METHODS FOR DIRECT CARBON–CARBON BOND FORMATION AND THEIR APPLICATION TO NATURAL PRODUCT SYNTHESIS

by

Guoqiang Zhou

Department of Chemistry
Duke University

Date:_______________________
Approved:

___________________________
Don M. Coltart, Supervisor

___________________________
Steven W. Baldwin

___________________________
Katherine J. Franz

___________________________
Eric J. Toone

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School of Duke University

2009
ABSTRACT

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Abstract

Direct carbon–carbon bond formation via soft enolization and in situ enolate generation provides a straightforward approach to certain key transformations of synthetic organic chemistry. Reactions are generally operationally simple and proceed under mild conditions using untreated, reagent-grade solvent open to the air. Using this direct approach as a basis, we have developed methods for the synthesis of β-hydroxy thioesters, β-keto thioesters, and 1,3-diketones, which are key intermediates for the synthesis of natural products, pharmaceuticals, and other biologically relevant compounds. In particular, four methodology projects are described: 1) a direct aldol addition of simple thioesters, 2) a direct synthesis of 1,3-diketones, 3) a direct crossed-Claisen reaction, and 4) an anti-selective four-component direct aldol cascade reaction.

Progress toward the total synthesis of apratoxin D is described. The key steps of the synthesis involve the asymmetric alkylation via chiral N-amino cyclic carbamate (ACC) hydrazones, a new technology recently developed by our group.
To My Family
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACC</td>
<td>amino cyclic carbamate</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>argon</td>
</tr>
<tr>
<td>BF$_3$OEt$_2$</td>
<td>boron trifluoride diethyl etherate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>$\textit{tert}$-butyloxy carbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bt</td>
<td>benzotriazole</td>
</tr>
<tr>
<td>$n$-Bu</td>
<td>$n$-butyl</td>
</tr>
<tr>
<td>$t$-Bu</td>
<td>$\textit{tert}$-butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyllithium</td>
</tr>
<tr>
<td>C</td>
<td>carbon</td>
</tr>
<tr>
<td>°C</td>
<td>degree(s) Celsius</td>
</tr>
<tr>
<td>ca.</td>
<td>approximately</td>
</tr>
<tr>
<td>CaH$_2$</td>
<td>calcium hydride</td>
</tr>
<tr>
<td>calc’d</td>
<td>calculated</td>
</tr>
<tr>
<td>cat</td>
<td>catalytic; catalyst</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>chloroform-d</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>chloroform</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>concn</td>
<td>concentration</td>
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<tr>
<td>$m$-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
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δ  chemical shift in ppm downfield from TMS

d  doublet

DBN  1,5-diazabicyclo[4.3.0]non-5-ene

DBU  1,8-diazabicyclo[5.4.0]undec-7-ene

dd  doublet of doublets

ddd  doublet of doublets of doublets

DMAP  4-(dimethylamino)pyridine

DME  1,2-dimethoxyethane

DMF  N,N-dimethylformamide

DMSO  dimethyl sulfoxide

dt  doublet of triplets

ea.  each

EDCI  N-(3-Dimethylaminopropyl)-N’-ethyldiisocyanate hydrochloride

ee  enantiomeric excess

e.g.  for example

equiv  equivalent

Et  ethyl

Et2O  ethyl ether

EtOAc  ethyl acetate

Et3N  triethylamine

FAB  fast atom bombardment

FTIR  Fourier transform infrared

g  gram(s)

h  hour(s)

hv  light
Hz: hertz
HCl: hydrochloric acid
H₂O: water
HPLC: high performance liquid chromatography
j: coupling constant
L: liter(s)
LDA: lithium diisopropylamide
LiOH: lithium hydroxide
μ: micro
m: milli, medium (FTIR), multiplet (NMR)
M: moles per liter
Me: methyl
MeOH: methanol sulfate
Me₂S: dimethyl sulfide
MgBr₂·OEt₂: magnesium bromide diethyl etherate
MgCl₂: magnesium chloride
MgI₂: magnesium iodide
Mg(OTf)₂: Magnesium trifluoroacetate
MgSO₄: magnesium sulfate
mp: melting point
MHz: megahertz
min: minute(s)
mol: mole(s)
mmol: milimole(s)
MS: mass spectrometry
m/z: mass to charge ratio
<table>
<thead>
<tr>
<th>Symbol</th>
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<tr>
<td>NH₄Cl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>NaCl</td>
<td>sodium chloride</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>sodium bicarbonate</td>
</tr>
<tr>
<td>NaIO₄</td>
<td>sodium periodate</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>Na₂SO₃</td>
<td>sodium sulfite</td>
</tr>
<tr>
<td>Na₂SO₄</td>
<td>sodium sulfate</td>
</tr>
<tr>
<td>Ni</td>
<td>nickel</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>N.R.</td>
<td>no reaction</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>OsO₄</td>
<td>osmium tetraoxide</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>O-Pfp</td>
<td>pentafluoro phenyl ester</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>hydrogen ion concentration</td>
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</tr>
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<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPh₃</td>
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</tr>
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<td>ppm</td>
<td>parts per million</td>
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<td>ppt</td>
<td>precipitate</td>
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<tr>
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<td>PPTS</td>
<td>pyridinium para-toluenesulfonic acid</td>
</tr>
<tr>
<td>i-Pr₂NEt</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet(NMR), strong(FTIR)</td>
</tr>
<tr>
<td>sat</td>
<td>saturated</td>
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<td>soln</td>
<td>solution</td>
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<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSBr</td>
<td>trimethylsilyl bromide</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
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<td>TMSI</td>
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<td>TBSOTf</td>
<td>tert-butyldimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulfonyl</td>
</tr>
<tr>
<td>p-TsOH-H₂O</td>
<td>p-toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>wt</td>
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Acknowledgements

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Chapter One: Direct Carbon–Carbon Bond Formation via Soft Enolization

1.1 Background and Introduction

1.1.1 Learning from Nature: Direct Carbon–Carbon Bond Formation

Of primary importance to synthetic organic chemistry is the formation of carbon–carbon bonds. In Nature, this occurs efficiently under mild conditions and in a highly sophisticated way. We seek to take lessons from the Nature in terms of how it carries out certain functions, and apply those lessons to the development of new chemistry. Biochemical reactions can provide a rich source of inspiration for the development of new synthetic methodology. Years of evolution have led to the refinement of these transformations, and much can be learned from the way they are carried out. This research program aims at developing efficient and operationally simple approaches to key carbon–carbon bond-forming reactions by mimicking the biochemical process, and applying the methodology to the total synthesis of natural products. Specifically, we focus on the development of direct carbon–carbon single bond formation. Here, the direct process refers reactions in which the starting materials are combined with the necessary reagents in a single reaction vessel, without any prior manipulations. Such approaches could also overcome, or at least diminish, the stringent
conditions and technical requirements of typical methods, such as low temperature and anhydrous conditions.

1.1.2 Hard and Soft Enolization

One of the most useful approaches to carbon–carbon single bond formation is the coupling reaction between an enolate and a carbon-based electrophile. The enolates are typically generated via kinetic deprotonation of the parent carbonyl species by a strong base (e.g., LDA) which ensures complete deprotonation, or so-called hard enolization (Scheme 1). Although it is effective and commonly used, the stepwise procedures used to generate such enolates can be time consuming, particularly if enolate trapping (e.g., silyl enol ether, silyl ketene acetal) and purification are called for, and require that all manipulations be conducted under anhydrous conditions and at low temperature.

Scheme 1. Hard and Soft Enolate Formation

An alternative method to this is to use soft enolization\(^1\) (Scheme 1), which provides a number of practical benefits. For example, soft enolization does not employ a strong base and, consequently, is 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 procedures. In soft enolization, 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. Here, the Lewis-acid interacts with the carbonyl oxygen to polarize it beyond its normal state, resulting in a substantial increase in the acidity of the \(\alpha\)-proton, such that it can be removed to an appreciable extent by the weak base. Since enolization in this case is reversible, it is conducted in a direct fashion in the presence of the electrophilic species, which may further simplify the procedure.

\section*{1.2 A Mild and Direct Aldol Addition of Simple Thioesters}

\subsection*{1.2.1 Aldol Reaction}

We first investigated the application of soft enolization strategy to the aldol reaction.\(^2\) The aldol reaction is among the most important chemical reactions.\(^3\) Substantial effort has gone into its development using preformed enolates, resulting in a

remarkable level of regio- and stereochemical control. However, the desire to develop milder and operationally-simplified chemical methods has spawned a renewed interest in the direct aldol reaction, without reliance on preformed enolates. While only a limited number of reports have appeared, initial investigations into these in situ enolization approaches clearly establish their potential.

The majority of this research, for both metal-assisted and organocatalytic processes, focuses on the use of ketone- and, to a lesser extent, aldehyde-based nucleophiles. However, owing to the inherent advantages of carboxylate-derived nucleophiles in aldol addition reactions, such as obviating the issue of regioselectivity of deprotonation and the iterative potential of the process, it is extremely desirable to develop related procedures based on these systems.

Recently, a small number of examples along these lines have appeared. Evans and co-workers have begun to explore magnesium halide catalyzed aldol reactions of chiral N-acyloxazolidinones and N-acylthiazolidine-thiones, as well as those of achiral N-acylthiazolidine-thiones with a chiral Ni(II) bis(oxazoline) catalyst. In addition, copper catalyzed decarboxylative enolization of malonic acid half thioesters has been demonstrated by Shair and co-workers, in both an asymmetric and nonasymmetric sense.

1.2.2 Acetyl Coenzyme A and Thioester
Figure 1. The Citrate Synthase Reaction

We were intrigued by the possibility of using readily accessible, simple thioesters in the direct aldol addition reaction. Our inspiration for this derives from Nature’s use of thioesters, typically in the form of acetyl coenzyme A (Figure 1), in carbon–carbon bond forming processes. Here, Nature’s choice of thioesters over oxoesters is undoubtedly a deliberate one, and may well be connected to the increased acidity of the thioester α-proton, compared to that of the corresponding oxoester. The sophistication of Nature’s aldol processes overcomes the need for prior enolate formation, lending simplicity and elegance to this important carbon–carbon bond-forming reaction. Of course, mimicking the direct nature of this reaction in the laboratory in a synthetic context would be advantageous in terms of procedural simplification and, potentially, reduced cost and environmental impact. From a practical point of view, the use of simple thioesters for such a direct aldol addition is desirable for a number of reasons.
For instance, they are readily accessible from inexpensive, commercially available thiols, or are themselves commercially available. They are also stable and easily handled, yet they undergo a number of important transformations under very mild conditions including reduction, hydrolysis and direct amidation.

1.2.3 Initial Investigation

To explore the possibility of using simple thioesters to develop a direct aldol addition reaction, we investigated the reaction of S-benzyl thioacetate (1) with benzaldehyde under a variety of conditions using different metal salts. To do so, the metal salt was added to a mixture of 1 and benzaldehyde in CH₂Cl₂, followed by addition of i-Pr₂NEt. The reaction was tried using magnesium bromide, zinc(II) chloride, and magnesium chloride.

Scheme 2. Mg²⁺ Promoted Direct Aldol Reaction of Thioester 1 and Oxoester 3 with Benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>MgX₂</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgCl₂</td>
<td>24 h</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>MgBr₂</td>
<td>24 h</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>MgI₂</td>
<td>25 min</td>
<td>95%</td>
</tr>
</tbody>
</table>

copper(II) acetate, and nickel(II) bromide. Only in the case of the Mg\textsuperscript{2+} salt was the desired β-hydroxy thioester 2 obtained, albeit in low yield (32%), after 24 hours (Scheme 2). Nonetheless, the formation of aldol product encouraged us to try other magnesium salts. Thus, magnesium bromide and iodide were examined under the same conditions and gave 2 in 83% and 95% isolated yield, respectively. Interestingly, the reaction with magnesium iodide required only 25 minutes to go to completion, whereas the magnesium bromide reaction took 24 hours. A control experiment was carried out in which 1 and benzaldehyde were combined in CH\textsubscript{2}Cl\textsubscript{2} in the presence of i-Pr\textsubscript{2}NEt, but in the absence of any Mg\textsuperscript{2+} salt, and gave only starting material after two days. The addition reaction was also attempted in the presence of magnesium iodide, but without any base added, with no product detected after two days.

1.2.4 Competition Experiments

Using magnesium iodide as the promoter, we next set out to evaluate our hypothesis regarding the beneficial reactivity of thioesters, as compared to other simple carboxylate derivatives. We began this by conducting the reaction using 3, the oxoester analogue of 1, which gave only 46% yield of the β-hydroxy ester 4 after 20 hours (see Scheme 2). We next carried out a series of competition experiments between thioester 1 and either ester 3, amide 5, or amide 6 (Scheme 3). Thus, equimolar amounts of the competing species were combined under the standard conditions and allowed to react for 30 min. In each case, only the β-hydroxy thioester 2 was obtained, and in the usual
Scheme 3. Competition Experiments to Establish Superior Reactivity of Thioester 1 over Ester 3 and Amides 5 and 6

excellent conversion (ratios are based on $^1$H NMR), thus confirming the superior reactivity of thioesters in this reaction.

1.2.5 Effect of Thiol Component

We next investigated the effect of the thiol component of the thioester on its reactivity. Thus, thioesters 7–11 (Table 1) were subjected to the conditions described above. Remarkably, thioesters 7, 8, and 9 provided the corresponding aldol products 12, 13, and 14 nearly quantitatively within only 20 minutes. Given the extremely rapid nature of the reaction in the case of 7, 8, and 9, we were unable to establish a clear preference for either thioester in the aldol addition. However, competition experiments involving 7, 8, and 9 with benzaldehyde showed a slight preference for the formation of 12 over 13 and 14. On this basis, and the fact that it is commercially available, 7 was chosen for subsequent studies. Significantly, a competition experiment between 5 and acetophenone gave a 3:1 mixture of the corresponding $\beta$-hydroxy ketone to 10,
Table 1. Investigation of the Effect of the Thiol on Thioester Reactivity in the MgI₂ Promoted Direct Aldol Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thioester</th>
<th>β-Hydroxythioester</th>
<th>Time (min)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcSBn</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>25</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>AcSPh</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>AcSMe</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>AcSMe</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>AcSN₂O₂</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>AcSFur</td>
<td>PhCHO, MgI₂, i-Pr₂NEt, CH₂Cl₂</td>
<td>30</td>
<td>96</td>
</tr>
</tbody>
</table>

demonstrating that the reactivity of a simple thioester in the direct aldol reaction is comparable to that of a highly reactive ketone.

1.2.6 Substituting MgBr₂·OEt₂ for MgI₂

Given the extremely rapid nature of the reaction with thioester 7, we wondered about the possibility of substituting MgBr₂·OEt₂ for MgI₂. This compound is
commercially available and very inexpensive and, like magnesium iodide, generates no toxic byproducts on aqueous workup. While the reaction with MgBr₂·OEt₂ would be expected to be slower, we hoped that this would be more than compensated for, not only by the low cost of the reagent, but also by allowing us to conduct the reactions open to the atmosphere using untreated, reagent grade solvent. To test this, compound 7 was first combined with benzaldehyde, i-Pr₂NEt, and MgBr₂·OEt₂ in untreated, reagent grade CH₂Cl₂ under anhydrous conditions (Table 2). For this experiment, the relative molar amount of all components used was the same as that for the magnesium iodide promoted reactions shown in Table 1. In this case, however, a slightly lower yield (88%) of β-hydroxy thioester 12 was obtained than when MgI₂ was used (95%).

Table 2. Condition Screen for Substituting MgBr₂·OEt₂ for MgI₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (min)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgI₂ (1.2 equiv), i-Pr₂NEt, CH₂Cl₂, r.t., anhydrous condition</td>
<td>25</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>MgBr₂·OEt₂ (1.2 equiv), i-Pr₂NEt, CH₂Cl₂, r.t., anhydrous condition</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>MgBr₂·OEt₂ (1.4 equiv), i-Pr₂NEt, CH₂Cl₂, r.t., anhydrous condition</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>MgBr₂·OEt₂ (1.4 equiv), i-Pr₂NEt, CH₂Cl₂ (untreated), r.t., open to air</td>
<td>30</td>
<td>96</td>
</tr>
</tbody>
</table>

---

 Aldrich ACS reagent grade, ≥99.5%.
Thus, we next did a cursory investigation of the effect of increasing the amount of each reactant, relative to the thioester component. No improvement in yield was observed when the amount of benzaldehyde was increased, but increasing the amount of either MgBr$_2$-OEt$_2$ or i-Pr$_2$NEt gave both a slightly faster reaction and a higher conversion. We eventually settled on the following conditions: 7 (1.0 equiv), benzaldehyde (1.2 equiv), MgBr$_2$-OEt$_2$ (1.4 equiv), and i-Pr$_2$NEt (2.0 equiv) in CH$_2$Cl$_2$ (concn 0.2 M). Significantly, under these conditions, not only was the reaction highly efficient, giving a 96% yield of 12, but it remained extremely facile, taking only 30 minutes to go to completion (See Table 2). No increase in yield or decrease in reaction time was observed when the reaction was conducted using anhydrous CH$_2$Cl$_2$ under an Ar atmosphere. In contrast, when MgI$_2$ was used in this manner, reaction yields were lower than when anhydrous conditions were employed.

### 1.2.7 Solvent and Base Screen

In our initial survey of metal salts to promote the direct aldol addition, we noted a pronounced difference in reactivity between MgCl$_2$, MgBr$_2$, and MgI$_2$, which is most likely attributable to solubility issues. As such, we decided to screen a variety of solvents for their effect on the outcome of the MgBr$_2$-OEt$_2$ reaction. Thus, the reaction between 7 and benzaldehyde was conducted in the presence of MgBr$_2$-OEt$_2$ and i-Pr$_2$NEt, but using THF, Et$_2$O, DMF, EtOAc, benzene, or toluene in place of CH$_2$Cl$_2$. However, in no case was there an improvement over the initial results obtained with CH$_2$Cl$_2$. 
We also explored the effect of the base in the context of the MgBr₂·OEt₂ promoted reaction using, in this case, thioester 8 and benzaldehyde, \( i\text{-Pr₂NEt} \) was found to be the best of those tried, giving clean and high-yielding (>90%) conversion into 13 after only 30 minutes. Et₃N gave a somewhat lower yield (75%) after one hour of reaction, and the formation of the bis-alkylated byproduct 17 (Figure 2) was also evident. With pyridine and 5-methoxybenzimidazole, no desired product was detected, even after 24 hours. 2,6-Lutidine, DBN, DBU, and Barton’s base (2-tert-butyl-1,1,3,3-tetramethylguanidine) all gave <50% conversion after one hour, with byproducts developing over extended periods of time.

![Figure 2. Bis-alkylated Byproduct](image)

**1.2.8 Reaction Scope**

Having confirmed the reaction conditions for the MgBr₂·OEt₂ promoted process, we investigated the scope of the reaction with 7 and a variety of aldehydes (Table 3). In all cases, reaction times were short and yields were excellent. Notably, the reaction could be conducted using an aldehyde having a single \( \alpha \)-proton 24 (entry 8) with only a small amount (<4%) of the self-addition product produced. In this case, best results were obtained when the thioester was used in a 1.5-fold excess, relative to the aldehyde.
Table 3. MgBr$_2$·OEt$_2$ Promoted Direct Aldol Addition between 7 and Various Aldehydes Using Untreated Solvent under Atmospheric Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldeneyde</th>
<th>β-Hydroxythioester</th>
<th>Time (min)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHO</td>
<td><img src="image" alt="12" /></td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>MeO-18</td>
<td><img src="image" alt="25" /></td>
<td>30</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>MeO-19</td>
<td><img src="image" alt="26" /></td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>O$_2$N-20</td>
<td><img src="image" alt="27" /></td>
<td>60</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Cl-21</td>
<td><img src="image" alt="28" /></td>
<td>60</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Ph-22</td>
<td><img src="image" alt="29" /></td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td><img src="image" alt="30" /></td>
<td>60</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td><img src="image" alt="31" /></td>
<td>60</td>
<td>92</td>
</tr>
</tbody>
</table>
The effect of α-substitution on the thioester was examined via the direct aldol addition between benzaldehyde and each of S-phenyl thiopropionate (32) and S-phenyl-α-benzylxyloxy thiopropionate (33) (Scheme 4). In both cases the reaction gave an excellent yield of the respective diastereomeric products in a reasonably short time.

**Scheme 4.** MgBr₂•OEt₂ Promoted Direct Aldol Reaction of α-Substituted Thioesters with Benzaldehyde

1.2.9 Catalytic Investigation

We also probed the possibility of using a catalytic amount of MgBr₂•OEt₂ in a manner similar to that reported by Evans,⁴a-c which involves utilizing the in-situ silylation of β-hydroxy aldol product to promote metal catalyst recycle. Thus, 7 was combined with benzaldehyde, MgBr₂•OEt₂ (0.2 equiv), i-Pr₂NEt (2.0 equiv) and TMSCl (2.0 equiv) (Scheme 5). After 96 h, only a moderate yield (53%) of the desired product was obtained. However, the reaction with TMSBr as the trapping agent was quite good, giving a 73% yield after 16 h. With TMSI, only 8% of β-hydroxy
thioester (12) was isolated, and another interesting major product (36) was formed in 55%.

1.2.10 Asymmetric Exploration

Based on the progress of trapping the kinetic product with TMSBr and using a catalytic amount of MgBr₂·OEt₂, we next sought to develop an asymmetric variant of this reaction. Commercially available chiral bidentated bis(oxazolinyl) (box) ligand⁶ 37 was first examined (Scheme 6). To do so, chiral ligand 37 (0.22 equiv) was mixed with MgBr₂·OEt₂ (0.2 equiv) in CH₂Cl₂ and allowed to stir for 4 h before adding 7, benzaldehyde, t-Pr₂NEt and TMSBr. Although this reaction gave 61% yield after 24 h, the product 12 showed no stereoselectivity on the basis of chiral HPLC result.

At this stage, we were not able to validate the binding activity of the chiral ligand with Mg²⁺ and the effect of providing facial bias through a closed Zimmerman–Traxler
transition state when the thioester enolate attacking benzaldehyde. Therefore, we designed an experiment to prove the effective participation of chiral ligand 37 in this reaction. We first ruled out the feasibility of the reaction with either stoichiometric amount of Mg(OTf)₂ or catalytic amount of Mg(OTf)₂ and TMSOTf. However, when we premixed chiral ligand 37 with Mg(OTf)₂ and conducted the reaction by subsequently adding 7, benzaldehyde, i-Pr₂NEt and TMSOTf, a good yield (79%) of product 12 was isolated after 48 h, thus conforming the participation of 37. As expected, the formation of product in this reaction was still not stereoselective. The future work will be the screening of other chiral bidentated or thidentated ligands.

Scheme 6. Exploration of Asymmetric Catalytic Direct Aldol Reaction of Thioesters

1.2.11 Section Summary
In summary, we have developed a mild and efficient direct aldol reaction using simple thioesters. The reaction is conducted using inexpensive MgBr₂·OEt₂ in untreated, reagent grade solvent under atmospheric conditions, and produces innocuous byproducts on workup. The superior reactivity of thioesters over oxoesters in this reaction was established via competition experiments and is fundamental to the facility of this procedure. This reaction can also be conducted using catalytic amount of MgBr₂·OEt₂ on the basis of trapping kinetic product with TMSBr. The asymmetric variant of this reaction requires further screening of suitable chiral ligands.

1.3 A Facile and Practical Approach to the Synthesis of 1,3-Diketone Compounds

1.3.1 1,3-Diketone Compounds

1,3-Diketones are important compounds in synthetic organic chemistry. They are widely represented in natural products, pharmaceuticals, and other biologically relevant compounds, or are key intermediates en route to such species. Indeed, their interesting and at times unusual chemical properties are often used to facilitate other synthetic methods, including the preparation of heterocycles and other aromatic compounds. Many naturally occurring 1,3-diketones exhibit biological activity.

including antioxidant, antitumor, antimicrobial, antiviral and antifungal activity (Figure 3).\textsuperscript{9, 10, 11}

Despite their prevalence, the synthesis of 1,3-diketones remains somewhat problematic. Considerable research has been conducted over the years on the development of methods for the synthesis of 1,3-diketones.\textsuperscript{9} The classic procedure, which is a modification of the well-known Claisen condensation,\textsuperscript{12} involves acylation of a ketone by an ester in the presence of an alkoxide base.\textsuperscript{9} This method has limited substrate scope, gives only modest to good yield, requires a large excess of the acylating agent, and often requires elevated temperatures and/or removal of the alcohol produced. Coupling yields are generally improved through the use of at least 2 equiv of sodium or lithium hydride in place of the alkoxide, but this approach is not applicable to substrates having even weakly acidic functionality elsewhere in the reactants. The current procedure of choice for 1,3-diketone synthesis uses a strong, non-nucleophilic base such
as LDA to preform the required enolate, which is followed by addition of the acylating agent, typically as an acid chloride. Yields generally improve under these conditions, but the presence of acidic functionality elsewhere in the reactants remains an issue. Furthermore, competing O-acylation and bis-acylation are common.\textsuperscript{12} The major drawback of this method is that at least 2-3 equiv of the enolate are required, making it inherently inefficient.\textsuperscript{12} This stems primarily from the fact that the 1,3-diketone product is significantly more acidic (pK\textsubscript{a} ~ 9) than the parent ketone (pK\textsubscript{a} ~ 20), so, as it forms, it protonates the unreacted ketone enolate preventing acylation.

\textbf{1.3.2 Method Design}

Given the reaction efficiency, mildness and operational simplicity with our initial stage development of MgBr\textsubscript{2}-OEt\textsubscript{2}-promoted direct aldol addition of simple thioesters based on soft enolization,\textsuperscript{2} we felt that it might provide the basis for workable solutions to the aforementioned problems associated with the synthesis of 1,3-diketones. We reasoned that the inefficiency of these conventional methods could be overcome if the required enolates were formed under soft rather than hard conditions. As introduced above, soft enolization does not employ a strong base and can be conducted under less stringent conditions than are required of hard enolization. In addition, since enolization is reversible, it is conducted in a direct fashion in the presence of the electrophilic species, further simplifying the procedure. In this case, when applied in acylation reactions the \(\beta\)-dicarbonyl product that forms would not be expected to interfere in a detrimental way,
as in situations employing hard enolization. Deprotonation of this species by the ketone
enolate or amine would undoubtedly occur, but in a reversible sense, such that the
intended ketone enolate could reform and ultimately undergo the desired acylation.
Given the relatively weak nucleophilic nature of the dicarbonyl enolate, bis-acylation
should not occur with appropriate choice of acylating agent.

