), 2.08 (t, $J$ = 6.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 140.0, 138.6, 136.9, 132.4, 129.0, 128.9, 128.8, 128.2, 127.9, 127.5, 127.2, 127.1, 63.2, 58.5, 54.1; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{21}NNaO_3S$: 390.1, found: 390.0.

**T14.14→F38.4**. **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 20.2 min (*syn*, major enantiomer), 34.6 min (*syn*, minor enantiomer). β:α = 87:13.




**F38.3→F38.4**. **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 20.1 min (*syn*, major enantiomer), 34.4 min (*syn*, minor enantiomer). β:α = 98:2.



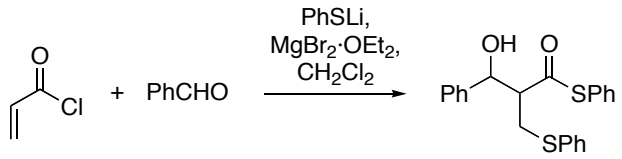
**F38.1→F38.2 (racemic)**. **HPLC** (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm): $t_R$ 20.0 min (*syn*), 21.9 min (*anti*), 34.2 min (*syn*), 41.0 (*anti*).

## *4.5* Anti-*Selective Four-Component Direct Aldol Addition via Chemoselective Thioester Enolate Formation*

**General Considerations.** In the cases where it was impossible to compute the *syn*:*anti* ratio directly from the $^1$H NMR of the crude spectrum due to overlapping peaks with other compounds, the *syn*:*anti* ratio was computed from the $^1$H NMR spectrum after chromatography. The relative *anti* configuration of 2-methyl-5-phenyl-1,3-pentanediol (**F36.3**) was assigned by chemical correlation to the known material.[166-168] Other relative configurations were assigned by analogy. $^1$H and $^{13}$C NMR were recorded on a 300 MHz spectrometer at ambient temperature. Only the major (*anti*) isomers are reported below.

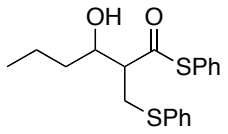
***The following reaction is representative of those depicted in Table 18:***

*The following reactions were conducted using untreated reagent grade $CH_2Cl_2$, open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*

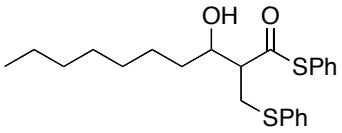



**β-Hydroxy-α-phenylthiomethyl thioester (T18.2).** $MgBr_2{\cdot}OEt_2$ (0.310 g, 1.2 mmol) was added to a stirred solution of benzaldehyde (**T1.2**) (0.106 g, 1.0 mmol) and acryloyl

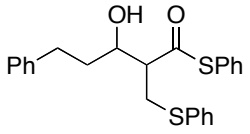
chloride (**F32.1**) (0.12 mL, 1.5 mmol) in $CH_2Cl_2$ (5 mL), followed by the addition of PhSLi (1.0 M solution in THF, 3.0 mL, 3.0 mmol). Stirring was continued for 30 min and EtOAc (5 mL) and 10% (v/v) aqueous HCl (5 mL) were added. Stirring was continued for 5 min and the mixture was partitioned between EtOAc (30 mL) and $H_2O$ (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T18.2** (0.334 g; 88%) as a pure, colorless solid, comprised of a 13:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.42–7.15 (m, 15H), 5.02 (t, *J* = 6.3 Hz, 1H), 3.34–3.00 (m, 3H), 2.87 (d, *J* = 6.6, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.2, 141.2, 135.1, 134.5, 130.2, 129.8, 129.3, 129.2, 128.8, 128.4, 127.2, 126.8, 126.3, 74.8, 59.6, 33.7; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{20}NaO_2S_2$: 403.1, found: 403.3.




**β-Hydroxy-α-phenylthiomethyl thioester (T18.4).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T18.4** (0.246 g; 71%) as a pure, colorless solid, comprised of a 11:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.44–7.19 (m, 10H), 3.98–3.84 (m, 1H), 3.39 (A of an ABX system, app dd, *J* = 7.8, 13.5 Hz, 1H), 3.28 (B of an ABX system, app dd, *J* = 6.3, 13.5 Hz, 1H), 2.98 (X of an ABX system, app ddd, *J* = 3.9, 6.6, 7.5 Hz, 1H), 2.39 (d, *J* = 9.3 Hz, 1H), 1.59–1.32 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.3, 135.3, 134.3, 130.1, 129.8, 129.3, 129.2, 127.1, 126.7, 72.0, 57.6, 37.7, 33.7, 19.4, 13.9; **ESI-MS** *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{22}NaO_2S_2$: 369.1, found: 369.3.

