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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

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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 ORGANOCATLYST.

by

Maria Shevyrev Shteynbuk

The University od Wisconsin-Milwaukee, 2014
Under the supervision of Professor M. Mahmun 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.

Acknowledgments

I would like to gratefully and sincerely thank my advisor Professor M. Mahmun Hossain for inspiring me to study organic chemistry. My interest started the first day I had class with him 7 years ago.

I would also like to thank my group members: Nazim Uddin, Eduardo A. Garcia, Md. Sharif Al Asad, Matthew Huisman, Joseph Ulicki, Colin Patrick Brook, Shamsul Arefin Ahmed and other members of the Hossain group for their friendship and support.

Additionally, I would like to thank my beloved parents that immigrated from Ukarine to Israel then from Israel to the United States to provide a brighter future for me. My father, Vladimir Shevyrev, always challenged me to become the person I am today and to open my horizon to the endless possibilities. My mother, Vera Shevyrev, is my mentor role modeling for me that with education, determination and wisdom, women can have it all: a successful career and a family. I hope to become a role model to my daughter just as my mother was to me. My parents opened the world to me and, for this, I will forever be grateful. I could not have done it without them.

Finally and most importantly, I want to thank my husband, Dmitry Shteynbuk, my best friend and the reason I have not given up on my studies. His constant encouragement and support are the reasons I am finishing this thesis. His belief in me has meant the world to me and I could not have accomplished my dream without him.

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.

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. Mahmun 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. Mahmun 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 $HBF_4{\cdot}OEt_2$ (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.

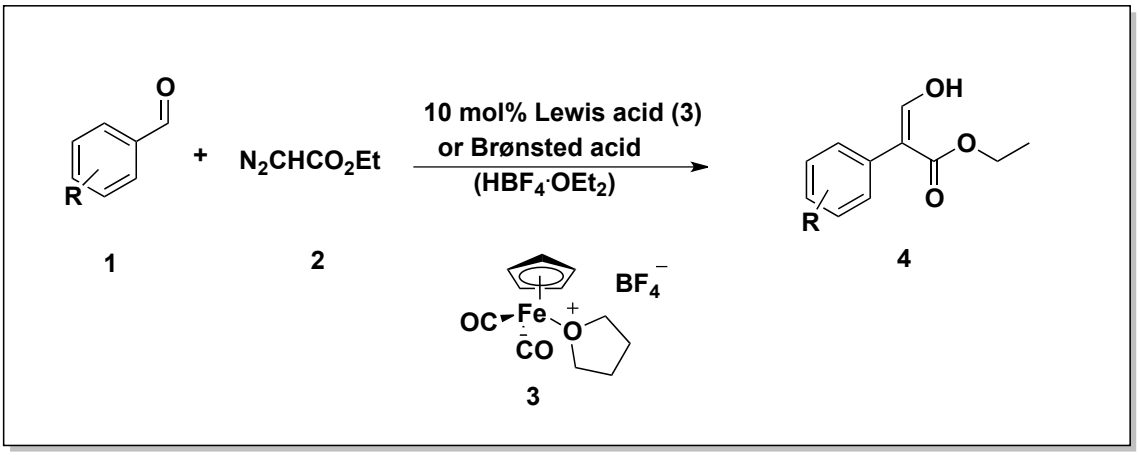
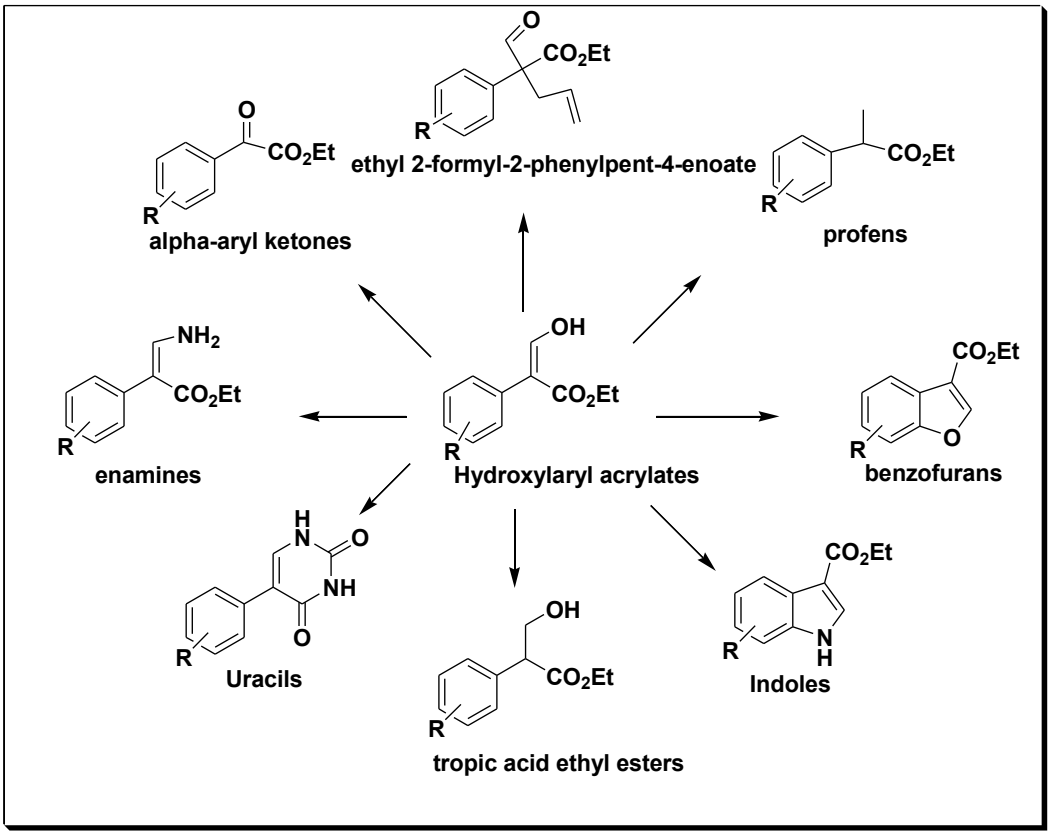


Figure 1: New compounds that were constructed from hydroxylarylacrylates.

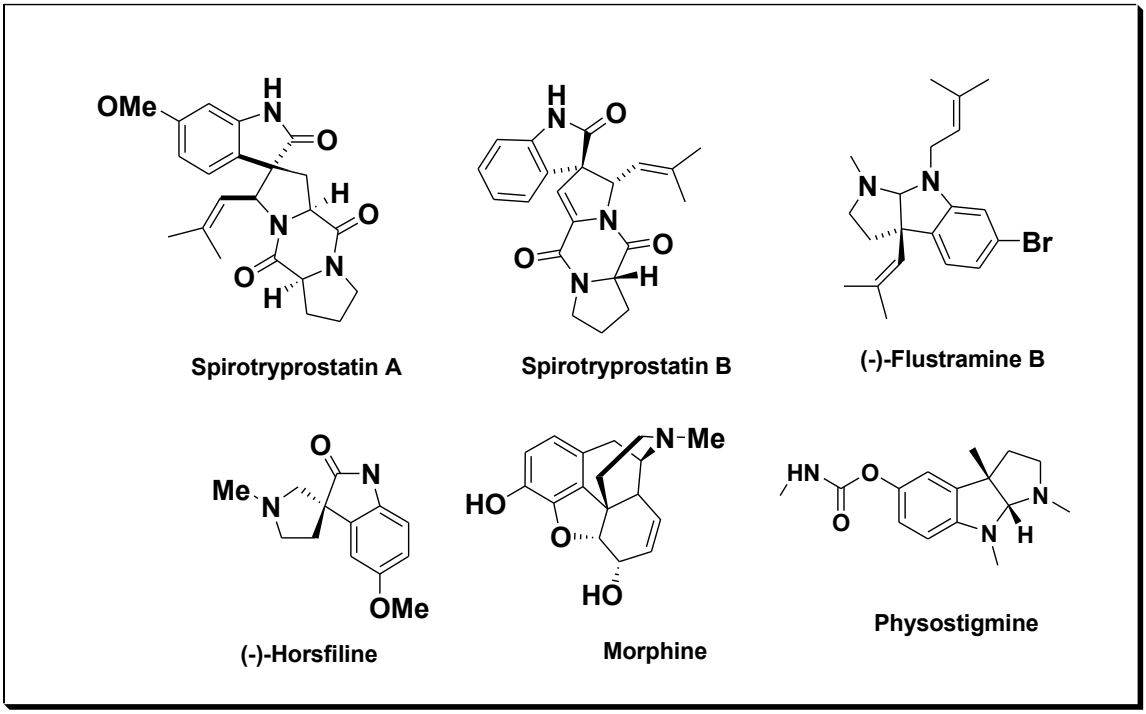


based on the development of asymmetric α-quaternary carbon centers through alpha halogenation and mechanistic studies that were done with NMR and DFT calculations on the alpha hydroxyl acrylate system with an organocatalyst in an attempt to synthesize a universal nucleophile.

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 pharmaceuticals[3]. 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 organocatlysis 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 2000[6]:

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.

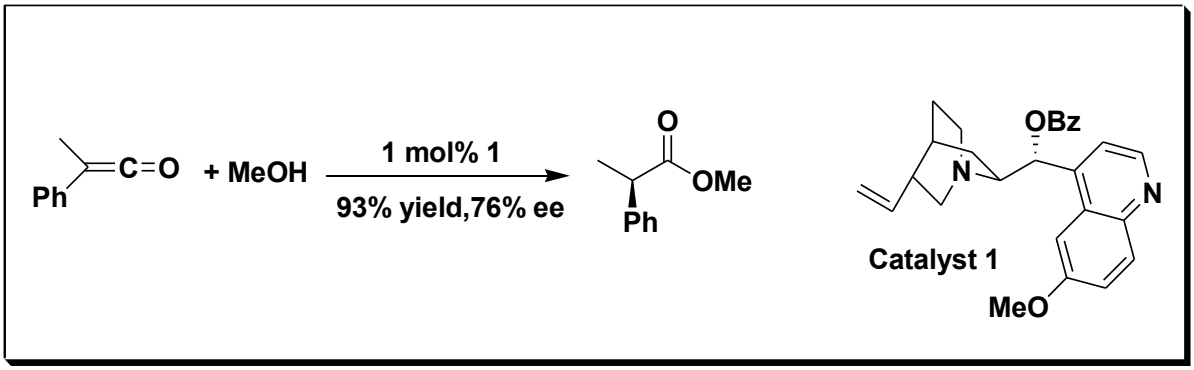
3. Organocatalysts are often stable in the presence of water or oxygen and as such they do not require any special reaction conditions. Organocatalytic transformations are also generally easy to perform and are more environmentally friendly than their metal-catalyzed counterpart.

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

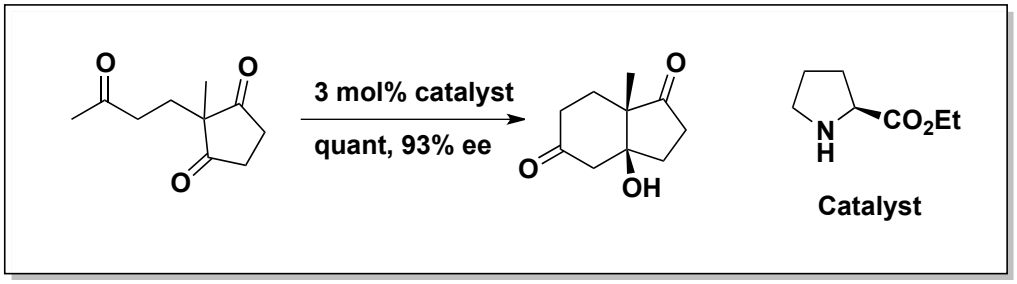
The first organocatalytic reaction was reported in 1912 by Bredig and Fiske[6]. These studies showed that cinchona alkaloids were successful in catalyzing the addition of hydrogen cyanide to benzaldehyde with low enantiomeric excess (<10% ee). 50 years later, Pracejus used *O*-benzoylquinine as an organocatalysts for enantioselective methanolysis of phenylmethylketene with up to 76% ee[6] (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 synthesis[6].

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

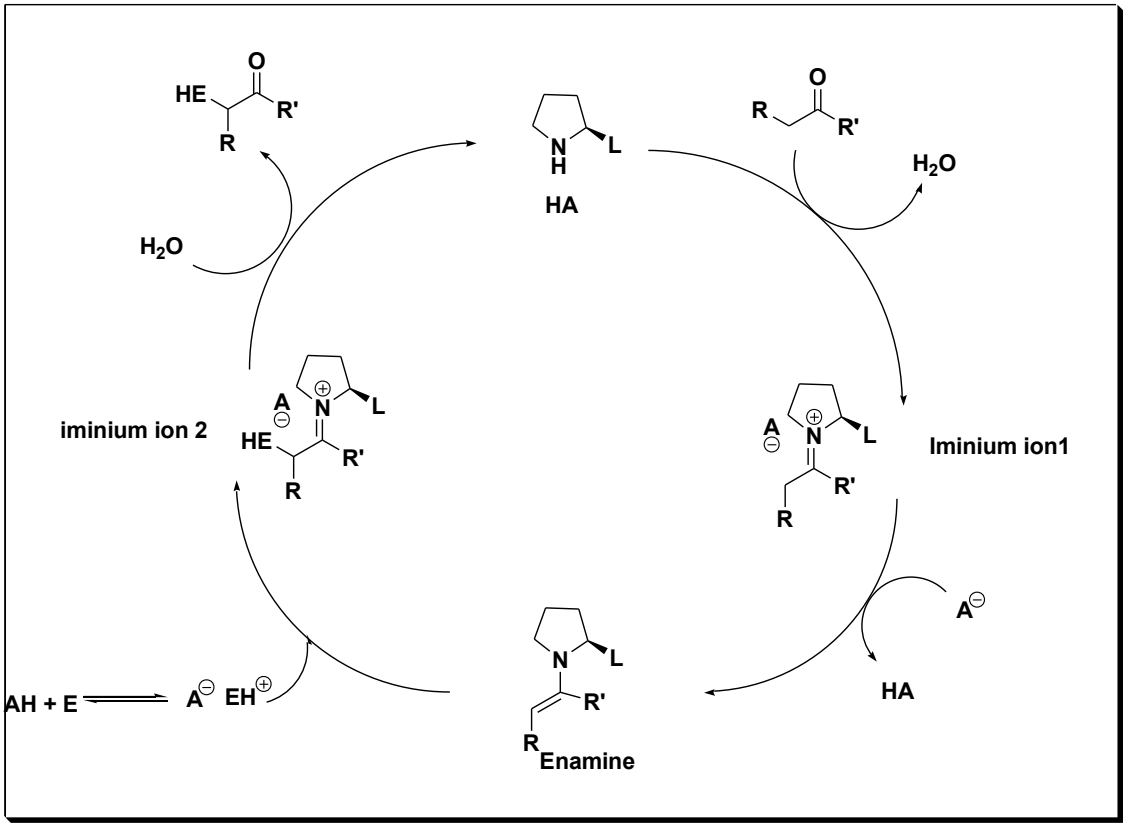
1.3.3.1.1 Enamine activation catalysis

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 enantioselectivity[8].

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 enemine catalysis reactions.

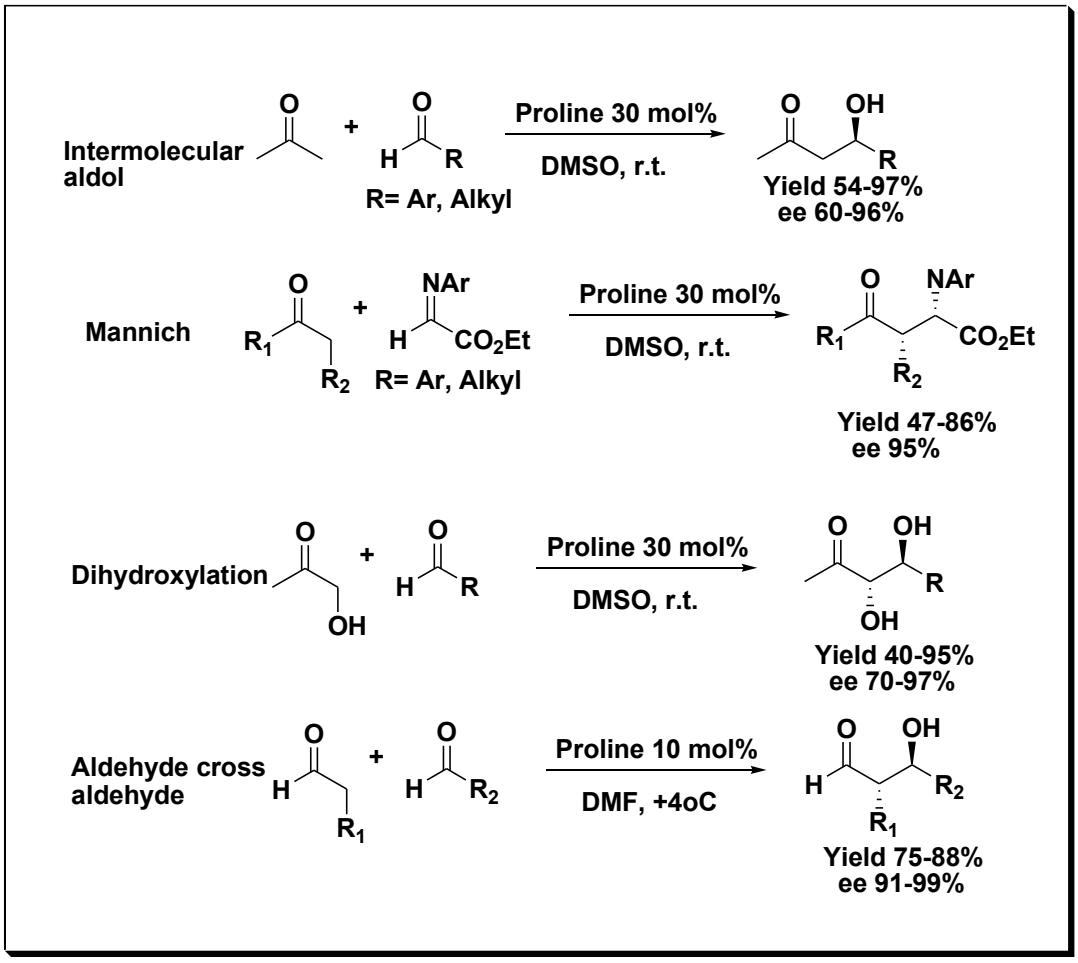


Figure 3: Stereochemical models for enamine reactivity.

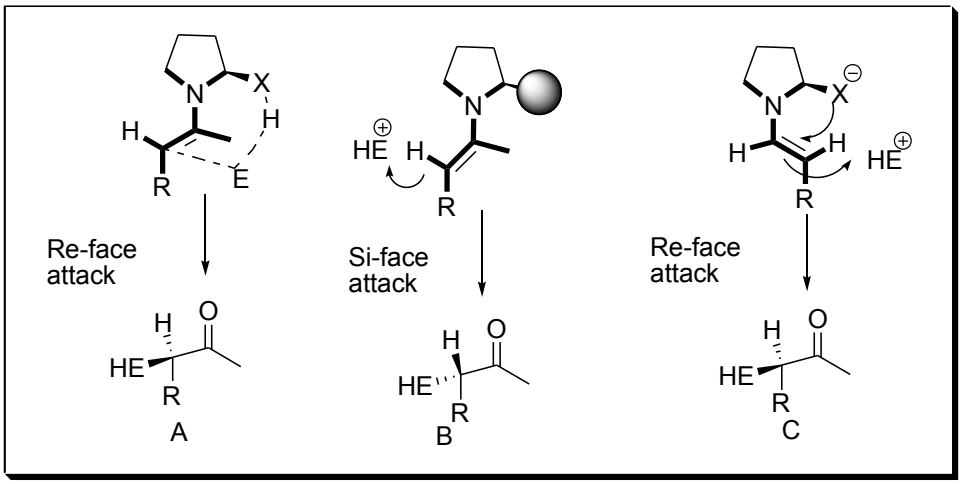


Figure 4: Examples of chiral secondary amines with hydrogen bond directing groups.

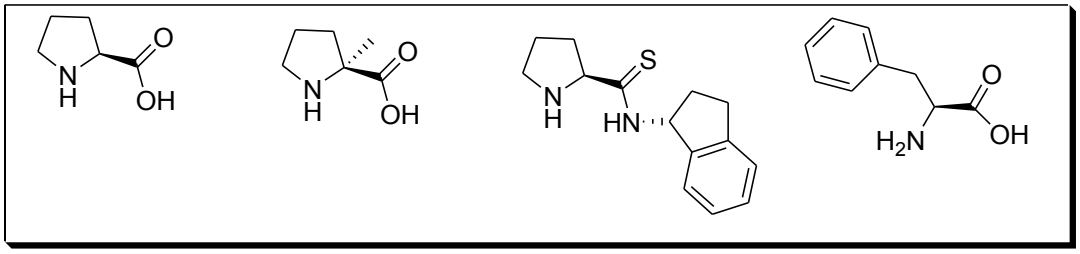
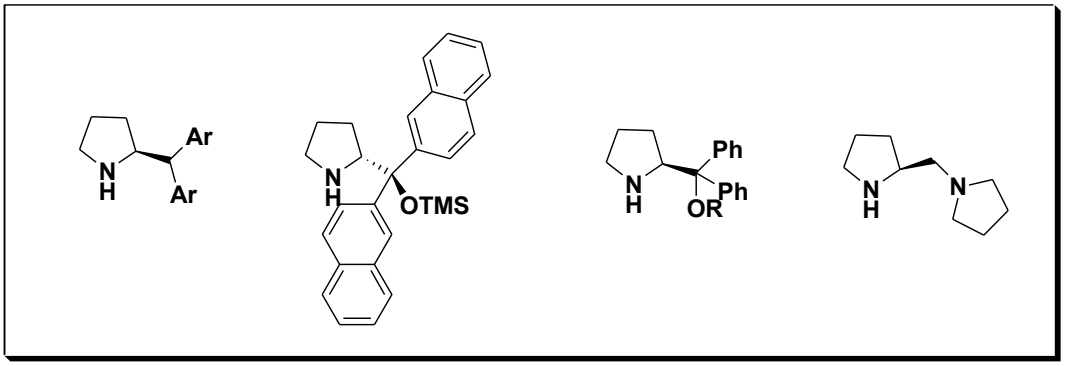


Figure 5: Examples of chiral secondary amines with bulky nonacidic groups.

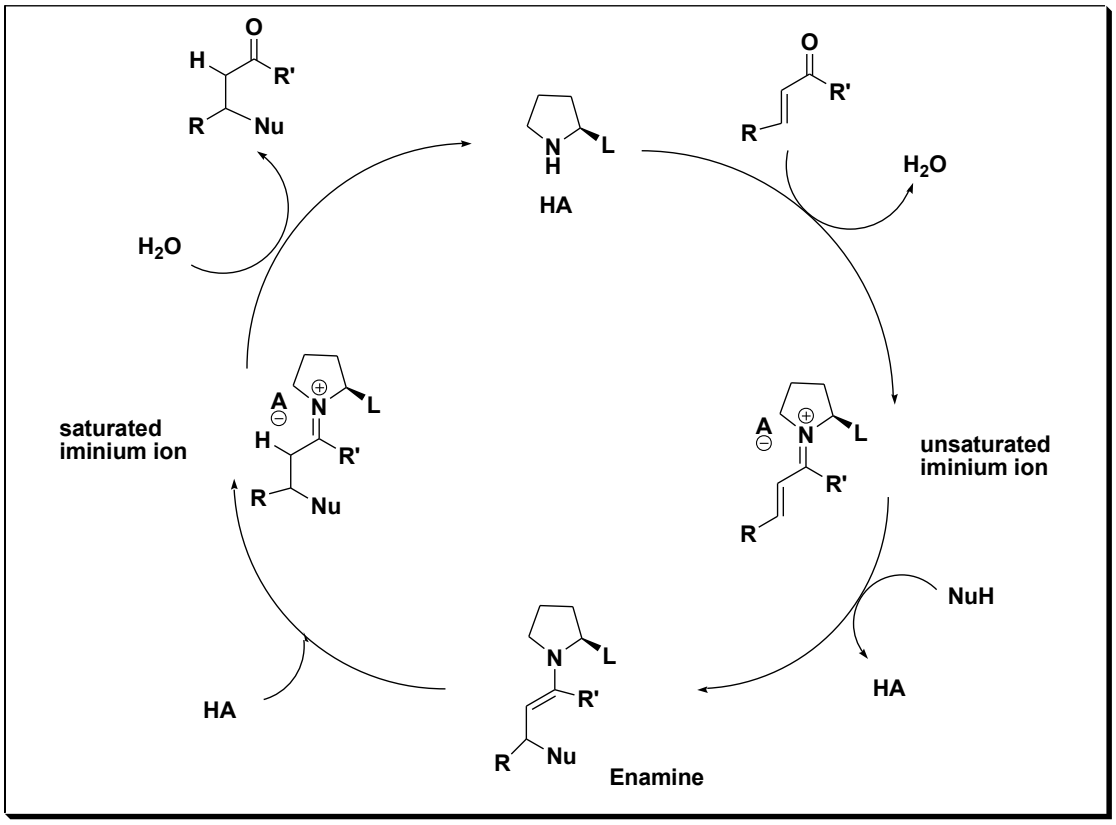


1.3.3.1.2 Iminium activation catalysis

Iminium activation catalysis is a general approach for the asymmetric conjugate addition of nucleophiles to α, β-unsaturated carbonyl compounds[7]. 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 than hydrolyzed yielding the desired product and regenerating the acid and catalyst.

Scheme 4: General mechanism for iminium activation.

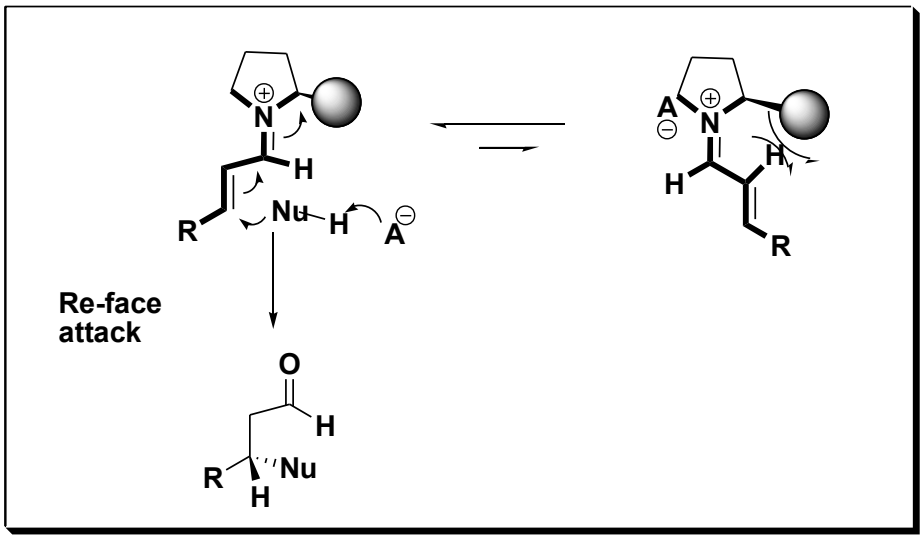


The catalysts that work best for this type of activation are amine substituted with bulky nonacidic groups. Examples of the most common catalysts are shown in figure 5, the most famous of them being MacMillans imidazolidinones. The stereochemical outcome of the reaction can be predicted according to 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 iminum type of activation reactions are: asymmetric organocatalytic Diels-Alder cycloaddition and intramolecular Michael additions to unsaturated carbonyl compounds.

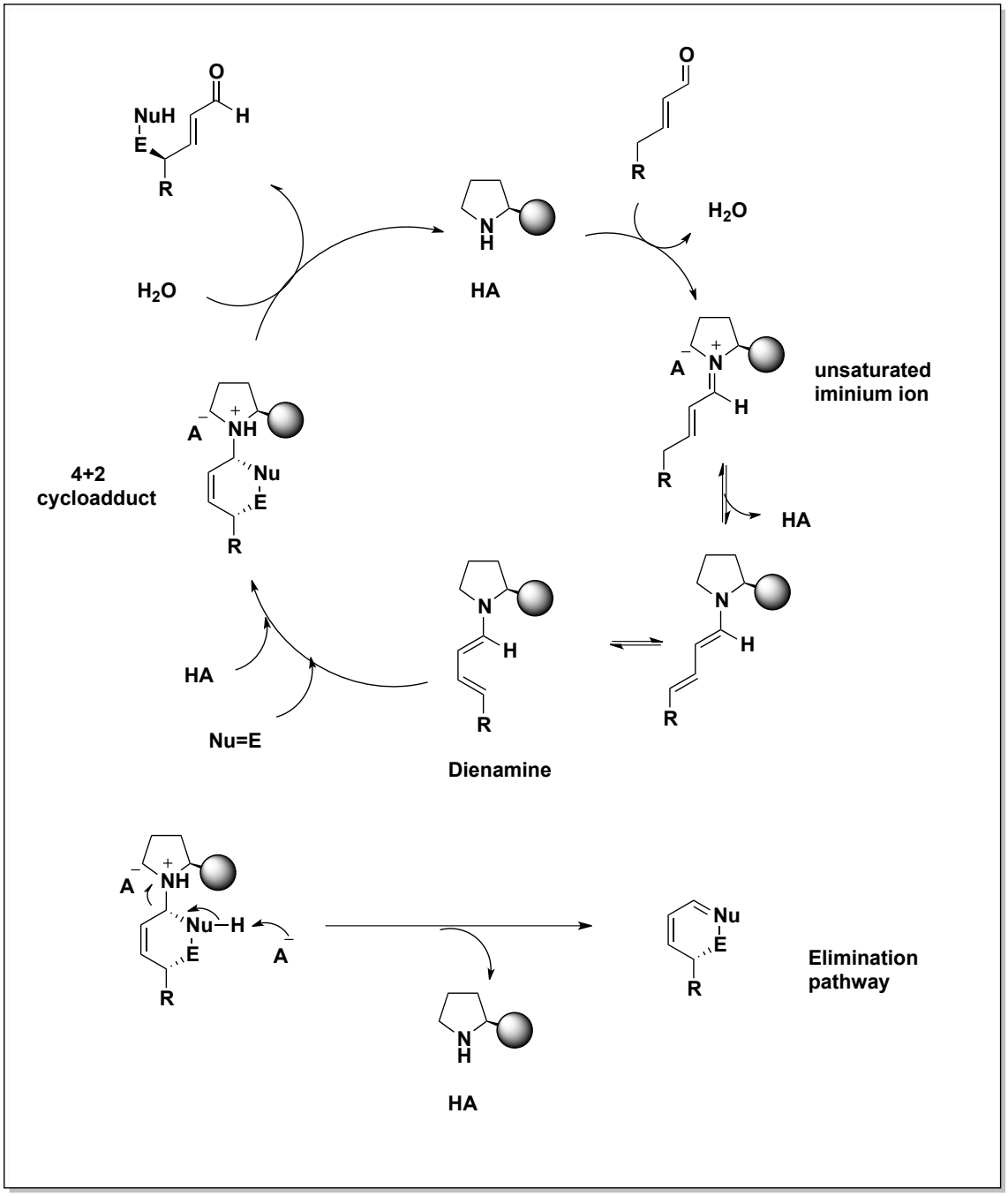
Figure 6: Stereochemical outcome of the amine catalyzed Michael addition to enals.



1.3.3.1.3 Dienamine activation catalysis

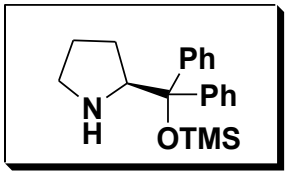
The first dienamine activation catalysis was shown in 2006[10]. Examples of this activation are the intramolecular Rauhut-Currier reaction and [4+2]-cycloaddition. The reaction mechanism is almost the same as with iminium

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.

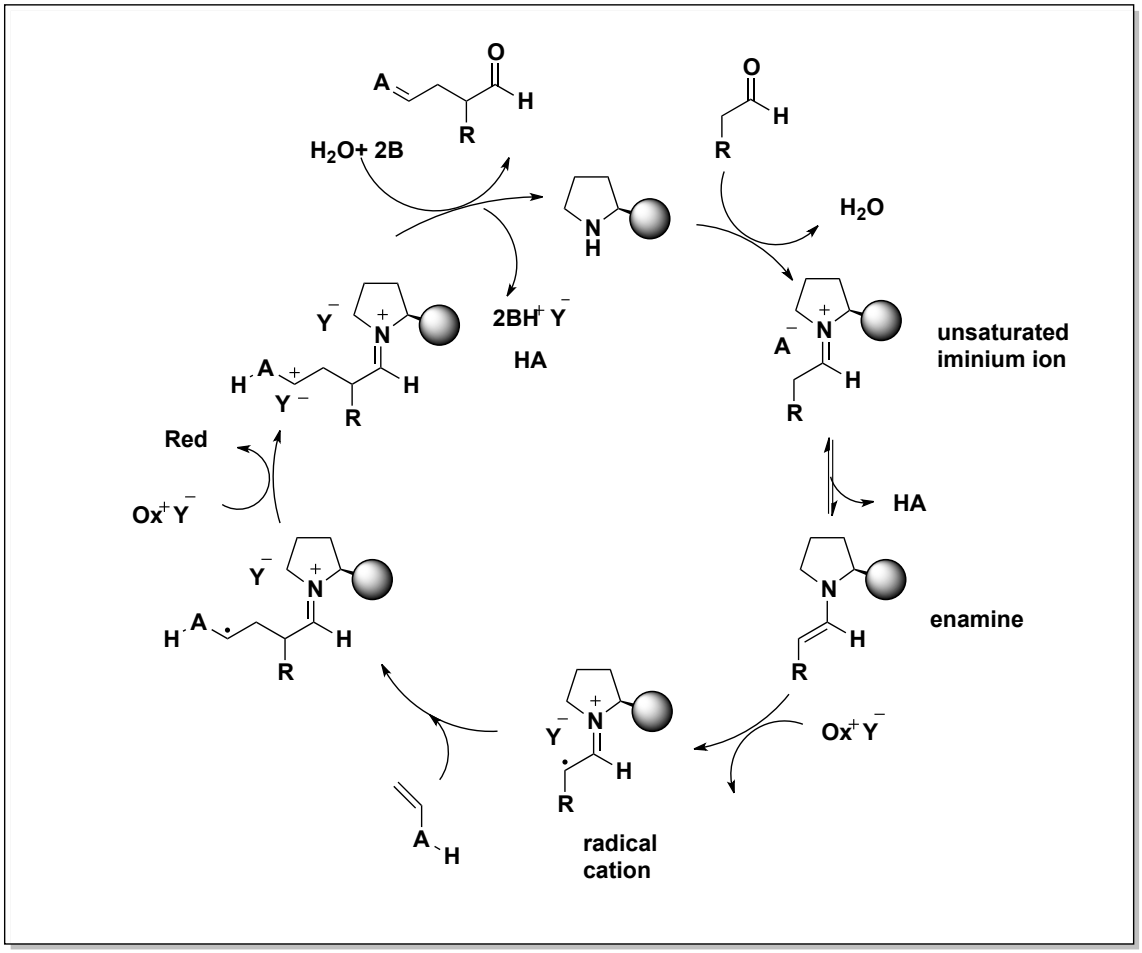
Figure 7: Example of dienamine activation catalyst.



1.3.3.1.4 SOMO activation catalyst

SOMO activation catalysis was first discovered by MacMillan and co-workers in 2007[11]. 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 imidazlidinone with a photoredox catalyst (Scheme 6).

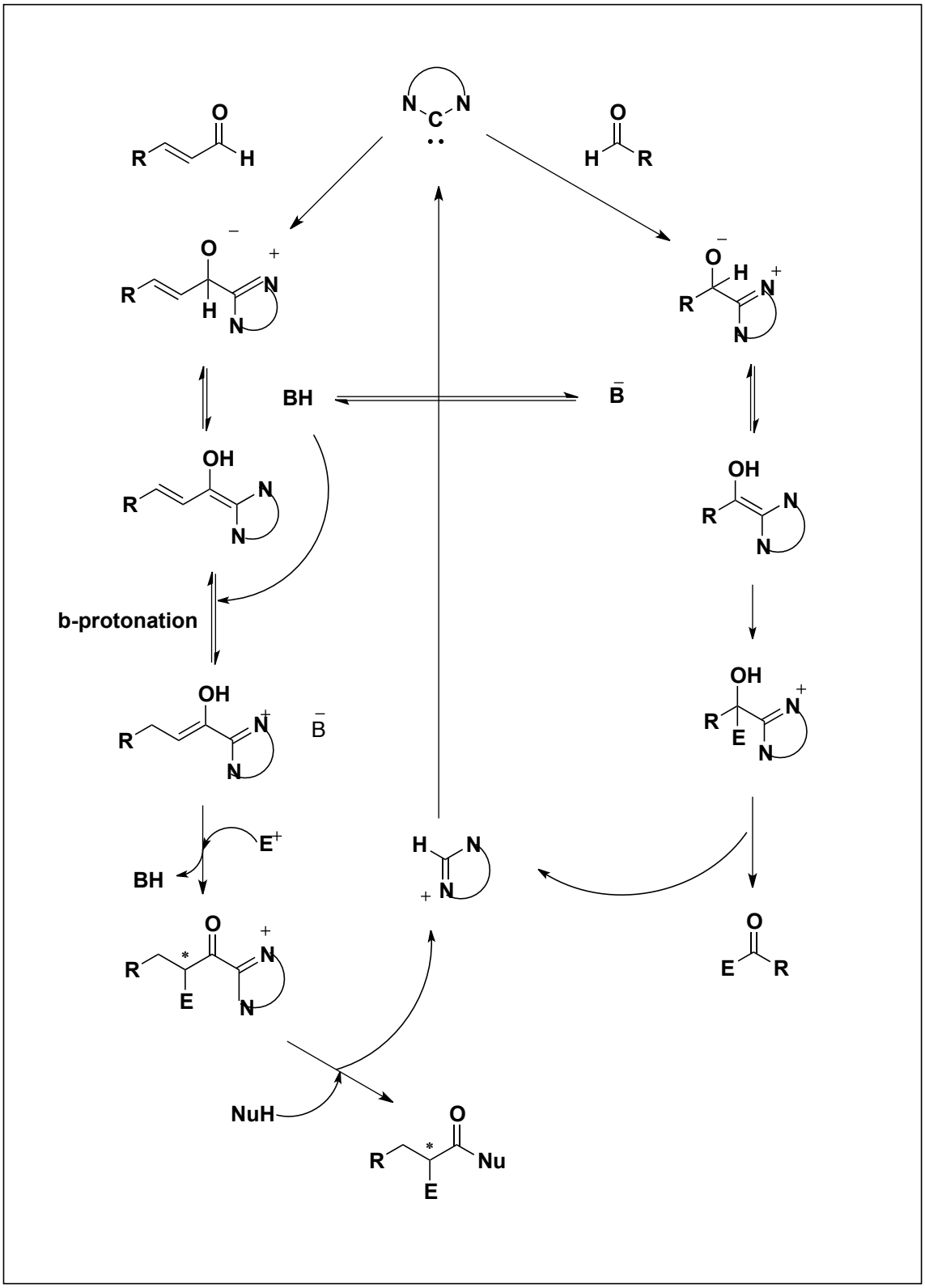
Scheme 6: Mechanism of Asymmetric Organo-SOMO Activation Catalysis.



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 reactions[12]. 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 synthesis[13]. 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 pathways[14]. 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.

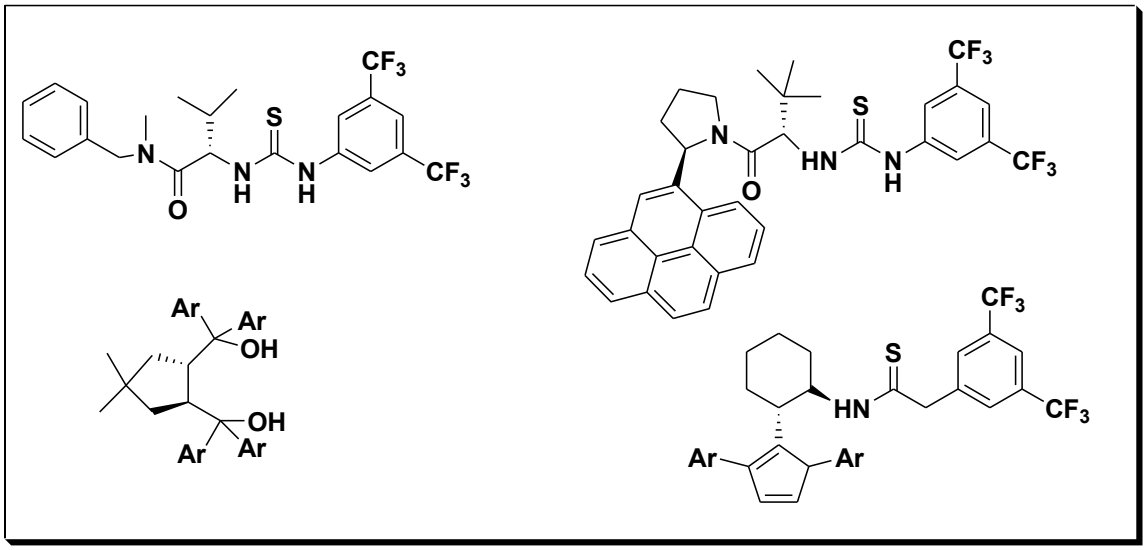


Figure 10 shows several modes of activation of organic compounds containing acidic hydrogen. Figure 10a shows Brønsted acid type of activation where the catalyst transfers a proton to a basic center of the substrate. Figure 10b and 10c show hydrogen-bonding type of catalysis by enhancement of electophilicity 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.

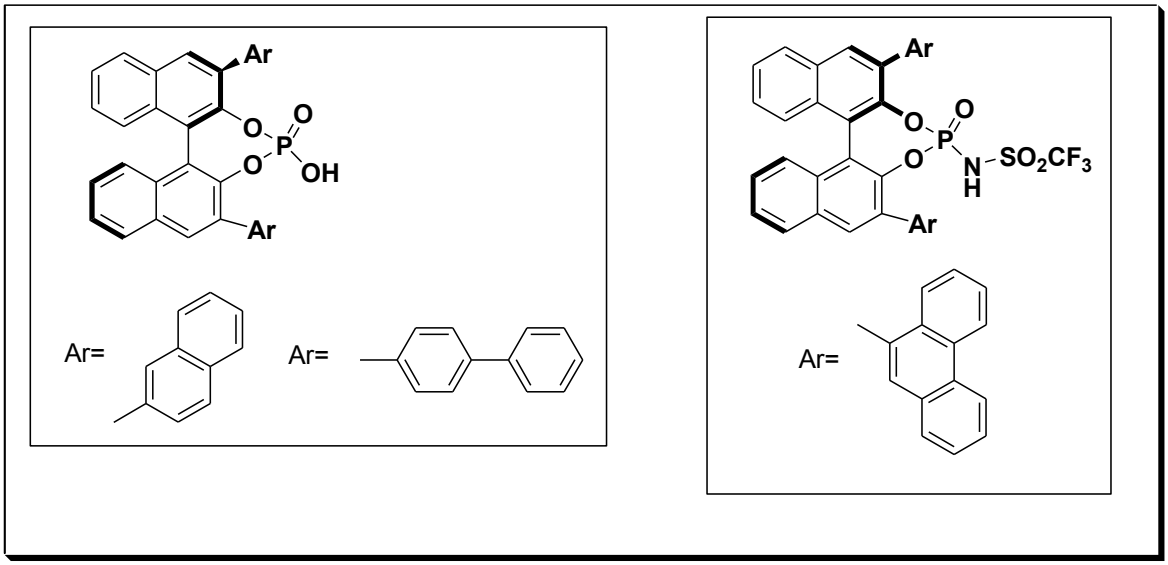
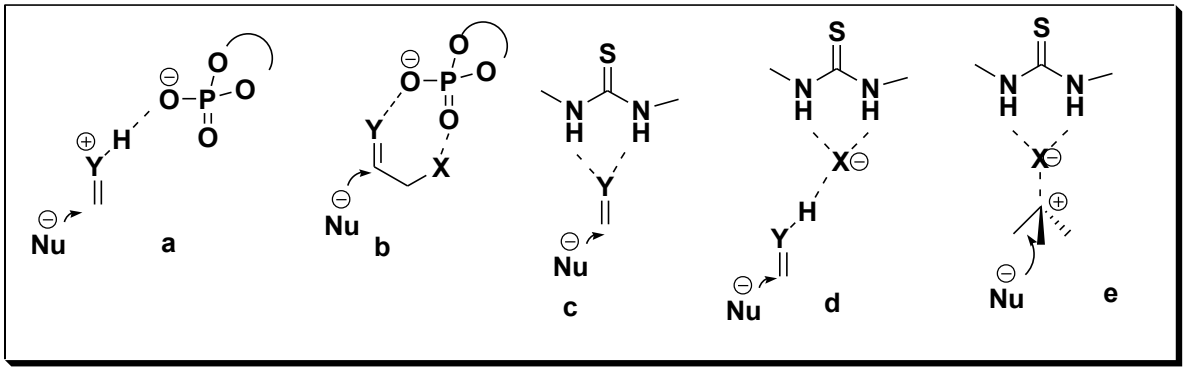


Figure 10: Brønsted acid type of activation.



1.3.3.2.2 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 moity of the substrate with the hydrogen bond donor of the catalyst and Brønsted base group on the catalyst[15] (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.

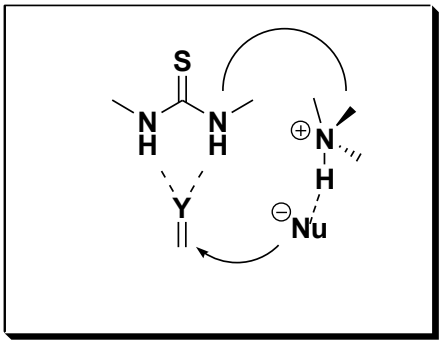
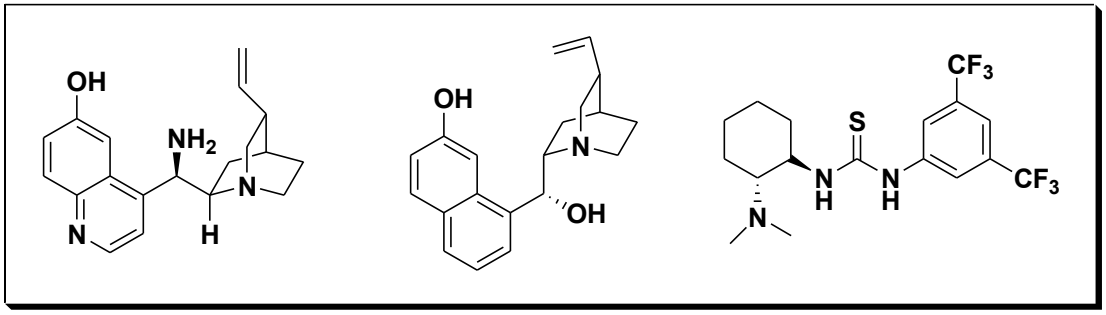


Figure 12: Examples of bifunctional catalysts.

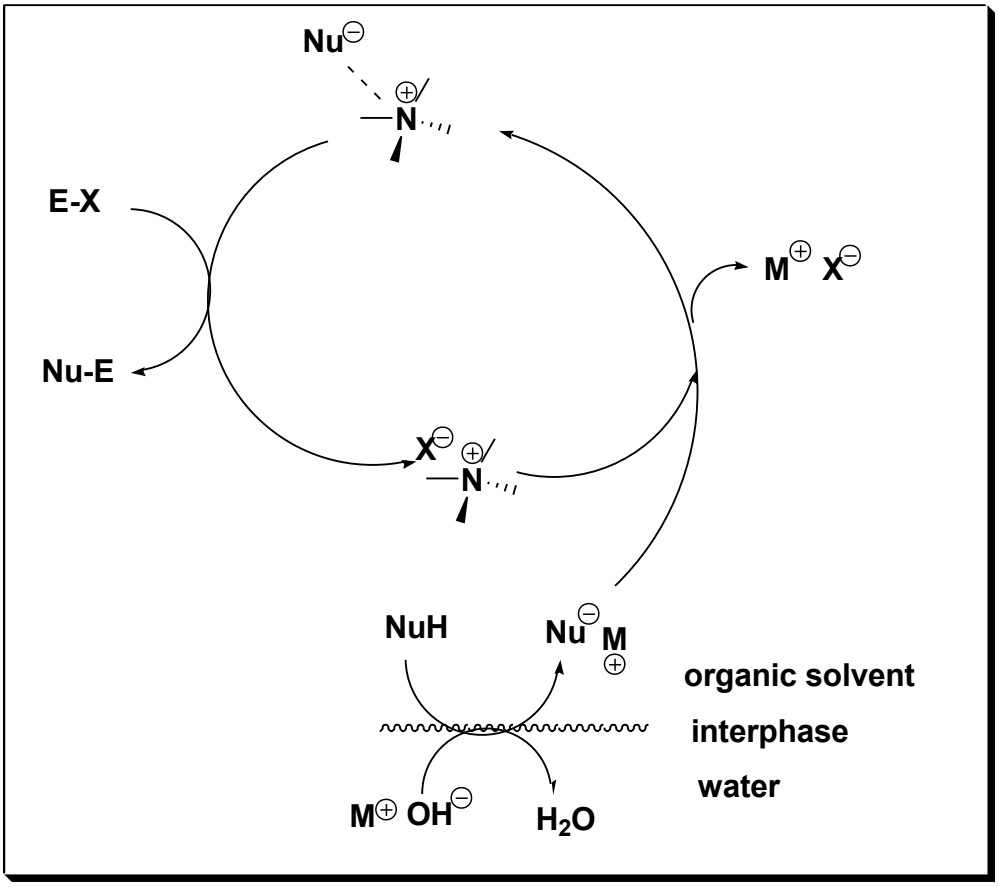


1.3.3.2.3 Phase transfer catalysis

Since 1984, with the implementation of quaternary *Cinchona* alkaloid salt for the chiral phase transfer catalyst, this field has seen major growth[16]. 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

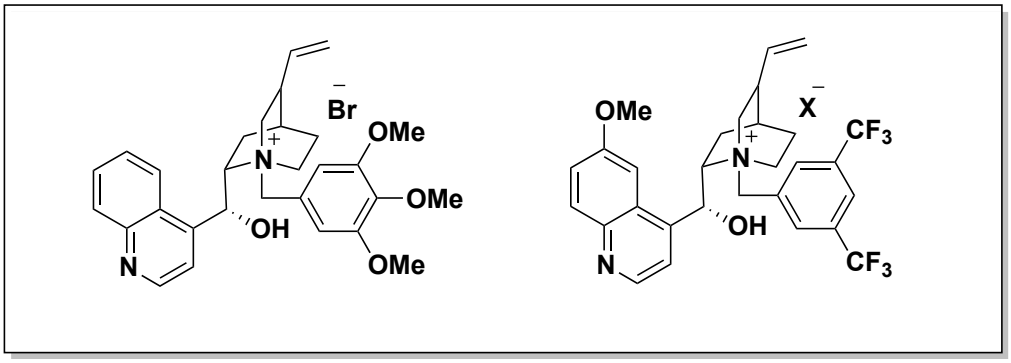
Figure 13: Mechanism of the phase transfer catalysis.



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.



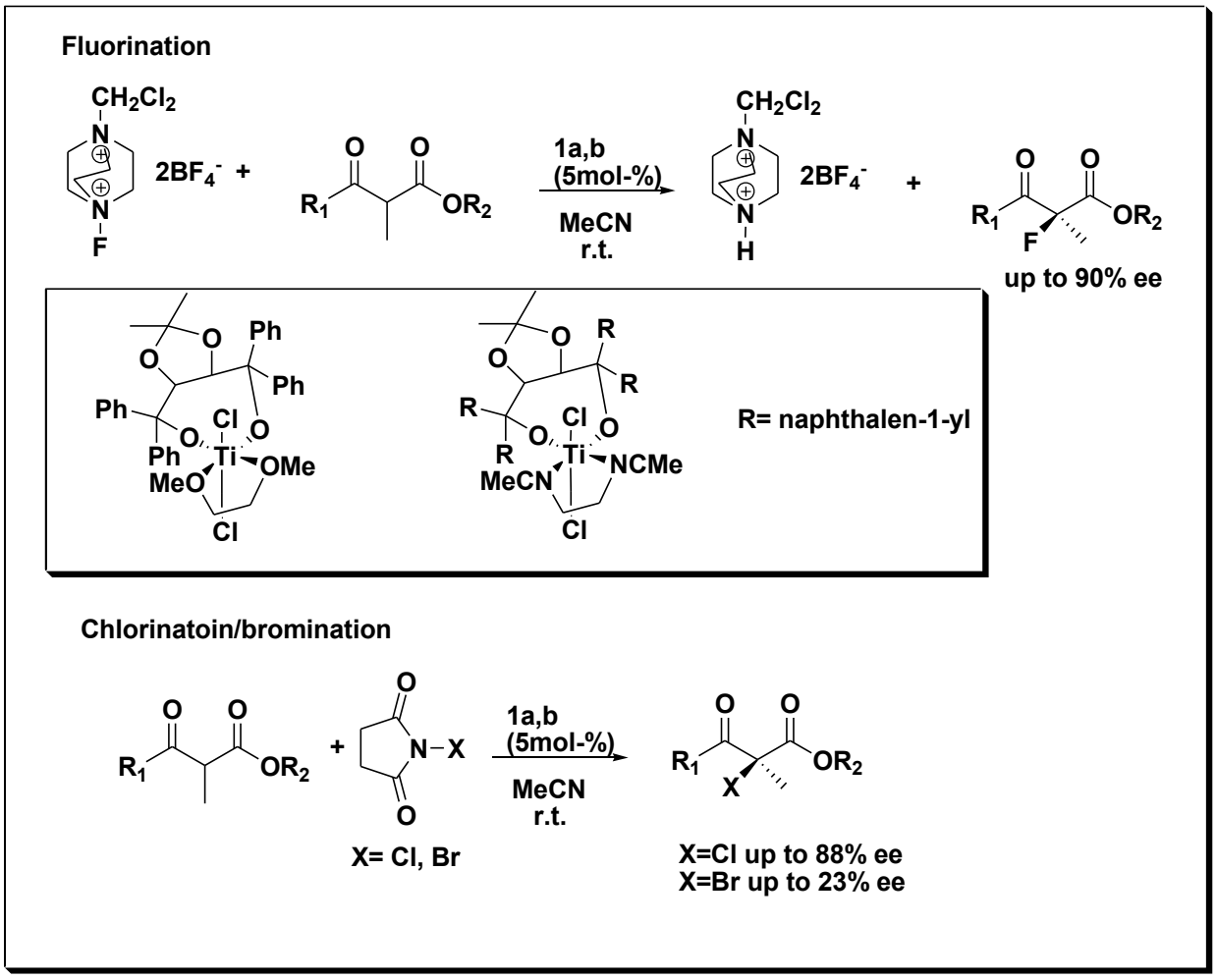
1.4 Asymmetric α-halogenation

1.4.1 Asymmetric α-halogenation introduction

Enantioselective α-halogenated compounds are highly useful molecules in organic chemistry[17]. 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 transformations[18]. Out of all enantioselective halogenated transformations, enantioselective α-fluorinations represent the major part, because of medicinal importance of fluorinated compounds[19]. 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.

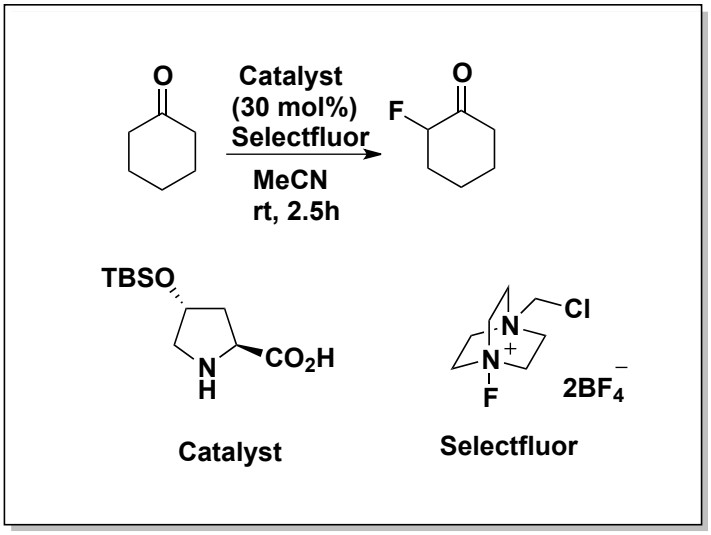
Asymmetric fluorination by chiral amines

In 2005, α-fluorinatoin of aldehydes and ketones was reported by Enders and Hüttl with Selectfluor as the fluorinating agent[20] 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 ee[21] (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 $NaBH_4$.

Barbas *et. al.* achived 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.

