The Study of the enantioselectivity of a chiral catalyst for the Interrupted Feist-Bénary Reaction

by

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Class of 2009

A thesis submitted to the faculty of Wesleyan University in partial fulfillment of the requirements for the Degree of Bachelor of Arts with Departmental Honors in Chemistry

Middletown, Connecticut April, 2009
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ACKNOWLEDGMENTS

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Acknowledgements

First and foremost I would like to thank Dr. Calter for giving me the opportunity to do research in his laboratory and his patience ever time I had to ask question, no matter how simple it seemed. I also want to thank the rest of Calter lab, Na for having answer to every lab question, Sasha for managing to coexist in the same hood, Max, Jun, Henry and the Sams. The Howard Hughes Fellowship deserves credit for allowing me to fully experience what doing research is like; the joy of successfully synthesizing a compound is truly unique.

I would like to thank my parents, beth and John, for giving making it possible for me to attend Wesleyan and all of the opportunities it has afforded me. My sister for being my muse every time I needed it. My house, Alex, Minsu, Silver, and Lex for putting up with me during this process.

Sameer for being my chemistry buddy from the beginning. Shuk Kei for being the master of the scanner in HasLab and everyone else at Wesleyan for making the experience for being so rich and formative during my time here.
Abstract

The Feist- Bénary reaction was initially designed to synthesize substituted furan rings from β-ketoesters and α-halocarboxyls. Calter group has been investigating the Interrupted Feist- Bénary and the achiral synthesis involved. This has important implications of the synthesis of medically relevant molecules such as glycinol and rocaglamide. Ryan Phillips had previously produced a highly enantioselective (QD$_2$)PYR catalyst.

My research concerns the modification of this catalyst on the pyrimidine ring in an attempt to better understand how the rest of the catalytic molecule affects the enantioselectivity. Initially results are promising and show that the replacement of the second quinidine with various substituents can dramatically alter the enantioselectivity of the reaction. This is based on the steric effect of the substituent and further research should help confirm this methodology.
Introduction to Chirality

1.1. Organic Chemistry and Chirality

Organic Chemistry was originally considered as the study of substances derived by living beings, but has now been redefined as the chemistry of carbon containing compounds. In organic chemistry, as in all other forms of chemistry, the physical and chemical properties of molecules depend on not only the atoms that are present in the molecule but also the spatial arrangement of the atoms. Spatial arrangement and its importance became abundantly clear when Friedrich Wohler demonstrated that ammonium cyanate, an inorganic compound, could be converted to Urea, an organic one, even though they contained the same elemental chemical composition\(^1\). Since this event, modern organic chemistry has devoted great time and effort to manipulating the spatial arrangement of functional groups and atom or groups atoms that are responsible for the molecules reactivity and chemical properties.

\[
\begin{align*}
\text{NH}_3\text{HCN}^+ + \text{O}^- & \rightarrow \text{H}_2\text{N}^-\text{C}^=\text{NH}_2\\
\text{Ammonium Cyanate} & \quad \text{Urea}
\end{align*}
\]

**Figure 1**: Conversion of Ammonium Cyanate to Urea

Given that carbon forms the basis for organic chemical compounds, the spatial arrangement of the functional groups around a central carbon atom is vital
to organic chemistry. Given that carbon contains four electrons in its valence electron shell, it can form up to four bonds and therefore hold up to four substituents. Valence Shell Electron Pair Repulsion (VSEPR) dictates how the substituents will arrange themselves around the central atoms, with the tetrahedral form being the most likely. This will allow for the most space between the substituents and reduce the repulsion created by the electron-electron interaction of the substituents. In Figure 2 all of the substituents are 109.5° away from each other.

![Figure 2: Tetrahedral form of substituents around a carbon center](image)

If two of the R groups are identical to each other then a mirror plane will exist, where if the molecule is rotated 180° around the plane, the rotated molecule can be superimposed on the original. The super-imposability can be tested by rotating molecule B (Figure 3) by 180°. If B and the original are super-imposable on each other then they are considered two different views of an identical molecule, and the molecule is considered achiral.
However, if there are four distinct functional groups bonded to the central carbon atom, no mirror plane will exist for the molecule, and rotation around a mirror plane will form two distinct three-dimensional structures. In this case the central atom is considered a chiral center. In this case, rotation of B by $180^\circ$ will not lead to the original molecule (A). The central atom is a chiral center and the two different images are classified as enantiomers.

