The *Anti* Selective Aldol Addition of Ketones to Aldehydes via N-Amino Cyclic Carbamate Chiral Auxiliaries and the Asymmetric Total Synthesis of (+)- and (-)-Mefloquine Hydrochloride

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

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ABSTRACT

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Abstract

In the first part of this dissertation, the first asymmetric \textit{anti} selective aldol addition of a ketone-derived donor that is independent of the structure of the ketone is described. This transformation is facilitated by the use of chiral \textit{N}-amino cyclic carbamate (ACC) auxiliaries. Under certain conditions, this transformation not only exhibits near perfect \textit{anti} selectivity and enantioselectivity but also does so via thermodynamic control. Simple manipulation of the reaction conditions allows for the \textit{O}-benzylolation of the prepared aldol products and the subsequent removal of the ACC auxiliary to give the \textit{\beta}-benzyloxy ketone. Both symmetric and asymmetric ketones can be utilized, and aldol products that would otherwise be difficult if not impossible to prepare via conventional methods are able to be prepared.

The second part of this dissertation describes the asymmetric total synthesis of (\(+\)- and (\(-\)-mefloquine hydrochloride, a potent antimalarial compound. The synthesis is based on an ACC-mediated asymmetric Darzens reaction between a $\alpha$-chloro ketone and a quinoline-based aldehyde. This novel methodology gives a highly enantioenriched epoxide that can be further functionalized to prepare both enantiomers of the antimalarial drug.
Dedicated to my parents – this accomplishment would have never occurred without their efforts in raising a son who was prepared to go far in life
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1. N-Amino Cyclic Carbamate Hydrazones and Their Use in an Anti-Selective Asymmetric Aldol Reaction.

This chapter discusses original work that was done without the collaboration of other lab members.

1.1 N-Amino Cyclic Carbamate (ACC) Auxiliaries

1.1.1 Carbon-Carbon Bond Formation

Carbon-carbon bond forming reactions are fundamental to synthetic organic chemistry. The value of these reactions is quite significant, and their application has seen wide use in academic research, pharmaceutical development, government research, and other forms of industrial research. One challenging aspect of developing these reactions is the required ability to have structural control over the synthetic products prepared. The past few decades has seen notable advances on this front.[1, 2]

Carbon-carbon bonding forming reactions can be categorized using simple mechanistic criteria as polar reactions, free-radical reactions, pericyclic reactions, or transition-metal mediated reactions. Of all of these categories, polar reactions are the most prevalent in synthetic organic chemistry. Historically, many of these polar reactions have involved the use of highly reactive or toxic metals along with strict technical requirements for carrying them out (e.g., low temperature, inert atmosphere,
and controlled rate of addition). In some cases, the outcome of the reaction can be very particular to the manner in which it was conducted. Because of these limitations, there is clearly still a need to development new reactions that can improve on previous work while at the same time diminishing or even overcoming the technical restrictions that are associated with common approaches to carbon-carbon bond formation.

1.1.2 Ketone-Based Chiral Auxiliaries

Classical carbonyl enolate chemistry is usually accompanied by the problem of side reactions. It has been shown, however, that the use of imine or hydrazone derivatives of ketones and aldehydes gives better selectivity and higher yields. Presumably, this is due to the enhanced nucleophilicity of the anionic azaenolate intermediate and the greater regioselectivity for C-alkylation. Several chiral auxiliaries for ketones and aldehydes have been developed over the last several decades. The first reported was Yamada’s (S)-proline derived chiral auxiliary in 1969 [3]. This auxiliary gave moderate selectivity for Michael-type addition reactions of cyclic derived enamines with unsaturated esters and nitriles. In this reaction, an enamine (1.1) served as the nucleophile to give the alkylated ketone (1.2), which was formed by the condensation of the parent ketone and the chiral auxiliary. While the approach was noteworthy at the time, the asymmetric induction achieved was moderate. Meyers and Koga independently reported the alkylation of lithiated azaenolates with an acyclic amino acid-derived chiral auxiliary in 1976 [4-6]. In both cases, imines (1.3 and 1.6) were
prepared from cyclohexanone and the chiral auxiliaries. Deprotonation with LDA followed by treatment with an alkylating reagent gave good selectivity for the alkylation of cyclohexanone (1.5 and 1.7). Unfortunately, these chiral auxiliaries gave significantly less asymmetric induction with acyclic ketones. Further limiting the use of these auxiliaries is the stability of the imine intermediates, which are difficult to form and purify. Examples of these types of auxiliaries for alkylation reactions can be found in Scheme 1.

Scheme 1. Early examples of asymmetric ketone $\alpha$-functionalization

The use of dialkyl hydrazones in carbon-carbon bond forming reactions was originally studied independently by Stork, Yamashito, and Corey and Enders [7-9]. Overall, they found that these hydrazones could be deprotonated with strong bases such as LDA to form the corresponding azaenolate and that the reactivity of these azaenolates
was generally superior to enolates. These hydrazones found use in alkylation chemistry where the use of the corresponding enolates failed to give the desired products. Although dialkyl hydrazones proved to be synthetically useful, only one effective asymmetric version of their use is available. In 1976, Enders introduced the (S)-1-amino-2-methoxymethylpyrroldine (SAMP) chiral auxiliary 1.8 [10]. This auxiliary is prepared from (S)-proline, and its corresponding (R) enantiomer 1.9 is able to be prepared from (R)-proline. Since their introduction, SAMP/RAMP hydrazones have seen wide use in alkylation chemistry and other reactions. Their use is not without disadvantage, however, as they typically require harsh reaction conditions such as the use of very strong bases (e.g., n-butyllithium) and very low temperatures (-110 °C) to achieve good selectivity. Although a variety of ways to remove the chiral auxiliaries has been reported, there is no single consistent method to accomplish this task. As an example, deprotonation of the SAMP hydrazone of 3-pentanone (1.10) with LDA followed by treatment with n-propyl iodide gives the corresponding alkylated hydrazone 1.11 in good yield. N-Quaternarization and acidic hydrolysis gives the α-propylated ketone 1.12 with very high selectivity [11]. Other methods of removal include ozonolysis, oxidation with hydrogen peroxide, and treatment with acidic resins. The use of these chiral auxiliaries in asymmetric aldol addition reactions is briefly described in section 1.2.3.
Scheme 2. Example of SAMP-mediated alkylation followed by auxiliary removal

1.1.3 \textit{N}-Amino Cyclic Carbamate Chiral Auxiliaries

In 2008, the Coltart group introduced the use of \textit{N}-amino cyclic carbamate (ACC) chiral auxiliaries for use in synthetic transformations involving ketones.[12] These auxiliaries proved to be more easily introduced to and removed from ketones, and the auxiliaries can also be quantitatively recycled using more mild and conventional means. Deprotonation of the resulting ACC hydrazones is more rapid than in previous ketone-based auxiliaries, and subsequent chemistry can be performed at relatively mild temperatures without compromising stereochemical control or yields. ACC chiral auxiliaries are derivatives of oxazolidinones, which are themselves a useful class of chiral auxiliaries that are routinely used as carboxylate-based chiral auxiliaries for the α-
alkylation of carboxylic acids. Oxazolidinones themselves are typically derived from amino alcohols or amino acids.

In the initial publication on ACC chiral auxiliaries, four different auxiliaries (1.13-1.16) were reported for the use of asymmetric \( \alpha \)-alkylation of 3-pentanone. As can be seen in Table 1, ACC hydrazones (1.17-1.20) of 3-pentanone were deprotonated with LDA at low temperature following by the addition of allyl bromide. The reaction mixture was allowed to warm to room temperature over the course of two hours. The alkyalted hydrazones (1.21-1.24) were then hydrolyzed using \( p \)-TsOH•H\( _2 \)O (2 eq.) in acetone to give the corresponding ketones (1.25-1.28). The stereochemical outcome of the reaction at the level of the ketone was determined using chiral gas chromatography. Out of the four ACC chiral auxiliaries screened, the camphor-derived ACC 1.13 gave the highest selectivity with an \( er \) of 96:4. ACC 1.14 gave the lowest level of selectivity with an \( er \) of 76:24.
In an attempt to rationalize the stereochemistry of the azaenolate intermediate, the 3-pentanone hydrazone 1.17 and the cyclohexanone analogue were deprotonated and alkylated with $p$-bromobenzyl bromide and allyl bromide, respectively, to give hydrazones 1.29 and 1.30. X-ray crystal structures of the alkylated hydrazones revealed that both alkylations generated the same configuration at the newly formed stereocenter (Figure 1).
Figure 1. Crystal structures from ACC alkylation

Because the cyclohexanone hydrazone is only able to adopt an $E_{cc}$ azaenolate geometry, the 3-pentanone system itself should also be adopting the same azaenolate geometry to give a stereocenter with the same configuration. Additionally, the crystal structures also showed that the alkylation reactions occurred regioselectively on the same said of the carbon-nitrogen double bond of the auxiliary. In order for this to occur, the $E_{cc}$ azaenolate must be configurationally stable and was formed via a directed deprotonation event. This directed deprotonation, also known as Complex Induced $Syn$ Deprotonation (CIS-D), would have to occur through coordination of the carbonyl oxygen of the auxiliary to the lithium counter ion of LDA. This would force deprotonation to occur on the same side that the auxiliary carbonyl was pointing on. (See Scheme 3)
1.1.4 Computational Studies of ACC Hydrazones [13]

Further investigations of the alkylation chemistry of ACC hydrazones was conducted in order to gain more insight into the stereochemical results of the reaction. A collaboration was established with the Houk group at the University of California, Los Angeles, and they focused their study on a simplified ACC hydrazone derived from acetone and 2-aminooxazolidinone (see Figure 2). Geometry optimization of this hydrazone using B3LYP/6-31G(d) led to two conformers being observed, 1.34-syn and 1.34-anti. The 1.34syn conformer has a synclinical arrangement of the N-C═O bond and the N—C double bond with a dihedral angle of 71°. Conformer 1.34-anti has the opposite arrangement of these bonds with a dihedral angle of 150°. It should be noted that 1.34-syn has the auxiliary carbonyl ideally oriented to facilitate a directed
deprotonation event, much like was proposed in the initial stereochemical model (Scheme 3), and this isomer was also found to be the most stable isomer. Presumably, this stability is a result of electronic repulsions between the C=N and C=O lone pair of electrons in the 1.34-anti isomer. Additionally, the average bond angle of the ring-containing nitrogen atom is 114° in both isomers, which is distinctly different from the 120° angle found in other carbamates. In effect, this would mean that ACC hydrazones are structurally closer to N,N-dialkylhydrazones than one would expect.

![Figure 2. ACC hydrazone conformers and bond angle comparison to other systems (kcal mol⁻¹ at 0 K)](image)

When the ACC hydrazone derived from ACC 1.13 was examined using the same parameters, only syn conformers (1.35-syn-front and 1.35-syn-back) were observed. This is most likely due to steric congestion of the rigid bicycle with the α-carbon of the hydrazone (Figure 3). It was expected that the “front” orientation of the carbonyl (1.35-syn-front) would be a more favorable arrangement due to less steric interactions, and this expectation was confirmed. 1.35-syn-front is 3.5 kcal/ml more stable than the 1.35-syn-back isomer. The lower stability of the 1.35-syn-back conformer can be attributed to the conformation about the N-C bond in the oxazolidinone ring. Examination of
Newman projections along this bond shows that 1.35-syn-back has substantial eclipsing interactions with CNCC and NNCC dihedral angles of 12° and 22°, respectively, The 1.35-syn-front isomer has larger dihedral angles of 29° and 56°, respectively.

![Diagram of camphor-derived ACC hydrazone conformations](image)

**Figure 3. Conformations of camphor-derived ACC hydrazone. Only the two syn conformations are available.**

The Houk group also studied the transition state for deprotonation using lithium dimethylamide solvated with THF to simplify the computational calculations. 1.34-syn and 1.34-anti were once again used to model two separate transition states undergoing directed deprotonation, in a manner consistent with the initial stereochemical model (Scheme 3). The syn transition state was found to be more stable by 1.4 kcal/mol. Examination of the two syn conformers of the camphor-derived ACC was also performed. The two transition states (TS-1.35-syn-front and TS-1.35-syn-back) were found to have the same rotational barriers and interactions as their corresponding hydrazones, but TS-1.35-syn-back was also found to have a destabilizing interactions between the hydrazone’s methyl group and one of the bridge methyl groups of the auxiliary (Figure 4). The auxiliary in effect effectively blocks deprotonation for the ‘back’ face of the hydrazone.
Figure 4. Transition states for deprotonation by Li(NMe₂)THF. Deprotonation of the ‘front’ face of the hydrazone is preferred over the ‘back’ face.

Figure 5. Conformers of acetone-derived hydrazone showing a clear bias towards a front orientation of the carbonyl group (heats of formation in kcal mol⁻¹).

Next, the geometry of the lithium azaenolate for the camphor-derived ACC was optimized and examined. The azaenolate is able to adopt two specific conformations with respect to the orientation of the carbonyl of the auxiliary (1.36-front and 1.36-back). The ‘front’ orientation of the carbonyl was significantly favored over the ‘back’ orientation just as in the initial hydrazone (1.35).
Figure 6. E\textsubscript{cc} and Z\textsubscript{cc} azaenolate structures with the heat of formation for the transition state leading to the azaenolate (kcal mol\textsuperscript{-1}). The transition states for deprotonation are also shown. Formation of the E\textsubscript{cc} azaenolate is favored over the Z\textsubscript{cc} azaenolate.

Throughout all the previous computational studies, the azaenolate geometry could not be studied as it lacked substitution. Examination of the hydrazone derived from 2-butaneone, however, was conducted (1.37) with the auxiliary oriented towards the more substituted side of the carbonyl. Examination of the transition states leading to the formation of the E\textsubscript{cc} and Z\textsubscript{cc} azaenolates found that the E\textsubscript{cc} transition state (1.37-\textsc{Ecc}) is favored by 2.9 kcal/mol over the Z\textsubscript{cc} transition state (1.37-\textsc{Zcc}). This is consistent with similar studies that have been performed on the SAMP/RAMP chiral auxiliaries. The C—C double bond rotational barrier between the E\textsubscript{cc} and Z\textsubscript{cc} azaenolates is most likely higher than the 43 kcal/mol found in the acetone system (1.36). It should be therefore expected that deprotonation of ACC hydrazones should lead to the E\textsubscript{cc} azaenolate. Furthermore, modeling of alkylation with methyl chloride to 1.37-\textsc{Ecc} was found to favor addition to the ‘front’ face of the azaenolate over the ‘back’ face by 6.9 kcal/mol. This is
entirely consistent with the proposed stereochemical model and the experimental results.

## 1.1.5 Further Examination of Alkylation Chemistry

Because the computation studies conducted by the Houk group predicted the formation of a single diastereomeric product, the results from the alkylation of ACC 3-pentanone hydrazone 1.17 were reexamined. The initial publication reported selectivity values after the alkylated hydrazones had been hydrolyzed to the corresponding ketones. No attempt was made to verify the selectivity of the alkylation reactions at the level of the hydrazone itself. The lack of near perfect selectivity for the initial alkylation reactions could be a result of several factors, including epimerization of the ketone after removal of the auxiliary, imperfect facial selectivity of the electrophile, imperfect regioselectivity with regards to deprotonation, or a combination of these factors.

Hydrazone 1.17 was once again allylated via the established alkylation conditions. Each of the product hydrazones was then examined via chiral HPLC against a separately prepared mixture of the four possible diastereomers that could result from the alkylation. As can be seen in Table 2., the camphor-derived ACC 1.13 gave near perfect levels of both regioselectivity and stereoselectivity at -78 °C. As low temperature reactions are prohibitive on an industrial scale, the ability to carry out a carbon-carbon bond forming reaction such as an alkylation at higher temperature would be invaluable. Currently with ketone-based chiral auxiliaries such as SAMP/RAMP, this ability does
not exist. Testing the stereocontrol of the ACC chiral auxiliaries at higher temperature would also indicate whether the coordinating ability of the carbonyl can maintain the tight 5-membered chelate. As can be seen in Table 2, ACC 1.13 effectively controls the regioselectivity and stereoselectivity of the alkylation reaction at temperatures up to -20 °C. Compared to the SAMP/RAMP chiral auxiliaries, temperatures as low as -110 °C are often required to achieve high levels of stereocontrol.

**Table 2. Temperature screen of ACC-mediated alkylation reactions.**

<table>
<thead>
<tr>
<th>Deprotonation Temperature (°C)</th>
<th>Alkylation Temperature (°C)</th>
<th>d&lt;sub&gt;r&lt;/sub&gt; (1.38:1.39)* α:α'</th>
</tr>
</thead>
<tbody>
<tr>
<td>-78</td>
<td>-78 to r.t.</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>-40</td>
<td>-40 to r.t.</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>-20</td>
<td>-20 to r.t.</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>0</td>
<td>0 to r.t.</td>
<td>97.3</td>
</tr>
</tbody>
</table>

* Determined by chiral HPLC

Because the hydrolysis conditions previously used were at this point believed to be causing epimerization of the ketone, an effort was made to find new hydrolysis conditions that could preclude any epimerization of the ketone, and thus maintain the near perfect stereocontrol imparted by ACC chiral auxiliaries. The original hydrolysis reaction was at heart a hydrazone exchange reaction where the ACC auxiliary was removed from the alkylated ketone and instead added to acetone. Recycling of the auxiliary could then be achieved by treating the acetone hydrazone with excess
hydroxylamine. It was quickly realized, however, that the simple addition of water to
the solution of TsOH·H₂O in acetone (1:4 mixture of water:acetone) eliminated any
epimerization of the alkylated ketone. This is presumably due to the more mild reaction
conditions, as the presence of significant amounts of water would convert almost all of
the TsOH (pKₐ = -2.8) to H₃O⁺ (pKₐ = -1.6). This increases the time necessary for complete
hydrolysis, but the required times were still found to be manageable. Using this method,
the near perfect selectivity achieved in the alkylation reaction can be maintained in the
ketone.

1.2 The Aldol Reaction
1.2.1 The Aldol Addition

The aldol reaction, or aldol addition, is a powerful carbon-carbon bond forming
reaction in organic synthesis. So-called aldol structural units are readily found in natural
products, and the reaction has found its use in the industrial scale production of
common stock materials and pharmaceutical drugs. In a standard aldol addition, an
enolizable carbonyl compound reacts with the carbonyl of either an aldehyde or a
ketone. The enolizable carbonyl compound serves as the nucleophile and the carbon of
the other carbonyl serves as the electrophilic center. Subsequent elimination of water can
occur to give an α,β-unsaturated carbonyl product, also known as the aldol
condensation reaction.
The first example of this reaction involved the acid-catalyzed self-condensation of acetone to give mesityl oxide (1.40) as reported by Kane (Figure 7) [14]. Independently, Schmidt and Claisen and Claparède reported the first base-mediated condensation of an aromatic aldehyde with aliphatic aldehydes or ketones (i.e., the Claisen-Schmidt condensation), as seen in the formation of dibenzylideneacetone (1.41) [15, 16]. In both of these cases, the products obtained gave the aldol condensation product. The formation of actual aldol addition products was reported in 1872 independently by Wurtz [17] and Borodin with the acid-catalyzed self-addition of acetaldehyde. It was recognized that this product (1.42) contained both aldehyde and alcohol moieties, and these ‘aldehyde alcohols’ or aldol products would give name to the reaction that produced them.

Figure 7. Wurtz’s original aldol addition of acetaldehyde and the structural motifs of aldol addition and condensation products.
Traditionally, aldol additions are restricted to reactions of ketones and aldehydes. These reactions occur reversibly (also known as retro-aldol) under thermodynamic control and are mediated by either acids or bases. In the modern sense, however, aldol additions apply to any enolizable carbonyl compound (e.g., esters, amides, nitriles, and carboxylic acids) that adds to aldehydes or ketones. These reactions typically rely on the irreversible formation of preformed enolates made using strong bases such as lithium diisopropylamide (LDA), and they are also generally conducted under conditions that favor kinetic control of the reaction. The electrophilic carbonyl is often an aldehyde as the addition to ketones is plagued by retro-aldol issues. Aldol addition reactions are capable of generating up to two asymmetric carbons, which can give rise to either a syn or anti diastereomer and the corresponding enantiomers (Figure 3).

Generally speaking, an aldol addition can occur through either an acidic or basic mechanism (Figure 8). In the acidic mechanism, catalytic protonation of the starting carbonyl leads to formation of enol (1.43), which subsequently reacts with an aldehyde (1.44) to give the β-hydroxy carbonyl product (1.45) product. Alternatively, deprotonation of the starting carbonyl by a base gives the corresponding enolate (1.46), which reacts with 1.44 to give the aldolate product (1.47). Subsequent protonation of this aldolate leads to 1.45. In the traditional sense, the reaction is reversible at each step. The β-hydroxy carbonyl product (1.45) is significantly stabilized by hydrogen bonding.
Likewise, the aldolate (1.47) formed under basic conditions is also stabilized through chelation of the counter ion. Modern aldol reactions eliminate the reversibility of the first step through preformed enolates. Thus, only the reversibility of the actual addition step remains.

![Diagram showing acidic and basic mechanisms for aldol addition reactions of ketones/aldehydes with aldehydes.]

Figure 8. Acidic and basic mechanisms for aldol addition reactions of ketones/aldehydes with aldehydes.

Carbonyl compounds that are substituted at their α-position can be deprotonated to give enolates of differing geometry based on the orientation of that substituent (Figure 9). These enolates (1.48-E<sub>cc</sub> and 1.48-Z<sub>cc</sub>) are distinguished by the geometry of their carbon-carbon double bond. This geometry of the reacting enolate is an important factor in determining the stereochemical outcome of the reaction. Typically, (Z)-enolates favor the formation of syn aldol products (1.49 and 1.50) while (E)-enolates favor the formation of anti aldol products (1.51 and 1.52). Six-membered chair-like transition states, such as the Zimmerman-Traxler model, have been proposed to account for this stereochemical outcome (Figure 9) though such models do not account for all observed
results. The challenge for modern aldol chemistry involves not only the selective formation of one of these diastereomers but also the selective formation of a particular enantiomer as a product.

Figure 9. Enolate geometry and diastereoselectivity in aldol additions based on the Zimmerman-Traxler model.

Although many methods have been developed to carry out an asymmetric aldol addition for carboxylate derivatives, particularly for syn aldol products, less attention has been focused on asymmetric aldol additions of ketones to aldehydes. This document will restrict its discussion solely to asymmetric aldol additions of ketones with achiral aldehydes.

1.2.2 Ketone-Based Aldol Additions Using Boron Enolates

Boron enolates, or borinates, in aldol chemistry has been extensively studied over the years for both ketones and carboxylate chemistry. The first reported use of a boron enolate to give an aldol adduct was by Mukaiyama and coworkers in 1971 [18].
Attempting to prepare ketene thioacetals from ketene and butylthioborane, they instead isolated a product that resulted from an aldol addition of butyl thioacetate with acetone that proceeded through a boron enolate intermediate. The use of boron enolates for aldol additions has distinct advantages over traditional aldol additions utilizing lithium or sodium counter ions.

Firstly, it is believed that boron enolate-mediated aldol additions proceed through a more rigid chair-like transition state than those of classical enolates (Scheme 5). As a result of shorter boron-carbon and boron-oxygen bonds, this transition state maximizes and steric interactions that may occur and allows for the formation of aldol products more stereoselectively than is possible using alkali metal enolates. Secondly, methods have been developed to generate boron enolates with a specific geometry. As can be seen in Scheme 5, treatment of propiophenone with dicyclohexylboron chloride and triethylamine generates almost exclusively the (E)-enolate 1.53, which subsequently reacts with benzaldehyde to give the anti aldol product 1.54 in a 95:5 anti: syn ratio [19]. Correspondingly, treatment of propiophenone with 9-BBNOTf and Hünig’s base leads to the formation of the (Z)-enolate 1.55. This enolate reacts with benzaldehyde to give the syn aldol adduct (1.56) in a > 98:2 syn:anti ratio [19].
Replacing the ligands on boron with chiral ligands allows for the enantioselective formation of aldol adducts as demonstrated by Paterson and co-workers [20]. They reported the generation of (Z)-enolates using (-)-diisopinocamphenyl boron triflate (1.57) and Hünig’s base. This enolate could be subsequently reacted with a variety of aldehydes to give the syn aldol products (1.59-1.61) in decent to high selectivity. Notably, using aromatic and unsaturated aldehydes gave higher selectivity than bulkier aliphatic aldehydes such as isobutyraldehyde. This selectivity can be further enhanced for ketones with other asymmetric carbons, which has allowed this method to be used in natural product synthesis.
Scheme 5. Syn selective aldol addition of ketones with aldehydes using chiral boron enolates.

Despite the selectivity achieved for enantioselectively forming syn aldol products, formation of the corresponding anti aldol adducts using the (E)-borinate results in rather poor enantioselectivity. Paterson and coworkers subsequently established a method for the highly selective formation of anti aldol products using a chiral lactate-derived ketone 1.62. This ketone can be converted to its (E)-borinate (1.63) using established conditions. Further reaction with aldehydes results in the formation of anti aldol products with an enantiomer ratio of > 99:1. It is proposed that the transition state for this addition reaction involves a formyl hydrogen bond between the carbonyl of the benzoyl group, which is necessary for the reaction to occur, and the aldehyde proton (Scheme 6). Subsequent chemical transformations can convert the lactate-derived ketone to either the corresponding aldehyde 1.65 or the ethyl ketone 1.66. This versatility of boron enolates has allowed for the use of this protocol in the asymmetric synthesis of natural polyketides [21-24]. It should be noted that use of the corresponding (Z)-borinate
under these reaction conditions also results in the highly selective formation of syn products. This versatility has allowed for the use of this protocol in the asymmetric synthesis of natural polyketides.

Scheme 6. Paterson’s lactate-derived anti selective aldol addition reaction.

1.2.3 SAMP/RAMP Aldol Reactions

Although the use of SAMP/RAMP chiral auxiliaries (1.8 and 1.9) in ketone and aldehyde alkylation reactions is widely known and considered by many to be the state-of-the-art for ketone α-alkylation, there are only limited reports in the literature of these auxiliaries being used in aldol reactions [10, 11, 25, 26]. The practical limitations for using and removing the auxiliaries and the greater complexity of the reaction undoubtedly have affected interest in this particular application. Some successes, however, have been reported, especially with achiral methyl ketones.
Scheme 7. Asymmetric synthesis of (+)-gingerol using a RAMP-mediated aldol addition reaction.

The first asymmetric intermolecular aldol reaction utilizing a SAMP hydrazone was reported in 1978. In this particular example, the chiral hydrazone of alkyl methyl ketones were prepared and then deprotonated using butyllithium. The resulting azaenolate was treated with aldehydes and ketones followed by in situ trapping with trimethylsilyl chloride. Auxiliary removal could be affected by the use of either buffered hydrogen peroxide or singlet oxygen. The aldol products were obtained in low to moderate enantioselectivity. This method, however, was useful in the preparation of (+)-gingerol 1.9 in 36% ee [27]. The use of SAMP was also used to prepare (-)-gingerol in a similar manner. More recently, Smith et al. have been able to utilize the SAMP chiral auxiliary in a syn selective aldol addition in the asymmetric total synthesis of nodulisporic acid A (1.75). As shown in Scheme 8, treatment of ketone 1.70 with the SAMP auxiliary (1.8) in refluxing cyclohexane affords the SAMP hydrazone 1.71 in very high yield. This hydrazone was then deprotonated with t-butyllithium at low
temperature and treated with aldehyde 1.72. An 11:2 ratio of syn and anti products (1.74) was obtained after ozonolysis. The absolute configurations of the products were determined by Mosher ester analysis [28]. Smith and coworkers have also established a new method for SAMP/RAMP auxiliary removal for β-hydroxyketone SAMP hyrazones [29].

Scheme 8. Smith’s use of a syn selective SAMP-mediated aldol addition in the synthesis of nodulisporic acid A.