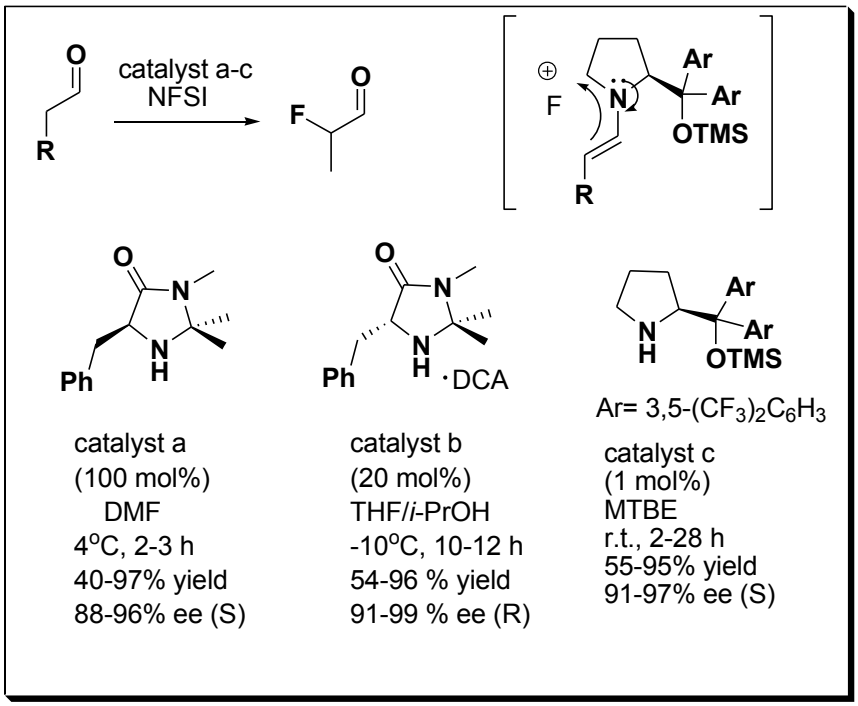
Scheme 8: α-fluorination of ketones by Enders and Hüttl.



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 acosolvent 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.

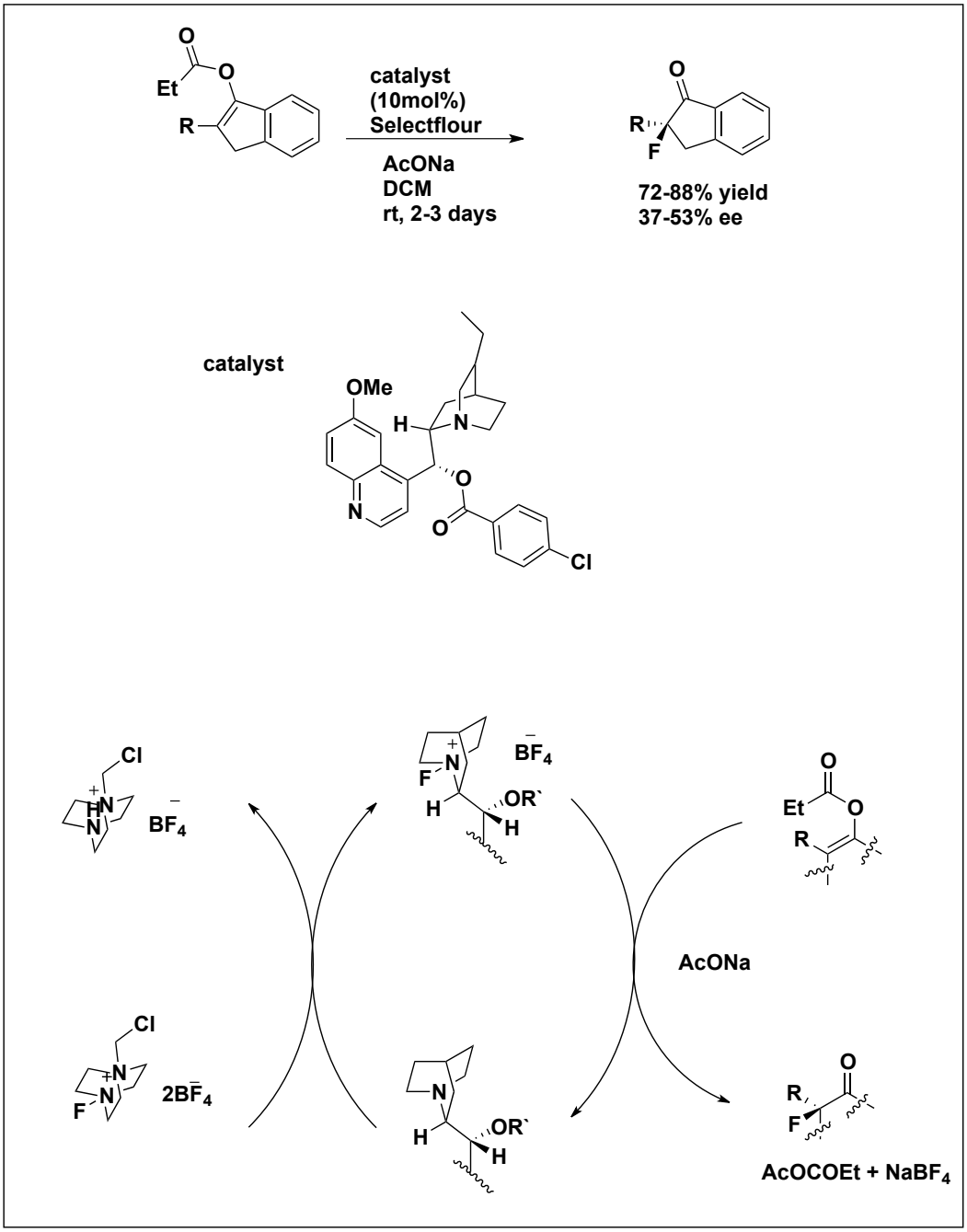


Asymmetric fluorination with tertiary amine

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 Selectfuor 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].

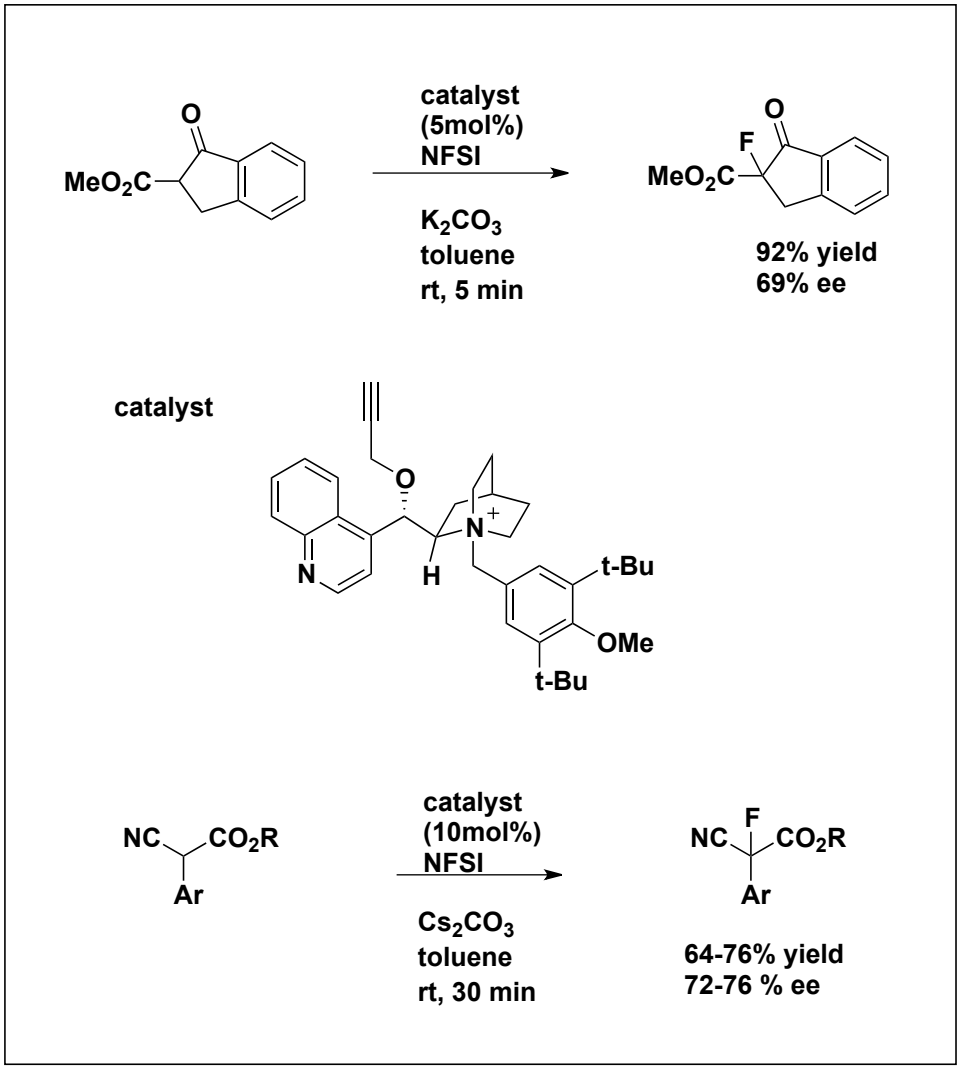
Scheme 10: α-Fluorination of acyl enol ethers.



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 solvent[23].

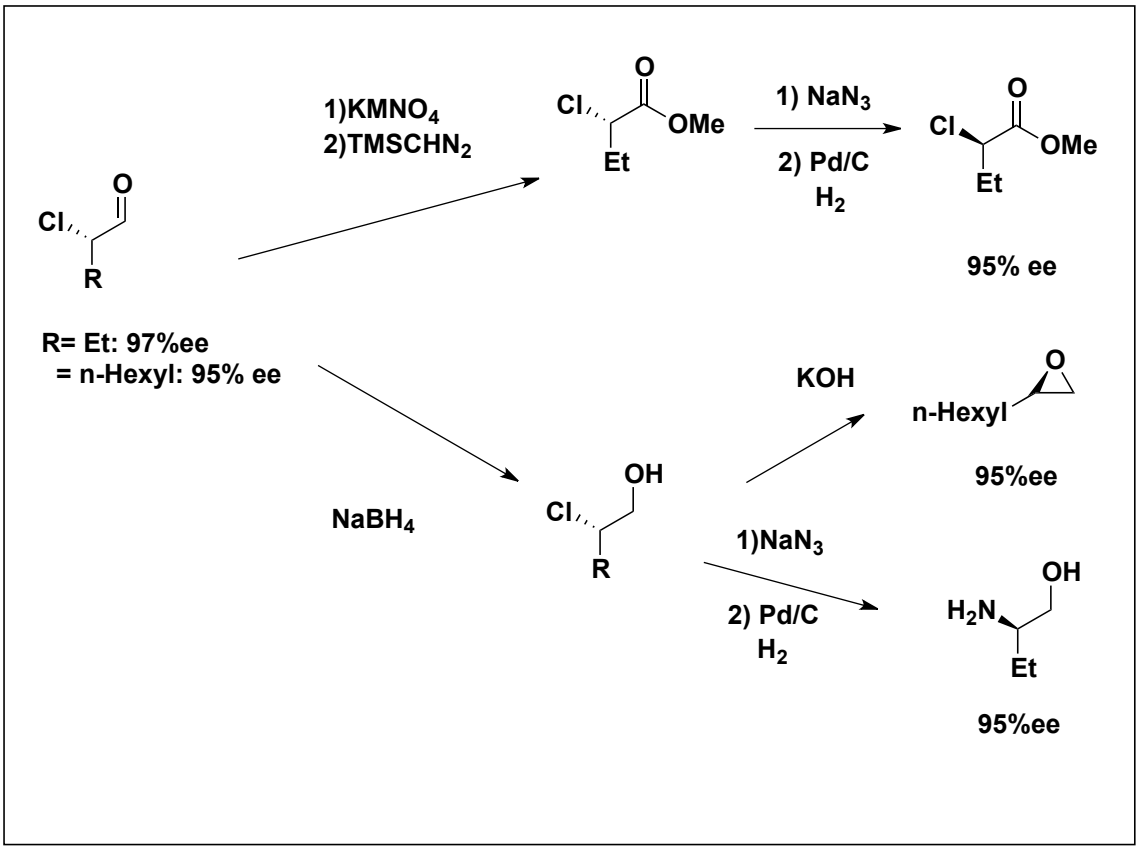
Scheme 11: α- Fluorination of β-ketoesters and α-cyanoesters.



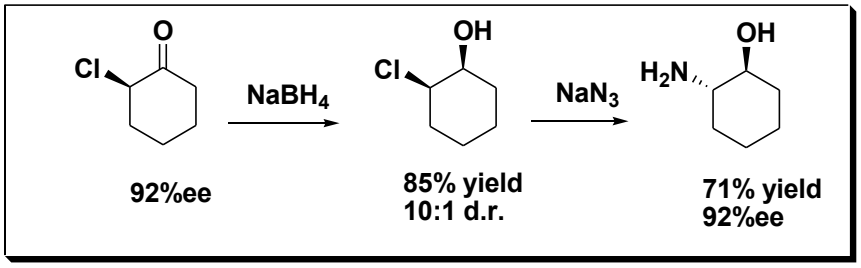
1.4.3 Asymmetric chlorination

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

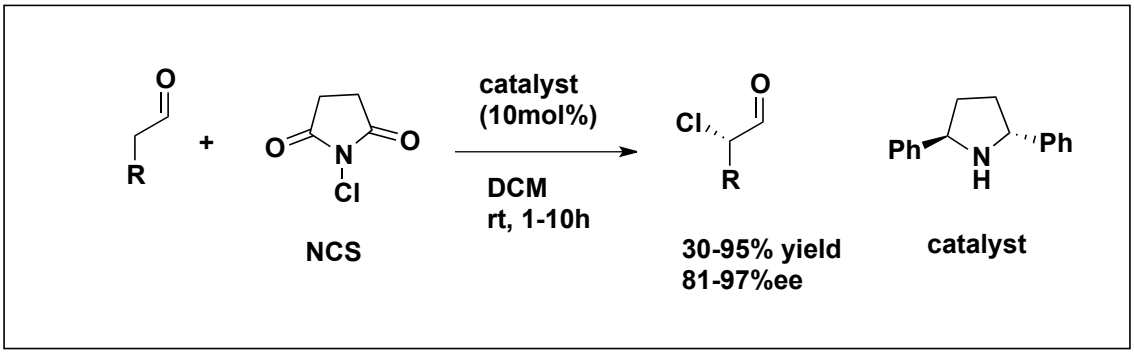
In 2004, both MacMillan and Jørgensen simultaneously reported asymmetric α-chlorination of unbranched aldehydes.

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.

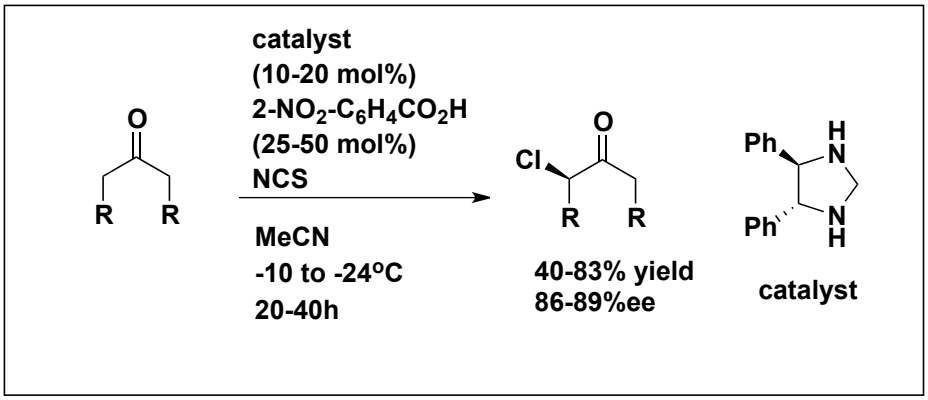
Jørgensen for the synthesis of α-chlorinated ketones applied imidazolidine as a catalyst (10-20 mol%) and NCS as the chlorinating agent. Use of acetonitrile as a solvent allowed monosubstituted product and the use of acid additive increase the reaction rate and enantioselectivity. The best acid additive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

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

Scheme 14: Jørgensen α-chlorination of aldehydes.



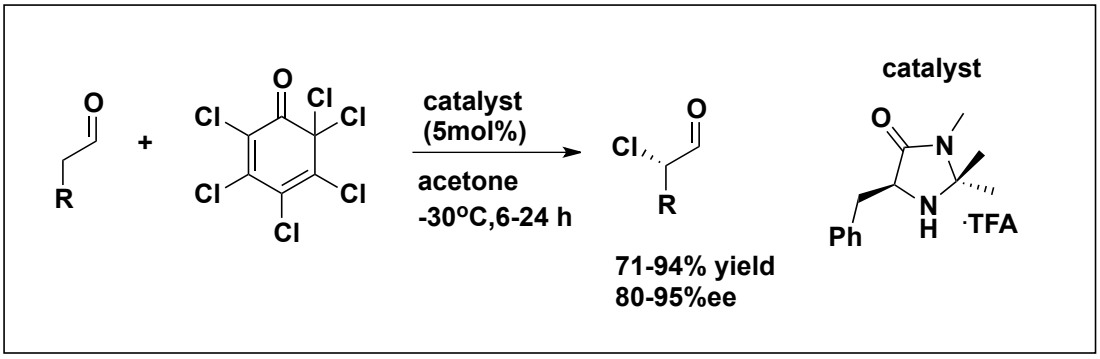
Scheme 15: Jørgensen α-chlorination of ketones.



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.

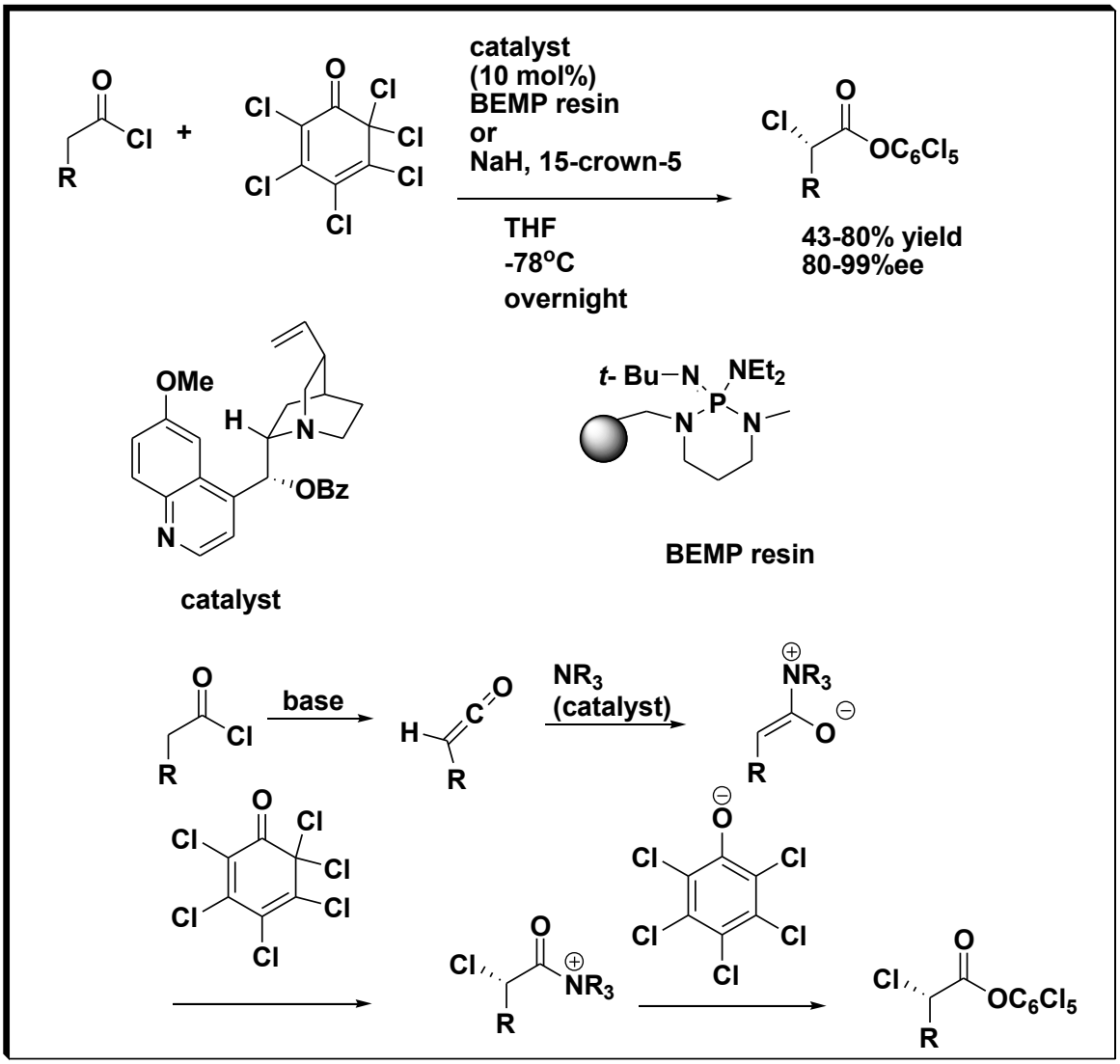


Asymmetric chlorination by chiral tertiary amines

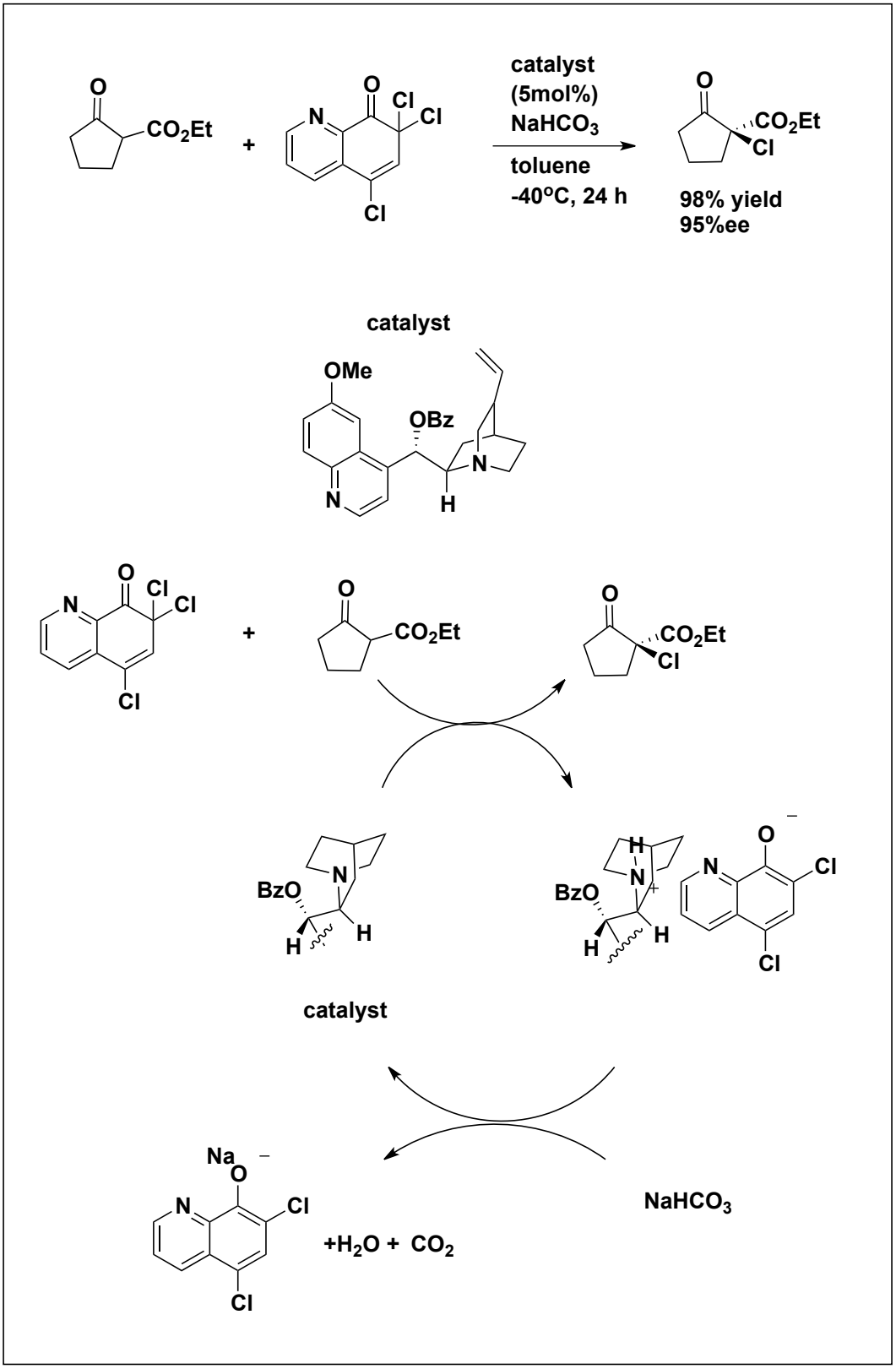
The first enantioselective α-chlorination of carbonyl compounds was developed by Lectka *et. al.* in 2001. They used benzoylquinine (10 mol%) as catalyst and perchlorinated quinine as chlorinating agent to form α-chlorinated esters from acid chlorides. The reaction occurs by chlorination of a chiral 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 agent[27]. 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.



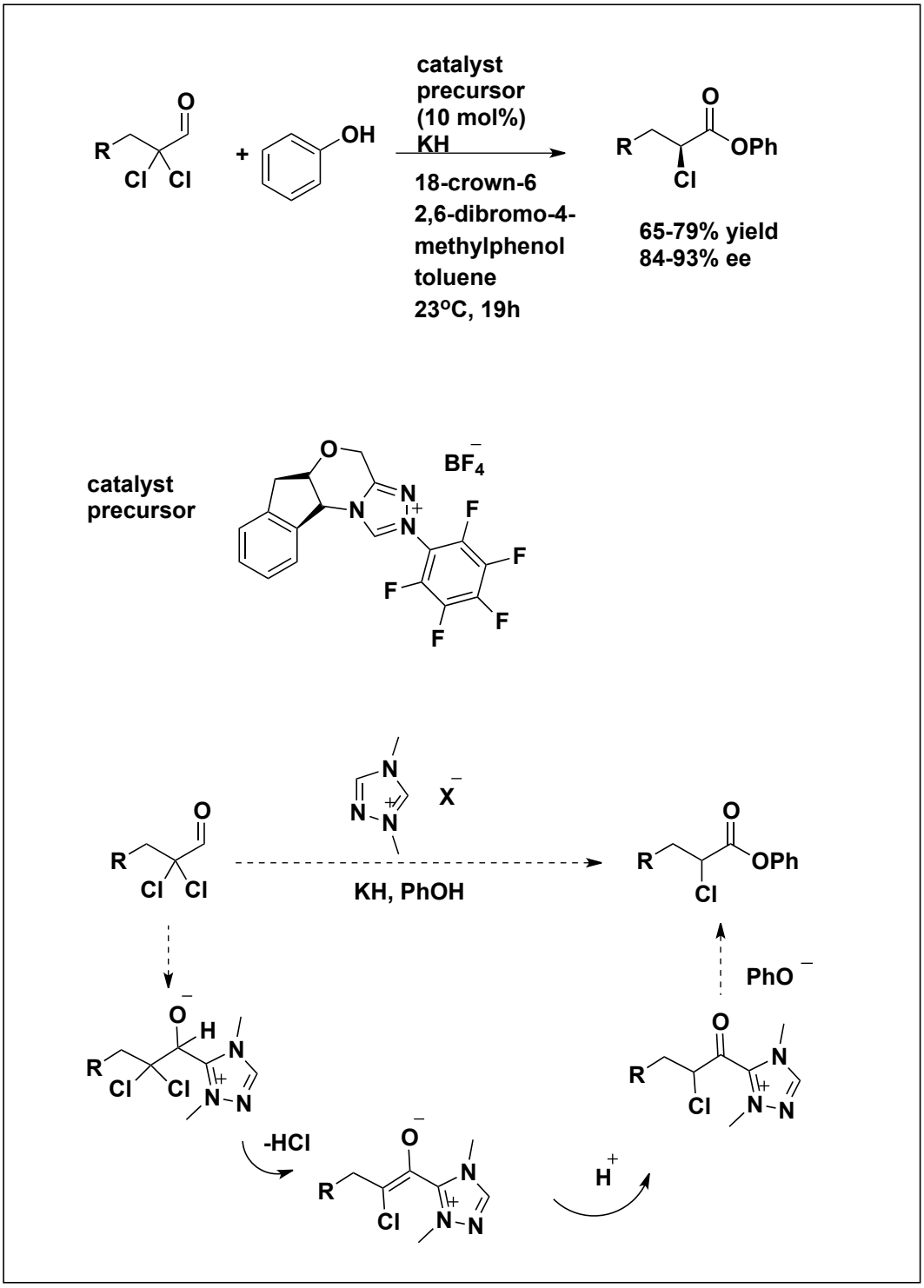
Asymmetric chlorination with chiral carbine catalyst

Rovis and Reynolds developed a method for the synthesis of α-chloroesters[28]. They used azolium salt (10 mol%) and made in solution chiral triazolinylidene carbine 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 carbine 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).

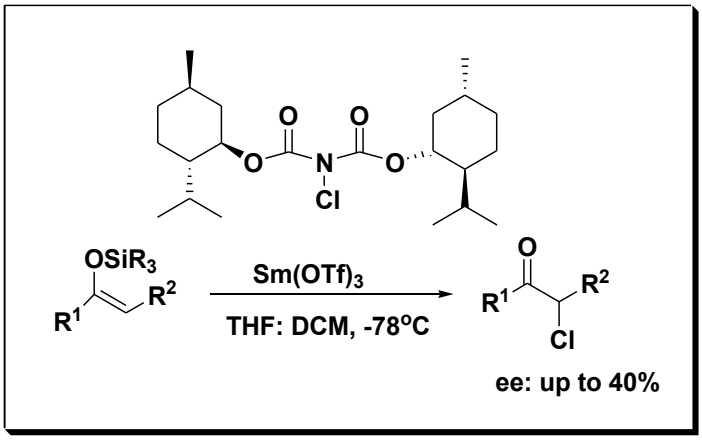
Asymmetric chlorination via chiral chlorinating agent

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 $Sm(OTf)_3$[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 carbine catalyst.



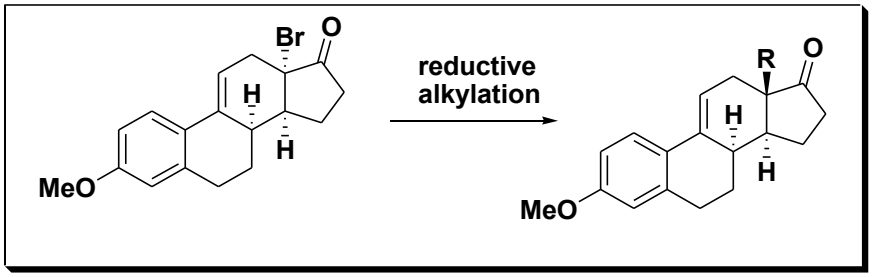
Scheme 20: Asymmetric chlorination by chiral *N*- Chloroimidodicarbonate.



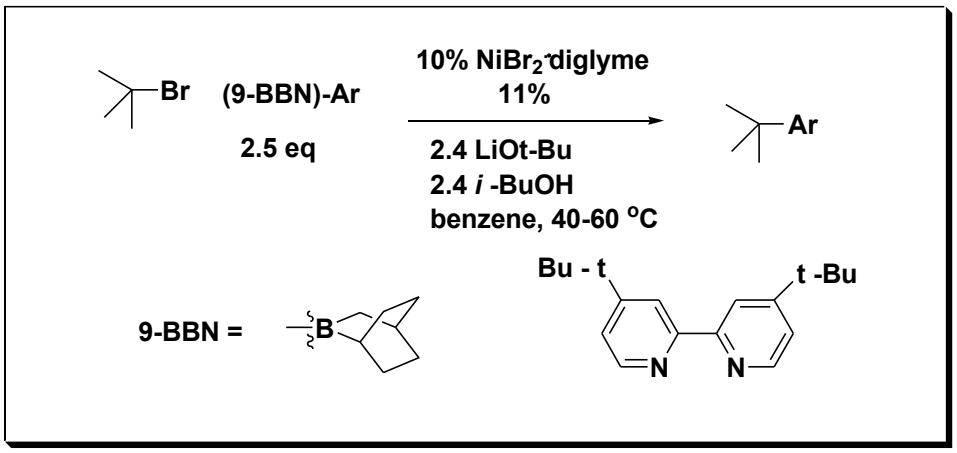
1.4.4 Asymmertic bromination

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 compounds[30]. 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 sp^3-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.

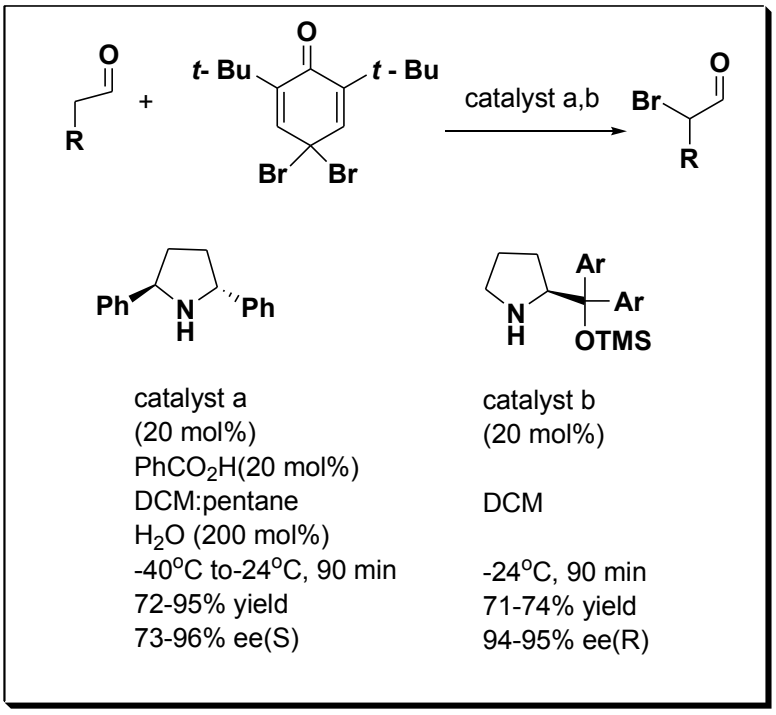


Asymmetric bromination by chiral amines

Jørgensen *et. al.* reported two methods for enantioselective α-bromination of aldehydes[30]. 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).

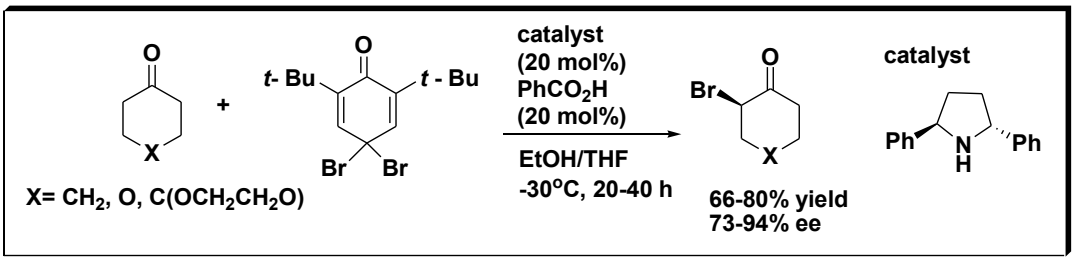
Scheme 23: α-bromination of aldehydes by Jørgensen *et. al.*



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 $NaBH_4$ prior to the purification with column chromatography.

Scheme 24: α- bromination of ketones.

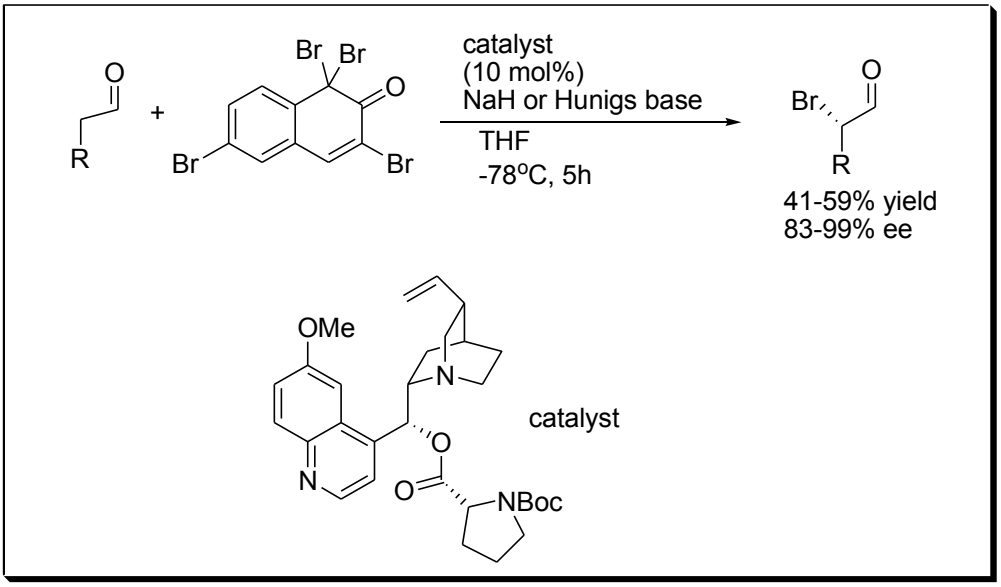


Asymmetric bromination by chiral *tert*-amines

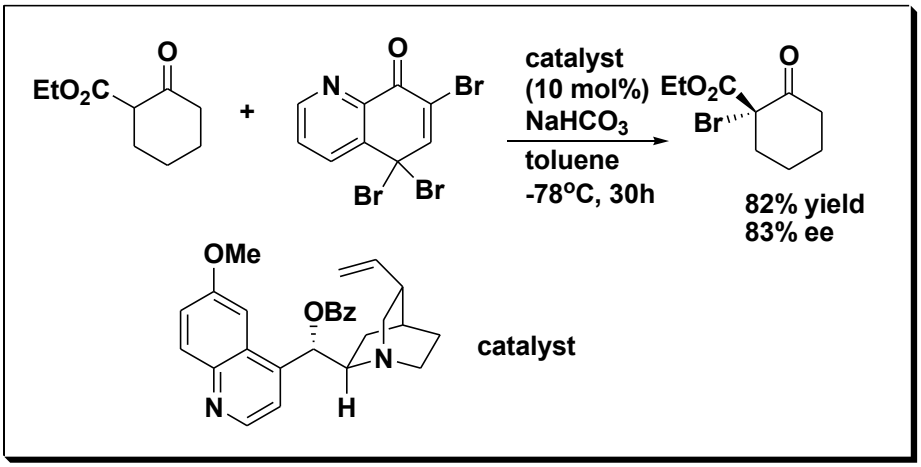
In 2001, Lectka developed enantioselective α-bromination of acid chlorides under similar conditions and same reaction mechanism as they did with α-chlorination. In this case they used 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone as the brominating agent and were able to achieve high enantioselectivity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

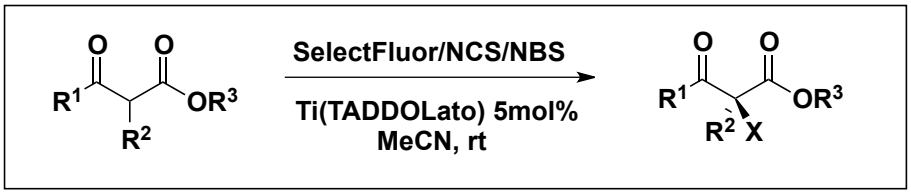


1.5 Metal catalyzed α-Haloganation

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 stereodefinding 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 diasteromeric 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 enatiomer has one of its *Si*-faces exposed and it was proposed that that is leading to destruction of enantioselectivity.

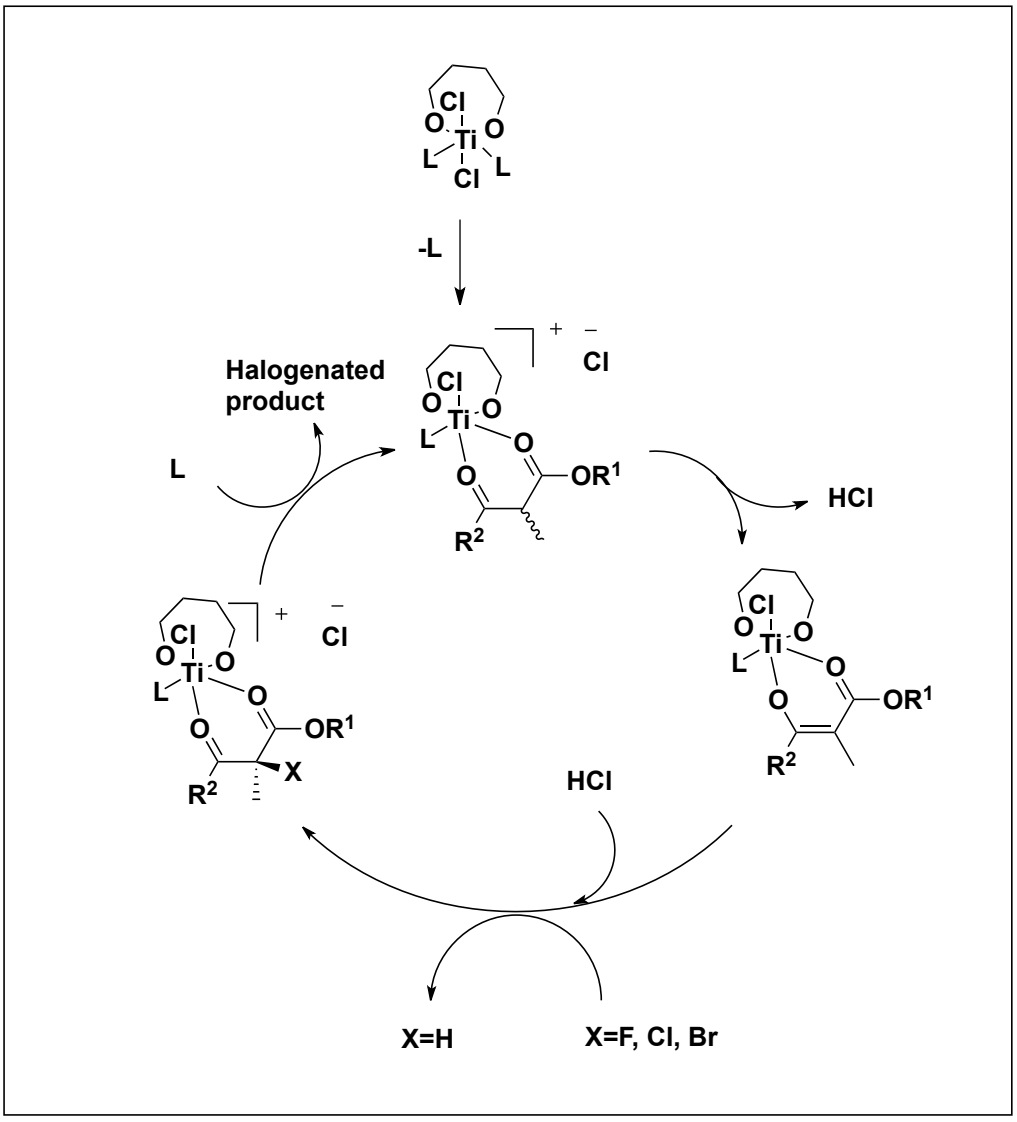
Equation 4: α- halogenation by Tongi and Hinterman.



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=

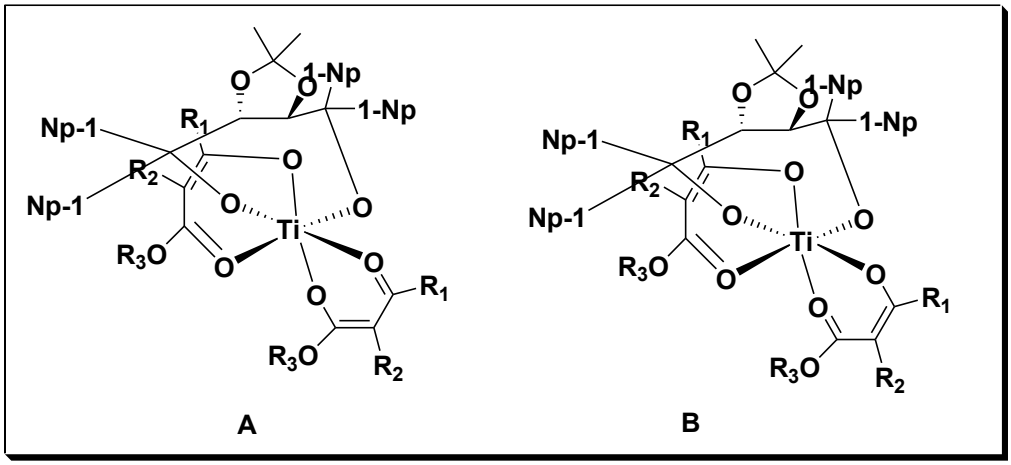
Figure 15: Lewis acid catalysis mechanism.



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 SEGPHOS and achieve high stereoselectivity[34]. These are air and moisture tolerable species can be used in

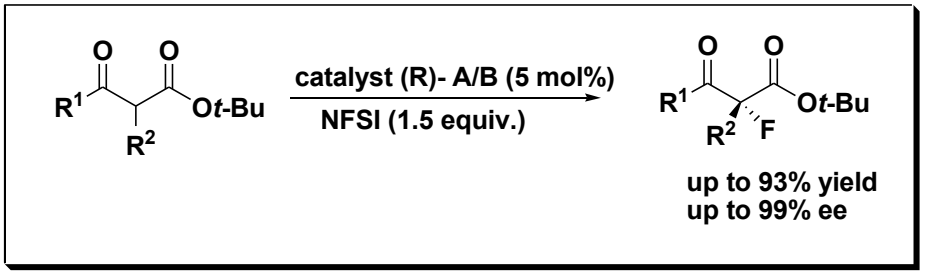
two forms: monomeric complex and dimeric complex (scheme 27). The dimeric complex can act as “bifunctional” catalyst with the hydroxyl group that bridges the complex and can be deprotonated and used as a Brønsted base and a Lewis acid in reaction simultaneously.

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

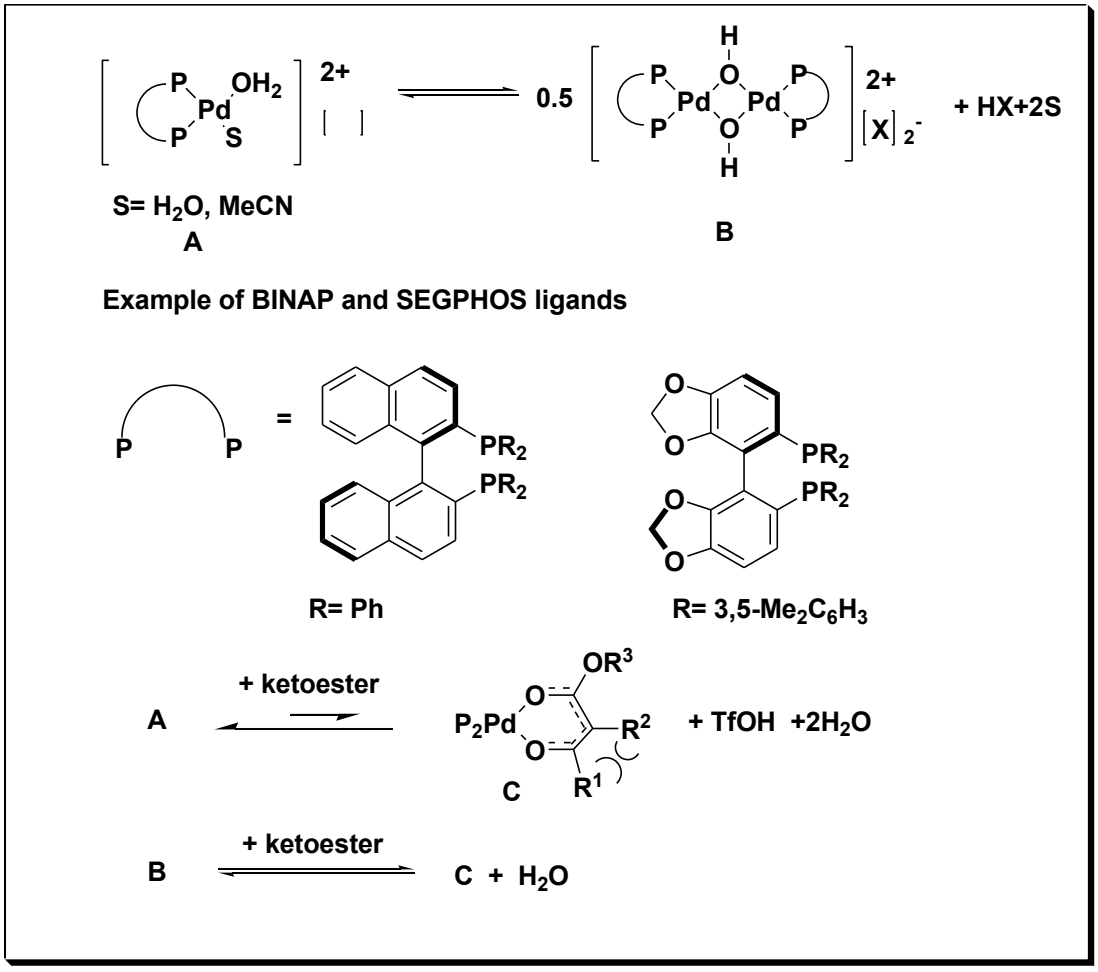


Pd catalyzed asymmetric α-fluorination of β-keto esters with NFSI was first reported by Sodeoka and co-workers using dimeric complex (equation 5) followed by report by Kim and co-workers with the monomeric complex (equation 6) with similar results[35,36]. Pd catalyzed asymmetric synthesis was applied towards β-ketophophonates, α-chloro-β-ketoesters,*tert*-butylα-aryl-α-cyanoacetates,α-aryl-α-cyanophophonates, 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 complaxes.



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 systems[37].

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 calculations[38].

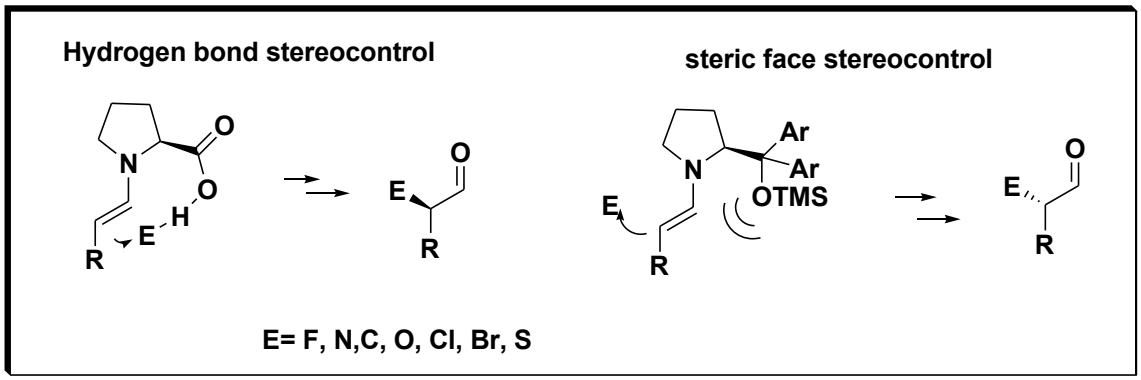
DFT calculations with B3LYP have known deficiencies such as the failure to correctly describe medium range correlations and photobranching effects, delocalization errors causing significant derivations in π to σ bonds and incorrect description of nonbonding and long range interactions, which are likely crucial for determining the stereoselectivity of the reaction outcome[39].

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 stereoselectivity[40].

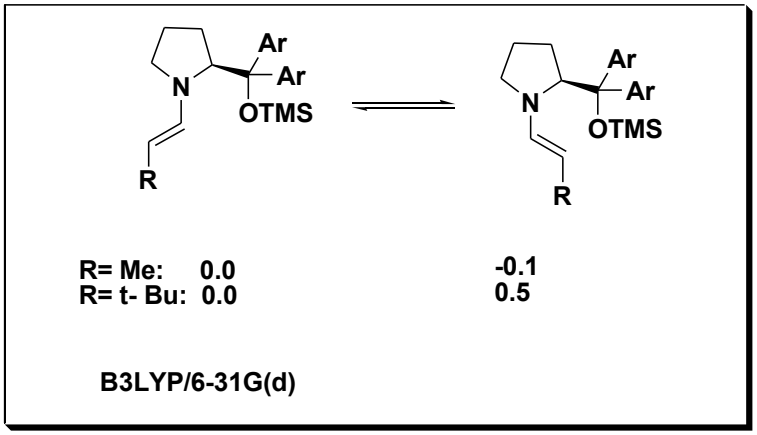
DFT calculations including the B3LYP are a useful tool for qualitative analysis but the energetic analysis may be deceptive for a larger system and cannot be completely relied on.

For the α-fluorination reaction that was published by Jørgensen and discussed earlier, DFT calculations were done to explain the enantioselectivity of the reaction[41]. 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.



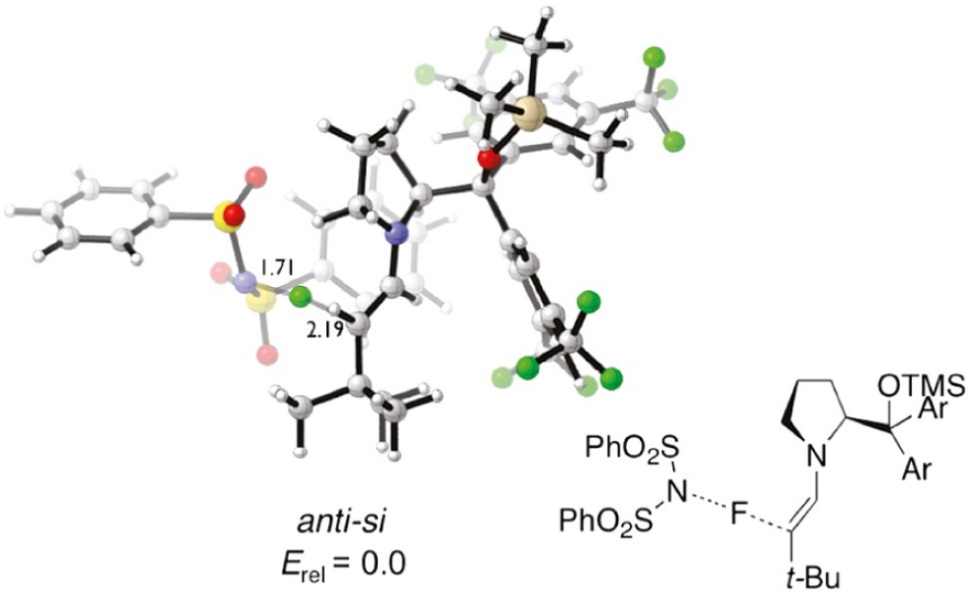
Both of the transition states for the α-fluorination of 3,3-dimethylbutanal by NFSI were found with B3LYP/^-31G(d). All geometries were taken under consideration. The lowest energy state was shown to be the one that leading to the (S) major and (R) minor enantiomer (figure 17). The minor (R) enantiomer 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. Lectkas group resorted to DFT calculation to explain the reaction and optimize the conditions[42].

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.



