Rh-Catalyzed Asymmetric C-H Bond Activation By Chiral Primary Amine

by

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A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfilment of the requirements of the degree of

MASTER OF SCIENCE

Department of Chemistry

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Abstract

Developing asymmetric C-H bond activation methods in order to achieve enantiopure products is crucial for the advancement of the field and for the production of novel chiral compounds. Therefore, we tried to develop this area of organic chemistry by presenting metal catalyzed stereoselective C-H bond activation utilizing chelation-assisted tools. The first section of this study involves Rh(I) catalyzed asymmetric C-H bond activation of a series of ketones via an intermolecular procedure. By this method, we examine *ortho*-alkylation of aromatic ketones and β-functionalization of α-β unsaturated ketones with a series of prochiral olefins. In the second section, we present an efficient three steps method for stereoselective intramolecular C-H bond activation of indol-3-carboxaldehyde with tethered prochiral olefins. The catalytic system in both methods involves a joint chiral primary amine and Rh(I) catalyst. Chiral primary amines can serve to induce enantioselectivity as well as acting as a useful directing group which has shown appropriate coordination to the transition metal catalyst, providing high regioselectivity.

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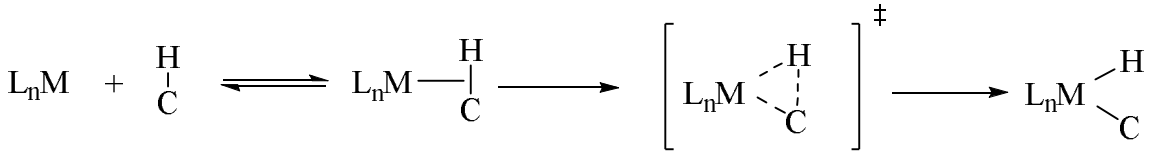
Chapter 1

Introduction

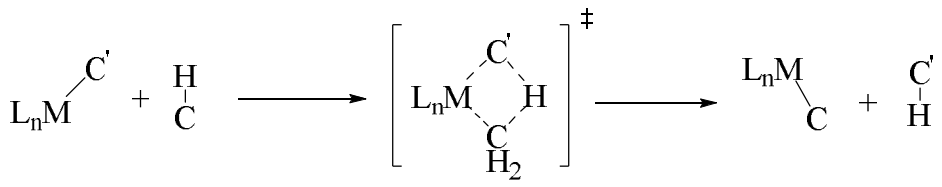
Carbon-Hydrogen bonds are ubiquitous in organic chemistry. The substitution of a C-H bond with a C-X bond, X being C, N, O, S, etc., is a highly desirable process as it allows for the rapid production of complex compounds such as drug molecules, natural products, and polymeric compounds. The issue with this strategy lies in the fact that C-H bonds are inherently unreactive. Transition metals such as Rh and Ru have been shown to be capable of inserting into a carbon-hydrogen bond, serving to activate and cleave the carbon-hydrogen bonds.[1] Once the metal is inserted in the C-H bond it can then complete the catalytic cycle by formation of a new C-X bond.

There are several mechanisms for C-H bond activation of which, oxidative addition and σ metathesis are the most common. Electron rich complexes of transition metals provide sufficient

Oxidative Addition:



σ- Metathesis:



Scheme 1

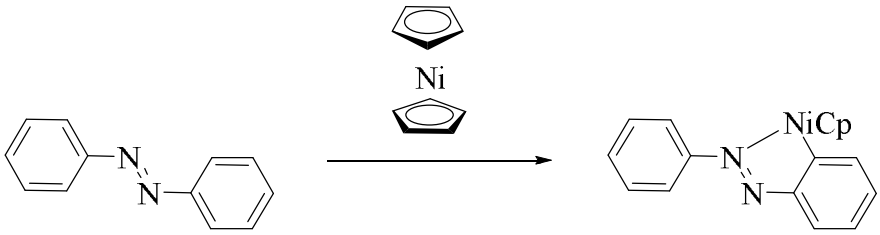
electron density in the metal's *d* orbitals to allow them to achieve higher oxidation number (by oxidative addition). Transition metals with empty *d* orbitals (by σ-metathesis) can activate C-H

bonds (Scheme 1). The interaction between metal's *d* orbitals and C-H antibonding orbitals ($\sigma^*_{C\text{-}H}$) results in cleavage of the C-H bond and formation of a new metal-carbon bond which can undergo further reactions to form carbon-carbon or carbon-heteroatom bonds.[2]

Numerous investigations have been done for developing desirable approaches to activate C–H bonds however due to their wide application in pharmaseutical chemistry, demands for new approaches for developing effective methods with high chemo and regio-selectivity are ever increasing.[3]

1.1.Primary Studies on C-H Bond Activation:

In 1963, Kleiman and Dubeck reported C-H bond activation by transition metals via the reaction of a dicyclopentadienyl nickel complex and azobenzene.[4] In this reaction Ni complex binds to the azobenzene by activating and cleaving the C-H bond of the phenyl group (Scheme 2).



Scheme 2

This method inspired many others in the field and in 1965, Copes and coworkers reported another C-H bond activation of azobenzene with palladium (II) dichloride and potassium tetrachloroplatinate (II).[5] In this method, Pd and Pt were shown to bind to the azobenzene phenyl ring by cleaving the C-H bond and forming complexes *1* and *2* (Figure 1).

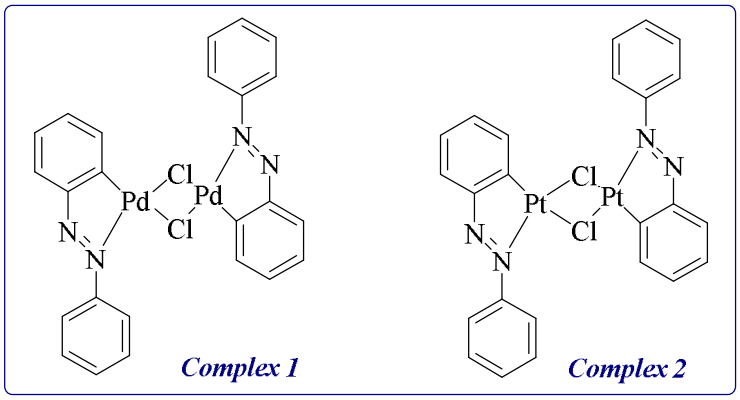


Figure 1

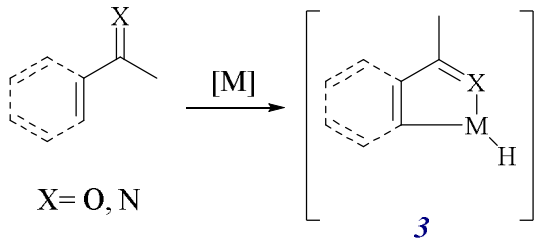
Since then researchers presented several methods for C-H bond activation of organic molecules utilizing a wide range of transition metals including; Cr, Mo, W, Fe, Ru, Os, Rh and Ir, which provide many reactive substances and useful organometal complexes.[6]

1.2.Intermolecular C-H Bond Activation:

Among all of the transition metal catalyzed C-H bond activation, developing methods utilizing chelation-assisted tools which are organic molecules containing heteroatoms such as nitrogen or oxygen has attracted remarkable attention.[7] They can serve as useful directing groups that appropriate coordination of transition metals to their heteroatoms provides efficient steric control on C-H bond activation.[8]

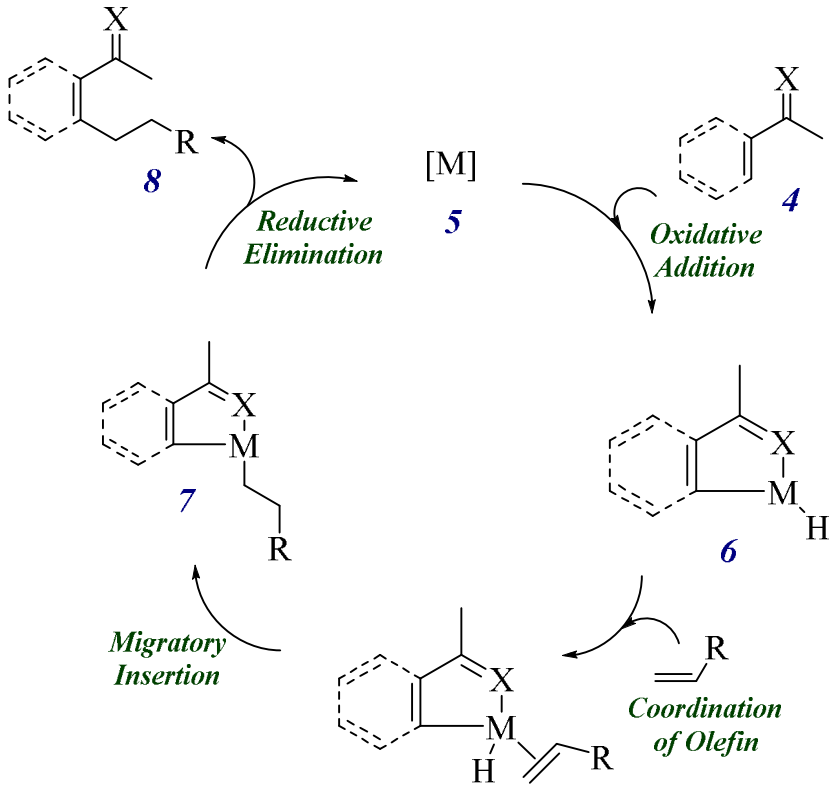
Coordination of transition metals to the directing groups can induce *ortho*-selectivity in aromatic substrates because this coordination brings the metal closer to the C-H bond at the *ortho* position of the aromatic ring therefore the short distance between the *ortho* C-H bond and coordinated metal increase the probability of C-H bond activation at this position.[9] This coordination facilitates C-H bond cleavage at the *ortho* position and results in the formation of a stable five-membered metallacycle, which increases the stability of the intermediate (Scheme 3). In these cases, C-M

bond formation and subsequently C-C bond formation is specific for the *ortho* position because the C-H bond at the *ortho* position has more efficient interaction with the metal coordinated to the directing group and this interaction leads to the formation of a stable intermediate *3*.



Scheme 3

Scheme 4 shows the accepted mechanism for transition metal catalyzed C-H bond activation of aromatic substrates in the presence of a directing group.[10] The first step is coordination of

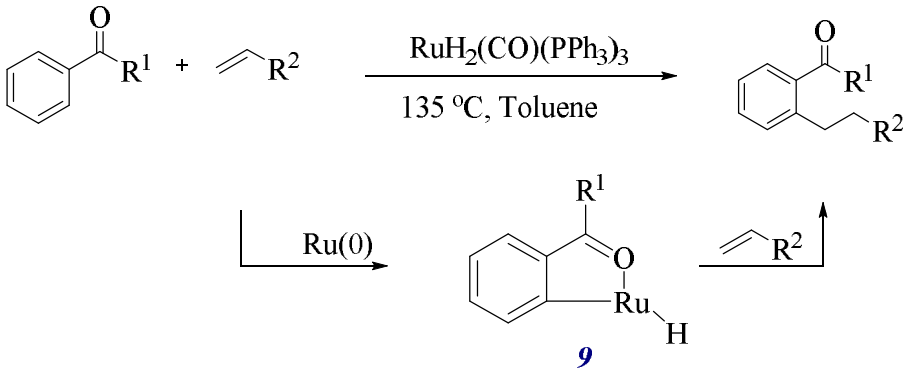


Scheme 4

transition metal (*5*) to the heteroatom of the directing group (*4*) which facilitates C-H bond cleavage specifically at the *ortho* position and results in the formation of a stable intermediate (*6*). The second step involves coordination of olefins to transition metal followed by a hydride insertion on the double bond which gives complex *7*. The last step is the reductive elimination of complex *7*, affording the final *ortho*-alkylated product *8* and regenerating the catalyst *5*.