For hyrazones derived from non-methyl ketones, the SAMP/RAMP chiral auxiliaries give rise to syn aldol adducts with decent to moderate selectivity (Scheme 8). It has been shown that deprotonation with a base such as LDA in both cyclic and acyclic ketones gives rise to the \( E_{\alpha}Z_{CN} \) azaenolate. This azaenolate geometry combined with the syn outcome of this reaction is supportive of an open-type transition state. It should be
noted that no attempt has been made to elucidate the transition states of these types of SAMP/RAMP reactions. Some success in modifying the chiral auxiliary structure to make the reaction more anti selective has been reported, although the anti selectivity was quite marginal [30].

### 1.2.4 Organocatalytic Aldol Additions

Synthetic organic chemists have accomplished much over the years with regards to indirect aldol additions involving preformed enolates, for example, but Nature has a distinctly different way of carrying out these important C—C forming reactions. Enzymes capable of catalyzing aldol addition reactions, also known as aldolases, are can be distinguished by their mode of enolization (Figure 10) [31]. One group of aldolases utilizes the Lewis basicity of a primary amine group while the other utilizes the Lewis acidity of a zinc(II) co-factor. These enzymes both work by effectively decreasing the pKₐ of the donor molecule (typically a ketone) so that it can be deprotonated under near-neutral and aqueous conditions. The resulting stabilized enolate-like intermediates then react with an acceptor molecule that the enzyme positions nearby. Amine-catalyzed aldolases generate iminium ions from ketones while zinc-catalyzed aldolases generate oxonium ions.
Figure 10. General representation of the two classes of aldolase enzymes.

The goal of recreating this efficient method of carrying out the aldol addition remained rather elusive to synthetic chemists for some time. The last decade, however, has seen considerable activity with regards to reactions that mimic the Class I aldolase enzymes described above. The first amine-catalyzed, asymmetric intermolecular aldol addition was reported by List, et al. in 2000 [32]. They found that the addition of (S)-proline to a solution of acetone and certain aldehydes in dimethylsulfoxide (DMSO) gave the corresponding acetone aldol products in good yield and enantioselectivity (Scheme 11). While aromatic and α-branched aldehydes proved to work well in this reaction, linear aliphatic aldehydes (1.80) did not as a result of side reactions. Modifications of the reaction conditions only somewhat alleviated this disadvantage [33].
Scheme 9. Examples of asymmetric, organocatalytic aldol additions using (S)-proline as a catalyst.

The reporting of this reaction led to a plethora of other reports concerning so-called organocatalytic aldol reactions. Although a full review of asymmetric, organocatalytic aldol reactions is beyond the scope of this document, a few points can still be made. Ketones other than acetone, such as cyclohexanone and α-hydroxyacetone, have been found to be useful donors in this type of reaction, and a variety of modified organocatalysts, such as proline derivatives, peptides, and amino alcohols, have been developed to improve the scope and selectivity of the reaction. Generally, these reactions are more anti selective than syn selective, but the degree of selectivity varies based on the starting ketone and organocatalysts [31, 34-36]. Cross-aldol reactions between aldehydes can also be conducted, which can be rather difficult to achieve.
selectively with preformed enolate chemistry due to the reactivity of the resulting intermediates.

Scheme 10. Asymmetric organocatalytic aldol of 3-pentanone.

There still remain challenges with respect to the development of this chemistry, however. Methyl ketones such as acetone are readily used as ketone donors, other ketones such as 3-pentanone (diethyl ketone) typically reacts too slowly or undergoes side reactions that make its use not synthetically useful. In the case of organocatalysts 1.84, for example, the reaction of 3-pentanone with 4-nitrobenzaldehyde (1.83) is only slightly more anti selective (Scheme 12). The enantioselectivity of the syn product in particular is significantly less than in the anti product. Despite these challenges, the synthetic potential combined with the practical benefit of not using stoichiometric basis, auxiliaries, or other reagents ensures that continued research on developing this type of reaction will continue.
1.3 ACC-Mediated Aldol Reaction

1.3.1 Synthesis of ACC 1.13

The successful use of ACC chiral auxiliaries such as 1.13 in the α-alkylation of ketones, we began to consider the use of these auxiliaries in other types of reactions. Due to its powerful utility, the aldol addition reaction immediately stood out. Although we had no compelling basis on which to predict the outcome of an ACC-mediated aldol reaction, we considered it a suitable test of how well these chiral auxiliaries can control the outcome of a more complicated reaction. As the camphor-derived ACC 1.13 consistently provided the best selectivity for alkylation chemistry, we decided to investigate aldol additions using this auxiliary. ACC 1.13 had previously been prepared on a large (>500 g) scale in the initial alkylation study[12], but the final N-amination step of the synthesis was less than ideal in terms of yield of final auxiliary prepared. Additionally, the workup method for the first step involving phosphorus pentachloride was changed to include extraction of the product rather than filtration. This was found to increase the yield of the reaction and alleviate any potential for hydrolysis back to the sulfonic acid.
Scheme 11. First generation synthesis of ACC 1.13.

The synthesis of ACC 1.13 begins with the commercially available and inexpensive (1S)-(+)‐camphorsulfonic acid (1.86), which is easily converted to its sulfonyl chloride derivative 1.87 using phosphorus pentachloride. Next, the sulfonyl chloride is treated with tosyl chloride and pyridine [37, 38], which abstracts oxygen to give the chlorosulfine 1.88. Ozonolysis of the sulfine, followed by the addition of oxalyl chloride to eliminate any hydrolysis, gives ketopinic acid chloride 1.89. Treatment of the acid chloride with sodium azide in acetone gives the corresponding acid azide, which is dissolved in toluene and heated to give isocyanate 1.90. This product is then reductively cyclized under Luche‐type conditions to give the oxazolidinone 1.91 [39].

Originally, N‐amination of oxazolidinone 1.91 involved deprotonation followed by treatment with so‐called aminating reagents (e.g., Ph₂POONH₂) [40]. Although a variety of aminating reagents have been developed, we found their use to be rather inconsistent for aminating ACC auxiliaries. The reagents have been prepared separately, and depending on the exact reagent being used can be moisture‐sensitive or shock‐
sensitive. Furthermore, we found the yield of amination reaction involving these types of reagents to never be consistently higher than 60%.

The use of chloramine in amination reactions of oxazolidinones has not been previously reported, but its use in aminating other nitrogen containing heterocycles has been investigated. Chloramine (NH$_2$Cl) is easily generated by combining ammonium chloride, ammonium hydroxide, and commercial-grade bleach in a biphasic mixture of diethyl ether and water [41, 42]. Treatment of oxazolidinone 1.91 with potassium tert-butoxide gives a suspension of the potassium salt of the oxazolidinone, which is subsequently treated with the ethereal solution of chloramine. This gives the desired N-aminated ACC 1.13 in yields consistently higher than 80%. It should be noted that protocol is equally as reliable for the N-amination of other oxazolidinones that have found use in the ACC-mediated alkylation chemistry.


The auxiliary of opposite configuration (1.98) can be prepared in a similar manner starting from (1R)-(−)-camphorsulfonic acid (1.92). All of the results in this chapter utilize chiral auxiliary 1.13 and not 1.98.
1.3.2 Initial Experiments

We started our investigation by first preparing the 3-pentanone hydrazone with the camphor-derived ACC 1.13. As 3-pentanone is simple, symmetrical ketone, we believed it would provide an effective starting point for use in an ACC-mediated aldol reaction just as with the ACC-mediate alkylation chemistry. Thus, ACC 1.13 was dissolved in methylene chloride with excess 3-pentanone and a catalytic amount of TsOH·H₂O. The resulting hydrazone 1.17 was prepared in high yield. It was decided to initially focus our attention on nonenolizable aldehydes such as 4-trifluoromethylbenzaldehyde rather than enolizable aldehydes (Table 3). In keeping
with the conventional approach to aldol additions, we conducted our first experiments under conditions that were expected to favor kinetic formation of the aldolate intermediate, which presumably would maximize any asymmetric induction from the chiral auxiliary. Hydrazone 1.17 was treated with excess LDA in THF at -78 °C followed by the addition of 4-trifluoromethylbenzaldehyde. The temperature was maintained for 5 minutes, and the reaction was quenched with the addition of aqueous ammonium chloride. Initially, the results of this reaction did not look encouraging as a 2.5:1 mixture of products was obtained (Table 3, entry 1). NMR analysis supported assigning the relative configuration of the major product as a syn (either 1.99 or 1.100) with the minor product as anti product (either 1.101 or 1.02). It was quickly noticed, however, that we only saw a single syn diastereomer and a single anti diastereomer and not all four possible diastereomers. It appeared that the ACC chiral auxiliary had some bias towards these particular two diastereomers.

**Table 3. Initial results of ACC-mediated aldol reaction under kinetic conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Solvent</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>5</td>
<td>THF</td>
<td>2.5:1</td>
</tr>
<tr>
<td>2</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>30</td>
<td>THF</td>
<td>2.5:1</td>
</tr>
<tr>
<td>3</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>60</td>
<td>THF</td>
<td>2.5:1</td>
</tr>
<tr>
<td>4</td>
<td>4-CF₃C₆H₄</td>
<td>-115</td>
<td>60</td>
<td>THF</td>
<td>2.8:1</td>
</tr>
</tbody>
</table>
This result prompted us to investigate the reaction conditions further. Conducting the same reaction at a lower temperature, -115 °C (entry 4), was found to have an impact on the selectivity of the reaction in that the amount of syn diastereomer increased. This increase, however, was only modest, and a mixture of 2.8:1 was obtained. We also found that varying the reaction times had absolutely no impact on the selectivity of the final product (entries 2-3).

Before progressing any further in our studies, we wished to establish the absolute configuration of the two aldol products prepared. We were fortunate that, in the case of benzaldehyde, the products were separable from one another and physically solid. Crystals suitable for x-ray crystallography were grown, and x-ray crystal structures were obtained that allowed for assigning the absolute configuration of each product (Figure 11). The original 1H NMR assignment of the relative configuration as syn (1.99) and anti (1.101) diastereomers was correct based on the crystal structures obtained. Notably, the two structures differ only at a single stereocenter, which was the original carbonyl carbon of the aldehyde. The crystal structure of 1.101 supports the existence of an intramolecular hydrogen bond between the hydroxyl group and the carbonyl of the ACC chiral auxiliary. 1H NMR also supports the presence of this hydrogen bond as the hydroxyl proton appears as a clearly defined doublet between 5 and 6 ppm. This feature is completely absent in the structure of 1.100, though intermolecular hydrogen bonds the hydroxyl group of one molecule and the ACC
carbonyl of another molecule are present in the crystal lattice. It should also be noticed that the orientation of the α-methyl group is indicative of the azaenolate intermediate having an $E_{cc}$ geometry.

![Figure 11](image)

**Figure 11. ORTEP diagrams obtained for the *anti* and the *syn* aldol products.**

Changing the nature of the solvent but keeping all other reaction variables the same did have an impact on the *syn:anti* selectivity of the product. As can be seen in Table 4, all other solvents (entries 2-6) gave a product mixture that favored the *syn* product less than was the case in THF (Table 4, entry 1). A trend can be seen in the Lewis basicity of the solvent (or its ability to coordinate cations, for example) and the degree to which the *syn* product is favored. THF gave the highest amount of *syn* product while diethyl ether and toluene gave 1:1 mixtures of *syn* and *anti* products.
Table 4. Variation of solvent on the ACC-mediated aldol reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Solvent</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF₃C₆H₄</td>
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<td>60</td>
<td>THF</td>
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</tr>
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<td>Et₂O</td>
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<tr>
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<td>60</td>
<td>cyclopentyl methyl ether</td>
<td>1.2:1</td>
</tr>
<tr>
<td>4</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>60</td>
<td>2-MeTHF</td>
<td>1.5:1</td>
</tr>
<tr>
<td>5</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>60</td>
<td>DME</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>60</td>
<td>toluene</td>
<td>1:1</td>
</tr>
</tbody>
</table>

An examination of other aromatic aldehydes also presented an interesting set of results (Table 5). While 4-trifluoromethylbenzaldehyde (entry 1) gave a 2.5:1 mixture of products in THF, the use of benzaldehyde (entry 3) gave only a 2:1 mixture in favor of the syn product. For p-bromobenzaldehyde (entry 2), a 1.53:1 mixture in favor of the syn product was obtained. The use of p-anisaldehyde (entry 4), however, completely reversed the syn:anti relationship and instead gave a 1:1.47 product mixture in favor of the anti product. It appeared that the electronics of the aldehyde itself also played a role in determining the final product composition. The more electron-withdrawn aldehyde (entry 1) clearly favored formation of the syn product at low temperature more than the anti product. In the case of the electron-enriched (entry 4), however, the anti product was favored.
Table 5. Variation of the aldehyde and its effect on the *syn:anti* ratio of the ACC-mediated aldol reaction.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Solvent</th>
<th><em>syn:anti</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-78</td>
<td>60</td>
<td>THF</td>
<td>2.5:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>-78</td>
<td>60</td>
<td>THF</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-78</td>
<td>60</td>
<td>THF</td>
<td>1.5:1</td>
</tr>
<tr>
<td>4</td>
<td>4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-78</td>
<td>60</td>
<td>THF</td>
<td>1:1.5</td>
</tr>
</tbody>
</table>

We next became interested in looking further into the impact of temperature on the reaction (Table 6, entries 1-4). To our surprise, increasing the temperature of the reaction beyond -78 °C had a significant impact on the selectivity of the reaction. Using 4-trifluoromethylbenzaldehyde, an increase in temperature to 4 °C gave a 1:1.7 product mixture in favor of the *anti* product (1.101) (entry 5). Increasing the temperature further to room temperature (21 °C) gave exclusively the *anti* product without any *syn* product (1.99) detected (entry 6). In a similar manner, the use of the other aldehydes used in Table 5 also produced exclusively the corresponding *anti* aldol products. Interestingly, the addition of HMPA (Table 6, entries 5-6) after deprotonation did not change the outcome of the reaction at room temperature, but it did change the reaction outcome at low temperature. In this case (entry 9), the amount of *syn* diastereomer 1.99 obtained significantly increased, though a small amount of the *anti* diastereomer 1.101 was still formed. Based on these results, it appeared that this ACC-mediated aldol reaction was...
operating under thermodynamic control with the *anti* product being the thermodynamically product.

Table 6. Effects of temperature and HMPA on the reaction on the aldol reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Solvent</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CF₃C₆H₄</td>
<td>4</td>
<td>60</td>
<td>THF</td>
<td>1:1.7</td>
</tr>
<tr>
<td>2</td>
<td>4-CF₃C₆H₄</td>
<td>21</td>
<td>120</td>
<td>THF</td>
<td>0:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>-78</td>
<td>5</td>
<td>THF</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>21</td>
<td>120</td>
<td>THF</td>
<td>0:1</td>
</tr>
<tr>
<td>5</td>
<td>4-CF₃C₆H₄</td>
<td>-78</td>
<td>60</td>
<td>THF/HMPA</td>
<td>9:1</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃C₆H₄</td>
<td>21</td>
<td>120</td>
<td>THF/HMPA</td>
<td>0:1</td>
</tr>
</tbody>
</table>

1.3.3 Preliminary Mechanistic Studies

Given that the *anti* selectivity of the ACC-mediated aldol reaction correlated well with increasing temperature and a prolonged reaction time (two hours), we decided to test the idea that the reaction was under thermodynamic control. Firstly, the ability of the *anti* aldolate formed *in situ* to undergo a retro-aldol reaction was examined (Scheme 17). Hydrazone 1.17 was deprotonated with LDA at -78 °C and treated with 4-trifluoromethylbenzaldehyde as previously mentioned. After warming to room temperature, a second aldehyde, 2-naphthaldehyde, was added to the reaction mixture. Stirring was continued at room temperature for two hours. If the initially formed aldolate intermediates (1.103 and 1.104) were capable of undergoing a retro-aldol process to reform the azaenolate precursor, then aldol addition products corresponding
to both aldehydes should be observed at the end of the reaction (1.101 and 1.05).

Surprisingly, this was not the case. Only the aldol product corresponding to 4-
trifluoromethylbenzaldehyde (1.101) was observed with no aldol product from 2-
naphthaldehyde present.

\[
\begin{align*}
&\text{Et}_2\text{CH}_3\text{N}^+\text{Y}^-\text{1.17} \xrightarrow{\text{LDA, THF, -78 °C, 45 min, then}} \\
&\quad \text{Et}_2\text{CH}_3\text{N}^+\text{Li}^-\text{1.103} + \text{Et}_2\text{CH}_3\text{N}^+\text{Li}^-\text{1.104} \xrightarrow{2.5:1} \\
&\quad \text{2.5 : 1} \\
&\quad \text{Et}_2\text{CH}_3\text{N}^+\text{Y}^-\text{1.101} \xrightarrow{\text{2 hours}} \\
&\quad \text{Et}_2\text{CH}_3\text{N}^+\text{Y}^-\text{1.105} \text{ not observed}
\end{align*}
\]

Scheme 15. First mechanistic study experiment involving the addition of a second
aldehyde at room temperature.

At this point, it was possible that electronic factors brought about by the 4-
trifluoromethyl group on the aromatic ring were affecting the outcome of this reaction.

A more electron-enriched aldehyde, \(\alpha\)-tolualdehyde, was used in place of 4-
trifluoromethylbenzaldehyde, and the reaction was repeated (Scheme 18). Once again,
no product corresponding to 2-naphthaldehyde (1.05) was observed. Only product
corresponding to the \(\alpha\)-tolualdehyde (1.08) was observed. These two experiments
supported the idea that the \textit{anti} aldol product is irreversibly (and thermodynamically)
formed.
Scheme 16. Second mechanistic study experiment involving the addition of yet a different aldehyde at room temperature.

Next, the ability of the syn aldolate to undergo a retro-aldol process at low temperature was examined. Hydrazone 1.17 was once again deprotonated with LDA at -78 °C and treated with 4-trifluoromethylbenzaldehyde. After five minutes of stirring at -78 °C, o-tolualdehyde was added to the reaction mixture, which was then brought to room temperature and stirred for two hours. If retro-aldol processes were able to occur at low temperature, then both products (corresponding to both aldehydes should be observed. Indeed, an approximately 2:1 mixture of anti aldol products was obtained (in favor of the product from 4-trifluoromethylbenzaldehyde). One might expect that a 1:1 mixture of products should result from this experiment. Presumably, this is a reflection of the greater stability of the syn aldolate for the more electron-withdrawn aldehyde. In effect, the electronegative trifluoromethyl group of the aldehyde stabilizes the syn aldolate and makes it less prone to undergoing a retro-aldol process. It can be predicted that a rather electron-enriched aldehyde (e.g., p-anisaldehyde) would destabilize the
corresponding syn aldolate, making it more prone to undergoing a retro-aldol, and thus more likely to form the more thermodynamically favored anti product.

Scheme 17. Third mechanistic study experiment involving the addition of a second aldehyde at low temperature.

As a final confirmation that the anti aldol product is irreversibly and thermodynamically formed, a sample of pure syn aldolate 1.99 was dissolved in THF and treated with LDA at -78 °C. The mixture was stirred at -78 °C for five minutes before being allowed to warm to room temperature over two hours. Upon work up of the reaction, only the anti product 1.101 was observed.

Scheme 18. Conversion of a pure sample of syn aldol product to the anti aldol product.
Exchanging of the lithium counter ion to sodium or potassium was not attempted, as lithium should be the best coordinating cation of the three. Furthermore, in the original alkylation study [12], the use of these cations led to significantly lower levels of selectivity.

1.3.4 Stability of Syn and Anti Aldol Products

Based on the preliminary mechanistic studies previously discussed, it was clear that the anti aldol product was not only favored at higher temperature but also formed irreversibly. The syn aldol product is favored at lower temperature but can undergo a retro-aldol reaction with increasing temperature. To account for these observations, it is necessary to look at the stability of the reaction products using the mechanistic study information, 1H NMR observations, and the x-ray crystal structure obtained for each product.

In the anti aldol addition, addition of the azaenolate to the si face of the aromatic aldehyde is required to give the absolute configuration observed in the x-ray crystal structure (Figure 12). In addition to minimizing any unfavorable steric interactions, the resulting alkoxide would be in position to form an intramolecular chelation of lithium with the carbonyl of the chiral auxiliary. The stabilizing influence of this chelation presumably prevents retro-aldol back to the azaenolate and aromatic aldehyde. Protonation of this aldolate would give a β-hydroxy hydrazone with a hydrogen bond
between the hydroxyl group and the carbonyl of the chiral auxiliary. This hydrogen bond is supported by the $^1$H NMR spectrum, which shows a rather downfield hydroxyl proton (5-6 ppm) as a clearly defined doublet. This hydrogen bond also presumably prevents isomerization about the C=N bond that could occur when the product is purified using untreated silica gel (see syn product discussion below).

**Figure 12. Aldolate and final product stability from the anti aldol addition.**

Addition to the re face of the aromatic aldehyde would be the only way to obtain a syn aldol product while conserving the $E_{ax}$ geometry of the azaenolate. While the resulting alkoxide could be positioned to form the same intramolecular chelation as in the anti aldolate (Figure 12), this would result in rather unfavorable Ar-CH$_3$ and Ar-hydrazone gauche interactions. Presumably, the intramolecular chelation of lithium is not stabilizing enough to overcome these steric interactions, and so bond rotation occurs to minimize them. The $^1$H NMR spectrum of this β-hydroxy hydrazone lacks any clearly defined hydroxyl proton. In some instances, this proton can be observed as a very broad
singlet (2-3 ppm). The lack of this hydrogen bond is further supported by purification of
the product. If silica gel that has not been pretreated with Et3N is used in flash
chromatography, isomerization about the C=N occurs. A similar outcome results when
attempting to purify alkylation products that are sterically more demanding.

![Figure 13](image_url)

**Figure 13. Aldolate and final product stability from syn addition**

### 1.3.5 Auxiliary Removal and O-Protection

Given our success up to this point in carrying out a selective ACC-mediated
aldol reaction, we next focused on removing the ACC auxiliary. As in all chiral
auxiliary-mediated reactions, the ability to remove the auxiliary without compromising
the product’s stereochemistry is imperative. The development of efficient and effective
hydrolysis conditions for the ACC-mediated alkylation chemistry provided us a starting
point for examining the hydrolysis of the β-hydroxy hydrazone products. Thus, the anti aldol product from benzaldehyde (1.109, Table 3, entry 8) was dissolved in acetone/water (4:1) and treated with two equivalents of TsOH•H₂O. Examination of the reaction by thin layer chromatography (TLC) showed rapid consumption of the starting hydrazone within half an hour, but examination of the crude product mixture by ¹H NMR indicated only the presence of ACC acetone 1.35 and benzaldehyde (1.76). This was indicative of a complete retro-aldol reaction occurring to give the parent aldehyde and 3-pentanone, which was most likely lost during work up.

![Scheme 19. Original hydrolysis attempt utilizing conditions from the alkylation chemistry.](image)

Moving to more mildly acidic conditions for hydrolysis had limited success with the alkylation chemistry, and so we reasoned that simple protection of the β-hydroxyl group could suppress the retro-aldol process. O-Protection would also make sense in the context of a total synthesis, as it is possible subsequent reactions would preclude the presence of a free hydroxyl in the molecule. Accordingly, the before mentioned aldol product was silylated using triethylsilyl (TES) chloride and 2,6-lutidine, which proceeded smoothly to give the O-TES silyl ether 1.110. Attempts to purify this material by silica gel chromatography – even when the silica gel had been pretreated with Et₃N – resulted in complete desilylation to the original aldol product 1.109. This is despite the
fact that O-TES groups are known to survive column chromatography. We next focused on the tert-butyldimethylsilyl (TBS) silyl ether 1.111, which was prepared in a similar manner in high yield using the corresponding chloride and 2,6-lutidine. This material proved amenable towards column chromatography. While subjecting 1.111 to the hydrolysis conditions previously mentioned did result in complete removal of the auxiliary, a significant amount of desilylation and subsequent retro-aldol addition. Only a small amount of the silylated β-hydroxy ketone (1.112) was obtained.

Scheme 20. Silylation of aldol products and attempted hydrolysis reactions.

We next tried to prepare other O-protected aldol products. Initially, there was success with adding dimethyl sulfate at the end of the ACC-mediated aldol reaction to give the O-methylated hydrazone 1.113. Although an O-methyl protecting group, given its difficulty in removal, is far from ideal from a synthetic standpoint, it did survive the hydrolysis conditions without issue to give ketone 1.114. This gave us assurance that
with the right protecting group it was possible to isolate the desired β-hydroxy ketone without compromising the stereochemistry.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[1.17\]

\[
\text{LDA, THF, -78 °C} \quad 45 \text{ min, then PhCHO to r.t.}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[1.113\]

\[
\text{dimethyl sulfate} \quad \text{(84%)}
\]

\[
\text{H}_3\text{C} \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3
\]

\[1.113\]

\[
\text{TsOH+H}_2\text{O} \quad \text{acetone/water (4:1)} \quad \text{(89%)}
\]

\[
\text{H}_3\text{C} \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3
\]

\[1.113\]

\[
\text{H}_3\text{C} \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3 \quad \text{Ph}
\]

\[1.113\]

\[
\text{H}_3\text{C} \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3 \quad \text{Ph}
\]

\[1.113\]

\[
\text{H}_3\text{C} \quad \text{N}^\text{Y} \\
\text{CH}_3 & \quad \text{CH}_3 \quad \text{Ph}
\]

\[1.113\]

**Scheme 21. O-Methylation of aldol product and subsequent hydrolysis.**

We next tried to prepare the O-benzyl or O-p-methoxybenzyl (PMB) derivatives 1.115 and 1.116. O-Benzyl protecting groups are synthetically useful as they typically can be removed by hydrogenolysis (H\textsubscript{2}/Pd(C)) or by other methods depending on the aromatic substitution. Unfortunately, it was not possible to do so using typical hydroxyl protection protocols. Even the addition of benzyl bromide into the aldol reaction mixture before workup gave no O-benzylation of the aldolate intermediate. Conveniently, while benzyl bromide failed under these conditions, we were able to produce the desired compounds 1.115 and 1.116 using benzyl iodide and PMB iodide, respectively, and allowing the reaction to sit overnight. Treatment of these β-benzyloxy hydrazones with TsOH•H\textsubscript{2}O in acetone/water (4:1) smoothly liberated the auxiliary without any competing retro-aldol or isomerization to give the corresponding β-benzyloxy ketones 1.117 and 1.118 in under 12 hours. Additionally, we found that the
use of just acetone as a solvent in the reaction, which caused epimerization for alkylated hydrazones, also was successful and affected hydrolysis in under six hours.

**Scheme 22. O-Benzyla­tion and subsequent hydrolysis.**

We now had a general method for the *anti*-aldol addition of nonenolizable aldehydes with ketones. As can be seen in Table 7, a wide variety of aromatic aldehydes, encompassing both electron-enriched and electron-withdrawn aldehydes, could be used in this reaction. The unsaturated aldehyde *trans*-cinnamaldehyde could also be used.
Table 7. O-Benzylolation of aldol products followed by hydrolysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Hydrazine Yield (%)</th>
<th>Ketone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>Bn</td>
<td>1.115</td>
<td>91</td>
<td>1.117</td>
</tr>
<tr>
<td>2</td>
<td>4-OMeC6H5</td>
<td>Bn</td>
<td>1.119</td>
<td>86</td>
<td>1.120</td>
</tr>
<tr>
<td>3</td>
<td>4-CF3C6H5</td>
<td>Bn</td>
<td>1.121</td>
<td>83</td>
<td>1.122</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Bn</td>
<td>1.123</td>
<td>85</td>
<td>1.124</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Bn</td>
<td>1.125</td>
<td>87</td>
<td>1.126</td>
</tr>
<tr>
<td>6</td>
<td>4-ClC6H5</td>
<td>Bn</td>
<td>1.127</td>
<td>80</td>
<td>1.128</td>
</tr>
<tr>
<td>7</td>
<td>4-BrC6H5</td>
<td>Bn</td>
<td>1.129</td>
<td>89</td>
<td>1.130</td>
</tr>
<tr>
<td>8</td>
<td>2-MeC6H5</td>
<td>Bn</td>
<td>1.131</td>
<td>85</td>
<td>1.132</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>Bn</td>
<td>1.133</td>
<td>91</td>
<td>1.134</td>
</tr>
<tr>
<td>10</td>
<td>4-NO2C6H4</td>
<td>Bn</td>
<td>1.135</td>
<td>87</td>
<td>1.136</td>
</tr>
<tr>
<td>11</td>
<td>C6H5</td>
<td>PMB</td>
<td>1.116</td>
<td>87</td>
<td>1.118</td>
</tr>
</tbody>
</table>

All aldol products were obtained in good to excellent yields, and hydrolysis of each was affected without issue.

