# ASYMMETRIC SYNTHESIS OF ALL-CARBON α-ARYL QUATERNARY CARBONYL COMPOUNDS BY PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION (Pd-AAA) AND THEIR APPLICATION TO THE SYNTHESIS OF BIOLOGICALLY IMPORTANT 3,3′-DISUBSTITUTED OXINDOLE AND α-DISUBSTITUTED QUATERNARY β-LACTONE FRAMEWORKS

by

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ABSTRACT

ASYMMETRIC SYNTHESIS OF ALL-CARBON α-ARYL QUATERNARY CARBONYL COMPOUNDS BY PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION (PA-AAA) AND THEIR APPLICATION TO THE SYNTHESIS OF BIOLOGICALLY IMPORTANT 3,3′-DISUBSTITUTED OXINDOLE AND α-DISUBSTITUTED QUATERNARY β-LACTONE FRAMEWORKS

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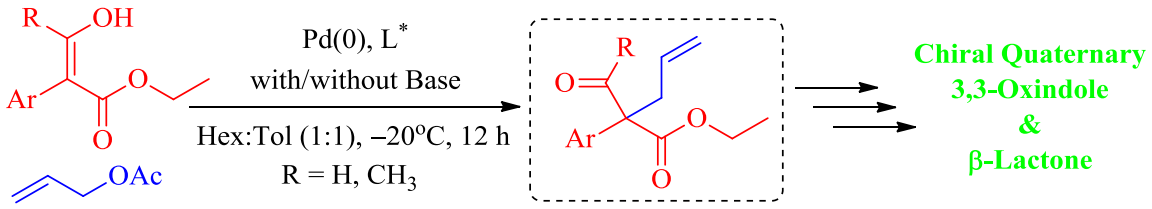
Md. Sharif A. Asad

The University of Wisconsin-Milwaukee, 2015
Under the Supervision of Professor M. Mahmun Hossain.

The development of catalytic, enantioselective methods for the construction of all-carbon quaternary stereocenters is an outstanding achievement in the recent history of organic chemistry. The palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reaction has played a key role in creating such stereocenters and has allowed researchers to synthesize a vast number of biologically potent natural products. However, synthetic methodologies to access compounds containing α-aryl groups to the quaternary carbon stereocenters are still rare. The increasing appearance of these all-carbon α-aryl quaternary stereocenters in a growing number of biologically active natural products and pharmaceutical agents creates a pressing need for the ability to construct this important motif enantioselectively. In this endeavor, a set of acyclic all-carbon α-aryl quaternary stereocenter has been synthesized *via* intermolecular Palladium catalyzed Asymmetric Allylic Alkylation (Pd-AAA). Here hydroxyacrylate was used as an unprecedented nucleophilic counterpart instead of the widely used ketonic substrate. This produced a very rare all-carbon

quaternary aldehydes with good to excellent yields (75–99%) and enantioselectivities ranges between 75–94%. This methodology is not only limited to produce aldehydes, as an analogous ketone with a quaternary α-carbon center has also been synthesized successfully.




Using this methodology, chiral 3,3′-disubstituted oxindole moiety was produced with high yield (80%) and enantioselectivity (82%) from *o*-nitrophenylhydroxyacrylate in three simple steps. The oxindole framework bearing a tetrasubstituted carbon stereocenter at 3-position is a privileged heterocyclic motif that constructs the core of a large family of bioactive natural products and a series of pharmaceutically active compounds. An intensive research has been conducted to synthesize 3,3′-disubstituted oxindole which resulted in a fair amount of methods to produce such an important moiety. However, to the best of our knowledge, all of the reported methodologies so far have used pre-formed oxindole ring itself or a highly specialized compound as a prochiral starting material to produce asymmetry. Another application of this method includes the synthesis of chiral α-disubstituted quaternary β-lactone from the parent phenylhydroxyacrylate in high yield (87%) and enantioselectivity (94%). β-lactones have recently emerged as important synthetic targets due to their occurrence in a variety of natural products, their utility as versatile synthetic intermediates, and their use as monomers for the preparation of biodegradable polymers.

To

my dear departed

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# CHAPTER 1: ORGANOCATALYTIC FORMATION OF ALL-CARBON QUATERNARY STEREOCENTERS

## 1.1. Introduction

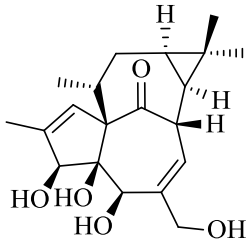
### 1.1.1. Importance of quaternary stereocenters and asymmetric catalysis

"*The construction of chiral tetrasubstituted carbon stereocenters, especially quaternary stereocenters, is one of the most important and difficult tasks in asymmetric catalysis*."[1]

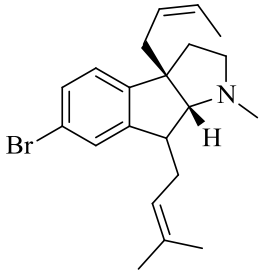
-Dr. Masakatsu Shibasaki

All-carbon quaternary stereocenters is extremely difficult to synthesize due to the inherent steric repulsion associated with the presence of four different carbon substituents on the same carbon atom (quaternary carbon) in the formation of these stereocenters. Owing to steric hindrance, relatively harsh reaction conditions are required and only limited combinations of nucleophiles and electrophiles can be employed. Despite extensive research in this area, the number of methods available for the construction of all carbon quaternary stereocenters is still limited and demand further investigation. Recent reviews have highlighted important contributions in this area of research.[2,3,4,5,6] Moreover, the development of methodologies for the asymmetric synthesis of quaternary stereocenters has attracted a huge attention to the scientific community, much of which is due to their ubiquitous presence in a series of bioactive natural products and pharmaceutically active compounds (Figure 1).[7,8,9]

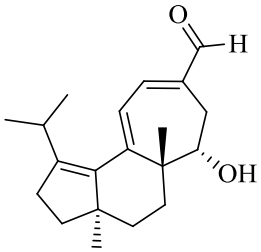
**Figure 1.** Natural products bearing chiral quaternary carbons.



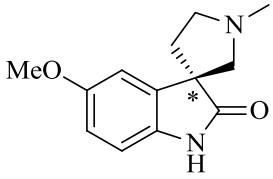

Ingenol
(Anti-leukemic agent)



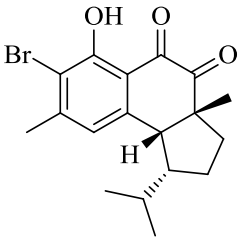

(-)-Flustramine B
(Potassium channel blocker)



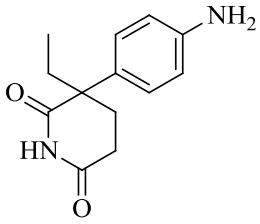

(+)-Allocyathin B2



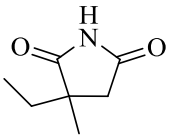

(-)-Horsfiline
(Analgesic properties)




(-)-Hamigeran B




Aminoglutethimide
(Aromatase inhibitor)




Ethosuximide
(Anticonvulsant)

Two enantiomers of a molecule can have drastically different biochemical effects in biological systems, and even in some cases, while one enantiomer has therapeutic properties, the opposite enantiomer can be highly toxic. Therefore there is an obvious interest to synthesize one enantiomer over other, i.e., chiral molecules, via an asymmetric route. As a result, remarkable progress has been achieved in the area of asymmetric catalysis, especially in last thirty years. Among the various techniques for creating quaternary stereocenters in an enantioselective fashion, employing catalyst as chiral inducing agent is the method of choice for several reasons: 1) it avoids the use of chiral auxiliaries which need to be added in stoichiometric amount and thereby costly; 2) high

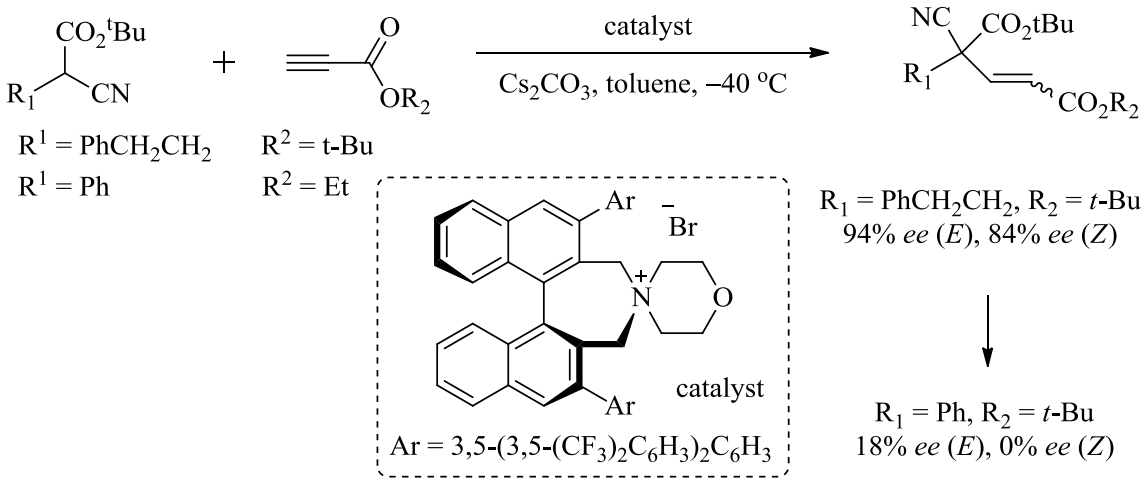
amounts of enantioselectivity can often be achieved with very little amount of catalyst; 3) milder reaction conditions are attainable by the introduction of correct catalyst; and 4) the substrate scope is often much greater in compare with enzyme catalysis, and both enantiomers of a molecule can be created merely by switching the chirality of the catalyst being employed.

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

Without employing a catalyst, conditions of a reaction to form quaternary stereocenters are usually quite harsh involving high temperatures and long reaction times. This is costly for an industrial-scale production. Moreover, increased reaction temperatures usually adversely affect the stereoselectivity of a reaction. Catalysts, either organo or metal complexes, can overcome these difficulties by allowing much milder reaction conditions, such as low temperature, which has the added benefit of often improving the stereoselectivity of a reaction significantly.

All reactions have certain limitations in their substrate scope. As an example, an $S_N2$ reaction with a prochiral tertiary carbon nucleophile is possible with a carbon electrophile, only if there is a primary carbon at the electrophilic position. The same reaction could not take place with an electrophile having a tertiary carbon. In the case of asymmetric synthesis, these limitations in substrate scope are particularly evident. Minor changes in the structure of a substrate can lead to profound changes in stereoselectivity,

the worst case being the loss of stereocontrol. These limitations are common to almost all catalytic asymmetric reactions. For example[10] (Scheme 1) nearly complete loss of stereoinduction was observed for α,β-unsaturated products when small modifications were made in asymmetric Michael reaction substrates. When the alkyl group of the Michael donor is changed from phenethyl to phenyl, the *ee* changes from 94% to 18% in the case of the (*E*) stereoisomer and from 84% to 0% in the case of the (*Z*)-stereoisomer of the Michael product. Unfortunately, often authors fail to report reasons of these limitations in the scope of substrates. Striking changes in stereoselectivity can also be observed by subtle changes in the catalyst structure. Choices of solvents as well as temperature of the reaction also have significant impact on the stereoselectivity. Considering these factors, a thorough screening of reaction conditions has to be carried out to optimize stereoselectivity and yield. Usually asymmetric catalysis leads to satisfactory results for only a few substrates and other conditions may need to be screened for other analogs for the same reaction.




**Scheme 1:** Striking effect in stereocontrol with subtle changes in structure.

### 1.1.3. General reaction classes to construct quaternary stereocenters

Catalytic asymmetric methods for the synthesis of quaternary stereocenters can be devided into three main categories: organocatalysis (the use of organic molecules as catalysts), chiral metal-Lewis acid catalysis and transition-metal catalysis. Lewis acid catalyzed asymmetric construction of quaternary stereocenters has been successfully achieved for the following reaction classes: Diels-Alder reactions, 1,3-dipolar [3+2] cycloadditions, the synthesis of β-lactams via overall [2+2] cycloadditions, cyclopropanations, 1,4 conjugate additions (Michael additions), the alkylation of tributyl tin enolates, Michael additions with hard nucleophiles, copper catalyzed $S_N2'$ allylation, reactions with carbonyl and imine electrophiles, metal catalyzed diene and enyne cyclizations, and Claisen rearrangements. Transition-metal catalyzed reactions that take place via oxidative addition-reductive elimination processes include, but is not limited to

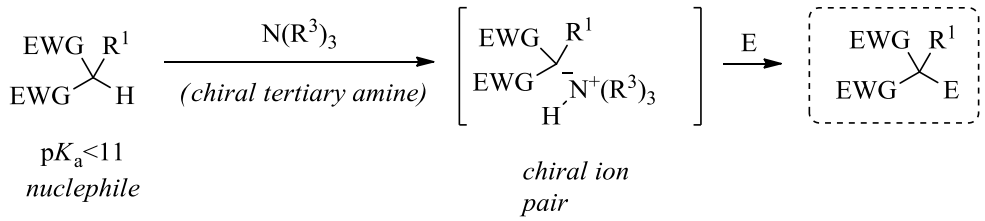
α-arylation and vinylation reactions of ketones and lactones, intramolecular Heck reactions, C-H insertions and allylation via palladium π-allyl intermediates.

A thorough literature survey reveals that the majority of methods involving the construction of quaternary stereocenters used cyclic substrates. As an example, in the review by Marco Bella[4] on the organocatalytic formation of quaternary stereocenters, only six out of a total of twenty-eight examples of Michael adducts bearing quaternary stereocenters are with acyclic substrates. For other reaction classes[3,11] (such as the asymmetric allylic alkylation), the use of acyclic substrates is, in some cases, non-existent. The challenge of attaining expected enantiodiscrimination associated with an increased numbers of degrees of freedom in regards to acyclic substrates is attributed to this finding.[5]

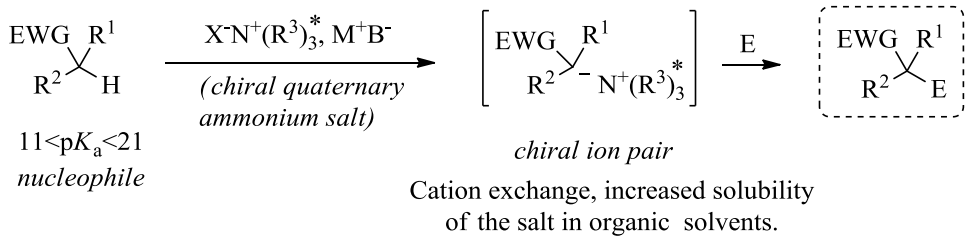
### 1.1.4. General mechanisms of activation for formation of quaternary stereocenters via organocatalysis

A general classification of the reaction classes used in organocatalysis shows that two general approaches are feasible: nucleophilic activation (Scheme 2; i-iii) and electrophilic activation (Scheme 3; iv and v).

**i) Via tertiary amine:**

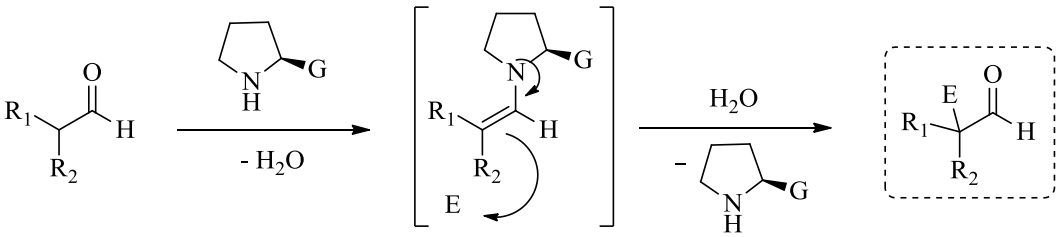



**ii) Via inorganic base-quaternary ammonium salt:**




Cation exchange, increased solubility
of the salt in organic solvents.

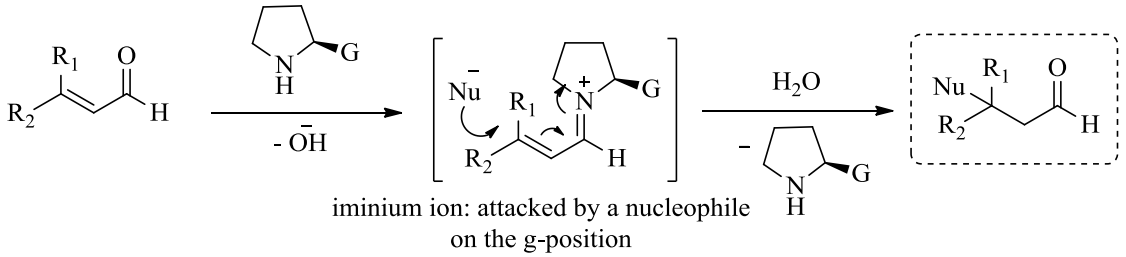
**iii) Via enamine:**



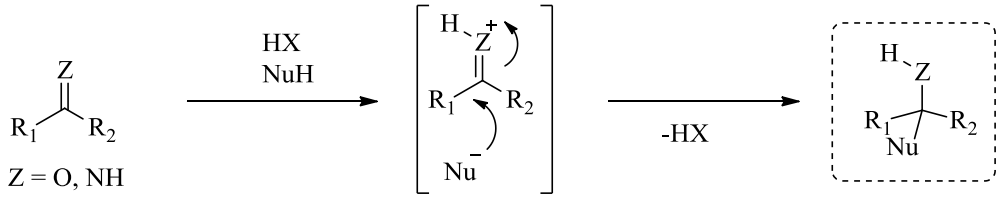

enamine adds to
an electrophile in the b-position

**Scheme 2.** Organocatalytic nucleophilic activation.

**iv) Via iminium ion:**




**v) Via Brønsted acid:**



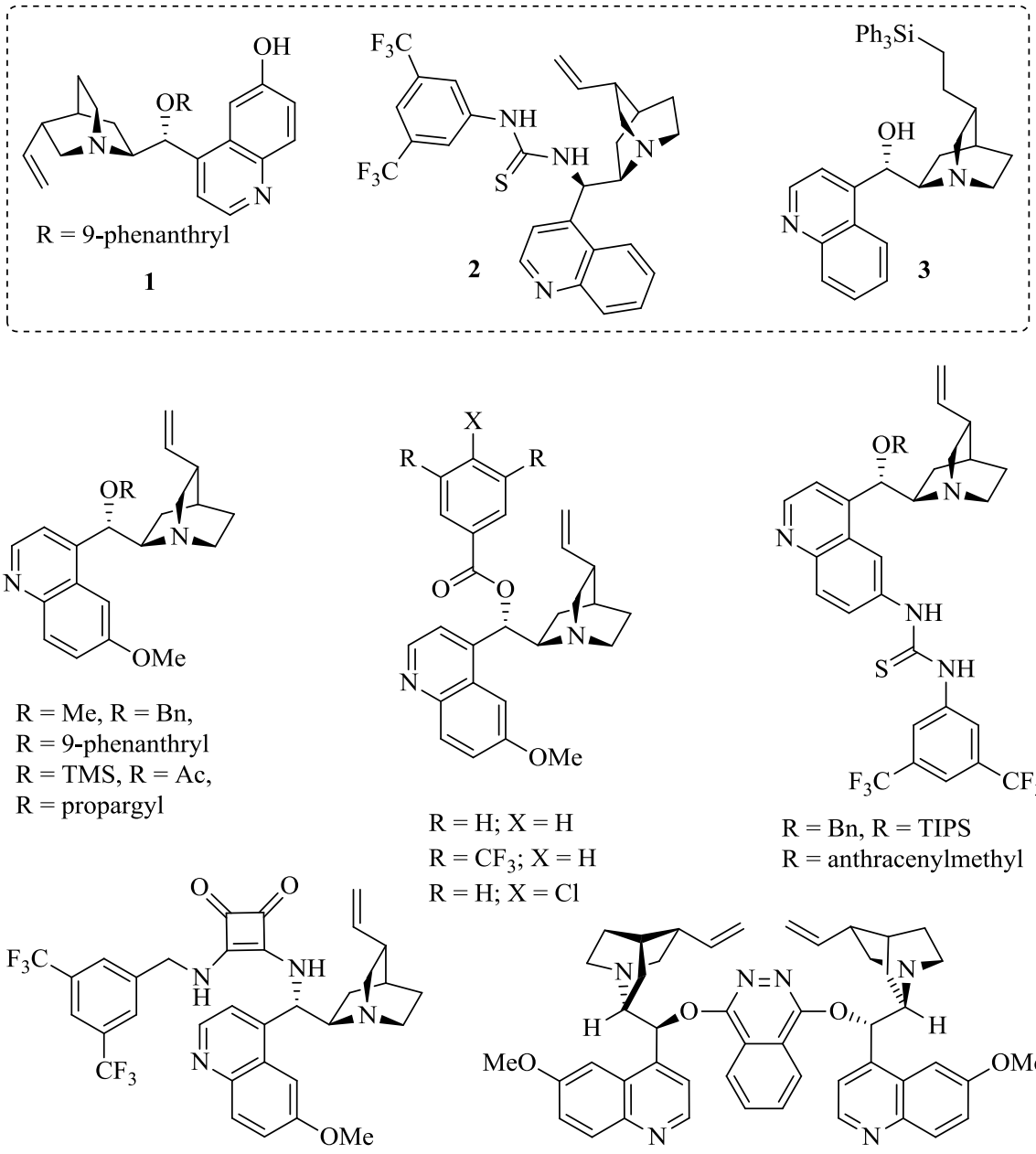

**Scheme 3.** Organocatalytic electrophilic activation.

Activation of the nucleophile can occur in various ways:

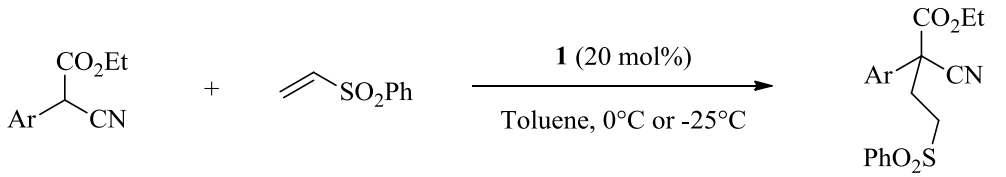
(i) Tertiary amines

Tertiary amines are able to deprotonate nucleophiles with a $pK_a$ < 10-11 exceptionally well. Upon deprotonation, a tight ion pair is formed between the conjugate base of the acid (typically an enolate) and the quaternary ammonium cation. In case a chiral tertiary amine, usually based on an alkaloid scaffold[12] is used, the formed nucleophile, usually an ion-paired salt, can attack the electrophile from the less hindered face (Scheme 4).[13,14,15] A number of catalysts employed recently involve transformations mostly at C-9 or C-6′ positions (Figure 2). The hydrogen bonding to a carbonyl group plays a crucial role to position and activate the electrophile by demethylating C-6′ position of the catalyst.

**Figure 2.** Cinchona alkaloid based catalysts.



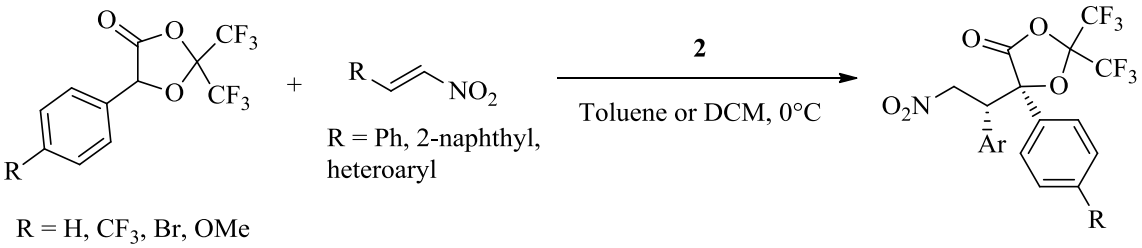
**Michael addition to vinyl sulfones:**




Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$FC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, 3-$ClC_6H_4$, 2-naphthyl, 2-thienyl

93-97% ee
86-98% yield

**Michael addition to b-nitrostyrene:**

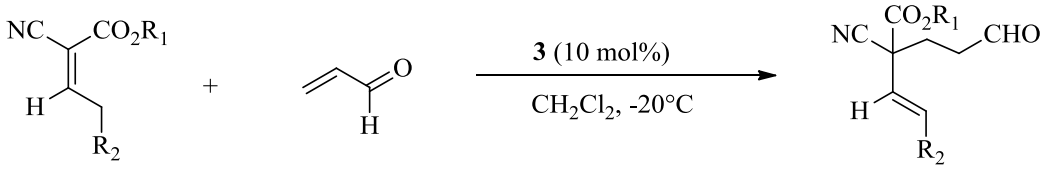



R = H, $CF_3$, Br, OMe

R = Ph, 2-naphthyl, heteroaryl

60-89% ee
>98:2 dr
65-88% yield

**Deconjugative Michael addition:**




$R^1$ = Me, *i*Pr, Bn
$R^2$ = Me, Et, *n*-Hex, allyl
*i*Pr, *t*-Bu, Bn

40-56% ee
39-50% yield

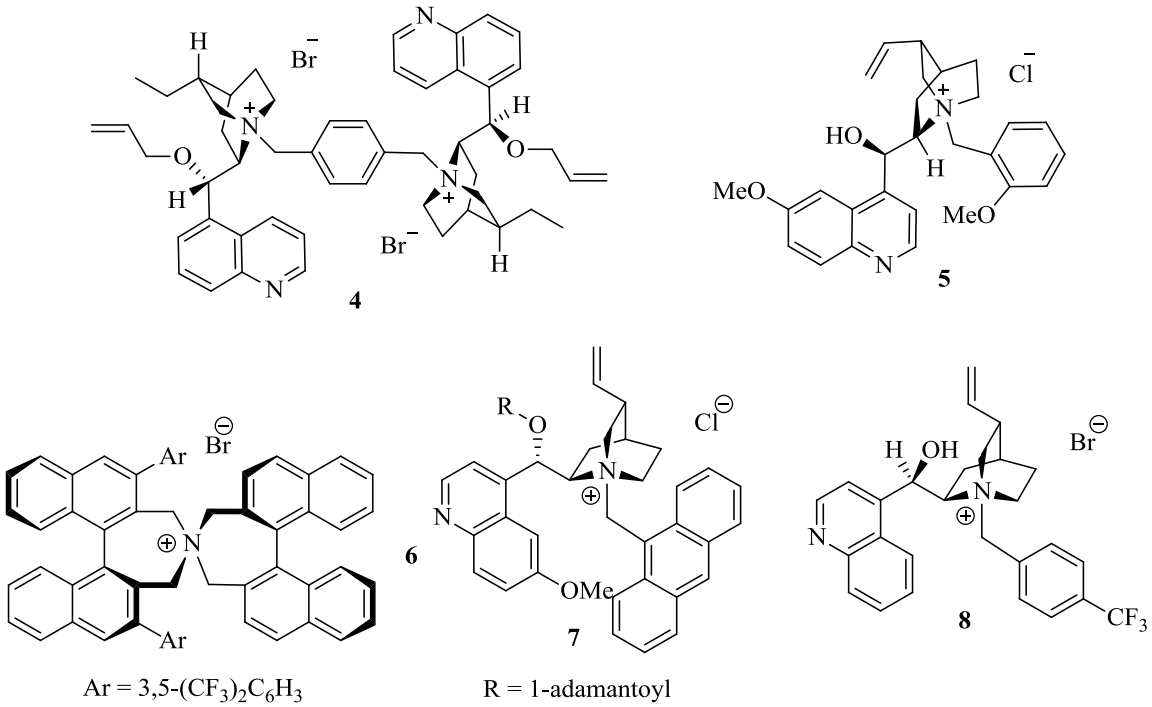
**Scheme 4.** Organocatalytic Michael additions using cinchona alkaloid catalysts.

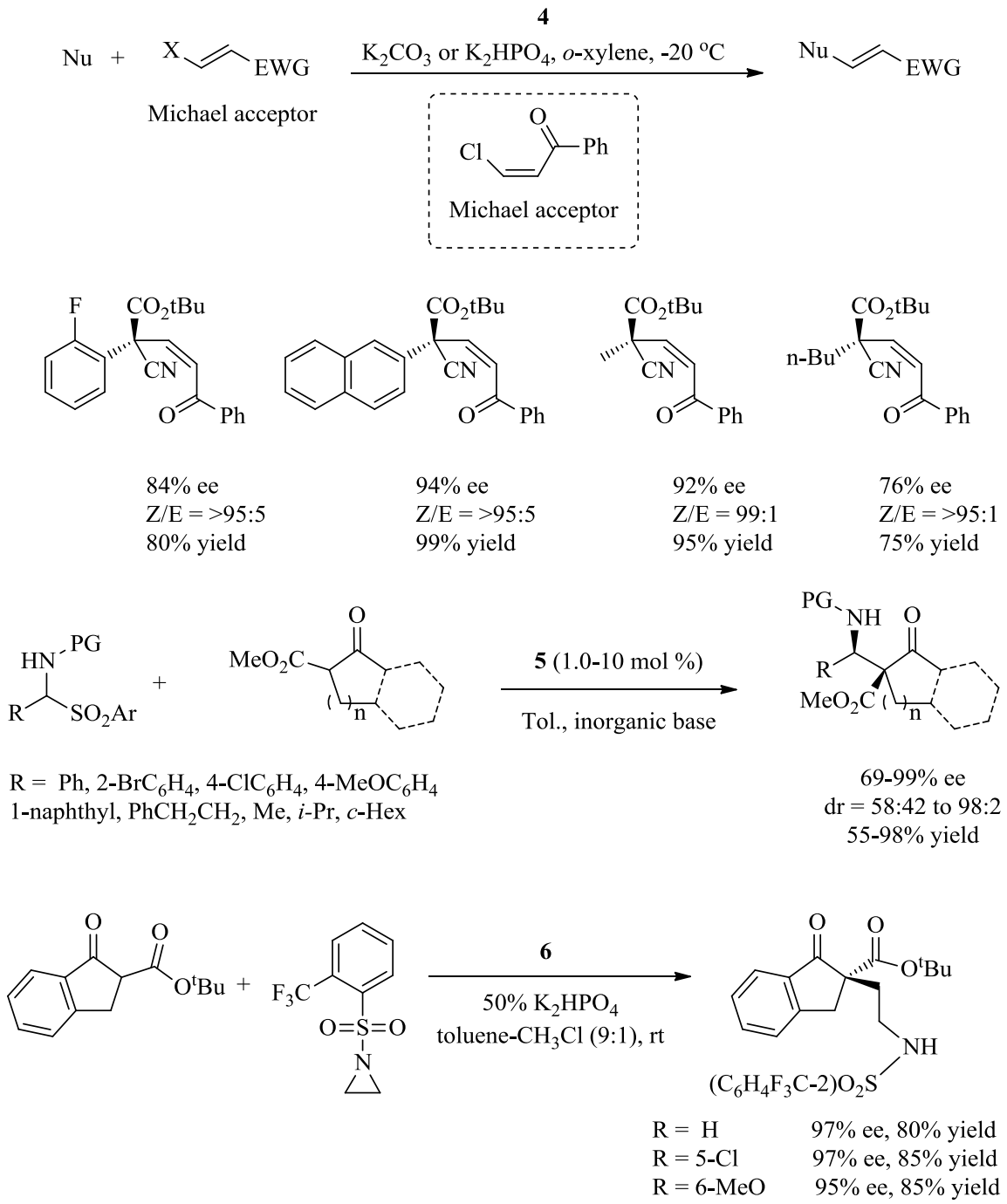
(ii) Inorganic bases and quaternary ammonium salts[16]

Nucleophiles with $pK_a$ values < 22 can be deprotonated by inorganic bases (either aqueous solutions or in solid form). Once a base deprotonates the nucleophile, an ion

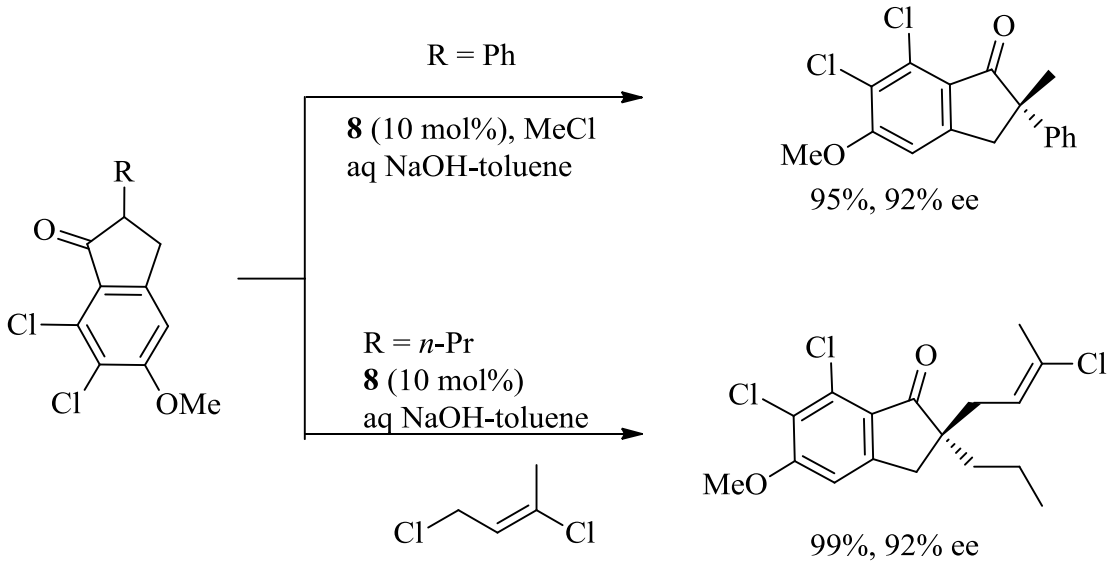
exchange takes place between the counter ion of the inorganic base and the chiral quaternary ammonium ion and thus, this chiral ion becomes the counterion of the activated nucleophile, leading to the nucleophile having much greater solubility in organic solvents and instills chiral induction to the product. Similar to approach (i), the nucleophile forms a tight ion pair with the chiral counterion, thus allowing for one face of the nucleophile to be blocked from attack by the electrophile (Scheme 5).[17,18,19] The quaternary ammonium salts employed are usually obtained from cinchona alkaloids or from axially chiral quaternary ammonium salts (Figure 3).[20] This approach has been used successfully for the asymmetric alkylation of cyclic ketones[21] (Scheme 6) and cyclic β-keto esters[22] (Scheme 7).

**Figure 3.** Chiral phase transfer catalysts.

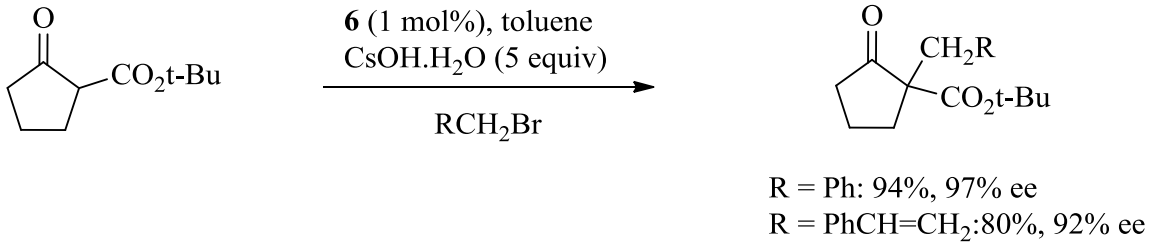





**Scheme 5.** Organocatalytic reactions with chiral phase transfer catalysts.




**Scheme 6.** Alkylation of indanones catalyzed by chiral phase transfer catalysts.



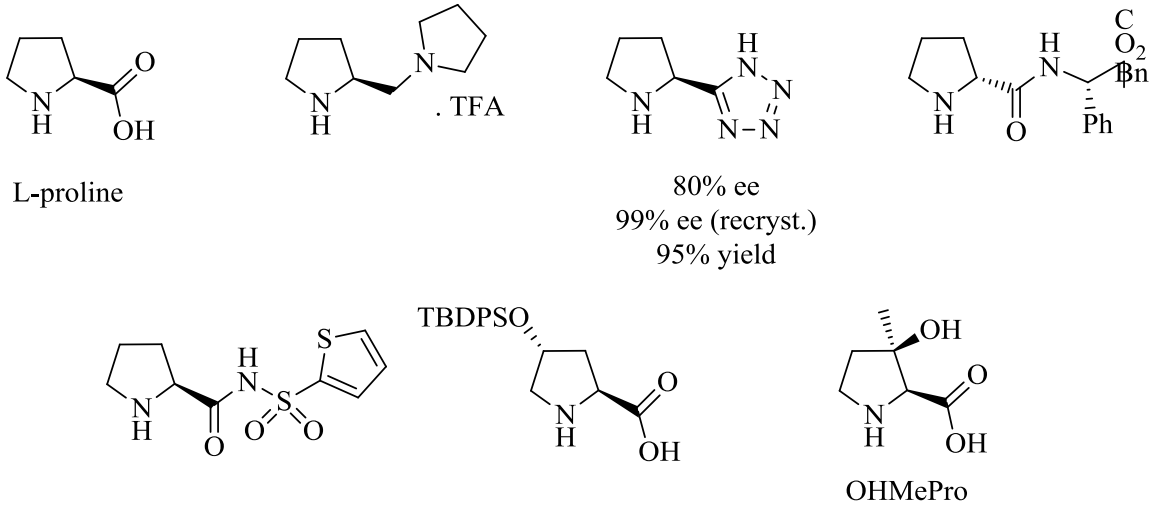

**Scheme 7.** Alkylation of β-keto esters by $C_2$ symmetric chiral phase transfer catalyst.

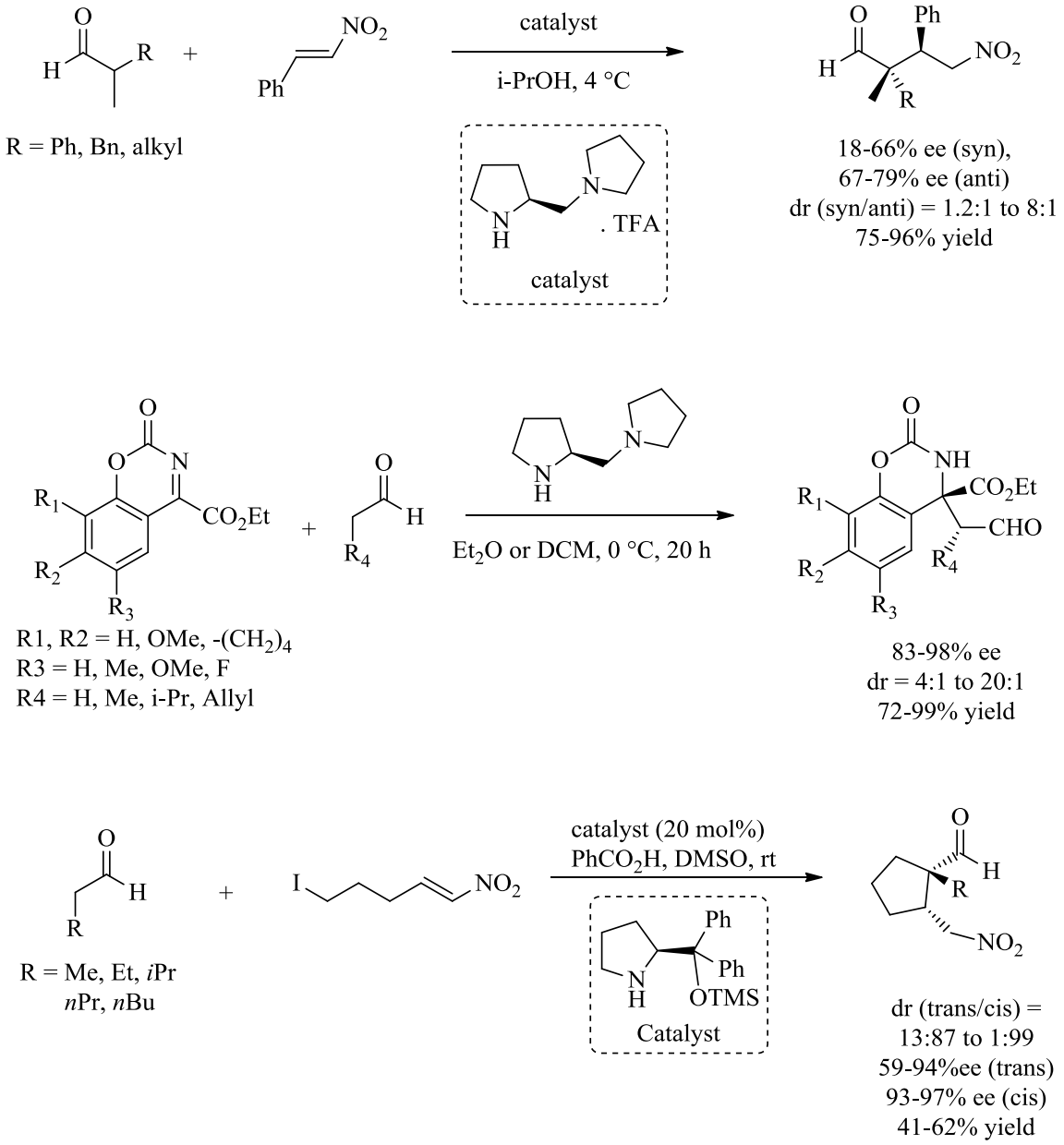
(iii) Enamine activation of aldehydes with primary or secondary amines

Aldehydes are usually activated by the formation of enamines from analogous pyrrolidine or proline catalysts or from primary amines (Scheme 8[23,24,25],Figure 4). Enamines derived from ketones are comparatively weaker nucleophiles and have not been used so far for

the asymmetric formation of quaternary stereocenters. Aldehydes with doubly substitution at the terminal position of the enamine are weak nucleophiles as well and require very strong electrophiles for the reaction.

**Figure 4.** Proline based catalysts.






**Scheme 8.** Organocatalytic Michael addition of aldehydes via enamine catalysis.

The most common methods for *electrophilic* activation are discussed below (Scheme 3):

(iv) Formation of iminium ions of α,β-unsaturated carbonyl compounds

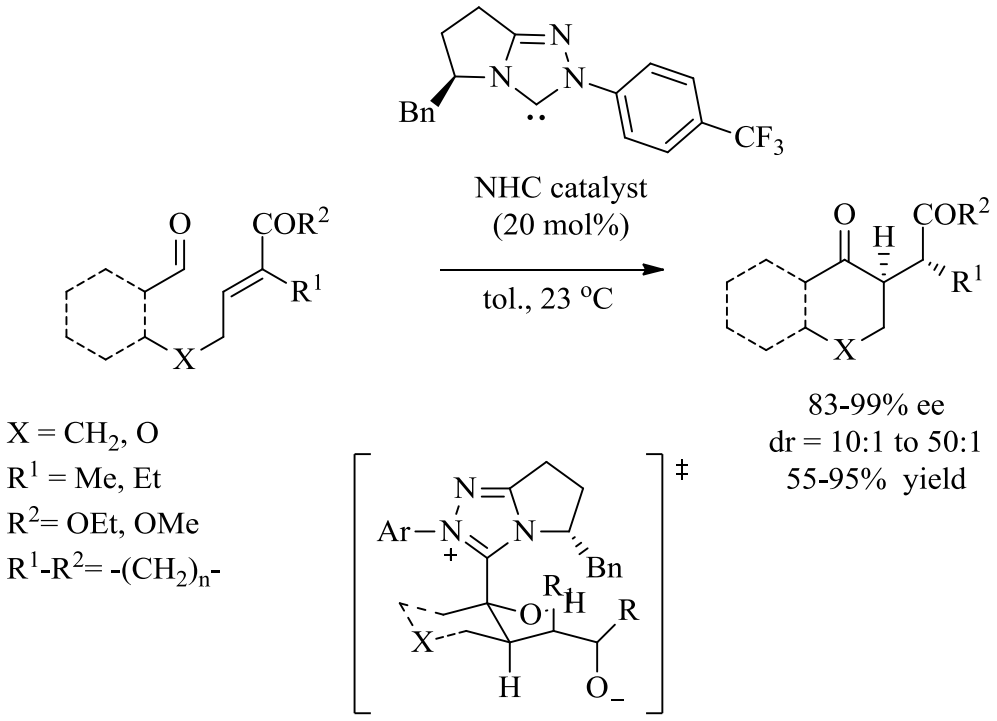
By employing a secondary amine (occasionally primary amines are also used), an α,β-unsaturated carbonyl compound can be converted to an iminium ion and thereby, activated for nucleophilc attack. In an iminium ion of an α,β-unsaturated carbonyl compound, the β-position is more electron deficient and therefore more susceptible to nucleophilic attack. So far, no examples have been reported in the literature for this approach. However, a dienophile has been successfully activated by a secondary amine catalyst for the Diels-Alder reaction, and various examples were found in the literature involving this approach.[26]

(v) Activation by Brønsted acids

Even though limited, axially chiral phosphoric acid has been used successfully as a catalyst to activate a ketone or an imine for nucleophilic attack. This approach is less reported in the literature in comparison to approaches i-iv due to the somewhat limited scope of substrates that have been proven to be successful thus far. However, the quaternary centers formed with ketones or imines by this approach provided comparatively high yields and satisfactory enantiomeric excesses. [27]

(vi) Activation via N-heterocyclic carbenes (NHC)

An NHC can act as a nucleophilic catalyst and activates a ketone or aldehyde by attacking the carbonyl carbon. The Stetter reaction has often been used in this approach (Scheme 9).[28]




**Scheme 9.** Catalytic intramolecular Stetter reaction.

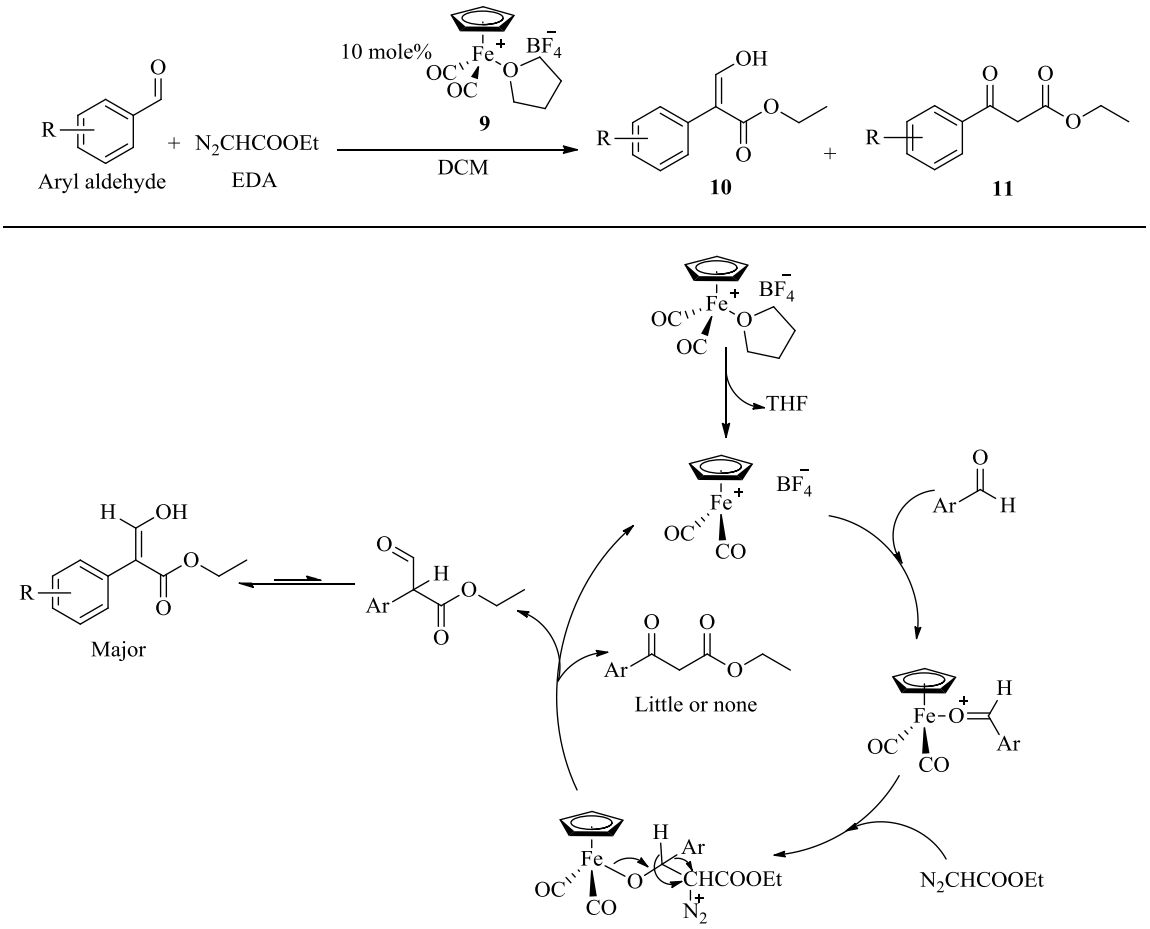
(vii) Mixed activation

A dual organocatalytic system has recently been employed successfully to counter reduced reactivity in some substrates, such as the reaction of di-substituted α-aryl

aldehydes to enones. It was found that the proline by itself did not catalyze the reaction. However, when a quinine based catalyst was introduced along with a proline catalyst to deprotonate the carboxylic acid proton in proline, the reactivity was dramatically enhanced.[29]

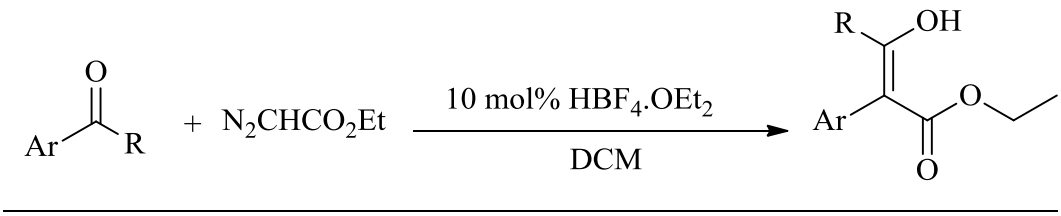
## 1.2. 3-Hydroxy aryl acrylates **10** and their potential utilities in synthetic transformations

The Hossain group, in 1998, reported the formation of 3-hydroxy aryl acrylates **10** via an unprecedented [1,2]-aryl shift, when aromatic aldehydes and EDA (ethyl diazoacetate) was allowed to react in the presence of an iron Lewis acid catalyst, [$\eta^5$-$(C_5H_5)Fe(CO)_2(THF)]BF_4$ **9** (Scheme 10). As a side reaction, it also produced very little or sometimes none of the β-keto esters **11** via a [1,2]-hydride shift.[30] The yield of 3-hydroxy acrylates **10** diminished with a resultant increase in the undesired β-keto ester **11** with electron poor aldehydes due to the increased difficulty of achieving the necessary [1,2]-aryl shift.




**Scheme 10.** Reaction and mechanism of arylaldehydes with EDA in the presence of catalyst **9**.

The same group, in 2004, reported that Brønsted acids such as $HBF_4 \cdot OEt_2$ are also able to effectively catalyze the same reaction with aromatic aldehydes as well as ketones (Scheme 11).[31] Again it was proved that the use of electron deficient aromatic aldehydes has a detrimental effect on the yield of the desired 3-hydroxy aryl acrylates formation.

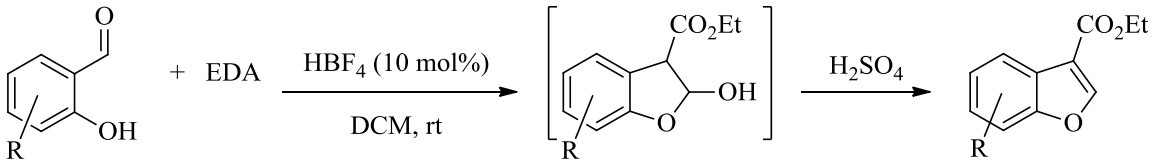



Ar = Ph, R = H, 74%
Ar = *p*-$CH_3$Ph, R = H, 67%
Ar = *p*-$OCH_3$Ph, R = H, 90%
Ar = *p*-BrPh, R = H, 62%
Ar = *p*-FPh, R = H, 60%

Ar = *o*-$NO_2$Ph, R = H, 45%
Ar = *p*-$NO_2$Ph, R = H, 35%
Ar = 2-Furyl, R = H, 70%
Ar = 2-Naphthyl, R = H, 61%
Ar = Ph, R = Me, 74%

**Scheme 11.** $HBF_4$ catalyzed reaction of aromatic aldehydes or ketones with EDA.

As a continuation, synthesis of 3-ethoxycarbonylbenzofuran analogs from 2-hydroxybenzaldehyde derivatives and ethyl diazoacetate was reported.[32] The final benzofuran product was isolated after the acid dehydration of the intermediate hemiacetal formed *in situ* (Scheme 12).

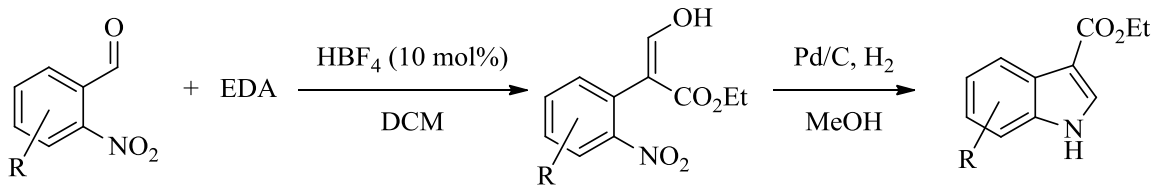



R = 5-chloro, 3,5-dichloro, 3-methoxysalicyladehyde, 3-hydroxy-2-napthaldehyde

**Scheme 12.** Formation of benzofurans via an *in situ* formed hemiacetal.

The versatility of the 3-hydroxyaryl acrylates to make heterocyclic aromatic compounds was further demonstrated by the same group in the synthesis of indoles employing

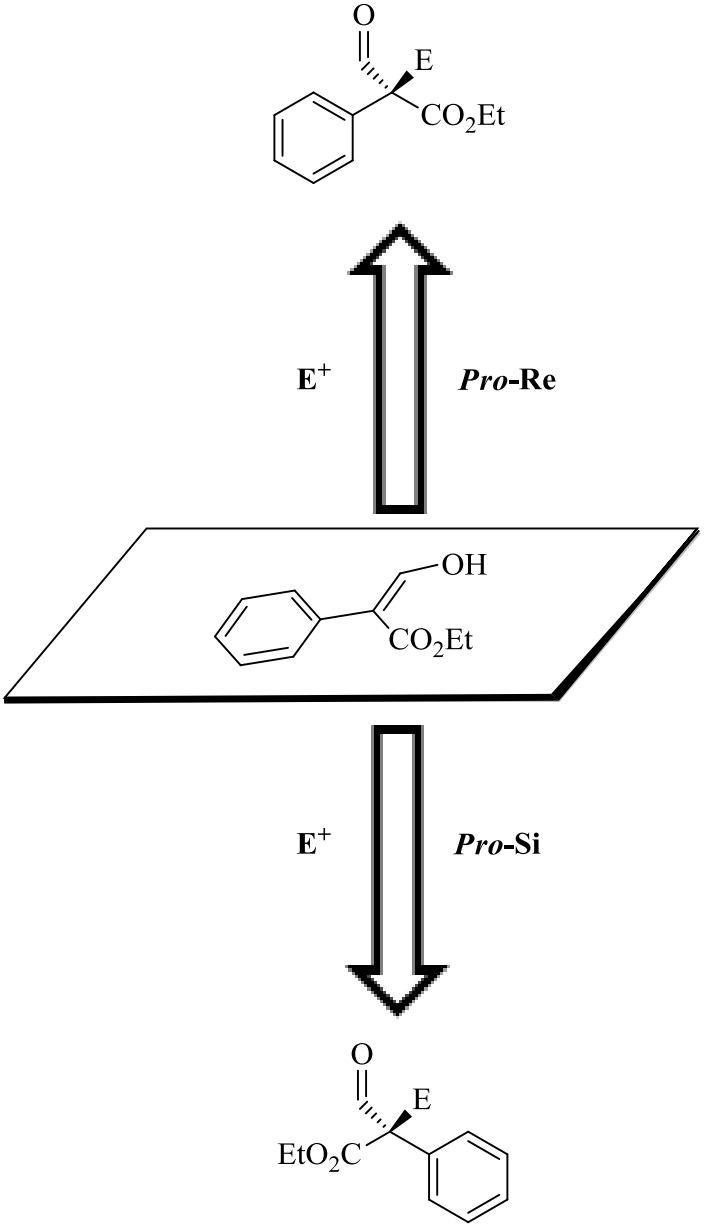
substituted *O*-nitroarylaldehydes to the $HBF_4$ catalyzed reaction and the subsequent reduction closes the ring to form the desired indole products (Scheme 13).[33]




**Scheme 13.** Formation of indoles via a one pot reductive ring closing.

It has become quite clear in this point that the usefulness of 3-hydroxy aryl acrylates can be extended further due to the presence of prochiral α-carbon with double substitution which makes it a suitable candidate to construct all-carbon quaternary stereocenter. Due to the previously mentioned importance of quaternary stereocenters in various bioactive natural products and pharmaceutically active compounds, and the enormous current attention for their synthesis via asymmetric catalytic routes, 3-hydroxy aryl acrylates became an obvious substrate choice to pursue this goal. The reaction of 3-hydroxy aryl acrylates with an appropriate electrophile would yield one of possible stereoisomers with all carbon quaternary stereocenters, depending on whether the electrophile approaches from the *Re* or *Si* faces. Therefore, the reaction should be more favorable towards one over the other two prochiral faces due to effectively blocking the unreactive face by the chiral catalyst (Figure 5).

**Figure 5.** Formation of quaternary stereocenters via 3-hydroxy aryl acrylates.




An aldehyde bearing a quaternary carbon center will be generated from such reaction of 3-hydroxy aryl acrylate with an electrophile, which is far less common in the literature than the corresponding ketones bearing α-quaternary carbon centers.

1.2.1. Development of a convenient work-up method of the synthesis of 3-hydroxy aryl acrylates **10**

Due to the reversible nature of the reaction, there is always unreacted arylaldehydes left in the reaction mixture along with the desired 3-hydroxy acrylates **10** and undesired β-keto esters **11**. This mixture of compounds in the crude reaction mixture makes the separation of the desired product difficult by column chromatography, especially due to fact that the $R_f$ values of **10** and starting arylaldehydes are almost identical. Thus, both of these compounds elute together in most cases, even when 100% hexane is employed. An alternate methodology to isolate the desired acrylates was needed.

By being acidic due to the extended conjugation in 3-hydroxy acrylates **10**, it can be easily converted to salts employing simple bases, i.e. $Et_3N$, by stirring the acrylate with $Et_3N$ in DCM for 5 mins. When the pH indicating paper shows that the solution is basic, it was passed through a thick pad of silica gel. The salt of acrylate stays at the top of silica gel and is easy to see due to the distinct brown color. After passing enough DCM through the silica plug to elute out excess arylaldehydes and undesired β-keto esters, the salt can be scraped out along with silica, stir to produce thick slurry in DCM and then treat with acid followed by extraction with DCM provides desired 3-hydroxy acrylates in pure form.

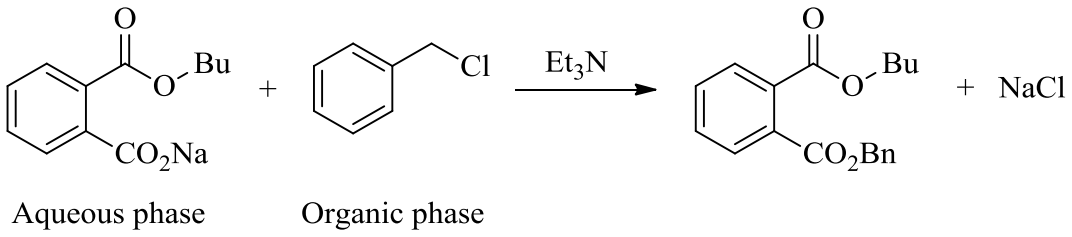
## 1.3. 3-Hydroxy aryl acrylates **10** as prochiral nucleophiles for organocatalytic asymmetric alkylation

### 1.3.1. Phase transfer catalysis (PTC): general concepts and mechanisms of action

The alkylation of aldehydes in α-carbon by organocatalysis is a fairly under explored area of research and none of the research has been reported to achieve a methodology that would be broadly applicable to a wide range of electrophiles. Currently employed methodologies to achieve this goal are: the amino-catalytic concept exploited by MacMillan et al. based on radical intermediates, using a combination of photoredox catalysis and amine catalysis and the use of electrophiles with highly stabilized carbenium ions such as: 3-substituted indoles or the use of benzylic carbocations, stabilized isolable carbenium ions.[34] A methodology with a much broader substrate scopes is highly desirable. Hence, we were interested to see whether the phase-transfer catalyzed alkylation is achievable to overcome these challeges. Theoretically, such a methodology should allow a much broader scope of electrophiles, and thereby might able to be deemed as a truly versatile method for the α-alkylation of aldehydes.

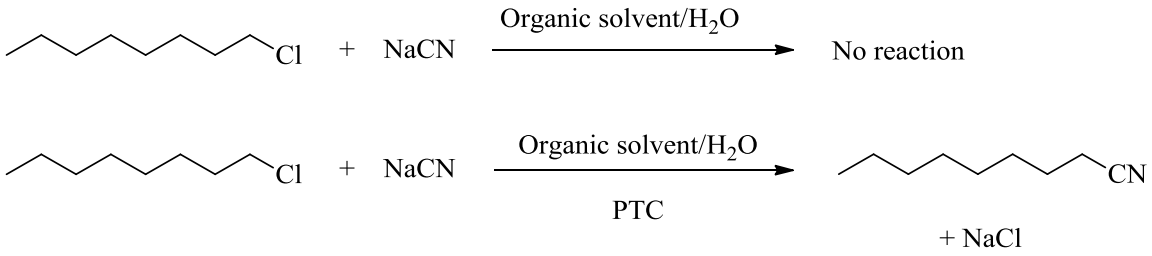
In order to achieve the successful alkylation of 3-hydroxy aryl acrylates **10**, a basic understanding of the processes underlying the phase transfer catalyzed reaction is required.

The first clear-cut example of a phase transfer catalyzed reaction was reported on the alkylation of a sodium carboxylate salt in 1946. Benzyltriethylammonium chloride, the phase transfer catalyst employed, is formed in situ by the reaction of triethylamine with benzyl chloride (Scheme 14).[35]



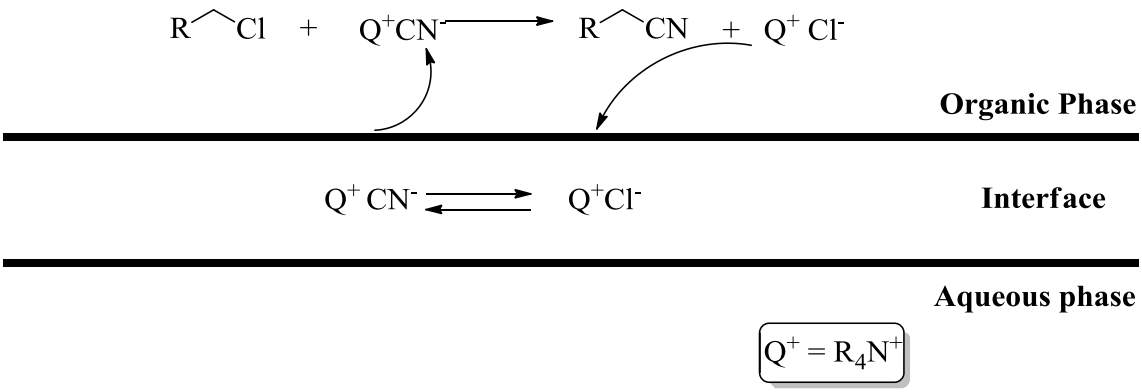

**Scheme 14.** First report of a true example of phase transfer catalysis.

However, the term *phase transfer catalysis* was first coined by Starks in 1971[36] where he described the dramatic increase in the rate of reaction between an organic solution of an alkyl halide and an inorganic solution of sodium cyanide when tetralkyammonium or tetralkylphosphonium was employed as catalyst (Scheme 15).




**Scheme 15.** Examples reported by Starks of phase transfer catalyzed reactions.

**Figure 6.** Mechanism for halide displacement by cyanide ion catalyzed by PTC.




Due to the insolubility of NaCN in the organic phase, the reaction is unable to proceed without the help from a phase transfer catalyst. Therefore, the phase transfer catalyst acts as a vehicle to carry the nucleophilic cyanide ion from aqueous phase to organic phase through ion exchange with the phase transfer catalyst at the interface. From there, the new ion pair ($Q^+CN^-$) which contains nucleophilic $CN^-$ travels to the organic phase to react with the electrophile (Figure 6). If the reaction in organic phase is rate determining (in the above example the reaction between cyanide and octyl bromide), the mechanism is known as the extraction mechanism. If the transfer of the nucleophile from aqueous phase to organic phase via the aid of the phase transfer catalyst (the transfer step) is rate determining, the mechanism is known as the interfacial mechanism.

Factors affecting the rate of transfer of ions into the organic phase from aquous phase include:

a) Interfacial tension: An increase in the interfacial tension results in a decrease of the interfacial area, which, in turns, lowers the rate at which ions can be shuttled from the aqueous into the organic phases. Highly concentrated solutions and non-polar solvents result in a decrease of the interfacial area due to an increased interfacial tension.

b) Stirring: The formation of tiny droplets resulting from high stirring speeds can greatly increase the interfacial area leading to enhanced reaction rates.

c) Nature of the counter anion of the phase transfer catalyst: Large anions that are weakly hydrated such as perchlorate and iodide allow easier access to the interface from the organic phase. The contrary holds true for small anions that are hydrated with much greater ease, such as fluoride or hydroxide.

d) The bulkiness of the counter cation in the PTC: Due to the low effective concentration of the larger cation in the interface, it decreases the rate of transfer. On the other hand, unsymmetrical cations allow closer approach of the cation to the interface, enhancing the transfer step.

Overall, a phase transfer catalyzed reaction is affected by following variables:

a) Quantity of water (concentration): Even though the use of more concentrated solutions leads to an increased interfacial tension and decreased transfer rate,

the transfer of anions into the organic phase is promoted with increased concentration, as long as this is not the limiting factor.

b) Catalyst: This is the most important variable. The shape and size of the catalyst may influence factors such as: the surfactant properties of the catalyst, its ability to promote the transfer of the substrate nucleophilic anion into the organic phase, transfer rates (as seen above bulkier cations lead to decreased rates). Furthermore, the catalyst could also play a role to activate the anionic nucleophile in the organic phase. Many phase transfer catalysts are able to undergo a Hoffmann elimination under base mediated reaction conditions, which is commonly employed in phase transfer catalysis.

c) Solvent: Solvent should be able to dissolve ionic phase transfer compounds. Dichloromethane is frequently used due to its ability to dissolve most phase transfer catalysts readily. Choice of solvents is important as it can affect both the rate of the reaction itself as well as the interfacial tension.

d) Temperature: The phase transfer catalyst might decompose at high temperature in the presence of base. Therefore, a temperature should be chosen considering these factors.

The use of phase transfer catalysis has several practical advantages:

1) Inorganic bases (such as NaOH, KOH, $K_2CO_3$) are cheaper and easy to handle compare to organic bases such as MHMDS bases, NaH, *t*-BuOK etc. The use of inorganic bases also makes the condition of the reaction easily attainable such as no requirement of inert atmosphere and also leads to a simplified work-up procedure.

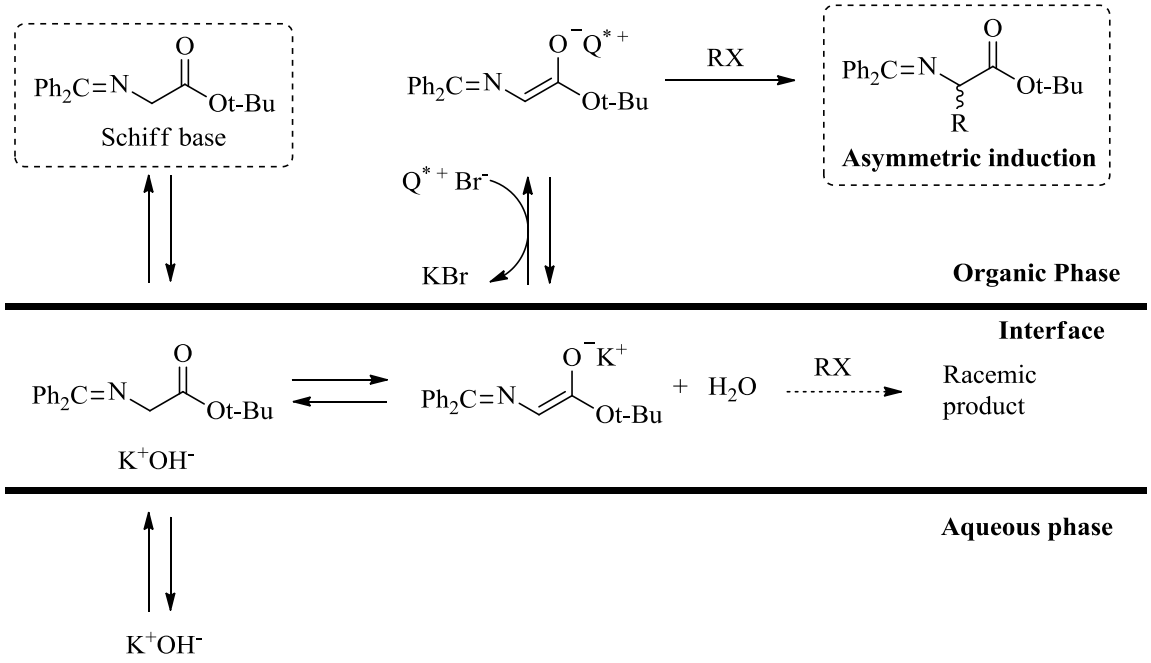
2) High yields and purity are often reported for many reactions.

3) The reactions are often susceptible to scale-up which is advantageous for industrial production.

4) Cost effective and minimum industrial wastes.

Just a few of the reactions that have successfully found application in asymmetric catalysis via phase transfer catalysis include: alkylations, Michael additions, aldol reactions, Darzens reactions, cyclopropanations, epoxidations, aziridinations and oxidations.[16a] The asymmetric alkylation of *t*-butyl glycinate esters will best serve to elucidate the mechanism of the asymmetric version of this reaction (Figure 7).

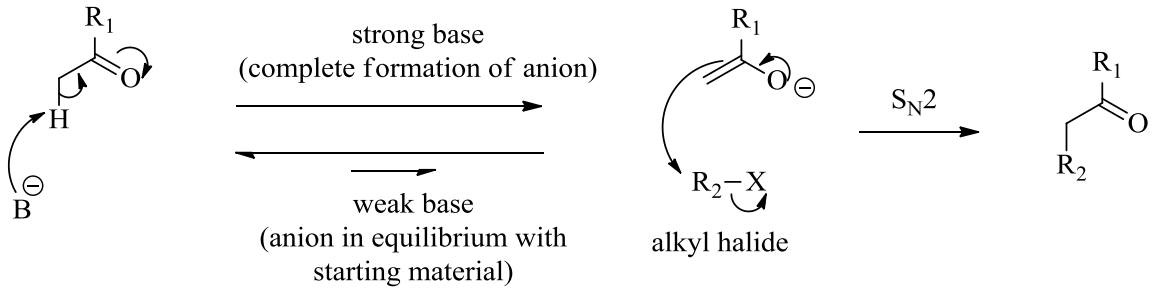
**Figure 7.** Mechanism for phase transfer catalyzed alkylation of Schiff bases.




In the mechanism, as soon as the glycinate Schiff base comes in the interface of the organic and aqueous faces, it meets with the water soluble base which pulls up the acidic proton from the Schiff base forming the corresponding enolate. At this point, it is crucial for the phase transfer catalyst to quickly exchange its chiral positive ion with the counter ion of enolate anion (in this case $K^+$). Otherwise, the enolate will directly react with the electrophile at the interface, leading to racemic product. Once the enolate exchanges ions with the phase transfer catalyst, it comes to the organic phase due to the high solubility of this new ion pair in organic solvent and reacts with the electrophile in a stereoselective manner by virtue of the tight ion pair formed between the prochiral enolate and the chiral quaternary ammonium ion.

1.3.2. General consideration on *C*- vs *O*-alkylation of carbonyl compounds

An alkylation reaction of a carbonyl compound usually consists of two steps. The first step is the deprotonation of the α-proton by a base to form stabilized enolate anion. The second step is a substitution reaction with an electrophile, e.g., alkyl halides. All the factors controlling $S_N1$ and $S_N2$ reactions are applicable in this step (Scheme 16).[37]




**Scheme 16.** Reaction mechanism of alkylation of carbonyl compounds.

Choosing a base for the deprotonation step of the carbonyl compound depend on several important factors:

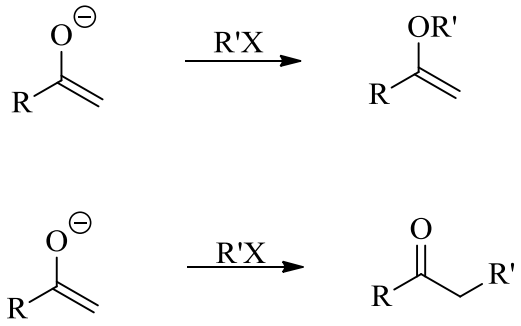
a) If a strong base is employed, there will be complete conversion of the carbonyl to the corresponding enolate.

b) Alternatively, a weaker base can be used, in which case, there will be an equilibrium established between the enolate and unreacted carbonyl compound, instead of the quantitative conversion of the starting carbonyl substrate. However,

more of the enolate will immediately be formed in the course of the reaction as it is consumed by the electrophile.

The first approach requires separate addition of base and nucleophile and usually prior to the addition of electrophile and as a result, can be tedious. However, it has advantages of its own as it requires no prior caution of whether the base and electrophiles are compatible to each other. On the other hand, the second approach is more practical in a sense that it allows mixing of the carbonyl compound, base and electrophile altogether. However, the base and electrophile must be compatible, or at least not react to any significant extent for this approach to work. Excess of base and electrophile can be introduced to overcome this problem in some extent.

The alkylation of carbonyl compounds requires consideration of another very important factor: enolates are ambident nucleophiles that consists an electron rich of both carbon and oxygen atoms, and either of these two can act as a nuclophile. Therefore, there is the question of whether alkylation will take place at the nuclephilic carbon atome or oxygen atom (Scheme 17).

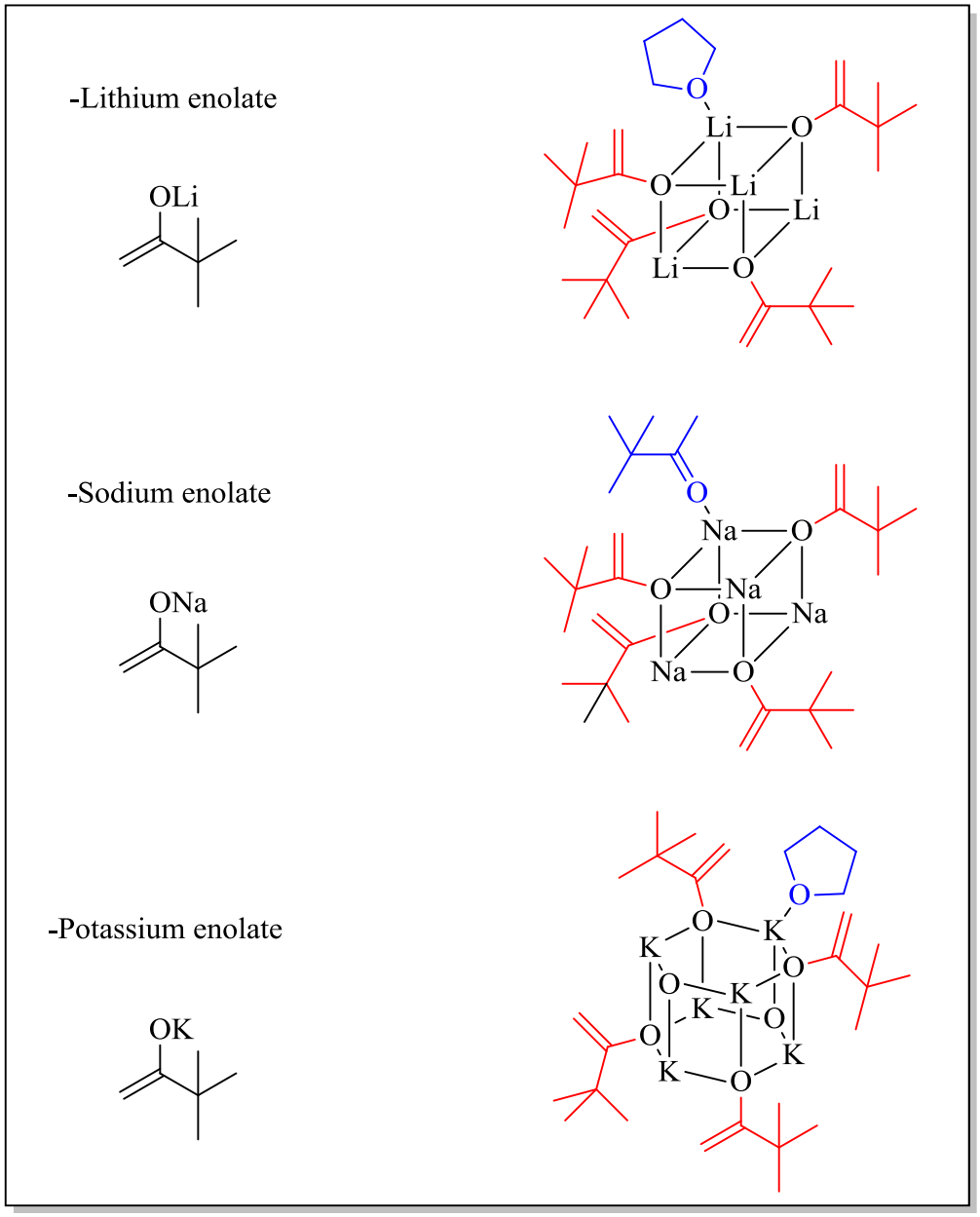



**Scheme 17.** *O- vs C*-alkylation of enolates.

There are various factors that determine whether *C*- or *O*-alkylation will occur:

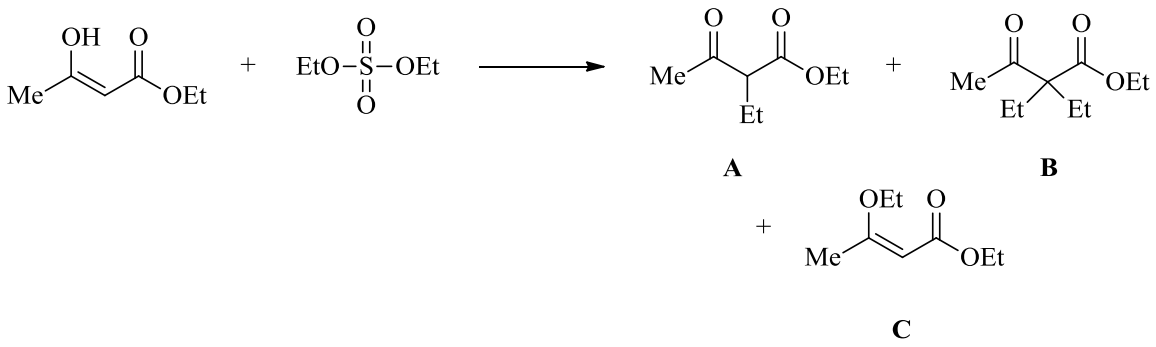
a) When an inorganic base is employed, it depends on whether the metal counter-ion will be dissociated or clustered (depends on the metal and solvent). *O*-alkylation is favored when the enolate is dissociated and it is *naked*, i.e., the oxygen is unhindered for the attack to the electrophile. *C*-alkylation is prevalent where metal clustering occurs. Examples of ion clustering using lithium, sodium and potassium enolates of pinacolone were described by Williard et al.[38] and Seeback et al.[39] Using lithium and sodium enolates, tetrameric clusters were obtained, while the use of potassium enolates resulted in the formation of hexameric clusters (Figure 8). In polar aprotic solvents the metal counter-ion tends to be solvated by a lone pair of electrons from the solvent leading to a slight dissociation of the metal ion from the enolate oxygen ion and thereby, the enolate oxygen atom is exposed for the electrophile. In addition, metal chelators can be added to the mixture to promote *O*-alkylation by creating naked enolate. On the contrary, *C*-alkylation is favored when harder, smaller counter-ions are present which makes a tighter coordination bonds with enolate oxygen, hence effectively blocking the oxygen from electrophilic attack. Protic solvent also favors *C*-alkylation. These solvents can form H-bond with the enolate oxygen atom and thereby, block it in a fashion similar to that of using harder counterions. Apolar solvents also tend to favor *C*-alkylation.

**Figure 8.** Clustering of enolates with different metal ions and THF.




The following is an appropriate example (Scheme 18, Table 1), which shows that the percentage of *O*-alkylation dramatically increases as dissociation of metal clusters is favored. THF promotes ion clustering of the potassium enolate, leading

to an increased amount of *C*-alkylation. Being able to form H-bonding with the enolate anion, *t*-BuOH also favors *C*-alkylation.[40]




**Scheme 18.** Reaction of enol with electrophile leading to *O*- and/or *C*-alkylation.

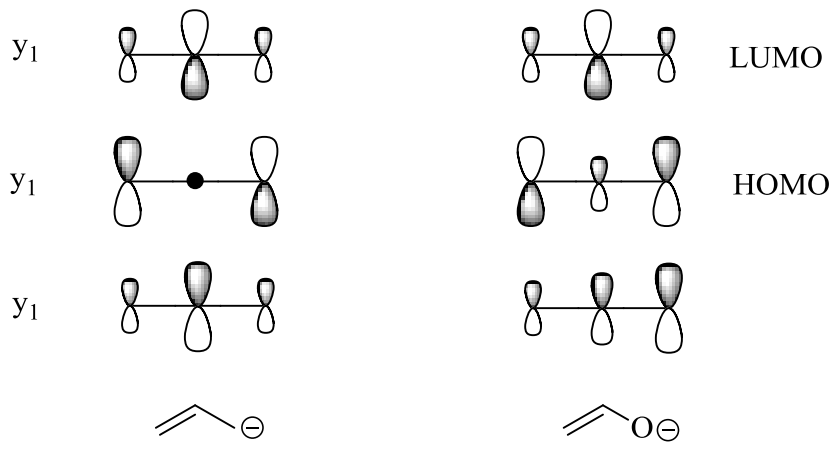
**Table 1.** Ratios of *O*- *vs C*-alkyltion with different solvents.

| Solvent | A | B | C |
|---|---|---|---|
| HMPA | 15% | 2% | 83% |
| *t*-BuOH | 94% | 6% | 0% |
| THF | 94% | 6% | 0% |

b) Charge vs. orbital control (Figure 9): Considering charge control, reaction occurs at the atoms carrying the highest total electron density.[41] This approach dominates when electrophiles contain hard leaving groups, or with charged electrophiles (e.g. $H^+$). In case of enolate nucleophiles, charge control provides *O*-alkylation since oxygen atom is harder compared to carbon atom and hard-hard interaction of electrophile and nucleophile prevails in this mode. Charge control is favored by an early transition state when charge distribution is the most important factor, as

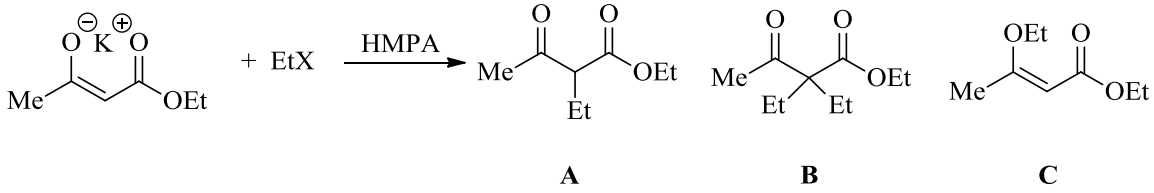
well as by conditions that favor dissociated enolate clusters. In orbital control, reaction takes place at the atom that has the highest frontier electron density, and is favored by neutral electrophiles with soft leaving groups that possesses relatively low-lying LUMO. For orbital control, the HOMO of nucleophile and LUMO of electrophile must be sufficiently close to permit effective overlap. In this case a later transition state is favorable. The *C*-alkylated product is the thermodynamic product, since the total bond energies for the C-alkylated product (C=O: 745 kJ $mol^{-1}$ + C-C bond: 347 kJ $mol^{-1}$ = 1097 kJ $mol^{-1}$) are greater than the total bond energies for the *O*-alkylated product (C=C: 614 kJ $mol^{-1}$ + C-O: 358 kJ $mol^{-1}$ = 972 kJ $mol^{-1}$).[42, 37]

**Figure 9.** Molecular orbital theory to illustrate charge vs orbital control.




c) Hard-soft compatibility: According to the hard-soft theory of acid (electrophiles) and bases (nucleophiles), hard acids will combine with hard bases, and similarly soft acids – soft bases interaction predominates. The hardness of the leaving

group of the electrophile is the determining factor on whether the electrophile will attach with oxygen (hard) or with carbon (soft) of the carbonyl nucleophile. The reaction of potassium enolate of ethyl 3-oxobutanoate with electrophiles with leaving groups of varying hardness serves to demonstrate the remarkable influence of this theory on the prediction of *O*- vs *C*-alkylation of enolates (Scheme 19,Table 2).[43] From the results, it becomes evident that harder leaving groups favor *O*-alkylation and softer leaving groups favor *C*-alkylation.



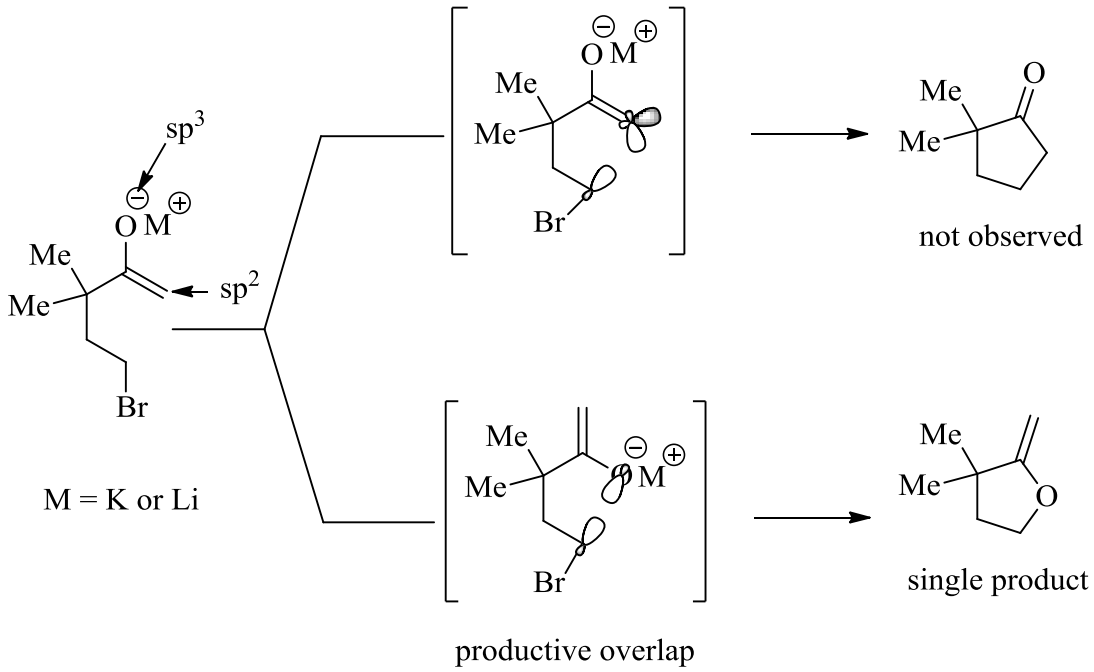

**Scheme 19.** Reaction of enolate with electrophile leading to *O*- and/or *C*-alkylation.

**Table 2.** Ratios of *O*- *vs C*-alkyltion with different solvents.

| X | A | B | C |
|---|---|---|---|
| OTs | 11% | 1% | 88% |
| Cl | 32% | 8% | 60% |
| Br | 38% | 23% | 39% |
| I | 71% | 16% | 13% |

d) Stereoelectronics: Alkylation will take place at the nucleophilic site that allows maximal orbital overlap (Scheme 20).[44] In an enolate, oxygen and carbon atom have different hybridizations ($sp^3$ and $sp^2$ respectively). As a result, their orbitals point in different directions and thereby, will have varying degrees of overlap

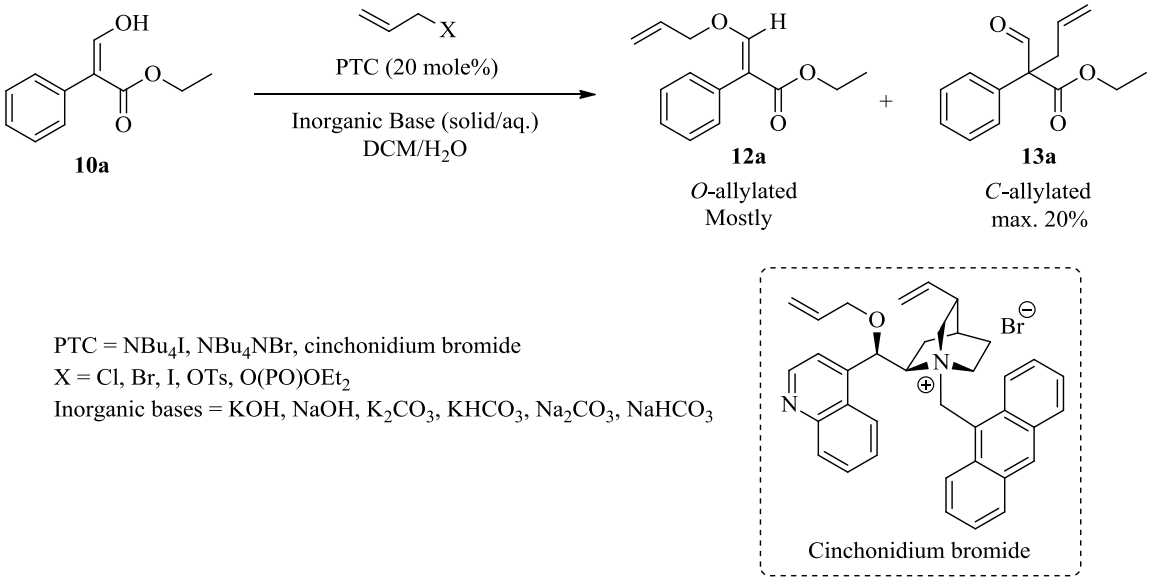
with the C-X $\sigma^*$ orbital. The orbital of the atoms in enolate that is able to achieve maximum overlap with electrophile's LUMO ($\sigma^*$) will be the one to ultimately produce the product via an $S_N2$ displacement reaction.




