Investigating the Mechanism to Enantioselective Induction of the “Interrupted” Feist-Bénary Reaction

by

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Abstract

This thesis describes the development of methodology on expanding the scope and investigating the mechanism to enantioselective induction of the catalytic, asymmetric Interrupted Feist-Bénary (IFB) reaction. We demonstrate the development of a new IFB reaction using 4-hydroxycoumarin as the nucleophile to synthesize a highly functionalized hydroxydihydrofuranoid with 60 to 90% yield. Based on previous work on the IFB reaction, pyrimidinyl bis-quinidine cinchona alkaloids catalysts were screened in hopes of producing the IFB product with synthetically useful enantioselectivities. At this point, we found that the addition of a 6-methoxypyridin-2-yl group on the front group of the catalyst increased the enantioselectivity to 29% ee.

In order to further understand the IFB reaction, we have implemented computational studies into our work and reinvestigated the classic IFB reaction. We first gauged the effects on the 6-position of the pyrimidinyl ring and synthesized a new set of catalysts. It was discovered experimentally and computationally that a chlorine at the 6-position had the highest level of enantioselective induction followed by a methoxy then a quinidine. We then probed the effects of the front group through a series of competition reactions and computational studies, where we discovered each catalyst’s mechanism to inducing enantioselectivity. In this thesis, we will report that our cinchona alkaloid catalysts increase the energy of the $Si$ face attack. However, certain front groups also lower the energy of the $Re$ face attack to further increase enantioselectivity. Meanwhile, other, less effective, catalysts maintain the $Re$ attack energy to be similar to the achiral pathway while destabilizing the $Si$ attack.
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1. Introduction

1.1 Chirality and its Applications in Biological Systems

The chemical and physical properties of a compound are often dependent on the spatial arrangement of the atoms that constitute the molecule of interest. Isomerism, or differences in molecular geometries, leads to these differences in physicochemical properties of compounds with the same chemical formula. There are two major forms of isomerism: structural isomerism and stereoisomerism, and the latter is dictated by a geometric property of the molecule called chirality. Certain molecules that are non-superimposable with their mirror image are said to be chiral, and chirality often originates from one or more carbon atoms in the molecule with four different substituents, otherwise known as a chiral center. At this center, two substituents are interchanged, leading to a stereoisomer. This type of chirality, aptly named point chirality, is the most common manifestation of chirality in organic chemistry. Stereoisomers are quite interesting since they have the exact same physical properties, e.g. melting point or boiling point, and are inseparable using standard achiral chromatographic techniques; however, two stereoisomers will rotate polarized light differently, can be separated through chiral chromatography, and, most importantly, can have very different biochemical properties.

![Figure 1: Alanine has two stereoisomers, otherwise known as enantiomers.](image-url)
Stereoisomers that have different configurations at all chiral centers are called enantiomers. These are distinguished from diastereomers, stereoisomers where only some, but not all, chiral centers have different configurations. However, diastereomers of one molecule could also have its own enantiomers, resulting in a multitude of possible stereoisomers for one compound. More precisely, according to the Le Bel-Van ’t Hoff rule, the theoretical maximum number of possible stereoisomers for a compound of \( n \) stereocenters is equal to \( 2^n \) stereoisomers. This is best exemplified by diastereomers threose and erythrose and their respective enantiomers, each having different (if any) functions in the body. D-erythrose, for example, is an important intermediate in carbohydrate metabolism, as it is either involved in the pentose phosphate pathway to yield fructose-6-phosphate or is used to synthesize aromatic amino acids.

**Figure 2:** Threose has two stereocenters and four possible stereoisomers.
There are three standard methods of naming chiral compounds: the molecule can be assigned through absolute configuration using the Cahn-Ingold-Prelog (CIP) priority rules or the molecule’s optical rotation, or the molecule can be assigned through relative configuration, where the molecule is being related to D-glyceraldehyde. While the latter two are useful, the CIP priority rules are of further use in predicting enantioselective reactions of prochiral molecules and thus will be mentioned more frequently in this thesis.

A molecule’s absolute configuration can be empirically determined through optical rotation, which depends on whether the specific enantiomer rotates the plane of polarized light clockwise (+) or counterclockwise (-). The CIP priority rules, on the other hand, are based on the atomic number of the atoms constituting the chiral center’s substituents. With the lowest priority substituent away from the viewer, if the substituents decrease in priority order in a clockwise manner, then the molecule is assigned to be the $R$ enantiomer—the opposite is the $S$ enantiomer. This rule can be extended to prochiral molecules, planar molecules that can be turned chiral using one reaction, where the $Re$ face of the molecule is the face where substituents are decreasing in priority in a clockwise manner. Suitably, the $Si$ face is its opposite.

Scheme 1: The two different enantiomers of glyceraldehyde
The relative configuration of molecules is a useful convention, particularly in biological systems. Most, if not all, naturally occurring amino acids are \textit{L}-amino acids, generating a handedness in protein structure and thus a chiral environment for molecules that interact with proteins. Conversely, most carbohydrates involved in central metabolism and formation of cell walls are \textit{D}-carbohydrates, the most prevalent one being \textit{D}-glucose.

Because organisms are chiral at the molecular level, targeting cellular pathways using small molecules and drugs in hopes of treating diseases or promoting well-being inherently requires stereoselective control when synthesizing these molecules. Often times, the mechanism of action of these drugs is through inhibition of a specific enzyme. For instance, COX-2, an enzyme involved in the production of prostaglandins from arachidonic acid in response to pain, is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.\textsuperscript{1} This, in turn, reduces inflammation and relieves pain. Ibuprofen is a chiral molecule; however, there are no reported side effects of taking either the \textit{R} or \textit{S} isomers of ibuprofen, although (\textit{S})-ibuprofen is the bioactive enantiomer.\textsuperscript{2} Therefore, ibuprofen can be sold as a racemic mixture, where equal quantities of (\textit{R})-ibuprofen and (\textit{S})-ibuprofen are included. But, there are several notable cases of racemic drugs doing more damage than good. The most notorious case was the birth defect crisis in the late 1950’s to early 1960’s, where pregnant mothers taking a racemic mixture of thalidomide for morning sickness gave birth to infants with severe cases of limb malformation.\textsuperscript{3} It was then eventually reported that (\textit{S})-thalidomide was the teratogenic enantiomer while (\textit{R})-thalidomide was the sedative enantiomer. Surprisingly, thalidomide is still used
nowadays in cancer therapy, and although asymmetric syntheses of thalidomide have been proposed, at physiological pH, the molecule is readily epimerized. Therefore, thalidomide may be used by women only if ensured that no child will be conceived.

![Scheme 2: Thalidomide can epimerize in the body, producing both enantiomers.](image)

The effects of the birth defect crisis are still tangible in the pharmaceutical industry and in the field of synthetic organic chemistry. Due to potentially dangerous side effects of chiral small molecules and their enantiomers, the FDA had strengthened regulations concerning the synthesis and sale of these drugs. The pharmaceutical industry does produce these compounds at large enough scales so that chiral resolution of enantiopure compounds from racemates is possible; however, this method is inefficient since fifty percent of the total product is wasted. As a result, in order to maximize overall yields, research on potential drug targets in modern synthetic chemistry tend to focus on synthesizing only one enantiomer of a target molecule. This is otherwise known as asymmetric synthesis.

1.2 Methods in Asymmetric Synthesis

1.2.1 Chiral Pool Synthesis and Diastereoselective Addition

In asymmetric synthesis, intermediates are submitted to further reactions in hopes of maintaining the stereochemistry while possibly adding new chiral centers. As daunting as that task may be, there are numerous ways maintain the stereochemistry. Furthermore, chiral centers can be introduced through well-studied
techniques including diastereoselective control, the addition of chiral auxiliaries, and, most excitingly, the use of specialized asymmetric catalytic reactions.

However, how is the first chiral center introduced to a molecule? There are several approaches to introducing new chiral centers, and in this thesis, we will later delve into a reaction that acts as a transformation to set up cores of complex natural products while introducing a chiral center from achiral sources. But, there are also other ways around it, a rather straightforward example of which is chiral pool synthesis where the total synthesis of a molecule begins with a readily available, chiral molecule. This strategy was used by Nicolau, et al. in the total synthesis of (-)-Platensimycin, a metabolite isolated from Streptomyces platensis with promising antibacterial properties. The source of chirality was the starting material, (R)-(−)-carvone, a compound commonly found in spearmint.

![Scheme 3](image)

**Scheme 3:** Naturally occurring chiral molecules can be used in asymmetric syntheses.

Using a chiral starting material, we then have a new method of introducing new stereocenters: through diastereoselective control of a direct addition to a carbonyl using a hydride or an organometallic compound. This implicates that neighboring chiral centers can stereochemically control further reactions and thus favor a specific diastereomer as a result of stereoelectronic effects, which can be
predicted and analyzed by transition state modeling. The Felkin-Anh model of carbonyl addition can predict the resulting diastereomer for a 1,2- or 1,3-induced diastereoselective reaction through an analysis of the transition state. In hydride reductions for instance, Felkin-Anh products have been reported to be obtained by the use of nucleophilic reducing agents. Meanwhile, anti Felkin-Anh reductions can be performed using electrophilic reducing reagents such disiamyl borane.

Scheme 4: Felkin-Anh reductions are observed with nucleophilic reducing agents.\(^5\)

In the Felkin-Anh model, the incoming hydride attacks opposite of the large group at an angle; however, two transition states that lead to two diastereomers are expected. However, as depicted in Scheme 4, the favored transition state prevents steric interactions between the incoming hydride and the methyl group as it approaches the carbonyl at the Bürgi-Dunitz angle, which is proposed to be the most optimal angle of trajectory for a nucleophile attack on a prochiral, trigonal center in a molecule. Therefore, because of steric interactions in the transition state, only one of the diastereomers is favored.
**Scheme 5:** The Anti Felkin-Anh product is favored when using disiamyl borane.\(^5\)

Meanwhile, it was observed that the Anti Felkin-Anh product was obtained when reducing the ketone above using disiamyl borane. Although there is an unfavorable steric interaction between the incoming hydride and the methyl group in the depicted transition state, this is a far more favorable steric interaction than in the Felkin-Anh model where the disiamyl borane moiety clashes with the methyl group. The use of an electrophilic reducing agent implies that the reducing agent must coordinate with the carbonyl oxygen first; therefore, the conformation of the molecule has to change to prevent the boron-methyl steric interaction in favor of the boron-hydrogen steric interaction. This then primes the carbonyl to be attacked at one face, the \(Si\) face in this case, favoring the synthesis of one diastereomer over the other.\(^5\)

The control over diastereoselectivity using nearby chiral centers have been extended to include heteroatoms in the 1,2- and the 1,3-positions. Most notably, 1,2- or 1,3-hydroxyl groups are quite useful in inducing diastereoselectivity through chelation.
Scheme 6: 1,2-hydroxyl groups can control diastereoselectivity through chelation.\textsuperscript{6}

Again, the hydride attack avoids unfavorable steric strain with the methyl group in the above transition state. However, it is important to note that the conformation of transition state in the chelate-controlled mechanism is fixed by chelation, which also stabilizes the transition state. Thus, the \textit{anti}-diastereomer is favored. The scope of 1,2-induced chelate control has been extended to include organometallic additions, giving us a powerful method with which we can create a new carbon-carbon bond stereoselectively depending on the reaction conditions.

Throughout this thesis, we will often refer back to how the stabilization of the transition state and the pathway to which a reaction commits can determine the reactivity and selectivity of a given reaction. For example, we can analyze the diastereoselectivity of an organometallic addition through 1,3-chelate control as an example of this phenomenon.
In 1983, Still, et al. performed the direct addition of dimethylcuprate to β-alkoxyaldehydes in chelating conditions, and the above reaction was observed to yield the product with >20:1 dr. It was hypothesized that this reaction goes through a chair-like transition state, which is stabilized by the chelating metal and the solvent of choice. Then, the observed diastereoselective addition of the alkyl group on the more favored Si face was hypothesized to be a result of the transition state being pyramidalized into a chair conformation where the new methyl group is added equatorially. As a result, this is an excellent example as to how the stabilization of the transition state and the resulting, more stable intermediate can work in tandem to give the observed reactivity and selectivity of a reaction.

1.2.2 Chiral Auxiliaries

While diastereoselective control over a reaction through an existing chiral center is rather useful in syntheses, they require chiral starting materials. Often times, however, we begin with achiral sources. Chiral auxiliaries are chiral groups that can be added onto a prochiral compound to induce selectivity in further reactions. The auxiliary is then subsequently removed and can be recovered for future use. There are various early examples of chiral auxiliaries including (-)-8-phenylmenthol and BINOL, the former of which was used in Corey’s synthesis of prostaglandins and the latter was used in Yamamoto’s synthesis of limonene.
Scheme 8: Corey’s use of (-)-8-phenylmenthol on the Diels-Alder reaction.\(^8\)

(-)-8-phenylmenthol was synthesized by first treating (S)-(-)-pulegone with phenylmagnesium bromide in the presence of cuprous chloride. The mixture eventually equilibrated to give the anti-diastereomer, which was submitted to a reduction. The alcohol, as expected, equilibrated to the equatorial alcohol to yield the enantiorich chiral auxiliary, which is then added to acryloyl chloride. The resulting acrylate was subsequently submitted to the Diels-Alder reaction with 5-benzylxoxymethylcyclopentadiene in the presence of aluminum trichloride. This gave a highly selective endo adduct with 89% yield.\(^8\) It was theorized that the other face of the olefin was blocked by the chiral auxiliary to afford the observed stereoisomer.

On the other hand, for the synthesis of limonene, (R)-1,1’-binaphthyl-2,2’-diol (R-BINOL) was used as a chiral auxiliary in the presence of (2,4,6-tri-tert-butylphenoxy)isobutylaluminum triflate in CFCl\(_3\) with promising enantioselectivity.\(^9\)
Scheme 9: Yamamoto’s asymmetric synthesis of D-limonene using BINOL.\textsuperscript{9}

Since then, the scope of BINOL as a chiral auxiliary has been extended to include more reactions, typically diastereoselective alkylations. For example, (S)-BINOL was used as an auxiliary by Tanaka et al in the synthesis of unnatural amino acids through a glycine equivalent.\textsuperscript{10}

Scheme 10: Tanaka’s synthesis of D-alanine.

Although chiral auxiliaries have been used since 1975, they were best popularized by Evans, where he pioneered the use of oxazolidinones for stereoselective alkylations and Aldol reactions, especially in his classic synthesis of Cytovaricin in 1990.\textsuperscript{11}
Figure 3: Evans’s synthesis of Cytovaricin used oxazolidinone auxiliaries to perform the disconnections synthetically.\textsuperscript{11}

The spiro system in cytovaricin was synthesized by fusing two subunits (the C17-C21 subunit and the C25-C34 subunit) prepared through asymmetric Aldol reactions using oxazolidinones as chiral auxiliaries. For example, the C19-C21 Aldol product was synthesized using the \((1S, 2R)\)-norephedrine derived oxazolidinone \((X_N)\) using dibutylboron triflate to yield the \(syn\) adduct with 87\% yield.\textsuperscript{11}

\begin{center}
\includegraphics[width=0.8\textwidth]{figure3.png}
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**Scheme 11**: The Evans asymmetric Aldol reaction.