1.3.6 Unsymmetrical Ketone Systems

Given the effectiveness of the above *anti* aldol addition reaction with the symmetrical ketone 3-pentanone, we wanted to investigate the possibility of extending the method to the synthesis of *anti* aldol products from unsymmetrical ketones having both α- and α'-protons. Despite the considerable effort that has been devoted to the study of the aldol addition, there currently exists no method for the selective addition of such a ketone with an aldehyde. In order to obtain such aldol products, we would use a
unique method that borrows from the enantioselective $\alpha,\alpha$-bisalkylation reaction of ketones developed in our laboratory[43].

In this approach (Figure 13), complex-induced $\textit{syn}$ deprotonation (CIS-D) is relied on to direct removal of the proton on the same side of the C–N double bond as the ACC auxiliary. The azaenolate of hydrazone 1.35 is first alkylated to give a monoalkylated hydrazone. Subsequent deprotonation and anti aldol addition would give the anti $\alpha$-methyl-$\beta$-benzyloxy hydrazone. The auxiliary can then be removed as previously described.

![Reaction Scheme](image)

**Figure 14. General reaction to produce unsymmetrical ketone aldol products**

As an initial test of this experimental protocol, acetone hydrazone 1.35 was deprotonated and then ethylated using ethyl iodide. This gave the ethylated hydrazone as a single double bond diastereomer. The hydrazone was then subjected to the anti aldol conditions with benzaldehyde and benzyl iodide, and, as expected, this provided the $\text{O-benzyl \textit{anti}}$ addition product 1.137 in good yield. Auxiliary removal was completed without issue in less than six hours to give ketone 1.138. In a similar way, the
allyl and prenyl-containing anti aldol products (1.140 and 1.142) were also obtained with no regio- or stereochemical issues.

Table 8. Unsymmetrical ketone aldol reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Hydrazone</th>
<th>Yield (%)</th>
<th>Ketone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ethyl</td>
<td>1.137</td>
<td>85</td>
<td>1.138</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>allyl</td>
<td>1.139</td>
<td>90</td>
<td>1.140</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>prenyl</td>
<td>1.141</td>
<td>84</td>
<td>1.142</td>
<td>92</td>
</tr>
</tbody>
</table>

These methyl ketone products are suitable for further elaboration in a number of synthetically useful ways. The most immediate example would be further alkylation at the α'-position (-CH₃) of the ketone. To test this, methyl ketone 1.141 was treated with LDA in THF at -78 °C followed by the addition prenyl bromide. We were surprised to see no alkylation of the ketone had occurred. It was found that the addition of excess hexamethylphosphoramide (HMPA) to the azaenolate before the addition of the alkylation agent was necessary to prepare the alkylated ketone 1.144. Presumably, the added HMPA assists in breaking down less reactive enolate aggregates in solution. It should be noted that a compound such as 1.144 has not been previously reported and could not be prepared via conventional ketone-based aldol addition reactions.
Scheme 23. α’-Alkylation of aldol product 1.140 to give an alkylated product that could not be prepared by any other conventional method.

1.3.7 Enolizable Aldehydes and Ketones


Although aromatic and nonenolizable aldehydes were successfully used in the anti selected aldol reaction, the use of aldehydes possessing acidic α-protons (e.g., isobutyraldehyde) proved disappointing. In each case, little to no aldol products were obtained under the established reaction conditions. It was reasoned that the ability of the kinetically formed syn aldolate to undergo a retro-aldol process, combined with the high basicity of the reaction medium, led to deprotonation of the aldehyde before a significant amount of the thermodynamic anti product could be obtained. It is likely that the use of this type of aldehyde would require considerable manipulation of the reaction conditions. The use of ketones as electrophiles (e.g., acetophenone) resulted in no
product being formed. This, again, is presumably the result of deprotonation of the ketone by the azaenolate to give the corresponding enolate of the ketone.

1.4 Conclusion

In summary, we have developed a new ACC-mediated asymmetric anti aldol addition for the addition of achiral ketones to aldehydes. The reaction appears to operate under thermodynamic control, with lower temperatures increasingly favoring the formation of a single *syn* aldol diastereomer and higher temperatures favoring a single *anti* diastereomer. To the best of our knowledge, this is the first asymmetric *anti* aldol addition reaction of a ketone-derived donor that is independent of the structure of the ketone itself. The reaction is capable of giving exclusively the *anti* aldol product with perfect enantioselectivity for a variety of aromatic and unsaturated aldehydes. At

\[
R^1 \quad \text{LDA} \quad \text{THF, -78 °C} \quad \text{ArCHO} \quad \text{syn addition} \quad \text{ArCHO} \quad \text{anti addition} \quad \text{ArCHO} \quad \text{retro-aldol with increasing temperature}
\]

**Figure 15. Summary of the ACC-mediated anti selective aldol addition.**
present, the reaction conditions are incompatible with enolizable aldehydes. The versatility of ACC chiral auxiliaries combined with their ability to direct deprotonation allowed for this anti aldol addition to be extended to the formation of products derived from asymmetric ketones, which could not be prepared selectively via conventional methods.

1.5 Experimental Section

General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 180 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 180 °C for at least 12 h prior to use. Hamilton microsyringes were dried in an oven at 60 °C for at least 12 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et₂O, CH₂Cl₂, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich.
Commercial grade solvents were used for routine purposes without further purification. Et$_3$N, pyridine, i-Pr$_2$NEt, 2,6-lutidine, i-Pr$_2$NH, TMEDA were distilled over CaH$_2$ under a N$_2$ atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230–400 mesh) or, where indicated, high-grade silica gel (5-20 mesh). The syn-anti ratios reported were computed from the $^1$H NMR spectrum of the crude material. Reactions were visualized on TLC plates using phosphomolybdic acid (PMA) stain. All $^1$H chemical shifts are reported in ppm ($\delta$) relative to TMS; $^{13}$C shifts are reported in ppm ($\delta$) relative to CDCl$_3$ (77.23).

![Chemical Structure](image)

**(+)-Camphorsulfonfyl chloride (1.87).** To a 1-liter round three-neck, round bottom flask, equipped with hydrogen chloride trap and containing (+)-(1S)-camphorsulfonfyl chloride (50.0 g, 215 mmol) was added phosphorus pentachloride (49.3 g, 237 mmol). The two solids were mixed together until an exothermic reaction began to occur. The resulting clear, colorless molten mixture was stirred at room temperature for 2 hours. Ice was then added, and the ice slurry was partitioned between CH$_2$Cl$_2$ (400 mL) and DI water (400 mL). The layers were separated before the aqueous layer was extracted once more with CH$_2$Cl$_2$ (250 mL). The combined extracts were dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo to give a white solid (50 g, 93%). Spectroscopic data was identical to previous reports in the literature.[37]
(±)-10-Chlorocamphor-10-sulfine (1.88). A solution of tosyl chloride (130 g, 681 mmol) in pyridine (115 mL) was heated to 100 °C. A separate solution of sulfonyl chloride 1.87 (155 g, 619 mmol) in 1,2-dichloroethane (130 mL) was then added dropwise over a 30 minute period. During this time, the reaction became dark-brown in color. After the addition was completed, the reaction was refluxed for 60 minutes before being allowed to cool to room temperature. Addition of the mixture into Et₂O (1 L) gave a dark brown precipitate (pyridinium tosylate), which was filtered and washed with additional Et₂O. The combined ethereal extracts were dried over solid MgSO₄ and concentrated in vacuo to give a dark brown oil that slowly solidified upon standing. The crude solid was recrystallized from hexanes/EtOAc to give crystals with a light tan color (108 g, 75%). Spectroscopic data was identical to previous reports in the literature.[37]

(+)-Ketopinic acid chloride (1.89). A 1 L three-neck, round bottom flask solution of sulfine 1.88 (77.5 g, 333 mmol) in CH₂Cl₂ (500 mL) and pyridine (29 mL, 352 mmol) was cooled to -78 °C (dry ice/acetone). Ozone gas was bubbled through the solution, creating a light brown suspension, and the reaction was monitored until TLC (20%
EtOAc/hexanes) showed all starting material had been consumed (2 hours). The mixture was then poured into liquid pentane (2 L), and the resulting precipitate was filtered off. Concentration of the filtrate gave a brown oil, which was dissolved in hexane (250 mL) and treated with oxalyl chloride (10.0 mL, 115 mmol). Filtration and concentration in vacuo gave a light brown solid (61.5 g, 92%). Spectroscopic data was identical to previous reports in the literature.[39]

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

(+)-1-isocyanato-7,7-dimethylbicyclo[2.2.1]heptan-2-one (1.90). To a stirring solution of sodium azide (31.4 g, 483 mmol) in water (600 mL) at 0 °C was added a solution of (+)-ketopinic acid chloride 1.89 (32 g, 161 mmol) in acetone (600 mL) over a 60 minute period. After the addition was complete, the mixture was allowed to warm to room temperature and stir an additional hour. The acetone co-solvent was removed in vacuo, and more DI water (200 mL) was added. Extraction of the suspension with Et2O (3 x 300 mL) was followed by drying over solid MgSO4. Concentration in vacuo gave an off-white solid, which was immediately dissolved in toluene (250 mL). The solution of acid azide was refluxed for 45 minutes, and the toluene was removed under reduced pressure. This gave an off-white solid (24.5 g, 85%), which was recrystallized from hexanes/EtOAc. 1H NMR (400 MHz, CDCl3): δ 2.49 (d, 1H, J = 18.7 Hz), 2.17-1.95 (m, 4H), 1.74-1.65 (m, 1H), 1.56-1.45 (m, 1H), 1.06 (s, 3H), and 0.90 (3H); 13C NMR (CDCl3, 100
MHz): δ 211.6, 128.6, 76.2, 47.3, 41.6, 40.2, 28.5, 26.8, 18.9, and 18.7; LRMS [m/z, (relative intensity)]: 179 (M+, 8), 135 (100), 110 (48).

(3aS,6R,7aR)-8,8-dimethylhexahydro-2H-3a,6-methanobenzo[d]oxazol-2-one (1.91). A solution of isocyanate 1.90 (5.0 g, 28.4 mmol) in methanol (150 mL) was treated with CeCl·7H2O (1.10 g, 2.84 mmol) and cooled to 0 °C. After stirring for 10 minutes, the solution was cooled to -78 °C. Solid NaBH₄ (1.5 g, 39 mmol in 4 portions) was added over a twenty minute period. The reaction mixture was warmed to -40 °C, and stirring was continued for 2 hours. After warming to room temperature, the methanol was partially removed in vacuo until a suspension developed. This suspension was diluted with DI water (250 mL) and extracted with EtOAc (3 x 400 mL). The combined extracts were dried over solid MgSO₄, filtered, and concentrated in vacuo to give an off-white solid (4.77 g, 93%). The solid was recrystallized from hexanes/EtOAc. ¹H NMR (400 MHz, CDCl₃): δ 6.85 (bs, 1H), 4.31 (dd, 1H, J = 8.1 Hz, 4.2 Hz), 2.30-2.25 (m, 1H), 2.01-1.96 (m, 1H0, 1.87-1.82 (m, 3H), 1.32-1.21 (m, 2H), 1.03 (s, 3H), and 0.97 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 161.5, 86.8, 69.7, 47.2, 42.2, 35.6, 27.3, 25.6, 19.3, and 19.2; ESI-MS m/z [M+H]+ calculated for C₁₀H₁₅O₂N: 181.11, found 181.1.
(3aS,6R,7aR)-3-amino-8,8-dimethylhexahydropyrido[2H]-3a,6-methanobenzo[d]-

oxazol-2-one (1.13). Aqueous NH₄OH (15 M, 12.1 mL) was added to a stirred suspension of NH₄Cl (8.22 g, 154 mmol) in Et₂O (300 mL) at -5 °C (ice/acetone). Household bleach (216 mL) was then added all at once. Gas evolution occurred, and the biphasic mixture was stirred an additional 15 minutes. The ethereal layer was separated and dried over solid MgSO₄ for 30 minutes at -20 °C. This solution (approximately 0.15M NH₄Cl) was filtered immediately prior to use.

Solid KOt-Bu (2.48 g, 22.1 mmol) was added to a solution of oxazolidinone 1.91 (2.0 g, 11.0 mmol) in THF (100 mL) under argon. A white suspension developed that was stirred for an additional 1 hour at room temperature. This suspension was then treated with the chloramine solution previously prepared (110 mL, 16.5 mmol) over a 15 minute period. A cream colored mixture developed that was stirred for 45 minutes. The reaction was then treated with a solution of 1 M Na₂S₂O₃ (100 mL). The layers were immediately separated, and the aqueous layer was extracted with Et₂O (2 x 100 mL). The extracts were combined, dried over solid MgSO₄, and concentrated in vacuo to give a clear, yellow oil that consisted in aminated product (90%) and a small amount of starting oxazolidinone (10%). ¹H NMR (400 MHz, CDCl₃): δ 4.16 (dd, 1H, J = 8.2 Hz, 4.1 Hz), 3.91 (s, 2H), 2.30-2.10 (m, 2H), 2.05-1.70 (m, 3H), 1.36-1.24 (m, 1H), 1.18 (s, 3H), and 1.0 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 160.2, 83.2, 72.1, 47.3, 42.7, 35.1, 25.8, 25.4, 20.7, and 19.5; ESI-MS m/z [M+H]⁺ calculated for C₁₀H₁₅O₂N₂: 197.26, found 197.1.
ACC 3-pentanone hydrazone (1.17). To a stirred solution of ACC auxiliary X (710 mg, 3.62 mmol, 1.0 eq.) in dichloromethane (30 mL) was added 3-pentanone (3.85 mL, 3.14 g, 36.18 mmol, 10.0 eq.) and p-toluenesulfonic acid (103 mg, 0.543 mmol, 0.15 eq.). After stirring for 12 hours at room temperature, the reaction mixture was treated with saturated sodium bicarbonate solution (2 mL) and then diluted with deionized water. Separation of the layers was followed by extraction of the aqueous layer with dichloromethane (2 x 50 mL), and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification via flash chromatography over silica gel (10% EtOAc/90% hexanes) gave X as an off-white solid (870 mg, 91%). Spectral characteristics of this compound were consistent with previous characterization in the literature.[12]

Benzyl iodide. A 100 mL round bottom flask was charged with of benzyl bromide (1.0 mL, 1.44 g, 4.09 mmol, 1.0 eq.), which was subsequently dissolved in 65 mL of acetone. The resulting clear solution was treated with solid sodium iodide (1.60 g, 5.32 mmol, 1.3
eq.), and the solid momentarily dissolved before a white precipitate formed. Stirring was continued in the dark for 12 hours. The mixture was then concentrated in vacuo, and the crude paste was taken up into 50 mL of deionized water. The aqueous mixture was extracted three times with diethyl ether (3 x 30 mL), and the combined extracts were washed with 1 M sodium thiosulfate solution to remove excess iodine. Drying over anhydrous magnesium sulfate and concentration in vacuo gave a light-yellow, lachrymatory oil (857 mg, 96%) that solidified upon storage in the freezer. Prior to use, the solid was allowed to melt at room temperature to allow for easy addition to the reaction flask. Spectral characteristics of this compound were consistent with previous characterization in the literature.[44]

![4-Methoxybenzyl iodide](image)

4-Methoxybenzyl iodide. This compound was prepared in the same manner described for benzyl iodide above using 4-methoxybenzyl chloride (346 µL, 400 mg, 2.55 mmol, 1.0 eq.), sodium iodide (1.15 g, 3.32 mmol, 1.30 eq.), and acetone (10 mL). A yellow, pleasant-smelling oil (563 mg, 89%) was obtained that quickly turned brown upon exposure to light. Due to the high light sensitivity of this compound in its pure form, it was dissolved in anhydrous THF to give a 0.15 M solution for use in subsequent reactions. Spectral characteristics of the neat compound were consistent with previous characterization in the literature.[45]
ACC acetone hydrazone (1.35). This hydrazone was made in a similar manner to X above using auxiliary X (716 mg, 3.65 mmol, 1.0 eq.), 2,2-dimethoxypropane (4.50 mL, 3.83 g, 36.5 mmol, 10.0 eq.), p-toluenesulfonic acid monohydrate (139 mg, 0.20 eq.), and 50 mL of methylene chloride. Purification via flash chromatography over silica gel (10% EtOAc/90% hexanes) gave X as an off-white solid (776 mg, 90%). Spectral characteristics were consistent with previous literature reports.[43]

ACC 2-Pentanone. n-Butyllithium (2.5 M in hexanes, 372 µL, 0.930 mmol, 1.10 eq.) was added to a stirred and cooled (-78 °C) solution of diisopropylamine (132 µL, 0.930 mmol, 1.10 eq.) in THF (5 mL). After being stirred for 20 min, 1.35 (200 mg, 0.846 mmol) was added directly into the solution of LDA. A slightly yellow solution developed that was stirred for 45 min at -78 °C. Then, excess ethyl iodide (680 µL, 8.46 mmol, 10.0 eq.) was added. The reaction mixture was warmed to 0 °C over a period of three hours. The reaction was then quenched with deionized water (5 mL) under vigorous stirring. The mixture was partitioned between Et2O (20 mL) and brine (20 mL), and the layers were
separated. The aqueous phase was extracted with Et₂O (2 x 15 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the resulting crude oil was achieved using flash chromatography over silica gel (pretreated with Et₃N, 5% EtOAc/95% Hexanes) to give the product hydrazone as a viscous, colorless oil (205 mg, 92% yield). Spectral characteristics were consistent with previous literature reports.[43]

**ACC 2-hex-5-enone hydrazone.** This compound was prepared in a manner similar to the above hydrazone using *n*-butyllithium (2.5 M in hexanes, 280 µL, 0.699 mmol, 1.10 eq.), diisopropylamine (99 µL, 0.699 mmol, 1.10 eq.), ACC acetone hydrazone (150 mg, 0.635 mmol, 1.0 eq.), and allyl bromide (60 µL, 0.699 mmol, 1.10 eq.). Purification of the resulting crude oil was achieved using flash chromatography over silica gel (pretreated with Et₃N, 5% EtOAc/95% Hexanes) to give the product hydrazone as viscous, colorless oil (157 mg, 90% yield). Spectral characteristics were consistent with previous literature reports.[43]
ACC 6-methyl-2-hept-5-enone hydrazone. This compound was prepared in a manner similar to the above hydrazone using n-butyllithium (2.5 M in hexanes, 280 µL, 0.699 mmol, 1.10 eq.), diisopropylamine (99 µL, 0.699 mmol, 1.10 eq.), ACC acetone hydrazone (150 mg, 0.635 mmol, 1.0 eq.), and prenyl bromide (81 µL, 0.699 mmol, 1.10 eq.). Purification of the resulting crude oil was achieved using flash chromatography over silica gel (pretreated with Et3N, 5% EtOAc/95% Hexanes) to give the product hydrazone as a viscous, colorless oil (184 mg, 95% yield). Spectral characteristics were consistent with previous literature reports.[43]

General procedure for anti selective ACC-mediated aldol additions using aromatic aldehydes. n-Butyllithium (2.5 M in hexanes, 90 µL, 0.270 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of diisopropylamine (38 µL, 0.270 mmol) in THF (1.5 mL). After being stirred for 20 min, 1.17 (50 mg, 0.1892 mmol) was added directly into the solution of LDA. A slightly yellow solution developed that was stirred for 45 min at -78 °C. Then, the aldehyde used was added to the azaenolate solution. The reaction mixture was allowed to room temperature over a period of two hours. The reaction was then quenched with saturated ammonium chloride solution (2 mL) under vigorous stirring. The mixture was partitioned between Et2O (10 mL) and H2O (10 mL), and the layers were separated. The aqueous phase was extracted with Et2O (2 x 10 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate,
filtered, and concentrated *in vacuo*. Purification of the resulting crude oil was achieved using flash chromatography over silica gel (10% EtOAc/90% Hexanes) gave the *anti* aldol diastereomer.

**General procedure for low temperature (syn selective) ACC-mediated aldol additions.** These reactions were conducted in a similar manner to the *anti* selective aldol reaction mentioned above except that the reaction mixture was kept at -78 °C after the addition of the aldehyde. After stirring for 30 minutes at this temperature, the reaction was quenched in the previously described manner. The crude product consisted of a mixture of unreacted 3-pentanone hydrazone, a *syn* aldol diastereomer, and an *anti* aldol diastereomer. Purification was achieved using flash chromatography over high-grade silica gel (pretreated with Et₃N, 7.5% EtOAc/92.5% Hexanes) to give the separate diastereomers.

![Chemical Structure](image)

**ACC (1S,2R)-1-hydroxy-2-methyl-1-phenylpentan-3-one.** This *anti* aldol diastereomer was isolated from the room temperature aldol reaction of SACC 3-pentanone hydrazone and benzoaldehyde. ¹H NMR (CDCl₃, 400 MHz): δ 7.35-7.33 (m, 4H), 7.29-7.23 (m, 1H), 5.45 (d, OH, J = 10.4 Hz), 4.46 (app. t, 1H, J = 10.4 Hz), 4.31 (dd, 1H, J = 4.5 Hz, 8.5 Hz), 3.25 (dq, 1H, J = 7.2 Hz, 14 Hz), 2.75 (dq, 1H, J = 7.2 Hz, 17.6 Hz), 2.57 (dq, 1H, J = 7.2 Hz,
17.6 Hz), 2.38-2.33 (m, 1H), 2.05-1.95 (m, 2H), 1.89 (dd, 1H, \( J = 8 \) Hz, 13.6 Hz), 1.81 (app. t, 1H, \( J = 4.4 \) Hz), 1.33-1.07 (m, 12H, containing a s at \( \delta = 1.28 \) (3H), a t at \( \delta = 1.22 \) (3H, \( J = 7.2 \) Hz), and a s at \( \delta = 1.18 \) (3H)), and 0.80 (d, 3H, \( J = 6.8 \) Hz); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz): 182.02, 156.47, 143.83, 128.49, 127.71, 127.21, 83.70, 73.94, 48.12, 44.18, 43.13, 35.49, 26.55, 25.76, 24.33, 21.47, 19.33, 15.94, and 10.24; ESI-MS \( m/Zepr \) calculated for C\(_{22}\)H\(_{30}\)N\(_2\)O\(_3\) (M+H): 370.23, found: 370.21.

**ACC (1R,2R)-1-hydroxy-2-methyl-1-phenylpentan-3-one.** This syn diastereomer was isolated from the low temperature aldol reaction of SACC 3-pentanone hydrazone and benzaldehyde. \( ^{1} \)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.42 \) (d, 2H, \( J = 7.5 \) Hz), 7.33 (app. t, 2H, \( J = 7.2 \) Hz), 7.25 (d, 1H, \( J = 7.2 \) Hz), 5.17 (app. s, 1H), 4.25 (dd, 1H, \( J = 4.5 \) Hz, 8.5 Hz), 3.31 (dq, 1H, \( J = 2.4 \) Hz, 7.2 Hz), 2.61 (dq, 1H, \( J = 7.2 \) Hz, 17.8 Hz), 2.51 (dq, 1H, \( J = 7.2 \) Hz, 17.8 Hz), 2.35-2.29 (m, 2H), 1.95-1.92 (m, 2H), 1.85 (dd, 2, \( J = 8 \) Hz, 13.6 Hz), 1.77 (app. t, 1H, 4.4 Hz), 1.27-1.08 (m, 12H, containing a s at \( \delta = 1.23 \) (3H), a s at \( \delta = 1.19 \) (3H, and a t at \( \delta = 1.03 \) (3H, \( J = 7.2 \) Hz)), and 0.96 (d, 3H, \( J = 7.2 \) Hz); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz): 189.67, 156.20, 143.74, 128.33, 127.32, 126.47, 83.28, 73.71, 73.51, 48.03, 43.06, 42.13, 35.55, 26.97, 26.51, 25.79, 21.49, 19.33, 10.75, and 10.61; ESI-MS \( m/Zepr \) calculated for C\(_{22}\)H\(_{30}\)N\(_2\)O\(_3\) (M+H): 370.23, found: 370.21.
ACC (1S,2R)-1-hydroxy-2-methyl-1-(4-(trifluoromethyl)phenyl)pentan-3-one. This anti diastereomer was isolated from the room temperature aldol reaction of SACC 3-pentanone hydrazone and 4-trifluoromethylbenzaldehyde. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.57 (d, 2H, $J = 8$ Hz), 7.43 (d, 2H, $J = 8$ Hz), , 5.66 (d, OH, $J = 10$ Hz), 4.51 (app. t, 1H, $J = 10.4$ Hz), 4.30 (dd, 1H, $J = 4$ Hz, 8 Hz), 3.18 (dq, 1H, $J = 6.8$ Hz, 10.4 Hz), 2.69 (dq, 1H, $J = 7.2$ Hz, 17.2 Hz), 2.53 (dq, 1H, $J = 7.2$ Hz, 17.2 Hz), 2.36-2.31 (m, 1H), 2.04-1.93 (m, 2H), 1.89 (dd, 1H, $J = 8.4$ Hz, 14 Hz), 1.80 (app. t, 1H, $J = 3.6$ Hz), 1.30-1.03 (m, 12H, containing a s at $\delta$ 1.26 (3H), a t at $\delta$ 1.20 (3H, $J = 7.2$ Hz), and a s at $\delta$ 1.15 (3H)), and 0.79 (d, 3H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): 181.21 156.55, 147.92, 129.99, 129.67, 127.58, 125.70, 125.41, 125.38, 123.00, 83.78, 76.05, 73.99, 48.09, 43.98, 43.04, 35.39, 26.44, 25.66, 24.39, 21.39, 15.72, and 10.16; ESI-MS $m/z$ calculated for C$_{23}$H$_{29}$F$_3$N$_2$O$_3$ (M+H)$^+$: 438.21, found: 438.19.

ACC (1R,2R)-1-hydroxy-2-methyl-1-(4-(trifluoromethyl)phenyl)pentan-3-one. This syn diastereomer was isolated from the low temperature aldol reaction of SACC 3-
pentanone hydrazone and 4-trifluoromethylbenzaldehyde. \(^1\)H NMR (CDCl\(_3\), 4 MHz): \(\delta\) 7.58-7.52 (m, 4H), 5.27 (app. s, 1H), 4.26 (dd, 1H, \(J = 3.6\) Hz, 7.6 Hz), 3.24 (m, 1H), 2.82 (bs, OH), 2.64 (dq, 1H, \(J = 7.2\) Hz, 17.6 Hz), 2.34-2.31 (m, 2H), 1.96-1.78 (m 5H), 1.30-1.04 (m, 12H, containing a s at \(\delta\) 1.24 (3H), a s at \(\delta\) 1.17 (3H), and a t at \(\delta\) 1.13 (3H, \(J = 7.2\) Hz), and 0.93 (d, 3H, \(J = 7.2\) Hz); \(^1\)C NMR (CDCl\(_3\), 100 MHz): 183.81, 156.20, 147.94, 126.84, 125.19, 83.41, 73.77, 72.76, 48.08, 43.06, 41.95, 35.54, 27.00, 26.52, 25.80, 21.50, 19.31, 10.62, and 10.44; ESI-MS \(m/\)Z calculated for \(\text{C}_{23}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_3\) (M+H): 438.21, found: 438.19.

