DISSERTATION

CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN

Submitted by
Philip Andrew Merris Wheeler
Department of Chemistry

In partial fulfillment of the requirements
For the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Spring 2013

Doctoral Committee:
Advisor: Tomislav Rovis
Yian Shi
Eric Ferreira
Matthew Shores
John D. Fisk
ABSTRACT

CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN

The first chapter of this dissertation describes the development of reactions involving the NHC-catalyzed acylation of carbon and nitrogen nucleophiles. The overall goal of this work was to expand the scope of the NHC-redox reaction manifold and improve its applicability to the synthesis of products that would be useful to the organic chemistry community. An efficient and simple procedure for the preparation of amides from amine hydrochloride salts and α,β-unsaturated aldehydes was developed. This procedure was then applied to the asymmetric synthesis of α-fluoroamides which are valuable building blocks for the preparation of fluorinated compounds that are highly sought after in pharmaceutical, material, and agrichemical applications.

The second chapter describes efforts toward the total synthesis of the complex polyketide natural product okilactomycin, enabled by the rhodium-catalyzed desymmetrization of 3,5-dimethylglutaric anhydride developed previously by our group. Progress includes construction of the entire carbon skeleton in two fragments, poised to be unified and elaborated to the natural product by closely precedented steps. This progress demonstrates the potential of the catalytic, enantioselective desymmetrization of anhydrides to build complexity in rapid fashion.
ACKNOWLEDGEMENTS

First, I’d like to thank my advisor, Tom Rovis, for his teaching, guidance, and most importantly patience. This experience would have been unbearable without an advisor as brilliant and flexible as Tom is. He has always inspired me to keep exploring new ideas while delving deeper into current ones, and despite their ever-increasing wear, the words “What else you got?” will stick with me for the foreseeable future.

Many thanks go to my committee members, Yian Shi, Matt Shores, Nick Fisk, and especially Eric Ferreira for agreeing to be a replacement on short notice. Also, I am grateful to John Wood for writing a reference letter.

I’d also like to thank my fellow group members for their input, both scientific and personal. Everyone in the group wants to see one another succeed, and with that in mind, we are always challenging each other’s ideas and providing (mostly) constructive criticism. Specifically, I’d like to thank Harit Vora and Stéphane Perrault for their mentorship while I was a young graduate student. Their feedback helped me tremendously.

I would be remiss not to thank a few other scientists who encouraged me to pursue a doctorate in the first place: Mike Achmatowicz, Oliver Thiel, Tiffany Thiel, and Johann Chan. Their mentorship while I was working as an associate was invaluable to my development as a chemist before I came to graduate school, and I am grateful for the opportunity I had to work with them. I’d also like to thank my undergraduate mentor Brian Gerstenberger for putting up with me as a nascent organic chemist and making me believe graduate school could be fun.

Finally, Jen, you were crazy to agree to come on this journey with me, but I am so lucky you did. You have been beyond supportive through this chapter of our lives, and I am so very
grateful to have you for the rest of the chapters. There’s nothing I could write to express how much better my life has been with you in it, so I’ll just say thank you and try to do the same for you.
DEDICATION

This work is dedicated the memory of Marjorie Yost and Roger Fernando.
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CHAPTER ONE: CATALYTICALLY GENERATED ACYL TRIAZOLIUMS AS VERSATILE ACYLATING REAGENTS

1.1 Introduction

The reversal of polarity of carbonyl compounds, or *umpolung*,¹ is a concept that furnishes new possibilities for bond disconnection in organic synthesis. By a variety of methods, carbonyl compounds that would normally be considered electrophilic at the carbon can be rendered nucleophilic. Polarity-reversed carbonyl compounds such as these are often referred to as acyl anion equivalents. These species can be utilized to access a number of otherwise challenging intermediates such as 1,4-dicarbonyls, which are important synths for a number of structural motifs including furans, pyrroles, and thiophenes.² Acyl anion equivalents can be formed stoichiometrically in the case of the Corey-Seebach reaction³ or catalytically in the case of thiamine-mode-of-action-related intermediates.⁴ These reactions have been utilized in the synthesis of achiral and racemic products for many years, one notable example being the preparation of atorvastatin (Lipitor™) via a thiamine-catalyzed Stetter reaction (Figure 1.1.1).⁵

Figure 1.1.1. Thiamine-catalyzed Stetter reaction applied to the synthesis of Lipitor.

Asymmetric variants of the Stetter reaction have been the subject of considerable interest within the field of organocatalysis, and our studies have resulted in the development of a number of chiral triazolium precatalysts that promote highly efficient and enantioselective reactions. Each of these triazoliums can be deprotonated with a variety of bases to form the active N-heterocyclic carbene (NHC) catalyst, which when reacted with an aldehyde generates an acyl anion equivalent. In our earliest examples, this acyl anion reacts with a tethered enoate or enone to give chromanone products (eq 1). Later, we reported an intramolecular desymmetrization of dienone substrates (eq 2). In subsequent work, we have demonstrated highly enantioselective intermolecular Stetter reactions on both alkylidene malonate (eq 3) and nitroalkene (eq 4) Michael acceptors.

---


The structure of the active nucleophile in these reactions was first proposed by Ronald Breslow and therefore coined the Breslow intermediate. It is formed by addition of the active catalyst (cyanide or carbene) to the aldehyde followed by proton transfer to generate nucleophilic alkene I (Figure 1.1.2). This nucleophilic alkene can also be represented in the resonance form.

---

that places an anion at the carbon that was formerly the aldehyde (the acyl anion equivalent) and is the key to the *umpolung* reactivity observed in these reactions.

![Chemical Structure](image)

**Figure 1.1.2. Mechanism of benzoin and Stetter reactions.**

During the course of the study of Stetter-type reactions, a pathway distinct from typical acyl anion reactivity was discovered. Namely, we found that aldehyde 1 bearing a phenol at the α-position did not participate in normal Stetter reactivity but rather through an internal redox process wherein the α-leaving group is eliminated and the aldehyde is converted to an acetyl group in the product 2 (eq 5).  

---

This reactivity can be explained by examination of the Breslow intermediate I (Figure 1.1.3). When a leaving group such as phenol is present, the nucleophilic alkene, rather than attack an electrophile in a bimolecular process, can unimolecularly eliminate the leaving group to furnish nucleophilic enol II. This enol tautomerizes to an activated carboxylate, acyl azolium III, which upon displacement with a suitable nucleophile such as an alcohol regenerates the catalyst and gives the observed product.10

Figure 1.1.3. Mechanism of NHC-redox esterification.

This reaction manifold was first discovered with cyanide by Wallach (eq 6)\(^{11}\) and has been applied by our group and others to facilitate the formation of a variety of products from simple esters, amides, and carboxylic acids to numerous heterocycles and carbocycles.\(^{12}\) For instance, \(\alpha\)-chloro and \(\alpha\)-bromoaldehydes can be converted to saturated ester products 3 (Equation 7).\(^{13}\) This family of reactions is characterized by concomitant reduction at the \(\alpha\)-position and oxidation at the carbonyl and is commonly referred to as NHC-redox.

\[
\text{Wallach (1873):} \\
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{Cl} \quad \text{H} \\
\text{H} \quad \text{Cl} \\
\text{aq. KCN}
\end{array} \\
\begin{array}{c}
\text{OH} \\
\text{Cl} \quad \text{Cl}
\end{array}
\]

\[
\text{(6)}
\]

\[
\text{Rovis (2004):} \\
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{X}
\end{array} \\
\begin{array}{c}
\text{H} \\
\text{BF}_{4}^{-}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \quad \text{N} \quad \text{Ph} \\
\text{Et}_3\text{N}, \text{ROH} \text{, PhMe}
\end{array} \\
\text{R}\text{O}\text{H} \text{R}^{1}
\]

\[
\text{(7)}
\]

55-99 %

In a related example, \(\alpha,\beta\)-unsaturated aldehydes can also be converted to saturated esters 4 by treatment with a benzimidazolium 5 and base in the presence of an alcohol (eq 8).\(^{14}\) This reaction occurs by addition of the active carbene to the aldehyde, forming the Breslow intermediate I (Figure 1.1.4). The presence of an olefin in conjugation with the nucleophilic alkene makes it possible for the Breslow intermediate to react in a vinylogous fashion with an exogenous electrophile, proton in the simplest cases. Substitution at the \(\beta\)-position leads to enol II which can tautomerize to the acyl azolium III. This is intercepted by a nucleophile to give the observed products.

\(^{11}\) Wallach, O. Annalen 1873, 6, 114-119.


This alternative umpolung has been termed “homoenolate” reactivity because this position in the α,β-unsaturated aldehyde would be normally considered electrophilic, and it is transformed into a nucleophile. This catalytic pathway has been studied by a number of groups, and can lead to a variety of carbon-carbon bond formations to give oxygen heterocycles,15 nitrogen heterocycles,16 and carbocycles.17
Figure 1.1.4. Homoenolate reactivity.

The scope of the NHC-redox reaction was extended to amines in 2007.\textsuperscript{18} Using a catalytic amount of triazolium 3b and 7-aza-1-hydroxybenzotriazole (HOAt), our group demonstrated that α-chloroamide products 6 can be prepared from a variety α,α-dichloroaldehydes 7 (Figure 1.1.5). This reaction constitutes a waste-reduced, greener alternative to traditional peptide bond forming reactions which commonly use at least one reagent in stoichiometric amount.\textsuperscript{19} Furthermore, α,β-epoxy and α,β-aziridinyl aldehydes can be elaborated to β-hydroxy 8 and β-amino amides 9, respectively, in excellent diastereoselectivity. Saturated amides 10 can also be formed from α,β-unsaturated aldehydes. Using chiral triazolium 11a, enantioselective formation of α-chloroamide


6a was also demonstrated, but the enantioselectivity of this reaction is modest (eq 9). The reasons for this low selectivity will be discussed in a later section.

\[
\begin{array}{cccc}
\text{R} & \text{O} & \text{Cl} & \text{HOAt} (20 \text{ mol }\%) \\
+ \text{NHR}_1\text{R}_2 & \text{Et}_3\text{N} (1.2 \text{ equiv}) & \text{t-BuOH} (1.0 \text{ equiv}) & \text{THF, } 25 \text{ °C}
\end{array}
\]

\[
\begin{array}{cccc}
\text{R} & \text{O} & \text{Cl} & \text{BnNH}_2, \text{Et}_3\text{N} \\
\text{Me} & \text{Et}_3\text{N} & \text{THF, } 25 \text{ °C} & 72-89\%
\end{array}
\]

\[
\begin{array}{cccc}
\text{Ph} & \text{O} & \text{N} & \text{Bn} \\
\text{Me} & \text{Et}_3\text{N} & \text{THF, } 25 \text{ °C} & 86\% >19:1 \text{ dr}
\end{array}
\]

\[
\begin{array}{cccc}
\text{Cl} & \text{Cl} & \text{N} & \text{BnNH}_2, \text{Et}_3\text{N} \\
\text{Ph} & \text{O} & \text{Me} & \text{BF}_4^{-}
\end{array}
\]

Figure 1.1.5. Selected NHC-redox amidation results.

Since the initial reports by our group and the group of Jeffrey Bode,\textsuperscript{18b} many related applications of the NHC-redox amidation have appeared,\textsuperscript{20} including an example used in total synthesis.\textsuperscript{21} Continued interest in the area speaks to the potential of the NHC-redox manifold, and this chapter will describe my efforts to further expand the scope of this versatile reaction type.


1.2. Examination of carbon nucleophiles in the NHC-redox manifold

When my work began on this project, alcohols\textsuperscript{12,13} and amines\textsuperscript{17} had been demonstrated as competent nucleophiles in this reaction manifold to form ester and amide products. Additionally, a number of NHC-catalyzed cycloadditions and annulation reactions of \(\alpha\)-reducible aldehydes to form carbon-carbon bonds had also been demonstrated,\textsuperscript{14-16} but none of these methods resulted in a carbon-carbon bond forming at the carbonyl of the reducible aldehyde (Figure 1.2.1).

![Diagram of transformations of reducible aldehyde substrates](image)

**Figure 1.2.1.** Representative transformations of reducible aldehyde substrates circa 2007.

We sought to expand the scope of this reaction manifold to include carbon nucleophiles, which could intercept the acyl azolium III (Figure 1.1.3) to provide ketones from aldehydes in a single step. Furthermore, this catalytic process could potentially be rendered asymmetric. However, the propensity of many carbon nucleophiles to add directly to aldehydes presented a significant challenge. Phosphorus ylides, enolates, and allylmetals all resulted in direct addition,
giving olefin products in the case of ylides and alcohol products in the others. No desired ketone product could be detected under any of these conditions, limiting our possible solutions to the problem of carbon nucleophiles to the acyl azolium (Figure 1.2.2).

![Figure 1.2.2. Attempted carbon nucleophile additions.](image)

One enol nucleophile was found to be effective at displacing the acyl azolium without significant direct addition to the aldehyde: cyclohexanedione (13). Under standard conditions using cinnamaldehyde 12 as the α-reducible aldehyde with diisopropylethylamine as the base, triketone 14 could be isolated in modest yield (eq 10). Attempts to optimize this reaction were made by screening solvent and base (Table 1.2.1), but conditions could not be identified to provide the triketone in greater than 55% yield. The mass balance in each of these reactions was made up of hydrocinnamic acid 15, which could come from hydrolysis of the acyl azolium or from O-acylation of cyclohexanedione to give ester 16, which upon workup would be expected to hydrolyze to the same product. Neither vigorous drying of the reaction vessel nor addition of excess aldehyde reduced the amount of this product; therefore, we hypothesized that O-acylation was the issue.

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22 This discovery was made by my colleague Stephen Lathrop while investigating another NHC-catalyzed reaction. The carbon addition product was found as a side product in his reaction.
With the goal of preventing $O$-acylation, we looked to methods for selective $C$-acylation of enolate nucleophiles. Particularly, we thought that a benzotriazole amide might be an effective acylating reagent for a carbon nucleophile under the NHC-redox reaction conditions, as Katritzky and others have demonstrated this kind of intermediate as a selective $C$-acylating reagent for enolates.\textsuperscript{23} Acylbenzotriazole 17 is prepared in good yield from cinnamaldehyde (Figure 1.2.3) and subsequent reaction with acetophenone under soft enolization conditions gives $\beta$-diketone 18 in 53\% yield. However, combining these two reactions into a single pot proved unsuccessful. When the reaction is conducted with all reagents present from the start, aldol

product 19 is obtained, and when 17 is prepared stoichiometrically and the acetophenone enolate is added slowly to that reaction mixture, no \( \beta \)-diketone 18 is obtained.

**Figure 1.2.3. Acylbenzotriazole as a selective C-acylation reagent.**

Another possible way to circumvent direct addition might be to couple the NHC-redox esterification reaction with a transition metal catalyzed acyl coupling. Since the first report of acid chlorides as suitable partners in the Stille coupling,\(^{24}\) a number of other acyl electrophiles, including acyl fluorides,\(^{25}\) anhydrides,\(^{26}\) thioesters\(^{27}\) and certain esters\(^{28}\) have been demonstrated in cross couplings to give ketone products. We were particularly interested in the precedent involving esters and thioesters (eqs 11-14) because the NHC-redox reaction manifold had also


been demonstrated to furnish these products efficiently.\textsuperscript{12-13} We were aware, however, that NHCs are good ligands for many of the transition metal catalysts employed for these reactions,\textsuperscript{29} but despite this fact, a number of examples of transition metal catalyzed processes in the presence of non-coordinated NHCs have been reported.\textsuperscript{30} Furthermore, the NHCs used as ligands for transition metals are considerably more Lewis basic that the electron deficient triazolium-derived carbenes we have used to catalyze the NHC-redox reaction.

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{S} \text{Et} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R} \text{ZnI} \\
PdCl_2(PPh_3)_2 \\
\text{THF or PhMe} \\
\end{array} \\
\begin{array}{c}
\text{R} \text{R}_1 \\
\text{50-99\%} \\
R_1 = \text{alkyl, aryl} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{S} \text{Ar} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R}_1 \text{B(OH)}_2 \\
Pd_{db}a_3, TFP \\
\text{CuTC} \\
\text{THF, 50 °C} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R} \text{R}_1 \\
\text{52-93\%} \\
R_1 = \text{aryl, vinyl} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{PhB(OH)}_2 \\
\text{Pd(OAc)}_2, PPh_3 \\
dioxane, 50 °C \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R} \text{Ph} \\
\text{68-97\%} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{PhB} \\
\text{O} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R}_3 \text{(CO)}_{12} \\
\text{PhMe, 140 °C} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{R} \text{Ph} \\
\text{41-83\%} \\
\end{array}
\end{equation}

Because reactive organometallic reagents had been found to add directly to the aldehyde substrates (\textit{vide supra}), we knew a mild nucleophile would be necessary for a successful co-catalytic process. A palladium-catalyzed cross coupling of aryl thioesters with boronic acids is known (eq 12).\textsuperscript{25f} I prepared thioester 20 from cinnmaldehyde under standard NHC-redox conditions and reproduced the cross coupling to give hydrochalcone 21 (Figure 1.2.4).


\textsuperscript{30} (a) 
Unfortunately, when the two process were conducted in the same reaction flask, no desired ketone products were obtained. There are many possibilities as to why this reaction fails in one pot. The most likely is that the carbene and transition metal coordinate in such a way to prevent one another from acting as an efficient catalyst.

Figure 1.2.4. Redox thioesterification and subsequent cross coupling.

Alternatively, we considered an NHC-redox esterification with pyridinecarbinol 22 and tandem cross coupling as a suitable reaction pair. I prepared pyridinecarbinol ester 23 which Chatani has reported in a ruthenium-catalyzed cross coupling with aryl boronic esters (eq 14). This ester was then treated under Chatani’s conditions to give dihydrochalcone 21 in comparable yield to the literature. After screening conditions to combine these reactions in one pot, I found that while the redox esterification with triazolium 3b is effective in the presence of ruthenium, the desired ketone product 21 can only be obtained when the reaction is run under an atmosphere of carbon monoxide (eq 15, Table 1.2.1). However, the yield of the reaction reflects a single turnover of ruthenium. This suggests that even the electron deficient NHC derived from 3b deactivates the ruthenium catalyst, and a catalytic process is not feasible.
Table 1.2.2. One-pot redox esterification and cross coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>3b (mol %)</th>
<th>Ru$<em>3$(CO)$</em>{12}$ (mol%)</th>
<th>Atm</th>
<th>Conversion to 23</th>
<th>Yield of 21 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>Ar</td>
<td>complete</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10</td>
<td>Ar</td>
<td>incomplete</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>5</td>
<td>CO</td>
<td>trace</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5</td>
<td>CO</td>
<td>incomplete</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>CO</td>
<td>complete</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>7.5</td>
<td>CO</td>
<td>incomplete</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>7.5</td>
<td>10</td>
<td>CO</td>
<td>complete</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>7.5</td>
<td>12.5</td>
<td>CO</td>
<td>complete</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>13</td>
<td>CO</td>
<td>complete</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>13</td>
<td>Ar</td>
<td>complete</td>
<td>0</td>
</tr>
</tbody>
</table>
1.3. Development of an operationally simple NHC-redox amidation procedure

At this point, the amidation of α-reducible aldehydes in the co-catalytic process developed by my colleague Harit Vora was revisited. At its inception, this reaction was envisioned to proceed as the earlier esterification had: by catalytic generation of an acyl azolium which could be intercepted by the nucleophilic amine. However, implementation of similar conditions was frustrated by the propensity of the amine to condense on the aldehyde to form an imine 24 (eq 16). This process was non-reversible under the reaction conditions; therefore, a modification was necessary. Namely, slow addition of the amine via syringe pump in the presence of catalytic HOAt or other acyl transfer reagents to accelerate the acylation process enabled the coupling of amines with α-reducible aldehyde substrates to give amide products in excellent yield (Figure 1.1.5). Both of these measures were necessary for efficient reactions; however, with the convenience and simplicity of this method in mind, we would prefer that slow addition was not necessary.

Mechanistically, this reaction is proposed to begin with attack of the carbene on the aldehyde followed by proton transfer to give the Breslow intermediate I. Then, the NHC-redox pathway ensues (Figure 1.1.3 or 1.1.4) to give the acyl azolium. Though it is highly efficient at acylating alcohols, the acyl azolium does not react efficiently with amines to give amide products.\(^{31}\) Rather, HOAt intercepts the acyl azolium to liberate the free carbene and give the

---

activated ester IV, which is subsequently attacked by the amine to displace HOAt and give the observed amide product 25.

Figure 1.3.1. Proposed co-catalytic cycle for NHC-redox amidation.

Although this work provided a general procedure for the amidation of a variety of α,α-dichloroaldehydes, α,β-epoxyaldehydes and α,β-unsaturated aldehydes, we sought a more convenient and robust method. Namely, we wished to eliminate the need for slow addition of the amine as we saw this as a procedural inconvenience. Early investigation by Dr. Vora into the acylation of amino esters revealed that alkylammonium chloride salts do not lead to imine
formation under the reaction conditions. The overall yield of these reactions was low, but it seemed that a door to an alternative to dropwise addition had opened.

After a number of conditions were screened using 12 and glycine methyl ester hydrochloride (26) as the substrates, we found that tertiary amine bases in toluene gave the best yields of amide product 27a with triazolium 3a (eq 17, Table 1.3.1). Catalyst screening revealed that trichlorophenyl-substituted 3b was also competent in the reaction, and it was noted that this catalyst gave cleaner crude reactions (eq 18, Table 1.3.2).

![Reaction Scheme](image)

Table 1.3.1. Solvent screening for NHC-redox amidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conc.</th>
<th>Yield</th>
<th>Entry</th>
<th>Solvent</th>
<th>Conc.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0.1M</td>
<td>&lt;20%*</td>
<td>5</td>
<td>CH₃CN</td>
<td>0.1M</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>0.1M</td>
<td>&lt;20%*</td>
<td>6</td>
<td>toluene</td>
<td>0.1M</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>ether</td>
<td>0.1M</td>
<td>trace</td>
<td>7</td>
<td>toluene</td>
<td>0.05M</td>
<td>23%</td>
</tr>
<tr>
<td>4</td>
<td>dioxane</td>
<td>0.1M</td>
<td>trace</td>
<td>8</td>
<td>toluene</td>
<td>0.025M</td>
<td>17%</td>
</tr>
</tbody>
</table>

* Although product is formed, crude ¹H-NMR showed significant impurities and imine formation

![Reaction Scheme](image)

Table 1.3.2. Catalyst screening for NHC-redox amidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>0%*</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>0%*</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>0%*</td>
</tr>
</tbody>
</table>

* No desired reaction observed after 24h. Aldehyde is decomposed completely.

