May 2015

I. Palladium (0)-Catalyzed Asymmetric Rearrangement of Allyl Enol Ether for the Synthesis of A -aryl Quaternary Carbon Center. II. Synthesis of Chiral Tryptophan Analogs and Studies Towards Synthesis of Tryprostatin A and B

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I. PALLADIUM (0)-CATALYZED ASYMMETRIC REARRANGEMENT OF ALLYL ENOL ETHER FOR THE SYNTHESIS OF α -ARYL QUATERNARY CARBON CENTER.

II. SYNTHESIS OF CHIRAL TRYPTOPHAN ANALOGS AND STUDIES TOWARDS SYNTHESIS OF TRYPROSTATIN A AND B.

By

Nazim Uddin

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ABSTRACT

I. PALLADIUM (0)-CATALYZED ASYMMETRIC REARRANGEMENT OF ALLYL ENOL ETHER FOR THE SYNTHESIS OF α -ARYL QUATERNARY CARBON CENTER.

II. SYNTHESIS OF CHIRAL TRYPTOPHAN ANALOGS AND STUDIES TOWARDS SYNTHESIS OF TRYPROSTATIN A AND B.

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Nazim Uddin

The University of Wisconsin - Milwaukee, 2015

Under the Supervision of Professor M. Mahmun Hossain

The development of efficient catalytic enantioselective synthesis of all carbon quaternary centers is a significant challenge in chemical synthesis due to the difficulties of carbon-carbon bond formation at quaternary center. Using phase transfer catalyst we attempted to create quaternary carbon center via direct C-alkylation of hydroxyarylacrylates, instead we obtained O-alkylated acrylates. We succeeded in C-alkylation which involves an indirect method via the O-alkylation of 3-hydroxy aryl acrylates and a subsequent [3, 3] sigmatropic rearrangement (Claisen rearrangement). The O-alkylated products are obtained in yields ranging from 65-85%, and the corresponding Claisen rearrangement products in yields ranging from 55-90%. Typically Pd(II) catalysts are used for this type of transformation. But several attempts at accomplishing an asymmetric Claisen rearrangement using metal Lewis acid catalysis failed due to insufficient activation of the Claisen substrate. Herein, we report the creation of all carbon stereocenters

starting from 3-hydroxyarylacrylates modified allyl enol ether rearrangement reaction. We believe this is the first example of allyl enol ether rearrangement employing Pd(0) catalysts. The rearrangement reaction analogs takes place in excellent yields ranging from 80-95% and enantioselectivity ranging from 50-90% ee.

Asymmetric synthesis of indole alkaloids is a major area in organic synthesis. Synthesis of chiral Tryptophans and its unnatural analogs has immense importance as they are building blocks for many natural products. Herein we describe the enantiospecific synthesis of ring-A substituted tryptophan derivatives from commercially available gramines using chiral phase transfer conditions. This one-pot reaction avoids protecting/de-protecting the indolylic nitrogen of gramine by choosing a chemoselective quaternization reagent, 4-(trifluoromethoxy)benzyl bromide to produce an electrophilic salt intermediate, which is subsequently alkylated in good yield and high %ee. In an application of chiral tryptophans we attempted to synthesize tryprostatins. Tryprostatins are potent cancer drug, tryptostatin A reverses the resistance of cancer cells against antitumor drugs by arresting cell cycle progression at the G2/M phase. We have been able to make tryprostatin B using our proposed synthesis scheme, where one of the key intermediate is C-2 alkylated chiral tryptophan. Several challenges in the synthesis protocol and optimization of the chiral phase transfer catalyzed reaction are described.

I dedicate this thesis to my parents.

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LIST OF ABBREVIATIONS

EDA	Ethyl diazoacetate
TBAI	Tetrabutylammonium iodide
PTC	Phase transfer catalyst
TLC	Thin layer chromatography
LiHMDS	Lithium bis(trimethylsilyl)amide
NaHMDS	Sodium bis(trimethylsilyl)amide
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Box	Bis-oxazolines
TFA	Trifluoroacetic acid
Eq.	Equivalents
EtOAc	Ethyl acetate
DCM	Dichloromethane
Tol.	Toluene
DME	1,2-dimethoxyethane
rt	Room temperature
sat.	Saturated
conc.	Concentrated
temp.	Temperature

ee	Enantiomeric excess
dr	Diastereomeric ratio
AVE	Allyl vinyl ether
AAA	Asymmetric allylic alkylation
DcA	Decarboxylative allylation
DAAA	Decarboxylative asymmetric allylic alkylation
NCS	N-chlorosuccinimide
MIDA	N-methyliminodiacetic acid
TMS	Trimethylsilyl
TES	Triethylsilyl
TBS	Tert-butylsilyl
TIPS	Triisopropylsily
DNPH	2,4-Dinitrophenylhydrazine
FOD	7,7,-dimethyl-1,1,2,2,2,3,3-heptafluoroocta-7,7-dimethyl-4,6-dionato
DPPBA	Diphenylphosphino benzoic acid

ACKNOWLEDGEMENTS

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I am very thankful to my parents for their encouragement, love and support throughout my life. Thank you both for giving me strength to pursue my goals and chase my dreams. My brothers, Khokon, Azim and Atique deserve my wholehearted thanks as well. Special thanks to my friend Momen, for the last couple of years his presence at UWM have made my graduate student life more bearable.

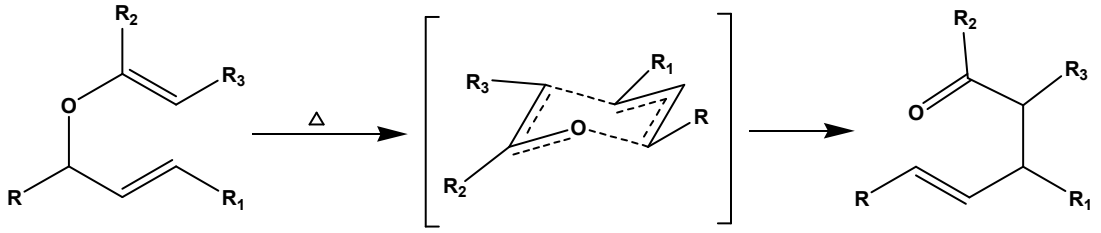
Finally, my wife Lutfun Naher and my son Rohan were a constant support throughout the process of my studies in Milwaukee. It would not have been possible without their support and patience, they were a great source of encouragement in my staying abroad and continuing my studies.

I. PALLADIUM (0)-CATALYZED ASYMMETRIC REARRANGEMENT OF ALLYL ENOL ETHER FOR THE SYNTHESIS OF α -ARYL QUATERNARY CARBON CENTER.

CHAPTER 1. CLAISEN REARRANGEMENT AS A ROUTE TO QUATERNARY STEREOCENTERS.

1.1.1. Introduction

The [3,3] sigmatropic rearrangement of allyl enol ethers for the formation γ,δ-enones is known as the *Claisen* rearrangement.[1] This reaction was discovered over 100 years ago [2] and it has proven to be a powerful tool in the arsenal of the organic chemist. The Claisen reaction is mechanistically analogous to the Cope rearrangement. The Claisen Rearrangement may be viewed as the oxa-variant of the Cope Rearrangement. Both the Claisen and Cope rearrangements are known procedures to create defined tertiary and quaternary carbon centers as well as carbon-heteroatom bonds. Between these two reaction types, the Claisen rearrangement is the most used [3,3]-sigmatropic rearrangement because of the facile synthesis of the allyl enol ether system. Due to the smooth and frequently irreversible product formation this reaction is widely applicable for the synthesis of numerous organic intermediates. The [3,3] sigmatropic rearrangement is characterized by a highly ordered transition state where the repulsive interactions are minimized (Scheme 1). The reaction proceeds preferably *via* a chair transition state.



Scheme 1. Transition state for Claisen rearrangement.

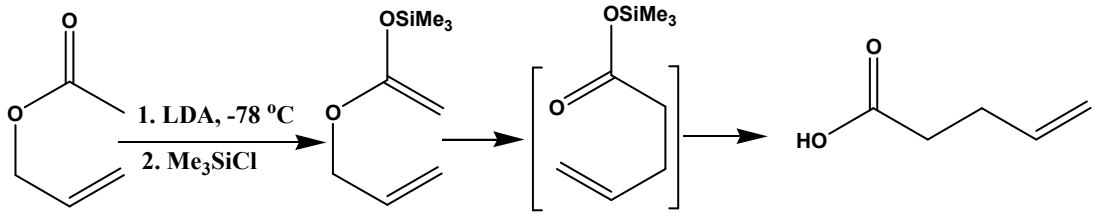
As a result of the highly ordered nature of the six membered transition state, predictions are possible on the stereochemical outcome of the reaction based on the stereochemistry at the double bond. In general, chiral, enantiomerically enriched starting materials give products of high optical purity.

Over the years the usefulness of the Claisen rearrangement has been realized and the reaction has drawn the attention of several research groups, which has been reflected in the large numbers of papers published in the literature on this reaction.[3] Because the product is a carbonyl compound, the equilibrium is usually favorable for product formation.

Most of the uncatalyzed Claisen Rearrangement reactions described to date require temperatures of > 100 °C. The observation that electron withdrawing groups at C-1 of the vinyl moiety exert a positive influence on the reaction rate and the yield has led to the development of the following variations:

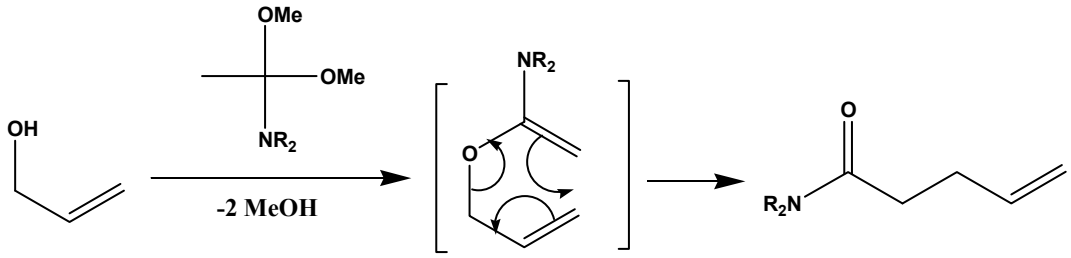
Ireland Claisen Rearrangement: This moderate variation of the Claisen rearrangement utilizes the allyl ester of a carboxylic acid instead of an allyl enol ether (Scheme 2). The ester is changed to its silyl-stabilized enolate, which rearranges at temperatures below 100 °C. The direct product of the

rearrangement, a carboxylic acid silyl ester, cannot be separated and is hydrolyzed during workup. The Ireland-Claisen Rearrangement thus presents ready access to chain-extended carboxylic acids.



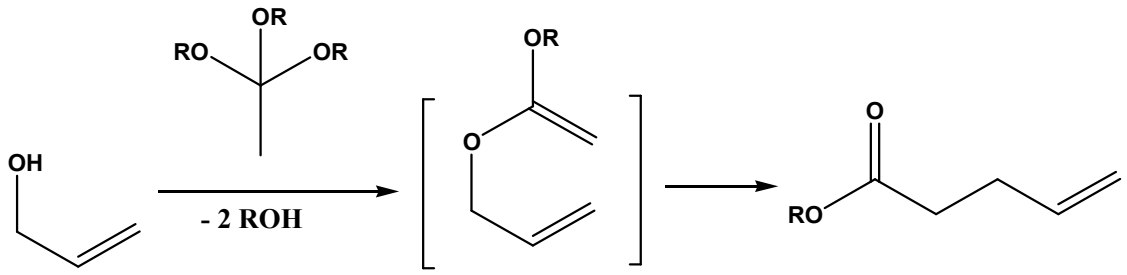
Scheme 2. Ireland-Claisen rearrangement.

The Eschenmoser–Claisen rearrangement : This reaction proceeds from an allylic alcohol to a γ,δ-unsaturated amide, and was developed by Albert Eschenmoser in 1964 (Scheme 3).



Scheme 3. Eschenmoser–Claisen rearrangement.

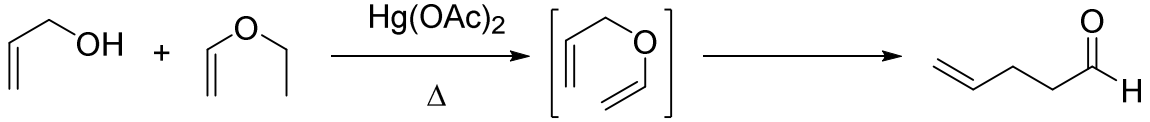
Johnson–Claisen rearrangement: is the reaction of an allylic alcohol with an orthoester containing a deprotonatable alpha carbon (e.g. triethyl orthoacetate) to give an γ,δ-unsaturated ester (Scheme 3).



Scheme 4. Johnson-Claisen rearrangement.

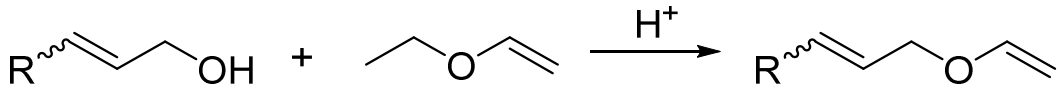
1.1.2. Synthesis of allyl enol ethers

In the literature there have been several efficient procedures developed to synthesize the required allyl enol ethers have been developed such as the enol ether Claisen, the Johnson orthoester Claisen, and the Ireland silyl ketene acetal Claisen. The reactants for the Claisen rearrangement can be made from allylic alcohols by mercuric ion-catalyzed exchange with ethyl vinyl ether.[4] The allyl vinyl ether does not necessarily have to be isolated but is usually prepared under conditions which lead to its rearrangement. The simplest of all Claisen rearrangements, the conversion of allyl enol ether to 4-pentenal, exemplifies this process (Scheme 5).



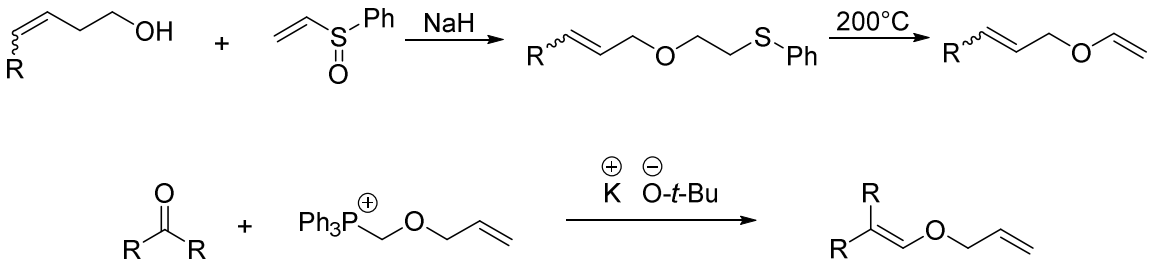
Scheme 5. In situ formation of allyl enol ether followed by Claisen rearrangement.

Acid catalyzed cleavage can also be used to prepare the vinyl ethers (Scheme 6):



Scheme 6. Preparation of allyl enol ethers through acid catalyzed cleavage.

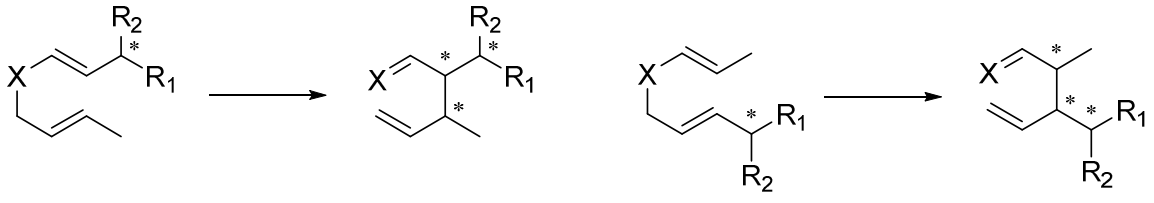
Allyl enol ethers can also be generated by thermal elimination reactions. For instance, base-catalyzed conjugate addition of allyl alcohols to phenyl vinyl sulfone generates 2-(phenylsulfinyl)ethyl ethers, which can undergo elimination at 200°C, and it is at this temperature that the [3,3] rearrangement proceeds. Allyl enol ethers have also been prepared by Wittig reactions using ylides generated from allyloxymethylphosphonium salts (Scheme 7).



Scheme 7. Preparation of allyl enol ethers through the Wittig reaction.

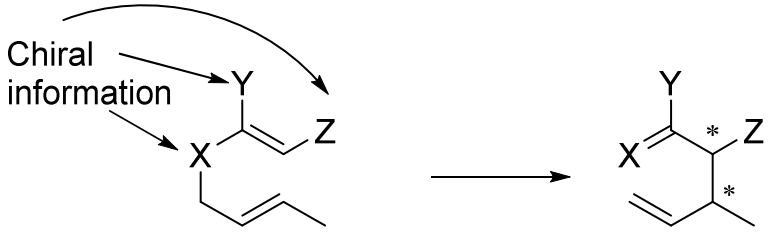
1.1.3. Asymmetric Claisen rearrangement

In order to make chiral Claisen rearrangement products using an asymmetric route there are several possibilities. If no external asymmetric induction is applied, the enantiomers can be separated via resolution but this method suffers from the disadvantage of losing half of the unwanted enantiomer, which is highly undesirable. The first option is to transfer chirality from either the allylic or vinylic fragment of the allyl enol ether to the chiral carbon through a complete [1,3]-chirality transfer (remote stereocontrol), although other positions in the allyl enol ether substrate have also be used to transfer the chirality. Alternatively, more than one chiral center can be used to transfer the stereochemical information. The chiral allylic fragment can be obtained by such well known processes like the Sharpless asymmetric epoxidation[5], enantioselective reduction of carbonyl compounds[6]and enzymatic processes.[7] In the diastereoselective reaction proceeding through remote stereocontrol the chiral center is usually present present to position one and six (Scheme 8).



Scheme 8. Diastereoselective reaction proceeding through remote stereocontrol.

Secondly, the asymmetric induction can be achieved through the use of a chiral auxiliary. A survey of literature reveals the prevalence of the chiral auxiliary in three main positions of the allyl enol ether (Scheme 9).

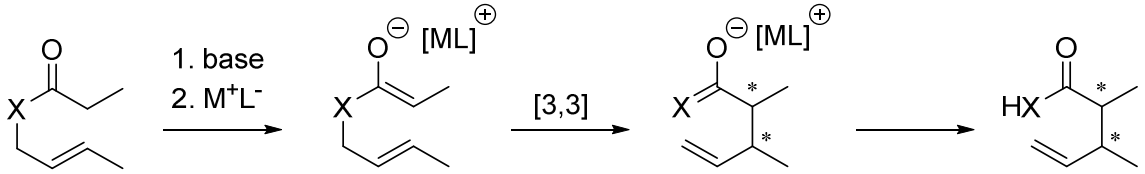


Positions of covalently bound chiral auxiliaries

Scheme 9. Use of chiral auxiliary for Asymmetric induction in Claisen rearrangement reaction.

Thirdly, chiral catalyst can be used to achieve asymmetric induction. Although there are many reports in the literature for examples that use stoichiometric quantities of catalyst, the use of catalytic quantities has thus far not found extensive application and is limited to particular types of substrate class. In the former case, where stoichiometric amounts are needed has usually been used in the ester and amide enolate Claisen rearrangement. The ester or amide substrate is reacted with a strong base at low temperature, forming the allyl enol ether Claisen substrate in situ. Next, a Lewis acid together with the corresponding chiral ligand is added which coordinates with the oxygen of the in situ formed enolate (Scheme 10). One of the limitation of this reaction is an equimolar quantities of chiral Lewis acid complexes need to be added, which is necessary y because the metal complex binds more strongly to the carbonyl product than to the starting

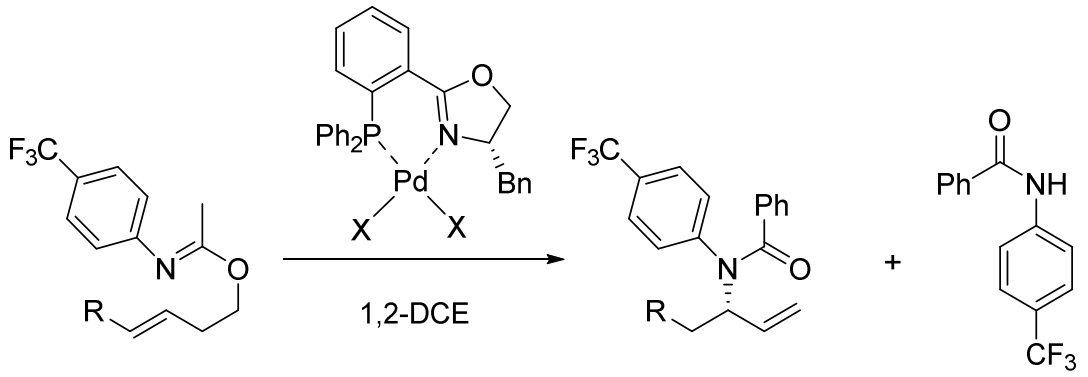
material. Therefore, the reason for the scarcity of examples in the literature for reaction that employ *catalytic* quantities of Lewis acid.



Scheme 10. Lewis acid catalyzed ester enolate Claisen rearrangement.

1.1.4. Asymmetric catalytic Claisen rearrangement

Overman et al.[8] reported the first examples of a truly catalytic reaction of the conversion of allyl amidates into the corresponding carbamates employing chiral palladium catalysts. A series of chiral oxazoline substituted ligands were tested by Uozumi and Hayashi in the palladium (II)-catalyzed rearrangement of a *N*-(4-(trifluoromethyl) phenyl)[i] substituted allyl imidate (Scheme11).

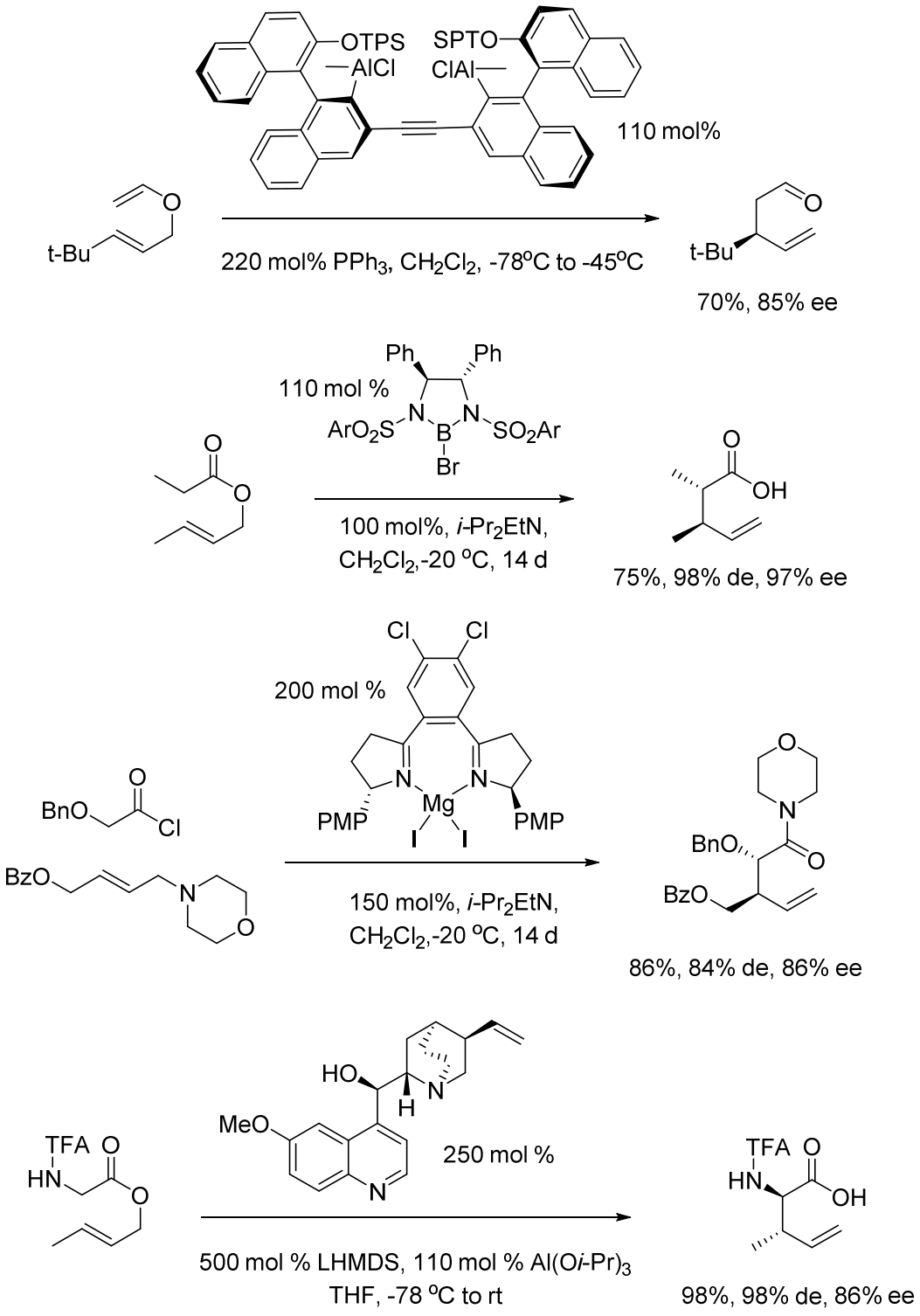


R = *n*Pr	83°C	81% (70% ee)	0%
R = *n*Pr	40°C	41% (76% ee)	3%
R = *i*Pr	83°C	30% (81% ee)	37%

Scheme11. First example of catalytic conversion of allyl amidates to carbamates.

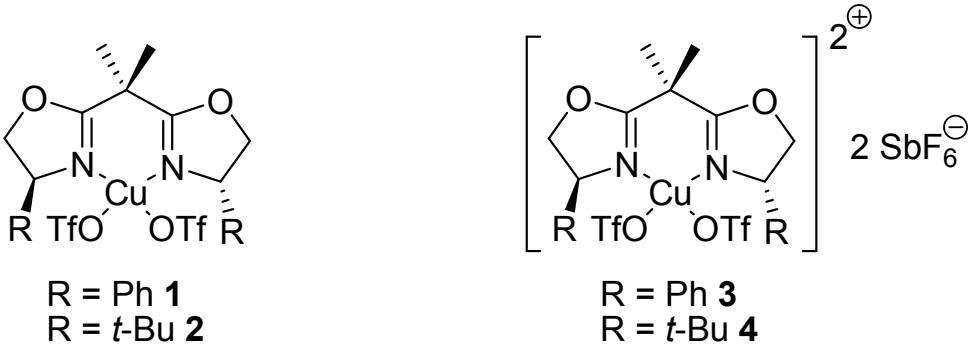
Achiral Al (III) Lewis acids are able to accelerate the aliphatic Claisen rearrangement, however, their applicability as catalysts is prevented by product inhibition.[10] Al (III), B (III), and Mg (II) *chiral* Lewis acid complexes have been efficient for the asymmetric reaction but have not found applicability for a catalytic version of the reaction.[11] Interestingly, quinine was used in more than stoichiometric amounts as a chiral base to effect an asymmetric Ireland-Claisen rearrangement (Scheme 12).[12]

A small number of catalytic *achiral* metal catalysts that speed up the Claisen rearrangement have been reported, for example Pd(II) complexes,[13] lanthanide (III) complexes [14]and $TiCl_4$[15]. In both metal promoted and metal catalyzed Claisen rearrangement reaction, substituents on allyl enol ether have a dramatic effect on the rate of rearrangement. Lewis acid catalysts are substrate specific, if one metal Lewis acid is found to catalyze the Claisen rearrangement of a specific allyl enol ether substrate, this does not make it suitable as a catalyst for a varied range of allyl enol ether substrates. Consequently, substrate structure, the nature of the Lewis acid and associated ligands along with the structure of the product have to be adjusted carefully to achieve effective metal catalysis and avoid side reactions such as ionization [16] and/or product inhibition of the catalyst.



Scheme 12. Asymmetric Claisen rearrangements by Al (III), Mg (II), quinine and Boron catalyst.

In 2001 Hiersemann et al. reported a catalytic version of the Claisen rearrangement of simple allyl enol ether, the findings that several metal triflates, such as $Cu(OTf)_2$, Lanthanide$(OTf)_3$ and $Sc(OTf)_3$, catalyzed the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl enol ethers.[17] The asymmetric version of the similar transformation catalyzed by Cu^{2+} complexes followed soon afterwards. [18] The recognition of $Cu(OTf)_2$ as an capable catalyst led to the report of the very first asymmetric catalytic Claisen rearrangement using the well celebrated chiral copper(II) bis(oxazolines) (Figure13).

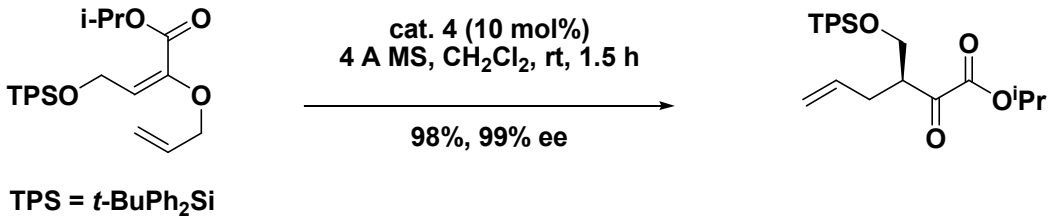


R = Ph **1**
R = *t*-Bu **2**

R = Ph **3**
R = *t*-Bu **4**

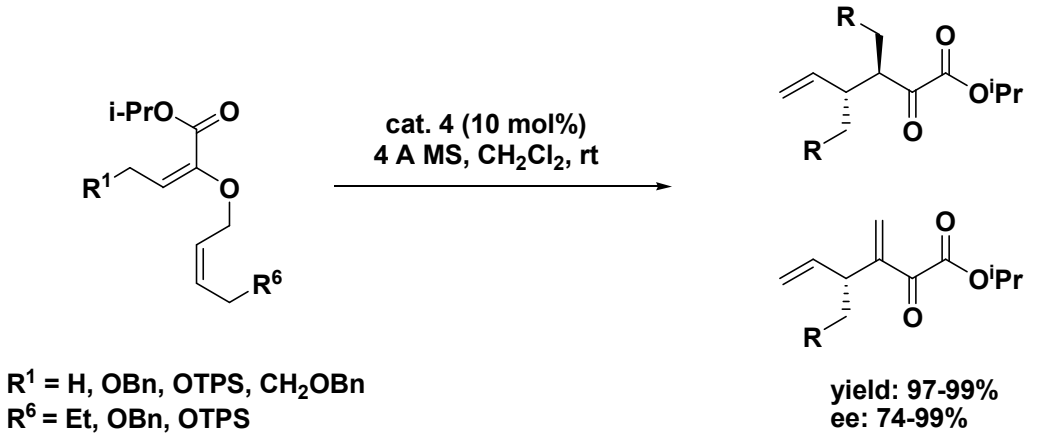
Figure 1 . Chiral copper (II) bis(oxazolines) catalysts for asymmetric Claisen rearrangement.

By means of this method enantiomeric excess values were reported in the range 80-90%. Additional studies into the substrate scope of the Claisen rearrangement with the aforesaid 2-alkoxycarbonyl-substituted allyl enol ethers led to the discovery that the known bench stable [Cu{(*S*,*S*)-*t*-Bu-box}]$(H_2O)(SbF_6)_2$ (Figure 1) complex combines efficient enantioface-differentiating capacity and high Lewis acidity, proving to be a powerful catalyst for the asymmetric Claisen rearrangement (Scheme 13).



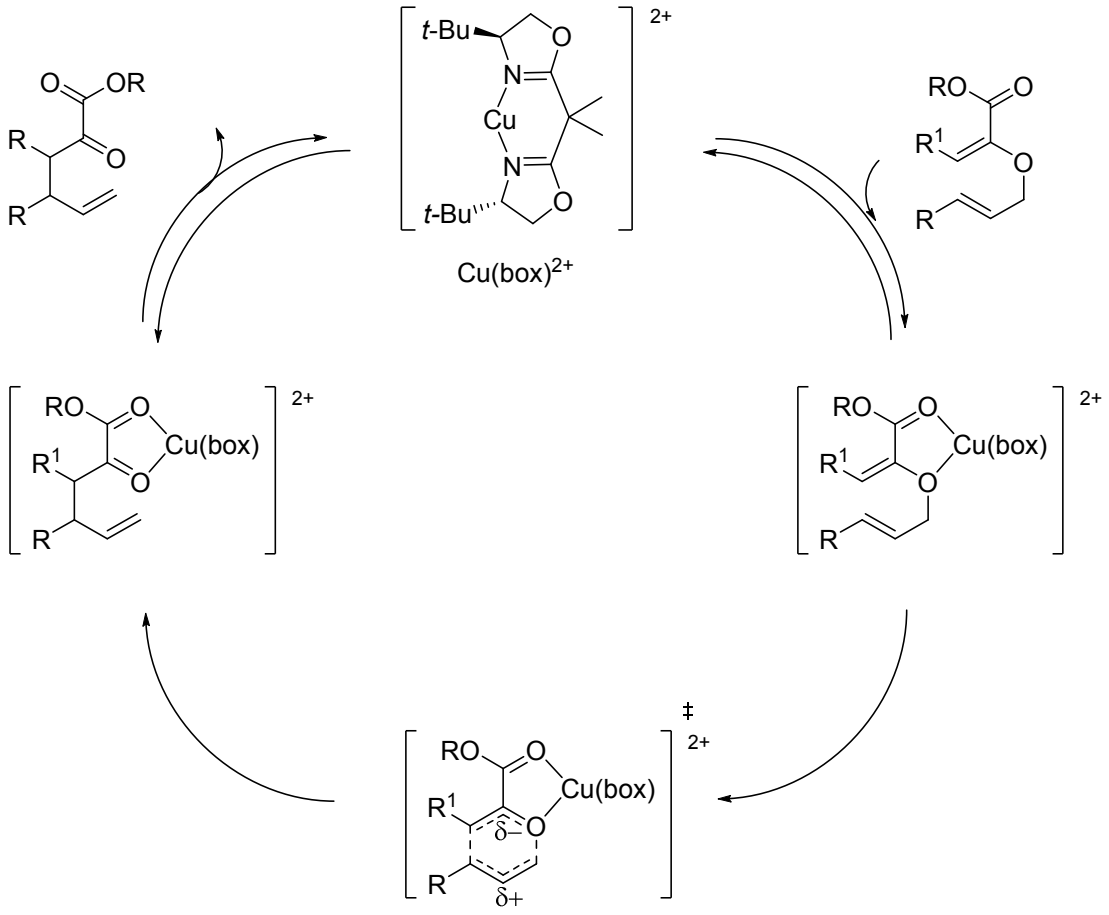
Scheme 13. Lewis acid catalyzed rearrangement with [Cu{(*S*,*S*)-*t*-Bu-box}]$(H_2O)(SbF_6)_2$ complex .

Further expansion of this work led to a report of the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl enol ethers containing two stereogenic double bonds (Scheme 14).[18b] The results clearly demonstrated a remarkable influence of the configuration of the double bond of the allyl enol ether and the nature of the catalyst on the stereoselectivity of the rearrangement. Generally, use of an allyl enol ether containing an *E*-configured allylic double bond frequently provides decreased diastereoselectivities [18b].



Scheme 14. Catalytic asymmetric Claisen rearrangement with catalyst **4**.

From the outcome of earlier studies on the thermal Claisen rearrangement, the authors propose the catalytic cycle for the Cu(box)-complex catalyzed reaction (Scheme 15) proceeds via a highly polarized pericyclic transition state of considerably lower activation energy (Figure 2).



Scheme 15. Proposed catalytic cycle for the (*S,S*)-**4**-catalyzed Claisen rearrangement.

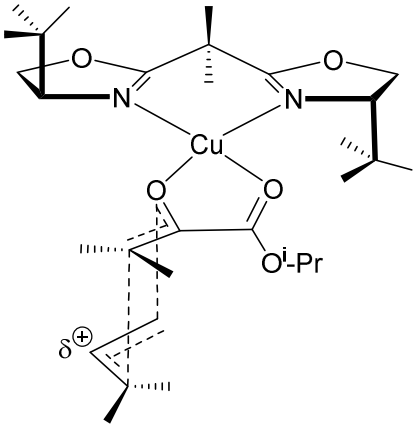
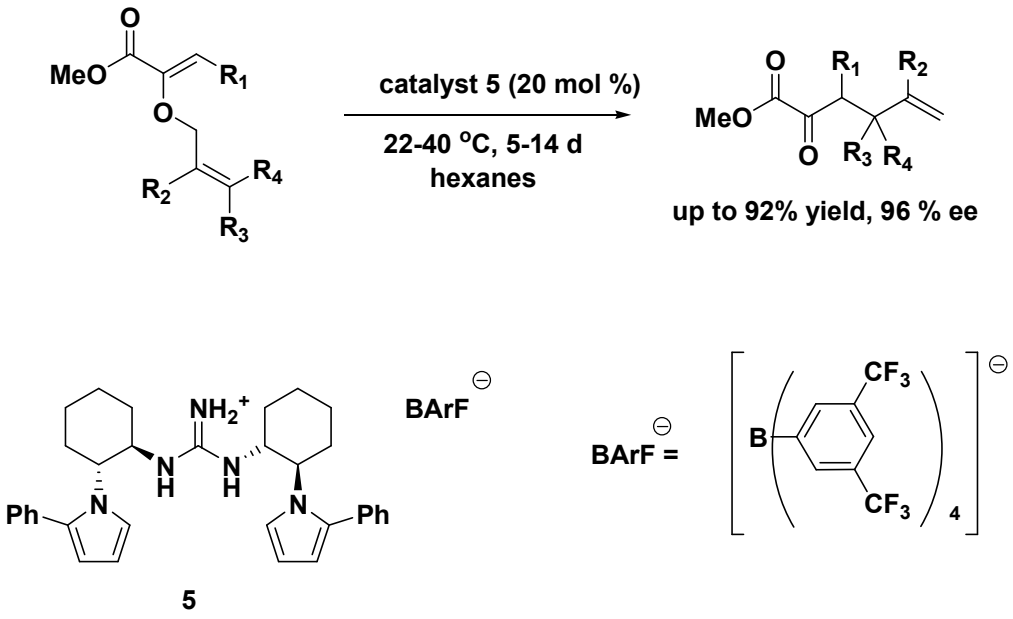


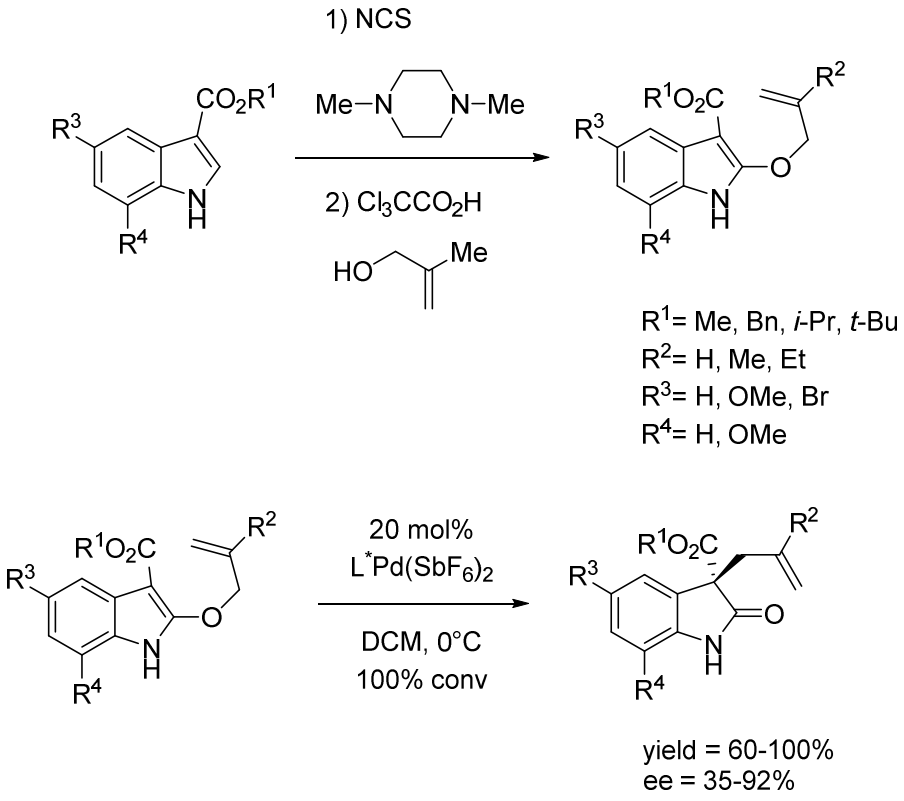
Figure 2. Transition state for the (*S*,*S*)-**4** catalyzed Claisen rearrangement.

In 2008 the Jacobsen group detailed the first catalytic asymmetric Claisen rearrangement with a hydrogen-bond donor catalyst. [19] Guanidinium catalysts were ineffective for asymmetric induction, while high enantioselectivities were attained in the reaction carried out between 20°C and 40°C over a period of several days with a guanidinium BArF catalyst **5** (Scheme 16).Despite the fact that the guanidinium BArF catalyst **5** is virtually insoluble in the solvent, use of dichloromethane or benzene resulted in slightly reduced enantioselection, while no catalytic effect was noticed with ethereal solvents such as TBME or Et_2O. Optimal rates and enantioselectivities for the reaction were found in n-hexanes.



Scheme 16. Catalytic Claisen rearrangement with chiral guanidinium catalyst.

Simultaneously with the report by Jacobsen, the Kozlowski group [20] reported that allyloxy-indoles are a new class of substrates that permit catalytic yield. By using palladium complexes, they reported on the first asymmetric catalytic Meerwein-Eschenmoser Claisen rearrangement, which engages the transformation of 2-amino allyl enol ethers to γ,δ-unsaturated amides. The formation of the intermediate hemiaminal usually requires forcing conditions, making the reaction incompatible for asymmetric catalysis in normal cases. Despite the high activation energy typically required for dearomatization accompanying the rearrangement, indole containing Claisen subtrates were used for the reaction. The substrates were suitable to catalysis probably due to the nucleophilic nature of the C-3 carbon of the indole ring (Scheme 17). The reaction was suggested to continue via a chair-like transition state, with both the oxygen of the allyl enol ether and the carbonyl oxygen of the ester group binding to the Pd(II) catalyst (Figure 3).



Scheme17. Catalytic Meerwein-Eschenmoser Claisen rearrangement.

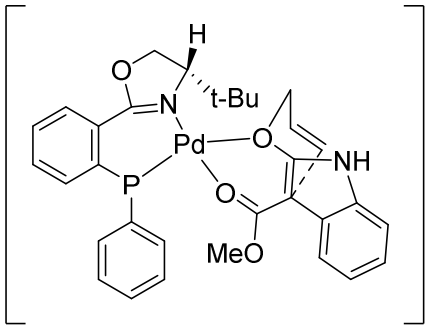
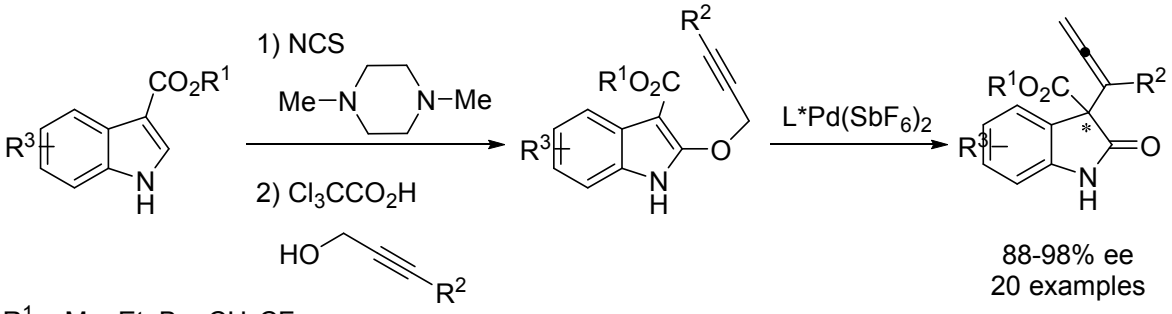


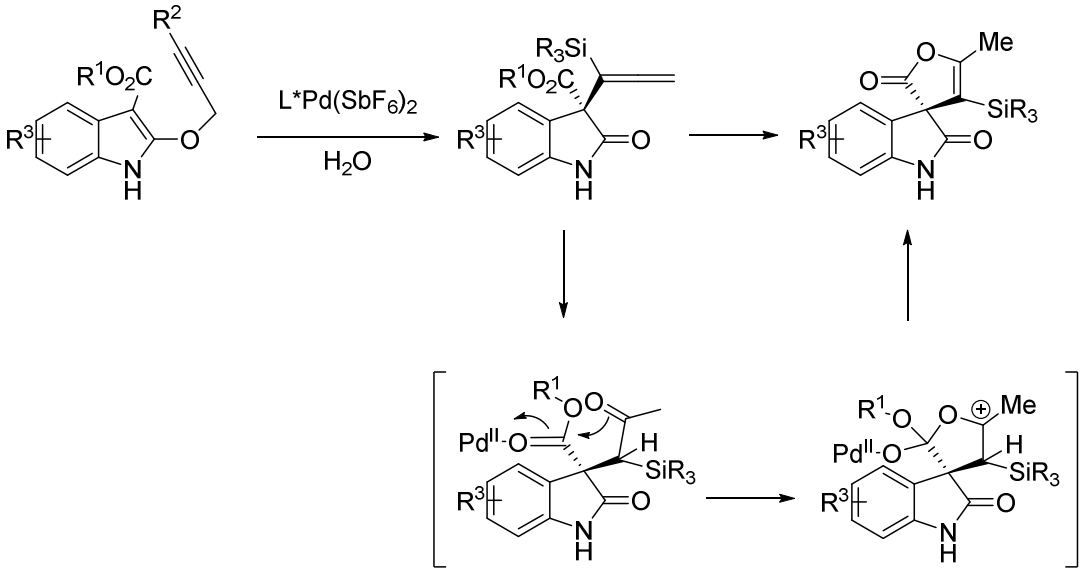
Figure 3. Proposed transition state for the Meerwein-Eschenmoser Claisen rearrangement.

In 2012 Marisa Kozlowski et al [21]reported the first asymmetric synthesis of allenyl oxindoles and spirooxindoles by the catalytic enantioselective Saucy-Marbet Claisen rearrangement, specifically, the transformation of propargyl ethers to afford β-substituted allenyl carbonyls (Scheme18). The reaction generates two classes of chiral oxindoles containing newly formed quaternary centers: allenyl compounds and spirocyclic lactones through a tandem rearrangement (Scheme 19). The tandem reactions of silyl-substituted substrates allow fast assemblage of complex spirooxindoles, an essential class of biologically active structures in one procedure. The findings offer a promise for the general use of alkynyl enol ethers in catalytic, asymmetric rearrangement reactions, providing an alternative route to valuable allenes.



R^1 = Me, Et, Bn, CH_2CF_3
R^2 = H, *t*Bu, MIDA, Ar, TMS, TES, TBS, TIPS
R^3 = H, 5-OMe, 7-OMe, 5-Br, 7-Me

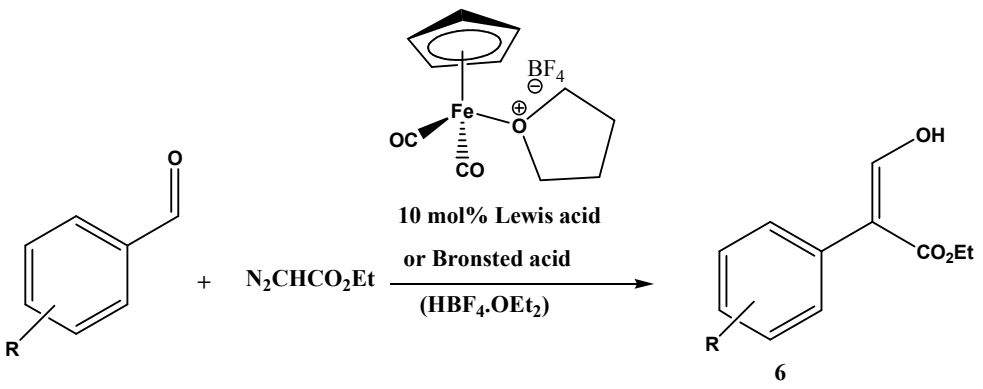
Scheme 18. Catalytic Saucy–Marbet Claisen rearrangement.



Scheme19. **Pd(II) catalyzed tandem formation of a spirocyclic oxindole.**

1.2.1. Hydroxyarylacrylate as a prochiral carbon center.

In Professor Hossain's lab we have access to a very interesting molecule, e.g., Hydroxyarylacrylate 6 which can be synthesized from simple aldehyde in one step (Scheme 20) [22]. This molecule furnished with three different functional groups that can be transformed into valuable intermediate molecules such as Indole 3-carbaldehyde [23], bezofuran [24] or Ibuprofen [25] in one or two steps (Figure 4).



Scheme 20: Brönsted acid catalyzed formation of hydroxylarylacrylate from substituted benzaldehydes.

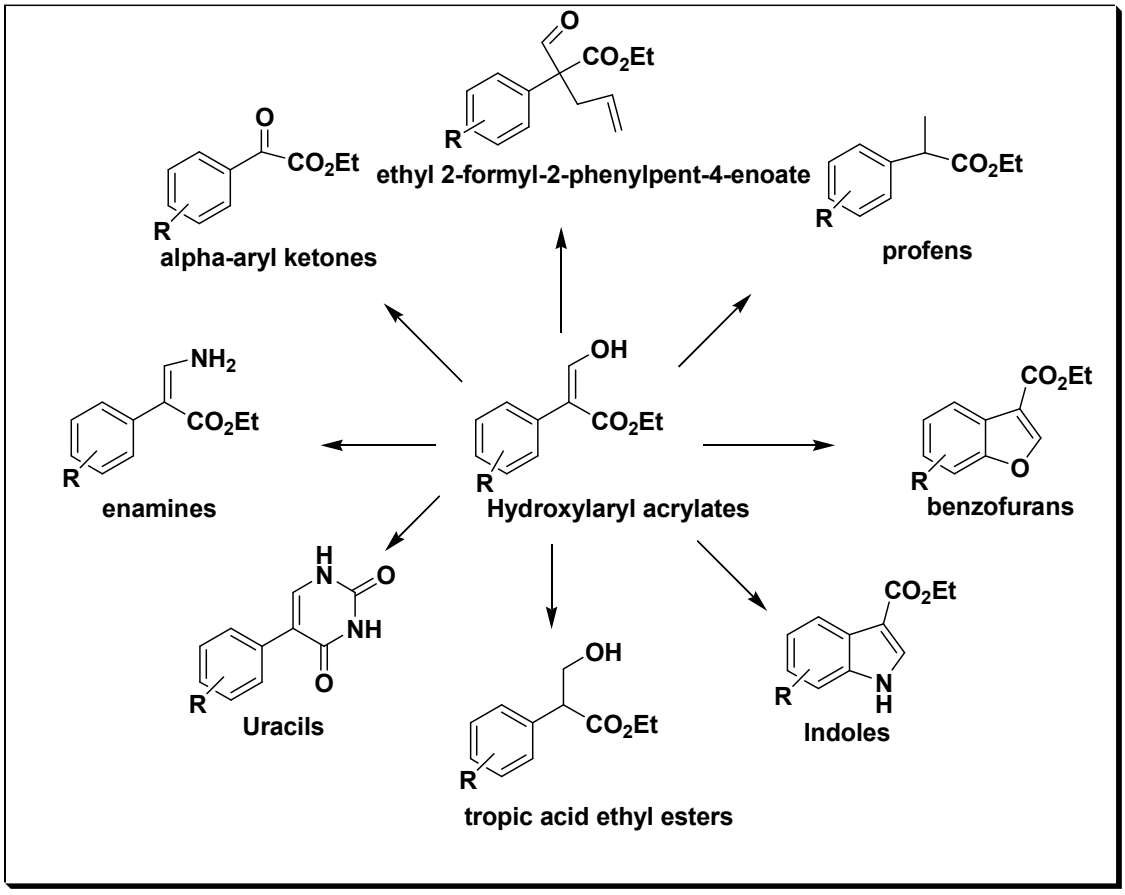
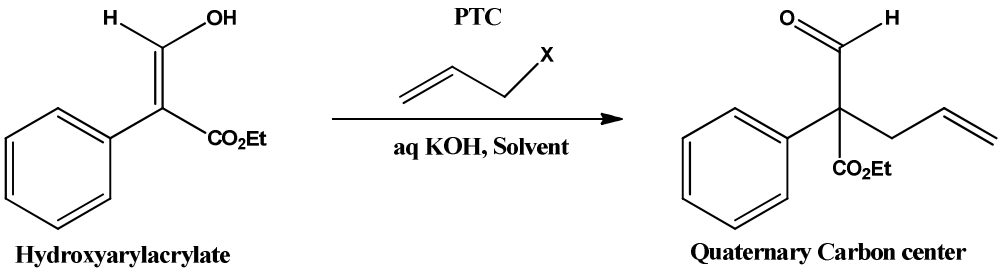


Figure 4. New compounds that were constructed from hydroxylarylacrylates.

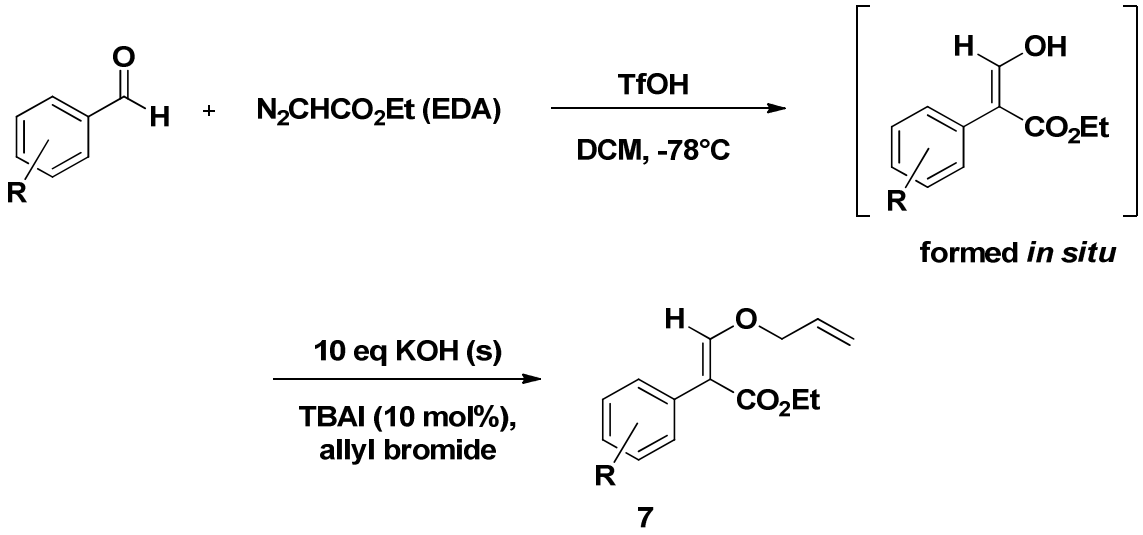
Because of its enolic double bond hydroxyarylacrylates seems to be an attractive prochiral center, hence allowing for the possibility of asymmetric synthesis under phase transfer catalysis conditions (Scheme 21).



Scheme 21. Hypothetical Phase Transfer catalyzed synthesis of Quaternary center.

However our initial approach for the construction of an α-aryl quaternary carbon starting from arylhydroxyacrylates 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 22), whilst the attempted alkylation with solid or aqueous NaOH only gave a small amount of C-alkylated product (ca 20% with allyl iodide). We believe that O-alkylation is much more favored since the high degree of conjugation present in the acrylate 3, preserved in O-alkylation, is however disrupted in C-alkylation. 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. An electrophile with a softer leaving group (allyl iodide instead of allyl bromide) resulted only in a slightly greater yield (by 5%) of C-alkylated product.

The allyl enol ether Claisen substrates can be made through a practical one-pot protocol (Scheme 22) whereby the in situ formed 3-hydroxy aryl acrylate is reacted with allyl bromide to provide the O-alkylated products in mostly good yields.

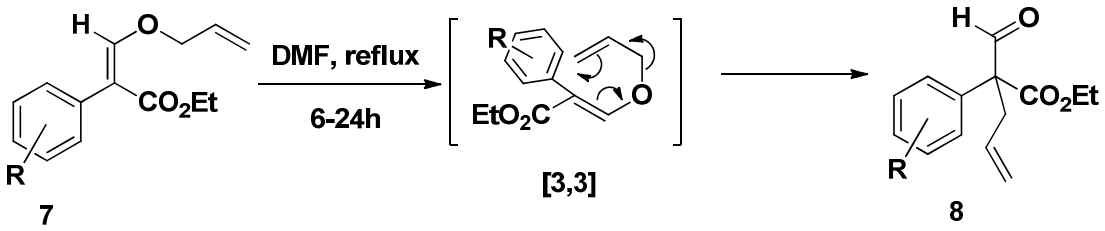


Scheme 22 . One-pot synthesis of O-alkylated allyl enol ethers.

1.2.2. Thermal Claisen rearrangement of allyl enol ethers derived from 3-hydroxy aryl acrylates

In our attempt to make direct C-alkylation of hydroxyarylacrylate we obtained predominantly O-alkylated product. However, we realized that the O-allyl enol ethers were suitable candidates for a Claisen rearrangement that would afford an indirect C-alkylation leading to the desired α-aryl quaternary carbon. (Scheme 23, Table 1).The O-alkylation of acrylates 3 was carried out in dichloromethane using allyl bromide under phase transfer catalysis conditions (using either Bu_4NI or Bu_4NBr) 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 yield of C-allylated products seems to be hindered by the presence of electron withdrawing substituents (Entries 3 and 5, **Table 1**). [26]



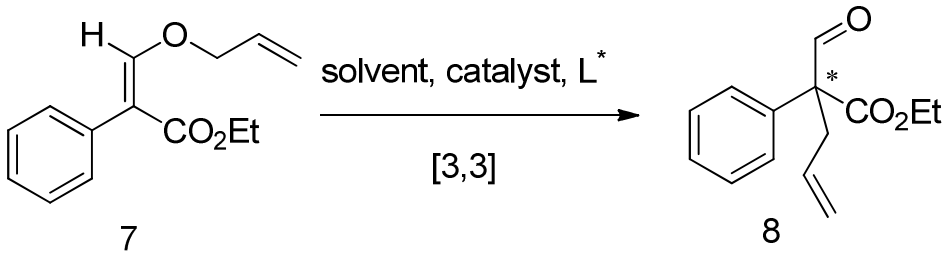
Scheme 23. Thermal Claisen rearrangement of O-alkylated substrates.

Table 1. Formation of O-alkylated and C-alkylated products.

Entry	Ar	Yield 7 (%)	Yield 8 (%)
1a,b	C_6H_5	71	89
2a,b	4-MeC_6H_4	80	85
3a,b	2,4-$Cl_2C_6H_3$	82	69
4a,b	4-$MeOC_6H_4$	66	88
5a,b	4-FC_6H_4	65	55
6a,b	5-Br-2-$MeOC_6H_3$	72	90
7a,b	4-*t*-BuC_6H_4	84	91

1.3.1. Synthesis of quaternary carbon center by Claisen rearrangement

With the knowledge that allyl enol ethers derived from 3-hydroxyarylacrylates are possible precursors for the thermal Claisen rearrangement, we set out to investigate whether the *catalytic* asymmetric Claisen rearrangement was a viable procedure (Scheme 24).



Scheme 24. Hypothetical asymmetric Claisen rearrangement of allyl enol ethers.

1.3.2. Significance of quaternary stereocenters and asymmetric catalysis

The creation of all carbon quaternary centers with enantiocontrol remains one of the most challenging and demanding topics in the organic synthesis of natural products. In the chemical sense the biological world can be regarded as a chiral world. Usually it happens in nature that one enantiomer shows biological activity whereas the other enantiomer does not. A large number of biologically active natural products contain quaternary carbon centers (Figure 5). Interest in asymmetric synthesis of these natural products in an optically active form is

reflected in the articles published recently. Due to their importance in pharmaceutical applications several new methods were developed for the construction of quaternary carbons. Recent reviews have also highlighted significant contributions in this research area. [27] Asymmetric synthesis of quaternary carbon center can be classified into two types, enantioselective and diastereoselective synthesis. Enantioselective reaction is carried out on an achiral molecule using an enantioselective reagent or catalyst. On the other hand, in a diastereoselective synthesis, chirality is transferred to a prochiral center of the same substrate.

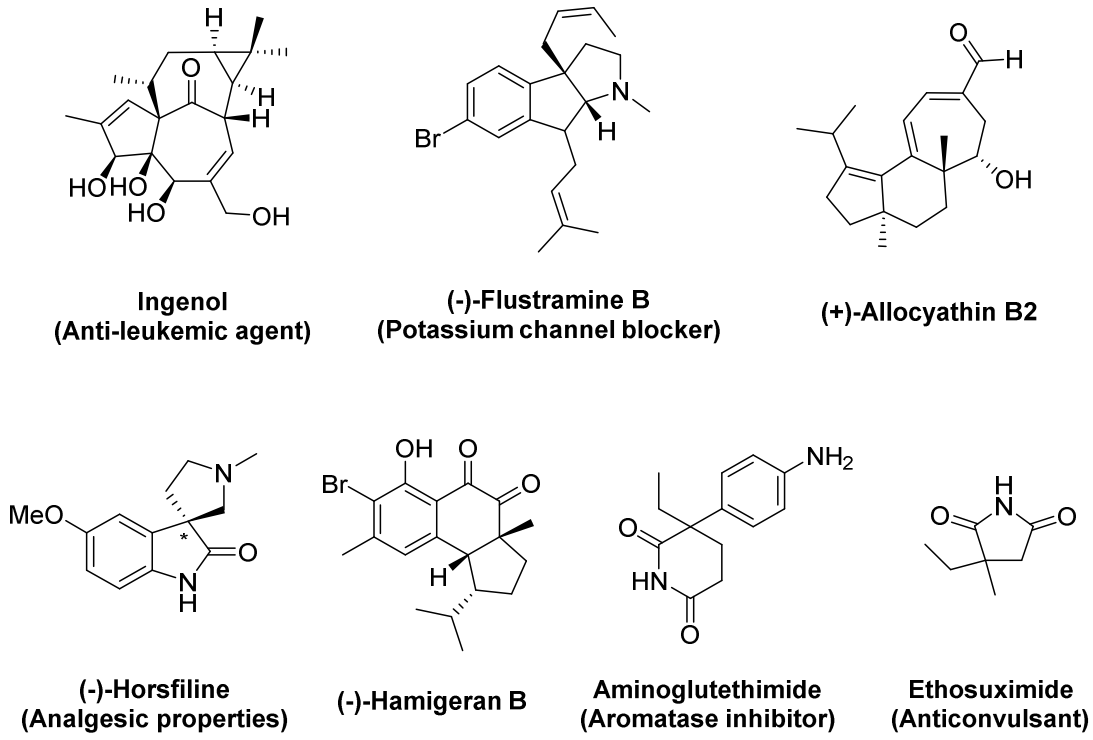


Figure 5. Natural products containing chiral quaternary carbon center.

1.3.3. General considerations in the formation of quaternary stereocenters via asymmetric catalysis

Non-catalytic formation of quaternary stereo centers involves harsh reaction conditions such as high temperatures and long reaction times. For this reason stereoselectivity of a reaction is adversely affected, but metal catalysis or organocatalysis allows for much milder reaction conditions, such as low temperature and thereby offers improved stereoselectivity of a reaction. Most reactions have some limitations in their substrate scope, in the case of asymmetric reactions this problem is most relevant [28,29].

Minor changes in the substrates structure can lead to significant changes in stereoselectivity, the worst case scenario is loss of stereocontrol with the change in substrate structure. It is common to most of the asymmetrically catalyzed reactions that they suffer from these limitations on the “partner combinations”. Subtle changes in the structure of the catalyst may led to unexpected changes in stereoselectivity. Other factors such as choice of solvent and temperature also have an important effect on the stereoselectivity of a reaction. Therefore, in order to find an optimum reaction condition for better stereoselectivity and improved yield, extensive screening of reaction conditions has to be carried out. Occasionally asymmetric catalysis will lead to suitable results for only a few substrates, and specific reaction conditions may need to be found in other cases.

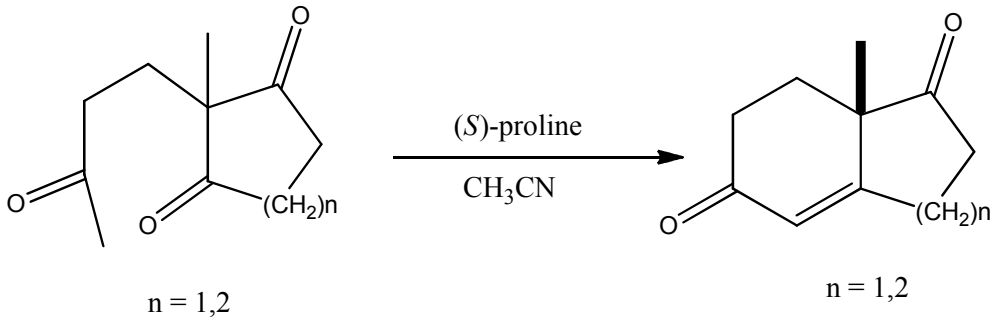
1.3.4. General reaction classes for formation of quaternary stereocenters.

There are two main classes of catalytic processes for the generation of quaternary stereocenters: via metal and Lewis acid catalysis or by organocatalysis. Lewis acid catalyzed asymmetric quaternary center formation reaction has been successfully achieved for the following reaction types: 1,3-dipolar [3+2] cycloadditions, the synthesis of β-lactams via overall [2+2] cycloadditions, cyclopropanations, Diels-Alder reactions, Michael additions, the alkylation of tributyl tin enolates, Michael additions with hard nucleophiles, copper catalyzed SN2' allylation, reactions with carbonyl and imine electrophiles, metal catalyzed diene and enyne cyclizations, rhodium catalyzed C-H insertions and Claisen rearrangements [28]. The reactions that take place through organometallic protocols such as oxidative addition-reductive elimination processes are intramolecular Heck reactions, vinylation and α-arylation reactions of ketones and lactones, and of course allylic alkylation via palladium π-allyl complex intermediates [28].

Literature survey reveals that the majority of reactions involving the synthesis of quaternary stereocenters involve cyclic systems. For instance, in the review done by Marco Bella [29] on the organocatalytic formation of quaternary stereocenters out of a total of twenty-eight examples of Michael adducts containing quaternary carbon centers, only six different acyclic substrates were used. The use of acyclic substrates is much fewer in case of the asymmetric decarboxylative allylic alkylation (DAAA), and for some reaction classes there are none [30]. Because of

the challenge of an increase in the number of degrees of freedom linked with acyclic structures there is a predominance of cyclic substrates in the literature.

In 1971, an intramolecular aldol cyclization of the achiral triketone using an optically active amino acid as a catalyst was reported by Eder et.al. Treatment of substrate triketone with (S)-proline in acetonitrile afforded good yield and optical purity. Detailed studies on the dilution effect on (S)-proline indicated a three-centered hydrogen bonded structure as transition state. This cyclization was extended to the acyclic ketone; although enantiomeric excess was moderate, interesting solvent effects were observed in this reaction(Scheme 25) [31].



Scheme 25: (S)-Proline catalyzed aldol cyclization of triketone.

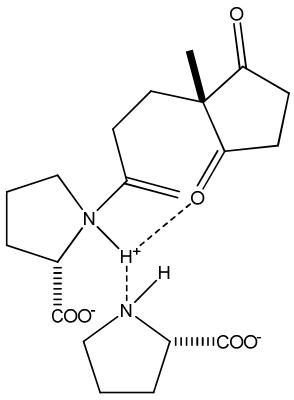
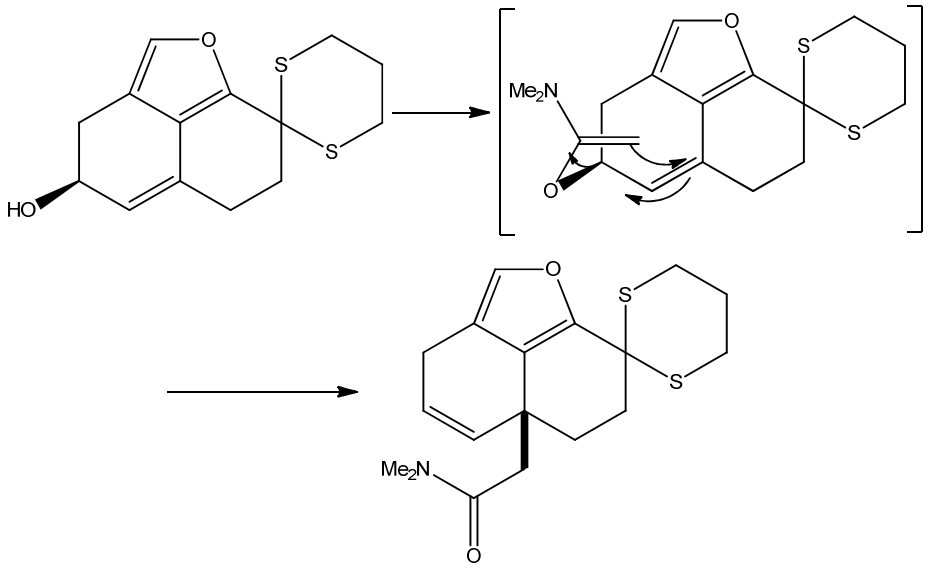


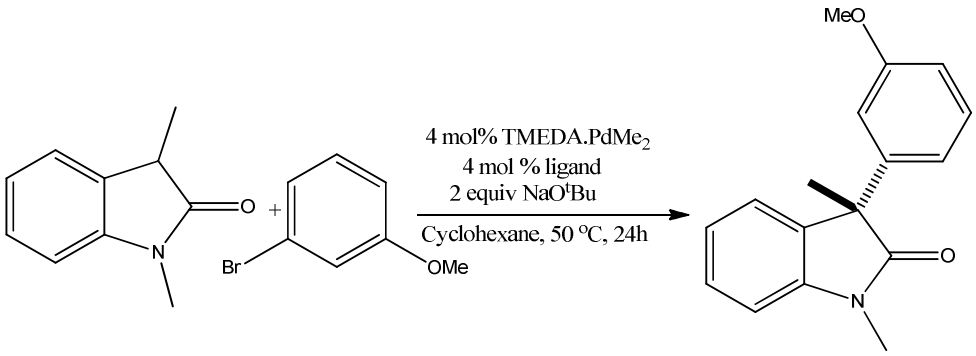
Figure 6. Proposed transition state of proline catalyzed reactions.

Shiro et al [32] reported the Claisen rearrangement of the optically active secondary alcohol center to produce in 51 % yields with 100% intramolecular chirality transfer. They achieved this result by treating alcohol with N,N-dimethylacetamide dimethyl acetal in refluxing o-xylene proceeded via intermediate (Scheme 26).



Scheme 26. Claisen rearrangement of optically active secondary alcohol.

Carbon-carbon bond formation using chiral palladium catalysts has been a particularly active field in recent years. Buchwald reported [33] the highly enantioselective Pd-catalyzed intermolecular coupling of oxindoles and aryl and vinyl bromides facilitated by a biaryl monophosphine ligand that contains two sources of asymmetry. They also found that KenPhos and (iPr)2MOP promoted the coupling of 1,3-dimthyloxindole with 3-bromoanisole in the presence of TMEDA.$PdMe_2$ and NaO*t*Bu in good yield and promising ee (Scheme 27).



Scheme 27. Pd-catalyzed enantioselective α-arylation of 1,3-dimethyloxindole with a biaryl monophospine ligand.

Enantioselective synthesis of quaternary center also has been reported by using Michael addition reactions, phase transfer catalyst system and of course using different metal catalyst system. Most of these reactions are substrate specific and further developments are needed in catalyst preparation and selectivity.

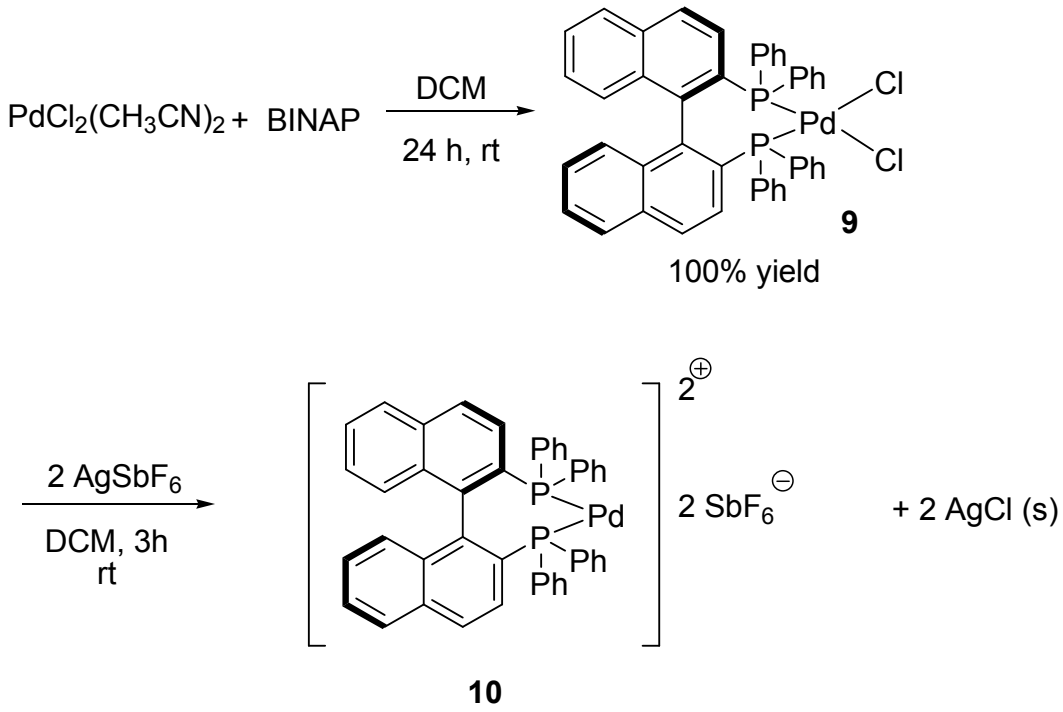
CHAPTER II: ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTERS

2.1. Catalytic asymmetric Claisen Rearrangement of allyl enol ether obtained from 3-hydroxyarylacrylates

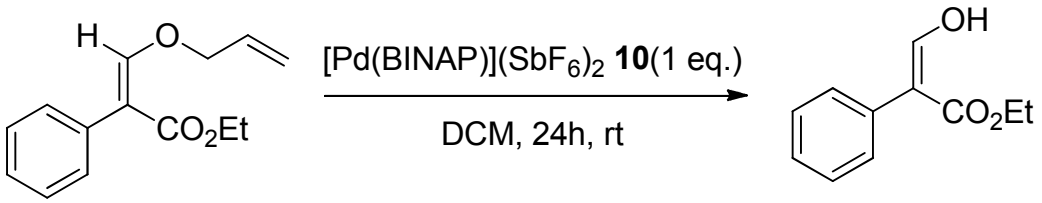
Because of our success in thermal Claisen rearrangement of O-allylated aryl acrylate **7**, we decided to pursue the asymmetric version of the same reaction by using chiral Lewis-acid catalyst. Towards that end, first of all, screening of organometallic Lewis acids and solvents are needed for the activation of allyl enol ether at room temperature.