In 1993, Murai shows the importance of chelation assisting groups for facilitating the C-H bond activation and achieving high regioselectivity by presenting an effective C-H bond activation utilizing ruthenium complex.[11]

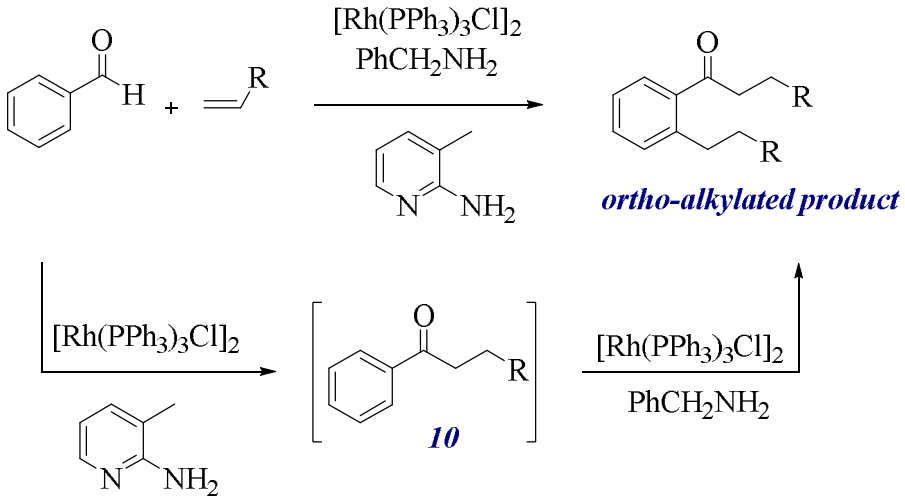
In this method oxygen atom of the carbonyl group acts as a directing group so that Ru complex coordinates to the oxygen and provide the five-membered metallacycle (*9*). Insertion of the olefin followed by reductive elimination produce the *ortho*-alkylated product (Scheme 5). Despite the high efficiency and important applications of this method in direct functionalization of diterpenoid ketones and copolymerization of acetophenone derivatives,[12] there were some limitations in utilizing olefins so that dienes, internal olefins or olefins with electron donation or electron withdrawing groups didn't show an appropriate reactivity in this reaction.[13]



Scheme 5

Most recently, Jun and coworkers presented several methods for C-H bond functionalization of aromatic aldehydes and ketones.[14] Their C-H activation methods are mostly in the presence of Rh(I) catalyst and utilize an imine as a directing group. This method had a relatively broader substrate scope in comparison to Murai's Ru-catalyzed C-H activation method.[15] Amine condensation with carbonyl compounds provides imines which are such a suitable directing groups that Rh can coordinate to their nitrogen atom efficiently. Moreover, a wide range of olefins such as electron rich or electron deficient and internal olefins can be employed as an alkylating agent in this method.[16]

Jun also reported an efficient method for hydroacylation of aromatic aldehyde followed by *ortho*-alkylation of the resulted ketone utilizing Wilkinson catalyst (Scheme 6).[17] The first step of this



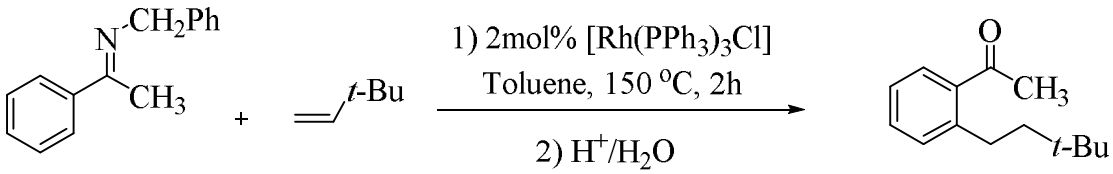
Scheme 6

method includes Rh(I)-catalyzed hydroacylation of aldehydes in the presence of 2-amino-3-picoline as a chelation-assisted tool which affords ketone *10*. At the second step, benzylamine has been served as a directing group and its condensation with ketone *10* provides ketimine which its

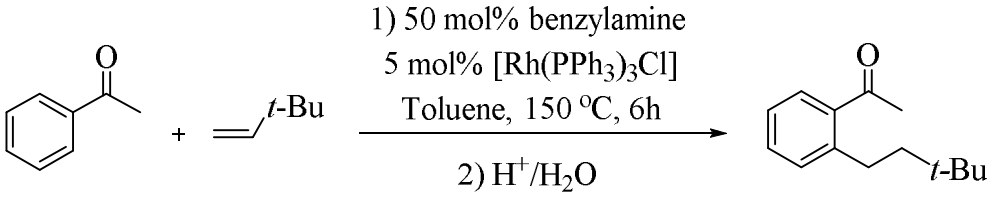
ortho-alkylation by Rh(I) catalyst affords the final *ortho*-alkylated product. This method involves in situ generation of imines for both steps (Scheme 6).

Followed by the domino reaction of hydroacylation and *ortho*-alkylation of aldehydes,[17] Jun and coworkers developed this scope by presenting Rh(I)-catalyzed *ortho*-alkylation of ketimines which are obtained from the condensation of aromatic ketones and benzylamine.[18] They have also reported the direct Rh(I)-catalyzed *ortho*-alkylation of aromatic ketones (Scheme 7). This method involves in situ generation of ketimine by utilizing benzylamine as a chelation-assisted tool. Based on the mechanism of this method, Rh metal coordinates to the ketimine and olefin inserts at the *ortho* position of the aromatic ring. In the next step, reductive elimination followed by a simple hydrolysis affords the *ortho*-alkylated product with high yield.

Ortho-Alkylatin of Ketimine



Direct Ortho-Alkylation of Ketones



Scheme 7

Intermolecular C-H bond activation especially the development of diverse regioselective methods has opened up one of the most promising ways for modifying and functionalizing unreactive bonds and rigid structures,[19] however, it has still some limitations with respect to the olefins scope. For example, 1,1- or 1,2-disubstitueted olefins have shown low reactivity in intermolecular methods and also, olefins contain heteroatoms such as vinyl ethers or amines are not reactive in these types of C-H bond activation.[20]

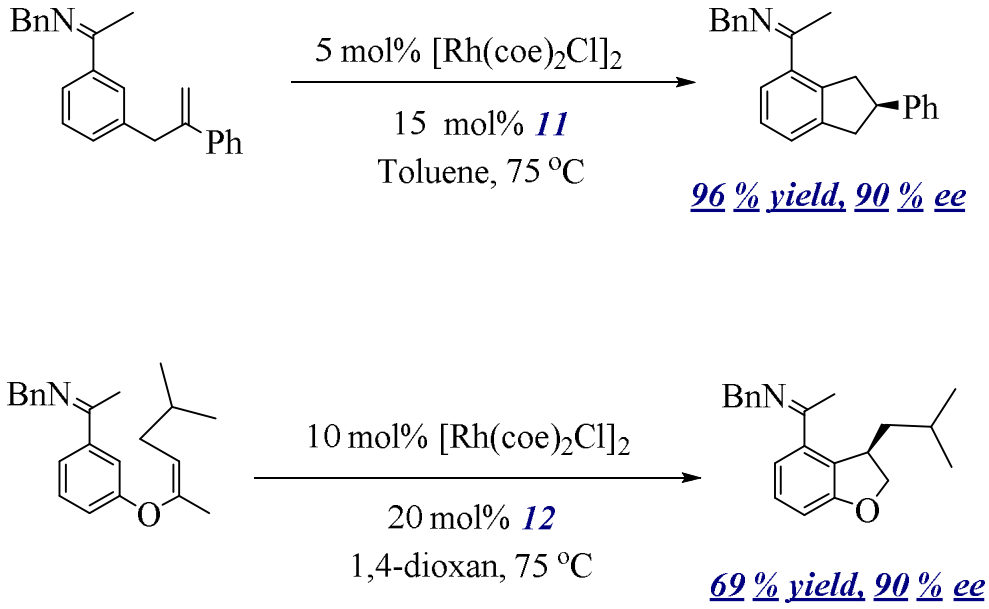
1.3.Stereoselective C-H Bond Activation:

Enantioselective synthesis (aka. asymmetric synthesis) is an important area in pharmaceutical and natural product chemistry since biologically active compounds often contain multiple stereocenters and the efficacy of these compounds is determined by their enantiopurity.[21] Usually, different enantiomers and diastereomers have different biological properties and activities, therefore developing efficient methods for achieving one stereoisomer as a major product instead of a mixtures of equal both (racemic mixture) is of great importance.[22] As mentioned earlier, unsaturated or aromatic hydrocarbons with polycyclic structures are common building blocks in biological systems, therefore, stereoselective C-H bond activation of such compounds is higly desirable as it will allow for the direct formation of previously unachivable stereocenters.

1.4.Stereoselective Intramolecular C-H Bond Activation:

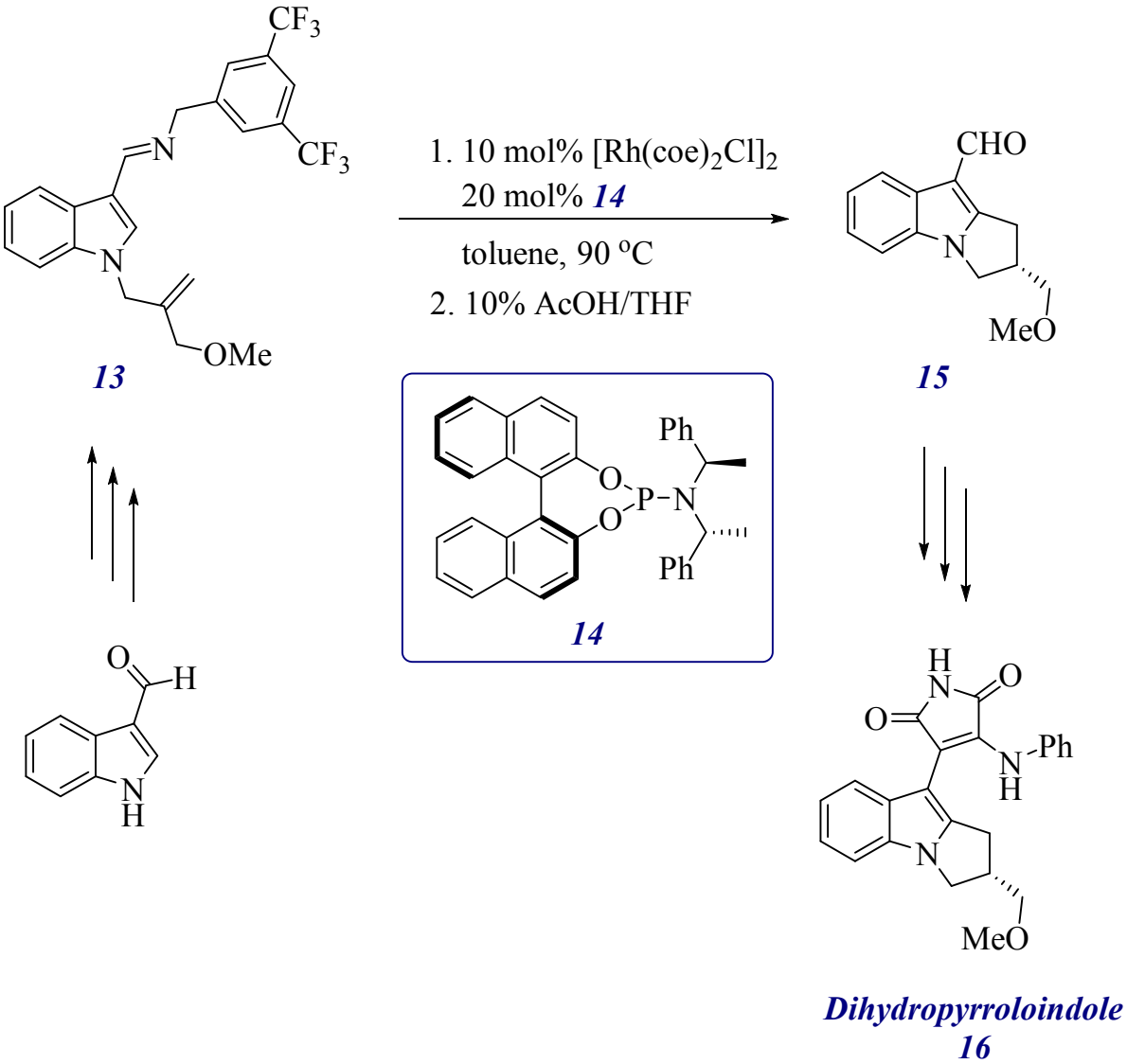
A few investigations have been done in developing intramolecular C-H bond activation of substrates having a tethered olefin [23] such as an enantioselective Rh(I)-catalyzed *ortho*-alkylation of aryl ketimines which is presented by Bergman and his coworkers.[24] They reported an intramolecular cyclization of aryl ketimines containing olefins tethered to the *meta* position, which results in the formation of the annulated product. This method is based on utilizing imine as a

chelation assistant tool and the catalytic system involves a mixture of Rh(I) catalyst and a series of chiral phosphoramidite ligands. Overall, high yields and enantioselectivities were obsereved with this method. A wide range of olefins can be used with this method including 1,1- or 1,2-disubstitueted olefins, which provide aryl and alkyl substituent chiral indanes. Olefins containing heteroatoms such as vinyl ethers are also tolerated and afford chiral dihydro benzofurans derivatives (Scheme 8).