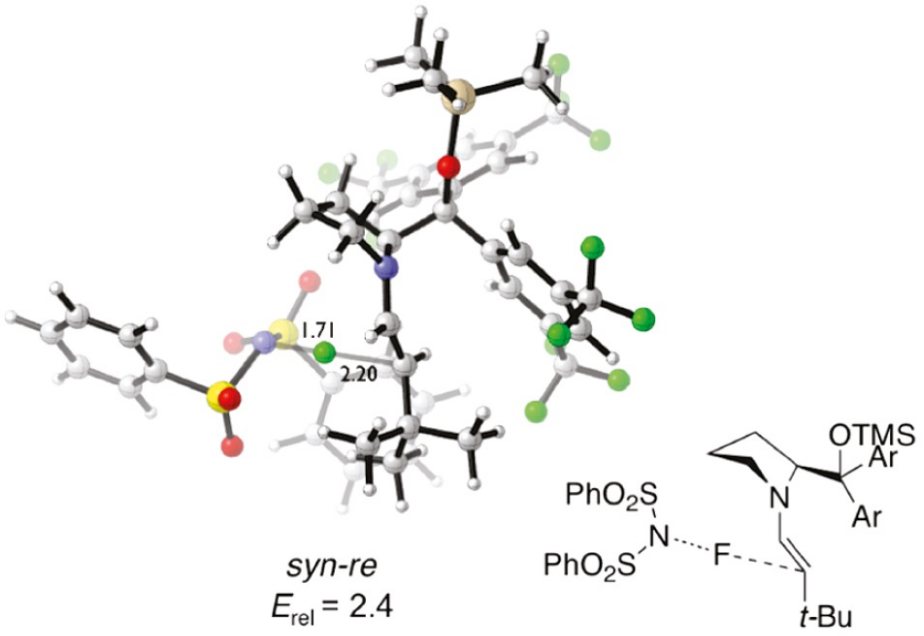
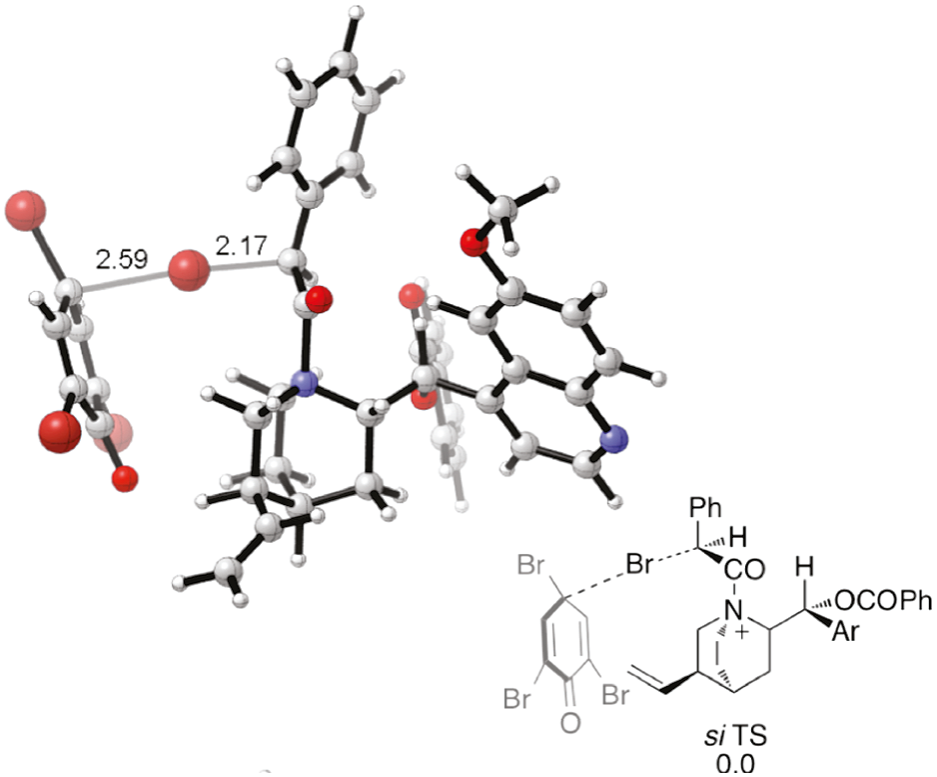
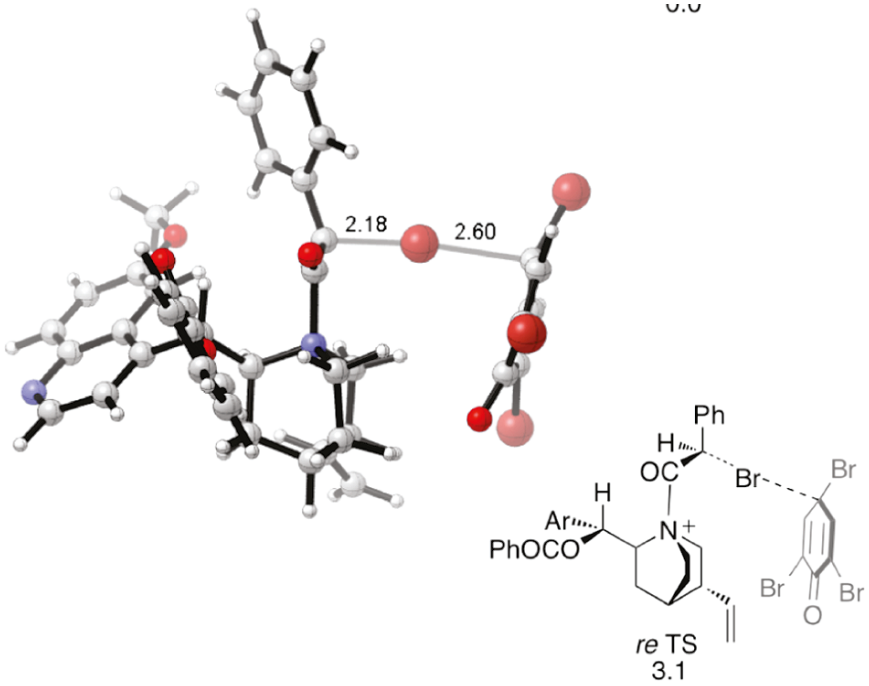
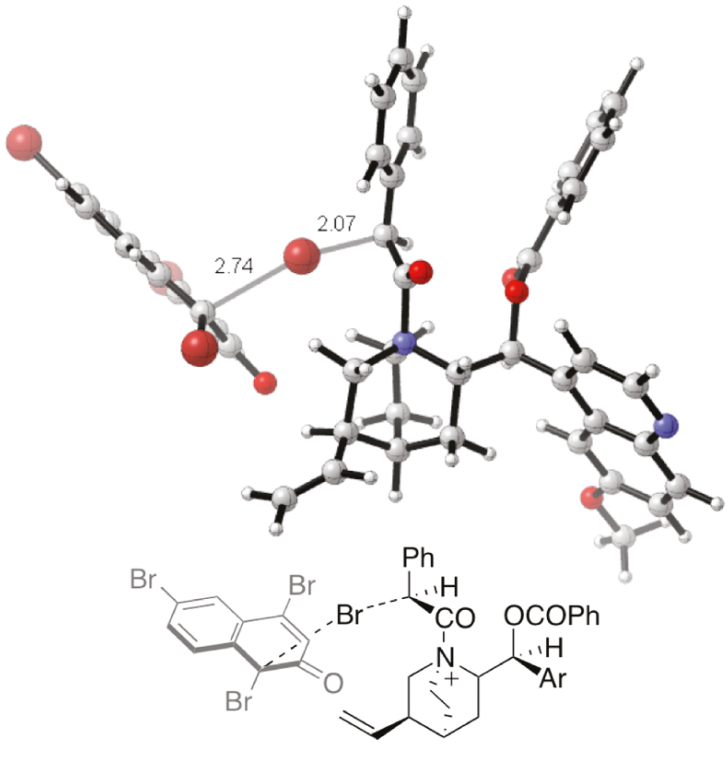


Figure 18: The *re* and *si* transition structure for brominating agent.

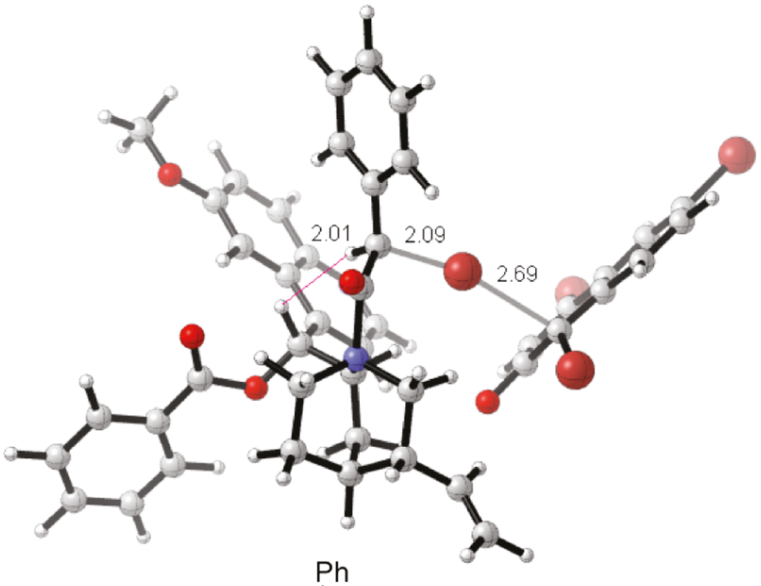


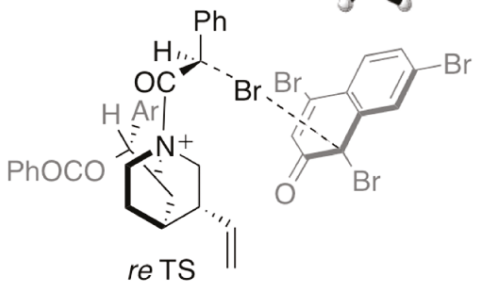


re TS
3.1



si TS
0.0





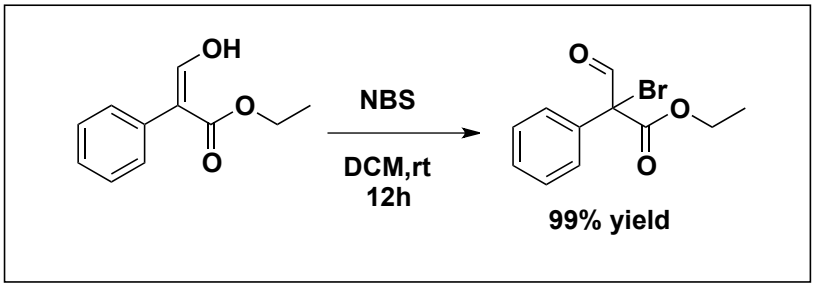
re TS
1.6

2. Results and discussion

2.1 Asymmetric bromination

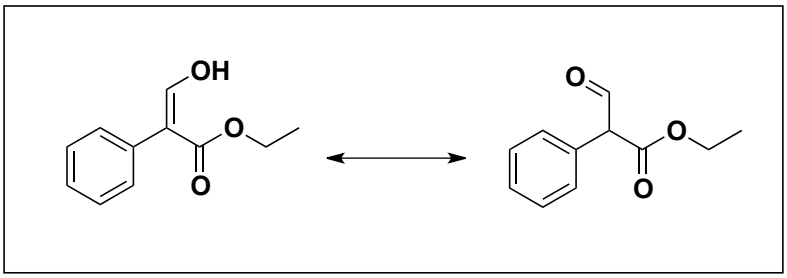
In the initial approach for α- halogenation, α-bromination was attempted first. NBS was chosen as the brominating agent because of previous examples in the literature and it's availability. Reaction temperature was room temperature and first reaction time was over night. After passing through a small 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).



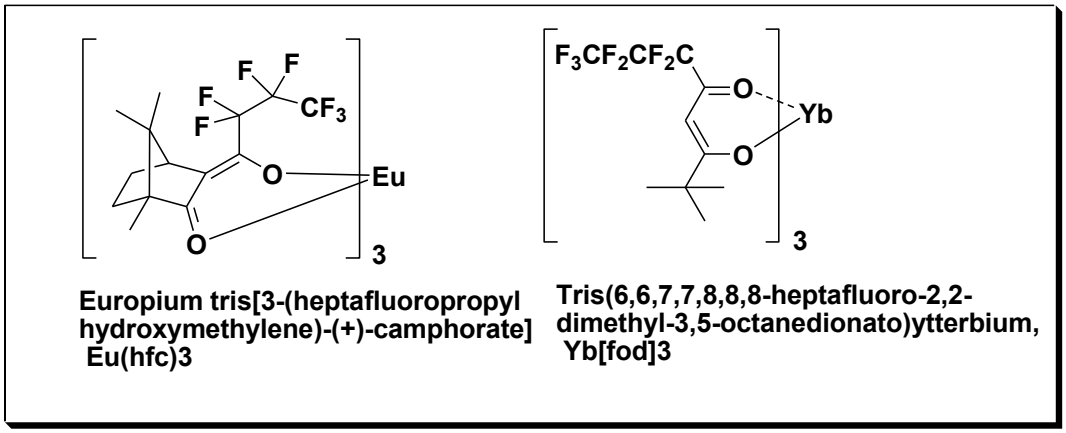
Following the racemic bromination reaction, asymmetric reaction was attempted. There is always aldehyde present in the starting material as a tatumer of the acrylate (figure 19) therefore L-Proline was chosen as the catalyst for the asymmetric reaction. L-proline was chosen because of its mode of activation 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^{o}C for 1 hour.

Figure 19: Acrylate and aldehyde tatumer.



In order to calculate ee, chiral shift reagents were tested in 1 equivalent with slow addition. $Eu(hfc)_3$ and $Yb[fod]_3$ (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.



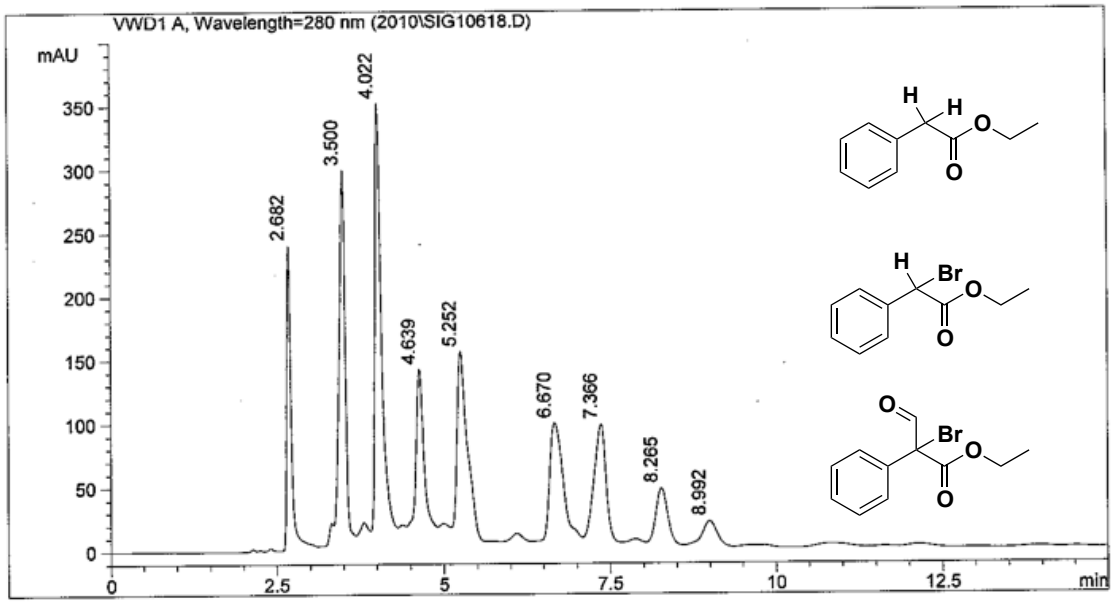
Temperature study experiments were conducted for the period of two hours at 0^oC, -10^oC and -20^oC with L-proline as chiral catalyst 20 mol% and NBS as brominating agent in DCM (see table 1).

Table 1: Temperature control experiment bromination reaction.

Entry	Temperature ^{o}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 corresponded 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: deformulated, dehalogenated and the actual substrate (figure 21).

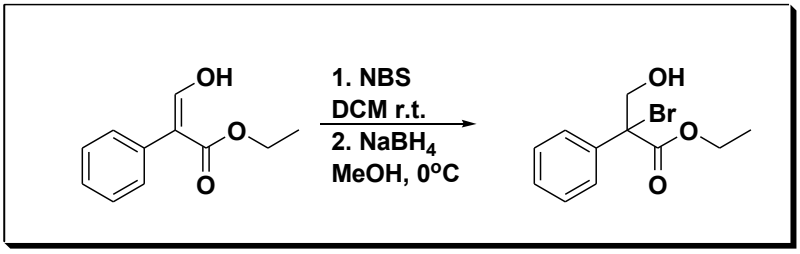
Figure 20: Data from Regis technologies.



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 $NaBH_4$.

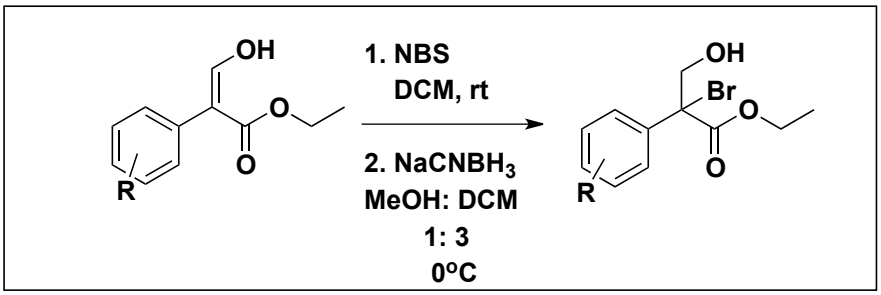
Reduction with $NaBH_4$ gave the reduced product but in low yield (Equation 6) with a lot of side product being formed. $NaBH_4$ proved to be too strong of reducing agent for this reduction and milder reducing agent was needed. Lowering the temperature of the reaction or slowing the addition of the $NaBH_4$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

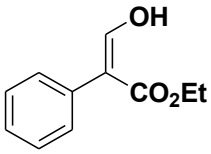
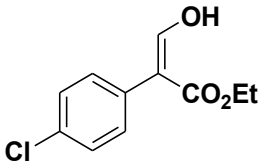
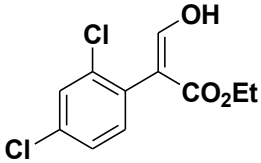
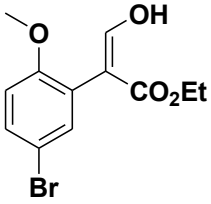
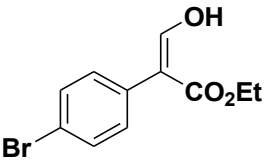
Equation 7: Reduction with $NaBH_4$.

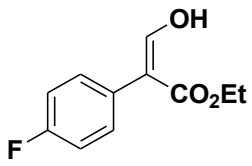
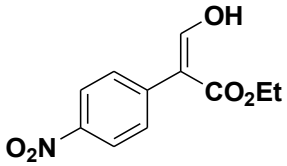
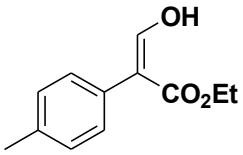


$NaCNBH_3$ proved to be a better reducing agent than $NaBH_4$ for this type of a system. Bromination and reduction can be done all in one pot, even though small samples were taken out before the reduction to monitor the progress of reaction and percent conversion through NMR. The brominated aldehyde 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		99%	95%
2		99%	61%
3		99%	85%
4		99%	55%
5		99%	52%

Entry	Substitution	% yield	%Isolated Yield
6		99%	67%
7		95%	45%
8		99%	75%

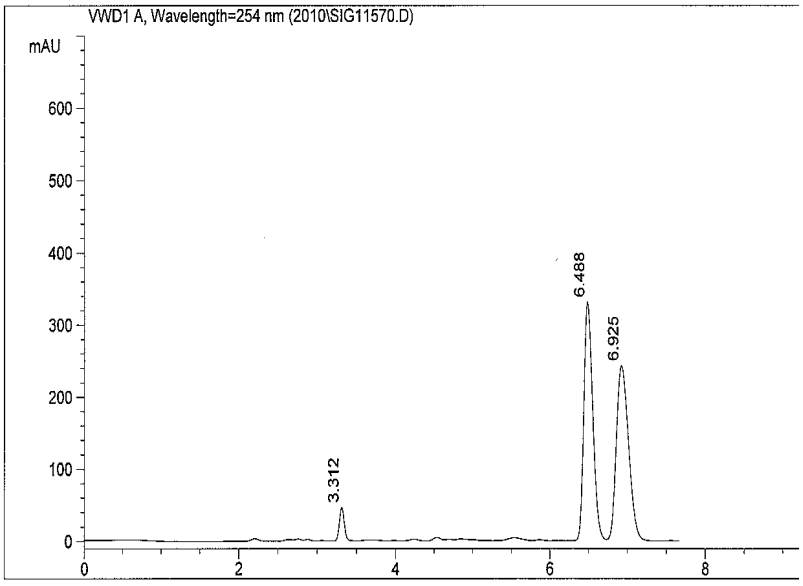
After finding a suitable reducing agent, a standard sample was brominated and reduced for analysis at Regis Technologies to match find a sutible chiral column for HPLC. The chiral column “RegisPack” (250mm*4.6 mm) from Regis Technologies was purchased and the optimized method was Hexane/Ethanol (95/5) 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

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

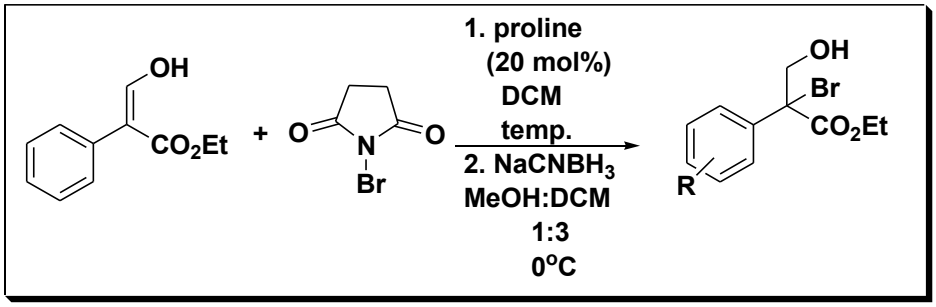


Peak #	RT [min]	Width [min]	Area	Area %
1	3.31	0.069	187.32	3.46
2	6.49	0.132	2610.77	48.27
3	6.92	0.180	2610.16	48.26

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^{o}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^{o}C.

Table 3: Temperature optimization chiral bromination reaction.

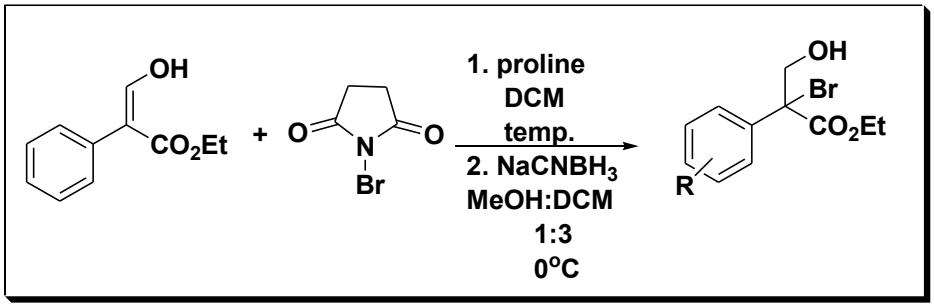


Entry	Temperature ^{o}C	% Yield	%ee
1	rt	99%	racemic
2	0^{o}C	99%	racemic
3	-20^{o}C	99%	13%
4	-78^{o}C	99%	39%

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^{o}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.

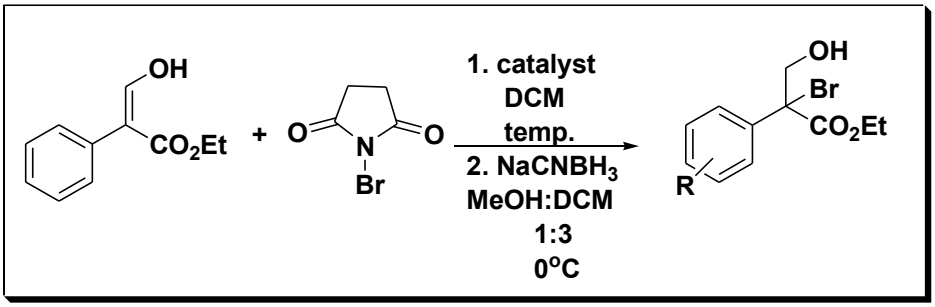


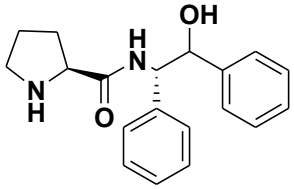
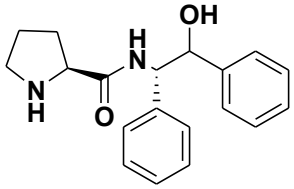
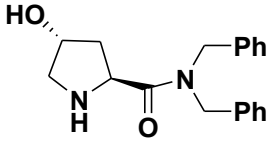
Entry	Catalyst loading (mol%)	% Yield	%ee
1	20	100	12
2	10	100	9

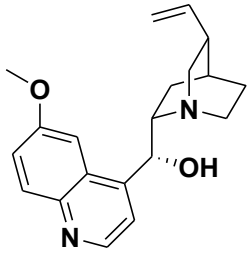
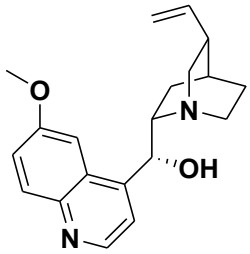
Changing the catalyst from proline to proline analogs on 100 mol% of catalyst gave increased ee of 34.6% with 100% yield. Lowering the temperature to -78^{o}C and lowering catalyst loading to 20 mol% did not show an increase in ee but instead lowered it to 33%. Changing the catalyst in entry 3 gave lower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

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

Table 5: Catalyst Screening- Bromination reaction.



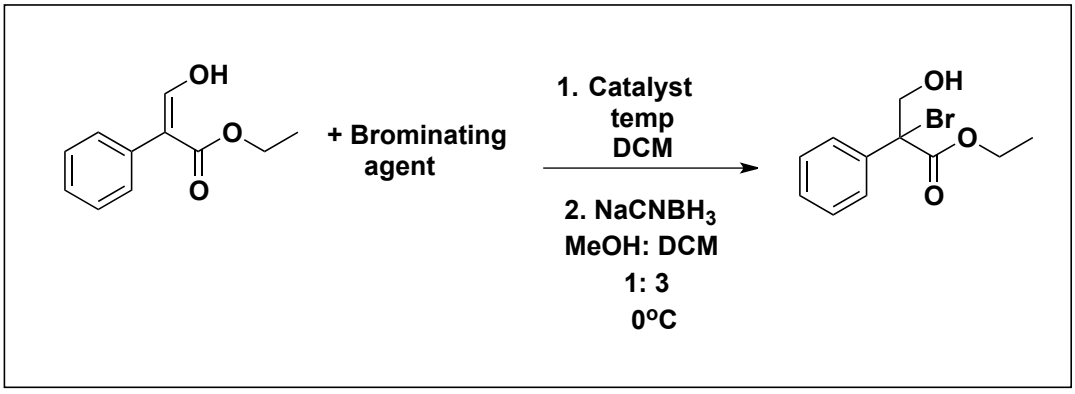
Entry	Catalyst	Temperature ^{O}C	%yield	%ee
1	 100 mol%	-25	100	34.6
2	 20 mol%	-78	100	33
3	 20 mol%	-25	100	9

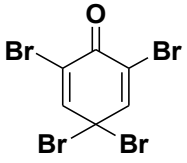
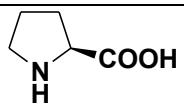
Entry	Catalyst	Temperature ^{O}C	%yield	%ee
4	 20 mol%	-25	100	9
5	 20 mol%	-78	100	8

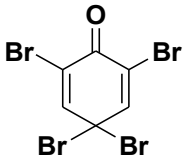
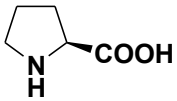
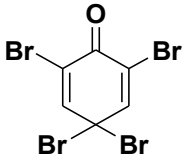
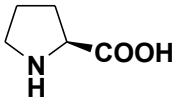
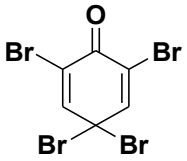
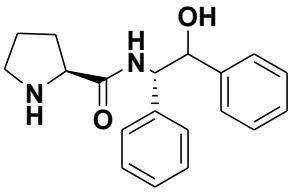
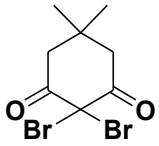
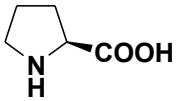
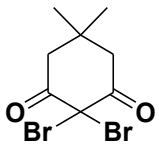
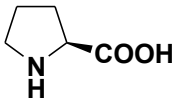
The conclusion that was achieved is that the brominating agent itself is too reactive and reacts faster than the catalytic reaction. In an attempt to increase the ee of the bromination reaction, a milder brominating agent was chosen, table 6 entry 1, at $-25^{0}C$ in DCM. % yield with a milder brominating 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

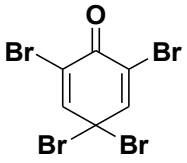
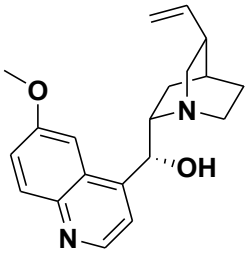
that the brominating agent is brominating the catalyst itself and therefore is not available for the bromination reaction, preventing catalytic induction. Altering the catalyst from proline to proline analog (entry 4) and quinine (entry 7) did not showed increase in % yield but did showed slight increase 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.



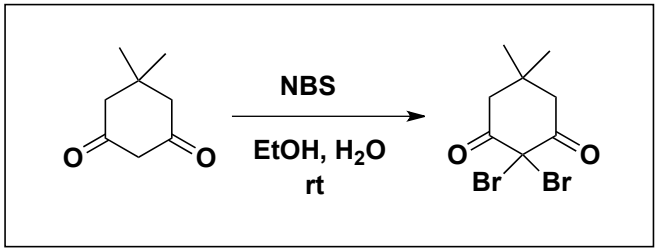
Entry	Brominating agent	Catalyst	Temp °C	%yield	%ee
1		 20 mol%	-20	50	racemic

Entry	Brominating agent	Catalyst	Temp ^{o}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 ^{o}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.

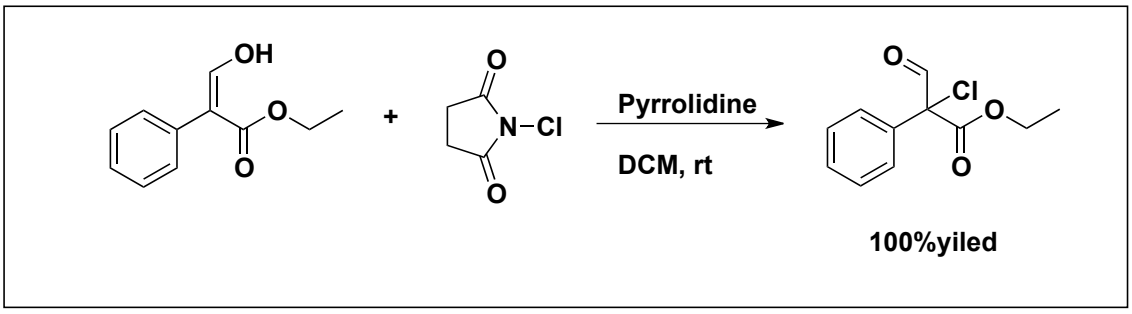
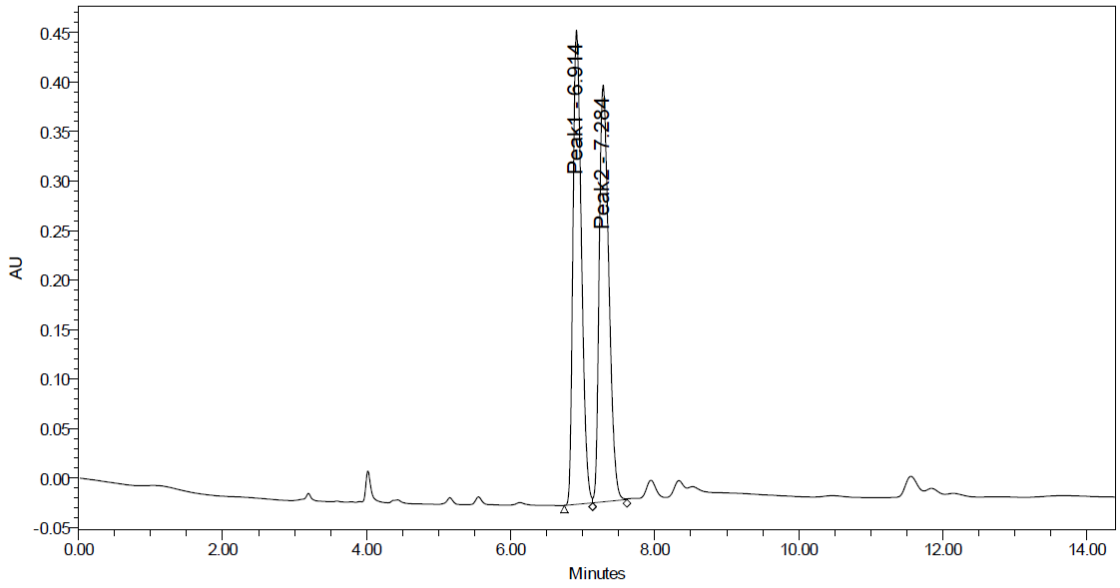


Figure 23: Optimization method for chlorination racemic sample.

SAMPLE INFORMATION

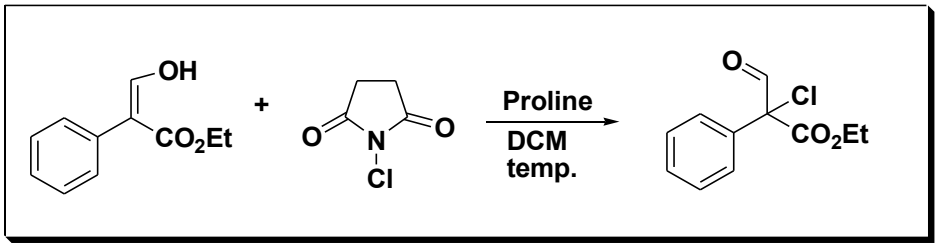
Sample Name:	Unk.	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/10/2011 1:54:28 PM CST
Vial:	1	Acq. Method:	chlorination
Injection #:	1	Date Processed:	11/10/2011 2:09:31 PM CST
Injection Volume:	10.00 ul	Channel Name:	220.1nm
Run Time:	25.00 Minutes	Sample Set Name	111011 st cl



	Peak Name	RT (min)	Area (µV*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^{o}C gave racemic mixture with 100% yield and -78^{0}C had 50% yield with slight ee (table 7). -20^{O}C was chosen because in the previous halogenation reaction it gave slightly better ee than rt.

Table 7: Temperature optimization- Chlorination reaction, proline.

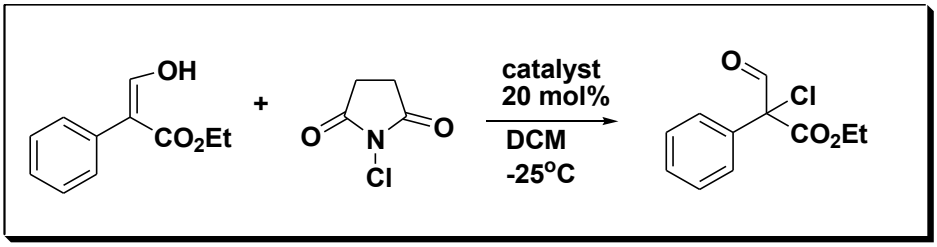


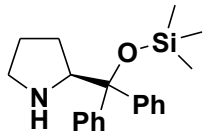
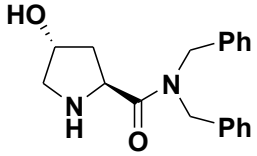
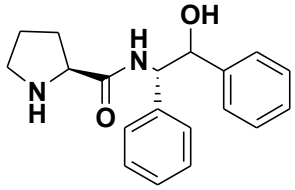
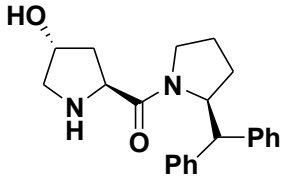
Entry	Temperature ^{o}C	%yield	%ee
1	rt	100	racemic
2	-20^{o}C	100	racemic
3	-78^{o}C	50	4

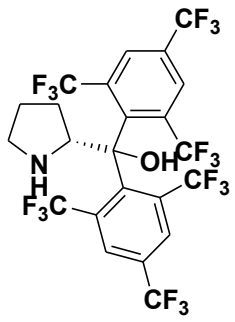
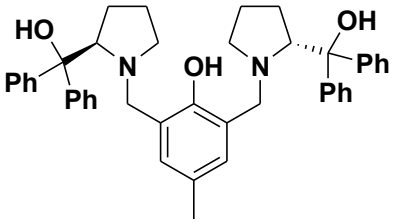
After choosing the optimal reaction temperature, catalyst screening was done. The first type of catalyst that was chosen were proline analogs because of their availability in the lab from the previous bromination reaction and in order to test the enamine activation mechanism that are suitable for aldehydes 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

analogs 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 analogs (table 9).

Table 8: Catalyst screening- Chlorination reaction proline analogs.



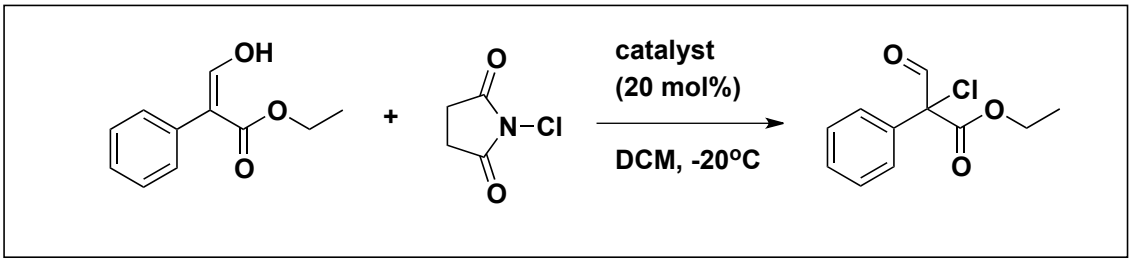
Entry	Catalyst	%yield	%ee
1		100	3
2		100	racemic
3		100	racemic
4		100	racemic

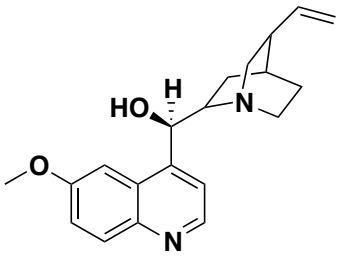
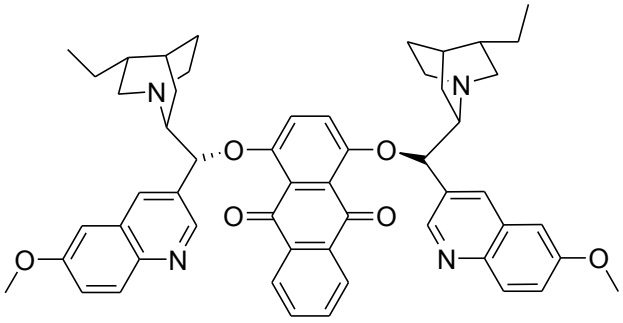
Entry	Catalyst	%yield	%ee
5		100	5
6		100	20

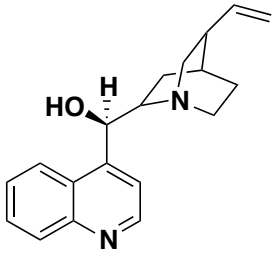
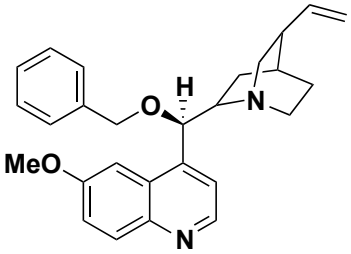
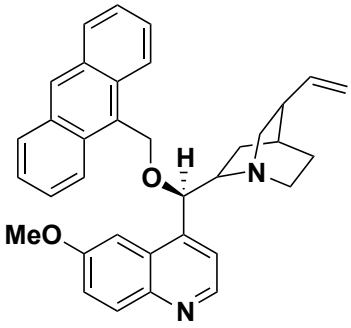
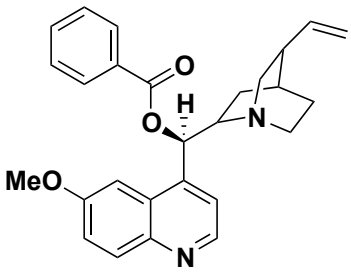
The next set of catalysts that were screened were quinine-based catalysts. Quinine based catalysts contain tertiary nitrogen that should deprotonated the acrylate as well as hydrogen bond to groups such as the hydroxyl that can hydrogen bond to the carbonyl group and create ion pair interaction according 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

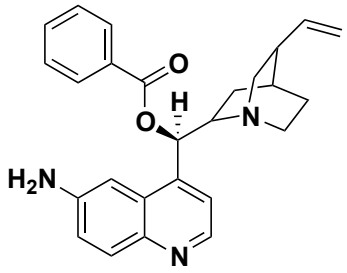
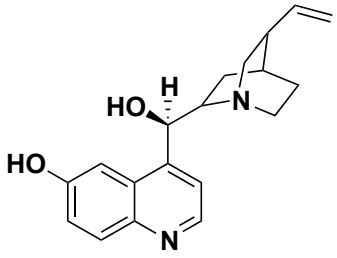
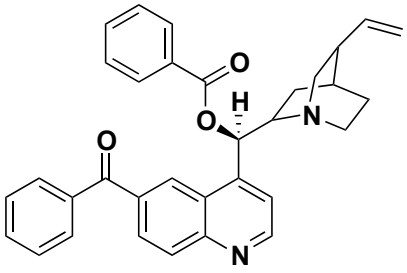
the ee. Next catalyst that was used, entry 3, was cinchonine and it showed lower ee than the quinine analog, indicating that there is significance to the substitution at the 6 position. Entries 4-6, were catalysts that had bulky substitutions instead of the hydroxyl group. All three of the catalysts 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

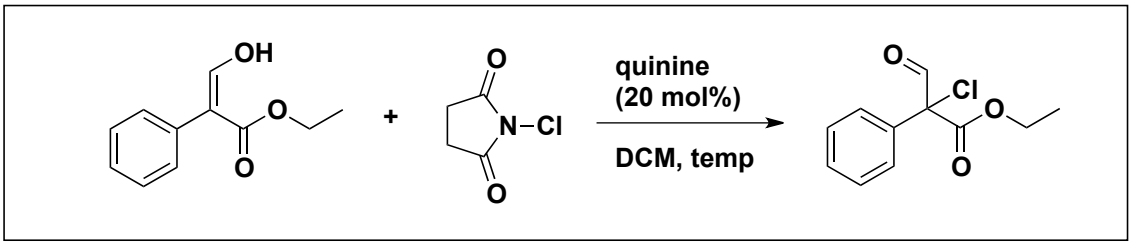
Entry	Catalyst	%yield	%ee
3		100	9
4		100	19*
5		100	15*
6		100	10

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.

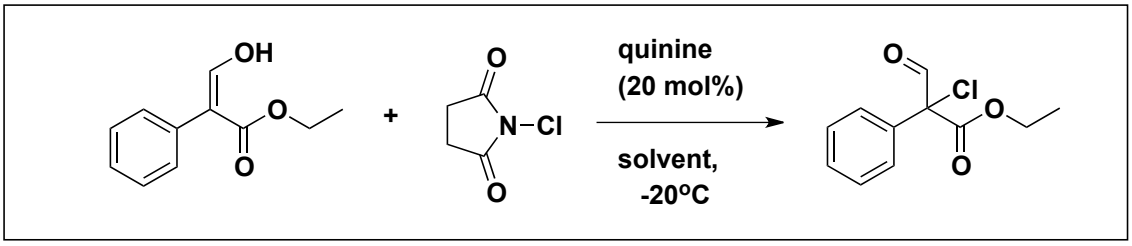
Table 10: Temperature screening- quinine NCS.



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.

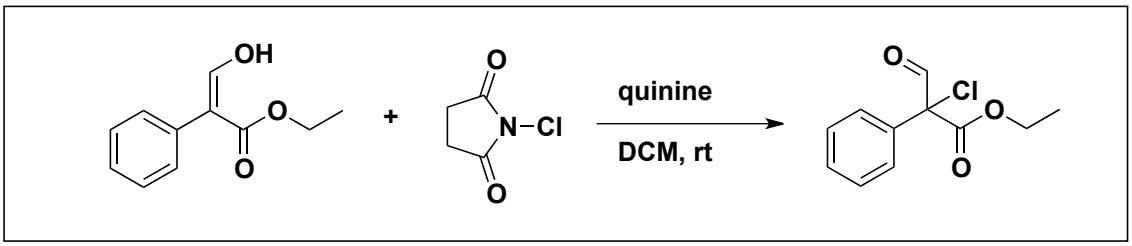


Entry	Solvent	%yield	%ee
1	DCM	100	24

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.

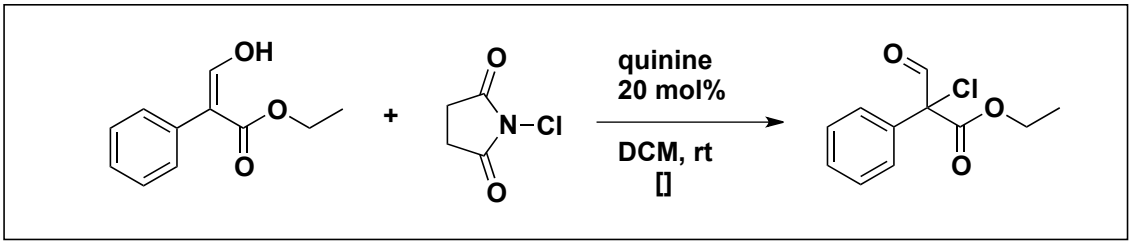
Table 12: Catalyst loading-Quinine, Chlorination.



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.

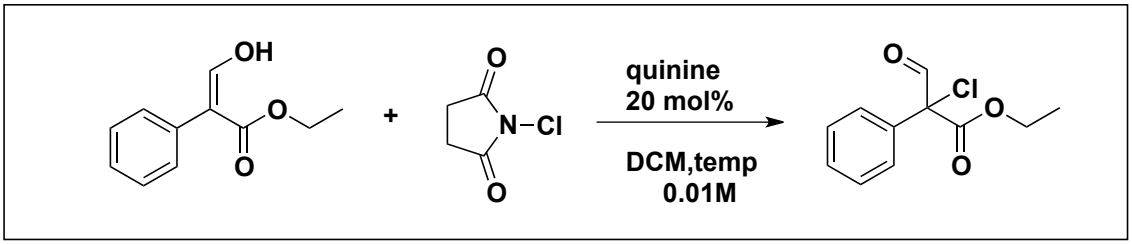
Table 13: Reaction concentration- Chlorination.



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^{o}C there was slightly lower ee than at -20^{0}C and heating the reaction gave results of racemic mixture, entry 3.

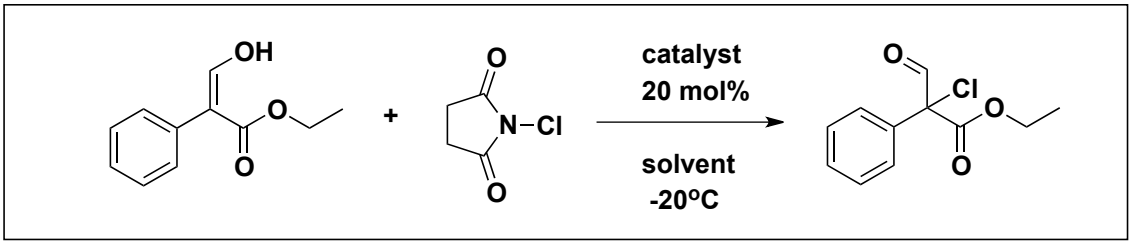
Table 14: High dilution Temperature screening-chlorination.

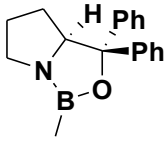
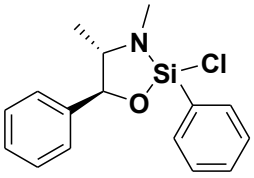
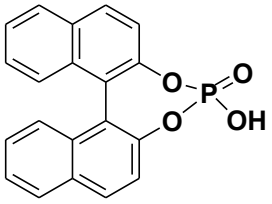


Entry	Temperature ^{o}C	%yield	%ee
1	-78	100	13
2	-20	100	16
3	50	100	racemic

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, entery 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.

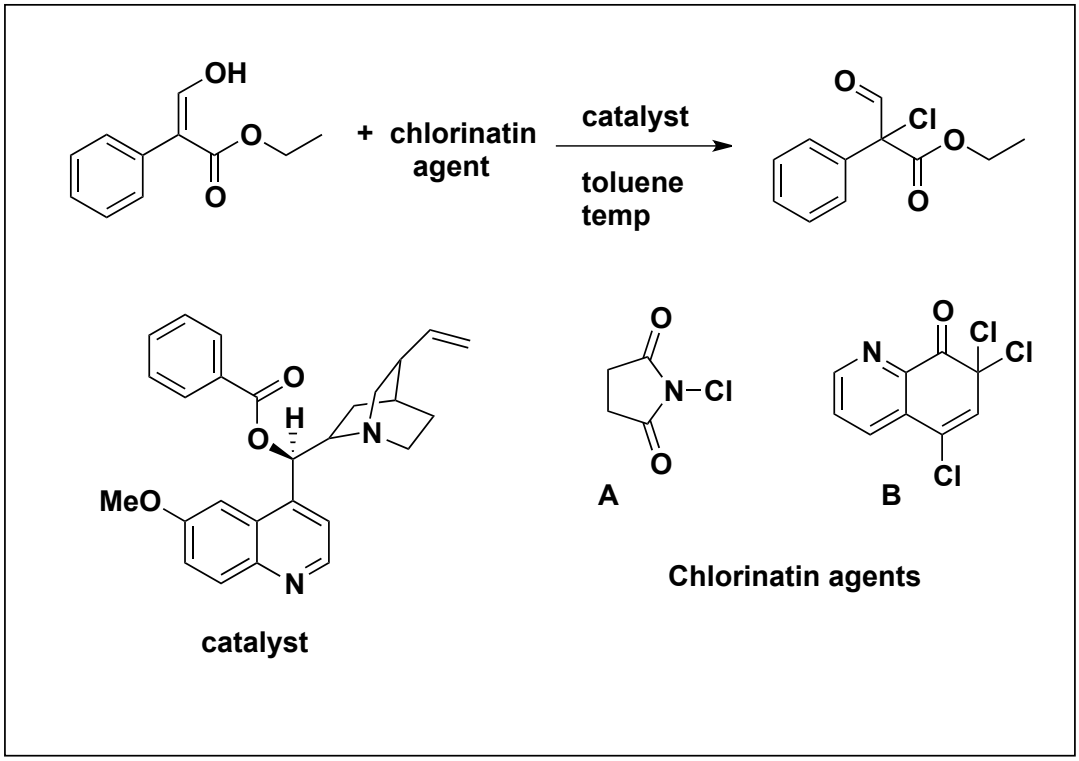


Entry	Catalyst	Solvent	%yield	%ee
1		Toluene	100	2
2		DCM	100	5
3		DCM	100	Racemic

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^{o}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 $NaHCO_3$ 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^{0}C in attempt to get higher results than in entry 1 did not yielded better ee.

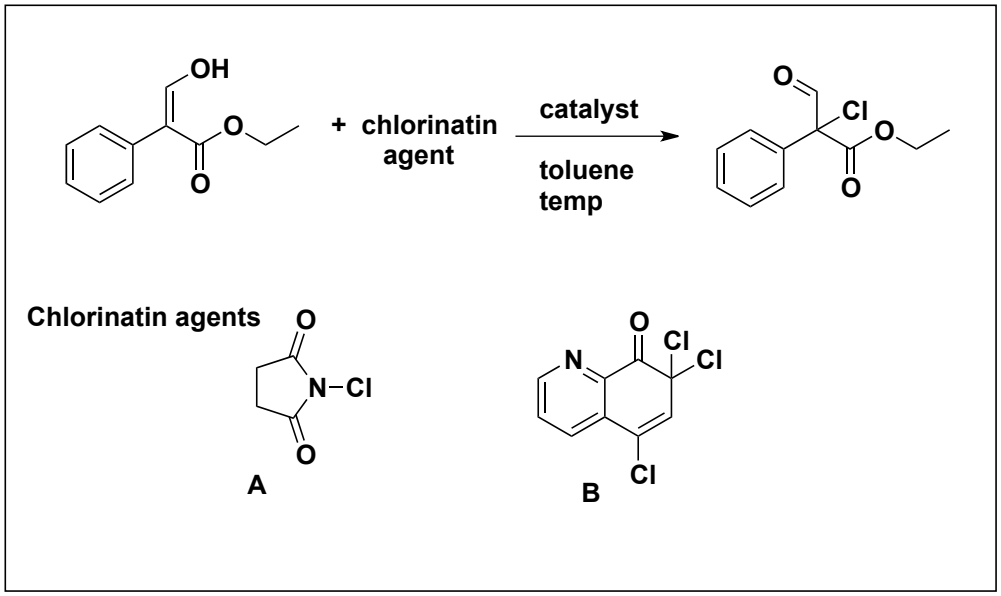
Table 16: Chlorination based on Bartoli and Melchiorres work.

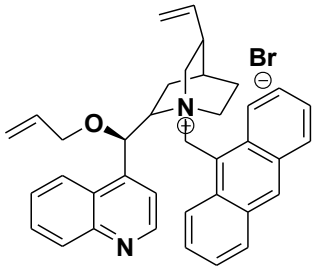
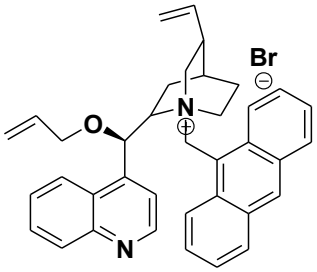


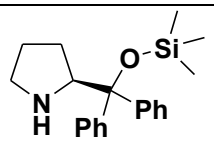
	Chlorinating agent	Temp. ^{o}C	%yield	%ee
1	A	-25	100	28
2	B	-25	73	15
3	B $NaHCO_3$	-25	100	21
4	A	-78	100	19

After getting improved ee with different catalyst and toluene as the reaction solvent different catalysts where screened (table 17). After screening phase transfer catalyst with both of the chlorinating agents and no improved ee was shown, entries1,2, repeating the reaction with proline analogs did not proved 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.

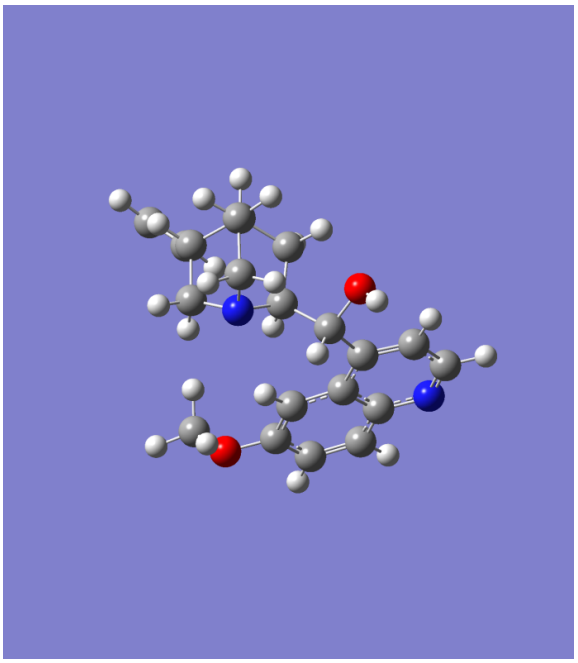


Entry	Catalyst	Chlorinating agent	%yield	%ee
1	 K_2CO_3	A	100	9
2	 K_2CO_3	B	10	11

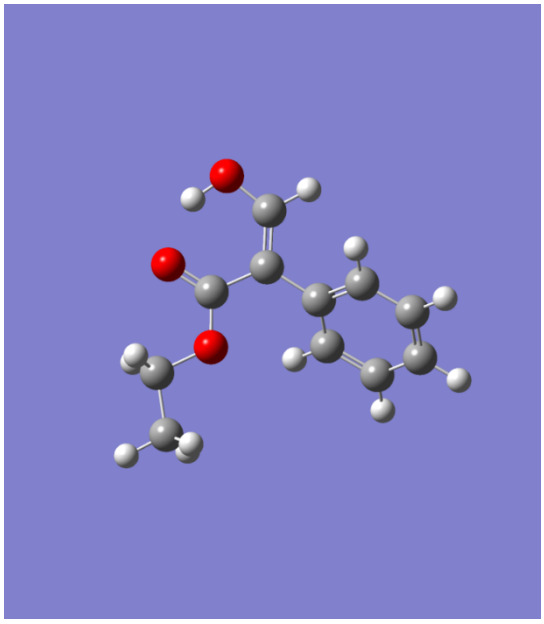
Entry	Catalyst	Chlorinating agent	%yield	%ee
3		B	7	12

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.