A temperature and concentration screen revealed that heating to 70 °C at 0.05M with 3c as the precatalyst gave the best results, but hydration of the acyl azolium intermediate to give
hydrocinnamic acid (15) represented a large portion of the reaction mixture (eq 19, Table 1.3.3).

Triazolium 3c also displayed the most favorable yields and ratio of 27a to 15.

\[
\begin{array}{c}
\text{Ph} \quad \text{H} \\
\text{Ph} \quad \text{N} \\
\text{O} \\
\text{OMe} \\
3b \text{ or } 3c (20 \text{ mol\%}) \\
\text{PhMe} \\
\end{array}
\]

\[
\text{Ph} \quad \text{H} \\
\text{Ph} \quad \text{N} \\
\text{O} \\
\text{OMe} \\
\text{Ph} \quad \text{OH} \\
27a \\
\]

\[
\text{PhMe} \\
(19)
\]

Table 1.3.3. Temperature and concentration screen for NHC-redox amidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield of 27a</th>
<th>27a:15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td>0.05M, 23 °C, 12h</td>
<td>23%</td>
<td>3.2:1</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>0.1M, 23 °C, 12h</td>
<td>32%</td>
<td>4.9:1</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>0.05M, 70 °C, 3h</td>
<td>23%</td>
<td>3.5:1</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>0.1M, 70 °C, 3h</td>
<td>24%</td>
<td>3.1:1</td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>0.05M, 23 °C, 12h</td>
<td>37%</td>
<td>2.1:1</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>0.1M, 23 °C, 12h</td>
<td>31%</td>
<td>1.5:1</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>0.05M, 70 °C, 3h</td>
<td>52%</td>
<td>4.3:1</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>0.1M, 70 °C, 3h</td>
<td>50%</td>
<td>3.6:1</td>
</tr>
</tbody>
</table>

The water necessary to hydrolyze the acyl azolium was presumably being carried in by the hygroscopic amine hydrochloride salt, the drying of which would represent a greater operational challenge than dropwise addition of the amine. Therefore, we screened drying agents and found that the addition of 4Å molecular sieves effectively inhibited hydration. Finally, increasing the equivalents of enal from 1 to 1.5 (eq 20, Table 1.3.4) gave yields in the good to excellent range. Attempts to lower the catalyst loading from 20 mol% led to reduced yield, even when the co-catalyst concentration was increased (eq 21, Table 1.3.5).
Table 1.3.4. Enal equivalents screening for NHC-redox amidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 27a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv 12</td>
<td>59%</td>
</tr>
<tr>
<td>2</td>
<td>1.1 equiv 12</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>1.2 equiv 12</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td>1.3 equiv 12</td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td>1.5 equiv 12</td>
<td>82%</td>
</tr>
</tbody>
</table>

Table 1.3.5. Further screening for NHC-redox amidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>3c (mol %)</th>
<th>HOAt (mol %)</th>
<th>Temp (°C)</th>
<th>Yield of 27a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>20</td>
<td>70</td>
<td>87-93%</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20</td>
<td>70</td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>20</td>
<td>70</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>30</td>
<td>70</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>30</td>
<td>70</td>
<td>82%</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>30</td>
<td>70</td>
<td>69%</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>20</td>
<td>23</td>
<td>64%</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>20</td>
<td>23</td>
<td>41%</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>30</td>
<td>23</td>
<td>59%</td>
</tr>
</tbody>
</table>

With optimal conditions in hand, the scope of the reaction was explored. Both secondary and primary amines are tolerated to give tertiary and secondary amide products (Figure 1.3.3). Cinnamaldehydes bearing both electron withdrawing and electron-releasing groups are tolerated, as are a number of aliphatic enals. It was noted, however, that aliphatic enals react more efficiently when 1-hydroxybenzotriazole (HOBt) is used as the acyl transfer reagent. Protected alcohols are tolerated, albeit in reduced yield. Enals bearing α-substitution are unreactive except when an electron withdrawing group is present at the β-position. This observation is consistent with that of the Bode group, and is likely due to allylic strain that would be necessary for the vinylogous Breslow intermediate (homoenolate) to protonate at the β-position (Figure 1.3.4).
We sought to understand the success of these reactions by elucidating the role of the hydrochloride salt. One hypothesis could be that the presence of a nonpolar proton source accelerates the protonation of extended Breslow intermediate II at the β-position to give enol III (Figure 1.1.4). However, when 1 equivalent of diisopropylethylammonium chloride is added to the reaction mixture along with an equivalent of benzylamine, imine formation still occurs, and slow degradation of cinamaldehyde is observed. Based on a reexamination of solvents for this reaction (eq 22, Table 1.3.6), we propose that a phase-transfer mechanism is operative. Solubility plays an integral role in product selectivity. In more polar solvents, faster equilibration of the excess diisopropylethylamine with the hydrochloride salt would be expected, resulting in high concentration of free amine in solution and therefore rapid imine formation. In THF, for
instance, imine formation is not observed at room temperature (entry 4), but it is the major product at 70 °C (entry 3). We attribute this change to the rapid dissolution of the ammonium salt, leading to rapid deprotonation in solution and condensation of the free amine onto the aldehyde. In solvents where the ammonium salt is less soluble, the tertiary amine base must react with the solid ammonium salt under biphasic conditions, resulting in phase transfer controlled release of the amine free base into solution. This effectively simulates dropwise addition without the need for a syringe pump.

![Chemical structure](image)

**Table 1.3.6. Reexamination of solvent effects.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp, Time</th>
<th>Yield</th>
<th>Entry</th>
<th>Solvent</th>
<th>Temp, Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>70 °C, 3h</td>
<td>93 %</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>23 °C, 12h</td>
<td>33 %</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>23 °C, 12h</td>
<td>64 %</td>
<td>6</td>
<td>MeCN</td>
<td>70 °C, 3h</td>
<td>85 %</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>70 °C, 3h</td>
<td>33 %</td>
<td>7</td>
<td>MeCN</td>
<td>23 °C, 12h</td>
<td>68 %</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>23 °C, 12h</td>
<td>82 %</td>
<td>8</td>
<td>MTBE</td>
<td>23 °C, 12h</td>
<td>7 %</td>
</tr>
</tbody>
</table>

These heterogeneous reactions are sufficiently rapid at 70 °C such that they are complete within 3h, and with the addition of molecular sieves to the reaction mixture, no pretreatment of any of the reagents is required. Co-catalysts HOAt and HOBt are used directly as received, and the enals are not distilled prior to use. Therefore, this method represents a significant step toward the robustness and procedural simplicity we envisioned.

We thought it might be possible to pre-mix the solid catalyst and co-catalyst, further simplifying the procedure. Ideally, the base would also be present in this pre-mixed reagent mixture such that a researcher could weigh out only an α,β-unsaturated aldehyde substrate, an amine hydrochloride and the reagent mixture, stir them at an appropriate temperature and isolate an amide product. To achieve this goal, a sampling of solid bases were screened, and *N,N-*
dimethyl-4-aminopyridine (DMAP) was found to be optimal (eq 23, Table 1.3.7). The base, triazolium and HOAt were weighed in appropriate ratio, ground in a scintillation vial, slurried in hexanes, stirred and dried to give a light brown solid. This solid was then tested in a battery of previously studied amidation reactions and found to perform comparably to the standard conditions (Figure 1.3.5). It should be noted, when DMAP is used as the base under the normal amidation conditions, inferior yields are observed without the addition of HOAt. Therefore, the HOAt is necessary for optimal yields.

\[
R\overset{\text{3c (20 mol%)}}{\text{\text{O}}^{\text{HOAt (20 mol %)}}}\overset{\text{Base, 26 \text{PhMe, 4Å M.S}}}{\text{\text{+H}}^{\text{27a}}\text{CO}_2\text{Me}} \tag{23}
\]

Table 1.3.7. Solid base screen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp, Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOAc</td>
<td>70 °C, 4h</td>
<td>20 %</td>
</tr>
<tr>
<td>2</td>
<td>NaOAc</td>
<td>23 °C, 16h</td>
<td>30 %</td>
</tr>
<tr>
<td>3</td>
<td>NaOBz</td>
<td>23 °C, 16h</td>
<td>27 %</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOK</td>
<td>23 °C, 16h</td>
<td>16 %</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>23 °C, 16h</td>
<td>59 %</td>
</tr>
<tr>
<td>6</td>
<td>DMAP</td>
<td>23 °C, 16h</td>
<td>68 %</td>
</tr>
<tr>
<td>7</td>
<td>DMAP</td>
<td>70 °C, 4h</td>
<td>89 %</td>
</tr>
</tbody>
</table>

\[
R\overset{\text{Redox-Amide Mix (RAm-mix)}}{\text{\text{N}}^{\text{R'}\text{NH}_3\text{Cl, 4Å M.S}}}\text{PhMe, 70 °C, 4h}} \overset{\text{\text{+Ph}}}{\text{\text{N}}^{\text{CO}_2\text{Me}}} \overset{\text{\text{O}}}{\text{\text{NMe}}} \overset{\text{\text{O}}}{\text{\text{NMe}}} \overset{\text{\text{NCO}_2\text{Me}}}{\text{\text{O}}^{\text{Ph}}} \overset{\text{\text{NMe}}}{\text{\text{NCO}_2\text{Me}}} \overset{\text{\text{NMe}}}{\text{\text{NCO}_2\text{Me}}} \overset{\text{\text{Bn}}}{\text{\text{NCO}_2\text{Me}}} \overset{\text{\text{O}}}{\text{\text{NMe}}} \overset{\text{\text{OMe}}}{\text{\text{NCO}_2\text{Me}}} \overset{\text{\text{OMe}}}{\text{\text{NCO}_2\text{Me}}} \overset{\text{\text{Ph}}}{\text{\text{NCO}_2\text{Me}}}
\]

* Stirred 16h at 70° C to obtain complete conversion

Figure 1.3.4. Redox-amide mix reactions.

In summary, the use of amine hydrochloride salts in the NHC-redox amidation overcomes the procedural limitation of slow addition. Furthermore, the solid reagents can be
weighed, mixed and stored together, making it possible to reduce the number of operations necessary to conduct the reaction even further. As it stands, a synthetic chemist wishing to perform an NHC-redox amidation would, in principle, need only weigh 4Å mol. sieves, an amine hydrochloride and the solid redox-amide mix (RAm-mix) into a reaction vessel, then add a solution of the desired aldehyde and stir for an appropriate period. We hope this brings the NHC-redox amidation closer in terms of practicality to more traditional peptide bond couplings and encourages the wider use of this catalytic amide bond formation.
1.4. Development of an asymmetric NHC-catalyzed preparation of α-fluoroamides

Included in our 2007 report\textsuperscript{18a} of NHC-redox amidation was a single asymmetric reaction generating an α-chloro amide in 80% ee (Section 1.1, eq 9). The modest selectivity was probed by a series of studies using deuterium labeled aldehyde starting materials in which Dr. Vora observed complete loss of α-deuteration over the course of the reaction (eqs 24 and 25).\textsuperscript{32} This, combined with the observation that enantioenriched product does not epimerize under the reaction conditions led us to invoke the tautomerization of II and III catalyzed by base, leading to epimerization of the newly installed stereocenter (eq 26).

Dr. Vora applied this hypothesis to develop an NHC-catalyzed hydration to give α-chloro and α-fluoro carboxylic acids in high enantioselectivity (eqs 27 and 28).\textsuperscript{33} To overcome the problem of epimerization, he employed an inorganic base and biphasic conditions leading to low


effective concentration of base in the organic layer and minimal epimerization of the acyl azolium. We thought that the method I developed, employing amine hydrochloride salts insoluble in the nonpolar solvent, might mimic these conditions and allow for a highly enantioselective amidation. Furthermore, the demonstration of \( \alpha \)-fluoroenals as the \( \alpha \)-reducible aldehyde component in the hydration opens the door to valuable enantioenriched \( \alpha \)-fluoroamides from readily available materials in a single, organocatalytic step (eq 29).

Fluorine is a unique and highly valuable element to chemists in many fields. Its high electronegativity and small size make it capable of strong polar interactions that can dramatically influence the physical and chemical properties of organic molecules.\(^{34}\) For instance, substitution of fluorine for hydrogen can modulate bioavailability, lipophilicity, conformation, and metabolic

stability of a drug candidate.\textsuperscript{35} However, practical access to fluorinated compounds is limited, and considerable effort has been invested in the development of mild reactions capable of forming carbon-fluorine bonds.\textsuperscript{36} A handful of examples of enantioselective installation of sp\textsuperscript{3}-fluorine substituents have been demonstrated (Fig 1.4.1),\textsuperscript{37} but the direct catalytic, asymmetric preparation of α-fluoroamides is a significant challenge that has only very recently been addressed (Fig 1.4.2).\textsuperscript{38} Although our approach would not constitute a fluorination \textit{per se}, we felt α-fluoroenals were a sufficiently simple and inexpensive source of a carbon-fluorine bond, and the fact that this position could be protonated asymmetrically to form a fluorine stereocenter makes the potential value of the products extremely high.

Figure 1.4.1. MacMillan’s catalytic asymmetric fluorination of aldehydes

Figure 1.4.2. Lectka’s asymmetric fluorination of acid chlorides

The preparation of the α-fluoroenal starting materials we envisioned as suitable precursors to α-fluoroamides is fairly straightforward from fluorinated Horner-Wadsworth-


Emmons reagent 28. Under strongly basic conditions, the $\alpha$-fluoro-$\alpha,\beta$-unsaturated ester 29a is obtained in excellent yield and $>19:1$ selectivity for the $E$-isomer (Figure 1.4.3).\textsuperscript{39} Reduction to the allylic alcohol 30a followed by oxidation with IBX provides the $\alpha$-fluoroenal 31a in good yield.

![Figure 1.4.3. Preparation of $E$-$\alpha$-fluoroenal 31a.](image)

The $E$-$\alpha$-fluoroenal was subjected to the reaction conditions with a variety of chiral triazolium precatalysts (Figure 1.4.4). The aminooindanol scaffold was found to outperform the phenylalanine scaffold in terms of both enantioselectivity and yield. To our satisfaction, enantioselectivity exceeding 90% ee was observed with trichlorophenyl substituted triazolium 11c; however, yields were poor (20-40%).

We thought the alkene geometry in the α-fluoroenal might play a role in the homoenolate protonation step and therefore affect catalyst turnover,\(^{40}\) so the Z-α-fluoroenal was synthesized by changing the conditions for the Horner-Wadsworth-Emmons reaction. Under soft enolization conditions at elevated temperature (Figure 1.4.5), the Z isomer of \(29a\) is obtained in 10:1 selectivity (Table 1.4.1). This change in selectivity can be attributed to the reversibility of the initial addition of the ylide to the aldehyde, allowing for the thermodynamic product to be formed under the reaction conditions.

The Horner-Wadsworth-Emmons reaction was combined with the reduction to the fluoroalcohol in one pot and used to prepare a number of Z-α-fluorenals in varying yields and diastereoselectivity (\(31a-f\), Table 1.4.1). In particular, aromatic fluoroesters \(29a-d\) can be obtained in high selectivity while aliphatic fluoroesters \(29e\) and \(29f\) are obtained in 1:1 dr. Aryl

substituted products also proved separable by chromatography; therefore, they were isolated at the alcohol stage as single diastereomers while the aliphatic substrates were carried on as an inseparable mixture of olefin isomers.

Figure 1.4.5.

Table 1.4.1.

<table>
<thead>
<tr>
<th>R = Fluoroester</th>
<th>Fluoroester dr</th>
<th>Yield of 30</th>
<th>Yield of 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>29a</td>
<td>10:1</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29b</td>
<td>7:1</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2N</td>
<td>29c</td>
<td>2:1</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>29d</td>
<td>3:1</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29e</td>
<td>1:1</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBSO</td>
<td>29f</td>
<td>1:1</td>
<td>66%</td>
</tr>
</tbody>
</table>

The reaction of Z-α-fluoroenal 31a with glycine methyl ester hydrochloride catalyzed by triazolium 11c was retried, and the yield improved in comparison to the reaction of the E isomer. Further screening of bases revealed that weak acetate bases performed favorably, giving excellent yield and comparable selectivity (Figure 1.4.4). Increasing sterics on the base gave improved enantioselectivity, up to 95% ee in the case of sodium pivalate. These two trends
suggest that epimerization is still an issue when an amine base is used, and that the conjugate acid of the chosen base plays a role in the enantiodetermining step (\textit{vide infra}).

![Reaction diagram]

\begin{align*}
31a & \xrightarrow{\text{Base (1.5 equiv)}} 32a \\
\text{PhMe, 4Å MS} & \text{11c (20 mol\%)} \text{ HOAt (20 mol\%)} \\
63 \%, 90 \% \text{ ee} & 78 \%, 82 \% \text{ ee} \quad 33 \%, 88 \% \text{ ee} \quad 48 \%, 90 \% \text{ ee}
\end{align*}

\textbf{Figure 1.4.6. Base screening.}

With these optimized conditions in hand, a scope of amine hydrochloride salts nucleophiles was explored. Both primary and secondary alkyl amines are suitable, as is $N,O$-dimethylhydroxylamine to give the Weinreb amide (Figure 1.4.7). The $\alpha$-fluoroenal scope includes aliphatic substitution at the $\beta$-position as well as both electron rich and electron poor aromatic substitution. When L-alanine methyl ester hydrochloride is subjected to the reaction conditions, the resultant amide is obtained as a 97:3 mixture of diastereomers.
We propose that this reaction proceeds through the following mechanism (Figure 1.4.8). Generation of enol II as in previous examples is followed by the enantiodetermining tautomerization to III. The identity of the proton source in this step is crucial, as a significant effect of the size of base used is observed. Larger bases, such as sodium pivalate, lead to greater discrimination of III with respect to facial approach (Fig 1.4.6). Enantioselectivity does change with amine nucleophile, indicating that some of the proton transfer in the tautomerization of II to III is mediated by the amine (or its hydrochloride salt). Additionally, the reversibility of this tautomerization is still an issue when stronger bases are used, leading to lower enantioselectivity (Fig 1.4.6).

Based on our mechanistic hypothesis, the fluorine stereocenter is set before the acyl azolium is displaced by HOAt. The resultant α-fluoroester is intercepted by the amine to give the observed α-fluoroamide product. Thus, the only chiral information on the active acylating
reagent is the fluorine stereocenter. While the stereoelectronic impact of a fluorine stereocenter can be significant in many cases, fluorine is isosteric with hydrogen and should have no steric impact on the approach of a nucleophile to α-fluoroester IV. Therefore, it seemed feasible that IV might acylate either enantiomer of a chiral amine at a similar rate. If this were the case, either enantiomer of catalyst would lead to opposite diastereomers of the α-fluoroamide product in similar selectivity.

Figure 1.4.8. Proposed mechanism of asymmetric NHC-catalyzed fluoroamide preparation.

Indeed, we found that chiral primary amines can be elaborated to either diastereomer of α-fluoroamide products 32. Using either (+) or (-)-11c, L-phenylalanine methyl ester hydrochloride can be acylated to give the syn or anti diastereomer in good yield and excellent selectivity (Figure 1.4.9). Similarly, either enantiomer of phenethylamine hydrochloride can be acylated with (-)-11c in excellent selectivity. The small difference in selectivity for each diastereomer of these products again implicates the amine (or its hydrochloride) as a proton source for the enantiodetermining tautomeriazation (vide supra). Here, a minimal match/mismatch between the two diastereomeric transition states is observed.

Figure 1.4.9.

The fluoroamide products furnished by this protocol are suitable precursors to a number of other interesting fluorinated motifs. Tertiary amide 32b can be reduced with lithium aluminum hydride to the corresponding tertiary amine 34 in good yield and retention of enantioenrichment (eq 30).
Additionally, Weinreb amide 32c can be doubly alkylated to fluorohydrin 35 in good diastereoselectivity and no appreciable erosion of enantioenrichment (Figure 1.4.10). Hydride additions to similar α-fluoroketones have been studied, with varying results for facial selectivity. Contrary to our belief that the Ahn-Eisenstein model would correctly predict the stereochemical outcome of the addition to α-fluoroketone 36, the observed diastereomer contains an anti relationship of the fluorine and hydroxyl groups, confirmed by conversion of 35 to epoxide 37 wherein a correlation between the benzyl and methyl protons is observed. This reflects either a traditional Felkin model in which the σ* of the C-F bond is not taken into account when determining the “large” substituent or approach of the nucleophile from the least hindered face of a lithium chelate per the Cram-chelate model. Based on Flowers and coworkers observation of a titanium chelate by 19F-NMR in the diastereoselective reduction of α-fluoroketones, the Cram-chelate model is the best explanation for this selectivity.

Figure 1.4.10. Double alkylation of Weinreb amide and models for addition to $\alpha'$-fluoroallyl ketone

Other double alkylations were also investigated, each giving poorer selectivity than the above transformation (Fig 1.4.11). The addition of titanium tetrachloride as per the reduction reported by Flowers and coworkers does lead to enhanced diastereoselectivity; however, epimerization of the fluoroketone is also observed. When butyllithium is used in the first alkylation, almost no diastereoselectivity is observed in the second step, suggesting the presence of magnesium is necessary. However, when methyllithium and allyl Grignard are added in the opposite order, only 70:30 selectivity is observed. This is an interesting problem; however, it is unclear how useful a detailed study of the preparation of fluorohydrins from the Weinreb amide would prove. Therefore, further investigation was not pursued.