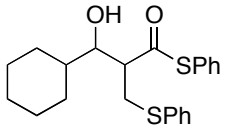



**β-Hydroxy-α-phenylthiomethyl thioester (T18.5).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T18.5** (0.274 g; 68%) as a pure, colorless solid, comprised of a 16:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.46–7.18 (m, 10H), 3.97–3.82 (m, 1H), 3.40 (A of an ABX system, app dd, $J$ = 7.8, 13.5 Hz, 1H), 3.29 (B of an ABX system, app dd, $J$ = 6.6, 13.5 Hz, 1H), 2.99 (X of an ABX system, app td, $J$ = 3.6, 7.1 Hz, 1H), 2.35 (d, $J$ = 9.6 Hz, 1H), 1.64–1.15 (m, 12H), 0.88 (t, $J$ = 6.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.5, 135.4, 134.4, 130.2, 129.8, 129.4, 129.2, 127.1, 126.8, 72.4, 57.5, 35.7, 33.9, 31.9, 29.4, 29.3, 26.0, 22.7, 14.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{23}H_{30}NaO_2S_2$: 425.2, found: 425.4.

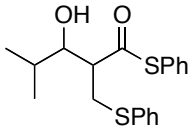



**β-Hydroxy-α-phenylthiomethyl thioester (T18.7).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T18.7** (0.290 g; 71%) as a pure, colorless solid, comprised of a 14:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.50–7.13 (m, 15H), 3.96–3.83 (m, 1H), 3.38 (A of an ABX system, app dd, $J$ = 8.1, 13.5 Hz, 1H), 3.25 (B of an ABX system, app dd, $J$ = 6.3, 13.5 Hz, 1H), 2.98 (X of an ABX system, app ddd, $J$ = 3.8, 6.5, 7.8 Hz, 1H), 2.87–2.59 (m, 2H), 2.52 (d, $J$ = 9.6 Hz, 1H), 1.83 (t, $J$ = 7.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.3, 141.4, 135.2, 134.3, 130.3, 130.2, 129.8, 129.3,

129.2, 128.5, 126.9, 126.8, 126.0, 71.5, 57.5, 37.3, 33.7, 32.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{24}H_{24}NaO_2S_2$: 431.1, found: 431.3.




**β-Hydroxy-α-phenylthiomethyl thioester (T18.8).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T18.8** (0.314 g; 81%) as a pure, colorless solid, comprised of a >20:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.50–7.20 (m, 10H), 3.58 (ddd, $J$ = 3.3, 8.1, 10.5 Hz, 1H), 3.42 (A of an ABX system, app dd, $J$ = 7.2, 13.5 Hz, 1H), 3.31 (B of an ABX system, app dd, $J$ = 6.9, 13.5 Hz, 1H), 3.14 (X of an ABX system, app td, $J$ = 3.6, 7.1, 1H), 2.37 (d, $J$ = 10.5 Hz, 1H), 2.06–0.90 (m, 11H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.7, 135.2, 134.2, 130.1, 129.7, 129.3, 129.1, 126.9, 126.7, 76.7, 54.2, 42.0, 34.4, 29.7, 28.7, 26.2, 26.0, 25.8; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{26}NaO_2S_2$: 409.1, found: 409.3.

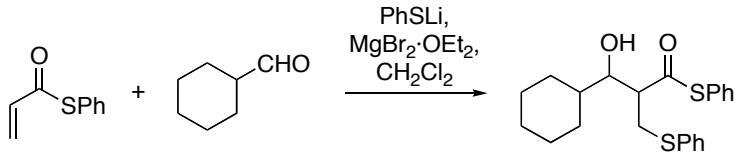



**β-Hydroxy-α-phenylthiomethyl thioester (T18.10).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T18.10** (0.264 g; 76%) as a pure, colorless solid, comprised of a >20:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.46–7.16 (m, 10H), 3.53 (ddd, $J$ = 3.9, 7.5, 9.6 Hz, 1H), 3.38 (A of an ABX system, app dd, $J$ = 7.7, 13.5, Hz 1H), 3.25 (B of an ABX system, app dd, $J$ = 6.6, 13.5 Hz, 1H), 3.11 (X of an