**Figure 3:** Rotation around a mirror plane for an achiral molecule
There are two possible configurations for a chiral center, R (Latin rectus, “right”) or S (Latin sinister, “left”). Each substituent around the chiral center is assigned a priority according to the Cahn-Ingold-Prelog notational system. The molecule is oriented so the group with the lowest precedence is pointing away from the viewer. If in order of decreasing priority the substituents appear in a clockwise order, then the absolute configuration of the chiral center is R, if the order is counterclockwise, then the configuration is S. For a molecule that contains more than one chiral center, enantiomers exist only if the molecules remain mirror images, i.e. if the opposite spatial arrangements exist at every chiral center, in all other instances the molecules are termed diastereomers.

Enantiomers share the same physical properties such as melting point, density, etc., with two exceptions. The first is that a pure enantiomeric substance will rotate a plane of polarized light by a specific angle. The mirror image will rotate the plane of
light by the same angle but in the opposite direction. If the enantiomer rotates the light in the clockwise sense it is taken as positive (+) or dextrorotatory (d, “to the right”0, if the rotation is counter-clockwise it is considered negative (-) or levorotatory (l, “to the left”).

The second property exhibited by enantiomers is how they interact with other chiral molecules. Given that the enantiomers have different spatial arrangements (faces), they can interact with other chiral molecules based on which face is presented to another chiral molecule. Figure 5 (below) shows how this interaction can occur.

**Figure 5**: Differences in electrostatic interaction between two enantiomers and another chiral molecule.
The two different faces presented by the enantiomers interact with the third chiral molecule in different ways. The R-R interaction is favored due to electrostatic attraction caused by the opposite charges on $R_1$ and $R_A$, and the $R_2$ and $R_B$. The R-S interaction is less likely to take place due to the electrostatic repulsion with the like charges between $R_2$ and $R_A$ along with the like charges on $R_1$ and $R_B$. The interaction between chiral molecules is not limited to electrostatic forces, steric interaction between large and small functional groups affect the interaction between chiral molecules as well.

**Figure 6**: Steric interaction between chiral molecules

Steric interactions also can determine how enantiomers interact with other chiral molecules. As Figure 6 above shows, two large groups will have steric repulsion and deactivate the interaction between the two molecules, while the smaller
hydrogen will not have the same steric repulsion leading to the R-S interaction being favored. Both the steric and electrostatic interactions determine how chiral molecules react and interact from a chemical standpoint. This has lead to chiral chemistry being at the forefront of the chemical and biological research.

To better understand how chiral molecules interact with the body in a chemical sense one can use the case of the compound Carvone. Carvone has two chiral forms, R-Carvone and S-Carvone. R-Carvone is the main component of spearmint oil, while S-Carvone is from caraway seed oil. The two compounds shown below in Figure 7 have very different smells. This markedly different characteristic is due to the different chiral centers. They interact with different receptors in the nose based on the different spatial configurations of the chiral centers.

Figure 7: Two Enantiomers of Carvone

The increased understanding of chiral molecules has allowed for a huge expansion in the medical and pharmaceutical fields. The role of chirality in the interaction of drugs with the human body cannot be understated. Chiral drugs are
consumed in massive quantities each day. Ibuprofen, the active ingredient in over the counter painkillers such as Advil and Aspirin contains two chiral forms. The S enantiomer is responsible for the pain relieving properties, while the R is inert and has none. Not all chiral forms, however, are inert, in many cases the other chiral forms can interact with the body in a negative fashion. A famous example of this is the case of Thalidomide, which was introduced in the late 1950’s as an anti-nausea drug and used to treat morning sickness in pregnant women. The two chiral forms of Thalidomide have very different effects, R-thalidomide acts as both a sedative and anti-nausea agent while S-thalidomide is severely teratogenic.
Figure 8: Enantiomers of Ibuprofen and Thalidomide

The role of these two drugs illustrates how important the role of chirality is in modern pharmaceuticals. The ability to selectively synthesize one enantiomer over the other becomes tremendously important when the enantiomers react differently with biological organisms. To this end both pharmaceutical companies and research groups have devoted time and resources to attempt to control the stereochemistry of chiral reactions and adjust the yield of the enantiomers.
1.2. **A Chiral Catalytic Synthesis**