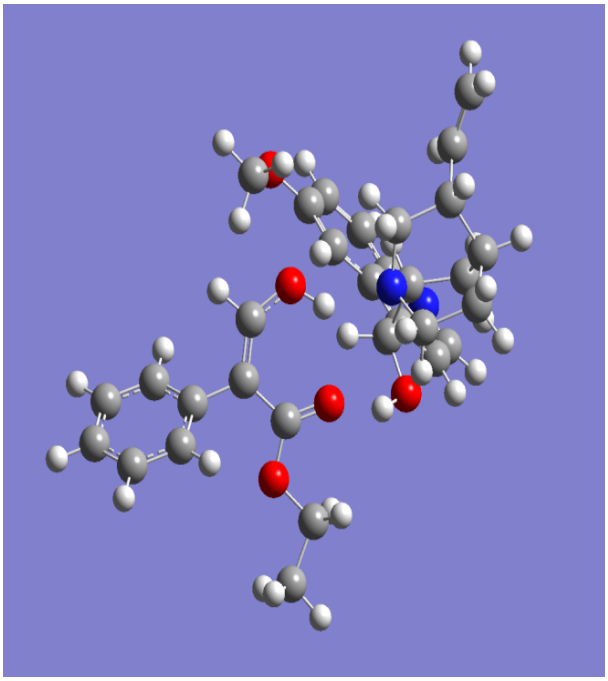


Quinine energy minimization:



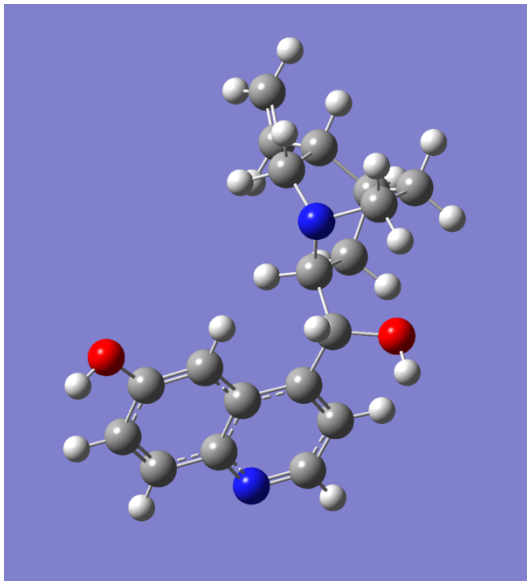
Acrylate energy minimization

Acrylte with quinine energy minimization:

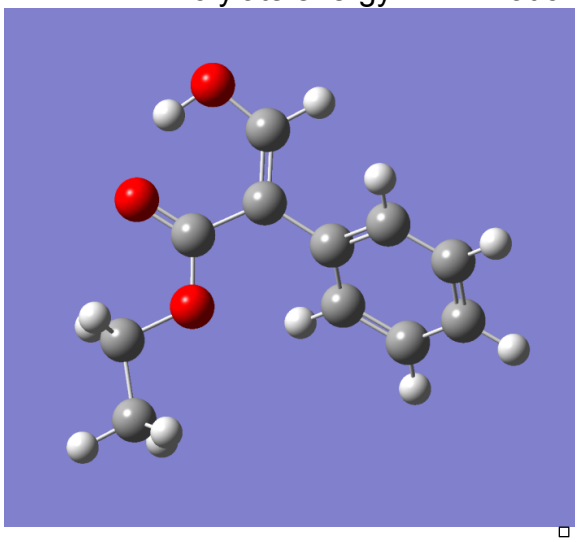


	Energy (a.u.)
Quinine	-1036.4791
Acrylate	-652.0752
Total energy	-1688.5543
Combined	-1688.5667
Difference (a.u.)	0.0124
Difference (kcal/mol)	7.7641

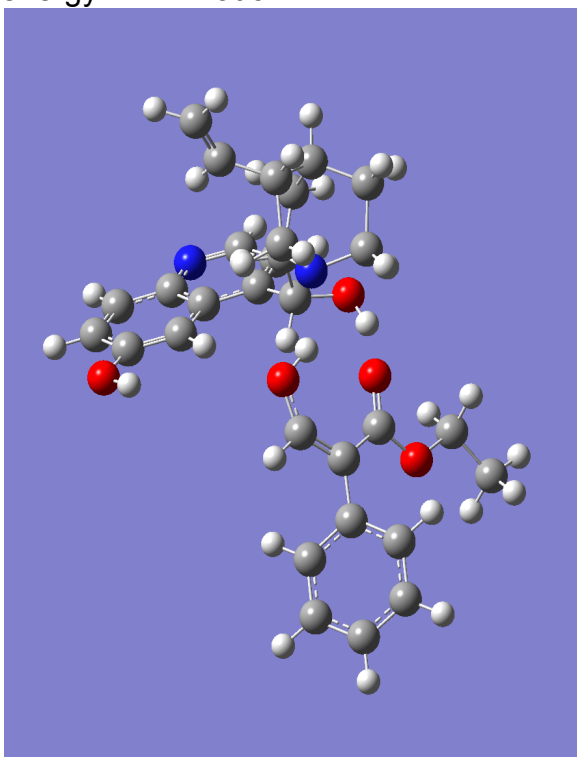
Quinine OH energy minimization:



Acrylate energy minimization:

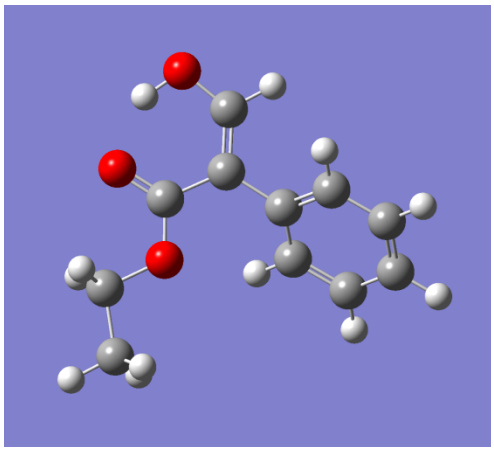


Acrrylate with quinine hydroxyl energy minimization:

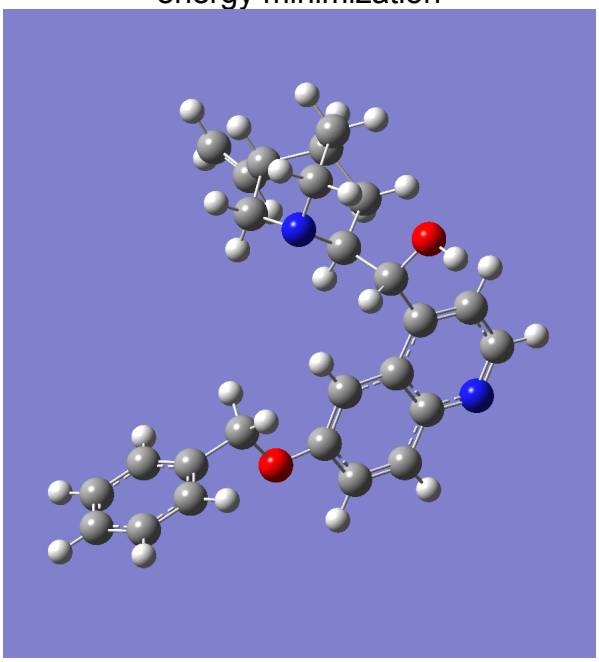


	Energy (a.u.)
Qunine OH	-997.1708
Acrylate	-652.0752
Total	-1649.2460
Combined	-1649.2598
Difference (a.u.)	0.0138
Difference (kcal/mol)	8.6643

Acrylate energy minimization:

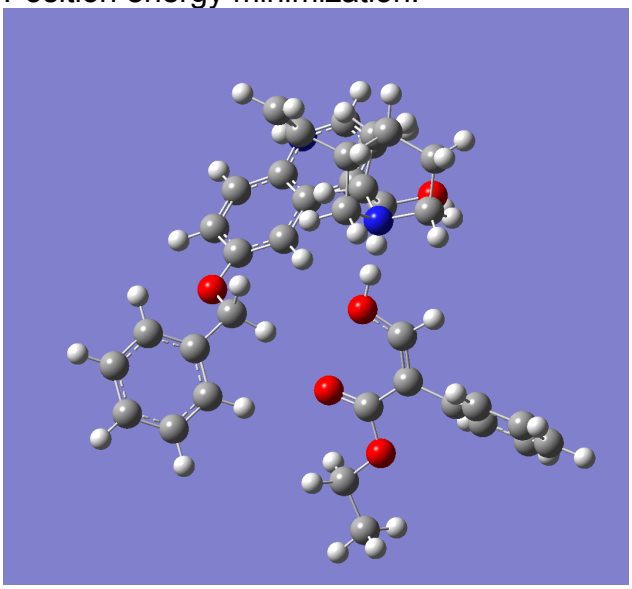


Quinine Benzyl at methoxy position energy minimization



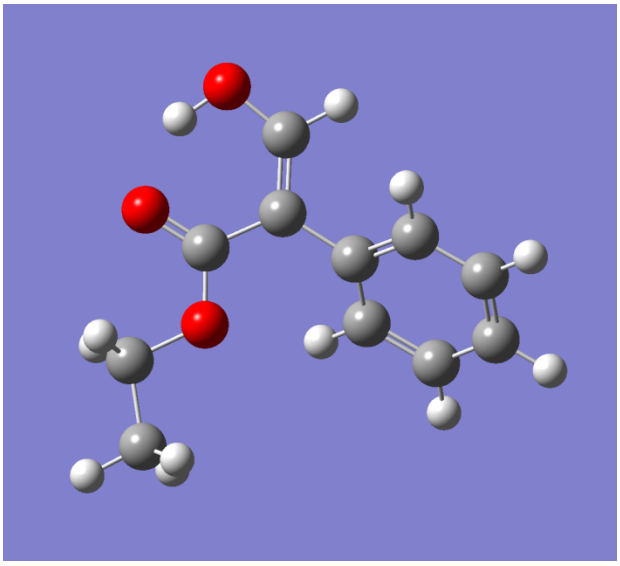
Acrylate with Quinine benzyl at methoxy

Position energy minimization:

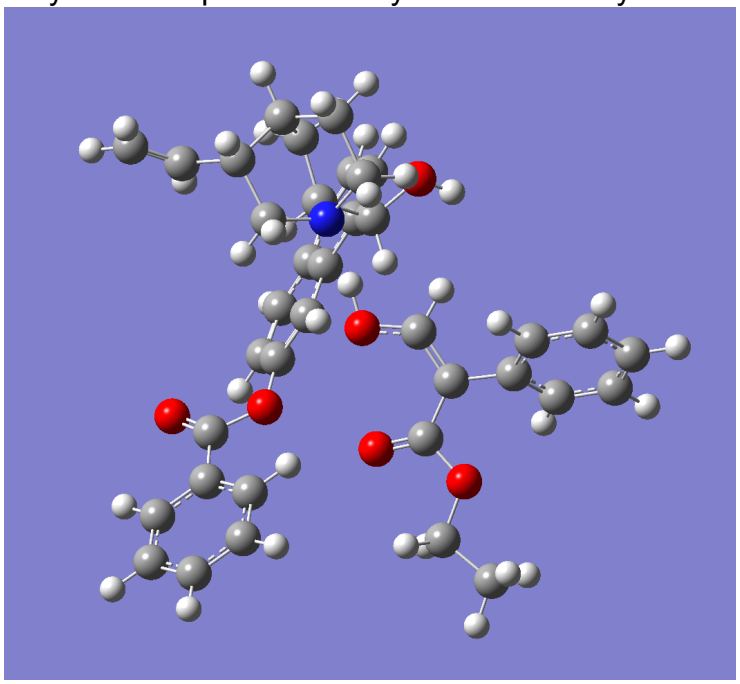


	Energy (a.u)
Quinine with Benzyl at OCH_3	-1267.177
Acrylate	-652.0752
Total energy	-1919.252
Combined	-1919.1099
Difference (a.u.)	0.142
Difference (kcal/mol)	3.2788

Acrylate energy minimization:

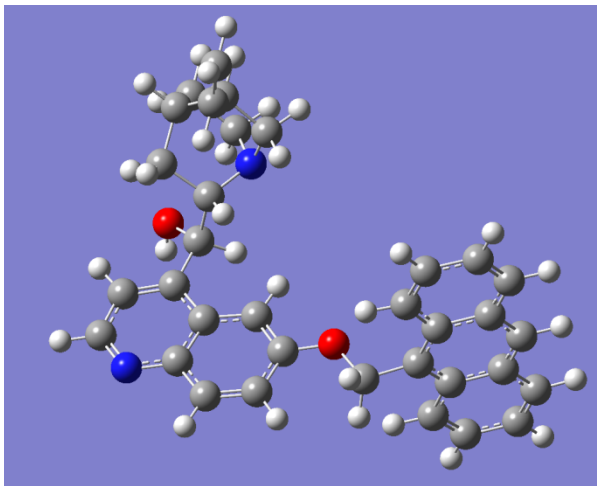


Acrylate with quinine benzoyl at the methoxy:

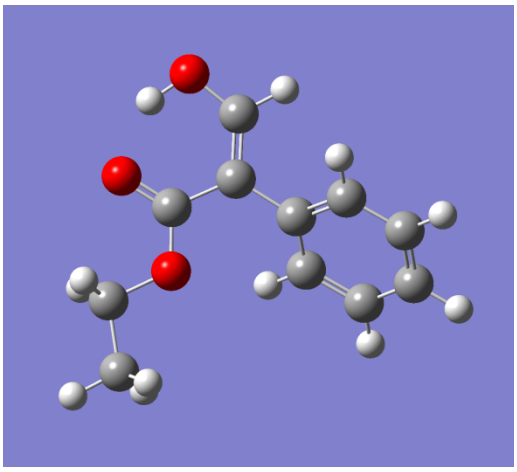


	Energy (a.u)
Quinine with Benzoyl at OCH_3	-1380.488
Acrylate	-652.0752
Total energy	-2032.563
Combined	-2033.633
Difference (a.u.)	1.073
Difference (kcal/mol)	671.04

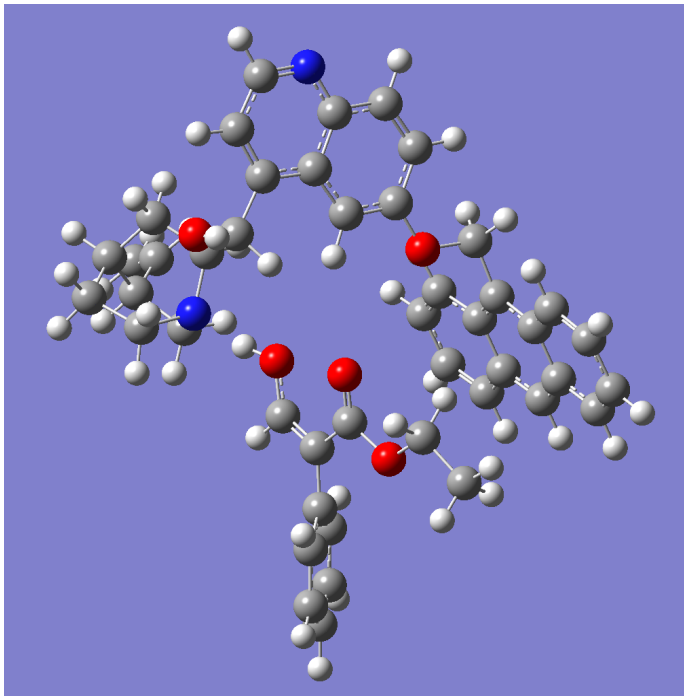
Quinine with anthracyn at OCH_3 position energy minimization:



Acrylate energy minimization:

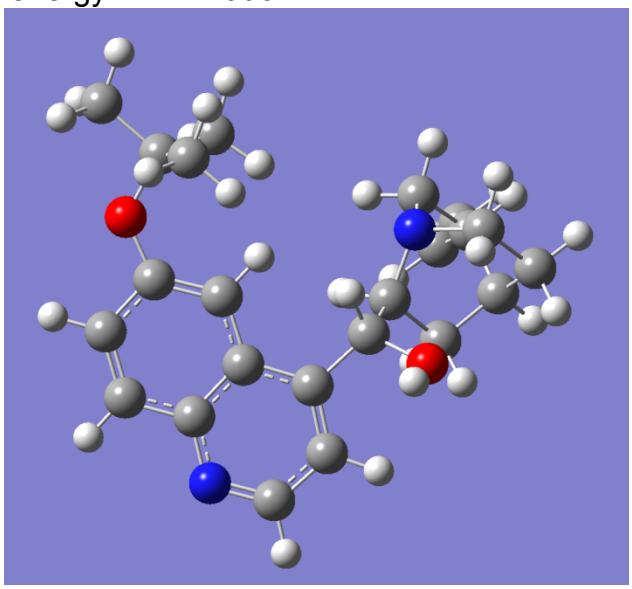


Acrylate and quinine with anthracyn at OCH_3 position combined energy minimization:

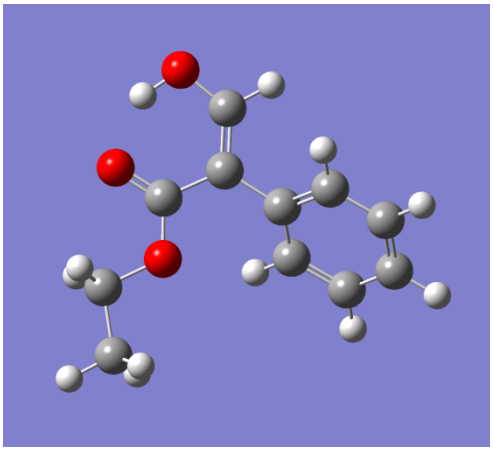


	Energy (a.u)
Quinine with anthracyn at OCH_3	-1574.349
Acrylate	-652.0752
Total energy	-2226.424
Combined	-2226.281
Difference (a.u.)	0.143
Difference (kcal/mol)	3.294

Quinine with t-Bu at OCH_3 position energy minimization:

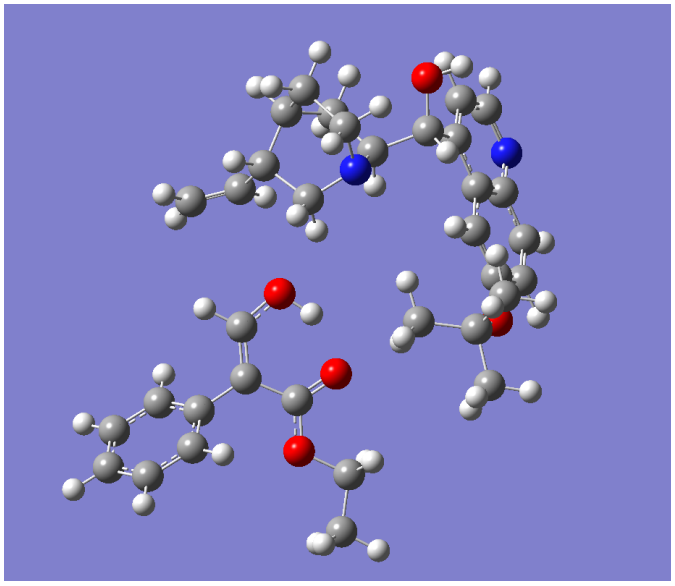


Acrylate energy minimization:



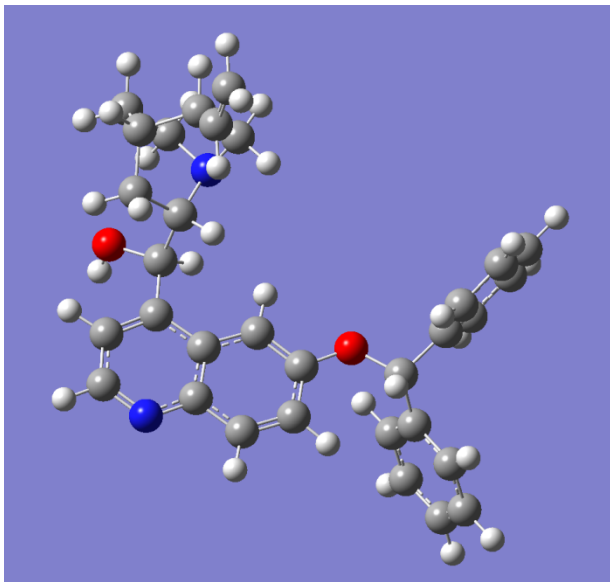
Acrylate with Quinine with t-Bu at OCH_3 position

energy minimization:

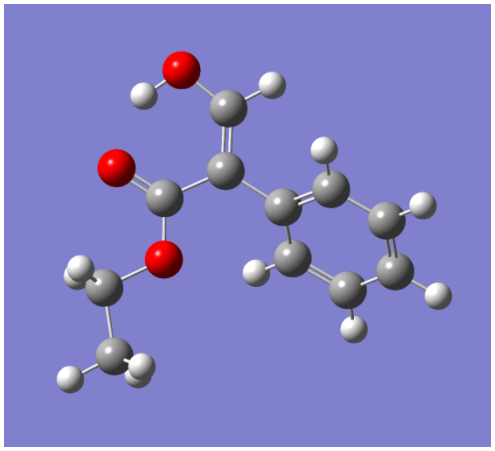


	Energy (a.u)
Quinine with t-Bu at OCH_3	-1154.093
Acrylate	-652.0752
Total energy	-1806.168
Combined	-1806.008
Difference (a.u.)	0.008
Difference (kcal/mol)	0.18529

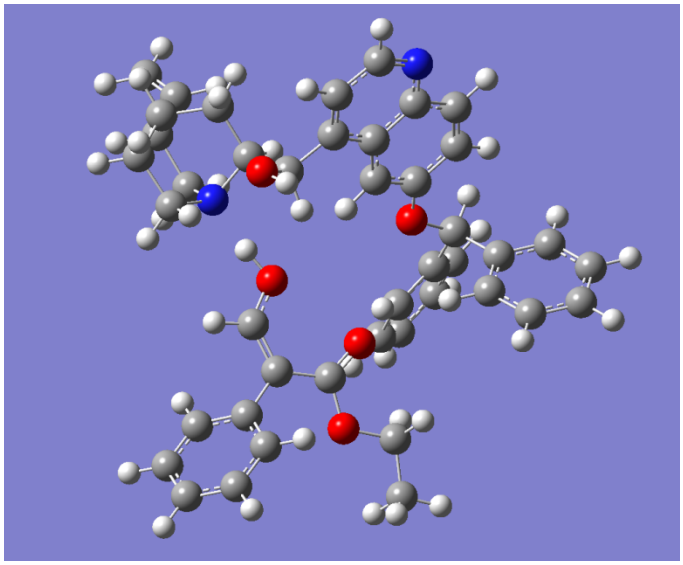
Quinine with diphenyl group at the position of OCH_3 energy minimization:



Acrylate energy minimization:



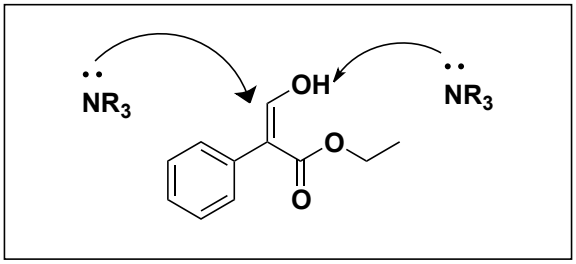
Acrylate with Quinine with diphenyl group at the position of OCH_3 energy minimization:



	Energy (a.u)
Quinine with diohenyl 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 acryalte and there is formation of salt and there is

Scheme 30: Catalyst binding.

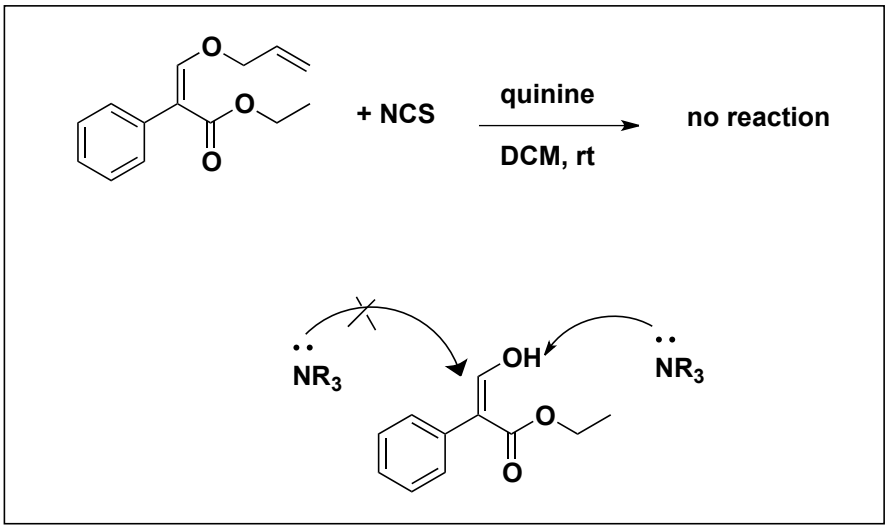


some hydrogen bonding to the carbonyl as predicted by the bifunctional catalyst mechanism. Another option is that the catalyst attacks the double bond itself and there is activation through the binding to the double bond. In order to prove one of the hypothesis, allylic group was attached to the oxygen 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.

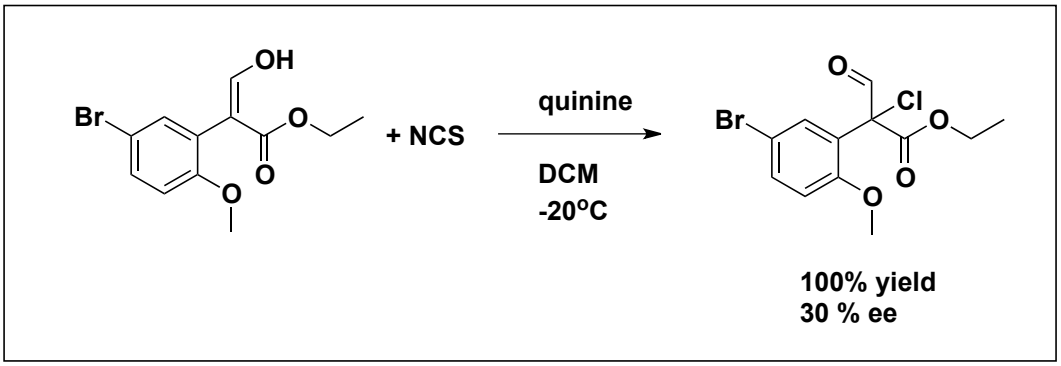
Another hypothesis was that the reason that there is no significant ee is because of rotation of the acrylate. In order to “freeze” the acrylate in one position, chlorination of disubstituted substrate was done. The substrate that was chosen was 2-OMe-5-Br disubstituted acrylate. The reaction was done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

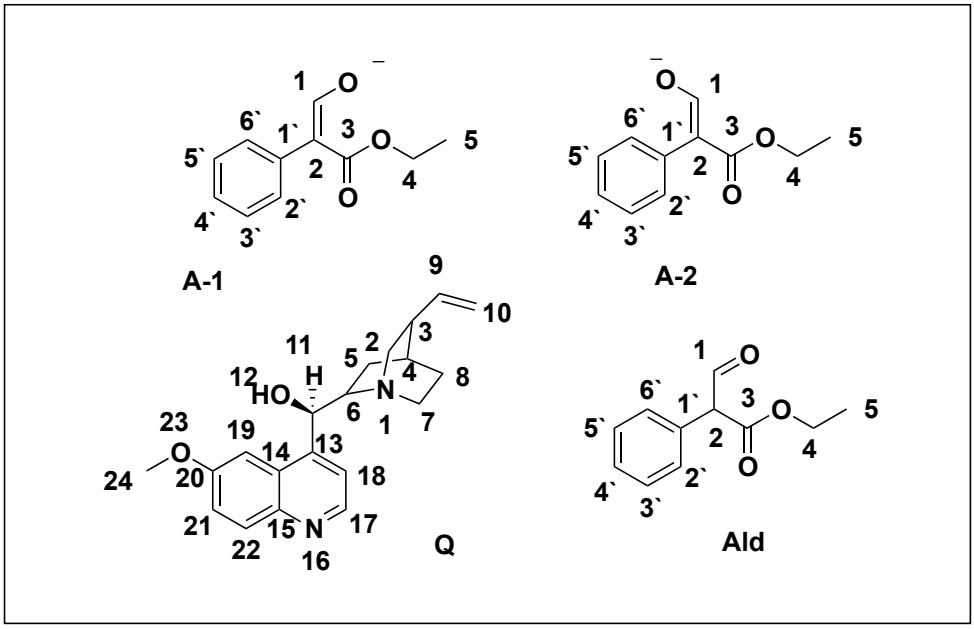


2.4 NMR Studies

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

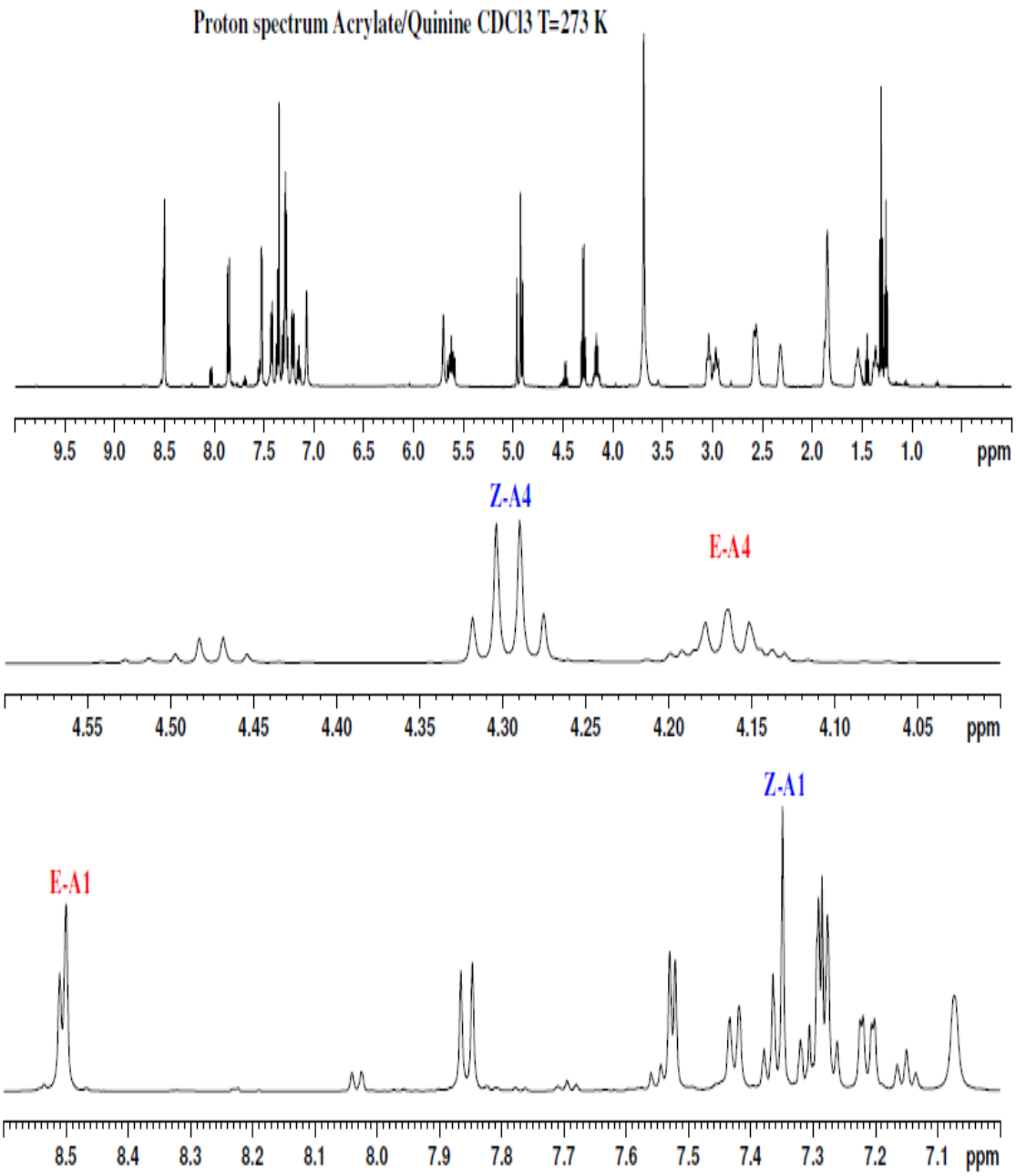
Figure 24: NMR assigned species.



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

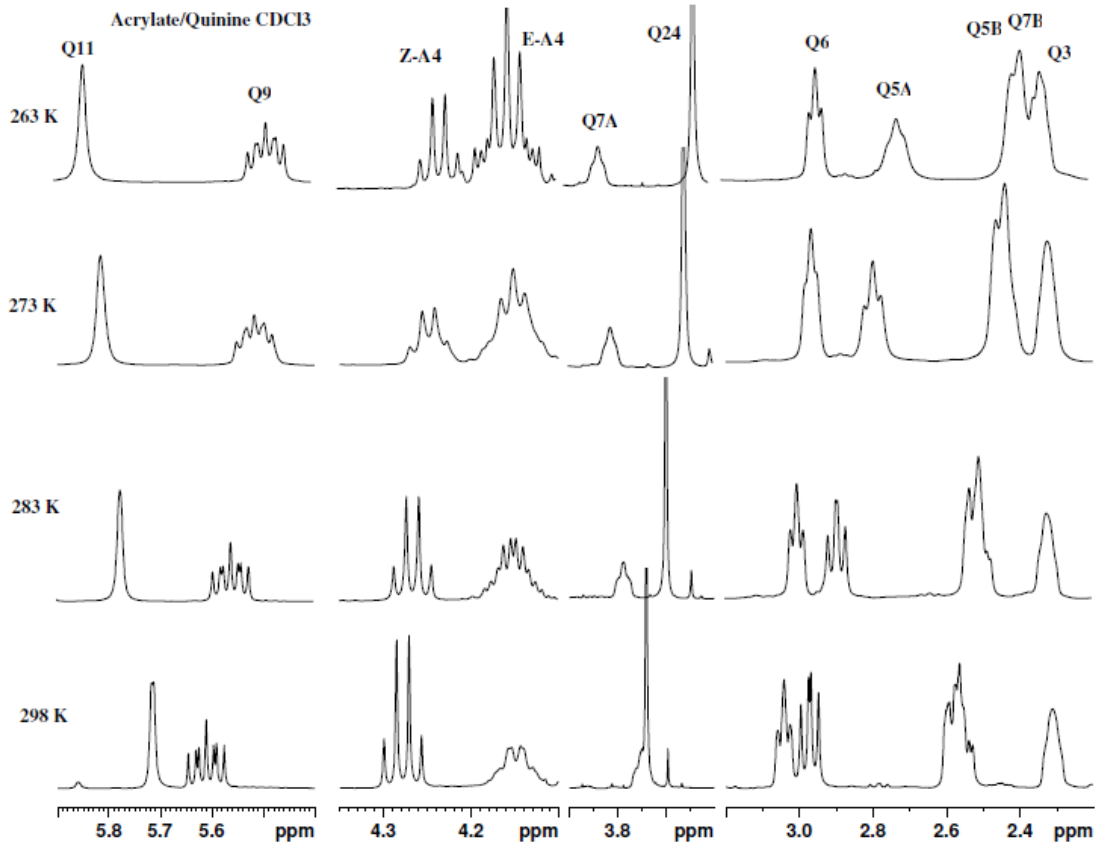
ppm observed for the equivalent proton in ***A-1*** (figure 25). Two dimensional $^{1}H\{^{13}C\}$ HSQC- and –HMBC experiments of both isomers were consistent with

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 that 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 i*somerization of the acrylate takes place through the tautomeric aldehyde form **AId** (figure 28). In the absence of

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

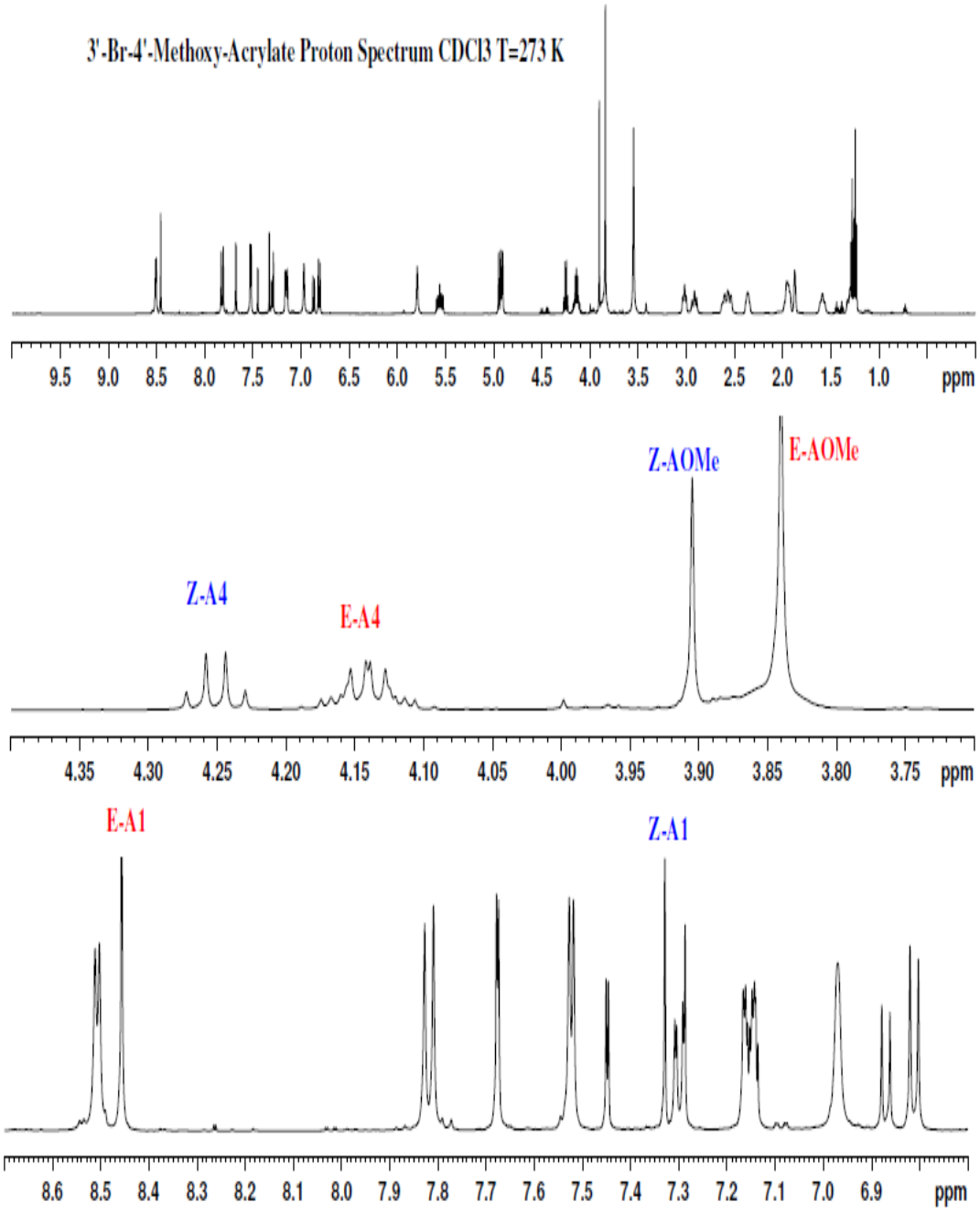
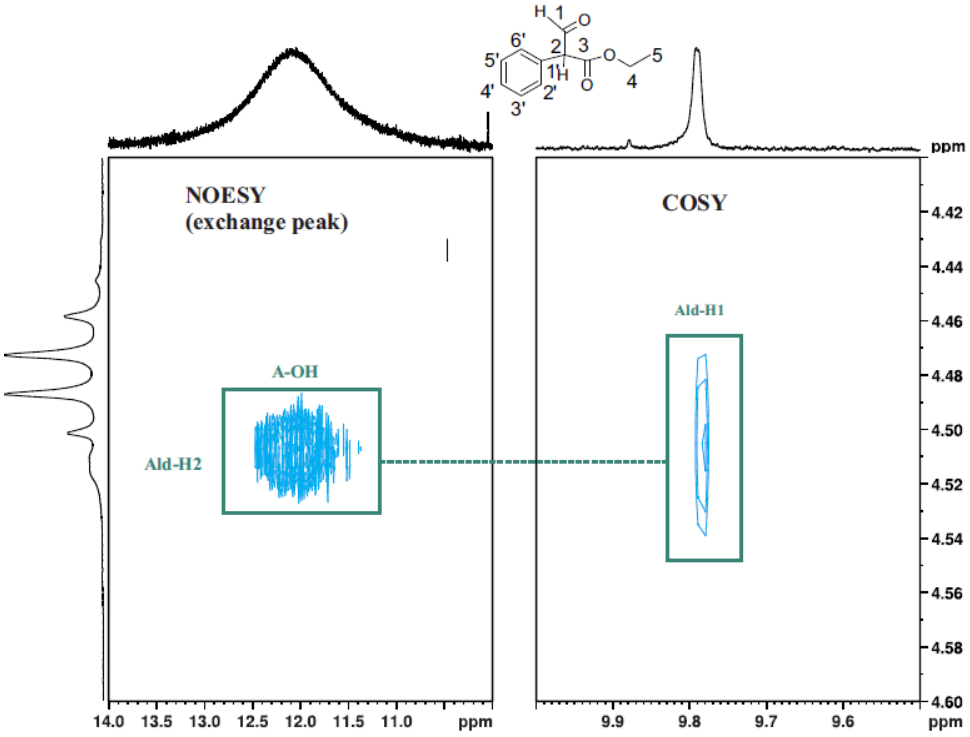


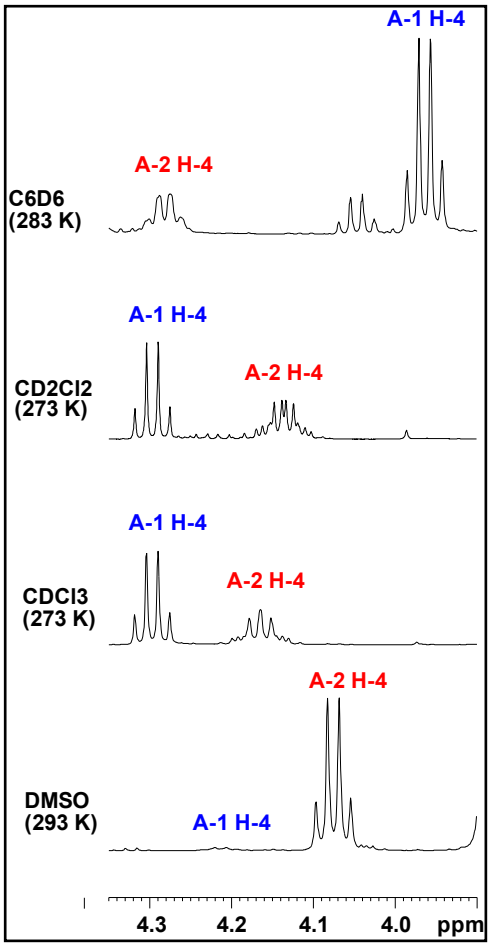
Figure 28: NMR spectra-aldehyde cross pick.



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···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 aboutthe 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 C_6D_6 the *Z*-form **A-1** dominates, while in very polar solvents like

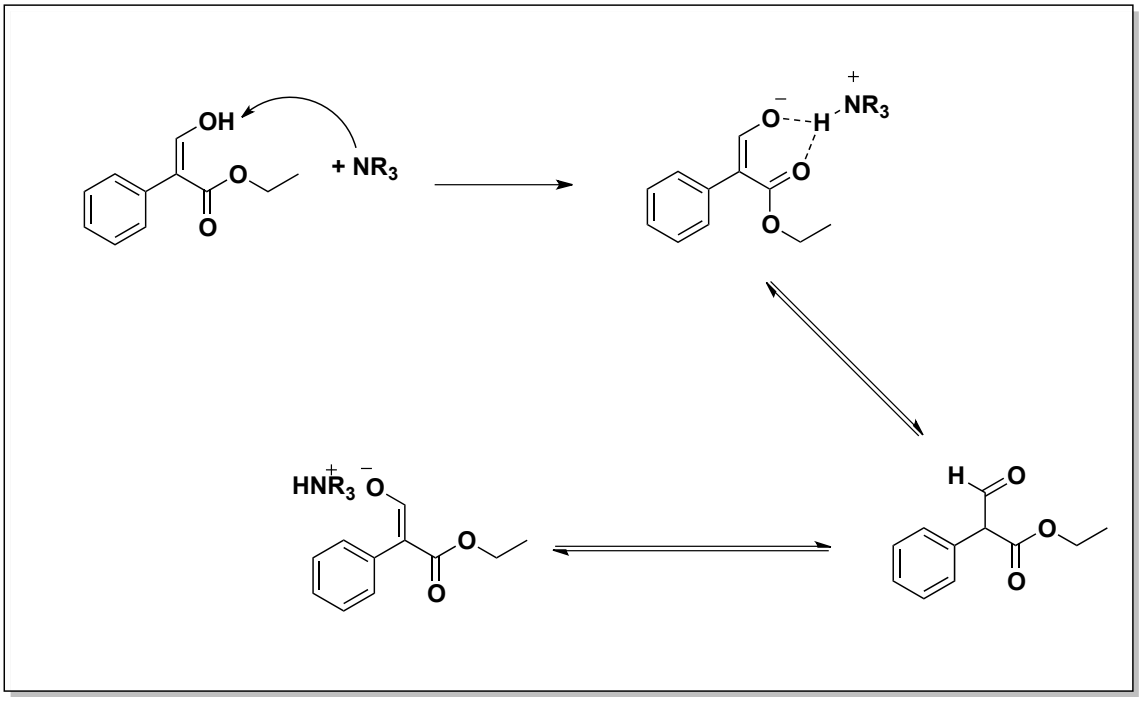
DMSO-d_6 the *E*-form **A-2** is prevalent. This behavior can be explained by the availability of *inter*-molecular hydrogen bonding in the polar solvents. Also the increased preference for the *E*- form **A-2** is consistent with better availability of *intra*-molecular hydrogen bonding at lower temperatures.

Table 18: Solvent dependence ratio.

Solvent	T / K	**A-2/A-1**
DMSO	293	38.7
$CDCl_3$	273	2.35
CD_2Cl_2	273	1.16
C_6D_6	283	0.52

Based on theses 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.

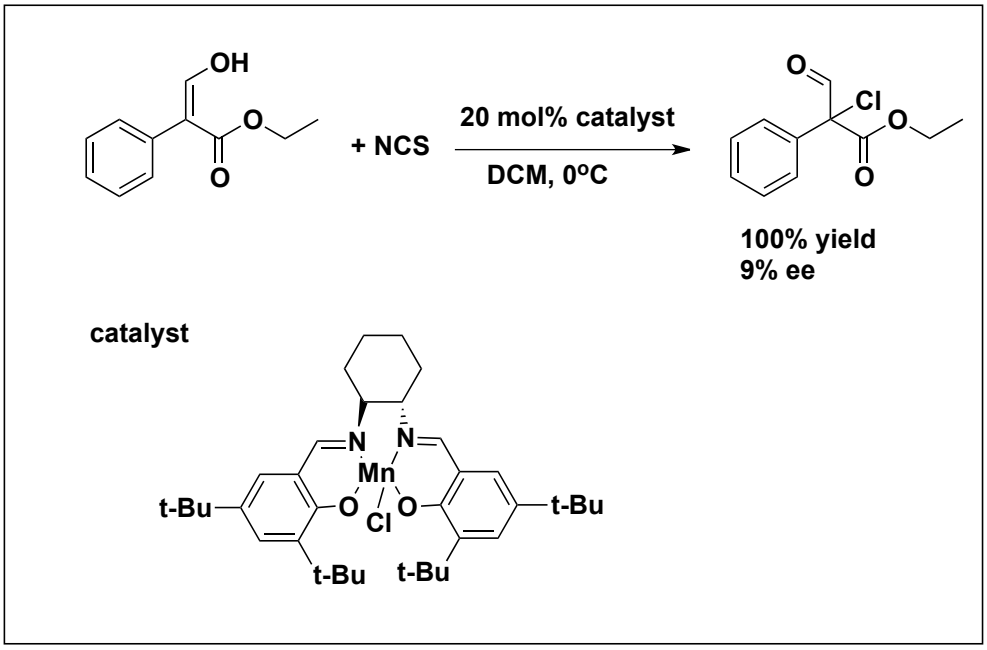
Figure 30: Proposed reaction mechanism based on NMR studies.



2.5 Metal Catalyzed Chlorination

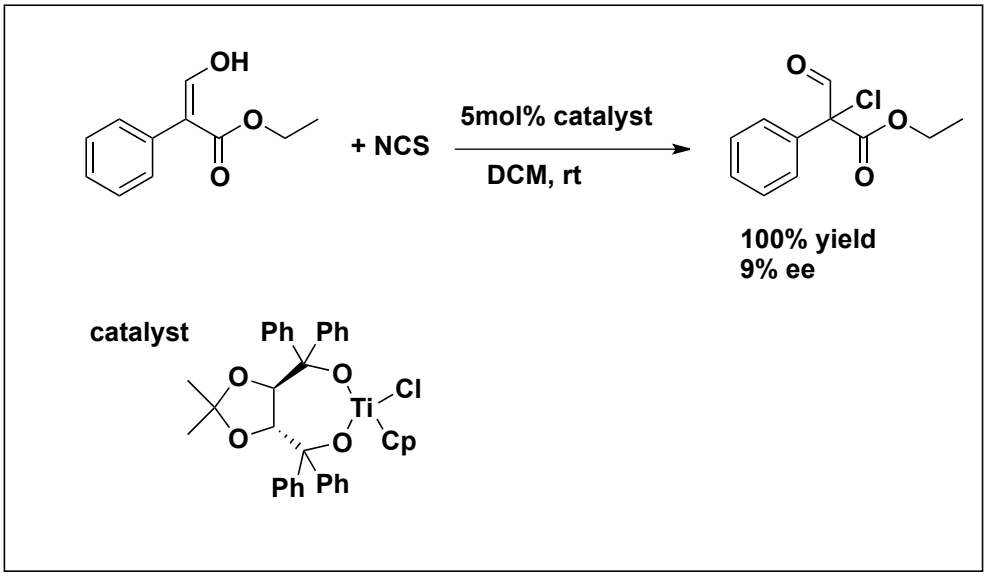
Based on the NMR results the next assumption was that the catalyst needs to be bound to both the carbonyl oxygen and the enolic oxygen in order to prevent isomerization and therefore recamization. The First catalyst that was attempted was Salen catalyst with Mn as the metal (figure 29). Salen catalyst 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 he 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.

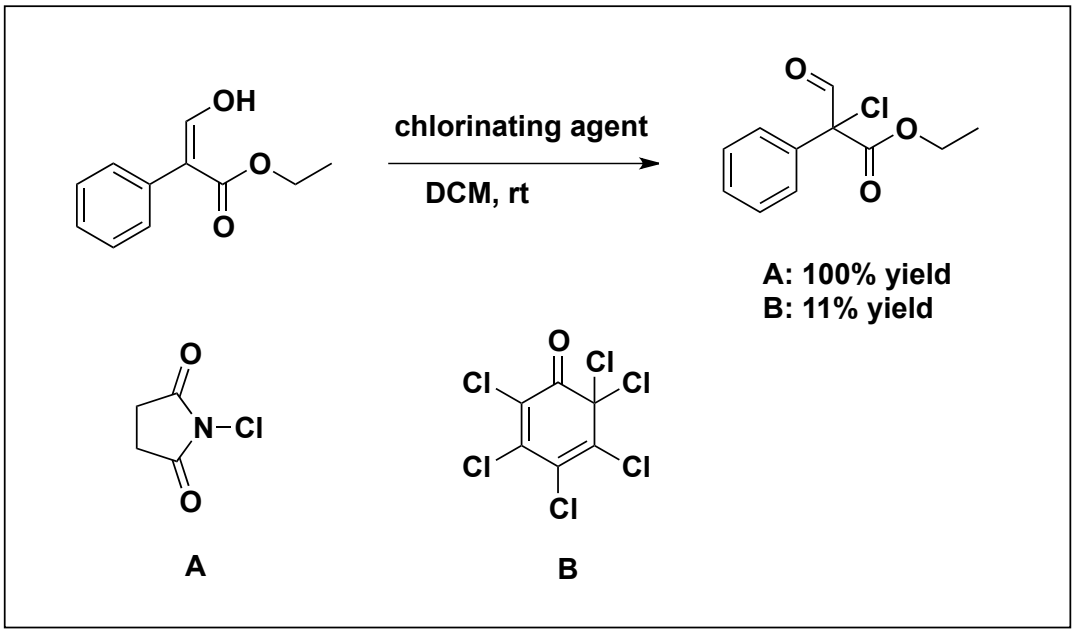
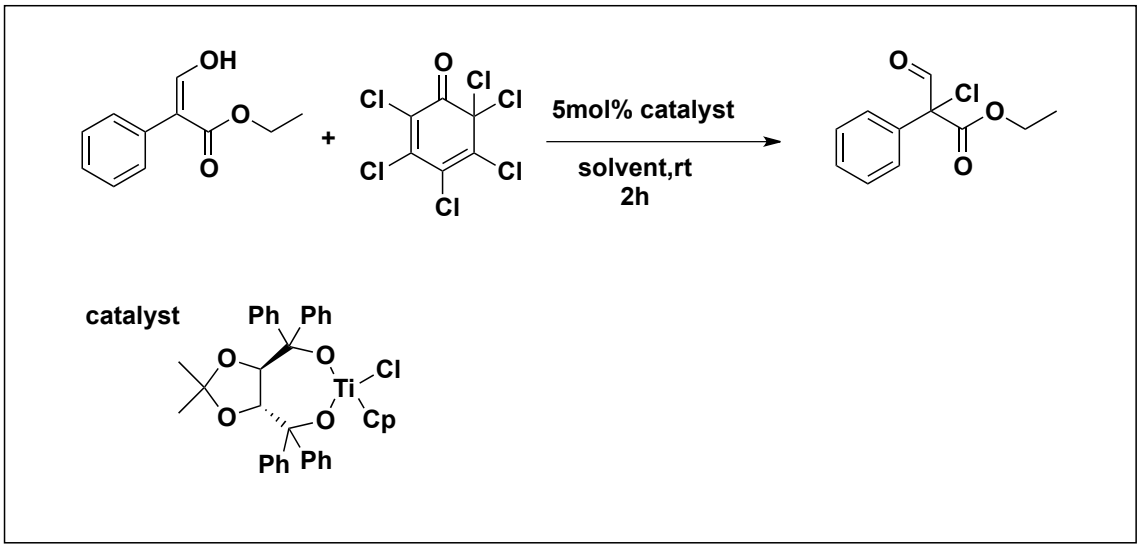


Table 19: Ti catalysed chlorination solvent screening.

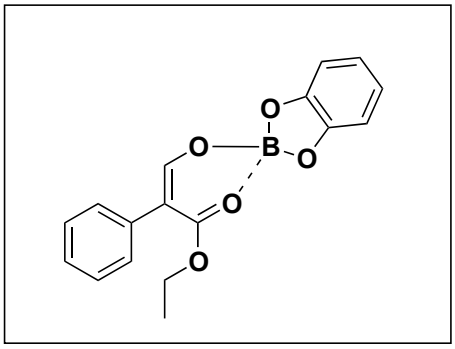


Entry	Solvent	%yield	%ee
1	DCM	28	racemic
2	Tolene	74	6
3	1:2 Toluene: hexane	58	4

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 system[44]. It showed

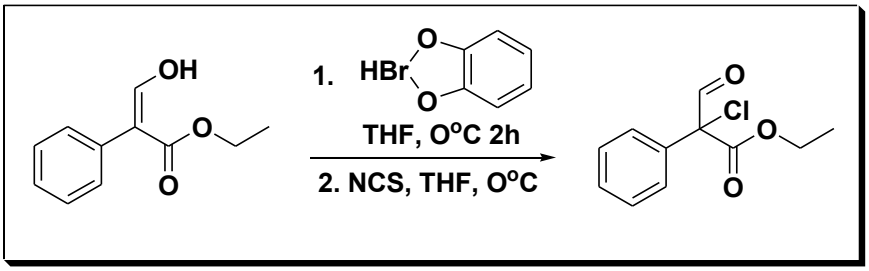
that borane is successfully binding to the enol and the carbonyl and “locks” the acrylate in the Z confirmation (figure 34). The question was if the chlorination reaction would occur with this system or not?

Figure 34: Borane binding to acrylate.



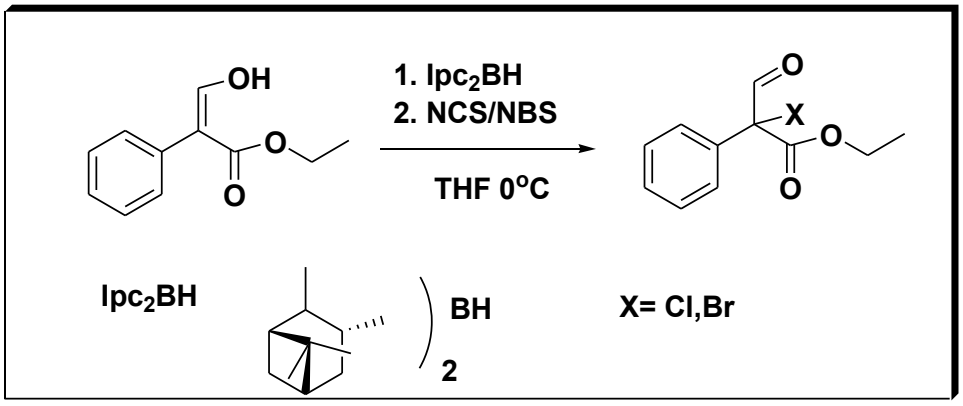
Camphor borane was used to set a test trial for the chlorination reaction (Equation 10). Camphor borane was used in 1.8 eq with the acrylate and let stir for 2 hours at 0^{o}C in THF. With addition of camphor borane to the acrylate bubbles in the reaction were observed indicating binding the acrylate 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^{o}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.