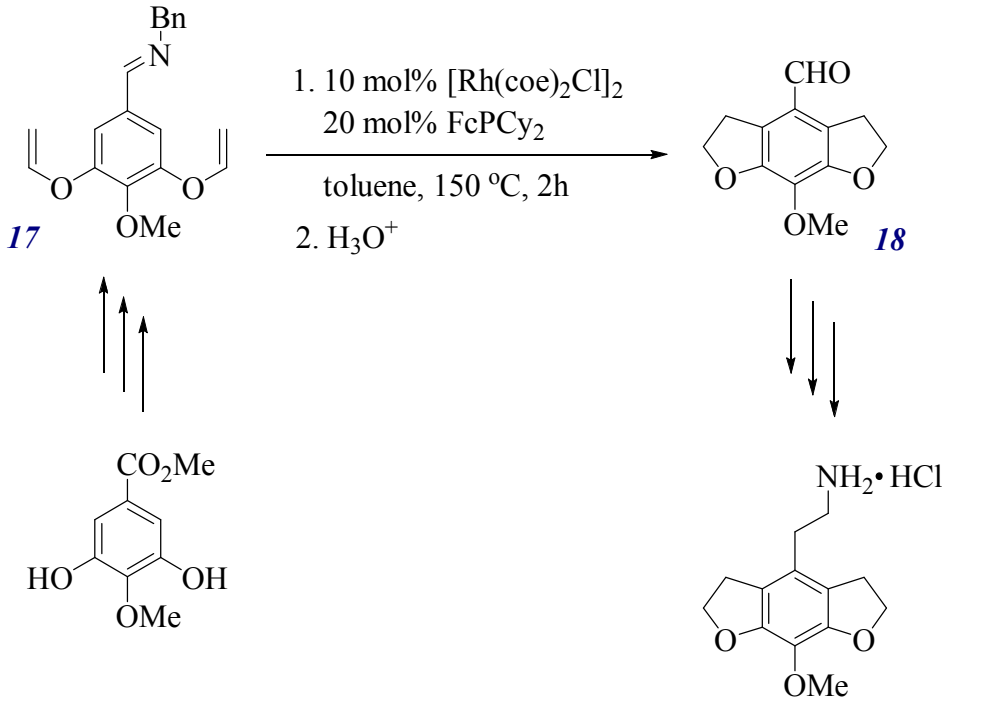
Scheme 8

In another effort, Bergman and his coworkers reported the enantioselective intramolecular C-H activation of indole derivatives and its application in synthesizing biologically active compounds.[25] This method involves intramolecular C-H bond activation of alkylated 3-iminoindole (*13*) in the presence of Rh(I) catalyst and chiral phosphoramidite ligand (*14*) which provide tricyclic chiral indole derivative (*15*) in 65% yield and 90% ee. Further modifications on tricyclic indole *15* results in the formation of dihydropyrroloindole core (*16*) which is a PKC inhibitor[26] (Scheme 9).



Scheme 9

They have also showed another application of intramolecular C-H bond activation of aryl ketimines in drug candidates synthesis by presenting a multistep procedure for synthesizing a tricyclic mescaline analog *19*[27] (Scheme 10). The third step of this method involves imine formation (*17*) which converts to a tricyclic aldehyde (*18*) through an intramolecular C-H bond activation. This step proceeds in the presence of a mixture of Rh(I) catalyst and $FcPCy_2$ as an electron-donating ligand, following a simple hydrolysis in the next step, the tricyclic aldehyde *18* obtained with 65% yield. Within the next steps, aldehyde *18* converts to the tricyclic mescalin analog *19* which has a wide range of medical usages[28] (Scheme 10).



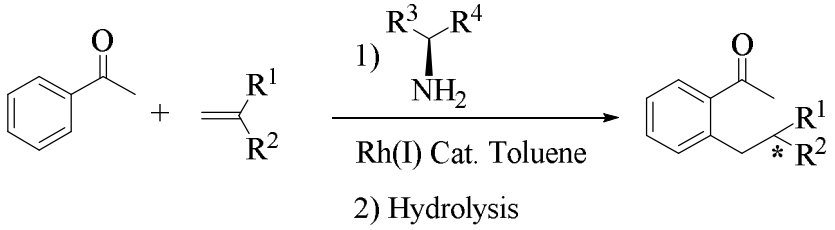
Scheme 10

1.5.Methodology:

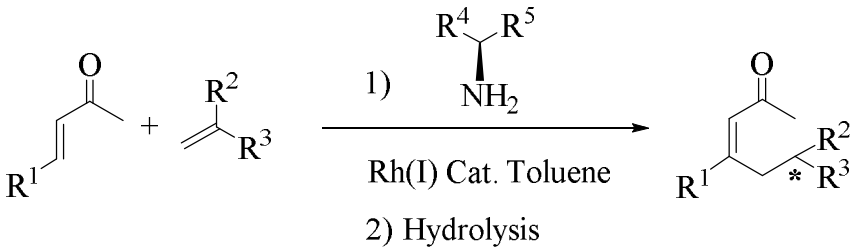
Although achieving enantioselectivity in C-H bond activation methods is a desirable outcome, due to their wide application in biomolecules synthesis, little research has been done in this context. This encouraged us to develop a novel and efficient stereoselective C-H bond activation method in order to improve this area of organic chemistry. We aimed to present a stereoselective C-H bond activation method utilizing asymmetric cooperative catalysis. This catalytic system involves a chiral organocatalyst, in order to induce enantioselectivity, and a transition metal catalyst, which will coordinate to the organocatalyst-substrate complex and promote C-H bond activation.

In this study, two different methods have been investigated; intermolecular C-H bond activation and intramolecular C-H bond activation. The first method is an intermolecular C-H bond activation

Ortho-Alkylation of Aromatic Ketones:



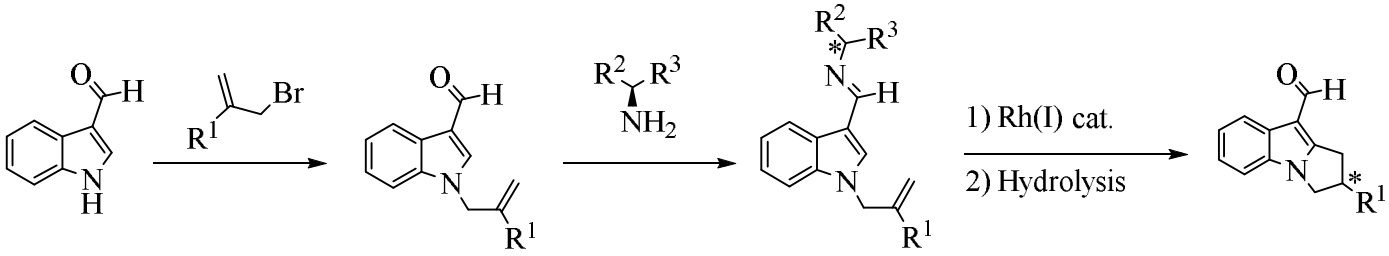
β –Functionalization of α-β Unsaturated Ketones:



Scheme 11

of the aromatic ketones and α-β unsaturated ketones. It was examined with a series of olefins in order to achieve an efficient method for functionalizing such substrates (Scheme 11). This method involves ketimine formation which is a suitable directing group for transition metal coordination furthermore, a broader range of olefins can be employed in the presence of ketimine in compare to other directing groups.[7-8]

The second method is an intramolecular C-H bond activation of indole-3-carboxaldehyde with tethered olefins, which is an important substrate in synthesizing drug candidates and natural product such as biologically active dihydropyrroloindole derivatives.[25-26] These systems can tolerate a wide range of substituted olefins with high ability to form an annulated product due to the short distance of olefin to the coordinated metal catalyst (Scheme 12).



Scheme 12

The catalytic system in both methods involves a chiral primary amine for inducing enantioselectivity and Rh(I) catalyst which has shown good reactivity in C-H bond activation methods.[15]

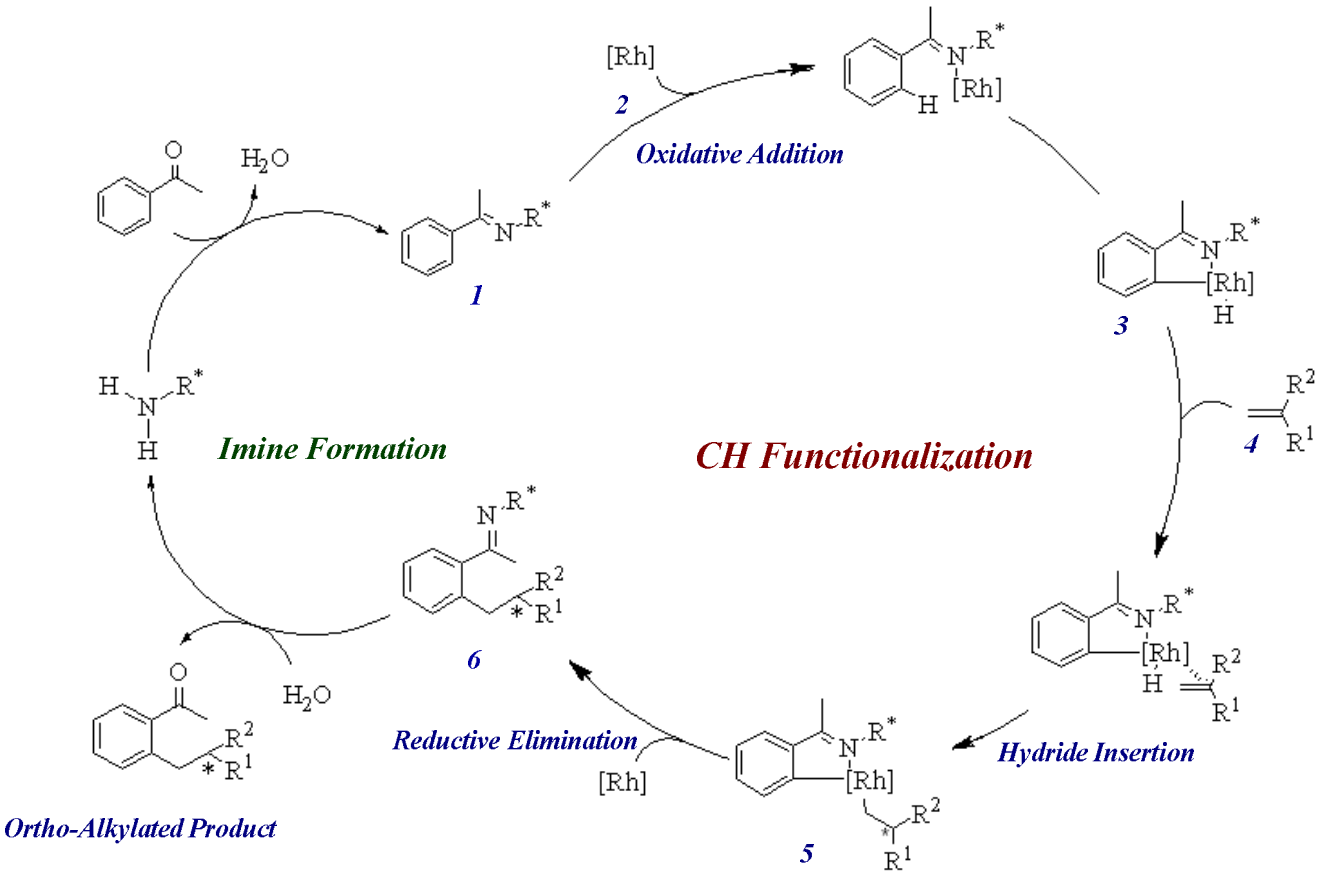
Chapter 2

Result & Discussion

Asymmetric C-H bond functionalization has been a major challenge in synthetic organic chemistry as it would provide rapid access to enantioenriched C-C and C-heteroatom functionalities that previously required multiple steps to achieve. The issue of stereoselective functionalization has not been widely explored with only a few known examples in which selectivity has been achieved through the introduction of chiral ligands.[1,23] This encouraged us to develop a highly stereoselective C-H activation method through a joint aminocatalytic/organometallic system.