Figure 1.4.11. Other conditions for the double alkylation with varying selectivity.
1.5. Simultaneous kinetic resolution of racemic secondary amines

Among the current developments within the field of NHC-catalysis, we were particularly interested in the kinetic resolution of secondary amines reported by Bode and coworkers. When chiral hydroxamic acid co-catalyst 38 is used in the NHC-redox amidation of 2-methylpiperidine 39 with hydroxyketone 40, the amide product 41 is obtained in 57% yield and 70% ee, corresponding to an $k_{rel}$ of 18 (eq 31). This resolution coupled with the enantioselective protonation demonstrated by our group (Section 1.4) would control stereocenters on either side of a newly formed amide bond, a transformation that is currently unknown. Based on our finding that either enantiomer of phenethylamine is acylated in nearly identical selectivity under the amidation conditions leading to α-fluoroamides (vide supra), we believed it should be possible to access any stereoisomer of a given tertiary α-fluoroamide product by changing triazolium and co-catalyst antipode (Figure 1.5.1).

\[ \text{PhOH} + \text{NMe}_2 \rightarrow \text{PhNMe}_3 \]

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To begin, 2-methylpiperidine hydrochloride 42 was tested in the NHC-redox amidation. Using our best conditions for the enantioselective protonation (sodium pivalate as the base), 42 was not acylated at room temperature. However, the use of sodium acetate or diisopropylethylamine as the base does afford desired product 43 (eq 32).

Surprisingly, using achiral catalyst 3c under the standard conditions leads to desired product in 4:1 dr (eq 33). This can only be explained by a significant stereoelectronic effect of the fluorine stereocenter in the active acylating reagent, α-fluoroester IV (Figure 1.4.8) that
discriminates between the enantiomers of amine. This effect is also reflected in the results with chiral triazolium 11c (eq 32); however, we found it difficult to rationalize those results quantitatively without detailed kinetic experiments.

We obtained a sample of chiral hydroxamic acid 44, generously donated by the Bode group, and screened conditions for the simultaneous kinetic resolution and α-fluoroamide preparation. When 44 is used in conjunction with triazolium 11c, however, no desired product is obtained, even with additional heat and longer reaction times (eq 34). We attribute the lack of reactivity to the steric demands of tetrahedral intermediate 45 (eq 35). The transition state leading to this catalytic intermediate must be prohibitively high in energy.
By switching to a less sterically demanding triazolium 33, we obtained the desired product with 44 as the co-catalyst (eq 36). Diastereoselectivity is modest, and the enantioenrichment of the major diastereomer is close to that obtained under our optimal NHC-redox amidation conditions (using more sterically demanding 11c as the NHC precursor). The minor diastereomer is enantioenriched with comparable selectivity to that obtained with 33 in the normal amidation reaction (70 % ee, Figure 1.4.4).

As this reaction was optimized, a discovery was made that changed our approach completely. When achiral triazolium 3c is used in the reaction, higher diastereoselectivity is obtained, and the enantioenrichment of the products is comparable to that obtained with 33 (eq 37). This result suggests that the chiral triazolium is doing nothing to control the fluorine stereocenter in these reactions.

We began to consider mechanistic possibilities that could explain the selectivity and arrived at the following hypothesis: under these reaction conditions, epimerization of the acyl azolium III is competitive with the acylation of amine 39 (Figure 1.5.2). If this is so, the
selectivity is determined by the relative rate of acylation of either diastereomer of IV (k₄ vs k₄'). Therefore, the selectivity of the protonation leading to acyl azolium III is irrelevant, and the fluorine stereocenter is resolved dynamically under the reaction conditions.

![Diagram showing reaction rates and products](image)

**Figure 1.5.2.**

If the hydroxamic acid is exerting control over the fluorine stereocenter by the above mechanism, the acylation of any amine by IV should lead to enantioenrichment. To test this, I subjected two achiral amines to the reaction with 44 as the co-catalyst. The results were illuminating. When piperidine hydrochloride is used as the nucleophile, α-fluoroamide 32c is obtained in 40% ee (eq 38), while glycine methyl ester gives 32d in 16% ee (eq 39). The size of the nucleophile relates directly to the enantioenrichment, suggesting that slower acylation leads to a more efficient dynamic kinetic resolution of the fluorine stereocenter. This is consistent with our hypothesis. When 41 is used as the nucleophile, it seems that the effect of the chiral triazolium is completely overridden by this process.
The revelation that the chiral triazolium is not involved in setting the fluorine stereocenter under these conditions led us to reevaluate our strategy. It may be necessary to optimize a new chiral co-catalyst in order to acylate the amine rapidly enough that epimerization does not occur. This project would be suitable for another student in collaboration with Prof. Jeffrey Bode, whose group has synthesized a number of other chiral co-catalysts for the purpose of resolving amines under their NHC-redox amidation conditions. Perhaps the right combination of a less sterically demanding chiral co-catalyst and the inherent effect of the fluorine (observed in experiments without a chiral co-catalyst) will lead to an efficient kinetic resolution.
1.6. Conclusion

Over the course of my study of the NHC-redox reaction manifold, I developed new conditions for the efficient acylation of amine nucleophiles as their hydrochloride salts. These conditions were applied to the development of the first highly selective asymmetric NHC-redox amidation, which furnishes valuable enantioenriched α-fluoroamide products in up to 97% ee. This work also led to early investigation of a simultaneous kinetic resolution and asymmetric NHC-redox amidation protocol, which remains to be studied further. Finally, my exploration into the addition of carbon nucleophiles to the acyl azolium broke new ground, and although I could not develop a practical procedure for the preparation of ketones in the NHC-redox manifold, my results will prove useful for the future exploration of this transformation.
CHAPTER TWO: PROGRESS TOWARD THE TOTAL SYNTHESIS OF OKILACTOMYCIN.

2.1 Introduction

Polyketides are a class of bacterial secondary metabolites with diverse bioactive profiles, ranging from antibiotics\(^\text{47}\) and immunosuppressants\(^\text{48}\) to cardiovascular\(^\text{49}\) and anticancer agents (Figure 2.1.1).\(^\text{50}\) Therefore, there has been great interest in the total synthesis of this class of natural product, which has served as the inspiration for the development of numerous synthetic methods. The most prominent among these is the stereoselective aldol reaction, one of the most studied reactions in the history of organic synthesis.\(^\text{51}\) Starting with R. B. Woodward’s historic synthesis of erythromycin in 1981,\(^\text{52}\) the aldol reaction has found use in nearly every polyketide synthesis published in the last thirty years.\(^\text{53}\)


Rapamycin antifungal, immunosuppressant inhibits human peripheral blood mononucleation (IC$_{50}$ = 1 nM)

Figure 2.1.1. Some polyketide natural products and their biological activities.

Over this period of time, many stereoselective methods have been developed, and among these the Evans auxiliary approach remains the most commonly used.$^{54}$ In this protocol, chiral enolate 46 is reacted with an aldehyde, setting two stereocenters simultaneously under auxiliary control. This method allows for the construction of multiple stereocenters with excellent control and gives products that map directly onto portions of polyketide natural products termed polypropionates (Figure 2.1.2). Biosynthetically, these fragments are constructed by iterative Claisen condensations of propionate subunits as their thioesters by a series of enzymes called polyketide synthases (PKS),$^{55}$ and the aldol method mimics nature’s disconnections.

Figure 2.1.2. Evans auxiliary-controlled aldol reactions.

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In many polyketides, some of the hydroxyl groups are absent, giving rise to substructures termed deoxypolypropionate subunits. These fragments are commonly constructed by an approach related to the Evans aldol, the Myers alkylation. This method also employs a chiral enolate derived from a psuedoephedrine chiral auxiliary and adds an alkyl iodide with stereochemical control making deoxypolypropionates accessible in high selectivity (Figure 2.1.3).

![Figure 2.1.3.](image)

Though both the Evans aldol reaction and Myers alkylation are extremely powerful transformations, there are some drawbacks. In both cases, the chiral auxiliary must be cleaved and several manipulations performed before another iteration can be carried out. Furthermore, these methods (and nature’s) typically stitch together a target only two or three carbon atoms at a time, leaving room for improvement in terms of convergency. In other words, the use of stoichiometric chiral auxiliaries is not ideal for either atom efficiency and step economy.

The issue of atom efficiency can be addressed directly by asymmetric catalysis. For instance, a number of groups have contributed to the development of the catalytic asymmetric Mukaiyama aldol reaction as an alternative to the Evans aldol. The issue of step economy, on

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the other hand, may be addressed by a more convergent strategy for the construction of polyketide fragments. Glutaric anhydride derivatives represent 5-carbon fragments from which the functionality present in many polyketides can be revealed (Figure 2.1.4).

![Figure 2.1.4. Desymmetrization strategy toward polyketide substructures](image)

Figure 2.1.4. Desymmetrization strategy toward polyketide substructures

One such compound, meso-3,5-dimethylglutaric anhydride 48 has been used by many groups as a starting material for deoxypolypropionate subunits. However, these sequences are lengthy and involve stoichiometric resolving agents. For example, in Paquette’s progress toward okilactomycin, 48 is treated with (+)-phenethylamine, reduced with borane and then recrystallized to give amide 49 (Figure 2.1.5). This is closed to lactone 50, giving an enantioenriched intermediate from meso-starting material. However, little complexity has been added to this substrate, and many more steps are necessary to elaborate this lactone to the desired polyketide fragment 51. Therefore, the advantage over traditional iterative methods is minimal.

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Our group has pursued a method for deoxypolypropionate synthesis which addresses the issues of atom efficiency, step economy and convergency: a catalytic, enantioselective desymmetrization of meso anhydrides with organozinc reagents (vide infra). This strategy allows for the introduction of a multiple carbon fragment while simultaneously generating an enantioenriched product, which may be applied to the rapid synthesis of polyketide fragments.

The development of this reaction began with the study of organozinc additions to succinic anhydrides using nickel phosphinooxazoline (PHOX) as the catalyst. Under optimized conditions, ketoacids such as 52 can be prepared in good yield and modest enantioselectivity (Figure 2.1.6). In 2004, we reported an improved catalyst system employing palladium and Josi-Phos to give increased enantioselectivity. A rhodium-catalyzed variant was then applied to the asymmetric total synthesis of the eupomatolone family of natural products.

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Figure 2.1.6. Transition metal catalyzed desymmetrizations of succinic anhydrides.

In 2007, the scope of electrophile was extended to 3,5-dimethylglutaric anhydride using a rhodium-PHOX catalyst system. A variety of organozincs are competent in this reaction, providing enantioenriched 1,3-dimethyl ketoacids in good yield and excellent selectivity (Figure 2.1.7). It should be noted that alkylzincs give consistently higher enantioselectivity than arylzincs. This method represents a general entry to the catalytic, asymmetric synthesis of deoxypolypropionate subunits.

Figure 2.1.7. Rhodium catalyzed desymmetrization of 3,5-dimethyl glutaric anhydride

Our mechanistic proposal for this reaction begins, in the case of rhodium, with transmetalation of the organozinc to generate an alkylrhodium(I) species (Figure 2.1.8). This then undergoes oxidative addition to the anhydride in a stereoselective fashion to give VI,

differentiating the carbonyls of 48 by control of the chiral ligand. This Rh(III) intermediate can then reductively eliminate to form the carbon-carbon bond and generate Rh-carboxylate VII. This Rh(I) then reenters the catalytic cycle, releasing the ketoacid product 53.

![Proposed catalytic cycle](image)

**Figure 2.1.8. Proposed catalytic cycle**

As stated above, this method provides entry to a variety of deoxypolypropionate structures, and we felt it should be applicable to the total synthesis of a number of natural products. One suitable target is okilactomycin (54), a complex polyketide isolated from bacteria found on Zamami Island in Okinawa, Japan. This compound exhibits modest antimicrobial activity against gram-positive cells and promising cytotoxicity against lymphoid leukemia cells (IC₅₀ = 0.2 nM) and leukemia P388 cells (IC₅₀ = 0.08 nM). Structurally, it contains a syn-deoxypolypropionate embedded within a macrocyclic ring, a fused cyclohexene, and a bicyclic pyranone which is itself fused to a spirocyclic lactone. Furthermore, a quaternary methyl stereocenter and sensitive exo-methylene Michael acceptor are present (Figure 2.1.9). This challenging target has been pursued by a number of groups, with two completing the total synthesis of okilactomycin in greater than 25 steps.


Figure 2.1.9. Key structural features of okilactomycin.

The first total synthesis of okilactomycin was achieved by Amos Smith and coworkers in 2007. Their key step involves a Petasis-Ferrier rearrangement that constructs the spirocyclic core and unites the upper and lower portions of okilactomycin as two chiral fragments 55 and 56 (Figure 2.1.10, a). The macrocyclic ring is closed via a late-stage ring-closing metathesis (RCM). The top fragment 55 arises from a Myers alkylation followed by an Evans auxiliary-controlled aldol (Figure 2.1.10, b) The bottom fragment 56 is made by a Rawal auxiliary-controlled Diels-Alder cycloaddition (Figure 2.1.10, c). Overall, the synthesis of (-)-okilactomycin is achieved in 29 linear steps, and the absolute configuration of the natural compound was confirmed as the enantiomer of Smith’s synthetic product.

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Figure 2.1.10. Summary of A. B. Smith’s synthesis of (-)-okilactomycin.

While we were working toward our own synthesis of okilactomycin, a second total synthesis was reported by Karl Scheidt and coworkers. Using similar disconnections as Smith, Scheidt unites the upper and lower portions of okilactomycin by a condensation/intramolecular aldol reaction (Figure 2.1.11, a). As in Smith’s synthesis, each of the requisite fragments 57 and 58 is prepared stereoselectively by auxiliary-controlled reactions, but Scheidt prepares each

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The deoxypolypropionate portion is constructed by a Myers alkylation and then subjected to a diastereoselective copper-catalyzed aldol reaction giving 59, which is elaborated by further steps to the completed top fragment 57 (Figure 2.1.11, b). The cyclohexene 58 is prepared by an Evans auxiliary-controlled Diels-Alder reaction (Figure 2.1.11, c). Because Scheidt’s strategy uses the same natural enantiomers of each auxiliary, he reaches the unnatural enantiomer of okilactomycin as did Smith.

**Figure 2.1.11. Summary of K. A. Scheidt’s synthesis of (-)-okilactomycin.**
Hoye and coworkers completed okilactomycin D in 2012.\textsuperscript{69} This member of the okilactomycin family lacks the closed 4-pyranone, quaternary methyl and exo-methylene of the parent compound but contains the same macrocycle and similar cyclohexene (Scheme 2.1.12). Hoye assembles the macrocycle and fused cyclohexene by an intramolecular Diels-Alder reaction of tetronate 60. This is built from 61, which is derived from the unification of the deoxypolypropionate constructed by Myers alkylation with the diene fragment by a Fouquet-Schlosser coupling.\textsuperscript{70}

![Figure 2.1.12. Summary of T. R. Hoye’s synthesis of okilactomycin D.](image)


2.2. Retrosynthetic strategy

Our retrosynthetic strategy toward okilactomycin would roughly halve the number of steps used by A. B. Smith in its first total synthesis. We planned to accomplish this by an extremely rapid synthesis of the top portion and a more convergent route to elaborate the lower fragment. We thought a late-stage substrate controlled Diels Alder reaction of a tetronic acid similar to that used by Sorenson in his synthesis of abyssomycin\(^{71}\) could assemble the spirocycle and the cyclohexene simultaneously (Figure 2.2.1). The Diels-Alder substrate 62 could be divided into bottom and top fragments 63 and 64, united via an sp\(^3\) cross coupling. After our proposal, similar steps were demonstrated by Hoye in his synthesis of okilactomycin D,\(^{72}\) validating this approach. The diene could be assembled by a fairly straightforward cross-coupling strategy while the dienophile would come from a short sequence employing a Dieckmann-type cyclization of enolcarbonate 65, which would come from methylation and oxidative transposition of 3-pyranone 66. This would, in turn come from an Achmatowicz rearrangement of furyl carbinol 67. A Rh-catalyzed desymmetrization of 48 with a furylzinc 68 followed by diastereoselective reduction to give 67 would constitute the key enantioselective step. The advantages of this route over the currently published syntheses would include a lower step count, but also the complete elimination of stoichiometric chiral reagents.

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Figure 2.2.1. Retrosynthesis.
2.3. Construction of the bottom fragment

The synthesis of the diene fragment is fairly straightforward. Starting from homopropargyl alcohol, TBS ether 69 is prepared under standard conditions, then hydroboration, oxidation and condensation of pinacol give the known pinacolboronic ester 70 (Figure 2.3.1).\(^{73}\) Vinyl iodide 71 is prepared by hydrostannation of ethyl butynoate\(^{74}\) followed by oxidation with iodine. These fragments are coupled by a Suzuki-Miyaura reaction with Pd(PPh\(_3\))\(_2\)Cl\(_2\) as the catalyst in the presence of CsF.\(^{75}\) The TBS ether is cleaved, and Appel reaction\(^{76}\) with carbon tetrabromide gives the requisite alkyl bromide 72, setting the stage for activation as the Grignard reagent to be coupled with our proposed top fragment.

\[\text{TBSO} \quad \text{69} \quad \text{84\%} \quad \text{TBSO} \quad \text{70}\]

\[\text{EtO} \quad \text{O} \quad \text{i. CuBH, THF} \quad \text{Me}_3\text{NO} \quad \text{iii. pinacol}\]

\[\text{i. Bu}_3\text{SnH, CuCl} \quad \text{PPh}_3, \text{t-BuOK} \quad \text{PhMe, 85\%}\]

\[\text{1. TsOH} \quad \text{MeOH}\]

\[\text{2. CBr}_4, \text{PPh}_3 \quad \text{CH}_2\text{Cl}_2, 76\% \quad \text{76}\]

\[\text{1. I}_2, \text{CH}_2\text{Cl}_2, 63\% \quad \text{71}\]

\[\text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \quad \text{CsF, K}_2\text{CO}_3 \quad \text{EtOH, 70 °C, 70\%}\]

\[\text{Br} \quad \text{Me} \quad \text{72}\]

\[\text{Me} \quad \text{CO}_2\text{Et}\]

\[\text{1. CBr}_4, \text{PPh}_3 \quad \text{CH}_2\text{Cl}_2, 74\% \quad \text{72}\]

Figure 2.3.1


2.4. Early exploration with unsubstituted furylzinc as the nucleophile

The preparation of furyl carbinol 67 is key to our strategy for constructing the upper portion of okilactomycin. Optimization of our Rh-catalyzed desymmetrization with a furyl nucleophile 68 would give the corresponding ketoacid 73, which we believed would be reduced diastereoselectively with LiBHEt3 to give 67 (Figure 2.4.1). Furylzincs had been demonstrated previously as nucleophiles for succinic anhydrides, but their use in glutaric anhydride desymmetrizations had been studied only briefly. Therefore, my first task was to optimize desymmetrization of 3,5-dimethyl glutaric anhydride with furylzincs.

![Figure 2.4.1. Planned desymmetrization and subsequent reduction](image)

Initially, I studied the reaction of unsubstituted furylzincs to give ketoacid product 74 (eq 40). A screen of rhodium precursor, ligands, and zinc salts revealed that the reaction was feasible; however, enantioselectivity fell short of satisfactory (Table 2.4.1). It should be noted that preparation of the difurylzinc by addition of 0.5 equiv of a zinc salt gave no desired product.

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Table 2.4.1.

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Regardless, proof of concept had been demonstrated for the initial step, and exploration of the subsequent steps was undertaken. The stereoselective reduction with LiBHEt₃ proceeds as expected, with >19:1 dr observed in lactone product 75 (Figure 2.4.2). Reduction to the diol 76 with LiAlH₄ followed by protection as the TBS ether 77 and oxidation of the furan ring with NBS gives the rearranged 3-pyranone 78. At this point, we thought it would be possible to install the requisite acetyl group by forming the thiolate at the lactol center, deprotonating, and adding to an acyl electrophile. Unfortunately, attempts to form thiolate 79 on greater than 10 mg scale led to decomposition.
Figure 2.4.2.
2.5. Optimization of protected acetylfuran addition and current route

Having demonstrated the desymmetrization with an unsubstituted furylzinc, I moved to furylzinics containing the two carbons that would comprise the dienophile of the late-stage Diels-Alder substrate 65 (Figure 2.5.1). Among these, ketal-protected acetylfuran 80 was both readily accessible and competent in the desymmetrization (eq 41).

![Figure 2.5.1. Possible precursors to the 2-carbon dienophile fragment.]

I optimized enantioselectivity with furylzinc nucleophile 81 (generated by lithiation and transmetalation of 80) on 25 mg scale (eq 41) and found that Bn-PHOX and Ph-TADDOL give the highest enantioenrichment of product at 50 °C (Table 2.5.1). However, the yield with TADDOL was less than 10%. On the other hand, 44% yield of keto acid 82 could be isolated using Bn-PHOX as the ligand, and lowering the reaction temperature to 23 °C improved selectivity to 83% ee.
Table 2.5.1.

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<td>t-Bu-PHOX</td>
<td>I</td>
<td>58</td>
<td>[Rh(nbd)Cl]₂</td>
<td>Bn-PHOX</td>
<td>l</td>
<td>81%</td>
</tr>
<tr>
<td>[Rh(nbd)Cl]₂</td>
<td>Bn-PHOX</td>
<td>I</td>
<td>72</td>
<td>[Rh(cod)Cl]₂</td>
<td>Bn-PHOX</td>
<td>l</td>
<td>83%</td>
</tr>
</tbody>
</table>

With these satisfactory results in hand, I moved on to exploring the forward route toward the top fragment 64 (Figure 2.5.2). The racemic reaction of 48 with furyl zinc iodide 81a is accomplished in 52% yield using achiral H-PHOX as the ligand. This is followed by diastereoselective reduction of the ketone to give lactone 83. The acidic workup causes the ketal to hydrolyze, and unprotected ketone is isolated. This intermediate is then transesterified to hydroxyester 84. At this point, oxidation of the furylcarbinol under a variety of conditions failed, presumably due to the electron withdrawing nature of the acetyl group.

![Figure 2.5.2.](image)
We thought we could prevent deactivation of the ring by keeping the ketal intact after the borohydride reduction, and did so by changing the workup from acidic to basic (Figure 2.5.3). Under these conditions, a mixture of hydroxy acid 85 and lactone 86 is obtained, which can be converted fully to 86 by addition of acetic anhydride. Thus, 86 is prepared in 90% yield and >19:1 dr. Reduction with Red-Al gives the diol which can be TBS protected to give primary silyl ether 87. The furyl ring can then be oxidized to yield 3-pyranone 88. A variety of methylation conditions were screened including the Wittig,79 Peterson,80 and Petasis81 protocols; however, only Tebbe’s reagent82 was found to be effective at preparing diene 89.

