

**PART I: STUDIES TOWARDS ASYMMETRIC α -
HALOGENATION AND MECHANISTIC STUDIES
OF THE ACRYLATE SYSTEM WITH
ORGANOCATALYST
AND
PART II: SYNTHESIS OF α -ARYL QUATERNARY
CARBON CENTERS**

By

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ABSTRACT
**PART I: STUDIES TOWARDS ASYMMETRIC α - HALOGENATION AND
MECHANISTIC STUDIES OF THE ACRYLATE SYSTEM WITH
ORGANOCATALYST.**

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The University of Wisconsin-Milwaukee, 2014
Under the supervision of Professor M. Mahmud Hossain

Organocatalytic transformations and asymmetric α -halogenation have become an important and dynamic research topic in organic chemistry in recent years. Despite the growing research in asymmetric halogenation of carbonyl compounds, such as aldehydes and ketones, there are no current examples in the literature of asymmetric halogenation of enolic systems even though many proposed reaction mechanisms go through enolate form. The research presented is the first example of enantioselective α -chlorination and α -bromination of α -hydroxyacrylate using organocatalysis and NMR studies towards achieving asymmetric induction of the enolic system. Despite the many publications that show when an organocatalyst binds to an aldehyde or ketone, the transition state goes through the enolate tautomer, that form is not stable otherwise and conforms back into starting material when the catalyst leaves the enolate. Whereas the α -hydroxyacrylate is stable in the enolic form by itself and does not need to be bound to any catalyst. Investigation into the mechanism of the reaction with the help of NMR studies showed that organocatalysts work as a base with the acrylate system and two major species are formed, E and Z

isomers. This along with the fact that the catalyst is only loosely bound to the substrate is preventing desirable asymmetric induction from occurring. α -chlorination and α -bromination were successfully achieved with 100% yield and up to 30% ee.

PART II: SYNTHESIS OF α -ARYL QUATERNARY CARBON CENTERS

The formation of quaternary carbon centers poses a particular challenge for organic chemists. The research conducted focused on the synthesis of all quaternary carbon centers via Claisen rearrangement of *o*-allylated acrylates, which were prepared using a known procedure with high yields.

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DEDICATION

I dedicate this thesis to my angel, my daughter: Nika Lillian Shteynbuk

"There are many things we know we know,
there is a lot more things we know we don't know
but there is a lot more things we don't know we don't know"

Anonymous quote

My angel: grow and explore, there is a whole world out there for you to discover.

I love you,

Mama

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Part I: Studies towards asymmetric α -halogenation and mechanistic studies of the acrylate system with organocatalyst.

Appendix A: NMR spectroscopic data and HPLC traces

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Part I:

**Studies towards asymmetric α -halogenation and
mechanistic studies of the acrylate system with
organocatalyst.**

1 Introduction

This thesis is based on three parts that evolved from each other and are based on catalytic reactions discovered in the laboratory of Dr. M. Mahmum Hossain at the University of Wisconsin- Milwaukee. The first section will describe the organocatalytic alpha halogenation of hydroxyaryl acrylate in order to form asymmetric quaternary carbon centers. The second section will focus on metal-based halogenation of hydroxyaryl acrylate for the formation of asymmetric quaternary carbon centers. Finally, the last section will focus on the mechanistic studies that were conducted on the acrylate system with quinine and DFT calculations for different quinine analogs in attempt to understand the reaction mechanism, design new organocatalyst as well as designing new chiral nucleophiles.

1.1 Background

In 1998, in an attempt to synthesize an epoxide, Dr. M. Mahmum Hossain's group discovered a new reaction between aromatic aldehydes (1) and Ethyl diazo acetate (EDA), (2) in the presence of an iron Lewis acid or $\text{HBF}_4 \cdot \text{OEt}_2$ (3) that formed alpha hydroxyl acrylate (3-hydroxy-2-phenylacrylic acid ethyl ester, (4)) (scheme 1)^{1,2}. This product showed a lot of potential and large versatility in construction of new molecules and development of new reactions (Figure 1). One important part of alpha hydroxyl acrylate is its prochiral center that can be utilized for the construction of an asymmetric α -quaternary carbon center. This thesis is

Scheme 1: The alpha hydroxyl acrylate reaction.

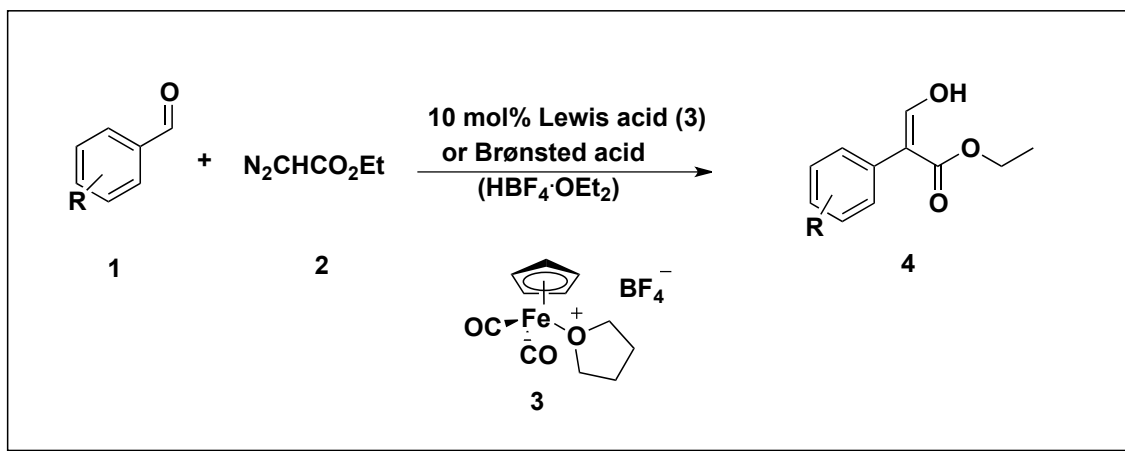
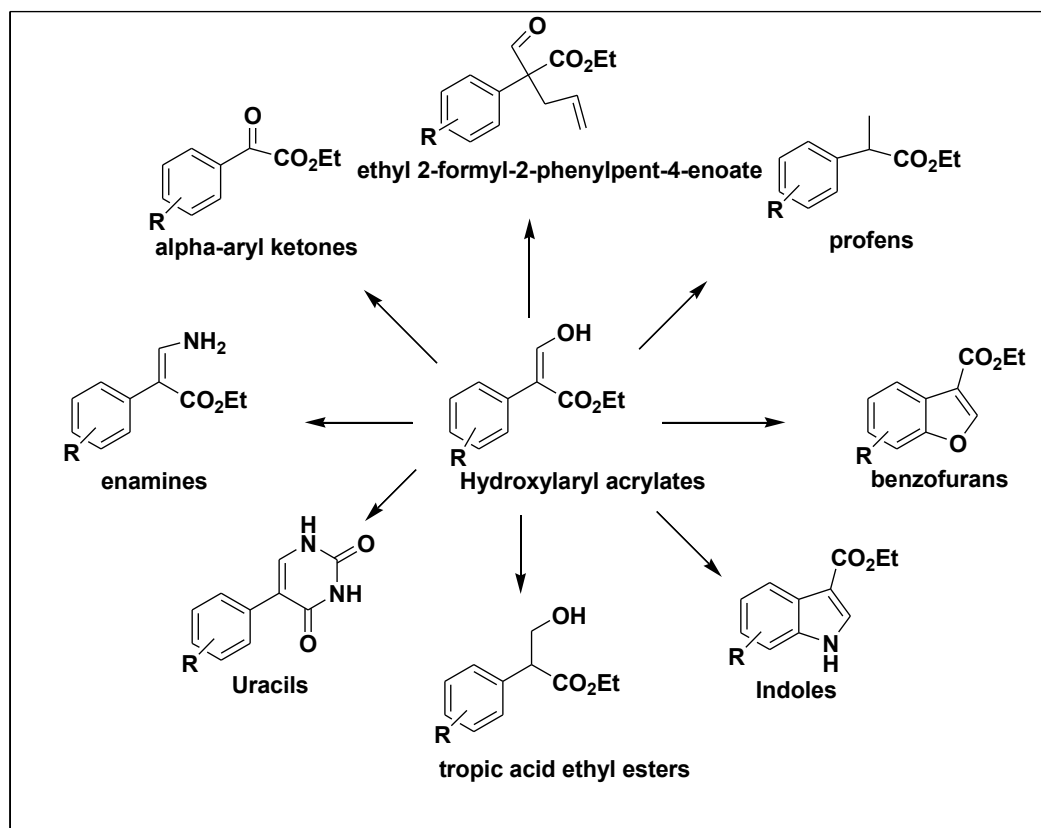


Figure 1: New compounds that were constructed from hydroxylarylacrylates.

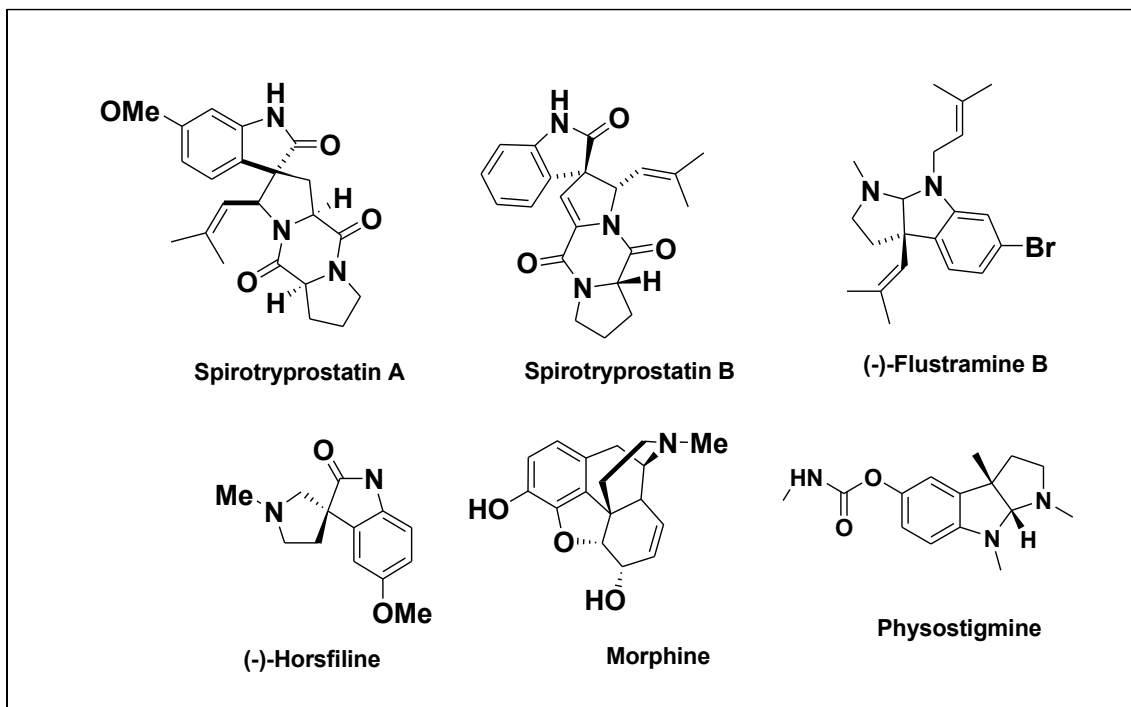


based on the development of asymmetric α -quaternary carbon centers through alpha halogenation and mechanistic studies that were done with NMR and DFT calculations on the alpha hydroxyl acrylate system with an organocatalyst in an attempt to synthesize a universal nucleophile.

1.2 Asymmetric quaternary carbon center

The Asymmetric synthesis of all carbon quaternary centers is a challenging task in organic chemistry. With the growth in population and extended life expectancy there is a high demand for the development of better methods to synthesize new as well as existing drugs in more cost and labor efficient ways. Many current drugs' active sites require one or more asymmetric quaternary carbon center (see figure 2) as well as many other organic compounds and natural products that can be used for the future development of new pharmaceuticals³. In spite of the growing demand and the major improvements in recent years in asymmetric synthesis, there are few general methods of transformations that can be used to form asymmetric chiral centers and can be utilized in large-scale industrial settings. One of the approaches to solving this problem is by designing a generic chiral nucleophile that can react with a wide variety of electrophiles for asymmetric synthesis. The first approach for achieving this goal was the use of organocatalysts based on two known activation mechanisms: enamine activation catalysis and bifunctional activation catalysis.

Figure 2: Examples of Asymmetric Quaternary Carbon Containing Compounds.



1.3 Organocatalysis

1.3.1 Organocatalysis introduction

The use of organocatalysis for asymmetric synthesis has grown and developed rapidly in recent years and has become one of the methods of choice along with biocatalysis and metal catalysis^{4,5}. There are four main attractions to organocatalysis that have made it a thriving area of research since 2000⁶:

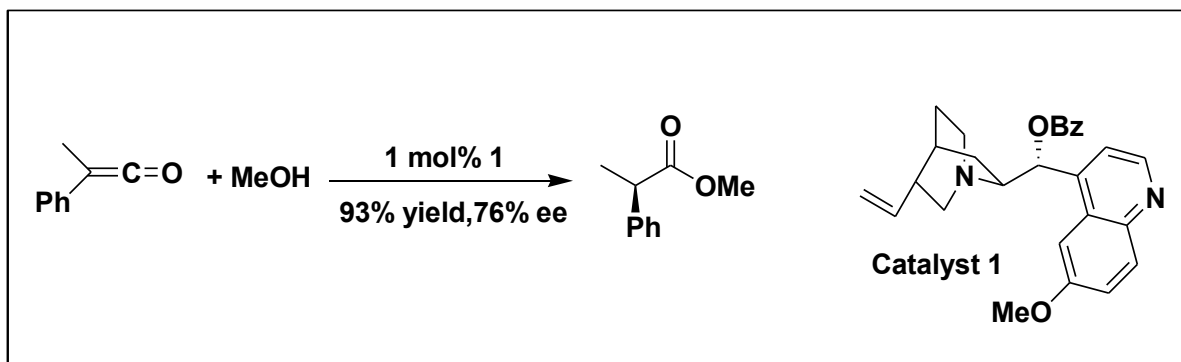
1. The simplicity of the catalyst and its modes of activation allow for predicting the reaction mechanism and its outcome. Therefore, it allows for the development of new transformations that previously were unknown or difficult to predict and control.

2. Organocatalytic processes are able to catalyze asymmetric transformations with chemo-, regio-, diastereo- or enantioselective control with ease and simplicity in the same manner that metal catalysts are able to perform but with greater advantage in that organocatalysts can often generate either form, R or S, just by switching chirality of the organocatalysts from one form to another. With both forms typically being readily available on the market.
3. Organocatalysts are often stable in the presence of water or oxygen and as such they do not require any special reaction conditions. Organocatalytic transformations are also generally easy to perform and are more environmentally friendly than their metal-catalyzed counterpart.
4. The majority of organocatalysts are natural compounds, such as proline and cinchonidine, and as such they are readily available in one enantiomeric form and are relatively inexpensive, commercially available for small and large-scale transformations as well as being easy and safe to handle.

1.3.2 Organocatalysis historical background

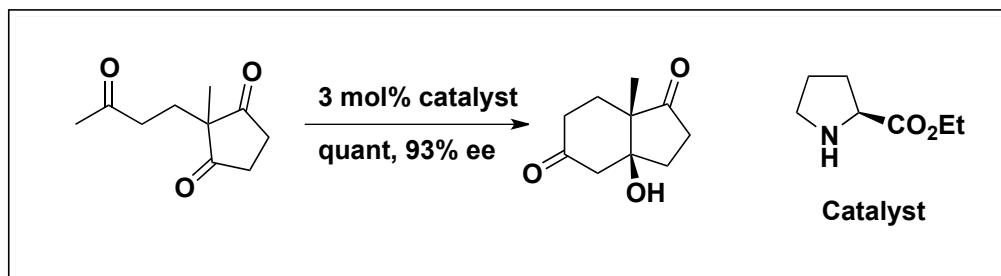
The first organocatalytic reaction was reported in 1912 by Bredig and Fiske⁶. These studies showed that cinchona alkaloids were successful in catalyzing the addition of hydrogen cyanide to benzaldehyde with low enantiomeric excess (<10% ee). 50 years later, Pracejus used *O*-benzoylquinine as an organocatalysts for enantioselective methanolysis of phenylmethylketene with up to 76% ee⁶ (Eq. 1).

Equation 1: Ketene methanolysis (Pracejus): 1960.



In 1971, Hajos and Wiechert reported the proline catalyzed intramolecular aldol condensation of prochiral triketones (*Hajos-Parrish reaction*) (Equation 2). It was the first example of asymmetric enamine catalysis and provided an enantioenriched bicyclic intermediate (>93% ee) useful in steroid and other natural product synthesis⁶.

Equation 2: Intramolecular aldol reaction (Hajosh, Wiechert):1971.



The enormous potential of this reaction was not realized for another 25 years, until Barbas et al. reported the first intermolecular aldol reaction with enamine

catalysis. This work brought about the curiosity of the scientific community for enamine catalysis, creating an explosion in growth of organocatalysis research.

1.3.3 Organocatalytic modes of activation

Organocatalytic reactions can be classified according to their covalent and non-covalent nature of the substrate-catalyst interaction or according to the catalyst type: Lewis acid/base, Brønsted acid/base as well as many “bifunctional catalysts”⁷ which can act as both.

Covalent catalysis includes: Enamine-, Iminium-, SOMO- catalysis, carbene- and Lewis base-activation catalysis.

Non-covalent catalysis includes: Hydrogen bonding-, Brønsted acid, Brønsted base- and bifunctional-activation catalysis as well as phase transfer catalysis.

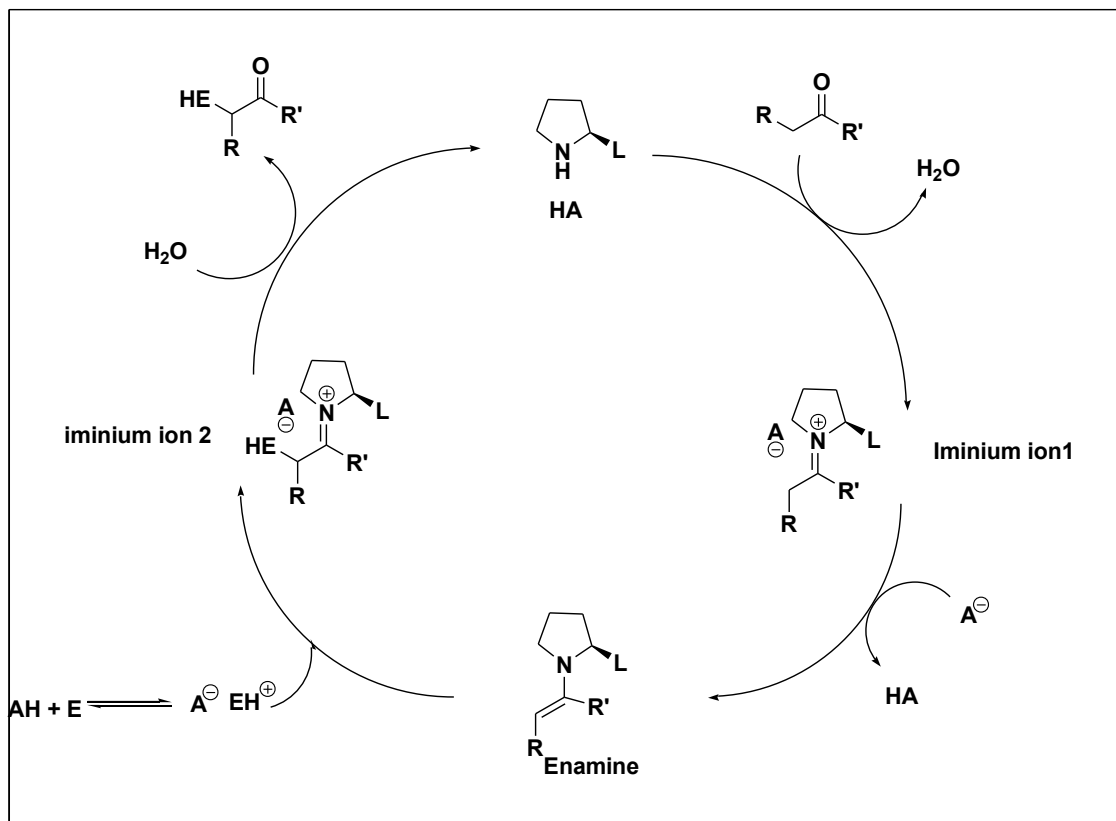
1.3.3.1 Covalent Catalysis

1.3.3.1.1 Enamine activation catalysis

Since the first report of proline-catalyzed intermolecular aldol and Mannich reactions, enamine catalysis has become one of the most wide spread modes of activation in organocatalysis. Working with a wide variety of electrophiles for the α -functionalization of enolizable aldehydes and ketones with very good enantioselectivity⁸.

Proposed mechanism for the pyrrolidine-catalyzed α -functionalization of carbonyl compounds are shown in scheme 2. The initial activation step involves acid promoted condensation to form an iminium ion (iminium ion 1). Removal of the basic counter ion creates the key intermediate, a nucleophilic enamine that can react with a wide variety of electrophiles. Reaction with the electrophile generates the second iminium species (iminium 2), followed with hydrolysis yields the desired product with regenerated acid and catalyst that can initiate another cycle.

There are two possible pathways that can incur enantioselectivity. The first possibility is if the chiral amine substituent contains a hydrogen-bond directing group (a carboxylic acid, amide, thioamide or a protonated amine). The attack of the electrophile will take place according to the List- Houk model (fig 3A), that is the attack occurs via intramolecular way via a cyclic transition state Figure 4 shows examples of chiral amines with hydrogen-bond directing groups. In the case that the amine substitute is bulky without the acidic proton (figure 5) the electrophilic attack is controlled

Scheme 2: General enamine activation mechanism

by steric effect with the opposite stereo selectivity (fig 3B). An alternative mechanism for the first example was proposed by Seebach et. all, stating that the electrophilic attack occurs by anchimeric assistance of the deprotonated amine substituent X (fig 3C)⁹. Examples of representative reactions of this mode of activation are: Intramolecular and Intermolecular aldol reactions, the Mannich reaction and dihydroxylation reactions (Scheme3).

Scheme 3: Examples of enamine catalysis reactions.

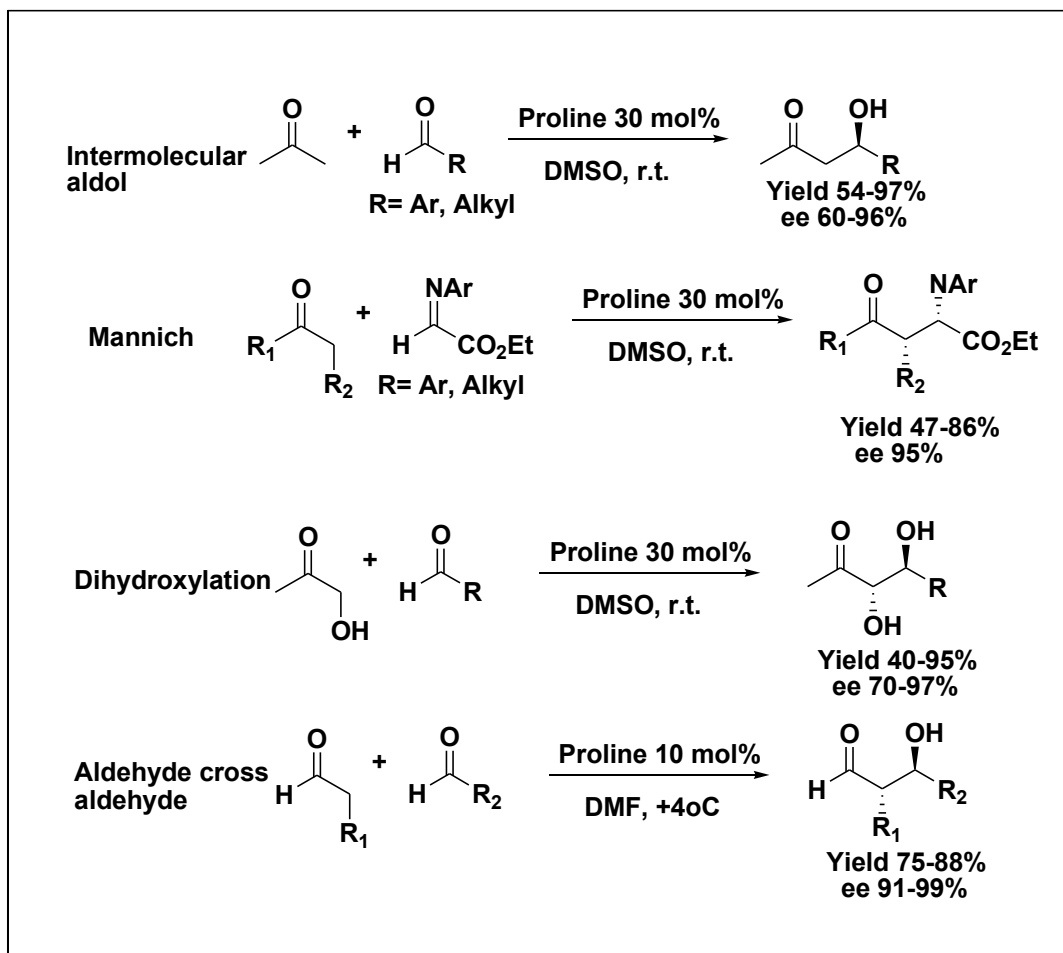


Figure 3: Stereochemical models for enamine reactivity.

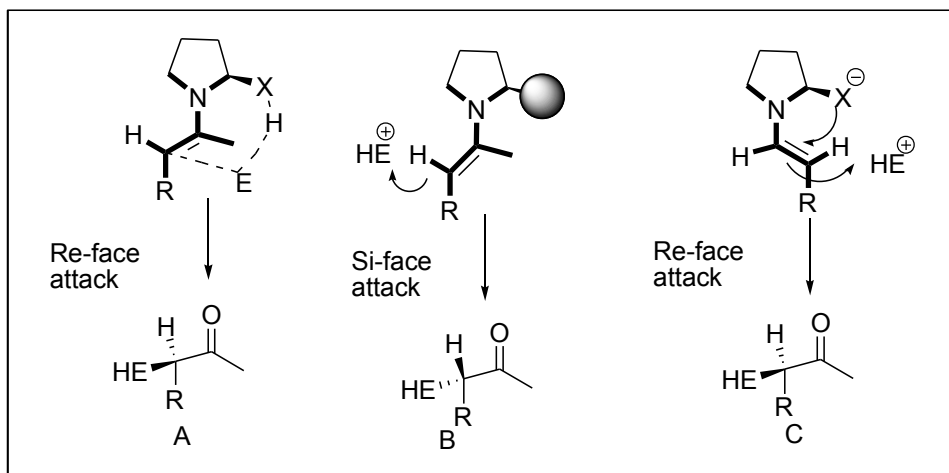


Figure 4: Examples of chiral secondary amines with hydrogen bond directing groups.

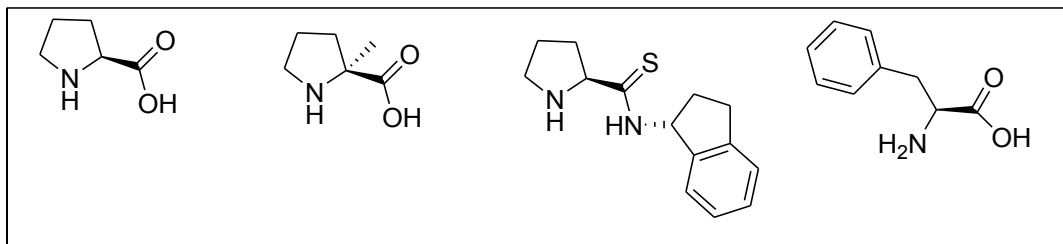
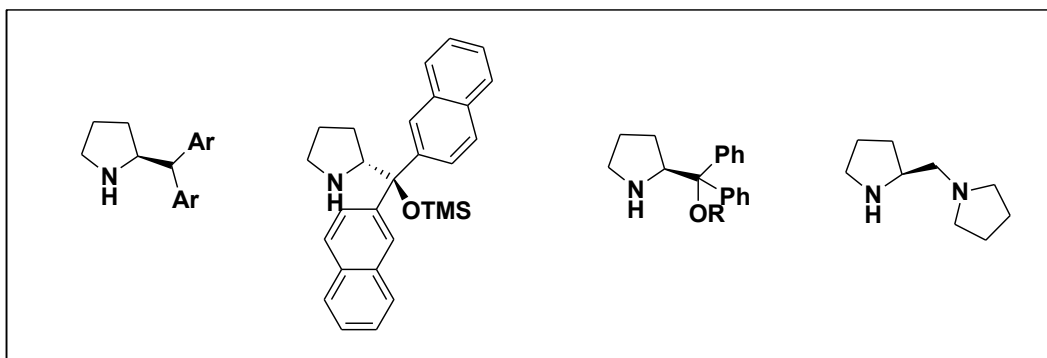


Figure 5: Examples of chiral secondary amines with bulky nonacidic groups.

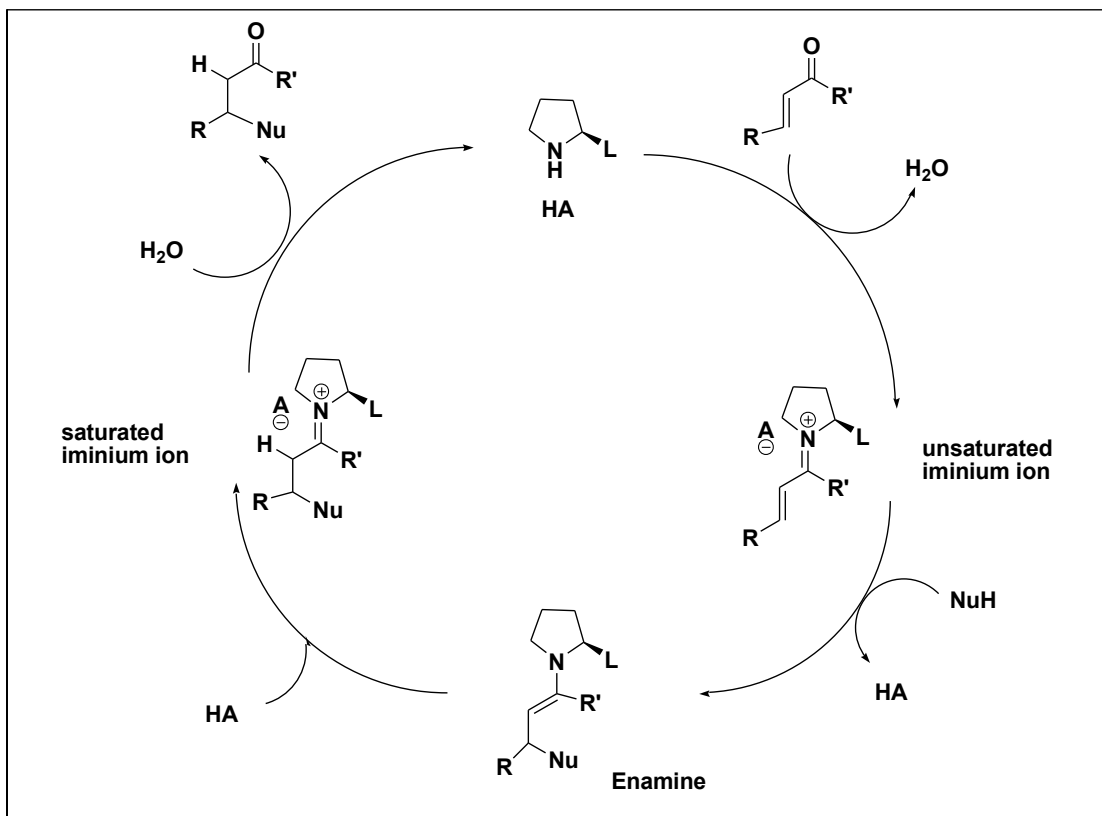


1.3.3.1.2 Iminium activation catalysis

Iminium activation catalysis is a general approach for the asymmetric conjugate addition of nucleophiles to α , β -unsaturated carbonyl compounds⁷. The catalytic cycle is shown in scheme 4. The cycle starts with the acid promoted condensation of the carbonyl with the amine to form an unsaturated iminium ion, followed by the addition of the nucleophile at the β -position and the formation of the β -functionalized enamine, which with protonation forms a saturated iminium

ion. The saturated iminium ion is then hydrolyzed yielding the desired product and regenerating the acid and catalyst.

Scheme 4: General mechanism for iminium activation.

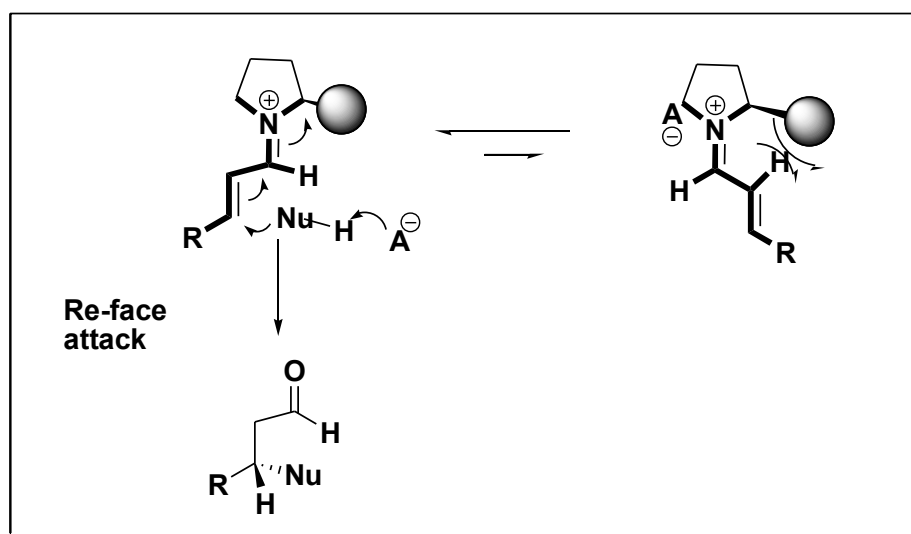


The catalysts that work best for this type of activation are amine substituted with bulky nonacidic groups. Examples of the most common catalysts are shown in figure 5, the most famous of them being MacMillans imidazolidinones. The stereochemical outcome of the reaction can be predicted according to the transition state shown in figure 6, which shows that the attack

occurs away from the bulky substitute, and therefore favors the s-trans conformer of the (E)-configured unsaturated iminium ion.

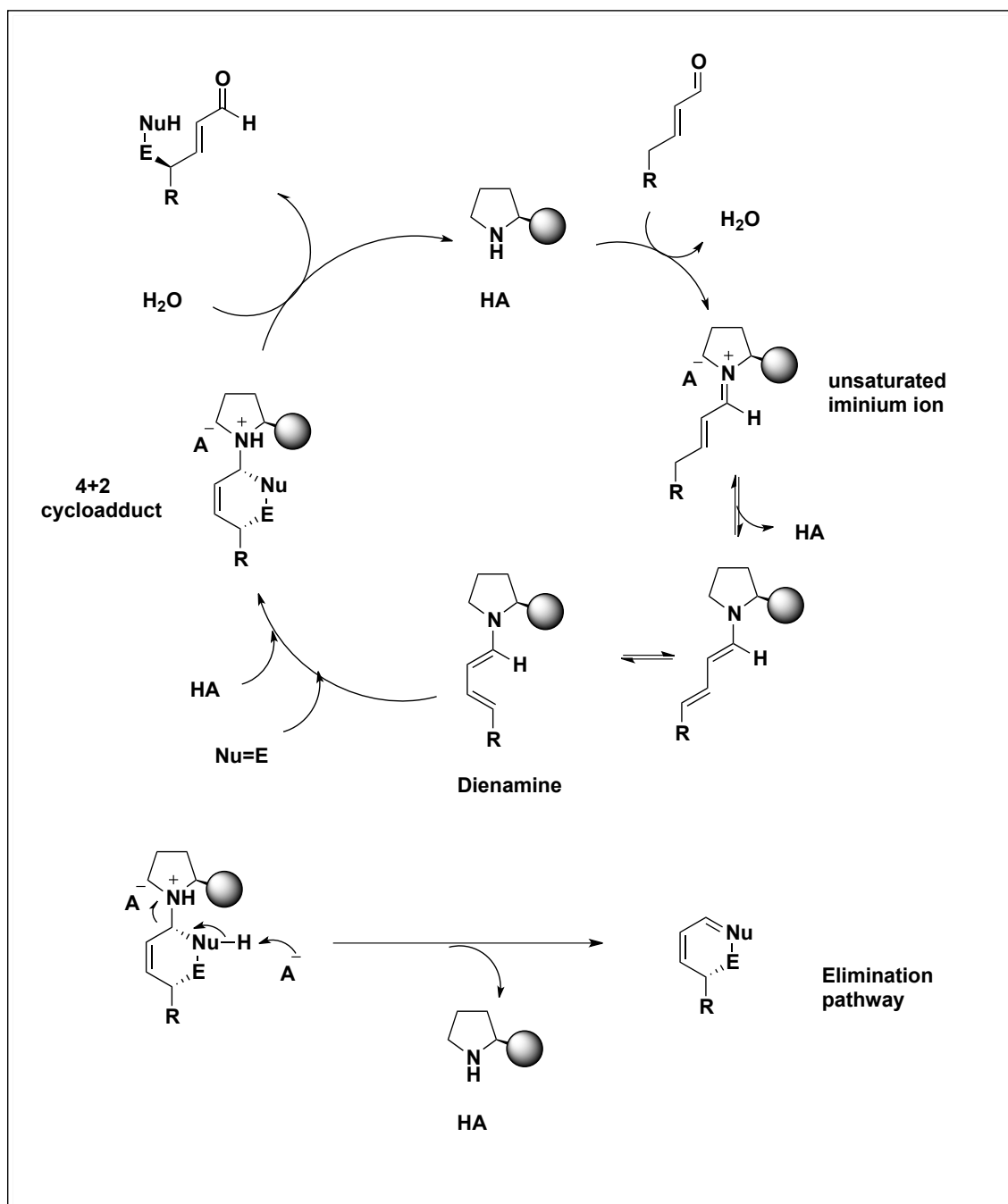
Examples of iminium type of activation reactions are: asymmetric organocatalytic Diels-Alder cycloaddition and intramolecular Michael additions to unsaturated carbonyl compounds.

Figure 6: Stereochemical outcome of the amine catalyzed Michael addition to enals.



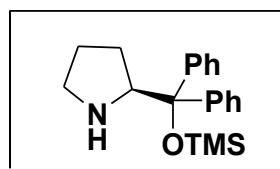
1.3.3.1.3 Dienamine activation catalysis

The first dienamine activation catalysis was shown in 2006¹⁰. Examples of this activation are the intramolecular Rauhut-Currier reaction and [4+2]-cycloaddition. The reaction mechanism is almost the same as with iminium

Scheme 5: Generalized mechanism of dienamine activation.

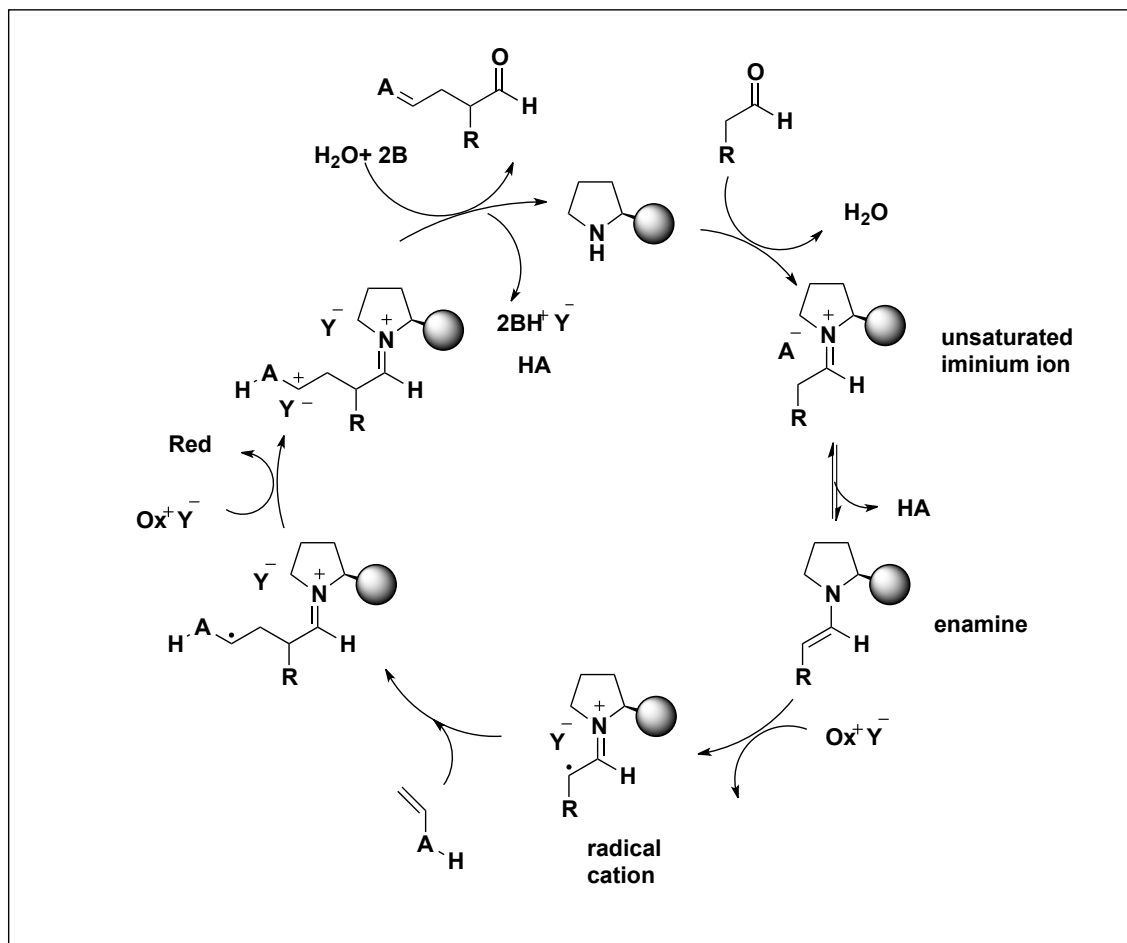
activation, with the exception that the acidic γ -hydrogen leads to the formation of the electron rich intermediate dienamine whose s-cis conformer undergoes a stereoselective [4+2] cycloaddition (Scheme 5). The best catalyst for this type of reaction is a prolinol derivative shown in figure 7.

Figure 7: Example of dienamine activation catalyst.



1.3.3.1.4 SOMO activation catalyst

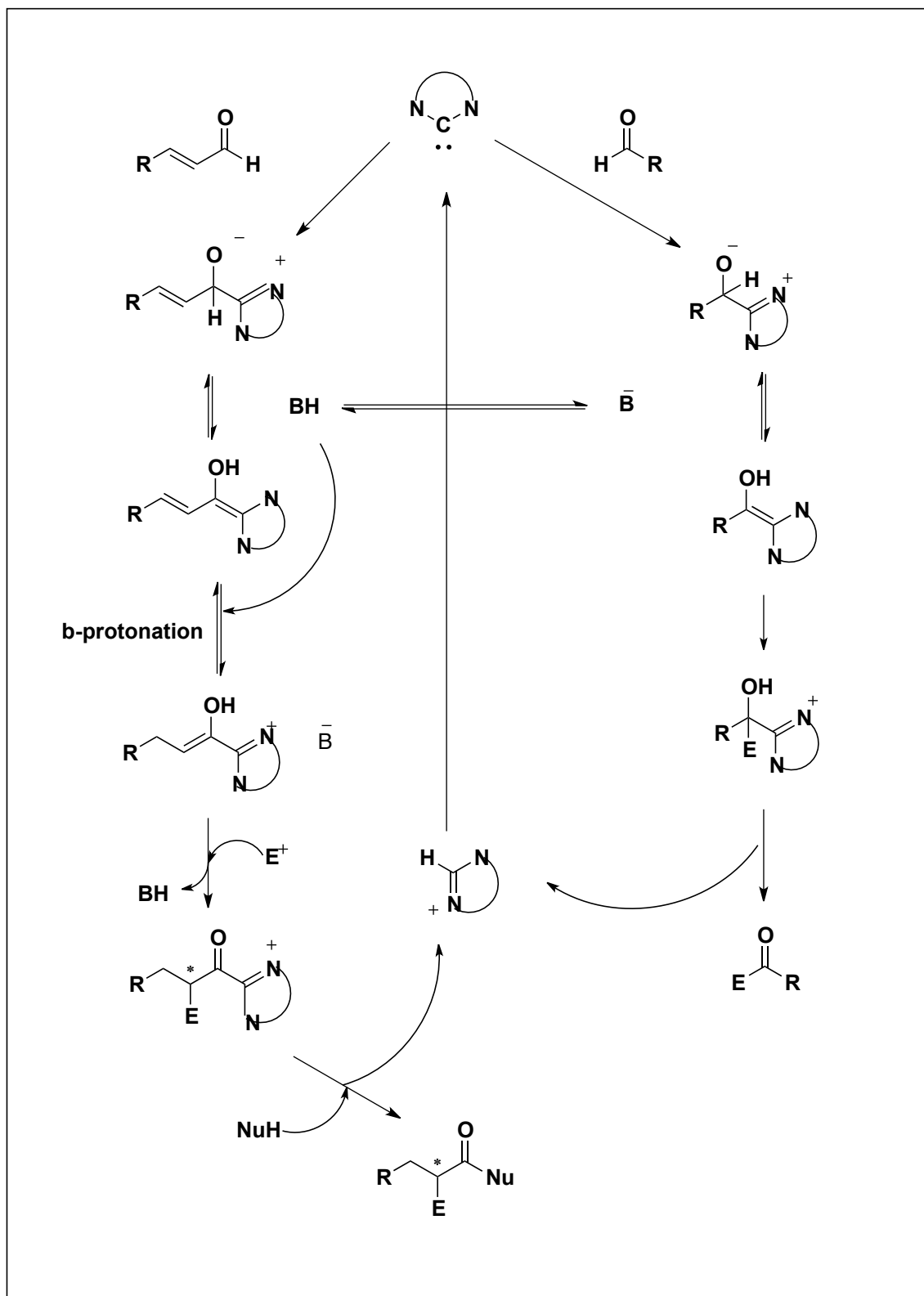
SOMO activation catalysis was first discovered by MacMillan and co-workers in 2007¹¹. It showed another method for asymmetric α -functionalization of carbonyl functional groups. The condensation between the catalyst and the carbonyl leads to an iminium ion which converts into an enamine followed by the formation of radical cation intermediate. At this point it reacts with a radicophile for the formation of new cation radical intermediate. Oxidation of the intermediate followed by hydrolysis yields the desired product and the catalyst. This reaction relies on the presence of imidazolidinone with a photoredox catalyst (Scheme 6).

Scheme 6: Mechanism of Asymmetric Organo-SOMO Activation Catalysis.

1.3.3.1.5 Carbene activation catalysis

Chiral *N*-heterocyclic carbenes (NHC's) are a unique class of Lewis Base catalysts that are used in the discovery of new asymmetric organocatalytic reactions¹². Two reactions that follow this mechanism are the ipsofunctionalization of saturated carbonyls and the enantioselective α -functionalization of unsaturated carbonyls (Scheme 7).

Scheme 7: Mechanism of carbene activation.



1.3.3.2 Noncovalent catalysis

1.3.3.2.1 Hydrogen bonding and Brønsted acid activation catalysis

Chiral small organic molecule that contains an acidic hydrogen can react with a wide variety of basic substrates and have been very useful in organic synthesis¹³. The type of interactions depends on the transition state and whether the hydrogen is bound to the catalyst or if proton transfer is a possible, giving rise to several different pathways¹⁴. The most used catalysts of this type of reaction are chiral-thioureas, -amidinium ions, -squaramides and -diols (figure 8). An example of Brønsted acid catalysis is chiral BINOL- derived phosphoric acids (figure 9).

Figure 8: Example of chiral hydrogen-bond-donor catalysts.

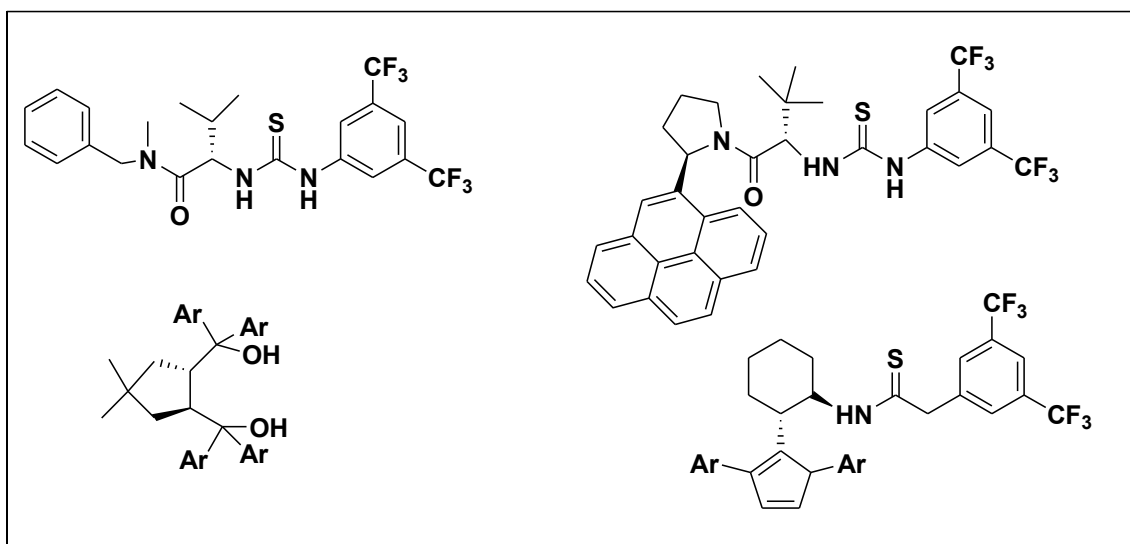


Figure 10 shows several modes of activation of organic compounds containing acidic hydrogen. Figure 10a shows Brønsted acid type of activation where the catalyst transfers a proton to a basic center of the substrate. Figure 10b and 10c show hydrogen-bonding type of catalysis by enhancement of electrophilicity of the substrate with hydrogen bonding. Figure 10d-e show hydrogen-bond donor activation catalysis by anion-binding where the chiral catalyst enhances the acidity of achiral Brønsted acid or makes the substrate more favorable toward nucleophilic attack.

Figure 9: Example of chiral BINOL-derived catalysts.

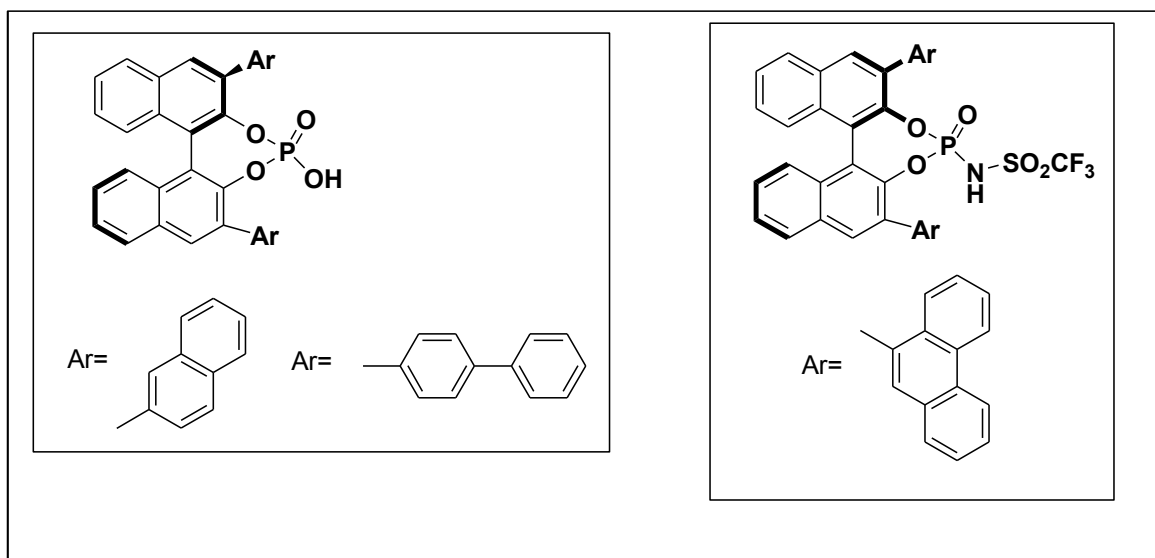
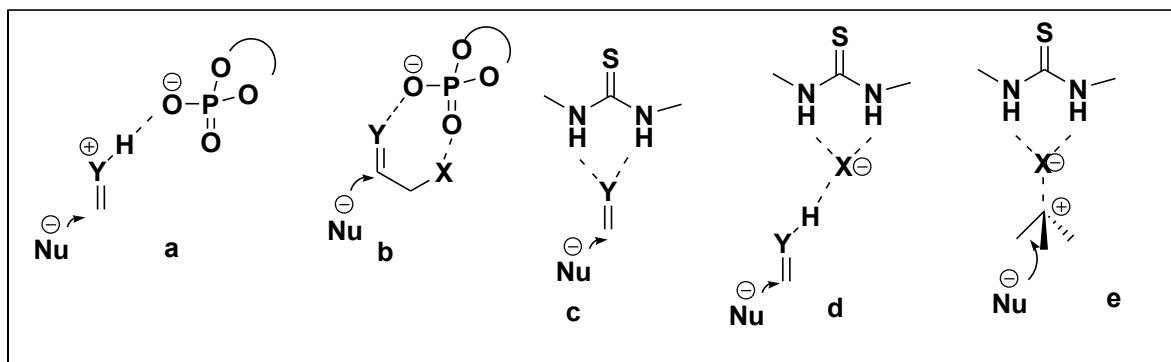


Figure 10: Brønsted acid type of activation.



1.3.3.2 Brønsted base and bifunctional activation catalysis

Cinchona alkaloid is the main example of Brønsted base catalysis. As a Brønsted base catalyst, this type of reaction lacks the high enantioselectivity as other organic catalysts due to the loose nature of catalyst substrate interactions, but the promising area of this type of catalysis is its bifunctional capabilities. The utility of catalysts that activate both the acidic and basic moiety of the substrate with the hydrogen bond donor of the catalyst and Brønsted base group on the catalyst¹⁵ (figure 11) is creating a tight ion pair, this has large potential and currently has shown to be very useful in intramolecular Michael additions. Examples of bifunctional catalyst are shown in figure 12.

Figure 11: Dual activation by bifunctional catalyst.

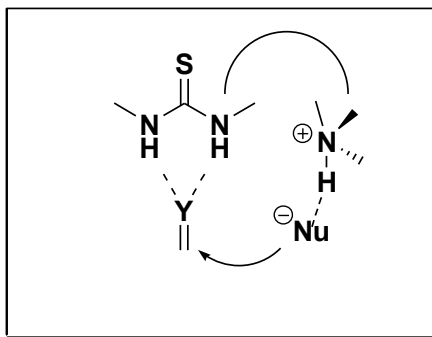
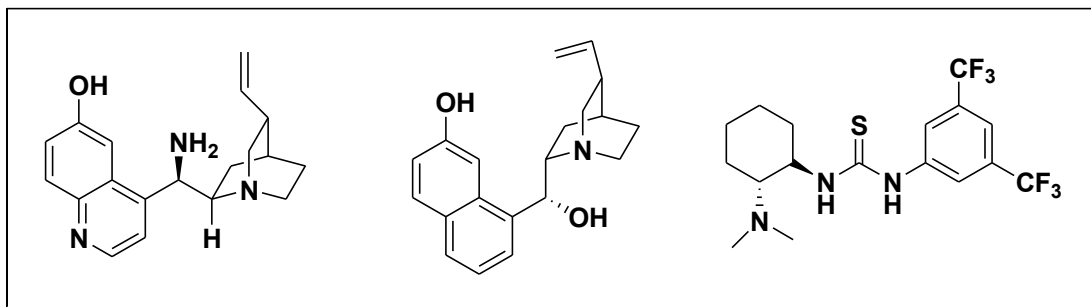


Figure 12: Examples of bifunctional catalysts.

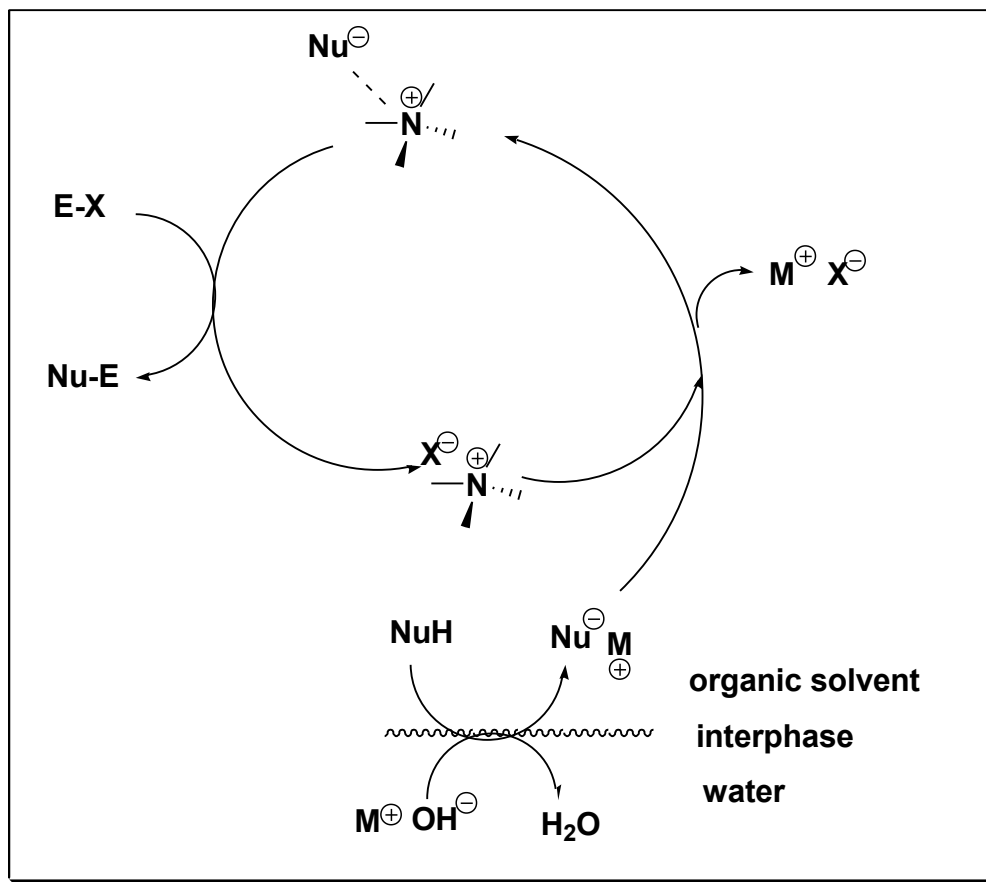


1.3.3.2.3 Phase transfer catalysis

Since 1984, with the implementation of quaternary *Cinchona* alkaloid salt for the chiral phase transfer catalyst, this field has seen major growth¹⁶. The asymmetric alkylation of glycine derived Schiff bases with organocatalytic phase transfer became one of the most reliable methods for the synthesis of α -amino acids.

The mechanism of phase transfer catalysis shown in figure 13 implies that the nucleophile anion is generated for pronucleophile at the interphase of the

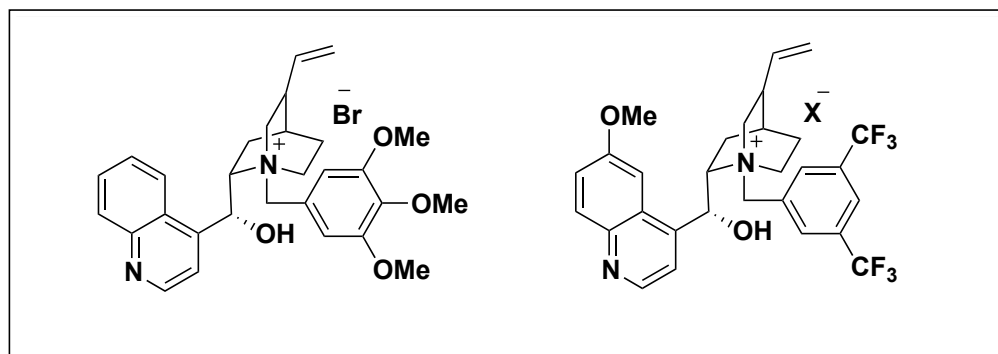
Figure 13: Mechanism of the phase transfer catalysis.



organic and aqueous phases by some alkaline hydroxide (most commonly KOH) and creates a tight ion pair with the quaternary ammonium salt (most common catalysts shown in figure 14). The ionic complex reacts with the electrophile followed by the release of the product and regeneration catalysts. The

asymmetric induction occurs at the chiral environment of the tight ion pair of the nucleophile and the quaternary ammonium salt.

Figure 14: Chiral phase-transfer organocatalysts.



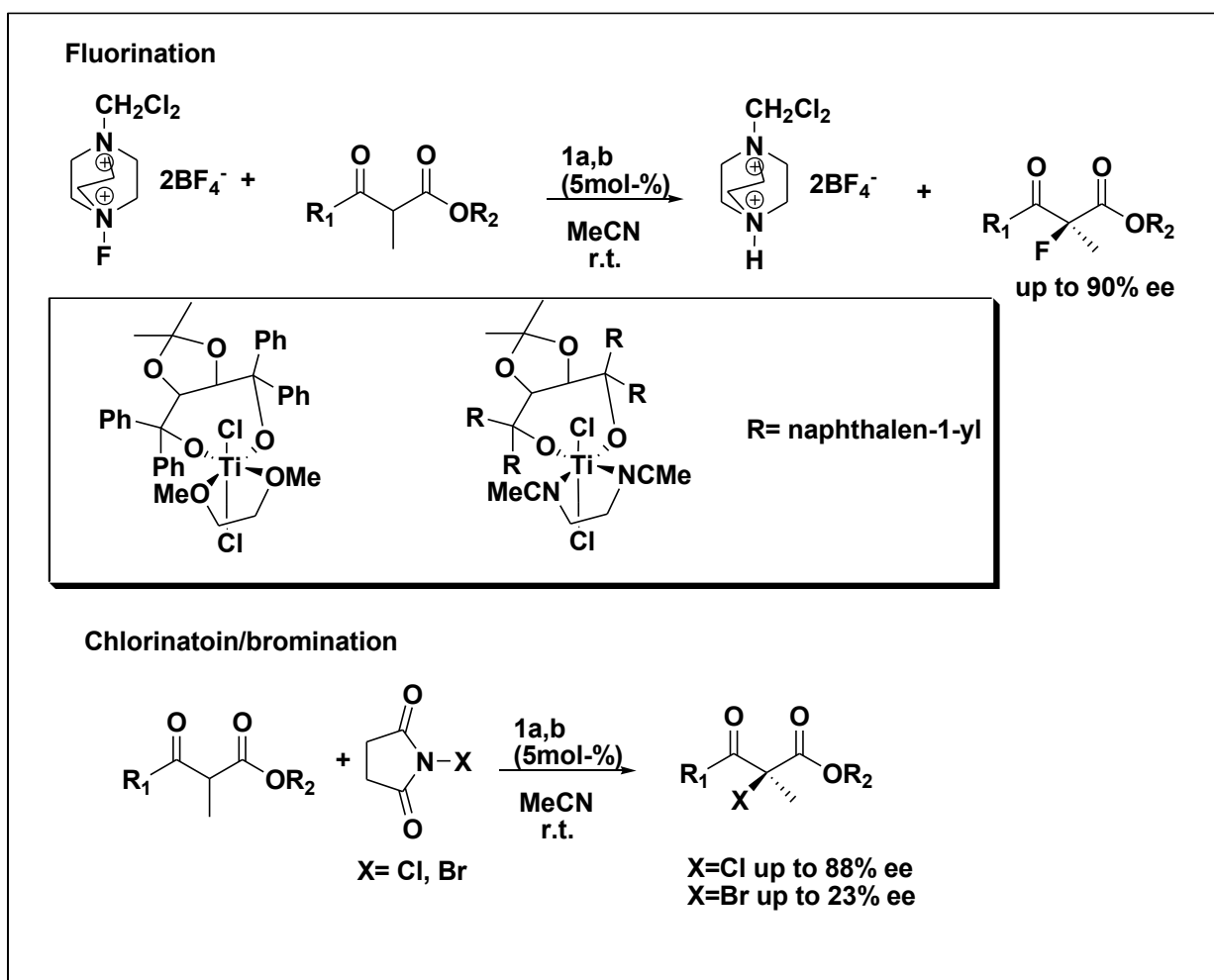
1.4 Asymmetric α -halogenation

1.4.1 Asymmetric α -halogenation introduction

Enantioselective α -halogenated compounds are highly useful molecules in organic chemistry¹⁷. In the current era, there are many heteroatom bond-forming reactions, but in comparison to those transformations, asymmetric α -halogenation represent a small percentage of the total heteroatom transformations¹⁸. Out of all enantioselective halogenated transformations, enantioselective α -fluorinations represent the major part, because of medicinal importance of fluorinated compounds¹⁹. Other asymmetric halogenated compounds represent an even smaller percentage of all heteroatom transformations, even though they are versatile molecules that can be used as

chiral intermediates in the total synthesis of a wide variety of compounds. The first catalytic enantioselective α -halogenation of carbonyl compounds by chiral Lewis acid

Equation 3: First enantioselective α -halogenation reaction.



(Equation 3) was reported in 2000 and since that time many other α -halogenated transformations were reported.

1.4.2 α -Fluorination reactions

Fluorine is the most electronegative element in the periodic table and due to this fact fluorinating a compound is alters the chemical properties of the organic molecules which they are a part of. E.g. the dipole moment and hydrogen bonding capability. Fluoroorganic drugs are of high interest in medicinal chemistry because of the C-F bond is stronger than C-H and therefore fluorinated drugs resist oxidative degradation in biological systems compared to their analogs. Due to these facts, asymmetric synthesis of fluorinated molecules has increased the curiosity of synthetic chemists.