1.3.3 Initial Investigation

To explore the use of soft enolization in 1,3-diketone synthesis, acetophenone
(38) was combined with benzoyl chloride (39), MgBr2·OEt2 and i-Pr2NEt in CH2Cl2 (Table
4). The desired 1,3-diketone (42) was indeed isolated from this reaction in very good
yield (83%) after only 1 h. A control experiment was carried out in which acetophenone

Table 4. MgBr2·OEt2-Promoted Direct Acylation of Acetophenone and Representative Acid
Chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chlorides</th>
<th>1,3-Diketone</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhOCl</td>
<td>PhOCl</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PhOCl</td>
<td>PhOCl</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PhOCl</td>
<td>PhOCl</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and benzoyl chloride were combined in CH₂Cl₂ in the presence of i-Pr₂NEt but in the absence of MgBr₂-OEt₂, with no coupled product observed after 24 h, thus confirming the essential nature of the Lewis-acid in enolization. Encouraged by the result with MgBr₂-OEt₂, we conducted a similar reaction with the aliphatic system, 3,3-dimethyl butanoyl chloride (40). In this case the desired product (43) was also obtained, but in a somewhat lower yield (65%). Use of pentanoyl chloride (41) as the acylating agent also gave the desired β-diketone (44), albeit in a much lower yield (30%) due to formation of the α,α-bis-acylation byproduct (45, Figure 4), as is typical when acid chlorides are used in enolate acylations. None of the reactions showed any improvement in yield when left for greater than 1 h.

![Figure 4. α,α-Bis-acylation Byproduct and Self-acylation Product](image)

Significantly, in the two reactions involving 40 and 41, no products were detected corresponding to self-acylation of the acid chloride (46 or 47, respectively, Figure 4). This is understandable if it is assumed that the reaction is facilitated by coordination of Mg²⁺ to the carbonyl oxygen (48 → 49) (Scheme 7), followed by deprotonation to form the enolate (49 → 50), rather than on the basis of α-proton acidity alone. In such a case, despite greater acidity predicted for the acid chloride α-protons
1.3.4 Acylating Agent and Lewis-Acid/Solvent Screen

To improve the yield for the aliphatic systems, we undertook an investigation into the effect of the acylating component on the outcome of the reaction. To do this we screened a variety of known acylating agents both with and without added DMAP\textsuperscript{14} as a nucleophilic acylation catalyst. The results are summarized in Table 5. Addition of DMAP was uniformly of no benefit with regard to either the time required for the reaction or the yield produced (entries 2, 5, 7 and 10, Table 5). O-succinimide ester 52 failed to react altogether, and, while thioester 53 did produce the desired product, yields were lower than for the corresponding acid chloride (40). O-Pfp ester 54 proved to be a suitable acylating agent, giving 79\% yield of the \(\beta\)-diketone within 12 h and 92\% within
Table 5. MgBr₂·OEt₂-Promoted Direct Acylation of Acetophenone with Different Acylating Agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylating Agent</th>
<th>Nucleophilic Acylation Catalyst</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O\textsuperscript{40}Cl</td>
<td></td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>O\textsuperscript{40}Cl</td>
<td>DMAP</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>O\textsuperscript{52}N₂O₅</td>
<td></td>
<td>24</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>O\textsuperscript{53}NO₂</td>
<td></td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>O\textsuperscript{53}NO₂</td>
<td>DMAP</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>O\textsuperscript{54}F₈</td>
<td></td>
<td>12</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>O\textsuperscript{54}F₈</td>
<td>DMAP</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>O\textsuperscript{54}F₈</td>
<td></td>
<td>24</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>O\textsuperscript{55}N₂N₂N</td>
<td></td>
<td>3</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>O\textsuperscript{55}N₂N₂N</td>
<td>DMAP</td>
<td>3</td>
<td>92</td>
</tr>
</tbody>
</table>
24 h. Even better yields and shorter reaction times resulted from the use of N-acylbenzotriazole 55 (entry 9, Table 5).

We next surveyed a variety of different Lewis-acid/solvent combinations to determine their effect on the course of the reaction with N-acylbenzotriazole 55 (Table 6). Of those combinations examined, MgBr₂·OEt₂ in CH₂Cl₂ (entry 1) was clearly superior, which was consistent with earlier observations on soft enolization,²,¹³ although ZnCl₂ in

Table 6. Effect of Reaction Conditions on Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgBr₂·OEt₂</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>MgBr₂·OEt₂</td>
<td>THF</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>MgBr₂·OEt₂</td>
<td>toluene</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl₂</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂</td>
<td>THF</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>ZnCl₂</td>
<td>toluene</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>THF</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)₂</td>
<td>toluene</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>NiI₂</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>N.R.</td>
</tr>
<tr>
<td>11</td>
<td>NiI₂</td>
<td>THF</td>
<td>18</td>
<td>N.R.</td>
</tr>
<tr>
<td>12</td>
<td>NiI₂</td>
<td>toluene</td>
<td>18</td>
<td>N.R.</td>
</tr>
</tbody>
</table>
CH₂Cl₂ also produced good results (entry 4, Table 6), while other combinations all gave unsatisfactory results.

In addition to their effectiveness in this reaction, another compelling reason for the use of MgBr₂·OEt₂ and N-acylbenzotriazoles or O-Pfp esters in this reaction is that they are relatively insensitive to air and moisture. This would potentially allow us to conduct the coupling reactions open to the air using untreated, reagent-grade CH₂Cl₂, resulting in even greater simplification of the procedure. To test this, N-acylbenzotriazole 55 and O-Pfp ester 54 were each combined with acetophenone, MgBr₂·OEt₂ and i-Pr₂NEt using untreated, reagent-grade CH₂Cl₂ open to the air. Under these conditions the desired 1,3-dicarbonyl product (43) was obtained with no change in either the isolated yield or reaction time, in comparison to the use of dry CH₂Cl₂ and an Ar atmosphere (see Table 7, Entry 1). In addition to these practical benefits, MgBr₂·OEt₂ and benzotriazole are extremely inexpensive, adding an economic advantage to the procedure. In contrast, however, pentafluorophenol is more costly and does not, outright, offer a substantial advantage in this regard. However, we found that it is readily recovered from the crude reaction mixture by simple extraction into saturated NaHCO₃, followed by acidification (10% HCl) and back extraction. Thus, both O-Pfp esters and N-acylbenzotriazoles were investigated in our subsequent studies.

1.3.5 Reaction Scope
Having secured a mild and straightforward method for the synthesis of β-diketone 43, we determined the scope of the method with respect to other N-acylbenzotriazoles and O-Pfp esters (see Table 7). In general, the N-acylbenzotriazoles

**Table 7. MgBr₂·OEt₂-Promoted Synthesis of 1,3-Diketones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylating Agent</th>
<th>1,3-Diketone</th>
<th>X</th>
<th>Time (min)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>55, X = Bt</td>
<td></td>
<td>2.5</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>54, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>56, X = Bt</td>
<td></td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>57, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>58, X = Bt</td>
<td></td>
<td>2.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>59, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>60, X = Bt</td>
<td></td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>61, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>62, X = Bt</td>
<td></td>
<td>2.5</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>63, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>64, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>65, X = Bt</td>
<td></td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>66, X = O-Pfp</td>
<td></td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>67, X = Bt</td>
<td></td>
<td>2.5</td>
<td>81</td>
</tr>
</tbody>
</table>
outperformed the O-Pfp esters in terms of both reaction time and yield. The isolated yields were typically excellent when N-acylbenzotriazoles were used. Significantly, the coupling reaction could be carried out in the presence of an acidic urethane nitrogen protecting group (entry 11), and also in the presence of an enone (entry 14), without detrimental results, as would be expected in the corresponding hard enolization processes.

We next explored the scope of the coupling reaction using a variety of ketones with various N-acylbenzotriazoles and O-Pfp esters (see Table 8). Once again, in all cases the desired 1,3-diketone was obtained in good to excellent yield. Notably, the coupling could be conducted using cyclohexanone as the nucleophile to give the corresponding mono-substituted 1,3-diketone (89) in excellent yield (entry 13). Entries 11 and 12 reveal that the process is even compatible with the presence of phenolic functionality. Such a substrate would not be amenable to traditional coupling methods without prior incorporation of a phenol protecting group. A significant result is shown in entry 18 where 1-[(E)-cinnamoyl]-1H-benzotriazole and 3-pentanone were coupled to give the desired 1,3-dicarbonyl (91) without subsequent cyclization to the corresponding 1,3-cyclohexanedione (93, Figure 5), as is typical of such systems.

Figure 5. Typical Cyclized Product
Table 8. MgBr$_2$-OEt$_2$-Promoted Synthesis of 1,3-Diketones

\[
\begin{align*}
\text{Entry} & \quad \text{Acylationg Agent} & \quad \text{Ketone} & \quad \text{1,3-Diketone} & \quad X & \quad \text{Time (min)} & \quad \text{Isolated Yield (\%)} \\
1 & \quad \text{RCH}_2\text{Me} & \quad \text{O} & \quad \text{OMe} & \quad \text{RCH}_2\text{Me} & \quad \text{O} & \quad \text{OMe} & \quad X = \text{Bt} & \quad 2.5 & \quad 82 \\
2 & \quad \text{Ph} & \quad \text{O} & \quad \text{73} & \quad \text{Ph} & \quad \text{O} & \quad \text{84} & \quad X = \text{O-Pf} & \quad 24 & \quad 68 \\
3 & \quad \text{Ph} & \quad \text{O} & \quad \text{74} & \quad \text{Ph} & \quad \text{O} & \quad \text{85} & \quad X = \text{Bt} & \quad 4 & \quad 99 \\
4 & \quad \text{Ph} & \quad \text{O} & \quad \text{OMe} & \quad \text{75} & \quad \text{O} & \quad \text{Ph} & \quad \text{86} & \quad X = \text{Bt} & \quad 2.5 & \quad 91 \\
5 & \quad \text{Ph} & \quad \text{O} & \quad \text{75} & \quad \text{O} & \quad \text{Ph} & \quad \text{87} & \quad X = \text{O-Pf} & \quad 24 & \quad 72 \\
6 & \quad \text{Ph} & \quad \text{O} & \quad \text{76} & \quad \text{O} & \quad \text{Ph} & \quad \text{88} & \quad X = \text{Bt} & \quad 4 & \quad 92 \\
7 & \quad \text{Ph} & \quad \text{O} & \quad \text{77} & \quad \text{O} & \quad \text{Ph} & \quad \text{88} & \quad X = \text{O-Pf} & \quad 24 & \quad 65 \\
8 & \quad \text{Ph} & \quad \text{O} & \quad \text{78} & \quad \text{OH} & \quad \text{Ph} & \quad \text{89} & \quad X = \text{O-Pf} & \quad 24 & \quad 65 \\
9 & \quad \text{Ph} & \quad \text{O} & \quad \text{79} & \quad \text{Ph} & \quad \text{90} & \quad X = \text{Bt} & \quad 3 & \quad 99 \\
10 & \quad \text{Ph} & \quad \text{O} & \quad \text{80} & \quad \text{Ph} & \quad \text{91} & \quad X = \text{O-Pf} & \quad 24 & \quad 58 \\
11 & \quad \text{Ph} & \quad \text{O} & \quad \text{81} & \quad \text{Ph} & \quad \text{92} & \quad X = \text{Bt} & \quad 3 & \quad 66 \\
12 & \quad \text{Ph} & \quad \text{O} & \quad \text{82} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{93} & \quad X = \text{Bt} & \quad 4 & \quad 88
\end{align*}
\]
To further explore the versatility of our method, we undertook the synthesis of 69 in an inverse sense by switching the respective ketone and acylbenzotriazole. Thus, methyl ketone 83 was prepared according to known procedures\textsuperscript{15} and was subjected to the coupling with 1-benzoylbenzotriazole. β-Diketone 69 was indeed produced from this reaction (Table 8, entry 17), and in a yield (88\%) comparable to that obtained when prepared from acetophenone and 60 (91\%) (Table 7, entry 7).

1.3.6 Examination of Stereochemical Integrity

Finally, we examined the impact of the coupling reaction on the stereochemical integrity of the starting materials. As mentioned above, conventional methods for β-dicarbonyl synthesis are limited to substrates lacking acidic functionality. This includes compounds having base epimerizable stereogenic centers α to a carbonyl group. To test the effect of our coupling conditions on such compounds, compound 69, prepared from 60 and acetophenone and from 83 and 1-benzoylbenzotriazole, was compared to the corresponding racemic material by HPLC using a chiral, non-racemic stationary phase. No racemization had occurred during either of the synthetic procedures, thus demonstrating that our method is also compatible with substrates prone to base-induced epimerization under conventional hard enolization conditions.

1.3.7 Section Summary
In summary, we have developed an efficient direct coupling reaction between ketones and N-acylbenzotriazoles or O-Pfp esters, based on soft enolization, that proceeds under mild conditions to generate 1,3-diketones. The reaction is conducted using inexpensive MgBr₂·OEt₂ in untreated, reagent-grade solvent open to the air, and produces innocuous by-products on workup, making it operationally simple. Furthermore, it is compatible with a range of substrates, including those having base-epimerizable centers adjacent to carbonyl groups, as well as those possessing other base sensitive functionality. Thus, syntheses employing this carbon–carbon bond-forming method may well benefit in the avoidance of protecting groups.

1.4 An Exceptionally Simple and Versatile Crossed-Claisen Reaction

1.4.1 Crossed-Claisen Reaction

The crossed-Claisen coupling reaction is an essential carbon–carbon bond-forming method. The β-keto ester moiety produced is found in countless natural products, pharmaceuticals and other compounds in either its native or derivatized form. Indeed, β-keto esters are unusually versatile intermediates, providing access to a very wide array of functionality. In the most general form of the crossed-Claisen reaction

---

both the nucleophilic precursor and the acylating component possess α-protons. However, in such cases four products may, in principle, result: two from self- and two from crossed-coupling (Scheme 8). Chemoselectivity is controlled using prior enolate formation.12, 16 While effective, the step-wise procedures required to generate the enolates are time consuming, particularly if trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperature. Moreover, a large excess of enolate (± acylating agent) is required for high conversion, making these transformations inherently inefficient.12, 16, 17 Given the central role that β-keto esters play in organic synthesis, it is clear that a simplified and more efficient version of this transformation would be beneficial.

1.4.2 Nature’s Use of Thioesters in Crossed-Claisen Reaction and Our Approach

We anticipated that soft enolization could provide the basis of a solution to the long-standing problems associated with the crossed-Claisen coupling, provided the
nucleophilic precursor could be chemoselectively enolized in the presence of the acylating agent. To achieve this, we turned to the use of simple thioesters as the enolate precursors. Interestingly, in Nature’s version of the crossed-Claisen condensation, such as in fatty acid synthesis (Figure 6), thioesters serve as both the enolate precursors and acylating agents. While such reactions produce a single crossed-product, chemoselective enolization is not achieved by selective deprotonation. Instead, the intended thioester enolate is formed via decarboxylation of the corresponding malonic acid half thioester (MAHT) (94). Although effective in a biological context, we sought a more convenient mode of chemoselective enolization that would avoid the additional steps and difficulties associated with the laboratory preparation of MAHTs. Fortunately, as a result of prior work we had conducted, we felt that chemoselective soft enolization of a simple thioester could be achieved while in the presence of an even more reactive acylating agent.

\[ \text{Figure 6. Fatty Acid Biosynthesis} \]

(ACP = Acyl-Carrier Protein; KS = β-Ketoacyl-ACP Synthase)

In our previous studies, we had found that thioesters and ketones are readily alkylated under soft enolization conditions, whereas oxoesters, acid chlorides and N-
acylbenzotriazoles are not. These observations are consistent with the notion that the propensity of the carbonyl species to enolize is not determined by Brønsted acidity alone, but by a balance between α-proton acidity and carbonyl Lewis basicity (Figure 7). Thus, a carbonyl species that is strongly acidic and, correspondingly, weakly Lewis basic (e.g., acid chloride, N-acylbenzotriazole), would be less prone to interaction with the Lewis acid, as required of soft enolization. In contrast, a somewhat less acidic species (e.g., thioester, ketone), being more strongly Lewis basic, would be prone to such interaction and, subsequently, enolization. However, there is a tipping point on this side of the equation too: even though oxoesters are more Lewis-basic than thioesters, their relatively low acidity decreases their susceptibility to soft enolization. Thioesters and ketones appear to strike a near ideal balance between Brønsted acidity and Lewis-basicity in the context of soft enolization. It is perhaps not surprising then that thioesters are used in biological carbon–carbon bond-forming processes employing soft enolization.

![Figure 7. Qualitative Relationship between Brønsted Acidity, Lewis-Basicity and Soft Enolization](image-url)
1.4.3 Thioester Screen and Comparison with Oxoester

Based on the above observations, we anticipated that the use of a thioester as the enolate precursor, in combination with an acid chloride or N-acetylbenzotriazole as an acyl donor, should enable chemoselective enolization leading to a controlled direct crossed-Claisen coupling. To test this idea we chose to use N-acetylbenzotriazoles, which are extremely inexpensive, versatile, and easily managed acylating agents. Gratifyingly, when N-acetylbenzotriazole 55 (1.0 equiv) and thioester 7 (1.0 equiv) were combined in CH2Cl2 (0.25 mmol/L concn) in the presence of MgBr2·OEt2 (3.0 equiv) and Hunig’s base (4.0 equiv) (Entry1, Table 9), the desired crossed coupling product 102 was obtained in excellent yield (93%). Neither the self-addition products nor the other crossed-Claisen product were detected. However, decreasing either the amount of Lewis-acid or base or the reaction concentration resulted in a longer reaction time and a lower yield. The attempt of increasing the relative amount of thioester to N-acetylbenzotriazole also gave a slightly lower conversion and a small amount of the thioester self-condensation product.

To confirm our suspicion regarding the importance of the thioesters in this transformation, oxoester 98 was treated under analogous conditions. In this case only a relatively low yield (44%) of β-keto oxoester (103) formed after an extended period of time.

*We have shown that O-Pfp esters are also excellent acylating agents under soft enolization conditions (see section 1.3 in this chapter), however, given the relatively high cost associated with their preparation we have focused on N-acetylbenzotriazoles for this work.*
Table 9. Comparison of the Direct Crossed-Claisen Coupling of Various Thioesters and Oxoester

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thio/oxoester</th>
<th>β-Keto Thio/oxoester</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>AcCPh</td>
<td>O</td>
<td>26</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>AcSPh</td>
<td>O</td>
<td>4</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 9 continued... 

...time, thus confirming the superiority of thioesters in the transformation. We also surveyed a variety of different thioesters to determine their effect on this coupling reaction. Of those thioesters examined, thioester 7 was found to be the best. Although the reaction proceeded faster with thioester 99 and 100, a small amount of the
corresponding thioester self-condensation product appeared; while the reaction with thioester 8, 101 and 1 offered somewhat lower yields.

One of the compelling features of conducting carbon–carbon bond formation via soft enolization is the mildness of the reaction conditions required. In avoiding the use of strong bases, not only are low temperature requirements overcome, but so too is the need for an inert atmosphere and the use of anhydrous conditions. To test that such conditions would not be deleterious in the present situation, the reaction between 55 and 7 was repeated, but this time open to the air using untreated, reagent grade solvent. We were pleased to find that under these very straightforward conditions there was no change in the outcome of the reaction in comparison to the use of an inert atmosphere and anhydrous conditions.

1.4.4 Reaction Scope

Having established proof of concept in the direct thioester crossed-Claisen coupling, and confirming that it could be conducted without the need for highly controlled conditions, we investigated its scope. We began with exploring the reaction with different α-substituted thioesters and 55 under the established conditions (Table 10). The reaction proved to be compatible with all α-alkyl and α-alkoxy thioesters that examined (entry1-4), while the β-alkoxy and β-silyloxy thioesters (entry 5 and 6) were not suitable for this reaction and underwent β-elimination or decomposition under the reaction conditions.
We next investigated the scope of the reaction with thioester 32 and a variety of N-acylbenzotriazoles (Table 11). In general, the transformation proceeded very well with a range of N-acylbenzotriazoles that have different functionalities, including ester,
Table 11. Investigation of a Variety of N-Acylbenzotriazoles with 32 under the Direct Crossed-Claisen Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thioester</th>
<th>β-Keto Thioester</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Ph}^\text{Bt} )</td>
<td>( \text{Ph}^\text{Bt} \text{SPh} )</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>( \text{N}^\text{Bt} )</td>
<td>( \text{N}^\text{Bt} \text{SPh} )</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Ph}^\text{Bt} )</td>
<td>( \text{Ph}^\text{Bt} \text{SPh} )</td>
<td>16</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>( \text{N}^\text{Bt} )</td>
<td>( \text{N}^\text{Bt} \text{SPh} )</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>( \text{N}^\text{Bt} )</td>
<td>N.R.</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>( \text{TBSO}^\text{Bt} \text{Ph} )</td>
<td>( \text{TBSO}^\text{Bt} \text{SPh} )</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>( \text{O}^\text{Bt} \text{CH} )</td>
<td>N.R.</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>( \text{O}^\text{Bt} \text{CO}_2\text{Me} )</td>
<td>( \text{O}^\text{Bt} \text{CO}_2\text{Et} )</td>
<td>12</td>
<td>87</td>
</tr>
</tbody>
</table>
\(\alpha\)-silyloxy\(^h\) and \(\alpha\beta\)-unsaturated carbonyl compounds. However, \(N\)-acylbenzotriazole \(43\) that contains a phenol functional group proceeded extremely slowly under the reaction condition and after 120 h reaction time, only the starting material and a noticeable amount of the thioester \(32\) self-condensation product were isolated. As to the reaction with \(N\)-acylbenzotriazole \(62\), only decomposed starting material was detected.

We also explored the reaction scope with sterically hindered substrates (Scheme 9). For both cases that we examined, good reaction yields were obtained with the extension of reaction time. Notably, the reaction even progressed quite well in the case of a very sterically hindered thioester that contains an acetal functional group (thioester \(128\)).

**Scheme 9.** Direct Thioester Crossed-Claisen Coupling with Sterically Hindered Systems

\[^h\text{Control experiments (cf. refs 23) showed that epimerization had not occurred during the formation of 31.}\]
1.4.5 Direct Transformations of β-Keto Thioester

As demonstrated, the use of thioesters in the direct crossed-Claisen coupling is advantageous in facilitating the reaction relative to oxoesters. However, in addition, the presence of the thioester moiety in the coupled product enables subsequent direct transformations that are not possible using β-keto oxoesters. Consequently, the β-keto

Table 12. Direct Transformations of β-Keto Thioester 102 to Esters and Amides

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
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<td>3</td>
<td>96</td>
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<tr>
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<td>t-Bu2SiO</td>
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<td>3</td>
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thioesters produced provide a convenient and stable alternative to the use of β-keto acids. For instance, esters were readily formed from β-keto thioester 102 in high yield from alcohols using AgCO$_2$CF$_3$ as a thiophilic promoter (Table 12). The use of allylic alcohols (cf. 131 and 132) provides straightforward access to Carroll rearrangement substrates (135 and 136). Direct amidation was also possible from β-keto thioester 102, as shown in the preparation of 137 and 138. When hydroxylamine hydrochloride was used as a starting material, a cyclized product (139) was formed rapidly.

An especially useful transformation involving β-keto thioester product 102 and 114 is seen in their conversion to β-diketone 140 and 141 using the Fukuyama protocol (Scheme 10). In particular, the transformation of 114 to 141 is equivalent to the regioselective acylation of 3-heptanone which, under conventional conditions, would be marginally selective at best.

**Scheme 10. Direct Transformation of β-Keto Thioesters to Ketones**

![Scheme 10](image)

1.4.6 Application to the Total Synthesis of LY294002

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The usefulness of the present method in preparing β-keto thioesters, along with the strategic advantage presented in their synthetic equivalence to β-keto acids, was demonstrated by a concise total synthesis of LY294002 (142), a potent and specific inhibitor of PI3-K.25 PI3-Ks play prominent roles in a variety of diseases including diabetes, cancer and chronic inflammation, and have attracted considerable recent interest as a new class of drug targets.26 Our plan for the synthesis of 142 is shown in a general sense in Scheme 11. Here, the direct crossed Claisen coupling of a salicylic acid-derived N-acylbenzotriazole and an aliphatic acid-derived thioester is used to merge the two halves of the molecule, and is followed by late-stage chemoselective amidation and cyclization. The timing of the amidation reaction (144 → 143), along with the established generality of our coupling method, makes this a very simple and flexible approach to structural analogues of LY294002 and related compounds. This should be beneficial for ongoing and future drug development initiatives involving PI3-K.26

To test this synthetic strategy, we first prepared O-benzyl-protected N-acetylbenzotriazole 150 from commercially available 3-phenyl salicylic acid (147) (Scheme 12). Treatment of 150 and thioester 7 under the conditions developed above smoothly generated β-keto thioester 151. The thioester function was then leveraged in the direct amidation reaction leading to 152. Hydrogenolysis followed by treatment with Tf2O generated the chromone core, thus providing LY294002 with an overall yield of 67% for 7 steps.27

Scheme 12. Synthesis of LY294002

1.4.7 Section Summary
In summary, we have developed an efficient direct crossed-Claisen reaction between thioesters and \( N \)-acylbenzotriazoles. The process does not require prior enolate formation and is conducted using untreated, reagent-grade solvent open to the air. In contrast to products obtained via conventional Claisen-condensations, the resulting \( \beta \)-keto thioesters serve as stable synthetic equivalents of \( \beta \)-keto acids and readily undergo direct conversion to esters, amides and ketones. The utility of this coupling procedure and the strategic advantage resulting from the presence of the thioester function has been demonstrated through the total synthesis of LY294002.