**Scheme 20.** Effect of stereoelectronics in *C*- vs *O*-alkylation.

## 1.4. Results and discussions

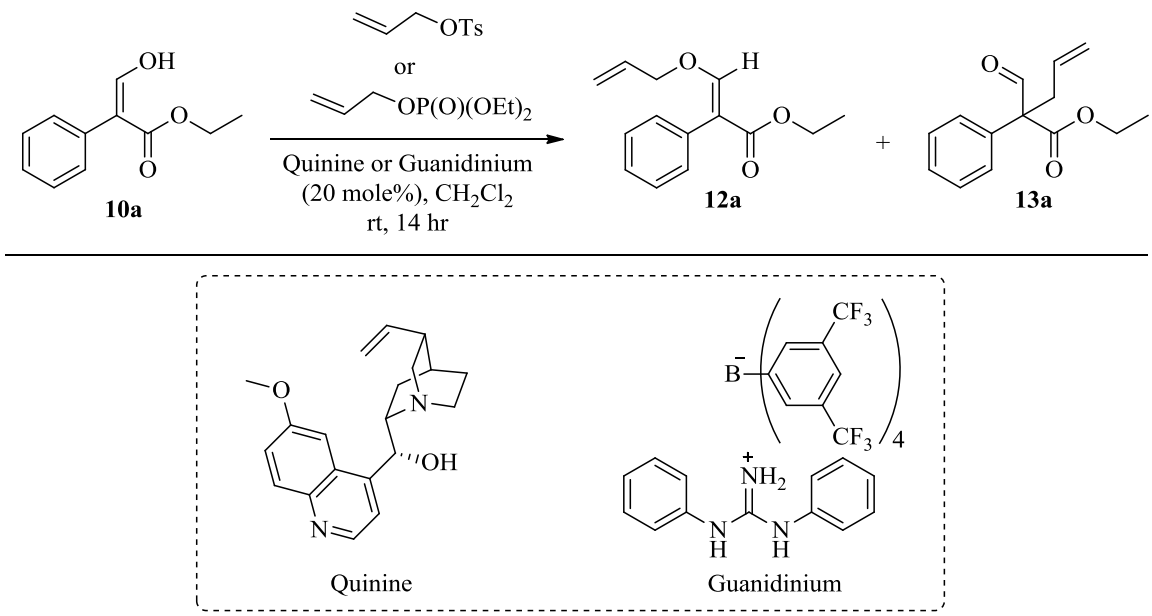
Due to the presence of aryl bound tertiary prochiral carbon centers in 3-hydroxyaryl acrylates **10a**, these compounds should allow us to synthesize chiral all-carbon α-aryl quaternary stereocenters. To prove this hypothesis, we first attempted allyltion of these substrates in phase transfer catalytic (PTC) conditions using achiral $Bu_4NI$, $Bu_4NBr$, or chinchonidium bromide as PTC catalyst with various allylic electrophiles. Allylation with bases such as solid or aqueous KOH and NaOH gives exclusive *O*-allylation product **12a** (Scheme 21), whilst the attempted allylation with solid or aqueous $KHCO_3$, $K_2CO_3$, $NaHCO_3$, and $Na_2CO_3$ gave only a small amount of *C*-allylated product **13a** (*ca* 20% with allyl iodide and allyl tosylate). NMR studies (NOESY experiment) showed *E*-stereochemistry of the double bond of *O*-allylated product, presumably due to steric hindrance between the oxygen of the allyl vinyl ether and the carbonyl oxygen of the ester. We believe that *O*-allylation is much more favored since the high degree of conjugation present in the acrylates **10a,** preserved in *O*-allylation, is disrupted in *C*-allylation. We have screened various electrophiles (allyl chloride, allyl bromide, allyl iodide, allyl tosylate, and allyl phosphate) and solvents (toluene, dichloromethane, THF); all reactions with KOH under any conditions provided exclusively *O*-allylated product. An electrophile with a softer leaving group (allyl iodide and allyl tosylate) resulted only a small amount (20%) of *C*-allylated products. As a continuation of the previously reported data,[45] some of the new allyl electrophiles have been employed during the course of this study.




**Scheme 21.** Phase transfer catalyzed allylic alkylation of 3-hydroxy aryl acrylates **10a**.

Disappointed by the findings, we turned our attention to the simpler organocatalytic reaction conditions instead of PTC conditions (Scheme 22, Table 3). This time we chose to use allyl tosylate and allyl phosphate as allyl electrophiles because of their softer nature, mainly due to the fact that it provided as much as 20% *C*-allylated product **13a** in PTC conditions while employing this class of electrophiles (allyl iodide, and allyl tosylate). Simple non-nucleophilic amine base, quinine and H-bond donor, guanidine have been employed as catalyst. H-bonding catalyst guanidine did not proceed to react with either of the electrophiles. On the other hand, while quinine did not allow the reaction with allyl phosphate, much to our delight, it provided solely desired *C*-allylated product **13a** with allyl tosylate. Even though the conversion was only 20%, this observation was crucial in the progress of the research. This was the first time we

observed exclusively *C*-allylated product. Not even a trace amount of *O*-allylated product **12a** was found, which was omnipresent in PTC condition.



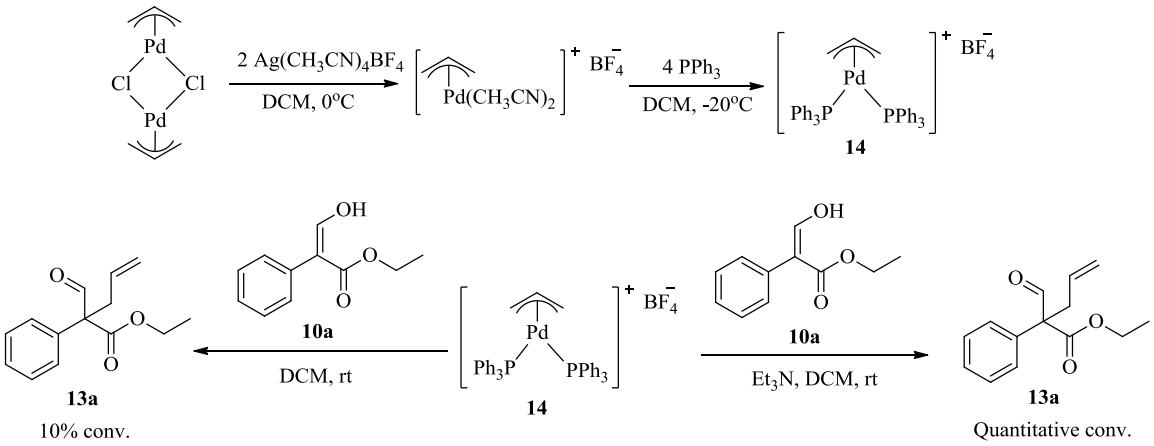

**Scheme 22.** Organocatalytic allylic alkylation of 3-hydroxy aryl acrylates **10a**.

**Table 3.** Organocatalytic allylic alkylation of 3-hydroxy aryl acrylates **10a**.

| Starting material | Catalyst | Electrophile | Alkylation (*C*/*O*) [%] |
|---|---|---|---|
| Acrylate | Guanidinium | Allyl phosphate | No Rxn. |
| Acrylate | Guanidinium | Allyl tosylate | No Rxn. |
| Acrylate | Quinine | Allyl phosphate | No Rxn. |
| Acrylate | Quinine | Allyl tosylate | 20% *C*, No *O* |

We attributed to the softer nature of allyl tosylate as electrophile to this encouraging finding and decided to use palladium-allyl complex due to its even softer electrophilic

properties (Scheme 23). We have used *in situ* prepared palladium allyl complex **14**[46] as electrophile for this purpose using existing procedure. As anticipated, the reaction provided quantitative conversion of the desired *C*-allylated product **13a** when $Et_3N$ was employed as base. Not even a trace amount of *O*-allylated **12a** was observed. Without base, only 10% conversion of the desired product was observed and there was no *O*-allylated product found in the crude.




**Scheme 23.** Palladium allyl complex **14** allyl electrophile for the allylic alkylation of 3-hydroxy aryl acrylates **10a**.

## 1.5. General methods and experimental

### *General considerations*

All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents used were freshly distilled prior to use. $^1H$ and $^{13}C$ spectra were recorded on a Bruker DRX 300 operating at 300 MHz and 75 MHz,

and referenced to the solvent used (7.27 and 77.00 ppm for $CDCl_3$). Analytical thin layer chromatography was performed using EMD Chemicals TLC Glass plates, Silica Gel 60 F254. Flash column chromatography was performed using Biosolve 60 Å (0.032–0.063 mm) silica gel.

### 1.5.1. Synthesis of 3-hydroxy phenyl acrylate **10a**

Benzaldehyde (0.77 ml, 7.6 mmol) was dissolved in DCM (19 mL), followed by addition of $HBF_4 \cdot OEt_2$ (52 μL, 0.381 mmol, 10 mol%). The mixture was allowed to cool down to -78 °C, at which point EDA (0.434 g, 3.81 mmol) was added dropwise over a period of 5 minutes. After complete consumption of EDA was identified by TLC analysis, the reaction mixture was allowed to slowly warm up to 0 °C, at which point the reaction mixture was passed through silica plug, and excess $Et_3N$ was introduced followed by stirring for 5 minutes. When the pH indicating paper showed that the solution was basic, it has been passed through a thick pad of silica gel. The salt of acrylate is not able to pass through silica and stays on the top. The light to dark brown color of the silica gel indicated the salt of phenyl acrylate. Enough DCM was passed through to elute out all unreacted arylaldehydes and β-keto esters. The region of silica indicating brown was then scraped out in a beaker with an appropriate (usually long that compliments the beaker) stir bar. DCM was added and stirred vigorously until it became slurry and distribution of solid silica particles was uniform. Then 6N HCl was added. Enough acid was added with continued stirring until the pH paper showed the solution acidic. The solution was then transferred to a separatory funnel along with solid silica and extracted with DCM three

times. The silica usually stays at the interface of the bottom organic (DCM) and top aqueous phase. the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated in *vacuo* to afford the desired 3-hydroxy phenyl acrylates **10a** (0.44 g, 60% yield) as a light yellow oil.

### 1.5.2. Alkylation reactions

***Reactions of 3-hydroxy phenyl acrylate 10a with electrophiles under phase transfer catalysis (PTC)***

As an example of a typical reaction, 3-hydroxy phenyl acrylate **10a** (50 mg, 0.26 mmol) was allowed to dissolve in DCM (2.6 ml) followed by the addition of *n*-$Bu_4NI$ (33 mg, 0.051 mmol, 20 mol%). Next, solid $Na_2CO_3$ (276 mg, 2.6 mmol, 10 eq.) was slowly added with vigorous stirring and allowed to stir for 5 minutes. At this point, allyl iodide (48 μL, 0.52 mmol) was slowly added via syringe. After a few minutes, the color of the reaction mixture changed from light yellow/brown to an almost colorless cloudy mixture. The reaction was allowed to stir overnight under $N_2$, at which point TLC analysis confirmed the completion of the reaction. The reaction was quenched with sat. $NH_4Cl$ and allowed to stir for a few minutes, the layers were separated and the aqueous layer was then extracted with DCM. The combined organic extracts were dried over $Na_2SO_4$ and passed through a 1 cm high Celite pad in a 4 cm diameter fritted funnel (medium porosity) to remove small amounts of residual precipitates. The resulting yellow solution

was then concentrated under vacuum, leaving dark yellow oil. The crude mixture was then analyzed by $^{1}$H NMR for the % conversion of **12a** and **13a**.

***Reactions of 3-hydroxy phenyl acrylate 10a with electrophiles employing organocatalysts (Et3N, quinine, or guanidine)***

As a typical example, palladium allyl complex **14** was prepared *in situ* in an evacuated, Argon-purged, and sealed round bottom flask following existing procedure. Meanwhile, in another evacuated, Argon-purged, and sealed round bottom flask 3-hydroxy phenyl acrylate **10a** (50 mg, 0.26 mmol) was allowed to dissolve in dry and degassed DCM (2.6 ml) followed by the addition of $Et_3N$ (43.5 µL, 0.312 mmol, 1.2 eq). The mixture was stirred for few minutes to allow the formation of enolate. At this point, the enolate solution was transferred to the other round bottom flask containing palladium allyl complex **14** via cannula. The reaction was allowed to stir for 2 h, at which point TLC analysis confirmed the completion of the reaction. Then the mixture passed through a thick pad of silica gel, and concentrated under vacuum. Purified products **13a** was obtained as light yellow oil (60.0 mg, >99% yield) by column chromatography of the crude mixture on silica gel eluted with EtOAc in Hexane.

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 7.44–7.23 (m, 5H), 5.76 (m, 1H), 5.13 (d, *J* = 18.3 Hz, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 4.30 (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), 1.30 (t, *J* = 7.1 Hz, 3H).
Analytical data matched previously reported data.[45]

# CHAPTER 2: ASYMMETRIC SYNTHESIS OF ALL-CARBON α-ARYL QUATERNARY CARBONYL COMPOUNDS INCLUDING BOTH ALDEHYDE AND KETONE BY PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION (Pd-AAA)

## 2.1. Introduction

### 2.1.1. Palladium

*"You would be forgiven if you thought the most important element in an organic transformation was carbon. Matthew Hartings argues that, for just over half a century in many of chemistry's most renowned organic reactions, it has actually been palladium."*[47]

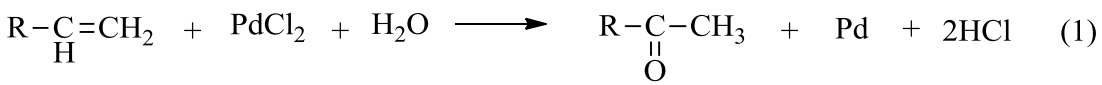
-Matthew R. Hartings

Even though the versatility of palladium was well known to industrial and chemical communities for long time, it truly reached far beyond in 2010 when Richard Heck, Ei-ichi Negishi, and Akira Suzuki received the Nobel Prize in recognition of their work on the development of palladium-catalyzed carbon-carbon bond formation. It's omnipotence is vividly evident in its ability to perform numerous reaction classes that includes, but not limited to, hydroarylation/alkenylation of bicycles, carbopalladation−addition/cyclization of allenes, enyne cycloisomerizations, carbonylation and cyclocarbonylation reactions, various kinds of cycloaddition reactions, addition of carbon nucleophiles to carbon-oxygen, carbon-nitrogen, and activated carbon-carbon double bonds, various cross-coupling reactions, allylation/arylation of ketone enolates, hydrosilylations, hydroamination of 1,3-dienes, fluorination of β-ketoesters, and hydrogenation of

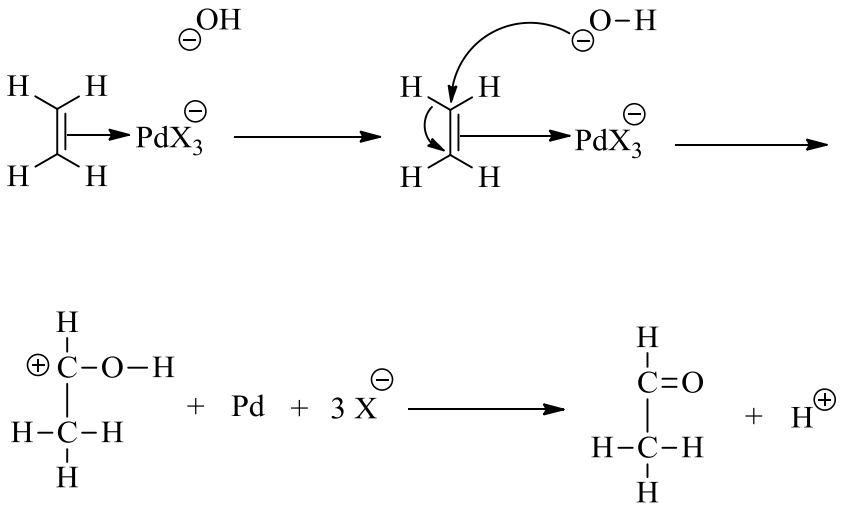
imines.[48] In addition, palladium has been employed as a catalyst in the Wacker process – regarded as the first industrially applied organometallic reaction. One of the important reasons behind this remarkable utility of palladium in organic transformation, as Dr. Hartings argues,[47] is the ability of palladium (II) to adopt square-planar geometries – which, conveniently, have two empty axial coordination sites necessary for oxidative addition. More importantly, to run reactions which involve activation of olefinic double bonds, a metal catalyst must be able to coordinate with the double bond first. Even though nickel, palladium, and platinum all have the proper orbital energies to do just that, palladium provided best activation. Platinum turned out to be a poor catalyst due to the slow coordination of the metal to olefin and only a few nickel complexes show catalytic activity towards olefin. Moreover, palladium has some exceptionally special characteristics. It is the only transition metal that possesses a completely filled *d* orbital along with an empty frontier *s* orbital, due to having ground-state electronic configuration $4d^{10}5s^{0}$. This, in combination with its low percentages of hybridization from the 5*s* and 5*p* orbitals due to the larger energy transition from lowest *d* to *p* makes palladium 'just right' as catalyst.

## 2.2. Palladium as transition metal catalyst

In 1962, Smidt reported the transformation of olefin to carbonyl by Palladium (II) chloride (eq 1).[49] In this publication, it was resolved that the activation of olefin is



accomplished by coordination of palladium to its double bond, which makes it electrophilic in nature and thereby, labile for the nucleophilic attack by hydroxide anion (Scheme 24).



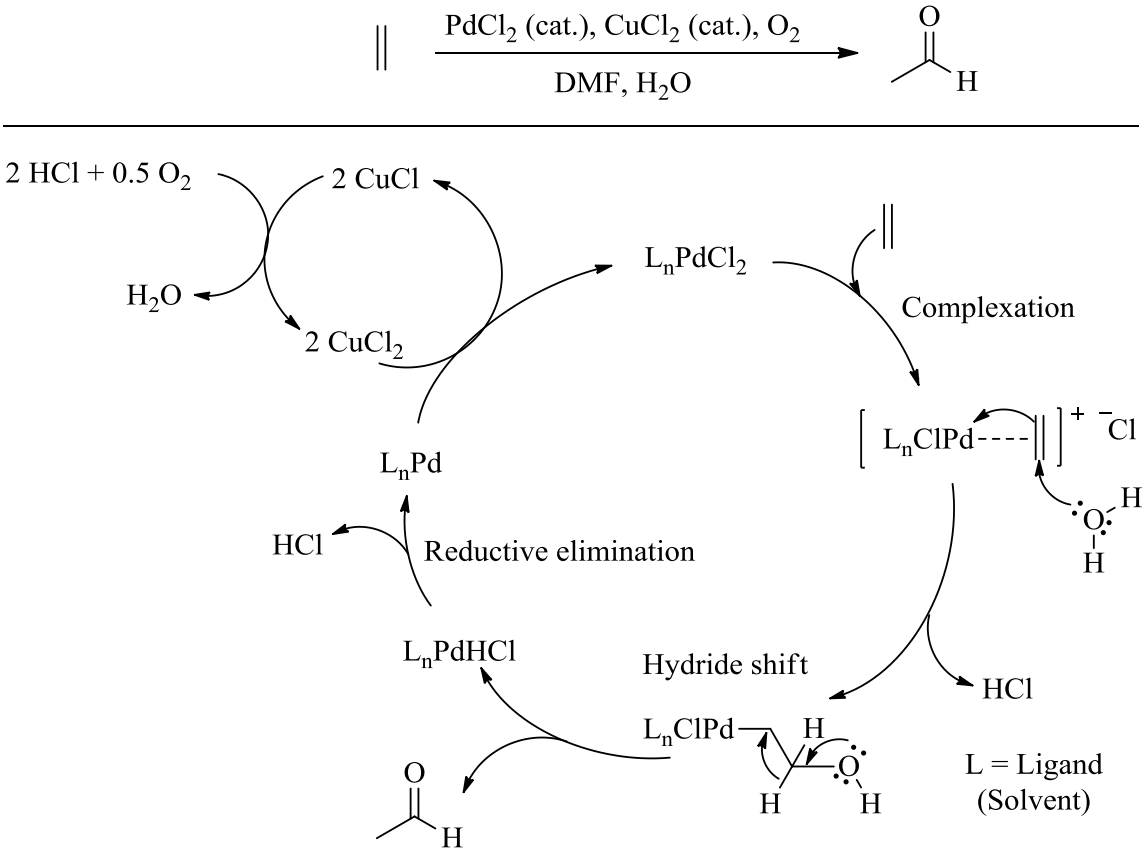
**Scheme 24.** Mechanism of the oxidation of olefin to carbonyl by $PdCl_2$.

He also succeeded in producing carbon dioxide from carbon monoxide using this methodology (eq 2).

$$CO + PdCl_2 + H_2O \longrightarrow CO_2 + Pd + 2HCl \quad (2)$$

Note that the above is a stoichiometric reaction. The resulting Pd (0) cannot be reoxidized to Pd (II) in the reaction, which is essential for it to act as a catalyst. Hence, a catalytic version of the reaction was developed later which is called Wacker-Tsuji Oxidation,[50] where additional copper (II) chloride and atmospheric oxygen were employed (Scheme

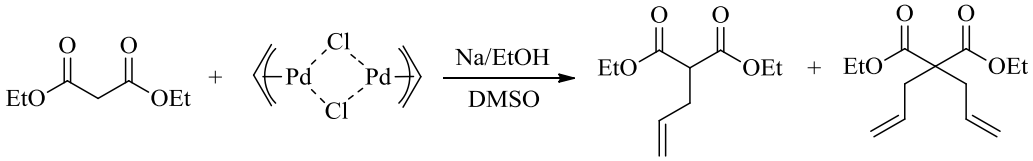
25). Copper (II) chloride serves as redox cocatalyst which regenerates Pd (II) catalyst by oxidizing the resulting Pd (0) in the reaction and in turns, Copper (II) becomes copper (I) chloride. Air, pure oxygen, or a number of other oxidizers can then oxidize the resultant copper (I) back to copper (II), hence allowing the cycle to continue.




**Scheme 25.** Catalytic oxidation of olefin by palladium (II) chloride.

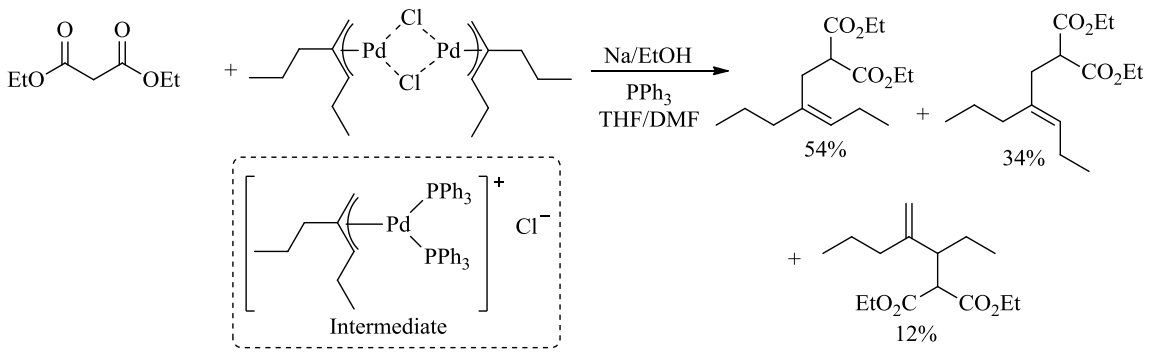
This newly found process to oxidize olefin to carbonyl by Palladium (II) provided very important insight to the scientific community and was picked up brilliantly by Tsuji. He hypothesized that this type of olefinic activation could also be employed to create new

carbon-carbon bond. The evidence to prove his hypothesis was published in 1965.[51] The group successfully produced a carbon-carbon bond by reacting a dimeric allylpalladium chloride complex with sodium salt of diethyl malonate, forming a mixture of both mono- and di-alkylated product (Scheme 26).




**Scheme 26.** First carbon-carbon bond formation using Palladium.

The next big breakthrough came in 1973, when Trost reported the necessity of at least 4 equivalent of triphenylphosphine for the alkylation to proceed with hindered allyl counterpart.[52] During the research on synthesizing acyclic sesquiterpenes to generate juvenile hormone derivatives, he was unable to alkylate malonate anion with alkyl-substituted allyl group. However, the problem was overcome with the addition of triphenylphosphine, which provided surprisingly quick reaction to products (Scheme 27).



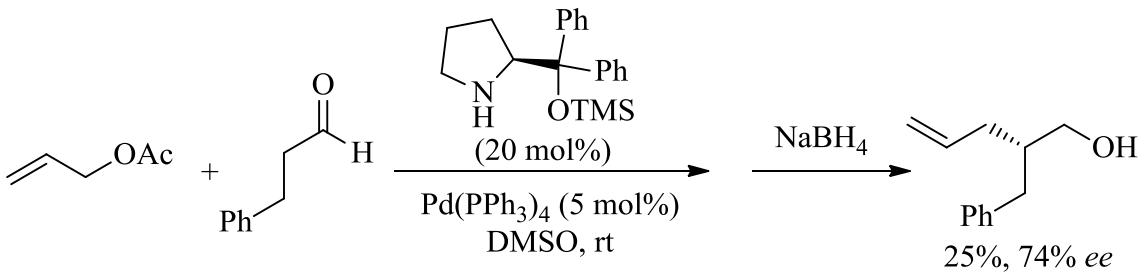

**Scheme 27.** Introduction of triphenylphosphine as a ligand for palladium.

He suggested the formation of a more reactive intermediate complex where both triphenylphosphine and allyl group are bound to palladium metal. This discovery soon initiated the research of employing chiral version of triphenylphosphine as ligand for palladium to investigate asymmetric version of the reaction.

## 2.3. Chiral induction by organo-cocatalyst in palladium catalyzed reaction

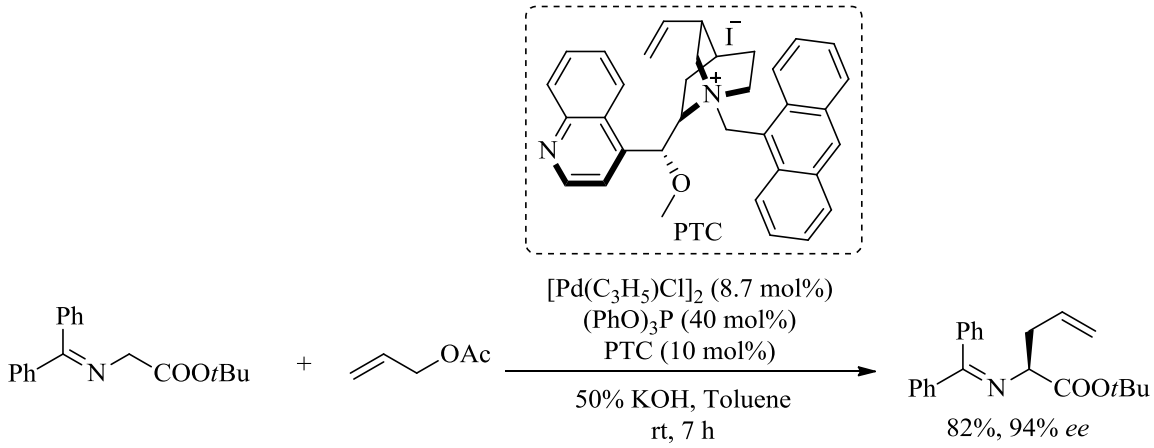
Enantioselective two-component catalytic system is fairly common in organic synthesis. In this kind of reaction, one component is usually transition metal catalyst and the other is organic co-catalyst. Well-designed, two-component activation systems with Pd that combine the metal catalyst with catalytic amounts of an organic catalyst have been successfully employed in allylic alkylation reactions as well.[53] One of the important advantages of this kind of reaction where organocatalyst is used as chiral inducing agent instead of chiral ligand lies in the easily accessible and cheap organocatalysts.

In 2006, Cordova and co-workers[54] reported the asymmetric allylic alkylation where enantiodiscrimination was achieved by organocatalytic chiral amine bases, which provided as much as 88% *ee* (Scheme 28).



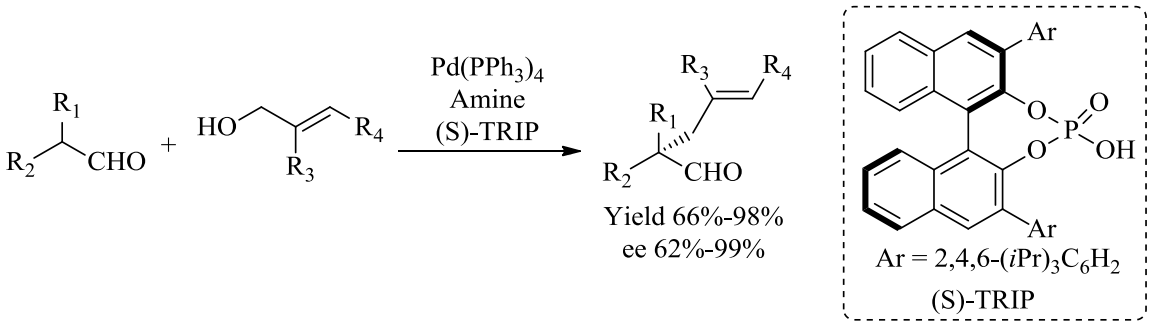

**Scheme 28.** Chiral induction by prolin based organocatalyst in Pd-catalyzed reaction.

In another research, Takemoto and co-workers[55] have used chiral phase-transfer catalyst for the first time as chiral inducing agent, along with palladium catalyst in asymmetric allylation of tert-butyl glycinate-benzophenone Schiff base with allyl acetate. This provided allylated products with good yields and enantioselectivity without using any chiral ligands for palladium (Scheme 29).



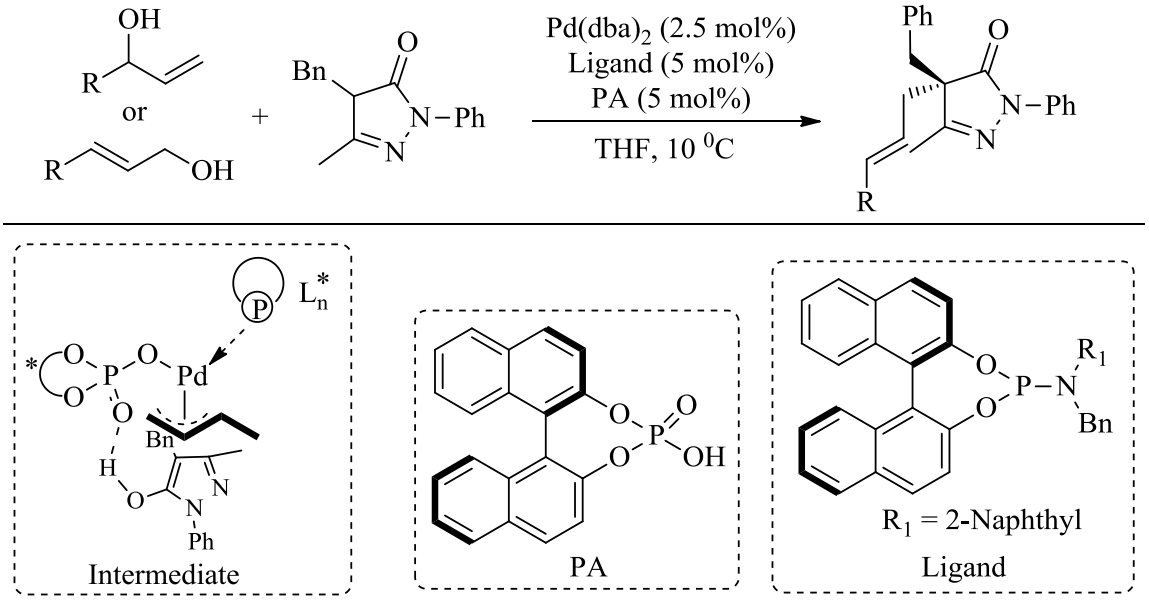

**Scheme 29.** PTC as chiral inducing agent in Pd-catalyzed reaction.

Very recently, List and co-workers[56] have shown a remarkable use of axially chiral binol-phosphoric acid as chiral inducing agent in Pd-catalyzed asymmetric allylic alkylation of α-enolizable aldehydes, where allyl alcohol has been employed as allylic counterpart instead of widely used allylic halides, esters, or carbonates. Use of allyl alcohols was widely commended due to its environment friendly nature as well as its wide synthetic reliability and step economy.[57] However, alcohols are not good of a leaving group. This problem was overcome by using catalytic amount of chiral phosphoric acid, where this facilitates the oxidative addition of Pd to allylic alcohols and controls the stereochemistry as well (Scheme 30).




**Scheme 30.** Chiral phosphoric acid as chiral inducing agent in Pd-catalyzed reaction.

In 2013, Gong and co-workers[58] used both of the catalytic components as chiral to enable Pd-AAA with high *ee* (Scheme 31). A chiral phosphoramidite ligand for the palladium complex and a chiral phosphoric acid were used for AAA of pyrazol-5-ones with allyl alcohols, which afforded multiply functionalized heterocyclic products in high yields with excellent enantioselectivity. Further investigation provided the clue about the important intermediate where conjugate base of chiral phosphoric acid acts as a counterion of the π-allylpalladium (II) complex and also participates in a hydrogen-bonding interaction with enolized substrate pyrazol-5-one (Scheme 31). In that way, both the chiral palladium complex and chiral phosphate counterion work cooperatively to keep the substrate in close proximity to the chiral environment and control the stereochemistry of the AAA reaction, affording the product with very high enantioselectivity.




**Scheme 31.** Both chiral Pd and chiral phosphoric acid in Pd-AAA.

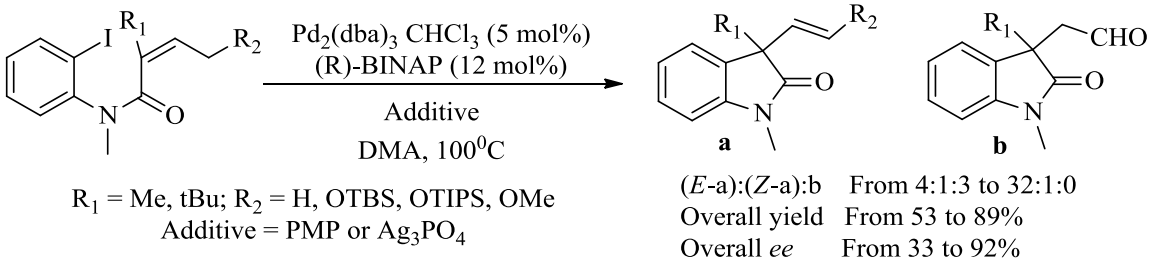
## 2.4. Asymmetric transformations catalyzed by palladium

The importance of Pd in organic synthesis is clearly visible from the huge number of reaction methodologies developed in connection with this field. Except Palladium catalyzed Asymmetric Allylic Alkylation (Pd-AAA) which will be discussed in details later, a few of the important Pd-catalyzed enantioselective transformations will be briefly presented in this section.

### 2.4.1. Heck reaction

After the discovery of this reaction in the late 1980s, it has been used as an important synthetic tool in organic chemistry since then. Between both inter- and intra-molecular

versions of this reaction, intramolecular Heck reaction, first reported by Shibasaki[59] and Overman,[60] has been proved to be the most powerful method for the enantioselective synthesis of both tertiary and quaternary stereogenic centers and has been used to synthesize an enormous number of natural products and their precursors. As an example, Overman and co-workers have reported the first example of an all-carbon quaternary stereocenters employing this method.[61] Subsequently, they have successfully created a series of 3,3′-disubstituted oxindoles employing the methodology (Scheme 32).[62]

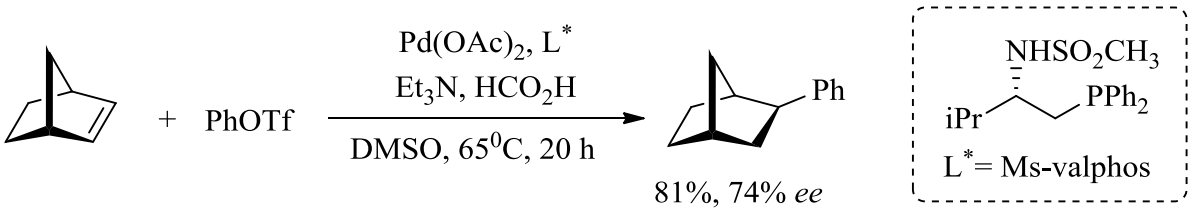



**Scheme 32.** An example of asymmetric Heck reaction.

2.4.2. Hydroarylation/Alkenylation of [2.2.1] bycycles

Just like the Heck reaction, hydroarylation/alkenylation of alkene involves the oxidative addition of arylhalides followed by alkene insertion to palladium. However, unlike the Heck reaction, reductive elimination of the palladium complex takes place instead of β-hydride elimination. Therefore, the generation of stereogenic center is more likely in this reaction compare to Heck type methods since β-hydride elimination often provides olefinic compounds. The reaction was discovered in 1991 by Brunner and Kramler[63] to

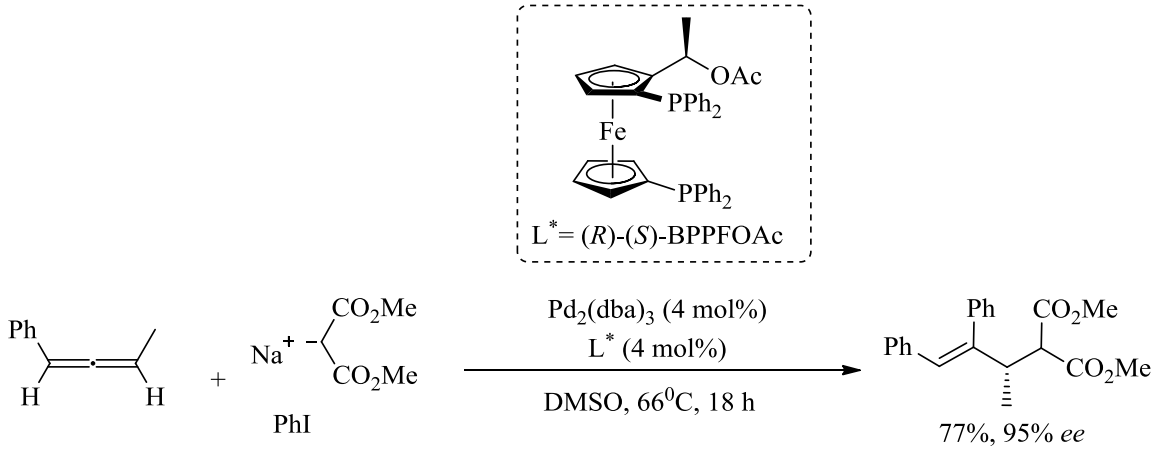
produce exo-2-arylnorbornanes with a maximum of 41% ee, which has been later improved by Achiwa and coworkers[64] to up to 74% (Scheme 33).




**Scheme 33.** An example of asymmetric hydroarylation/alkenylation reaction of [2.2.1] bycycles.

2.4.3. Carbopalladation - addition/cyclization of alenes

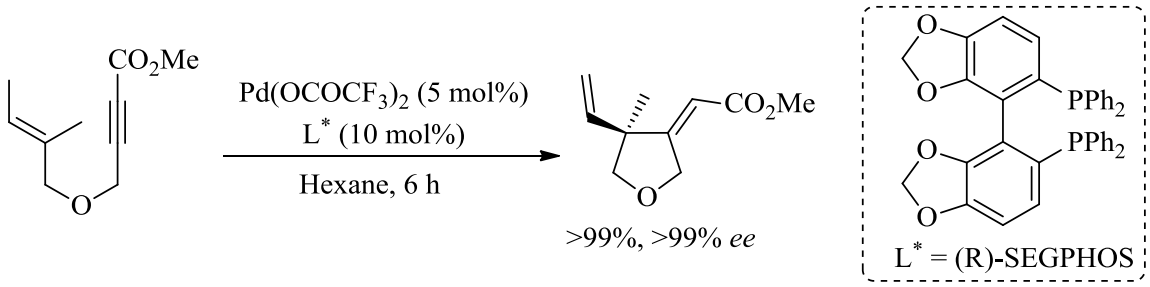
This reaction proceeds with the formation of intermediate β-aryl π-allylpalladium complex by asymmetric carbopalladation of allenes, followed by nucleophilic attack of the intermediate. It is a powerful synthetic tool for the synthesis of enantioenriched hetero- and carbocycles as well as α,β-functionalized olefins. As an example, Hiroi and co-workers recently have reported palladium-catalyzed asymmetric α,β-functionalization of allene with high yield and enantioselectivity (Scheme 34).[65]




**Scheme 34.** An example of asymmetric Carbopalladation - addition/cyclization of alenes.

2.4.4. Enyne cycloisomerizations

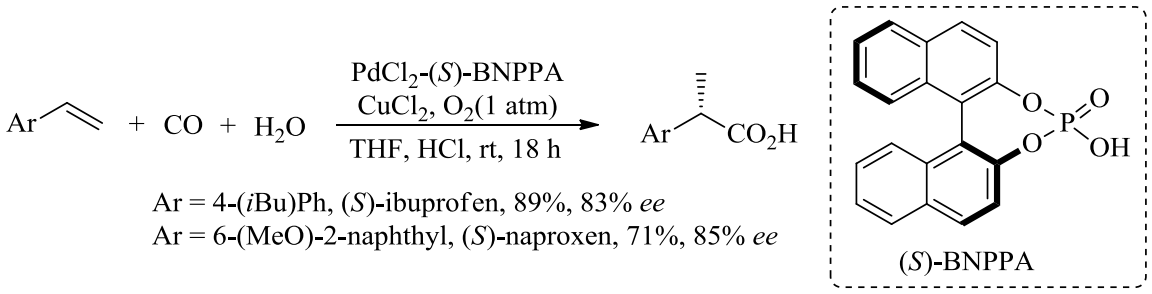
Enyne cycloisomerizations, originally developed by Trost and co-workers,[66] is a very useful method to create cyclic and polycyclic compounds asymmetrically. Recently, Mikami and co-workers[67] have reported a highly efficient palladium catalyzed reaction of this class where enantiopure five-membered fural ring with a quaternary chiral center has been synthesized with >99% *ee*. Further investigation provided an innovative use of $Pd(OCOCF_3)_2$ as palladium source instead of $Pd(OAc)_2$ or $Pd_2(dba)_3$, which was deemed as the reason behind this surprisingly high enantioselectivity (Scheme 35).




**Scheme 35.** An example of asymmetric enyne cycloisomerizations.

2.4.5. Carbonylation and cyclocarbonylation reactions

Palladium catalyzed carbonylation is one of the most efficient tool for homologation, and the corresponding asymmetric hydroformylation, hydrocarboxylation, and hydroesterification of prochiral olefins. One of the important aspects of this reaction is the use of carbon monoxide. This method provided very efficient enantioselective synthesis of most widely used anti-inflammatory agents, (*S*)-ibuprofen and (*S)*-naproxen. These drugs have been produced with very high yield and *ee* using 4-(isobutyl)-styrene and 2-vinyl-6methoxynaphthalene respectively as starting material, under exceptionally mild conditions (Scheme 36).[68] The reaction emerges as one of the most lucrative synthesis in this field.




**Scheme 36.** An example of asymmetric carbonylation and cyclocarbonylation reactions.

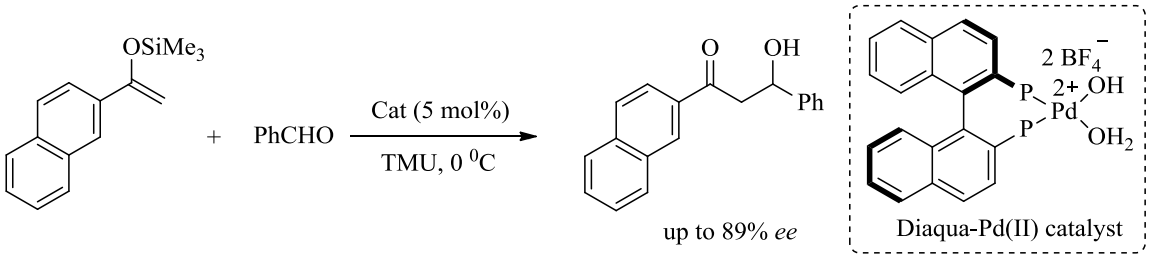
### 2.4.6. Cycloaddition reactions

The asymmetric cycloaddition reactions are one of the most powerful and versatile in organic chemistry. The ability to form new ring systems, especially heterocyclic rings made this reaction as such. Chiral Lewis acids have been used to induce enantioselectivity in this reaction class which extended the scope and utility of this reaction significantly.[69] However, there was always a need to find new methodology to increase the efficiency of the reaction. Palladium has been successful employed in different kinds of cycloaddition reaction, including but not limited to, Diels-Alder reactions,[70] hetero Diels-Alder reactions,[71] [3+2] dipolar cycloaddition reaction.[72]

### 2.4.7. Nucleophilic addition to C=O bonds

The catalytic asymmetric aldol reaction has been an excellent tool to access a huge number of natural products and pharmaceutical intermediates. In 1997, Shibashaki and co-workers[73] have reported the preparation of the air- and moisture-stable crystalline

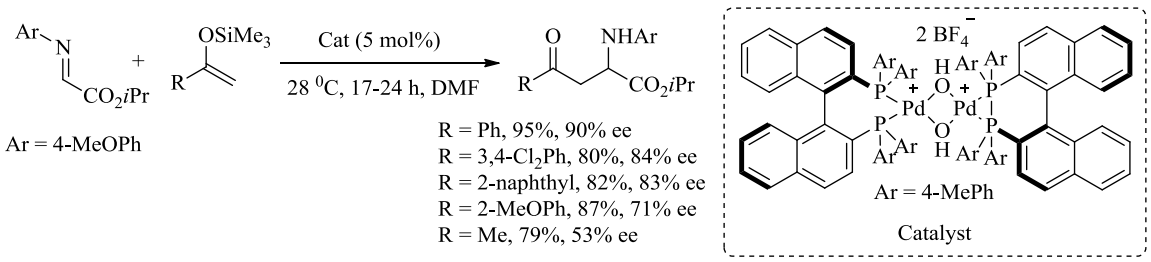
diaqua-Pd(II) complex. This remarkable catalyst, which itself was a great achievement, was subsequently used to synthesize aldol product with high yield and *ee* (Scheme 37).




**Scheme 37.** Enantioselective aldol condensation by palladium catalyst.

2.4.8. Nucleophilic addition to C=N bonds

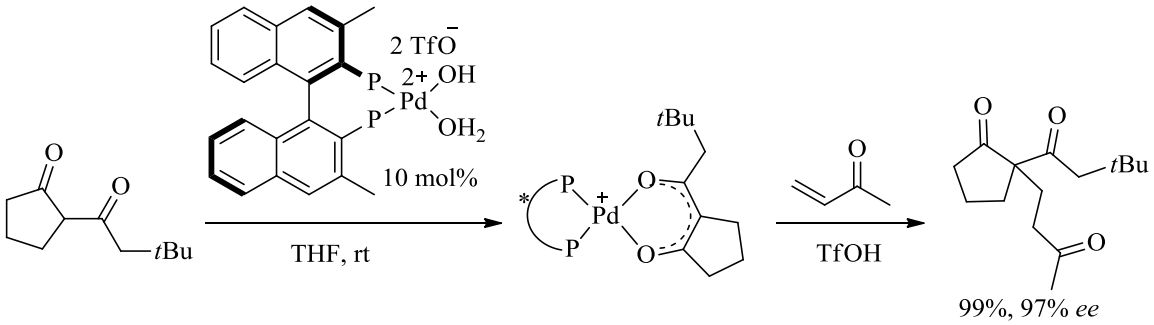
The first reported Pd (II) catalyzed asymmetric addition of silylenol ethers to imine was by Sodeoka and co-workers[74] in 1998, where an innovative use of novel binuclear Pd (II) complex as catalyst provided excellent yield and enantionselectivity with a series of silylenol ethers (Scheme 38).




**Scheme 38.** Asymmetric Mannich reaction by palladium catalyst.

2.4.9. Nucleophilic addition to C=C bonds by Michael addition

In 2002, Sodeoka and co-workers[75] have reported a mechanistically interesting and highly efficient Michael addition of 1,3-dicarbonyl compounds with α,β-unsaturated ketones where, once again, the diaqua palladium complex was used as catalyst effectively. Treatment of the diketone with the diaqua complex showed the formation of a stable palladium diketonato complex which did not react at all with the Michael acceptor methyl vinyl ketone. However, when TfOH was added, the reaction was found to go to completion with high enantioselectivity (Scheme 39).

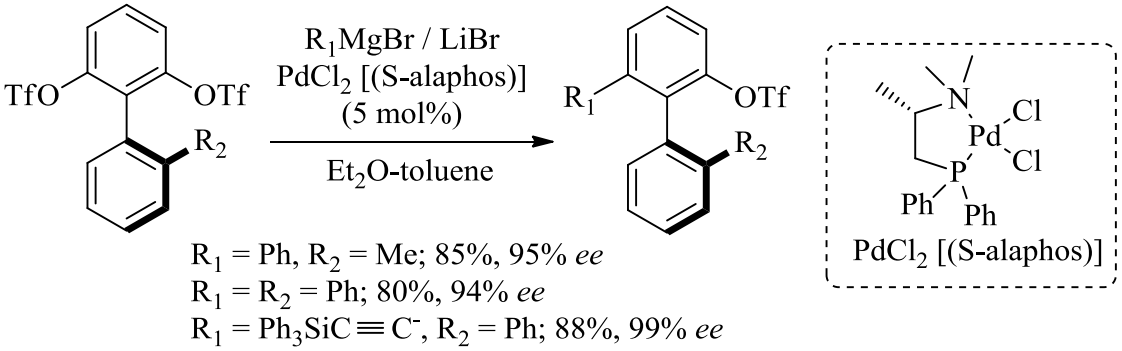



**Scheme 39.** Asymmetric Michael addition.

2.4.10. Cross-coupling reactions

Most probably, transition metal catalyzed cross-coupling is the most frequently used reaction in organometallic chemistry. It represents one of the most straight-forward methods for aryl C-C bond formation. This reaction class has been studied most intensively which produces a number of name reactions. Among those, Kumada cross

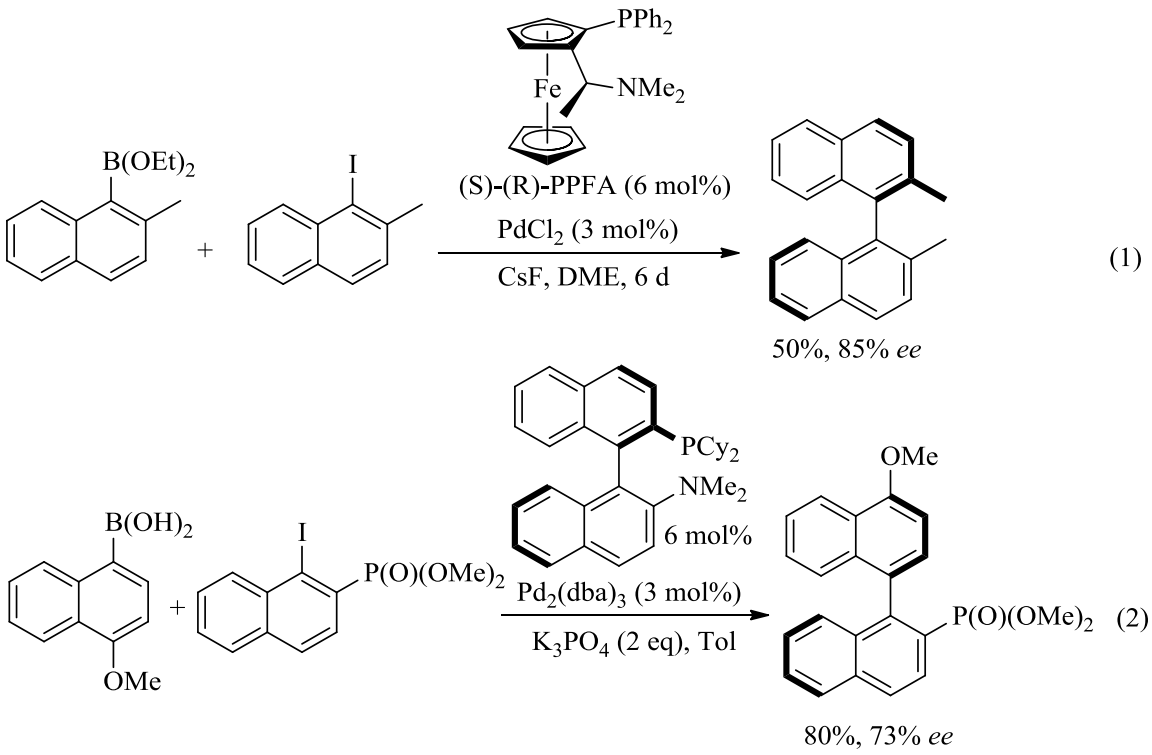
coupling is one demands discussion. Hayashi's defining work has shown that the axially chiral biaryls can be synthesized by Pd-catalyzed asymmetric Kumada coupling reaction with high yield and enantioselectivity using chiral phosphine ligands. It's important to note that the addition of lithium bromide was found to be essential for high enantioselectivity as well as for high catalytic activity (Scheme 40).[76] The product was found to be useful as a building block for the synthesis of chiral phosphine ligands.




**Scheme 40.** Kumada cross coupling reaction.

Another important types of cross-coupling reaction needs to be discussed is Suzuki-type cross coupling reaction. Along with Richard Heck and Ei-ichi Negishi, Suzuki received the prestigious Nobel prize in 2010 for discovering this reaction class. One of the notable achievement as an application of this reaction is the ability to synthesize axially chiral biaryl compounds. In 2000, both Cammidge[77] and Buchwald[78] simultaneously reported the first example of the synthesis of axially chiral biaryls by Suzuki cross coupling reaction. Cammidge and co-workers[25] obtained binaphthyl product with a maximum *ee* of 85% (Scheme 41, eq 1). Buchwald[26] synthesized chiral biaryls with phosphonate moiety

which was shown to be suitable for their further functionalization and has been used to produce new chiral ligands (Scheme 41, eq 2).

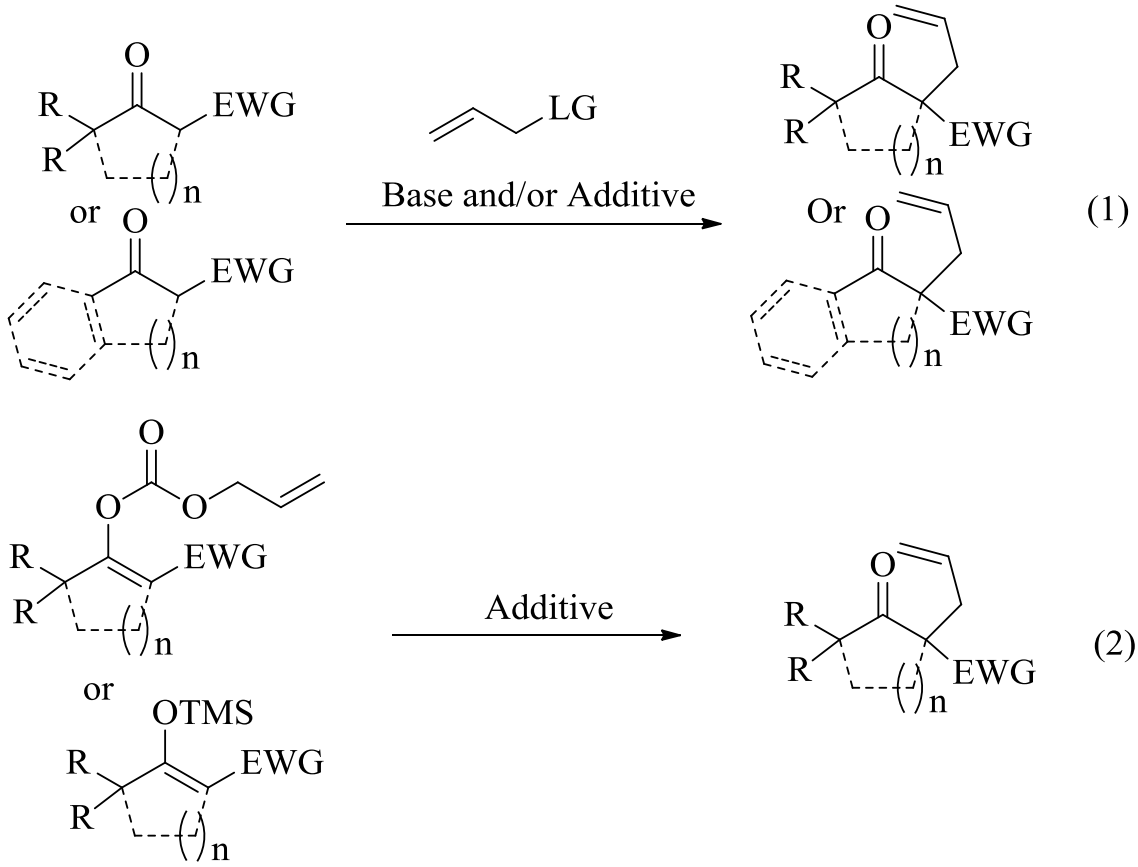



**Scheme 41.** Suzuki cross-coupling reactions.

## 2.5. Palladium-catalyzed asymmetric allylic alkylation (Pd-AAA)

The Pd-AAA[79] (Tsuji-Trost reaction) reaction has emerged as a powerful tool for the creation of quaternary stereocenters with high chemo-, regio-, and stereoselectivity.[80] The term "Tsuji-Trost reaction" is a generic term used to describe two reaction classes. The first class, called Pd-AAA, utilizes a nucleophile that is coupled intermolecularly with a Pd π-allyl complex, typically generated from allyl acetate or allyl carbonate (Scheme 42,

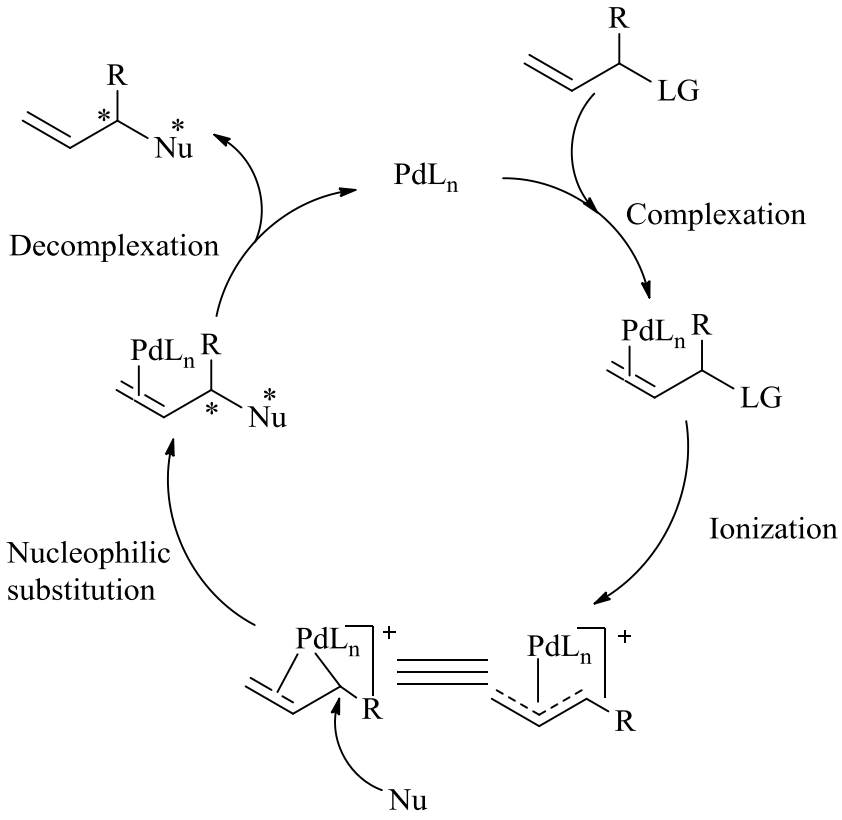
eq 1). In the second class an allyl enol carbonate or silyl enol ether forms an *in situ* generated enolate nucleophile via decarboxylation (hence called Pd-catalyzed decarboxylative asymmetric allylic alkylation, Pd-DAA) that reacts intramolecularly with the corresponding *in situ* generated Pd π-allyl complex (Scheme 42, eq 2). "Soft" nucleophiles such as malonates (p$K_a$ < 20) are often used for attack on the $\pi$-allyl palladium intermediate in the intermolecular version of the reaction.




R = H, Alkyl, etc.; EWG = Ester, Acyl, Cyano, Nitro, etc.

**Scheme 42.** Kinds of palladium catalyzed asymmetric allylic alkylation.

The basic mechanism (Scheme 43)[81] of intermolecular Pd-AAA reaction involves complexation of Pd metal to the olefinic double of the allyl complex, followed by ionization where Pd by being electron rich attacks the electron deficient carbon on allyl electrophile by $S_N2$ fashion and forms π-allylpalladium complex *in situ*. Subsequent $S_N2$ attack of nucleophile on allyl group in π-allylpalladium and decomplexation provides the desired product. In both intermolecular (Pd-AAA) and intramolecular (Pd-DAAA) reactions, a common electrophilic π-allylpalladium complex is formed, which can be reacted with a variety of nucleophiles.[82, 79e] Quaternary stereocenters can be formed either on a prochiral nucleophilic partner or, more commonly, on the electrophilic partner.



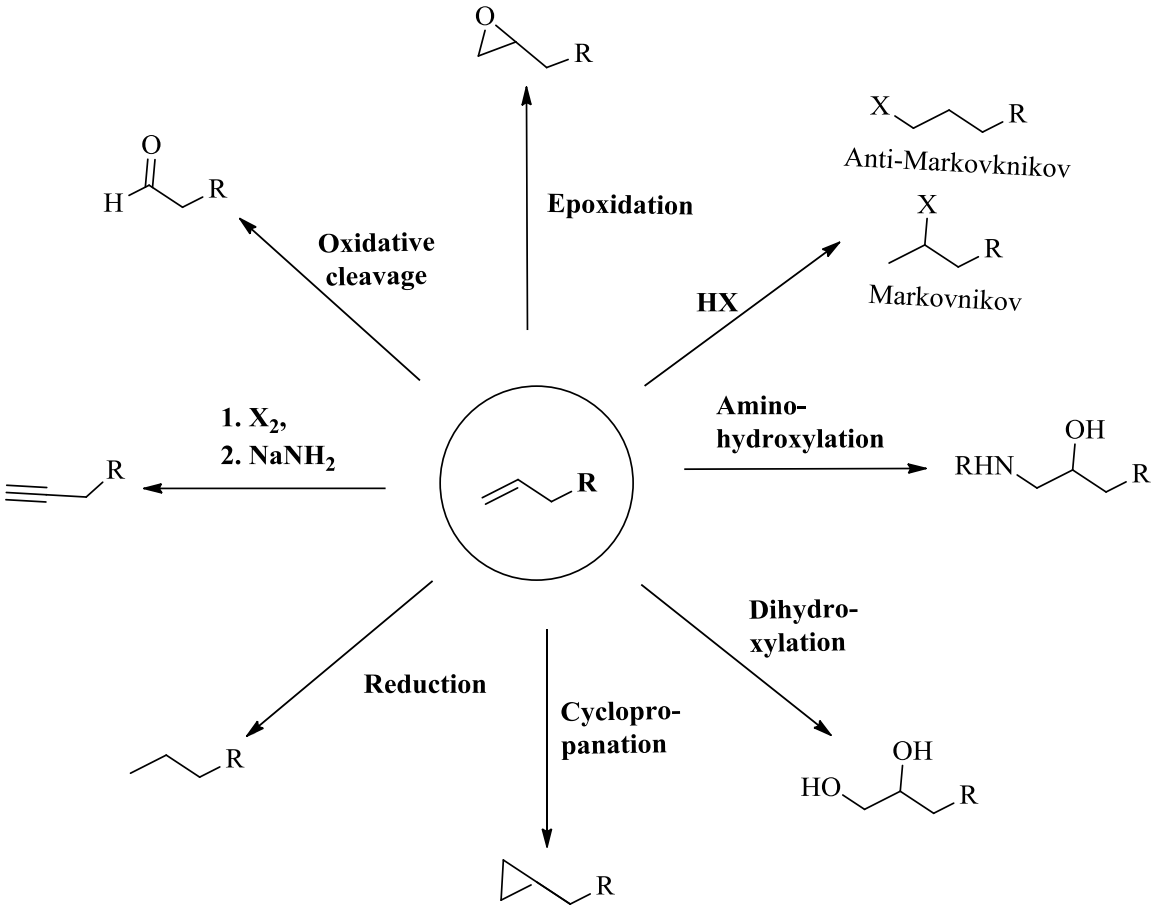

**Scheme 43.** Mechanism of Pd-AAA.

One of the inherent difficulties to get better enantioselectivity, which is evident in this mechanism, is the fact that both bond breaking (ionization) and making (nucleophilic substitution) events occur outside of the coordination sphere of the metal, i.e., on the face of the π-allyl unit opposite to the palladium and its chiral inducing ligands. Thus, both the leaving group and nucleophile are segregated from the chiral environment of the ligand by π-allyl moiety. For this very reason, it took a notable amount of time to harness the enantiodiscriminative potential of this reaction with a wide range of substrates in a predictable manner. Only recently these reactions have developed into processes with a variety of substrates, even though the first report of the enantioselective variant of this reaction was in 1977. This lag time may be due to the fact that the chiral ligand must somehow reach across the plane of the ally fragment in order to transfer their chirality to the electrophile or nucleophile. Also, it is much harder to induce chirality to nucleophile compare to electrophile, since nucleophile is only approaching towards the π-allyl moiety from outside and is further from the chiral environment of the metal.

With all these difficulties, still Pd-AAA has become an extremely powerful method for asymmetric synthesis and provided extremely high *ee* with chiral centers on both nucleophiles and electrophiles. This reaction differentiates itself from other catalytic methods in its ability to form multiple types of bonds such as C−C, C−O, C−S, C−N, and C−H. Moreover, the conditions of this reaction are mild and it is tolerant to most functional groups. Furthermore, this Pd-AAA reaction is unique in a sense that it has multiple mechanisms for enantiodiscrimination (which will be discussed later in this chapter) compare to most other metal-catalyzed asymmetric reactions where

enantioselectivity is derived only from differentiation of the enantiotopic π-faces of an unsaturated system.

Besides, the allylic moiety which is attached to the nucleophilic carbon by this reaction possesses great synthetic utility (Scheme 44), and is one of the main reasons for the great success of this Pd-AAA reaction.




**Scheme 44.** Possible synthetic transformations of the allyl group.

### 2.5.1. Mechanisms for enantiodiscrimination

Each step in the mechanism (Scheme 43) of Pd-AAA reaction offers an opportunity for enantiodiscrimination. Therefore, several ways to achieve enantioselection are available. The potential sources of enantiodiscrimination in Pd-AAA are (a) metal-olefin complexation, (b) ionization, (c) enantioface discrimination of the π-allyl complex, (d) nucleophilic attack at enantiotopic termini, and (e) enantioface discrimination in the nucleophile.[83]

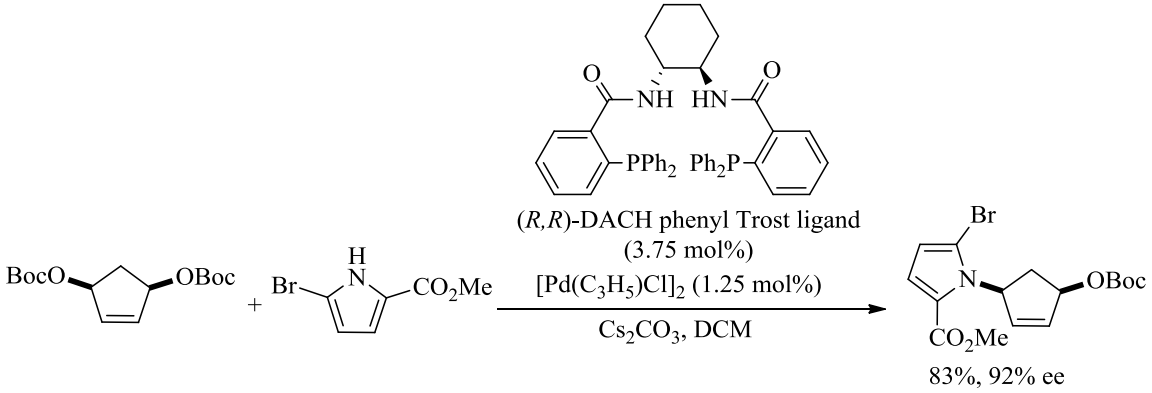
(a) Enantiofacial complexation

Metal-olefin complexation is a potential source of stereoinduction. Pd must distinguish between different faces of the olefin, if it is not symmetrically $C_{2h}$ disubstituted. During this step, if one diastereomer of the complexes ionizes faster compare to other diastereomer and the capture of the π-allyl complex formed from that diastereomer by nucleophile is faster in relation to π-σ-π equilibration, then the complexation of the enantiotopic faces of olefin becomes enantiodetermining step.

(b) Enantiotopic ionization of leaving groups

In Pd-AAA reaction, stereoinduction is greatly influenced by ionization of the leaving group. With *meso*-allyl or achiral *gem*-disubstituted allyl electrophiles, the selective ionization of one of the two enantiotopic leaving groups becomes enantiodetermining

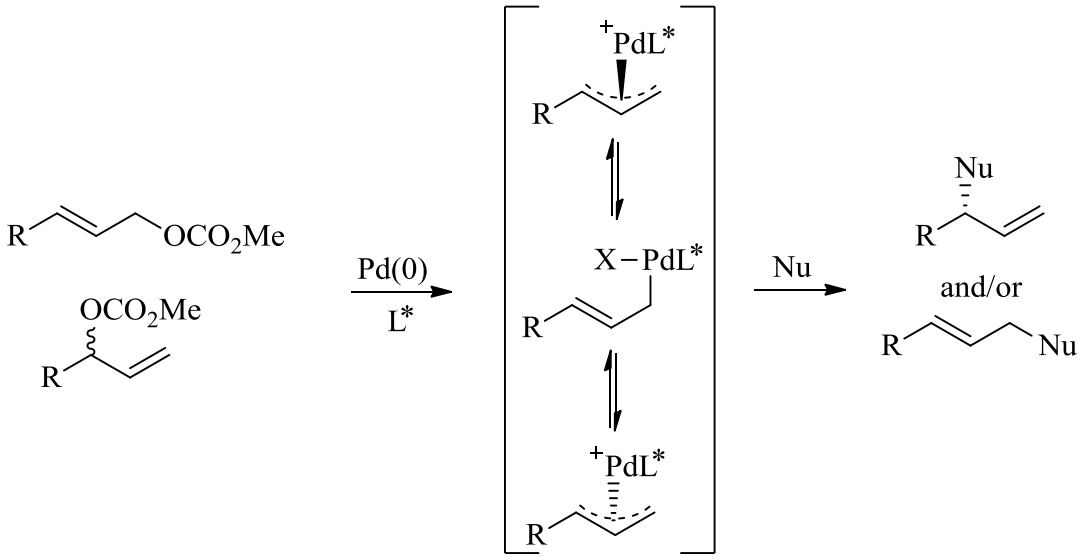
step. As an example, the *meso*-cyclopentene-1,4-diol can selectively form one enantiomer over other with a pyrrole nucleophile (Scheme 45).




**Scheme 45.** Enantiodiscrimination via enantioselective ionization.

(c) Enantiofacial exchange of the $\eta^3$–allyl complex

In an unsymmetrical acyclic allylic system, enantioselection is determined by which face of the allylic fragment palladium metal presents to the nucleophile. When the initial olefinic complexation is rapid and reversible, or when π-σ-π equilibration is significantly faster than nucleophilic capture, two diastereomeric π-allylic palladium complexes can form *via* Pd-σ-allylic complex (Scheme 46). However, these two π-allylic palladium complexes can equilibrate through π-σ-π equilibration. For this very reason, both of the enantiomers can be formed if the rate of nucleophilic capture for both complexes is similar. However, if the rate of attack by nucleophile is significantly faster with one complex compare to another, high enantioselectivity should be observed.



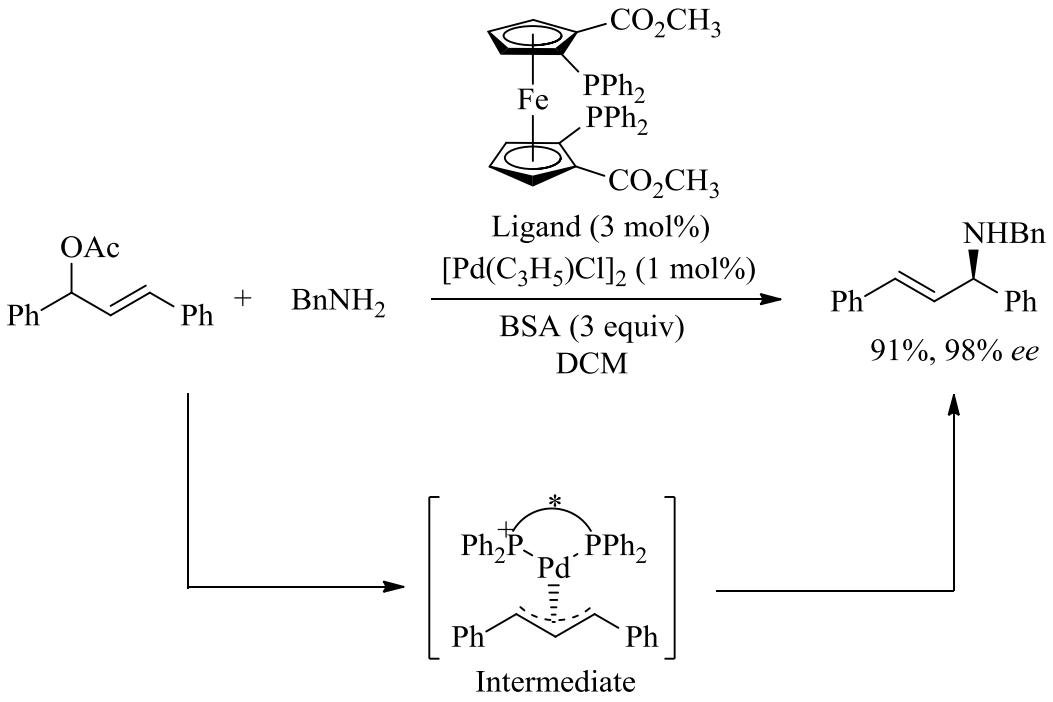

**Scheme 46.** Enantioselection by discrimination of the π-allyl intermediates.

(d) Differentiation of the enantiotopic allyl termini

When the $\eta^3$-allyl moiety has $C_{2h}$ symmetry, i.e., when the starting allylic system is a chiral racemic mixture but the ionization leads to a *meso*-π-allyl ligand, nucleophilic attack to either one of the enantiotopic termini becomes enantiodetermining step and provides a chiral product.

As an example (Scheme 47), 1,3-diphenylallyl acetate in Pd-AAA reaction forms the intermediate π-allylpalladium complex where π-allyl ligand is now *meso*. If a chiral ligand is introduced with palladium, one terminus of this π-allyl ligand will be preferentially attacked by the nucleophile to furnish one enantiomer of the product. In this particular example, benzylamine has been used as the nucleophile which yielded an

allylic amine product in excellent *ee*.[84] Even though the chiral ligand resides opposite to the π-allyl moiety on the palladium metal, yet it provided remarkable enantiodiscriminative control (98% *ee*).

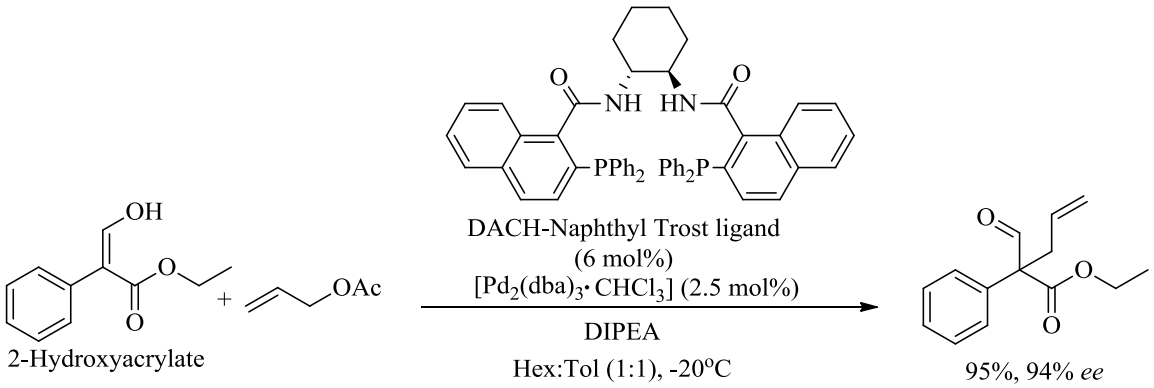



**Scheme 47.** Deracemization through desymmetrization of an intermediate *meso*- π-allyl ligand.

(e) Enantiofaces of prochiral nucleophile

Enantioselectivity can be achieved on nucleophiles as well, by reacting π-allylpalladium complex with prochiral nucleophiles. This occurs by enantioface discrimination of the nucleophile. Prochiral nucleophiles, such as 3-hydroxy-2-aryl-acrylic acid ethyl ester can

lead to enantioselective alkylation with symmetrically substituted or unsubstituted allylic moieties (Scheme 48).[85]




**Scheme 48.** Enantioselection by discrimination of enantiofaces of prochiral nucleophile.

Another mechanism of action comes from equilibrating mixture of enantiomers of racemic nucleophiles where one enantiomer is favored for nucleophilic attack over other. If the allyl unit is also prochiral, a potential double enantioselectivity provides diastereoselectivity.

### 2.5.2. General considerations and rationale of ligand design

The mechanism (Scheme 43) of Pd-AAA clearly shows that both bond breaking and bond making events occur outside of the coordination sphere of the metal, opposite to the chirality control element and thereby, distal to the chiral environment. This difficulty created a big challenge to design a suitable ligand that would be able to induce chirality by overcoming the drawbacks, and as a result, it has stimulated a great deal of work.

Three concepts have gained ground:

(a) Attaching a substituent to the ligand via a tether long enough to reach the other side of the π-allyl moiety to intereact with any incoming nucleophile. The ferrocenyl ligands family represents this class of ligands.[86]

(b) Employing electronic desymmetrization to the ligand due to which the bond length between Pd and carbon on one allyl termini will be different than other allyl termini and thus creating a biasness of nucleophile to attack towards one terminus over other. Oxazolines are an example of this class of ligands.[87]

(c) Creating a chiral space for the substrate to immerse wherein the enantiodiscriminative step can occur in that chiral space. This can be generated by the conformational bias for edge-face interactions of the phenyl groups of the diarylphosphino moieties induced by the stereogenic centers. Trost ligands solely represent this class.

Even though, both ferrocenyl and oxazoline ligands have shown success in various cases, Trost ligands[88] have proven to be the most general in inducing chirality in Pd-AAA to date.[89]

The concept of creating a chiral space in Trost ligand class has been inspired by enzymatic catalysis. Enzymes, depending on the substrate, create chiral spaces by

conformational change, and induce asymmetry by keeping the substrate and making the reaction happens inside the chiral space. Similarly, a chiral space was envisioned in ligands that envelops the ally substrate situated on the other side of the metal (Figure 10, image I). To do so, a chiral scaffold, similar to folding in enzyme, was needed (Figure 10, image II) that will produce primary chirality. This chiral scaffold would, in turns, induce conformational chirality of the diarylphosphino moieties and a linker, i.e., amide in this case, can create the chiral space for the substrate to reside (Figure 10, image III), just like the catalytically active site in enzyme.

**Figure 10.** Cartoon model for ligand design.

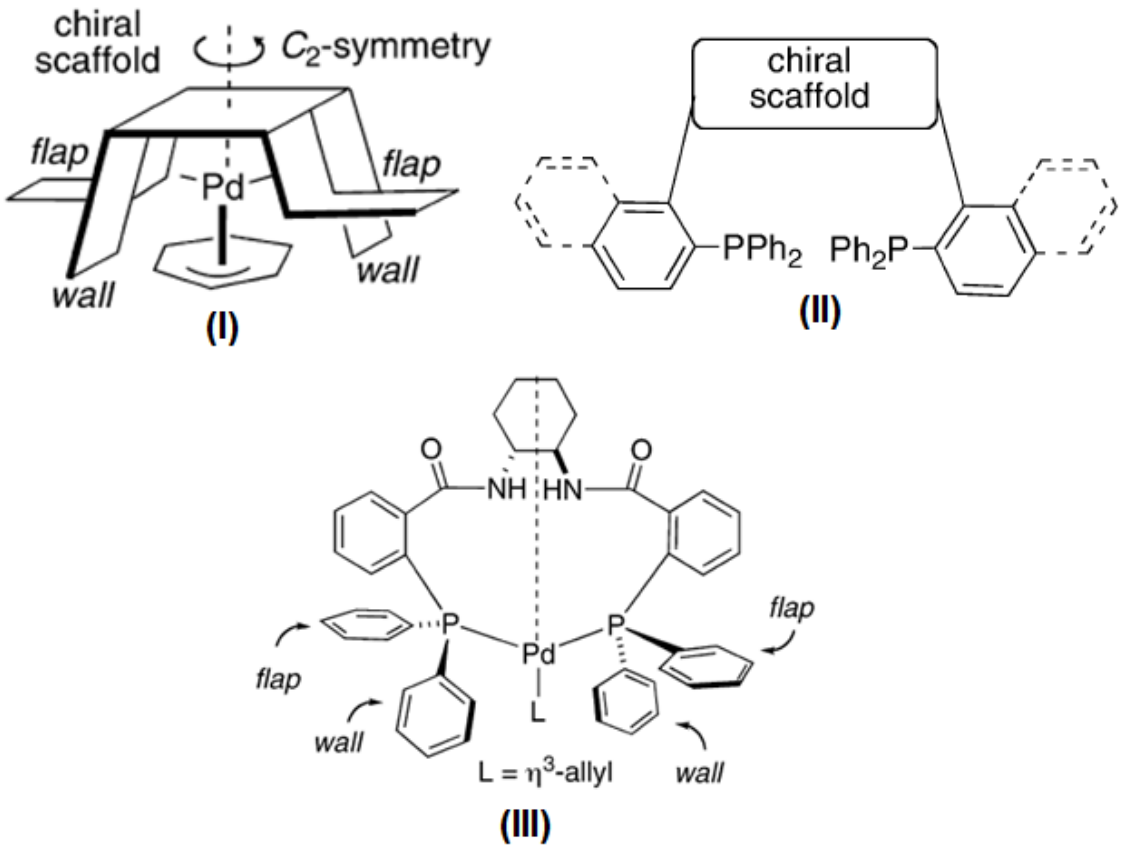
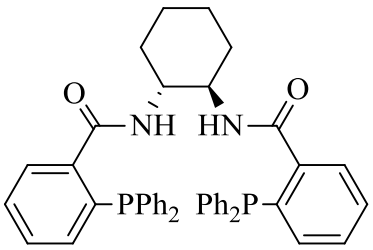
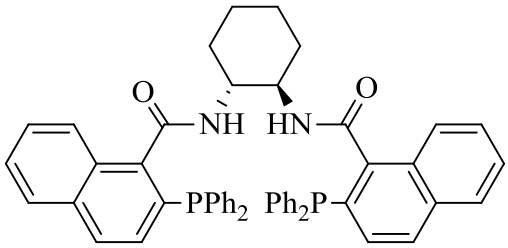


Figure 11 shows a few examples of the Trost ligands that have been developed depending on the cartoon image II, Figure 10. All of These ligands have proven to be successful in producing enantiopure compounds with one substrate classes or other.

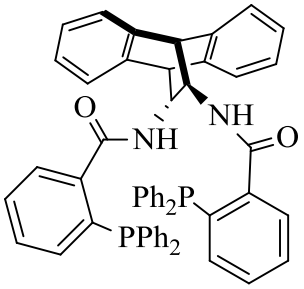
**Figure 11.** Typical Trost ligands for Pd-AAA.



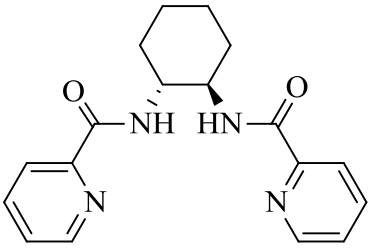

DACH-Phenyl Trost




DACH-Naphthyl Trost



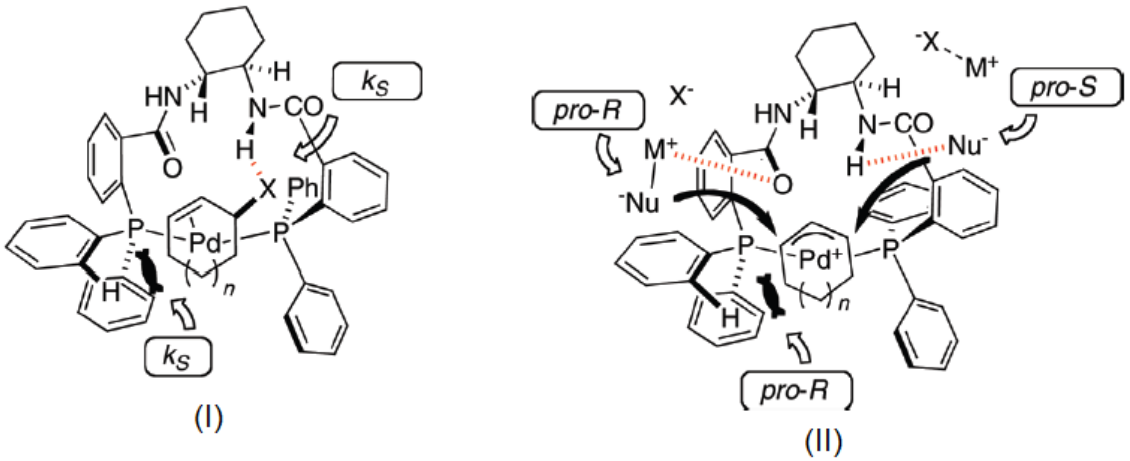

ANDEN-Phenyl Trost




DACH-Pyridyl Trost

Recent structural and mechanistic studies consolidated the analogy to an active site of an enzyme by the fact that the H-bonding interactions between the N-H of the linker amides with either the leaving group when the ionization is enantiodetermining or the nucleophile when nucleophilic capture is enantiodetermining are vital for the chiral recognition (Figure 12).[90]

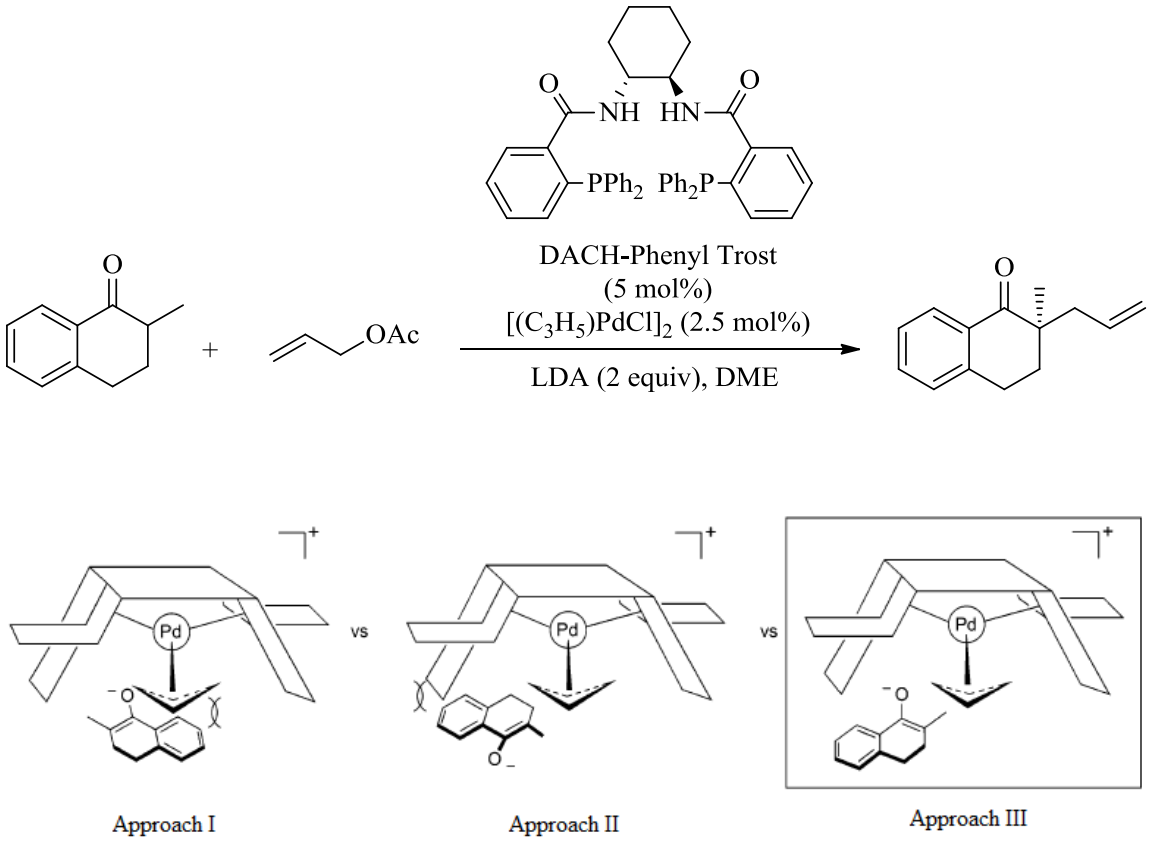
**Figure 12.** Cartoon models for kinetic resolution (I) and asymmetric induction (II) in Pd-AAA with Trost ligand showing the ability of the ligand to act as both H-bond donor and acceptor.