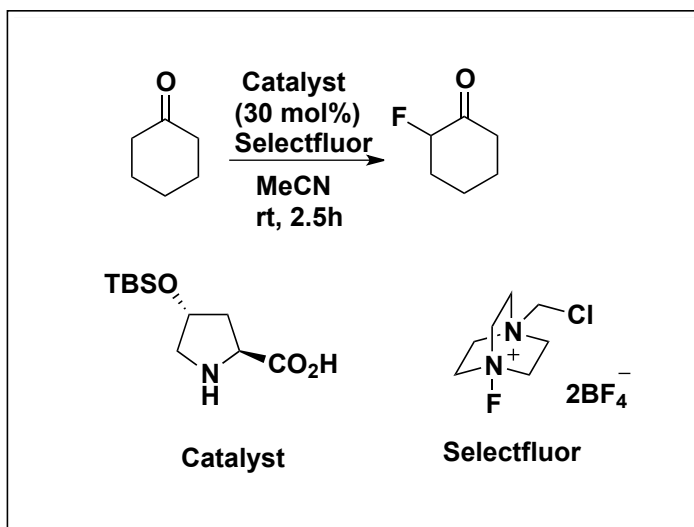
Asymmetric fluorination by chiral amines

In 2005, α -fluorination of aldehydes and ketones was reported by Enders and Hüttl with Selectfluor as the fluorinating agent²⁰ and L-proline derivatives (30 mol%) as the catalyst (scheme 8). The reaction was proposed to proceed via enamine activation mechanism and had 43% conversion with 34% ee.

Following Enders' and Hüttl's report, Barbas, MacMillan, and Jørgensen reported α -fluorination of aldehydes with high ee²¹ (Scheme 9). All of the reactions proceeded via enamine activation. All three of the groups used NFSI as the fluorinating agent. Fluorinated aldehydes are not stable under column purification conditions, therefore all of the products were reduced to alcohol using NaBH₄.

Barbas *et. al.* achieved α -fluorination of aldehydes with ee ranging from 88-96% with modest to high yields of 40-97%. The catalyst that was chosen for this reaction was chiral imidazolidinone with 100mol%. Selection of solvent was crucial for the reaction to prevent difluorination of the aldehyde. The best solvent for this reaction was DMF.

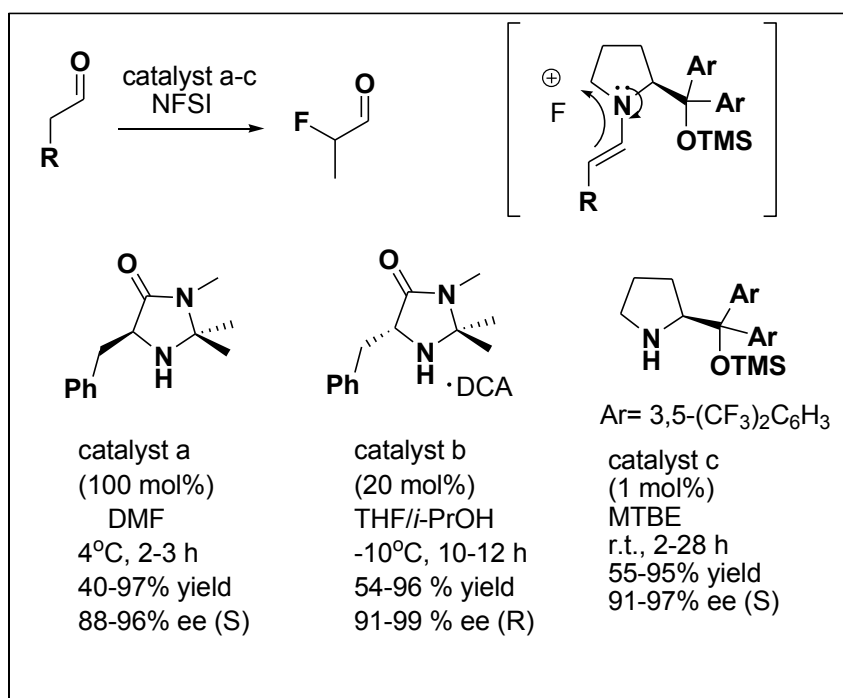
Scheme 8: α -fluorination of ketones by Enders and Hüttl.



MacMillan and Beeson reported that using chiral imidazolidinone as a chiral salt with dichloroacetic acid (DCA) allowed lower catalyst loading of 20 mol% in THF/*i*-PrOH (9/1). Addition of *i*-PrOH as a cosolvent allowed improved yields and higher ee's (54-96% yield, 91-97% ee). Under these conditions wide functional groups could be used such as olefins, esters, amines, carbamates and aryl rings.

Jørgensen *et. al* applied diarylprolinol silyl ether as a catalyst with 1 mol% of catalyst loading. Small amount of catalyst loading and the use of MTBE as solvent was critical for the reaction in order to prevent catalyst fluorination and difluorination of aldehydes. Under these conditions, 55-98% yield and 91-97% ee was achieved.

Scheme 9: α -fluorination of aldehydes.

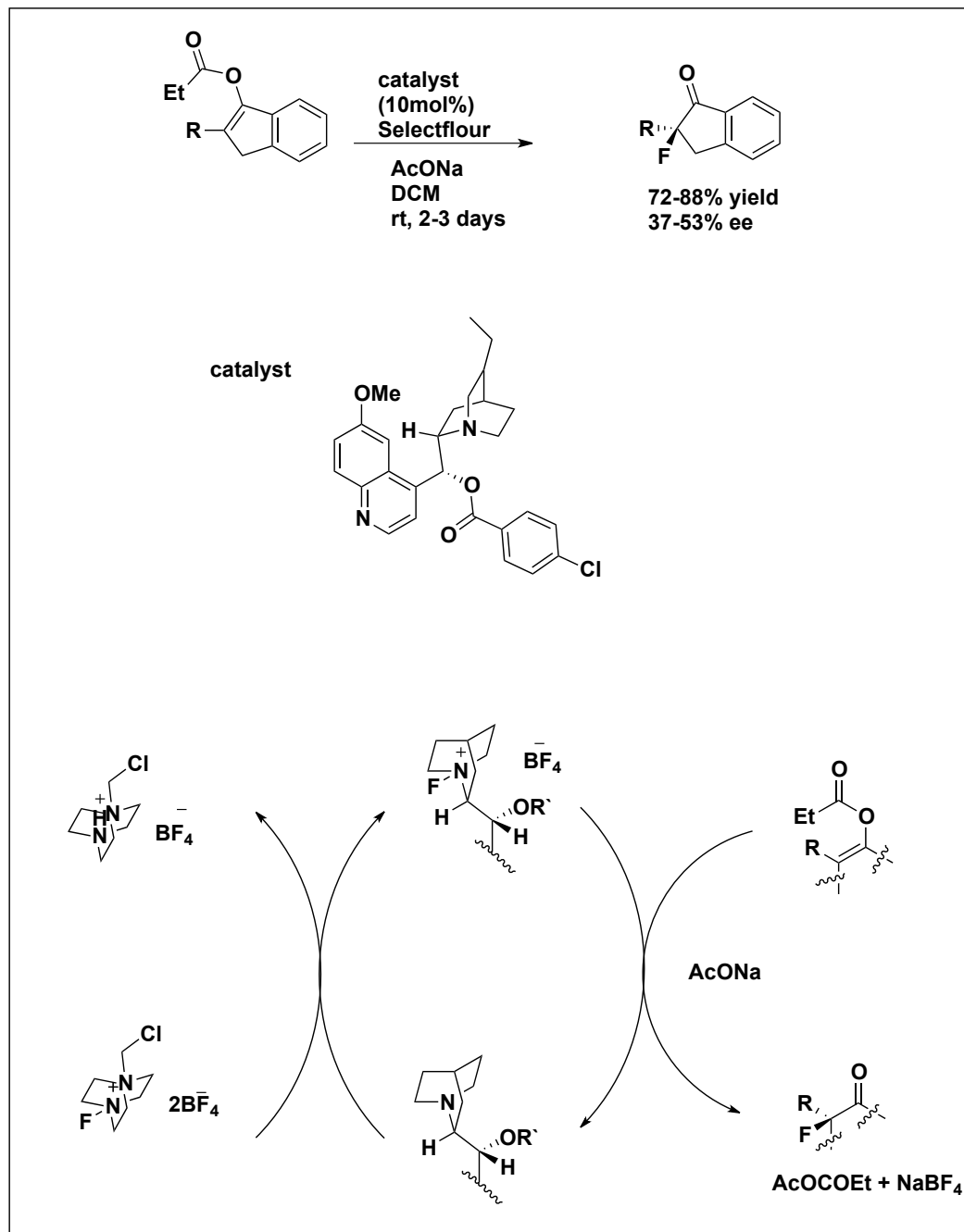


Asymmetric fluorination with tertiary amine

In 2005, Shibata and Toru used a *Cinchona* alkaloid derivative for the α -fluorination of acyl enol ethers of ketones (scheme 10). 10 mol% of catalyst

loading was chosen as optimal and Selectfluor as the fluorinating agent with sodium acetate. Sodium acetate helped to trap the actual fluorinating intermediate, fluorinated *Cinchona* alkaloid derivative, and traps the acetyl cation with BF_4^{-22} .

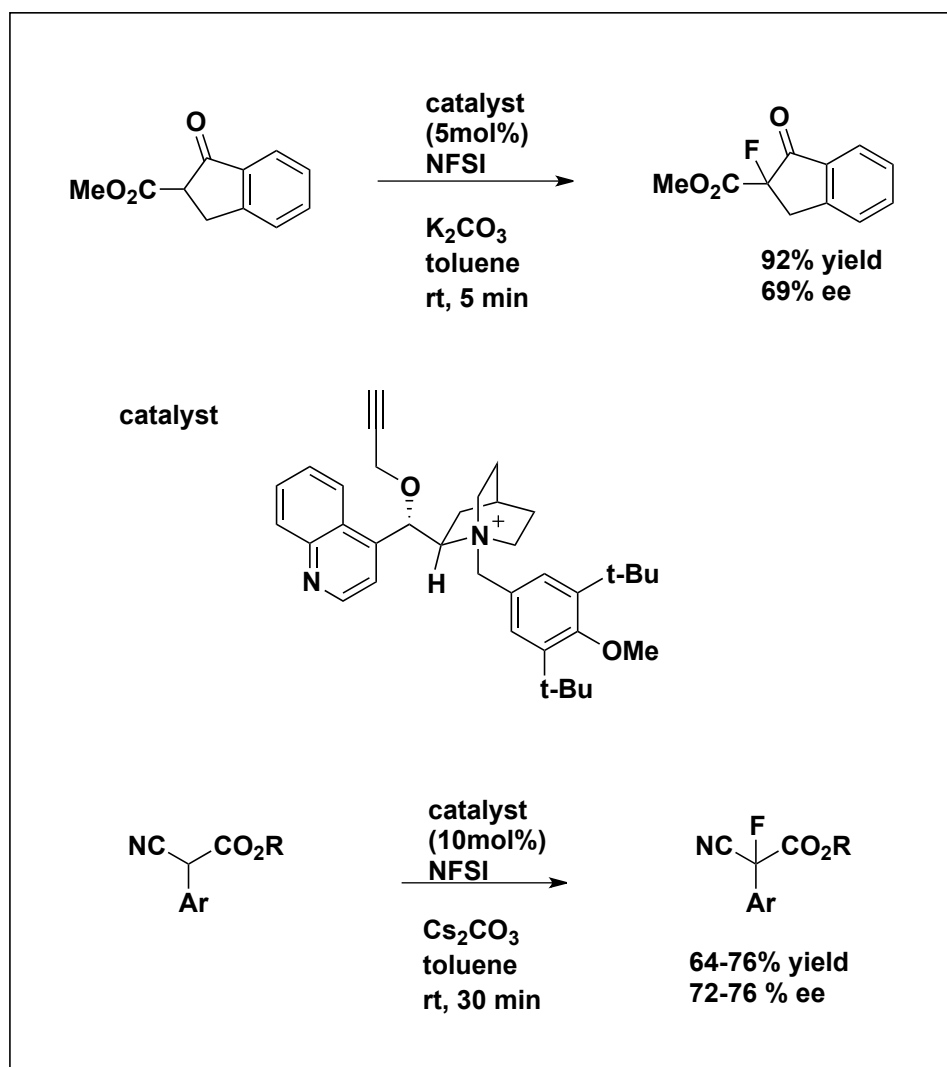
Scheme 10: α -Fluorination of acyl enol ethers.



Asymmetric fluorination by chiral PTC

In 2002, Kim and park showed successful α -fluorination of β -ketoesters (scheme 11) and α -cyano esters (scheme11) with high yields and moderate ee. For both of the reactions NFSI was chosen as the fluorinating agent and toluene as reaction solvent²³.

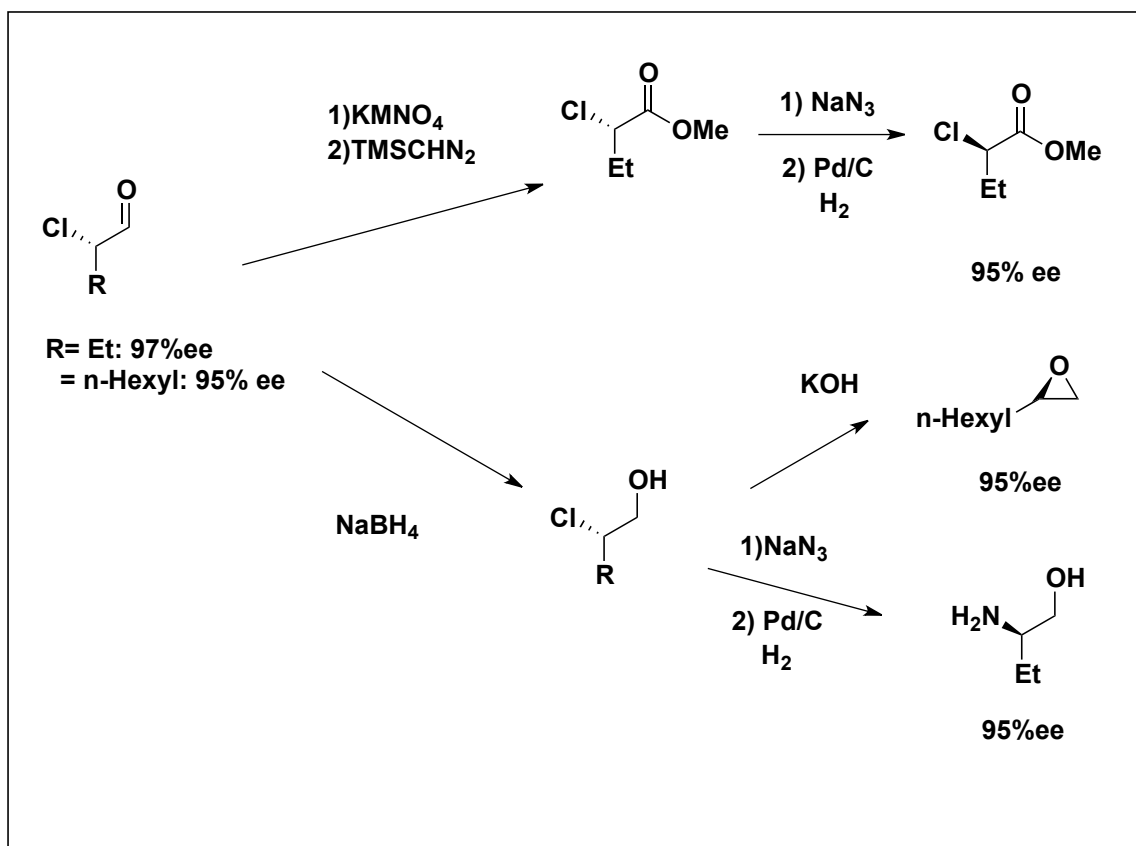
Scheme 11: α - Fluorination of β -ketoesters and α -cyanoesters.

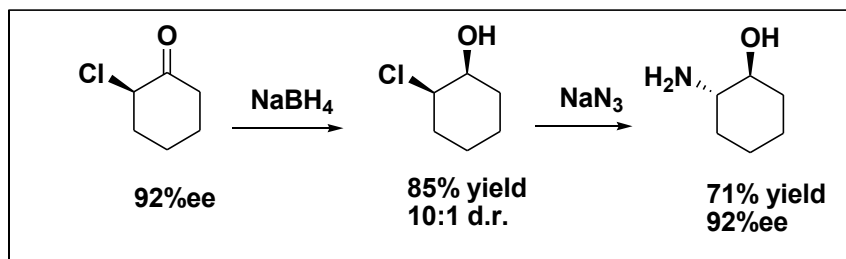


1.4.3 Asymmetric chlorination

Asymmetric chiral compounds are highly versatile intermediates and can be used as chiral intermediates in total synthesis of many molecules. Jørgensen *et. al* showed that chiral α -chloro aldehydes can be further transformed into amino acid derivatives, epoxides and amino alcohols without racemization (scheme 12)²⁴. Jørgensen *et. al* also showed that α -chlorinated ketones can be used to make chiral azide alcohols (scheme 13)²⁵.

Scheme 12: Application of α -chloro aldehydes.



Scheme 13: Application of α -chloro ketones.

Asymmetric chlorination with chiral amines

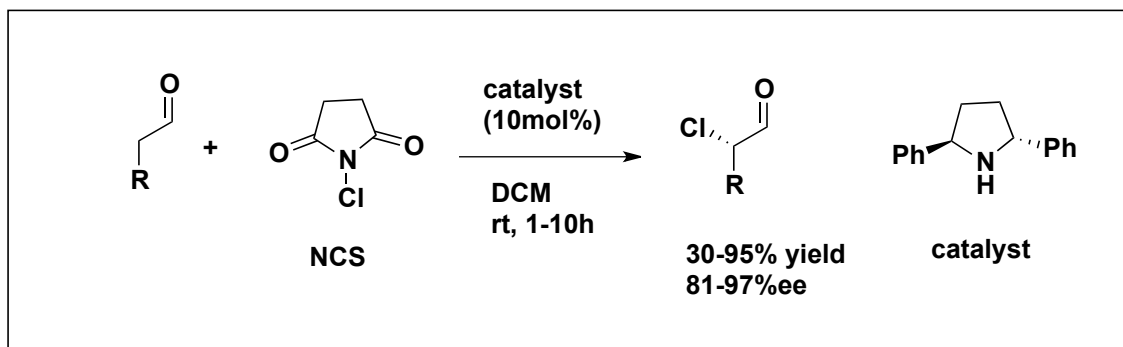
In 2004, both MacMillan and Jørgensen simultaneously reported asymmetric α -chlorination of unbranched aldehydes.

Jørgensen reported that the use of (2R,5R)-diphenylpyrrolidine (10 mol%) with NCS as the chlorinating agent can get α -chlorinated aldehydes with good yields and ee. This reaction is highly solvent dependent and the best solvent that was chosen was DCE to allow up to 97% ee (scheme 14). There were no dichlorinated byproducts like in the case of fluorination reaction and the chlorinated aldehydes were stable under column chromatography purification conditions.

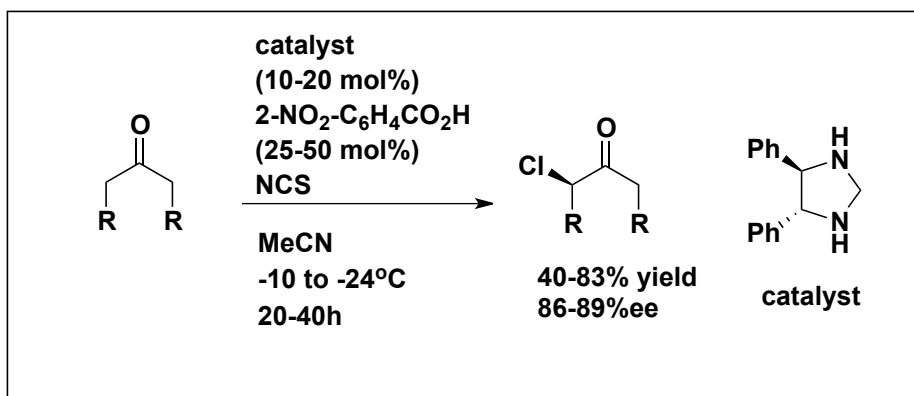
Jørgensen for the synthesis of α -chlorinated ketones applied imidazolidine as a catalyst (10-20 mol%) and NCS as the chlorinating agent. Use of acetonitrile as a solvent allowed monosubstituted product and the use of acid additive increase the reaction rate and enantioselectivity. The best acid additive that was

chosen was 2-nitrobenzoic acid. These reaction conditions allowed the formation of various monosubstituted ketones (scheme 15).

Scheme 14: Jørgensen α -chlorination of aldehydes.



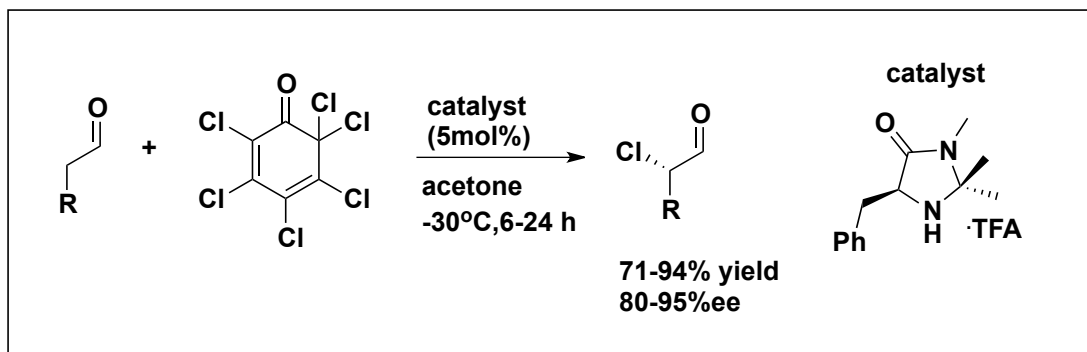
Scheme 15: Jørgensen α -chlorination of ketones.



MacMillan *et al.* reported that chiral imidazolidinone salt with trifluoroacetic acid (TFA) (5 mol%) with perchlorinated quinine as the chlorinating agent can produce α -chlorinated aldehydes. There was no special solvent effect on the

reaction with acetone giving the best result and minimizing the formation of dichlorinated product (scheme 16).

Scheme 16: MacMillan α -chlorination of aldehydes.

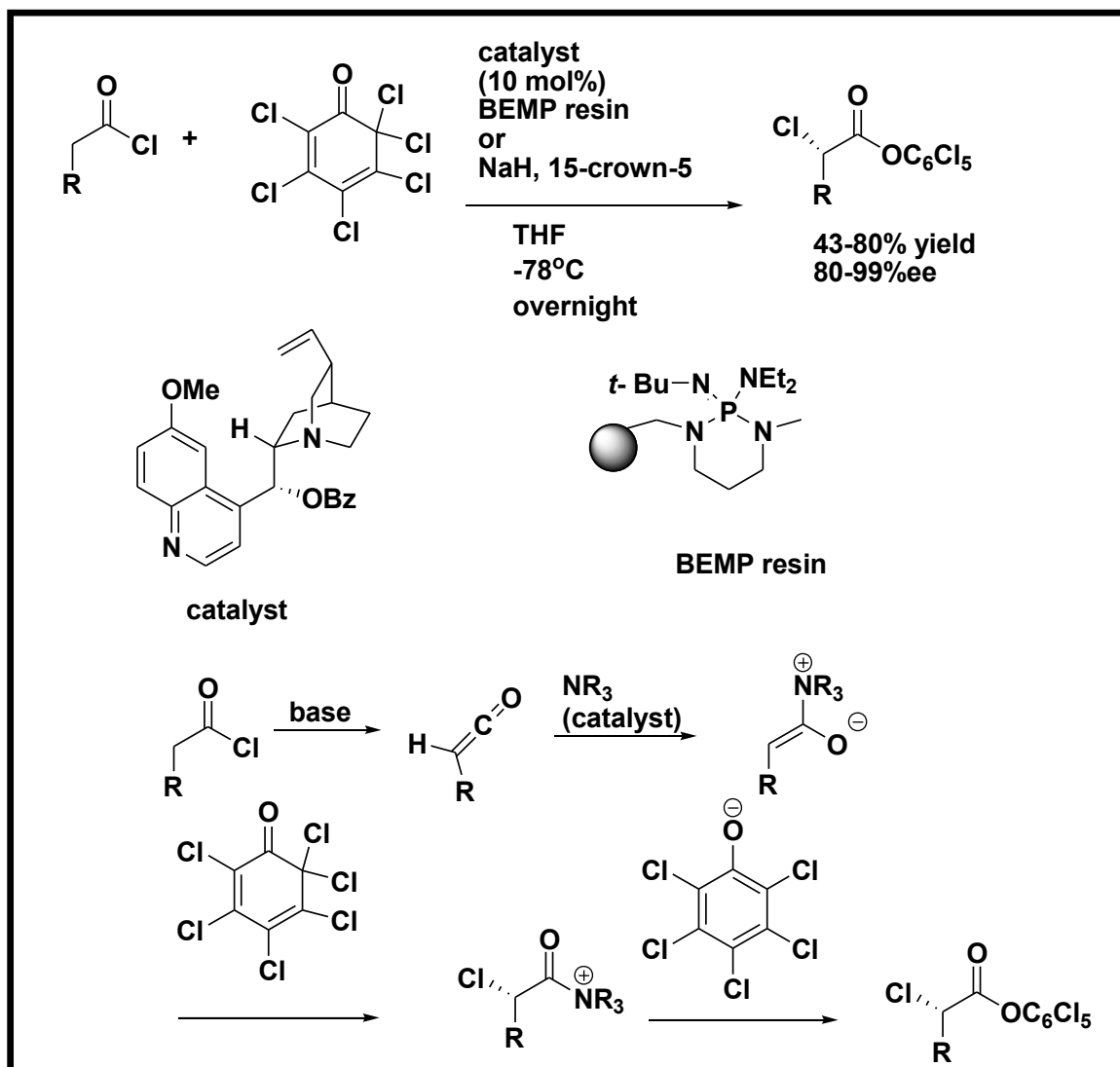


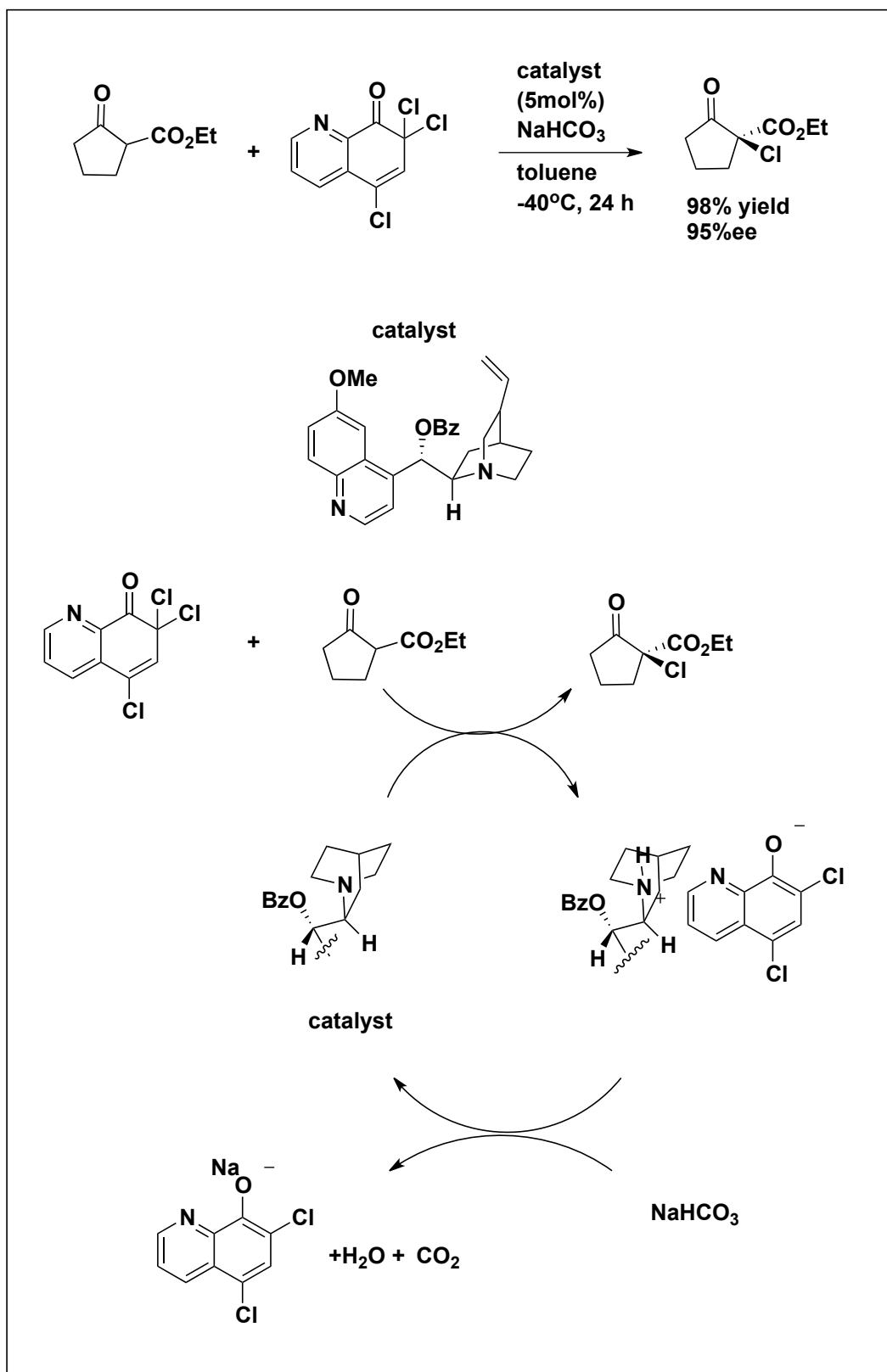
Asymmetric chlorination by chiral tertiary amines

The first enantioselective α -chlorination of carbonyl compounds was developed by Lectka *et. al.* in 2001. They used benzoylquinine (10 mol%) as catalyst and perchlorinated quinone as chlorinating agent to form α -chlorinated esters from acid chlorides. The reaction occurs by chlorination of a chiral ketone formed from the catalyst and base. The choice of base is important for enantioselectivity and the best base that was used was BEMP resin. Later the choice of base was changed to NaH, with 15-crown-5 as a phase transfer catalyst. The reaction proceeded smoothly with moderate to good yield of 43-80% with 80-99% ee (scheme 17)²⁶.

Four years later, Bartoli and Melchiorre *et. al.* used benzoylquinidine as a catalyst (5 mol%) for α -chlorination of 1,3-dicarbonyl compounds with a trichloroquinolinone as the chlorinating agent²⁷. Addition of NaHCO_3 is for catalyst turnover and acceleration of the reaction. Under these reaction conditions they achieved chlorination of β -keto ester to get α -chlorinated β -keto ester in 98% yield and 95% ee (scheme 18).

Scheme 17: Lectka asymmetric chlorination.



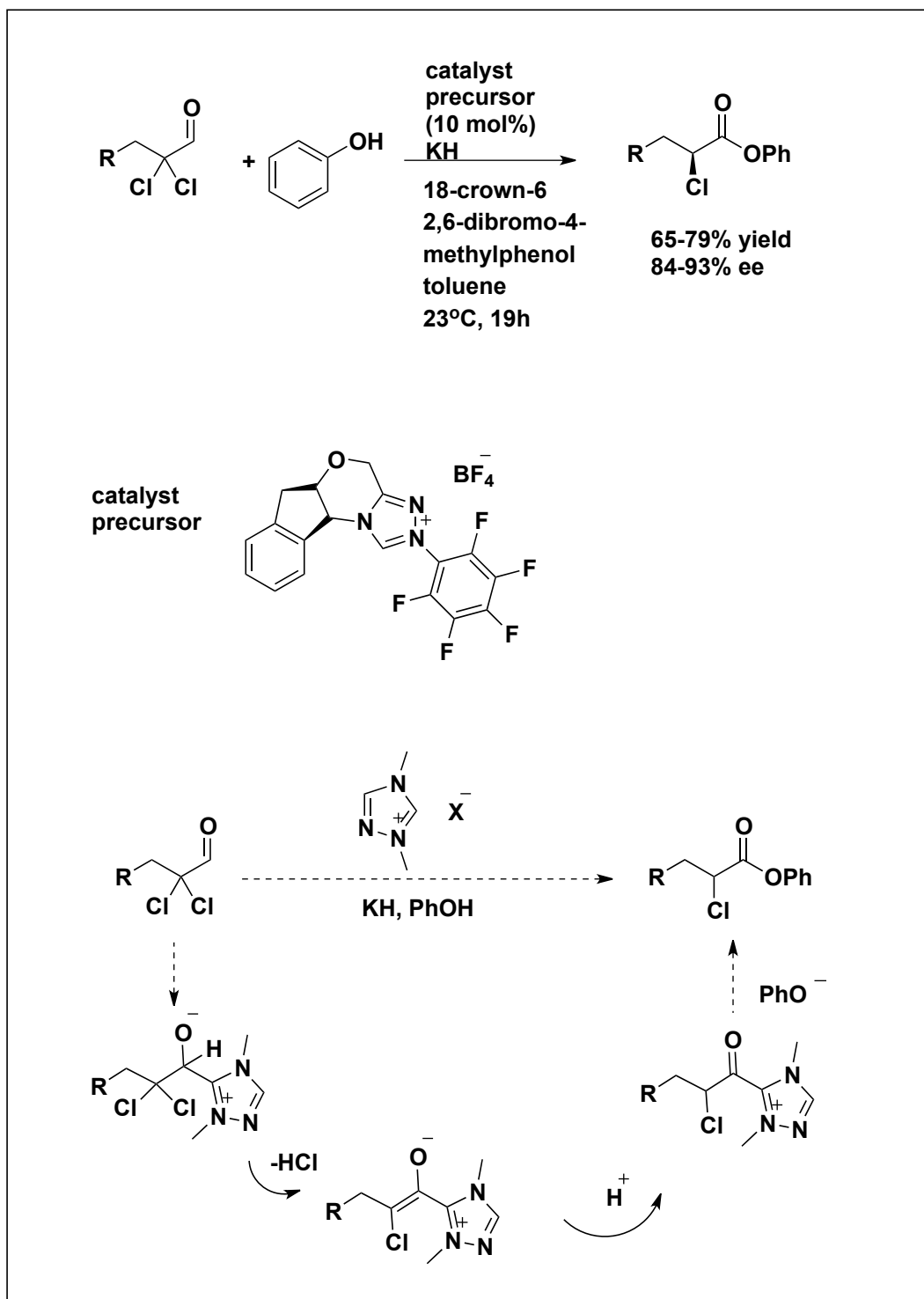
Scheme 18: Bartoli and Melchiorre work with reaction mechanism.

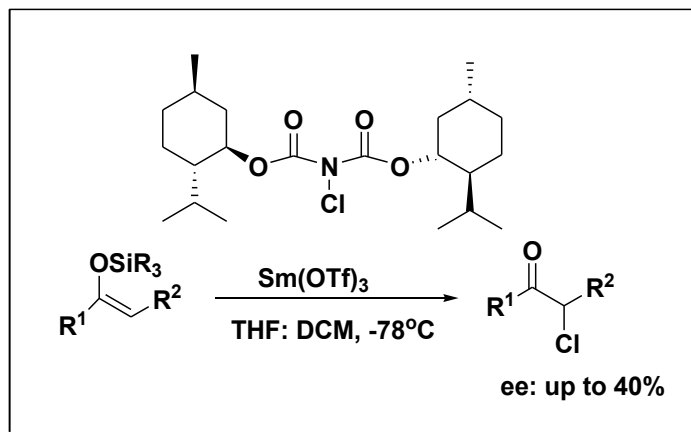
Asymmetric chlorination with chiral carbene catalyst

Rovis and Reynolds developed a method for the synthesis of α -chloroesters²⁸. They used azolium salt (10 mol%) and made in solution chiral triazolinylidene carbene as the active catalyst and 2,2-dichloroaldehydes with phenols to form α -chloro esters. The step that determines the enantioselectivity of the reaction is the protonation of the chiral enolate derived from α,α -dichloroaldehydes and carbene catalyst. Addition of buffer to the reaction mixture, 2,6-dibromo-4-methylphenol, increased the enantioselectivity of the reaction due to minimization of racemization reaction that was occurring. These reaction conditions allowed good yield of (65-79 %) and ee (84-93%ee) (scheme 19).

Asymmetric chlorination via chiral chlorinating agent

In 2007, Sinha *et. al.* reported chiral chlorination of silyl enol ethers via chiral *N*-Chloroimidodicarbonates that was designed by their group with Lewis acids such as $\text{Sm}(\text{OTf})_3$ ²⁹. This was one of the few chlorination reactions that used chiral electrophile (chlorinating agent). These reaction conditions gave up to 93% yield with up to 40% ee with high variety of functional groups (scheme 20).

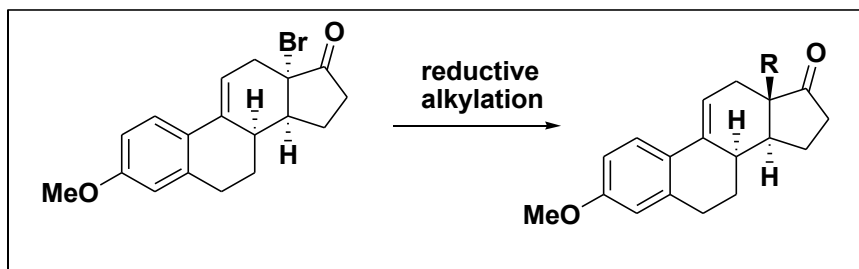
Scheme 19: Asymmetric chlorination with chiral carbene catalyst.

Scheme 20: Asymmetric chlorination by chiral *N*-Chloroimidodicarbonate.

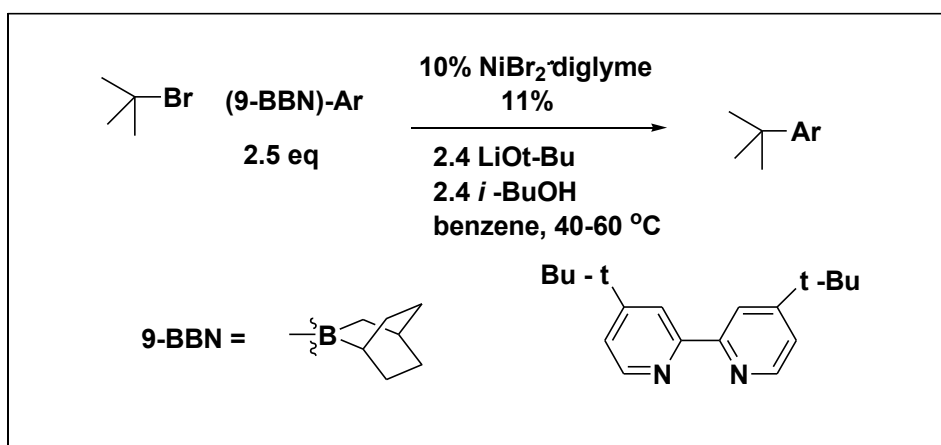
1.4.4 Asymmetric bromination

α -Brominated compounds are useful synthetic intermediates in total synthesis as well as their chlorinated analogs, and there are only a few efficient enantiospecific methods that were developed for the synthesis of brominated compounds³⁰. Brominated chiral cycloadducts can be converted to all carbon chiral quaternary centers via reductive alkylation with inversion of configuration. An example of such a transformation was reported by Yamamoto (Scheme 21)¹⁹. Greg. Fu and his group have a lot of research done on utilizing brominated compound for Negishi coupling and recently they have reported $\text{sp}^3\text{-sp}^3$ coupling via Suzuki coupling with inactivated tertiary alkyl bromide (scheme 22)³¹.

Scheme 21: Yamamoto reductive alkylation.



Scheme 22: Coupling of unactivated tertiary alkyl bromide.

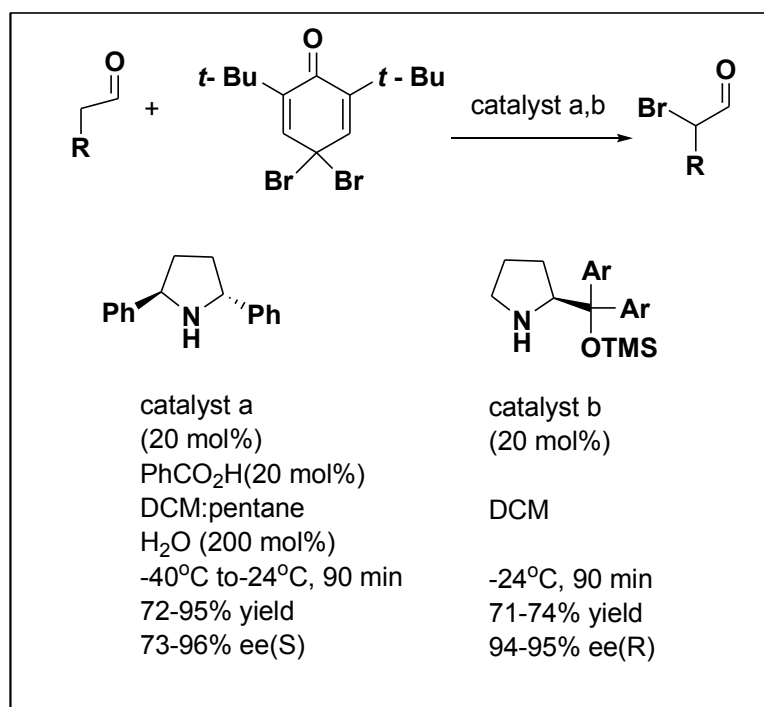


Asymmetric bromination by chiral amines

Jørgensen *et. al.* reported two methods for enantioselective α -bromination of aldehydes³⁰. In the first method they used the same catalyst as for chlorination reaction with 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone as the brominating agent. The reaction proceeded smoothly with high yields and high ee

(up to 96% ee). This reaction is highly solvent dependent with the best results of 1:1 mixture of DCM and pentane. Addition of benzoic acid and water was crucial for obtaining the optimal yields and ee. However, changing the catalyst allowed almost the same results but with no need for addition of water, benzoic acid or pentane (scheme 23).

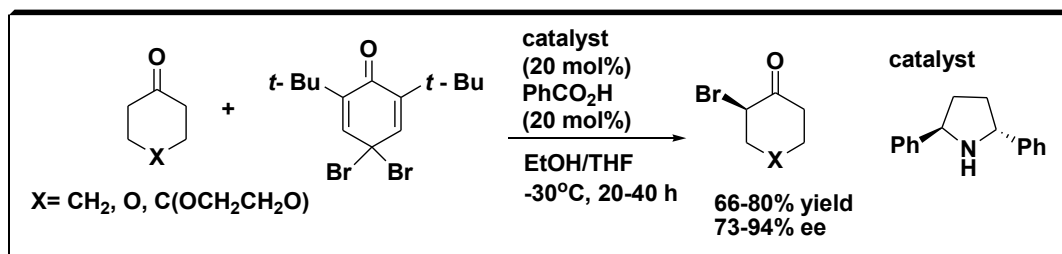
Scheme 23: α -bromination of aldehydes by Jørgensen *et. al.*



α - bromination of ketones was done in a similar way as with α -bromination of aldehydes. They have used the same brominating agent and catalyst in a 20 mol% catalyst loading. The difference in the reaction condition was changing the solvent to EtOH or THF (scheme 24). The yields and the ee`s were slightly lower

compared to bromination of the aldehydes. All of the brominated products had to be reduced with NaBH₄ prior to the purification with column chromatography.

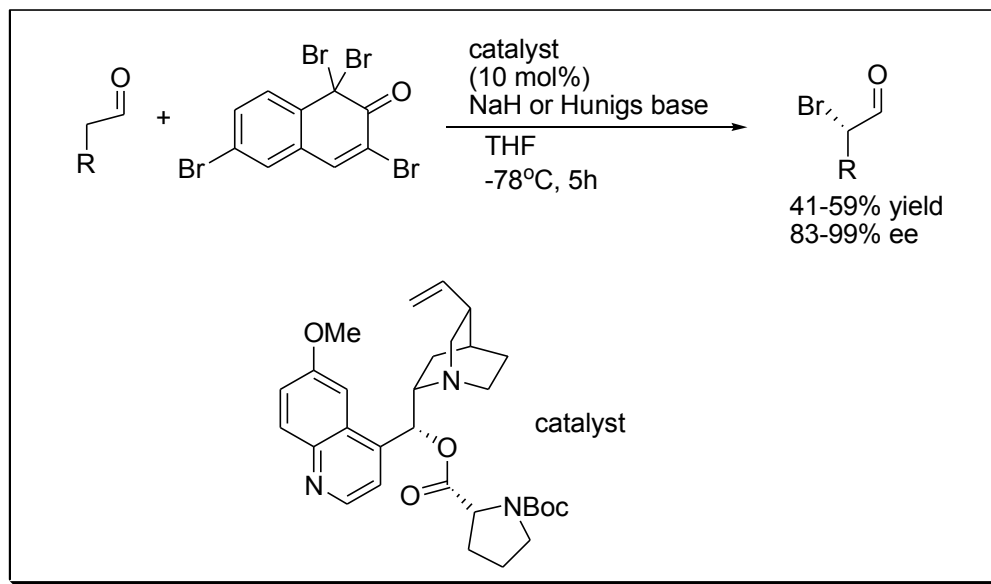
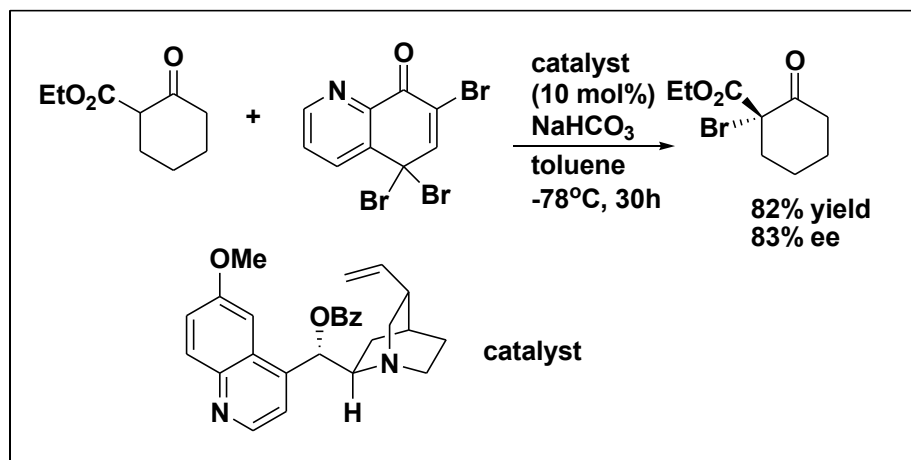
Scheme 24: α - bromination of ketones.



Asymmetric bromination by chiral *tert*-amines

In 2001, Lectka developed enantioselective α -bromination of acid chlorides under similar conditions and same reaction mechanism as they did with α -chlorination. In this case they used 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone as the brominating agent and were able to achieve high enantioselectivity with up to 99% ee (Scheme 25)³².

Bartoli and Melchiorre *et. al.* achieved α -bromination of 1,3-dicarbonyl compounds under similar reaction conditions and mechanism as they did with chlorination. They used tribromoquinoline as the brominating agent and achieved 82% yield and 83% ee (scheme 26)²⁷.

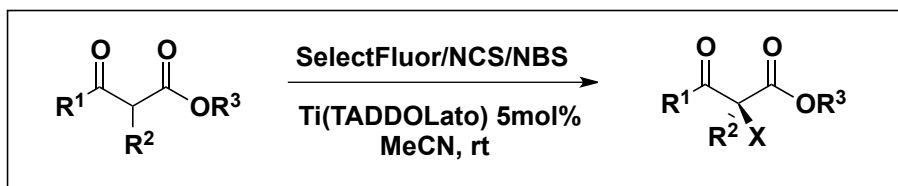
Scheme 25: α -bromination of acid chlorides.**Scheme 26:** α -bromination of 1,3-dicarbonyl compounds.

1.5 Metal catalyzed α -Halogenation

1.5.1 Ti(TADDOLato)- Catalyzed α -Halogenations

The first enantioselective α -fluorination of β -ketoesters was reported by Hintermann and Tongi in 2000, with Ti(TADDOLato) as the catalyst, which was found to be applicable to chlorination and bromination as well (see Equation 4)³³. The stereodefining atom transfer is controlled by the orientation of the naphthyl groups, which provide steric shielding of the prochiral faces of the bound enolate (figure 15). In reaction these complexes exist in two diastomeric forms (figure 16). In form A, both of the *Re* faces of the bound enolate are open for electrophilic attack, yielding *S*-enantiomer. Form B enantiomer has one of its *Si*-faces exposed and it was proposed that that is leading to destruction of enantioselectivity.

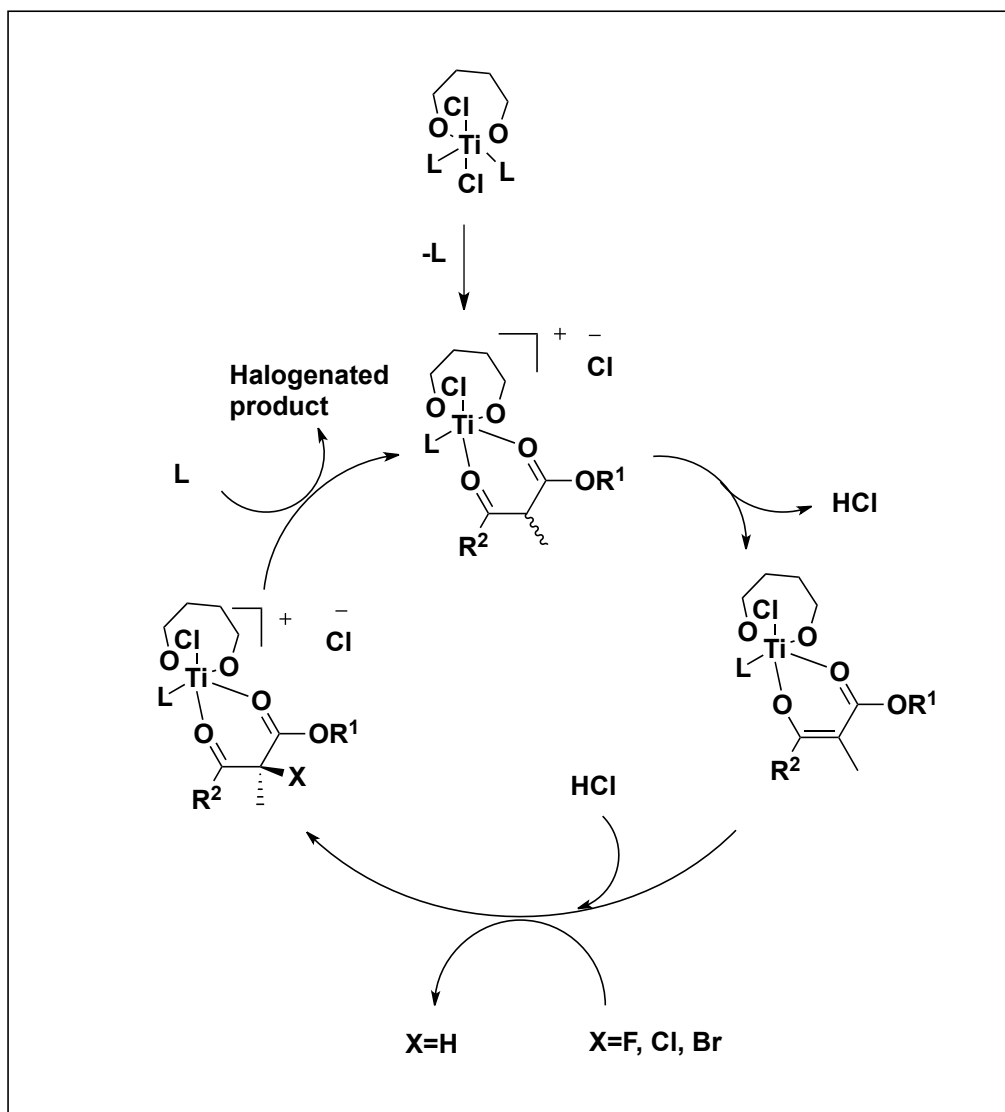
Equation 4: α - halogenation by Tongi and Hinterman.



1.5.2 Pd(II) Diphosphine complexes

Another example of metal catalyzed α -halogenation is the use of Pd(II) complex. Pd (II)-diphosphine complex with noncoordinating counter anion (X=

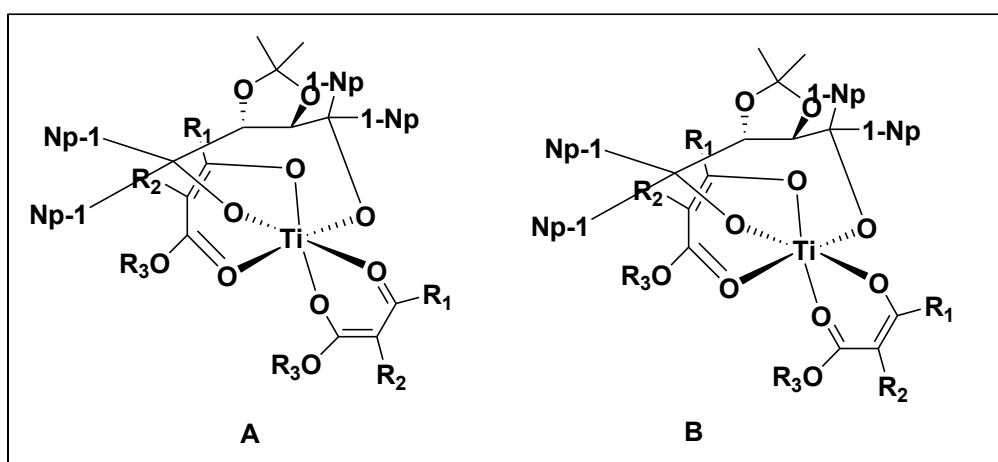
Figure 15: Lewis acid catalysis mechanism.



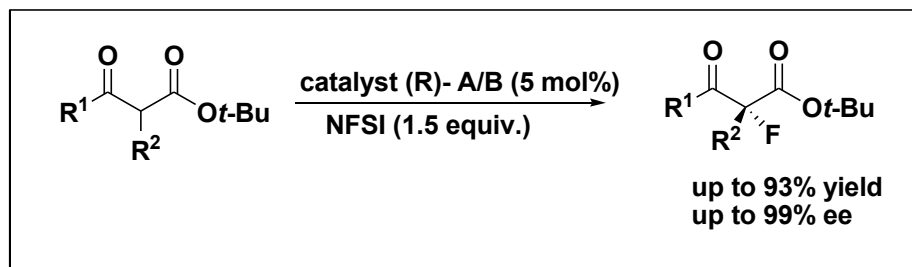
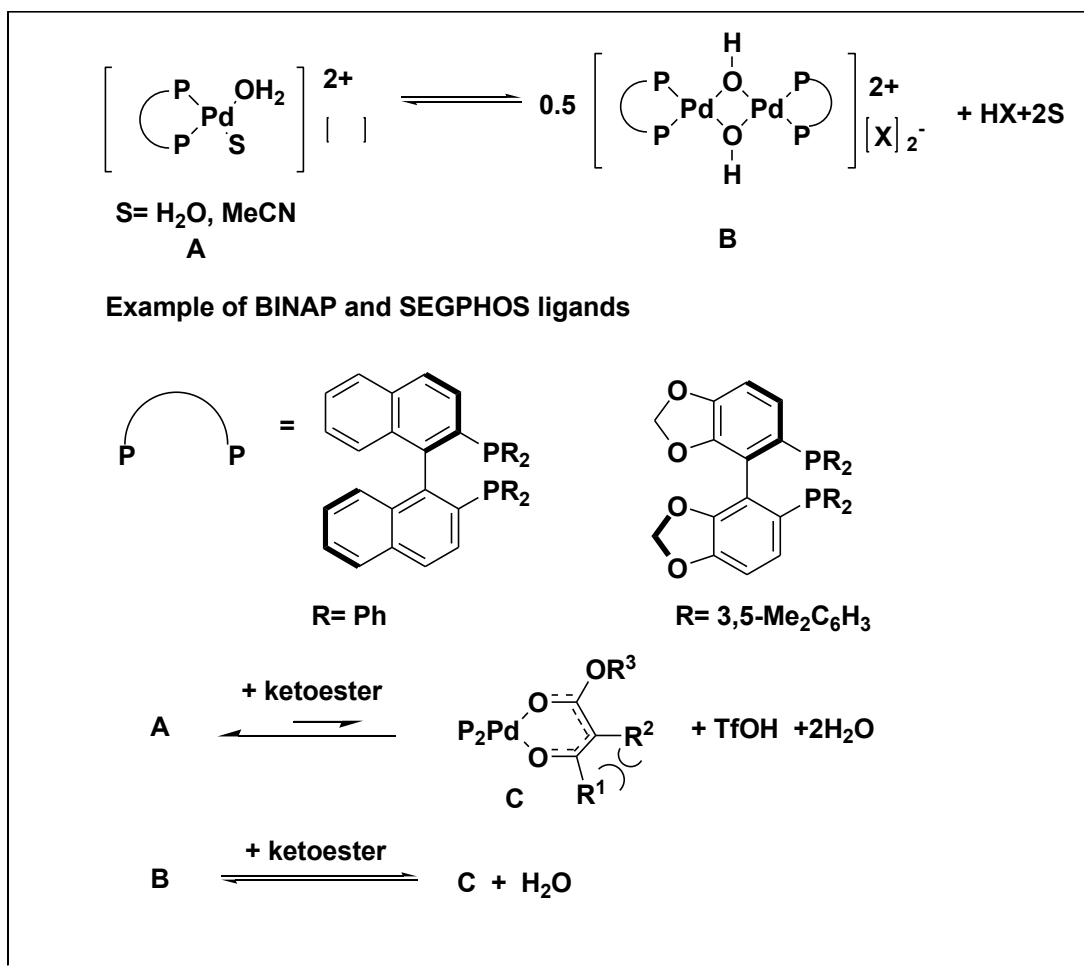
PF_6 , BF_4 , OTf , SbF_6) is used as chiral chelating agent in chiral α -halogenation reactions with β -ketoesters. Typical ligands that are used for asymmetric halogenation reactions are BINAP and SECPHOS and achieve high stereoselectivity³⁴. These are air and moisture tolerable species can be used in

two forms: monomeric complex and dimeric complex (scheme 27). The dimeric complex can act as “bifunctional” catalyst with the hydroxyl group that bridges the complex and can be deprotonated and used as a Brønsted base and a Lewis acid in reaction simultaneously.

Figure 16: Major diastereomers of substrate bound complex to Ti(TADDOLato)



Pd catalyzed asymmetric α -fluorination of β -keto esters with NFSI was first reported by Sodeoka and co-workers using dimeric complex (equation 5) followed by report by Kim and co-workers with the monomeric complex (equation 6) with similar results^{35,36}. Pd catalyzed asymmetric synthesis was applied towards β -ketophosphonates, α -chloro- β -ketoesters, *tert*-butyl- α -aryl- α -cyanoacetates, α -aryl- α -cyanophosphonates, lactones and lactams as well as 3-substituted oxindoles.

Equation 5: Asymmetric fluorination of β -ketoesters.**Scheme 27:** Pd diphosphine complexes and formation of active chelating complexes.

1.6 Density functional theory (DFT) calculations

Since the recent growth in organocatalysis research, new method development and prediction of the reaction outcome is of great interest to the scientific community. The development and improvement in quantum mechanical calculations such as DFT allows for application towards real chemical systems³⁷.

DFT calculations for organocatalysis became the method of choice when dealing with lowering the cost in chemical systems and increasing the accuracy. The majority of calculations related to organocatalysis are done with B3LYP functional with the 6-31G(d) basis set, which appears to be the most common in quantum mechanical calculations³⁸.

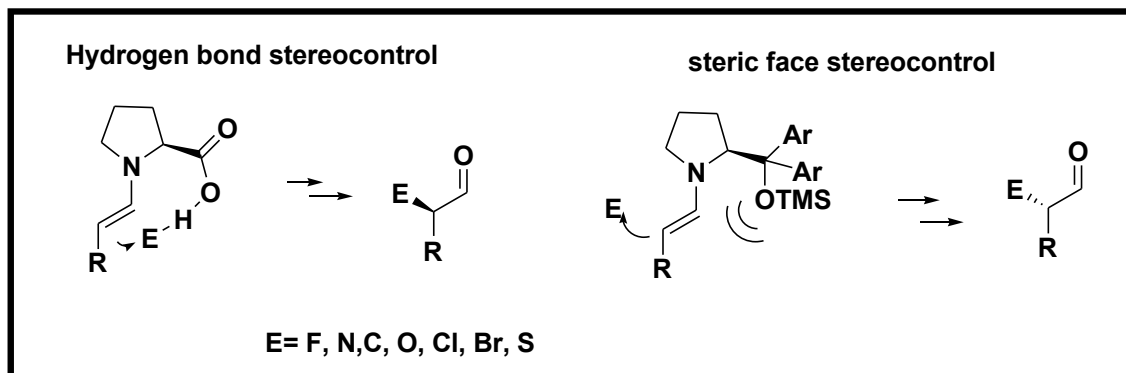
DFT calculations with B3LYP have known deficiencies such as the failure to correctly describe medium range correlations and photobranched effects, delocalization errors causing significant derivations in π to σ bonds and incorrect description of nonbonding and long range interactions, which are likely crucial for determining the stereoselectivity of the reaction outcome³⁹.

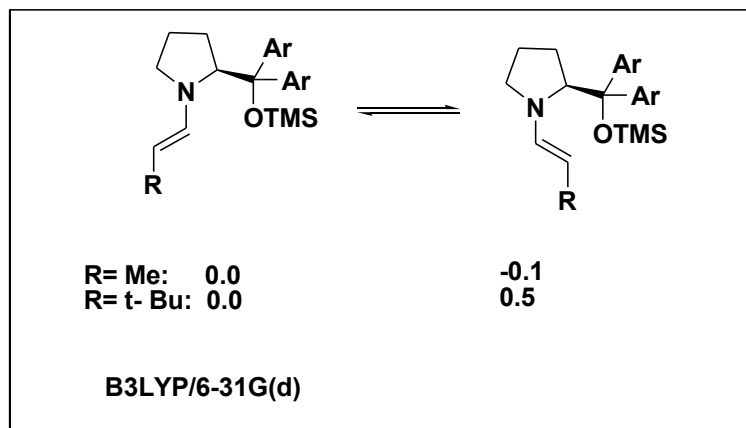
The majority of the calculations focus on the energetics of the system and not the stereoselectivity because of the difficulties in obtaining accurate results and requiring longer and more complicated calculations. Only a few calculations are currently available to predict accurate stereoselectivity⁴⁰.

DFT calculations including the B3LYP are a useful tool for qualitative analysis but the energetic analysis may be deceptive for a larger system and cannot be completely relied on.

For the α -fluorination reaction that was published by Jørgensen and discussed earlier, DFT calculations were done to explain the enantioselectivity of the reaction⁴¹. The catalyst of the reaction lacks the carboxylic acid group of proline and therefore doesn't have the electrophile directed towards the upper face of the enamine intermediate with the hydrogen bonding. The larger and bulkier group on the catalyst (TMS) directs the electrophile towards the lower face of the intermediate due to its steric shielding (scheme 28). It was shown that there is no favorability for the *anti* or *syn* enamines for the attack (scheme 29) so both of the structures were calculated.

Scheme 28: Hydrogen bond and stereocontrol.



Scheme 29: Relative free energies for anti vs syn.

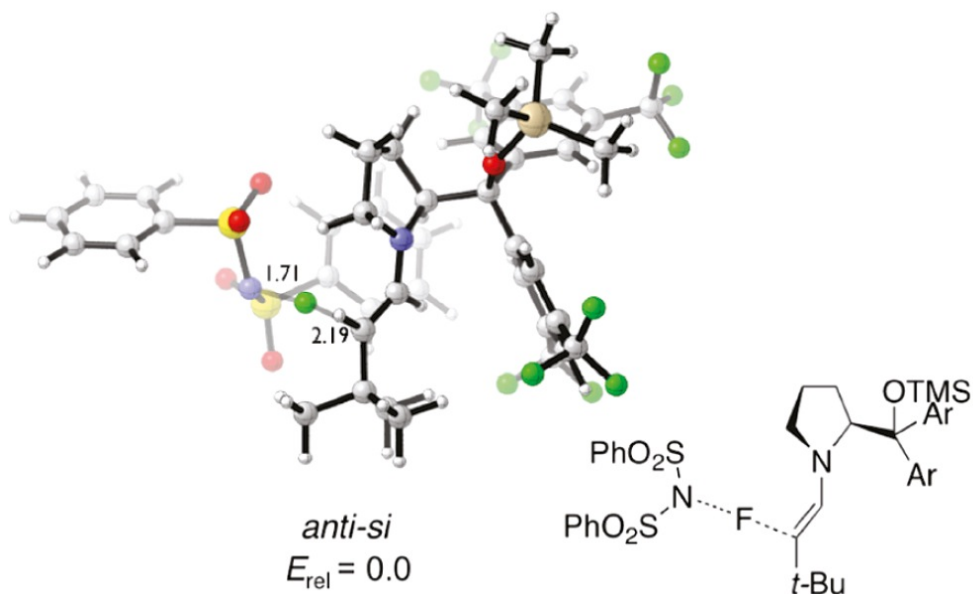
Both of the transition states for the α -fluorination of 3,3-dimethylbutanal by NFSI were found with B3LYP/6-31G(d). All geometries were taken under consideration. The lowest energy state was shown to be the one that leading to the (S) major and (R) minor enantiomer (figure 17). The minor (R) enantiomer was 2.4 kcal/mol higher in energy than the major (S) enantiomer. These calculations predicted selectivity of 96% ee and the experimental were 97% ee. The experimental and the calculated values were very close, confirming the calculations that were done on this system.