Asymmetric Cooperative catalysis, which takes advantage of the high stereoselectivity invoked by chiral aminocatalyst and the C-C bond forming abilities of transition metal catalysts, holds great promise as a method for expanding the range of biologically relevant, enantiopure compounds available. It is envisioned that with this method, the chiral amioncatalysts will serve not only to induce stereoselectivity but will also serve as a directing group for the transition metal due to the efficient coordination of metal to the imine, providing considerable regioselectivity.[29]

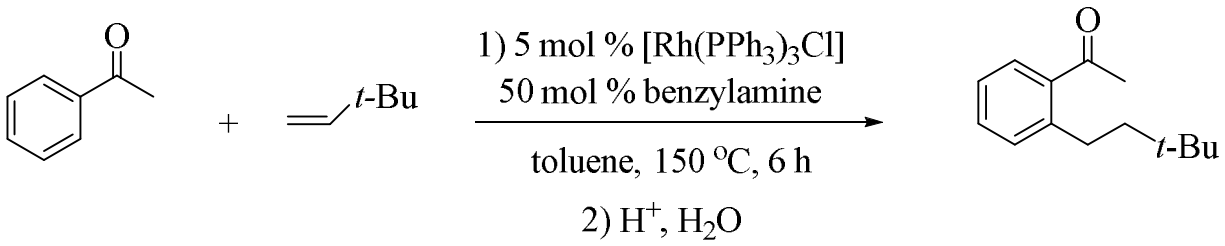
Scheme 1 shows the proposed mechanism of a cooperative catalytic *ortho*-alkylation reaction. The reaction begins with condensation of the primary amine with the ketone to produce the imine (*1*). This is followed by coordination of the Rh(I) complex (*2*) to the imine nitrogen of *1* via oxidative addition. This facilitates the C-H bond cleavage at the *ortho* position of the ketimine and results in the formation of five-membered rhodacycle ring *3* which is the key step of this reaction. Then, coordination of olefin *4* to the Rh metal and hydride insertion gives complex *5*. The next step is reductive elimination step which affords the *ortho*-alkylated ketimine *6* and its hydrolysis regenerates the amine along with the formation of the final *ortho*-alkylated product.[10-18]



Scheme 1

2.1. Rh(I) Catalyzed Stereoselective Intermolecular C-H Bond Activation

Initial development of this asymmetric, cooperative catalytic C-H functionalization began with Rh-catalyzed *ortho*-alkylation reaction. The achiral variant of this reaction has previously been shown to work with in situ formation of the imine. In 2002, Jun and coworkers reported

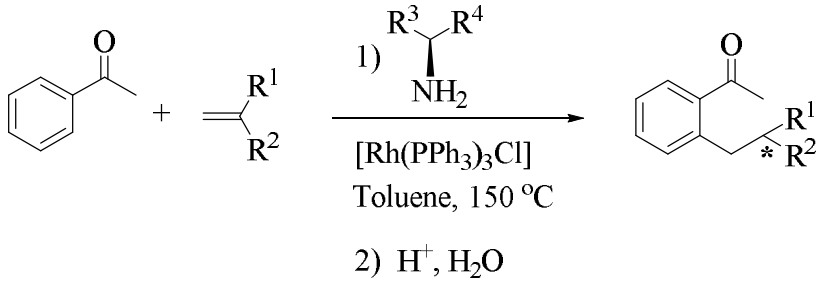


Scheme 2

the *ortho*-alkylation of acetophenone using a catalytic amount of an achiral amine and Wilkinson's catalyst (Scheme 2).[18]

2.2. Stereoselective Ortho-Alkylation of Aromatic Ketones

Our first attempt at asymmetric C-H bond activation involved the Rh(I)-catalyzed *ortho*-alkylation of the aromatic ketones (Scheme 3). Based on previous research[18] these substrates have shown remarkable reactivity in the presence of Rh(I) catalysts and using our proposed method would result in the formation of a chiral substituent on phenyl ring (Scheme 3). Wilkinson catalyst ($Rh(PPh_3)_3Cl$) was chosen as the Rh(I) catalyst as it is relatively stable toward air and moisture and shows a good coordination to the nitrogen atom of the directing group.

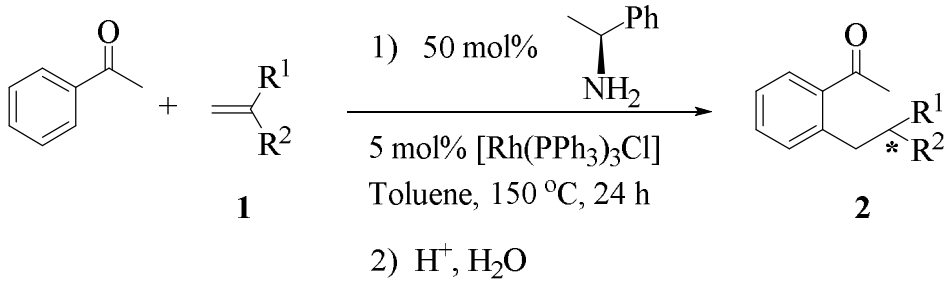


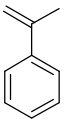
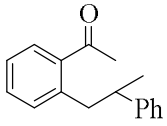
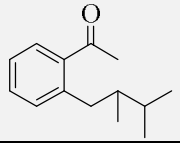
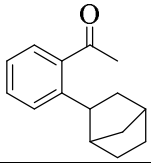
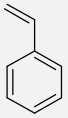
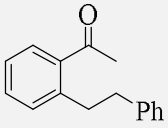
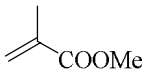
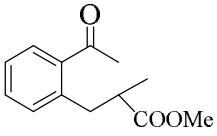
Scheme 3

One pot *ortho*-alkylation of acetophenone was examined with a series of olefins in the presence of Wilkinson catalyst (5 mol%) and 50 mol% of (*S*)-(−)-*α*-methylbenzylamine in toluene. Therefore, based on the model reaction we tried the reaction of acetophenone with a series of aliphatic and aromatic olefins in order to examine their regioselectivity and reactivity in this cooperative catalytic method (Table 1).

In order to achieve stereoselectivity in this reaction, geminally disubstituted olefin was necessary. This substitution pattern allows for the formation of a stereocenter. The prerequisite germinal

Table 1: One Pot Ortho-Alkylation of Acetophenone: Scope of Olefins

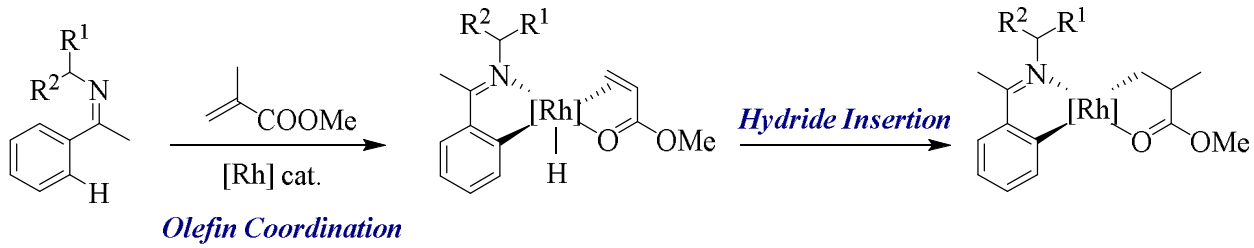


Entry	1	2	Yield
1			N.R*
2			N.R
3			N.R
4			N.R
5			N.R

*N.R.: No Reaction

substitution increases the bulk of these olefins and could decrease the rate of coordination with the Rh catalyst. The first olefins employed contained methyl substituents along with bulky isopropyl and phenyl groups and were unsuccessful in the C-H functionalization reaction (Table 1, entries 1 and 2). We next tried a cycloalkane that should be driven to react by release of the strain imposed by the internal double bond. This too was unsuccessful in the cooperative catalytic method (Table

1, entry 3). To determine if the bulk of the olefin was preventing reaction, we next tried phenylethylene. While this substrate has previously been shown to work in *ortho*-alkylations with Wilkinson's catalyst, it showed no reactivity in this methodology (Table 1, entry 4). We also tried methyl methacrylate which is an electron deficient functionalized olefin (Table 1, entry 5). Based on previously reported mechanistic studies,[30] at the olefin coordination step, the Rh catalyst can coordinate to both double bond and the carbonyl of this olefin, which results in the formation of another five-member rhodacycle ring and stabilize the formed intermediate at this step (Scheme 4). This stabilization can be an efficient factor for promoting this type of C-H activation. We expected to see the *ortho*-alkylated product from these reactions but NMR results didn't show the *ortho*-alkylated product. This left us to question if the combination of Wilkinson's catalyst and methyl benzylamine were appropriate for this C-H functionalization process.



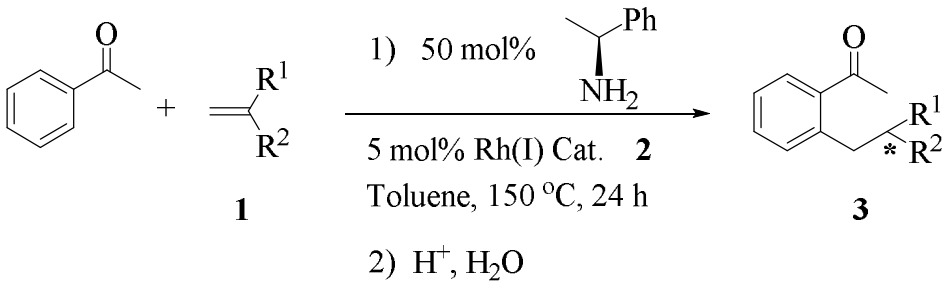
Scheme 4

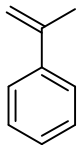
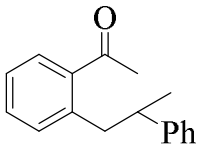
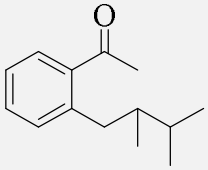
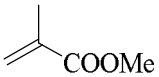
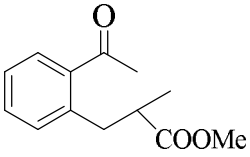
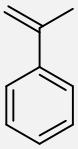
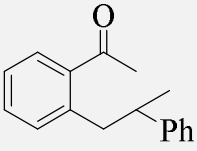
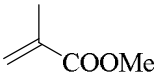
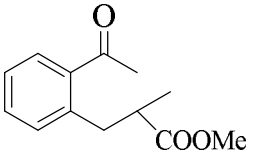
2.3. Examination of Rh(I) Catalysts

In order to examine the activity of the transition metal catalysts, Rh(I) catalysts with different types of ligands such as Chlorobis(cyclooctene)rhodium(I) $[Rh(coe)_2Cl]_2$ and Chloro(1,5-cyclooctadiene)rhodium(I) $[Rh(COD)Cl]_2$ were examined. Compared to Wilkinson catalyst, these catalysts have less bulky ligands with more electron donating properties, which can increase coordination of Rh to the directing group and olefins. Table 2 shows the one pot *ortho*-alkylation of acetophenone with a series of olefins in the presence of these two Rh(I) catalysts and (*S*)-(−)-*α*-

methylbenzylamine. NMR data revealed that these two Rh(I) catalysts didn't make any changes in the final result and the *ortho*-alkylated product was not obtain from these reactions. This left us to consider that the (*S*)-(−)-*α*-methylbenzylamine was preventing the transition metal catalyzed C-H activation of acetophenone.