Previous studies on Evans’s asymmetric Aldol methodology had shown that the use of the \(X_N\) chiral auxiliary and dibutylboron triflate consistently yielded adducts with high \(syn\)-diastereoselectivity (<1\% \textit{anti}-adduct in the reaction mixture) and high enantioselectivity (>500:1 enantiomeric ratio, e.r.).\textsuperscript{12}
Scheme 12: Evans’s methodology yields Aldol adducts with >500:1 e.r. Boron enolates yield high syn-diastereoselectivity.\textsuperscript{12}

The mechanism through which the asymmetric Aldol reaction proceeds involves blocking one face of the molecule from nucleophilic attack to induce enantioselectivity. This ultimately depends on the stereochemistry of the auxiliary. For instance, while the norphedrine-derived oxazolidinone (X\textsubscript{N}) favors one enantiomer, the L-valine-derived oxazolidinone (X\textsubscript{V}) favors the other. Similarly, the L-phenylalanine-derived (X\textsubscript{P}) auxiliary favors the same enantiomer as X\textsubscript{V}, the D-phenylalanine-derived (X\textsubscript{D}) auxiliary favors the opposite.

The Aldol is especially important because it sets up two stereocenters, giving us a chance to control diastereoselectivity.\textsuperscript{13} While the Evans’ method of using boron enolates yielded syn-Aldol adducts, a method was developed by Oppolzer, et. al to yield the anti-Aldol adduct with high diastereoselectivity and enantioselectivity using a chiral auxiliary derived from camphorsultam.
Scheme 13: The use of Lewis acids gives high stereoselectivity.

Chiral auxiliaries have been discovered to be useful for a myriad of reactions. As such, they are commercially available for convenience, although they can be synthesized from their respective amino alcohols. In addition to their usefulness and availability, adding oxazolidinones to acyl chlorides is rather straightforward. Finally, there are several methods in cleaving oxazolidinones while generating useful functional groups, making this an essential tool in asymmetric synthesis.

Although there are several advantages to using chiral auxiliaries, adding and cleaving auxiliaries add steps to the synthesis, and there is an inherent decrease in the overall yield with every additional step. In other words, this process has poor atom economy along with consistently decreasing overall yield. As a result, several reactions have been optimized to be catalytic and asymmetric, introducing new stereocenters in a single step while using a limited amount of compounds.
1.2.3. Catalytic, Asymmetric Reactions

We begin our examples of catalytic, asymmetric reactions with a straightforward, nucleophilic attack of a carbonyl group, i.e. the introduction of a stereocenter through direct addition. The Corey-Itsuno reduction or the Corey-Bakshi-Shibata (CBS) reduction is a useful, asymmetric hydride addition that can be applied to a wide range of ketones. The facial selectivity of the CBS reduction depends on the difference in the size of the groups on the ketone, dictating which lone pair on the oxygen coordinates to the catalyst.

Scheme 14: The proposed mechanism for the CBS reduction. The lone pair syn to the smaller group coordinates to the boron, inducing facial selectivity.

Catalyzed reactions are attractive for several reasons. First, there is a relatively small loading of catalysts, typically from 5 mol% to 20 mol% loading, because of catalyst turnover. In addition, by finding conditions that eliminate background reactions, we can expect that the reaction would commit through a
pathway that involves the catalyst. Therefore, with the use of a chiral catalyst, the reaction must proceed through a mechanism with some level of enantioselective induction. As such, similar to the CBS reduction, a catalytic, asymmetric reaction was optimized for organometallic additions to aldehydes using a dialkyl zinc with titanium tetraisopropoxide (TTIP) and \(\alpha,\alpha,\alpha',\alpha'-\text{tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs).} \) The reaction is theorized to be mediated by the titanate formed in situ with the TADDOL, inducing high enantioselectivity.\(^{15}\)

![Scheme 15: A catalytic, asymmetric organometallic addition using TADDOLs.](image)

TADDOLs are derived from their respective enantiomers of tartaric acid, a common starting material for many chiral pool syntheses. Due to the availability of tartaric acid, many other organocatalysts are also derived from it. One of the best examples of this is the use of tartrate diesters for the Sharpless epoxidation.

In 1980, Sharpless and Katsuki published the first practical method to asymmetric epoxidation of an allylic alcohol using diethyl tartrate (DET), TTIP, and \(\tau\)-butyl hydroperoxide as an oxidizing agent.\(^{16}\) Later on, the scope of the Sharpless epoxidation was improved to include cis and trans disubstituted and trisubstituted
olefins, as well low molecular weight olefins using only catalytic amounts of DET (or diisopropyl tartrate, DIPT) and TTIP.\textsuperscript{17}

Scheme 16: The Sharpless epoxidation yields highly asymmetric epoxides.

While the Sharpless epoxidation is useful for a myriad of allylic alcohols, Jacobsen, et al. developed a complementary asymmetric reaction for the epoxidation of aryl or alkyl substituted olefins using bleach (NaOCl) as the oxidizing agent and salen-type ligands complexed with manganese(III) as the chiral catalyst.\textsuperscript{18}

Scheme 17: The Jacobsen epoxidation does not require allylic alcohols.

The mechanism to enantioselective induction for the Jacobsen epoxidation involves unfavorable steric interactions in the transition state for one facial attack, as seen in Scheme 18, rationalizing the observed enantioselectivity. Furthermore, the scope of the reaction was extended to include trisubstituted olefins and other
oxidizing agents such as iodomesitylene, also with high yields and enantioselectivity.\(^{19}\)

\begin{center}
\includegraphics[width=\textwidth]{scheme18.png}
\end{center}

**Scheme 18:** A proposed mechanism to the Jacobsen epoxidation.\(^{20}\)

In 1988, Jacobsen and Sharpless published the first paper on the asymmetric dihydroxylation of olefins with promising levels of enantioselectivity.\(^{18}\) Using catalytic amounts of osmium tetroxide with stoichiometric amounts of N-methylmorpholine N-oxide (NMO) as per the Upjohn dihydroxylation, the Sharpless asymmetric dihydroxylation uses cinchona alkaloids as a chiral ligand and is one of the earliest examples of using cinchona alkaloids as part of a catalytic system.

\begin{center}
\includegraphics[width=\textwidth]{scheme19.png}
\end{center}

**Scheme 19:** One of the earliest examples of the Sharpless asymmetric dihydroxylation.
Sharpless later developed a new method to improve the scope and process of the asymmetric dihydroxylation using a new class of ligands and catalytic system known as the AD-mix, which yielded highly asymmetric products for various substituted olefins with enantiomeric excesses ranging from 70% to >99.5%ee.\textsuperscript{21}

\begin{center}
\textbf{Scheme 20:} The Sharpless asymmetric dihydroxylation.
\end{center}

Kinetic studies on the Sharpless asymmetric dihydroxylation by Corey, et al. demonstrated that the bis-cinchona alkaloid catalyst acts somewhat like an enzyme.
binding pocket, which justifies the high enantioselectivity observed with this reaction. The nitrogen on the cinchona alkaloid coordinates to the osmium tetroxide source, and the dihydroxylation’s reactivity is dependent on the rotation of this Os-N bond. The equatorial oxygen atoms on the OsO₄ originally eclipse the C-N bonds on the quinuclidine moiety; therefore, the rotation along this C₃ axis yields more favorable, staggered quinuclidine•OsO₄ torsional interactions. According to the transition state model proposed by Corey, this rotation then augments the reactivity since this also spatially primes the oxygen atoms to produce the pentacoordinate transition state necessary for the reaction to proceed.

Scheme 21: Proposed transition state model using the (DHQD)₂PYDZ catalyst.

Finally, the favorable π-interactions between the allyl and 4-methoxybenzoate moieties from the starting material with the methoxyquinoline moieties from the cinchona alkaloid in the facial attack shown in Scheme 21 give rise to the high enantioselectivity for this particular reaction (98% ee). The other facial attack on the other hand would lack these interactions, resulting in a difference of transition state energies large enough for the reaction to commit to one pathway and theoretically selectively produce only one enantiomer. As a result, chiral catalysts are attractive since their use gives us this level of control for asymmetric synthesis.
While there are numerous classes of chiral organocatalysts that exist, such as thiourea catalysts and derivatives of TADDOLs and BINOL, we will primarily focus on catalysts based off of biomolecules. The cinchona alkaloids will be a major focus in this thesis, but proline catalysts will also be mentioned. In addition, many of these catalysts facilitate important carbon-carbon bond forming reactions and other reactions that functionalize molecules such as the epoxidation and dihydroxylation. However, we return to the Aldol reaction and Aldol-like reactions to explain a method with which a racemate can resolve to one enantiomer throughout the course of the reaction.

1.3 Dynamic Kinetic Resolution

One of the earliest examples of an asymmetric Aldol reaction was reported in 1971 by the Hajos and Parrish group and the Eder, Sauer, and Wichert group. The reaction is catalyzed by \((\alpha\)-proline and later was extended to related enolate reactions such as \(\alpha\)-alkylation, \(\alpha\)-aminations, the Mannich reaction, and the Michael addition.

![Scheme 22: The proposed mechanism for the proline-catalyzed Aldol.](image-url)
In the proposed mechanism, the proline bonds covalently to the carbonyl, forming an enamine. The carboxylic acid-ketone hydrogen bond sets the stereochemistry of the resulting alcohol as the Aldol reaction proceeds through a chair-like transition state. Since only one facial attack has these favorable interactions, high enantioselectivity is expected and observed. While this does not necessarily demonstrate that this reaction proceeds through dynamic kinetic resolution (DKR), it is a pioneering discovery for the Aldol reaction that paved the way for reactions that do proceed via DKR.


Dynamic Kinetic Resolution can be explained using the Curtin-Hammett Principle, which involves two rapidly interconverting intermediates each going to different products irreversibly. According to the Curtin-Hammett principle, the product ratio is dependent on the difference in energy barrier ($\Delta G^\ddagger$) to each product, not the difference in energy between the intermediates. Therefore, for DKR of the
Aldol reaction, reaction conditions can lead to racemization of chiral carbonyl compounds, forming the two rapidly interconverting intermediates. Depending on the mechanism through which the Aldol proceeds, one enantiomer reacts more quickly, i.e. has a lower energy transition state. A large difference in transition state energy would thus be indicated through a large product ratio (the e.r.).

Scheme 24: An NHC catalyzed Aldol-Lactonization via DKR.25

An Aldol-Lactonization was reported by Modal, et al. via DKR, where the racemization of the intermediate possibly give rise to two diastereomers. However,
for one enantiomer of the starting material, the Aldol transition state conformation would result in an unfavorable 1,3-interaction (interaction shown in intermediate). This would increase the energy barrier for that enantiomer to react, giving rise to the high diastereoselectivity via DKR.

![Scheme 25: Enantioselective, proline catalyzed Aldol via DKR.](image)

In 2005, Ward, et al. reported an example of a proline-catalyzed, asymmetric Aldol reaction. The enantiomer was synthesized with >98% ee using either (R)- or (S)-proline, and a racemic mixture of the starting material was recovered; therefore, Ward, et al. concluded that this particular Aldol reaction proceeded via DKR. They thus concluded that the (S)-enantiomer of the chiral aldehyde acceptor reacts much faster than the (R)-enantiomer, thus yielding the product enantioselectively.

As such, DKR is a powerful method in controlling both the reactivity and selectivity of a reaction while only depending on the difference in transition state energies. Nonetheless, transition states cannot be isolated nor can transition state energies be measured, and so transition state modeling can be arduous and investigating enantioselective induction is often highly empirical. However, with the advent of using computational chemistry to aid organic synthesis, kinetic-controlled reactions and kinetic resolutions can now be analyzed theoretically and can possibly help to predict enantioselectivity.
1.4 Cinchona Alkaloids and Computational Studies

Scheme 26: The cinchona alkaloids.

The cinchona alkaloids are compounds primarily obtained from species of Cinchona, a genus of flowering plants. Quinine, especially, has been widely used for human consumption as a bitter additive and as treatment against malaria. In 1853, Pasteur discovered that cinchona alkaloids were useful in racemic resolution, acting as a chiral resolving agent.\(^\text{27}\) However, cinchona alkaloids were not exploited for asymmetric reactions until 1912, when Bredig and Fiske discovered that quinine and quinidine catalyzed the reaction between HCN and benzaldehyde, which yielded optically active products albeit with a low enantiomeric excess.\(^\text{27}\) Nonetheless, they discovered that the cyanohydrins were of the opposite chirality to each other depending on which cinchona alkaloid was used.

Research on asymmetric induction using cinchona alkaloids eventually began to flourish around the late 1970’s after significant studies were conducted by Wynberg, et al. Soon after, cinchona alkaloids were used as organocatalysts for a variety of organic reactions, including the Sharpless asymmetric dihydroxylation. With studies on chiral organocatalysis gaining interest steadily, experimental-theoretical studies on this versatile class of compounds have also gained traction.
Scheme 27: The four low-energy conformations of quinidine

The conformations of cinchona alkaloids have been studied extensively through NMR and computational studies. The first study was reported by Dijkstra, et al. in 1989, where they reported four low-energy conformers of quinidine using NMR, molecular mechanics, and x-ray crystallography. Numerous other experimental-theoretical studies on cinchona alkaloids have followed suit. Most notably, Berg, et al. reported in 1998 that the most stable conformer of cinchonidine at room temperature in apolar solvents is the anti-open conformer through NMR techniques and solvated DFT calculations. The resulting theory, where the anti-open
conformer is usually responsible for enantioselectivity in apolar solvents, was further augmented in 2015, where Dedeoglu, et al. reported that the most stable conformer for QD and QN is also the anti-open conformer with M06-2X/6-31+G(d,p). With the advent of experimental-theoretical studies on cinchona alkaloid (CA) conformations and the efficient use of CAs for most classes of organic reactions, computational studies on CA-catalyzed reactions have burgeoned, integrating quantum chemistry and physical organic chemistry in hopes of finding methods towards DKR-controlled asymmetric reactions. While there are many examples of using computational chemistry to aid asymmetric synthesis, we will first delve into the CA-catalyzed Aldol reaction as an example.

Scheme 28: Catalytic, asymmetric intramolecular Aldol condensation.