Inspired by the report by Kozlowski of the Meerwein-Eschenmoser Claisen rearrangement we assumed that the transition state for the rearrangement of allyl enol ethers obtained from 3-hydroxy aryl acrylates should be extraordinarily similar to the one reported by Kozlowski. We decided to try the Pd^{2+} Lewis acid catalyzed Claisen rearrangement as reported by Kozlowski [28 b,c].

The Pd^{2+} catalyst complex was prepared by displacing chloride from $Pd(BINAP)Cl_2$ complex via a displacement reaction with $AgSbF_6$ to form the corresponding SbF_6^- complex. Weakly coordinating counter ion (SbF_6^-) was chosen to increase the Lewis acidity of the metal complex. The reaction precipitated out a white AgCl, which was then filtered off through a PTFE filter (Scheme 28).



Scheme 28. Synthesis of $[Pd(BINAP)](SbF_6)_2$ Lewis acid.

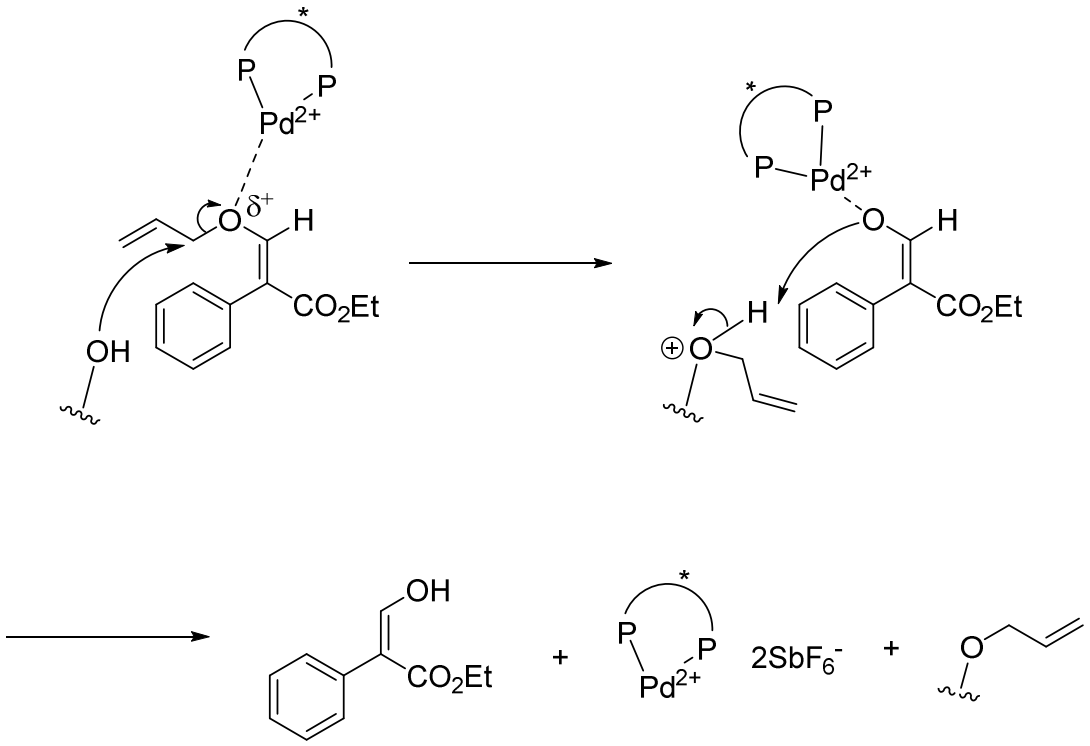


Scheme 29. Attempted $[Pd(BINAP)](SbF_6)_2$ catalyzed Claisen rearrangement.

Our experimental data suggests that asymmetric Claisen rearrangement with $[Pd(BINAP)](SbF_6)_2$ was ineffective, furthermore the metal was found to cleave the allyl-oxygen bond of the substrate forming 3-hydroxyarylacrylate (Scheme 29).

Most probably, the oxygen of the allyl enol ether binds to the Pd^{2+} catalyst, and the bond between the oxygen and the allylic carbon is then cleaved with ease during

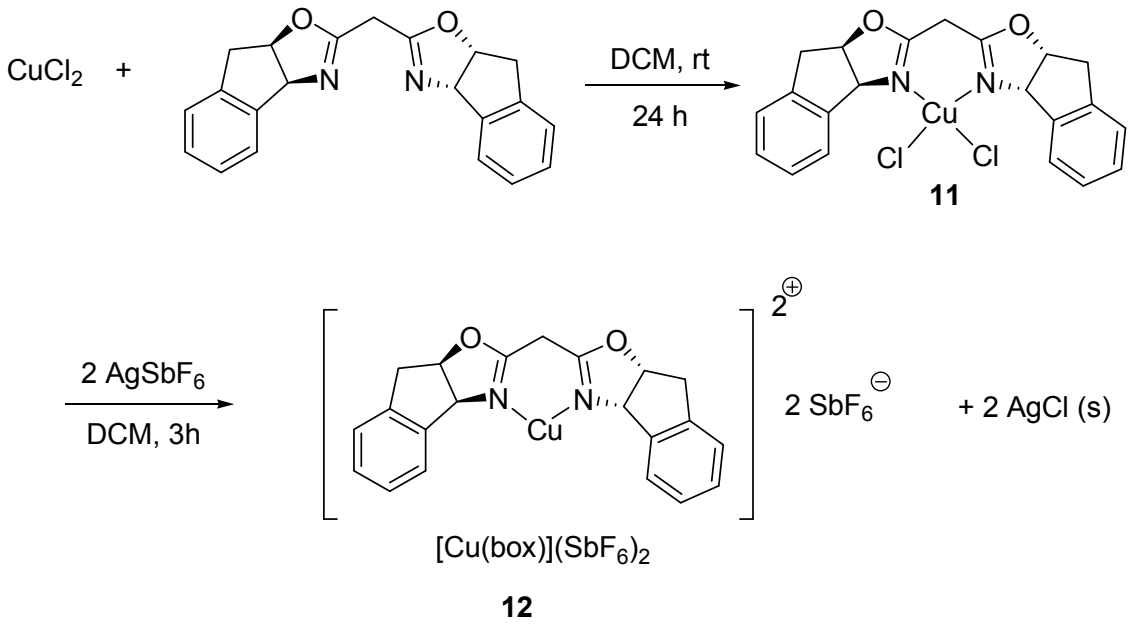
the work-up when the reaction mixture is passed through a silica plug (Scheme 30).



Scheme 30. Proposed mechanism for cleavage of oxygen-allylic carbon bond.

Next we thought that other Lewis acids such as Cu^{2+} might avoid the problem of the enol oxygen-allylic carbon bond cleavage. The first use of chiral bis(oxazoline) ligands for the Lewis acid catalysed Claisen rearrangement resulting in excellent enantiomeric excesses was reported in 2004 by Hiersemann and coworkers. In our initial attempt, we used $Cu(TfO)_2$ (1 eq) as a Lewis acid catalyst in DMF. No product formation was observed even after 72 h, and we believe DMF deactivated the Cu^{2+} catalyst.

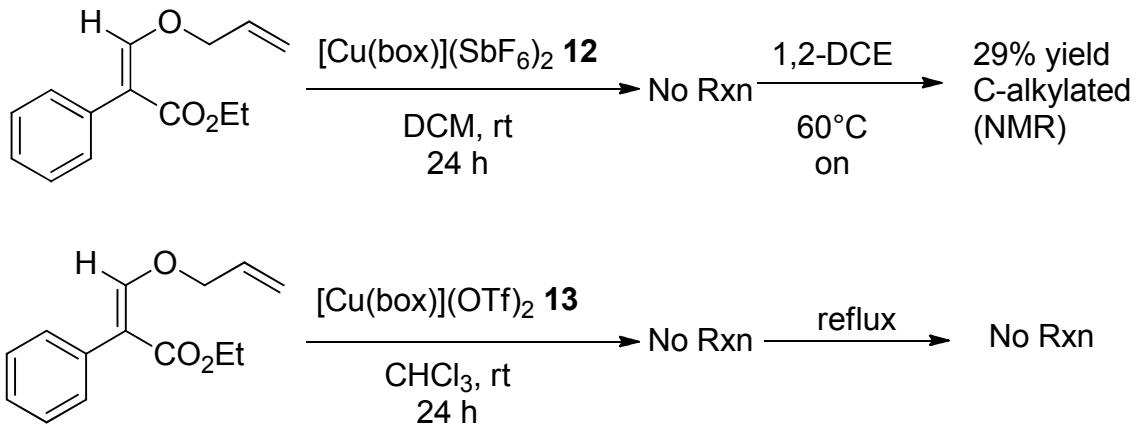
We then synthesized a $Cu(box)^{2+}$ complex, where $Cu(box)Cl_2$ complex is first formed, and the chlorides are then replaced with SbF_6^- via a displacement reaction with $AgSbF_6$ to form the desired Cu^{2+} catalyst (Scheme 31).



Scheme 31. Formation of $[Cu(box)](SbF_6)_2$ Lewis acid complex **12**.

With Cu^{2+} catalyst no product formation was observed via Claisen rearrangement at room temperature. We the removed the solvent under N_2 and dry 1,2-Dichloroethane was added to the reaction mixture. It was then heated to 60 ^oC and a small amount of C-alkylated product (29%) was observed in the NMR analysis of a crude product. Another catalyst $[Cu(box)](OTf)_2$ was made by the addition of $Cu(OTf)_2$ to 1 eq. of box ligand bearing the more strongly coordinating triflate counter ion. This counter ion may decrease the Lewis acidity of the catalyst and in turn decrease decrease the probability of enol oxygen-allylic carbon bond cleavage. Unfortunately, in this case also no product was formed at both room

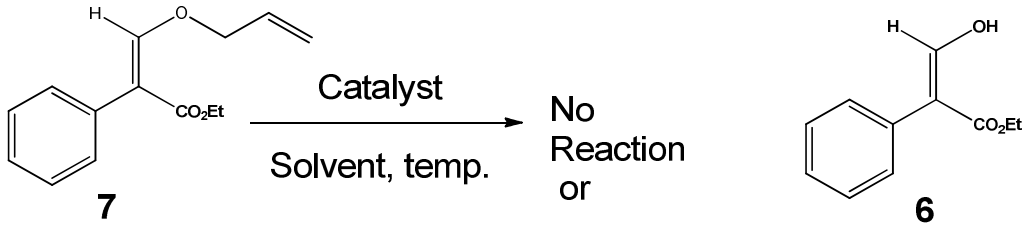
temperature and under refluxing $CHCl_3$ condition. However, this time the cleavage product (acrylate) was not formed which seems to point out that Cu^{2+} catalyst **13** is a weaker Lewis acid (Scheme 32).



Scheme 32. Attempted Claisen rearrangements using Cu^{2+} complexes **12** and **13**.

Along with these catalyst in our group Eduardo tried other Lewis acid catalysts for asymmetric Claisen rearrangement of compound **7**. In most cases no reaction was observed except for catalyst **12** (entry 11, Table 2).

Table 2. Attempted Claisen rearrangement with Lewis acids.



7 **6**

Entry	Metal	Ligand	Product	Temp.(^{o}C)
1	$Zn(OTf)_2$	Box	NR	rt
2	$Zn(SbF_6)_2$	Box	NR	rt
3	$Ni(SbF_6)_2$	BINAP	NR	rt
4	$PdCl_2(CH_3CN)_2$	-	6+7	rt
5	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	-	NR	rt to 50
6	$BF_3 \cdot OEt_2$	-	6+7	rt
7	$Fe(SbF_6)_2$	PyBox	NR	rt
8	$[Rh(COD)Cl]_2$	(*R,R*)-L3	NR	50
9	$(Cp^*RhCl)_2$	-	NR	rt to 50
10	$Cu(SbF_6)_2$	Box	NR	rt
11	$Cu(SbF_6)_2$	Box	**8** (29%)	60

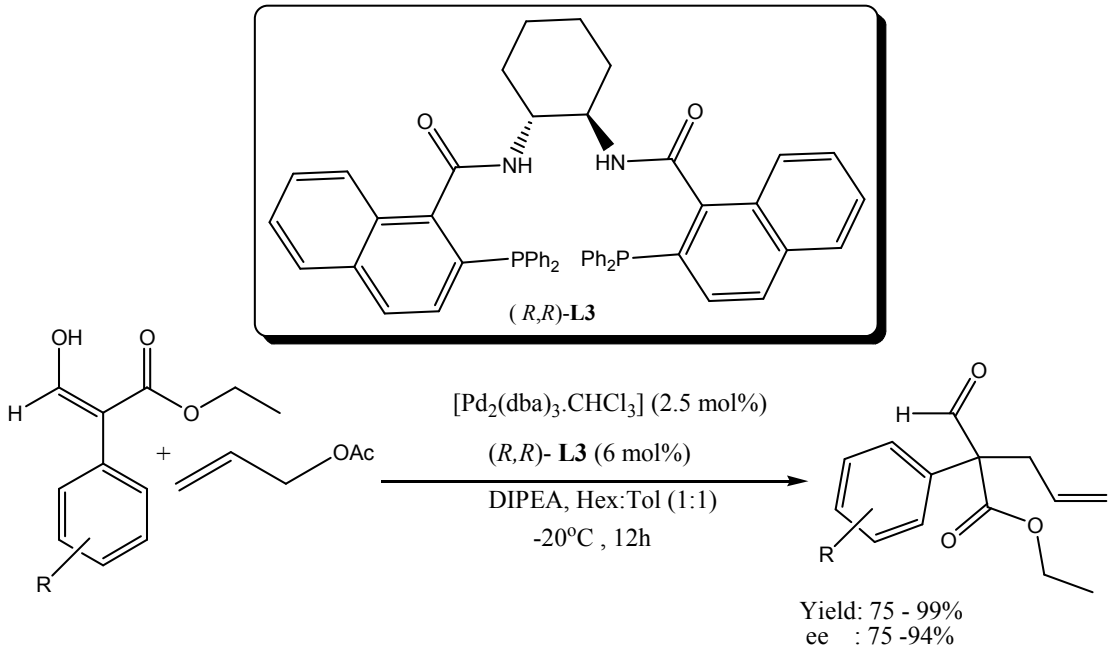
NR = No Reaction.

2.2. Metal catalyzed Asymmetric Allylic Alkylation for the synthesis of quaternary stereocenter.

Asymmetric allylic alkylation has been known to be an alternative for Claisen rearrangement. After our initial attempt to convert allyl enol ether compound **7** to quaternary aldehyde **8** in an asymmetric fashion, we moved to a Pd(0)-catalyzed asymmetric allylic alkylation protocol. This reaction can be broadly classified into two categories, namely intermolecular and intramolecular asymmetric allylic alkylation.

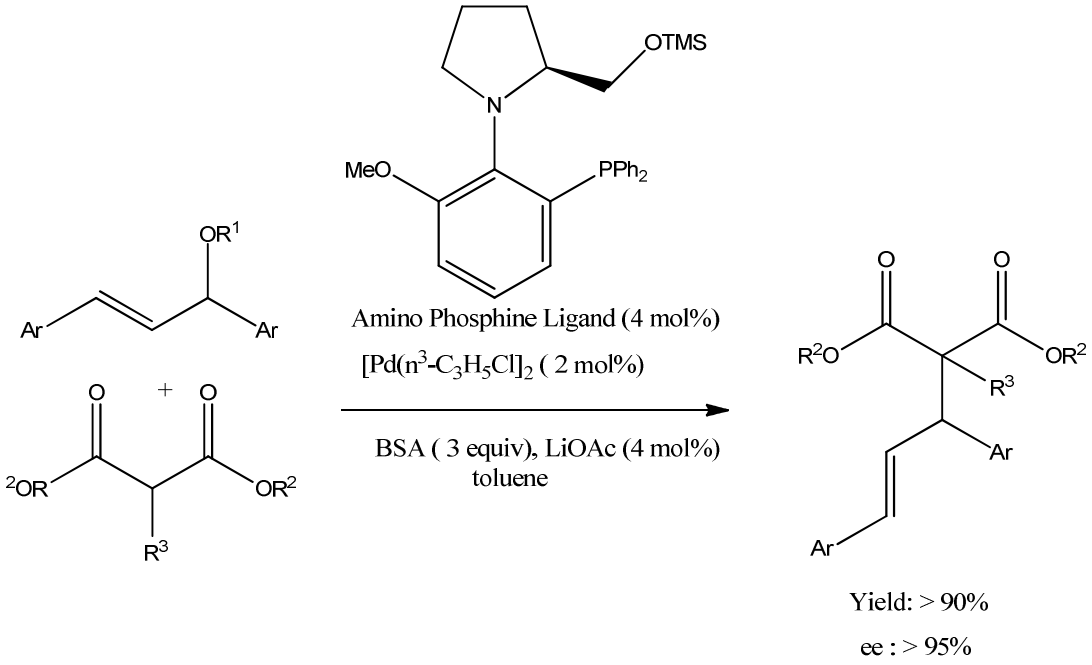
2.2.1 Intermolecular Pd-catalyzed asymmetric allylic alkylation reaction

Recently we published the first example of the intermolecular palladium-catalyzed AAA of hydroxyacrylates [34] which enabled us to synthesize all-carbon α-aryl quaternary aldehydes in good yield and enantioselectivity. In this protocol we developed a new intermolecular Pd-AAA reaction, in which hydroxyarylacrylates are used as nucleophiles for the first time to produce acyclic all-carbon quaternary aldehydes. Substituted hydroxyarylacrylates were used as nucleophiles and provided α-allylated α-aryl all-carbon quaternary aldehydes in high yields with high enantioselectivities. We believe this methodology possesses potential to be investigated further and utilized for the synthesis of a vast number of natural products containing α-aryl quaternary stereocenters (Scheme 33).



Scheme 33. Pd-catalyzed intermolecular AAA reactions of hydroxyarylacrylates with allyl acetate.

Tanaka et al reported[35] palladium-catalyzed asymmetric allylic alkylation using novel pyrrolidinyl-containing chiral aminophosphine ligands possessing hydroxyl groups in the terminal of the side chain. They have reported excellent yield and %ee for the asymmetric allylic alkylation reaction (Scheme 34).



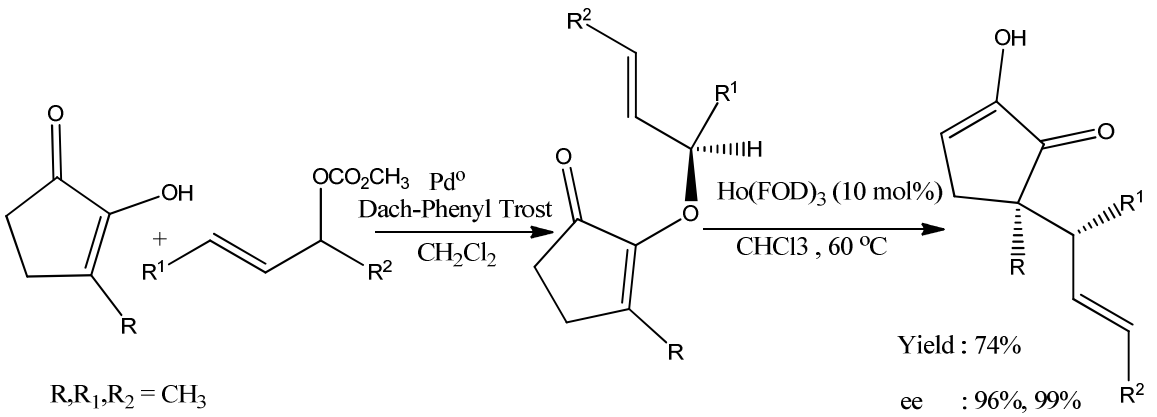
Scheme 34. Pd-catalyzed intermolecular asymmetric allylic alkylation using chiral amino phosphine ligand.

2.2.2. Intramolecular AAA reaction for the synthesis of quaternary stereocenter

Since the first example, reported by Trost in 1977, [36] intermolecular AAA has undergone a remarkable development, and is now a well established method. In contrast, to the best of our knowledge, successful carbanion based intramolecular AAA have been reported only by the groups of Yamamoto and Tsuji, Genet, Pfaltz,Trost and Ready, with only Genet being able to concurrently control two stereogenic centers in this step [37]. The paucity of successful examples in this field may stem from the intrinsic complexity of the reaction mechanism. Indeed in a

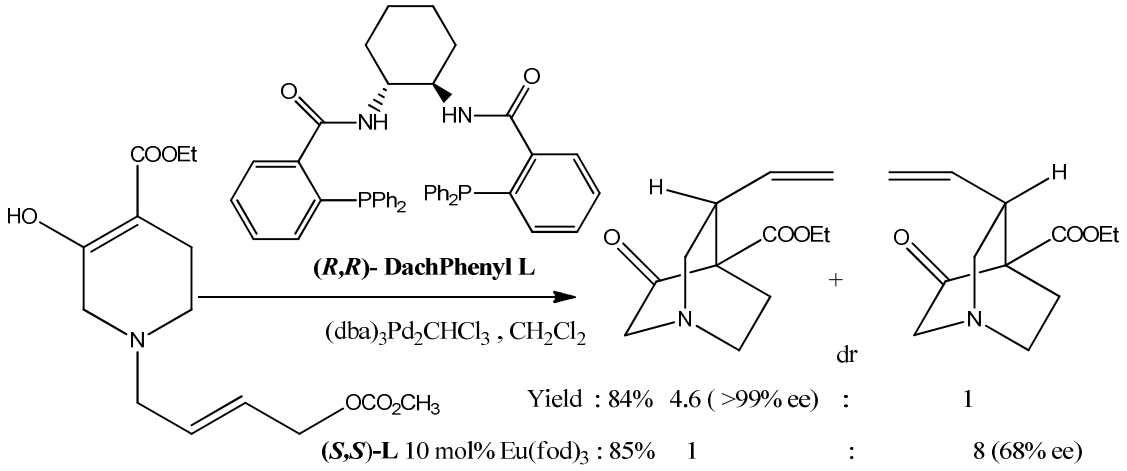
classical benchmark intermolecular AAA, the enantiodiscriminating step is the C-C bond formation, due to the C_g symmetry of the η^3-allyl moiety. On the other hand, the scenario is more complicated in an intramolecular AAA, wherein the oxidative addition or the C-C bond-formation step can be the enantiodiscriminating event, dependent on relative kinetics [38].

In 2000, Trost reported [39] Pd-catalyzed asymmetric O-alkylation of 3-substituted cyclic 1,2-diketones. This O-alkylated product then undergoes further rearrangement to give C-alkylation product at 3 positions, thereby creating a quaternary stereocenter. The fact that 3-substituted cyclic 1,2-diketones exist as single tautomeric species raised the prospect of an asymmetric synthesis of cycloalkenones. This was achieved by decarbonylative intramolecular AAA-Claisen rearrangement protocol. The chirality transfer in a Claisen rearrangement was examined in the case of the cyclic substrate, thermal process (>110 ^oC) was found to be ineffective with a great deal of ionization. Classical Lewis acids such as $Hg(OAc)_2$ and $Al(Me)_2Cl$ as well as $PdCl_2.(CH_3CN)_2$ gave no reaction or cleavage of the allylic ether bond. Lanthanide triflates such as lanthanum and europium triflate were proved too reactive. Finally they found that the FOD ligand complexes of the lanthanides are effective and among the lanthanides Ho is the most effective catalyst. Therefore, use of 10 mol % $Ho(fod)_3$ in a minimal amount of chloroform at 50-80 °C was adopted as the standard protocol for Claisen transformation(Scheme 35).



Scheme 35. Asymmetric O-alkylation of 1,2-diketones followed by $Ho(fod)_3$ catalyzed Claisen rearrangement.

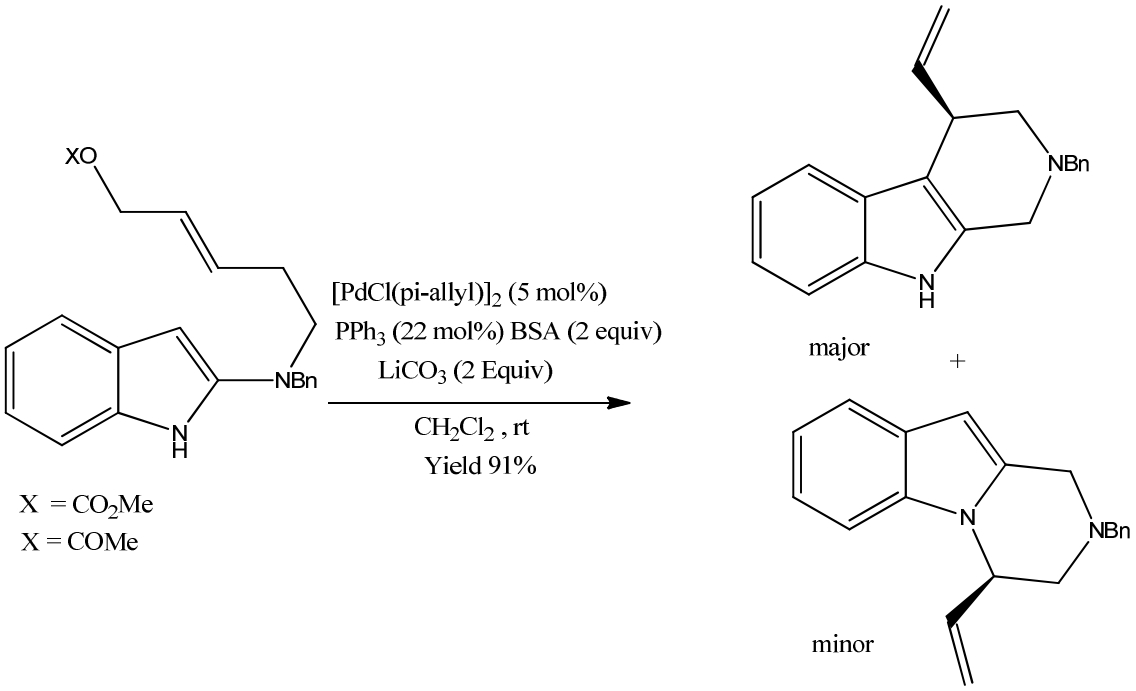
In 2002 Trost reported intramolecular palladium-catalyzed allylic alkylation to give cyclized quinuclidinones [40], which is an important building block for the synthesis of quinolone Cinchona alkaloids. The mechanism of this reaction was elucidated and found to consist of ligand matched ionization of carbonate substrate, π-allyl equilibration, and then finally nucleophilic attack. They reported no solvent for the reaction but various additives were found to have a dramatic effect on the reaction and $Eu(fod)_3$ had a profound impact on reactivity and reversed the diastereoselectivity. Trost group presented an intra-molecular Pd-catalyzed AAA to generate [2,2,2] bicycles in good enantio- and diastereoselectivity. This could be a route for the asymmetric synthesis of quinine and quinidine from the cyclization of prochiral nucleophile β-keto esters (Scheme 36).



Scheme 36. Pd-catalyzed AAA reaction of β-keto esters in formation of bicycle[2,2,2] octan-2,3-diones and quiniclidin-2-ones reported by Trost.

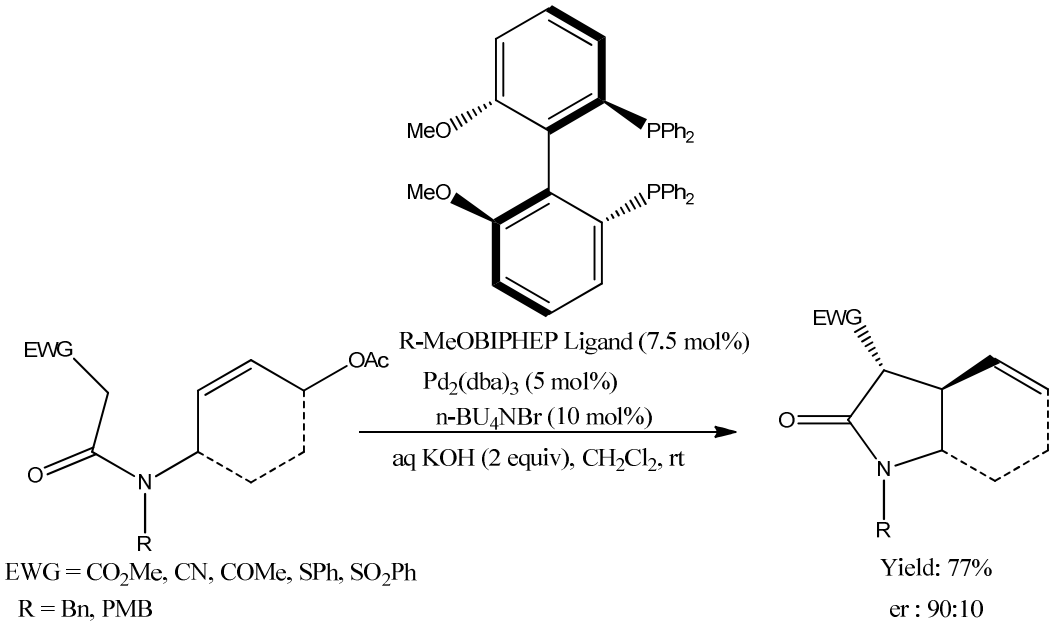
In 2006 Bandini M. reported [41] a highly enantioselective synthesis of tetrahydro-β-carbolines and tetrahydro-γ-carbolines via Pd-catalyzed intramolecular allylic alkylation. Pictet-Spengler reaction still represents the primary route to the preparation of the biologically active β-carbolines, intramolecular AAA could be an alternative to that. This group also reported allylic alkylation as an substitute procedure for the conventional Friedel-Crafts reaction.

Among the chiral promoters employed they found that the DPPBA-based Trost ligands furnished the highest level of regio- and stereoselectivity. The excellent enantiomeric excess suggest this strategy as a valuable candidate for the preparation of stereochemically defined polycyclic aromatic compounds.



Scheme 37. Synthesis of 4-vinyl tetrahydro-β-carbolines via Pd-catalyzed intramolecular AAA reaction.

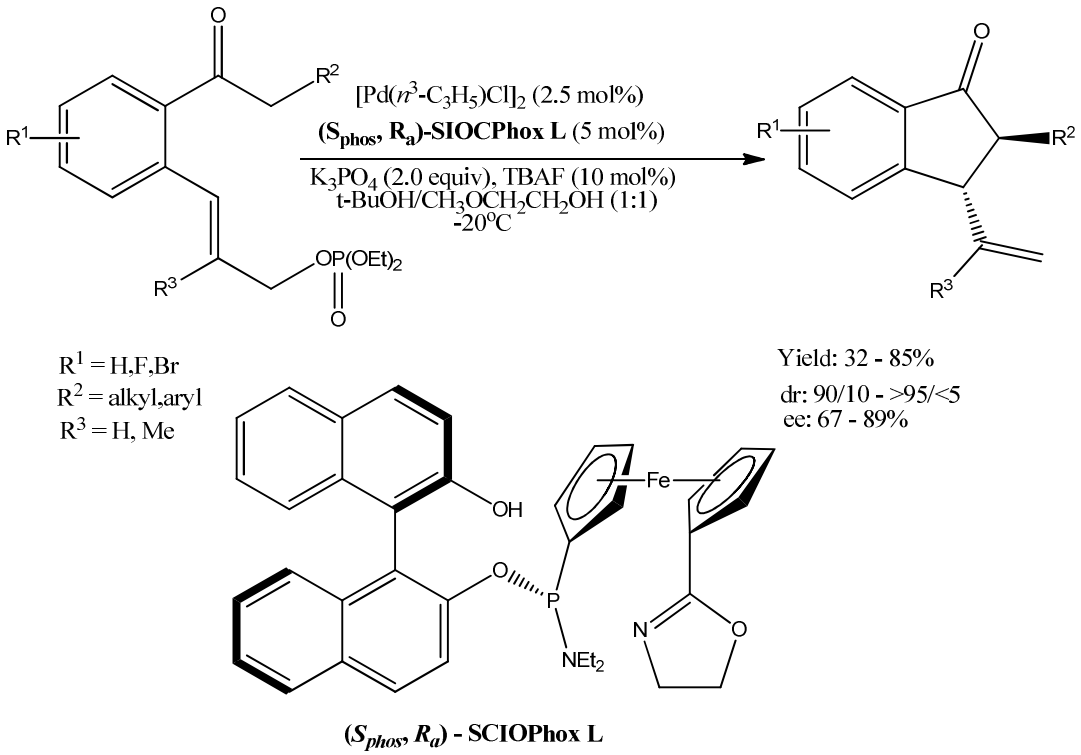
Bantreil et. al. employed[42] diphosphine MeoBIPHEP ligand with Pd(0) catalyst for the synthesis of optically active pyrrolidine system. The reaction proceeded through a basic phase transfer catalyst system that helped in enolization process, whereas Pd catalyst replace actetate leaving group easily formed π-allyl complex with the substrate (Scheme 38).



Scheme 38. Intramolecular allylic alkylation using R-MeOBIPHEP ligand.

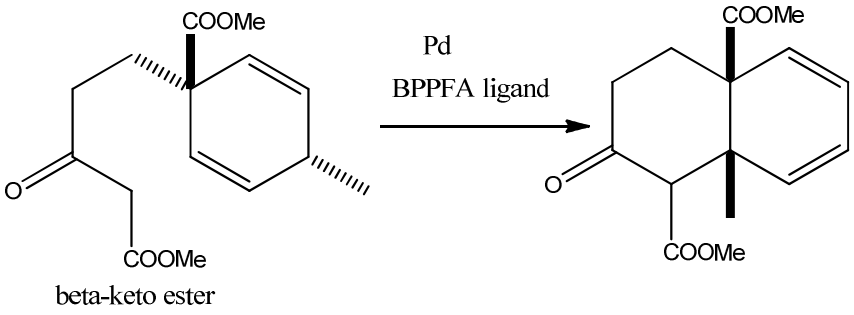
Recently Huo et. Al published [43] an enantioselective synthesis of 2,3-disubstituted indanones by an intramolecular Pd-catalyzed AAA with a hard carbanion as a nucleophile (Scheme 39). They have experimented only on two P,N-ferrocene-based SIOCPhox chiral ligands, ee was higher with (*Sphos, Ra*)-SIOCPhox than with (*Rphos, Ra*)-SIOCPhox. In their optimization study, it was found that O-alkylation is a more favorable process to form 5-membered ether than 5-membered cyclic ketone formation. They overcame this chemoselectivity issue by using *tert*-Butanol as a solvent and $LiOH.H_2O$ as a base. Both base and solvent were found to have an effect on selectivity. Using diethyl phosphate as a more stable substrate under basic condition increased yield of the reaction to a great extent. In summary, using SIOCPhox chiral ligand Hou group has achieved a Pd-

catalyzed intramolecular reaction with high diastereo- and enantioselectivity (Scheme 39).



Scheme 39. A Pd-catalyzed intramolecular AAA reaction affording 2,3-disubstituted indanones with high diastereo- and enantioselectivity.

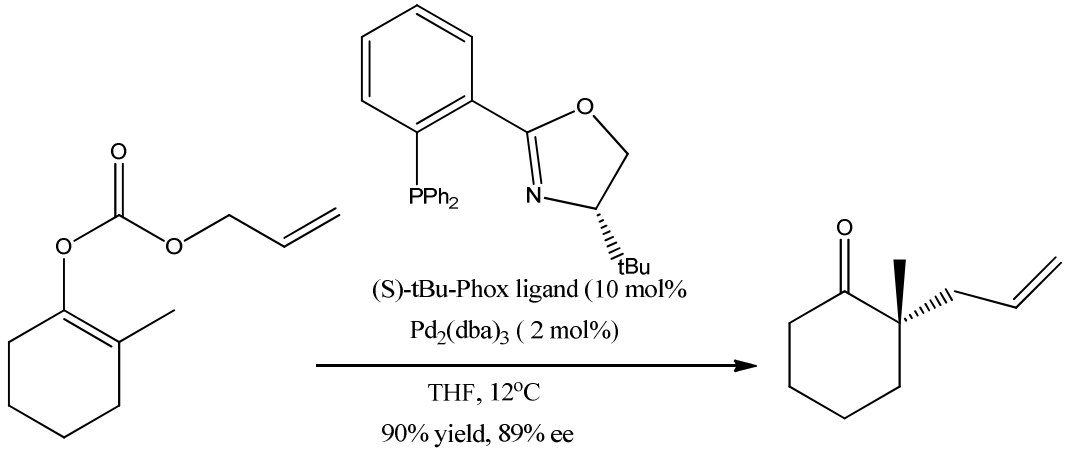
The intramolecular palladium-catalyzed cyclization of the β-keto ester with Ferrocenyl ligand provided moderate yield and ee. [44] Other chiral ligands such as chiraphos and (S)-BINAP, gave poorer results both in yield and %ee (Scheme 40)



Scheme 40. O-allylation and rearrangement towards C-alkylation.

2.2.3. Decarboxylative asymmetric allylic alkylation

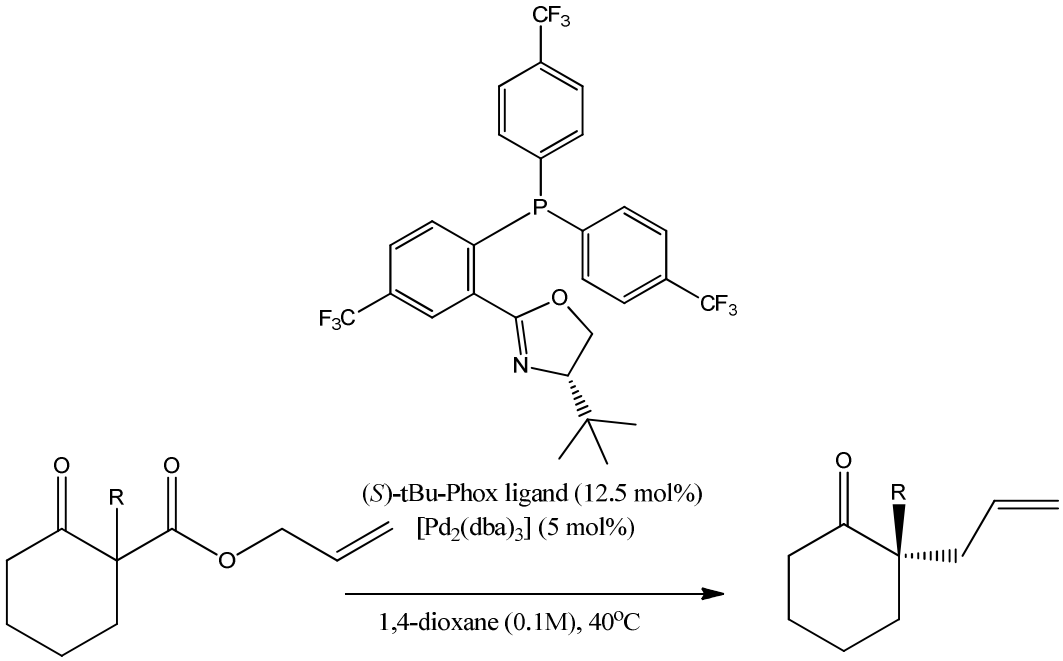
In Pd-catalyzed decarboxylated allylation Stolz group reported [45] the formation of quaternary stereocenter using Phox type ligand (Scheme 41).



Scheme 41. Decarboxylative asymmetric allylic alkylation using (*S*)-*t*-Bu-Phox ligand.

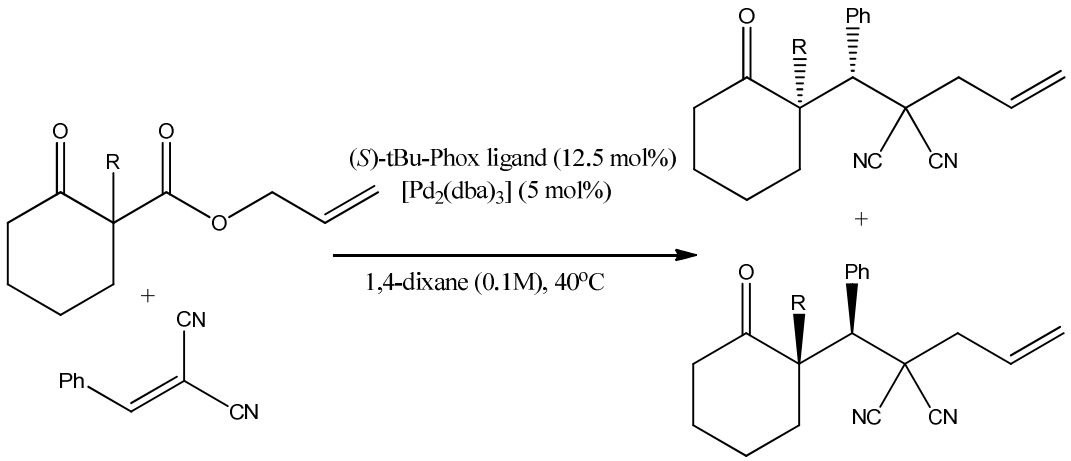
In 2010 Stolz group published another article [46] in nature chemistry describing the synthesis of all-carbon quaternary stereocenter by asymmetric α-alkylation of

ketones (Scheme 42). Readily available β-ketoesters were used as starting material. They have shown the formation of palladium enolate as a key intermediate for this type transformation which can be intercepted by acidic proton or another electrophile.



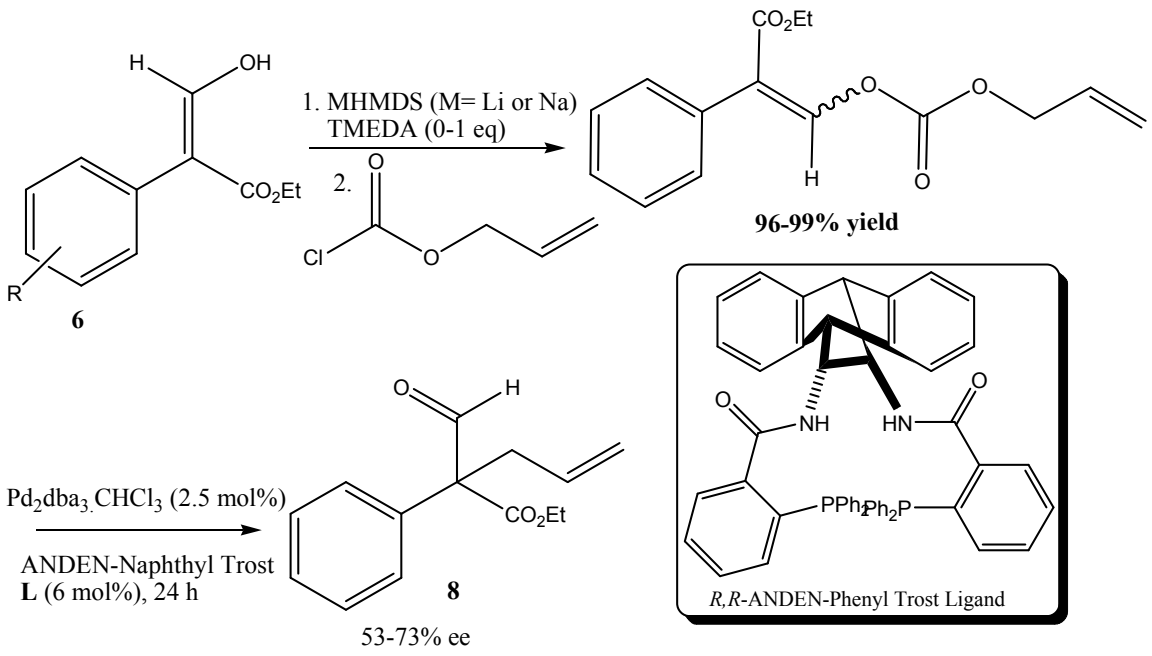
Scheme 42. Decarboxylative asymmetric allylic alkylation using modified (*S*)-*t*-Bu-Phox ligand.

Using a different prochiral electrophile enolate-trapping has been extended to the synthesis of vicinal stereocenters (Scheme 43).



Scheme 43. Formation of vicinal stereocenter using DAAA protocol.

In our group after unsuccessful attempt to induce enatioselectivity in catalytic Claisen rearrangement, E. Alberch pursued DAAA method to synthesize quaternary aldehyde **8** from hydroxyarylarylacrylate **6**. Recently we published a decarboxylative protocol [47] to get an alternate route to make compound **8**. In this method, a stereoselective synthesis of carbonates derived from 3-hydroxy-2-aryl acrylates was devised that can form the Z- or E-stereoisomer in very high Z/E ratios (50:1 and 1:99, respectively). The stereochemical outcome depends on the choice of base, addition of TMEDA and reaction temperature. The Z- and E-stereoisomers have different reactivities towards the DAAA reaction, with the E-stereoisomer displaying both greater reactivity and enantiodifferentiation with chiral ligands. The DAAA of E-stereoisomer analogues takes place in excellent yields ranging from 96–99% and enantioselectivities ranging from 42–78% ee (Scheme 44).

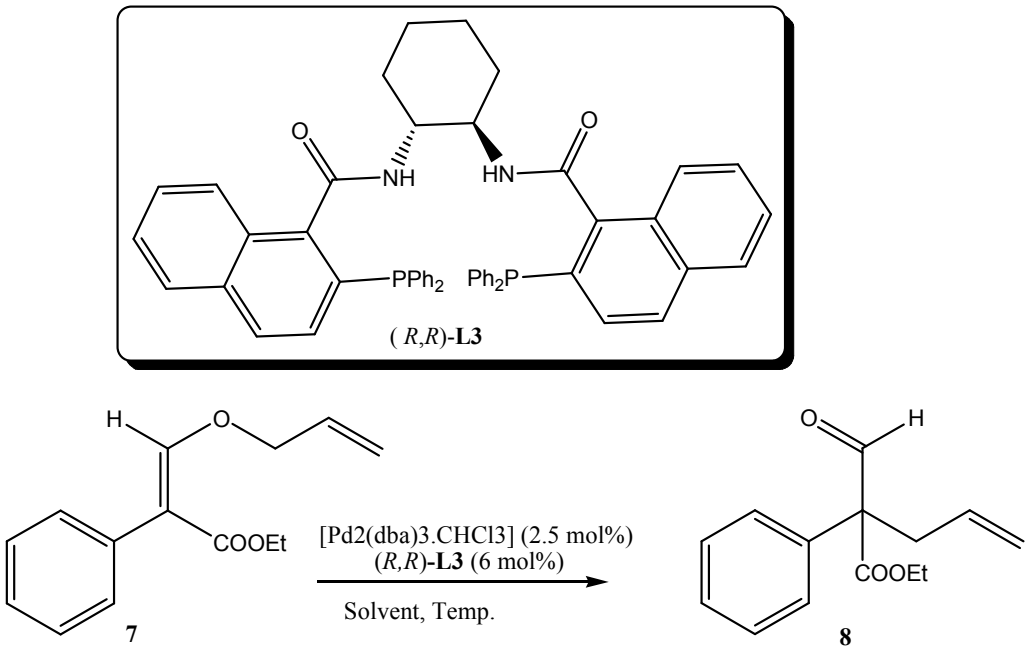


Scheme 44. Pd (0) catalyzed Decarboxylative asymmetric allylic alkylation of allyl enol carbonates modified from hydroxy-arylacrylate **6**.

2.3. RESULTS AND DISCUSSION

Inspired by the example reported by Trost and our experience with intermolecular and decarboxylative AAA reaction, we envisioned similar reaction conditions using Pd(0) as a metal source for the rearrangement reaction. In a preliminary approach with Pd(0) catalyst we proceeded with a $Pd(PPh_3)_4$ catalyzed reaction of allyl enol ether derived from 3-hydroxyarylacrylate in dichloromethane at room temperature. We found that allyl enol ether **7** underwent a Pd (0)-catalyzed rearrangement to give α-aryl quaternary carbon compound. As a Pd (0) source we found that both $Pd(PPh_3)_4$ and $Pd_2(dba)_3.CHCl_3$ were equally effective in the catalytic transformation of O-allylated compound to products.

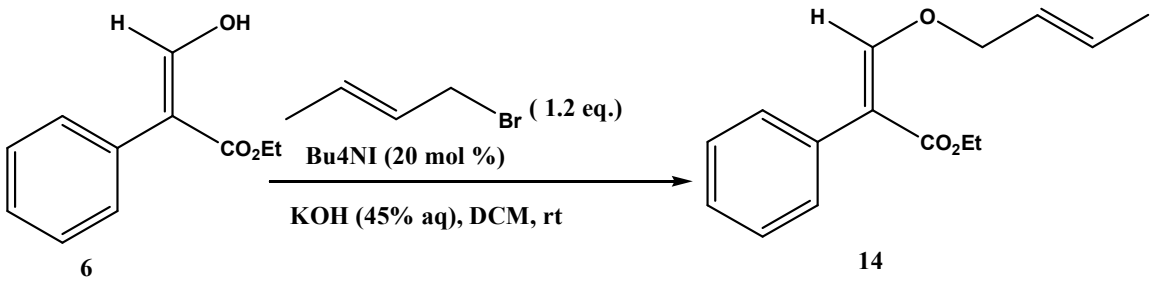
We then attempted a catalytic intramolecular asymmetric allylic alkylation of **7** using DACH-Naphthyl Trost ligand (*R,R*)-**L3** and $Pd_2(dba)_3.CHCl_3$ in dichloromethane at room temperature. The reaction gave quantitative yield and 30% ee (Scheme 45).



Scheme 45. Pd-catalyzed intramolecular AAA reactions of allyl enol ether.

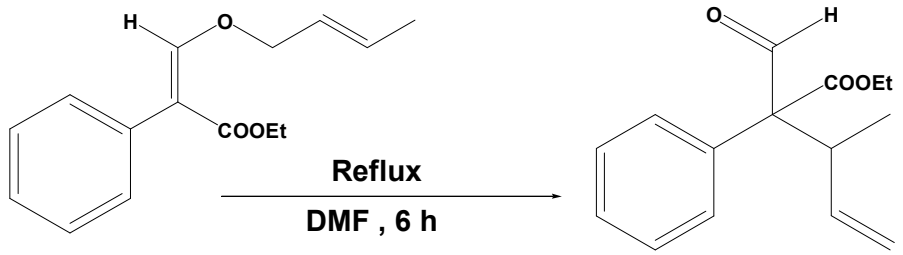
2.3.1. Mechanistic investigation

Having found our desired catalytic reaction we need to develop the reaction protocol. To understand the mechanism of the reaction, we investigated the reaction by making crotyl vinyl ether **14** from the reaction of arylhydroxyacrylate **6** and crotyl bromide under phase transfer catalysis (Scheme 46).



Scheme 46. Synthesis of O-crotylated acrylate **14**.

Reaction of this O-crotyl compound **14** with Pd^o generated both product **15** and **16** (Figure 7), whereas thermal Claisen rearrangement of crotyl phenylvinyl ether produced exclusively product **15** (Scheme 47).



O-Crotylated hydroxyarylacrylate

14

100% Conversion

15

Scheme 47. Thermal Claisen rearrangement of O-crotylated substrate **14**.

We believe formation of Pd-allyl complex is responsible for both products, where nucleophilic attack on π-allyl complex can occur in both ends. Consequently the reaction formed product **16** (75%) and product **15** (15%) from the sterically more hindered site (Figure 7).

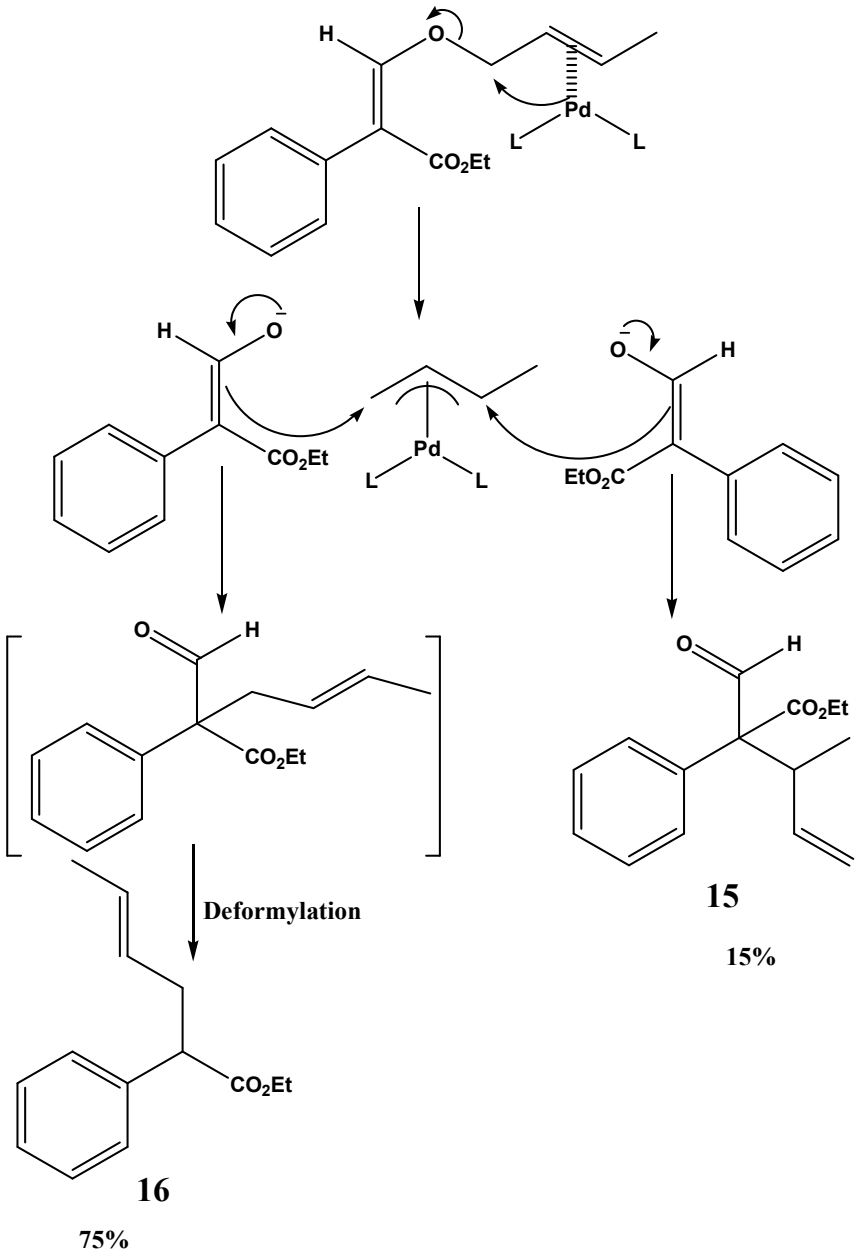


Figure 7. Pd(0) catalyzed reaction of O-crotylated substrate **14**.

Based on this study we propose a reaction mechanism for intramolecular AAA reaction of allyl enol ether (Figure 8). In the first step the ligand substituted to form a chiral ligand bound active Pd(0) complex. Second is the oxidative addition and formation of metal allyl complex changing palladium oxidation state from Pd(0) to Pd (II). In the following step, enolate carbon nucleophile attacks onto the allyl complex forming C-alkylated product and lastly the incoming ligand approaches to the metal in elimination of quaternary carbon product and regeneration of active catalyst

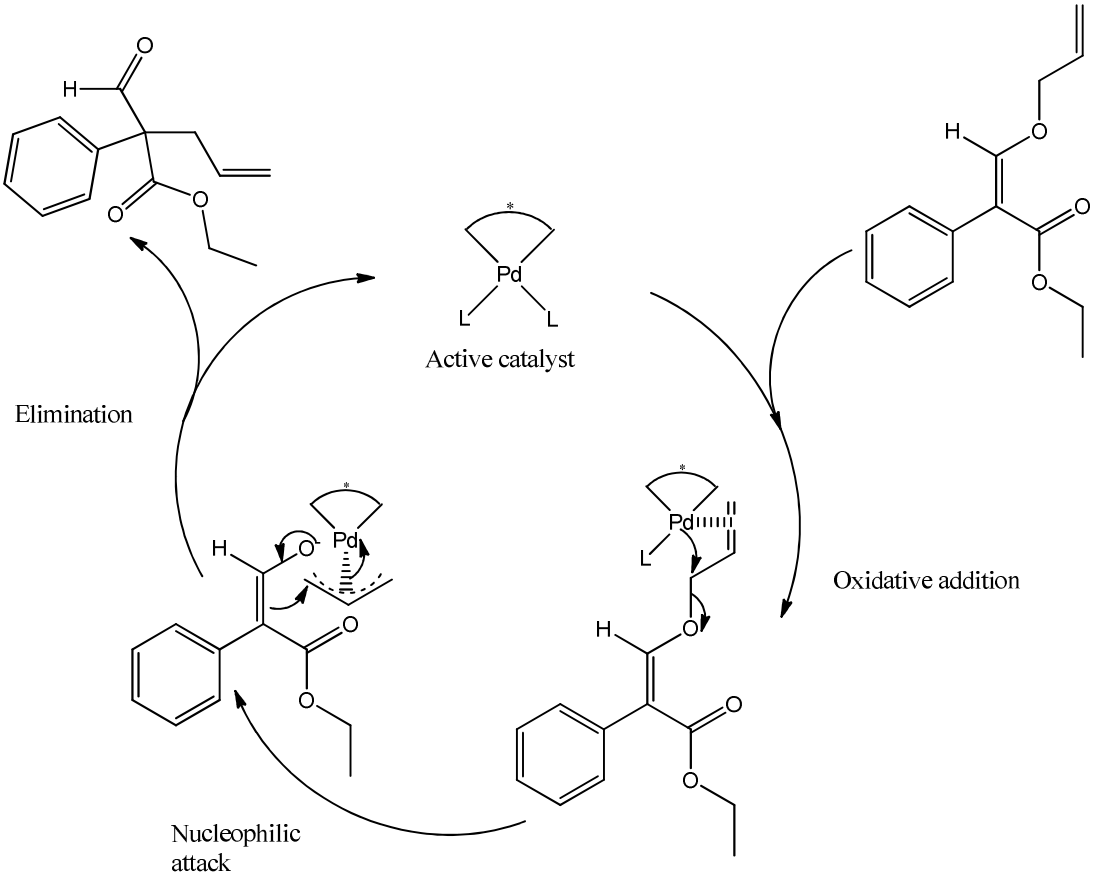
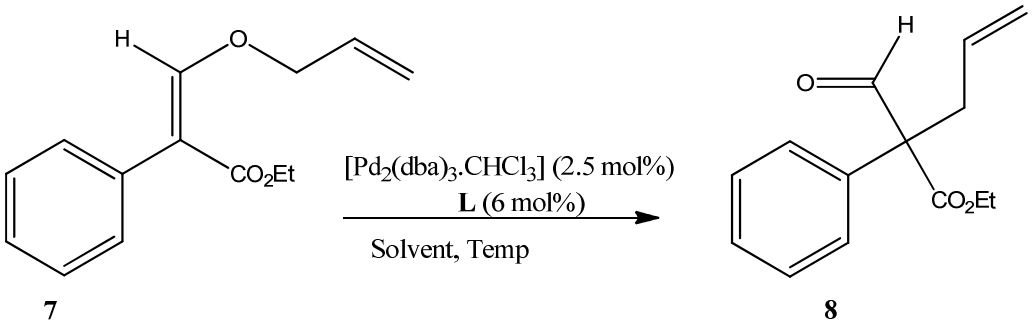


Figure 8. Proposed mechanism of intramolecular AAA reaction for allyl enol ether **7**

2.3.2. Optimization of catalytic rearrangement for the synthesis of quaternary aldehydes

Ligand Screening: In order to optimize reaction conditions for better enantioselectivity we investigated different ligands and solvent at various temperatures. For our ligand screening we selected C2 symmetric Trost ligands and Phosphinooxazolines(PHOX) which are well-known for Pd-catalyzed asymmetric allylic alkylation reactions. It was demonstrated from our studies that *C2* symmetric Trost ligands (*R,R*)-**L2**, (*R,R*)-**L3** (Figure 9) are more effective in enantiodiscrimination than the PHOX type ligands (*S*)-**L2**. Among the Trost ligands Dach-Napthyl Trost Ligand (*R,R*)-**L3** is the most effective(Table 3, entry 8), Anden-phenyl Trost (*R,R*)-**L4** gave only 30% ee, whereas with Dach-pyridyl ligand (*R,R*)-**L4** there was no reaction at all(Table 3, entry 6,7).

Table 3. Screening of Trost's ligand



7 **8**

Entry	Ligand	Solvent	Temp.(°C)	% Conversion	%ee
1.	(*R*,*R*)-**L2**	Tol:Hex (1:1)	rt	100	20
2.	(*R*,*R*)-**L2**	Tol:Hex (1:1)	-20	100	30
3.	(*R*,*R*)-**L1**	Tol:Hex (1:1)	rt	80	racemic
4.	(*R*,*R*)-**L1**	Tol:Hex (1:1)	-20	80	20
5.	(*R*,*R*)-**L4**	Tol:Hex (1:1)	rt	No Reaction	
6.	(*R*,*R*)-**L4**	Tol:Hex (1:1)	-20	No Reaction	
7.	(*R*,*R*)-**L3**	Tol:Hex (1:1)	rt	95	35
8.	(*R*,*R*)-**L3**	Tol:Hex (1:1)	-20	90	65

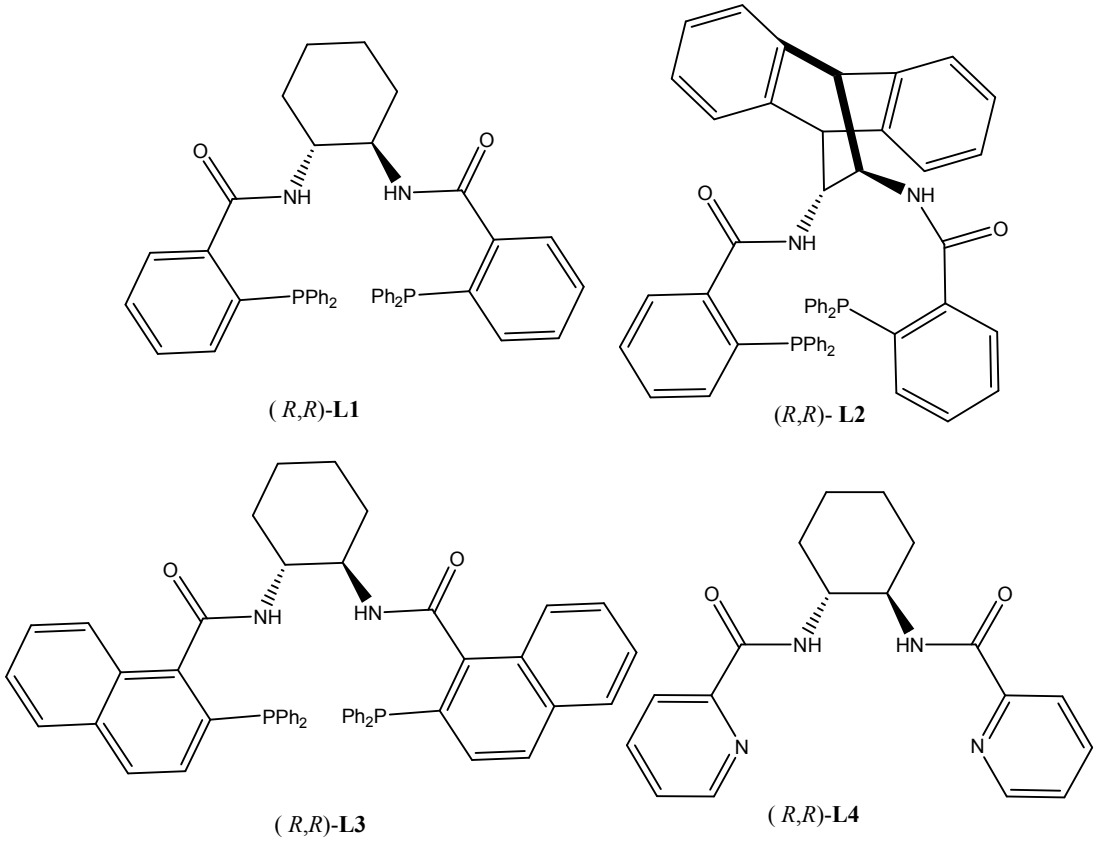
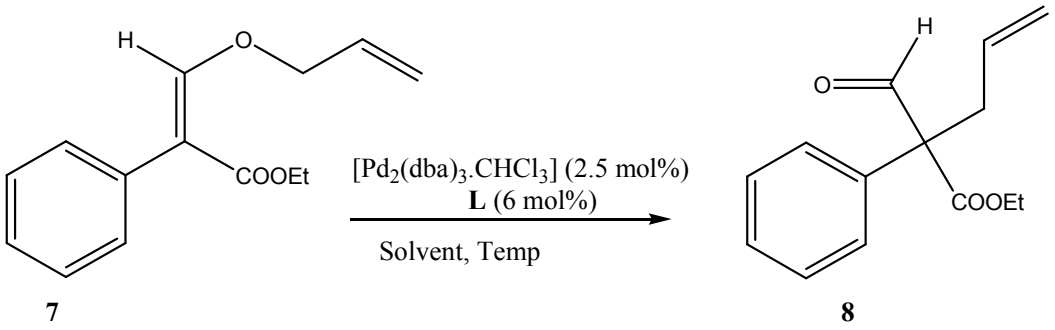


Figure 9 . C2 symmetric Trost ligands.

Other ligands such as monophosphines, BINAP type (Figure 10) and Bis-oxaziline(BOX) were also found to be less active in the transformation and in all cases they failed to induce any enantioselectivity. For BINAP and monophosphines ligands quantitative conversion is obsereved but they failed to induce enantioselectivity to the product. Results from the screening of chiral monophosphines and BINAP ligands are summarized in Table 4.

Table 4. Screening of ligands.



7 **8**

Entry	Ligand	Temperature(°C)	% Conversion	%ee
1.	XPhos	rt	100	racemic
2.	XPhos	-20	100	racemic
3.	SPhos	rt	100	racemic
4.	R-BINAP	rt	100	racemic
5.	R-BINAP	-20	100	racemic
6.	S-Tol-BINAP	rt	100	racemic
7.	S-Tol-BINAP	-20	100	racemic

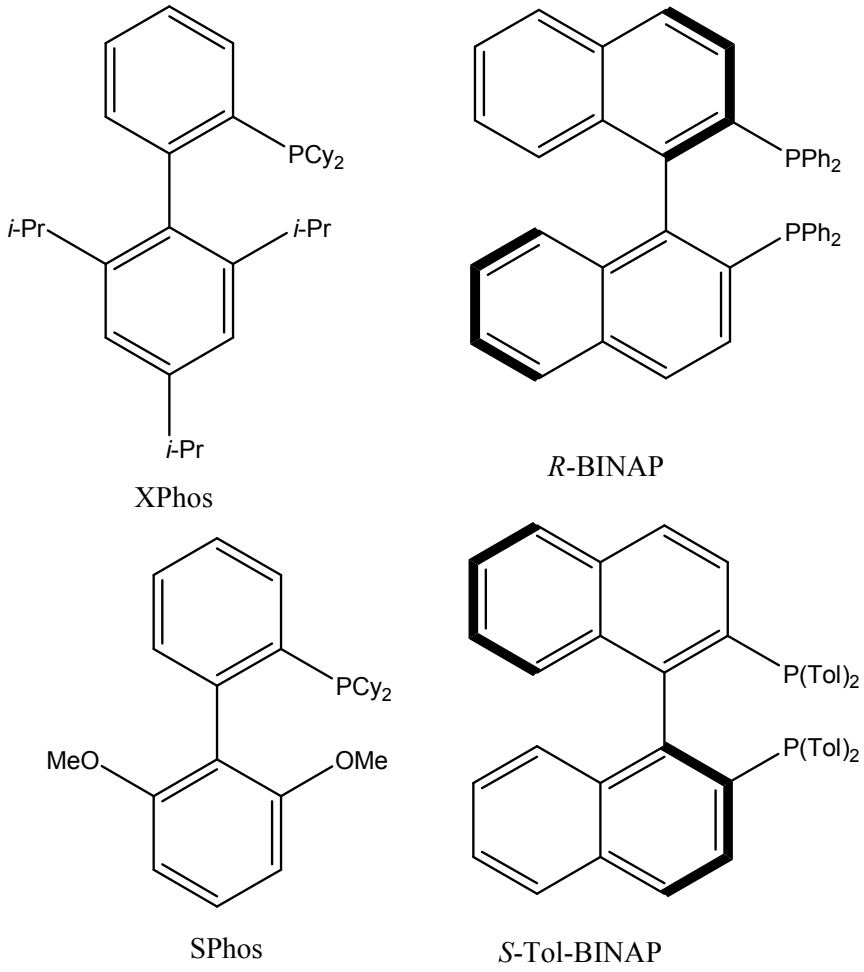
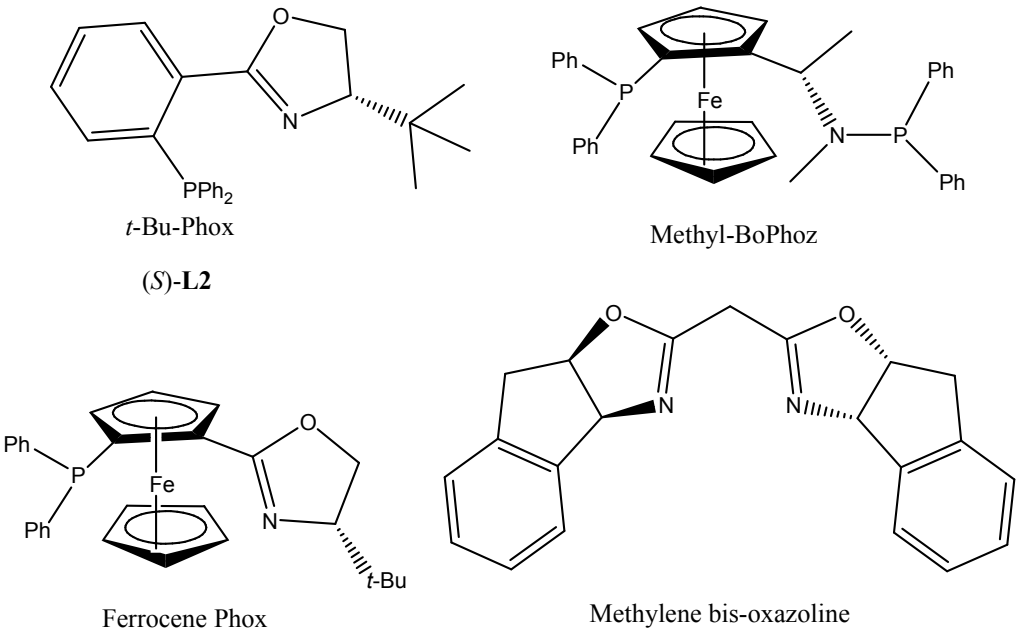


Figure 10 . Monophosphine and BINAP ligands.

Phox type ligands were reported to be an effective chirality inducing agent for asymmetric allylic alkylation and decarboxylative asymmetric allylic alkylation (DAAA) reactions. But in our reaction we found Phox ligands (S)-**L2** (Figure 11) induce moderate enantioselectivity with high conversion (Table 5, entry 1,2). However, Box and other modified Phox ligand types were not effective at all in transfering chirality to the product.



t-Bu-Phox

(*S*)-**L2**

Methyl-BoPhoz

Ferrocene Phox

Methylene bis-oxazoline

Figure 11 . Methyl-BoPhoz and Oxazoline ligands.

Table 5. Bis-oxazoline (Box) and Phox type Ligand screening.