When it provided very high enantio- and stereo-selectivity on electrophilic allylic moiety, the Trost ligand class has shown a significant enantioselective control on nuclephiles as well, which is very challenging due to the fact that the nucleophile is rather approaching towards the electrophilic allyl group from outside of the power-sphere of the chiral ligand. So, for a successful reaction, the chiral ligands must influence the trajectory of the approach and impart a facial bias to the incoming nucleophile. Clearly, this idea was proven possible by Trost ligands since various stabilized and unstabilized enolates are allylated asymmetrically with high *ee*.[89, 91]

As an example, for the Pd-AAA of tetralone, it produces allylated product with 99% yield and 88% *ee* (Scheme 49).[92] There are several approaches that may be considered for the

nucleophile to approach the π-allylpalladium complex (Scheme 49, Approach I, II, and III). **Approach I** is eliminated due to the assumption that the preferred transition state will place the sterically bulky aryl ring under the flap rather than under the allyl moiety. Approaches II and III can be differentiated by the same steric reason between the substrate and ligand. In **approach II**, there's a steric interaction of both ring systems with the back wall of the ligand since enolate anion which actuall works as nucleophile is other side of these rings in regards to electrophilic allylic moiety. However, these steric interactions are minimized in **approach III**. According to this analysis, the predicted stereochemistry is (*S*) as was determined experimentally.

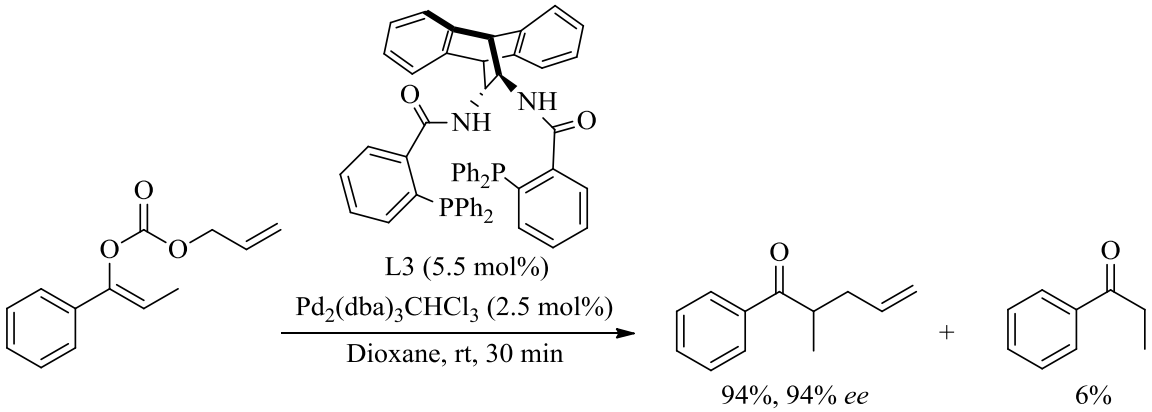



**Scheme 49.** Chirality at the nucleophile in Pd-AAA.

### 2.5.3. Pd-AAA employing acyclic nucleophile

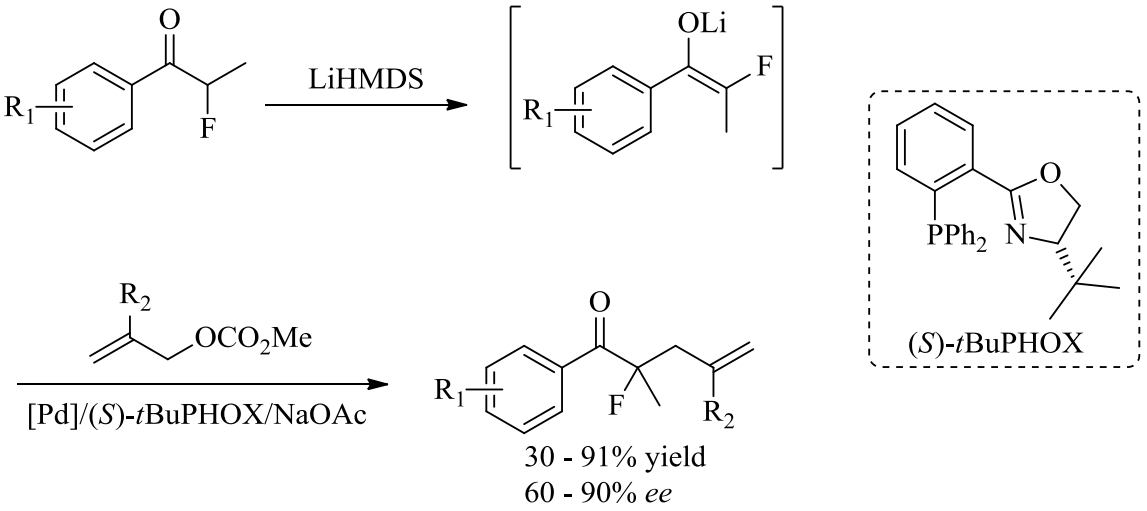
Even though the asymmetric synthesis of compounds containing chiral centers on nucleophiles is difficult to achieve compare to that on electrophilic allyl moieties, numerous amount of work has been carried out to accomplish it. This produces a large number of accounts in various peer reviewed journals all over the world. However, most of these works have been carried out with cyclic substrates, using mainly cyclic enolates as starting material. It is even more challenging to achieve desired stereoinduction on the nucleophile when acyclic enolates are employed. The reason is that the conformationally non-rigid acyclic substrates possess more degrees of freedom. However, high enantioselection requires proper matching of the substrate in the chiral pocket of the Pd-π-allyl complex and thereby less randomness. This factor decreases the probability of achieving high degree of stereoselctivity when acyclic substrates are employed, since it contains greater number of rotatable bonds, which in turns increases the entropy and probability of mismatching.

While the first example of an enantioselective Pd-AAA reaction was reported in 1977,[93] it's only in 2005 when the first account of asymmetric induction on acyclic nucleophile was published, although by decarboxylative (Pd-DAAA) version of the reaction (Scheme 50).[94]




**Scheme 50.** First example of using acyclic substrate in palladium catalyzed reaction.

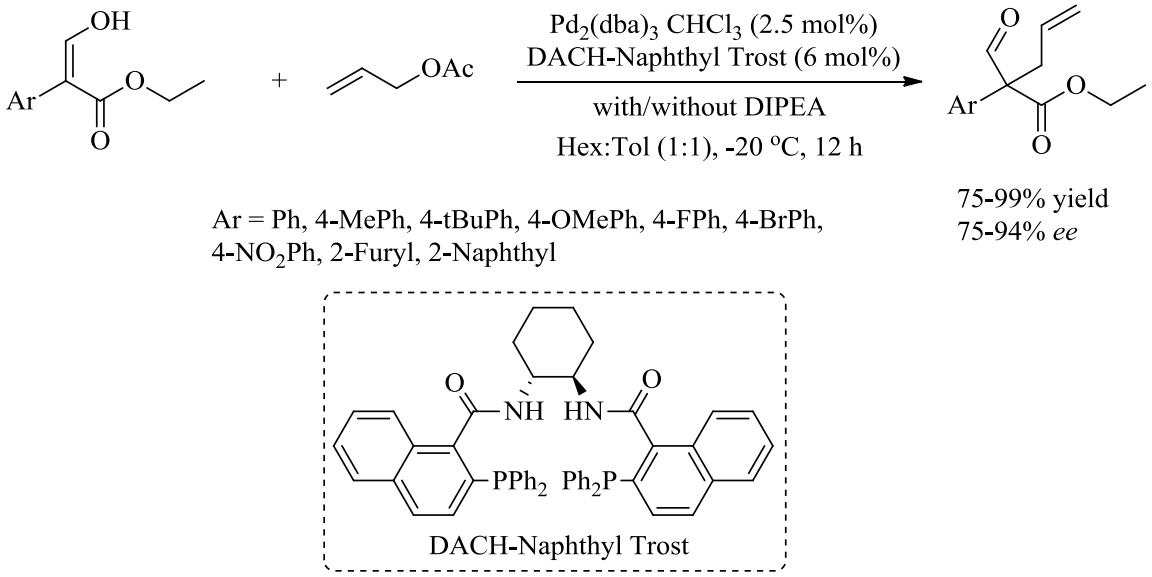
Recently in 2014, Guo and co-workers[95] have synthesized a series of α-fluorinated quaternary ketones by Pd-AAA reaction using *t*BuPHOX as chiral ligand (Scheme 51). Fluorinated compounds are potentially useful molecules for the development of drugs, agrochemical, and functional materials. Before this account, few accounts[96] have been reported to synthesize similar compounds containing fluorine in α-position, but with less success in regards to enantioselectivity.




$R_1$ = Ph, 4-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-PhPh, 3-BrPh, 2-$CF_3$Ph, 2-Naphthyl
$R_2$ = H, Me

**Scheme 51.** Acyclic α-fluorinated quaternary ketones by Pd-AAA.

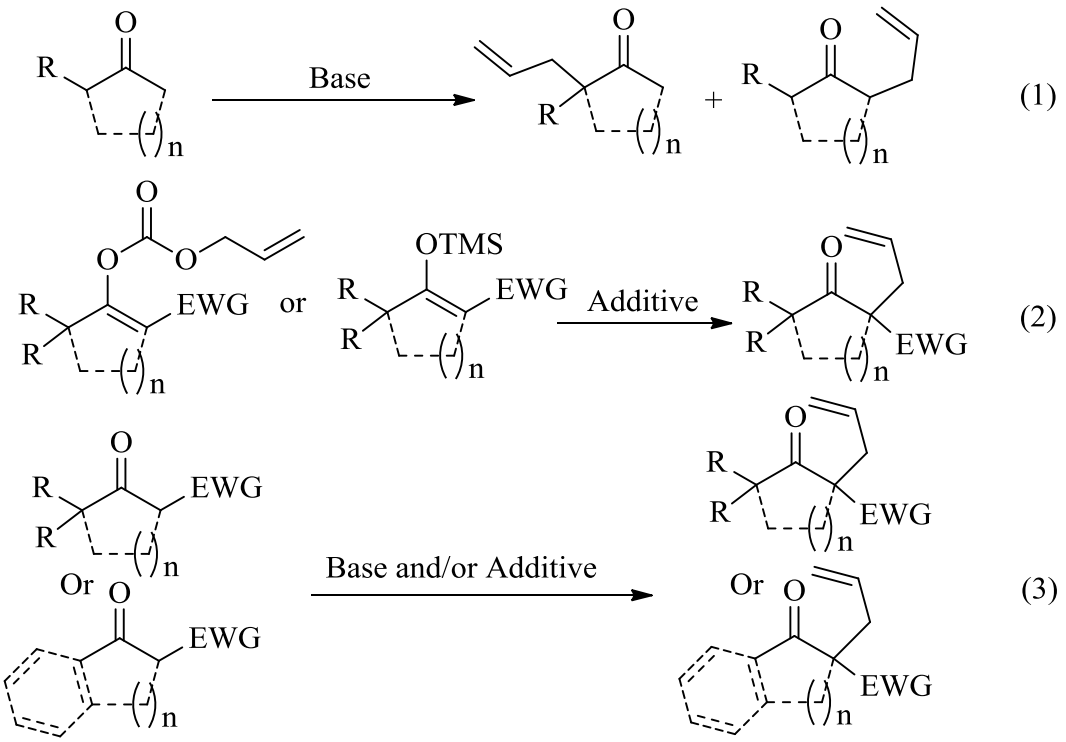
An outstanding finding has been reported by Hossain and co-workers[39] in 2014 where a set of acyclic all-carbon α-aryl quaternary stereocenter has been synthesized via Pd-AAA using hydroxyacrylate as unprecedented nucleophilic counterpart instead of the widely used ketonic substrates. This produced a very rare all-carbon quaternary aldehydes with high yield and *ee* (Scheme 52).




**Scheme 52.** Acyclic all-carbon α-aryl quaternary aldehydes by Pd-AAA.

This group argues that the above reaction methodology possesses significant advantage over other Pd-AAA reaction due to its unprecedented use of hydroxyacrylate as nucleophile, while most researches reported so far was with ketones. However, one of the obvious problems of ketones as starting material is their tendency to form multiple products in presence of bases[8] (Scheme 53, Eq. 1). To avoid this structural difficulty, allyl enol carbonates[97] and silyl enol ethers[98] have been introduced successfully (Scheme 53, Eq. 2). However, it requires one more extra step to make these substrates. Substrates either lacking an α- proton or containing an α-electron withdrawing groups on one site, or a combination of both, have also been successfully employed (Scheme 53, Eq. 3),[99] even though the substrate is now biased towards certain functionalities. These above mentioned problems associated with ketones as starting material can be avoided in this

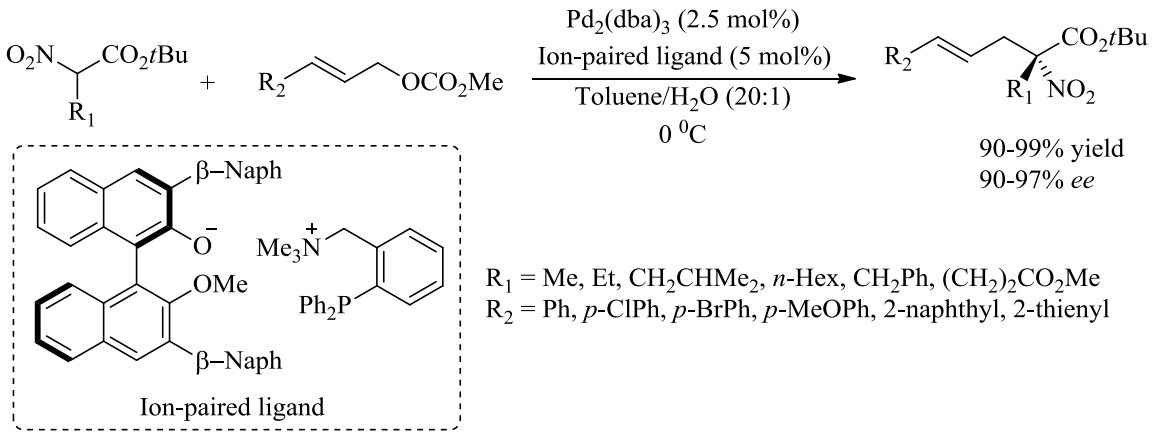
protocol. Moreover, aldehydes are more reactive than ketones which might increase the scope of further research.




**Scheme 53.** Formation of mixed products while ketonic substrates used as nucleophile in Pd-AAA and approaches investigated to curb this phenomenon.

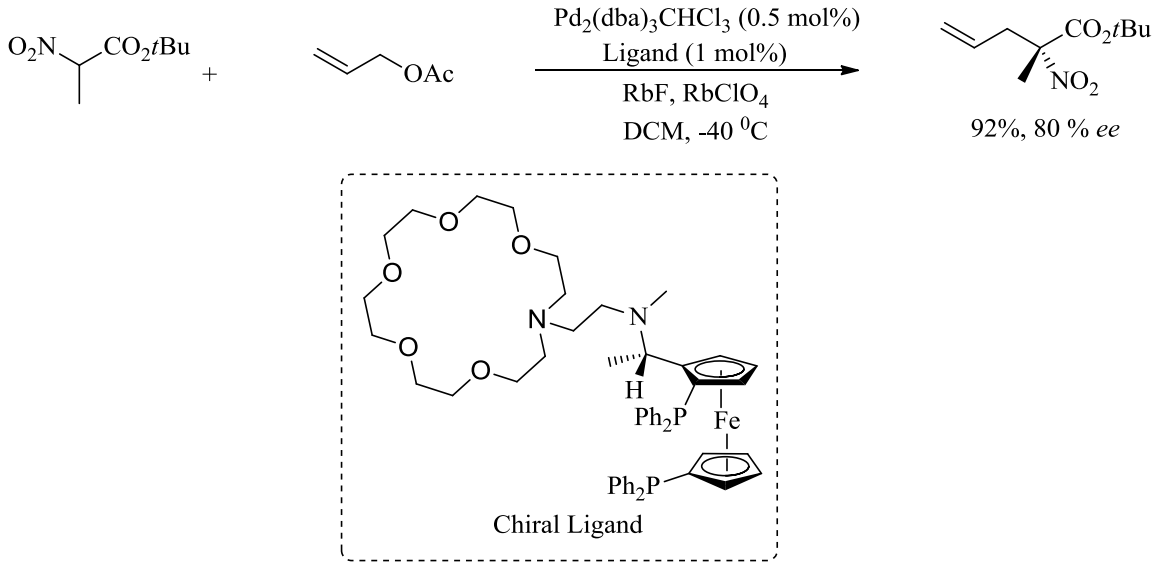
Another remarkable research has been published in early 2012 by Ooi and co-workers, where a novel ion-paired chiral ligand has been developed for Pd-AAA of α-nitrocarboxylates. This novel ligand consists of an achiral cationic ammonium-phosphine hybrid ligand coupled with a chiral binaphtholate anion. This ion-paired chiral ligand

provided remarkable stereocontrolling ability to its palladium complex, affording 91-97% *ee* with a series of substituted α-nitrocarboxylates (Scheme 54).



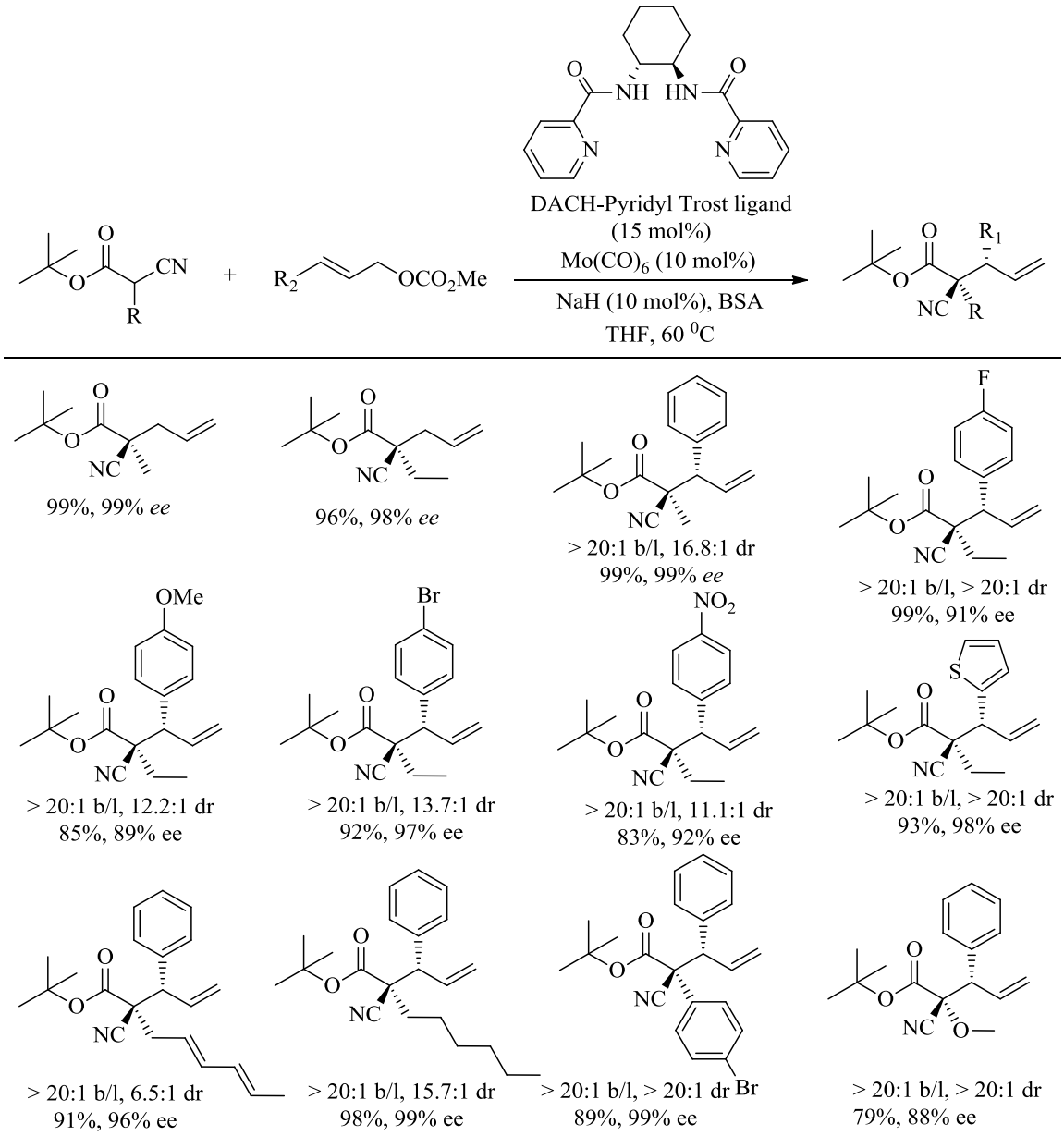

**Scheme 54.** Ion-paired ligand in Pd-AAA of acyclic α-nitrocarboxylates.

In 1996, Ito and co-workers[100] reported the synthesis of similar acyclic α-nitrocarboxylate comounds with good yield and enantioselectivity. This time, another innovative design of a novel ligand containing crown-ether moiety was instrumental for this success. Use of additive was also a key component in this reaction, which is a fairly common practice in Pd-AAA reaction (Scheme 55).




**Scheme 55.** Chiral crown-ether phosphine ligand in Pd-AAA reaction of acyclic substrate.

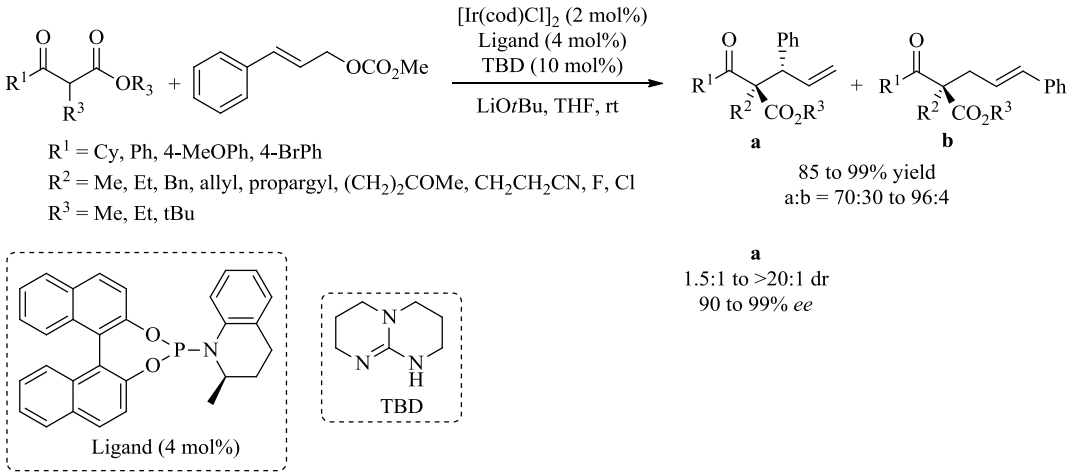
Other transition-metal catalysts instead of palladium, e.g., molybdenum, Irridium, etc., have also been successfully employed. Recently, Trost and co-workers[101] have reported a number of highly functionalized branched acyclic cyanoesters containing a quaternary carbon stereocenter with a vicinal tertiary stereocenter by a prudent use of Molybdenum as a transition-metal catalyst. Surprisingly, the reaction was highly enantio- and diastereoselective (Scheme 56).




**Scheme 56.** Enantioselective synthesis of acyclic compounds by Mo-AAA.

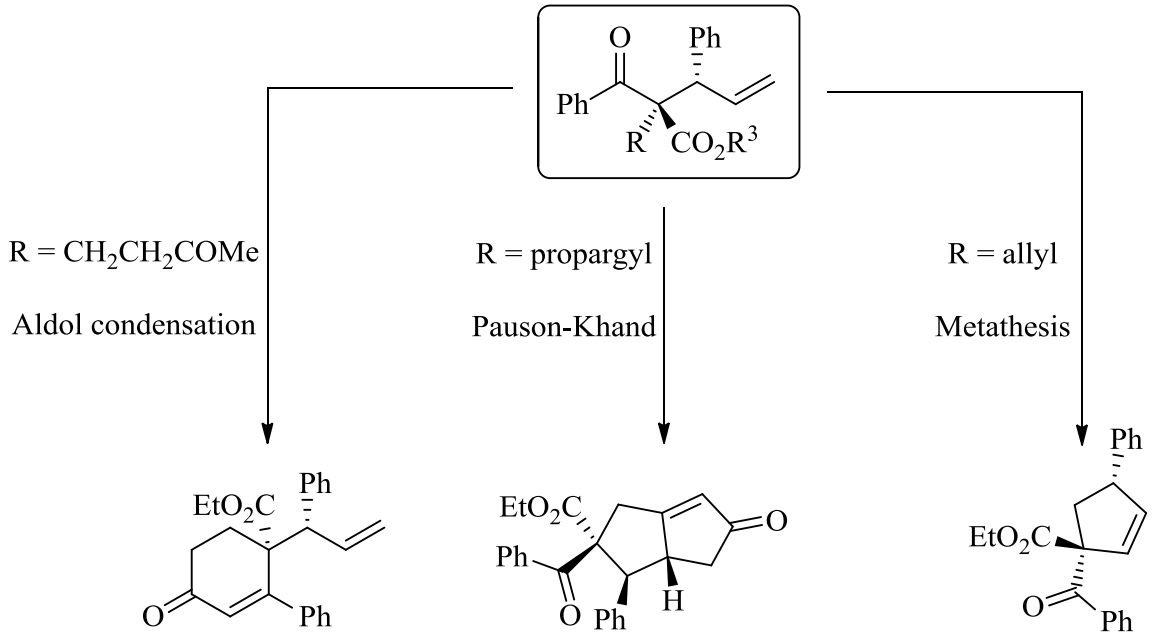
Another important transition metal frequently used for the synthesis of acyclic quaternary all-carbon or tertiary stereocenters by AAA reaction is iridium.[102] As an example, the first regio-, diastereo-, and regioselective Ir-AAA reaction of acyclic β-ketoesters to form vicinal tertiary and all-carbon quaternary stereocenters was reported recently by Stoltz

and coworkers (Scheme 57).[103] This iridium catalyzed asymmetric allylic alkylation reaction showed broad functional group tolerance at the keto-, ester-, and α-position of β-ketoester.




**Scheme 57.** Enantioselective synthesis of linear quaternary compounds by Ir-AAA.

In order to demonstrate the utility of this method, Aldol condensation, Pauson-Khand cyclization and ring closing metathesis reactions were carried out with the alkylation product to synthesize biologically important building blocks (Scheme 58).




**Scheme 58.** Derivatization of β-ketoester products.

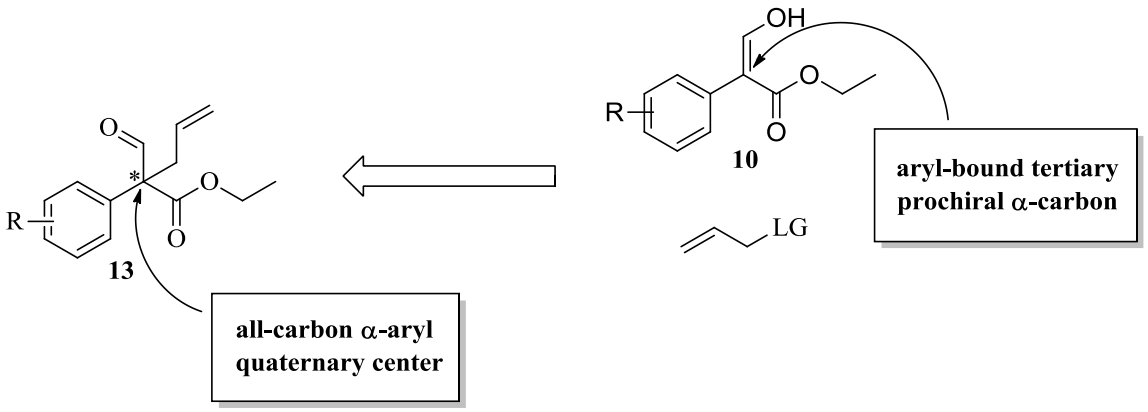
Previously, it has also proved to be a powerful transition metal catalyst in accessing vicinal all-carbon quaternary and tertiary stereocenters by the regio-, diastereo-, and enantioselective asymmetric allylic alkylation of cyclic substratess.[104]

## 2.6. Results and discussions: Pd-AAA of 3-hydroxy aryl acrylates **10** for the synthesis of all-carbon α-aryl quaternary carbonyl compounds

The development of catalytic, enantioselective methods for the construction of all-carbon quaternary stereocenters[2,3,4,5,6] is an outstanding achievement in the recent history of organic chemistry. The Pd-AAA reaction has played a key role in creating such stereocenter and allowed researchers to synthesize a vast number of biologically potent

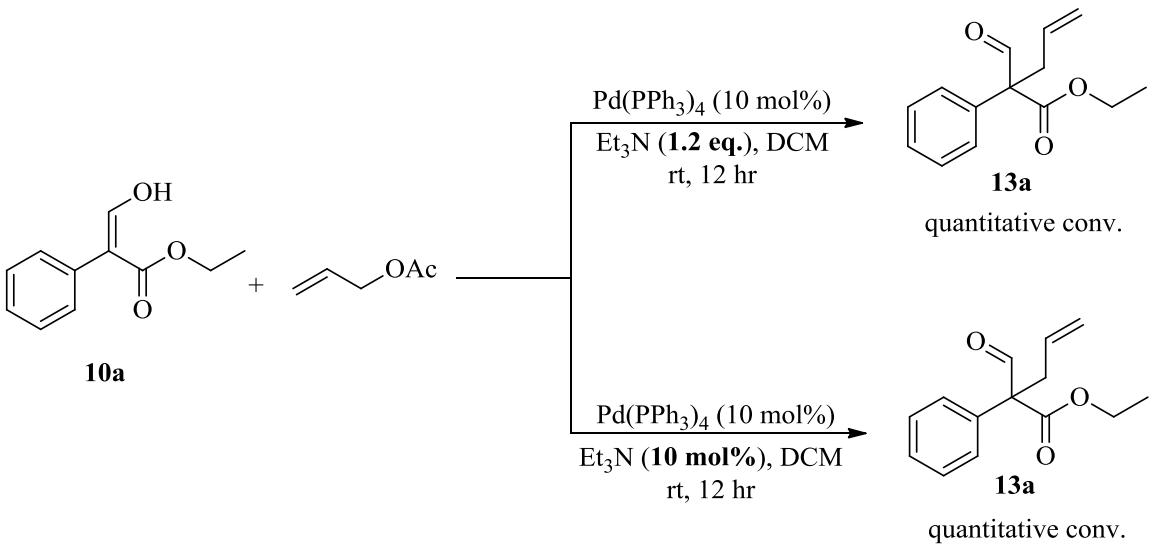
natural products.[7,8,9] However, synthetic methodologies to access compounds containing α-aryl groups to the quaternary carbon stereocenters are still rare. The increasing appearance of these all-carbon α-aryl quaternary stereocenters[105] in a growing number of biologically active natural products and pharmaceutical agents[106] creates a pressing need for the ability to construct this important motif enantioselectively.

We envisioned the possibility of constructing this vitally important all-carbon α-aryl quaternary stereocenters employing 3-hydroxy aryl acrylates **10** as substrates, since it features aryl-bound tertiary prochiral α-carbon which should be easily converted to quaternary carbon. We chose allyl group to be attached to this tertiary carbon due to it versatile synthetic utility (Scheme 59, to see versatility of allyl group Scheme 44).




**Scheme 59.** Rationale for 3-hydroxy aryl acrylate as a suitable candidate for the construction of all-carbon α-aryl quaternary stereocenters.

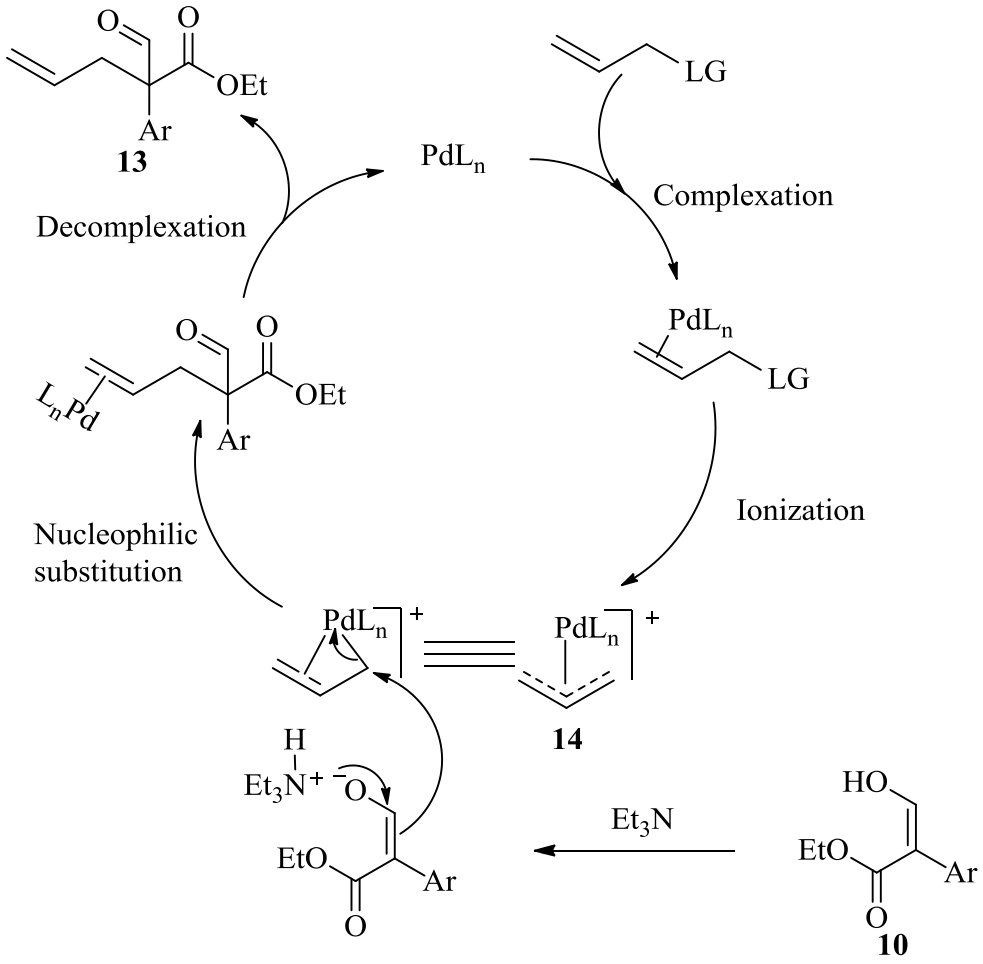
Since we have already achieved quantitative conversion of the desired *C*-allylated product **13a** from 3-hydroxy phenyl acrylate **10a** employing stoichiometric amount of π-allylpalladium complex **14** (Scheme 23, section 1.4), our next goal was to obtain catalytic version of this reaction. $Pd(PPh_3)_4$ has been employed as a catalyst and allyl acetate as allyl electrophile. We knew that base is essential for the reaction to proceed, which has been proved earlier (see scheme 43). This time we wanted to check whether it would need in catalytic or stoichiometric amounts. Thus, two sets of reactions was investigated at this point; one with stoichiometric and other with catalytic amount of base $Et_3N$. Both of these reactions provided quantitative conversion of desired all-carbon α-aryl quaternary stereocenter **13a** from 3-hydroxy phenyl acrylate **10a** using only 5 mol% of catalyst $Pd(PPh_3)_4$ (Scheme 60).




**Scheme 60.** Catalytic allylic alkylation of 3-hydroxy phenyl acrylate **10a**.

From the above observation, we concluded that the reaction is going through using base as a co-catalyst whereas Pd (0) is the catalyst. Thus we proposed the following

mechanism (Scheme 61): Pd (0) is first complexed with the olefinic double-bond of allyl group, and then in the ionization step, π-allylpalladium complex **14** is formed. Meanwhile, 3-hydroxy aryl acrylates **10** are deprotonated to reactive enolate by the action of the base. This enolate now attacks the electrophilic allyl terminus of the π-allylpalladium complex **14** by $S_N2$ fashion. In this step, co-catalytic base is regenerated along with byproduct acetic acid. In the final step, Pd (0) is regenerated by decomplexation from the allylic double-bond of the product **13**.

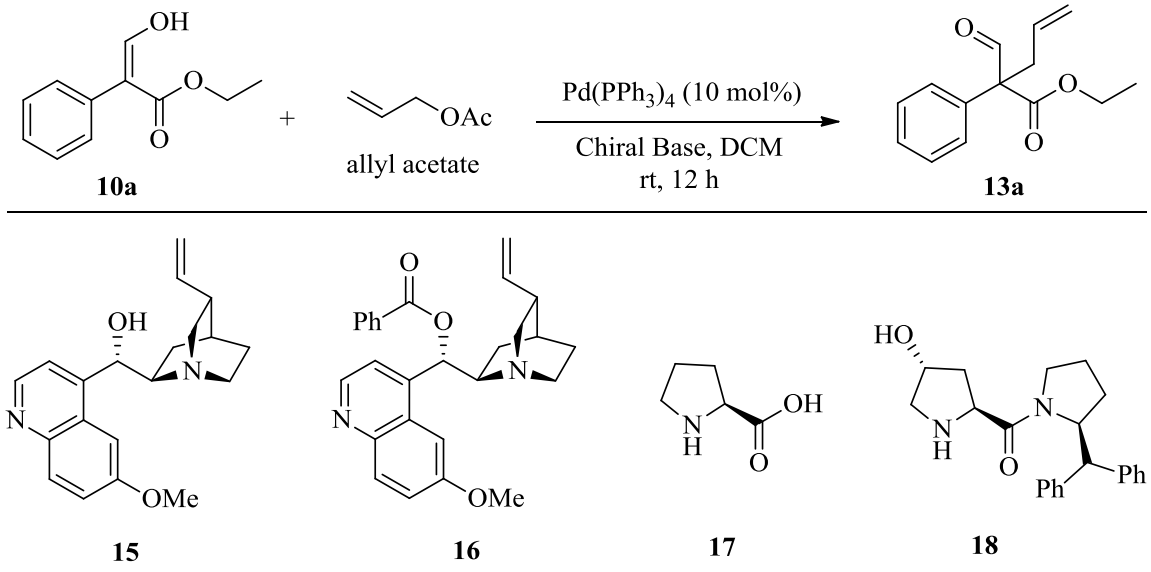



**Scheme 61.** Mechanism of catalytic allylic alkylation showing Pd(0) as catalyst and $Et_3N$ as co-catalyst.

This, in turn, means that there are two ways to achieve enantioselectivity: by (i) chiral base, or (2) chiral ligand.

2.6.1. Chiral induction by chiral amine bases

Our first approach was to achieve enantiodiscrimination by employing chiral bases. We have selected both quinine- and proline-based amines for the purpose. Two quinine based amines **15** and **16** as well as two proline-based amines **17** and **18** were employed for the reaction of **10a** in DCM at rt with the presence of $Pd(PPh_3)_4$ as catalyst. Unexpectedly, *ee* values for **13a** never exceeded more than 10%, even though conversion to **13a** was always quantitative. More surprisingly, the *ee* for even the stoichiometric amount of **15** was similarly unusually low (Scheme 62, Table 4).

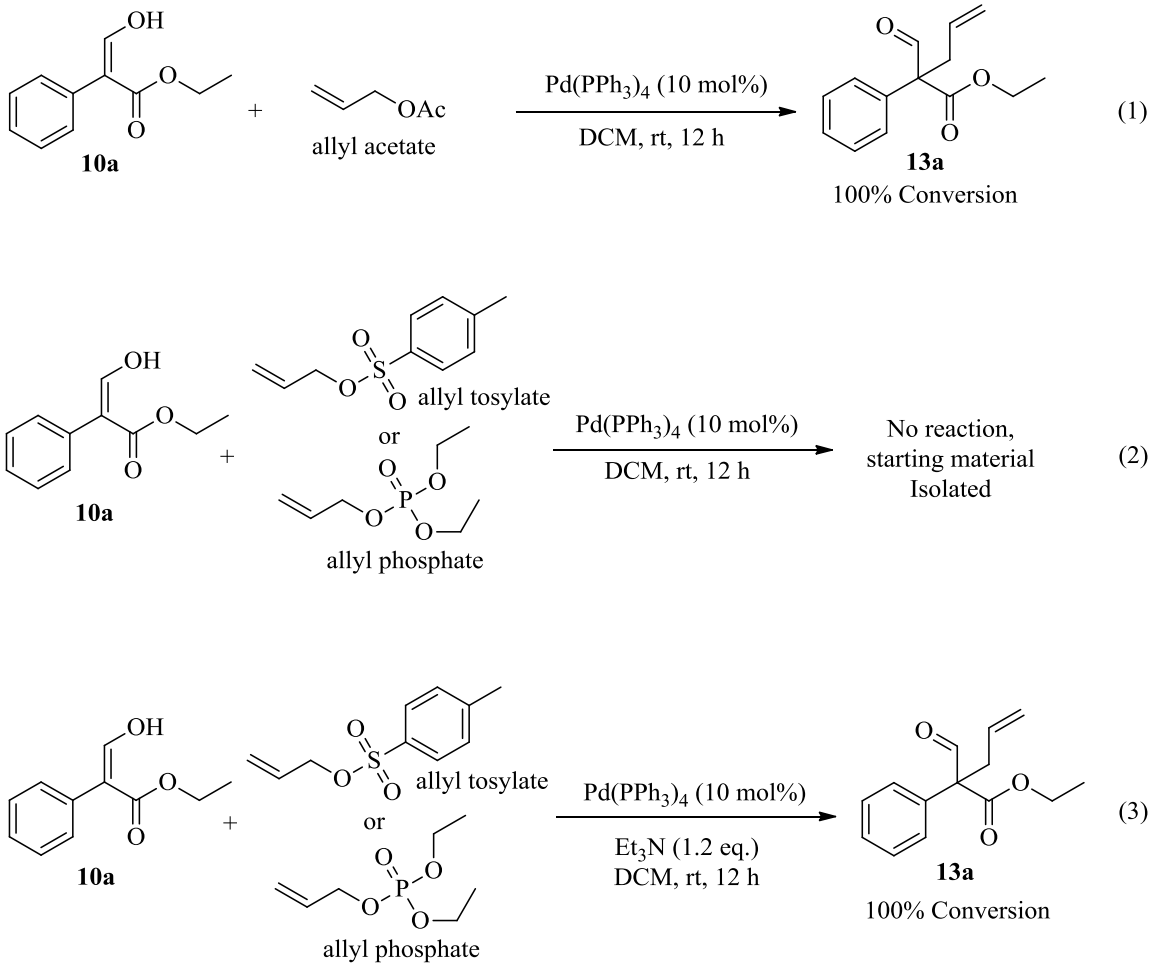



**Scheme 62.** Chiral induction by chiral bases.

**Table 4.** Optimization studies for chiral induction by chiral bases.

| Entry | Chiral Base [Eq] | Conv. [%] | *ee* [%] |
|---|---|---|---|
| 1 | **15** (1.1 eq) | Quantitative | 10 |
| 2 | **15** (10 mol%) | Quantitative | 10 |
| 3 | **16** (10 mol%) | Quantitative | 10 |
| 4 | **17** (10 mol%) | Quantitative | Racemic |
| 5 | **18** (10 mol%) | Quantitative | 5 |

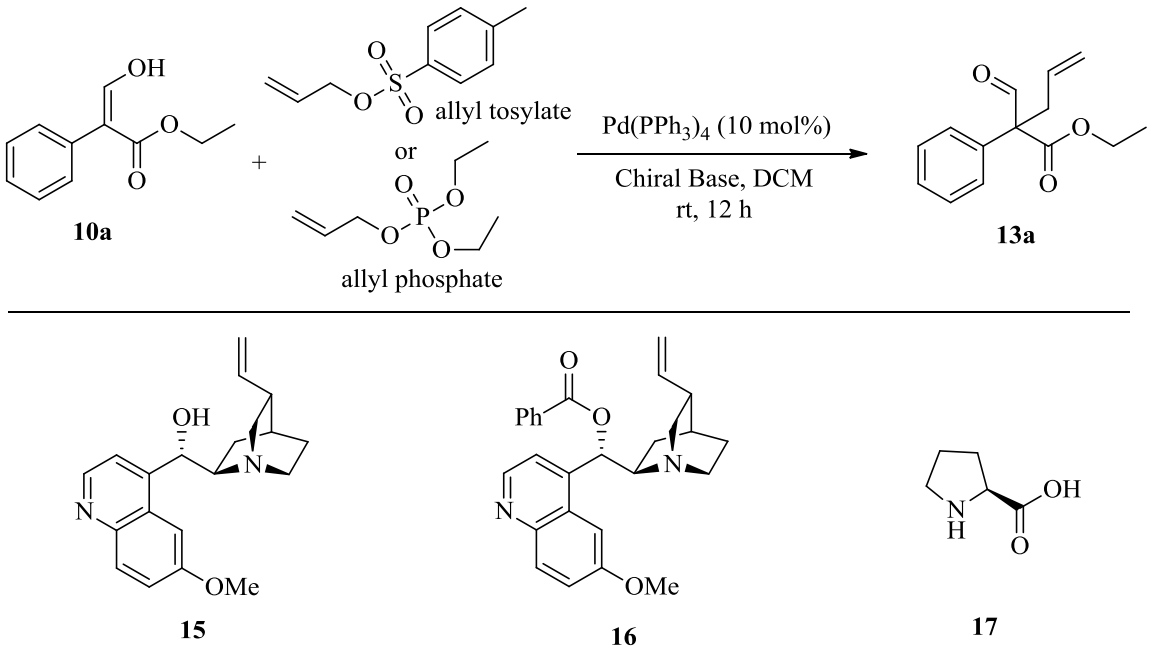
Puzzled by the outcome of this investigation, we questioned ourselves whether the base was even participating in the reaction (Scheme 63). Hence, we carried out a reaction without the introduction of any base and used allyl acetate as electrophile. To our surprise, complete conversion was detected by $^{1}$H NMR analysis (Scheme 63, eq 1). That means, the counterion of π-allylpalladium complex or the leaving group of the allyl electrophile, acetate anion, was basic enough to remove a proton from the starting acrylate **10a**. Furthermore, we questioned if allyl tosylate or allyl phosphate can be employed instead of allyl acetate. As expected, both allyl tosylate and allyl phosphate did not give any reaction (Scheme 63, eq 2). However, when base $Et_3N$ was employed, they too reacted quickly and yielded the desired product **13a** quantitatively (Scheme 63, eq 3).




**Scheme 63.** Pd-AA employing allyl acetate, allyl tosylate, and allyl phosphate as allyl electrophiles; reaction with allyl tosylate or allyl phosphate require base to proceed.

Now that we found that allyl tosylate and allyl phosphate did not react without introduction of bases, we optimize the reaction again for the chiral induction employing various chiral bases. This time, we investigated quinine-based amines **15** and **16** and one proline-base amine **17** in DCM at rt (Scheme 64, Table 5). This time too, similar disappointing results were obtained in terms of *ee*. A slightly better *ee* was observed with **16** for both allyl tosylate (25%, entry 8) and allyl phosphate (18%, entry 11), even though

only when stoichiometric amount of **16** was employed. However, this investigation assured the participation of the bases in the course of the reaction, since most of the reaction showed almost identical conversion to the equivalence of bases employed. When stoichiometric amount of bases were introduced, the conversions were quantitative (entry 1, 4, 8, and 11). The conversions were also increased linearly with the amou nt of bases used (entry 2, 3, 5, 6, 7, and 10).




**Scheme 64.** Investigation of chiral induction when ally tosylate and allyl phosphate were allyl electrophiles.

**Table 5.** Optimization studies for the chiral induction of the reaction between **10** and allyl tosylate or allyl phosphate.

| Entry | Electrophile | Chiral Base [equiv] | Conv. [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | Allyl tosylate | **15** (1.2 eq.) | Quantitative | 7 |
| 2 | Allyl tosylate | **15** (5 mol%) | 5 | - |
| 3 | Allyl tosylate | **15** (10 mol%) | 10 | - |
| 4 | Allyl tosylate | **17** (1.2 eq.) | Quantitative | 10 |
| 5 | Allyl tosylate | **17** (10 mol%) | 10 | 5 |
| 6 | Allyl tosylate | **16** (10 mol%) | 10 | - |
| 7 | Allyl tosylate | **15** (10 mol%) & $Cs_2CO_3$ | 10% C, rest O | - |
| 8 | Allyl tosylate | **16** (1.2 eq.) | Quantitative | 25 |
| 9 | Allyl phosphate | - | - | - |
| 10 | Allyl phosphate | **15** (10 mol%) | 18 | 9 |
| 11 | Allyl phosphate | **16** (1.2 eq.) | Quantitative | 18 |
| 12 | Allyl phosphate | **17** (1.2 eq.) | 9 | - |

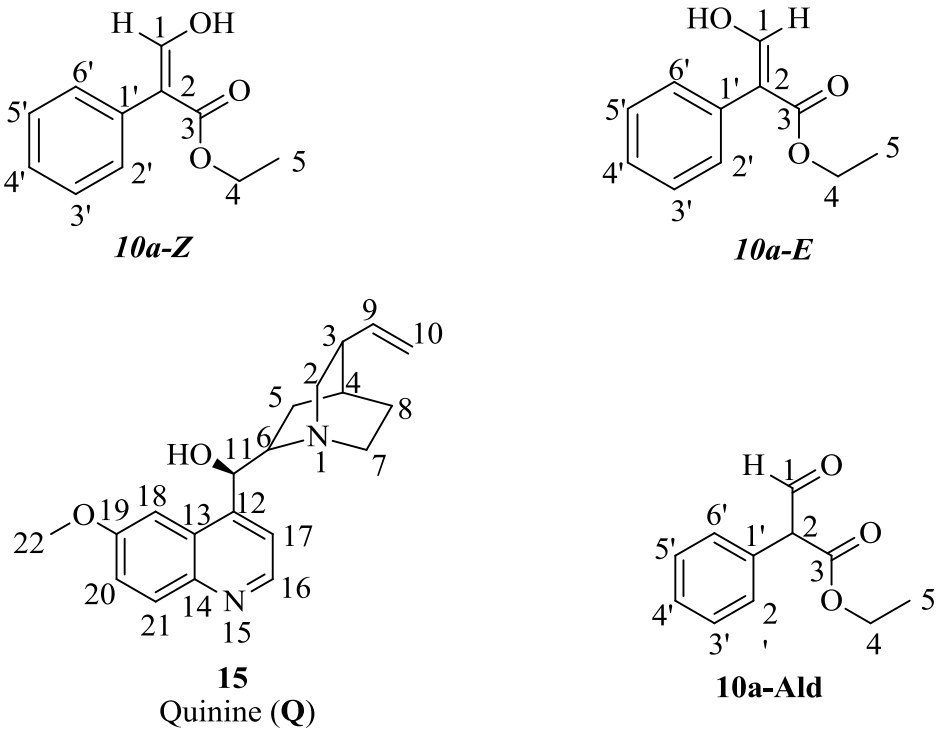
2.6.1.1. NMR investigation[107]

The above results raised a well-deserved question: why was desired chiral induction not achieved by a chiral base even though it completely participated in the progress of the reaction? To find out the answer, we will have to know what is occurring mechanistically in the reaction and how the substrate 3-hydroxy aryl acrylates and the chiral amine

catalysts binding and is it a favorable process. Thus, we went on to study the interaction of chiral base **15** with nucleophile **10a** by NMR.

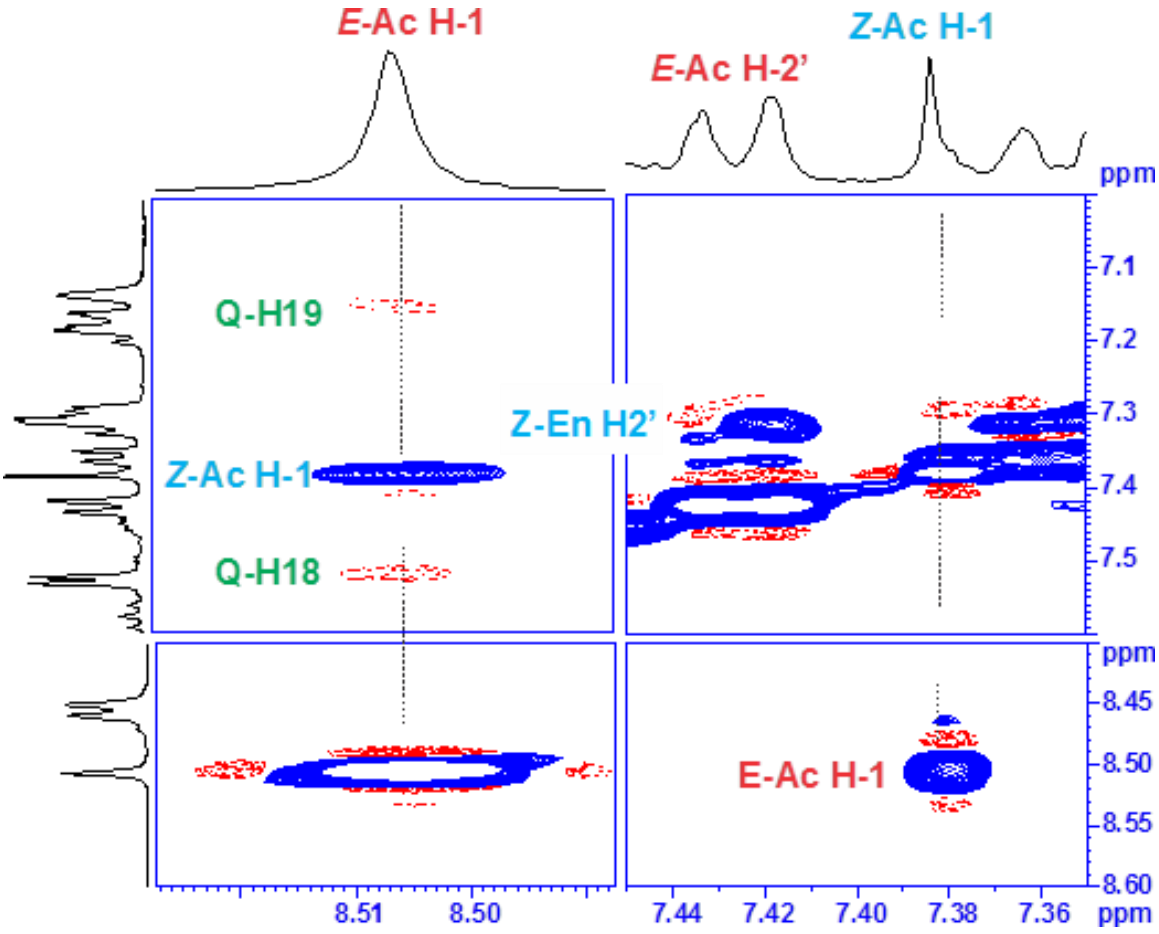
In chloroform or methylene chloride, the acrylate **10a** assumes the *Z* configuration **10a-*Z*** (Figure 13), with only small amount of the tautomeric aldehyde form **10a-Ald** (Figure 13) present. Upon mixing **10a-*Z*** with the quinine base **15** in a 1:1 ratio in chloroform or methylene chloride, the proton spectra showed two major sets of signals that can be assigned to an acrylate species, a minor set of signals attributed to the aldehyde tautomer **10a-Ald** and one set of signal from quinine **15** (Figure 13). Of the two acrylate species, one set of signals is virtually identical with the initial *Z*-acrylate, with the exception of the signal from the OH hydrogen, which is not visible at room temperature, and a significant broadening observed for the H-1 signal. The second set of acrylate signals exhibits a signal for H-1 that is shifted downfield to 8.51 ppm compared to 7.38 ppm observed for the equivalent proton in **10a-*Z*** (Figure 14).

**Figure 13.** NMR assigned positions.




Two dimensional $^{1}H\{^{13}C\}$ HSQC- and HMBC spectra are consistent with both **10a-*Z*** and **10a-*E*** present in the mixture (Figure 14), with carbon chemical shifts 163.5 ppm and 163.0 respectively for C-1 and 108.6 and 107.8 ppm for C-2 in the two species. A NOESY spectrum at room temperature showed strong positive cross peaks arising from exchange between the two acrylate species (Figure 14). In addition, exchange peaks between the *acrylate* forms and the minor aldehyde form were observed.[108] These data indicate that in the presence of quinine **15** the intramolecular hydrogen bond stabilizing the *Z*-form gets weakened, resulting in a lowering of the barrier of acrylate to aldehyde tautomerization, and a loss in thermodynamic preference for the *Z* configuration.

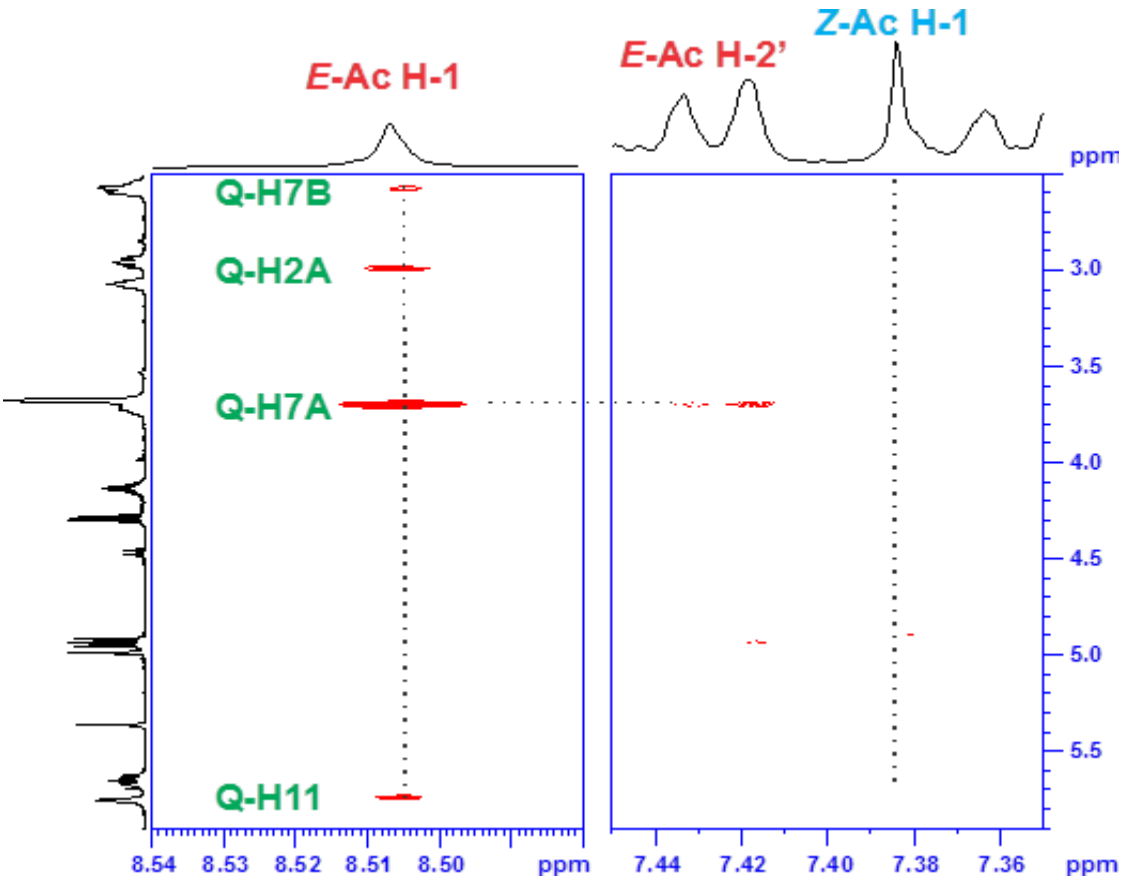
**Figure 14.** Expanded NOESY spectrum regions of a 1:1 mixture of **10a** and **15** in DCM at 273 K. Displayed are correlations of the **10a** H1 protons to aromatic/olefinic protons. Positive cross peaks due to exchange are shown in blue, negative cross peaks arising from NOE are shown in red. Exchange between *E* and *Z isomer* is observed both for the H-1 protons and the H-2′ protons of **10a**.




More interestingly, NOESY spectra exhibited negative NOE cross peaks between **10a-*E*** and quinine **15**, mainly between H-1 and H-2′ with hydrogens near the OH group in **15** and with its aromatic ring.[108] On the other hand, not a single cross peak between **10a-*Z*** and quinine **15** was observed, indicating that only **10a-*E*** is binding to **15** (Figures 14 and

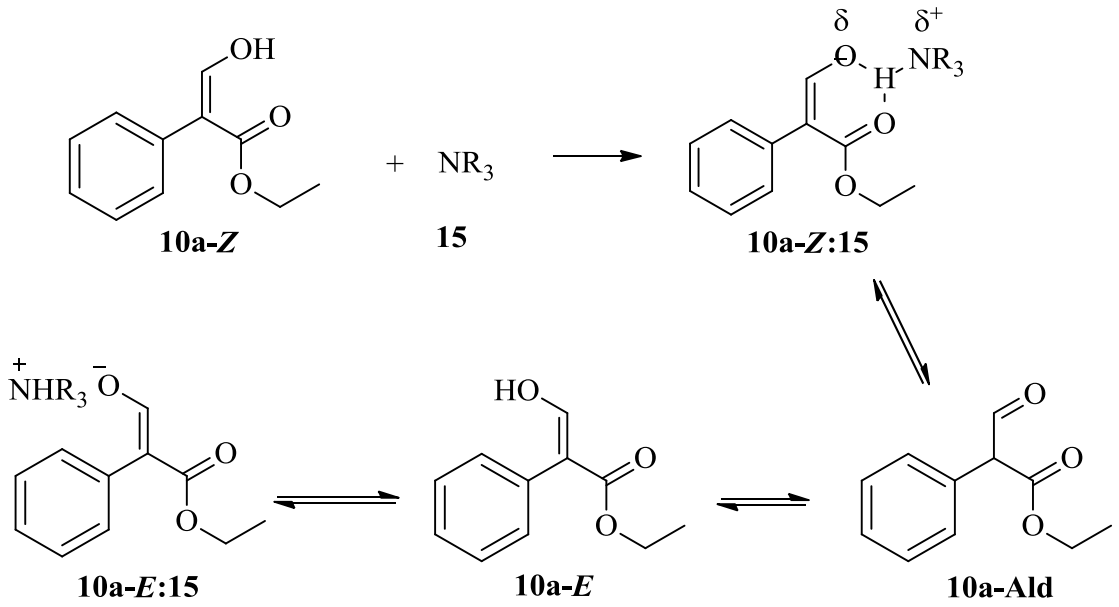
15). A closer analysis of the relative signal integrals shows that the ratio of ***10a-E***: **15** is non-stoichiometric, but only the sum (**10a**-***Z*** + **10a**-***E***): **15** as expected from the ratio at which the two components were mixed. Further experiments using either an excess of **10a** or **15** displayed a similar picture with only one set of signal present for **15** but two sets of signals for **10a**.

**Figure 15**. Expanded **10a**-H-1 to aliphatic crosspeaks of the NOESY spectrum of a 1:1 mixture of **10a** and **15** in DCM at 273 K. Negative NOE cross peaks are shown in red. Intermolecular NOEs between **10a** and **15** are only observed for the **10a**-***E*** but not for **10a**-***Z***.



Chemical shifts of protons in **10a**-***E*** and **15** exhibited a much larger dependence on concentration that did the ones in **10a**-***Z*,** and studies at different temperatures (263 – 308K) showed a remarkable temperature dependence of the proton shifts for **10a**-***Z*** and **15** compared to **10a**-***Z***. From those data it appears that **10a**-***E*** is in fast exchange between a **10a**/**15** complex and the free **10a**-***E***.

The NOESY data indicate that *Z*- to *E*-*i*somerization of the acrylate **10a** takes place through the tautomeric aldehyde form **10a**-**Ald**. In the absence of quinine **15** this tautomer is present in small quantities, but no exchange between the two species is observed on the NMR time scale. Most likely the acrylate form of **10a**-***Z*** is stabilized by the intramolecular OH···O=C hydrogen bond. In the presence of a base like quinine the breakage of this hydrogen bond is catalyzed as evidenced by the disappearance of the OH proton signal in **10a**-***Z*** after the addition of quinine **15** and the presence of exchange between**10a**- ***Z*** and **10a**-**Ald** peaks in the mixture. Free rotation about the C1-C2 single bond in **10a**-**Ald** then results in formation of the **10a**-***E*** in equilibrium with **10a**-***Z*** and **10a**-**Ald** (Scheme 65).




**Scheme 65.** Interaction of 3-hydroxy phenyl acrylate **10a** with quinine **15**.

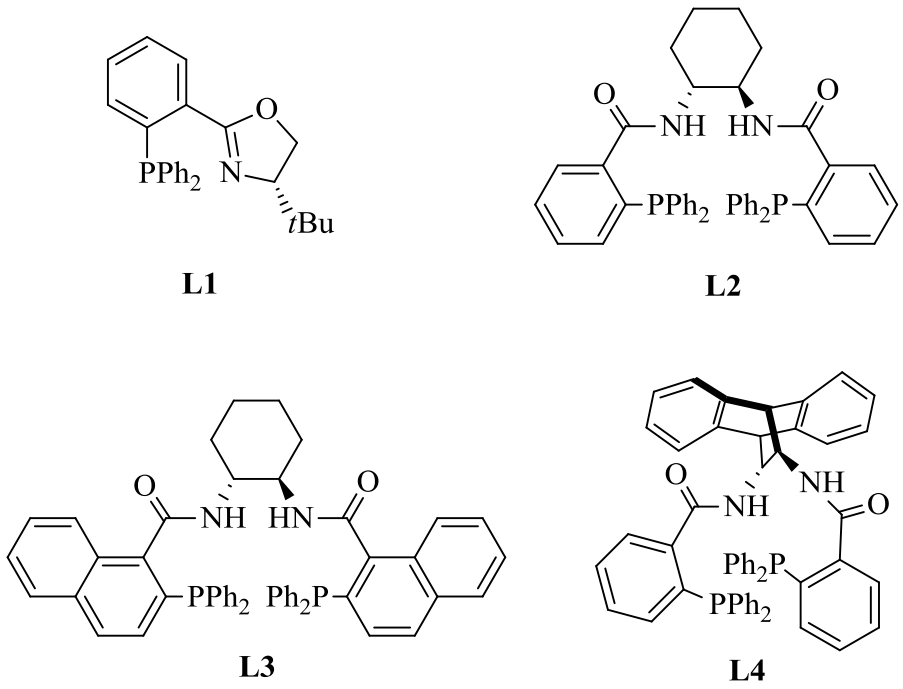
In conclusion, NMR investigation suggested that quinine **15** acts as regular base when comes in contact with the 3-hydroxy aryl acrylate and there is rapid inter-conversion of *E* and *Z* isomers which is preventing us from obtaining high asymmetric induction.

### 2.6.2. Chiral induction by chiral ligands

Since NMR analysis showed that enantiodiscrimination is unlikely employing chiral bases, we have to find a way to effectively blocking one form between *E* and *Z* of 3-hydroxy aryl acrylates over the other. Therefore, we moved on to employing chiral ligands instead for the asymmetric variant of this Pd-catalyzed allylic alkylation reaction. To optimize the reaction conditions for high asymmetric induction, we first started

investigating the effects of systematic variations in the solvent, ligand, and temperature on enantiodiscrimination. Both C2-symmetric Trost modular ligands (diphenylphosphino)benzoic Acid (DPPBA) as well as mixed P/N-type phosphinooxazoline (PHOX) ligands were selected for the investigation (Figure 16).

**Figure 16.** Chiral ligands used for optimization.

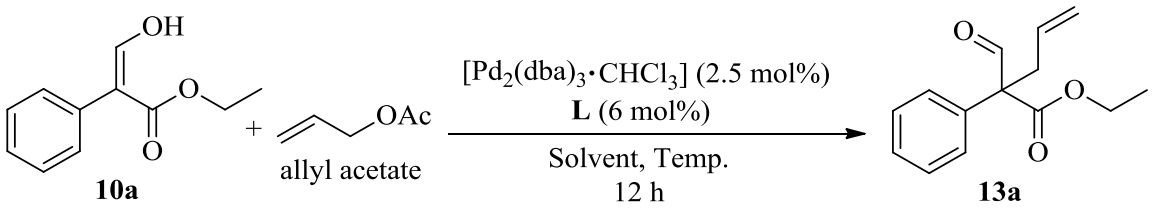



It should be noted, however, that the DPPBA ligands class, such as *(R,R)*-**L2**, *(R,R)*-**L3**, and *(R,R)*-**L4** showed greater levels of enantioselectivity compared to PHOX ligands, *S*-**L1** (Table 6, entry 1-5) yielding α-tetrasubstituted aldehyde **13a** quantitatively at room temperature with around 30% *ee* for both *(R,R)*-**L3**, and *(R,R)*-**L4** in DCM (entry 3 and 4). Increasing the polarity of the solvent did not have much effect on enantioselectivity for *(R,R)*-**L3** (entry 7). Even though a significant increase from 30 to 49% in *ee* was

observed for ligand *(R,R)*-**L4** in THF (entry 8), it showed little or no further improvement on chiral recognition towards variation of solvents and temperatures. In summary, we only found a slight increase in enantioselectivity by changing solvents to toluene and hexane:toluene (1:1) at rt with this ligand (entry 13 and 20). Lowering the temperature too from rt to −20˚C via −10˚C showed a minimal effect (entry 14, 15, and 21). On the other hand, ligand *(R,R)*-**L3** demonstrated a high level of enatiodiscriminative sensitivity towards polarity of solvents and temperature changes of the reaction. As the solvent system became more non-polar, from toluene to a 1:1 mixture of hexane:toluene, a sharp increase in *ee* was observed at rt from 30% to 79% (entry 9 and 18). The use of hexane:toluene solvent mixtures has been reported earlier by Stoltz[109] and it is thought that this very low polarity system increases stereoinduction by helping to form tight ion pairs via 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)*-**L4,** was instrumental in this dramatic increase in enantioselectivity. However, a noticeable decrease in conversion (64%) was observed with hexane:toluene (1:1) as solvent at rt. Unlike ligand *(R,R)*-**L4**, ligand *(R,R)*-**L3** is also extremely sensitive to temperature. At rt the *ee* of the reaction using *(R,R)*-**L3** was 30% in toluene, and it increased substantially (up to 72%) by decreasing the temperature to −10˚C with 80% conversion (entry 9 and 10). Interestingly, it failed to show further improvement in enantioselectivity beyond −10˚C in toluene (entry 11). However, when hexane:toluene (1:1) was employed as solvent at −20˚C, a remarkable increase in *ee* (94%) was observed

even though with a significant decrease in conversion (entry 19). No reaction was observed below −20˚C (entry 12 and 16).

**Table 6.** Selected optimization studies.[a]

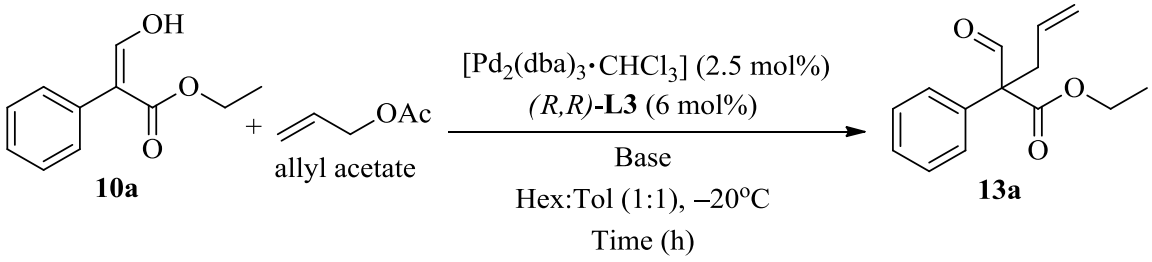



| Entry | Ligand | Solvent | *T* [˚C][b] | Conv. [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | *S*-**L1** | DCM | rt | > 99 | 5 |
| 2 | *(R,R)*-**L2** | DCM | rt | > 99 | 10 |
| 3 | *(R,R)*-**L3** | DCM | rt | > 99 | 29 |
| 4 | *(R,R)*-**L4** | DCM | rt | > 99 | 30 |
| 5 | *S*-**L1** | THF | rt | > 99 | 4 |
| 6 | *(R,R)*-**L2** | THF | rt | > 99 | 10 |
| 7 | *(R,R)*-**L3** | THF | rt | > 99 | 27 |
| 8 | *(R,R)*-**L4** | THF | rt | > 99 | 49 |
| 9 | *(R,R)*-**L3** | Toluene | rt | > 99 | 30 |
| 10 | *(R,R)*-**L3** | Toluene | −10 | 80 | 72 |
| 11 | *(R,R)*-**L3** | Toluene | −20 | 45 | 70 |
| 12 | *(R,R)*-**L3** | Toluene | −41 | 0 | - |
| 13 | *(R,R)*-**L4** | Toluene | rt | > 99 | 55 |
| 14 | *(R,R)*-**L4** | Toluene | −10 | 54 | 55 |
| 15 | *(R,R)*-**L4** | Toluene | −20 | 70 | 62 |
| 16 | *(R,R)*-**L4** | Toluene | −41 | 0 | - |
| 17 | *(R,R)*-**L2** | Hex:Tol | rt | 58 | 57 |
| 18 | *(R,R)*-**L3** | Hex:Tol | rt | 64 | 79 |
| **19** | *(R,R)*-**L3** | **Hex:Tol** | **−20** | **33** | **94** |
| 20 | *(R,R)*-**L4** | Hex:Tol | rt | 66 | 55 |
| 21 | *(R,R)*-**L4** | Hex:Tol | −20 | 34 | 51 |

[a]All reactions were performed with 0.26 mmol of **10a** and 0.30 mmol of allyl acetate in solvent (5.0 mL).
[b]Optimized temperature for the best *ee* value and conversion.
[c]Determined by $^1$H NMR analysis of the reaction mixture.
[d]Determined by HPLC analysis using a chiral stationary phase.

Having identified a set of reaction conditions that provided 94% *ee*, we then directed our focus to increasing the conversion while keeping the enantioselectivity unaffected. We did this by adjusting the equivalence of reactants, or by introducing exogenous bases (Table 7). While addition of excess allyl acetate showed no effect (entry 1), excess nucleophilic counterpart demonstrated an almost linear increase in conversion (entry 1-4) along with enantioselective fidelity unaffected, reaching >99% with 4.0 equivalent of acrylate nucleophile **10a** (entry 4). This phenomena is explained by the fact that anionic acetate ion, which is the counterion of the Pd-allyl complex, is nucleophilic itself and can compete with the desired acrylate nucleophile, thereby reducing the percent yield. This can thus be improved by increasing the presence of the substrate to outweigh the concentration of competing acetate ion in the system. However, we hypothesized that there must be an ideal base which would enable the reaction to proceed without using an excessive amount of expensive nucleophile by forming more reactive enolate. Thus, we examined KO*t*Bu, $Et_3N$, and DIPEA as bases (entry 5-11). Both $Et_3N$ and KO*t*Bu proved to be damaging to the enantioselective fidelity (entry 5 and 6). However, when DIPEA was employed, a significant increase in percent conversion was observed without lowering the percent *ee* (entry 7-11). Eventually, 2.0 equivalent of DIPEA was found to be optimal affording 98% conversion (95% isolated yield) and 94% *ee* (entry 10). Therefore, the optimum condition is to use *(R,R)*-DACH-naphthyl Trost ligand **L3** (6.0 mol%) in hexane:toluene (1:1) as solvent along with $[Pd_2(dba)_3.CHCl_3]$ (2.5 mol%) in the presence of DIPEA (2.0 eq) as base. It should be noted, however, that the use of base is not absolutely necessary as the substrate is acidic enough to proceed on its own with a similar level of selectivity if excess is introduced.

**Table 7.** Key results from further optimization studies on additional bases and reactants loading.[a]

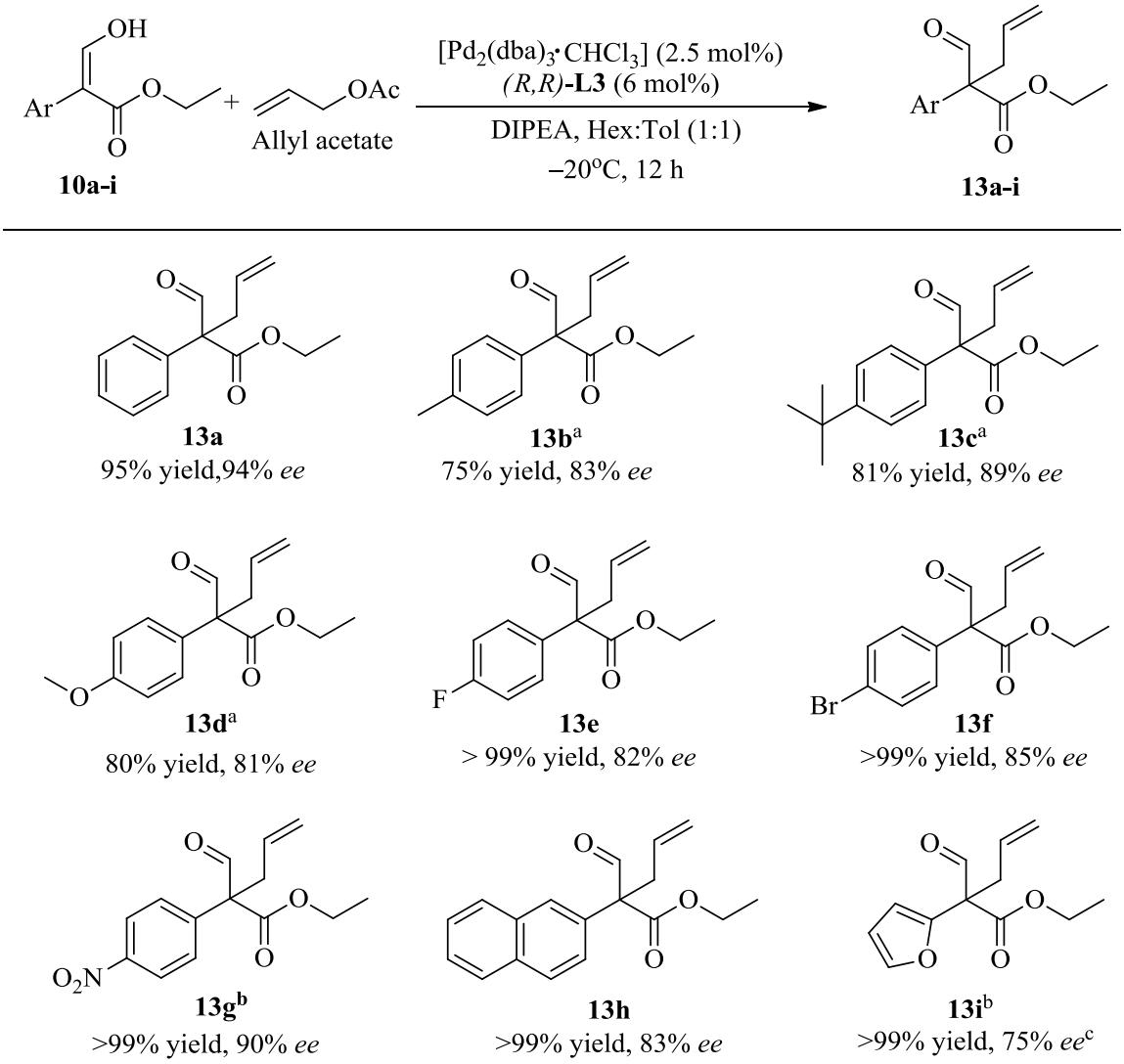



| Entry | **10a** [Equiv] | Allyl acetate [Equiv] | Base [Equiv] | Time [h] | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 4.0 | - | 120 | 33 | 92 |
| 2 | 2.0 | 1.0 | - | 120 | 56 | 92 |
| 3 | 3.0 | 1.0 | - | 120 | 63 | 92 |
| **4** | **4.0** | **1.0** | - | **120** | **> 99** | **94** |
| 5 | 1.0 | 1.2 | $Et_3N$ [1.0] | 48 | > 99 | 52 |
| 6 | 1.0 | 1.2 | KO*t*Bu [1.0] | 24 | 74 | 33 |
| 7 | 1.0 | 1.2 | DIPEA [1.0] | 72 | 84 | 91 |
| 8 | 1.0 | 1.2 | DIPEA [1.2] | 12 | 84 | 90 |
| 9 | 1.0 | 1.2 | DIPEA [1.5] | 72 | 98 | 91 |
| **10** | **1.0** | **1.2** | **DIPEA [2.0]** | **12** | **98** | **94** |
| 11 | 1.0 | 1.2 | DIPEA [2.2] | 12 | 96 | 87 |

[a]All reactions were performed on a 0.26 mmol scale in 1:1 mixture of hexane:toluene (5.0 mL).
[b]Determined by $^1H$ NMR analysis of the reaction mixture.
[c]Determined by HPLC analysis using a chiral stationary phase.

With the optimized reaction conditions in hand, we then investigated the scope of the reaction by subjecting a variety of substituted aryls and a heteroaryl analogs to the Pd-AAA process (Scheme 66). In general, good to excellent yields (75-99%) and enantioselectivities (75-94%) were obtained. Interestingly, unsubstituted one **13a** exceeded any other examined analogs in terms of enantiodiscriminative selectivity. Both electron withdrawing (**13e-g**) and electron donating (**13b-d**) substituents on the aromatic

ring were tested by this process. Surprisingly, either of the analog classes functioned well, yielding *ee* ranges from 81% for the *para*-methoxy substrate **13d** to as much as 90% for the *para*-nitro substituted substrate **13g**. Bulky *tert*-Butyl analog **13c** provided better *ee* (89%) than any other electron donating substituents. The heteroaryl substituted analog **13i** also shared similar impressive reactivity (99% yield), but with a little less enantioselectivity (75%). The sterically bulky, and hence, theoretically more challenging naphthyl analog **13h** provided a high yield (99%) and enantioselectivity (83% *ee*) as well.



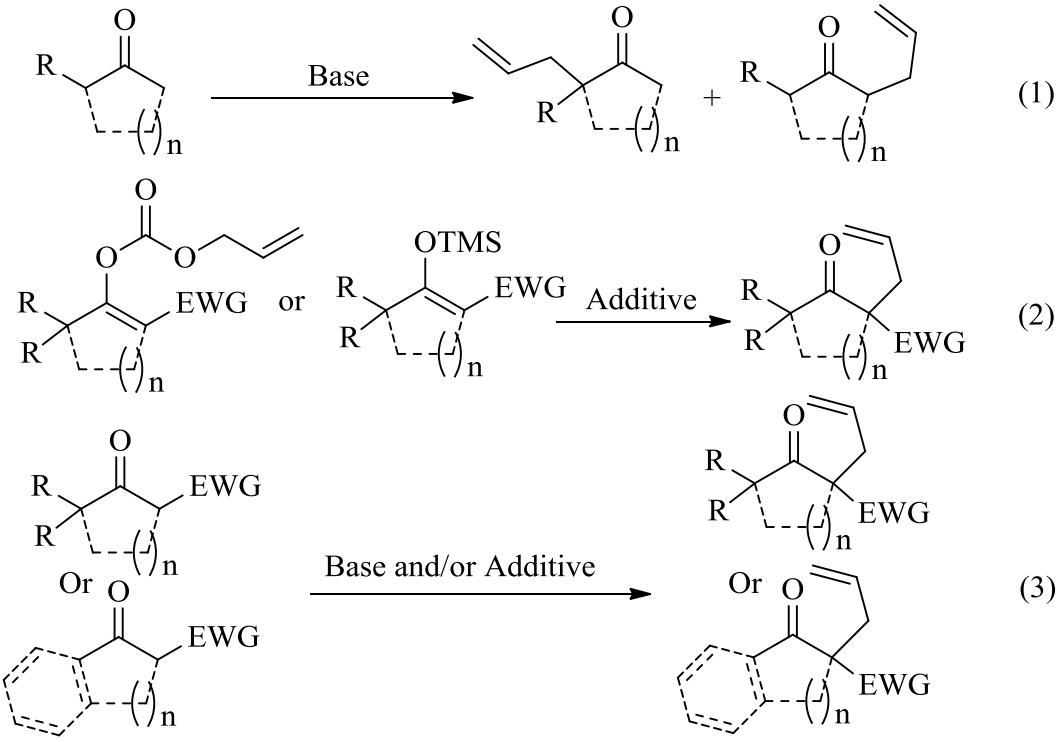

**Scheme 66.** Scope of the Pd-AAA of 3-hydroxy-2-arylacrylates **10a-i**. All reactions were performed on 0.16-0.26 mmol scale in solvent (5.0 mL). The yields shown are of isolated products and the *ee* values were determined by HPLC analysis using a chiral stationary phase.

[a]Reactions run for 72 h.
[b]Reactions run without DIPEA.
[c]*ee* value of fural analog reported is for alcohol reduced from quaternary aldehyde.

To the best of our knowledge, this Pd-AAA methodology is the very first example of intermolecular transition metal-catalyzed AAA of a hydroxyacrylate. In addition, this method allowed access to chiral quaternary aldehydes, which is still surprisingly limited. List and coworkers recently have reported the only example of a synthesis of quaternary α-allylated all-carbon aldehyde, which, however, requires the presence of additional chemical entities in the system.[56] Besides this above mentioned account, only ketonic compounds with a quaternary α-stereogenic center have been synthesized asymmetrically to date by Pd-AAA.

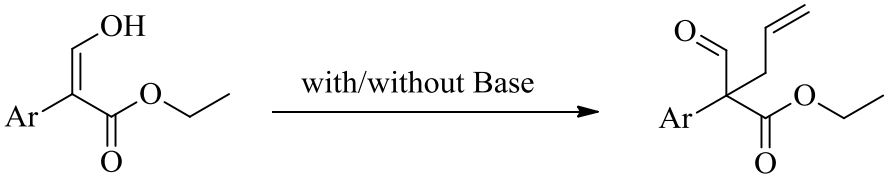
One of the potentially inevitable problems in producing chiral ketonic compounds by AAA from α-substituted ketones is the formation of multiple isomeric enolates in base-mediated reaction conditions and the consequent formation of mixed products (Scheme 67a, Eq. 1).[8] To overcome this structural difficulty inherent to ketones, allyl enol carbonates[97] and silyl enol ethers[98] have been introduced to impart position control of the enolate (Scheme 67a, Eq. 2). Substrates either lacking an α- proton or containing an α-electron withdrawing groups on one site, or a combination of both, have also been successfully employed (Scheme 67a, Eq. 3).[99] However, these strategies require either one extra step to create selective enolate nucleophiles or a biasness of the substrate towards certain functionalities. We believe that the above mentioned problems associated with ketonic substrates can be avoided in this protocol while maintaining the step economy intact and the substrate unbiased (Scheme 67b). Moreover, aldehydes are more reactive than ketones which might increase the scope of further research.

**a) Previous work**




R = H, Alkyl, etc.; EWG = Ester, Acyl, Cyano, Nitro, etc.