1.5 Conclusion

On the basis of using soft enolization strategy, we approached the issue of direct carbon-carbon bond formation from three categories, namely 1) a direct aldol addition reaction of simple thioesters; 2) a direct coupling reaction between ketones and \( N \)-acylbenzotriazoles or \( O \)-Pfp esters; and 3) a direct crossed-Claisen reaction between thioesters and \( N \)-acylbenzotriazoles. We have demonstrated the advantage of applying soft enolization over conventional methods in terms of the reaction efficiency, mildness, compatibility with a variety of substrates as well as operational simplicity, and have also shown the application of direct crossed-Claisen reaction in natural product synthesis. Given the importance of these reactions in general, and the predominance over previous research, we expect that the methods will meet wide application.
1.6 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, Et₂O, CH₂Cl₂, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Brine (NaCl), NaHCO₃, and NH₄Cl refer to saturated aqueous solutions. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ¹H and ¹³C NMR were recorded on a Varian Mercury 300 MHz spectrometer or Varian INOVA 400 MHz
spectrometer at ambient temperature. All $^1$H chemical shifts are reported in ppm ($\delta$) relative to TMS; $^{13}$C shifts are reported in ppm ($\delta$) relative to CDCl$_3$ (77.16). MS data were collected from Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was performed on a 4.6 X 250 nm Chiralpak AD-H column (Chiral Technologies).

1.6.1 Supporting Information for Direct Aldol Addition of Thioesters

*The following reaction is representative of those depicted in Scheme 2 and Table 1:*

$$
\begin{align*}
\text{MgI}_2, \text{i-Pr}_2\text{NEt, CH}_2\text{Cl}_2 \\
\text{PhCHO} \\
\text{PhSO}_2\text{Ph} + \text{PhCHO} & \rightarrow \text{PhSO}_2\text{Ph} \\
\end{align*}
$$

**$\beta$-Hydroxy thioester (12).** MgI$_2$ (0.167 g, 0.6 mmol) was added to a stirred solution of thioester 7 (0.076 g, 0.5 mmol) and benzaldehyde (61 µL, 0.6 mmol) in CH$_2$Cl$_2$ (2.5 mL), followed by the addition of i-Pr$_2$NEt (0.17 mL, 1.0 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$_2$O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO$_4$), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 12 (0.121 g; 94%) as a pure, colorless solid: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.50-7.26 (m, 10H), 5.21 (X of an ABX system, apparent td, $J = 3.4,$
8.7 Hz, 1H), 3.12 (A of an ABX system, apparent dd, \( J = 8.8, 16.0 \) Hz, 1H), 3.03 (B of an ABX system, apparent dd, \( J = 3.8, 16.0 \) Hz, 1H), 2.97 (d, \( J = 3.3 \) Hz, 1H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 300 MHz): \( \delta \) 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\(_2\)S: 281.1, found: 280.8.

\[
\text{\( \beta \)-Hydroxy thioester (2).} \quad \text{Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 2 (0.1294 g; 95%) as a pure, colorless solid:} \\
\text{\(^1\text{H NMR}\) (CDCl\(_3\), 300 MHz): } \delta 7.42-7.18 (m, 10H), 5.20 (X of an ABX system, apparent td, } \delta = 3.6, 8.7 \text{ Hz, 1H), 4.17 and 4.15 (AB q, } \Delta_{\text{AB}} = 6.6 \text{ Hz, } \delta = 13.8 \text{ Hz, 2H), 3.08-2.88 [m, 3H, including A of an ABX system, apparent dd, at } \delta 3.02 (J = 9.0, 15.9 \text{ Hz, 1H) and B of an ABX system, apparent dd, at } \delta 2.93 (J = 3.9, 15.9 \text{ Hz, 1H})); \\
\text{\(^{13}\text{C NMR}\) (CDCl\(_3\), 300 MHz): } \delta 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\(_2\)S: 295.1, found: 294.9.

\[
\text{\( \beta \)-Hydroxy thioester (13).} \quad \text{Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 13 (0.1413 g; 98%) as a pure, colorless solid:} \\
\text{\(^1\text{H NMR}\) (CDCl\(_3\), 300 MHz): } \delta 7.39-7.20 (m, 7H), 7.00-6.90 (m, 2H), 5.20 (X of an ABX system, apparent td, } \delta =
3.3, 8.7 Hz, 1H), 3.14-2.97 [m, 3H, including A of an ABX system, apparent 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, apparent dd, at δ 2.99 (J = 3.3, 15.9 Hz, 1H)]; 13C NMR (CDCl3, 300 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 C16H16NaO3S: 311.1, found: 310.9.

![Image of compound 14](image)

**β-Hydroxy thioester (14).** Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 14 (0.1384 g; 96%) as a pure, light-yellow solid: 1H NMR (CDCl3, 300 MHz): δ 7.45-7.20 (m, 7H), 7.06-6.97 (m, 2H), 5.20 (X of an ABX system, apparent dd, J = 8.1, 4.5 Hz, 1H), 3.85 (s, 3H), 3.24-2.96 [m, 3H, including A of an ABX system, apparent dd, at δ 3.15 (J = 5.4, 15.9 Hz, 1H), and B of an ABX system, apparent dd, at δ 3.05 (J = 4.2, 15.9 Hz, 1H)]; 13C NMR (CDCl3, 300 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 C16H16NaO3S: 311.1, found: 310.9.

![Image of compound 15](image)

**β-Hydroxy thioester (15).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 15 (0.1395 g; 92%) as a pure, light-yellow solid: 1H NMR (CDCl3, 300 MHz): δ 7.45-7.20 (m, 7H), 7.06-6.97 (m, 2H), 5.20 (X of an ABX system, apparent dd, J = 8.1, 4.5 Hz, 1H), 3.85 (s, 3H), 3.24-2.96 [m, 3H, including A of an ABX system, apparent dd, at δ 3.15 (J = 5.4, 15.9 Hz, 1H), and B of an ABX system, apparent dd, at δ 3.05 (J = 4.2, 15.9 Hz, 1H)]; 13C NMR (CDCl3, 300 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 C16H16NaO3S: 311.1, found: 310.9.
300 MHz): \( \delta 8.30-8.20 \) (m, 2H), 7.70-7.55 (m, 2H), 7.50-7.22 (m, 5H), 5.26 (X of an ABX system, apparent td, \( J = 3.6, 9.0 \text{ Hz}, 1\text{ H} \)), 3.25-3.00 [m, 2H, including A of an ABX system, apparent dd, at \( \delta 3.19 \) (\( J = 9.0, 15.9 \text{ Hz}, 1\text{ H} \))], 2.64 (d, \( J = 3.6 \text{ Hz}, 1\text{ H} \)); \(^{13}\text{C NMR} \) (CDCl\(_3\), 300 MHz): \( \delta 194.5, 148.4, 142.1, 135.7, 134.9, 128.9, 128.4, 125.8, 124.2, 70.9, 52.8 \); **ESI-MS** m/z [M + Na]\(^+\) calcd for C\(_{15}\)H\(_{13}\)NNaO\(_4\)S: 326.0, found: 325.9.

\[
\text{OH} \quad \text{S} \quad \text{Ph}
\]

\( ^{13} \text{C NMR} \) (CDCl\(_3\), 300 MHz): \( \delta 197.5, 150.1, 142.4, 142.3, 128.7, 128.0, 125.7, 110.7, 108.2, 70.8, 52.4, 25.8 \); **ESI-MS** m/z [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{14}\)NaO\(_3\)S: 285.1, found: 284.8.

**β-Hydroxy thioester (16).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 16 (0.1259 g; 96%) as a pure, light-yellow oil: \(^1\text{H NMR} \) (CDCl\(_3\), 300 MHz): \( \delta 7.41-7.23 \) (m, 6H), 6.33-6.18 (m, 2H), 5.20 (X of an ABX system, br apparent td, \( J = 2.7, 8.7 \text{ Hz}, 1 \text{ H} \)) 4.20 and 4.17 (AB q, \( \Delta \nu_{AB} = 10.4 \text{ Hz}, J = 15.3 \text{ Hz}, 2 \text{ H} \)), 3.09-2.88 [m, 3H, including A of an ABX system, apparent dd, at \( \delta 3.03 \) (\( J = 8.8, 15.8 \text{ Hz} \))], B of an ABX system, apparent dd, at \( \delta 2.93 \) (\( J = 3.9, 15.8 \text{ Hz} \)), overlapping a br d at \( \delta 2.92 \) (\( J = 2.4 \text{ Hz} \));

\[^{13}\text{C NMR} \) (CDCl\(_3\), 300 MHz): \( \delta 197.5, 150.1, 142.4, 142.3, 128.7, 128.0, 125.7, 110.7, 108.2, 70.8, 52.4, 25.8 \); **ESI-MS** m/z [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{14}\)NaO\(_3\)S: 285.1, found: 284.8.

*The following reaction is representative of those depicted in Scheme 3:*

\[
\text{O} \quad \text{O} \quad \text{O} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}
\]

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \]

\[ \text{PhCHC} \quad \text{Mgl}_2 \quad \text{IrPr}_2 \text{NET}, \text{CHCl}_3 \quad 30 \text{ min} \]

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**β-Hydroxy thioester (2).** MgI₂ (0.278 g, 1.0 mmol) was added to a stirred solution of thioester 1 (0.16 mL, 1.0 mmol), acetate 3 (0.14 mL, 1.0 mmol) and benzaldehyde (0.10 mL, 1.0 mmol) in CH₂Cl₂ (5.0 mL), followed by the addition of i-Pr₂NEt (0.17 mL, 1.0 mmol). Stirring was continued for 2 h and EtOAc (5.0 mL) and 10% (v/v) aqueous HCl (5.0 mL) were added. Stirring was continued for 15 min and the mixture was partitioned between EtOAc (15 mL) and H₂O (2 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow solid. The results were obtained from the ¹H NMR of the crude material.

*The following reaction is representative of those depicted in Table 3 and Scheme 4:*

*The following reactions were conducted using untreated CH₂Cl₂, open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*

\[
\begin{align*}
\text{O} & \quad \text{MgBr₂·OEt₂, i-Pr₂NEt} \\
\text{7} & \quad \text{CH₂Cl₂ (untreated)} \\
\text{atmospheric condition} & \quad \text{12}
\end{align*}
\]

**β-Hydroxy thioester (12).** MgBr₂·OEt₂ (0.181 g, 0.7 mmol) was added to a stirred solution of thioester 7 (0.076 g, 0.5 mmol) and benzaldehyde (61 μL, 0.6 mmol) in CH₂Cl₂ (2.5 mL), followed by the addition of i-Pr₂NEt (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 H2O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO4), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 12 (0.1240 g; 96%) as a pure, colorless solid. Spectroscopic data was identical to that reported above.

\[ \beta \text{-Hydroxy thioester (25).} \]

Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 25 (0.1399 g; 97%) as a pure, colorless solid. \( ^1 \text{H NMR} \) (CDCl_3, 300 MHz): \( \delta \) 7.44-6.84 [m, 9H, including apparent d at \( \delta \) 7.30 (\( J = 8.8 \) Hz), and apparent d at \( \delta \) 6.89 (\( J = 8.8 \) Hz)], 5.16 (X of an ABX system, br apparent d (\( J = 8.7 \) Hz, 1H), 3.80 (s, 3H), 3.11 (A of an ABX system, apparent dd, \( J = 8.7, 15.9 \) Hz, 1H), 3.00 (B of an ABX system, apparent dd, \( J = 3.6, 15.9 \) Hz, 1H), 2.90 (br apparent s, 1H); \( ^{13} \text{C NMR} \) (CDCl_3, 300 MHz): \( \delta \) 197.1, 159.3, 134.53, 134.50, 129.7, 129.3, 127.2, 127.0, 114.0, 70.4, 55.3, 52.2; \text{ESI-MS m/z} [M + Na]^+ calcd for C_{16}H_{16}NaO_3S: 311.1, found: 310.8.
**β-Hydroxy thioester (26).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 26 (0.1384 g; 96%) as a pure, colorless solid. \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta 7.50-7.22\) (m, 6H), 6.98-6.78 (m, 3H), 5.19 (X of an ABX system, apparent 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, apparent dd, at \(\delta 3.10\) (\(J = 8.5, 16.0\) Hz), B of an ABX system, apparent dd, at \(\delta 3.02\) (\(J = 3.6, 16.0\) Hz), and a d at \(\delta 2.97\) (\(J = 3.6\) Hz)]; \(^{13}\)C NMR (CDCl₃, 300 MHz): \(\delta 197.0, 159.8, 144.0, 134.5, 129.7, 129.3, 127.2, 118.0, 113.6, 111.1, 70.6, 55.3, 52.2\) (2 peaks overlapping); ESI-MS \(m/z\) [M + Na]⁺ calcd for C₁₆H₁₆NaO₃S: 311.1, found: 310.8.

\[
\text{OH} \quad \text{O} \quad \text{SPh} \\
\text{O} \quad \text{Me} \\
\text{HO} \quad \text{O} \quad \text{SPh}
\]

**β-Hydroxy thioester (27).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 27 (0.1355 g; 94%) as a pure, colorless solid. \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta 8.22\) (apparent d, \(J = 8.7\) Hz, 2H), 7.56 (apparent 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 (CDCl₃, 300 MHz): \(\delta 197.3, 149.4, 147.7, 134.6, 130.1, 129.6, 126.7, 124.0, 69.9, 51.6\) (2 peaks overlapping); ESI-MS \(m/z\) [M + Na]⁺ calcd for C₁₅H₁₃NNaO₄S: 326.0, found: 325.8.
**β-Hydroxy thioester (28).** Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 28 (0.1420 g; 95%) as a pure, colorless solid. $^1$H NMR (CDCl₃, 300 MHz): δ 7.46-7.36 (m, 6H), 7.34-7.20 (m, 3H), 5.18 (X of ABX system, apparent overlapping td, $J = 3.9$, 7.8 Hz, 1H), 3.14-2.96 [m, 3H, including A of an ABX system, apparent 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, apparent dd, at δ 3.01 ($J = 4.4$, 15.9 Hz)]; $^{13}$C NMR (CDCl₃, 300 MHz): 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 (2 peaks overlapping); ESI-MS $m/z$ [M + Na]$^+$ calcd for C₁₅H₁₃ClNaO₂S: 315.0, found: 314.8.

**β-Hydroxy thioester (29).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 29 (0.1307 g; 92% with trace impurities) as a colorless solid. $^1$H NMR (CDCl₃, 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 (apparent d, $J = 6.6$ Hz, 2H), 2.74 (d, $J = 4.2$ Hz, 1H); $^{13}$C NMR (CDCl₃, 300 MHz): δ 197.1, 136.4, 134.6, 131.2, 129.8, 129.4, 128.4, 128.7, 128.0, 127.2, 126.7, 69.5, 50.3; ESI-MS $m/z$ [M + Na]$^+$ calcd for C₁₇H₁₆ClNaO₂S: 307.1, found: 306.9.
**β-Hydroxy thioester (30).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 30 (0.1120 g; 94%) as a pure, light-yellow oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.44-7.40 (m, 5H), 3.78 (X of an ABX system, apparent d, \(J = 10.2\) Hz, 1H), 2.94-2.58 [m, 3H, including A of an ABX system, apparent dd, at \(\delta\) 2.88 \((J = 2.0, 15.8\) Hz), B of an ABX system, apparent dd, at \(\delta\) 2.71 \((J = 10.2, 15.8\) Hz), and a d at \(\delta\) 2.62 \((J = 3.3\) Hz)], 0.93 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 300 MHz): \(\delta\) 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\(_2\)S: 261.1, found: 260.9.

**β-Hydroxy thioester (31).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 31 (0.1084 g; 82%) as a pure, colorless solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 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, apparent dd, at \(\delta\) 2.86 \((J = 3.3, 15.9\) Hz), B of an ABX system, apparent dd, at \(\delta\) 2.77 \((J = 8.7, 15.9\) Hz), and a d at \(\delta\) 2.68 \((J = 3.9\) Hz)], 1.94-0.88 (m, 11H); \(^{13}\)C NMR (CDCl\(_3\), 300 MHz): \(\delta\) 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\(_2\)S: 287.1, found: 286.9.
β-Hydroxy thioester (34). Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 34 (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): 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$_3$, 300 MHz): 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, 76.4, 74.0, 55.3, 55.1, 15.4, 11.9; ESI-MS $m/z$ [M + Na]$^+$ calcd for C$_{16}$H$_{16}$NaO$_2$S: 295.1, found: 294.8.

α-Benzylkoxy-β-hydroxy thioester (35). Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 35 (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): 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 ($\Delta v_{AB} = 16.0$ Hz, $J = 11.1$ Hz)].
Hz) and an AB q at δ 4.43 and 4.26 (ΔνAB = 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)]; 13C NMR (CDCl3, 300 MHz): 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 (some peaks overlapping); ESI-MS m/z [M + Na]+ calcd for C22H20NaO3S: 387.1, found: 386.8.

The following reactions are representatives of those depicted in Scheme 5.

β-Hydroxy thioester (12). MgBr2·OEt2 (0.026 g, 0.1 mmol) was added to a stirred solution of thioester 7 (0.076 g, 0.5 mmol) and benzaldehyde (61 μL, 0.6 mmol) in CH2Cl2 (2.5 mL), followed by the addition of TMSBr (0.13 mL, 1.0 mmol) and i-Pr2NEt (0.17 mL, 1.0 mmol). Stirring was continued for 16 h 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 H2O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO4), and evaporated to give a light-yellow solid.
Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 12 (0.0939 g; 73%) as a pure, colorless solid. Spectroscopic data was identical to that reported above.

\[
\begin{align*}
\text{PhCHO, MgBr}_2\cdot\text{OEt}_2 (0.2 \text{ equiv}) & \quad \text{i-Pr}_2\text{NEt, TMSI, } \text{CH}_2\text{Cl}_2 \\
\text{O} & \quad \text{OH} \\
\text{7} & \quad \text{12} + \text{36}
\end{align*}
\]

**S-Phenyl 5-oxo-3,5-diphenylpentanethioate (36).** MgBr₂-OEt₂ (0.026 g, 0.1 mmol) was added to a stirred solution of thioester 7 (0.135 g, 1.0 mmol) and benzaldehyde (0.053 g, 0.5 mmol) in CH₂Cl₂ (2.5 mL), followed by the addition of TMSI (0.36 mL, 2.5 mmol) and i-Pr₂NEt (0.35 mL, 2.0 mmol). Stirring was continued for 22 h 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 H₂O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 12 (0.0099 g; 8%) and 36 (0.1078 g, 55%) as colorless solid. For compound 36: **¹H NMR** (CDCl₃, 300 MHz): δ 7.45-7.20 (m, 15H), 3.88-3.74 (m, 1H), 3.18-2.95 (m, 4H); **¹³C NMR** (CDCl₃, 300 MHz): δ 195.7, 141.6, 134.7, 129.7, 129.4, 129.0, 127.8, 127.5, 49.2, 39.5; **ESI-MS** m/z [M + Na]⁺ calcd for C₂₁H₁₈NaO₂S₂: 415.1, found: 414.9.

*The following reaction is representative of those depicted in Scheme 6.*
**β-Hydroxy thioester (12).** Mg(OTf)₂ (0.032 g, 0.1 mmol) was mixed with chiral ligand 37 (0.032 g, 0.11 mmol) in CH₂Cl₂ (2.5 mL). Stirring was continued for 4 h and then thioester 7 (68 μL, 0.5 mmol), benzaldehyde (61 μL, 0.6 mmol), TMSOTf (0.18 mL, 1.0 mmol) and i-Pr₂NEt (0.17 mL, 1.0 mmol) were added to the solution respectively. Stirring was continued for 44 h 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 H₂O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 12 (0.1027 g; 79%) as a pure, colorless solid. Spectroscopic data was identical to that reported above.

*The following reaction is representative of the synthesis of thioesters 1, 9, 10 and 11.*

![Reaction scheme](image)

S-(2-Methoxy)phenyl thioacetate (9). Ac₂O (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 CH₂Cl₂ (19 mL). The mixture was allowed to stir for 12 h and then partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was washed with water, saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 6:94 EtOAc-hexanes gave 9 (2.7551 g; 92%) as a pure, colorless liquid. **¹H NMR** (CDCl₃, 300 MHz): δ 7.48-7.34 (m, 2H), 7.04-6.92 (m, 2H), 3.86 (s, 3H), 2.41 (s, 3H); **¹³C NMR** (CDCl₃, 300 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 C₉H₁₀NaO₂S: 205.0, found: 204.8.

![S-Benzyl thioacetate](image1.png)

**S-Benzyl thioacetate (1).** Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave 1 (1.6637 g; 87%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.²⁸

![S-(4-Methoxy)phenyl thioacetate](image2.png)

**S-(4-Methoxy)phenyl thioacetate (8).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 8 (2.1141 g; 93%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.²⁸
N-benzylacetamide (5). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 5 (0.54 g; 72%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.40-7.22 (m, 5H), 6.05 (s, 1H), 4.48-4.36 (m, 2H, including a s at $\delta$ 4.41 and a s at $\delta$ 4.39), 2.01 (s, 3H).

N-methyl- N-benzylacetamide (6). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 6 (0.60 g; 74%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.40-7.12 (m, 5H), 4.65-4.50 (m, 2H, including a s at $\delta$ 4.59 and a s at $\delta$ 4.53), 2.96-2.90 (s, 2H, including a s at $\delta$ 2.94 and a s at $\delta$ 2.92), 2.16 (s, 3H).

S-Phenyl benzyloxythioacetate (33). 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 PhSH (0.95 mL; 9.29 mmol). The mixture was allowed to stir for 3 h and was partitioned between EtOAc and water. The organic phase was washed with
saturated aqueous NaHCO₃, saturated aqueous NaCl, dried (MgSO₄) and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 33 (1.5081 g; 94%) as a pure, colorless liquid. ¹H NMR (CDCl₃, 300 MHz): δ 7.48-7.29 (m, 10H), 4.73 (s, 2H), 4.27 (s, 2H); ¹³C NMR (CDCl₃, 300 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 C₁₅H₁₄NaO₂S: 281.1, found: 280.8.

![Chemical reaction](image)

**β-Hydroxy oxoester (4).** MgI₂ (0.167 g, 0.6 mmol) was added to a stirred solution of O-benzyl acetate (3) (0.075 g, 0.5 mmol) and benzaldehyde (61 μL, 0.6 mmol) in CH₂Cl₂ (2.5 mL), followed by the addition of i-Pr₂NEt (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 H₂O (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 4 (0.0593 g; 46%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.²⁹

**1.6.2 Supporting Information for the Synthesis of 1,3-Diketones**
The acids used to make the O-Pfp esters in Table 7 were all commercially available except perfluorophenyl 2-(tert-butyldimethylsilyloxy)-2-phenylacetate, which was prepared as described in the literature.\textsuperscript{30} The ketones shown in Table 8 were all commercially available except 2-(tert-butyldimethylsilyloxy)-1-phenylethanone, which was prepared as described in the literature.\textsuperscript{31}

![Chemical structure](image)

**2,5-Dioxopyrrolidin-1-yl 3,3-dimethylbutanoate (52).** DCC (1.9 g, 7.9 mmol) was added to a stirred solution of 3,3-dimethyl butyric acid (1 mL, 7.9 mmol) and N-hydroxysuccinimide (0.92 g, 7.9 mmol) in THF (25 mL) (Ar atmosphere). Stirring was continued for 12 h, by which time a colorless precipitate had formed. The mixture was filtered and evaporated to give a yellow oil. Flash chromatography over silica gel using 35:65 EtOAc-hexanes gave 52 (0.8133 g, 49\%) as a pure, white solid. Spectroscopic data was identical to that reported previously.\textsuperscript{32}

![Chemical structure](image)

**Thioester (53).** 3,3-Dimethyl-butyryl chloride (0.380 mL, 2.7 mmol) was added drop-wise via syringe over ca. 30 sec to a stirred and cooled (ice-water bath) solution of
4-nitro-benzenethiol (0.419 g, 2.7 mmol) and pyridine (0.220 mL, 2.7 mmol) in CH₂Cl₂ (3.0 mL) (Ar atmosphere). Stirring was continued for 5 min, the cooling bath was removed, and stirring was continued for an additional 30 min. The mixture was combined with H₂O and the aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were dried (MgSO₄), and evaporated to give a yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 53 (0.8133 g, 49%) as a pure, light-yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 8.30-8.20 (m, 2H), 7.70-7.55 (m, 2H), 2.59 (s, 2H), 1.09 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 193.8, 148.2, 137.1, 134.7, 124.1, 56.9, 32.3, 29.9; ESI-MS m/z [M + Na]⁺ calcd for C₁₂H₁₅NNaO₃S: 276.07, found: 276.0.

The following procedure is representative of the synthesis of O-Pfp esters.

O-Pfp Ester (54). DCC (1.1 g, 4.4 mmol) was added to a stirred solution of 3,3-dimethyl butyric acid (0.5 mL, 3.9 mmol) and pentafluoro phenol (0.8174 g, 4.4 mmol) in 1,4-dioxane (16 mL) (Ar atmosphere). Stirring was continued for 12 h, by which time a colorless precipitate had formed. The mixture was filtered and evaporated to give a yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 54 (0.995 g, 90%) as a pure, colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 2.54 (s, 2H), 1.14 (s,
9H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 167.9, 46.9, 31.1, 29.3; ESI-MS m/z [M+H]$^+$ calcd for C$_{12}$H$_{12}$F$_5$O$_2$: 283.2, found: 99 (C$_5$H$_{11}$CO), 183 (C$_6$F$_5$O).

![Chemical Structure](image)

**O-Pfp Ester (57).** Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 57 (0.941 g, 81%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.40 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 174.8, 39.7, 27.1; ESI-MS m/z [M + Na]$^+$ calcd for C$_{11}$H$_9$F$_5$NaO$_2$: 268.2, found: 85 (C$_5$H$_9$O), 183(C$_6$F$_5$O), 268.