Table 2: One Pot *Ortho*-Alkylation of Acetophenone: Scope of Rh(I) Catalyst



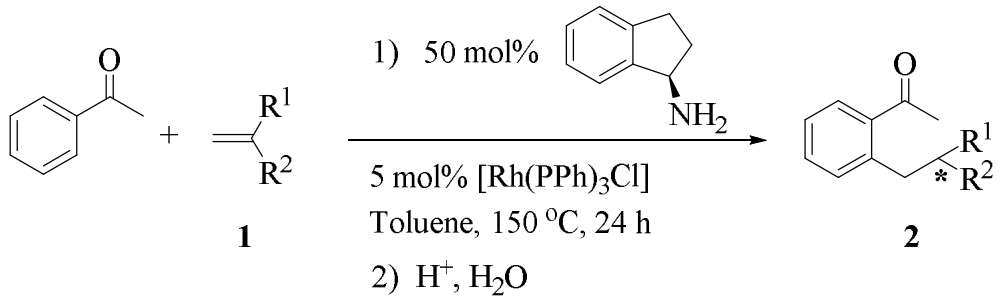
Entry	1	2	3	Yield
1		$[Rh(coe)_2Cl]_2$		N.R*
2		$[Rh(coe)_2Cl]_2$		N.R
3		$[Rh(coe)_2Cl]_2$		N.R
4		$[Rh(COD)Cl]_2$		N.R
5		$[Rh(COD)Cl]_2$		N.R

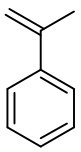
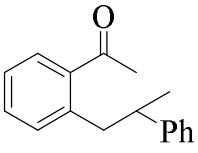
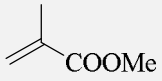
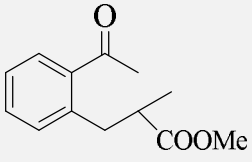
*N.R.: No Reaction

2.4. Examination of Chiral Amine

Benzyl amine is commonly used to form imine directing groups in C-H activation chemistry with Rh(I) catalysts. Therefore it was surprising to think that (*S*)-(−) -*α*-methylbenzylamine, which differs only by the addition of a single methyl group, would have a large impact on the reactivity of this reaction. To investigate the role of amine in the presented method, another chiral primary amine was examined. (*R*)-(−)-1-aminoindane, which has a more rigid structure compared to (*S*)-(−)-*α*-methylbenzylamine, was selected as it might control the stereoselectivity and coordination of Rh catalyst to its nitrogen more efficiently. Table 3 shows the one pot *ortho*-alkylation of acetophenone with two different types of olefins in the presence of 5 mol% Wilkinson catalyst and

Table 3: One Pot *Ortho*-Alkylation of Acetophenone: Utilizing (*R*)-(−)-1-Aminoindane



Entry	1	2	Yield
1			N.R*
2			N.R

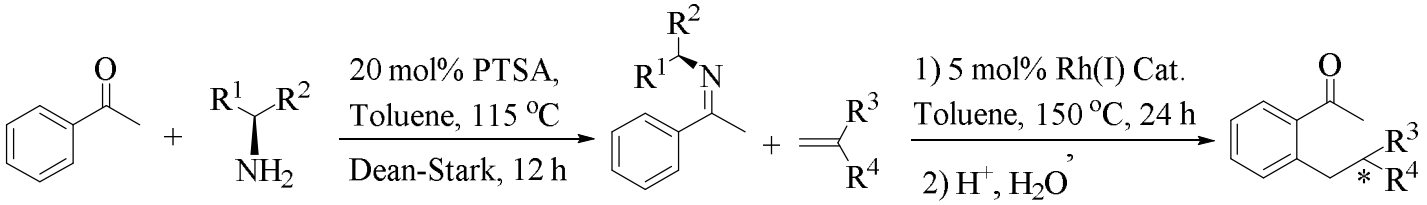
*N.R.: No Reaction

50 mol% of (*R*)-(−)-1-aminoindane in toluene. Once again, NMR result of these two reactions showed no conversion of starting material into *ortho*-alkylated product.

The lack of reactivity observed in our cooperative catalytic method could be due to a number of factors. The condensation of the amine may be slow and thus prevent the C-H activation from occurring. The rate of condensation is typically enhanced by the addition of acid, however, in these reactions, the addition of an acid can lead to competing for side reactions or deactivation of the Rh(I) catalyst. It is also possible that the added bulk of the amine could be preventing coordination of the Rh(I) catalyst.

2.5. Two-Step Stereoselective Intermolecular C-H Bond Activation

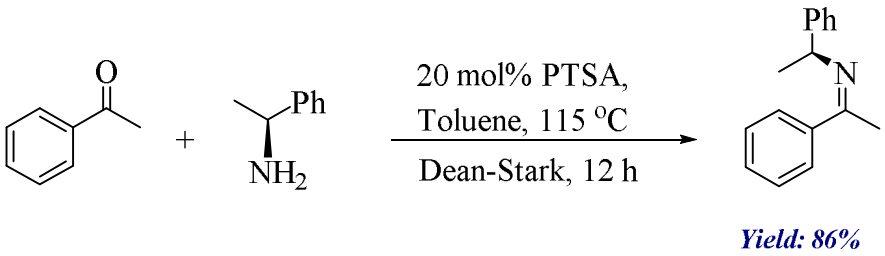
To investigate these issues, we needed to take a step back and look at the reactivity of chiral amines in a two-step process where the rate of condensation and bulk of the amine could be addressed separately. This reaction is designed to provide the imine as an isolated intermediate and should provide insight into the influence of the steric bulk of the imine on the C-H activation step (Scheme 5). The first step in this process involves ketimine formation through the reaction of ketone and amine. The corresponding ketimine would be isolated and purified at this step. The second step is the C-H bond functionalization of the isolated ketimine with olefin and in the presence of Rh catalyst.



Scheme 5

2.6. Ortho-Alkylation of Aryl Ketones

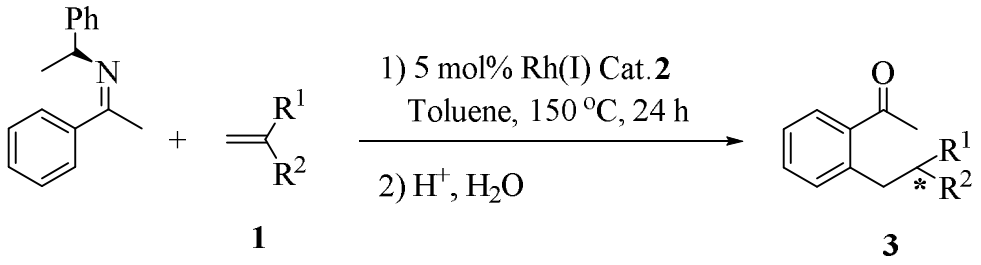
Based on the one pot *ortho*-alkylation results, we decided to attempt the *ortho*-alkylation of aromatic ketones via a two-step reaction. We began with the reaction of acetophenone and (*S*)-(−)-*α*-methylbenzylamine in the presence of catalytic amount of *para*-toluyl sulfonic acid, PTSA (20 mol%) (Scheme 6). PTSA was added to activate the ketone and promote the condensation of the amine. The reaction is performed under reflux in a Dean-Stark apparatus, which allows for removal of water and drives the equilibrium in favor of the product. This reaction afforded the corresponded imine with 86% yield. The product was characterized by ^{1}HNMR and ^{13}CNMR.



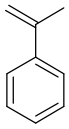
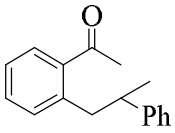
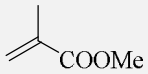
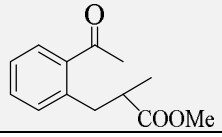
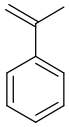
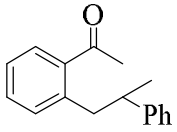
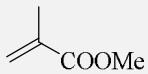
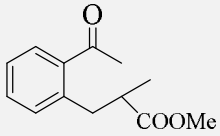
Scheme 6

In the next step, the functionalization of the aromatic ring of the ketimine with the olefins using 5 mol% of Rh(I) catalysts was examined (Table 4). The use of Wilkinson's catalyst with two separate olefins provided no conversion to the desired product and only starting material was recovered from these reactions (Table 4, entries 1 and 2). When we employed a more active Rh(I) complex as a catalyst we again saw no conversion to product with the disubstituted olefins (Table 4, entries 1 and 2). Although the imine was achieved in good yields, the C-H functionalization of the aryl imine was not successful.

Table 4: *Ortho*-Alkylation of Ketimine: Examination of Olefins & Rh(I) catalysts



1 3

Entry	1	2	3	Yield
1		$[Rh(PPh)_3Cl]$		N.R*
2		$[Rh(PPh)_3Cl]$		N.R
3		$[Rh(coe)_2Cl]_2$		N.R
4		$[Rh(coe)_2Cl]_2$		N.R

*N.R.: No Reaction

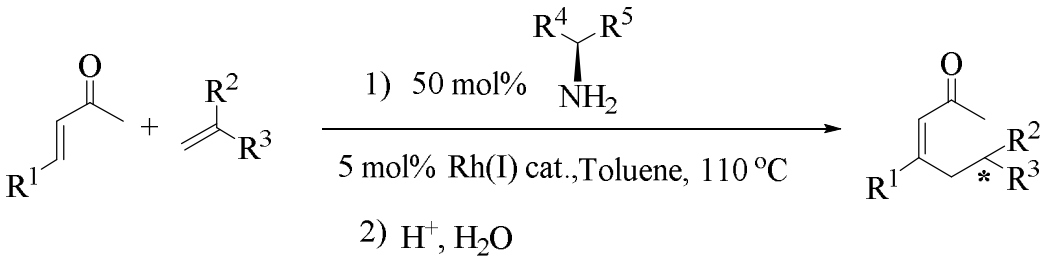
2.7. β-functionalization of Nonaromatic α-β Unsaturated Ketones

α-β unsaturated carbonyl compounds are another class of promising substrates that can serve as an important building blocks in bioactive compounds, therefore stereoselective functionalization of these compounds can lead to develop useful strategies in biomolecules synthesis.[31] However, only a few efforts of C-H functionalization of these compounds can be seen in the literature. [32]

Therefore we aimed to develop a stereoselective *β*-functionalization of nonaromatic *α*-*β*-unsaturated ketones, which was based on activation of ketone's *β* position by means of the cooperative catalytic system.