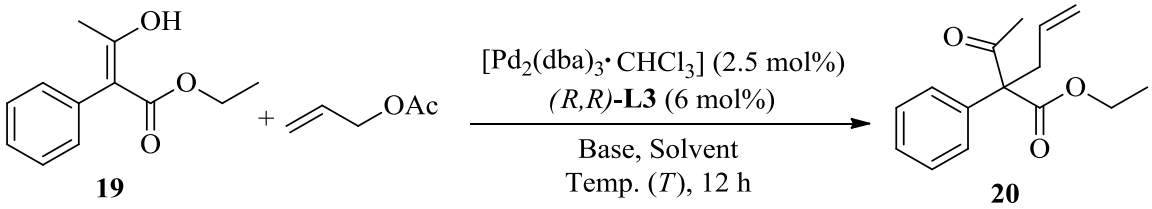
**b) Our work** : First example. High yield and % *ee* values obtained.




**Scheme 67.** Pd-AAA reaction; a) Formation of mixed products while ketonic substrates used as nucleophile and approaches investigated to curb this phenomenon. b) A new approach to avoid above mentioned problem by using prochiral hydroxyacrylates as nucleophile.

In order to consolidate our claim, we have produced an all-carbon α-aryl quaternary ketonic compound (**20**) with high yield and moderate enantioselectivity using Ethyl 3-hydroxy-2-phenylbut-2-enoate (1**9**) as starting material (Table 8). We did not observe mixture of compounds even though the product has another unblocked α-carbon and an excess of both allyl acetate and base have been employed. This substrate proved to be less reactive and did not allow the reaction to happen when previously optimized condition was employed (entry 2). However, a slight decrease in temperature from −20˚C to −10˚C afforded a descent yield (39%) of product with 44% *ee* (entry 3). Using base is essential as no reaction was observed when not applied (entry 1 and 4). Introduction of strong bases is proved to be vital in terms of yield as LiHMDS and KO*t*Bu provided better yield (entry 6,7,9, and 12) compare to DIPEA (entry 2,3,5,8,10, and 11). Once again, 1:1 mixture of hexane:toluene solvent delivered best in regards to both yield and enantioselectivity, eventually providing desired product **20** with 97% yield and 52% *ee* at −10˚C temperature with KO*t*Bu as base (entry 7). Even though both toluene (entry 9) and THF (entry 12) came near, these never exceeded hexane:toluene (1:1) as solvents in terms of enantioselectivity.

**Table 8.** Selected optimization studies of Pd-AAA of Ethyl 3-hydroxy-2-phenylbut-2-enoate 1**9**.[a]




**19** **20**

| Entry | Solvent | *T* [˚C] | Base[b] | Conv. [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | Hex:Tol | −20 | - | 0 | - |
| 2 | Hex:Tol | −20 | DIPEA | Trace | - |
| 3 | Hex:Tol | −10 | DIPEA | 39 | 44 |
| 4 | Hex:Tol | rt | - | Trace | - |
| 5 | Hex:Tol | rt | DIPEA | 67 | 22 |
| 6 | Hex:Tol | −10 | LiHMDS | 93 | 25 |
| **7** | **Hex:Tol** | **−10** | **KO*t*Bu** | **97**[e] | **52** |
| 8 | Tol | −10 | DIPEA | 53 | 44 |
| 9 | Tol | −20 | KO*t*Bu | 83 | 41 |
| 10 | THF | rt | DIPEA | 90 | 30 |
| 11 | THF | 0 | DIPEA | 82 | 34 |
| 12 | THF | −10 | KO*t*Bu | 99 | 37 |

[a]All reactions were performed on a 0.12 mmol scale in 5.0 mL of solvent.
[b]1.2 equivalent.
[c]Determined by $^1$H NMR analysis of the reaction mixture.
[d]Determined by HPLC analysis using a chiral stationary phase.
[e]Isolated yield.

In conclusion, we have developed a new intermolecular Pd-AAA reaction where, 3-hydroxyl aryl acrylates **10** have been used as nucleophiles for the first time to produce acyclic all-carbon α-aryl quaternary carbonyl compounds including both aldehyde and ketone. Hydroxyarylacrylates with a variety of substitution patterns were used as nucleophiles which yielded desired products with high yields and enantioselectivities.

## 2.7. General methods and experimental

### *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 vaccum. 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, or 500 and 125 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 Biotechnology Center Mass Spectrometry laboratory (E-Mail: mass spec@biotech.wisc.edu) or the Mass Spectroscopy facility, department of Chemistry & Biochemistry, University of Wisconsin –Milwaukee.

### 2.7.1. Preparation of 3-hydroxy aryl acrylates **10** for Palladium-Catalyzed Asymmetric Allylic Alkylation (Pd-AAA)

Hydroxyarylacrylates **10a,**[30] **10b,**[30] **10c,**[110] **10d,**[30] **10e,**[111] **10f,**[111] **10g,**[30] **10i,**[31] and **19**[31] were prepared according to previously existing procedures. Work-up procedure described in sections 1.2.1 and 1.5.1 was followed.

***Ethyl 3-hydroxy-2-(naphthalen-2-yl)acrylate (10h)***

2-naphthaldehyde (1.56 g, 10.0 mmol) was dissolved in freshly distilled dichloromethane (50 mL) under nitrogen. $HBF_4.OEt_2$ (0.14 mL, 1.0 mmol) was added followed by another portion of dichloromethane (50 mL) and then the reaction mixture was stirred at $-78^0$C for at least 15 minutes. Ethyl diazoacetate (1.45 mL, 12.0 mmol) contains 87% by wt. was diluted in freshly distilled dichloromethane (25 mL) and drawn into a gas-tight

syringe. The diluted Ethyl diazoacetate was then added to the aldehyde over a period of 5-6 h with the help of a syringe pump. The reaction mixture was allowed to stir for an additional 12 h. The reaction was quenched by adding THF (10 mL), to remove any product that might be bound to catalyst. Then it was filtered through a silica plug and the solvent removed *in vacuo*. At this point, the crude was then dissolved in enough DCM and excess $Et_3N$ was introduced followed by stirring for 5 minutes. When the pH indicating paper showed that the solution was basic, it has been passed through a thick pad of silica gel. The salt of acrylate is not able to pass through silica and stays on the top. The light to dark brown color of the silica gel indicated the salt of **10h**. Enough DCM was passed through to elute out all unreacted 2-naphthaldehyde and β-keto esters. The region of silica indicating brown was then scraped out in a beaker with an appropriate (usually long that compliments the beaker) stir bar. DCM was added and stirred vigorously until it became slurry and distribution of solid silica particles was uniform. Then 6N HCl was added. Enough acid was added with continued stirring until the pH paper showed acidity of the solution. The solution was transferred to a separatory funnel along with solid silica and extracted with DCM three times. The silica usually stays at the interface of the bottom organic (DCM) and top aqueous phase. the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo to afforded the desired **10h** (1.48g, 61% yield) as yellowish solid.

**$^1$H NMR** (CDCl3, 300 MHz): δ 12.30 (d, j = 12.6 Hz, 1H), 7.89 (m, 3H), 7.75 (s, 1H), 7.54 (m, 4H), 4.38 (q, j = 7.2 Hz, 2H), 1.35 (t, j = 7.2 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 171.8, 163.7, 133.5, 132.4, 131.8, 128.1, 127.9, 127.7, 127.6, 127.5, 126.2, 126.0, 108.8, 61.1, 14.2.

**HRMS (ESI):** Calculated (m/z) for C15H15O3 $(M+H)^+$ : 243.1021, Found 243.1017.

2.7.2. General procedures for palladium-catalyzed allylic alkylation reactions

***Method 1**: General Procedure for Pd-AAA Reaction Optimization Studies (**13a**, Table 6 & 7)*

In an oven dried and desiccator-cooled sealable test tube was added $Pd_2(dba)_3{\cdot}CHCl_3$ (6.7 mg, 0.0065 mmol, 0.025 equivalent) and chiral ligand (L1-L4, 0.0156 mmol, 0.06 equivalent). The test tube was then evacuated and backfilled with Ar three times. Previously degassed solvent (5 mL) was added to the test tube and the mixture was stirred for 15 min until it was homogeneous and an orange color persisted. Then allyl acetate (33.7 µL, 0.3122 mmol, 1.2 equivalent) was introduced into the system and the solution was stirred at room temperature for an additional 5 min. (Then the test tube was introduced into the appropriate cooling bath if conditions required and stirred for another 15 min). At this point, the catalyst solution was charged with ethyl 3-hydroxy-2-phenylacrylate **10a** (50.0 mg, 44.3 µL, 0.2601 mmol, 1.0 equivalent) followed by the appropriate base ($Et_3N$/KO*t*Bu/DIPEA, 0.2601-0.5722 mmol, 1.0-2.2 equivalent), if mentioned. The reaction was then stirred for 12 h, unless otherwise mentioned. The reaction mixture was then passed through a thick pad of silica plug and the solvent was evaporated under reduced pressure. The resulting crude residue was then analyzed by $^1$H

NMR to calculate % conversion. Purification by flush column chromatography with 95:5 hexane:EtOAc provided analytical samples of **13a** for chiral HPLC analysis.

***Method 2**: General Procedure for Pd-AAA Reaction Optimization Studies (**20**, Table 8)*

In an oven dried and desiccator-cooled sealable test tube was added $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 0.0030 mmol, 0.025 equivalent) and chiral ligand *(R,R)*-L3 (5.7 mg, 0.0073 mmol, 0.06 equivalent). The test tube was then evacuated and backfilled with Ar three times. Previously degassed solvent (2 mL) was added to the test tube and the mixture was stirred for 15 min until it was homogeneous and an orange color persisted. Then allyl acetate (15.7 µL, 0.1454 mmol, 1.2 equivalent) was introduced into the system and the solution was stirred at room temperature for an additional 5 min. (Then the test tube was introduced into the appropriate cooling bath if conditions required and stirred for another 15 min). At this point, the catalyst solution was charged with ethyl 3-hydroxy-2-phenylbut-2-enoate 1**9** (25.0 mg, 0.1212 mmol, 1.0 equivalent) followed by the appropriate base (LiHMDS/KO*t*Bu/DIPEA, 0.1454 mmol, 1.2 equivalent), if mentioned. The reaction was then stirred for 12 h. The reaction mixture was then passed through a thick pad of silica plug and the solvent was evaporated under reduced pressure. The resulting crude residue was then analyzed by $^1$H NMR. Purification by flush column chromatography with EtOAc in Hexane provided analytical samples for chiral HPLC analysis. Purified products **20** were obtained as a light yellow oil (29.0 mg, 97% Yield) by column chromatography of the crude mixture on silica gel eluted with 95:5 hexane:EtOAc (Table 4, entry 7).

***Method 3*: *General Procedure for Pd-AAA Reaction (13a-i, Scheme 66)***

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 (1:1) Hex:Tol (3 mL) was added to the flask and the mixture was stirred for 15 min until it was homogeneous and an orange color persisted. Then allyl acetate (23.9-35.6 µL, 0.2213-0.3294 mmol, 1.2 equivalent) was introduced into the system and the solution was stirred at room temperature for an additional 5 min. In the meantime, another test tube was charged with hydroxyarylacrylates **10a-i** (50.0 mg, 0.1844-0.2745 mmol, 1.0 equivalent), evacuated and backfilled with Ar, and then degassed solvent (1:1) Hex:Tol (2 mL) was introduced followed by DIPEA (64.2-95.6 µL, 0.3688-0.5490 mmol, 2.0 equivalent), 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 12 h, unless otherwise mentioned. The reaction mixture was then passed through a thick pad of silica plug and the solvent was removed *in vacuo*. Purified products **13a-i** were obtained (55 − >99% Yield) by column chromatography of the crude mixture on silica gel eluted with EtOAc in Hexane.

***Method 4***: *General Procedure for Racemic Pd-Catalyzed Allylic Alkylation Reaction (compounds **13a-i, 20**)*

An oven dried, evacuated, and Ar flushed two-neck round-bottomed flask (RBF) was charged with a stir bar and $Pd(PPh_3)_4$ (21.3-31.8 mg, 0.0184-0.0275 mmol, 0.1 equivalent) against the flow of Ar. Previously degassed dichloromethane (5 mL) was added to the flask and the mixture was stirred for 15 min. Then allyl acetate (23.9-35.6 µL, 0.2213-0.3294 mmol, 1.2 equivalent) was introduced into the system and the solution was stirred for an additional 5 min. At this point, the catalyst solution was charged with substrates **10a-i, and 19** (50.0 mg, 0.1844-0.2745 mmol, 1.0 equivalent) against Ar flow, followed by the addition of KO*t*Bu (32.6 mg, 0.2908 mmol, 1.2 equivalent), only when substrate 1**9** was employed. Then, the reaction was stirred at room temperature for 2-5 h. The reaction mixture was then passed through a thick pad of silica plug and the solvent was evaporated under reduced pressure to afford a crude residue. Purified products (95-99% Yield) were obtained by column chromatography of the crude mixture on silica gel eluted with EtOAc in Hexane.

***Ethyl 2-formyl-2-phenylpent-4-enoate (13a)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4)** using hydroxyarylacrylate **10a** (50.0 mg, 0.2601 mmol, 1.0 eq), $Pd(PPh_3)_4$ (30.0 mg, 0.0260 mmol, 0.1 eq), and allyl acetate (33.7 µL, 0.3121 mmol, 1.2 eq) in

dichloromethane (5 mL) at rt for 5h to provide the above mentioned compound as a light yellow oil (60.0 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10a** (50.0 mg, 44.3 µL, 0.2601 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (6.7 mg, 0.0065 mmol, 0.025 eq), *(R,R)*-L3 (12.3 mg, 0.0156 mmol, 0.06 eq), allyl acetate (33.7 µL, 0.3121 mmol, 1.2 eq) and DIPEA (90.6 µL, 0.5202 mmol, 2.0 eq) at $-20^0$C to provide the above mentioned compound as a light yellow oil (57.4 mg, 95% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 7.44–7.23 (m, 5H), 5.76 (m, 1H), 5.13 (d, *J* = 18.3 Hz, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 4.30 (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), 1.30 (t, *J* = 7.1 Hz, 3H).

**Chiral HPLC:** 94% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.8 mL/min, 220 nm, 12.35 min (minor), 15.52 min (major).

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

Analytical data matched previously reported data.[45]

***Ethyl 2-formyl-2-p-tolylpent-4-enoate (13b)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10b** (50.0 mg, 0.2424 mmol, 1.0 eq), $Pd(PPh_3)_4$ (27.9 mg, 0.0242 mmol, 0.1 eq), and allyl acetate (31.4 µL, 0.2909 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 5h to provide the above mentioned compound as a yellow oil (59.5 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10b** (50.0 mg, 0.2424 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (6.2 mg, 0.0061 mmol, 0.025 eq), *(R,R)*-L3 (11.5 mg, 0.0145 mmol, 0.06 eq), allyl acetate (31.4 µL, 0.2909 mmol, 1.2 eq), and DIPEA (84.4 µL, 0.4848 mmol, 2.0 eq) at $-20^0$C to provide the above mentioned compound as a yellow oil (44.8 mg, 75% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.89 (s, 1H), 7.28–7.11 (m, 4H), 5.75 (m, 1H), 5.16 (d, *J* = 16.8 Hz, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.12 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 2.37 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

**Chiral HPLC:** 83% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 13.54 min (minor), 14.66 min (major).

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

Analytical data matched previously reported data.[45]

***Ethyl 2-(4-(tert-butyl)phenyl)-2-formylpent-4-enoate (13c)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10c** (50.0 mg, 0.2014 mmol, 1.0 eq), $Pd(PPh_3)_4$ (23.2 mg, 0.0201 mmol, 0.1 eq), and allyl acetate (26.1 µL, 0.2417 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a yellow oil (52.9 mg, 91% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10c** (50.0 mg, 0.2014 mmol , 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.2 mg, 0.0050 mmol, 0.025 eq),

*(R,R)*-L3 (9.6 mg, 0.0121 mmol, 0.06 eq), allyl acetate (26.1 µL, 0.2417 mmol, 1.2 eq) and DIPEA (70.1 µL, 0.4028 mmol, 2.0 eq) at -20$^0$C to provide the above mentioned compound as a yellow oil (47.0 mg, 81% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.89 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 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 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H).

**Chiral HPLC:** 89% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 99:01 hexane/ethanol, 1.0 mL/min, 220 nm, 6.86 min (minor), 7.46 min (major).

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

Analytical data matched previously reported data.[45]

***Ethyl 2-formyl-2-(4-methoxyphenyl)pent-4-enoate (13d)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10d** (50.0 mg, 0.2250 mmol, 1.0 eq), $Pd(PPh_3)_4$ (26.0 mg, 0.0225 mmol, 0.1 eq), and allyl acetate (29.2 µL, 0.2700 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 5h to provide the above mentioned compound as a yellow oil (58.5 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10d** (50.0 mg, 0.2250 mmol, 1.0 eq, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.8 mg, 0.0056 mmol, 0.025 eq), *(R,R)*-L3 (10.6 mg, 0.0135 mmol, 0.06 eq), allyl acetate (29.2 µL, 0.2700

mmol, 1.2 eq) and DIPEA (78.4 µL, 0.4500 mmol, 2.0 eq) at -20$^0$C to provide the above mentioned compound as a yellow oil (47.2 mg, 80% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.87 (s, 1H), 7.16 (d, *j* = 8.7, 2H), 6.93 (d, *j* = 8.7, 2H), 5.76 (m, 1H), 5.16 (d, *J* = 18.6 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H ), 3.83 (s, 3H), 3.08 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.85 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

**Chiral HPLC:** 81% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 96:04 hexane/ethanol, 0.5 mL/min, 220 nm, 18.2 min (minor), 20.5 min (major).

**$[\alpha]_D^{27}$:** = + 36.5$^0$ (c = 0.080, EtOAc).

Analytical data matched previously reported data.[45]

***Ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate (13e)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10e** (50.0 mg, 0.2379 mmol, 1.0 eq), $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol, 0.1 eq), and allyl acetate (30.8 µL, 0.2855 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a yellow oil (59.0 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10e** (50.0 mg, 0.2379 mmol, 1.0 eq, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (6.1 mg, 0.0059 mmol, 0.025 eq), *(R,R)*-L3 (11.3 mg, 0.0143 mmol, 0.06 eq), allyl acetate (30.8 µL, 0.2855 mmol, 1.2 eq) and DIPEA (82.7 µL, 0.4758 mmol, 2.0 eq) at -20$^0$C to provide the above mentioned compound as a yellow oil (59.0 mg, >99% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.89 (s, 1H), 7.22–7.10 (m, 4H), 5.73 (m, 1H), 5.11 (m, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.08 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.88 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

**Chiral HPLC:** 82% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 13.57 min (minor), 14.36 min (major).

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

Analytical data matched previously reported data.[45]

***Ethyl 2-(4-bromophenyl)-2-formylpent-4-enoate (13f)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10f** (50.0 mg, 0.1844 mmol, 1.0 eq), $Pd(PPh_3)_4$ (21.3 mg, 0.0184 mmol, 0.1 eq), and allyl acetate (23.9 µL, 0.2213 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a yellow oil (57.0 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10f** (50.0 mg, 0.1844 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (4.8 mg, 0.0046 mmol, 0.025 eq), *(R,R)*-L3 (8.7 mg, 0.0111 mmol, 0.06 eq), allyl acetate (23.9 µL, 0.2213 mmol, 1.2 eq) and DIPEA (64.2 µL, 0.3688 mmol, 2.0 eq) at $-20^0$C to provide the above mentioned compound as a yellow oil (57.0 mg, >99% yield).

**$^{1}$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:** 85% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 14.89 min (minor), 15.96 min (major).

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

**HRMS (ESI):** Calculated (m/z) for C14H16O3Br $(M+H)^+$ : 311.0283, Found 311.0274.

***Ethyl 2-formyl-2-(4-nitrophenyl)pent-4-enoate (13g)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10g** (50.0 mg, 0.2108 mmol, 1.0 eq), $Pd(PPh_3)_4$ (24.3 mg, 0.0211 mmol, 0.1 eq), and allyl acetate (27.3 µL, 0.2530 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a yellow oil (58.0 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10g** (50.0 mg, 0.2108 mmol , 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.4 mg, 0.0053 mmol, 0.025 eq), *(R,R)*-L3 (10.0 mg, 0.0126 mmol, 0.06 eq), and allyl acetate (27.3 µL, 0.2530 mmol, 1.2 eq) at $-20^0$C to provide the above mentioned compound as a yellow oil (58.0 mg, >99% yield).

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 8.26 (d, *j* = 8.7, 2H), 7.45 (d, *j* = 8.7, 2H), 5.72 (m, 1H), 5.14 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.10 (dd, J = 6.3, 13.8 Hz, 1H), 2.97 (dd, J = 8.1, 13.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 195.4, 169.7, 147.5, 142.1, 131.5, 128.7, 124.0, 120.3, 65.6, 62.4, 37.2, 14.0.

**Chiral HPLC:** 90% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 1.24:0.01 hexane/ethanol, 1.25 mL/min, 220 nm, 22.85 min (minor), 24.01 min (major).

**$[\alpha]_D^{27}$:** = + $72.5^0$ (c = 0.072, EtOAc).

**HRMS (ESI):** Calculated (m/z) for C13H14NO4 $(M-H)^+$ : 248.0923, Found 248.0922.

***Ethyl 2-formyl-2-(naphthalen-2-yl)pent-4-enoate (13h)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **3h** (50.0 mg, 0.2064 mmol, 1.0 eq), $Pd(PPh_3)_4$ (23.8 mg, 0.0206 mmol, 0.1 eq), and allyl acetate (26.7 µL, 0.3121 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 5h to provide the above mentioned compound as a yellow solid (57.8 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **3h** (50.0 mg, 0.2064 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.3 mg, 0.0052 mmol, 0.025 eq), *(R,R)*-L3 (9.8 mg, 0.0124 mmol, 0.06 eq), allyl acetate (26.7 µL, 0.3121 mmol, 1.2 eq) and DIPEA (71.9 µL, 0.4128 mmol, 2.0 eq) at $-20^0$C to provide the above mentioned compound as a yellow solid (57.8 mg, >99% yield).

**$^{1}$H 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:** 83% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 98:02 hexane/ethanol, 0.5 mL/min, 220 nm, 28.06 min (minor), 32.98 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-formyl-2-(furan-2-yl)pent-4-enoate (13i)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10i** (50.0 mg, 0.2745 mmol, 1.0 eq), $Pd(PPh_3)_4$ (31.7 mg, 0.0275 mmol, 0.1 eq), and allyl acetate (35.6 µL, 0.3294 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a brownish yellow oil (60.5 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10i** (50.0 mg, 0.2745 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (7.1 mg, 0.0069 mmol, 0.025 eq), *(R,R)*-L3 (13.0 mg, 0.0165 mmol, 0.06 eq), and allyl acetate (35.6 µL, 0.3294 mmol, 1.2 eq) at $-20^0$C to provide the above mentioned compound as a brownish yellow oil (60.5 mg, >99% yield).

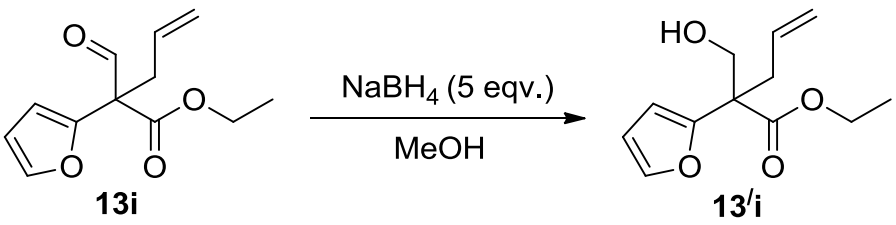
**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 9.81 (s, 1H), 7.44 (s, 1H), 6.40 (d, *j* = 4.8, 2H), 5.72 (m, 1H), 5.17 (d, *J* = 1.2 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.03 (dd, *J* = 7.2, 14.1 Hz, 1H), 2.93 (dd, *J* = 7.5, 14.1 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 193.8, 168.4, 148.3, 143.2, 132.0, 119.4, 110.7, 109.3, 62.5, 62.0, 35.6, 14.1.

**$[\alpha]_D^{27}$:** = + $56.0^0$ (c = 0.089, EtOAc).

**HRMS (ESI):** Calculated (m/z) for C12H15O4 $(M+H)^+$ : 223.0970, Found 223.0943.

***Procedure*** *for the reduction of ethyl 2-formyl-2-(furan-2-yl)pent-4-enoate (**13i**) to ethyl 2-(furan-2-yl)-2-(hydroxymethyl)pent-4-enoate (**13′i**)*




To a 50 mL round bottom flask with **13i** (150.0 mg, 0.6750 mmol, 1.0 eq) was charged with MeOH (25 mL) and cooled to 0°C. Next, $NaBH_4$ (127.0 mg, 3.3750 mmol, 5.0 eq) were added as a solid and let the mixture stir for 2h. The reaction was quenched with $H_2O$ (15 mL) at 0°C and then was extracted three times with dichloromethane. The organic layer was washed with brine, then dried over anhydrous $Na_2SO_4$, and concentrated in *vacuo.* Column chromatography on silica gel with 9:1 hexane: EtOAc provided 122 mg (82% yield) of the reduced quaternary alcohol product **13′i** as a yellow oil.

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ (ppm) 7.39 (s, 1H), 6.36(m, 1H), 6.31 (d, *j* = 3.3 Hz, 1H), 5.71 (m, 1H), 5.16 (d, J = 19.5 Hz, 1H), 5.12 (d, J = 11.1 Hz, 1H), 4.24 (q, j = 7.2 Hz, 2H), 4.04 (q, j = 11.4 Hz, 2H), 2.83 (d, j = 7.2 Hz, 2H), 2.07 (s, 1H), 1.27 (t, j = 7.2 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 172.5, 152.7, 141.9, 132.8, 118.9, 110.2, 107.6, 64.9, 61.4, 53.2, 37.1, 14.1.

**Chiral HPLC:** 75% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 99:01 hexane/ethanol, 1.0 mL/min, 210 nm, 14.51 min (minor), 15.97 min (major).

**$[\alpha]_D^{27}$:** = - $5.0^0$ (c = 0.036, EtOAc).

**HRMS (ESI):** Calculated (m/z) for C12H17O4 $(M+H)^+$ : 225.1127, Found 225.1110.

***Ethyl 2-acetyl-2-phenylpent-4-enoate (20)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **19** (50.0 mg, 0.2424 mmol, 1.0 eq), $Pd(PPh_3)_4$ (28.0 mg, 0.0242 mmol, 0.1 eq), allyl acetate (31.4 µL, 0.2909 mmol, 1.2 eq) and KOtBu (32.6 mg, 0.2909 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 5h to provide the above mentioned compound as a yellow oil (58.0 mg, 97% yield).

**Chiral:** General procedure for Pd-AAA (**Method 2**) reaction using hydroxyarylacrylate **19** (25.0 mg, 0.1212 mmol, 1.0 equivalent), $Pd_2(dba)_3CHCl_3$ (3.1 mg, 0.0030 mmol, 0.025 equivalent), *(R,R)*-L3 (5.7 mg, 0.0073 mmol, 0.06 equivalent), allyl acetate (15.7

µL, 0.1454 mmol, 1.2 equivalent) and KO*t*Bu (16.3 mg, 0.1454 mmol, 1.2 eq) at -10$^0$C to provide the above mentioned compound as a yellow oil (29.0 mg, 97% Yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 7.35–7.28 (m, 5H), 5.75 (m, 1H), 5.01 (m, 2H), 4.27 (q, J = 6.0 Hz, 2H), 3.10 (dd, J = 6.3, 13.8 Hz, 1H), 2.86 (dd, J = 7.8, 13.8 Hz, 1H), 2.07 (s, 3H), 1.27 (t, J = 9.0 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 203.0, 170.5, 136.9, 133.5, 129.3, 128.8, 128.4, 127.9, 127.7, 118.4, 68.8, 61.4, 39.8, 28.7, 14.1.

**Chiral HPLC:** 52% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 99:01 hexane/*i*PA, 1.0 mL/min, 210 nm, 9.70 min (major), 11.07 min (minor).

**HRMS (ESI):** Calculated (m/z) for C15H18O3 $(M+H)^+$ : 247.1329, Found 247.1333.

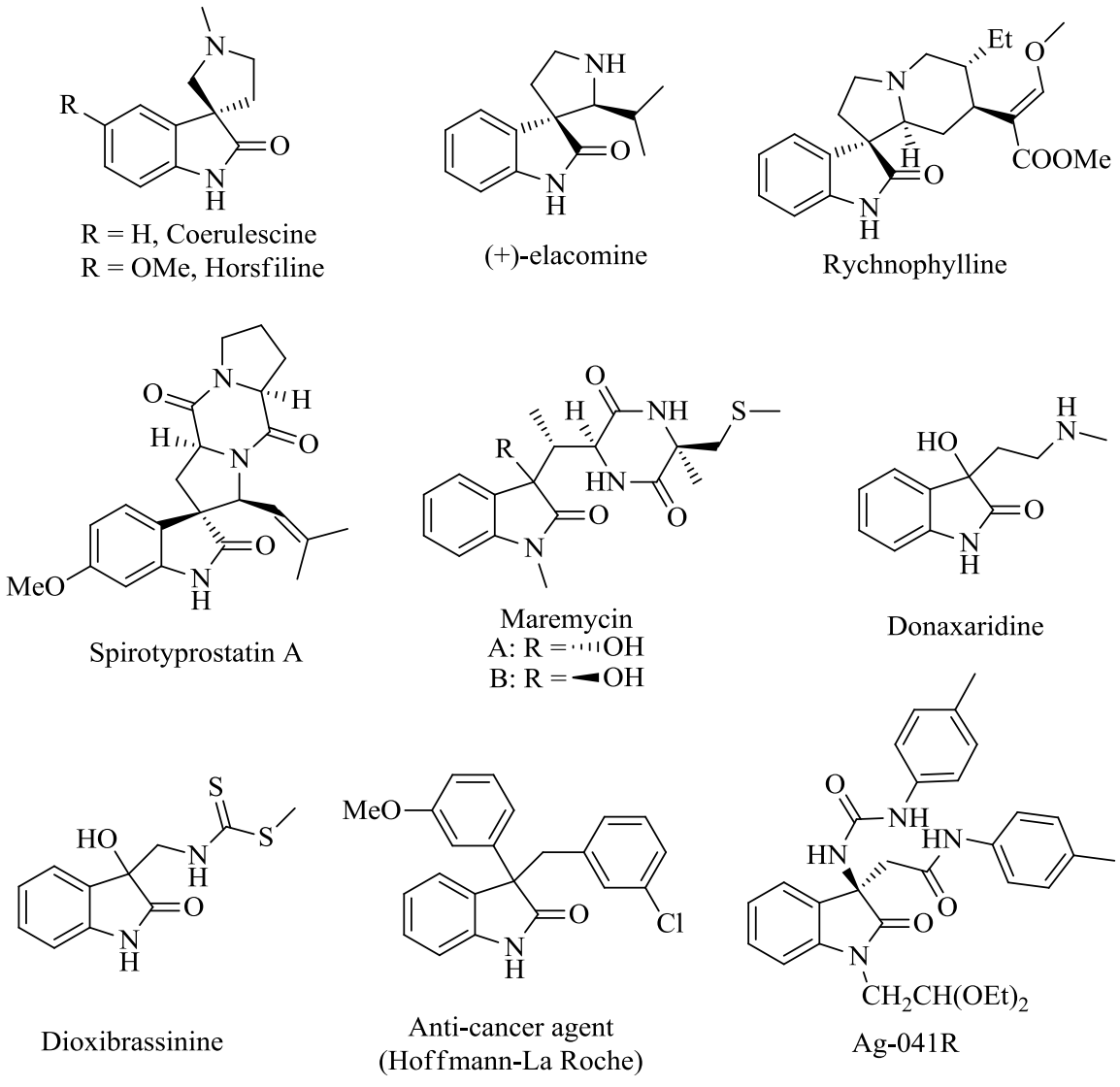
# CHAPTER 3: APPLICATION TO THE SYNTHESIS OF 3,3′-DISUBSTITUTED OXINDOLE AND α-DISUBSTITUTED QUATERNARY β-LACTONE FRAMEWORKS

## 3.1. 3,3′-disubstituted oxindole frameworks in medicinal chemistry

3,3′-disubstituted oxindole framework is one of the most classic and privileged heterocyclic motif that is present in a large family of bioactive natural products and pharmaceutically active compounds (Figure 17).[112] Horsfiline is an oxindole alkaloid found in the plant *Horsfieldia superba* and was first isolated in 1991 by Bodo and co-workers.[106c] It has analgesic effects. It is also active against human breast cancer cells. Coerulescine, an analog of horsfiline, has a moderate local anesthetic effect. Elacomine is naturally occurring hemiterpene spirooxindole alkaloids isolated from the root of a shrub *Elaeagnus commutata*.[113] It showed cell cycle inhibition activities and is known as tumor suppressor. Rychnophyllin is another antineoplastic agent. Rhynchophylline is found in *Uncaria rhynchophylla*, native to Thailand. It is a non-competitive NMDA antagonist and calcium channel blocker.[114] Sprotryprostatins are indole alkaloids from diketopiperazine class of natural products. It is found in a fungus, *Aspergillus fumigatus*. They are microtubule inhibitor and prevent cell division by mytosis. Recently, they have attracted a lot of attention as anti-cancer drug.[115] Maremycin A and B are first sulfur-containing diketopiperazine oxindole alkaloids isolated from the culture broth of marine bacteria, *Streptomyces*.[116] Donaxaridine was isolated from the giant reed plant *Arundo donax*, is a secondary metabolites used by the plant in response to microorganism.[117]

Dioxibrassinine is another sulfur-containing oxindole alkaloid. In addition, the 3,3′-disubstituted oxindole scaffold is part of pharmaceutically active compounds, such as AG-041R, which is a potent gastrin/CCK-B receptor antagonist.[118]

**Figure 17.** Representative natural products and bioactive compounds with the 3,3′-disubstituted oxindole framework.

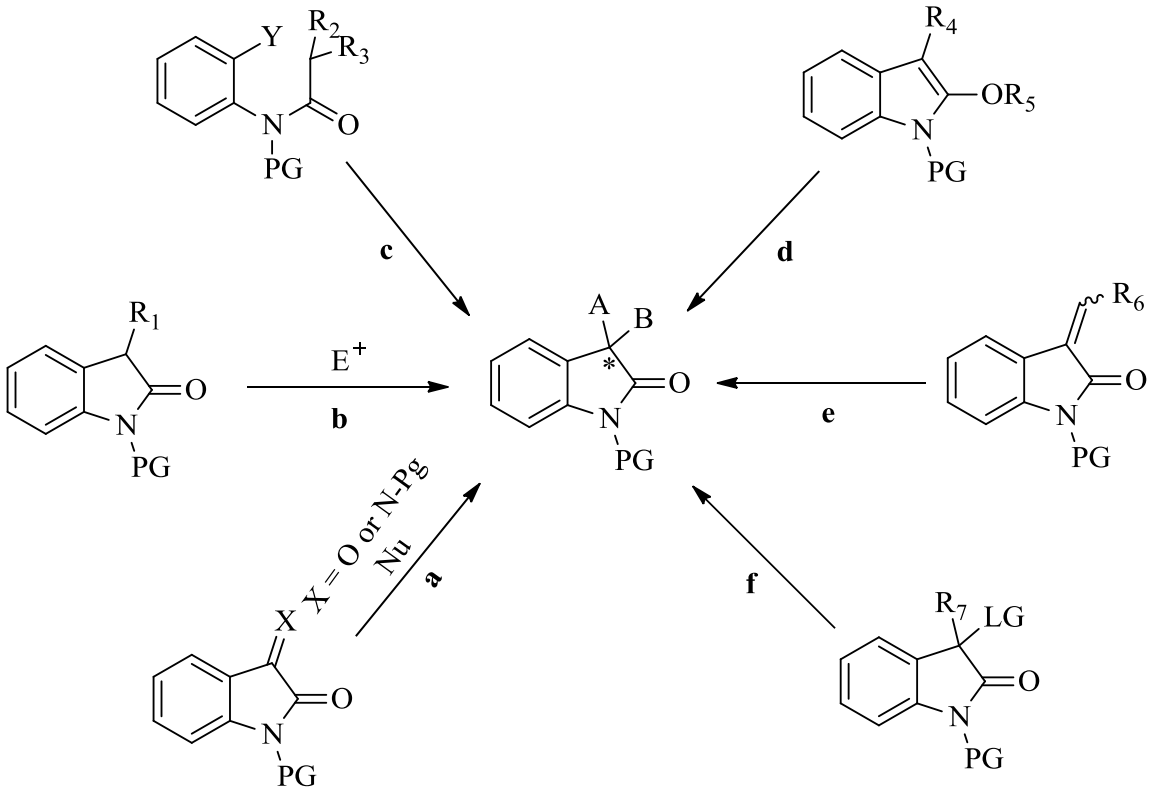


### 3.1.1. General considerations on the asymmetric synthesis of 3,3′-disubstituted oxindole

The frequent presence of 3,3′-disubstituted oxindole in natural products, drugs, and related analogs has initiated investigantions into its formation by asymmetric synthesis. The goal has been to synthesize enough material of the desired natural products and related analogs to enable biological evaluation, studies on structure-activity relationships, and eventual development of new therapeutic agents.

As we know, it is very challenging to asymmetrically synthesize compounds containing tetrasubstituted carbon stereocenters. It's even more difficult to synthesize 3,3′-disubstituted oxindoles due to the presence of multiple tetrasubstituted carbon stereocenters, including all-carbon or heteroatom-containing ones. These challenges provided an ideal testing ground for organic chemists to develop new catalytic synthetic methodologies.

A number of catalytic enantioselective methods have been developed to synthesize the tetrasubstituted carbon at the C-3 position of the oxindole framework, which could be classified into the following categories by the substrates employed: (a) nucleophilic additions to isatins; (b) direct functionalization of 3-substituted oxindoles; (c) intramolecular coupling reactions; (d) reactions based on *O*-substituted oxindoles; (e) methyleneindolinones as substrates; and (f) oxindoles as electrophiles (Scheme 68).[119]



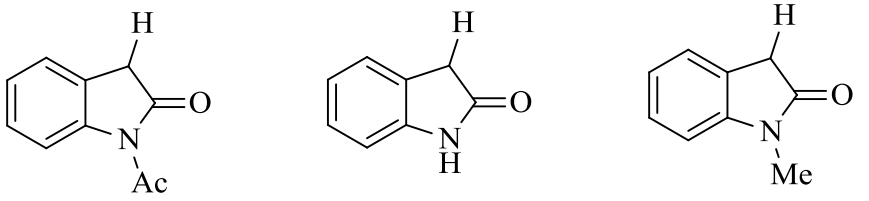

**Scheme 68.** Synthetic strategies for the catalytic asymmetric synthesis of 3,3′-disubstituted oxindoles.

Using 3-prochiral oxindoles as nucleophile to react with a variety of electrophiles and thereby constructing tetrasubstituted carbon stereocenter at the C-3 position is one of the most versatile methodology. This allows the synthesis of the desired tetrasubstituted carbon stereocenter with all carbon substituents as well as with a heteroatom substituent.

The $pK_a$ value is one of essential charcateristics of a pseudo-prochiral oxindole that is crucial for the functionalization at C-3 position. The $pK_a$ of unsubstituted oxindole is 18.2. However, it changes substantially depending on the substituents. The higher the $pK_a$

value, the stronger the bases is needed to activate the prochiral oxindole by deprotonation. While alkyl substituents in C-3 position and *N*-protecting groups increase the $pK_a$ substantially to as much as 18.5, acetyl protecting groups for nitrogen in oxindoles decreases it significantly from 18.2 to 13 (Figure 18). Considering this, a number of current methods employ *N*-Boc-3-substituted oxindoles as starting material, due to (1) suitable $pK_a$ value for efficient activation by deprotonation; (2) bidentate coordination of the substrate to a chiral metal complex as well as the necessity of bulkier group for better enantioselectivity (Figure 18). Moreover, it is still very challenging to construct the desired quaternary carbon stereocenter at C-3 position from *N*-unprotected oxindole.

**Figure 18.** $pK_a$ values of protected and unprotected oxindoles.




$pK_a$ 13 $pK_a$ 18.2 $pK_a$ 18.5

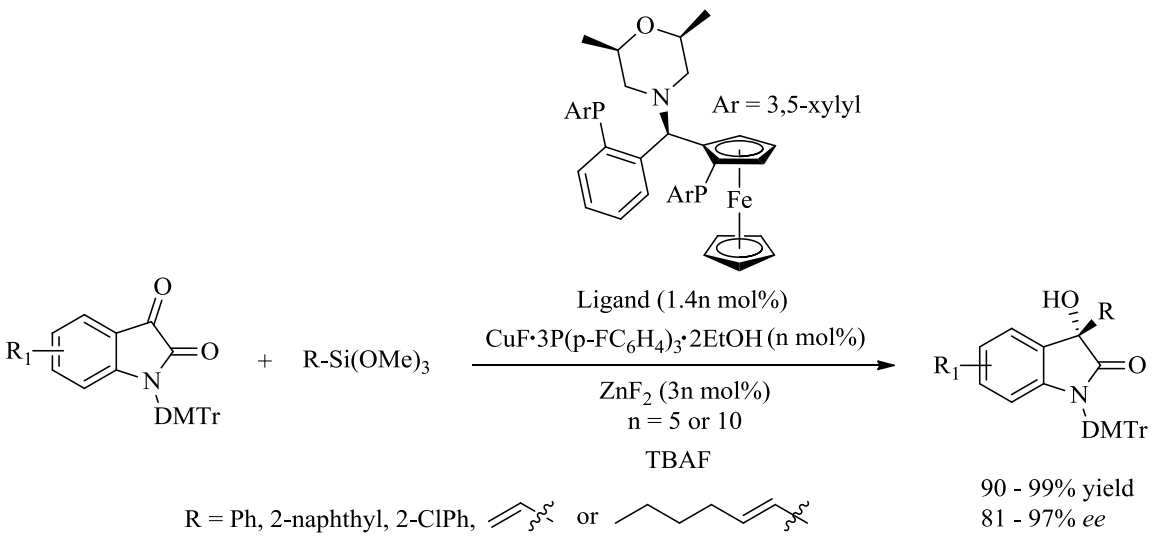

Less acidic carbon nucleophiles free from protection and deprotection

More acidic carbon nucleophiles facilitate Lewis acid coordination and activation *via* bidentate chelation

### 3.1.2. Recent advances in asymmetric synthesis of 3,3′-disubstituted oxindole

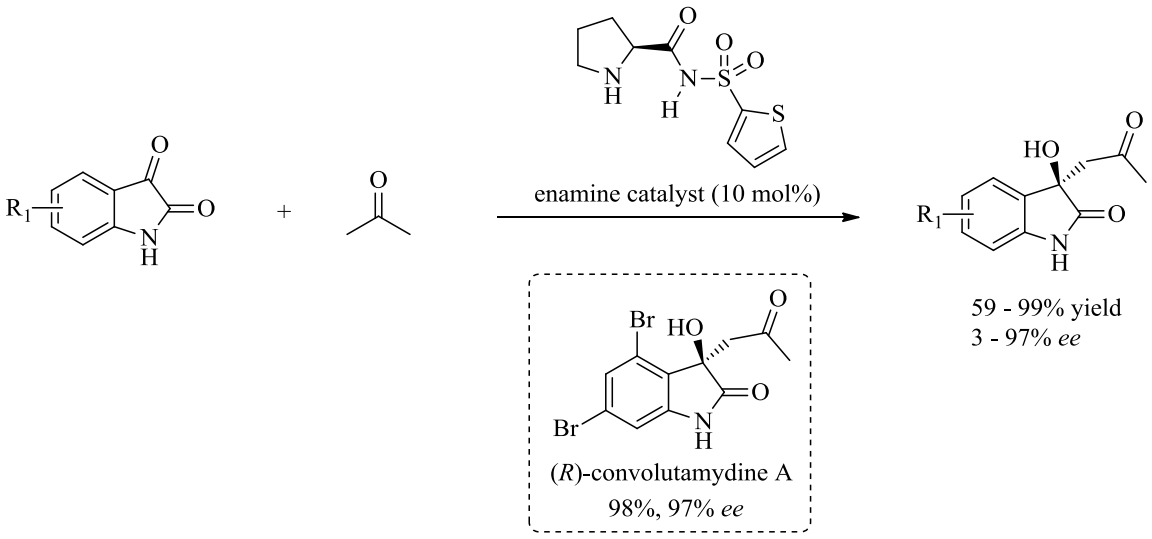
Isatin or 1*H*-indole-2,3-dione has been widely used as an intermediate for the synthesis of various oxindole compounds. It is an indole derivative, which was first synthesized by Erdmann[120] and Laurent[121] in 1840 as a product of the oxidation of indigo dye. It has been isolated from many plants as well, such as *Isatis tinctoria*, *Calanthe discolor* and *Couroupita guianensis*.[112e]

In 2009, Shibasaki and co-workers[122] reported the alkenylation and arylation of isatins using silicon-based nucleophiles to produce biologically relevant 3-aryl-3-hydroxy-2-oxindoles. The reaction was performed with copper catalyst. The group found that the use of bulkier protecting group influence the enantioselectivity greatly and finally, di(*p*-methoxyphenyl)phenylmethyl (DMTr) as protecting group afforded the desired product with as much as 97% *ee*. The addition of $ZnF_2$ was used to accelerate the reaction and eventually, 3 equivalents relative to the copper catalyst was found to be optimal (Scheme 69).



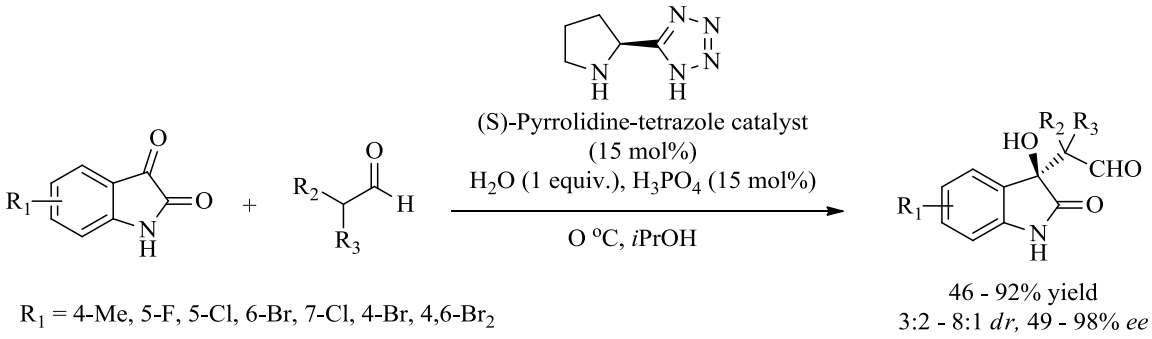

**Scheme 69.** Synthesis of 3,3′-disubstituted oxindole by arylation and alkenylation of isatins.

Direct cross-aldol reaction of donor carbonyl compounds with highly reactive isatins in the presence of chiral enamine catalyst has become another facile method for the construction of 3,3′-disubstituted oxindole ring. Toru and co-workers[123] published an excellent research that described a L-proline based bifunctional catalyst promoting the reaction between acetone and isatins affording the desired product with high yield and *ee*. Soon this method was applied to the total synthesis of (*R*)-convolutamydine A using 4.6-dibromoisatin as starting material by the same group with 98% yield and 97% *ee* (Scheme 70).




**Scheme 70.** Aldolization of acetone to isatins and synthesis of (*R*)-convolutamydine A.

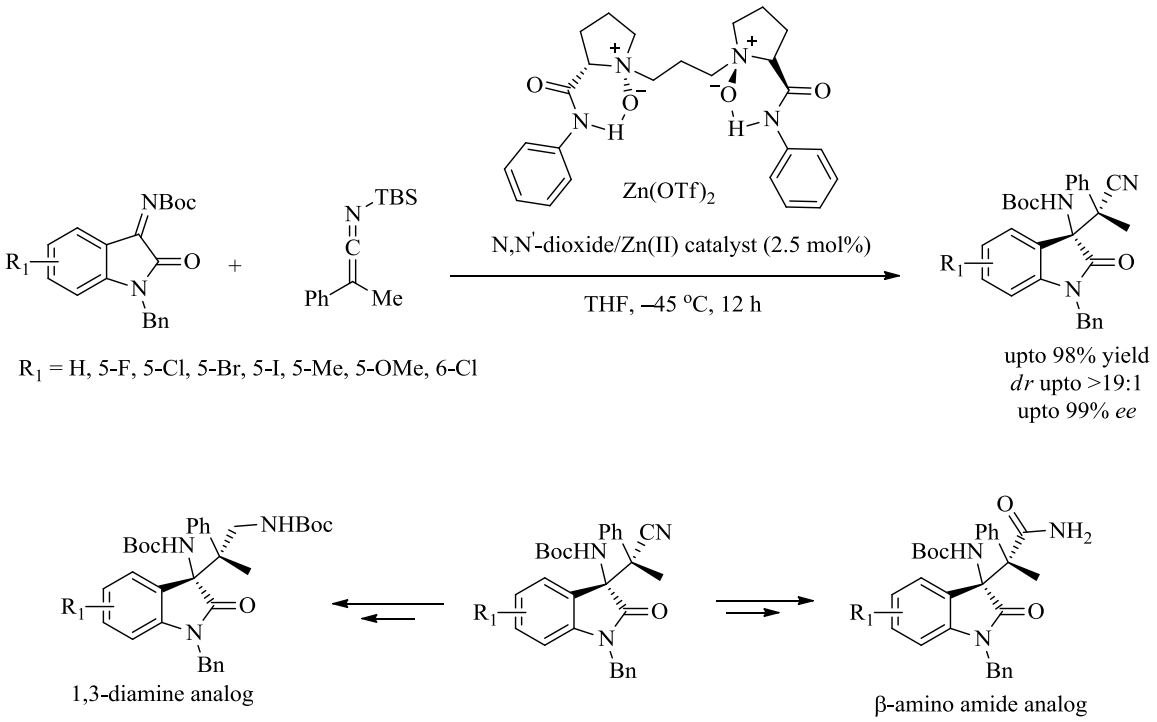
Later in 2009, Wang and co-workers[124] reported the cross-aldol reaction of isatins with α-branched aldehydes to synthesize two vicinal quaternary centered 3-substituted 2-hydroxyindol-2-ones with high enantioselectivity. This time, (*S*)-Pyrrolidine-tetrazole was used as a catalyst (Scheme 71).




**Scheme 71.** The aldolization of α-substituted aldehydes and isatins.

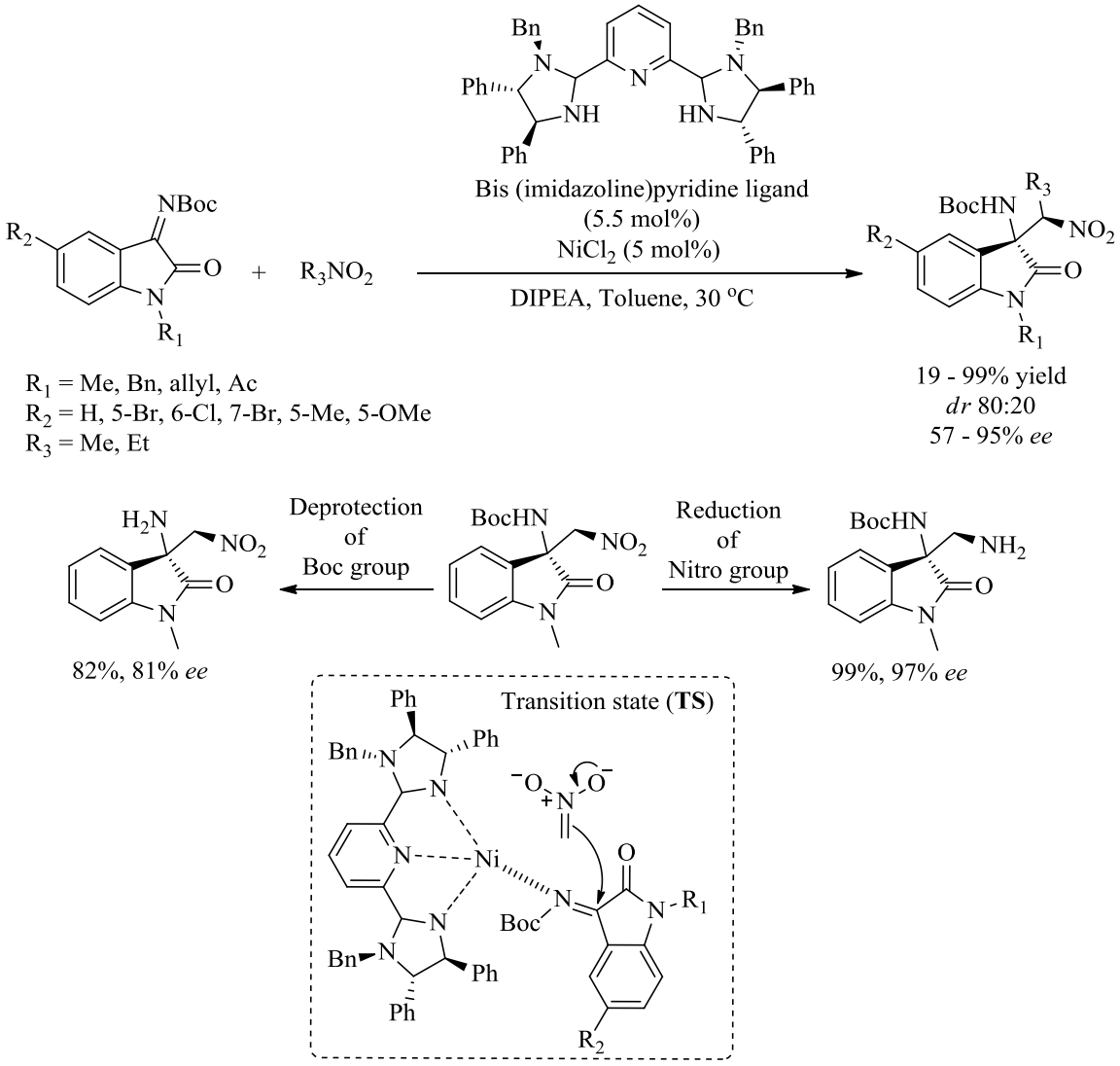
3-substituted-3-amino-2-oxindoles, which is also a privileged core structure of a variety of natural products and biologically active compounds,[125] have also been producted from isatin imines. Isatine imines are one of the most effective precursors to the synthesis of 3-substituted-3-amino-2-oxindoles due to its ability to accept addition of nucleophile enantioselectively by various nucleophilic addition reactions.[126]

Recently in 2015, Feng and co-workers[127] reported the reaction of silyl ketene imines with isatin imines by Mannich reaction using *N*,*N*′-dioxide/Zn(II) as organocatalyst. The reaction produced a variety of β-amino nitriles containing vicinal tetrasubstituted stereocenters in excellent yield (upto 98%) with *dr* upto >19:1 and with excellent enantioselectivity ranging from 91 – 99% *ee* (Scheme 72). Then the desired product was efficiently transformed to 1,3-diamine and β-amino amide, which is similar to the potent gastrin/CCK-B receptor antagonist AG-041R (see Figure 16).




**Scheme 72.** Enantioselective Mannich reaction of silyl ketene imines with isatin imine.

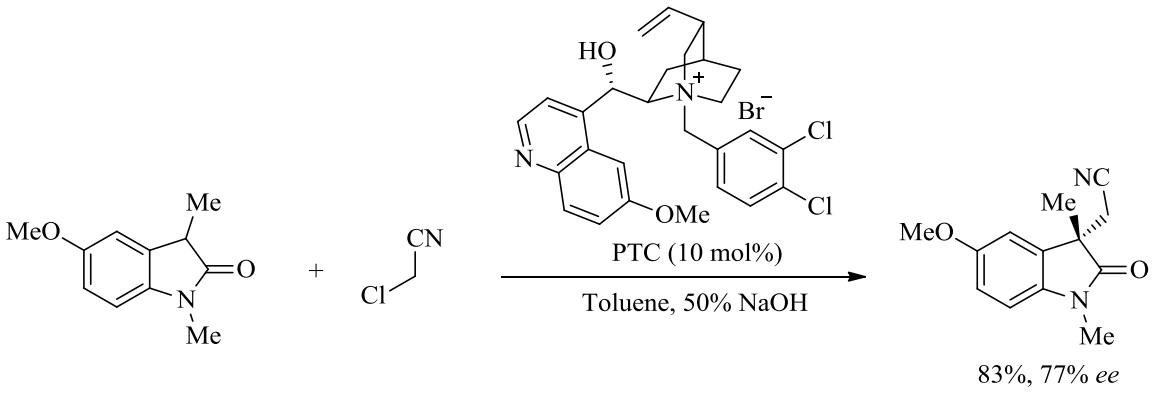
In 2014, Arai and co-workers[128] reported the exciting reaction of nitroalkanes with isatin imine using chiral Ni (II) as catalyst. Bis(imidazoline)pyridine was used as chiral ligand. The desired product, 3-amino-2-oxindole was isolated with excellent yield and enantioselectivity. To demonstrate the synthetic ability of the method, they showed the reduction of nitro group as well as the deprotection of Boc group yielding desired product without loss of *ee*. They also went on to propose transition state where pyridine-$NiCl_2$ complex acts as Lewis acid and activates the ketimines through nickel coordination by lone pair on nitrogen in isatin imine. Then this activated isatin imine is attacked by nitronate carbanion (Scheme 73).




**Scheme 73.** Bis(imidazoline)pyridine-$NiCl_2$ catalyzed asymmetric reaction of nitroalkanes with isatin imine.

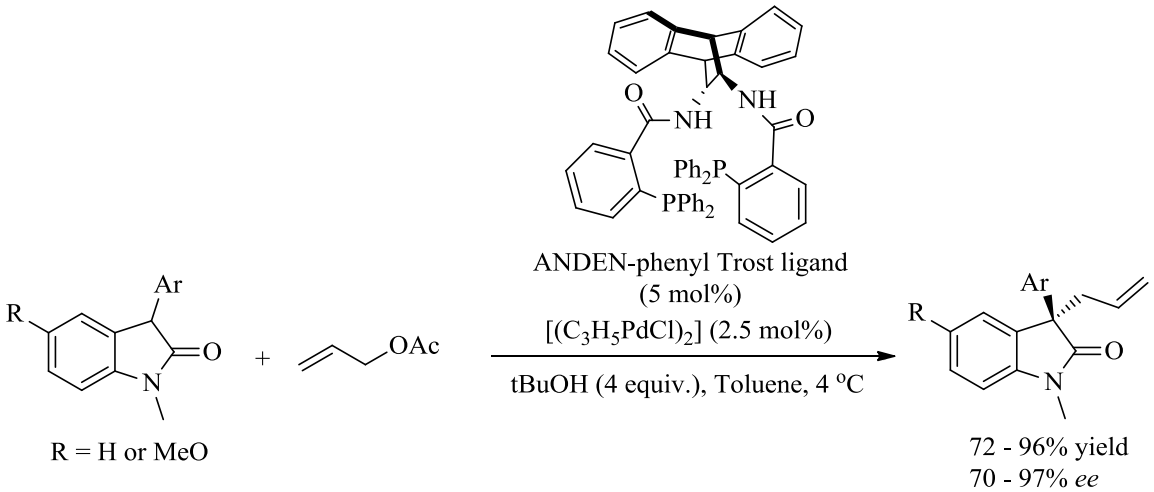
Wong and co-workers[129] reported the first enantioselective catalytic alkylation of 3-prochiral oxindole to produce the C-3 quaternary stereocenter in 1991. They have used phase-transfer catalytic (PTC) conditions employing chinchona based PTC catalyst

(Scheme 74). Employing this methodology, they have demonstrated the synthesis of (−)-esermethole which is a known intermediate in the synthesis of (+)-physostigmine.



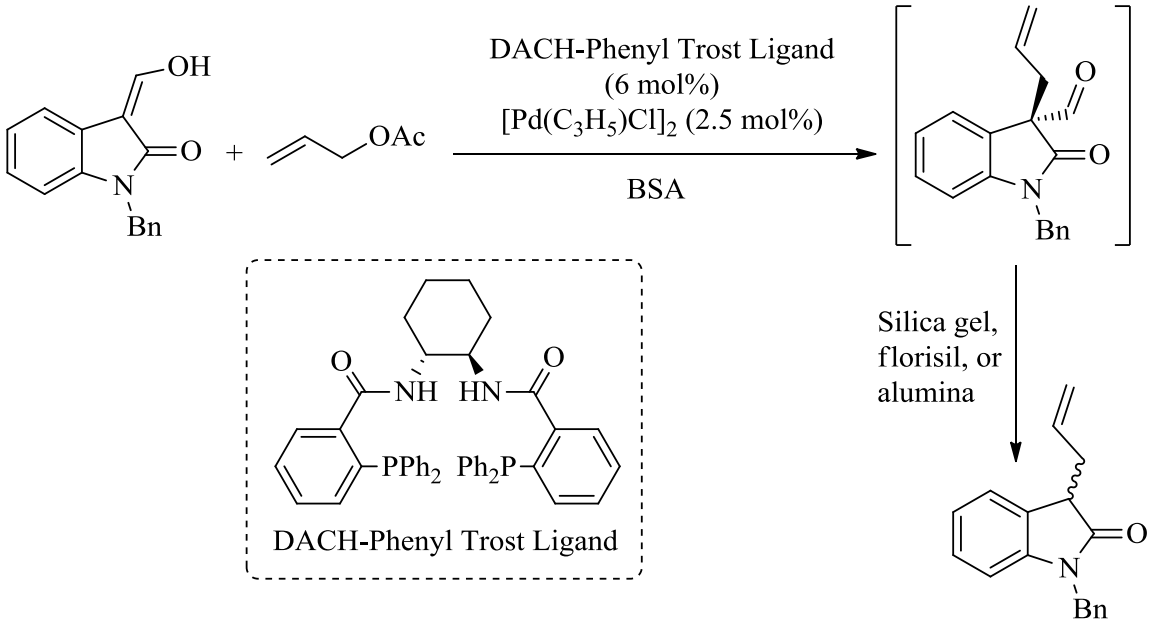

**Scheme 74.** PTC-catalyzed alkylation of oxindole.

Then in 2005, Trost and co-workers[130] reported asymmetric allylic alkylation reaction of 3-aryl oxindoles using Pd as catalyst (Pd-AAA). The reaction afforded very high *ee* (Scheme 75).

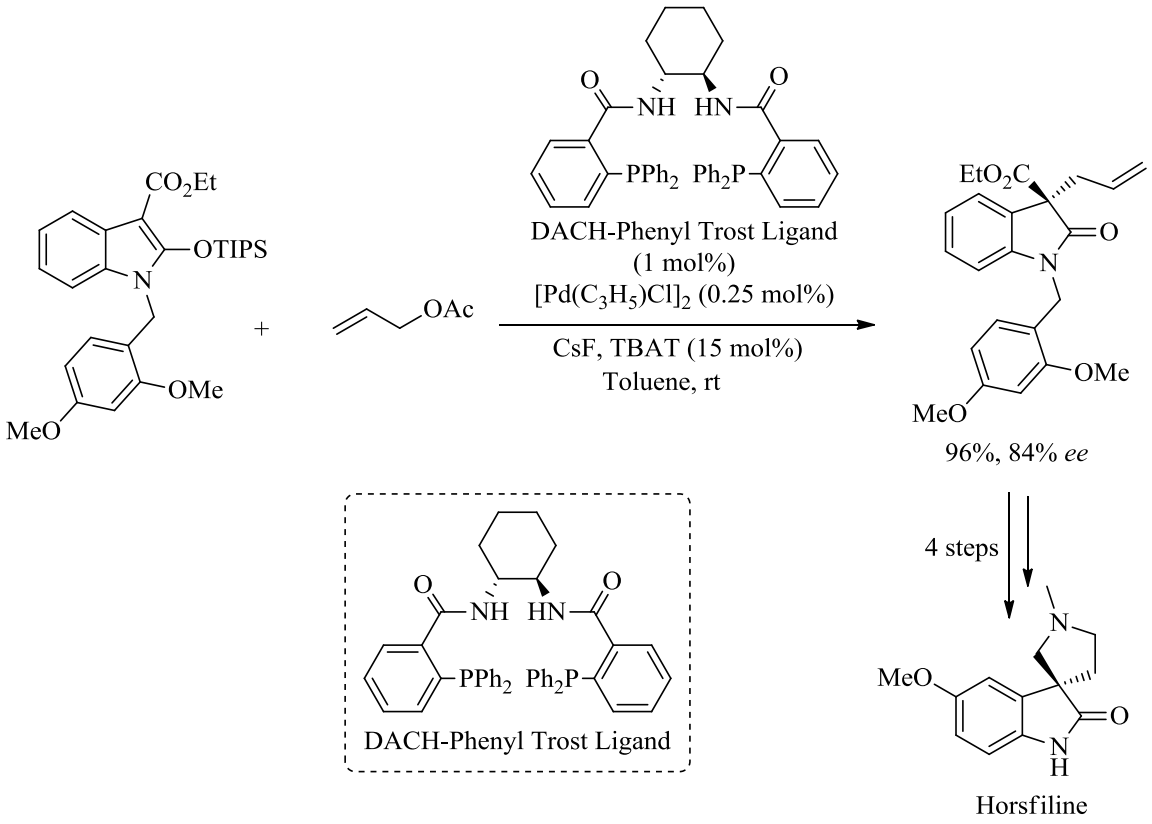



**Scheme 75.** Pd-AAA of 3-aryloxindoles.

As a continuation, in 2006, the same group reported the use of aldehyde and ester substituents in the C-3 position of oxindole as nucleophiles for Pd-AAA reaction.[131] While the product from the AAA reaction of 3-aldehyde substituted oxindole with allyl acetate was unstable to purification and providing deformylated product in the end (Scheme 76), the reaction with ester-substituted oxindole yielding desired product with high yield and *ee* (Scheme 77). They went on to synthesize natural product Horsfiline to show the application of this methodology.

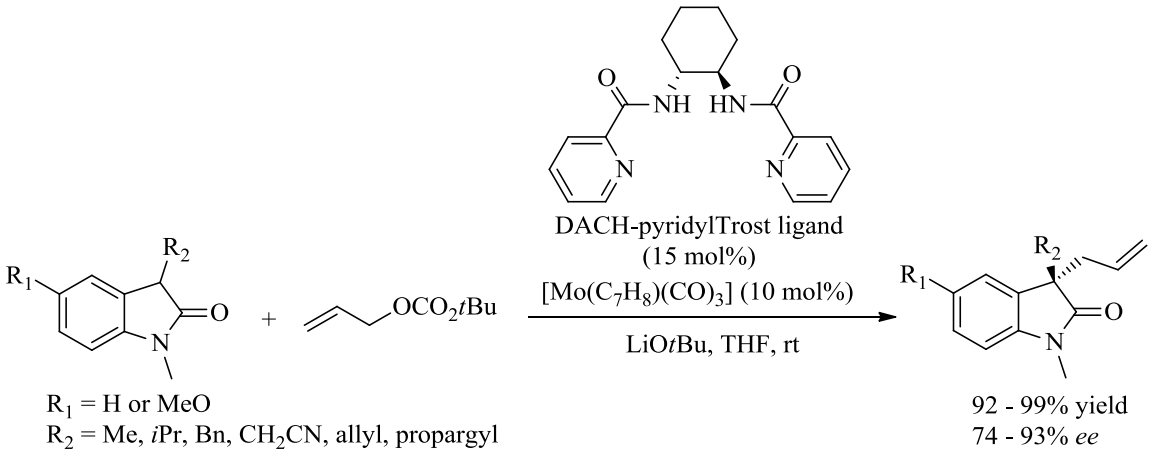



**Scheme 76.** Deformylation of the initial Pd-AAA aldehyde adduct.




**Scheme 77.** Pd-AAA reaction of 3-esteroxindole and its application.

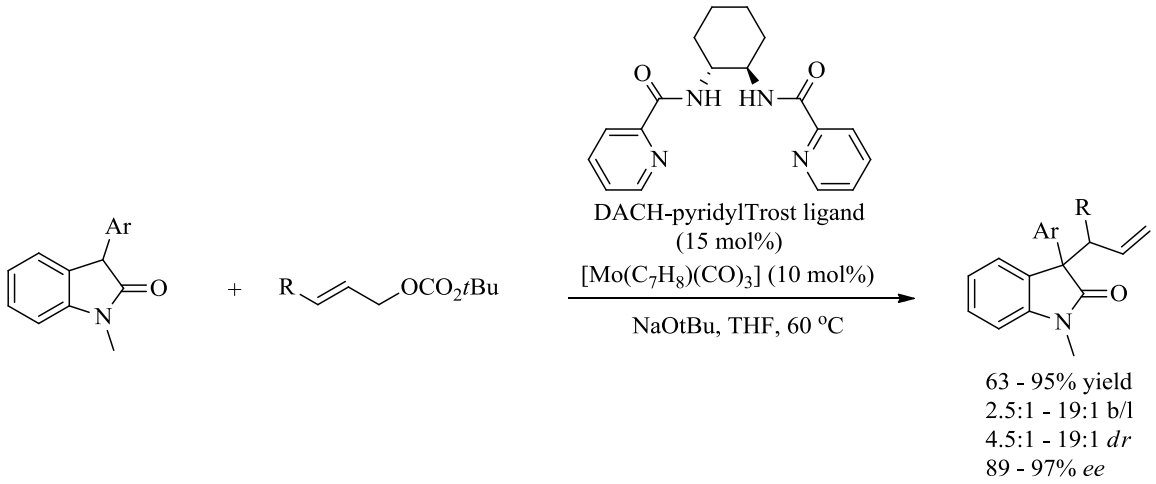
Soon, the same group reported that molybdenum provided better enantioselectivity compare to palladium as a catalyst in asymmetric allylic alkylation reaction of 3-alkyl substituted oxindoles. They argued that molybdenum goes through inner-sphere mechanism of coordination unlike palladium that undergoes predominantly outer-sphere mechanism. It was the first time molybdenum was used as a catalyst in AAA reaction which produced a number of 3-allyl-3-alkyloxindoles with good to excellent yield and enantioselectivity (Scheme 78).[106g]




**Scheme 78.** Mo-AAA of 3-alkyloxindole.

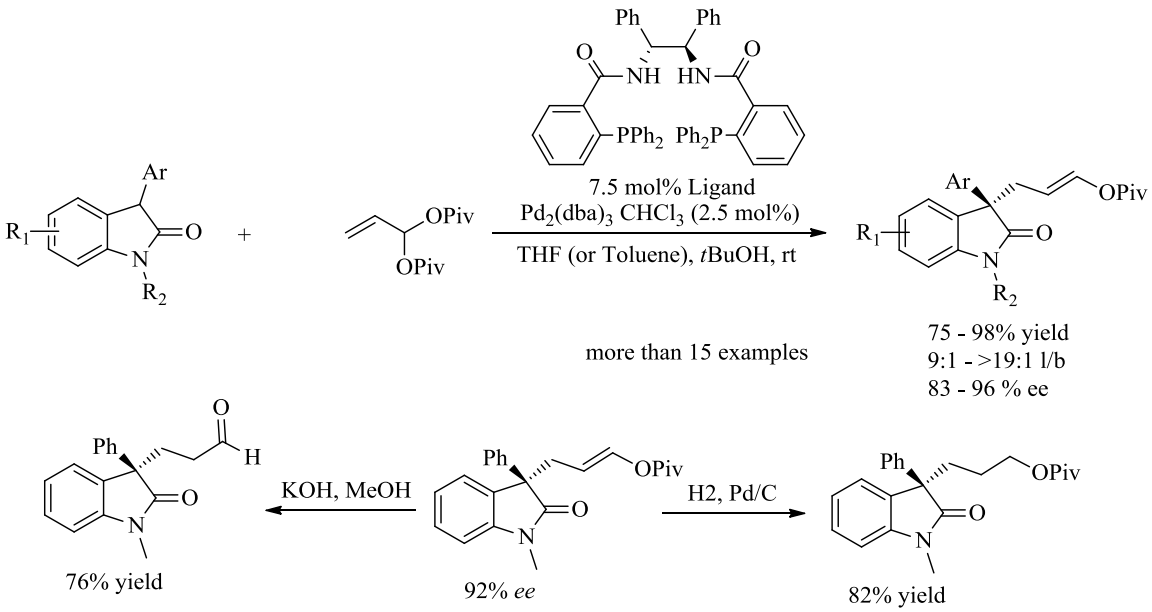
Later in 2011, the same research group demonstrated this Mo-AAA reaction of 3-alkyloxindoles to synthesize biologically active (−)-physostigmine and (−)-phenserine, as well as *ent*-(−)-debromoflustramine B.[106n]

This Mo-AAA reaction is not limited to the 3-alkyl substituted oxindoles, as the reaction has been successfully employed with 3-aryloxindoles as substrate as well. A series of 3-allyl-3-aryloxindoles containing vicinal quaternary and tertiary stereogenic centers have been synthesized by Mo-AAA reaction using substituted allyl electrophiles. The reaction provided branched product as the major product with excellent *dr* and *ee* (Scheme 79).[132]



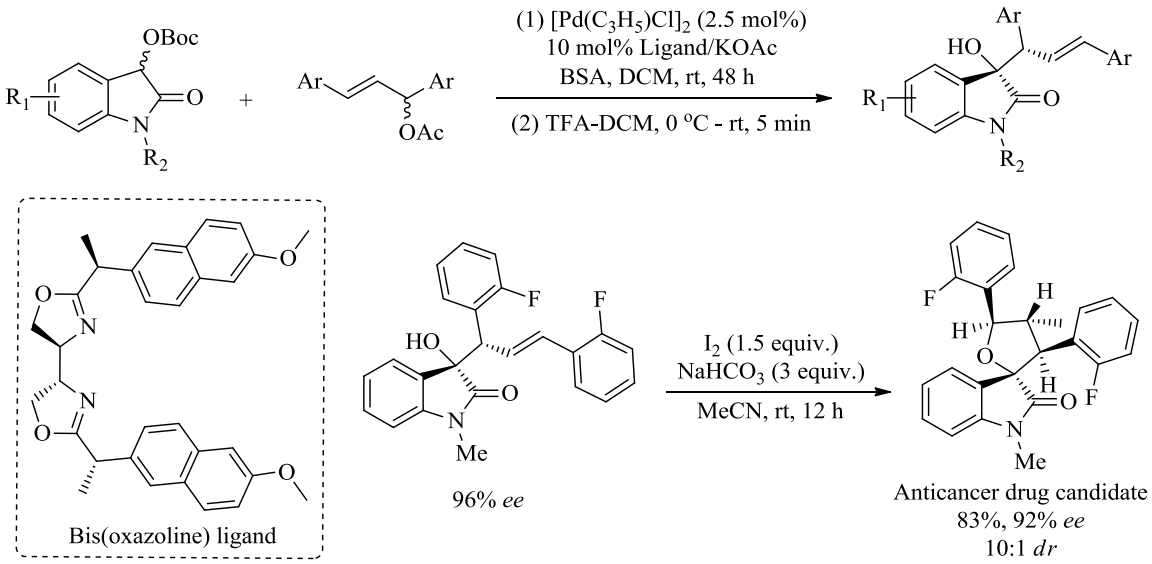

**Scheme 79.** The catalytic asymmetric construction of vicinal quaternary and tertiary chiral centers *via* Mo-AAA of 3-aryloxindoles.

Trost *et al* also used Pd-AAA reaction with 3-aryl substituted oxindole.[133] This time they have used allylidene dipivalate as allyl source to construct a useful allyl enol pivalate product with high yield and enantioselectivity. The reaction favored linear over branched product. Later, in order to show the utility of this enantiorich enol pivalate product, desired aldehyde has been produced by treating it with methanolic KOH. The reaction showed very clean aldehyde product without the formation of competitive aldol or retro-Michael products. In addition, the catalytic hydrogenation of the product ally enol pivalate has been carried out which provided functionalized protected alcohol in good yield (Scheme 80).



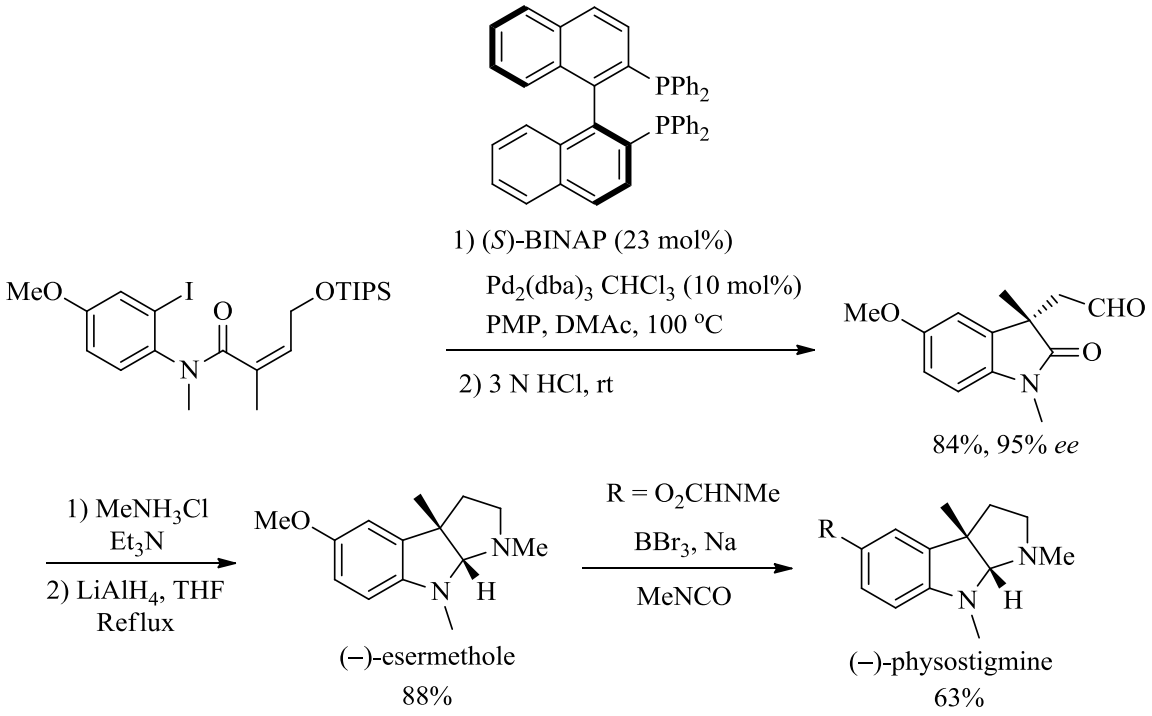

**Scheme 80.** Pd-AAA of 3-aryloxindoles with allylidene dipivalate.

Recently in 2015, Kesavan and co-workers[134] synthesized enantiorich 3-allyl-3-hydroxyoxindoles from 3-OBoc oxindole using tartrate drived bis(oxazoline) as a ligand. The reaction produced the desired product with high enantio- and diastereoselectivity. Using the methodology, they demonstrated the application by synthesizing a spirooxindole comprising a 3,2′-tetrahydrofuran moiety which is an important anticancer drug candidate (Scheme 81).[135]




**Scheme 81.** Synthesis of 3-allyl-3-hydroxyoxindoles from 3-OBoc oxindole and the application of the reaction.

Intramolecular Heck reaction has been brilliantly applied by Overman and co-workers[136, 61b] to synthesize 3,3′-disubstituted oxindole framework. The reaction employed (*Z*)-2-butenanilide as starting material and Pd (0) as catalyst. After investigating the reaction for optimum conditions, they found that 20 mol% of a BINAP derived chiral palladium catalyst, in addition to PMP as an additive, yielded the desired product with good yield and up to 95% *ee*. This methodology was then applied to synthesize biologically active natural product, (−)-physostigmine (Scheme 82). However, as is always the case, the limitation of this intramolecular coupling reaction is that it requires highly specialized substrate to produce quaternary stereocenter at C-3 position of oxindole.

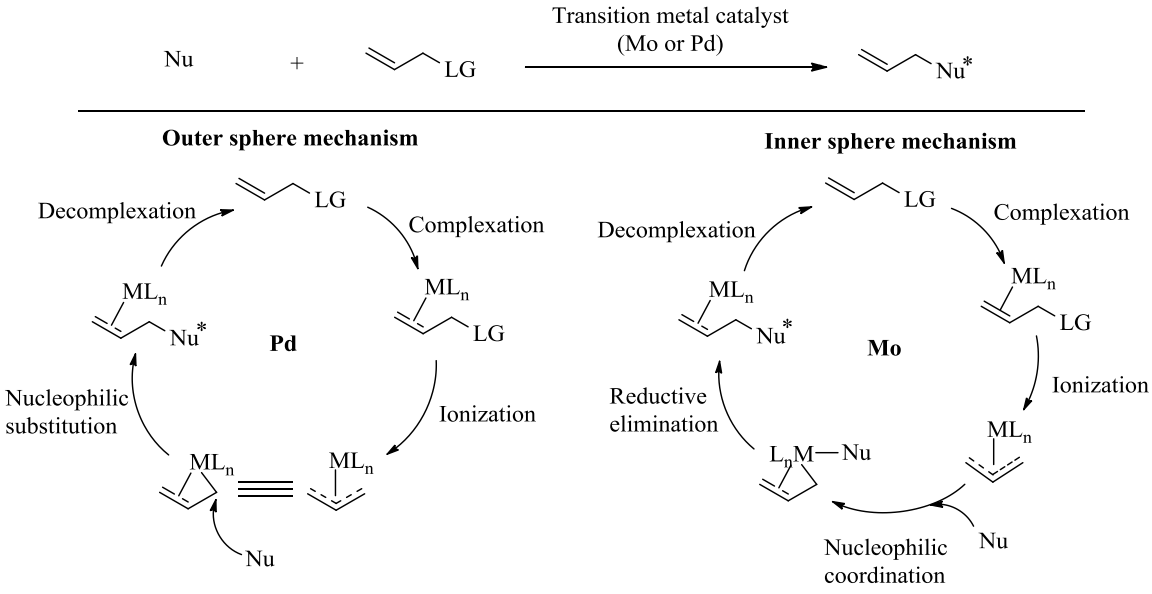



**Scheme 82.** Synthesis of 3,3′-disubstituted oxindole *via* intramolecular Heck cyclization and total synthesis of (−)-physostigmine.

### 3.1.3. Palladium *vs.* Molybdenum in AAA

Molybdenum is claimed to be better in some cases for inducing enantiodiscrimination compared to palladium in AAA reaction.[106n] Trost argues that it is because of the ability of molybdenum to go through inner-sphere mechanism of coordination of nucleophile to the metal instead of palladium where outer-sphere mechanism is more prominent (Scheme 83). The catalytic cycle for the transition-metal-catalyzed AAA reaction of prochiral nucleophiles is as follows: coplexation of the olefin to the metal, ionization of the metal to generate π-allylmetal complex, alkylation of the nucleophilic substrate, and

finally decomplexation to regenerate the catalyst by dissociation of the olefinic double bond of the allylic product from the metal. The chiral induction at the nucleophile depends on the step where the nucleophile attacks the π-allylmetal complex. There are two possible mechanisms for this step: outer-sphere mechanism and inner-sphere mechanism. An outer sphere mechanism is where an $S_N2$ attack of the nucleophile to one of the terminal carbons of the allyl group of the π-allylmetal complex takes place. Palladium is assumed to go through AAA reaction by this mechanism. In this mechanism, the alkylation steps occurs outside of the coordination sphere of the metal since the nucleophile is not inside the chiral environment created by the chiral ligand but it's approaching towards it from outside. Hence, high enantioselectivity is difficult to achieve with palladium as catalyst under standard reaction conditions. On the other hand, molybdenum, by being electron deficient compare to palladium, it sees nucleophile as an electron source or in other words, ligand. As a consequence, the nucleophile pre-coordinates to the metal first and subsequent reductive elimination provides the product. Due to this pre-coordination, the nucleophile in under the total influence of the chiral ligand before performing the reductive elimination step, which is enantioselectivity determining in the inner-sphere process. The inner-sphere process places the nucleophile and the chiral ligand in close proximity, and thereby, should provide more opportunity for enantiodiscrimination.



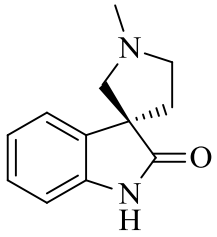

**Scheme 83.** Outer-sphere and inner-sphere mechanism of transition-metal-catalyzed AAA.

### 3.1.4. Catalytic enantioselective total synthesis of Coerulescine and Horsfiline

Coerulescine and Horsfiline are spirooxindole alkaloids. Horsfiline was first isolated by Bodo and co-workers[106c] in 1991 from *Horsfieldia superba* and Coerulescine was by Willing and co-workers[137] in 1998 from the blue canary grass *Phalaris coerulescens* (Figure 19). The spirocyclic oxindoles have showed a variety of biological activities; for instance, anticancer activities,[138] contraceptive activities,[139] and antimigraine activity.[140] Due to such diverse activities, spirooxindole alkaloids have become attractive targets in medicinal chemistry and drug discovery.[112a] Coerulescine and Horsfiline, the simplest molecules of this alkaloid family, have also garnered attentions to synthetic chemists.

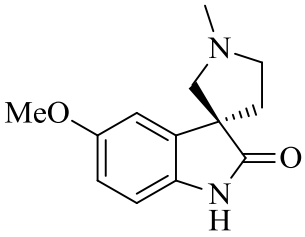
Even though several reports[141] have been publish to synthesize racemic Coerulescine and Horsfiline, the asymmetric version of the synthesis of both of these compounds is very rare. There is only one report,[142] to the best of my knowledge, for the synthesis of enantiorich Coerulescine and six reports[133, 142, 143] for enantioselective synthesis of Horsfiline have been published to date.

**Figure 19.** Coerulescine and Horsfiline




**21**

Coerulescine

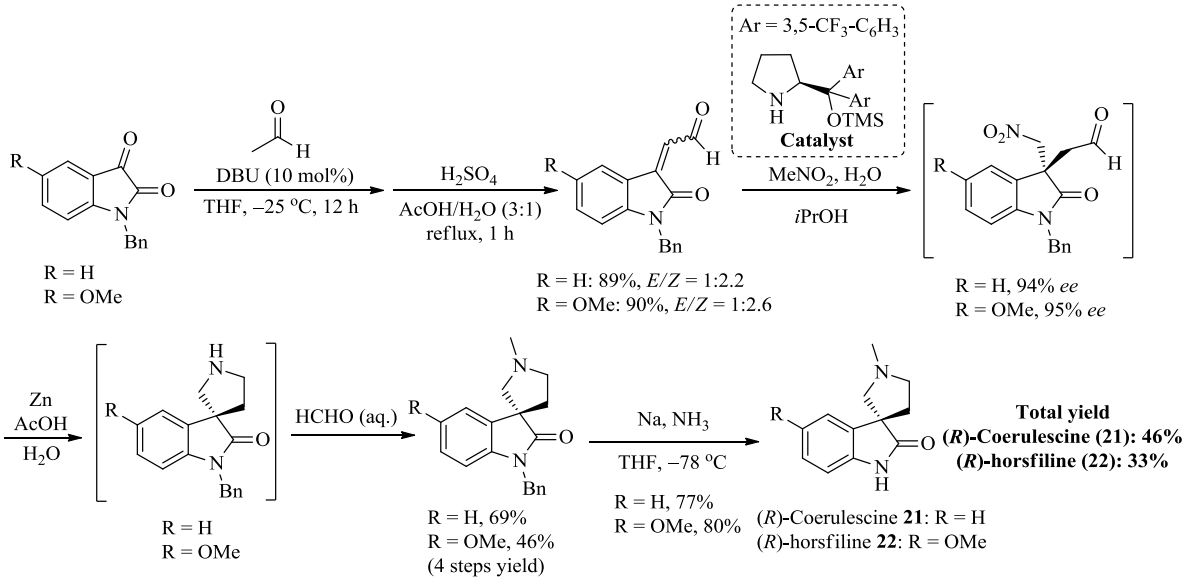



**22**

Horsfiline

Recently, in 2014, Hayashi and co-workers[142] reported the three one-pot enantioselective synthesis of both (−)-coerulescine **21** and (−)-horsfiline **22** (Scheme 84). A one-pot method is effective and economical because it avoids several purification processes and thereby, minimizes the use of chemicals and decreases the total production time as well as cost. The two key reactions in this total synthesis was (1) the synthesis of a 2-oxoindoline-3-ylidene acetaldehyde from acetaldehyde and an isatin derivative by aldol reaction, (2) the organocatalytic asymmetric Michael addition of nitromethane to the 2-oxoindoline-3-ylidene acetaldehyde to construct all-carbon quaternary stereogentic center.