![Chemical Structure](image)

**O-Pfp Ester (59).** Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 59 (0.802 g, 55%) as a pure, white solid. Spectroscopic data was identical to that reported previously.$^{33}$

![Chemical Structure](image)
**O-Pfp Ester (64).** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 64 (0.777 g, 72%) as a pure, white solid. Spectroscopic data was identical to that reported previously.\textsuperscript{34}

![O-Pfp Ester (64)](image)

**O-Pfp Ester (61).** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 61 (0.325 g, 87%) as a pure, colorless oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ 7.56-7.37 (m, 5H), 5.54 (s, 1H), 0.95 (s, 9H), 0.18 (s, 3H), 0.09 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): δ 168.6, 139.7, 137.8, 129.1, 128.9, 126.7, 74.4, 56.0, 35.2, 25.8, 25.7, 24.9, 18.5, -5.0; ESI-MS m/z [M+Na]\textsuperscript{+}calcd for C\textsubscript{21}H\textsubscript{23}F\textsubscript{5}NaO\textsubscript{2}Si: 455.5, found: 182.6, 239.0, 454.8.

![O-Pfp Ester (61)](image)

**O-Pfp Ester (63).** Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 63 (0.875 g, 71%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.\textsuperscript{35}
**O-Pfp Ester (66).** Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 66 (0.570 g, 87%) as a pure, colorless oil. \(^1H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 5.95-5.81 (m, 1H), 5.18-5.07 (m, 2H), 2.78 (t, \(J = 7.4\) Hz, 2H), 2.52 (m, 2H); \(^13C\) NMR (CDCl\(_3\), 75 MHz): \(\delta\) 168.9, 135.5, 116.5, 32.8, 28.7; ESI-MS \(m/z\) [M+Na]\(^+\) calcd for C\(_{11}\)H\(_8\)F\(_5\)NaO\(_2\): 288.1, found: 182.6, 263.7, 287.9.

The following procedure is representative of the synthesis of the following N-acylbenzotriazoles.

\[\text{N-Acylbenzotriazole (55).}\]

Et\(_3\)N (2.3 mL, 16.5mmol) was added drop-wise via syringe to a stirred and cooled (ice-H\(_2\)O bath) solution of 1\(H\)-1,2,3-benzotriazole (1.64 g, 14.0 mmol) in anhydrous CH\(_2\)Cl\(_2\) (40 mL), followed by addition of 3,3-dimethyl butyroyl chloride (2.0 mL, 14.0 mmol) (Ar atmosphere). Stirring was continued for 4 h, by which time a solution had formed. 10% aqueous HCl (20 mL) was added and stirring was continued for 15 min. The organic phase was washed with 10% aqueous HCl (2 x 10 mL), H\(_2\)O (10 mL), dried (MgSO\(_4\)), and evaporated to give a white powder.
Recrystallization from 2-propanol gave 55 (2.7680 g, 91%) as a white solid. Spectroscopic data was identical to that reported previously.36

\[ \text{N-Acylbenzotriazole } (56). \] Recrystallization from 2-propanol gave 56 (1.40 g, 69%) as a white solid. Spectroscopic data was identical to that reported previously.7

\[ \text{N-Acylbenzotriazole } (58). \] Recrystallization from 2-propanol gave 58 (1.04 g, 51%) as colorless needles. Spectroscopic data was identical to that reported previously.7

\[ \text{N-Acylbenzotriazole } (62). \] Recrystallization from 2-propanol gave 62 (2.77 g, 91%) as a white powder. Spectroscopic data was identical to that reported previously.37
**N-Acylbenzotriazole (67).** Recrystallization from 2-propanol gave 67 (2.76 g, 91%) as a white powder. Spectroscopic data was identical to that reported previously.\(^{38}\)

*The following procedure is representative of the synthesis of the following N-acylbenzotriazoles.*

\[
\begin{align*}
\text{BocHN} & \quad \text{C} \\
\text{Br} & \quad \text{OH} \\
\text{EDCI, EDCI, CH}_2\text{Cl}_2 & \quad \rightarrow \\
\text{BocHN} & \quad \text{C} \\
\text{Br} & \quad \text{N} \equiv \text{N}
\end{align*}
\]

*N-Acylbenzotriazole.* EDCI (2.30 g, 12 mmol) was added to a stirred solution of 1\(H\)-1,2,3-benzotriazole (1.19 g, 10 mmol) and \(N\)-**tert**-Boc-phenylalanine (3.18 g, 12 mmol) in anhydrous \(\text{CH}_2\text{Cl}_2\) (50 mL) (Ar atmosphere). Stirring was continued for 48 h, the solvent was evaporated and the residue was partitioned between \(\text{EtOAc}\) and \(\text{H}_2\text{O}\). The organic phase was washed with saturated \(\text{NaHCO}_3\), brine, dried (\(\text{MgSO}_4\)) and evaporated. Flash chromatography over silica gel using 5:95 \(\text{EtOAc-hexanes}\) gave \(N\)-acylbenzotriazole (3.2812 g, 90%) as a white powder. Spectroscopic data was identical to that reported previously.\(^{39}\)

\[
\begin{align*}
\text{TBSO} & \quad \text{O} \\
\text{Ph} & \quad \text{N} \equiv \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

**N-Acylbenzotriazole (60).** Flash chromatography over silica gel using 4:96 \(\text{EtOAc-hexanes}\) gave 60 (1.67 g, 91%) as a white powder. \(^1\text{H} \text{NMR} (\text{CDCl}_3, 400 \text{ MHz}): \delta
8.21 (d, J = 8.1 Hz), 8.12 (d, J = 8.2 Hz), 7.70 (d, J = 8.0 Hz), 7.53-7.22 (m, 5H), 1.19 (s, 9H),
0.19 (s, 3H), 0.23 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 170.7, 146.2, 138.3, 131.5, 130.7,
129.0, 128.9, 128.4, 128.0, 126.8, 126.5, 120.3, 114.7, 74.0, 26.0, 25.6, 18.5, -4.6. ESI-MS m/z
[M+Na]$^+$ calcd for C$_{20}$H$_{25}$N$_3$NaO$_2$Si: 390.51, found: 337.2, 390.1.

$N$-Acylbenzotriazole (65). SOCl$_2$ (0.73 mL, 10 mmol) was added to a stirred
solution of 1H-1,2,3-benzotriazole (4.8 g, 40 mmol) in anhydrous CH$_2$Cl$_2$ (50 mL) at room
temperature (Ar atmosphere). The mixture was stirred for 30 min and pentenoic acid
(1.02 mL, 10 mmol) was added in one portion and stirring was continued for 2 h. The
resulting suspension was filtered and washed with 2M NaOH (3 x 50 mL), dried (MgSO$_4$)
and evaporated to give a light-yellow oil. Flash chromatography over silica gel using
8:92 EtOAc-hexanes gave 65 (1.63 g, 82%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 300
MHz): δ 8.22-8.11 (m, 2H), 7.68-7.61 (m, 1H), 7.48-7.40 (m, 1H), 6.10-5.85 (m, 1H), 5.20-
5.07 (m, 2H), 3.54 (t, J = 7.5 Hz, 2H), 2.64 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.0,
146.3, 136.2, 131.2, 130.5, 126.3, 120.3, 116.4, 114.5, 34.9, 28.3; ESI-MS m/z [M+Na]$^+$ calcd
for C$_{11}$H$_{11}$N$_3$NaO: 224.2, found: 224.0.

*The following reaction is representative of those depicted in Table 7 and Table 8.*
The following reactions were conducted using untreated CH₂Cl₂, open to the air.

Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.

\[
\begin{align*}
55 & \quad + \quad 38 \quad \xrightarrow{\text{MgBr₂·OEt₂}} \quad \text{Pr₂NEt, CH₂Cl₂} \quad \rightarrow \\
& \quad \text{Ph} \quad \text{Ph} \\
\end{align*}
\]

1,3-Diketone (43). Acetophenone (0.065 mL, 0.63 mmol) was added drop-wise via syringe to a stirred mixture of 43 (0.164 g, 0.76 mmol) and MgBr₂·OEt₂ (0.414 g, 1.58 mmol) in CH₂Cl₂ (10 mL), followed by i-Pr₂NEt (0.33 mL, 1.90 mmol). The resulting suspension changed from colorless to yellow while the i-Pr₂NEt was added. The reaction mixture was stirred for 2.5 h, by which time a solution had formed. 10% aqueous HCl (10 mL) was then added and stirring was continued for 5 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic extracts were dried (MgSO₄) and evaporated to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 43 (0.4168 g, 96%) as a pure, yellow oil. Spectroscopic data was identical to that reported previously.⁴⁰
**1,3-Diketone (43).**  i-Pr₂NEt (0.22 mL, 1.3 mmol) was added drop-wise via syringe over ca. 30 sec to a stirred mixture of acetophenone (0.050 mL, 0.43 mmol) and MgBr₂·OEt₂ (0.281 g, 1.07 mmol) in CH₂Cl₂ (4 mL). The resulting suspension was stirred for 2 min, during which time the solution changed from colorless to yellow, and then 54 (0.181 g 0.64 mmol) was added drop-wise by Pasteur pipette, using CH₂Cl₂ (0.5 mL) as a rinse. The reaction mixture was stirred for 24 h, by which time a solution had formed. 10% aqueous HCl (4 mL) was then added and stirring was continued for 5 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts were dried (MgSO₄) and evaporated to give a dark-red oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 43 (0.088 g, 92%) as a pure, yellow oil. Spectroscopic data was identical to that reported previously.¹¹

1,3-Diketone (68). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 68 (0.179 g, 99%).

Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 68 (0.043 g, 81%) as a pure, yellow oil. Spectroscopic data was identical to that reported previously.⁴¹
1,3-Diketone (42). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 42 (0.332 g, 95%). Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 42 (0.083 g, 87%) as a pure, yellow solid. Spectroscopic data was identical to that reported previously.42

1,3-Diketone (69). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 69 (0.0467 g, 57%). Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 69 (0.128 g, 86%) as a pure, yellow oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 15.80 (s, 1H), 7.93-7.37 (m, 10H), 6.77 (s, 1H), 5.26 (s, 1H), 1.03 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 199.1, 182.4, 140.4, 134.8, 132.6, 128.9, 128.7, 128.3, 127.2, 126.6, 92.5, 78.0, 26.1, 18.6, -4.6, -4.7; ESI-MS \(m/z\) [M+Na]\(^+\)calcd for C\(_{22}\)H\(_{28}\)NaO\(_3\)Si: 391.5, found: 390.9.
1,3-Diketone (70). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 70 (0.0467 g, 57%). Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 70 (0.115 g, 73%) as a pure, yellow oil. Spectroscopic data was identical to that reported previously.43

\[
\text{\begin{tikzpicture}
  \draw (0,0) -- (0.5,0) -- (0.5,0.5) -- (0,0.5) -- (0,0);
  \node at (0.25,0.25) {44};
\end{tikzpicture}}
\]

1,3-Diketone (44). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 44 (0.1344 g, 79%). Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 2:98 EtOAc-hexanes gave 44 (0.067 g, 61%) as a pure, yellow oil. Spectroscopic data was identical to that reported previously.44

\[
\text{\begin{tikzpicture}
  \draw (0,0) -- (0.5,0) -- (0.5,0.5) -- (0,0.5) -- (0,0);
  \node at (0.25,0.25) {44};
\end{tikzpicture}}
\]

1,3-Diketone (71). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 71 (0.1059 g, 70%). Starting from the corresponding O-Pfp ester: Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 71 (0.044 g, 53 %) as a pure, yellow oil. \textbf{H NMR} (CDCl₃, 300 MHz): δ; 16.13 (s, 1H), 8.0-7.83 (m, 2H), 7.51-7.41 (m, 3H), 6.18 (s, 1H), 5.93-5.79 (m, 1H),
5.13-5.01 (m, 2H), 2.57-2.43 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 196.3, 183.4, 137.1, 134.5, 129.0, 128.8, 127.2, 115.8, 96.4, 38.7, 29.8; ESI-MS \(m/z\) [M+Na]\(^{+}\) calcd for C\(_{15}\)H\(_{14}\)NaO\(_2\): 225.1, found: 224.9.

**1,3-Diketone (72).** Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 72 (0.1013 g; 81%) as a pure, yellow crystals. Spectroscopic data was identical to that reported previously.\(^9\)

\[\text{Ph} \equiv \text{C} \quad \text{O} \quad \text{O} \quad \text{Ph} \]

**1,3-Diketone (84).** Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 84 (0.135 g, 92%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 84 (0.062 g, 68%) as a pure, yellow oil. \(^{1}H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 16.31 (s, 1H), 7.84 (dd, \(J = 1.8\) Hz, 5.9 Hz, 1H), 7.42 (m, 1H), 7.01-6.94 (m, 2H), 6.34 (s, 1H), 3.89 (s, 3H), 2.26 (s, 2H), 1.06 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 194.3, 133.0, 130.4, 120.9, 111.8, 103.8, 55.9, 52.7, 32.1, 30.3, 30.2; ESI-MS \(m/z\) [M+Na]\(^{+}\) calcd for C\(_{15}\)H\(_{20}\)NaO\(_3\): 271.3, found: 270.9.
**1,3-Diketone (85).** Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 85 (0.107 g, 99%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 85 (0.107 g, 99%) as a pure, yellow oil. **1H NMR** (CDCl₃, 300 MHz): δ 16.47 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 6.06 (s, 1H), 3.85 (s, 3H), 2.24 (s, 3H), 1.05 (s, 9H); **13C NMR** (CDCl₃, 75 MHz): δ 191.8, 186.0, 163.3, 129.4, 114.1, 97.5, 55.6, 52.1, 32.0, 30.2; **ESI-MS m/z** [M+Na]+ calcd for C₁₅H₂₀NaO₃: 271.3, found: 270.9.

![1,3-Diketone (85)](image)

**1,3-Diketone (86).** Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 86 (0.101 g, 91%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 86 (0.058 g, 72%) as a pure, orange oil. **1H NMR** (CDCl₃, 300 MHz): δ 15.62 (s, 1H), 7.55 (m, 1H), 7.15 (m, 1H), 6.53-6.61 (m, 1H), 6.00 (s, 1H), 2.21 (s, 2H), 1.04 (s, 9H); **13C NMR** (CDCl₃, 75 MHz): δ 190.0, 177.8, 146.1, 115.8, 112.7, 97.8, 51.4, 32.1, 30.1; **ESI-MS m/z** [M+Na]+ calcd for C₁₂H₁₆NaO₃: 231.2, found: 230.9.
1,3-Diketone (87). Starting from N-acetylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 87 (0.111 g, 92%). Starting from O-Pfp ester 54: Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave 87 (0.065 g, 65%) as a pure, yellow oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.98-7.95 (m, 2H), 7.62-7.41 (m, 3H), 4.48-4.41 (q, \(J = 7.0\) Hz, 1H), 2.43-2.28 (m, 2H), 1.41 (d, \(J = 7.0\) Hz, 3H), 0.97 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 206.4, 197.7, 136.3, 133.8, 129.1, 128.8, 128.3, 128.1, 57.8, 52.9, 30.9, 30.3, 29.7, 13.7; ESI-MS \(m/z\) [M+Na]\(^{+}\) calcd for C\(_{15}\)H\(_{20}\)NaO\(_2\): 255.31, found: 254.9.

1,3-Diketone (88). Starting from N-acetylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 88 (0.056 g, 65%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 2:98 EtOAc-hexanes gave 88 (0.048 g, 68%) as a pure, yellow oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): (keto-enol mixture) \(\delta\) 14.7(s, 1H), 8.02-7.39 (m, 9H), 5.16 (s, 1H), 2.48 (d, \(J = 3.3\) Hz, 4H), 1.084 (s, 9H), 0.96 (s, 9H), 0.92 (s, 8H), 0.88 (s, 9H), 0.096 (s, 3H), -0.01 (s, 3H), -0.34 (s, 4H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 205.9, 195.8, 192.4, 175.2, 134.8, 134.6, 133.8, 131.4, 131.1, 130.5, 130.0, 129.6, 129.5, 129.0.
128.6, 128.1, 86.7, 49.5, 46.9, 32.9, 31.0, 30.1, 29.9, 29.7, 26.0, 25.8, 18.4, 18.1, -4.7, -4.8; ESI-MS m/z [M+Na]+ calcd for C_{30}H_{52}NaO_3Si: 371.2, found: 371.0.

1,3-Diketone (89). Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 89 (0.111 g, 50%). Starting from O-Pfp ester 54: Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave 89 (0.065 g, 65%) as a pure, yellow oil. ^1H NMR (CDCl_3, 300 MHz): δ 14.98 (s, 1H), 12.11 (s, 1H), 7.64-7.40 (m, 2H), 6.98-6.84 (m, 3H), 6.10 (s, 1H), 2.22 (s, 2H), 1.06 (s, 9H); ^13C NMR (CDCl_3, 75 MHz): δ 195.5, 183.3, 162.8, 135.9, 128.9, 119.2, 118.9, 97.1, 50.5, 32.3, 30.2, 29.8; ESI-MS m/z [M+Na]+ calcd for C_{14}H_{18}NaO_3: 257.12, found: 257.0.

1,3-Diketone (90). Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 90 (0.1066 g, 99%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 90 (0.046 g, 58%) as a pure, yellow oil. ^1H NMR (CDCl_3, 75 MHz): δ 16.61 (s, 1H), 2.35-2.32 (m, 4H), 2.27 (s, 1H), 1.67-1.65 (m, 4H), 1.03 (s, 9H); ^13C NMR (CDCl_3, 300 MHz): δ 198.2,
186.3, 108.2, 47.7, 32.6, 32.4, 30.3, 25.1, 23.4, 22.0; ESI-MS m/z [M+Na]^+ calcd for C_{12}H_{20}NaO_{2}: 217.3, found: 216.9.

1,3-Diketone (91). Starting from N-acylbenzotriazole 55: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 91 (0.066 g, 66%). Starting from O-Pfp ester 54: Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 91 (0.050 g, 62%) as a pure, yellow oil. ^1H NMR (CDCl₃, 300 MHz): δ 16.77 (s, 1H), 2.27 (s, 2H), 1.19 (d, J = 7.11 Hz, 3H), 1.06-1.04 (m, 4H), 1.03 (s, 9H), 1.02-0.99 (m, 4H); ^13C NMR (CDCl₃, 75 MHz): δ 197.8, 190.0, 107.6, 47.8, 36.7, 32.4, 30.6, 30.3, 29.9, 25.7, 21.3, 18.1; ESI-MS m/z [M+Na]^+ calcd for C_{12}H_{20}NaO_{2}: 233.3, found: 232.9.

1,3-Diketone (72). Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 72 (0.1013 g; 81%) as pure, yellow crystals. Spectroscopic data was identical to that reported previously. 9
**1,3-Diketone (92).** Starting from the corresponding N-acylbenzotriazole: Flash chromatography over silica gel, using 4:96 EtOAc-hexanes gave 92 (0.0774 g; 72%) as pure, yellow crystals. **1H NMR** (CDCl₃, 400 MHz): δ 16.23 (d, J = 1.6 Hz, 1H), 7.65 (d, J = 16.0 Hz, 1H), 7.61 (d, J = 16.0 Hz, 1H), 7.57-7.30 (m, 5H), 6.95 (dd, J = 1.2 Hz, 15.6 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 3.96 (q, J = 7.2 Hz, 1H), 2.56 (q, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H); **13C NMR** (CDCl₃, 100 MHz): δ 207.8, 204.5, 196.5, 171.6, 144.7, 139.4, 135.9, 134.3, 131.1, 129.7, 129.2, 129.0, 128.8, 128.0, 124.0, 119.8, 105.5, 59.7, 34.7, 32.1, 13.2, 12.1, 8.7, 7.9; **ESI-MS m/z** [M+Na]+ calcd for C_{14}H_{16}O_{2}: 239.3, found: 239.1.

![Chemical Structure](image)

**MeLi (0.670 mL of a 1.6 M solution in ether, 1.07 mmol) was added drop-wise via syringe over ca. 1 min to a stirred and cooled (ice-water bath) solution of 2-(tert-butyldimethyl-silyloxy)-N-methoxy-N-methyl-2-phenyl-acetamide (0.110 g, 0.356 mmol) in THF (2 mL) (Ar atmosphere). Stirring was continued for 1 h, by which time the starting material had been consumed (TLC control, silica gel, 30:70 EtOAc-hexanes). Saturated aqueous NH₄Cl was added and the mixture was extracted with Et₂O (3 x 30 mL). The combined organic extracts were dried (MgSO₄) and evaporated to give a yellow oil. Flash
chromatography over silica gel using 5:95 EtOAc-hexanes gave 83 (0.0776 g, 82%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.\textsuperscript{45}

**1.6.3 Supporting Information for Crossed-Claisen Reaction**

*The following reaction is representative of those depicted in Table 9, 10, 11 and Scheme 9:*

*The following reactions were conducted using untreated reagent grade CH$_2$Cl$_2$, open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.*

\[
\begin{align*}
\text{Keto thioester} & \ (102) \\
\text{MgBr}_2\cdot\text{OEt}_2 & \ (0.387 \text{ g, 1.5 mmol}) \\
\text{was added to a stirred solution of N-acylbenzotriazole} & \ (55) \ (0.109 \text{ g, 0.5 mmol}) \text{ in CH}_2\text{Cl}_2 \ (2 \text{ mL}), \\
\text{followed by the addition of S-phenyl thioacetate} & \ (7) \ (68 \mu\text{L, } 0.5 \text{ mmol}) \text{ and } \text{i-Pr}_2\text{NEt} \ (0.35\text{mL, 2.0 mmol}). \\
\text{Stirring was continued for 4 h (monitored by TLC) and 10\% aqueous HCl} & \ (2 \text{ mL}) \text{ was added. Stirring was continued for 5 min and the mixture was partitioned between EtOAc} \ (30 \text{ mL}) \text{ and H}_2\text{O} \ (5 \text{ mL}). \\
\text{The aqueous phase was extracted with EtOAc} \ (2 \times 10 \text{ mL}) \text{ and the combined organic extracts were washed with brine, dried over MgSO}_4, \\
\text{and evaporated to give a light red oil. Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave} & \ (102) \ (0.117 \text{ g; 93\%}) \text{ as a pure, light red oil, comprised of a mixture of*}
\(\text{\(\beta\)-keto thioester} \text{ and its tautomeric enol form in a ratio of 1:1.8. Both tautomers are reported below:} \quad \text{\(\text{\(1H\ NMR (CDCl}_3, 400 \text{ MHz):} \delta 12.57 \text{ (s, 1H), 7.55-7.38 (m, 5H), 5.42 (s, 1H), 3.71 (s, 2H), 2.45 (s, 2H), 2.04 (s, 2H), 1.03 (s, 9H), 1.00 (s, 9H);} \quad \text{\(\text{\(13C\ NMR (CDCl}_3, 400 \text{ MHz):} \delta 201.3, 193.1, 190.6, 177.0, 135.2, 134.5, 129.9, 129.4, 129.3, 127.3, 127.2, 100.4, 58.9, 55.3, 49.0, 31.9, 31.1, 30.0, 29.6; \quad \text{\(\text{\(\text{ESI-MS} \ m/z [M} + \text{Na}^+ \text{] calcld for C}_{14}\text{H}_{18}\text{NaO}_{2}\text{S: 273.1, found: 273.0.}\}

\begin{center}
\includegraphics[width=0.2\textwidth]{113}
\end{center}

**\(\text{\(\beta\)-Keto thioester} \text{ (113).}** \ (Reaction time 6 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 113 (0.115 g; 87%) as a pure, light pink oil, comprised of a mixture of \(\text{\(\beta\)-keto thioester} \text{ and its tautomeric enol form in a ratio of 4:1. Both tautomers are reported below:} \quad \text{\(\text{\(1H\ NMR (CDCl}_3, 400 \text{ MHz):} \delta 13.46 \text{ (s, 1H), 7.52-7.34 (m, 5H), 3.81 (q,} \ J = \text{7.2 Hz, 1H), 2.49 (s, 2H), 2.24 (s, 2H), 2.00 (s, 3H), 1.41 (d,} \ J = \text{8.0 Hz, 3H), 1.04 (s, 9H), 1.03 (s, 9H);} \quad \text{\(\text{\(13C\ NMR (CDCl}_3, 400 \text{ MHz):} \delta 203.8, 196.0, 194.8, 174.1, 135.5, 134.5, 129.8, 129.6, 129.4, 129.3, 127.7, 127.1, 105.3, 62.7, 53.6, 45.6, 33.3, 31.1, 30.3, 29.7, 13.6, 13.1; \quad \text{\(\text{\(\text{ESI-MS} \ m/z [M} + \text{Na}^+ \text{] calcld for C}_{15}\text{H}_{20}\text{NaO}_{2}\text{S: 287.1, found: 287.1.}\}

\begin{center}
\includegraphics[width=0.2\textwidth]{113}
\end{center}

81
β-Keto thioester (114). (Reaction time 12 h, monitored by TLC) Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave 114 (0.124 g; 85%) as a pure, colorless oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 18:1. Both tautomers are reported below: ¹H NMR (CDCl₃, 400 MHz): δ 13.61 (s, 1H), 7.55-7.35 (m, 5H), 3.76 (t, J = 7.2 Hz, 1H), 2.48 (s, 2H), 2.41-2.31 (m, 2H), 2.21 (s, 2H), 1.98-1.80 (m, 2H), 1.65-1.54 (m, 2H), 1.44-1.28 (m, 2H), 1.04 (s, 9H), 0.98 (s, 9H), 0.95 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H). Only the major tautomer is reported below: ¹³C NMR (CDCl₃, 400 MHz): δ 203.1, 193.8, 134.4, 129.8, 129.4, 127.2, 69.0, 53.9, 31.3, 31.0, 29.6, 20.8, 14.0; ESI-MS m/z [M + Na]⁺ calcd for C₁₇H₂₄NaO₂S: 315.1, found: 315.2.

β-Keto thioester (115). (Reaction time 12 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 115 (0.150 g; 88%) as a pure, colorless oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 10:1. Both tautomers are reported below: ¹H NMR (CDCl₃, 400 MHz):
δ 13.91 (s, 1H), 7.50-7.10 (m, 10H), 4.07 (t, J = 7.6 Hz, 1H), 3.85 (s, 2H), 3.30-3.12 (m, 2H), 2.42 (dd, J = 16.8, 47.2 Hz, 2H), 2.21 (s, 2H), 1.00 (s, 9H), 0.97 (s, 9H). Only the major tautomer is reported below: $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 202.2, 192.9, 137.8, 134.4, 129.8, 129.4, 129.1, 128.7, 126.9, 70.2, 54.9, 35.0, 31.0, 30.3, 29.5; ESI-MS m/z [M + Na]$^+$ calcd for C$_{21}$H$_{24}$NaO$_2$S: 363.1, found: 363.1.