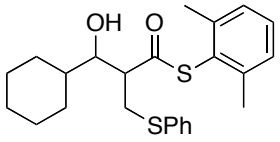
ABX system, app dt, $J$ = 3.9, 7.1 Hz, 1H), 2.61 (d, $J$ = 9.6 Hz, 1H), 1.72 (octet, $J$ = 6.6 Hz, 1H), 0.93 (dd, $J$ = 6.6, 11.1 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.5, 135.1, 134.2, 130.1, 129.6, 129.2, 129.0, 126.9, 126.7, 77.5, 54.7, 34.4, 32.3, 19.6, 18.3; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{19}H_{22}NaO_2S_2$: 369.1, found: 369.3.

***The following reaction is representative of those depicted in Table 19:***

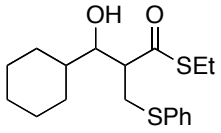
*The following reactions were conducted using untreated reagent grade $CH_2Cl_2$, open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*




**β-Hydroxy-α-phenylthiomethyl thioester (T18.8).** $MgBr_2{\cdot}OEt_2$ (0.310 g, 1.2 mmol) was added to a stirred solution of cyclohexanecarboxaldehyde (**T4.13**) (0.112 g, 1.0 mmol) and *S*-phenyl thiopropenoate (**T19.1**) (0.164 g, 1.5 mmol) in $CH_2Cl_2$ (5 mL), followed by the addition of PhSLi (1.0 M solution in THF, 1.5 mL, 1.5 mmol). Stirring was continued for 30 min and EtOAc (5 mL) and 10% (v/v) aqueous HCl (5 mL) were added. Stirring was continued for 5 min and the mixture was partitioned between EtOAc (30 mL) and $H_2O$ (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T18.8** (0.306 g; 79%) as a pure, colorless solid, comprised of a >20:1 *anti*:*syn* mixture of diastereomers. Spectroscopic data was identical to that reported above.

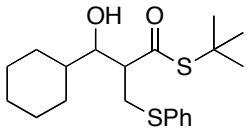



**β-Hydroxy-α-phenylthiomethyl thioester (T19.3).** Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave **T19.3** (0.328 g; 79%) as a pure, colorless solid, comprised of a 11:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.48–7.12 (m, 8H), 3.51 (ddd, *J* = 3.3, 8.6, 10.4 Hz, 1H), 3.40 (A of an ABX system, app dd, *J* = 7.8, 13.2 Hz, 1H), 3.31 (B of an ABX system, app dd, *J* = 6.6, 13.5 Hz, 1H), 3.14 (X of an ABX system, app ddd, *J* = 3.3, 6.6, 7.8, 1H), 2.46 (d, *J* = 10.2 Hz, 1H), 2.38 (s, 6H), 2.08–0.84 (m, 11H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 200.3, 142.7, 135.4, 134.4, 130.2, 129.2, 128.4, 126.8, 126.4, 77.2, 53.6, 42.6, 34.7, 29.8, 29.2, 26.3, 26.0, 25.9, 21.9; **ESI-MS** *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{30}NaO_2S_2$: 437.2, found: 437.4.

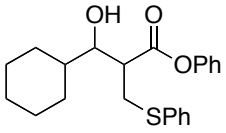



**β-Hydroxy-α-phenylthiomethyl thioester (T19.5).** Flash chromatography over silica gel, using 4:96 EtOAc-hexanes gave **T19.5** (0.278 g; 82%) as a pure, colorless solid, comprised of a 4:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.50–7.12 (m, 5H), 3.58–3.49 (m, 1H), 3.34 (A of ABX pattern, app dd, *J* = 7.2, 13.2 Hz, 1H), 3.26 (B of ABX pattern, app dd, *J* = 7.2, 13.2 Hz, 1H), 3.00 (X of ABX pattern, app td, *J* = 3.6, 6.9 Hz, 1H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.49 (d, *J* = 9.9 Hz, 1H), 2.00–0.85 [m, 14H, including a t at δ 1.26 (*J* = 7.5 Hz, 3H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 202.6, 135.4, 130.0,

129.0, 126.6, 76.6, 54.2, 42.0, 34.4, 29.7, 28.9, 26.3, 26.0, 25.8, 23.6, 14.5; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_2S_2$: 361.1, found: 361.3.