Lam and Houk investigated the mechanism to enantioselective induction in their catalytic, asymmetric Aldol condensation, where they substituted the hydroxyl on the CA with a primary amine. The primary amine was added in hopes of forming an enamine complex with the substrate as per the proline-catalyzed Aldol reaction.
Theoretically, this should give promising levels of enantioselectivity, which was observed experimentally. Certainly, one enantiomer was favored over the other. Their observations were then explored through computational studies, where transition state energies for two low energy conformations of the CA, the anti-open and the syn-open, were calculated. Through *ab initio* transition state calculations\(^1\), Lam and Houk reported that there are several transition state conformations for the Aldol step, the lowest energy conformations having been named boat-chair and crown. As expected, the CA is bifunctional, as the protonated quinuclidine nitrogen activates the accepting carbonyl group through hydrogen bonding and the primary amine activates the nucleophilic carbonyl covalently.\(^{30}\)

Scheme 29: Proposed mechanism to the intermolecular Aldol condensation.\(^{30}\)

---

\(^{1}\) B3LYP-D3(BJ)/def2-TZVPP-IEF-PCM(toluene)//B3LYP/6-31G(d)-IEF-PCM(toluene)
In the transition state towards the major enantiomer, the reagents proceed through the more favorable boat-chair TS conformation and the R group assumes an equatorial position. Therefore, this is the most favorable transition state for the Aldol, which is observed experimentally since the reaction has some level of enantioselectivity (R = Me: 24% e.r.).\textsuperscript{30} Meanwhile, the minor enantiomer is accounted for with two possible transition states structures that were calculated to have relatively similar stabilities and thus could be responsible for forming the minor enantiomer. In the crown TS, the R group is positioned equatorially, generating a mismatch in the ring conformation of the TS but a match in the position of the R group. On the other hand, the R group is positioned axially in the boat-chair TS, thus creating a match in its ring conformation but a mismatch in the position of the R group. Surprisingly, although this TS structure has the more favorable ring conformation, the axial R group actually is so unfavorable that the crown TS is the lower energy structure towards the minor enantiomer. Although the reaction was not as selective as the calculations imply, it is nonetheless important to note that such mechanistic analysis of a reaction can still provide plenty of information that could help to optimize other related reactions.

A most enticing aspect of using cinchona alkaloids is how they are bifunctional catalysts. Lam’s cinchona alkaloid is bifunctional, as exhibited through hydrogen bonding and covalent catalysis. However, for the most part, cinchona alkaloids tend to act as hydrogen-bond catalysts, where the electrophile is activated by forming a hydrogen bond to one part of the molecule as does the nucleophile to another part of the molecule.\textsuperscript{31} By activating the substrates, the reaction is then
accelerated, and by controlling the spatial orientation of the hydrogen bond donors, the substrates can react with high facial selectivity. So, by probing these different positions at which the catalyst can interact with substrates, we can direct the molecules with high levels of control much like an enzyme. But, how do substrates really interact with cinchona alkaloids?

In 1977, Wynberg reported that cinchona alkaloids can catalyze the reaction between aromatic thiols and cycloalkenones with high enantioselectivity. This was a pioneering study on cinchona alkaloids that inspired further research on organocatalysis via CAs and was a significant contribution to hydrogen-bond catalysis.31

Scheme 30: Cinchonidine-catalyzed addition of aromatic thiols to cycloalkenones.31

For decades, the Wynberg model for facial selectivity was generally used. In this model the nucleophile forms an ion pair with the protonated quinuclidine nitrogen while the enone forms a hydrogen bond with the alcohol. However, Grayson and Houk recently modified this model through DFT calculations.32
Scheme 31: DFT calculations indicate that a lower energy transition state exists.

Indeed, the prereaction complex favored the Wynberg model by 5.5 kcal/mol\(^2\), but as the reaction proceeds through the transition state, the Grayson-Houk model was calculated to be the lower energy transition state by 5.3 kcal/mol using the same level of theory.\(^3\) Furthermore, it was reported that the prereaction complex to the Grayson-Houk TS model and the complex to the Wynberg model were in rapid equilibrium and thus acts under Curtin-Hammett conditions.\(^3\) Therefore, the energy difference between the two complexes does not determine the enantioselectivity of the reaction, the difference in transition state energy does. Finally, enantioselective induction was then rationalized through the destabilization of the transition state towards the minor enantiomer. As the thiol attacks on the other side of the enone, a methyl group moves to the axial position as the ring goes into a chair conformation, and this incoming methyl group would generate torsional strain with the quinuclidine, making this a higher energy transition state.\(^3\)

\(^2\) M06-2X/def2-TZVPP-IEFPCM(benzene)//M06-2X/6-31G(d)-IEFPCM(benzene)
Basing our work on previous computational work on cinchona alkaloids, we can logically take similar steps to our reaction, the CA-catalyzed, asymmetric “Interrupted” Feist-Bénary (IFB) reaction, a reaction that proceeds through an initial Aldol step much like the aforementioned examples.

1.5 The “Interrupted” Feist-Bénary Reaction

Scheme 32: The “Interrupted” Feist-Bénary Reaction.

The IFB reaction was first developed in 2005 by Phillips and Calter. As the name suggests, the reaction is related to the Feist-Bénary (FB) reaction, developed in the early 1900’s to form highly substituted furan compounds. The reaction is catalyzed by amines, but as the reaction proceeds, the hydrobromic acid produced leads to a dehydration step that forms a highly stable aromatic system. However, the main disadvantage of the reaction is the lack of chiral centers that could potentially be synthetically useful.
The addition of another base—Proton Sponge (PS) in this instance—quenches the hydrobromic acid, interrupting the condensation step and yielding a synthetically useful intermediate by introducing up to two stereocenters. The reaction was discovered to be catalyzed by DABCO albeit yielding a racemic mixture; therefore, DABCO was replaced with a chiral catalyst containing a similar bridged amine moiety, i.e. the cinchona alkaloids. By using the bis-cinchona alkaloid pyrimidinyl (bis-Q PYR) catalyst shown above, the IFB product was obtained with great yields and synthetically useful enantioselectivity. Furthermore, the scope of the IFB reaction was then extended to include substituted α-halogen ketones to introduce diastereoselectivity, which was also observed to be highly selective.

![Scheme 33: The IFB reaction scope increased to include O-conjugation additions.](image)

The scope of the IFB reaction was further increased by Korotkov and Calter, having obtained hydroxyfuranoids through O-conjugation additions with high yields and enantioselectivities. Like the original IFB reaction, bis-cinchona alkaloid pyrimidinyl catalysts were used in the reaction. However, it was determined that, for this set of reagents, substituting a t-Butyl group on the 2-position of the pyrimidine
ring increased the enantioselectivity, indicative of a significant effect according to the groups on the pyrimidine ring.\textsuperscript{36}

![Chemical structure and reaction scheme](image)

**Scheme 34:** Scope further extended to include $\alpha$-tosyloxyacetophenones.

Korotkov then further extended the range of electrophiles that can be used for the IFB reaction, using a tosylate as the leaving group while still obtaining desirable yields and high enantioselectivity.\textsuperscript{37} In this case, the best catalyst was one where the 2-position is substituted by a 1-napthyl group. It was then hypothesized that the ortho- and meta-positions of an aryl substituent on the pyrimidine ring could be a contributing factor to the catalyst’s enantioselective induction.\textsuperscript{37}

Initial computational studies on the catalyst structure by Calter indicated that the phenyl group on the 5-position of the pyrimidine ring rotates almost 90° out of conjugation from the plane of the pyrimidine ring to increase favorable $\pi$-interactions between the phenyl ring and the vinyl group on the quinuclidine moiety of the cinchona alkaloid. Meanwhile, aryl substituents on the 2-position tend not to rotate too far out of conjugation from the plane of the pyrimidine ring, so the ortho- and
meta-positions can high influence the transition state as the reacting substrates are forming hydrogen bonds with the nearby quinuclidine.

Scheme 35: The IFB reaction in the total synthesis of (-)-Variabilin.

The IFB reaction was best showcased in Li’s asymmetric total synthesis of (-)-variabilin and (-)-glycinol, where it was used as a major transformation towards the natural products. Here, a mono-QD PYR catalyst was used to yield the IFB product with high diastereoselectivity and enantioselectivity of over 90% ee.\textsuperscript{38}

In this thesis, the scope of the IFB reaction will also be investigated through the development of an IFB reaction with a hydroxycoumarin nucleophile. Furthermore, we will delve into the mechanism to enantioselective induction for the IFB reaction between ethyl bromopyruvate and cyclohexadione through computational and mechanistic studies. Finally, we will attempt to find trends in catalyst selectivity by comparing transition state models from calculations with experimental results, which potentially can then be used as a predictor for related IFB reactions.
References


2. Development of an IFB reaction using a Hydroxycoumarin Nucleophile

2.1 Initial Studies

Gmelinol was first isolated by Birch and Lions in 1938, and the compound has been held up as a potential therapeutic because its plant source, *Gmelina arborea*, had been used in traditional medicine throughout history to treat a variety of illnesses.\(^1\) In addition, gmelinol has significant activity against the fungus Basidiomycetes and anti-malarial activity against *P. falciparum*.\(^2\) The first total synthesis of (±)-Gmelinol was reported in 2006 by Pohmakotr, et al.\(^3\); however, the asymmetric total synthesis has yet to be reported. On the progress to the asymmetric total synthesis of (+)-Gmelinol, Dworak concluded in 2014 that the synthesis could be more efficient if the aryl groups were introduced earlier in her proposed retrosynthesis (not shown), which was later applied in Bhatawdekar’s proposed retrosynthesis in 2018.\(^4\),\(^5\)

![Scheme 36: Retrosynthesis for (+)-Gmelinol proposed by Bhatawdekar.\(^5\)](image)

In Bhatawdekar’s proposed synthesis of (+)-Gmelinol, the first stereocenter is introduced via an IFB reaction between 3-aryl-1-phenylpropan-1,2-dione and the commercially available 4-hydroxycoumarin to synthesize 3. In order to simplify the
synthesis, we first modeled the electrophile using a phenyl group in the 3-position by brominating 1-phenylpropane-1,2-dione.

![Scheme 37: Bromination of 1-phenylpropane-1,2-dione.](image)

This reaction yielded 1 with 41% yield. With a commercially available nucleophile and an electrophile that was simple to synthesize, the logical next step was to optimize the IFB reaction through solvent and base screening.

![Table 1: Optimization of the IFB reaction.](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Time</th>
<th>Temperature</th>
<th>kBackground competing with kCatalyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>KHCO₃</td>
<td>3 h</td>
<td>-10°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Toluene</td>
<td>KHCO₃</td>
<td>23 h</td>
<td>-45°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Toluene</td>
<td>KHCO₃</td>
<td>24 h</td>
<td>-78°C</td>
<td>Yes</td>
</tr>
<tr>
<td>DCM</td>
<td>PS</td>
<td>2 h 30 min</td>
<td>RT</td>
<td>Yes</td>
</tr>
<tr>
<td>DCM</td>
<td>KHCO₃</td>
<td>16 h</td>
<td>RT</td>
<td>No</td>
</tr>
<tr>
<td>DCM</td>
<td>KHCO₃</td>
<td>64 h</td>
<td>4°C</td>
<td>No</td>
</tr>
</tbody>
</table>

The IFB reaction shown above was screened with different solvents and bases to check for the background reaction competing with the catalyzed reaction. It was eventually discovered that DCM as the solvent of choice using KHCO₃ as a base slowed down the background reaction while the addition of DABCO increased the
rate of the reaction. This primed the IFB reaction to be catalytic; therefore, we screened for synthetically useful levels of enantioselectivity by screening several cinchona alkaloid catalysts.

2.2 Catalyst Screening

Using DCM as a solvent and KHCO$_3$ as the base, the IFB reaction proceeded nearly to completion with DABCO as our representative catalyst within 16 hours. We then began our catalyst screening with AAAA and AACA (see Scheme 38 for structures) due to their ready availability and our prior understanding of these catalysts from Phillips’s and Korotkov’s works.$^6,7$ While these induced some enantioselectivity, we sought to improve upon this reaction and optimize it for synthetic utility. From Korotkov’s studies on acetoxyphenones, it was observed that the addition of bulkier groups on the meta-position of the aryl front group (i.e., the 2-position of the pyrimidine ring) of the catalyst appeared to increase enantioselectivity, possibly pointing to steric effects in the transition state of his reaction.$^8$ Furthermore, the ortho-position also appeared to play a steric and electronic role that could affect the enantioselective induction of the reaction. Finally, we hypothesized that the use of aryl front groups on the cinchona alkaloid catalysts would result in increased interactions between the catalyst and the electrophile through π-stacking, decreasing the encounter complex energy and resulting in a more favored asymmetric pathway for the substrates. As a result, we screened several aryl catalysts substituted with functional groups of different electronic and steric effects in hopes of understanding the mechanism to this reaction’s enantioselective induction and optimizing the reaction to further pursue the asymmetric total synthesis of (+)-Gmelinol.
Scheme 38: Catalyst screening for the IFB reaction of 3.

As shown in Scheme 38, we have not optimized this IFB reaction past 30% ee. We sought to utilize the electronic nature of different functional groups and garner its effects on enantioselectivity, starting with QD-1. There was no significant increase
in enantioselectivity from the AACA catalyst, and there was no significant trend based on the donating or withdrawing character of the substituent. Similarly, Bhatawdekar looked at varying the electronic nature of the meta group of the front aryl ring, which was ultimately observed to be irrelevant to asymmetric induction.

**Scheme 39:** Bhatawdekar’s screening of meta-substituted aryl front group catalysts.⁵

In general, adding a substituent at the front aryl group increases the enantioselectivity. But interestingly enough, it appears as though the trifluoromethyl and dimethylamine substituents act similarly. For this series of catalysts, if these substituents are located in the ortho-position, the observed enantiomeric excess (13% and 13% ee, respectively) was only slightly higher than AACA (11% ee). But, if NMe₂ or CF₃ are located on the meta-position, the enantioselectivity increases to 21% ee and 23% ee, respectively. Meanwhile, the methoxy group acts in an opposite manner, where having a methoxy group in the ortho-position (18% ee) is slightly more favorable than when located in the meta-position (16% ee). While making predictions based on electronics would be difficult, it is curious that groups with A-values larger than a methoxy group (such as CF₃ and NMe₂) tend to enhance enantioselective induction if located on the meta-position. Likewise, we observed that the addition of bulky groups on both meta-positions of the aryl front group indeed
increased the enantioselectivity of the reaction; however, this also decreased the yield (QD-8 to QD-11).

Reproducibility had also been a constant issue with this optimization. We first presumed that this was a result of a base-catalyzed, *in situ* epimerization of 3 via the Pinacol rearrangement (Scheme 40). As a result, we would lose enantiomeric excess during the reaction.

![Scheme 40: The base-catalyzed Pinacol Rearrangement of 3.](image)

We also observed that the enantiomeric excess tends to increase in saturated HPLC samples, where the product begins to precipitate, which is filtered off. But, it is important to note that racemic crystals have different solubilities than enantiopure crystals. Therefore, for scalemic mixtures such as those prepared for HPLC analysis, the difference in solubilities between racemate crystals and enantiopure crystals could answer our problem in reproducibility. The results reported in this thesis were all from fully dissolved samples.

As a result, after re-screening the catalysts, we have determined that the most reliable catalyst for this particular IFB reaction is the 2-(6-methoxypyridin-2-yl)-5-phenylpyrimidine-bis-(9-O-quinidine)ether catalyst (QD-5), yielding 3 with 91% yield and 29% ee. This followed our expectations on the aryl group’s structure, where the pyridinyl nitrogen would be smaller than the phenyl C-H at the ortho-position, while the methoxy group would provide bulk at the meta-position. As a result, we
then replaced the methoxy group with a phenyl group (QD-6); however, this actually decreased the enantioselectivity of the reaction. It may be interesting to discern how the meta-position could possibly have electrostatic effects if the aryl front group is a pyridinyl group.