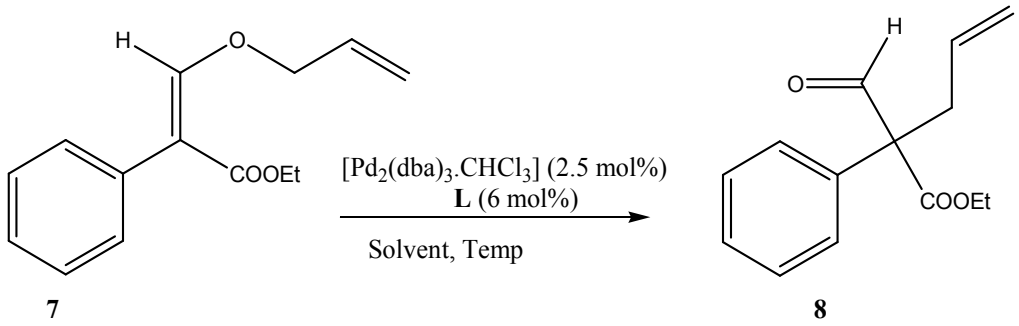
Entry	Ligand	Temperature(°C)	% Conversion	%ee
1.	t-Bu-Phox (*S*)-**L2**	rt	100	20
2.	t-Bu-Phox (*S*)-**L2**	-20	100	30
3.	Methyl-BoPhoz	rt	100	racemic
4.	Methyl-BoPhoz	-20	100	racemic
5.	Ferrocenyl Phox	rt	No Reaction	
6.	Methylene Box	rt	No Reaction	

Solvent study:

In our ligand screening we found that ligand (*R,R*)-**L3** demonstrated a high level of enantiodiscriminative sensitivity towards polarity of solvents and temperature changes of the reaction. The use of hexane/toluene solvent mixtures was previously reported by Stoltz, and it is thought that this very low polarity system increases stereoinduction by helping to form tight ion pairs through the formation of “solvent cages”. We thus reasoned that the combined effect of the formation of “solvent cages” by using low-polarity hexane/toluene (1:1) solvent and tightening the ligand pocket by switching to naphtholinker, (R,R)- **L3**, from the phenyl linker, (R,R)-**L1**, was instrumental in this dramatic increase in enantioselectivity.

Experimental results showed solvent polarity played a major role in the reaction rate and enantioselectivity, for instance under similar condition %ee for the reaction in THF was 33% whereas in mixed solvent toluene:hexane(1:1) %ee jumped to 65% (Table 3, entry 8). We believe the ideal solvent polarity which afforded us with maximum yield and enantioselectivity for our parent system comes from mixed solvent toluene:methanol (50:1) (Table 2, entry 9). We believe a plausible explanation for this lies in the solubility and complex formation of ligand and metal. Nonpolar solvents help dissolving the ligand slowly to form the metal complex; and it has better interaction with the substrate enolate in ‘tight ion pair’ formation for a longer period of time during the course of the reaction.

Table 6. Solvent effect on the reaction.



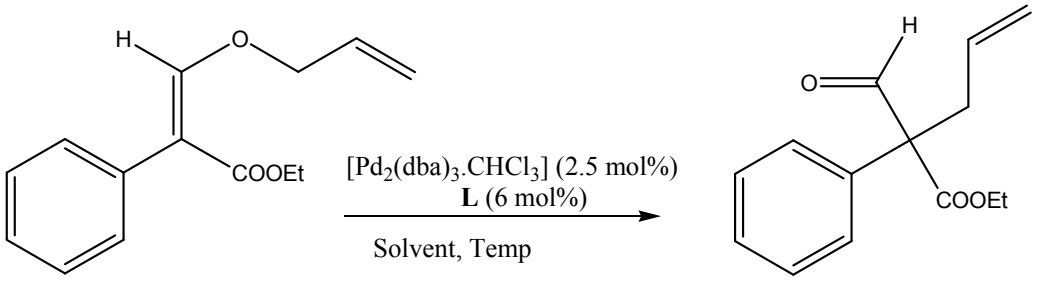
7 **8**

Entry	Solvent	Temp.(°C)	% Conv.	% ee
1.	Toluene:Hexane (1:1)	rt	100	10
2.	Toluene:Hexane (1:1)	-78 to rt	80	53
3.	Toluene:Hexane (1:1)	-20	95	65
4.	Dichloromethane	rt	100	racemic
5.	DMSO	rt	80	18
6.	Acetonitrile	rt	90	racemic
7.	THF	-20	100	33
8.	Toluene	-20	100	50
9.	Toluene:Ethanol (50:1)	-20	100	70
10.	Toluene:Methanol (50:1)	-20	100	75
11.	Toluene:Methanol (50:1)	rt	100	30
12.	Toluene:*t*-Butanol (50:1)	-20	90	33
13.	Toluene: IPA (50:1)	-20	85	35
14.	Toluene:H_2O (50:1)	-20	80	35
15.	Toluene:H_2O (50:1)	rt	85	52

Temperature effect

After ligand screening we investigated the effect of temperature on reaction rate and enantioselectivity, our results showed Temperature also has a profound effect in both yield and %ee. The reaction is found to be working best at -10 ^{o}C to -20 ^{o}C. At lower temperature i.e.,-40^{o}C or -78 ^{o}C there were no reaction at all (Table 7. entry 6 and 7) and at 0^{o}C or room temperature reaction rate was faster but resulted with reduced enantioselectivity (Table 7, entry 1-3).

Table 7. Effect of temperature on the asymmetric quaternary carbon formation.



7 **8**

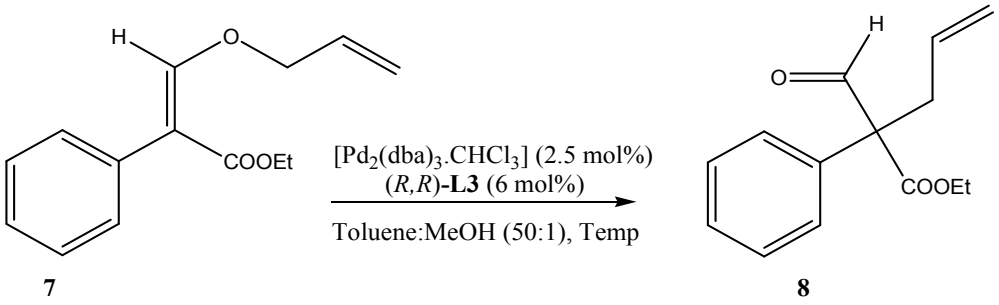
Entry	Temp. (^{o}C)	Solvent	Ligand	%Conv.	%ee
1	rt	Tol:Hex (1:1)	DACH-Naphthyl	100	30
2	rt	Dichloromethane	DACH-Naphthyl	100	racemic
3	0	Tol:Hex (1:1)	Phox	25	20

4	-20	Tol:Hex (1:1)	DACH-Naphthyl	100	60
5	-40	Tol:Hex (1:1)	DACH-Naphthyl	No Reaction	
6	-78	Tol:Hex (1:1)	DACH-Naphthyl	No Reaction	
7	-78	Tol:Hex (1:1)	Phox	No reaction	
8	-78 to rt	Tol:Hex (1:1)	DACH-Naphthyl	80	53

Additives:

In order to get optimum solvent polarity and help tight ion pair formation during the reaction we employed several additives. Addition of base has been reported to promote Pd-catalyzed alkylation reaction. We have tried several base such as triethyl amine, di-isopropylethyl amine, KOtBu, none of them were capable of producing better result (Table 8, entry 10-14). Among the additives best results were obtained for phase transfer agent such as tetrabutyl ammonium iodide which gave 52% ee at -20 oC, and RbF afforded 50% ee(Table 8, entry 6 and 9).

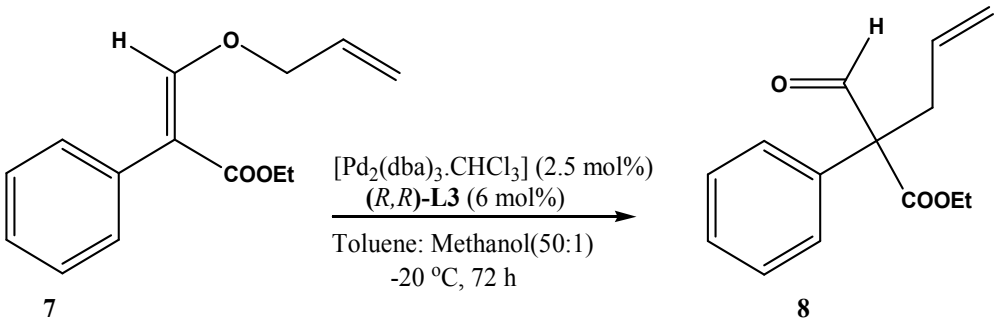
Table 8. Effects of additive on the enantioselectivity.



7 **8**

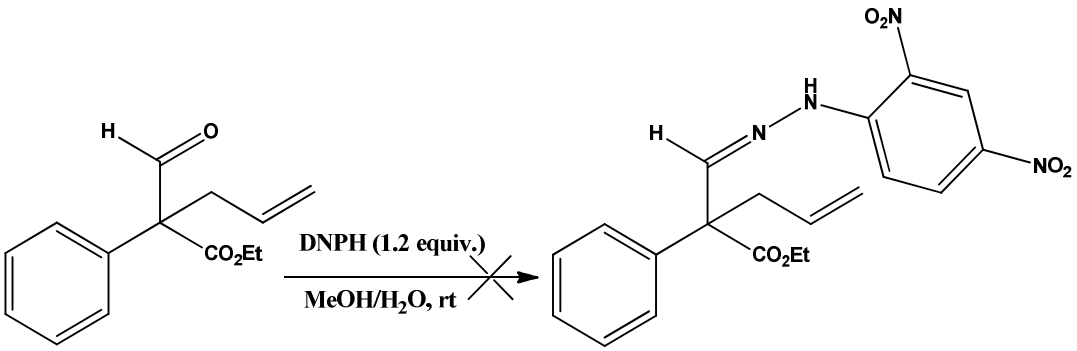
Entry	Additives	Temp. (°C)	% Conv.	% ee
1.	$LiBF_4$	rt	100	10
2.	$LiBF_4$	-78	No Rxn	
3.	NaOAc	rt	No Reaction	
4.	NaOAc	-78	No Reaction	
5.	NBu_4I	rt	100	15
6.	NBu_4I	-20	100	52
7.	NBu_4I	-78	No Reaction	
8.	$NaClO_4$	rt	No Reaction	
9.	RbF	-20	25	50
10.	KO*t*Bu	rt	No Reaction	
11.	KF	rt	No Reaction	
12.	Net_3	-78	No Reaction	
13.	Net_3	-40	No Reaction	
14	Di-isopropyl ethyl amine	-20	100	15

Finally optimized reaction condition involves (R,R)-**L3** catalyst in mixed toluene-methanol (50:1) solvent at -20 °C for 72 hours. This condition provided us with 95% conversion and 75% ee for the parent sytem (Scheme 48).



7 8

Scheme 48. Optimized reaction condition for asymmetric rearrangement reaction. Although we were able to get optical rotation of the compound **8** { **$[\alpha]_D^{27}$:** = + 73.5^0 (c = 0.082, EtOAc)} our attempt to crystallize it has been a failure. We tried to crystallize quaternary aldehydes by making it a solid hydrazone, but the reaction didn't work, instead we observed deformylation of quaternary compound (Scheme 49).



Scheme 49. Attempted reaction for the formation of solid hydrazone.

2.4. Scope of the reaction

In order to determine the scope of this rearrangement reaction, a number of analogs were subjected to the newly optimized reaction conditions. Studies

showed that electron donating or electron withdrawing groups did not appreciably affect the yields of the products, but EWG favored enantioselectivity (**8c, 8e** Figure 12). The reaction was also found to have steric effect; o-substituents have shown lower yield and enantioselectivity (**8i, 8j** Figure 12). Interestingly nitro variant of o-allylated compound needed much polar solvent than our optimized solvent system, therefore THF was the solvent choice for compound **8j** and **8m**. Electron donating methoxy substituent was found to be notorious in the optimized reaction condition, they either deformylate or catalyst failed to induce enantioselectivity (**8l, 8n, 8o**, Figure 13). However, our best result comes from the substrates with bulky substituent at the para position(8f, Figure 12). Substituent with 5-Bromo, 2-methoxy functional groups in the benzene ring provided best yield and %ee. Apparently the deleterious effect of methoxy groups was minimized by the bromo functionality and made it a ideal substrate for the transformation (compare **8d** and **8l**) .

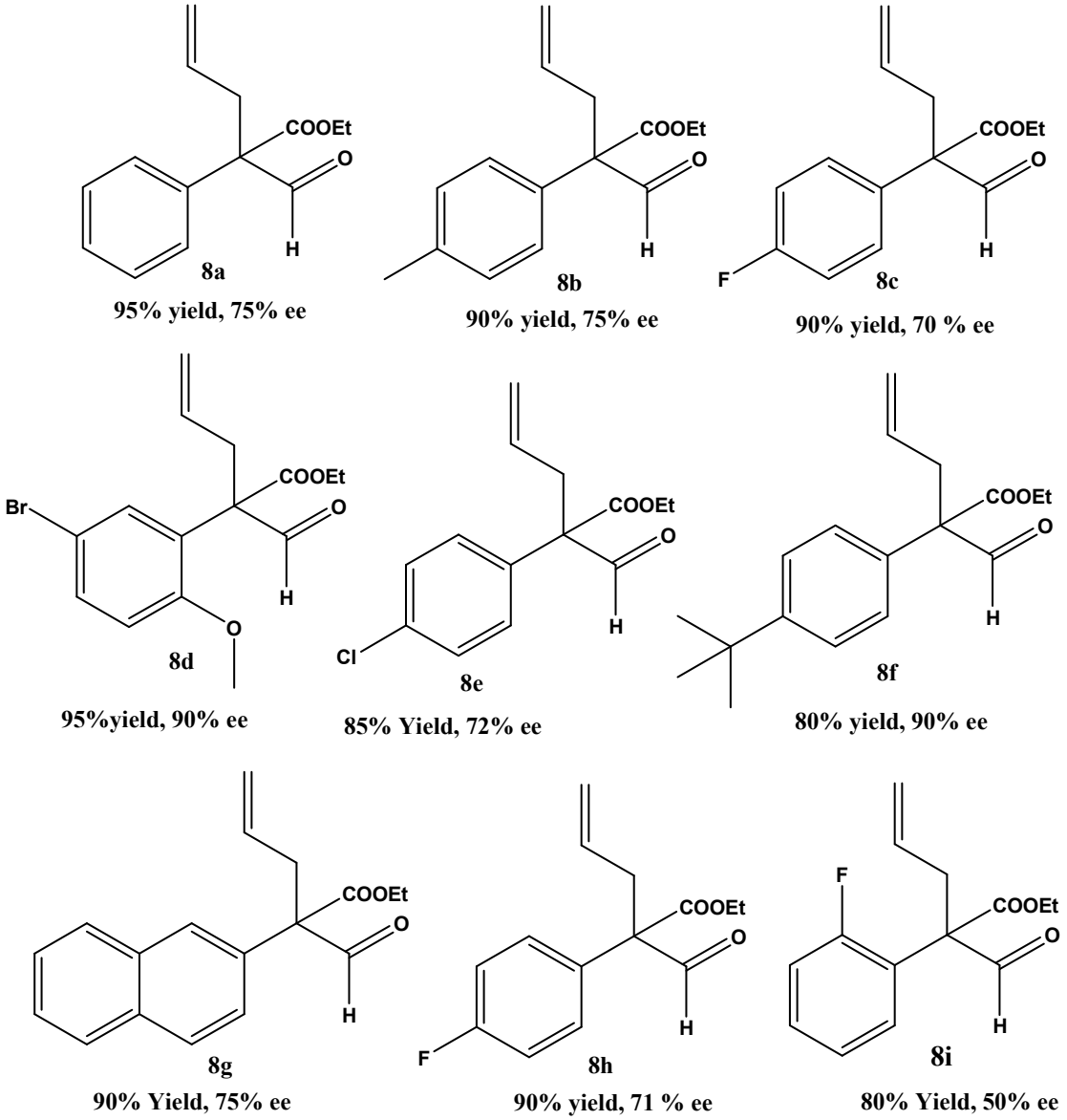


Figure 12. Scope of Pd(0) catalyzed asymmetric rearrangement of allyl enol ether **7**.

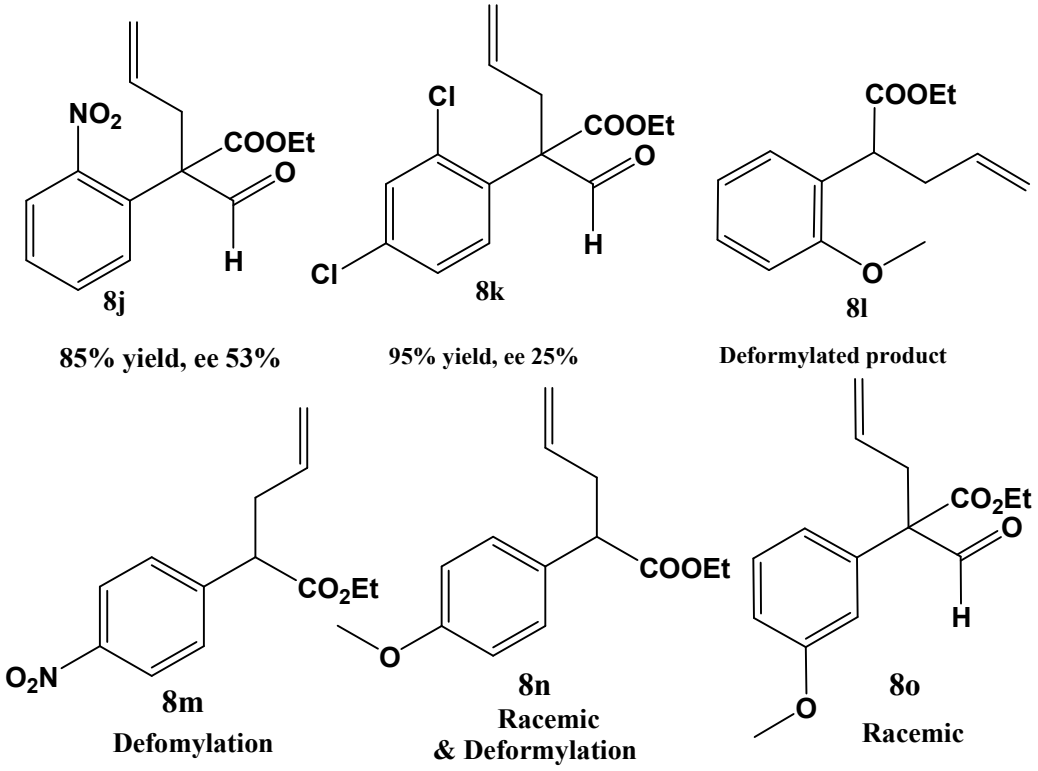
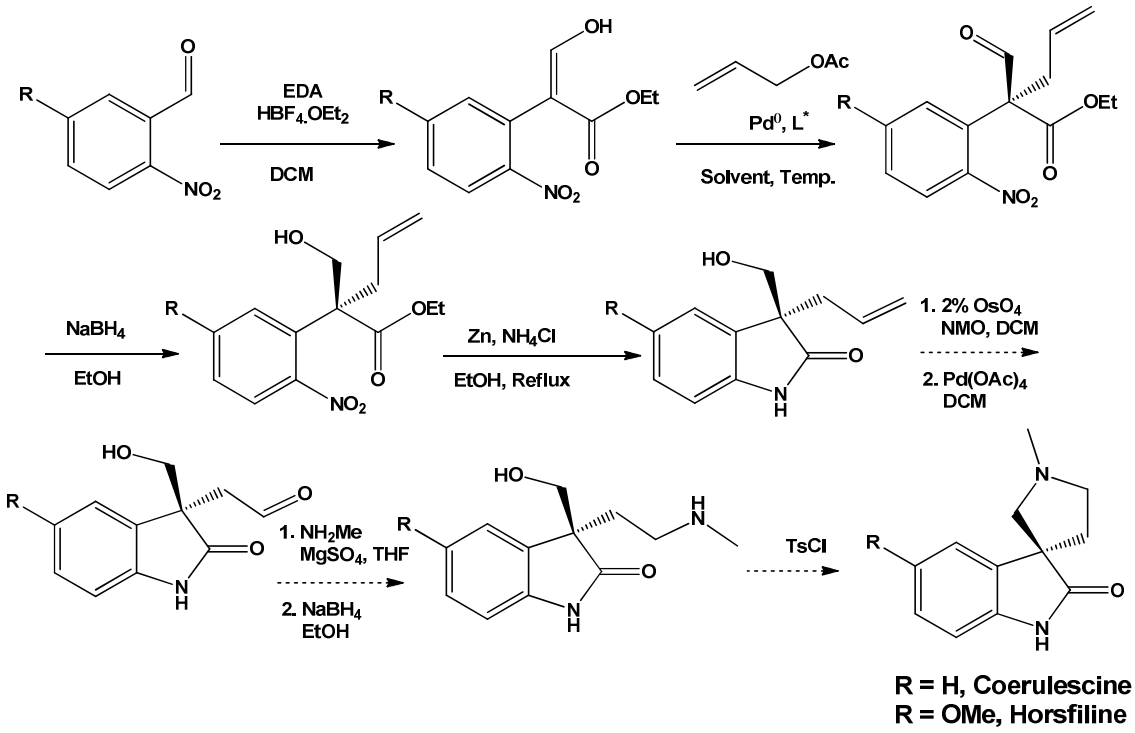


Figure 13. Scope of Pd(0) catalyzed asymmetric rearrangement of allyl enol ether **7**.

2.5. Summary and Future work:

We have accomplished the first example of Pd(0) catalyzed Claisen type rearrangement with good % yield and enantioselectivity. We believe the reaction proceed through asymmetric allylic alkylation protocol. Further optimization is necessary for better enantioselectivity of important analogs which can be used for downstream synthesis. This method can utilized for the synthesis of α-aryl quaternary aldehydes. These aldehydes have potential for the synthesis of quaternary carbon center bearing natural product, for instance, indole containing Horsefiline can be synthesized starting from o-nitroaldehydes (Scheme 50)..



Scheme 50. Synthesis of Horsfiline starting from substituted nitrobenzaldehyde.

CHAPTER 3.GENERAL METHODS AND EXPERIMENTAL

3.1. Experimental Procedures

a) General Considerations

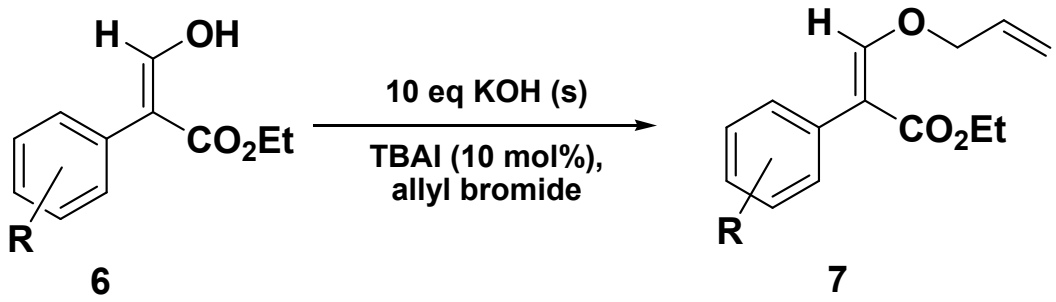
All reactions were performed under argon atmosphere in oven-dried glassware with magnetic stirring. Air and moisture-sensitive liquids and solutions were transferred via oven-dried, stainless steel syringe and were introduced into the reaction vessel through rubber septa. CH_2Cl_2 was distilled from calcium hydride. Other solvents used were distilled from sodium-benzophenone. Freshly distilled solvents were then degassed for Pd-catalyzed reactions by freeze-pump-thaw techniques under vacuum. Previously reported compounds were identified by ^1H NMR (nuclear magnetic resonance) spectrum. All new compounds were characterized by additional ^{13}C NMR and high resolution mass spectroscopy. Analytic thin layer chromatography (TLC) was performed on silica gel plates (Merck $60F_{254}$) visualized either with a UV lamp (254 nm) or by using iodine chamber. Flash chromatography was performed using 40-60 μm silica gel (Silicycle). The eluent employed for flash chromatography is reported as volume/volume ratios. Organic extracts were dried over anhydrous Na_2SO_4. ^1H and ^{13}C NMR spectra were performed on a Bruker NMR at 300 and 75 MHz, respectively. ^1H NMR data are reported as follows: chemical shift (δ) in parts per million (ppm) from tetramethylsilane as an internal standard (CDCl3 δ7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration. ^{13}C data were reported as follows: chemical shifts (δ) are reported in

parts per million (ppm) from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ77.16 ppm). Chiral HPCL analysis was performed using Waters 1500 Series HPLC equipped with Regis Technologies Pirkle Covalent chiral stationary phase column. HPLC retention times of enantiomers were determined by comparison to racemic materials. Optical rotations were measured by Jasco DIP-370 digital polarimeter using 1 cm glass cells with a sodium 589 nm filter and are reported as $[\alpha]_D^{27}$, concentration (mol/L) and solvent. High-resolution mass spectra were acquired by the University of Wisconsin Milwaukee Mass Spectrometry laboratory.

b. Synthesis of (*Z*)-ethyl 2-aryl-3-hydroxyacrylates: Compounds **6a-h** was synthesized by using our published procedure.[48] The identity of these compounds was confirmed by ^1H and ^{13}C NMR.

c. Synthesis of (*Z*)-ethyl-3-(allyloxy)-2-arylacrylates (7): 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 (Scheme 51). 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.



Scheme 51. Synthesis of O-allylated compound **7**.

(*Z*)-Ethyl 3-(allyloxy)-2-phenylacrylate (7a). Yellow oil. HRMS: 233.1169 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 167.6, 157.6, 132.7, 132.4, 130.2, 127.6, 126.9, 119.3, 111.9, 74.9, 60.2, 14.3.

(Z)-Ethyl 3-(allyloxy)-2-*p*-tolylacrylate (7b). Yellow oil. HRMS: 247.1358 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1363]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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.

(Z)-Ethyl 3-(allyloxy)-2-(4-fluorophenyl) acrylate (7c). Yellow oil. HRMS: 253.1237 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083]. ^{1}H NMR (300 MHz, $CDCl_3$): δ

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, $CDCl_3$): δ 167.4, 163.3, 158.2, 132.3, 131.8, 128.5, 118.9, 114.7, 111.0, 75.0, 60.3, 14.3.

(*Z*)-Ethyl 3-(allyloxy)-2-(5-bromo-2-methoxyphenyl)acrylate (7d). Yellow oil. HRMS: 341.0120 [calcd. for $C_{15}H_{17}BrO_4$ (M+H): 341.0388]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.39–7.28 (m, 2H), 6.77 (d, *J* = 8.7 Hz), 5.93 (m, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 157.8, 156.4, 134.2, 132.4, 131.4, 124.2, 118.6, 112.4, 112.1, 108.0, 74.8, 60.1, 55.6, 14.3.

(*Z*)-Ethyl 3-(allyloxy)-2-(4-chlorophenyl) acrylate (7e). Yellow oil**.** HRMS: 267.0788 [calcd. for $C_{14}H_{15}ClO_3$ (M+H): 267.0782]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (s,1H), 7.50-7.25 (m, 4H), 5.90 (m, 1H), 5.34 (m,1H), 4.53 (d,1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 158.5, 132.3, 131.8, 128.5, 120.8, 118.9, 110.9, 75.0, 60.3, 14.3.

(*Z*)-Ethyl 2-(4-*t*-butylphenyl)-3-(allyloxy) acrylate (7f). Yellow oil. HRMS: 289.1797 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1803]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.41–7.35 (m, 4H), 5.93 (m, 1H), 5.38 (d, *J* = 18.9 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 157.8, 149.5, 132.5, 129.5, 128.3, 124.5, 118.7, 111.6, 74.9, 60.2, 34.4, 31.2, 14.3.

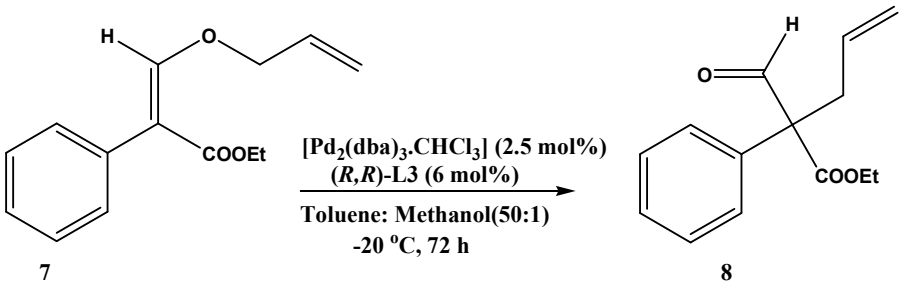
(*Z*)-ethyl 3-(allyloxy)-2-naphthalen-2-yl) acrylate (7g). Yellow solid. HRMS: 283.1329 [calcd. for $C_{18}H_{18}O_3$ (M+H): 283.1329]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.46 (m, 8H), 5.97 (m, 1H), 5.41 (m, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 133.1 132.7, 132.4, 130.2, 129.3, 128.1, 127.6, 127.0, 125.8, 125.7, 118.9, 112.0, 75.0, 60.4, 14.3.

(*Z*)-Ethyl 3-(allyloxy)-2-(4-bromophenyl) acrylate (7h). Yellow oil**.** $C_{14}H_{15}BrO_3$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.25 (m, 5H), 5.90 (m, 1H), 5.34 (m,1H), 4.53 (d,1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 158.5, 132.3, 131.8, 128.5, 120.8, 118.9, 110.9, 75.0, 60.3, 14.3.

d. Synthesis of ethyl 2-formyl-2-arylpent-4-enoates (8) General procedure.

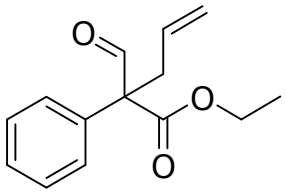
In an oven dried and desiccator-cooled sealable test tube was added $Pd_2(dba)_3$ $CHCl_3$ (4.7-7.0 mg, 0.0045-0.00675 mmol, 0.025 equivalent) and *(R,R)*-**L3** (8.5-12.8 mg, 0.0108-0.0162 mmol, 0.06 equivalent). The test tube was then evacuated and backfilled with Ar three times. Previously degassed (50:1) Tol:MeOH (5 mL) was added to the flask and the mixture was stirred for 15 min until it was homogeneous and an orange color persisted. In the meantime, another test tube was charged with (*E*)-ethyl-3-(allyloxy)-2-arylacrylate **7** (50.0 mg, 0.1844-0.2745 mmol, 1.0 equivalent), evacuated and backfilled with Ar, and then degassed solvent Toluene:MeOH (5 mL: 100 µL) was introduced, unless otherwise mentioned and was stirred the mixture to dissolve. Both of the test tubes were then put into -20^{0}C cooling bath and stir for another 15 min before transferring the

substrate solution into the catalyst mixture *via* a cannula. The reaction was stirred for 72 h, unless otherwise mentioned. The reaction mixture was then passed through a thick pad of silica plug and the solvent was removed *in vacuo*. The pure product was isolated by column chromatography (5–10% ethyl acetate in Hexane) and identified by ^{1}H NMR. ^{1}H, ^{13}C NMR and HRMS were applied to characterize the new compounds.



Scheme 52. Optimized reaction condition for the synthesis of compound **8**.

Ethyl 2-formyl-2-phenylpent-4-enoate (8a).

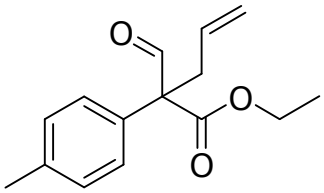


Light yellow oil. HRMS: 233.1000 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177]. ^{1}H NMR (300 MHz, $CDCl_3$): □ 9.95 (s, 1H), 7.44–7.23 (m, 5H), 5.76 (m, 1H), 5.13 (d, *J* = 18 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.14 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): □ 196.3, 170.6, 135.0, 132.6, 129.0, 128.5, 127.8, 119.1, 65.6, 61.6, 37.5, 14.0.

Chiral HPLC: 75% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 15.99 min (minor), 18.04 min (major).

$[\alpha]_D^{27}$: = + 73.5^0 (c = 0.082, EtOAc).

Ethyl 2-formyl-2-*p*-tolylpent-4-enoate (8b).

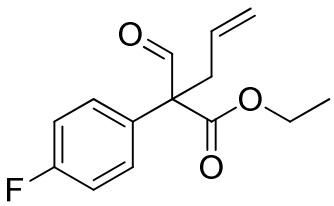


Yellow oil. HRMS: 247.1346 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1334]. ^{1}H NMR (300 MHz, $CDCl_3$): □ 9.90 (s, 1H), 7.28–7.12 (m, 4H), 5.75 (m, 1H), 5.15 (d, *J* = 18.3 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.12 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): □ 196.3, 170.8, 137.9, 132.8, 130.0, 129.0, 127.4, 118.9, 65.3, 61.5, 36.5, 20.8, 14.0.

Chiral HPLC: 75% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 14.00 min (minor), 15.35 min (major).

$[\alpha]_D^{27}$: = + 42.5^0 (c = 0.081, EtOAc).

Ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate (8c).



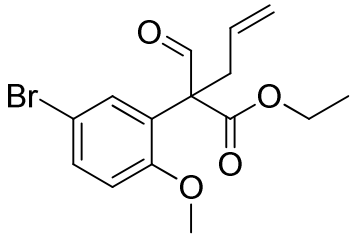
Yellow oil. HRMS: 251.1072 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083]. ^{1}H NMR (300MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.28–7.07 (m, 4H), 5.73 (m, 1H), 5.20-5.05 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.11 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.88 (dd, *J* = 7.8, 14.1 Hz,

1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 170.5, 160.5, 132.3, 130.7, 129.2, 116.1, 115.8, 65.0, 61.8, 36.8, 14.0.

Chiral HPLC: 70% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 16.00 min (minor), 17.48 min (major).

$[\alpha]_D^{27}$: = + 40.6^0 (c = 0.072, EtOAc).

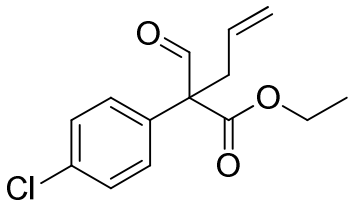
Ethyl 2-(5-bromo-2-methoxyphenyl)-2-formylpent-4-enoate (8d).



Yellow oil. HRMS: 347.0244 [calcd. for $C_{15}H_{17}BrO_4$ (M+Li): 346.9698]. ^{1}H NMR δ: 10.1 (s, 1H), 7.42-7.31 (m, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.15-5.05 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.00 (dd, *J* = 6.6, 13.8 Hz, 1H), 2.80 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR δ: 197.8, 170.6, 155.5, 132.0, 130.8, 128.7, 128.0, 119.1, 113.4, 112.6, 68.0, 61.2, 55.7, 36.5, 14.0.

Chiral HPLC: 90% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 13.57 min (minor), 15.99 min (major).

Ethyl 2-(4-chlorophenyl)-2-formylpent-4-enoate (8e)

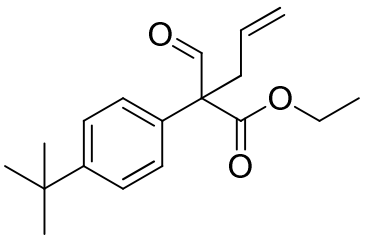


yellow oil. HRMS: 267.0788 [calcd. for $C_{14}H_{15}ClO_3$(M+H): 267.0782].^{1}H NMR (300 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.54 (d, *j* = 8.7, 2H), 7.13 (d, *j* = 8.7, 2H), 5.73 (m, 1H), 5.11 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.10 (dd, J = 6.3,

13.8 Hz, 1H), 2.86 (dd, J = 7.8, 13.8 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 170.3, 134.1, 132.2, 129.1, 128.7, 128.535, 128.4, 122.5, 119.7, 65.2, 61.9, 36.7, 14.1.

Chiral HPLC: 73% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 13.89 min (minor), 14.81 min (major).

Ethyl 2-(4-tert-butylphenyl)-2-formylpent-4-enoate (8f).

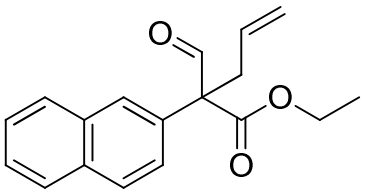


Yellow oil. HRMS: 289.1809 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1804]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.42 (d, *J* = 6.7 Hz, 2H), 7.18 (d, *J* = 6.7 Hz, 2H), 5.90 (m, 1H), 5.15 (d, *J* = 18.9 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.15 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.86 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 170.8, 151.0, 132.8, 131.8, 126.8, 126.4, 119.3, 65.2, 61.5, 36.5, 34.4, 31.1, 14.0.

Chiral HPLC: 79% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 11.59 min (minor), 12.33 min (major).

$[\alpha]_D^{27}$: = + 83.0^0 (c = 0.035, EtOAc).

Ethyl 2-formyl-2-(naphthalen-2-yl)pent-4-enoate (8g).



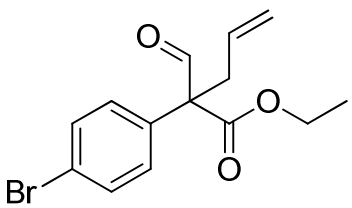
yellow solid. HRMS: 283.1360 [calcd. for $C_{18}H_{19}O_3$ $(M+H)^+$: 283.1328] ^1H NMR (300 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.91–7.34 (m, 7H), 5.82 (m, 1H), 5.19 (d, J = 18 Hz, 1H), 5.13 (d, J = 9.9 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.25 (dd, J = 6.3, 13.8 Hz, 1H), 3.01 (dd, J = 8.1, 13.8 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 170.8, 133.3, 132.7, 132.4, 128.9, 128.4, 128.2, 127.6, 126.8, 126.7, 126.6, 124.7, 119.3, 65.8, 61.8, 36.8, 14.1.

Chiral HPLC: 75% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 28.17 min (minor), 32.92 min (major).

$[\alpha]_D^{27}$: = + 48.5^0 (c = 0.067, EtOAc).

HRMS (ESI): Calculated (m/z) for C18H19O3 $(M+H)^+$: 283.1328, Found 283.1360.

Ethyl 2-(4-bromophenyl)-2-formylpent-4-enoate (8h).



Yellow oil. HRMS $(M+H)^+$: 311.0274 [calcd. for $C_{14}H_{16}O_3Br$ $(M+H)^+$: 311.0283].^1H NMR (300 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.54 (d, *j* = 8.7, 2H), 7.13 (d, *j* = 8.7, 2H), 5.73 (m, 1H), 5.11 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.10 (dd, J = 6.3, 13.8 Hz, 1H), 2.86 (dd, J = 7.8, 13.8 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 195.9, 170.3, 134.1, 132.2, 129.1, 128.7, 128.535, 128.4, 122.5, 119.7, 65.2, 61.9, 36.7, 14.1.

Chiral HPLC: 71% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 14.57 min (minor), 15.57 min (major).

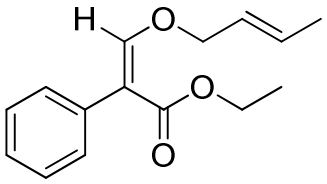
$[\alpha]_D^{27}$: = + 78.3^0 (c = 0.058, EtOAc).

HRMS (ESI): Calculated (m/z) for $C_{14}H_{16}O_3Br$ $(M+H)^+$: 311.0283, Found 311.0274.

3.2. Synthesis of (Z)-ethyl 3-((E)-but-2-en-1-yloxy)-2-phenylacrylate (14): 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.), crotyl bromide (1.2 equiv.), and potassium hydroxide (10 equiv.) were added, and the reaction mixture was stirred at room temperature until reaction completion was confirmed by NMR. The reaction was quenched by adding saturated NH_4Cl, and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The organic extracts were combined and dried over Na_2SO_4. The organic layer was then passed through a silica plug and the solvent was removed by rotary evaporation. Pure product was isolated by column chromatography (5–10% ethyl acetate in pentane) and identified by ^1H NMR. ^1H, ^{13}C NMR and HRMS were applied to characterize the new compounds.

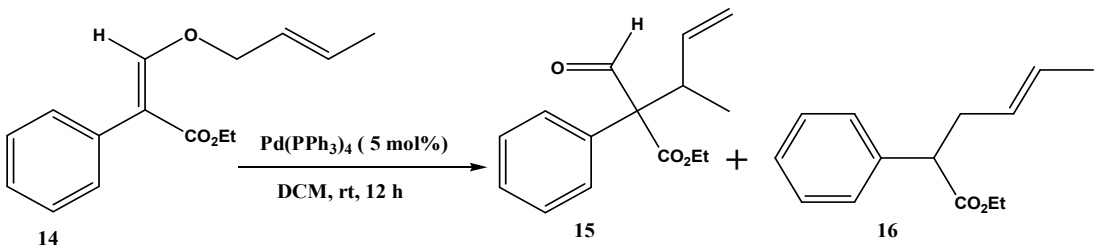
(Z)-ethyl 3-((E)-but-2-en-1-yloxy)-2-phenylacrylate (14):



Yellow oil. HRMS: 247.1334 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1329]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.45-7.30 (m, 5H), 5.85 (m, 1H), 5.63 (m, 1H), 4.47(d, *J* = 4.0 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.77(d, *J*= 6Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 167.9, 157.8, 132.7, 132.4, 130.2, 127.6, 126.9, 124.7, 111.7, 75.1, 60.2, 17.8, 14.3. **HRMS (ESI):** Calculated (m/z) for $C_{15}H_{18}O_3$ $(M+H)^+$: 247.1329, Found 247.1334.

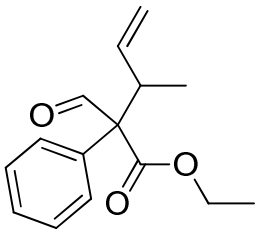
General procedure for the synthesis of compound 15 and 16:

In an oven dried and desiccator-cooled sealable test tube was added $Pd(PPh_3)_4$ (5.0 mg, 0.0045-0.01mmol, 0.050 equivalent) at room temperature under argon. Previously degassed dichloromethane (3 mL) was added to the flask and the mixture was stirred for 15 min until it was homogeneous and a golden yellow color persisted. (Z)-Ethyl 3-((E)-but-2-en-1-yloxy)-2-phenylacrylate **14** (50.0 mg, 0.203 mmol, 1.0 equivalent) was then added via syringe. The reaction was stirred for overnight, unless otherwise mentioned. The reaction mixture was then passed through a thick pad of silica plug and the solvent was removed *in vacuo*. The pure product **15** and deformylated product **16** was isolated by column chromatography (5–10% ethyl acetate in Hexane) and identified by ^{1}H NMR. ^{1}H, ^{13}C NMR and HRMS were applied to characterize the new compounds.



Scheme 53. Synthesis of compound **15** and **16** from o-crotylated substrate **14**.

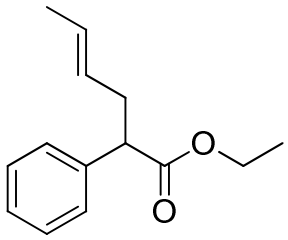
(E)-ethyl 2-formyl-3-methyl-2-phenylpent-3-enoate (15):



Yellow oil. HRMS: 247.1334 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1329]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.40-7.21 (m, 5H), 5.90 (m, 1H), 5.1 (m, 1H), 4.98(m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.46 (m, 1H), 1.33(t, 3H), 1.1 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 196.2, 170.3, 139.1, 134.2, 128.8, 128.6, 127.9, 116.3, 69.4,61.6, 41.2, 16.5, 14.1.

HRMS (ESI): Calculated (m/z) for $C_{15}H_{18}O_3$ $(M+H)^+$: 247.1329, Found 247.1334.

(E)-ethyl 2-phenylhex-4-enoate (16):



Yellow oil. HRMS: 219.1385 [calcd. for $C_{14}H_{18}O_2$ (M+H): 219.1380] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 5.50 (m, 1H), 5.34 (m, 1H), 4.14 (m, 2H), 3.60 (m, 1H), 2.78 (m, 1H), 2.45(m, 1H), 1.63(d, 3H), 1.24 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 138.9, 128.5, 127.9, 127.8, 127.6, 127.1, 60.6, 52.1, 36.7, 17.9, 14.2.

HRMS (ESI): Calculated (m/z) for $C_{14}H_{18}O_2$ $(M+H)^+$: 215.1380, Found 215.1385.

II. SYNTHESIS OF CHIRAL TRYPTOPHAN ANALOGS AND STUDIES TOWARDS SYNTHESIS OF TRYPROSTATIN A AND B.

CHAPTER 4. SYNTHESIS OF ASYMMETRIC TRYPTOPHAN

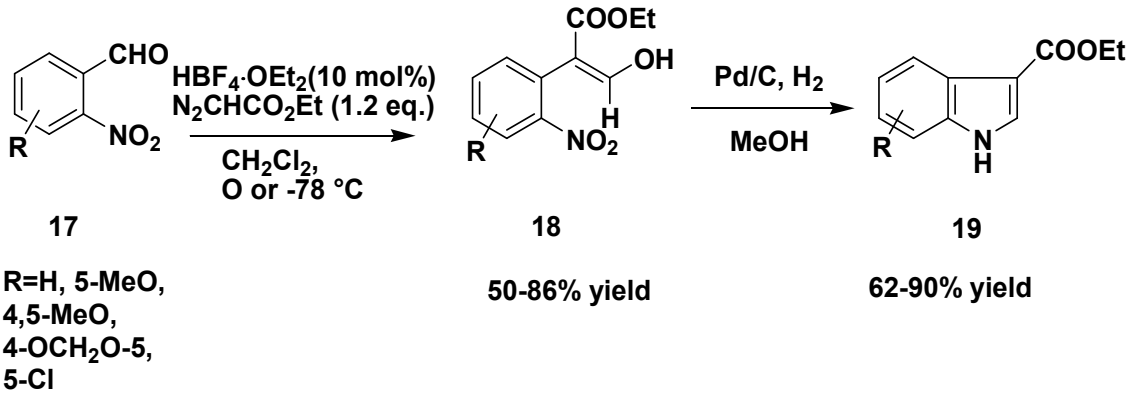
4.1.1. Introduction

Optically active tryptophans have been regarded as important components in the areas of both synthetic and medicinal chemistry.[49] Ring-A substituted tryptophans have been utilized in the design and synthesis of many biologically active compounds, including indole-based alkaloids, which have recently been receiving attention for their anti-cancer properties.[50] Several methods are known to effectively synthesize enantiopure tryptophans, but most strategies are only suitable for a particular species of tryptophan. [51] Many of these methods use stoichiometric amounts of chiral auxiliaries and extensive multistep syntheses, and often involve problematic separation of isomers obtained in the alkylation and annulation steps.[51] In recent years, asymmetric phase-transfer catalysis (PTC) has been established as a powerful tool in the synthesis of chiral mono- and di-substituted α-amino acids.[52, 53] To date, the only reported asymmetric substitution of this type utilizes a relatively unstable Boc-protected indole to synthesize α-methyl tryptophan in 78% yield and 91% ee,[53e] but there has not been a general synthesis of chiral tryptophans via PTC reported. In this paper, we describe a simple, cost-effective, one-pot synthetic procedure that can be used to prepare chiral tryptophan derivatives via a phase-transfer-catalyzed (PTC) asymmetric

alkylation reaction. We believe that this approach is the most economical and versatile process for synthesizing these important chiral building blocks.

4.1.2. Indole and Tryptophan chemistry

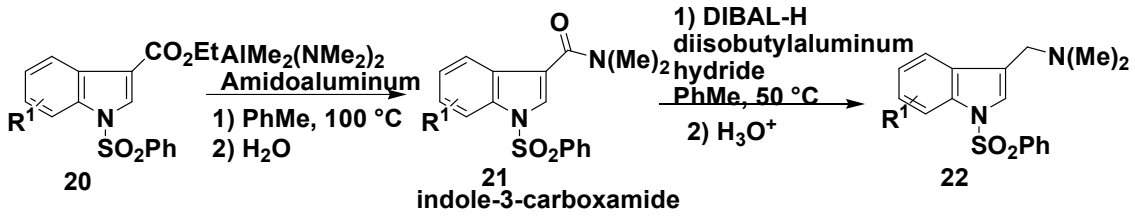
In our group we have a procedure [54] for the synthesis of substituted indole ethyl ester **19**, starting from substituted o-nitro aldehyde **17** in two steps. In the first step Bronsted acid catalyzed formation of hydoxyarylacrylate **18** , which after hydrogenation fromed indole compound 19 in good yield (**Scheme 54**).



Scheme 54. Synthesis of indole-3-ethyl ester **19**, from substituted o-nitrobenzaldehyde.

A series of indole-based indole-3-carboxamides could be efficiently synthesized [55] from various indole-3-carboxylates using an amidoaluminum-mediated strategy (Scheme 55). The treatment of ethyl indole-3-carboxylates bearing a range of substitution patterns on the indole ring with various amidoaluminum complexes, led to the corresponding 1*H*-indole-3-carboxamides in yields up to 75%. Reduction by diisobutylaluminum hydride afforded the corresponding gramines in 63-85% yield. This is the first reported example of amidoaluminum complexes of type

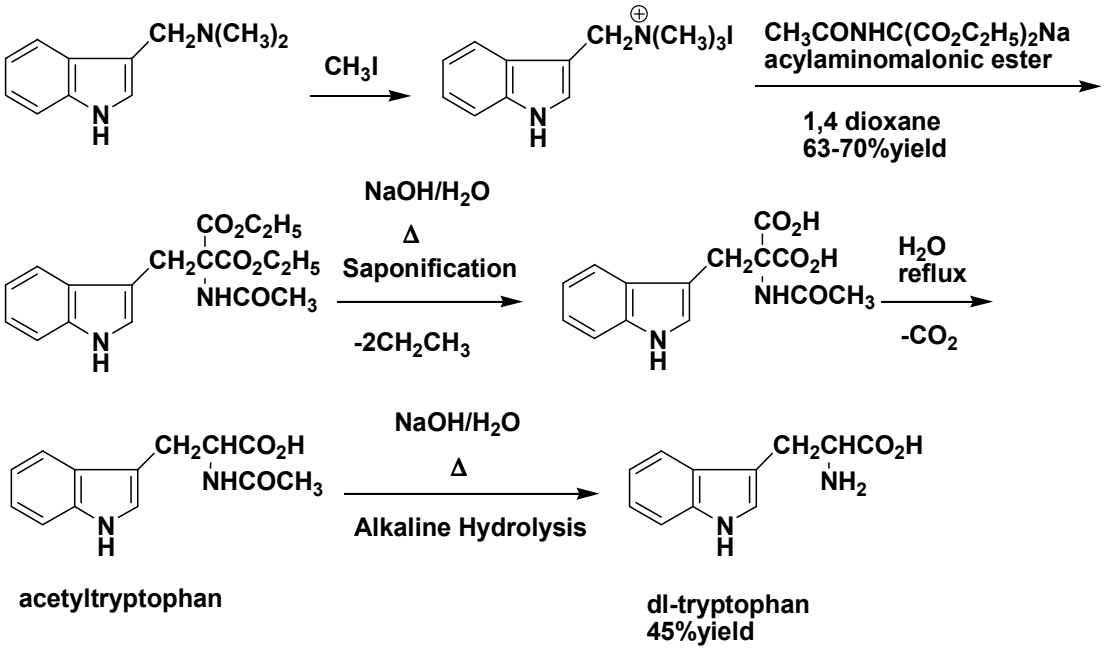
$Al_2(CH_3)_4(NR_2)_2$ promoting facile amidation of relatively inert indole esters.



R¹	Yield 21	Yield 22
H	77	94
5-MeO	73	87
6-MeO	64	90
5-Br	61	65

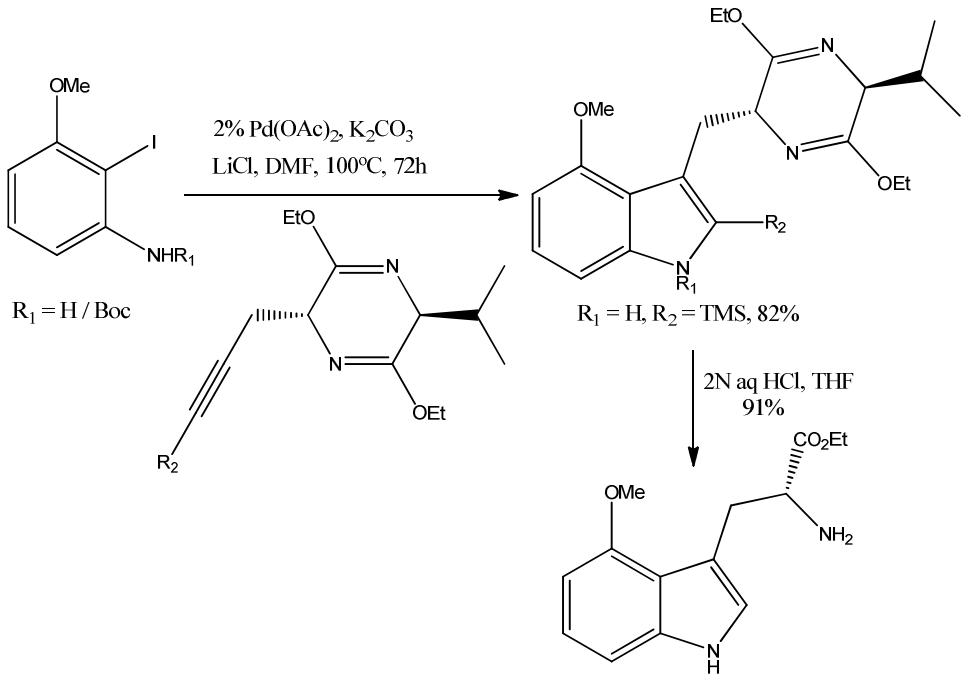
Scheme 55. Synthesis of gramine analogs from indole ethyl ester.

Since first report by Snyder [56], gramine and its methiodide salts has been used for the synthesis of tryptophan. The quaternary ammonium salt was condensed with compounds having active methylene groups such as acetylaminomalonic ester to give aminodiester compound. After subsequent hydrolysis racemic tryptophan was synthesized in moderate yield (Scheme 56).



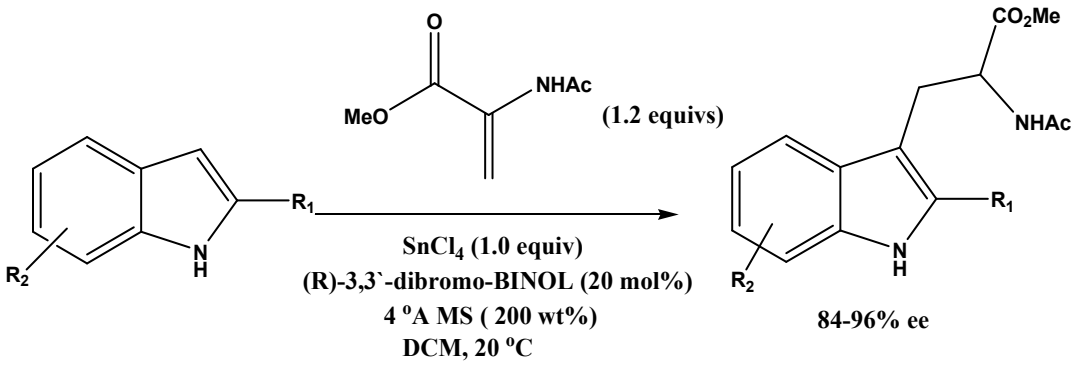
Scheme 56. Synthesis of racemic tryptophan from gramine.

In 2007 Cook group reported [51e] the synthesis of 4-methoxytryptophan in good yield and optical purity. Before that it was made via a kinetic resolution of tryptophan produced by the use of immobilized penicillin G acylase reported by Ley et al. In previous studes they found that the Larock heteroannulation concomitant with Schollkopf chiral auxiliary is a powerful method for the synthesis of ring-A substituted indole derivatives and has been utilized for the regiospecific synthesis of both 11- and 12-methoxy-substituted indole alkaloids. Hydrolysis of the Schollkopf chiral auxiliary along with the loss indole 2-silyl group provided with a high yielding synthesis of 4-methoxy tryptophan (Scheme 57). Better selectivity was achieved when a bulky silyl-substituted internal alkyne is used as a substrate also from the steric interactions between the ortho substituent and the substituent on the alkyne.



Scheme 57. Synthesis of chiral 4-methoxytryptophan using Larock hetero annulations and chiral Schollkopf auxiliary.

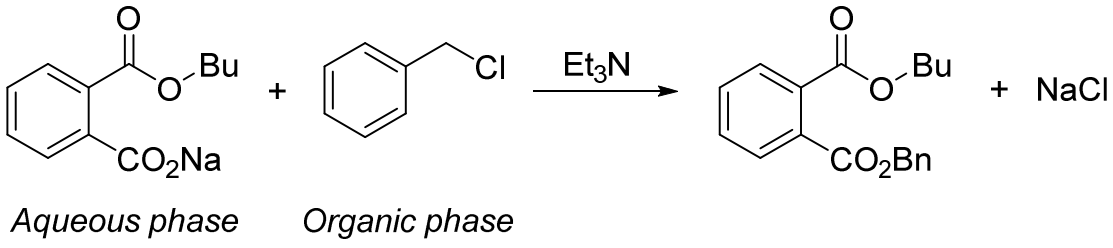
Reisman group in 2012 reported [57] the tandem Friedel−Crafts conjugate addition/ asymmetric protonation reaction between 2-substituted indoles and methyl 2-acetamidoacrylate. The reaction is catalyzed by (R)-3,3′ -dibromo-BINOL in the presence of stoichiometric amount of $SnCl_4$. BINOL·SnCl4 complex acts as a catalyst for this tandem conjugate addition /asymmetric protonation reaction. They have reported a range of indoles furnished synthetic tryptophan derivatives in good yields and high levels of enantioselectivity (Scheme 58).



Scheme 58. Enantioselective Synthesis of Tryptophan Derivatives by a TandemFriedel−Crafts Conjugate Addition/Asymmetric Protonation Reaction.

4.1.3. Phase transfer catalysis: general concepts and mechanisms of action

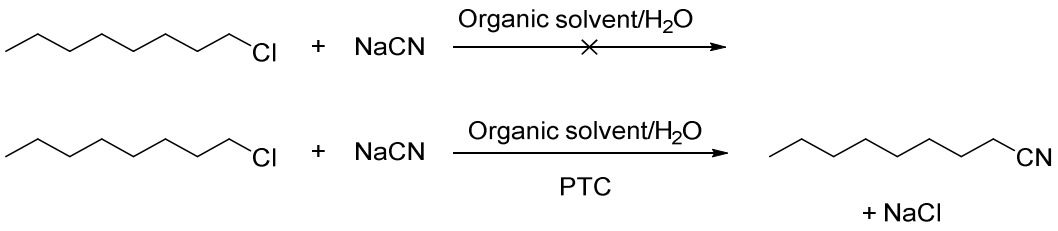
In 1946, the first example of a phase transfer catalyzed reaction was reported on the alkylation reaction of a sodium carboxylate salt. During the reaction the phase transfer catalyst, benzyltriethylammonium chloride is formed in situ by the attack of trimethylamine base to benzyl chloride (Scheme 59).[58]



Scheme 59. First report of phase transfer catalysis .

Starks established the fact that there is a significant increase in the reaction rate for the tetralkyammonium or tetralkylphosphonium catalyzed reaction between an

aqueous solution of sodium cyanide and organic solution of an alkyl halide (Scheme 60). It was in 1971 that Starks for the first time reported the term 'phase transfer catalysis'[59].



Scheme 60. Phase transfer catalyzed reactions reported by Starks.

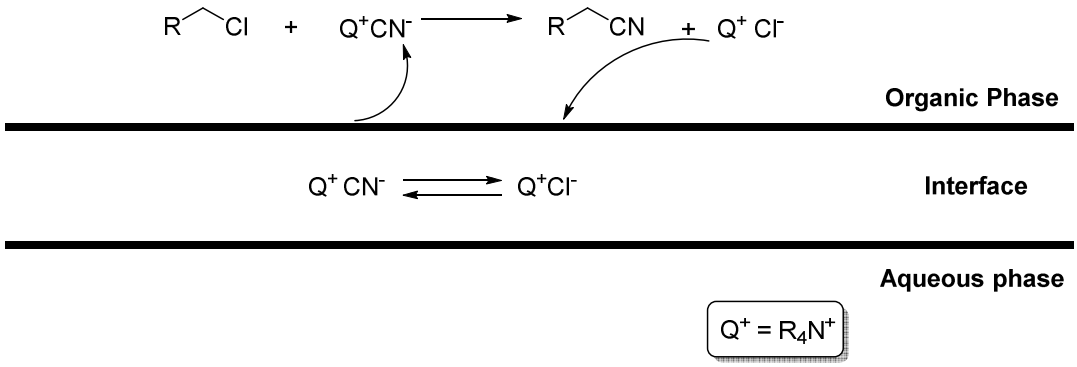


Figure 14. Mechanism for halide displacement by cyanide ion catalyzed by PTC.

Because of the insolubility of NaCN in the organic phase the reaction is incapable to proceed without the help of a PTC. Therefore, electrophile and nucleophile are unable to meet and react. By using ion exchange at the interface of organic and aqueous phase PTC "shuttle" the cyanide ion into the organic phase. From the interface, the new ion pair (Q^+CN^-) then travels to the organic phase where it is

permitted to readily react with the electrophile (Figure 14). This mechanism is known as the *extraction mechanism,* when the organic phase reaction is rate determining step, like the reaction between cyanide and octyl bromide in the above example. On the other hand, when the transfer of the ion from aqueous solution to the organic phase (the transfer step) is rate determining step, the mechanism is known as the *interfacial mechanism*.

Factors affecting the rate at which the transfer of ions into the organic phase takes place include:

a) Interfacial tension: An increase in the interfacial tension resulted from the decrease of the interfacial area, which resulted in lowering the transfer rate from the aqueous into the organic phases. Due to an increased interfacial tension, highly concentrated solutions and non-polar solvents result in a decrease of the interfacial area.

b) Stirring: Formation of tiny droplets present in emulsions can greatly increase the interfacial area leading to enhanced reaction rates. High stirring speeds can help to form these tiny droplets thereby generate larger surface area..

c) The cation bulkiness of PTC: Typically, unsymmetrical cations allow closer approach of the cation to the interface, boosting the transfer step. Bulkier alkyl groups lower the rate in the transfer step by a decrease of the effective concentration of the cations at the interface.

d) Nature of the anion in the PTC: Larger anions that are weakly hydrated for example iodide and perchlorate allow easier access to the interface from the organic phase. The reverse is true for small anions such as hydroxide or fluoride that are hydrated with much greater ease.

Phase transfer catalyzed reaction are affected by the following variables:

a) Catalyst: There are some factors such as catalysts ability to promote the transfer of the substrate anion into the organic phase, the surfactant property of the catalyst, transfer rates depends on the shape and size of the catalyst. Moreover, in the activation of the anion for reaction towards reactant in the organic phase, the catalyst may perhaps be a major factor. Under the commonly used basic conditions, many phase transfer catalysts are capable to go through a Hoffmann elimination. For that reason a catalyst should be selected that will be practically stable under the strong basic conditions employed.

b) Concentration: Concentration plays an important role in phase transfer catalysis. The use of more concentrated solutions leads to an increased interfacial tension and a decreased transfer rate. The transfer of anions into the organic phase will be promoted by using more concentrated solutions, provided that this is not the limiting factor, thereby promoting formation of the catalyst substrate complex.

c) Solvent: Choice of solvent plays important role because it can affect both the rate of the reaction taking place in the organic solvent and the interfacial tension, which can affect the transfer rate. Commonly dichloromethane is used as a solvent because of its capacity to readily dissolve most phase transfer catalysts.

d) Temperature: Generally, in the presence of base and at high temperature phase transfer catalyst decomposes, therefore a temperature should be

selected for optimal rate of reaction while circumventing decomposition of the catalyst.

The use of phase transfer catalysis also presents severak practical advantages:

1) Expensive and stronger, moisture sensitive organic soluble bases such as MHMDS bases (M= Li, Na, K etc.), NaH, *t*-BuOK etc can be replaceded by inexpensive inorganic bases e.g., K_2CO_3, NaOH, KOH. The work-up process is also simplified and reaction can be done in ambient condition it does not require special conditions such as an inert atmosphere.
2) There are many reactions that have been reported with High % yields, enantioselectivity and purity.
3) The reactions are generally cost effective and be likely to decrease industrial waste.
4) The reactions are low maintenance and have the potential for scale-up, which is advantageous for industrial processes.

There are many different reactions that have been successfully accomplished using phase transfer catalysis. To mention just a few of the reactions that have found application in asymmetric catalysis via phase transfer catalysis include: alkylations, Michael additions, aldol reactions, cyclopropanations, epoxidations, Darzens reactions, oxidations and aziridinations.[60] To illustrate the mechanism of the asymmetric phase transfer catalyzed reaction,the asymmetric alkylation of t-butyl glycinate esters is described (Figure 25).

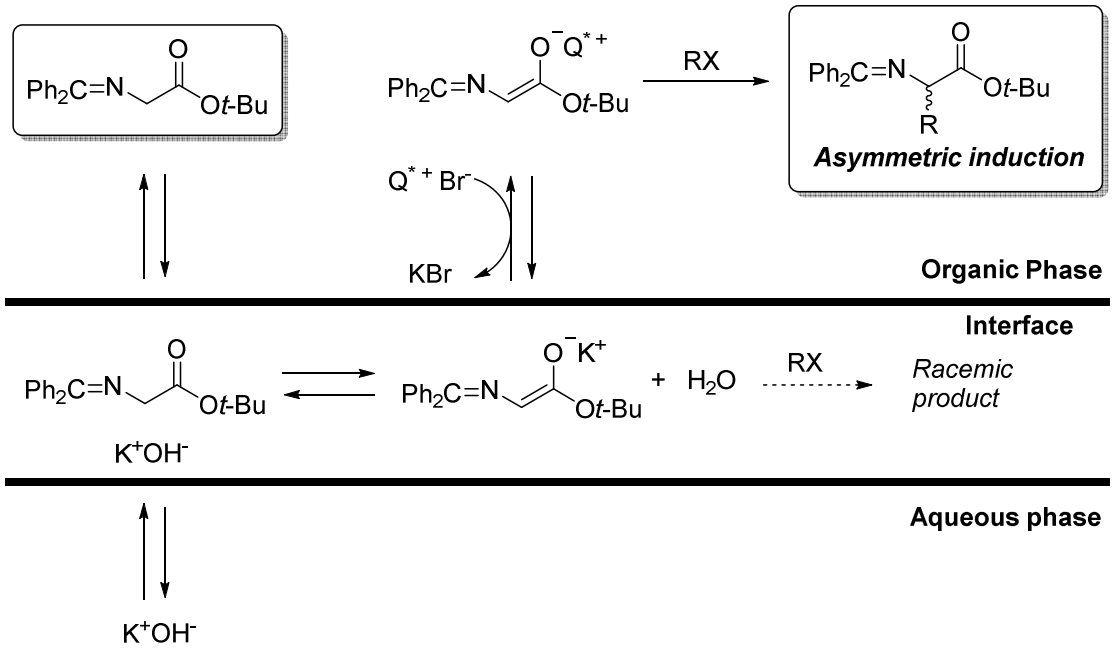


Figure 15. Mechanism for phase transfer catalyzed alkylation of Schiff bases.

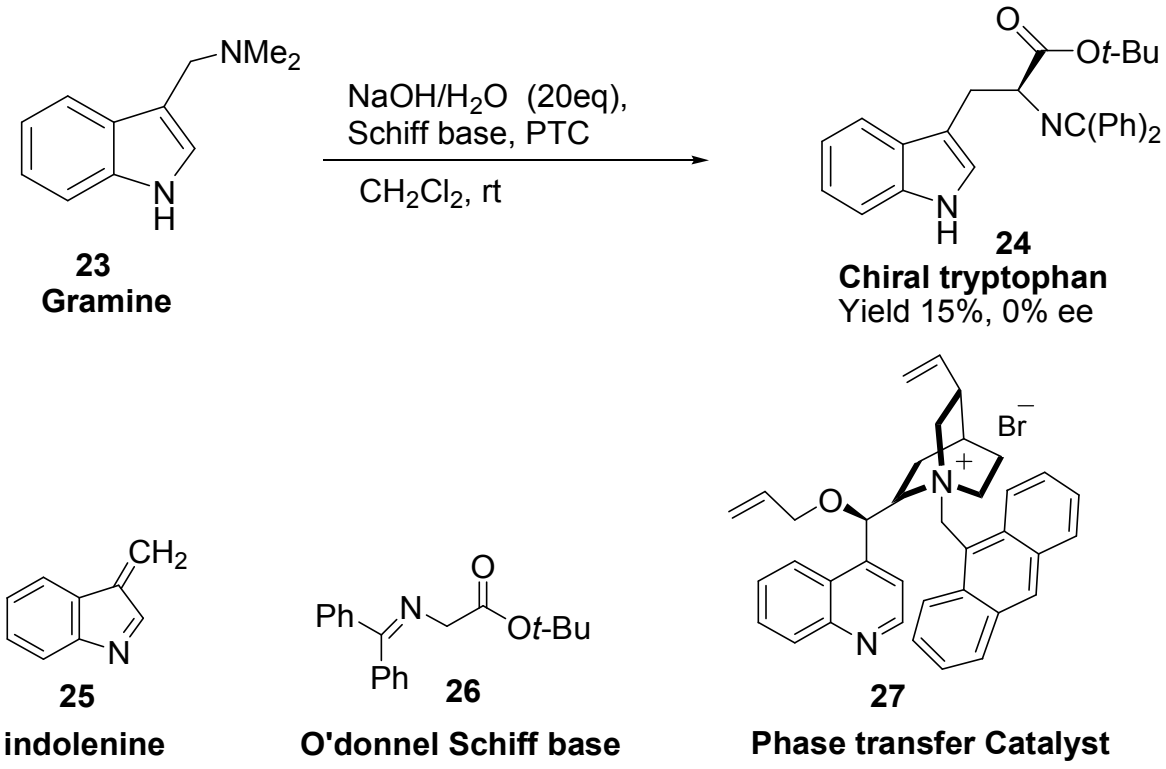
Active methylene or methine hydrogens alkylation happens via the interfacial mechanism. Specifically, the exchange of ions taking place at the interface between the conjugate base of the substrate and the quaternary ammonium salt is the rate determining step (RDS). Therefore organic soluble enolate comes in contact with a quaternary ammonium ion as the counter ion. At the interface, when the glycinate Schiff base comes in contact with water soluble base, the glycinate becomes deprotonated, resulting the related enolate ion (Figure 25). At this point it is critical for the phase transfer catalyst to quickly exchange ions with the enolate, or else the enolate will directly react with the electrophile at the interface, forming racemic product. At the interface, after the ion exchanges between enolate and the PTC, it become organic soluble and goes into the organic phase, where it will react

with the electrophile in an asymmetric fashion with the help of the close-fitting ion pair formed between the chiral quaternary ammonium ion and prochiral enolate.

4.2. Results and discussion

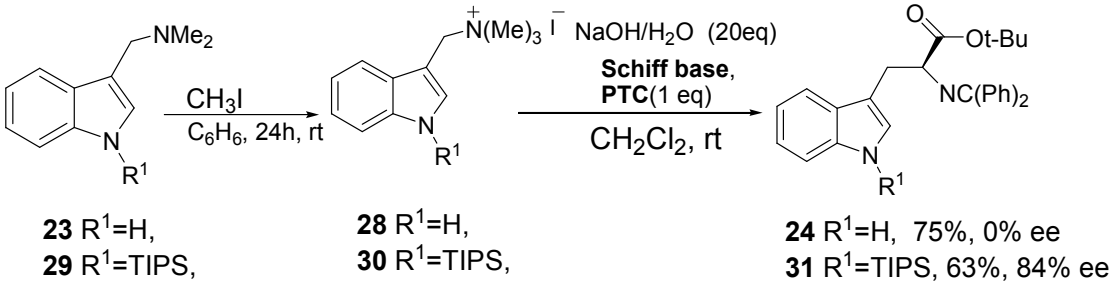
4.2.1 Procedure for the synthesis of Tryptophan

In this study, a *cinchona*-derived phase-transfer catalyst was employed in the first reported PTC synthesis of chiral tryptophans, with varying substitution patterns, using a protected glycine Schiff base and various gramine derivatives. The first experiment, using substrate, glycine Schiff base , catalyst , and 50% aqueous NaOH/CH_2Cl_2 resulted in a disappointing racemic mixture of product with a chemical yield of 15% and reaction time of 50 h (Scheme 61). Such alkylation using gramine has been thoroughly studied in achiral systems with an intermediate 3-methylene- indolenine (Scheme 61) being identified.[6] Low chemical yield was attributed to the arduous task of eliminating $(CH_3)_2NH$ to generate the product. To offset this matter, gramine was converted to a quaternary salt using CH_3I, which resulted in a much improved chemical yield of 75% (Scheme 62), albeit no asymmetric induction. This may be due to the fact that gramine salt is very soluble in water, and very insoluble in dichloromethane, which is not an ideal condition for an asymmetric PTC reaction.



Scheme 61. Reaction of gramine **23** with glycinate Schiff base **26** in the presence of the phase transfer catalyst **27** and an external base.

4.2. 2. Optimization study for the synthesis of chiral Tryptophan analogs.