**General procedure for anti selective ACC-mediated aldol additions with in situ \(O\)-benzylation.** \(n\)-Butyllithium (1.20 eq.) was added dropwise to a stirred and cooled (-78 °C) solution of diisopropylamine (1.20 eq.) in THF (0.5 mL). After being stirred for 20 min, hydrazone \textit{1.17} (50 mg, 1.0 eq., in 1.0 mL of THF) was added to the solution of LDA A slightly yellow solution developed that was stirred for 45 min at -78 °C. Then, the aldehyde (1.25 eq.) was directly added to the azaenolate solution, which was allowed to warm to room temperature. After stirring for two hours at room temperature, neat benzyl iodide (1.30 eq.) was added to the solution. Stirring was continued for 12 hours, and the reaction mixture was then quenched with saturated ammonium chloride solution (2 mL) and partitioned between Et\(_2\)O (10 mL) and H\(_2\)O (10 mL). The layers were separated, and the aqueous phase was extracted with Et\(_2\)O (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and
concentrated in vacuo. Purification of the resulting crude oil was achieved using flash chromatography over silica gel (pretreated with triethylamine, 10% EtOAc/90% Hexanes, phosphomolybdic acid (PMA) TLC stain) to give the O-benzylated ACC anti aldol product.

ACC (1S,2R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-1-phenylpentan-3-one (1.111).

This compound was prepared in the general manner for anti aldol products as described above except that tert-butyldimethylsilyl triflate (1.0 eq) was added after the reaction had stirred at room temperature for 2 hours. The reaction was quenched 30 minutes after the addition of dimethyl sulfate, and workup was conducted as already described (%).\textsuperscript{1H} NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.36 (d, 2H, \(J = 7.6\) Hz), 7.26-7.20 (m, 3H), 4.89 (d, 1H, \(J = 6.4\) Hz), 4.26 (dd, 1H, \(J = 4.0\) Hz, 8.0 Hz), 3.48 (m, 1H), 2.33-2.29 (m, 1H), 1.94-1.81 (m, 5H), 1.76-1.66 (m, 2H), 1.29-1.22 (m, 5H). 118-1.12 (m, 4H), 0.96 (t, 3H, \(J = 7.2\) Hz), 0.89 (d, 3H, \(J = 6.0\) Hz), 0.85 (s, 9H), -0.03 (s, 3H), and -0.27 (s, 3H).

(1S,2R)-1-((tert-butyldimethylsilyl)oxy)-2-methyl-1-phenylpentan-3-one (1.111). To a 10 mL round bottom flask was added a solution of 1.113 (89 mg, 0.2159 mmol) dissolved
in 10.0 mL of acetone. This solution was then treated with solid \textit{para}-toluenesulfonic acid monohydrate (103 mg, 0.6476 mmol). The clear solution was allowed to stir at room temperature for 30 minutes, after which it was quenched with the addition of saturated sodium bicarbonate solution and water. The mixture was extracted with diethyl ether (3 x 10 mL) followed by drying of the organic extracts over anhydrous magnesium sulfate. Concentration \textit{in vacuo} gave a crude oil that consisted of ACC acetone hydrazone and the $\beta$-methoxy ketone. The ketone could be isolated via flash chromatography over silica gel (5% EtOAc, 95% Hexanes) to give 15 mg (27%) as a viscous oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.42-7.26 (m, 5H), 4.65 (d, 1H, $J = 8.6$ Hz), 2.93-2.84 (m, 1H), 2.70-2.50 (m, 2H), 1.05 (t, 3H, $J = 7.2$ Hz), 0.77 (s, 9H), 0.70 (d, 3H, $J = 6.8$ Hz), -0.07 (s, 3H), and -0.33 (s, 3H).

\textit{ACC (1S,2R)-1-methoxy-2-methyl-1-phenylpentan-3-one} (1.113). This compound was prepared in the general manner for \textit{anti} aldol products as described above except that dimethyl sulfate was added after the reaction had stirred at room temperature for 2 hours. The reaction was quenched 30 minutes after the addition of dimethyl sulfate, and workup was conducted as already described (%).$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.35-7.28 (m, 5H), 4.23 (dd, 1H, $J = 4.0$ Hz, 8.0 Hz), 4.11 (d, 1H, $J = 8.6$ Hz), 3.50-3.38 (m, 1H), 3.12
(s, 3H, OCH₃), 2.60-2.19 (m, 4H), 2.02-1.74 (m, 5H), 1.28-1.05 [m, containing a s at δ 1.21 (3H), a s at δ 1.19 (3H), and a t at δ 1.17 (3H, J = 6.8 Hz)], and 0.72 (d, 3H, J = 6.8 Hz).

(1S,2R)-1-methoxy-2-methyl-1-phenylpentan-3-one (1.114). To a 10 mL round bottom flask was added a solution of 1.113 (83 mg, 0.2159 mmol) dissolved in 10.0 mL of acetone. This solution was then treated with solid para-toluenesulfonic acid monohydrate (112 mg, 0.6476 mmol). The clear solution was allowed to stir at room temperature for 1 hour, after which it was quenched with the addition of saturated sodium bicarbonate solution and water. The mixture was extracted with diethyl ether (3 x 10 mL) followed by drying of the organic extracts over anhydrous magnesium sulfate. Concentration in vacuo gave a crude oil that consisted of ACC acetone hydrazone and the β-methoxy ketone. The ketone could be isolated via flash chromatography over silica gel (15% EtOAc, 85% Hexanes). ¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.27 (m, 5H), 4.21 (d, 1H, J = 8.6 Hz), 3.08 (s, 3H, OCH₃), 2.88 (dq, 1H, J = 7.2 Hz, 8.6 Hz), 2.68-2.50 (m, 2H), 1.10 (t, 3H, J = 7.6 Hz), and 0.73 (d, 1H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 100 MHz): 214.62, 139.70, 128.59, 128.27, 127.77, 86.62, 56.86, 52.42, 36.88, 14.05, and 7.75; ESI-MS m/z calculated for C₁₃H₁₈O₂ (M+H)^+: 207.14, found: 207.1.
ACC (1S,2R)-1-(benzyloxy)-2-methyl-1-phenylpentan-3-one (1.115). This compound was isolated in 91% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, benzaldehyde, and benzyl iodide. 

**1H NMR** (CDCl₃, 500 MHz): δ 7.41-7.24 (m, 10H), 4.43 (d, 1H, J = 12.5 Hz), 4.35 (d, 1H, J = 9 Hz), 4.23 (dd, 1H, J = 4 Hz, 8Hz), 4.17 (d, 1H, J = 12.5 Hz), 3.55-3.50 (m, 1H), 2.43-2.18 (m, 4H), 1.97-1.64 (m, 5H), 1.25-1.23 (multiplet containing methyl singlet at 1.23, 4H), 1.17-1.12 (multiplet containing methyl singlet at 1.17, 5H), 1.08 (t, 3H, J = 7 Hz), and 0.77 (d, 3H, J = 7 Hz); 

**13C NMR** (CDCl₃, 125 MHz): 184.31, 155.89, 139.82, 138.36, 128.51, 128.36, 128.30, 127.92, 127.39, 83.05, 81.90, 73.59, 69.87, 47.85, 42.65, 35.55, 26.69, 19.49, 14.04, and 10.47; **ESI-MS** m/Z calculated for C₂₉H₃₆N₂O₃ (M+H): 460.27, found: 460.26.

ACC (1S,2R)-1-((4-methoxybenzyl)oxy)-2-methyl-1-phenylpentan-3-one (1.116). This compound was isolated in 87% yield as a single diastereomer from the *anti*-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, benzaldehyde,
and para-methoxybenzyl iodide. \textbf{\textit{1H NMR}} (CDCl$_3$, 500 MHz): $\delta$ 7.39-7.30 (m, 5H), 7.21 (d, 2H, $J = 8.5$ Hz), 6.85 (d, 2H, $J = 8.5$ Hz), 4.39 (d, 1H, $J = 12$ Hz), 4.31 (d, 1H, $J = 9$ Hz), 4.22 (dd, 1H, $J = 4$ Hz, 8 Hz), 4.07 (d, 1H, $J = 12$ Hz) 3.88 (s, 3H), 3.49 (dq, 1H, $J = 7$ Hz, 9 Hz), 2.32-2.30 (m, 1H), 2.20-2.14 (m, 2H), 1.90-1.88 (m, 2H), 1.82 (dd, 1H, $J = 9$ Hz, 14 Hz), 1.73 (app. s, 1H), 1.26-1.06 (m, 12H, containing a s at $\delta$ 1.22, a s at $\delta$ 1.16, and a t at $\delta$ 1.08 with $J = 7$ Hz), and 0.75 (d, 3H, $J = 7.5$ Hz); \textbf{\textit{13C NMR}} (CDCl$_3$, 125 MHz): 184.40, 159.06, 155.90, 139.92, 128.49, 128.18, 113.70, 83.04, 81.34, 73.58, 69.37, 55.41, 42.66, 35.55, 26.68, 25.81, 25.44, 21.37, 19.49, 14.07, and 10.47; \textbf{ESI-MS} $m/Z$ calculated for C$_{30}$H$_{38}$N$_2$O$_4$ (M+H)$^+$: 490.28, found: 490.26.

\[\text{\textit{ACC} (1S,2R)-1-(benzyloxy)-2-methyl-1-(4-(trifluoromethyl)phenyl)pentan-3-one}}\]

\textbf{(1.121)}. This compound was isolated in 83% yield as a single diastereomer from the \textit{anti}-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, 4-trifluoromethylbenzaldehyde, and benzyl iodide. \textbf{\textit{1H NMR}} (CDCl$_3$, 500 MHz): $\delta$ 7.62 (d, 2H, $J = 8$ Hz), 7.54 (d, 2H, $J = 8$ Hz), 7.33-7.25 (m, 5H), 4.45-4.42 (m, 2H), 4.22 (dd, 1H, $J = 4$ Hz, 8 Hz), 4.19 (d, 1H, $J = 12$ Hz), 3.53 (dq, 1H, $J = 7.5$ Hz, 10 Hz), 2.33-2.30 (m, 1H), 2.19 (m, 2H), 1.92-1.81 (m, 3H), 1.75 (app. t, 1H, $J = 4$ Hz), 1.27-1.07 (m, 12H, containing a s at $\delta$ 1.22, a s at $\delta$ 1.18, and a t at 1.09 with $J = 7$ Hz), and 0.79 (d, 3H, $J = 7.5$ Hz); \textbf{\textit{13C NMR}}
(CDCl₃, 125 MHz): 183.47, 155.91, 144.18, 137.83, 128.40, 127.62, 125.51, 125.48, 125.45, 123.19, 83.09, 81.26, 73.62, 70.27, 47.84, 42.52, 35.53, 25.57, 19.28, 13.75, and 10.39; ESI-MS m/z calculated for C₃₀H₃₆F₃N₂O₅ (M+H)⁺: 528.26, found: 528.25.

**ACC (1S,2R)-1-(benzo[d][1,3]dioxol-5-yl)-1-(benzyloxy)-2-methylpentan-3-one (1.123).**

This compound was isolated in 85% yield as a single diastereomer from the *anti*-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, piperonal, and benzyl iodide. **¹H NMR** (CDCl₃, 500 MHz): δ 7.32-7.24 (m, 5H), 6.94 (s, 1H), 6.82-6.76 (m, 2H), 5.96 (s, 2H), 4.44 (d, 1H, J = 12.5 Hz), 4.27-4.23 (m, 2H), 4.16 (d, 1H, J = 12.5 Hz), 3.51-3.46 (m, 1H), 2.32-2.17 (m, 3H), 1.86-1.81 (m, 3H), 1.74-1.72 (m, 1H), 1.27-1.06 (multiplet containing methyl singlets at 1.20 and 1.16 and a triplet at 1.08 (J = 7 Hz), 15H), and 0.78 (d, 3H, J = 7 Hz); **¹³C NMR** (CDCl₃, 125 MHz): 184.20, 155.88, 147.57, 133.76, 127.92, 122.13, 108.05, 107.98, 101.21, 83.04, 73.58, 69.70, 47.84, 43.02, 42.63, 35.56, 26.70, 25.82, 25.46, 21.38, 19.48, 14.10, and 10.46; **ESI-MS** m/z calculated for C₃₀H₃₆N₂O₅ (M+H)⁺: 504.26, found: 504.24.
ACC (4R,5R,E)-5-(benzyloxy)-4-methyl-7-phenylhept-6-en-3-one (1.125). This compound was isolated in 87% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, trans-cinnamaldehyde, and benzyl iodide. 1H NMR (CDCl₃, 500 MHz): δ 7.43-7.24 (m, 9H), 6.60 (d, 1H, J = 16 Hz), 6.13 (dd, 1H, J = 8 Hz, 16 Hz), 4.65 (d, 1H, J = 12.5 Hz), 4.39 (d, 1H, J = 12.5 Hz), 4.25 (dd, 1H, J = 4 Hz, 8 Hz), 4.04 (app. t, 1H, J = 8 Hz), 4.38 (dq, 1H, J = 7.5 Hz, 8 Hz), 2.38-2.27 (m, 3H), 1.94-1.92 (m, 2H), 1.84 (dd, 2H, J = 8 Hz, 13.5 Hz), 1.74 (app. t, 1H, J = 3.5 Hz), 1.28-1.08 (m, 12H, containing a s at δ 1.21, a s at δ 1.17, and a t at 1.10 with J = 7.5 Hz), and 1.01 (d, 3H, J = 7 Hz); 13C NMR (CDCl₃, 125 MHz): 184.29, 156.01, 138.65, 136.48, 134.68, 128.38, 127.96, 127.88, 127.41, 126.82, 83.05, 81.17, 73.64, 70.10, 47.88, 40.60, 35.57, 25.82, 19.45, 14.30, and 10.54; ESI-MS m/Z calculated for C₃₁H₅₈N₂O₃ (M+H)⁺: 486.29, found: 486.27.

ACC (1S,2R)-1-(benzyloxy)-1-(4-chlorophenyl)-2-methylpentan-3-one (1.127). This compound was isolated in 80% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, 4-chlorobenzaldehyde, and benzyl iodide. 1H NMR (CDCl₃, 500 MHz): δ 7.34-7.26 (m, 9H), 4.42 (d, 1H, J = 12 Hz), 4.35 (d, 1H, J = 9 Hz), 4.22 (dd, 1H, J = 4 Hz, 8 Hz), 4.16 (d, 1H, J =...
12 Hz), 4.39 (dq, 1H, $J = 7.5$ Hz, 9 Hz), 2.42-2.30 (m, 1H), 2.19-2.17 (m, 2H), 1.90-1.84 (m, 1H), 1.82 (dd, 2H, $J = 8.5$ Hz, 13.5 Hz), 1.74 (app. s, 1H), 1.44-1.06 (m, 12H, containing a s at δ 1.17, a s at δ 1.14, and a t at 1.07 with $J = 7$ Hz), and 0.77 (d, 3H, $J = 7$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): 183.8, 155.95, 138.42, 138.06, 133.98, 129.72, 128.76, 128.39, 128.35, 127.95, 127.56, 83.11, 81.09, 73.64, 70.04, 47.87, 42.58, 35.58, 26.69, 19.49, 13.78, and 10.45; ESI-MS m/Z calculated for C$_{29}$H$_{35}$ClN$_2$O$_3$ (M+H)$^+$: 494.23, found: 494.20.

ACC (1S,2R)-1-(benzyl)oxy)-1-(4-bromophenyl)-2-methylpentan-3-one (1.129). This compound was isolated in 89% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, 4-bromobenzaldehyde, and benzyl iodide. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.49 (d, 2H, $J = 8.5$ Hz), 7.34-7.26 (m, 7H), 4.43 (d, 1H, $J = 12$ Hz), 4.33 (d, 1H, $J = 9$ Hz), 4.23 (dd, 1H, $J = 4$ Hz, 8 Hz), 4.16 (d, 1H, $J = 12$ Hz), 3.49 (dq, 1H, $J = 7$ Hz, 9 Hz), 2.33-2.30 (m, 1H), 2.22-2.16 (m, 2H), 1.92-1.81 (m, 3H), 1.75 (app. t., 1H, $J = 3.5$ Hz), 1.26-1.06 (m, 12H, containing a s at δ 1.22, a s at δ 1.17, and a t at 1.08 with $J = 7$ Hz), and 0.77 (d, 3H, $J = 7$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): 183.81, 155.93, 138.96, 138.02, 131.69, 127.56, 127.55, 122.16, 83.08, 81.14, 73.63, 70.05, 70.03, 47.87, 43.03, 42.53, 35.57, 25.59, 19.48, 13.78, 13.77, and 10.44; ESI-MS m/Z calculated for C$_{29}$H$_{35}$BrN$_2$O$_3$ (M+H)$^+$: 539.50, found: 539.48.
ACC (1S,2R)-1-(benzyloxy)-2-methyl-1-(o-tolyl)pentan-3-one (1.131). This compound was isolated in 85% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, ortho-tolualdehyde, and benzyl iodide. 

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.48 (d, 1H, $J$ = 7 Hz), 7.30-7.18 (m, 7H), 7.13 (d, 1H, $J$ = 7.5 Hz), 4.64 (d, 1H, $J$ = 9.5 Hz), 4.21 (d, 1H, $J$ = 12 Hz), 4.24 (dd, 1H, $J$ = 4 Hz, 8 Hz), 4.11 (d, 1H, $J$ = 12 Hz), 3.60 (dq, 1H, $J$ = 7.5 Hz, 9.5 Hz), 2.45-2.25 (m, 8H, containing a s at $\delta$ 2.32), 1.91-1.81 (m, 4H), 1.74 (app. t, 1H, $J$ = 4 Hz), 1.26-1.12 (m, 12H, containing a s at $\delta$ 1.23, a s at $\delta$ 1.18, and a t at 1.14 with $J$ = 7 Hz), and 0.74 (d, 3H, $J$ = 7 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): 184.16, 155.64, 138.45, 137.02, 130.48, 128.31, 127.95, 127.80, 127.38, 126.62, 82.99, 69.59, 47.90, 43.03, 35.58, 25.34, 19.51, 14.30, and 10.57.; ESI-MS m/z calculated for C$_{30}$H$_{38}$N$_2$O$_3$ (M+H)$^+$: 474.29, found: 474.27.

ACC (1S,2R)-1-(benzyloxy)-2-methyl-1-(naphthalen-2-yl)pentan-3-one (1.133). This compound was isolated in 91% yield as a single diastereomer from the anti-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, 2-
napthaldehyde, and benzyl iodide. \textbf{\textsuperscript{1}H NMR} (CDCl$_3$, 500 MHz): $\delta$ 7.88-7.85 (m, 3H), 7.80 (s, 1H), 7.60 (d, 1H, $J$ = 8.5 Hz), 7.50 (m, 2H), 4.52 (d, 1H, $J$ = 9 Hz), 4.87 (d, 1H, $J$ = 12 Hz), 4.25 (dd, 1H, $J$ = 4 Hz, 8 Hz), 4.21 (d, 1H, $J$ = 12 Hz), 3.65 (dq, 1H, $J$ = 7.5 Hz, 9 Hz), 2.34-2.22 (m, 4H), 1.93-1.90 (m, 2H), 1.84 (dd, 1H, $J$ = 8 Hz, 13.5 Hz), 1.75 (app. t, 1H, $J$ = 4 Hz), 1.30-1.21 (m, 6H, containing a s at $\delta$ 1.23), 1.19 (s, 3H), 1.15-1.09 (m, 5H, containing a t at $\delta$ 1.11 with $J$ = 7.5 Hz), and 0.80 (d, 1H, $J$ = 7.5 Hz); \textbf{\textsuperscript{13}C NMR} (CDCl$_3$, 125 MHz): 184.22, 155.90, 137.36, 128.35, 127.98, 127.81, 126.33, 125.73, 83.07, 82.12, 73.63, 69.99, 47.89, 43.06, 42.51, 35.60, 26.74, 25.85, 25.53, 21.43, 19.54, 14.31, and 10.52; \textbf{ESI-MS} m/$Z$ calculated for C$_{33}$H$_{38}$N$_2$O$_3$ (M+H)$^+$: 510.29, found: 510.28.

ACC (1S,2R)-1-(benzyloxy)-1-(4-nitrophenyl)-2-methylpentan-3-one (1.135). This compound was isolated in 87% yield as a single diastereomer from the \textit{anti}-selective ACC aldol reaction described above using ACC 3-pentanone hydrazone, 4-nitrobenzaldehyde, and benzyl iodide. \textbf{\textsuperscript{1}H NMR} (CDCl$_3$, 500 MHz): $\delta$ 8.23 (d, 2H, $J$ = 8.5 Hz), 7.62 (d, 2H, $J$ = 8.5 Hz), 7.56-7.29 (m, 5H), 4.55 (d, 1H, $J$ = 8.5 Hz), 4.46 (d, 1H, $J$ = 12 Hz), 4.26-4.22 (m, 2H), 3.57 (dq, 1H, $J$ = 7 Hz, 8.5 Hz), 2.36-2.32 (m, 1H), 2.24-2.21 (m, 2H), 1.94-1.85 (m, 3H), 1.78 (app. t, 1H, $J$ = 4 Hz), 1.28 (d, 1H, $J$ = 7.5 Hz), 1.23 (s, 3H), 1.19 (s, 3H), 1.09 (t, 3H, $J$ = 7 Hz), and 0.84 (d, 3H, 7 Hz); \textbf{\textsuperscript{13}C NMR} (CDCl$_3$, 125 MHz): 183.06,
156.06, 147.65, 137.53, 128.50, 127.96, 127.83, 123.77, 83.19, 80.89, 73.70, 70.68, 47.88, 43.03, 42.42, 35.43, 25.81, 19.45, 13.49, and 10.41; \textbf{ESI-MS} m/Z calculated for C_{29}H_{35}N_{3}O_{5} (M+H)^+: 505.26, found: 505.23.

\[ \text{ACC (R)-3-} \text{((S)-(benzyloxy)(phenyl)methyl} \text{pentan-2-one (1.137). This compound was isolated in 85\% yield as a single diastereomer from the} \text{anti-selective ACC aldol reaction described above using ACC 2-pentanone hydrazone, benzaldehyde, and benzyl iodide.}\]

\textbf{H NMR} (CDCl$_3$, 500 MHz): δ 7.44 (d, 2H, J = 8.5 Hz), 7.34-7.23 (m, 8H), 4.51 (d, 1H, J = 9 Hz), 4.43 (d, 1H, J = 15 Hz), 4.22-4.19 (m, 2H), 3.43 (dt, 1H, J = 5 Hz, 9 Hz), 2.33-2.26 (m, 2H), 2.04-1.1 (m, 7H), 1.67 (s, 3H), 1.65-1.60 (m, 1H), 1.27-1.10 (m, 9H, containing a s at δ 1.20 and a s at δ 1.17), and 0.69 (t, 3H, J = 9.5 Hz); \textbf{C NMR} (CDCl$_3$, 125 MHz): 179.94, 156.07, 139.80, 138.61, 128.30, 128.11, 127.76, 127.35, 82.87, 81.19, 73.68, 70.03, 48.04, 42.92, 40.85, 35.46, 21.52, 19.41, and 12.24; \textbf{ESI-MS} m/Z calculated for C_{28}H_{36}N_{2}O_{3} (M+H)^+: 460.27, found: 460.25.
ACC (R)-3-((S)-(benzyloxy)(phenyl)methyl)hex-5-en-2-one (1.139). This compound was isolated in 90% yield as a single diastereomer from the *anti*-selective ACC aldol reaction described above using ACC 2-pentanone hydrazone, benzaldehyde, and benzyl iodide. 

$^1$H NMR (CDCl$_3$, 500 MHz): δ 7.45 (d, 2H, $J = 8$ Hz), 7.34-7.29 (m, 7H), 7.27-7.24 (m, 1H), 5.54-5.46 (m, 1H), 4.96-4.91 (m, 2H), 4.61 (d, 1H, $J = 7$ Hz), 4.45 (d, 1H, $J = 12$ Hz), 4.24-4.20 (m, 2H), 3.63 (dt, 1H, $J = 7$ Hz, 11 Hz), 2.51-2.46 (m, 1H), 2.33-2.28 (m, 1H), 2.09-1.90 (m, 5H), 1.82 (dd, 2H, $J = 8$ Hz, 14 Hz), 1.73 (app. t, 1H, $J = 4$ Hz), 1.69 (s, 3H), 1.27-1.23 (m, 2H), 1.20 (s, 3H), and 1.15-1.11 (m, 5H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 179.54, 156.21, 139.31, 138.46, 135.67, 127.41, 116.99, 82.98, 80.58, 73.64, 70.10, 47.99, 47.71, 42.89, 35.43, 31.59, 26.80, 26.74, 25.83, 25.74, 21.48, 20.64, 19.38, 19.27, and 19.23; ESI-MS m/z calculated for C$_{30}$H$_{36}$N$_2$O$_3$ (M+Na)$^+$: 475.27, found: 475.25.

ACC (R)-3-((S)-(benzyloxy)(phenyl)methyl)-6-methylhept-5-en-2-one (1.141). This compound was isolated in 84% yield as a single diastereomer from the *anti*-selective ACC aldol reaction described above using ACC 2-pentanone hydrazone, benzaldehyde, and benzyl iodide. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.46 (d, 2H, $J = 8.5$ Hz), 7.40-7.25 (m, 8H), 4.82 (app. t, 1H, $J = 6.5$ Hz), 4.60 (d, 1H, $J = 7$ Hz), 4.45 (d, 1H, $J = 12$ Hz), 4.25-4.201
(m, 2H), 3.57 (X, 1H, J = 7 Hz), 2.48-2.41 (m, 1H), 2.34-2.28 (m, 1H), 2.02-1.89 (m, 4H), 1.83 (dd, 1H, J = 8 Hz, 13.5 Hz), 1.74-1.71 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H), 1.29-1.22 (m, 2H), 1.20 (s, 3H), and 1.17-1.10 (m, 4H, containing a s at δ 1.15); ^13C NMR (CDCl₃, 125 MHz): 180.62, 156.52, 139.51, 138.74, 133.48, 128.54, 128.46, 128.36, 128.17, 127.69, 127.39, 121.41, 82.98, 80.76, 73.81, 70.17, 48.17, 48.05, 42.97, 35.58, 26.74, 25.95, 25.59, 21.52, 20.69, 19.47, and 18.07; ESI-MS m/z calculated for C₃₂H₄₀N₂O₃ (M+Na)+: 523.30, found: 523.28.

**General procedure for hydrolysis of ACC hydrazones to ketones.** To a 10 mL round bottom flask was added a solution of hydrazone aldol product (1.0 eq) dissolved in 4 mL of acetone. This solution was then treated with solid para-toluenesulfonic acid monohydrate (2.5 eq). The clear solution was allowed to stir at room temperature for 6 hours, after which it was quenched with the addition of saturated sodium bicarbonate solution and water. The mixture was extracted with diethyl ether (3 x 10 mL) followed by drying of the organic extracts over anhydrous magnesium sulfate. Concentration in vacuo gave a crude oil that consisted of ACC acetone hydrazone and the β-benzyloxy ketone. The ketone could be isolated via flash chromatography over silica gel (7.5% EtOAc, 92.5% Hexanes).
(1S,2R)-1-(benzylxy)-2-methyl-1-phenylpentan-3-one (1.117). This compound was isolated in 91% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.38-7.24 (m, 8H), 7.17 (d, 2H, \(J = 8\) Hz), 4.44 (d, 1H, \(J = 10\) Hz), 4.30 (d, 1H, \(J = 11.5\) Hz), 4.19 (d, 1H, \(J = 11.5\) Hz), 2.97 (dq, 1H, \(J = 7\) Hz, 10 Hz), 2.66 (dq, 1H, \(J = 7\) Hz, 14.5 Hz), 2.54 (dq, 1H, \(J = 7\) Hz, 14.5 Hz), 1.09 (t, 3H, \(J = 7\) Hz), and 0.75 (d, 3H, \(J = 7\) Hz); \(^1\)C NMR (CDCl\(_3\), 125 MHz): 214.68, 139.82, 138.38, 128.42, 128.39, 127.90, 127.86, 127.68, 84.82, 70.87, 52.43, 37.19, 14.03, and 7.75; ESI-MS \(m/Z\) calculated for \(C_{19}H_{22}O_2\) (M+Na): 305.16, found: 305.14.