Lectka's group developed asymmetric α -chlorination reaction with a *Cinchona* alkaloid derivative and extended the scope of the reaction to α -bromination, as was discussed before. Upon changing the reaction scope there was a loss of enantioselectivity on almost identical systems. Lectka's group resorted to DFT calculation to explain the reaction and optimize the conditions⁴².

Based on their molecular mechanistic design they substituted the benzoyl quinine with α -proline–quinine conjugate. Changing the catalyst caused improvement in ee. Following the change in the catalyst, they changed the brominating agent as well and the following increased the selectivity of the reaction as well.

Computational studies were done on the bromination step with both of the brominating agents. The *si* and the *re* shown in figure 18. The preference for the *si* TS in the bromination step with brominating agent is due to the van der Waals repulsion between the α -enolate α -hydrogen and the C-H hydrogen α to the benzoyl in the catalyst in the *re* TS state. The preference for the *si* face with the brominating agent is due to 3-point H-bond network with the quinuclidine ring.

Figure 17: Transition states of α -fluorination.



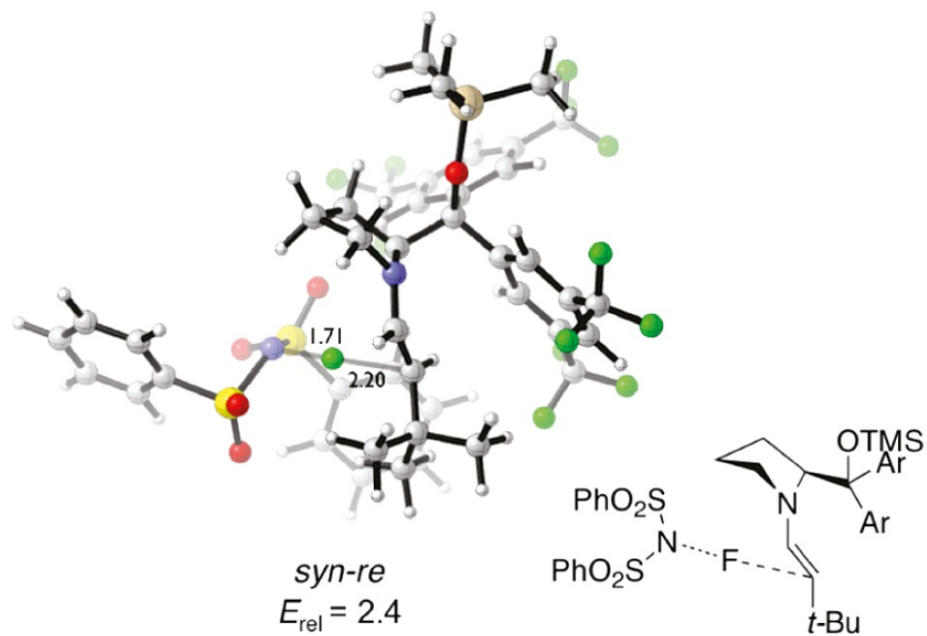
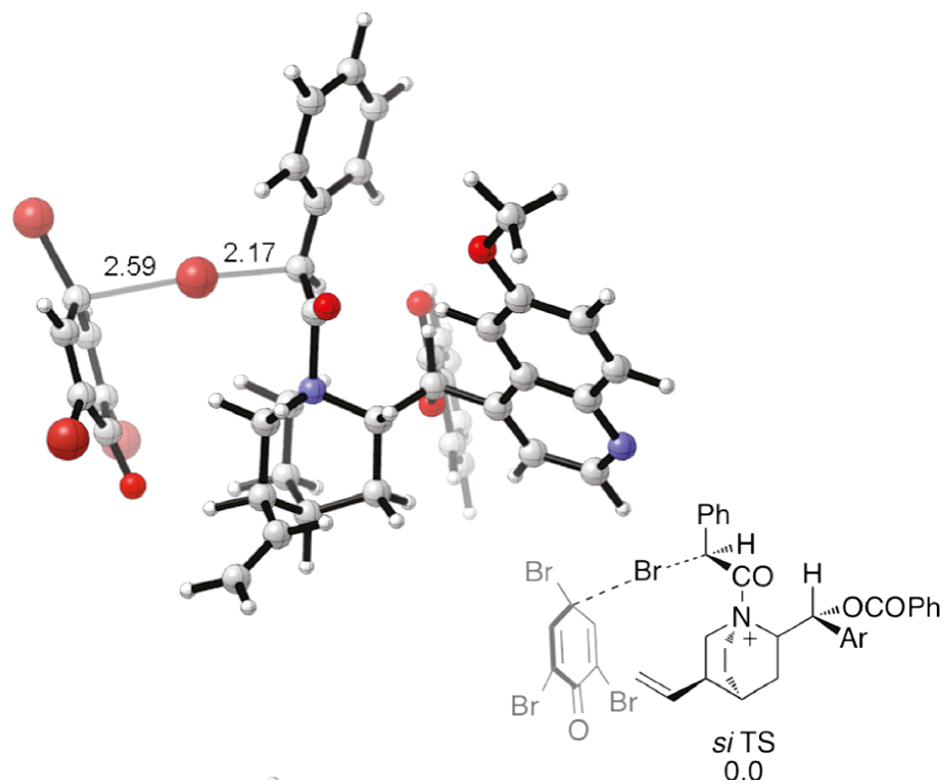
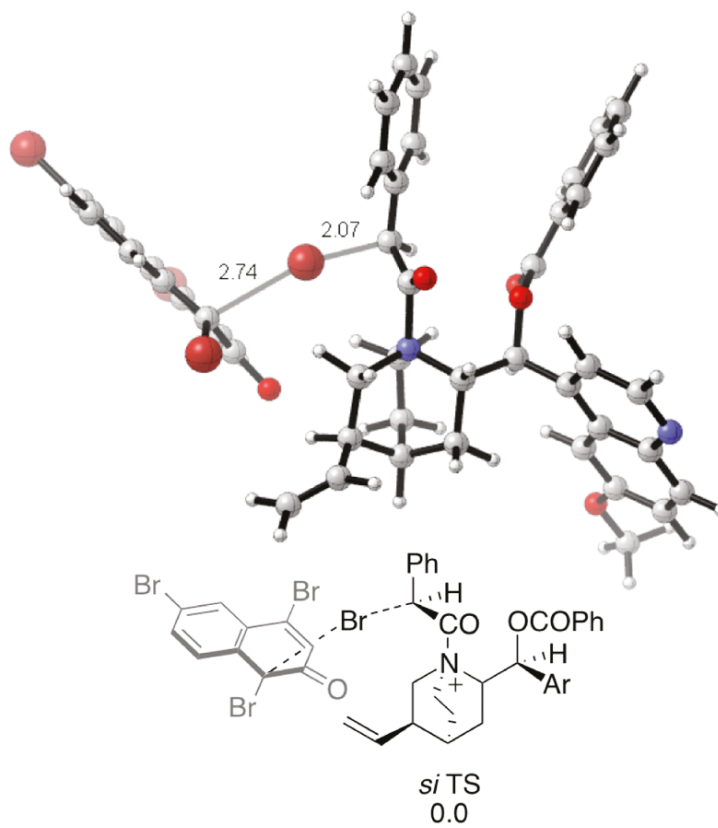
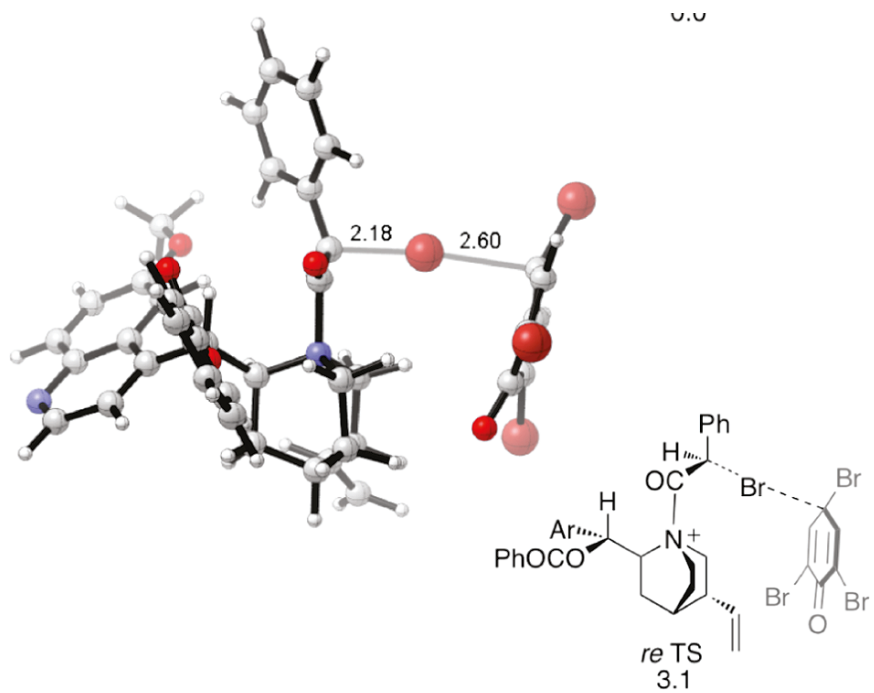
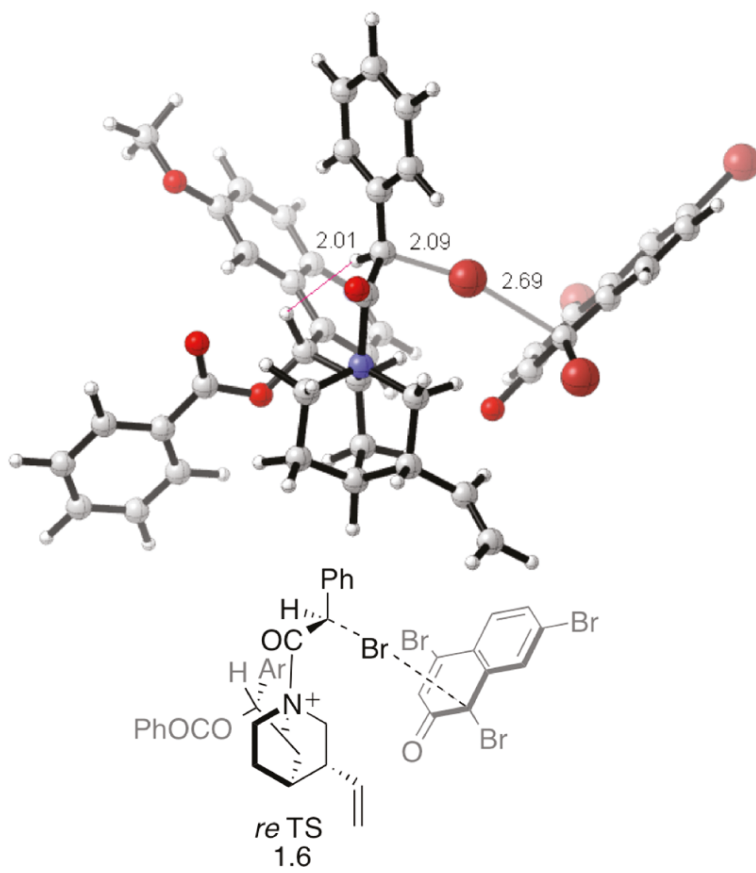


Figure 18: The *re* and *si* transition structure for brominating agent.





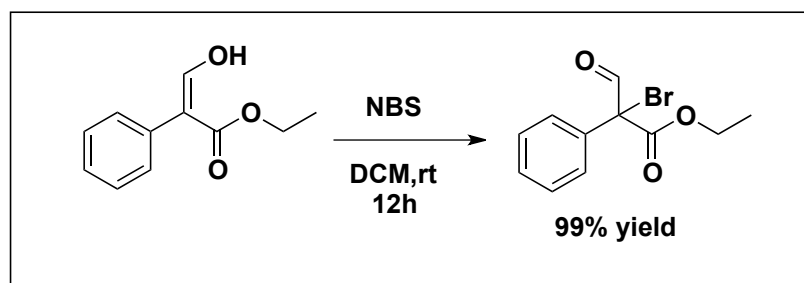


2. Results and discussion

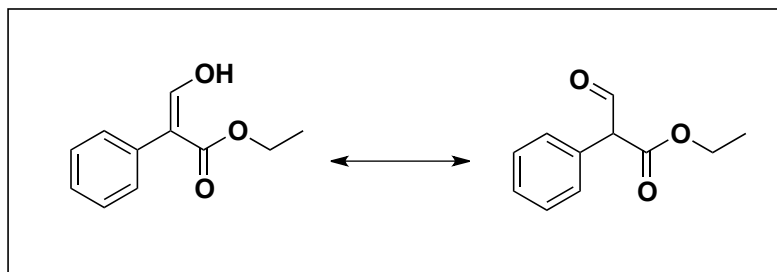
2.1 Asymmetric bromination

In the initial approach for α -halogenation, α -bromination was attempted first. NBS was chosen as the brominating agent because of previous examples in the literature and its availability. Reaction temperature was room temperature and first reaction time was over night. After passing through a small silica plug there was only one spot on the TLC and the reaction had 99% yield (Equation 6, appendix 1).

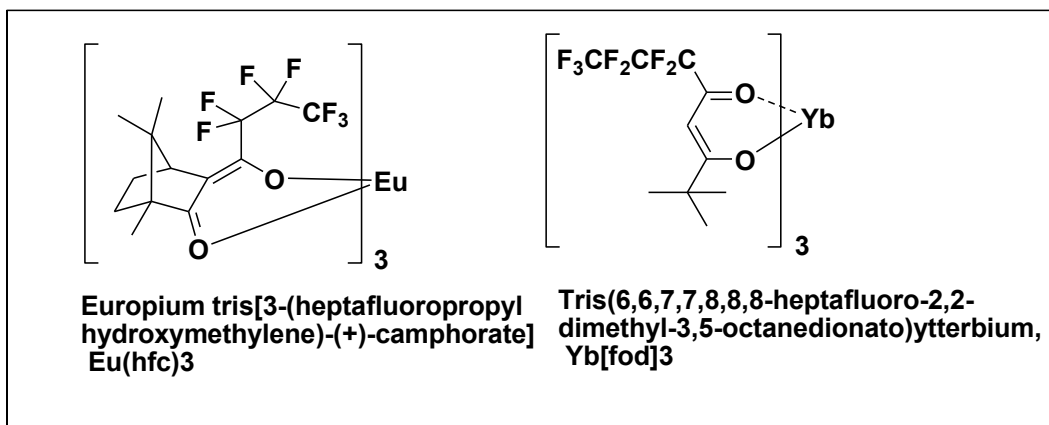
Equation 6: α -bromination (racemic).



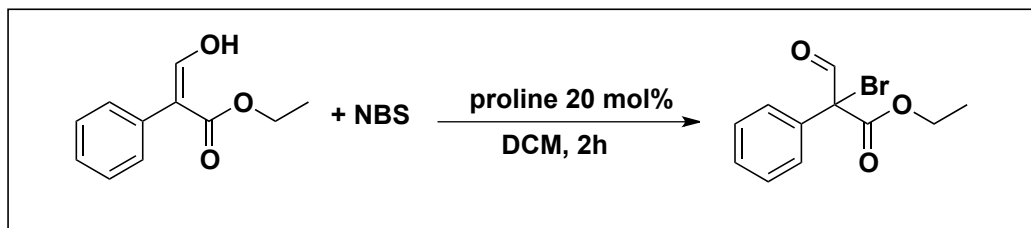
Following the racemic bromination reaction, asymmetric reaction was attempted. There is always aldehyde present in the starting material as a tautomer of the acrylate (figure 19) therefore L-Proline was chosen as the catalyst for the asymmetric reaction. L-proline was chosen because of its mode of activation that is suitable for aldehydes through enamine activation catalysis. Another reason that L-Proline was chosen is because of its availability and low cost. Reaction proceeded smoothly at -78°C for 1 hour.

Figure 19: Acrylate and aldehyde tautomer.

In order to calculate ee, chiral shift reagents were tested in 1 equivalent with slow addition. $\text{Eu}(\text{hfc})_3$ and $\text{Yb}[\text{fod}]_3$ (see figure 20) were tested and monitored through NMR. None of the chiral shift reagents were successful in resolving the brominated product.

Figure 20: chiral shift reagents.

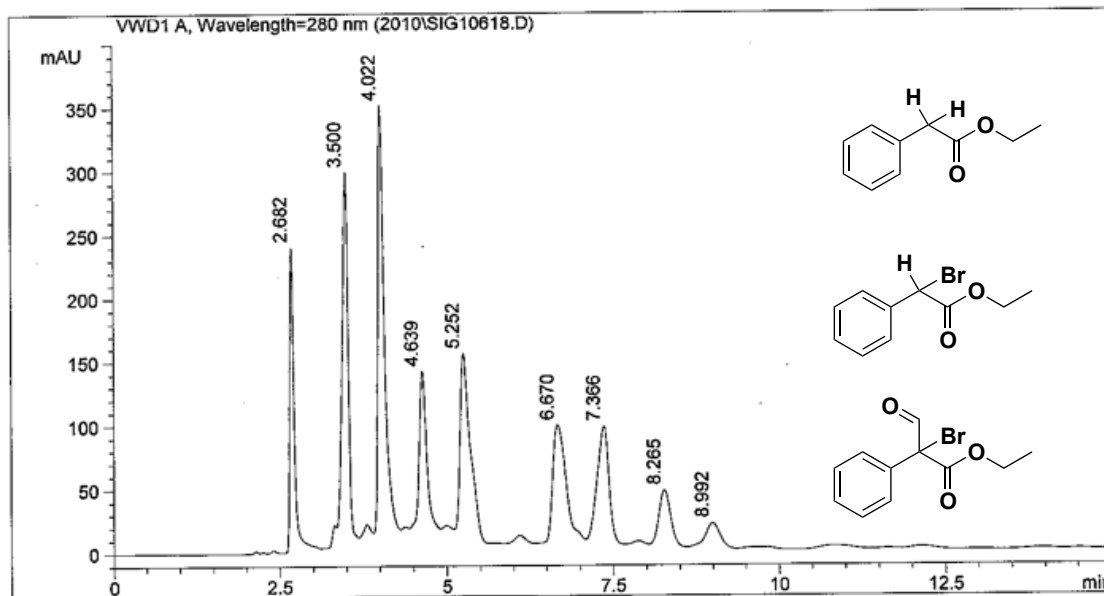
Temperature study experiments were conducted for the period of two hours at 0°C , -10°C and -20°C with L-proline as chiral catalyst 20 mol% and NBS as brominating agent in DCM (see table 1).

Table 1: Temperature control experiment bromination reaction.

| Entry | Temperature °C | Yield% |
|-------|----------------|--------|
| 1 | 0 | 100 |
| 2 | -10 | 40 |
| 3 | -20 | 20 |

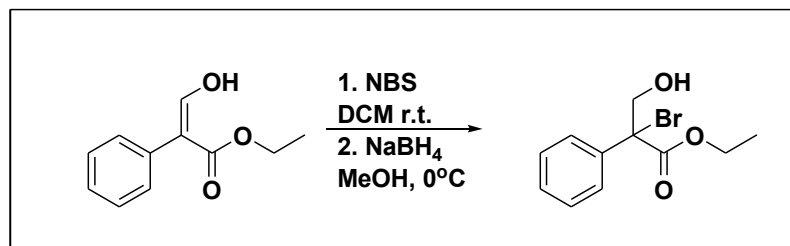
In order to find a suitable chiral HPLC separation method, a pure racemic sample was sent to Regis technologies for analysis. The data that was received contained multiple peaks that did not correspond to a pure sample. A second attempt to send a pure sample gave identical results. The third time the sample was purified and sent under nitrogen over night. After receiving the same results, the conclusion that we had is that the sample is not decomposing over time but it is decomposing inside of the column and there are three racemic substrates that are formed: deformed, dehalogenated and the actual substrate (figure 21).

Figure 20: Data from Regis technologies.



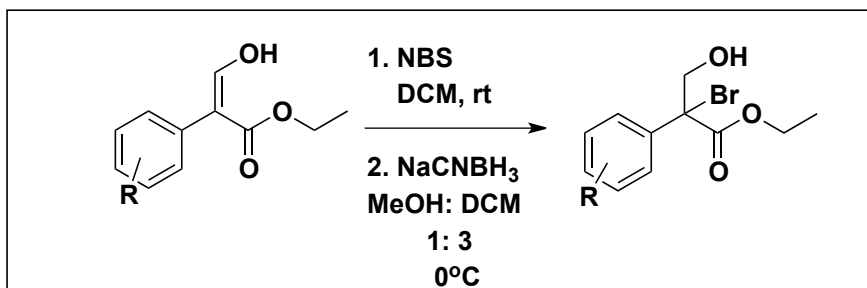
After the realization that the α -brominated compound decomposes when using HPLC, we came to the conclusion that the aldehyde needs to be reduced to an alcohol. The first reduction was done using NaBH_4 .

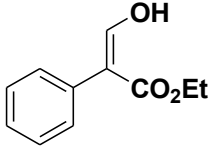
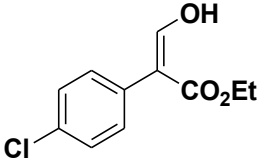
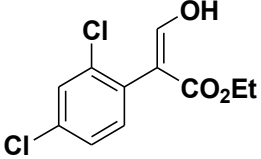
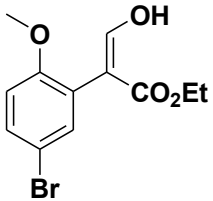
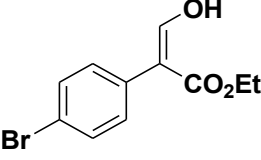
Reduction with NaBH_4 gave the reduced product but in low yield (Equation 6) with a lot of side product being formed. NaBH_4 proved to be too strong of reducing agent for this reduction and milder reducing agent was needed. Lowering the temperature of the reaction or slowing the addition of the NaBH_4 gave the desired alcohol product but the yields were too low and showed a lot of side product as well.

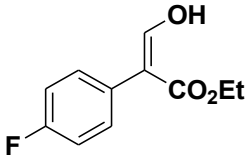
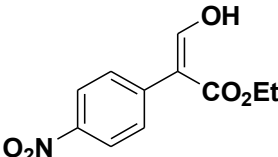
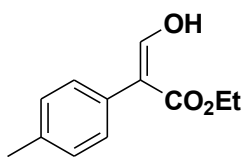
Equation 7: Reduction with NaBH₄.

NaCNBH₃ proved to be a better reducing agent than NaBH₄ for this type of a system. Bromination and reduction can be done all in one pot, even though small samples were taken out before the reduction to monitor the progress of reaction and percent conversion through NMR. The brominated aldehyde is pure enough to be used in a total synthesis without the need for purification and the reduction is needed only for identification or measuring the ee of the reaction. Bromination and reduction worked very well for wide variety of substituted α -hydroxyacrylate under mild reaction conditions (table 2).

Table 2: one pot bromination and reduction of different substituted α -hydroxyacrylates.



| Entry | Substitution | % yield | %Isolated Yield |
|-------|--|---------|-----------------|
| 1 |  <chem>CCOC(=O)C(O)=Cc1ccccc1</chem> | 99% | 95% |
| 2 |  <chem>CCOC(=O)C(O)=Cc1ccc(Cl)cc1</chem> | 99% | 61% |
| 3 |  <chem>CCOC(=O)C(O)=Cc1cc(Cl)cc(Cl)c1</chem> | 99% | 85% |
| 4 |  <chem>CCOC(=O)C(O)=Cc1cc(OC)c(Br)cc1</chem> | 99% | 55% |
| 5 |  <chem>CCOC(=O)C(O)=Cc1ccc(Br)cc1</chem> | 99% | 52% |

| Entry | Substitution | % yield | %Isolated Yield |
|-------|--|---------|-----------------|
| 6 |  <chem>CCOC(=O)C(O)=Cc1ccc(F)cc1</chem> | 99% | 67% |
| 7 |  <chem>CCOC(=O)C(O)=Cc1ccc([N+](=O)[O-])cc1</chem> | 95% | 45% |
| 8 |  <chem>CCOC(=O)C(O)=Cc1ccc(C)cc1</chem> | 99% | 75% |

After finding a suitable reducing agent, a standard sample was brominated and reduced for analysis at Regis Technologies to match find a suitable chiral column for HPLC. The chiral column "RegisPack" (250mm*4.6 mm) from Regis Technologies was purchased and the optimized method was Hexane/Ethanol (95/5) 1.5 mL/min with pressure of around 46.6 bar (figure 22). All of the % ee data for the α -bromination was collected using this column and the method developed by Regis Technologies.

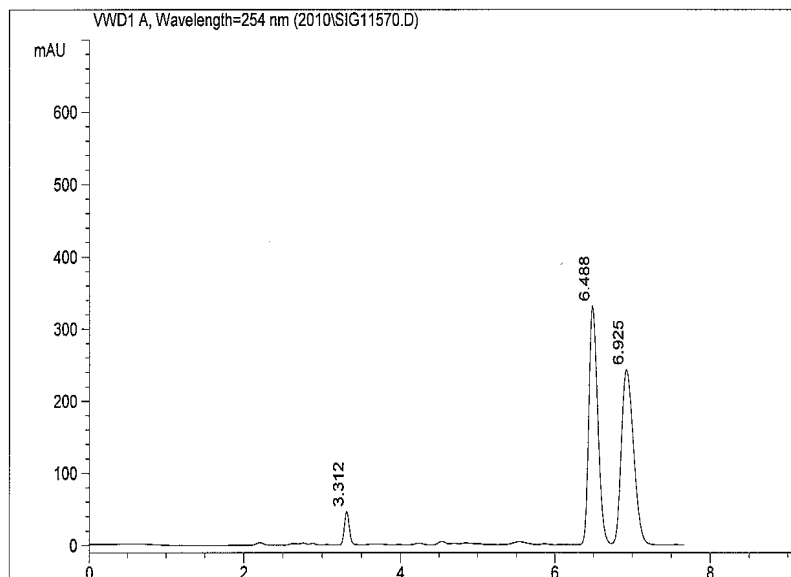
Figure 21: LC chiral screening data report.

LC Chiral Screening Data Report

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8/23/2010      C:\HPCHEM\1\DATA\2010\SIG11570.D

Column Name   : RegisPack
Catalog #    : 783104
Column Size   : 250 mm x 4.6 mm
Particle Size : 5 micron
Sample Name   : Ethyl 2-bromo-3-hydroxy-2-phenylpropanoate
Mobile Phase  : Hexane/Ethanol (95/5)
Flow Rate    : 1.5 mL/min
Injection Vol : 5.0 uL
Pressure     : 46.6 bar
  
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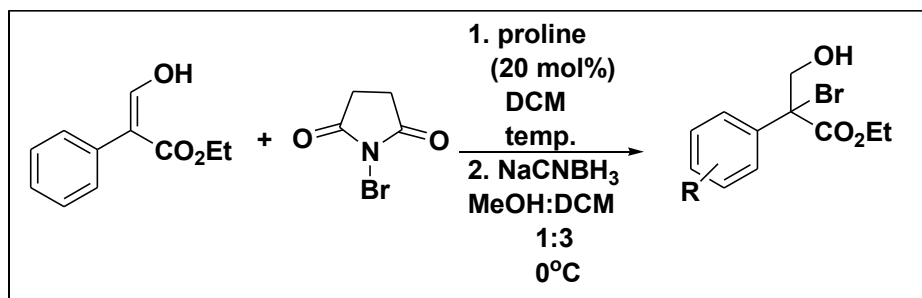


| Peak # | RT [min] | Width [min] | Area | Area % |
|--------|----------|-------------|---------|--------|
| 1 | 3.31 | 0.069 | 187.32 | 3.46 |
| 2 | 6.49 | 0.132 | 2610.77 | 48.27 |
| 3 | 6.92 | 0.180 | 2610.16 | 48.26 |

Temperature studies were done using proline as the catalyst with 20 mol% catalyst loading and NBS as the brominating agent with DCM as the reaction solvent. While decreasing the reaction temperature, it showed that there is an increase in ee (table 3). At -78°C there was the highest percent yield but with

longer reaction time that was difficult to control, therefore the 09 majority of bromination reaction were run at -25°C .

Table 3: Temperature optimization chiral bromination reaction.

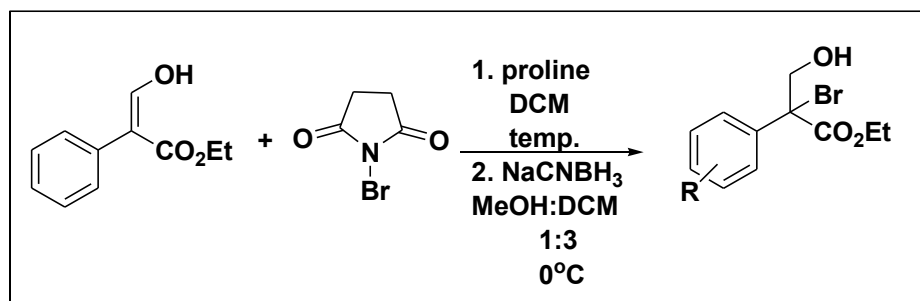


| Entry | Temperature $^{\circ}\text{C}$ | % Yield | %ee |
|-------|--------------------------------|---------|---------|
| 1 | rt | 99% | racemic |
| 2 | 0°C | 99% | racemic |
| 3 | -20°C | 99% | 13% |
| 4 | -78°C | 99% | 39% |

Altering the equivalence of the catalyst loading from 20 mol% to 10 mol% has not improved the ee% (table 4). Proline was chosen as the catalyst and reaction temperature was set at -20°C with DCM as the solvent and NBS as the

brominating agent. Reduction was done in the same pot. Percent yield was 100% and monitored by NMR before the reduction.

Table 4: Catalyst loading optimization reaction bromination.

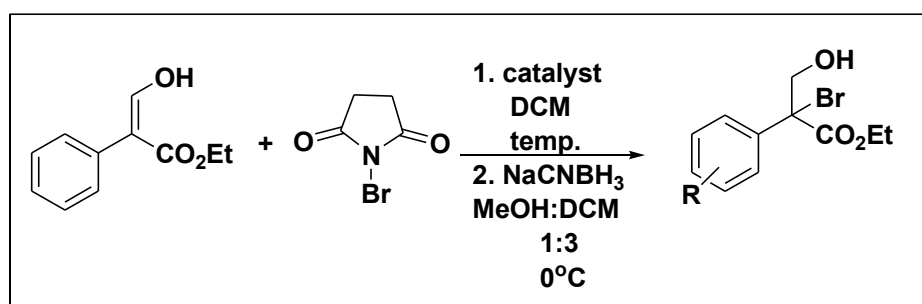


| Entry | Catalyst loading (mol%) | % Yield | %ee |
|-------|----------------------------|---------|-----|
| 1 | 20 | 100 | 12 |
| 2 | 10 | 100 | 9 |

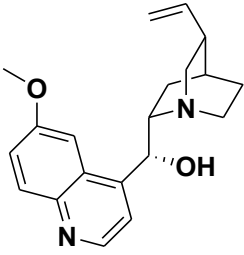
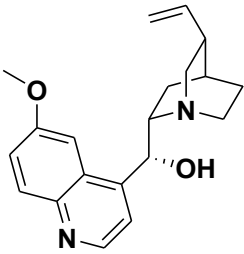
Changing the catalyst from proline to proline analogs on 100 mol% of catalyst gave increased ee of 34.6% with 100% yield. Lowering the temperature to -78°C and lowering catalyst loading to 20 mol% did not show an increase in ee but instead lowered it to 33%. Changing the catalyst in entry 3 gave lower ee of

9% and switching from proline analogs to quinine analog did not improved the ee either, even by lowering reaction temperature to -78°C .

Table 5: Catalyst Screening- Bromination reaction.



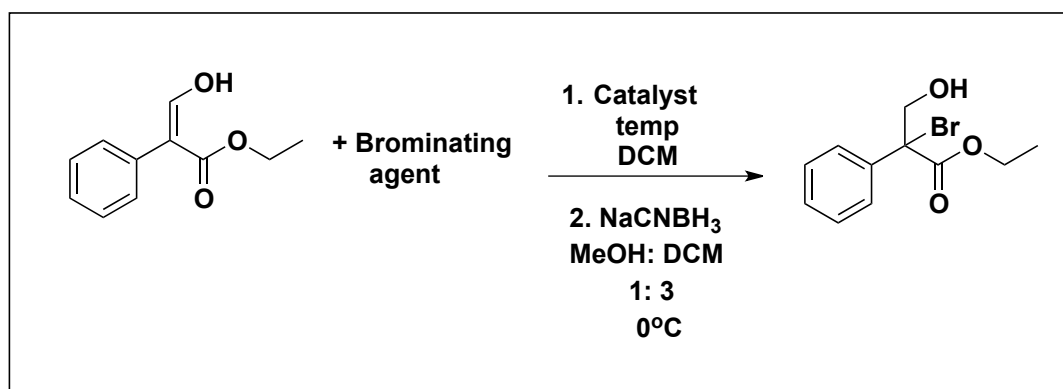
| Entry | Catalyst | Temperature $^{\circ}\text{C}$ | %yield | %ee |
|-------|--------------|--------------------------------|--------|------|
| 1 | 100 mol% | -25 | 100 | 34.6 |
| 2 | 20 mol% | -78 | 100 | 33 |
| 3 | 20 mol% | -25 | 100 | 9 |

| Entry | Catalyst | Temperature °C | %yield | %ee |
|-------|--|----------------|--------|-----|
| 4 |  20 mol% | -25 | 100 | 9 |
| 5 |  20 mol% | -78 | 100 | 8 |

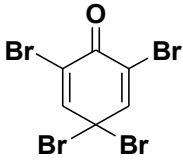
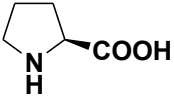
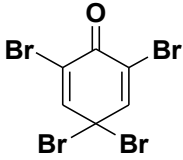
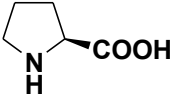
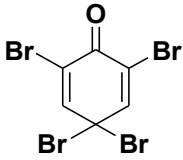
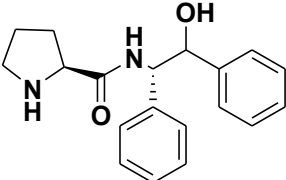
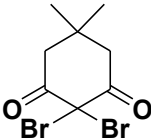
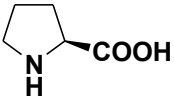
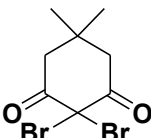
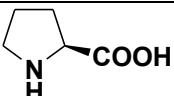
The conclusion that was achieved is that the brominating agent itself is too reactive and reacts faster than the catalytic reaction. In an attempt to increase the ee of the bromination reaction, a milder brominating agent was chosen, table 6 entry 1, at -25°C in DCM. % yield with a milder brominating agent was very low relatively to the NBS and the reaction time was about 12 hours. Bringing reaction temperature higher to room temperature, entry 2, provided identical results as with lower reaction temperature. Curious to what was causing the low yield, even with significant higher brominating agent loading, catalyst loading was done in two portions and monitored by NMR (entry 3). Dividing the catalyst loading in to two portions showed increase in % yield and the conclusion

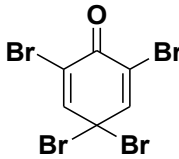
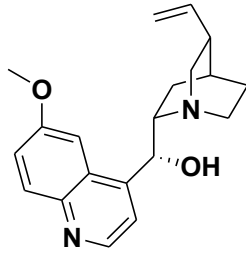
that the brominating agent is brominating the catalyst itself and therefore is not available for the bromination reaction, preventing catalytic induction. Altering the catalyst from proline to proline analog (entry 4) and quinine (entry 7) did not show increase in % yield but did show slight increase in ee. Changing the brominating reagent to a milder one (entry 5) lowered the % yield with no ee and adding PDA (entry 6) did not improve % yield or ee.

Table 6: Changing the brominating agent to mild brominating agent.



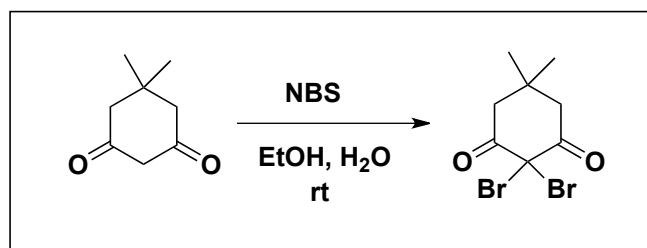
| Entry | Brominating agent | Catalyst | Temp °C | %yield | %ee |
|-------|-------------------|-------------|---------|--------|---------|
| 1 | | 20 mol% | -20 | 50 | racemic |

| Entry | Brominating agent | Catalyst | Temp °C | %Conversion | %ee |
|-------|---|--|---------|-------------|---------|
| 2 |  |  20 mol% | rt | 50 | racemic |
| 3 |  |  10 mol% 10mol% | -20 | 32 58 | racemic |
| 4 |  |  20 mol% | -20 | 50 | 6 |
| 5 |  |  20 mol% | rt | 18 | racemic |
| 6 |  |  20 mol% PDA | rt | 10 | racemic |

| Entry | Brominating agent | Catalyst | Temp °C | %Conversion | %ee |
|-------|---|--|---------|-------------|-----|
| 7 |  |  20 mol% | -20 | 30 | 10 |

NBS and 2,4,4,6-tetrabromo-2,5-cyclohexadienone were purchased from Aldrich chemical but 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione was synthesized (see equation 7)⁴³.

Equation 7: Synthesis of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione.



2.2 Asymmetric chlorination

After bromination reaction proved to be challenging and the brominating reagents that are available were too reactive or too unreactive towards the

bromination of the acrylate, asymmetric chlorination reaction was attempted. The NCS is a readily available chlorinating agent and milder halogenating agent compared to NBS. The chlorinated product is relatively more stable than the brominated product and there is no need for reduction unlike in the case of the brominated product to measure the ee.

The first chlorination reaction worked very well (equation 8). The method development for the HPLC proved to be challenging because, compared to the brominated product, the chlorinated product was highly non polar and it was difficult to find the appropriate solvent system for the chiral resolution. The best solvent was found to be 100% Hexane. The challenge in using this system was that the peaks were inconsistent and the baseline that followed was higher and trailing was observed. The problem was found to be the different water content in Hexane and the solution to the problem was to prepare 99.9%/0.01% Hexane /IPA in order to avoid water content problem. The method was set at 1mL/min with 99.9%/0.01% Hexane/IPA (figure 23).

Equation 8: Chlorination reaction.

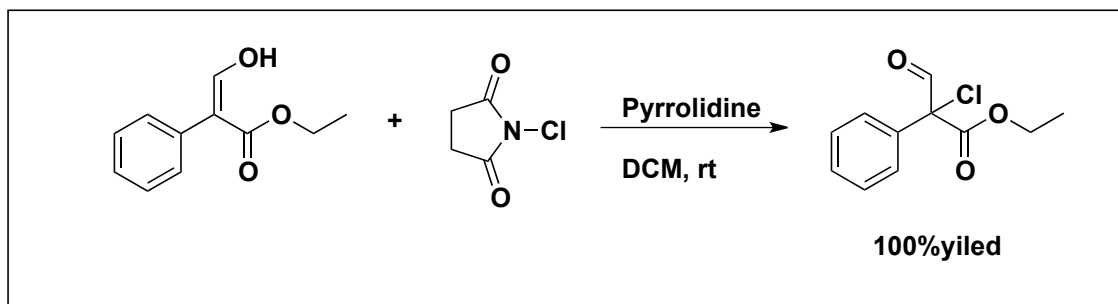
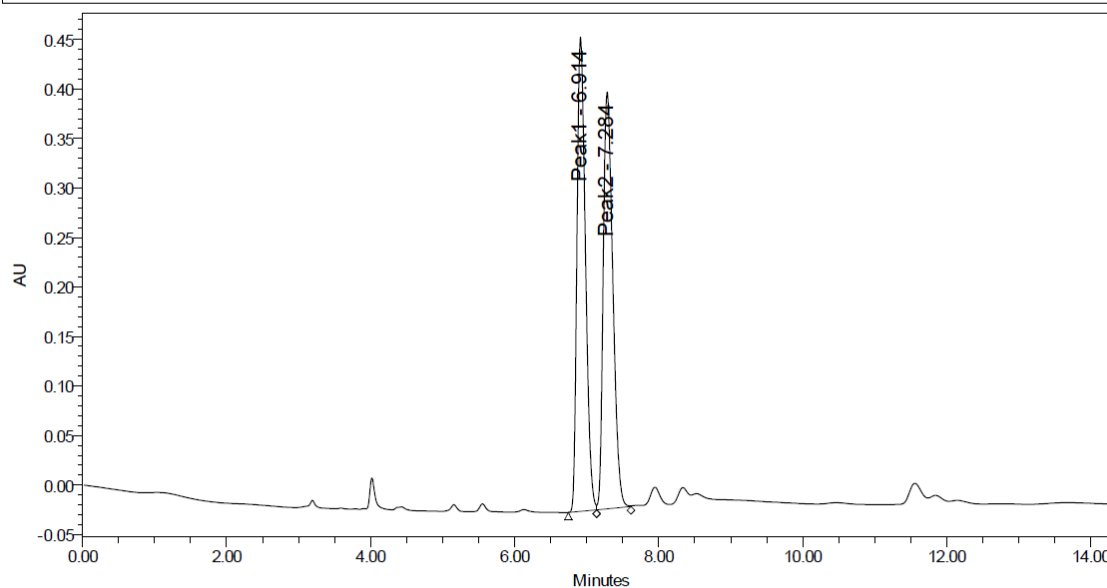


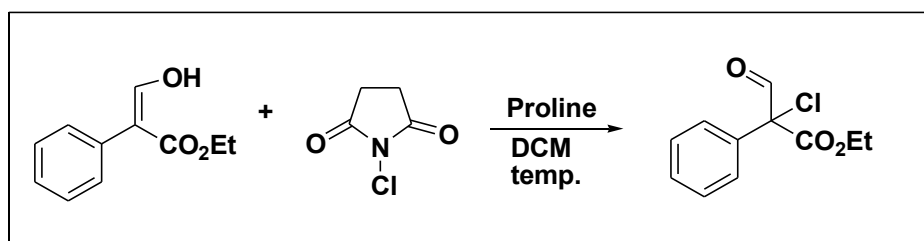
Figure 23: Optimization method for chlorination racemic sample.

| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/10/2011 1:54:28 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/10/2011 2:09:31 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 25.00 Minutes | Sample Set Name: | 111011 st cl |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.914 | 3922566 | 50.19 | 478666 | 53.22 |
| 2 | Peak2 | 7.284 | 3893299 | 49.81 | 420742 | 46.78 |

In order to find the optimal reaction temperature several experiments under different reaction temperature were done. Both room temperature and -20°C gave racemic mixture with 100% yield and -78°C had 50% yield with slight ee (table 7). -20°C was chosen because in the previous halogenation reaction it gave slightly better ee than rt.

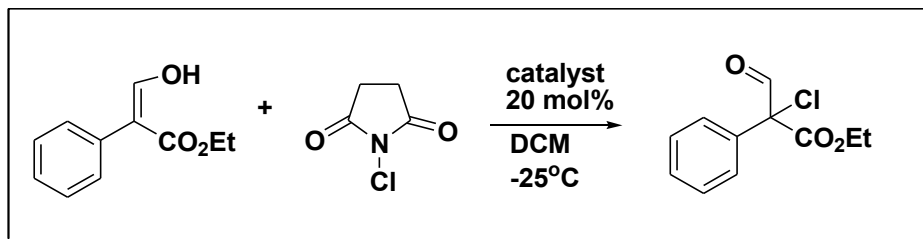
Table 7: Temperature optimization- Chlorination reaction, proline.

| Entry | Temperature °C | %yield | %ee |
|-------|----------------|--------|---------|
| 1 | rt | 100 | racemic |
| 2 | -20°C | 100 | racemic |
| 3 | -78°C | 50 | 4 |

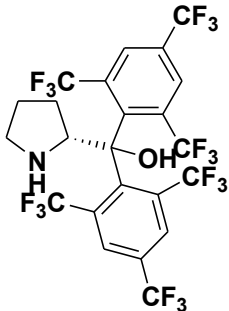
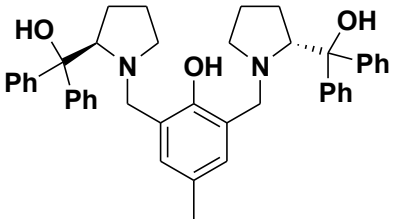
After choosing the optimal reaction temperature, catalyst screening was done. The first type of catalyst that was chosen were proline analogs because of their availability in the lab from the previous bromination reaction and in order to test the enamine activation mechanism that are suitable for aldehydes with proline analogs as the chiral catalyst. Proline analogs proved to be unsuccessful in chiral induction of the chlorinating reactions (table 8 entries 1-5). Entry 6 had an interesting result with 20 %ee and 100% yield. The catalyst was derived from proline analogs but had a tertiary amine on both sides. Because prior proline

analogues were unsuccessful in the asymmetric induction but the tertiary amine showed promising results, the next set of catalysts that were screened were tertiary amines as quinine analogues (table 9).

Table 8: Catalyst screening- Chlorination reaction proline analogs.

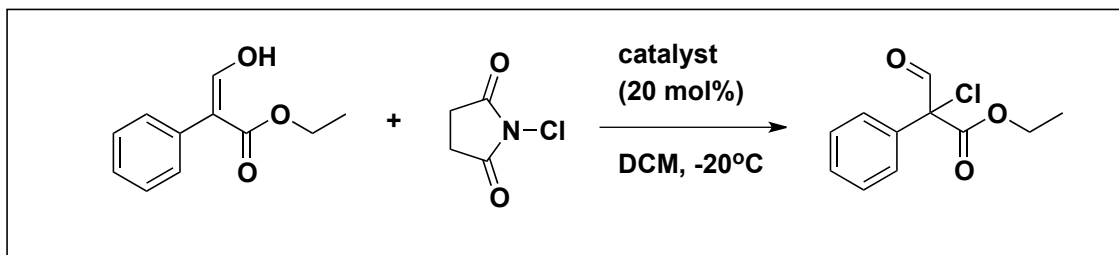


| Entry | Catalyst | %yield | %ee |
|-------|----------|--------|---------|
| 1 | | 100 | 3 |
| 2 | | 100 | racemic |
| 3 | | 100 | racemic |
| 4 | | 100 | racemic |

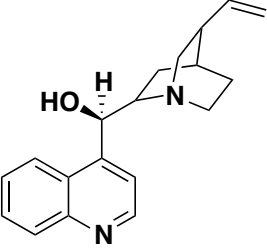
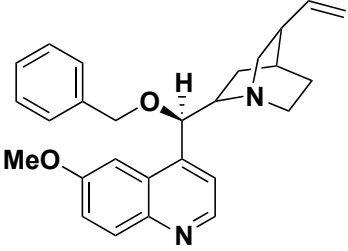
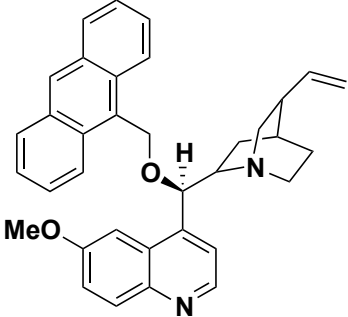
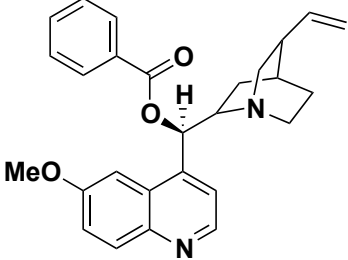
| Entry | Catalyst | %yield | %ee |
|-------|--|--------|-----|
| 5 |  | 100 | 5 |
| 6 |  | 100 | 20 |

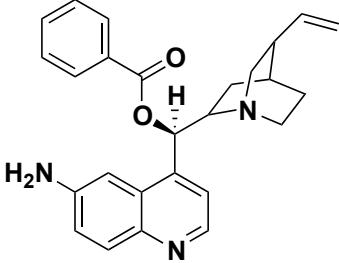
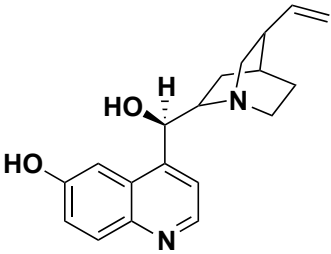
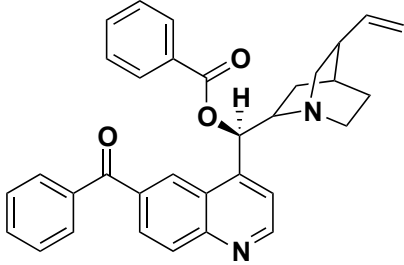
The next set of catalysts that were screened were quinine-based catalysts. Quinine based catalysts contain tertiary nitrogen that should deprotonated the acrylate as well as hydrogen bond to groups such as the hydroxyl that can hydrogen bond to the carbonyl group and create ion pair interaction according to the bifunctional catalyst mechanism. With the exception of quinine that was purchased from Aldrich, all of the catalysts were synthesized from quinine. The first reaction was done with quinine and gave promising results of 24% ee, entry 1. In an attempt to improve the ee a double substituted quinine analog was used (DHQ)₂AQN, entry 2. The use of disubstituted quinine lowered

the ee. Next catalyst that was used, entry 3, was cinchonine and it showed lower ee than the quinine analog, indicating that there is significance to the substitution at the 6 position. Entries 4-6, were catalysts that had bulky substitutions instead of the hydroxyl group. All three of the catalysts did not show any improved ee but had inversion of the stereochemistry instead. These results indicate that there is importance of the hydroxyl group and maybe a network of hydrogen bonding that by changing it from hydroxyl group to a bulky group causes steric shielding instead of hydrogen bonding and therefore causes inversion of configuration. The next catalyst that was screened contained an amino group instead of the methoxy group at the 6 position, entry 7, in order to allow hydrogen bonding with the bulky substitution as well. There was no increase in ee as in previous cases. The next catalyst that was attempted had on both of the positions hydroxyl group to allow hydrogen-bonding network with the substrate and the chlorinating agent as well, entry 8. This catalyst did not improve the ee as well. Entry 9, the catalyst that was used contains bulky substitution on both the 6 position and the hydroxyl position in attempt to see if bulkier substitutions on both of the positions instead of the hydrogen bond network would cause improved ee but this was not the case. In attempt to see if there is more significance to the reaction temperature on the ee, next set of experiments was temperature screening.

Table 9: Catalyst screening- Chlorination- Quinine analogs.

| Entry | Catalyst | %yield | %ee |
|-------|----------|--------|-----|
| 1 | | 100 | 24 |
| 2 | | 100 | 6 |

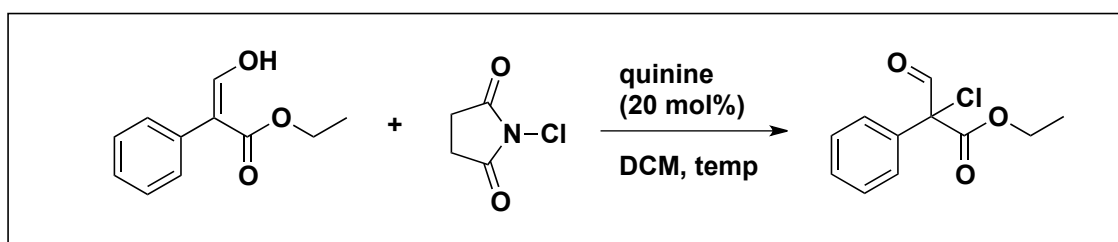
| Entry | Catalyst | %yield | %ee |
|-------|---|--------|-----|
| 3 |  | 100 | 9 |
| 4 |  | 100 | 19* |
| 5 |  | 100 | 15* |
| 6 |  | 100 | 10 |

| Entry | Catalyst | %yield | %ee |
|-------|---|--------|-----|
| 7 |  | 100 | 12 |
| 8 |  | 100 | 5 |
| 9 |  | 100 | 20 |

The next set of experiments was set to try and screen reaction temperature with quinine as the catalyst, DCM as the reaction solvent and NCS as the chlorinating agent (table 10). The temperatures that were screened were rt,

-20°C and -78°C. There was no significant difference between rt and -25°C with only slight increase in ee with lowering the reaction temperature. Lowering reaction temperature even lower than -20°C caused the opposite effect and lowered the ee to 13%, see entry 3. The decreased % ee at lower temperature was probably caused by slower activity of the catalyst at this low temperature and increases reaction background by NCS causing chlorinated product without the catalyst participation.

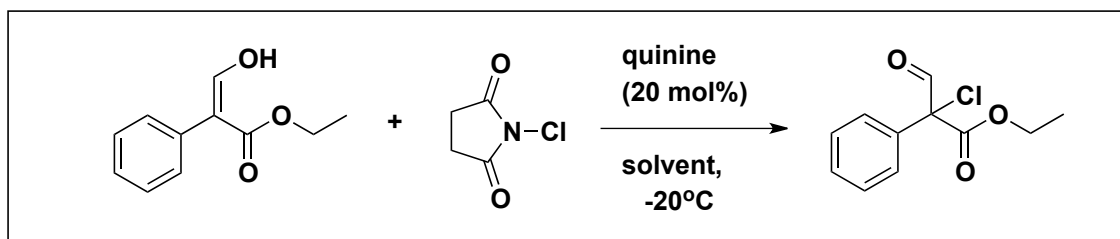
Table 10: Temperature screening- quinine NCS.



| Entry | Temperature °C | %yield | %ee |
|-------|----------------|--------|-----|
| 1 | rt | 100 | 20 |
| 2 | -20 | 100 | 24 |
| 3 | -78 | 90 | 13 |

Next step to improve the %ee of the reaction was solvent screening (table 11) changing the solvent from DCM to toluene had no significant effect on the reaction but slightly lowering the ee to 19% (entry 1,2) showing that lowering the solvent polarity has no significant effect on the reaction. Changing the solvent to highly polar solvent such as DMSO, entry 3 drastically lowered the ee to 5%. This result was not a surprise because the previous publications showed that the use of highly polar solvent in these type of reaction lowering the significantly and even bringing it to racemic mixture. Use of highly polar solvent disturbs the ion contact pair so there was another attempt to lower the solvent polarity event lower to promote the tight ion pair intermediate. Attempts to lower the solvent polarity even lower than toluene with 1:2 ratio of toluene: hexane did not increased the ee and therefore proven to be not a suitable system to this reaction and causing suspicion that there is some other type of reaction occurring.

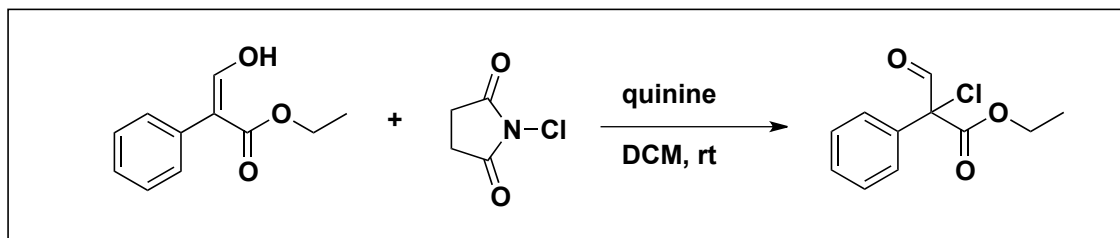
Table 11: Solvent screening- Quinine, chlorination.



| Entry | Solvent | %yield | %ee |
|-------|---------|--------|-----|
| 1 | DCM | 100 | 24 |

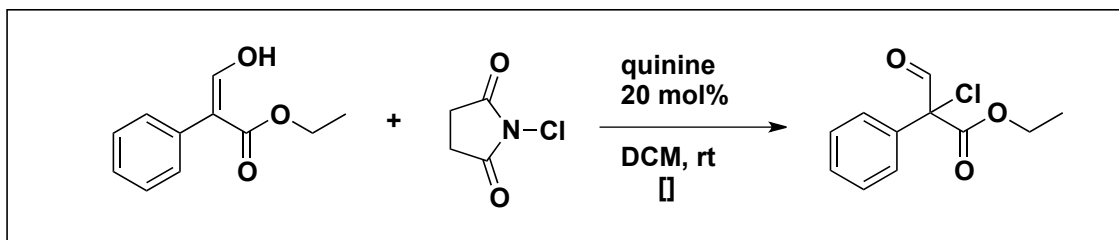
| Entry | Solvent | %yield | %ee |
|-------|------------------------|--------|-----|
| 2 | Toluene | 100 | 18 |
| 3 | DMSO | 100 | 5 |
| 4 | toluene: Hexane 1:2 | 100 | 8 |

Next step was to screen catalyst loading of the reaction with quinine as the catalyst, DCM as the reaction solvent, NCS as the chlorinating reagent and for the simplicity of operation the experiments were conducted under rt (table 12). All of the reactions were set at the same time for the period of 1 hour. Increasing the catalyst loading did show improved ee but not significantly. Increasing the catalyst loading should have increased drastically the ee of the reaction but when it did not it raised the question of reaction kinetics, whether there is a tight binding between the catalyst and the acrylate. Addition of stoichiometric amounts of catalyst should have caused, in theory, 100% ee with slight % error. When the experimental results showed only 23% ee with 100% catalyst loading it was indication that there is no efficient catalyst binding with the substrate and the background chlorination reaction was taking over the reaction.

Table 12: Catalyst loading-Quinine, Chlorination.

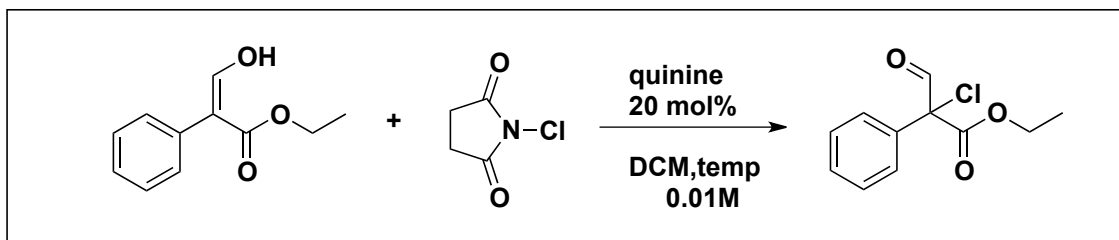
| Entry | Catalyst loading | %yield | %ee |
|-------|------------------|--------|-----|
| 1 | 20 mol% | 100 | 10 |
| 2 | 60 mol% | 100 | 26 |
| 3 | 100 mol% | 100 | 23 |

After the catalyst loading experiments, in order to try and slow down the kinetics of the reaction, concentration-screening experiments were set. The solvent was DCM, reaction temperature was set to rt, chlorinating agent as NCS and quinine as the catalyst with 20 mol% catalyst loading (table 13). These sets of experiments showed that there is some kinetics issues in the reaction and bringing the reaction at high dilution increased reaction ee to 16%, entry 4. This result was not drastic enough for the reaction optimizations, but combining high dilution with changing reaction temperature could be a promising lead.

Table 13: Reaction concentration- Chlorination.

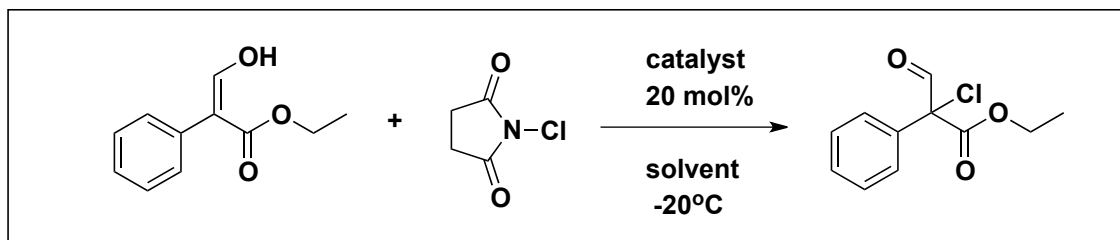
| Entry | Concentration | %yield | %ee |
|-------|---------------|--------|-----|
| 1 | 3.54M | 100 | 4 |
| 2 | 1M | 100 | 2 |
| 3 | 0.1M | 100 | 10 |
| 4 | 0.01M | 100 | 16 |

The next step was combining high dilution with changing reaction temperature with quinine as catalyst at 20 mol%, NCS as the chlorinating agent, DCM as reaction solvent with exception of higher temperature where toluene was chosen as the solvent (table 14). As in previous results at -78°C there was slightly lower ee than at -20°C and heating the reaction gave results of racemic mixture, entry 3.

Table 14: High dilution Temperature screening-chlorination.

| Entry | Temperature °C | %yield | %ee |
|-------|----------------|--------|---------|
| 1 | -78 | 100 | 13 |
| 2 | -20 | 100 | 16 |
| 3 | 50 | 100 | racemic |

Because previous attempts to increase the %ee of the reaction with quinine as the catalysts were not yielding positive results, a new type of organocatalysts were screened for the chlorination reaction (table 15). Organocatalysts that were chosen were based on existing tertiary amine, entry 1,2 as well as chiral BINOL-derived phosphoric acid (entry 3). Screening different types of organocatalyst did not show any improvement in the reaction results.

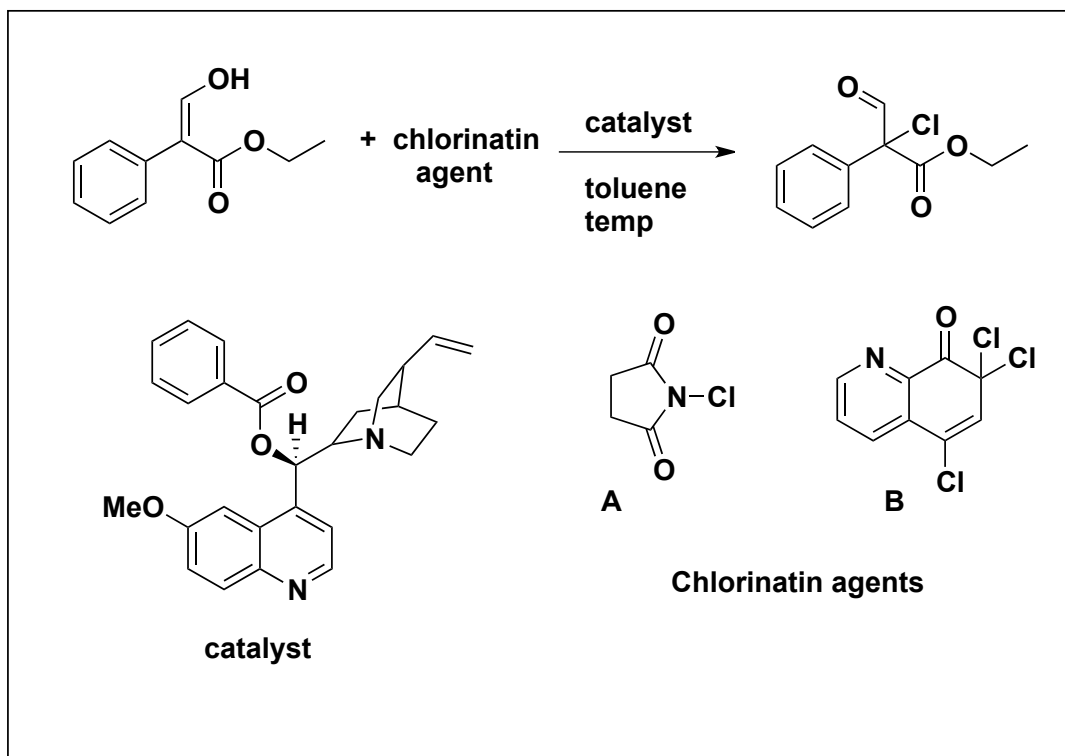
Table 15: Catalyst screening- chlorination.

| Entry | Catalyst | Solvent | %yield | %ee |
|-------|----------|---------|--------|---------|
| 1 | | Toluene | 100 | 2 |
| 2 | | DCM | 100 | 5 |
| 3 | | DCM | 100 | Racemic |

Based on Bartoli and Melchiorre *et. al* work , scheme 18, that had very impressive yields and ee, there was an attempt to replace the chlorination system. Chlorination reaction was done with toluene as the reaction solvent, and benzoylquinidine as a catalyst at 20 mol% (table 16). The first reaction that was done was with NCS as the chlorinating agent and at -20°C it had promising ee of

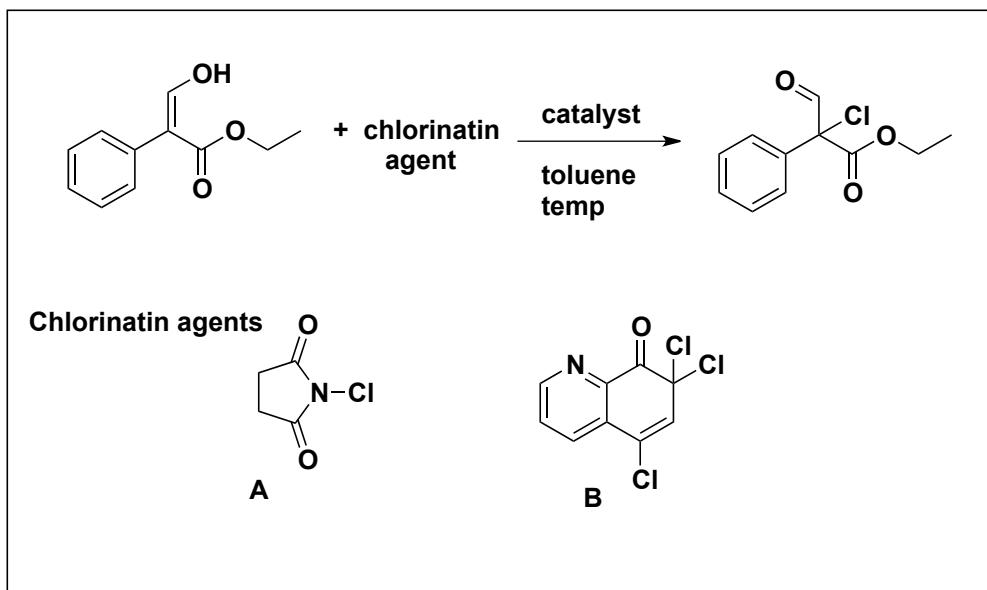
28%, that showing that maybe this catalyst works better with toluene as the the reaction solvent. Entry 2 shows the same reaction conditions but with milder chlorinating agent, the yield went down to 73% with ee that cannot justify this lower yield. Adding NaHCO₃ as additive in order to recycle the catalyst indeed improved the %yield to 100% and raised the %ee to 21%, entry 3. Attempts to use NCS as the chlorinating agent but lowering reaction temperature to -78°C in attempt to get higher results than in entry 1 did not yielded better ee.