In order to understand the mechanism to the substrates’ interactions with the catalyst more deeply, we began running preliminary calculations at the Hartree-Fock level with this reaction, using QD-7 to gauge the effects of the meta-position.

![Figure 4: TS structures for QD-7, the Re face attack (right) is lower in energy by 0.774 kcal/mol. Reacting atoms highlighted.](image)

While the low-level calculations were not telling of how structural changes in the catalyst affects the $\Delta\Delta G^\ddagger$, it was interesting to observe that the meta-position of the aryl front group is important in interacting with the substrates, especially through $\pi$-stacking. Looking at the structures on Figure 4, the more favorable TS appears to include the nucleophile stacking in between the electrophile and the meta-phenyl

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3 HF/3-21G//HF/3-21G
substituent. However, in the unfavorable TS structure, while we lose the steric strain between the second quinidine (omitted in figure) and the bromine of the electrophile, some degree of $\pi$-stacking between the electrophile, nucleophile, and the pyrimidinyl ring is maintained. This possible stabilization of this transition state may be indicative of the reason as to why we observe low enantioselectivity with this IFB reaction from various catalysts. Therefore, it may be interesting to try the CAXY catalysts for this reaction to decrease steric strain and make the more favorable TS even lower in energy. Furthermore, the enantioselective induction of the catalyst may be further increased by introducing a structural component that would destabilize the unfavorable transition state, as shown with CACA and CAEA in the classic IFB reaction (Chapter 3). At this point, however, we have observed only up to 29% ee with our new IFB reaction. Further optimization and catalyst strategy are still needed to achieve synthetically useful levels of enantioselectivity.

2.3 The IFB Reaction in the Presence of Water

Following the seminal paper on proline-assisted asymmetric aldol reactions in DMSO by List, et al., polar organic solvents have been a popular choice for similar reactions. However, taking solvent effects to the next level, several studies have used aqueous-organic conditions to run the aldol reaction, reporting that the presence of water significantly accelerates the rate of the reaction and increases enantioselectivity. For example, in a 2004 paper by Torii, et al., an asymmetric aldol reaction assisted by water and catalyzed by a proline-derived tetrazole was demonstrated with high enantioselectivity.
Scheme 41: Asymmetric aldol reaction in the presence of water.\textsuperscript{11}

Because the proposed rate-determining and stereochemistry-determining step of the IFB reaction is the aldol step, we were curious if a similar rate acceleration in the presence of water can be observed for this IFB reaction. Furthermore, from Bhatawdekar’s initial studies, the use of a polar, organic solvent such as acetonitrile had indeed accelerated the rate of the reaction to complete within 3 hours at -10°C. However, because this background reaction competed with the catalyzed reaction, using acetonitrile as the solvent was too risky, as some of the substrates would instead react without the catalyst. As such, the addition of a small amount of water while using DCM as a co-solvent would slightly increase the polarity and possibly demonstrate a similar increase in enantioselectivity. In addition, due to the aqueous base, we hypothesized that the reaction can be accelerated by increased interactions between the surface of the organic layer where the reagents are dissolved and the aqueous layer where the base is dissolved.

Scheme 42: The IFB reaction with 1 equivalent of water.
Unfortunately, the yield and enantioselectivity decreased, possibly due to the lack of function of water in the catalytic cycle in our mechanism as opposed to a proline-mediated catalytic cycle, which was delineated by Zotova, et al., on preliminary kinetic studies of aldol reactions in the presence of water.

![Scheme 43: Catalytic cycle for a proline-catalyzed aldol, reported with 64-69% ee.](image)

While our results were disappointing, this does give us insight into optimizing the conditions of this reaction and its dependence on solvent polarity. Furthermore, from our studies on the other IFB reaction, we have discovered that each pyrimidinyl catalyst has its own mechanism to inducing enantioselectivity based on the 2-position and that the 6-position is a frontier to explore due to its possible steric interactions with the substrates. As a result, there are still more studies that can be run on this particular reaction and increase the scope of the IFB reaction to include structurally diverse nucleophiles and electrophiles. Since this would be a daunting task, we return back to the classic IFB reaction and discuss our new understanding of the mechanism to enantioselective induction in the next chapter, where we hope our studies will augment catalyst screening and optimization in a more guided manner.
References


3. The Catalytic, Asymmetric “Interrupted” Feist-Bény reaction between Ethyl Bromopyruvate and Cyclohexadione

3.1 Initial Studies

**Scheme 44:** The IFB reaction between ethyl bromopyruvate and cyclohexadione.

Calter and Phillips reported in 2005 that the “Interrupted” Feist-Bény reaction between ethyl bromopyruvate and cyclohexadione (CHD) was catalyzed by cinchona alkaloids with synthetically useful enantioselectivities.1

**Scheme 45:** Legend for catalyst structure.

From Phillips’ studies, it was discovered that the 5-phenylpyrimidine-bis-(9-O-quinidine)ether catalyst, otherwise known as catalyst AAAA, yielded the IFB product, 4, with 98% yield and 92% ee. Furthermore, it appeared as though adding
bulkier substituents such as a phenyl or $t$-butyl group on the 2-position of the pyrimidine ring lowered the enantioselectivity.

**Table 2: Phillips’s results for the $R$ configuration of 4.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>equiv. of PS</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinuclidine</td>
<td>0</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Quinuclidine•HCl</td>
<td>0</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Quinuclidine</td>
<td>1.1</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>QDH</td>
<td>1.1</td>
<td>99</td>
<td>21</td>
</tr>
<tr>
<td>AAAA</td>
<td>1.1</td>
<td>98</td>
<td>91</td>
</tr>
<tr>
<td>AACA•2HBr</td>
<td>0</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>AABA</td>
<td>1.1</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>AACA</td>
<td>1.1</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td>AAEA</td>
<td>1.1</td>
<td>94</td>
<td>64</td>
</tr>
<tr>
<td>AAEB</td>
<td>1.1</td>
<td>96</td>
<td>61</td>
</tr>
</tbody>
</table>

As shown in **Table 2**, quinuclidine (with 1.1 equiv PS) and quinuclidine•HCl (without PS) catalyzed the reaction with 90% yield and 92% yield respectively, indicating that active form of the catalyst is protonated throughout the reaction. This was later extended to the chiral catalyst where AAAA•2HBr without PS yielded 4 with 88% yield and 92% ee. As a result, we postulate that the active catalyst remains protonated throughout the reaction. Protonated cinchona alkaloids have been reported to activate electrophiles through hydrogen-bond catalysis and was thus the basis for our proposed mechanism for the asymmetric induction of the IFB reaction (**Scheme 46**). Here, the protonated catalyst and the electrophile form a hydrogen bond, rendering the latter to be more electrophilic for attack by the enol or enolate form of the nucleophile. When the cinchona alkaloid used is quinidine, the $Re$ face is less
hindered and thus the *Re* attack would be more favorable, yielding the (R) configuration of 4.

![Scheme 46: The original, proposed mechanism to the IFB reaction.](image)

Building off of this initial discovery, we asked two questions: how does the catalyst affect the transition state energies at the Aldol step, i.e. what is the mechanism to the catalyst’s enantioselective induction, and how can we use this knowledge to predict catalysts for other IFB reactions?
Figure 5: Reaction coordinate diagram for various catalysts.

We attempted to answer the first question by testing the effects of the concentration of the electrophile on enantioselectivity. We proposed that the pre-reaction encounter complex (EC) is expected to be in dynamic equilibrium between the two pro facial attacks, the pro-R and the pro-S complexes. Preliminary calculations by Calter demonstrate that the free energy decreases with the addition of the catalyst to CHD (SM to CHD+Cat), which decreases even further when the electrophile coordinates (CHD+Cat to Total EC). As the reaction proceeds, we observe that the aldol step indeed has the largest energy barrier (Total EC to Aldol), and a large drop in energy was calculated with the cyclization and condensation of the intermediate (Cond.) to yield the IFB product. In order to gauge this mechanism, we first hypothesized that the rate of interaction between the pro-R and pro-S complexes
was dependent on substrate concentration. To observe this experimentally, we altered the ratio between the electrophile and the nucleophile with control being 1:1. We expected the enantiomeric excess to decrease when we run the reaction with lower amounts of electrophile, hypothesizing that the CHD-Cat to EC energy barrier could be decreased through an associative substitution mechanism from the excess nucleophile.

**Figure 6:** Substrate concentration studies on the formation of 4.

As seen on the graph above, we did not observe a definite substrate concentration dependence on enantioselectivity. There was no significant decrease in enantioselectivity with lower amounts of electrophile and the values tended to hover around 80% to 90% ee, indicating that the rate of the reaction was not slowed down enough by decreasing the amount of the electrophile.

It is possible that a different factor would affect enantioselectivity, so we returned to the transition state modeling of the catalyst-electrophile complex and obtain theoretical ΔΔG‡ values based on the calculated transition state energy.
difference between the \textit{Re} and \textit{Si} attacks. From preliminary calculations done by Calter, it was observed that these theoretical $\Delta \Delta G^\dagger$ values tended to match with our experimental values. The bis-quinidine catalysts were used experimentally; however, when modeling, the second quinidine moiety was replaced with a methoxy group to save computational energy.

Surprisingly, the AACA catalyst in particular was predicted to yield the IFB product with a much higher enantiomeric excess than reported by Phillips. As a result, we began another round of catalyst screening and developed a method to synthesize a new set of catalysts, the MAXY catalysts, to match our calculations.

3.2 Catalyst Screening

We first ran standard conditions on the classic IFB reaction using the bis-quinidine pyrimidinyl (AAXY) catalysts to check Phillips’s initial work and determine whether or not the reaction with the AACA catalyst was supposed to make the reaction more enantioselective. From our screening, we have shown that the IFB reaction using the AACA catalyst is indeed more enantioselective than reported, similar to when using the AAAA or AABA catalysts (Table 3). Furthermore, we found an interesting trend when replacing the 6-position of the pyrimidinyl ring, where the enantioselectivity of the reaction increases as we vary the 6-position substituent from a quinidine (QD), to a methoxy group, then finally to a chlorine. This observed increase in enantioselectivity was later observed in our transition state calculations. However, we first need to convert our data into thermodynamic data for comparison.
Assuming that the $\Delta G$ of the reaction stays constant, we can relate our enantiomeric excess to the difference in transition state energies ($\Delta \Delta G^\ddagger$) between the $Re$ and $Si$ attacks using the Eyring equation (Equation 1).

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} \quad (1)$$

We then assert the Curtin-Hammett principle, in which the product ratio is dependent on the activation energies leading to each product.

$$\frac{[R]}{[S]} = \frac{k_R}{k_S} = \frac{e^{-\Delta G_R^\ddagger}}{e^{-\Delta G_S^\ddagger}} = e^{-\Delta \Delta G^\ddagger}, \text{where } \Delta \Delta G^\ddagger = \Delta G_R^\ddagger - \Delta G_S^\ddagger \quad (2)$$

From a crystal structure reported by Phillips, the major enantiomer obtained from this IFB reaction is the $R$-enantiomer; therefore, $\Delta G^\ddagger_R < \Delta G^\ddagger_S$.

$$\frac{[R]}{[S]} = e^{-\Delta \Delta G^\ddagger} \therefore [R] = [S] e^{-\Delta \Delta G^\ddagger}$$

$$\%ee = \frac{[R] - [S]}{[R] + [S]} = \frac{[S] e^{-\Delta \Delta G^\ddagger} - [S]}{[S] e^{-\Delta \Delta G^\ddagger} + [S]} = \frac{1 - e^{-\Delta \Delta G^\ddagger}}{1 + e^{-\Delta \Delta G^\ddagger}}$$

By rearranging the above equation, we can approximate a $\Delta \Delta G^\ddagger$ for our reaction based on the enantiomeric excess.

$$e^{-\frac{\Delta \Delta G^\ddagger}{RT}} = \frac{1 - \%ee}{1 + \%ee}$$

$$\therefore \Delta \Delta G^\ddagger = -RT \times \ln \left( \frac{1 - \%ee}{100} \frac{1}{1 + \%ee} \right) \quad (3)$$

Using the above equation, we convert our enantiomeric excess into $\Delta \Delta G^\ddagger$ and compare experimental data to $\Delta \Delta G^\ddagger$ values we calculated by $ab\ initio$ methods.
Table 3: New catalyst screening and comparison to \textit{ab initio} calculations.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>% ee</th>
<th>Observed $\Delta G^\ddagger$ (kcal/mol)</th>
<th>HF 3-21G* (kcal/mol)</th>
<th>HF 3-21G* SMD 1.2 (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAAA</td>
<td>83</td>
<td>0.92</td>
<td>3.27</td>
<td>-</td>
</tr>
<tr>
<td>AABA</td>
<td>87</td>
<td>1.03</td>
<td>3.30</td>
<td>-</td>
</tr>
<tr>
<td>AACA</td>
<td>84</td>
<td>0.95</td>
<td>4.15</td>
<td>-</td>
</tr>
<tr>
<td>MAAA</td>
<td>92</td>
<td>1.23</td>
<td>3.44</td>
<td>2.60</td>
</tr>
<tr>
<td>MABA</td>
<td>86</td>
<td>1.00</td>
<td>3.46</td>
<td>2.44</td>
</tr>
<tr>
<td>MACA</td>
<td>87</td>
<td>1.03</td>
<td>3.82</td>
<td>2.53</td>
</tr>
<tr>
<td>CAAA</td>
<td>94</td>
<td>1.35</td>
<td>3.53</td>
<td>3.01</td>
</tr>
<tr>
<td>CABA</td>
<td>94</td>
<td>1.35</td>
<td>3.54</td>
<td>2.84</td>
</tr>
<tr>
<td>CACA</td>
<td>90</td>
<td>1.14</td>
<td>3.85</td>
<td>2.99</td>
</tr>
</tbody>
</table>

As mentioned, we observe a general trend in which the enantiomeric excess was highest if the catalyst had a chlorine in the 6-position of the pyrimidinyl ring. Our observations were also augmented by \textit{ab initio} calculations at the Hartree-Fock level of theory with a small basis set, where the $\Delta G^\ddagger$ increased with each replacement of the 6-position.

\textbf{Figure 7}: Optimized favorable TS structures for CACA (right) and MACA (left). \footnote{B3LYP/GD3/6-31G(d,p)//B3LYP/GD3/6-31G(d,p).}
As shown on the transition state structures, we propose that having a methoxy group in the 6-position would increase the more favorable TS energy because of steric interactions between the methoxy and the bromine on the electrophile. Therefore, enantioselectivity is decreased since this steric consideration is less significant for the unfavorable TS. DFT calculations on the more favorable transition state suggest that the distance between the methyl hydrogen and the bromine (2.90 Å) is smaller than the distance between the chlorine and the bromine (3.90 Å). With the addition of the larger quinidine at the 6-position, the steric strain increases in the more favorable TS and thus enantioselectivity would decrease even more. Furthermore, we hypothesize that there is a possibility of increased favorable interactions between the chlorine and bromine in the more favorable TS with the CAXY catalysts. In conclusion, the ΔΔG‡ tends to follow this trend theoretically, which is also consistent with our experimental results.