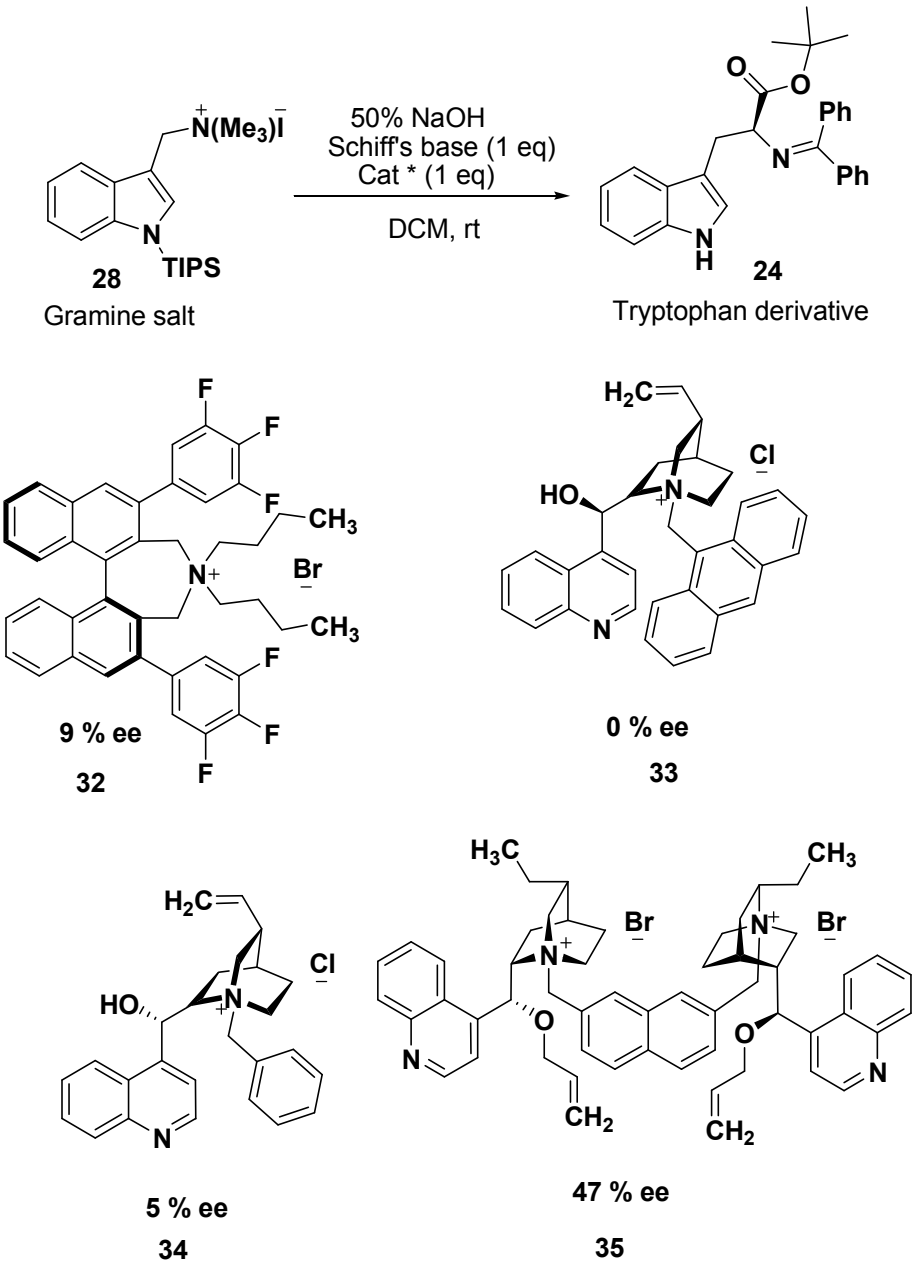
23 R^1=H,
29 R^1=TIPS,

28 R^1=H,
30 R^1=TIPS,

24 R^1=H, 75%, 0% ee
31 R^1=TIPS, 63%, 84% ee

Scheme 62. Synthesis of quaternary salt by reaction of gramine with CH_3I, followed by alkylation with glycinate under phase-transfer conditions using phase transfer catalyst and external base.

In order to improve the asymmetric induction, we attempted to change the polarity of the quaternary salt, so it became very soluble in dichloromethane and partially soluble in water. By introducing a bulky hydrophobic triisopropylsilyl (TIPS) protecting group on the indolylic nitrogen of the substrate (Scheme 62), we managed to improve the optical yield (84 %ee) of the PTC alkylation reaction using 1 eq of catalyst (Scheme 62). In addition, the TIPS group was removed during the alkylation process. We screened some other commercially available catalysts to determine if there are any other catalysts that would be more effective than O-Allyl-N-(9-anthracenylmethyl)-cinchonidinium bromide catalyst (scheme 61) for this alkylation reaction. From our results as summarized in Scheme 63 it was revealed that 9-anthracenyl catalyst was the catalyst of choice for best optical yields.



Scheme 63. Results from some commercially available phase-transfer catalysts in the alkylation reaction.

Further studies revealed that changing the quaternization reagent from CH_3I to 4-(trifluoromethoxy) benzyl bromide (Scheme 63) eliminated the protection/de-protection steps, allowing for the quaternization and chiral alkylation steps to be

carried out in one-pot (Scheme 64). The one-pot asymmetric alkylation was a success due to fact that the salt formed from 4-(trifluoromethoxy) benzyl bromide and gramine was found to be insoluble in water. Changing quaternization reagents from CH_3I to 4-(trifluoromethoxy) benzyl bromide (Scheme 64), not only rendered a one-pot transformation feasible, but also resulted in both an increase in overall percent yield and a shorter reaction time (<1h) (Figure 16). The ^1H NMR studies showed no evidence of indolenine formation in the one-pot process using 4-(trifluoromethoxy) benzyl bromide at 25 °C, which suggests that alkylation might be occurring via nucleophilic substitution rather than elimination-addition. This was further supported by methylating the indolylic nitrogen and observing minimal loss in yield and induction (Scheme 64).

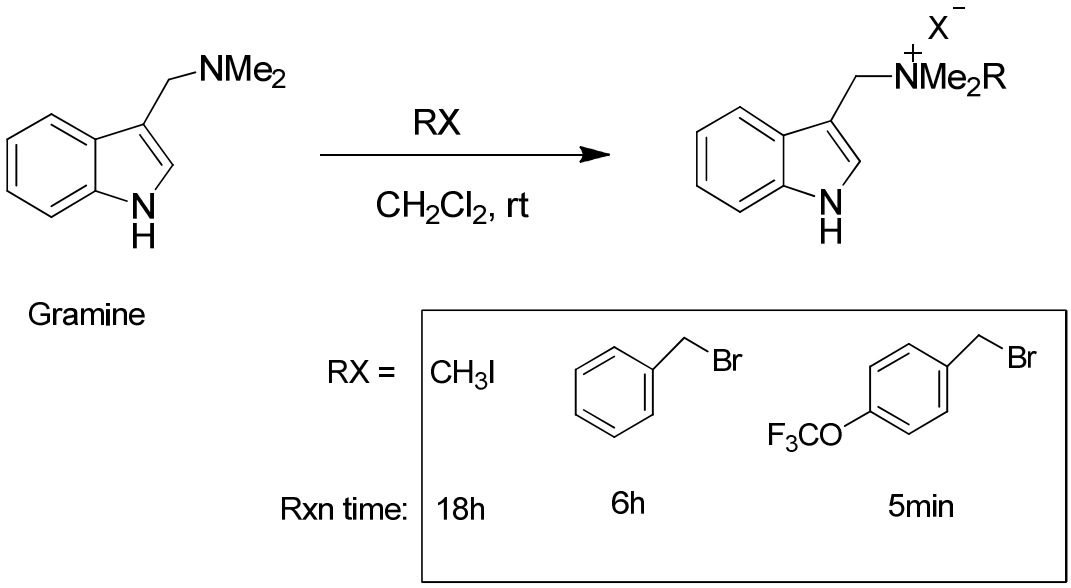
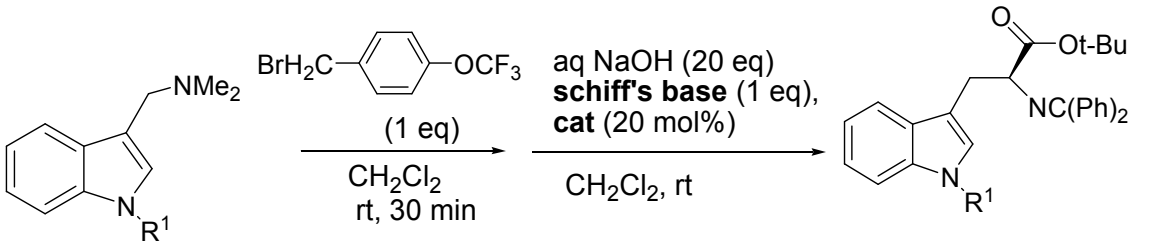


Figure 16. Screening of quaternization reagents using gramine under ambient conditions



23 R^1= H,
36 R^1 = Me,

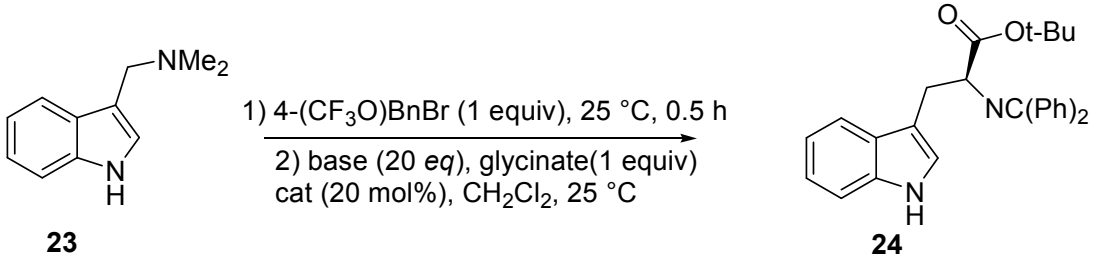
24 R^1= H, 72%, 65%ee
37 R^1 = Me, 69%, 61%ee

Scheme 64. One-pot synthesis of chiral tryptophanate by reaction of gramines with glycinate and 9-anthracenyl chinchonindin catalyst respectively using quaternization reagent **7** under ambient conditions.

In order to further improve the chemical and optical yields some variables were studied for the alkylation reaction in dichloromethane. Increasing the concentration of aqueous NaOH from 10% to 50% resulted in increase of optical yield. Changing base from 50% aqueous NaOH to 45% aqueous KOH resulted an increase in optical yield from 65% ee to 80% ee. Other common bases such as CsOH and $Ba(OH)_2$ did not improve the chemical or optical yields of the product. Further screening of solvents like THF (6% ee), dioxane (84% ee) and toluene (71% ee) showed that similar results were obtained with CH_2Cl_2 and dioxane, leading to slightly higher enantioselectivity. Lowering the reaction temperature from 25 °C to –30 °C resulted in a further increase in optical yield; temp (% ee, time): 25 °C (80%, 2h), -30 °C (84%, 8h). However, further cooling (-78 °C) increase the reaction time to 15h but gave no additional improvement in optical yield. The low temperature

reactions were run in dichloromethane as the dioxane freezes at subzero temperature. Although we had determined that increased reaction rates and selectivity is achieved with higher base concentrations, the effect of water on enantioselectivity was also studied (Table 9). We discovered that a minimum of 6 equivalents of water is needed to achieve an excellent optical yield of the product (entry 2, Table 9). In these reactions, a minimum 20 mol% of catalyst is required for best chemical and optical yields.

Table 9. Effects of base and substrate concentration on asymmetric PTC of gramine**.**

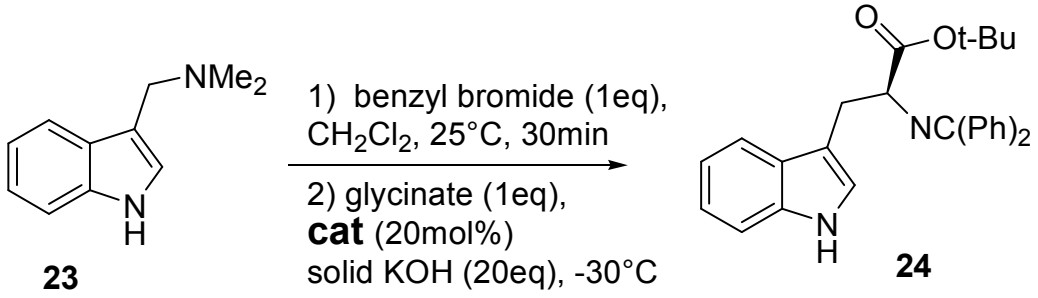


23 **24**

Run	Conc(gramine)[c]	Base (% aq)	Time (h)	% Yield[d]	% ee[e]
1	0.10	10% NaOH	> 24	18	50
2	0.10	50% NaOH	8	47	75
3[b]	0.01	50% NaOH	16	42	71
4	0.10	10% KOH	5	65	65
5	0.10	45% KOH	2	>95	84
6	0.10	10% KOH	2	97	80
7	0.10	10% CsOH	3	18	59
8	0.10	10% $Ba(OH)_2$	13	16	46
9	0.10	25% K_2CO_3	N.R.[f]	0	0

[a] 0.10 M gramine in CH_2Cl_2/aq base (20 equiv), 25 °C. [b] 0.01 M gramine in CH_2Cl_2. [c] Molar. [d] Yield determined by HPLC. [e] Determined by chiral HPLC using: Chiralcel-OD column, 5% IPA in heptane, 254 nm DAD, 1 mL/min flow rate, 40 °C column temperature. [f] No reaction.

Table 10. Results of PTC reaction in varying amount of water.

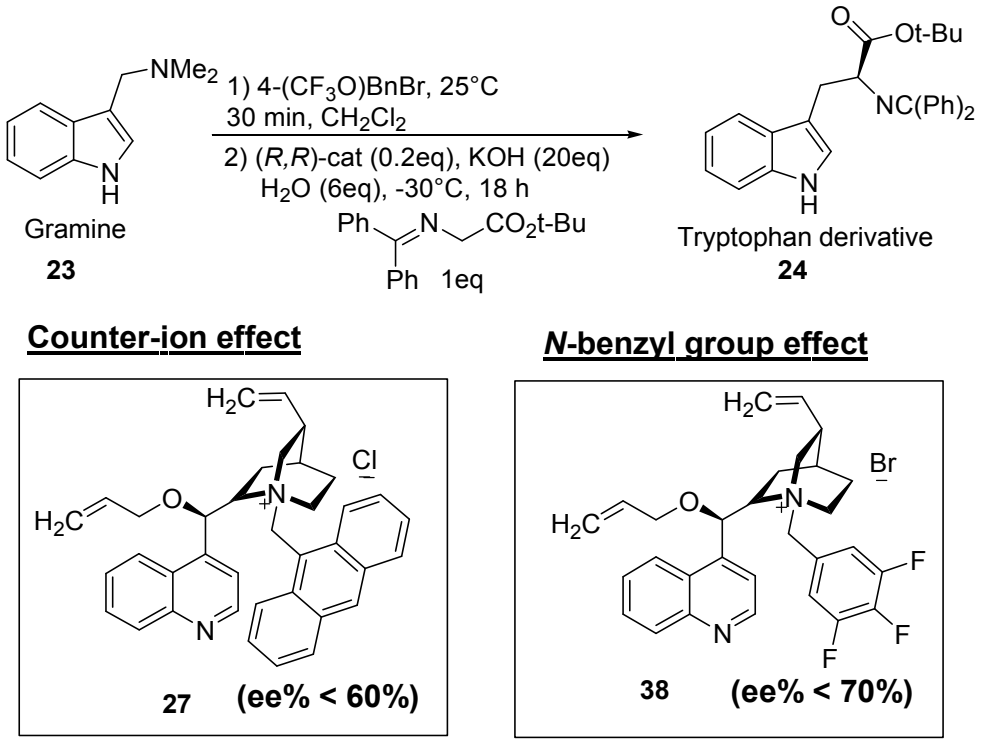


Entry	Water (eq)	Time (h)	% Yield[a]	% ee[b]
1	100	8	80	85
2	6	18	80	92
3	3	19	>95	83

[a] Yield determined by HPLC. [b] Determined by chiral HPLC using: Chiralcel-OD column, 5% IPA in heptane, 254 nm DAD, 1 mL/min flow rate, 40 °C column temperature.

Once the alkylation variables were optimized, we began structure-activity-relationship studies of catalyst (Scheme 64) in the asymmetric one-pot alkylation of gramine and glycinate schiff's base in CH_2Cl_2 at –30°C using solid KOH with 6 eq of water. The study revealed that both the bromide counter-anion and the *N*-anthracenyl group play an intimate role in the ability of catalyst to induce high

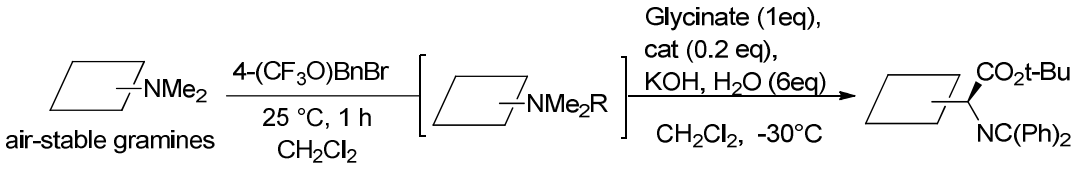
optical yield. Changing the counter-anion from bromide to chloride resulted in a decrease in optical yield to 60% (Scheme 64), which may be due to increased solubility of the catalyst in water. Substituting the anthracenyl group with a less bulky 3,4,5-trifluorobenzyl group also resulted in a decrease in optical yield to 70% (Scheme 65). Steric influences were believed to be the contributing factor toward increasing enantiodifferentiation.

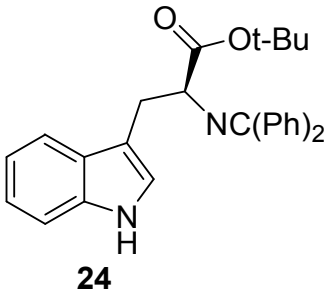


Scheme 65. Structure-activity-relationship (SAR) studies in the asymmetric alkylation of gramine with glycinate with external base in a one-pot reaction.

4.3. Scope of chiral phase transfer catalyzed reaction for the synthesis of Tryptophan analogs.

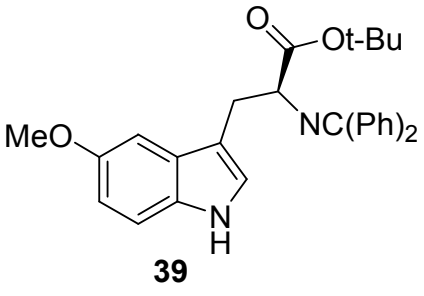
After optimizing our reaction with gramine**,** which resulted in a good yield and excellent %ee, we expanded the scope of our study to other gramine-type substrates, specifically ring-A substituted gramines such as 5-methoxy, 6-methoxy, and 5-bromogramine (Scheme 66). All the gramines tested are commercially available and provided good yields with excellent optical purity. In conclusion, a systematic study of substrate, catalyst, reagents, and reaction conditions has led to a simple, enantioselective synthesis of L-tryptophan derivatives using chiral phase-transfer catalysis in a three-component/one-pot fashion [61]. The configuration of compounds was determined by converting them to the known L-tryptophans and by measuring their optical rotations.





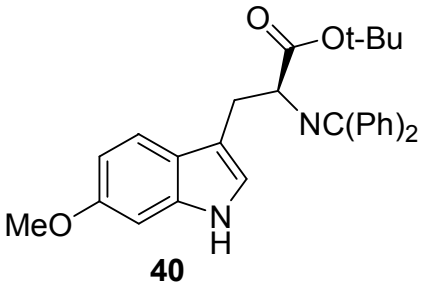
24

(80% yield, 92% ee)



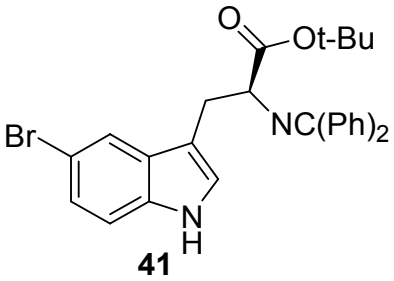
39

(75% yield, 91% ee)



40

(65% yield, 95% ee)



41

(73% yield, 90% ee)

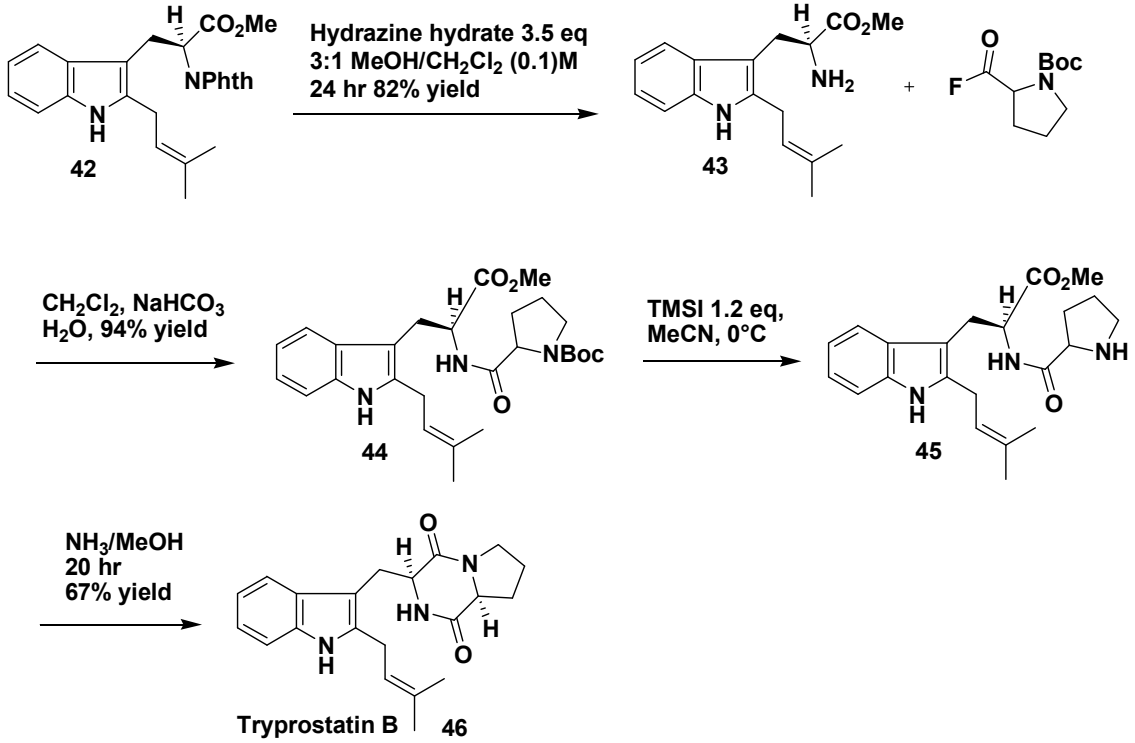
Scheme 66. Optimal asymmetric alkylation conditions of various gramines.

CHAPTER 5. APPLICATION OF TRYPTOPHAN CHEMISTRY TOWARDS THE TOTAL SYNTHESIS OF TRYPROSTATINS.

5.1. Synthesis of Tryprostatins

Tryprostatins are diketopiperazine, tryprostatin A reverses the resistance of cancer cells against antitumor drugs by arresting cell cycle progression at the G2/M phase and also known to inhibits the ABC-transporter breast cancer resistance protein. Early synthesis of Tryprostatin was done by Danishefsky's group in 1996 using the following scheme [61]. This goal was achieved by cleavage of the *N*-phthaloyl group **42**, followed by coupling of the resultant amino ester with *N*-Boc-L-proline acid fluoride to afford first amide linkage **44**. Deprotection of Boc-group led to the next

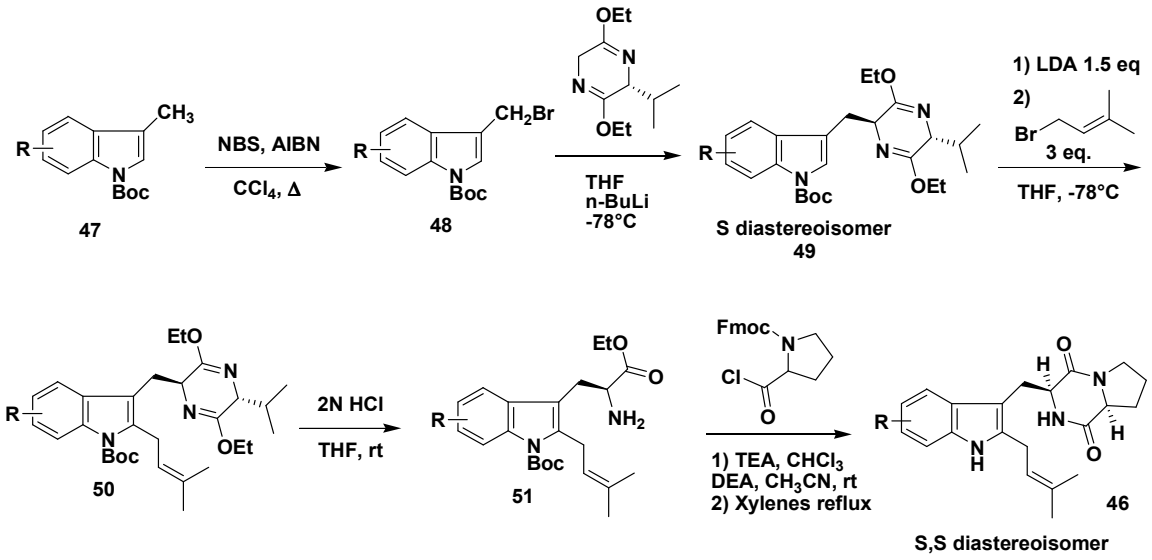
intermediate **45** and then, by diketopiperazine formation, to Tryprostatin B **46**(Scheme 67).



Scheme 67. Total synthesis of Tryprostatin B starting from chiral tryptophan.

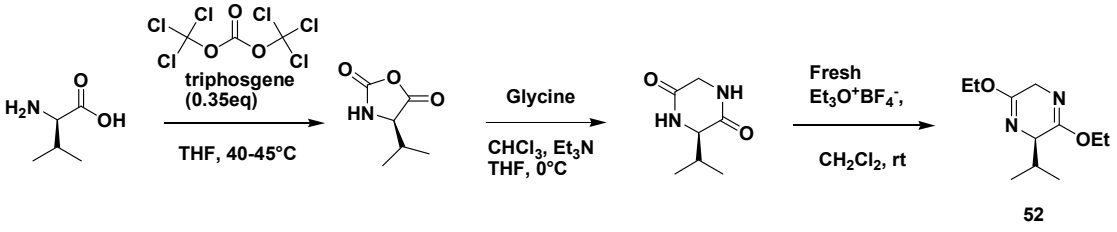
Professor Cook's group synthesized Tryprostatins in 2002 and 2008 using slightly different procedures [62]. They achieved this using the reaction scheme shown below (Scheme 68). The synthesis began with indoles **47**, which were then coupled with the anion of the Scho¨llkopf chiral auxiliary, to afford the trans diastereomer **49** with 100% diastereoselectivity. The 2-isoprenylpyrazine derivatives of Indoles **50** were obtained by treating with LDA at -78 ^{o}C, followed by addition of isoprenyl bromide. The pyrazine group was removed under acidic conditions in 94% yield to afford the 2-isoprenyl tryptophan **51**. The coupling of 2-isoprenyl tryptophan with Fmoc -D-proline using triethylamine as the base was

followed by formation of the diketopiperazine ring. The Boc protecting group was removed from the indole N(H) function in refluxing xylene to afford Tryprostatin A and B **46**.



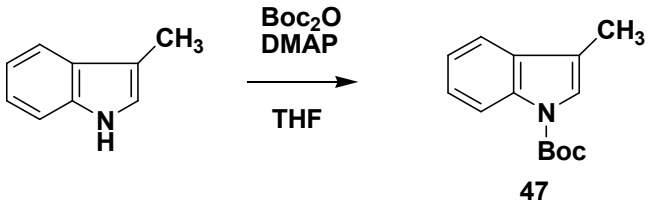
Scheme 68. Total synthesis of Tryprostatin A and B starting from 3-methyl indoles.

In Professor Cook's synthesis the Schöllkopf Chiral Auxiliary **52** is made from triphosgene and L-valine (Scheme 69).



Scheme 69. Synthesis of Schöllkopf chiral auxiliary.

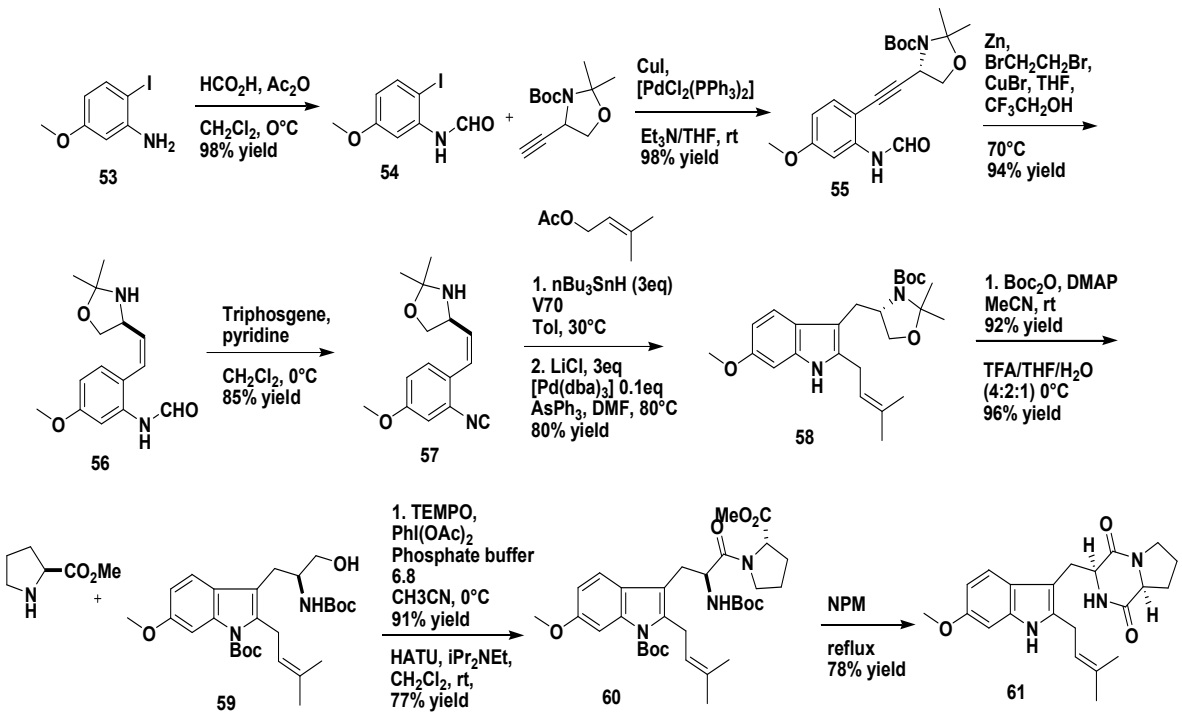
In the synthesis they also have to Boc protected skatole **47** shown below which is not reported as a step in the synthesis (Scheme 70). There are very few substituted skatoles commercially available to make derivatives with.



47

Scheme 70. Boc protection of indole amino group.

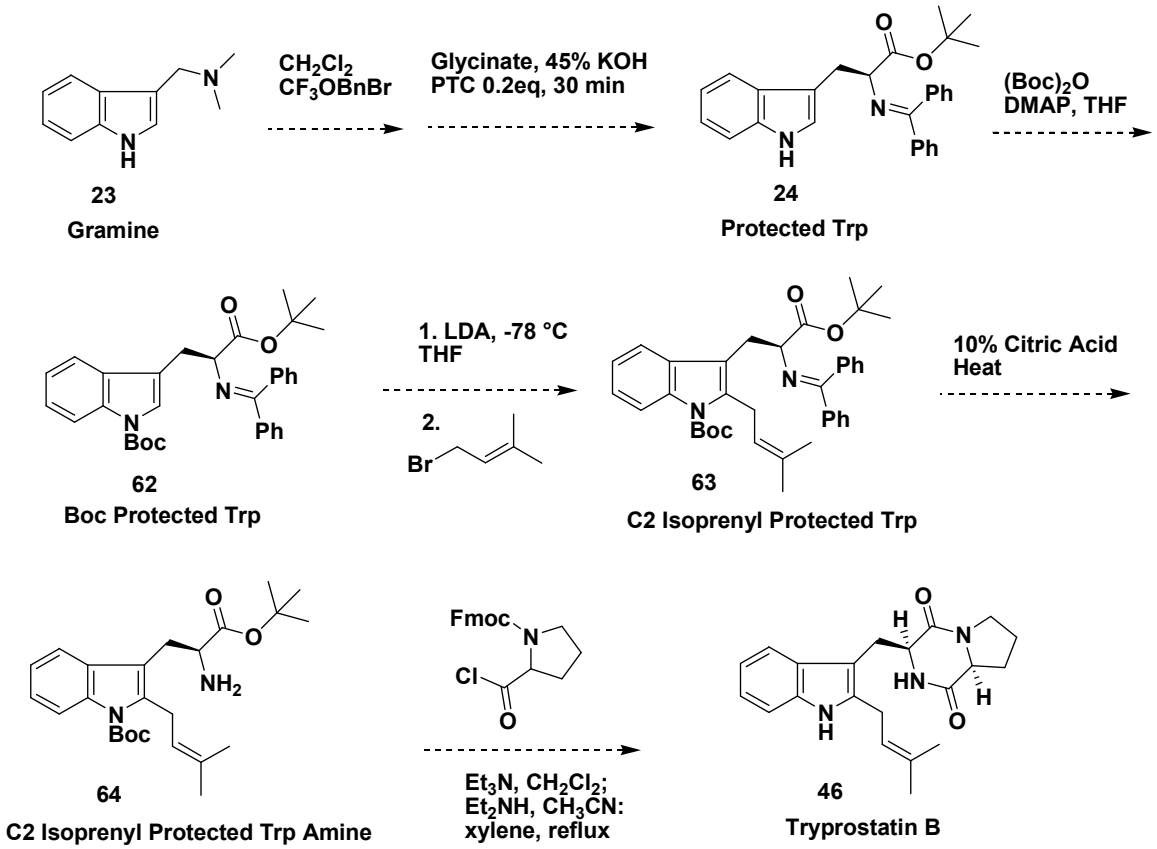
One of the more current syntheses [63] from 2010 is shown in the synthetic scheme shown below (Scheme 71). This synthesis has 11 steps a 30% yield and utilizes a toxic tin coupling reagent and triphosgene. In this radical-mediated cyclization they focused on the synthesis of the isocyanide compound as a radical-cyclization precursor. After the Sonogashira coupling between terminal alkyne and 2-iodoformanilide **54** the resultant compound was selectively reduced to cis alkene **56**. Subsequent dehydration with triphosgene afforded the ortho-alkenyl isocyanide **57** and thus ready for a radical-mediated cyclization. Isocyanide compound was then subjected to established radical-cyclization conditions to give the 2-stannylindole followed by Pd mediated isoprenyl coupling at C-2 position to get compound **58**. It was then transformed into the corresponding amino acid in a three-step sequence consisting of protection of the indole with a Boc group, hydrolysis of the acetonide, and oxidation of the resulting alcohol to the carboxylic acid withTEMPO. After condensation with l-proline methyl ester, the removal of the two Boc groups and cyclization completed the construction of diketopiperazine **61**.



Scheme 71. Total synthesis of Tryprostatin A from 2-iodo,5-methoxy aniline.

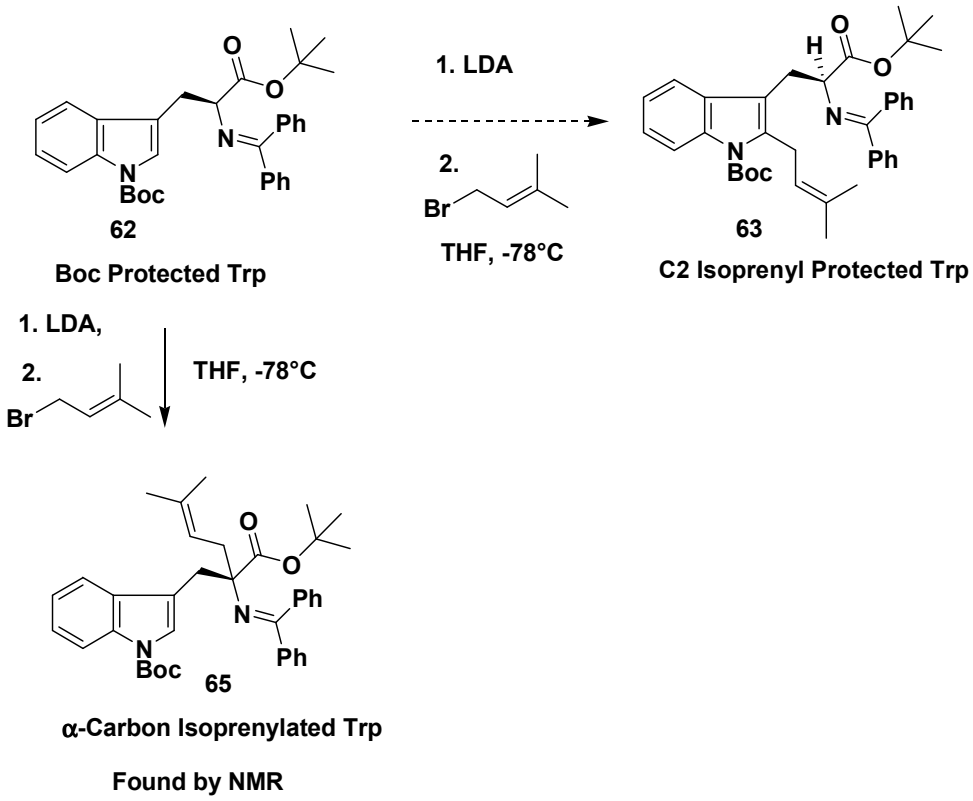
5.2. RESULTS AND DISCUSSIONS

In our attempt to synthesize tryprostatins, Huisman proceeded with our proposed scheme which is complementary to the Cook group synthesis (Scheme 72). After synthesis of asymmetric tryptophan **24** via phase transfer catalyzed reaction Indole will be protected with Boc-group **62**. The compound will then undergo a C-2 alkylation reaction to get compound **63** with isoprenyl bromide in presence of LDA at -78 ^{o}C. Subsequent hydrolysis and coupling of Fmoc-proline will afford tryprostatin B **46** (Scheme 72).



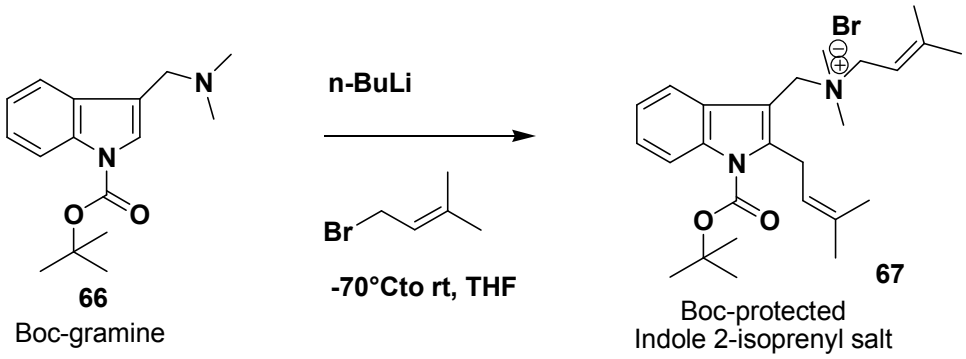
Scheme 72. Proposed total synthesis of Tryprostatins.

This procedure was working well up until the synthesis of Boc-protected tryptophan **62**. C-2 alkylation of **62** seems to be a problematic reaction in chiral tryptophan, after alkylation reaction Huisman isolated compound **65** that had the isoprenylation on the amino acids α-carbon. Alkylation happen at the most acidic proton at chiral center instead of C-2 position of indole structure for compound **63** (Scheme 73).



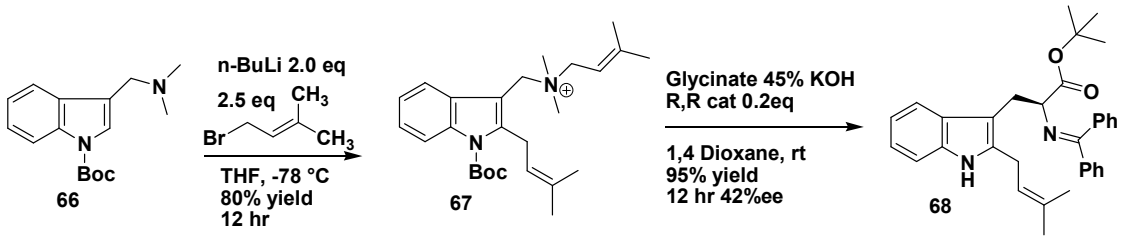
Scheme 73. Synthesis of indole C2-isoprenylated tryptophan.

The problem was circumvented by making quaternary gramine salt **67** necessary for the PTC reaction and C2-alkylation at the same step using 2.5 equivalent of isoprenyl bromide (Scheme 74). Then we proceeded with our proposed scheme.



Scheme 74. Procedure for quaternary di-isoprenyl bromide salt **67** of gramine.

The next step is phase transfer catalyzed tryptophan synthesis, and we found that C-2 alkylation of gramine quaternary ammonium salt **67** is a totally different substrate than unsubstituted regular tryptophan. Our established procedure for chirality induction via PTC reaction is ineffective for this new substrate, after optimization Huisman reported only 42% ee in 1,4-Dioxane solvent at room temperature (Scheme 75).



Scheme 75. Preparation of tryptophan using gramine isoprenyl salt.

At this point of synthesis we avoided the alkylation at chiral center **65**, but we are in need of a protocol to improve the enantioselectivity of phase transfer catalyzed reaction of C-2 alkylated substrate **67**. In order to optimize the reaction for new substrate we again screened phase transfer catalysts (Figure 17) with our established protocol. Alkylation at C-2 position with bulky isoprenyl group might interfere with the chiral catalyst, so we tried different catalyst which is more open in their ammonium core such as catalyst **32**. We found that catalyst **32** is moderately effective to induce higher enantioselectivity (50% ee) for the phase transfer catalysis reactions(Table 11, entry 4).

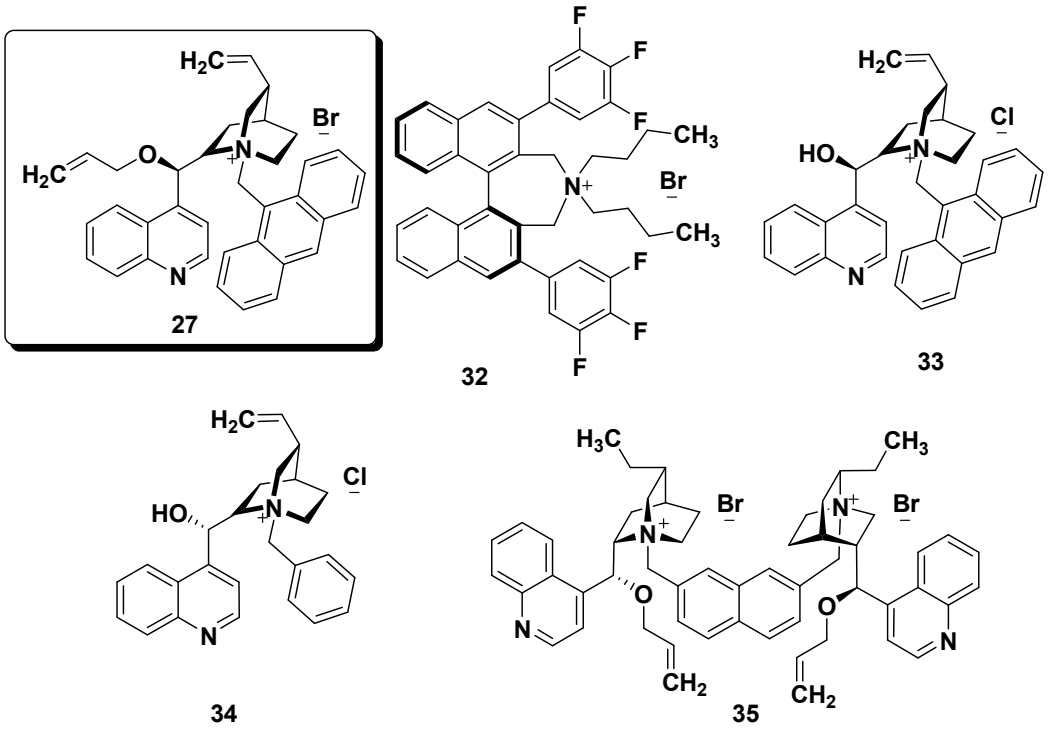
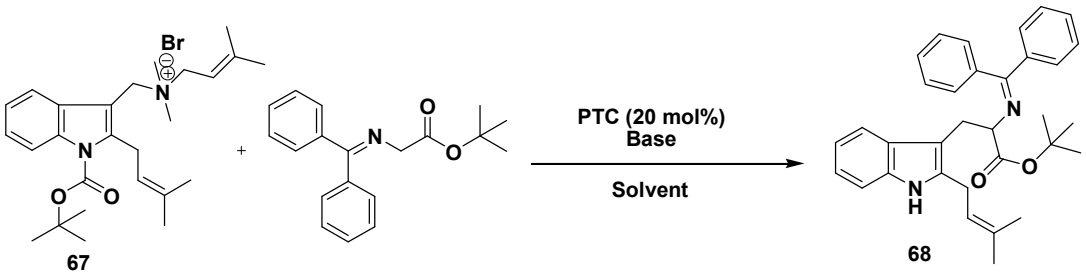


Figure 17 . Chiral phase transfer catalysts.

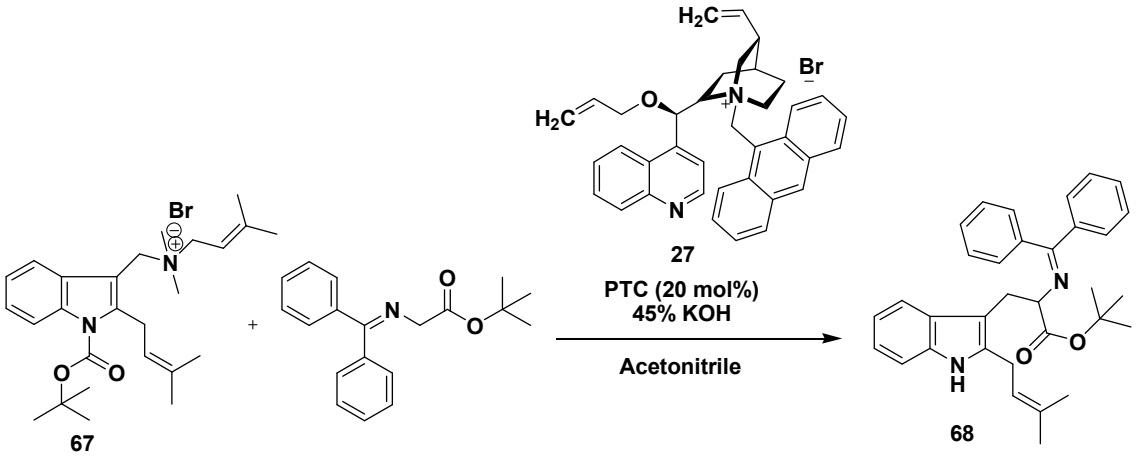
Table 11. Catalyst screening for the synthesis of **68**.



Entry	Catalyst	Solvent	Base	%ee
1.	27	1,4-Dioxane	CsOH	39
2.	34	1,4-Dioxane	CsOH	39
3.	33	1,4-Dioxane	CsOH	racemic
4.	32	1,4-Dioxane	CsOH	50%

5.	27	Tol:Dioxane(1:1)	CsOH	65%
6.	27	Tol:$CHCl_3$(4:1)	CsOH	49%

Among the chiral catalysts screened for the transformation of **67**, we found catalyst **27** is the most effective one (Table 11, entry 5) which has previously been used for the synthesis of unsubstituted chiral protected tryptophan (Scheme 76).

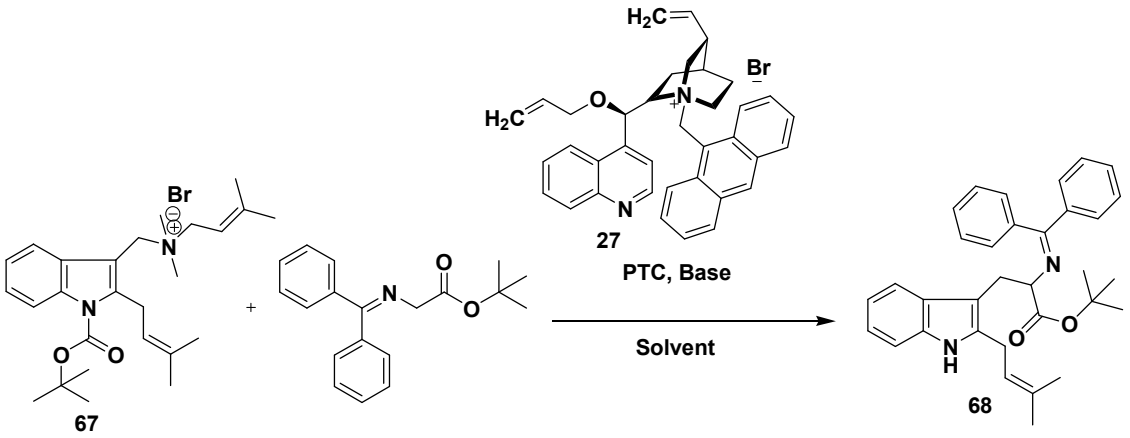


Scheme 76. Synthesis of 2-isoprenyl-N-diphenylmethylene-t-butyl ester tryptophan **68**.

For further optimization we then screened different solvent system, base, and concentration of reactions using catalyst **27**. Solvent polarity plays an important role in dissolving phase transfer catalyst and in maintaining the concentration of catalyst in organic phase and above all in the transfer process. Polar solvent can dissolve catalysts easily, but were found to be ineffective to induce chirality to the product (Table 12, entry 5,8,9). Toluene and Dioxane were observed to be the most promising solvent for optimal catalyst solubility thereby found to afford more %ee than other solvents. So far equal mixture of toluene and dioxane provided the

highest enantioselectivity (Table 11, entry 7) .Surprisingly in the case of 1,4-dioxane:hexane (1:1) lowering the polarity for dioxane, resulted in lower enantioselectivity(Table 12, entry 14)

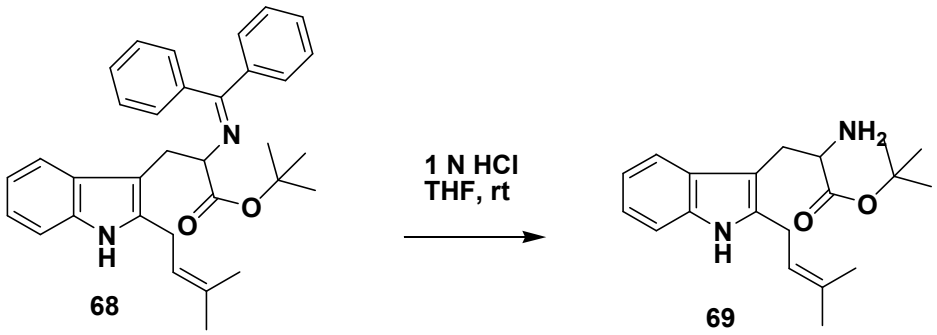
Table 12. Optimization of C-2 alkylated asymmetric Tryptophan synthesis.



Entry	Base	Solvent	Temp. (°C)	Time in hours	% Conv.	% ee
1.	45% KOH	THF	rt	18	95	racemic
2.	45% KOH	Ether	rt	18	7	30
3.	45% KOH	Toluene	rt	18	80	50
4.	45% KOH	EtOAc	rt	18	10	37
5.	45% KOH	CH_2Cl_2		18	90	racemic
6.	45% KOH	1,4 Dioxane		18	95	42
7.	45% KOH	Acetonitrile		18	80	20
8.	Anhyd.KOH	THF	rt	18	85	racemic
9.	Anhyd.KOH	DMSO	rt	12	80	15
10.	Anhyd.KOH	Toluene	rt	12	85	50
11.	KOH (solid)	Toluene	0	12	50	30

12.	KOH (solid)	Toluene: Methanol (5:1)	rt	12	85	45
13.	LiOH	Toluene:MeOH (5:1)	rt	12	No reaction	
14.	KOH	Dioxane:Hexane	rt	12		25

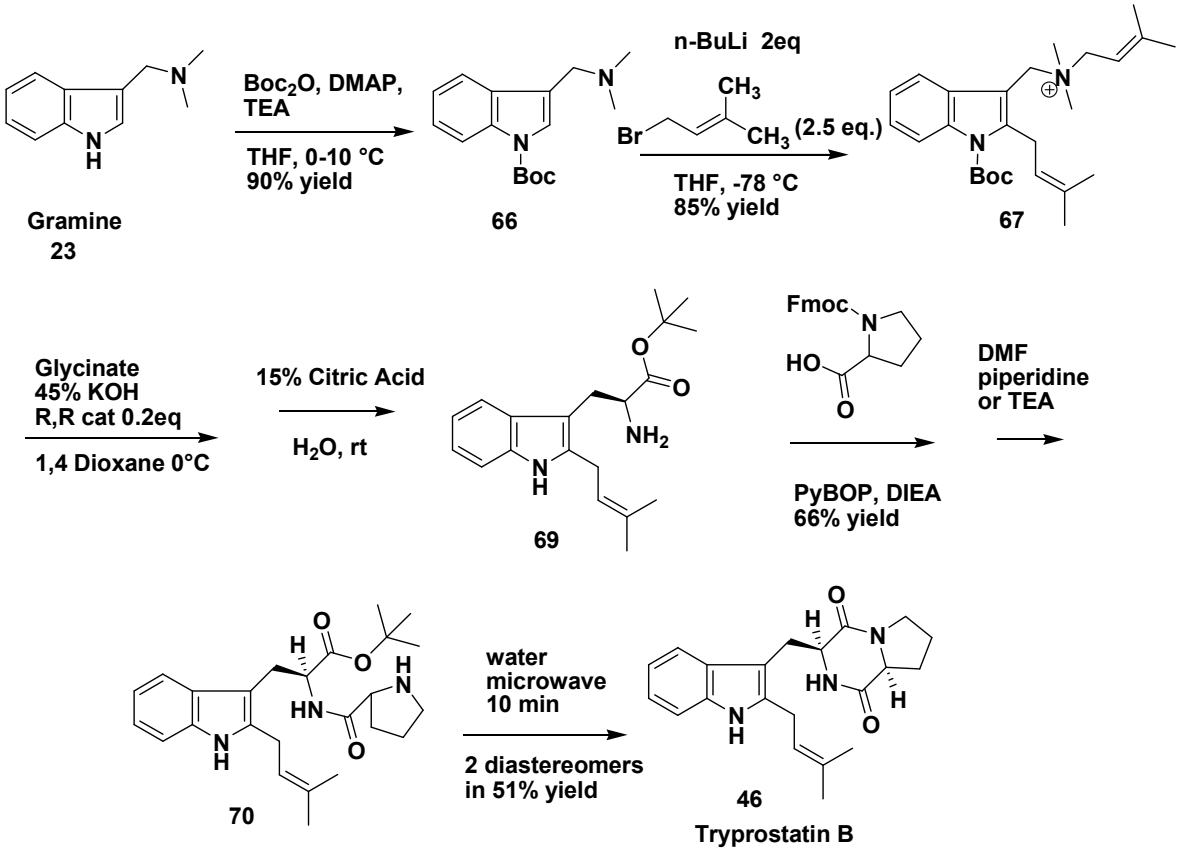
In the mean time, Huisman completed the synthesis of achiral tryprostatin B. After asymmetric synthesis of tryptophan, deprotection of amino group proceeded smoothly under 1M HCl in THF at room temperature(Scheme 77)



Scheme 77. Deprotection of tryptophan amino group.

In the next step Fmoc-proline coupling of compound **69** was also achieved in 66% yield (Scheme 78), but the last step of the synthesis i.e., ring closing was found to be a difficult reaction. The bulky *tert*-butile group of tryptophan ester made amide cyclization an unfavored choice in the diketopiperizine **46** formation. Refluxing compound **70** in xylene didn't work as reported by professor cook's group. Our attempts to tranesterfication reaction with methanol and ethanol to make it into methyl and ethyl ester were found to be unsuccessful. This is due to the stability of the compound rendered by t-butyl ester, primary and secondary alcohol couldn't

replace t-butyl group. This problem was avoided by running the cyclization reaction under microwave condition for just 10 min .



Scheme 78. Total synthesis of Tryprostatin B from gramine.

5.3. Future work:

Synthesis of Tryprostatin A is in progress, corresponding tryptophan analogs has already been made. Once we have tryprostatin B made, our group can focus on making tryprostatin A. Several other tryprostatin analogs could be made by varying R^1 for Ring A substitution variation, R^2 N alkylation, R^3 C 2-position functionalization, R^4 Different amino acid condensation (Figure 18 and 19). Some derivatives at all positions have been tested by Professor Cook's group.

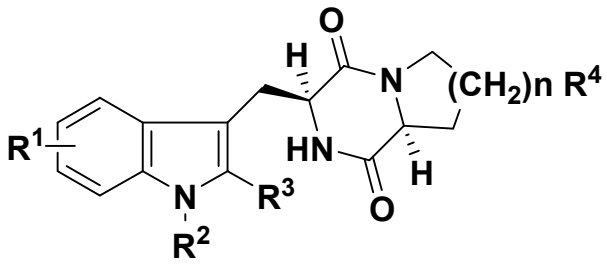


Figure 18 . Substitution at different position of tryprostatin.

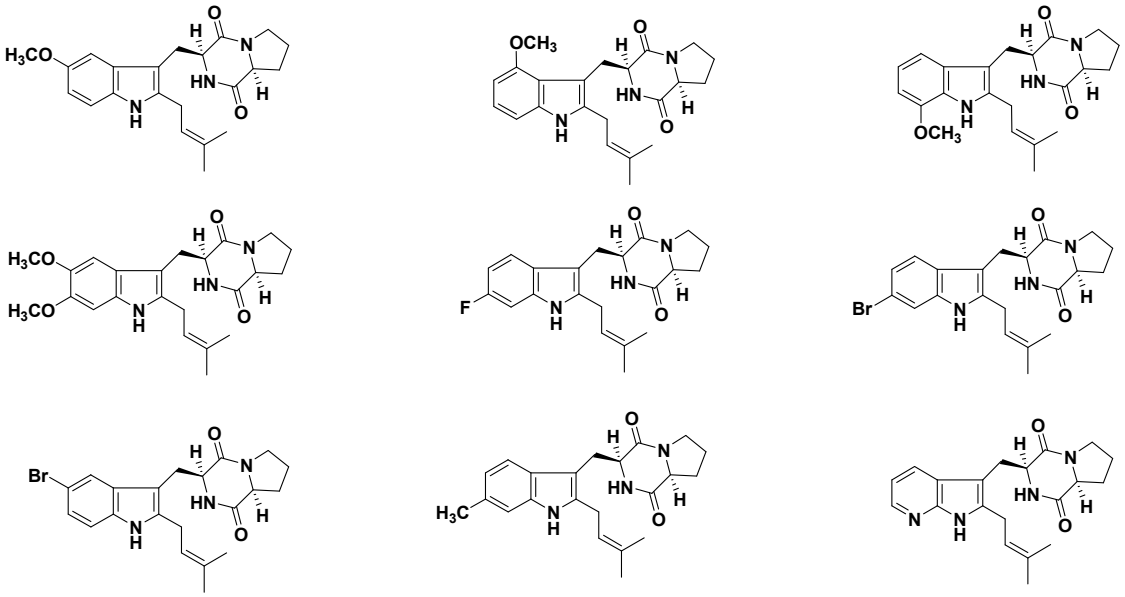


Figure 19. Potential targets for tryprostatin analogs by varying ring A substitution.

5.3. General methods and Experimental

General procedure: All procedures were performed under a dry nitrogen atmosphere using standard Schlenk techniques unless otherwise noted, all reaction vessels were flame dried under vacuum and filled with nitrogen prior to use. Reagents were purchased from Aldrich Chemicals and used as is. Flash chromatography was performed using EM Science F_{254} silica gel 60. N-(diphenylmethylene) glycine tert-butyl ester, sodium hydroxide, phase transfer catalysts and anhydrous sodium sulfate were purchased from Aldrich. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. $CDCl_3$ was used as the solvent. Previously ^1H NMR or GC identified reported compounds. All new compounds were additionally characterized by ^1H NMR, ^{13}C NMR and GCMS.

Instrumentation:

All ^1H (300 MHz), and ^{13}C (75.5 MHz) NMRs were performed with a Burker 300 and samples dissolve ni $CDCl_3$ unless otherwise noted. Enantioselectivity was obtained via chiral HPLC using a Waters setup including an Inline Degasser AF, 2998 Photodiode Array Detector, 1525 Binary HPLC Pump equipped with Breeze Software. This was equipped with a Chiralcel OD (column no. OD00CE-FF071) column using hexane and isopropanol at 254nm and a broad range channel from 200-600nm column temperature was room temperature flow rate was 1 mL/min unless otherwise stated. HPLC grade solvents were used in all HPLC analysis.

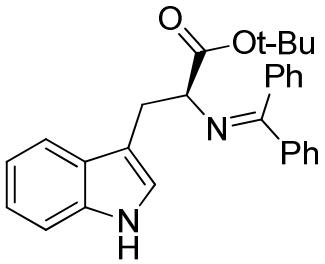
General Procedure for the Synthesis of tert-butyl 2-(diphenylmethyleneamino)-3-(1H-indol-3-yl)propanoate:

For each experiment, 1.0-5.0 mmol of the substituted gramine dissolved in 5-25 mL of freshly distilled dichloromethane under nitrogen. 1 equivalent of 4-(trifluoromethoxy) benzyl bromide was added and allowed to react. A tan slurry immediately resulted. After 1 hour *N* (diphenylmethylene) glycine-*tert*butyl ester, 1 equivalent, *O*-allyl-N-(9-anthracenylmethyl)-cinchoninium bromide, 0.2 equivalents, were charged to solution through open air at ambient temperature. The reaction mixture was then cooled to –30 °C. While stirring, solid KOH 20 equivalents were charged to the reaction mixture along with deionized water 6 equivalents. Stirring was maintained at –30 °C for 8 hours. The crude reaction mixture was directly charged onto silica gel and subjected to flash chromatography, using 10% ethyl acetate pentane mixture. Product was then confirmed by NMR spectroscopy by comparing spectra to known ^{1}H NMR. 1H, 13C NMR, High Resolution Mass spectra and elemental analysis were used to characterize the new compounds. %ee determined by HPLC. All HPLC chromatograms were run using Chiralcel OD column number OD00CE-FFO71.

tert-butyl 2-(diphenylmethyleneamino)-3-(1H-indol-3-yl)propanoate(Scheme 65; Compound 24);

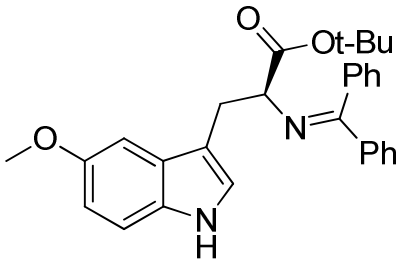
The general procedure was followed (10-20 hrs). Gramine (300 mg, 1.7 mmol), CH2Cl2 (10 mL) 4-(trifluoromethoxy) benzyl bromide (0.43 g, 1.7 mmol), *N*-(diphenylmethylene) glycine-*tert*-butyl ester (0.502 g, 1.7 mmol), *O*-allyl-N-(9-

anthracenylmethyl)-cinchoninium bromide (0.209 g, 0.3 mmol), solid KOH (2.0 g, 36 mmol) and de-ionized water (0.2 mL, 11.1 mmol) were used to obtain the product (578 mg, 80% yield) as yellow oil. ^{1}H NMR spectra matched.[65]



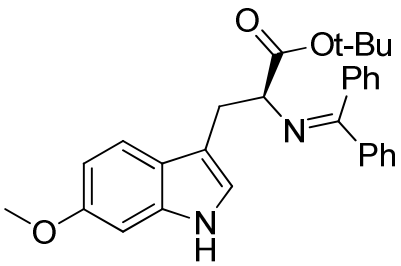
^{1}H 1.5 (s, 9H); 3.2-3.35(m, 2H); 4.1-4.4 (m, 1H; 6.6-7.7 (m, 15H); 8.0(br. S 1H)

tert-Butyl 2-(Diphenylmethyleneamino)-3-(5-methoxy- 1_H_-indol-3-yl)propanoate (Scheme 65; Compound 39):



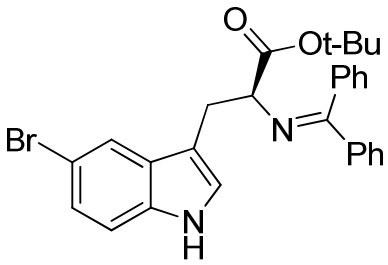
^{1}H NMR (300 MHz, CDCl3): δ = 8.19 (s, 1 H), 7.59 (d, *J* = 7.9 Hz, 2 H), 7.27–7.43 (m, 4 H), 7.15–7.20 (m, 3 H), 6.93 (s, 1 H), 6.78–6.83 (m, 2 H), 6.61 (d, *J* = 7.5 Hz, 2 H), 4.33 (dd, *J* = 8.7, 4.5 Hz, 1 H), 3.69 (s, 3 H), 3.44 (dd, *J* = 14.1, 4.5 Hz, 1 H), 3.30 (dd, *J* = 14.1, 8.7 Hz, 1 H), 1.47 (s, 9 H). ^{13}C NMR (75 MHz, CDCl3): δ = 171.4, 170.1, 153.6, 139.6, 136.1, 131.1, 130.0, 128.7, 128.3, 128.0, 127.9, 127.6, 124.0, 112.0, 111.8, 111.6, 100.5, 81.0, 66.6, 55.7, 45.2, 29.3, 28.0. HRMS: *m*/*z* [M + H]+ calcd. for $C_{29}H_{30}N_2O_3$: 455.2335; found: 455.2353.

tert-Butyl 2-(Diphenylmethyleneamino)-3-(6-methoxy-1_H_-indol-3-yl)propanoate (Scheme 65; Compound 40):



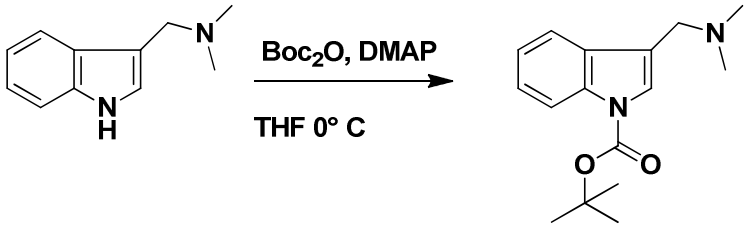
^{1}H NMR (300 MHz, CDCl3): δ = 8.39 (s, 1 H), 7.63–7.71 (d, *J* = 7.9 Hz, 2 H), 7.28–7.41 (m, 4 H), 7.18–7.25 (m, 3 H), 6.84 (d, *J* = 2.4 Hz, 2 H), 6.67–6.80 (m, 3 H), 4.36 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.82 (s 3 H), 3.46 (dd, *J* = 14.1, 4.8 Hz, 1 H), 3.27 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.48 (s, 9 H). ^{13}C NMR (75 MHz, CDCl3): δ = 171.5, 170.2, 156.1, 139.6, 136.7, 136.2, 130.1, 128.7, 128.1, 128.0, 127.9, 127.6, 122.0, 119.4, 111.7, 109.0, 94.4, 80.9, 66.8, 55.6, 45.2, 29.4, 28.0. HRMS: *m*/*z* [M + H]+ calcd. for $C_{29}H_{30}N_2O_3$: 455.2335; found: 455.2349.

***tert*-Butyl 3-(5-Bromo-1*H*-indol-3-yl)-2-(diphenylmethyleneamino) propanoate (Scheme 65; Compound 41):**



^{1}H NMR (300 MHz, CDCl3): δ = 8.09 (s, 1 H), 7.80–7.90 (d,*J* = 7.9 Hz, 2 H), 7.60–7.70 (m, 3 H), 7.18–7.41 (m, 9 H), 7.00 (s, 1 H), 6.65 (d, *J* = 3.32 Hz, 2 H), 4.24 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.36 (dd, *J* = 14.1, 4.8 Hz, 1 H), 3.21 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, CDCl3): δ = 171.0, 170.2, 135.9, 134.5, 130.0, 129.9, 128.6, 128.3, 128.2, 128.0, 127.9, 127.4, 124.4, 124.3, 121.6, 112.4, 112.2, 112.0, 81.0, 66.4, 28.9, 28.0. HRMS: *m*/*z* [M +H]+ calcd. for $C_{28}H_{27}BrN_2O_2$: 503.1334; found: 503.1297.

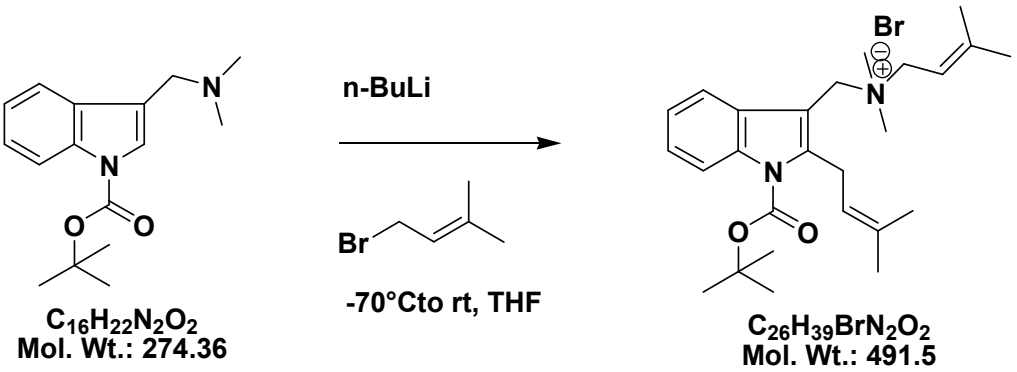
Synthetic procedure for N Boc Gramine:



Scheme 79. Preparation of Boc-protected gramine.

This reaction was modeled after a very similar reaction discussed in Tetrahedron 55 (1999) 10989-11000, compound 8 to 9. A solution of gramine (3.7 g 0.021 mol 1 eq.) in THF (90 mL) was made. This solution was put into an addition funnel on a 250 mL three necked reaction vessel in an ice water cooling bath and added dropwise to a stirred solution of di-*t*-butyl dicarbonate (5.50 g 0.025 mol 1.2 eq.), 4-(dimethylamino)pyridine (257 mg, 0.0021 mol 0.1 eq.), triethylamine (3.5 mL, 0.0025 mol, 0.12 eq.) in THF (50 mL). After stirring for 1.5 hours at room temperature, water was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extract was washed three times with water and then with brine solution and dried over sodium sulfate, and evaporated. The residue was chromatographed over silica gel using hexane:ethyl acetate (5:1) as an eluent to give 5.18 g of Boc Gramine product in 90.0% yield.

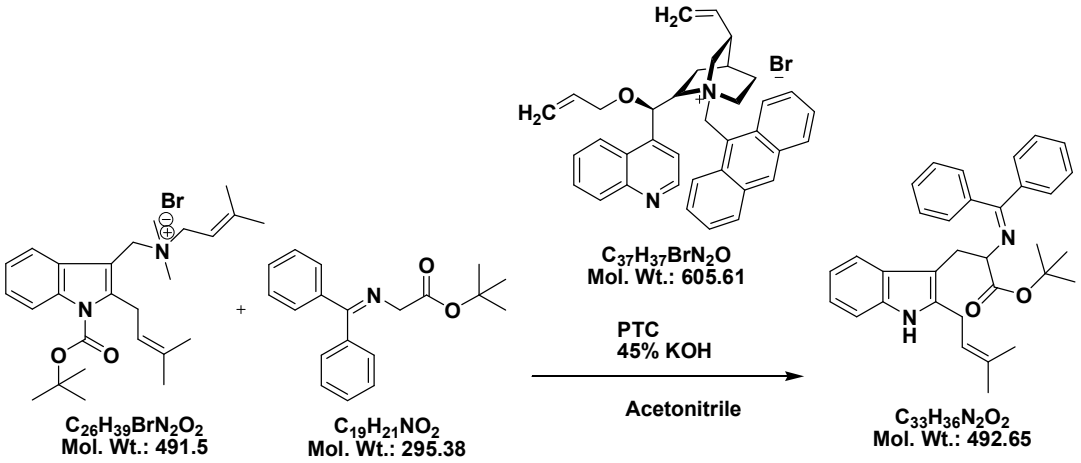
Synthetic procedure for N+ diisoprenyl bromide salt of gramine



Scheme 80. Synthesis of gramine quaternary salt **68**.

5.0 g (0.0182 mol, 1 eq.) Boc Gramine was weighed out in a beaker. 500 mL three-neck with thermometer adapter round bottom flask was oven dried for 3 hours with stir bar inside. It was removed from the oven and clamped. On one neck rubber septum was inserted, in the other nitrogen outlet was inserted, at this point the boc gramine was charged to the flask via a powder funnel, and in the last neck nitrogen inlet was inserted, as quickly as possible. To the reaction vessel blue distilled THF (245) mL was charged via syringe. The reaction mixture was allowed to stir for 1 hour to insure that all of the starting material was dissolved in the solution. At this point solution is orange/peach in color. Reaction vessel was cooled in a dry ice/acetone bath until reaction was -70 °C. At this time n-butyl lithium (14.58 mL 2.5 M 0.03644 mol 2.0 eq.) was added dropwise to the reaction vessel via a syringe over 1 hour, maintaining a temperature range between -65 and -70 °C. At this point the reaction is bright red/orange. After addition of n-butyl lithium reaction was let stir undisturbed for 1 hour and 30 minutes at -70 °C. Isoprenyl bromide (9.4 mL 0.08199 mol 4.5 eq.) was added to the reaction

dropwise. After addition of isoprenyl bromide the color of the reaction mixture is orange. At this point the reaction was left to warm overnight. When returning the next day color of the reaction mixture was clear orange. Deionized water (5 mL) was added to the reaction vessel, no reaction indicated that the n-butyl lithium was quenched. At this point the solvent was removed using the roto vap. After organic solvent was removed the water and residue was poured into a separatory funnel and extracted with dichloromethane three times (50 mL). Organic layer was dried over sodium sulfate. Solvent was removed via roto vap and high vac with cold finger. Residue was purified using flash chromatography (10 x 6 cm silica gel) eluent was 5% methanol: 95% dichloromethane to provide a light brown solid 6.14 g in 69% yield. See TLC plate developed in 9:1 Dichloromethane:Methanol observed with short range UV lamp and stained with ninhydrin stain and heated on a hot plate until colored. Spot with Rf of 0.5 is product and has a purple/violet color when the TLC plate is developed in the ninhydrin stain.