Table 16: Chlorination based on Bartoli and Melchiorres work.

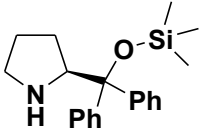


| | Chlorinating agent | Temp. °C | %yield | %ee |
|---|----------------------|----------|--------|-----|
| 1 | A | -25 | 100 | 28 |
| 2 | B | -25 | 73 | 15 |
| 3 | B NaHCO ₃ | -25 | 100 | 21 |
| 4 | A | -78 | 100 | 19 |

After getting improved ee with different catalyst and toluene as the reaction solvent different catalysts were screened (table 17). After screening phase transfer catalyst with both of the chlorinating agents and no improved ee was shown, entries 1,2, repeating the reaction with proline analogs did not prove to be successful. It seemed to be that the NCS works by itself and even though the catalyst does have some effect on the reaction it is not effective and further investigation into the reaction mechanism and kinetics is required. The next step was to conduct DFT calculation on the catalyst binding with the acrylate.

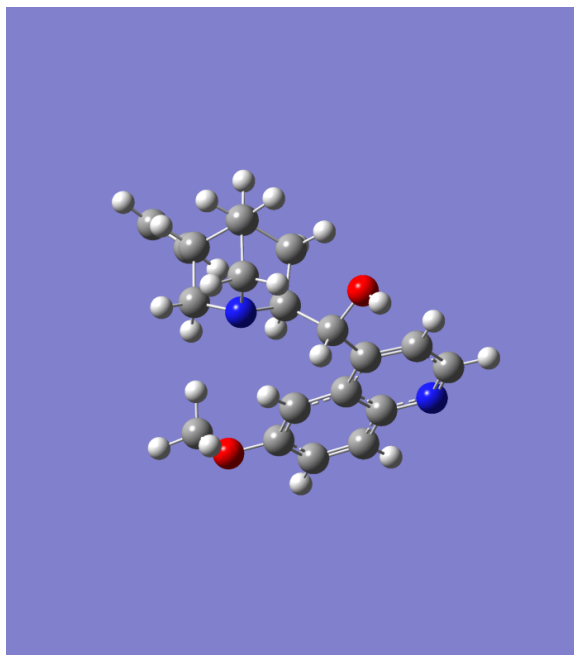
Table 17: Catalysts screening- Chlorination, toluene.

| Entry | Catalyst | Chlorinating agent | %yield | %ee |
|-------|------------------------------------|--------------------|--------|-----|
| 1 | K ₂ CO ₃ | A | 100 | 9 |
| 2 | K ₂ CO ₃ | B | 10 | 11 |

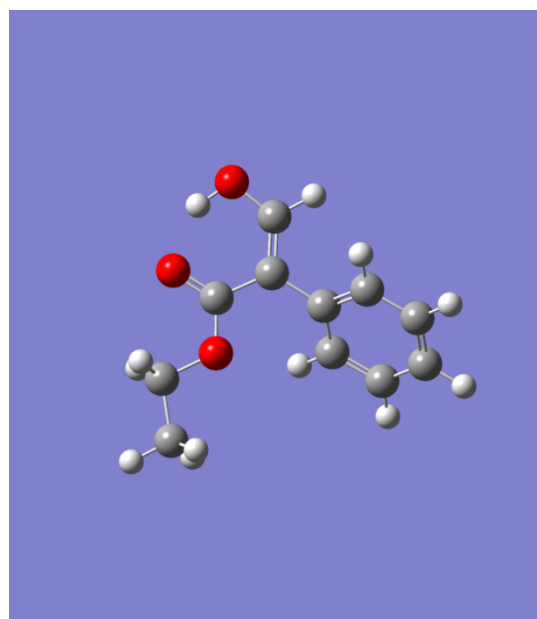
| Entry | Catalyst | Chlorinating agent | %yield | %ee |
|-------|---|--------------------|--------|-----|
| 3 |  | B | 7 | 12 |

2.3 DFT Calculations

DFT calculations were done on 7 catalysts with Gass View software All energy optimizations done with B3LYP, and the Pople style 6-311G+ (2df,2dp) basis set and a COSMO model for solvent DCM. All of the calculations have energy minimization and geometry optimizations by themselves and then energy optimizations and geometry optimizations all together, the catalyst and the substrate. All of the results do indicate that the overall energy of the reaction taken with the catalyst is lower than the individual energies themselves, a result that indicating that it is a favorable processes. The surprising result was that there was no dual binding, the carbonyl group was not binding to the hydroxyl and the bulky groups were far apart from the double bond and therefore there was no steric shielding, meaning there's no preference of one side over the other. One promising result was with anthracyn group at the hydroxyl position that did show some steric shielding of the double bond. The catalyst with the anthracyn group was not available commercially and there was no know procedure to synthesize it. The synthesis was done using the previous procedure of similar analogs, and had positive results.

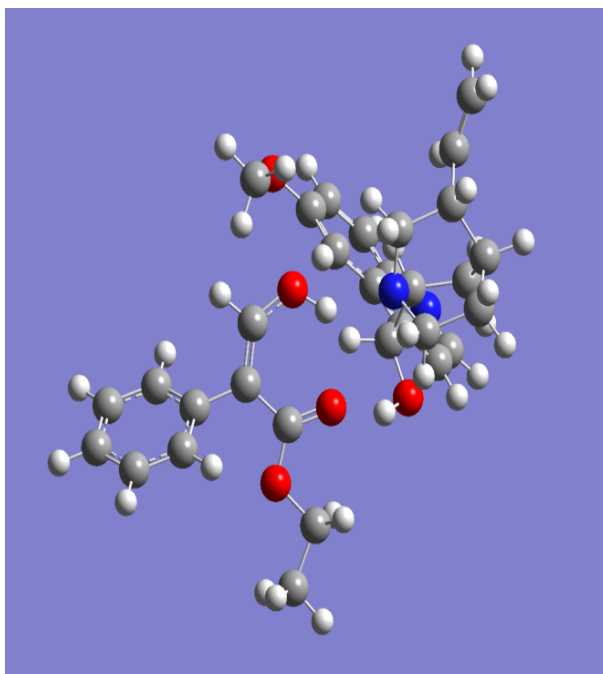


Quinine energy minimization:



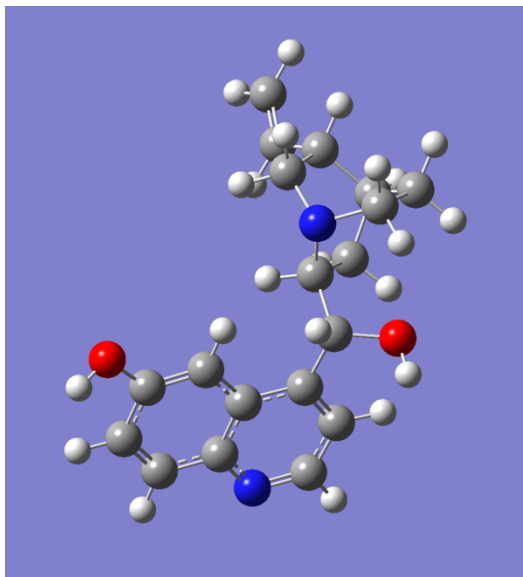
Acrylate energy minimization

Acrylate with quinine energy minimization:

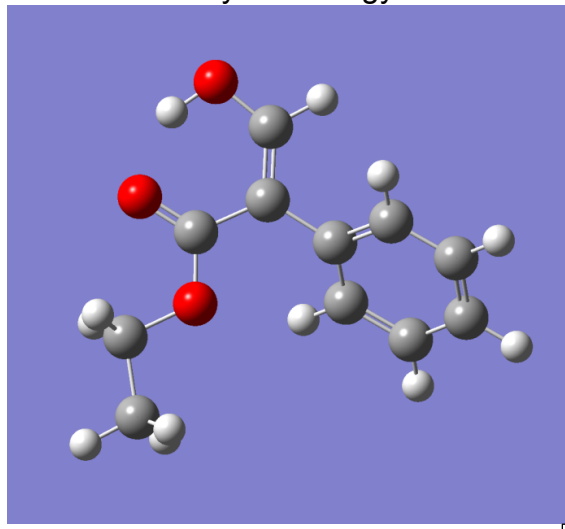


| | |
|-----------------------|---------------|
| | Energy (a.u.) |
| Quinine | -1036.4791 |
| Acrylate | -652.0752 |
| Total energy | -1688.5543 |
| Combined | -1688.5667 |
| Difference (a.u.) | 0.0124 |
| Difference (kcal/mol) | 7.7641 |

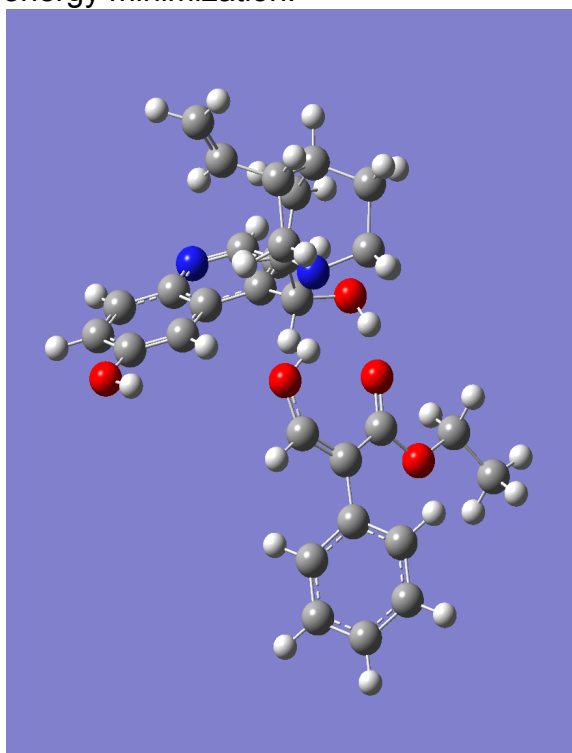
Quinine OH energy minimization:



Acrylate energy minimization:

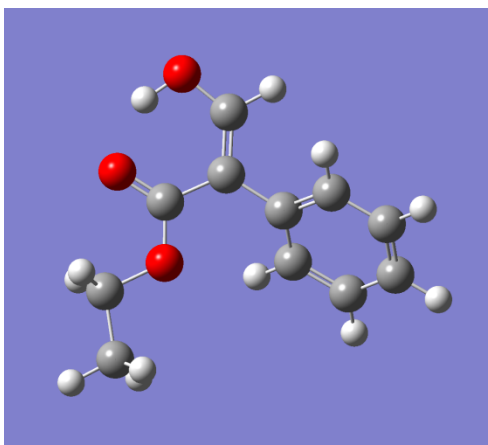


Acrylate with quinine hydroxyl energy minimization:

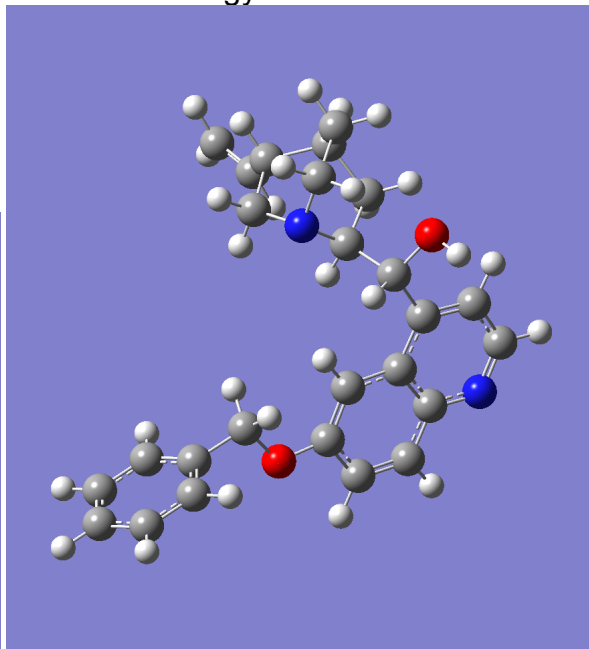


| | Energy (a.u.) |
|--------------------------|------------------|
| Quinine OH | -997.1708 |
| Acrylate | -652.0752 |
| | - |
| Total | 1649.2460 |
| | - |
| Combined | 1649.2598 |
| Difference (a.u.) | 0.0138 |
| Difference (kcal/mol) | 8.6643 |

Acrylate energy minimization:

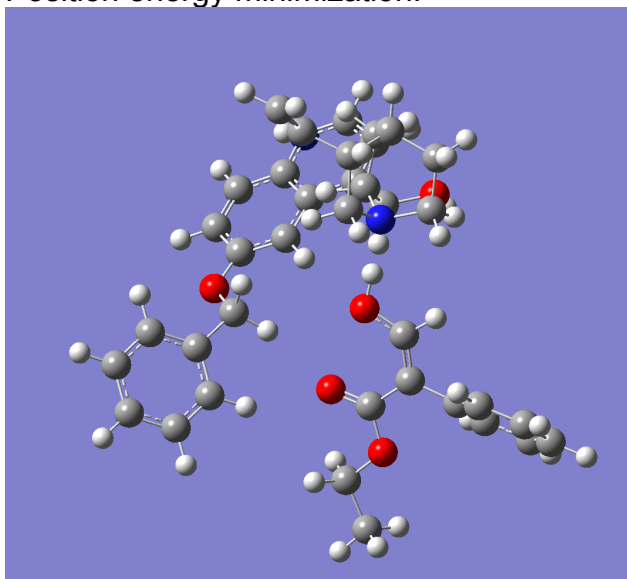


Quinine Benzyl at methoxy position
energy minimization



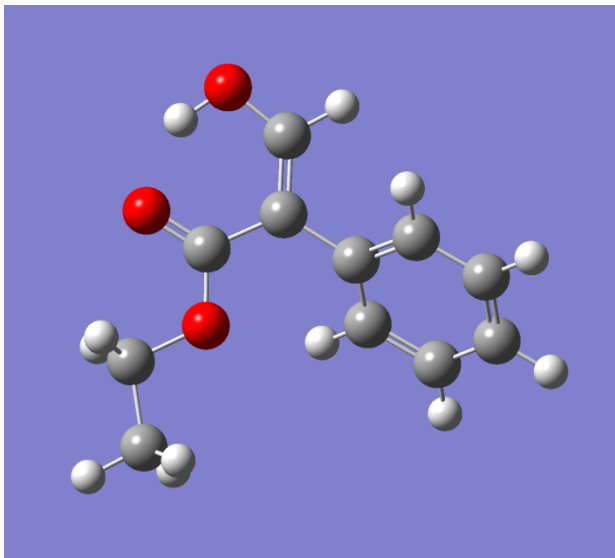
Acrylate with Quinine benzyl at methoxy

Position energy minimization:

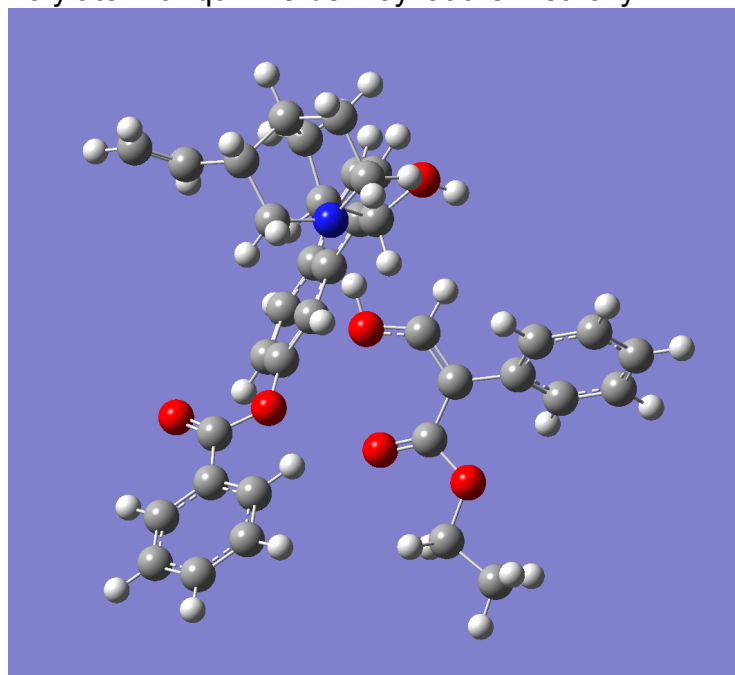


| | Energy (a.u) |
|--|-----------------|
| Quinine with Benzyl at OCH ₃ | -1267.177 |
| Acrylate | -652.0752 |
| Total energy | -1919.252 |
| Combined | -1919.1099 |
| Difference (a.u.) | 0.142 |
| Difference (kcal/mol) | 3.2788 |

Acrylate energy minimization:

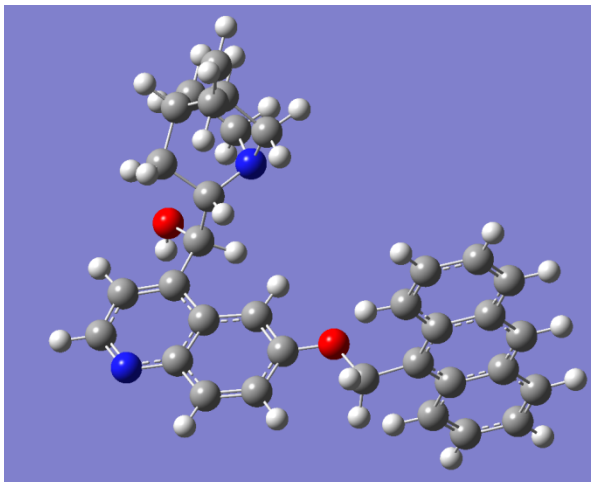


Acrylate with quinine benzoyl at the methoxy:

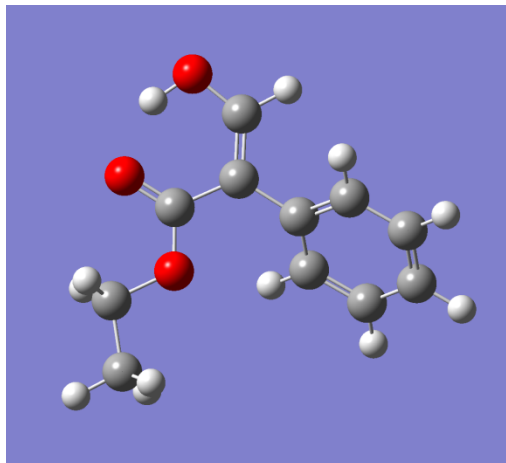


| | Energy (a.u) |
|---|-----------------|
| Quinine with Benzoyl at OCH ₃ | -1380.488 |
| Acrylate | -652.0752 |
| Total energy | -2032.563 |
| Combined | -2033.633 |
| Difference (a.u.) | 1.073 |
| Difference (kcal/mol) | 671.04 |

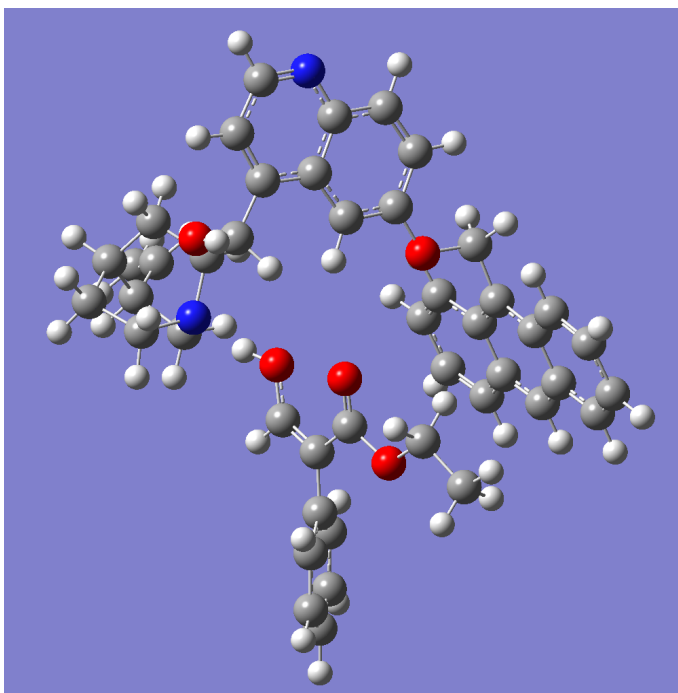
Quinine with anthracyn at OCH₃ position
energy minimization:



Acrylate energy minimization:

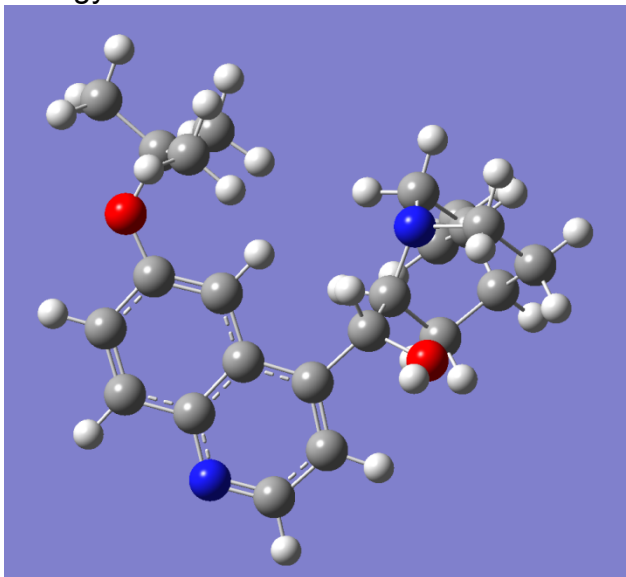


Acrylate and quinine with anthracyn at OCH₃
position combined energy minimization:

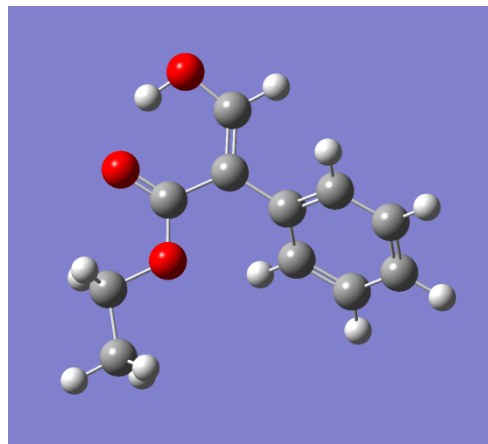


| | Energy (a.u) |
|--|-----------------|
| Quinine with anthracyn at OCH ₃ | -1574.349 |
| Acrylate | -652.0752 |
| Total energy | -2226.424 |
| Combined | -2226.281 |
| Difference (a.u.) | 0.143 |
| Difference (kcal/mol) | 3.294 |

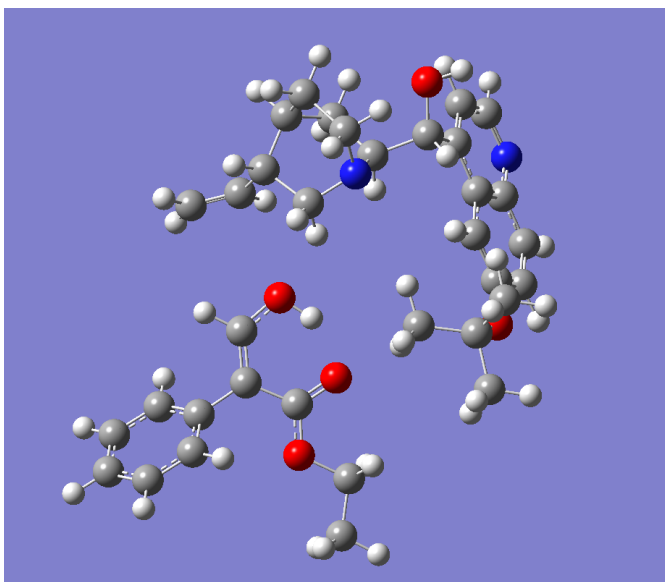
Quinine with t-Bu at OCH₃ position
energy minimization:



Acrylate energy minimization:

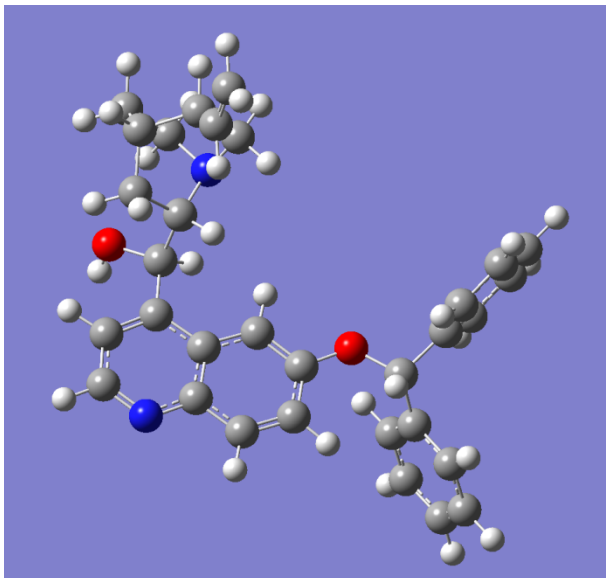


Acrylate with Quinine with t-Bu at OCH₃ position
energy minimization:

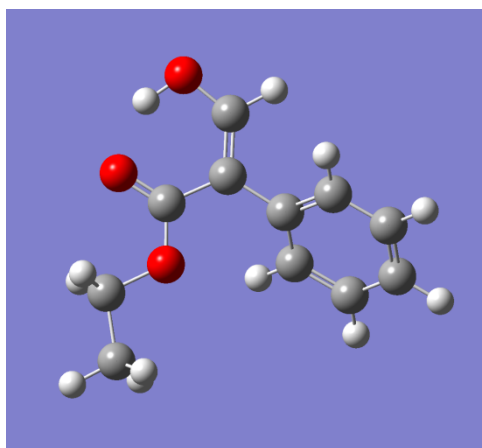


| | Energy (a.u) |
|--|-----------------|
| Quinine with t-Bu at OCH ₃ | -1154.093 |
| Acrylate | -652.0752 |
| Total energy | -1806.168 |
| Combined | -1806.008 |
| Difference (a.u.) | 0.008 |
| Difference (kcal/mol) | 0.18529 |

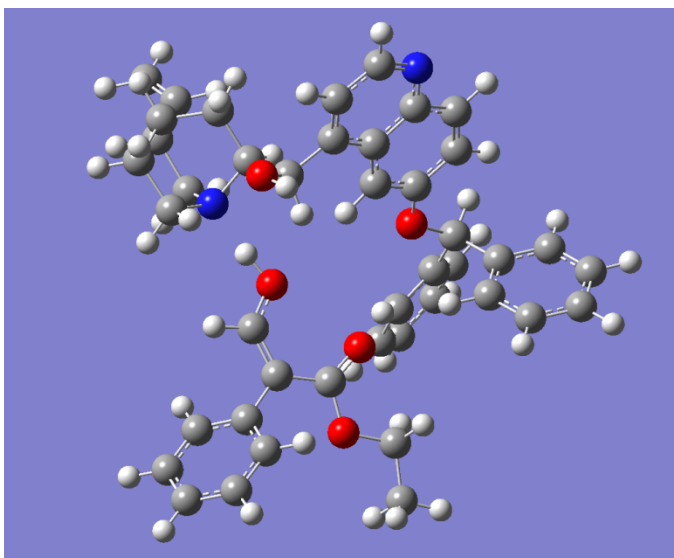
Quinine with diphenyl group at the position of
OCH₃ energy minimization:



Acrylate energy minimization:



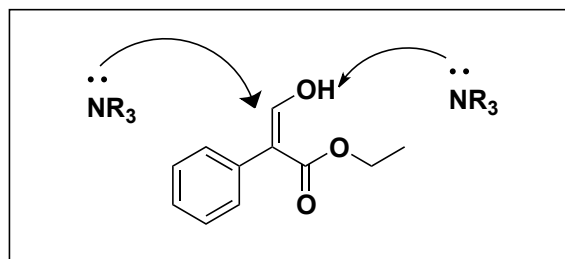
Acrylate with Quinine with diphenyl group at the
position of OCH₃ energy minimization:



| | Energy (a.u) |
|---|-----------------|
| Quinine with diphenyl at OCH ₃ | -1498.1499 |
| Acrylate | -652.0752 |
| Total energy | -2150.4103 |
| Combined | -2150.0815 |
| Difference (a.u.) | 0.329 |
| Difference (kcal/mol) | 7.578 |

In order to truly understand what is occurring in the reaction, several mechanistic studies were done. The first experiment was done to test where is the activation of the nucleophile occurs (scheme 30). The hypothesis was that the catalyst deprotonates the acrylate and there is formation of salt and there is

Scheme 30: Catalyst binding.

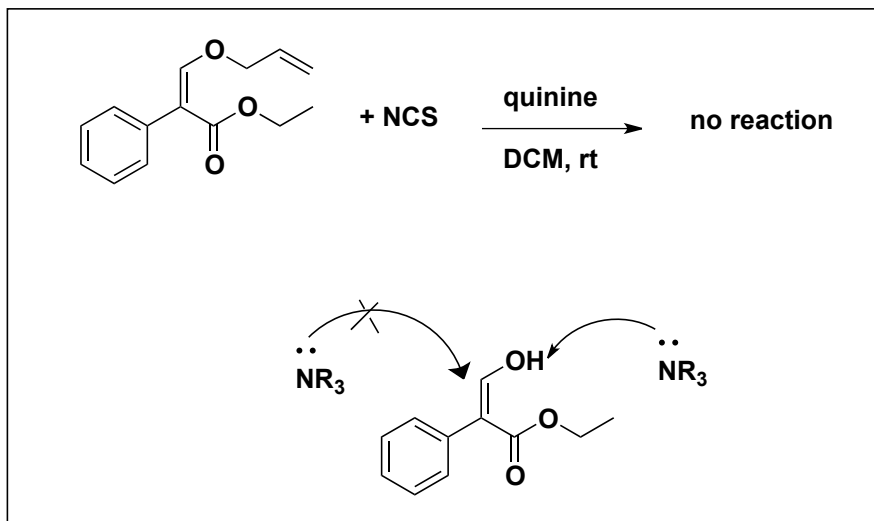


some hydrogen bonding to the carbonyl as predicted by the bifunctional catalyst mechanism. Another option is that the catalyst attacks the double bond itself and there is activation through the binding to the double bond. In order to prove one of the hypothesis, allylic group was attached to the oxygen and therefore protecting one side and chlorination reaction was done (scheme 31). There was no reaction at all, therefore the reaction has to occur through deprotonation of the acrylate.

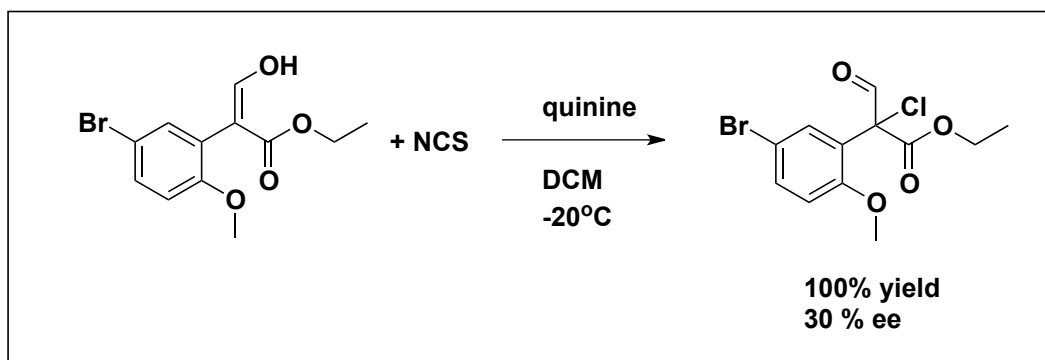
Another hypothesis was that the reason that there is no significant ee is because of rotation of the acrylate. In order to “freeze” the acrylate in one position, chlorination of disubstituted substrate was done. The substrate that was chosen was 2-OMe-5-Br disubstituted acrylate. The reaction was done under standard conditions with DCM as a solvent at -20°C with quinine as the catalyst

(equation 9) there was no significant change in ee indicating that there was no issue of rotation of acrylate.

Scheme 31: Catalyst binding experiment.



Equation 9: Chlorination of disubstituted acrylate.

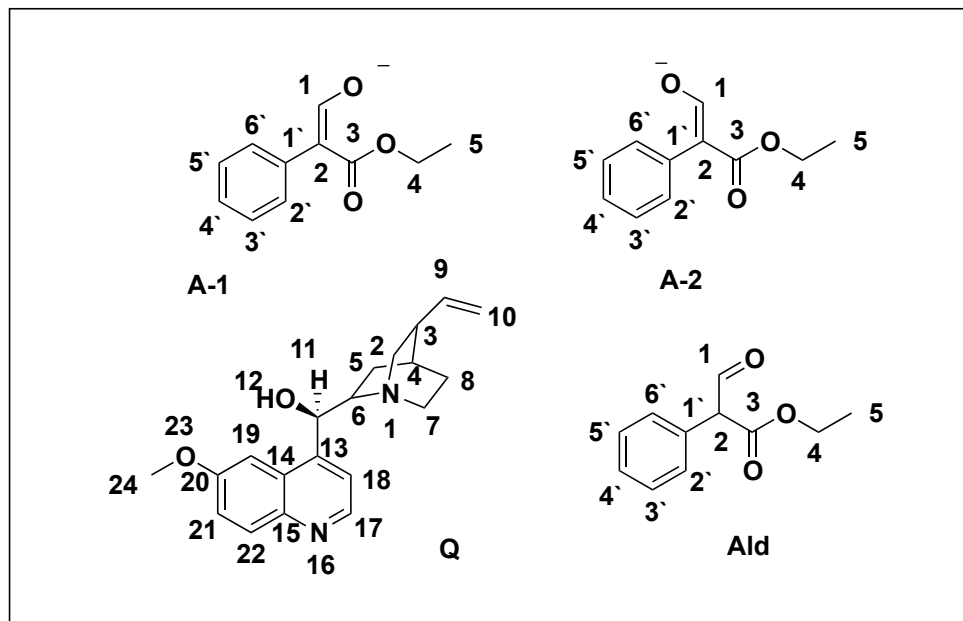


2.4 NMR Studies

The next stage of the investigation was to conduct NMR studies in order to inquire what is truly occurring in the reaction. The previous mechanistic studies

showed that in the transition state the catalyst with the substrate go through enolate form, so what is occurring in the solution when the acrylate form already present? Upon mixing the acrylate **A** with the quinine (Q) in a 1:1 ratio the proton spectra showed two major sets of signals that can be assigned to an acrylate species, a minor set of signals attributed to the aldehyde tautomer (**Ald**) and one set of signal from quinine (**Q**) (figure 24). Of the two acrylate species, one set of signals is virtually identical with free acrylate, with the exception of the signal from the OH hydrogen, which is not visible at room temperature, and a significant

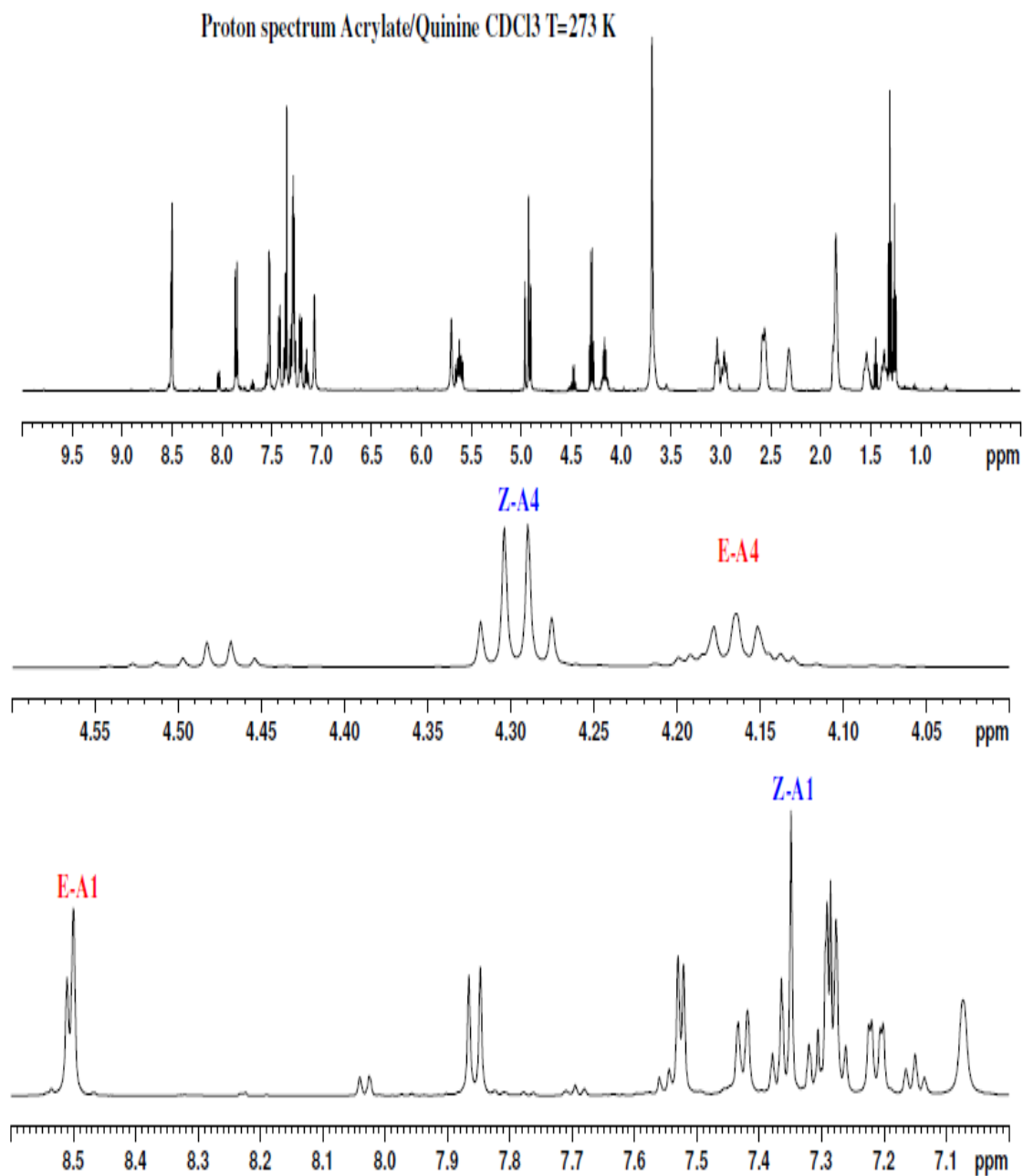
Figure 24: NMR assigned species.



broadening observed for the H-1 signal (**A-1**). The second set of acrylate signals (**A-2**) exhibits a signal for H-1 is shifted downfield to 8.41 ppm compared to 7.34

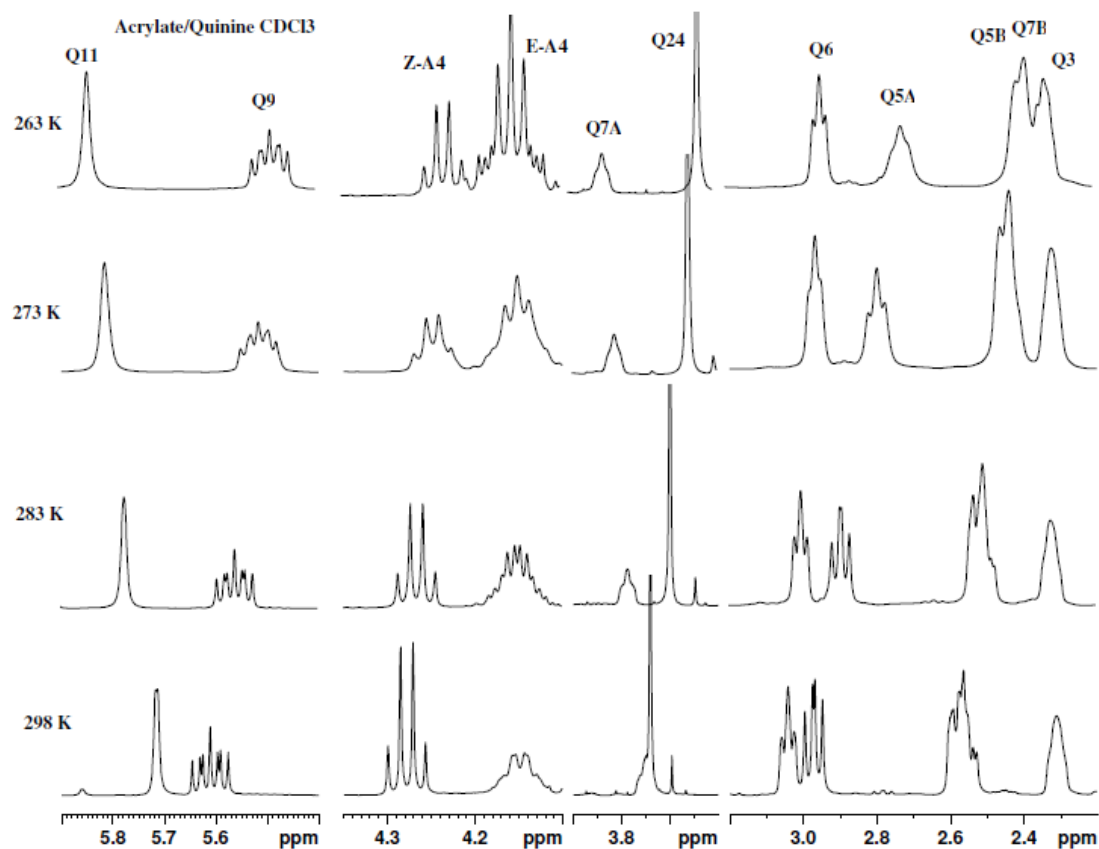
ppm observed for the equivalent proton in **A-1** (figure 25). Two dimensional $^1\text{H}\{^{13}\text{C}\}$ HSQC- and -HMBC experiments of both isomers were consistent with

Figure 25: Proton NMR spectra



the structure of the acrylate, with carbon chemical shifts 163.5 ppm and 163.0 respectively for C-1 and 108.6 and 107.8 ppm for C-2 in the two species. A NOESY spectrum at room temperature showed strong cross peaks arising from exchange between the two acrylate species and the minor aldehyde form that were particularly prominent for the H-1 signals due to their large chemical shift separation. NOESY spectra also exhibited NOE cross peaks between **A-2** and quinine, mainly between H-1 and H-2' in **A-2** with hydrogens near the OH group in **Q** and with its aromatic ring. Not a single cross peak between **A-1** and quinine was observed. It is tempting to explain the differences between **A-1** and **A-2** as free versus quinine bound acrylate. However a closer analysis of the relative signal integrals shows that the ratio of **A-2** : **Q** is non-stoichiometric, but only the sum (**A-1** + **A-2**) : **Q** as expected from the ratio at which the two components were mixed. Further experiments using either an excess of **A** or **Q** displayed a similar picture with only one set of signal present for **Q** but two sets for **A**. Chemical shifts of protons in **A-2** and **Q** exhibited a much larger dependence on concentration than did the ones in **A-1**. Studies at different temperatures (263 – 308K) showed a remarkable temperature dependence of the proton shifts for **A-2** and **Q** compared to **A-1** (figure 26). It appears that **A-2** is in fast exchange between an **A-2/Q** complex and the free form. Closer analysis of the NOESY spectra of the 3'-Bromo-4'Methoxy substituted acrylate (**2B4M-A**) both by itself and in mixture with **Q** revealed that H-1 NOE cross peaks between H-1/H-6' and H-1/H2' were only present in **2B4M-A-1** but not in **2B4M-A-2**, indicating that **A-2**

Figure 26: Temperature dependence NMR spectra.



exhibits *E*-configuration about the double bond instead of the *Z*-configuration observed for **A-1** (figure 27). This experiment was only possible with the substituted acrylate as in the unsubstituted version H-1 overlapped with H-2'/H-6'.

The NOESY data indicate that *Z*- to *E* isomerization of the acrylate takes place through the tautomeric aldehyde form **Ald** (figure 28). In the absence of

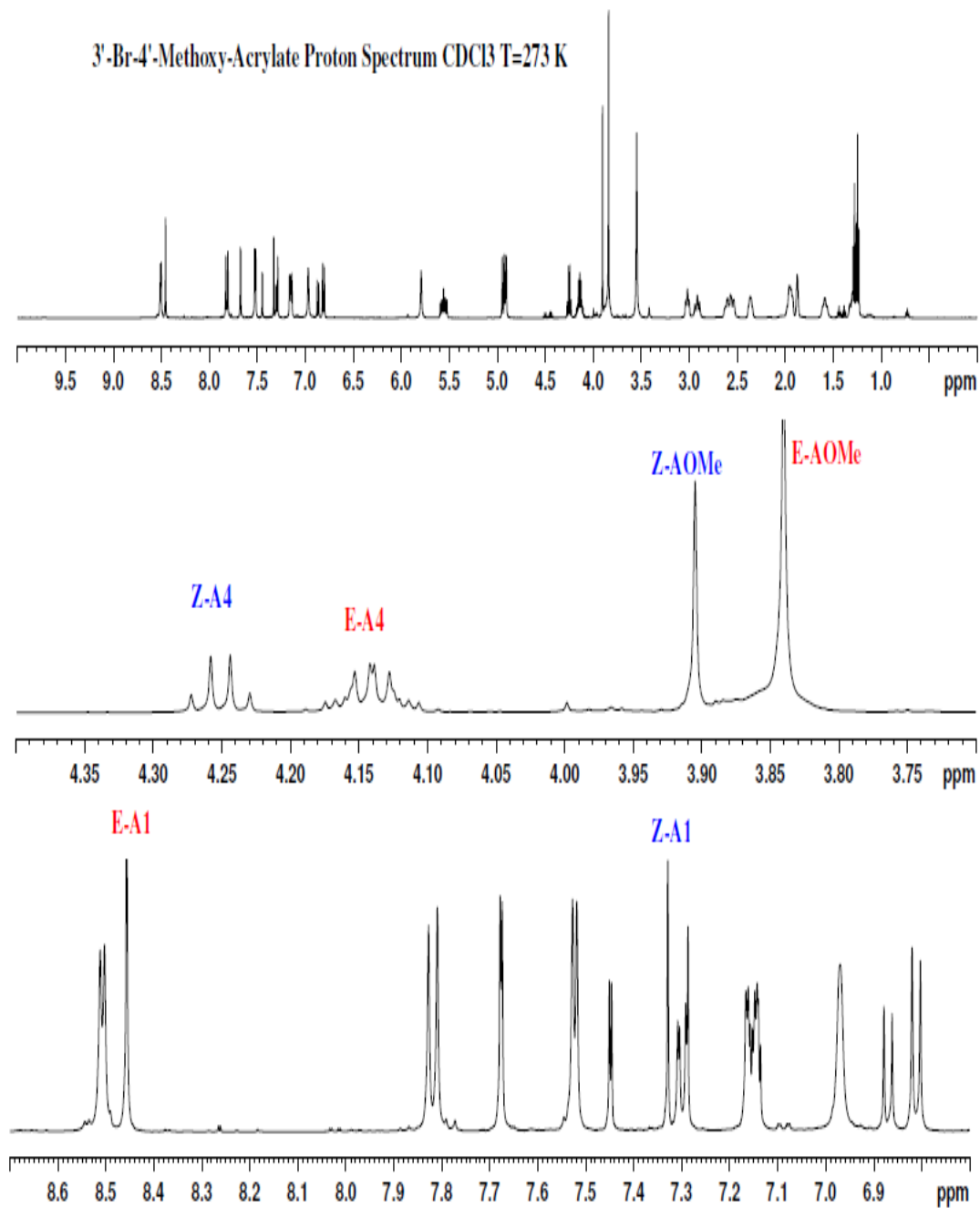
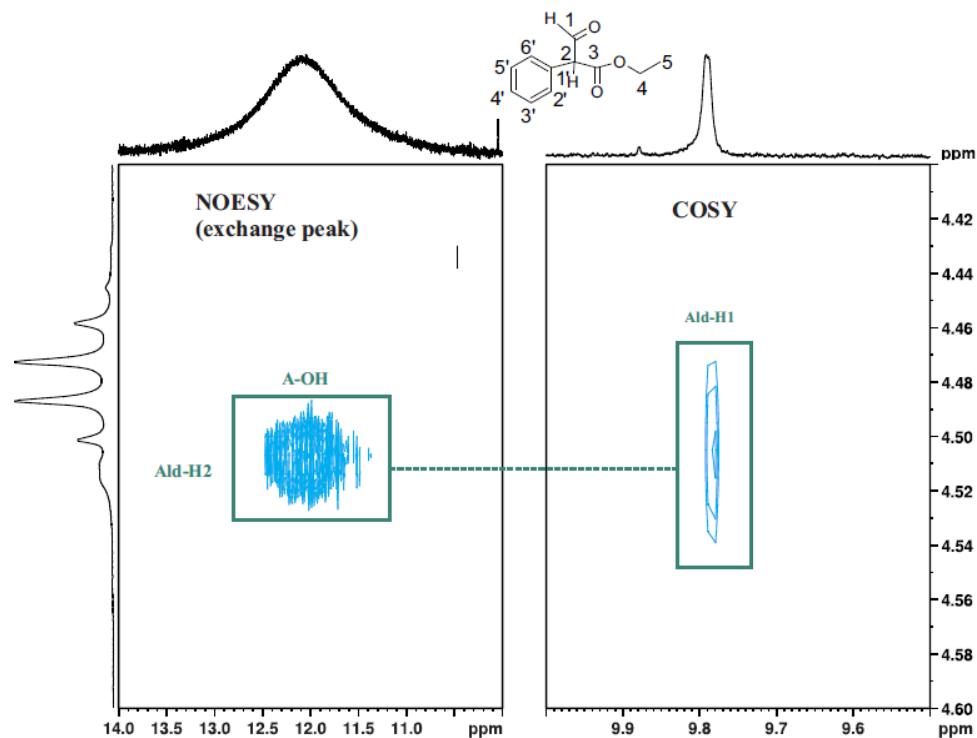
Figure 27: NMR spectra of 3Br, 4OMe substituted acrylate.

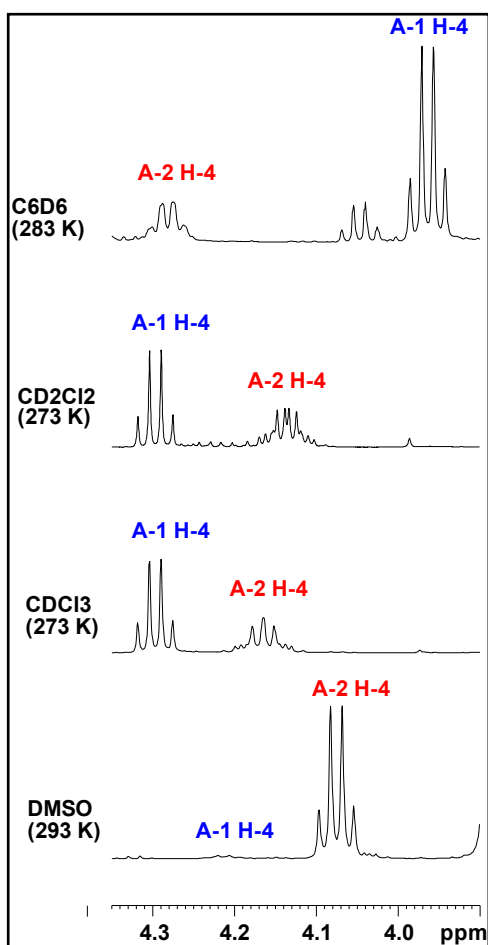
Figure 28: NMR spectra-aldehyde cross pick.



quinine this tautomer is present in small quantities, but no exchange between the two species is observed on the NMR time scale. Most likely the *enol* form of **A-1** is stabilized by the intramolecular OH \cdots O=C hydrogen bond. In the presence of a base like quinine the breakage of this hydrogen bond is catalyzed as evidenced by the disappearance of the OH proton signal in **A-1** after the addition of quinine and the presence of exchange between **A-1** peaks in the mixture. Free rotation about the C1-C2 single bond in **Ald** then results in formation of the *E*-acrylate isomer **A-2**. From the NOE data it becomes evident that only the *E* form **A-2** binds significantly with the quinine, resulting in an NMR spectrum that is an

average of free **A-2** and **A-2/Q** complex. The importance of weakening the *intermolecular* hydrogen bond is also evident when looking at the solvent dependence of the proton NMR spectra. Figure 29 shows the H-4 region of proton NMR spectra of **A/Q** mixtures taken in different solvents. For each solvent, assignment of peaks was done. There is a dependence between the

Figure 29: NMR spectra- solvent dependence.



Polarity of the solvent and the ratio of **A-2** : **A-1** (*E/Z*) (table 18). For apolar solvents like C₆D₆ the *Z*-form **A-1** dominates, while in very polar solvents like

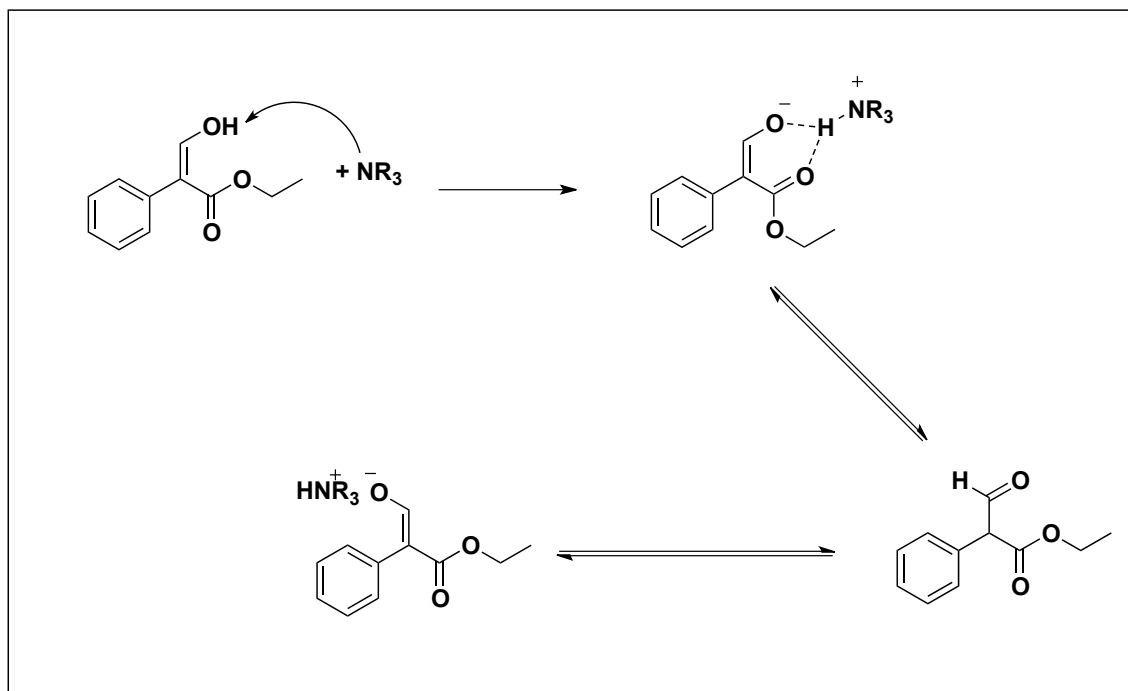
DMSO-d₆ the *E*-form **A-2** is prevalent. This behavior can be explained by the availability of *inter*-molecular hydrogen bonding in the polar solvents. Also the increased preference for the *E*- form **A-2** is consistent with better availability of *intra*-molecular hydrogen bonding at lower temperatures.

Table 18: Solvent dependence ratio.

| Solvent | T / K | A-2/A-1 |
|---------------------------------|-------|----------------|
| DMSO | 293 | 38.7 |
| CDCl ₃ | 273 | 2.35 |
| CD ₂ Cl ₂ | 273 | 1.16 |
| C ₆ D ₆ | 283 | 0.52 |

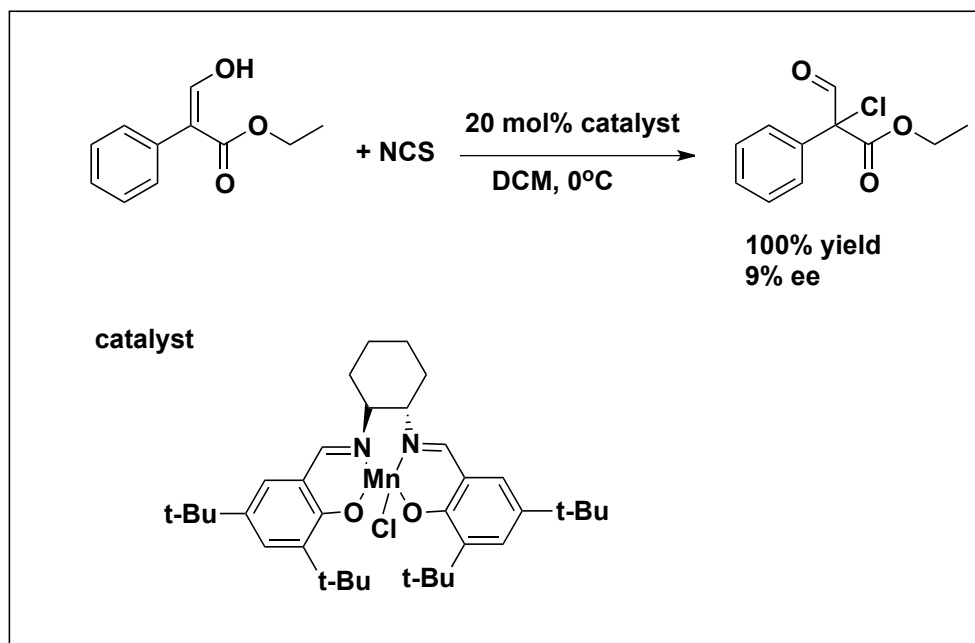
Based on these results explained why there is no significance in ee in the reaction and we came up with proposed reaction mechanism (figure 28). As soon as quinine is added to the solution it acts as a base not as catalyst in the reaction mixture therefore it deprotonates the acrylate and with fast exchange it converts from *Z* to *E* with fast exchanging equilibrium. Due to the presence of two isomers there is no possible way to achieve asymmetric induction. One of the ways to go around these results is with metal catalysis that will bind to the substrate and lock the intermediate in one conformation.

Figure 30: Proposed reaction mechanism based on NMR studies.

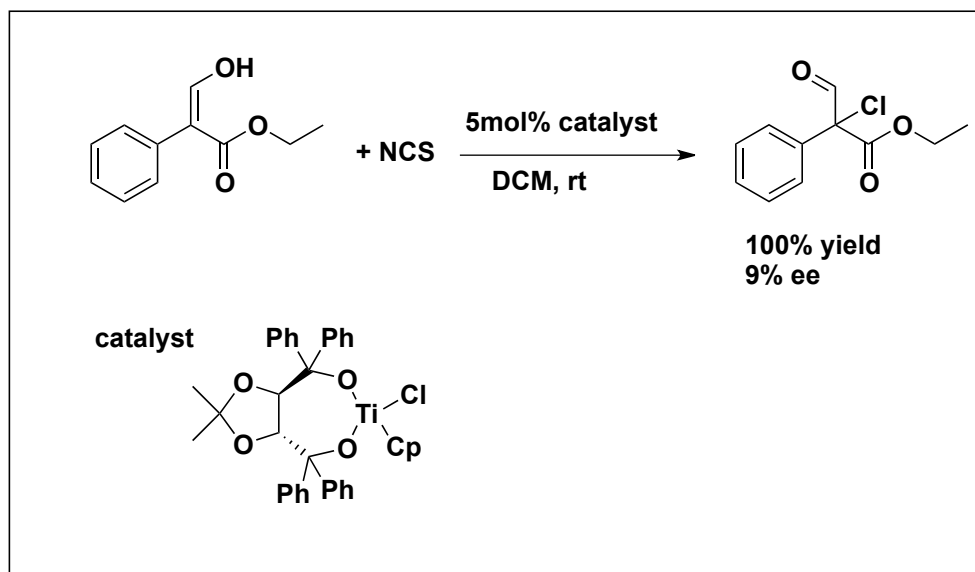


2.5 Metal Catalyzed Chlorination

Based on the NMR results the next assumption was that the catalyst needs to be bound to both the carbonyl oxygen and the enolic oxygen in order to prevent isomerization and therefore racemization. The first catalyst that was attempted was Salen catalyst with Mn as the metal (figure 29). Salen catalyst was chosen because of previous examples and the relative simplicity of use compared to other metal catalysts. The yield was 100% while the ee was only 9% proving that there was no efficient binding between the catalyst and the acrylate for sufficient asymmetric induction.

Figure 31: Mn Salen catalyzed chlorination reaction.

Next catalyst that was chosen was Ti catalyst like in example with Tongi. Ti is known to love oxygen and there were previous publications with similar system that showed efficient asymmetric α -chlorination through the enolic intermediate reaction. The first reaction was done with NCS as the chlorinating agent, DCM as the solvent and reaction temperature was rt with 5 mol% of catalyst loading (figure 30). In spite of previous publications with almost identical system this reaction was proved to have no significant ee (9% ee). The low ee was due to the fast non-catalyzed chlorination reaction that was faster than the actual catalyst binding with the starting material that was shown in the similar systems.

Figure 32: Ti catalyzed α -chlorination NCS.

The rate-determining step was the chlorination through the catalyst binding. In previous systems first the catalyst bonded to the substrate and went through conformation change to the bonded enolic form. The second step was chlorination of the catalyst and the chlorination of the substrate itself was done through the ligand and not the chlorinating agent in solution. Our system did not require to be bound to the catalyst with NCS as the chlorinating agent. The milder chlorinating agent showed promising results with low conversion by itself compared to NCS (figure 31).

Followed by the control reaction a milder chlorinating agent was chosen to slow down the reaction. The reaction time was 2 hours, chlorinating agent B was chosen for all of the reactions and all of the reactions were done in rt. The solvent of the reactions was varied between polar to non-polar (DCM, toluene,

1:2 mixture of toluene: hexane) (Table 19). Reaction with DCM as the solvent had only 28% yield (entry 1), a drastic drop from the usual chlorination 100 % yield that was done with NCS. This result was promising but showed that there was no asymmetric induction and the reaction was racemic. Changing the solvent to toluene with the same reaction conditions showed dramatic improvement in the reaction yield with slight increase in ee from racemic to ~6%ee (entry 2). Lowering even further reaction solvent to 1:2 toluene: hexane gave 58% yield with about 4% ee (entry 3).

Figure 33: Control reaction chlorination without a catalyst.

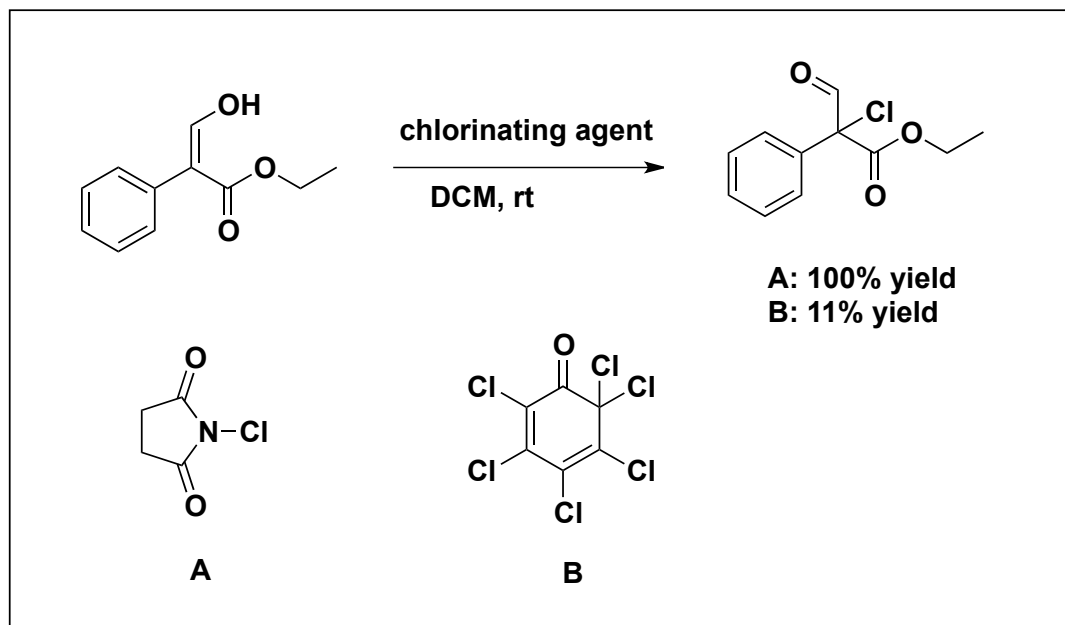
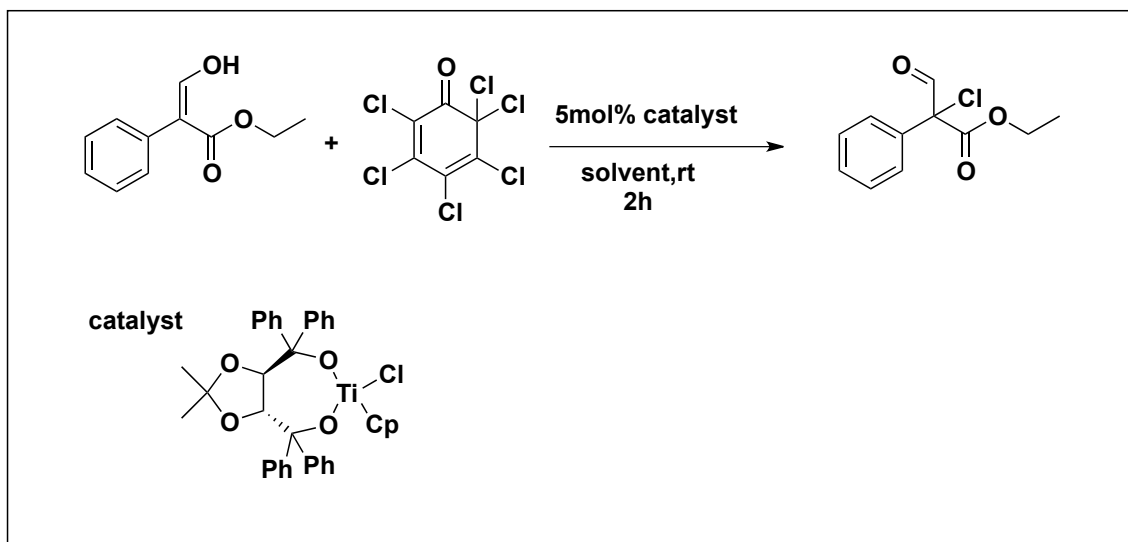


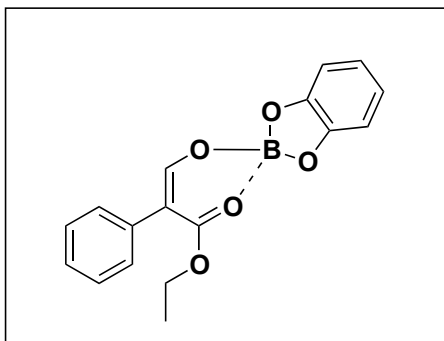
Table 19: Ti catalysed chlorination solvent screening.

| Entry | Solvent | %yield | %ee |
|-------|---------------------|--------|---------|
| 1 | DCM | 28 | racemic |
| 2 | Toluene | 74 | 6 |
| 3 | 1:2 Toluene: hexane | 58 | 4 |

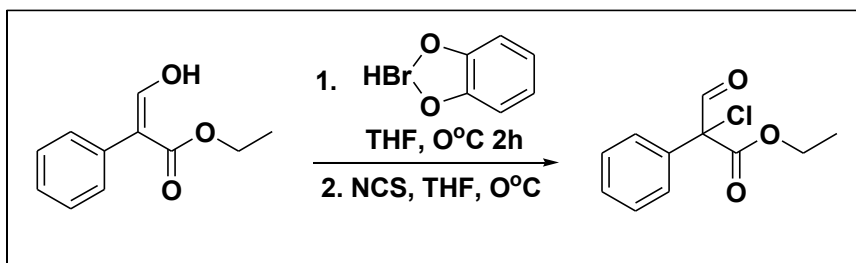
These results showed that Ti actually not binding to both the enol and the carbonyl oxygen and further investigation was needed to find a more suitable catalyst. From previous publication in Dr. Hossain group there was detailed investigation of borane compound binding with the acrylate system⁴⁴. It showed

that borane is successfully binding to the enol and the carbonyl and “locks” the acrylate in the Z confirmation (figure 34). The question was if the chlorination reaction would occur with this system or not?

