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Silylation-Based Kinetic Resolution of **A**-Hydroxy Carbonyl Compounds and Synthesis of Chiral Isothiourea Catalysts

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SILYLATION-BASED KINETIC RESOLUTION OF α-HYDROXY CARBONYL COMPOUNDS AND SYNTHESIS OF CHIRAL ISOTHIOUREA CATALYSTS

by

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ABSTRACT

The thesis describes the silylation-based kinetic resolution for α-hydroxy carbonyl compounds catalyzed by isothiourea catalysts as well as our efforts to make novel chiral isothiourea catalysts.

In Chapter 1, general background will be introduced, including chirality, general methods to obtain enantiopure compounds and kinetic resolution. Kinetic resolution is an very important method to obtain enantiopure compounds. Several catalysts were developed for the kinetic resolution and isothiourea catalysts will be focused in this thesis.

In Chapter 2, The mechanism of the chiral recognition was discussed. A novel isothiourea catalyst was design to investigate the mechanism. The synthesis of the new catalyst was also described in this chapter.

In Chapter 3, the silylation-based kinetic resolution for α-hydroxy carbonyl compounds will be discussed. Since silylation-based kinetic resolution have already been proven very effective to make enantiopure monofunctional secondary alcohol, it is interesting to investigate the application of this methodology to α-hydroxy carbonyl compounds, which have similar core structure with monofunctional secondary alcohol for the chiral recognition. The optimized reaction conditions have already established and the substrate-scope have already been studied.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Enantiopure compounds are important in pharmaceutical industry. Several methods have already developed to obtain enantiopure compounds. Kinetic resolution is one of these methods. In this chapter, general background about enantiopure and kinetic resolution will be introduced.

1.1 CHIRALITY

Chirality is an important principle in chemistry and the pharmaceutical industry.[1] A chiral molecule is a molecule that cannot be superposed onto its mirror image.[1] These non-superposable mirror images are enantiomers of one another. If a chiral compound consists of equal amounts of both enantiomers, it is called a racemic mixture, or racemate. Otherwise, the compound is enantioenriched or enantiopure.

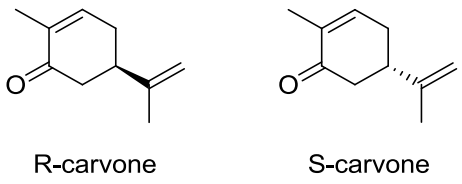

Figure 1.1 The structures of both enantiomers of carvone

Because most biomolecules are chiral, such as proteins, nucleic acids and sugars, when a chiral compound is introduced into these environments, each enantiomer can have a different biological effect than its mirror image. For example, as shown in Figure 1.1,

carvone has two different enantiomers, called (*R*)-(-)-carvone and (*S*)-(+)-carvone, respectively. The two enantiomers smell quite different from one another; (*R*)-(–)-carvone smells like spearmint, while its mirror image, (*S*)-(+)-carvone, smells like caraway.[2] Different enantiomers can have different smells mainly resulting from their interactions with the receptors in the human nose, which consists of chiral molecules.[2]

In the pharmaceutical industry, different enantiomers of drug compounds may also have different physiological effects. In many cases, only one enantiomer of the molecule may have the desired effect while the other one may be useless or interact with the body in a different way causing side effects or even be toxic. As a result, single enantiomer drugs have significant advantages over racemic drugs due to their high efficiency and low toxicity.

In the past, most drug molecules come directly from plants or animals with little attention being paid to the chirality of the molecules. In the 1950s, the situation began to change because fully synthetic molecules became an important class of drugs. A famous example is thalidomide, which is used to treat morning sickness in pregnant women. Different forms of birth defects were discovered to have been caused by thalidomide. Further investigation showed that only (*R*)-thalidomide has the desired effect while the (*S*)-thalidomide is toxic. In the late 1980s, the Food and Drug Administration (FDA) released a set of regulations on chiral drugs, leading to the rapid development of chiral drugs.[3] FDA now requires that drugs be sold as a single enantiomer unless both enantiomers have been tested for safety in the body. From 1989 to 2001, the ratio of single enantiomer drugs to racemic drugs increased continuously. In 2001, single

enantiomer drugs comprised over 85% of the total drug market for drugs which contain one or more chiral centers.[4]

The enantiopurity of compounds can be represented by the term enantiometric excess (ee). Enantiometric excess is defined as the absolute difference between the amounts of the two enantiomers over the total amount of both enantiomers.[5] Equation 1.1 describes the definition of enantiometric excess. R and S are the amount of (*R*)-enantiomer and (*S*)-enantiomer, respectively. For example, if the compound has 95% (*R*)-enantiomer and 5% (*S*)-enantiomer, the ee value of the compound is 90%.

$$\text{enantiometric exess (ee)} = \frac{|\mathrm{R} - \mathrm{S}|}{\mathrm{R} + \mathrm{S}} \times 100\% \qquad \text{Equation 1.1}$$

1.2 APPROACH TO ENANTIOPURE COMPOUNDS

Due to the advantage of enantiopure drugs, large efforts have already been devoted to making single enantiomer drugs. Usually, chirality is desired to be introduced in the early stages of the synthetic process.[6] A report from several major pharmaceutical companies[6] showed that over half of all chiral centers in drug compounds originate from chiral starting materials or intermediates from the fine chemical industry. This indicates that there is a high demand for enantiopure small molecules. To obtain such enantiopure compounds, several methods have already been developed and will be discussed below.

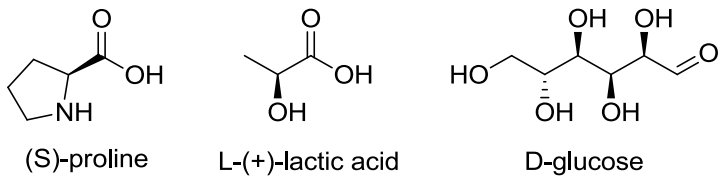

Figure 1.2 Typical enantiopure starting material from nature.

1.2.1 NATURE

In the past, the only source of chirality in synthesis was precursors derived from natural sources.[7] Today, nature's chiral pool of compounds still provides a variety of enantiopure building blocks and auxiliaries, such as alkaloids, amino acids, hydroxy acids and carbohydrates. Several examples are shown in Figure 1.2. However, the variety of available enantiopure compounds in nature is still limited and the quantity usually cannot meet the requirement. As a result, alternative methods are needed to synthesize enantiopure compounds.

1.2.2 ASYMMETRIC SYNTHESIS

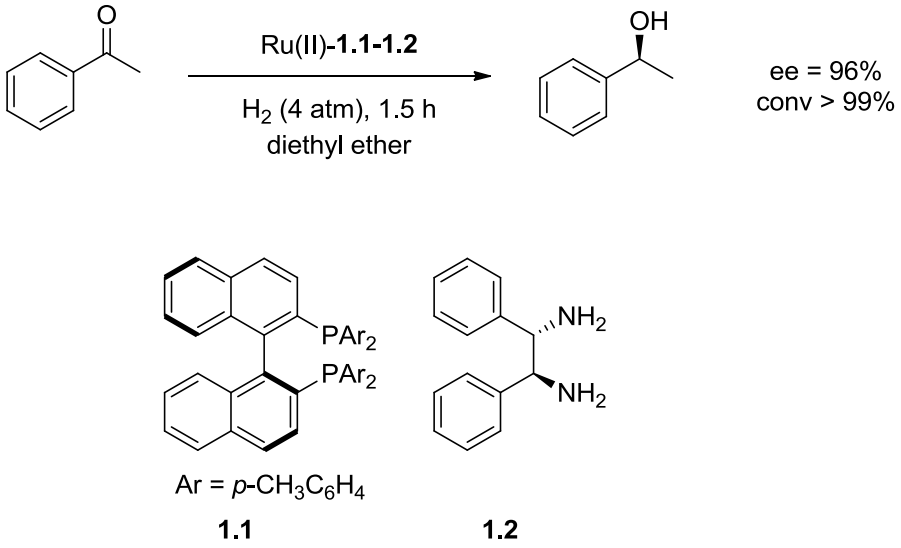

Figure 1.3 Asymmetric hydrogenation of ketone by Ohkuma.

Asymmetric synthesis starts with achiral materials and generate enantioenriched chiral products via chiral catalysts or reagents. One typical example is an asymmetric hydrogenation of a ketone as shown in Figure 1.3.[8] In this asymmetric reaction, a prochiral aromatic ketone reacts with hydrogen gas and is transformed into an

enantioenriched secondary alcohol in the presence of a ruthenium catalysts. Chiral bisphosphine **1.1** and diamine **1.2** are chiral ligands that create a chiral environment to induce enantioselectivity.[8]

Currently, there are many successful cases of asymmetric reactions achieving more than 99% ee. However, for many other substrates, asymmetric reactions can only achieve moderate ee (50%-80%) or even low ee (1%-50%). Alternative methods should be developed when asymmetric reactions cannot obtain the desired level of enantiopurity.

1.2.3 RESOLUTION

A chiral resolution is a sorting process to make enantiopure compounds from racemic mixtures. The chiral resolution is a very important method in the process of making single enantiomer drugs.[6] There are two major types of chiral resolutions for different substrates: resolutions using crystallization and kinetic resolutions.

Resolution using crystallization

The enantioenriched salt can crystallized from the solution, which provides a method to obtain the enantioenriched compounds. The sample is made into a salt by adding another enantiopure compound. The salt is diastereomers and one is more soluble than the other. Therefore, the enantioenriched compound can be obtained through crystallization. Several typical examples include methadone base, threonine and glutamic acid.[9] However, the scope of resolution using crystallization is limited because many kinds of compounds, such as low melting point compounds, cannot be crystallized from the solution.[10] In addition, not all compounds can be made into salts. This process works better for amines or carboxylic acids.

Kinetic Resolution

Another sorting method that is used to get enantioenriched compounds from a racemate is a kinetic resolution, which will be the main focus of this thesis. Kinetic resolutions obtain enantioenriched compounds from racemic mixtures by selectively derivatizing one enantiomer to form a product through differences in activation energies by reacting with chiral catalysts or reagents, thereby the unreacted starting material is enantioenriched (Figure 1.4). After a kinetic resolution, the enantioenriched unreacted starting material can be separated by regular separation methods, such as column chromatography, distillation, or recrystallization.

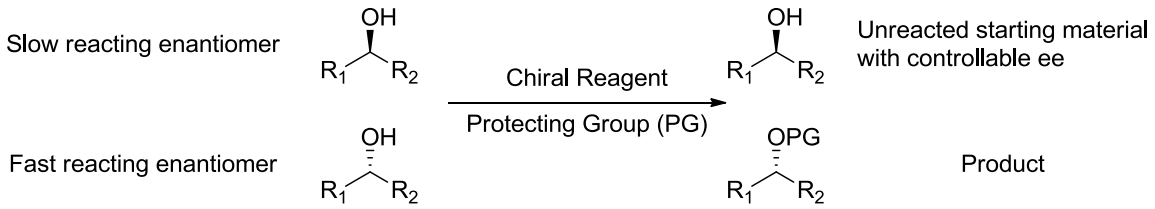

Figure 1.4 General Scheme for a kinetic resolution.