(1S,2R)-1-((4-methoxybenzyl)oxy)-2-methyl-1-phenylpentan-3-one (1.118). This compound was isolated in 93% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.39-7.32 (m, 5H), 7.08 (d, 2H, \(J = 8.5\) Hz), 6.83 (d, 2H, \(J = 8.5\) Hz), 4.40 (d, 1H, \(J = 9.5\) Hz), 4.23 (d, 1H, \(J = 11.5\) Hz), 4.10 (d, 1H, \(J = 11.5\) Hz), 3.78 (s, 3H), 2.94 (dq, 1H, \(J = 9.5\) Hz, 7 Hz), 2.64 (dq, 1H, \(J = 7\) Hz, 14 Hz), 2.501 (dq, 1H, \(J = 7\) Hz, 14 Hz), 1.08 (t, 3H, \(J = 7\) Hz), and 0.73 (d, 3H, \(J = 7\) Hz); \(^1\)C NMR (CDCl\(_3\), 125 MHz): 184.40, 159.06, 155.90, 139.92, 128.49, 128.18, 113.70, 83.04, 81.34, 73.58, 69.37, 55.41, 42.66, 35.55, 26.68, 25.81, 25.44, 21.37, 19.49, 14.07, and 10.47; ESI-MS \(m/Z\) calculated for \(C_{20}H_{24}O_3\) (M+Na): 355.17, found: 335.14.

(1S,2R)-1-(benzo[d][1,3]dioxol-5-yl)-1-(benzylxy)-2-methylpentan-3-one (1.120). This compound was isolated in 94% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\)
7.29-7.24 (m, 3H), 7.17 (d, 2H, J = 7 Hz), 6.87 (s, 1H), 6.80-6.76 (m, 2H), 5.98 (s, 1H), 4.34 (d, 1H, J = 10 Hz), 4.30 (d, 1H, J = 11.5 Hz), 4.16 (d, 1H, J = 11.5 Hz), 2.91 (dq, 1H, J = 7 Hz, 10 Hz), 2.63 (dq, 1H, J = 7 Hz, 14.5 Hz), 2.51 (dq, 1H, J = 7 Hz, 14.5 Hz), 1.07 (t, 3H, J = 7 Hz), and 0.75 (d, 3H, J = 7 Hz); ^13C NMR (CDCl₃, 125 MHz): 214.57, 148.28, 147.68, 128.41, 127.65, 121.83, 108.14, 107.39, 101.30, 1.22, 84.55, 70.66, 52.40, 37.16, 14.03, 7.72; ESI-MS m/z calculated for C₂₀H₂₂O₄ (M+Na)^+: 349.15, found: 349.07.

(1S,2R)-1-(benzylxoy)-2-methyl-1-(4-(trifluoromethyl)phenyl)pentan-3-one (1.122). This compound was isolated in 91% yield as a viscous oil. ^1H NMR (CDCl₃, 500 MHz): δ 7.65 (d, 2H, J = 8 Hz), 7.48 (d, 2H, J = 8 Hz), 7.30-7.24 (m, 3H), 7.16 (d, 2H, J = 8 Hz), 4.52 (d, 1H, J = 10 Hz), 4.28 (d, 1H, J = 11.5 Hz), 4.20 (d, 1H, J = 11.5 Hz), 2.91 (dq, 1H, J = 7 Hz, 10 Hz), 2.65 (dq, 1H, J = 7 Hz, 14.5 Hz), 2.54 (dq, 1H, J = 7 Hz, 14.5 Hz), 1.09 (t, 3H, J = 7 Hz), and 0.75 (d, 3H, J = 7 Hz); ^13C NMR (CDCl₃, 125 MHz): 213.91, 144.11, 144.09, 137.85, 128.77, 127.89, 125.74, 123.19, 84.05, 70.29, 52.20, 37.16, 13.87, 7.70; ESI-MS m/z calculated for C₂₀H₂₁F₃O₂ (M+Na)^+: 373.15, found: 373.17.

(4R,5R,E)-5-(benzyloxy)-4-methyl-7-phenylhept-6-en-3-one (1.126). This compound was isolated in 92% yield as colorless oil that solidified upon standing. ^1H NMR (CDCl₃,
500 MHz): δ 7.41 (d, 2H, J = 7 Hz), 7.36-7.22 (m, 8H), 6.60 (d, 1H, J = 15.5 Hz), 6.04 (dd, 1H, J = 16, 8.5 Hz), 4.54 (d, 1H, J = 11.5 Hz), 4.32 (d, 1H, J = 11.5 Hz), 4.08 (app. t, 1H, J = 9 Hz), 2.90-2.83 (dq, 1H, J = 7 Hz, 9 Hz), 2.64-2.56 (dq, 1H, J = 7.5 Hz, 14.5 Hz), 2.54-2.46 (dq, 1H, J = 7 Hz, 14.5 Hz), 1.06 (t, 3H, J = 7 Hz), 0.98 (d, 3H, J = 7 Hz); 13C NMR (CDCl₃, 125 MHz): 214.27, 138.41, 136.37, 134.84, 134.83, 128.86, 127.89, 127.88, 127.69, 126.80, 83.71, 70.84, 50.47, 37.16, 13.87, 7.70; ESI-MS m/Z calculated for C₂₁H₂₄O₂ (M+Na)+: 331.18, found: 331.11.

(1S,2R)-1-(benzyloxy)-1-(4-chlorophenyl)-2-methylpentan-3-one (1.128). This compound was isolated in 92% yield as thick film. ¹H NMR (CDCl₃, 500 MHz): δ 7.35 (d, 2H, J = 8.5 Hz), 7.31-7.25 (m, 5H), 7.15 (d, 2H, J = 8 Hz), 4.42 (d, 1H, J = 10Hz), 4.27 (d, 1H, J = 11.5 Hz), 4.16 (d, 1H, J = 11.5 Hz), 2.91 (dq, 1H, J = 7 Hz, 10 Hz), 2.63 (dq, 1H, J = 7 Hz, 14.5 Hz), 2.52 (dq, 1H, J = 7 Hz, 14.5 Hz), 1.08 (t, 3H, J = 7 Hz), and 0.74 (d, 3H, J = 7 Hz); ¹³C NMR (CDCl₃, 125 MHz): 214.18, 138.41, 138.03, 134.10, 129.19, 128.93, 127.86, 127.79, 83.99, 71.00, 52.26, 37.21, 13.91, 7.70; ESI-MS m/Z calculated for C₁₀H₁₉ClO₂ (M+Na)+: 339.12, found: 339.06.
(1S,2R)-1-(benzyloxy)-1-(4-bromophenyl)-2-methylpentan-3-one (1.130). This compound was isolated in 93% yield as a viscous oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.51 (d, 2H, $J = 8.5$ Hz), 7.31-7.22 (m, 5H) 7.25 (app. d, 2H, $J = 7$ Hz), 4.40 (d, 1H, $J = 10$ Hz), 4.27 (d, 1H, $J = 11.5$ Hz), 4.17 (d, 1H, $J = 11.5$ Hz), 2.91 (dq, 1H, $J = 7$ Hz, 10 Hz), 2.64 (dq, 1H, $J = 7$ Hz, 14.5 Hz), 2.52 (dq, 1H, $J = 7$ Hz, 14.5 Hz), 1.08 (t, 3H, $J = 5$ Hz), and 0.74 (d, 3H, $J = 5$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): 214.11, 138.89, 137.96, 127.71, 122.21, 84.00, 70.98, 52.19, 37.16, 13.86, and 7.65; ESI-MS m/Z calculated for C$_{19}$H$_{21}$BrO$_2$ (M+Na)$^+$: 383.07, found: 383.04.

(1S,2R)-1-(benzyloxy)-2-methyl-1-(o-tolyl)pentan-3-one (1.132). This compound was isolated in 95% yield as clear film. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.42 (d, 1H, $J = 7$ Hz), 7.30-7.14 (m, 8H), 4.79 (d, 1H, $J = 10$ Hz), 4.26 (d, 1H, $J = 11.5$ Hz), 4.14 (d, 1H, $J = 11.5$ Hz), 3.05 (dq, 1H, $J = 7$ Hz, 10 Hz), 2.68 (dq, 1H, $J = 7$ Hz, 14.5 Hz), 2.54 (dq, 1H, $J = 7$ Hz, 14.5 Hz), 2.35 (s, 3H), 1.09 (t, 3H, $J = 7$ Hz), 0.76 (d, 3H, $J = 7$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): 214.71, 138.46, 137.07, 128.38, 127.80, 127.62, 127.51, 126.60, 70.56, 37.33, 19.82, 13.47, 7.75; ESI-MS m/Z calculated for C$_{20}$H$_{24}$O$_2$ (M+H)$^+$: 296.18, found: 296.16.
(1S,2R)-1-(benzyloxy)-2-methyl-1-(naphthalen-2-yl)pentan-3-one (1.134). This compound was isolated in 93% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.90-7.85 (m, 3H), 7.77 (s, 1H), 7.54-7.30 (m, 3H), 7.27-7.23 (m, 3H), 7.17 (d, 2H, \(J = 7.5\) Hz), 4.60 (d, 1H, \(J = 10\) Hz), 4.31 (d, 1H, \(J = 11.5\) Hz), 4.21 (d, 1H, \(J = 11.5\) Hz), 3.09 (dq, 1H, \(J = 7\) Hz, 10 Hz), 2.70 (dq, 1H, \(J = 7\) Hz, 14 Hz), 2.58 (dq, 1H, \(J = 7\) Hz, 14 Hz), 1.11 (t, 3H, \(J = 7\) Hz), 0.77 (d, 3H, \(J = 7\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 214.52, 128.77, 128.44, 128.36, 128.05, 127.86, 127.80, 127.77, 127.60, 127.50, 126.41, 126.28, 124.84, 124.80, 84.93, 70.88, 52.10, 37.17, 14.03, and 7.71; ESI-MS \(m/Z\) calculated for C\(_{23}\)H\(_{24}\)O\(_2\) (M+Na): 355.18, found: 355.16.

(1S,2R)-1-(benzyloxy)-2-methyl-1-(4-nitrophenyl)pentan-3-one (1.136). This compound was isolated in 92% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.27 (d, 2H, \(J = 8.5\) Hz), 7.55 (d, 2H, \(J = 8.5\) Hz), 7.32-7.28 (m, 3H), 7.16 (m, 2H), 4.60 (d, 1H, \(J = 9.5\) Hz), 4.29 (d, 1H, \(J = 11.5\) Hz), 4.24 (d, 1H, \(J = 11.5\) Hz), 2.93 (dq, 1H, \(J = 7\) Hz, 9.5 Hz), 2.69-2.54 (m, 2H), 1.10 (t, 3H, \(J = 7\) Hz), and 0.77 (d, 3H, \(J = 7\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 213.45, 147.62, 137.52, 128.66, 128.55, 128.05, 127.94, 123.98, 83.62, 71.65, 37.30, 13.82, and 7.70; ESI-MS \(m/Z\) calculated for C\(_{19}\)H\(_{21}\)NO\(_4\) (M+Na): 350.15, found: 350.12.
(R)-3-((S)-(benzyloxy)(phenyl)methyl)pentan-2-one (1.138). This compound was isolated in 90% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.38-7.25 (m, 8H), 7.18 (app. d, 2H, \(J = 8\) Hz), 4.39 (d, 1H, \(J = 10\) Hz), 4.30 (d, 1H, \(J = 15\) Hz), 4.15 (d, 1H, \(J = 15\) Hz), 2.85 (dt, 1H, \(J = 3.5\) Hz, 15 Hz), 2.24 (s, 3H), 1.43 (m, 1H), 1.01 (m, 1H), and 0.70 (t, 3H, \(J = 7.5\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 212.41, 139.81, 138.20, 128.75, 128.84, 128.43, 127.92, 127.71, 84.11, 76.97, 70.64, 61.05, 32.23, 22.23, and 11.84; ESI-MS \(m/Z\) calculated for C\(_{19}\)H\(_{22}\)O\(_2\) (M+Na): 305.14, found: 305.14.

![Chemical structure](attachment:structure1.png)

(R)-3-((S)-(benzyloxy)(phenyl)methyl)hex-5-en-2-one (1.140). This compound was isolated in 93% yield as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.41-23 (m, 8H), 7.18 (app. d, 2H, \(J = 8.5\) Hz), 5.57-5.47 (m, 1H), 4.91-4.87 (m, 2H), 4.43 (d, 1H, \(J = 14.5\) Hz), 4.31 (d, 1H, \(J = 14.5\) Hz), 4.15 (d, 1H, \(J = 11.5\) Hz), 3.03 (dt, 1H, \(J = 5\)Hz, 13.5 Hz), 2.21 (s, 3H), 2.18-2.08 (m, 1H), and 1.77-1.71 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 212.75, 139.41, 138.10, 134.77, 127.73, 117.22, 83.75, 70.71, 58.95, 33.50, and 32.64; ESI-MS \(m/Z\) calculated for C\(_{20}\)H\(_{22}\)O\(_2\) (M+H): 294.16, found: 294.14.

![Chemical structure](attachment:structure2.png)

(R)-3-((S)-(benzyloxy)(phenyl)methyl)-6-methylhept-5-en-2-one (1.142). This compound was isolated in 92% yield as a very viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\)
7.37-7.24 (m, 8H), 7.18 (app. d, 2H, J = 10 Hz), 4.86 (app. t, 1H, J = 12.5 Hz), 4.43 (d, 1H, J = 14 Hz), 4.29 (d, 1H, J = 14 Hz), 4.16 (d, 1H, J = 12 Hz), 2.96 (dt, 1H, J = 5 Hz, 13.5 Hz) 2.20 (s, 3H), 1.69-1.58 (m. containing singlet methyl (1.58), 4H), and 1.39 (s, 3H). $^1$C NMR (CDCl$_3$, 125 MHz): 212.20, 128.76, 128.51, 128.43, 127.94, 127.90, 127.70, 127.54, 127.49, 127.35, 127.76, 120.42, 83.70, 70.29, 59.31, 32.63, 27.94, 25.84, and 17.72; ESI-MS m/z calculated for C$_{22}$H$_{26}$O$_2$ (M+H)$^+$: 322.19, found: 322.18.

(R)-4-((S)-(benzyloxy)(phenyl)methyl)-9-methyldeca-1,8-dien-5-one (1.143). n-Butyllithium (2.5 M in hexanes, (53 µL, 0.1325 mmol, 1.20 eq.) was added dropwise to a stirred and cooled (-78 °C) solution of diisopropylamine (19 µL, 0.1325 mmol, 1.20 eq.) in THF (0.25 mL). After being stirred for 20 min, 1.140 (33 mg, 0.1040 mmol, 1.00 eq) dissolved in 1.0 mL of THF was added directly into the solution of LDA. A bright yellow solution developed that was stirred for 30 min at -78 °C. Then, hexamethylphosphoramide (42 µL, 0.2429 mmol, 2.2 eq.) was added. The solution was stirred an additional 15 minutes at -78 degrees. This was followed by the addition of prenyl bromide (16 µL, 0.1325 mmol, 1.25 eq.), and the reaction mixture was warmed to 0 °C over a period of six hours. It was then quenched with deionized water (2 mL) under vigorous stirring. The mixture was partitioned between Et$_2$O (10 mL) and brine (10 mL), and the layers were separated. The aqueous phase was extracted with Et$_2$O (2 x 10 mL),
and the combined organic extracts were washed once with deionized water (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the resulting crude oil was achieved using flash chromatography over silica gel (2.5% EtOAc/97.5% Hexanes) to give the prenylated ketone in 95% yield as a clear film. 

**H NMR** (CDCl$_3$, 500 MHz): δ 7.4-7.24 (m, 8H), 7.16 (d, 2H, $J = 10$ Hz), 5.54-5.46 (m, 1H), 5.07 (app. t, 1H, $J = 5$ Hz), 4.43 (d, 1H, $J = 10$ Hz), 4.27 (d, 1H, $J = 11.5$ Hz), 4.15, (d, 1H, $J = 11.5$ Hz), 2.99 (dt, 1H, $J = 4$ Hz, 10.5 Hz), 2.68-2.63 (m, 2H), 2.43-2.39 (m, 1H), 2.1-2.16 (m, 1H), 2.15-2.12 (m, 1H), 1.69-1.65 (m, containing methyl singlet (1.65), 4H), and 1.59 (s, 3H); 

**C NMR** (CDCl$_3$, 125 MHz): 212.93, 139.65, 138.26, 134.95, 132.40, 128.42, 123.46, 117.20, 84.60, 58.30, 46.20, 33.71, 25.87, 21.91, and 17.83; 

**ESI-MS** $m$/Z calculated for C$_{25}$H$_{30}$O$_2$ (M+H)$^+$: 360.22, found: 360.21.
2. Asymmetric Total Synthesis of (+)- and (-)-Mefloquine Hydrochloride from N-Amino Cyclic Carbamate (ACC) Hydrazones

This chapter discusses work that was partially done in collaboration with Scott J. Sauer, who, in addition to assisting with reagent preparation and investigating some of the epoxide opening reactions, was responsible for the synthesis of (-)-mefloquine hydrochloride once the route to (+)-mefloquine hydrochloride had been established.

2.1 Malaria & Mefloquine Hydrochloride

2.1.1 Malaria

Malaria is undoubtedly the greatest cause of mortality of any parasitic disease in humans [46]. Each year brings over 500 million new reported cases of the disease, and this number is most likely conservative due to the poor health infrastructure of areas where malaria is prevalent. Historically, the disease was endemic to large parts of the continental United States. Virtually all cases of the disease reported in the United States today, however, are imported from other areas of the globe as a result of modern medicinal practices [46]. Many American physicians are unable to initially diagnose the disease due to the low number of cases seen.

Malarial parasites are members of the genus Plasmodium, which are capable of infecting humans, birds, reptiles, and several species of mammals [47, 48]. In humans,
the disease itself is caused by *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium knowlesi.* *Plasmodium vivax* is responsible for the greatest number of infections worldwide, but *Plasmodium falciparum* is responsible for the vast majority of deaths, up to 1.5 to 2.7 million a year, due to its more severe symptoms [46]. High-risk individuals, especially African children less than five years of age, pregnant women, and immunosuppressed adults traveling to endemic areas, have highest mortality from the disease. Sadly, many deaths occur despite the availability of treatments for the disease.

The primary means by which the malarial parasite infects humans is through the common mosquito. When a female mosquito bites her human prey, the parasite is introduced into the bloodstream in its sporozoite form [49, 50] These sporozoites initially travel to and infect liver cells before maturing into schizonts. There is a dormant phase between initial infection of liver cells and subsequent rupture back into the bloodstream that can last a matter of hours or several years. Rupturing of the schizonts releases the parasite in its merozoite form, which then proceeds to infect red blood cells. This infection is rapid, occurring in a matter of seconds, and the host’s immune system is unable to effectively respond. Once inside a red blood cell, where it is completely protected from the immune system, the parasite develops through the ring, trophozoite, and schizont stages to produce daughter merozoites. These new merozoites violently burst from the infected red blood cell leading to a febrile episode in the host as a result
of toxic heme release into the bloodstream. The cycle begins repeating within a matter of minutes. This causes the host to experience symptoms of the disease in a periodic fashion, which can eventually wear down the host without treatment. *Plasmodium falciparum* is particularly deadly to its host because the length of time between initial infection and rupturing of blood cells is shorter (three days) compared to other species of the parasite (four days or longer). Eventually, regardless of the *plasmodium* species involved, some of the intra-erythrocytic parasites differentiate into sexual gametocytes that can be ingested by a different mosquito when it bites an infected individual. These gametocytes mate in the gut of the mosquito, and the life cycle of the parasite begins anew.

Most symptoms of malaria occur from the intra-erythrocytic stages of the parasites’ life cycle. Infected red blood cells tend to adhere to the vascular endothelium of post-venular capillaries, particularly in locations such as the brain. This can lead to cerebral malaria, which commonly results in coma and death. Severe cases of the disease also include Blackwater Fever, where the rapid bursting of red blood cells leads to a buildup of toxic levels of hemoglobin within the bloodstream. The intra-erythrocytic stages of the parasites’ life cycle are also the stages most susceptible to targeting by anti-malarial drugs.
2.1.2 Treatment of Malaria

One of the most important ways to control the spread of malaria is the use of anti-malarial drugs (Figure 15) through prophylaxis and treatment of established infections [51]. Travelers to endemic areas of the world are routinely prescribed various drugs to prevent infection. Efforts to develop a vaccine to the parasites, however, have not met with success, and the widespread use of anti-malarial drugs in areas with less than desirable health practices has led to increasing resistance. Currently, the United States Food and Drug Administration has approved the use of chloroquine, sulfadoxine-pyrimethamine, mefloquine, quinidine, primaquine, atovaquone-proguanil, hydroxychloroquine, and doxycycline for the treatment of malaria. Other agents in use worldwide include quinine, amodiaquine, artemisinin-lumefantrine, and other artemisinin derivatives. The most recent anti-malarial drug approved by the FDA was atovaquone-proguanil in 2000, which was approximately 30 years after the last FDA-approved anti-malaria drug. More recent artemisinin-derived drugs have been put into general use worldwide over the last four to six years, but these drugs have not been approved for use in the United States. Resistance to these newer drugs has also begun to be reported [52]. Additionally, the mechanism of action for some antimalarial drugs is unknown. It is thus clear that more effective anti-malarial drugs and a better understanding of how these drugs work are needed.
Figure 16. Various anti-malarial drugs routinely used today.
2.1.3 Mefloquine

Mefloquine (Figure 2) is a highly effective anti-malarial drug that has been used both for treatment of established infections and prophylaxis. The drug is manufactured commercially as a racemic mixture of the (+)-enantiomer 2.1 and the (-)-enantiomer 2.2 with the initial manufacturer being Roche Pharmaceuticals. It consists of two enantiomers that may not have equal activity against malarial parasites. Although the exact mechanism of action against the malarial parasites is unknown, it has been suggested that the drug disrupts the ability of the parasite to process and remove toxic heme compounds effectively poisoning the parasite [53]. The drug becomes distributed across many different types of tissue within the human body, but evidence suggests that the (-)-enantiomer 2.2 has a shorter half-life in vivo due to higher blood plasma concentrations [54].

Figure 17. The two enantiomers of mefloquine and their similarities to the cinchona alkaloids quinidine and quinine
Structurally, mefloquine is a simpler analogue of quinine and quinidine (Figure 16). It consists of the same anti 1,2-amino alcohol core found in the cinchona alkaloids, yet mefloquine differs by possessing a rather electron deficient quinolone ring system as opposed to the methoxy substituted quinolone system of quinidine and quinine. The bicyclic quinuclidine ring of the latter compounds is instead replaced by a piperidine ring system, and there is no vinyl group present in mefloquine. The ability of the amino alcohol functionality to hydrogen bond is critical to the biological activity of mefloquine as acylation or etherification of the alcohol destroys the anti-malarial activity of the drug [55]. Also, substitution of the saturated piperidine system with an unsaturated pyridine system also results in a complete loss of activity [55]. The absolute stereochemistry of 2.2 has been established through x-ray crystallography to be similar to quinine, and thus 2.2 has the same configuration of quinidine [56]. It has been well established that quinidine is up to 2-3 times more active against *P. falciparum* than quinine [57]. Likewise, initial studies have shown that 2.1 is up to 1.5-1.8 times more active against *P. falciparum* than 2.2 [56].

While highly effective against malarial parasites, mefloquine causes serious side effects that have limited its use and given the drug a negative reputation [51, 53]. These side effects include nausea, diarrhea, dizziness, weakness, pruritus, mouth ulcers, severe depression, anxiety, paranoia, aggression, nightmares, insomnia, and other central nervous system complications [58-60]. Suicidal thoughts have also been associated with
the long-term use of the drug. The milder central nervous problems have been reported to occur in up to a quarter of all patients taking the drug. The more severe events occur in 1/6,000 to 1/13,000 patients [54]. These issues have led to the decreased use of mefloquine as a prophylactic, particularly in the military where incidents of soldiers suffering severe side effects after deploying to malaria endemic areas have occurred.

To date, there is no definitive biochemical basis for the neurotoxicity of the drug. Research has suggested that mefloquine may interfere with calcium homeostasis in the endoplasmic reticulum within neuron cells [61]. This type of disruption is known to lead to problems in protein synthesis and folding in eukaryotic cells [61]. Additional research has suggested a link between the more severe psychotropic side effects and the (-)-enantiomer 2.2, which may specifically bind to adenosine receptors in neuronal cells [62].

As previously mentioned, these side effects, along with the ever present threat of drug resistance, have led to the overall elimination of this otherwise potent drug. In order to use this drug safely, the origin of toxicity and how it can be avoided must be determined. The ability to produce this drug in significant quantities as single enantiomers would be required in order to carry out cell-based, animal, and clinical studies. This goal is most reasonably achieved via asymmetric total synthesis. An effective total synthesis would allow one to prepare sufficient quantities of the enantiomers 2.1 and 2.2 to enable a definitive description of the biological activity of
each enantiomer and to set the stage for its reformulation as a safer, more efficacious single enantiomer entity. Such a synthesis would also presumably lead to the ability to readily derivatize the drug to improve activity and combat any potential resistance.

2.1.4 Prior Syntheses of Mefloquine Hydrochloride

Mefloquine hydrochloride was first prepared in a racemic fashion by investigators at the Walter Reed Army Institute of Research as part of an effort to synthesize analogues of quinine. The first published account of its synthesis by Ohnmacht, *et al.* appeared in 1971, and it started from commercially available 2.3 and 2.4 [63]. Quinolinol 2.5 is prepared via a Conrad-Limpach condensation and subsequently converted to the 4-bromoquinoline 2.6 via nucleophilic aromatic substitution. Lithium-halogen exchange with *n*-butyllithium gives the corresponding 4-lithioquinoline, which is reacted immediately with nicotinaldehyde (2.7). The key step of the synthesis involves a diastereoselective hydrogenation of the racemic alcohol (2.8). Presumably, a special coordination event between the hydroxyl group of 2.8 and the surface of the activated platinum catalyst occurs, and this allows for the hydrogenation of the protonated pyridine system from the same face as the alcohol. Thus, only *anti* (*erythro*) isomers (2.1 and 2.2) are obtained and not the *syn* (*threo*) isomers [63]. Optimization of this route led to a patented production method by Hoffman-La Roche in 1978 that produced racemic mefloquine hydrochloride (2.1 and 2.2) in kilogram quantities (Scheme 29). The overall
yield of this synthesis is rather good, but the product drug is, as previously mentioned, produced as a racemate.

Scheme 25. Ohnmacht’s racemic mefloquine synthesis

Alternative syntheses that also resulted in racemic mefloquine hydrochloride were developed over the next 20 years. One such synthesis involves the use a fluoride-mediated Wittig rearrangement to give racemic alcohol 2.8 and avoid the use of the 4-bromoquinoline 2.6 from the original synthesis (Scheme 25) [64]. 4-quinolinol 2.5 is alkylated using the hydrochloride salt of 2-(chloromethyl)pyridine (2.10) to give ether 2.11. Subsequent metalation of this ether and C-silylation gave ether 2.12. Treatment with tetrabutylammonium fluoride liberates a carbanion that undergoes a [1,2]-Wittig rearrangement to the desired racemic alcohol (2.8), which can then be put through the same diastereoselective hydrogenation of the original synthesis. This method, however, involved an additional step relative to the original synthesis by Ohnmacht, et al., and alcohol 2.8 was prepared in an equal amount to a ketone byproduct (2.13). Although
separable, this leads to an almost 50% loss of desired product, and thus the overall synthesis is considerably less attractive.

Scheme 26. Mefloquine Synthesis Featuring a [1,2]-Wittig Rearrangement

Another racemic synthesis by Kumar, et al. utilized a special sulfoxide-Grignard route (Scheme 27) [65]. 4-Bromoquinoline 2.6 was converted to thioether 2.15 via nucleophilic aromatic substitution with the thiolate of 2.14. Oxidation of 2.15 to the sulfoxide 2.16 with m-chloroperoxybenzoic acid (m-CPBA) was followed by treatment with phenylmagnesium bromide. This liberated a 4-magnesioquinoline intermediate that subsequently reacted with nicotinaldehyde 2.7 to give racemic alcohol 2.8. This synthesis has the advantage of forgoing the use of n-butyllithium, which can be problematic to work with on industrial scale reactions. As in the previous syntheses, however, the product alcohol 2.8 must be diastereoselectively hydrogenated to give racemic mefloquine hydrochloride.
Work in the late 1990’s led to a synthesis patented by Fletcher, et al. where the two *erythro* isomers of mefloquine were separated by a chiral resolution method developed by Carroll and Blackwell [62]. While this process allowed access to all the stereoisomers of mefloquine in both its *erythro* and *threo* forms, multiple manipulations of the initially racemic material were required, and only a small amount of the enantiopure material could be obtained.