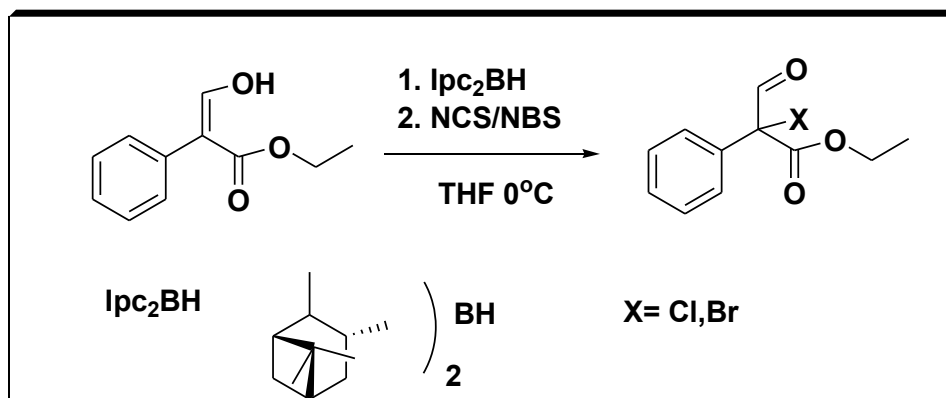
Figure 34: Borane binding to acrylate.



Camphor borane was used to set a test trial for the chlorination reaction (Equation 10). Camphor borane was used in 1.8 eq with the acrylate and let stir for 2 hours at 0°C in THF. With addition of camphor borane to the acrylate bubbles in the reaction were observed indicating binding the acrylate with the borane reagent. After 2 hours 1.1 eq of NCS was added. After 3 hours reaction mixture was passed through a plug. The solvent was removed under vacuum. Based on crude NMR there was only the starting material and the chlorinated product with 54% yield. This low yield proves the binding of camphor borane the enol and the carbonyl compound. It can be compared to 100% yield to chlorinated product without the borane with NCS -20°C in DCM.

Equation 10: Chlorination with camphor borane.

Following the promising results with the racemic borane reagent, chiral borane reagent was synthesized (Ipc_2BH) and chiral reaction was screened. The first reaction was under the same conditions as the racemic and after 3 hours there was no reaction. Increasing reaction time to 24 hours increased % conversion to 10% Scheme 32. Followed by these results more active

Scheme 32: Chlorination with chiral borane reagent.

halogenating agent was used, NBS. After 3 days there was only 43% conversion. The % ee for this reaction was 4 % ee. Based on these results there was no further investigation with this type of chiral auxiliary reagent.

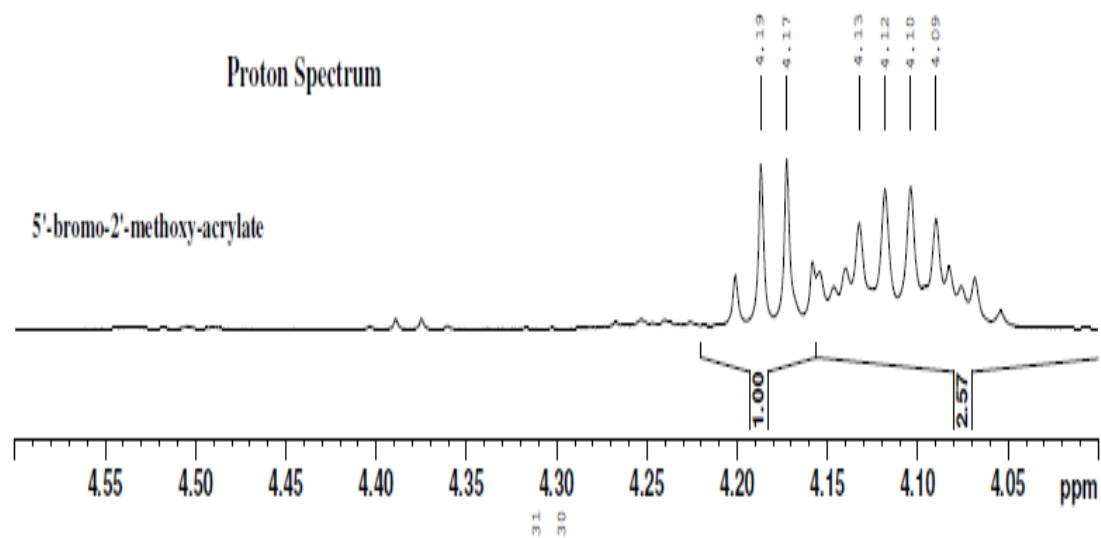
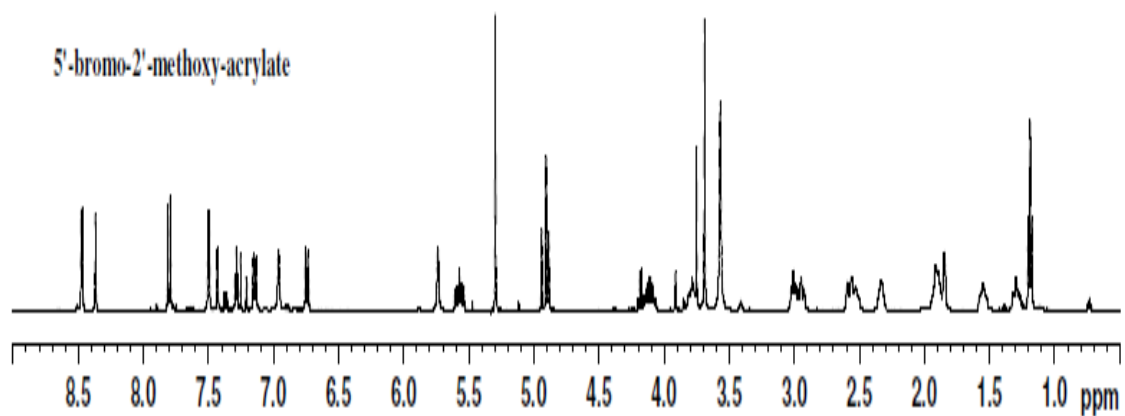
The conclusion from this set of experiments was that only one isomer is not enough but sufficient chiral environment is necessary for this reaction. Further NMR studies were done in order to investigate whether addition of bulky groups on the phenyl ring will cause steric hinders to promote only one isomer and chiral bifunctional catalyst will supply sufficient enough chiral environment.

2.6 NMR studies with substituted acrylate

Now that we came upon realizing that there is two isomers in the system and screening many catalysts was very time consuming we attempted to try the other approach and work with substituted acrylates. Working with disubstituted acrylate may cause steric hinders and lock one isomer. According to the previous results the unsubstituted acrylate favors the E conformation and adding two bulky groups around the 2 and 6 position may cause the Z isomer to be more favored. The first NMR study was done on the previous system that gave 30% ee. The 5-Br, 2-OMe substituted acrylate has methoxy group at the 2 position that should have caused some repulsion of the oxygen and causing the Z isomer to be favored. Based on the NMR results the E isomer was still favored in a E/Z of 2.57

ratio (figure 35). These results can be explained based on the rotation around the single bond and positioning of the methoxy group away from the enolic oxygen.

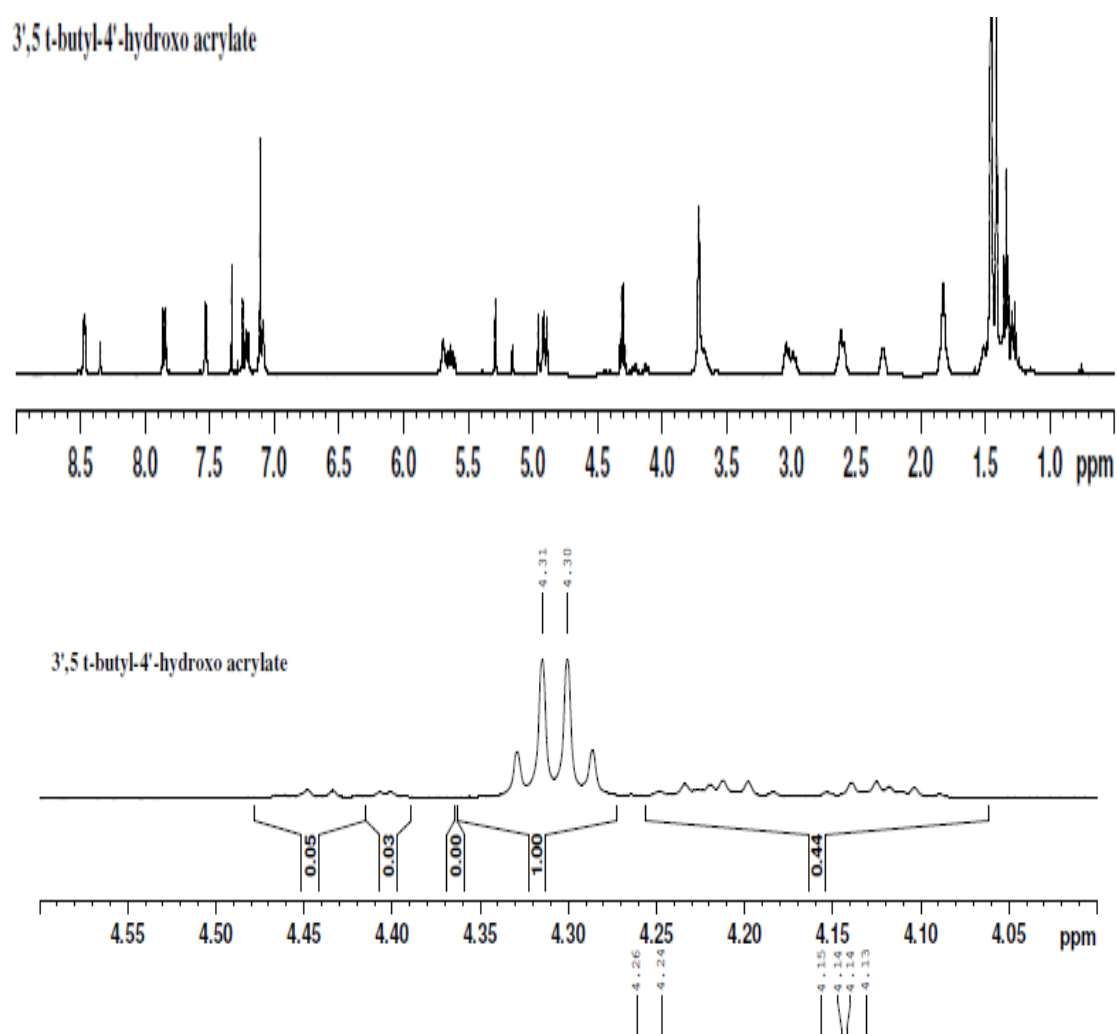
Figure 35: NMR results 5-Br, 2-OMe substituted acrylate proton spectra.



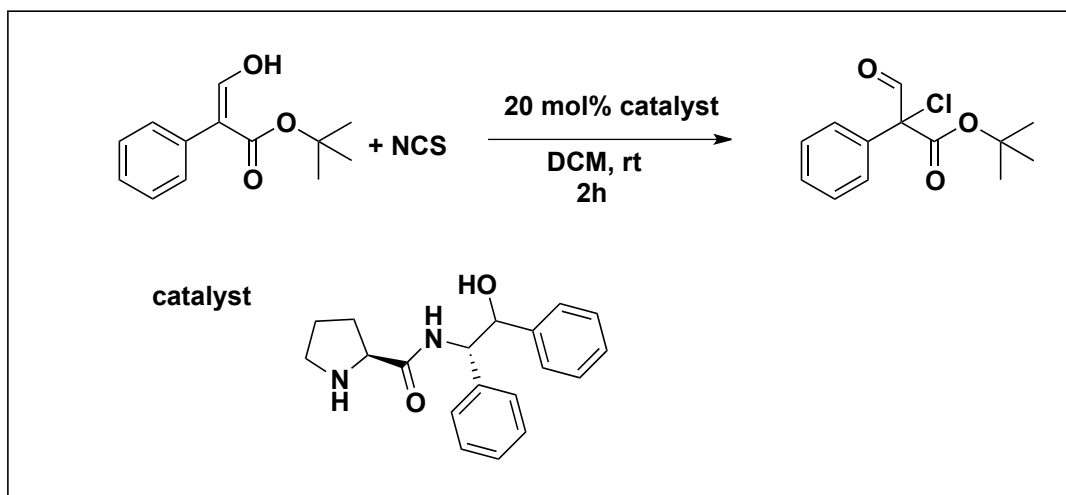
Based on the previous results the conclusion that was derived is that in order to prevent rotation for accurate results symmetrical starting material with

bulky groups should be considered. The next starting material that was chosen was 3,5-t-Bu,-4-OH acrylate. The first preference was to choose substituted substrate at the 2, 6 position but it was not commercially available. As predicted the Z isomer was favored over the E isomer in a E/Z of 2.27 ratio (figure 36). This ratio was not satisfying and further investigation into the substrate itself was done.

Figure 36: NMR results 3,5 t-Bu, 4-OH substituted acrylate proton spectra.



Following the NMR studies next experiment that was set is altering the ester group of the acrylate itself. If the ethyl group can be altered to a bulkier group, such as t-butyl group, will that cause the complete preference of the E isomer versus the Z isomer? In order to study this hypothesis acrylate with t-butyl needed to be made. *tert*-Butyl diazoacetate was purchased from Sigma-Aldrich and acrylate with t-Butyl group was synthesized according to the standard acrylate procedure previously published. The racemic sample was done with NCS as the chlorinating agent; DCM as reaction solvent and reaction was done at rt. Reaction time was significantly longer than previously. It took 3 days to achieve 70 % conversion. Next asymmetric reaction was attempted with NCS as the chlorinating agent, DCM as reaction solvent, rt. The catalyst was chosen based on the best results that were previously achieved in the halogenating reaction (scheme 33). Reaction temperature was at room temperature. Asymmetric reaction yielded only 16% ee. This result can be explained by the fact that t-butyl group is further away from the prochiral center. There can be further attempt to combine both disubstituted acrylate and further altering of the ester group in order to achieve asymmetric induction. Further investigation into different catalysts may be required as well, but at the current time, with the difficulty of synthesizing the starting material, and disappointing results, of only 16% ee (see appendix A), there was no further investigation into this reaction.

Scheme 33: Chlorination of *tert*-Butyl substituted acrylate.

3. Conclusion

In conclusion, this is the first example of halogenation of acrylate system and mechanistic investigation. There are current many examples of asymmetric halogenation of aldehydes and ketones but never of acrylate even though many of the mechanism propose going through the enolate form. It was discovered that in the presence of quinine the acrylate is being deprotonated and two major forms are formed, E and Z, this fact prevents asymmetric induction. Attempts to find a catalyst that locks the acrylate in one isomer were done but further investigation is still needed in order to achieve efficient asymmetric halogenation and creation of “universal nucleophile”. There may be needed combination of both metal catalysis with organocatalysis to create sufficient enantioselectivity.

4. Experimental

4.1 General considerations

All of the reactions unless specified were done in open air without special drying of the glass flasks and solvents. Column chromatography was performed with silica gel (40-140 mesh). HPLC grade solvents were purchased from VWR. All of the halogenating reagents, catalysts, and Ethyl diazoacetate were purchased from Sigma- Aldrich.

All organometallic operations were performed under dry Ar atmosphere with standard Schlenk techniques. All of the glass were dried and filled in a glove box.

All ^1H (300 MHz), ^{13}C NMR (75.5 MHz) were performed with a Bruker 300 MHz NMR system and samples were dissolved in deuterated solvents. NMR investigations were done with a Bruker 500 MHz NMR system. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and CDCl_3 was used as the solvent. % yield was calculated by crude ^1H NMR. Chiral HPLC was performed in room temperature utilizing Regis chiral peck column and Regis chiral (s,s) Whelk-O-1 column. Bromination %ee was calculated using 1.5mL/min 5%EtOH/95%Hexane mixture. Chlorination % ee was calculated using 1mL/min 99.9%Hexane/0.01%IPA mixture.

4.2 α – Bromination: General Procedure

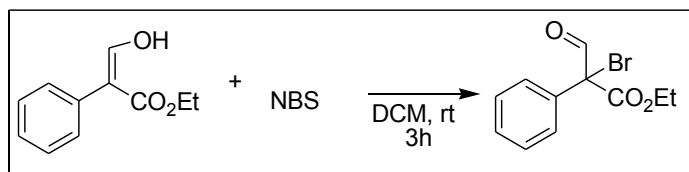
For each experiment, 0.5-5.0 mmol of the acrylate was dissolved in 5 mL of dichloromethane. A 0.2-equivalent of catalyst was added to the reaction

mixture and was stirred for 20 minutes. A 1.1-equivalent of brominating agent was added to the mixture. The reaction mixture was allowed to stir for 1 hour. After 1 hour small fraction of the mixture was passed through a silica plug and the solvent removed under vacuum. Crude ^1H NMR was taken to evaluate % yield. To the rest of the mixture 1.5 mL of methanol was added and reaction mixture was brought to pH 4 with slow addition of HCl followed by addition of a 1.2- equivalent NaCNBH_3 . After 3 hours reaction was quenched with saturated NH_4Cl solution and extracted 3*10 mL of dichloromethane and dried over Na_2SO_4 . Product was isolated by column chromatography (10% ethyl acetate in hexane) and identified by ^1H NMR. % ee was calculated using HPLC 1.5 mL/min 5%EtOH/ 95% Hexane.

4.2.1 Synthesis of ethyl 2-bromo-2-formyl-2-phenylacetate

Ethyl 2-bromo-2-formyl-2-phenylacetate had 99% yield from 0.5 g (2.604mmol) of acrylate, 0.51g (2.865 mmol) of NBS 3 mL dichloromethane at rt. ^1H NMR (CDCl_3 , 300 MHz): δ 9.65 (s,1H), 7.5-7.4 (m, 5H), 4.35 (q, 2H), 1.35 (t 3H).

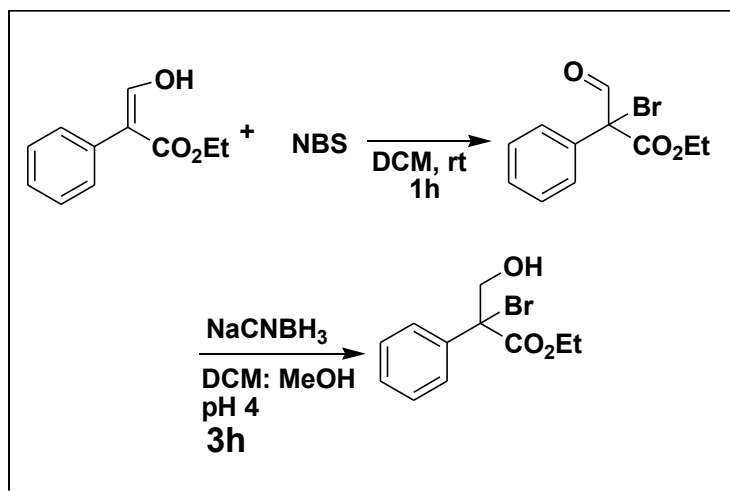
Equation 11: Racemic bromination of acrylate.



4.2.2 Synthesis of ethyl 2-bromo -3- hydroxyl-2-phenylpropanoate

Ethyl 2-bromo -3- hydroxyl-2-phenylpropanoate was isolated with 52% yield from 1 g (5.21 mmol) of acrylate, 1.02 g (5.73 mmol) of NBS, in 10 mL of dichloromethane (100% yield to aldehyde) followed by addition of 3 mL of Methanol and bringing the mixture to pH4, with addition of .393 (6.252 mmol) NaCNBH₃. ¹H NMR (CDCl₃, 300 MHZ): δ 7.54(d,2H), 7.41-7.34 (m, 3H), 4.36 (q, 2H), 4.199 (d, 2H), 3.1 (s, 1H), 1.32 (t, 3H).

Equation 12: Racemic bromination of acrylate and Reduction.

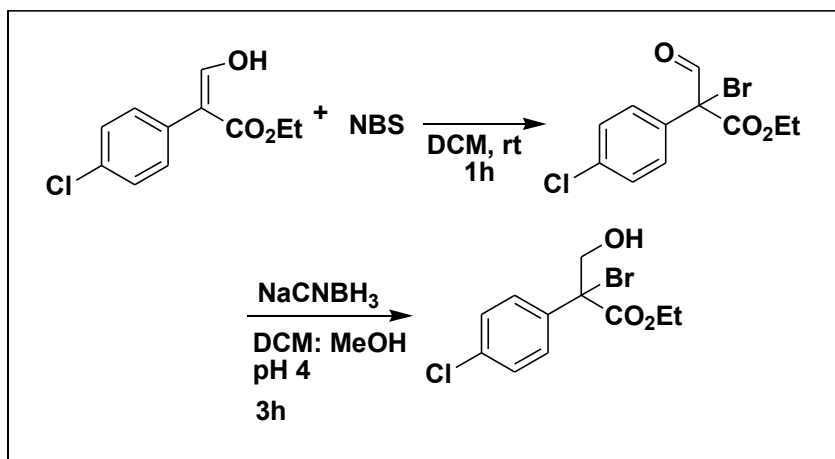


4.2.3 Synthesis of ethyl 2-bromo-2-(4- chlorophenyl)-3-hydroxypropanoate:

Ethyl 2-bromo-2-(4- chlorophenyl)-3-hydroxypropanoate was isolated with 41% yield from 0.18g (0.794 mmol) of acrylate, 0.1555g (0.875 mmol) of NBS, in 5 mL dichloromethane, (100% yield to aldehyde) 1.5 mL methanol, and 59mg

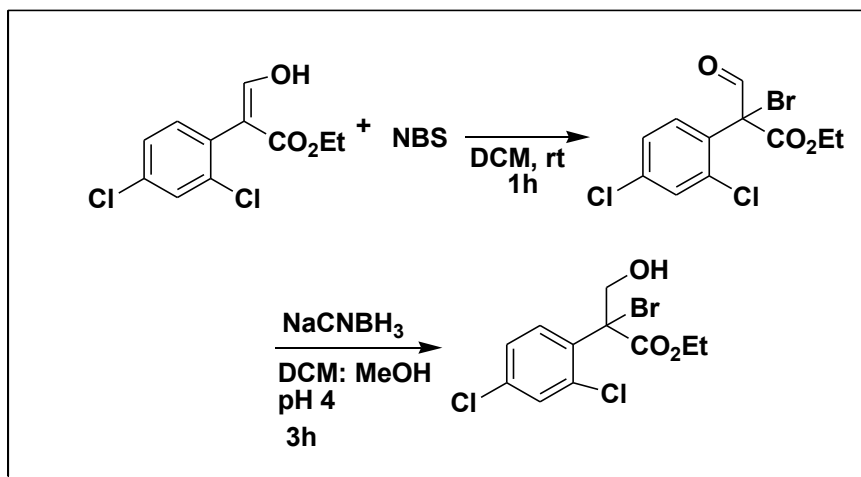
(0.9528 mmol) of NaCNBH_3 . $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.50(d,2H), 7.40 (d, 2H), 4.38 (q, 2H), 4.2 (q, 2H), 3.1 (s, 1H), 1.32 (t, 3H).

Equation 13: Racemic brominated and reduced 4- chloro acrylate.

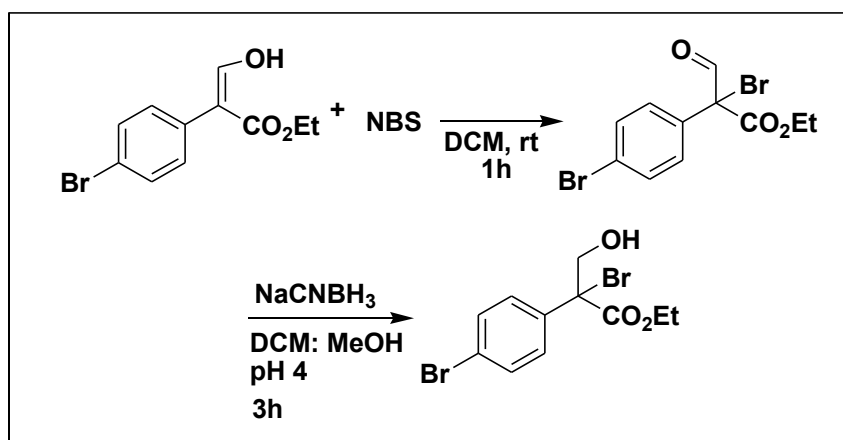


4.2.4 Synthesis of ethyl 2-bromo-2-(2,4-dichlorophenyl)-3-hydroxypropanoate

Ethyl 2-bromo-2-(2,4-dichlorophenyl)-3-hydroxypropanoate was isolated in 83% yield from 0.221g (0.845 mmol) of acrylate, 0.16g (0.9311 mmol) of NBS, 5 mL of dichloromethane (100% yield to aldehyde), 1.5 mL methanol and 69mg (1.1 mmol) of NaCNBH_3 . $^1\text{H NMR}$ of the aldehyde (CDCl_3 , 300 MHz): δ 9.99 (s,1H) 7.80(d,1H), 7.45 (s, 1H), 7.35 (d, 1H) 4.35 (q, 2H), 1.32 (t, 3H).

Equation 14: Racemic brominated and reduced 2,4 –dichloro-acrylate.**4.2.5 Synthesis of ethyl 2-bromo-2-(4-bromophenyl)-3-hydroxypropanoate**

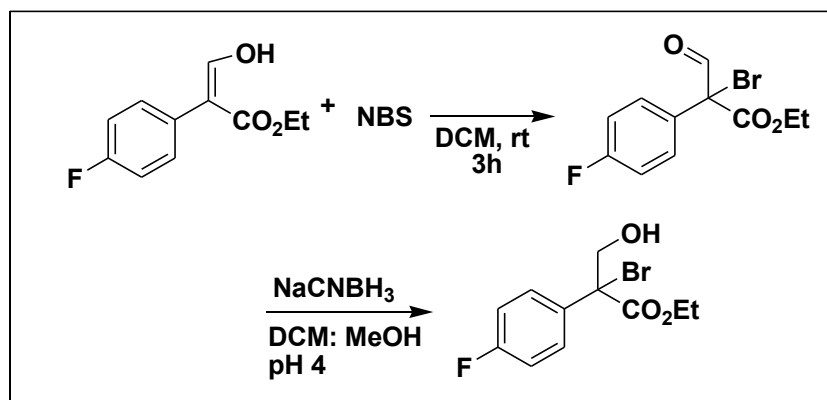
Ethyl 2-bromo-2-(4-bromophenyl)-3-hydroxypropanoate was isolated with 52% yield from 0.250g (0.9295 mmol) of 4-bromo acrylate, 0.182g (1.022 mmol) of NBS, in 5 mL of dichloromethane (100% yield to aldehyde), 1.5 mL of methanol and 70mg (1.12 mmol) of NaCNBH₃. ¹H NMR (CDCl₃, 300MHZ): δ 7.50(d,2H), 7.40 (d, 2H), 4.38 (q, 2H), 4.2 (q, 2H), 3.1 (s, 1H), 1.32 (t, 3H).

Equation 15: Racemic brominated and reduced 4 –bromo-acrylate.

4.2.6 Synthesis of ethyl 2-bromo-2-(4-florophenyl)-3-hydroxypropanoate

Ethyl 2-bromo-2-(4-florophenyl)-3-hydroxypropanoate was isolated with 47% yield from 0.37 g (1.76 mmol) of 4-floro acrylate, 0.345g (1.94 mmol) of NBS, in 5 mL of dichloromethane (95% yield to aldehyde), 1.5 mL of methanol and 0.133g (2.112 mmol) of NaCNBH₃. ¹H NMR (CDCl₃, 300 MHz): δ 7.50(d,2H), 7.40 (d, 2H), 4.38 (q, 2H), 4.2 (q, 2H), 3.1 (s, 1H), 1.32 (t, 3H).

Equation 16: Racemic brominated and reduced 4 –floro-acrylate.

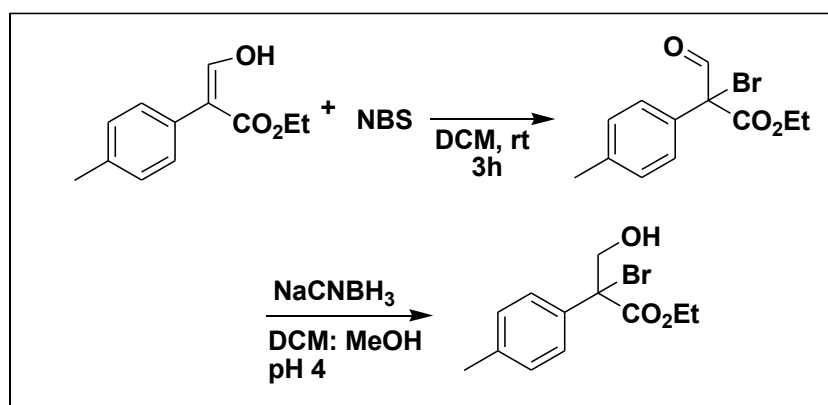


4.2.7 Synthesis of ethyl 2-bromo-3-hydroxy-2-*p*-tolylpropanoate:

2-bromo-3-hydroxy-2-*p*-tolylpropanoate was isolated with 95% yield from 0.30g (1.56 mmol) of acrylate, 0.180g (1.56 mmol) of proline, 0.305g (1.72 mmol) NBS, in 5 mL of dichloromethane (100% yield to aldehyde) in rt, 2 mL of

methanol, 98 mg (1.56 mmol) of NaCNBH_3 . $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.40(d,2H), 7.20 (d, 2H), 4.38 (q, 2H), 4.2 (q, 2H), 3.1 (s, 1H), 2.37 (s, 3H), 1.32 (t, 3H).

Equation 17: Racemic brominated and reduced 4-tol-acrylate.



4.3 Reaction Optimization asymmetric bromination

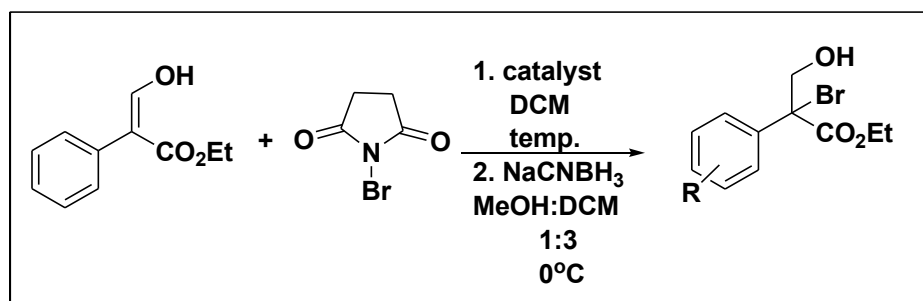
4.3.1 Temperature study:

All of the temperature studies were done with .1g (.52 mmol) of the acrylate 1 eq, 13 mg (.114mmol) of proline .2 eq, .11g (63mmol) of NBS 1.1 eq in 5 mL of DCM as the reaction solvent. % yield was monitored by NMR and reduction was done in situ according to the previous procedure. Reaction was done in open air. All of the HPLC and NMR data can be found in appendix 1.

4.3.2 Catalyst screening: Bromination

All of the catalyst screenings were done with .1g (.52 mmol) of the acrylate 1 eq, (.114mmol) of the catalyst .2 eq, .11g (63mmol) of NBS 1.1 eq in 5 mL of DCM as the reaction solvent. % Yield was monitored by NMR and reduction was done in situ according to the previous procedure. Reaction was done in open air. All of the HPLC and NMR data can be found in appendix 1.

Equation 18: Catalyst screening bromination General reaction.



4.4 Milder brominating agent screening

4.4.1 General

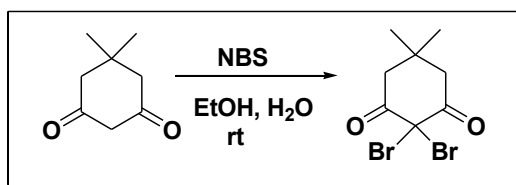
NBS and 2,4,4,6-tetrabromo-2,5-cyclohexadienone were purchased from Aldrich chemical. 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione was synthesized.

4.4.2 Synthesis of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione.

5,5-dimethylcyclohexane-1,3-dione was purchased from Sigma Aldrich. Followed procedure from Adv. Synth. Catal 2009,351 1483-1487. 1.4 g 1 mmol in

a 20 mL solution of Ethanol: water (15:5) was stirred till clear. NBS 1.959 (2.1 mmol) was added in 4 portions. The solution was slightly yellow. After 24 hours 20 mL of water was added and a white precipitate was formed, filtered and washed with water.

Equation 19: Synthesis of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione.



4.4.3 Bromination with mild brominating agent

All of the bromination reactions were done with .1g (.52 mmol) of the acrylate 1 eq, (.114mmol) of the catalyst .2 eq, brominating agent 1.1 eq in 5 mL of DCM as the reaction solvent. % yield was monitored by NMR and reduction was done in situ according to the previous procedure. Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5 α – Chlorination: General Procedure

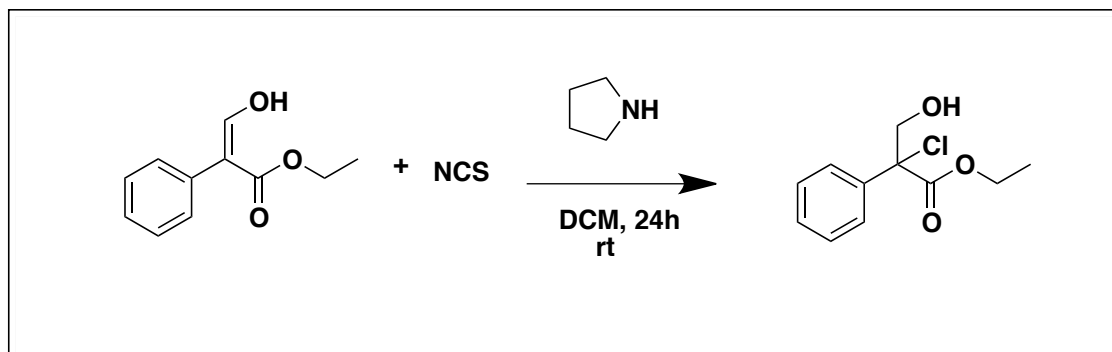
For each experiment, 0.5-5.0 mmol of the acrylate was dissolved in 5 mL of solvent. A 0.2-equivalent of catalyst was added and reaction mixture was stirred for 20 minutes. A 1.1-equivalent of chlorinating agent was added to the mixture. The reaction mixture was allowed to stir for 1 hour. After 1-hour reaction

mixture was passed through a silica plug and the solvent removed by rotary evaporation. Crude ^1H NMR was taken to evaluate % yield. % ee was calculated using HPLC 1 mL/min 99.9%Hexane/0.01% IPA.

4.5.1 Synthesis of ethyl 2-chloro-3-hydroxy-2-phenylpropanoate

2-chloro-3-hydroxy-2-phenylpropanoate was isolated with 95% yield from 0.1g (0.52 mmol) of acrylate, 7mg (0.10 mmol) of pyrrolidine, 76 mg (0.57 mmol) NCS, in 5 mL of dichloromethane in rt (Equation). ^1H NMR (CDCl_3 , 300 MHz): Gave δ 9.614 (s, 1H), 7.50 (m, 5H), 4.38 (q, 2H), 1.32 (t, 3H).

Equation 20: Synthesis of ethyl 2-chloro-3-hydroxy-2-phenylpropanoate.



4.5.2 Temperature optimization reaction with proline as catalyst

All of the temperature optimization reactions were done with .1g (.52 mmol) of the acrylate 1 eq, 13 mg (.114mmol) of proline .2 eq, 76 mg (.57mmol)

of NCS 1.1 eq in 5 mL of DCM as the reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in DCM at reaction temperature for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour. After 1-hour reaction mixture passed through a plug. % yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.3 Catalyst screening – chlorination reaction proline analogs

All of the catalyst screening reactions were done with .1g (.52 mmol) of the acrylate 1 eq,.114mmol of catalyst .2 eq, 76 mg (.57mmol) of NCS 1.1 eq in 5 mL of DCM as the reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in DCM at -20°C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -25°C. After 1-hour reaction mixture passed through a plug. % yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.4 Catalyst screening – chlorination reaction Quinine analogs

All of the catalyst screening reactions were done with .1g (.52 mmol) of the acrylate 1 eq,.114mmol of catalyst .2 eq, 76 mg (.57mmol) of NCS 1.1 eq in 5

mL of DCM as the reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in DCM at at -20°C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -20°C . After 1 hour reaction mixture passed through a plug. % yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.6 Temperature optimization reaction with Quinine as catalyst

All of the temperature optimization reactions were done with .1g (.52 mmol) of the acrylate 1 eq, 37 mg (.114mmol) of quinine .2 eq, 76 mg (.57mmol) of NCS 1.1 eq in 5 mL of DCM as the reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in DCM at reaction temperature for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at the screened reaction temperature. After 1-hour reaction mixture passed through a plug. % yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.7 Solvent screening reaction with Quinine as catalyst

All of the solvent optimization reactions were done with .1g (.52 mmol) of the acrylate 1 eq, 37 mg (.114mmol) of quinine .2 eq, 76 mg (.57mmol) of NCS

1.1 eq in 5 mL of reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in reaction solvent at -25°C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -25°C . After 1-hour reaction mixture passed through a plug. % Yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.8 Catalyst loading Quinine as catalyst

All of the catalyst loading reactions was done with .1g (.52 mmol) of the acrylate 1 eq, quinine as a catalyst, 76 mg (.57mmol) of NCS 1.1 eq in 5 mL of reaction solvent. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in reaction solvent at rt for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at rt. After 1-hour reaction mixture passed through a plug. % Yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.9 Reaction concentration studies

All of the reaction concentration studies were done with .1g (.52 mmol) of the acrylate 1 eq, 37 mg (.114 mmol) quinine as a catalyst, 76 mg (.57mmol) of NCS 1.1 eq in different DCM concentrations. Acrylate and the catalyst were

added to 25 mL round bottom flask and let to stir in DCM at rt for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at rt. After 1-hour reaction mixture passed through a plug. % Yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.10 High dilution temperature screening

All of the high dilution temperature screening studies were done with .1g (.52 mmol) of the acrylate 1 eq, 37 mg (.114 mmol) quinine as a catalyst, 76 mg (.57mmol) of NCS 1.1 eq in 0.01M DCM concentrations. Acrylate and the catalyst were added to 25 mL round bottom flask and let to stir in DCM at different reaction temperatures for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at different reaction temperatures. After 1-hour reaction mixture passed through a plug. % Yield was monitored by NMR. % ee was calculated by chiral HPLC 1 mL/min 99.9%Hexane/0.01% IPA Reaction was done in open air. All of the HPLC data can be found in appendix 1.

4.5.11 Chlorination with Mild chlorinating agent

All of the chlorination reactions were done with .1g (.52 mmol) of the acrylate 1 eq, (.114mmol) of the catalyst .2 eq, chlorinating agent 1.1 eq in 5 mL

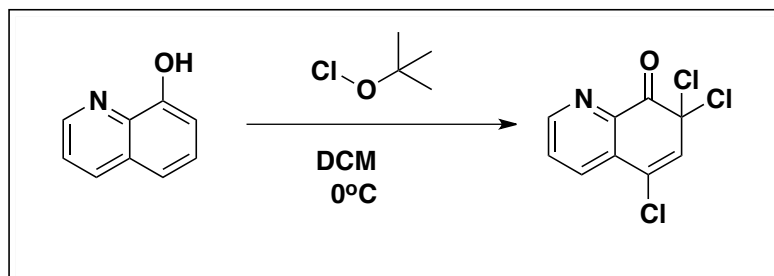
of DCM as the reaction solvent. % Yield was monitored by NMR. Reaction was done in open air. All of the HPLC data can be found in appendix 1.

NCS and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone were purchased from Sigma Aldrich. 5,7,7-trichloroquinolin-8(7H)-one was synthesized from 8-hydroxyquinoline.

4.5.12 Synthesis of 5,7,7-trichloro-7H-quinolin-8-one.

To a solution of 8-hydroxyquinoline (725 mg, 5 mmol, 1 equiv) in DCM (15 mL) was slowly added t-butylhypochlorite (2.3 mL, 3.6 equiv) at 0°C. The reaction was stirred at room temperature for 3 hours. After removal of the solvent under reduced pressure, 5 mL of Et₂O was added to the crude residue. The solid was collected by vacuum filtration and washed with 5 mL of cold hexane to get 5,7,7-trichloroquinolin-8(7H)-one (Equation). As pale solid in 85% yield. ¹H NMR (CDCl₃): δ = 6.81 (s, 1H), 7.68 (dd, 1H), 8.10 (dd, 1H), 8.83 (dd, 1H).

Equation 21: Synthesis of 5,7,7-trichloroquinolin-8(7H)-one.



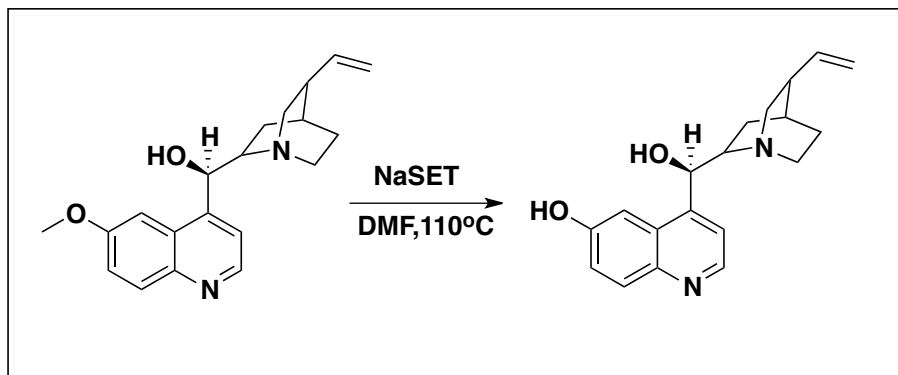
4.6 Organocatalyst synthesis

Proline based catalyst were purchased from Sigma- Aldrich as well as quinine. All of the quinine analogs were synthesized from quinine.

4.6.1 Synthesis of 4-((1*R*)-hydroxy((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-ol⁴⁵.

To a three necked round bottom flask fitted with condenser and a thermometer were added quinine (.5 g, 1.54 mmol) followed by NaSEt (0.519 g, 6.16 mmol) and anhydrous DMF via syringe (10 mL). The reaction was heated to 110°C with the aid of oil bath and let stirred for 12 hours, under Ar. After 12 hours the reaction was quenched with sat. NH₄Cl to get pH 7-8 and diluted with water (10 mL). The solution was diluted with EtOAc (50 mL), the layers were separated and the aqueous layer extracted with EtOAc (2×50 mL). The combined organic layers were washed with water (4× 10 mL) and dried over Na₂SO₄. The DMF was removed by azeotropic distillation with xylenes, leaving a white solid. The crude mixture was purified by column chromatography (SiO₂, EtOH: EtOAc: NH₄OH= 4:6:0.5) to yield the product as white solid (445 mg, 93% yield).

Equation 22: Synthesis of 4-((1*R*)-hydroxy((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-ol.

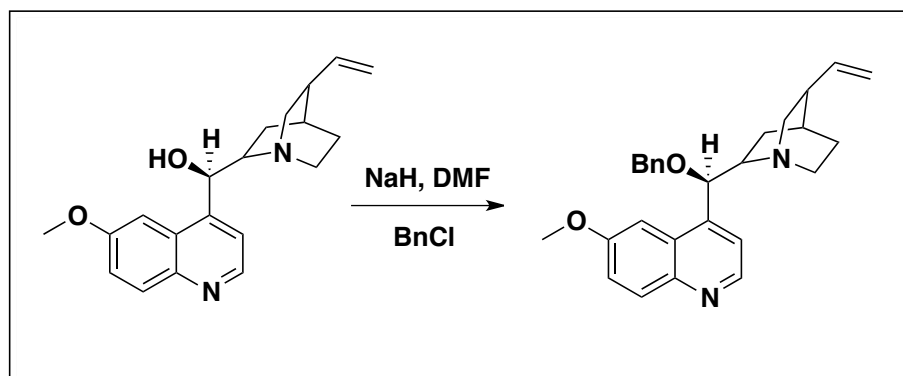


4.6.2 Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(benzyloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine⁴⁵.

A flask was charged with quinine (1 g, 3.08 mmol) and anhydrous DMF (31 mL) via syringe under Ar. The reaction mixture was cooled down to 0°C, followed by slow addition of NaH (60% dispersion in mineral oil; 0.148 g, 2.696 mmol). The mixture was stirred at this temperature for 30 minutes. After 30 minutes, benzyl chloride (425 μ L, 3.696 mmol) was slowly added via syringe to the reaction mixture which was then allowed to warm up to room temperature and stirred under Ar for 12 hours. After 12 hours the reaction mixture was cooled to 0°C and quenched by slow addition of NH₄Cl (50 mL). The crude mixture was diluted with 50 mL of EtOAc allowing separation of two layers, followed by extraction of aqueous layer with EtOAc (3 \times 30 mL). The combined organic layers were washed with water (5 \times 15 mL), washed with brine and dried over Na₂SO₄.

Remaining DMF was removed by azeotropic distillation with xylenes, with the pure product as a beige-yellow oil (1.27 g, 99% yield).

Equation 23: Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(benzyloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine.

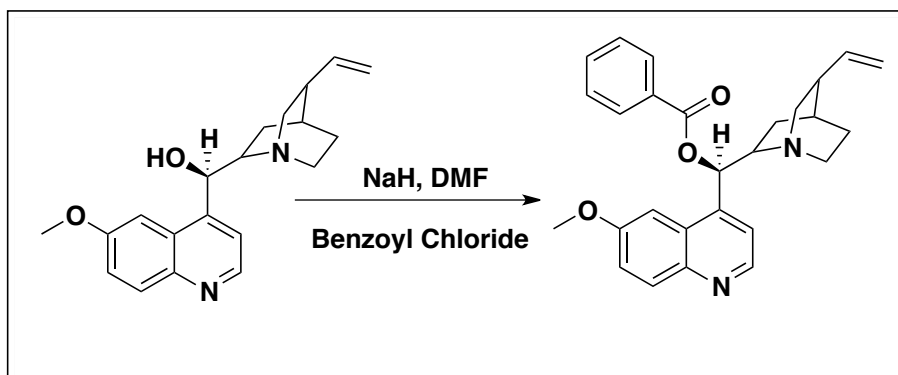


4.6.3 Synthesis of (1*R*)-(6-methoxyquinolin-4-yl)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl benzoate⁴⁵.

A flask was charged with quinine (1 g, 3.08 mmol) and anhydrous DMF (31 mL) via syringe under Ar. The reaction mixture was cooled down to 0°C, followed by slow addition of NaH (60% dispersion in mineral oil; 0.148 g, 2.696 mmol). The mixture was stirred at this temperature for 30 minutes. After 30 minutes, benzoyl chloride (429 μ L, 3.696 mmol) was slowly added via syringe to the reaction mixture which was then allowed to warm up to room temperature and stirred under Ar for 12 hours. After 12 hours the reaction mixture was cooled to 0°C and quenched by slow addition of NH₄Cl (50 mL). The crude mixture was

diluted with 50 mL of EtOAc allowing separation of two layers, followed by extraction of aqueous layer with EtOAc (3×30 mL). The combined organic layers were washed with water (5×15 mL), washed with brine and dried over Na₂SO₄. Remaining DMF was removed by azeotropic distillation with xylenes, with the pure product as a beige-yellow oil (1.29g, 99% yield).

Equation 24: Synthesis of (1*R*)-(6-methoxyquinolin-4-yl)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl benzoate.

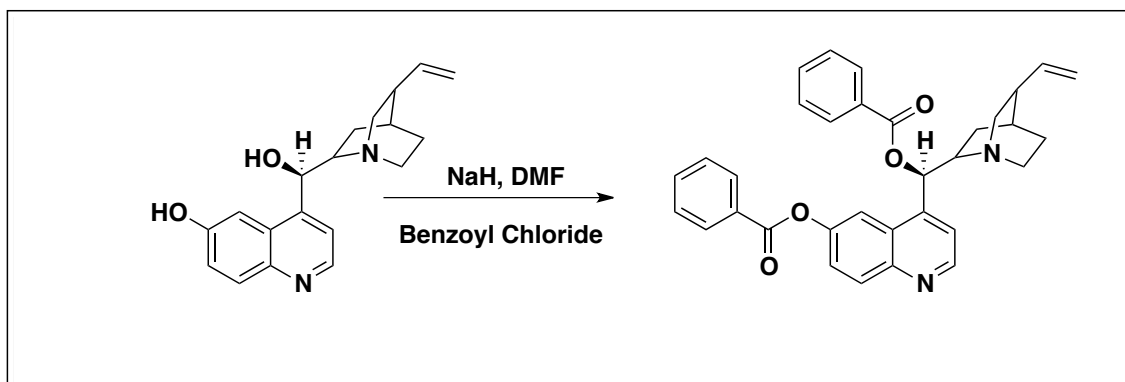


4.6.4 Synthesis of 4-((1*R*)-(benzoyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl benzoate⁴⁵.

A flask was charged with 4-((1*R*)-hydroxy((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-ol (1 g, 3.22 mmol) and anhydrous DMF (31 mL) via syringe under Ar. The reaction mixture was cooled down to 0°C, followed by slow addition of NaH (60% dispersion in mineral oil; 0.300 g, 6.4 mmol). The mixture was stirred at this temperature for 30 minutes. After 30 minutes, benzoyl chloride

(860 μ L, 7.4 mmol) was slowly added via syringe to the reaction mixture which was then allowed to warm up to room temperature and stirred under Ar for 12 hours. After 12 hours the reaction mixture was cooled to 0°C and quenched by slow addition of NH_4Cl (50 mL). The crude mixture was diluted with 50 mL of EtOAc allowing separation of two layers, followed by extraction of aqueous layer with EtOAc (3 \times 30 mL). The combined organic layers were washed with water (5 \times 15 mL), washed with brine and dried over Na_2SO_4 . Remaining DMF was removed by azeotropic distillation with xylenes, with the pure product as a beige-yellow oil (1.63g, 99% yield).

Equation 25: Synthesis of 4-((1*R*)-(benzoyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl benzoate.

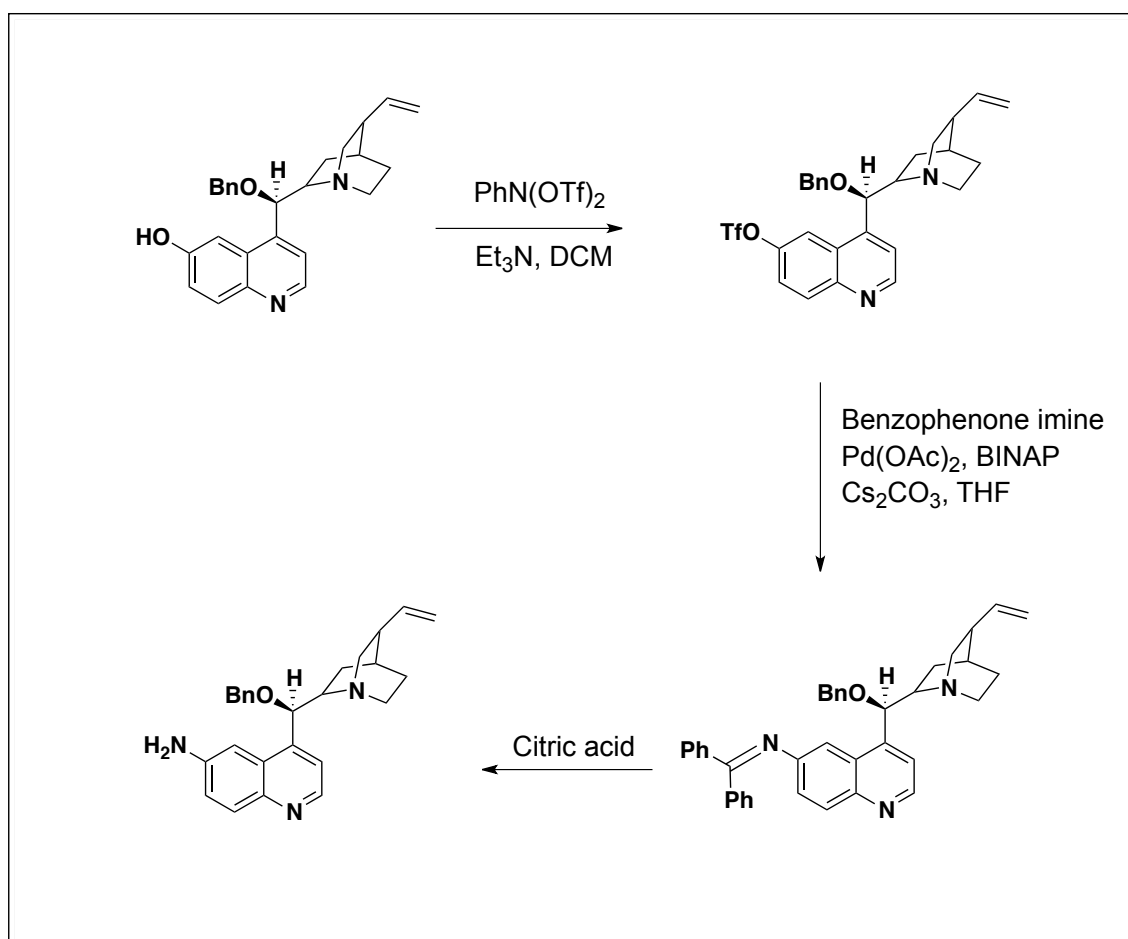


4.6.5 Synthesis of 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-amine⁴⁵.

To a flask was added 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-ol (928 mg, 2.31 mmol), followed by anhydrous DCM (17 mL) and *N,N*-bis(trifluoromethylsulfonyl) aniline (993 mg, 2.78 mmol). Next, Et₃N (0.74 mL, 5.33 mmol) was added via syringe and the mixture was allowed to stir for 12 hours under Ar. After 12 hours the solvent was removed under vacuum, leaving a dark yellow oil. The crude mixture was purified by chromatography (SiO₂, EtOAc: EtOH: NH₄OH =100:1:1) to yield 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl trifluoromethanesulfonate (987 mg, 80% yield) as a dark yellow solid. A flask under Ar was charged with the intermediate (227 mg, 0.43 mmol) and dissolved in THF (1.9 mL). To the reaction flask were next added with stirring Pd(OAc)₂ (5.7 mg, 0.0255 mmol), BINAP (24 mg, 0.0388 mmol), Cs₂CO₃ (198 mg, 0.609 mmol) and benzphenone imine (74 μL, 0.44 mmol). The reaction mixture was then heated to 70 °C with the aid of oil bath and after a few minutes of stirring the solution gradually turned a light red color. After 24 hours of stirring at that temperature, the reaction mixture was cooled to rt, diluted down with DCM (10 mL) and filtered through a high Celite pad which was washed with DCM (10 mL). The solvent was concentrated under reduced pressure, leaving a crude imine as an orange solid. To the crude solid was next added THF (1.6 mL), followed by 10% citric acid (3.3 mL), and the mixture was allowed to stir for 24 hours. After this time, the mixture was

quenched by slow addition of saturated Na_2CO_3 and was then diluted with EtOAc (10mL). The layers were separated and the aqueous layer extracted with DCM (2×25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to yield a crude green solid. The crude mixture was purified by chromatography (SiO_2 , EtOAc:MeOH: NH_4OH =100:15:1) to get the product (111 mg, 65% yield) as yellow solid.

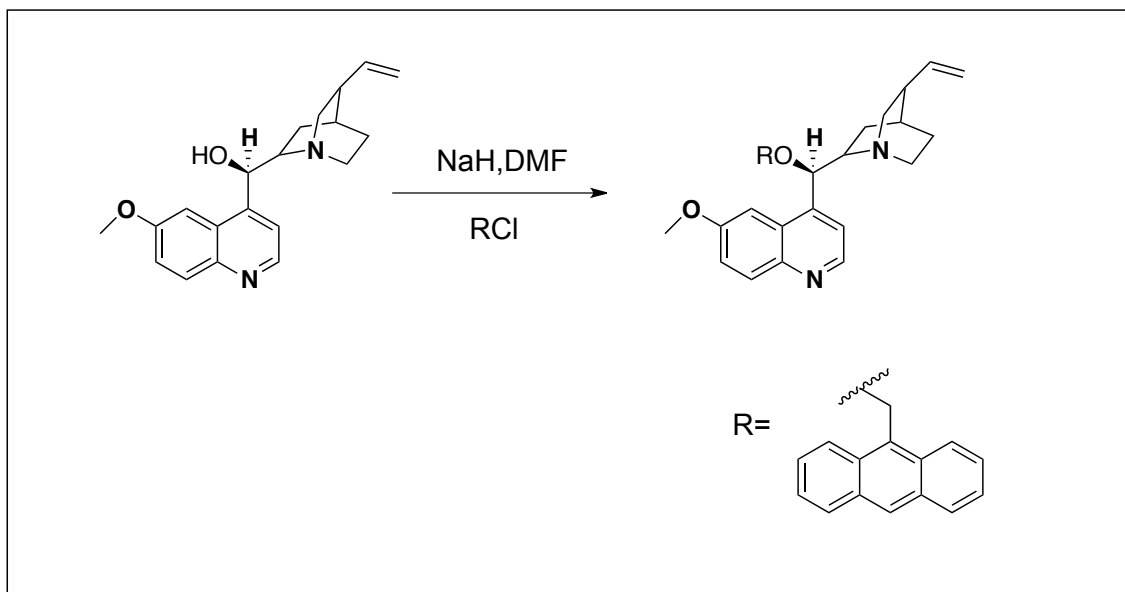
Equation 26: Synthesis of 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-amine.



4.6.6 Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(anthracen-9-ylmethoxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine⁴⁵.

A flask was charged with quinine (680mg, 2.10 mmol) and anhydrous DMF (4 mL) via syringe under Ar. Followed by slow addition of NaH (60% dispersion in mineral oil; 235 mg, 5.87 mmol). The mixture was stirred at room temperature for 1 hour and 30 minutes. After 1 hour and 30 minutes, 9-(Chloromethyl)anthracene (475 mg, 2.10 mmol) was slowly added via syringe to the reaction mixture which was then stirred for additional 2 hours. After 2 hours 2 mL of DMF was added to reaction mixture and the reaction was allowed to stir for another 12 hours. After 12 hours the reaction mixture was quenched with brine (50 mL). The undissolved solid was dissolved with EtOAc (25 mL). The two layers were separated, followed by extraction of aqueous layer with EtOAc (3×30 mL). The combined organic layers were washed with water (5×15 mL), washed with brine and dried over Na₂SO₄. Remaining DMF was removed by azeotropic distillation with xylenes with The crude product was purified by chromatography (SiO₂, MeOH:EtOAc: Et₃N = 20:80:0.5) to yield the product as a yellow solid (765 mg, 71% yield).

Equation 27: Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(anthracen-9-ylmethoxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine.



4.7 DFT Calculations

All of the structures were drawn in Gauss View and All energy optimizations done with B3LYP, and the Pople style 6-311G+ (2df,2dp) basis set and a COSMO model for solvent DCM.

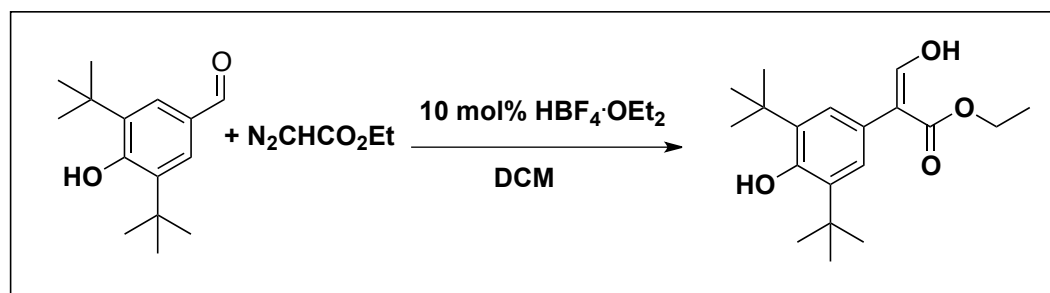
4.8 NMR studies disubstituted substrate

4.8.1 Synthesis of (*Z*)-ethyl 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-hydroxyacrylate.

3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (1 g, 4.26 mmol) was dissolved in DCM (29 mL) under N₂, followed by addition of HBF₄ · OEt₂ (60 μL, 0.426 mmol)

and the reaction mixture was cooled to -78°C . Ethyl diazoacetate (0.58 mL, 5.11 mmol) was then added dropwise *via* syringe at this temperature over a period of 5 minutes. The reaction mixture was allowed to stir at -78°C for a period of 4 h, at which time the mixture was warmed to room temperature and quenched by the addition of H_2O (20 mL). The aqueous layer was extracted with DCM (2×25 mL), the combined organic extracts were dried over Na_2SO_4 and the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2 , 98/2 hexane/EtOAc) to afford the product in 62% yield as a yellow oil. ^1H NMR (300 MHz, CDCl_3): 12.00 (d, 1H), 7.082 (s, 2H), 5.15 (s, 1H), 4.38 (q, 2H), 1.43 (t, 3H), 1.32 (s, 18H).

Equation 28: Synthesis of (Z)-ethyl 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-hydroxyacrylate.

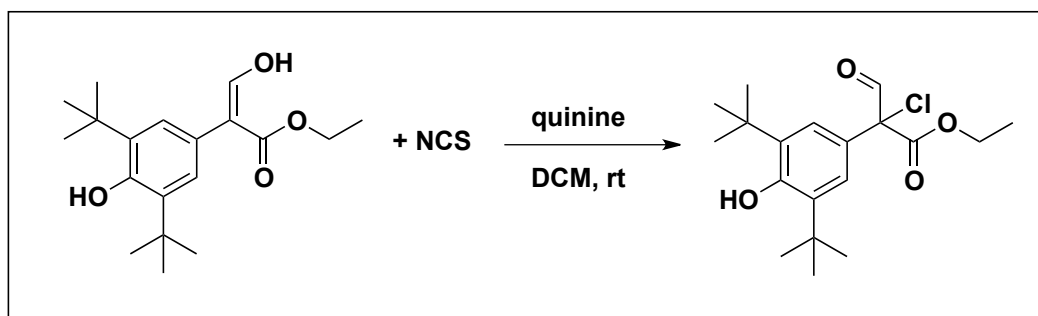


4.8.2 Synthesis of ethyl 2-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-oxopropanoate.

2-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-oxopropanoate was isolated with 95% yield from 0.1g (0.31 mmol) of acrylate, 32mg (0.10 mmol) of quinine, 76 mg (0.57 mmol) NCS, in 5 mL of dichloromethane in rt (Equation). ^1H NMR

(CDCl₃, 300 MHz): Gave δ 10.304(s,1H), 7.882 (s, 1H), 7.382 (d, 2H), 4.38 (q, 2H), 1.43 (s, 18H), 1.32 (t, 3H).

Equation 29: Synthesis of 2-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-oxopropanoate.