Ideally, kinetic resolutions could obtain the enantiopure product of both enantiomers by having very high selectivity. However, in practice, only unreacted starting material is obtained, because the product usually contains some of both enantiomers. Therefore, the highest possible yield for a kinetic resolution is 50%. To describe the enantioselectivity of a kinetic resolution, selectivity factor (*s*) is introduced. A selectivity factor is the ratio of rates of the fast reacting enantiomer over the slow reacting enantiomer. From the view of an energy diagram, a selectivity factor is described

by the activation energy difference between the two enantiomers in the reaction (Equation 1.2)

$$s = \frac{k_{fast}}{k_{slow}} = e^{\frac{\Delta\Delta G^{\ddagger}}{RT}} \qquad \textbf{Equation 1.2}$$

The main advantage of a kinetic resolution is that the enantiomeric excess changes as a function of conversion. Consequently, high enantiomeric excess (over 99%) can always be achieved even with moderate selectivity.[11] This relationship between enantiometric excess and conversion is shown in Figure 1.5. Selectivity factors over 10 are considered to be synthetically useful.[12]

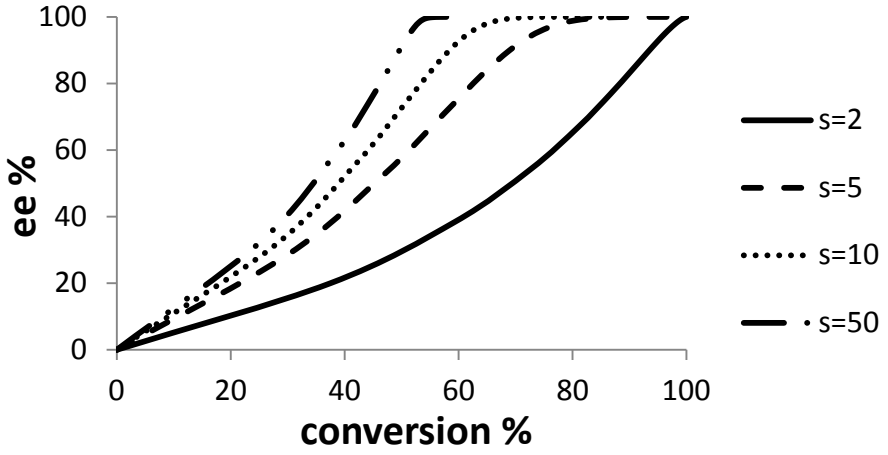

Figure 1.5 Correlation between conversion and enantiometric excess in a kinetic resolution.

1.3 CATALYST FOR THE KINETIC RESOLUTION

As mentioned above, a kinetic resolution is an important method to make enantiopure compounds. Currently, a variety of chiral catalysts have been developed for

the kinetic resolutions. Two major classes of catalysts will be discussed below, enzymatic and non-enzymatic catalysts.

Enzymes

As a catalyst for kinetic solution, enzymes have been widely used in industry to make enantiopure compounds.[13] One typical example is the production of L-amino acid, which is classed as a non-proteinogenic amino acid and cannot be obtained from nature. An enzyme-catalyzed kinetic resolution is employed to obtain L-amino acid from a ten to thousand ton scale every year by selective hydrolysis of the undesired primary amide.(Figure 1.6) [13] The remaining primary amide is separated and hydrolyzed to form L-amino acid. However, enzymatic kinetic resolutions have limited substrate scopes. In many cases, small molecule catalysts need to be developed to resolve certain substrates via a kinetic resolution reaction.

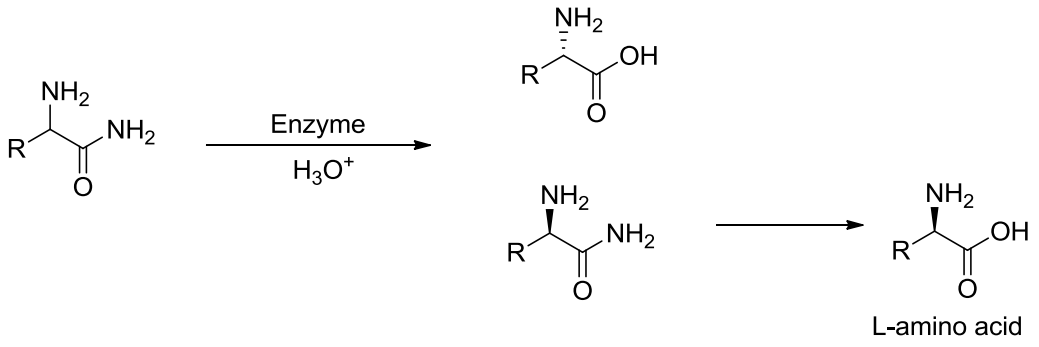

Figure 1.6 Enzymatic kinetic resolution in industry to make L-amino acid by Schmid.

Non-enzymatic catalyst

Non-enzymatic catalyst kinetic resolutions have been mentioned in the literature since the 1910s.[14] However, non-enzymatic catalyzed kinetic resolutions did not draw

much attention until the milestone which was established in 1981 by Sharpless (Figure 1.7).[15] A kinetic resolutions was developed to sort allylic alcohols by selective epoxidation of one enantiomer with a titanium catalyst and the chiral ligand (+)-diisopropyl tartrate, achieving selectivity factors up to 104.

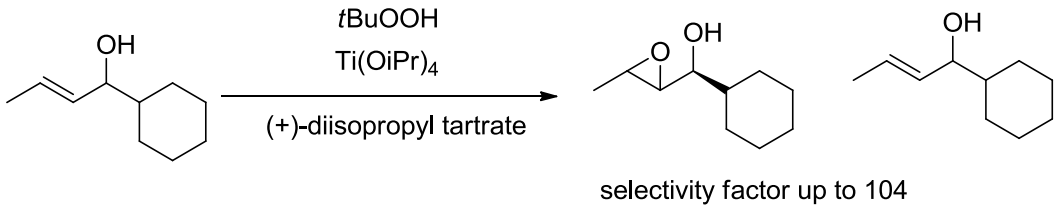

Figure 1.7 Sharpless epoxidation kinetic resolution

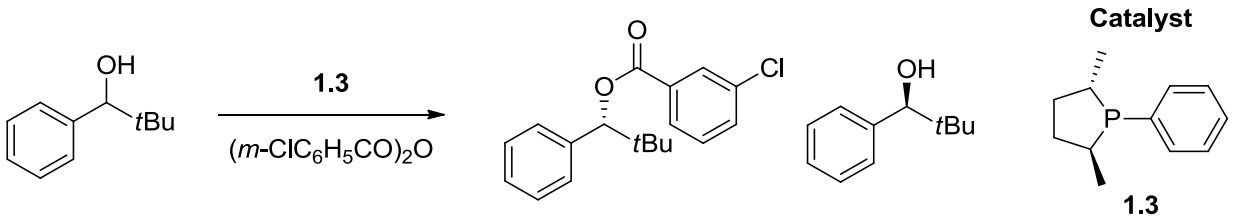

Figure 1.8 Nucleophilic chiral phosphine catalysts for the kinetic resolution of alcohols by Vedejs

Since this initial accomplishment, non-enzymatic kinetic resolutions have been successfully applied to a variety of substrates, including alcohols,[16] amines,[17] olefins,[18] and epoxides.[19] In this section, I will highlight the kinetic resolution of alcohols via chiral nucleophilic catalysts. These nucleophilic catalysts have mainly been employed in acylation reactions. The first practical kinetic resolution of secondary alcohols by a chiral nucleophilic catalyst was develop by Vedejs and coworkers in 1996.[20] The chiral phosphine (**1.3**) activates the *m*-chlorobenzoic anhydride (Figure 1.8) for the selective acylation of one alcohol enantiomer. Since that time, several types of chiral nucleophilic

catalysts were developed. Some examples are shown in Figure 1.9, including DMAP catalyst,[21] chiral phosphine catalyst [22], and dihydroimidazole catalyst[23]

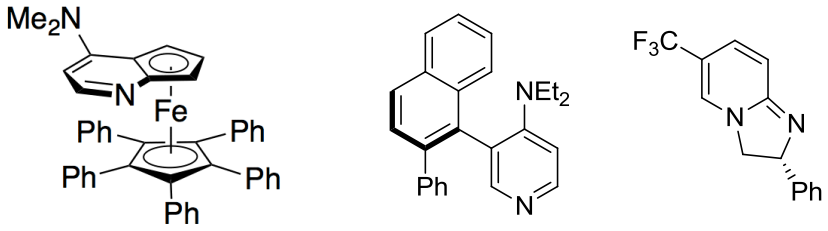

Figure 1.9 Several examples of chiral nucleophilic catalyst for kinetic resolutions.

Silylation reaction

Silylation is an important method to protect alcohols,[24] but until recently had not been used as a derivatization method in kinetic resolutions. The silylation-based kinetic resolution was first introduced by the Ishikawa group. Their method employed organocatalyst **1.4** and triisopropyl silyl chloride as silyl source but the stereoselectivity was low (Figure 1.10a).[25] Hoveyda, Snapper, and coworkers developed a method to obtain enantioenriched diols by employing *tert*-butyldimethylsilyl chloride and organocatalyst **1.5** (Figure 1.10b). However, their methods work exclusively for 1,2-diols.[26] Later, the Oestreich group employed enantiopure chiral silane **1.6** in combination with transition metal catalysts to run a dehydrogenative coupling kinetic resolution, achieving selectivity factors up to 900 (Figure 1.10c) for pyridine substituted secondary amines. However, the reaction needed stoichiometric chiral silane **1.6** which is not commercially available.[27]