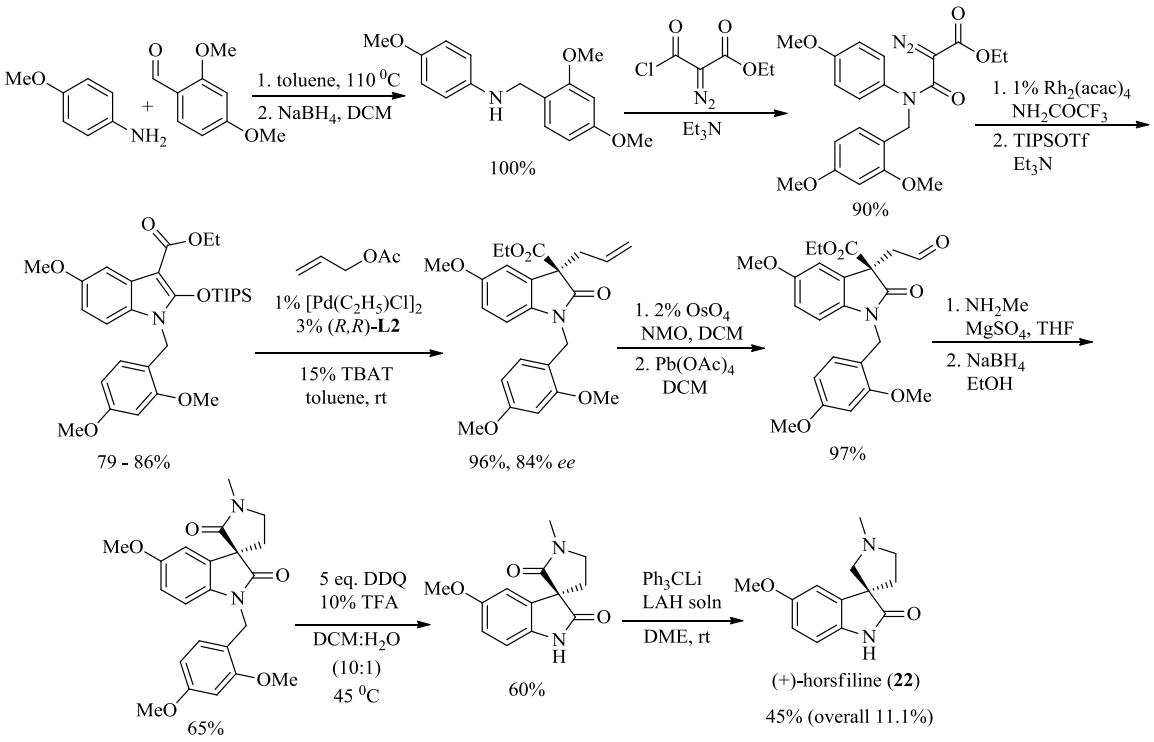
The first step of the synthesis was to employ an aldol reaction of acetaldehyde with the isatin derivatives, followed by dehydration yielding 2-oxoindoline-3-ylidene acetaldehydes as *E/Z* isomeric mixtures in excellent yields. The catalytic enantioselective conjugate addition of these aldehydes with nitromethane provided desired quaternary stereocenters with excellent *ee*. Very simple chiral diarylprolinol silyl ether has been employed as a catalyst to induce enantioselectivity. Next, Zn/AcOH, and water were introducted to the same reaction vessel to reduce the nitro group into an amine. This amine, at the same time, provided an intramolecular reductive amination to afford the pyrolidino spirocycles. Then the reaction mixture was introduced with formaldehyde to install methyl group on nitrogen by an intermolecular reductive amination. These four steps starting from the formation of quaternary centers have been performed in the same vessel. Deprotection of the benzyl group performed under Birch condition provided desired (*R*)-coerulescine **21** and (*R)*-horsfiline **22** with overall 46% and 33% yield; and 94% and 95% *ee* respectively.




**Scheme 84.** Three one-pot sequential syntheses of (*R*)-coerulescine **21** and (*R)*-horsfiline **22**.

In another research in 2005, Trost and co-workers[133] synthesized (+)-horsfiline **22** with moderate yield and enantioselectivity (Scheme 85). They have used both *O*- and *N*-protected and 3-ester substituted prochiral oxindole as substrate. This unique substrate has been prepared by four steps. In the first step, p-anisidine was refluxed with 2,4-dimethoxybenzaldehyde in toluene followed by reduction of the intermediate imine adduct with sodium borohydride in methanol resulted quantitative yield of the desired amine. Then acylation was carried out in the presence of triethylamine with the acid chloride derivative of ethyl diazoacetate afforded amide with 90% yield. The subsequent C−H insertion of amide using $Rh_2(CF_3CONH_2)_4$ as catalyst provided desired oxindole product. The protection of oxindole was performed with TIPSOTf which yielded 3-ester substituted and both *O*- and *N*-protected prochiral oxindole in 79-86% yield. With the desired substrate in hand, next step was to perform Pd-AAA reaction to introduce allyl

group on C-3 position of the oxindole. After thorough optimization studies, 1 mol% $[Pd(C_2H_5Cl)]_2$ with 3% chiral DACH pheny Trost ligand, **L2** in the presence of 15% TBAT as an additive was found to be the best which provided as much as 84% *ee* and 96% yield of the desired 3,3′-disubstituted oxindole product. Then, oxidative cleavage of the allyl group was performed by catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) followed by cleavage of the diol by lead tetraacetate in dichloromethane yielded the aldehyde in 97% yield. The subsequent reductive amination of this aldehyde ensued the β-lactam product in 65% yield. Then deprotection of the benzyl group from oxindol nitrogen was performed with 60% yield by refluxing with DDQ. Once deprotected β-lactam was formed, only step remained was chemoselective reduction which proved to be a difficult challenge. A suitable reducing agent was needed which would have the ability to successfully differentiate the two amides in lactam. After rigorous optimization studies, it was found that the addition of enough amount of tritylllithium just to completely deprotonate the secondary amide followed by the addition of 2 hydride equivalent of the LAH solution at 0 ˚C provided the best result in terms of yield (45%) of (+)-horsfiline **22**. This catalytic enantioselective total synthesis of horsfiline required eight steps and the overall yield was 11.1%.



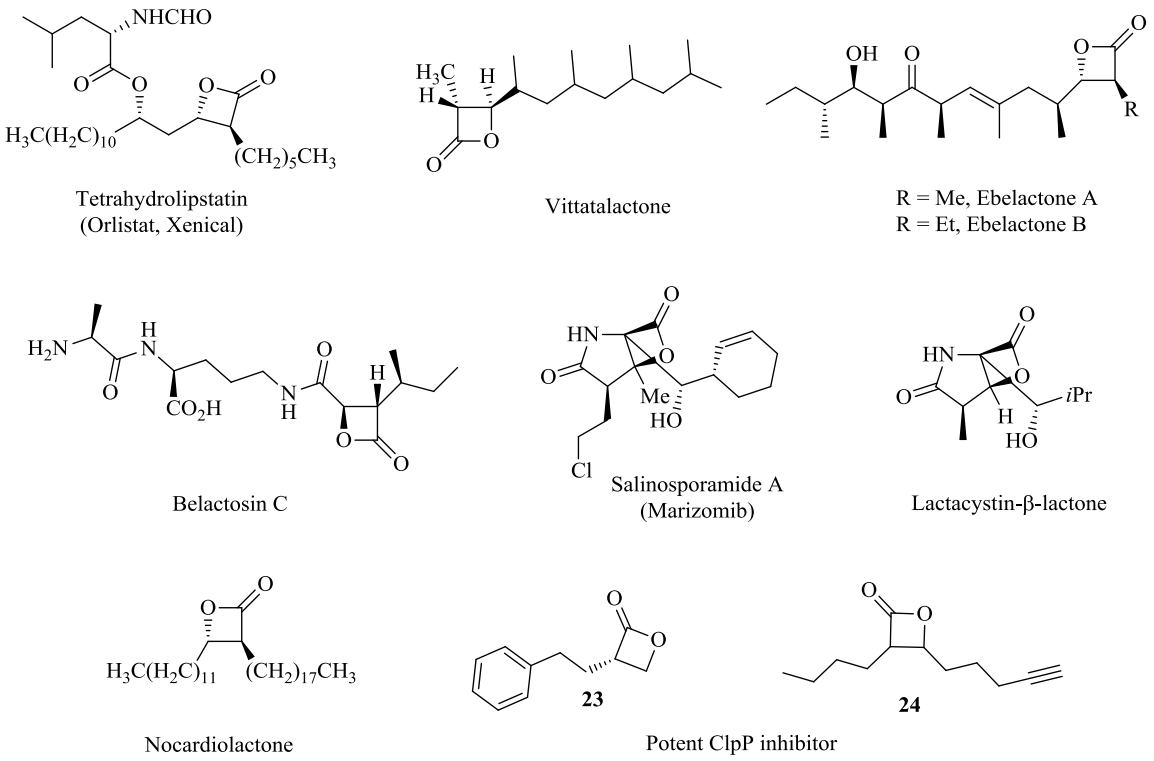

**Scheme 85.** Catalytic enantioselective synthesis of horsfiline **22**.

## 3.2. α-disubstituted β-lactone frameworks in medicinal chemistry

β-lactones have shown great potential as an important synthetic target due to their frequent presence in variety of bioactive natural products (Figure 20),[144] their all-around usefulness as synthetic intermediate to more complex structure,[145] and their utility as monomer in the synthesis of biodegradable polymers.[146] Tetrahydrolypstatin inhibits pancreatic lipase enzyme. It is a water-soluble enzyme secreted by the pancreas. One of the primary tasks of pancreatic lipase is to break down lipids and dietary fats *via* hydrolysis by breaking hydrogen bonds. This is critical since lipids and fats cannot be absorbed through the intestinal lining without undergoing hydrolysis first.

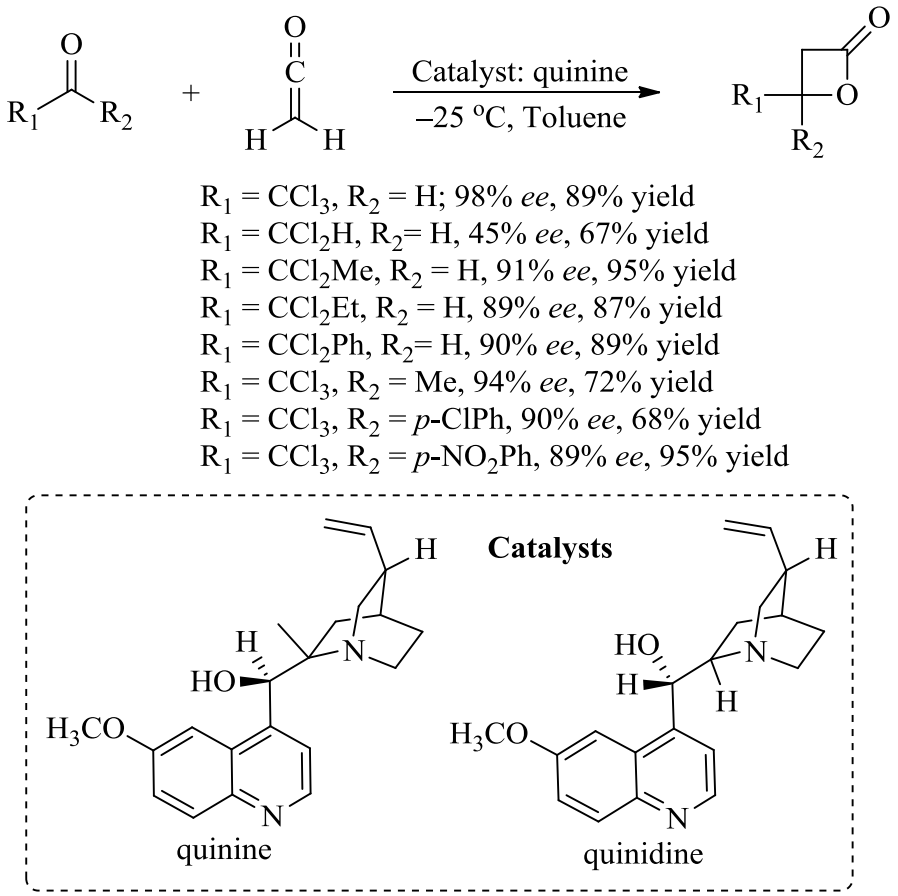
Tetrahydrolypstatin is an FDA approved drug for treating obesity, a new global health problem. Vittatalactone is a pheromone released by striped cucumber beetle. It is a serious pest of curcurbit crops in North America. These beetles aggregate in numbers and feed on young crops during springs, causing serious damage. A field study suggested that these beetles generate a hormone that contains vittatalactone to direct them to aggregate in great numbers. Ebelactones and belactosin C are human fatty acid synthase (FAS) inhibitor. FAS is attracting huge attention in carcer drug reseach due to the fact that it is up-regulated in most solid tumors, including breast,[147] prostate,[148] and ovary.[149] Moreover, studies indicated the pharmacologic blockade of this enzyme can be cytostatic and cytotoxic to cancer cells.[150] Marizomib is a phase one clinical candidate for cancer. Lactacystin-β-lactone which is an analog of marizomib showed great potential as well. Compound **23** and **24** inhibit caseinolytic protein protease (ClpP) enzyme. ClpP, a phylogenetically highly conserved serine protease, was found to be instrumental in producing virulence by many bacterial pathogens. Recent study showed the inhibition of this enzyme by **23** and **24** in *Staphylococcus aureus* significantly attenuated their capability to produce virulence factors such as life threating toxins.[151]

**Figure 20.** Representative natural products and bioactive compounds containg β-lactone moiety.




3.2.1. Recent advances in the asymmetric synthesis of β-lactones

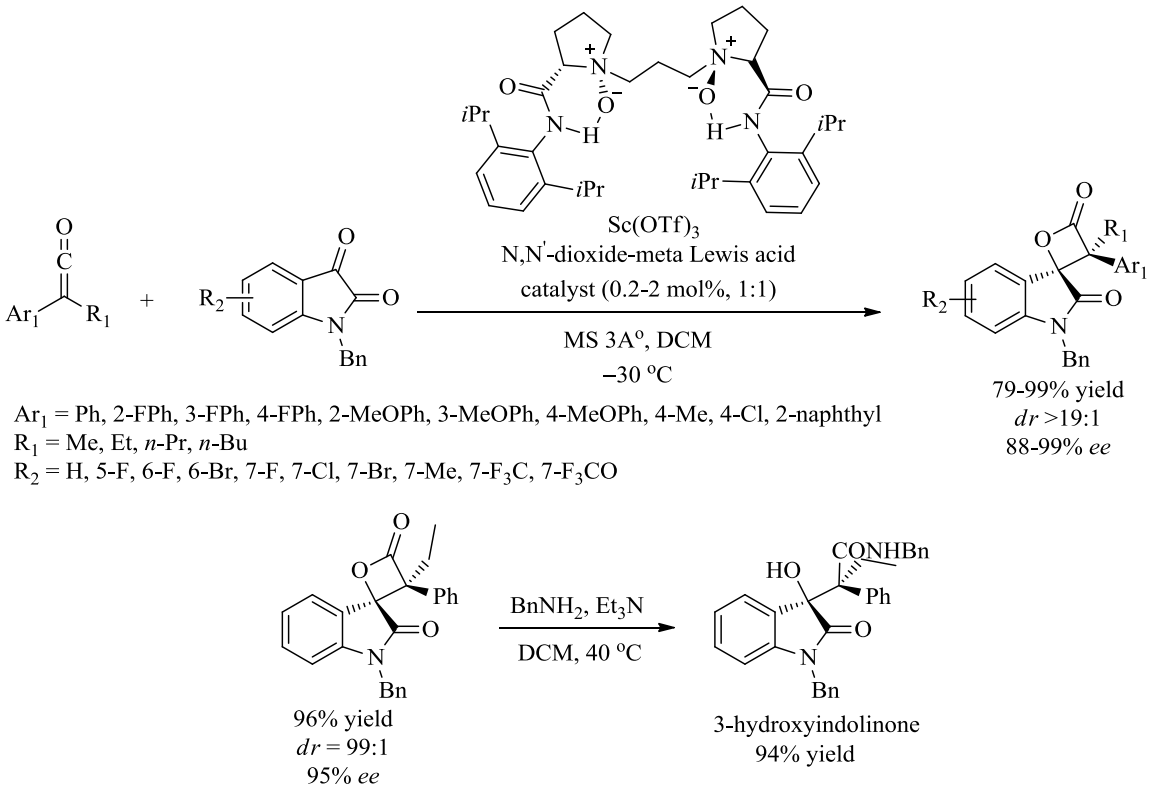
The first enantioselective synthesis of β-lactones was reported by Wynberg and co-workers[152] in 1985. Quinine and quinidine has been studied as chiral inducing catalyst. Quinidine provided better *ee* compared to quinine. In the reaction, chlorinated aldehydes and ketones are employed in the presence of quinidine as catalyst which yielded chiral β-lactones with as much as 98% *ee* (Scheme 86).




**Scheme 86.** First example of the synthesis of asymmetric β-lactone.

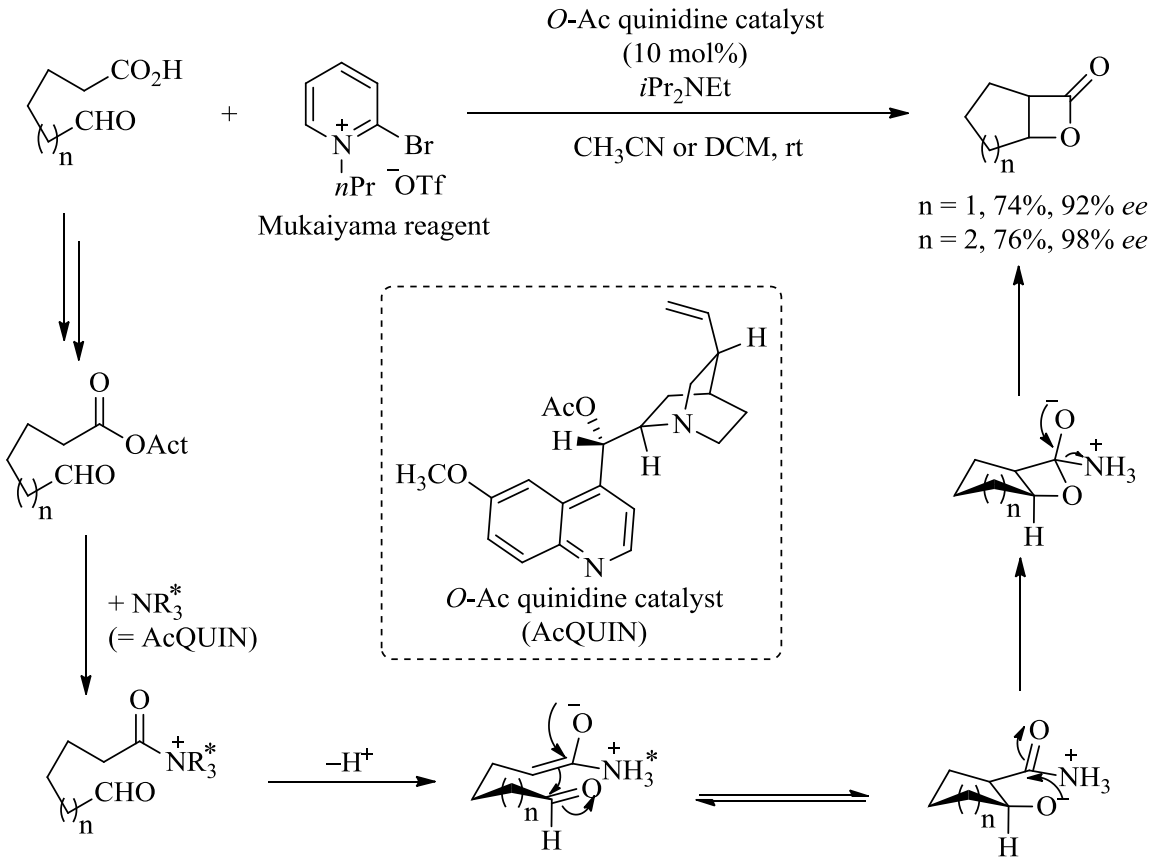
Since then, a large number of researches have been published to synthesize β-lactones asymmetrically employing ketene as starting material along with aldehydes for [2+2] cycloaddition reaction.[153] Various kinds of catalysts has been used, among which chiral Lewis acids,[154] Lewis acids in combination with nucleophilic catalysis,[155] and chiral Lewis bases, such as, cinchona alkaloids,[156] planar chiral ferrocenylamine catalysts,[157] chiral N-heterocyclic carbines,[158] and chiral phosphines[159] are notable.

Recently in 2014, Feng and co-workers[160] reported the highly diastereo- and enantioselective [2+2] cycloadditions of disubstituted ketenes employing modular chiral Lewis acid *N,N′*-dioxide-metal complex as catalyst (Scheme 87). A series of arylalkylketenes reacted with isatins yielding optically active β-lactones with vicinal chiral centers in excellent yields (up to 99%) and enantioselectivities (up to 99%). To demonstrate the synthetic values of the reactions, one of the β-lactones has been transformed to highly substituted 3-hydroxyindolinone containing two quaternary centers through ring-opening by introducing benzylamine.




**Scheme 87.** Asymmetric synthesis of β-lactones by chiral Lewis acid catalyst.

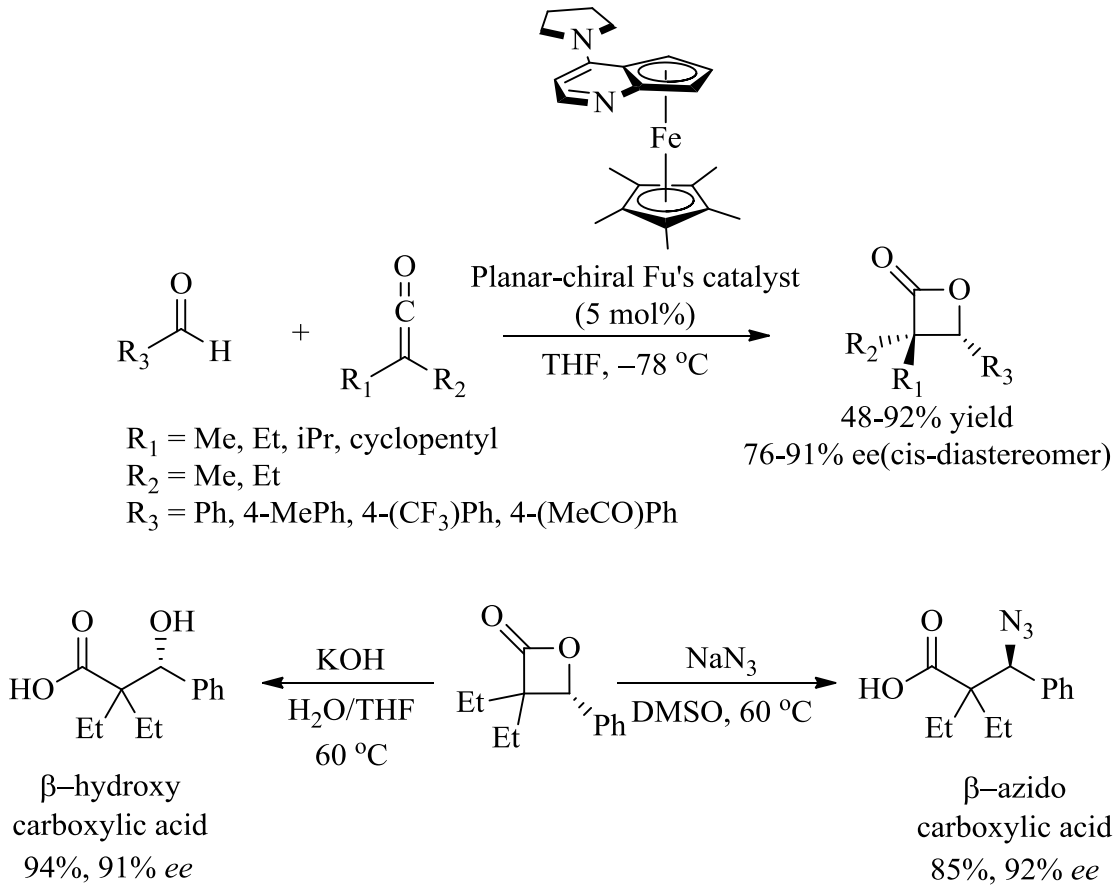
Nucleophilic quinidine catalyst has employed along with innovative use of Mukaiyama reagent by Romo and co-workers[161] in the following nucleophile-catalyzed aldol lactonization (NCAL) reaction to synthesize enantioselective bicylic-β-lactones (Scheme 88). Mukaiyama reagent is widely used for the activation of carboxylic acids to provide esters, amides, or lactones.[162] The introduction of this reagent in the reaction led to increased conversion and efficiency (70-82% yield) with shorter reaction time. The reaction provided desired products with excellent enantioselectivity (91-98%). The proposed mechanism of this process consists the activation of carboxylic acids, acylammonium formation, ammonium enolate generation by deprotonation, intramolecular aldol reaction, rate-determining oxetane formation, and finally, regeneration of the nucleophilic catalyst.




**Scheme 88.** Asymmetric synthesis of bicyclic β-lactones via intramolecular, nucleophile-catalyzed aldol lactonization.

Remarkably, planar chiral DMAP and PPY derivative has also been employed as nucleophilic catalyst by Fu and co-workers[157] for the asymmetric synthesis of highly substituted β-lactones (Scheme 89). It was the first example of the [2+2] cycloaddition of disubstituted ketenes. The reaction didn't yield to β-lactones at high temperature. Interestingly, however, at low temperature it provided the desired product with high yield and *ee*. It has been found that this planar-chiral catalyst prefers *cis*-diastereomer of the β-lactones (ca. 4.5:1 selectivity) with very good enantioselectivity (up to 91%). In order to

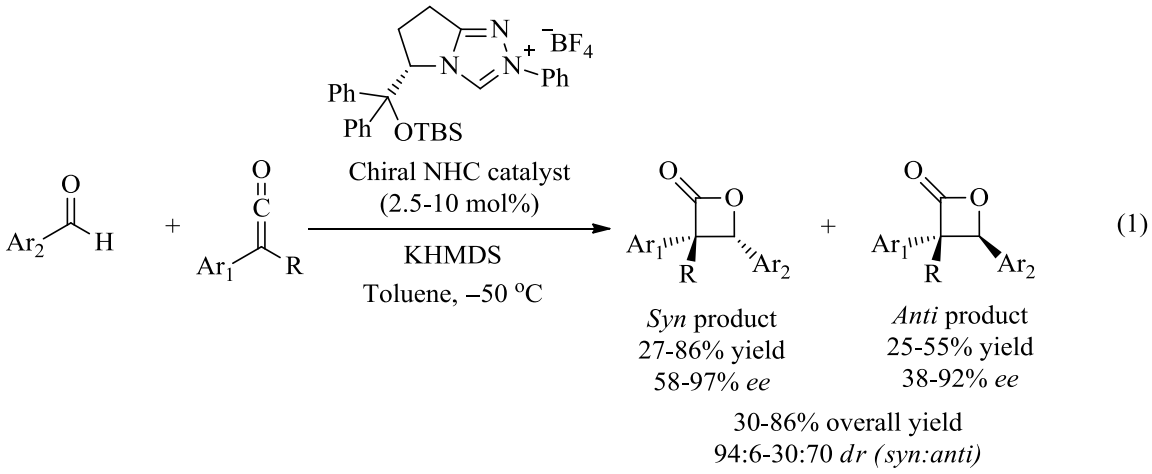
show the synthetic ability of the methodology, they went on to synthesize β-hydroxy carboxylic acid and β-azido carboxylic acid with high yield and *ee*.



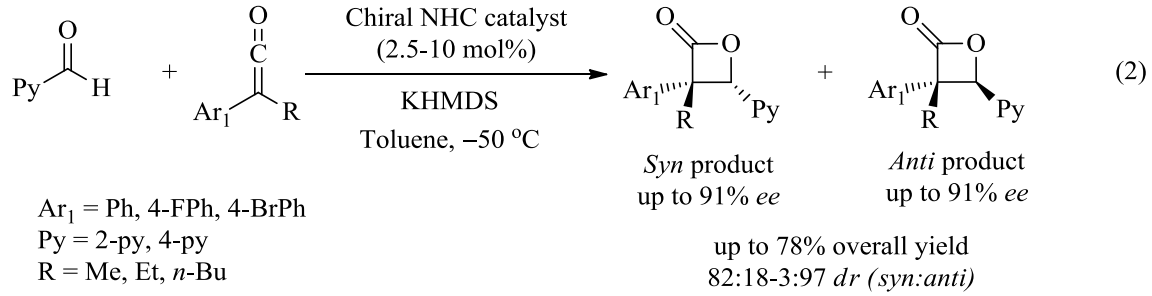

**Scheme 89.** Asymmetric synthesis of highly substituted β-lactones by Greg Fu's catalyst.

Recently, Smith and co-workers[158d] published NHC-catalyzed asymmetric β-lactone formation from arylalkylketenes and electron-deficient substituted benzaldehydes as well as pyridinecarboxaldehydes (Scheme 90). The reaction provided highly substituted β-lactones with vicinal tertiary or quaternary stereocenters. In respect to benzaldehydes, 2-nitrobenzaldehyde provided best result in terms of diastereo- and enantioselectivity (up to

93:7 *dr* and 93% *ee*) (Scheme 90, eq. 1). Substituted 2- and 4-pyridinecarboxaldehydes were tested as well in this methodology instead of benzaldehydes, yielded the desired β-lactones in good yield and *ee* (Scheme 90, eq. 2). However, it has been found that the diastereocontrol is highly dependent on the aldehyde substituent when employing pyridinecarboxaldehydes.



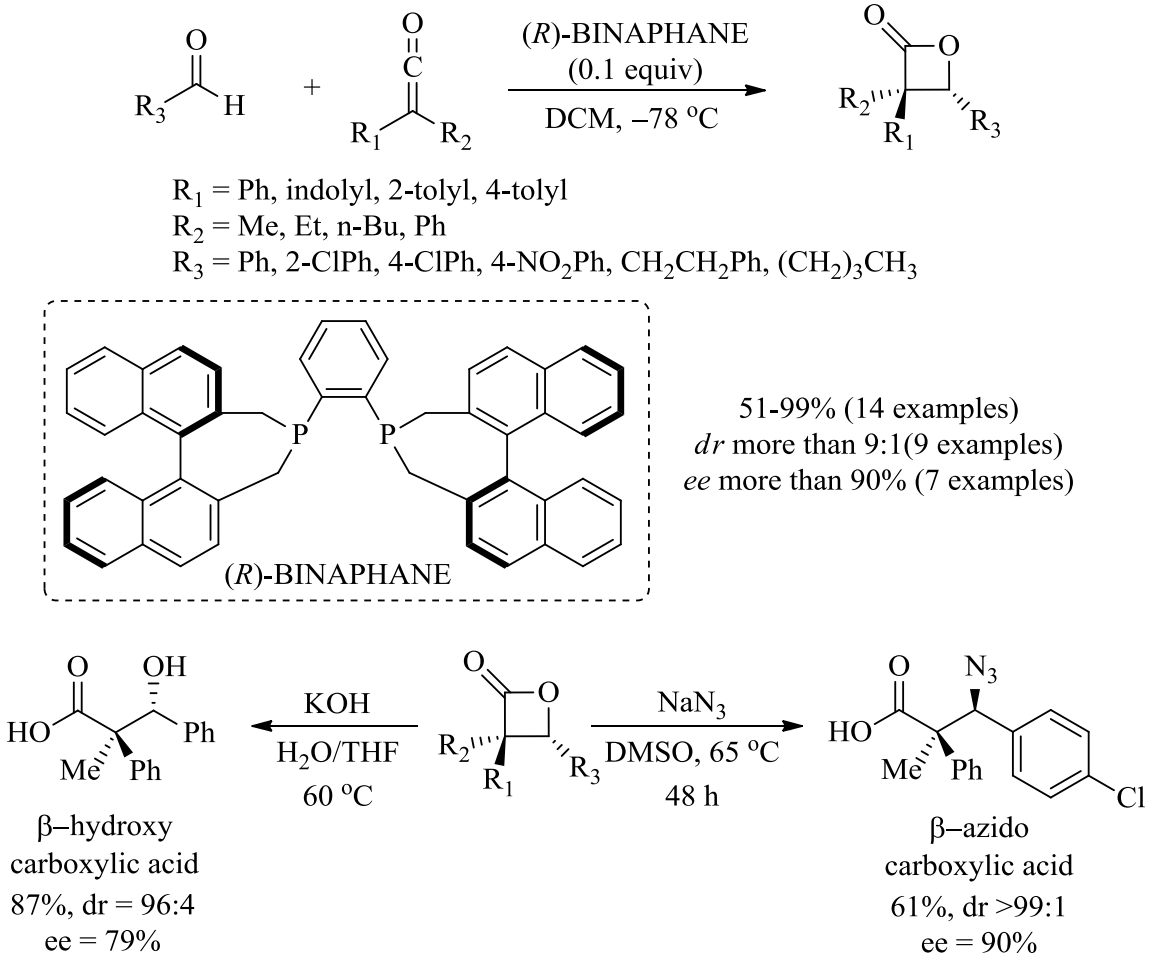

$Ar_1$ = Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-MePh, 4-MeOPh, 2-$(CH_3)$Ph, 2-thienyl, 1-Naphthyl
$Ar_2$ = Ph, 4-$(CF_3)$Ph, 4-$(NO_2)$Ph, 2-$(NO_2)$Ph, 2-FPh, 2-ClPh, 2-BrPh
R = Me, Et, *i*-Pr, *n*-Bu, *i*-Bu.




$Ar_1$ = Ph, 4-FPh, 4-BrPh
Py = 2-py, 4-py
R = Me, Et, *n*-Bu

**Scheme 90.** NHC-promoted asymmetric β-lactone formation from arylalkylketenes and substituted benzaldehydes or pyridinecarboxaldehydes.

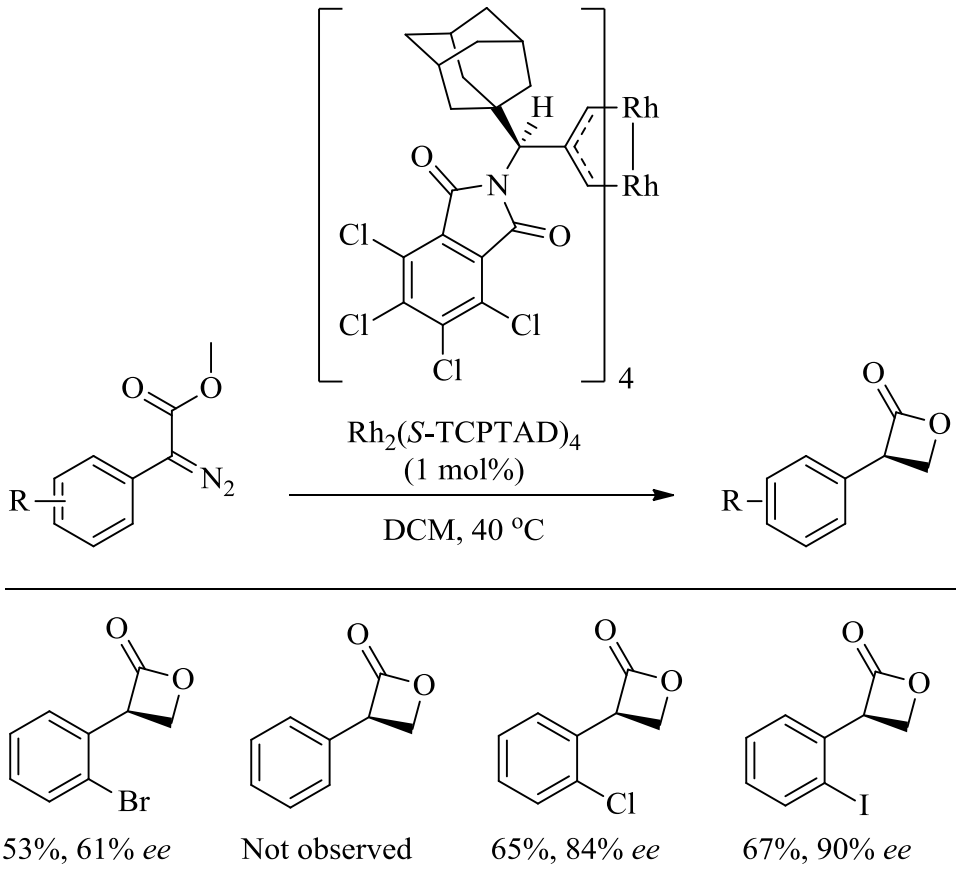
In 2010, Kerrigan and co-workers[159] reported the use of chiral phosphine as catalyst to synthesize asymmetric all-carbon quaternary β-lactones employing arylketoketenes and aromatic aldehydes as starting material (Scheme 91). This [2+2] cycloaddition reaction provided the desired highly substituted β-lactones with high enantio- (seven examples with *ee* ≥ 90%) and diastereoselectivity (nine examples with *dr* ≥ 9:1). (R)-BINAPHANE has been employed as catalyst. This time, they showed the ability of this cycloaddition reaction with less reactive aromatic aldehydes which were not tolerated as substrates by earlier NHC catalyst system. They went on to show the synthetic utility of this reaction by converting the highly substituted β-lactones to synthons such as β-hydroxy carboxylic acids and β-azido carboxylic acids.



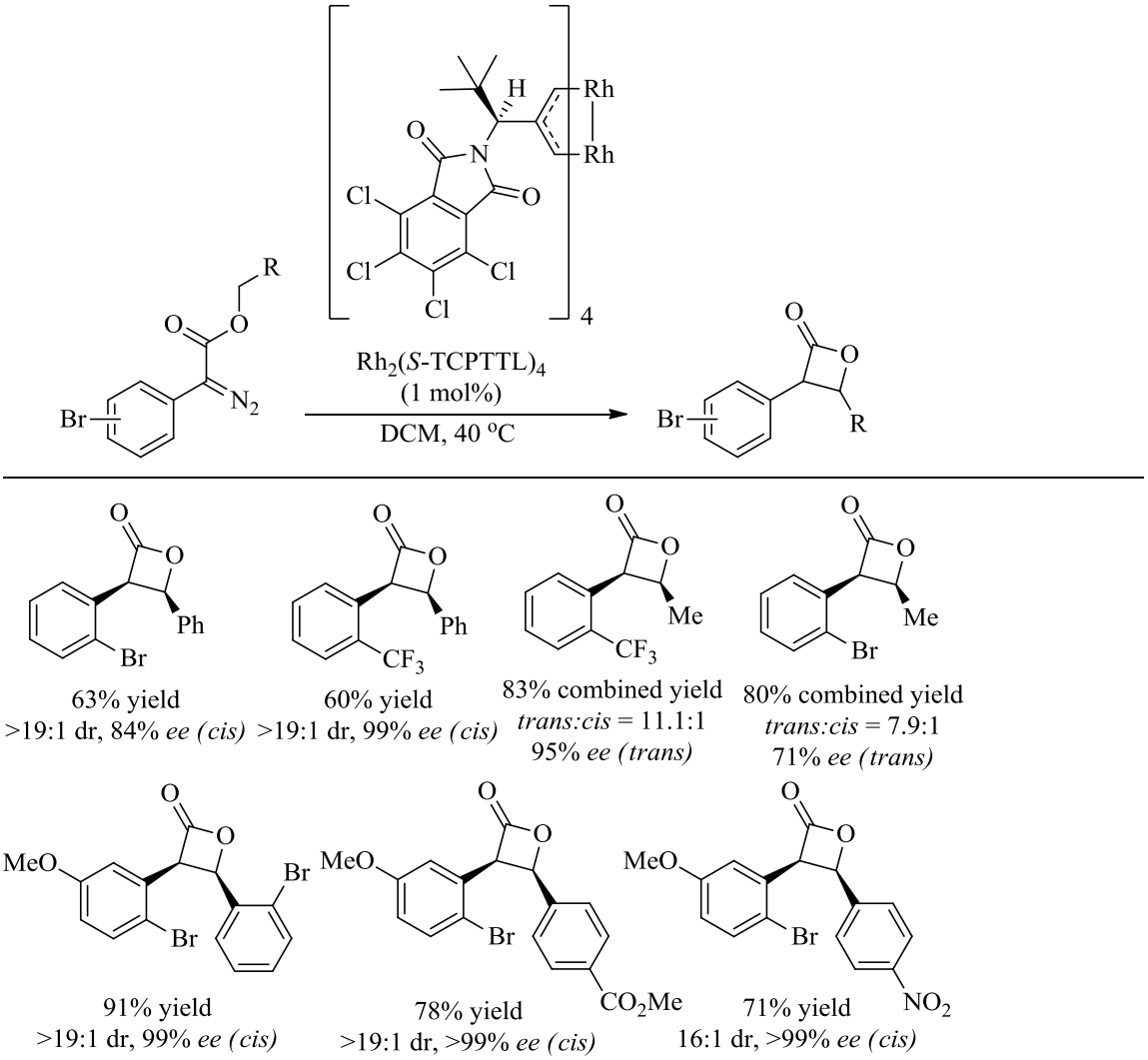

**Scheme 91.** Phosphene-catalyzed asymmetric synthesis of β-lactones from arylketoketenes and aromatic aldehydes.

Transition-metals have also been employed as a catalyst for the asymmetric synthesis of β-lactones.[163] As an example, Davies and co-workers[164] recently synthesized β-lactones in high yield and with high levels of diastereo- and enantioselectivity using rhodium as catalyst (Scheme 92, 93, and 94). This reaction goes through intramolecular C-H insertion of aryldiazoacetate. Ortho substitution on the aryl group of aryldiazoacetate was found to play a crucial role on this C-H insertion reaction. The reaction was not even

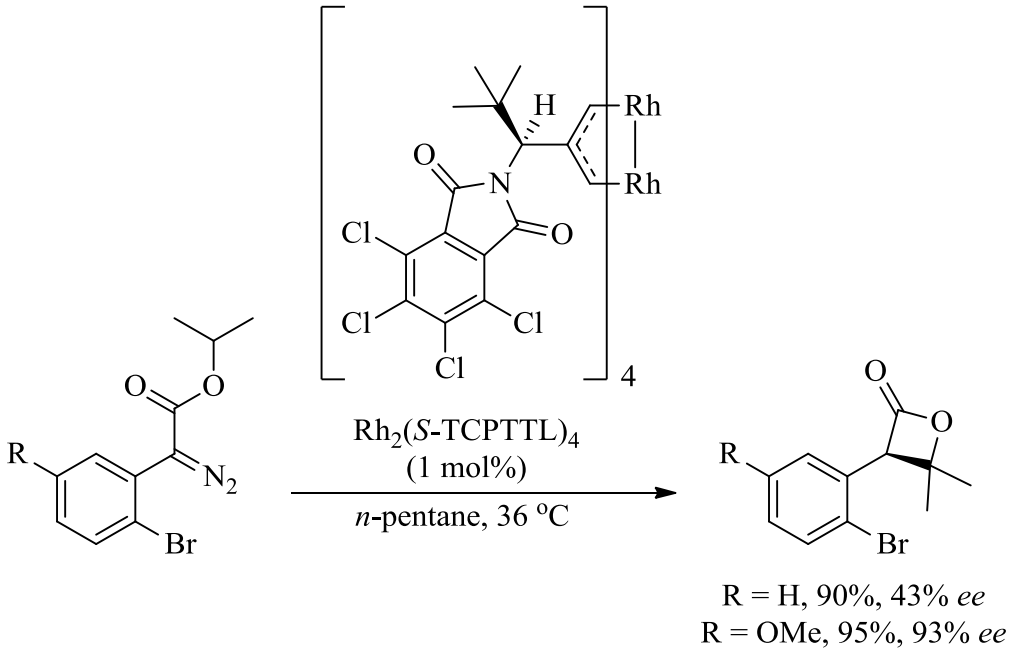
observed when unsubstituted phenyldiazoacetate was employed. Unexpectedly, the reaction provided desired β-lactones with the activation of methylene C-H bonds (Scheme 93) as well as relatively unreactive methyl (Scheme 92) and methine (Scheme 94) C-H bonds on ester groups.




**Scheme 92.** Methyl C-H insertion for the formation of β-lactones by rhodium catalyst.




**Scheme 93.** Methylene C-H insertion for the formation of β-lactones by rhodium catalyst.



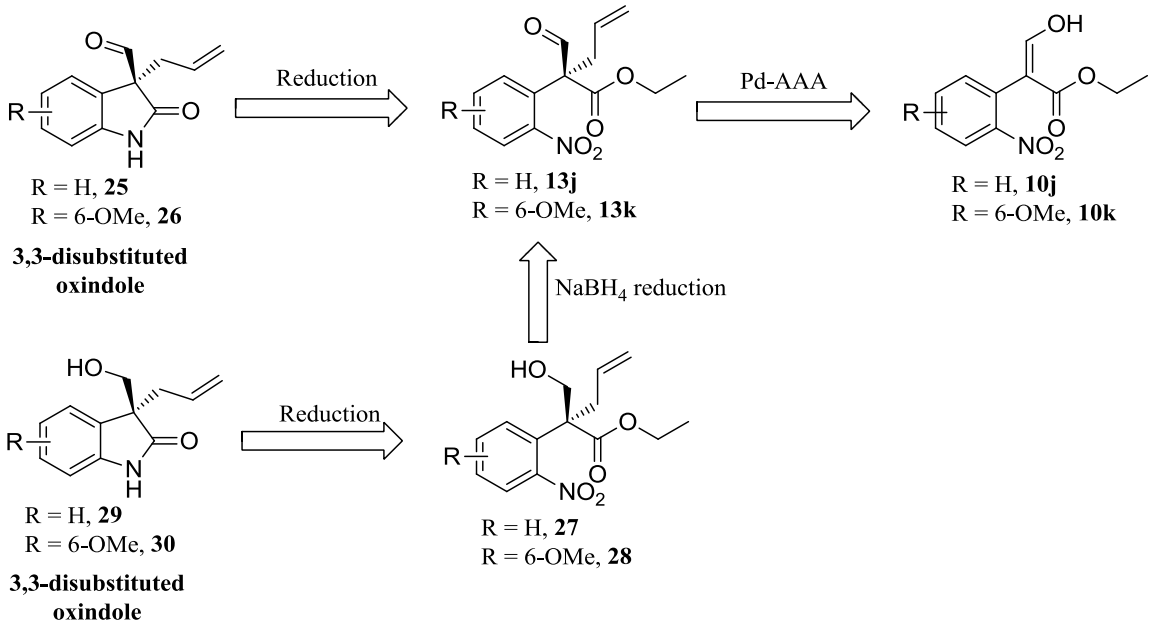

**Scheme 94.** Methine C-H insertion for the formation of β-lactones by rhodium catalyst.

## 3.3. Results and discussions

### 3.3.1. Asymmetric synthesis of 3,3′-disubstituted oxindole from 3-hydroxy-2-nitro aryl acrylates

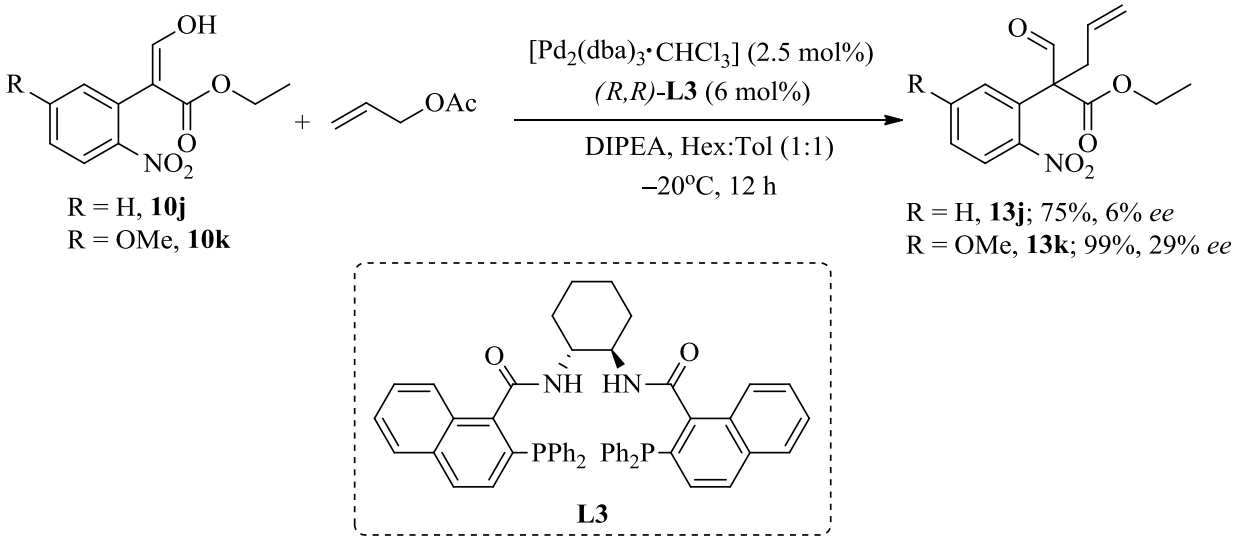
Now that we have got our developed methodology in hand, we wanted to show the utility of this Pd-AAA reaction by synthesizing 3,3′-disubstituted oxindole framework, one of the most previledged and classical building blocks present in a large family of bioactive natural products and pharmaceutical agents.

As shown in the retrosynthetic analysis (Scheme 95), 3,3′-disubstituted oxindole **25** and **26** can be obtained by selective reduction of nitro group of all-carbon quaternary stereocenters **13j** and **13k**, which, in turns, are easy accessible from our Pd-AAA methodology employing 3-hydroxy-2-nitro aryl acrylates **10j** and **10k** as starting material. However, literature search suggested that compound **25** and **26** might not be easy to isolate since aldehydes on the C-3 position of oxindoles have a tendency to defomylate.[132] If that is the case, we can also make the desired oxindole **29** and **30** by first reducing the aldehyde on **13j** and **13k** by $NaBH_4$ reduction followed by reduction of nitro group which should close the ring.




**Scheme 95.** Retrosynthetic analysis of 3,3′-disubstituted oxindole using our newly developed Pd-AAA methodology.

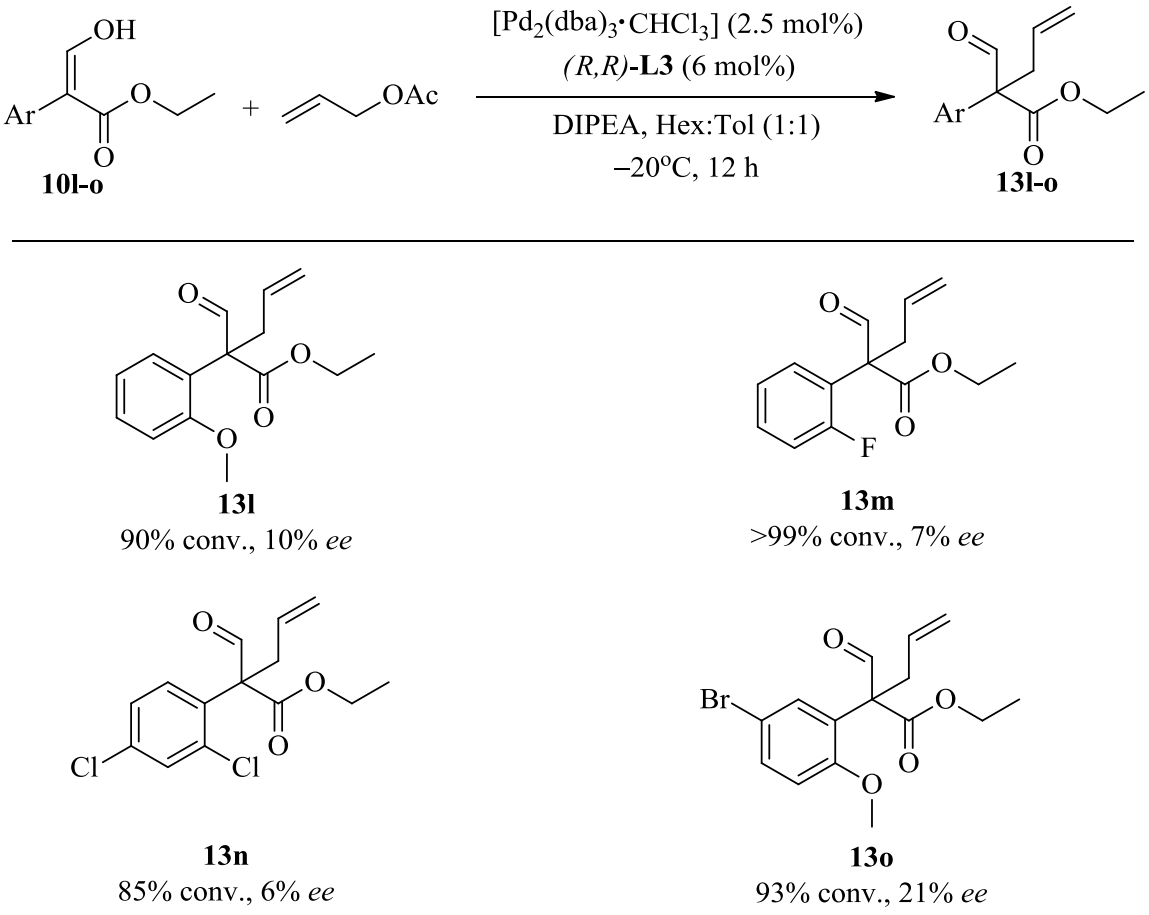
First, we wanted to subject 3-hydroxy-2-nitro-phenyl acrylate **10j** to our developed Pd-AAA methodology which should give us desired all-carbon α-aryl quaternary stereocents **13j**. We expected high yield and *ee*, however, only found out very poor stereoselectivity (6%). The yield was low as well. We also used 5-methoxy-2-nitro analog **10k** with a hope that it might give better *ee* and wanted to carry on with our planned total synthesis. However, it too provided the desired product **13k** with only slightly better enantioselectivity (29%), which was unsatisfactory (Scheme 96).




**Scheme 96.** Pd-AAA of **10j** and **10k** using previously optimized conditions.

Disappointed by the results, we wanted to find out whether the low enantioselectivity is due to the electronic or steric effect (Scheme 97). To find out if it's electronic, we applied the same conditions to methoxy-substituted analog **10l** at the same C-2 position on benzene ring, since its electron donating whereas nitro is electron withdrawing. It provided **13l** with similar *ee* (10%). So, we concluded that it's not electronic. In order to

prove the steric effect behind this unexpected result, we hypothesized that 2-fluoro analog **10m** would be the best candidate since fluorine is almost similar in size compared to hydrogen atom and it should provide similar enantiodiscriminative selectivity compared to **10a** (94%) if steric congestion is the reason. Thus we subjected **10m** to the optimized condition, only to find out it too ensued similar result (7% *ee*). Unsatisfied by these results, we subjected the same reaction conditions to different analogs, namely, 2,4-dichloro **10n**, and 5-bromo-2-methoxy **10o**. While **10n** provided similar disappointing results, **10o** yielded **13o** with slightly better *ee* (21%).



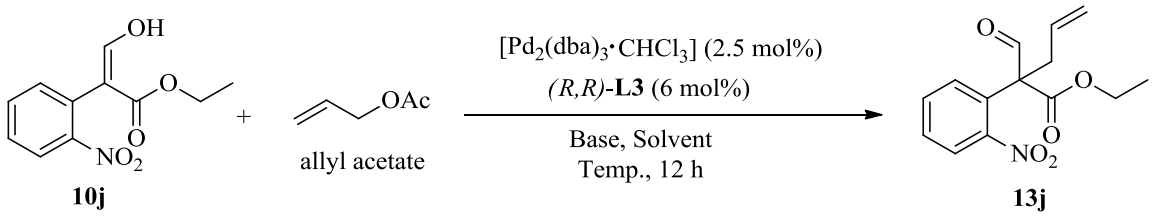

**Scheme 97.** Steric vs electronic effects in Pd-AAA of **10l-o**.

Even though the results were dissatisfactory, the slight increase in *ee* for **13k** and **13o** provided a clue that it might be only because of the optimized condition, which is not good enough for ortho-substituted analogs. We just have to optimize the reaction again and find out a different condition for this class of analogs.

First we decided to keep our previously optimized ligand fixed but vary solvent, temperature, and bases (Table 9). We have studied variable polarity solvents of both protic and aprotic classes, namely DCM, DME, ether, toluene, MeOH, EtOH, *i*PA, *t*BuOH, Acetonitrile, DMSO, DMF, Nitromethane, HMPA, and THF. Surprisingly we didn't observe any *O*-allylation with any of these solvents. Conversion is always good at room temperature (entry 1, 2, 7, 9, 16, 17, 18, 20, and 21) and even at low temperature in some cases (entry 12, 13, 14, 15, and 28) without employing bases. However, for some cases at low temperature, base was needed to increase the conversion (entry 4 vs 3 and 5; 22 vs 23-27). We didn't find a patterened correlation of enantioselectivity with the change in polarity of solvents. For example, toluene provided 38% *ee* at rt (entry 9) and increasing the polarity seemed like decreasing *ee* at the beginning as with DCM and ether provided ony 5 and 7 %*ee* respectively (entry 2 and 7). Polar protic solvents did not provide enough *ee* to study further (entry 12, 13, 14, and 15). However, polar aprotic solvent proved to be another better class of solvents besides non-polar toluene, as among acetonitrile, DMSO, DMF, nitromethane, HMPA and THF (entry 16-21), HMPA provided 31% (entry 20) and THF provided maxiumum 41% *ee* at rt (entry 21). On the other hand, temperature does have an effect on *ee* in some cases (entry 2 vs 3-5; 21 vs 23-28). We found best conditions (*ee* 57%) with THF at −10 ˚C (entry 27 and 28). It seems

like the reaction goes to completion without any base in THF at as low as −10 ˚C without affecting %conversion or %*ee* (entry 28) because no reaction was observed at −20 ˚C in THF without bases (entry 22).

**Table 9.** Optimization studies for the Pd-AAA of 3-hydroxy-2-nitro phenyl acrylate **10j**.

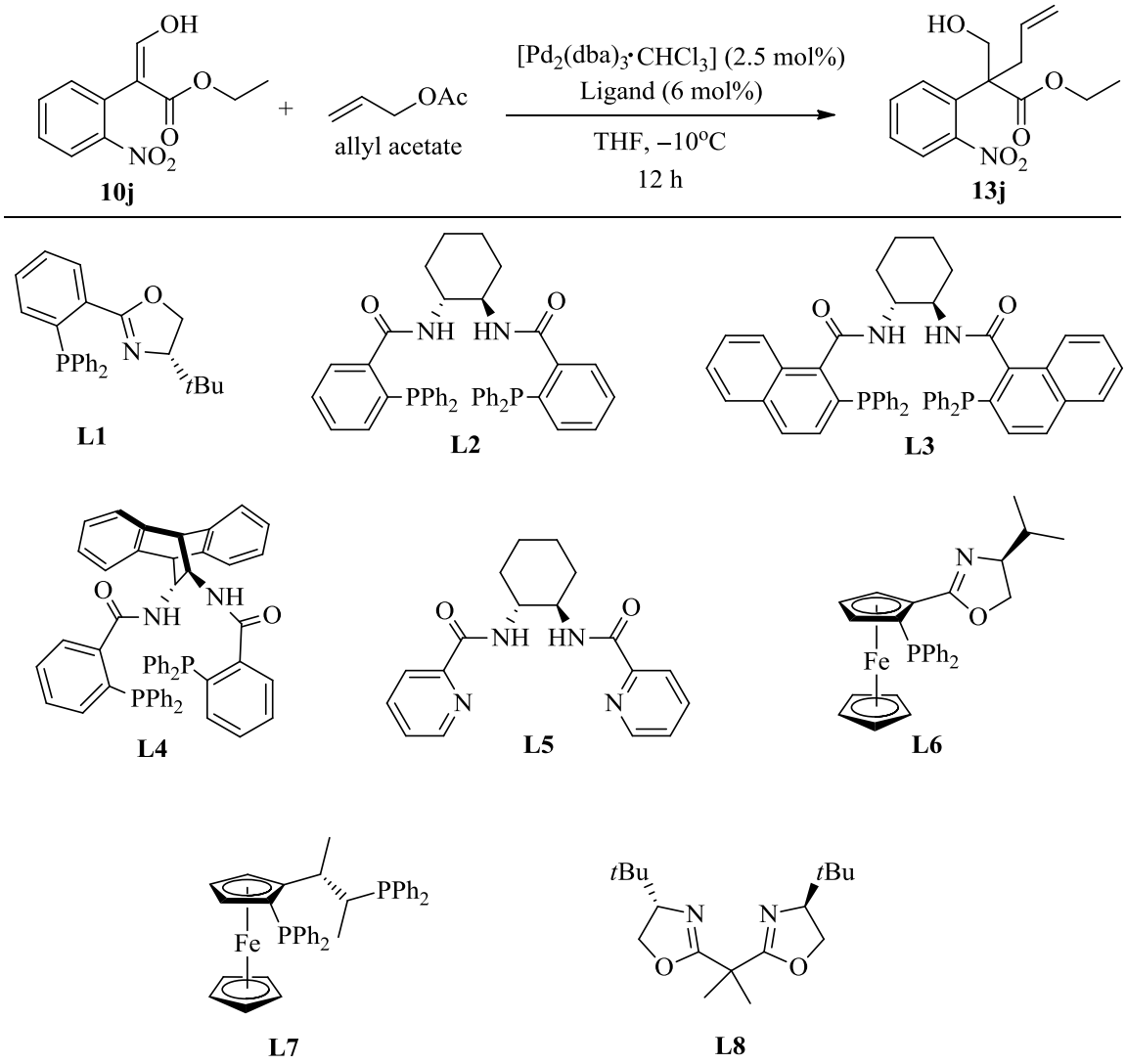



| Entry | Solvent | Base | Temp. [$^0$C] | Conv. [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1 | DCM | DIPEA | rt | 100 | 0 |
| 2 | DCM | - | rt | 100 | 5 |
| 3 | DCM | DIPEA | -20 | 100 | 10 |
| 4 | DCM | - | -20 | 30 | 14 |
| 5 | DCM | CsF | -20 | 100 | 20 |
| 6 | DME | - | -20 | 55 | 20 |
| 7 | Ether | - | rt | 100 | 7 |
| 8 | Toluene | CsF | -20 | 75 | 35 |
| 9 | Toluene | CsF | rt | 100 | 38 |
| 10 | Toluene | DIPEA | -20 | 70 | 34 |
| 11 | Toluene | DIPEA | -10 | 81 | 36 |
| 12 | MeOH | - | -10 | 100 | 10 |
| 13 | EtOH | - | -10 | 100 | 0 |
| 14 | *i*PA | - | -10 | 100 | 24 |
| 15 | *t*BuOH[a] | - | -10 | 100 | 42 |
| 16 | Acetonitrile | - | rt | 85 | 20 |
| 17 | DMSO | - | rt | 100 | 9 |

| | | | | | |
|---|---|---|---|---|---|
| 18 | DMF | - | rt | 82 | 20 |
| 19 | Nitromethane | - | rt | 100 | 12 |
| 20 | HMPA | - | rt | 100 | 31 |
| 21 | THF | - | rt | 100 | 41 |
| 22 | THF | - | -20 | No Rxn. | - |
| 23 | THF | DIPEA | -20 | 100 | 53 |
| 24 | THF | CsF | -20 | 100 | 55 |
| 25 | THF | Quinine | -20 | 100 | 50 |
| 26 | THF | KOtBu | -20 | 100 | 45 |
| 27 | THF | CsF | -10 | 100 | 57 |
| 28 | THF | - | -10 | 100 | 57 |

[a]Reaction run at room temperature.

Next, we kept the solvent and temperature constant to THF and −10 ˚C that provided maximum 57% *ee* (Table 9, entry 24) and studied ligands. This time, we have employed four new ligands (L5-L8) along with four others (L1-L5) which have been used previously (Scheme 98, Table 10). Unfortunately, none of these ligands proved better than **L3** in terms of enantioselectivity. **L2** provided 46% *ee* (entry 2), which was the closest one compared to **L3**. **L4** also provided a decent *ee* (38%), however, with poor conversion (35%) to the desired product **13j** along with undesired *O*-allylated product (entry 3). Interestingly, **L5**, another Trost ligand that contains pydine ring instead of pheyl or naphthyl ring, did not give any reaction at all (entry 4). Two different ferrocenyl ligands **L6** and **L7** have also been employed, which ensued racemic product with very poor yield (entry 5 and 6). One BOX ligand **L8** has been tried as well without much success (entry 7).



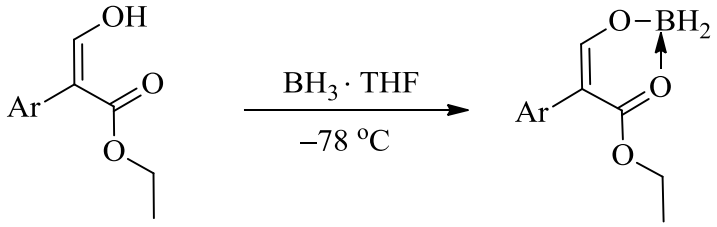

**Scheme 98.** Optimization of ligands for Pd-AAA of **10j**.

**Table 10.** Optimization of ligands for Pd-AAA of **10j**.

| Entry | Ligand | Conv. [%] | ee [%] |
|---|---|---|---|
| 1 | L1 | 80[a] | 34 |
| 2 | L2 | 100 | 46 |
| 3 | L4 | 35[a] | 38 |
| 4 | L5 | - | - |
| 5 | L6 | 29[a] | 0 |
| 6 | L7 | 45[a] | 0 |
| 7 | L8 | 100 | 10 |

[a]Rest are *O*-allylated product.

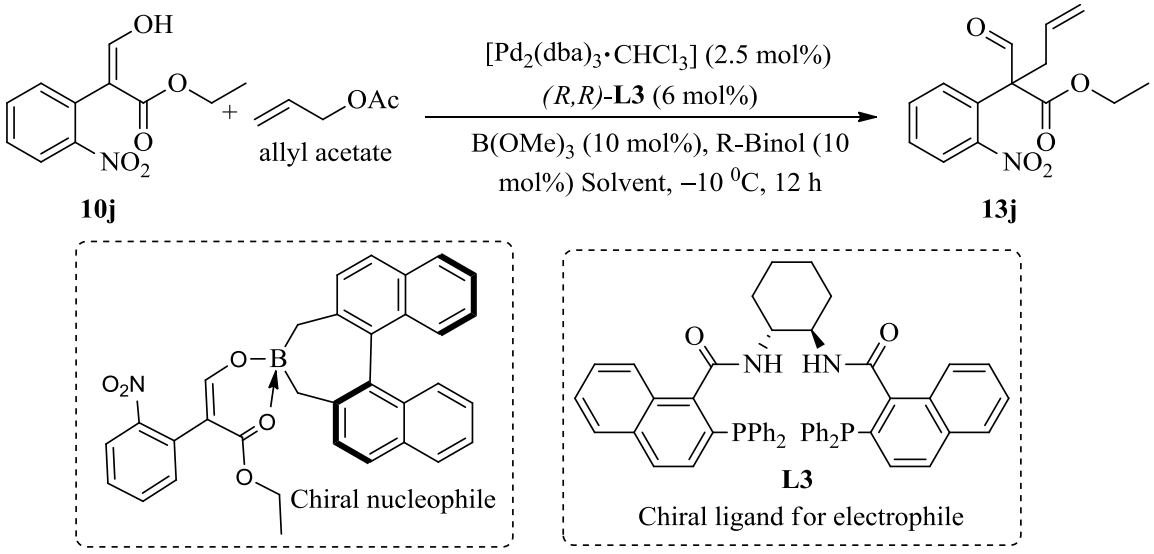
In 2008, our group[165] published an interesting work that showed a novel RO-$BH_2$ intermediate with 3-hydroxy aryl acrylates **10** and $BH_3$ at −78 ˚C by the innovative use of $^1H\{^{11}B\}$ and $^1H\{^{13}C, ^{11}B\}$ NMR spectroscopy (Scheme 99).




**Scheme 99.** Locking the *Z* isomer of **10** by $BH_3$.

Thus, we envisioned that the introduction of $BH_3$ or even chiral borane (Scheme 100) can overcome the problem associtated with the interconversion of *E* and *Z* stereoisomers of **10** and thereby locking one isomer over other which might be beneficial. So, we were

hopeful that the combined effect of chiral borane on one hand, which could lock the nucleophile **10** by bonding with carbony- and enolate-oxygen atoms as well as block one side of the enolate double bond by chiral ligand for boron (Scheme 100, Table 11) and on the other hand, chiral ligand for palladium to creat chiral environment around electrophile might be helpful in our cause. Chiral BINOL has been used as a chiral inducing agent for nucleophile. Both THF and toluene were tested as solvents (entry 1, 2, and 3). None was proved better than using **L3** alone (57% *ee*). Without using chiral ligand **L3**, racemic product was ensued, which proved that the chiral borane was probably not binding at all (entry 1).




**Scheme 100.** Pd-AAA reactions employing both chiral electrophile and chiral nucleophile.

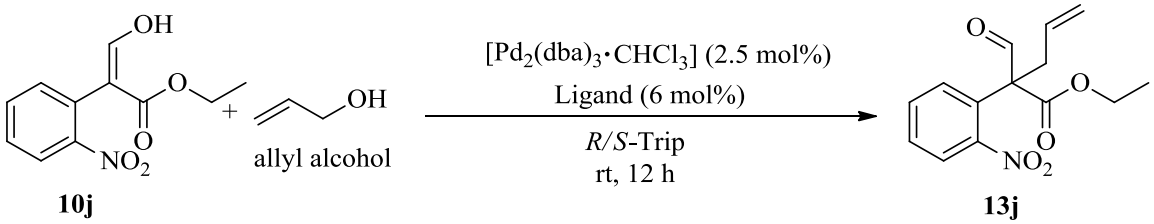
**Table 11.** Pd-AAA reactions employing both chiral electrophile and chiral nucleophile.

| Entry | Solvent | Conv. [%] | *ee* [%] |
|---|---|---|---|
| 1[a] | THF | 100 | 0 |
| 2 | THF | 100 | 56 |
| 3 | Tol | 100 | 45 |

[a]Without **L3**.

We also employed chiral phosphoric acid as an additional chiral inducing agent along with/without chiral ligand **L3** and **L8** for palladium due to the reason explained earlier (see Section 2.3, Scheme 30 and 31). Allyl alcohol was used as electrophile instead of ally acetate. We used chiral phosphoric acid of both (*R*)- or (*S*)-Trip (Table 12). This time too, without any ligand, the reaction yielded racemic product (entry 1 and 2). Surprisingly, the reaction did not occur with the use of **L8** along with (*R*)-Trip (entry 4). **L3** provided 40% *ee* which is little lower than earlier (57%), probably due to the temperature (rt) of the reaction which is higher that earlier temperature (entry 3).

**Table 12.** Pd-AAA employing chiral phosphoric acid along with chiral ligand.

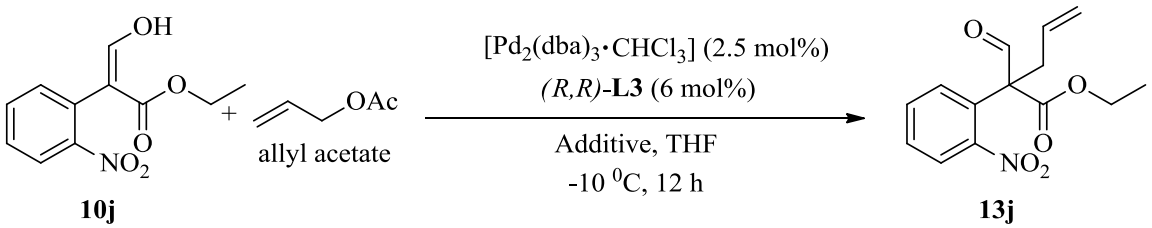



**10j** **13j**

| Entry | Ligand | Solvent | TRIP *(R/S)* | Conv. [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1 | - | THF | *R* | >99 | Racemic |
| 2 | - | THF | *S* | >99 | Racemic |
| 3 | **L3** | THF | *R* | >99 | 40 |
| 4 | **L8** | THF | *R* | 0 | - |

Since none of these investigantions provided enantioselectivity satisfactory to us, we then kept **L3** fixed and went on to study the effect of various additives in the reactions (Table 13). The use of exogenous additives is a fairly common practice in asymmetric synthesis.

**Table 13.** Optimization of additives for Pd-AAA of **10j**.




**10j** **13j**

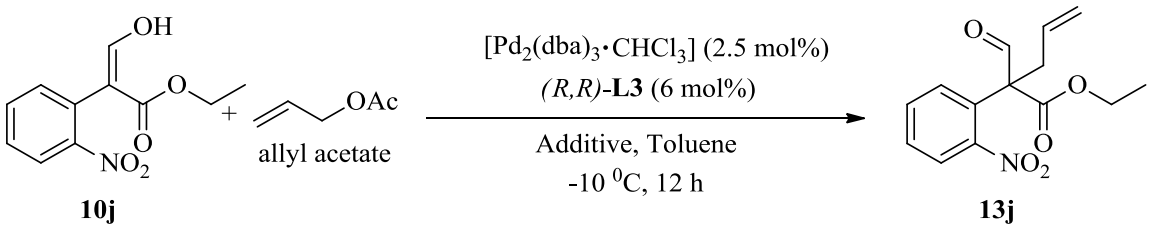
| Entry | Additive[a] | Conv. [%] | *ee* [%] |
|---|---|---|---|
| 1 | HMPA | 100 | 50 |
| 2 | $n$Bu$_4$NI[a,b] | 100 | 0 |
| 3 | $n$Bu$_4$NF[a,b] | 100 | 44 |
| 4 | 1,3-Diphenylguanidine[a] | 100 | 48 |
| 5 | Ph$_3$SiCl[a] | - | - |
| 6 | KCl[a] | 100 | 44 |
| 7 | B(OMe)$_3$[a] | 100 | 35 |
| 8 | BSA[a,b] | 100 | 60 |
| 9 | R-Trip[c] | 100 | 40 |
| 10 | *R*-Binol[c] | 100 | 30 |
| 11 | MeOH[d] | 100 | 66 |
| 12 | EtOH[d] | 100 | 40 |
| 13 | *i*PA[d] | 100 | 67 |
| 14 | *t*BuOH[d] | 100 | 82 |
| 15 | H$_2$O[d] | 100 | 23 |
| 16 | NaHSO$_3$[d] | 100 | 77 |
| 17 | 1,10-Diaza-18-crown-6[e] | 85 | 63 |

[a]1.2 equivalent of additives, unless otherwise mentioned.
[b]30 mol%.
[c]10 mol%.
[d]2-3 equivalent.
[e]The reaction was run at rt and enantiomeric reversal was observed.

Most of these additives were selected from the literature, besides $NaHSO_3$ which has never been used as additive in an asymmetric reaction, to the best of our knowledge. Some of these additives which provided mentionable enantiselectivity in our case are HMPA, BSA, most of the alcohols including MeOH, *i*PA, and *t*BuOH, $NaHSO_3$, and one of the diaza crown ether derivatives (entry 1, 8, 11, 13, 14, 16, and 17 respectively). *t*BuOH as additives has been employed before by Trost and co-workers[166] with significant improvement in *ee*, which proved to be true for our case as well. It participated in the enantiodiscriminative process most satisfactorily so far with 82% *ee* (entry 14). $NaHSO_3$ is another interesting additive we have found that provided us as much as 77% *ee* (entry 16). Suprisingly, 1,10-diaza-18-crown-6 has provided a decent 63% *ee* of the desired product **13j** at rt with reversal of enantiomers (entry 17).

Since alcohols as a general class of compounds provided better overall results as additives and from earlier optimization studies (see Table 9, entry 8-11) we found that toluene is another better solvent for this Pd-AAA of **10j** along with THF, we wanted to employ these alcohols as additives using toluene as reaction solvent. However, none of these additives in toluene provided better result than that in THF (Table 14). Maximum 60% *ee* was observed with *t*BuOH (entry 4). Moreover, undesired *O*-allylated product was also observed for all of these reactions.

**Table 14.** Further optimization of additives employing toluene as reaction solvent.

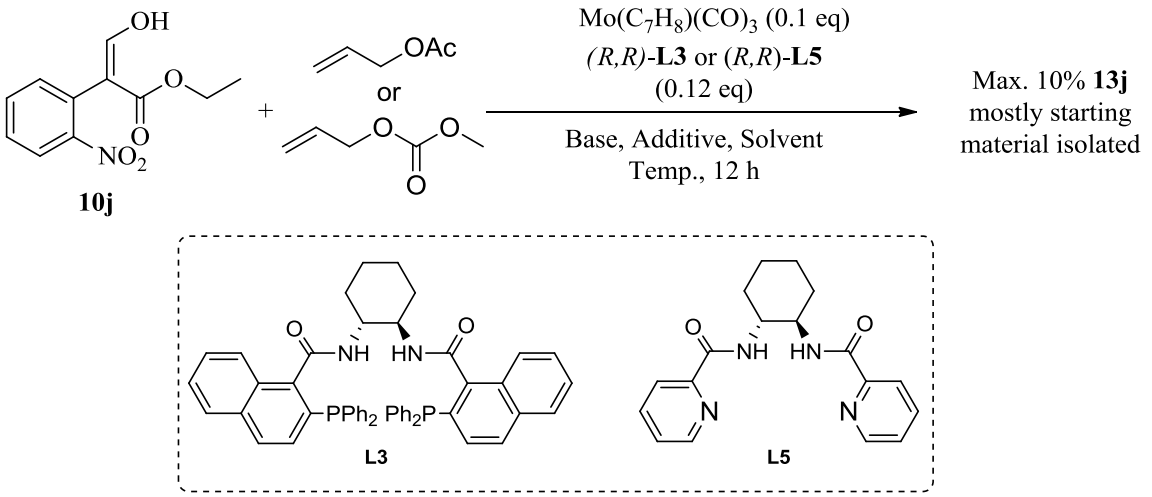



**10j** **13j**

| Entry | Additives[a] | Conv.[b] [%] | *ee* [%] |
|---|---|---|---|
| 1 | MeOH | 75 | 0 |
| 2 | EtOH | 70 | 44 |
| 3 | *i*PA | 45 | 35 |
| 4 | *t*BuOH | 45 | 60 |

[a]2-3 equivalent of additives.
[b]Rest are *O*-allylated product.

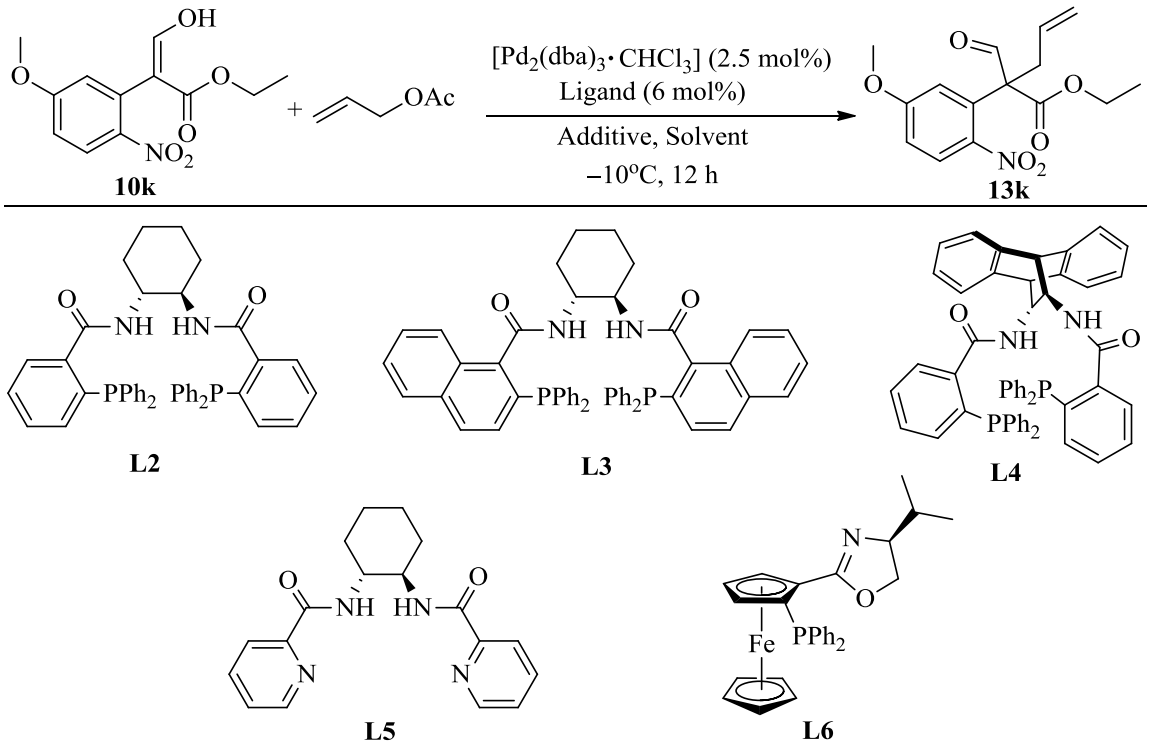
We have also tried molybdenum (Mo) instead of palladium (Pd) as catalyst due to the reason explained in details in section 3.1.3 (Scheme 101). Essentially, molybdenum goes through inner-sphere mechanism of co-ordination and is thought to be more effective in enantiodiscrimination compared to outer-sphere mechanism which is operational with palladium. Both allyl acetate and allyl methyl carbonate have been employed as electrophile for these study. We have examined **L3** and **L5** as ligands for molybdenum together with hexane: toluene (1:1), toluene, and THF as solvents; DIPEA, KOtBu, and LiHMDS as bases; *t*BuOH, *i*PA, BSA, and $NaHSO_3$ as additives; and all of these reactions have been tested at rt as well as at 50 ˚C. Surprisingly, no product was obtained for most of the reactions. Only starting material was isolated. For a very few reactions, maximum 10% of the desired **13j** was found by $^1$H NMR in the crude mixture.




**Scheme 101.** Attempted Mo-AAA reaction with **10j**.

Due to the importance of 5-methoxy-2-nitro analog of the acrylate **10k** which can be used for the asymmetric synthesis of Horsfiline, we have also explored the Pd-AAA reaction with this compound. Earlier, we have employed the previously optimized condition to this analog, however, without much success (see Scheme 96). This time, we optimized the condition again by the systemetic variations of ligands, solvents, and additives, while the temperature of the reaction was kept fixed at −10 ˚C (Scheme 102, Table 15). **L2 - L5** has been used for the investigation. **L3** again proved to be the best ligand in terms of enantiomeric excess which provided 5%, 50%, 29%, and again 29% *ee* respectively in DCM, THF, toluene, and hexane: toluene (1:1) mixture (entry 2, 7, 11, and 13 respectively). Since THF and toluene provided better *ee* compared to other solvents, we decided to explore the effect of additives in these solvents with **L3** as the ligand of choice (entry 14-18). While toluene did not show any further improvement with either BSA or (*R*)-BA as additives (entry 14, and 15), THF provided as much as 70% *ee* when BSA was

employed (entry 17). Unlike with **10j**, *t*BuOH was not found to be that much effective with **10k**, which provided **13k** with only 55% *ee* (entry 16).

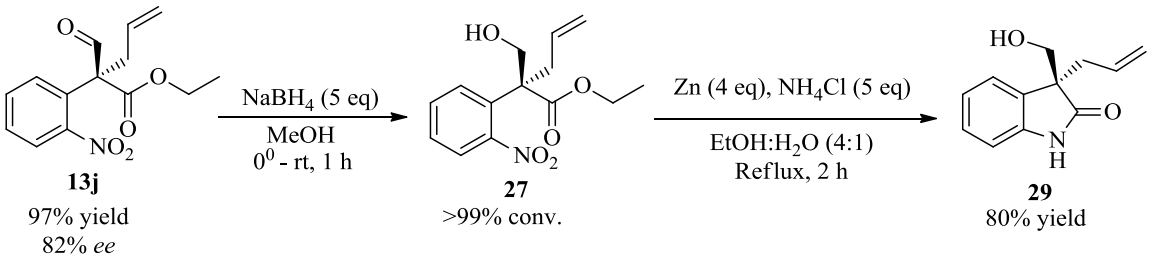



**Scheme 102.** Ligands for Pd-AAA of **10k**.

**Table 15.** Optimization studies of Pd-AAA of **10K**.

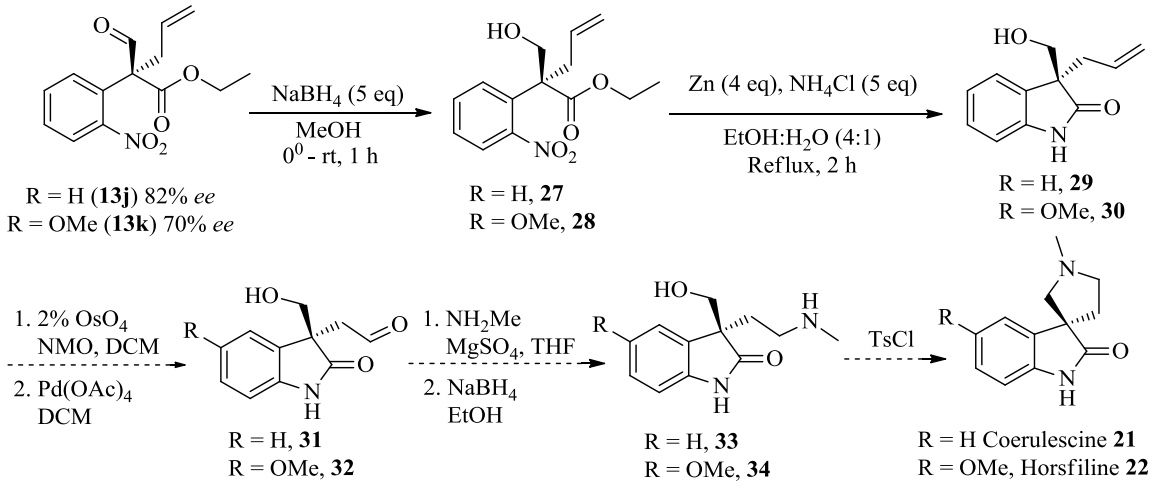
| Entry | Ligand | Solvent | Additive | Conv. [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1 | *(R,R)*-L2 | DCM | - | > 99 | Racemic |
| 2 | *(R,R)*-L3 | DCM | - | > 99 | 5 |
| 3 | *(R,R)*-L4 | DCM | - | 73 | Racemic |
| 4 | *(R,R)*-L5 | DCM | - | 0 | - |
| 5 | *(R,R)*-L6 | DCM | - | 0 | - |
| 6 | *(R,R)*-L2 | THF | - | > 99 | 45 |
| 7 | *(R,R)*-L3 | THF | - | > 99 | 50 |
| 8 | *(R,R)*-L4 | THF | - | 79 | 44 |
| 9 | *(R,R)*-L5 | THF | - | 0 | - |
| 10 | *(R,R)*-L6 | THF | - | 0 | - |
| 11 | *(R,R)*-L3 | Toluene | - | > 99 | 29 |
| 12 | *(R,R)*-L6 | Toluene | - | 0 | - |
| 13 | *(R,R)*-L3 | Hex:Tol | - | >99 | 29 |
| 14 | *(R,R)*-L3 | Tol | BSA | >99 | 35 |
| 15 | *(R,R)*-L3 | Tol | R-BA | 20 | 24 |
| 16 | *(R,R)*-L3 | THF | tBuOH | > 99 | 55 |
| 17 | *(R,R)*-L3 | THF | BSA | > 99 | 70 |
| 18 | *(R,R)*-L3 | THF | R-BA | 0 | - |

Since we have achieved 82% *ee* of **13j** from the Pd-AAA reaction of **10j** (see Table 12, entry 14), we went on to synthesize 3,3′-disubstituted oxindole framework **29** in order to show the application of this methodology in the synthesis of natural building blocks (Scheme 103). Reduction of aldehyde of **13j** to **27** provided quantitative yield. Then selective reduction of nitro group of **27** with $Zn/NH_4Cl$ in ethanol-water (4:1) mixture provided the desired 3,3′-disubstituted oxindole **29** with 80% yield.




**Scheme 103.** Asymmetric synthesis of 3,3′-disubstituted oxindole **29**.

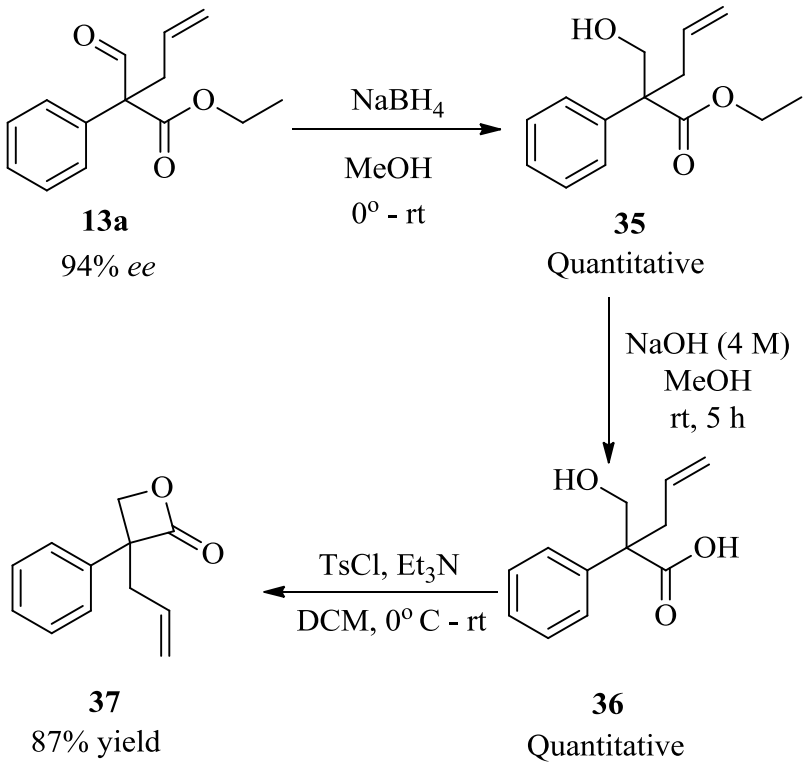
Currently, the work is in progress to synthesize Coerulescine **21** and Horsfiline **22** using this methodology (Scheme 104). **31** or **32** can be achieved from **29** or **30** respectively by oxidative cleavage of the allyl group. Then reductive amination followed by ring closing should provide Coerulescine **21** or Horsfiline **22**.