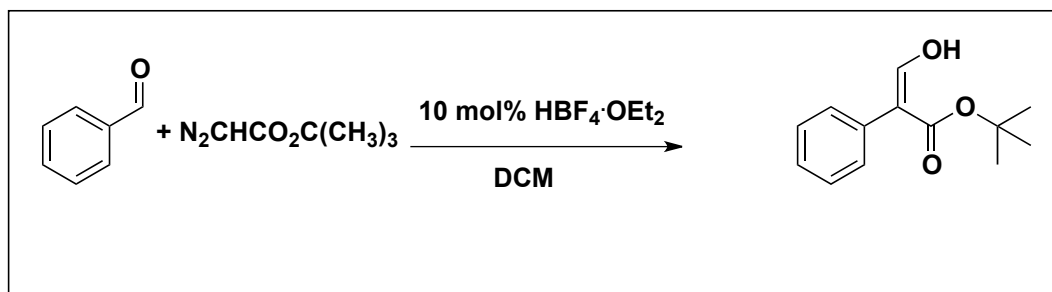


4.8.3 Synthesis of (*Z*)-*tert*-butyl 3-hydroxy-2-phenylacrylate

Benzaldehyde (1 g, 9.61 mmol) was dissolved in DCM (29 mL) under N₂, followed by addition of HBF₄ · OEt₂ (135 μ L, 0.961 mmol) and the reaction mixture was cooled to -78°C. *tert*-butyl diazoacetate (1.6 mL, 11.54 mmol) was then added dropwise *via* syringe at this temperature over a period of 5 minutes. The reaction mixture was allowed to stir at -78°C for a period of 4 h, at which time the mixture was warmed to room temperature and quenched by the addition of H₂O (20 mL). The aqueous layer was extracted with DCM (2 \times 25 mL), the combined organic extracts were dried over Na₂SO₄ and the mixture was concentrated under reduced pressure. The crude oil was purified by flash

chromatography (SiO₂, 98/2 hexane/EtOAc) to afford the product in 62% yield as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 12.05 (d, *J* = 12.7 Hz, 1H), 7.4 (s, 1H), 7.3-7.1 (m, 3H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

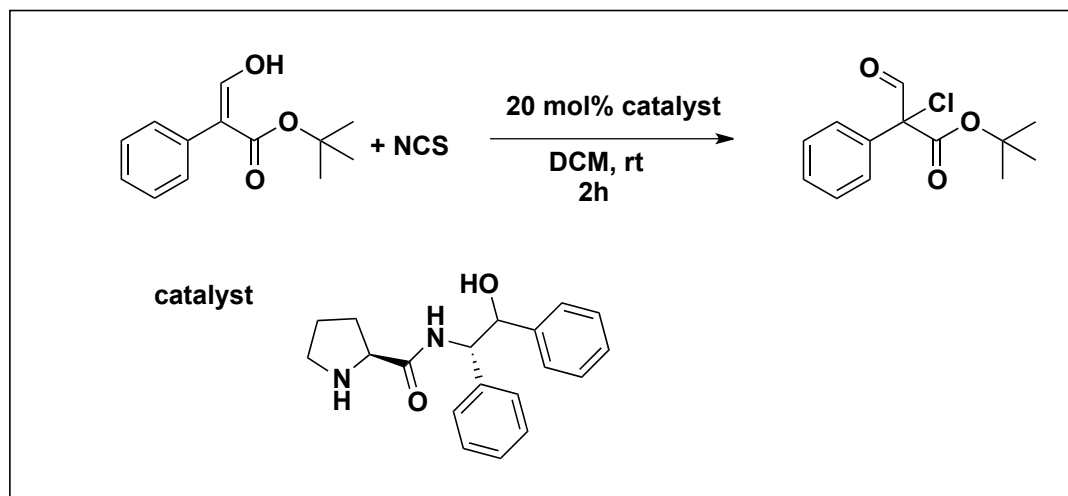
Equation 30: Synthesis of (*Z*)-*tert*-butyl 3-hydroxy-2-phenylacrylate.



4.8.4 Synthesis of *tert*-butyl 2-chloro-3-oxo-2-phenylpropanoate

tert-butyl 2-chloro-3-oxo-2-phenylpropanoate was isolated with 95% yield from 0.1g (0.31 mmol) of acrylate, 32mg (0.10 mmol) of proline based catalyst, 76 mg (0.57 mmol) NCS, in 5 mL of dichloromethane in rt (Equation 31). ¹H NMR (CDCl₃, 300 MHz): δ 9.614 (s, 1H), 7.50 (m, 5H), 1.53 (s, 9H), 1.32 (t, 3H).

Equation 31: Synthesis of *tert*-butyl 2-chloro-3-oxo-2-phenylpropanoate.



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Part II:

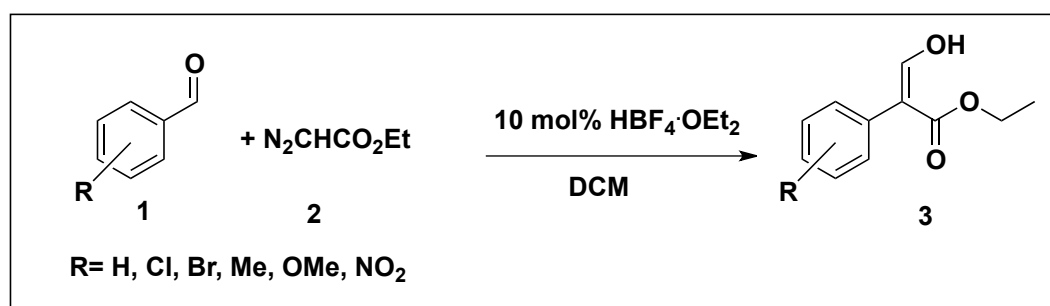
Synthesis of α -aryl quaternary carbon centers

1. Introduction

The development of catalytic, enantioselective methods for the construction of α -aryl quaternary carbon centers represents a daunting challenge in organic chemistry. Excellent reviews have been published on this topic.^{1,2} The formation of α -aryl quaternary carbon centers, present in a growing number of biologically active natural products and pharmaceutical agents, poses a unique challenge due to the steric congestion encountered during the C-C bond formation process. Generally, a quaternary aryl carbon center is formed using strongly basic lithium arenes.^{2,3} The aryl anion, while quite reactive, suffers from being unstable to air, non-catalytic, and potentially tedious and expensive when used on larger scales. Furthermore, when used stereoselectively, the aryl anion must attack a stereogenic electrophile. Because most inexpensive electrophiles are prochiral, this approach requires using an additional chiral auxiliary to block the *re*- or *si*-face of the prochiral electrophile. Additionally, sp^2 -hybridized electrophiles, such as carbonyls and imines, usually lack tertiary carbons. To circumvent this problem, the nucleophile must undergo an S_N2 attack at a tertiary bound carbon or undergo Michael-type addition. These considerations make arylhydroxyacrylates **3** (Scheme 1) attractive alternatives, because their α -carbon is tertiary, hence allowing for the possibility of asymmetric synthesis under phase transfer catalysis conditions.⁴

Our group was successful in the development of a novel reaction involving the formation of arylhydroxyacrylates **3** in high yields from aromatic aldehydes **1** and ethyl diazoacetate **2** in the presence of a Brønsted acid catalyst (Scheme 1).^{5a} Herein, we describe a Claisen rearrangement process for generating α -aryl quaternary carbon centers from 3-allyloxy-2-arylacrylates **4**, made from arylhydroxyacrylates **3** (Scheme 2). Although Claisen rearrangements have been used previously for making quaternary carbon centres⁶⁻⁸, the use of Claisen rearrangements to afford α -aryl quaternary carbon centers is very rare. In fact, the only example we were able to find is an asymmetric Pd Lewis acid-catalyzed Meerwein-Eschenmoser-Claisen rearrangement⁹ involving the rearrangement of 2-amino allyl vinyl ethers into oxindoles bearing an α -aryl quaternary center.

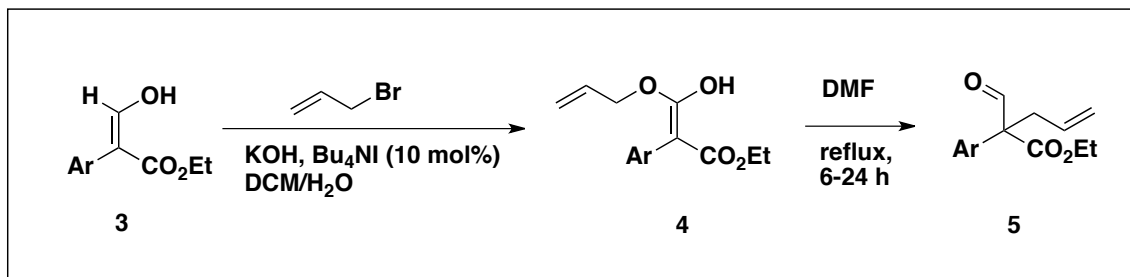
Scheme 1. Synthesis of α -arylhydroxyacrylates **3**.



2. Results and Discussion

Our initial approach for the construction of an α -aryl quaternary carbon starting from arylhydroxyacrylates **3** involved direct alkylation of the enolate of **3** with an alkyl halide. Alkylation with bases such as solid or aqueous KOH gives exclusive O-alkylation (Scheme 2), whilst the attempted alkylation with solid or aqueous NaOH only gives a small amount of C-alkylated product (ca 20% with allyl iodide). We believe this is due to the extensive conjugation present in the enolate form of the acrylate that is strongly favored over the carbanion form. We have screened various electrophiles for the reaction (allyl iodide, allyl bromide, ethyl iodide, 4-(trifluoromethoxy) benzyl bromide) and solvents (toluene, dichloromethane, THF); all reactions with KOH under any conditions provided exclusively the O-alkylated product. In the case of using NaOH, increasing the polarity of the solvent by using THF resulted in even lower amounts of C-alkylated product. As expected, an electrophile with a softer leaving group (allyl iodide instead of allyl bromide) resulted in a slightly greater yield (only by 5%) of C-alkylated product. However, we realized that the O-allyl vinyl ethers were suitable candidates for a Claisen rearrangement that would afford an indirect C-alkylation leading to the desired α -aryl quaternary carbon. (Scheme 2, Table 1).

Scheme 2. Phase transfer catalyzed O-alkylation of acrylate **3** followed by Claisen rearrangement of ethyl 3-allyloxy-2-arylacrylates **4** affording ethyl 2-aryl-2-formyl-2-pent-4-enoates **5**.



| | |
|-----|---|
| 3,4 | Ar |
| a | C ₆ H ₅ |
| b | 4-MeC ₆ H ₄ |
| c | 2,4-Cl ₂ C ₆ H ₃ |
| d | 4-MeOC ₆ H ₄ |
| e | 4-FC ₆ H ₄ |

| | |
|---|---|
| 5 | Ar |
| c | 2,4-Cl ₂ C ₆ H ₃ |

The O-alkylation of acrylates **3** was carried out in dichloromethane using allyl bromide under phase transfer catalysis conditions (using either NBu₄I or NBu₄Br) and aqueous or solid KOH as base. Reactions carried out in the absence of a phase transfer catalyst resulted in very low yields of product. The attempted alkylation with *n*-butyl lithium in dry THF provided complex mixtures of products.

Table 1. Yields of ethyl 3-allyloxy-2-arylacrylates **4** and ethyl 2-aryl-2-formyl-2-pent-4-enoates **5**.

| 4, 5 | Ar | 4 | 5 |
|-------------|---|------------------------|------------------------|
| | | Yield ^a [%] | Yield ^a [%] |
| a | C ₆ H ₅ | 71 | |
| b | 4-MeC ₆ H ₄ | 80 | |
| c | 2,4-Cl ₂ C ₆ H ₃ | 82 | 69 |
| d | 4-MeOC ₆ H ₄ | 66 | |
| e | 4-FC ₆ H ₄ | 65 | |

^aIsolated yields

The Claisen rearrangement of the allyl vinyl ethers **4** (Scheme 2) was performed in refluxing DMF for 6–24 h. The products were isolated by column chromatography in good to moderate yields (Table 1), and were identified and characterized by ¹H and ¹³C NMR, as well as HRMS. NMR studies (NOESY experiment) showed *E*-stereochemistry of the double bond, presumably due to steric hindrance between the oxygen of the allyl vinyl ether and the carbonyl oxygen of the ester.

For the Claisen rearrangement product the yield overall was good with the other analogs that were synthesized in the publication. We did notice, however, a slight decomposition of the product upon purification with flash chromatography to the deformylated product, presumably due to the high steric strain present in the *o*-aryl quaternary carbon. The Claisen rearrangement was carried out in DMF

as solvent due to the lower conversion to product for most of the substrates **4** if a lower boiling solvent such as xylenes was used. For example, under refluxing xylenes, the conversion of substrate **4c** into product **5c** was only about 40%; with DMF, the conversion was considerably higher at 74% (NMR yield).

We believe that the highly functionalized Claisen rearrangement products **5** could prove to be powerful building blocks for the synthesis of molecules bearing α -aryl quaternary carbon centers. The aldehyde, ester and allyl functional groups are easily converted into intermediates, which could be useful precursors for the synthesis of a wide variety of molecules including natural products such as the spirooxindole horsfiline.¹⁰

3. Conclusions

In summary, we have developed a general procedure for making α -aryl quaternary carbons in two steps from arylhydroxyacrylates. The overall reaction sequence starting from an aldehyde and EDA (Scheme 1) and leading in two further steps to the Claisen rearrangement product via the O-alkylated allyl vinyl ether (Scheme 2) is an atom economic process for the synthesis of a number of compounds bearing α -aryl quaternary carbons. The synthesis of chiral quaternary carbon centers from O-allylated substrates via the asymmetric Claisen rearrangement is currently under investigation.

4. Experimental Section

4.1 General.

All ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker 300 spectrometer (^1H 300 MHz, ^{13}C 75 MHz) at room temperature in CDCl_3 . Analytical thin layer chromatography was performed using EMD Chemicals TLC Glass plates, Silica Gel 60 F254. Flash column chromatography was performed using Biosolve 60 Å (0.032–0.063 mm) silica gel.

All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use.

4.2 Synthesis of (Z)-ethyl 2-aryl-3-hydroxyacrylates: **3a**^{5a-e}

((Z)-ethyl 3-hydroxy-2-phenylacrylate), **3b**^{5a,c-e} ((Z)-ethyl 3-hydroxy-2-(p-tolyl)acrylate), **3c** ((Z)-ethyl 2-(2,4-dichlorophenyl)-3-hydroxyacrylate), **3d**^{5a,c-e} ((Z)-ethyl 3-hydroxy-2-(4-methoxyphenyl)acrylate), **3e**^{5c-e} ((Z)-ethyl 2-(4-fluorophenyl)-3-hydroxyacrylate), **3f**^e ((Z)-ethyl 2-(5-bromo-2-methoxyphenyl)-3-hydroxyacrylate), and **3g**^{5b} ((Z)-ethyl 2-(4-(tert-butyl)phenyl)-3-hydroxyacrylate) were synthesized using our published procedure.^{5a} The identity of these compounds was confirmed by ^1H and ^{13}C NMR.

4.3 (Z)-ethyl 2-(2,4-dichlorophenyl)-3-hydroxyacrylate (**3c**).

2,4-dichlorobenzaldehyde (1 g, 5.71 mmol) was dissolved in CH_2Cl_2 (29 mL) under N_2 , followed by addition of $\text{HBF}_4 \cdot \text{OEt}_2$ (65 μL , 0.48 mmol) and the

reaction mixture was cooled to -78°C . Ethyl diazoacetate (0.5 mL, 4.76 mmol) was then added drop wise *via* syringe at this temperature over a period of 5 minutes. The reaction mixture was allowed to stir at -78°C for a period of 4 h, at which time the mixture was warmed to room temperature and quenched by the addition of H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×25 mL), the combined organic extracts were dried over Na_2SO_4 and the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2 , elution gradient: 0 to 8% Et_2O /pentane) to afford **3c** in 62% yield as a yellow oil. HRMS: 261.0092 [calcd. for $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{O}_3$ (M+H): 261.0085]. ^1H NMR (300 MHz, CDCl_3): d 12.05 (d, $J = 12.7$ Hz, 1H), 7.4 (s, 1H), 7.3-7.1 (m, 3H), 4.25 (q, $J = 7.0$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): d 170.6, 163.5, 134.1, 132.9, 131.5, 129.2, 127.5, 126.9, 105.6, 60.9, 14.0.

4.4 Synthesis of (*E*)-ethyl-3-(allyloxy)-2-aryacrylates (4): General Procedure.

Ethyl 2-aryl-3-hydroxyacrylate **3** (1.0–5.0 mmol) was dissolved in freshly distilled dichloromethane (5–10 mL) under nitrogen. Bu_4NI (0.1 equiv.), allyl bromide (1.2 equiv.), and potassium hydroxide (10 equiv.) were added, and the reaction mixture was stirred at room temperature until reaction completion was confirmed by NMR. The reaction was quenched by adding saturated NH_4Cl , and the aqueous layer was extracted with diethyl ether (2×25 mL). The organic extracts were combined and dried over Na_2SO_4 . The organic layer was then

passed through a silica plug and the solvent was removed by rotary evaporation. Pure product was isolated by column chromatography (5–10% ethyl acetate in pentane) and identified by ^1H NMR. ^1H , ^{13}C NMR and HRMS were applied to characterize the new compounds.

(E)-Ethyl 3-(allyloxy)-2-phenylacrylate (4a). Yellow oil. HRMS: 233.1169 [calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_3$ (M+H): 233.1177]. ^1H NMR (300 MHz, CDCl_3): d 7.67 (s, 1H), 7.45-7.30 (m, 5H), 5.92 (m, 1H), 5.4 (d, $J = 17.4$ Hz, 1H), 5.3 (d, $J = 10.5$ Hz, 1H), 4.53 (d, $J = 4.0$ Hz, 2H), 4.28 (q, $J = 7.1$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): d 167.6, 157.6, 132.7, 132.4, 130.2, 127.6, 126.9, 119.3, 111.9, 74.9, 60.2, 14.3.

(E)-Ethyl 3-(allyloxy)-2-*p*-tolylacrylate (4b). Yellow oil. HRMS: 247.1358 [calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3$ (M+H): 247.1363]. ^1H NMR (300 MHz, CDCl_3): d 7.66 (s, 1H), 7.37-7.22 (m, 4H), 5.95 (m, 1H), 5.4 (d, $J = 18.8$ Hz, 1H), 5.35 (d, $J = 10.5$ Hz, 1H), 4.53 (d, $J = 5.1$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.42 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): d 167.7, 157.5, 136.5, 132.6, 129.7, 129.3, 127.7, 118.6, 111.9, 74.9, 60.2, 21.2, 14.4.

(E)-Ethyl 3-(allyloxy)-2-(2,4-dichlorophenyl)acrylate (4c). Yellow oil. HRMS: 301.0472 [calcd. for $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_3$ (M+H): 301.0398]. ^1H NMR (300 MHz, CDCl_3): d 7.65 (d, $J = 2.6$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.27-7.17 (m, 2H), 5.86 (m, 1H), 5.35 (d, $J = 12.5$ Hz, 1H), 5.3 (d, $J = 4.4$ Hz, 1H), 4.52 (d, $J = 4.2$ Hz, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75MHz, CDCl_3): d

166.6, 158.7, 135.2, 133.8, 133.0, 132.1, 130.7, 130.2, 129.1, 119.0, 109.3, 75.1, 60.4, 14.2.

(E)-Ethyl 3-(allyloxy)-2-(4-methoxyphenyl)acrylate (4d). Yellow oil. HRMS: 263.1260 [calcd. for C₁₅H₁₈O₄ (M+H): 263.1283]. ¹H NMR (300 MHz, CDCl₃): d 7.59 (s, 1H), 7.33 (m, 2H), 6.92 (m, 2H), 5.93 (m, 1H), 5.4 (d, *J* = 17.9 Hz, 1H), 5.3 (d, *J* = 10.4 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): d 167.8, 157.1, 132.5, 131.2, 129.5, 124.9, 118.7, 113.8, 111.5, 74.8, 60.2, 55.1, 14.3.

(E)-Ethyl 3-(allyloxy)-2-(4-fluorophenyl)acrylate (4e). Yellow oil. HRMS: 253.1237 [calcd. for C₁₄H₁₅FO₃ (M+H): 251.1083]. ¹H NMR (300 MHz, CDCl₃): d 7.63 (d, *J* = 4.0 Hz, 1H), 7.36 (m, 2H), 7.05 (m, 2H), 5.90 (m, 1H), 5.35 (d, *J* = 14.7 Hz, 1H), 5.3 (d, *J* = 5.4 Hz, 1H), 4.53 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): d 167.4, 163.3, 158.2, 132.3, 131.8, 128.5, 118.9, 114.7, 111.0, 75.0, 60.3, 14.3.

Synthesis of ethyl 2-formyl-2-arylpent-4-enoates 5. General procedure. (*E*)-ethyl-3-(allyloxy)-2-arylacrylate **4** (1.0–5.0 mmol) was dissolved in anhydrous DMF (5–10 mL) under nitrogen. The reaction mixture was then refluxed for 6–24 hours (until completion of the reaction was confirmed by TLC), cooled to room temperature and diluted with water. The aqueous layer was extracted two times with diethyl ether. The combined organic extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residual DMF was removed by azeotropic distillation with xylenes. The pure product was isolated by

column chromatography (5–10% ethyl acetate in pentane) and identified by ^1H NMR, ^{13}C NMR and HRMS were applied to characterize the new compounds.

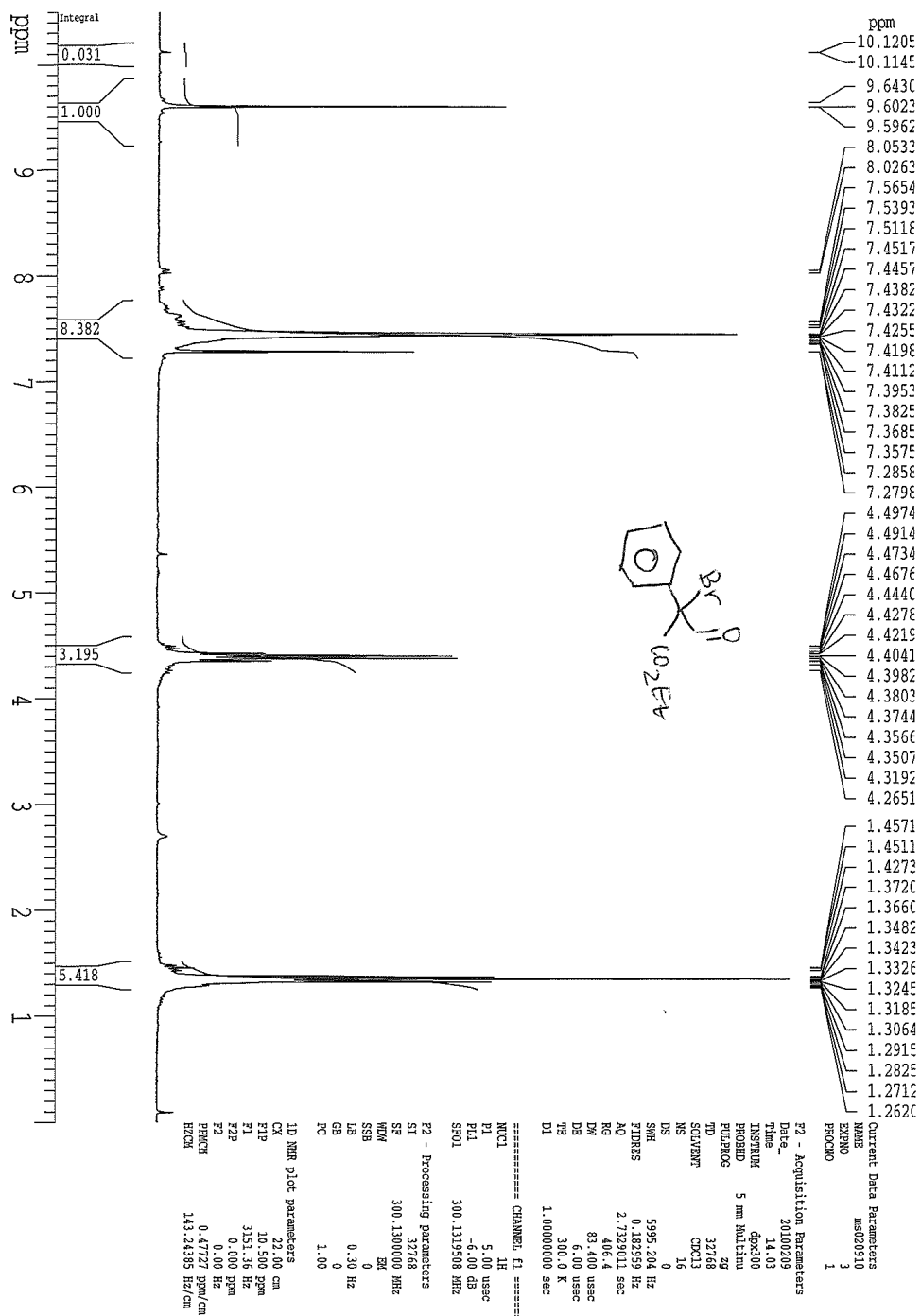
Ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate (5c). Yellow oil. HRMS: 301.0397 [calcd. for $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_3$ (M+H): 301.0398]. ^1H NMR (300 MHz, CDCl_3): d 10.32 (s, 1H), 7.72 (s, 1H), 7.44–7.28 (m, 2H), 5.75 (m, 1H), 5.2–5.1 (m, 2H), 4.25 (q, $J = 7.1$, 2H), 3.10 (dd, $J = 6.3, 13.8$ Hz, 1H), 2.94 (dd, $J = 7.2, 14.1$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75MHz, CDCl_3): d 198.0, 169.9, 134.6, 134.5, 133.9, 131.1, 130.5, 127.3, 119.9, 64.0, 61.9, 37.7, 13.9.

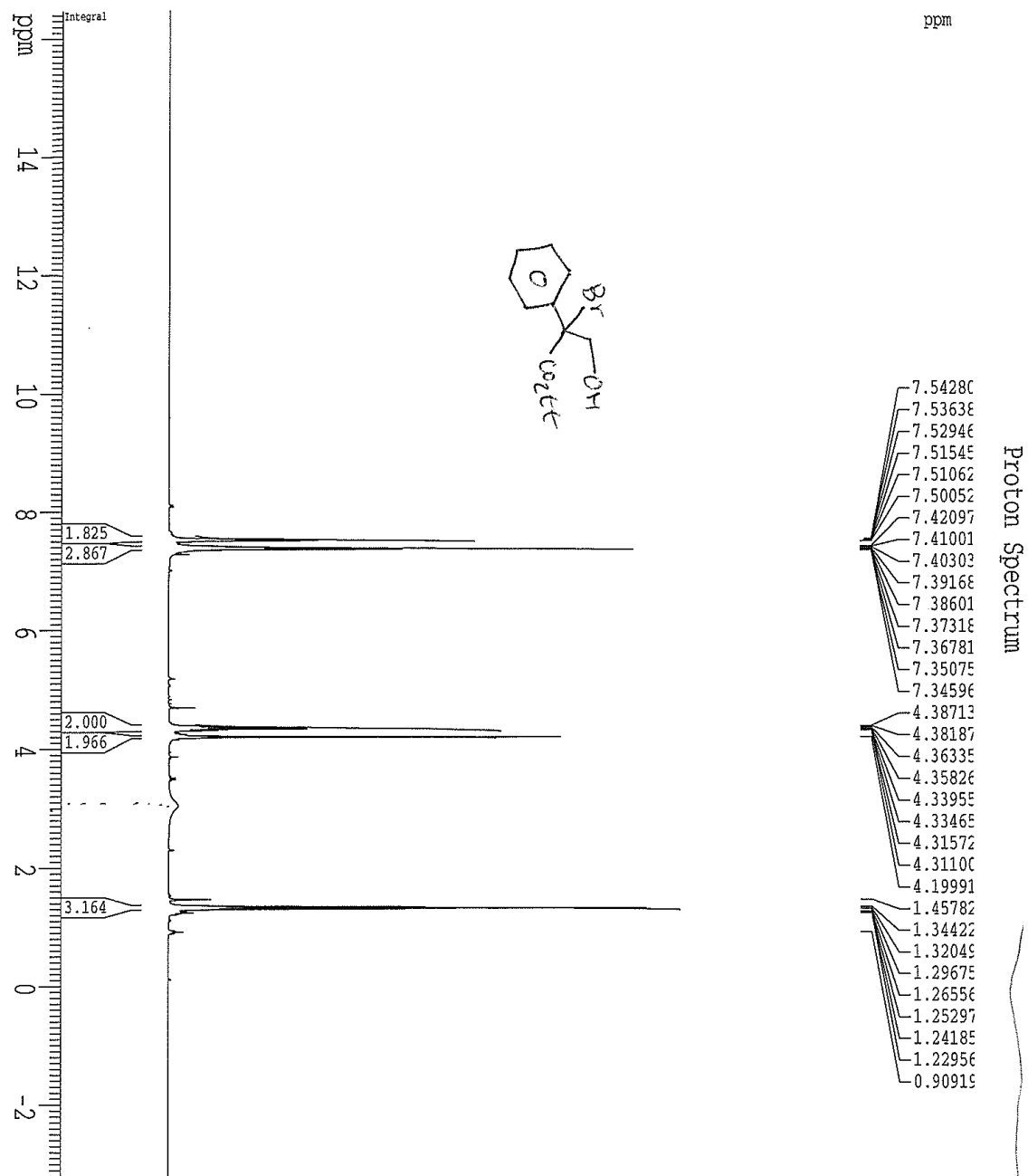
References

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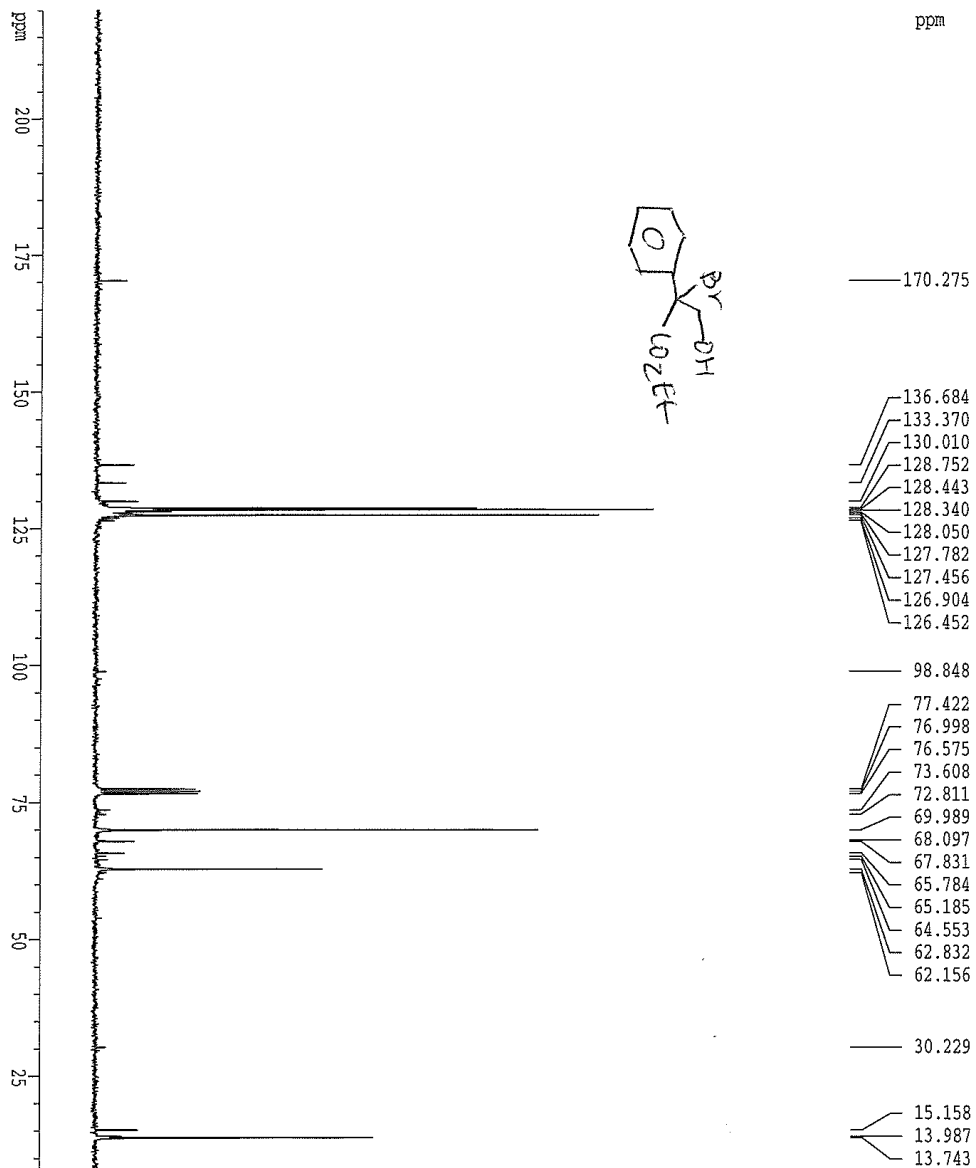
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Appendix:
NMR Data





Carbon Spectrum



```

Current Data Parameters
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EXPNO         6
PROCNO        1

F2 - Acquisition Parameters
Date_         20100803
Time          17.31
INSTRUM      dxs300
PROBHD       5 mm Multinu
PULPROG      zgdc
TD            65536
SOLVENTF     CDCl3
NS            1024
DS            0
SWH           18115.941 Hz
FIDRES       0.226427 Hz
AQ            1.8096436 sec
RG            728.1
DE            27.600 usec
TE            300.2 K
D1            0.10000000 sec
d11           0.03000000 sec

===== CHANNEL f1 =====
NUC1          13C
P1            6.80 usec
PL1           -6.00 dB
SFO1          75.4758695 MHz

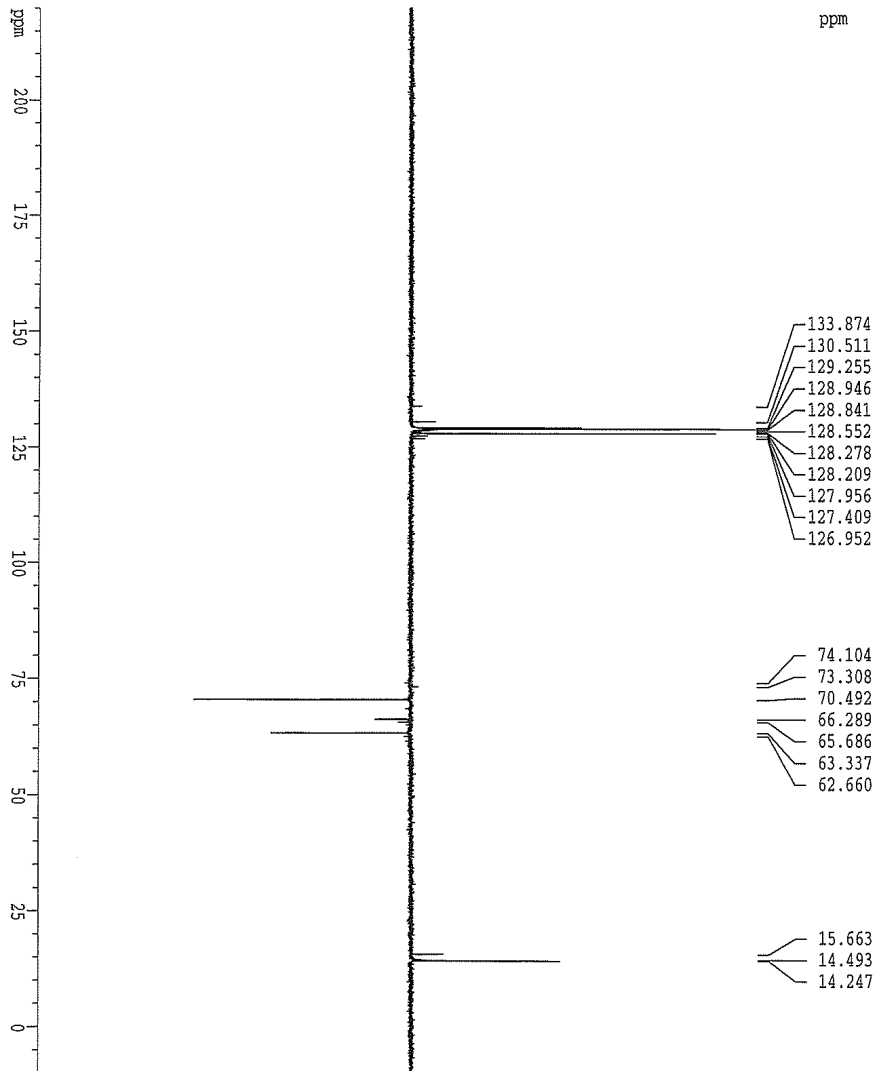
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NUC2          1H
PCPD2        100.00 usec
PL2           -6.00 dB
PL12         16.60 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI            32768
SF            75.4677567 MHz
WDW           EM
SSB           0
LB            3.00 Hz
GB            0
PC            1.40

1D NMR plot parameters
CX            22.00 cm
IP            220.000 ppm
F1            16602.90 Hz
F2           -5.000 ppm
PCMC          -377.34 Hz
HSCM          771.82935 Hz/cm
    
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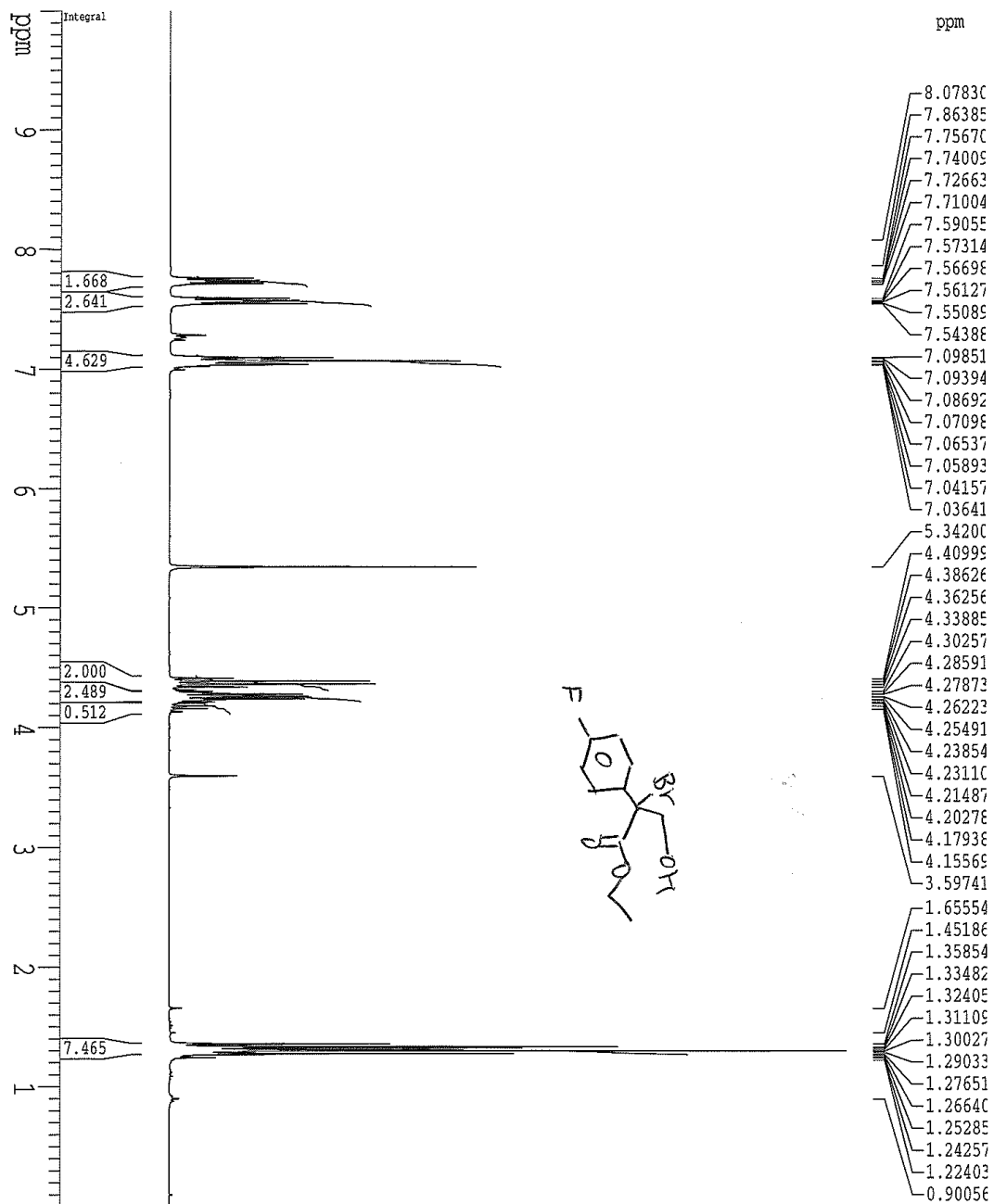


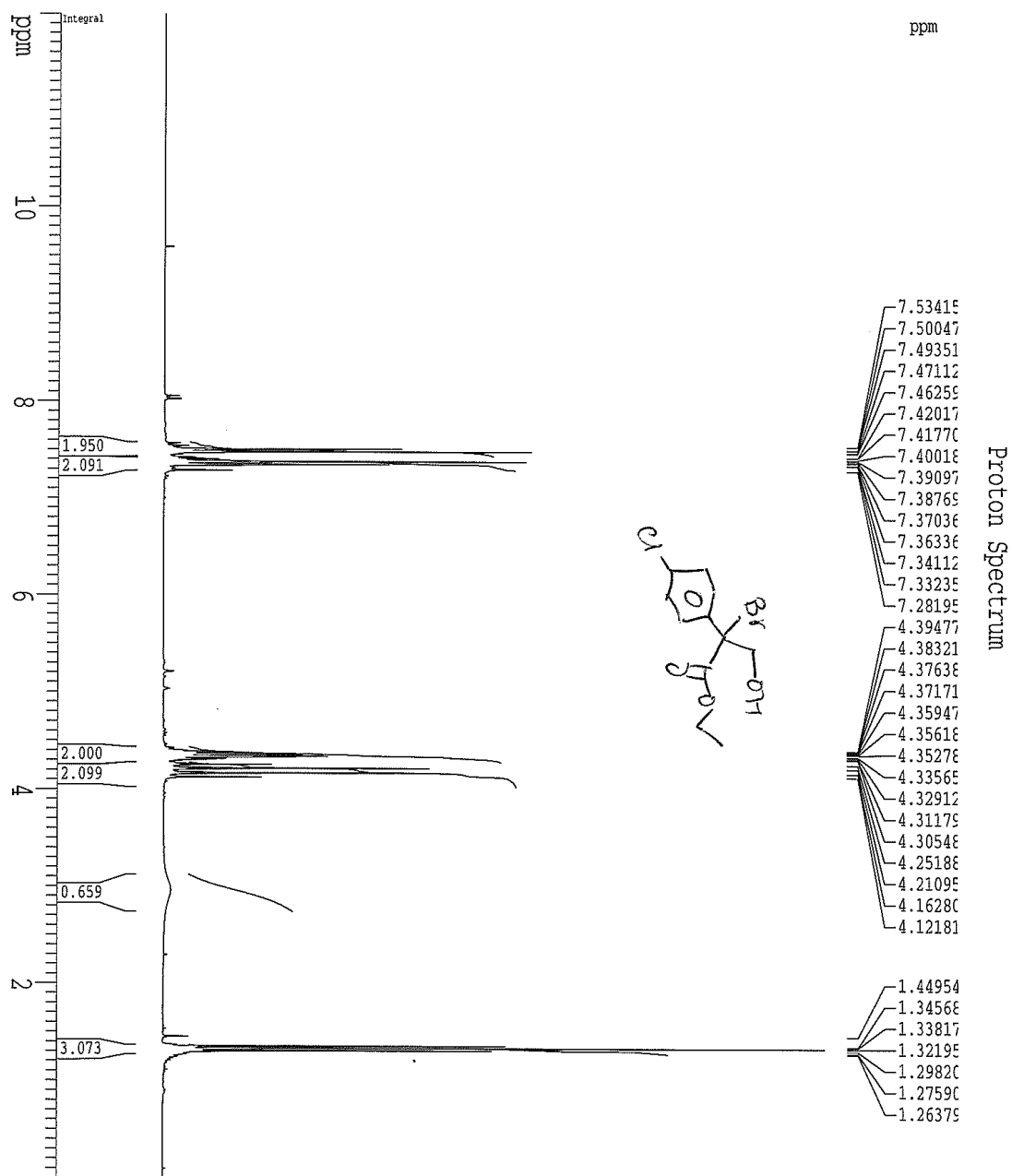

C-13 DEPT 135



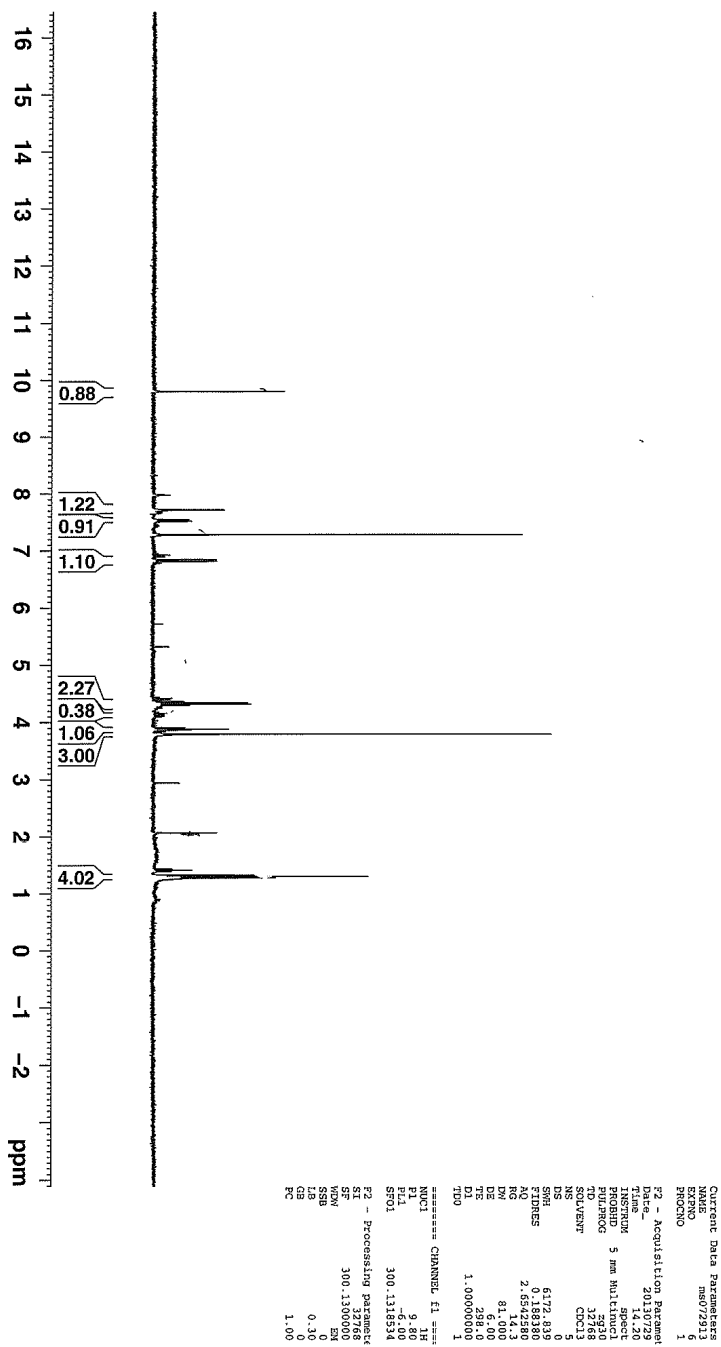
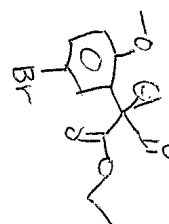
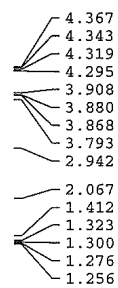
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PROCNO        1
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PULPROG       zgpg30
DEPT135       135
NUC1          13
NUC2          13
NUC3          13
DS            4
SFO1          125
SFO2          125
SF            125.013111 Hz
AQ            0.264910 Hz
RG            1.8874868 sec
DE            28.800 usec
TE            300.2 K
===== CHANNEL f1 =====
NUC1          13C
P1            6.63 usec
PC            13.26 usec
===== CHANNEL f2 =====
NAME          msr0310
EXPNO         8
PROCNO        1
-----
F2 - Processing parameters
SI            32768
SF            75.467190 MHz
SFO1          125.013111 MHz
SFO2          300.1312005 MHz
PC            1.40
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ID NMR plot parameters
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F1            16692.90 Hz
F2P           -10.000 ppm
F2            -74.088 Hz
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HZCM          861.8798 Hz/cm
    
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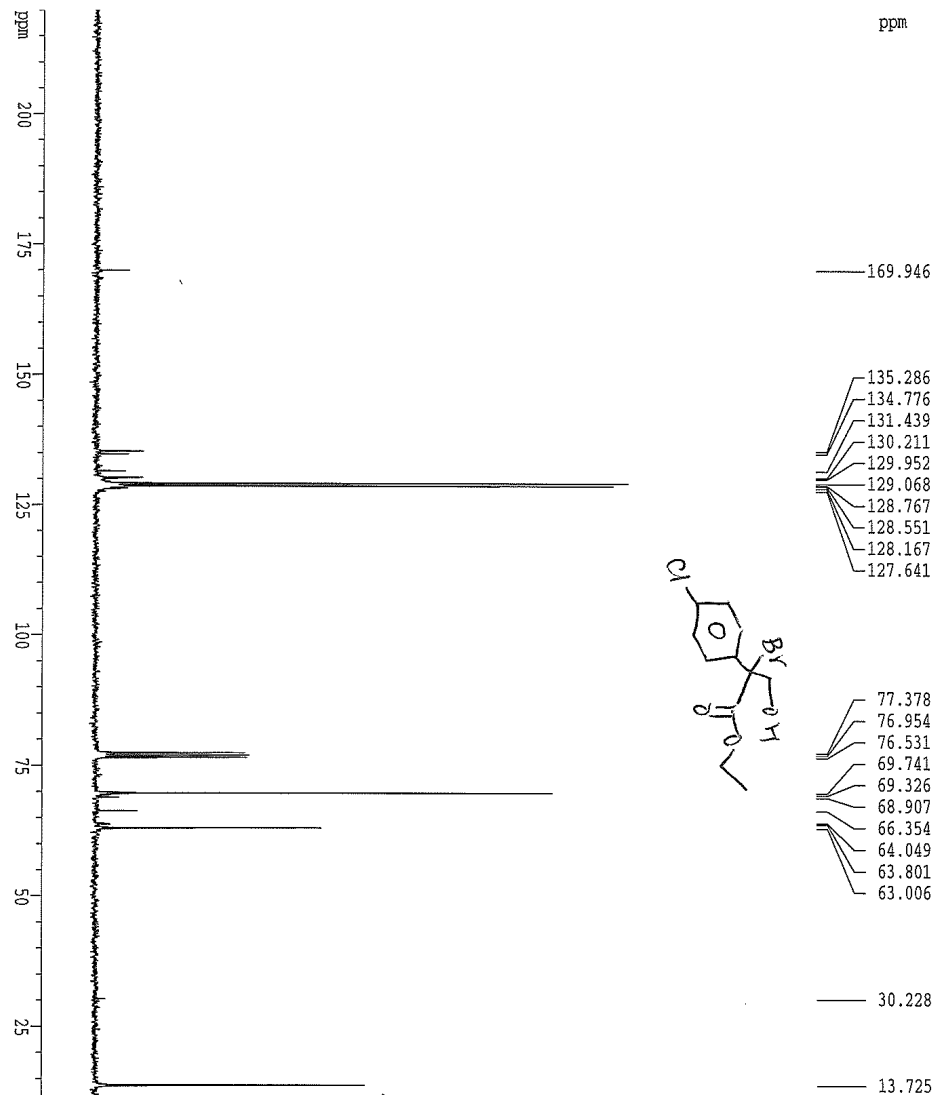


Proton Spectrum



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NOV 20 2003
PROCNO 1
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Pulseprog zgpg30
PROCNO 1
PULPROG zgpg30
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SFO 500.13
AQ 6.5542880
RG 81.600
DE 6.00
TE 298.10
TDO 1.00000001
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PL 0.00
SFO1 300.131534
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SF 300.1300000
WDW EM
SS 0.30
LB 0
GB 0
PC 1.00

Carbon Spectrum



```

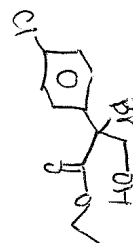
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PULPROG      zgpgc
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SOLVENTPR    CDCl3
NS            1500
DS            0
SMH           18115.941 Hz
FIDRES       0.276427 Hz
AQ           1.80888436 sec
RG            645.1
RG2           27.600 usec
DM            6.00 usec
TE           300.0 K
D1            0.10000000 sec
d11           0.03000000 sec

===== CHANNEL F1 =====
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P1            6.80 usec
PL1           -6.00 dB
SFO1          75.4758695 MHz

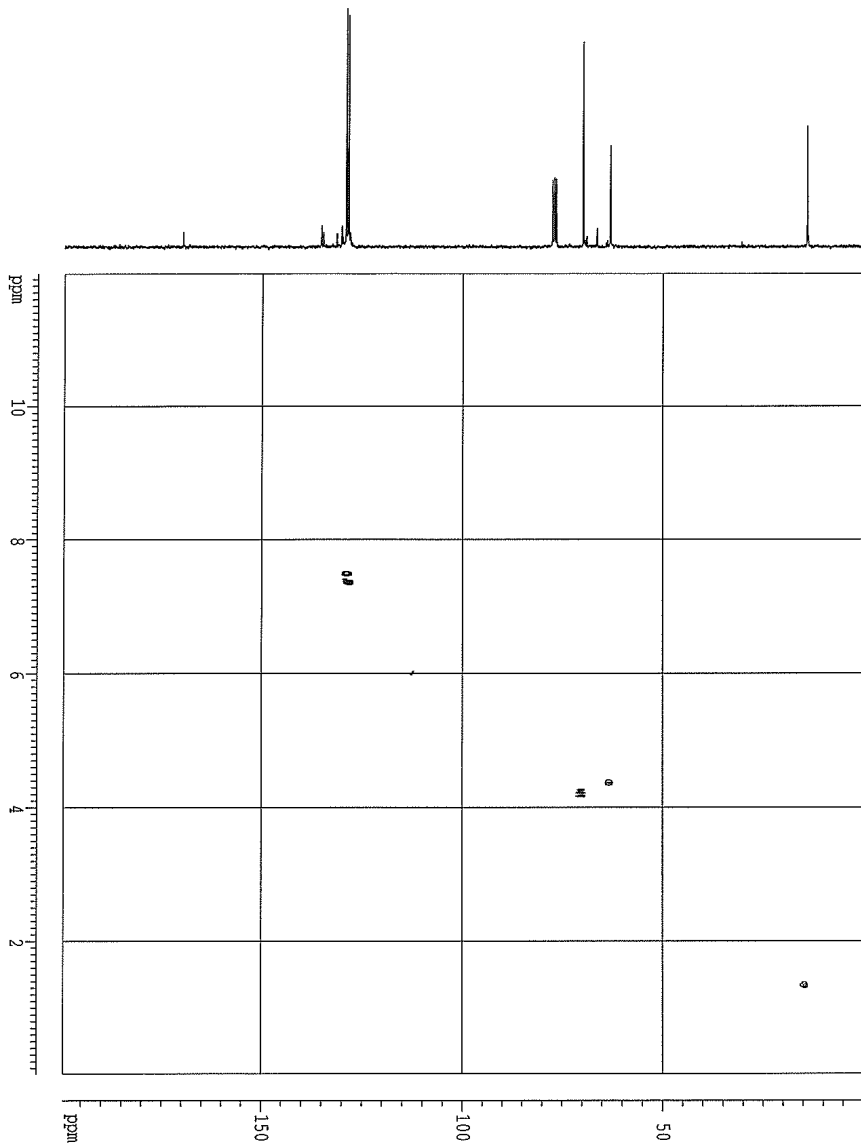
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NUC2          1H
PCPD2        100.00 usec
PL2           -6.00 dB
PL12         16.60 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI            32768
SF           75.4677567 MHz
WDW           EM
SSB           0
LB            3.00 Hz
GB            0
PC            1.40

1D NMR plot parameters:
CX           22.00 cm
FIDP         220.000 ppm
SI           16602.90 Hz
F2P          5.000 ppm
F2           -177.34 Hz
SFOCM        10.2222 ppm/cm
MDCM         771.92953 Hz/cm
    
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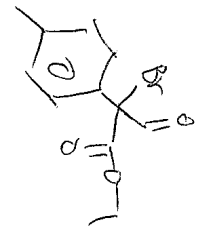
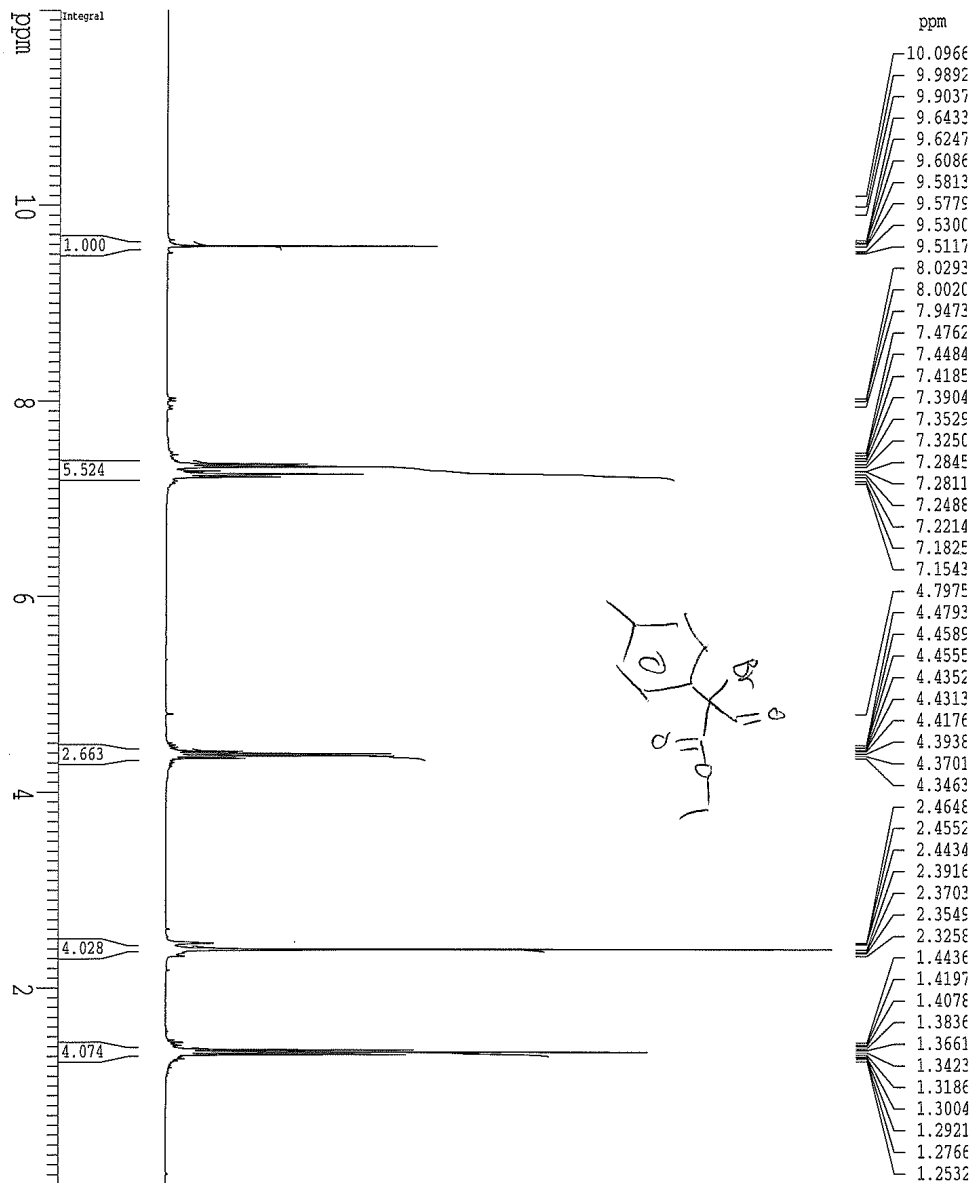


H-13C-13} HSQC spectrum



NAME: Current Data Parameters
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 PROCNO: 1
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 Time: 12.00
 INSTRUM: spect
 P1: 5.00
 P2: 0.00
 SFO: 500.1364000 MHz
 AQ: 1.0000000 sec
 RG: 655
 DQ: 32768
 FWHM: 0.3000000 Hz
 SFO2: 125.7603000 MHz
 AQC: 0.0000000 sec
 CQ: 1.0000000 sec
 F2 - Processing parameters
 SI: 32768
 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
 EQ: 1.0000000 sec
 F1 - Acquisition parameters
 SI: 655
 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
 EQ: 1.0000000 sec
 F1 - Processing parameters
 SI: 655
 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
 EQ: 1.0000000 sec
 F2 - Acquisition parameters
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 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
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 F2 - Processing parameters
 SI: 655
 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
 EQ: 1.0000000 sec
 F2 - Acquisition parameters
 SI: 655
 SF: 500.1364000 MHz
 DSF: 125.7603000 MHz
 AS: 0.3000000 Hz
 EQ: 1.0000000 sec
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 SI: 655
 SF: 500.1364000 MHz
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Proton Spectrum



Current Data Parameters
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PROCNO 1

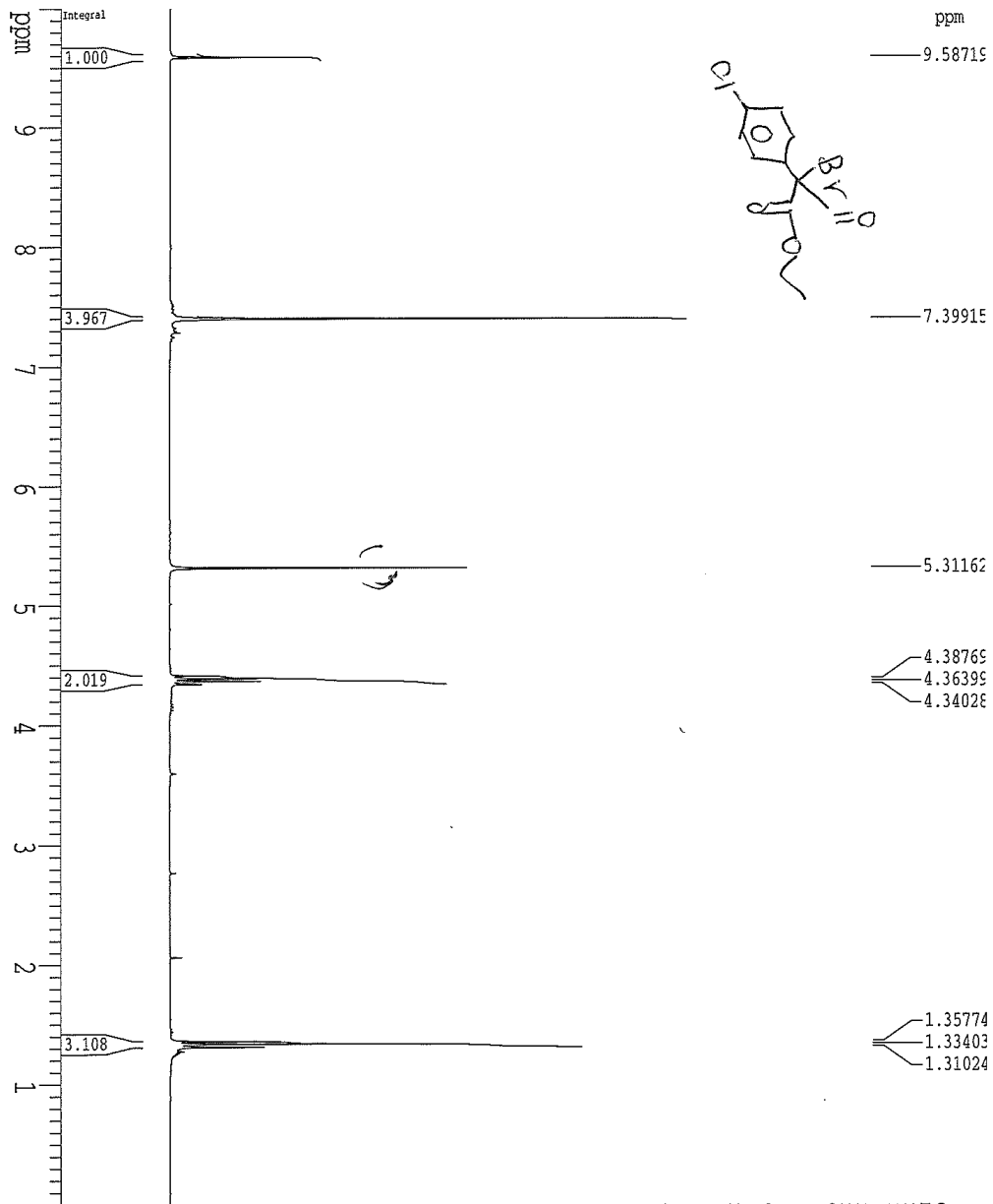
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PULPROG zgpg30
TD 32768
SOLVENT CHCl3
NS 16
DS 0
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 114
TM 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

***** CHANNEL f1 *****
NUC1 1H
P1 5.00 usec
PL -6.00 dB
SFO1 300.1319508 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 22.00 cm
F1P 12.000 ppm
F1 3601.56 Hz
F2P 0.000 ppm
F2 0.00 Hz
P1MC1D 0.54545 ppm/cm
HRCM 163.70728 Hz/cm

Proton Spectrum



Current Data Parameters
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 EXNO 1
 PROCNO 1

F2 - Acquisition Parameters

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 TD 32768
 SOLVENT CDCl3
 NS 1
 DS 0
 SWH 5995.204 Hz
 FIDRES 0.182959 Hz
 AQ 2.7329011 sec
 RG 114
 DW 83.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

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 P1A -6.00 dB
 SFO1 300.1319508 MHz