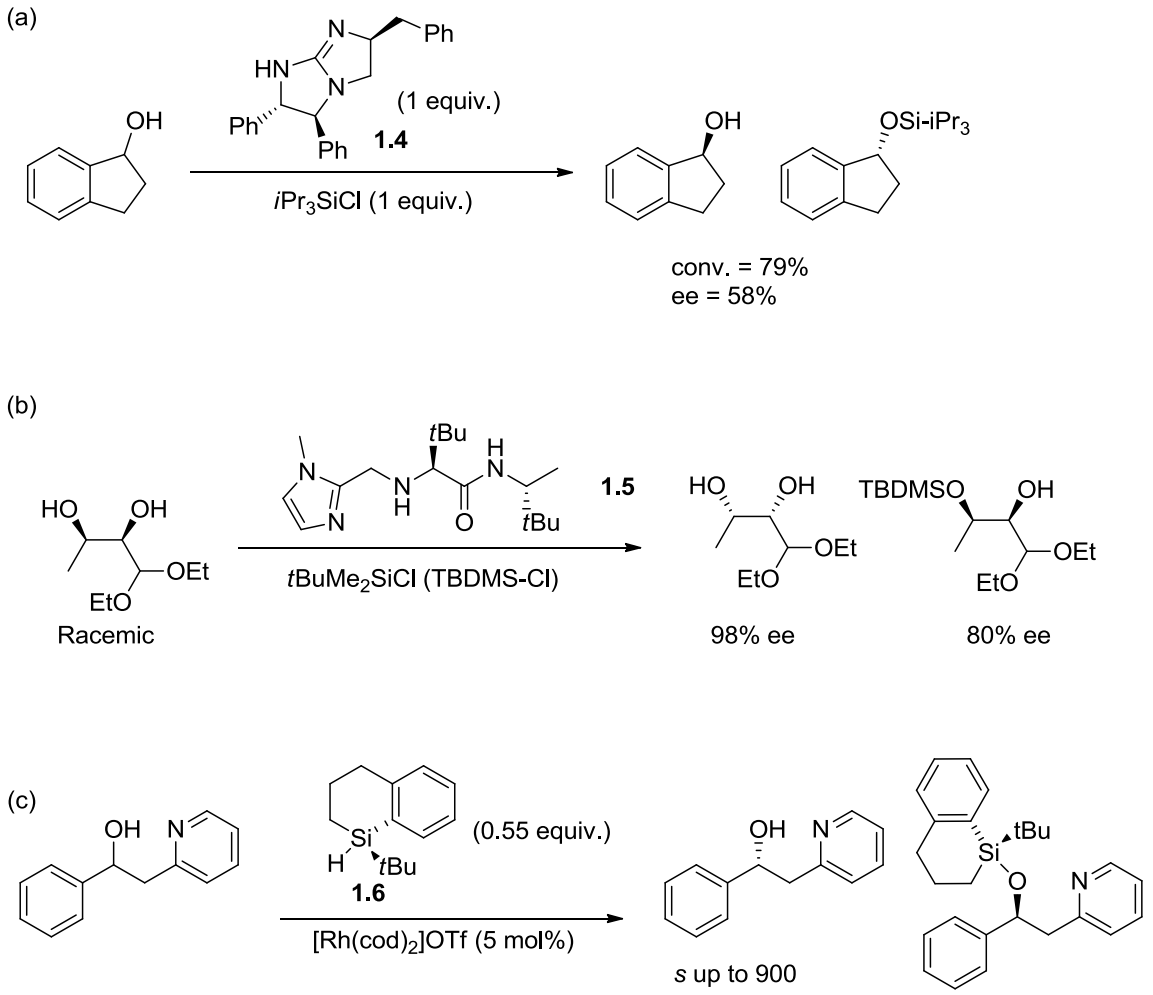

Figure 1.10 Several examples of silylation-based kinetic resolutions.

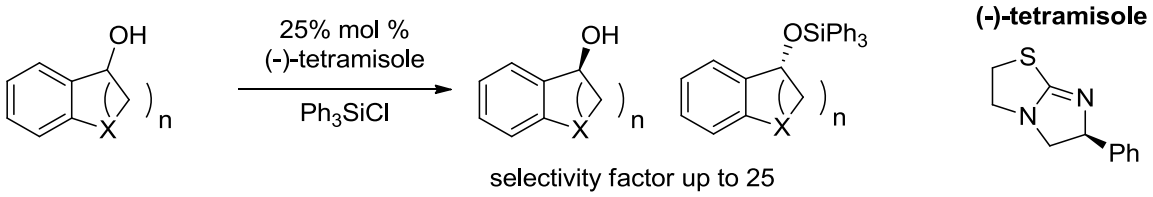

Figure 1.11 Silylation-based kinetic resolution developed by the Wiskur group.

Another synthetic-practical silylation-based kinetic resolution was developed by Wiskur and coworkers.[28] Commercially available reagents, triphenylsilyl chloride (Ph_3SiCl) and (-)-tetramisole, were employed to obtain enantioenriched secondary

alcohols from a racemic mixture. The system works well with a wide range of monofunctional secondary alcohols. Selectivity factors up to 25 were achieved for monofunctional secondary alcohols. (Figure 1.11)

1.4 SUMMARY

Enantiopure compounds are desired by the pharmaceutical industry and many synthetic methods have already been developed to obtain enantiopure compounds. Kinetic resolutions are one approach to enantiopure compounds with the desired enantiopurity controlled by conversion. Non-enzymic catalysts for kinetic resolution have already developed for several substrates and silylation-based kinetic resolution is an important method to obtain the enantioenriched compounds.

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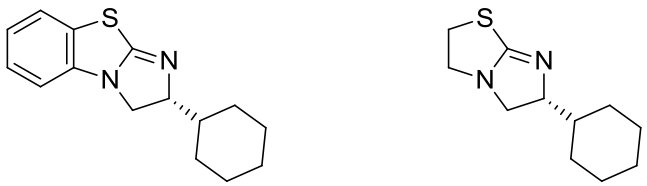
CHAPTER 2

APPROACH TO ISOTHIOUREA CATALYSTS FOR KINETIC RESOLUTIONS

Isothiourea is an important class of organocatalyst. We plan to synthesized isothiourea catalyst for the kinetic resolution reactions to get an insight view of the reaction mechanisms.

2.1 INTRODUCTION



2.1 **2.2**

Figure 2.1 Target compounds

In this chapter, the design and effort to make isothiourea catalysts **2.1** and **2.2** in Figure 2.1 is discussed. Chiral isothiourea compounds have already proven to be promising catalysts for kinetic resolutions, including acylation[1] and silylation[2] based kinetic resolutions. The structure of chiral isothiourea catalysts plays an important role in catalytic reactivity and selectivity. To study the structure effect of the catalysts, modifications to different isothiourea catalysts were proposed. The design and synthesis of novel chiral isothiourea catalysts will be discussed in this chapter.

2.2 ISOTHIOUREA CATALYST

The isothiourea compound (-)-tetramisole (**2.3)** was first found to work as a nucleophilic catalyst for the kinetic resolution of secondary alcohols by Birman and coworkers.[1] The catalyst was employed to activate anhydrides for the asymmetric acylation of one alcohol enantiomer. Therefore, one enantiomer of the alcohol was reacting with anhydride much fast than the other one. The tetramisole catalyzed reaction is shown in Figure 2.2.

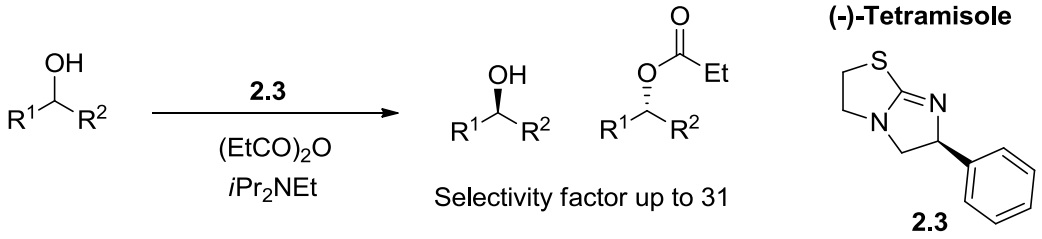


Figure 2.2 Tetramisole-catalyzed acylation-based kinetic resolution of alcohols.

After the milestone discovery of tetramisole as a nucleophilic catalyst, a series of tetramisole derivatives were synthesized and studied by Birman's group (Figure 2.3 & 2.4).[3] The derivatives included modifications to tetramisole by expanding ring sizes (**2.5** & **2.6**) as well as extending conjugated π-system (**2.4** & **2.6**). Different structures showed different activity and selectivity. The general preparation procedure is shown in Figure 2.4. [3] The synthesis begins with the enantiopure amino alcohol **2.7**, coupling with thiazoline **2.8** or benzothiazoline **2.9** derivatives to form an isothiourea. The finished bicyclic isothiourea catalysts are finished by a ring closing procedure of an internal nucleophilic displacement of the activated terminal alcohol by the isothiourea nitrogen.

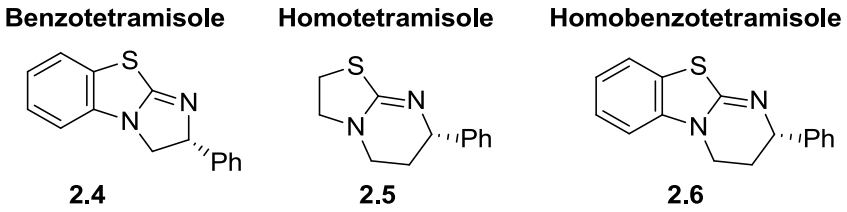


Figure 2.3 Isothiourea catalyst derivatives of tetramisole.

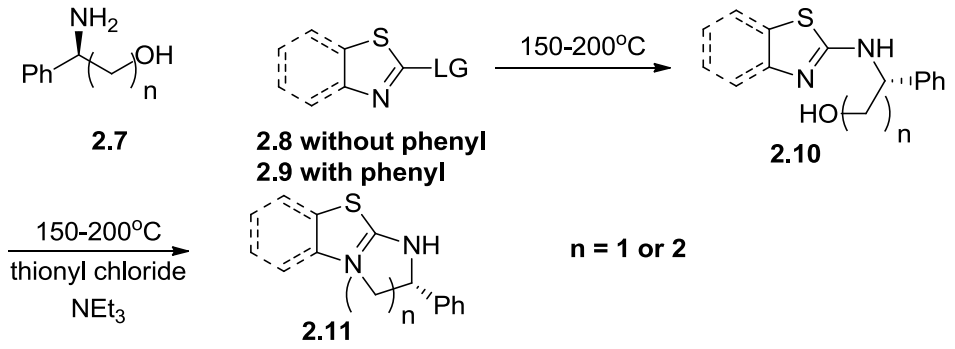
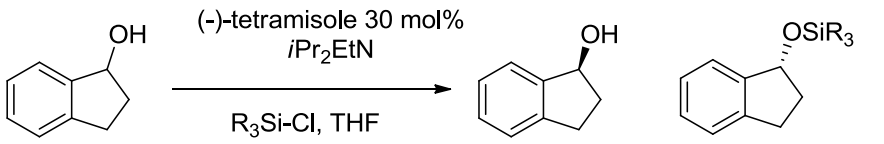


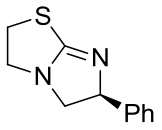
Figure 2.4 General synthetic routes for tetramisole derivatives

As mentioned in the previous chapter, the silylation-based kinetic resolution developed by the Wiskur group drew much attention in recent years.[2] Silyl Chloride is employed as silyl source. In this methodology, it is noteworthy to mention the silyl chloride study, where triphenylsilyl chloride was the silyl chloride that gave the highest selectivity. As shown in Table 2.1, the selectivity decreased significantly when the phenyl groups were replaced with methyl groups or if triethylsilyl chloride was employed. If the phenyl group was replaced by sterically hindered alkyl groups, such as *t*-butyl or *i*-propyl, the reaction did not proceed.

Table 2.1 Silyl chloride optimization for the kinetic resolution developed by Wiksur.