There are several methods through which the enantiomeric selectivity of a reaction can be controlled. This first method is to produce a racemic mixture of the enantiomers and then to purify the product to obtain the desired enantiomer. This however limits the theoretical yield of the reaction to 50%, or even less if more than one chiral center is present. The next method uses “chiral auxiliaries” to bind with a chiral starting material and direct the outcome of the reaction, by raising the reaction energy of one enantiomer thereby making it a minor product. The chiral auxiliary is then cleaved from the reactant. This method, while useful has several drawbacks, such as the auxiliary must be used in stoichiometric amounts and requires additional steps to cleave it from the product.

The method that is the most efficient and promising in directing chiral reactions is the use of chiral catalysts. With several exceptions, enantiomers have the same chemical and physical properties, meaning they share the same energy and enthalpy; which means that in a non-catalyzed reaction, the activation energy needed to produce either enantiomer is identical. The uses of a chiral catalyst can selectively lower the activation energy needed to produce one enantiomer. As Figure 9 shows below, a chiral catalyst lowers the transition state energy for one enantiomer facilitating the formation of it. The effectiveness of a chiral catalyst is measured by the enantiomeric excess that it produces (%ee). The measurement is taken by calculating the amount of enantiomer that is produced over racemic (50% ratio). To ensure the best use of starting materials and to minimize byproducts, catalysts that
produce at least a minimum of 90%ee are desired for industrial uses. 90%ee would require that for every 10 units of racemic mixture, 90 units of the selected enantiomer is produced, leading to a 95 to 5 ratio of enantiomers.

**Figure 9:** Reaction pathway with change in activation energy due to a chiral catalyst, leading to S enantiomer being favored.

2. **Interrupted Feist-Bénary Reaction and Enantioselective Catalyst**

   2.1. **General Interrupted Feist-Bénary Mechanism**

   The Feist-Bénary (FB) reaction was developed in the early 1900s by Franz Feist and Erich Bénary as method of combining β-ketoesters and α-halocarbonyls to create a substituted furan ring as shown below in Figure 10\(^3\,^4\).
The primary focus of Dr. Calter’s group is on a derivation of the Feist-Bénary reaction. The FB traditionally occurs with an enolization of β-dicarbonyl followed by the addition of the α-halocarbonyl, the enolate reforms and then ring closure occurs. This was followed by treatment with a strong acid to remove the hydroxyl group and form an additional double bond; however the reaction can be “interrupted” immediately after ring closure to form the Interrupted Feist-Bénary (IFB) product as shown below in Figure 11.

**Figure 10:** Feist-Bénary Reaction
The IFB product has several interesting features for synthetic organic chemists. The first is the creation of a carbon-carbon bond, which is the basis of organic chemistry. The second important feature is the second chiral center that forms during the ring closing, adjacent to the one formed beforehand. These two features give chemist a high degree of both enantioselective and diastereoselective control.

**Figure 11:** Feist-Bénary Reaction and Interrupted Feist-Bénary Reaction Mechanism
Based on the above reaction Ryan Phillips created the general procedure for the formation of the IFB products based on the following reaction below in Figure 12.

![Reaction Scheme]

**Figure 12**: General Procedure for the IFB reaction

### 2.2. Exploration of Chiral Catalysts for the IFB Reaction

Previous work in Calter’s group had focused on the creation of a catalyst that would present a high degree of enantioselectivity for the IFB. Ryan Phillips found that the Sharpless’s dihydroxylation catalyst (Figure 13) presented with a high degree of enantioselectivity (68%ee) compared to previously screened catalysts\(^5\). This finding led to further study of derivatives of the Sharpless’s catalyst in an attempt to create a catalyst with greater enantioselectivity.
Based on the high enantioselectivity of the Sharpless’s catalyst, analogs of it were constructed to attempt to improve selectivity\(^6\). Using 4,6-dichloro-2-tiethyl-5-phenyl pyrimidine as a starting material, the 5-phenylpyrimidine-bis(9-O-quinidine) ether \(((QD_2)PYR)\) was synthesized using the reaction scheme in Figure 14 by Ryan Phillips and the IFB reaction conditions were optimized until 98% yield was obtained with 92% ee\(^7\).
Figure 14: Construction of \((\text{QD}_2\text{PYR})\) Catalyst and Structure of Quinidine (QD)

2.3. Analysis of the Catalyst Mechanism

While the basic formation of the IFB reaction is presented in Figure 11, a deeper analysis is needed to understand the role the \((\text{QD}_2\text{PYR})\) catalyst plays in the
enantioselectivity of the reaction. The initial step in the reaction is the equilibrium formation of the enol β-diketone as shown below in Figure 15.