The first method to gain access enantiopure mefloquine hydrochloride without chiral resolution involved the use of enantioselective hydrogenation of ketone 2.13 [66]. Schmid, et al. began with the synthesis established by Adam (Scheme 28) to obtain ketone 2.13, and this ketone was hydrogenated in the presence of a chiral rhodium/(bis)-phosphine complex to give 2.1 and 2.2. The (*R*)-catalyst complex gave 2.1 in 92% ee (Scheme 28), and the (*S*)-catalyst complex formed 2.2 in equally high selectivity. Optical
purity was achieved by recrystallization of the material. The synthesis was then completed using the same diastereoselective hydrogenation reaction as found in the original racemic mefloquine synthesis (Scheme 4). While this method was highly enantioselective, the use of multiple recrystallizations to reach optical purity and an expensive asymmetric rhodium-ligand complex that requires multiple steps to prepare makes the process less attractive.

![Scheme 28. Enantioselective Hydrogenation Synthesis](image)

A more recent example of an asymmetric synthesis of (+)-mefloquine 2.1 utilizes an organocatalytic aldol reaction as the key asymmetric step (Scheme 29) [67]. The reaction of 4-formylquinoline 2.18 and cyclopentanone with L-proline as a catalyst gave aldol products 2.20 (syn) and 2.19 (anti) in a 6.8:1 ratio, respectively. The desired syn product (2.20), which was obtained in 71% ee, was used in subsequent steps of synthesis. Formation of oxime 2.21 gave a substrate that could be used in a Beckmann rearrangement to give lactam 2.22. Interestingly, deoxygenation of this lactam utilizing
borane-dimethyl sulfide complex gave (+)-mefloquine 2.1 in 95% ee. As no other asymmetric steps were employed in the synthesis after the organocatalytic aldol, the authors posited that the use of borane leads to a form of kinetic resolution through an amino alcohol-borane intermediate. Overall, this synthesis has the advantage of not using transition metal-based catalysis and instead using an inexpensive, non-toxic amino acid. The organocatalytic aldol reaction, however, only has modest selectivity, especially when compared to other simple organocatalytic aldol reactions (see 1.2.4 of this document). Additionally, a small portion (at least 15%) of the aldol product consists of the undesired anti diastereomer 2.19. If one were to try to use this synthesis to produce (-)-mefloquine 2.2, the use of the far more expensive and less readily available D-proline amino acid would be required.
Scheme 29. Xie’s organocatalytic aldol synthesis of (+)-mefloquine hydrochloride.

2.1.5 Single Enantiomer Drugs

Pharmaceutical research has become increasingly focused on the formulation of enantiomerically pure drugs due its potential to expedite the FDA approval process, extend any current drug patents, and provide an easier entry to the generic drug market. Chiral drugs have most commonly been marketed in racemic form, and historically there have been notable cases where no knowledge was available concerning the activity of the specific enantiomers within a racemate. The FDA has responded to increasing concerns over the potentially unknown or even harmful side effects of racemic drug formulations by issuing new guidelines that require a report justifying the submission of a racemate as well as its safety, quality, efficacy, and risk-benefit ratio. Without sufficient
justification, it is expected that a drug would have to be submitted for approval as a single enantiomer. Additionally, the FDA has allowed single enantiomer drugs to be marketed under different brand names than the racemate, and the United States Patent Office has granted patents in specific cases for a single enantiomer of drugs that were previously available as racemates.

In simple terms, different enantiomers of a single drug may bind or interact differently with target receptors/enzymes in vivo. In notable cases, one enantiomer may have a desired beneficial effect while the other enantiomer may not be as beneficial or may even be harmful. Some cases have even seen both enantiomers give beneficial yet completely different effects.

![Figure 18. Drugs whose separate enantiomers have different biological activities.](image)

A classic example of a drug whose individual enantiomers have distinct biological effects is thalidomide [68]. The (R)-enantiomer 2.23 is effective in treating morning sickness while the (S)-enantiomer 2.26 is known to inhibit the protein cereblon, which leads to teratogenic birth defects in limb development [69]. These two
enantiomers rapidly interconvert in vivo, however, and so isolating the beneficial enantiomer is not practical. Another example includes the analgesic naproxen (Aleve®). The (S)-enantiomer of the drug (2.24) is responsible for its analgesic properties, yet the (R)-enantiomer 2.27 has been reported to be more toxic to the liver [70]. One final example involves cetirizine. In its racemic form (Zyrtec®), cetirizine (2.25 and 2.28) is used as an antihistamine. Research on behalf of the manufacturer, however, has shown that the (R)-enantiomer (levocetirizine, 2.25) is more active as an antihistamine, and it has been approved and marketed as a single enantiomer drug under the name Xyzal® in the United States [71, 72].

2.2 Asymmetric Darzens Reaction of α-Chloro Ketones

2.2.1 The Darzens Reaction

The Darzens reaction, also sometimes called the Darzens condensation, involves the formation of an α,β-epoxy carbonyl compound from an α-halo carbonyl compound (e.g., α-chloroacetophenone) and an aldehyde or ketone. First observed by E. Erlenmeyer in the condensation of benzaldehyde with ethyl chloroacetate in the presence of sodium metal [73], the reaction was later generalized and developed by Auguste George Darzens in the early 1900’s [74, 75]. Originally, the reaction applied explicitly to the use of α-halo esters with aldehydes, but it has since been extended to the use of other reactants, such as α-halo ketones, sulfones, nitriles, ketimines, thioesters, and amides,
with addition to aldehydes and ketones. It has provided a useful alternative to the epoxidation of $\alpha,\beta$-unsaturated carbonyls with peroxides and base.

![Scheme 30. Original condensation reaction as reported by E. Erlenmeyer.](image)

The Darzens reaction is at heart an aldol reaction followed by ring-closure to form an epoxide. The stereochemistry of the final epoxide product is therefore determined by the stereochemical outcome of first the aldol reaction and the steric requirements of the ring-closure step. The first general step of the reaction involves the deprotonation by base of the $\alpha$-halocarbonyl compound to give the corresponding enolate. This enolate then attacks the carbonyl of the reacting aldehyde or ketone to give an $\alpha$-halo-$\beta$-alkoxy intermediate. A subsequent intramolecular $S_N^2$ reaction to form an epoxide completes the reaction. In general, the trans epoxy carbonyl product is favored over the cis epoxy carbonyl product, but this outcome is heavily dependent on the type of base, solvent, and substitution of the reactants. All of the stereochemical considerations that are required for the aldol reaction such as enolate geometry must also be taken into account.
The Darzens reaction has found significant use in organic synthesis for its ability to form C–C bonds and the reactive possibilities of the epoxide moiety. As in the case of the aldol reaction, there have been many reported modifications of the Darzens reaction in order to control not only the relative configuration of the epoxide formed but also the absolute configuration. A thorough review of asymmetric Darzens chemistry is beyond the scope of this document. Therefore, further discussion of the Darzens reaction in this document will focus solely on the reaction of α-halo ketones with aldehydes, which is the specific variation of the Darzens reaction found in the asymmetric synthesis of (+)- and (-)-mefloquine hydrochloride.

**Figure 19. Generalized possible outcomes of the Darzens reaction.**
2.2.2 Asymmetric Darzens Reactions of α-Halo Ketones with Aldehydes

Asymmetric variations of the Darzens reaction of α-halo ketones and aldehydes have received considerable attention due to the utility of the α,β-epoxy ketone products produced. These α,β-epoxy ketones can undergo subsequent reactions, including Wittig olefination, epoxide ring-opening reactions, carbonyl reductions, and organometallic addition reactions, at either epoxy carbon and also at the ketone carbonyl itself [76]. The ability to prepare a single diastereomer of an α,β-epoxy ketone would be particularly useful in total syntheses.

Figure 20. General reactivity of α,β-epoxy ketones.

These asymmetric reactions typically fall into three particular categories: chiral phase transfer catalysis, ketone auxiliary-based reactions, and aldehyde auxiliary-based reactions. Phase-transfer catalytic Darzens reactions have seen more interest within the
last two decades while there is one report of a Darzens reaction with a chiral auxiliary based on the aldehyde.

One notable example of an asymmetric Darzens reaction mediated by a phase transfer catalyst was reported by Liu [77]. Chiral phase-transfer catalysts were developed from quinine and found to facilitate the Darzens reaction of a substituted α-chloroacetophenone derivative (2.29) and aromatic aldehydes in high yield and high enantioselectivity to give products in the general form of 2.30 (Table 9). The use of a trifluorobenzyl group and a free phenolic group in the catalyst (2.31) proved essential as the overall selectivity was reduced considerably otherwise. In each case, only the trans epoxy ketone diastereomer was isolated. The use of aliphatic aldehydes (e.g., n-butyraldehyde) was less promising as the enantioselectivity was generally lower. It should be noted that attempts to use this catalyst with an aliphatic α-chloroketone, such as chloroacetone, were unsuccessful. The authors postulated chloroacetone was not acidic enough under the reaction conditions used.
Table 9. Phase transfer Darzens reaction using a quinine-derived catalyst.

\[
\begin{align*}
\begin{array}{c|c|c|c}
\text{Ar} & \text{R} & \text{yield} & \text{ee (\%)}^* \\
\hline
\text{Ph} & \text{Ph} & 94 & 96 \\
\text{Ph} & 4-\text{ClC}_6\text{H}_4 & 96 & 96 \\
\text{Ph} & 3-\text{ClC}_6\text{H}_4 & 92 & 90 \\
\text{Ph} & 4-\text{BrC}_6\text{H}_4 & 90 & 95 \\
\text{Ph} & 4-\text{MeC}_6\text{H}_4 & 95 & 91 \\
\text{Ph} & 1-\text{naphthyl} & 96 & 91 \\
\text{Ph} & 2-\text{naphthyl} & 93 & 98 \\
\text{Ph} & n-\text{Pr} & 93 & 81 \\
4-\text{FC}_6\text{H}_4 & 2-\text{naphthyl} & 92 & 97 \\
4-\text{ClC}_6\text{H}_4 & 2-\text{naphthyl} & 96 & 99 \\
\end{array}
\end{align*}
\]

* ee was determined by chiral HPLC

An example of a phase-transfer catalytic Darzens reaction was reported by Bako (Table 10) [78]. Utilizing a chiral crown ether (2.34) derived from an α-D-glucopyranoside, Darzens reactions of 2-chloroacetothiophene 2.32 with aromatic aldehydes proceeded in moderate yields and enantioselectivity to give trans epoxy ketones 2.33. Other heteroaromatic α-chloro ketones gave similar results. As in the previous example, only the trans diastereomer of the epoxy ketone was formed.

Table 10. Darzens reaction catalyzed by a chiral crown ether.

\[
\begin{align*}
\begin{array}{c|c|c|c|c}
\text{Ar} & \text{time} & \text{yield} & \text{ee (\%)}^* \\
\hline
\text{Ph} & 5 & 63\% & 71 (84) \\
2-\text{ClC}_6\text{H}_4 & 4.5 & 53 & 51 \\
3-\text{ClC}_6\text{H}_4 & 6 & 56 & 60 (75) \\
4-\text{ClC}_6\text{H}_4 & 20 & 54 & 65 (79) \\
4-\text{FC}_6\text{H}_4 & 22 & 55 & 62 (73) \\
2-\text{MeC}_6\text{H}_5 & 3 & 79 & 68 (85) \\
1-\text{naphthyl} & 5 & 87 & 64 (75) \\
2-\text{naphthyl} & 6 & 54 & 86 (100) \\
piperonyl & 5 & 57 & 86 (100) \\
\end{array}
\end{align*}
\]

* % in parentheses indicates post-recrystallization purity
There exists one noteworthy example (Table 11) of an asymmetric Darzens reaction utilizing a ketone-based auxiliary [79]. A chiral α-bromo-α'-hydroxy ketone (2.35) was prepared from (R)-camphor, and its corresponding dianion was formed by treatment with excess LDA. The addition of an aldehyde to this dianion led to the formation of epoxy ketone products (2.36 and 2.37) in high yield. For aromatic aldehydes, the trans epoxy ketone was formed almost exclusively. The use of aliphatic aldehydes, however, favors the cis epoxy ketone diastereomer instead of the trans. Removal of the camphor-derived auxiliary was performed by treating the epoxy ketones with excess ceric ammonium nitrate (CAN) to give the epoxy carboxylic acids (2.38) (isolated in the original report as their dicyclohexylammonium salts) and (R)-camphor.

**Table 11. Asymmetric Darzens reaction of a camphor-derived ketone system.**
There exists one example of an asymmetric Darzens reaction with an α-halo ketone and chiral complexed aldehydes (Table 12) [80]. Baldoli, et al. was successful in forming chiral $\eta^6$-chromium complexes of aromatic aldehydes (2.39). The use of these chiral complexes under general conditions for a Darzens reaction with α-chloroacetophenone, followed by oxidative removal of the chromium, gave exclusively trans epoxy ketones (2.40) in high enatioselectivity. Only three examples, however, were reported, which is indicative of the lack of generality for this variation of the Darzens reaction.

**Table 12. Asymmetric Darzens reaction with $\eta^6$-chromium-complexed aldehydes.**

<table>
<thead>
<tr>
<th>Ar yield</th>
<th>cis:trans</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>66</td>
<td>0:100</td>
</tr>
<tr>
<td>$\text{OCH}_3$</td>
<td>76</td>
<td>0:100</td>
</tr>
<tr>
<td>Cl</td>
<td>68</td>
<td>0:100</td>
</tr>
</tbody>
</table>

1) Aromatic aldehydes were in $\eta^6$-complexes with Cr
2) TOAB = tetraoctylammonium bromide

**2.4 Efforts Towards the Synthesis of (+)-Mefloquine Hydrochloride**

**2.4.1 Purpose**

There remain ongoing questions concerning the biological activity of the separate enantiomers of mefloquine and their individual relation to the severe side effects
associated with the drug. To date no definitive study has been made despite the asymmetric syntheses that have been accomplished. Although samples of the separate enantiomers have been prepared, this must be done through chiral resolution or through the use of asymmetric reactions that, while highly selective, are not completely selective. The ability to synthesize each enantiomer separately without the presence of the other enantiomer while doing so in significant quantity is still needed.

We thus set out to establish a new synthetic route to both enantiomers using the N-amino cyclic carbamate (ACC) auxiliaries developed in our laboratory. The results from the methodology study of the ACC-mediated aldol reaction led us to believe that we could adapt this methodology, in ways initially unexpected to establish the necessary 1,2-amino alcohol stereochemistry found in mefloquine.

### 2.4.2 Initial Reactions

Efforts towards the synthesis of (+)-mefloquine began with the preparation of 4-quinoline carboxyaldehyde 2.18 starting from the commercially available quinolinol 2.5. Following known literature procedure [67], quinolinol 2.5 was converted to the 4-bromoquinoline 2.6 via electrophilic aromatic substitution with phosphorus oxybromide. Compound 2.6, was carried forward without purification from the previous reaction, and treated with n-butyllithium to generate a 4-lithioquinoline intermediate in situ, which was immediately reacted with N,N-dimethylformamide
(DMF) to give aldehyde 2.18. Each of these reactions can easily be done under large scale in good yields (Scheme 35).

### Scheme 31. Preparation of quinoline carboxyaldehyde 2.18.

Mefloquine is at heart an *anti* amino alcohol, and so we envisioned the potential to utilize our ACC-mediated aldol reaction to set this stereochemistry (Scheme 36). This would involve the use of aldehyde 2.19 and a specific stereoisomer of an ACC hydrazone of 3-piperidone 2.42. Although straightforward, this route was not without its apparent challenges. Firstly, up to this point, no ACC-mediated aldol reaction with such a functionalized ketone had been performed. Secondly, we were not sure if the 3-substitution of the starting ketone would provide any sort of bias in the ratio of stereoisomers formed during hydrazone formation. Lastly, it was also not known if the stereoisomers could in fact be separated from one another.
Scheme 32. Initial aldol-based retrosynthetic analysis.

We first set out to prepare the ACC hydrazones of N-benzyl-3-piperidone 2.42 and N-Boc-3-piperidone 2.44. Both ketones were reacted with ACC auxiliary 1.13 under standard hydrazone formation conditions (Scheme 37). Up to this point, no ACC hydrazone of a 3-substituted cyclohexanone-type ketone had been prepared, and it was thus not known what the ratio of hydrazone stereoisomers would be. In the case of both ketones, the substituted 3-position of the ring provided no bias, and a 1:1 mixture of stereoisomers was obtained. Attempts to separate the two stereoisomers for the Boc-protected hydrazone 2.45 were unsuccessful, but separation was possible for the N-benzyl hydrazone 2.44 using column chromatography. It was not possible at this time to determine exactly which stereoisomer was which, and so both were isolated with intention of determining the exact configuration later on.
Scheme 33. Formation of N-substituted 3-piperidone ACC hydrazones.

Before attempting an aldol reaction with either of the isolated stereoisomers of hydrazone 2.43 and aldehyde 2.19, it was decided to attempt a simple aldol reaction with benzaldehyde (Scheme 38). One of the stereoisomers of 2.43 was treated with excess LDA to generate the corresponding azaenolate in situ, and then benzaldehyde was added. After allowing the reaction to warm to room temperature, it was found that no reaction between the hydrazone and benzaldehyde had occurred. Further attempts of this reaction yielded the same result. It was then decided to try a simple alkylation of one of the hydrazone stereoisomers with methyl iodide (Scheme 38). We were surprised to see that the reaction of hydrazone 2.43 with excess methyl iodide did in fact occur, and by 'H NMR it appears the dimethylated quaternary ammonium salt was isolated (2.46). The failure of any aldol reaction to occur, which was found to be consistent with the lack of reactivity in other sterically-demanding hydrazone systems, immediately forced us to consider alternative routes that still could take advantage of our aldol methodology.
2.4.3 Initial ACC-Mediated Darzens Reactions and Stereochemical Outcome

After careful consideration, it was decided that any synthetic route to (+)-mefloquine 2.1 would have to involve building the piperidine ring system rather than starting with it already intact (Scheme 11). This could potentially be accomplished through cross metathesis to give the unsaturated form of mefloquine (2.47). The amine of the amino alcohol could be derived from an azide, and so one could envision retrosynthetically going back to 2.49. Ultimately, 2.50 could be formed through the use of an anti aldol using an α-functionalized ACC hydrazone 2.51 and aldehyde 2.18.
Based on the results of the previous synthetic route, we decided to test the feasibility of an aldol reaction using an α-functionalized ACC hydrazone. Unfortunately, enolates (and presumably azaenolates) of α-azido ketones readily decompose before they can react, and this precluded the initial use of an α-azido hydrazone for our synthesis. Instead, we decided to use an α-halo ketone with the intention of installing the azide at a later step. Thus, the ACC hydrazone of α-chloroacetophenone, which was initially utilized to limit the amount of undesirable hydrazone stereoisomer 2.54, was prepared using standard hydrazone formation conditions previously mentioned. It was found, however, that this reaction was quite sluggish compared to other hydrazone formation reactions. By adding solid MgSO₄, switching the solvent to chloroform, and conducting the reaction at reflux for 12 hours, however, a 69% yield of just hydrazone
isomer 2.52 can be isolated. No trace of stereoisomer 2.53 was found. Previous efforts had shown that a similar reaction between our auxiliary and propiophenone (switching a –CH₃ for –Cl) gives a mixture of stereoisomers.

Scheme 36. Initial α-chloro ketone hydrazone formation.

Hydrazone 2.52 was then treated with excess LDA to give the corresponding azaenolate, and aldehyde 2.18 was added (Scheme 41). Although we were initially unsure if the product(s) of this ACC-mediated aldol reaction could be isolated or if the reaction would proceed on to the epoxide, we still expected that the syn aldol product 2.57 would be favored over the anti aldol product 2.56 due to the heavily electron deficient aldehyde used (see 1.3.2 of this document). Surprisingly, only epoxide diastereomers 2.54 and 2.55 (92:8 ratio) were obtained with no trace of halohydrin intermediates 2.56 and 2.57 when the reaction was allowed to come to room temperature, which was indicative of the aldolate immediately undergoing a ring-closing reaction. Based on ¹H NMR coupling constants of the epoxy protons, the major product was a trans epoxide while the minor product was a cis epoxide. Separation of the two products was easily achieved using flash chromatography. It should be noted that when the reaction was kept at -78 °C, the same ratio of products was obtained as
when it was allowed to warm to room temperature. To establish the absolute configuration of the trans epoxy hydrazone product 2.54, an x-ray crystal structure was obtained from a crystal grown in diethyl ether (Figure 6).

![Chemical structure](image)

Scheme 37. Initial ACC-mediated Darzens reaction.

![Chemical structure](image)

Figure 21. X-ray crystal structure of 2.55 used to determine absolute configuration.

We then became interested in assessing the utility of this new ACC-mediated Darzens reaction. The ACC hydrazones of 1-chloro-2-butanone and 1-bromo-3-methyl-2-butanone were prepared in a manner similar to that of hydrazone 2.52. Although hydrazone 2.58 was obtained in a roughly 1:1 ratio of stereoisomers, which were readily
separable, hydrazone 2.61 was obtained as a single stereoisomer. Upon treating both of these hydrazones with LDA and then with aldehyde 2.18 *trans* and *cis* epoxide products were obtained just as in the α-chloroacetophenone example (Scheme 42). For the 1-chloro-2-butane system, a 1:1 ratio of 2.59 and 2.60 was obtained while the 1-bromo-3-methyl-2-butane system gave a nearly 2:1 ratio of 2.62 and 2.63. All of the epoxide products were separable from one another, and it was clear that the steric bulk of the starting hydrazone played a major role in determining the ratio of *trans* and *cis* epoxide products.

Scheme 38. Subsequent Darzens reactions with less sterically demanding ketones.
2.4.4 Stereochemical Model

Based on the absolute configuration of trans epoxide 2.54 and the results with the other \( \alpha \)-halo hydrazones, it is possible to rationalize the stereochemical outcome of the ACC-mediated Darzens reaction. As the first step of the reaction is an aldol reaction, it can be assumed that all factors affecting the ACC-mediated aldol reaction also apply. Upon treatment of the hydrazone with excess LDA, the \( E \)azaenolate 2.64 is formed exclusively, and it is capable of reacting with aldehyde 2.18 in either a syn or anti addition. A key point with regards to reaction outcome involves the affect of temperature on the reaction. Unlike the previously described aldol methodology described in Chapter 1, the outcome of the ACC-mediated Darzens reaction does not depend on the temperature of the reaction conditions. Thus, the products of the Darzens reaction are kinetically trapped out, and the stability of the final products is not as important as the transition state that formed that products.

Figure 22. Transition state for the anti aldol addition of the hydrazone to the aldehyde.

The trans epoxy hydrazone results from an initial anti aldol addition (Figure 22) of azaenolate 2.64 to aldehyde 2.18. The known geometry of the azaenolate combined
with the configuration of the final epoxide product supports a closed transition state. In this transition state, the oxygen of the aldehyde is coordinated to the lithium cation, and the azaenolate adds to the *si* face of the aldehyde. The resulting *anti* aldolate 2.65 is able to readily undergo elimination of chloride to generate a *trans* epoxide product 2.66 as a result of the antiperiplanar relationship between the alkoxide and the chlorine atom. This *trans* epoxide hydrazone has the same absolute configuration observed in the x-ray crystal structure of 2.54.

![Diagram](image)

**Figure 23. Epoxide formation resulting from the *anti* aldolate**

Addition of the azaenolate to the *re* face of the aldehyde in a closed transition state would be less favorable as a result of diaxial-like interactions with the large aromatic ring system. Instead, addition of the aldehyde through an open transition state would lead to the formation of *syn* aldolate 2.66.

![Diagram](image)

**Figure 24. Unfavorable transition state leading to *syn* addition.**
This aldolate is not able to readily undergo ring-closure and generate an epoxide, however, and a bond rotation about the C(α)–C(β) bond must occur to arrange the alkoxide antiperiplanar to the chlorine atom (Figure 25). This has the effect of placing the large heteroaromatic ring system in an unfavorable gauche interaction with the rest of the hydrazone (2.68). Ring-closure at this step generates the cis epoxy hydrazone product 2.69.

![Figure 25. Open transition state leading to a syn aldolate and subsequent ring closure.](image)

With regards to the less sterically demanding hydrazones 2.58 and 2.61, the syn reaction pathway would presumably possess a less severe gauche interaction, which would allow for a greater amount of syn aldolate to form and then undergo ring-closure.
2.4.5 Subsequent Reactions

With the ability to prepare and isolate single diastereomer trans epoxy hydrazones in hand, the next task involved removal of the ACC auxiliary and conversion to a vinyl epoxide. Each of the trans epoxide products (2.54, 2.59, and 2.62) was treated with excess TsOH•H$_2$O in acetone, which was the standard hydrazone hydrolysis method in the aldol methodology (see 1.3.5). There was initially some uncertainty as to whether the hydrolysis would proceed efficiently given the steric bulk of the epoxy hydrazones, but we were grateful to find that the reaction was complete in 4-6 hours to give the epoxy ketone and the corresponding acetone ACC hydrazone 1.35 in high yield (Scheme 39). No reaction of the epoxide occurred. In the case of the acetophenone-derived system, the epoxy ketone 2.70 proved to be inseparable from the acetone ACC hydrazone (1.35), but a simple substitution of 3-pentanone for acetone solved this issue.
Scheme 39. Hydrolysis reactions of epoxy hydrazones.

The next step involved in the conversion of an epoxy ketone to a vinyl epoxide. Originally, we focused on the use of epoxy ketones 2.71 and 2.72, as the acetophenone-derived system was not amenable to the chemistry we intended to utilize. Our first attempt at forming the vinyl epoxide focused on the use of elimination reactions. In a one-pot process, epoxy ketone 2.71 was reduced with sodium borohydride to diastereomeric epoxy alcohols, which were not isolated but instead treated with methanesulfonyl chloride and triethylamine to give the corresponding mesylate 2.73 (Scheme 40). Our attempts to initiate an elimination of the mesylate to give a vinyl epoxide (2.74), however, did not meet with success. Variations of basic conditions were used, but only unreacted starting material was obtained in each instance with no trace of an eliminated product found. The Burgess reagent is useful for the syn-dehydration of alcohols, but it is also known to open epoxides to give cyclic heterocycles [81]. We
shifted our focus onto other methods for generating vinyl epoxides. The use of Martin’s sulfurane, useful for the elimination of secondary and tertiary alcohols [82], disappointingly gave inconsistent results. We next looked into the possibility of forming a vinyl epoxide through the use of palladium catalysis (Scheme 41). Ketones can be readily converted into the corresponding vinyl triflates through the use of LDA and either N-phenyl-bis(trifluoromethanesulfonimide) or the Comins reagent (2.75). These vinyl triflates can then react with tributyltin hydride in the presence of LiCl and a palladium(0) catalyst (e.g., Pd(PPh)₄) to give the corresponding olefin. Our attempts to facilitate this transformation in our system gave mixed results. Epoxy ketone 2.59 was easily converted into its vinyl triflate (2.76) with LDA and the Comins reagent[83] (2.75), but all attempts at affecting the palladium catalyzed reaction proved unsuccessful.