Scheme 81. Synthesis of protected C-2 alkylated tryptophan.

N-isoprenyl-2-isoprenylbocgramine (2 g, 0.004069 mol, 1 eq.) N-(diphenylmethylene) glycine tert-butyl ester (0.004069 mol, 1.202 g) and O-allyl-N-(9-anthracenylmethyl) cinchonidinium bromide (0.8192 mmol, 0.4961 g 0.2 eq) dissolved in acetonitrile (30 mL) in a 250 mL round bottom flask with a stir bar. Reaction mixture was allowed to stir for 30 minutes. At this point the reaction mixture is a dark brown color with a light yellow precipitate that appears to be the phase transfer catalyst. At this point 20 mL 45% KOH solution was added to the reaction mixture and allowed to stir, the aqueous layer was on the bottom and was clear and light yellow and the organic layer was dark brown and on the top. Reaction was allowed to stir for 20 hours; at this point the reaction has a dark layer on top and a clear orange layer on bottom. A small sample was pulled from the reaction vessel, dissolved in $CDCl_3$ and taken to the 300 NMR where I looked for the singlet at 4.1 representing the CH_2 peak from the glycinate, disappearance of this peak indicates that the reaction has gone to completion. From previous attempts at this experiment if the singlet at 4.1 remains add more KOH and let the reaction continue. After confirmation that the reaction has gone to completion, solvent was removed from the reaction by rotovap leaving water and an orange residue on top of the water. Dichloromethane (3x 50 mL) was added to the reaction vessel this solution was put into a separatory funnel with 50 mL deionized water diluting the water layer enough that the density becomes less than the dichloromethane. Organic layer was collected and dried over sodium sulfate. Solvent was removed weight of this portion is 2.9158 g. Thin layer chromatography (TLC) was used to identify a solvent system for column

chromatography, TLC indicated that mobile phase for the column should be 9:1 Hexane:Ethyl Acetate. Column used was 9 cm tall by 6 cm wide, isolating 1.21 g of product in 60.5 % yield.

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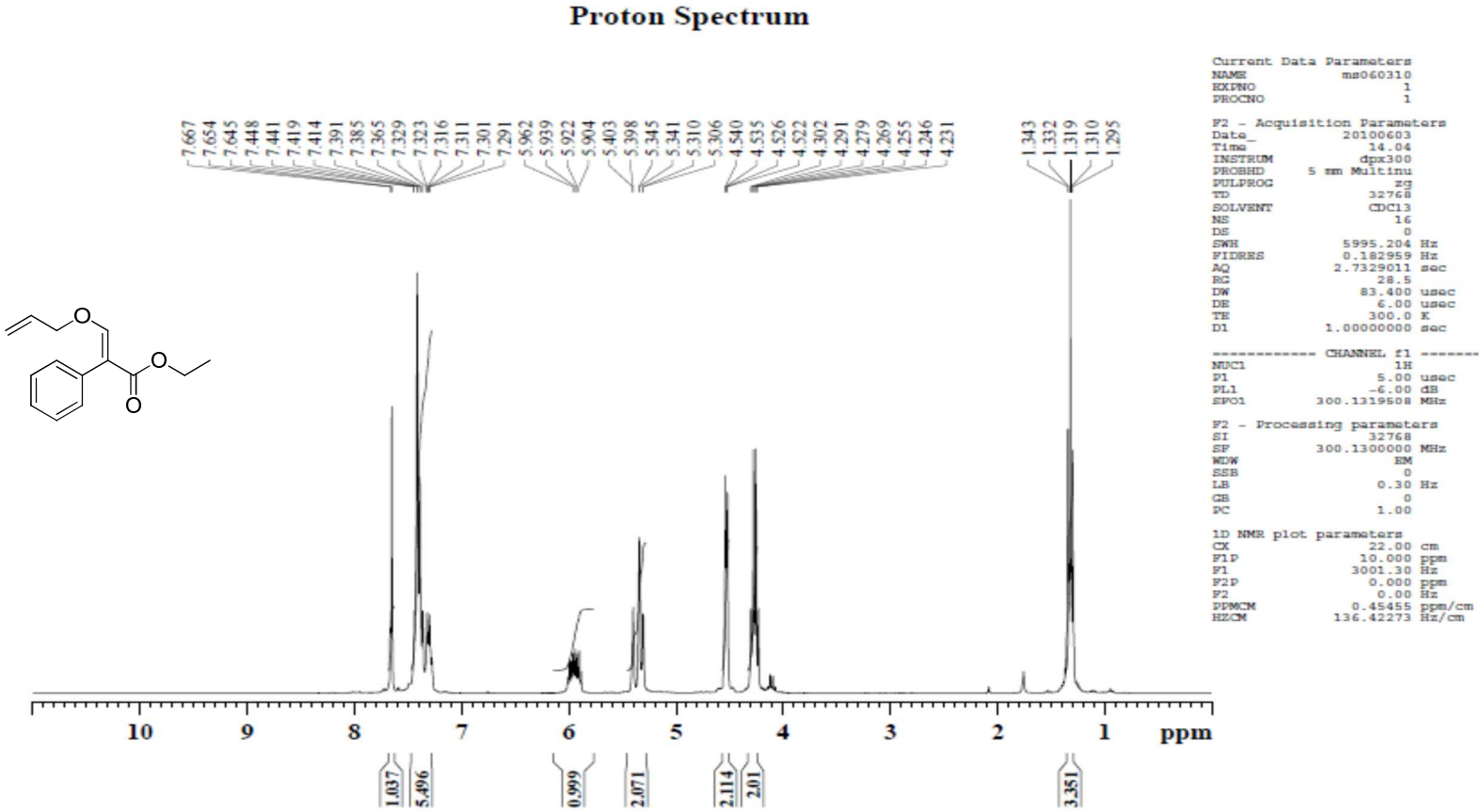
APPENDIX A : PART I: Analytical Data

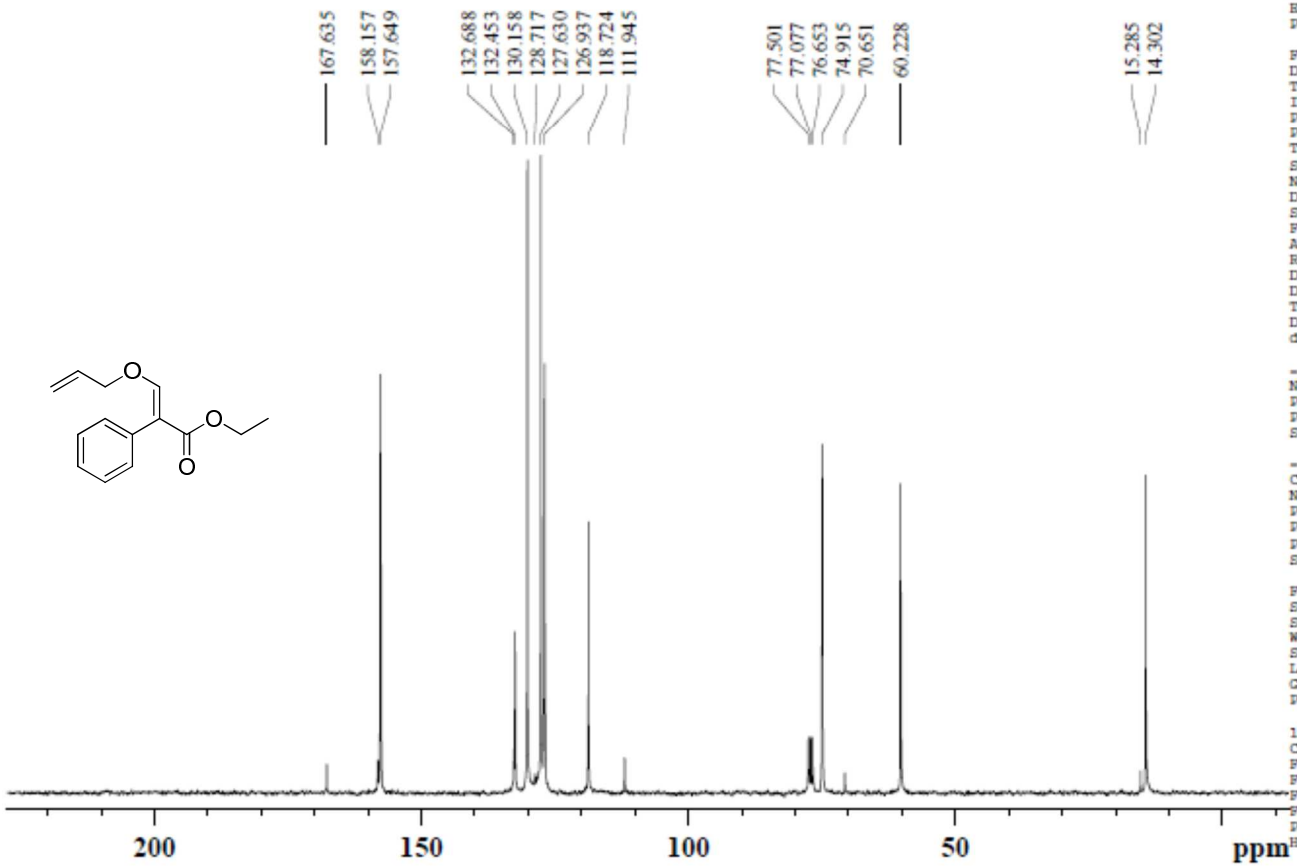
a) Copies of ^{1}H, ^{13}C, HRMS, and HPLC Spectral Data

Portrait 1, Compound 7a



Portrait 2

Carbon Spectrum

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Current Data Parameters
NAME                ms060310
EXPNO                      5
PROCNO                     1

F2 - Acquisition Parameters
Data_               20100603
Time                   15.08
INSTRUM                dpx300
PROBHD     5 mm Multinu
PULPROG                zgdc
TD                    65536
SOLVENT               CDCl3
NS                      804
DS                        0
SWH                18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                      512
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

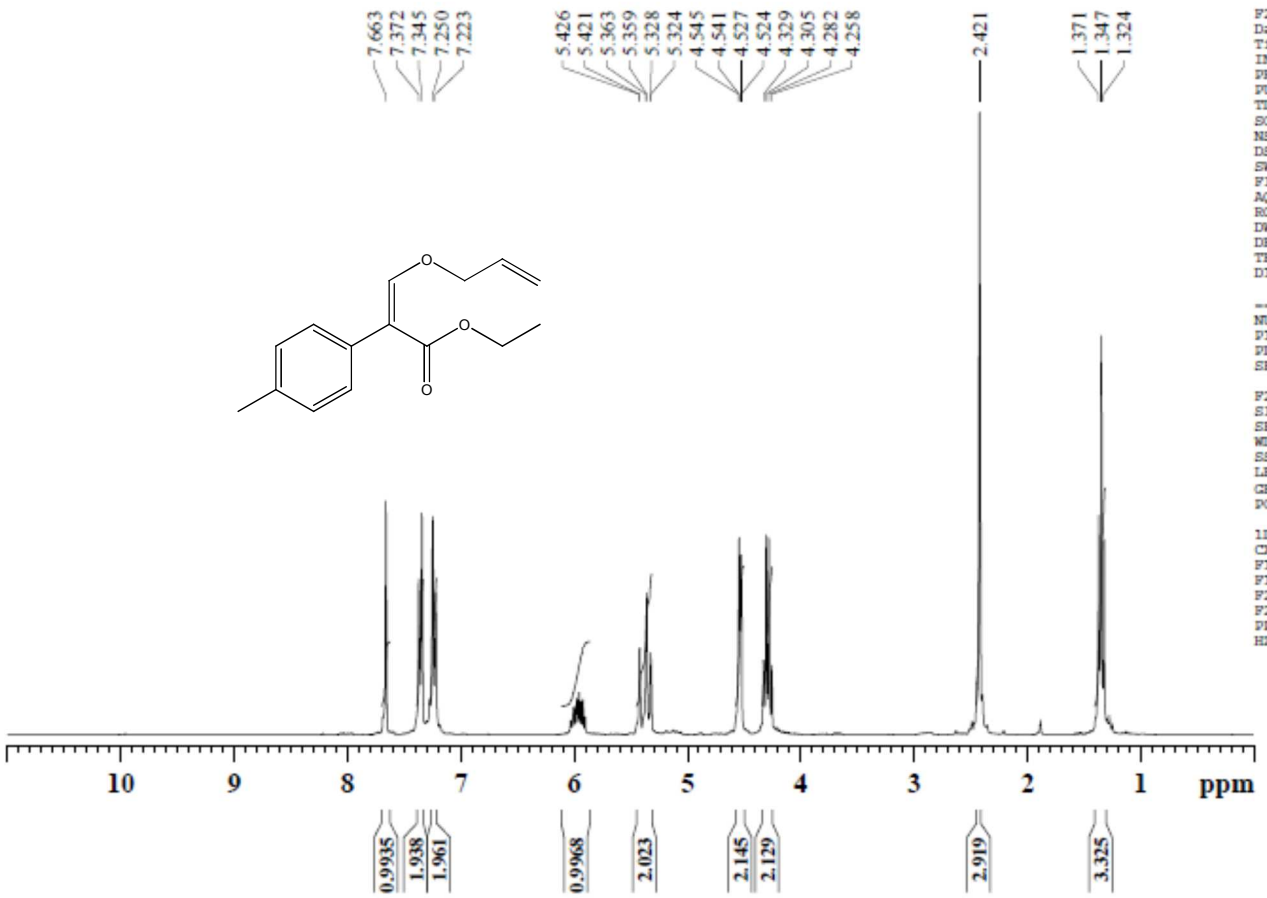
========== CHANNEL f2 =======
CPDPRG2              waltz16
NUC2                    1H
PCPD2                100.00 usec
PL2                  -6.00 dB
PL12                 16.60 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
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
PPMCM               10.22727 ppm/cm
HZCM               771.82935 Hz/cm
```

Portrait 3, Compound 7b

Proton Spectrum

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Current Data Parameters
NAME            ms052710
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100527
Time               12.28
INSTRUM          dpx300
PROBHD     5 mm Multinu
PULPROG              zg
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    0
SWH            5995.204 Hz
FIDRES         0.182959 Hz
AQ             2.7329011 sec
RG                14.3
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               10.000 ppm
F1              3001.30 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.45455 ppm/cm
HZCM         136.42273 Hz/cm
```
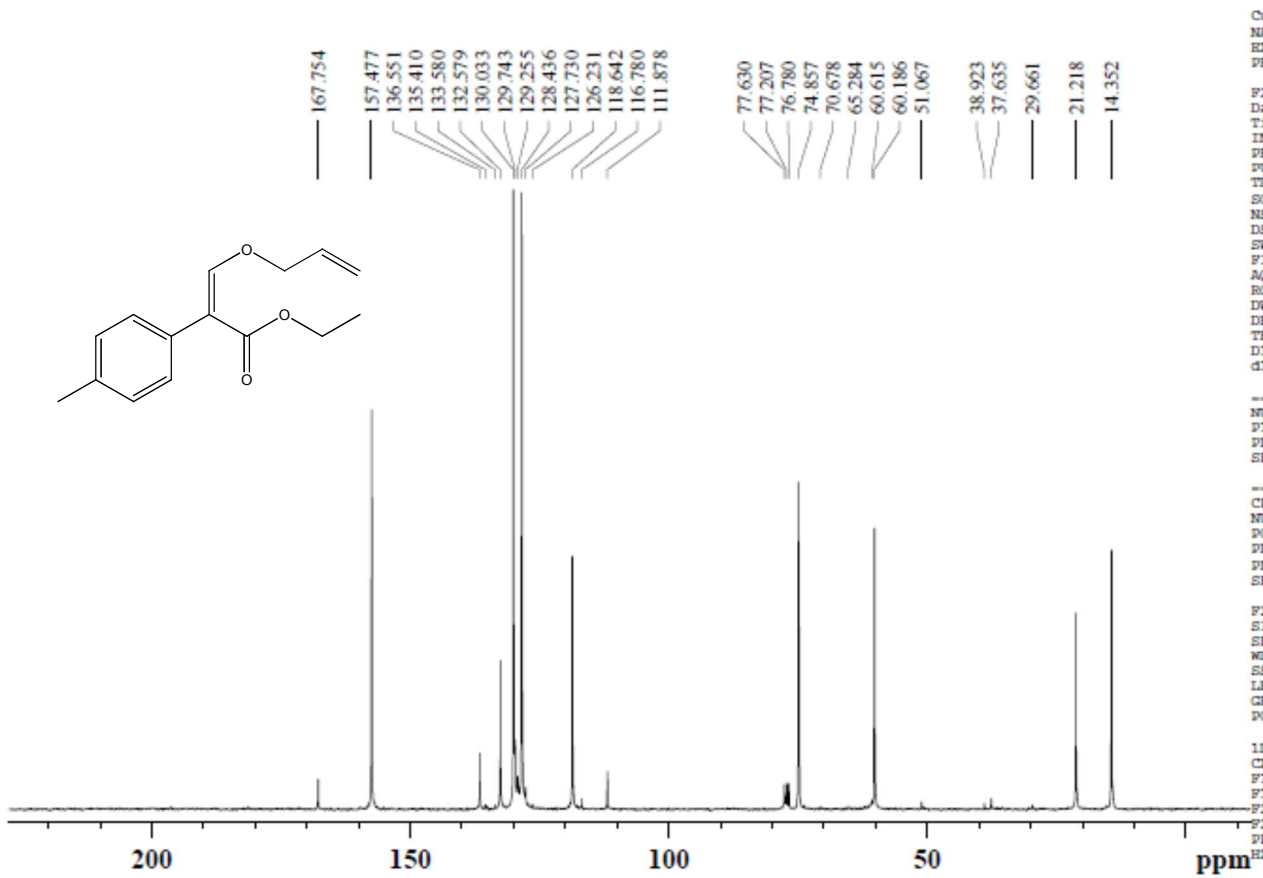

Portrait 4

Carbon Spectrum

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Current Data Parameters
NAME                ms052710
EXPNO                      5
PROCNO                     1

F2 - Acquisition Parameters
Date_              20100527
Time               15.38
INSTRUM            dpx300
PROBHD     5 mm Multinu
PULPROG            zgdc
TD                 65536
SOLVENT            CDC13
NS                 1024
DS                 0
SWH                18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                 574.7
DW                 27.600 usec
DE                 6.00 usec
TE                 300.0 K
D1                 0.10000000 sec
d11                0.03000000 sec

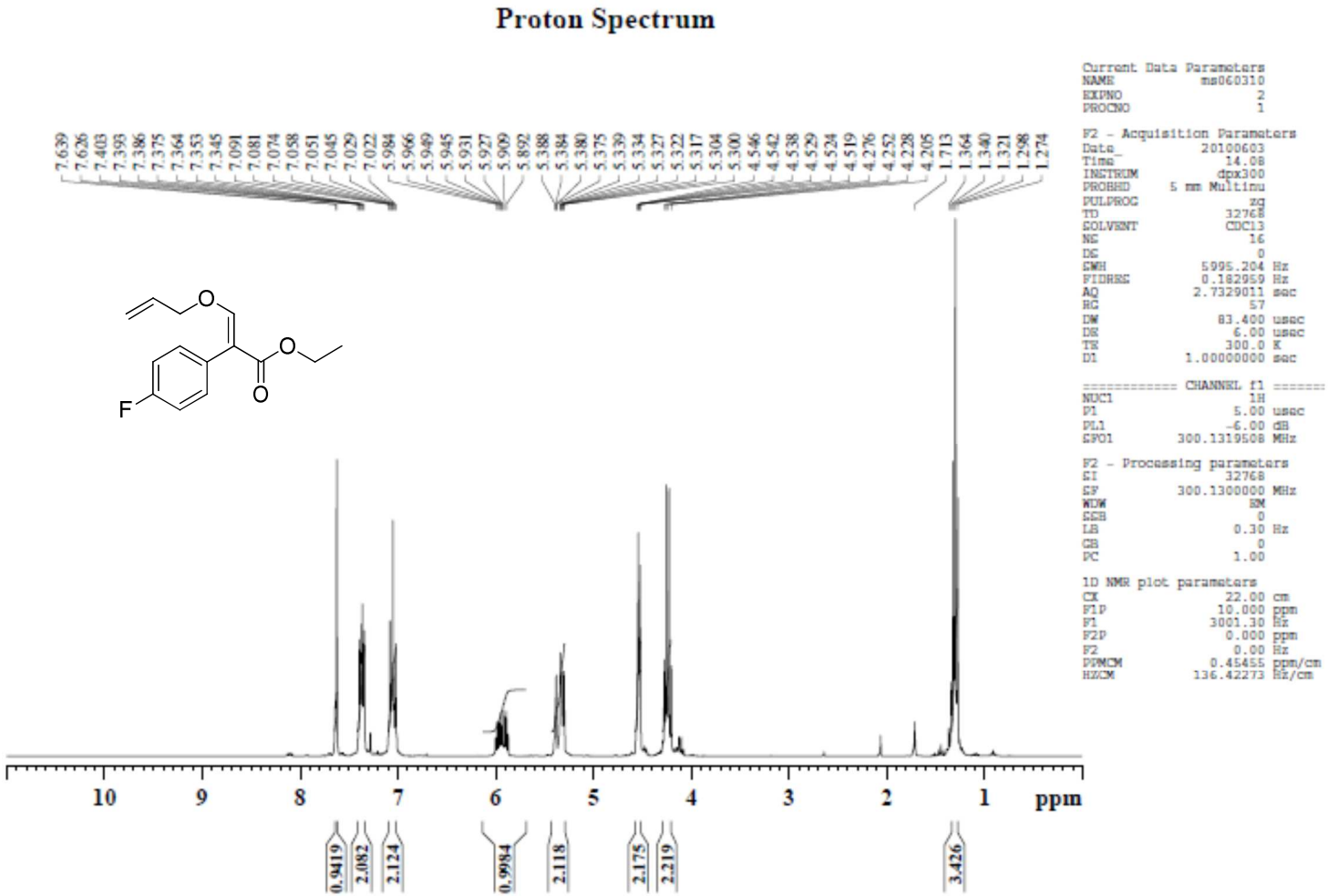
========== CHANNEL f1 =======
NUC1               13C
P1                 6.80 usec
PL1                -6.00 dB
SFO1               75.4758695 MHz

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

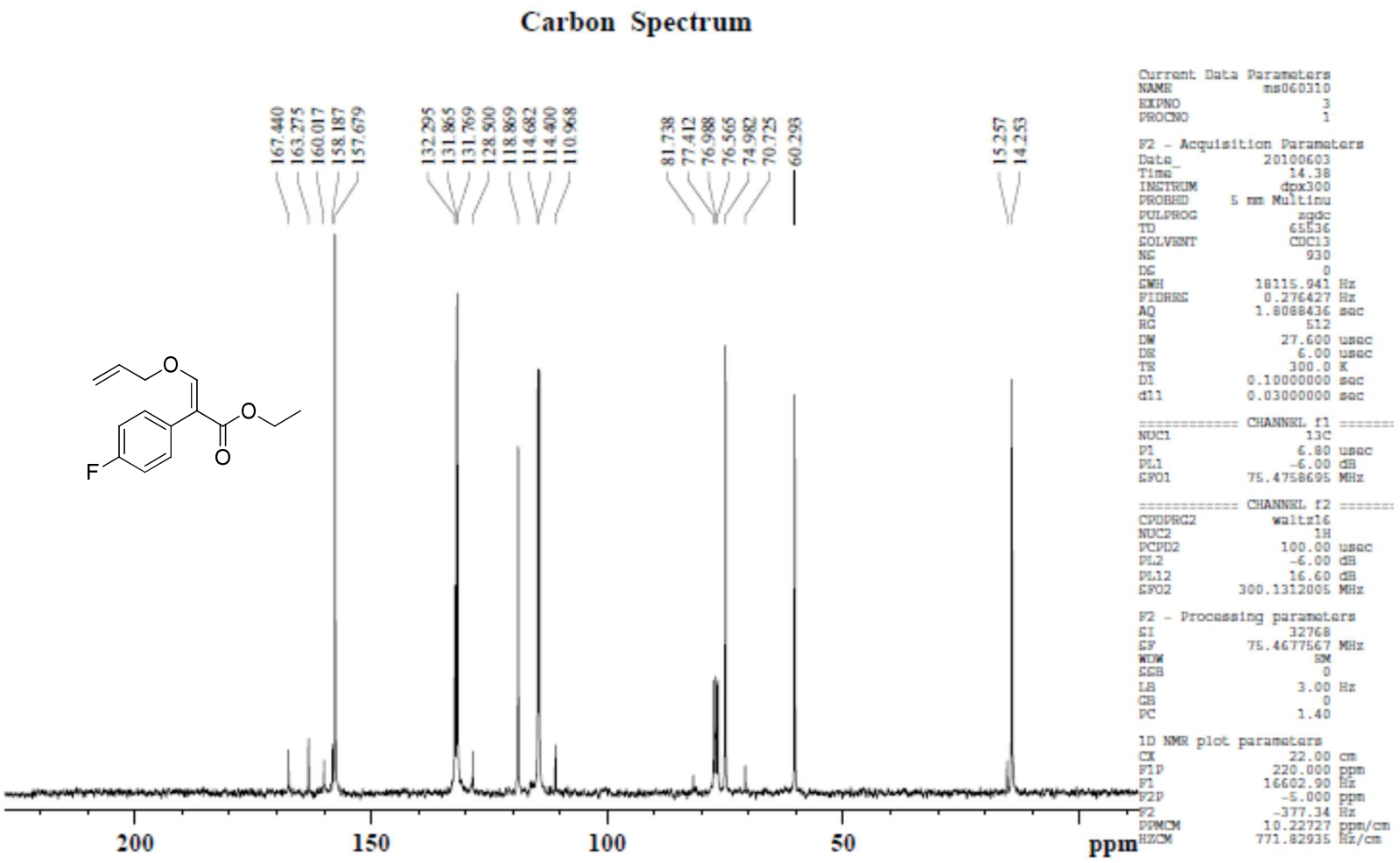
F2 - Processing parameters
SI                 32768
SF                 75.4677567 MHz
WDW                EM
SSB                0
LB                 3.00 Hz
GB                 0
PC                 1.40

1D NMR plot parameters
CX                 22.00 cm
F1P                220.000 ppm
F1                 16602.90 Hz
F2P                -5.000 ppm
F2                 -377.34 Hz
PPMCM              10.22727 ppm/cm
HZCM               771.82935 Hz/cm
```

Portrait 5, Compound 7c



Portrait 6


Carbon Spectrum
167.440
163.275
160.017
158.187
157.679
132.295
131.865
131.769
128.500
118.869
114.682
114.400
110.968
81.738
77.412
76.988
76.565
74.982
70.725
60.293
15.257
14.253
O
O
O
F
200
150
100
50
ppm
Current Data Parameters
NAME ms060310
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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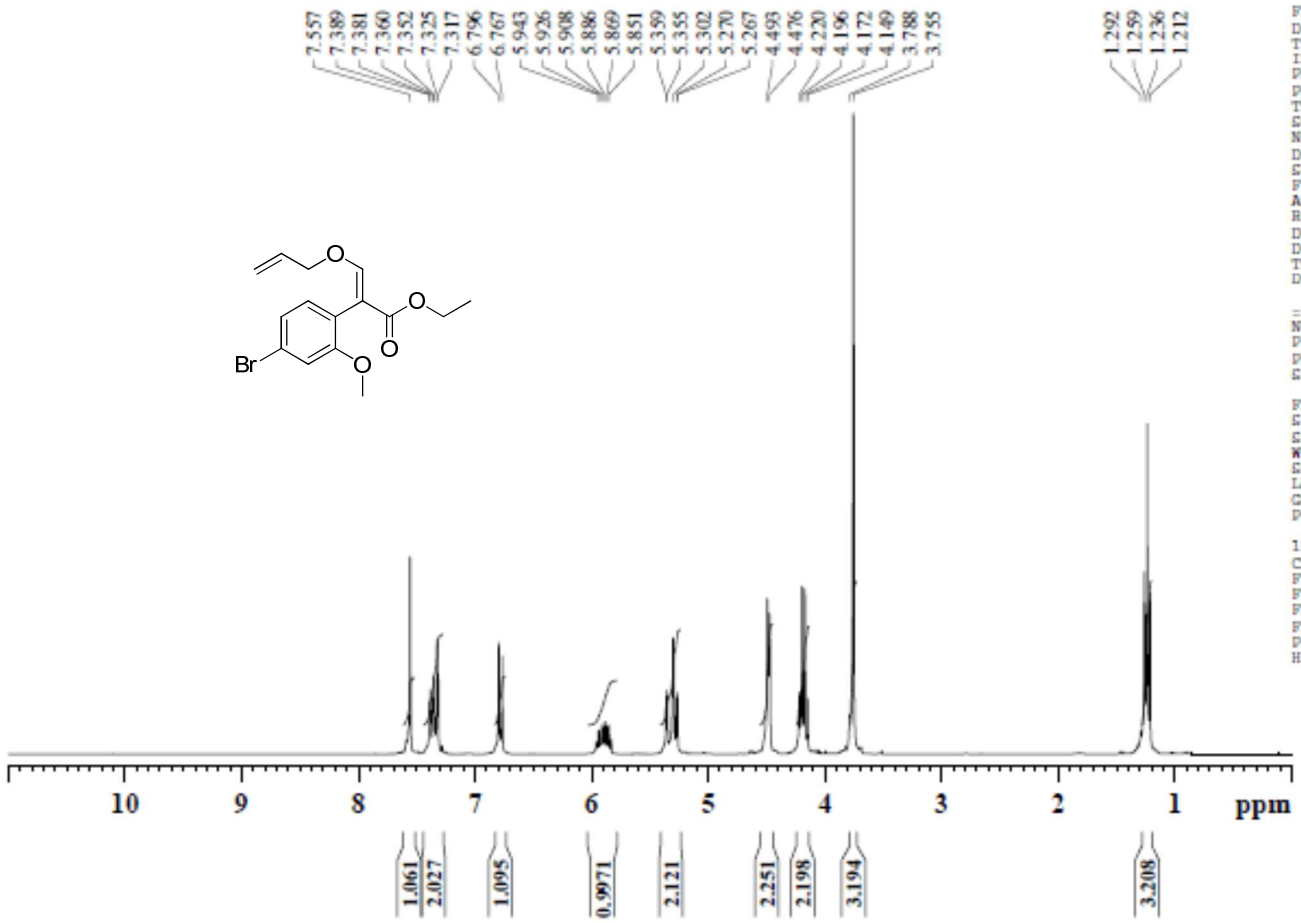
Time 14.38
INSTRUM dpx300
PROBHD 5 mm Multinu
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 930
DS 0
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 512
DW 27.600 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 -6.00 dB
SFO1 75.4758695 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 16.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
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
PPMCM 10.22727 ppm/cm
HZCM 771.82935 Hz/cm

Portrait 7, Compound 7d

Proton Spectrum




```
Current Data Parameters
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PROCNO                   1

F2 - Acquisition Parameters
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PROBHD     5 mm Multinu
PULPROG                 zg
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH               5995.204 Hz
FIDRES            0.182959 Hz
AQ                2.7329011 sec
RG                     28.5
DW                  83.400 usec
DE                   6.00 usec
TE                  300.0 K
D1                1.00000000 sec

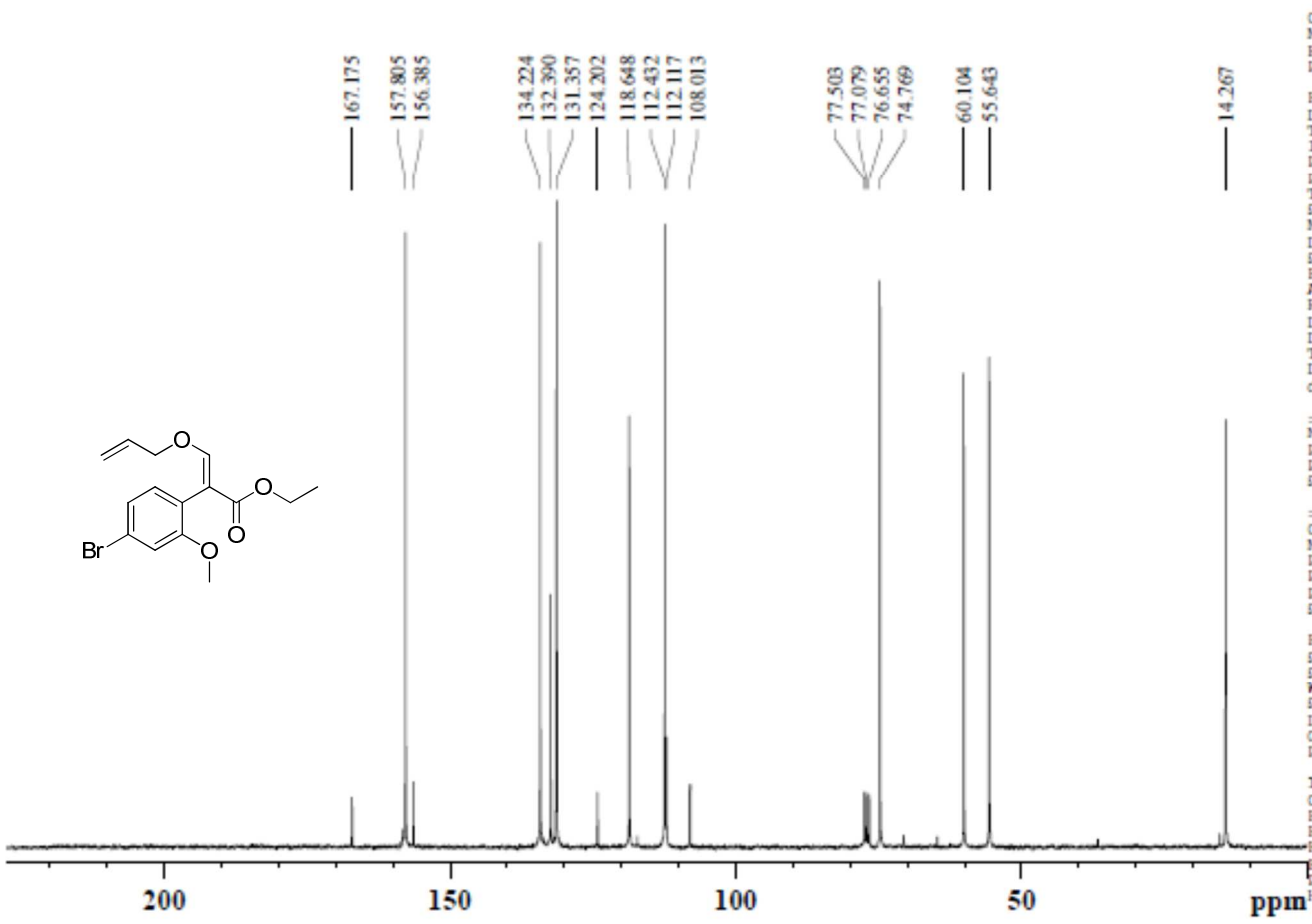
========== CHANNEL f1 =======
NUC1                    1H
P1                   5.00 usec
PL1                 -6.00 dB
SFO1           300.1319508 MHz

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                 10.000 ppm
F1                3001.30 Hz
F2P                  0.000 ppm
F2                   0.00 Hz
PPMCM              0.45455 ppm/cm
HZCM             136.42273 Hz/cm
```

Portrait 8

Carbon Spectrum

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Current Data Parameters
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EXPNO                        3
PROCNO                       1

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PROBHD     5 mm Multinu
PULPROG                  zgpg
TD                       65536
SOLVENT                  CDCl3
NS                        1024
DS                           0
SWH                  18115.941 Hz
FIDRES                0.276427 Hz
AQ                    1.8088436 sec
RG                       1625.5
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
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                     200.000 ppm
F1                     15093.55 Hz
F2P                       0.000 ppm
F2                        0.00 Hz
PPMCM                  9.09091 ppm/cm
HZCM                 686.07056 Hz/cm
```
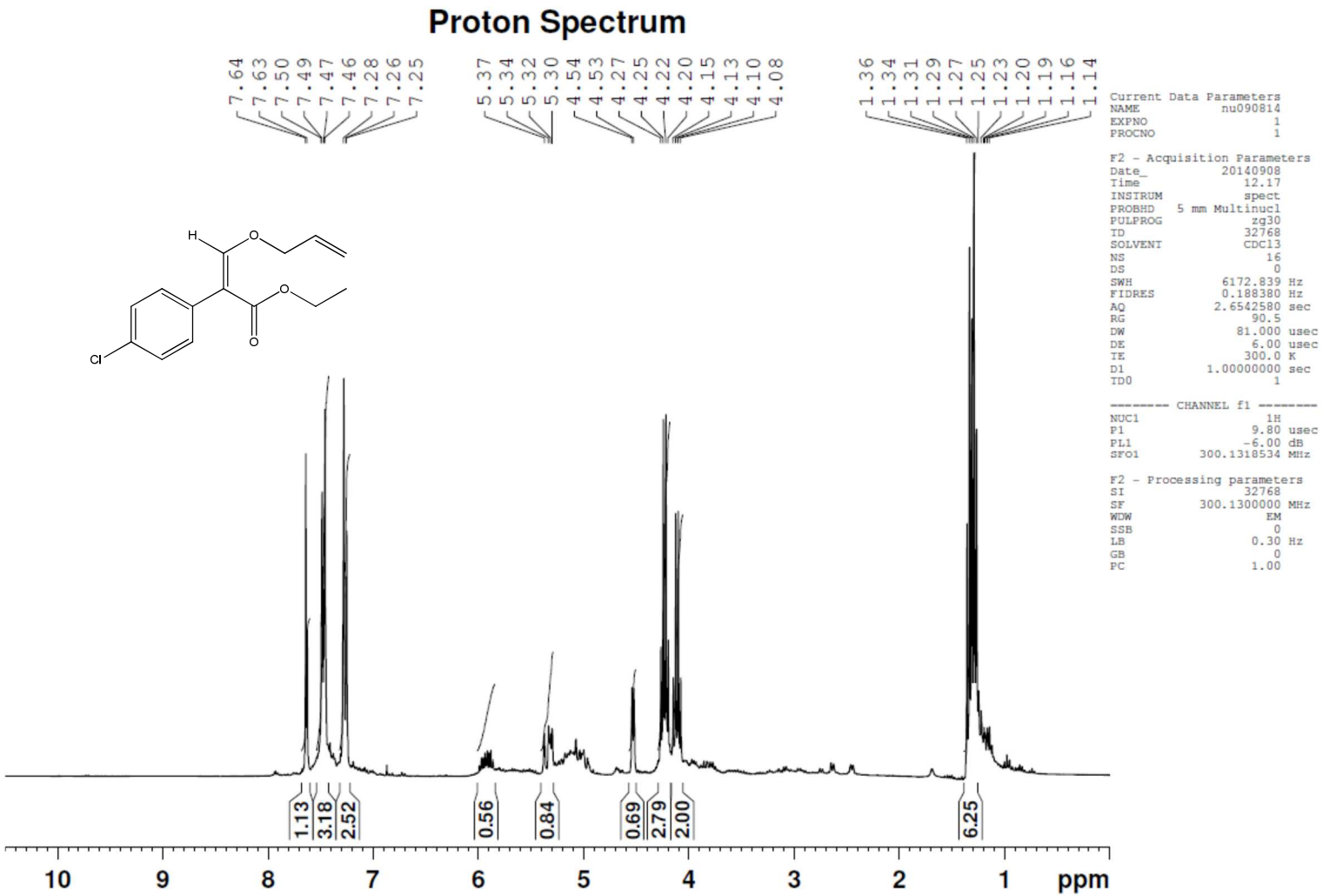
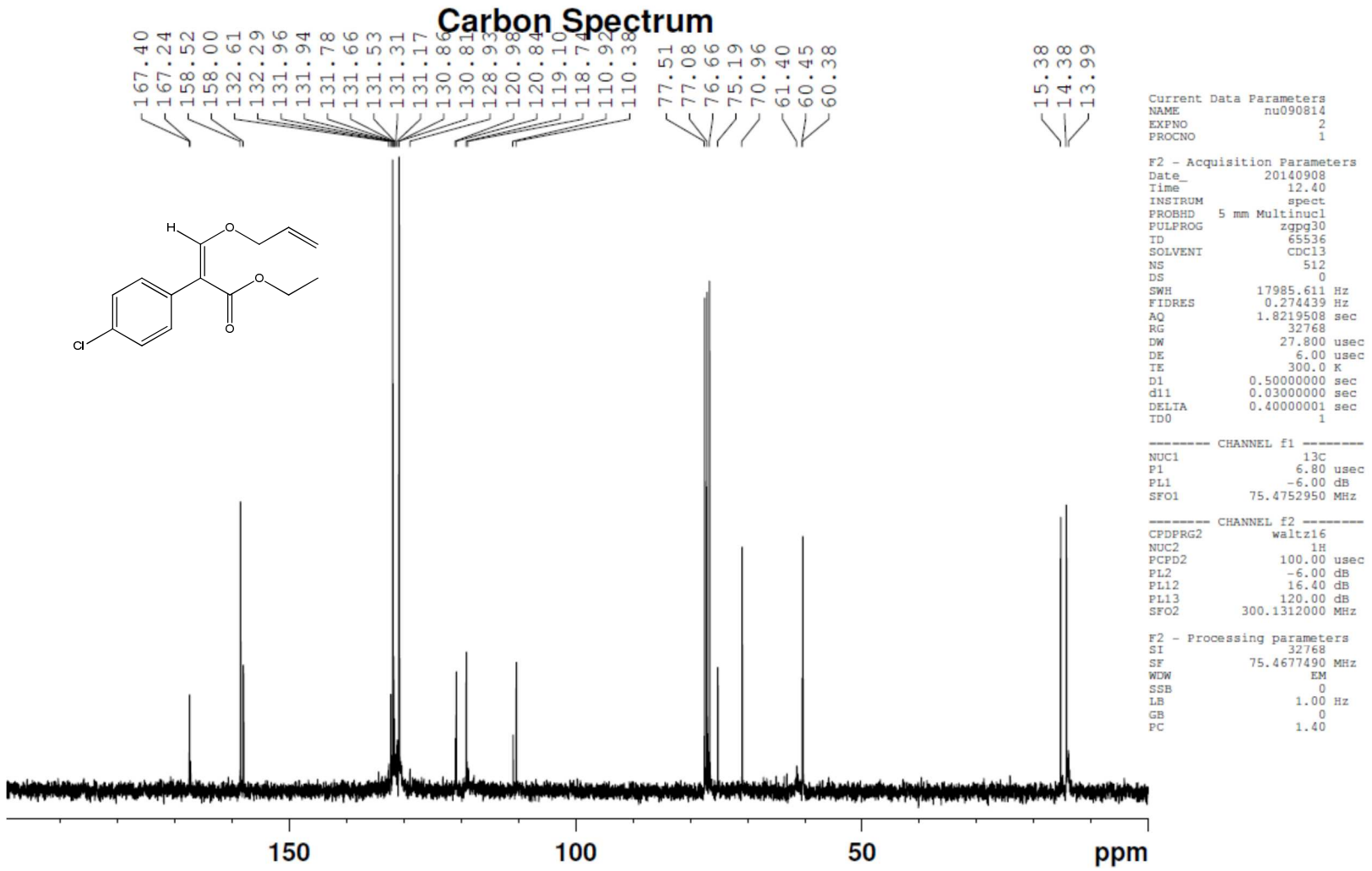

Portrait 9, Compound 7e



Portrait 10


Carbon Spectrum
167.40
167.24
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158.00
132.61
132.29
131.96
131.94
131.78
131.66
131.53
131.31
131.17
130.86
130.81
128.93
120.98
120.84
119.10
118.74
110.92
110.38
77.51
77.08
76.66
75.19
70.96
61.40
60.45
60.38
15.38
14.38
13.99
H
O
O
O
Cl
150
100
50
ppm
Current Data Parameters
NAME nu090814
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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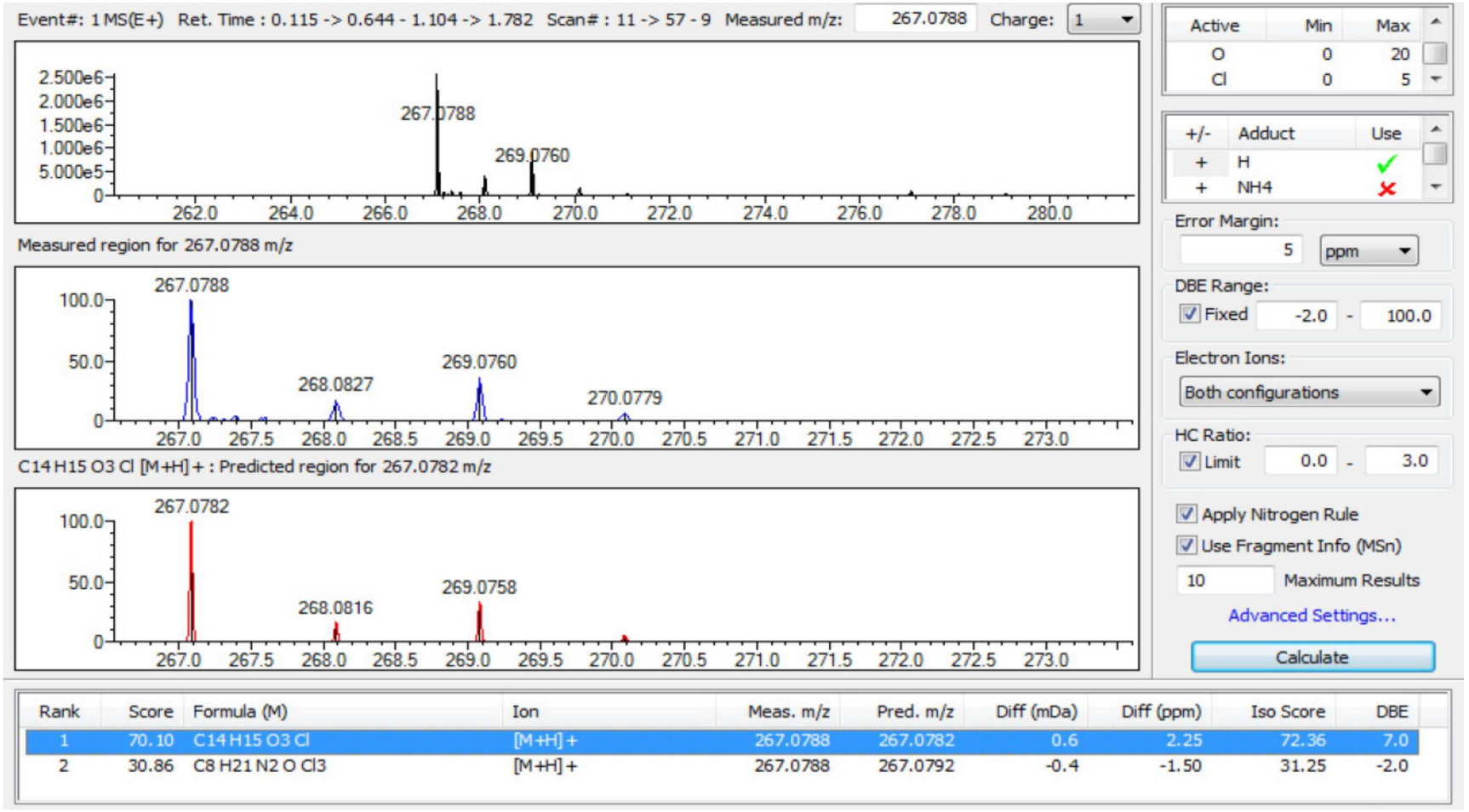
Time 12.40
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 0
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 0.50000000 sec
d11 0.03000000 sec
DELTA 0.40000001 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 -6.00 dB
SFO1 75.4752950 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 16.40 dB
PL13 120.00 dB
SFO2 300.1312000 MHz
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

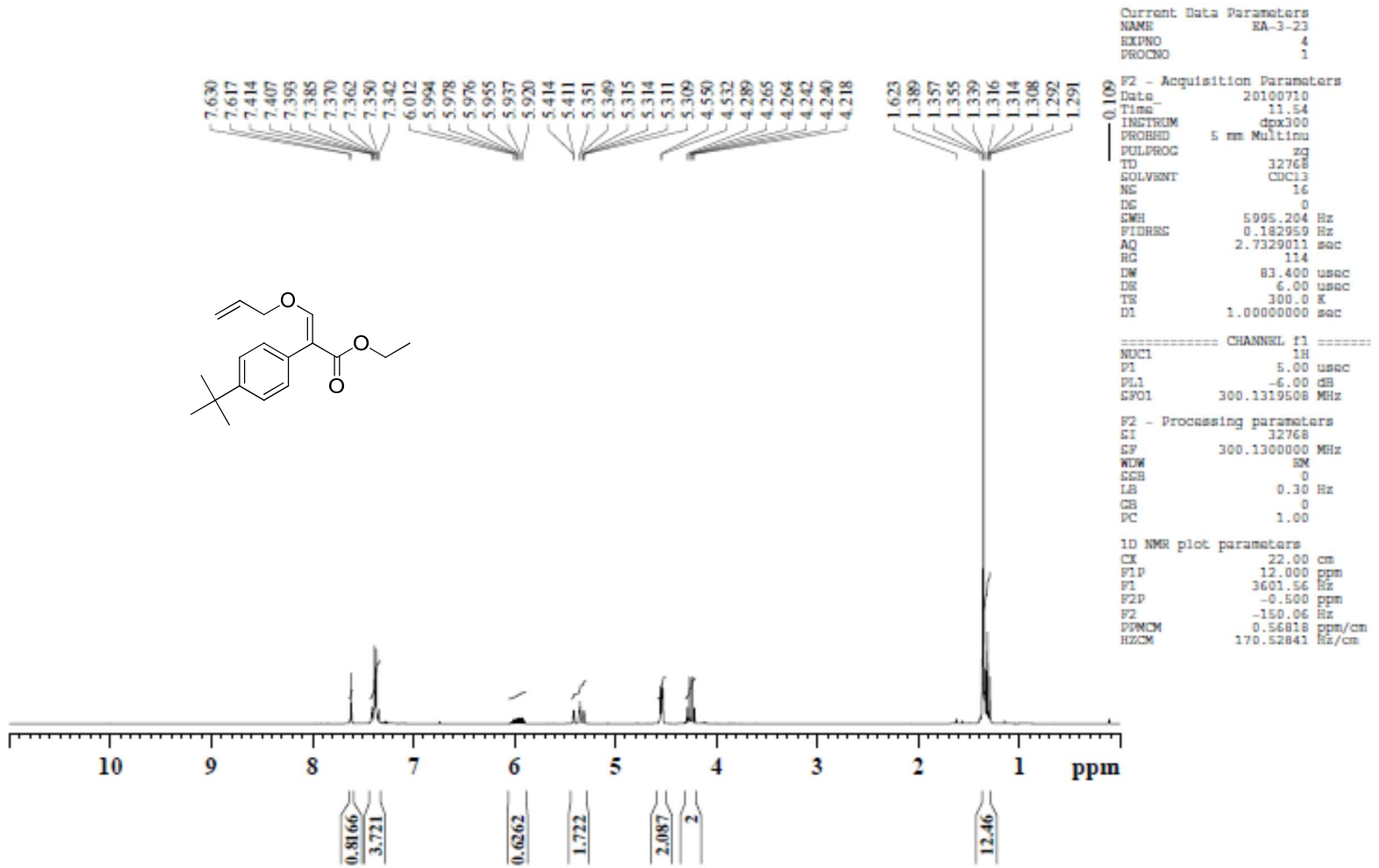
Portrait 11, HRMS



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Diff (mDa)	Diff (ppm)	Iso Score	DBE
1	70.10	C14 H15 O3 Cl	[M+H]+	267.0788	267.0782	0.6	2.25	72.36	7.0
2	30.86	C8 H21 N2 O Cl3	[M+H]+	267.0788	267.0792	-0.4	-1.50	31.25	-2.0

Portrait 12, Compound 7f

Proton Spectrum

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PROCNO                      1

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INSTRUM            dpx300
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PULPROG                 zg
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH               5995.204 Hz
FIDRES            0.182959 Hz
AQ                2.7329011 sec
RG                     114
DW                  83.400 usec
DE                   6.00 usec
TE                  300.0 K
D1                1.00000000 sec

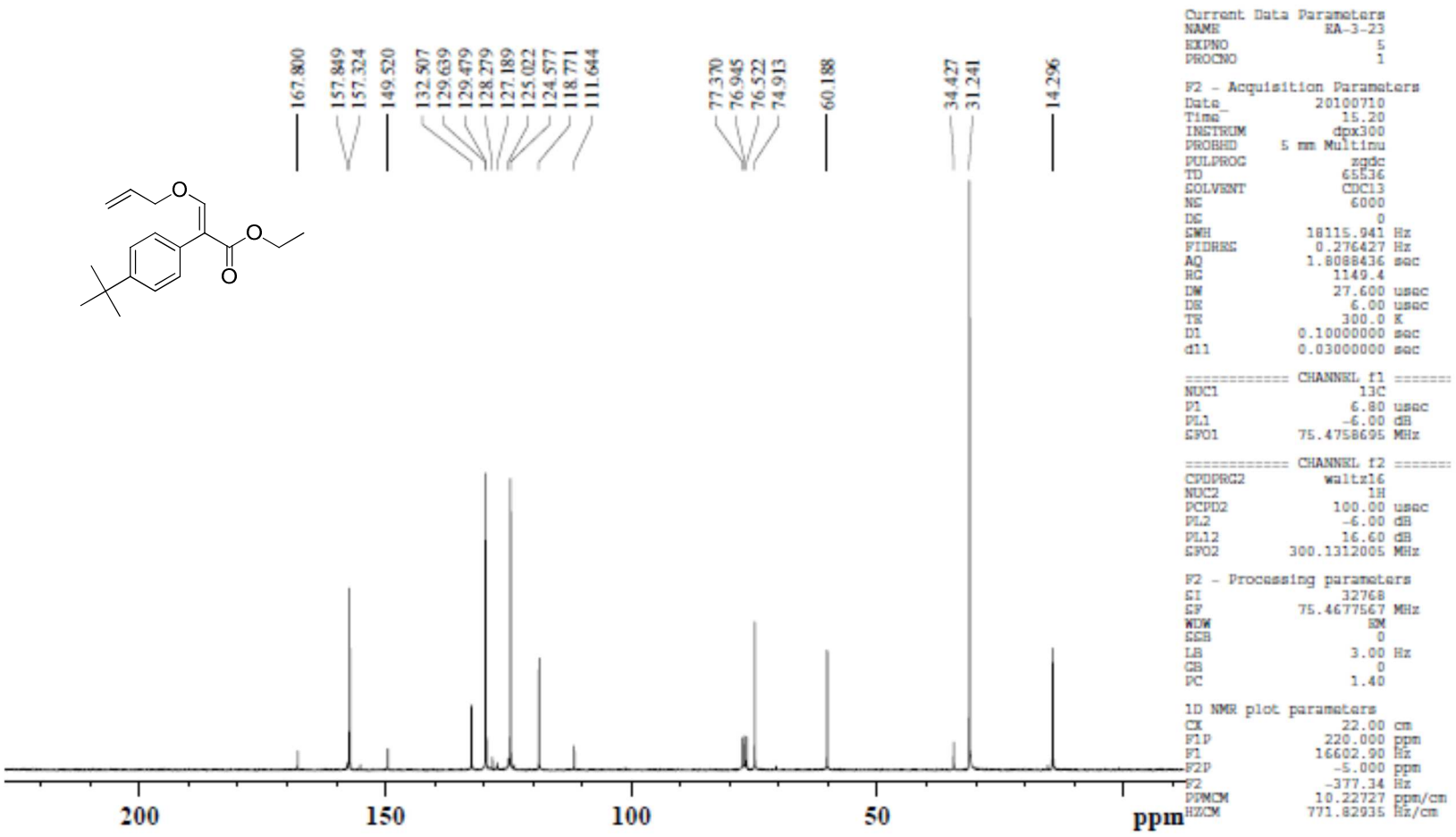
============ CHANNEL f1 =======
NUC1                    1H
P1                   5.00 usec
PL1                 -6.00 dB
SFO1          300.1319508 MHz

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                 12.000 ppm
F1                3601.56 Hz
F2P                 -0.500 ppm
F2                -150.06 Hz
PPMCM              0.56818 ppm/cm
HZCM             170.52841 Hz/cm
```

Portrait 13

Carbon Spectrum




```
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PROCNO                      1

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PROBHD     5 mm Multinu
PULPROG               zgdc
TD                   65536
SOLVENT              CDCl3
NS                    6000
DS                       0
SWH               18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                    1149.4
DW                   27.600 usec
DE                    6.00 usec
TE                   300.0 K
D1                0.10000000 sec
d11               0.03000000 sec

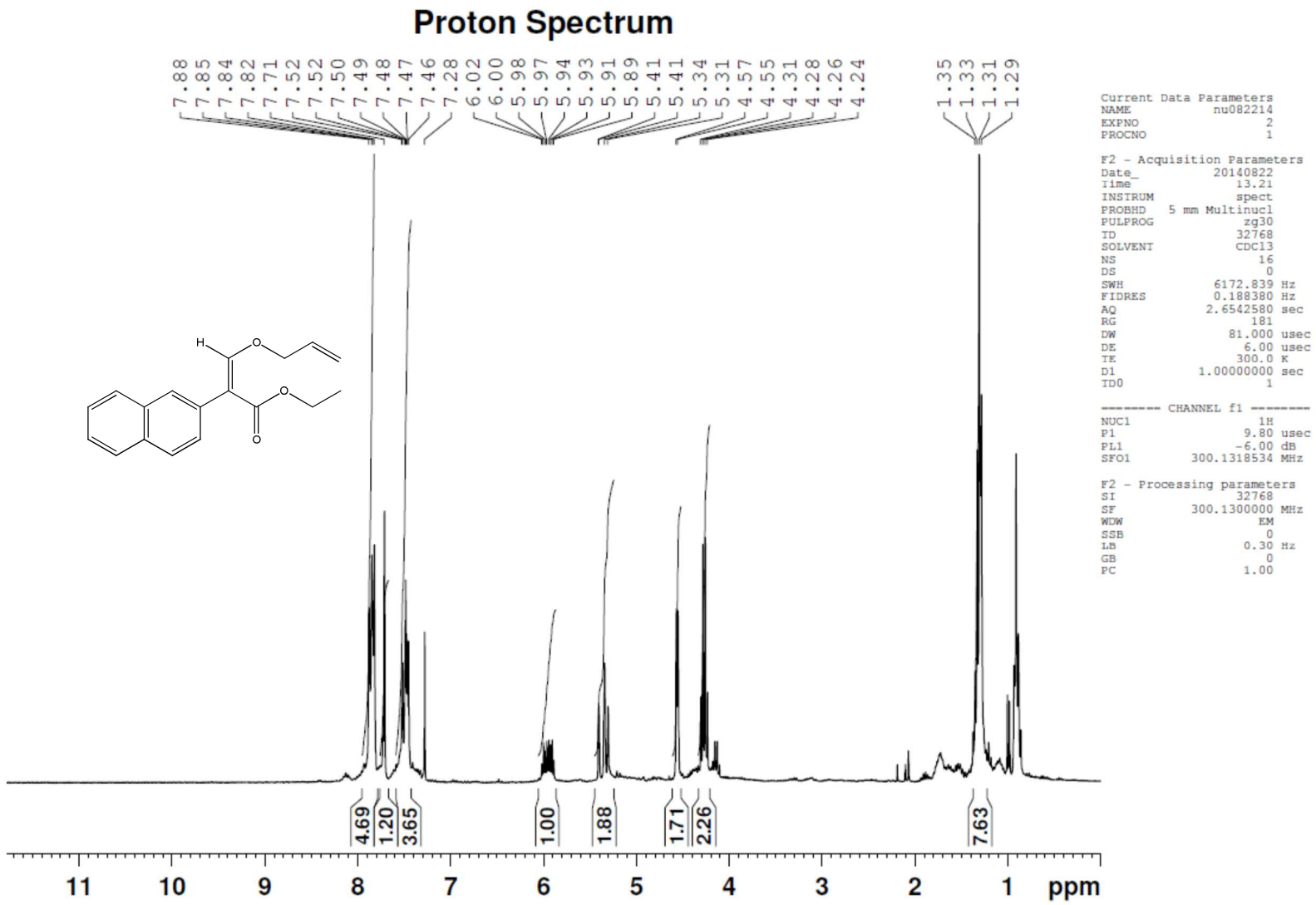
============ CHANNEL f1 =======
NUC1                    13C
P1                     6.80 usec
PL1                   -6.00 dB
SFO1              75.4758695 MHz

============ 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
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
PPMCM                10.22727 ppm/cm
HZCM                771.82935 Hz/cm
```

Portrait 14, Compound 7g

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Current Data Parameters
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EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
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Time                      13.21
INSTRUM                   spect
PROBHD     5 mm Multinucl
PULPROG                   zg30
TD                       32768
SOLVENT                  CDCl3
NS                          16
DS                           0
SWH                  6172.839 Hz
FIDRES               0.188380 Hz
AQ                   2.6542580 sec
RG                         181
DW                      81.000 usec
DE                       6.00 usec
TE                      300.0 K
D1                   1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       9.80 usec
PL1                     -6.00 dB
SFO1             300.1318534 MHz

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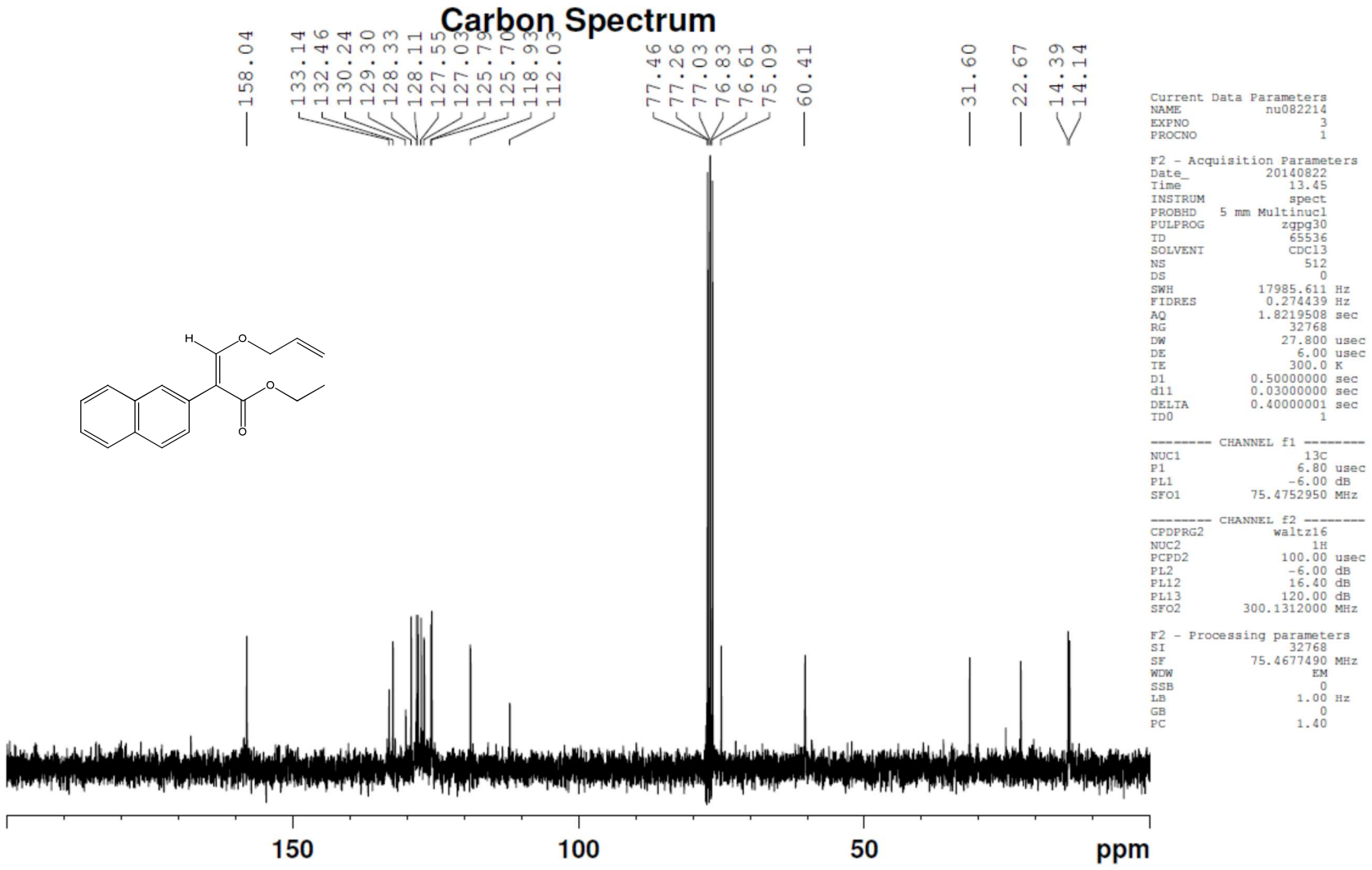
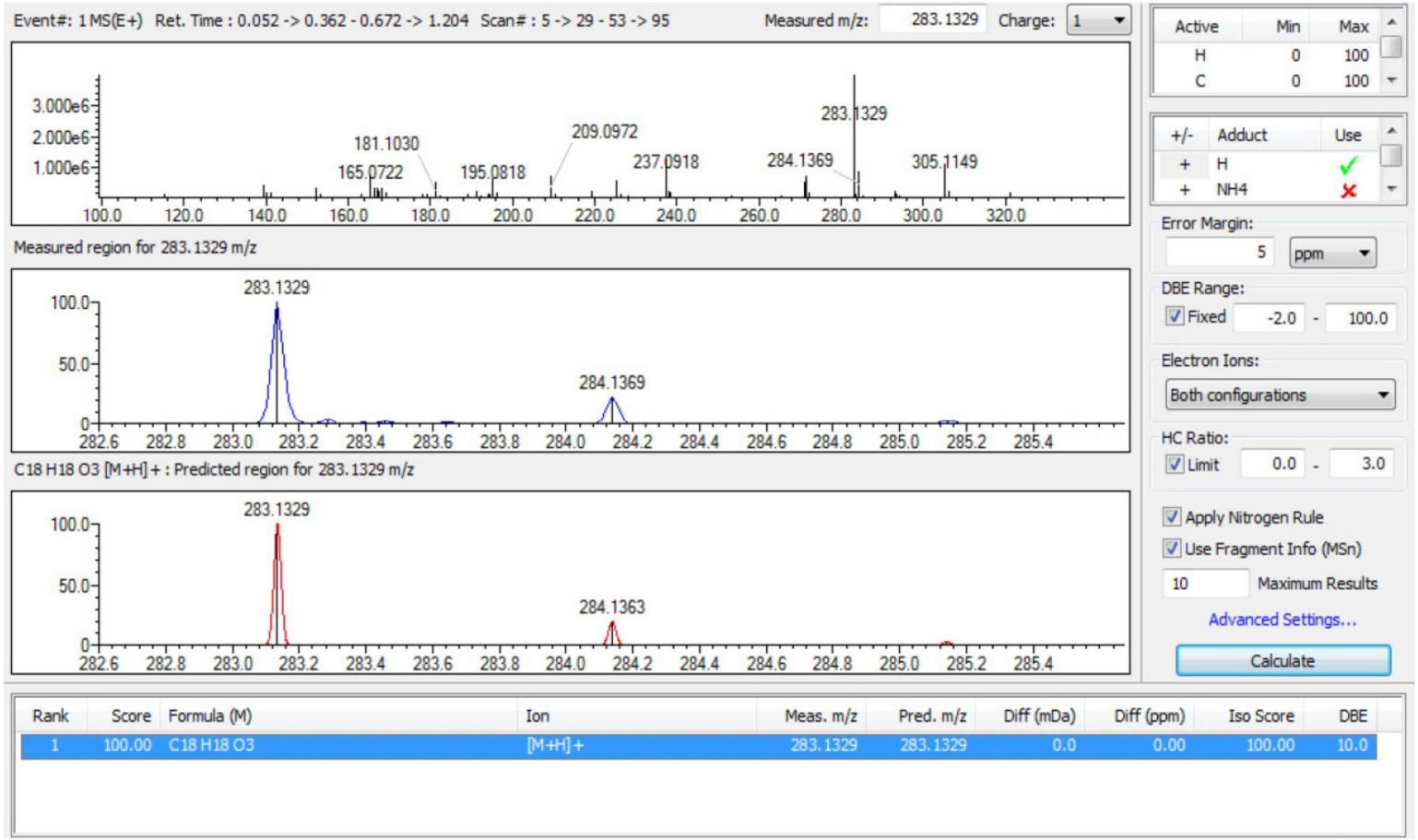

Portrait 15

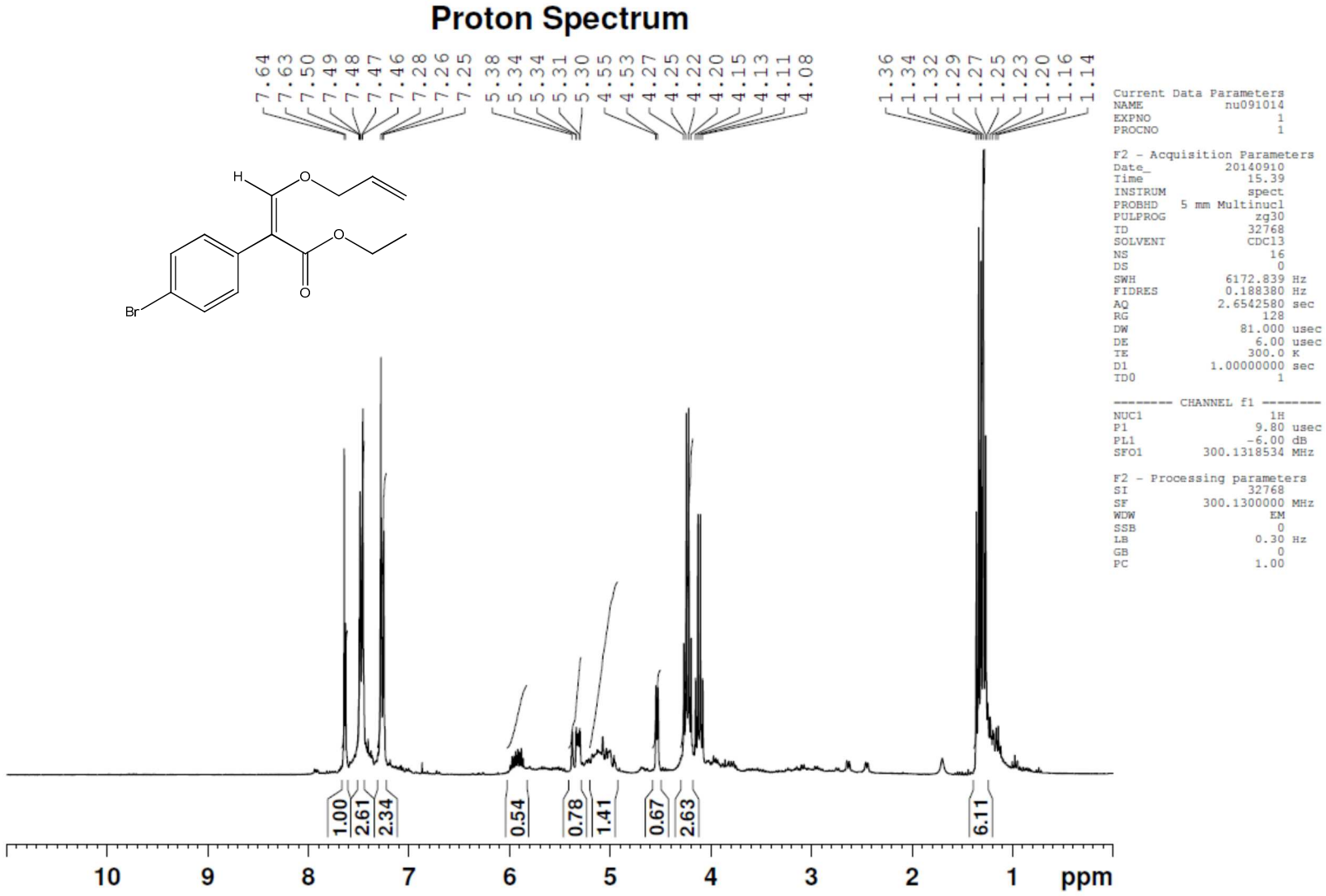



```
Current Data Parameters
NAME            nu082214
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140822
Time               13.45
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    0
SWH           17985.611 Hz
FIDRES         0.274439 Hz
AQ             1.8219508 sec
RG                32768
DW                27.800 usec
DE                 6.00 usec
TE                300.0 K
D1            0.50000000 sec
d11           0.03000000 sec
DELTA         0.40000001 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                   6.80 usec
PL1                 -6.00 dB
SFO1          75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 -6.00 dB
PL12                16.40 dB
PL13               120.00 dB
SFO2         300.1312000 MHz