2.8. One-Pot β-Functionalization

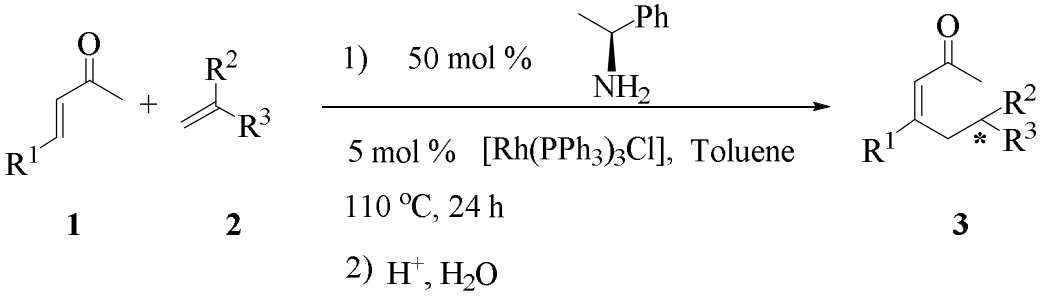
As with the *ortho*-alkylation of aromatic ketones, the one pot *β*-functionalization was based on utilizing catalytic amount of a chiral primary amine which during the reaction with *α*-*β*-unsaturated ketone provides corresponded imine as an effective directing groups and without any purification the resulted imine goes through the C-H activation step in the presence of Rh(I) catalyst that results in formation of *β*-functionalized product (Scheme 7).



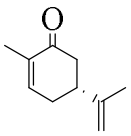
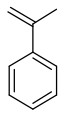
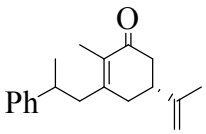
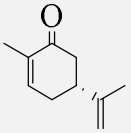
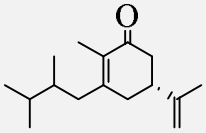
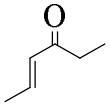
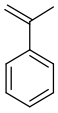
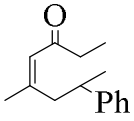
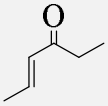
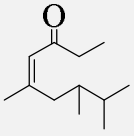
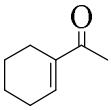
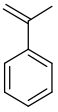
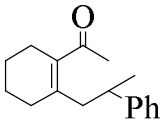
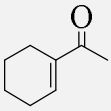
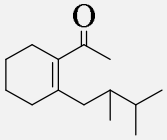
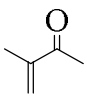
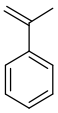
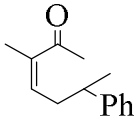
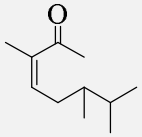
Scheme 7

Base on the model reaction, we tried one-pot *β*-functionalization of a series of *α*-*β*-unsaturated ketones with *α*-methyl styrene and 2,3-dimethy-1-butene as two different types of aromatic and aliphatic olefins. The reactions were carried out in the presence of 50 mol% of (*S*)-(−)-*α*-methylbenzylamine and 5 mol% of Wilkinson catalyst (Table 5). Based on NMR spectra of the reaction mixture after 24 hours, *β*-functionalized was not achieved with this method.

Table 5: *β*-Functionalization of Nonaromatic *α-β* Unsaturated Ketones: Substrate Scope



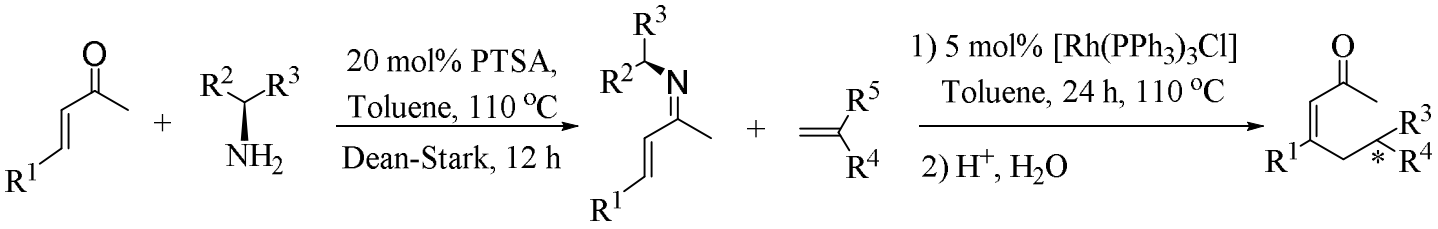
1 **2** **3**

Entry	1	2	3	Yield
1				N.R*
2				N.R
3				N.R
4				N.R
5				N.R
6				N.R
7				N.R
8				N.R

*N.R.: No Reaction

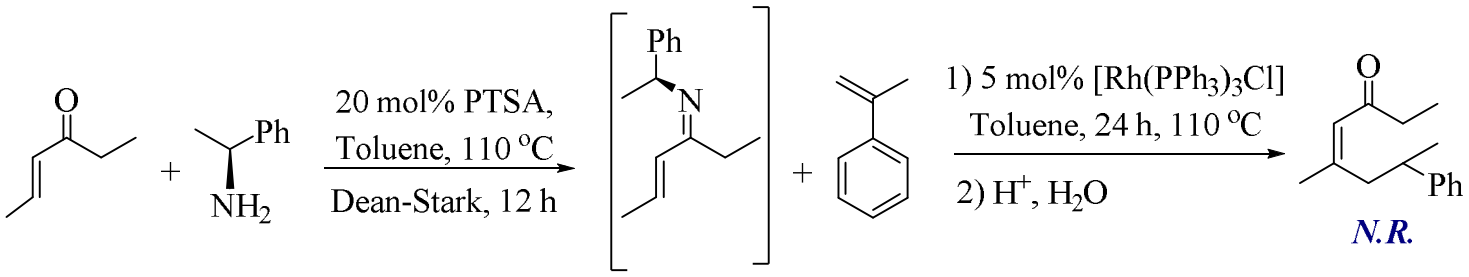
2.9. Two-Step β-Functionalization

Following the same procedure used in the study of the two-step *ortho*-alkylation, we tried *β*-functionalization via a two-step procedure. The model reaction includes two steps (Scheme 8). First step is ketimine formation and the second step is the Rh catalyzed functionilzation of the *β*-C-H bond of the imine.



Scheme 8

Ketimine synthesis from the reaction of 4-hexane-3-one and (*S*)-(−)-*α*-methylbenzylamine and its reaction with 3-methyl-3-butene-2one in the second step was the only effort that has been done for this method (Scheme 9). Based on the NMR spectra of these reactions, corresponded ketimine was not achieved with a remarkable yield in the first step so that, we couldn't perform any purification and isolation however we employed the crude directly in the second step but the *β*-functionalized product was not observed.

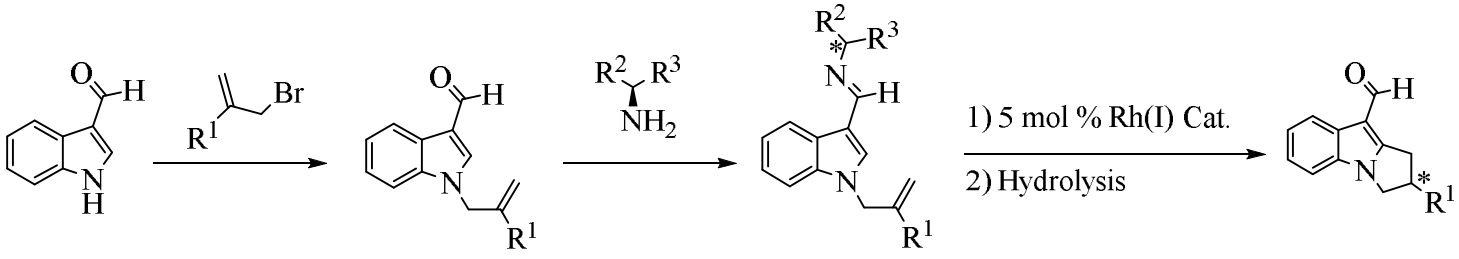


Scheme 9

2.10. Rh(I)-Catalyzed Stereoselective Intramolecular C-H Bond Activation

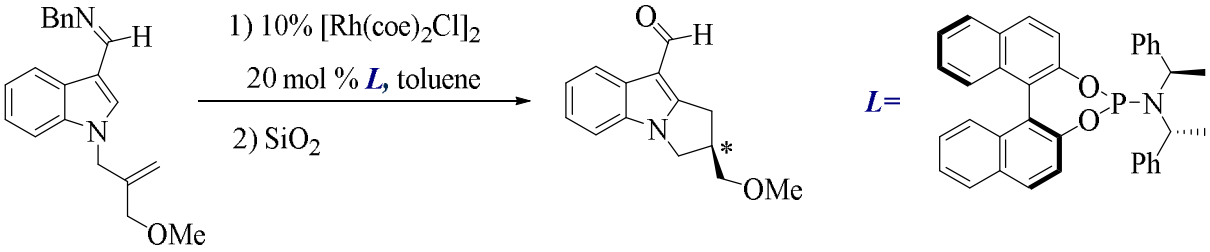
As the cooperative catalytic and stepwise forms of the intermolecular asymmetric C-H activation proved unsuccessful, we next tuned to the develop an intramolecular C-H activation method by utilizing same chiral primary amines and Rh(I) catalysts. It was thought that part of the problem faced by the intermolecular variant was the steric bulk of the imine and olefin that prevented coordination of the olefin to the Rh catalyst and hindered the reaction. The use of a tethered olefin would increase the probability of coordination by placing the olefin in close proximity to the Rh-imine complex. Additionally, the tethered system would require a less substituted double bond in order to produce a stereocenter, decreasing the steric hindrance caused by the olefin and increasing its ability to coordinate to the metal center.

Our initial intramolecular methodology involves developing a stereoselective C-H bond activation of indole-3-carboxaldehyde derivatives through a multistep procedure (Scheme 10). As with the intermolecular method described previously, we planned to induce enantioselectivity to the C-H activated product by utilizing chiral primary amine and Rh(I) catalyst as a metal catalyst. Bases on the model reaction (Scheme 10) the first step involves the synthesis of the alkylated indole via alkylation of indole-3-carboxaldehyde with an alkyl bromide. The second step is 3-iminoindole formation and the last step is C-H activation step in the presence of Rh(I) catalyst which results in the formation of the annulated product.



Scheme 10

Bergman and his coworkers have previously reported the production of chiral indole derivatives using C-H activation in 2006.[25] However, their procedure is based on utilizing an achiral amine and achieving stereoselectivity by means of a chiral phosphoramidite ligand (Scheme 11). In our method, instead of utilizing chiral ligands, we aim to induce selectivity by asymmetric cooperative catalytic system, which includes a chiral primary amine and metal catalyst. The advantage of a chiral amine over a chiral ligand is that the amine can serve to induce selectivity as well as acting as a chelation-assisted tool, which has a significant ability in coordination to the metal catalysts and can induce high regio- and stereo-selectivity.[8,16] Furthermore, chiral amines are cheap and commercially accessible reagents compared to chiral phosphoramidite ligands.

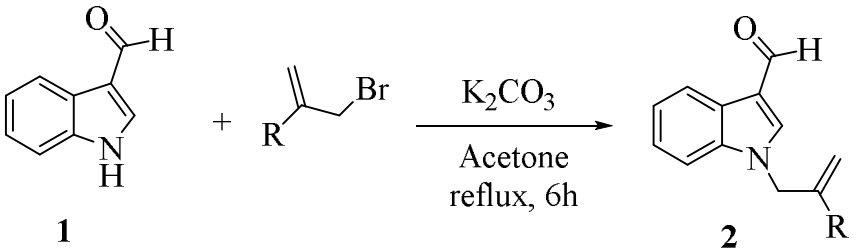


Scheme 11

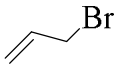
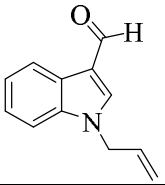
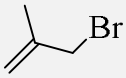
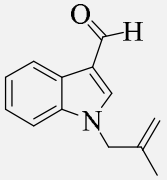
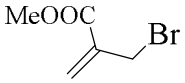
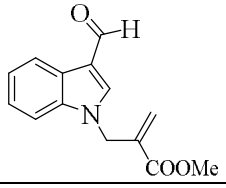
2.11. Alkylation of Indole-3-Carboxaldehyde

In order to develop an intramolecular C-H activation method, we first had to synthesize the alkylindoles. We started with alkylation of indole-3-carboxaldehyde using allyl bromide and two allyl bromide derivatives (Table 6). Given the low cost of allyl bromide, relative to its derivatives, it was chosen as a test substrate to ensure the alkylation procedure was effective as well as to test subsequent steps of the C-H functionalization procedure. Methallyl bromide and Methyl 2-(bromomethyl)acrylate were chosen as alkylating agents as they would provide stereocenters when reacted in the C-H functionalization procedure (Table 6, entries 2 and 3). Results of these reaction were favorable and alkylated indoles were isolated with high yields from all of these reactions.