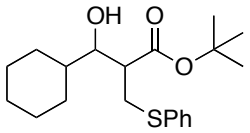



**β-Hydroxy-α-phenylthiomethyl thioester (T19.7).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **T19.7** (0.282 g; 77%) as a pure, colorless solid, comprised of a 1.5:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.42–7.15 (m, 5H), 3.59–3.52 (m, 1H), 3.27 (A of an ABX system, app dd, $J$ = 10.2, 13.2 Hz, 1H), 3.17 (B of an ABX system, app dd, $J$ = 3.6, 13.2 Hz, 1H), 2.90 (X of an ABX system, app td, $J$ = 3.9, 9.9 Hz, 1H), 2.45 (d, $J$ = 3.6 Hz, 1H), 2.04–0.81 [m, 20H, including a s at δ 1.47 (9H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 203.2, 136.0, 130.4, 129.0, 126.6, 76.7, 55.8, 48.9, 40.6, 31.5, 29.7, 29.3, 28.4, 26.3, 26.1, 25.9; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{20}H_{30}NaO_2S_2$: 389.2, found: 389.3.

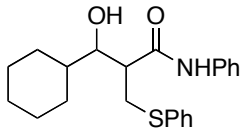



**β-Hydroxy-α-phenylthiomethyl oxoester (T19.9).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T19.9** (0.266 g; 72%) as a pure, colorless solid, comprised of a 2:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.46–7.03 (m, 10H), 3.65–3.56 (m, 1H), 3.41 (A of an ABX system, app dd, $J$ = 9.0, 13.2 Hz, 1H), 3.26 (B of an ABX system, app dd, $J$ = 5.7, 13.2 Hz, 1H), 3.14–3.03 (X of an ABX

system, m, 1H), 2.67 (d, $J$ = 9.0 Hz, 1H), 2.09–0.92 (m, 11H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 172.7, 150.3, 135.0, 130.5, 129.4, 129.1, 126.9, 126.1, 121.5, 76.4, 47.6, 42.1, 34.4, 29.5, 28.2, 26.2, 26.0, 25.8; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{26}NaO_3S$: 393.2, found: 393.3.



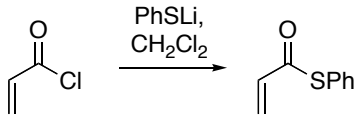

**β-Hydroxy-α-phenylthiomethyl oxoester (T19.11).** Flash chromatography over silica gel, using 6:94 EtOAc-hexanes gave **T19.11** (0.273 g; 78%) as a pure, colorless solid, comprised of a 1:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.40–7.12 (m, 5H), 3.57–3.38 (m, 1H), 3.34–3.11 (m, 2H), 2.91–2.77 (m, 1H), 2.77–2.67 (m, 1H), 2.02–0.83 [m, 20H, including a s at δ 1.46 (9H)]; **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 173.5, 136.1, 129.9, 128.9, 126.3, 81.8, 76.2, 49.1, 42.5, 34.3, 29.5, 28.9, 28.0, 26.2, 26.0, 25.8; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{20}H_{30}NaO_3S$: 373.2, found: 373.3.




**β-Hydroxy-α-phenylthiomethyl amide (T19.13).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave **T19.13** (0.236 g; 64%) as a pure, colorless solid, comprised of a 2:1 *anti*:*syn* mixture of diastereomers: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 7.49–7.05 (m, 10H), 3.70–3.61 [m, 2H, including a dd at δ 3.66 ($J$ = 3.3, 7.8 Hz, 1H)], 3.42 (A of an ABX system, app dd, $J$ = 7.2, 13.2 Hz, 1H), 3.29 (B of an ABX system, app dd, $J$ = 7.5, 13.2 Hz, 1H), 2.72 (X of an ABX system, app dt, $J$ = 3.3, 7.5 Hz, 1H),

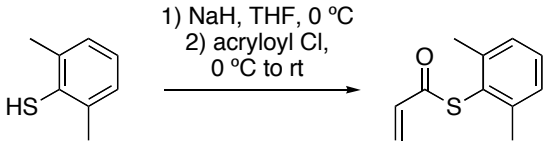
2.04–0.83 (m, 12H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 172.3, 137.4, 135.4, 129.7, 129.2, 129.0, 126.6, 124.6, 120.5, 76.0, 49.0, 42.0, 34.9, 29.6, 29.0, 26.2, 25.9, 25.8; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{22}H_{27}NNaO_2S$: 392.2, found: 392.3.