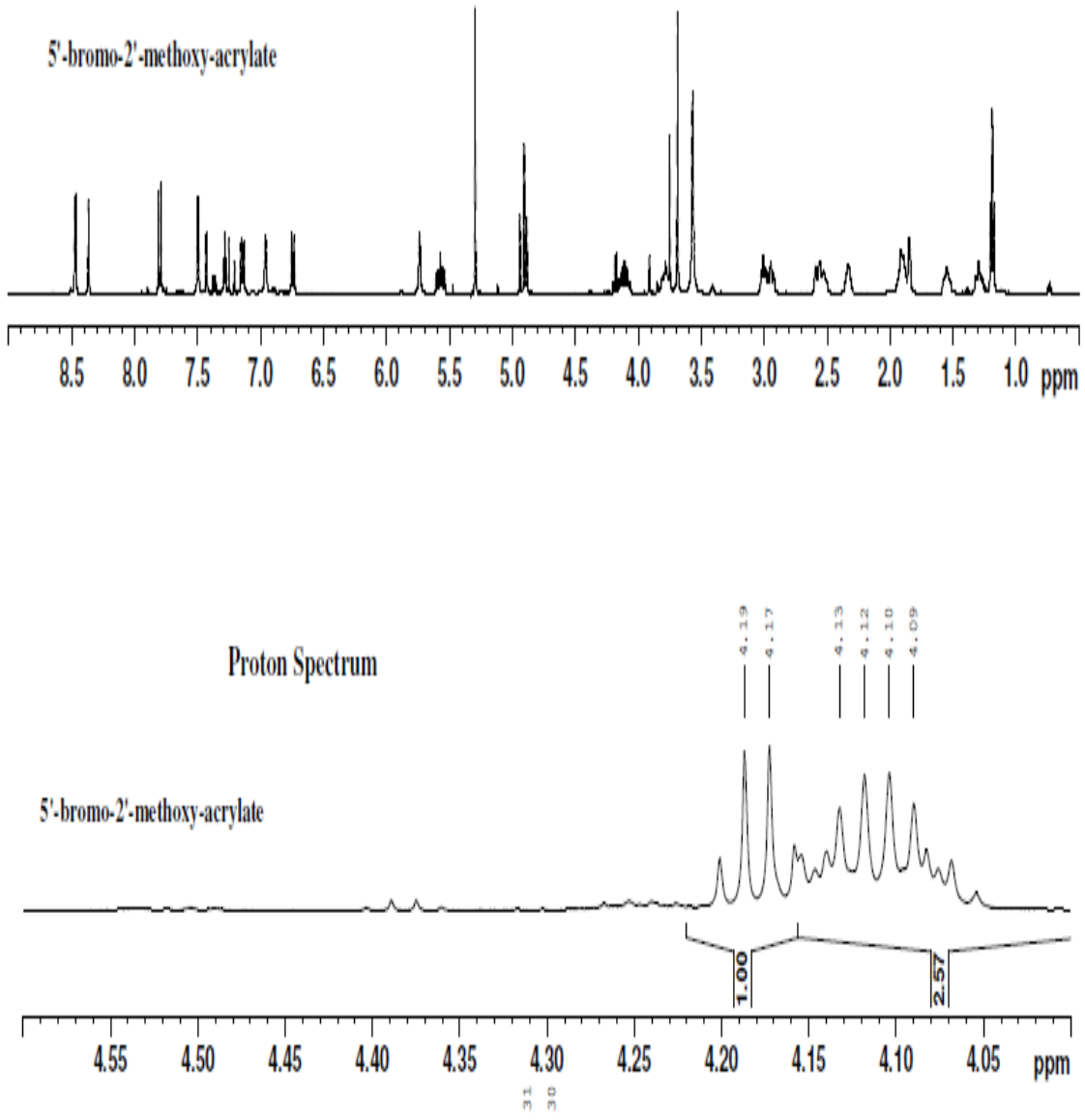
The conclusion from this set of experiments was that only one isomer is not enough but sufficient chiral environment is necessary for this reaction. Further NMR studies were done in order to investigate whether addition of bulky groups on the phenyl ring will cause steric hinders to promote only one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

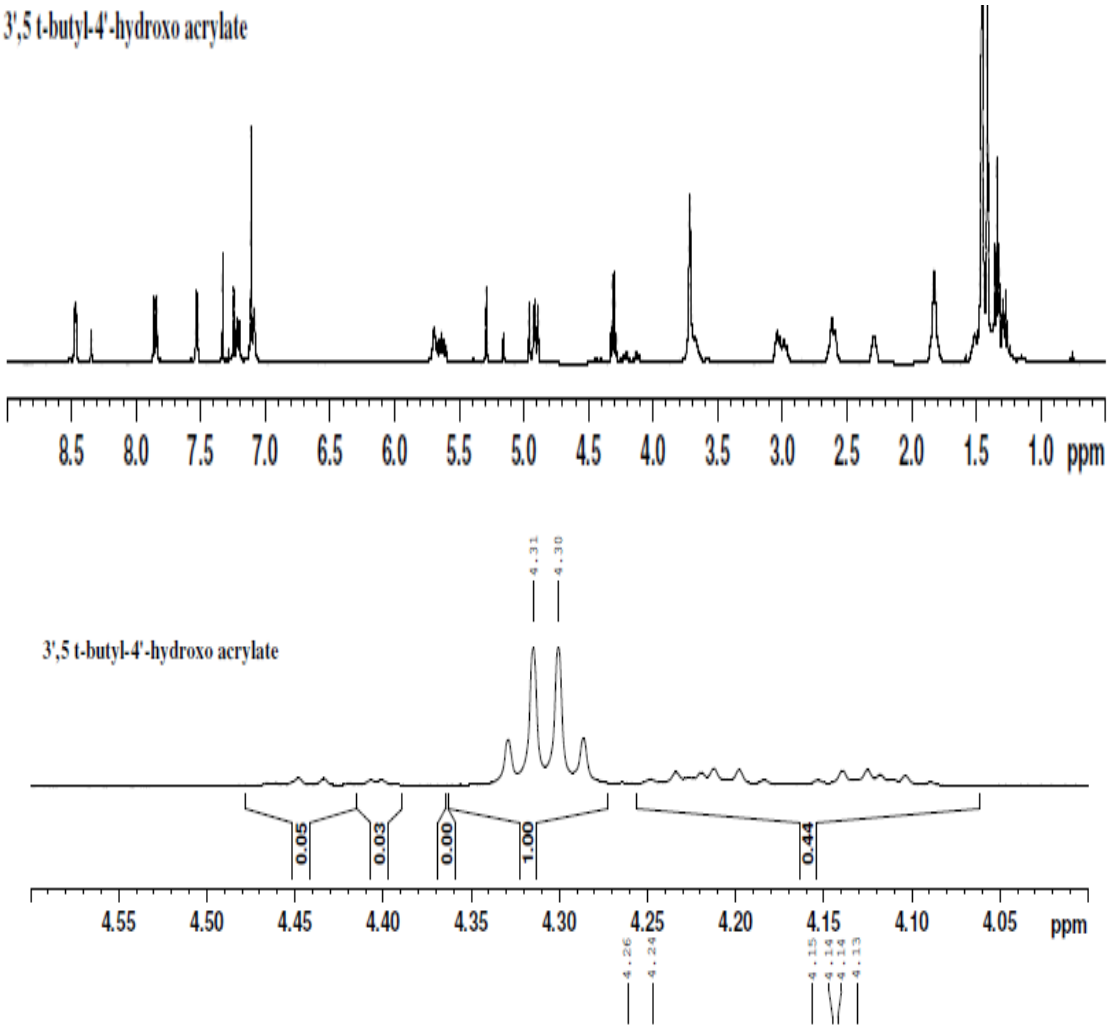
Figure 35: NMR results 5-Br, 2-OMe substituted acrylate proton spectra.



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

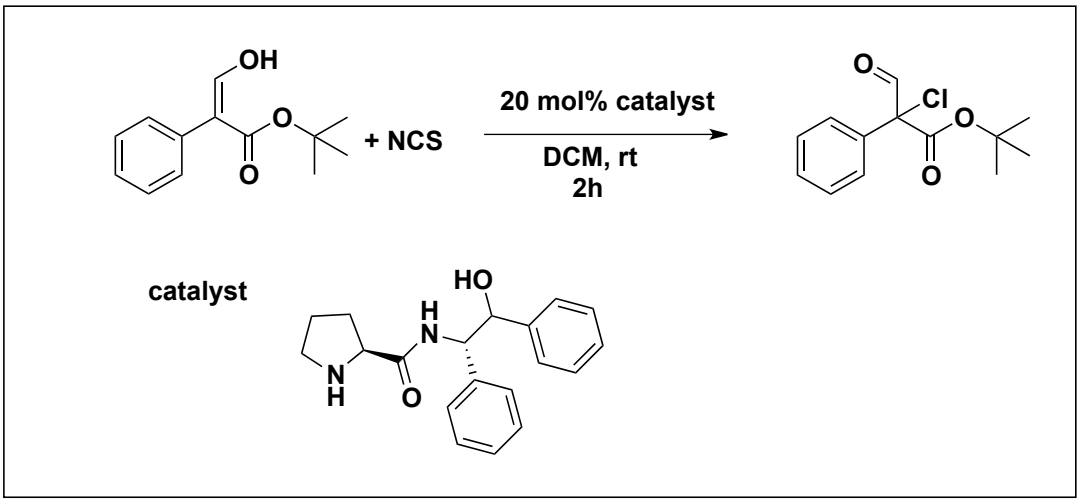
bulky groups should be considered. The next starting material that was chosen was 3,5-t-Bu,-4-OH acrylate. The first preference was to choose substituted substrate at the 2, 6 position but it was not commercially available. As predicted the Z isomer was favored over the E isomer in a E/Z of 2.27 ratio (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 furthere 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), 13C NMR (75.5 MHz) were performed with a Bruker 300 MHz NMR system and samples were dissolved in deuterated solvents. NMR invistigations 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

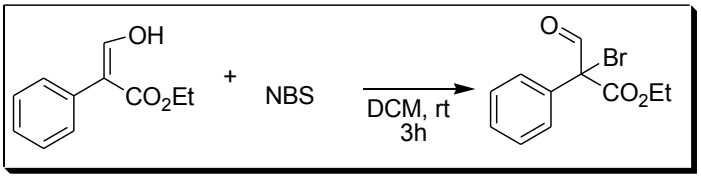
For each experiment, 0.5-5.0 mmol of the acrylate was dissolved in 5 mL of dichloromethane. A 0.2-equivalent of catalyst was added to the reaction

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 ^{1}H 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 ^{1}H 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. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.65 (s,1H), 7.5-7.4 (m, 5H), 4.35 (q, 2H), 1.35 (t 3H).

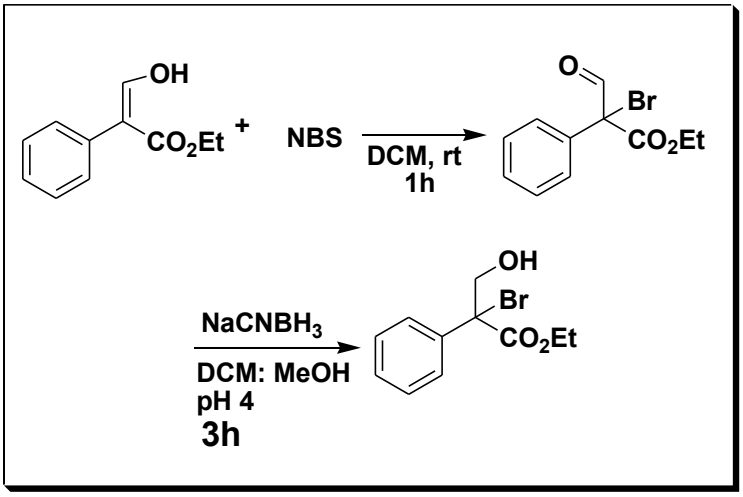
Equation 11: Racemic bromination of acrylate.



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) $NaCNBH_3$. ^1H NMR ($CDCl_3$, 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.

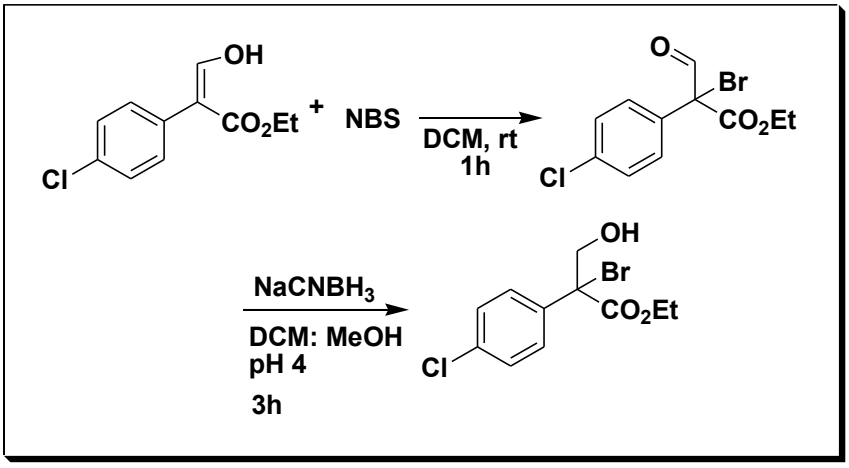


4.2.3 Synthesis of ethyl 2-bromo-2-(4- chlorophenyl)-3-hydroxypropanoate:

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 $NaCNBH_3$. ^1H 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).

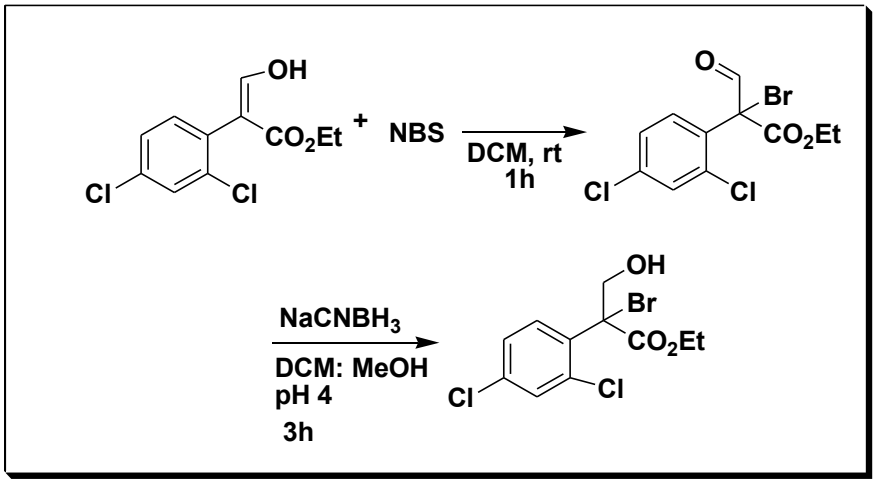
Equation 13: Racemic brominated and reduced 4- chloro acrylate.



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 $NaCNBH_3$. ^1H 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).

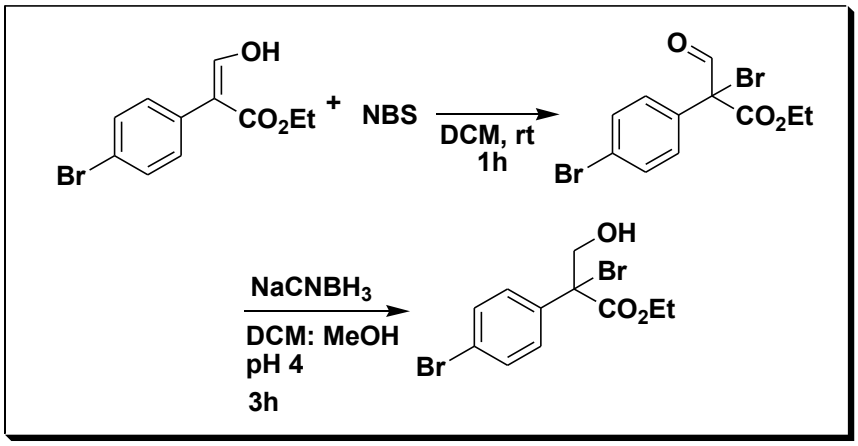
Equation 14: Racemic brominated and reduced 2,4 –dichloro-acrylate.



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 $NaCNBH_3$. ^1H NMR ($CDCl_3$, 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).

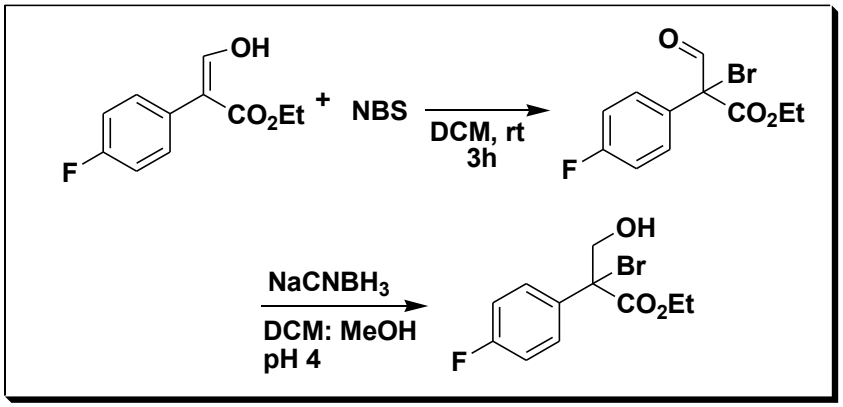
Equation 15: Racemic brominated and reduced 4 –bromo-acrylate.



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 $NaCNBH_3$. ^1H 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 16: Racemic brominated and reduced 4 –floro-acrylate.

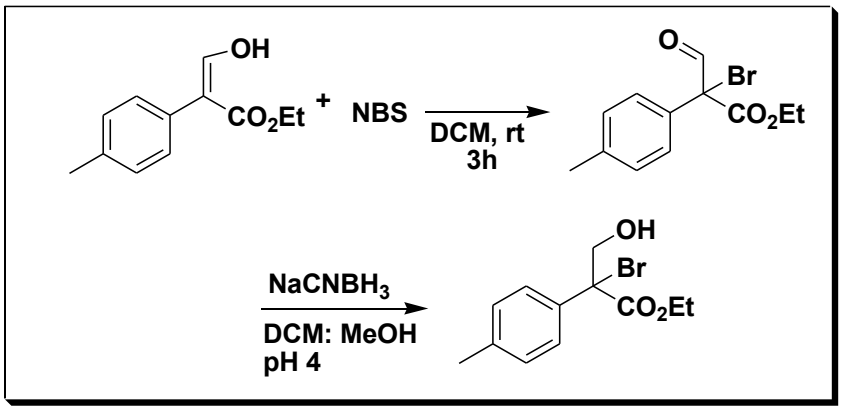


4.2.7 Synthesis of ethyl 2-bromo-3-hydroxy-2-*p*-tolylpropanoate:

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 $NaCNBH_3$. ^1H NMR ($CDCl_3$, 300 MHZ): δ Gave 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

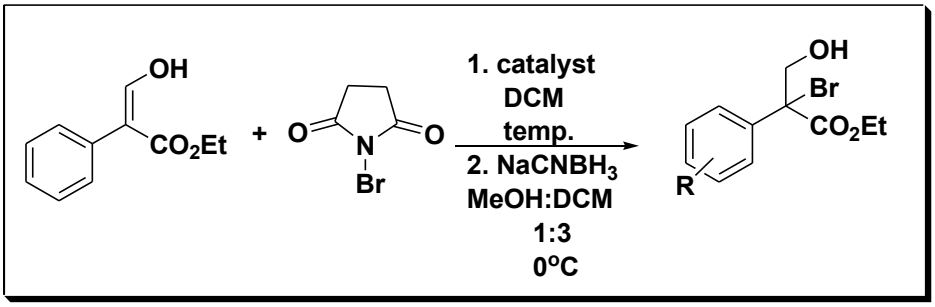
4.3.1 Temperature study:

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

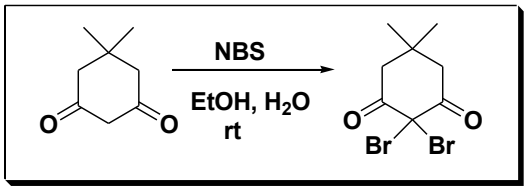
NBS and 2,4,4,6-tetrabromo-2,5-cyclohexadienone were purchased from Aldrich chemical. 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione was synthesized .

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 I mmol in

a 20 mL solution of Ethanol: water (15:5) was stirred till clear. NBS 1.959 (2.1 mmol) was added in4 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

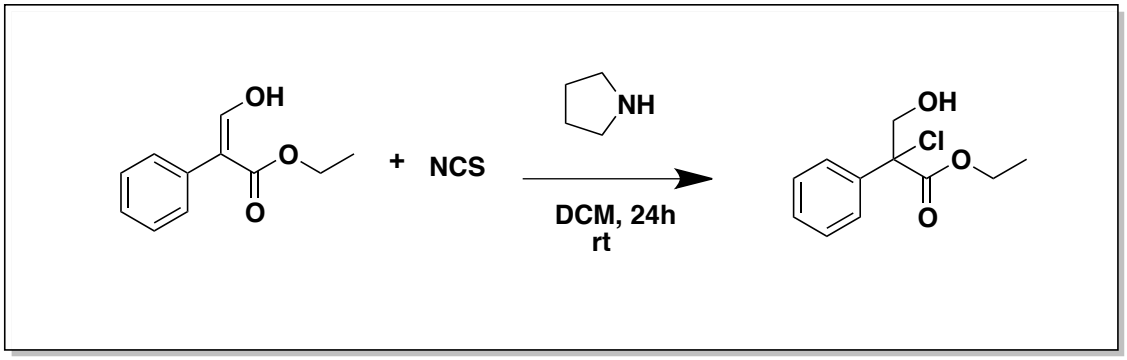
For each experiment, 0.5-5.0 mmol of the acrylate was dissolved in 5 mL of solvent. A 0.2-equivalent of catalyst was added and reaction mixture was stirred for 20 minutes. A 1.1-equivalent of chlorinating agent was added to the mixture. The reaction mixture was allowed to stir for 1 hour. After 1-hour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

mixture was passed through a silica plug and the solvent removed by rotary evaporation. Crude ^{1}H 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). ^{1}H 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^{o}C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -25^{0}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^{o}C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -20^{0}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^{o}C for 20 minutes. After 20 minutes NCS was added and reaction mixture was stirred for 1 hour at -25^{o}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

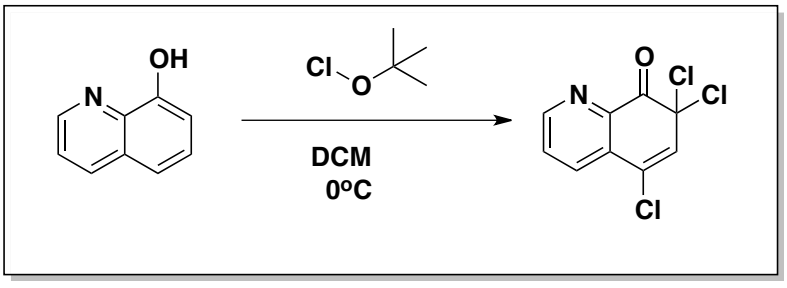
of DCM as the reaction solvent. % Yield was monitored by NMR. Reaction was done in open air. All of the HPLC data can be found in appendix 1.

NCS and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone were purchased from Sigma Aldrich. 5,7,7-trichloroquinolin-8(7*H*)-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^{o}C. The reaction was stirred at room temperature for 3 hours. After removal of the solvent under reduced pressure, 5 mL of Et_2O 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(7*H*)-one (Equation). As pale solid in 85% yield. ^{1}H NMR ($CDCl_3$): 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(7*H*)-one.



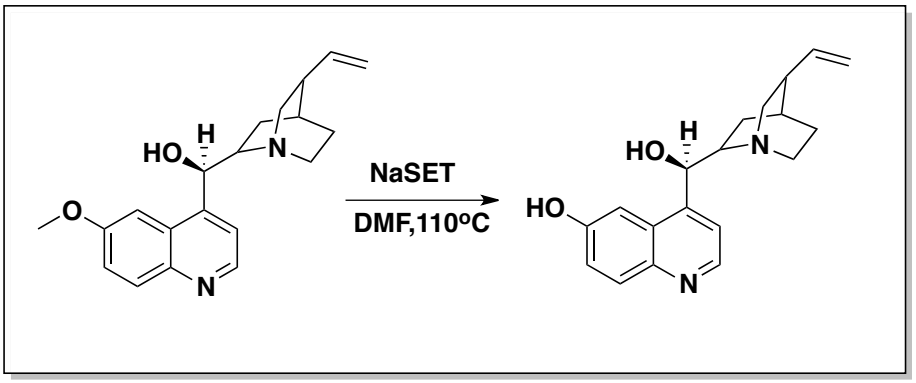
4.6 Organocatalyst synthesis

Proline based catalyst were purchased fro 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-ol[45].

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^{o}C with the aid of oil bath and let stirred for 12 hours, under Ar. After 12 hours the reaction was quenched with sat. NH_4Cl 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 Na_2SO_4. The DMF was removed by azeotropic distillation with xylenes, leaving a white solid. The crude mixture was purified by column chromatography (SiO_2, EtOH: EtOAc: NH_4OH= 4:6:0.5) to yield the product as white solid (445 mg, 93% yiled).

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

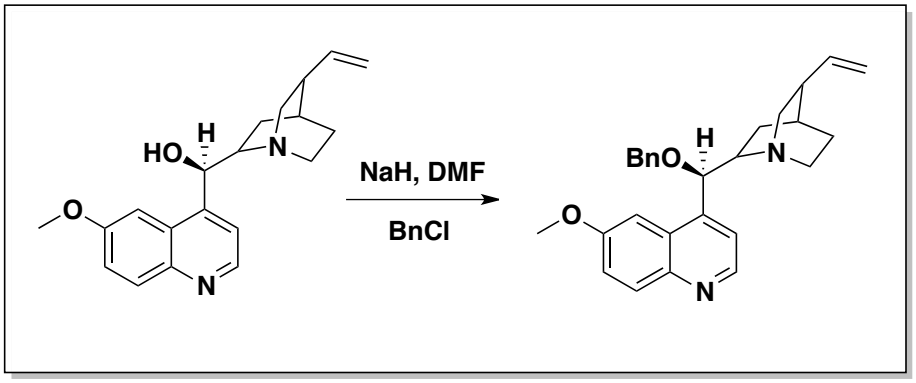


4.6.2 Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(benzyloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine[45].

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 µL, 3.696 mmol) was slowly added via syringe to the reaction mixture which was than 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 (3×30 mL). The combined organic layers were washed with water (5×15 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 (1.27 g, 99% yield).

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

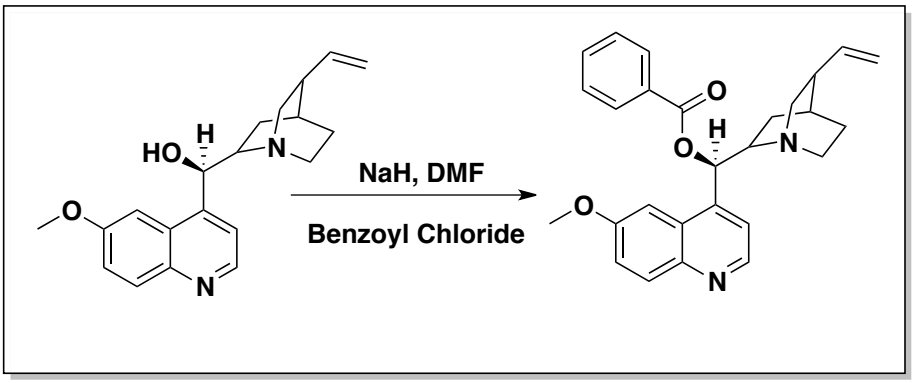


4.6.3 Synthesis of (1*R*)-(6-methoxyquinolin-4-yl)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl benzoate[45].

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^{o}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 µL, 3.696 mmol) was slowly added via syringe to the reaction mixture which was than allowed to warm up to room temperature and stirred under Ar for 12 hours. After 12 hours the reaction mixture was cooled to 0^{o}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 (3×30 mL). The combined organic layers were washed with water (5×15 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 (1.29g, 99% yield).

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

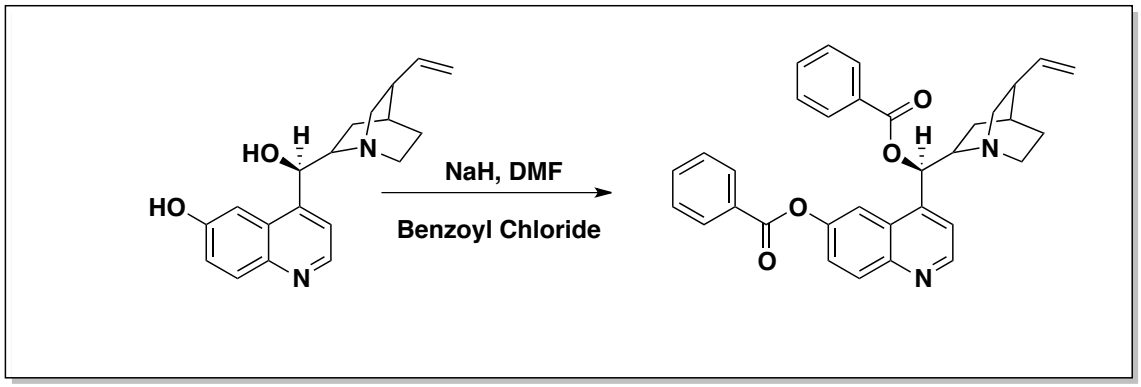


4.6.4 Synthesis of 4-((1*R*)-(benzoyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl benzoate[45].

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^{o}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 µL, 7.4 mmol) was slowly added via syringe to the reaction mixture which was than allowed to warm up to room temperature and stirred under Ar for 12 hours. After 12 hours the reaction mixture was cooled to 0^{o}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 (3×30 mL). The combined organic layers were washed with water (5×15 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 of4-((1*R*)-(benzoyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl benzoate.

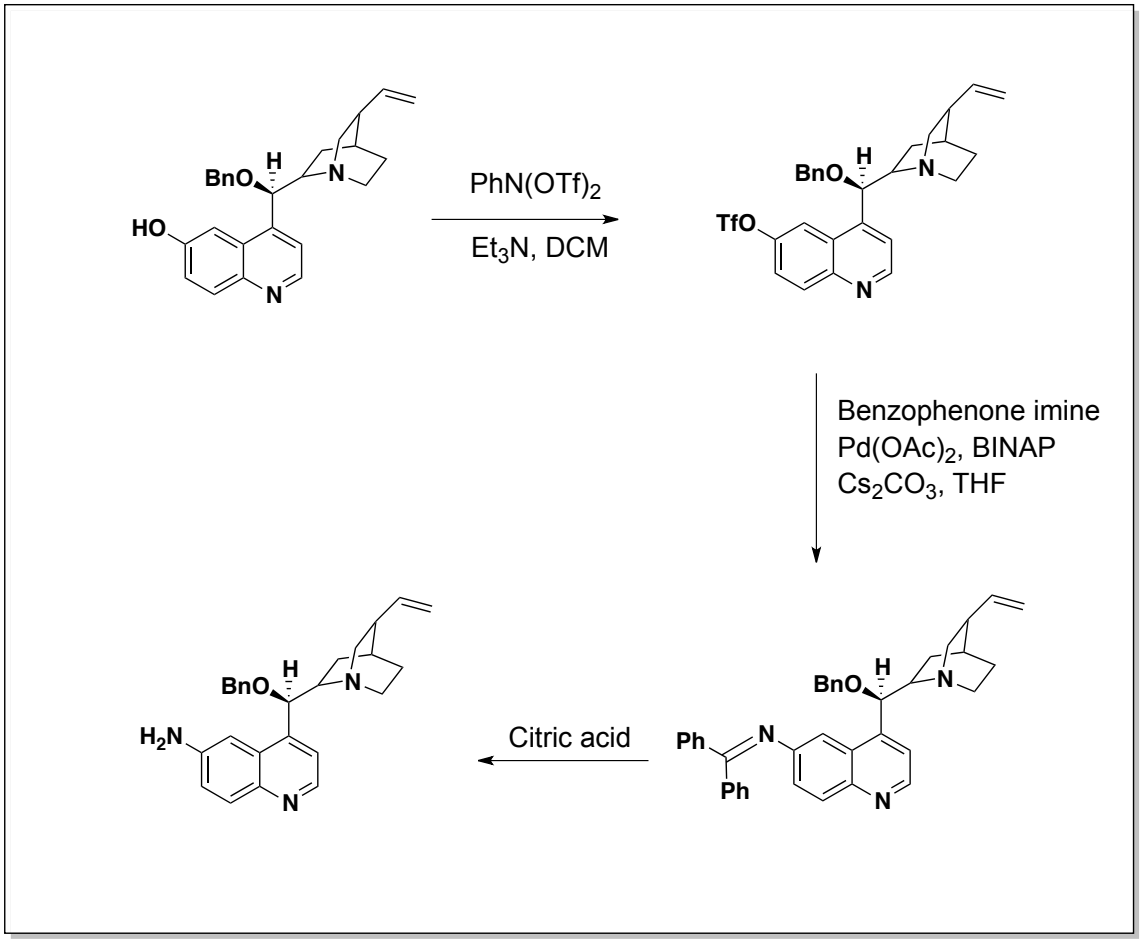


4.6.5 Synthesis of 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-amine[45].

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. Et_3N (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 chromotagrophy (SiO_2, EtOAc: EtOH: NH_4OH =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), Cs_2CO_3 (198 mg, 0.609 mmol) and benzphenone imine (74µL, 0.44 mmol). The reaction mixture was than heated to 70 ^oC 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.

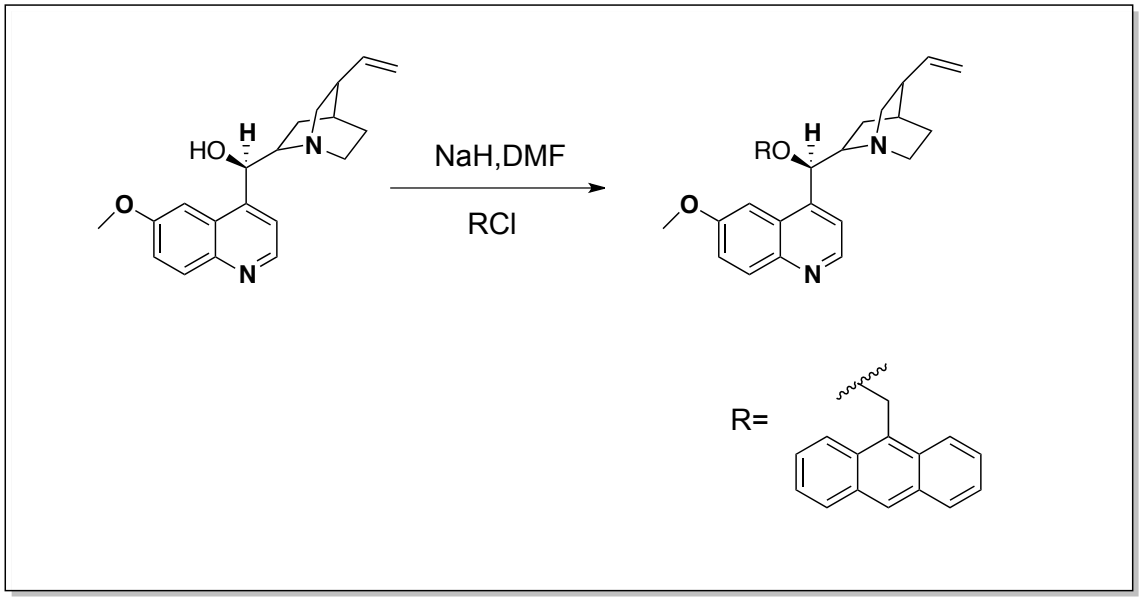
Equation 26: Synthesis of 4-((1*R*)-(benzyloxy)((1*S*,4*S*,5*S*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-amine.



4.6.6 Synthesis of (1*S*,4*S*,5*S*)-2-((*R*)-(anthracen-9-ylmethoxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine[45].

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 than 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 Na_2SO_4. Remaining DMF was removed by azeotropic distillation with xylenes with The crude product was purified by chromatography (SiO_2, MeOH:EtOAc: Et_3N = 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.

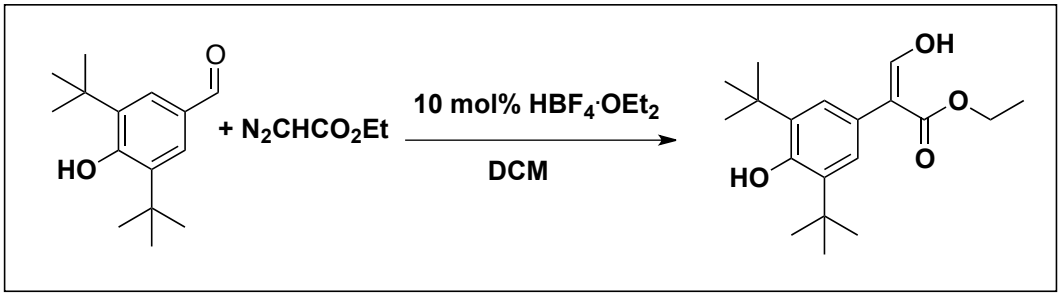
4.8 NMR studies disubstituted substrate

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 N_2, followed by addition of $HBF_4 \cdot OEt_2$ (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. ^{1}H 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.

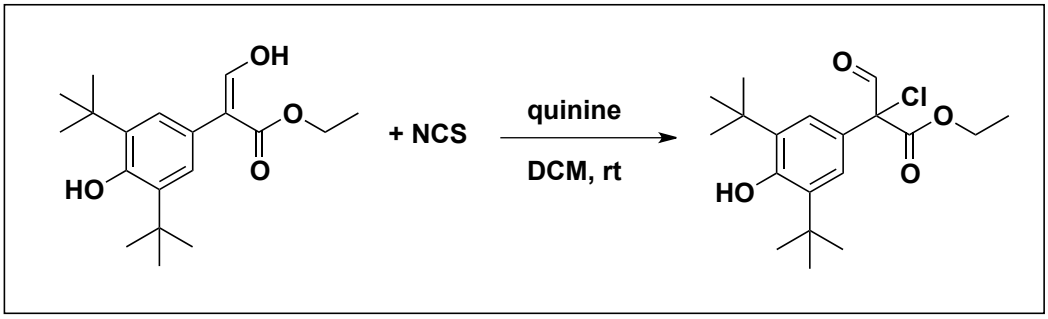


4.8.2 Synthesis of ethyl 2-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-oxopropanoate.

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). ^{1}H NMR

($CDCl_3$, 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.

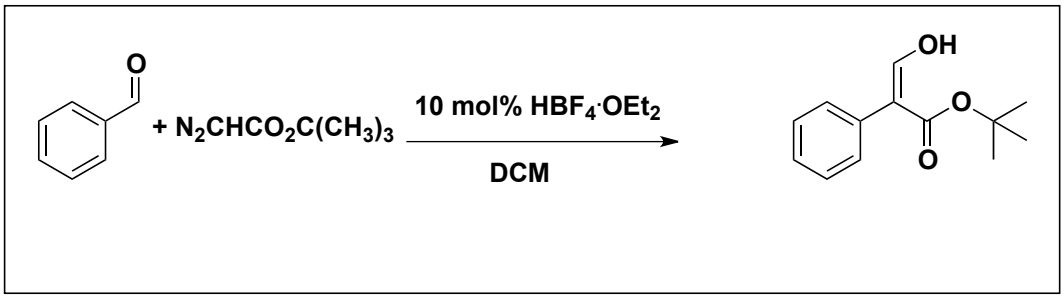


4.8.3 Synthesis of (*Z*)-*tert*-butyl 3-hydroxy-2-phenylacrylate

Benzaldehyde (1 g, 9.61 mmol) was dissolved in DCM (29 mL) under N_2, followed by addition of $HBF_4 \cdot OEt_2$ (135 µL, 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 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. ^{1}H 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).

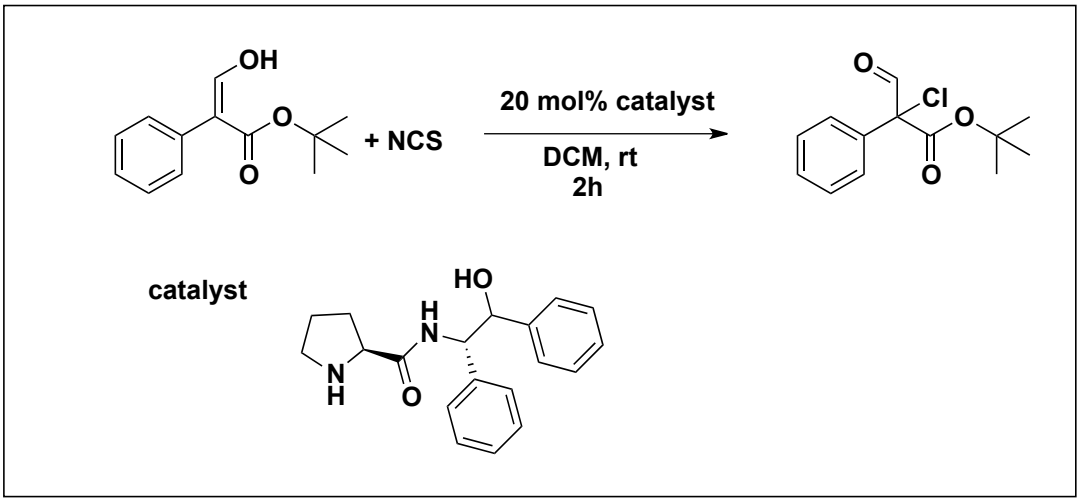
Equation 30: Synthesis of (*Z*)-*tert*-butyl 3-hydroxy-2-phenylacrylate.



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). ^{1}H NMR ($CDCl_3$, 300 MHZ): Gave 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:

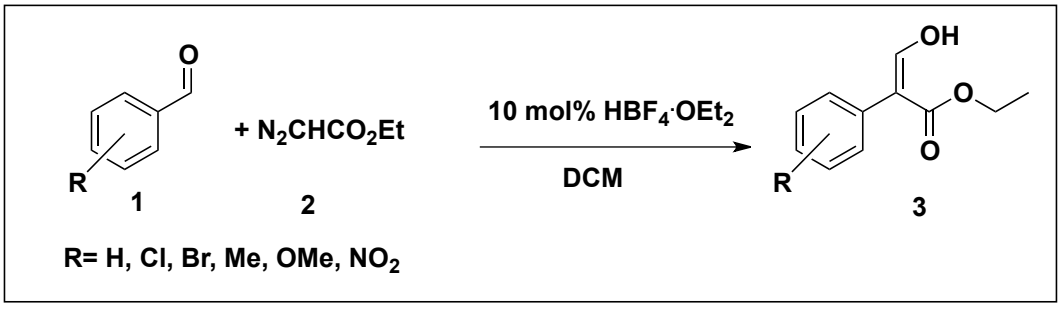
Synthesis of α-aryl quaternary carbon centers

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 a-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 centres[6-8], the use of Claisen rearrangements to afford a-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 rearrangement[9] involving the rearrangement of 2-amino allyl vinyl ethers into oxindoles bearing an a-aryl quaternary center.

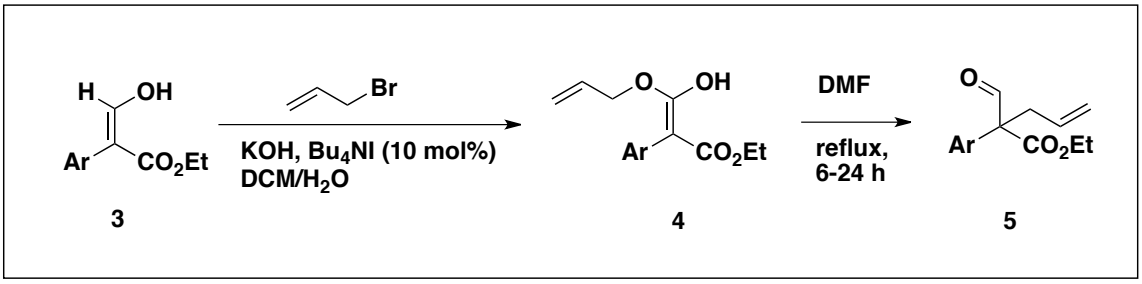
Scheme 1. Synthesis of a-arylhydroxyacrylates **3**.



2. Results and Discussion

Our initial approach for the construction of an a-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_6H_5
b	4-MeC_6H_4
c	2,4-$Cl_2C_6H_3$
d	4-$MeOC_6H_4$
e	4-FC_6H_4

5	Ar
c	2,4-$Cl_2C_6H_3$

The O-alkylation of acrylates **3** was carried out in dichloromethane using allyl bromide under phase transfer catalysis conditions (using either NBu_4I or NBu_4Br) 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** Yield[a] [%]	**5** Yield[a] [%]
a	C_6H_5	71	
b	4-MeC_6H_4	80	
c	2,4-$Cl_2C_6H_3$	82	69
d	4-$MeOC_6H_4$	66	
e	4-FC_6H_4	65	

[a]Isolated 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 ^{1}H and ^{13}C 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 a-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 a-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 ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker 300 spectrometer (^{1}H 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 ^{1}H 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 $HBF_4 \cdot OEt_2$ (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 $C_{11}H_{10}Cl_2O_3$ (M+H): 261.0085]. ^{1}H 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 ^{1}H NMR. ^{1}H, ^{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 $C_{14}H_{16}O_3$ (M+H): 233.1177]. ^{1}H 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 $C_{15}H_{18}O_3$ (M+H): 247.1363]. ^{1}H 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 $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398]. ^{1}H 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 $C_{15}H_{18}O_4$ (M+H): 263.1283]. ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{14}H_{15}FO_3$ (M+H): 251.1083]. ^{1}H NMR (300 MHz, $CDCl_3$): 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) . ^{13}C NMR (75 MHz, $CDCl_3$): 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 Na_2SO_4 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 ^{1}H NMR. ^{1}H, ^{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 $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398]. ^{1}H 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.

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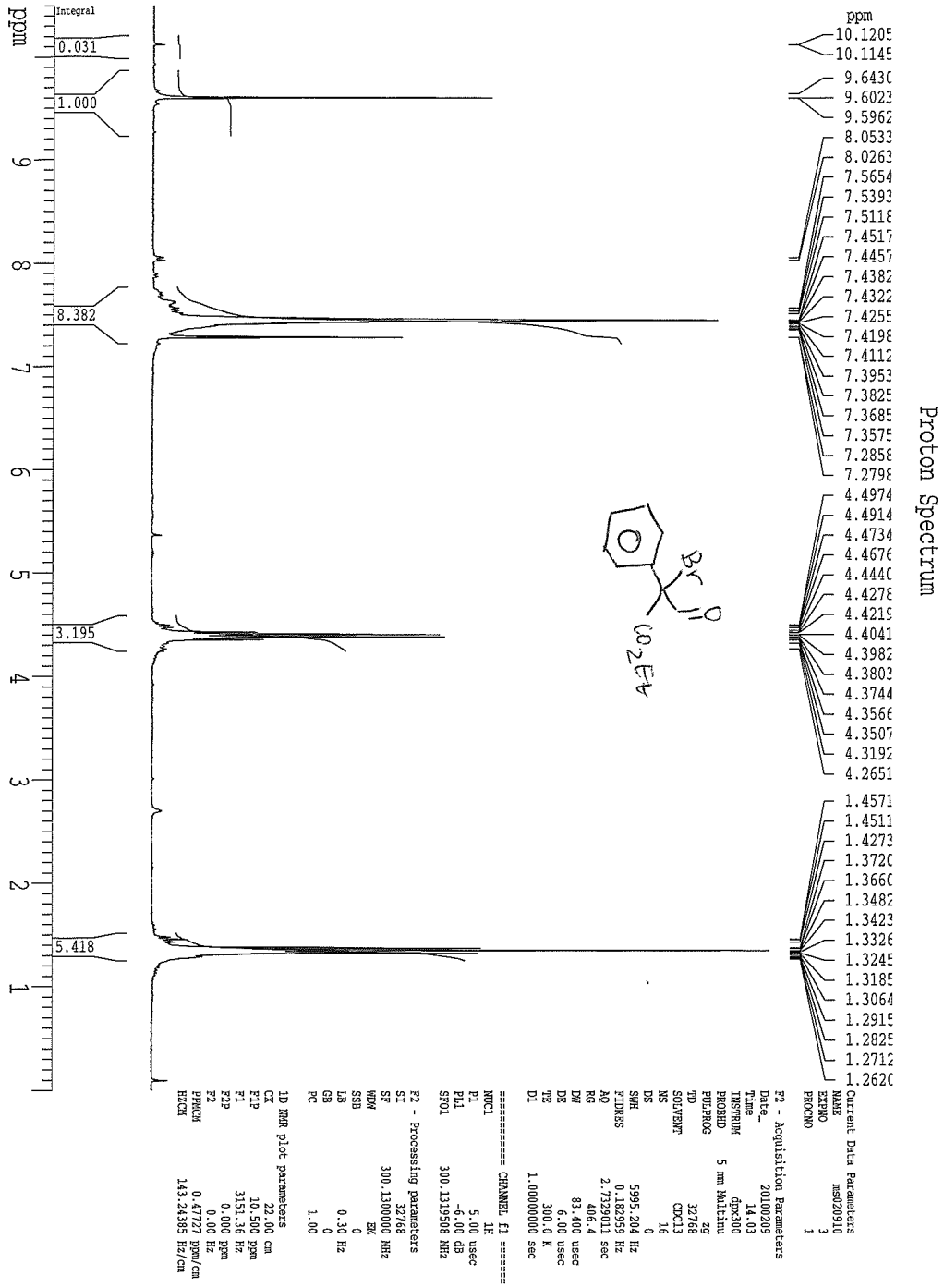
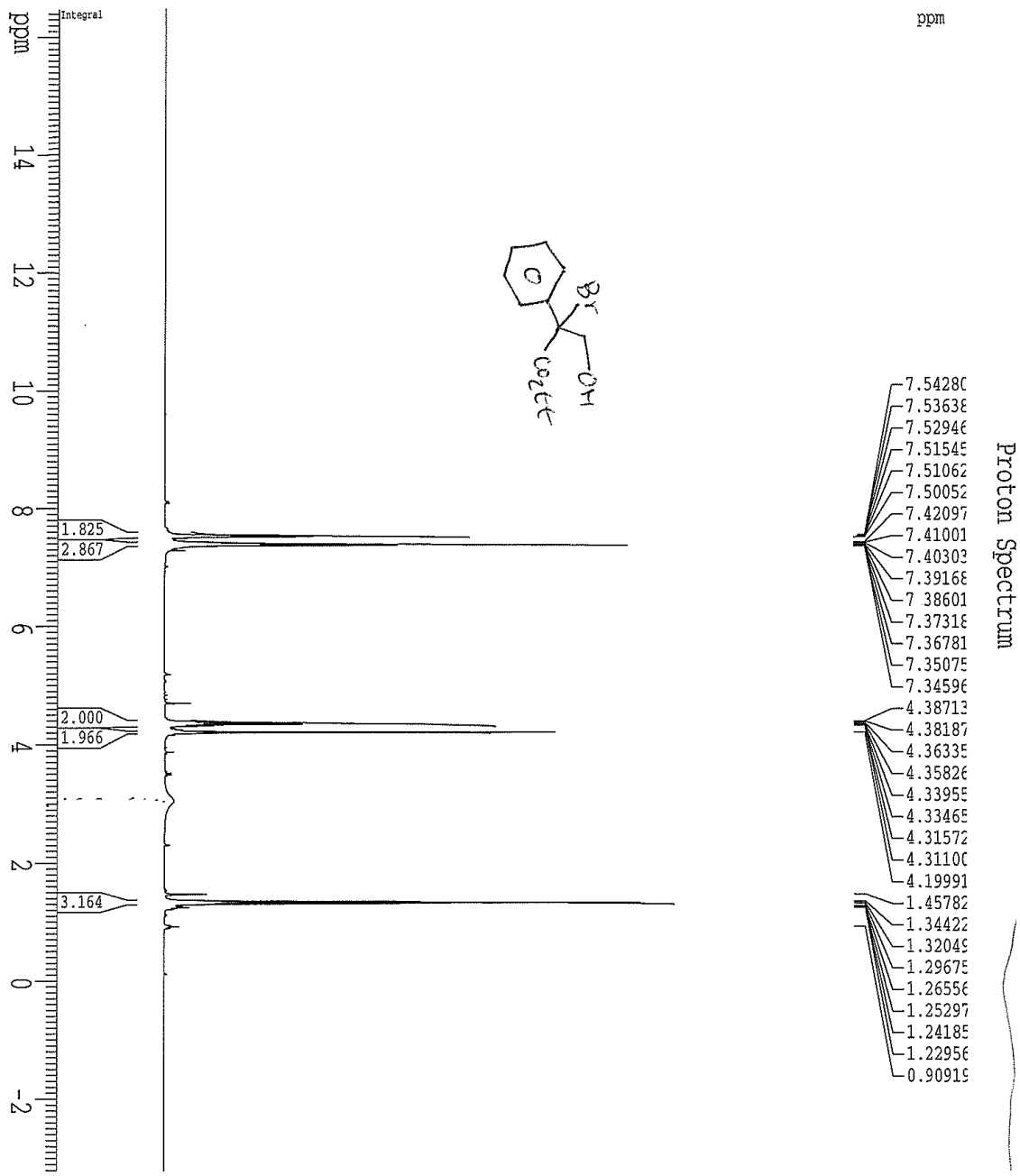
Appendix:

NMR Data

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1.966
3.164
Br
OH
CO2Et
ppm
Proton Spectrum
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7.53638
7.52946
7.51545
7.51062
7.50052
7.42097
7.41001
7.40303
7.39168
7 38601
7.37318
7.36781
7.35075
7.34596
4.38713
4.38187
4.36335
4.35826
4.33955
4.33465
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4.31100
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1.25297
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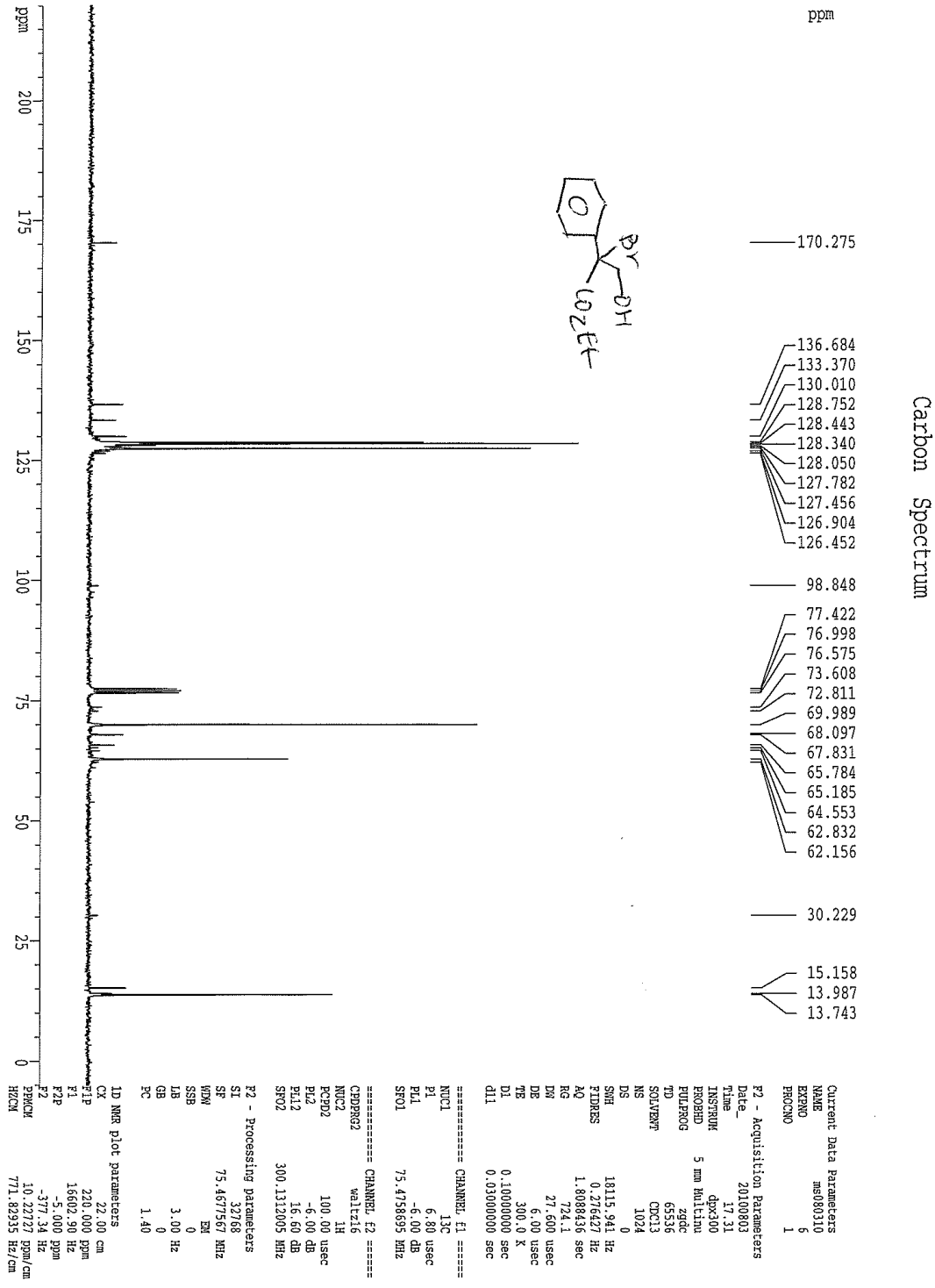
1.22956
0.90919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126.904
126.452
98.848
77.422
76.998
76.575
73.608
72.811
69.989
68.097
67.831
65.784
65.185
64.553
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62.156
30.229
15.158
13.987
13.743
Br
OH
CO2Et
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PROCNO 1
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Time 17.31
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PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 1024
DS 0
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 724.1
DW 27.600 usec
DE 6.00 usec
TE 300.0 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
========== CHANNEL f2 ======
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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
F1P 220.000 ppm
F1 16602.90 Hz
F2P -5.000 ppm
F2 -377.34 Hz
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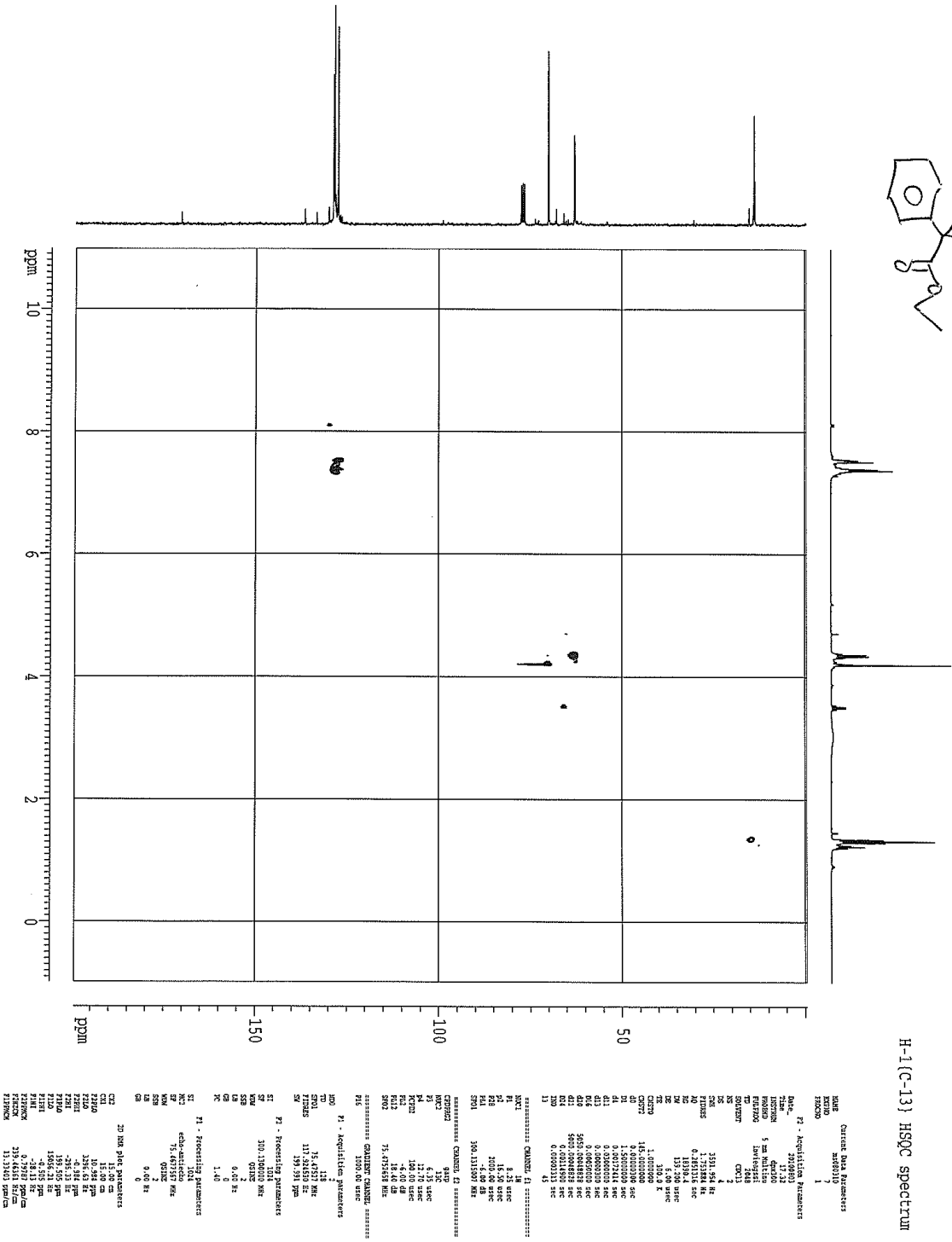
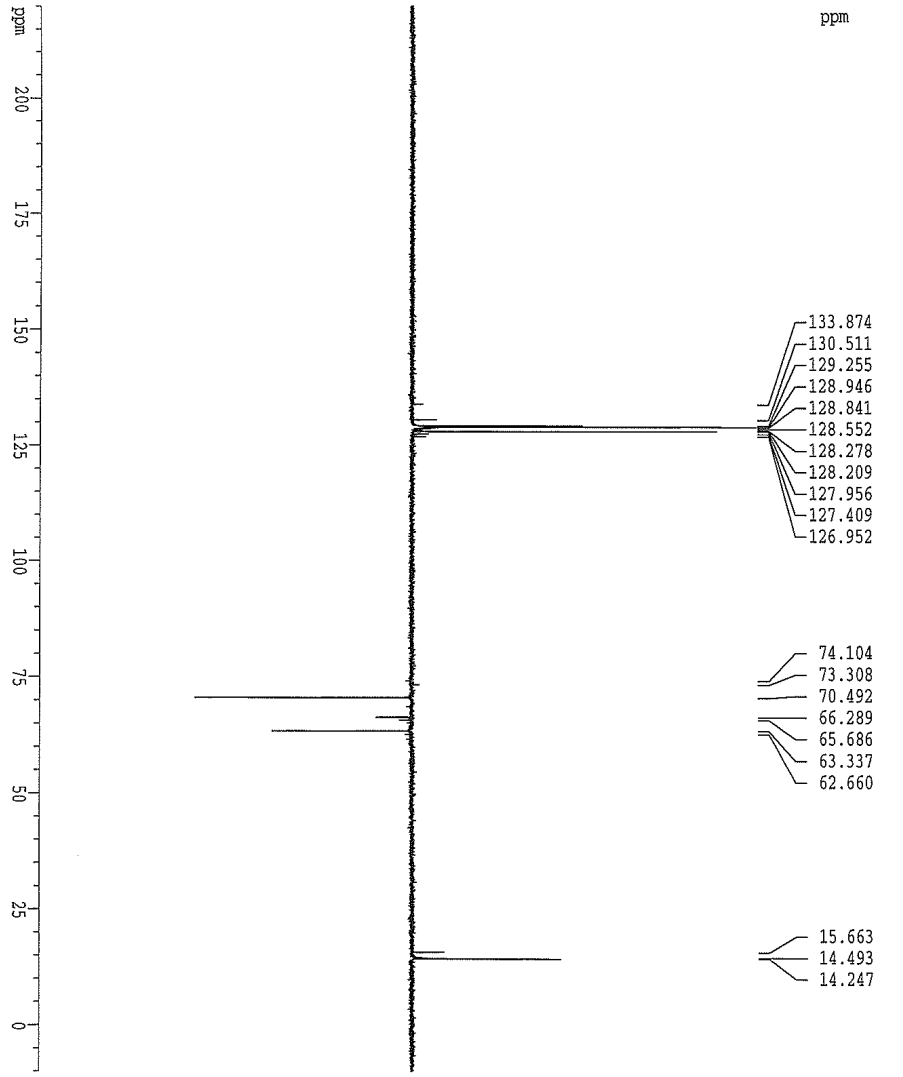
HZCM 771.82935 Hz/cm
ppm
200
175
150
125
100
75
50
25
0



H-1(C-13) HSQC spectrum



C-13 DEPT 135

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PROCNO                       1

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PULPROG              dept135
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NS                       128
DS                         4
SWH                17361.111 Hz
FIDRES                0.264910 Hz
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RG                       8192
DW                     28.800 usec
DE                      6.00 usec
TE                     300.0 K
CNST2                145.0000000
D1                     3.0000000 sec
D2                     0.0034828 sec
d12                    0.0000200 sec
DELTA          6366.1826719 sec
======== CHANNEL f1 ========
NUC1                      13C
P1                       6.63 usec
p2                      13.26 usec
PL1                     -6.00 dB
SFO1           75.4756431 MHz
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CPDPRG2                waltz16
NUC2                       1H
P3                       9.45 usec
p4                      18.90 usec
PCPD2                  100.00 usec
PL2                     -6.00 dB
PL12                    16.60 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
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WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40

1D NMR plot parameters
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F1P                  220.000 ppm
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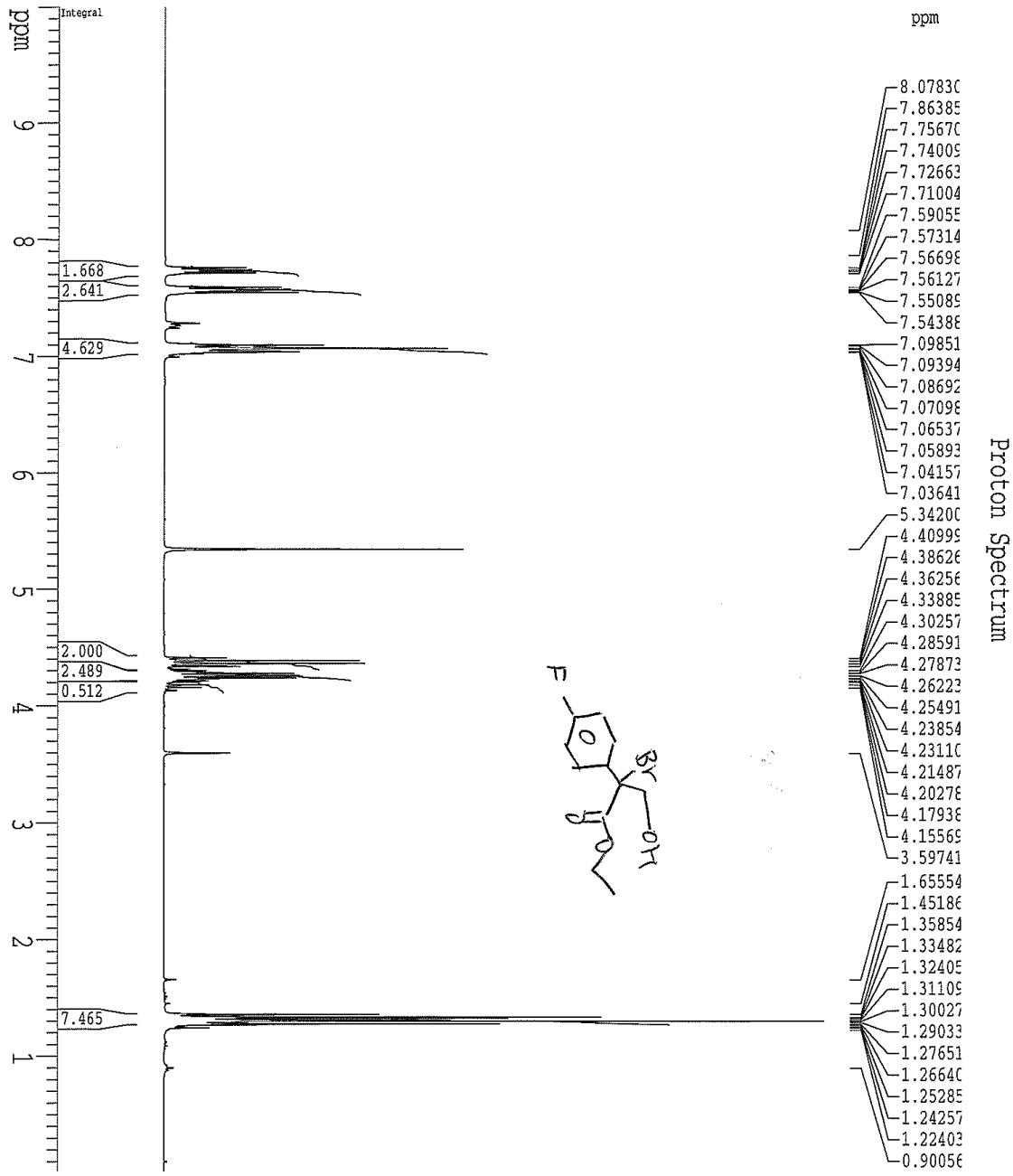
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ppm
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7.56127
7.55089
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F
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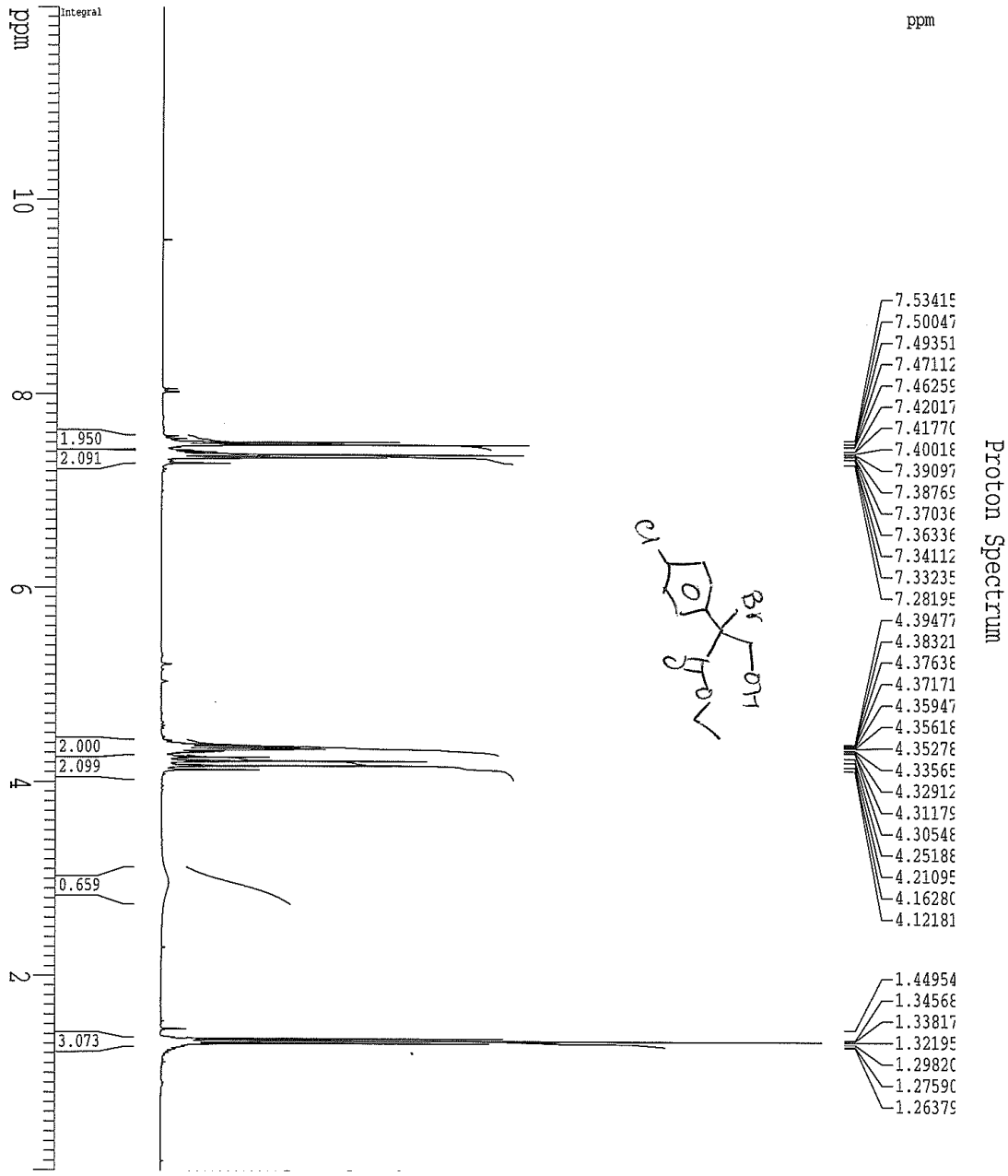
OH
O
Proton Spectrum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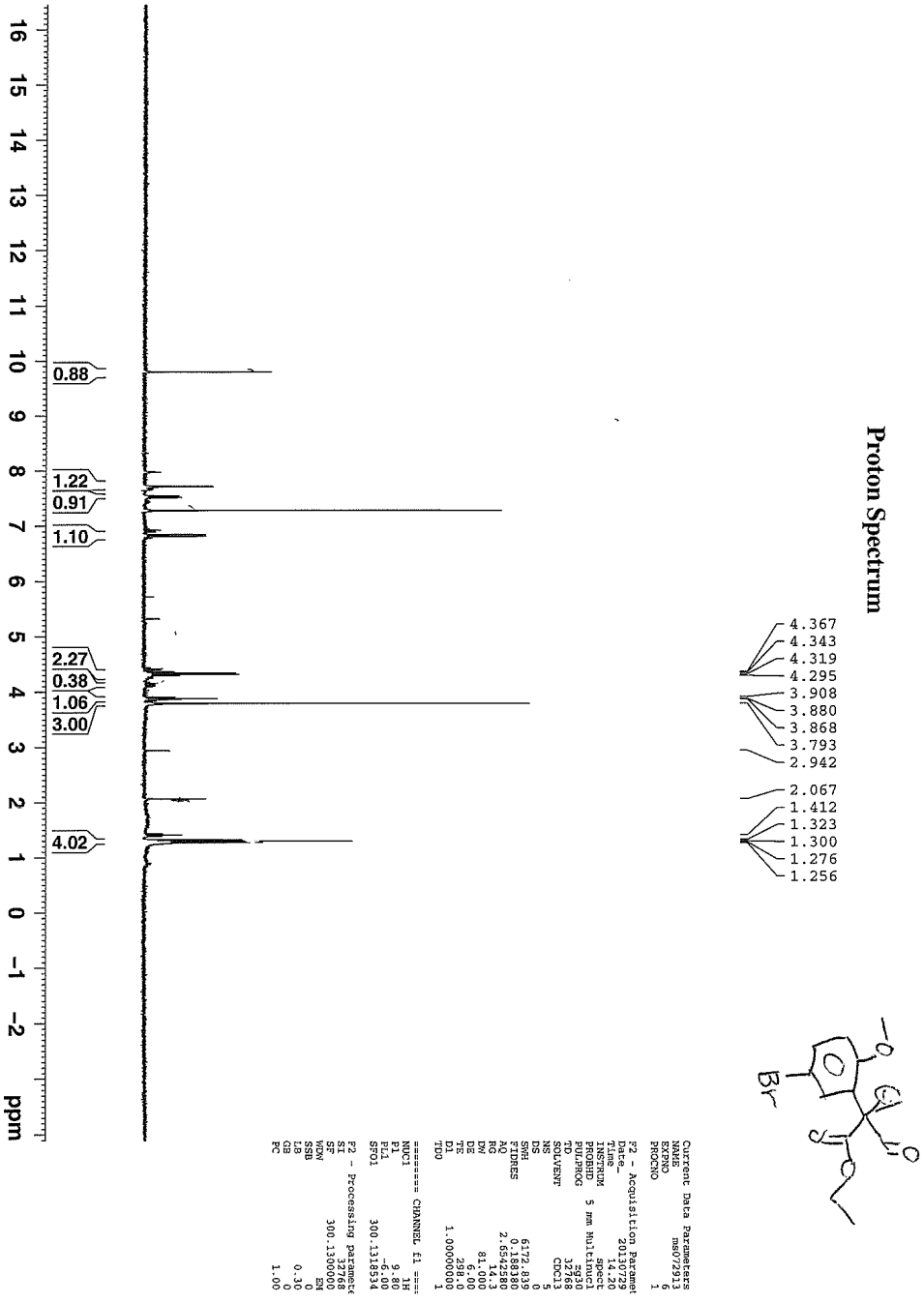
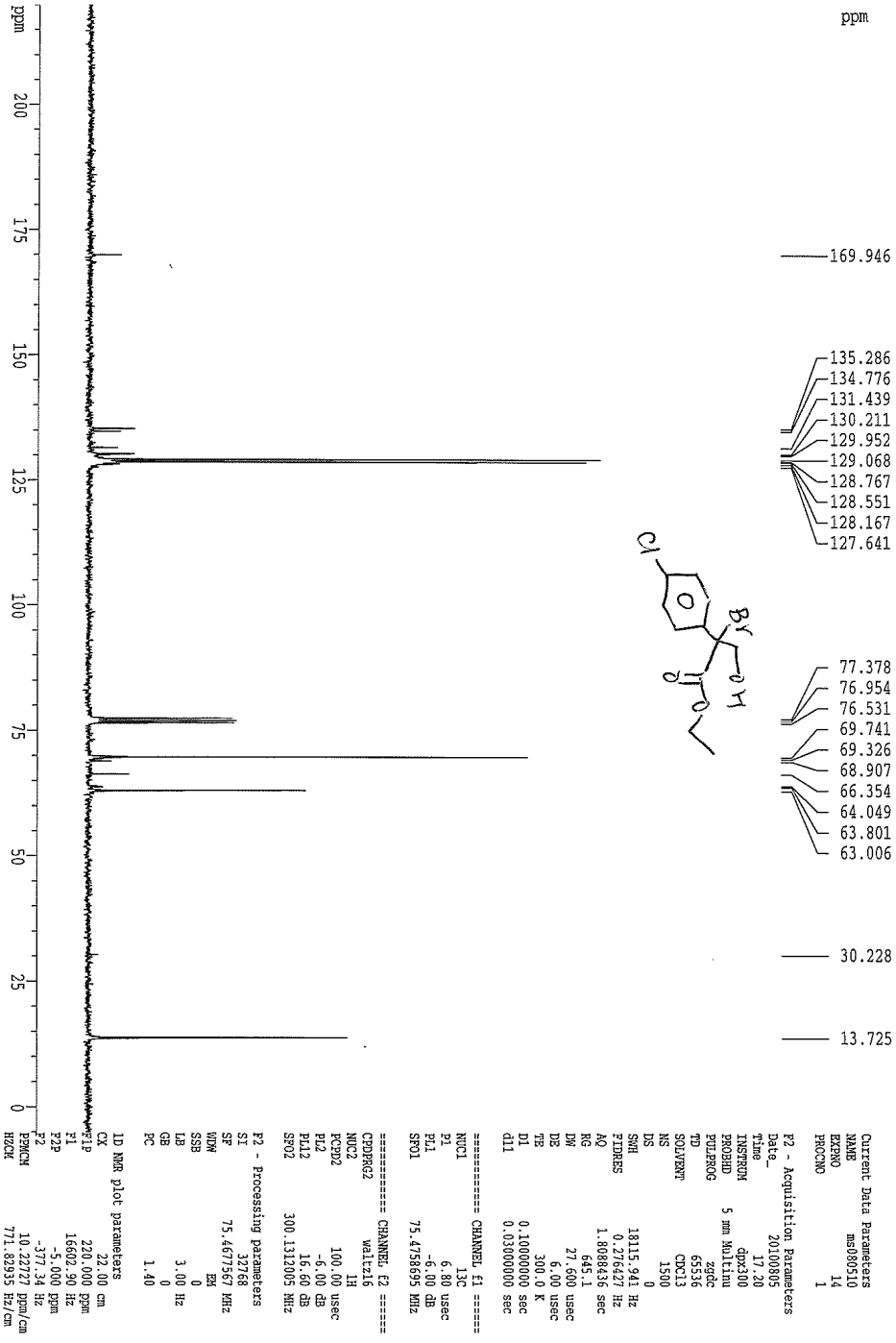
Proton Spectrum

Proton Spectrum



Carbon Spectrum

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PULPROG              zgpdc
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SOLVENT              CDCl3
NS                    1500
DS                       0
SWH              18115.941 Hz
FIDRES               0.276427 Hz
AQ                1.8088436 sec
RG                     645.1
DW                27.600 usec
DE                 6.00 usec
TE                 300.0 K
D1              0.10000000 sec
d11             0.03000000 sec

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P1                    6.80 usec
PL1                  -6.00 dB
SFO1          75.4758695 MHz

============== CHANNEL f2 ======
CPDPRG2             waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                  -6.00 dB
PL12                 16.60 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
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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
F1P                 220.000 ppm
F1                 16602.90 Hz
F2P                 -5.000 ppm
F2                 -377.34 Hz
PPMCM              10.22727 ppm/cm
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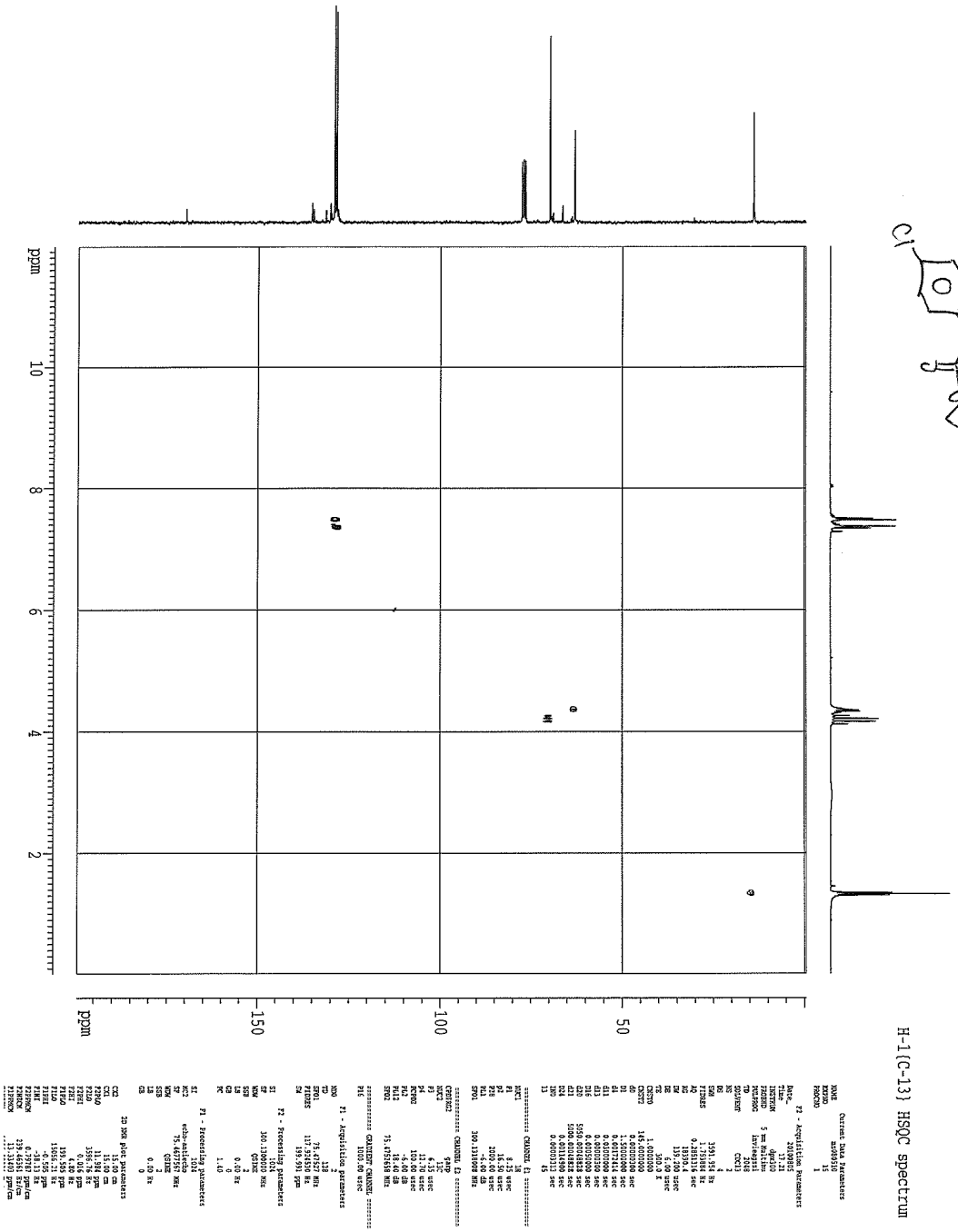
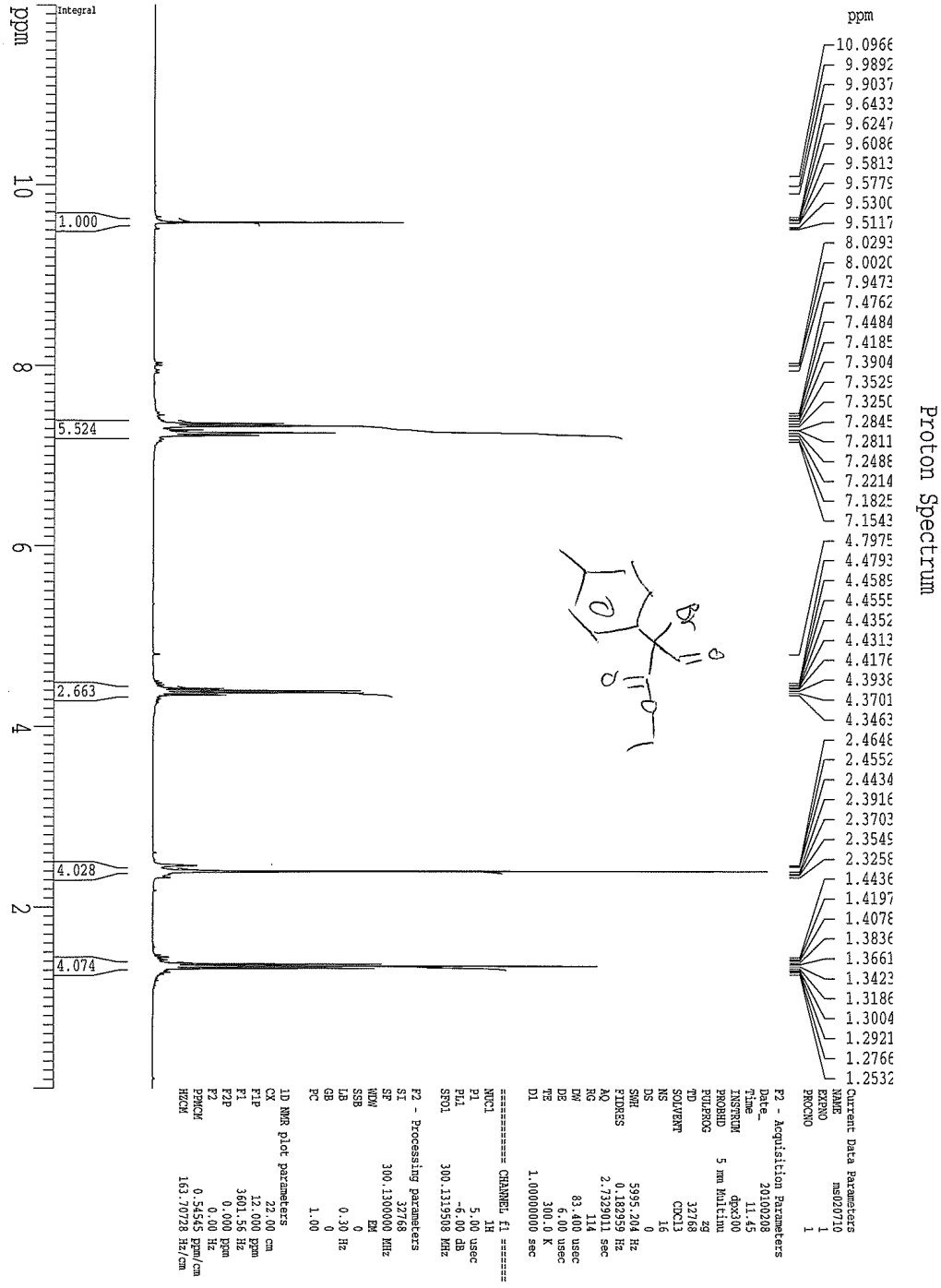


H-1[C-13] HSQC spectrum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O
O
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PROCNO 1
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PULPROG zg
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SOLVENT CDCl3
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RG 114
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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PL1 -6.00 dB
SFO1 300.1319508 MHz
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
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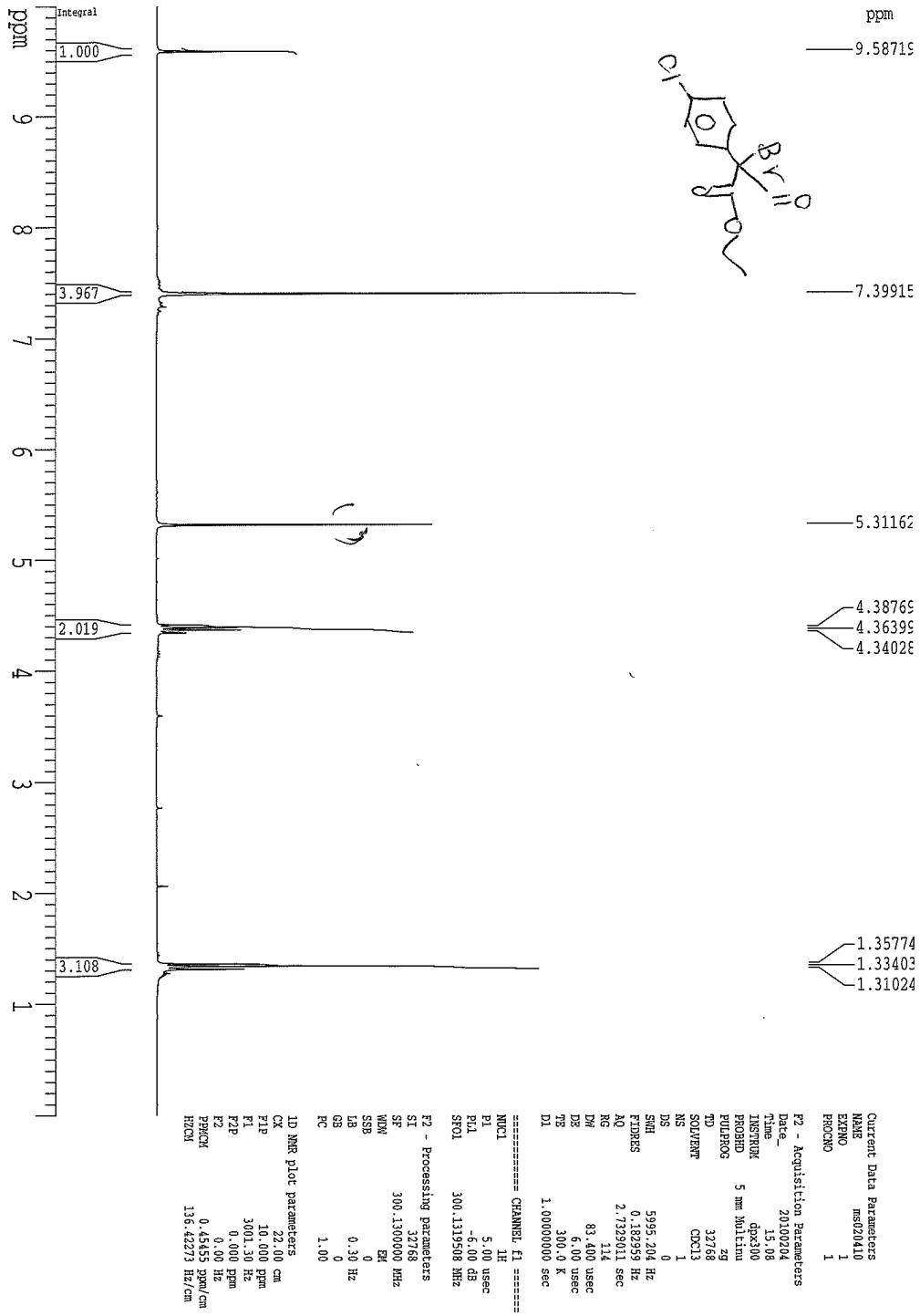
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Integral
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2.019
3.108
ppm
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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PULPROG zg
TD 32768
SOLVENT CDCl3
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DS 0
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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NUC1 1H
P1 5.00 usec
PL1 -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
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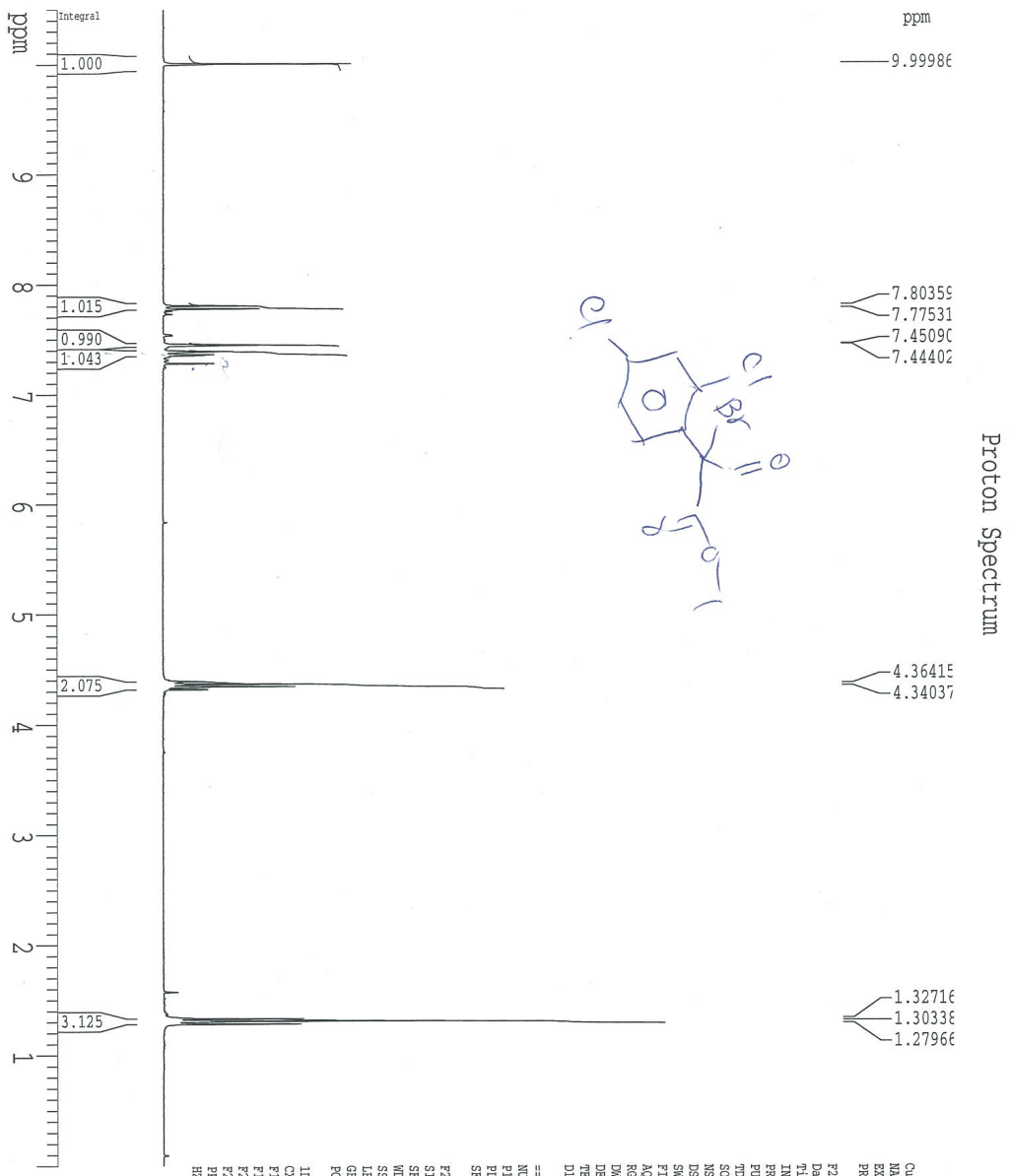
HZCM 136.42273 Hz/cm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Cl
Br
O
O
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PROCNO 1
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TE 300.0 K
D1 1.00000000 sec
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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F2 0.00 Hz
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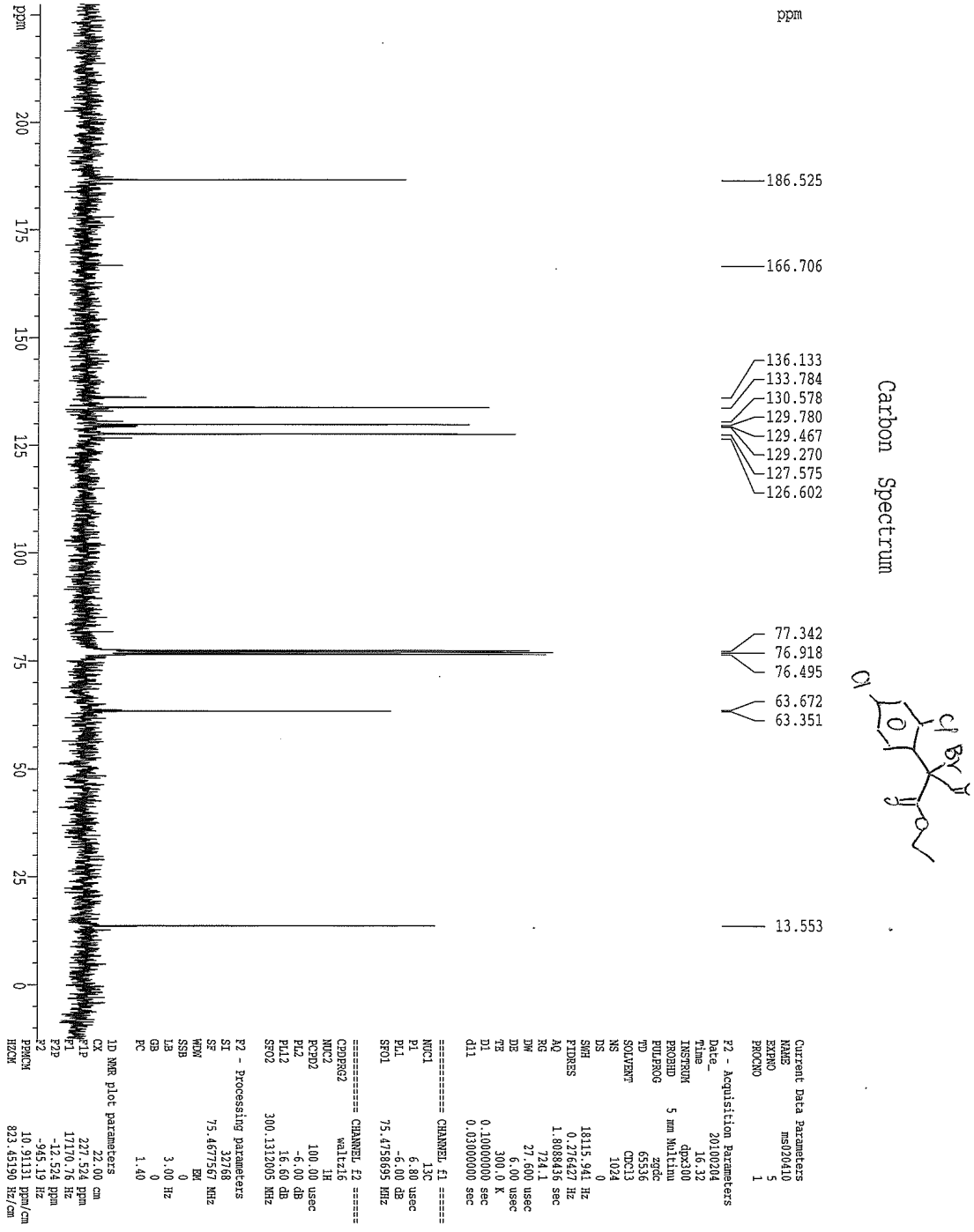
HZCM 143.24385 Hz/cm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76.918
76.495
63.672
63.351
13.553
Cl
Br
O
ppm
200
175
150
125
100
75
50
25
0
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PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 1024
DS 0
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 724.1
DW 27.600 usec
DE 6.00 usec
TE 300.0 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
========== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 16.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
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WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 22.00 cm
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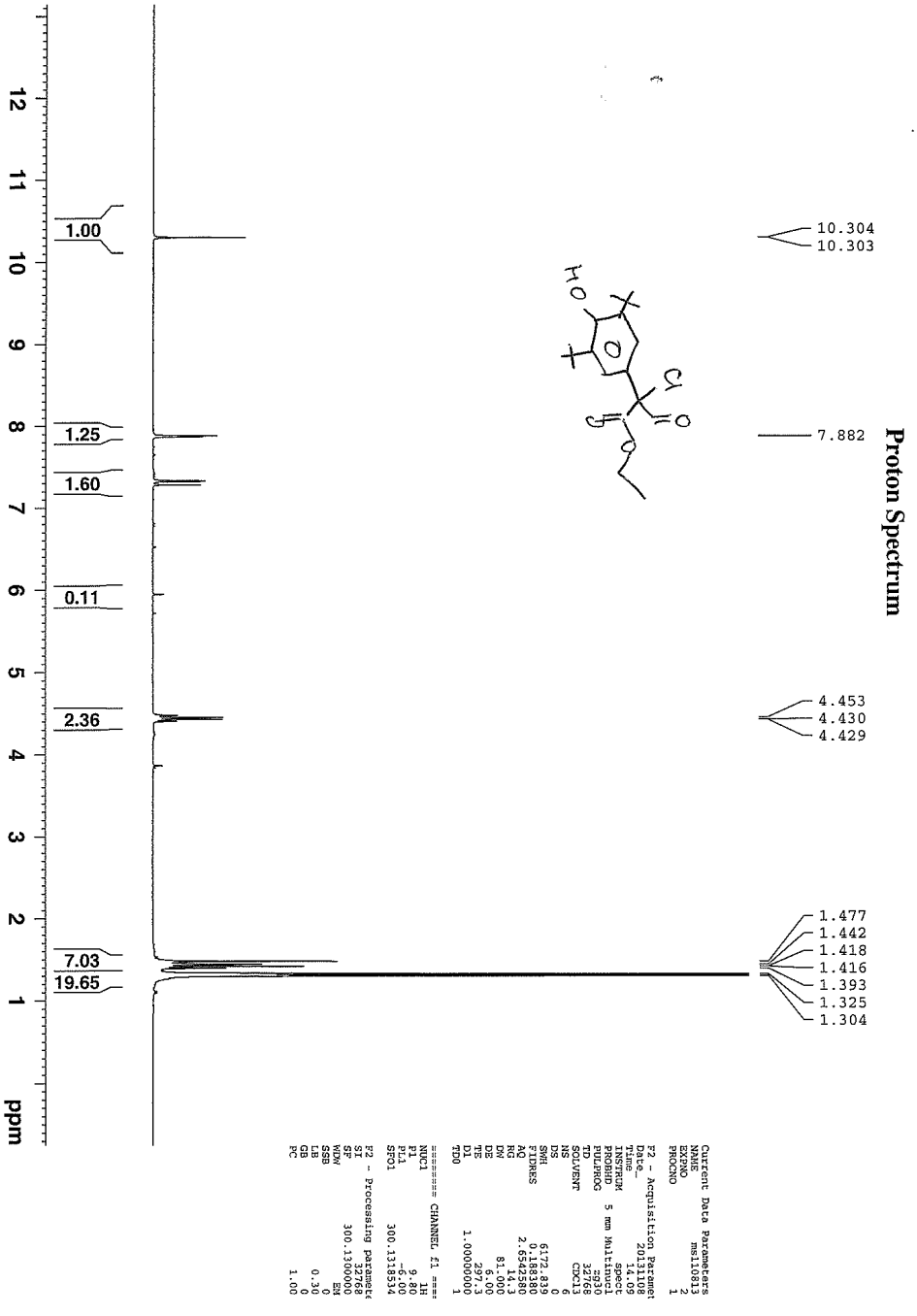
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1.304
1.00
1.25
1.60
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2.36
7.03
19.65
ppm
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PROCNO 1
F2 - Acquisition Paramet
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Time 14.09
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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
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FIDRES 0.188380
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RG 1.003
DW 81.000
DE 6.00
TE 297.3
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NUC1 1H
P1 9.80
PL1 -5.00
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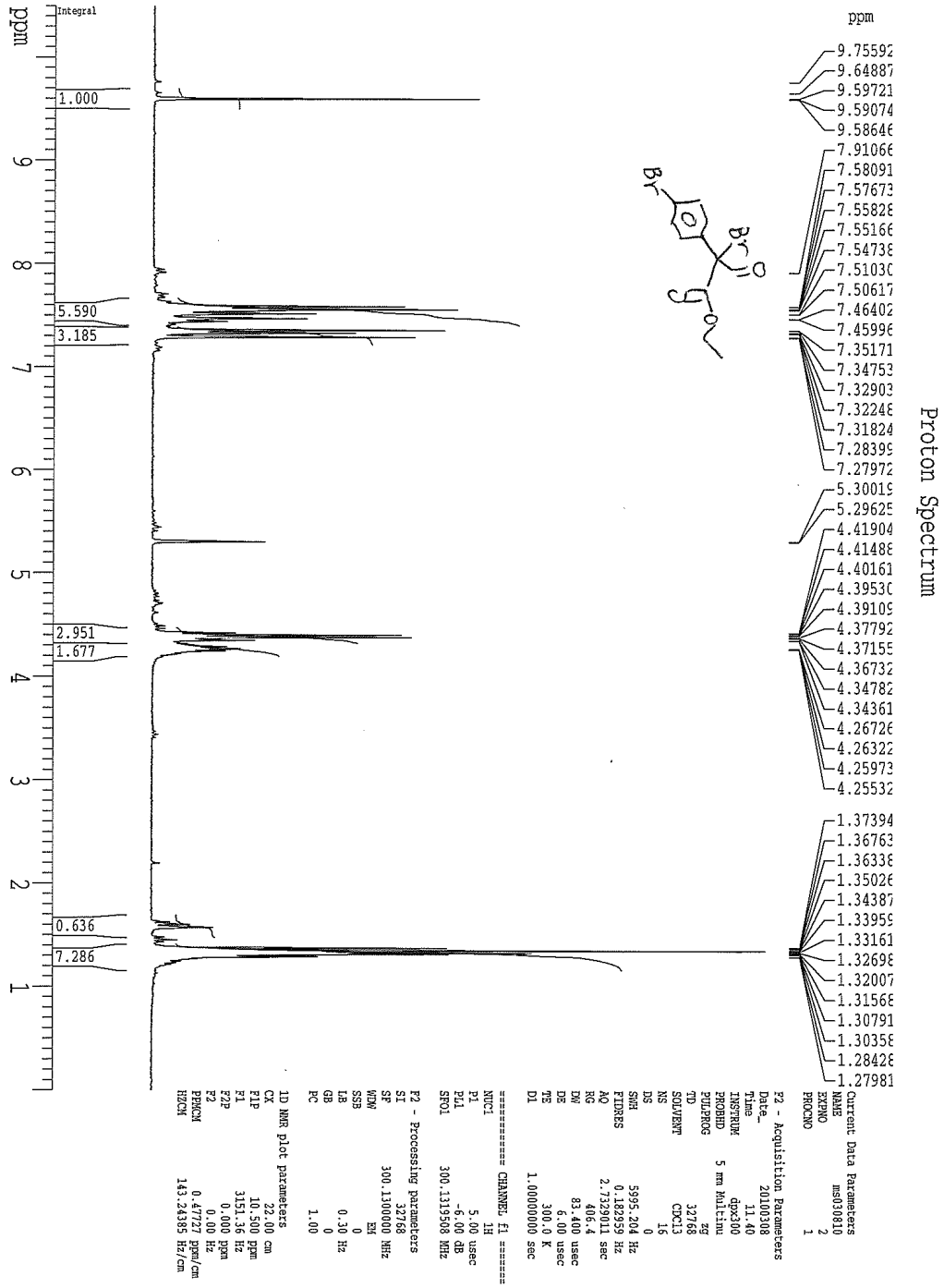
PC 1.00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Br
O
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PROCNO 1
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PULPROG zg
TD 32768
SOLVENT CDCl3
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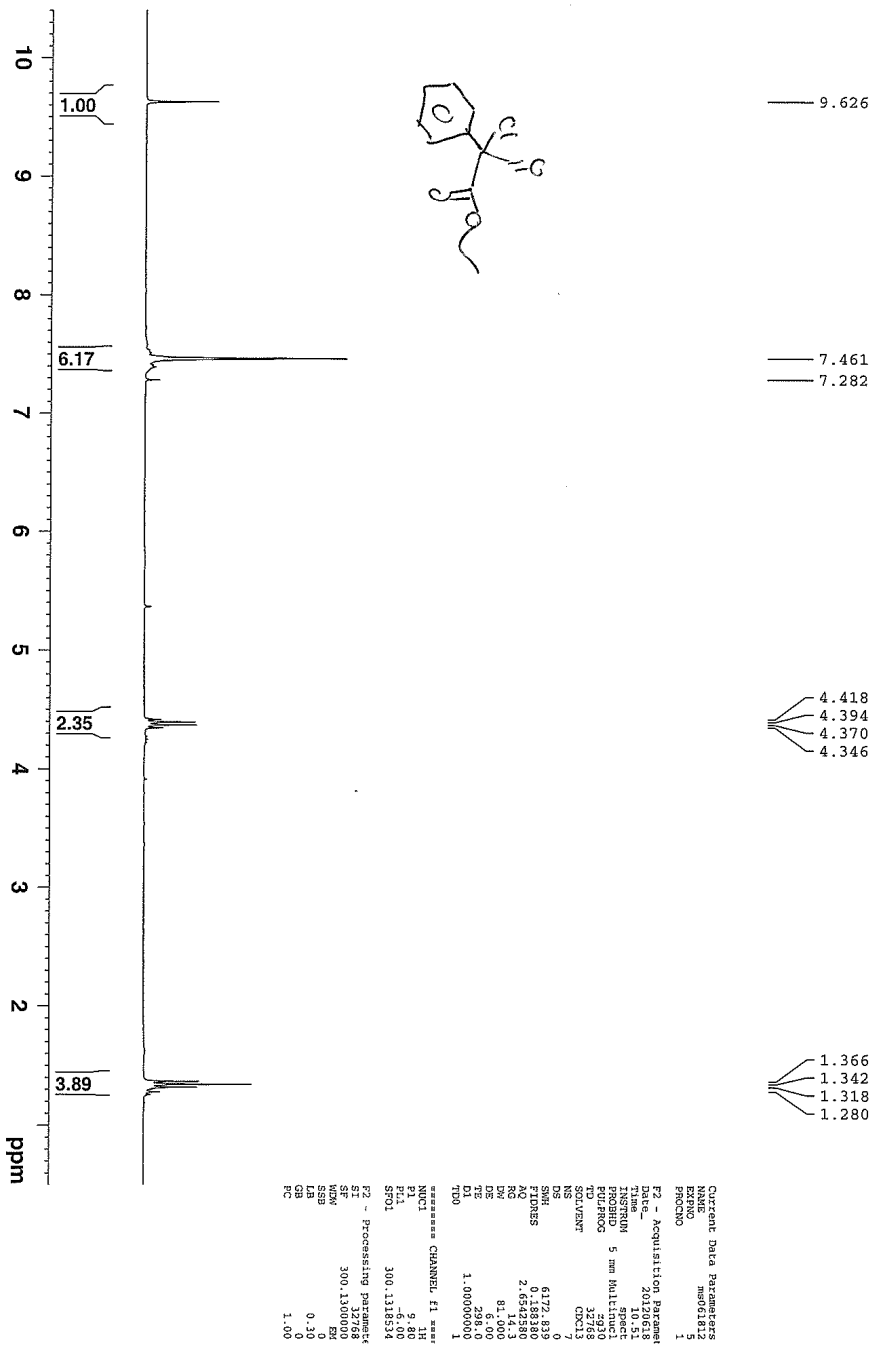
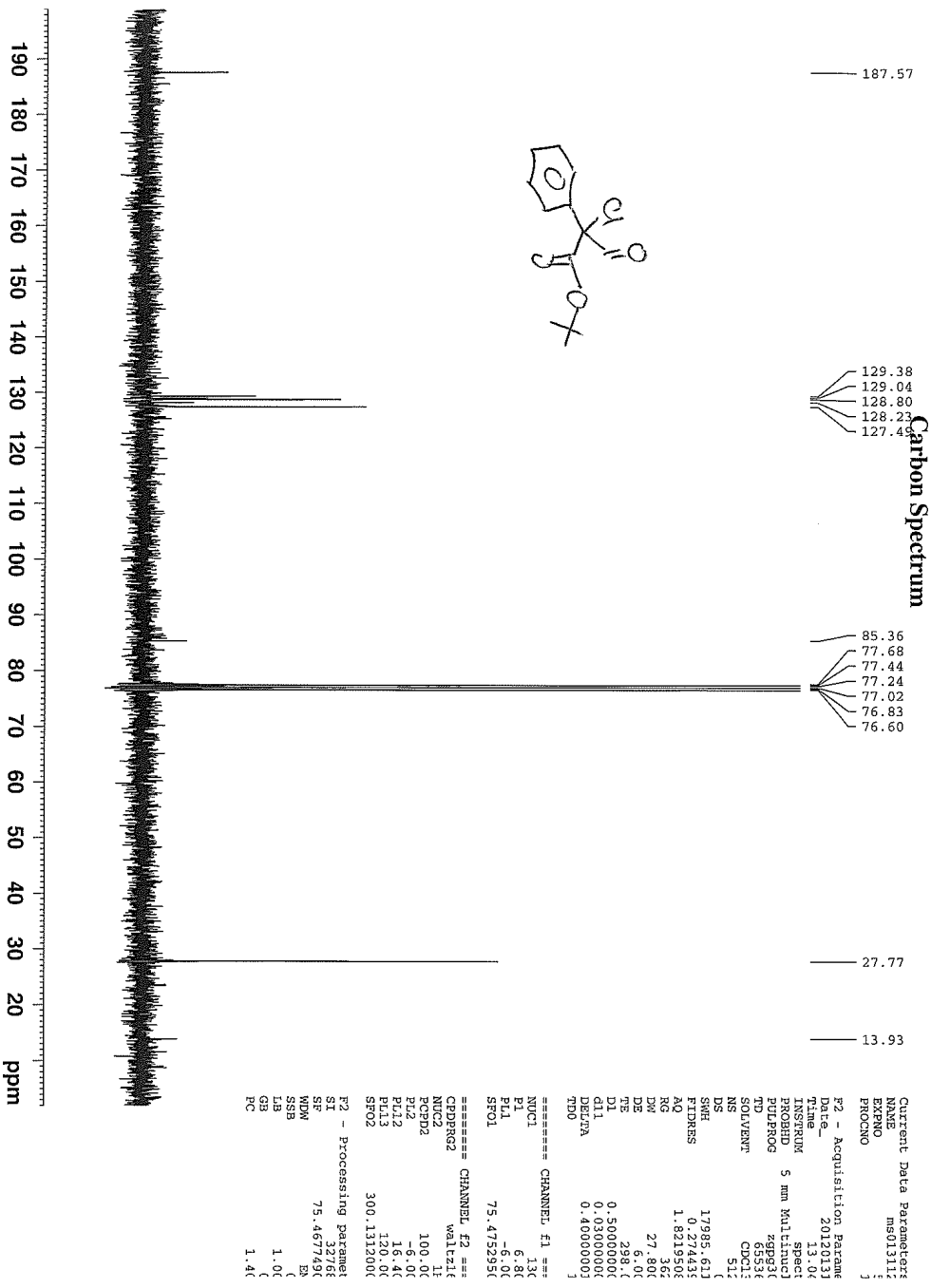
DS 0
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 406.4
DW 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 -6.00 dB
SFO1 300.1319508 MHz
F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
F1P 10.500 ppm
F1 3151.36 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.47727 ppm/cm
HZCM 143.24385 Hz/cm