Figure 2.5.3.

80 Peterson, D. J. J. Org. Chem. 1968, 33, 780-784
Our next envisioned step was the oxidative transposition of the allylic lactol in 89 to give 4-pyranone 90. This proved to be a difficult task, as many conditions for oxidative transposition failed (eq 42).

![Chemical structure](image)

At this point, we began to consider alternative strategies to prepare 4-pyranone 90. We sought to isomerize the lactol in 89 by acid catalysis. A screen of conditions and nucleophiles revealed that a number of alcohols could be added at the 4-position of the pyran to give doubly allylic ethers 91 (eq 43). Deprotection of the TBS ether and intramolecular addition of the alcohol to give 92 was also observed in the case of t-BuOH. However, the hydration product 91a (R=H) could not be isolated in appreciable amounts. Oxidation protocols on the allylic ethers were unsuccessful, and this strategy was also abandoned.

![Chemical structure](image)

A second alternative could be the preparation of a lactol thioether 93, which could be oxidized to sulfoxide 94 (Figure 2.5.4). This could then undergo a Mislow-Evans rearrangement to give oxygenation at the 4-position of the pyrone in 91a. Unfortunately,

---


treatment of diene 89 under standard conditions to form the thiolate\textsuperscript{85} lead to 1,6-addition of the thiol followed by ring opening to 95.

![Chemical Structure](image)

Figure 2.5.4.

In order to conserve time and rhodium catalyst, we examined further strategies on a model system, readily accessible from the ketal-protected furan 80 and isobutyraldehyde (Figure 2.5.5). The initial aldehyde addition is followed by Achmatowicz rearrangement to 3-pyrone 96, and methylenation with Tebbe’s reagent gives diene 97.

![Chemical Structure](image)

Figure 2.5.5.

We thought a sigmatropic rearrangement of an $O$-acylated allylic lactol might give the correct olefin substitution and leave an oxidation step to prepare the pyranone (Figure 2.5.6).

The acetylation of sterically encumbered lactol 97 to give the rearrangement substrate 98 proved very difficult, even under forcing conditions, and this strategy was abandoned.

\[
\begin{align*}
\text{97} & \quad \text{\[3,3\]} \quad \text{98} \\
\end{align*}
\]

Figure 2.5.6.

With gram-quantities of model substrate 97 available, I decided to reexamine conditions for the oxidative transposition. Treatment of 97 with 2 equivalents of freshly prepared iodoxybenzoic acid (IBX) gave a trace amount of the desired 4-pyranone product 99. Increasing to 4 equivalents gave 10% yield, and with 8 equivalents of IBX, 40% yield of the desired 4-pyranone was isolated (eq 44). While modest, this yield was sufficient to try in the real system, and I moved forward with the synthesis.

As I began another batch of starting material to try the oxidative transposition, I thought the TBS protection I had used earlier might be unnecessary. Indeed, the Achmatowicz rearrangement proceeds smoothly on diol 100 to give primary alcohol 101 (Figure 2.5.7). This can then be tosylated for use in the planned Fouquet-Schlosser coupling and methylenated to arrive at diene 103. Subjection of 103 to the oxidative transposition conditions gave the 4-pyranone in slightly better yield than the model system. This sequence comprises the current optimal route to advanced intermediate 104. It contains the carbon skeleton and stereochemical
relationships present in okilactomycin, minus the 5-membered lactone and quaternary methyl center.

![Chemical diagram]

Figure 2.5.7. Current optimal route to 104.

To elaborate 104 to the completed top fragment, we intended to reduce the vinylogous ester to give 105, still containing the exo-methylene (eq 45). We thought that treatment with a Lewis acid and a mild reductant might favor direct 1,2-reduction of the oxocarbenium and studied to model system to test our hypothesis. Unfortunately, with a variety of Lewis acids and triethylsilane as the reductant, only 1,4-reduction of the exo-methylene Michael acceptor to give 106 is observed.
Similarly, hydrogenation with Pd/C, Pt/C, Rh/Al₂O₃ or Crabtree’s catalyst⁸⁶ in a variety of solvents gave exo-methylene reduction to 106 in poor yield. In addition, double bond isomerization to pyrone 107 and 6π-electrocyclic ring opening of 106 to 108 were observed (eq 46). No hydrogenation of the vinylogous ester was observed under any of the conditions tried, despite similar conditions being reported for the hydrogenation of such double bonds.⁸⁷

We believed it should still be possible to hydrogenate the olefin in the exo-methylene-reduced product 106 to give saturated pyranone 109. A screen of conditions was run under 1 atm H₂ and no hydrogenation was observed. Hydrogenation was attempted in a Parr bomb at 50 psi H₂, still with no success. Finally, a glass pressure vessel was charged with 60 psi H₂, the reaction run overnight, and 109 was isolated in 40% yield (eq 47).

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Further steps have been explored on the model system. The synthesis of model substrate 110 is carried out in identical steps from 99 (Figure 2.5.8). After reduction of the exo-methylene, pyrone 111 is hydrogenated, then treated immediately with formic acid at 60 °C to cleave the ketal, giving 110. Then using Trost’s conditions for selective $O$-acylation, enolcarbonate 112 can be prepared.\(^{88}\)

![Chemical structure](image)

Figure 2.5.8.

We hoped treatment with base to generate enolate 113 would result in cyclization onto the carbonyl of the carbonate, giving lactone 114.\(^{89}\) So far, a number of bases have failed to close the lactone ring (Figure 2.5.9). The desired enolate does bear a $\beta$-leaving group; however, the elimination of the ether to form enone 115 should be reversible and the irreversible condensation of the enolate onto the carbonate should proceed. It is unclear if this ring opening is actually occurring, as epimerization at the 4-position of the Michael acceptor in 115 is not observed.


Figure 2.5.9.
2.6. Conclusion

At this point, the synthesis of okilactomycin stands with the bottom portion fully assembled and the top fragment a few steps from complete, provided conditions to close the lactone can be identified. The lower fragment alkyl bromide is synthesized in 5 linear steps (7 total) by a Suzuki-Miyaura coupling. The most advanced intermediate toward the top fragment is assembled in 9 steps from 3,5-dimethyl glutaric anhydride (Figure 2.6.1). Though the synthesis is incomplete, the first few steps demonstrate the utility of our asymmetric Rh-catalyzed desymmetrization of 3,5-dimethyl glutaric anhydride to generate complexity in a rapid fashion.

![Chemical Reaction](image)

To complete the synthesis, we propose the following sequence. First, intermediate 109 must be elaborated to the completed top fragment by deprotection of the ketal and generation of the enolcarbonate 116 (Figure 2.6.2.), which have been demonstrated on the model system.
Then, the ketone enolate must be condensed onto the carbonate to generate the lactone, which contains a β-ketoester that will be methylated stereoselectively to give 117 following the precedent of Scheidt. From here, the top and bottom fragments must be coupled by a Fouquet-Schlessler or similar alkyl-alkyl coupling to give the Diels-Alder substrate 118. The intramolecular Diels-Alder reaction should follow, then installation of the selenide at the ketone of 119 will set up an elimination as per Smith’s completed total synthesis. Saponification of the ethyl ester will then deliver okilactomycin. Should these steps be accomplished, our synthesis of okilactomycin would be completed in 18 linear steps.

![Chemical Structures](image)

**Figure 2.6.2.**

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CHAPTER 1 EXPERIMENTAL

General methods

All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Tetrahydrofuran was degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on SiliCycle®SilicaFlash® P60, 40-63µm 60A. Thin layer chromatography was performed on SiliCycle® 250µm 60A plates. Visualization was accomplished with UV quench, KMNO₄, or aqueous ceric ammonium molybdate dips followed by heating. Infrared Spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer. ¹H spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift is parts per million (δ, ppm) for chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants (Hz). ¹³C spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec.

Anhydrous HOAt was purchased from Advanced Chem Tech and used as received. N,O-dimethylhydroxylamine hydrochloride, glycine methyl ester hydrochloride, L-alanine methyl ester hydrochloride, and L-phenylalanine methyl ester hydrochloride were purchased from Aldrich Chemical Co. and used without further purification. Benzylamine hydrochloride, piperidine hydrochloride, piperazine 1-carboxylic acid ethyl ester hydrochloride, L-phenethylamine hydrochloride and D-phenethylamine hydrochloride were prepared by treatment of the corresponding amine with an equimolar amount of anhydrous hydrogen chloride in ether.
(purchased from Aldrich Chemical Co. and used as received) followed by filtration. Triethylamine and diisopropylethylamine were distilled over calcium hydride and stored over 4Å MS. 3-((tert-butyldimethylsilyl)oxy)propanal was prepared according to known procedures. Other aldehydes were obtained from Aldrich Chemical Co. and used without further purification.

Racemic products were obtained by treating the corresponding fluoroenal with amine hydrochloride and HOAt in the presence of sodium pivalate and achiral triazolium salt in toluene. Enantiomeric ratio was determined by high pressure liquid chromatography on an Agilent Technologies 1100 Series using Daicel™ chiral columns.
**NHC-redox amidation of amine hydrochlorides**

![Chemical structure](image)

**General procedure for NHC-catalyzed amidation reactions of enals:** To a 25 mL round-bottom flask equipped with a magnetic stir bar was added ca. 200 mg of molecular sieves (4Å). The sieves were flame activated under vacuum, and the vessel was purged with argon. Glycine methyl ester hydrochloride (50 mg, 0.4 mmol, 1.0 eq.), triazolium catalyst 3c (30 mg, 0.08 mmol, 0.2 eq.), and 1-hydroxy-7-azabenzotriazole (10.8 mg, 0.08 mmol, 0.2 eq.) were weighed into the flask, which was then evacuated and flushed with argon. Toluene (8 mL) was added, and the reaction vessel was heated to 70 °C. Trans-cinnamaldehyde (75 µL, 0.6 mmol, 1.5 eq.) was added, followed by diisopropylethylamine (104 µL, 0.6 mmol, 1.5 eq.), and the reaction was stirred at 70 °C for 3h. The crude reaction mixture was loaded directly onto silica gel, and the product isolated by column chromatography (3:2 hexanes:ethyl acetate) yielding 32a as a yellow oil (82 mg, 93% yield).

**Yellow oil**

\[ ^{1}H\text{-NMR (400 MHz, CDCl}_3\text{)} \delta \text{ (ppm)} \: 7.27-7.15 \text{ (m, 5H)}; \: 6.04 \text{ (br s, 1H)}; \: 4.54 \text{ (d, 2H, } J = 5.2 \text{ Hz)}; \: 3.71 \text{ (s, 3H)}; \: 2.95 \text{ (dd, 2H, } J_1 = 7.5 \text{ Hz, } J_2 = 8.1 \text{ Hz)}; \: 2.53 \text{ (dd, 2H, } J_1 = 7.5 \text{ Hz, } J_2 = 8.1 \text{ Hz)}; \: ^{13}C\text{-NMR (100 MHz, CDCl}_3\text{)} \delta \text{ (ppm)} \: 172.56; \: 170.66; \: 140.83; \: 128.72; \: 128.49; \: 126.46; \: 52.58; \: 41.42; \: 38.14; \: 31.62 \]
off-white solid, m.p. 82-85 °C; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.26-7.15 (m, 5H); 6.13 (br s, 1H); 4.54 (dq, 1H, J₁ = 7.2 Hz, J₂ = 1.7 Hz); 3.67 (s, 3H); 2.95 (t, 2H, J = 7.9 Hz); 2.54-2.41 (m, 2H); 1.29 (d, 3H, J = 7.2 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 173.7; 171.9; 140.9; 128.7; 128.5; 126.4; 52.6; 48.1; 38.3; 31.7; 18.6; IR (cm⁻¹) 3299.0; 3028.6; 2952.7; 1746.1; 1650.1; 1497.3; 1453.9; 1378.3; 1210.2; 1167.2; HR-MS (ESI-APCI): Calc’d (m+h): 236.1208; Found (m+h): 236.1279; Rf = 0.28 (1:1 Hexanes: Ethyl Acetate)

white solid, m.p. 71-73 °C; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.28-7.16 (m, 7H); 6.92-6.90 (m, 2H); 5.80 (br d, 1H, J = 7.5 Hz); 4.86 (dt, 1H, J₁ = 7.8 Hz, J₂ = 5.6 Hz); 3.68 (s, 3H); 3.04 (d, 2H, J = 5.6 Hz); 2.94-2.89 (m, 2H); 2.54-2.39 (m, 2H) ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 172.1; 171.6; 140.8; 135.9; 129.4; 128.7; 128.6; 127.3; 126.5; 53.1; 52.5; 38.4; 38.1; 31.6; IR (cm⁻¹) 3028.9; 2951.6; 1745.5; 1650.1; 1604.0; 1536.6; 1497.0; 1453.9; 1371.2; 1213.7; 1121.0; 1077.6; 1029.9; HR-MS (ESI-APCI): Calc’d (m+h): 312.1521; Found (m+h): 312.1594; Rf = 0.46 (1:1 Hexanes: Ethyl Acetate)

colorless oil, ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.24-7.16 (m, 5H); 5.99 (br d, 1H, J = 8.2 Hz); 4.52 (ddd, 1H, J₁ = 8.7 Hz, J₂ = 5.0 Hz, J₃ = 1.8 Hz); 3.67 (s, 3H); 2.94 (t, 2H, J = 9.7 Hz); 2.55-2.50 (m, 2H); 2.07-2.01 (m, 1H), 0.82-0.77 (m, 6H); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm)
172.8; 172.2; 140.8; 128.7; 128.5; 126.4; 57.1; 52.3; 38.4; 31.8; 31.4; 19.0; 17.9; IR (cm⁻¹)
3028.9; 2965.1; 1744.7; 1651.5; 1540.0; 1497.7; 1454.2; 1436.4; 1373.1; 1310.8; 1265.3;
1206.7; 1156.3; 1076.9; 1024.4; HR-MS (ESI-APCI): Calc’d (m+h): 264.1521; Found (m+h):
264.1592; Rf = 0.5 (1:1 Hexanes: Ethyl Acetate)

![Structural formula of compound 1]

**colorless oil, **¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.26-7.22 (m, 2H); 7.16 (dd, 3H, J₁ = 7.2
Hz, J₂ = 5.1 Hz); 6.31 (br d; J = 7.6 Hz); 5.70 (br s, 1H); 4.49 (dt, 1H, J₁ = 8.0 Hz, J₂ = 4.0 Hz);
3.69 (s, 3H); 2.92 (t, 2H, J = 7.7 Hz); 2.43 (t, 2H, J = 7.7 Hz); 1.98 (s, 3H); 1.77-1.73 (m, 1H);
1.63 (ddt, 1H, J₁ = 8.1 Hz, J₂ = 3.9 Hz, J₃ = 14.5 Hz); 1.46-1.38 (m, 2H); 1.29-1.20 (m, 2H);

¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 173.2; 172.6; 170.3; 141.0; 128.7; 128.5; 126.4; 52.6;
52.0; 38.9; 38.6; 32.0; 32.0; 29.0; 23.3; 22.4; IR (cm⁻¹) 3278.6; 3064.7; 2949.4; 2862.7; 2364.2;
1745.0; 1648.1; 1547.1; 1497.1; 1436.8; 1373.4; 1263.0; 1210.6; 1176.6; 1146.5; 1074.8;
1006.0; HR-MS (ESI-APCI): Calc’d (m+h): 335.1983; Found (m+h): 335.1971; Rf = 0.22 (1:1
Hexanes: Ethyl Acetate)

![Structural formula of compound 2]

**yellow oil, **¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.26-7.14 (m, 5H); 3.57 (s, 4H) 3.52 (t, 2H, J
eq 5.5 Hz); 3.30 (t, 2H, J = 5.5 Hz); 2.94 (t, 2H, J = 8.0 Hz), 2.57 (t, 2H, J = 8.0 Hz); ¹³C-NMR
(100 MHz, CDCl₃) δ (ppm) 171.04; 141.25; 128.72; 126.46; 67.02; 66.64; 46.15; 42.13; 35.00;
31.68; IR (cm⁻¹) 3483.9; 3061.23; 3026.6; 2962.2; 2920.4; 2856.7; 1652.6; 1495.3; 1433.8;
HR-MS (ESI-APCI): Calc’d (m+h): 220.1259; Found (m+h): 220.1330; \( R_f = 0.15 \) (1:1 Hexanes: Ethyl Acetate)

brown oil, \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.29-7.16 (m, 10H, rotamers A and B); 4.56 (s, 2H, rotamer A); 4.33 (s, 2H, rotamer B); 3.82 (t, 2H, \( J = 6.4 \) Hz, rotamer B); 3.57 (t, 2H, \( J = 6.2 \) Hz, rotamer A); 3.05-2.86 (m, 8H, rotamers A and B); 2.68-2.51 (m, 4H, rotamers A and B);

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 170.7; 170.4; 141.2; 128.7; 128.6; 126.5; 49.2; 48.7; 48.4; 37.4; 37.1; 31.3; 31.2; 29.8; \( \text{IR (cm}^{-1}\) 3059.9; 3026.2; 2394.7; 2873.5; 1650.1; 1495.7; 1418.3; 1339.3; 1261.0; 1077.6; 1029.7; HR-MS (ESI-APCI): Calc’d (m+h): 222.0874; Found (m+h): 222.0942; \( R_f = 0.28 \) (1:1 Hexanes: Ethyl Acetate)

brown solid, m.p. 142-145 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 8.06 (d, 2H, \( J = 8.4 \) Hz); 7.32 (d, 2H, \( J = 8.4 \) Hz); 6.22 (br s, 1H); 3.96 (d, 2H, \( J = 5.2 \) Hz); 3.68 (s, 3H); 3.02 (t, 2H, \( J = 7.7 \) Hz); 2.56 (t, 2H, \( J = 7.7 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 171.6; 170.5; 142.0; 146.7; 129.5; 123.9; 52.6; 41.4; 37.0; 31.2; \( \text{IR (cm}^{-1}\) 3287.2; 3092.8; 2955.8; 1742.6; 1649.2; 1598.4; 1554.3; 1515.0; 1431.9; 1386.6; 1344.2; 1215.6; 1108.0; 1021.7; HR-MS (ESI-APCI): Calc’d (m+h): 267.0903; Found (m+h): 267.0979; \( R_f = 0.13 \) (1:1 Hexanes: Ethyl Acetate)
yellow oil $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 9.93 (s, 1H) 7.68 (s, 1H); 7.67 (d, 2H, $J = $ Hz); 7.46-7.38 (m, 2H); 6.11 (br s, 1H); 3.98 (d, 2H, $J = $ Hz); 3.69 (s, 3H); 3.03 (t, $J = $ Hz); 2.55 (t, 2H, $J = $ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 192.7; 171.9; 170.5; 142.0; 136.8; 134.9; 129.5; 129.4; 128.2; 52.6; 41.4; 37.5; 31.1; IR (cm$^{-1}$) 3310.3; 3066.7; 2953.7; 2850.4; 2736.4; 1750.0; 1604.8; 1585.8; 1543.6; 1438.7; 1408.9; 1374.5; 1209.9; 1144.5; 1083.4; 1037.8; 1010.4; HR-MS (ESI-APCI): Calc’d (m+h): 250.1001; Found (m+h): 250.1076; $R_f$ = 0.14 (1:1 Hexanes: Ethyl Acetate)

![Chemical structure 1](image1)

yellow oil $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.83 (d, 2H, $J = $ Hz); 7.25 (d, 2H, $J = $ Hz); 6.07 (br s, 1H); 3.98 (d, 2H, $J = $ Hz); 3.70 (s, 3H); 3.00 (t, $J = $ Hz); 2.55-2.51 (m, 5H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 198.0; 171.9; 170.5; 146.7; 135.6; 128.8; 128.7; 52.6; 41.4; 37.4; 31.4; 26.7; IR (cm$^{-1}$) 3324.9; 2954.2; 1750.4; 1680.0; 1606.1; 1534.7; 1413.4; 1360.3; 1269.8; 1207.6; 1183.0; 1017.6; HR-MS (ESI-APCI): Calc’d (m+h): 264.1158; Found (m+h): 264.1237; $R_f$ = 0.05 (1:1 Hexanes: Ethyl Acetate)

![Chemical structure 2](image2)

yellow oil $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.17-7.09 (m, 2H); 6.85-6.79 (m, 2H); 6.12 (br s, 1H); 3.98 (d, 2H, $J = $ Hz); 3.78 (s, 3H); 3.69 (s, 3H); 2.92 (t, $J = $ Hz); 2.50 (t, $J = $ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 173.0; 170.7; 130.2; 129.1; 127.8; 120.7; 110.4; 55.4; 52.5; 41.4; 36.4; 26.7; IR (cm$^{-1}$) 3286.4; 2956.2; 1752.2; 1654.7; 1541.9; 1494.5; 1483.3;
HR-MS (ESI-APCI): Calc’d (m+h): 252.1158  Found (m+h): 252.1085  \( R_f = 0.22 \) (1:1 Hexanes: Ethyl Acetate)

![White solid](image1)

\( \text{white solid } \)  \( ^1H\)-NMR (400 MHz, CDCl₃) \( \delta \) (ppm) 7.38 (d, 2H, \( J = 8.3 \) Hz); 7.06 (d, 2H, \( J = 8.3 \) Hz); 5.83 (br s, 1H); 4.00 (d, 2H, \( J = 5.1 \) Hz); 3.73 (s, 3H); 2.91 (t, 2H, \( J = 7.6 \) Hz); 2.50 (t, 2H \( J = 7.6 \) Hz); 2.35 (t, \( J = 7.3 \) Hz); 1.84 (dt, \( J_1 = 7.3 \) Hz, \( J_2 = 13.9 \) Hz); 1.04-0.99 (m, 18H)

\( ^{13}C\)-NMR (100 MHz, CDCl₃) \( \delta \) (ppm) 173.7; 170.7; 130.2; 129.1; 127.8; 120.7; 110.4; 55.4; 52.5; 41.4; 36.4; 26.7; 13C-MS (ESI-APCI): Calc’d (m+h): 332.2179  Found (m+h): 332.2231  \( R_f = 0.5 \) (1:1 Hexanes: Ethyl Acetate)

![Colorless oil](image2)