Figure 15: Equilibrium reaction between ketol and enol form

Once the enol form of the diketone is present it allows for the next step in the reaction to proceed. The enol oxygen will form a hydrogen bond with the nitrogen present in the quinidine, shown below in Figure 16.

Figure 16: Hydrogen bond formation between diketone and catalyst
After the α-bromoketone is added to the reaction, the nitrogen on the quinuclidine moiety remains integral to the reaction. The basicity of the nitrogen helps hold the enol in the place while the oxygens located on the α-bromoketone form two hydrogen bonds (bifurcated) with the hydrogen now held by the quinuclidine moiety nitrogen. The bifuracted hydrogen bond leads to the selective formation of one enantiomer by forcing the α-bromoketone to orient itself in space and not rotate.

**Figure 17:** The Addition of Ethylbromopyruvate and the Subsequent Orientation

After the bifurcated hydrogen bond forms, the ketone form of the enol/ketone equilibrium provides a nucleophile that attacks the carbonyl carbon that is closet to the halogen because the additional electrons present the carbon-carbon bond must find an acceptable Lewis acid. In this case the carbonyl carbon fulfills this role after having lost electron density when the oxygen formed the hydrogen bond. This forms the new carbon-carbon bond while the hydrogen remains the coordination center, between the nitrogen on the catalyst and carbonyl groups helping to lock everything in place spatially.
**Figure 18**: Transition State in which New Carbon-Carbon Bond Forms

This spatial arrangement is shown above in Figure 18. The ethylbromopyruvate is locked in place by the bifurcated hydrogen bond while the new carbon-carbon bond forms, this means the ketone must attack from the same plane, in this case (into the page as represented above). This will cause the hydroxyl group that is formed to be pointing in the page as well.

Following this transition state a new equilibrium is established, then oxygen in the enol form will attack the carbon to which the halogen is bonded in an intermolecular SN2 reaction. This will cause the cyclization to occur and form the new 5 membered ring as shown below in Figure 19. The proton sponge (PS) which is present in the reaction (as indicated in Figure 12), prevents the formation of the acidic HBr. This is important because the presence of a strong acid such as HBr would promote the removal of the newly formed hydroxyl group and cause the reaction to proceed to a full Feist-Bénary reaction rather than the desired Interrupted Feist-Bénary reaction.
Figure 19: Final catalysis step leading to formation of the new 5-membered ring and finished IFB product

This illustrates the importance of the quinuclidine ring in the catalyst in conferring enantioselectivity, however the rest of the catalytic molecule is also vitally important. The aromatic ring bonded at the 9th carbon prevents either the β-dicarbonyl or the α-halocarbonyl from attacking from plane behind the page, while the hydrogen atom (is the smallest possible substituent which allows both of the bonding molecules to become coordinated with quinuclidine core easier.

Other elements of the \((\text{QD}_2\text{PYR})\) catalyst are also important in providing enantioselectivity for the reaction. First is the hydrogen located at the 2nd position on the pyrimidine ring, which in conjunction with the phenyl ring at the 5th position allows for the quinidine rings to move away from the phenyl group to assume the optimal position to help the reactants coordinate.

There is however another possible enantiomer that can form. In this case the α-bromoketone will introduce itself in the opposite orientation, shown below in Figure 20, and lead to the formation of the S enantiomer, which is the minor product. This spatial orientation however is less desirable as α-bromoketones would prefer to
orient themselves such that the halide is opposite from the incoming nucleophile, as shown by the Cram-Felkin-Nguyen model. Otherwise the larger halide will present a larger steric hindrance between itself and the pyrimidine ring.