(-)-tetramisole



R_3Si	Conv %	*s*
Et_3Si	48	4.0
Me_2PhSi	50	3.4
Ph_2MeSi	46	5.2
Ph_3Si	59	8.6
t$BuMe_2$	<5	–
iPr_3Si	<5	–

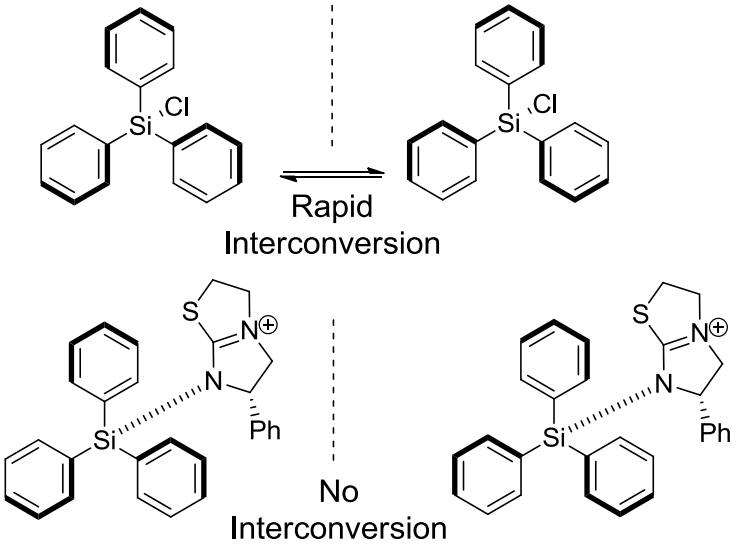


Figure 2.5 Hypothesis of propeller model of the chiral recognition.

The silyl source study indicated that the phenyl groups have a unique role in the chirality transfer from the chiral catalyst to the chiral alcohol. It is known that three phenyl groups around a central atom can form a propeller, creating two enantiomers. Triphenylsilyl chloride can also form this propeller model as shown in Figure 2.5. Normally, the two enantiomers interconvert rapidly. We propose that when the propeller

is attached to a chiral ligand, such as tetramisole, the interconversion between the two propeller enantiomers is frozen[4] and a diastereomer is formed. As a result, the intermediate is chiral, which will only react with one alcohol enantiomer because of the difference in activation energies between the two enantiomers.

2.3 CATALYST DESIGN

To test the hypothesis of the propeller conformation, new catalysts were designed. The phenyl group of tetramisole is directly attached to the chiral carbon on the catalyst which may have a π-π interaction with the phenyl rings on the silyl chloride. This interaction may be essential for locking in one of the chiral propellers. Therefore, altering that phenyl group to either increasing the pi system or eliminating it all together is one way to explore the mechanism.

In the Wiskur lab, the (+)-naphthalene-benzotetramisole catalyst (**2.15**) has already been synthesized, and the selectivity factor is not much different than with (+)-benzotetramisole (**2.14)** for D,L-pantolactone **2.12** (Figure 2.6).[5] The naphthalene has an increased pi system over just a phenyl, but the selectivity is nearly the same, which indicates that the chiral recognition is not fully depended on increasing the pi system. To further explore the importance of the π-π interaction on the chiral recognition in the silylation system, the cyclohexane derivatized tetramisole **2.1** and the cyclohexane derivatized benzotetramisole **2.2** is proposed to be synthesized (Figure 2.1).

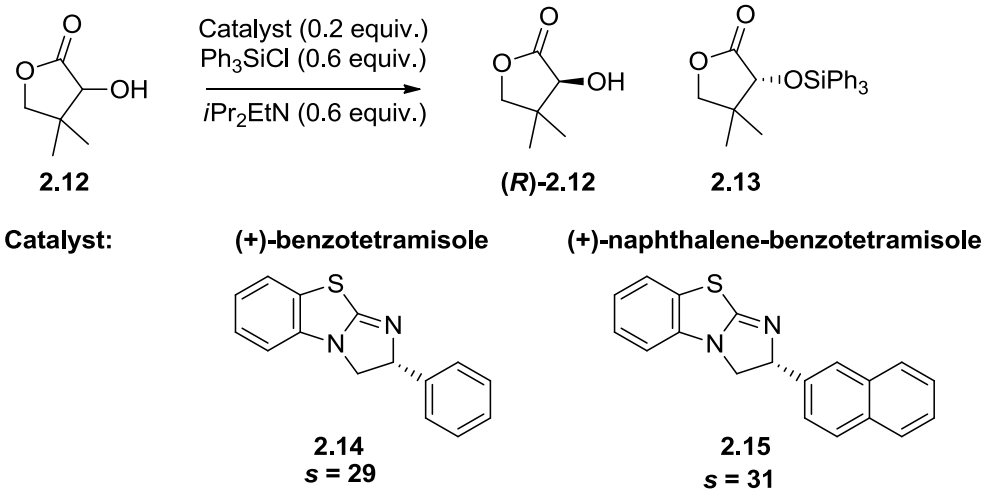


Figure 2.6 Comparison of isothiourea catalysts with different aromatic rings.

2.4 APPROACH TO THE CATALYST

In order to practice the synthesis, without employing expensive starting materials, the synthesis of (+)-tetramisole **2.16** was first attempted as shown in Figure 2.7. The synthesis starts with 2-thiazolidinethione **2.17**, which contains one ring of the final product. The compound 2-thiazolidinethione was reacted with methyl iodine in a substitution reaction to form 2-(methylthio)-4, 5-dihydrothiazole **2.18.** This compound was coupled with the amino alcohol 2-amino-2-phenylethanol to form the isothiourea intermediate **2.19** by performing a solid melt or in methanol at 100 °C. The outcome of the reactions has no difference between in solid melt or in methanol. The final step involved activating the alcohol with thionyl chloride to make it into a good leaving group for an intramolecular S_N2 reaction between the isothiourea nitrogen and the activated alcohol to close the ring. However, the proposed intermediate **2.19** was not obtained with the desired purity level. Several experiments were carried from crude intermediate **2.19** but it is unable to obtain pure tetramisole.

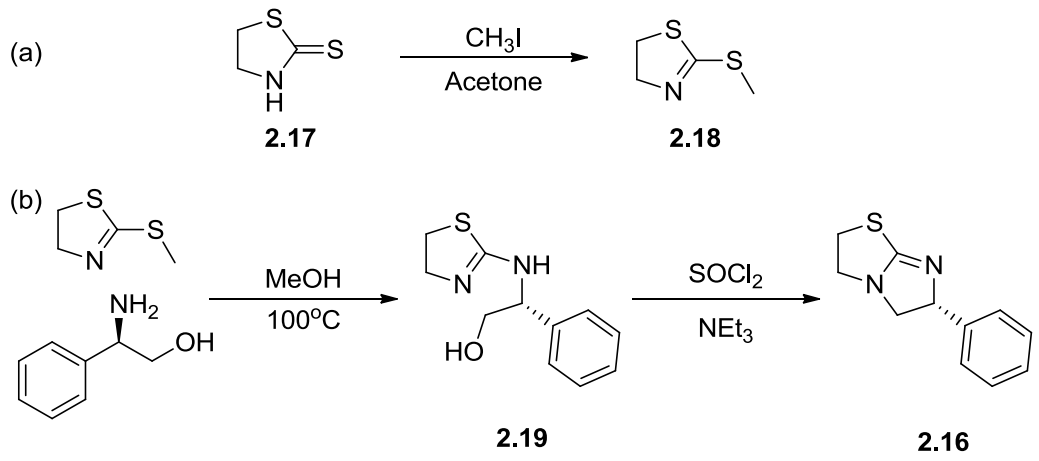


Figure 2.7 Synthetic route for (+)-tetramisole

Because the synthetic route to tetramisole was unsuccessful, we changed our focus to target *c*-hex-benzotetramisole (**2.1**). To start the synthesis of *c*-hex-benzotetramisole, the enantiopure amino alcohol **2.20** was needed. However, this is not a commercially available starting material. Therefore, amino acid **2.21** was converted into the amino alcohol via a reduction reaction employing lithium borohydride and TMSCl (Figure 2.8).[6]

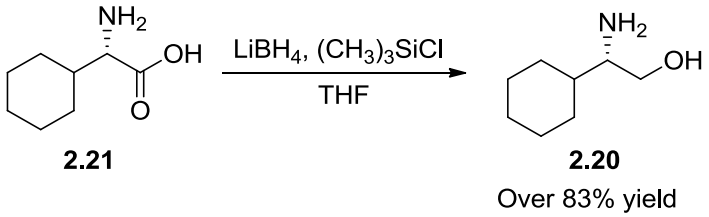
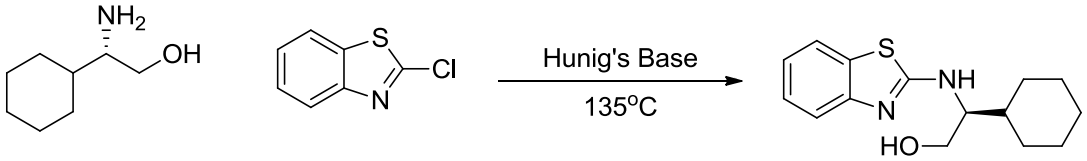


Figure 2.8 Preparation of the (S)- 2-amino-2-cyclohexylethanol.

Next amino alcohol was coupled with 2-chlorobenzothiazole **2.22** through an addition-elimination reaction to form the isothiourea intermediate **2.23** with 35% yield as shown in Figure 2.9. Finally, ring close reaction was attempted twice by reacting with methanesulfonyl chloride and triethyl amine but the desired product was not obtained. At

lower temperature, the starting material was recovered. While at higher temperature, the intermediate turned to black and decompose.



2.22 **2.23** 35% yield

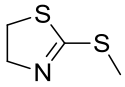
Figure 2.9 Coupling reaction between amino alcohol and 2-chlorobenzothiazole.

In conclusion, the synthesis of tetramisole was attempted but was unsuccessful. In the reactions, side-reactions occurred. It is difficult to purify the intermediate to proceed to the final product. Therefore, the synthesis of *c*-hex-benzotetramisole was also studied and only the ring closing reaction is needed to obtain the target compound. In the next stage, the work should be focused on establishing conditions so the intermediate does not decompose and the desired ring closing reaction can occur.

2.5 EXPERIMENTAL SECTION

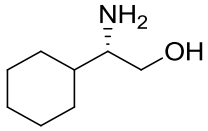
General conditions

All reaction was carried out under the nitrogen or argon. All glassware and stir bars used in the reaction were oven dried. 4 Å molecular sieves were activated in an oven above 160 °C for more the 24 hours prior to use as the manufacturer's instruction. All reagents used in the thesis are from main chemical suppliers without further purification unless otherwise stated. Flash column chromatography was performed on silica gel without any pretreatment.