*The following reactions were conducted under anhydrous conditions, as described in the general considerations section.*



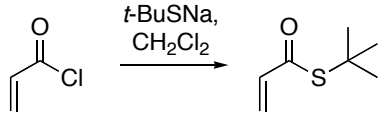

***S*-Phenyl thiopropenoate (T19.1).** PhSLi (1.0 M solution in THF, 7.43 mL, 7.43 mmol) was added to a stirred solution of acryloyl chloride (**F32.1**) (0.72 mL, 8.55 mmol) in $CH_2Cl_2$ (50 mL). Stirring was continued for 2.5 h and $H_2O$ (50 mL) was added. Stirring was continued for 20 min and the mixture was diluted with EtOAc (150 mL). The organic phase was isolated and washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 $Et_2O$-pentanes gave **T19.1** (0.342 g; 28%) as a pure, colorless oil.[Q] Spectroscopic data was identical to that reported previously.[169]

[Q] Compound polymerized both on the column and under high vacuum, which resulted in the low isolated yield.



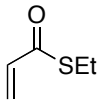

***S*-2,6-Dimethylphenyl thiopropenoate (T19.2).** NaH (0.216 g, 9.01 mmol) was added to a stirred solution of 2,6-dimethylbenzenethiol (1.00 mL, 7.13 mmol) in THF (50 mL) at 0 °C. Stirring was continued for 30 min at 0 °C and acryloyl chloride (0.73 mL, 8.64 mmol) was added. The reaction was warmed to rt and stirring was continued for an additional 30 min. Saturated aqueous $NaHCO_3$ was then slowly added at 0 °C, and stirring was continued for 20 min. The mixture was diluted with EtOAc (150 mL) and the organic phase was isolated and washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **T19.2** (0.439 g; 32%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.30–7.10 (m, 3H), 6.50 (A of an ABX system, app dd, $J$ = 9.9, 17.1 Hz, 1H), 6.39 (B of an ABX system, app dd, $J$ = 1.5, 17.4 Hz, 1H), 5.76 (X of an ABX system, app dd, $J$ = 1.5, 9.9 Hz, 1H), 2.36 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 187.8, 143.1, 134.7, 130.1, 128.5, 127.2, 126.6, 21.8; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{11}H_{12}NaOS$: 215.1, found: 214.9.

***The following reaction is representative of the synthesis of thioesters T19.4 and T19.6:***

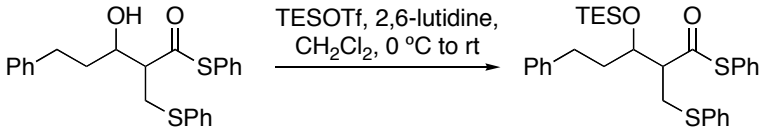



***S*-*t*-Butyl thiopropenoate (T19.6).** Sodium 2-methyl-2-propanethiolate (2.00 g, 17.83 mmol) was added to a stirred solution of acryloyl chloride (**F32.1**) (1.73 mL, 20.54 mmol) in $CH_2Cl_2$ (50 mL). Stirring was continued for 2.5 h and $H_2O$ (50 mL) was added.

Stirring was continued for 20 min and the mixture was diluted with EtOAc (150 mL). The organic phase was isolated and washed with brine, dried ($MgSO_4$), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 2.5:97.5 EtOAc-hexanes gave **T19.6** (0.694 g; 27%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 6.61–5.94 (m, 2H), 5.57 (dd, $J$ = 2.7, 8.7 Hz, 1H), 1.51 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 191.2, 136.0, 125.2, 48.3, 30.0; **FAB-MS** $m/z$ calcd for $C_7H_{12}OS$: 144.1, found: 144.1.