We noticed a relatively good fit between the experimental data and the theoretical data for the XAAA and XABA catalysts. However, with the addition of an aromatic ring on the 2-position, we noticed that the calculated ΔΔG‡ values are much higher than observed. From this, it was clear that we needed to improve our calculation methods, so we proceeded with trying higher levels of theory and larger basis sets to model our transition states.
Table 4: Current progress on DFT calculations using the B3LYP functional.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Observed $\Delta \Delta G^\ddagger$ (kcal/mol)</th>
<th>6-31G/D3 (d,p)</th>
<th>6-31G/D3(d,p) SMD 1.2</th>
<th>GD3/6-311(2d,2p) SMD 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAAA</td>
<td>1.23</td>
<td>6.14</td>
<td>5.52</td>
<td>2.08</td>
</tr>
<tr>
<td>MABA</td>
<td>1.00</td>
<td>5.26</td>
<td>5.60</td>
<td>1.47</td>
</tr>
<tr>
<td>MACA</td>
<td>1.03</td>
<td>6.78</td>
<td>6.12</td>
<td>2.89</td>
</tr>
<tr>
<td>CAAA</td>
<td>1.35</td>
<td>4.66</td>
<td>4.55</td>
<td>1.08</td>
</tr>
<tr>
<td>CABA</td>
<td>1.35</td>
<td>3.77</td>
<td>4.51</td>
<td>0.46</td>
</tr>
<tr>
<td>CACA</td>
<td>1.14</td>
<td>4.95</td>
<td>4.58</td>
<td>1.84</td>
</tr>
<tr>
<td>CAEA</td>
<td>0.92</td>
<td>4.52</td>
<td>4.39</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Using improved methods and basis sets on DFT calculations tends to get us closer to the magnitudes of our observed $\Delta \Delta G^\ddagger$ values, as demonstrated on Table 4. The addition of the phenyl group in the 2-position is still quite problematic, however. We discovered that the calculated $\Delta \Delta G^\ddagger$ for CACA was lower than that of CAAA by using Truhlar’s SMD as the solvent model and specifying the scaling factor to 1.2 at the Hartree-Fock level (Table 3). We used this scaling factor to avoid unnatural solvation in surface cavities, which would affect our TS energies. When applying this to DFT calculations, however, this does not prove to be the easy fix to the inflated $\Delta \Delta G^\ddagger$. As a result, further optimization of our computational methods is necessary in order to pursue using computational models as a way to predict asymmetric catalysis.
3.3 Competition Reactions

![Reaction scheme for the competition reactions.](image)

**Scheme 47:** Reaction scheme for the competition reactions.

In order to probe the mechanism to enantioselective induction, we were first interested in how changing the catalyst in the 2-position (R₁) affects the difference in transition state energies. More specifically, when increasing the ΔΔG‡ of this reaction by changing the catalyst structure, is the favorable TS (TS₁) decreasing in energy or is the unfavorable TS (TS₂) increasing in energy? While the actual ΔΔG‡ would be the same either way, we can use competition reactions to answer this question, which could then be applied in deducing why certain catalyst structures would not be useful synthetically. Eventually, with enough data to create a large catalyst library, we hope to use a machine learning program to be able to predict catalysts for future IFB reactions. In general, we want catalysts that would lower TS₁, as decreasing TS₁ would give overall higher rates and a more useful reaction than raising TS₂.

In this set of reactions, two catalysts, one chiral and one achiral, are competing for the substrates, and from the observed enantiomeric excess, we can compare the rate constants between the chiral and achiral pathways of the reaction towards each enantiomer. Here, we use quinuclidine•HCl as an achiral catalyst instead of DABCO, due to its structural similarity to the active site of our chiral catalysts. While standard reaction conditions are followed, there is a total of 20 mol% catalyst loading in order to maintain accurate weighing of catalysts.
**Table 5:** Competition experiments between achiral and chiral catalysts.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>[Achiral]:[Chiral]</th>
<th>%ee ± s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAAA</td>
<td>H</td>
<td>Ph</td>
<td>0</td>
<td>90 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:3</td>
<td>62 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:1</td>
<td>39 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>CABA</td>
<td>SMe</td>
<td>Ph</td>
<td>0</td>
<td>86 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:3</td>
<td>62 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:1</td>
<td>35 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>CACA</td>
<td>Ph</td>
<td>Ph</td>
<td>0</td>
<td>86 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:3</td>
<td>49 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:1</td>
<td>30 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>CADA</td>
<td>1-naphthyl</td>
<td>Ph</td>
<td>0</td>
<td>80 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:3</td>
<td>59 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:1</td>
<td>38 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>CAEA</td>
<td>t-Butyl</td>
<td>Ph</td>
<td>0</td>
<td>83 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:3</td>
<td>52 ± 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1:1</td>
<td>23 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3:1</td>
<td>13 ± 1</td>
</tr>
</tbody>
</table>

When comparing each set of catalysts to each other, it is notable that changing the substituent on the 2-position of the pyrimidinyl ring can greatly affect the rate of catalysis compared to quinuclidine. In general, we observe that the enantiomeric excess declines more quickly as we increase the ratio of achiral catalyst to chiral catalyst as we replace the 2-position substituent from a hydrogen or a thiomethyl group to a phenyl or napthyl group then finally to a t-butyl group. This indicates that the addition of the latter groups generally tends to slow down the rate of catalysis.
Despite the size of the achiral catalyst, the reaction was still primarily catalyzed through the chiral pathway since we observe that the reactions are still enantioselective, even with higher amounts of quinuclidine. In other words, the reaction through the chiral catalyst is more favorable than the reaction through the achiral catalyst. Therefore, the hydrogen-bonding of the electrophile to the chiral catalyst is not simply disfavored by sterics but is actually favored by electronics.

Recalling past literature on modeling transition states for hydrogen-bonded asymmetric catalysis with quinidine-catalyzed reactions and our current computational models, we find that favorable interactions arise between the substrates and the electron poor 4-position of the pyrimidinyl ring on the chiral catalyst when coordinated. As a result, the reaction proceeds more favorably through the asymmetric pathway.

**Figure 8:** Competition reactions between quinuclidine and pyrimidinyl catalysts.
**Scheme 48**: Curtin-Hammett conditions with two catalysts. TS energies arbitrary.

As the competition reaction proceeds, there are four possible transition states to yield the IFB product (**Scheme 48**), with the formation of one enantiomer having two possible transition states each. In order to simplify our comparison, we can find the ratio between the rate constants for the chiral pathway and the achiral pathway only towards the more favorable enantiomer, for example. We know that, through the achiral catalyst, the rate constants for Achiral\(_R\) is equal to that of Achiral\(_S\) since we would expect a racemate from this process. Furthermore, the enantiomeric ratio that we obtain from our chiral catalysts as a standard can be represented as a ratio of the rate constants, i.e. the ratio between Chiral\(_R\) and Chiral\(_S\), as per the Curtin Hammett principle. Finally, from the competition experiments, we also obtain an enantiomeric ratio, which is the dependent on the amount of chiral and achiral catalysts added for each competition reaction.
We assign the variable Q as the rate constant for the achiral processes and the variable K as the rate constant for the chiral processes. In addition, we assign \( E_r_C \) as the control enantiomeric ratio and Er for each competition reaction’s enantiomeric ratio. Assuming that the rate constant does not change with each reaction,

\[
Er = \frac{K_R + Q_R}{K_S + Q_S} \tag{4}
\]

Since \( E_r_C = \frac{K_R}{K_S} \), and given that \( Q_R = Q_S \)

\[
Er = \frac{K_R + Q_R}{E_r_C + Q_R} \tag{5}
\]

In order to determine the factor between the rate of catalysis for the achiral catalyst and for the chiral catalyst, we can obtain \( \frac{K_R}{Q_R} \) by rearranging Equation 5.

\[
\frac{ErK_R}{E_r_C} + ErQ_R = K_R + Q_R
\]

\[
ErK_R + ErE_r_CQ_R = E_r_CK_R + E_r_CQ_R
\]

\[
\therefore K_R(Er - E_r_C) = Q_R(E_r_C - ErE_r_C) \tag{6}
\]

It is again important to note that the variable Er is dependent on the ratio, which we will define as \( R_{KQ} \). Equation 4 can be rewritten with this new factor to give

\[
Er = \frac{R_{KQ}K_R + Q_R}{R_{KQ}K_S + Q_S}
\]

For brevity, several steps will be omitted; however, the derivation follows as above to give the final equation of interest, Equation 7.

\[
\frac{K_R}{Q_R} = \frac{E_r_C(1 - Er)}{R_{KQ}(Er - E_r_C)} \tag{7}
\]
Similarly, we can find the ratio between the rate of the reaction for the unfavored transition state, $K_S$, through the chiral pathway and the rate of the reaction through the achiral pathway, i.e. we can relate $\frac{K_S}{Q_S}$ to our competition experiments.

$$\frac{K_S}{Q_S} = \frac{1 - Er}{R_{KQ}(Er - Er_c)} \quad (8)$$

Using these equations, we can determine how each chiral catalyst increases or decreases either transition state energies compared to quinuclidine. Finally, the energy difference between the achiral and chiral TS for each catalyst, which we will define as $\Delta \Delta G^\dagger_{KQX}$ with $X$ being either $R$ or $S$ depending on the transition state, can be found using the equation:

$$\Delta \Delta G^\dagger_{KQX} = -RT \cdot \ln \left( \frac{K_x}{Q_x} \right) \quad (9)$$

From our initial competition reactions, we have calculated these factors for each catalyst with excellent results.

**Table 6:** Experimental $\frac{K}{Q}$ values and their respective $\Delta \Delta G^\dagger$.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Average $\frac{K_R}{Q_R}$</th>
<th>Average $\frac{K_S}{Q_S}$</th>
<th>$\Delta \Delta G^\dagger_{KQR}$ (kcal/mol)</th>
<th>$\Delta \Delta G^\dagger_{KQS}$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAAA</td>
<td>1.64</td>
<td>0.0865</td>
<td>-0.19 ± 0.08</td>
<td>0.95 ± 0.08</td>
</tr>
<tr>
<td>CABA</td>
<td>1.42</td>
<td>0.107</td>
<td>-0.13 ± 0.04</td>
<td>0.87 ± 0.04</td>
</tr>
<tr>
<td>CACA</td>
<td>0.87</td>
<td>0.0661</td>
<td>0.05 ± 0.04</td>
<td>1.05 ± 0.04</td>
</tr>
<tr>
<td>CADA</td>
<td>1.39</td>
<td>0.189</td>
<td>-0.1 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>CAEA</td>
<td>0.915</td>
<td>0.0850</td>
<td>0.04 ± 0.08</td>
<td>0.96 ± 0.08</td>
</tr>
</tbody>
</table>

It is important to note that, although all five catalysts have yielded the IFB product with relatively high enantioselectivity (80-90% ee), the variation on how the catalysts increase or decrease each transition state is fully realized through our competition reactions. For instance, CAAA (90% ee) was observed to decrease TS1
by 0.19 kcal/mol and increase TS2 by 0.95 kcal/mol. Similarly, CABA (86% ee) also
decreases TS1 by 0.13 kcal/mol and increases TS2 by 0.87 kcal/mol. This is also
reflective of the lower level of enantioselective induction by CABA compared to
CAA, where the ΔΔG‡ of the reaction is -1.00 kcal/mol with CABA and -1.14
kcal/mol with CAA, calculated using Equation 10.

\[
\Delta \Delta G^\ddagger = - (|\Delta G^\ddagger_{KQR}| + \Delta G^\ddagger_{KQS})
\]

(10)

We also notice that TS1 is significantly increased in energy when using
CACA or CAEA (ΔΔG‡KQR ≈ 0.05 kcal/mol). These catalysts increase
enantioselectivity by slightly destabilizing TS2, but the significant destabilization of
TS1 ultimately worsens the enantioselectivity of the reaction. In Figure 9, we
visualize our data from Table 6 and demonstrate that the transition state energies are
affected is highly dependent on the structure of the catalyst, although these catalysts
may catalyze the IFB reaction with somewhat similar enantioselectivities.
Figure 9: Relative TS energies of each catalyst compared to quinuclidine (black).

In general, we can conclude that the enantioselectivity of the reaction from our cinchona alkaloid catalysts is primarily induced by highly destabilizing TS2. We have previously mentioned that the carbonyl groups of the substrates are favorably interacting with the 4-position of the pyrimidinyl ring in either transition state, locking the substrate in the pocket. However, the destabilization of TS2 could be the result of the nucleophile not fitting within the pocket due to its less rigid structure and the potential repulsive forces between the alkyl carbons and the pyrimidine. The increased destabilization of TS2 within each catalyst as observed in Figure 9 will be delineated in the following section. We will also discuss considerable stereoelectronic effects from the addition of substituents in the 2-position for each catalyst that can destabilize TS1 (CAAA having the least amount of steric or electronic considerations.
and thus will act as the basis for comparison). With this in mind, we will then expound upon the mechanism of each catalysts’ enantioselective induction using our competition experimental data augmented by computational studies.

3.4 Mechanism to Enantioselective Induction

At this point, we have DFT calculations for the CAAA, CABA, CACA, and CAEA TS and encounter complexes. The calculated ΔΔG‡_KOR for CACA was -0.73 kcal/mol and the ΔΔG‡_KOS was 0.17 kcal/mol (B3LYP/6-311+(2d,2p) SMD 1.2), and we find that this is a step in the correct direction where CAAA indeed stabilizes TS1 while destabilizing TS2. Thus, we hope to find a similar correlation with the other catalysts and their encounter complexes to our experimental data.

CACA is our other prototypical catalyst for calculations and will be the first to be discussed and compared to CAAA in this section. However, it is also important to note that the ΔΔG‡ for CACA is overestimated possibly through systematic errors and thus further optimization of our calculation method is also necessary in the future.

As mentioned earlier in this chapter, we observed enantioselectivity despite a larger amount of the smaller, less sterically hindered achiral catalyst in our competition reactions. As seen in the following figures in this section, the positive charge on the 4-position (C1) results in favorable electronic interaction with either carbonyl oxygens from the electrophile or the nucleophile. From our analysis, this is indicative of how the addition of the pyrimidinyl moiety is indeed favorable for substrate-catalyst coordination; as a result, the reaction proceeds through the chiral pathway more favorably.
When comparing the catalysts to each other and observing the effects of substituents on the 2-position, we initially base our analysis on CAAA, our most selective catalyst, for a more simplified analysis. It has been demonstrated experimentally and theoretically that CAAA induces enantioselectivity by decreasing TS1 while increasing TS2. When comparing the experimental $\Delta\Delta G^\ddagger_{KQR}$ between CAAA and CACA (-0.19 kcal/mol and 0.05 kcal/mol, respectively), it was observed that TS1 is higher in energy for CACA than CAAA. From preliminary calculations and analysis of the structure, we expect that CACA should destabilize the transition states through steric and electrostatic effects compared to CAAA.