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

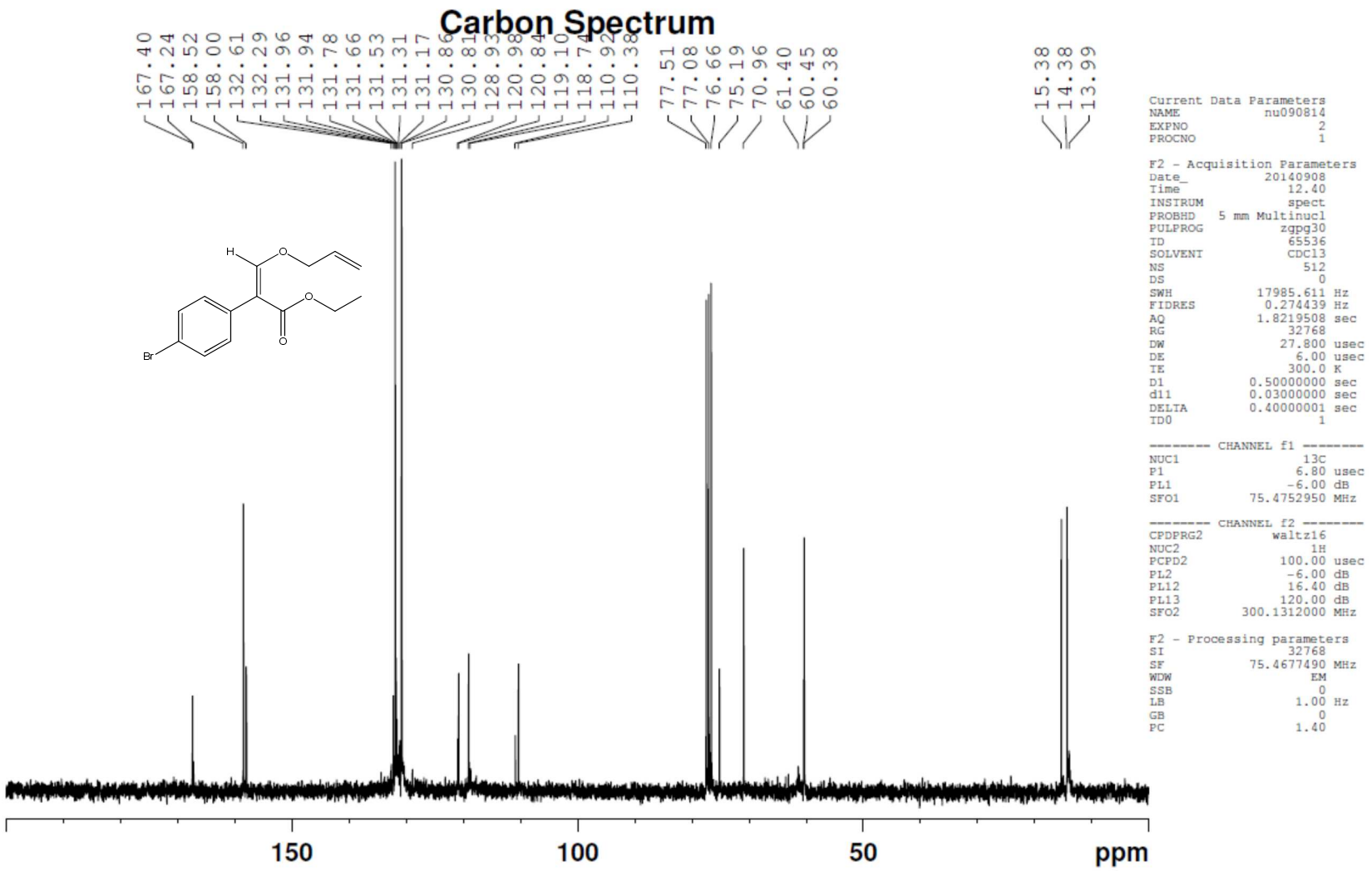
Portrait 16, HRMS



Portrait 17, Table 3, Compound 7h

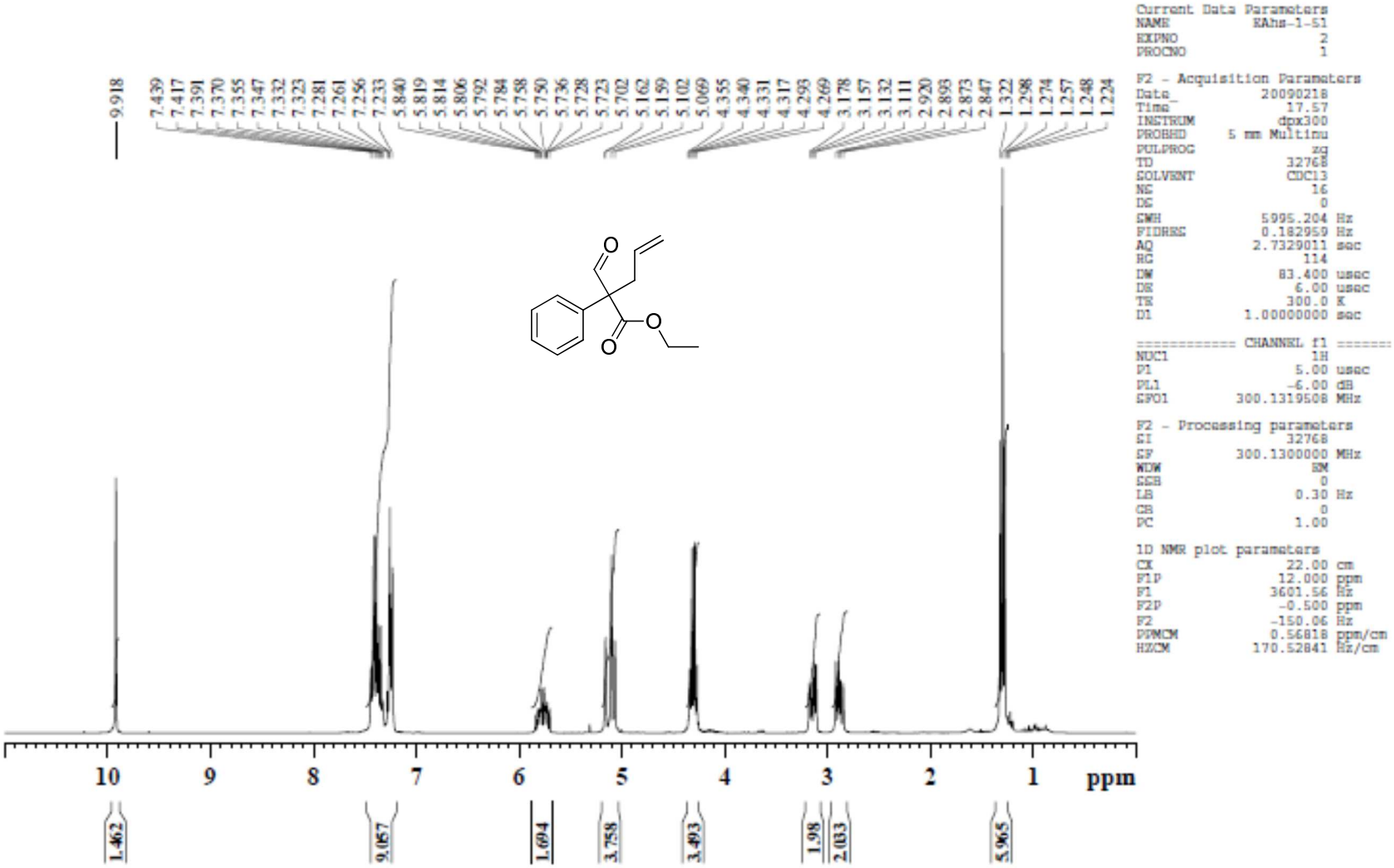


Portrait 18




```
Current Data Parameters
NAME                  nu090814
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20140908
Time                     12.40
INSTRUM                  spect
PROBHD    5 mm Multinucl
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         512
DS                           0
SWH                 17985.611 Hz
FIDRES                0.274439 Hz
AQ                    1.8219508 sec
RG                       32768
DW                      27.800 usec
DE                       6.00 usec
TE                       300.0 K
D1                 0.50000000 sec
d11                0.03000000 sec
DELTA              0.40000001 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       13C
P1                        6.80 usec
PL1                      -6.00 dB
SFO1               75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   100.00 usec
PL2                      -6.00 dB
PL12                     16.40 dB
PL13                    120.00 dB
SFO2              300.1312000 MHz

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

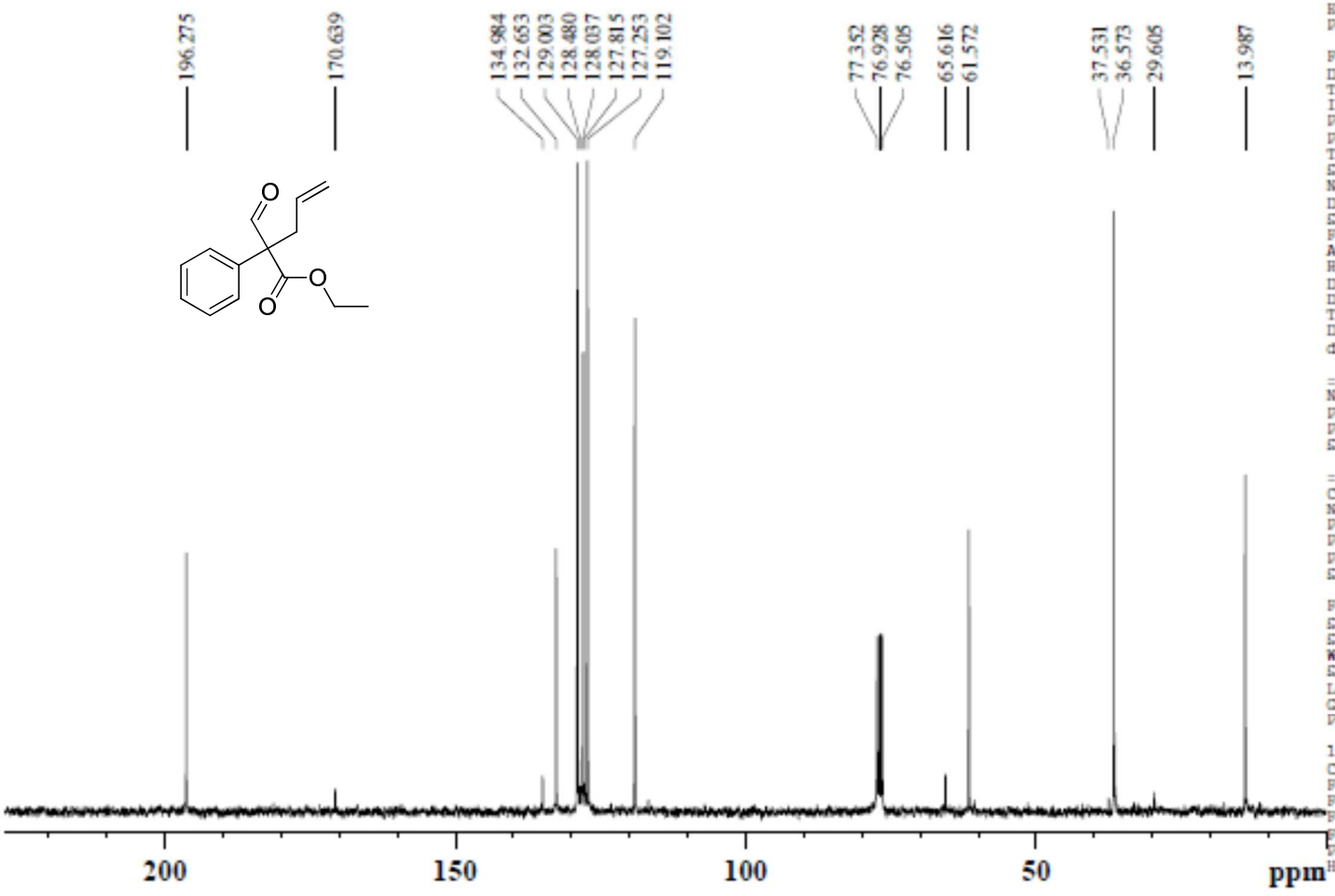
Portrait 19, Compound 8a




```
Current Data Parameters
NAME                  EAhs-1-51
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20090218
Time                      17.57
INSTRUM                  dpx300
PROBHD       5 mm Multinu
PULPROG                      zg
TD                        32768
SOLVENT                   CDCl3
NS                           16
DS                            0
SWH                    5995.204 Hz
FIDRES                 0.182959 Hz
AQ                     2.7329011 sec
RG                          114
DW                       83.400 usec
DE                        6.00 usec
TE                       300.0 K
D1                    1.00000000 sec

============ CHANNEL f1 =======
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                       12.000 ppm
F1                      3601.56 Hz
F2P                       -0.500 ppm
F2                      -150.06 Hz
PPMCM                  0.56818 ppm/cm
HZCM                 170.52841 Hz/cm
```

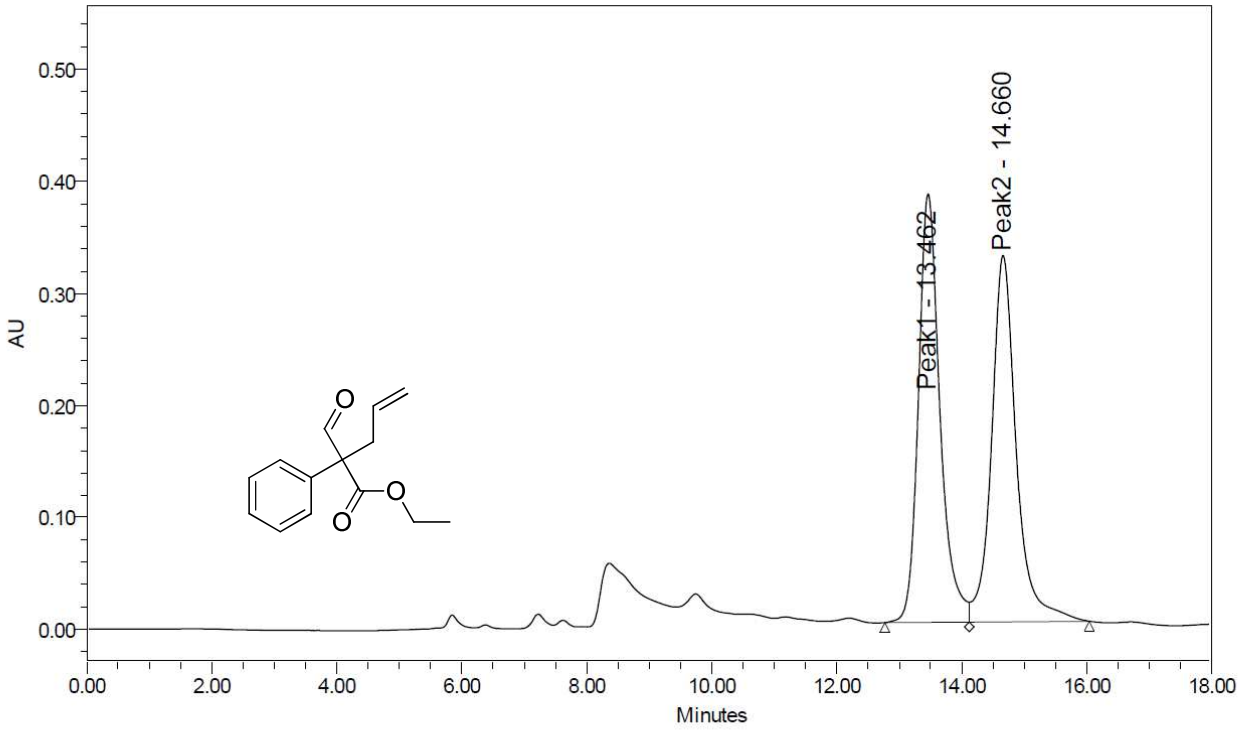
Portrait 20

Carbon Spectrum



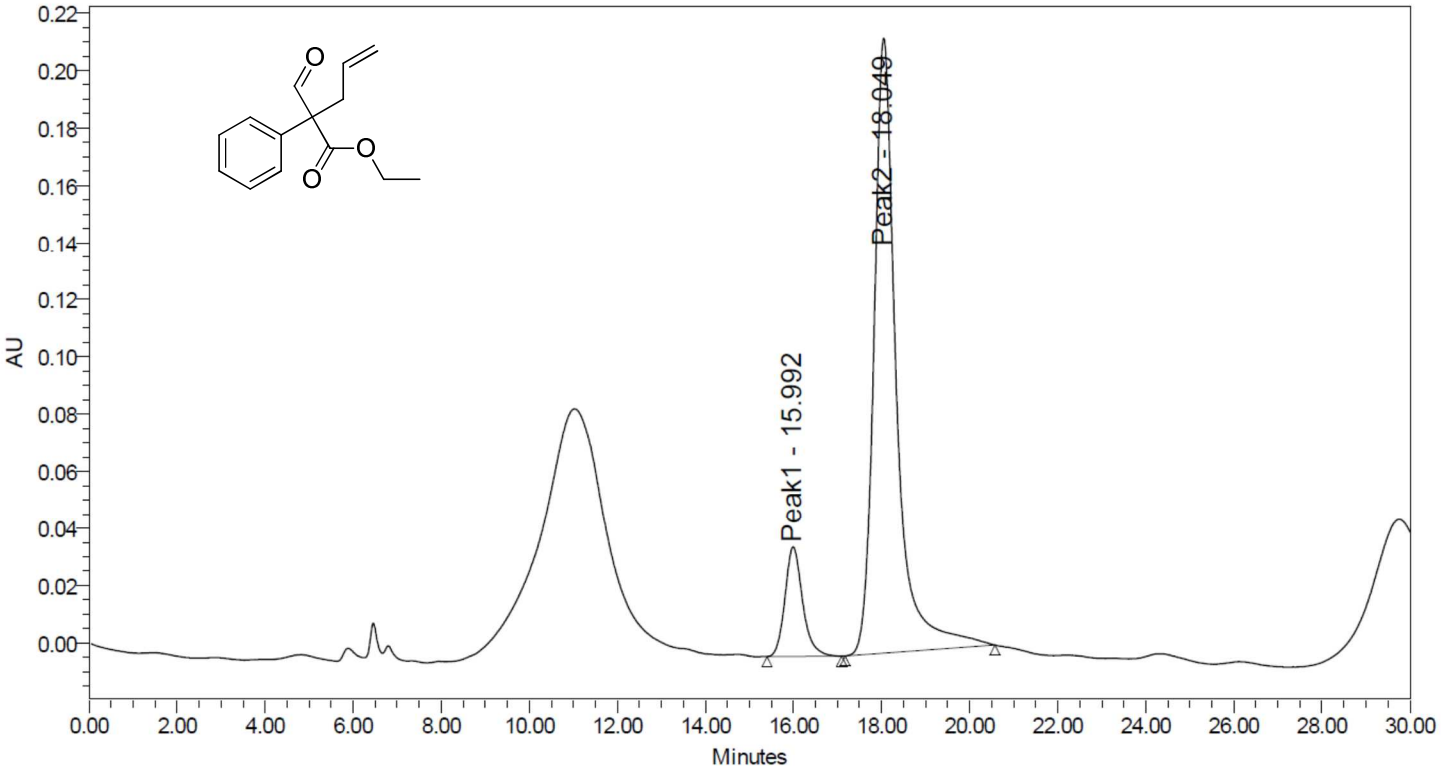

```
Current Data Parameters
NAME                  EAhs-1-51
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20090219
Time                      18.41
INSTRUM                 dpx300
PROBHD       5 mm Multinu
PULPROG                   zgdc
TD                       65536
SOLVENT                   CDCl3
NS                         2000
DS                            0
SWH                   18115.941 Hz
FIDRES                0.276427 Hz
AQ                    1.8088436 sec
RG                          512
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
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                     180.000 ppm
F1                    13584.20 Hz
F2P                     100.000 ppm
F2                     7546.78 Hz
PPMCM                  3.63636 ppm/cm
HZCM                 274.42822 Hz/cm
```

Portrait 21, HPLC Data(Racemic)



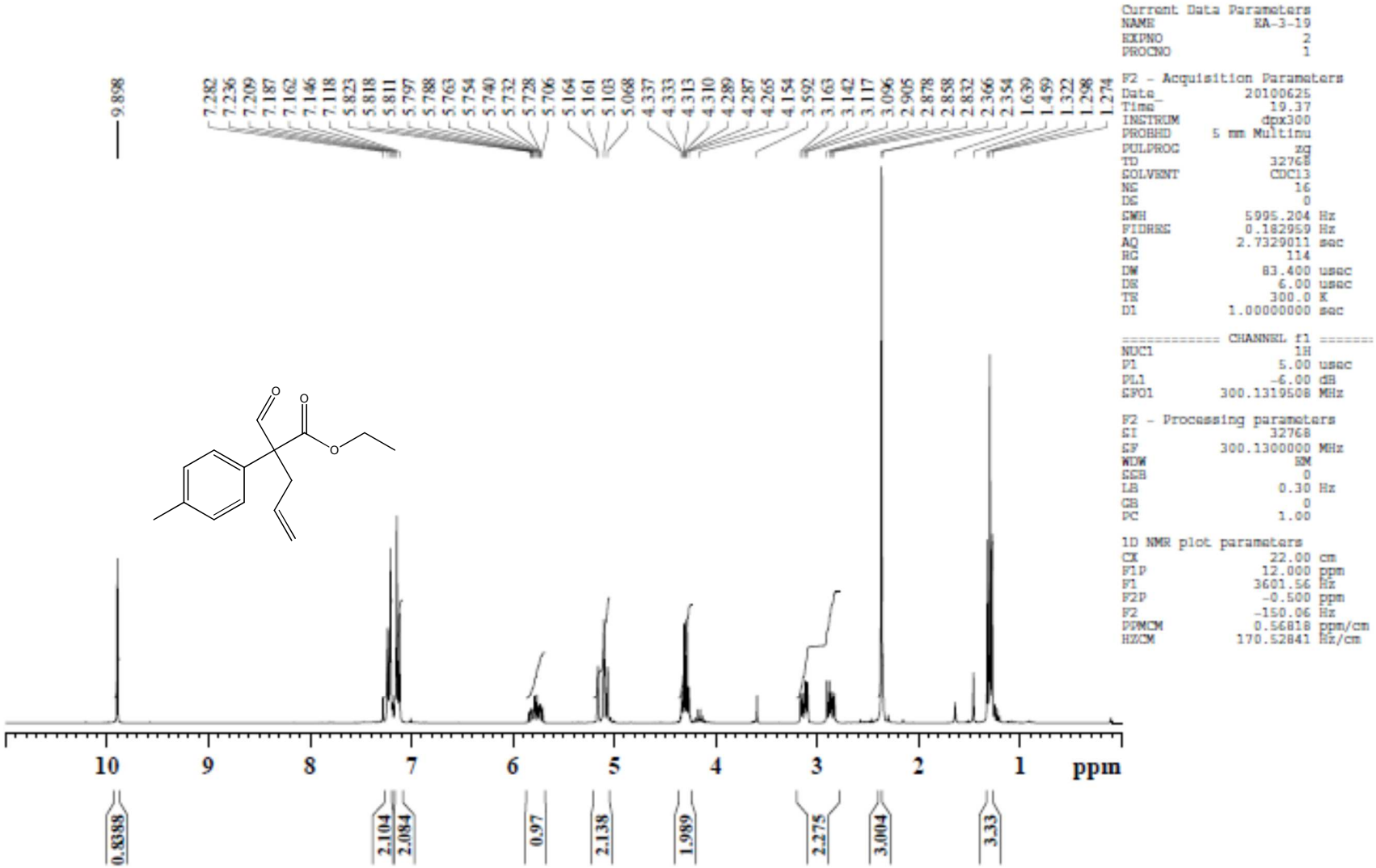
	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	13.462	Found	9151334	50.38	382792	53.89	BV	9.151e+006	Q20
2	Peak2	14.660	Found	9014297	49.62	327473	46.11	VB	9.014e+006	Q20

Portrait 22, HPLC Data(chiral)



	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	15.992	Found	1062211	12.29	38114	15.07	BB	1.062e+006	Q20
2	Peak2	18.049	Found	7583589	87.71	214866	84.93	BB	7.584e+006	Q20

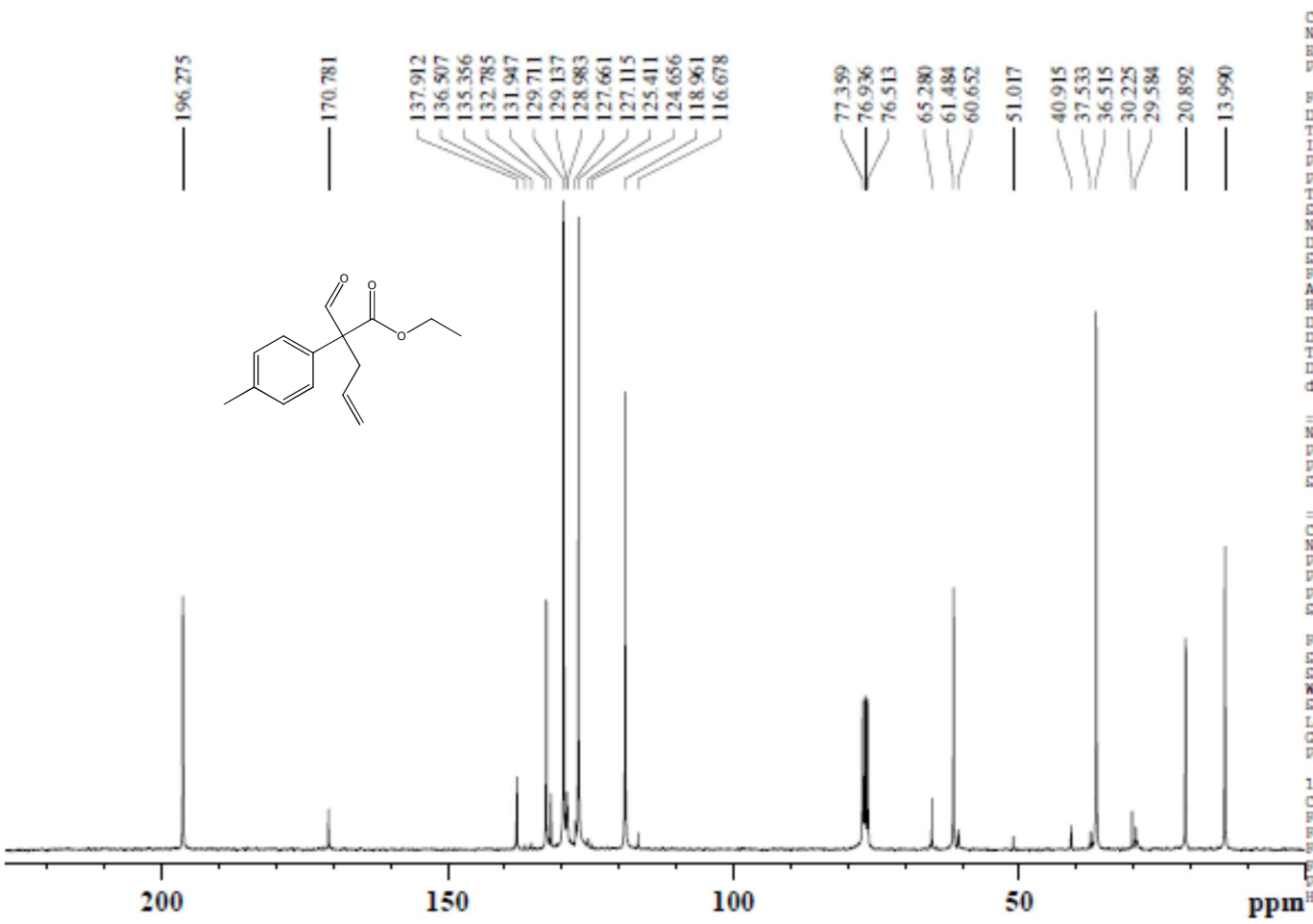
Portrait 23, Compound 8b




```
Current Data Parameters
NAME                  EA-3-19
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100625
Time_                 19.37
INSTRUM               dpx300
PROBHD     5 mm Multinu
PULPROG                   zg
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                 5995.204 Hz
FIDRES              0.182959 Hz
AQ                2.7329011 sec
RG                       114
DW                    83.400 usec
DE                     6.00 usec
TE                    300.0 K
D1                1.00000000 sec

============ CHANNEL f1 =======
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                   12.000 ppm
F1                  3601.56 Hz
F2P                   -0.500 ppm
F2                  -150.06 Hz
PPMCM                0.56818 ppm/cm
HZCM               170.52841 Hz/cm
```

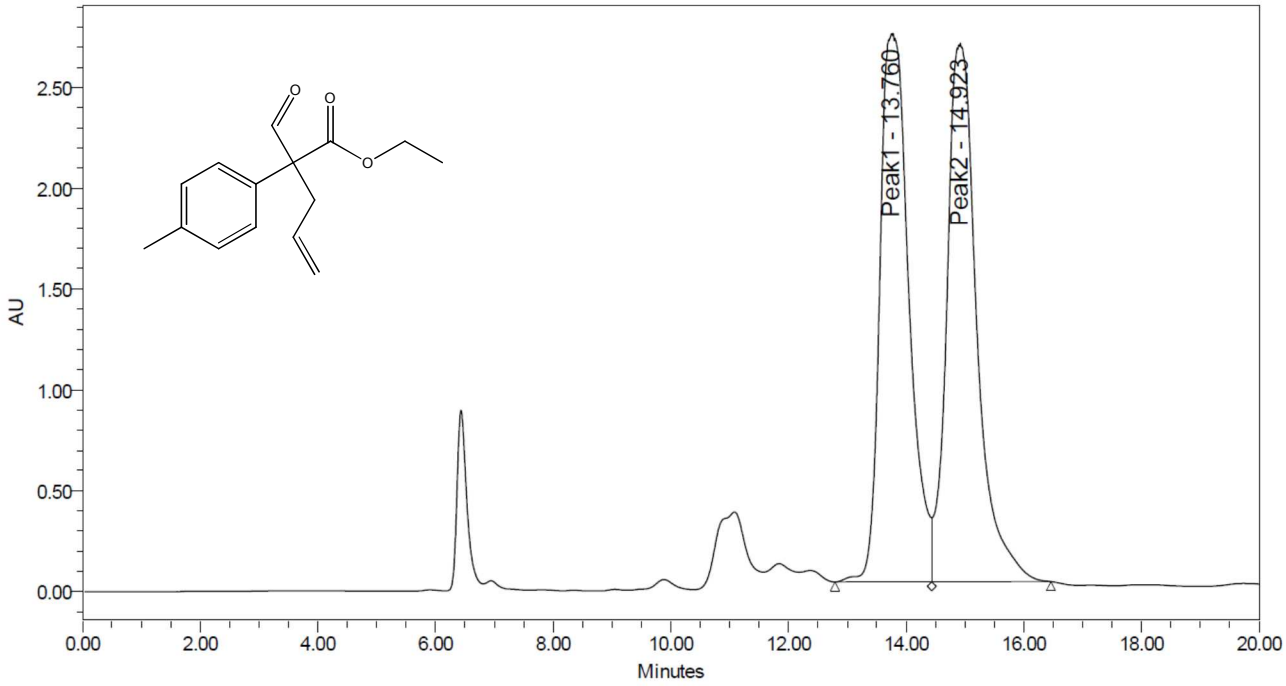
Portrait 24

Carbon Spectrum



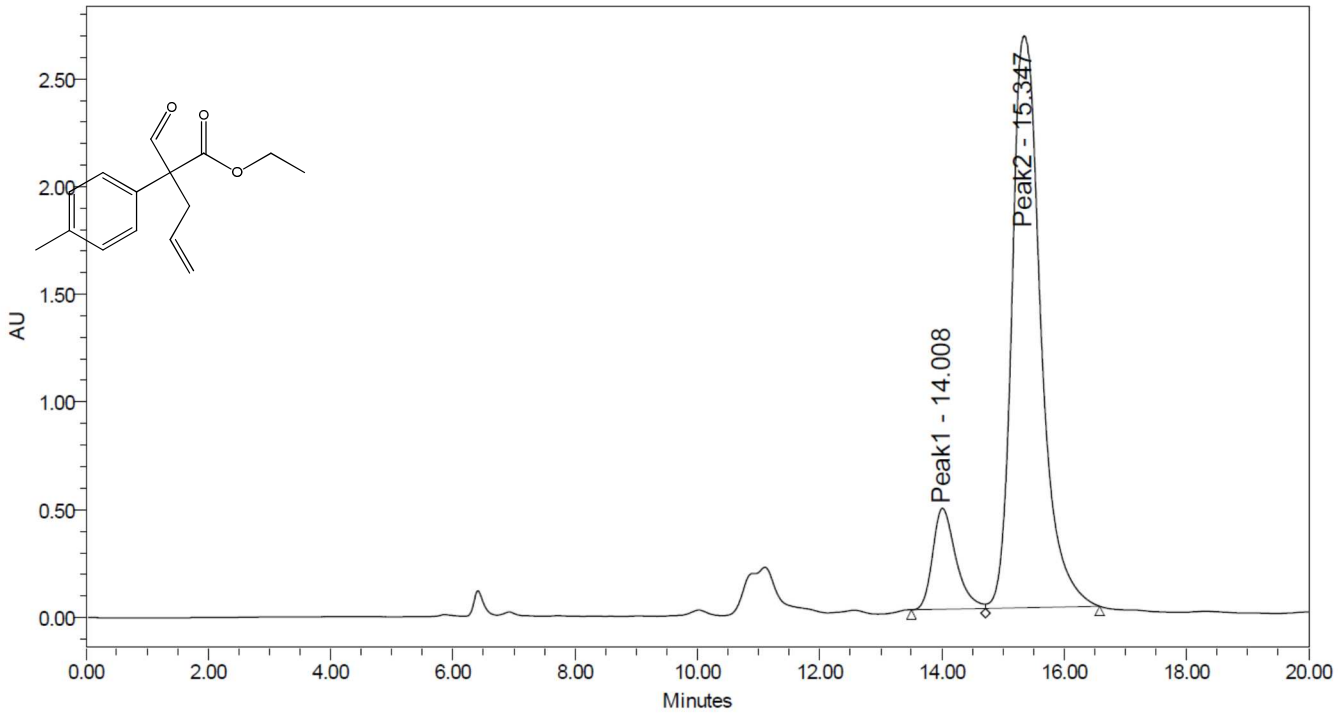

```
Current Data Parameters
NAME                  EA-3-19
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100626
Time_                  6.23
INSTRUM               dpx300
PROBHD     5 mm Multinu
PULPROG                zgdc
TD                    65536
SOLVENT               CDCl3
NS                    20000
DS                        0
SWH               18115.941 Hz
FIDRES                0.276427 Hz
AQ                1.8088436 sec
RG                    912.3
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
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
PPMCM                10.22727 ppm/cm
HZCM                771.82935 Hz/cm
```

Portrait 25, HPLC Data(racemic)



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	13.760	Found	93120835	49.64	2719736	50.44	BV	9.312e+007	Q20
2	Peak2	14.923	Found	94470011	50.36	2671937	49.56	VB	9.447e+007	Q20

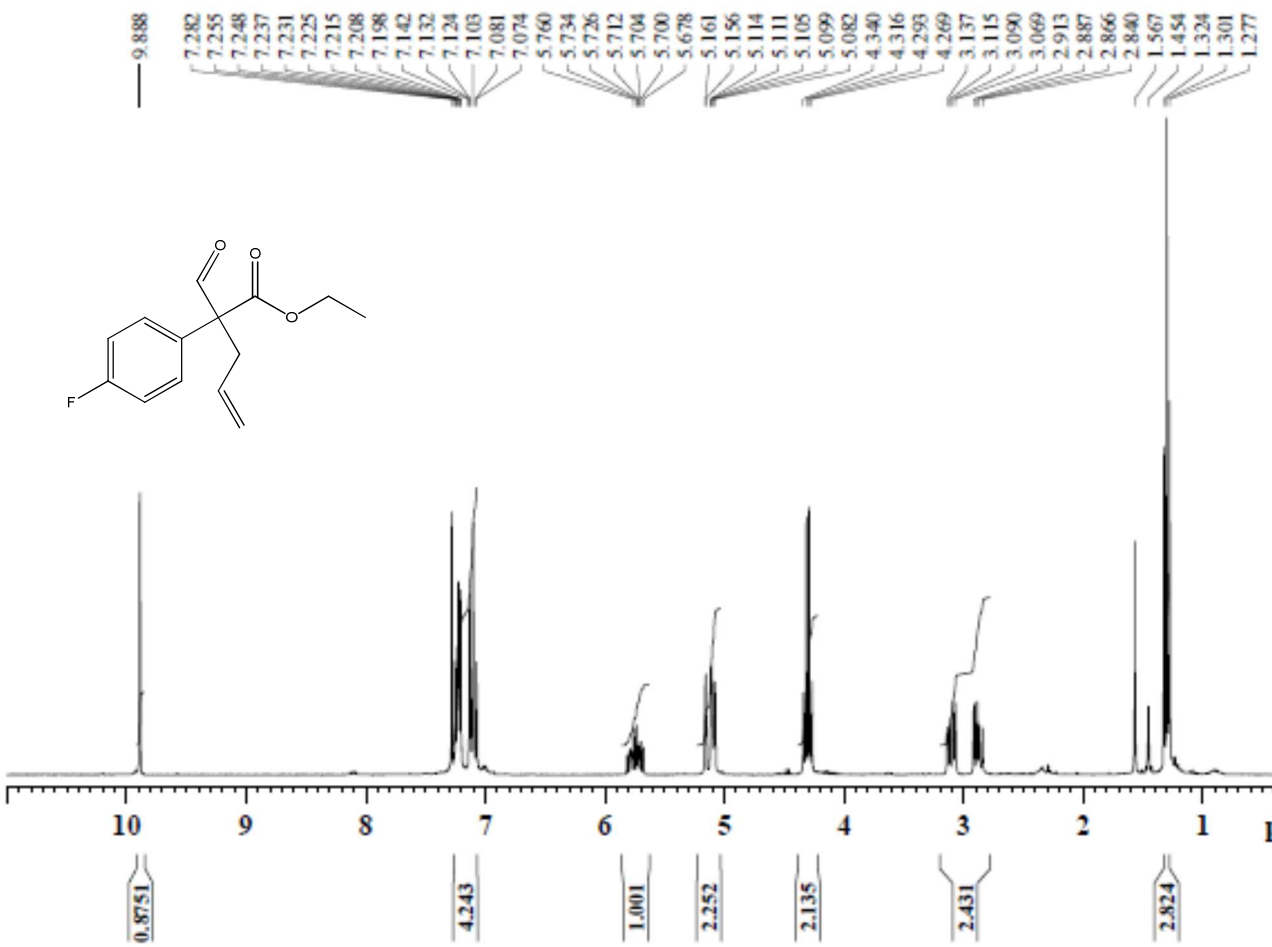
Portrait 26, HPLC Data(chiral)



	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	14.008	Found	12350058	12.42	467433	14.97	BV	1.235e+007	Q20
2	Peak2	15.347	Found	87080646	87.58	2655532	85.03	VB	8.708e+007	Q20

Portrait 27, Compound 8c

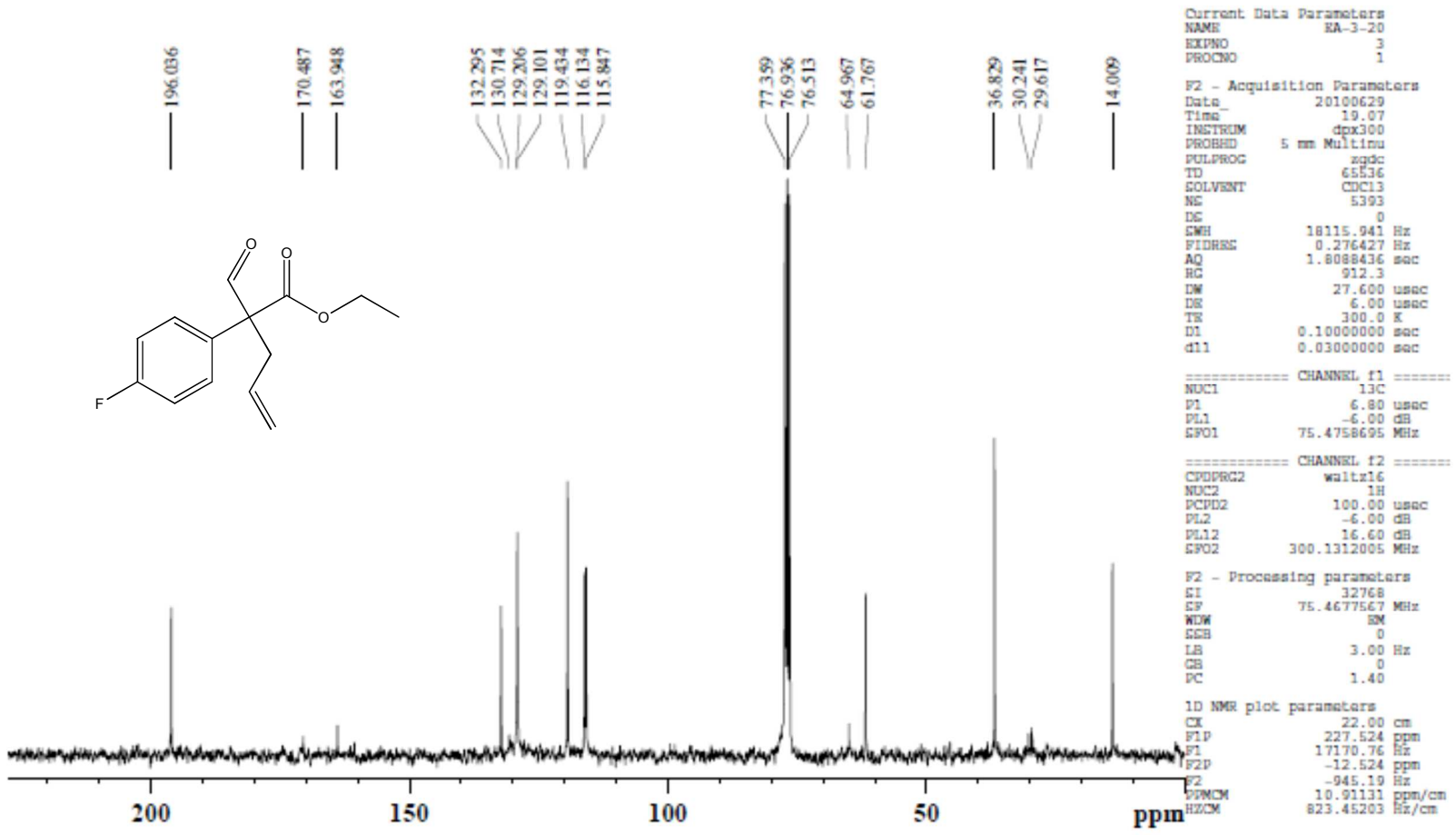
Proton Spectrum




```
Current Data Parameters
NAME                  RA-3-20
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100629
Time               11.57
INSTRUM            dpx300
PROBHD     5 mm Multinu
PULPROG                 zg
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH               5995.204 Hz
FIDRES            0.182959 Hz
AQ                2.7329011 sec
RG                    322.5
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                 12.000 ppm
F1                 3601.56 Hz
F2P                 -0.500 ppm
F2                 -150.06 Hz
PPMCM               0.56818 ppm/cm
HZCM              170.52841 Hz/cm
```

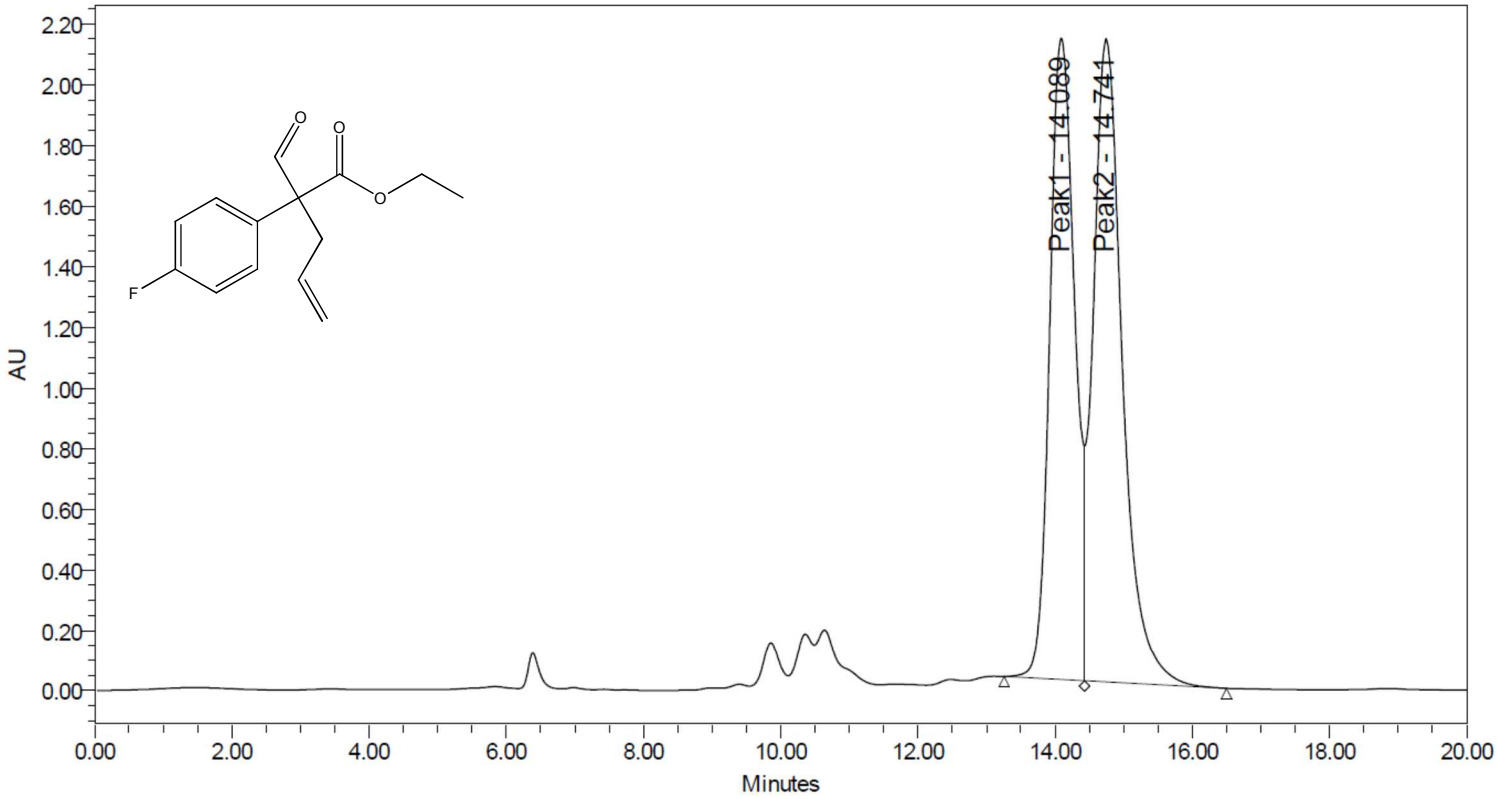
Portrait 28

Carbon Spectrum



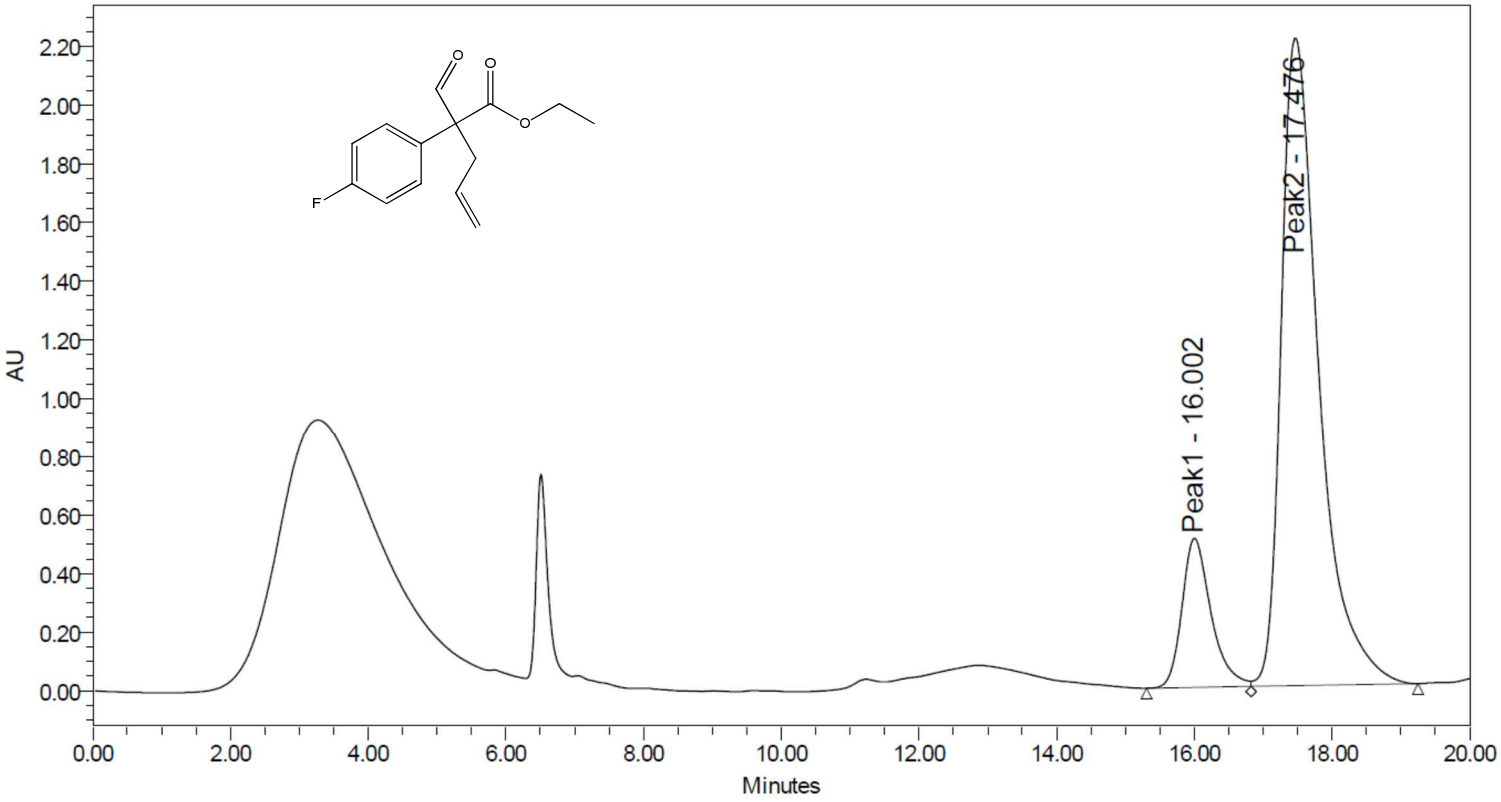

```
Current Data Parameters
NAME                  EA-3-20
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100629
Time               19.07
INSTRUM            dpx300
PROBHD     5 mm Multinu
PULPROG            zgdc
TD                 65536
SOLVENT            CDCl3
NS                 5393
DS                 0
SWH                18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                 912.3
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
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                227.524 ppm
F1                 17170.76 Hz
F2P                -12.524 ppm
F2                 -945.19 Hz
PPMCM              10.91131 ppm/cm
HZCM               823.45203 Hz/cm
```

Portrait 29, HPLC Data(racemic)



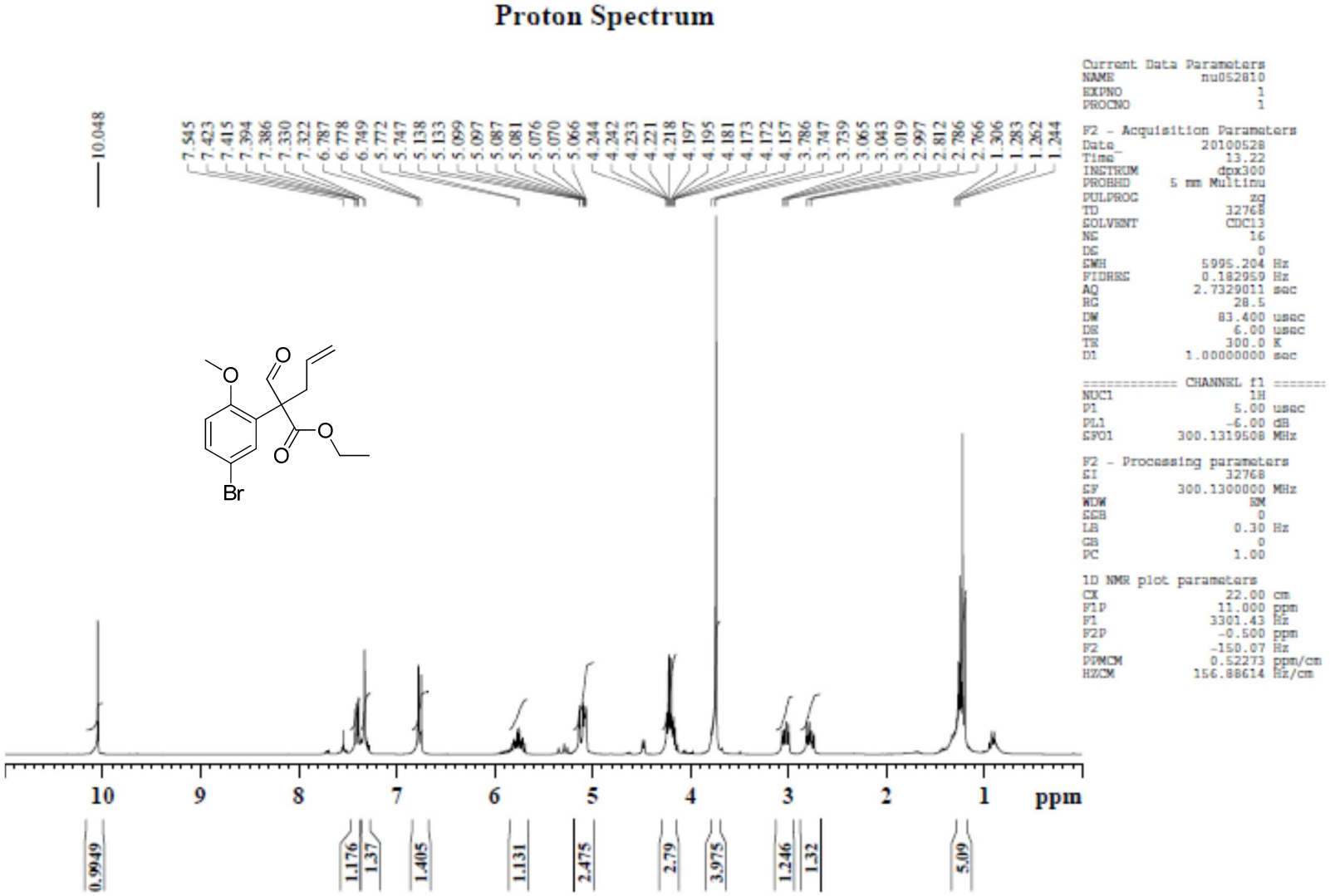
	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	14.089	Found	53373657	45.79	2116777	49.94	BV	5.337e+007	Q20
2	Peak2	14.741	Found	63177837	54.21	2122128	50.06	VB	6.318e+007	Q20

Portrait 30, HPLC Data (chiral)



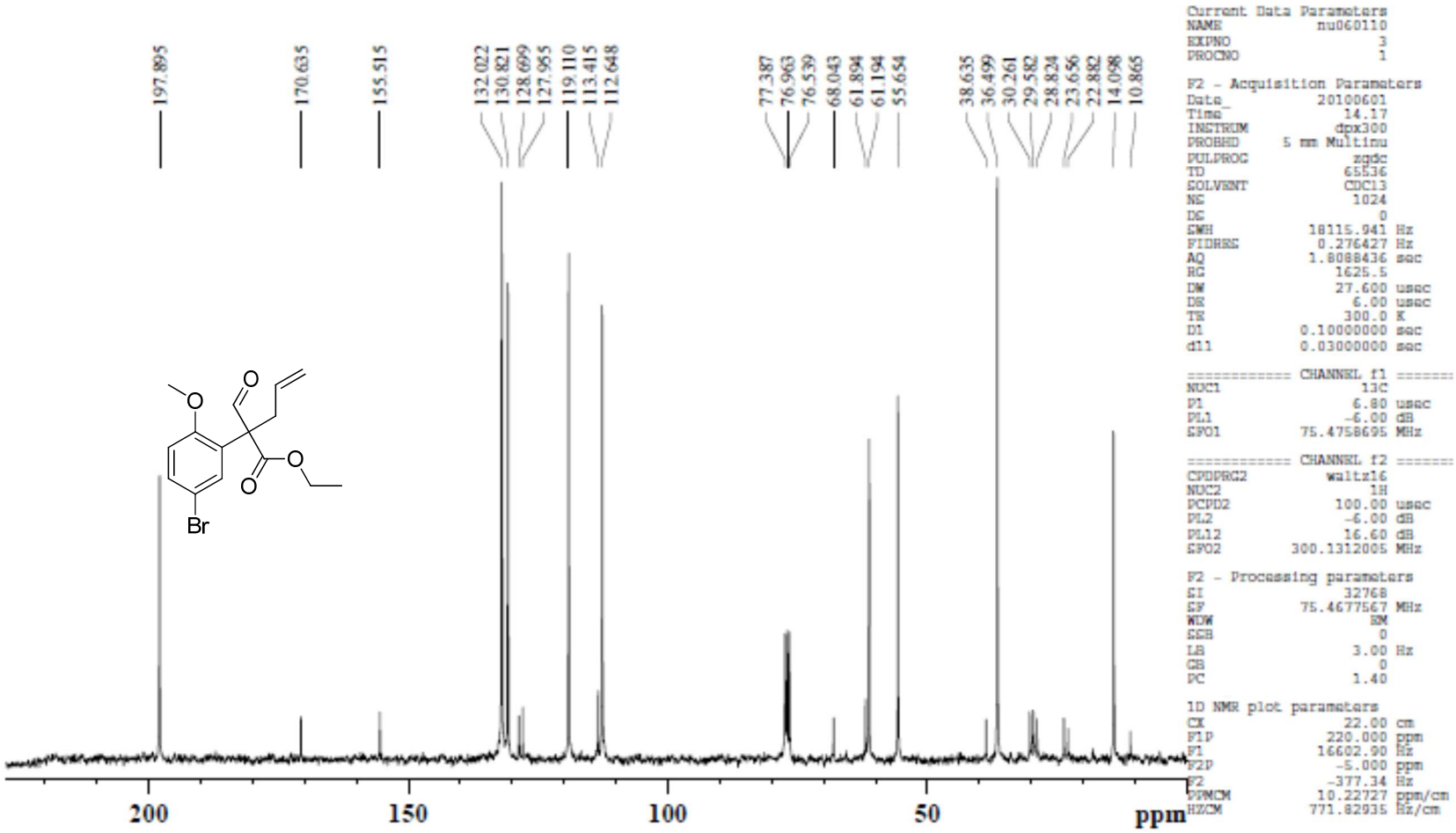
	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	16.002	Found	14922650	15.07	508607	18.70	BV	1.492e+007	Q20
2	Peak2	17.476	Found	84115408	84.93	2210877	81.30	VB	8.412e+007	Q20

Portrait 31, Compound 8d



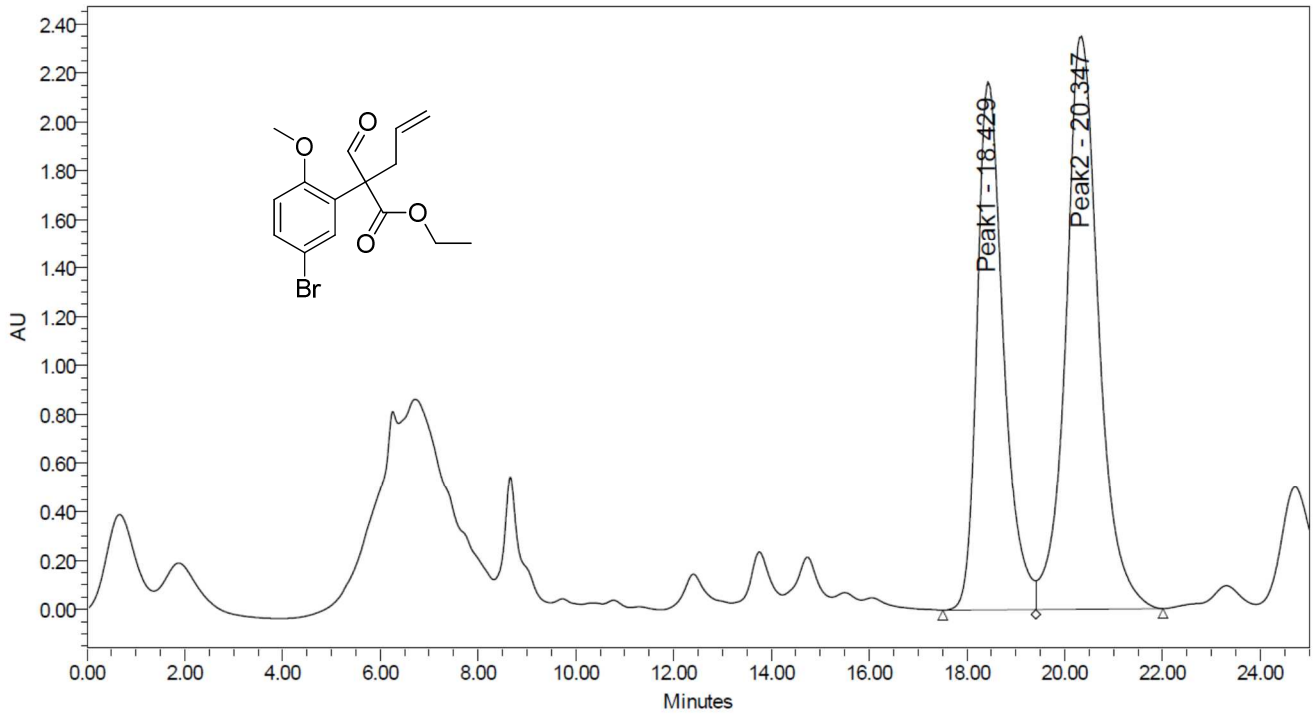
Portrait 32

Carbon Spectrum



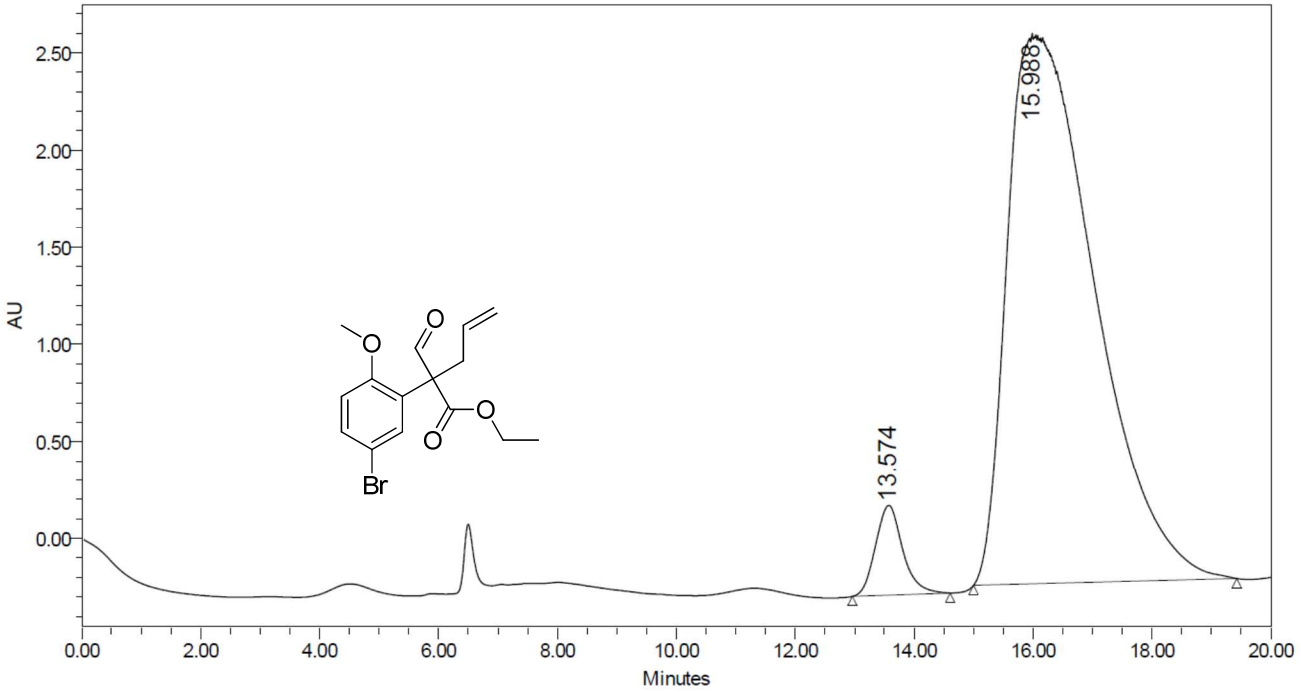

```
Current Data Parameters
NAME                  nu060110
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20100601
Time                  14.17
INSTRUM               dpx300
PROBHD     5 mm Multinu
PULPROG                zqdc
TD                    65536
SOLVENT                CDCl3
NS                     1024
DS                        0
SWH               18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                    1625.5
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
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
PPMCM              10.22727 ppm/cm
HZCM              771.82935 Hz/cm
```

Portrait 33, HPLC Data (racemic)



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	18.429	Found	81414090	42.62	2165704	47.95	BV	8.141e+007	Q20
2	Peak2	20.347	Found	109624621	57.38	2350643	52.05	VB	1.096e+008	Q20

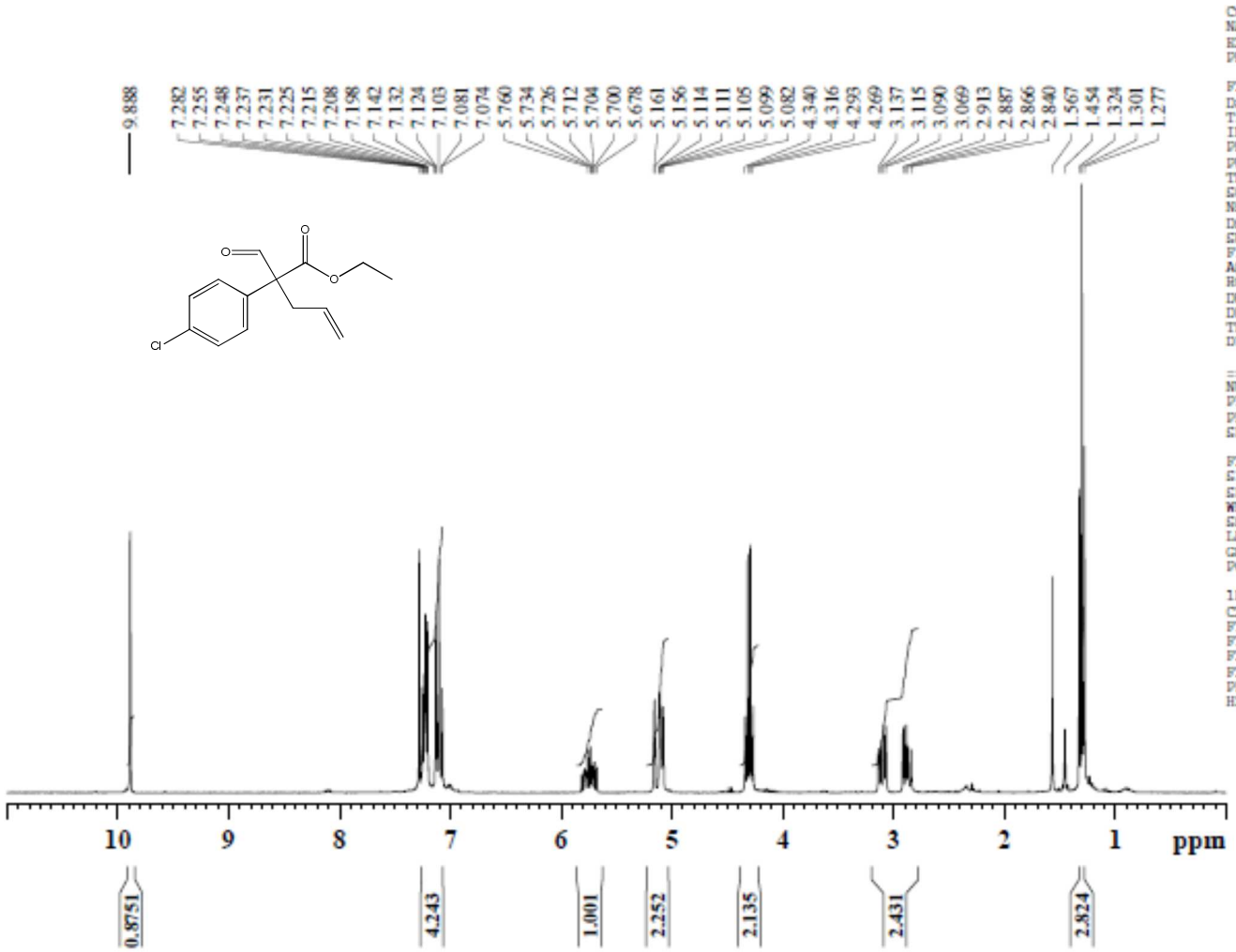
Portrait 34, HPLC Data (chiral)



	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)
1	13.574	Unknown	14631883	4.82	460265	13.98	bb	985	12.962
2	15.988	Unknown	288868012	95.18	2832426	86.02	bb	2655	15.001

Portrait 35, Compound 8e

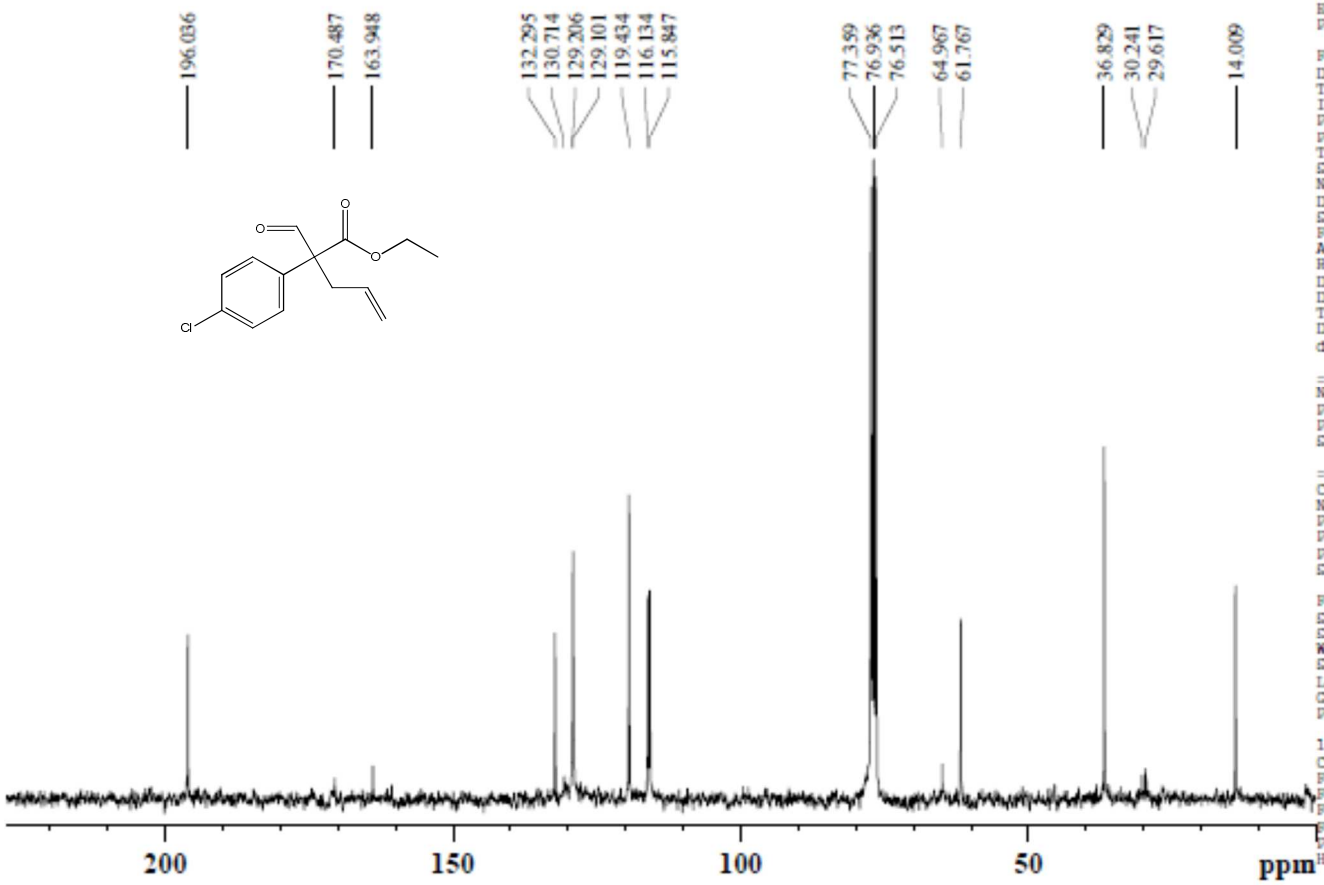
Proton Spectrum