**Figure 20**: Two possible orientations of the α-bromoketone and resulting enantiomers

3. **Formation of additional catalyst and their enantioselectivity**

3.1. **Production of Additional Catalysts and Analysis**

The library of catalysts previously created in Calter group includes the modification of the substituent at the 4th position, as shown in the Figure 21 below.
Figure 21: Catalyst with possible modification at the 4\textsuperscript{th} position

My research focused on expanding the knowledge regarding the role of the substituent at this position and the role it plays in the enantioselectivity of the IFB reaction. As discussed above the quinidine substituent plays a huge role in the enantioselectivity of the reaction, however as more research was conducted on the catalyst it became clear that the other substituents on the pyrimidine ring also play a large role. Ryan Phillips optimized the catalyst by placing hydrogen and phenyl group at the 2 and 5 positions respectively on the pyrimidine ring. This leaves on possible position to be optimized on the pyrimidine ring, the 4\textsuperscript{th} position as highlighted above in Figure 21.

First a modified version of the catalyst that contained a Cl at the 4-position was reacted with ethanol to provide the molecule shown below in Figure 22.
The reaction occurs under basic conditions with sodium hydroxide. The starting material is shown above in Figure 22 and was confirmed via H\textsuperscript{1} NMR (Spectra 1). The reaction will be driven by the basic conditions which deprotonated the ethanol. The deprotonated alcohol will attack the chloro bound carbon causing the double bond the break and electron density to form on the adjacent nitrogen forming a tetrahedral intermediated (Figure 22). The double bond will reform and the chlorine will be forced off the hydrogen leading to formation of the product. The reaction was confirmed by the NMR of the product that shows additional peaks corresponding to the new ethoxy group in the δ 4.5-4.0 region (Spectra 2). The product was purified and then run via HPLC on a chiral column, from this the area under the peaks was taken and the enantioselectivity of the reaction was calculated (Figure 23).
Figure 23: HPLC on an ODH chiral column of IFB reaction using Ethoxy Catalyst

All of the catalysts shown below in Figure 26 were screened using the reaction conditions shown in Figure 12.
Figure 24: Library of catalysts

The reaction was also run with 1,4-diazabicyclo[2.2.2]octane (DABCO) shown above in Figure 24 used as a control. DACBO should produce a racemic mixture of the products as it will provide the nitrogen necessary to catalyze the reaction but will provide no enantioselectivity.

After the IFB reaction was run using all of the above catalysts, the products were purified using flash column chromatography. The purified product was then run through a chiral column on the HPLC in Calter laboratories. The purified products lead to the following enantioselectivity as shown below in Table 1.
Table 1: Catalysts and resulting enantioselectivity

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>X group</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>QD</td>
<td>84 (R)</td>
</tr>
<tr>
<td>1b</td>
<td>Cl</td>
<td>77 (R)</td>
</tr>
<tr>
<td>1c</td>
<td>EtO</td>
<td>44 (R)</td>
</tr>
<tr>
<td>1d</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

3.2. Analysis of the Enantioselectivity of Catalyst Library

As shown above there is a clear difference to the enantioselectivity of the catalysts screened against the IFB reaction. The catalyst containing two quinidine groups continues to show results consistent with the previously reported figures by Ryan Phillips. The Chloro catalyst shows a similar degree of high enantioselectivity also. The interesting result occurs when the IFB reaction is run with the catalyst that contains the ethoxy group at the 4-position on the pyrimidine ring (Figure 25: 1c). The HPLC of the purified product shows an enantioselectivity of only 44%, which is significantly lower then either the di-Quinidine or the chloro containing catalyst.

While on the surface it might appear steric is not the determining factor in the different enantioslectivity’s of the catalyst, this changes when an in-depth look is taken at the overall chemical factors for the different substituants. While the quinidine substituent is clearly the largest of the three screened catalysts, the chlorine atom is
smaller than the ethoxy group, however it presents with much better enantioselectivity. Therefore there must be a reason that causes the chloro containing catalyst to present with higher selectivity than the ethoxy catalyst.