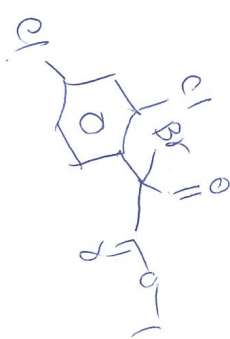
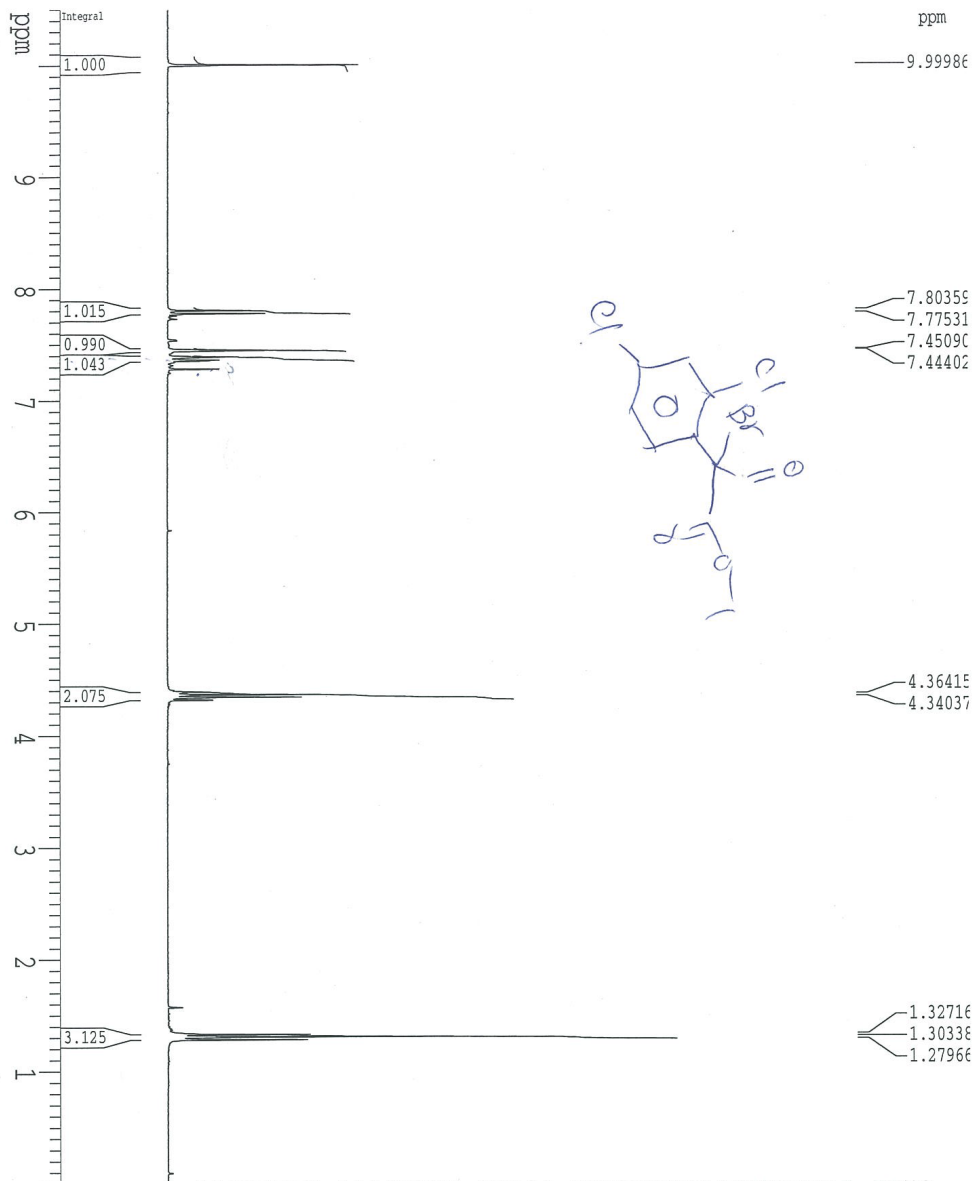
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ID NMR plot parameters

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Proton Spectrum



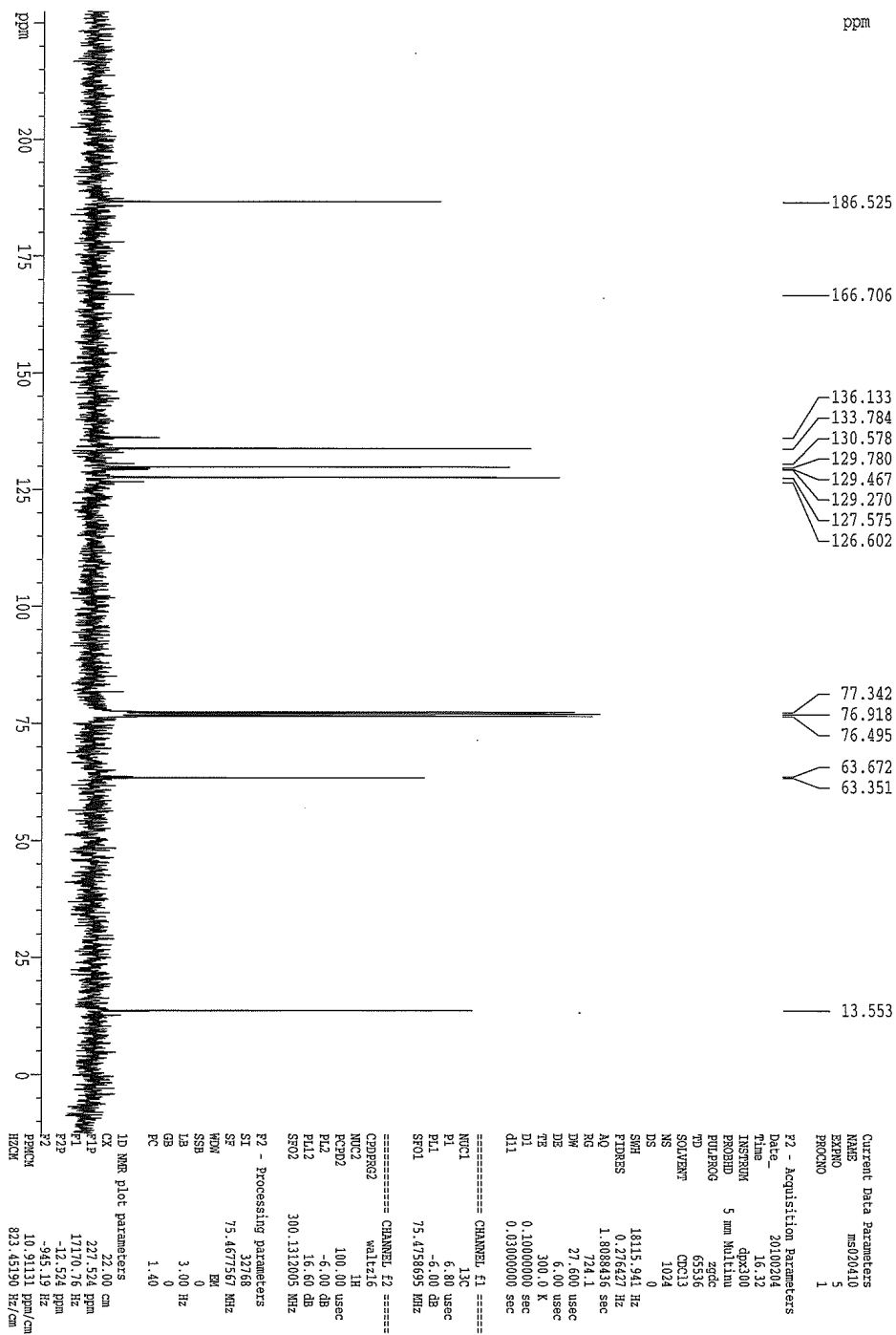
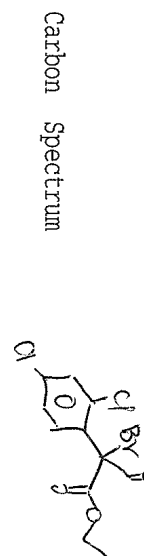
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PROCNO 1

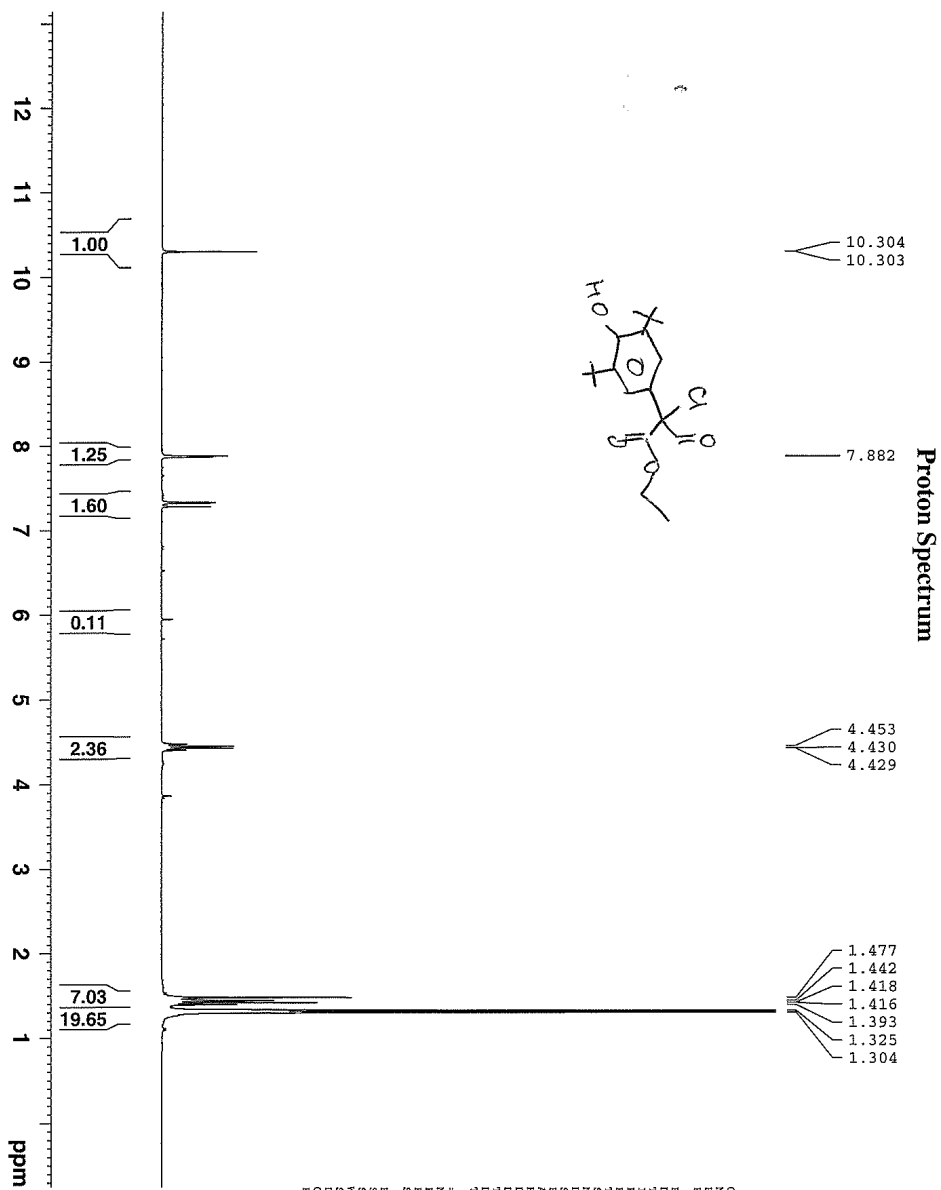
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SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 406.4
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TE 300.0 K
D1 1.00000000 sec

***** CHANNEL F1 *****
NUC1 1H
P1 5.00 usec
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SFO1 300.1319508 MHz

F2 - Processing parameters
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SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

ID NMR plot parameters
CX 22.00 cm
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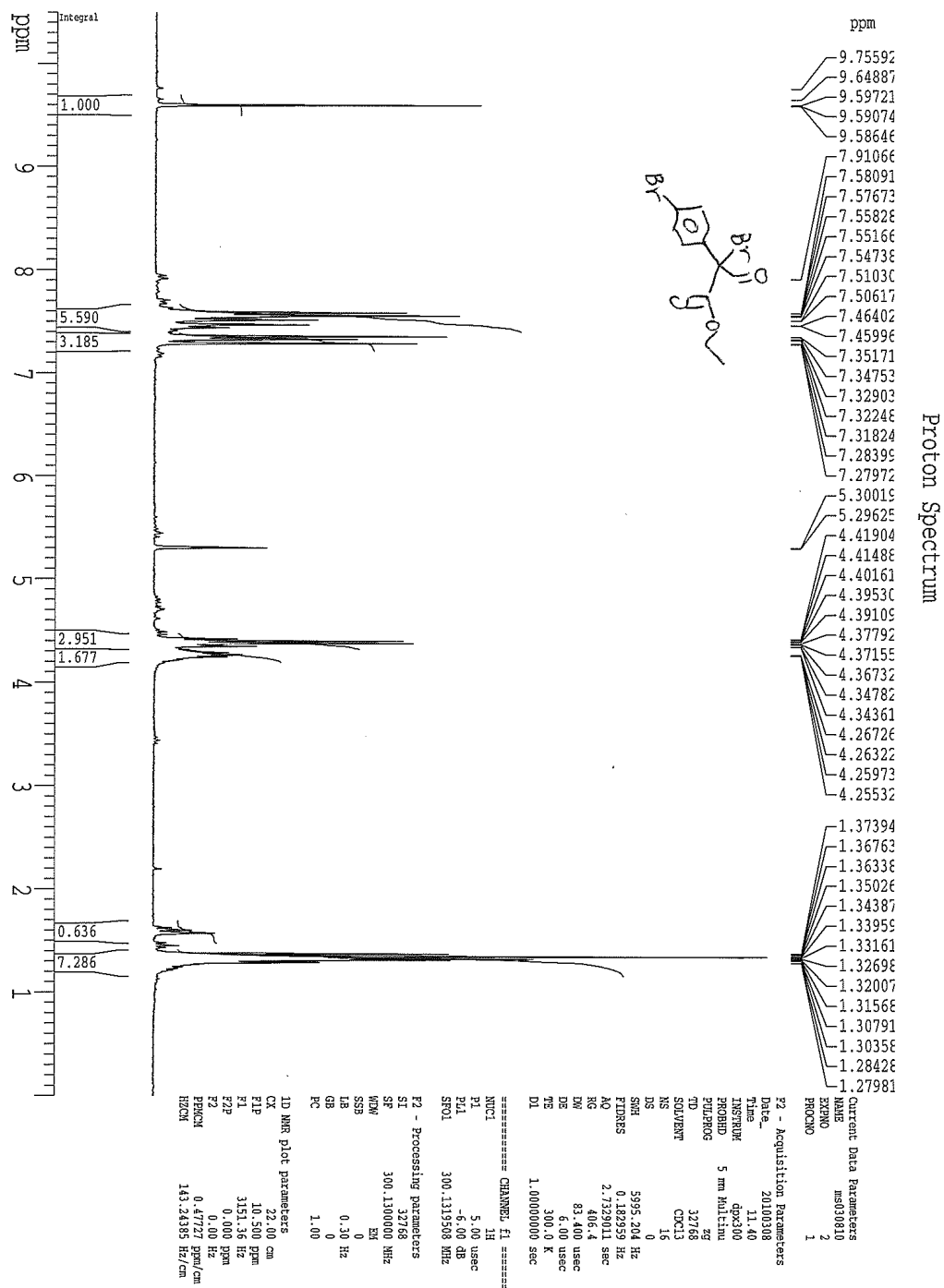




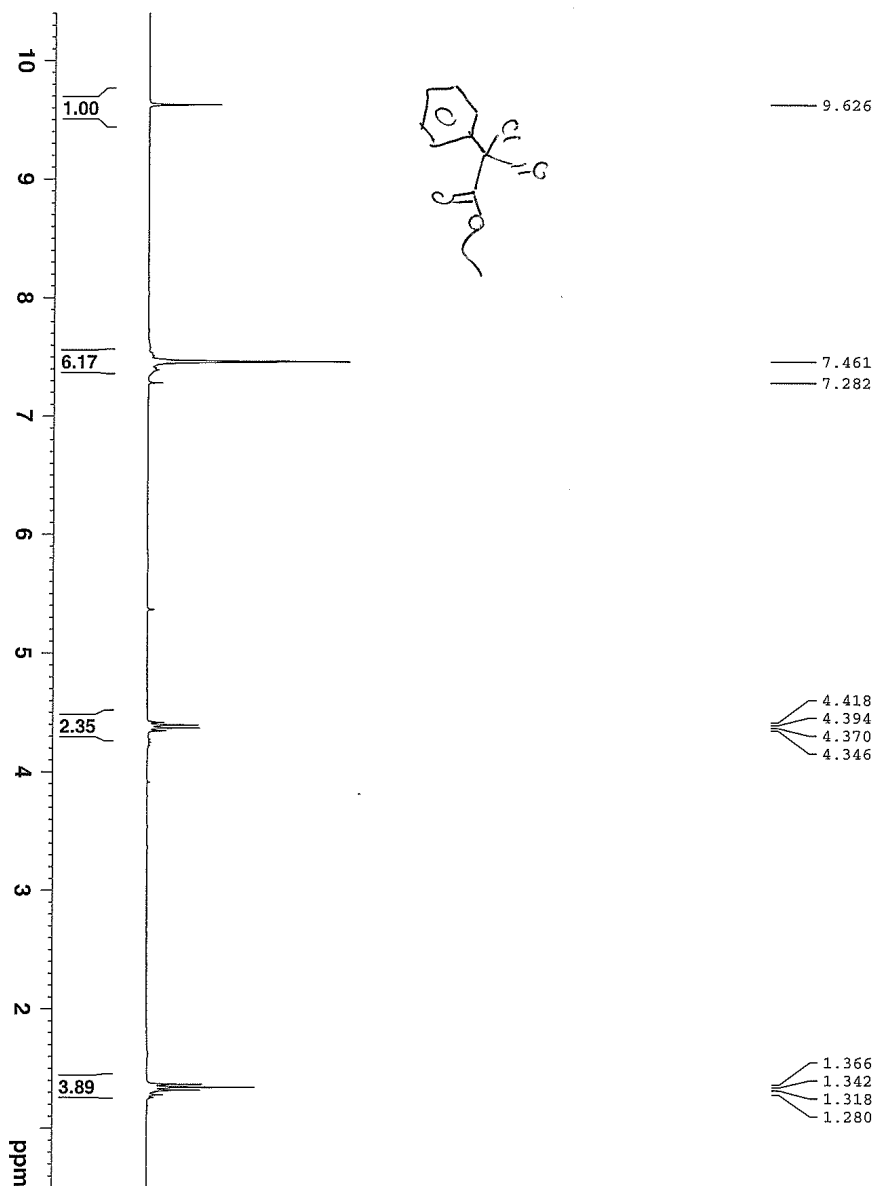
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TD           32768
SOLVENT      CDCl3
NS           64
DS           4
SWH          6172.834
FIDRES      0.168380
AQ          2.6542580
RG          61.443
WDW         EM
SS          6.00
LB          297.3
GB          0
PC          1.00000001

===== CHANNEL f1 =====
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P1           9.80
PL1          -8.00
SFO1        300.136354
F2 - Processing parameters
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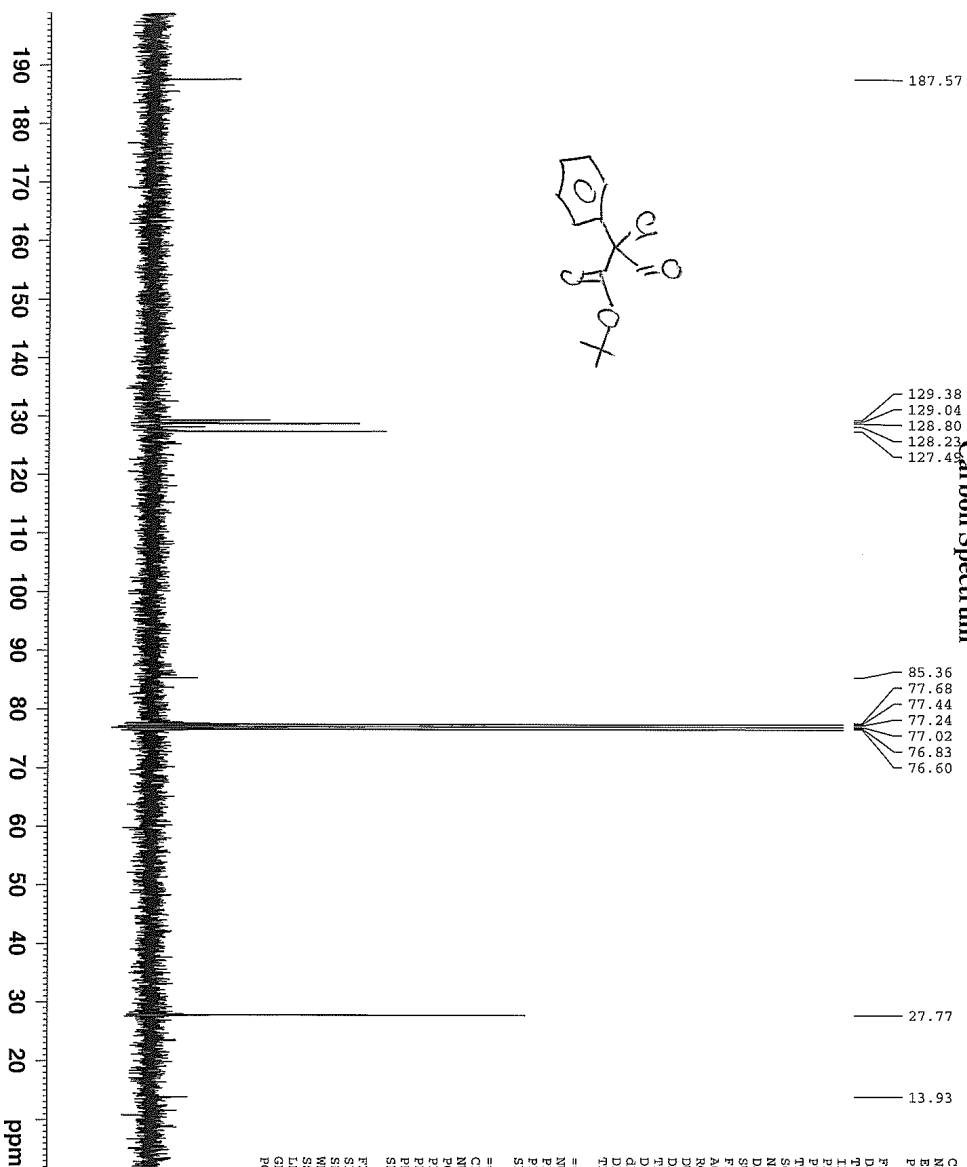
Proton Spectrum



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PROCNO     1
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DS          4
AQ          6.1728330
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AQ          2.6542580
RG          329.000
SI          81.000
DE          5.000
DI          1.0000000
TD          1
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NUC1       1H
P1         2.00
PC         0.00
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F2 - Processing parameters
SI         300.1300000
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DE         5.000
DI         1.0000000
PC         1.00
  
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Carbon Spectrum



```

Current Data Parameters
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PROCNO    1

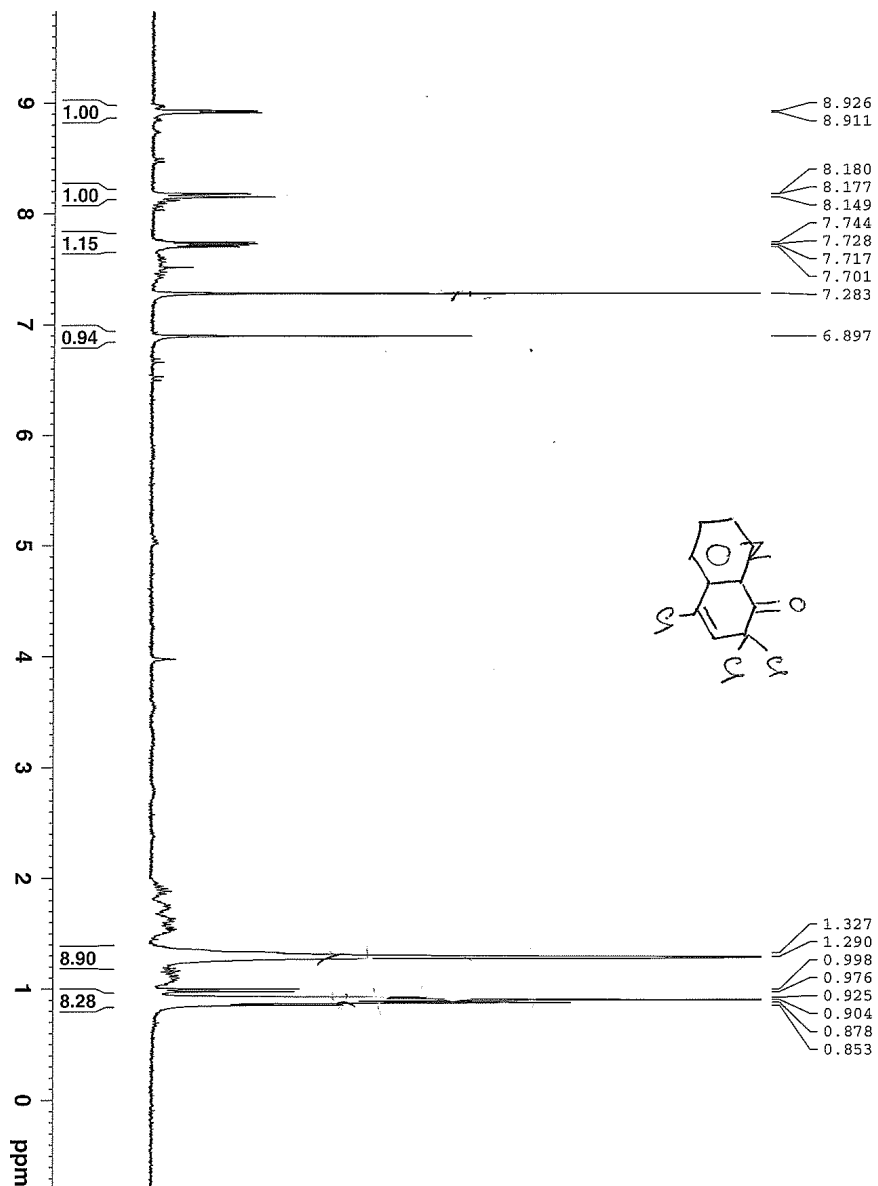
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SOLVENT   CDCl3
NS         512
DS         4
SWH        17995.611
FIDRES     0.274431
AQ         1.8219506
RG         362
DM         27.800
DE         6.00
TE         298.15
D1         0.5000000
d11        0.0000000
DELTA     0.4000000
TDO        1

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PL1        5.00
SFO1       75.4752936

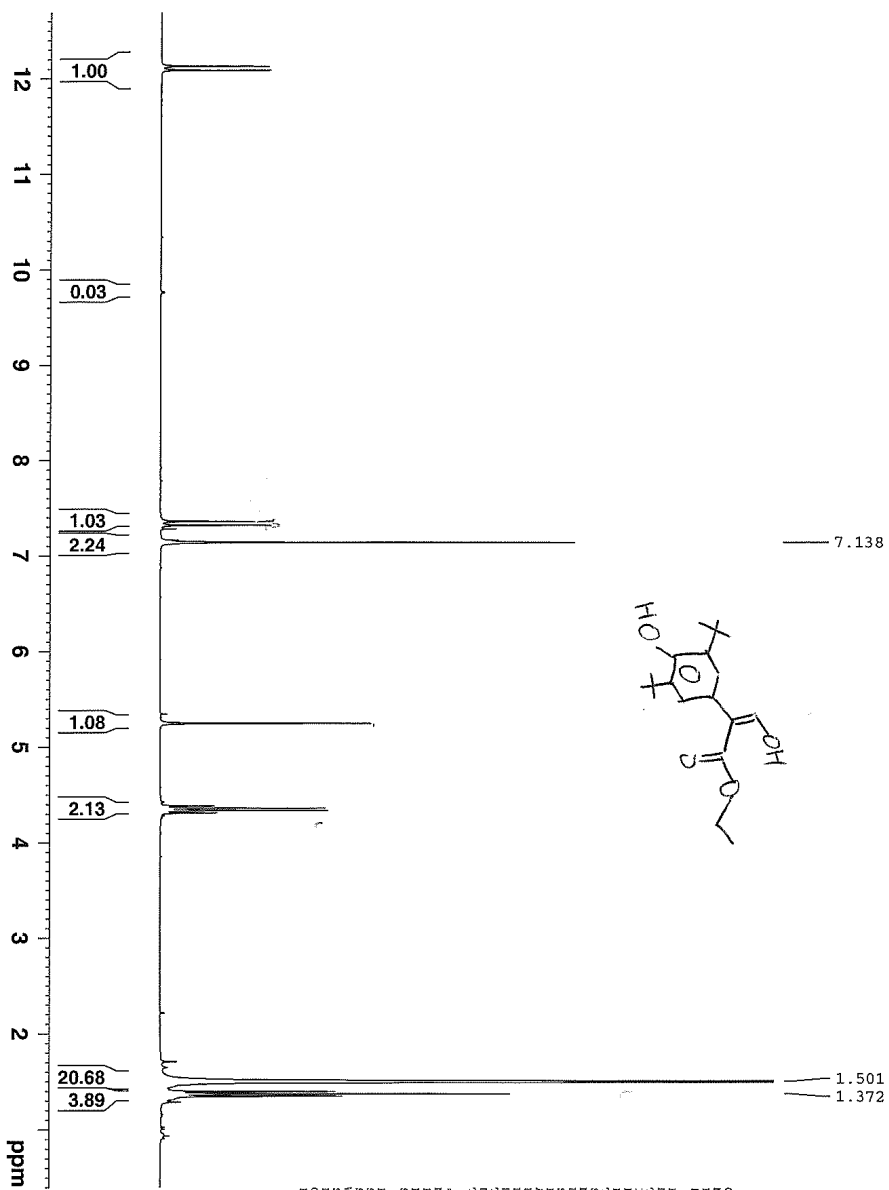
===== CHANNEL f2 =====
CDDPRG2   waltz16
NUC2       1H
PCPD2     100.00
PL2        5.00
PC13      18.40
PL13      120.00
SFO2      300.1312000

F2 - Processing parameters
SI         32768
SF         75.4677490
WDW        EM
SSB        0
LB         1.00
GB         0
PC         1.40
    
```

Proton Spectrum

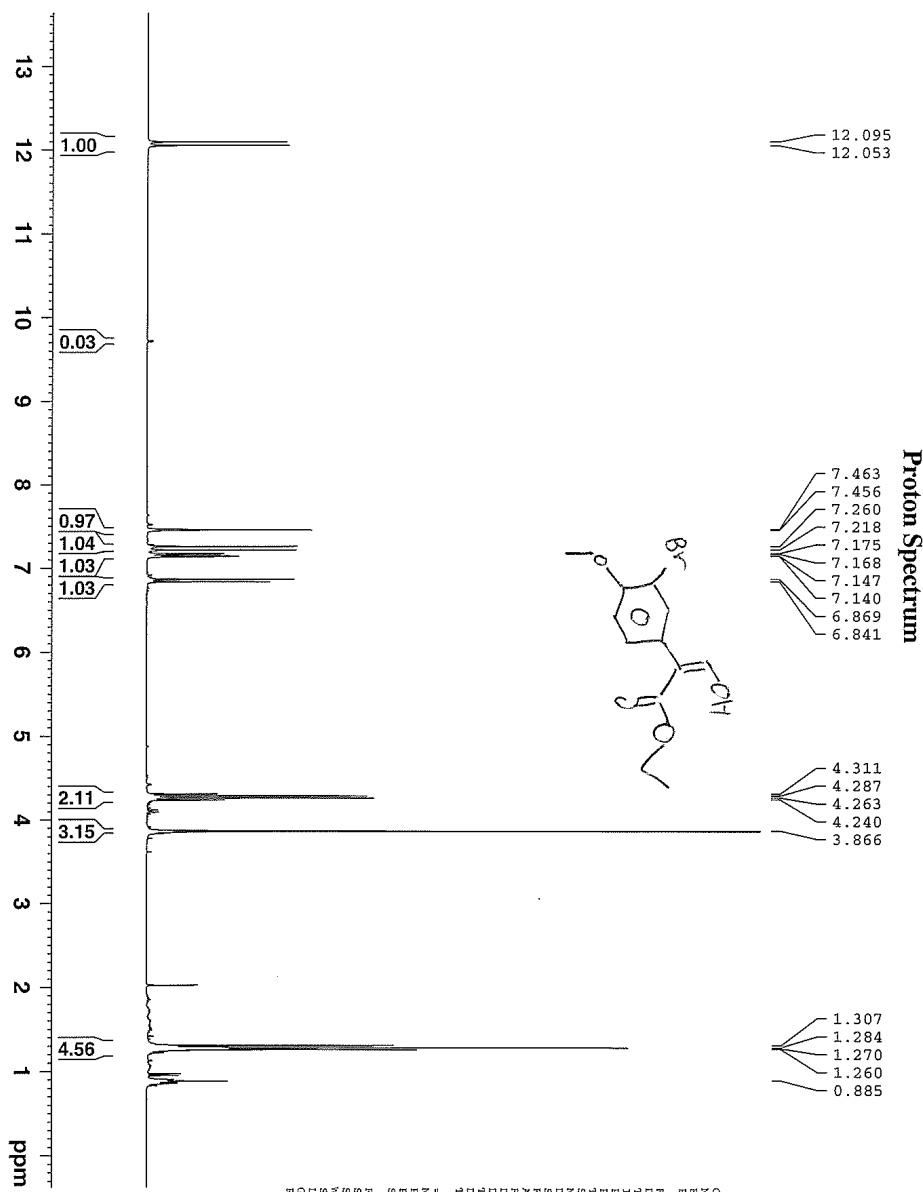


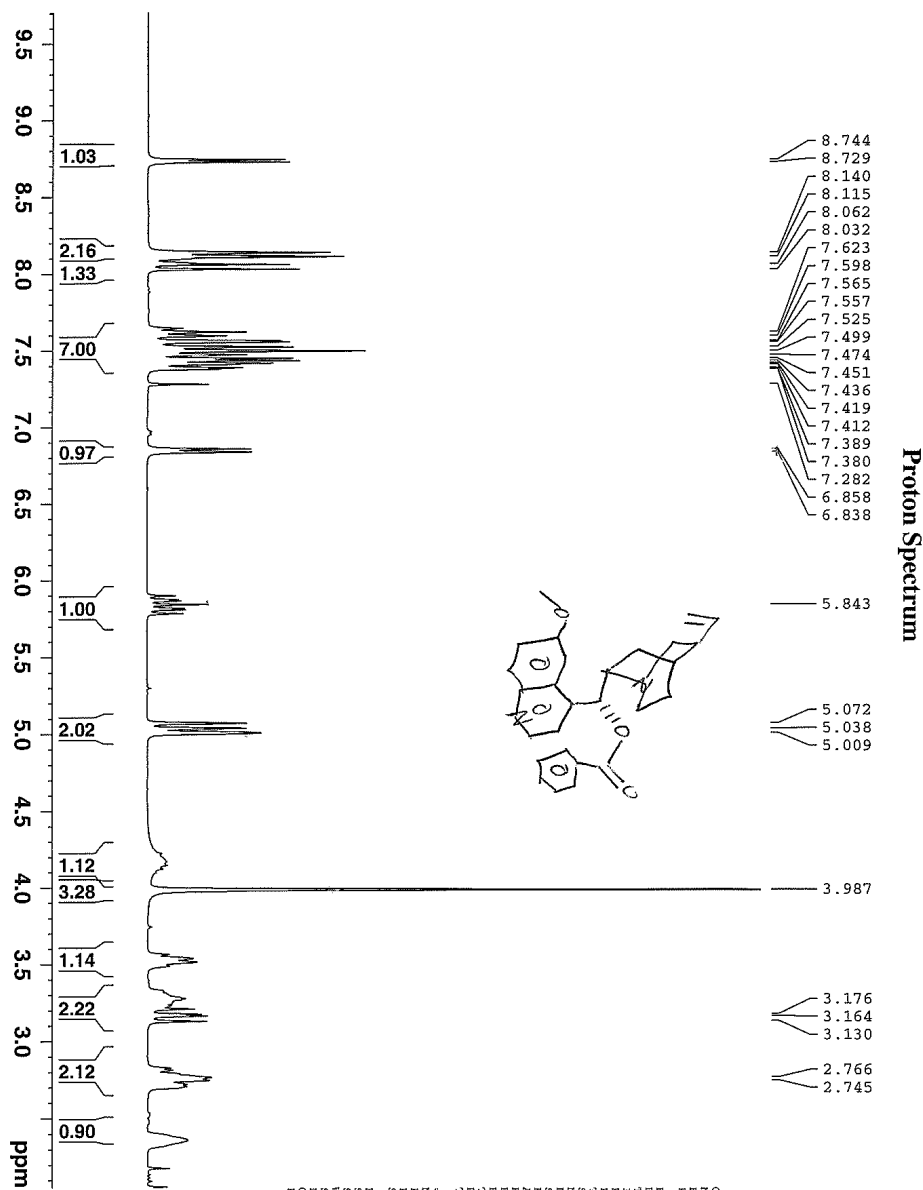
Proton Spectrum



```

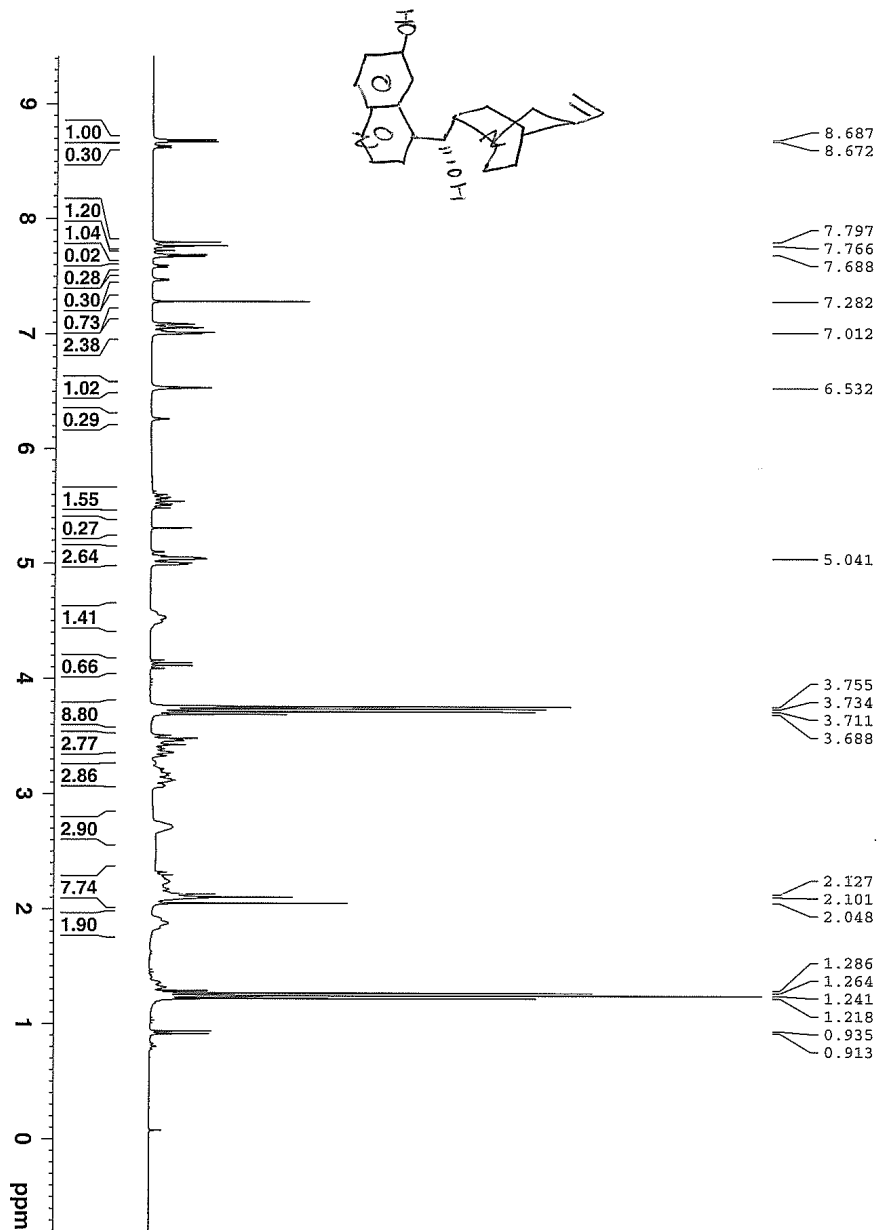
Current Data Parameters
NAME          ms07211
EXPNO        1
PROCNO       1
F2 - Acquisition Parameters
Date_         20130722
Time          12.00
PROBHD        5 mm Multiblock
PULPROG       zgpg30
TD            65536
SFO1          300.13534
AQ            0.146380
RG            81.000
DE            2.6100
DI            1.00000000
TP0          1
===== CHANNEL f1 =====
NUC1          1H
P1            9.80
PC            1
SFO1         300.13534
F2 - Processing parameters
SI            300.130000
WDW           EM
SSB           0
GB            0
PC            1.00
  
```





```

Current Data Parameters
NAME      ms072211
EXPNO     1
PROCNO    1
PROCNAME  1
F2 - Acquisition Parameters
Date_     20130722
Time      12.19
INSTRUM   spect
PROBHD    5 mm Multinuc1
PULPROG   zgpg30
TD        32730
SFO       300.136334
AQ        0.188880
RG         320
AQ        0.188880
FIDRES    2.6502990
AQ        0.188880
WDW        EM
SSB        0
GB         0
PC         1.00000000
===== CHANNEL f1 =====
NUC1       1H
P1         9.80
PL1        -2.00
SFO1       300.136334
F2 - Processing parameters
SI         32730
SF         300.1300000
WDW        EM
SSB        0
GB         0
PC         1.00
  
```



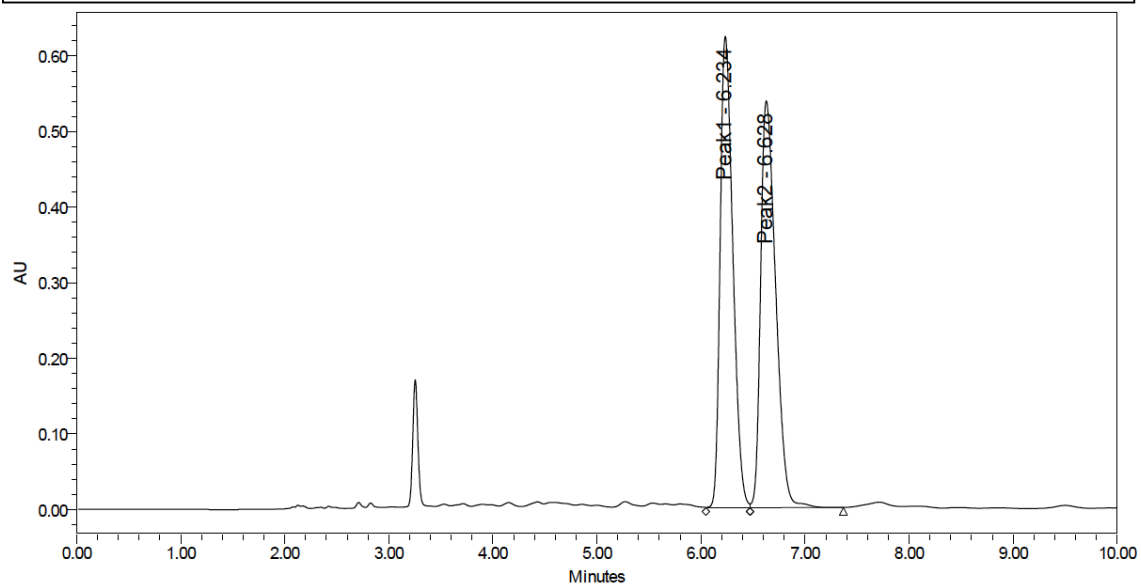
```

Current Data Parameters
NAME          ms070312
PROCNO       1
F2 - Acquisition Parameters
Date_         20120703
Time          10.05
INSTRUM      spect
PULPROG      zgpg30
TD            32768
SFO1          300.136354
AQ            2.6542580
RG            81.000
DE            5.00
TE            298.0
TDO           1.0000000
===== CHANNEL f1 =====
NUC1          1H
P1            9.80
SFO1          300.136354
F2 - Processing parameters
SF            300.1300000
WDW           EM
SSB           0.30
LB            0
GB            0
PC            1.00
  
```

HPLC Data:

Racemic Br

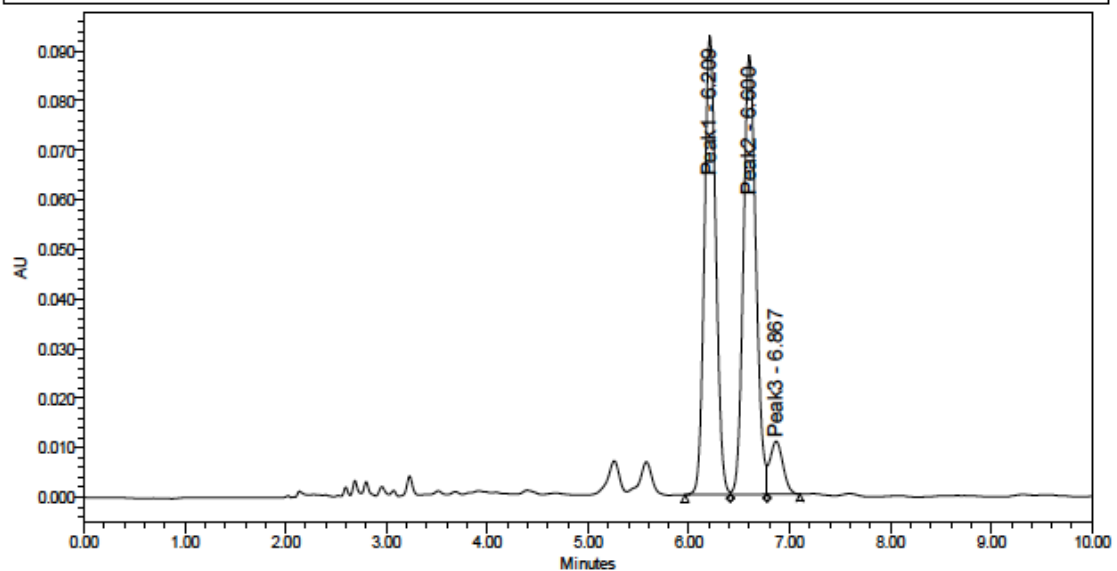
| SAMPLE INFORMATION | |
|---------------------------|--|
| Sample Name: Unk | Acquired By: Breeze |
| Sample Type: Unknown | Date Acquired: 10/4/2010 1:07:09 PM CDT |
| Vial: 1 | Acq. Method: Alcohol Br |
| Injection #: 1 | Date Processed: 10/4/2010 1:33:16 PM CDT |
| Injection Volume: 5.00 ul | Channel Name: 2998 Ch1 254nm@1.2nm |
| Run Time: 10.00 Minutes | Sample Set Name: Alcohol br expt 1 st |



| Peak | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|------|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.234 | 5275019 | 49.49 | 623692 | 53.69 |
| 2 | Peak2 | 6.628 | 5384482 | 50.51 | 537877 | 46.31 |

Table 3 Entry 1

| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/4/2010 2:51:20 PM CDT |
| Vial: | 1 | Acq. Method: | Alcohol Br |
| Injection #: | 1 | Date Processed: | 10/4/2010 3:16:46 PM CDT |
| Injection Volume: | 5.00 ul | Channel Name: | 2998 Ch1 254nm@1.2nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | proline rt |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.209 | 733751 | 45.88 | 92464 | 48.23 |
| 2 | Peak2 | 6.600 | 769477 | 48.12 | 88567 | 46.20 |
| 3 | Peak3 | 6.867 | 95913 | 6.00 | 10679 | 5.57 |

Table 3 Entry 2

UW - Milwaukee

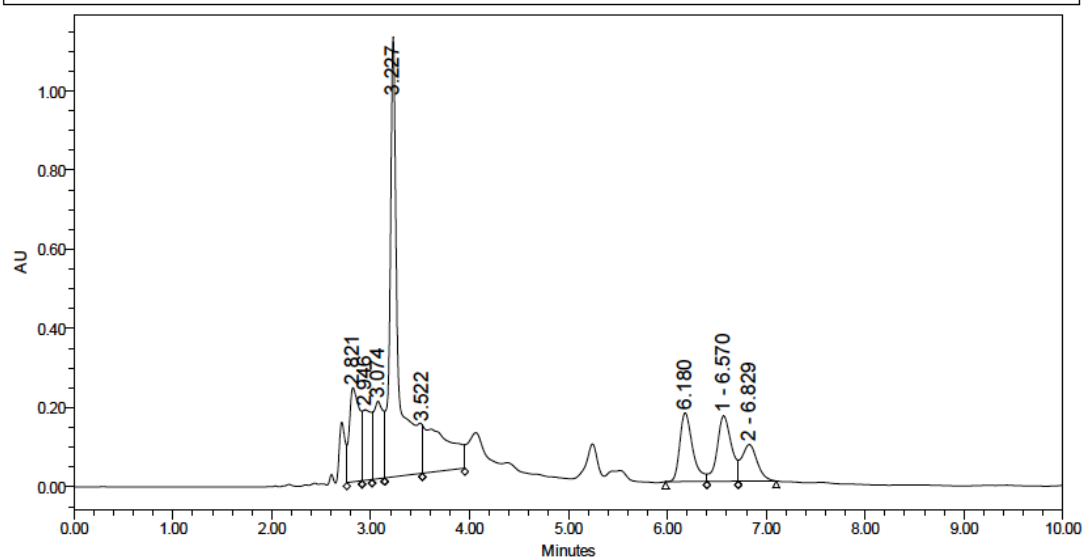
Project Name Masha

Reported by User: Breeze user (Breeze)



SAMPLE INFORMATION

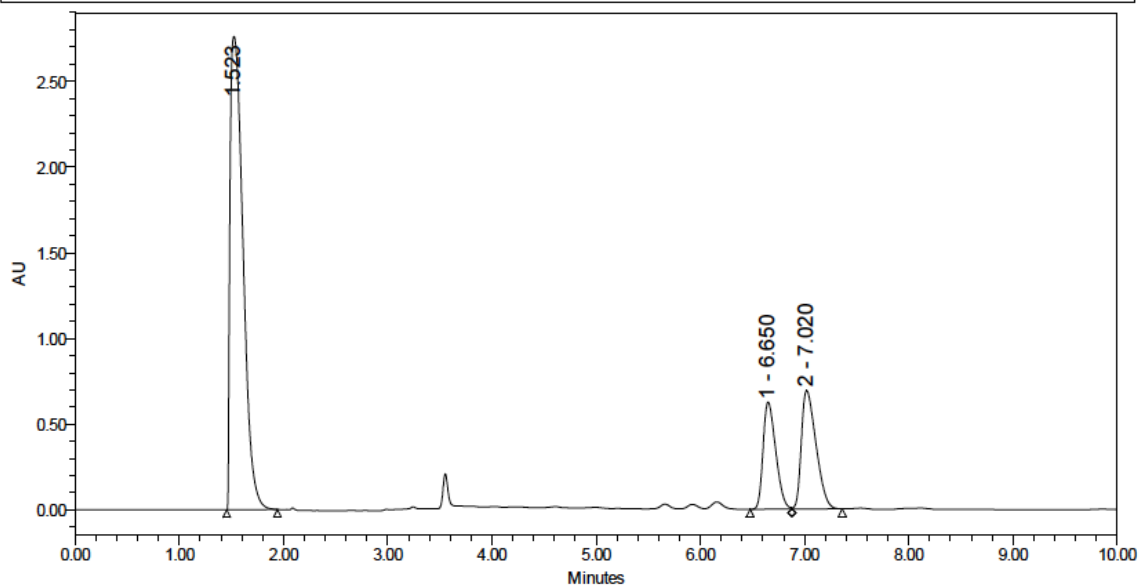
| | | | |
|-------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/4/2010 3:49:40 PM CDT |
| Vial: | 1 | Acq. Method: | Alcohol Br |
| Injection #: | 1 | Date Processed: | 10/4/2010 4:02:39 PM CDT |
| Injection Volume: | 5.00 ul | Channel Name: | 2998 Ch1 254nm@1.2nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | expt 6 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | | 2.821 | 1717909 | 9.99 | 237891 | 10.45 |
| 2 | | 2.946 | 1081859 | 6.29 | 178037 | 7.82 |
| 3 | | 3.074 | 1368432 | 7.95 | 195660 | 8.59 |
| 4 | | 3.227 | 6574563 | 38.22 | 1111460 | 48.82 |
| 5 | | 3.522 | 2216643 | 12.89 | 122100 | 5.36 |
| 6 | | 6.180 | 1577581 | 9.17 | 173566 | 7.62 |
| 7 | 1 | 6.570 | 1662915 | 9.67 | 165166 | 7.26 |
| 8 | 2 | 6.829 | 1003360 | 5.83 | 92638 | 4.07 |

Table 3 Entry 3

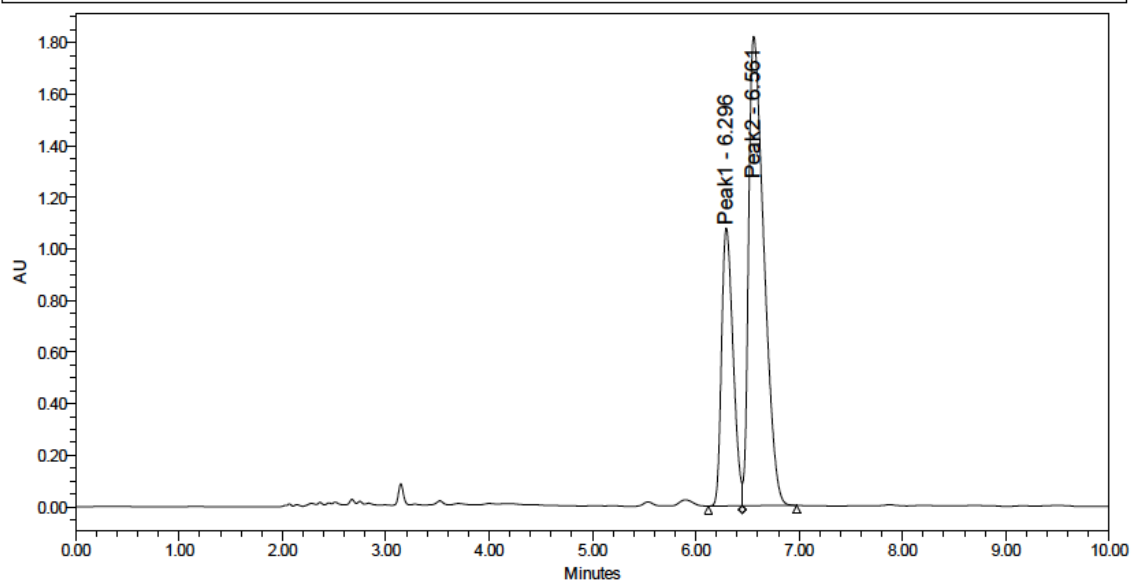
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/4/2010 1:54:00 PM CDT |
| Vial: | 1 | Acq. Method: | Alcohol Br |
| Injection #: | 1 | Date Processed: | 10/4/2010 2:14:50 PM CDT |
| Injection Volume: | 5.00 ul | Channel Name: | 2998 Ch1 254nm@1.2nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | expt 2 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | 1.523 | 23873159 | 66.54 | 2759945 | 67.72 |
| 2 1 | 6.650 | 5261795 | 14.67 | 624646 | 15.33 |
| 3 2 | 7.020 | 6742295 | 18.79 | 690979 | 16.95 |

Table 3 Entry 4

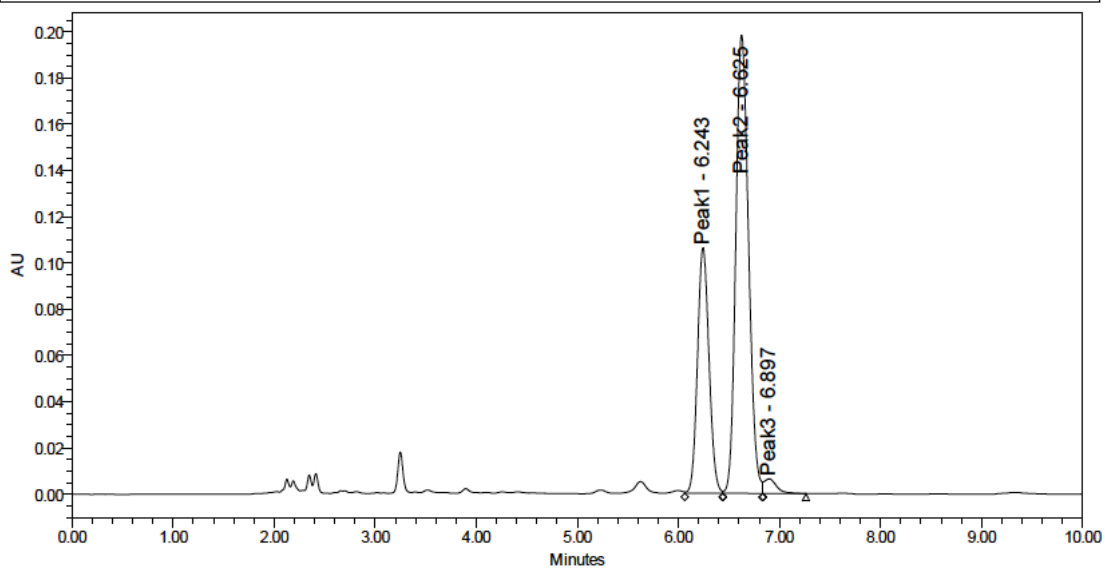
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/11/2010 3:18:19 PM CST |
| Vial: | 1 | Acq. Method: | masha chiral alcohol |
| Injection #: | 1 | Date Processed: | 11/11/2010 3:29:49 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 237.1nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 111110 78 nbs 2 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.296 | 8331254 | 30.81 | 1076881 | 37.19 |
| 2 | Peak2 | 6.561 | 18713784 | 69.19 | 1818467 | 62.81 |

Table 5 Entry 1

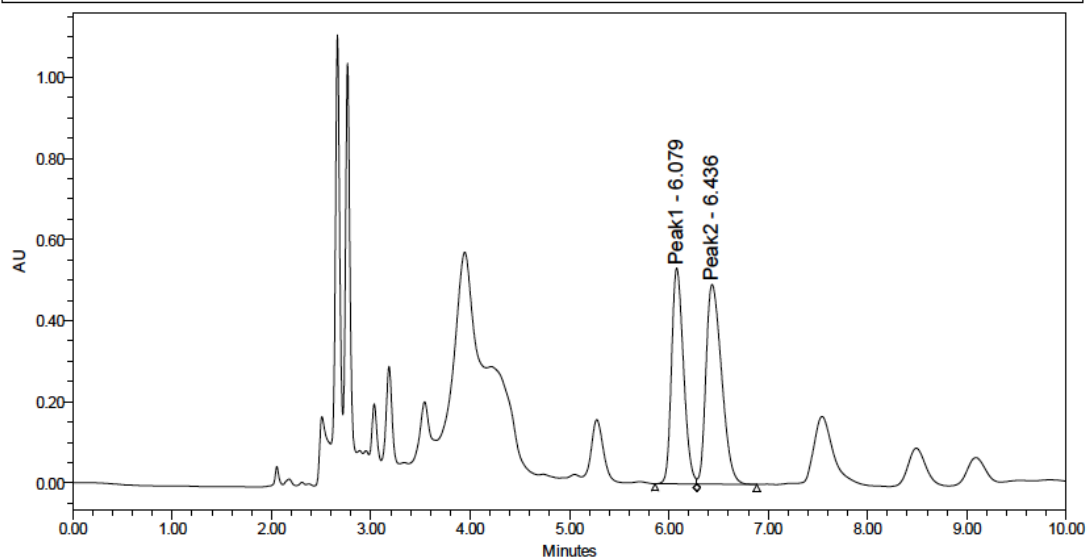
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/4/2010 2:22:17 PM CDT |
| Vial: | 1 | Acq. Method: | Alcohol Br |
| Injection #: | 1 | Date Processed: | 10/4/2010 3:30:14 PM CDT |
| Injection Volume: | 5.00 ul | Channel Name: | 2998 Ch1 254nm@1.2nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | expt 2 193 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.243 | 841134 | 31.94 | 106185 | 34.18 |
| 2 | Peak2 | 6.625 | 1737553 | 65.97 | 198197 | 63.79 |
| 3 | Peak3 | 6.897 | 54989 | 2.09 | 6301 | 2.03 |

Table 5 Entry 3

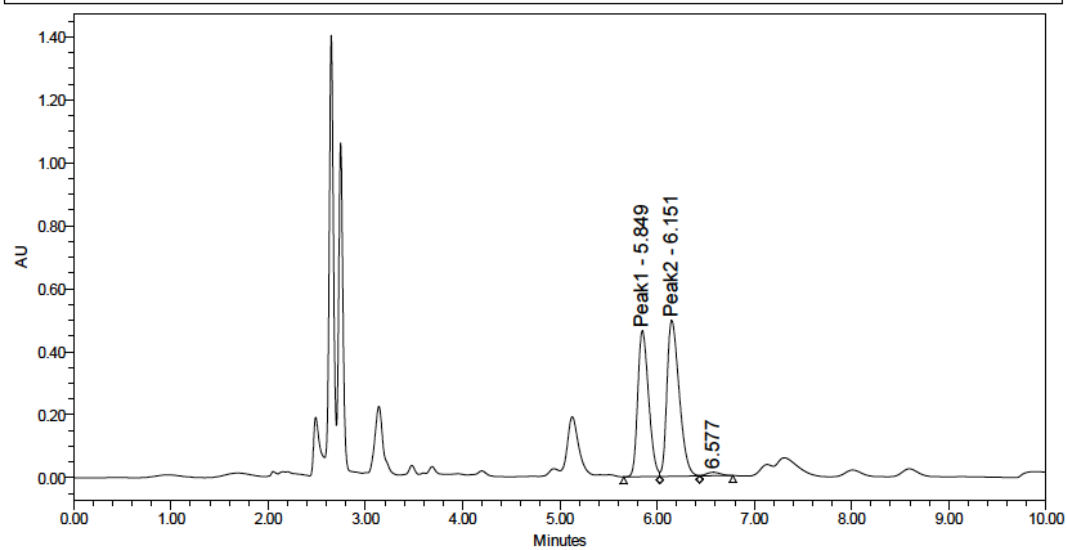
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/28/2011 2:28:18 PM CST |
| Vial: | 1 | Acq. Method: | masha chiral alcohol |
| Injection #: | 1 | Date Processed: | 1/28/2011 2:43:28 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 237.1nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 012811 p84 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 6.079 | 4445485 | 45.27 | 531523 | 51.93 |
| 2 Peak2 | 6.436 | 5375450 | 54.73 | 492089 | 48.07 |

Table 5 Entry 4

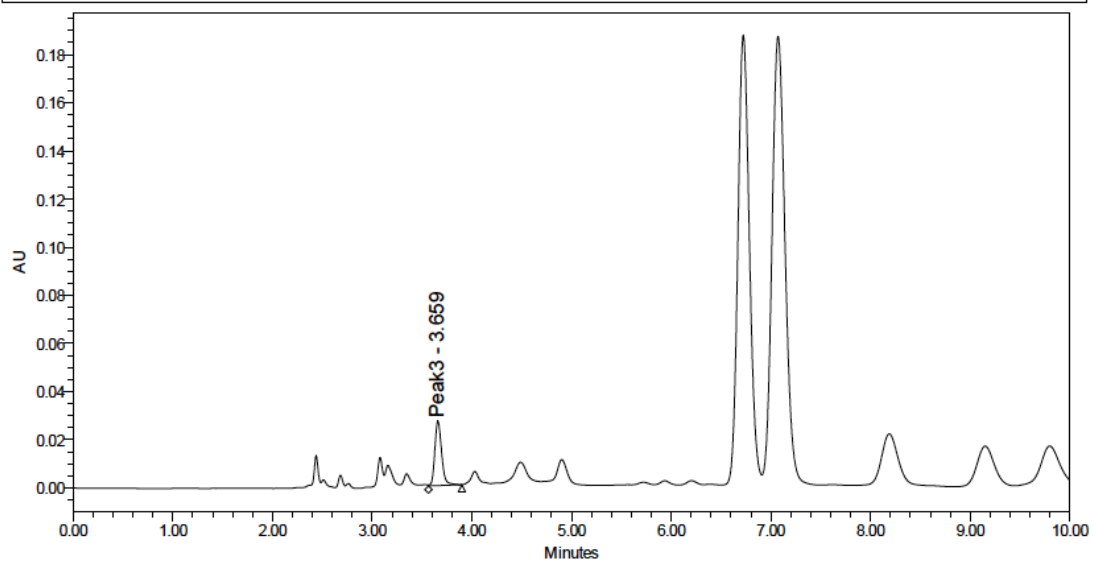
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 2/17/2011 3:33:34 PM CST |
| Vial: | 1 | Acq. Method: | masha chiral alcohol |
| Injection #: | 1 | Date Processed: | 2/17/2011 3:43:37 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 2998 Ch1 254nm@1.2nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 021711 p91 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 5.849 | 3595556 | 44.72 | 463312 | 47.81 |
| 2 Peak2 | 6.151 | 4334572 | 53.91 | 494732 | 51.05 |
| 3 | 6.577 | 110742 | 1.38 | 11076 | 1.14 |