**β-Keto thioester (116).** (Reaction time 12 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 116 (0.140 g; 78%) as a pure, purple oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 1.5:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 11.75 (s, 1H), 7.56-7.26 (m, 10H), 4.85 (s, 2H), 4.75 (dd, J = 11.6, 54.4 Hz, 2H), 4.51 (s, 1H), 2.51 (dd, J = 16.4, 26.4 Hz, 2H), 2.25 (s, 2H), 1.02 (s, 9H), 0.98 (s, 9H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 201.5, 195.1, 193.1, 168.0, 136.8, 136.1, 135.3, 134.7, 133.6, 129.7, 129.6, 129.4, 129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 126.9, 126.7, 90.6, 76.9, 73.6, 50.7, 43.2, 32.7, 30.9, 30.3, 29.6; ESI-MS m/z [M + Na]$^+$ calcd for C$_{21}$H$_{24}$NaO$_3$S: 379.1, found: 379.1.
**β-Keto thioester (121).** (Reaction time 48 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 121 (0.123 g; 91%) as a pure, light yellow oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 18:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 13.60 (s, 1H), 8.05-7.99 (m, 2H), 7.62-7.30 (m, 8H), 4.73 (q, $J = 6.8$ Hz, 1H), 2.08 (s, 3H), 1.60 (d, $J = 6.8$ Hz, 3H). Only the major tautomer is reported below: $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 194.9, 194.7, 135.8, 134.6, 133.7, 129.7, 129.3, 128.9, 128.8, 126.9, 56.2, 14.8; ESI-MS m/z [M + Na]$^+$ calcd for C$_{16}$H$_{14}$NaO$_2$S: 293.1, found: 293.0.

![β-Keto thioester (121)](image)

**β-Keto thioester (122).** (Reaction time 6 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 122 (0.123 g; 91%) as a pure, colorless oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 6:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 13.63 (s, 1H), 7.50-7.34 (m, 5H), 4.03 (q, $J = 7.2$ Hz, 1H), 2.96-2.84 (m, 1H), 2.84-2.74 (m, 1H), 1.99 (s, 3H), 1.43 (d, $J = 7.2$ Hz, 3H), 1.17-1.10 (m, 1H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 208.4, 195.9, 194.7, 179.1, 135.4, 134.5, 129.7, 129.5, 129.4, 129.2, 127.7, 127.0, 102.0, 59.1, 40.3, 30.8, 19.1, 18.8, 18.2, 14.0, 11.4; ESI-MS m/z [M + Na]$^+$ calcd for C$_{13}$H$_{16}$NaO$_2$S: 259.1, found: 259.0.
**β-Keto thioester (123).** (Reaction time 16 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 123 (0.112 g; 76%) as a pure, yellow solid, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 1:1.8. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 13.28 (s, 1H), 7.75-7.28 (m, 11H), 6.98-9.74 (m, 1H), 4.15 (q, $J$ = 7.2 Hz, 1H), 2.17 (s, 3H), 1.54 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 196.3, 194.8, 193.5, 164.5, 144.8, 141.6, 139.3, 135.7, 135.4, 134.7, 134.2, 131.0, 129.6, 129.4, 129.3, 129.1, 128.9, 128.7, 127.8, 127.5, 127.0, 124.2, 123.4, 118.9, 105.3, 60.1, 14.0, 11.7; ESI-MS m/z [M + Na]$^+$ calcd for C$_{18}$H$_{16}$NaO$_2$S: 319.1, found: 319.0.

**β-Keto thioester (124).** (Reaction time 6 h, monitored by TLC) Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 124 (0.125 g; 90%) as a pure, colorless oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 6:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 13.64 (s, 1H), 7.50-7.32 (m, 5H), 4.01 (q, $J$ = 7.2 Hz, 1H), 2.72-2.54 (m, 1H), 2.50-2.38 (m, 1H), 1.99 (s, 3H), 1.96-1.10 [m, 13H, contains a d (1.42, $J$ = 7.2 Hz, 3H)]; $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 195.4, 193.6, 181.8, 169.4, 169.2, 163.8, 146.3, 141.4, 135.2, 134.7, 134.1, 131.2, 129.9, 129.3, 129.1, 128.9, 128.6, 127.9, 127.6, 124.4, 123.4, 118.9, 105.3, 60.1, 14.0, 11.4; ESI-MS m/z [M + Na]$^+$ calcd for C$_{18}$H$_{16}$NaO$_2$S: 319.1, found: 319.0.
400 MHz): δ 207.6, 195.8, 194.7, 178.6, 135.4, 134.5, 129.7, 129.6, 129.4, 129.2, 127.7, 127.0, 102.3, 59.3, 50.3, 41.2, 29.1, 29.0, 28.4, 26.0, 25.8, 25.4, 14.0, 11.5; **ESI-MS** m/z [M + Na]+ calcd for C_{16}H_{20}NaO_{2}S: 299.1, found: 299.1.

**β-Keto thioester (125).** (Reaction time 6 h, monitored by TLC) Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave 125 (0.133 g; 64%) as a pure, colorless oil, comprised of a mixture of 1:1 β-keto thioester diastereomers and its tautomeric enol form in a ratio of >20:1. Both the major diastereomers are reported below: **\(^1\)H NMR** (CDCl\(_3\), 400 MHz): δ 7.48-7.16 (m, 10H), 5.28 (s, 1H), 5.19 (s, 1H), 4.42 (q, J = 7.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 1H), 1.36 (d, J = 7.2 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H), 0.01 (d, J = 10.8 Hz, 6H); **\(^{13}\)C NMR** (CDCl\(_3\), 400 MHz): δ 204.7, 203.4, 193.7, 193.6, 138.2, 137.6, 134.5, 134.4, 129.6, 129.5, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5, 127.4, 127.1, 127.0, 126.3, 81.1, 80.9, 54.7, 53.9, 26.0, 25.9, 18.5, 18.4, 15.9, 14.9, -4.7, -4.8; **ESI-MS** m/z [M + Na]+ calcd for C_{23}H_{30}NaO_{3}SSi: 437.2, found: 437.1.
**β-Keto thioester (126).** (Reaction time 12 h, monitored by TLC) Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 126 (0.143 g; 87%) as a pure, colorless oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 6:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 13.48 (s, 1H), 8.05-7.96 (m, 1H), 7.64-7.22 (m, 8H), 4.39 (q, $J = 7.2$ Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.82 (s, 3H), 1.63 (d, $J = 7.2$ Hz, 3H). Only the major tautomer is reported below: $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 200.2, 195.0, 166.7, 142.6, 134.4, 132.8, 130.2, 130.1, 129.8, 129.4, 127.8, 127.4, 127.1, 61.2, 52.8, 14.5; ESI-MS m/z [M + Na]$^+$ calcd for C$_{18}$H$_{16}$NaO$_4$S: 351.1, found: 351.0.

![Structure of 129](image.png)

**β-Keto thioester (129).** (Reaction time 24 h, monitored by TLC) Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 129 (0.175 g; 92%) as a pure, white solid, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of >20:1. Only the major tautomer is reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.06-7.94 (m, 1H), 7.62-7.18 (m, 8H), 5.24-5.12 (m, 1H), 4.30 (apparent dd, $J = 5.6$, 9.2 Hz, 2H), 3.89 (s, 3H), 2.98-2.68 (m, 2H), 1.72 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 199.1, 193.8, 166.7, 142.3, 135.2, 134.3, 132.6, 130.2, 130.1, 129.7, 129.3, 128.2,
127.4, 127.3, 119.7, 66.9, 52.8, 28.6, 25.9, 18.0; **ESI-MS** $m/z$ [M + Na]$^+$ calcd for $C_{22}H_{22}NaO_4S$: 405.1, found: 405.0.

$\beta$-Keto thioester (130). (Reaction time 48 h, monitored by TLC) Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 130 (0.183 g; 80%) as a pure, colorless oil, comprised of a mixture of $\beta$-keto thioester and its tautomeric enol form in a ratio of >20:1. Only the major tautomer is reported below: **$^{1}H$ NMR** (CDCl$_3$, 400 MHz): $\delta$ 8.06-7.94 (m, 1H), 7.68-7.08 (m, 8H), 4.76-4.60 (m, 1H), 4.00-3.72 [4H, contains a d ($J = 16.8, 3H$) and a dd (1H)], 2.56-2.30 (m, 1H), 2.20-2.00 (m, 1H), 1.56-1.10 (m, 12H); **$^{13}$C NMR** (CDCl$_3$, 400 MHz): $\delta$ 198.4, 197.9, 193.6, 193.0, 166.9, 166.6, 142.0, 141.8, 135.5, 134.2, 134.1, 132.5, 132.3, 130.5, 130.4, 130.3, 130.0, 129.8, 129.7, 129.4, 129.3, 128.9, 128.4, 127.7, 127.5, 127.2, 127.1, 107.1, 107.0, 80.5, 80.3, 79.9, 64.3, 64.0, 52.8, 52.7, 29.2, 29.0, 28.7, 28.6, 26.9, 26.8, 25.9, 25.8, 23.0, 22.9; **FAB-MS** $m/z$ [M + H]$^+$ calcd for $C_{25}H_{29}O_6S$: 457.2, found: 457.2.

*The following reaction is representative of those depicted in Table 12:*
**β-Keto ester (134).** AgCF$_3$CO$_2$ (0.073 g, 0.33 mmol) was added to a stirred solution of β-keto thioester 102 (0.075 g, 0.30 mmol) and benzyl alcohol (34 µL, 0.33 mmol) in THF (2 mL). Stirring was continued for 3 h (monitored by TLC). Then EtOAc (20 mL) was added and the mixture was passed through a pad of celite. The filtrate was concentrated to give a yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 134 (0.077 g; 96%) as a pure, orange oil, comprised of a mixture of β-keto ester and its tautomeric enol form in a ratio of 3:1. Both tautomers are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 12.02 (s, 1H), 7.47-7.28 (m, 5H), 5.17 (s, 2H), 4.99 (s, 1H), 3.45 (s, 2H), 2.39 (s, 2H), 2.06 (s, 2H), 1.01 (s, 9H), 1.00 (s, 9H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 202.2, 178.2, 172.5, 167.1, 136.0, 135.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 91.1, 67.1, 65.8, 55.1, 51.3, 49.1, 31.6, 31.1, 30.0, 29.6; ESI-MS m/z [M + Na]$^+$ calcd for C$_{15}$H$_{20}$NaO$_3$: 271.1, found: 271.1.

**β-Keto ester (135).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 135 (0.120 g; 94%) as a pure, orange oil, comprised of a mixture of β-keto
ester and its tautomeric enol form in a ratio of 2:1. Both tautomers are reported below:

\[ ^1H \text{NMR (CDCl}_3, 400 \text{ MHz)}: \delta 12.03 (s, 1H), 6.33 (d, J = 6.0 \text{ Hz}, 1H), 5.47-5.40 (m, 1H), 4.99 (s, 1H), 4.80-4.73 (m, 1H), 4.24-4.12 (m, 2H), 4.04-3.86 (m, 2H), 3.46 (s, 2H), 2.44 (s, 2H), 2.08 (s, 2H), 1.10-0.94 (m, 27H); ^{13}C \text{NMR (CDCl}_3, 400 \text{ MHz): } \delta 201.9, 178.1, 172.7, 167.2, 145.4, 145.1, 100.7, 100.2, 91.4, 73.8, 73.6, 73.3, 73.0, 72.9, 71.9, 65.9, 65.8, 55.0, 51.5, 49.1, 31.6, 31.2, 30.0, 29.7, 27.5, 27.0, 22.8, 19.9; \text{ESI-MS m/z [M + Na]}^+ \text{ calcd for C}_{42}H_{38}NaO_6Si: 449.23, found: 449.4. \]

**β-Keto ester (136).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 136 (0.081 g; 93%) as a pure, light pink oil, comprised of a mixture of β-keto ester and its tautomeric enol form in a ratio of 2:1. Both tautomers are reported below: \[ ^1H \text{NMR (CDCl}_3, 400 \text{ MHz): } \delta 12.10 (s, 1H), 5.64-5.58 (m, 1H), 5.57-5.45 (m, 1H), 4.94 (s, 1H), 4.80-4.64 (m, 2H), 3.44 (s, 2H), 2.43 (s, 2H), 2.40-1.85 [contains a m (4H) and a s (2.07, 2H)], 1.72 (s, 3H), 1.65 (s, 3H), 1.58-1.44 (m, 1H), 1.04 (s, 9H), 1.01 (s, 9H); ^{13}C \text{NMR (CDCl}_3, 400 \text{ MHz): } \delta 202.2, 177.9, 172.7, 167.2, 148.4, 148.2, 133.0, 132.6, 126.4, 126.1, 109.6, 109.5, 91.4, 74.4, 72.8, 55.2, 51.6, 49.1, 40.4, 40.3, 34.2, 34.0, 31.6, 31.2, 30.9, 30.8, 30.0, 29.6, 20.6, 19.0; \text{ESI-MS m/z [M + Na]}^+ \text{ calcd for C}_{42}H_{38}NaO_6: 315.2, found: 315.3. \]
**β-Keto amide (137).** AgCF₃CO₂ (0.073 g, 0.33 mmol) was added to a stirred solution of β-keto thioester 102 (0.075 g, 0.30 mmol) and N-benzyl methylamine (43 µL, 0.33 mmol) in THF (2 mL).²³ Stirring was continued for 3 h (monitored by TLC). Then EtOAc (20 mL) was added and the mixture was passed through a pad of celite. The filtrate was concentrated to give a yellow oil. Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 137 (0.075 g; 96%) as a pure, red oil, comprised of a mixture of β-keto amide and its tautomeric enol form in a ratio of 1.5:1. Both tautomers (containing rotamers) are reported below: ¹H NMR (CDCl₃, 400 MHz): δ 15.00-14.50 (m, 1H), 7.50-7.10 (m, 5H), 5.09 (s, 1H), 4.62 (s, 2H), 4.51 (s, 2H), 3.66-3.48 (m, 2H), 2.96 (s, 3H), 2.90 (s, 3H), 2.54-2.40 (m, 2H), 2.14-1.96 (m, 2H), 1.04 (s, 9H), 1.02 (s, 9H); ¹³C NMR (CDCl₃, 400 MHz): δ 204.2, 204.0, 136.9, 136.2, 129.1, 128.7, 128.0, 127.9, 127.8, 127.5, 126.6, 126.4, 88.4, 55.1, 54.9, 50.9, 49.9, 35.5, 34.0, 31.4, 31.1, 30.0, 29.6, 29.5; ESI-MS m/z [M + Na]⁺ calcd for C₁₆H₂₃NNaO₂: 284.2, found: 284.1.

**β-Keto amide (138).** Flash chromatography over silica gel, using 30:70 EtOAc-hexanes gave 138 (0.087 g; 90%) as a pure, orange oil, comprised of a mixture of β-keto
ester and its tautomeric enol form in a ratio of 7:1. Both tautomers (containing rotamers) are reported below: $^1$H NMR (CDCl$_3$, 400 MHz): δ 13.36 (s, 1H), 7.48-7.36 (m, 1H), 7.34-7.15 (m, 5H), 5.86-5.73 (m, 1H), 4.98-4.75 (m, 1H), 3.70 (s, 3H), 3.33 (s, 2H), 3.23-3.00 (m, 2H), 2.37 (s, 2H), 1.99 (s, 2H), 1.00 (s, 9H), 0.99 (s, 9H). Only the major tautomer is reported below: $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 205.9, 171.7, 135.9, 129.4, 129.3, 128.6, 127.1, 55.9, 53.5, 52.3, 37.9, 31.2, 29.9, 29.6; ESI-MS m/z [M + Na]$^+$ calcd for C$_{18}$H$_{25}$NNaO$_4$: 342.2, found: 342.2.

![3-Neopentylisoazol-5(4H)-one](image)

3-Neopentylisoazol-5(4H)-one (139). Flash chromatography over silica gel, using 25:75 EtOAc-hexanes gave 139 (0.041 g; 87%) as a pure, light yellow oil: $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.44 (s, 2H), 2.37 (s, 2H), 1.05 (s, 9H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 175.5, 165.6, 42.7, 37.9, 31.4, 29.8; ESI-MS m/z [M + Na]$^+$ calcd for C$_{18}$H$_{25}$NNaO$_4$: 178.1, found: 178.0.

![β-Diketone](image)

β-Diketone (141). EtZnI (2.0 mL, 0.9 M in THF, 1.80 mmol)$^{24}$ was added to a stirred solution of β-keto thioester 114 (0.175 g, 0.60 mmol) and PdCl$_2$(PPh$_3$)$_2$ (0.042 g, 0.06 mmol) in toluene (2.0 mL). Stirring was continued for 1 h. Then EtOAc (50 mL)
was added and the mixture was passed through a pad of celite. The filtrate was washed with 10% aqueous HCl, sat. NaHCO₃, brine, dried over MgSO₄, and concentrated to give a red oil. Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave 141 (0.122 g, 96%) as a pure, colorless oil, comprised of a mixture of β-diketone and its tautomeric enol form in a ratio of 4:1. Both tautomers are reported below: **1H NMR** (CDCl₃, 400 MHz): δ 16.96 (s, 1H), 3.61 (t, J = 7.2 Hz, 1H), 2.52-2.43 (m, 2H), 2.43-2.38 (m, 2H), 2.35 (s, 2H), 2.27 (s, 2H), 2.24-2.16 (m, 2H), 1.84-1.74 (m, 2H), 1.44-1.36 (m, 2H), 1.30-1.18 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H), 1.07-0.98 (m, 12H), 0.98-0.86 (m, 3H); **13C NMR** (CDCl₃, 400 MHz): δ 207.2, 206.0, 199.5, 188.3, 111.0, 69.3, 54.1, 46.2, 35.0, 32.4, 30.9, 30.6, 30.4, 29.7, 29.6, 29.2, 24.5, 21.1, 14.3, 14.1, 9.5, 7.7; **ESI-MS m/z** [M + Na⁺] calcd for C₁₃H₂₄NaO₂: 235.2, found: 235.1.

**β-Diketone (140).** Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 140 (0.102 g; 100%) as a pure, light yellow oil, comprised of a mixture of β-diketone and its tautomeric enol form in a ratio of 1:10. Only the major tautomer is reported below: **1H NMR** (CDCl₃, 400 MHz): δ 15.59 (s, 1H), 5.44 (s, 1H), 2.34 (q, J = 7.2 Hz, 2H), 2.12 (s, 2H), 1.14 (t, J = 7.6 Hz, 3H), 1.01 (s, 9H); **13C NMR** (CDCl₃, 400 MHz): δ 197.9, 190.6, 100.8, 51.4, 32.3, 31.8, 30.0, 9.6; **ESI-MS m/z** [M + Na⁺] calcd for C₁₀H₁₈NaO₂: 193.1, found: 193.0.
Methyl 2-(1H-benzo[d][1,2,3]triazole-1-carbonyl)benzoate (120). SOCl₂ (0.80 mL, 11 mmol) was added to a stirred solution of benzotriazole (4.80 g, 40 mmol) in CH₂Cl₂ (50 mL). Stirring was continued for 30 min. Then mono-methyl phthalate (1.80 g, 10 mmol) was added to the reaction mixture and stirring was continued for another 16 h. The white precipitate was filtered off and washed with CH₂Cl₂. The combined filtrate was washed with 10% NaOH aqueous solution, brine, dried over MgSO₄, and concentrated to give a white solid. Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 120 (2.71 g, 96%) as a pure, white powder: ¹H NMR (CDCl₃, 400 MHz): δ 8.54-8.44 (m, 1H), 8.20-8.08 (m, 2H), 7.80-7.62 (m, 4H), 7.60-7.50 (m, 1H), 3.67 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 168.3, 165.7, 146.0, 135.3, 132.6, 131.3, 130.9, 130.4, 129.9, 129.2, 128.4, 126.3, 120.0, 114.3, 52.5; ESI-MS m/z [M + Na]⁺ calcd for C₁₅H₁₁N₃NaO₃: 304.1, found: 304.0.

S-phenyl 5-methylhex-4-enethioate (127). DCC (0.908 g, 4.4 mmol) was added to a stirred solution of 5-methylhex-4-enoic acid (0.514 g, 4.0 mmol) and PhSH (0.61 mL,
6.0 mmol) in CH₂Cl₂ (20 mL), followed by the addition of DMAP (0.050 g, 0.4 mmol). Stirring was continued for 6 h. The white precipitate was filtered off and washed with CH₂Cl₂. The combined filtrate was washed with H₂O, sat. NaHCO₃ brine, dried over MgSO₄, and concentrated to give a colorless oil. Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave 127 (0.758 g, 86%) as a pure, colorless oil: ¹H NMR (CDCl₃, 400 MHz): δ 7.48-7.30 (m, 5H), 5.18-5.05 (m, 1H), 2.74-2.60 (m, 2H), 2.46-2.30 (m, 2H), 1.70 (s, 3H), 1.63 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 197.2, 134.6, 133.6, 129.4, 129.3, 128.4, 121.9, 43.8, 25.8, 24.3, 17.8; ESI-MS m/z [M + Na]⁺ calcd for C₁₃H₁₆NaOS: 243.1, found: 243.0.

\[
\text{S-phenyl 3-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)propanethioate (128).} \quad \text{PhSH (0.28 mL, 2.70 mmol) was added to a stirred solution of AlMe₃ (1.35 mL, 2.0 M in hexane, 2.70 mmol) in CH₂Cl₂ (8 mL) at 0°C. Stirring was continued for 20 min at 0°C, then methyl 3-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)propanoate}^{47} \ (0.293 \text{ g, 1.35 mmol}) \text{ in CH₂Cl₂ (2 mL) was added to the reaction mixture via cannula. The mixture was stirred and allowed to warm to rt. Stirring was continued for 16 h at rt and 150 mL EtOAc was added. Sat. NH₄Cl was added dropwise to quench the reaction and the mixture was passed through a pad of celite. The filtrate was washed with 10% aqueous NaOH.}
\]
solution, brine, dried over MgSO₄, and concentrated to give a yellow oil. Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave 128 (0.167 g, 42%) as a pure, light yellow oil: \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.54-7.34 (m, 5H), 3.76-3.66 (m, 1H), 3.02-2.88 (m, 1H), 2.85-2.70 (m, 1H), 1.90-1.78 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H); \(^{13}\)C NMR (CDCl₃, 400 MHz): δ 197.1, 134.5, 129.5, 129.3, 127.7, 107.0, 82.2, 80.2, 41.0, 28.6, 27.0, 26.0, 25.2, 23.0; ESI-MS m/z [M + Na]⁺ calcd for C₁₆H₂₂NaO₃S: 317.1, found: 317.1.

**Benzyl 2-(benzyloxy)biphenyl-3-carboxylate (148).** K₂CO₃·1.5H₂O (0.826 g, 5.0 mmol) was added to a stirred solution of 3-phenylsalicylic acid (52) (0.428 g, 2.0 mmol) in acetone (5 mL), followed by the addition of BnBr (0.59 mL, 5.0 mmol). The mixture was heated to reflux for 12 h and then cooled to rt. The mixture was filtered and the filtrate was concentrated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 148 (0.781 g, 99%) as a pure, white solid: \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.84-7.74 (m, 1H), 7.60-7.45 (m, 3H), 7.44-7.28 (m, 8H), 7.25-7.12 (m, 4H), 7.00-6.90 (m, 2H), 5.33 (s, 2H), 4.54 (s, 2H); \(^{13}\)C NMR (CDCl₃, 400MHz): δ 166.3, 155.8, 137.8, 137.3, 136.7, 136.0, 134.9, 130.5, 129.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2,
127.9, 127.7, 126.5, 124.2, 76.0, 67.0; ESI-MS \( m/z \) [M + Na]\(^+\) calcd for C\(_{27}\)H\(_{22}\)NaO\(_3\): 417.2, found: 417.1.

2-(Benzylxylobiphenyl-3-carboxylic acid (149). LiOH-H\(_2\)O (0.252 g, 6.0 mmol) was added to a stirred solution of compound 148 (0.781 g, 2.0 mmol) in mixed THF: H\(_2\)O (3:1, 10 mL). The mixture was heated to reflux for 12 h and then diluted with EtOAc (50 mL). 10% aqueous HCl was added to the mixture to adjust pH to 2. The organic phase was isolated, washed with brine, dried over MgSO\(_4\), and concentrated to give a white solid. Flash chromatography over silica gel, using 25:75 EtOAc-hexanes gave 149 (0.595 g, 97\%) as a pure, white powder: \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 11.8-10.4 (bs, 1H), 8.24-8.08 (m, 1H), 7.78-7.16 (m, 10H), 7.14-6.96 (m, 2H), 4.57 (s, 2H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \( \delta \) 166.3, 155.2, 137.1, 136.8, 136.1, 134.3, 132.3, 129.4, 129.3, 129.2, 129.0, 128.8, 128.4, 125.5, 123.3, 77.4; ESI-MS \( m/z \) [M + Na]\(^+\) calcd for C\(_{28}\)H\(_{16}\)NaO\(_3\): 327.1, found: 327.1.
The procedure was the same as described in synthesizing N-acyl benzotriazole 120. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 150 (0.725g, 94%) as a pure, white powder: ¹H NMR (CDCl₃, 400 MHz): δ 8.40-8.26 (m, 1H), 8.18-8.04 (m, 1H), 7.80-7.30 (m, 10H), 7.04-6.86 (m, 3H), 6.80-6.66 (m, 2H), 4.48 (s, 2H); ¹³C NMR (CDCl₃, 400 MHz): δ 166.8, 154.7, 146.2, 137.6, 136.1, 136.0, 134.9, 131.6, 130.4, 129.3, 129.1, 128.9, 128.7, 128.2, 128.0, 127.9, 127.8, 126.3, 124.2, 120.3, 114.5, 75.8; ESI-MS m/z [M + Na]⁺ calcd for C₂₆H₁₉NNaO₂: 428.1, found: 428.2.