Proton Spectrum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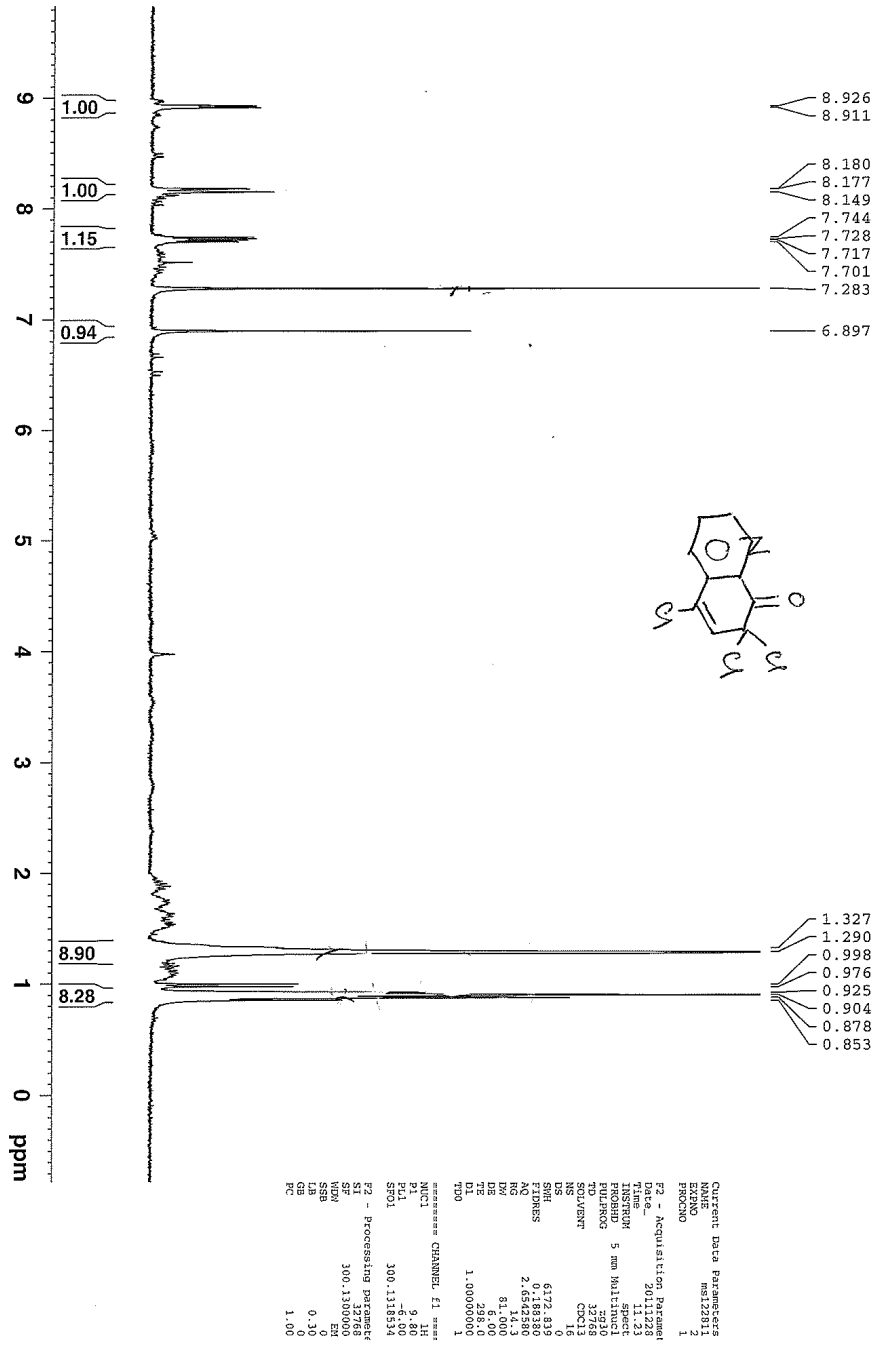
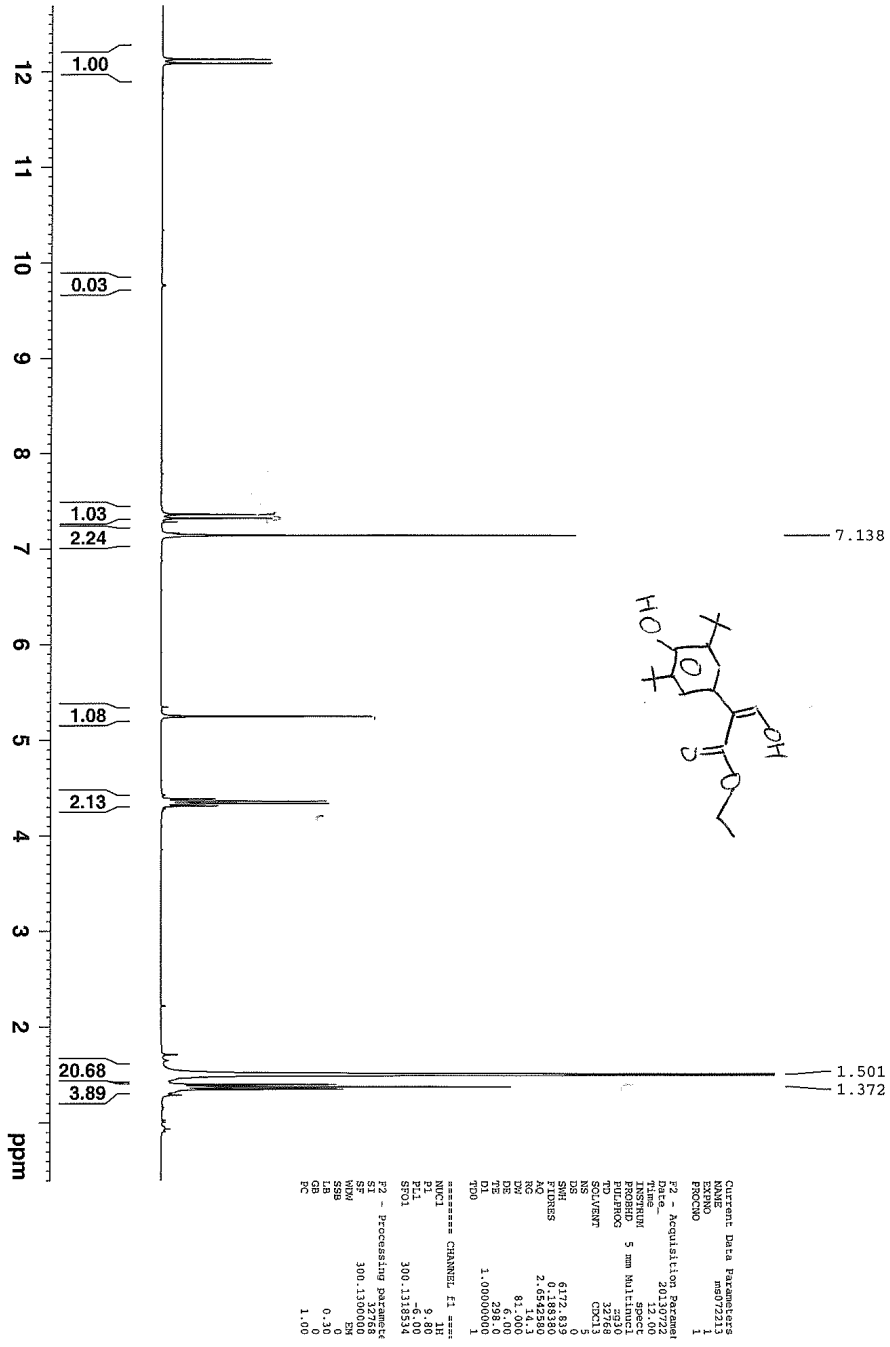
76.60
27.77
13.93
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

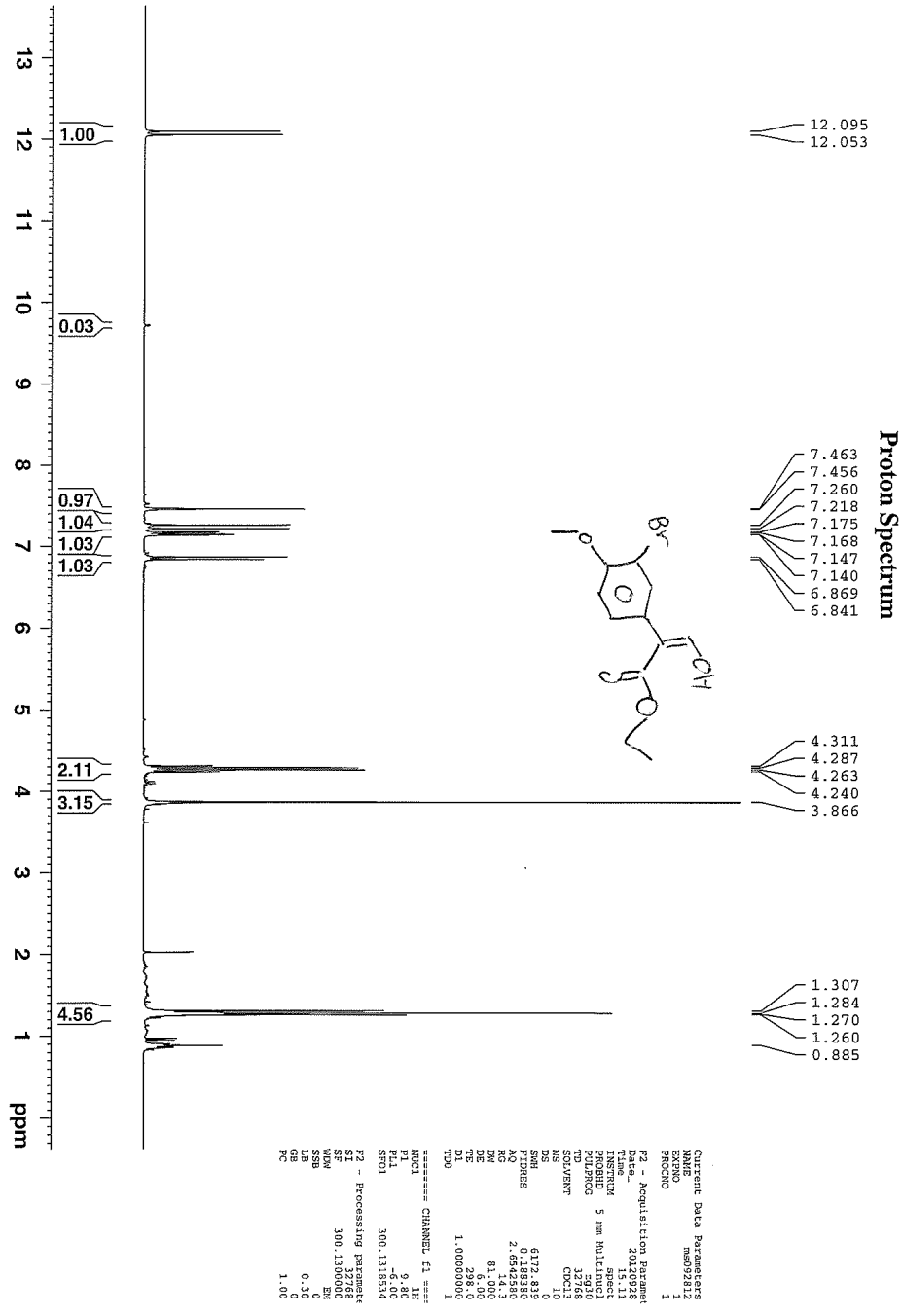


Proton Spectrum

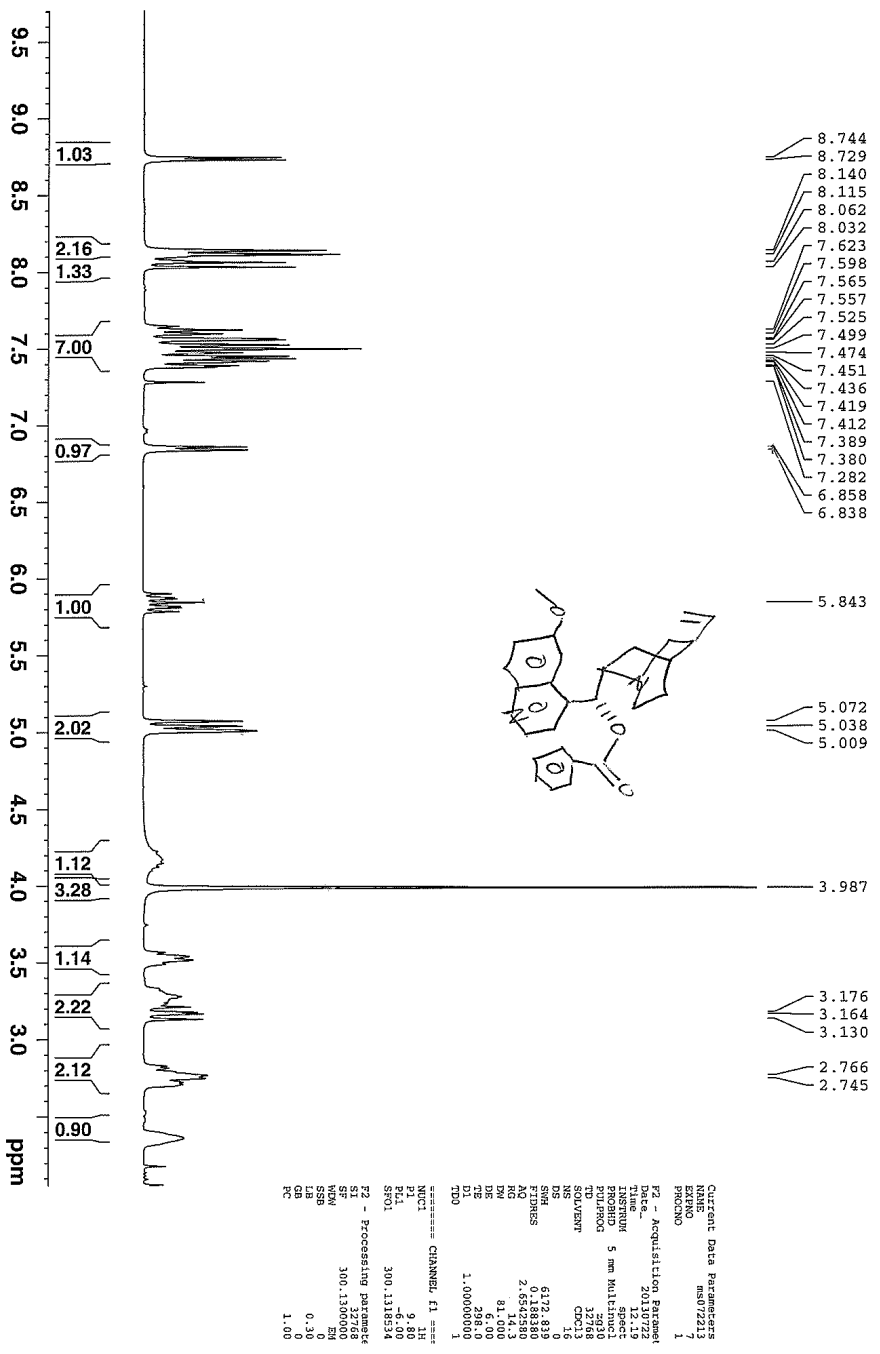
Proton Spectrum

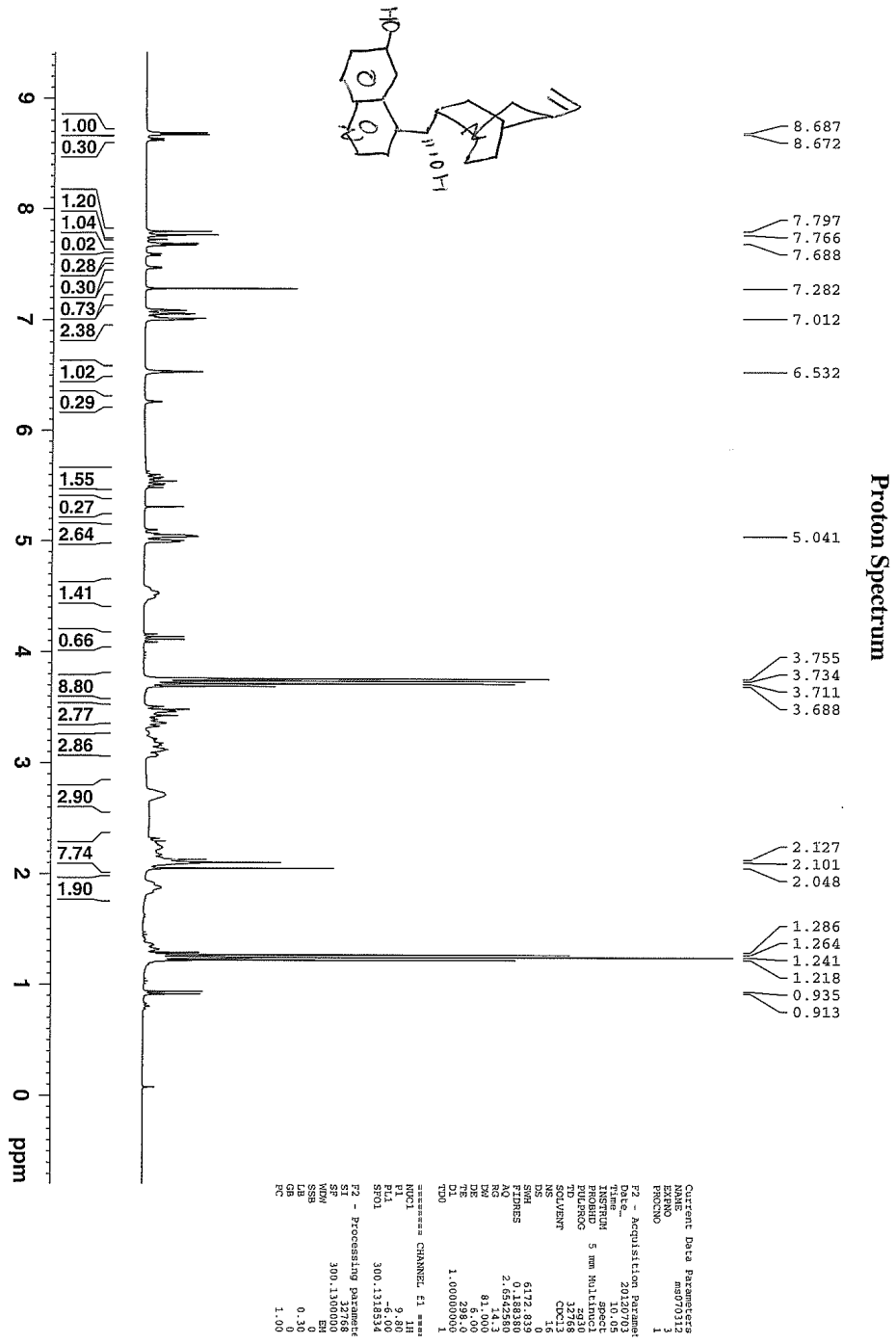


Proton Spectrum



Proton Spectrum





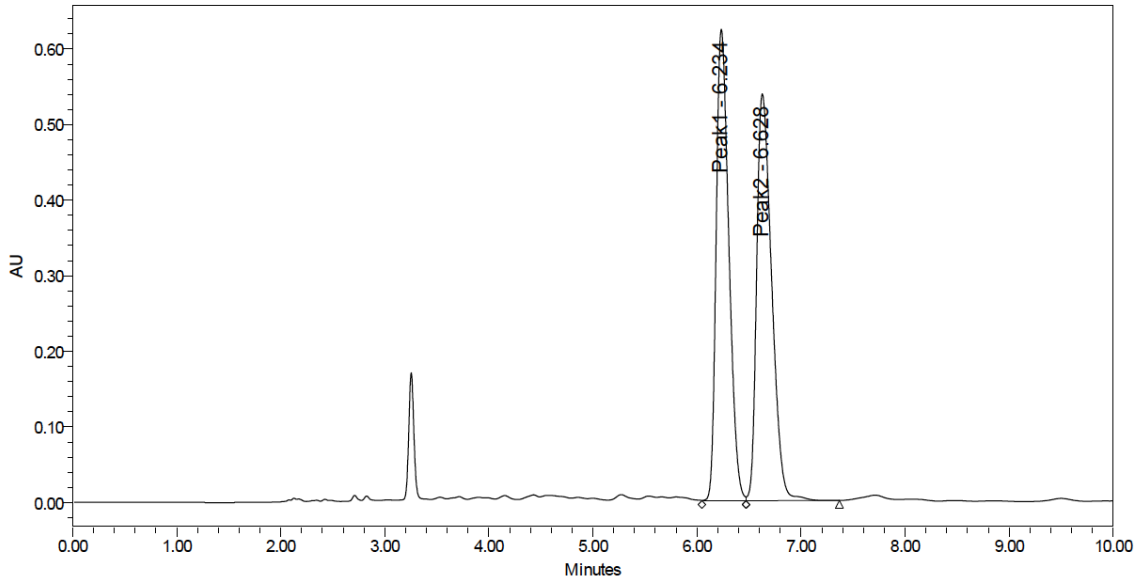
Proton Spectrum

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

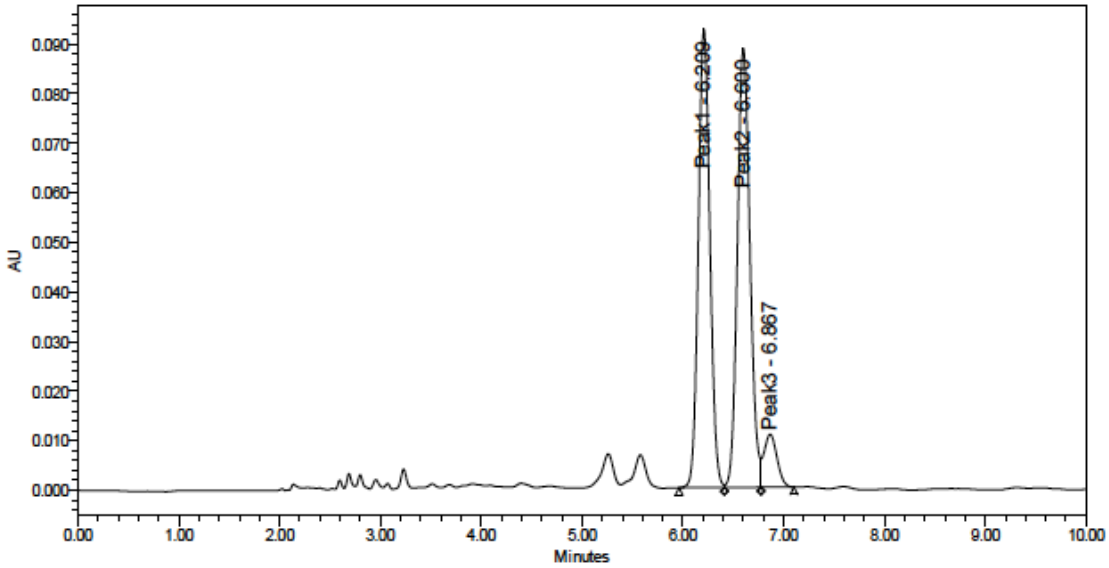


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.234	5275019	49.49	623692	53.69
2	Peak2	6.628	5384482	50.51	537877	46.31

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 (µV*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

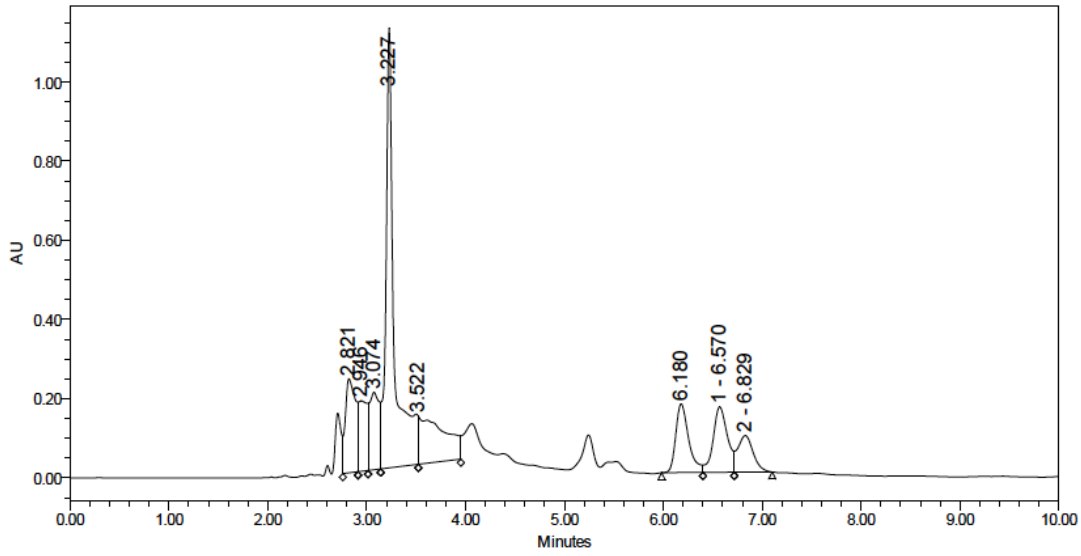
Project Name Masha

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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

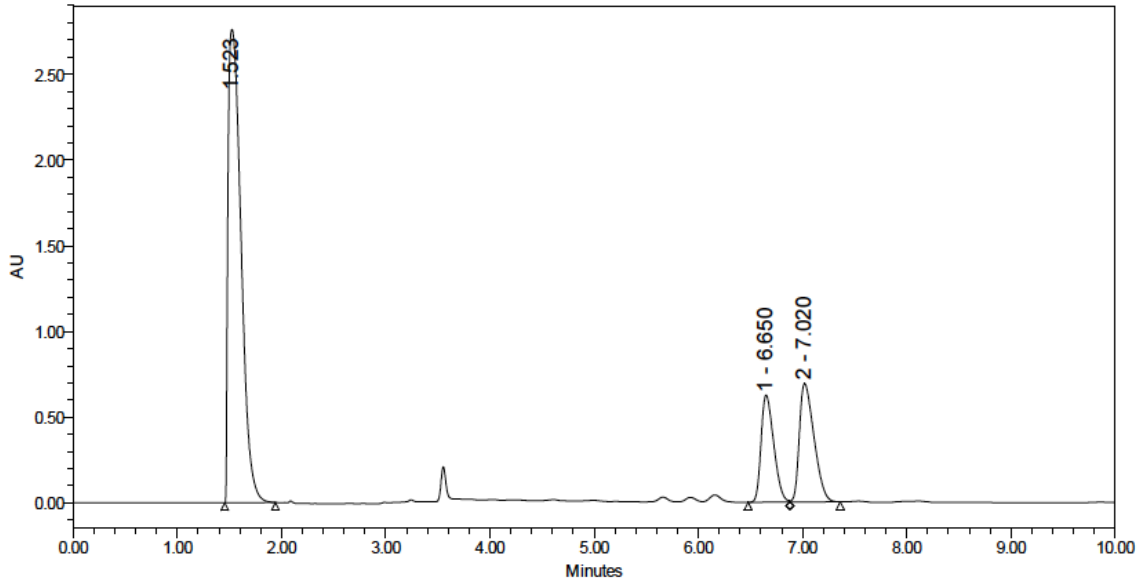


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1		2.821	1717909	9.99	237891	10.45
2		2.946	1081859	6.29	178037	7.82
3		3.074	1368432	7.95	195660	8.59
4		3.227	6574563	38.22	111146(	48.82
5		3.522	2216643	12.89	122100	5.36
6		6.180	1577581	9.17	173566	7.62
7	1	6.570	1662915	9.67	165166	7.26
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

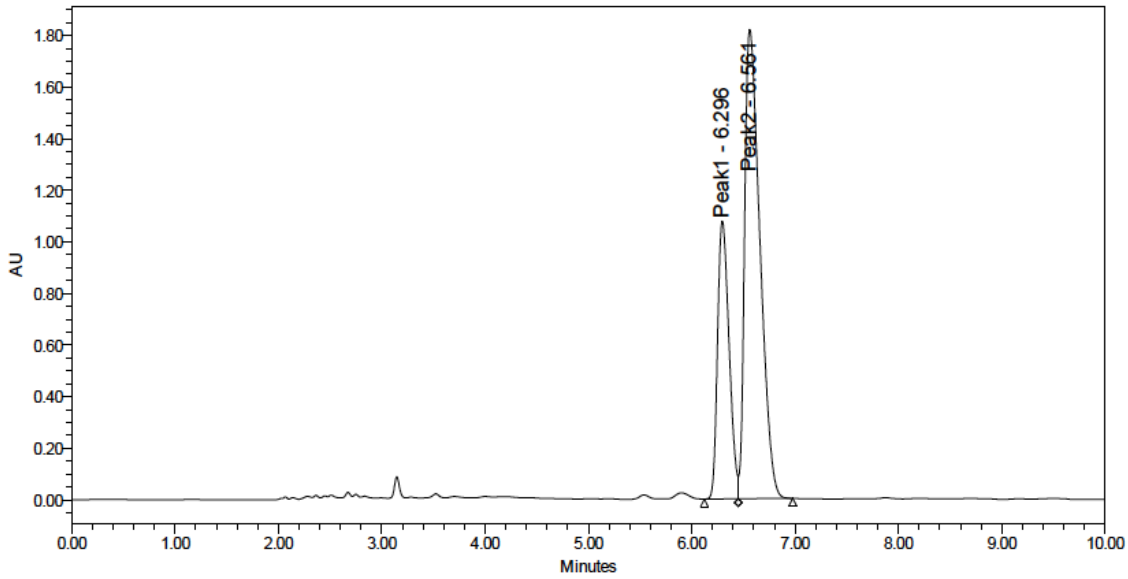


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1		1.523	23873159	66.54	2759945	67.72
2	1	6.650	5261795	14.67	624646	15.33
3	2	7.020	6742295	18.79	690979	16.95

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

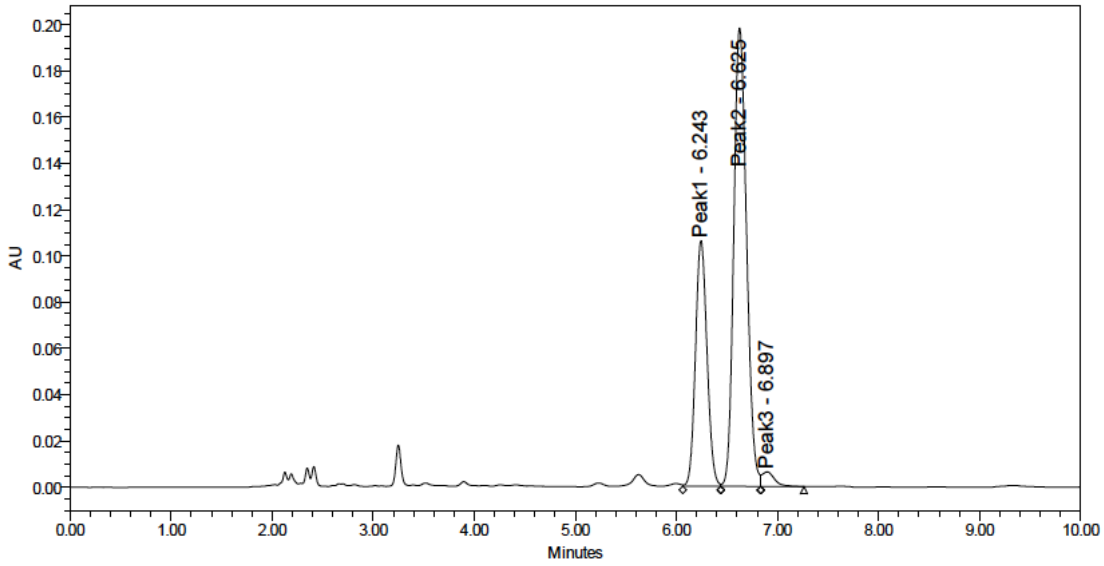


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.296	8331254	30.81	1076881	37.19
2	Peak2	6.561	18713784	69.19	1818467	62.81

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

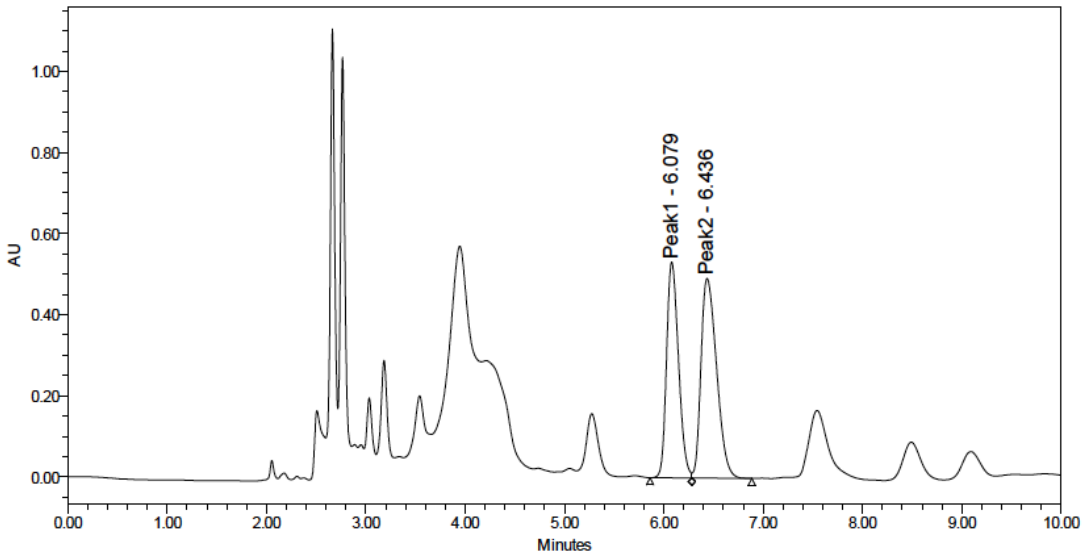


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.243	841134	31.94	106185	34.18
2	Peak2	6.625	1737553	65.97	198197	63.79
3	Peak3	6.897	54989	2.09	6301	2.03

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

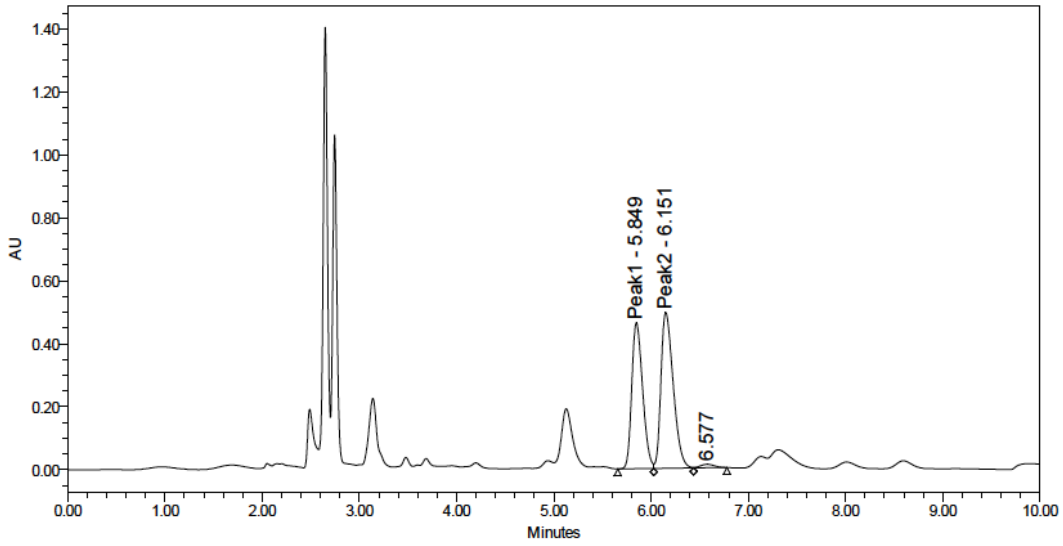


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.079	4445485	45.27	531523	51.93
2	Peak2	6.436	5375450	54.73	492089	48.07

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

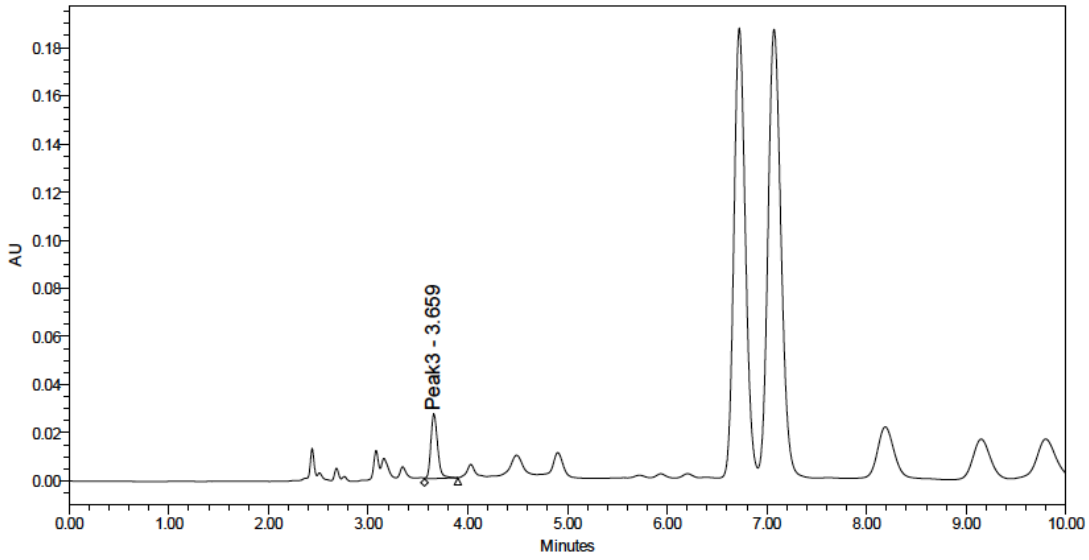


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	5.849	3595556	44.72	463312	47.81
2	Peak2	6.151	4334572	53.91	494732	51.05
3		6.577	110742	1.38	11076	1.14

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

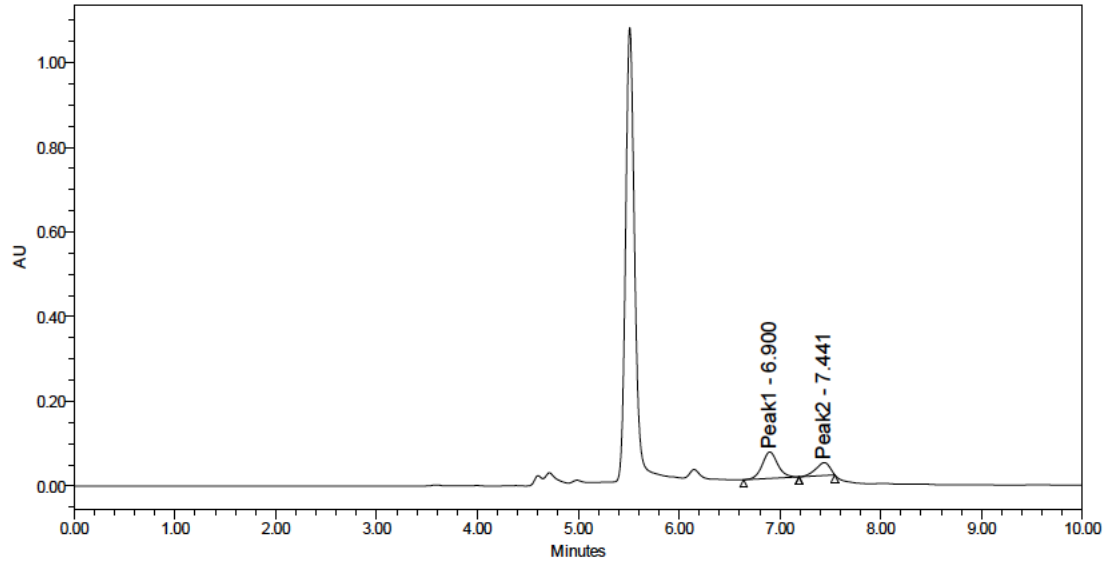


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	3.105				
2	Peak2	3.183				
3	Peak3	3.659	126725	100.00	26723	100.00
4	Peak4	3.768				

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

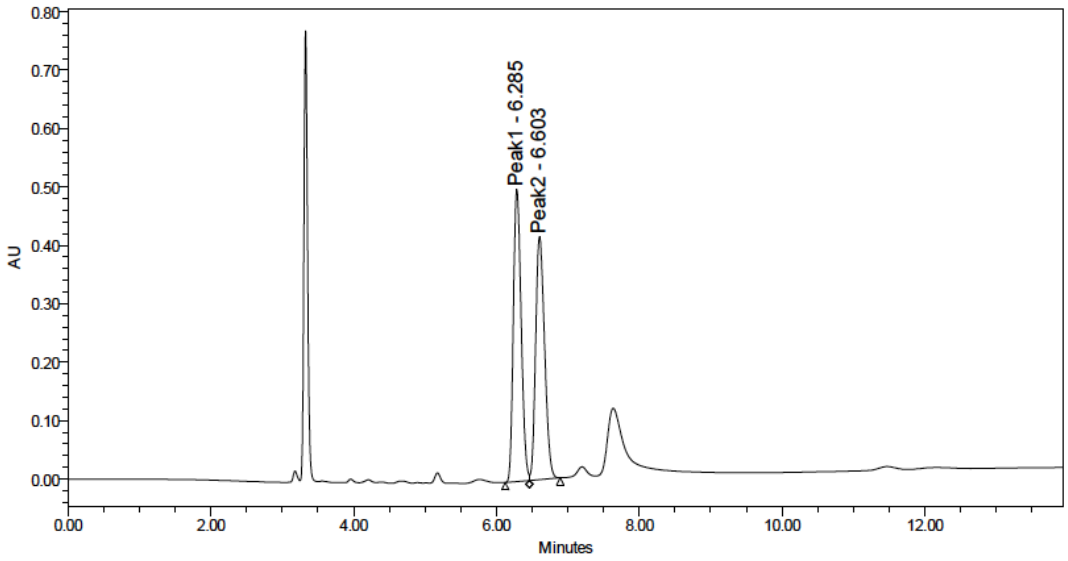


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.900	663874	69.63	62261	67.19
2	Peak2	7.441	289505	30.37	30401	32.81

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

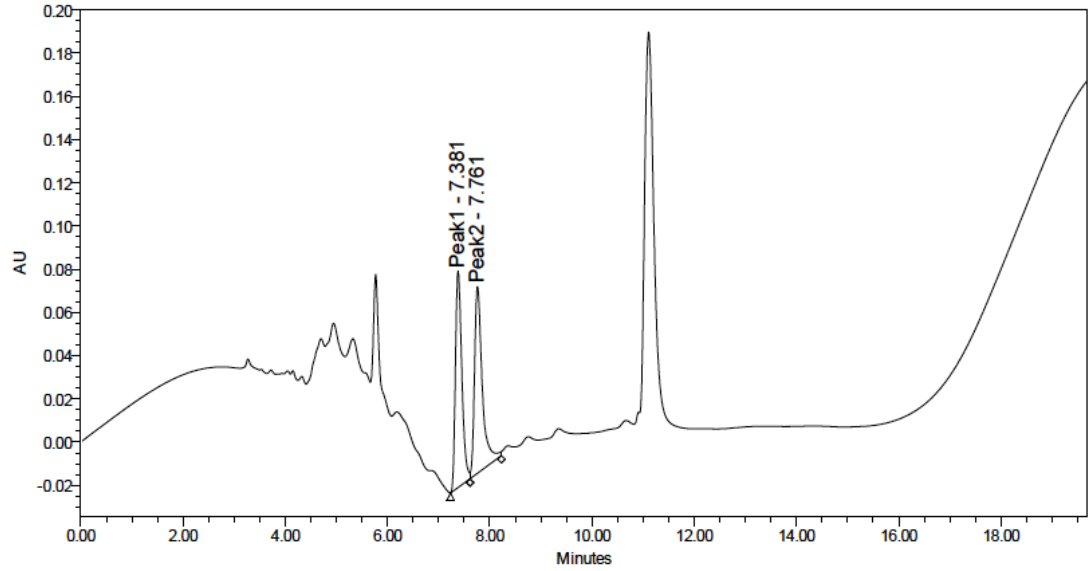


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.285	3804724	51.20	499996	54.59
2	Peak2	6.603	3626786	48.80	415933	45.41

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

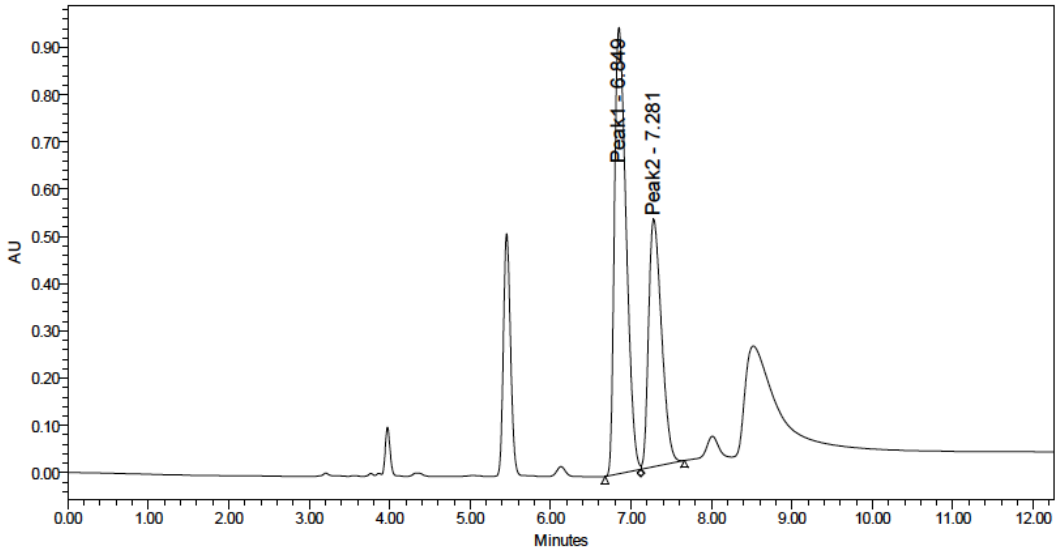


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.381	870107	48.89	100113	53.71
2	Peak2	7.761	909646	51.11	86286	46.29

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

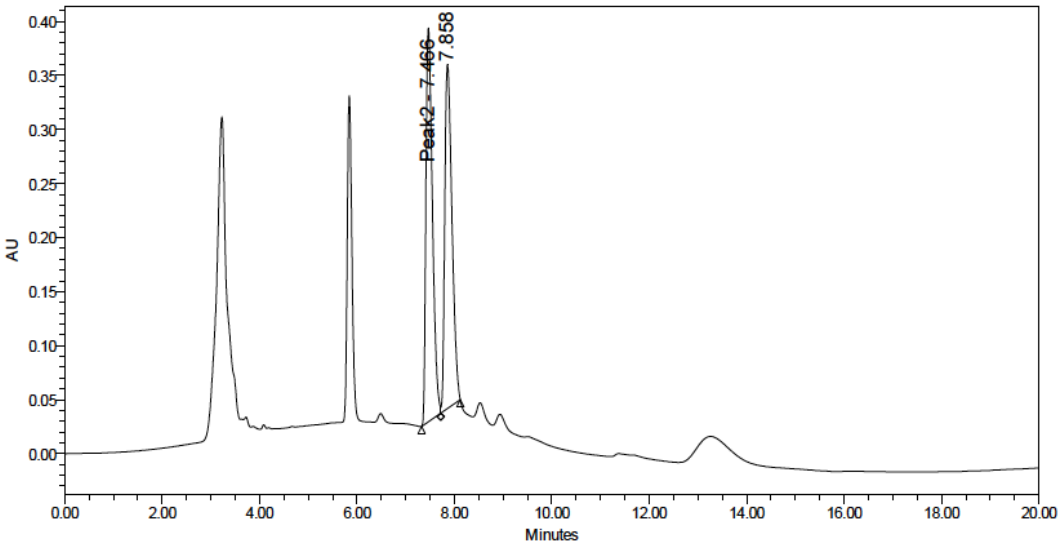


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.849	9530707	61.94	944583	64.33
2	Peak2	7.281	5856064	38.06	523741	35.67

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

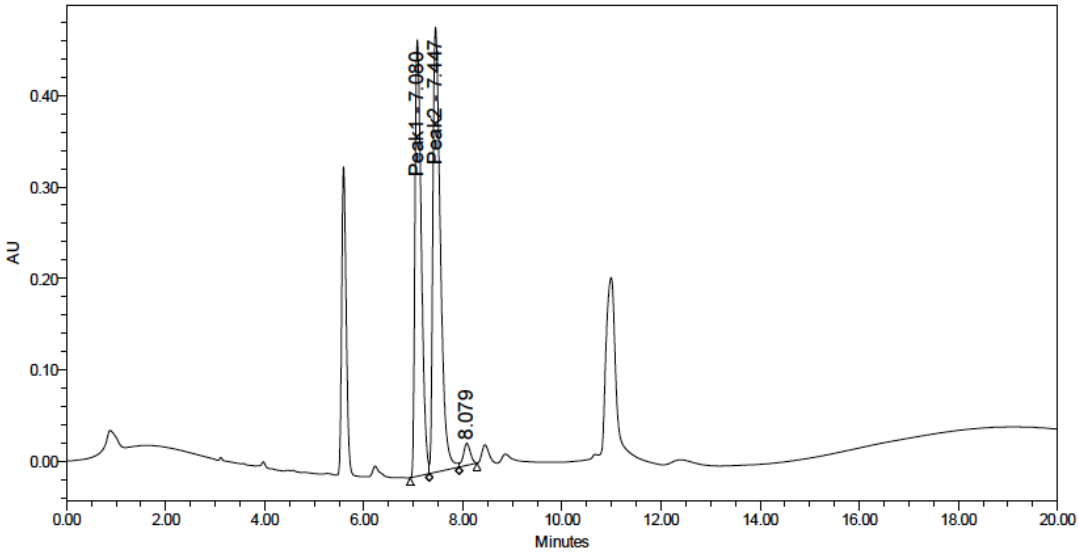


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.012				
2	Peak2	7.466	3383815	50.88	364397	53.36
3		7.858	3267051	49.12	318487	46.64

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

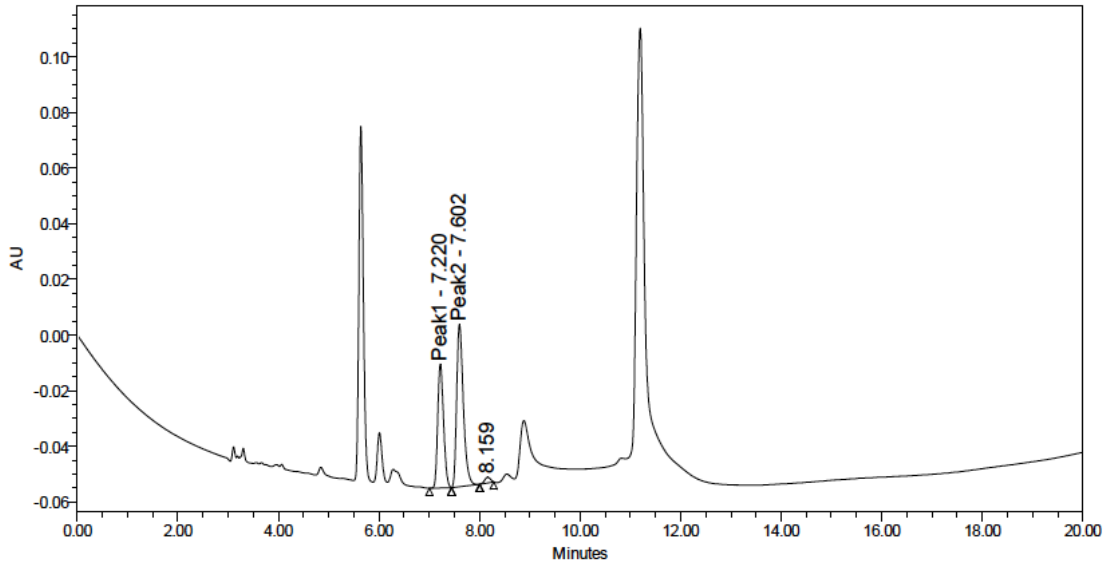


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.080	4252651	44.20	477307	48.31
2	Peak2	7.447	5131556	53.34	486725	49.26
3		8.079	236813	2.46	24073	2.44

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

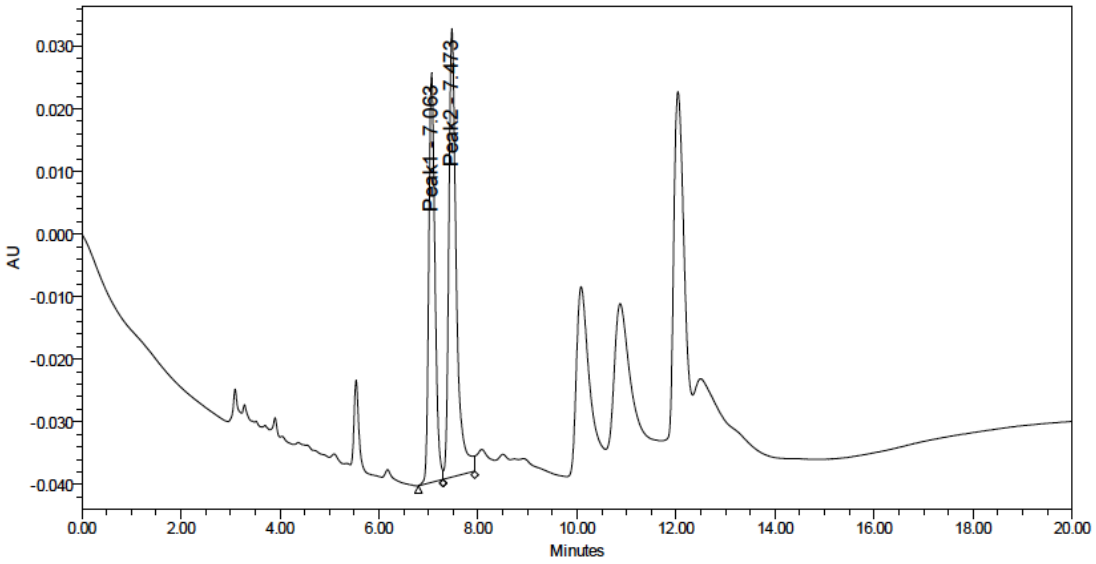


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.220	359457	39.35	44499	42.45
2	Peak2	7.602	538021	58.89	58289	55.61
3		8.159	16100	1.76	2028	1.93

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

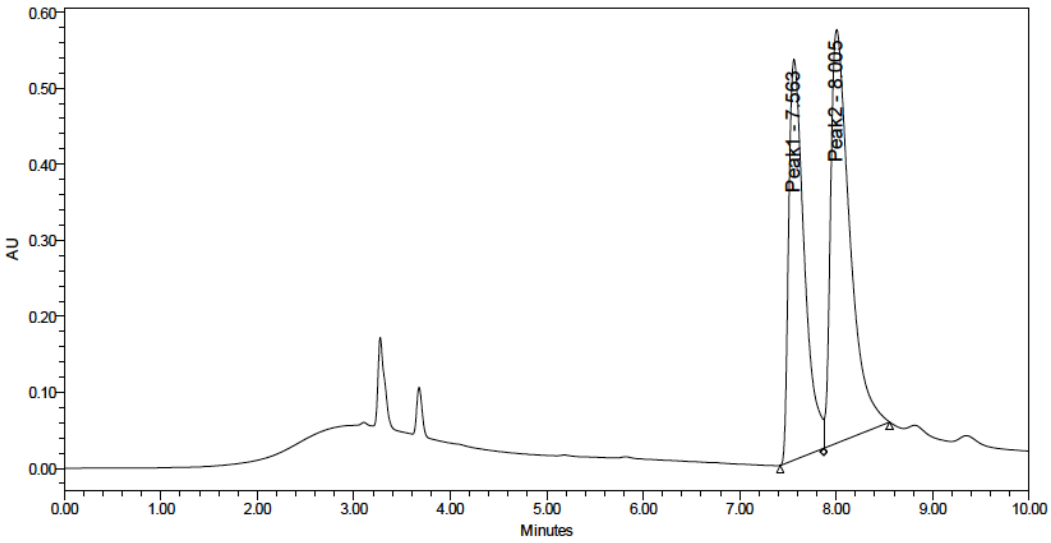


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.063	565899	42.72	65376	47.71
2	Peak2	7.473	758646	57.28	71638	52.29