\( \text{colorless oil; } \)  \( ^1H\)-NMR (400 MHz, CDCl₃) \( \delta \) (ppm) 6.16 (br s, 1H); 4.00 (d, 2H, \( J = 5.2 \) Hz); 3.72-3.69 (m, 4H); 2.35 (t, \( J = 7.3 \) Hz); 1.84 (dt, \( J_1 = 7.3 \) Hz, \( J_2 = 13.9 \) Hz); 1.04-0.99 (m, 18H)

\( ^{13}C\)-NMR (100 MHz, CDCl₃) \( \delta \) (ppm) 173.0; 170.7; 130.2; 129.1; 127.8; 120.7; 110.4; 55.4; 52.5; 41.4; 36.4; 26.7; 2866.9; 1757.9; 1656.3; 1543.3; 1463.5; 1438.5; 1369.2; 1207.6; 1180.6; 1106.0; 1066.3;  HR-MS (ESI-APCI): Calc’d (m+h): 332.2179  Found (m+h): 332.2231  \( R_f = 0.5 \) (1:1 Hexanes: Ethyl Acetate)

![Yellow oil](image3)

\( \text{yellow oil; } \)  \( ^1H\)-NMR (400 MHz, CDCl₃) \( \delta \) (ppm) 6.06 (br s, 1H); 4.00 (d, \( J = 5.2 \) Hz); 3.71 (s, 3H); 2.21 (t, 2H, \( J = 7.4 \) Hz); 1.58-1.47 (m, 3H); 0.86 (d, 6H, 6.2 Hz);  \( ^{13}C\)-NMR (100 MHz, CDCl₃) \( \delta \) (ppm) 173.7; 170.8; 52.5; 41.3; 34.5; 27.9; 22.5;  IR (cm⁻¹) 3304.9; 2957.1; 2861.9;
1757.5; 1654.9; 1543.3; 1438.2; 1371.5; 1207.7; **HR-MS (ESI-APCI):** Calc’d (m+h): 188.1208

Found (m+h): 188.1287  \( R_f = 0.28 \) (1:1 Hexanes: Ethyl Acetate)

![Chemical Structure](image)

eyellow oil;  \(^1\text{H-NMR (400 MHz, CDCl}_3\) \( \delta \) (ppm) 6.06 (br s, 1H); 4.00 (d, \( J = 5.2 \) Hz); 3.71 (s, 3H); 2.21 (t, 2H, \( J = 7.4 \) Hz); 1.58-1.47 (m, 3H), 0.86 (d, 6H, \( J = 6.2 \) Hz);  \(^{13}\text{C-NMR (100 MHz, CDCl}_3\) \( \delta \) (ppm) 173.7; 170.8; 52.5; 41.3; 34.5; 27.9; 22.5;  \( \text{IR (cm}^{-1}) \) 3078.1, 2957.2, 2871.8; 1757.1; 1654.5; 1542.2; 1438.0; 1408.2; 1368.9; 1207.4; 1088.2; 1039.1; **HR-MS (ESI-APCI):**

Calc’d (m+h): 188.1208 Found (m+h): 188.1287  \( R_f = 0.3 \) (1:1 Hexanes: Ethyl Acetate)

![Chemical Structure](image)

eyellow oil;  \(^1\text{H-NMR (400 MHz, CDCl}_3\) \( \delta \) (ppm) 7.29-7.22 (m, 5H) 6.29 (br s, 1H); 4.39 (d, \( J = 5.8 \) Hz); 4.05 (q, 2H, \( J = 7.1 \) Hz); 2.79-2.72 (m, 2H); 2.38-2.29 (m, 1H), 1.22-1.17 (m, 6H)  \(^{13}\text{C-NMR (100 MHz, CDCl}_3\) \( \delta \) (ppm) 175.2; 172.7; 138.6; 128.8; 127.8; 127.5; 60.8; 43.7; 38.3; 37.3; 18.1; 14.3. **HR-MS (ESI-APCI):** Calc’d (m+h): 232.1117 Found (m+h): 232.1184  \( R_f = 0.35 \) (1:1 Hexanes: Ethyl Acetate).
Preparation of α-fluoroenals for asymmetric amidation

![Chemical Structure]

General procedure for preparation of fluoroenoates 29. 2-fluoro-triethylphosphonoacetate (2.42 g, 10 mmol, 1.0 equiv) was dissolved in dry THF (50 mL, 0.2 M) at ambient temperature. Triethylamine (2.8 mL, 20 mmol, 2.0 equiv) was added, followed by magnesium bromide (1.84 g, 10 mmol, 1.0 equiv). An exotherm is observed, and while the reaction was hot (ca. 50 °C), benzaldehyde (1.06 g, 10 mmol, 1.0 equiv) was added. The reaction was stirred and monitored by TLC. Upon completion (ca. 1h), the reaction was diluted with 50 mL diethyl ether, then filtered on a medium porosity fritted funnel. The filtrate was washed with saturated ammonium chloride solution, which was then extracted with ether (2x50 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated to give 1.95 g of colorless oil, ethyl 2-fluoro-3-phenylacrylate as a 7:1 mixture of olefin isomers favoring Z (100 % crude). Spectral data for this compound matched literature, and it was carried to the next step without further purification.

\[ ^1{\text{H-NMR}} (400\text{ MHz, CDCl}_3) \delta \text{(ppm)} 7.53-7.50 (m, 2H); 7.37-7.32 (m, 3H); 6.92 (d, 1H, } J = 35.2 \text{ Hz}); 4.36 (q, 2H, } J = 7.1 \text{ Hz}); 1.39 (t, 3H, } J = 7.2 \text{ Hz})

General procedure for the preparation of fluoroalcohols 30. Ethyl 2-fluoro-3-phenylacrylate (1.94 g, 10 mmol, 1 equiv) was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (50 mL, 0.2M). The solution was cooled to 0 °C, and 1M diisobutylaluminum hydride solution in hexanes (30 mL, 30 mmol, 3 equiv) was
added slowly with stirring. The mixture was warmed to ambient temperature and monitored by TLC. Upon completion (ca. 30 min), the reaction was carefully quenched by addition of saturated Rochelle’s salt solution (50 mL). The mixture was stirred vigorously until phase separation was observed (ca. 1h), then extracted into ether (3x50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give 2-fluoro-3-phenylprop-2-en-1-ol as a light yellow oil (7:1 mixture of olefin isomers). The oil was purified by flash chromatography (10% to 20% EtOAc in hexanes) and the Z isomer isolated as 1.02 g colorless oil (67 %, 2 step, 77 % overall yield).

**1H-NMR (400 MHz, CDCl₃)** δ (ppm) 7.51-7.48 (m, 2H); 7.36-7.22 (m, 3H); 5.77 (d, J = 38.7 Hz, 1H); 4.27 (d, J = 14.3 Hz, 2H); 1.78 (s, 2H). **13C-NMR (100 MHz, CDCl₃)** δ (ppm). 158.1 (d, J = 266.8 Hz); 140.8; 132.6; 128.7 (d, J = 7.2 Hz); 128.5; 127.5 (d, J = 2.3 Hz); 127.0; 107.4 (d, J = 6.3 Hz); 61.9 (d, J = 32.7 Hz). **LR-MS** Calc’d (m+h): 153.06; Found (m+h) 153.1. **IR** Wavenumber (cm⁻¹, NaCl) 3343.6; 1691.9; 1494.6; 1449.1; 1345.7; 1221.6; 1164.4; 1072.4; 1020.0.

![Structural formula](image)

3:1 Z:E, 53% 2-step yield of Z-isomer (70 % overall). **1H-NMR (400 MHz, CDCl₃)** δ (ppm) 7.67 (t, J = 1.7 Hz, 1H); 7.43-7.37 (m, 2H); 7.20 (t, J = 7.9 Hz, 1H); 5.74 (d, J = 38.1 Hz, 1H); 4.29 (d, J = 13.3 Hz, 2H); 1.87 (s, 1H). **13C-NMR (100 MHz, CDCl₃)** δ (ppm) 159.1 (d, J = 268.6 Hz); 134.7; 131.4 (d, J = 7.9 Hz); 130.4; 129.9; 127.2 (d, J = 7.0 Hz); 122.5; 106.0 (d, J = 6.4 Hz), 61.6 (d, J = 33.0 Hz). **LR-MS** Calc’d (m+h): 230.97; Found (m+h) 231.0. **IR**
Wavenumber (cm$^{-1}$, NaCl) 3291.7; 1690.8; 1592.1; 1560.1; 1475.9; 1420.8; 1333.9; 1220.7; 1159.5; 1074.4; 1020.7

2:1 Z:E, 48% 2-step yield of Z-isomer (72% overall). $^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm) 8.19 (d, $J = 9.0$ Hz, 2H); 7.65 (d, $J = 9.0$ Hz, 2H); 5.92 (d, $J = 37.8$ Hz, 1H); 4.35 (d, $J = 11.4$ Hz, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ (ppm) 139.3, 129.1, 127.0, 123.8, 105.3, 98.4, 61.3 (d, $J = 33.6$ Hz). LR-MS Calc’d (m+h): 198.05; Found (m+h) 198.1. IR Wavenumber (cm$^{-1}$, NaCl) 3505.9; 1696.9; 1595.2; 1502.4; 1412.9; 1344.6; 1248.0; 1163.7; 1110.2; 1080.1.

1:1 Z:E, inseparable, 90% yield. $^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm) Z-isomer: 4.70 (dd, $J = 37.7, 9.3$ Hz), 4.09 (d, $J = 16.0$ Hz, 2H), 2.46-2.43 (m, 1H); 1.73-1.63 (m, 6H), 1.33-1.02 (m, 4H). E-isomer: 5.09 (dd, $J = 21.3, 10.2$ Hz, 1H); 4.23 (d, $J = 21.4$ Hz); 2.12-2.04 (m, 1H); 1.73-1.63 (m, 6H), 1.33-1.02 (m, 4H). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ (ppm) mixture of E and Z: 157.8; 155.4; 115.4; 115.1; 114.0; 61.7; 61.4; 57.7; 57.4; 35.0; 33.9; 32.9; 25.9; 25.7; 26.7. LR-MS Calc’d (m+h): 151.06; Found (m+h) 151.1. IR Wavenumber (cm$^{-1}$, NaCl) 3331.8; 2926.5; 2852.6; 1699.16; 1449.0; 1287.8; 1245.5; 1162.7; 1120.1; 1069.5; 1025.0.

1:1 Z:E, inseparable, 66% yield. $^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm) Z-isomer: 4.87 (dt, $J = 37.1, 7.5$ Hz, 1H); 4.06 (d, $J = 15.6$ Hz, 2H); 3.60-3.56 (m, 2H); 2.28-2.18 (m, 2H); 0.85 (s, 9H); 0.02 (s, 6H). E-isomer: 5.15 (dt, $J = 20.6, 8.6$ Hz, 1H); 4.15 (d, $J = 19.4$ Hz, 2H); 3.60-3.56 (m,
2H); 2.28-2.18 (m, 2H); 0.84 (s, 9H); 0.00 (s, 6H). $^{13}$C-NMR ($\text{100 MHz, CDCl}_3$) $\delta$ (ppm) 159.6, 157.3, 105.2 (d, $J = 21.0$ Hz); 104.5(d, $J = 14.1$ Hz); 62.2, 61.5, 61.2, 58.0, 57.7, 28.3, 27.2 -5.5.

**LR-MS** Calc’d (m+h): 235.15; Found (m+h) 235.2. **IR** Wavenumber (cm$^{-1}$, NaCl) 3368.6; 2955.2; 2930.5; 2859.1; 1703.6; 1472.0; 1387.7; 1361.5; 1303.1; 1255.7; 1152.3; 1101.0.

![Chemical Structure](image)

**General procedure for preparation of fluoroenals 31.** (Z)-2-fluoro-3-phenylprop-2-en-1-ol (1.02 g, 6.7 mmol, 1.0 equiv) was dissolved in ethyl acetate (67 mL, 0.1 M). IBX (5.63 g, 20.1 mmol, 3 equiv) was added and the slurry was stirred and heated to 80 °C. After consumption of starting material was observed by TLC (ca. 3h), the reaction was cooled to ambient temperature, then diluted with 67 mL diethyl ether. The slurry was then filtered and the cake rinsed with 30 mL diethyl ether. The filtrate was concentrated to give (Z)-2-fluoro-3-phenylacrylaldehyde as an off-white solid (0.89 g, 89 %). This was found to be of sufficient purity for the subsequent reaction; however, it can be purified by column chromatography (10% EtOAc in hexanes).

$^1$H-NMR ($\text{400 MHz, CDCl}_3$) $\delta$ (ppm) 9.37 (d, $J = 16.9$ Hz, 1H); 7.73-7.71 (m, 2H); 7.46-7.45 (m, 3H); 6.63 (d, $J = 34.2$ Hz, 1H). $^{13}$C-NMR ($\text{100 MHz, CDCl}_3$) $\delta$ (ppm) 184.0 (d, $J = 25.1$ Hz); 154.8 (d, $J = 271$ Hz); 130.9 (d, $J = 2.8$ Hz); 130.7; 130.6; 129.0; 126.8. **LR-MS** Calc’d (m +h): 151.06; Found (m+h) 151.1. **IR** Wavenumber (cm$^{-1}$, NaCl) 1691.5; 1647.6; 1494.7; 1450.8; 1396.2; 1358.1; 1322.7; 1295.7; 1170.8.

![Chemical Structure](image)
72 % yield. $^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 9.30 (d, $J = 16.4$ Hz, 1H); 7.77 (s, 1H); 7.56 (d, $J = 7.8$ Hz, 1H); 7.49 (d, $J = 8.0$ Hz, 1H); 7.25 (t, $J = 7.9$ Hz, 1H), 6.49 (d, $J = 33.5$ Hz, 1H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 183.7 (d, $J = 26.0$ Hz); 155.0 (d, $J = 273.1$ Hz); 133.7; 133.2 (d, $J = 8.5$ Hz); 132.5; 130.5; 129.1; 124.6; 123.0. LR-MS Calc’d (m+h): 228.96; Found (m+h) 229.0. IR Wavenumber (cm$^{-1}$, NaCl) 1683.7; 1645.7; 1557.5; 1475.0; 1423.7; 1393.0; 1353.5; 1286.5; 1166.2; 1096.9.

![Image]

55 % yield. $^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 9.46 (d, $J = 15.6$ Hz, 1H); 8.30 (d, $J = 8.9$ Hz, 2H); 7.88 (d, $J = 8.9$ Hz, 2H); 6.71 (d, $J = 33.0$ Hz, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 183.5 (d, $J = 27.8$ Hz); 157.0; 154.3; 148.4; 136.5; 131.2; 124.1; 122.4. LR-MS Calc’d (m+h): 196.03; Found (m+h) 196.1. IR Wavenumber (cm$^{-1}$, NaCl) 1687.2; 1657.5; 1595.6; 1509.6; 1170.6; 1101.9.

![Image]

46 % yield. $^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) Z-isomer: 9.11 (d, $J = 18.2$ Hz, 1H); 5.73 (dd, $J = 33.1, 9.6$ Hz, 1H); 2.81-2.73 (m, 1H); 1.73-1.61 (m, 4H); 1.31-1.13 (m, 6H). E-isomer: 9.70 (d, $J = 17.2$ Hz, 1H); 6.00 (dd, $J = 18.7, 11.1$ Hz, 1H); 2.67-2.57 (m, 1H); 1.73-1.61 (m, 4H); 1.31-1.13 (m, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 184.0 (d, $J = 24.9$ Hz); 181.8 (d, $J = 28.1$ Hz); 156.4; 154.2; 153.8; 151.7; 136.2; 133.3; 34.4; 33.8; 33.3; 31.7; 25.6; 25.4; 25.2. LR-
MS Calc’d (m+h): 157.10; Found (m+h) 157.1. IR Wavenumber (cm⁻¹, NaCl) 2926.4; 2852.8; 1706.9; 1449.3; 1124.6.

TBSO

78% yield. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) Z-isomer: 9.19 (d, J = 18.3 Hz, 1H); 6.02 (dt, J = 32.7, 7.5 Hz, 1H); 3.73-3.68 (m, 2H); 2.66-2.61 (m, 1H); 2.56-2.51 (m, 1H); 0.85 (s, 9H); 0.02 (s, 6H). E-isomer: 9.69 (d, J = 16.6 Hz, 1H); 6.20 (dt, J = 18.0, 8.9 Hz, 1H); 3.73-3.68 (m, 2H); 2.66-2.61 (m, 1H); 2.56-2.51 (m, 1H); 0.83 (s, 9H); 0.02 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 182.9 (d, J = 130.0 Hz), 61.2, 60.9, 28.4, 27.7 (d, J = 5.6 Hz), 25.8, 25.6, 18.2, -5.5. LR-MS Calc’d (m+h): 233.14; Found (m+h) 233.2. IR Wavenumber (cm⁻¹, NaCl) 2597.2; 2931.3; 2858.4; 1702.2; 1665.6; 1472.4; 1389.3; 1361.0; 1316.8; 1256.5; 1180.2; 1101.2.
Asymmetric preparation of $\alpha$-fluoroamides

\[
\begin{array}{c}
\text{OMe} \\
\text{O} \\
\text{N} \\
\text{CO}_2\text{Me}
\end{array}
\]

**General procedure for NHC-catalyzed amidation reactions of fluoroenals (preparation of 32a):** To a 10 mL round-bottom flask equipped with a magnetic stir bar was added ca. 100 mg of molecular sieves (4Å). The sieves were flame activated under vacuum, and the vessel was purged with argon. Glycine methyl ester hydrochloride (25 mg, 0.2 mmol, 1.0 equiv), morpholinone-derived triazolium catalyst 11c (19 mg, 0.04 mmol, 0.2 equiv), and 1-hydroxy-7-azabenzotriazole (5.4 mg, 0.04 mmol, 0.2 equiv) were weighed into the flask, which was then evacuated and flushed with argon. Toluene (4 mL, 0.05M) was added. (Z)-2-fluoro-3-(2-methoxyphenyl)acrylaldehyde (54 mg, 0.3 mmol, 1.5 equiv) was added, followed by sodium benzoate (44 mg, 0.3 mmol, 1.5 equiv), and the reaction was stirred overnight (ca. 16h). The crude reaction mixture was loaded directly onto silica gel, and the product isolated by column chromatography (3:2 hexanes:ethyl acetate) yielding 5a as a yellow oil (47 mg, 87% yield).

**$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 17.21-7.10 (m, 2H); 6.86-6.80 (m, 2H); 6.74 (s, 1H, rotamer 1); 6.10 (s, 1H, rotamer 2); 5.14 (ddd, J = 49.7, 9.5, 3.2 Hz, 1H); 4.03 (d, J = 5.4 Hz, 2H, rotamer 1); 3.97 (d, J = 5.0 Hz, 2H, rotamer 2); 3.77 (s, 3H); 3.72 (s, 3H, rotamer 1); 3.70 (s, 3H, rotamer 2); 3.44 (ddd, J = 36.7, 14.7, 3.2 Hz, 1H); 2.89 (ddd, J = 18.7, 14.7, 9.5 Hz, 1H).**

**$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 178.6; 170.7; 170.0; 169.7; 157.6; 131.2; 128.4; 124.0; 120.4; 90.9 (d, J = 187.2 Hz); 55.3; 52.4; 52.3; 41.3; 40.7; 38.6; 33.6 (d, J = 20.5 Hz); 27.4.**

**LR-MS**
Calc’d (m+h): 218.16; Found (m+h) 218.1. **IR Wavenumber (cm$^{-1}$, NaCl) 3366.4; 2957.1; 1753.9; 1672.6; 1602.5; 1589.0; 1530.3; 1496.3; 1464.1; 1439.1; 1407.7; 1369.0; 1290.7;
Chiral HPLC Method: IC column; 30% isopropanol in hexanes; $t_R(\text{maj}) = 12.9$ min, $t_R(\text{min}) = 11.4$ min, 91% ee.

\[
\text{Ph}\begin{array}{c}
\text{F} \\
\text{N} \\
\end{array}
\text{O}
\]

$^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.26-7.16 (m, 5H); 5.29-5.14 (m, 1H); 3.55-3.09 (m, 6H); 1.57-1.30 (m, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 166.4 (d, $J = 19.6$), 136.0, 129.5, 128.5, 126.9, 89.7 (d, $J = 182.6$), 46.3, 43.5, 38.5 (d, $J = 21.8$ Hz), 26.3, 25.5, 24.5. LR-MS Calc’d (m+h): 236.14; Found (m+h) 236.2. IR Wavenumber (cm$^{-1}$, NaCl) 3029.2; 2936.1; 2857.6; 1653.6; 1496.4; 1453.6; 1367.9; 1248.7; 1194.4; 1139.2; 1069.6; 1026.8. $[\alpha]_D^{26.2} = +32.9$ ° ($c = 1.5$, CH$_2$Cl$_2$).

\[
\text{Ph}\begin{array}{c}
\text{F} \\
\text{N} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

$^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.28-7.18 (m, 5H); 5.24 (ddd, 1H, $J = 48.8$, 7.1, 6.5 Hz); 4.07 (q, 2H, $J = 7.1$ Hz), 3.56-3.13 (m, 8H); 1.19 (t, $J = 7.1$ Hz) $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 166.8 (d, $J = 19.9$ Hz); 155.2; 135.4; 129.6; 128.6; 127.2; 90.2 (d, $J = 184.2$ Hz); 61.7; 45.0; 42.2; 38.4 (d, $J = 21.3$ Hz); 28.3; 27.1; 14.6. LR-MS Calc’d (m+h): 309.15; Found (m+h) 309.2. IR Wavenumber (cm$^{-1}$, NaCl) 2982.3; 2929.1; 2866.5; 1700.2; 1662.1; 1432.0; 1384.9; 1354.8; 1286.7; 1230.9; 1172.7; 1126.6; 1071.1; 1032.9. $[\alpha]_D^{26.2} = -5.1$ ° ($c = 2.0$, CH$_2$Cl$_2$).
Chiral HPLC Method: OJH column; 30% isopropanol in hexanes; $t_R$(maj) = 10.2 min, $t_R$(min) = 11.3 min, 92 % ee.