2-(Methylthio)-4,5-dihydrothiazole (2.18)

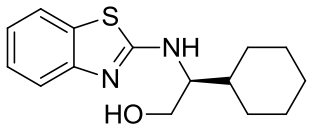
2-Mercaptothiazoline (357.6 mg, 3 mmol) and methyl iodine (209.2 μL, 3.36 mmol) were dissolved in 15 mL distilled acetone in a round bottom flask with a condenser and stir bar. Then the mixture was refluxed for 2 hours. Acetone was removed under reduced pressure and ethanol was added and the product crashed out. The product was collected by filtration as a yellow solid. Yield was 42.3% (329.6 mg, 1.25 mmol). **^{1}H NMR (300 MHz, Chloroform-d)** δ 4.51 (t, J = 8.6 Hz, 2H), 3.78 (t, J = 8.5 Hz, 2H), 2.97 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 182.17, 54.35, 32.85, 19.92, .



(*S*)-2-Amino-2-cyclohexylethanol (2.12)

Trimethyl silyl chloride (3014 μL, 24 mmol) was added to 12 mL of a commercially available lithium boron hydride solution (2M solution in THF) in round-bottom flask under nitrogen. The mixture was stirred in an ice bath for 10 minutes and 2-cyclohexyl-L-glycine (**2.21)** (943.3 mg, 6 mmol) was added as solid under the nitrogen. The mixture was stirred in an ice bath in 2 hrs and then followed by slowly warming room temperature for 12 hrs. Methanol (0.5 mL) was added to the mixture to quench the reaction under N_2. The solution was cooled down to 0 ^{o}C and 1 mL of a 20% KOH solution was added and extracted with dichloromethane 3 times. Combine the organic layer then removed the solvent and the crude product was recrystallized by two solvent systems of ethyl acetate and hexane to obtain 532 mg of product with a little of solvent residue. The yield is 62%. **^{1}H NMR (300 MHz, Chloroform-d)** δ 4.70 – 4.59 (dd, 1H),

3.21 – 3.35 (t, 1H), 2.49-2.62 (m, 1H), 6.48 (w, 1H), 1.58-1.89 (m, 8H), 0.85 – 1.20 (m, 8H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.78, 137.28, 135.33, 132.94, 130.66, 129.00, 128.26, 127.89, 124.37, 119.54, 77.35, 77.03, 76.72, 71.37, 21.71. **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 64.53, 57.65, 41.72, 29.57, 29.00, 26.44, 26.21, 26.17.



(*S*)-2-(Benzo[d]thiazol-2-ylamino)-2-cyclohexylethanol (2.23)

(*S*)-2-Amino-2-phenylethanol (**2.12)** (100.2 mg, 0.7 mmol) was mixed together with 2-chlorobenzothiazole (**2.22)** (100.47 μL, 0.77 mmol) and triethyl amine (195.27 μL, 1.4 mmol) in an oven-dried pressure vessel with a stir bar. The mixture was heated up to 140 ^{o}C and stirred for 72 hours. The mixture was cooled and basified by 30 mL of a 20% NaOH solution after cooled down, then extracted with dichloromethane. Combine the organic phase and remove solvent at reduced pressure and purified by column chromatography (50% ethyl acetate in hexanes). The product was generated (97 mg) and the yield was 50% with a slight impurity in the product. **^{1}H NMR (300 MHz, Chloroform-d)** δ 7.59 – 7.47 (m, 2H), 7.33 – 7.20 (m, 2H), 7.05 (ddt, J = 8.1, 7.4, 1.0 Hz, 1H), 6.48 (w, 1H), 4.00 (s, 1H), 3.91 – 3.71 (m, 2H), 3.40 (ddd, J = 8.7, 5.8, 3.2 Hz, 1H), 1.83 – 1.53 (m, 6H), 1.34 – 0.76 (m, 7H).

2.6 REFERENCES

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CHAPTER 3

KINETIC RESOLUTION OF α-HYDROXY CARBONYL COMPOUNDS

α-hydroxy carbonyl compounds are important intermediates in pharmaceutical industry. We employed kinetic resolution method to get the enantioenriched product from racemic mixture.

3.1 INTRODUCTION

In this chapter, the silylation-based kinetic resolution for α-hydroxy carbonyl compounds will be discussed. After the successful development of silylation-based kinetic resolution for secondary alcohols in 2011,[1] we were seeking to expand this methodology to other substrate classes. Initial studies for the silylation-based kinetic resolution for DL-pantolactone shows it has potential for α-hydroxy carbonyl compounds. A series of studies were performed on this substrate class. Optimized reaction conditions were established and several acyclic forms of α-hydroxy carbonyl compounds were studied.

3.2 BACKGROUND

Importance of α-hydroxy carbonyl compounds

Enantiomerically pure α-hydroxyl carbonyl compounds are a class of important intermediates to build biologically active compounds due to a wide presence of relevant

structures in natural products. Enantiomerically pure α-hydroxy carbonyl compounds are also key intermediates to build enantiopure drugs which have enhanced biological activity.[2] Several typical compounds include leiodolide A (**3.1**)[3] a cytotoxic compound with anti-cancer activity, harringtonine (**3.2**)[4] a cytotoxic alkaloid, and okadaic acid **3.3**[5] a protein phosphatase inhibitor.

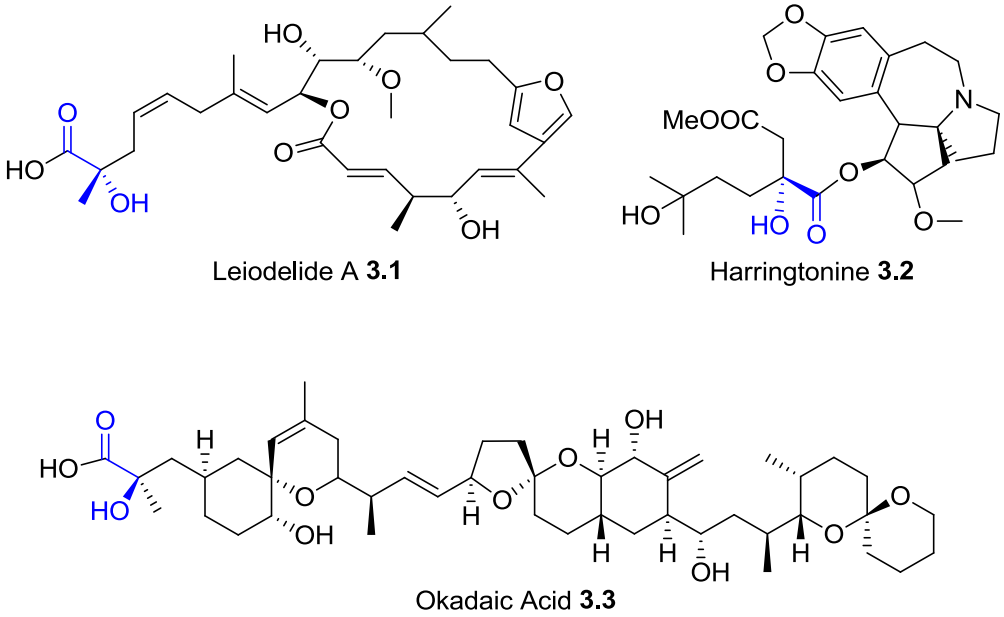


Figure 3.1, Bioactive compounds with α-hydroxy carbonyl functionalities.

Methods to obtain α-hydroxy carbonyl compounds

There are several ways to obtain α-hydroxy carbonyl compounds. The most common way is to find a natural source;[6] however, nature has a limited scope. Therefore, chemical methods are needed to obtain this class of compounds. Currently, asymmetric catalysis is the most common way to get α-hydroxy carbonyl compounds.[7] In asymmetric catalysis, as mentioned in Chapter 1, a prochiral starting material is converted into enantioenriched products using a chiral catalyst or chiral reagent. In this method,

enantiomeric excess (ee) remains constant regardless of conversion, and enantiopurity can be difficult to optimize to higher levels. Thus, if higher enantioenrichment is required, an entirely different method may be required, resulting in an increase in cost and time.

Silylation-based kinetic resolution for secondary alcohols

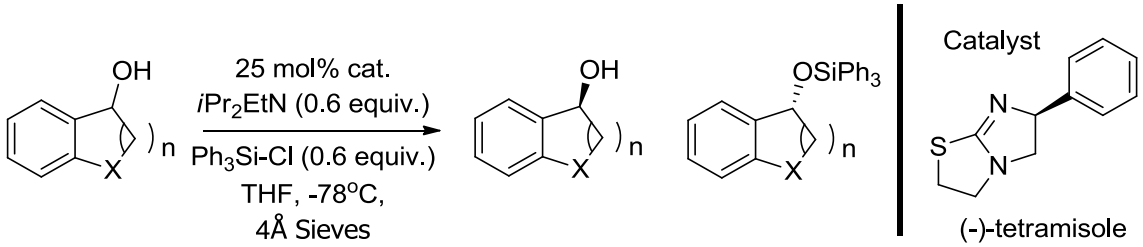


Figure 3.2 Silylation-based kinetic resolutions for secondary alcohols.

In 2011, the Wiskur group developed a novel silylation-based kinetic resolution for secondary alcohols employing a small molecule organic compound as a catalyst. As shown in Fig 3.2, the secondary alcohol was converted from racemic mixture to enantioenriched compound. The methodology works well for a series of secondary alcohols, achieving a selectivity factor of up to 25.

Hypothesized reaction mechanism

Mechanistically, we proposed that the chiral nucleophile reacts with the silyl chloride **3.4** to form an activated complex **3.5**. Once the chiral silyl complex forms **3.5**, one enantiomer of the alcohol **3.6** reacts faster than the other one to generate a silylated alcohol. The proposed mechanism for the isothiourea catalyzed silylation reaction is shown the Figure 3.3.

The success of the silylation-based kinetic resolution inspired us to broaden the substrate scope for this methodology. The chiral recognition model is proposed in Figure 3.4(a). For the secondary alcohols, one side is a conjugated π-system, which can be regarded as the small side; the other side is an alkyl group, which can be described as the large side. In Figure 3.4(b), there is a comparison between simple cyclic secondary alcohols and α-hydroxy carbonyl compounds. Similar to the cyclic secondary alcohols, the α-hydroxy carbonyl compounds also have both sides different in size. Usually, the conjugated pi side is the small side. We hypothesized the α-hydroxy carbonyl compounds will potentially work well for our silylation-based kinetic resolution method.