Scheme 40. Attempted elimination reactions to form a vinyl epoxy.
Attempts at using sulfoxide-mediated *syn* elimination also ultimately proved unsuccessful. Alcohol 2.77 (prepared by the simple reduction of ketone 2.71) was converted to the thioether 2.78 under standard Mitsunobu reaction conditions. Attempts to oxidize the sulfide to the sulfoxide with *meta*-chloroperoxybenzoic acid (*m*-CPBA), however, gave significant amounts of over oxidation to unreactive sulfone 2.79. We were ultimately unsuccessful at preventing this over oxidation reaction (Scheme 42).
2.4.6 Baeyer-Villiger and Further Reactions

It was this point in our synthetic efforts that we fortuitously came upon a reference relating to the oxidation of epoxy chalcones to the corresponding phenyl epoxy esters [84]. Baures, et al. reported a method for the Baeyer-Villiger oxidation of aryl-substituted epoxy chalcones (2.80) using \( m \)-CPBA (Scheme 43). Although excess oxidant and thermal conditions were required, this method provided the corresponding phenyl epoxy esters (2.81) in good to decent yields without affecting the configuration of the epoxide moiety. Migration of the epoxide was only seen in the case of the 4-chlorophenyl system where a small amount of rearranged byproduct (2.82) was isolated.
We immediately recognized the utility of this reaction for our own synthesis. Up until this point, we had been unable to utilize epoxy ketone 2.70 due to its inability to undergo elimination reactions, but the conversion of the epoxy ketone to its phenyl epoxy ester 2.83 would provide a separate route for preparing a vinyl epoxide. We were grateful to find that treatment of epoxy ketone 2.70 with excess m-CPBA in refluxing CH₂Cl₂ gave phenyl ester 2.83 in good yield, but subsequent attempts at purification of this ester led to decomposition (Scheme 44). We then decided to not isolate the phenyl ester but instead immediately reduce it to the corresponding epoxy alcohol (2.84) using lithium aluminum hydride (LAH) in Et₂O at -78 °C, conditions which have been shown to cleanly reduce the carbonyl of epoxy thioesters without affecting the epoxide [85]. The epoxy alcohol 2.84 was obtained in good yield and purified by filtration through a pad of silica gel to avoid column chromatography. Oxidation of 2.84 to the epoxy aldehyde (2.85) using Dess-Martin periodinane (DMP) was achieved cleanly in quantitative yield. With 2.85 in hand, we now had a substrate to directly convert into a vinyl epoxide through the use of carbonyl chemistry as opposed to elimination chemistry.

**Scheme 43. Original report of a Baeyer-Villiger reaction on epoxy chalcones.**

<table>
<thead>
<tr>
<th>R</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅</td>
<td>&gt; 99</td>
<td>74</td>
</tr>
<tr>
<td>4-OMeC₆H₄</td>
<td>90</td>
<td>57</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>88</td>
<td>63</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>&gt; 99</td>
<td>80</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>&gt; 99</td>
<td>59</td>
</tr>
</tbody>
</table>
Scheme 44. Baeyer-Villiger oxidation followed by formation of epoxy aldehyde.

Olefination of aldehyde 2.85 under standard non-stabilized Wittig conditions gave vinyl epoxide 2.86 in moderate yield. We next began to focus on opening the epoxide and building the piperidine ring system found in mefloquine. We first looked into opening the epoxide with nitrogen nucleophiles such as sulfonamide 2.87, which was prepared through the tosylation of homoallyl amine, to give 2.88 (Scheme 45). Sulfonamides have been shown to add to epoxide selectively under a Lewis acid-mediated reaction with tetraalkylammonium salts and Cs$_2$CO$_3$ [86]. Attempts to apply this chemistry to our system under both thermal and microwave conditions to give 2.88 proved unsuccessful, however, due to the apparent decomposition of the vinyl epoxide under the reaction conditions. Substitution of 2.87 for para-toluenesulfonamide did not affect the outcome of the reaction.

We next looked into using sodium azide to open the epoxide (Scheme 45). Because the azide functionality acts like a protected amine, the opening of the epoxide with the azide anion would establish the necessary anti amino alcohol functionality
found in mefloquine. The addition of epoxide 2.86 to an aqueous ethanol solution of sodium azide and ammonium chloride gave a single product that encouragingly had characteristics of the desired product (2.89). Further investigation of the results of this reaction, however, showed that the desired product was not in fact obtained. While the initial epoxide opening reaction with azide did in fact occur, previous literature reports have shown that the resulting ally azide (2.89) quickly undergoes a [3,3]-sigmatropic rearrangement to give the more stable allyl azide 2.90 [87]. We next attempted the direct addition of ammonia to epoxide 2.86, which appeared to be successful. The resulting amino alcohol 2.91, however, proved difficult to isolate due to its presumed significant water solubility and polarity (Scheme 45).

Scheme 45. Attempts at epoxide opening with nitrogen nucleophiles.
2.4.7 Azido-Wittig Olefination and Cyclization

Up until this point in our synthetic efforts, we had only considered adding the nitrogen functionality first to the epoxide followed by subsequent chemistry to construct the piperidine ring system. With the difficulties encountered in following this approach, however, we began to consider an alternative route (Scheme 46). As we initially prepared vinyl epoxide 2.86 through an unstabilized Wittig-olefination, the idea of using that same chemistry to prepare a substituted vinyl epoxide possessing the desired nitrogen functionality, such as through the use of azido ylide 2.92, was considered. An examination of the literature showed that this idea was not without precedence. Chenn, and coworkers previously prepared ylide 2.92 by the simple azide substitution of phosphonium salt 2.93 with sodium azide [88]. Ylide 2.95 is then prepared by treatment of the phosphonium salt 2.93 with a strong base such as potassium hexamethyldisilazide (KHMD). It was shown that this ylide reacts apparently without issue (unlike the corresponding ylide formed from phosphonium salt 2.93), and the reaction of this ylide with simple aldehydes yielded the corresponding Z-olefins in good yield [88]. Because the Z-olefin would be advantageous towards later cyclization reactions, we decided to look into the reaction of ylide 2.95 with our previously prepared epoxy aldehyde 2.85 (Scheme 46). This reaction proceeded in comparable yield to the literature report to give olefin epoxide 2.96, yet we unfortunately obtained a 5:1 mixture of Z/E olefins instead of
exclusively the Z-olefin. The two olefins were inseparable from one another. Attempts to modify the reaction conditions to further favor the Z-olefin proved unsuccessful.

Scheme 46. Formation of azidophosphorane and subsequent use in a Wittig olefination.

We were fortunate that Chenn and coworkers had also looked into utilizing their chemistry in the ring-opening of epoxides [89]. As shown in Scheme 51, olefin 2.97, previously prepared through the azido-Wittig reaction of ylide 2.95 with propionaldehyde, was epoxidized with m-CPBA to epoxide 2.98. Treatment of this azido epoxide with standard Staudinger reduction conditions gave the amino epoxide 2.99, which could be isolated and cyclized by refluxing in toluene to give the amino alcohol 2.100 (Scheme 47). Our attempts to follow this protocol in our own system were met with limited success. Reduction of the azide functionality in epoxide 2.96 to the amine was apparently successful, but we had difficulty isolating and purifying this product presumably due to solubility and polarity issues. Taking the crude material on to the cyclization step yielded similar difficulties. Working under the assumption that the amine functionality was responsible for these difficulties, we decided to modify our
reaction conditions to allow for the protection of the amine nitrogen. As amines can be readily protected using Boc anhydride under refluxing conditions without base, we originally believed this protection could be affected at the same time as the cyclization step. Thus, 2.96 was treated with triphenylphosphine in refluxing aqueous THF for two hours followed by the addition of Boc anhydride. We were grateful to find that the only products produced were N-Boc protected 2.101 and the N-Boc protected E-olefin (not shown), which was derived from the small of amount of E-olefin produced in our azido-Wittig reaction and was structurally unable to undergo the cyclization step. This one-pot, three-step reaction presumably proceeded as shown in Figure 26. First, azido epoxide 2.96 was reduced to the corresponding amino epoxide (2.102). Under the refluxing conditions used, however, 2.102 could then undergo the cyclization step to give compound 2.103, which is inherently an unsaturated form of (+)-mefloquine itself. The addition of Boc anhydride under these conditions would have led to the protection of the piperidine nitrogen to give 2.104. The overall yield for this reaction was 72% compared to the previous literature method’s overall yield of 65% for the separate reduction and cyclization steps. We were now in a position to complete the total synthesis of (+)-mefloquine (2.1) by reducing the unsaturation and removing the Boc protecting group.
Scheme 47. Original multi-step cyclization procedure and the new one-pot procedure.

Figure 26. Overview of one-pot cyclo-Staudinger reaction.

2.4.8 Completion of Synthesis

To complete the synthesis of (+)-mefloquine we next focused our efforts on hydrogenating the alkene left over from the previous Wittig olefination reaction. We found the simple hydrogenation of 2.104 with H₂ over palladium catalyst proceeded slowly, but complete hydrogenation could be achieved in 24 hours (Scheme 48). With N-
Boc protected (+)-mefloquine 2.104 in hand, we next removed the Boc protecting group using trifluoroacetic acid in dichloromethane (1:4 by vol.). We found this reaction proceeded readily and quickly, and the resulting (+)-mefloquine (as the free base) could be treated with ethereal hydrogen chloride to give the hydrochloride salt of (+)-mefloquine (2.1), which was confirmed by NMR [90].

Scheme 48. Completion of (+)-mefloquine hydrochloride.

Verification of the enantiopurity of the product was achieved both quantitatively and experimentally. Firstly, the sample of (+)-mefloquine hydrochloride prepared using our synthetic route possessed different physical properties compared to the racemic drug. Its solubility in NMR solvents, in particular, was particularly striking, as the racemic drug was soluble in CDCl$_3$ yet our compound was completely insoluble in this solvent. Secondly, racemic mefloquine hydrochloride (as prescribed for use) was treated with Boc anhydride in the presence of triethylamine to give racemic N-Boc mefloquine. The individual enantiomers were then resolved using chiral HPLC. Analysis of a sample
of N-Boc mefloquine prepared using our synthesis showed that our product (+)-mefloquine (2.1) consisted of a single enantiomer (See Experimental Section for more information).

2.5 Synthesis of (-)-Mefloquine Hydrochloride

The asymmetric total synthesis of (-)-mefloquine hydrochloride (2.2) should be able to be conducted in a very similar manner to the method described for (+)-mefloquine hydrochloride (2.1) except for the use of the ACC chiral auxiliary of opposite configuration. Thus, ACC 1.98 auxiliary was prepared from (1R)-camphorsulfonic acid (1.93) according to the synthetic route described (1.3.1). Formation of hydrazone 2.106 was achieved using ACC 1.98 auxiliary and α-chloroacetophenone. We were grateful to find that using this hydrazone in the original asymmetric Darzens reaction gave epoxy hydrazone 2.107 in comparable yield and the exact same cis:trans ratio of 92:8. The rest of the synthesis proceeded without any new issues or difficulties with respect to the synthesis of (+)-mefloquine hydrochloride previously described (Scheme 49).
2.6 Sharpless Modification to the Synthetic Route of (+)-Mefloquine Hydrochloride

Scheme 50. Modified asymmetric epoxidation to epoxy alcohol 2.111.

In addition to our novel ACC-mediate asymmetric synthesis of (+)- and (-)-mefloquine hydrochloride, we also developed a modified synthesis to take advantage of the well-known and utilized Sharpless asymmetric epoxidation reaction (Scheme 50).
Aldehyde 2.18 was first reacted with ethyl (triphenylphosphoranylidene)acetate to give unsaturated ester 2.109 exclusively as the E-isomer. This ester was then reduced to the allylic alcohol 2.110 using excess diisobutylaluminum hydride (DIBAL-H). Initial attempts at utilizing the allylic alcohol 2.110 in a Sharpless asymmetric epoxidation reaction met with limited success, and it quickly became apparent that the allylic alcohol suffered from solubility issues under the reaction conditions. Extending the reaction time to a minimum of 48 hours allowed for complete oxidation to occur and give epoxy alcohol 2.111 in a 93:7 enantiomeric ratio as determined by chiral HPLC. The enantiopurity could be increased to >99:1 by recrystallizing the epoxy alcohol in diethyl ether/hexanes. The enriched epoxy alcohol could then be put through the necessary subsequent chemical transformations as described in the ACC-mediate mefloquine synthesis. The use of the (+)-diisopropyl tartrate (DIPT) ligand in the Sharpless asymmetric epoxidation reaction gives an epoxy alcohol that could be used to prepare (-)-mefloquine hydrochloride (2.2). Use of the (-)-DIPT ligand would be required to prepare (+)-mefloquine hydrochloride (2.1).

### 2.7 Conclusion

In conclusion, we have developed an effective asymmetric synthesis of (+)-mefloquine[91] and (-)-mefloquine as their hydrochloride salts. Establishment of the necessary stereochemistry is achieved using a novel ACC-mediated Darzens reaction.
that is an extension of the previously discussed ACC-mediated aldol reaction (Chapter 1). Known transformations along with the use of a one-pot Staudinger reduction/cyclization/N-Boc protection allows for the formation of the amino alcohol core of the drug. We also further modified the synthesis to take advantage of the rather well known Sharpless asymmetric epoxidation reaction to establish the necessary stereochemistry. The product of the Sharpless asymmetric epoxidation can then be put through most of the subsequent steps of the original synthesis. Both enantiomers can be prepared in sufficient quantities for biological testing.

2.8 Experimental Section

General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and
cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et₂O, CH₂Cl₂, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230–400 mesh) or, where indicated, high purity silica gel (5-20 mesh). All ¹H chemical shifts are reported in ppm (δ) relative to TMS; ¹³C shifts are reported in ppm (δ) relative to CDCl₃ (77.16).

**ACC hydrazone of N-benzyl-3-piperidone (2.43).** This compound was prepared in a manner similar to hydrazone 1.17 using N-benzyl-3-piperidone and ACC 1.13 (87%). A 1:1 mixture of hydrazone isomers was obtained. Both hydrazone isomers could be separated using column chromatography (5% EtOAc/Hexanes) over silica gel.

**¹H NMR (isomer A) (CDCl₃, 400 MHz):** δ 7.33-7.24 (m, 5H), 4.14 (dd, 1H, J = 8.2 Hz, 4.1 Hz), 3.67 (d, 1H, J = 11.6 Hz), 3.61 (d, 1H, J = 13.6 Hz), 3.52 (d, 1H, J = 13.6 Hz), 2.87 (app. d, 1H, J = 11.2 Hz), 2.73 (d, 1H, J = 11.6 Hz), 2.60 (app. d, 1H, J = 11.2 Hz), 2.32-
2.23 (m, 3H), 2.11 (td, 1H, \( J = 4.8 \) Hz, 11.6 Hz), 1.99-1.88 (m, 1H), 1.84-1.79 (m, 4H), 1.75 (t, 1H, \( J = 4 \) Hz), 1.29-1.24 (m, 5H, containing a s at \( \delta = 1.26 \)), and 1.09 (s, 3H).

\(^1\)H NMR (isomer B) (CDCl\(_3\), 400 MHz): \( \delta = 7.38-7.25 \) (m, 5H), 4.20 (dd, 1H, \( J = 8.1, 4.2 \) Hz), 3.63 (d, 1H, \( J = 13.2 \) Hz), 3.53 (d, 1H, \( J = 11.2 \) Hz), 3.52 (d, 1H, \( J = 13.2 \) Hz), 2.96 (d, 1H, \( J = 11.2 \) Hz), 2.81-2.78 (m, 1H), 2.62-2.56 (m, 1H), 2.34-2.21 (m, 5H0, 1.95-1.88 (m, 1H), 1.80-1.71 (m 3H), 1.28-1.12 (m, 8H, containing a s at \( \delta = 1.22 \)), and 1.06 (s, 3H).

![2,8-bis(trifluoromethyl)quinoline-4-carbaldehyde](image)

2,8-bis(trifluoromethyl)quinoline-4-carbaldehyde (2.18). This compound was prepared from 4-bromo-2,8-bis(trifluoromethyl)quinoline (2.6), \( n\)-butyllithium, and \( N,N\)-dimethylformamide according to the literature procedure. Spectral data was identical to previously reported data.[67]

![ACC hydrazone of 2-chloroacetophenone](image)

ACC hydrazone of 2-chloroacetophenone (2.51). To a stirred solution of 2-chloroacetophenone (1.75 g, 11.3 mmol) and ACC 1.13 (2.22 g, 11.3 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was added \( p\)-toluenesulfonic acid (215 mg, 1.13 mmol) and anhydrous magnesium sulfate (5.44 g, 45.2 mmol). The reaction mixture was brought to reflux and stirred for 6 h. It was then cooled to room temperature, diluted with water (60 mL), and the layers
were separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification via flash chromatography over silica gel (3.5% EtOAc/97.5% hexanes) gave 2.51 as a very viscous, colorless oil (2.60 g, 69%). ¹H NMR (CDCl₃, 500 MHz): δ 7.85-7.43 (m, 2 H), 7.46-7.42 (m, 3 H), 4.71 (d, J = 13 Hz, 1 H), 4.45 (d, J = 13.0 Hz, 1 H), 4.39 (dd, J = 8.1, 4.02 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz): 165.97, 154.90, 134.63, 130.77, 128.55, 127.78, 83.50, 73.80, 48.16, 43.13, 36.48, 35.45, 26.92, 25.81, 21.55, 19.26; ESI-MS m/z calcd for C₁₈H₂₂ClN₂O₂ (M + H): 333.1, found: 333.2.

*N-tert-butoxycarbonyl-3-piperidone*. This ketone was prepared according to the literature procedure using commercially available 3-hydroxy-piperidine[92]. ¹H NMR (CDCl₃, 400 MHz): 3.98 (s, 2H), 3.56 (t, 2H, J = 6 Hz), 2.44 (t, 2H, J = 6.8 Hz), and 1.98-1.92 (m, 2H).

ACC Hydrazone of trans-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)(phenyl)methanone (2.54). *n*-butyllithium (2.5 M in hexanes, 1.53 mL, 3.84 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of
diisopropylamine (543 µL, 3.84 mmol) in THF (9 mL). After being stirred for 20 min, a solution of 2.52 (982 mg, 2.95 mmol) in THF (8 mL) was added via cannula. The resulting orange solution was stirred for 45 min at -78 °C. A separate solution of 2.18 (863 mg, 2.95 mmol) in THF (8 mL) was then added to the azaenolate. The solution became deeply colored, and the reaction flask was allowed to warm to room temperature and stir for 2 h. The reaction was quenched with saturated NH₄Cl (10 mL) under vigorous stirring. The mixture was partitioned between Et₂O (25 mL) and H₂O (25 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (2 x 10 mL), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. This gave a 92:8 mixture of trans:cis epoxides. Flash chromatography over silica gel (10% EtOAc/90% hexanes) gave the trans epoxide 2.54 as a light-yellow solid (1.20 g, 69%). ¹H NMR (CDCl₃, 500MHz): δ 8.39 (d, J = 8.5 Hz, 1 H), 8.21 (d, J = 7 Hz, 1 H), 8.07-8.01 (m, 2 H), 7.89 (s, 1 H), 7.78 (t, J = 7.5 Hz, 1 H), 7.52-7.47 (m, 3 H), 4.57 (apparent s, 1 H), 4.42 (apparent s, 1 H), 4.33 (dd, J = 4, 8 Hz, 1 H), 2.42-2.30 (m, 2 H), 2.15-2.07 (m, 1 H), 1.98-1.87 (m, 2 H, [containing an apparent dd at δ 1.95, J = 8, 13.75 Hz]), 1.45-1.08 (m, 8 H, [containing a s at δ 1.44 and a s at δ 1.10]) ; ¹³C NMR (CDCl₃, 125 MHz): 161.5, 154.6, 149.1, 148.8, 145.0, 143.8, 134.7, 131.1, 130.1, 129.9, 129.31, 129.27, 128.7, 127.8, 127.7, 127.4, 126.8, 124.6, 122.4, 122.2, 120.0, 114.07, 114.06, 83.3, 73.8, 58.9, 55.3, 48.4, 42.9, 35.5, 27.3, 26.0, 21.5, 19.2; ESI-MS m/Z calcd for C₃₀H₂₂F₀N₃O₅ (M + Na): 612.2, found: 612.1.
ACC hydrazone of 1-chloro-2-butanone (2.58). This compound was prepared in a manner similar to hydrazone 2.52 above using 1-chloro-2-butanone and ACC 1.13 (93%). A 1:1 ratio of hydrazone isomers was obtained. The desired hydrazone isomer could be separated using flash chromatography over silica gel (5% EtOAc/95% hexanes).

'H NMR (CDCl₃, 500 MHz): δ 4.37 (d, 1H, J = 8.6 Hz), 4.25 (dd, 1H, J = 8.2 Hz, 4.1 Hz), 3.98 (d, 1H, J = 8.6 Hz), 2.76-2.48 (m, 2H), 2.28-2.24 (m, 1H), 2.01-1.92 (m, 2H), 1.85 (dd, 1H, J = 2.8 Hz, 13.6 Hz), 1.76 (app. t, 1H, J = 4.8 Hz), 1.31-1.11 [m, 12H, containing s at δ 1.23, and a d at δ 1.14 (J = 7.2 Hz)], and 1.07 (s, 3H).

ACC hydrazone of trans/cis-1-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)propan-1-one (2.60). This compound was prepared in a manner similar to hydrazone 2.54 using hydrazone 2.58 and aldehyde 2.18. A 3:2 mixture of trans:cis epoxide isomers was obtained. 'H NMR (CDCl₃, 400 MHz): 8.34 (d, J = 8.4 Hz, cis), 8.24 (t, 1H, J = 8.8 Hz, trans), 8.18 (d, 1H, J = 8.4 Hz, trans), 7.83-7.73 (m), 7.49 (s, 1H, cis), 4.83
(d, 1H, \( J = 4.4 \) Hz, cis), 4.52 (d, 1H, \( J = 4.4 \) Hz, cis), 4.43 (d, 1H, \( J = 2 \) Hz, trans), 4.11 (dd, 1H, \( J = 8.2 \) Hz, 4.1 Hz, trans), 4.03 (d, 1H, \( J = 2 \) Hz, trans), 2.75-2.49 (m, 4H), 2.41 (dd, 1H, \( J = 8.2 \) Hz, 4.1 Hz, cis), 2.29-2.19 (m, 2H), 1.46-1.30 (m 4H), 1.29 (s, 3H, cis), 1.25 (t, 3H, \( J = 7.6 \) Hz, trans, 1.15 (t, 3H, \( J = 7.6 \) Hz, cis), 1.07 (s, 3H, trans), 0.91 (s, 3H, cis), and 0.79 (s, 3H, cis).

**ACC hydrazone of 1-bromo-3-methyl-2-butanone (2.61).** This compound was prepared in a manner similar to hydrazone 2.52 above using 1-bromo-3-methyl-2-butanone and ACC 1.13 (82%). 

\( ^1H \) NMR (CDCl\(_3\), 500 MHz): \( \delta \) 4.28 (dd, 1H, \( J = 8.1 \) Hz, 4.2 Hz), 4.22 (d, 1H, \( J = 11.6 \) Hz), 3.21 (d, 1H, \( J = 11.6 \) Hz), 3.00 (sep, 1H, \( J = 6.8 \) Hz). 2.30-2.26 (m, 1H), 2.06-1.89 (m, 2H), 1.85 (dd, 1H, \( J = 2.8 \) Hz, 13.6 Hz), 1.76 (app. t, 1H, \( J = 4.8 \) Hz), 1.30-1.12 [m, 15H, containing s at \( \delta 1.22 \), d at \( \delta 1.20 \) (\( J = 4 \) Hz), and a d at \( \delta 1.80 \) (\( J = 4 \) Hz)], and 1.07 (s, 3H).

**ACC hydrazone of trans/cis-1-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)-2-methylpropan-1-one (2.63).** This compound was prepared in a
manner similar to hydrazone 2.54 using hydrazone 2.61 and aldehyde 2.18. A 2:1 mixture of trans:cis epoxide isomers was obtained. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 8.37 (d, 1H, \(J = 8.4\) Hz, cis), 8.30 (d, 1H, \(J = 8.4\) Hz, trans), 8.26 (d, 1H, \(J = 7.2\) Hz, cis), 8.21 (d, 1H, \(J = 7.2\) Hz, trans), 7.84 (app. t, 1H, \(J = 8\) Hz, cis), 7.80 (s, 1H, trans), 7.76 (app. t, 1H, \(J = 8\) Hz), 7.50 (s, 1H, cis), 4.87 (d, 1H, \(J = 4\) Hz, cis), 4.63 (d, 1H, \(J = 4\) Hz, cis), 4.41 (d, 1H, \(J = 2\) Hz, trans), 4.14 (dd, 1H, \(J = 8\) Hz, 4 Hz), 4.11 (d, 1H, \(J = 2\) Hz, trans), 3.10 (m, 1H, cis), 2.95 (m, 1H, trans), 2.45 (dd, 1H, \(J = 8\) Hz, 4 Hz, cis), 2.31-2.23 (m, 2H), 2.11-1.77 (m, 6H), 1.51-1.04 (m, containing app. d at 1.36 (\(J = 6.8\) Hz), s at 1.33, app. d at 1.24 (\(J = 6.8\) Hz), app. d at 1.13 (\(J = 6.8\) Hz), and s at 1.08), 0.93 (s, 3H), and 0.81 (s, 3H).

![trans-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)-(phenyl)methanone (2.70)](image)

\(\text{trans-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)-(phenyl)methanone (2.70)}\). Epoxyhydrazone 2.54 (311 mg, 0.56 mmol) was dissolved in 3-pentanone (25 mL), and the clear solution was treated with \(p\)-toluenesulfonic acid (213 mg, 1.12 mmol). After stirring for 18 h at room temperature, the reaction was quenched by the addition of saturated aqueous NaHCO\textsubscript{3} (3 mL). The mixture was partitioned between CH\textsubscript{2}Cl\textsubscript{2} (40 mL) and H\textsubscript{2}O (3 mL), and the layers were separated. The organic phase was dried over magnesium sulfate, filtered, and concentrated \textit{in vacuo}. Flash chromatography over silica gel (15% EtOAc/85% hexanes) gave 2.70 as a light-yellow solid (170 mg, 74%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 8.31-8.18 (m, 2 H, [containing a d at \(\delta\)}}
8.28, $J = 8.5$ Hz and a d at $\delta$ 8.22, $J = 7.5$ Hz), 8.06 (d, $J = 7.5$ Hz, 2 H), 7.91 (s, 1 H), 7.78 (t, $J = 8$ Hz, 1 H), 7.68 (t, $J = 7.5$ Hz, 1 H), 7.53 (t, $J = 7.5$ Hz, 2 H), 4.83 (apparent s, 1 H), 4.33 (apparent s, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 191.8, 149.0, 148.8, 144.6, 143.6, 135.1, 134.8, 130.0, 129.7, 129.6, 129.55, 129.50, 129.46, 129.3, 128.7, 128.3, 127.2, 126.9, 124.5, 124.4, 122.2, 120.0, 113.72, 113.71, 60.0, 55.6; ESI-MS $m$/Z calcd for C$_{20}$H$_{11}$F$_{6}$NNaO$_2$ (M): 434.1, found: 434.0.

$\textit{trans}-1-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)propan-1-one (2.71)$. This compound was prepared in a similar manner to ketone 2.70 above using hydrazone 2.60, p-toluenesulfonic acid and acetone as a solvent (90%). $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ 8.23-8.19 (m, 2H), 7.80-7.74 (m, 2H), 4.64 (app. s, 1H), 3.53 (app. s, 1H), 2.72-2.55 (m, 2H), and 1.16 (t, 3H, $J = 7.2$ Hz).

$\textit{trans}-1-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)-2-methylpropan-1-one (2.72)$. This compound was prepared in a similar manner to ketone 2.70 above using hydrazone 2.63, p-toluenesulfonic acid and acetone as a solvent (86%).
**1H NMR** (CDCl₃, 400MHz): δ 8.21-8.18 (m, 2H), 7.84-7.71 (m, 2H), 4.17 (app. s, 1H), 3.62 (app. s, 1H), 2.89 (sep, 1H, J = 6.8 Hz), 1.23-1.21 (m, 6H).

**1-((2R,3S)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)propyl methanesulfonate (2.73).** A solution of ketone 2.71 (30 mg, 0.083 mmol) was dissolved in methanol (2 mL) and cooled to 0 °C. To this solution was added solid NaBH₄ (4 mg, 0.106 mmol). Stirring was continued at 0 °C for 30 minutes, and the mixture was partitioned between DI water (10 mL) and Et₂O (10 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (2 x 5 mL). The combined extracts were dried over MgSO₄ and concentrated *in vacuo* to give a clear, colorless oil consisting of the epoxy alcohol.