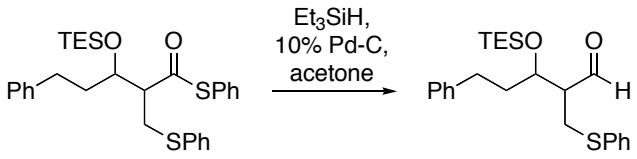

***S*-Ethyl thiopropenoate (T19.4).** Vacuum distillation (30 torr) gave **T19.4** (0.435 g; 21%) as a pure, colorless oil.[R] Spectroscopic data was identical to that reported previously.[170]




**β-Triethylsilyloxy-α-phenylthiomethyl thioester (F36.1).** A solution of aldol adduct **T18.7** (0.417 g, 1.02 mmol) in $CH_2Cl_2$ (5.0 mL) was cooled to 0 °C and treated dropwise with 2,6-lutidine (0.48 mL, 4.08 mmol) and triethylsilyl trifluoromethanesulfonate (0.46 mL, 2.04 mmol). The reaction mixture was warmed to rt and stirring was continued for 4 h. The reaction was quenched by the addition of MeOH (1 mL), diluted with EtOAc (100 mL), washed with 0.1 M $NaHSO_4$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave **F36.1** (0.511 g; 96%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.48–7.09 (m, 15H),

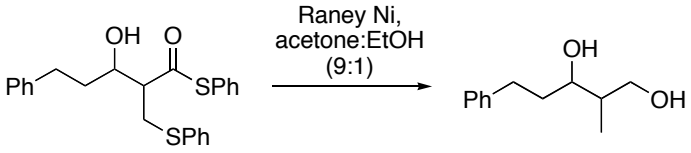
[R] Compound polymerized during the vacuum distillation, which resulted in the low isolated yield.

4.13 (td, $J$ = 4.5, 6.9 Hz, 1H), 3.32–3.11 (m, 3H), 2.71–2.51 (m, 2H), 1.96–1.68 (m, 2H), 0.96 (t, $J$ = 7.8 Hz, 9H), 0.60 (q, $J$ = 7.8 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 197.4, 141.8, 135.6, 134.4, 131.0, 129.5, 129.3, 129.2, 128.6, 128.4, 127.9, 127.0, 126.0, 72.4, 59.7, 35.5, 31.8, 31.5, 7.1, 5.1; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{30}H_{38}NaO_2S_2Si$: 545.2, found: 545.2.

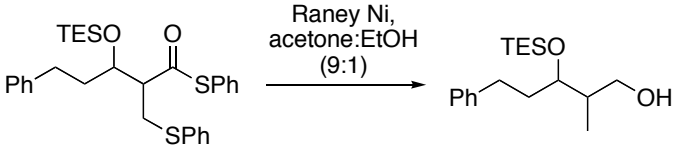



**β-Triethylsilyloxy-α-phenylthiomethyl aldehyde (F36.2).** Triethylsilane (0.51 mL, 3.22 mmol) was added to a stirred solution of **F36.1** (0.239 g, 0.46 mmol) in acetone (5.5 mL). The reaction stirred for 5 min at rt, then 10% palladium on carbon (0.055 g, 0.052 mmol) was added in a single portion. After the reaction stirred vigorously for 1 h, additional triethylsilane (0.22 mL, 1.38 mmol) was added.[S] Vigorous stirring was continued for 1 h and the mixture was poured over a pad of celite, washed with EtOAc, and evaporated. Flash chromatography over silica gel, using 4:96 EtOAc-hexanes gave **F36.2** (0.171 g; 90%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 9.78 (d, $J$ = 2.1 Hz, 1H), 7.40–7.06 (m, 10H), 4.15 (td, $J$ = 3.3, 6.4 Hz, 1H), 3.33 (A of an ABX system, app dd, $J$ = 7.8, 13.5 Hz, 1H), 3.09 (B of an ABX system, app dd, $J$ = 6.4, 13.5 Hz, 1H), 2.67–2.54 (m, 3H), 1.95–1.80 (m, 2H), 0.94 (t, $J$ = 7.8 Hz, 9H), 0.58 (q, $J$ = 7.8 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 203.0, 141.4, 135.2, 130.3, 129.3, 128.6, 128.4, 126.9, 126.2, 72.1, 55.3, 37.5, 32.0, 30.6, 7.0, 5.2; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{24}H_{34}NaO_2SSi$: 437.2, found: 437.4.

[S] $MgSO_4$ can also be added to the reaction to help increase conversions.