```
Current Data Parameters
NAME                  EA-3-20
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100629
Time                  11.57
INSTRUM               dpx300
PROBHD     5 mm Multinu
PULPROG                   zg
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                5995.204 Hz
FIDRES             0.182959 Hz
AQ                 2.7329011 sec
RG                     322.5
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                       12.000 ppm
F1                      3601.56 Hz
F2P                       -0.500 ppm
F2                      -150.06 Hz
PPMCM                  0.56818 ppm/cm
HZCM                 170.52841 Hz/cm
```

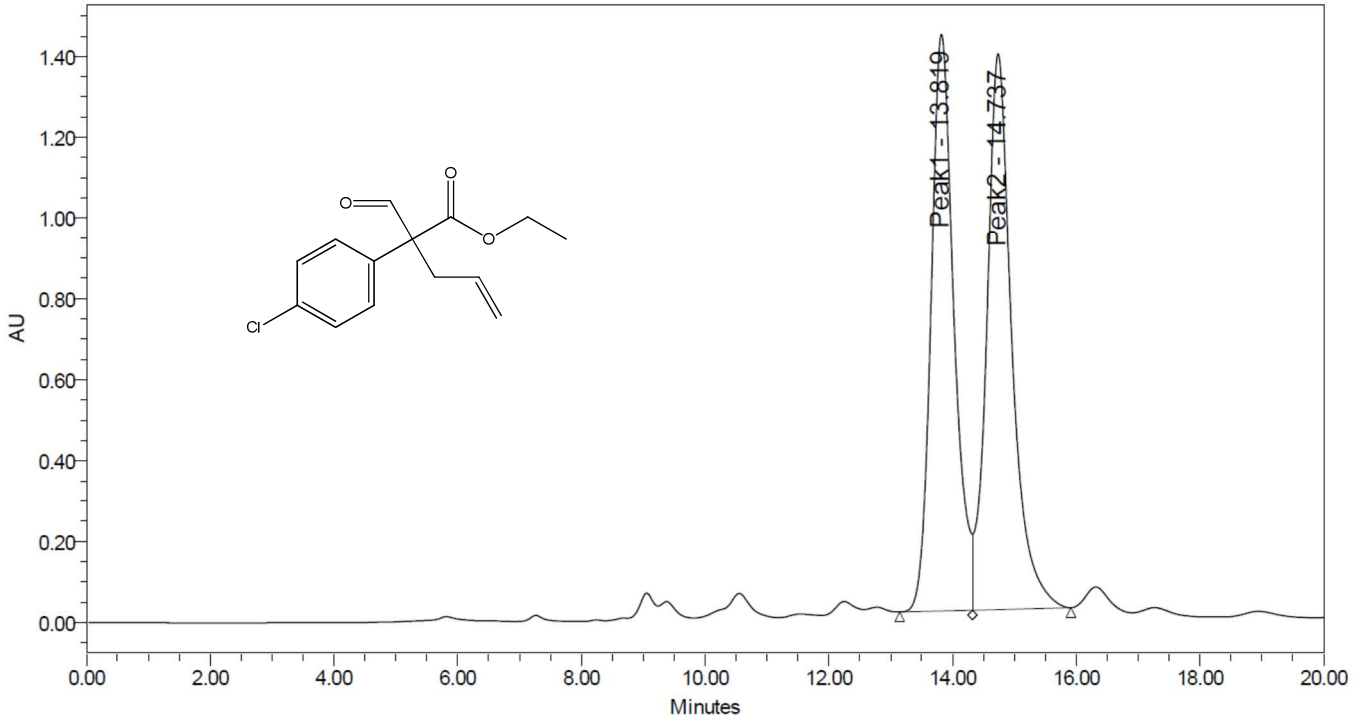
Portrait 36

Carbon Spectrum



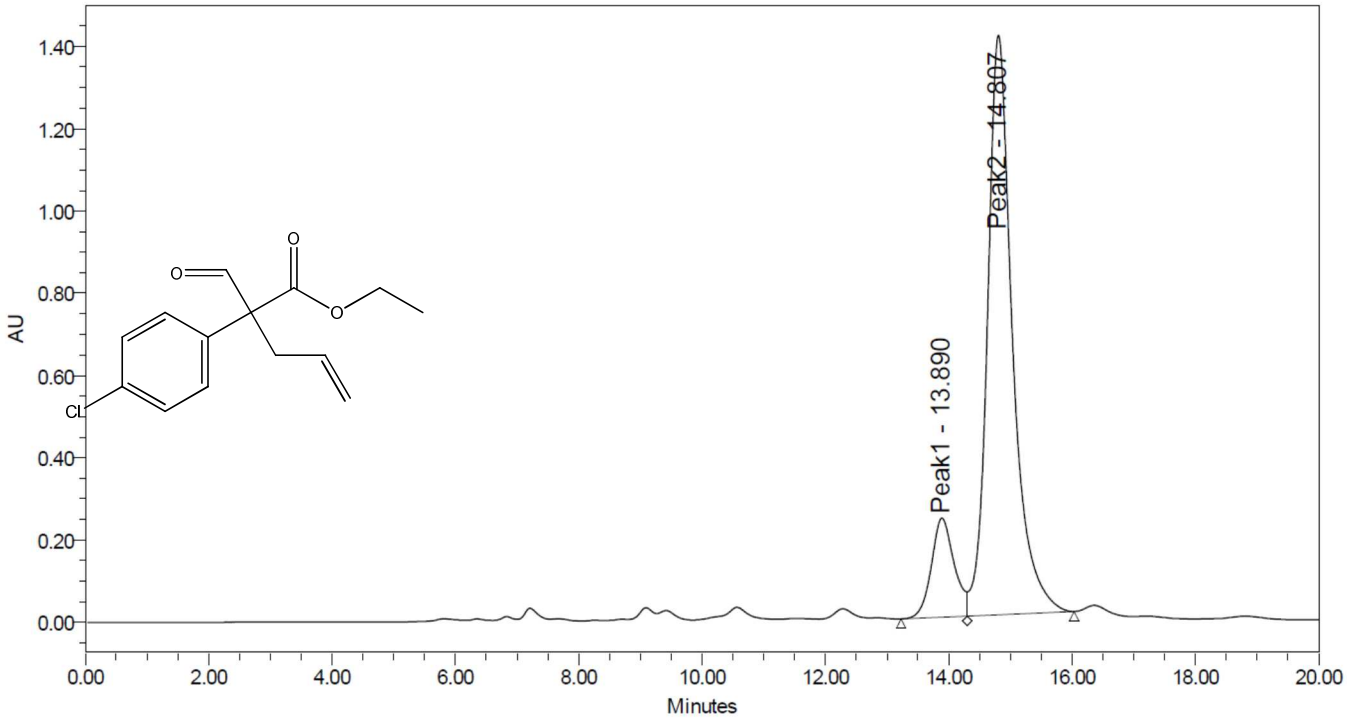

```
Current Data Parameters
NAME                  EA-3-20
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100629
Time                  19.07
INSTRUM             dpx300
PROBHD     5 mm Multinu
PULPROG               zgdc
TD                   65536
SOLVENT              CDCl3
NS                    5393
DS                       0
SWH               18115.941 Hz
FIDRES            0.276427 Hz
AQ                1.8088436 sec
RG                   912.3
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
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                  227.524 ppm
F1                 17170.76 Hz
F2P                  -12.524 ppm
F2                  -945.19 Hz
PPMCM               10.91131 ppm/cm
HZCM               823.45203 Hz/cm
```

Portrait 37, HPLC Data(racemic)



	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	13.819	Found	36559068	48.53	1426601	50.93	BV	3.656e+007	Q20
2	Peak2	14.737	Found	38771194	51.47	1374514	49.07	VB	3.877e+007	Q20

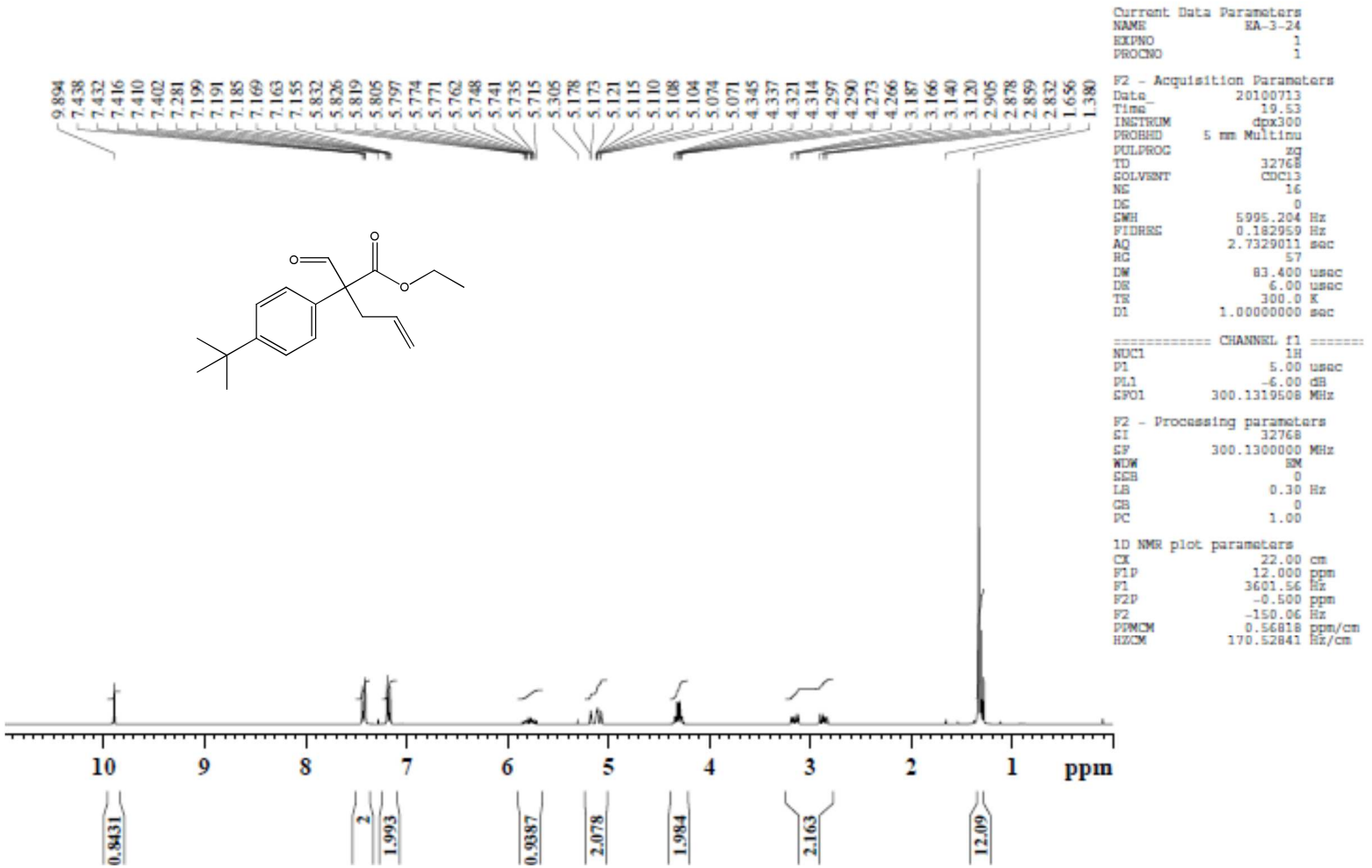
Portrait 38, HPLC Data(chiral)



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	13.890	Found	6155862	13.47	239444	14.54	BV	6.156e+006	Q20
2	Peak2	14.807	Found	39555073	86.53	1407820	85.46	VB	3.956e+007	Q20

Portrait 39, Compound 8f

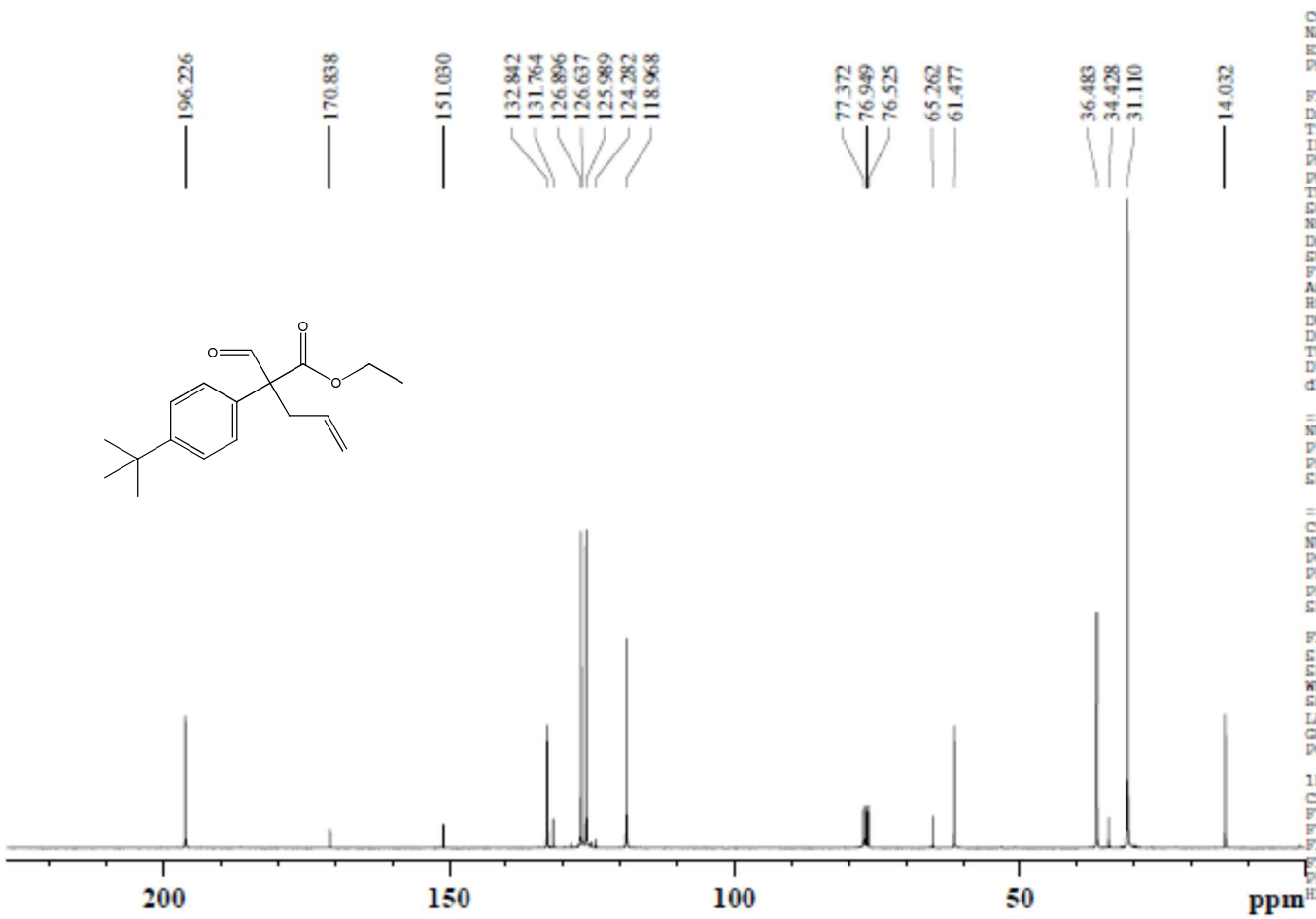
Proton Spectrum




```
Current Data Parameters
NAME                  KA-3-24
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100713
Time               19.53
INSTRUM            dpx300
PROBHD     5 mm Multinu
PULPROG            zg
TD                 32768
SOLVENT            CDCl3
NS                 16
DS                 0
SWH                5995.204 Hz
FIDRES             0.182959 Hz
AQ                 2.7329011 sec
RG                 57
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                12.000 ppm
F1                 3601.56 Hz
F2P                -0.500 ppm
F2                 -150.06 Hz
PPMCM              0.56818 ppm/cm
HZCM               170.52841 Hz/cm
```

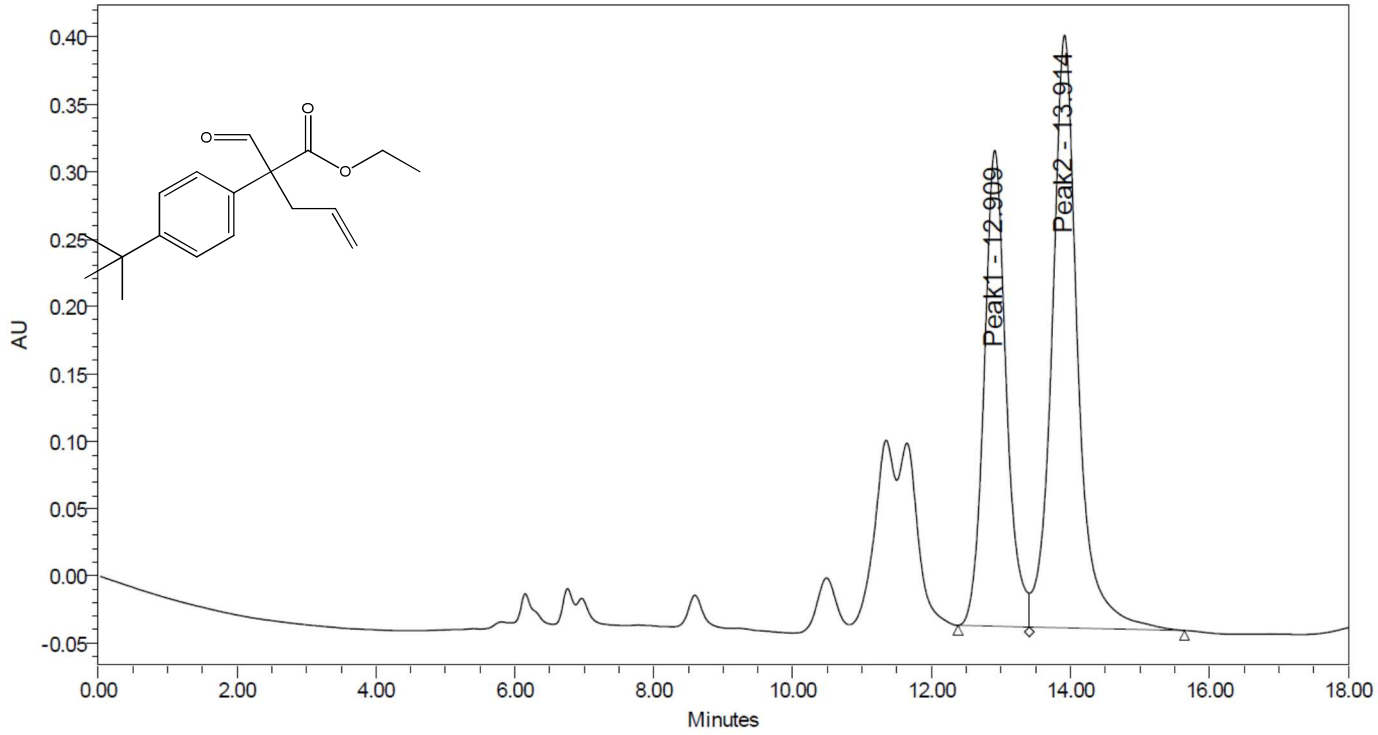
Portrait 40

Carbon Spectrum



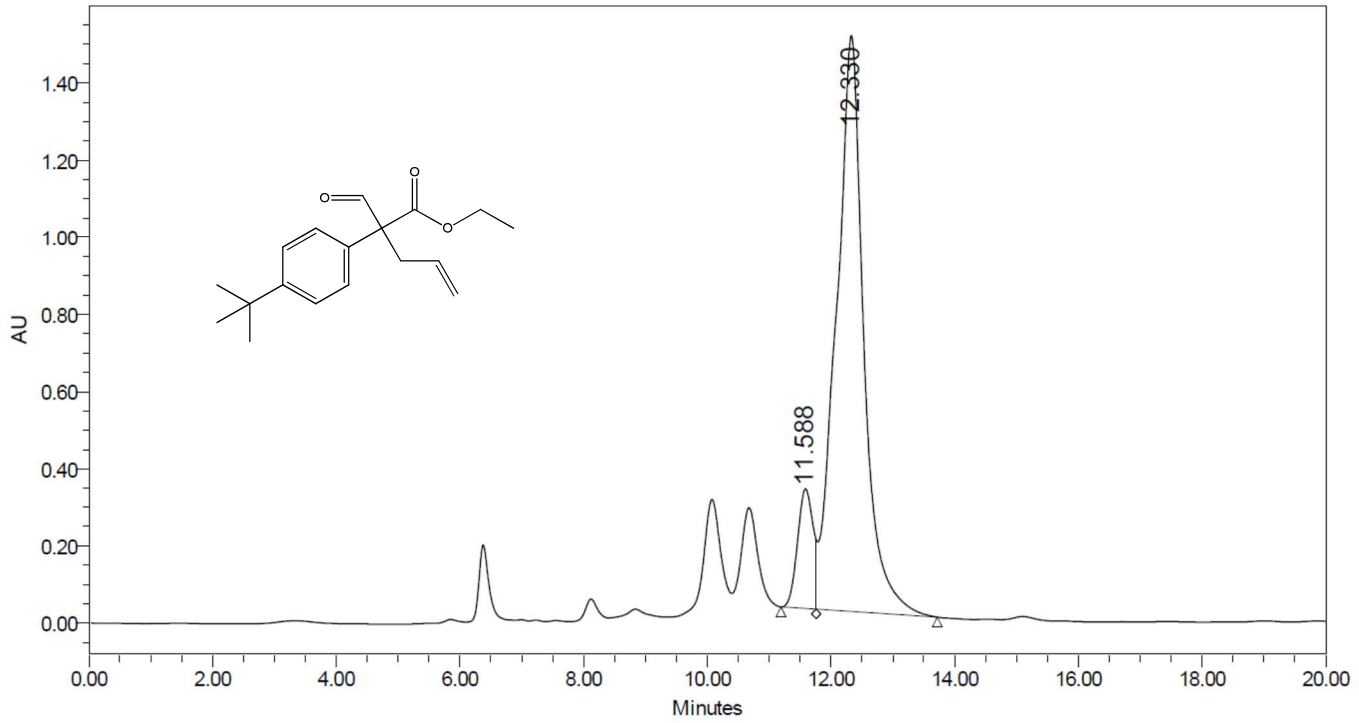

```
Current Data Parameters
NAME                  EA-3-24
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20100714
Time_                  6.06
INSTRUM              dpx300
PROBHD     5 mm Multinu
PULPROG                zgdc
TD                    65536
SOLVENT               CDCl3
NS                    19000
DS                        0
SWH               18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                    1824.6
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
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
PPMCM                 10.22727 ppm/cm
HZCM                 771.82935 Hz/cm
```

Portrait 41, HPLC Data (racemic)



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	12.909	Found	7845862	40.82	353442	44.55	BV	7.846e+006	Q20
2	Peak2	13.914	Found	11374376	59.18	439886	55.45	VB	1.137e+007	Q20

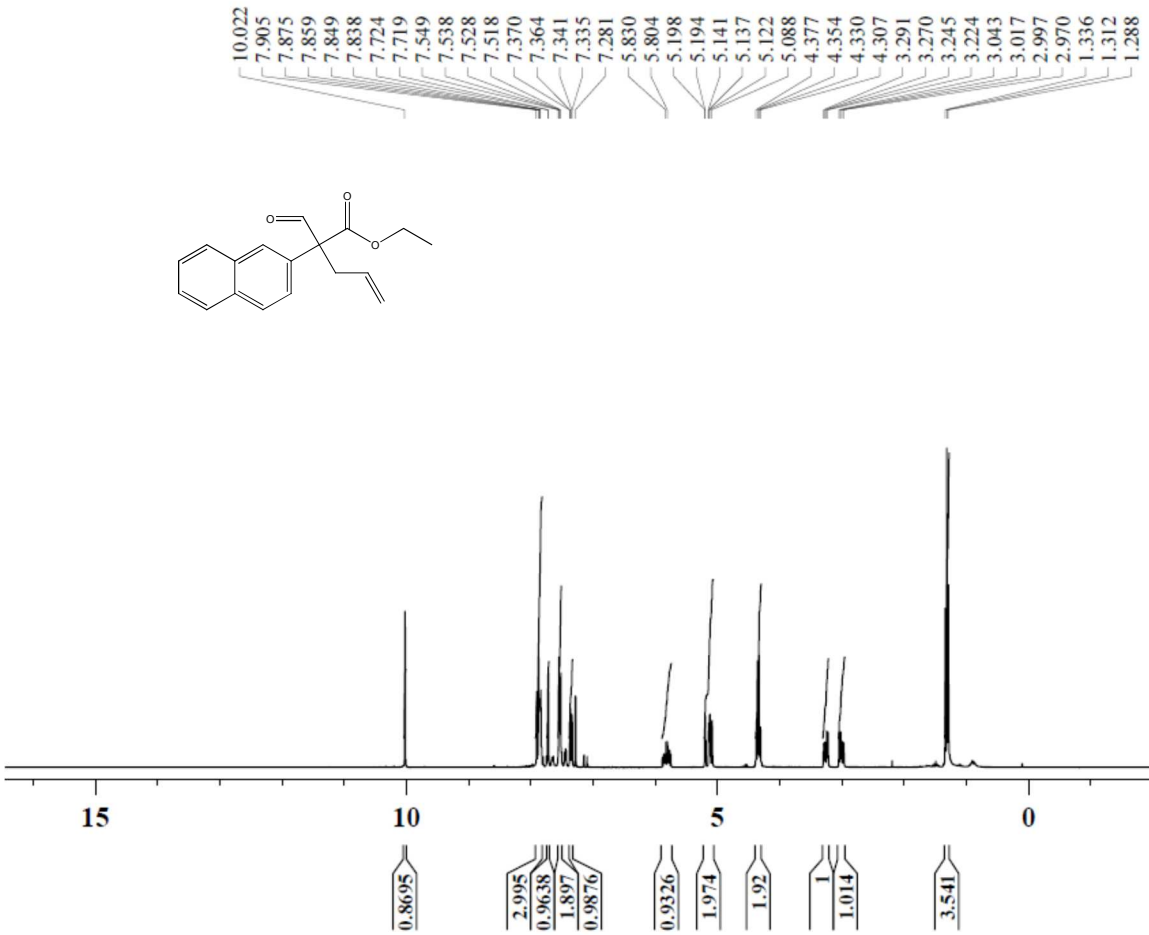
Portrait 42, HPLC Data (chiral)



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	11.588	Unknown	5310576	10.31	309094	17.15	Bv	5.610e+006	340
2	12.330	Unknown	46200718	89.69	1493035	82.85	vB	4.590e+007	1177

Portrait 43, Compound 8g

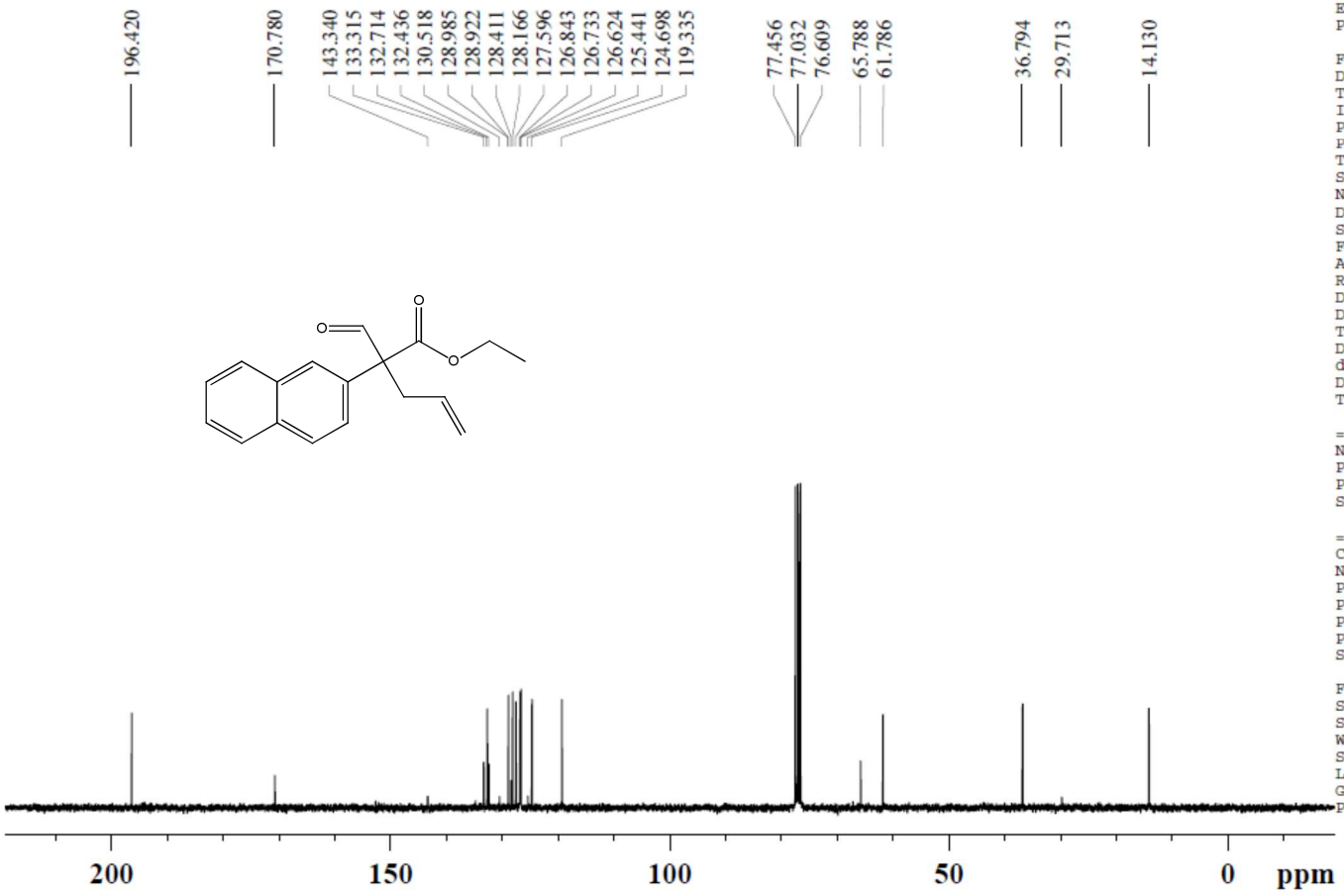
Proton Spectrum




```
Current Data Parameters
NAME                  sa-011414
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20140114
Time                      16.58
INSTRUM                   spect
PROBHD    5 mm Multinucl
PULPROG                   zg30
TD                       32768
SOLVENT                  CDCl3
NS                          16
DS                           0
SWH                   6172.839 Hz
FIDRES                0.188380 Hz
AQ                    2.6542580 sec
RG                          256
DW                     81.000 usec
DE                      6.00 usec
TE                      298.0 K
D1                  1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        9.80 usec
PL1                      -6.00 dB
SFO1               300.1318534 MHz

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

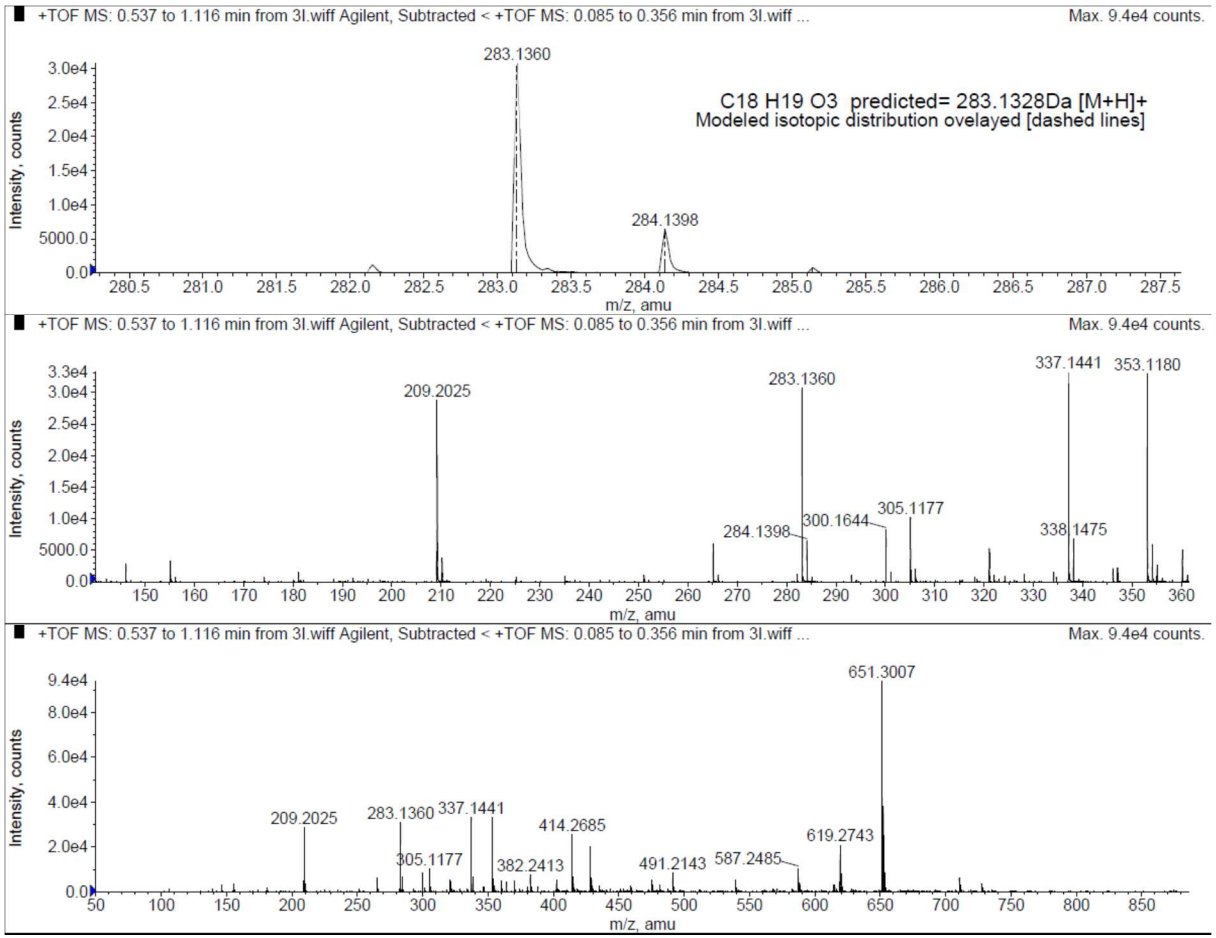
Portrait 44

Carbon Spectrum

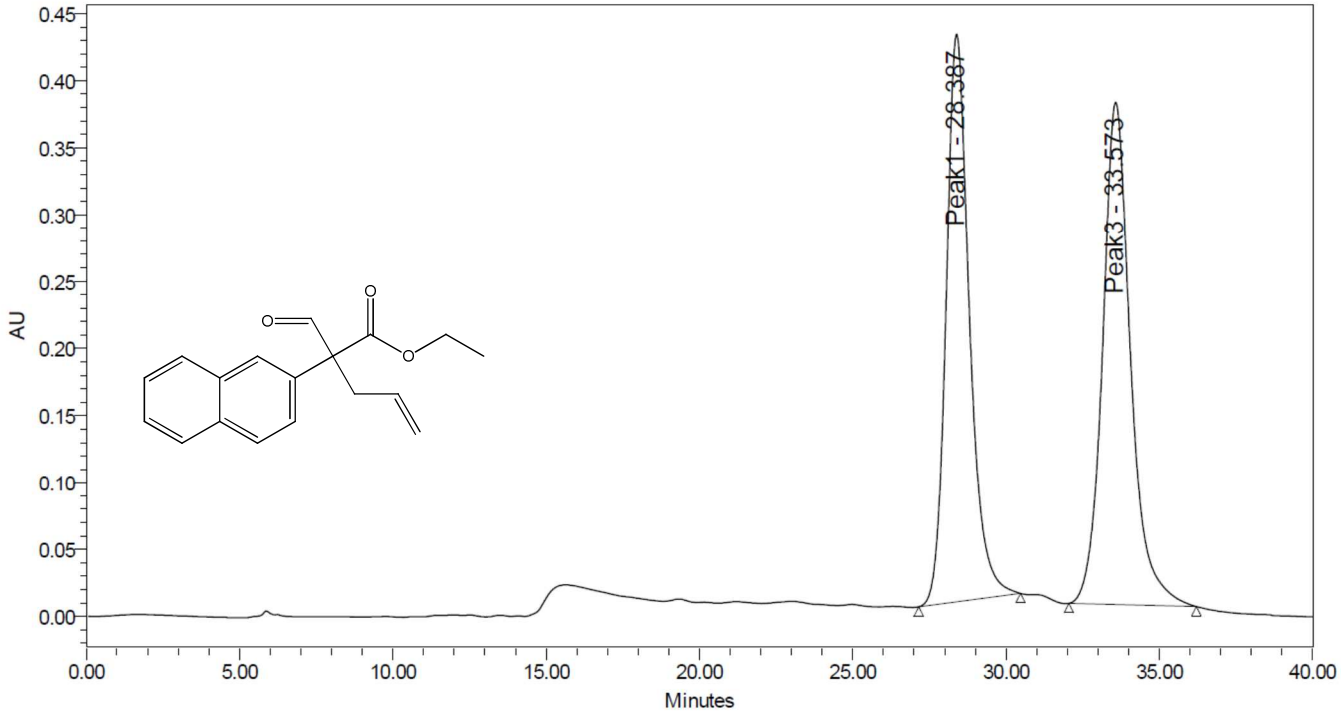



```
Current Data Parameters
NAME                  sa-011414
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20140114
Time                      17.44
INSTRUM                   spect
PROBHD    5 mm Multinucl
PULPROG                 zgpg30
TD                         65536
SOLVENT                  CDCl3
NS                          1024
DS                             0
SWH                  17985.611 Hz
FIDRES                0.274439 Hz
AQ                    1.8219508 sec
RG                         32768
DW                        27.800 usec
DE                         6.00 usec
TE                        298.0 K
D1                   0.50000000 sec
d11                  0.03000000 sec
DELTA                0.40000001 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                         6.80 usec
PL1                       -6.00 dB
SFO1                 75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    100.00 usec
PL2                       -6.00 dB
PL12                      16.40 dB
PL13                     120.00 dB
SFO2                300.1312000 MHz

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

Portrait 45, HRMS, Compound 8g

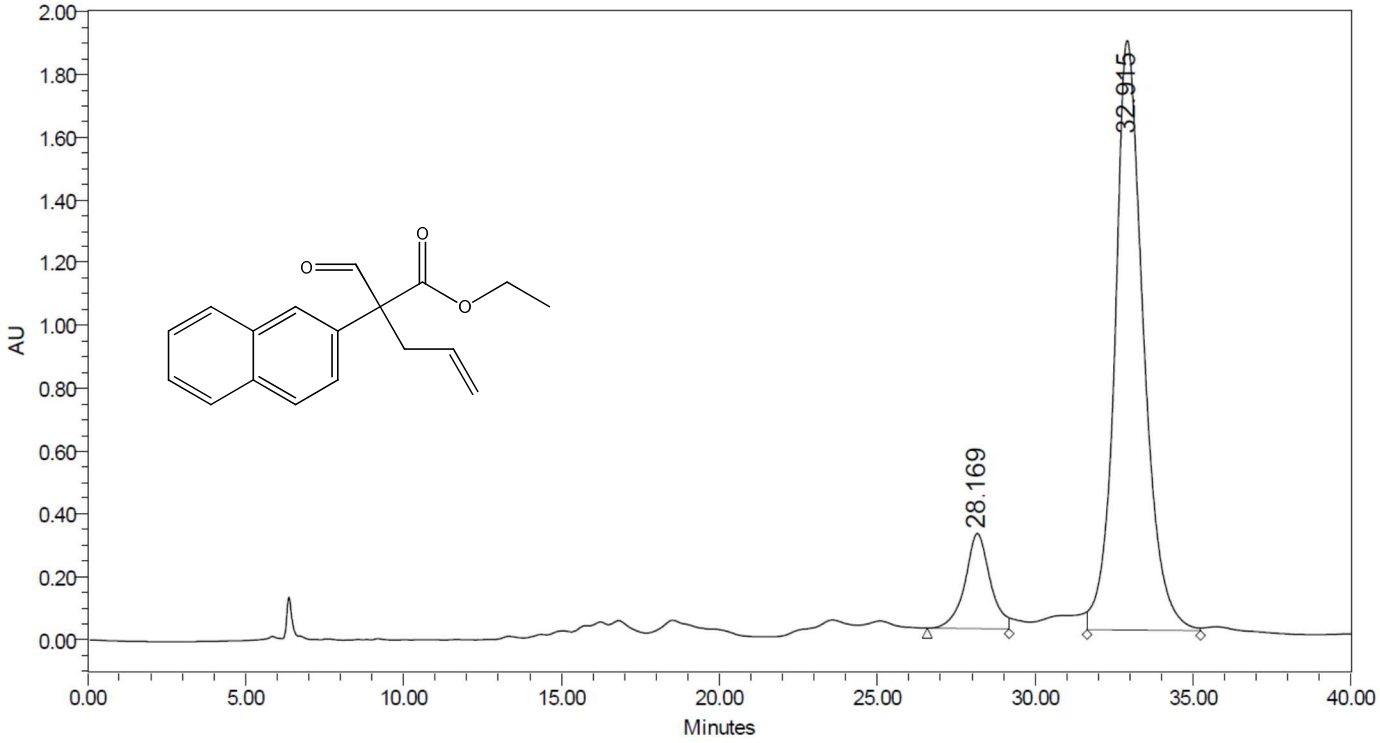


Portrait 46, HPLC Data(racemic)



	Peak Name	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Response	Peak Codes
1	Peak1	28.387	Found	22339350	48.42	424024	53.06	BB	2.234e+007	Q20
2	Peak3	33.573	Found	23801634	51.58	375160	46.94	BB	2.380e+007	Q20

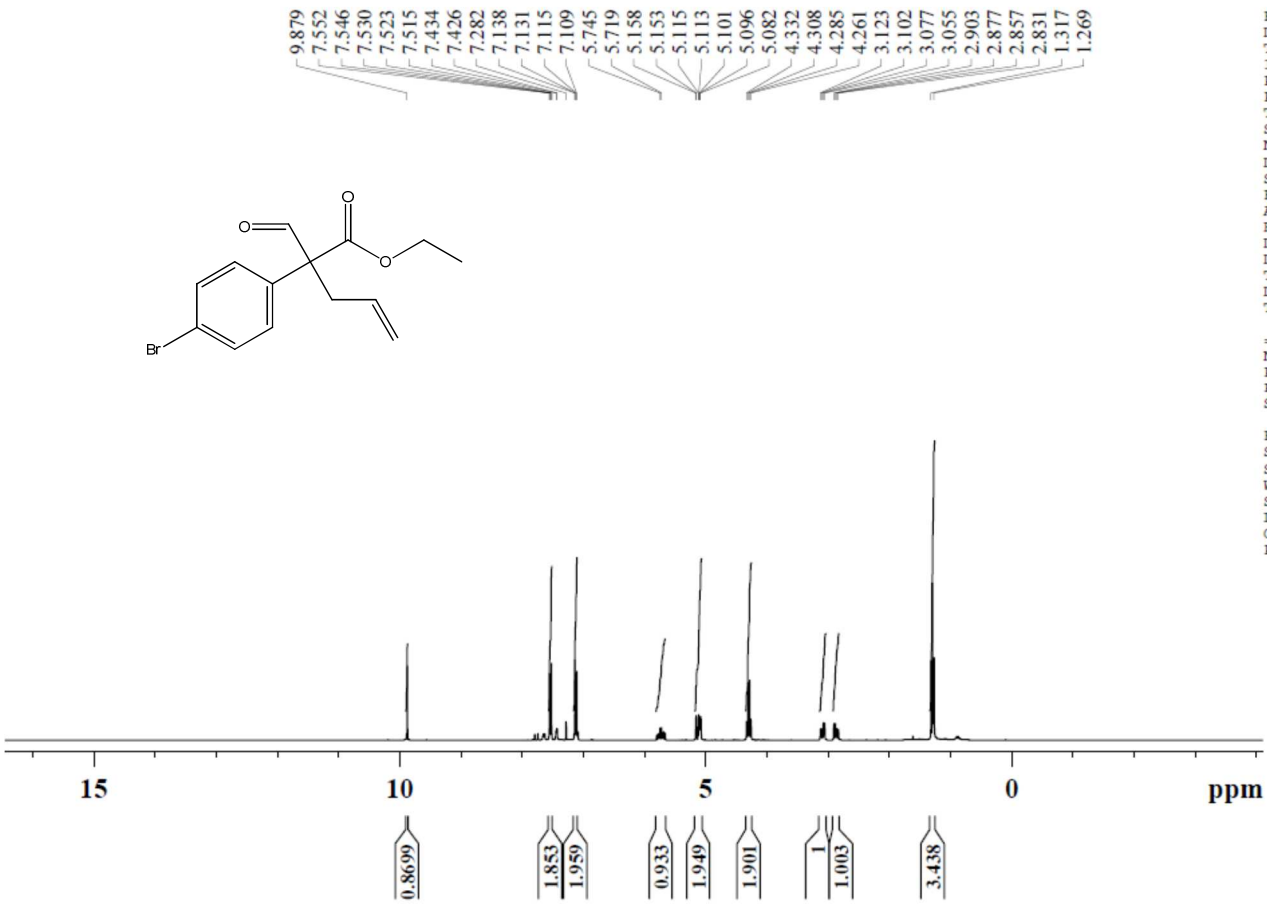
Portrait 47, HPLC Data (chiral)



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	28.169	Unknown	16664383	12.37	301451	13.84	Bv	1.773e+007	1555
2	32.915	Unknown	118101299	87.63	1877142	86.16	vV	1.200e+008	2156

Portrait 48, Compound 8h

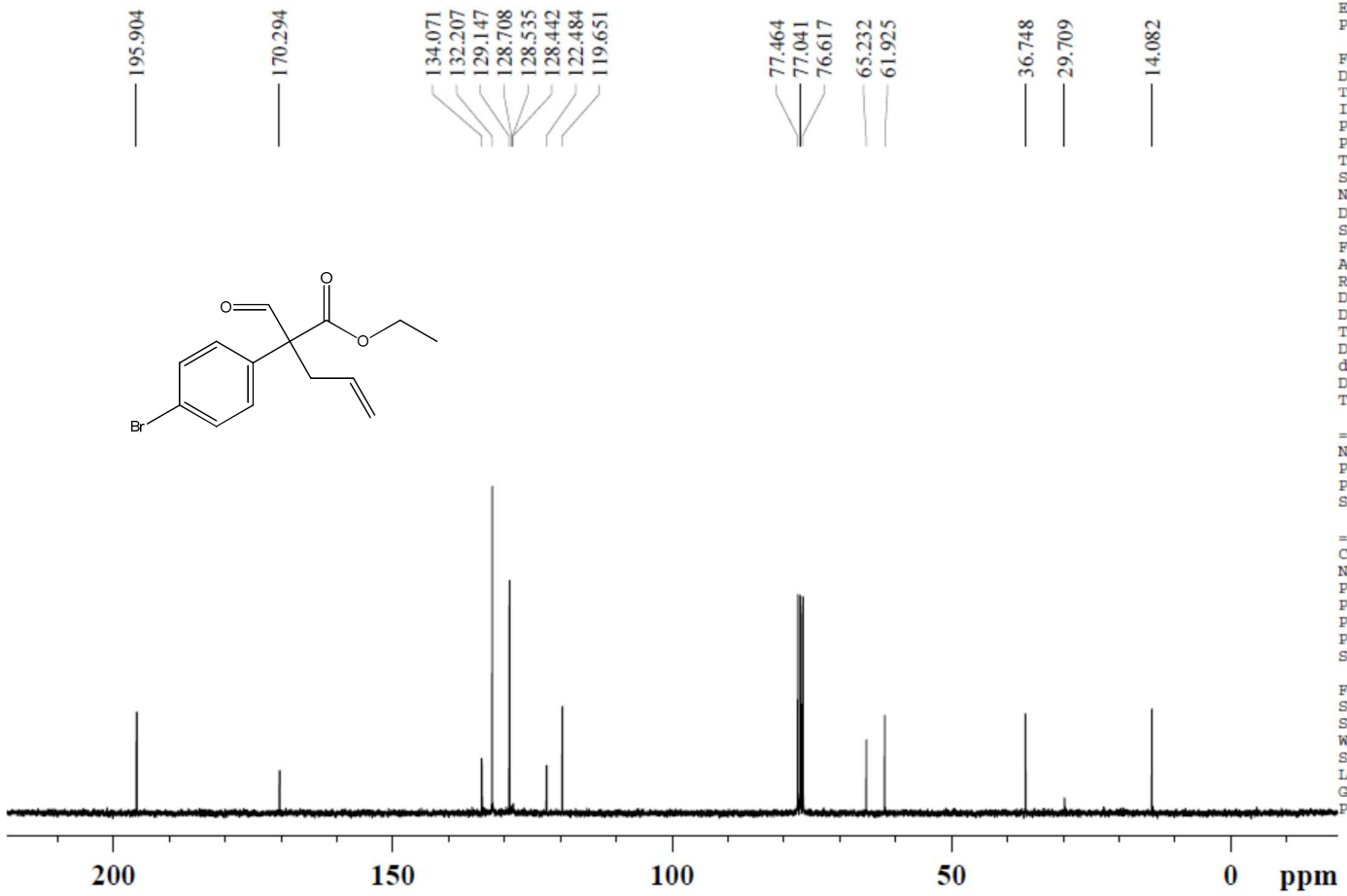
Proton Spectrum




```
Current Data Parameters
NAME         sa-1204132a
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20131207
Time               17.47
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     0
SWH             6172.839 Hz
FIDRES          0.188380 Hz
AQ              2.6542580 sec
RG                   128
DW                81.000 usec
DE                 6.00 usec
TE                297.2 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.80 usec
PL1                -6.00 dB
SFO1         300.1318534 MHz

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

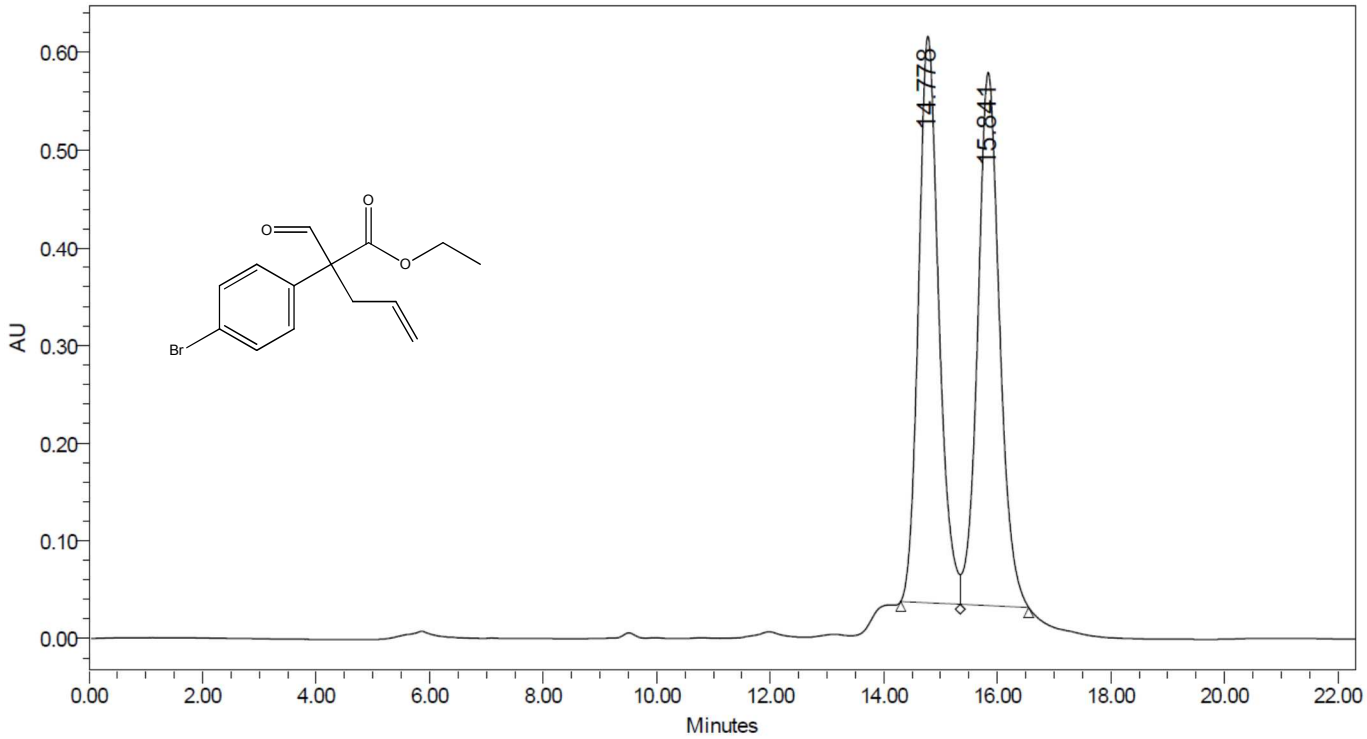
Portrait 49

Carbon Spectrum



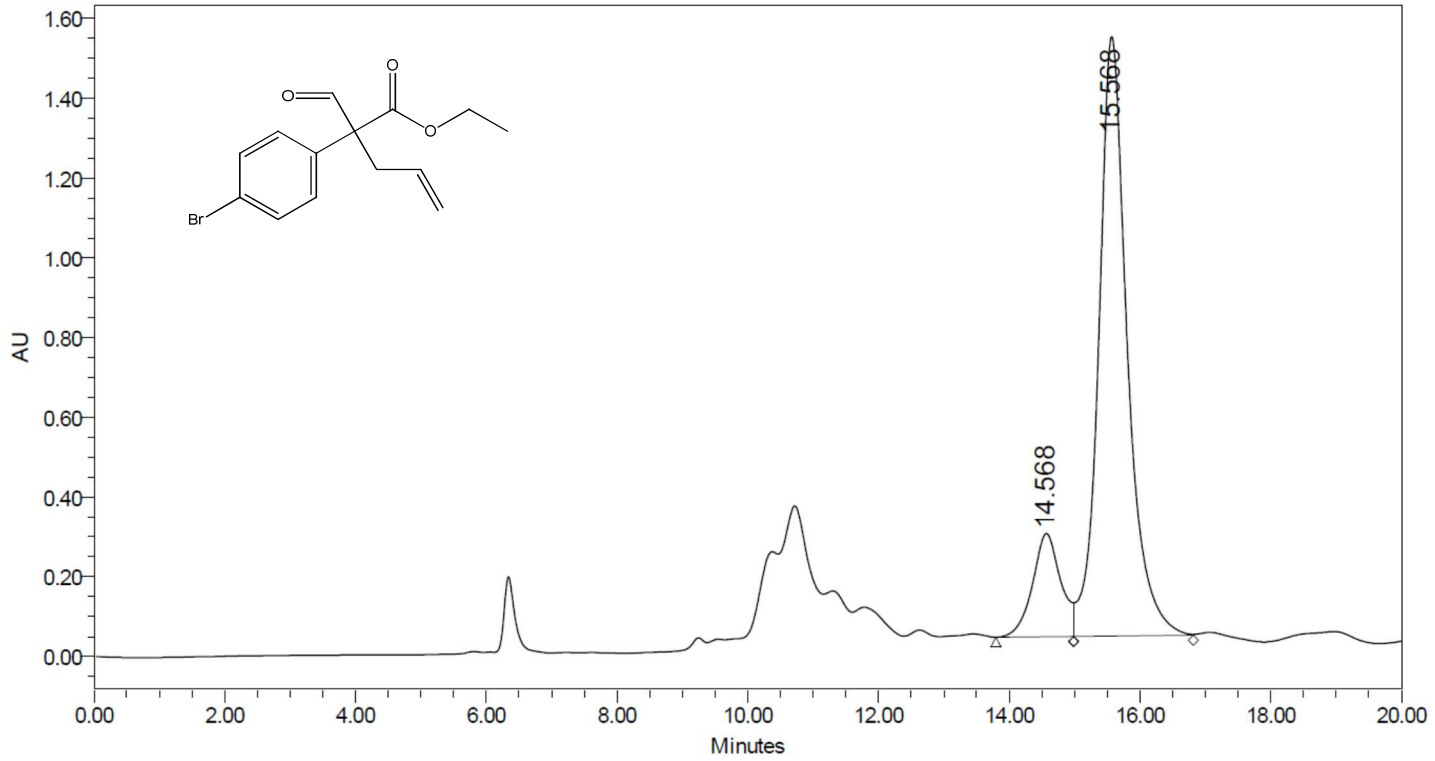

```
Current Data Parameters
NAME         sa-1204132b
EXPNO                  2
PROCNO                 2

F2 - Acquisition Parameters
Date_           20131206
Time               14.21
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    0
SWH           17985.611 Hz
FIDRES         0.274439 Hz
AQ             1.8219508 sec
RG                2580.3
DW                27.800 usec
DE                 6.00 usec
TE                297.2 K
D1            0.50000000 sec
d11           0.03000000 sec
DELTA         0.40000001 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                  6.80 usec
PL1                -6.00 dB
SFO1         75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                -6.00 dB
PL12               16.40 dB
PL13              120.00 dB
SFO2        300.1312000 MHz

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

Portrait 50, HPLC Data (racemic)



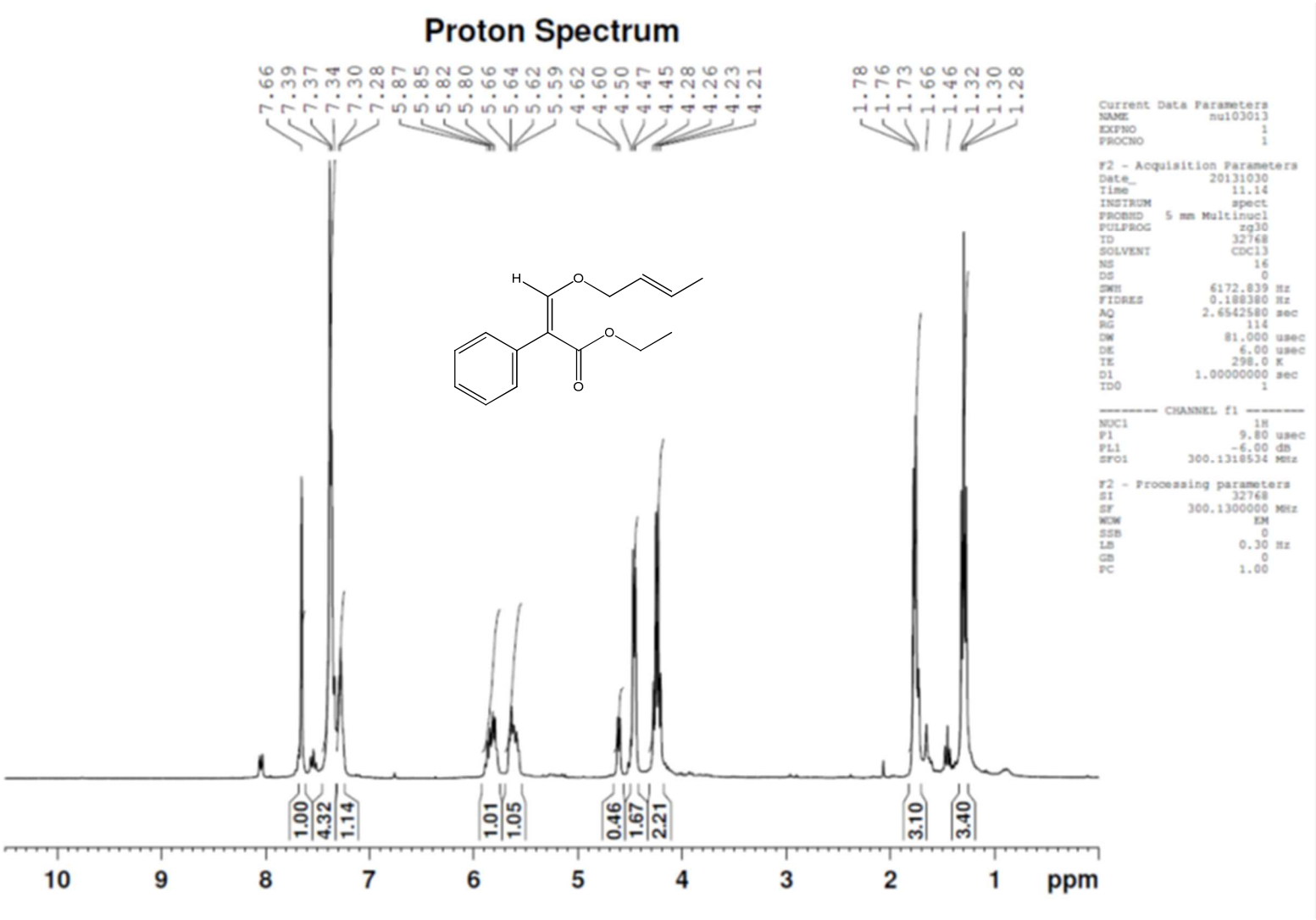
	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	14.778	Unknown	14459353	49.64	580126	51.51	bV	1.554e+007	629
2	15.841	Unknown	14667723	50.36	546039	48.49	Vb	1.599e+007	723

Portrait 51, HPLC Data (chiral)

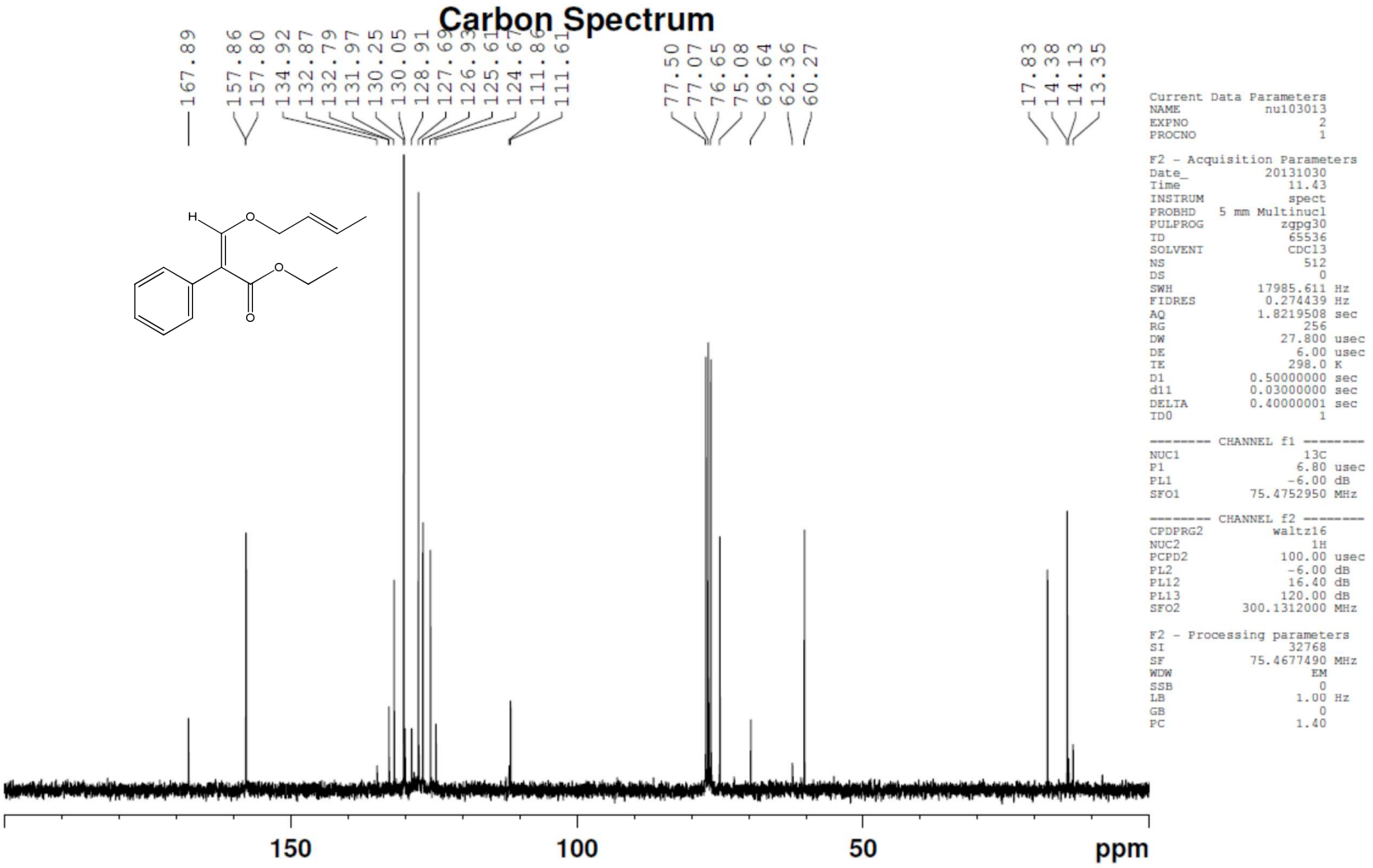


	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	14.568	Unknown	7718264	14.49	257984	14.66	BV	7.718e+006	713
2	15.568	Unknown	45552570	85.51	1501929	85.34	VV	4.555e+007	1099

Portrait 52, Compound 14

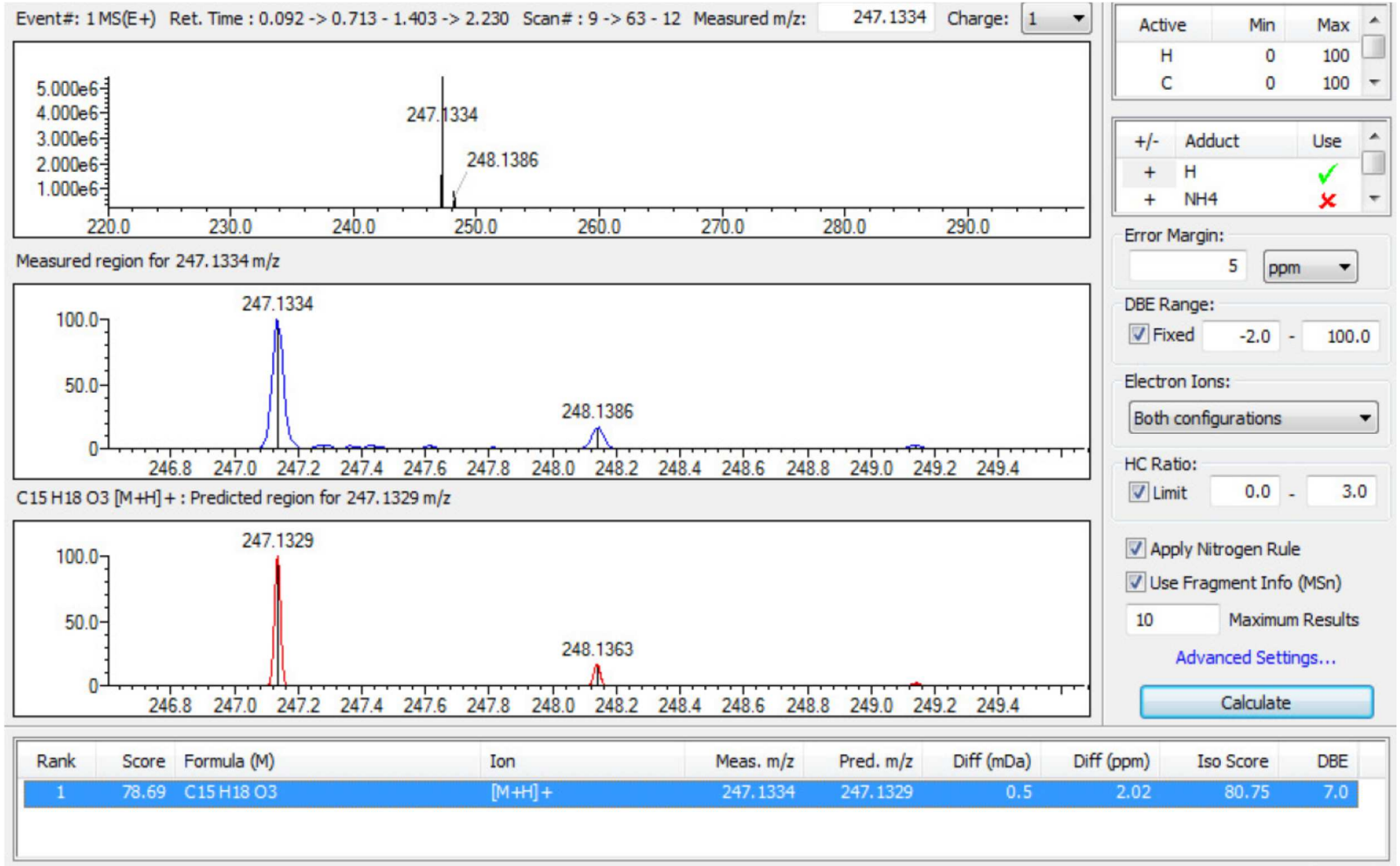


Portrait 53

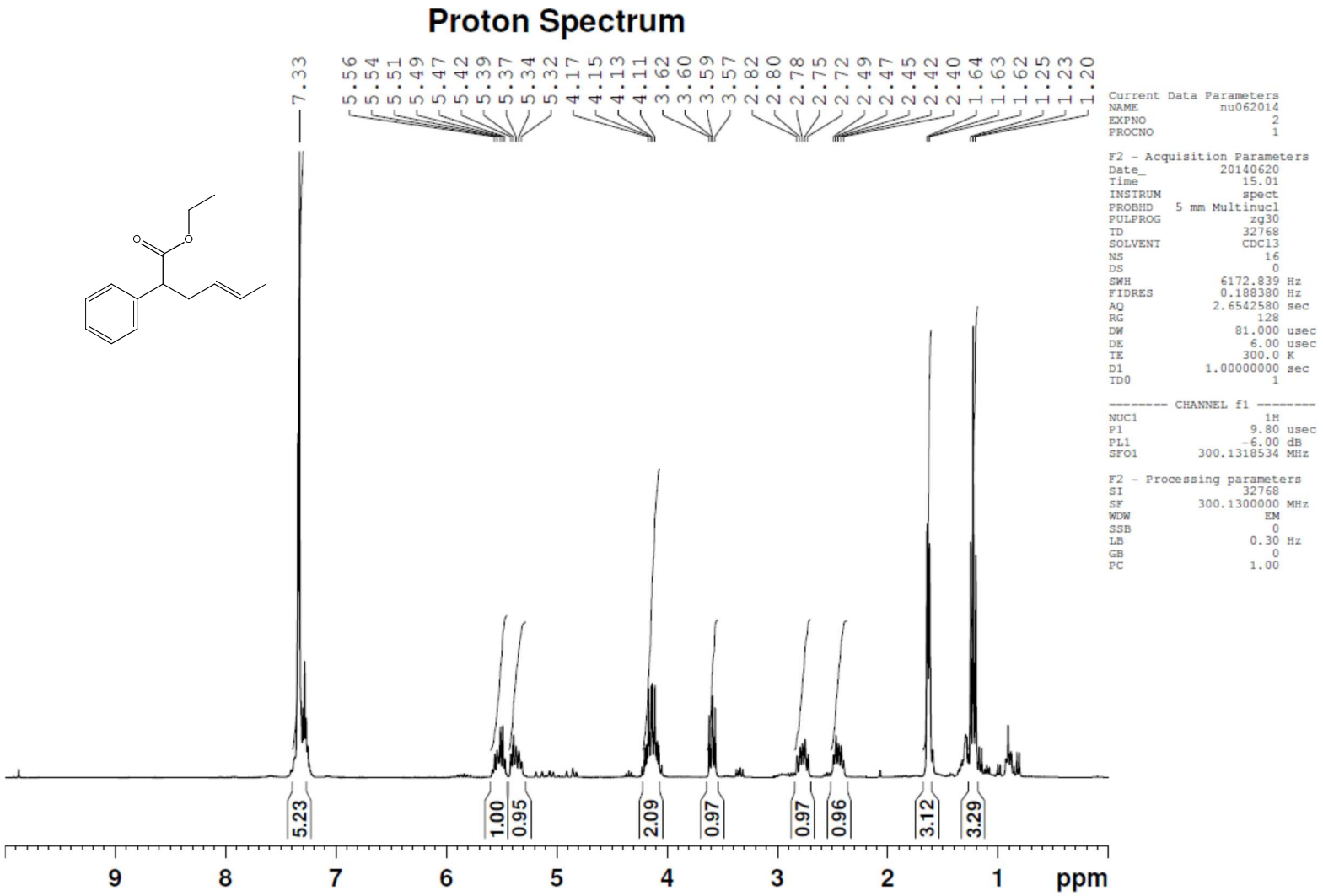



```
Current Data Parameters
NAME                nu103013
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20131030
Time                  11.43
INSTRUM               spect
PROBHD    5 mm Multinucl
PULPROG               zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       512
DS                         0
SWH               17985.611 Hz
FIDRES             0.274439 Hz
AQ                1.8219508 sec
RG                       256
DW                  27.800 usec
DE                   6.00 usec
TE                  298.0 K
D1                0.50000000 sec
d11               0.03000000 sec
DELTA             0.40000001 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                    6.80 usec
PL1                  -6.00 dB
SFO1             75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2               100.00 usec
PL2                  -6.00 dB
PL12                 16.40 dB
PL13                120.00 dB
SFO2            300.1312000 MHz