**Scheme 104.** Proposed synthesis of Coerulescine **21** and Horsfiline **22**.

3.3.2. Asymmetric synthesis of α-disubstituted β-lactones from 3-hydroxy aryl acrylate **10a**

Asymmetric α-disubstituted all-carbon quaternary β-lactone **37** has also been synthesized applying our methodology from parent quaternary aldehyde analog **13a** by three simple steps with high overall yield (87%) and enantioselectivity (94% *ee*). $NaBH_4$ reduction of **13a** provided quaternary alcohol **35** with >99% yield. The diacid compound **36** was prepared quantitatively from **35** by stirring in NaOH solution, followed by ring closing yielded desired α-disubstituted all-carbon quaternary β-lactone **37** with 87% yield (Scheme 105).




**Scheme 105.** Asymmetric synthesis of quaternary β-lactone **37** from **13a**.

## 3.4. General methods and experimental

### 3.4.1. Preparation of 3-hydroxy aryl acrylates **10j-10o** for Palladium-Catalyzed Asymmetric Allylic Alkylation (Pd-AAA)

Hydroxyarylacrylates **10j**,[33] **10k**,[33] **10n**,[45] and **10o**[45] were prepared according to previously existing procedures. Work-up procedure described in sections 1.2.1 and 1.5.1 was followed.

Hydroxyarylacrylates **10l** and **10m** prepared folloing the procedure for **10h** described in section 2.7.1.

***(Z)-ethyl 3-hydroxy-2-(2-methoxyphenyl)acrylate (10l)***

2-methoxybenzaldehyde (1.36 g, 10.0 mmol), Ethyl diazoacetate (1.45 mL, 12.0 mmol), $HBF_4.OEt_2$ (0.14 mL, 1.0 mmol) in dichloromethane (100 mL) at -78$^0$C to rt for 5h to provide the above mentioned compound as a clear oil (1.46g, 65% yield).

**$^1$H NMR (CDCl3, 300 MHz):** δ 11.99 (d, j = 12.6 Hz, 1H), 7.41 – 6.75 (5H), 4.35 (q, j = 9.0 Hz, 2H), 3.78 (s, 3H), 1.24 (t, j = 7.2 Hz, 3H).

***(Z)-ethyl 2-(2-fluorophenyl)-3-hydroxyacrylate (10m)***

2-fluorobenzaldehyde (1.24 g, 10.0 mmol), Ethyl diazoacetate (1.45 mL, 12.0 mmol), $HBF_4.OEt_2$ (0.14 mL, 1.0 mmol) in dichloromethane (100 mL) at -78 $^0$C to rt for 5h to provide the above mentioned compound as a clear oil (1.49g, 71% yield).

3.4.2. General procedures for palladium-catalyzed allylic alkylation reactions

All-carbon quaternary aldehydes **13j-13o** were prepared following the procedure described in section 2.7.2.

***Ethyl 2-formyl-2-(2-nitrophenyl)pent-4-enoate (13j)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10j** (50.0 mg, 0.1803 mmol, 1.0 eq), $Pd(PPh_3)_4$ (20.8 mg, 0.0180 mmol, 0.1 eq), and allyl acetate (23.4 µL, 0.2164 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a off-white solid (55.7 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10j** (50.0 mg, 0.1803 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (4.7 mg, 0.0045 mmol, 0.025 eq), *(R,R)*-L3 (8.5 mg, 0.0108 mmol, 0.06 eq), allyl acetate (23.4 µL, 0.2164 mmol, 1.2 eq), *t*BuOH (43.1 µL, 0.4508 mmol, 2.5 eq) in THF (5 mL) at -10$^0$C to provide the above mentioned compound as a off-white solid (55.7 mg, >99% yield).

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 10.16 (s, 1H), 8.16 (d, j = 9 Hz, 1H), 7.74 (m, 1H), 7.63 (m, 1H), 7.57 (m, 1H), 5.72 (m, 1H), 5.24 (m, 2H), 4.22 (q, j = 8.0 Hz, 2H), 3.06 (d, j = 6.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 196.9, 169.4, 148.4, 133.7, 131.1, 130.7, 130.5, 129.0, 125.9, 120.4, 63.9, 62.0, 37.8, 14.0.

**Chiral HPLC:** 82% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 95:05 hexane/ethanol, 1.0 mL/min, 220 nm, 12.16 min (major), 14.26 min (minor).

**HRMS (ESI):** Calculated (m/z) for C14H16NO5 $(M+H)^+$ : 278.1023, Found 278.1033.

***Ethyl 2-formyl-2-(5-methoxy-2-nitrophenyl)pent-4-enoate (13k)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10k** (50.0 mg, 0.1627 mmol, 1.0 eq), $Pd(PPh_3)_4$ (18.8 mg, 0.0163 mmol, 0.1 eq), and allyl acetate (21.1 µL, 0.1952 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a brown solid (50.3 mg, 100% conversion).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10k** (25.0 mg, 0.0814 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (2.1 mg, 0.0020 mmol, 0.025 eq), *(R,R)*-L3 (3.9 mg, 0.0049 mmol, 0.06 eq), allyl acetate (10.6 µL, 0.0976 mmol, 1.2 eq), BSA (23.9 µL, 0.0976 mmol, 1.2 eq) in THF (3 mL) at $-10^0$C to provide the above mentioned compound as a brown solid (24.13 mg, 100% conversion).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 10.16 (s, 1H), 8.28 (d, j = 9 Hz, 1H), 7.45-6.93 (2H), 5.9 (m, 1H), 5.26 (m, 2H), 4.22 (q, j = 8.0 Hz, 2H), 3.94 (s, 3H), 3.00 (d, j = 6.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

**Chiral HPLC:** 70% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 90:10 hexane/ethanol, 0.5 mL/min, 220 nm, 27.40 min (major), 29.63 min (minor).

***Ethyl 2-formyl-2-(2-methoxyphenyl)pent-4-enoate (13l)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10l** (50.0 mg, 0.1908 mmol, 1.0 eq), $Pd(PPh_3)_4$ (21.2 mg, 0.0191 mmol, 0.1 eq), and allyl acetate (24.8 µL, 0.2290 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a yellow oil (59.2 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10l** (50.0 mg, 0.1908 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.0 mg, 0.0048 mmol, 0.025 eq), *(R,R)*-L3 (9.0 mg, 0.0114 mmol, 0.06 eq), allyl acetate (24.8 µL, 0.2290 mmol, 1.2 eq), in hexane: toluene (1:1) at $-20^0$C to provide the above mentioned compound as a yellow oil (59.2 mg, >99% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 10.06 (s, 1H), 7.34-6.90 (m, 4H), 5.95 (m, 1H), 5.10 (m, 2H), 4.22 (q, j = 8.0 Hz, 2H), 3.79 (s, 3H), ), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.87 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H).

**Chiral HPLC:** 10% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 96:04 hexane/ethanol, 0.5 mL/min, 220 nm, 18.36 min (major), 20.28 min (minor).

***Ethyl 2-(2-fluorophenyl)-2-formylpent-4-enoate (13m)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10m** (50.0 mg, 0.1998 mmol, 1.0 eq), $Pd(PPh_3)_4$ (23.0 mg, 0.0200 mmol, 0.1 eq), and allyl acetate (25.9 µL, 0.2398 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as a clear oil(61.7 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10m** (50.0 mg, 0.1998 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (5.2 mg, 0.0050 mmol, 0.025 eq), *(R,R)*-L3 (9.4 mg, 0.0120 mmol, 0.06 eq), allyl acetate (25.9 µL, 0.2398 mmol, 1.2 eq), in hexane: toluene (1:1) at $-20^0$C to provide the above mentioned compound as a clear oil (61.7 mg, >99% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 7.37-7.08 (m, 4H), 5.80 (m, 1H), 5.11 (m, 2H), 4.28 (q, j = 7.5 Hz, 2H), 3.16 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.91 (dd, *J* = 7.8, 13.8 Hz, 1H),1.27 (t, J = 7.5 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 195.6, 170.0, 162.2, 134.1, 132.1, 130.2, 129.7, 124.7, 119.4, 116.1, 62.7, 61.9, 36.0, 14.0.

**Chiral HPLC:** 10% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 99:01 hexane/ethanol, 1.0 mL/min, 220 nm, 8.61 min (major), 9.19 min (minor).

***Ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate (13n)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10n** (50.0 mg, 0.1660 mmol, 1.0 eq), $Pd(PPh_3)_4$ (19.1 mg, 0.0166 mmol, 0.1 eq), and allyl acetate (21.5 µL, 0.1992 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as an yellow oil (51.3 mg, >99% yield).

**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10n** (50.0 mg, 0.1660 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (4.3 mg, 0.0042 mmol, 0.025 eq), *(R,R)*-L3 (8.1 mg, 0.0100 mmol, 0.06 eq), allyl acetate (21.5 µL, 0.1992 mmol, 1.2 eq), in hexane: toluene (1:1) at $-20^0$C to provide the above mentioned compound as an yellow oil (48.2 mg, 93% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** δ 10.32 (s, 1H), 7.72 (s, 1H), 7.44–7.28 (m, 2H), 5.75 (m, 1H), 5.2-5.1 (m, 2H), 4.25 (q, *J* = 7.1, 2H), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.94 (dd, *J* = 7.2, 14.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

**Chiral HPLC:** 6% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 96:04 hexane/ethanol, 0.5 mL/min, 220 nm, 13.46 min (major), 14.66 min (minor).

Analytical data matched previously reported data.[45]

***Ethyl 2-(5-bromo-2-methoxyphenyl)-2-formylpent-4-enoate (13o)***

**Racemic:** General procedure for racemic Pd-catalyzed allylic alkylation reaction (**Method 4**) using hydroxyarylacrylate **10o** (50.0 mg, 0.1465 mmol, 1.0 eq), $Pd(PPh_3)_4$ (16.9 mg, 0.0147 mmol, 0.1 eq), and allyl acetate (19.0 µL, 0.1758 mmol, 1.2 eq) in dichloromethane (5 mL) at rt for 2h to provide the above mentioned compound as an yellow oil (45.3 mg, >99% yield).

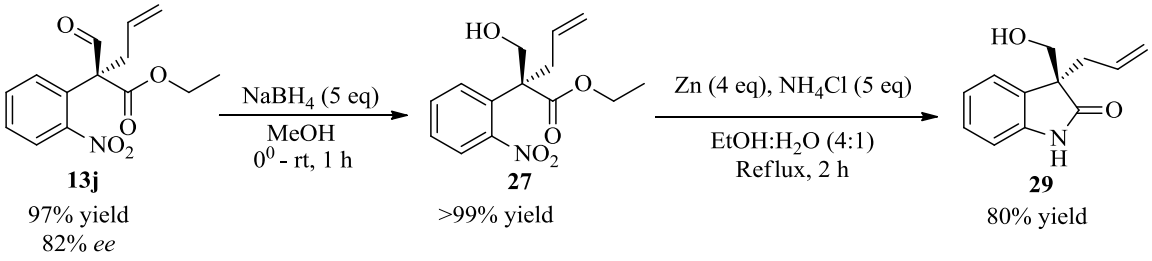
**Chiral:** General procedure for Pd-AAA reaction (**Method 3**) using hydroxyarylacrylate **10o** (50.0 mg, 0.1465 mmol, 1.0 eq), $Pd_2(dba)_3CHCl_3$ (3.8 mg, 0.0037 mmol, 0.025 eq), *(R,R)*-L3 (7.1 mg, 0.0088 mmol, 0.06 eq), allyl acetate (19.0 µL, 0.1758 mmol, 1.2 eq), in hexane: toluene (1:1) at $-20^0$C to provide the above mentioned compound as an yellow oil (44.4 mg, 97% yield).

**$^1$H NMR (300 MHz, $CDCl_3$):** 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) .

**Chiral HPLC:** 21% *ee*, Regis Technologies Pirkle Covalent chiral stationary phase column, 96:04 hexane/ethanol, 0.5 mL/min, 220 nm, 18.83 min (minor), 19.80 min (major).

Analytical data matched previously reported data.[45]

3.4.3. Synthesis of 3,3′-disubstituted oxindole **29**




**13j**
97% yield
82% *ee*

**27**
>99% yield

**29**
80% yield

***Ethyl 2-(hydroxymethyl)-2-(2-nitrophenyl)pent-4-enoate (27)***

Ethyl 2-formyl-2-(2-nitrophenyl)pent-4-enoate **13j** (430.0 mg, 1.44 mmol, 1.0 eq) was added to a 100 mL round bottomed flask and placed in an argon atmosphere. 30mL dry methanol was then added via syringe and the mixture was allowed to stir until all starting material was dissolved. The reaction flask was then brought down to 0 $^{o}$C and $NaBH_4$ (294.0 mg, 7.76 mmol, 5.0 eq) was added to the stirring mixture. Subsequently, the mixture was removed from the ice bath and allowed to stir for 5 minutes and then returned to ice and monitored by TLC until completion. After no starting material remained, 10 mL of water was added to quench the reaction mixture. The mixture was then extracted three times with 15 mL portion of DCM, dried, and concentrated in *vacuo*. The resultant crude was purified by column chromatography on silica gel eluted with 5% EtOAc in Hexane to afford the above mentioned product **27** as brownish viscous liquid (430.0 mg, > 99% conv.).

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 7.88 (d, j = 9 Hz, 1H), 7.59 (m, 2H), 7.44 (m, 1H), 5.59 (m, 1H), 5.12 (m, 2H), 4.31 (d, j = 12 Hz, 1H), 4.10 (m, 2H), 3.98 (d, j = 12 Hz, 1H), 3.00 (dd, j = 6.0, 12.0 Hz, 2H), 2.70 (s, 1H), 1.19 (t, J = 7.5 Hz, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$):** δ 172.7, 150.1, 133.1, 132.1, 129.9, 128.0, 126.1, 125.2, 119.5, 67.1, 61.2, 55.1, 39.2, 14.0.

**HRMS:** Calculated (m/z) for C14H17NO5 $(M+H)^+$ : Predicted 280.1179, Found 280.1180.

***3-allyl-3-(hydroxymethyl)indolin-2-one (29)***

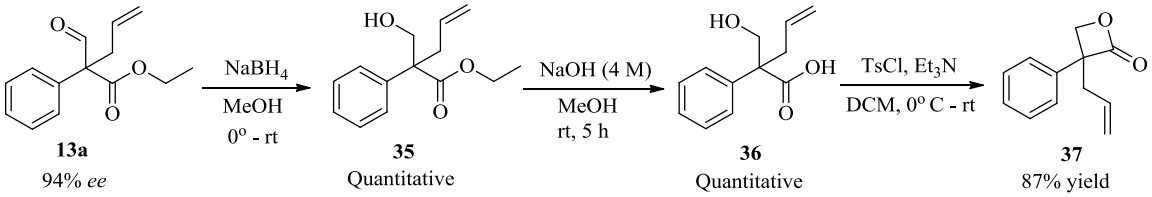
Ethyl 2-(hydroxymethyl)-2-(2-nitrophenyl)pent-4-enoate 27 (200.0 mg, 0.72mmol, 1 eq), zinc powder (400.0 mg, 6.12 mmol, 8.5eq), 370.0 mg of solid $NH_4Cl$ (6.92 mmol, 9.6eq) were taken in a flask and placed in an argon atmosphere. A dry and degassed 10.0 mL of the ethanol: water (4:1) mixture was added to the flask via syringe followed by vigorous stirring. Then heat was applied to bring the mixture to reflux. The mixture was allowed to react for 2 hours and monitored by TLC before being cooled down to room temperature. The zinc dust was then removed by filtering through a cotton plug and ethanol was removed in the rotary evaporator before extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The crude was purified *via* column chromatography using basic or neutral $Al_2O_3$ as a stationary phase with 100% ethyl acetate, which yielded the desired oxindole **29** as white solid (0.12 g, 80% yield).

**$^{1}$H NMR (300 MHz, ($CDCl_3$):** δ 8.12 (s, 1H), 7.26-6.91 (m, 4H), 5.51 (m, 1H), 5.10 (m, 2H), 3.89 (dd, J =12.0, 36.0 Hz, 2H), 2.70 (m, 2H), 2.04 (s, 1H).

**$^{13}$C NMR (75 MHz, ($CDCl_3$):** δ 180.8, 141.1, 131.6, 129.9, 128.5, 123.7, 122.7, 119.2, 109.9, 66.5, 54.7, 37.3.

**HRMS:** Calculated (m/z) for C12H13NO2 $(M+H)^+$ : Predicted 204.1009, Found 204.1019.

3.4.4. Synthesis of α-disubstituted all-carbon quaternary β-lactone **37**




***Ethyl 2-(hydroxymethyl)-2-phenylpent-4-enoate (35)***

To a 10 mL round bottom flask with **13a** (50.0 mg, 0.2153 mmol, 1.0 eq) was charged with MeOH (5 mL) and cooled to 0°C. Next, $NaBH_4$ (40.5 mg, 1.0765 mmol, 5.0 eq) were added portion wise and let the mixture stir for 3h. The reaction was quenched with $H_2O$ (3 mL) at 0°C and then was extracted three times with dichloromethane. The organic layer was washed with brine, then dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. Column chromatography on silica gel with eluted with hexane and EtOAc provided 50.3 mg (>99% yield) of the reduced quaternary alcohol product **35** as a clear oil.

**$^{1}$H NMR (300 MHz, CDCl3):** δ (ppm) 7.39-7.28 (m, 5H), 5.75 (m, 1H), 5.21-5.09 (m, 2H), 4.26-4.18 (m, 2H), 4.05 (q, j = 12.0 Hz, 2H), 2.8 (d, j = 9.0 Hz, 2H), 2.48 (s, 1H), 1.25 (t, j = 7.5 Hz, 3H).

**$^{13}$C NMR (75 MHz, CDCl3):** δ 174.7, 140.1, 133.7, 129.0, 128.8, 127.2, 126.8, 126.3, 118.7, 66.5, 61.1, 55.7, 38.3, 14.1.

**HRMS (ESI):** Calculated (m/z) for C14H18O3 $(M+H)^{+}$ : 235.1329, Found 235.1334.

***2-(hydroxymethyl)-2-phenylpent-4-enoic acid (36)***

Aq. NaOH (4 M, 0.32 mL) was added to a solution of ester **35** (50.0 mg, 0.2134 mmol, 1.0 equiv) in methanol (not dried, 3.0 mL) under air at 0 °C. The cold bath was removed and the mixture stirred at room temperature until all starting material was consumed (5 h). The solution was diluted with water and the aqueous layer washed three times with diethyl ether before it was carefully acidified using concentrated aq. HCl. The aqueous phase was extracted three times with diethyl ether, the combined extracts were dried over $Na_2SO_4$, filtered and evaporated to yield the crude hydroxyacid **36** as white solid (44.0 mg, >99% yield), which was used in the next step without further purification.

**$^{1}$H NMR (300 MHz, CDCl3):** δ (ppm) 7.34-7.28 (m, 5H), 6.57 (br., 2H), 5.68-5.63 (m, 1H), 5.18 (d, j = 15.0 Hz, 1H), 5.11(d, j = 12.0 Hz, 1H), 4.25 (m, 1H), 4.15 (m, 1H), 2.87 (d, j = 6.0 Hz, 2H).

**$^{13}$C NMR (75 MHz, CDCl3):** δ 179.5, 138.9, 133.3, 128.7, 128.0, 127.5, 126.8, 126.7, 119.0, 65.3, 55.7, 38.5.

**HRMS (ESI):** Calculated (m/z) for C12H14O3 $(M-H)^{-}$ : 205.0870, Found 205.0869.

***3-allyl-3-phenyloxetan-2-one (37)***

A dry 10 mL flask was charged with acid **36** (50 mg, 0.2424 mmol, 1.0 equiv) from the previous step, a stir bar, and dichloromethane (3.0 mL) under argon. The resulting solution was then cooled to 0 °C. Triethylamine (100 µL, 0.7272 mmol, 3.0 equiv) and tosyl chloride (50.8 mg, 0.2666 mmol, 1.1 equiv) were subsequently added and the mixture was stirred for 2 h. It was then warmed to rt and stirred for another 30 minutes. TLC showed the consumption of starting material. Water (4.0 mL) and $CH_2Cl_2$ (4.0 mL) were added and the organic phase was separated. The aqueous layer was then further extracted with $CH_2Cl_2$ (3 X 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude was purified by preparative TLC (elutes at 10:90 EtOAc/hexanes) to afford β- lactone **37** as a white solid (39.7 mg, 87%).

**$^{1}$H NMR (500 MHz, CDCl3):** δ (ppm) 7.43-7.28 (m, 5H), 5.81-5.73 (m, 1H), 5.24-5.20 (m, 2H), 4.55 (dd, j = 5.0, 15.0 Hz, 2H), 2.85 (dd, j = 10.0, 15.0 Hz, 1H), 2.75 (dd, j = 5.0, 15.0 Hz, 1H).

**$^{13}$C NMR (125 MHz, CDCl3):** δ 171.8, 137.3, 131.4, 128.9, 127.9, 126.1, 120.5, 69.7, 65.1, 44.0.

**MS:** Compound decomposed during HRMS.

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[108] We used ROESY experiments to confirm our assignment of cross peaks to be NOE or exchange peaks. In the ROESY experiment cross peaks due to spatial proximity (ROE) will always be opposite in sign to the diagonal, whereas exchange peaks will always have the same sign as the diagonal peaks. We could thus exclude the possibility that cross peaks assigned as exchange peaks in the NOESY spectrum arose from NOEs in a species with a particular long correlation time.

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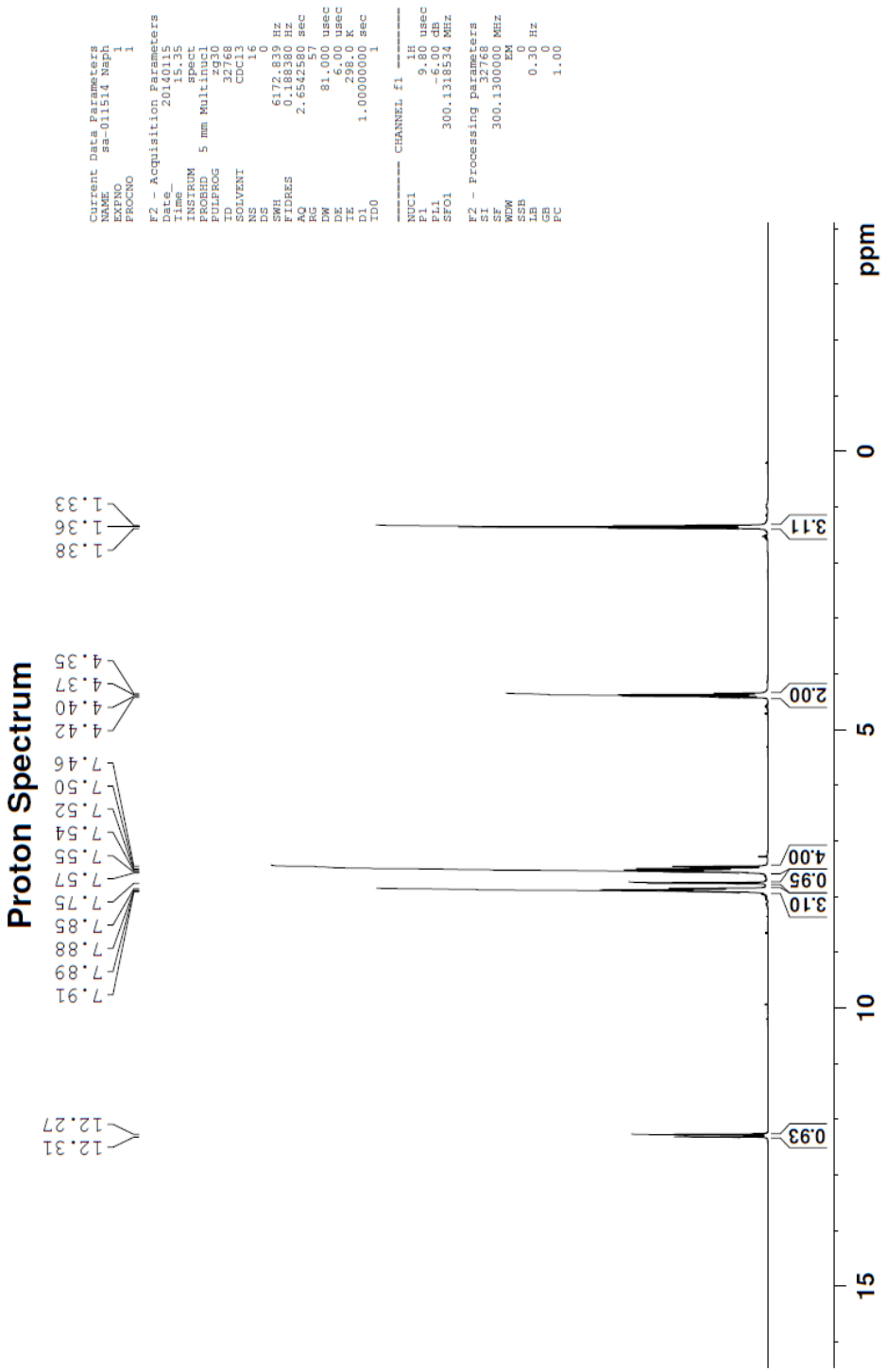
# APPENDIX A:

## NMR Data

Compound **10h**



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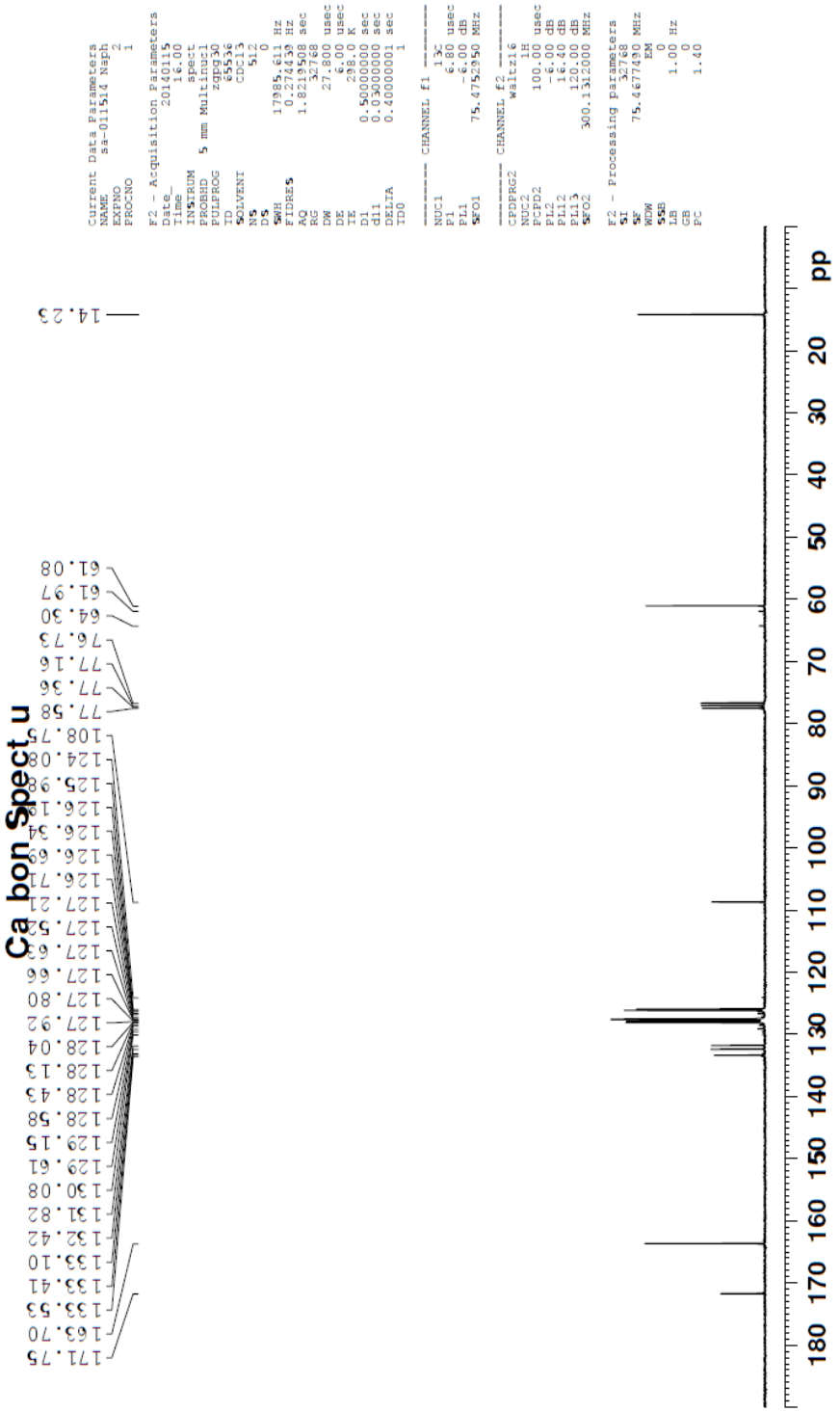
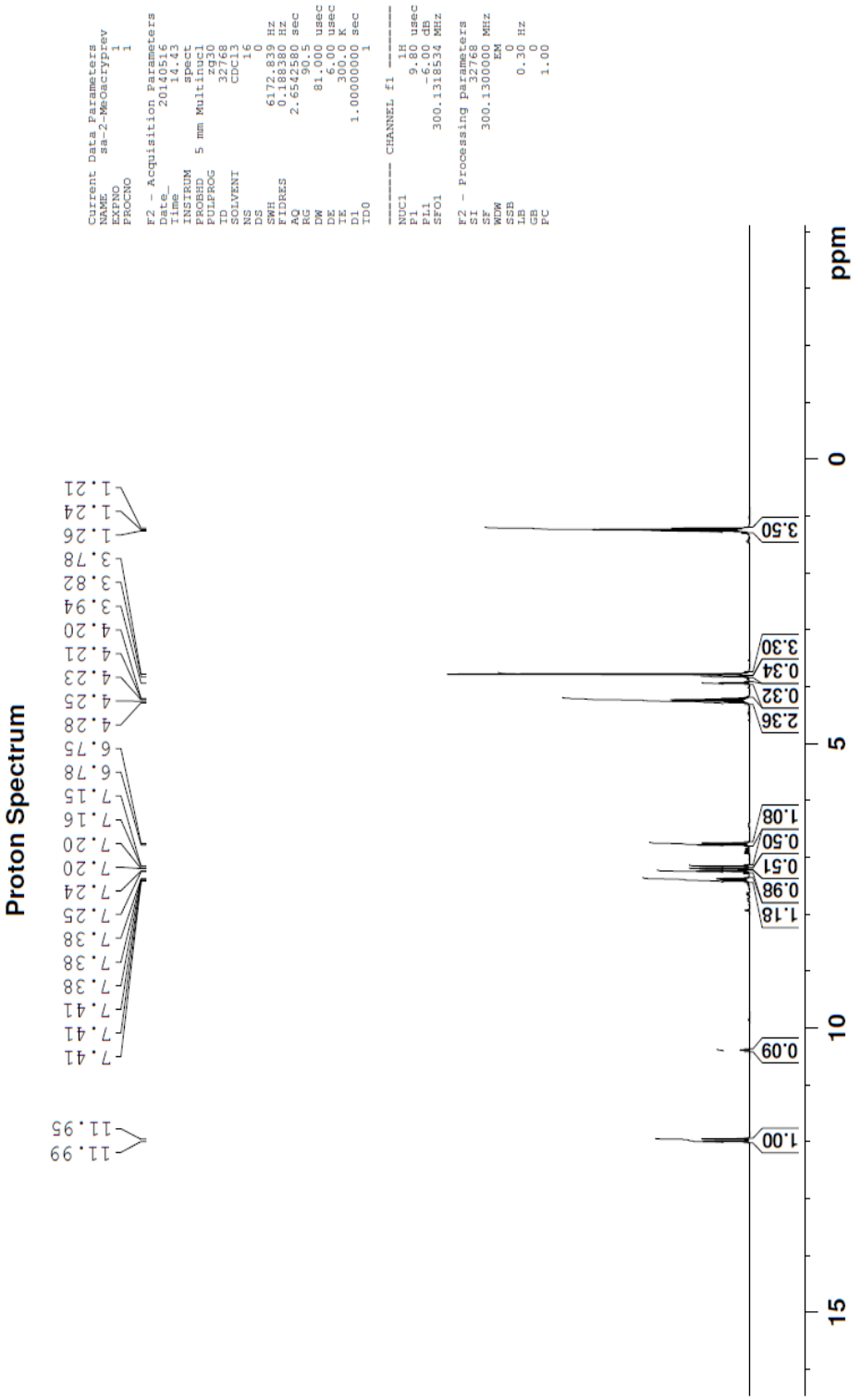


Compound **10l**



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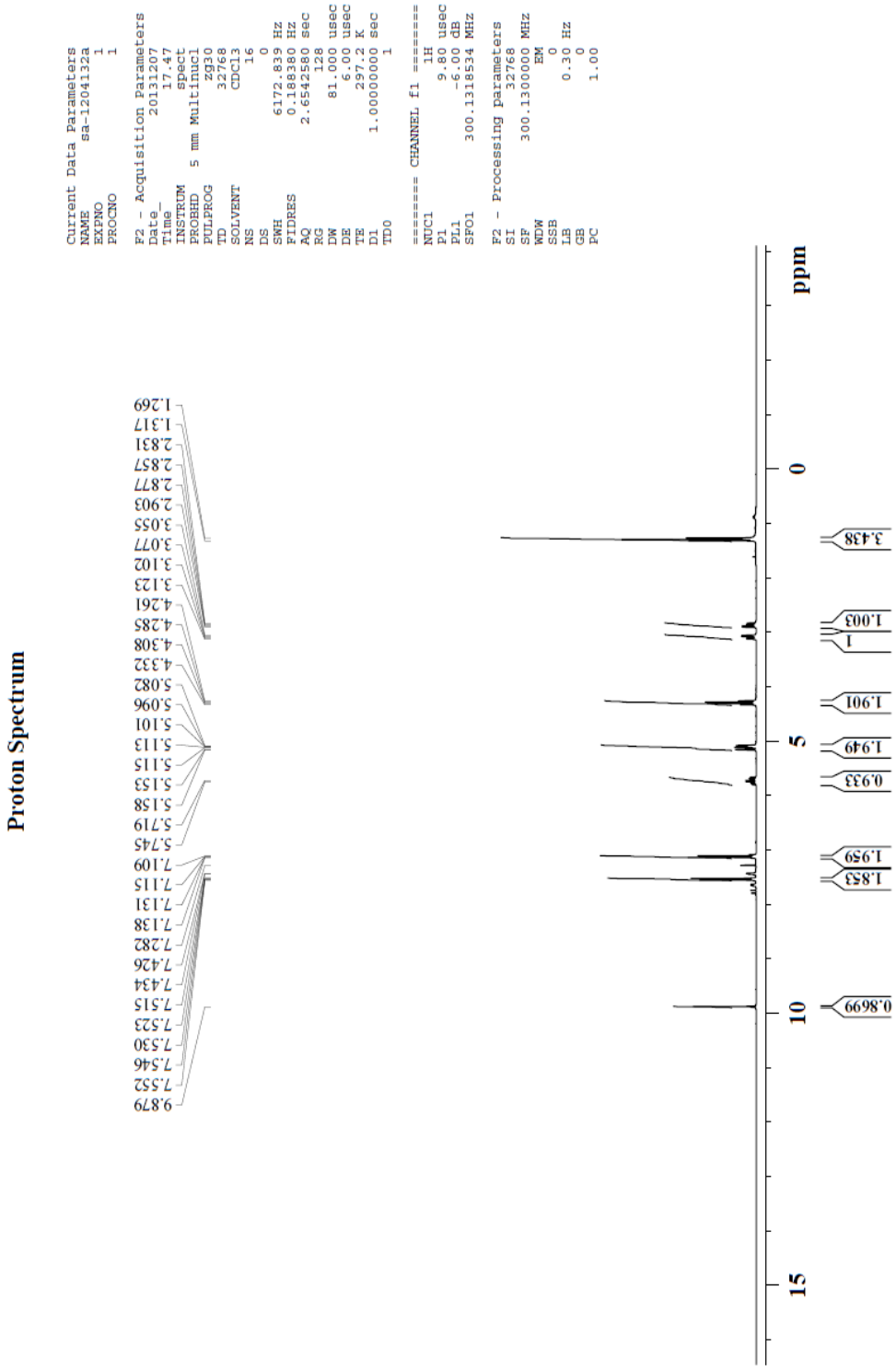

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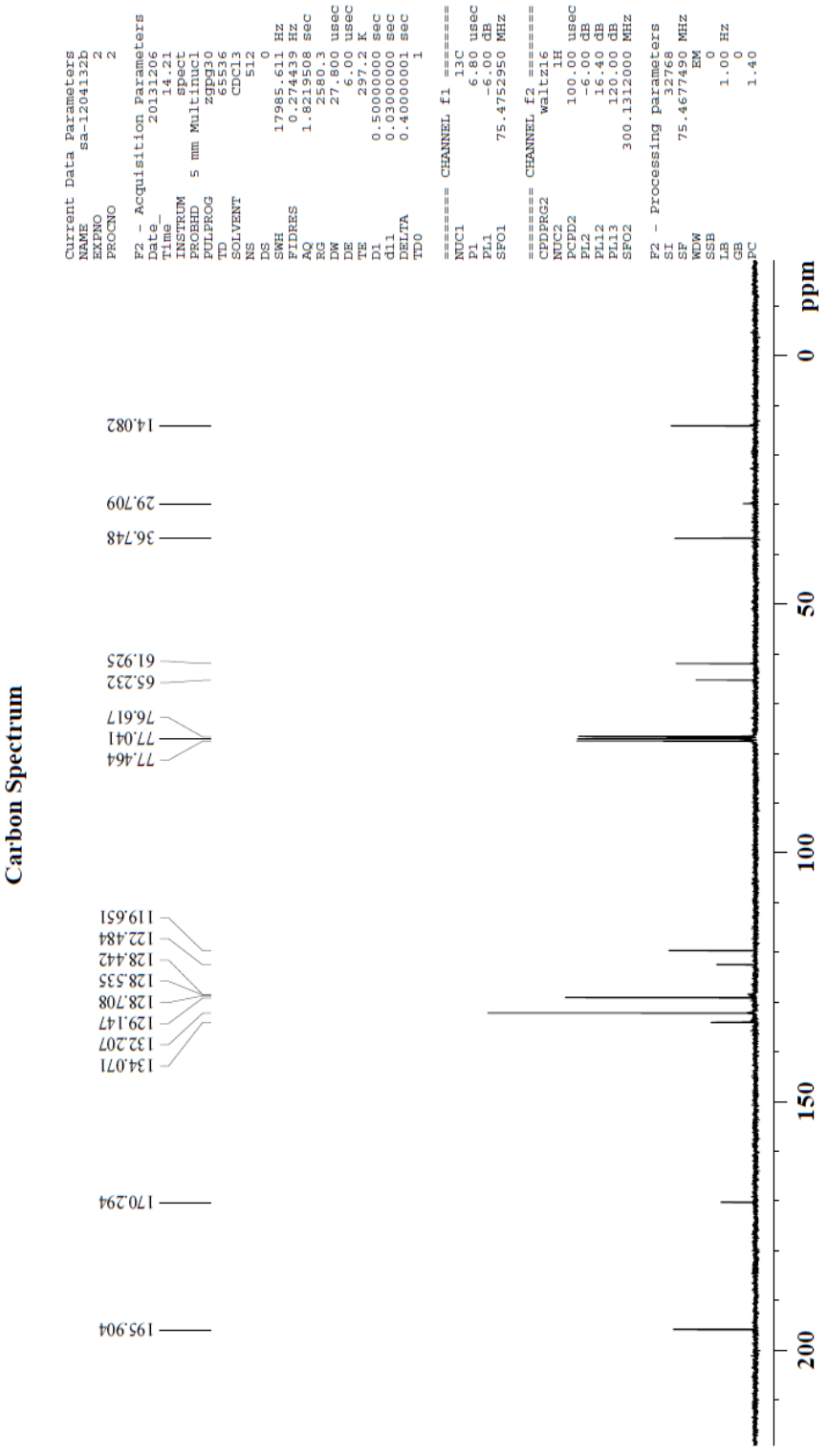

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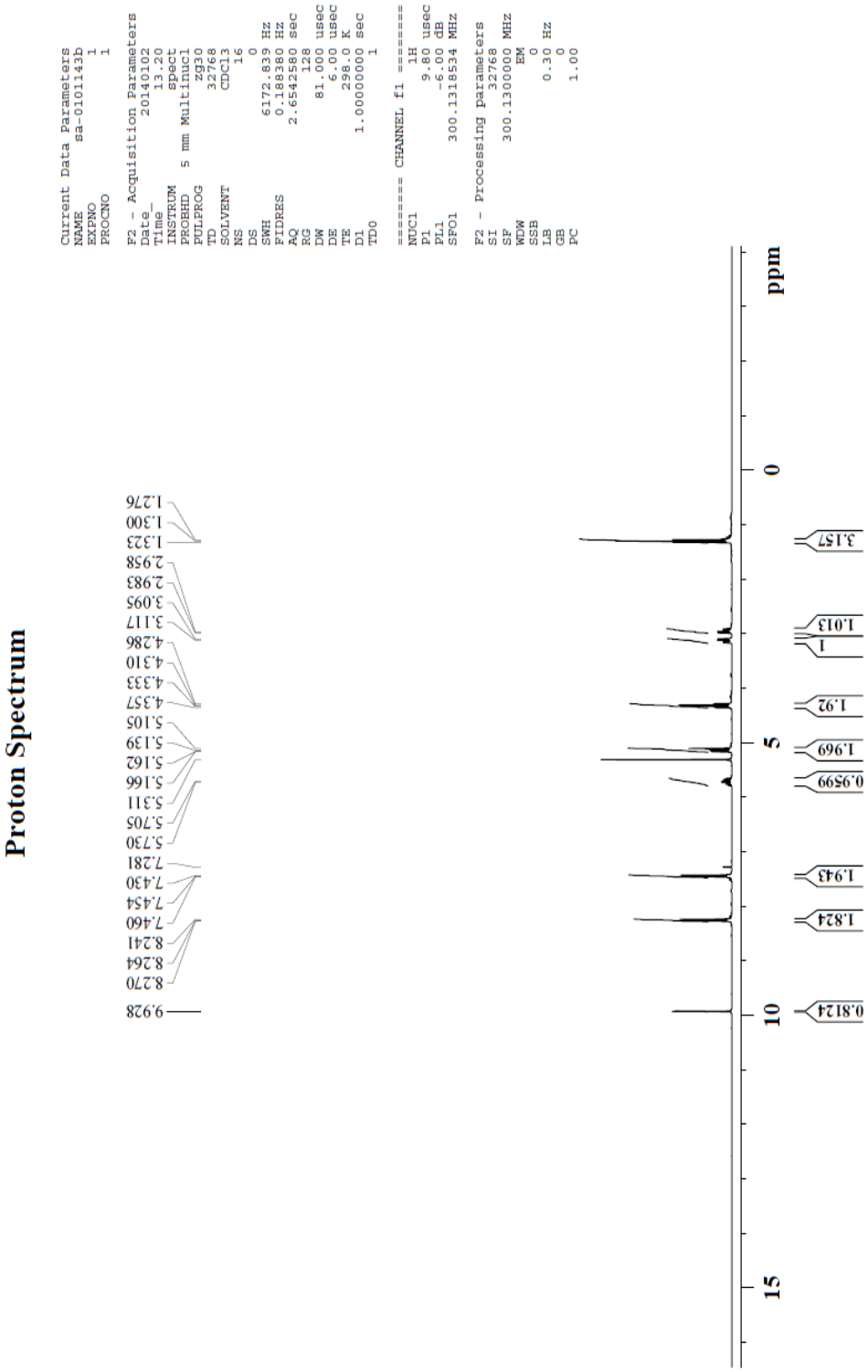

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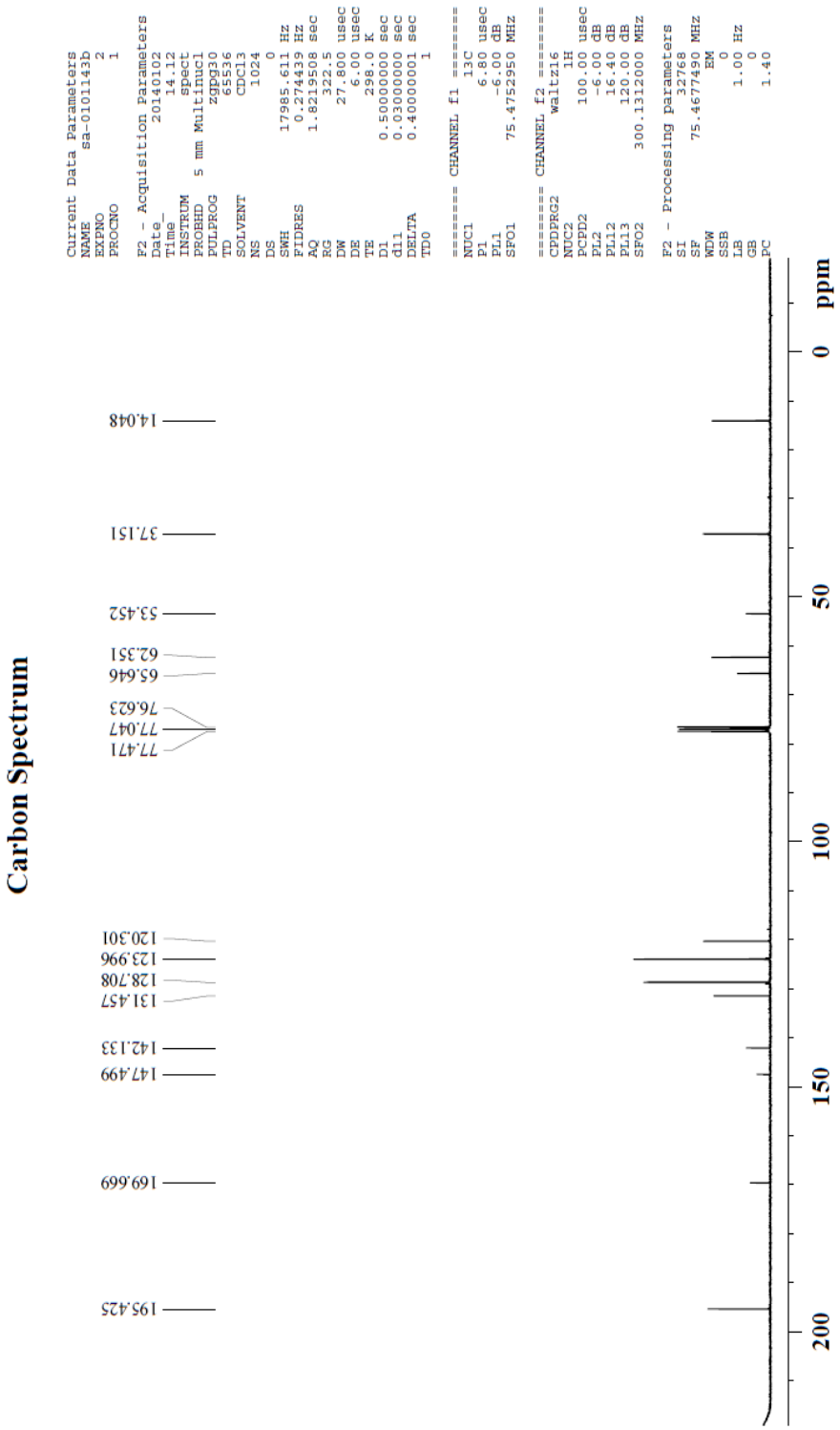
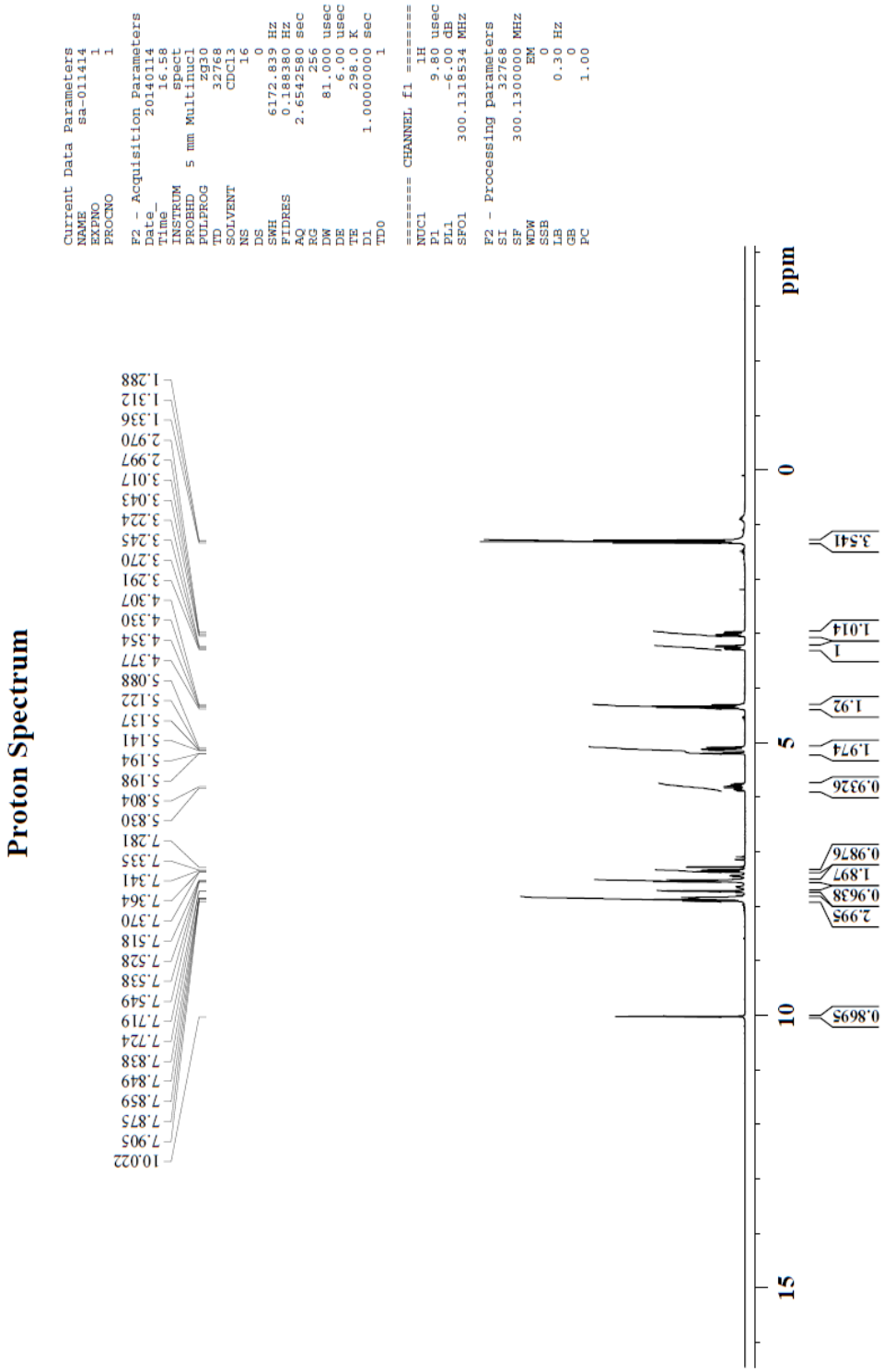


Compound **13h**



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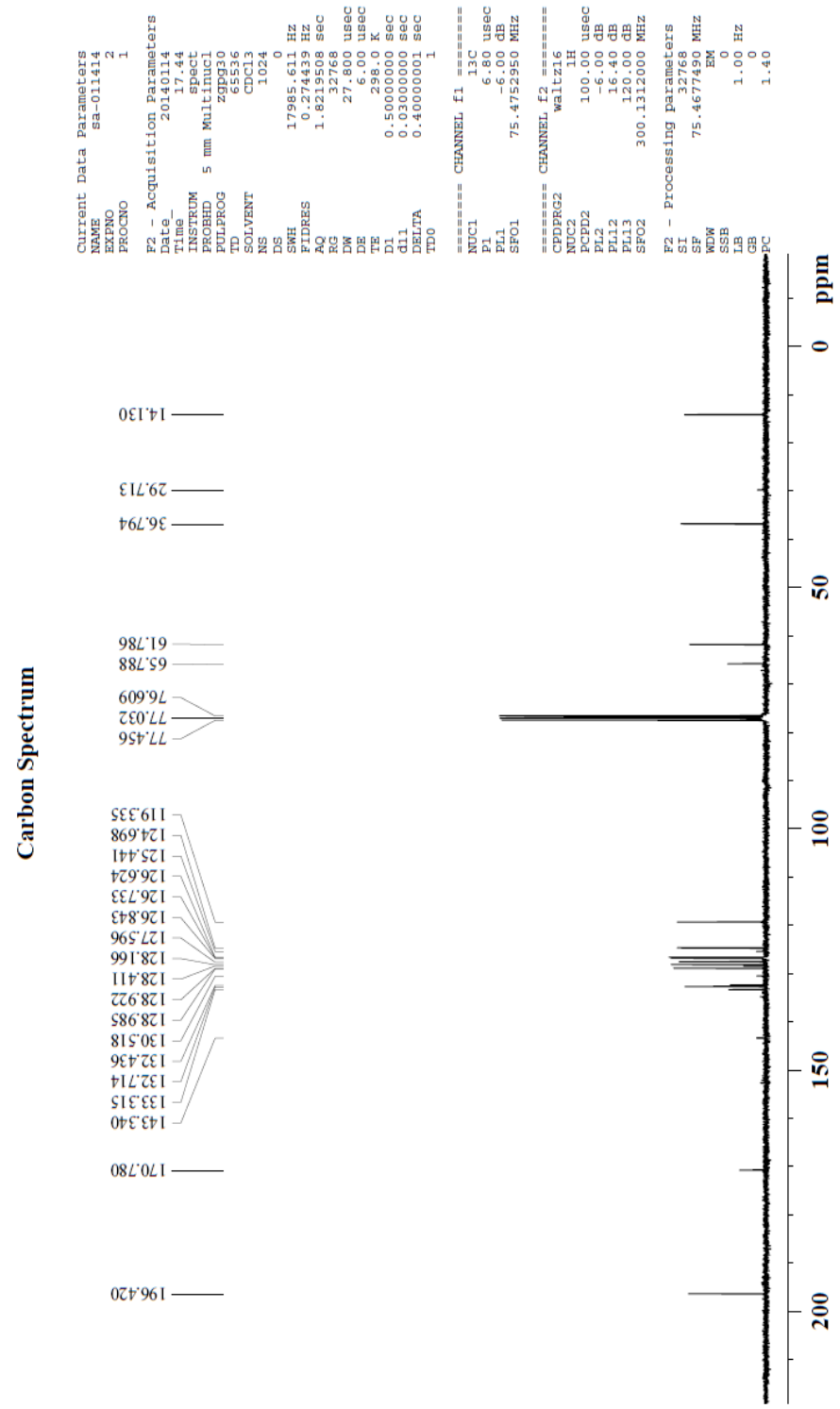
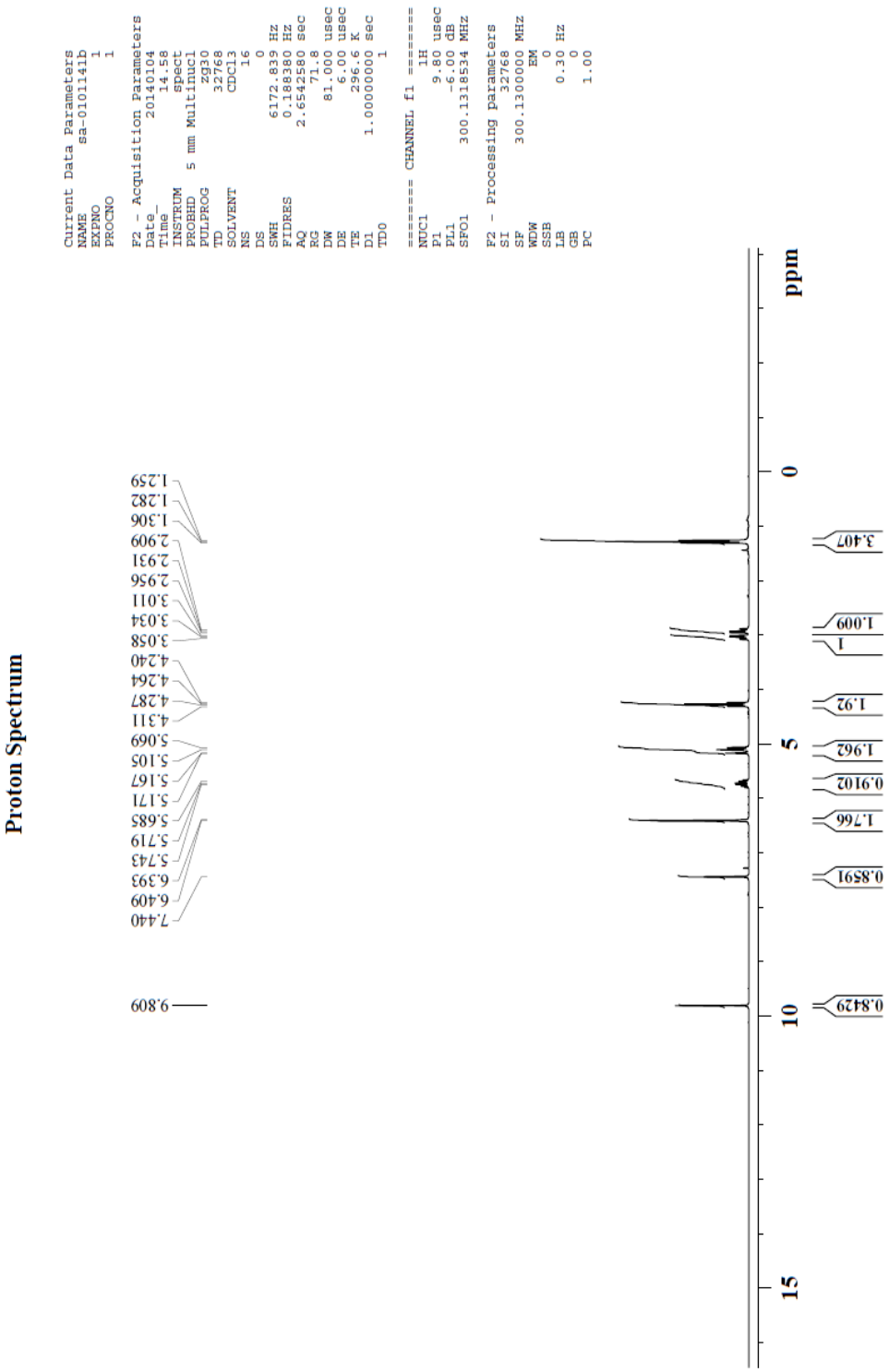
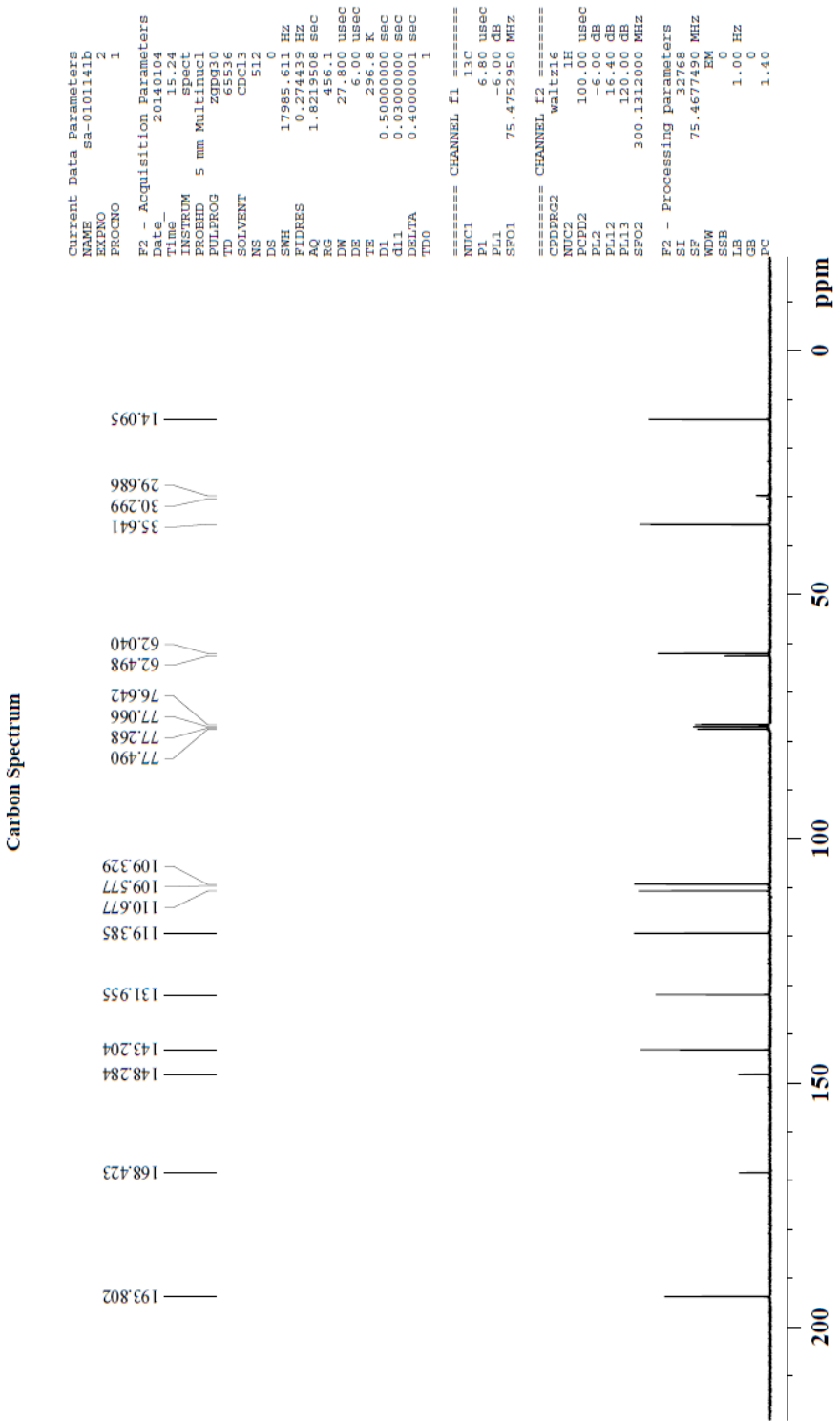