Table 6: Alkylation of Indole 3-Carboxaldehyde: Scope of Allyl Bromide



1 **2**

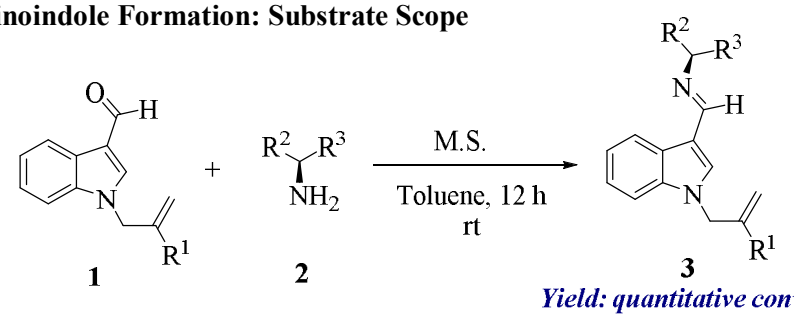
Entry	1	2	Yield
1			95
2			92
3			87

2.12. Iminoindole Synthesis

The next step involves 3-iminoindole formation from the reaction of alkylated indoles and chiral primary amine (Table 7). The scope of chiral primary amines includes (*S*)-(−)-*α*-methylbenzylamine (Table 7, entries 1 and 4) and (*R*)-(−)-1-aminoindane. These amines were chosen for their relatively flexible and rigid structures respectively which can be effective in the coordination of Rh metal to their nitrogen in the last step (Table 7, entries 3, 5 and 6). We also tried phenylalanine methyl ether, which is a chiral amino acid with a relatively similar structure to benzyl amine (Table 7, entry 2). Based on the other research works, benzyl amine shows good reactivity in this types of reactions, therefore, we thought about utilizing a chiral amine with a

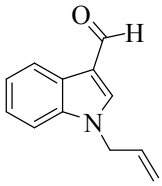
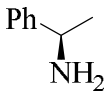
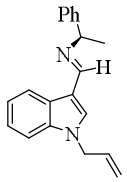
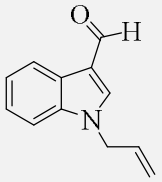
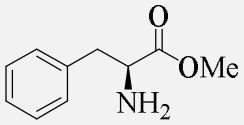
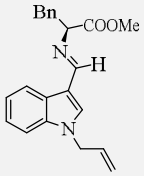
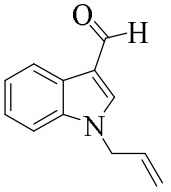
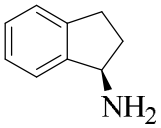
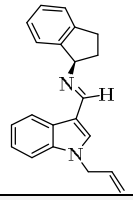
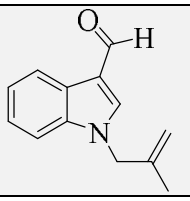
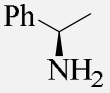
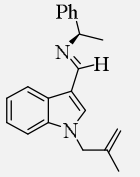
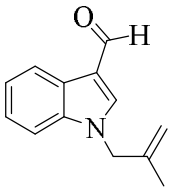
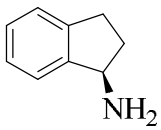
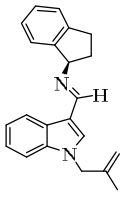
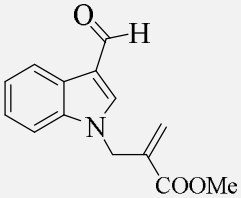
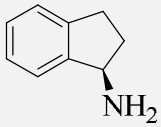
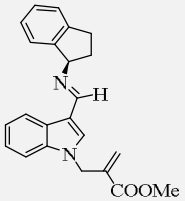
similar structure to benzyl amine which might be effective for promoting this C-H activation.

Table 7: 3-Iminoindole Formation: Substrate Scope



1 **2** **3**

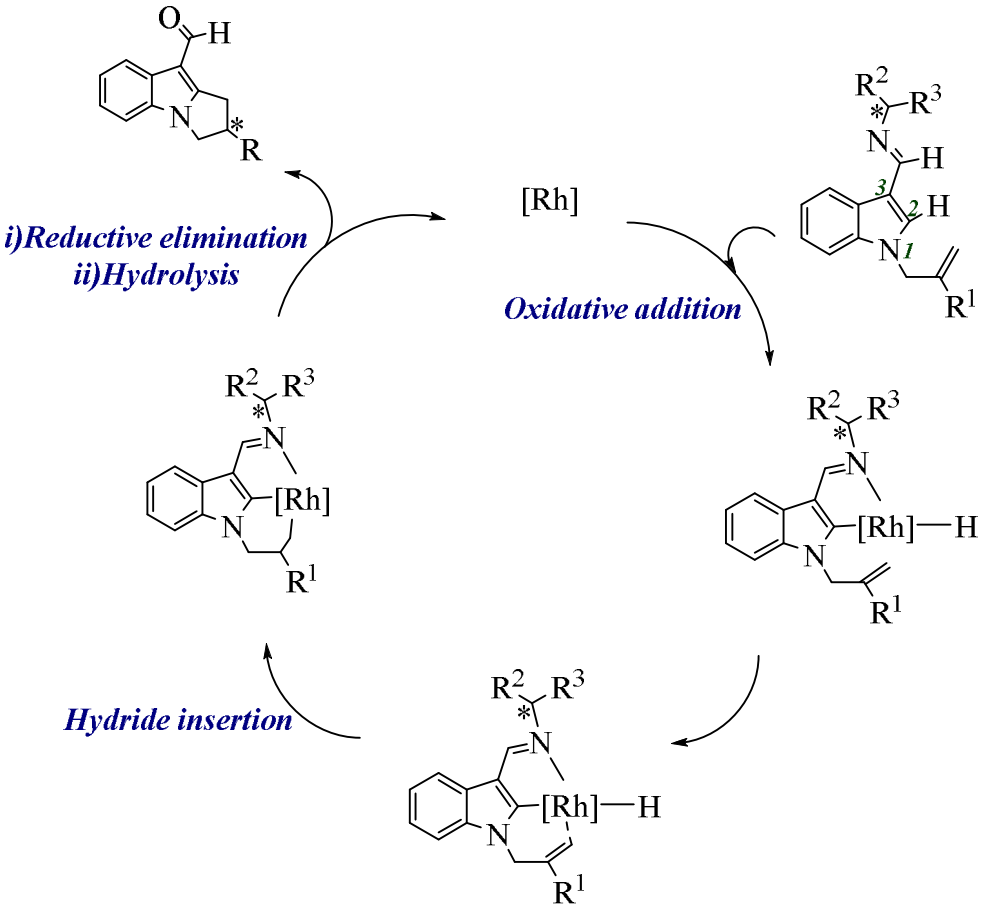
Yield: quantitative conversion

Entry	1	2	3
1			
2			
3			
4			
5			
6			

Desirable results were achieved from all of the imine formation reactions with and the corresponding 3-iminoindoles were obtained with almost quantitative conversations. These imines were then used for the next step without any further purification and isolation.

2.13. C-H Bond Activation of 3-Iminoindole Utilizing Rh(I) Catalysts

C-H bond activation of the resulted 3-iminoindoles followed by imine moiety hydrolysis is the last step of our intramolecular method which provides the annulated product (Scheme 10). Based on the proposed mechanism, this reaction involves coordination of Rh catalyst to the nitrogen of the imine via oxidative addition and cleaving the C-H bond at *C-2* which result in the formation of a



Scheme 12

five-member rhodacycle. Coordination of the tethered olefin to the Rh followed by hydride insertion, reductive elimination and hydrolysis of the imine affords the final product (Scheme 12).

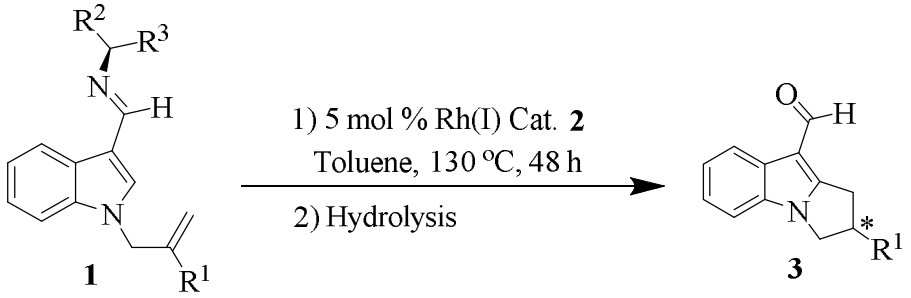
2.14. Scope of Rh(I) Catalysts

Table 8 shows a series of Rh(I) catalysts which have been used in C-H bond activation of 3-iminoindoles. In the case of the iminoindoles achieved from (*S*)-(−)-*α*-methylbenzylamine (Table 8, entries 1 and 6), the annulated product was not observed when reacted with Wilkinson catalyst and NMR spectra showed corresponds alkylated indole which has been formed after hydrolysis. In the case of the iminoindole resulted from phenylalanine (Table 8, entry 4), NMR results didn't show any C-H activated product. We also tried iminoindoles obtained from (*R*)-(−)-1-aminoindane, which is an amine with more rigid structure compared to (*S*)-(−)-*α*-methylbenzylamine and therefore might control the Rh metal coordination more efficiently (Table 8, entries 5 and 8). In the case of this amine we expected to see the annulated product but results were not favorable and annulated product was not achieved.

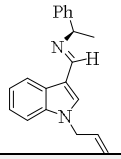
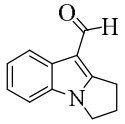
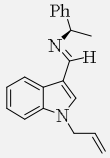
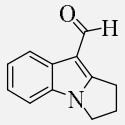
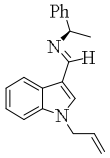
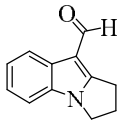
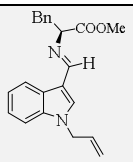
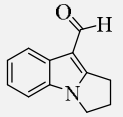
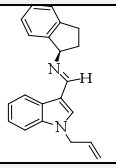
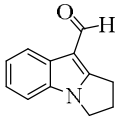
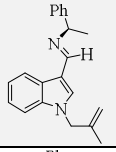
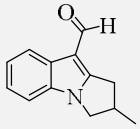
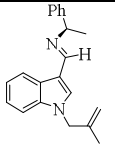
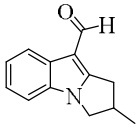
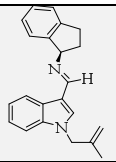
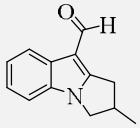
In another effort we tried Chlorobis(cyclooctene)rhodium(I) $[Rh(coe)_2Cl]_2$ and Chloro(1,5-cyclooctadiene)rhodium(I) $[Rh(COD)Cl]_2$ which have less bulkiest ligands with more electron donating properties that might be effective in better coordination of Rh to the directing group or internal olefin (Table 8, entries 2-3, 7). However, these Rh(I) catalysts were not effective and the corresponding alkylated indole starting substrates were isolated after hydrolysis.

This results left us to consider that electron donating properties of Rh(I) catalysts might not be enough for this type of C-H activation method. Rhodium metal is bonded to different ligands with covalent or dative bonds, which has an effect on electron donating properties of the catalyst.