**2-Methyl-5-phenyl-1,3-pentanediol (F36.3).** An excess of Raney Ni[T] (5 mL, slurry in $H_2O$) was added to a stirred solution of aldol adduct **T18.7** (0.300 g, 0.734 mmol) in acetone:EtOH (9:1, 5.0 mL). Vigorous stirring was continued for 3 h and the mixture was quickly poured over a pad of celite, washed extensively with EtOH and EtOAc, and evaporated to yield **F36.3** (0.133 g; 94%) as a light yellow solid. No further purification was conducted. Spectroscopic data was identical to that reported previously.[167, 168]




**2-Methyl-5-phenyl-3-(triethylsilyloxy)pentan-1-ol (F36.4).** An excess of Raney Ni[T] (5 mL, slurry in $H_2O$) was added to a stirred solution of **F36.1** (0.200 g, 0.382 mmol) in acetone:EtOH (9:1, 5.0 mL). Vigorous stirring was continued for 3 h and the mixture was quickly poured over a pad of celite, washed extensively with EtOH and EtOAc, and evaporated to yield a clear, colorless oil. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave **F36.4** (0.098 g; 83%) as a pure, colorless oil: **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.34–7.13 (m, 5H), 3.82–3.73 (m, 2H), 3.62–3.54 (m, 1H), 2.80–2.56 (m, 3H), 1.92–1.81 (m, 3H), 1.03–0.93 [m, 12H, including a d at δ 1.01 ($J$ = 6.9 Hz, 3H) overlapping a t at δ 0.98 ($J$ = 7.5 Hz, 9H)], 0.64 (q, $J$ = 7.5 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 142.3,

[T] Aldrich, Cat. No. 221678, W. R. Grace and Co. Raney® 2800, slurry, in $H_2O$, active catalyst.

128.6, 128.4, 126.0, 77.1, 65.9, 38.4, 36.9, 31.3, 14.5, 7.0, 5.2; **ESI-MS** $m/z$ $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_2Si$: 331.2, found: 331.4.

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# Biography

## JULIANNE M. YOST

Born in Baltimore, Maryland on January 18, 1982.

### *EDUCATION*

| | |
|---|---|
| 2003–2009 | Ph.D. Chemistry, Biological Chemistry certificate |
| | Duke University, Durham, NC |
| | Thesis Advisor: Professor Don M. Coltart |
| 1999–2003 | B.S. Biochemistry, Mathematics minor, *summa cum laude* |
| | Cedar Crest College, Allentown, PA |

### *PUBLICATIONS*

1. Yost, J. M.; Zhou, G.; Coltart, D. M. "A facile and efficient direct aldol addition of simple thioesters." *Org. Lett.* **2006**, *8*, 1503–1506. *Featured in Synfacts, September **2006**, 591.*
2. Zhou, G.; Yost, J. M.; Coltart, D. M. "A direct aldol addition of simple thioesters employing soft enolization." *Synthesis* **2007**, 478–482. *Invited Paper.*
3. Zhou, G.; Yost, J. M.; Sauer, S. J.; Coltart, D. M. "A facile and efficient *anti*-selective four-component direct aldol addition via chemoselective thioester enolate formation." *Org. Lett.* **2007**, *9*, 4663–4665. *Featured in Synfacts, January **2008**, 56.*
4. Yost, J. M.; Knight, J. D.; Coltart, D. M. "Tris(2-carboxyethyl)phosphine hydrochloride." *Electronic Encyclopedia of Reagents for Organic Synthesis* **2008**, DOI: 10.1002/047084289X.rn00973.

5. Yost, J. M.; Garnsey, M. R.; Kohler, M. C.; Coltart, D. M. "Direct carbon–carbon bond formation via soft enolization of thioesters: an operationally simple Mannich addition reaction." *Synthesis* **2009**, 56–58. *Invited Paper.*
6. Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. "Proximity accelerated organocatalytic soft enolization of thioesters: development of a biomimetic asymmetric Mannich reaction." **2009**, submitted.

### *GRADUATE HONORS AND AWARDS*

1. Dean's Award for Excellence in Mentoring, Duke University, 2008
2. Conference Travel Fellowship, Duke University Graduate School, 2008
3. Charles Bradsher Fellowship, Department of Chemistry, Duke University, 2008
4. AFAR-GlaxoSmithKline Foundation Award, American Foundation for Aging Research, 2006–2007
5. CR Hauser Fellowship, Department of Chemistry, Duke University, 2006
6. Paul M. Gross Fellowship, Department of Chemistry, Duke University, 2006
7. Conference Travel Award for Outstanding Students, ISOCS-22, Saitama, Japan, 2006
8. Conference Travel Fellowship, Duke University Graduate School, 2006
9. AAAS/Science Program for Excellence in Science Award, Duke University, 2005
10. Biological Chemistry Program, NIH training grant, Duke University, 2003–2005

### *MEMBERSHIPS*

American Chemical Society

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