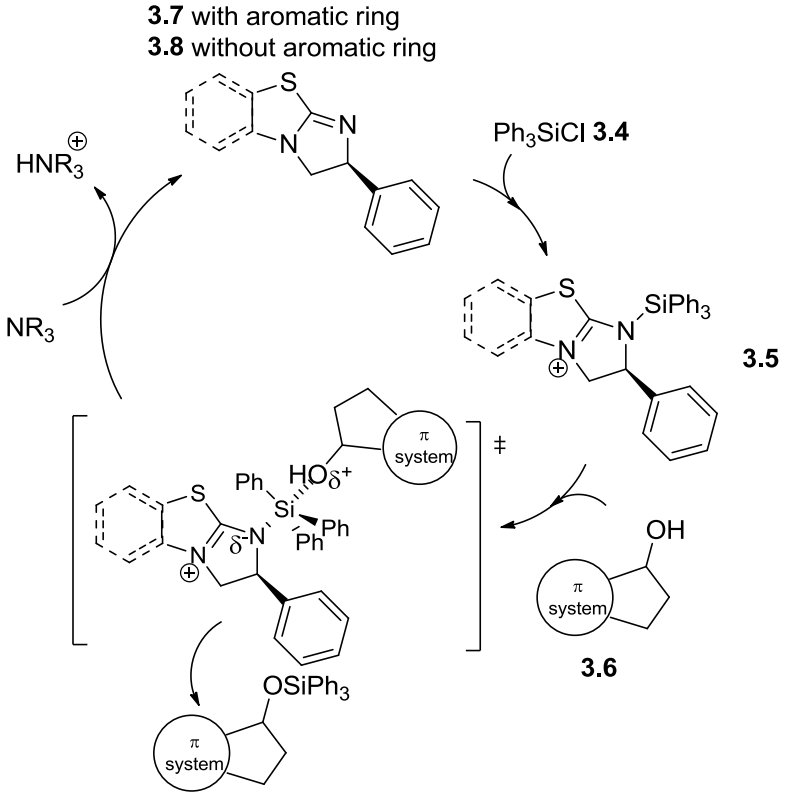


Figure 3.3 Mechanism of silylation-based kinetic resolution.

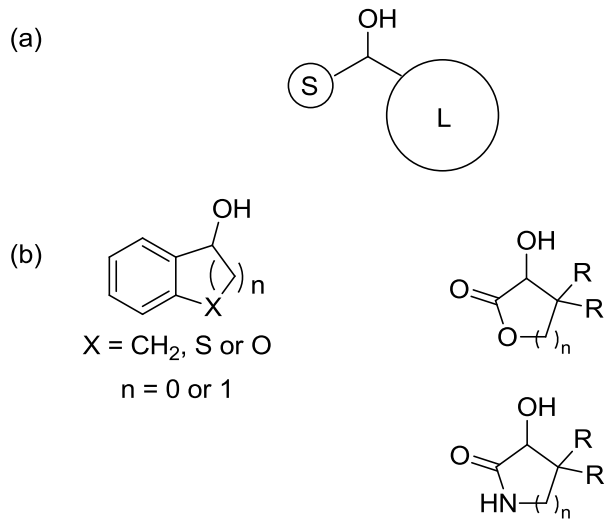


Figure 3.4 (a) Chiral recognition model and (b) Comparison of cyclic secondary alcohols and α-hydroxy carbonyl compounds.

3.3 Optimizations of the silylation-based kinetic resolution for α-hydroxy carbonyl compounds

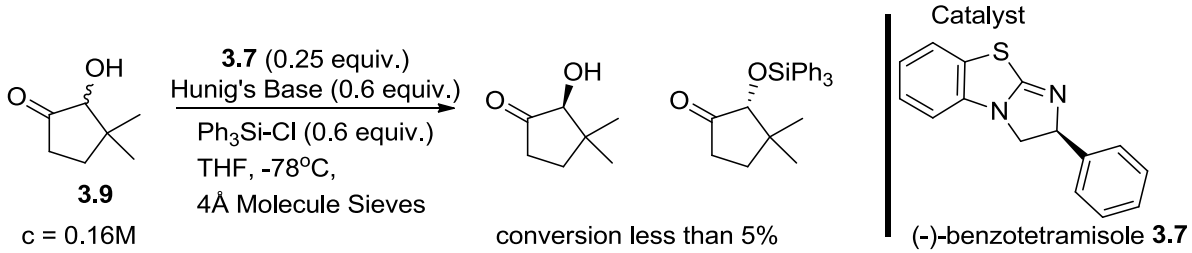
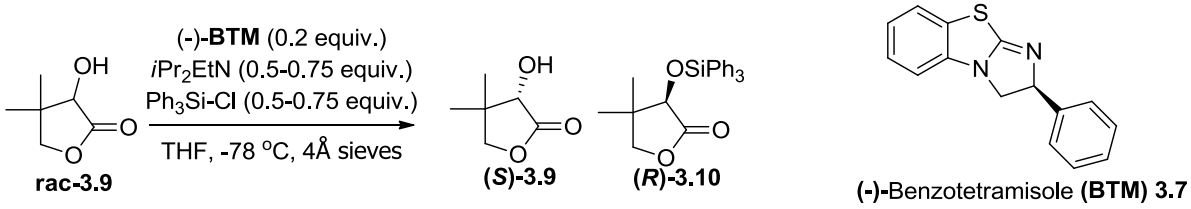


Figure 3.5 Silylation-based kinetic resolution for α-hydroxy carbonyl compounds.

Initially, reaction conditions applied for α-hydroxy lactones were similar to that used for previous work with secondary alcohols,[1] but unfortunately poor conversion was observed. Therefore, our preliminary investigation required re-optimizing the reaction conditions. These conditions included a change in concentration of the alcohol, alternating amine bases and testing a variety of different solvents, using commercially available 3,3-dimethylated α-hydroxy lactone, named D,L-pantolactone (**3.9**) as a

substrate. Also, the previously employed catalyst, tetramisole (**3.8**), did not show any selectivity, therefore, the catalyst was changed to another commercially available isothiourea based catalyst, (-)-benzotetramisole (BTM) (**3.7**) (Table 1). We started our investigation simply by changing the concentration of alcohol.

Table 3.1 Optimization of the reaction conditions of concentration and equivalents of reagents.

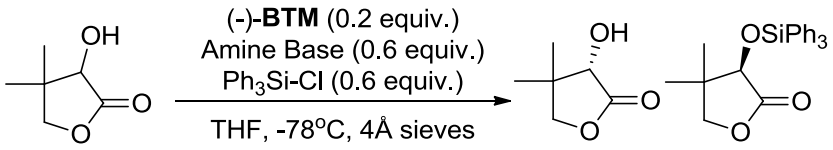


Entry	Conc. of Lactone (mM)	Reaction Time (h)	Equiv. of Silyl Chloride & Amine	Conv.%	*s*	er
1	0.16	24	0.5	5	24	52:48
2	0.26	24	0.5	18	20	61:39
3	0.26	24	0.75	21	22	61:39
4	0.26	48	0.75	42	11	59:41
5	0.42	24	0.75	48	16	85:15
6	0.42	48	0.75	55	13	91:9
7	0.42	24	0.6	45	27	88:12
8	0.45	24	0.6	45	27	88:12
9	0.35	24	0.6	34	23	74:26
10	0.42	24	0.6	46	24	86:14
11	0.42	24	0.75	50	24	90:10

When the concentration was changed from 0.16 M to 0.26 M (Table 1, Entry 1 & 2), the conversion increased significantly. Increasing the equivalents of triphenylsilyl chloride (Ph_3SiCl) and Hunig's base (iPr_2EtN) (Table 1, Entries 2 & 3) did not affect the

conversion very much. Apparently, the concentration of the reaction is the key factor to increasing the conversion. Therefore we increased the concentration of the alcohol from 0.26 M to 0.42 M (Table 1, Entries 5-7) to achieve an acceptable conversion. Elongation of the reaction time at 0.42 M (Table 1, Entries 5 & 6) did not increase the conversion much. We also tried other ways to enhance the selectivity, which included slow addition of Ph_3SiCl and changing its concentration (Table 1, Entries 10 & 11), but no enhancement in selectivity was observed. After getting an acceptable conversion, we turned our attention towards selectivity factors by exploring bases as well as solvents.

Table 3.2 Kinetic resolution reaction with different amine base.

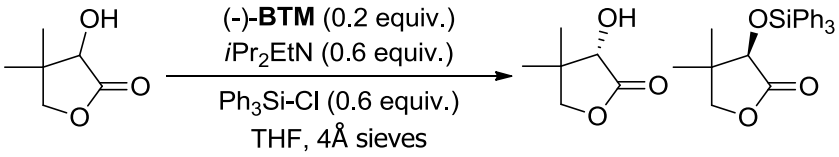


Entry	Base	Conv (%)	*s*	er
1	Triethyl Amine	43	31	84:16
2	*N,N*-Diisopropylethyl Amine	45	31	88:12
3	Tribenzyl Amine	21	31	62:38
4	Triisobutyl Amine	23	31	65:35
5	Tributyl Amine	39	25	70:30
6	No base	<5	ND	ND

In the isothiourea catalyzed silylation of the alcohol, a proton is generated. As a result, a Brønsted base is needed. Several reports[1, 8] in similar kinetic resolutions, as well as our

previous results,[1] have shown that the amine base can affect the selectivity. Therefore, we explored several bases with different steric and electronic properties (Table 2). The more sterically hindered amines, including tribenzyl amine and triisobutyl amine (entry 3 & 4), decrease the conversion significantly compared with the less sterically hindered amines, such as *N,N*-diisopropylethyl amine and triethyl amine (Table 2, entry 1 & 2). Interestingly, the selectivity factors remain unaffected.

Table 3.3 Kinetic resolution reaction in different solvent.



Entry	Solvent	Temp °C	Conv. %	s	er
1	THF	-78	46	27	86:14
2	CH_2Cl_2	-78	53	7	83:17
3	DMF	-40	43	2	57:43
4	DME*	-40	41	5	57:43
5	Toluene	-78	56	10	89:11
6	10% CH_2Cl_2 in THF	-78	51	19	90:10
7	10% Toluene in THF	-78	51	25	95:5
8	5% Toluene in THF	-78	59	26	89:11

*The conversion and selectivity is determined by NMR

Next, we turned our attention towards different solvents to see the effect they had on selectivity. In our previous study, tetrahydrofuran (THF) proved to be the best solvent.[1] Polar aprotic solvents were investigated to determine their effect on the reaction. We are limited to these solvents because we are developing an ionic intermediate that needs to be

solubilized and the reaction presumamble an S_N2 reaction. As expected, THF still obtained the highest selectivity, achieving a selectivity factor of 27 (Table 3, Entry 1). All the other solvents tested demonstrated lower selectivity (Table 3, Entries 2-5). Interestingly, both toluene and dichloromethane showed enhanced conversions, which may be due to an increase in solubility of the intermediate. Therefore, mixed solvent systems between THF and dichloromethane or toluene were also tested (Table 3, Entries 6-8). While there were increases in the conversion, these reactions were less selective than those in THF. Finally, we determined that in order to maintain high selectivity and high conversion, the reaction needed to be run at a higher concentration of alcohol (0.42 M) using THF and Hunig's base.

3.4 EXPANSION OF THE SUBSTRATE

After the establishment of the optimized reaction conditions, other substrates were studied.

α-hydroxy ketone compounds

As mentioned above, the conjugated π-system is very important for the chiral recognition. Therefore, it is interesting to study the α-hydroxy ketone with an aromatic ring next to the carbonyl group as shown in Figure 3.6. Benzoin (**3.11**) is commercially available while the other substrate is not. As a result, the synthesis of 2-hydroxy-1-phenylpropan-1-one **3.12** is needed. The synthetic method was obtained from other researchers work.[9] The commercially available 2-bromopropiophenone **3.13** was added to methanol with sodium formate and then refluxed overnight. After column chromatography, the yield is 23% (Figure 3.7)

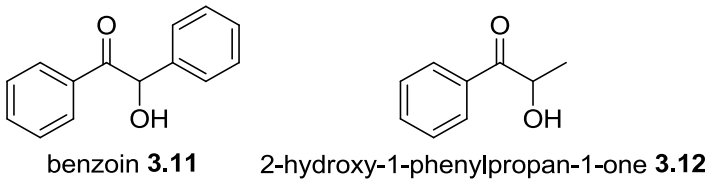


Figure 3.6 α-Hydroxy ketones with extended p-systems.