Ph\begin{array}{c}
\text{F}\\
\text{O}\\
\text{N}\\
\text{Ph}
\end{array}

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.22-7.16 (m, 8H); 7.00-6.97 (m, 2H); 6.38 (br s, 1H); 5.09 (ddd, $J = 49.3$, 6.5, 3.6 Hz, 1H); 4.41 (dd, $J = 14.8$, 6.3 Hz, 1H); 4.25 (dd, $J = 14.8$, 5.3 Hz, 1H); 3.27 (ddd, $J = 27.2$, 14.9, 3.6 Hz, 1H); 3.10 (ddd, $J = 31.6$, 14.9, 6.5 Hz, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 168.9 (d, $J =19.1$ Hz); 137.3; 135.2; 129.7; 128.7; 128.4; 127.6; 127.5;127.0; 91.8 (d, $J = 189.0$ Hz); 42.9; 38.3 (d, $J = 19.9$ Hz); 27.1. LR-MS Calc’d (m+h): 258.13; Found (m+h) 258.1. IR Wavenumber (cm$^{-1}$, NaCl) 1650.1; 1542.1; 1494.7; 1453.3; 1287.2; 1233.4; 1058.1. $[\alpha]_{D}^{26.2} = +64.6 ^\circ$ (c = 1.1, CH$_2$Cl$_2$).

Chiral HPLC Method: IC column; 10% isopropanol in hexanes; $t_R$(maj) = 12.2 min, $t_R$(min) = 13.0 min, 91 % ee.

Ph\begin{array}{c}
\text{F}\\
\text{O}\\
\text{N}\\
\text{CO}_2\text{Me}
\end{array}

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.13-8.11 (m, 1H); 7.50-7.46 (m, 1H); 7.33-7.24 (m, 3H); 6.75 (br s, 1H); 5.14 (ddd, $J = 49.3$, 7.8, 3.4 Hz, 1H); 4.04 (qd, $J = 19.7$, 5.4 Hz, 2H); 3.75 (s, 3H); 3.34 (ddd, $J = 31.3$, 14.9, 3.4 Hz, 1H); 3.13 (ddd, $J = 27.0$, 14.9, 7.8 Hz, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 171.0; 169.6 (d, $J = 7.5$ Hz); 135.4; 133.6; 130.1; 129.5; 128.4; 127.0; 91.9 (d, $J = 189.4$ Hz); 52.5; 40.6; 38.4 (d, $J = 20.0$ Hz). LR-MS Calc’d (m+h): 240.10; Found (m+h) 240.1. IR Wavenumber (cm$^{-1}$, NaCl) 1752.1; 1684.8; 1541.1; 1452.6; 1438.6; 1373.7; 1215.5; 1121.8; 1068.3. $[\alpha]_{D}^{26.2} = +3.7 ^\circ$ (c = 0.37, CH$_2$Cl$_2$). Chiral HPLC Method: IC column; 30% isopropanol in hexanes; $t_R$(maj) = 9.7 min, $t_R$(min) = 11.6 min, 92 % ee. $[\alpha]_{D}^{26.2} =$
+60.0° (c = 0.57, CH₂Cl₂). **Chiral HPLC Method:** ODH column; 20% isopropanol in hexanes; 
\[ t_R(\text{maj}) = 9.1, \quad t_R(\text{min}) = 8.3 \text{ min}, \quad 91 \% \text{ ee.} \]

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

**¹H-NMR (400 MHz, CDCl₃)** δ (ppm) 7.27-7.17 (m, 5H); 5.37-5.22 (m, 1H); 3.59 (s, 3H); 3.14-3.05 (m, 5H). **¹³C-NMR (100 MHz, CDCl₃)** δ (ppm) 135.9; 129.3; 128.5; 127.0; 88.4 (d, \( J = 177.9 \) Hz); 61.6; 38.2 (d, \( J = 22.3 \) Hz); 32.2; 27.0. **LR-MS** Calc’d (m+h): 212.10; Found (m+h) 212.1. **IR** Wavenumber (cm⁻¹, NaCl) 1677.3; 1496.9; 1454.6; 1391.2; 1331.1; 1178.0; 1062.4; 1014.7. \( [\alpha]_D^{26.2} = +8.7° \) (c = 0.73, CH₂Cl₂). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; \( t_R(\text{maj}) = 9.5 \text{ min}, \quad t_R(\text{min}) = 11.2 \text{ min}, \quad 96 \% \text{ ee.} \)

\[ \text{OMe} \quad \text{N} \quad \text{OMe} \quad \text{Ph} \quad \text{F} \quad \text{Me} \]

**¹H-NMR (400 MHz, CDCl₃)** δ (ppm) 7.20-7.14 (m, 2H); 6.85-6.79 (m, 2H); 5.42 (br d, 1H); 3.76 (s, 3H); 3.60 (s, 3H); 3.26-2.98 (m, 2H) 3.13 (s, 3H) **¹³C-NMR (100 MHz, CDCl₃)** δ (ppm) 157.5; 131.7; 128.4, 123.9; 120.5; 110.2; 86.6 (d, \( J = 176.2 \) Hz); 61.5; 55.2; 33.2 (d, \( J = 22.6 \) Hz). **LR-MS** Calc’d (m+h): 242.11; Found (m+h) 242.1. **IR** Wavenumber (cm⁻¹, NaCl) 1683.1; 1602.5; 1495.8; 1465.3; 1440.1; 1391.5; 1330.3; 1291.4; 1246.5; 1177.7; 1120.5; 1050.5; 1030.9. \( [\alpha]_D^{26.2} = +81.5° \) (c = 1.4, CH₂Cl₂). **Chiral HPLC Method:** IC column; 30% isopropanol in hexanes; \( t_R(\text{maj}) = 13.6 \text{ min}, \quad t_R(\text{min}) = 13.0 \text{ min}, \quad 93 \% \text{ ee.} \)

\[ \text{Br} \quad \text{F} \quad \text{N} \quad \text{OMe} \quad \text{Ph} \quad \text{F} \quad \text{Me} \]

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\[ ^1\text{H-NMR (400 MHz, CDCl}_3 \] \delta (ppm) 7.41-7.38 (m, 2H); 7.20-7.18 (m, 2H); 5.41-5.26 (m, 1H); 3.70 (s, 3H); 3.22 (s, 3H); 3.17-3.08 (m, 2H). \[ ^{13}\text{C-NMR (100 MHz, CDCl}_3 \] \delta (ppm) 138.2; 132.3; 130.1; 128.1; 122.5; 88.0 (d, \( J = 180.8 \) Hz); 61.7, 37.7 (d, \( J = 22.1 \) Hz); 32.2. \[ \text{LR-MS} \] Calc’d (m+h): 290.01; Found (m+h) 290.0. \[ \text{IR Wavenumber (cm}^{-1}, \text{NaCl}) \] 1683.9, 1595.9; 1568.9; 1474.6; 1428.6; 1328.6; 1178.3; 1071.4. \[ \beta \text{D}^{26.2} = +17.3 ^\circ \] (c = 1.6, CH\(_2\)Cl\(_2\)). \[ \text{Chiral HPLC Method: IC column; 30\% isopropanol in hexanes; } t_R(\text{maj}) = 8.7 \text{ min, } t_R(\text{min}) = 9.4 \text{ min, 88 \% ee.} \]

\[ \text{O}_2\text{N} \]
\[ \text{F} \]
\[ \text{Me} \]
\[ \text{O}_2\text{N} \]
\[ \text{F} \]
\[ \text{Me} \]

\[ ^1\text{H-NMR (400 MHz, CDCl}_3 \] \delta (ppm) 8.11 (d, \( J = 8.8 \) Hz, 2H); 7.37 (d, \( J = 8.4 \) Hz, 2H); 5.39-5.23 (m, 1H); 3.67 (s, 3H); 3.25-3.10 (m, 2H); 3.16 (s, 3H). \[ ^{13}\text{C-NMR (100 MHz, CDCl}_3 \] \delta (ppm) 147.1, 143.5, 130.4, 129.2, 123.7, 123.2, 98.4, 87.6 (d, \( J = 181.0 \) Hz), 61.8, 61.4, 37.8 (d, \( J = 22.0 \) Hz), 32.2. \[ \text{LR-MS} \] Calc’d (m+h): 257.09; Found (m+h) 257.1. \[ \text{IR Wavenumber (cm}^{-1}, \text{NaCl}) \] 1683.6; 1602.4; 1520.2; 1440.5; 1391.4; 1348.1; 1179.8; 1110.3; 1063.2; 1016.2. \[ \beta \text{D}^{26.2} = +23.6 ^\circ \] (c = 1.1, CH\(_2\)Cl\(_2\)). \[ \text{Chiral HPLC Method: IC column; 30\% isopropanol in hexanes; } t_R(\text{maj}) = 19.0 \text{ min, } t_R(\text{min}) = 20.3 \text{ min, 88 \% ee.} \]

\[ \text{O}_2\text{N} \]
\[ \text{F} \]
\[ \text{Me} \]
\[ \text{O}_2\text{N} \]
\[ \text{F} \]
\[ \text{Me} \]

\[ ^1\text{H-NMR (400 MHz, CDCl}_3 \] \delta (ppm) 5.30-5.15 (m, 1H); 3.65 (s, 3H); 3.15 (s, 3H); 1.81-1.46 (m, 7H); 1.25-1.07 (m, 4H); 0.98-0.83 (m, 2H). \[ ^{13}\text{C-NMR (100 MHz, CDCl}_3 \] \delta 152.9; 86.5 (d, \( J = 177 \) Hz); 61.4; 39.2 (d, \( J = 21.6 \) Hz); 33.8; 32.2; 26.3; 26.1; 25.9. \[ \text{LR-MS} \] Calc’d (m+h):
218.16; Found (m+h) 218.1. IR Wavenumber (cm\(^{-1}\), NaCl) 2924.9; 2852.6; 1686.4; 1448.9; 1390.8; 1330.3; 1178.5; 1066.2; 1007.8. \([\alpha]_D^{26.2} = +16.5^\circ\) (c = 2.3, CH\(_2\)Cl\(_2\)). **Chiral HPLC Method:** ODH column; 10% isopropanol in hexanes; \(t_R(maj) = 5.1\) min, \(t_R(min) = 5.8\) min, 97% ee.

![NMR structure](image)

**1H-NMR (400 MHz, CDCl\(_3\))** \(\delta\) (ppm) 5.28-5.13 (m, 1H); 3.67 (s, 3H); 3.63 (dt, \(J = 12.5, 5.8\) Hz, 2H); 3.18 (s, 3H); 1.94-1.84 (m, 2H); 1.70-1.60 (m, 2H); 0.84 (s, 9H); 0.00 (s, 6H). **13C-NMR (100 MHz, CDCl\(_3\))** \(\delta\) (ppm) 88.1 (d, \(J = 173.9\) Hz); 62.3; 61.5; 28.6; 28.3; 27.9 (d, \(J = 2.9\) Hz); 27.0; 25.9; 18.2; -5.4. **LR-MS** Calc’d (m+h): 294.19; Found (m+h) 294.2. IR Wavenumber (cm\(^{-1}\), NaCl) 2955.4; 2931.4; 2858.2; 2360.8; 1686.3; 1472.2; 1389.7; 1361.6; 1327.4; 1255.0; 1179.3; 1101.1; 1005.0. \([\alpha]_D^{26.2} = +6.7^\circ\) (c = 2.1, CH\(_2\)Cl\(_2\)). **Chiral HPLC Method:** IC column; 5% isopropanol in hexanes; \(t_R(maj) = 5.1\) min, \(t_R(min) = 5.8\) min, 93% ee.

![NMR structure](image)

**1H-NMR (400 MHz, CDCl\(_3\))** \(\delta\) (ppm) 4.10 (q, \(J = 7.1, 2H\)); 3.76 (s, 3H); 3.19 (s, 3H); 2.83 (dd, \(J = 16.8, 9.6\) Hz, 1H); 2.30 (dd, \(J = 16.8, 5.1\) Hz, 1H); 1.28-1.20 (m, 4H), 1.13 (d, \(J = 7.1\) Hz, 3H). **13C-NMR (100 MHz, CDCl\(_3\))** \(\delta\) (ppm) 178.7; 176.2; 172.5; 61.3; 60.4; 37.5; 35.4; 32.0; 17.2; 16.8; 14.1; 14.1. **LR-MS** Calc’d (m+h): 204.12; Found (m+h) 204.1. IR Wavenumber (cm\(^{-1}\), NaCl) 2980.6; 2941.3; 1734.4; 1663.0; 1465.6; 1419.9; 1376.8; 1350.8; 1276.7; 1189.4; 1092.1; 1029.6. \([\alpha]_D^{26.2} = +11.1^\circ\) (c = 1.8, CH\(_2\)Cl\(_2\)). **Chiral HPLC Method:** ODH column; 5% isopropanol in hexanes; \(t_R(maj) = 6.9\) min, \(t_R(min) = 13.6\) min, 71% ee.
**1H-NMR (400 MHz, CDCl₃) δ (ppm)** 7.25-7.17 (m, 5H); 6.68 (br s, 1H); 5.01 (dd, J = 49.5, 8.2, 3.2 Hz, 1H); 4.55-4.48 (m, 1H); 3.66 (s, 3H); 3.25 (dd, J = 32.8, 14.9, 3.2 Hz, 1H); 3.03 (ddd, J = 25.6, 14.9, 8.2 Hz, 1H); 1.36 (d, J = 7.2 Hz, 3H). **13C-NMR (100 MHz, CDCl₃) δ (ppm)** 172.5; 168.8 (d, J = 19.8 Hz); 135.5; 129.4; 128.4; 127.0; 92.0 (d, J = 187.0 Hz); 52.5; 47.6; 38.5 (d, J = 20.1 Hz); 18.3. **LR-MS** Calc’d (m+h): 254.12; Found (m+h) 254.1. **IR** Wavenumber (cm⁻¹, NaCl) 3294.0; 2989.5; 2937.2; 1735.2; 1649.72; 1546.1; 1498.0; 1451.0; 1432.2; 1372.4; 1324.0; 1273.3; 1121.0; 1115.1; 1081.9; 1046.3; 1021.8. \([α]_D^{26.2} = +77.5° \text{ (c = 1.1, CH}_2\text{Cl}_2).} \) **Chiral HPLC Method:** OJH column; 20% isopropanol in hexanes; tᵣ(maj) = 16.3 min, tᵣ(min) = 9.9 min, 97:3 dr.

**1H-NMR (400 MHz, CDCl₃) δ (ppm)** 7.22-7.14 (m, 8H); 7.01 (dd, J = 7.9, 1.6 Hz, 2H); 6.58 (br s, 1H); 4.96 (dd, J = 49.5, 8.2, 3.2 Hz, 1H); 4.81-4.76 (m, 1H); 3.61 (s, 3H); 3.22 (ddd, J = 32.7, 15.0, 3.2 Hz, 1H); 3.10-2.93 (m, 3H). **13C-NMR (100 MHz, CDCl₃) δ (ppm)** 171.1; 168.8 (d, J = 19.6 Hz); 135.5; 135.4; 129.4; 129.1; 128.6; 128.4; 127.2; 127.0; 91.9 (d, J = 188.9 Hz); 52.7; 52.4; 38.4 (d, J = 20.1 Hz); 38.0. **LR-MS** Calc’d (m+h): 330.15; Found (m+h) 330.1. **IR** Wavenumber (cm⁻¹, NaCl) 3031.3; 2953.2; 1804.9; 1745.4; 1678.4; 1528.0; 1497.8; 1454.7; 1216.6; 1124.7; 1064.9; 1030.9. \([α]_D^{26.2} = +10.3° \text{ (c = 1.9, CH}_2\text{Cl}_2).} \) **Chiral HPLC Method:** IC column; 10% isopropanol in hexanes; tᵣ(maj) = 13.5 min, tᵣ(min) = 15.9 min, 99:1 dr.
1H-NMR (400 MHz, CDCl₃) δ (ppm) 7.26-7.13 (m, 8H); 6.71-6.68 (m, 2H); 6.56 (br s, 1H); 5.03 (ddd, J = 49.1, 6.4, 3.7 Hz, 1H); 4.85-4.80 (m, 1H); 3.62 (s, 3H); 3.20 (ddd, J = 26.5, 14.8, 3.7 Hz, 1H); 3.10-2.94 (m, 2H); 2.80 (dd, J = 13.8, 5.8 Hz, 1H). 13C-NMR (100 MHz, CDCl₃) δ (ppm) 171.1; 168.4 (d, J = 19.8 Hz); 135.2; 135.1; 129.9; 129.1; 128.5; 128.4; 127.2; 127.1; 52.3; 38.3; 38.1 (d, J = 3.7 Hz); 27.3; 27.0. LR-MS Calc’d (m+h): 330.15; Found (m+h) 330.2.

IR Wavenumber (cm⁻¹, NaCl) 3031.6; 2954.3; 1804.9; 1745.0; 1679.0; 1524.8; 1497.5; 1454.8; 1367.7; 1215.6; 1124.3; 1079.9; 1050.5; 1012.8. [α]D²⁶⁺ = +190.9 ° (c = 0.6, CH₂Cl₂). Chiral HPLC Method: IC column; 10% isopropanol in hexanes; t_R(maj) = 11.6 min, t_R(min) = 16.7 min, 98:2 dr.

1H-NMR (400 MHz, CDCl₃) δ (ppm) 7.20-7.11 (m, 8H); 6.96-6.94 (m, 2H); 6.28 (s, 1H); 5.15-5.00 (m, 2H); 3.23 (ddd, J = 26.2, 14.9, 3.8 Hz, 1H); 3.07 (ddd, J = 32.5, 14.9, 6.2 Hz, 1H); 1.41 (d, J = 7.0 Hz, 3H). 13C-NMR (100 MHz, CDCl₃) δ (ppm) 167.9; 142.2; 135.1; 129.7; 128.6; 128.4; 127.3; 126.9; 125.9; 91.8 (d, J = 188.7 Hz); 48.1; 38.2 (J = 19.5 Hz); 21.6. LR-MS Calc’d (m+h): 272.14; Found (m+h) 272.1. IR Wavenumber (cm⁻¹, NaCl) 1687.0; 1654.9; 1603.4; 1584.3; 1537.7; 1496.0; 1453.5; 1425.4; 1376.3; 1325.8; 1291.9; 1210.8; 1181.9; 1130.0; 1101.0; 1066.8; 1026.9. [α]D²⁶⁺ = +67.3 ° (c = 0.6, CH₂Cl₂). Chiral HPLC Method: ODH column; 5% isopropanol in hexanes; t_R(maj) = 13.3 min, t_R(min) = 10.7 min, 96:4 dr.
\[\text{Ph} - \text{F} - \text{N} - \text{Me}\]

**1H-NMR (400 MHz, CDCl}_3\]** δ (ppm) 7.45-7.39 (m, 2H); 7.31-7.17 (m, 8H); 6.22 (br s, 1H); 5.12-4.97 (m, 2H); 3.26 (ddd, \(J = 26.4, 14.8, 3.7\) Hz, 1H); 3.11 (ddd, \(J = 32.4, 14.8, 6.3\) Hz, 1H); 1.23 (d, \(J = 6.9\) Hz, 3H).

**13C-NMR (100 MHz, CDCl}_3\]** δ (ppm) 170.5, 133.7, 130.1, 129.7, 128.7, 128.45, 128.35, 127.0, 126.1, 88.5 (d, \(J = 179.0\) Hz), 48.2, 38.4 (d, \(J = 19.6\) Hz), 21.4.

**LR-MS** Calc’d (m+h): 272.14; Found (m+h) 272.1. **IR** Wavenumber (cm\(^{-1}\), NaCl) 1686.4; 1653.2; 1540.8; 1325.9; 1291.8; 1180.7; 1129.0; 1100.8; 1072.9; 1048.4. \([\alpha]D^{26.2} = -35.8^\circ\) (c = 0.7, CH\(_2\)Cl\(_2\)). **Chiral HPLC Method:** ODH column; 5% isopropanol in hexanes; \(t_R\)(maj) = 8.6 min, \(t_R\)(min) = 6.7 min, 95:5 dr.

\[\text{Ph} - \text{F} - \text{N} - \text{Me}\]

**1H-NMR (400 MHz, CDCl}_3\]** δ (ppm) 7.25-7.18 (m, 5H); 5.28-5.13 (m, 1H); 4.78 (br s, 0.5 H); 4.39 (br s, 0.5 H); 4.19 (br s, 0.5 H); 3.52 (br s, 0.5 H); 3.18-3.05 (m, 2.5 H); 2.95-2.63 (m, 1.5 H); 1.62-1.23 (m, 6H); 1.1 (d, 3H, \(J = 7.0\) Hz). **13C-NMR (100 MHz, CDCl}_3\]** δ (ppm) 129.5, 128.5; 126.9; 44.7; 38.7; 38.5; 29.7; 25.9; 25.4; 18.6; 16.9. **LR-MS** Calc’d (m+h): 250.15; Found (m+h) 250.2. **Chiral HPLC Method:** IC column; 20% isopropanol in hexanes; \(syn\) diastereomer: \(t_R = 10.6\) min, 11.2 min, \(anti\) diastereomer: \(t_R= 11.6\) min, 12.6 min.
Derivatization of α-fluoroamides

Reduction of fluoroamide 32b to fluoroamine 34. To an argon purged round bottom flask equipped with a stir bar and reflux condenser was added 2-fluoro-3-phenyl-1-(piperidin-1-yl)propan-1-one (39 mg, 0.166 mmol, 1 equiv) followed by dry THF (1.7 mL, 0.1M). Lithium aluminum hydride (25 mg, 0.66 mmol, 4 equiv) was added portionwise and the reaction heated under argon to reflux. Upon consumption of starting material (monitored by TLC, ca. 1h), the reaction was cooled to ambient temperature and quenched slowly with saturated Rochelle’s salt solution (1.7 mL). The product was extracted into ether (3x2 mL), and the combined organic extracts washed with brine (3 mL). The organic extracts were concentrated to give 1-(2-fluoro-3-phenylpropyl)piperidine as a colorless oil (27 mg, 73 % yield).

1H-NMR (400 MHz, CDCl3) δ (ppm) 7.33-7.12 (m, 5H); 5.00-4.77 (m, 1H); 3.00-2.90 (m, 2H); 2.74-2.28 (m, 6H); 1.62-1.40 (m, 6H). 13C-NMR (100 MHz, CDCl3) δ (ppm) LR-MS Calc’d (m+h): 222.16; Found (m+h) 222.2. IR Wavenumber (cm⁻¹, NaCl) 2934.3; 2582.8; 1496.3; 1453.8; 1157.4; 1119.7; 1075.8; 1030.6. [α]D26.2 = -5.6 ° (c =0.8, CH2Cl2). Chiral HPLC Method: OC column; 3% isopropanol in hexanes; tR(maj) = 4.3 min, tR(min) = 4.5 min, 90 % ee.