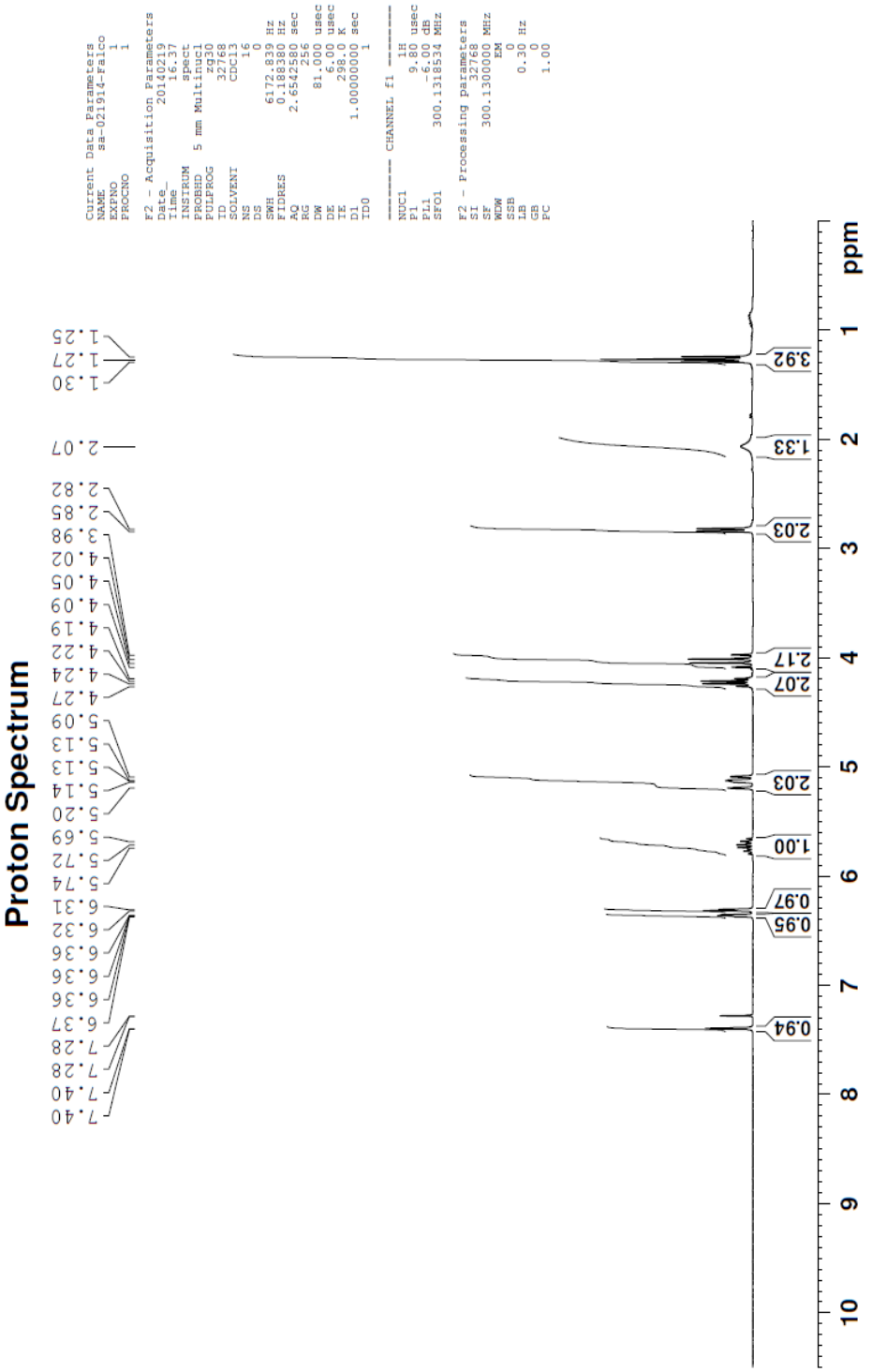
Compound **13i**



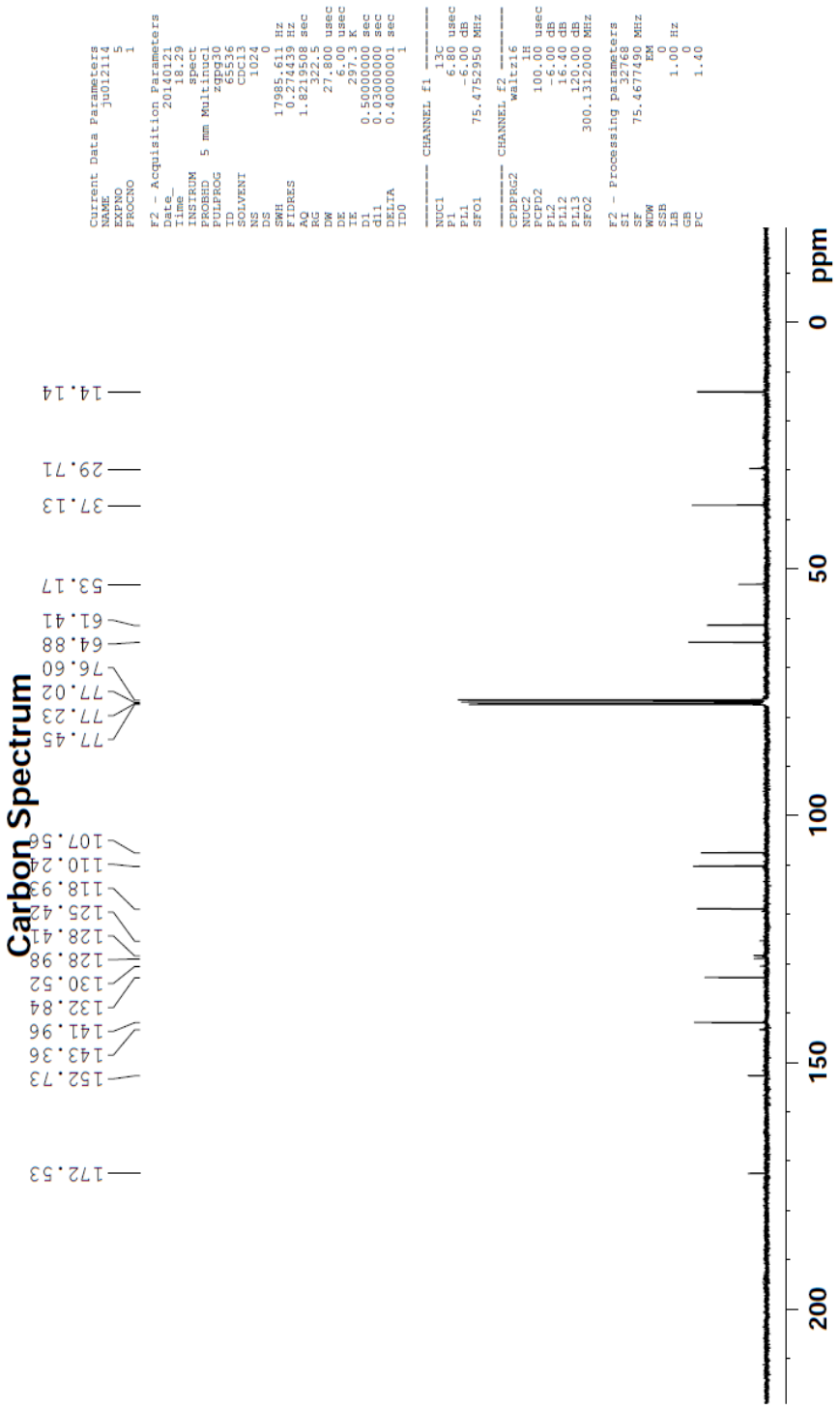
Compound **13i**



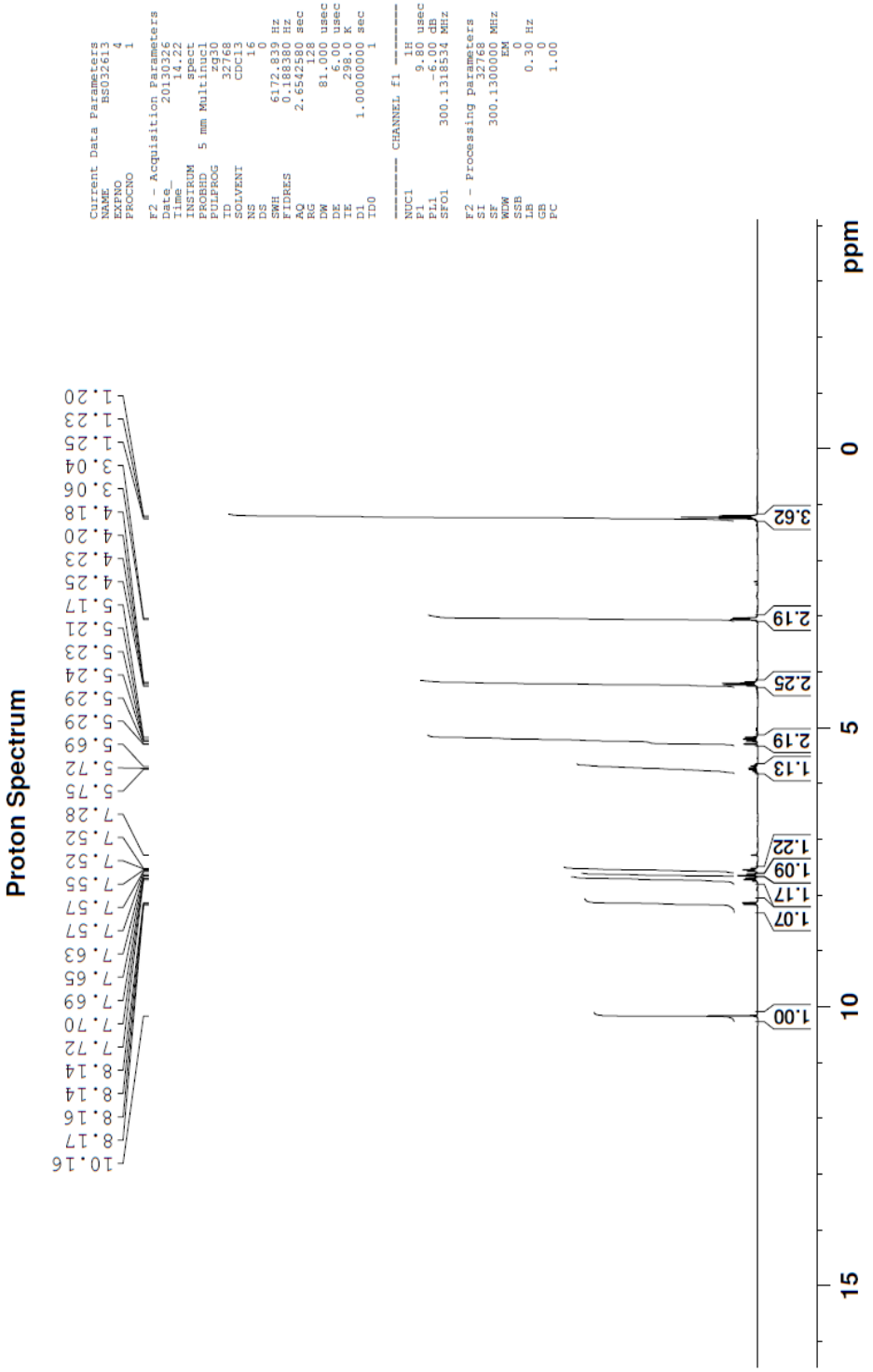
Compound **13′i**



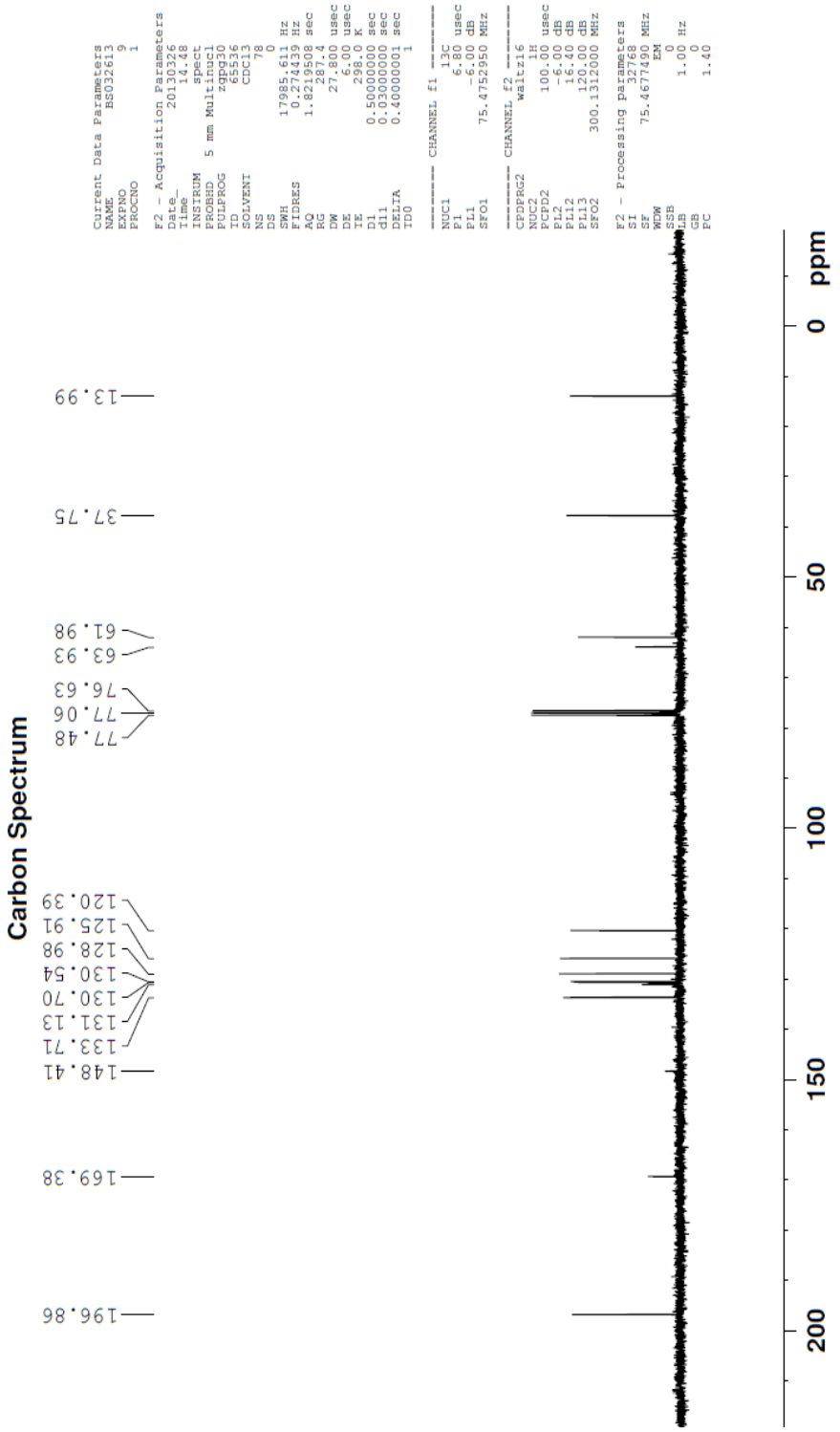
Compound **13′i**



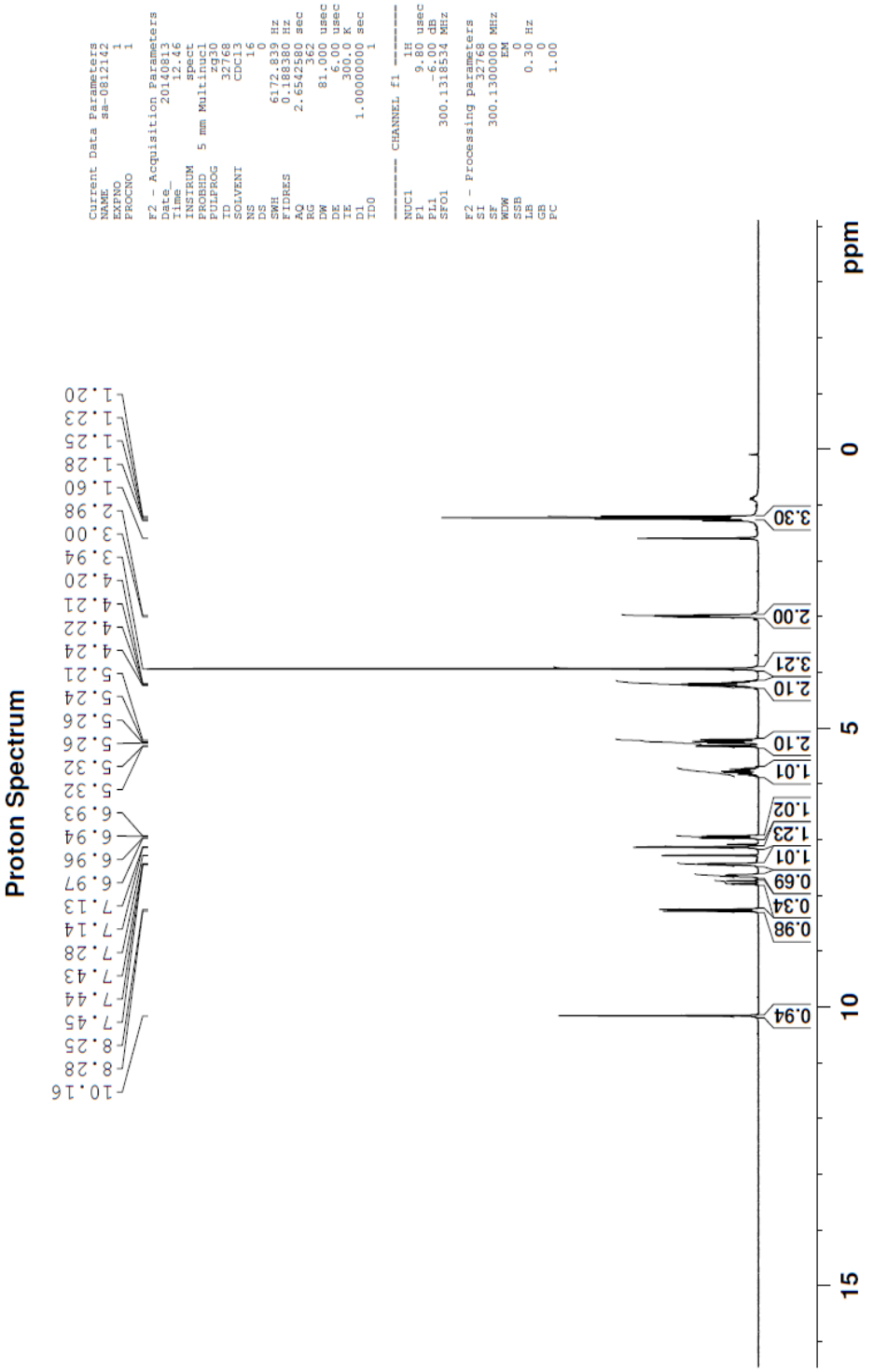
Compound **13j**



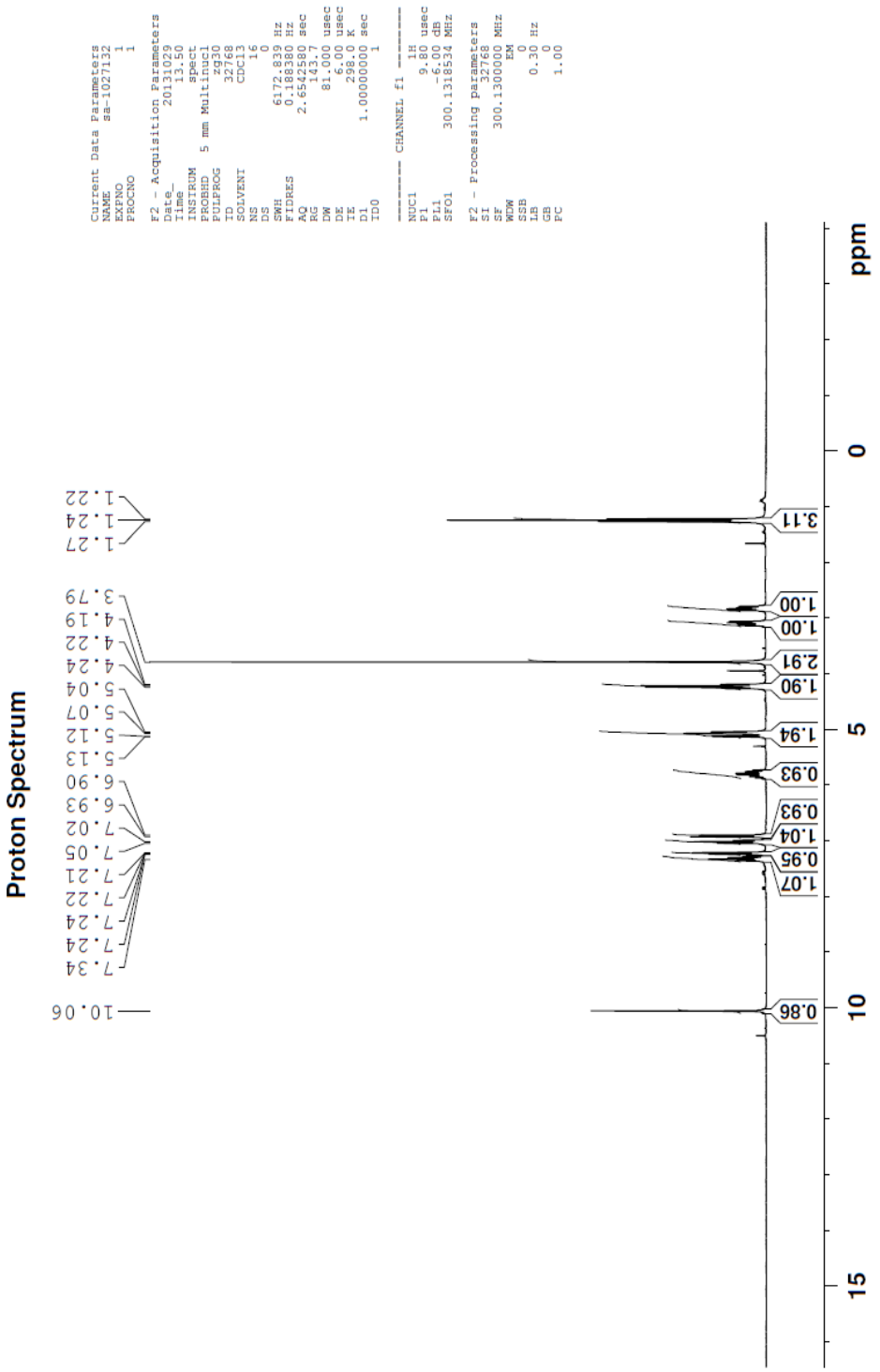
Compound **13j**



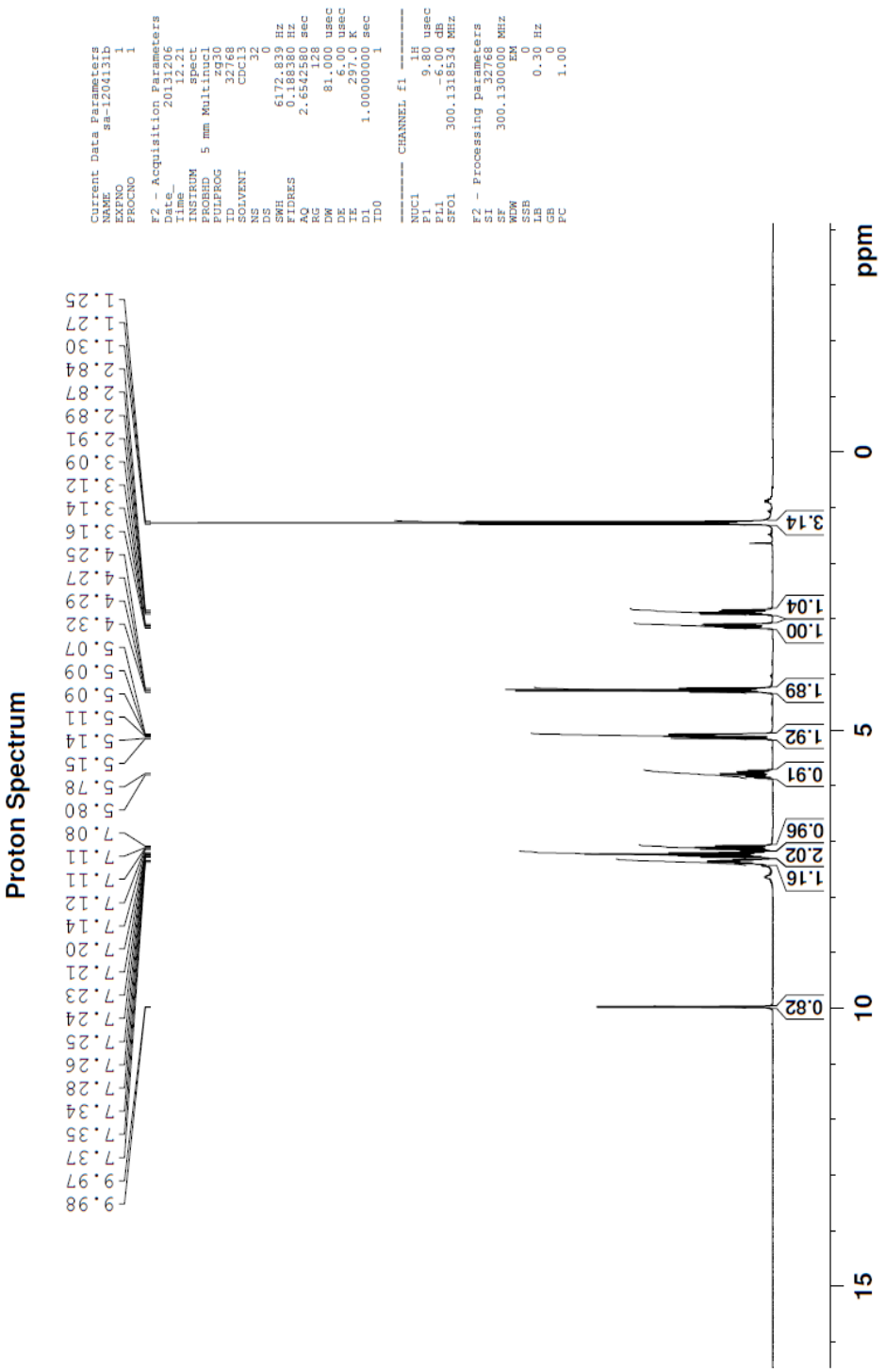
Compound **13k**



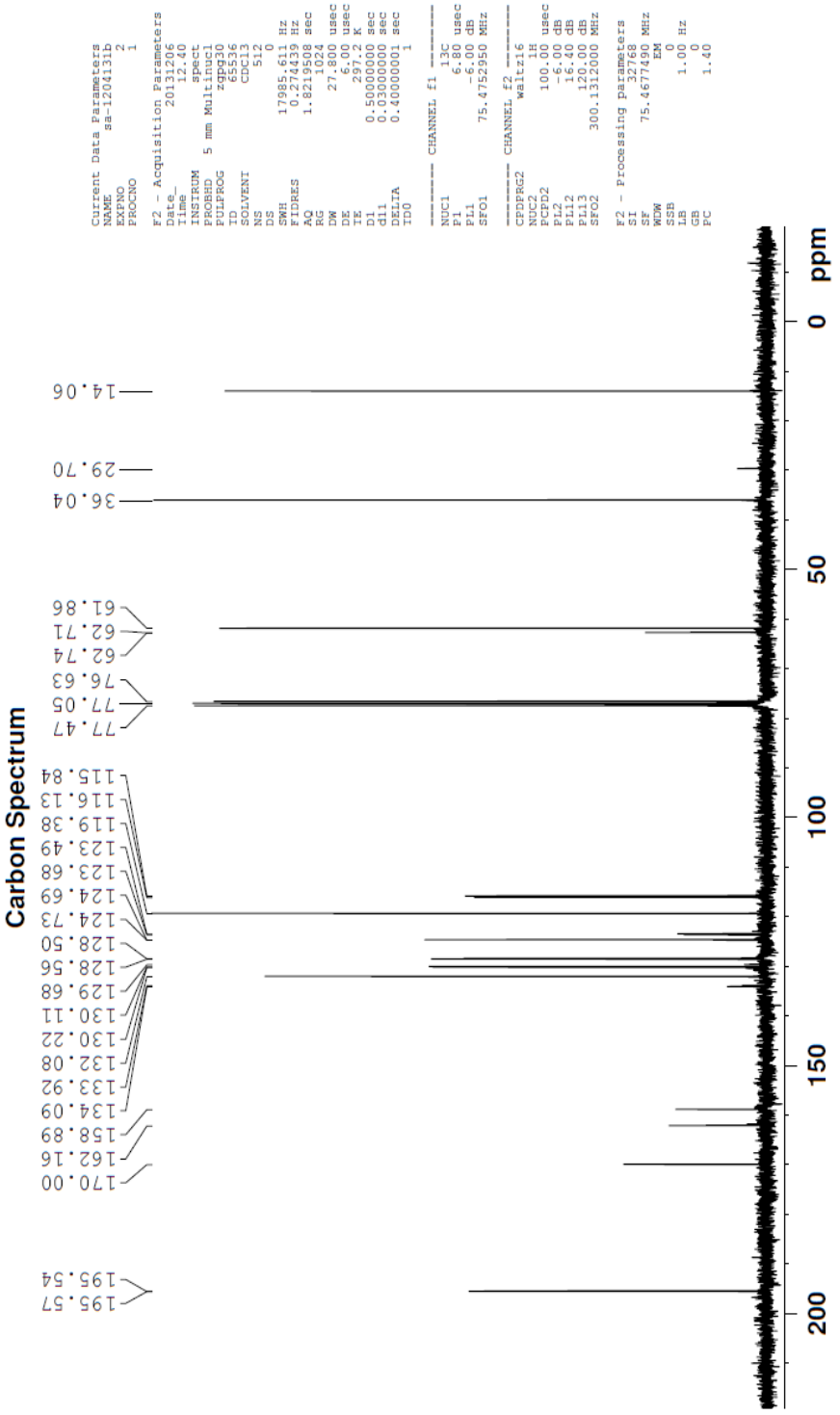
Compound **13l**



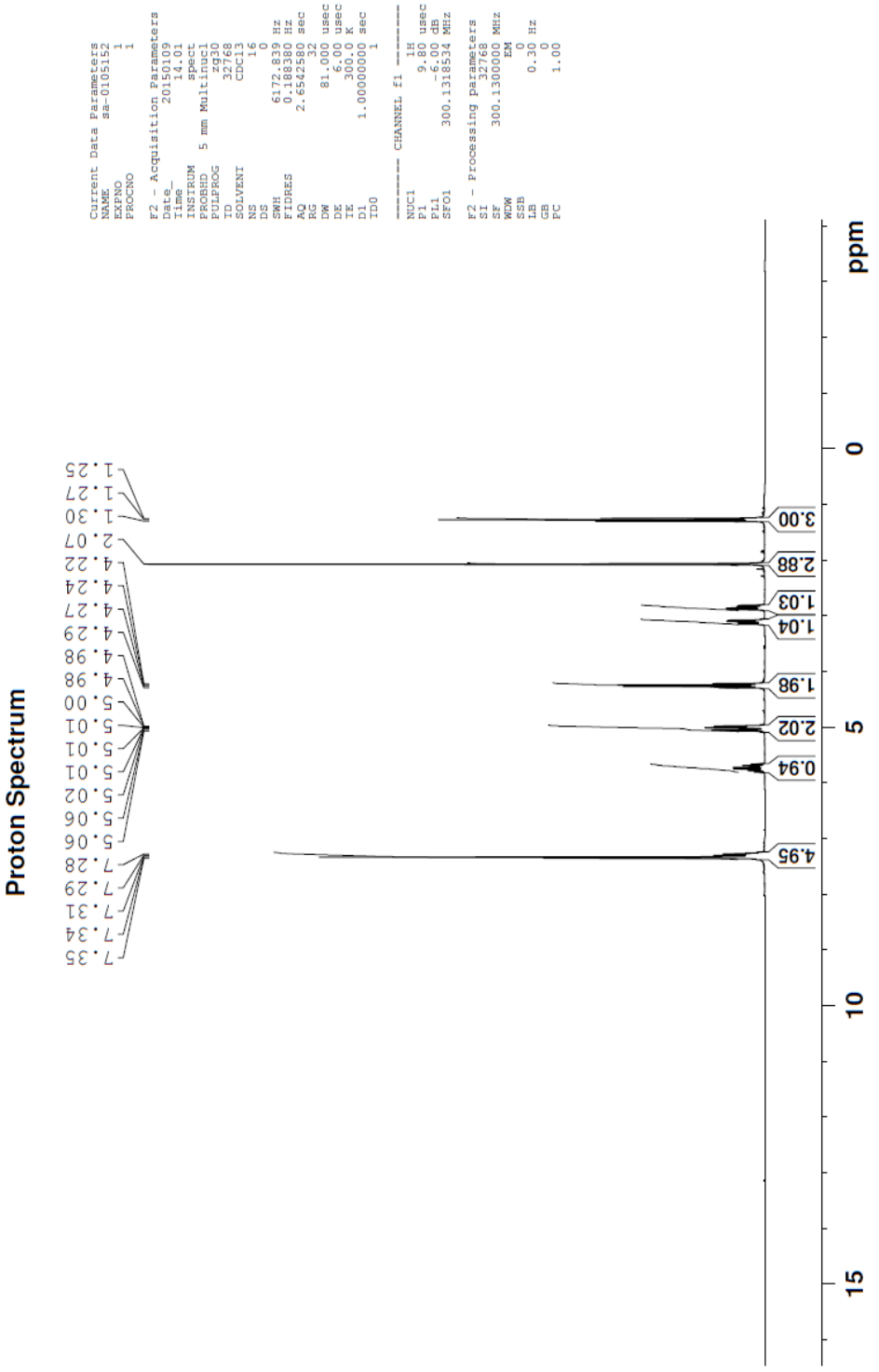
Compound **13m**



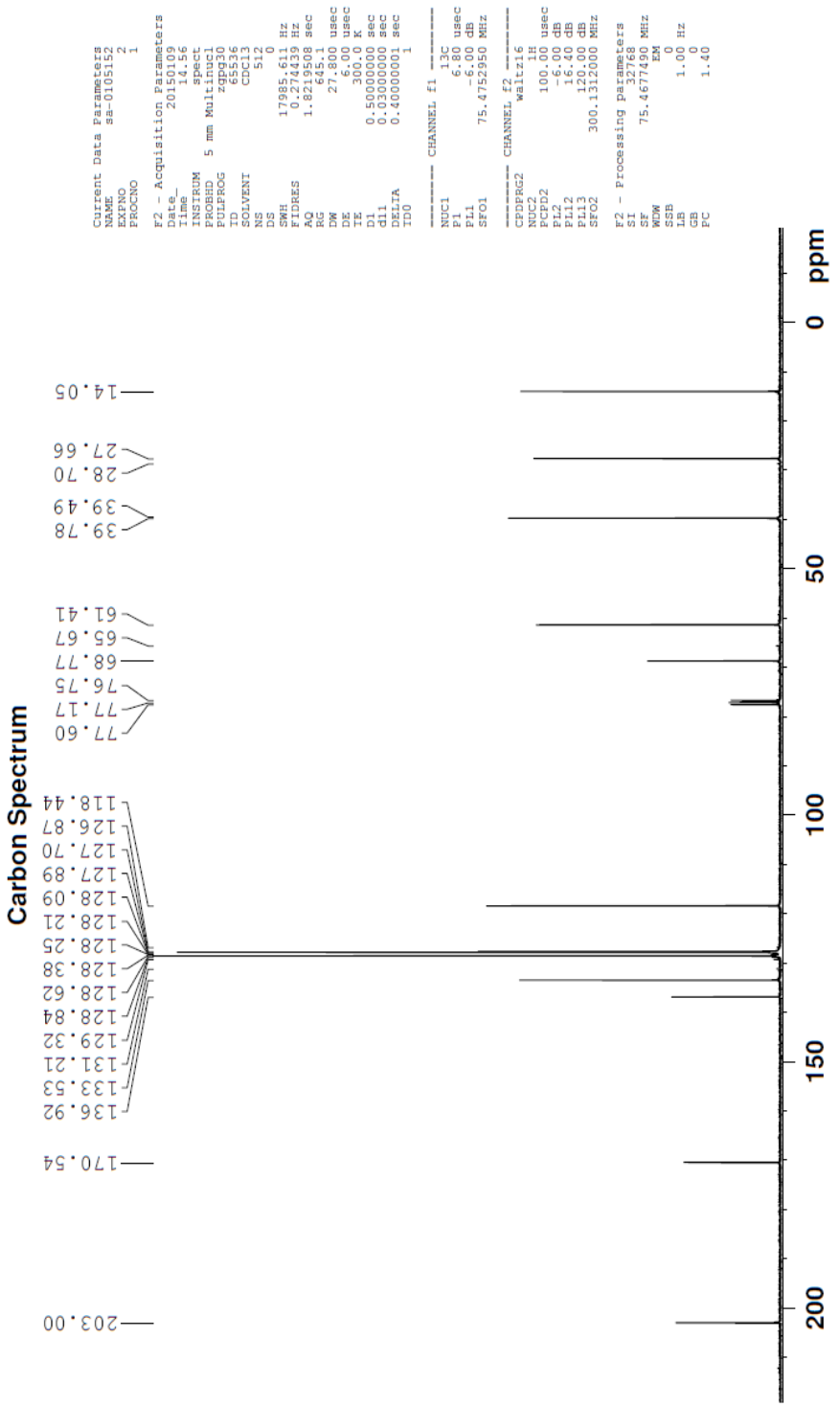
Compound **13m**



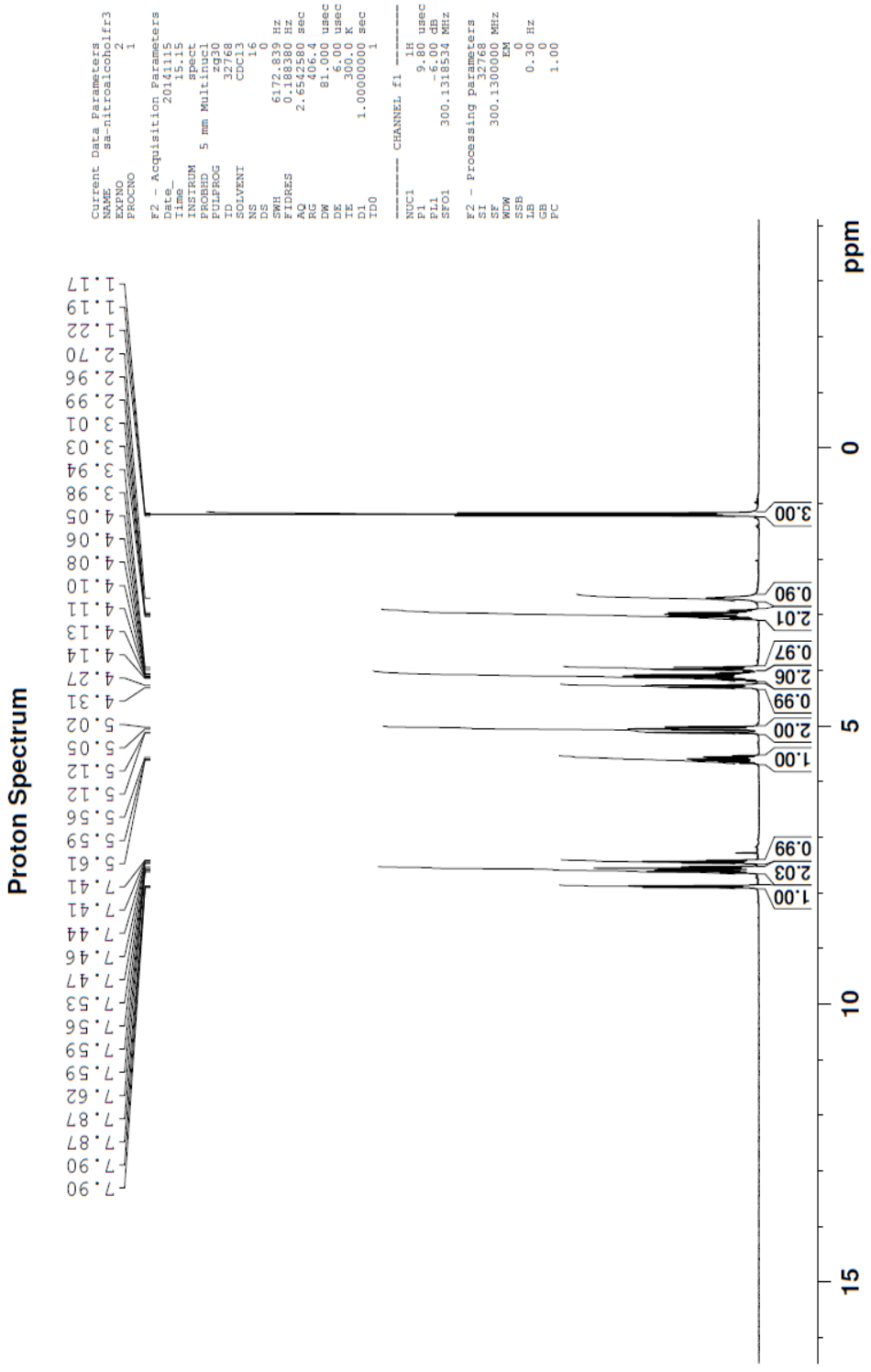
Compound **20**


Proton Spectrum
ppm
0
5
10
15
3.00
2.88
1.03
1.04
1.98
2.02
0.94
4.95
1.25
1.27
1.30
2.07
4.22
4.24
4.27
4.29
4.98
4.98
5.00
5.01
5.01
5.01
5.02
5.06
5.06
7.28
7.29
7.31
7.34
7.35
Current Data Parameters
NAME sa-0105152
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150109
Time 14.01
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 2.654252 sec
RG 81.000
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

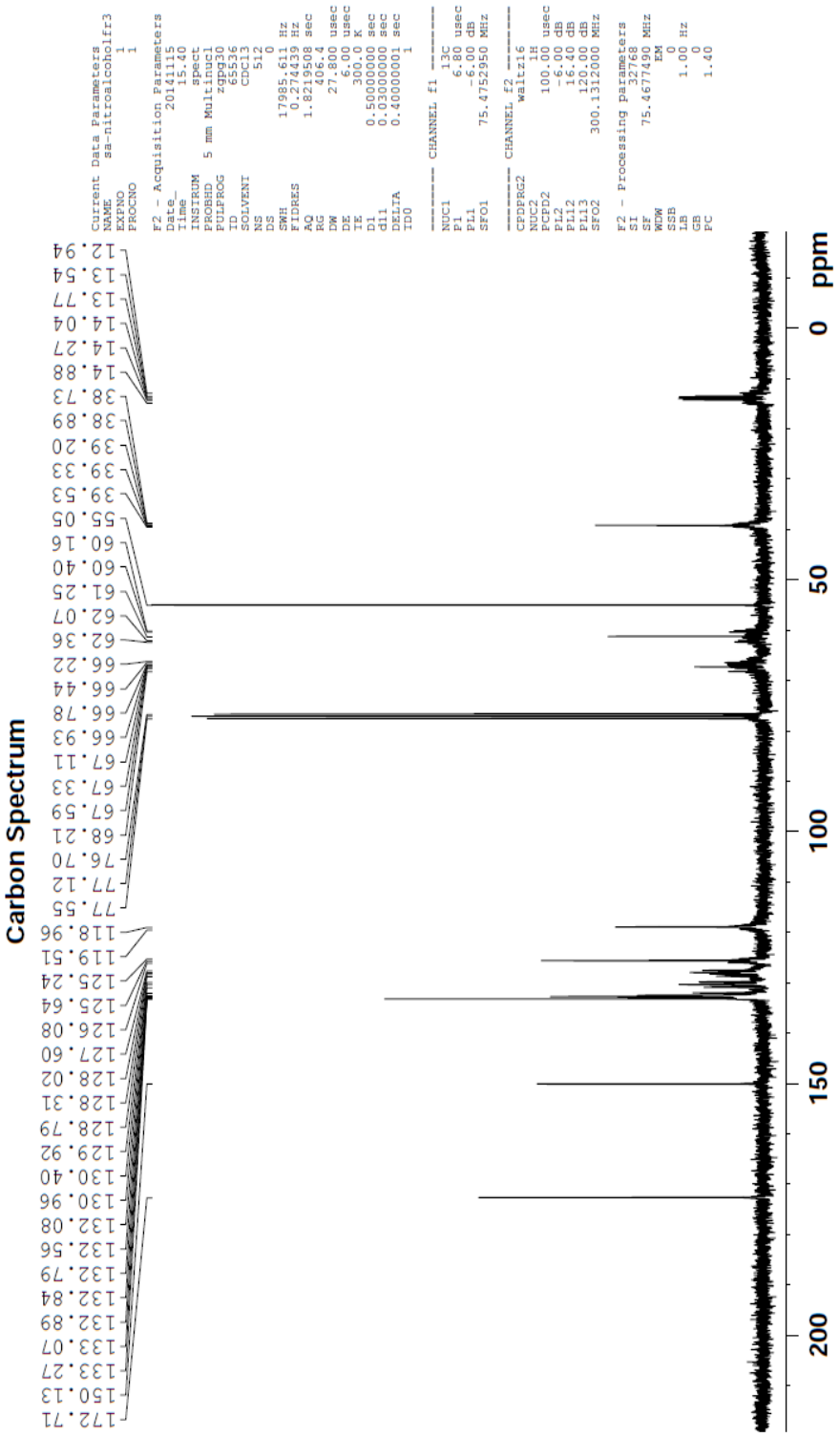
Compound **20**


Carbon Spectrum
ppm
0
50
100
150
200
14.05
27.66
28.70
39.49
39.78
61.41
65.67
68.77
76.75
77.17
77.60
118.44
126.87
127.70
127.89
128.09
128.21
128.25
128.38
128.62
128.84
129.32
131.21
133.53
136.92
170.54
203.00
Current Data Parameters
NAME sa-0105152
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150109
Time 14.56
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 645.1
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

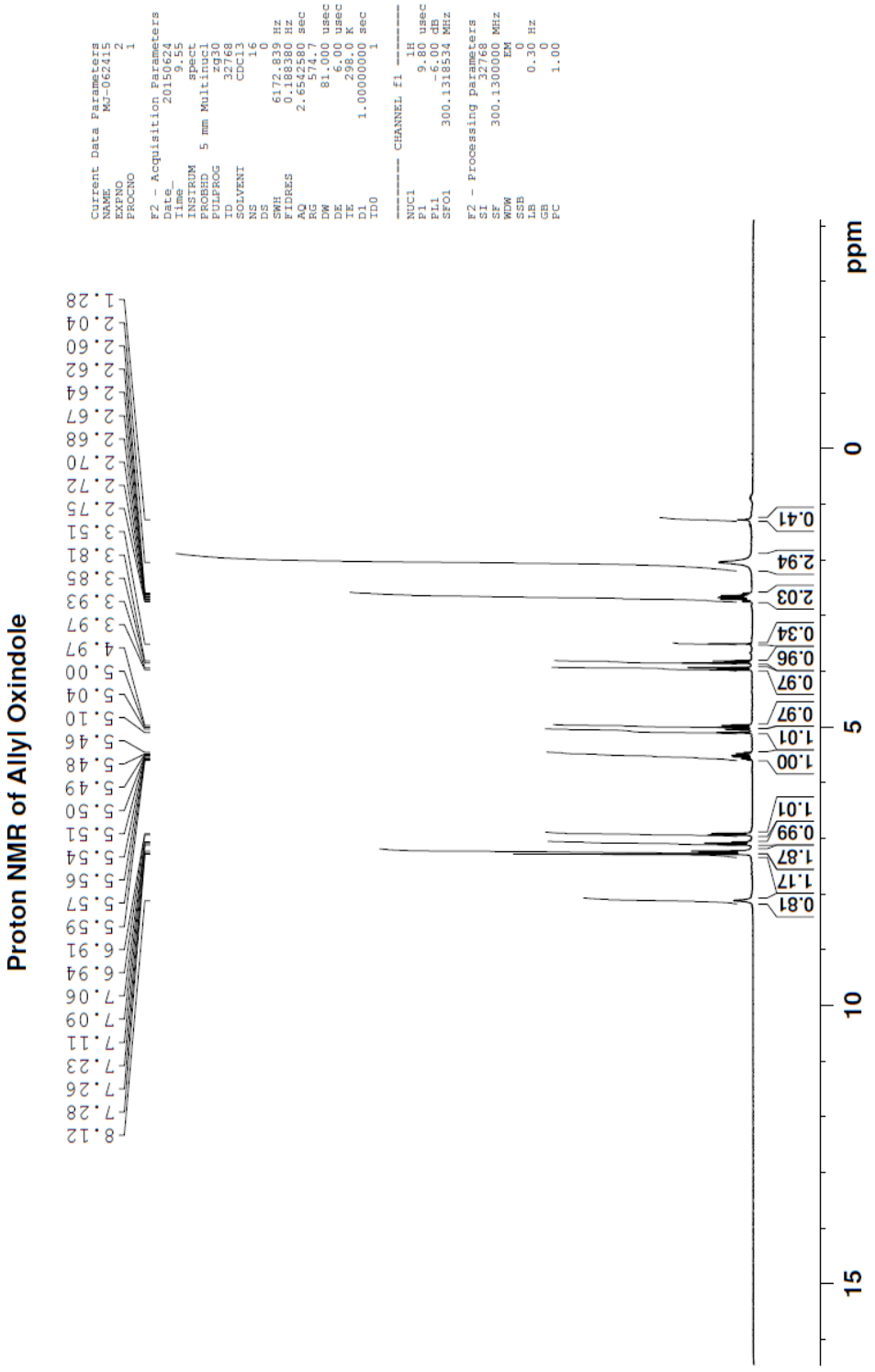
Compound **27**


Proton Spectrum
Current Data Parameters
NAME sa-nitroalcohol1fr3
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141115
Time 15.15
INSTRUM spect
PROBHD 5 mm Multinuc1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542464 sec
RG 64
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
ppm
0
5
10
15
3.00
0.90
2.01
0.97
2.06
0.99
2.00
1.00
0.99
2.03
1.00
7.90
7.87
7.87
7.62
7.59
7.59
7.56
7.53
7.47
7.46
7.44
7.41
7.41
5.61
5.59
5.56
5.12
5.12
5.05
5.02
4.31
4.27
4.14
4.13
4.11
4.10
4.08
4.06
4.05
3.98
3.94
3.03
3.01
2.99
2.96
2.70
1.22
1.19
1.17

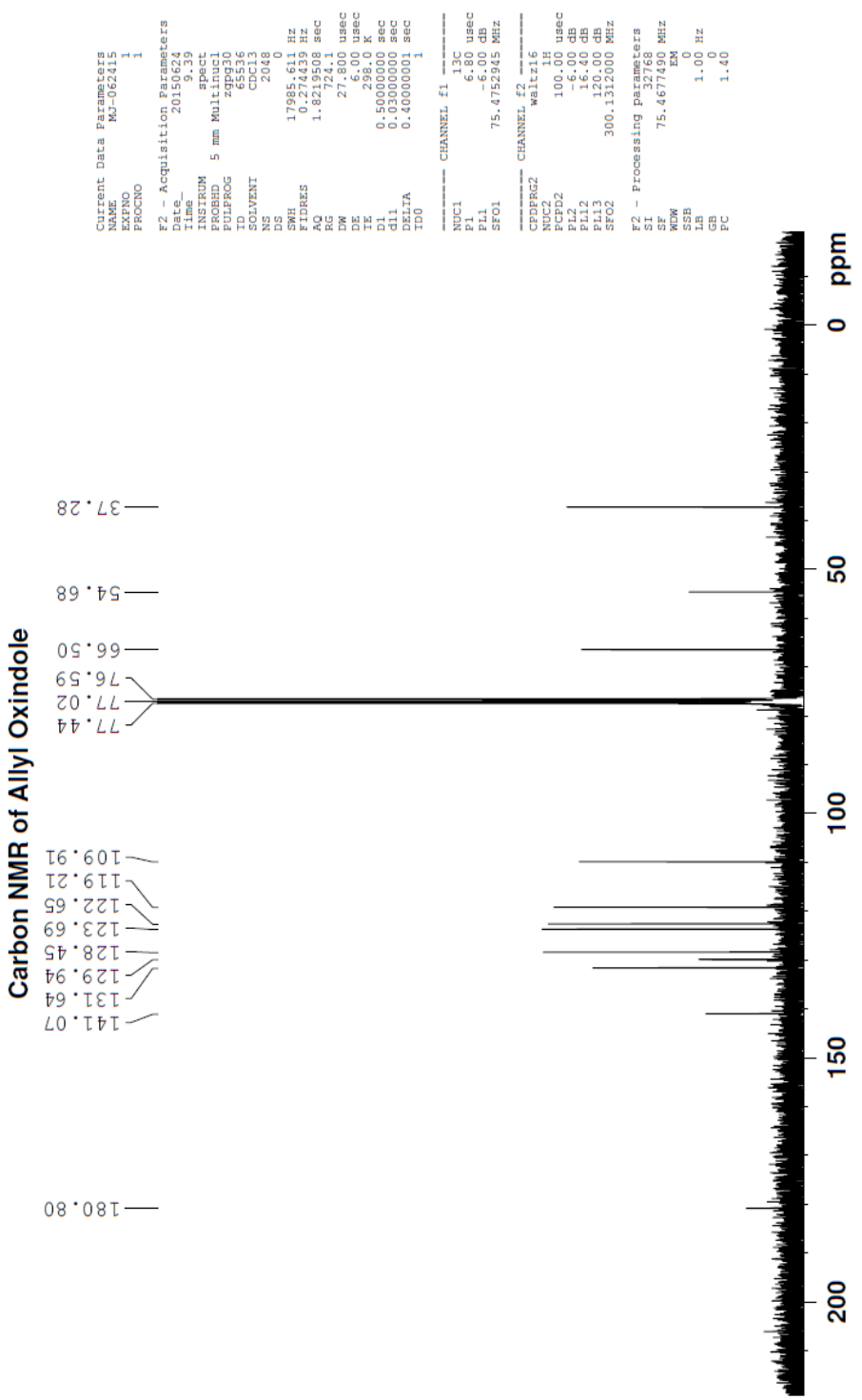
Compound **27**


Carbon Spectrum
ppm
0
50
100
150
200
12.94
13.54
13.77
14.04
14.27
14.88
38.73
38.89
39.20
39.33
39.53
55.05
60.16
60.40
61.25
62.07
62.36
66.22
66.44
66.78
66.93
67.11
67.33
67.59
68.21
76.70
77.12
77.55
118.96
119.51
125.24
125.64
126.08
127.60
128.02
128.31
128.79
129.92
130.40
130.96
132.08
132.56
132.79
132.84
132.89
133.07
133.27
150.13
172.71

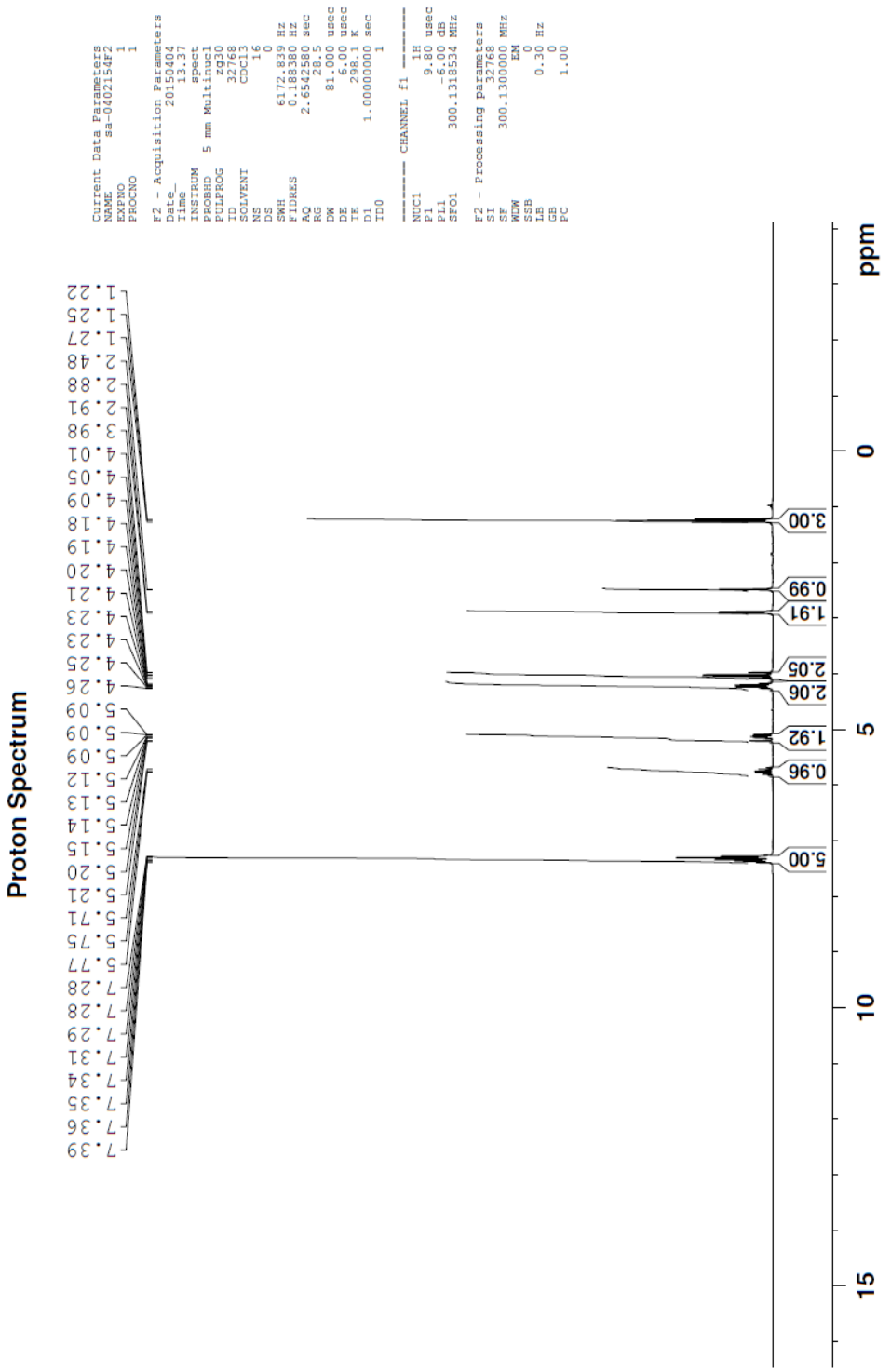
Compound **29**


Proton NMR of Allyl Oxindole
Current Data Parameters
NAME MJ-062415
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150624
Time 9.55
INSTRUM spect
PROBHD 5 mm Multinuc1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542207 sec
RG 64
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
0.41
2.94
2.03
0.34
0.96
0.97
0.97
1.00
1.01
1.01
0.99
1.87
1.17
0.81
ppm
0
5
10
15

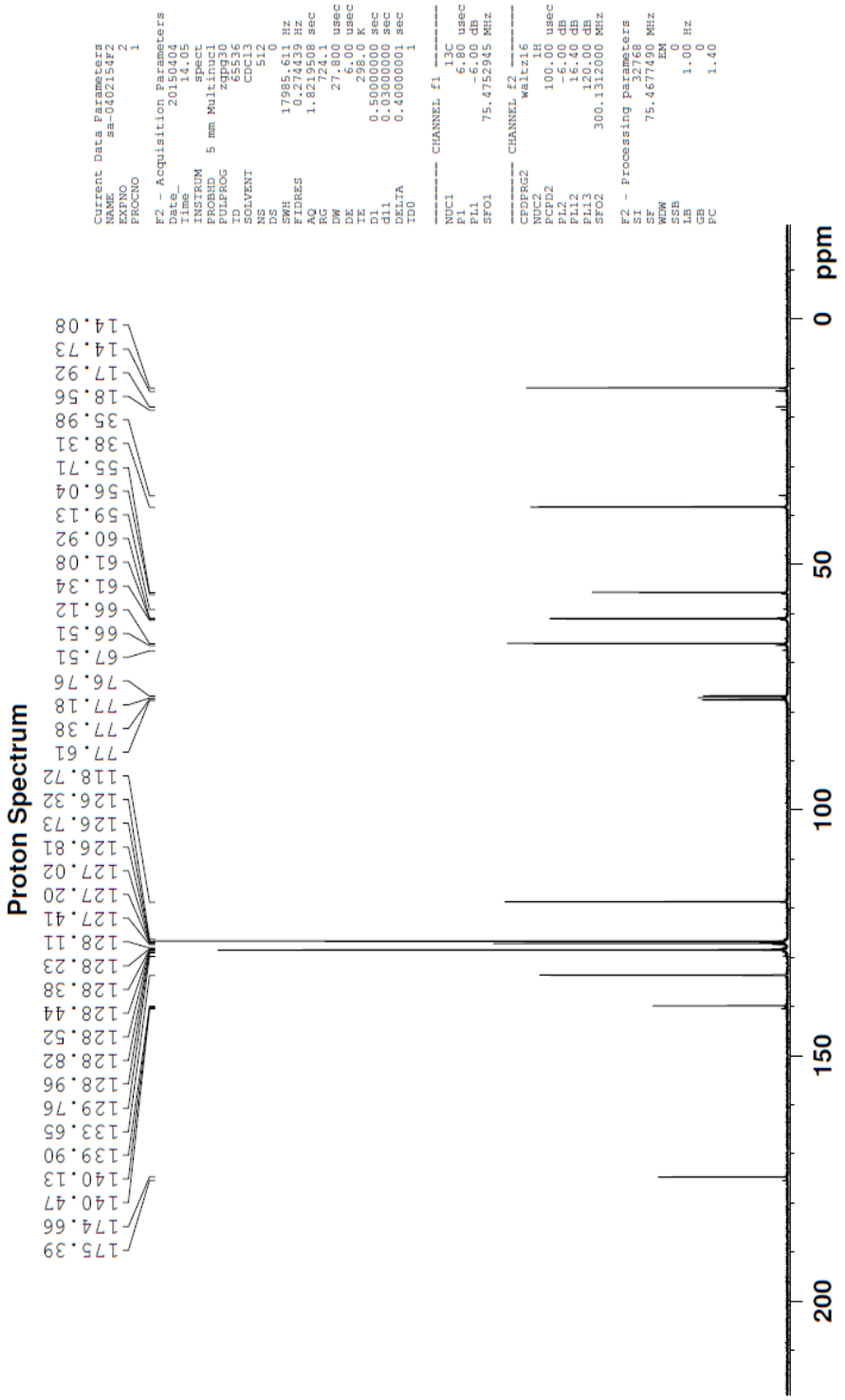
Compound **29**


Carbon NMR of Allyl Oxindole
180.80
141.07
131.64
129.94
128.45
123.69
122.65
119.21
109.91
77.44
77.02
76.59
66.50
54.68
37.28
ppm
200
150
100
50
0

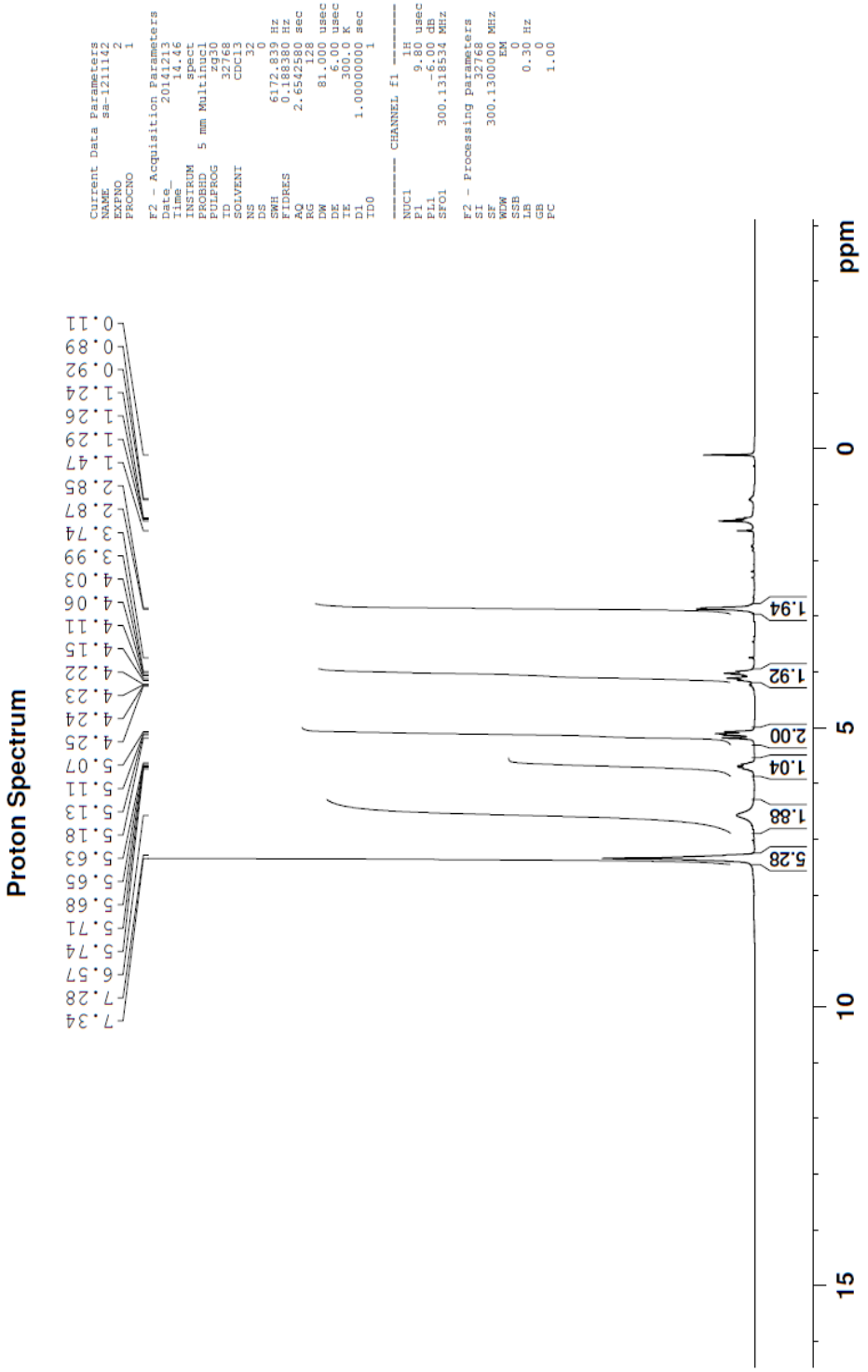
Compound **35**


Proton Spectrum
ppm
0
5
10
15
3.00
0.99
1.91
2.06
2.05
1.92
0.96
5.00
Current Data Parameters
NAME sa-04021542
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150404
Time 13.37
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 16
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542250 sec
RG 285
DW 81.000 usec
DE 6.00 usec
TE 298.1 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

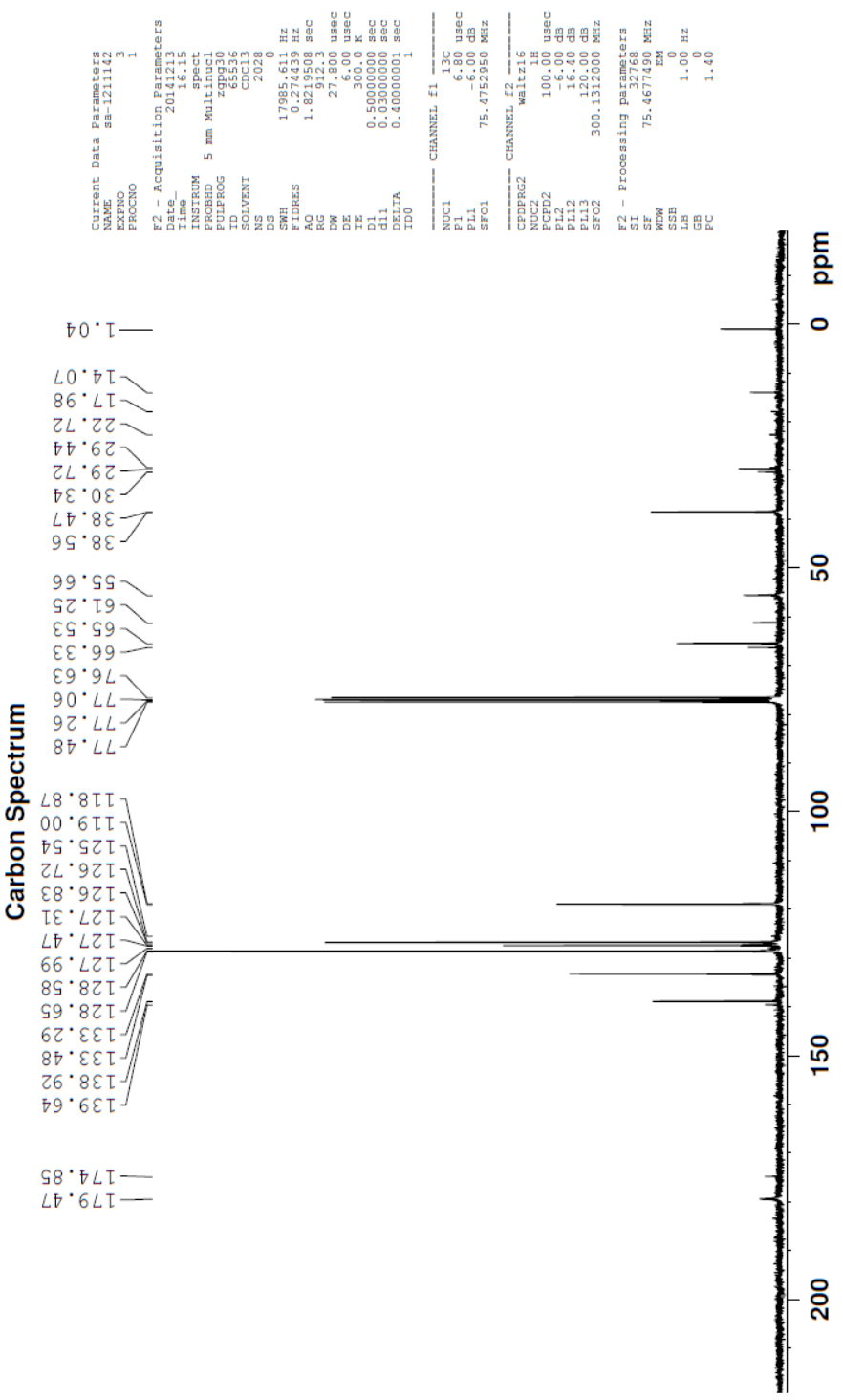
Compound **35**


Proton Spectrum
ppm
0
50
100
150
200
14.08
14.73
17.92
18.56
35.98
38.31
55.71
56.04
59.13
60.92
61.08
61.34
66.12
66.51
67.51
76.76
77.18
77.38
77.61
118.72
126.32
126.73
126.81
127.02
127.20
127.41
128.11
128.23
128.38
128.44
128.52
128.82
128.96
129.76
133.65
139.90
140.13
140.47
174.66
175.39

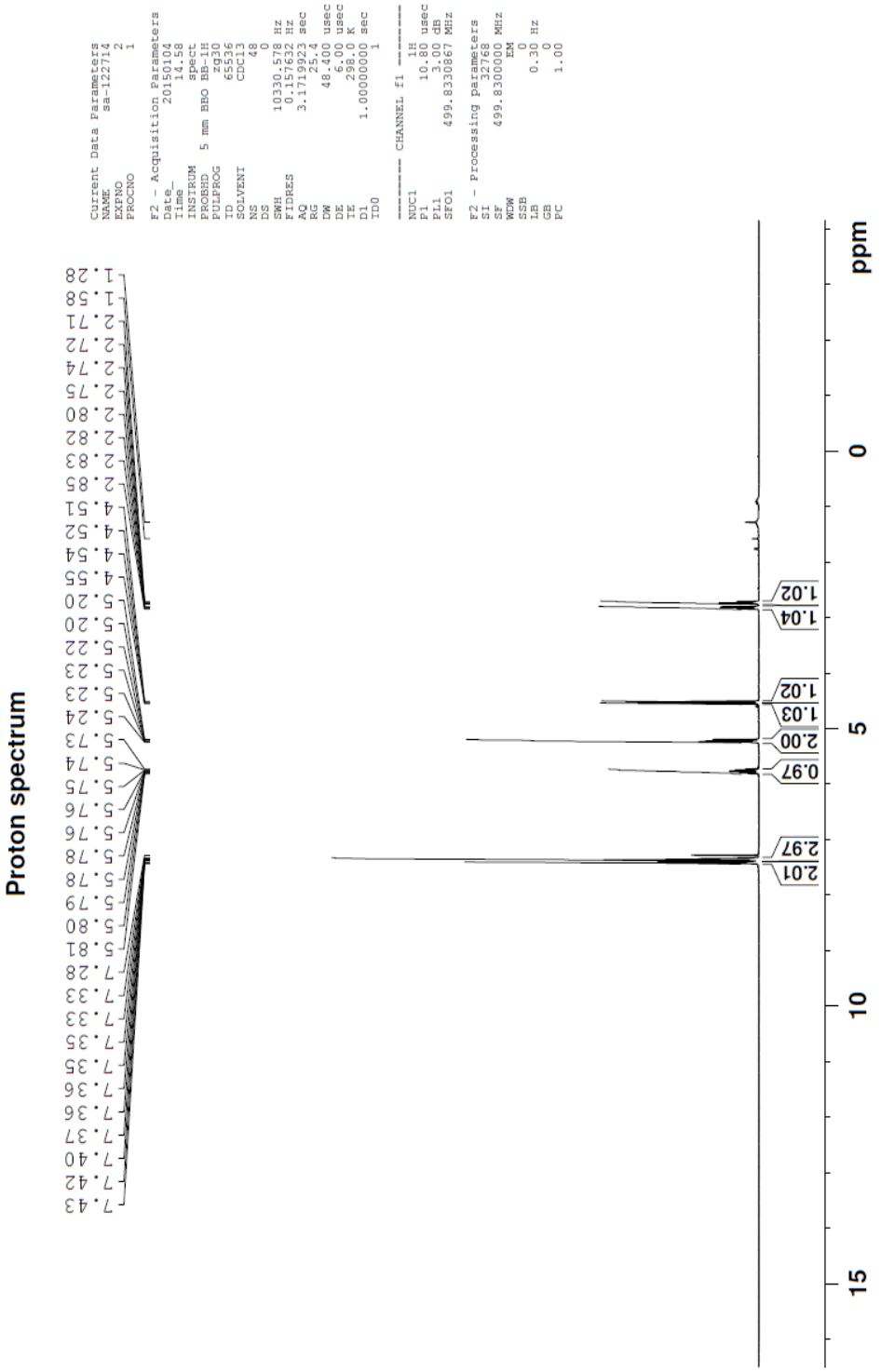
Compound **36**


Proton Spectrum
Current Data Parameters
NAME aa-1211142
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141213
Time 14.16
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
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 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
ppm
0
5
10
15
1.94
1.92
2.00
1.04
1.88
5.28
0.11
0.89
0.92
1.24
1.26
1.29
1.47
2.85
2.87
3.74
3.99
4.03
4.06
4.11
4.15
4.22
4.23
4.24
4.25
5.07
5.11
5.13
5.18
5.63
5.65
5.68
5.71
5.74
6.57
7.28
7.34

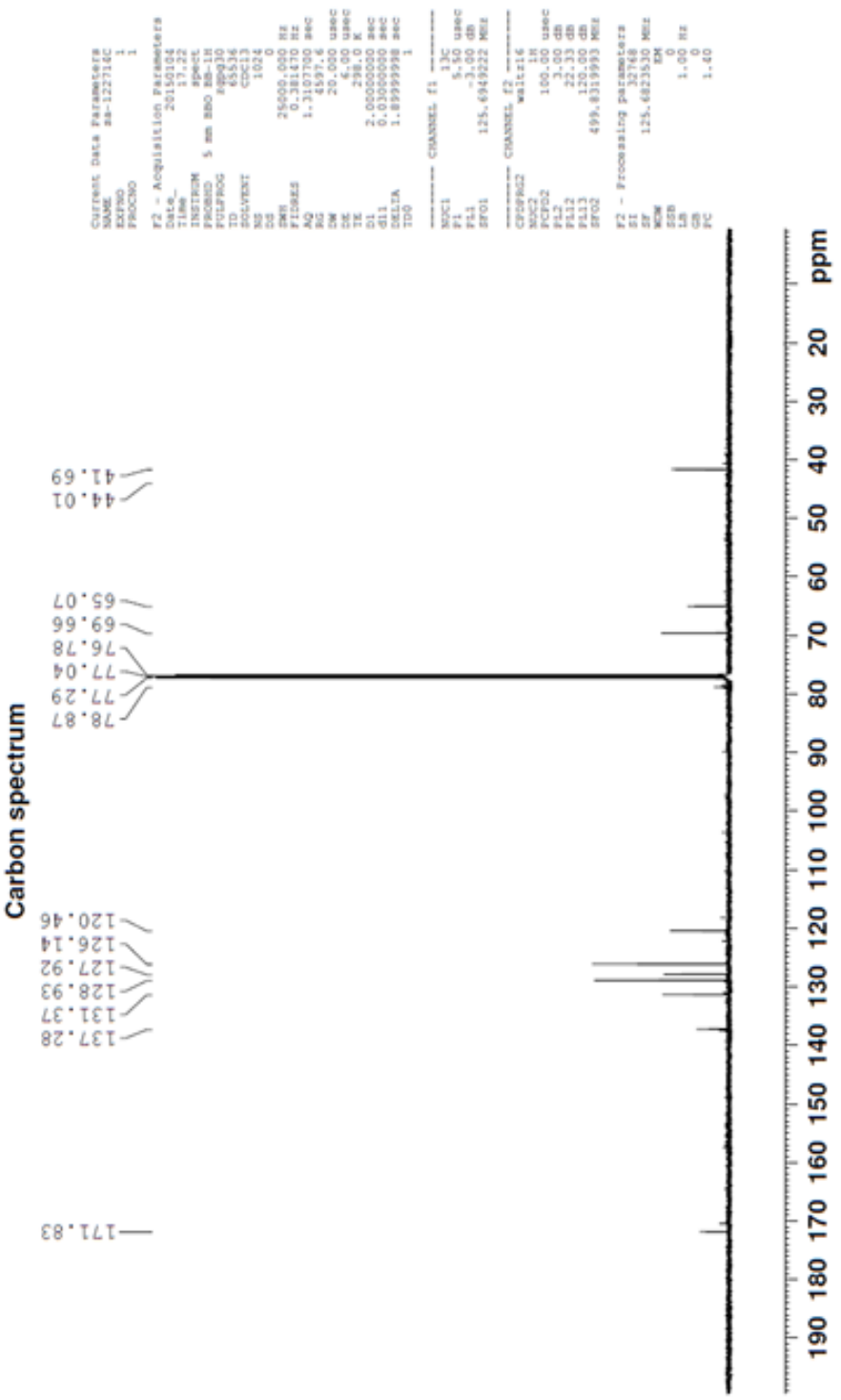
Compound **36**


Carbon Spectrum
ppm
0
50
100
150
200
1.04
14.07
17.98
22.72
29.44
29.72
30.34
38.47
38.56
55.66
61.25
65.53
66.33
76.63
77.06
77.26
77.48
118.87
119.00
125.54
126.72
126.83
127.31
127.47
127.99
128.58
128.65
133.29
133.48
138.92
139.64
174.85
179.47

Compound **37**


Proton spectrum
Current Data Parameters
NAME sa-122714
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150104
Time 14.58
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 48
DS 0
SWH 10330.578 Hz
FIDRES 0.157523 Hz
AQ 3.1719923 sec
RG 25.4
DW 48.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.80 usec
PL1 3.00 dB
SFO1 499.8330867 MHz
F2 - Processing parameters
SI 32768
SF 499.8300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.02
1.04
1.02
1.03
2.00
0.97
2.97
2.01
ppm
0
5
10
15

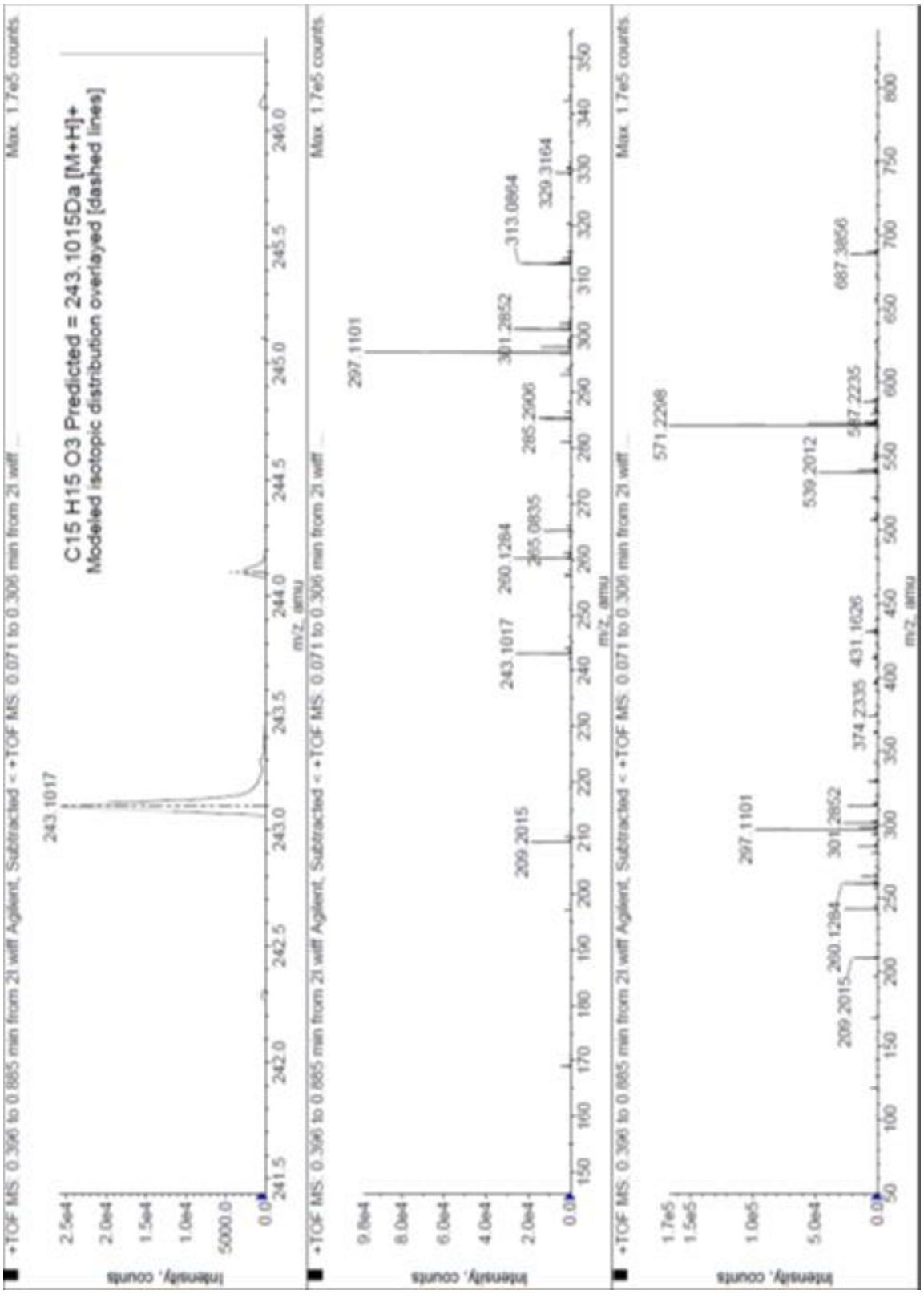
Compound **37**


Carbon spectrum
ppm
41.69
44.01
65.07
69.66
76.78
77.04
77.29
78.87
120.46
126.14
127.92
128.93
131.37
137.28
171.83

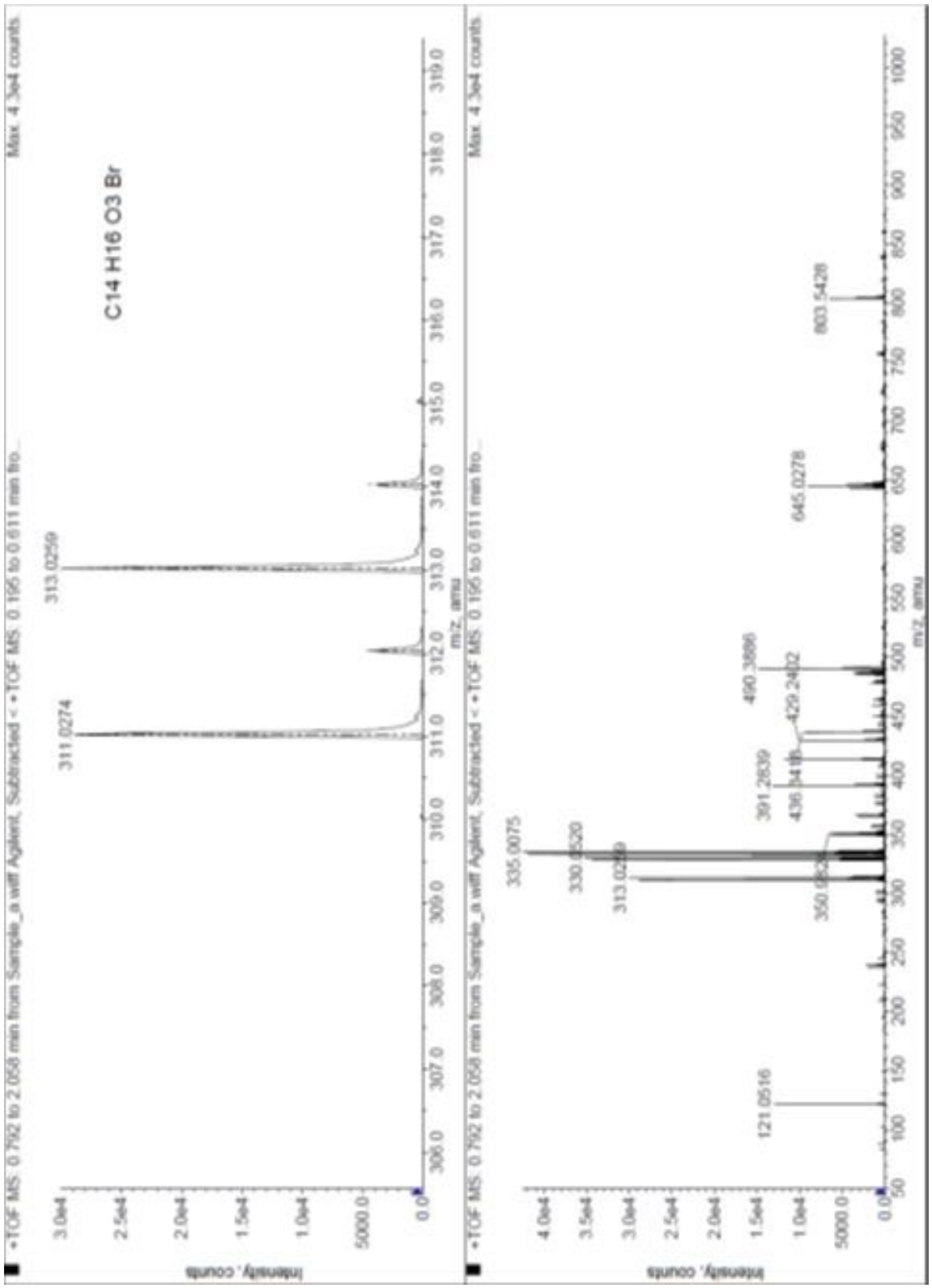
# APPENDIX B:

HRMS Data

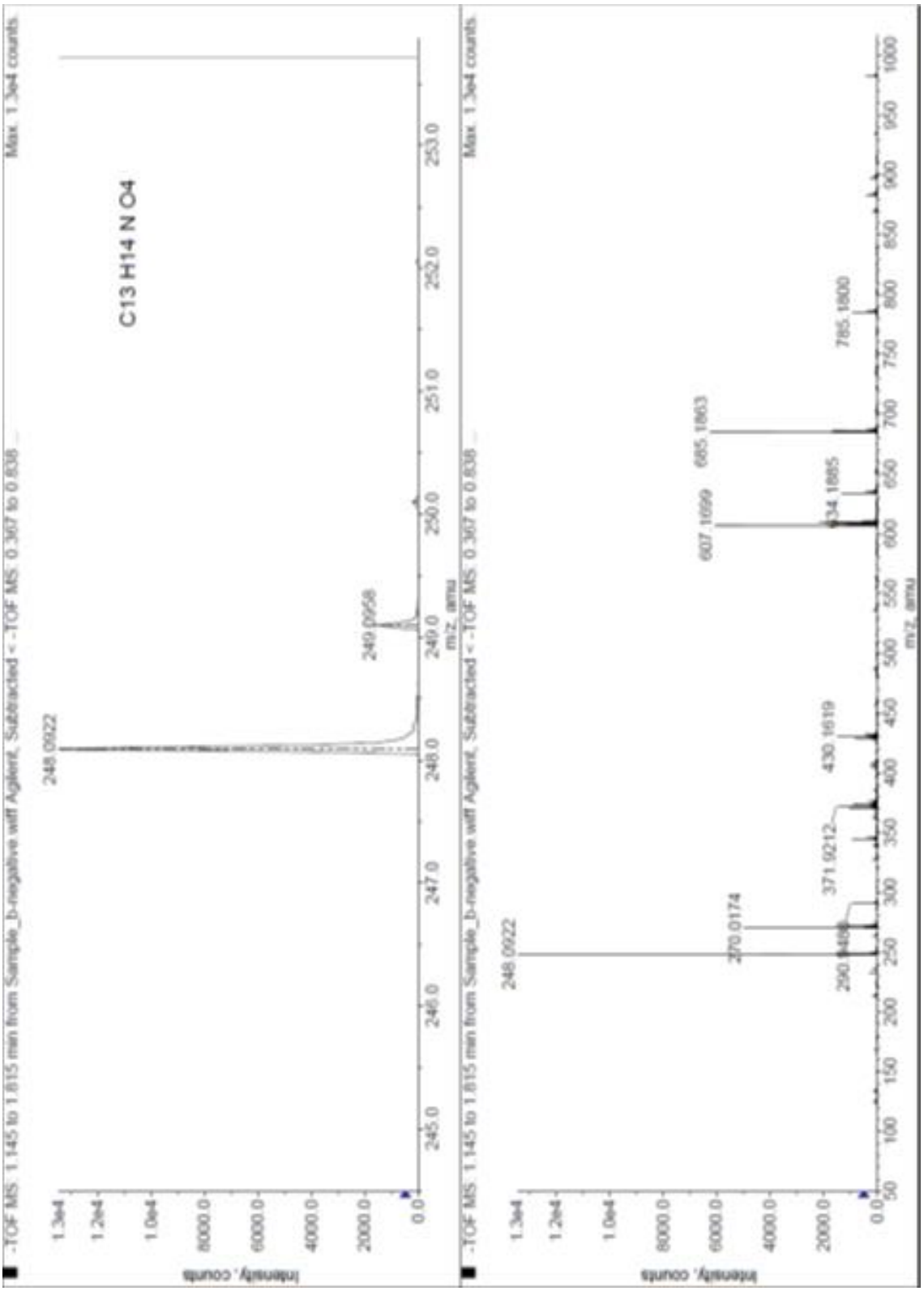
Compound **10h**



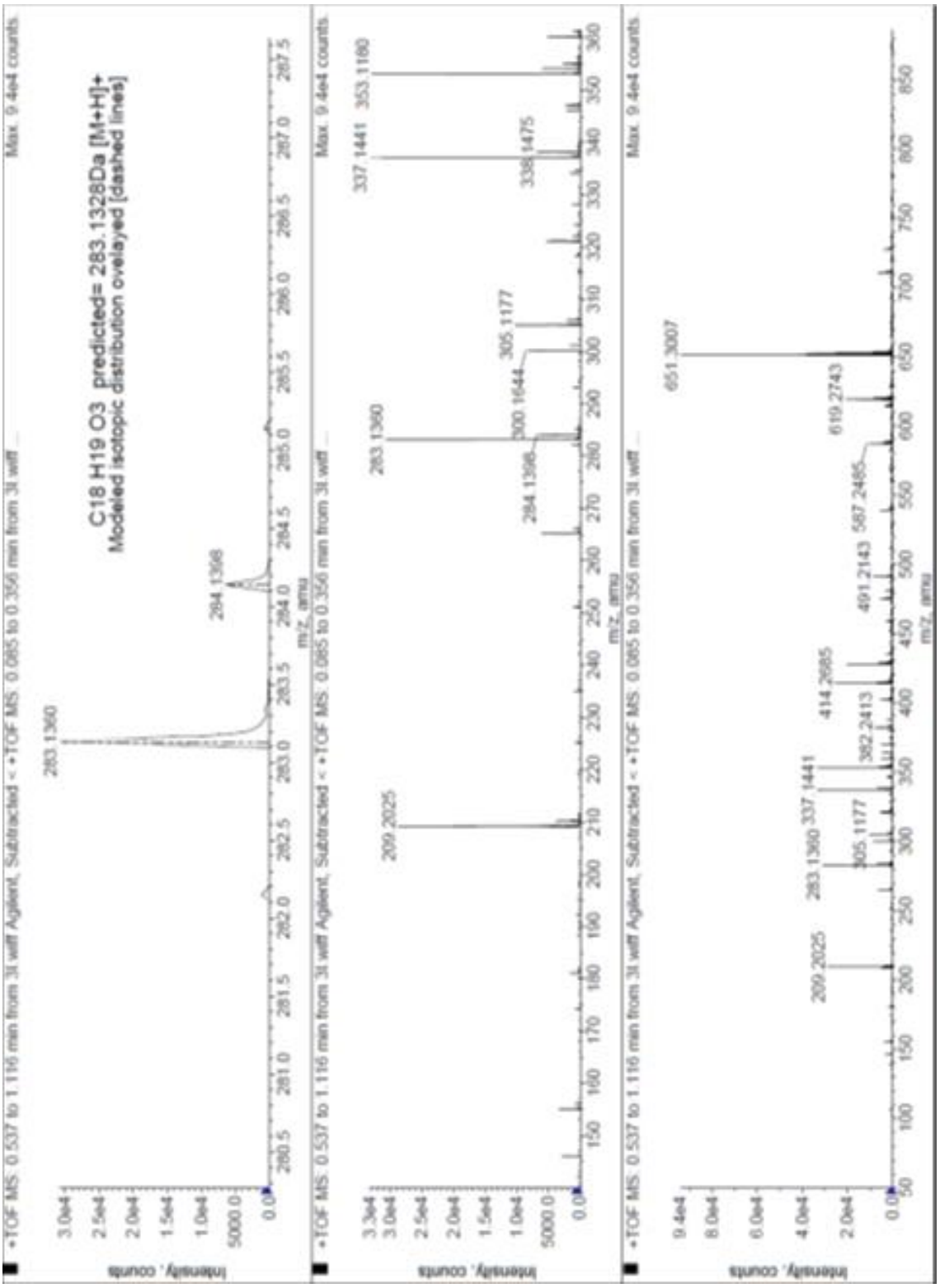
Compound **13f**



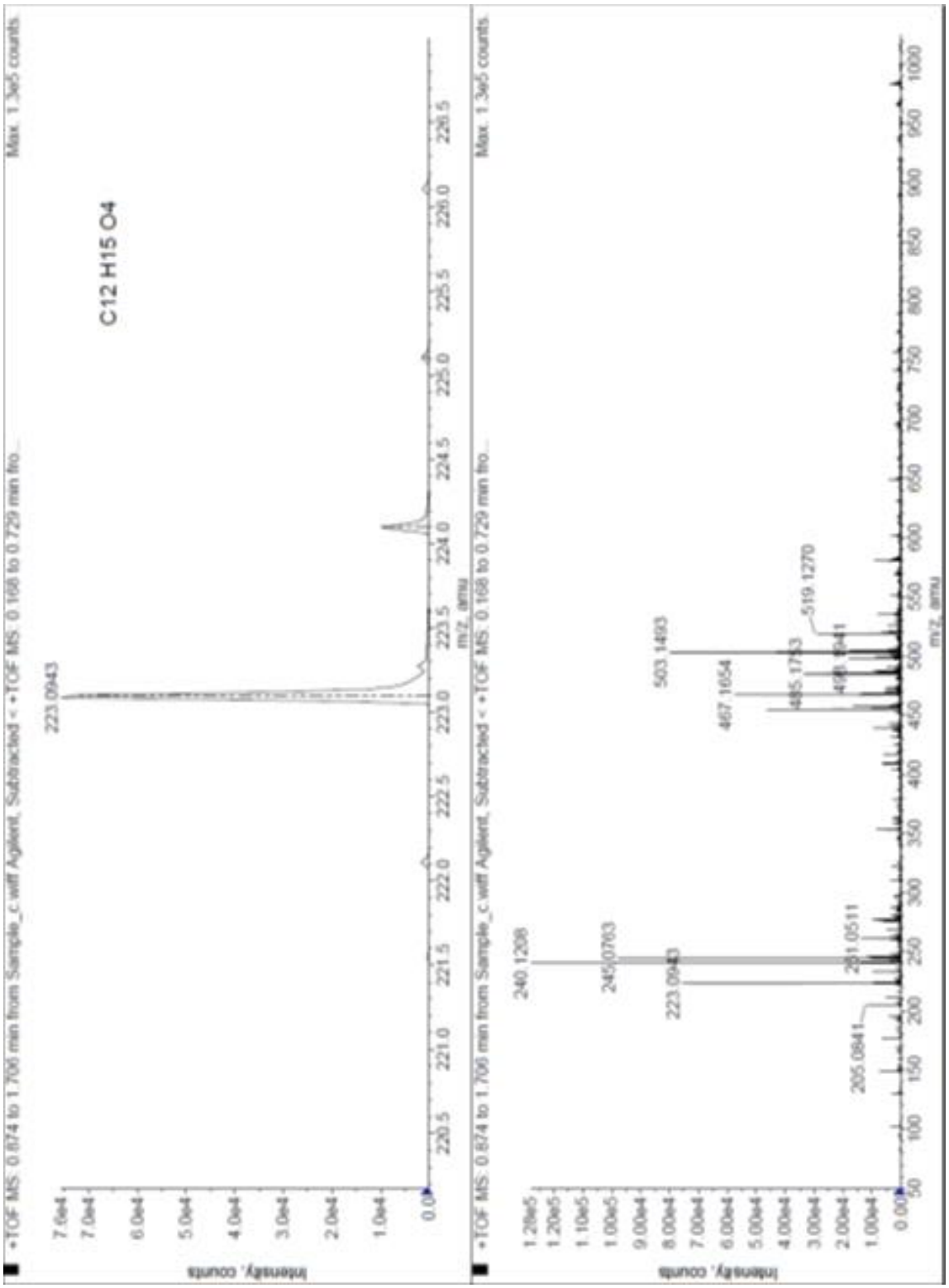
Compound **13g**



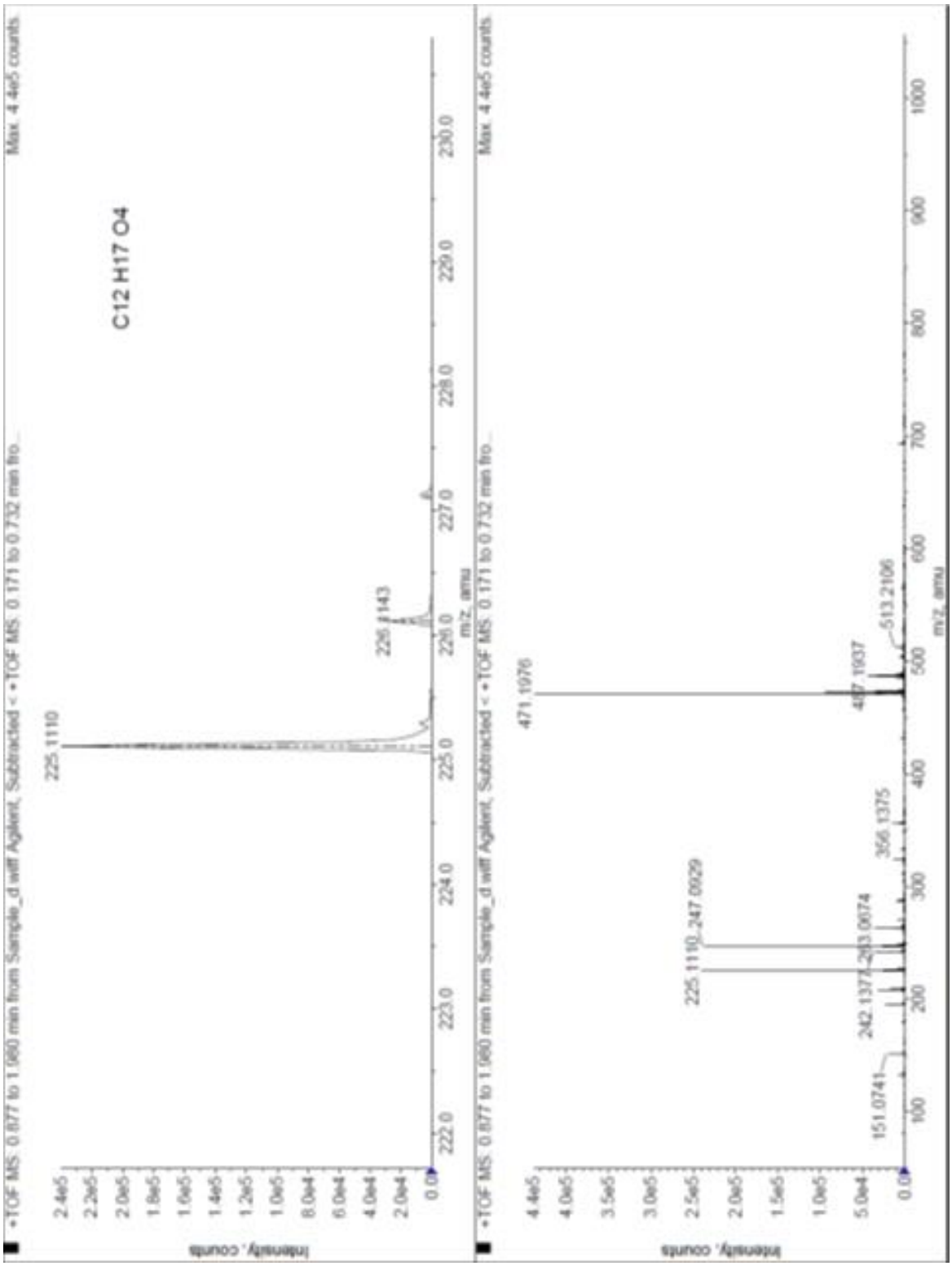
Compound **13h**



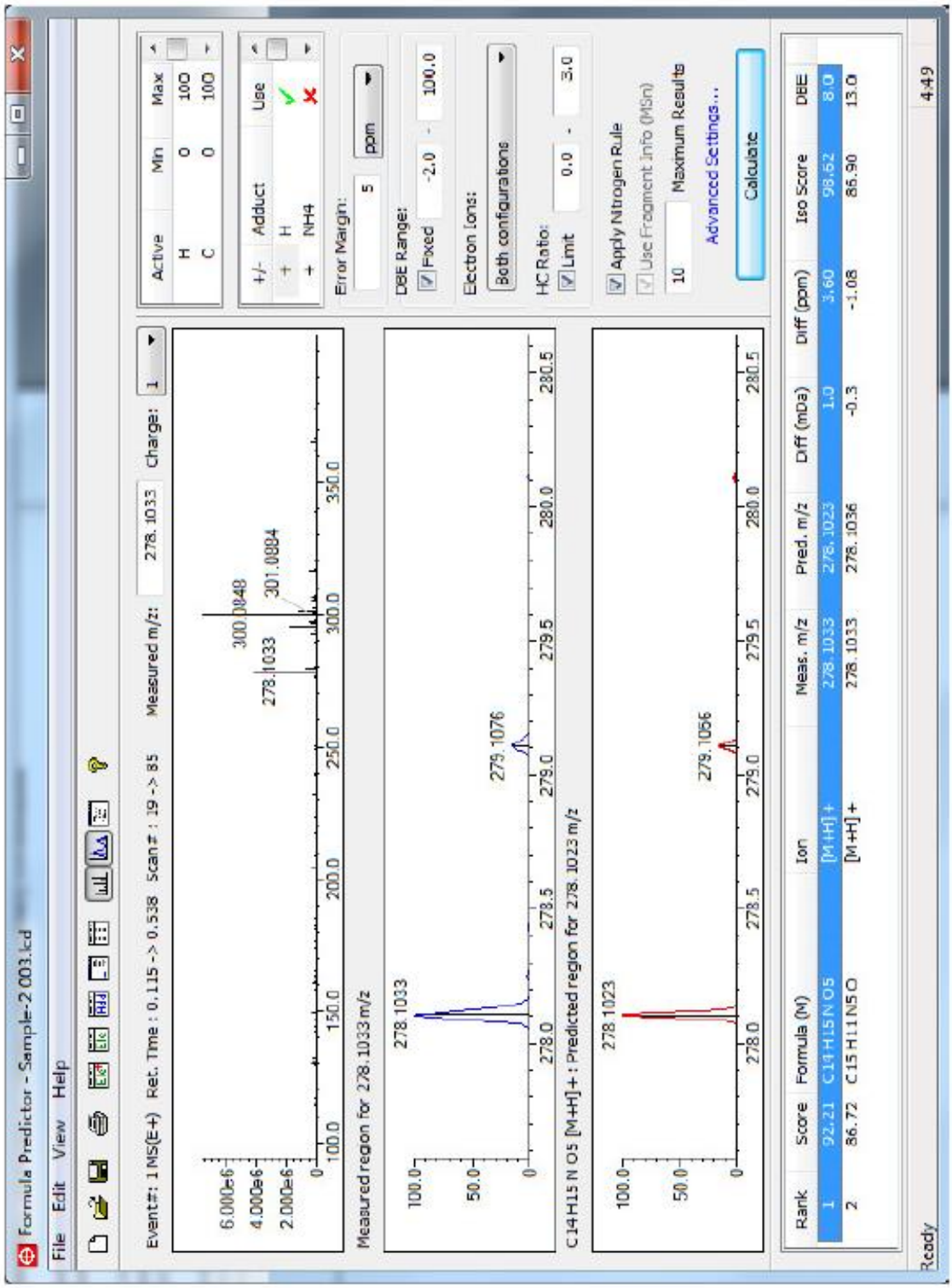
Compound **13i**



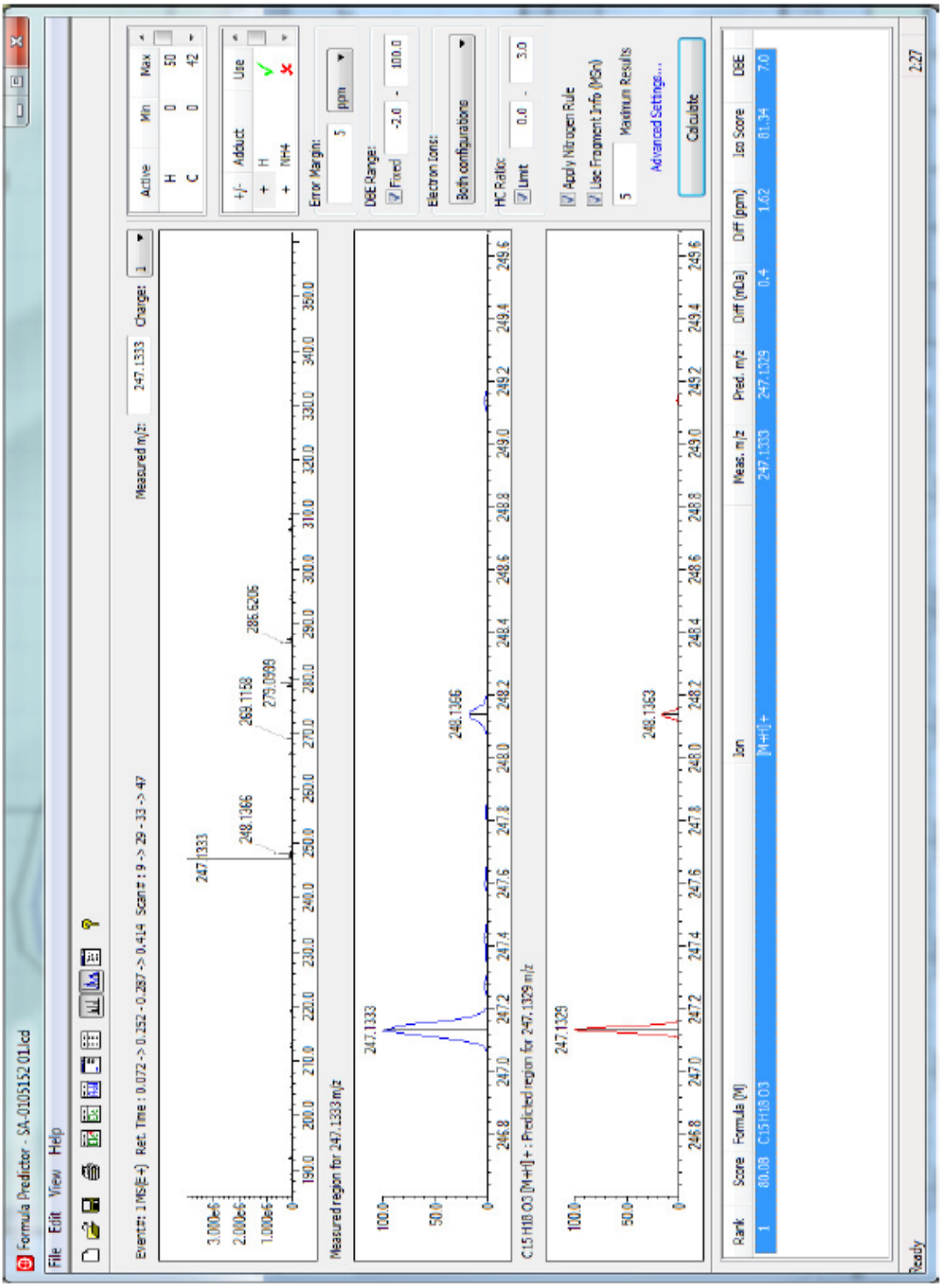
Compound **13′i**



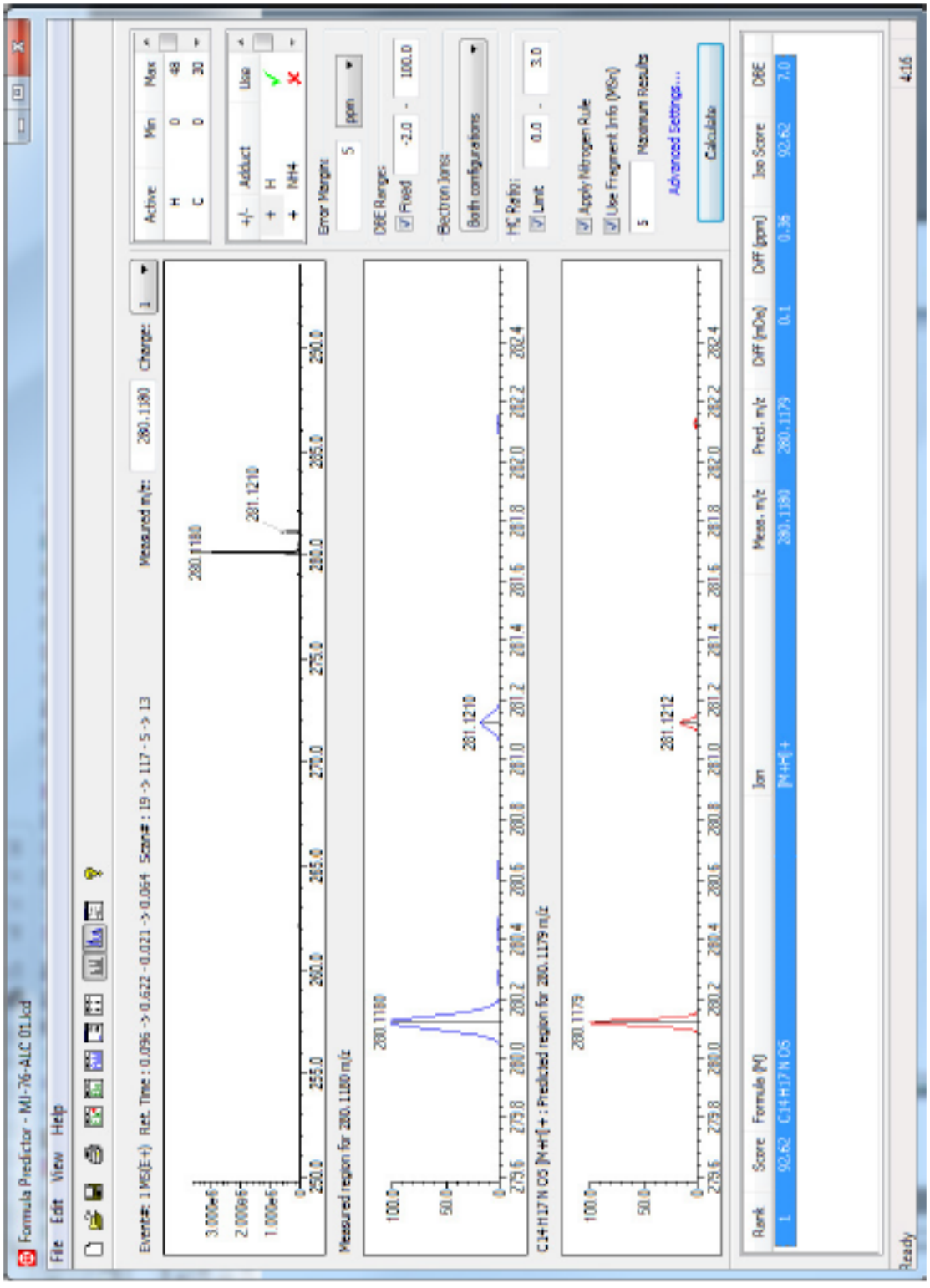
Compound **13j**



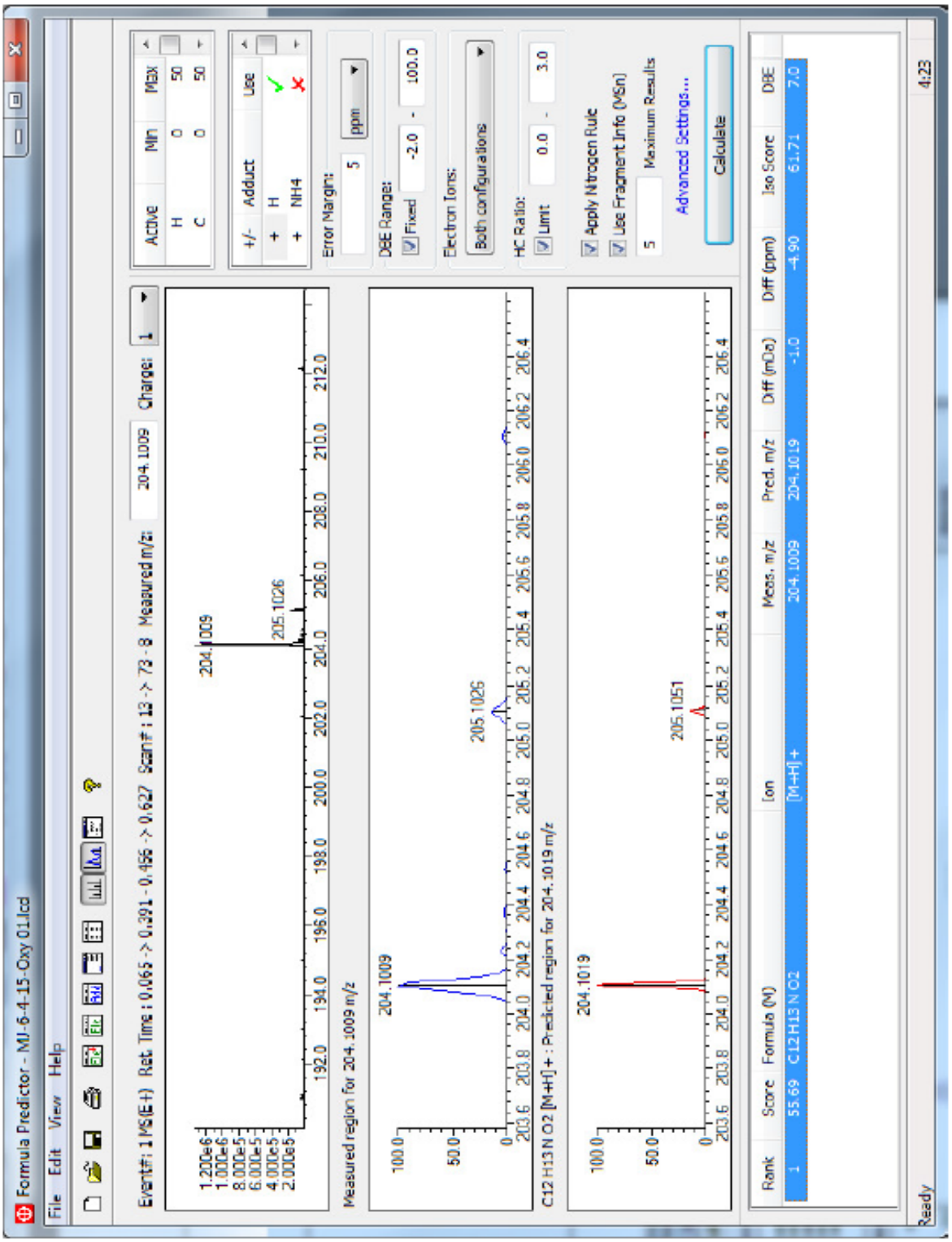
Compound **20**


Formula Predictor - SA-0105152-01.fcd
File Edit View Help
Measured m/z: 247.1333 Charge: 1
Active Min Max
H 0 50
C 0 42
+/- Adduct Use
+ H
+ NH4
Error Margin: 5 ppm
DBE Range: Fixed -2.0 - 100.0
Electron Ions: Both configurations
HC Ratio: Limit 0.0 - 3.0
Apply Nitrogen Rule
Use Fragment Info (MSn)
5 Maximum Results
Advanced Settings...
Calculate
Event#: 1 MS(E+) Ret. Time: 0.072 -> 0.252 - 0.287 -> 0.414 Scan#: 9 -> 29 - 33 -> 47
247.1333
248.1366
269.1158
279.0999
286.6206
Measured region for 247.1333 m/z
C15 H18 O3 [M+H]+ : Predicted region for 247.1329 m/z
Rank Score Formula (M) Ion Meas. m/z Pred. m/z Diff (mDa) Diff (ppm) Iso Score DBE
1 80.08 C15 H18 O3 [M+H]+ 247.1333 247.1329 0.4 1.62 81.34 7.0
Ready
2.27