There are two difference main differences besides the size of the substituent. The first is the fact that while the ethoxy group is moderately electron donating, the chlorine possesses three lone pairs in its valence electron shell. These lone pairs make the chlorine electronically larger than the ethoxy group. This hypothesis is confirmed by literature that shows based on Crystallographic Analyses the chloro group presents itself as 20% larger than the ethoxy group\textsuperscript{8,9}. The other is the bond length between the carbon and the chlorine. The chlorine-carbon bond has a length of 174.3pm opposed to the carbon oxygen bond that has a length of 136pm\textsuperscript{10,11}. While these measurements are based on an aromatic benzene system, research by Morrison, et. al., shows that bond length of a chlorine carbon bond is a pyrimidine system is similar to the length of the bond in a phenyl ring (172.8 opposed to 174.3)\textsuperscript{12}.

These two contributing effects that would help provide enantioselectivity for the chloro-substituted catalyst. The fact that the chloro substituent presents as a larger, would lead to more steric repulsion with the halide during the catalyzed reaction helping to provide greater enantioselectivity (Figure 25).
Figure 25: Different view of the catalyst showing halide and substituent at the 4 position in the same plane, during the formation of the minor (S) product

4. Conclusion and Future Research

It is clear based on the data obtained in my research that the size of the substituent at the 4 position on the pyrimidine ring of the catalyst plays a large role in the enantioselectivity of the reaction. Based on these results further study done in to the reaction should help to clarify the exact role catalytic mechanism that occurs during the reaction. Calter group has gained an excellent working knowledge of the role the quinidine plays in formation of the IFB product from the β-dicarbonyl and the α-halocarbonyl. Further work should include the synthesis of catalyst containing different groups at the 4 position on the pyrimidine. Synthesis of the hydrogen at this position would be particularly helpful. Given that this would be the smallest possible
substituent, a drop in the enantioselectivity of the catalyst would help to confirm the hypothesis that the size of the substituent plays a large role in the enantioselectivity.
5. Experimental

$^1$H NMR were obtained using a Varian-300Mhz or 400Mhz spectrometer. All of the HPLC analysis was done using a Thermo Separation Product Spectra Series P200 HPLC, Spectra 100 variable UV-Vis detector and Hewlett Packard HP-3394a integrator on a Daicel Chiralpack OD-H column. All reagents were obtained from commercial sources unless otherwise noted.

**Synthesis of 4-Ethoxy-5-phenylpyrimidine-mono-(9-O-quinidine) ether**

\[
\text{Cl} \quad \text{Ph} \\
\text{N} \quad \text{N} \\
\text{H} \\
\text{O} \quad \text{Me} \\
\text{EtOH} \quad \text{NaOH, 78°C} \\
\text{N} \quad \text{N} \\
\text{H} \\
\text{O} \quad \text{Me}
\]

0.043g (0.078mmol) of 4-Chloro-5-phenylpyrimidine-mono-(9-O-quinidine) ether (Spectra 1) was added to a 10 mL round bottom flask. 3 mL of ethanol and 3 ml distilled H$_2$O was added along with 0.8g (0.02 mol) of NaOH. The reaction was refluxed at 78 °C for 31 minutes. The reaction was cooled to room temperature and washed with sodium carbonate. The solvent was removed through rotary evaporation and the reaction yielded 33mg of product (confirmed via NMR, Spectra 2) for 77% yield.
Procedure for Formation of “interrupted Feist-Benary product

All IFB reaction products were confirmed via NMR analysis:

H\textsuperscript{1} NMR (CDCl\textsubscript{3}, 300Mhz) \(\delta\) 4.68 (d, 1H), 4.46 (d, 1H), 4.23 (q, 3H), 4.07 (s, OH), 2.50 (t, 2H), 2.29 (app. Q, 2H), 2.03 (m, 2H), 1.23 (t, 3H)

The HPLC analysis was done using a Daicel Chiralpack ODH column in a 90:10 hexanes:i-propanol mixture at 257 nm with a flow rate of 0.42 mL/min. The 4-Chloro-5-phenylpyrimidine-mono-(9-O-quinidine) and (QD\textsubscript{2})PYR were synthesized by Na Li of Calter Group.

1.