Double alkylation of fluoro Weinreb amide 32c to tertiary alcohol 35. To a flame dried, argon purged 10 mL round bottom flask equipped with a stir bar was added 32c (64 mg, 0.30 mmol), dissolved in 3 mL dry THF (0.1M). The solution was cooled to -20 °C and stirred.
Allylmagnesium bromide (1M in ether, 0.40 mL, 1.33 equiv) was added dropwise and the reaction stirred for 15 min. Upon complete reaction as judged by TLC, saturated ammonium chloride solution (3 mL) was added and the mixture warmed to ambient temperature. The product was extracted into ether (3x3 mL) and the combined organic layers washed with brine (3 mL). The organic extract were then dried over magnesium sulfate, filtered and concentrated to give the allyl ketone as a colorless oil (50 mg crude, 83 %).

The crude ketone was transferred to a 10 mL round bottom flask to which was added an oven dried stir bar, and the flask evacuated and flushed with argon. The ketone was redissolved in dry THF (3 mL), cooled to -78 °C and to it was added MeLi dropwise (1.5M in ether, 0.60 mL, 3.0 equiv). The reaction was stirred at -78 °C until complete reaction was verified by TLC, quenched into cold ammonium chloride solution and extracted into ether (3x3 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to give tertiary alcohol 35 as a colorless oil. The product was purified by flash chromatography (10% ethyl acetate in hexanes) to yield 42 mg (67% yield).

$^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.31-7.22 (m, 4H), 5.93-5.86 (m, 1H), 5.18-5.12 (m, 2H), 4.49 (ddd, $J = 47.8, 8.4, 4.1$ Hz, 1H), 2.98-2.88 (m, 2H), 2.37 (dd, $J = 7.2, 2.9$ Hz, 2H), 1.98 (s, 1H), 1.24 (s, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 137.8, 132.9, 129.2, 128.4, 126.5, 119.1, 99.4, 97.7, 73.4, 43.1, 35.8, 22.3. LR-MS Calc’$d$ (m+h); Found (m+h). Chiral HPLC Method: ODH column; 1% isopropanol in hexanes; First diastereomer: $t_R1 = 12.0$ min, $t_R2 = 12.4$ min; Second diastereomer: $t_R1 = 12.8$ min, $t_R2 = 14.4$ min.
CHAPTER 2 EXPERIMENTAL

General methods

All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Tetrahydrofuran, dichloromethane, toluene and diethyl ether used as reaction solvents were degassed with argon and passed through two columns of neutral alumina. ACS reagent grade pyridine was ordered from Sigma-Aldrich and used as received. Column chromatography was performed on SiliCycle®SilicaFlash® P60, 40-63µm 60A. Thin layer chromatography was performed on SiliCycle® 250µm 60A plates. Visualization was accomplished with UV quench, KMNO₄, or aqueous ceric ammonium molybdate dips followed by heating. ¹H spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift is parts per million (δ, ppm) for chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants (Hz). ¹³C spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm.

Reagents were purchased from Aldrich and used as received unless otherwise specified. Iodoxybenzoic acid (IBX) was prepared from 2-iodobenzoic acid by known procedures and stored at 0 °C.⁹¹ Tebbe’s reagent was synthesized by Grubbs’ method and stored in a Schlenk vessel at 0 °C.⁹²

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Synthesis of the bottom fragment diene

Preparation of vinylstannane 120. To a flame-dried, argon-purged 100 mL round-bottom flask was added copper(I) chloride (99 mg, 1 mmol, 0.1 equiv), triphenylphosphine (393 mg, 1.5 mmol, 0.15 equiv) and potassium tert-butoxide (112 mg, 1 mmol, 0.1 equiv). The flask was evacuated and flushed with argon, then dry toluene (20 mL, 0.5M) was added. To the resulting orange-red mixture was added tributyltin hydride (4 mL, 15 mmol, 1.5 equiv). The reaction was stirred for 1h at ambient temperature, at which time a color change to dark red was observed. Ethyl butynoate (1.12g, 10 mmol, 1 equiv) was then added and the reaction stirred overnight at room temperature. When complete consumption of ethyl butynoate was observed by TLC (ca. 16h), the reaction was purified on a short plug of silica gel, then concentrated to a red oil. The
crude oil was loaded onto silica gel, then purified by chromatography (0% to 5% EtOAc in hexanes) to yield 120 as a colorless oil (3.42g, 85%).

**1H-NMR (400 MHz, CDCl₃) δ (ppm)** 6.16 (q, J = 6.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.00 (d, J = 6.8 Hz, 3H), 1.49-1.43 (m, 6H), 1.33-1.24 (m, 6H), 0.94-0.85 (m, 15H). **13C-NMR (100 MHz, CDCl₃) δ (ppm)** 194.7, 171.2, 147.9, 136.9, 133.6, 59.9, 28.9, 27.3, 18.2, 14.4, 13.6, 10.2.

**Preparation of vinyl iodide 71.** To a 25 mL argon-purged round-bottom flask equipped with a magnetic stir bar was added a solution of 120 (403 mg, 1 mmol) in dichloromethane (5 mL, 0.2M). Iodine (254 mg, 1 mmol, 1 equiv) was added and the reaction stirred at ambient temperate and monitored by TLC. Upon consumption of 120 (ca. 90 min), the reaction was quenched with saturated sodium thiosulfate solution and extracted into DCM (3x5 mL). The combined organic extracts were washed with KF solution (10 wt%, 5 mL) and brine, then dried over magnesium sulfate, filtered and concentrated to a yellow oil. The crude product was purified by silica gel chromatography (0% to 5% EtOAc in hexanes) to yield 71 as a colorless oil (inseparable mixture 2:1 with Bu₃SnI, 145 mg corrected, 60%).

**1H-NMR (400 MHz, CDCl₃) δ (ppm)** 6.98 (q, J = 7.4 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.00 (d, J = 7.4 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). **13C-NMR (100 MHz, CDCl₃) δ (ppm)** 194.7, 191.8, 150.8, 62.1, 26.8, 17.5.

**Preparation of vinylpinacolboronic ester 70.** In a 100 mL round bottom flask equipped with a magnetic stir bar, a solution of freshly distilled cyclohexene (1.64 g, 20 mmol, 2 equiv) in THF
(40 mL, 0.25M) was prepared and cooled to 0 °C. Borane-THF complex (1M in THF, 10 mL, 1 equiv) was added. The resultant solution was stirred and warmed to ambient temperature over 1h, then cooled back to 0 °C. TBS-protected 3-butyln-1-ol 69 (1.84 g, 10 mmol) was then added and the reaction stirred and warmed again to ambient temperature. After 1h, trimethylamine N-oxide dihydrate (2.28 g, 20 mmol, 2 equiv) was added, and the reaction was stirred for another hour. Pinacol (1.18 g, 10 mmol, 1 equiv) was then added, and the reaction was stirred overnight (ca. 14h). The reaction was diluted with 40 mL ether, filtered over a sintered glass frit and concentrated to a colorless oil. The crude product was purified by silica gel chromatography (5% to 10% EtOAc in hexanes) to give the 70 as a colorless oil (2.6g, 83%).

**1H-NMR (300 MHz, CDCl₃) δ (ppm)** 6.62-6.54 (m, 1H), 5.49 (d, J = 17.9 Hz, 1H), 3.68 (t, J = 7.1 Hz, 2H), 2.41-2.35 (m, 2H), 1.24 (d, J = 8.3 Hz, 12H), 0.90-0.88 (m, 9H), 0.04 (s, 6H).

**Coupling of vinyl iodide 71 and pinacolboronic ester 70.** To a 100 mL round bottom flask equipped with a magnetic stir bar in an inert atmosphere glove box was added cesium fluoride (481 mg, 3.16 mmol, 1 equiv), bistriphenylphosphine palladium chloride (111 mg, 0.18 mmol, 0.05 equiv) and potassium carbonate (1.31 g, 9.5 mmol, 3 equiv). The flask was sealed with a rubber septum, removed from the glove box, evacuated and flushed with argon. Absolute ethanol (32 mL, 0.1M) was added, and the mixture stirred and degassed with argon for 30 min. Vinyl iodide 71 (1.07 g, 3.16 mmol, 1 equiv) was added, followed by vinylboronic ester 70 (0.99 g, 3.16 mmol, 1 equiv). The reaction was heated to 70 °C and stirred overnight (ca. 16h). The mixture was then cooled to ambient temperature and concentrated to remove ethanol. The
resultant brown oil was then diluted with ether (30 mL) and water (30 mL) and phase split. The aqueous layer was extracted with ether (2x30 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to a brown oil. This crude oil was then distilled (130-140 °C at 10 mm Hg) to give diene 121 as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 6.06 (d, $J = 15.8$ Hz, 1H), 5.88 (d, $J = 7.3$ Hz, 1H), 5.68 (d, $J = 15.9$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.64 (t, $J = 6.8$ Hz, 2H), 2.29 (dd, $J = 7.6$, 7.4 Hz, 2H), 1.86 (d, $J = 7.3$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

**Deprotection of TBS ether 121.** In a 25 mL round bottom flask equipped with a magnetic stir bar, 121 (606 mg, 2 mmol) was dissolved in methanol (10 ml, 0.2M). Para-toluenesulfonic acid (77 mg, 0.2 equiv) was added, and the reaction was stirred for 2h. The reaction mixture was concentrated and the product distilled directly to give 122 as a colorless oil (280 mg, 76% yield).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 6.15-6.09 (m, 1H), 5.93 (t, $J = 7.3$ Hz, 1H), 5.70-5.65 (m, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.67 (q, $J = 6.1$ Hz, 2H), 2.36 (d, $J = 6.4$ Hz, 2H), 1.87 (d, $J = 7.3$ Hz, 3H), 1.34 (t, $J = 7.1$ Hz, 3H).

**Preparation of bromide 72.** In an argon-purged 25 mL round bottom flask equipped with a magnetic stir bar, 72 (280 mg, 1.5 mmol) was dissolved in methylene chloride (15 mL, 0.1M). Carbon tetrabromide (550 mg, 1.65 mmol, 1.1 equiv) and triphenylphosphine (433 mg, 1.65 mmol, 1.1 equiv) were added and the reaction stirred for 24h. The reaction was diluted with
water and extracted into methylene chloride (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to an oil. The crude product was purified by silica gel chromatography (20% to 50% EtOAc in hexanes) to give 72 as a colorless oil (274 mg, 74%).

\[ ^{1}H\text{-NMR (300 MHz, CDCl}_3\delta (\text{ppm}) \] 6.11 (d, \( J = 15.3 \text{ Hz})\), 5.97 (q, \( J = 7.4 \text{ Hz})\), 5.68 (dt, \( J = 15.3, 7.4 \text{ Hz})\), 4.28 (q, \( J = 7.1 \text{ Hz})\), 3.40-3.36 (m, 2H), 2.64 (q, \( J = 7.1 \text{ Hz})\), 1.88 (d, \( J = 7.3 \text{ Hz})\), 1.36-1.31 (m, 3H).
Synthesis of the model system top fragment

Preparation of dioxolane 80: To a 2L round-bottom flask equipped with a magnetic stir bar, reflux condenser and Dean-Stark apparatus was added 2-acetylfuran (55g, 0.5 mol) and benzene (1L, 0.5M). Ethylene glycol (200 mL, 3.6 mol, 7.2 equiv) was then added, followed by p-toluenesulfonic acid (9.5g, 0.05 mol, 0.1 equiv). The reaction mixture was heated to reflux and stirred vigorously until 90% completion could be observed by crude NMR (ca. 2d). At this point, the reaction was cooled to ambient temperature and quenched into 500 mL of a mixture of saturated sodium bicarbonate and ice. The resultant biphasic mixture was phase split and the aqueous later extracted into ether (3x500 mL). The organic layers were combined, washed with brine and dried over magnesium sulfate. The crude mixture was filtered and concentrated to a brown oil. The crude oil was purified by silica gel chromatography (5% to 10% EtOAc in hexanes) then distilled (ca. 70 °C at 10 mm Hg) to give 80 as a colorless oil (43.1g, 56%).
\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.35 (dd, \(J = 1.6, 1.1\) Hz, 1H), 6.29 (m, 2H), 4.06-3.96 (m, 4H), 1.72 (s, 3H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 194.7, 117.6, 111.6, 81.1, 37.1, 36.2, 32.8, 26.1, 17.1.

Preparation of furylcarbinol 123. To an argon-purged 500 mL round-bottom flask equipped with a magnetic stir bar was added dry THF (200 mL, 0.1M), then cooled to -78 °C. \(t\)-butyllithium solution (1.7M in hexanes, 12.3 mL, 21 mmol, 1.05 equiv) was added dropwise. To the resultant yellow solution was slowly added furyldioxolane 80 (3.09 g, 20 mmol). The mixture was warmed to 0 °C with vigorous stirring, then back to -78 °C. Freshly distilled isobutyraldehyde (2.16g, 30 mmol, 1.5 equiv) was then added and the mixture allowed to warm to ambient temperature with stirring then monitored by TLC. When complete consumption of 80 was observed, the reaction was quenched with 200 mL saturated ammonium chloride solution and extracted into ether (3x200 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give 123 as a yellow oil (4.45g, 99% crude).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 6.22 (d, \(J = 3.2\) Hz, 1H), 6.12-6.11 (m, 1H), 4.33 (d, \(J = 5.2\) Hz, 1H), 4.01-3.95 (m, 4H), 2.05 (m, \(J = 6.8\) Hz, 1H), 1.69 (s, 3H), 0.97 (d, \(J = 6.7\) Hz, 3H), 0.84 (d, \(J = 6.8\) Hz, 3H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 156.1, 153.3, 106.9, 106.6, 104.6, 73.4, 65.0, 33.3, 24.2, 18.6, 18.1.
**Preparation of 3-pyrone 96.** To an argon-purged 500 mL round-bottom flask equipped with a magnetic stir bar was added crude 123 (4.45g, 20 mmol), dissolved in 100 mL THF (0.2 M). To this solution was added water (33 mL). To this vigorously stirred solution was added sodium bicarbonate (3.36g, 40 mmol, 2 equiv) and sodium acetate (1.64g, 20 mmol, 1 equiv). Upon dissolution of the salts, N-bromosuccinimide (3.56g, 20 mmol, 1 equiv) was added, and the reaction mixture stirred at ambient temperature and monitored by TLC. Upon consumption of 123 (ca 3h), the reaction was diluted with water (66 mL) and extracted into ether (3x100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 96 as a yellow oil. The crude oil was purified by silica gel chromatography (20% to 40% EtOAc in hexanes) to give 96 as a colorless oil (4.07g, 84% over 2 steps).

**1H-NMR (400 MHz, CDCl3) δ (ppm)** 7.03 (d, $J = 10.4$ Hz, 1H), 6.14 (d, $J = 10.3$ Hz, 1H), 4.37 (s, 1H), 4.16-4.04 (m, 5H), 2.45 (td, $J = 6.9$, 2.6 Hz, 1H), 1.37 (s, 3H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H).

**13C-NMR (100 MHz, CDCl3) δ (ppm)** 196.4, 144.6, 129.8, 110.0, 95.0, 78.4, 66.3, 65.7, 28.7, 20.7, 19.0, 16.2.

**Preparation of diene 97.** To a flame-dried, argon purged 500 mL round bottom flask equipped with a magnetic stir bar was added 96 (1.21g, 5 mmol), dissolved in dry THF (40 mL) and ACS reagent grade pyridine (10 mL, 0.1M total). The solution was cooled to -78 °C and stirred, then Tebbe’s reagent (0.5-0.9M in toluene, pre-titrated, 10 mmol, 2 equiv) was added dropwise. The reaction is checked by TLC to ensure complete conversion, and more Tebbe’s reagent is added if necessary. Then, the reaction is warmed to 0 °C and stirred (Note: the reaction goes to
completion in the capillary when it warms, the reaction must be warmed to 0 °C to ensure complete conversion). After stirring for 1h, the reaction is quenched carefully with 15% NaOH (10 mL) in an ice bath. Note: HAZARD. The aqueous solution must be added slowly. Vigorous methane gas evolution and exotherm are observed. The resultant red to green slurry is stirred and warmed to ambient temperature, then diethyl ether is added (100 mL). The resultant orange solid is removed by filtration over a bed of Celite and the filtrate concentrated by rotary evaporation (Note: the remaining pyridine is codistilled by several additions of toluene and reconcentration). The crude product is then purified by silica gel chromatography (10% to 20% EtOAc in hexanes) and isolated as a yellow wax (1.90g, 79%).

\[ ^1H \text{-NMR (400 MHz, CDCl}_3 \] \( \delta \) (ppm) 6.36 (d, \( J = 10.2 \) Hz, 1H), 5.94 (d, \( J = 10.1 \) Hz, 1H), 5.02-4.97 (m, 2H), 4.46 (d, \( J = 2.1 \) Hz, 1H), 4.12-4.00 (m, 4H), 2.24 (td, \( J = 6.8, 2.2 \) Hz, 1H), 1.31 (s, 3H), 1.08 (d, \( J = 6.9 \) Hz, 3H), 0.89 (d, \( J = 6.8 \) Hz, 3H). \[ ^{13}C \text{-NMR (100 MHz, CDCl}_3 \] \( \delta \) (ppm) 140.3, 132.4, 125.5, 112.1, 98.4, 95.6, 72.9, 66.1, 65.6, 28.3, 20.4, 20.0, 15.2.

Preparation of 4-pyrone 99. To an argon-purged 100 mL round bottom flask equipped with a magnetic stir bar was added 97 (481 mg, 2 mmol), dissolved in DMSO (20 mL, 0.1M). IBX (4.48g, 16 mmol, 8 equiv) was then added and the reaction mixture heated to 50 °C and stirred until complete consumption of starting material is observed by TLC (ca. 6h). The reaction mixture was then cooled to 0 °C and quenched by the addition of 20 mL of sat. NaCl solution. The resultant slurry was extracted into ether (3x20 mL). The combined organic extracts were washed successively with sat. NaHCO\textsubscript{3} (20 mL) and brine (20 mL), dried over magnesium
sulfate and filtered to give crude 99 as a yellow oil. The crude oil was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give 99 as a colorless oil (240 mg, 50%).

**1H-NMR (400 MHz, CDCl3) δ (ppm)**

6.14 (s, 1H), 5.67 (s, 1H), 5.25 (s, 1H), 4.71 (dt, $J = 7.4, 1.2$ Hz, 1H), 3.98-3.85 (m, 4H), 2.10-1.99 (m, 1H), 1.53 (s, 3H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H).

**13C-NMR (100 MHz, CDCl3) δ (ppm)**

172.2, 139.7, 121.9, 105.9, 101.3, 88.2, 65.2, 31.5, 22.9, 18.7, 18.1.

**Preparation of 4-pyranone 111.** To an argon-purged 50 mL round bottom flask equipped with a magnetic stir bar was added 99 (240 mg, 1 mmol) dissolved in dry CH2Cl2 (10 mL, 0.1M). The solution was cooled to -78 °C, and BF3•OEt2 (126 µL, 1 mmol, 1 equiv) was added. The mixture was stirred and warmed to 0 °C, then triethylsilane (595 µL, 4 mmol, 4 equiv) was added and the reaction allowed to warm to ambient temperature. When complete consumption of starting material was observed by TLC (ca. 20h), the reaction was cooled to 0 °C and quenched with sat. NaHCO₃ (10 mL). The mixture was phase split and extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 111 as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give 111 as a yellow oil (180 mg, 75%).

**1H-NMR (400 MHz, CDCl3) δ (ppm)**

5.46 (s, 1H), 4.28 (d, $J = 6.5$ Hz, 1H), 3.76 (d, $J = 10.2$ Hz, 1H), 2.36-2.34 (m, 1H), 2.02-1.98 (m, 1H), 1.36 (dd, $J = 6.7, 3.1$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 1H).
Hz, 3H), 0.97 (d, J = 7.4 Hz, 2H), 0.83 (d, J = 6.8 Hz, 3H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 99.6, 87.6, 67.4, 41.5, 28.5, 20.8, 19.4, 17.7, 9.5.

Preparation of saturated hemiketal 124. To an argon purged glass pressure vessel equipped with a regulator and a magnetic stir bar was added 111 (180 mg, 0.75 mmol) dissolved in MeOH (7.5 mL, 0.1M). Pd/C (10 wt%, 180 mg) was added, and the vessel pressurized to 60 psi with hydrogen gas. The mixture was stirred at ambient temperature for 6h, then hydrogen pressure released and the vessel purged with argon (Note: to avoid fire, make sure there is no hydrogen left in the reaction vessel). The reaction mixture was run down a short plug of silica, eluted with EtOAc. The eluent was concentrated to a yellow oil (180 mg, 100% crude). Crude 124 was carried to the next step without further purification.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 3.95-3.91 (m, 4H), 3.37 (dd, J = 11.9, 2.4 Hz, 1H), 3.15 (d, J = 4.5 Hz, 3H), 3.09 (dd, J = 10.0, 2.1 Hz, 1H), 1.92-1.90 (m, 1H), 1.80-1.64 (m, 2H), 1.33 (s, 3H), 0.97 (d, J = 6.4 Hz, 3H), 0.85 (dd, J = 11.6, 7.1 Hz, 2H), 0.79 (q, J = 6.0 Hz, 4H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 194.7, 109.2, 101.9, 85.3, 83.1, 80.5, 78.4, 65.6, 65.0, 47.4, 46.7, 35.5, 29.4, 27.1, 20.4, 17.9, 7.6.

Preparation of dione 110. To an argon purged 50 mL round bottom flask equipped with a stir bar was added crude 124 (180 mg, 0.75 mmol). Formic acid (5 mL) was added and the reaction
heated to 60 °C and stirred for 2h. Sat. NaHCO₃ (10 mL) was added and the mixture extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 110 as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give 110 as a yellow oil (80 mg, 54%).