β-Keto thioester (151). MgBr₂·Et₂ (0.619 g, 2.4 mmol) was added to a stirred solution of compound 150 (0.324 g, 0.8 mmol) in CH₂Cl₂ (3.2 mL), followed by the addition of S-phenyl thioacetate (108 µL, 0.8 mmol) and i-Pr₂NEt (0.56mL, 3.2 mmol). Stirring was continued for 16 h and 10% aqueous HCl (4 mL) was added. Stirring was continued for 5 min and the mixture was partitioned between EtOAc (50 mL) and H₂O (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, and evaporated to give a yellow oil. Flash chromatography over silica gel, using 6:94 EtOAc-hexanes gave 151.
(0.302 g; 86%) as a pure, dark red oil, comprised of a mixture of β-keto thioester and its tautomeric enol form in a ratio of 1:2.3. Both tautomers are reported below: \(^1\)H NMR (CDCl\(_3, 400\) MHz): \(\delta\) 13.09 (s, 1H), 7.80-7.76 (m, 1H), 7.65-7.18 (m, 15H), 7.08-6.96 (m, 2H), 6.62 (s, 1H), 4.48 (s, 2H), 4.46 (s, 2H), 4.32 (s, 2H); \(^{13}\)C NMR (CDCl\(_3, 400\) MHz): \(\delta\) 194.9, 194.3, 191.1, 168.2, 155.2, 155.0, 138.0, 137.7, 137.2, 136.6, 136.1, 135.8, 135.7, 135.1, 134.6, 134.3, 133.7, 129.8, 129.7, 129.6, 129.4, 129.4, 129.3, 129.25, 129.21, 128.8, 128.7, 128.6, 128.54, 128.5, 128.46, 128.42, 128.0, 127.9, 127.5, 127.3, 124.8, 124.7, 101.3, 77.0, 76.0, 57.1; FAB-MS m/z [M + H]\(^+\) calcd for \(\text{C}_{28}\text{H}_{23}\text{O}_{3}\text{S}\): 439.1, found: 439.1.

\[
\begin{align*}
\text{151} & \xrightarrow{\text{morpholine, AgCF}_3\text{CO}_2, \text{THF}} \text{152}
\end{align*}
\]

\textbf{1-(2-(Benzyloxy)biphenyl-3-yl)-3-morpholinopropane-1,3-dione} (152).

AgCF\(_3\)CO\(_2\) (0.073 g, 0.33 mmol) was added to a stirred solution of β-keto thioester 151 (0.132 g, 0.30 mmol) and morpholine (29 μL, 0.33 mmol) in THF (2 mL). Stirring was continued for 4 h. Then EtOAc (20 mL) was added and the mixture was passed through a pad of celite. The filtrate was concentrated to give a colorless oil. Flash chromatography over silica gel, using 30:70 EtOAc-hexanes gave 152 (0.115 g; 93%) as a pure, white solid, comprised of a mixture of β-keto amide and its tautomeric enol form in a ratio of 1:1.8. Both tautomers are reported below: \(^1\)H NMR (CDCl\(_3, 400\) MHz): \(\delta\)
15.21 (s, 1H), 7.90-7.86 (m, 1H), 7.68-7.20 (m, 10H), 7.12-6.98 (m, 2H), 6.30 (s, 1H), 4.49 (s, 2H), 4.46 (s, 2H), 4.08 (s, 2H), 3.75-3.55 (m, 4H), 3.50-3.30 (m, 2H), 3.15-2.90 (m, 2H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 196.6, 171.5, 169.2, 166.0, 155.0, 154.6, 138.2, 137.8, 137.1, 136.8, 136.3, 136.2, 135.3, 133.9, 133.2, 129.7, 129.4, 129.3, 129.2, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 124.8, 124.7, 89.1, 76.7, 75.2, 66.8, 66.6, 49.4, 46.7, 42.1; ESI-MS $m/z$ [M + Na]$^+$ calcd for C$_{26}$H$_{25}$NNaO$_4$: 438.2, found: 438.2.

2-Morpholino-8-phenyl-4H-chromen-4-one (LY294002, 142). 10% Pd-C (small spatula tip) was added to a stirred solution of compound 152 (0.121 g, 0.29 mmol) in EtOH-EtOAc (3:1, 4 mL). The reaction flask was evacuated and purged with H$_2$ three times. Stirring was continued for 2 h (monitored by TLC) under H$_2$. EtOAc (20 mL) was then added and the mixture was passed through a pad of celite. The filtrate was concentrated to give a white solid that was dissolved in CH$_2$Cl$_2$ (5 mL) and to this solution was added Tf$_2$O (0.27 mL, 1.53 mmol). Stirring was continued for 8 h, H$_2$O was added and the mixture was diluted with CH$_2$Cl$_2$ (20 mL). The organic phase was washed with H$_2$O (2 x 5 mL), brine (5 mL), dried over MgSO$_4$, and evaporated to give a yellow oil. Flash chromatography over silica gel using 50:50 EtOAc-hexanes gave 142
(0.0828 g, 93%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.\textsuperscript{27}
Chapter Two: Direct Carbon-Carbon Bond Formation via in situ Enolate Generation and Domino Reaction

2.1 Background and Introduction

2.1.1 Chemoselectivity Issue in Direct Aldol Reaction

As introduced in Chapter One Section 1.2, the importance of the aldol addition reaction cannot be overstated.1 Extensive research has resulted in remarkable advances in stereo-, regio-, and chemoselectivity.3 Much of the control that is possible stems from the use of carboxylate-derived, preformed enolates.3 Although effective, the step-wise procedures used to generate such enolates are time consuming, particularly if enolate trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperatures. The desire to develop milder and operationally-simplified methods for carbon–carbon bond formation has spawned a renewed interest in the direct aldol reaction.4 To be of general use, such a direct reaction must possess control elements to ensure chemoselective enolate formation. The chemoselectivity issue arises when the aldehyde acceptor has one or more α-protons, as it too can enolize and the pKa of its α-proton (~16) is usually much lower than that of common carboxylate-derived species, leading predominantly to self-

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addition products. Overcoming this selectivity challenge is, thus, the critical first step in developing a generally applicable direct aldol addition.

2.1.2 Domino Reaction and in situ Enolate Generation

A tandem reaction, or so-called domino reaction, has been long known and widely used for the construction of carbon-carbon bonds.\textsuperscript{49} This type of reaction not only forms at least two new bonds in a single chemical operation, but can also circumvent protection and deprotection steps, thus shortening the processes and operations.\textsuperscript{50, 51} Its application has been embodied in the synthesis of numerous biologically active compounds, including steroids, prostaglandins, and terpenes.\textsuperscript{52}

Scheme 13. Twofold Anionic Domino Reaction and in situ Enolate Generation

The most often encountered domino process, anionic domino reaction, is usually initiated by the conjugate addition of a nucleophile to an enone, thus generating an enolate in situ, which can be easily trapped by an electrophile, such as another $\alpha,\beta$-unsaturated carbonyl compound, an aldehyde, a ketone, an imine, an ester, or an alkyl halide (Scheme 13).\textsuperscript{49} For instance, the well-known Robinson annulation, double Michael reaction, Pictet-Spengler cyclization, etc., all fall into this category.
Although the Morita-Baylis-Hillman (MBH) reaction,\textsuperscript{53} which is catalyzed by a tertiary amine or phosphine, is also a typical example of domino reaction and consists of tandem Michael aldol-retro-Michael reactions to give \( \alpha \)-alkenyl-\( \beta' \)-hydroxy carbonyl product, it is remarkably slow under mild conditions.\textsuperscript{54} Furthermore, the yields of MBH reaction are often quite low and it is by no means a general process, as it has scarcely been reported in the context of \( \beta \)-substituted \( \alpha,\beta \)-unsaturated carbonyl species. At this stage, we would like to utilize the in situ enolate generation and domino process strategy and seek more efficient approaches to direct aldol addition reaction that is fully compatible with enolizable aldehydes.

## 2.1.3 Reaction Design

Due to their strong nucleophilicity, thiols can be selectively acylated in the presence of other common nucleophiles\textsuperscript{55} and readily undergo conjugate addition.\textsuperscript{56} Thus, we reasoned that combining two equivalents of a thiolate, along with one equivalent each of an \( \alpha,\beta \)-unsaturated acid chloride and an aldehyde, would initiate a four-component cascade sequence leading to a single aldol addition product (Scheme 14). The first thiolate equivalent and the acid chloride would combine to generate an

\textbf{Scheme 14.} Four-Component Direct Aldol Cascade Reaction
α,β-unsaturated thioester (153→154), which would be followed by 1,4-addition of the second thiolate equivalent to generate a thioester enolate (155) in situ and, ultimately, aldol addition (155→156). This chemoselective mode of enolate formation would preclude aldehyde enolization and, consequently, self-addition. Thus, the need for prior enolate formation would be eliminated, while maintaining the level of chemoselectivity associated with such techniques. Moreover, since the cascade sequence is initiated by thiolate addition, background reactions involving trace amounts of moisture in the atmosphere or solvent should not be a factor, and low temperatures would not be required, further simplifying the process. Additionally, the organosulfur aldol products could participate in numerous subsequent transformations, leading to an array of useful structures.

2.2 An Efficient Anti-Selective Four-Component Direct Aldol Cascade Reaction

2.2.1 Condition Screen

To test the feasibility of the proposed four-component aldol addition reaction,57 PhSNa (2 equiv) was added to a mixture of acryloyl chloride (153) (1 equiv) and PhCHO (1 equiv) in CH₂Cl₂ (Table 13). However, no aldol adduct was obtained and, instead, protonated 155 (R = Ph) was isolated in 92% yield. Varying the solvent and counter ion (Li⁺, K⁺) gave no improvement. We next tried PhSLi in the presence of MgBr₂·OEt₂,2 13,18 which gave the aldol addition product (157) in 67% yield within only 30 min.
Table 13. Condition Screen for Four-Component Direct Aldol Cascade Reaction

![Chemical Structure]

Remarkably, the reaction was highly selective for the anti diastereomer, which is less common in aldol additions,\textsuperscript{3,58} with an anti-syn ratio of 13:1. Prolonged reaction time did not improve the yield or affect the diastereomeric ratio. However, the efficiency was improved using 3 equiv of PhSLi, 1.5 equiv of 153, 1.2 equiv of MgBr\textsubscript{2}·OEt\textsubscript{2}, and 1 equiv of PhCHO, which gave 88% yield of 157, with the same anti-syn ratio (Table 13, Entry 4). As hypothesized, control experiments showed no difference between anhydrous and non-anhydrous conditions (Table 13, Entry 5).

2.2.2 Reaction Pathway

Two reaction pathways are possible in this case (Scheme 15). One (path A) could
**Scheme 15. Possible Reaction Pathways**

be initiated by $\text{Cl} \rightarrow \text{S}$ acyl transfer to give $\alpha,\beta$-unsaturated thioester 158, then the conjugate addition of thiolate to 158 would generate thioester enolate 159 in situ, which could attack PhCHO to produce 160. The alternative reaction pathway (path B) might be initiated by the thiolate 1,4-addition to 153 to give an acid chloride enolate intermediate 161, which would then undergo aldol addition, followed by $\text{Cl} \rightarrow \text{S}$ acyl transfer to give 160. We ruled out path B by conducting the reaction with only 1.5 equiv of PhSLi (equimolar to 153), along with PhCHO (1 equiv) and MgBr$_2$·OEt$_2$ (1.2 equiv), which gave acrylate thioester 158 in 93% conversion, with <4% of 157 based on the NMR of the crude material (Scheme 16).

**Scheme 16. Reaction Pathway Investigation Experiment**
Table 14: Four-Component Direct Aldol Cascade Reaction with Various Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Addition Product (anti-shown)</th>
<th>Isolated Yield (%)</th>
<th>anti-syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHO</td>
<td>![Chemical Structure]</td>
<td>88</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td>163</td>
<td>![Chemical Structure]</td>
<td>71</td>
<td>11:1</td>
</tr>
<tr>
<td>3</td>
<td>164</td>
<td>![Chemical Structure]</td>
<td>68</td>
<td>16:1</td>
</tr>
<tr>
<td>4</td>
<td>165</td>
<td>![Chemical Structure]</td>
<td>71</td>
<td>14:1</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>![Chemical Structure]</td>
<td>81</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>166</td>
<td>![Chemical Structure]</td>
<td>76</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
With simple and efficient conditions established for the aldol addition with PhCHO, we investigated the reaction scope with other aldehydes, both with and without α-protons (Table 14). In all cases the four-component transformation proceeded efficiently with short reaction times (30 min). No aldehyde self-addition products were obtained, thus confirming the compatibility of the method with enolizable aldehydes. Adding further to the significance of this result was that, in each case, the anti product was strongly favored over the more commonly obtained syn diastereomer.3,58

2.2.4 Reversibility Test

We next investigated the origin of the anti-selectivity. Assuming standard models,3 this could originate from either kinetic addition of the E-(O)-enolate to the aldehyde, or from the relative thermodynamic stability of the anti and syn products.

Several attempts to trap the enolate or kinetic addition intermediate under a variety of

Scheme 17. Reversibility Test for Four-Component Direct Aldol Cascade Reaction
conditions were unsuccessful. However, we did establish that the reaction is reversible, suggesting that the diastereoselectivity is thermodynamically controlled. To do this, PhSLi was added to a mixture of MgBr$_2$:OEt$_2$, 153 and PhCHO and, after the reaction was complete, 4-methylbenzaldehyde 172 was added and the reaction was continued for 15 min (See Scheme 17). This gave an approximately 1:1 mixture of addition products 157 and 173, with a 13:1 anti-syn ratio in each case.

### 2.2.5 Thioester Effect

The inherent thermodynamic preference for the anti or syn addition product with different acrylate derivatives was examined (See Table 15). Thus, a series of $\alpha$,\,$\beta$-unsaturated carbonyl compounds (1.5 equiv) was combined with cyclohexanecarboxaldehyde 24 (1.0 equiv), along with PhSLi (1.5 equiv) and MgBr$_2$:OEt$_2$ (1.2 equiv). With the exception of 176, all thioesters showed a significant preference for the anti product. The oxoesters and the amide showed modest or no anti-selectivity.

### 2.2.6 Reaction with PhSNa

We also surveyed the substitution of PhSNa salt for PhSLi solution (1.0 M in THF) (See Table 16). In general, the reaction with PhSNa requires a longer reaction time (2 h) than that with PhSLi (30 min), and gives modest or no anti-selectivity, which suggests that, instead of playing a passive role in this transformation, Li$^+$ may be strongly involved with generating the anti-selective aldol product.
Table 15. Effect of Acrylate Structure on Diastereoselectivity

![chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Addition Product (anti-shown)</th>
<th>Isolated Yield (%)</th>
<th>anti-syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="158" alt="image" /></td>
<td><img src="170" alt="image" /></td>
<td>79</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="174" alt="image" /></td>
<td><img src="180" alt="image" /></td>
<td>60</td>
<td>11:1</td>
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<td><img src="175" alt="image" /></td>
<td><img src="181" alt="image" /></td>
<td>82</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="176" alt="image" /></td>
<td><img src="182" alt="image" /></td>
<td>77</td>
<td>1.5:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="177" alt="image" /></td>
<td><img src="183" alt="image" /></td>
<td>72</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="178" alt="image" /></td>
<td><img src="184" alt="image" /></td>
<td>78</td>
<td>1:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="179" alt="image" /></td>
<td><img src="185" alt="image" /></td>
<td>64</td>
<td>2:1</td>
</tr>
</tbody>
</table>

111
**Table 16. Four-Component Direct Aldol Cascade Reaction with PhSNa**

![Chemical Reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Addition Product (anti-shown)</th>
<th>Isolated Yield (%)</th>
<th>anti-syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHO</td>
<td><img src="157" alt="Chemical Structure" /></td>
<td>82</td>
<td>3.5:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="163" alt="Chemical Structure" /></td>
<td><img src="167" alt="Chemical Structure" /></td>
<td>83</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="24" alt="Chemical Structure" /></td>
<td><img src="170" alt="Chemical Structure" /></td>
<td>84</td>
<td>2.5:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="166" alt="Chemical Structure" /></td>
<td><img src="171" alt="Chemical Structure" /></td>
<td>83</td>
<td>2:1</td>
</tr>
</tbody>
</table>

**2.2.7 Li⁺ Effect**

To test the Li⁺ effect, we attempted the aldol addition with 153, 24 and MgBr₂·OEt₂, but using PhSMgBr in place of PhSLi. This gave aldol addition product 170 with a 2:1 preference for the syn product, suggesting that Li⁺ was actually a key component in achieving anti-selectivity. To confirm the importance of PhSLi in this regard, the reaction using PhSMgBr was repeated but, after 30 min, PhSLi was added...
and the reaction was continued for 15 min. The ratio of the aldol addition products obtained from this procedure was restored to >20:1 in favor of the anti product. Taken collectively, these results show that the stereochemical outcome of the reaction is strongly tied to the nature of the thiolate counter ion.

2.2.8 Rationale of Reaction Mechanism

A rationale (Scheme 19) for this outcome that is consistent with a reversible process is that, in the presence of Li\(^+\), coordination with sulfur\(^{59}\) leads to the E-(O)-enolate (186), which then reacts via the lower energy Zimmerman-Traxler transition state to give intermediate 188 preferentially over 189 and, consequently, the anti product (192). In the absence of Li\(^+\), both the E-(O)-enolate (186 minus Li\(^+\)) and Z-(O)-enolate (187) exist, allowing syn product 193 to form via 191, in addition to 192. However, when PhSLi is added to the latter system prior to work up, syn intermediate 191 is converted to Li\(^+\)-complexed E-(O)-enolate 186 via a thermodynamically-driven conformational ring
inversion of 190 to 194. Addition from 186 then gives anti product 192, analogously to the first reaction containing only PhSLi.

**Scheme 19.** Stereochemical Model of the Aldol Addition

![Stereochemical Model of the Aldol Addition](image)

**2.2.9 Subsequent Transformations and Applications**

As an initial demonstration of the utility of the organosulfur products in subsequent transformations, 169 was silylated to 195 and treated under Fukuyama reduction\(^6\) conditions to give aldehyde 196 in high yield (Scheme 20). As well, diols 197 and 198 were prepared from 169 and 195, respectively, by treatment with Raney nickel.
Another important transformation of the organosulfur products was developed by our group recently. Through an oxidative-elimination protocol, the α-alkenyl-β’-hydroxy thioesters products 200 can be directly generated from the organosulfur products (Scheme 21). This reaction provides a significant alternative to the MBH reaction with substantially greater synthetic scope and utility.

2.3 Conclusion

In conclusion, we have developed a facile and efficient anti-selective four-component direct aldol addition of thioester enolates that is fully compatible with
enolizable aldehydes, and able to be conducted open to the air using untreated, reagent grade solvent. Our method avoids the need for prior enolate formation while maintaining complete chemoselectivity. The organosulfur products can easily undergo direct transformations and provide access to a number of important structures. Profound mechanistic investigations of this highly practical and stereochemically intriguing reaction will be the future work, as is the development of related asymmetric versions.

2.4 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, Et₂O, CH₂Cl₂, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Brine (NaCl), NaHCO₃, and NH₄Cl refer to saturated aqueous solutions. Flash column chromatography was performed on silica gel 60 (230–400 mesh). In each instance (except 29), the syn and anti isomers were inseparable by chromatography. In the cases where it was impossible to compute the syn-anti ratio directly from the crude ¹H NMR spectrum due to overlapping peaks with other compounds, the syn-anti ratio was computed from the ¹H NMR spectrum after chromatography. Relative configuration of 43 assigned by chemical correlation to known material.⁶²,⁶³ Other relative configurations assigned by analogy. ¹H and ¹³C NMR were recorded on a Varian Mercury 300 MHz spectrometer or Varian INOVA 400 MHz spectrometer at ambient temperature. All ¹H chemical shifts are reported in ppm (δ) relative to TMS; ¹³C shifts are reported in ppm (δ) relative to CDCl₃ (77.16). Only the major (anti) isomers are reported below. MS data were collected from Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was performed on a 4.6 X 250 nm Chiralpak AD-H column (Chiral Technologies).

*The following reaction is representative of those depicted in Table 14:*
The following reactions were conducted using untreated reagent grade \( \text{CH}_2\text{Cl}_2 \), open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere.

\[
\begin{array}{c}
\text{PhCHO} + \begin{array}{c}153\
\text{Cl}^-
\end{array} \rightarrow \begin{array}{c}157\
\text{OH} \quad \text{SPh}
\end{array}
\end{array}
\]

**\( \beta \)-Hydroxy-\( \alpha \)-phenylthiomethyl thioester (157).** \( \text{MgBr}_2\cdot\text{OEt}_2 \) (0.310 g, 1.2 mmol) was added to a stirred solution of benzaldehyde (0.106 g, 1.0 mmol) and acryloyl chloride (0.12 mL, 1.5 mmol) in \( \text{CH}_2\text{Cl}_2 \) (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\( \text{O} \) (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (\( \text{MgSO}_4 \)), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 157 (0.334 g; 88\%) as a pure, colorless solid, comprised of a 1:13 (syn : anti) mixture of diastereomers: \( ^1\text{H NMR} \) (CDCl\( _3 \), 300 MHz): \( \delta 7.42-7.15\) (m, 15H), 5.02 (t, \( J = 6.3 \) Hz, 1H), 3.34-3.00 (m, 3H), 2.87 (d, \( J = 6.6 \), 1H); \( ^{13}\text{C NMR} \) (CDCl\( _3 \), 300 MHz): \( \delta 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

\( m/z [M + \text{Na}]^+ \) calcd for C\( _{22} \)H\( _{20} \)NaO\( _2 \)S\( _2 \): 403.1, found: 403.3.
β-Hydroxy-α-phenylthiomethyl thioester (167). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 167 (0.246 g; 71%) as a pure, colorless solid, comprised of a 1:11 (syn : anti) mixture of diastereomers: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.44-7.19 (m, 10H), 3.98-3.84 (m, 1H), 3.39 (A of an ABX system, $J = 7.8$, 13.5 Hz, 1H), 3.28 (B of an ABX system, $J = 6.3$, 13.5 Hz, 1H), 2.98 (X of an ABX system, apparent 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$_3$, 300 MHz): $\delta$ 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$_2$S$_2$: 369.1, found: 369.3.

β-Hydroxy-α-phenylthiomethyl thioester (168). Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 168 (0.274 g; 68%) as a pure, colorless solid, comprised of a 1:16 (syn : anti) mixture of diastereomers: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.46-7.18 (m, 10H), 3.97-3.82 (m, 1H), 3.40 (A of an ABX system, $J = 7.8$, 13.5 Hz, 1H), 3.29 (B of an ABX system, $J = 6.6$, 13.5 Hz, 1H), 2.99 (X of an ABX system, apparent td, $J = 3.6$, 1H).
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$_3$, 300 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$_2$S$_2$: 425.2, found: 425.4.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{O} \\
& \quad \text{SPh} & \quad \text{SPh} \\
\text{169}
\end{align*}
\]

**β-Hydroxy-α-phenylthiomethyl thioester (169).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 169 (0.290 g; 71%) as a pure, colorless solid, comprised of a 1:14 (syn : anti) 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, J = 8.1, 13.5 Hz, 1H), 3.25 (B of an ABX system, J = 6.3, 13.5 Hz, 1H), 2.98 (X of an ABX system, apparent 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$_3$, 300 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$_2$S$_2$: 431.1, found: 431.3.

\[
\begin{align*}
\text{CH} & \quad \text{O} & \quad \text{SPh} \\
& \quad \text{SPh} & \quad \text{SPh} \\
\text{170}
\end{align*}
\]
β-Hydroxy-α-phenylthiomethyl thioester (170). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 170 (0.314 g; 81%) as a pure, colorless solid, comprised of a 1: >20 (syn : anti) 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, $J$ = 7.2, 13.5 Hz, 1H), 3.31 (B of an ABX system, $J$ = 6.9, 13.5 Hz, 1H), 3.14 (X of an ABX system, apparent 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$_3$, 300 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$_2$S$_2$: 409.1, found: 409.3.

β-Hydroxy-α-phenylthiomethyl thioester (171). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 171 (0.264 g; 76%) as a pure, colorless solid, comprised of a 1: >20 (syn : anti) 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, $J$ = 7.7, 13.5, Hz 1H), 3.25 (B of an ABX system, $J$ = 6.6, 13.5 Hz, 1H), 3.11 (X of an ABX system, apparent 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$_3$, 300 MHz): δ 200.5, 135.1, 134.2, 130.1, 129.6,
The following reaction is representative of those depicted in Table 15:
The following reactions were conducted using untreated reagent grade CH₂Cl₂, 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 (170).** MgBr₂·OEt₂ (0.310 g, 1.2 mmol) was added to a stirred solution of cyclohexane carboxaldehyde (0.112 g, 1.0 mmol) and S-phenyl thiopropenoate (0.164 g, 1.5 mmol) in CH₂Cl₂ (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 H₂O (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow solid. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 170 (0.306 g; 79%) as a pure, colorless solid, comprised of a 1:
>20 (syn : anti) mixture of diastereomers. Spectroscopic data was identical to that reported above.

\[
\beta\text{-Hydroxy-}\alpha\text{-phenylthiomethyl thioester (180).} \quad \text{Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave 180 (0.328 g; 79%) as a pure, colorless solid, comprised of a 1:11 (syn : anti) mixture of diastereomers: } ^1\text{H NMR (CDCl}_3, 300 MHz): \delta \\
7.48-7.12 (m, 8H), 3.51 (ddd, } J = 3.3, 8.6, 10.4 \text{ Hz, 1H}, 3.40 (A of an ABX system, } J = 7.8, 13.2 \text{ Hz, 1H}), 3.31 (B of an ABX system, } J = 6.6, 13.5 \text{ Hz, 1H}), 3.14 (X of an ABX system, apparent ddd, } J = 3.3, 6.6, 7.8, 1H), 2.46 (d, } J = 10.2 \text{ Hz, 1H}), 2.38 (s, 6H), 2.08-0.84 (m, 11H); ^13\text{C NMR (CDCl}_3, 300 MHz): } \delta 200.3, 142.7, 135.4, 134.4, 130.2, 129.2, 128.4, 126.8, 126.4, 77.2, 53.6, 42.6, 34.7, 29.8, 29.2, 26.3, 26.0, 25.9, 21.9; \text{ESI-MS } m/z [M + Na]^{+} \text{calcd for C}_{26}\text{H}_{30}\text{NaO}_{2}\text{S}: 437.2, \text{found: 437.4.}
\]

\[
\beta\text{-Hydroxy-}\alpha\text{-phenylthiomethyl thioester (181).} \quad \text{Flash chromatography over silica gel, using 4:96 EtOAc-hexanes gave 181 (0.278 g; 82%) as a pure, colorless solid, comprised of a 1:4 (syn : anti) mixture of diastereomers: } ^1\text{H NMR (CDCl}_3, 300 MHz): \delta \\
\]

123
7.50-7.12 (m, 5H), 3.58-3.49 (m, 1H), 3.34 (A of ABX pattern, \(J = 7.2, 13.2\) Hz, 1H), 3.26 (B of ABX pattern, \(J = 7.2, 13.2\) Hz, 1H), 3.00 (X of ABX pattern, apparent 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 \(\delta 1.26 (J = 7.5\) Hz, 3H)]; \(\text{\textsuperscript{13}C NMR}\) (CDCl\(_3\), 300 MHz): \(\delta 202.6, 135.4, 130.0, 129.0, 126.6, 76.6, 54.2, 42.0, 34.4, 29.7, 28.9, 26.3, 26.0, 25.8, 23.6, 14.5\); \textbf{ESI-MS} \(m/z [M + Na]^+\) calcd for C\(_{18}\)H\(_{26}\)NaO\(_2\)S\(_2\): 361.1, found: 361.3.