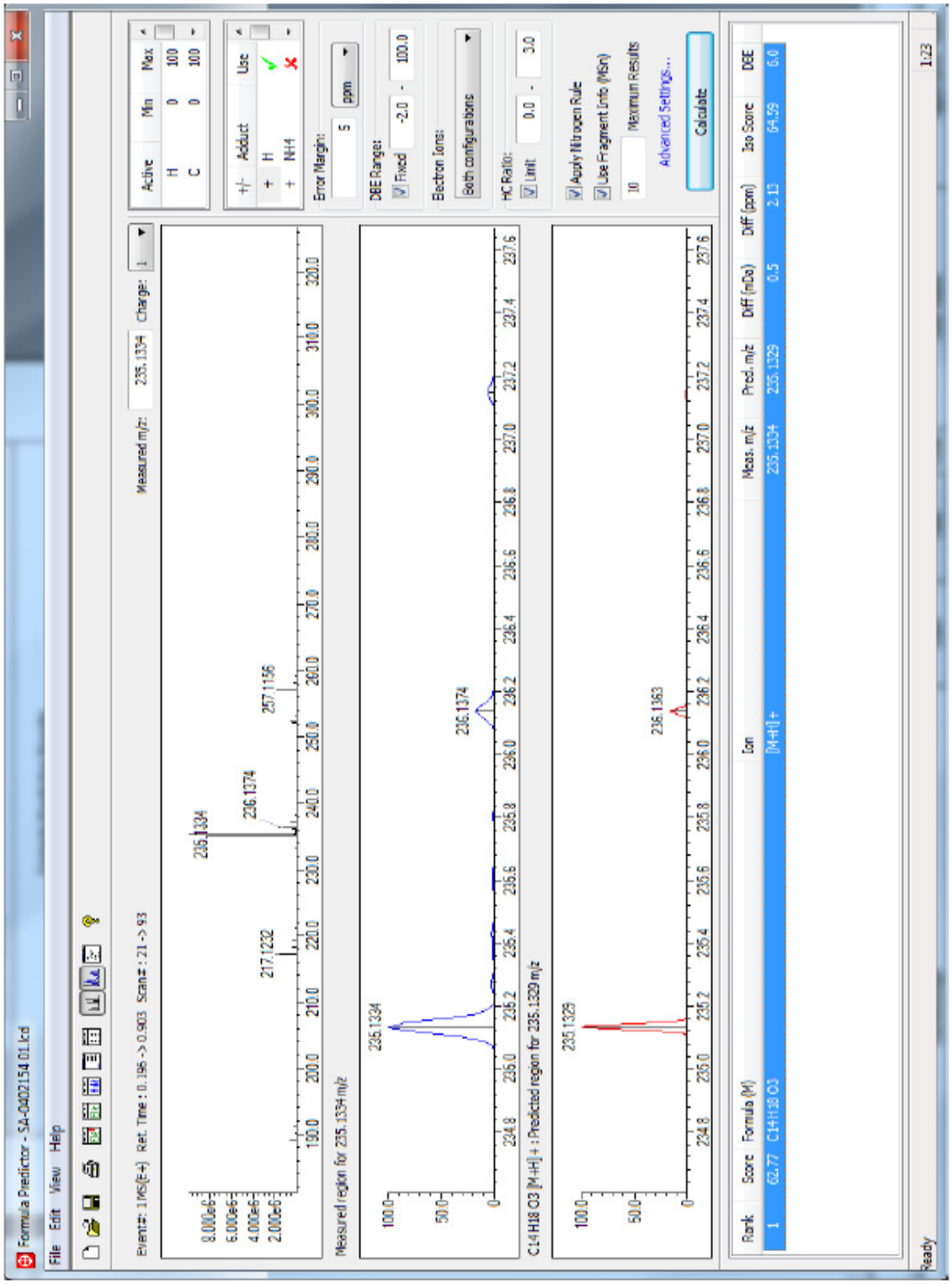
Compound **27**


Formula Predictor - MJ-76-ALC 01.kcd
File Edit View Help
Event#: 1 MS(E+) Ret. Time : 0.096 -> 0.622 -0.021 -> 0.064 Scan# : 19 -> 117 - 5 -> 13
Measured m/z: 280.1180 Charge: 1
Active Min Max
H 0 48
C 0 30
+/- Adduct Use
+ H
+ NH4
Error Margin: 5 ppm
DBE Range:
Fixed -2.0 - 100.0
Electron Ions:
Both configurations
H: C Ratio:
Limit 0.0 - 3.0
Apply Nitrogen Rule
Use Fragment Info (MSn)
5 Maximum Results
Advanced Settings...
Calculate
280.1180
281.1210
Measured region for 280.1180 m/z
281.1210
C14 H17 N O5 (N+H)+ : Predicted region for 280.1179 m/z
281.1212
Rank Score Formula (N) Ion Meas. m/z Pred. m/z Diff (mDa) Diff (ppm) Iso Score DBE
1 92.62 C14 H17 N O5 (N+H)+ 280.1180 280.1179 0.1 0.36 92.62 7.0
Ready
4:16

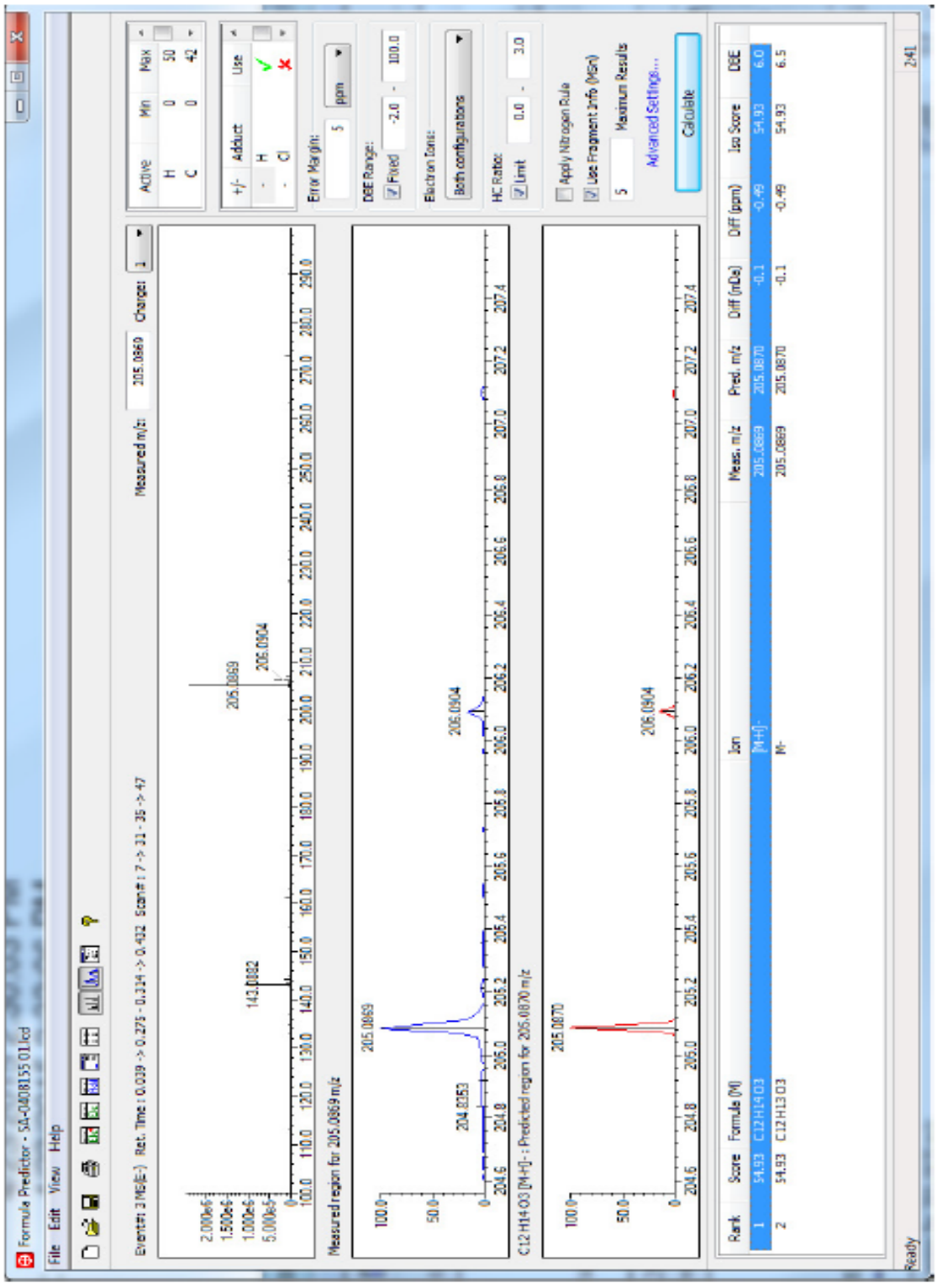
Compound **29**


Formula Predictor - MJ-6-4-15-Oxy 01.fcd
File Edit View Help
Event#: 1 MS(E+) Ret. Time : 0.065 -> 0.391 - 0.466 -> 0.627 Scan# : 13 -> 73 - 8 Measured m/z: 204.1009 Charge: 1
Measured region for 204.1009 m/z
C12 H13 N O2 [M+H]+ : Predicted region for 204.1019 m/z
Active Min Max
H 0 50
C 0 50
+/- Adduct Use
+ H
+ NH4
Error Margin: 5 ppm
DBE Range:
Fixed -2.0 - 100.0
Electron Ions:
Both configurations
HC Ratio:
Limit 0.0 - 3.0
Apply Nitrogen Rule
Use Fragment Info (MSn)
5 Maximum Results
Advanced Settings...
Calculate
Rank Score Formula (M) Ion Meas. m/z Pred. m/z Diff (mDa) Diff (ppm) Iso Score DBE
1 55.69 C12 H13 N O2 [M+H]+ 204.1009 204.1019 -1.0 -4.90 61.71 7.0
Ready
4:23

Compound **35**


Formula Predictor - SA-04021154 01.kd
File Edit View Help
Measured m/z: 235.1334 Charge: 1
Active Min Max
H 0 100
C 0 100
Adduct Use
H
NH4
Error Margin: 5 ppm
DBE Range:
Fixed -2.0 - 100.0
Electron Ions:
Both configurations
HC Ratio:
Limit 0.0 - 3.0
Apply Nitrogen Rule
Use Fragment Info (MSn)
10 Maximum Results
Advanced Settings...
Calculate
Event#: 1 MS(E+) Ret. Time : 0.196 -> 0.903 Scan# : 21 -> 93
235.1334
236.1374
257.1156
217.1232
Measured region for 235.1334 m/z
C14 H18 O3 [M+H]+ : Predicted region for 235.1329 m/z
Rank Score Formula (M) Ion Meas. m/z Pred. m/z Diff (mDa) Diff (ppm) Iso Score DBE
1 62.77 C14 H18 O3 [M+H]+ 235.1334 235.1329 0.5 2.13 64.59 6.0
Ready
1:23

Compound **36**


Formula Predictor - SA-040815S 01.fcd
File Edit View Help
Measured m/z: 205.0869 Charge: 1
Active Min Max
H 0 50
C 0 42
+/- Adduct Use
- H
- Cl
Error Margin: 5 ppm
DBE Range: Fixed -2.0 - 100.0
Electron Ions: Both configurations
HC Ratio: Limit 0.0 - 3.0
Apply Nitrogen Rule
Use Fragment Info (MSn)
5 Maximum Results
Advanced Settings...
Calculate
Measured region for 205.0869 m/z
C12 H14 O3 [M+H]- : Predicted region for 205.0870 m/z
Rank Score Formula (M) Ion Meas. m/z Pred. m/z Diff (mDa) Diff (ppm) Iso Score DBE
1 54.93 C12 H14 O3 [M+H]- 205.0869 205.0870 -0.1 -0.49 54.93 6.0
2 54.93 C12 H13 O3 M- 205.0869 205.0870 -0.1 -0.49 54.93 6.5
Ready

# APPENDIX C:

## HPLC Data

Compound **13a** (racemic)

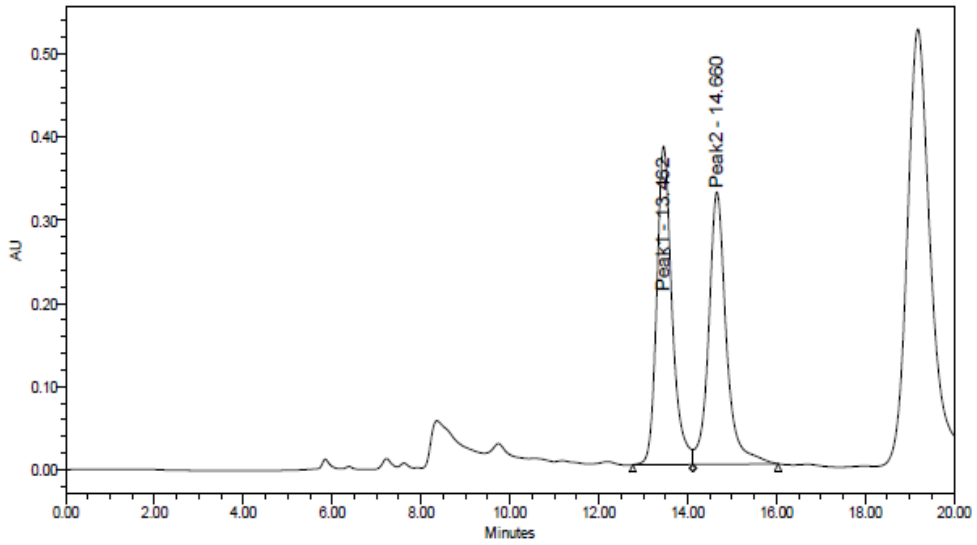
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0912131 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 1:32:16 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/29/2013 2:16:45 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm@29 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 0912131 |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | 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 |

Compound **13a** (chiral)

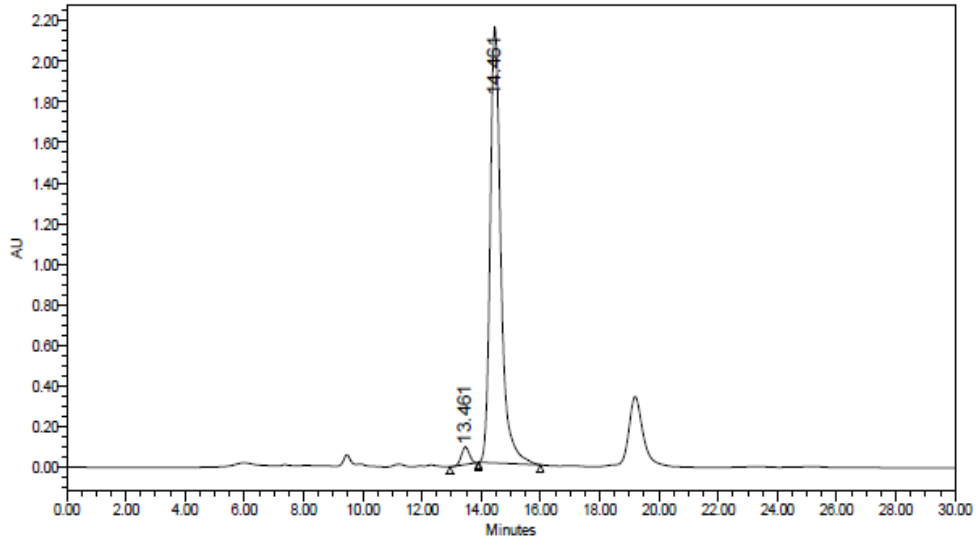
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | test | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/26/2013 2:28:17 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/26/2013 3:06:00 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sddf |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Peak Codes | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.461 | Unknown | 1620669 | 2.90 | 85643 | 3.84 | bb | I08 | 569 |
| 2 | 14.461 | Unknown | 54231732 | 97.10 | 2146383 | 96.16 | bb | | 1244 |

Compound **13b** (racemic)

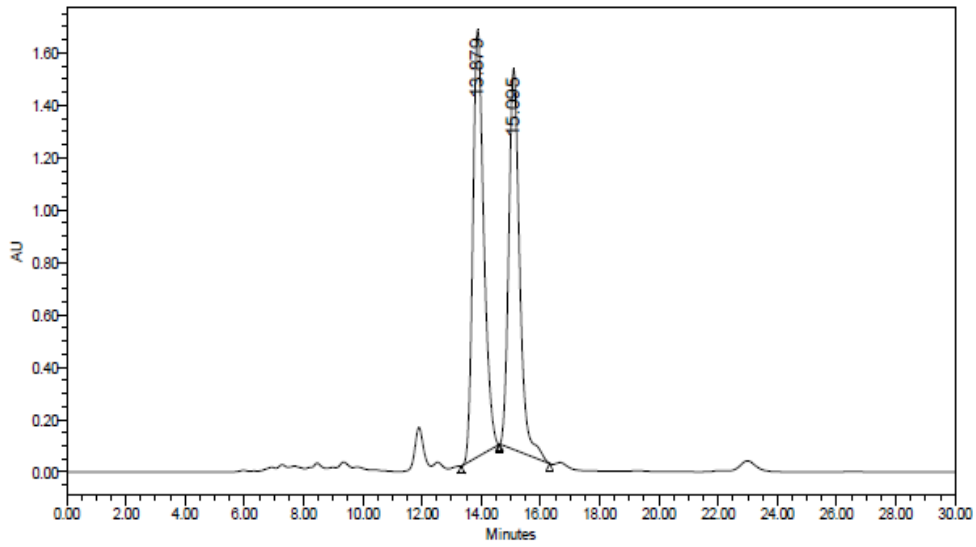
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | race p-tolyl | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 5:14:13 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/29/2013 6:41:51 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | rac p tolyl |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Points Across Peak | Start Time (min) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.879 | Unknown | 41616522 | 52.83 | 1631595 | 52.88 | bb | 760 | 13.331 |
| 2 | 15.095 | Unknown | 37155138 | 47.17 | 1454150 | 47.12 | bb | 1009 | 14.628 |

Compound **13b** (chiral)

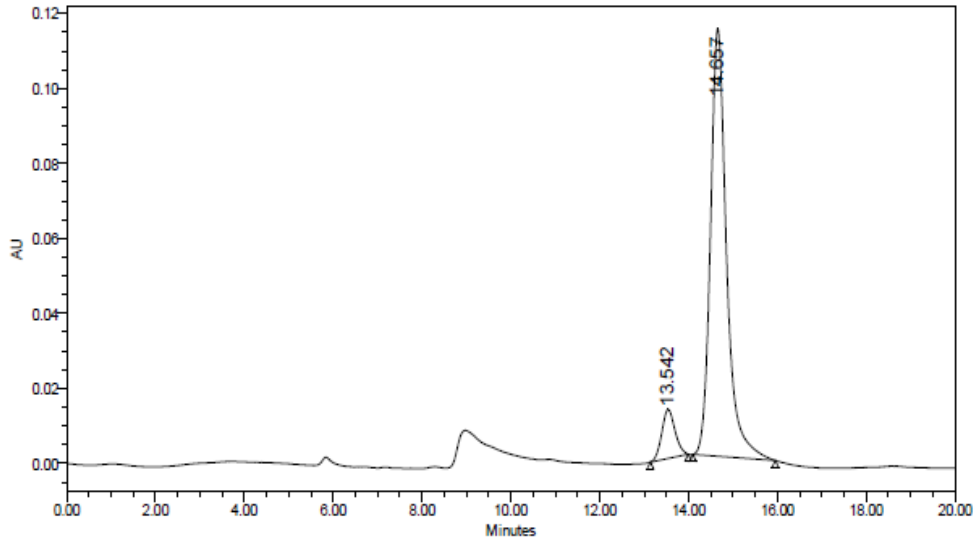
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-1005132 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/12/2013 3:41:15 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 10/12/2013 4:03:34 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sa 1005132 |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.542 | Unknown | 270871 | 8.64 | 13061 | 10.27 | bb | | 513 |
| 2 | 14.657 | Unknown | 2862951 | 91.36 | 114121 | 89.73 | bb | 3.073e+006 | 1116 |

Compound **13c** (racemic)

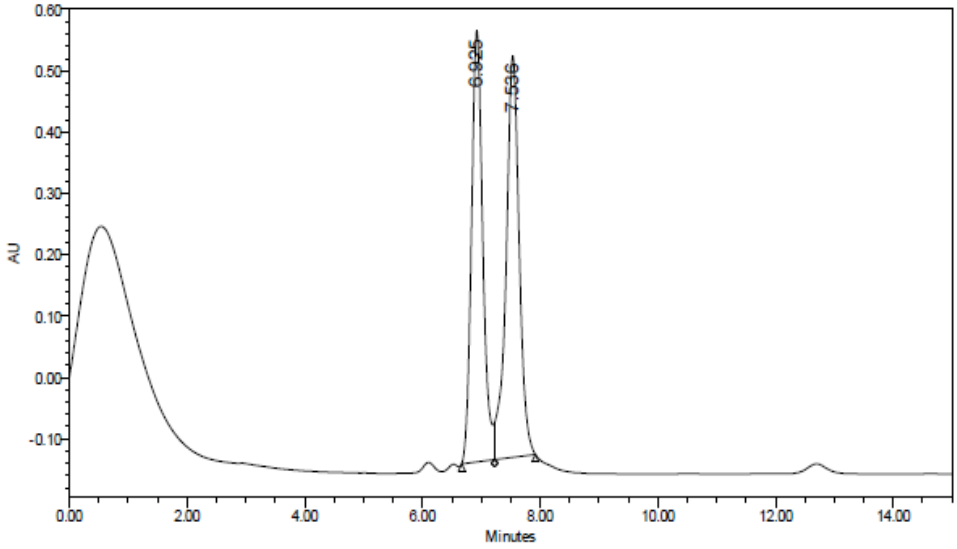
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Racemic tBu | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/24/2014 12:24:02 PM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 1/24/2014 12:54:50 PM CST |
| Run Time: | 15.00 Minutes | Channel Name: | 220.0nm@17 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | race tBu |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.925 | Unknown | 9376182 | 48.06 | 702713 | 51.77 | bv | 9.520e+006 | 335 |
| 2 | 7.536 | Unknown | 10132328 | 51.94 | 654708 | 48.23 | vb | 1.092e+007 | 416 |

Compound **13c** (chiral)

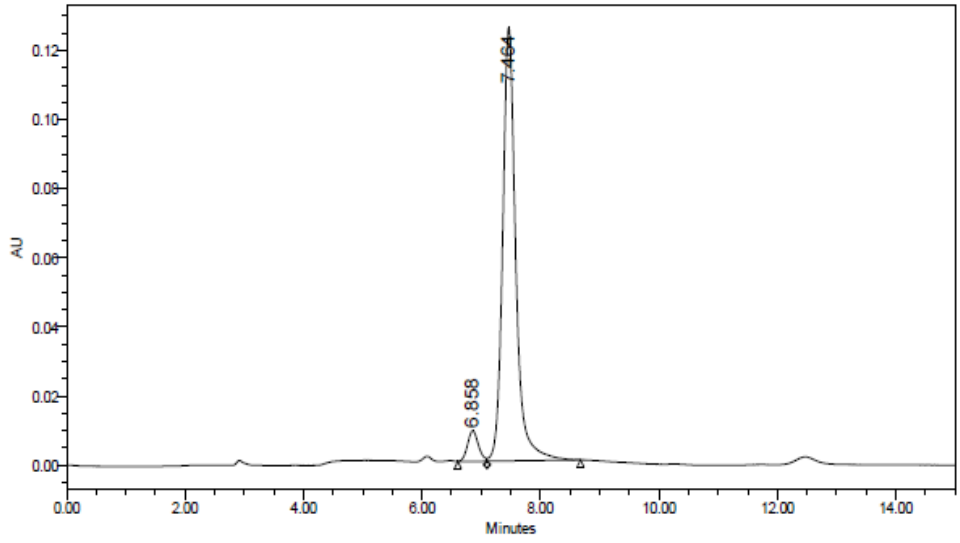
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0101142a | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/11/2014 6:02:05 PM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 1/11/2014 6:19:56 PM CST |
| Run Time: | 15.00 Minutes | Channel Name: | 220.0nm@10 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sa 0101142a |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.858 | Unknown | 112026 | 5.51 | 8866 | 6.60 | BV | 1.120e+005 | 296 |
| 2 | 7.464 | Unknown | 1922697 | 94.49 | 125470 | 93.40 | VB | 1.923e+006 | 947 |

Compound **13d** (racemic)

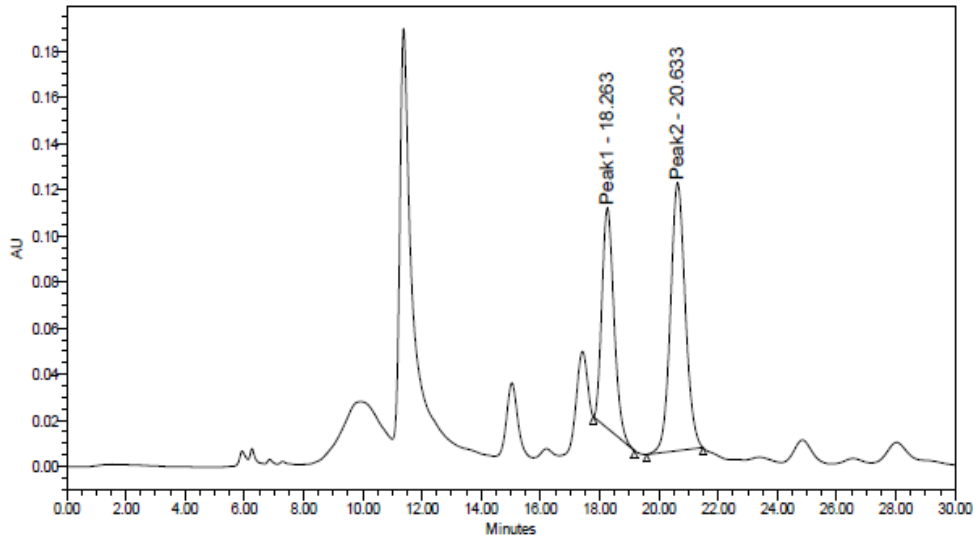
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | race 4 MeO | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 2:20:45 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/29/2013 3:15:33 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@30 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | race4MeO |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 18.263 | Found | 2689417 | 39.93 | 95365 | 45.12 | BB | 2.689e+006 | I08 Q20 |
| 2 | Peak2 | 20.633 | Found | 4045241 | 60.07 | 115996 | 54.88 | BB | 4.045e+006 | Q20 |

Compound **13d** (chiral)

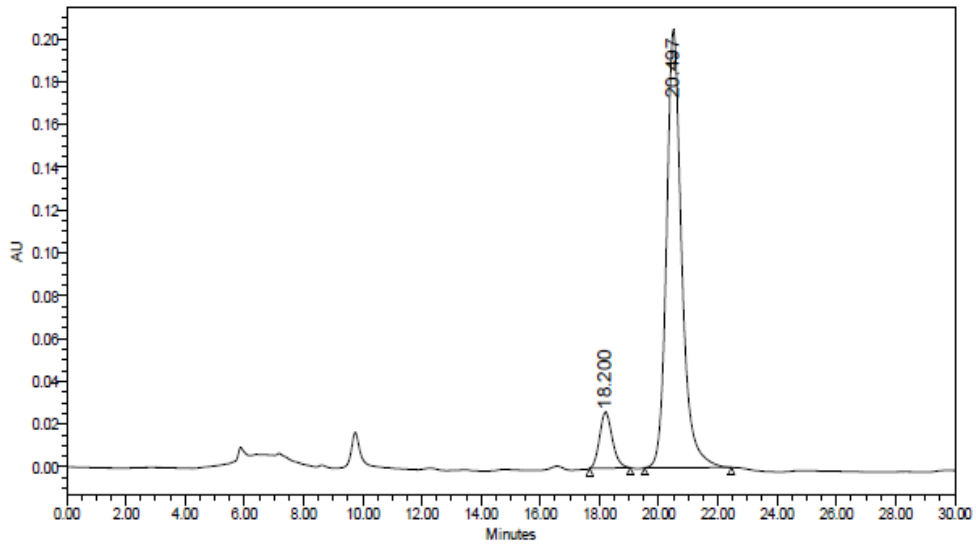
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0822132 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 3:21:50 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/29/2013 4:05:01 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@31 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 0822132 |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Points Across Peak | Start Time (min) | End Time (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.200 | Unknown | 784443 | 9.72 | 26114 | 11.32 | bb | 821 | 17.670 | 19.039 |
| 2 | 20.497 | Unknown | 7287705 | 90.28 | 204654 | 88.68 | bb | 1754 | 19.527 | 22.451 |

Compound **13e** (racemic)

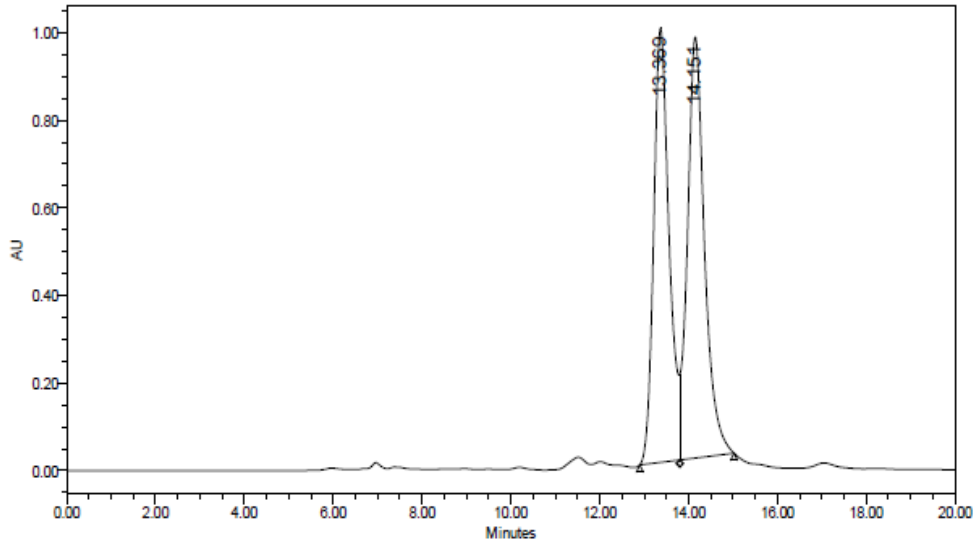
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Race 4-F | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 5/6/2014 5:24:47 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/6/2014 5:55:29 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | race 4F |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.369 | Unknown | 23766656 | 48.03 | 991628 | 50.78 | bv | 2.420e+007 | 540 |
| 2 | 14.151 | Unknown | 25711806 | 51.97 | 961267 | 49.22 | vb | 2.847e+007 | 732 |

Compound **13e** (chiral)

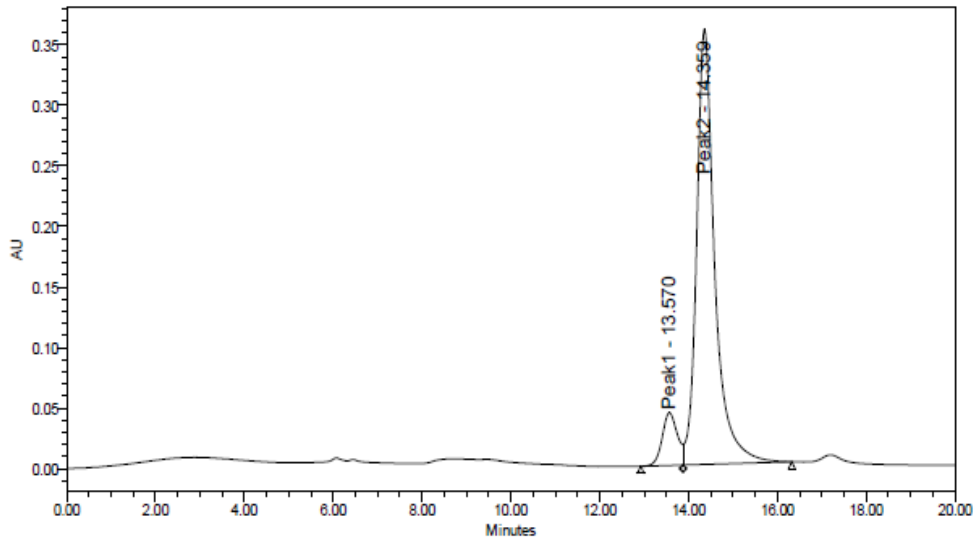
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Chiral 4F | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 5/3/2014 4:12:40 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/3/2014 5:33:58 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | Chiral 4F |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 13.570 | Found | 1031160 | 9.20 | 43567 | 10.82 | BV | 1.031e+006 | Q20 |
| 2 | Peak2 | 14.359 | Found | 10176745 | 90.80 | 359076 | 89.18 | VB | 1.018e+007 | Q20 |

Compound **13f** (racemic)

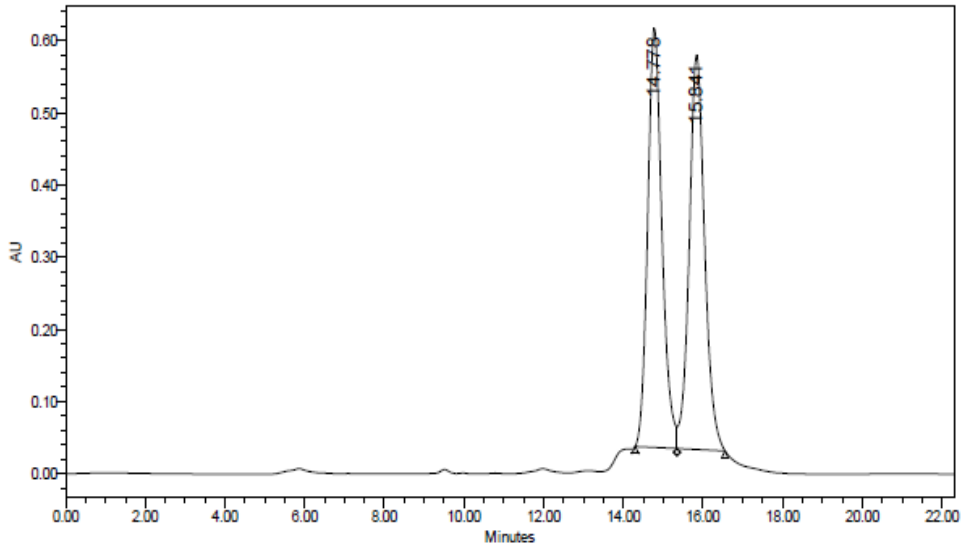
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | 4-Br racemic | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/13/2013 12:31:27 PM CST |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 12/13/2013 12:55:09 PM CST |
| Run Time: | 40.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | 4 Br race |

Sample Values
Used in Calculations




| | 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 |

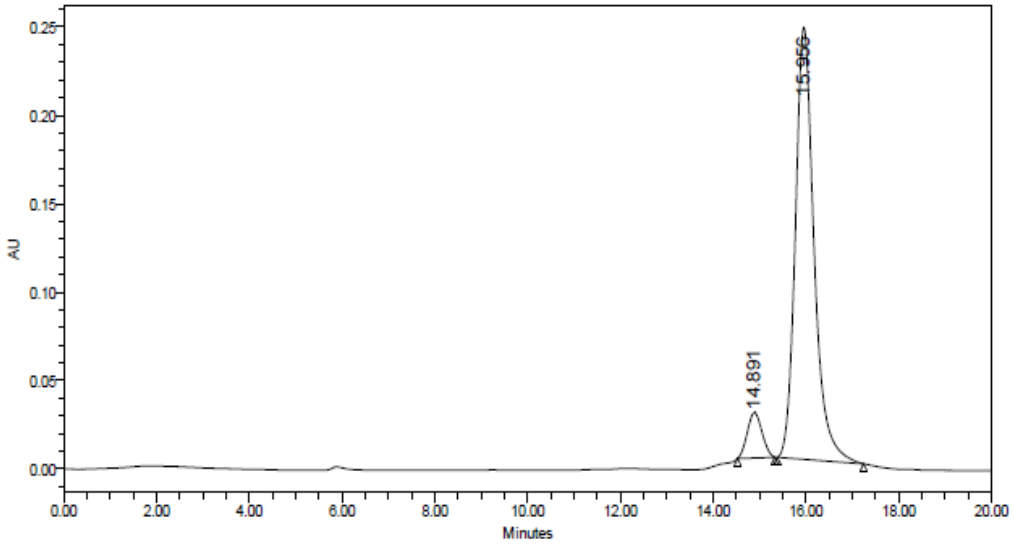
Compound **13f** (chiral)

UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | 4-Br racemic | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/13/2013 1:50:11 PM CST |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Date Processed: | 12/13/2013 2:58:55 PM CST |
| Injection Volume: | 10.00 ul | Channel Name: | 220.0nm |
| Run Time: | 20.00 Minutes | Sample Set Name | sa 1204132a |




| | RT (min) | Area (µV*sec) | % Area | Height (µV) | % Height |
|---|---|---|---|---|---|
| 1 | 14.891 | 565136 | 7.64 | 25611 | 9.49 |
| 2 | 15.956 | 6828150 | 92.36 | 244346 | 90.51 |

Report Method: Untitled
Page: 1 of 1

Printed: 12/13/2013
3:00:14 PM US/Central

Compound **13g** (racemic)

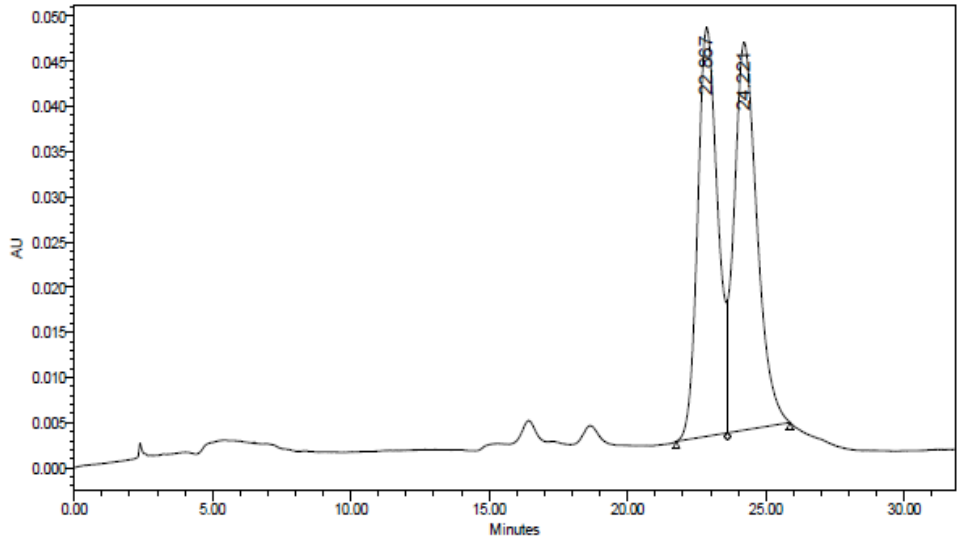
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Racemic p-NO2 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/12/2014 7:59:01 PM CST |
| Vial: | 1 | Acq. Method: | 124 A 001B |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 1/12/2014 8:34:01 PM CST |
| Run Time: | 60.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | jklgfyyu |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22.867 | Unknown | 2279482 | 48.08 | 45260 | 51.33 | Bv | 2.280e+006 | 1112 |
| 2 | 24.221 | Unknown | 2461295 | 51.92 | 42921 | 48.67 | vb | 2.657e+006 | 1350 |

Compound **13g** (chiral)

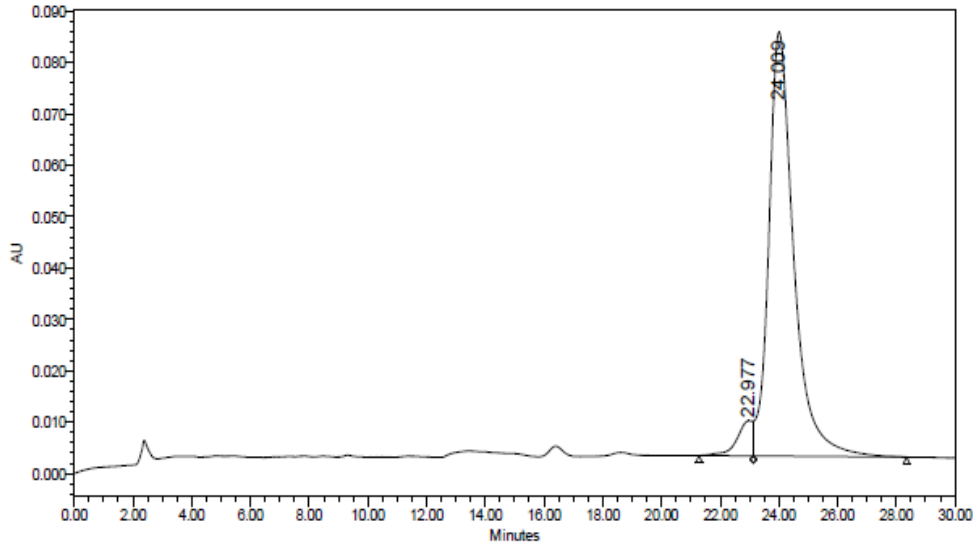
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0101143a | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/12/2014 11:39:53 PM CST |
| Vial: | 1 | Acq. Method: | 124 A 001B |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/3/2014 1:14:22 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 0101143a |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Points Across Peak | Start Time (min) | End Time (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 22.977 | Unknown | 253244 | 4.93 | 6831 | 7.64 | Bv | 1109 | 21.281 | 23.129 |
| 2 | 24.009 | Unknown | 4883919 | 95.07 | 82554 | 92.36 | vB | 3131 | 23.129 | 28.349 |

Compound **13h** (racemic)

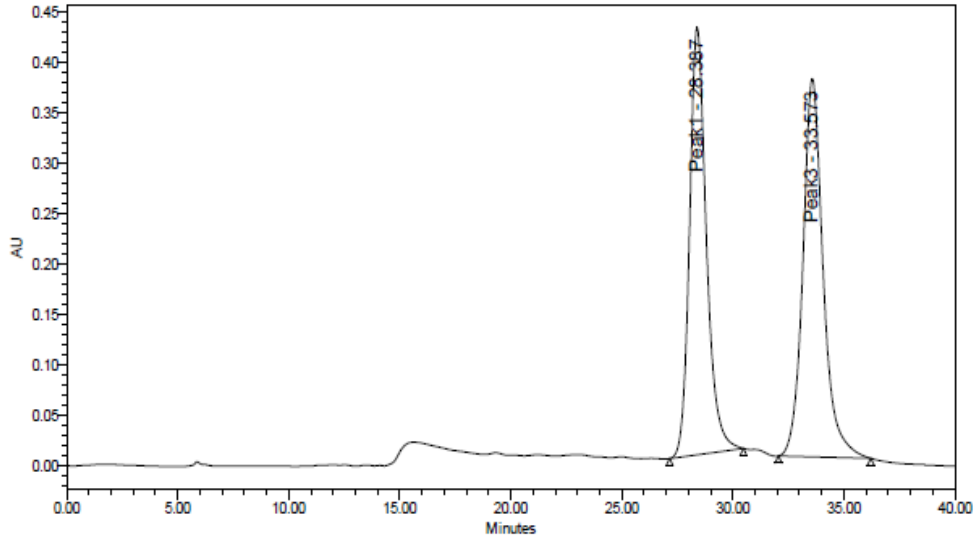
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-Race Naphthyl | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/2/2013 5:57:48 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 11/2/2013 7:03:03 PM CDT |
| Run Time: | 40.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | Race Naph |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | 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 |

Compound **13h** (chiral)

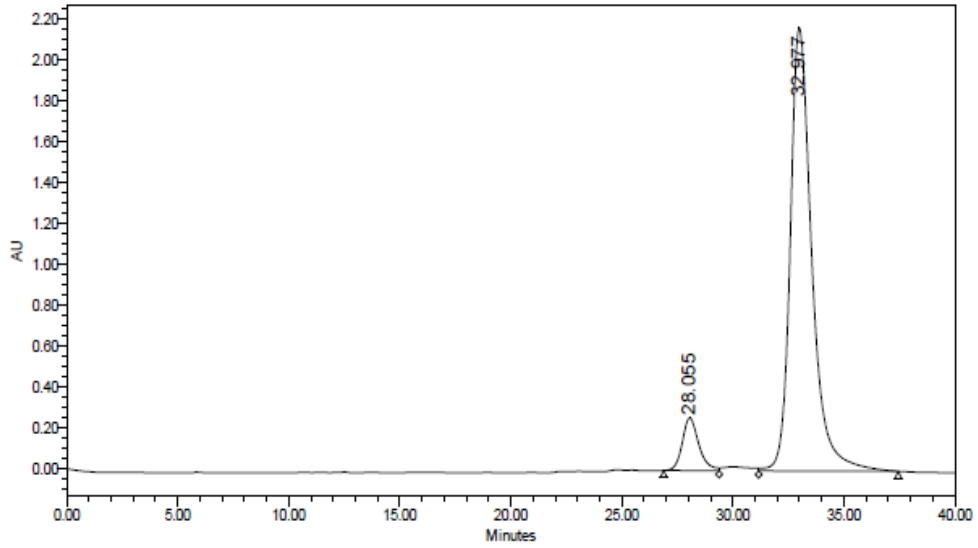
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-1005133 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 10/12/2013 4:08:48 PM CDT |
| Vial: | 1 | Acq. Method: | 2% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 10/12/2013 4:55:47 PM CDT |
| Run Time: | 40.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sa 1005133 |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 28.055 | Unknown | 13268447 | 8.32 | 257659 | 10.63 | BV | 1.327e+007 | 1498 |
| 2 | 32.977 | Unknown | 146173024 | 91.68 | 2165129 | 89.37 | VB | 1.462e+008 | 3774 |

Compound **13′i** (racemic)

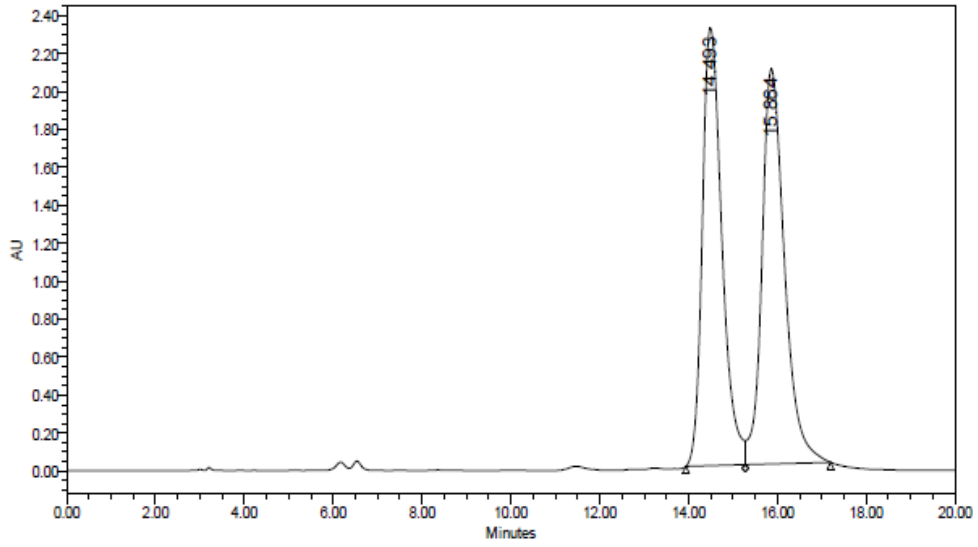
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Racemic furylalc | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/24/2014 11:52:19 AM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 1/24/2014 12:17:51 PM CST |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm@16 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | race furylalc |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 14.493 | Unknown | 70659736 | 49.02 | 2306605 | 52.54 | bV | 7.216e+007 | 799 |
| 2 | 15.864 | Unknown | 73490328 | 50.98 | 2083585 | 47.46 | Vb | 7.760e+007 | 1154 |

Compound **13′i** (chiral)

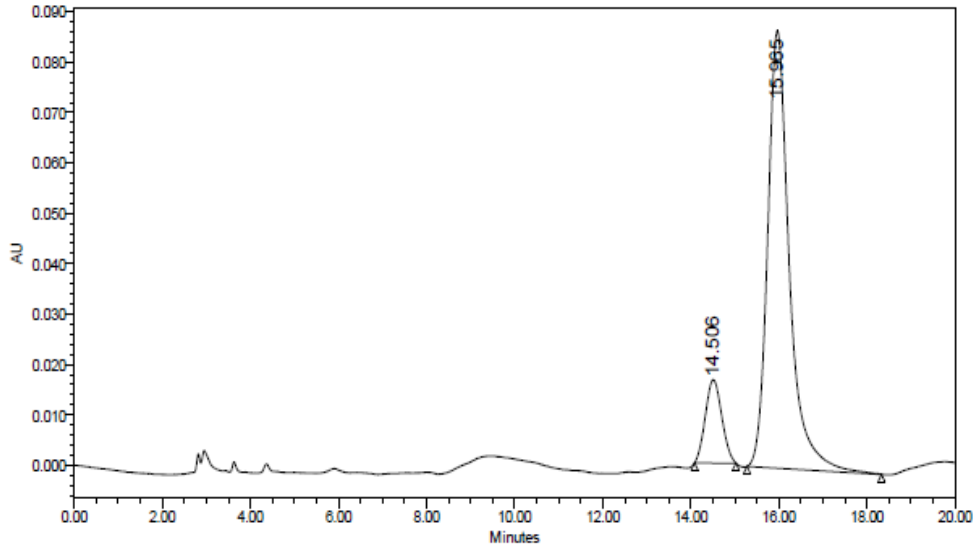
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Racemic furylalco | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 1/24/2014 11:16:58 AM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 1/24/2014 11:40:06 AM CST |
| Run Time: | 20.00 Minutes | Channel Name: | 210.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | fyutgui |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 14.506 | Unknown | 428257 | 12.64 | 16538 | 15.99 | bb | | 563 |
| 2 | 15.965 | Unknown | 2959491 | 87.36 | 86861 | 84.01 | bB | 3.031e+006 | 1830 |

Compound **13j** (racemic)

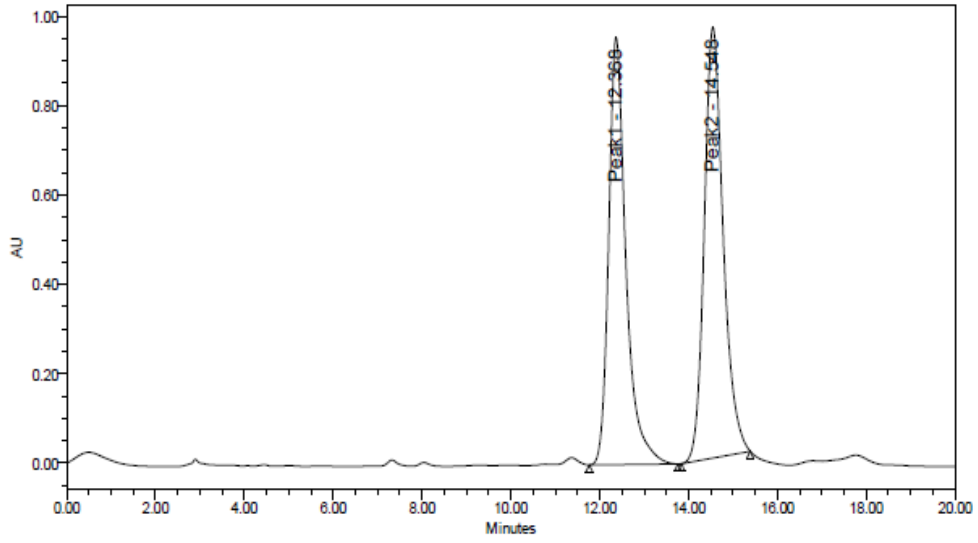
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0410142 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 4/14/2014 3:29:56 PM CDT |
| Vial: | 1 | Acq. Method: | 95% Hex and 5% EtOH |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 4/14/2014 3:54:39 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-600)nm |
| | | Sample Set Name | sa 0410142 |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 12.368 | Found | 25777425 | 47.50 | 956268 | 49.80 | BB | 2.578e+007 | Q20 |
| 2 | Peak2 | 14.548 | Found | 28490909 | 52.50 | 963798 | 50.20 | BB | 2.849e+007 | Q20 |

Compound **13j** (chiral)

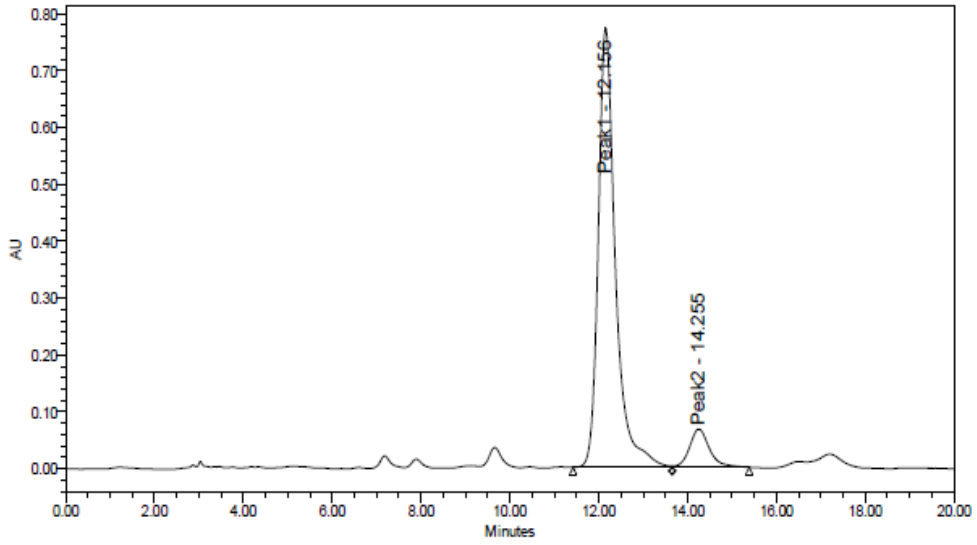
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0530143 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 6/3/2014 3:02:48 PM CDT |
| Vial: | 1 | Acq. Method: | 95% Hex and 5% EtOH |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 6/3/2014 3:31:20 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-600)nm |
| | | Sample Set Name | sa 053014 3 |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 12.156 | Found | 20664610 | 90.79 | 772274 | 91.97 | BV | 2.066e+007 | Q20 |
| 2 | Peak2 | 14.255 | Found | 2096341 | 9.21 | 67435 | 8.03 | VB | 2.096e+006 | Q20 |

Compound **13k** (racemic)

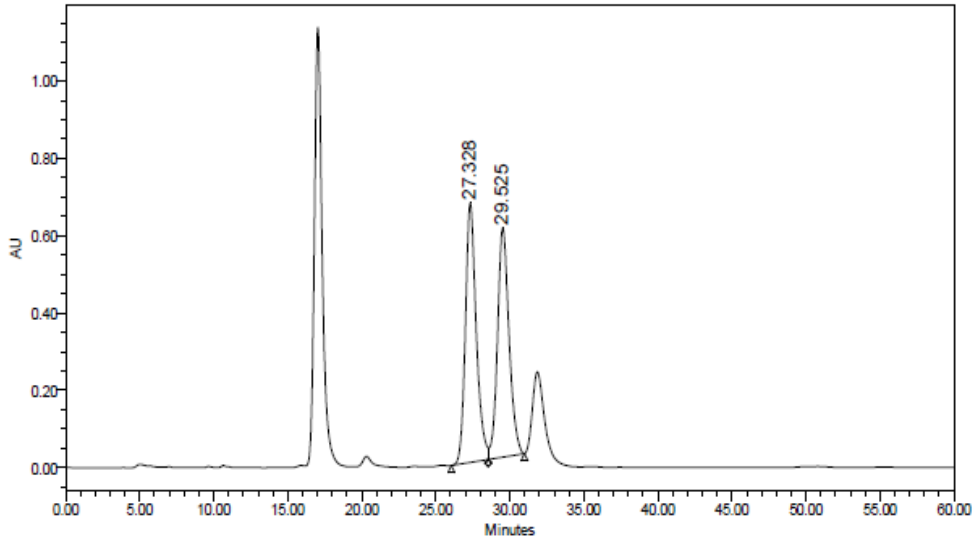
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-2NO2-5MeO-Racemic | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 8/14/2014 10:54:03 AM CDT |
| Vial: | 1 | Acq. Method: | 10% B half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 8/14/2014 11:58:48 AM CDT |
| Run Time: | 60.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 2NO25MeORacemic |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 27.328 | Unknown | 33928131 | 51.40 | 671155 | 53.09 | Bv | 3.400e+007 | 1498 |
| 2 | 29.525 | Unknown | 32075922 | 48.60 | 593116 | 46.91 | vB | 3.201e+007 | 1466 |

Compound **13k** (chiral)

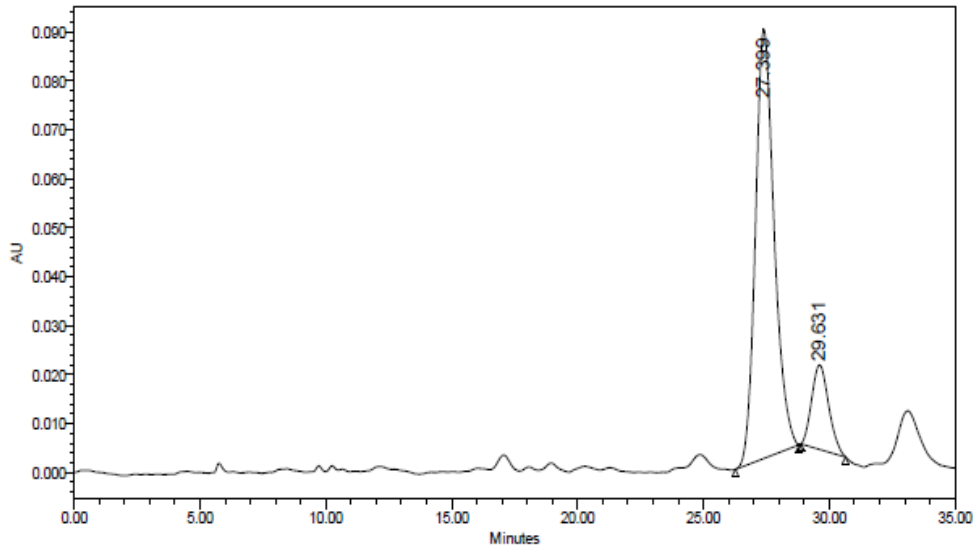
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0916141 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/17/2014 3:48:12 PM CDT |
| Vial: | 1 | Acq. Method: | 10% B half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/25/2015 2:53:26 PM CDT |
| Run Time: | 35.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa0916141 |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 27.399 | Unknown | 4539327 | 84.81 | 87659 | 83.53 | Bb | 4.899e+006 | |
| 2 | 29.631 | Unknown | 813127 | 15.19 | 17279 | 16.47 | bb | | I08 |

Compound **13l** (racemic)

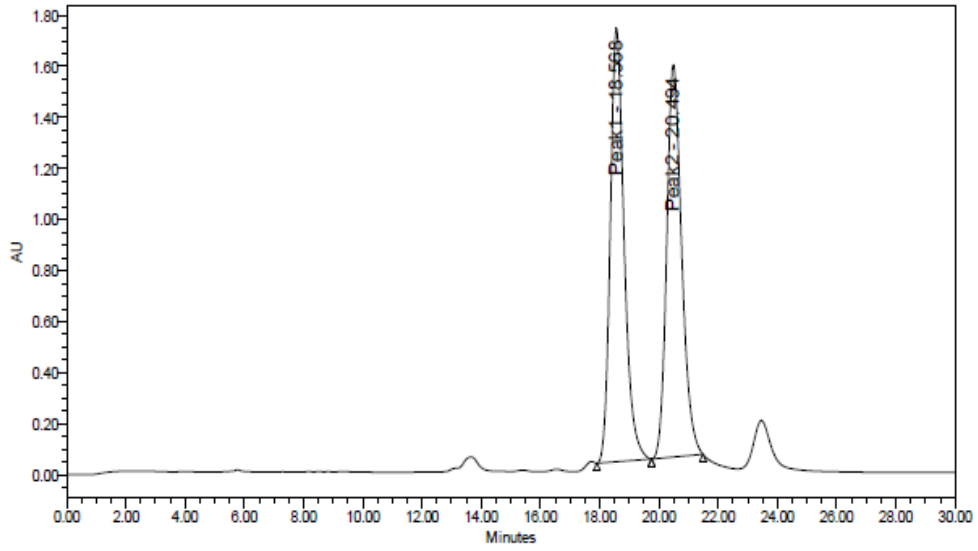
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-2MeO Race | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/2/2013 4:53:24 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 11/2/2013 5:27:52 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@31 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | 2MeO race |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 18.568 | Found | 55128858 | 50.57 | 1698390 | 52.50 | BB | 5.513e+007 | Q20 |
| 2 | Peak2 | 20.494 | Found | 53880035 | 49.43 | 1536568 | 47.50 | BB | 5.388e+007 | Q20 |

Compound **13l** (chiral)

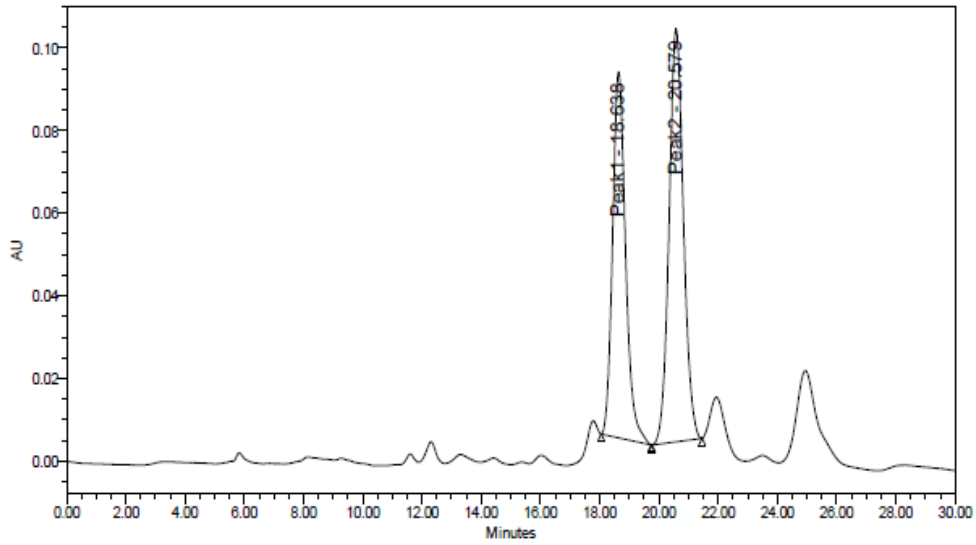
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-1027131 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/2/2013 4:06:49 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 11/2/2013 4:39:12 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@34 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 1027131 |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 18.638 | Found | 2698626 | 44.52 | 88589 | 46.99 | BB | 2.699e+006 | Q20 |
| 2 | Peak2 | 20.579 | Found | 3362412 | 55.48 | 99930 | 53.01 | BB | 3.362e+006 | Q20 |

Compound **13m** (racemic)

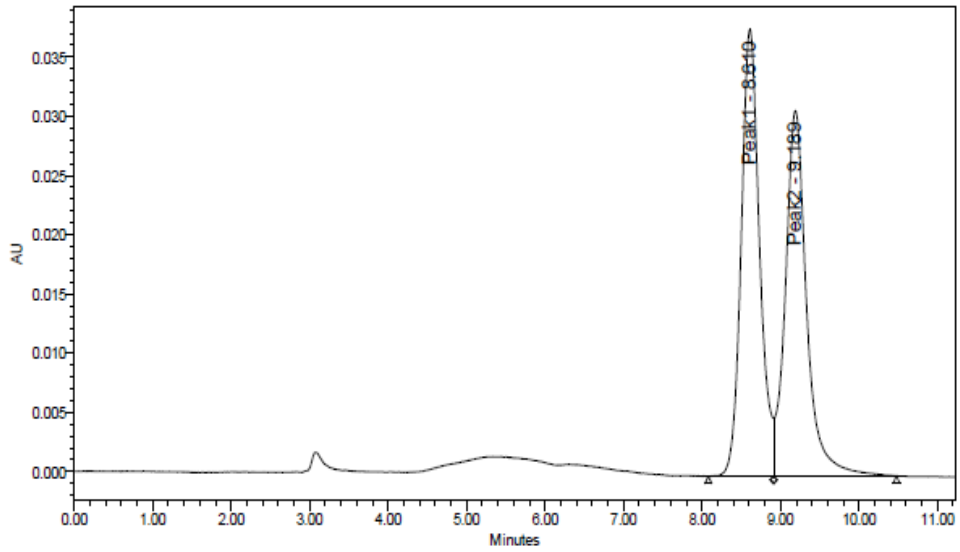
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-1204131a | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/11/2013 4:55:28 PM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 12/11/2013 5:07:05 PM CST |
| Run Time: | 15.00 Minutes | Channel Name: | 220.0nm |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sa 1204131 a |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 8.610 | Found | 611134 | 51.16 | 37740 | 55.02 | BV | 6.111e+005 | Q20 |
| 2 | Peak2 | 9.189 | Found | 583317 | 48.84 | 30858 | 44.98 | VB | 5.833e+005 | Q20 |

Compound **13m** (chiral)

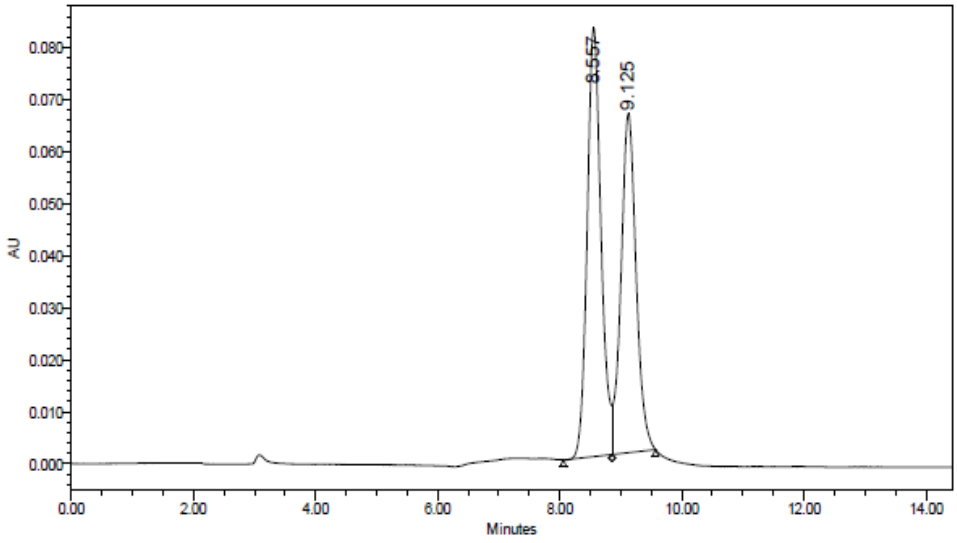
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-1204131a | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 12/11/2013 4:33:40 PM CST |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/25/2015 3:20:27 PM CDT |
| Run Time: | 15.00 Minutes | Channel Name: | 220.0nm@22 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | sa 1204131a |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 8.557 | Unknown | 1297929 | 53.65 | 82483 | 55.84 | BV | 1.332e+006 | 479 |
| 2 | 9.125 | Unknown | 1121436 | 46.35 | 65230 | 44.16 | Vb | 1.242e+006 | 427 |

Compound **13n** (racemic)

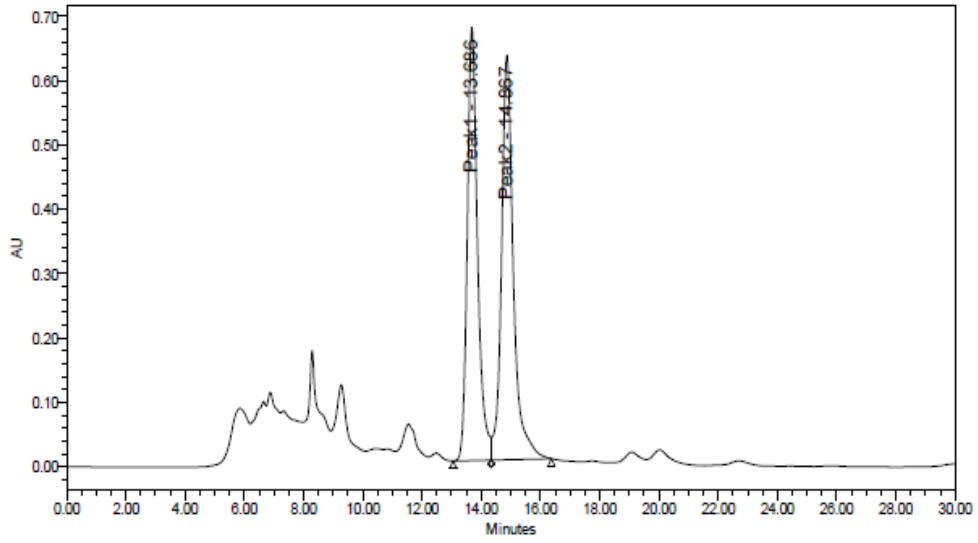
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | race 2, 4 - Dichloro | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 12:53:47 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/29/2013 1:27:28 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@28 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | race dichloro |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 13.686 | Found | 16190703 | 48.06 | 672780 | 51.69 | BV | 1.619e+007 | Q20 |
| 2 | Peak2 | 14.867 | Found | 17495366 | 51.94 | 628852 | 48.31 | VB | 1.750e+007 | Q20 |

Compound **13n** (chiral)

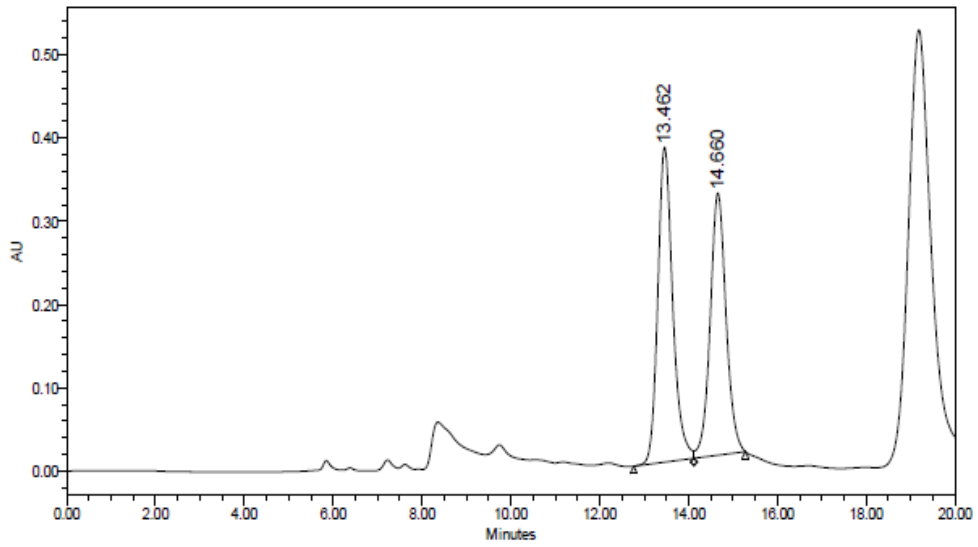
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0912131 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/29/2013 1:32:16 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/25/2015 3:46:01 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 220.0nm@43 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 0912131 |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13.462 | Unknown | 8792310 | 52.94 | 378242 | 54.56 | BV | 9.139e+006 | 814 |
| 2 | 14.660 | Unknown | 7814633 | 47.06 | 315041 | 45.44 | Vb | 8.937e+006 | 694 |

Compound **13o** (racemic)

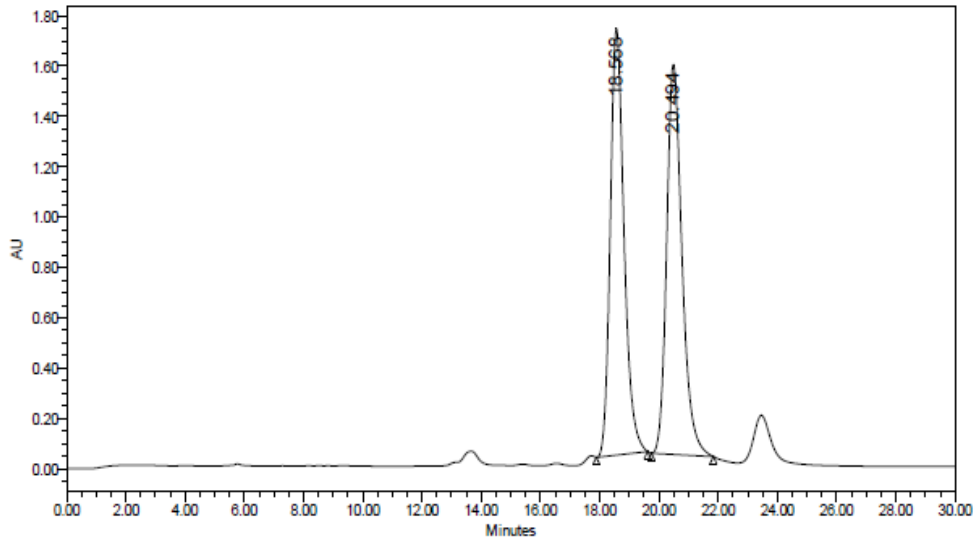
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-2MeO Race | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 11/2/2013 4:53:24 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 11/2/2013 5:28:31 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@36 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | 2MeO race |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Points Across Peak | Start Time (min) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.568 | Unknown | 54692792 | 49.54 | 1695206 | 52.25 | bb | 1037 | 17.888 |
| 2 | 20.494 | Unknown | 55712473 | 50.46 | 1549428 | 47.75 | bb | 1258 | 19.745 |

Compound **13o** (chiral)

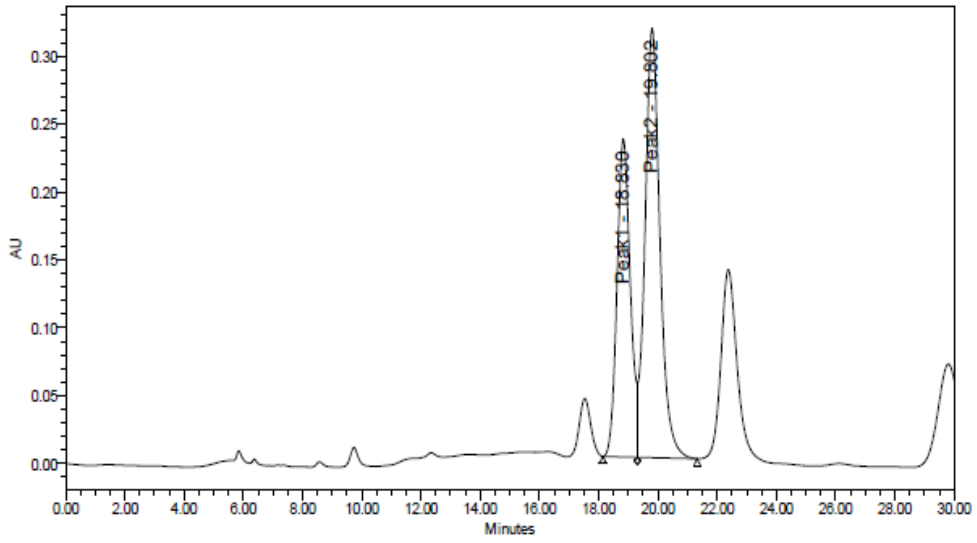
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0912132 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 9/26/2013 7:15:02 PM CDT |
| Vial: | 1 | Acq. Method: | 4% EtOH half ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 9/26/2013 7:50:24 PM CDT |
| Run Time: | 30.00 Minutes | Channel Name: | 220.0nm@27 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-400)nm |
| | | Sample Set Name | sa 0912132 |

Sample Values Used in Calculations: Injection Volume = 10.00 SampleWeight = 1.00000 Dilution = 1.00000




| | Peak Name | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Peak Codes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 18.830 | Found | 7264148 | 39.58 | 234094 | 42.55 | BV | 7.264e+006 | Q20 |
| 2 | Peak2 | 19.802 | Found | 11089047 | 60.42 | 316131 | 57.45 | VB | 1.109e+007 | Q20 |

Compound **20** (racemic)

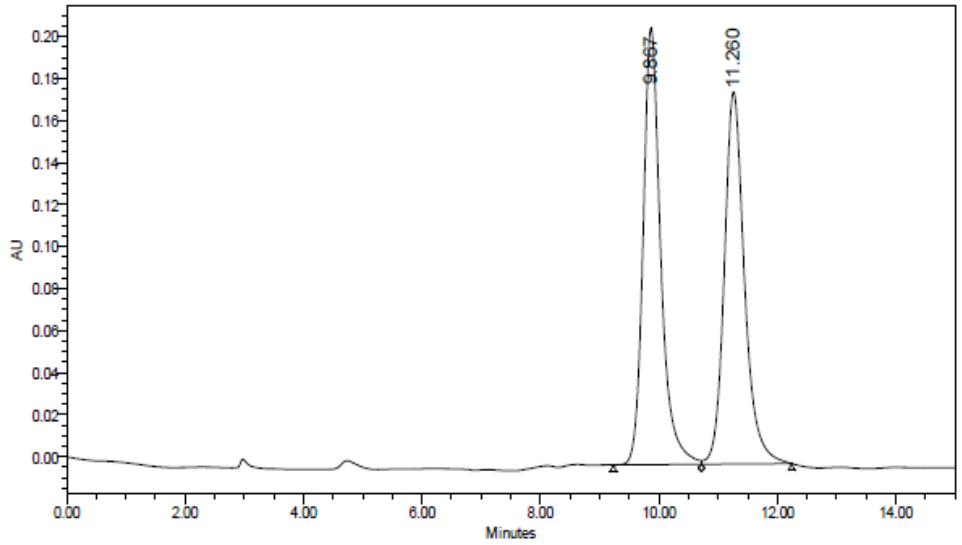
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-Race Keto | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 3/14/2015 2:40:54 PM CDT |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 3/14/2015 2:58:28 PM CDT |
| Run Time: | 15.00 Minutes | Channel Name: | 210.0nm@5 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | racemic keto |

Sample Values
Used in Calculations




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 9.867 | Unknown | 4289111 | 50.56 | 207842 | 53.98 | BV | 4.289e+006 | 892 |
| 2 | 11.260 | Unknown | 4193748 | 49.44 | 177209 | 46.02 | VB | 4.194e+006 | 914 |

Compound **20** (chiral)

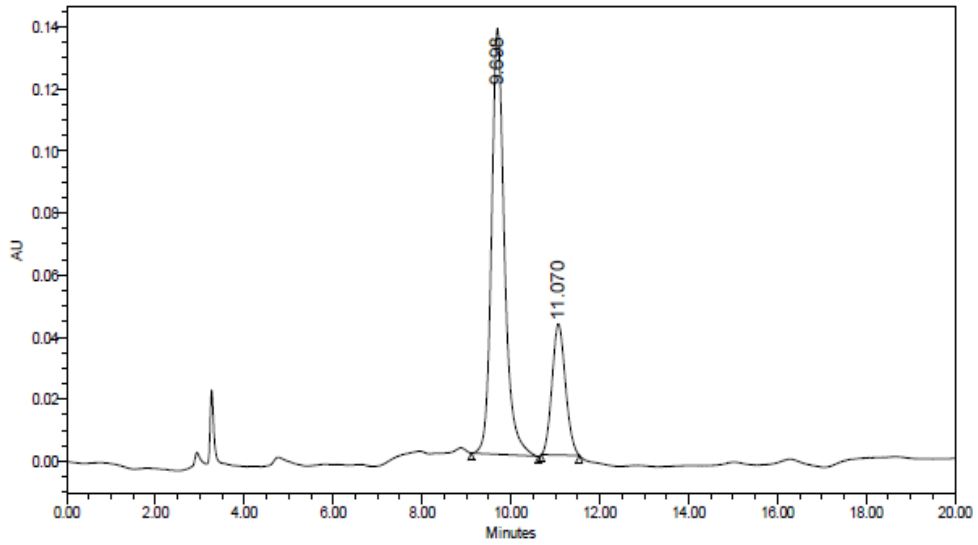
UW - Milwaukee
Project Name Asad
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sa-0403152 | Acquired By: | Breeze |
| Sample Type: | Unknown | Date Acquired: | 4/7/2015 3:38:28 PM CDT |
| Vial: | 1 | Acq. Method: | 1% EtOH 1ml min |
| Injection #: | 1 | Processed By: | Breeze |
| Injection Volume: | 10.00 ul | Date Processed: | 5/23/2015 5:23:59 PM CDT |
| Run Time: | 20.00 Minutes | Channel Name: | 210.0nm@21 |
| Sampling Rate: | 10.00 per sec | Channel Desc.: | 2998 (190-300)nm |
| | | Sample Set Name | uilgfyuyg |

Sample Values
Used in Calculation:




| | RT (min) | Peak Type | Area (µV*sec) | % Area | Height (µV) | % Height | Integration Type | Response | Points Across Peak |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 9.698 | Unknown | 2773335 | 75.77 | 137184 | 76.46 | Bb | 2.795e+006 | 907 |
| 2 | 11.070 | Unknown | 886843 | 24.23 | 42235 | 23.54 | bb | | 512 |

# CURRICULUM VITAE

Md. Sharif A. Asad

## Highlights

| | | |
|---|---|---|
| Organic Synthesis | Asymmetric Synthesis | Organometallic Chemistry |
| Palladium | Method Development | Catalyst Design |
| Medicinal Chemistry | Scale-up | NMR |
| HPLC | LCMS | MALDI-TOF |
| FT-IR | Team Motivator | Team Builder |
| Analytical writing | Teaching | Communication Skill |

## Education

**University of Wisconsin – Milwaukee** Milwaukee, WI

PhD, Department of Chemistry & Biochemistry. Expected to graduate in Aug. 2015. Research focuses on the asymmetric synthesis of all-carbon α-aryl quaternary stereocenters and their subsequent application in the synthesis of biologically active natural products.

**University of Dhaka** Dhaka, Bangladesh

MS, Department of Applied Chemistry & Chemical Engineering, 2009. Passed with distinction (first class). Thesis: Extraction and bioassay of the extracts from the medicinal plant *Gynura procumbens*.

**University of Dhaka** Dhaka, Bangladesh

BSc (Honors), Department of Applied Chemistry & Chemical Engineering, 2007. Passed with distinction (first class). Project Work: Fluxing Agents in Iron and Steel Industries.

## Research Experience

**UWM Dept. of Chemistry & Biochemistry** Milwaukee, WI

Advisor: Professor M. Mahmun Hossain

A new methodology for the Palladium catalyzed Asymmetric Allylic Alkyltion (Pd-AAA) has been developed where unprecedented hydroxyacrylates were used as substrates instead of widely used ketones and synthesized all-carbon α-aryl quaternary aldehydes with high yield and enantioselectivity. Applying this methodology, currently work on progress synthesizing quaternary β-lactone and β-lactam moieties, containing O- and N- respectively on the β-carbon in the ring, as well as 3,3′-disubstituted oxindol ring. These above mentioned structural motifs are very frequent in natural products and pharmaceutical agents. (September 2009 - present)

**University of Dhaka** Dhaka, Bangladesh
Advisor: Professor A. M. Sarwaruddin Chowdhury

*Gynura procumbens* is a medicinal plant native to Indo-china and well known for its antidiabetic and hepatoprotective properties. The dried and grounded plant has been extracted successively with cold n-Hexane, DCM, Methanol, and Ethyl Acetate. Later brine shrimp lethality bioassay, antitumor activity, microbiological investigation, and antioxidant activity evaluation of each of the four crude extracts has been studied. The overall result was quite satisfactory, earning commendation by the dissertation review committee and resulted in appointing a new PhD student for further research. (2007-2009)

## Teaching Experience

**UWM Dept. of Chemistry & Biochemistry** Milwaukee, WI

Mentor for Teaching Assistants.

Supervised and instructed newly appointed teaching assistants. (Sep 2013-Sep 2014)

Organic Chemistry. Teaching Assistant.

Supervised and instructed students in organic chemistry laboratory techniques. Emphasized on keeping complete and accurate scientific notes. Prepared teaching materials including problem sets and exams. (September 2009 - present)

General Chemistry. Teaching Assistant.

Taught laboratory and discussion classes for all 100 level Chemistry courses. Assisted students individually with home-work problems or materials they found difficult to understand. (September 2009 - present)

## Awards

Chancellor's Fellowship (2009 – 2014), Graduate School Travel Award (2014), Graduate Student Council Award (2014).

## Presentations

"Synthesis of All-Carbon α-Aryl Quaternary Aldehydes: A Convenient Route to Horsfiline." S. A. Asad, M. M. Hossain. CRC International Symposium in Chicago: Asymmetric C-C Bond Formation & Organometallics. October 4, 2014.

"Asymmetric Synthesis of All Carbon Quaternary Centers." S. A. Asad, M. M. Hossain. Annual Symposium at the Dept. of Chemistry & Biochemistry, UWM. April 20, 2013.

## Publications

"First Example of Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of Hydroxyacrylates: Synthesis of All-Carbon α-Aryl Quaternary Aldehydes." **S. A. Asad**, J. Ulicki, M. Shevyrev, N. Uddin, E. Alberch, M. M. Hossain, *Eur. J. Org. Chem.*, **2014**, *26*, 5695. "Editorial Board of *SYNFACTS* selected and reprinted as the *Synfact* of the month for its important insights." *Synfacts*, **2014**, *10(12)*, 1296.

"Stereoselective allyl enol carbonates for synthesis of chiral aldehydes bearing all carbon quaternary stereocenters *via* the decarboxylative asymmetric allylic alkylation (DAAA)." E. Alberch, C. Brook, **S. A. Asad**, M. Shevyrev, J. Ulicki, M. M. Hossain, *Synlett* ***2015,*** *26, 388–392.*

E. Alberch, J. Ulicki, **Md. S. Asad**, M. Mahmun Hossain in *The Chemistry of Organoiron Compounds* (Eds: Ilan Marek, Zvi Rappoport), Wiley, Sussex, UK, **2014**, pp. 249-297.

"A Novel route to Access Asymmetric 3,3′-disubstituted Oxindole." **S. A. Asad**, M. M. Hossain, *Manuscript in preparation*.

"First Example of Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of Hydroxyacrylates: Synthesis of All-Carbon α-Aryl Quaternary Carbonyl Compounds." **S. A. Asad**, M. M. Hossain, *Manuscript in Preparation*.

"Synthesis of α-Aryl Quaternary Carbon Center *via* Palladium Catalyzed Intramolecular Asymmetric Allylic Alkylation." N. Uddin, E. Alberch, **S. A. Asad**, M. M. Hossain, *Manuscript submitted*.

"Concise Synthesis of Tryprostatin B." M. Huisman, **S. A. Asad**, S. Oehm, S. Novin, A. Rheingold, M. Mahmun Hossain, *Manuscript in preparation*.