![Image of CAAA and CACA structures]

**Figure 10:** NBO population analysis for TS1. (B3LYP/6-311+(2d,2p) SMD 1.2).

Several factors can result in this increase; however, we propose that the addition of the phenyl group not only adds steric bulk to the catalyst, it can also result in electronic repulsion between C3 and C7. Analysis of the Mulliken population charges indicate that the 2-position of the pyrimidinyl ring (C4) is positively charged to stabilize C3 and increases in charge with the addition of a phenyl group. For a more rigorous analysis, a natural population analysis (NPA) was then conducted (Table 7).
Table 7: Natural charges through Natural Population Analysis (NPA).

<table>
<thead>
<tr>
<th></th>
<th>Atom of Interest</th>
<th>CAAA</th>
<th>CACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>C₁</td>
<td>0.627</td>
<td>0.634</td>
</tr>
<tr>
<td></td>
<td>O₁</td>
<td>-0.792</td>
<td>-0.796</td>
</tr>
<tr>
<td></td>
<td>C₂</td>
<td>0.328</td>
<td>0.328</td>
</tr>
<tr>
<td></td>
<td>N₁</td>
<td>-0.539</td>
<td>-0.544</td>
</tr>
<tr>
<td></td>
<td>C₃</td>
<td>-0.429</td>
<td>-0.437</td>
</tr>
<tr>
<td></td>
<td>C₄</td>
<td>0.305</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>C₇</td>
<td>-</td>
<td>-0.113</td>
</tr>
<tr>
<td>TS2</td>
<td>C₁</td>
<td>0.632</td>
<td>0.639</td>
</tr>
<tr>
<td></td>
<td>O₂</td>
<td>-0.768</td>
<td>-0.658</td>
</tr>
<tr>
<td></td>
<td>C₄</td>
<td>0.313</td>
<td>0.463</td>
</tr>
<tr>
<td></td>
<td>C₆</td>
<td>0.193</td>
<td>-0.453</td>
</tr>
<tr>
<td></td>
<td>C₅</td>
<td>0.501</td>
<td>0.542</td>
</tr>
<tr>
<td></td>
<td>N₁</td>
<td>-0.547</td>
<td>-0.553</td>
</tr>
<tr>
<td></td>
<td>C₈</td>
<td>-</td>
<td>-0.180</td>
</tr>
<tr>
<td></td>
<td>O₃</td>
<td>-</td>
<td>-0.622</td>
</tr>
</tbody>
</table>

As a result, we expect that the energy of TS₁ for CACA is increased compared to CAAA. Nonetheless, considering that the calculated ΔΔG‡ for CACA is incongruent with our results, we cannot form a quantitative conclusion from our computational studies. But, we can conclude experimentally that the difference between the selectivity of the CACA-catalyzed and the CAAA-catalyzed IFB reaction is indeed primarily dependent on the significant destabilization of TS₁, and we use our computational studies as a qualitative basis for our hypotheses to the reaction mechanism.
Figure 11: NBO analysis of TS2. (B3LYP/6-311+(2d,2p) SMD 1.2).

Comparing the experimental $\Delta \Delta G_{KQS}^+$ between CAAA and CACA (0.95 kcal/mol and 1.05 kcal/mol, respectively), TS2 is only slightly higher in energy for CACA. Here, we demonstrate that TS2 of CACA is further destabilized by steric and electrostatics compared to CAAA. The addition of the phenyl group extends the catalyst to be near the negatively charged carbonyl oxygen ($O_3$). Therefore, this would result in the repulsion between $O_3$ and $C_8$, increasing the energy of TS2.

All in all, the reaction using CACA is not as selective as CAAA. As such, we propose that CACA induces lower levels of enantioselectivity compared to CAAA because TS1 is highly destabilized. Nonetheless, CACA-TS2 does slightly compensate for this, being slightly more destabilized compared to CAAA-TS1; therefore, the reaction is still enantioselective. This is indicative, however, that CACA is less efficient as a catalyst, since it does not lower TS1 to catalyze the reaction and to induce enantioselectivity.
Figure 12: CAEA demonstrates significant, destabilizing steric interactions unobserved in CAAA. (B3LYP/6-311+(2d,2p) SMD 1.2).

Although our competition data for CAEA is quite similar to CACA, we propose that CAEA induces enantioselectivity (less effectively) through steric interactions instead. Again, to simplify our analysis we first compare CAEA to CAAA: both TS1 and TS2 energies are increased for CAEA, indicating that the addition of the t-butyl group affects the rate of catalysis for CAEA. From initial TS calculations, we notice that considerable steric interactions can be expected between the t-butyl group and the electrophile in TS1 at the lowest energy rotamer of the t-butyl group. More specifically, H2 and H3 sterically clash with H4 in the front group, while H1 clashes with H5. As a result, TS1 is higher in energy, agreeing with CAEA having a higher observed ΔΔG‡KQR. Furthermore, when comparing TS2 between these two catalysts, we expect a similar destabilization phenomenon, except the steric interaction is between the nucleophile and the t-butyl group. CACA and CAEA are relatively similar in TS1 energies, where both are highly destabilized, but CACA has a
significantly higher TS2 energy—we can relate this back to how CAEA is less effective as an asymmetric catalyst. We observed higher levels of enantioselective induction for CACA compared to CAEA because CACA-TS2 is more destabilized while CAEA-TS2 is lower in energy, similar to CAAA-TS2 experimentally. This is congruent with our observed enantiomeric excess for CAEA (83% ee), one of the lower values in this series.

We conclude our analysis of each catalyst’s transition state structures with the lowest energy rotamer of CABA, which was on par with CAAA in enantioselectivity. (TS structures for CADA have not been calculated since we still need to scan for its lowest energy rotamer). From our competition experiments, we observed an effect similar to CAAA, where enantioselectivity arises from the decrease in energy of TS1 with the concurrent increase in energy of TS2. Here, we observe certain steric and electrostatic effects absent in CAAA that would increase both TS1 and TS2 of CABA as expected from the competition experiments (Figure 13).

![Figure 13: TS structures for CABA and locations of interest. (B3LYP/6-311+(2d,2p) SMD 1.2).](image-url)
In **TS1**, we can already expect steric strain between H₁ and the thiomethyl group (2.360Å), increasing this transition state energy compared to CAAA. However, this is not destabilized to the same extent as CAEA or CACA, lacking the second steric interaction in CAEA or the electronic repulsion in CACA between the front group and C₃. While the natural charge of the sulfur could possibly result in favorable interactions between it and C₃ (**Table 8**) and thus stabilize **TS1**, the two atoms are too far from each other for this interaction to be significant (4.223Å). As a result, CABA-**TS1** is at an intermediate energy, in between CAAA and CACA or CAEA, precisely because the steric strain or electrostatic repulsion between the thiomethyl group and the substrates would be destabilizing compared to CAAA but not to the extent of CAEA or CACA, respectively. This was successfully observed in our competition experiments (**Figure 9**), where the energy of **TS1** increases from CAAA to CABA to CAEA and finally to CACA.

**Table 8**: Natural Atomic Charges for CABA TS Structures

<table>
<thead>
<tr>
<th>Atom of Interest</th>
<th>Natural Charge</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TS1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>-0.432</td>
<td>4.223Å</td>
</tr>
<tr>
<td>S1</td>
<td>0.301</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>0.241</td>
<td>2.360</td>
</tr>
<tr>
<td>H6</td>
<td>0.219</td>
<td></td>
</tr>
<tr>
<td><strong>TS2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O3</td>
<td>-0.633</td>
<td>3.661</td>
</tr>
<tr>
<td>S1</td>
<td>0.315</td>
<td></td>
</tr>
<tr>
<td>O3</td>
<td>-0.633</td>
<td>3.337</td>
</tr>
<tr>
<td>C9</td>
<td>-0.711</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>0.247</td>
<td>2.250</td>
</tr>
<tr>
<td>H6</td>
<td>0.219</td>
<td></td>
</tr>
</tbody>
</table>

As for **TS2**, it was observed that there is some sort repulsion between O3 and C9 but not to the same extent as the repulsion in CACA because attractive forces between O3 and the sulfur can help to combat this. This attraction would not be
present in CAAA and thus could correlate to the decreased energy for CABA-TS2, as demonstrated in our experiments. As such, CABA exemplified intermediate effects of our catalyst structure and helped to explain what we observed from the competition experiments quite well.

In summary, we expect that TS1 is destabilized for CABA compared to CAAA because of steric strain, but not as extreme as for CAEA. Meanwhile, CABA-TS2 is not as high in energy as the others, which we propose is partially due to attractive forces between the sulfur and one of the carbonyl oxygens from the nucleophile. In conclusion, contrary to CACA and CAEA, CABA is relatively more dependent on its stabilization of TS1 in order to increase the $\Delta \Delta G^\ddagger$ of the reaction. As a result, this makes CABA a more efficient catalyst, but not as much as CAAA.

Table 9: Calculated $\Delta \Delta G^\ddagger_{KQX}$ versus Experimental $\Delta \Delta G^\ddagger_{KQX}$.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Exp. $\Delta \Delta G^\ddagger_{KQR}$</th>
<th>Calc. $\Delta \Delta G^\ddagger_{KQR}$</th>
<th>Exp. $\Delta \Delta G^\ddagger_{KQS}$</th>
<th>Calc. $\Delta \Delta G^\ddagger_{KQS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAAA</td>
<td>-0.19 kcal/mol</td>
<td>-0.73 kcal/mol</td>
<td>0.95 kcal/mol</td>
<td>0.17 kcal/mol</td>
</tr>
<tr>
<td>CABA</td>
<td>-0.13 kcal/mol</td>
<td>-0.33 kcal/mol</td>
<td>0.87 kcal/mol</td>
<td>0.79 kcal/mol</td>
</tr>
<tr>
<td>CACA</td>
<td>0.05 kcal/mol</td>
<td>-0.87 kcal/mol</td>
<td>1.05 kcal/mol</td>
<td>0.54 kcal/mol</td>
</tr>
<tr>
<td>CAEA</td>
<td>0.04 kcal/mol</td>
<td>-0.26 kcal/mol</td>
<td>0.96 kcal/mol</td>
<td>0.83 kcal/mol</td>
</tr>
</tbody>
</table>

As mentioned, we have DFT calculations on the transition state and encounter complex structures for CAAA, CABA, CACA, and CAEA (Table 9). We observed that the $\Delta \Delta G^\ddagger_{KQS}$ for both CAAA and CACA correlate with each other, where the latter catalyst is more destabilized in TS-2. However, $\Delta \Delta G^\ddagger_{KQR}$ for CACA is much lower than for CAAA and thus CACA-TS1 is highly stabilized, contrary to our previous discussion. Again, it is important to note that the calculated $\Delta \Delta G^\ddagger$ is inflated,

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5 B3LYP/6-311G+(2d,2p) SMD 1.2/B3LYP/6-31G+(d,p)
and this observation could answer that problem. Surprisingly, the calculated $\Delta\Delta G^\ddagger_{KQX}$ values for CABA were rather well behaved, only being $\pm 0.2$ kcal/mol away from the observed values. CAEA follows in a similar fashion, where the calculated values were also only $\pm 0.2$ kcal/mol away from the observed values. The differences between the calculated and experimental $\Delta\Delta G^\ddagger_{KQX}$ values were analyzed based on the size of the basis set and solvation.

![Figure 14: Differences in Calculated and Experimental $\Delta\Delta G^\ddagger_{KQX}$ in kcal/mol.](image)

We demonstrate that, at the 6-311+(2p,2d) SMD 1.2 level, this difference converges near zero. This is promising for the future optimization of our computational methods to increase accuracy and obtain a clearer correlation between our computational and experimental studies.

In conclusion, our pyrimidinyl catalysts generally induce enantioselectivity by destabilizing TS2; however, we also now have knowledge on how these catalysts...
work and how we can increase enantioselectivity for future IFB reactions based on whether we want the catalyst to decrease TS1, further increase TS2, or decrease TS1 while increasing TS2 at the same time. With this methodology in mind, we can apply our studies in the future as a strategy to future asymmetric IFB reactions. By predicting how structural changes could affect steric effects and electronic effects at the cavity of the catalyst-substrate complex, we now have a powerful tool in strategic catalyst screening, which we hope can be optimized and automated through a machine-learning program for use in the future.
References


4. Conclusions

4.1 Conclusions

In conclusion, we have optimized a new IFB reaction using 4-hydroxycoumarin to synthetically useful yields, expanding our scope to new classes of nucleophiles. However, we have only observed enantioselectivities up to 30% ee for this IFB reaction. In hopes of increasing enantioselectivity, we have attempted running the IFB reaction in the presence of water, with precedent from multiple studies on the rate acceleration of aldol reactions in water or in the presence of water. This did not prove to be fruitful since the water actually did not participate in the catalytic cycle, such as in proline-mediated aldol reactions. Because of the gap of our knowledge on the mechanism through which our cinchona alkaloid catalysts work, we attempted to guide our catalyst screening of this new IFB reaction through ab initio methods.

We extended this idea to investigate the classic IFB reaction. First, a new method to synthesizing the MAXY series of catalysts was developed. Then, we compared our experimental results from computational studies on the classic IFB reaction using the AAXY, MAXY, CAXY catalysts. It was determined theoretically and experimentally that the CAXY series induced the highest levels of enantioselectivity, then the MAXY series, and finally the AAXY series, which we reasoned was due to the increase in steric interactions in the more favorable TS as the substituent at the 6-position of the pyrimidinyl ring increases in size. Our experimental results also coincided with our computational results, except the XXCA catalysts tended to have much higher theoretical $\Delta\Delta G^\dagger$ values than observed. As such,
we have also attempted to increase our level of theory, use larger basis sets, and model with solvation. While this did not provide conclusive results, the optimization of our computational methods appears to be moving in a favorable direction and could be improved in the future.

We then attempted to answer the fundamental question as to how the cinchona alkaloid catalysts induce enantioselectivity. Experimentally, our catalysts were competed with a structurally-similar achiral catalyst, quinuclidine hydrochloride, to gauge its effects on enantioselectivity and the transition state energies. By using a simple Curtin-Hammett model, we derived an equation to compare the rate constants for the chiral and achiral pathways for both transition states and related these factors to their respective changes in transition state energies ($\Delta \Delta G^\dagger_{KQ}$). The competition experiments proved to be effective since, by setting the baseline energy to the achiral TS energy, we were able to compare catalysts to each other. In general, we demonstrated that enantioselectivity is induced by increasing the TS energy of the $Si$ face attack ($TS2$). However, while some catalysts stabilized $TS1$ compared to the achiral TS while still destabilizing $TS2$, other catalysts did not have the same mechanism. We have presented two catalysts, CACA and CAEA, where $TS1$ is highly destabilized, similar in energy to the achiral TS, while $TS2$ is slightly more destabilized to still give relatively impressive levels of enantioselective induction. In order to reason these observations, we returned to modeling the TS structure for most of the catalysts. Here, we found areas within the TS complexes where favorable or unfavorable steric or electrostatic interactions can be located, coinciding with our experimental methods to further augment our theories. Our methodology is quite
fruitful in comparing catalysts to each other, and as a result, we now have further understanding of our cinchona alkaloid catalysts and their mechanisms to enantioselective induction.