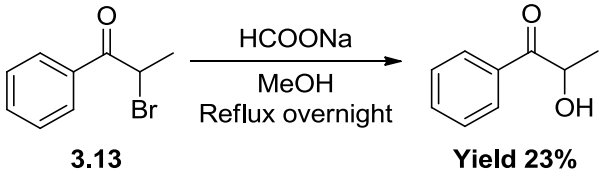


Figure 3.7 Synthesis of 2-hydroxy-1-phenylpropan-1-one

The kinetic resolution reactions of these substrates were carried out. However, the HPLC did not give a consistent ee value as the starting material easily transforms to other compounds on the shelf as well as in the work up process after the kinetic resolution.

α-Hydroxy lactam compounds

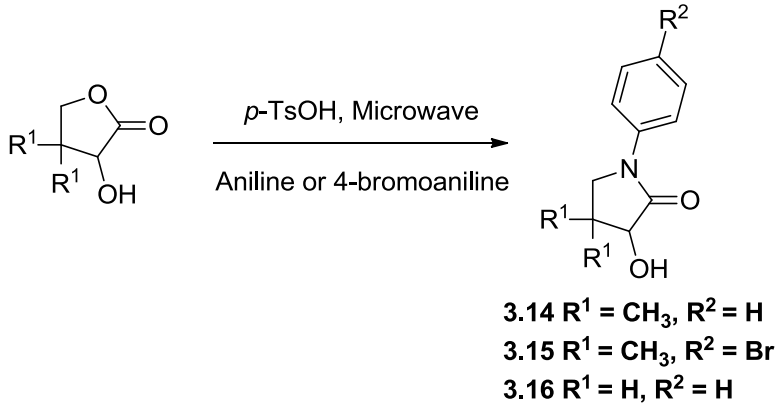


Figure 3.8 Aminolysis of the α-hydroxy lactone compound.

α-hydroxy lactam compounds can be synthesized from the α-hydroxy lactone compounds via aminolysis as shown in Figure 3.8.[10] The D,L-pantolactone was mixed with aniline and *p*-toluenesulfonic acid (*p*-TsOH). The mixture was reacted in the microwave reactor at 210 ^{o}C for 20-40 minutes. Afterward, the mixture was washed by 6N HCl to remove the extra aniline and then by saturated $NaHCO_3$ to remove the *p*-TsOH. The crude product is recrystallized in ethyl acetate and hexane to give the pure product **3.14**. After successful synthesis of phenyl lactam **3.4**, 4-bromoaniline was employed to synthesize *p*-bromophenyl lactam **3.15**. The 4-bromoaniline is not very stable at high temperature and it is easy to decompose to generate a gaseous bromine compound. As a result, the reaction process needed to be carefully monitored to avoid overheating. The two lactam-derivatives of D,L-pantolactone were successfully synthesized and submitted to colleagues to continue the next step.

Lactam **3.16** was synthesized similarly from aniline and 3-hydroxydihydrofuran-2(3H)-one. The kinetic resolution was carried out at the optimized reaction conditions. However, the substrate 3.3 showed no selectivity at all.

α-Hydroxy ester compounds

DL-lactic acid **3.17** is commercially available and it is a good starting material to synthesize α-hydroxy esters compounds. A benzyl group is a common protecting group for the carboxylic acid. Benzyl lactic acid **3.18** can be synthesized by adding benzyl bromide to lactic acid (Figure 3.9). Benzyl lactic acid has a relatively high boiling point to stay liquid under the work up process and its phenyl group is UV active, which is important for the HPLC detector. Initially, the reaction took place in dichloromethane and triethyl amine was added as a base However, the yield is only about 10%. An alternative

method was then employed.[11] The lactic acid was first dissolved in a methanol/water mixture and the pH was adjusted to 7 by $CsCO_3$. Then benzyl bromide was added and the reaction carried out in DMF overnight resulting in a yield up to 93%. The selectivity factor is 5.7 with 51% conversion.

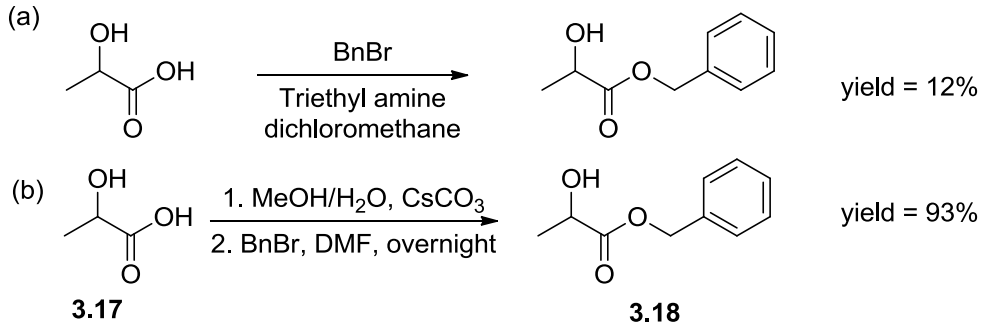


Figure 3.9 Synthesis of benzyl lactic acid (a) initial method (b) improved method.

α-Hydroxy amide compounds

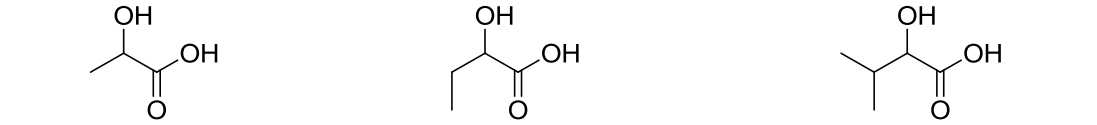


Figure 3.10 Commercially available α-hydroxy carboxylic acid.

Besides lactic acid, several kinds of α-hydroxy carboxylic acids were commercially available as shown in Figure 3.10. The nitrogen atom on aniline is very nucleophilic and can react with the partially positive-charged carbon on the carboxylic acid under acid catalysis. Therefore, a series of reactions were designed to synthesize the α-hydroxy amide as shown in Figure 3.10. *p*-TsOH, which is soluble in the organic phase, was chosen as the acid catalyst for the reaction. Microwave reaction was employed to shorten

the reaction time. After mixing all reagents, the reaction vessel was placed in a microwave reactor and reacted about 30-40 min at 215 ^{o}C as shown in Figure 3.11. After the reaction, the mixture was washed by 6N HCl and saturated $NaHCO_3$ to remove aniline and *p*-TsOH, respectively. The yield ranges from 30% to 90% depending on the substrates.

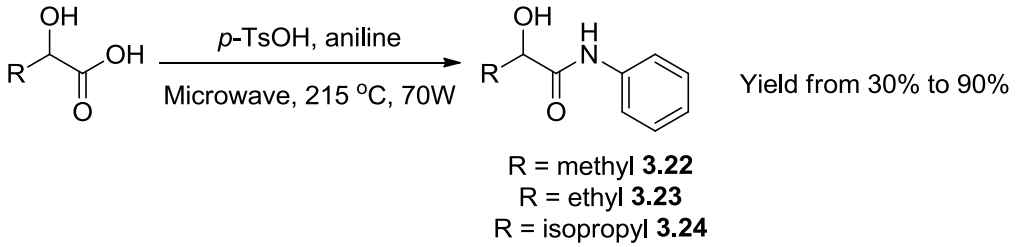
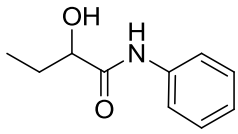
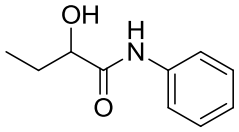
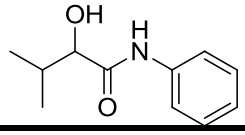


Figure 3.11 Synthesis of α-hydroxy amide compounds.

Table 3.4 Kinetic resolution for α-hydroxy amide compounds.

Entry	Recovered Alcohol	time (h)	er of recovered alcohol	% conv[a]	*s*[b]
1		24	76:24	47	**6.1**
2		24	86:14	37	**7.5**
3		24	99:1	55	**13**

The result of the kinetic resolution of α-hydroxy amides further confirms our hypothesis that the origin of selectivity is dependent upon the size difference between the two sides of the secondary alcohol. The result is shown in Table 3.4

3.5. SUMMARY

The optimized conditions for the kinetic resolution of α-hydroxy carbonyl compounds has been established. Several classes of substrates were studied, including α-hydroxy ketones, lactams, esters and amides were successfully synthesized and their selectivity in our silylation-based kinetic resolution was also investigated. The result indicated our silylation-based kinetic resolution works for a wide range of substrates and provided us an insight view of the reaction mechanism.

3.6. Experimental

General procedure for the kinetic resolution

Approximately 20-25 mg of activated 4 Å molecular sieves was added to an oven dried 1 dram vial containing a Teflon coated stir bar. (+)-Benzotetramisole (0.1mmol or 0.125 mmol) was weighed out under N_2 and added to the vial. Most of the substrates were directly weighed and added to the 1 dram vial then 900 µL of THF was added. If the substrate is D,L-pantolactone, weigh 260 mg (2 mmol) D, L-pantolactone and add to an oven dried 2 mL volumetric flask as quickly as possible and then fill with solvent to make a solution under argon. Employ an air tight syringe to add 500 µL solutions to the 1 dram vial followed by another 400 µL pure solvent to the vial. In the next step, 0.3 mmol of the amine base was added to the vial. If the amine base is a solid, the base is

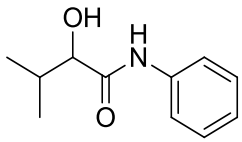
added before the addition of any other liquid. After all reagents excluding triphenylsilyl chloride were added, electrical tape was used to seal the cap of the 1 dram vial and it was cooled to -78 °C. Recrystallized triphenylsilyl chloride (Ph_3SiCl) (296 mg) was weighed into an oven dried 1 mL volumetric flask and dissolve in THF to make a 1M Ph_3SiCl solution. 300 µL of this 1 M Ph_3SiCl solution was added to the reaction vial(s) that have already been cooled to -78 °C. After react 24-48 hours, the reaction was quenched by 0.5 ml of methanol. The NMR of the crude mixture was taken.

Column chromatography was performed to separate the product and unreacted starting material employing the solvent system ethyl acetate/hexane 50:50. For the amide substrate, the starting material and the catalyst is still the co-elute. This mixture was washed with 1.5 mL 5% HCl and extracted by diethyl ether three times. The organic layers were combined then dried over anhydride Na_2SO_4. The product was then reacted with 2 mL of a 1M TBAF solution in THF to remove the silyl group.