115mg (1.3 equivalent, 1.036mmol) of 1,3 Cyclohexadione was added to a 10ml round bottom flask along with 8 ml of distilled CH\textsubscript{2}Cl\textsubscript{2}. 171mg (1 equivalent, 0.797mmol) of Proton Sponge (PS) and 9 mg (0.1 equivalent, 0.0797mmol) of DABCO was added. The reaction was cooled to -78\textdegree C. 0.1ml (1 equivalent) was
added in a dropwise manner and the reaction was stirred under nitrogen for 11 minutes. The reaction was returned to room temperature and the solvent was removed by rotary evaporation. The product was purified via flash chromatography on a 2 cm column (silica gel, CH$_2$Cl : MeOH, 100,1) for a yield of 40mg (23% yield). The product was confirmed via NMR (Spectra 3) and the HPLC analysis of the purified separated enantiomers ($R_{t (R)} = 28$ min; $R_{t (S)} = 34$ min), to give 5%ee of the $S$ enantiomer (Spectra 4).

2.

75mg (1.3 equivalent, 0.676mmol) of 1,3 Cyclohexadione was added to a 10ml round bottom flask along with 8 ml of distilled CH$_2$Cl$_2$. 110mg (1 equivalent, 0.516mmol) of Proton Sponge (PS) and 27 mg (0.1 equivalent, 0.0516mmol) of 4-Ethoxy-5-phenylpyrimidine-mono-(9-O-quinidine) was added. The reaction was cooled to -78$^\circ$C. 0.065ml (1 equivalent) was added in a dropwise manner and the reaction was stirred under nitrogen for 10 minutes. The reaction was returned to room temperature and the solvent was removed by rotary evaporation. The product was purified via flash chromatography on a 2 cm column (silica gel, CH$_2$Cl : MeOH, 100,1) for a yield of 42mg (36% yield). The product was confirmed via NMR
(Spectra 5) and the HPLC analysis of the purified separated enantiomers ($R_{t (R)} = 31$ min; $R_{t (S)} = 38$ min) give 43% ee of the R enantiomer (Spectra 6).

3.

70mg (1.3 equivalent, 0.63mmol) of 1,3 Cyclohexadione was added to a 10ml round bottom flask along with 8 ml of distilled CH$_2$Cl$_2$. 104mg (1 equivalent, 0.49mmol) of Proton Sponge (PS) and 25 mg (0.1 equivalent, 0.049mmol) of 4-Chloro-5-phenylpyrimidine-mono-(9-O-quinidine) was added. The reaction was cooled to -78°C. 0.061ml (1 equivalent) was added in a dropwise manner and the reaction was stirred under nitrogen for 10 minutes. The reaction was returned to room temperature and the solvent was removed by rotary evaporation. The product was purified via flash chromatography on a 2 cm column (silica gel, CH$_2$Cl$_2$ : MeOH, 100,1) for a yield of 93mg (84% yield). The product was confirmed via NMR (Spectra 7) and the HPLC analysis of the purified separated enantiomers ($R_{t (R)} = 27$ min; $R_{t (S)} = 33$ min) give 77% ee of the R enantiomer (Spectra 8).
36mg (1.3 equivalent, 0.325mmol) of 1,3 Cyclohexadione was added to a 10ml round bottom flask along with 5 ml of distilled CH$_2$Cl$_2$. 52mg (1 equivalent, 0.25mmol) of Proton Sponge (PS) and 20mg (0.1 equivalent, 0.025mmol) of (QD)$_2$PYR (Spectra 9) was added. The reaction was cooled to -78°C. 0.03ml (1 equivalent) was added in a dropwise manner and the reaction was stirred under nitrogen for 10 minutes. The reaction was returned to room temperature and the solvent was removed by rotary evaporation. The product was purified via flash chromatography on a 2 cm column (silica gel, CH$_2$Cl$_2$ : MeOH, 100:1) for a yield of 33mg (59% yield). The product was confirmed via NMR (Spectra 9) and the HPLC analysis of the purified separated enantiomers ($R_{t(R)} = 29$ min; $R_{t(S)} = 36$ min) give 85%ee of the R enantiomer (Spectra 10)
Spectra
Spectra 4

![Diagram]

Catalyst Used

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TOTAL AREA=2.2435E+07
MUL FACTOR=1.0000E+00
Spectra 6

Catalyst Used

[Chemical structure image]
Spectra 8
7. References


2. Pasteur, L. *Cloth*. **1897**, 44.

3. Feist, F. *Cherm Ber.* **1902**, 35, 1545