**1H-NMR (400 MHz, CDCl₃) δ (ppm)** 3.95 (dd, J = 11.8, 3.8 Hz, 1H), 3.12 (dd, J = 9.7, 2.4 Hz, 1H), 2.57-2.46 (m, 3H), 2.28 (s, 3H), 1.91 (dt, J = 9.7, 6.6 Hz, 1H), 1.09 (t, J = 6.8 Hz, 6H), 0.82 (d, J = 6.8 Hz, 3H). **13C-NMR (100 MHz, CDCl₃) δ (ppm)** 209.9, 206.3, 85.6, 81.3, 47.2, 39.2, 29.0, 26.1, 20.0, 17.6, 10.4.

Preparation of enol carbonate 112. To an argon purged 10 mL round bottom flask equipped with a stir bar was added NaHMDS (55 mg, 0.3 mmol, 1.2 equiv). Dry THF was added (1.5 mL) and the slurry was cooled to -78 °C. TMEDA (45 µL, 0.3 mmol, 1.2 equiv) was added and the mixture stirred and allowed to warm until a clear solution was observed. The mixture was cooled back to -78 °C, followed by the addition of 110 (50 mg, 0.25 mmol) in 1 mL dry THF (2.5 mL total, 0.1M). The reaction was stirred at -78 °C for 30 min, then ethyl chloroformate (29 µL, 0.3 mmol, 1.2 equiv) was added. The reaction was stirred at -78 °C for 30 min, then quenched with sat. NH₄Cl (2.5 mL). After warming to ambient temperature, the mixture was extracted into ether (3x5mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 112 as a brown oil. The crude product was purified by silica gel chromatography (10% to 20% EtOAc in hexanes) to give 112 as a yellow oil (60 mg, 94%).
$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 5.14-5.07 (m, 2H), 4.28-4.17 (m, 2H), 3.23-3.09 (m, 1H), 2.69-2.32 (m, 2H), 1.93-1.80 (m, 1H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.14-1.04 (m, 6H), 0.84 (dd, $J = 15.5, 6.8$ Hz, 3H).
Exploratory synthesis of top fragment

Preparation of ketoacid 74. To a flame-dried, argon purged 250 mL round-bottom flask equipped with a magnetic stir bar was added THF (100 mL, 0.05M), cooled to -78 °C. t-BuLi was added (4.4 mL, 1.7 M, 7.5 mmol, 1.5 equiv), followed by furan (510 mg, 7.5 mmol, 1.5 equiv). The resultant solution was stirred and warmed until a colorless solution was observed. The solution was then cooled back to -78 °C and transferred by cannula to another flame-dried 250 mL round bottom flask containing zinc iodide (3.19 g, 10 mmol, 2 equiv). The resultant slurry was warmed to ambient temperature and stirred for 2h. Then, Rh(cod)Cl dimer (62 mg, 0.125 mmol, 0.025 equiv) and H-PHOX (83 mg, 0.25 mmol, 0.05 equiv) were added, followed by 3,5-dimethylglutaric anhydride (711 mg, 5 mmol). The resultant dark red mixture was heated to 50 °C and stirred for 24h. The reaction was cooled to ambient temperature and quenched with sat. NaHCO₃ (100 mL). The mixture was extracted into ether (2x100 mL). The organic extracts
were then washed with water (100 mL). The aqueous layers were combined and acidified with hydrochloric acid to pH = 1. This aqueous layer was then extracted into ether (3x100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 74 as a brown oil. The crude product was taken to the next step without further purification.

Preparation of lactone 75. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved 74 (5 mmol theor.) in dry THF (50 mL, 0.1M). The solution was cooled to -78 °C and stirred. Lithium triethylborohydride (1M in THF, 10 mL, 2 equiv) was added dropwise and the reaction monitored by crude NMR of aliquots. After complete reaction (ca. 2h), 1M HCl (50 mL) was added and the reaction stirred vigorously while warming to ambient temperature. The reaction mixture was extracted into ether (3x200 mL), and the combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 75 as a brown oil. The crude lactone was then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) to give 75 as a colorless oil (456 mg, 47 % 2-step).

\[^1\text{H}-\text{NMR (300 MHz, CDCl}_3\text{)}\ \delta (\text{ppm})\]

7.41 (dd, \(J = 1.8, 0.8\ Hz, 1\text{H}\)), 6.37 (dd, \(J = 5.8, 1.3\ Hz, 2\text{H}\)), 4.91 (d, \(J = 10.7\ Hz, 1\text{H}\)), 2.68-2.60 (m, 1H), 2.41 (ddddd, \(J = 12.2, 10.6, 6.6, 3.4\ Hz, 1\text{H}\)), 2.06 (ddd, \(J = 13.3, 6.3, 3.1\ Hz, 1\text{H}\)), 1.53-1.40 (m, 1H), 1.32 (d, \(J = 7.0\ Hz, 3\text{H}\)), 0.90 (d, \(J = 6.6\ Hz, 3\text{H}\)).
Synthesis of diol 76. To an argon-purged 100 mL round bottom flask containing 75 (456 mg, 2.35 mmol) was added THF (23.5 mL, 0.1M) and a magnetic stir bar. The resultant solution was cooled to 0 °C and stirred vigorously. Lithium aluminum hydride (178 mg, 4.7 mmol, 2 equiv) was then added portionwise and the reaction monitored by TLC. When complete consumption of starting material was observed (ca. 1h), the reaction was quenched with water (0.18 mL), then 15% NaOH solution was added (0.18 mL) followed by water (0.54 mL). The resultant slurry was filtered over Celite and the filtrate concentrated to give a colorless oil (452 mg, 97% crude). The crude product was purified by silica gel chromatography (50% to 80% EtOAc in hexanes) to give 76 as a colorless oil (419 mg, 90%).

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm) 7.37-7.36 (m, 1H), 6.33 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.24 (dd, $J = 2.6$, 0.7 Hz, 1H), 4.46-4.44 (m, 1H), 3.76-3.72 (m, 1H), 3.50 (dt, $J = 5.0$, 2.4 Hz, 2H), 2.11-2.02 (m, 1H), 1.87-1.83 (m, 1H), 1.76-1.64 (m, 3H), 0.99-0.96 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H).

Synthesis of TBS ether 77. To a solution of 76 (419 mg, 2.1 mmol, 1.05 equiv) in methylene chloride (20 mL, 0.1M) was added TBSCl (301 mg, 2 mmol), imidazole (163 mg, 2.4 mmol, 1.2 equiv), and triethylamine (334 µL, 2.4 mmol, 1.2 equiv). The resultant solution was stirred at ambient temperature for 24h, then quenched with sat. ammonium chloride solution (20 mL). The mixture was extracted into DCM (3x20 mL) and the combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated to give a colorless oil. The crude product was purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give 77 as a colorless oil (481 mg, 77%).
Synthesis of 3-pyranone 78. In an argon purged 100 mL round bottom flask equipped with a magnetic stir bar was dissolved 77 (481 mg, 1.54 mmol) in THF (7.5 mL) and water (2.5 mL, 0.15M total). NaHCO₃ (259 mg, 3.08 mmol, 2 equiv) and NaOAc (126 mg, 1.54 mmol, 1 equiv) were added and the mixture stirred vigorously until the salts dissolve. Then, N-bromosuccinimide (279 mg, 1.54 mmol, 1 equiv) was added and the mixture stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was diluted with water (10 mL) and extracted into ether (3x10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 78 as a yellow oil. The crude product was then purified by silica gel chromatography (20% to 30% EtOAc in hexanes) to give 78 as a colorless oil (374 mg, 74%).

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta (ppm) \]
\[ 7.36 (dd, J = 1.8, 0.8 Hz, 1H), 6.32 (dd, J = 3.2, 1.8 Hz, 1H), 6.23-6.22 (m, 1H), 4.46 (dd, J = 6.5, 5.2 Hz, 1H), 3.48 (dd, J = 9.8, 5.3 Hz, 1H), 3.36 (dd, J = 9.8, 6.3 Hz, 1H), 2.10-2.05 (m, 1H), 1.76-1.56 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H). \]

\[ \text{0}_1 \text{Me} \text{Me} \text{O} \text{TBSO} \text{OH} \text{SPh} \]
Preparation of thiolate 79. To a solution of 78 (33 mg, 0.1 mmol) in methylene chloride (1mL, 0.1M) was added zinc iodide (96 mg, 0.3 mmol, 3 equiv), tetrabutylammonium iodide (37 mg, 0.1 mmol, 1 equiv) and PhSTMS (18 mg, 0.1 mmol, 1 equiv). The reaction was monitored by TLC, and when complete consumption of starting material was observed (ca. 2h), the reaction was quenched with sat. sodium bicarbonate solution (1 mL). The mixture was extracted into methylene chloride (3x1 mL) and the combined organic extracts washed with brine, dried over magnesium sulfate, filtered and concentrated to a brown oil. The crude product was purified by silica gel chromatography (5% EtOAc in hexanes) to give 79 as a yellow oil (20 mg, 48%)

\[^{1}\text{H-NMR (300 MHz, CDCl}_3\text{)}\] 7.56-7.48 (m, 3H), 7.34-7.30 (m, 2H), 7.07 (dd, \(J = 10.0, 4.0\) Hz, 1H), 6.07 (dd, \(J = 10.0, 1.2\) Hz, 1H), 5.94 (dd, \(J = 4.0, 1.1\) Hz, 1H), 3.53 (dd, \(J = 9.9, 4.9\) Hz, 1H), 3.25 (dd, \(J = 9.8, 7.1\) Hz, 1H), 2.52-2.47 (m, 1H), 1.61-1.55 (m, 1H), 1.35 (ddd, \(J = 13.5, 8.1, 5.2\) Hz, 1H), 1.05 (d, \(J = 7.0\) Hz, 3H), 0.88 (m, 12H), 0.03 (s, 6H).
Preparation of keto acid 82. To a flame-dried, argon purged 500 mL round bottom flask was added dry THF (200 mL), cooled to -78 °C. t-BuLi was added (14.7 mL, 1.7 M, 25 mmol, 1.25 equiv), followed by furyl dioxolane 80 (3.92 g, 25 mmol, 1.25 equiv). The mixture was stirred and warmed until the orange color fades to pale yellow. In a separate 1000 mL 3-neck RBF equipped with a magnetic stir bar, ZnI₂ (9.58 g, 30 mmol, 1.5 equiv) was flame-dried, then slurried in 200 mL dry THF. The solution of lithiated furan was cooled back to -78 °C, then cannulated to the slurry of ZnI₂. The reaction was allowed to warm to ambient temperature and
stirred for 2h. Rh(cod)Cl dimer (247 mg, 0.5 mmol, 0.025 equiv) and H-PHOX (331 mg, 1.0 mmol, 0.05 equiv) were added and the mixture heated to 50 °C and stirred for 10 min. 3,5-dimethylglutaric anhydride (2.48 g, 20 mmol) was then added and the reaction was stirred at 50 °C for 24h. The reaction was cooled to ambient temperature and quenched with sat. NaHCO₃ (200 mL). The mixture was extracted into ether (2x400 mL). The organic extracts were then washed with water (100 mL). The aqueous layers were combined and acidified with glacial acetic acid to pH = 4. This aqueous layer was then extracted into ether (3x400 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 82 as a brown oil. The crude product was taken to the next step without further purification.

Preparation of lactone 86. In an argon purged 500 mL round bottom flask equipped with a magnetic stir bar was dissolved 82 (20 mmol theor.) in dry THF (200 mL, 0.1M). The solution was cooled to -78 °C and stirred. Lithium triethylborohydride (1M in THF, 40 mL, 2 equiv) was added dropwise and the reaction monitored by crude NMR of aliquots. After complete reaction (ca. 2h), 15% aq. NaOH (100 mL) is added and the reaction stirred vigorously while warming to ambient temperature. After 1h, the mixture is acidified with glacial acetic acid to pH = 4 and extracted into ether (3x200 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 86 as a brown oil. Acetic anhydride (ca. 10 mL) was added to the crude product (a mixture of lactone and hydroxy acid), then concentrated by rotary evaporation. Toluene (ca. 10 mL) was then added and concentrated again. The crude
lactone was then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) to give 86 as a colorless oil (2.4g, 43 % 2-step).

**1H-NMR (400 MHz, CDCl₃)** δ (ppm) 6.29-6.25 (m, 2H), 4.86 (d, J = 10.7 Hz, 1H), 4.04-3.92 (m, 4H), 2.61 (t, J = 6.6 Hz, 1H), 2.42-2.35 (m, 1H), 2.02-2.01 (m, 1H), 1.69 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H). **13C-NMR (100 MHz, CDCl₃)** δ (ppm) 173.5, 154.9, 150.6, 110.0, 107.1, 104.5, 98.6, 81.5, 65.0, 37.3, 36.2, 32.5, 24.4, 17.3, 17.1.

**Characterization data for side product 83.** **1H-NMR (400 MHz, CDCl₃)** δ (ppm) **1H-NMR (400 MHz; CDCl₃):** δ 7.12 (d, J = 3.5 Hz, 1H), 6.51 (d, J = 3.5 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 2.66 (dt, J = 13.1, 6.5 Hz, 1H), 2.46-2.40 (m, 4H), 2.07 (ddd, J = 13.6, 6.2, 3.3 Hz, 1H), 1.49 (dd, J = 25.9, 12.5 Hz, 2H), 1.32 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H). **13C-NMR (100 MHz, CDCl₃)** δ (ppm) 222.3, 194.7, 172.9, 117.6, 111.6, 81.1, 37.1, 36.2, 32.8, 26.1, 17.1.

**Preparation of diol 100.** In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved 86 (2.26 g, 3.8 mmol) in dry THF (80 mL, 0.1M). The solution was cooled to 0 °C and stirred. Red-Al (3.73 g, 65 wt%, 12 mmol, 1.5 equiv) was added dropwise and the reaction monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was quenched with water (40 mL) then sat. NH₄Cl (40 mL). The mixture was extracted into EtOAc (3x80 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 100 as a brown oil. The crude
product was then purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give 100 as a colorless oil (1.84 g, 81%).

\[\text{1H-NMR (400 MHz, CDCl}_3\text{) } \delta \text{ (ppm)} \]

6.23 (d, \( J = 3.2 \text{ Hz, 1H} \)), 6.13 (d, \( J = 3.2 \text{ Hz, 1H} \)), 4.42 (d, \( J = 6.5 \text{ Hz, 1H} \)), 4.01-3.95 (m, 4H), 3.44 (dd, \( J = 7.5, 5.0 \text{ Hz, 2H} \)), 2.03 (s, 1H), 1.68 (s, 3H), 0.92 (d, \( J = 6.6 \text{ Hz, 3H} \)), 0.84 (d, \( J = 6.8 \text{ Hz, 3H} \)).

\[\text{13C-NMR (100 MHz, CDCl}_3\text{) } \delta \text{ (ppm)} \]

194.8, 156.0, 153.2, 107.1, 106.8, 104.6, 72.6, 67.0, 65.1, 36.2, 35.9, 33.2, 24.2, 18.1, 16.6.

**Preparation of 3-pyranone 101.** In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved 100 (1.84 g, 6.5 mmol) in THF (34 mL) and water (9 mL, 0.15M total). NaHCO\(_3\) (1.09 g, 13 mmol, 2 equiv) and NaOAc (533 mg, 6.5 mmol, 1 equiv) were added and the mixture stirred vigorously until the salts dissolve. Then, \( N \)-bromosuccinimide (1.16 g, 6.5 mmol, 1 equiv) was added and the mixture stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (ca. 2h), the reaction was diluted with water (45 mL) and extracted into ether (3x65 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 101 as a yellow oil. The crude product was then purified by silica gel chromatography (50% to 70% EtOAc in hexanes) to give 101 as a colorless oil (1.74 g, 89%).

\[\text{1H-NMR (400 MHz, CDCl}_3\text{) } \delta \text{ (ppm)} \]

7.02 (d, \( J = 10.4 \text{ Hz, 1H} \)), 6.14 (d, \( J = 10.3 \text{ Hz, 1H} \)), 4.41 (s, 1H), 4.15-3.99 (m, 4H), 3.49-3.43 (m, 2H), 2.39 (dt, \( J = 4.4, 2.3 \text{ Hz, 1H} \)), 1.59-1.53 (m, 1H), 1.35 (s, 3H), 1.09-0.99 (m, 3H), 0.93-0.86 (m, 3H).

\[\text{13C-NMR (100 MHz, CDCl}_3\text{) } \delta \text{ (ppm)} \]

197.0, 144.9, 129.6, 109.9, 95.1, 78.5, 67.1, 66.2, 65.7, 35.4, 33.2, 31.0, 20.6, 18.1, 17.0.
Preparation of tosylate 102. In an argon purged 250 mL round bottom flask equipped with a magnetic stir bar was dissolved 101 (1.74 g, 5.8 mmol) in CH₂Cl₂ (29 mL, 0.2M). Triethylamine (3.23 mL, 23.2 mmol, 4 equiv) and p-toluenesulfonyl chloride (2.21 g, 11.6 mmol, 2 equiv) were added, followed by DMAP (71 mg, 0.58 mmol, 0.1 equiv). The reaction was stirred at ambient temperature and monitored by TLC. After complete consumption of starting material was observed (6-18h), the reaction was quenched with sat. NH₄Cl (29 mL) and extracted into ether (3x30 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered to give crude 102 as a yellow oil. The crude product was then purified by silica gel chromatography (20% to 50% EtOAc in hexanes) to give 102 as a colorless oil (2.21 g, 84%).

¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.74 (d, J = 8.3 Hz, 2H), 7.33-7.28 (m, 2H), 6.13 (dd, J = 5.4, 0.6 Hz, 1H), 4.99 (d, J = 10.3 Hz, 1H), 4.23 (s, 1H), 3.84-3.76 (m, 2H), 2.93 (dd, J = 6.5, 4.1 Hz, 1H), 2.42 (s, 3H), 1.69 (td, J = 6.6, 3.5 Hz, 1H), 1.45 (ddd, J = 13.7, 10.6, 4.0 Hz, 1H), 1.23 (t, J = 7.1 Hz, 2H), 1.05 (dd, J = 11.2, 6.7 Hz, 3H), 0.85 (dd, J = 11.8, 6.7 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 169.9, 149.2, 144.7, 143.6, 139.3, 132.9, 129.8, 127.8, 121.9, 119.3, 75.2, 40.1, 31.3, 29.1, 21.6, 21.3, 15.9.
Preparation of diene 103. To a flame-dried, argon purged 100 mL round bottom flask equipped with a magnetic stir bar was added 103 (2.21 g, 4.9 mmol). Dry THF (20 mL) was added and the solution cooled to -78 °C. Pyridine (5 mL, 0.2M total) was then added, followed by Tebbe’s reagent (20 mL, 0.5M in PhMe, 10 mmol, 2 equiv). The reaction was monitored by TLC (mini workup with HCl to remove pyridine). After complete consumption of starting material was observed, the reaction was warmed to 0 °C and stirred for 30 min (Note: the reaction goes to completion in the capillary when it warms, the reaction must be warmed to 0 °C to ensure complete conversion). The reaction was then quenched with 15% NaOH (10 mL) at 0 °C. Note: HAZARD. The aqueous solution must be added slowly. Vigorous methane gas evolution and exotherm are observed. The resultant red to green slurry is stirred and warmed to ambient temperature, then diethyl ether is added (25 mL). The resultant orange solid is removed by filtration over a bed of Celite and the filtrate concentrated by rotary evaporation (Note: the remaining pyridine is codistilled by several additions of toluene and reconcentration). The crude product is then purified by silica gel chromatography (30% to 40% EtOAc in hexanes) and isolated as a yellow oil (1.71g, 77%).

\[ \text{1H-NMR (300 MHz, CDCl3)} \]

\[ \delta \text{ (ppm)} \]

7.78 (d, \( J = 7.9 \ Hz \), 2H), 7.34 (d, \( J = 8.0 \ Hz \), 2H), 6.36 (d, \( J = 10.1 \ Hz \), 1H), 5.96-5.93 (m, 1H), 5.00 (d, \( J = 0.6 \ Hz \), 1H), 4.91 (d, \( J = 0.6 \ Hz \), 1H), 4.48 (t, \( J = 0.7 \ Hz \), 1H), 4.13-3.84 (m, 6H), 3.01 (s, 1H), 2.45 (s, 3H), 2.13-2.04 (m, 1H), 1.88-1.82 (m, 1H), 1.57-1.46 (m, 2H), 1.28 (d, \( J = 0.7 \ Hz \), 3H), 1.05 (d, \( J = 6.8 \ Hz \), 3H), 0.89 (dd, \( J = 6.7 \), 0.6 Hz, 3H).
Preparation of 4-pyrone 104. In an argon purged 100 mL round bottom flask equipped with a magnetic stir bar was dissolved 103 (1.71 g, 3.8 mmol) in DMSO (38 mL, 0.1M). IBX (8.51 g, 30.4 mmol, 8 equiv) was then added and the reaction was heated to 50 °C, stirred and monitored by TLC. After complete consumption of starting material was observed, the reaction mixture was then cooled to 0 °C and quenched by the addition of 38 mL of sat. NaCl solution. The resultant slurry was extracted into ether (3x40 mL). The combined organic extracts were washed successively with sat. NaHCO₃ (40 mL) and brine (40 mL), dried over magnesium sulfate and filtered to give crude 104 as a yellow oil. The crude oil was purified by silica gel chromatography (30% to 50% EtOAc in hexanes) to give 104 as a colorless oil (856 mg, 50%).

1H-NMR (400 MHz, CDCl₃) δ (ppm) 7.83-7.73 (m, 2H), 7.36-7.30 (m, 2H), 6.20 (s, 1H), 5.71 (d, J = 0.7 Hz, 1H), 5.29 (t, J = 0.5 Hz, 1H), 4.81-4.77 (m, 2H), 4.04-3.73 (m, 6H), 2.44 (d, J = 6.3 Hz, 3H), 1.97-1.88 (m, 2H), 1.71-1.50 (m, 6H), 1.10-1.02 (m, 2H), 0.95-0.81 (m, 6H).
APPENDIX

Spectral Data for Chapter 1
NO
OMe
Br
F
Spectral Data for Chapter 2
$\text{Bu}_3\text{Sn}-\text{Me}$

$\text{CO}_2\text{Et}$
$\text{Bu}_3\text{Sn} \xrightarrow{\text{Me}} \text{CO}_2\text{Et}$