\(\text{\textsuperscript{13}C NMR}\) (CDCl\(_3\), 300 MHz): \(\delta 203.2, 136.0, 130.4, 129.0, 126.6, 76.7, 55.8, 48.9, 40.6, 31.5, 29.7, 29.3, 28.4, 26.3, 26.1, 25.9\); \textbf{ESI-MS} \(m/z [M + Na]^+\) calcd for C\(_{30}\)H\(_{36}\)NaO\(_2\)S\(_2\): 389.2, found: 389.3.

\(\beta\)-Hydroxy-\(\alpha\)-phenylthiomethyl thioester (182). Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 182 (0.282 g; 77%) as a pure, colorless solid, comprised of a 1:1.5 (\textit{syn} : \textit{anti}) mixture of diastereomers: \(\text{\textsuperscript{1}H NMR}\) (CDCl\(_3\), 300 MHz): \(\delta 7.42-7.15 (m, 5H), 3.59-3.52 (m, 1H), 3.27 (A of an ABX system, \(J = 10.2, 13.2\) Hz, 1H), 3.17 (B of an ABX system, \(J = 3.6, 13.2\) Hz, 1H), 2.90 (X of an ABX system, apparent 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 \(\delta 1.47 (9H)\)]; \(\text{\textsuperscript{13}C NMR}\) (CDCl\(_3\), 300 MHz): \(\delta 203.2, 136.0, 130.4, 129.0, 126.6, 76.7, 55.8, 48.9, 40.6, 31.5, 29.7, 29.3, 28.4, 26.3, 26.1, 25.9\); \textbf{ESI-MS} \(m/z [M + Na]^+\) calcd for C\(_{30}\)H\(_{36}\)NaO\(_2\)S\(_2\): 389.2, found: 389.3.
β-Hydroxy-α-phenylthiomethyl oxoester (183). Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 183 (0.266 g; 72%) as a pure, colorless solid, comprised of a 1:2 (syn : anti) mixture of diastereomers: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.46-7.03 (m, 10H), 3.65-3.56 (m, 1H), 3.41 (A of an ABX system, $J$ = 9.0, 13.2 Hz, 1H), 3.26 (B of an ABX system, $J$ = 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$_3$, 300 MHz): $\delta$ 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$_3$S: 393.2, found: 393.3.

β-Hydroxy-α-phenylthiomethyl oxoester (184). Flash chromatography over silica gel, using 6:94 EtOAc-hexanes gave 184 (0.273 g; 78%) as a pure, colorless solid, comprised of a 1:1 (syn : anti) mixture of diastereomers: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 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 $\delta$ 1.46 (9H)]; $^{13}$C NMR (CDCl$_3$, 300 MHz): $\delta$ 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\(_3\)S: 373.2, found: 373.3.

\[\text{\beta-Hydroxy-\(\alpha\)-phenylthiomethyl amide (185).} \]

Flash chromatography over silica gel, using 20:80 EtOAc-hexanes gave 185 (0.236 g; 64\%) as a pure, colorless solid, comprised of a 1:2 (syn : anti) mixture of diastereomers: **\(^1\)H NMR** (CD\(_3\)Cl, 300 MHz): \( \delta \)
8.44 (s, 1H), 7.49-7.05 (m, 10H), 3.70-3.61 [m, 2H, including a dd at \( \delta \) 3.66 (\( J = 3.3, 7.8 \) Hz, 1H)], 3.42 (A of an ABX system, \( J = 7.2, 13.2 \) Hz, 1H), 3.29 (B of an ABX system, \( J = 7.5, 13.2 \) Hz, 1H), 2.72 (X of an ABX system, apparent dt, \( J = 3.3, 7.5 \) Hz, 1H), 2.04-0.83 (m, 12H); **\(^{13}\)C NMR** (CD\(_3\)Cl, 300 MHz): \( \delta \) 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\(_2\)S: 392.2, found: 392.3.

*The remaining reactions were conducted as described in the general considerations section.*
**S-phenyl thiopropenoate (158).** PhSLi (1.0 M solution in THF, 7.43 mL, 7.43 mmol) was added to a stirred solution of acryloyl chloride 153 (0.72 mL, 8.55 mmol) in CH₂Cl₂ (50 mL). Stirring was continued for 2.5 h and H₂O (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 saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 Et₂O-pentanes gave 158 (0.342 g; 28%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.⁶⁴

![Chemical Structure](image)

**S-2,6-dimethylphenyl thiopropenoate (174).** NaH (0.216 g, 9.01 mmol) was added to a stirred solution of 2,6-dimethyl benzenethiol (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 153 (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 NaHCO₃ 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 saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel.

¹ Compound polymerized on column and/or high vacuum, which resulted in the low isolated yield.
gel, using 10:90 EtOAc-hexanes gave 174 (0.439 g; 32%) as a pure, colorless oil:\(^1\)\(^\text{H NMR}\) (CDCl\(_3\), 300 MHz): \(\delta\) 7.30-7.10 (m, 3H), 6.50 (A of an ABX system, \(J = 9.9, 17.1\) Hz, 1H), 6.39 (B of an ABX system, \(J = 1.5, 17.4\) Hz, 1H), 5.76 (X of an ABX system, \(J = 1.5, 9.9\) Hz, 1H), 2.36 (s, 6H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 300 MHz): \(\delta\) 187.8, 143.1, 134.7, 130.1, 128.5, 127.2, 126.6, 21.8; \textbf{ESI-MS} \(m/z\) [M + Na]\(^+\) calcd for C\(_{11}\)H\(_{12}\)NaOS: 215.1, found: 214.9.

\textit{The following reaction is representative of the synthesis of thiopropenoate 175 and 176:}

\begin{center}
\begin{align*}
\text{COCl} & \xrightarrow{t-\text{BuSNa, CH}_2\text{Cl}_2} \text{S-CH}=\text{CH}-\text{CH}_2\text{CO} \\
153 & \quad 176
\end{align*}
\end{center}

\textbf{S-t-butyl thiopropenoate (176).} Sodium-2-methyl-2-propane thiolate (2.00 g, 17.83 mmol) was added to a stirred solution of acryloyl chloride 153 (1.73 mL, 20.54 mmol) in CH\(_2\)Cl\(_2\) (50 mL). Stirring was continued for 2.5 h and H\(_2\)O (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 saturated aqueous NaCl, dried (MgSO\(_4\)), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 2.5:97.5 EtOAc-hexanes gave 176 (0.694 g; 27%) as a pure, colorless oil:\(^1\)\(^\text{H NMR}\) (CDCl\(_3\), 300 MHz): \(\delta\) 6.61-5.94 (m, 2H), 5.57 (dd, \(J = 2.7, 8.7\) Hz, 1H), 1.51 (s, 9H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 300 MHz): \(\delta\) 191.2, 136.0, 125.2, 48.3, 30.0; \textbf{FAB-MS} \(m/z\) [M + H]\(^+\) calcd for C\(_7\)H\(_{12}\)OS: 144.1, found: 144.1.
S-ethyl thiopropenoate (175). Vacuum distillation at 30 torr gave 169 (0.435 g; 21%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.\textsuperscript{65}

\[
\begin{align*}
\text{CH}_3\text{CH}=\text{C}(\text{SPh})\text{Ph} &\rightarrow \text{CH}_3\text{CH}=(\text{TES})\text{C}(\text{SPh})\text{Ph} \\
169 &\rightarrow 195
\end{align*}
\]

\textbf{β-Triethylsilyloxy-α-phenylthiomethyl thioester (195).} A solution of 169 (0.417 g, 1.02 mmol) in CH\textsubscript{2}Cl\textsubscript{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\textsubscript{4} (5 mL) and saturated aqueous NaCl (5 mL), dried (MgSO\textsubscript{4}), and evaporated. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 195 (0.511 g; 96%) as a pure, colorless oil: \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta 7.48-7.09\) (m, 15H), 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); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta 197.4, 141.8,\)

\textsuperscript{1} Compound polymerized during vacuum distillation, which resulted in the low isolated yield.
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_{2}S_{2}Si: 545.2, found: 545.2.

**β-Triethylsilyloxy-α-phenylthiomethyl aldehyde (196).** Triethylsilane (0.51 mL, 3.22 mmol) was added to a stirred solution of 195 (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. 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 196 (0.171 g; 90%) as a pure, colorless oil: **^1H NMR** (CDCl₃, 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, apparent dd, J = 7.8, 13.5 Hz, 1H), 3.09 (B of an ABX system, apparent 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);

**^13C NMR** (CDCl₃, 300 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_{2}SSi: 437.2, found: 437.4.
2-methyl-5-phenylpentane-1,3-diol (41). An excess of Raney Ni\(^\text{V}\) (5 mL, slurry in H\(_2\)O) was added to a stirred solution of 14 (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 with EtOH and EtOAc, and evaporated to yield 41 (0.133 g; 94\%) as a light yellow solid. No further purification was conducted. Spectroscopic data was identical to that reported previously.\(^6^6\)

2-methyl-5-phenyl-3-(triethylsilyloxy)pentan-1-ol (42). An excess of Raney Ni\(^\text{V}\) (5 mL, slurry in H\(_2\)O) was added to a stirred solution of 39 (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 with EtOH and EtOAc, and evaporated to yield a clear, colorless oil. Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 42 (0.098 g; 83\%) as a pure, colorless oil: \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 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, 9H).

\(^1\) Aldrich, Cat. No. 221678, W.R. Grace and Co. Raney® 2800, slurry, in H\(_2\)O, active catalyst.
3H), 1.03-0.93 [m, 12H, including 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$_3$, 300 MHz): δ 142.3, 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$_2$Si: 331.2, found: 331.4.
Chapter Three: Progress toward the Total Synthesis of Apratoxin D

3.1 Background and Introduction

3.1.1 Isolations, Biological Activities and Syntheses of Apratoxins

Apratoxins A–E (201–205, respectively, Figure 8) are a family of marine natural products of mixed biogenetic origin. These compounds are all cyclodepsipeptides that consist of peptide–polyketide hybrid backbones and exhibit potent cancer cell growth inhibitory activity by inducing G1 phase specific cell cycle arrest and apoptosis.

![Structures of Apratoxins A-E](image)

Figure 8. Structures of Apratoxins A-E

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Apratoxin A (201) was isolated from the marine cyanobacterium *Lynigbya majuscula* and collected in Guam and Palau by Moore, Paul, and co-workers in 2001.67 One year later, apratoxin B and C (202 and 203) were discovered by further organism collections and isolations.68 It has been reported that 201–203 show potent in vitro cytotoxicity against the KB (0.52–21.3 nM) and LoVo cell lines (0.36–10.8 nM). However, in vivo antitumor investigation indicated that 201 was poorly tolerated in mice mainly due to lack of selectivity for different cell lines.67,68

Three total syntheses of apratoxin A (201) have been reported by the groups of Forsyth,72 Takahashi,73 and Ma74. In Ma’s report, particularly, four oxazoline analogues of apratoxin A were synthesized. It was found that replacement of the thiazoline ring with an oxazoline ring had only a marginal effect on potency. Furthermore, studies also established that the two methyl groups at C-37 and C-40 as well as the stereochemistry at C-37 were essential for cellular inhibitory activity of these apratoxin analogues.

Apratoxin D (204) was obtained from collections of two other species of cyanobacteria, *L. majuscula* (Oscillatoriaceae, Harvey ex Gomont 1892) and *L. sordida* (Oscillatoriaceae, Gomont ex Gomont 1892), both of which was collected in Papua New Guinea in 2008.69 Apratoxin D showed potent in vitro cytotoxicity against H-460 human lung cancer cells with an IC50 value of 2.6 nM, which is nearly equipotent to that of 201, thus indicating that the activity of the drug is not strongly impacted by the larger lipopeptide tail.69 This result could be of significance to the design of analogue
structures for probing the mechanism of action of the apratoxins, which makes the synthesis of this target much more important.

Apratoxin E (205) was isolated from the marine cyanobacterium *Lyngbya bouillonii* from Guam in 2008. Studies showed that 205 also displayed strong cytotoxicity against several cancer cell lines derived from colon, cervix, and bone, ranging from 21 to 72 nM, suggesting that the α,β-unsaturation of the modified cysteine residue is not essential for apratoxin activity. The 5- to 15-fold reduced activity compared with apratoxin A is attributed to the dehydration in the long-chain polyketide unit, which could affect the conformation of the molecule.

Given the biological importance of apratoxin D and E, it is desirable to develop synthetic route for making these two compounds as well as their structural analogues. The following research project will only focus on the total synthesis of apratoxin D, as parallel investigation of synthesizing apratoxin E is also going in our lab.

### 3.1.2 Retrosynthetic Analysis of Apratoxin D

We plan to synthesize 204 in a convergent manner as shown in Scheme 22. Since the tetrapeptide 206 is known, our initial target becomes the fragment 207.

Our group recently reported the development of a simple and efficient asymmetric α-alkylation and α,α-bisalkylation of acyclic ketones by using chiral N-
Amino cyclic carbamate (ACC) hydrazones (Scheme 23). This method does not require extremely low temperature as is commonly used in conventional methods, yet proceeds with excellent stereoselectivity and substantially higher yields. Furthermore, the auxiliary used to achieve the selectivity is easily introduced into and removed from ketone with near quantitative recovery. Given the efficiency and advantage of this method, we felt it might provide a convenient basis to synthesize the fragment 207.

Scheme 23. Asymmetric Alkylation of ACC Hydrazones

Our synthetic approach of fragment 207 begins with acetone-derived ACC hydrazone and rapidly builds complexity in a stepwise manner, providing numerous opportunities for subsequent analogue preparation (Scheme 24).
Scheme 24. Proposed Synthetic Approach of Fragment 207 Starting from Acetone Hydrozone 213
To test the ACC hydrazone–alkylation strategy, we decided to approach the target from a simple asymmetric α-allylation reaction to generate the stereo center of the original C-37 in apratoxin D (Scheme 25). Since the diastereoselectivity (E-Z stereoisomers) of the hydrazone formation step must be controlled, a single-side sterically hindered methyl ketone 229 was proposed. Therefore, effort has been made in terms of the stereoselective formation of ACC hydrazone and subsequent α-alkylation reactions.

Scheme 25. Alternative Approach of Synthesizing Fragment 207

3.2 Result and Discussion

3.2.1 Initial Synthesis of ACC Hydrazone
For the synthesis of 229, a primary alcohol 235 was prepared through Evans’ oxazolidinone aldol chemistry according to a four-step literature procedure (Scheme 26). The tosylation of 235 afforded 236 in 88% yield. Treatment of the primary tosylate 236 (0.2 g scale) with lithium di(tert-butyl)cuprate reagent at -20°C for 20 h produced the coupling product 237 in a moderate yield (Table 17, entry 1). However, the attempt to scale up the reaction (2.5 g scale) gave unsatisfactory results, with only less than 5% desired C-substituted product 237 formed and a significant amount of the S-substituted product 235 isolated instead. An alternative method, copper-catalyzed cross-coupling reaction of Grignard reagent with primary tosylate, was then investigated (entry 3 and 4, Table 17). With the originally reported conditions (entry 3), a 50% yield of 237 was isolated after 12 h. A cursory optimization with increased amount of catalyst and extended reaction time provided better yield (64%) (entry 4).

Scheme 26. Synthesis of Tosylate 236
Table 17. Condition Screen for the Synthesis of 237

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(t-Bu)_2CuLi, Et_2O, -20°C (0.2 g scale)</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>(t-Bu)_2CuLi, Et_2O, -20°C (2.5 g scale)</td>
<td>20</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>t-BuMgCl, 2% CuCl_2, 10% Ph—Me, THF, reflux</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>t-BuMgCl, 10% CuCl_2, 25% Ph—Me, THF, reflux</td>
<td>24</td>
<td>64</td>
</tr>
</tbody>
</table>

Ozonolysis of 237 led to the methyl ketone 238 (Scheme 27), however, when PPh_3 was used as a quenching reagent, due to its similar polarity as 238 in a variety of solvent combinations that tested, the excess amount of PPh_3 was hardly separated from the product through chromatography; while Me_2S was used instead, a lower yield (38%) of 238 was isolated.

Scheme 27. Ozonolysis Reaction of 237

The ACC hydrazone formation reaction\textsuperscript{75} of methyl ketone 238 was then explored. Under room temperature, the reaction proceeded very slowly with only trace
amount of the desired product 239 detected by TLC after 20 h. When the reaction was then heated under refluxing for another 20 h, 239 was isolated in 25% yield of 5:1 diastereomers, while a de-silyl protected form of product 240 could also be seen and 50% of the unreacted starting material 238 was recovered (Scheme 28).

Scheme 28. ACC Hydrazone Formation of Methyl Ketone 238

3.2.2 Switching Protecting Groups

Given the relatively weak stability of a triethylsilyl group under acidic conditions, we next screened proper hydroxyl protecting groups for methyl ketone 238 to enhance its stability in the hydrazone formation reaction.

Scheme 29. Protecting Group Switching from TES to Benzyl Group

With the deprotection of TES group of 237 by TBAF and re-protection with benzyl group, we could obtain compound 242 (Scheme 29). At this stage, we would like to further develop the synthetic procedure of converting the terminal olefin to ketone
instead of using the problematic ozonolysis reaction. Thus, a two-step reaction was investigated,\(^7\) which gave the methyl ketone 243 in 90% yield (Scheme 30).

**Scheme 30.** A Two-Step Procedure of Converting Terminal Olefin 242 to Ketone 243

![Scheme 30](image)

243 was subjected to the ACC hydrazone formation reaction. After 12 h refluxing, a 1:1 mixture of diastereomers was isolated in 95% yield (Scheme 31). As either the E-Z stereoisomers of hydrazone could be generated or the reaction condition might have epimerized the stereo center next to ketone carbonyl, a verification experiment was carried out. Hence, product 244 was resubjected to hydrazone cleavage reaction (Scheme 31). Under this condition, the ketone was recovered in 90% yield but with a 1:1 mixture of diastereomers, which validated the epimerization during the hydrazone formation step.

**Scheme 31.** ACC Hydrazone Formation of Methyl Ketone 243

![Scheme 31](image)

We reasoned that the epimerization during hydrazone formation is a thermodynamic process, and a sterically bulkier hydroxyl protecting group would
probably prevent or slow down this process, thus the kinetic product might be isolated before the epimerization happens and this problem could be overcome or diminished. To test our hypothesis, we synthesized TBS protected α-hydroxyl ketone 247 (Scheme 32). The hydrazone formation reaction with 247 gave an exciting result, with a single diastereomer isolated in 91% yield after 24 h refluxing (Scheme 33).

3.2.3 α-Alkylation Reactions with ACC Hydrazone

Since the goal of stereoselective formation of ACC hydrazone has been achieved, we next investigated the subsequent α-alkylation reactions. The treatment of 248 with LDA and followed by methyl iodide addition afforded α-methylated product 249 in 85% yield (Scheme 34). However, the following α-allylation reaction with 249 led to no product, which might be attributed to the steric bulkiness of TBS group and ACC hydrazone itself as well.
A sterically smaller benzyl group was switched instead. Under the deprotection and re-protection reaction conditions, compound 251 was acquired in 50% yield from 249 (Scheme 35).

The α-allylation reaction with 251 was then explored (Scheme 36). After the deprotonation of 251 by LDA, ally bromide was added at -40°C. This reaction gave a 6:1 mixture of diastereomers in 71% yield, which demonstrated the effectiveness of ACC auxiliary on directing the stereoselectivity in the α-alkylation reaction.
3.2.4 Removing ACC Auxiliary

Several cleavage conditions to remove the ACC auxiliary and reinstall ketone functionality in 252 and 253 (R₁R₂C=N-Y → R₁R₂C=O) have been tried, such as 1) p-TsOH with acetone; 2) p-TsOH with formaldehyde; 3) CuCl₂ in THF and H₂O. However, due to the steric bulkiness adjacent to the hydrazone group, only starting materials were recovered in each case. In addition, given the high acidity of the α-proton of a α-hydroxyl/benzyloxy ketone, a potential problem of epimerization may occur when the ketone is finally converted to alkane under reductive conditions (e.g., TsNHN₃/NaCNBH₃).

Scheme 37. Transformation of Hydrazone 254 into Dithiane 255

An alternative strategy to the conversion of hydrazone → ketone → alkane is to transform the hydrazone into a dithiane and next undergo Raney Ni reduction to give the alkane. This protocol was initially developed on a model system (Scheme 37). A promising result was obtained by the reaction with 1,3-propanedithiol and catalytic amount of BF₃·OEt₂ in CH₂Cl₂. Without further optimization, a 36% yield of dithiane 255 was acquired with 55% unreacted starting material 254 recovered after 16 h.
3.3 Conclusion

In conclusion, our primary objective of demonstrating the utility of ACC hydrazone–asymmetric α-alkylation chemistry in the synthesis of apratoxin D has been achieved with the preparation of 252 and 253 (Scheme 36). Although the ACC auxiliary was difficult to remove under typical conditions, an alternative route of converting to dithiane and subjecting to Raney Ni reduction has been proposed to solve the problem. A promising result showed in the model study, which still requires further optimization and application to the real molecule.

3.4 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, Et₂O, CH₂Cl₂, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Brine (NaCl), NaHCO₃, and NH₄Cl refer to saturated aqueous solutions. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ¹H and ¹³C NMR were recorded on a Varian INOVA 400 MHz spectrometer at ambient temperature. All ¹H chemical shifts are reported in ppm (δ) relative to TMS; ¹³C shifts are reported in ppm (δ) relative to CDCl₃ (77.16). MS data were collected from Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was performed on a 4.6 X 250 nm Chiralpak AD-H column (Chiral Technologies).

(2S,3R)-2,4-Dimethyl-3-(triethylsilyloxy)pent-4-enyl 4-methylbenzenesulfonate (236). p-Toluenesulfonyl chloride (0.137 g, 0.72 mmol) was added to a stirred solution of (2S,3R)-2,4-dimethyl-3-(triethylsilyloxy)pent-4-en-1-ol⁷⁶ (235) (0.147 g, 0.6 mmol) in neat pyridine (2.0 mL). Stirring was continued for 12 h and the mixture was
quickly poured into a mixture of H₂O and ice (30 mL), extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% (v/v) aqueous HCl (20 mL) and saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 236 (0.211 g; 88%) as a pure, colorless oil: \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.78 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.87–4.85 (m, 1H), 4.82–4.80 (m, 1H), 3.97 (d, J = 6.0 Hz, 1H), 3.94 (A of an ABX system, apparent dd, J = 6.0, 9.6 Hz, 1H), 3.82 (B of an ABX system, apparent dd, J = 6.0, 9.6 Hz, 1H), 2.45 (s, 3H), 1.96–1.85 (X of an ABX system, m, 1H), 1.59 (s, 3H), 0.90 (apparent t, J = 8.0 Hz, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.57-0.48 (m, 6H); \(^{13}\)C NMR (CDCl₃, 400 MHz): δ 145.3, 144.8, 133.2, 129.9, 128.0, 112.5, 76.0, 72.9, 36.7, 21.7, 18.1, 11.3, 6.9, 4.8; ESI-MS m/z [M + Na]⁺ calcd for C₃₀H₄₅NaO₄Si: 421.2, found: 421.1.

**The following reactions are representatives of those depicted in Table 17:**

\[
\begin{align*}
\text{TosC} & \quad \overset{\text{(t-Bu)}_2\text{CuLi, Et}_2\text{O, -20°C}}{\text{OTES}} \quad \text{236} \\
& \quad \text{OTES} \quad \text{237}
\end{align*}
\]

**Triethyl((3R,4S)-2,4,6,6-tetramethylhept-1-en-3-yloxy)silane (237).** 

\(t\)BuLi (2.9 mL, 5.0 mmol, 1.7 M in pentane) was added to a suspension of copper(I) iodide (0.476 g, 2.5 mmol) in Et₂O (3.0 mL) at -40°C. Stirring was continued for 30 min at-40°C and then allowed to warm to -20°C. A solution of 236 (0.199 g, 0.5 mmol) in Et₂O (1.5 mL) was slowly added to the cuprate solution over ca. 30 min. Stirring was continued for 20
h at 20°C and then allowed to warm to 0°C. Saturated aqueous NH₄Cl was added to the reaction mixture. Stirring was continued for 10 min and allowed to warm rt. The mixture was partitioned between EtOAc (30 mL) and H₂O (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using neat hexane gave 237 (0.067 g; 47%) as a pure, colorless oil and recovered 235 (0.050 g; 41%), of which spectroscopic data was identical to that reported previously.⁷⁶ For compound 237: ¹H NMR (CDCl₃, 400 MHz): δ 4.87–4.85 (m, 1H), 4.84–4.82 (m, 1H), 3.72 (d, J = 6.4 Hz, 1H), 1.67 (s, 3H), 1.64–1.54 (X of an ABX system, m, 1H), 1.35 (A of an ABX system, apparent dd, J = 2.4, 14.0 Hz, 1H), 0.98–0.90 [13H, contains a m (B of an ABX system, 1H), a d (J = 6.8 Hz, 3H), and an apparent t (J = 8.0 Hz, 9H)], 0.88 (s, 9H), 0.59 (apparent q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 400 MHz): δ 146.9, 112.3, 82.2, 47.5, 33.3, 31.1, 30.3, 18.3, 17.8, 7.1, 5.1; ESI-MS m/z [M + Na]+ calcd for C₁₇H₃₆NaOSi: 307.2, found: 307.2.