4.2 Future Directions

The IFB reaction with 4-hydroxycoumarin has yet to be optimized to synthetically useful enantioselectivities, and we hope to utilize the knowledge gained from our studies on the classic IFB reaction to guide this and future optimizations to come. As for the classic IFB reaction itself, we also have yet to optimize our computational methods in transition state searching to be reflective of our experimental observations. In addition, competition reactions for the MAXY and AAXY catalysts could give us insight on the effects of the 6-position on enantioselectivity, which would be an interesting question to pursue. Also, modeling CADA and comparing our results to the competition experiments would complete the CAXY series of catalysts; however, we need to determine which rotamer is the lowest in energy and search for a transition state structure at that point. Finally, we wish to use our principles from past and present studies on the asymmetric induction of IFB reactions to build a machine learning program that can be used to supply potential catalysts to strategically guide and expedite catalyst screening for future IFB reactions.
5. Methods

5.1 Computational Methods

Calculations were carried out with the Gaussian16 program. Optimization calculations were performed with frozen coordinates between the bond-forming carbons (~2.13Å) and were conducted with either the Hartree-Fock method with the 3-21G* basis set or the functional hybrid B3LYP with the 6-31G+(d,p) basis set for all atoms. TS(berny) optimization calculations were also performed with either of the aforementioned methods without the frozen coordinates. Vibrational analyses of the optimized structures were performed in order to determine whether they corresponded to a saddle point in the potential energy curve. Single point energy analyses were performed for solvation effects and transition state energies at the 6-311+(2d,2p) basis set. Mulliken charges and NBO analyses were used to find possible locations in each catalytic complex for electronic repulsion and/or attraction.
5.2 Experimental

General Procedures

All reagents were used as received unless otherwise stated in the following experimental procedures. DCM, diethyl ether, and toluene were used from a solvent purification system by filtering through an activated alumina column. Flash silica gel 60 Å, 40-63 µm was obtained from Dynamic Adsorbent Inc. or Silicycle, and basic alumina activity III was obtained from EcoChrom. Thin-layer chromatography was performed with Silicycle 0.25 mm, 60 Å pore size silica gel plates with an F-254 indicator or basic alumina III plates. TLC plates were visualized by a 254 nm UV lamp.

HPLC analyses were performed by a Thermo Separation Product Spectra Series P200 HPLC equipped with a Dynamax Absorbance Model UV-D detector, a Hewlett-Packard 3395 integrator, and a Chiralpac AD or OD-H chiral column. A Richo Aficio MP C6501 SP copier was used to scan paper traces, and Adobe Acrobat 8 Pro was used to integrate the peak areas.

All $^1$H and $^{13}$C NMR spectra were obtained on either a 300 MHz or a 400 MHz Varian instrument. Specific rotation was taken on a Perkin-Elmer 241 Polarimeter. High resolution mass spectra were run at University of Illinois at Urbana-Champaign. All aqueous phases that were used to wash crude reaction mixtures were backwashed with the organic solvent unless otherwise stated.
Methods and Materials

Synthesis of 1-phenylpropane-1,2-dione. To a flame dried RBF equipped with a magnetic stir bar and a condenser under nitrogen was added 1 g of 1-phenylpropane-1,2-dione (6.76 mmol) and 3 mL of chloroform. To mixture was added 0.382 mL of bromine (7.43 mmol) and an additional 3.8 mL of chloroform. The reaction mixture was allowed to reflux for 24 hours then cooled to RT. The reaction mixture was washed with 5 mL of 10% Na₂S₂O₃ then another 5 mL of saturated aqueous NaHCO₃. The collected organic layers were dried with sodium sulfate, and the solvents were removed in vacuo. The crude mixture was purified through a silica plug to yield a yellow oil, 1, with 41% yield. This compound has been previously characterized in the literature.³ ¹H-NMR (300 MHz, CDCl₃): δ8.03 (m, 2H), 7.68 (m, 1H), 7.53 (m, 3H), 4.39 (s, 2H).

General Procedure for the IFB reaction using Hydroxycoumarin:

To a flame dried RBF equipped with a magnetic stir bar and rubber septum under nitrogen was added 35.6 mg of 4-hydroxycoumarin (0.220 mmol) and 4 mL of dry DCM. Then, 22 mg of KHCO₃ (0.220 mmol) was added, followed by 10 mol% of catalyst. To the reaction mixture was added 50 mg of 1 and the reaction was allowed...
to stir for 16 hr at RT. After 16 hr, the reaction was washed with 10 mL saturated aqueous NaHCO₃ and 10 mL NaHSO₄. The collected organic layers were dried over sodium sulfate, and the solvents were removed in vacuo. The crude mixture was purified by silica flash chromatography (1% EtOAc:DCM) to afford a white solid, 3, with 60-90% yield. HPLC analysis was conducted using Daicel Chiralpak OD-H, 90:10 hexanes:ethanol, 1 mL/min, 260 nm, Rᵳ = 13.180 min, 17.030 min. This compound has been previously characterized.³ ¹H-NMR (300 MHz, CDCl₃): δ7.88 (m, 3H), 7.67 (m, 1H), 7.57 (m, 1H), 7.41 (m, 4H), 5.35 (s, 1H), 5.25 (m, 1H), 4.92 (m, 1H).

**General Procedure for the IFB reaction using Ethyl Bromopyruvate:**

![Chemical Reaction Diagram]

To a flame dried RBF equipped with a rubber septum and magnetic stir bar under nitrogen was added 29 mg (0.256 mmol) of cyclohexadione and 4 mL of dry DCM at room temperature. 55 mg (0.256 mmol) of Proton Sponge was added, which was then followed by 10 mol% of the catalyst. For the competition reactions, the respective mol% of Quinuclidine•HCl is added after the chiral catalyst. After several minutes of stirring, the reaction is cooled down to -78°C, and 0.032 mL (0.256 mmol) of ethyl bromopyruvate is dissolved in 1 mL of dry DCM. The ethyl bromopyruvate solution is then added dropwise to the reaction mixture at -78°C, and the reaction is allowed to stir for 10 minutes. After 10 minutes, the reaction is washed with 10 mL of saturated NaHCO₃ and then followed by 10 mL of 1M NaHSO₄. The combined
organic layers were dried with sodium sulfate and the solvent was removed \textit{in vacuo} to yield an orange oil. The crude mixture was purified by flash chromatography (1:100 MeOH:DCM) to afford a white solid, \textbf{4}, with 60-80\% yield. Two different HPLC conditions were used to analyze \textbf{4}. For \textbf{Table 3}: Daicel Chiralpak OD-H, 95:5 hexanes:ethanol, 1 mL/min, 257 nm, R\text{t} = 15.934 min, 18.977 min. For \textbf{Table 5}: Daicel Chiralpak AD, 90:10 hexanes:ethanol, 1 mL/min, 257 nm, R\text{t} = 20.88 min, 26.31 min. This compound has been characterized in the literature.\textsuperscript{4} \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 4.73 (d, \( J = 10.6 \) Hz, 1H), 4.49 (d, \( J = 10.6 \) Hz, 1H), 4.28 (q, \( J = 7.3 \) Hz, 2H), 3.99 (bs, 1H), 2.54 (m, 2H), 2.34 (m, 2H), 2.08 (m, 2H), 1.28 (t, \( J = 7.1 \) Hz, 3H).

\begin{center}
\begin{tikzpicture}
\node (5) [draw] at (0,0) {5};
\node (6) [draw] at (2,0) {6};
\draw [->, thick] (5) -- node [midway, above] {2.2 eq MCPBA} node [midway, below] {CHCl\textsubscript{3}, 12 hr. RT} (6);
\end{tikzpicture}
\end{center}

\textbf{Synthesis of 4,6-dichloro-2-methylsufone-5-phenylpyrimidine}. To a flame dried RBF under nitrogen equipped with a rubber septum and a magnetic stir bar was added 2 g (7.38 mmol) of 4,6-dichloro-2-thiomethyl-5-phenylpyrimidine in 20 mL of chloroform. To this mixture was added 4 g of MCPBA (70\% by wt), and the reaction was allowed to stir for 12 hours at RT. The resulting white precipitate was filtered off through a frit, and the filtrate was washed with saturated 40 mL NaHCO\textsubscript{3}. The organic layer was dried over sodium sulfate, and the solvent was removed \textit{in vacuo} to yield an off-white solid, \textbf{6}, with 98\% yield. This compound has been previously characterized in the literature.\textsuperscript{5}
Synthesis of 4-6-Dichloro-5-phenylpyrimidine. To a flame dried RBF equipped with a rubber septum and a magnetic stir bar was added 2.20 g (7.26 mmol) of 6, 36 mL of CHCl₃, and 36 mL of MeOH. The reaction mixture is allowed to cool to 0°C, and 0.275 g (7.26 mmol) of NaBH₄ was added in small portions. The reaction was then allowed to warm up to RT, and the reaction was tracked by TLC (silica gel, 50:50 EtOAc:Hexanes). After completion, the solvents were removed under reduced pressure, and the crude mixture was dissolved in CHCl₃ and washed with DI H₂O. The crude mixture was dried over sodium sulfate and the solvents were removed under reduced pressure. The resulting white solid is then dissolved in MeOH, and 5 drops of formic acid was added. The solvent was removed in vacuo to afford a white solid. The crude mixture was purified by silica gel flash chromatography (1% EtOAc:Hexanes) to provide a white solid, 7, with 68% yield. This compound has been previously characterized in the literature.⁵
Representative Procedure for the Metal-Halogen Exchange:

To a flame dried RBF equipped with a rubber septum and a magnetic stir bar under nitrogen, 1.5 equiv. of the aryl bromide was added in 4 mL dry diethyl ether at -10°C. 0.222 mL of 1.2 M \( n\)-BuLi (1.5 equiv.) was added at -10°C, and the reaction mixture was allowed to stir for 20-40 minutes. The reaction mixture was cooled down to -35°C, and 200 mg of 7 dissolved in ether was added dropwise. The reaction was allowed to stir at -30°C for another 20-40 minutes, after which the reaction was warmed up to 0°C. To the reaction mixture was added 10 drops of acetic acid, 10 drops of distilled H\(_2\)O, and 2 mL of THF. A solution of 202 mg of DDQ (1 equiv.) dissolved in THF was then added, and the reaction was allowed to stir at RT for 10 minutes. To the flask was added 10 mL of 1 M NaOH. The organic layer was collected, and the aqueous layer was washed with DCM. The combined organic layers were dried over sodium sulfate, and the solvents were removed \textit{in vacuo}. The crude mixture was purified by silica gel flash chromatography (1-50\% DCM:Hexanes) to provide the respective 4,6-dichloro-2-aryl-5-phenylpyrimidine compound.
4,6-dichloro-2,5-diphenylpyrimidine. (37% yield, white powder). This compound was prepared using the representative procedure above. This compound has been previously characterized.\textsuperscript{6}

4,6-dichloro-2-(naphthalen-1-yl)-5-phenylpyrimidine. (35% yield, white powder). This compound was prepared using the representative procedure above. This compound has been previously characterized.\textsuperscript{6}

**Preparation of \textit{t}-Butyl Substituted Pyrimidines:**

![Chemical reaction diagram]

To a stirred solution of 0.5 M sodium ethoxide prepared from sodium (3.38 equiv.) in EtOH under nitrogen was added \textit{t}-butylcarbamidine hydrochloride (1.14 equiv.)
equiv.). After 5 minutes, 1 equiv. of 9 was added to the suspension. The reaction mixture was refluxed for 48 hours, then cooled to RT. The reaction mixture was then diluted with H₂O until the precipitate dissolves. Then, the pH was adjusted to 3 by adding concentrated aqueous HCl dropwise. The white precipitate was collected and dried in vacuo to afford a white powder, 10.

2-(tert-butyl)-5-phenylpyrimidine-4,6-diol. (19% yield, white powder). This compound was prepared using the representative procedure above. This compound has been previously characterized.⁷

2,5-di-tert-butylpyrimidine-4,6-diol. (11% yield, white powder). This compound was prepared using the representative procedure above. This compound has been previously characterized.⁷
Chlorination of Substituted Pyrimidine-4,6-Diols:

To 10 (1 equiv.) was added POCl$_3$ (0.5 M), pyridine hydrochloride (6.2 equiv.), and H$_3$PO$_4$ (1.4 equiv.). The resulting reaction mixture was refluxed for 48 hours. Then, most of the POCl$_3$ was removed in vacuo, and the residue was poured onto ice. The mixture was then neutralized with a saturated aqueous solution of NaHCO$_3$ and extracted with EtOAc. The combined organic layers were dried with Na$_2$SO$_4$, and the solvents were removed in vacuo. The crude mixture was purified silica flash chromatography in hexanes to provide 11 as a colorless oil.

2-(tert-butyl)-4,6-dichloro-5-phenylpyrimidine. (34% yield, yellow oil). This compound was prepared using the representative procedure above. This compound has been previously characterized.$^6$
**2,5-di-tert-butyl-4,6-dichloropyrimidine.** This compound was prepared using the representative procedure above. This compound has been previously characterized.\(^6\)

**Representative Procedure for the Synthesis of AAXY:**

![Reaction Scheme]

To a flame dried round bottom flask equipped with a Dean-Stark condenser is added 2 eq. quinidine, 6 eq. potassium hydroxide, and toluene (0.04 M). The reaction mixture is heated to 110°C and refluxed for one hour. At this point, 1 eq. of the respective dichloropyrimidine is added and the reaction is allowed to continue refluxing for another hour. An additional 0.5 eq of the dichloropyrimidine is added to the mixture and the reaction mixture is refluxed for one more hour. The reaction mixture is allowed to cool to room temperature and the solvent is removed *in vacuo*. The crude mixture is dissolved in DCM and washed with DI H\(_2\)O. The combined organic layers are dried over sodium sulfate and concentrated *in vacuo*. The crude solid is then purified by flash column chromatography (activity III basic alumina, 40% EtOAc:Hex) to yield the product as a white foam.
5-phenylpyrimidine-bis-(9-O-quinidine)ether catalyst. This compound was prepared using the representative procedure above. This compound has been previously characterized in the literature. 

2-thiomethyl-5-phenylpyrimidine-bis-(9-O-quinidine)ether catalyst. This compound was prepared using the representative procedure above. This compound has been previously characterized. 

2,5-diphenylpyrimidine-bis-(9-O-quinidine)ether catalyst. This compound was prepared using the representative procedure above. This compound has been previously characterized. 

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Representative Procedure for the Synthesis of CAXY:

To a flame dried RBF equipped with a Dean-Stark condenser was added 1 equiv. of quinidine and charged with dry toluene (0.05 M). 3 equiv. of powdered KOH was then added, and the reaction mixture was allowed to reflux for 1 hour. The respective dichloropyrimidine is added, and the reaction mixture was refluxed for another hour. Another equivalent of KOH was added, and the reaction mixture was allowed to reflux for an additional hour, after which the solvents were removed in vacuo. The crude mixture was purified by alumina flash chromatography (activity III basic alumina, 40% EtOAc:Hexanes) to afford the product, 12.