Table 5 Entry 5

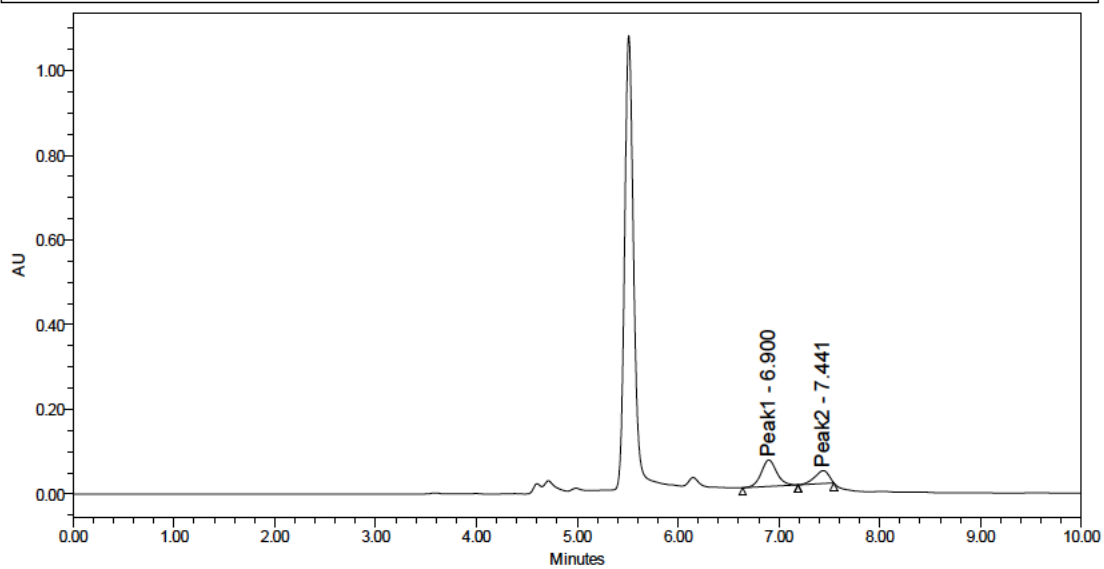
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|----------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/10/2011 12:41:54 PM CDT |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 10/10/2011 12:51:59 PM CDT |
| Injection Volume: | 10.00 ul | Channel Name: | 232.6nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 101011 b3 p5 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 3.105 | | | | |
| 2 | Peak2 | 3.183 | | | | |
| 3 | Peak3 | 3.659 | 126725 | 100.00 | 26723 | 100.00 |
| 4 | Peak4 | 3.768 | | | | |

Table 7 Entry 2

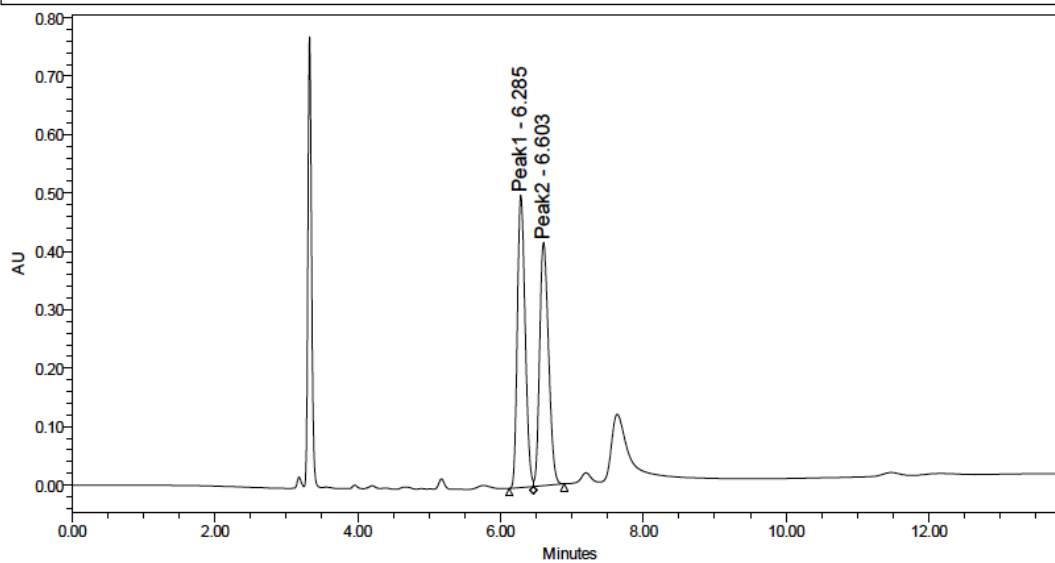
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/10/2011 2:22:16 PM CDT |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 10/10/2011 2:32:21 PM CDT |
| Injection Volume: | 10.00 ul | Channel Name: | 232.6nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 101011 be p3 3 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.900 | 663874 | 69.63 | 62261 | 67.19 |
| 2 | Peak2 | 7.441 | 289505 | 30.37 | 30401 | 32.81 |

Table 8 Entry 1

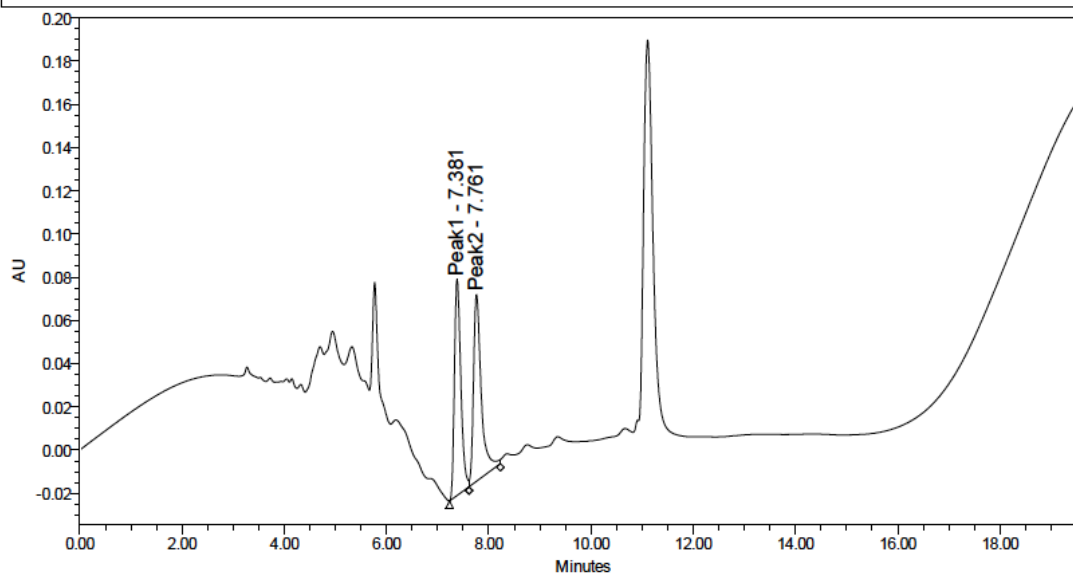
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/9/2011 1:40:19 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/9/2011 1:56:22 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 110911 b3 p7 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.285 | 3804724 | 51.20 | 499996 | 54.59 |
| 2 | Peak2 | 6.603 | 3626786 | 48.80 | 415933 | 45.41 |

Table 8 Entry 4

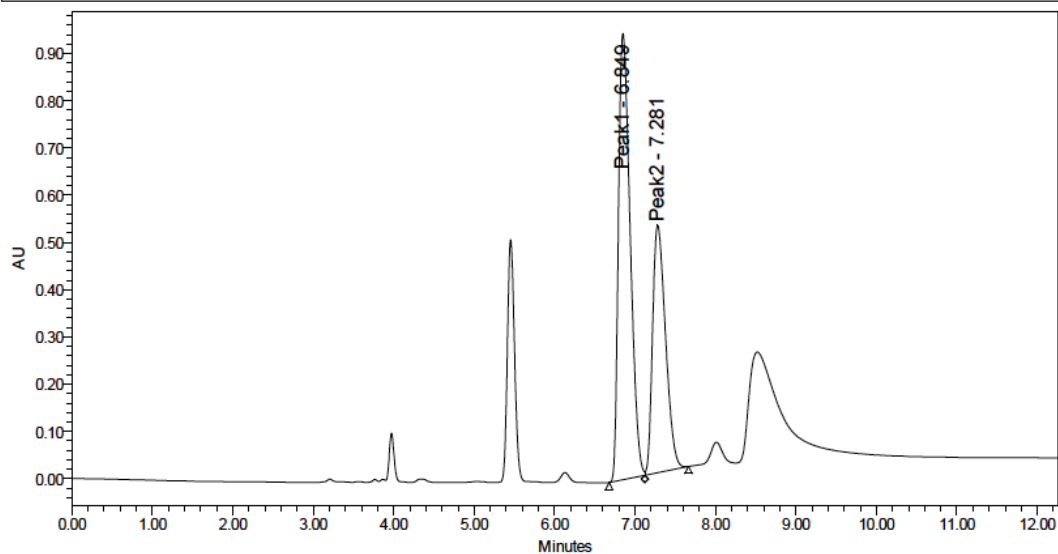
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/14/2011 4:19:00 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/14/2011 4:45:15 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 111411 b3 p24 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 7.381 | 870107 | 48.89 | 100113 | 53.71 |
| 2 Peak2 | 7.761 | 909646 | 51.11 | 86286 | 46.29 |

Table 9 entry 1

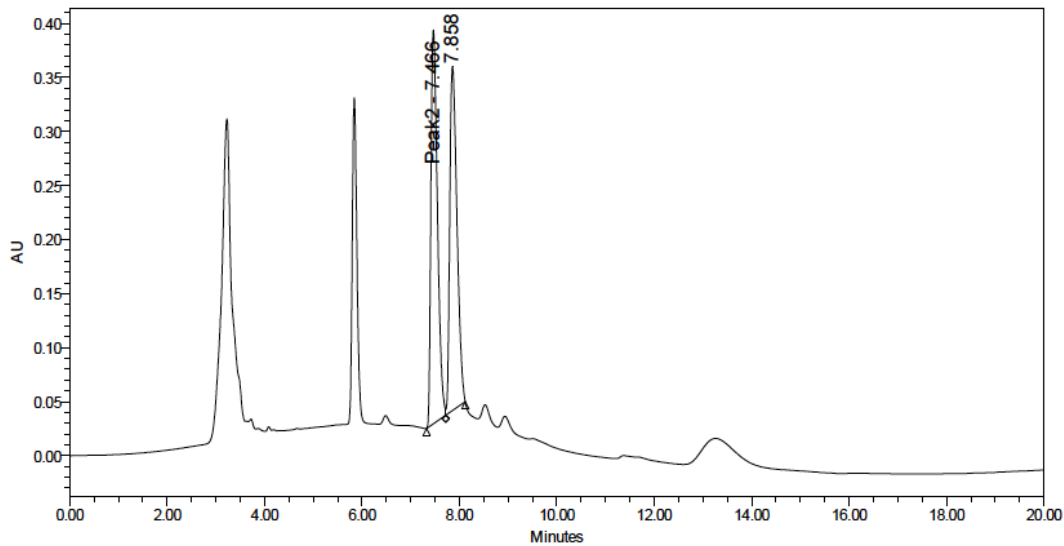
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/9/2011 3:27:25 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/9/2011 3:41:17 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 110911 b3 p6 3 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 6.849 | 9530707 | 61.94 | 944583 | 64.33 |
| 2 | Peak2 | 7.281 | 5856064 | 38.06 | 523741 | 35.67 |

Table 9 Entry 2

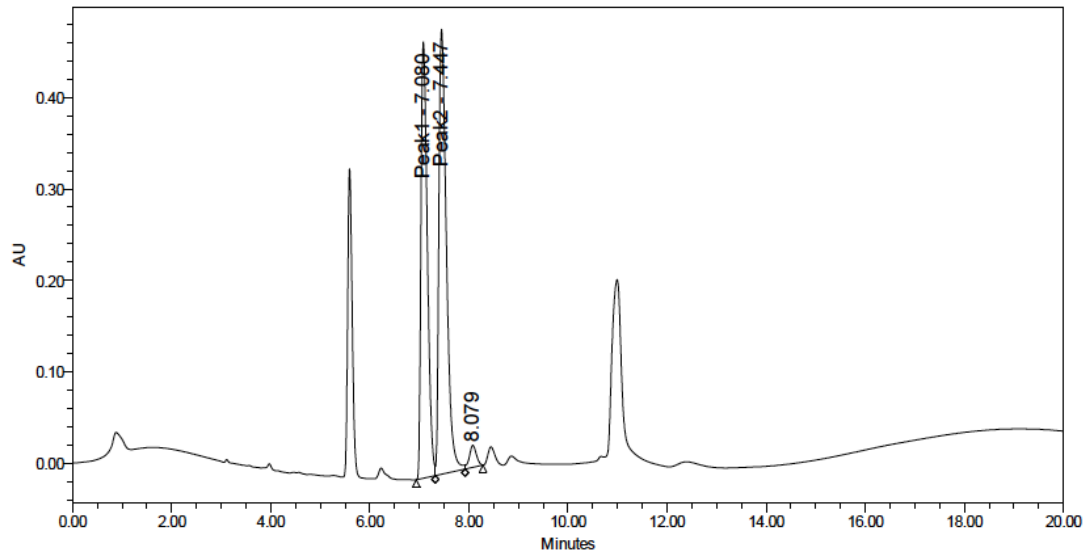
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/14/2011 2:52:39 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/14/2011 3:12:43 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 111411 b3 p16 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.012 | | | | |
| 2 | Peak2 | 7.466 | 3383815 | 50.88 | 364397 | 53.36 |
| 3 | | 7.858 | 3267051 | 49.12 | 318487 | 46.64 |

Table 9 Entry 3

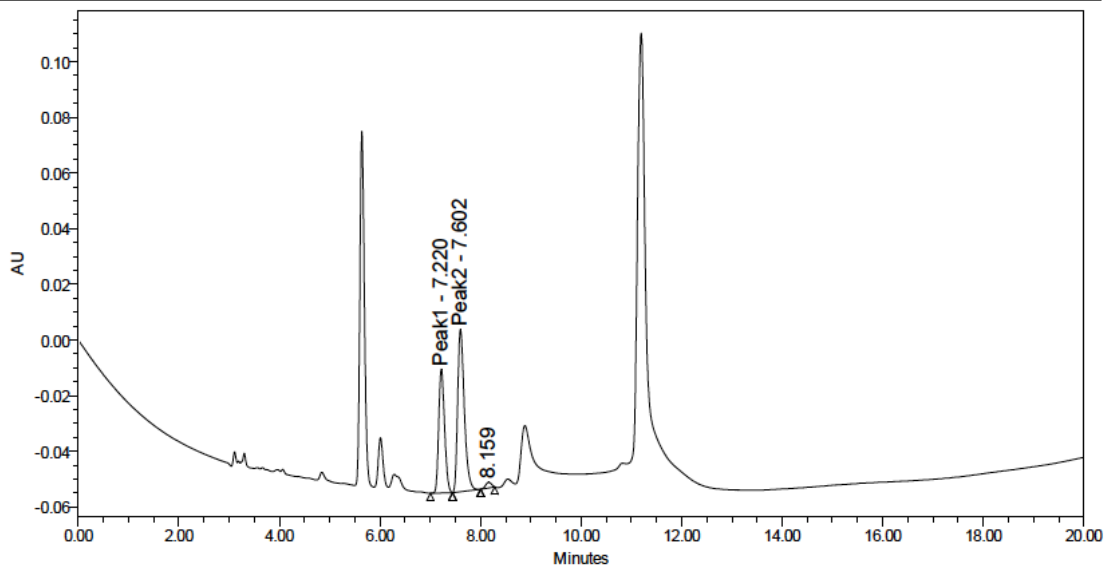
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/2/2011 3:26:11 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 12/2/2011 3:46:14 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 120211 b3 p33 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 7.080 | 4252651 | 44.20 | 477307 | 48.31 |
| 2 Peak2 | 7.447 | 5131556 | 53.34 | 486725 | 49.26 |
| 3 | 8.079 | 236813 | 2.46 | 24073 | 2.44 |

Table 9 Entry 4

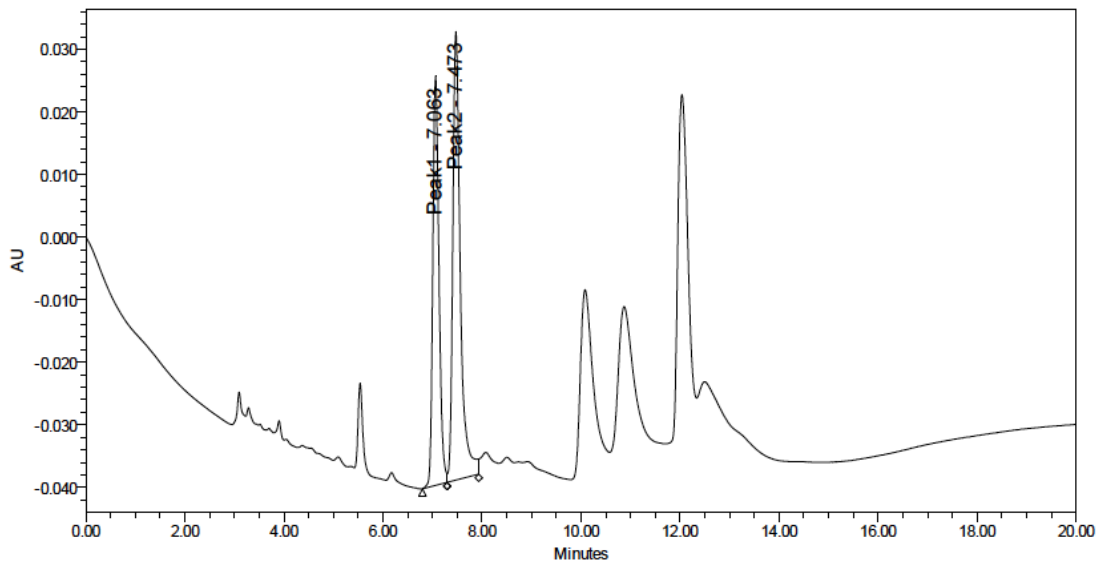
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/2/2011 3:03:41 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 12/2/2011 3:23:44 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 120211 b3 p30 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 7.220 | 359457 | 39.35 | 44499 | 42.45 |
| 2 Peak2 | 7.602 | 538021 | 58.89 | 58289 | 55.61 |
| 3 | 8.159 | 16100 | 1.76 | 2028 | 1.93 |

Table 9 Entry 5

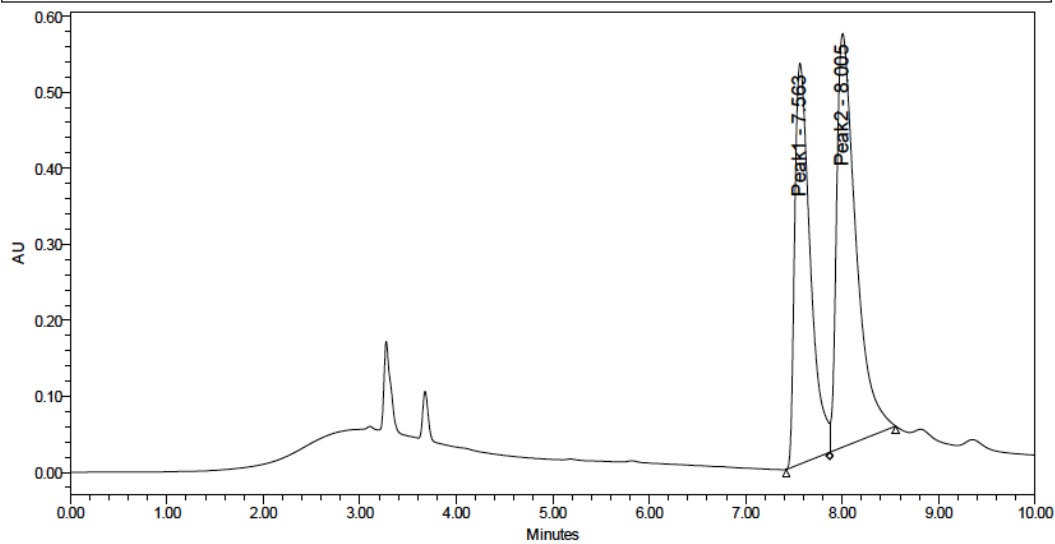
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/8/2011 12:39:06 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 12/8/2011 12:59:10 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 120811 b3 p39 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.063 | 565899 | 42.72 | 65376 | 47.71 |
| 2 | Peak2 | 7.473 | 758646 | 57.28 | 71638 | 52.29 |

Table 9 Entry 7

| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|-------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 4/4/2012 1:53:25 PM CDT |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 4/4/2012 2:03:28 PM CDT |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 040412 b3 p80 |

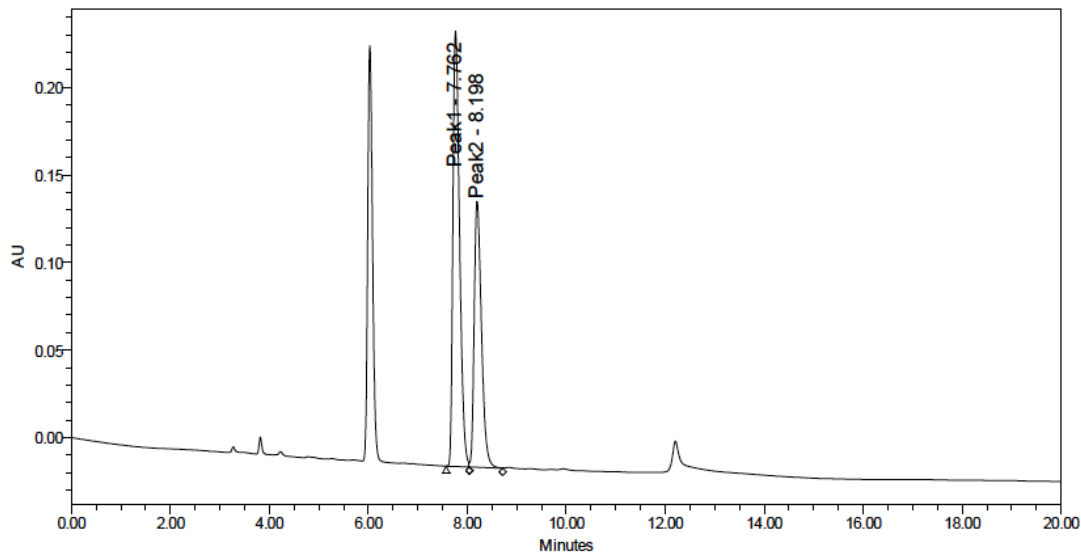


| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.563 | 5891199 | 43.78 | 526749 | 49.20 |
| 2 | Peak2 | 8.005 | 7565442 | 56.22 | 543824 | 50.80 |

Table 10 Entry 1

SAMPLE INFORMATION

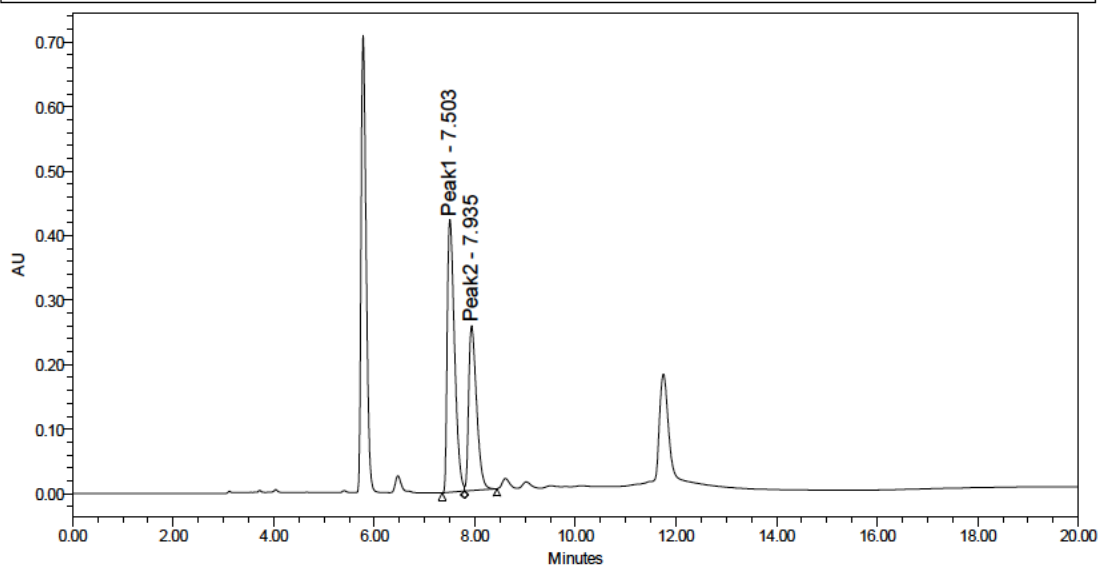
| | |
|----------------------------|---|
| Sample Name: Unk | Acquired By: Breeze |
| Sample Type: Unknown | Date Acquired: 11/15/2011 1:49:52 PM CST |
| Vial: 1 | Acq. Method: chlorination |
| Injection #: 1 | Date Processed: 11/15/2011 2:09:36 PM CST |
| Injection Volume: 10.00 ul | Channel Name: 220.1nm |
| Run Time: 20.00 Minutes | Sample Set Name: 111511 b3 p27 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 7.762 | 2319940 | 59.98 | 248704 | 62.09 |
| 2 Peak2 | 8.198 | 1548217 | 40.02 | 151862 | 37.91 |

Table 10 Entry 2

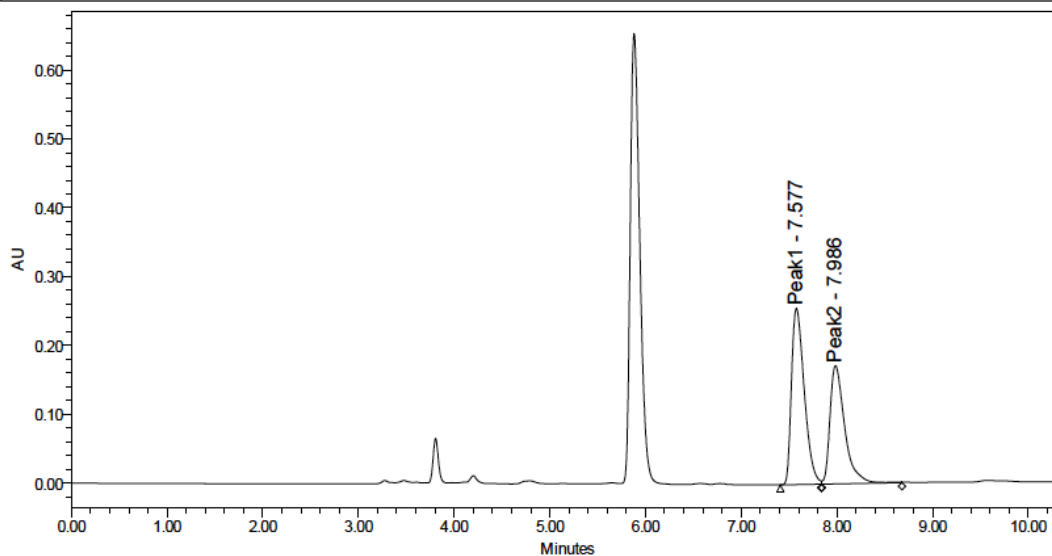
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/8/2011 1:21:10 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 12/8/2011 1:41:14 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 120811 b3 p36 |



| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 7.503 | 4268477 | 60.44 | 422912 | 62.33 |
| 2 Peak2 | 7.935 | 2793742 | 39.56 | 255645 | 37.67 |

Table 10 Entry 3

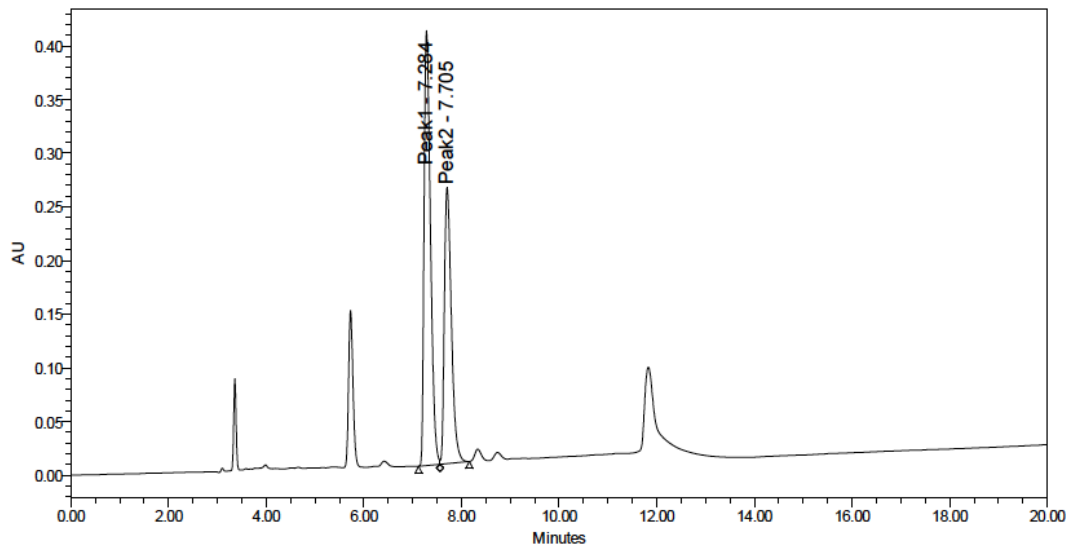
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/15/2011 4:01:44 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 11/15/2011 4:12:45 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 111511 b3 p26 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.577 | 2371055 | 56.33 | 255860 | 59.86 |
| 2 | Peak2 | 7.986 | 1838138 | 43.67 | 171599 | 40.14 |

Table 11 Entry 2

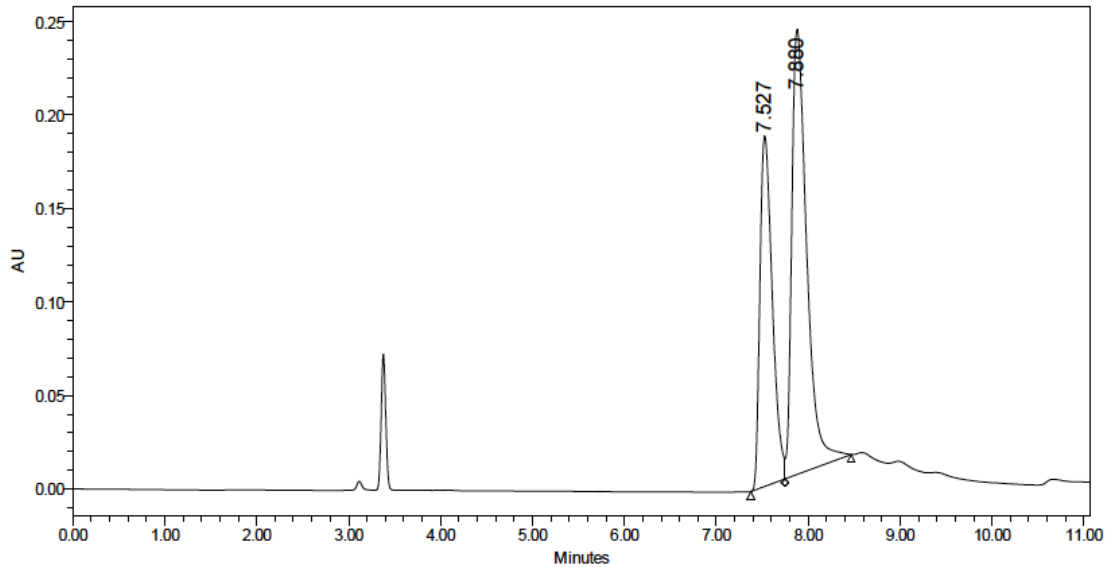
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|--------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/5/2011 2:08:01 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 12/5/2011 2:33:05 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 120511 b3 p32 |



| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.284 | 3676218 | 58.92 | 405289 | 61.17 |
| 2 | Peak2 | 7.705 | 2563558 | 41.08 | 257220 | 38.83 |

Table 16 Entry 3

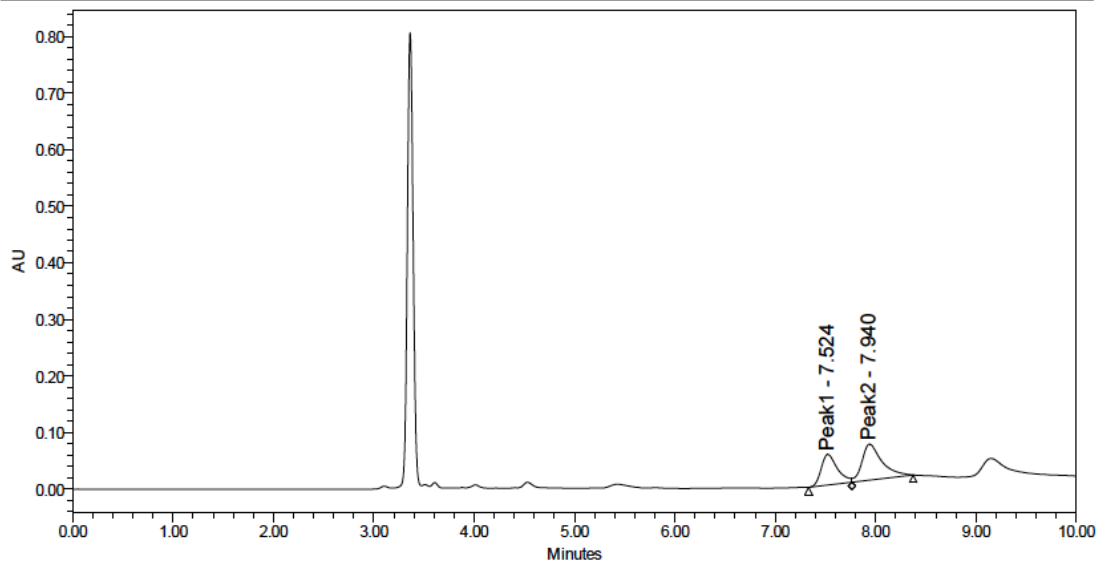
| SAMPLE INFORMATION | | | | | |
|--------------------|---------------|------------------|---------------------------|--|--|
| Sample Name: | Unk | Acquired By: | Breeze | | |
| Sample Type: | Unknown | Date Acquired: | 1/10/2012 11:35:25 AM CST | | |
| Vial: | 1 | Acq. Method: | chlorination | | |
| Injection #: | 1 | Date Processed: | 1/10/2012 11:46:46 AM CST | | |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm | | |
| Run Time: | 20.00 Minutes | Sample Set Name: | 011012 b3 p59 1 | | |



| | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-------------|--|--------|-----------------------------|-------------|
| 1 | 7.527 | 1748863 | 39.41 | 187399 | 44.03 |
| 2 | 7.880 | 2688581 | 60.59 | 238177 | 55.97 |

Table 16 Entry 4

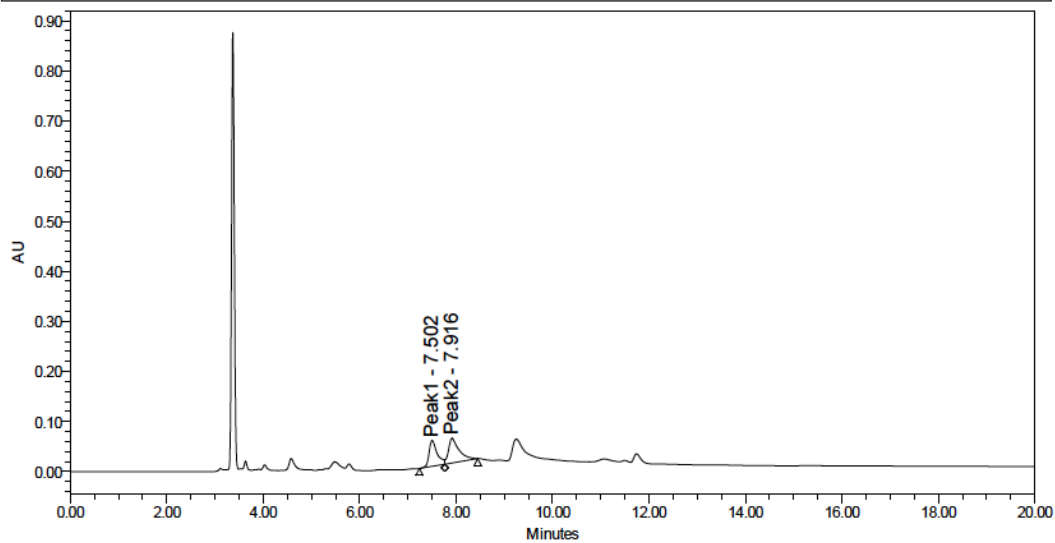
| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/18/2012 11:34:12 AM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 1/18/2012 11:44:16 AM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 10.00 Minutes | Sample Set Name: | 011812 b3 p64 |



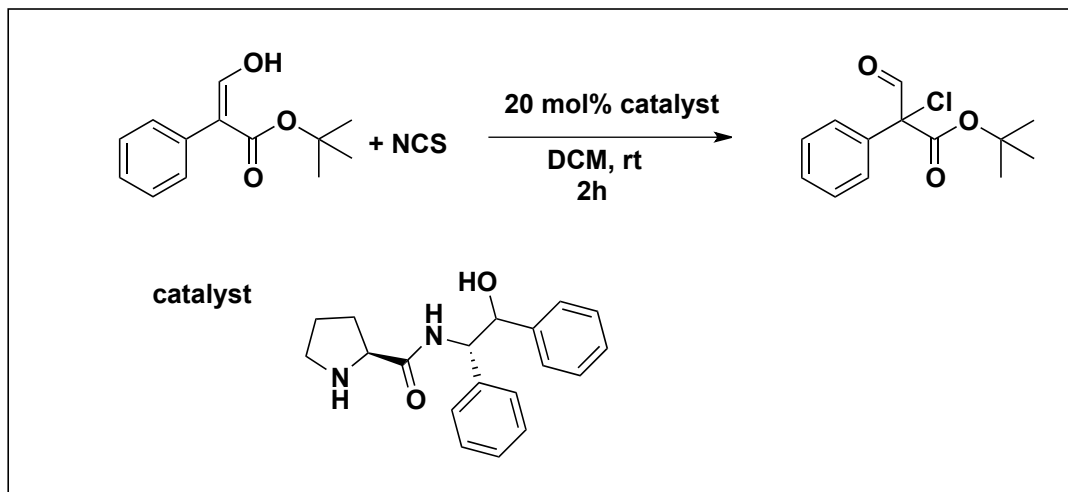
| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.524 | 606417 | 40.58 | 54101 | 45.93 |
| 2 | Peak2 | 7.940 | 887914 | 59.42 | 63699 | 54.07 |

Table 17 Entry 2

| SAMPLE INFORMATION | | | |
|--------------------|---------------|------------------|---------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/18/2012 12:13:09 PM CST |
| Vial: | 1 | Acq. Method: | chlorination |
| Injection #: | 1 | Date Processed: | 1/18/2012 12:33:13 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.1nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 011812 b3 p66 |



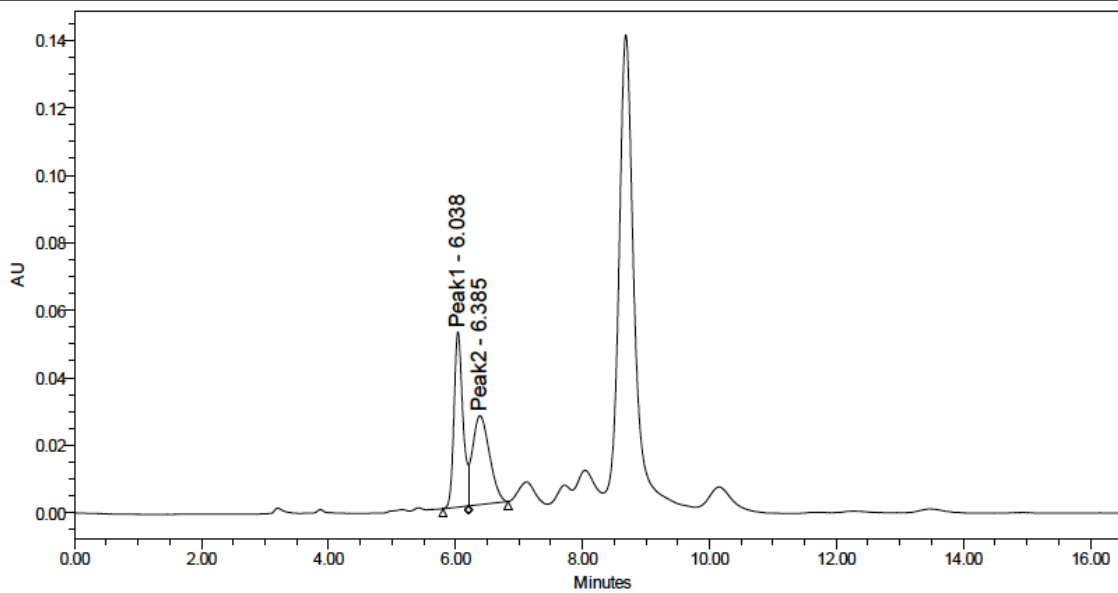
| | Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|---|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 | Peak1 | 7.502 | 600795 | 44.53 | 51811 | 51.38 |
| 2 | Peak2 | 7.916 | 748250 | 55.47 | 49019 | 48.62 |



Racemic

SAMPLE INFORMATION

| | | | |
|-------------------|---------------|------------------|-------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/5/2014 2:31:20 PM CST |
| Vial: | 1 | Acq. Method: | tbueda |
| Injection #: | 1 | Date Processed: | 1/5/2014 2:47:34 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 219.4nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 010514 tbueda racemic |

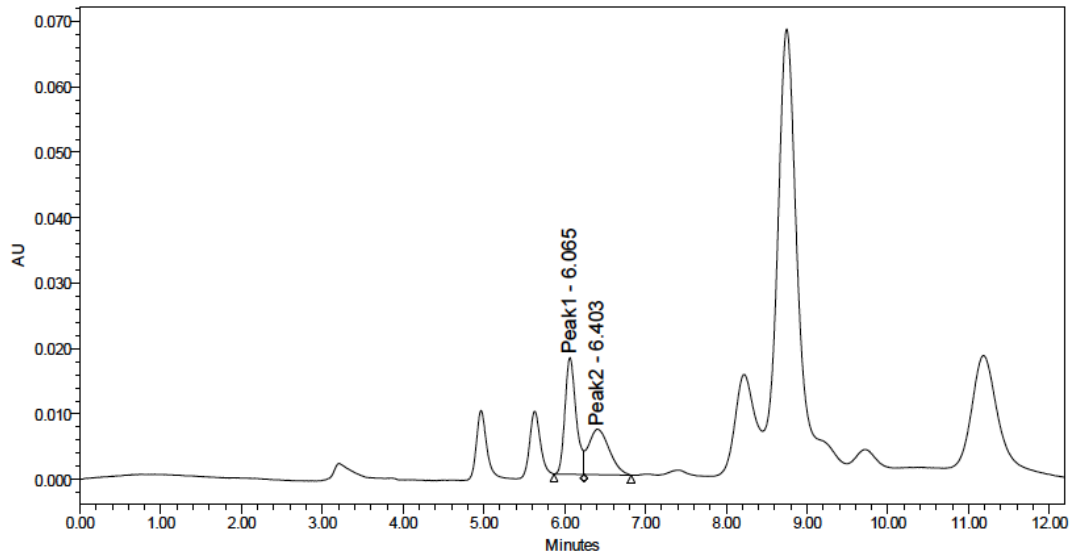


| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 6.038 | 504239 | 50.60 | 51947 | 66.34 |
| 2 Peak2 | 6.385 | 492289 | 49.40 | 26359 | 33.66 |

Chiral

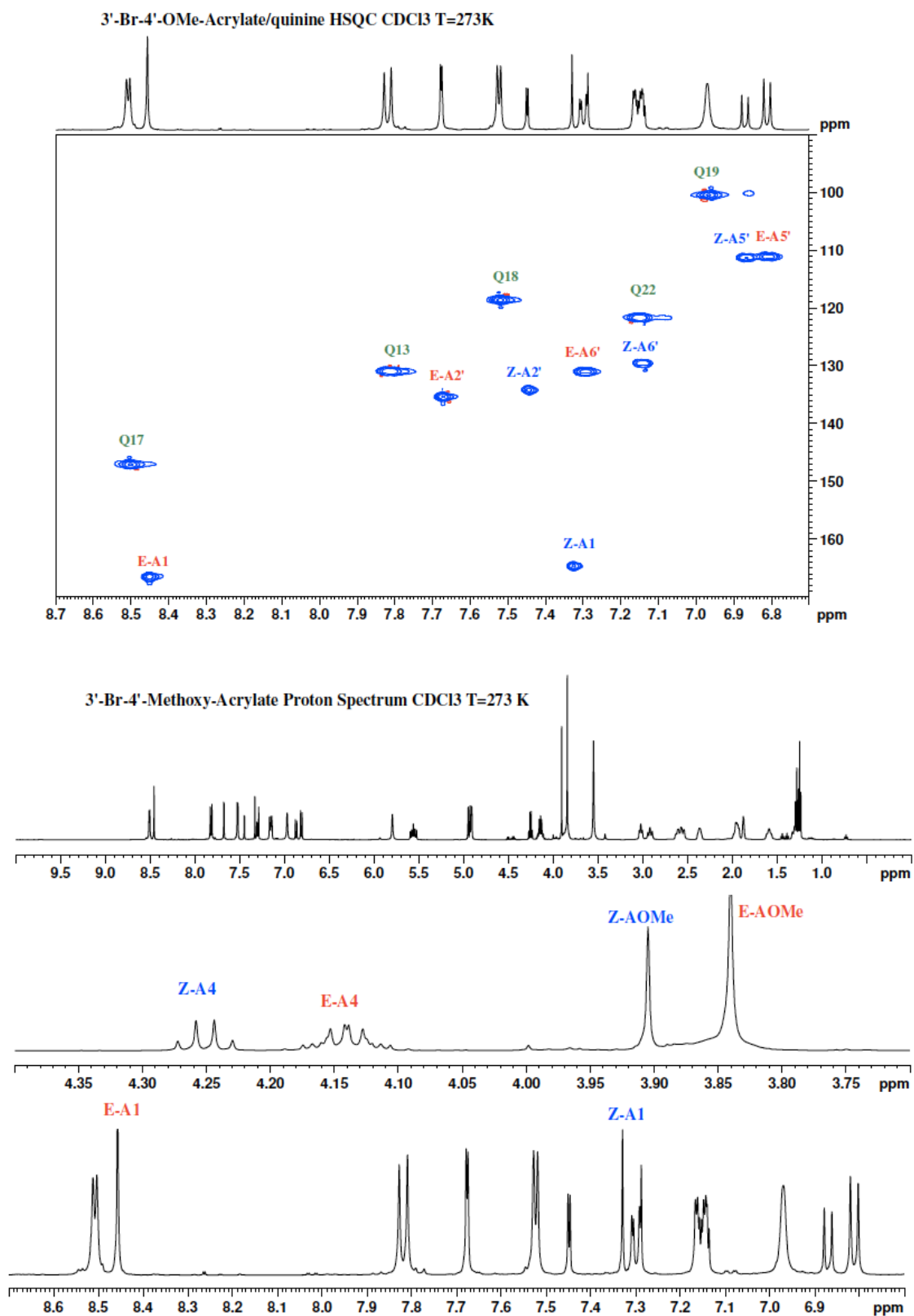
SAMPLE INFORMATION

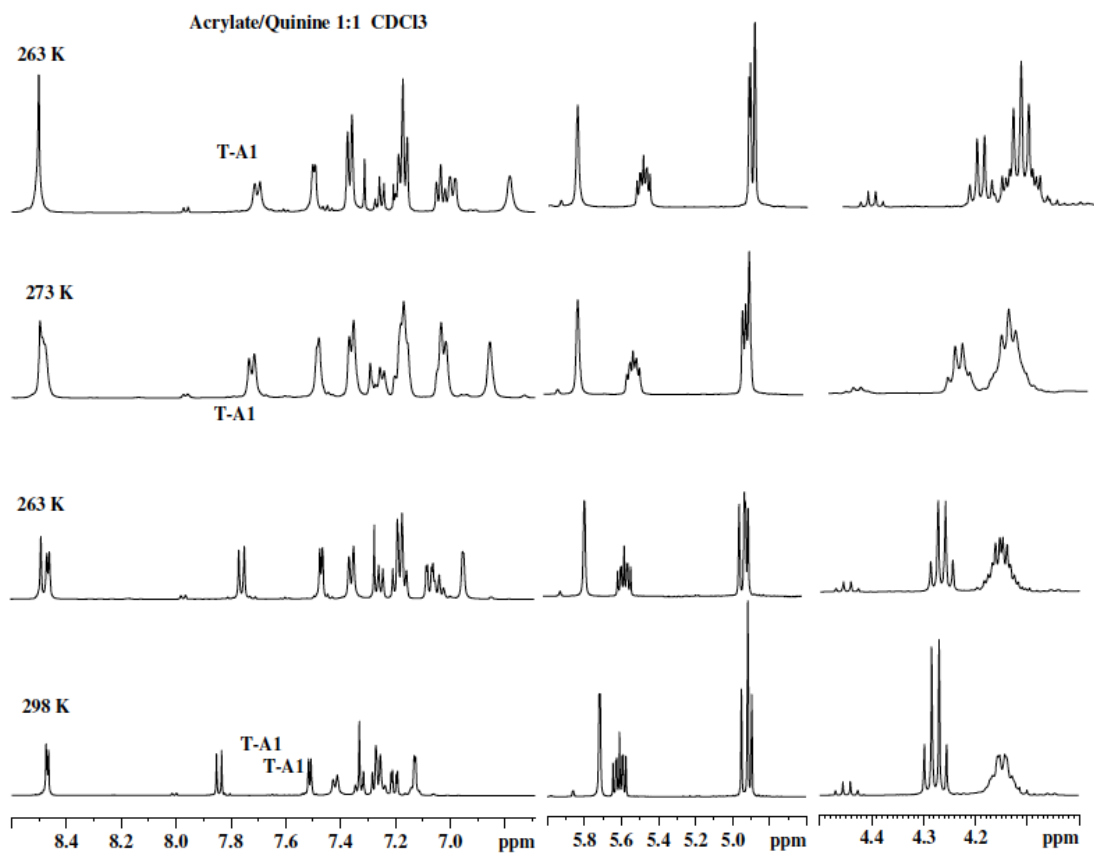
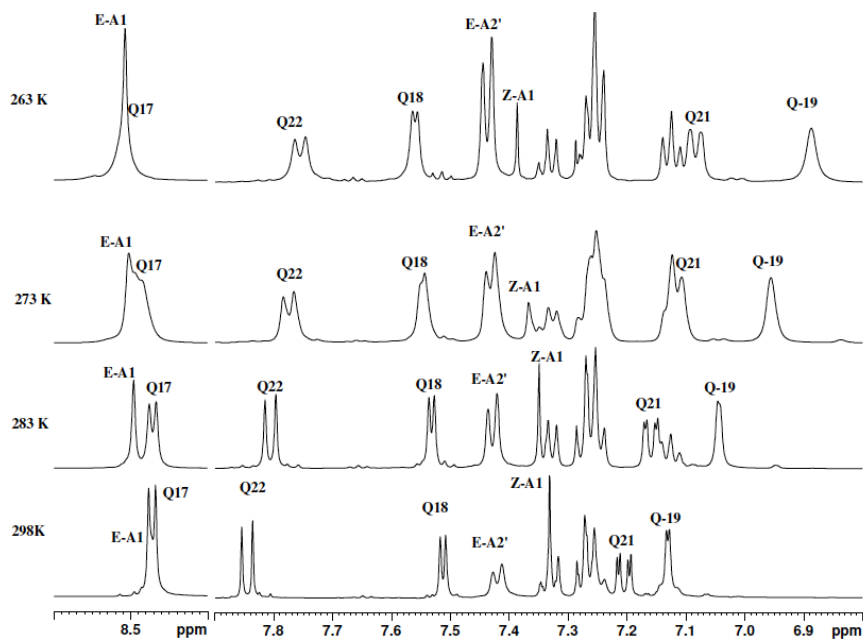
| | | | |
|-------------------|---------------|------------------|-------------------------|
| Sample Name: | Unk | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/5/2014 2:09:17 PM CST |
| Vial: | 1 | Acq. Method: | tbueda |
| Injection #: | 1 | Date Processed: | 1/5/2014 2:50:30 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 219.4nm |
| Run Time: | 20.00 Minutes | Sample Set Name: | 010514 tbvued chiral |



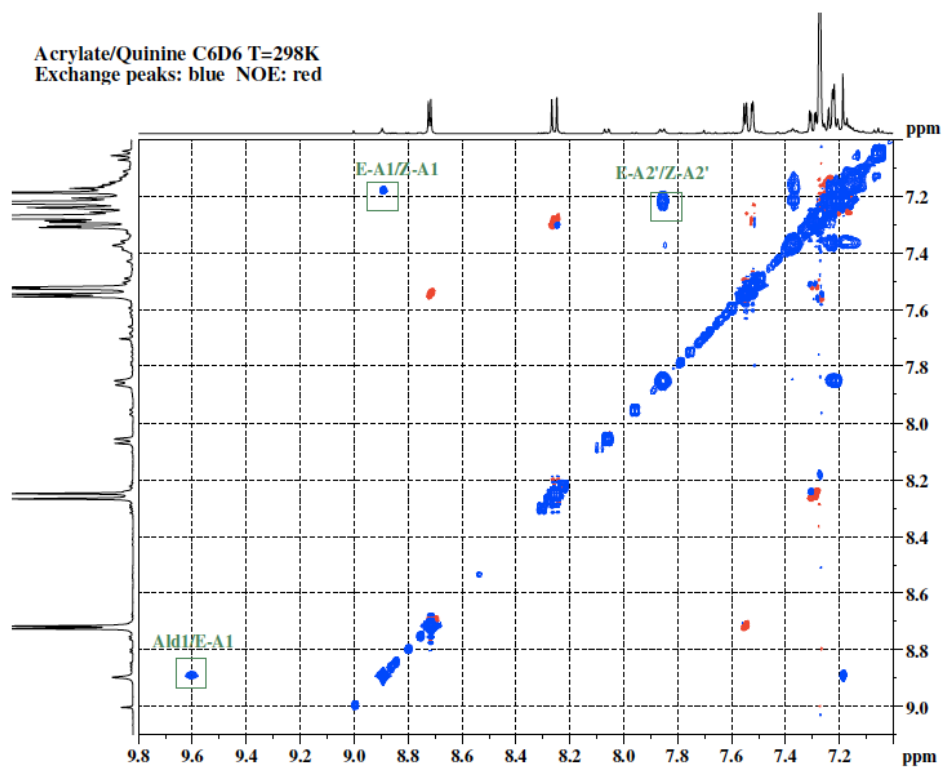
| Peak Name | RT (min) | Area ($\mu\text{V}\cdot\text{sec}$) | % Area | Height (μV) | % Height |
|-----------|----------|---------------------------------------|--------|--------------------------|----------|
| 1 Peak1 | 6.065 | 172080 | 58.03 | 17834 | 72.02 |
| 2 Peak2 | 6.403 | 124443 | 41.97 | 6930 | 27.98 |

NMR Data



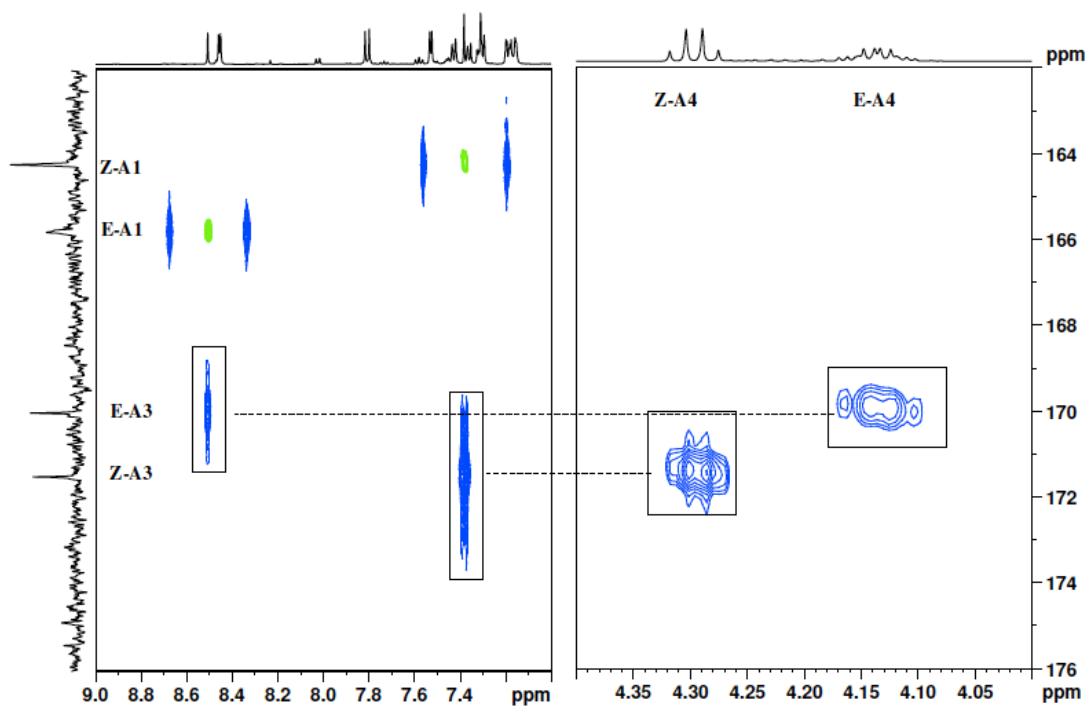


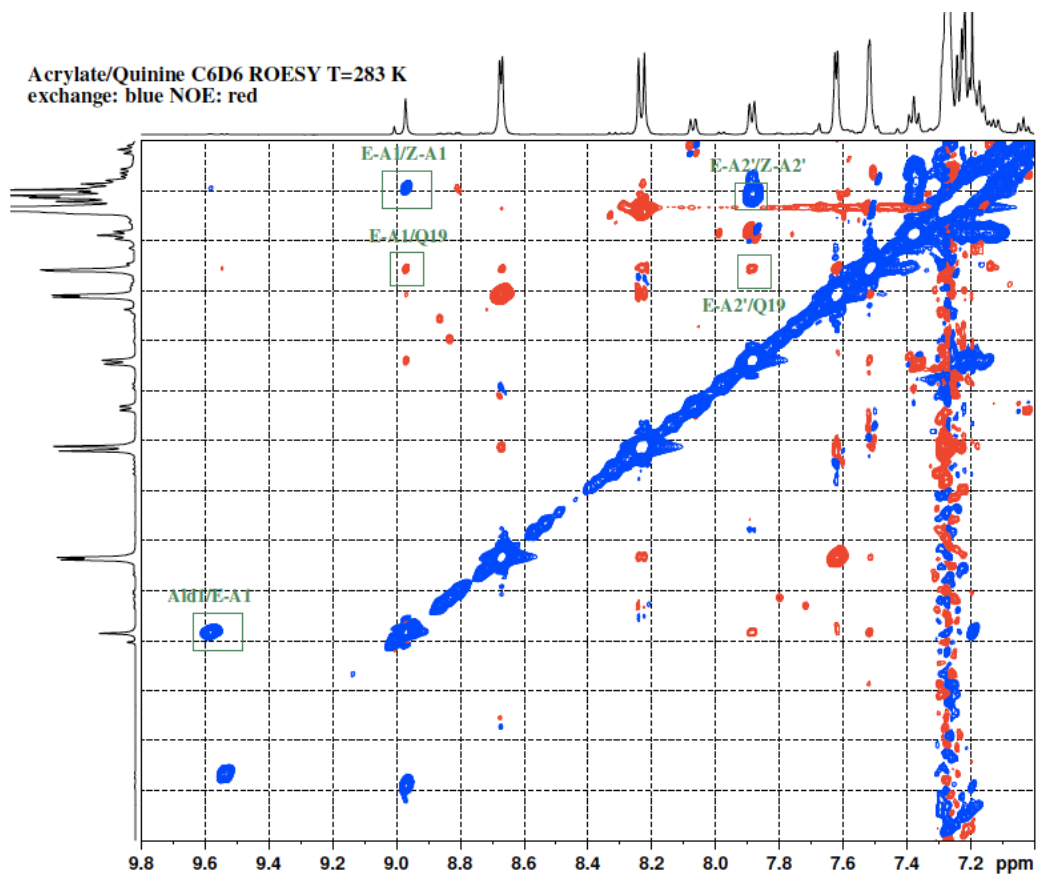
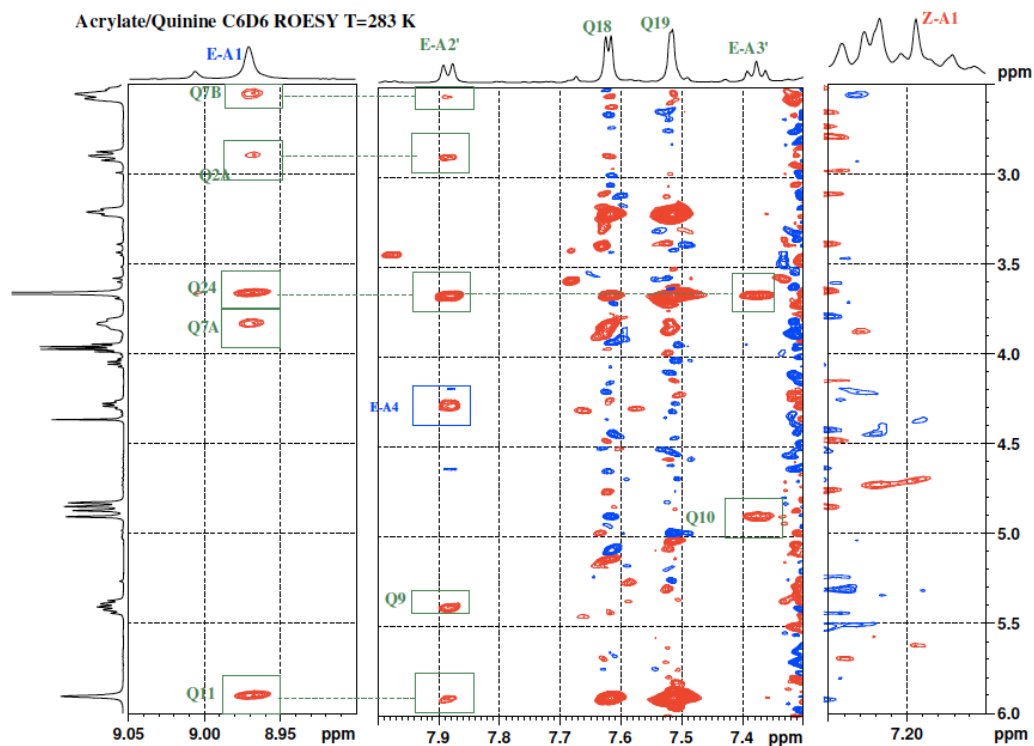
Acrylate/Quinine C6D6 T=298K
Exchange peaks: blue NOE: red



Acrylate/Quinine CD2Cl2 273K

■ HMBC
■ HSQC





Maria S. (Shevyrev) Shteynbuk**Objective**

I am organic chemist with extensive technical expertise in asymmetric catalysis and method development. I also have excellent communication skills and team work skills. My objective is to find a challenging career where I can utilize my communication skills with my chemistry knowledge.

Qualifications

- Experience in multi-step synthesis
- Strong organic and organometallic background
- Knowledgeable in current organic instrumentations
- Familiarity in ChemDraw, MOE and Gauss View
- Managed undergraduate students in the lab
- Strong communication skills
- Extensive experience working with groups
- Taught undergraduate level discussions and labs

Education

Ph.D., Organic Chemistry, UW-Milwaukee, WI May 2014

- Advisor: Dr. M. Mahmud Hossain
- Thesis title: "A New Method to Synthesize α -Halogenated Asymmetric Quaternary Centers using Organocatalysts"

BS, Biochemistry, UW-Milwaukee, WI 2008

Experience

Research Assistant, UW-Milwaukee, WI 2009- Present

- Designed new methods of asymmetric halogenations for construction of asymmetric quaternary carbon
- Synthesized and tested a new organocatalyst based on DFT calculations for constructions of asymmetric quaternary carbon
- Designed a new route for synthesis of natural product, physostigmine, with fewer steps and cost efficient synthesis
- Designed a new method for the synthesis of an asymmetric all carbon quaternary center
- Developed HPLC separation method for new compounds

Undergraduate Research, UW-Milwaukee, WI 2007-2008

- Developed a new method for the synthesis of carcumins analogs
- Organized laboratory space
- Negotiated price reduction in chemical purchasing

Publications

- M. Mahmum Hossain, Eduardo Alberch, Nazim Uddin and Maria Shevyrev *ARKIVOC*, January 2011 p139-146 "Synthesis of compounds containing α -aryl quaternary carbon centers"
- M. Mahmum Hossain, Maria S. Shteynbuk, Frank Holger Försterling "Asymmetric α -chlorination of α -hydroxyacrylate and mechanistic studies" Manuscript in process.
- M. Mahmum Hossain, Eduardo Albrech, Colin Brook, Maria S. Shteynbuk, Sharif Asad, Joseph Ulicki "Stereoselective synthesis of allyl enol carbonates for synthesis of aldehydes bearing all carbon quaternary stereocenters via the decarboxylative asymmetric allylic alkylation (DAAA) Manuscript in process.
-

Presentations

- M.S. Shteynbuk, Chemistry and Biochemistry Awards Day Poster Session "Asymmetric α - Halogenation", May 2012
- M. Shevyrev, 241th ACS National Meeting, "Synthesis of asymmetric α -bromination", March 2011
- M. Shevyrev, YCC Annual Poster Session, "Synthesis of asymmetric α -bromination", April 2011
- M. Shevyrev, UW-Milwaukee Seminar: "Click chemistry" Oct 2011

Skills

- Strong organic synthesis and purification background with five years of experience
- Practical knowledge in organometallic synthesis
- Comfortable with multi-gram and milligram scale synthesis
- Carried out experiments in the glove box
- Experience running air and moisture-sensitive reactions
- Familiar with different characterization methods of compounds
- Working knowledge of NMR (^1H , ^{13}C), chiral HPLC
- Familiar with ChemDraw, MOE molecular modeling , GaussView
- Experienced in lowering synthesis costs
- Fluent in English, Russian and Hebrew
- Strong oral and written communication skills
- Excellent management skills in large group settings, lab work and TA responsibilities
- Ability to explain and teach chemical concepts and techniques

Affiliations

- American Chemical Society