![Chemical Structure](image)

**Triethyl((3R,4S)-2,4,6-tetramethylhept-1-en-3-yloxy)silane** (237). t-BuMgCl (5.0 mL, 5.0 mmol, 1.0 M in THF) was added to a stirred solution of 236 (1.0 g, 2.5 mmol), copper(II) chloride (0.034 g, 0.25 mmol) and 1-phenyl-1-propyne (78 μL, 0.625 mmol) in
THF (25 mL). The reaction mixture was heated to reflux for 24 h and then allowed to cool to rt. Saturated aqueous NH₄Cl (25 mL) was added to the reaction mixture. Stirring was continued for 10 min. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using neat hexane gave **237** (0.456 g; 64%) as a pure, colorless oil. Spectroscopic data was identical to that reported above.

![Chemical Structure](image)

(3R,4S)-4,6,6-Trimethyl-3-(triethylsilyloxy)heptan-2-one (**238**). At -78°C, to a stirred solution of **237** (0.882 g, 3.1 mmol) in CH₂Cl₂ (50 mL) was passed a steady stream of ozone until a blue coloration appeared. Air was then passed for an additional 20 min. Me₂S (2.28 mL, 31 mmol) was added to the reaction mixture at -78°C. Stirring was continued for 12 h and the temperature was allowed to slowly warm to rt. The mixture was partitioned between EtOAc (100 mL) and H₂O (30 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a light-yellow oil. Flash chromatography over silica gel, using 2:98 EtOAc-hexanes gave **238** (0.338 g; 38%) as a pure, colorless oil: ¹H NMR (CDCl₃, 400 MHz): δ 3.79 (d, J = 5.2 Hz, 1H), 2.15 (s, 3H),
1.90–1.80 (X of an ABX system, m, 1H), 1.40 (A of an ABX system, apparent dd, J = 2.8, 14.4 Hz, 1H), 1.00–0.92 [13H, contains a m (B of an ABX system, 1H), a d (J = 6.8 Hz, 3H), and an apparent t (J = 8.0 Hz, 9H)], 0.90 (s, 9H) 0.62 (apparent q, J = 8.0 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 212.2, 84.1, 46.5, 34.1, 31.1, 30.0, 26.3, 17.5, 6.9, 5.0; ESI-MS m/z [M + Na]$^+$ calcd for C$_{16}$H$_{34}$NaO$_2$Si: 309.2, found: 309.2.

*The following reaction is representative of those depicted in Scheme 29 and Scheme 35:*

![Reaction Scheme](image)

*(3R,4S)-2,4,6,6-Tetramethylhept-1-en-3-ol (241).* TBAF (2.5 mL, 2.5 mmol, 1.0 M in THF) was added dropwise to a stirred solution of 237 (0.356 g, 1.25 mmol) in THF (20 mL) at 0°C. Stirring was continued for 2 h at 0°C. Saturated aqueous NaHCO$_3$ (5 mL) was then added to the reaction mixture. Stirring was continued for 5 min and the temperature was allowed to warm to rt. The mixture was partitioned between EtOAc (50 mL) and H$_2$O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO$_4$), and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 241 (0.162 g; 76%) as a pure, colorless oil: $^1$H NMR (CDCl$_3$, 400 MHz): δ 4.97–4.95 (m, 1H), 4.91–4.89 (m, 1H), 3.89–3.84 (m, 1H), 1.71 (s, 3H), 1.56–1.52 (X of an ABX system, m, 1H), 1.45 (A of an ABX system, apparent dd, J = 3.2,
14.0 Hz, 1H), 1.08 (B of an ABX system, apparent dd, J = 6.8, 14.0 Hz, 1H), 0.92 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 146.8, 111.2, 80.5, 47.9, 31.9, 31.2, 30.1, 19.1, 15.9; ESI-MS \(m/z\) [M + Na]\(^+\) calcd for C\(_{11}\)H\(_{22}\)NaO: 193.2, found: 193.2.

**ACC Hydrazone (250).** Flash chromatography over silica gel, using 15:85 EtOAc-hexanes gave 250 (0.031 g; 84%) as a pure, white powder: \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.44–4.39 (m, 1H), 4.30 (t, J = 4.0, 1H), 3.78 (d, J = 6.0, 1H), 2.80–2.67 (m, 2H), 2.40–1.60 (m, 8H), 1.36–1.16 [5H, contains a s (1.26, 3H) and a m (2H)], 1.13 (s, 3H), 1.08 (t, J = 8.0 Hz, 3H), 0.97 (s, 9 H), 0.86 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 178.7, 154.4, 83.3, 76.0, 73.2, 48.6, 48.0, 43.2, 35.4, 32.5, 31.3, 30.1, 26.6, 25.7, 23.7, 22.0, 19.4, 14.5, 10.7; ESI-MS \(m/z\) [M + H]\(^+\) calcd for C\(_{21}\)H\(_{37}\)N\(_2\)O\(_3\): 365.3, found: 365.3, [M + Na]\(^+\) calcd for C\(_{23}\)H\(_{38}\)N\(_2\)NaO\(_3\): 387.3, found: 387.3.

The following reaction is representative of those depicted in Scheme 29 and Scheme 35:

\[
\begin{align*}
\text{241} & \quad \xrightarrow{1) \text{NaH, THF, DMF, 0°C}} \quad \text{242} \\
\text{t-Bu} & \quad \text{OH} & \quad 1) \quad \text{NaH, THF, DMF, 0°C} \\
\text{241} & \quad \xrightarrow{2) \text{BnBr, -10°C -> r.t., 12 h}} \quad \text{242} \\
\text{t-Bu} & \quad \text{OH} \quad \text{t-Bu} & \quad \text{Bn} \\
\end{align*}
\]

\(((3R,4S)-2,4,6,6-Tetramethylhept-1-en-3-yloxy)methyl)benzene (242). A solution of 241 (0.255 g, 1.5 mmol) in THF (3.0 mL) was added dropwise via cannula to a
stirred suspension of NaH (0.108 g, 4.5 mmol) in DMF (3.0 mL) at 0°C. Stirring was continued for 15 min at 0°C and the temperature was cooled to -10°C. Benzyl bromide (0.27 mL, 2.25 mmol) was then added in one portion. Stirring was continued for 1 h at -10°C and the temperature was allowed to slowly warm to rt. Stirring was continued for an additional 12 h. Saturated aqueous NaHCO₃ (5 mL) was added to the reaction mixture. Stirring was continued for 5 min. The mixture was partitioned between EtOAc (30 mL) and H₂O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 242 (0.355 g; 91%) as a pure, colorless oil: \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.40–7.22 (m, 5H), 5.06–5.02 (m, 1H), 4.95–4.88 (m, 1H), 4.52 and 4.22 (AB q, \(\Delta v_{AB} = 121.0 \text{ Hz} \), \(J = 12.0, 121.0 \text{ Hz} \), 2H), 3.34 (d, \(J = 7.6 \text{ Hz} \), 1H), 1.77–1.61 [4H, contains a s (1.69, 3H) and a m (X of an ABX system, 1H)], 1.33 (A of an ABX system, apparent dd, \(J = 2.0, 14.0 \text{ Hz} \), 1H), 1.03 (d, \(J = 6.4 \text{ Hz} \), 3H), 0.92 (B of an ABX system \(J = 8.0, 14.0 \text{ Hz} \), 1H), 0.87 (s, 9H); \(^{13}\)C NMR (CDCl₃, 400 MHz): δ 143.6, 139.2, 128.4, 128.0, 127.4, 114.9, 88.8, 70.6, 47.2, 32.0, 31.0, 30.3, 18.7, 17.8; ESI-MS m/z [M + Na]⁺ calcd for C₁₈H₂₈NaO: 283.2, found: 283.2.
ACC Hydrazone (251). Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 251 (0.015 g; 60%) as a pure, white powder: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.42–7.24 (m, 5H), 4.71 and 4.38 (AB q, $\Delta\nu_{AB} = 132.8$ Hz, $J = 12.0$, 132.8 Hz, 2H), 4.30 (t, $J = 7.6$ Hz, 1H), 3.74 (d, $J = 6.8$ Hz, 1H), 2.56–2.45 (m, 1H), 2.38–2.24 (m, 2H), 2.05–1.80 (m, 4H), 1.80–1.74 (m, 1H), 1.44–1.00 [16H, contains a m (4H), two s (1.20, 3H; 1.18, 3H), a t (1.12, $J = 7.6$ Hz, 3H), and a d (1.08, $J = 6.8$ Hz, 3H)], 0.88 (s, 9H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 180.3, 155.0, 138.5, 128.4, 128.3, 127.6, 86.5, 83.2, 73.4, 71.3, 48.0, 47.1, 43.0, 35.5, 32.6, 31.1, 30.4, 26.8, 25.8, 22.9, 21.5, 19.3, 17.7, 10.9; ESI-MS m/z [M + Na]$^+$ calcd for C$_{30}$H$_{42}$N$_2$NaO$_3$: 477.3, found: 477.4.

The following reaction is representative of those depicted in Scheme 30 and Scheme 32:

(3R,4S)-3-(Benzyloxy)-4,6,6-trimethylheptan-2-one (243). 242 (0.143 g, 0.55 mmol) was dissolved in a mixture of THF (2.0 mL), t-BuOH (2.0 mL) and H$_2$O (0.5 mL)$^{79}$ NMO (0.129 g, 1.10 mmol) and OsO$_4$ (0.31 mL, 0.025 mmol, 2.5 wt% in t-BuOH) were then added to the stirred solution respectively. The mixture was vigorously stirred for 16 h. Na$_2$SO$_3$ (0.25 g) was added, followed by the addition of H$_2$O (3.0 mL). Stirring was continued for 30 min. The mixture was partitioned between EtOAc (20 mL) and H$_2$O (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined
organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a yellow oil. The crude material was redissolved in a mixture of MeOH (4.0 mL) and H₂O (2.0 mL) and then cooled to 0°C. NaIO₄ (0.235 g, 1.10 mmol) was added portionwise at 0°C and then the temperature was allowed to slowly warm to rt. Stirring was continued for 3 h. The mixture was partitioned between EtOAc (20 mL) and H₂O (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 243 (0.128 g; 90%) as a pure, colorless oil: ¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.26 (m, 5H), 4.62 and 4.37 (AB q, ΔνAB = 101.6 Hz, J = 11.6, 101.6 Hz, 2H), 3.56 (d, J = 5.2 Hz, 1H), 2.17 (s, 3H) 2.02–1.88 (X of an ABX system, m, 1H), 1.36 (A of an ABX system, apparent dd, J = 3.2, 14.4 Hz, 1H), 1.06 (B of an ABX system, apparent dd, J = 6.8, 14.4 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H); ¹³C NMR (CDCl₃, 400 MHz): δ 211.6, 137.7, 128.5, 128.0, 127.9, 90.0, 73.0, 46.8, 32.5, 31.0, 29.9, 26.6, 17.9; ESI-MS m/z [M + Na]⁺ calcd for C₁₅H₂₆NaO₂: 285.2, found: 285.2.

(3R,4S)-3-(tert-Butyldimethylsilyloxy)-4,6,6-trimethylheptan-2-one (247). Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 247 (0.127 g; 67%) as a
pure, colorless oil: \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 3.72 (d, \(J = 5.2\) Hz, 1H), 2.11 (s, 3H) 1.88–1.75 (X of an ABX system, m, 1H), 1.36 (A of an ABX system, apparent dd, \(J = 2.4, 14.4\) Hz, 1H), 0.95 (B of an ABX system, apparent dd, \(J = 7.6, 14.4\) Hz, 1H), 0.93–0.85 [21H, contains two s (0.91, 9H; 0.87, 9H) and a d (3H)], 0.03 (s, 3H), 0.00 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 212.2, 84.0, 46.5, 34.1, 31.1, 30.0, 26.4, 25.9, 18.3, 17.7, -4.6, -4.8; ESI-MS \(m/z\) [M + Na]\textsuperscript{+} calcd for C\textsubscript{16}H\textsubscript{34}NaO\textsubscript{2}Si: 309.2, found: 309.2.

\textit{tert}-Butyldimethyl(3R,4S)-2,4,6,6-tetramethylhept-1-en-3-yl)oxy)silane \quad (246).

2,6-Lutidine (0.12 mL, 1.0 mmol) was added to a stirred solution of 241 (0.110 g, 0.7 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (4.0 mL) at 0\textdegree C, followed by the addition of TBSOTf (0.19 mL, 0.84 mmol). Stirring was continued for 12 h and the temperature was allowed to warm to rt. The mixture was partitioned between EtOAc (50 mL) and H\textsubscript{2}O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO\textsubscript{4}), and evaporated to give a colorless oil. Flash chromatography over silica gel, using neat hexane gave 246 (0.190 g; 95%) as a pure, colorless oil: \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 4.88–4.81 (m, 2H), 3.70 (d, \(J = 6.0\) Hz, 1H), 1.67 (s, 3H), 1.66–1.55 (X of an ABX system, m, 1H), 1.37 (A of an ABX system, apparent dd, \(J = 2.0, 14.0\) Hz, 1H), 1.66–1.55 [22H, contains a m (B of an ABX system, 1H),

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two s (0.91, 9H; 0.89, 9H), and a d (3H), 0.05 (s, 3H), -0.01 (s, 3H); \textsuperscript{\textbf{13}}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 146.7, 112.4, 82.1, 47.5, 33.3, 31.1, 30.3, 26.1, 18.5, 18.4, 17.8, -4.3, -4.8; ESI-MS m/z [M + Na]\textsuperscript{+} calcd for C\textsubscript{17}H\textsubscript{36}NaOSi: 307.2, found: 307.2.

The following reaction is representative of the synthesis of ACC hydrazone:

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {t-Bu \hspace{1cm} O\text{TB5}};
\node (B) at (2,0) {247 \hspace{1cm} NH\textsubscript{3}OH, p-TsOH \hspace{1cm} \text{H}_2\text{O} \hspace{1cm} \text{CH}_2\text{Cl}_2};
\node (C) at (4,0) {reflux, 24 h \hspace{1cm} t-Bu \hspace{1cm} N, Y \hspace{1cm} \text{OTBS}};
\node (D) at (0,0.5) {\text{247}};
\node (E) at (4,0.5) {\text{248}};
\draw[->] (A) -- (B) -- (C);
\end{tikzpicture}
\end{center}

ACC Hydrazone (248). \(p\)-TsOH-H\textsubscript{2}O (0.017 g, 0.09 mmol) was added to a stirred solution of 247 (0.126 g, 0.44 mmol) and ACC auxiliary (0.122 g, 0.62 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (8.0 mL). The reaction mixture was heated to reflux and stirring was continued for 24 h. The temperature was then cooled to rt and the mixture was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO\textsubscript{3} (8 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO\textsubscript{4}), and evaporated to give a yellow oil. Flash chromatography over silica gel, using 8:92 EtOAc-hexanes gave 248 (0.186 g; 91\%) as a pure, white powder: \textsuperscript{\textbf{1}}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 4.24 (t, \(J = 4.0\) Hz, 1H), 3.83 (d, \(J = 8.8\) Hz, 1H), 2.33–2.24 (m, 1H), 2.04–1.66 [8H, contains a s (1.91, 3H) and a m (5H)], 1.44–1.36 (m, 1H), 1.32–1.06 [9H, contains a m (3H) and two s (1.23, 3H; 1.13, 3H)], 1.03 (d, \(J = 6.4\) Hz, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); \textsuperscript{\textbf{13}}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 176.9, 154.3, 82.9, 81.6, 73.1, 48.0, 45.9, 43.0, 35.5, 34.0, 30.9, 30.2, 27.1, 26.0, 25.8, 21.4, 19.3,
19.2, 18.3, 15.3, -4.5, -4.9; **ESI-MS m/z** [M + H]^+ calcd for C_{28}H_{40}N_{2}O_{3}Si: 465.4, found: 465.4, [M + Na]^+ calcd for C_{28}H_{42}N_{2}NaO_{3}Si: 487.3, found: 487.4.

**ACC Hydrazine (254).** Flash chromatography over silica gel, using 10:90 EtOAc-hexanes gave 254 (0.426 g; 86%) as a pure, white powder, comprised of a mixture of 1:1 diastereomers. Both diastereomers are reported below: **¹H NMR** (CDCl₃, 400 MHz): δ 7.50–7.22 (m, 5H), 4.65 and 4.33 (AB q, Δν_{AB} = 126.8 Hz, J = 12.0, 126.8 Hz, 1H), 4.44 (t, J = 12.0 Hz, 1H), 4.31–4.25 (m, 1H), 4.01–3.91 (m, 1H), 2.38–2.25 (m, 1H), 2.16–1.54 (m, 9H), 1.46–1.10 (m, 14H), 0.94–0.80 (m, 3H); **¹C NMR** (CDCl₃, 400 MHz, including both diastereomers; due to overlapping, two peaks did not display): δ 176.1, 174.8, 154.6, 154.1, 138.2, 138.1, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 83.2, 83.0, 82.4, 82.0, 73.1, 73.0, 70.9, 70.8, 48.1, 48.0, 43.0, 35.4, 33.0, 32.8, 31.6, 27.0, 26.8, 25.8, 25.7, 25.2, 24.9, 22.7, 22.6, 21.4, 21.3, 19.3, 19.2, 14.1, 14.0, 13.9, 13.6; **ESI-MS m/z** [M + Na]^+ calcd for C_{28}H_{38}N_{2}NaO_{3}: 435.3, found: 435.2.

*The following reaction is representative of the α-alkylation reaction of ACC hydrazine:*
**ACC Hydrazone (249).** nBuLi (0.28 mL, 0.7 mmol, 2.5 M in hexane) was added dropwise over ca. 2 min to a stirred solution of diisopropylamine (0.12 mL, 0.84 mmol) in THF (2.0 mL) at -78°C. The mixture was transferred to an ice bath. Stirring was continued for 30 min and then the temperature was cooled to -40°C. A solution of 248 (0.166 g, 0.35 mmol) in THF (4.0 mL) was added to the LDA solution via cannula. Stirring was continued for 1 h at -40°C. Iodomethane (0.43 mL, 7.0 mmol) was then added to the reaction mixture at -40°C. Stirring was continued for 12 h and the temperature was allowed to slowly warm to rt. The mixture was partitioned between EtOAc (30 mL) and H2O (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO4), and evaporated to give a yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 249 (0.142 g; 85%) as a pure, white powder: **1H NMR** (CDCl3, 400 MHz): δ 4.25 (t, J = 4.0 Hz, 1H), 4.00 (d, J = 6.8 Hz, 1H), 2.60–2.43 (m, 1H), 2.42–2.26 (m, 2H), 2.10–1.72 (m, 5H), 1.52–1.42 (m , 1H), 1.34–0.84 [33H, contains four s (1.24, 3H; 1.14, 3H; 0.92, 9H; 0.91, 9H), an apparent t (1.10, J = 8.0 Hz, 3H), a d (1.02, J = 6.4 Hz, 3H), and a m (3H)], 0.10 (s, 3H), 0.09 (s, 3H); **13C NMR** (CDCl3, 400 MHz): δ 181.2, 154.5, 83.0, 80.9, 73.2, 48.0, 46.8, 43.0, 35.5, 34.3, 31.1, 30.6, 26.7, 26.1, 25.9, 22.8, 21.6, 19.3, 18.4, 17.5, 10.8, -4.1, -4.8; **ESI-MS** m/z [M + Na]+ calcd for C27H50N2NaO3Si: 501.4, found: 501.4.
ACC Hydrazone (252 and 253). nBuLi (120 μL, 0.30 mmol, 2.5 M in hexane) was added dropwise over ca. 2 min to a stirred solution of diisopropylamine (50 μL, 0.36 mmol) in THF (1.0 mL) at -78°C. The mixture was transferred to an ice bath. Stirring was continued for 30 min and then the temperature was cooled to -40°C. A solution of 251 (0.014 g, 0.03 mmol) in THF (1.0 mL) was added to the LDA solution via cannula. Stirring was continued for 1 h at -40°C. Allyl bromide (26 μL, 0.30 mmol) was then added to the reaction mixture at -40°C. Stirring was continued for 20 h and the temperature was allowed to slowly warm to rt. The mixture was partitioned between EtOAc (30 mL) and H₂O (5 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a yellow oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave a white powder (0.010 g; 71%), comprised of a mixture of 6:1 diastereomers. Only the major isomer is reported below: ¹H NMR (CDCl₃, 400 MHz): δ 7.42–7.22 (m, 5H), 5.84–5.60 (m, 2H), 4.60 and 4.33 (AB, ⁰̵ΔVAB = 110.0 Hz, ⁰̵J = 11.6, 110.0 Hz, 2H), 4.29 (t, ⁰̵J = 4.0 Hz, 1H), 4.02 (d, ⁰̵J = 4.8 Hz, 1H), 3.07–2.94 (m, 1H), 2.63–2.53 (m, 1H), 2.37–2.27 (m, 1H), 2.17–1.72 (m, 6H), 1.58–1.44 (m, 1H), 1.34–1.12 (m, 10H), 1.12–1.04 (m, 5H), 0.91 (s, 9H); ¹³C NMR (CDCl₃, 400 MHz): δ 179.6, 155.1, 138.8,
136.7, 128.4, 127.8, 127.5, 117.0, 83.1, 83.0, 73.5, 70.0, 48.8, 48.1, 43.1, 37.0, 35.6, 35.3, 32.3, 31.2, 30.5, 27.0, 25.8, 21.5, 19.3, 17.1, 16.5; **ESI-MS** *m/z* [M + H]+ calcd for C₃₁H₄₇N₂O₃: 495.4, found: 495.3, [M + Na]+ calcd for C₃₁H₄₆N₂NaO₃: 517.3, found: 517.3.

![Chemical reaction](image)

**2-(1-(Benzyloxy)hexyl)-2-methyl-1,3-dithiane (255).** BF₃·OEt₂ (4.0 μL, 0.03 mmol) was added to a stirred solution of 254 (0.041 g, 0.10 mmol) and 1,3-propanedithiol (15.0 μL, 0.15 mmol) in CH₂Cl₂ (1.0 mL). Stirring was continued for 16 h. 10% aqueous NaOH (0.5 mL) was added to the reaction mixture. Stirring was continued for 5 min. The mixture was partitioned between EtOAc (20 mL) and H₂O (2 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated to give a colorless oil. Flash chromatography over silica gel, using 5:95 EtOAc-hexanes gave 255 (0.023 g; 36%) as a pure, colorless oil and recovered unreacted starting material 254 (0.046 g; 55%).

For compound 255: **¹H NMR** (CDCl₃, 400 MHz): δ 7.50–7.24 (m, 5H), 4.94 and 4.64 (AB q, ΔνAB = 120.4 Hz, J = 10.8, 120.4 Hz, 2H), 3.72 (dd, J = 2.4, 9.2 Hz, 1H), 3.02–2.72 (m, 5H), 2.04–1.85 (m, 3H), 1.66–1.54 (m, 4H), 1.44–1.24 (m, 5H), 0.93–0.84 (m, 3H), **¹³C NMR** (CDCl₃, 400 MHz): δ 138.7, 128.3, 127.8, 127.5, 84.4, 75.6, 54.2, 32.0, 31.6, 26.9, 26.6, 26.5, 25.0, 23.4, 22.6, 14.1; **ESI-MS** *m/z* [M + Na]+ calcd for C₁₈H₂₈NaO₅: 347.2, found: 347.1.
References


5. The pKa of the thioester -proton has been reported to be 2 units less than that of a corresponding oxoester. See Bordwell, F. G.; Fried, H. E. J. Org. Chem. 1991, 56, 4218–4223.


17. In a recent modification of the crossed-Claisen reaction, 1:1 mixtures of esters and 2-substituted N-acyl-N-methylimidazolium chlorides were treated with TiCl4 and Bu3N, lending some efficiency to the coupling. Unfortunately, the reaction still requires anhydrous conditions and low temperature, and a large excess (3 equiv) of TiCl4 is needed. See: Misake, T.; Nagase, R; Matsumoto, K.; Tanabe, Y. J. Am. Chem. Soc. 2005, 127, 2854–2855.


27. In an earlier synthesis, 142 was obtained from 147 in 33% overall yield. See: Abbott, B.; Thompson, P. Aust. J. Chem. 2003, 56, 1099–1106.


Biography

Guoqiang Zhou was born on February 7, 1981 in Changchun, Jilin Province, China. In 1997, he attended the High School Attached to Northeast Normal University and started learning college chemistry courses under the guidance of Professor Jianing Xu and Professor Yingjie Lin from Jilin University. He was then selected to attend the Chinese National Chemistry Olympic Contest in Hangzhou, 2000 and won the second-class prize.

In 2004, he received his B. S. in Chemistry from Fudan University where he joined Professor Dongyuan Zhao’s group and studied the synthesis and structural topology of metal-organic frameworks. During his time at Fudan, he was honored “Chun-Tsung” Scholar for outstanding undergraduate research, nominated by Dr. Tsung-Dao Lee, a Chinese Nobel laureate.

In the fall of 2004, he began his Ph.D. study in the Department of Chemistry at Duke University under the supervision of Professor Don M. Coltart and altered his interest to synthetic organic chemistry.

He receives his Ph.D. from Duke in May 2009 and will move to Philadelphia, Pennsylvania, where he has accepted a postdoctoral position in the laboratory of Professor Jeffrey D. Winkler at the University of Pennsylvania.