The alcohol was then immediately dissolved in CH₂Cl₂ (3 mL) and treated with methanesulfonyl chloride (10 µL, 0.125 mmol) and Et₃N (34 µL, 0.25 mmol). After stirring for 30 minutes at room temperature, the reaction was quenched with the addition of saturated NH₄Cl (3 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (15% EtOAc/85% hexanes) gave the desired mesylate as an inseparable mixture of diastereomers (55:45, 93%). **1H**
NMR (CDCl₃, 400MHz): δ 8.54 (d, 1H, J = 8.6 Hz), 8.38 (d, 1H, J = 8.6 Hz), 8.21-8.18 (m, 2H), 7.81-7.73 (m, 4H), 5.28 (app. s, 1H), 4.82-4.78 (m, 1H), 4.69 (m, 2H), 4.62-4.7 (m, 1H), 3.66 (app. s, 1H), 3.19 (s, 3H), 3.14 (s, 3H), 2.06-1.87 (m, 4H), 1.13 (app. t, 6 Hz, J = 7.2 Hz).

1-((2S,3R)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)prop-1-en-1-yl trifluoromethanesulfonate (2.76). A solution of ketone 2.71 (40 mg, 0.111 mmol) in THF (3 mL) at -78 °C was treated with solid potassium hexamethyldisilazide (KHMDS, 27 mg, 0.133 mmol). After stirring for 30 minutes, Comins’ reagent[83] (48 mg, 0.122 mmol) was added to the enolate solution. Stirring was continued at -78 °C for 1 hour. The reaction was quenched by the addition of saturated NH₄Cl (3 mL). The resulting mixture was partitioned between Et₂O (20 mL) and H₂O (20 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (2 x 15 mL), and the combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography over silica gel (20% EtOAc/80% hexanes) gave the desired vinyl triflate as a light-yellow oil. ¹H NMR (CDCl₃, 400MHz): δ 8.34 (d, 1H, J = 8.6 Hz), 8.20 (d, 1H, J = 8.6 Hz), 7.81-7.77 (m, 2H), 5.98 (q, 1H, J = 7.2 H), 4.63 (app. s, 1H), 3.51 (app. s, 1H0, and 1.91 (d, 3H, J = 7.2 Hz).
To a stirred solution of epoxyketone 70 (130 mg, 0.32 mmol) in CH$_2$Cl$_2$ (10 mL) was added $m$-chloroperoxybenzoic acid ($m$-CPBA) (276 mg, 1.60 mmol, 77% by titration). The reaction mixture was brought to reflux and stirred for 24 h. It was then cooled to room temperature, and saturated aqueous NaHSO$_3$ was added dropwise to the reaction until all of the excess peroxyacid was consumed (bubbling stops). The resulting mixture was partitioned between dichloromethane (30 mL) and water (~5 mL). The layers were separated, and the organic phase was washed with saturated NaHCO$_3$ solution (3 x 5 mL). After drying over magnesium sulfate and concentrating in vacuo, an off-white solid was obtained as a crude mixture of ester and $m$-CPBA byproducts. This material was dried under high-vacuum and used as is in the next step.

Crude phenyl ester from above was dissolved in Et$_2$O (10 mL), and the solution was cooled to -78 °C under argon. This solution was then treated with solid lithium aluminum hydride (39 mg, 1.02 mmol), and the resulting greenish-colored mixture was stirred for 1-2 h at -78 °C. The reaction was quenched by the slow addition of H$_2$O followed by 10% aqueous HCl (until solution becomes acidic). After warming to room temperature, the mixture was partitioned between Et$_2$O (10 mL) and H$_2$O (~3 mL). The layers were separated, the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 20 mL), the
combined extracts were dried over magnesium sulfate and concentrated in vacuo. The crude material was filtered through a pad of silica gel (100 mL of 40% EtOAc/80% hexanes to remove phenol followed by 100 mL of EtOAc) to give epoxy alcohol 2.84 as a colorless oil (73 mg, 64% over two steps). $^1$H NMR (CDCl$_3$, 500MHz): δ 8.35 (d, $J = 8.5$ Hz, 1 H), 8.21 (d, $J = 7$ Hz, 1 H), 7.84-7.76 (m, 2 H), 4.69 (apparent s, 1 H), 4.23-4.01 (m, 2 H), 3.23 (apparent s, 1 H), 1.90-1.82 (apparent br s, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 149.0, 148.7, 146.3, 143.4, 129.8, 129.5, 129.34, 129.31, 129.27, 129.23, 127.8, 127.3, 127.2, 124.6, 122.4, 122.3, 120.1, 113.6, 62.60, 62.57, 60.3, 51.94, 51.89; ESI-MS m/z calcd for C14H10F6NO2 (M + H): 338.1, found: 338.1.

(3-(2,8-bis(trifluoromethyl)-4-quinolinyl)oxirane-2-carboxaldehyde (2.85). To a stirred solution of epoxy alcohol 2.84 (94 mg, 0.28 mmol) in CH$_2$Cl$_2$ (10 mL) was added Dess-Martin periodinane (119 mg, 0.28 mmol). The reaction was stirred for 1 h at room temperature and quenched by the addition of aqueous 10% KOH (5 mL). The mixture was partitioned between EtOAc (40 mL) and H$_2$O (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to give 2.85 as a light-yellow solid (93 mg, quantitative). The product was used as is without further purification as it was unstable on silica. $^1$H NMR of the crude (CDCl$_3$, 500MHz):
400MHz): δ 9.39 (apparent d, J = 5.6 Hz, 1 H), 8.22 (d, J = 8 Hz, 2 H), 7.87-7.74 (m, 2 H), 4.85 (apparent s, 1 H), 3.50 (apparent d, J = 6 Hz, 1 H);

trans-2,8-bis(trifluoromethyl)-4-((2R,3R)-3-vinylloxiran-2-yl)quinoline (2.86). A suspension of methyltriphenylphosphonium iodide (90 mg, 0.222 mmol) in THF (1 mL) was cooled to -78 °C before being treated with n-butyllithium (89 µL, 0.222 mmol, 2.5 M in hexanes). A yellow solution developed that was stirred for 1 h. Then, a solution of epoxy aldehyde 2.85 (50 mg, 0.143 mmol) in THF (2 mL) was added via cannula to the solution of ylide. A brown color immediately developed. The mixture was stirred at -78 °C for 1 h and then at room temperature for 3 h. The reaction was quenched with methanol (10 drops), the resulting mixture was partitioned between Et₂O (20 mL) and H₂O (20 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (2 x 10 mL), and the combined organic extracts were washed with saturated aqueous NH₄Cl, dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (20% EtOAc/80% hexanes) gave a light-yellow solid (62%). ¹H NMR (CDCl₃, 400MHz): δ 8.27 (d, 1H, J = 8.4 Hz), 8.18 (d, 1H, J = 8.4 Hz), 7.79-7.75 (m, 2H), 5.90-5.81 (m, 1H), 5.64 (d, 1H, J = 11.2 Hz), 5.50 (d, 1H, J = 10.4 Hz), 4.43 (app. s, 1H), 4.39 (app. s, 1H).
N-(but-3-en-1-yl)-4-methylbenzenesulfonamide (2.87). This compound was prepared according to the literature procedure starting with 3-butenenitrile.[93, 94] $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ 7.72 (d, 2H, $J = 6.4$ Hz), 7.29 (d, 2H, $J = 6.4$ Hz), 5.65-5.45 (m, 1H), 5.07-4.99 (m, 1H), 4.38 (s, NH), 3.01 (t, 2H, $J = 6.4$ Hz), and 2.20 (tq, 2H, $J = 1.2$ Hz, 6.8 Hz).

(3-azidopropyl)triphenylphosphonium bromide (2.94). Phosphonium salt 2.94 was prepared according to literature precedent.[88] Compound 2.94 was obtained as a white solid and used as is. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.88-7.69 (m, 15 H), 4.02-3.94 (m, 2 H), 3.84 (apparent t, $J = 6.5$ Hz, 2 H), 1.95-1.87 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 135.3 (d, $J = 2.1$ Hz), 133.7 (d, $J = 10.4$ Hz), 130.7 (d, $J = 12.5$ Hz), 117.9 (d, $J = 85.6$ Hz), 50.8 (d, $J = 17.6$ Hz), 22.7 (d, $J = 3.1$ Hz), 20.21 (d, $J = 52.1$ Hz); ESI-MS m/z calcd for C$_{21}$H$_{21}$BrN$_3$P (M): 346.2, found: 346.2.

4-((2R,3R)-3-((Z)-4-azidobut-1-en-1-yl)oxiran-2-yl)-2,8-bis(trifluoromethyl)-quinoline (2.96). A suspension of 2.94 (69 mg, 0.20 mmol) in THF (3 mL) was cooled to -
78 °C before being treated with potassium hexamethyldisilazide (440 µL, 0.22 mmol, 0.5 M in toluene). A yellow suspension developed that was stirred for 1 h. Then, a solution of epoxy aldehyde 2.85 (57 mg, 0.17 mmol) in THF (2 mL) was added via cannula to the solution of ylide. A brown color immediately developed. The mixture was stirred at -78 °C for 1 h and then at room temperature for 2 h. The reaction was quenching MeOH (10 drops), the resulting mixture was partitioned between Et₂O (20 mL) and H₂O (20 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (2 x 10 mL), and the combined organic extracts were washed with saturated aqueous NH₄Cl, dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (15% EtOAc/85% hexanes) gave a light-yellow oil consisting of a 5:1 mixture of inseparable E/Z double bond isomers of 122 (40.9 mg, 60%). ¹H NMR (CDCl₃, 400MHz):

δ 8.32-8.18 (m, 2 H, [containing a d at δ 8.30, J = 8.4 Hz, and a d at 8.21, J = 6.8 Hz]), 7.86-7.75 (m, 2 H), 6.12-5.90 (m, 1 H), 5.69-5.51 (m, 1 H, [containing an apparent dd at δ 5.65, J = 7.6, 15.6 Hz]), 4.50-4.45 (m, 1 H), 3.65-3.61 (m, 1 H), 3.45-3.31 (m, 2 H), 2.51-2.45 (m, 2 H); ¹³C NMR (CDCl₃, 75 MHz): 146.0, 143.3, 134.2, 134.1, 129.14, 129.08, 128.8, 128.5, 127.6, 127.2, 127.0, 126.9, 125.2, 122.9, 121.6, 119.2, 113.3, 62.3, 58.6, 56.7, 56.5, 50.6, 32.1, 27.7; ESI-MS m/z calcd for C₁₇H₁₂F₆N₄NaO (M + Na): 425.1, found: 425.1.
(S)-tert-butyl 2-((R)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate (2.101). Wittig product 2.96 (63 mg, 0.22 mmol) was dissolved in THF (10 mL) and water (~5 drops) and treated with solid triphenylphosphine (64 mg, 0.24 mmol). After being heating to reflux for 2 h, di-tert-butyl dicarbonate (48 mg, 0.22 mmol) was added. Stirring was continued an additional 1 h at the reflux temperature. The mixture was then cooled to room temperature and partitioned between Et₂O (10 mL) and H₂O (10 mL). The layers were separated, and the aqueous layer was extracted with additional Et₂O (10 mL). After drying over magnesium sulfate and filtering, the organic layers were concentrated in vacuo. Flash chromatography over silica gel (20% EtOAc/80% hexanes) gave 2.101 as a colorless oil (58 mg, 72%). ¹H NMR (CDCl₃, 400MHz): δ 8.88-8.72 (m, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 8.00 (s, 1 H), 7.82-7.73 (m, 1 H), 6.08-5.99 (m, 1 H), 5.92-5.85 (m, 1 H), 5.35-5.29 (m, 1 H), 4.90-4.81 (m, 1 H), 4.13-3.95 (m, 1 H), 3.61-3.48 (m, 1 H), 2.90-2.72 (m, 1 H), 2.17-2.04 (m, 1 H), 2.03-1.88 (m, 1 H), 1.51 (apparent br s, 9 H); ¹³C NMR (CDCl₃, 750 MHz): 150.4, 143.6, 130.1, 128.93, 128.87, 128.5, 127.2, 126.8, 125.4, 121.5, 115.4, 80.9, 73.1, 56.6, 39.4, 28.4, 24.5; ESI-MS m/Z calcd for C₂₂H₂₂F₆N₂NaO₃ (M + Na): 499.1, found: 499.1.

(ESI-MS)

(S)-tert-butyl 2-((R)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy)methyl)-piperidine-1-carboxylate (N-Boc-mefloquine). To a stirred solution of 2.101 (56 mg,
0.12 mmol) in EtOAc (10 mL) was added palladium catalyst (5% Pd over alumina, 43 mg, 0.02 mmol Pd). The mixture was placed under a balloon of hydrogen gas, and stirring was continued for 24 h. After removal of the balloon, the mixture was filtered through a pad of Celite using EtOAc (50 mL), and the solution was concentrated in vacuo. Flash chromatography over silica gel (10% EtOAc/90% hexanes) gave the hydrogenated product as a colorless solid (55 mg, quantitative). $^1$H NMR (CDCl₃, 500MHz): δ 8.60 (d, J = 8.5 Hz, 1 H), 8.14 (d, J = 7 Hz, 1 H), 8.00 (s, 1 H), 7.72 (t, J = 8 Hz, 1 H), 5.76 (apparent s, 1 H), 4.32-4.23 (m, 1 H), 3.88-3.76 (m, 1 H), 3.48-3.37 (br s, 1 H), 3.25-3.16 (m, 1 H), 1.92-1.20 (m, 15, [containing a s at δ 1.28]); $^{13}$C NMR (CDCl₃, 125 MHz): 155.7, 151.3, 148.4, 148.1, 144.0, 129.7, 129.3, 129.01, 128.97, 128.92, 128.88, 128.5, 127.3, 127.2, 124.8, 122.7, 122.6, 120.4, 115.82, 115.80, 80.5, 71.7, 57.2, 42.2, 28.3, 24.5, 23.0, 20.1; ESI-MS m/z calcd for C₂₂H₂₄F₆N₂NaO₃ (M + Na): 501.2, found: 501.2.

(+)-Mefloquine hydrochloride (2.1). The N-Boc protected mefloquine (25 mg, 0.05 mmol) was dissolved in CH₂Cl₂ (2.7 mL) and treated dropwise with neat trifluoroacetic acid (300 µL). After stirring for 1 h, the reaction was quenched with saturated NaHCO₃ solution (1 mL). The mixture was partitioned between CH₂Cl₂ (10 mL) and H₂O (1 mL) layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL). After drying over magnesium sulfate and filtering, the organic layers
were concentrated in vacuo to give the free base as a colorless solid and the solid was used without further purification.

The free base was immediately taken up into Et₂O (3.5 mL), and the solution was treated with a solution of hydrogen chloride in Et₂O (2.0 M, 500 μL, 1 mmol). The solution became cloudy after 30 min. Removal of the solvent in vacuo gave mefloquine hydrochloride as a white solid (18 mg, 89% over two steps). Spectral data was identical to previously reported data in the literature.[67]

\[
\text{(E)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)prop-2-en-1-ol (2.110).}
\]

To a solution of aldehyde 2.18 (375 mg, 1.27 mmol) in THF (25 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (490 mg, 1.40 mmol). The resulting solution was then refluxed for 30 minutes and cooled down to room temperature. Concentration of the solution gave a white suspension, which was partitioned between DI water (50 mL) and Et₂O (25 mL). The layers were separated, and the aqueous layer was extracted twice more with ether (2 x 25 mL). The combined extracts were dried over MgSO₄ and concentrated in vacuo to give a white solid. This solid was then dissolved in EtOAc (5 mL) and filtered through a plug of silica gel using 20% EtOAc/80% hexanes (250 mL). Concentration of the filtrate gave the desired α,β-unsaturated ester, which was immediately taken forward. \text{'H NMR (CDCl₃, 400MHz): δ 8.41 [m, 2H, containing a d at}}
δ 8.40 (J = 8.6 Hz) and a d at δ 8.37 (J = 16 Hz)], 8.21 (d, 1H, J = 8.6 Hz), 7.92 (s, 1H), 7.79 (t, 1H, J = 8 Hz, 4.33 (q, 2H, J = 7.2 Hz), and 1.37 (t, 3H, J = 6.8 Hz).

The ester was dissolved in toluene (20 mL) and cooled to -78 °C. This solution was then treated with diisobutylaluminum hydride (2.80 mL, 2.80 mmol, 1.0 M in toluene). The solution was allowed to warm to 0 °C and stirred for 2 hours. The reaction was quenched with the addition of 2 mL 10% KOH and 15 mL of DI water. Extraction of the resulting biphasic mixture with CH₂Cl₂ (3 x 20 mL) followed by drying over MgSO₄ and concentration gave the allylic alcohol as an off-white solid. The alcohol was purified using flash chromatography (40% EtOAc/60% hexanes) over silica gel (347 mg, 87% over two steps).

1H NMR (CDCl₃, 500MHz): δ 8.36 (d, 1H, J = 8.5 Hz), 8.14 (d, 1H, J = 7 Hz), 7.83 (s, 1H), 7.69 (t, 1H, J = 8.0 Hz), 7.39 (dt, 1H, J = 15.5 Hz, 2 Hz), 6.68 (dt, 1H, J = 15.5 Hz, 4.5 Hz), 4.52 (dd, 2H, J = 4.5 Hz, 2.0 Hz), and 1.76 (bs, OH). 13C NMR (CDCl₃, 125 MHz): 148.68, 145.81, 144.32, 138.50, 129.67, 129.48, 129.24, 128.19, 127.36, 127.16, 124.84, 123.45, 114.33, and 63.10; ESI-MS m/Z calcd for C₁₄H₁₉F₆NO (M + H): 322.07, found: 322.1.

**Sharpless Epoxidation of Allylic Alcohol 2.110 (2.111).** A 50 mL round-bottom flask was purged with argon and cooled to -20 °C. To this flask was added 25 mL of anhydrous CH₂Cl₂, 195 µL (0.640 mmol) of Ti(i-O-iPr)₄, 200 mg of crushed molecular sieves, and 148 µL (0.720 mmol). The resulting mixture was stirred for 5 minutes at -20
°C, and 500 mg of solid allylic alcohol 2.110 (1.60 mmol) was added. Stirring was continued for 15 minutes. Next, 5.93 mL of t-BuOOH in toluene (14.90 mmol, 2.51 M) was added slowly to the reaction mixture. Stirring was continued for 48 hours at -20 °C.

The reaction was quenched by the addition of 2 mL of 30% NaOH in brine. The flask was removed from the cold bath and diluted with 10 mL of Et₂O. After stirring an additional 15 minutes, a scoop of solid MgSO₄ and celite were added. Stirring was continued an additional 10 minutes before the mixture was filtered through a pad of celite. Removal of the solvents in vacuo gave a yellow oil that consisted of the epoxy alcohol and left over peroxide. The alcohol could be purified using flash chromatography over silica gel (40% EtOAc/60% hexanes). Spectral characteristics were identical to those reported for 2.111. Chiral HPLC separation showed a 93:7 mixture of enantiomers in 83% yield (See Figure 23).

![Figure 27. Chiral HPLC traces for racemic epoxy alcohol made using m-CPBA on 2.110 (A), the Sharpless epoxidation product (B), and the product of the ACC-mediated Darzens reaction (C)](image-url)
Appendix – X-Ray Crystallography Data

A colorless stable crystal, 0.40 x 0.18 x 0.08 mm in size, was mounted on a 0.1 mm glass capillary with oil. The crystal was cooled to 150 K using an Oxford Cryostream 600 low temperature device. Crystal data were collected with a Bruker platform diffractometer equipped with a Smart6000 detector[95] (graphite-monochromated, MoKa = 0.071073 nm). Data were integrated using SAINT 6.45A[96]; correction for absorption, decay and inhomogeneity of the X-ray beam were applied using SADABS.[97] A partial structure solution was obtained by direct methods, and the remaining non-hydrogen atoms were located with difference Fourier techniques showing disorder in one of the CF3 group. As a result, SADI geometrical restraints were used to restrain the distances between the disordered Fluorine atoms as well as C-F bonds in each of the different CF3-groups to be similar. All non-disordered atoms were refined with anisotropic atomic displacement parameters. Calculations were performed using SHELXTL 6.12.[98] All unique reflections were used for the refinement by full matrix least squares on F2. Views of the structures were prepared using Diamond 3.2c.[99]
Table 13. X-ray crystallographic information for epoxy hydrazone 2.54

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A specimen of C$_{22}$H$_{30}$N$_2$O$_3$, approximate dimensions 0.160 mm x 0.410 mm x 0.460 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The integration of the data using an orthorhombic unit cell yielded a total of 35155 reflections to a maximum $\theta$ angle of 25.89° (0.81 Å resolution), of which 2371 were independent (average redundancy 14.827, completeness = 99.2%, $R_{int} = 3.80\%$, $R_{sig} = 1.45\%$) and 1953 (82.37%) were greater than 2$\sigma$(F$^2$). The final cell constants of $a = 6.9150(4)$ Å, $b = 12.5529(8)$ Å, $c = 24.5201(14)$ Å, volume = 2128.4(2) Å$^3$, are based upon the refinement of the XYZ-centroids of 1547 reflections above 20 $\sigma$(I) with 4.782° < $\theta$ < 44.52°. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9655 and 0.9878.

The structure was solved and refined using the Bruker SHELXTL Software Package[98], using the space group P 21 21 21, with $Z = 4$ for the formula unit, C$_{22}$H$_{30}$N$_2$O$_3$. The final anisotropic full-matrix least-squares refinement on F$^2$ with 242 variables converged at $R1 = 3.91\%$, for the observed data and $wR2 = 10.87\%$ for all data. The goodness-of-fit was 1.054. The largest peak in the final difference electron density synthesis was 0.224 e/Å$^3$ and the largest hole was -0.196 e/Å$^3$ with an RMS deviation of 0.030 e/Å$^3$. On the basis of the final model, the calculated density was 1.156 g/cm$^3$ and F(000), 800 e$^-$. 

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### Table 14. X-ray crystallographic information for the *anti* aldol product with ORTEP diagram

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<tr>
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<td>c = 24.5201(14) Å, (\gamma = 90.00^\circ)</td>
</tr>
<tr>
<td><strong>V (Å\textsuperscript{3})</strong></td>
<td>2128.4(2)</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>D\textsubscript{calc} (Mg/m\textsuperscript{3})</strong></td>
<td>1.156</td>
</tr>
<tr>
<td><strong>abs coeff (mm\textsuperscript{-1})</strong></td>
<td>0.077</td>
</tr>
<tr>
<td><strong>total no. of reflns</strong></td>
<td>35155</td>
</tr>
<tr>
<td><strong>no. of unique reflns</strong></td>
<td>2371</td>
</tr>
<tr>
<td><strong>no. params refined/restrained</strong></td>
<td>242/0</td>
</tr>
<tr>
<td><strong>R\textsubscript{int}</strong></td>
<td>0.0518</td>
</tr>
<tr>
<td><strong>crystal size (mm\textsuperscript{3})</strong></td>
<td>0.160 ↔ 0.410 ↔ 0.460</td>
</tr>
<tr>
<td><strong>color and habit</strong></td>
<td>colorless plate</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on (F^2)</strong></td>
<td>1.054</td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2\sigma(I)]</strong></td>
<td>(R1 = 0.0391), (wR2 = 0.0990)</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>(R1 = 0.0518), (wR2 = 0.1087)</td>
</tr>
<tr>
<td><strong>max, min (\Delta\rho) (e/Å\textsuperscript{3})</strong></td>
<td>0.224, -0.196</td>
</tr>
</tbody>
</table>
A specimen of C_{22}H_{30}N_{2}O_{3}, approximate dimensions 0.050 mm x 0.240 mm x 0.260 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The integration of the data using a monoclinic unit cell yielded a total of 15398 reflections to a maximum θ angle of 25.15° (0.84 Å resolution), of which 1945 were independent (average redundancy 7.917, completeness = 99.0%, R_{int} = 8.33%, R_{ag} = 4.89%) and 1336 (68.69%) were greater than 2σ(F^2). The final cell constants of a = 7.5478(11) Å, b = 9.9201(14) Å, c = 13.996(2) Å, β = 100.024(10)°, volume = 1032.0(3) Å^3, are based upon the refinement of the XYZ-centroids of 2025 reflections above 20σ(I) with 5.755° < 2θ < 35.57°. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9797 and 0.9961.

The structure was solved and refined using the Bruker SHELXTL Software Package[98], using the space group P 1 21 1, with Z = 2 for the formula unit, C_{22}H_{30}N_{2}O_{3}. The final anisotropic full-matrix least-squares refinement on F^2 with 245 variables converged at R1 = 4.43%, for the observed data and wR2 = 11.27% for all data. The goodness-of-fit was 1.027. The largest peak in the final difference electron density synthesis was 0.163 e/Å^3 and the largest hole was -0.143 e/Å^3 with an RMS deviation of 0.043 e/Å^3. On the basis of the final model, the calculated density was 1.192 g/cm^3 and F(000), 400 e^-.
Table 15. X-ray crystallographic information for the syn aldol product with ORTEP diagram

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>empirical formula</td>
<td>C_{22}H_{30}N_{2}O_{3}</td>
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<tr>
<td>fw</td>
<td>370.49</td>
</tr>
<tr>
<td>T (K)</td>
<td>296(2)</td>
</tr>
<tr>
<td>λ (Å)</td>
<td>0.71073</td>
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<tr>
<td>crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>space group</td>
<td>P 2₁</td>
</tr>
<tr>
<td>unit cell dimensions</td>
<td>a = 7.5478(11) Å, α = 90.00°</td>
</tr>
<tr>
<td></td>
<td>b = 9.9201(14) Å, β = 100.02(1)°</td>
</tr>
<tr>
<td></td>
<td>c = 13.996(2) Å, γ = 90.00°</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>1031.95</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>D_{calc} (Mg/m³)</td>
<td>1.192</td>
</tr>
<tr>
<td>abs coeff (mm⁻¹)</td>
<td>0.079</td>
</tr>
<tr>
<td>total no. of reflns</td>
<td>15398</td>
</tr>
<tr>
<td>no. of unique reflns</td>
<td>1945</td>
</tr>
<tr>
<td>no. params refined/restrained</td>
<td>245/1</td>
</tr>
<tr>
<td>R_{int}</td>
<td>0.0833</td>
</tr>
<tr>
<td>crystal size (mm³)</td>
<td>0.260 ↔ 0.240 ↔ 0.050</td>
</tr>
<tr>
<td>color and habit</td>
<td>colorless plate</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.027</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>R1 = 0.0443, wR2 = 0.0983</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0759, wR2 = 0.1127</td>
</tr>
<tr>
<td>max, min Δρ (e⁻/Å³)</td>
<td>0.163, -0.143</td>
</tr>
</tbody>
</table>
Bibliography


Biography

John Derrick Knight was born May 1st, 1985 in Charleston, South Carolina. His hometown is Summerville, South Carolina. After attending and graduating Summerville High School with honors in 2003, he graduated magna cum laude with a B.S. in Chemistry and a minor in Meteorology from the College of Charleston in May 2007. While there, he performed undergraduate research with Dr. Charles F. Beam on the strong base synthesis of heterocycles. He also received various awards, including Departmental Honors (2007), the Outstanding Undergraduate Chemistry Major award (2007), the Major Field Test award (2007), the Hypercube Scholar award (2007), the Outstanding Undergraduate Research award (2006 and 2007), and the South Carolina Palmetto Fellows Scholarship (2003-2007).

In August of 2007, he began work towards his doctoral degree in synthetic organic chemistry at Duke University. During this period he worked in the synthetic organic and methodology lab of Dr. Don Coltart. During the course of his studies, he was a recipient of the Pelham Wilder Fellowship. His published works include “Asymmetric Total Synthesis of the Antimalarial Drug (+)-Mefloquine Hydrochloride via Chiral N-Amino Cyclic Carbamate Hydrazones” in Organic Letters (2011) with more on the way pertaining to the ACC-mediated aldol addition reaction and the asymmetric total synthesis of (-)-mefloquine hydrochloride.