When the substrate is DL-pantolactone, both recovered starting material and desilylated product need to be benzoylated for the HPLC analysis. The recovered DL-pantolactone from the kinetic resolution reactions is reacted with excess 80 µL benzoyl chloride (80 µL) and triethylamine (110 µL) catalyzed by 4-dimethylaminopyridine (DMAP) (12mg, 0.1 mmol) in 2 mL dichloromethane. The reaction was quenched by saturated sodium bicarbonate ($NaHCO_3$) and extracted with dichloromethane (2*2 mL). Then column chromatography was run in 1:9 ethyl acetate/hexane to afford benzoylated starting material.

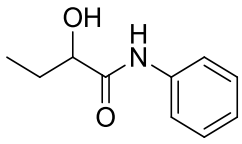
General procedure to make α-hydroxy carboxylic acid (GP1).

To a 10 mL microwave reaction vessel with a Teflon coated-stir bar was added the α-hydroxy carboxylic acid, aniline and p-toluenesulfonic acid. The vessel was put into the microwave reactor (CEM DiscoverSP with SynergyD software). The microwave reactor was set as follows: Maximum pressure, 75 MPa; Maximum power, 75W. After the reaction, the vessel was cooled down by flowing nitrogen. The NMR conversion was checked right after the cooling process. The sample was transfered to a separatory funnel by dichloromethane. The sample was washed with 6N HCl, sat. $NaHCO_3$ and sat. NaCl. Then the organic phase was dried over $NaSO_4$, filtered and evaporated at reduced pressure.



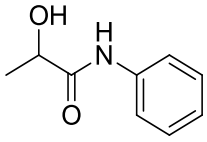
2-Hydroxy-3-methyl-*N*-phenylbutanamide

According to the GP1, 2-hydroxy-3-methylbutanoic acid (3 mmol, 354.39 mg) was react with aniline (6 mmol, 559.8 mg) with catalytic amount of *p*-toluenesulfonic acid monohydrate (0.6 mmol, 114.12mg). The yield of 2-hydroxy-3-methyl-N-phenylbutanamide is 475 mg, 2.49 mmol, 83% yield. It's pale yellow solid **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 7.62 – 7.53 (m, 2H), 7.39 – 7.29 (m, 2H), 7.17 – 7.08 (m, 1H), 4.13 (d, J = 3.1 Hz, 1H), 2.56 (s, 1H), 2.32 (pd, J = 6.9, 3.1 Hz, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.10, 137.16, 129.05, 124.49, 119.76, 77.32, 77.21, 77.00, 76.79, 76.69, 55.81, 31.90, 19.19, 15.44



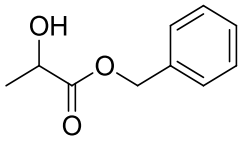
2-Hydroxy-*N*-phenylbutanamide

According to the GP1, D,L-2-hydroxybutyric acid (5 mmol, 520.5 mg) was reacted with aniline (10 mmol, 933 mg) under a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.1 mmol, 19.02 mg). The yield of 2-hydroxy-*N*-phenylbutanamide is 792 mg, 4.4 mmol, 88% yield. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 8.37 (s, 1H), 7.62 – 7.54 (m, 2H), 7.39 – 7.29 (m, 2H), 7.18 – 7.08 (m, 1H), 4.24 (dt, J = 8.1, 4.3 Hz, 1H), 2.49 (d, J = 5.3 Hz, 1H), 1.99 (dtd, J = 15.0, 7.5, 4.0 Hz, 1H), 1.81 (dp, J = 14.6, 7.3 Hz, 1H), 1.05 (t, J = 7.4 Hz, 3H).). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm δ 171.33, 132.43, 129.05, 124.47, 119.68, 104.99, 77.32, 77.01, 76.69, 73.63, 27.88, 9.17



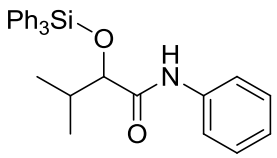
2-Hydroxy-*N*-phenylpropanamide

According to the GP1, D,L-lactic acid (5 mmol, 450.4 mg) was reacted with aniline (15 mmol, 1.40 g) under a catalytic amount of *p*-toluenesulfonic acid monohydrate (1 mmol, 190.2 mg). The yield of 2-hydroxy-*N*-phenylpropanamide is 308 mg, 1.87 mmol, 37% yield. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 8.52 (s, 1H), 7.59 – 7.51 (m, 2H), 7.37 – 7.24 (m, 2H), 7.17 – 7.08 (m, 1H), 4.35 (q, J = 6.8 Hz, 1H), 3.21 (s, 1H), 1.52 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 172.57, 137.12, 129.04, 124.58, 119.80, 77.34, 77.02, 76.70, 68.87, 21.17.



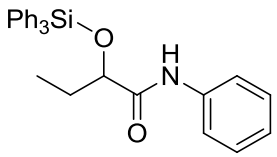
Benzyl-2-hydroxypropanoate

To a round bottom flask with Teflon-coated stir bar and DL lactic acid (3.45 mmol, 313.26 mg) was added 7 mL MeOH-water (1:9) solution and then a 20% $CsCO_3$ solution was added dropwisely to make pH=7. The solvent was removed under reduced pressure. DMF was added to the flask and removed under reduced pressure again. The flask was put in an ice bath and benzyl bromide (3.11 mmol, 560.4 mg) was added dropwise. The reaction was run at room temperature for 18 h then partitioned between water and ether. The aqueous layer was extracted by ether three times then the ether extracts were combined and dried over $NaSO_4$. The solution was decanted and the solvent was removed under reduced pressure. The yield is 523 mg, 3.21 mmol, 93% yield. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 7.37 (tt, J = 7.1, 4.0 Hz, 5H), 5.26 – 5.14 (m, 2H), 4.40 – 4.27 (m, 1H), 2.79 (s, 1H), 1.44 (dd, J = 6.9, 3.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 175.54, 135.18, 128.65, 128.63, 128.54, 128.52, 128.24, 128.23, 128.17, 77.35, 77.23, 77.03, 76.71, 69.49, 69.37, 67.30, 67.25, 66.83, 66.73, 66.70, 20.42, 20.37, 20.07, 16.85.



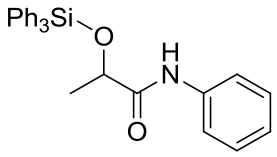
3-Methyl-*N*-phenyl-2-((triphenylsilyl)oxy)butanamide//YZ-2-91

mp range = 36-37°C. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 8.39 (s, 1H), 7.69 – 7.60 (m, 6H), 7.51 – 7.35 (m, 9H), 7.32 – 7.17 (m, 4H), 7.07 (ddt, J = 7.1, 6.4, 1.8 Hz, 1H), 4.32 (d, J = 3.0 Hz, 1H), 2.19 (hd, J = 6.9, 3.0 Hz, 1H), 0.97 (dd, J = 24.2, 6.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 170.70, 137.06, 135.58, 132.95, 130.64, 128.90, 128.29, 128.26, 128.23, 124.33, 119.64, 79.52, 77.40, 77.08, 76.76, 33.32, 18.91, 16.79. . **IR** (neat, cm^-) 3393, 3070, 3051, 2963, 2930, 1671, 1601, 1521, 1441, 1428, 1315, 1178, 1116, 1050, 872, 822, 740, 692. **HRMS** (ESI) calculated for ($C_{29}H_{29}NO_2Si$) : 451.1969, Observed: 451.1968. **Optical Rotation** $[\alpha]^{25}_D$: = +43.9 (c = 8.3) $CHCl_3$



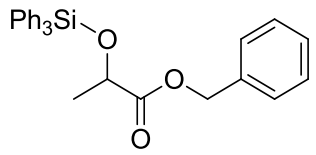
***N*-Phenyl-2-((triphenylsilyl)oxy)butanamide**

mp range = 56-59 °C. **^{1}H NMR:** (300 MHz, $CDCl_3$) 8.57 (s, 1H), 7.69 – 7.20 (m, 19H), 7.09 (tt, J = 7.3, 1.3 Hz, 1H), 5.27 (d, J = 1.4 Hz, 1H), 4.49 (td, J = 4.7, 1.4 Hz, 1H), 2.02 – 1.83 (m, 1H), 1.83 – 1.55 (m, 1H), 0.94 (td, J = 7.4, 1.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.01, 158.70, 137.18, 135.39, 132.97, 130.67, 130.61, 128.96, 128.29, 128.25, 128.21, 124.37, 119.59, 77.47, 77.04, 76.62, 75.58, 75.46, 27.92, 8.33. **IR** (neat, cm^-) 3389, 3069, 2969, 2933, 1689, 1600, 1521, 1442, 1428, 1312, 1237, 1187, 1115, 1012, 885, 833, 743, 692. **HRMS** (ESI) calculated for ($C_{28}H_{27}NO_2Si$): 437.1811, Observed: 437.1811. **Optical Rotation** $[\alpha]^{25}_D$: = +41.6 (c = 8.3) $CHCl_3$



***N*-Phenyl-2-((triphenylsilyl)oxy)propanamide .**

mp range = 94-97 ^{o}C **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ppm 8.68 (s, 1H), 7.68-7.06 (m, 20H), 4.51 (q, J = 6.7 Hz, 1H), 1.46 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 171.78, 137.28, 135.33, 132.94, 130.66, 129.00, 128.26, 127.89, 124.37, 119.54, 77.35, 77.03, 76.72, 71.37, 21.71. **IR** (neat, cm^{-}) 3390, 3069, 3024, 2929, 2686, 1600, 1522, 1441, 1428, 1368, 1313, 1240, 1187, 1115, 1079, 1048, 1028, 970, 910, 787, 739, 710. **HRMS** (ESI) calculated for ($C_{27}H_{25}NO_2Si$): 423.1651, Observed: 423.1655. **Optical Rotation** $[\alpha]^{25}_{D}$: = +30.8 (c = 8.3) $CHCl_3$



Benzyl 2-((triphenylsilyl)oxy)propanoate//YZ-2-87.

Oil liquid,

^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 7.67 – 7.52 (m, 6H), 7.48 – 7.27 (m, 12H), 7.21 (dd, J = 6.9, 3.3 Hz, 2H), 4.98 (d, J = 3.4 Hz, 2H), 4.49 (q, J = 6.8 Hz, 1H), 1.47 (d, J = 6.7 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 173.28, 135.58, 135.51, 135.39, 133.71, 130.14, 130.07, 128.50, 128.25, 128.24, 128.22, 127.89, 127.86, 77.46, 77.34, 77.03, 76.61, 69.03, 66.49, 21.23. **IR** (neat, cm^{-}) 3430, 2957, 1722, 1178, 1118, 1033, 989, 919, 854, 743, 711. **HRMS** (ESI) calculated for ($C_{28}H_{27}O_3Si$-C_6H_5) : 361.1254, Observed: 361.1260. **Optical Rotation** $[\alpha]^{25}_{D}$: = +10.2 (c = 8.3) $CHCl_3$

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