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

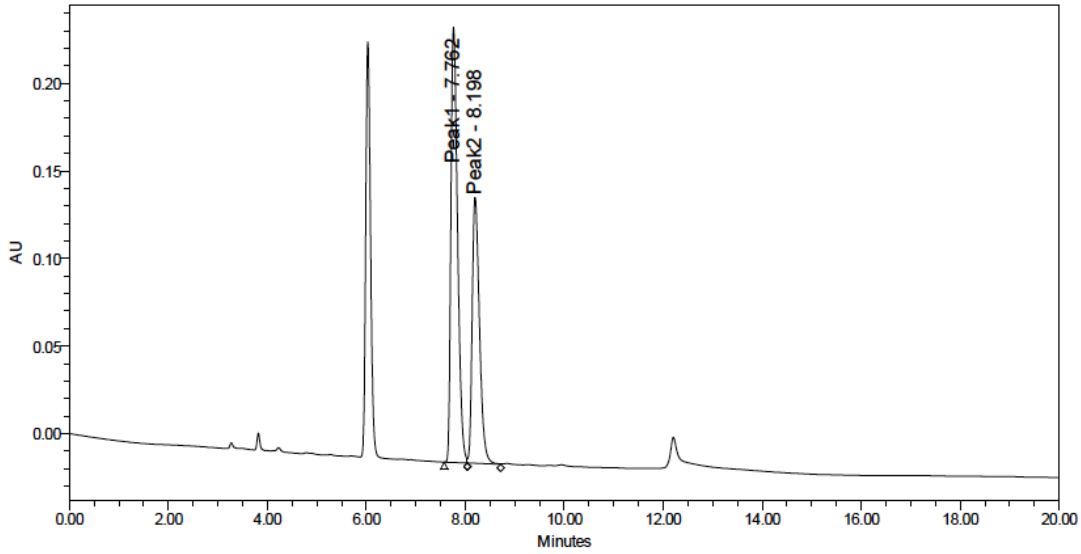


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.563	5891199	43.78	526749	49.20
2	Peak2	8.005	7565442	56.22	543824	50.80

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

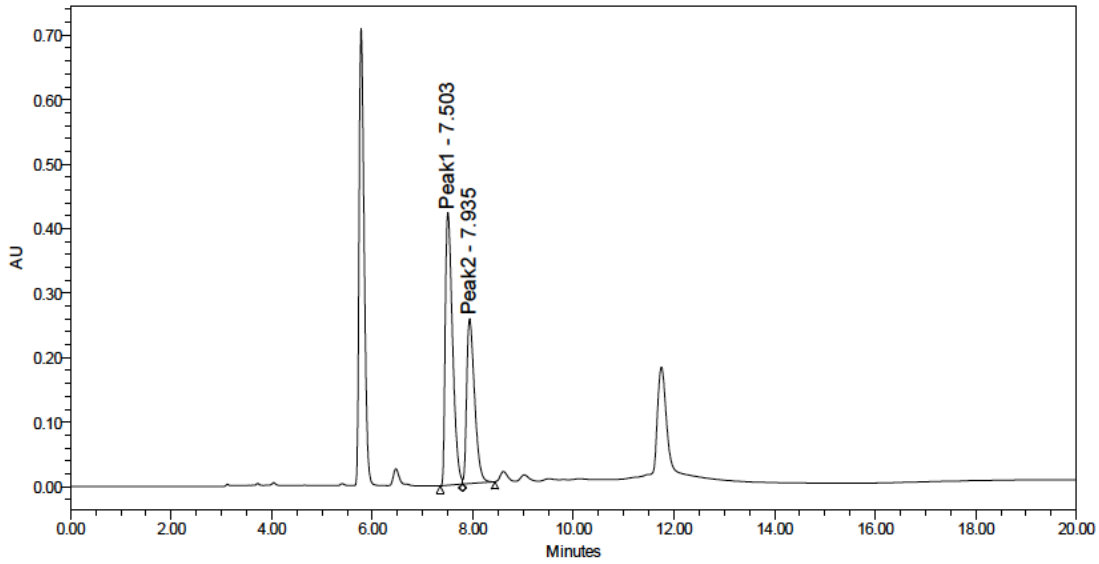


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.762	2319940	59.98	248704	62.09
2	Peak2	8.198	1548217	40.02	151862	37.91

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

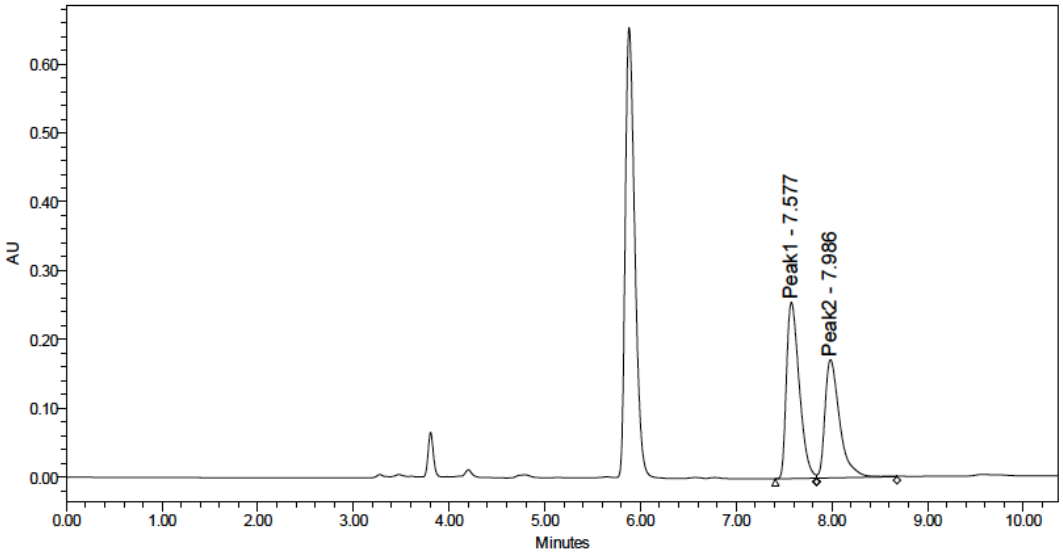


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.503	4268477	60.44	422912	62.33
2	Peak2	7.935	2793742	39.56	255645	37.67

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

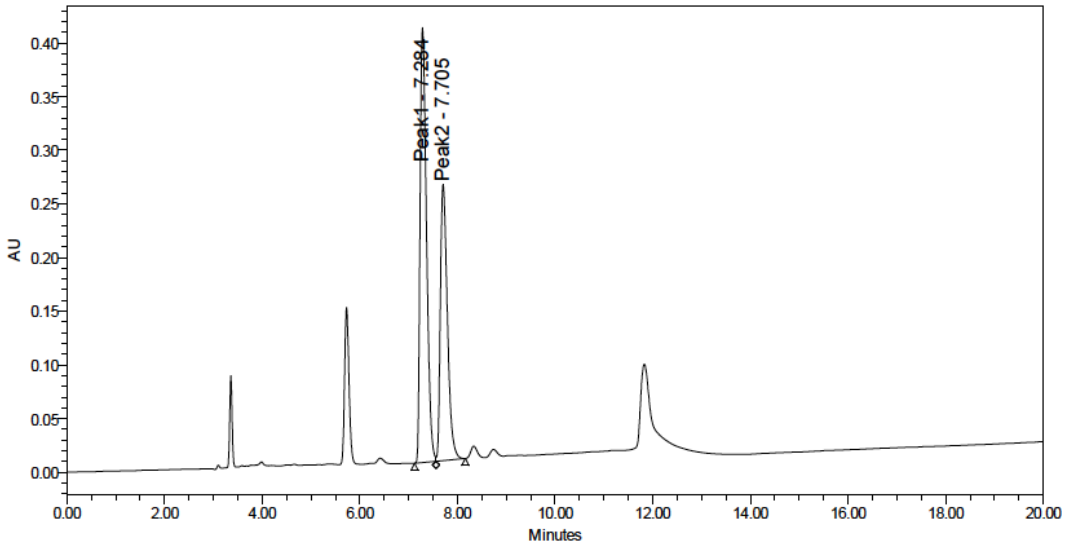


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.577	2371055	56.33	255860	59.86
2	Peak2	7.986	1838138	43.67	171599	40.14

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

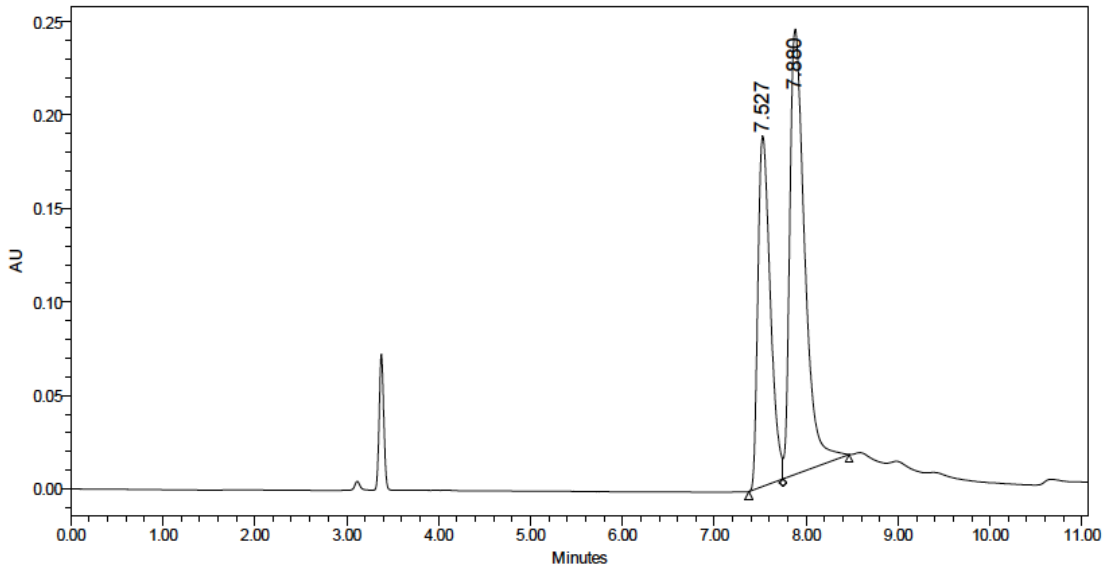


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.284	3676218	58.92	405289	61.17
2	Peak2	7.705	2563558	41.08	257220	38.83

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

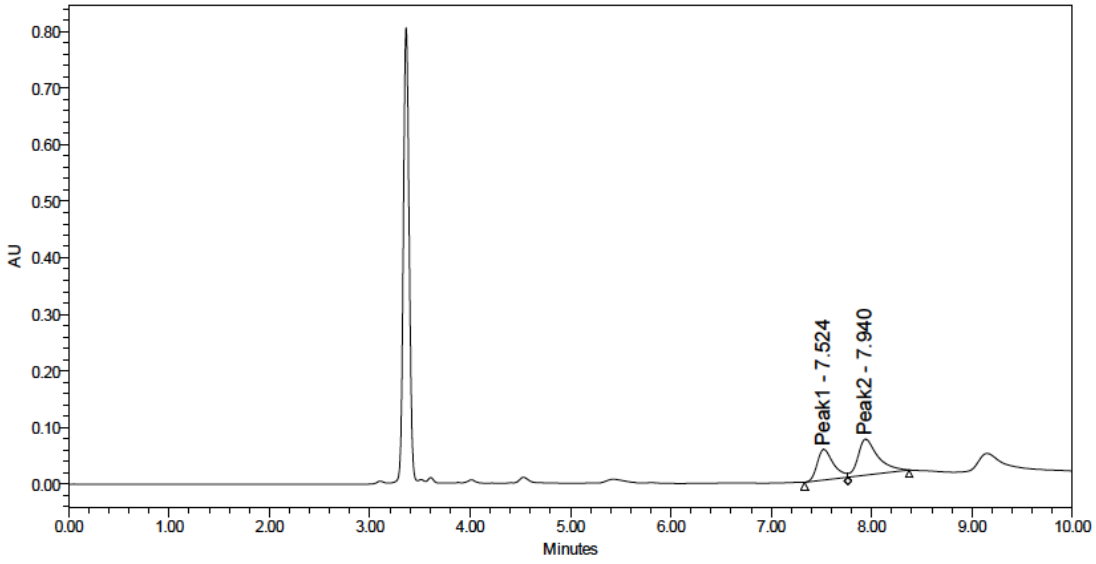


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.527	1748863	39.41	187399	44.03
2	7.880	2688581	60.59	238177	55.97

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

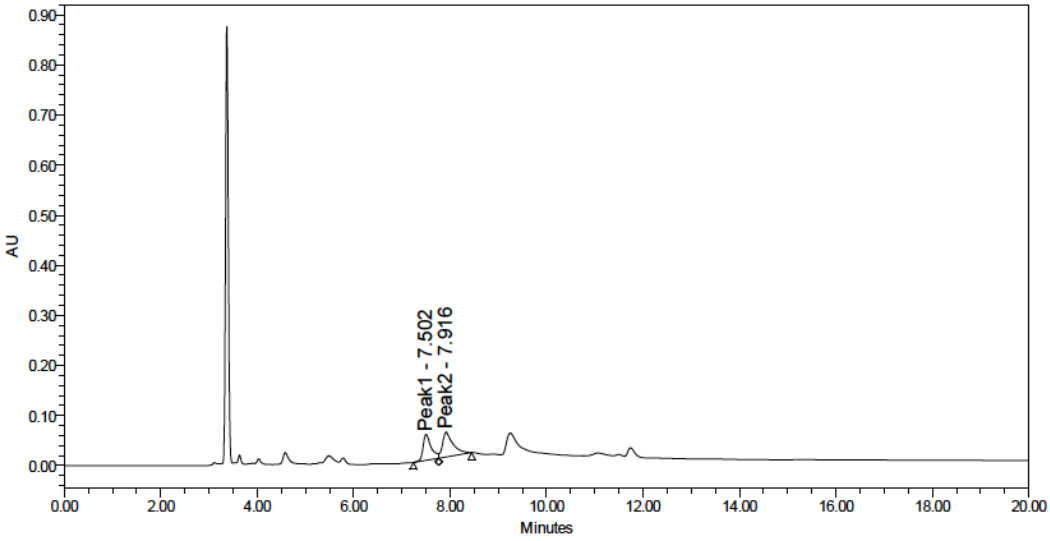


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.524	606417	40.58	54101	45.93
2	Peak2	7.940	887914	59.42	63699	54.07

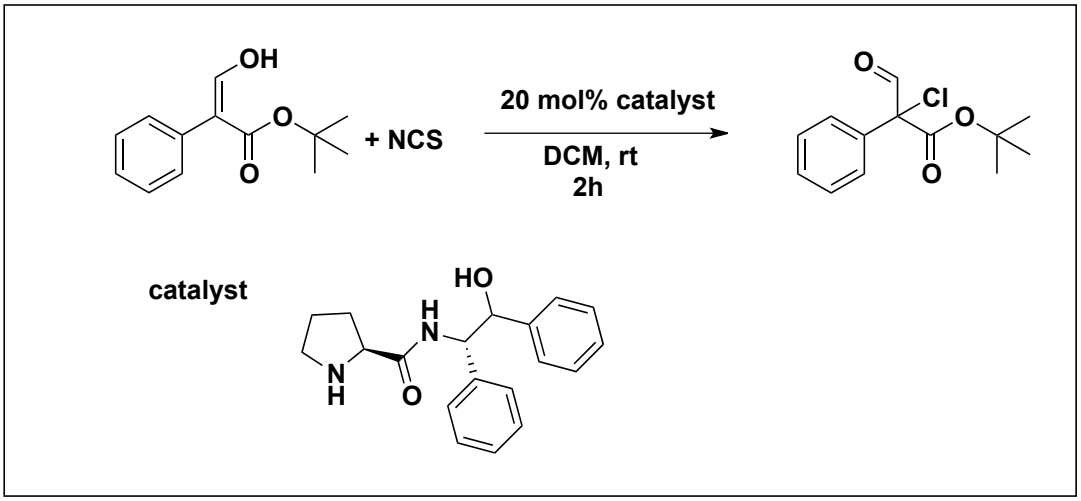
Table 17 Entry 2

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



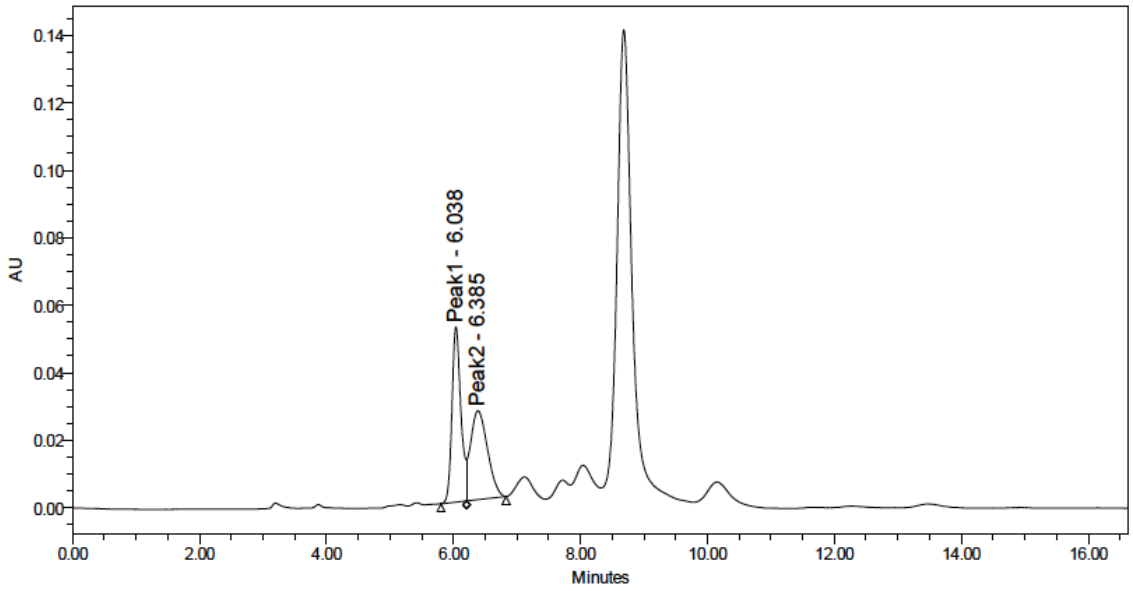
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	7.502	600795	44.53	51811	51.38
2	Peak2	7.916	748250	55.47	49019	48.62



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

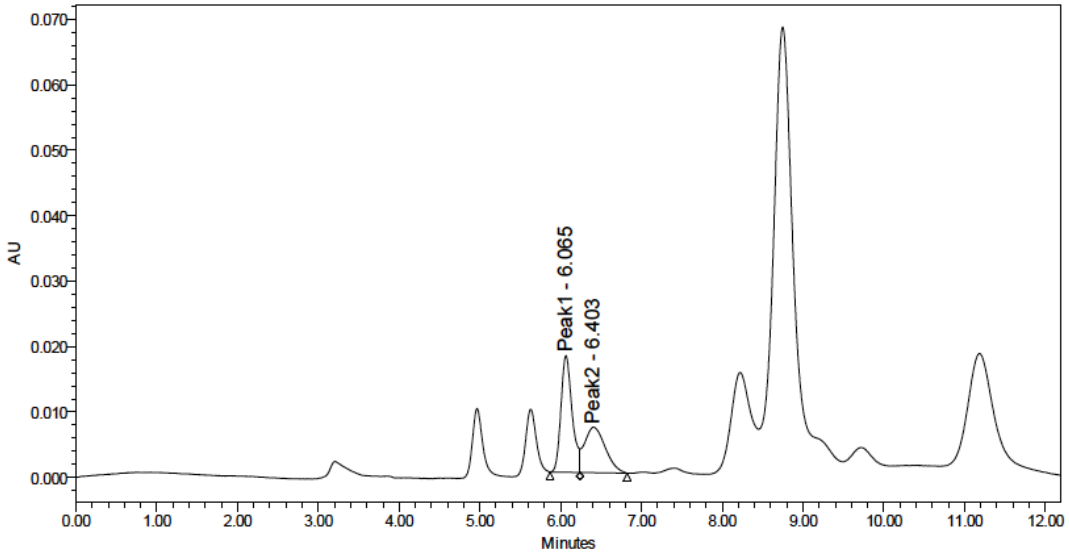


	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.038	504239	50.60	51947	66.34
2	Peak2	6.385	492289	49.40	26359	33.66

Chiral

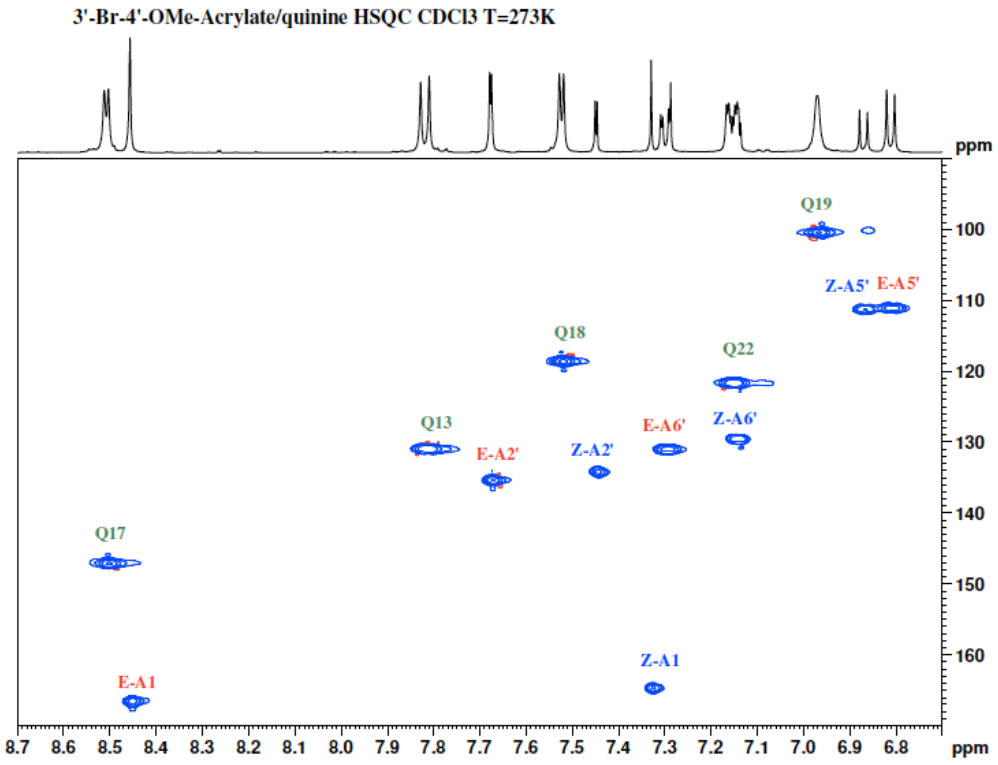
SAMPLE INFORMATION

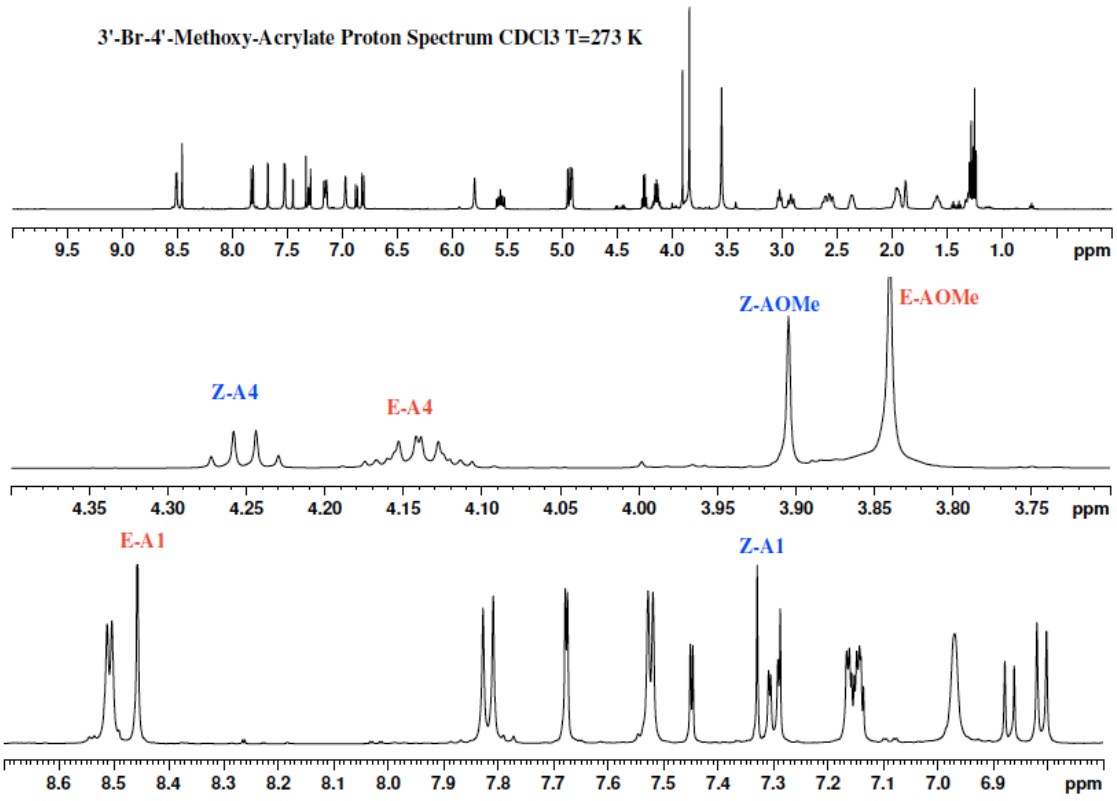
Sample Name:	Unk.	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	1/5/2014 2:09:17 PM CST
Vial:	1	Acq. Method:	tbueda
Injection #:	1	Date Processed:	1/5/2014 2:50:30 PM CST
Injection Volume:	10.00 ul	Channel Name:	219.4nm
Run Time:	20.00 Minutes	Sample Set Name	010514 tbvued chiral

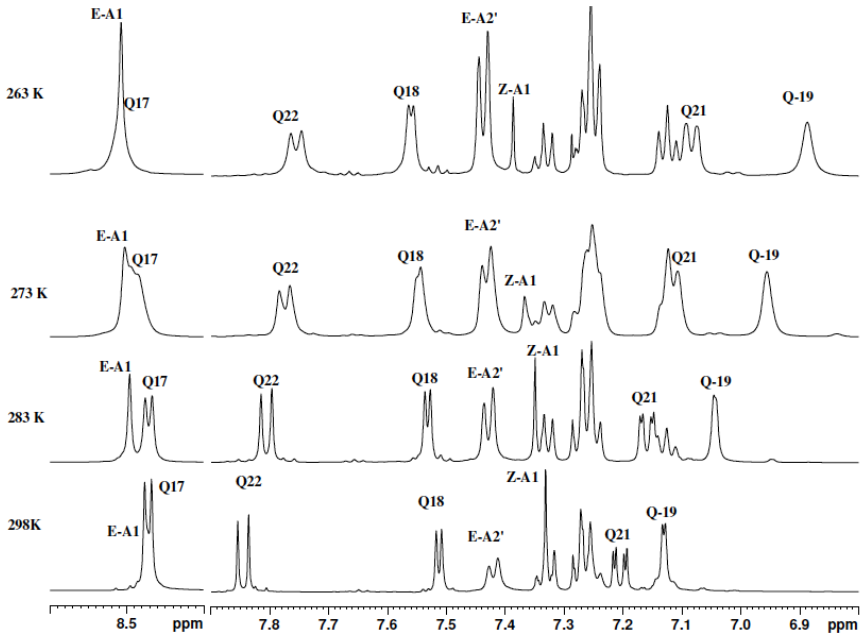


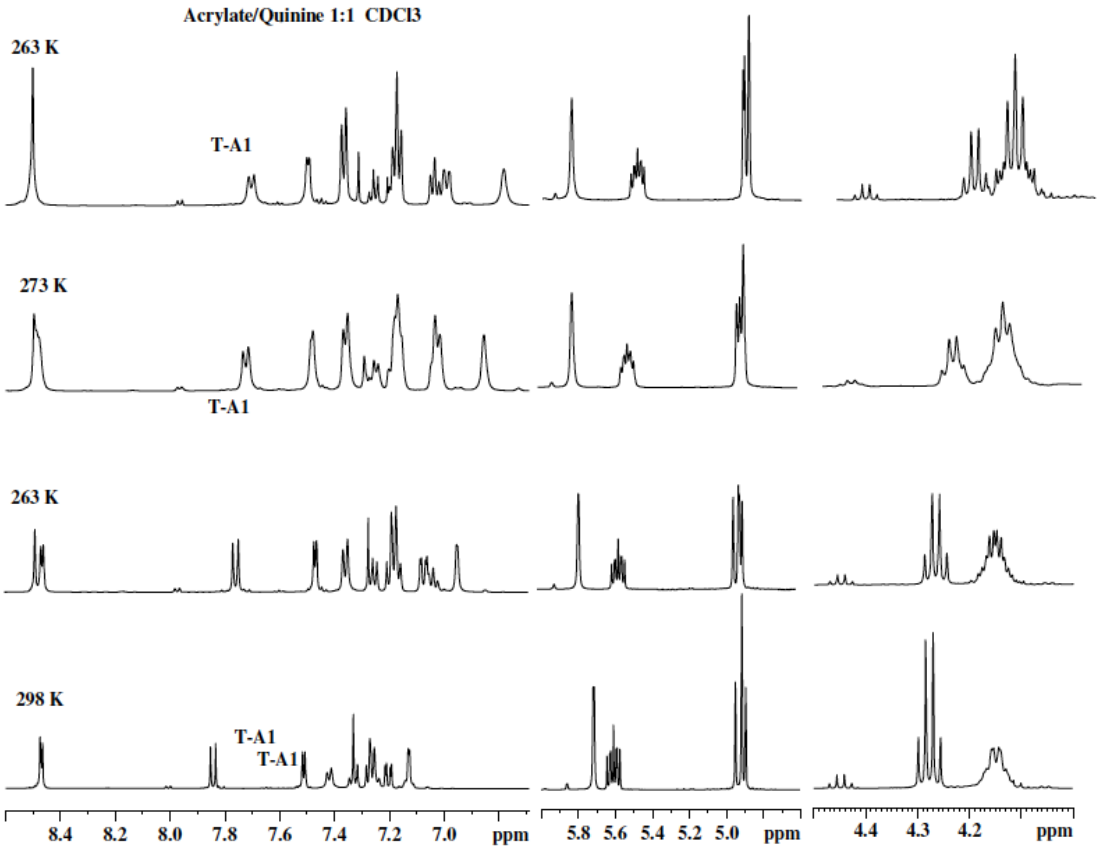
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.065	172080	58.03	17834	72.02
2	Peak2	6.403	124443	41.97	6930	27.98

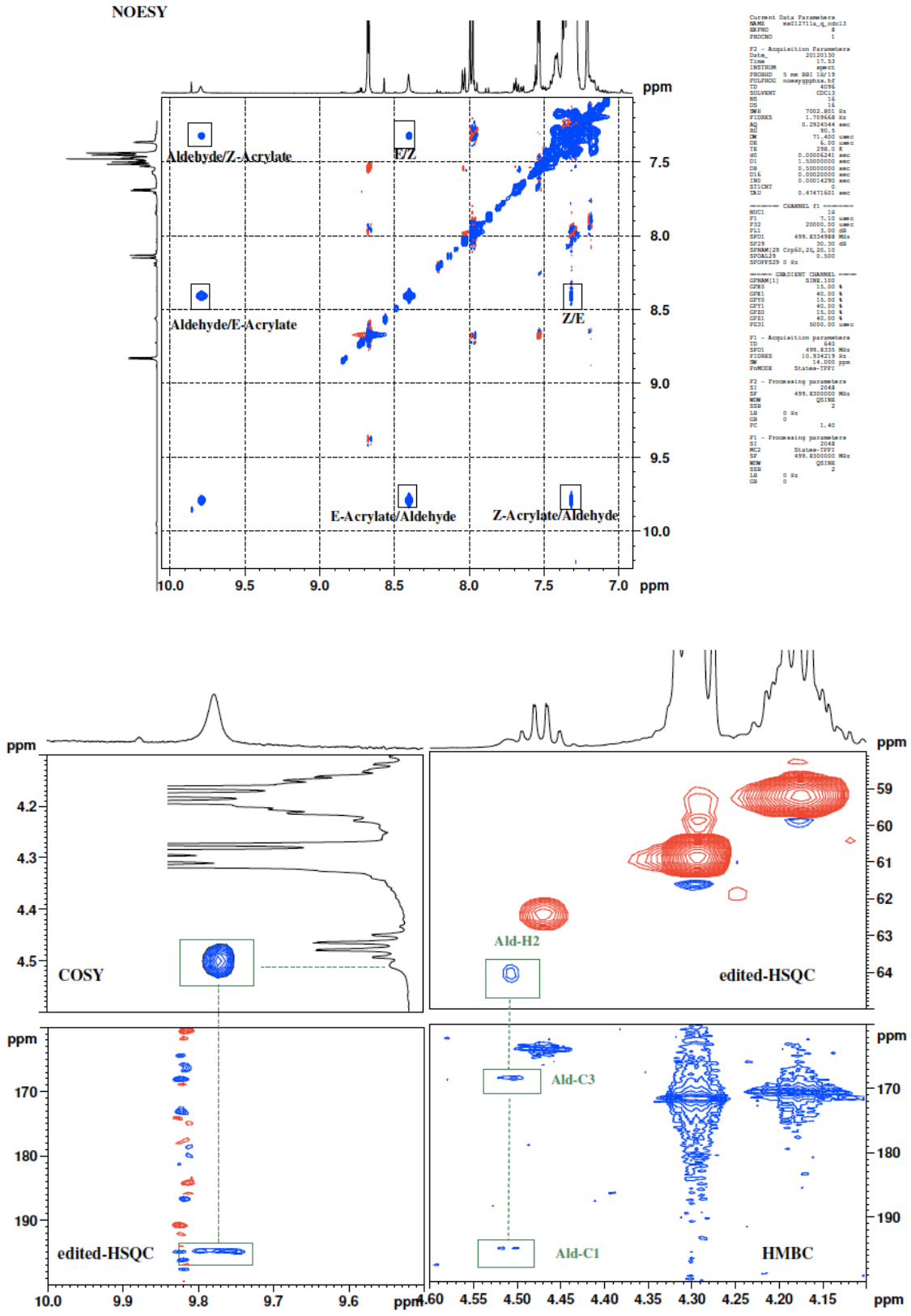
NMR Data

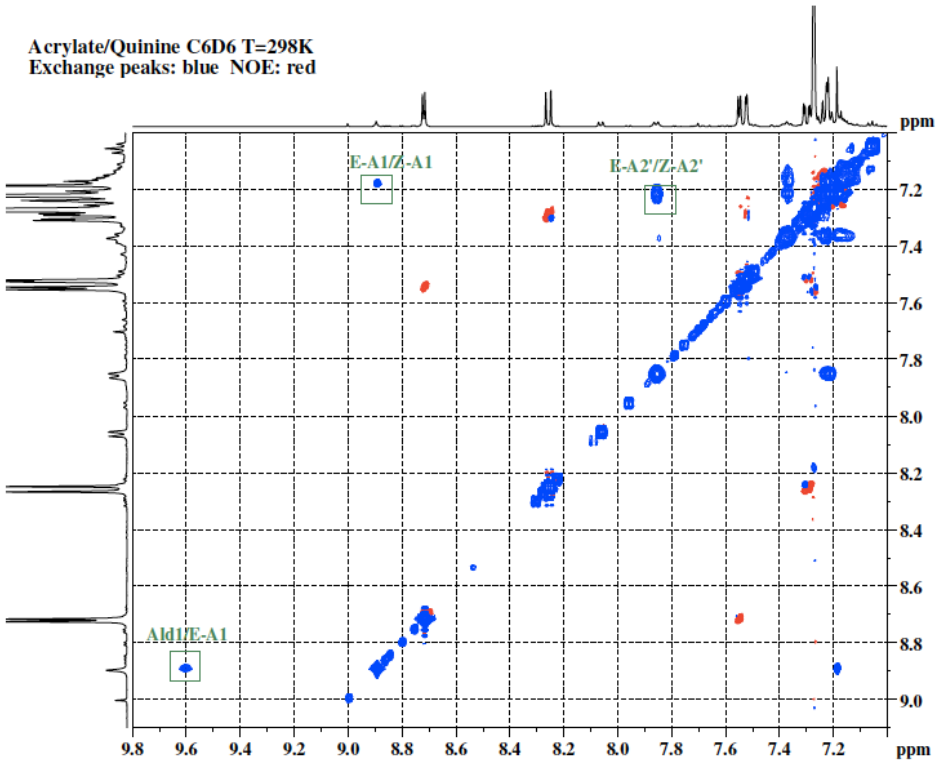

3'-Br-4'-OMe-Acrylate/quinine HSQC CDCl3 T=273K
ppm
Q19
Z-A5'
E-A5'
Q18
Q22
Q13
E-A2'
Z-A2'
E-A6'
Z-A6'
Q17
E-A1
Z-A1
8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
ppm
100
110
120
130
140
150
160

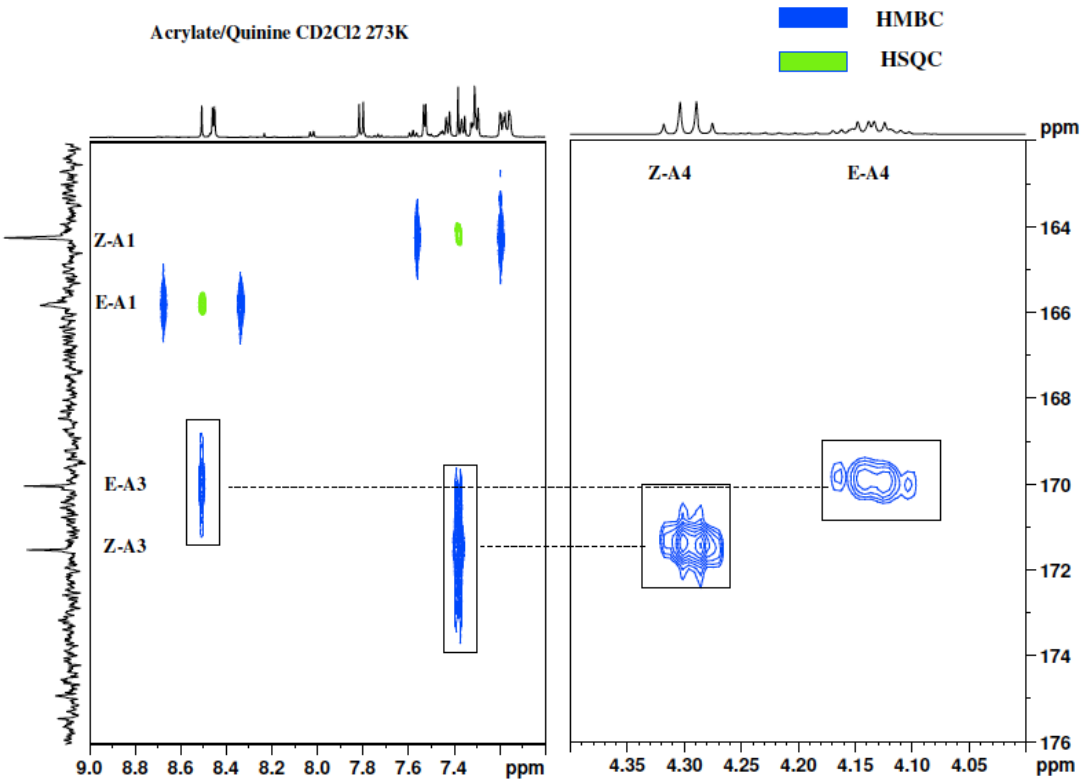

3'-Br-4'-Methoxy-Acrylate Proton Spectrum CDCl3 T=273 K
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
Z-AOMe
E-AOMe
Z-A4
E-A4
4.35 4.30 4.25 4.20 4.15 4.10 4.05 4.00 3.95 3.90 3.85 3.80 3.75
ppm
E-A1
Z-A1
8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
ppm


263 K
273 K
283 K
298K
E-A1
Q17
Q22
Q18
E-A2'
Z-A1
Q21
Q-19
8.5 ppm
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm

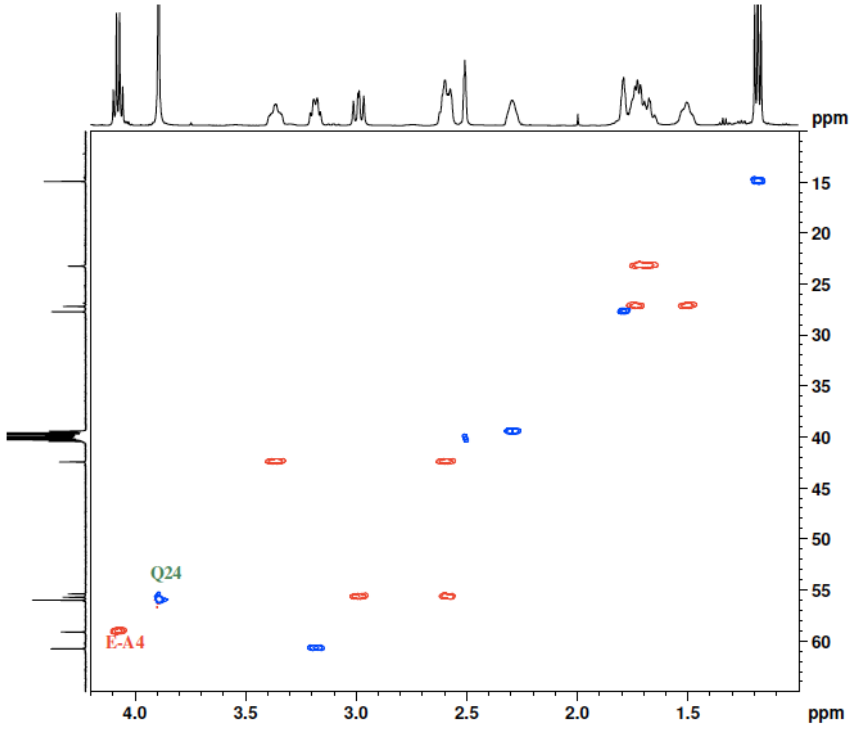

Acrylate/Quinine 1:1 CDCl3
263 K
T-A1
273 K
T-A1
263 K
298 K
T-A1
T-A1
8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 ppm
5.8 5.6 5.4 5.2 5.0 ppm
4.4 4.3 4.2 ppm


NOESY
Aldehyde/Z-Acrylate
E/Z
Aldehyde/E-Acrylate
Z/E
E-Acrylate/Aldehyde
Z-Acrylate/Aldehyde
ppm
COSY
edited-HSQC
Ald-H2
Ald-C3
Ald-C1
HMBC

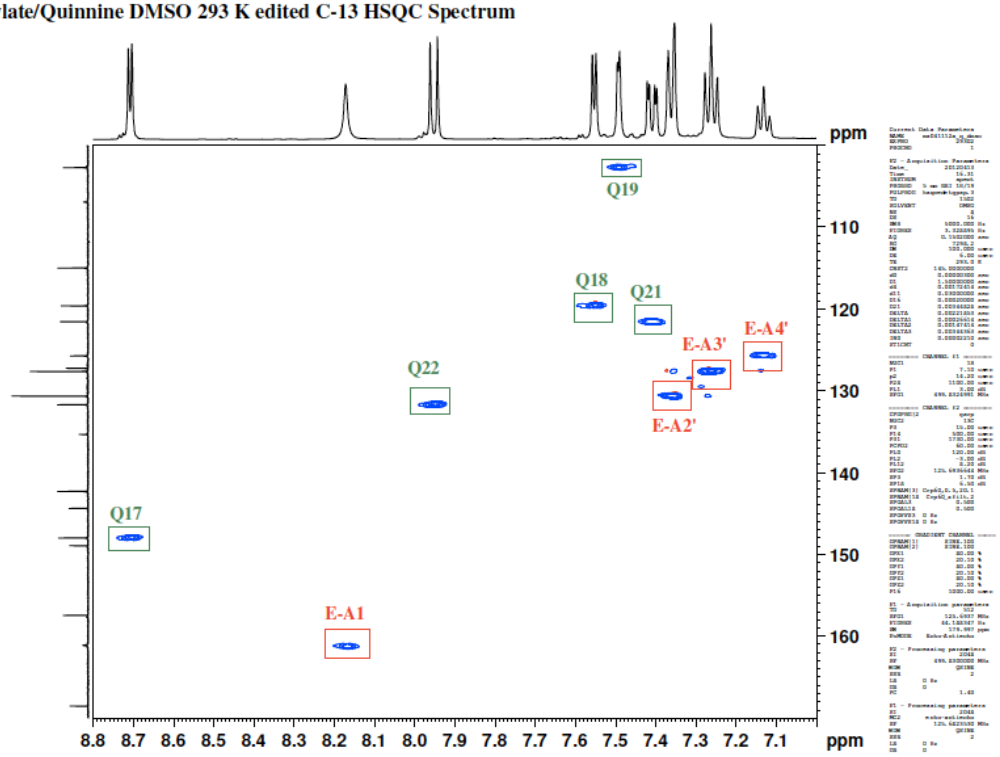

Acrylate/Quinine C6D6 T=298K
Exchange peaks: blue NOE: red
E-A1/Z-A1
E-A2'/Z-A2'
Ald1/E-A1
ppm
9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 ppm
7.2 7.4 7.6 7.8 8.0 8.2 8.4 8.6 8.8 9.0


Acrylate/Quinine CD2Cl2 273K
HMBC
HSQC
Z-A1
E-A1
E-A3
Z-A3
Z-A4
E-A4
ppm
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
4.35 4.30 4.25 4.20 4.15 4.10 4.05 ppm
164 166 168 170 172 174 176

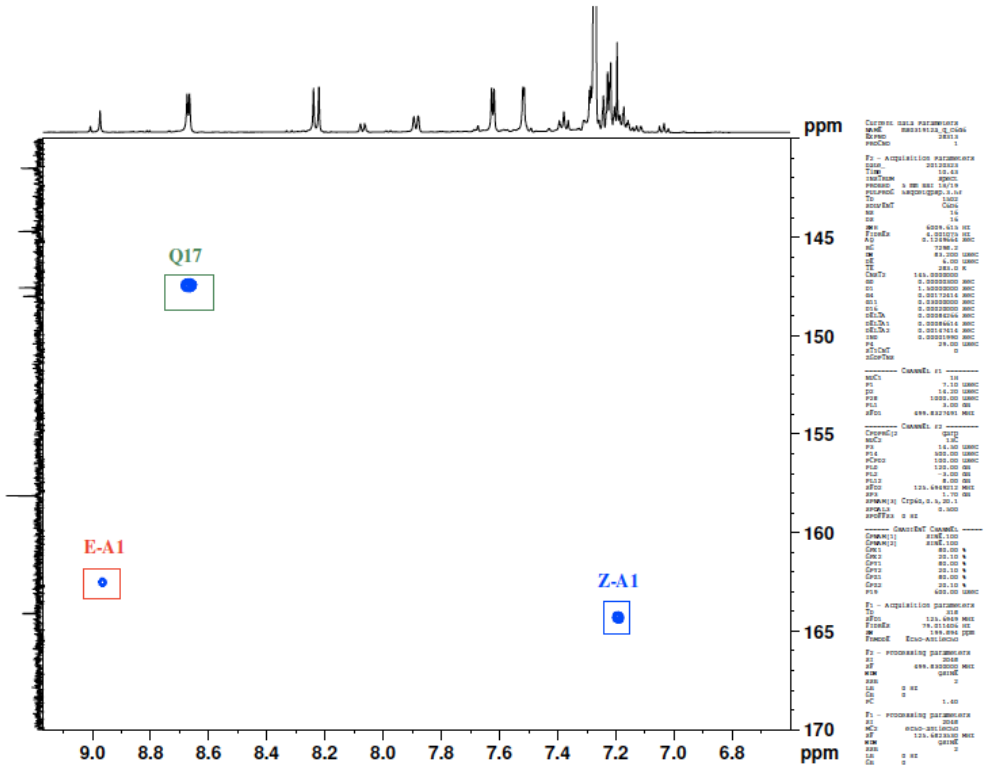
Acrylate/Quinine DMSO 293 K edited C-13 HSQC Spectrum



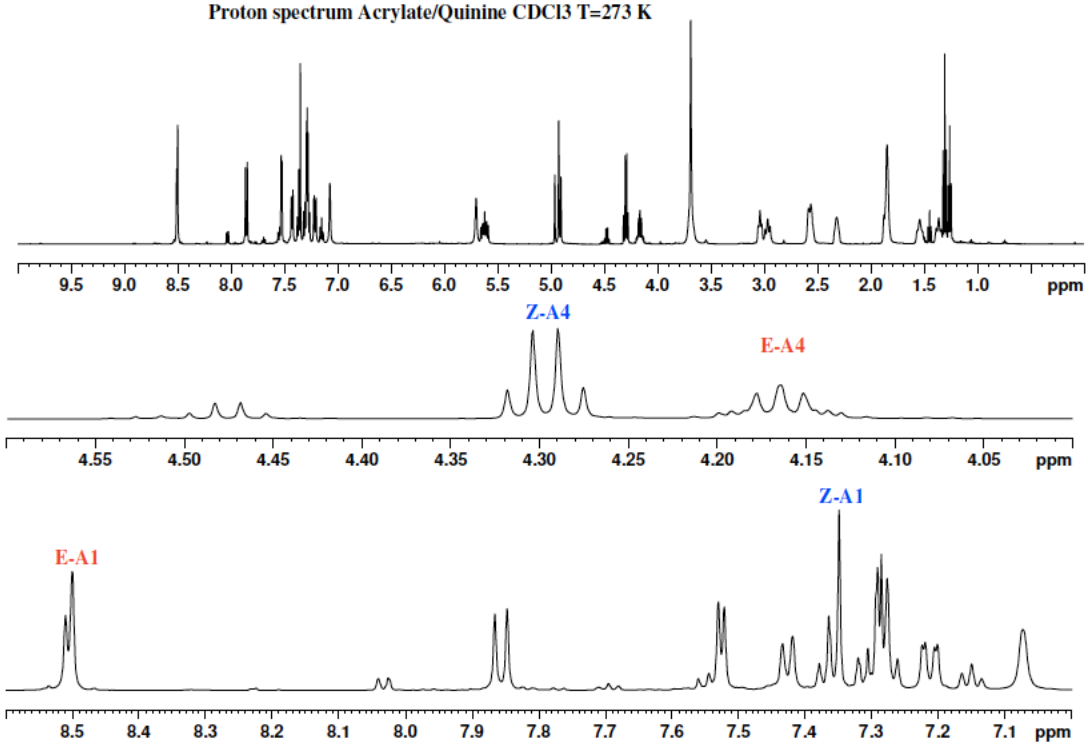
Acrylate/Quinnine DMSO 293 K edited C-13 HSQC Spectrum

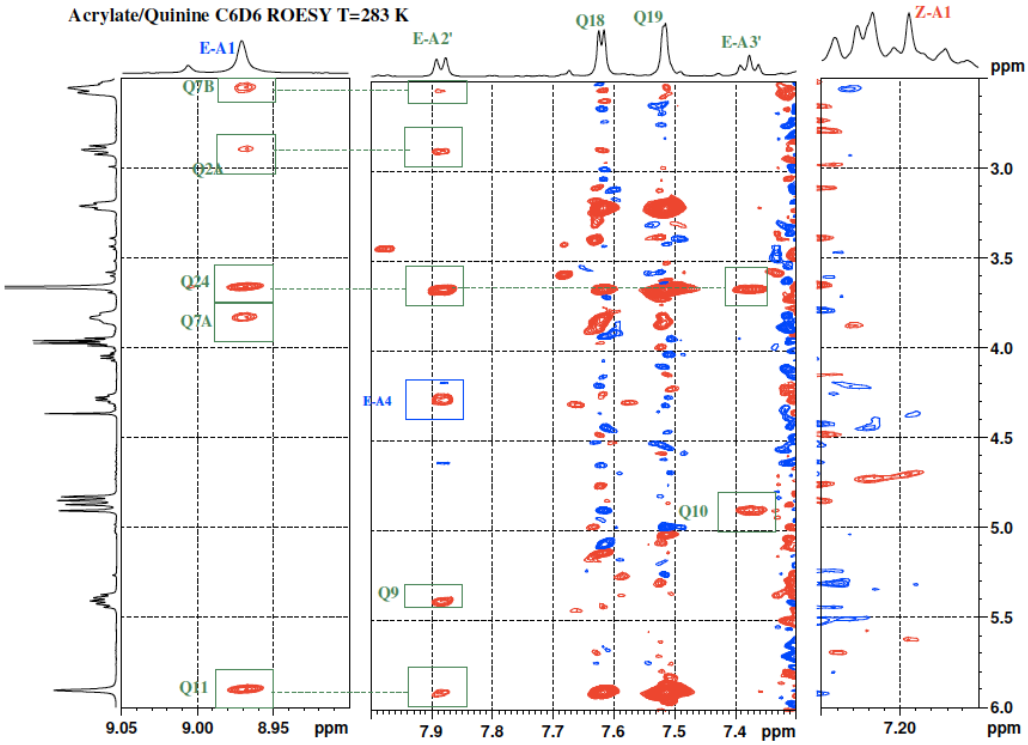


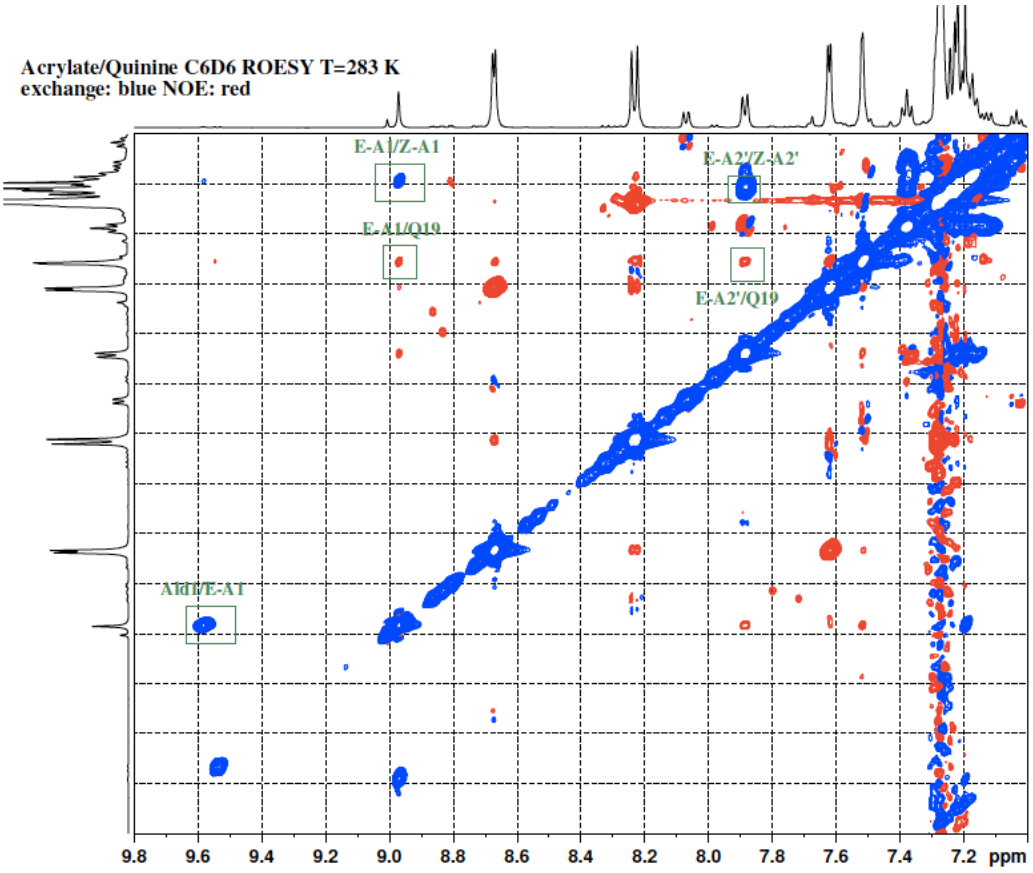
Q+A C6D6 283 K C-13 HSQC Spectrum



Proton spectrum Acrylate/Quinine CDCl3 T=273 K




Acrylate/Quinine C6D6 ROESY T=283 K
E-A1
E-A2'
Q18
Q19
E-A3'
Z-A1
Q7B
Q2a
Q24
Q7A
E-A4
Q10
Q9
Q11
ppm
9.05
9.00
8.95
7.9
7.8
7.7
7.6
7.5
7.4
7.20
3.0
3.5
4.0
4.5
5.0
5.5
6.0


Acrylate/Quinine C6D6 ROESY T=283 K
exchange: blue NOE: red
E-A1/Z-A1
E-A2'/Z-A2'
E-A1/Q19
E-A2'/Q19
AldH/E-A1
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
ppm

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. Mahmun 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 carcumin analogs
- Organized laboratory space
- Negotiated price reduction in chemical purchasing

Publications

- M. Mahmun Hossain, Eduardo Alberch, Nazim Uddin and Maria Shevyrev *ARKIVOC,* January 2011 p139-146 “Synthesis of compounds containing α-aryl quaternary carbon centers**”**
- M. Mahmun Hossain, Maria S. Shteynbuk, Frank Holger Försterling “Asymmetric α-chlorination of α-hydroxyacrylate and mechanistic studies” Manuscript in process.
- M. Mahmun 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 (^{1}H, ^{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