6-chloro-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst. This compound was prepared using the representative procedure above. This compound has been previously characterized in the literature.\(^5\)
2-thiomethyl-6-chloro-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst. (58% yield, white powder). This compound was prepared using the representative procedure above. $[\alpha]_{D}^{25} = -137.2^\circ$ (c 0.01, CH$_2$Cl$_2$). IR (thin film) $\nu_{\text{max}}$: 2933, 1620, 1227, 792, 667 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (d, $J = 4.8$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 7.53-7.45 (m, 4H), 7.36-7.35 (m, 5H), 7.22 (d, $J = 4.8$ Hz, 1H), 6.89 (d, $J = 4.8$ Hz, 1H), 5.34-5.22 (m, 1H), 4.94-4.85 (m, 2H), 3.85 (s, 3H), 3.16-3.08 (m, 1H), 2.81-2.72 (m, 4H) 2.11-2.08 (m, 4H), 1.80-1.72 (m, 1H), 1.63 (bs, 1H), 1.42-1.40 (m, 2H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 170.56, 165.79, 159.55, 157.92, 147.38, 144.61, 143.70, 140.03, 131.79, 130.04, 128.66, 128.58, 128.50, 128.31, 126.56, 121.96, 118.29, 115.88, 114.89, 101.14, 59.13, 55.64, 50.05, 49.70, 40.22, 28.35, 26.09, 25.92, 22.35, 13.93, 12.21. HRMS (ESI) m/z: 559.1932 (M + H$^+$), Calculated for C$_{31}$H$_{31}$ClN$_4$O$_2$SH$^+$ 559.1929.
6-chloro-2,5-diphenylpyrimidine-4-(9-O-quinidine)ether catalyst. (55% yield, white powder). This compound was prepared using the representative procedure above. \([\alpha]^{25}_D = -172.0^\circ \text{ (c 0.01, CH}_2\text{Cl}_2)\). IR (thin film) \(\nu_{max}: 2936, 1719, 1620, 1568, 1518, 1408, 1229, 1027, 992, 914, 847, 778, 706 \text{ cm}^{-1}\). \(^1\text{H}-\text{NMR (400 MHz, CDCl}_3\): \(\delta 8.71 \text{ (d, } J = 4.8 \text{ Hz, 1H), 8.05-8.00 (m, 4H), 7.57-7.23 (m, 15H), 7.05 \text{ (m, 1H), 5.42-5.33 (m, 1H), 4.98-4.88 (m, 2H), 3.95 (s, 3H), 3.21-3.15 (m, 1H), 2.88-2.64 (m, 5H), 2.17-2.03 (m, 1H), 1.84-1.82 (m, 1H), 1.70 \text{ (bs, 1H), 1.47-1.42 (m, 2H).} \(^{13}\text{C}-\text{NMR (400 MHz, CDCl}_3\): \(\delta 166.45, 162.42, 160.12, 158.08, 147.47, 144.69, 144.33, 140.11, 135.61, 132.10, 131.99, 131.29, 129.98, 129.66, 128.64, 128.58, 128.32, 128.23, 126.89, 121.98, 118.69, 118.29, 114.86, 101.16, 69.20, 63.99, 56.63, 55.67, 49.95, 40.24, 29.69, 29.26, 26.15, 24.67, 22.85, 12.18. HRMS (ESI) m/z: 589.2365 (M + H\(^+\)), Calculated for C\(_{36}\)H\(_{33}\)ClN\(_4\)O\(_2\)H\(^+\) 589.2365.
2-(naphthalen-1-yl)-6-chloro-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst. (72% yield, white powder). This compound was prepared using the representative procedure above. \([\alpha]^{25}_D = -210.4^\circ\) (c 0.01, CH\(_2\)Cl\(_2\)). IR (thin film) \(\nu_{\text{max}}:\)

- 2936, 1947, 1720, 1565, 1380, 1301, 1228, 1049, 991, 913, 860, 800, 735, 671, 604 cm\(^{-1}\).
- \(1^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta 8.77\) (d, \(J = 4.8 \text{ Hz}, 1H\)), \(8.33\) (d, \(J = 8.8 \text{ Hz}, 1H\)), \(8.08\) (d, \(J = 8.8 \text{ Hz}, 1H\)), \(7.88\) (d, \(J = 8 \text{ Hz}, 1H\)), \(7.81\) (d, \(J = 8 \text{ Hz}, 1H\)), \(7.69\) (d, \(J = 7.2 \text{ Hz}, 1H\)), \(7.63-7.53\) (m, 6H), \(7.39-7.33\) (m, 5H), \(7.04-7.00\) (m, 2H), \(5.43-5.26\) (m, 1H), \(4.96-4.87\) (m, 2H), \(3.54\) (s, 3H), \(3.22-3.16\) (m, 1H), \(2.82-2.59\) (m, 5H), \(2.17-2.10\) (m, 1H), \(1.86-1.80\) (m, 1H), \(1.69\) (s, 1H), \(1.44-1.42\) (m, 2H).
- \(13^C\)-NMR (400 MHz, CDCl\(_3\)): \(\delta 166.29, 164.57, 159.90, 157.94, 147.47, 144.73, 144.17, 140.10, 133.82, 133.69, 131.85, 131.18, 130.62, 130.04, 129.92, 128.69, 128.63, 128.34, 126.88, 126.78, 125.75, 125.33, 125.78, 122.19, 118.55, 114.84, 101.54, 59.57, 55.37, 49.86, 49.66, 40.24, 28.203, 26.16, 22.93, 12.19. HRMS (ESI) m/z: 639.2527 (M + H\(^+\)). Calculated for C\(_{40}\)H\(_{35}\)ClN\(_4\)O\(_2\)H\(^+\) 639.2521.
2-(tert-butyl)-6-chloro-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst. (79% yield, white powder). This compound was prepared using the representative procedure above. $[\alpha]_{D}^{25} = -113.6^\circ$ (c 0.01, CH$_2$Cl$_2$). IR (thin film) $\nu_{\text{max}}$: 2934, 1720, 1621, 1575, 1519, 1410, 1303, 1227, 916, 765, 736, 699 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.66 (d, $J = 4.8$ Hz, 1H), 8.03-8.00 (m, 1H), 7.55-7.46 (m, 4H), 7.40-7.35 (m, 5H), 7.23 (m, 1H), 6.88 (m, 1H), 5.28-5.24 (m, 1H), 4.94-4.85 (m, 2H), 3.84 (s, 3H), 3.13-3.10 (m, 1H), 2.84-2.63 (m, 4H), 2.14-2.08 (m, 1H), 1.82-1.77 (m, 1H), 1.64 (bs, 1H), 1.44-1.40 (m, 2H), 1.02 (s, 9H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 175.76, 165.92, 159.51, 157.84, 147.29, 144.63, 144.19, 140.17, 132.25, 131.86, 129.88, 129.65, 128.65, 128.56, 128.42, 128.31, 126.62, 121.92, 118.36, 117.64, 114.77, 101.21, 69.19, 63.98, 59.11, 55.56, 50.06, 49.73, 40.27, 39.17, 29.64, 28.4, 28.37, 26.12. HRMS (ESI) m/z: 569.2681 (M + H$^+$), Calculated for C$_{34}$H$_{37}$ClN$_4$O$_2$H$^+$ 569.2678.

6-chloro-5-di(tert-butyl)pyrimidine-4-(9-O-quinidine)ether catalyst. (27% yield, white powder). This compound was prepared using the representative procedure
above. $[\alpha]^{25}_D = -106.1^\circ$ (c 0.01, CH$_2$Cl$_2$). IR (thin film) $\nu_{max}$: 2932, 1506, 1364, 1340, 1030, 1001, 846, 713 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.70 (d, $J = 4.8$ Hz, 1H), 8.45-7.98 (m, 1H), 7.54-7.51 (m, 1H), 7.41-7.34 (m, 1H), 6.97-6.94 (m, 1H), 6.05-5.93 (m, 1H), 5.12-5.06 (m, 2H), 3.96 (s, 3H), 3.50-3.42 (m, 1H), 3.00-2.90 (m, 2H), 2.70-2.67 (m, 2H), 2.30-2.28 (m, 1H), 1.84-1.72 (m, 5H), 1.63-1.51 (m, 12H), 1.28-1.25 (m, 3H), 1.05 (m, 9H). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ 172.31, 167.25, 158.94, 157.49, 147.50, 144.58, 140.20, 132.97, 131.79, 129.66, 128.32, 127.90, 122.47, 121.56, 118.97, 114.86, 102.27, 69.20, 63.99, 61.42, 55.43, 49.61, 49.32, 39.78, 38.41, 35.12, 31.61, 31.45, 29.68, 28.83, 27.73, 26.41, 26.20. HRMS (ESI) m/z: 549.2993 (M + H$^+$), Calculated for C$_{32}$H$_{41}$ClN$_4$O$_2$H$^+$ 549.2991.

**Representative Procedure for the Synthesis of MAXY:**

To a flame dried RBF equipped with a magnetic stir bar and a rubber septum was charged 12 and a 50:50 mixture of MeOH:H$_2$O (0.01 M). 256 equiv. of powdered KOH was added, and the reaction was allowed to reflux for 7 hours to overnight and checked for completion by NMR. After which, the reaction was allowed to cool to RT and washed with NaCO$_3$. The aqueous layer was then washed with DCM, and the combined organic layers was dried with Na$_2$SO$_4$. The solvents were then removed *in vacuo*. The resulting crude mixture was purified with alumina flash chromatography (activity III basic alumina, 30% EtOAc:Hexanes) to afford the product, 13.
6-methoxy-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst. (56% yield, white powder). This compound was prepared using the representative procedure above. 

\[ \alpha^D = -52.0^\circ \text{ (c 0.01, CH}_2\text{Cl}_2). \]  

IR (thin film) \( \nu_{\text{max}} \): 2931, 1716, 1566, 1112, 914, 808 cm\(^{-1}\).  

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta 8.67 (d, J = \ , 1H), 8.24 (s, 1H), 8.05-7.99 \) (m, 2H), 7.56-7.35 (m, 10H), 7.28-7.26 (m, 2H), 7.04-6.99 (m, 1H), 5.424 (m, 1H), 4.97-4.89 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.21 (m, 1H), 2.74-2.12 (m, 5H), 2.05-1.82 (m, 1H), 1.73-1.67 (m, 1H), 1.61 (s, 2H), 1.56-1.42 (m, 3H).  

\(^{13}\)C-NMR (400 MHz, CDCl\(_3\)): \( \delta 167.85, 155.66, 155.55, 147.37, 144.68, 132.97, 131.75, 130.76, 130.40, 129.66, 128.32, 128.27, 127.82, 126.71, 121.82, 110.00, 106.30, 101.61, 85.91, 69.25, 69.20, 63.99, 59.23, 55.55, 55.00, 54.46, 49.95, 49.53, 29.68, 28.30, 26.20, 22.64, 14.10. HRMS (ESI) m/z: 509.2544 (M + H\(^+\)\), Calculated for C\(_{31}\)H\(_{32}\)N\(_4\)O\(_3\)H\(^+\) 509.2547.

2-thiomethyl-6-methoxy-5-phenylpyrimidine-4-(9-O-quinidine)ether catalyst.  

(34% yield, white powder). This compound was prepared using the representative
procedure above. \([\alpha]^{25}_{D} = -99.2^\circ (c \ 0.01, \text{CH}_2\text{Cl}_2).\) IR (thin film) \(\nu_{\text{max}}: 2933, 2358, 1578, 1508, 1354, 1230, 1119, 914, 799 \text{ cm}^{-1}.\) \(^1\text{H}-\text{NMR} (400 \text{ MHz, CDCl}_3): \delta 8.71 (d, \(J = 4.8 \text{ Hz, 1H}), 8.05-8.00 (m, 1H), 7.54-7.34 (m, 7H), 7.29-7.26 (m, 2H), 6.95 (m, 1H), 5.47-5.26 (m, 1H), 4.96-4.86 (m, 2H), 3.86 (s, 6H), 3.17-3.13 (m, 1H), 2.86-2.67 (m, 4H), 2.13 (s, 3H), 1.91-1.85 (m, 2H), 1.67 (s, 1H), 1.47-1.43 (m, 2H).\) \(^{13}\text{C}-\text{NMR} (400 \text{ MHz, CDCl}_3): \delta 169.62, 168.78, 167.48, 165.29, 157.80, 147.73, 144.64, 140.22, 132.97, 131.80, 131.24, 130.99, 130.70, 130.56, 129.66, 128.32, 128.25, 127.84, 127.51, 127.37, 126.69, 121.90, 118.60, 114.76, 101.46, 69.20, 63.99, 59.26, 55.65, 54.51, 49.91, 49.66, 40.37, 36.66, 29.69, 28.99, 26.59, 22.50, 13.83. HRMS (ESI) m/z: Found 555.2431, Calculated for C\(_{32}\)H\(_{34}\)N\(_4\)O\(_3\)SH\(^+\) 555.2424.

![](image)

**6-methoxy-2,5-diphenylpyrimidine-4-(9-O-quinidine)ether catalyst.** (81% yield, white powder). This compound was prepared using the representative procedure above. \([\alpha]^{25}_{D} = -119.1^\circ (c \ 0.01, \text{CH}_2\text{Cl}_2).\) IR (thin film) \(\nu_{\text{max}}: 2939, 1602, 1541, 1411, 1362, 1229, 1118, 1027, 993, 706 \text{ cm}^{-1}.\) \(^1\text{H}-\text{NMR} (400 \text{ MHz, CDCl}_3): \delta 8.71 (d, \(J = 4.8 \text{ Hz, 1H}), 8.09-8.00 (m, 4H), 7.57-7.23 (m, 16H), 7.13-7.00 (m, 1H), 5.43-5.30 (m, 1H), 4.97-4.90 (m, 2H), 4.00-3.91 (m, 6H), 3.25-3.16 (m, 1H), 2.98-2.65 (m, 5H), 2.18-2.16 (m, 1H), 1.99-1.96 (m, 1H), 1.94-1.82 (m, 1H) 1.71 (s, 1H), 1.50-1.47 (m,
$^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$167.95, 162.43, 160.98, 158.09, 157.95, 147.47, 144.71, 136.93, 135.61, 132.11, 131.99, 131.93, 131.28, 131.16, 130.57, 130.55, 129.97, 128.63, 128.57, 128.32, 128.21, 128.03, 127.61, 127.02, 126.87, 121.94, 118.67, 114.89, 104.04, 101.36, 101.16, 59.63, 59.55, 55.68, 54.28, 49.94, 49.86, 49.71, 40.31, 40.21, 28.33, 28.26. HRMS (ESI) m/z: 585.2866 (M + H$^+$), Calculated for C$_{37}$H$_{36}$N$_4$O$_3$H$^+$ 585.2860.
References


S. Spectra