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

Portrait 53, HRMS, Compound 14

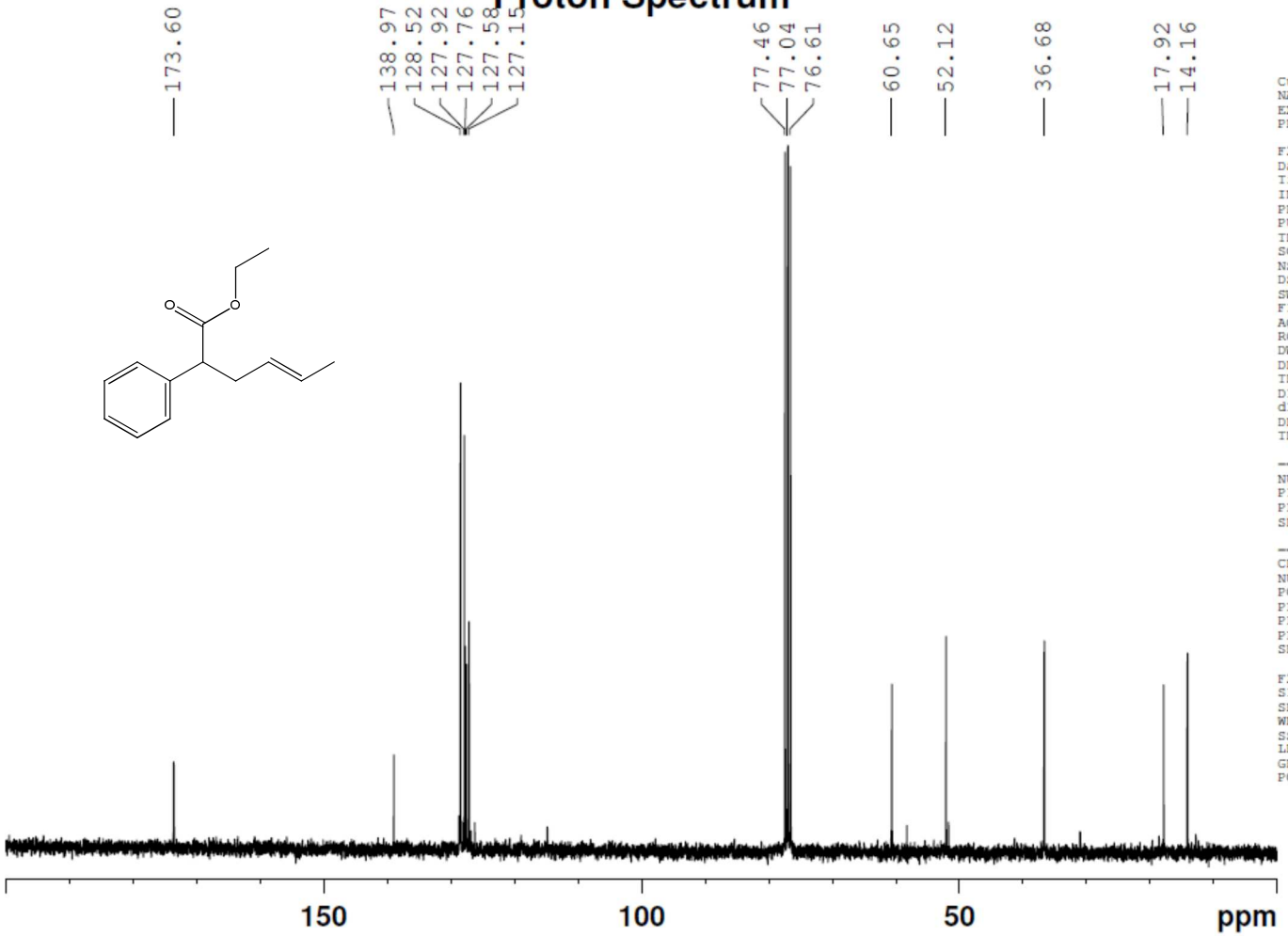


Portrait 54, Compound 15



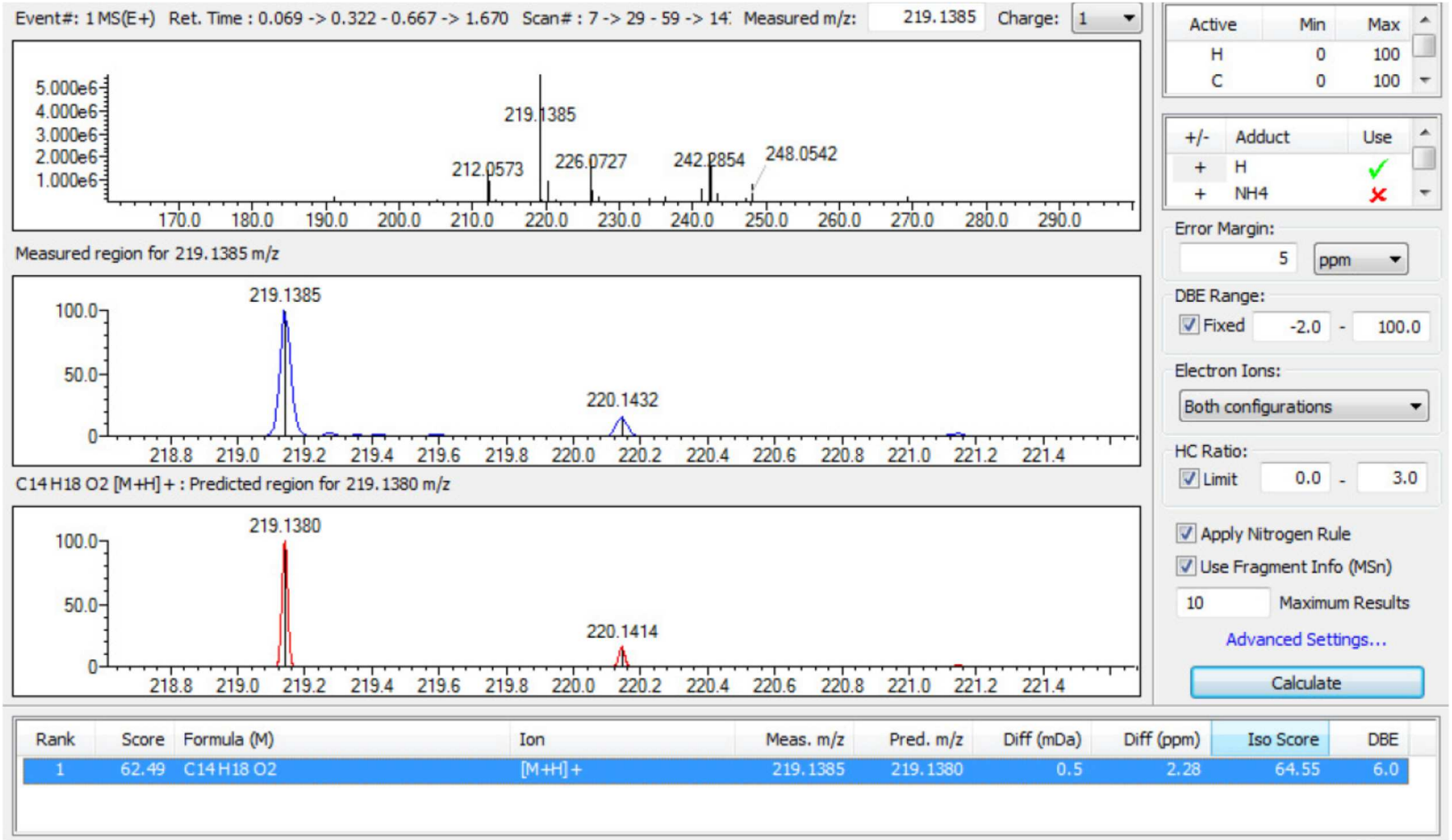
Portrait 55

Proton Spectrum

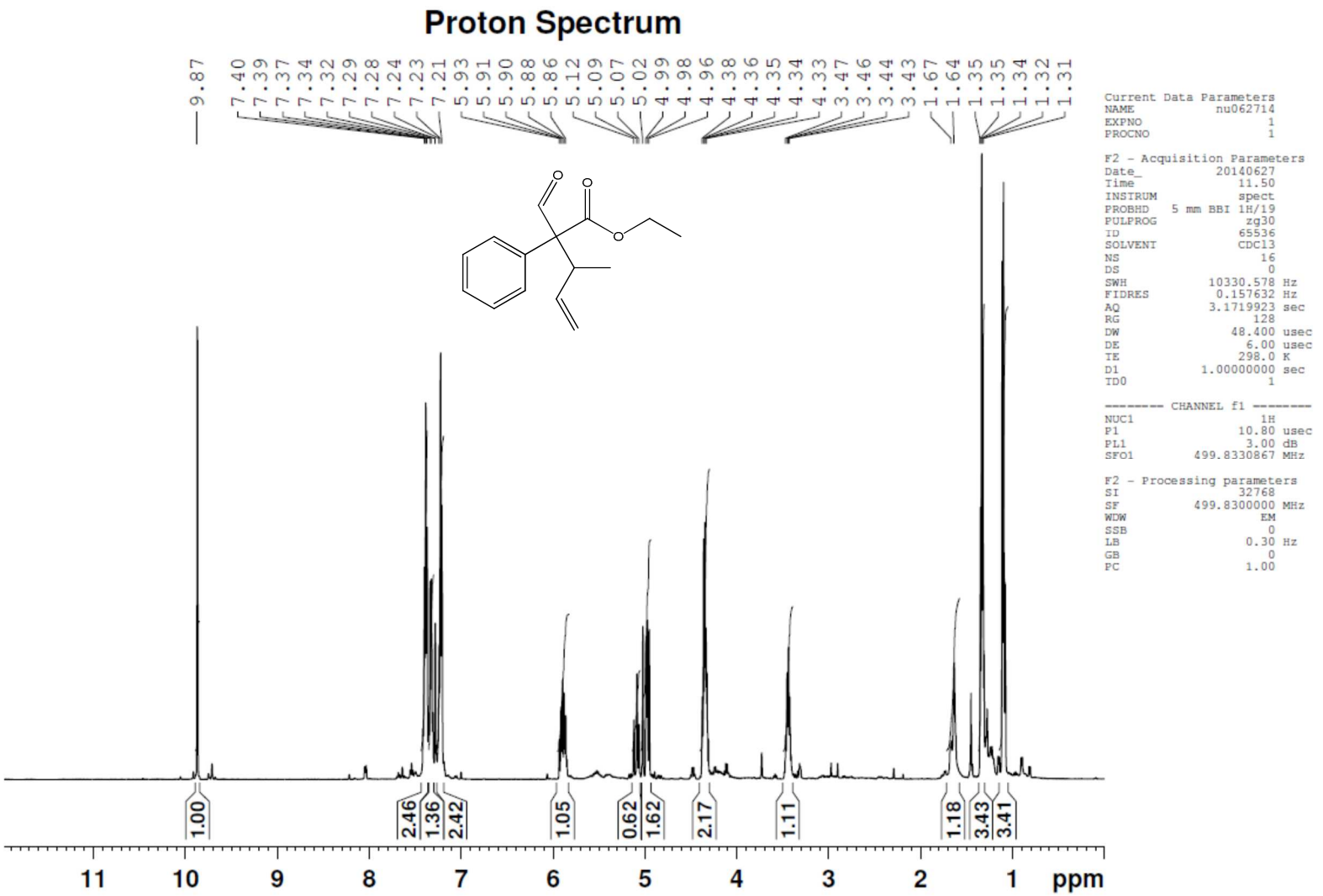



```
Current Data Parameters
NAME                nu061914
EXPNO                      4
PROCNO                     1

F2 - Acquisition Parameters
Date_              20140619
Time                 16.07
INSTRUM              spect
PROBHD    5 mm Multinucl
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     256
DS                       0
SWH              17985.611 Hz
FIDRES            0.274439 Hz
AQ                1.8219508 sec
RG                   1149.4
DW                  27.800 usec
DE                   6.00 usec
TE                  300.0 K
D1               0.50000000 sec
d11              0.03000000 sec
DELTA            0.40000001 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                    13C
P1                     6.80 usec
PL1                   -6.00 dB
SFO1           75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                100.00 usec
PL2                   -6.00 dB
PL12                  16.40 dB
PL13                 120.00 dB
SFO2          300.1312000 MHz

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

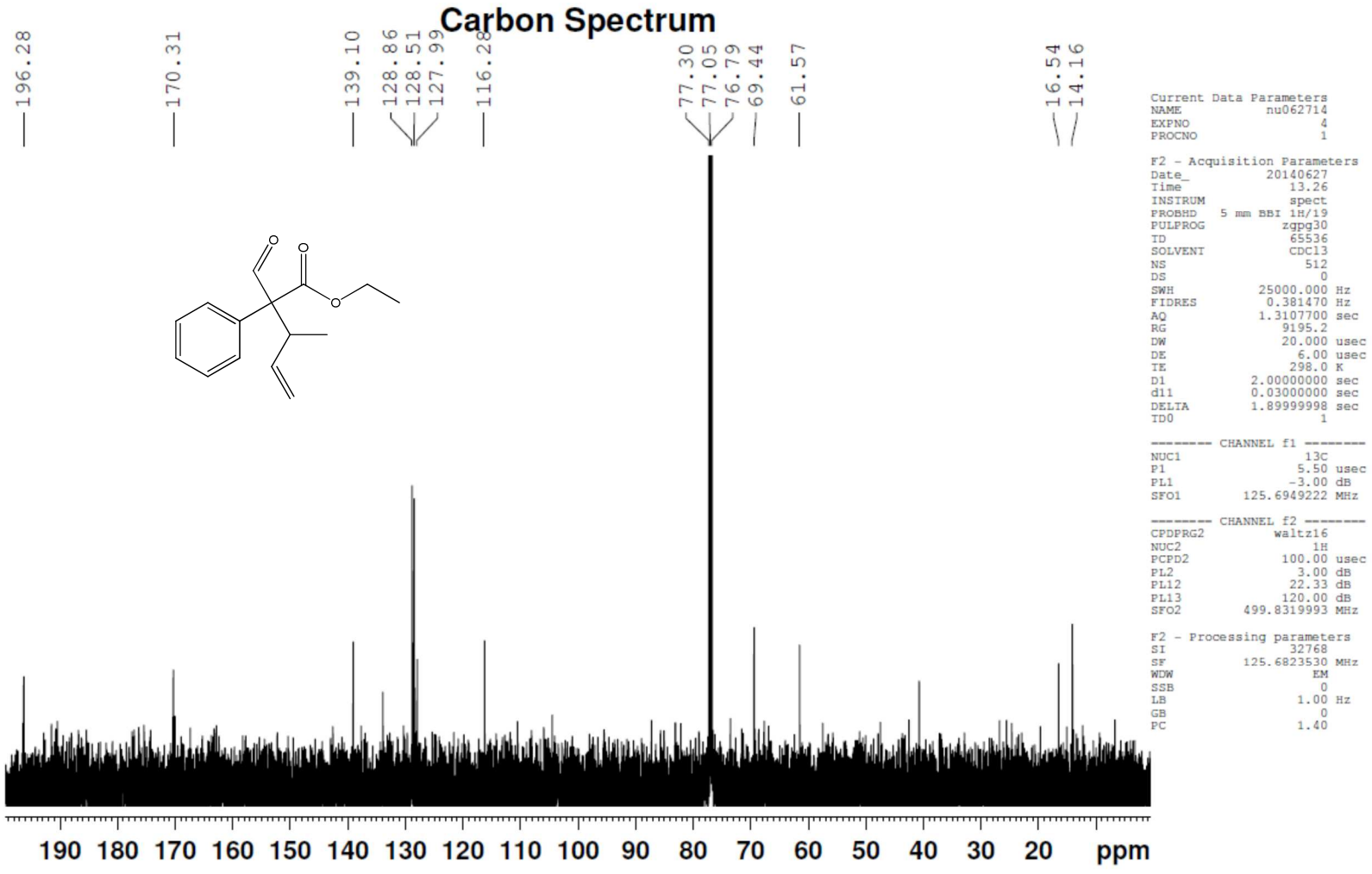
Portrait 56, HRMS, Compound 15



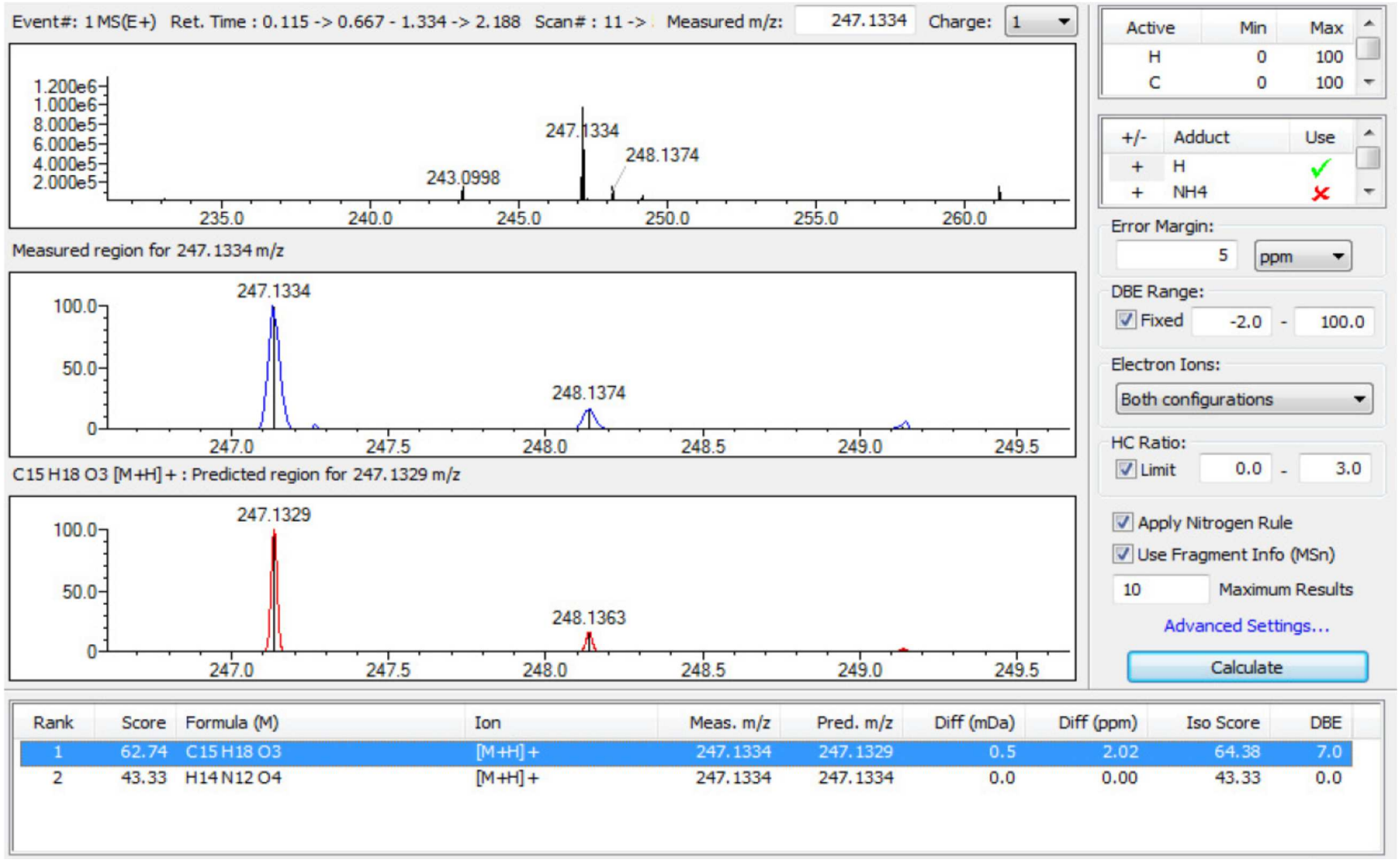
Portrait 57, Compound 16



Portrait 58

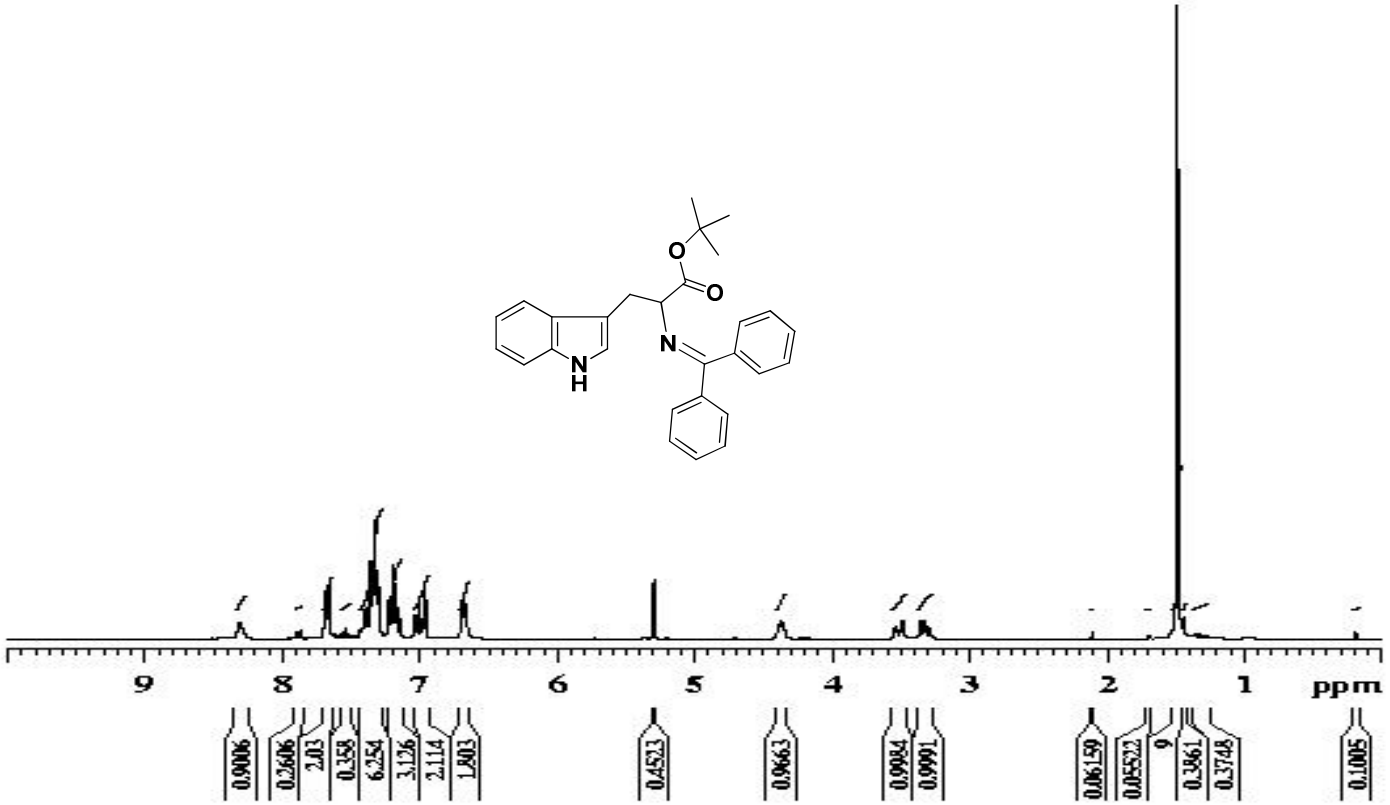

Carbon Spectrum
196.28
170.31
139.10
128.86
128.51
127.99
116.28
77.30
77.05
76.79
69.44
61.57
16.54
14.16
Current Data Parameters
NAME nu062714
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140627
Time 13.26
INSTRUM spect
PROBHD 5 mm BBI 1H/19
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 0
SWH 25000.000 Hz
FIDRES 0.381470 Hz
AQ 1.3107700 sec
RG 9195.2
DW 20.000 usec
DE 6.00 usec
TE 298.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 5.50 usec
PL1 -3.00 dB
SFO1 125.6949222 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 3.00 dB
PL12 22.33 dB
PL13 120.00 dB
SFO2 499.8319993 MHz
F2 - Processing parameters
SI 32768
SF 125.6823530 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Portrait 59, HRMS, Compound 16

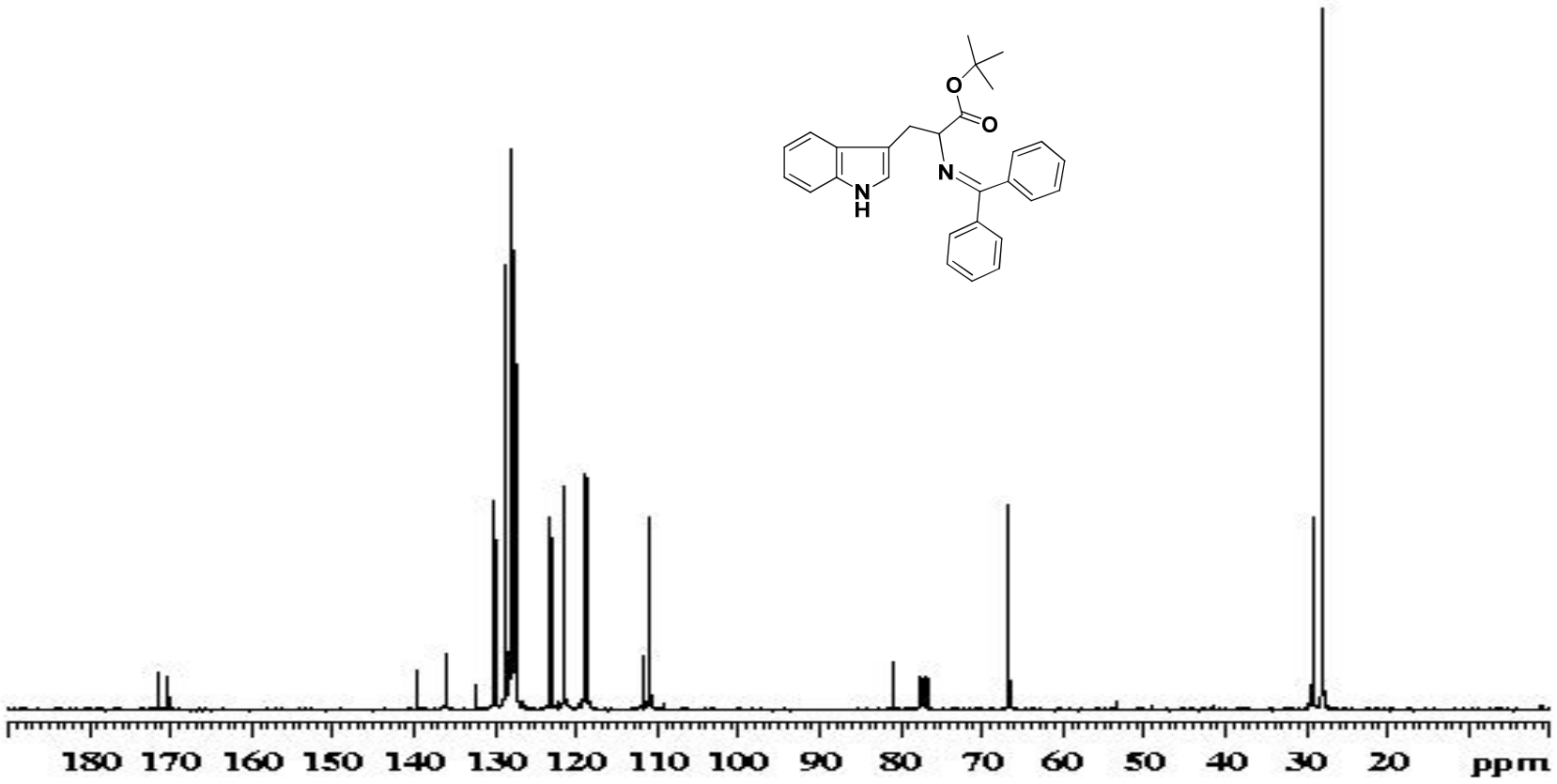


APPENDIX B: PART II, Analytical Data **Portrait 60**

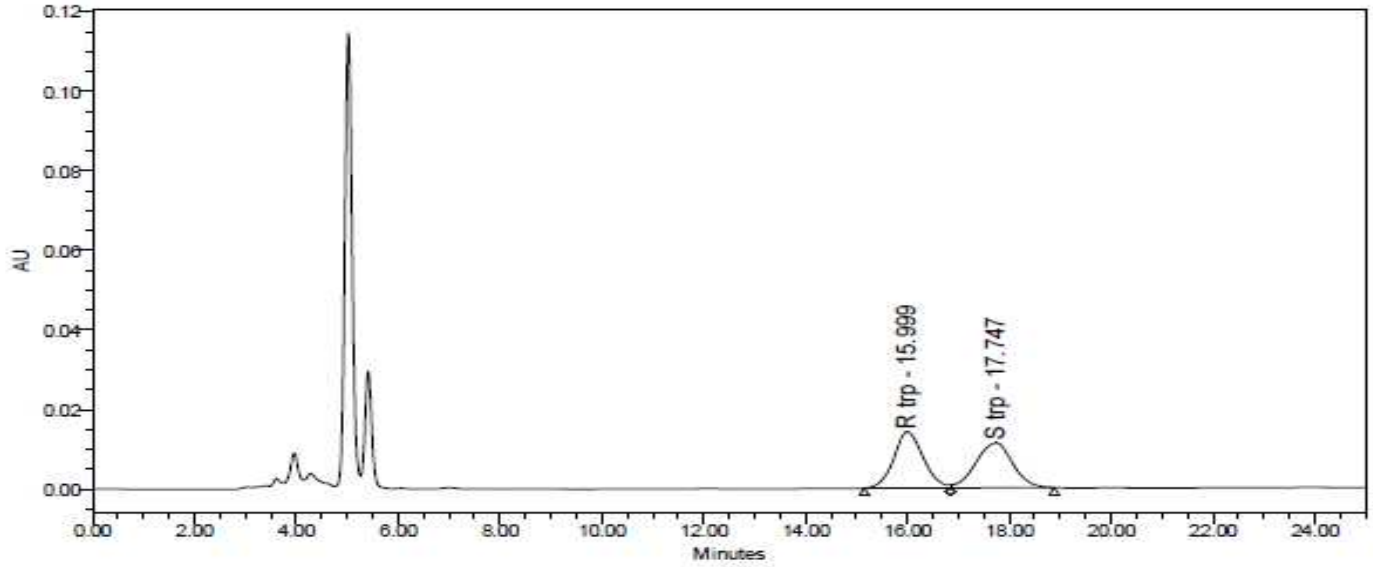
tert-butyl 2-(diphenylmethyleneamino)-3-(1H-indol-3-yl)propanoate(Scheme 65; Compound 24);



Portrait 61

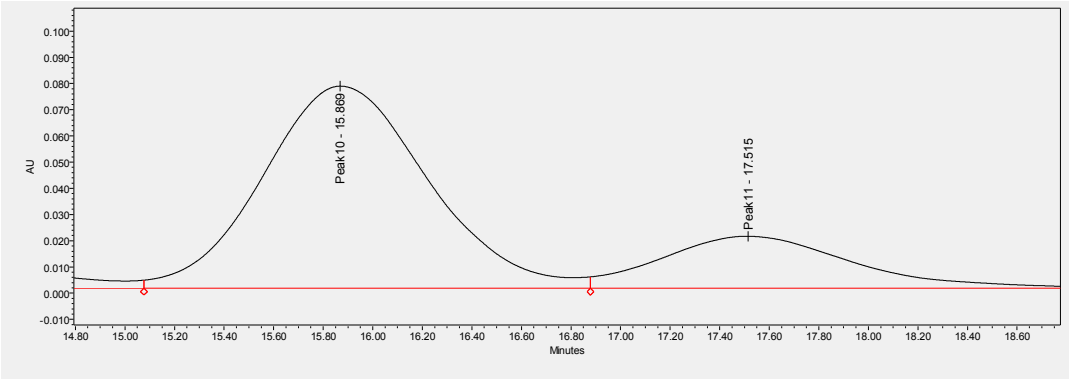

O
O
N
N
H
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Portrait 62, HPLC traces for racemic tryptophan:



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Peak Codes
1	R trp	15.999	Found	566447	50.15	14127	55.70	BV	5.664e+005	Q20
2	S trp	17.747	Found	563089	49.85	11235	44.30	VB	5.631e+005	Q20

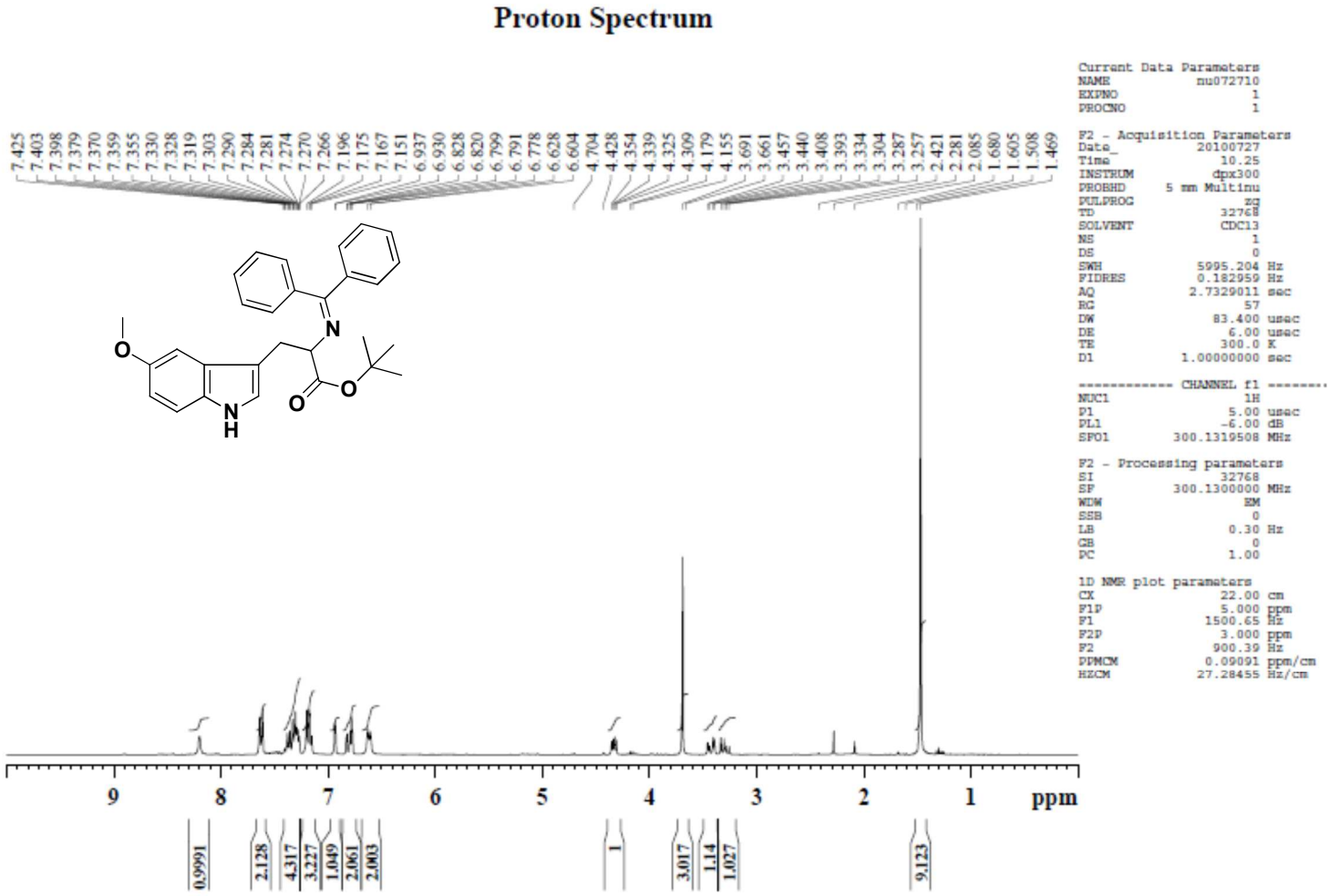
Portrait 63, HPLC traces for Chiral Tryptophan:



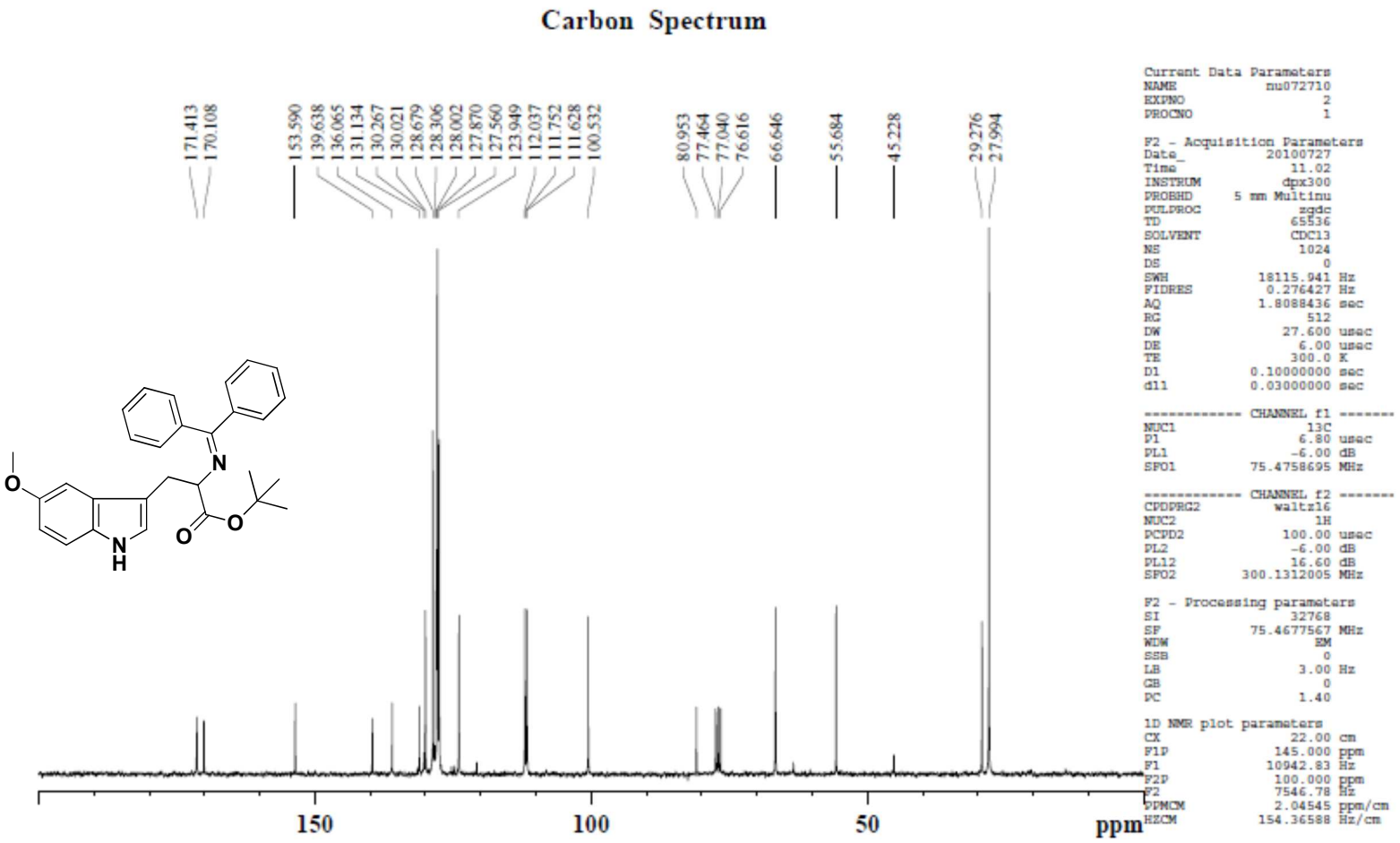
	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
10	Peak10	15.869	3585419	7.33	77144	VV			Found	Q20
11	Peak11	17.515	1076641	2.20	19864	VB			Found	Q20

Portrait 64

***tert*-Butyl 2-(Diphenylmethyleneamino)-3-(5-methoxy- 1*H*-indol-3-yl)propanoate (Scheme 65; Compound 39)**:

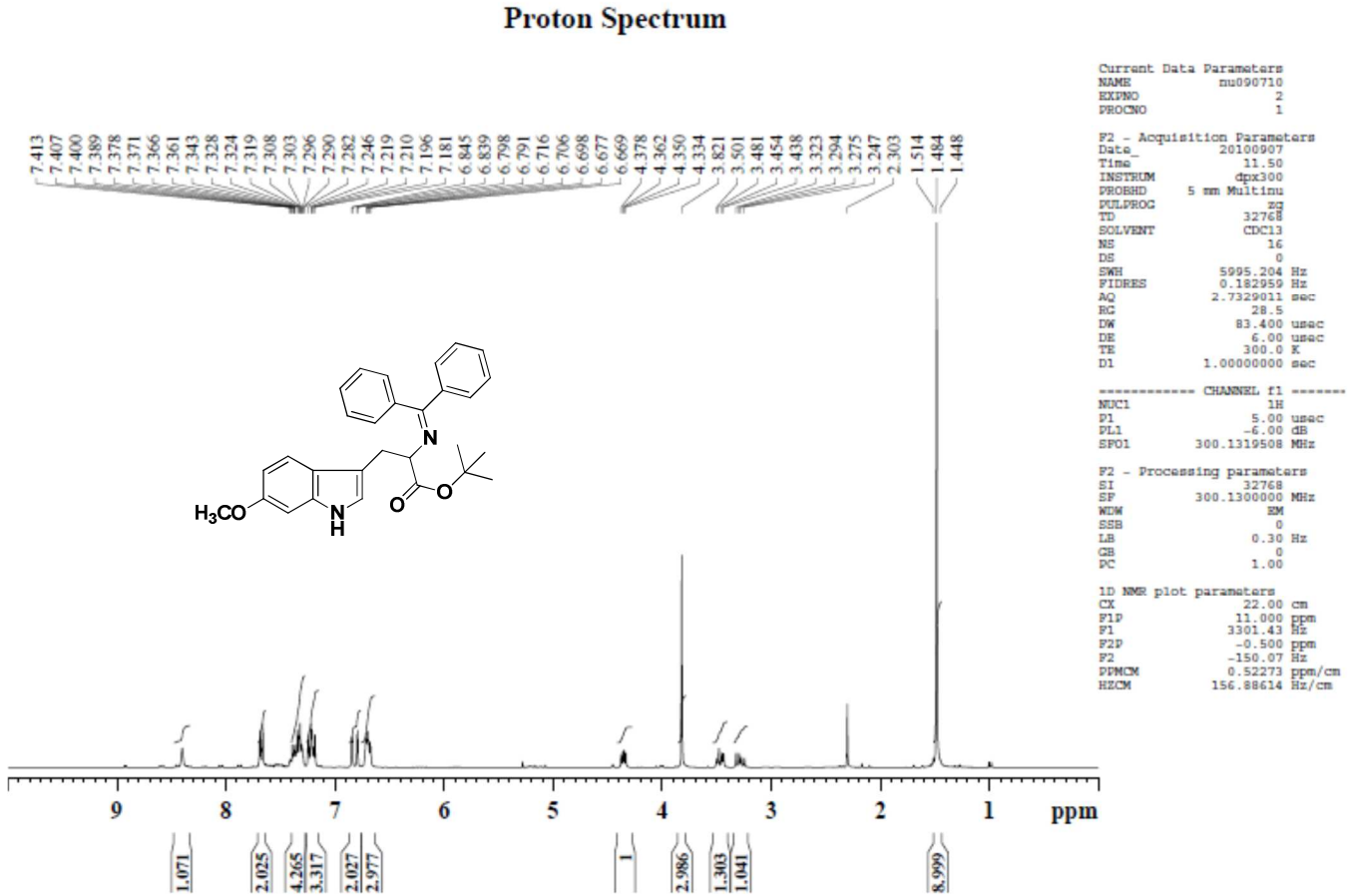


Portrait 65


Carbon Spectrum
171.413
170.108
153.590
139.638
136.065
131.134
130.267
130.021
128.679
128.306
128.002
127.870
127.560
123.949
112.037
111.752
111.628
100.532
80.953
77.464
77.040
76.616
66.646
55.684
45.228
29.276
27.994
150
100
50
ppm
Current Data Parameters
NAME nu072710
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100727
Time 11.02
INSTRUM dpx300
PROBHD 5 mm Multinu
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 1024
DS 0
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 512
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
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 145.000 ppm
F1 10942.83 Hz
F2P 100.000 ppm
F2 7546.78 Hz
PPMCM 2.04545 ppm/cm
HZCM 154.36588 Hz/cm

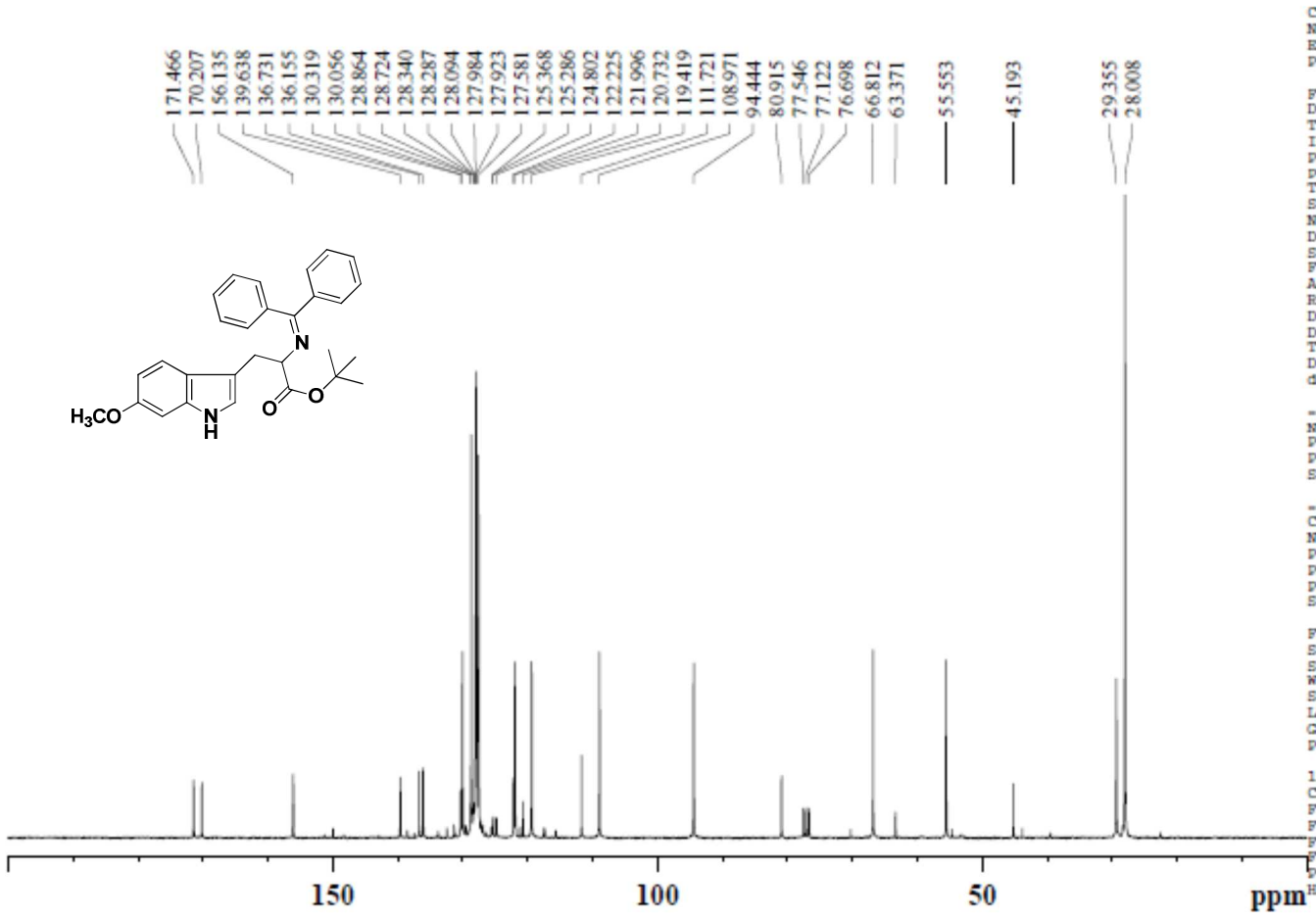
Portrait 66

***tert*-Butyl 2-(Diphenylmethyleneamino)-3-(6-methoxy-1*H*-indol-3-yl)propanoate (Scheme 65; Compound 40):**



Portrait 67

Carbon Spectrum




```
Current Data Parameters
NAME                nu090710
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
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Time                   12.30
INSTRUM                dpx300
PROBHD      5 mm Multinu
PULPROG                zgdc
TD                     65536
SOLVENT                CDCl3
NS                      1024
DS                         0
SWH                18115.941 Hz
FIDRES             0.276427 Hz
AQ                 1.8088436 sec
RG                     812.7
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
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                     180.000 ppm
F1                    13584.20 Hz
F2P                       0.000 ppm
F2                        0.00 Hz
PPMCM                  8.18182 ppm/cm
HZCM                 617.46350 Hz/cm
```
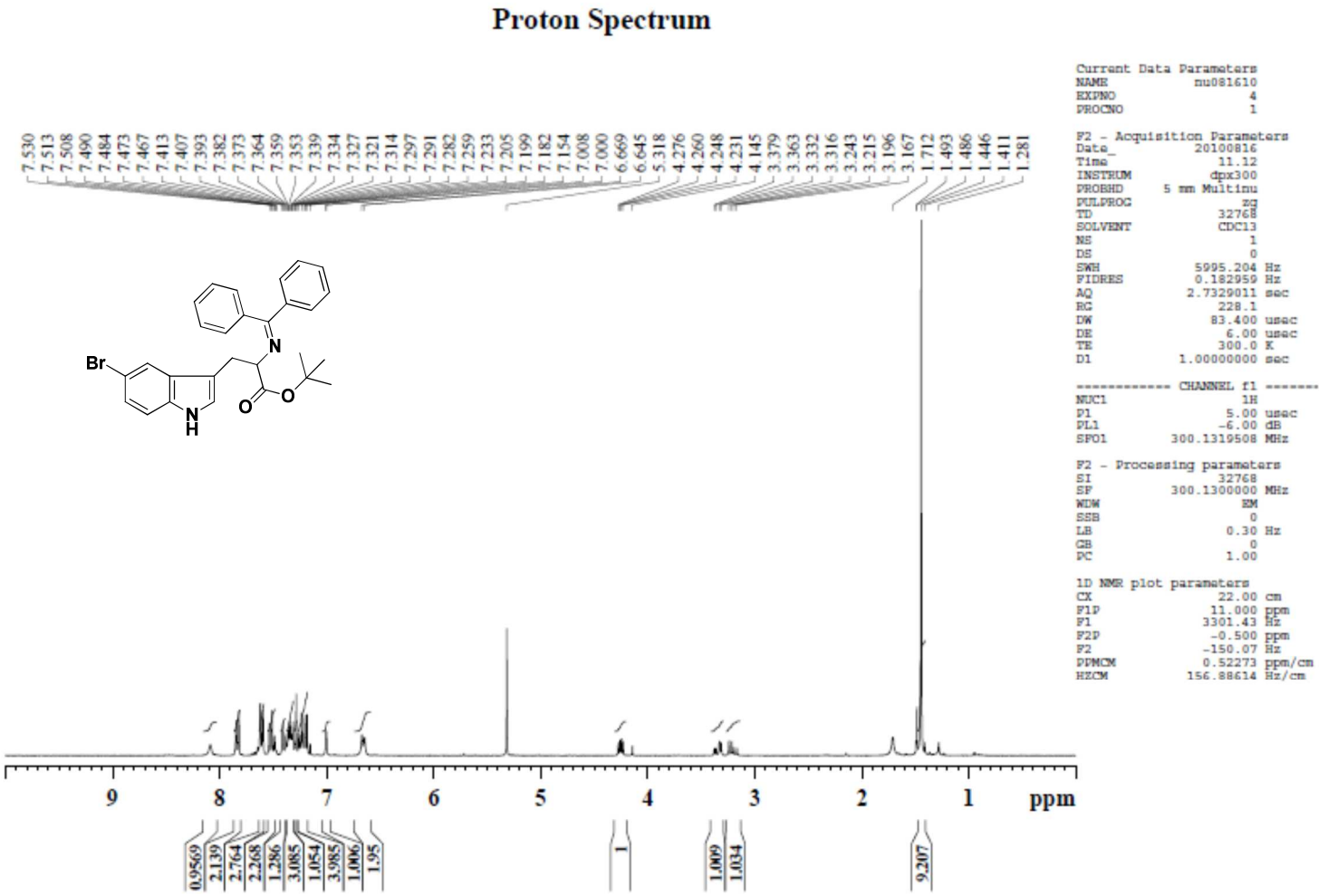
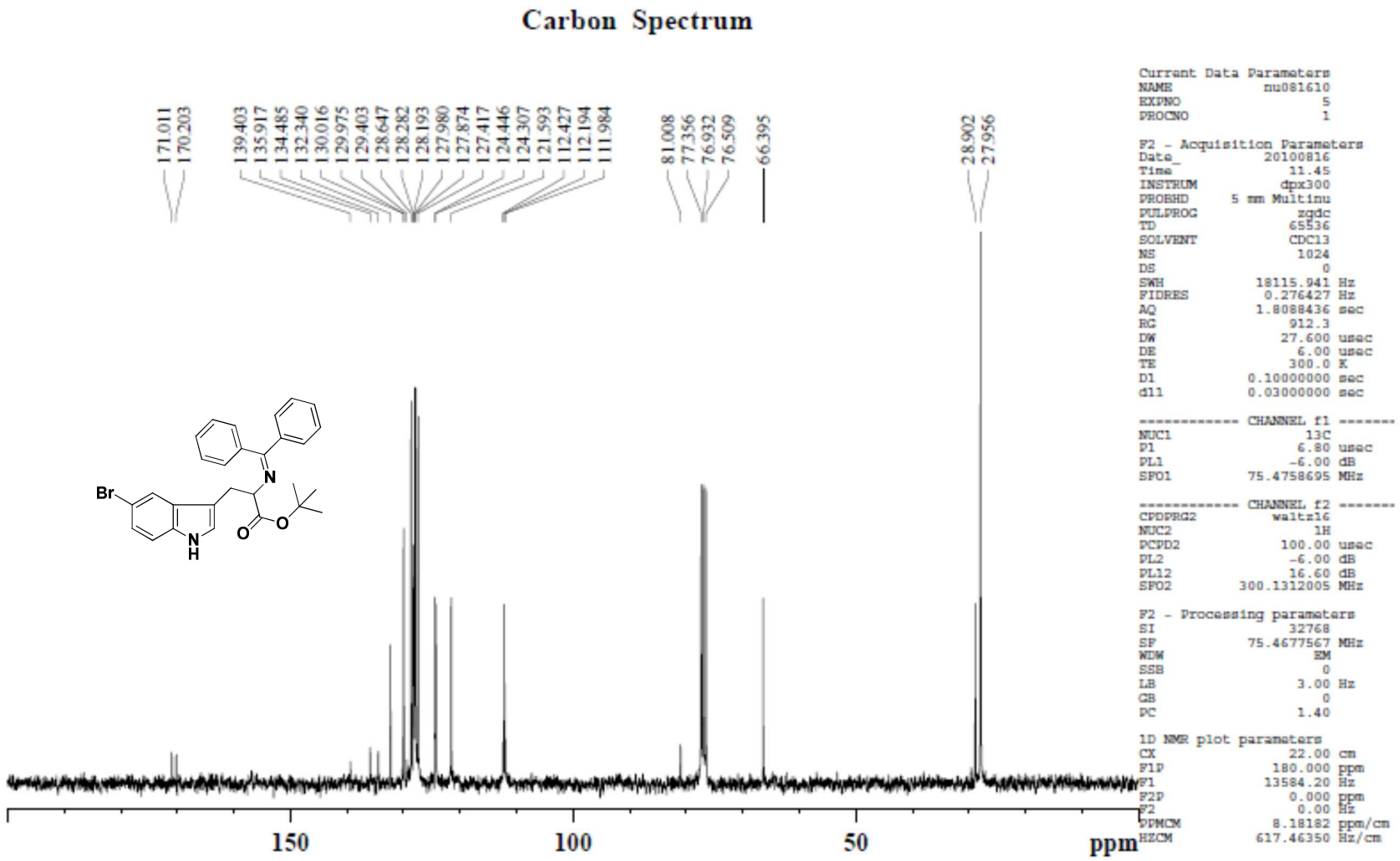

Portrait 68

***tert*-Butyl 3-(5-Bromo-1*H*-indol-3-yl)-2-(diphenylmethyleneamino) propanoate (Schem 65; Compound 41):**

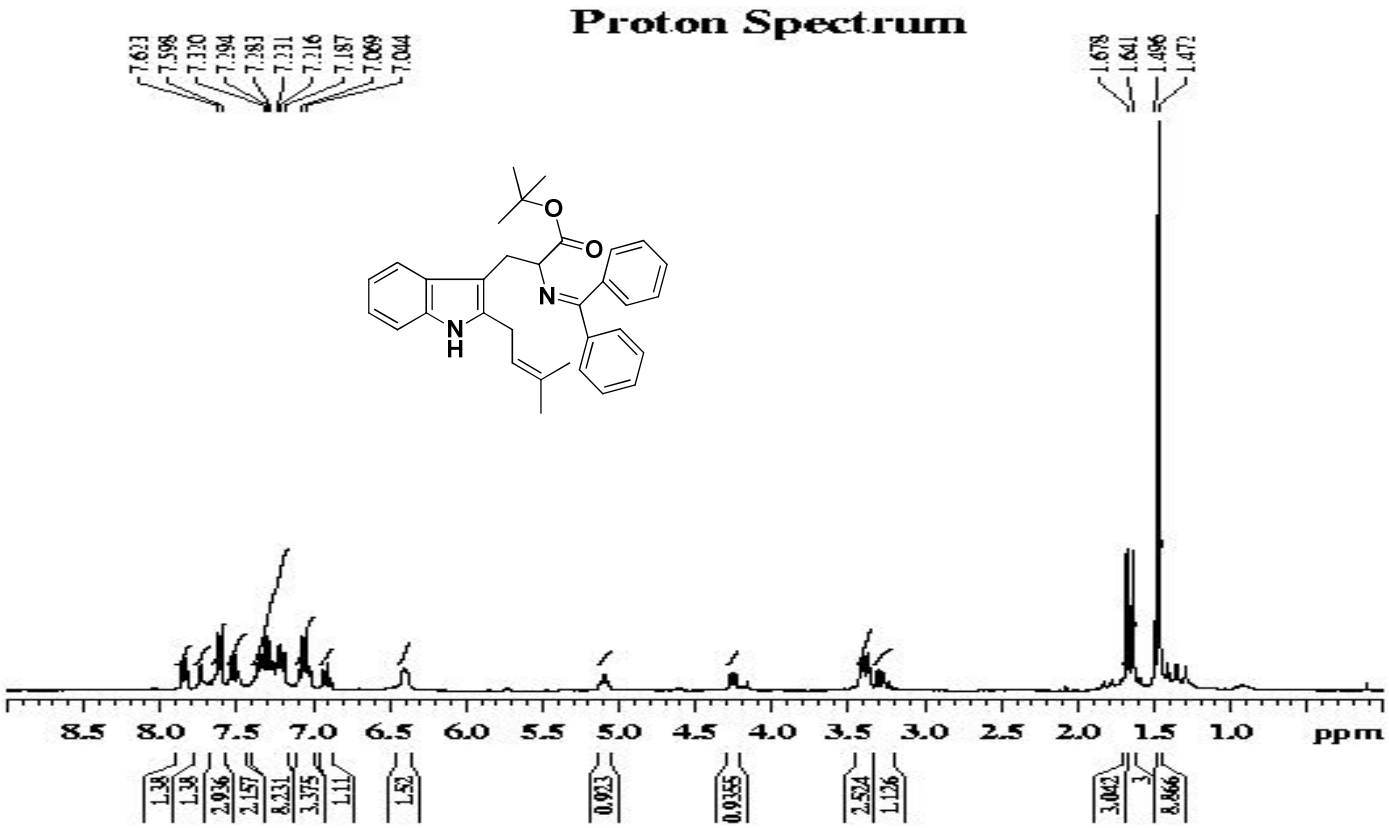


Portrait 69

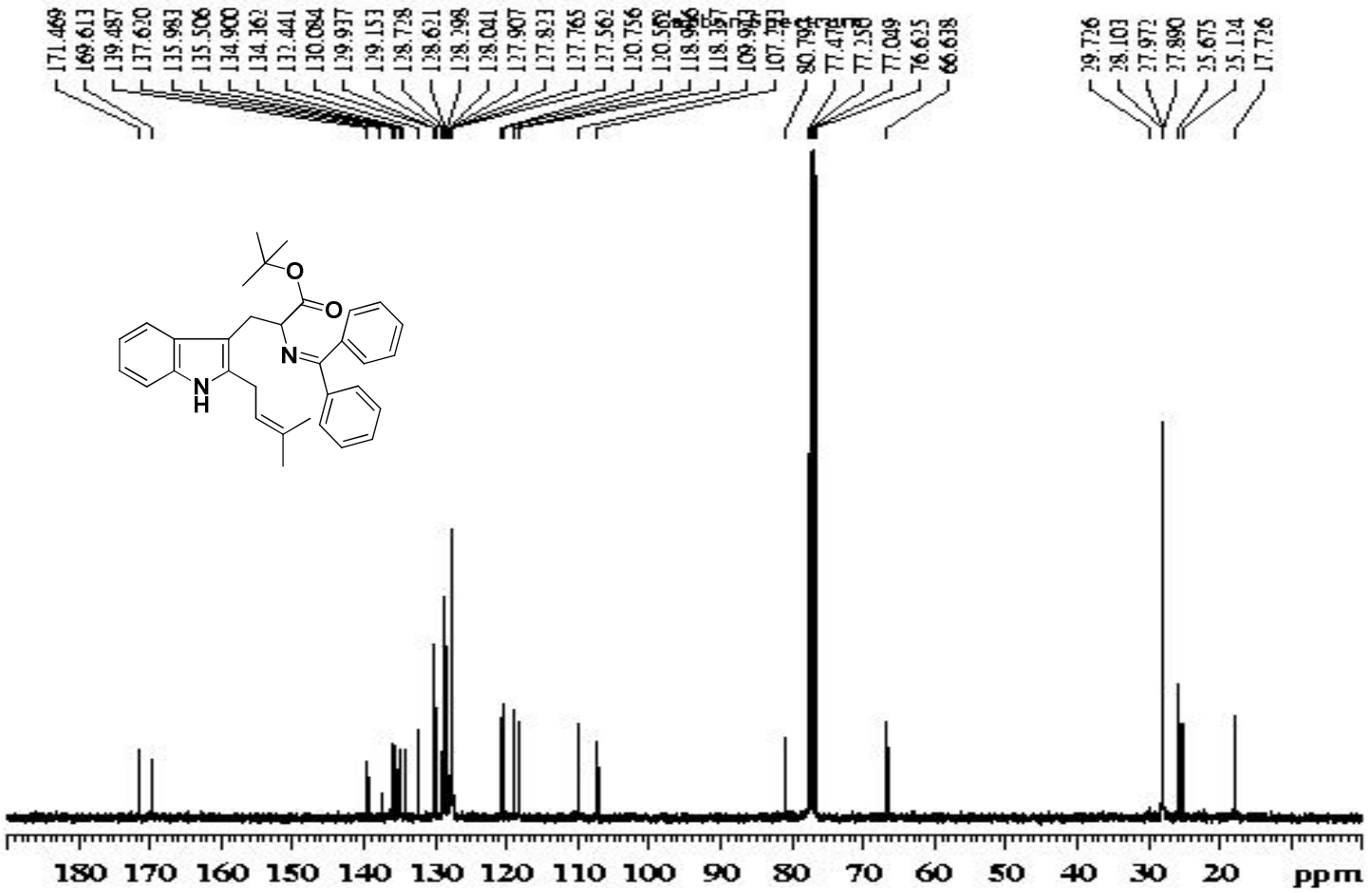

Carbon Spectrum
171.011
170.203
139.403
135.917
134.485
132.340
130.016
129.975
129.403
128.647
128.282
128.193
127.980
127.874
127.417
124.446
124.307
121.593
112.427
112.194
111.984
81.008
77.356
76.932
76.509
66.395
28.902
27.956
Br
N
N
H
O
O
150
100
50
ppm
Current Data Parameters
NAME nu081610
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100816
Time 11.45
INSTRUM dpx300
PROBHD 5 mm Multinu
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 1024
DS 0
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 912.3
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
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 180.000 ppm
F1 13584.20 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 8.18182 ppm/cm
HZCM 617.46350 Hz/cm

Portrait 70

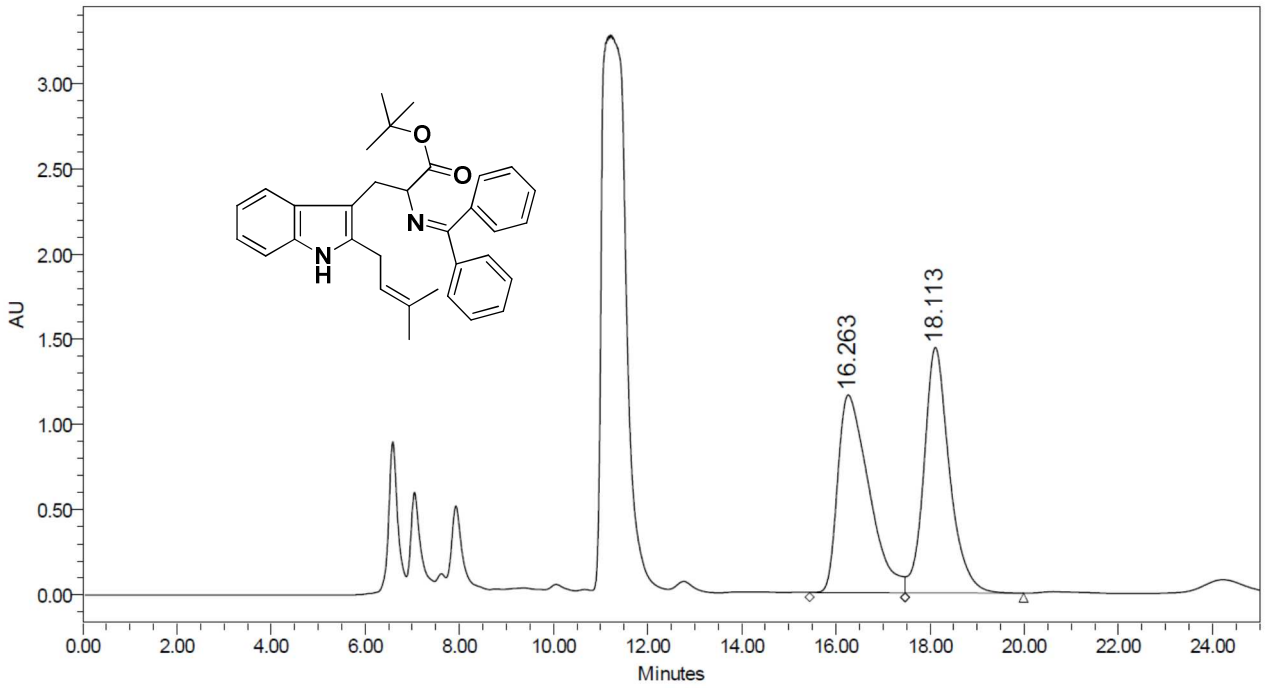
***tert*-butyl2-((diphenylmethylene)amino)-3-(2-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoate (Compound 68):**



Portrait 71

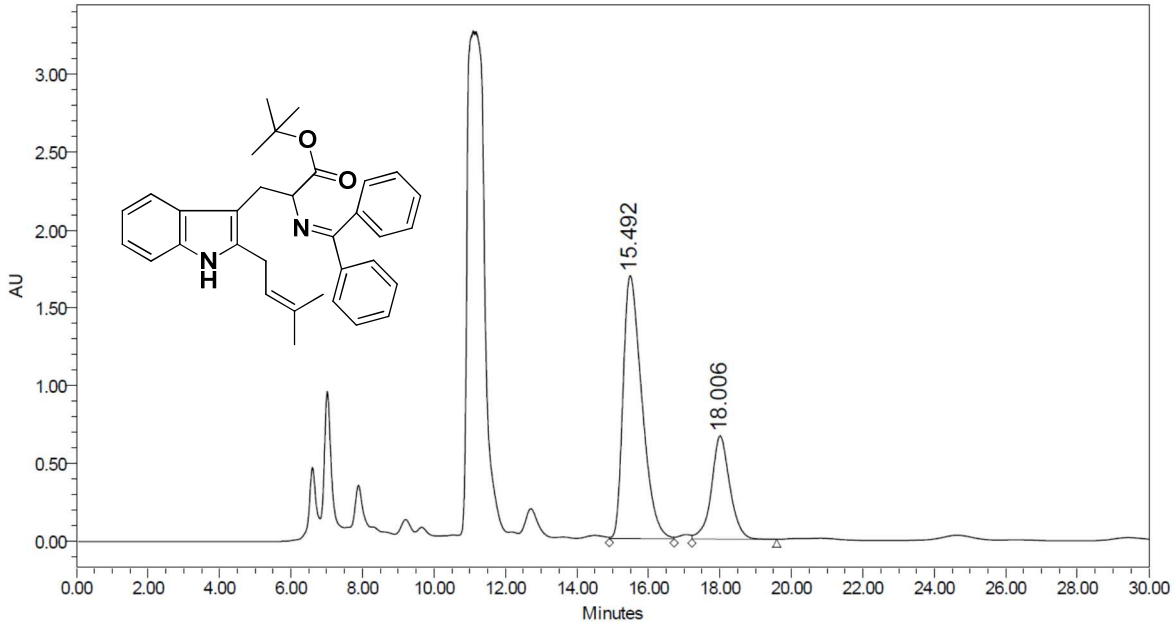

171.469
169.613
139.487
137.620
135.983
135.506
134.900
134.362
132.441
130.084
129.937
129.153
128.728
128.621
128.298
128.041
127.907
127.823
127.765
127.562
120.756
118.357
109.963
107.293
80.794
77.474
77.358
77.049
76.625
66.638
29.726
28.103
27.972
27.890
25.675
25.124
17.726
O
O
N
N
H
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Portrait 72, HPLC Traces for racemic compound 68:



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	16.263	Unknown	53358102	49.64	1159875	44.61	VV	5.336e+007	1217
2	18.113	Unknown	54132384	50.36	1439915	55.39	VB	5.413e+007	1511

Portrait 73, HPLC Traces for chiral compound 68:



	RT (min)	Peak Type	Area (µV*sec)	% Area	Height (µV)	% Height	Integration Type	Response	Points Across Peak
1	15.492	Unknown	61551025	72.34	1691099	71.91	VV	6.155e+007	1087
2	18.006	Unknown	23534168	27.66	660503	28.09	VB	2.353e+007	1421

CURRICULUM VITAE

Nazim Uddin

Place of Birth: Lakshmipur, Bangladesh

Education:

B.Sc., Department of Chemistry, University of Dhaka, Bangladesh, June 1999.

Major: Chemistry, Minor: Physics and Mathematics

M.Sc. in Chemistry, Department of Chemistry, University of Dhaka, Bangladesh, June 2001.

M.S. in Chemistry, University of Wisconsin-Milwaukee, WI 53211, USA, December 2008.

Dissertation: An investigation into the Bronsted acid catalyzed Mannich and nitro-Mannich reactions and application to the synthesis of oxazinanones derivatives.

Postgraduate Diploma in Pharmaceutical QA and QC, Toronto Institute of Pharmaceutical Technology, August 2012.

PhD. in Chemistry, Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, WI 53211, USA.

Dissertation: I. Pd (0)-catalyzed asymmetric rearrangement of allyl enol ether for the synthesis of α -aryl quaternary carbon center.

II. Synthesis of chiral tryptophan analogs and studies towards the synthesis of Tryprostatin A and B.

Research Experience:

2006-2015 Advisor: Professor M. Mahmun Hossain, Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee

- Extensive experience in multi-step large and small-scale organic synthesis, including separation, purification, and characterization of organic molecules.
- Syntheses of chiral Tryptophan analogs and total synthesis of Tryprostatins.
- Design and syntheses of asymmetric α-aryl Quaternary carbon center.
- Design and syntheses of novel organometallic catalysts.
- Design and syntheses of chiral Brønsted acids.
- Experienced in Laboratory Information Management Systems (LIMS).
- Experienced in handling air/moisture sensitive compounds.
- Practical experiences in using the following analytical equipment: HPLC, TLC, NMR, FT-IR, UV, Mass Spectroscopy, Thermal Analysis (TGA), Polarimetry, Karl- Fisher water detection, Ultrasonic water bath.
- Large scale syntheses of ethyl diazoacetate and other pybox compounds.

Teaching Experience at UW-Milwaukee:

- Teaching assistant for introductory chemistry courses in undergraduate laboratory.
- Experienced in Vernier Labquest software for undergraduate Laboratory.
- Led discussion and review classes for general, nursing and engineering chemistry.

Publications:

1. First Example of the Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of Hydroxyacrylates: Synthesis of All-Carbon α-Aryl Quaternary Aldehydes. Sharif A. Asad, Joseph Ulicki, Maria Shevyrev, Nazim Uddin, Eduardo Alberch, M. Mahmun Hossain. *Eur. J. Org. Chem.* **2014**, 26, 5695–5699.
2. One-Pot Enantioselective Synthesis of Tryptophan Derivatives via Phase-Transfer Catalytic Alkylation of Glycine Using a Cinchona-Derived Catalyst. Robert Todd, Matthew Huisman, Nazim Uddin, Sarah Oehm, M. Mahmun Hossain. *Synlett* **2012**; 23(18): 2687-2691.
3. Brønsted acid-catalyzed C–C bond forming reaction for one step synthesis of oxazinanones. Nazim Uddin, Joseph S. Ulicki, F. Holger Foersterling, M. Mahmun Hossain. *Tetrahedron Letters* **2011**, 52, 4353–4356.

4. Synthesis of compounds containing α-aryl quaternary carbon centers. Eduardo Alberch, Nazim Uddin, Maria Shevyrev, and M. Mahmun Hossain. *ARKIVOC* **2010** (iv) 139-146.

5. Synthesis of asymmetric α-aryl Quaternary Carbon center via Palladium catalyzed asymmetric allylic alkylation. Nazim Uddin, Eduardo Alberch, Sharif A. Asad, M.Mahmun Hossain. (Manuscript in preparation).

Presentations:

1. Nazim Uddin; M. Shahid Islam; Robert C.Todd; M. Mahmun Hossain. Convenient synthesis toward chiral tryptophan and its analogs. Abstracts of Papers, 233rd ACS National Meeting, Chicago, IL, United States, March 25-29, 2007.

2. Nazim Uddin; Robert C.Todd; Matthew E.Dudley ; M. Shahid Islam; M. Mahmun Hossain. Synthesis of (Z)-2-acetamido-3-(1H-indol-3-yl) acrylic acid derivatives as tryptophan precursors from relatively inexpensive 2-nitrobenzaldehydes and ethyl diazoacetate. Abstracts of Papers, 233rd ACS National Meeting, Chicago, IL, United States, March 25-29, 2007.

3. Nazim Uddin; Joe Ulicki ; M. Mahmun Hossain. Bronsted Acid Catalyzed Synthesis of Oxazinanones Derivatives. Abstracts of paper, 38th Great Lakes Regional Meeting of the American Chemical Society, Chicago, IL, United States, May 13-16 (2009).

Special Honors and Awards

- Chancellor's Graduate Student Award, University of Wisconsin-Milwaukee, 2005 to 2009.

Professional Affiliations

Member of the American Chemical Society, USA.