Table 8: C-H Bond Activation of Various 3-Iminoindoles: Scope of Rh(I) Catalyst



1 **3**

Entry	1	2	3	Yield
1		$[Rh(PPh_3)Cl]$		N.R*
2		$[Rh(coe)_2Cl]_2$		N.R
3		$[Rh(COD)Cl]_2$		N.R
4		$[Rh(PPh_3)Cl]$		N.R
5		$[Rh(PPh_3)Cl]$		N.R
6		$[Rh(PPh_3)Cl]$		N.R
7		$[Rh(coe)_2Cl]_2$		N.R
8		$[Rh(PPh_3)Cl]$		N.R

*N.R.: No Reaction

Therefore if these catalysts coordinate to the heteroatom of the directing group without any steric hindrance, the rhodium metal might not be electron rich enough to transfer electrons from its σ orbital to the σ^* orbital of C-H bond in order to activate and cleavage this bond, which means our C-H activation methods might need more electron rich metals.

2.15. Modification of Rh(I) Catalytic System

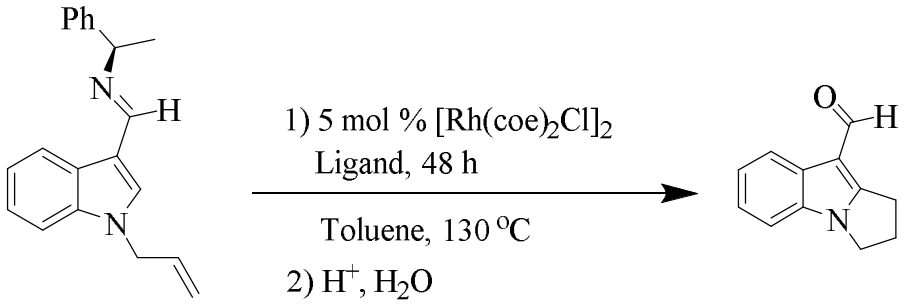
The inefficiency of the examined Rh(I) catalysts in the methods discussed above led to modification of Rh(I) catalytic systems. We aimed to use more electron rich Rh(I) catalyst combined with electron donating ligands to increase the electron donating properties of the catalytic system.

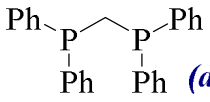
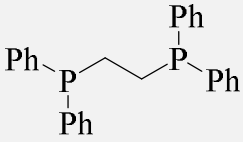
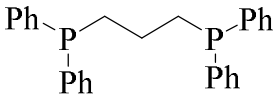
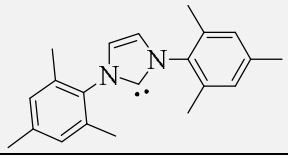
Chlorobis(cyclooctene)rhodium(I) $[Rh(coe)_2Cl]_2$ is a dimer Rh(I) catalyst. The rhodium in this catalyst forms a covalent bond with one chloride and two dative bonds with two cyclooctene rings. These dative bonds have a strong π-donation but a weak π-back donation which makes the rhodium-cyclooctene bonds easier to break.

We employed Chlorobis(cyclooctene)rhodium(I) catalyst with a series of electron donating ligands such as 1,1-Bis(diphenylphosphino)methane (dppm), 1,2-Bis(diphenylphosphino)ethane (dppe), 1,3-Bis(diphenylphosphino)propane (dppp), tri-tert-butylphosphin and tricyclohexylphosphine ($P(Cy)_3$). These ligands can exchange with the cyclooctene rings of the Rh(I) catalyst and increase the electron donating properties of Rh(I) catalytic system. As shown in Table 9, the annulated product was achieved in the presence of $[Rh(coe)_2Cl]_2$ catalyst and dppm or P(*t*-Bu)$_3$ as an electron donating ligands with a ratio of 1:2 (Catalyst : Ligand). However, NMR spectra showed only trace amounts of the product under these conditions, suggesting no catalyst turn over (Table 9, entries 1

and 5). These results were improved with a 1:2 ratio of $[Rh(coe)_2Cl]_2$ catalyst and $P(Cy)_3$ ligand. Although, in this case, the product yield was still less than 15% (Table 9, entry 6).

Table 9: C-H Bond Activation of 3-Imioindoles: Examination of Electron Donating Ligands



Entry	Ligand	% Ligand	% Yield
1	 *(dppm)*	10	Trace
2	 *(dppe)*	10	0
3	 *(dppp)*	10	0
4		10	0
5	$P(t\text{-}Bu)_3$	10	Trace
6	$P(Cy)_3$	10	≤15
7	$P(Cy)_3$	30	28

Encouraged by these resluts, we tried to optimize the Catalyst : Ligand ratio in order to improve the yield. Lim and his co-worker presented regioselective alkylation of aromatic ketimines via C-H bond activation by utilizing 1:6 ratio of $[Rh(coe)_2Cl]_2$ catalyst and $P(Cy)_3$ ligand.[33] Based on this method, we employed 1:6 ratio of $[Rh(coe)_2Cl]_2$ catalyst and $P(Cy)_3$ ligand in the last step which afforded the annulated product with 28% yield (Table 9, entry 7).

2.16. C-H Activation of 3-Iminoindoles Utilizing Rh(I) Catalyst & Electron Donating Ligand

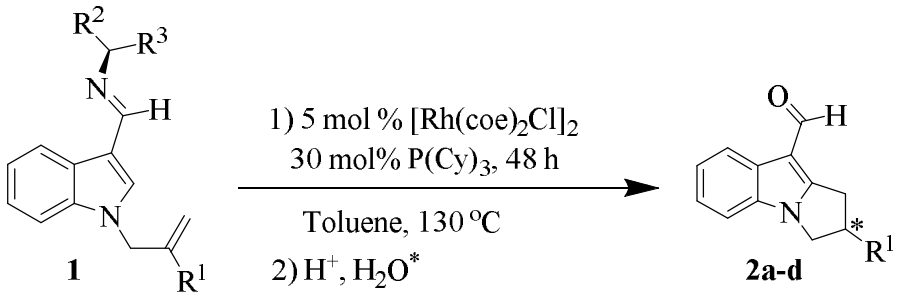
Utilizing the 1:6 ratio of $[Rh(coe)_2Cl]_2$ catalyst and $P(Cy)_3$ ligand that was identified in the optimization of the reaction conditions we then examined the scope of 3-aminoindoles that could be applied in this reaction. C-H bond activation of imines obtained from indoles and (*S*)-(−)-*α*-methylbenzylamine provided the annulated products *2a* with 28% yield and *2b* with 35% yield (Table 10, entries 1 and 2). We also tried 3-iminoindoles resulted from (*R*)-(−)-1-aminoindane, its two different derivatives with a methyl or methoxycarbonyl substituents on the internal alkene afforded products *2c* with 32% and *2d* with 26% yield (Table 10, entries 3 and 4).

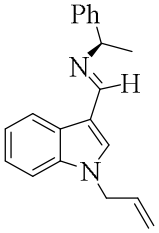
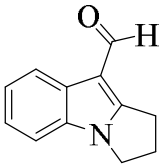
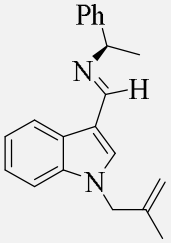
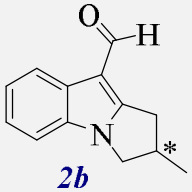
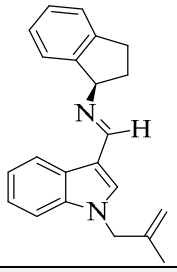
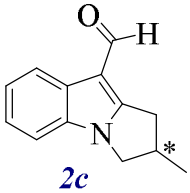
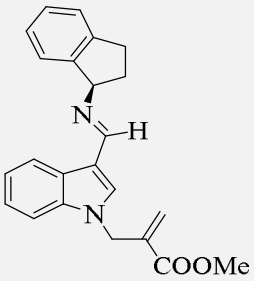
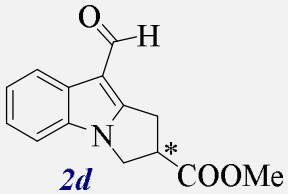
2.17. Analysis of Stereoselectivity of Annulated Products

The main purpose of developing this method was achieving enantioselectivity, which can be induced by utilizing a chiral amine. Therefore, we analyzed the pure annulated products (Table 10) by chiral HPLC in order to determine enantioselectivity. In order to identify the exact area of two enantiomers in HPLC, a racemic mixture of annulated products was prepared by utilizing a racemic mixture of methylbenzylamine (Scheme 13). Chiral HPLC analysis were performed on a chiral column with a flow rate of 1 mL/min and 10 % THF: 90 % Hexane as eluent.

The three annulated products produced in the scope (*2b*, *2c* and *2d*) with a chiral center on the newly formed five member ring were analyzed with this method. Based on HPLC results, product

Table 10: C-H Bond Activation of Various 3-Iminoindoles by $[Rh(coe)_2Cl]_2$ Catalyst & $P(Cy)_3$



Entry	1	2	% Yield	% ee
1		 *2a*	28	-
2		 *2b*	35	0
3		 *2c*	32	73
4		 *2d*	26	95

2b, which has a methyl substituent and achieved its enantioselectivity from (*S*)-(−)-*α*-methylbenzylamine, didn't show any enantiselectivity. The HPLC trace for this compound displays two peaks with equal areas, which means equal amount of each enantiomer has been achieved therefore it seems that (*S*)-(−)-*α*-methylbenzylamine wasn't effective enough for inducing enantioselectivity to the annulated product. In other words, size and the steric status of methyl and phenyl substituent of this amine doesn't make a significant selectivity between two enantiomers.

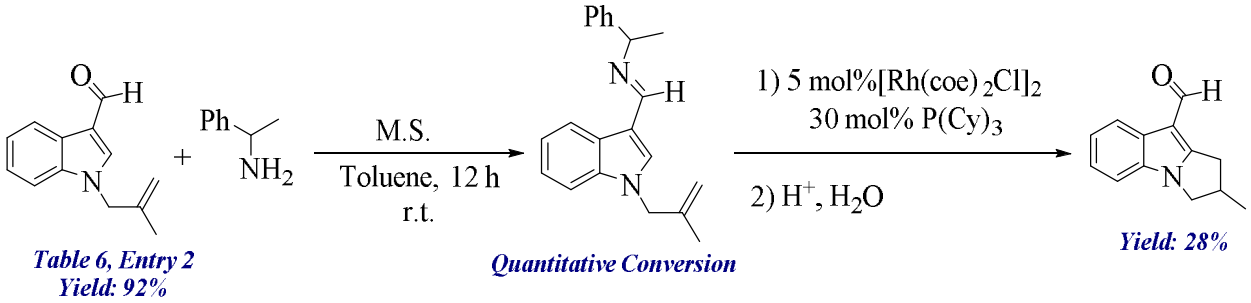


Table 6, Entry 2
Yield: 92%

Quantitative Conversion

Yield: 28%

Scheme 13

In the case of products *2c* and *2d,* we observed higher enantioselectivities. HPLC results of *2c* revealed that the annulated product was achieved with 75% ee. More significantly, HPLC results of *2d* shows one sharp peak which means this annulated product with a methyl ester substituent on the new formed five member ring was observed with almost 95% enantiomeric excess. These results indicate that high enantioselectivity can be achieved with the (*R*)-(−)-1-aminoindane as the chiral directing group.

Chapter 3

Conclusion & Future Works

3.1. Conclusion

In order to develop a stereoselective C-H bond activation, several methods have been studied. Our first efforts were based on the intermolecular *ortho*-alkylation of aromatic ketones and the *β*-functionalization of *α*-*β* unsaturated ketones. Both of these methods were examined via a one-pot, cooperative catalytic procedure. These reactions were examined with a series of geminally disubstituted olefins as alkylating agents, to provide a stereocenter in the product. Two different types of chiral primary amines and a series of Rh(I) catalysts with different ligands were employed as the catalytic system. The results of these studies didn't show any C-H activated product. The lack of reactivity observed in these methods might be due to the bulk of the amine and olefins which prevented appropriate coordination of Rh(I) catalyst to these groups, also the combination of employed Rh(I) catalysts with these chiral primary amines might not be appropriate for promoting these types of C-H bond activation methods. We also tried these two methods by a two-step procedure which includes imine purification and isolation. The scope of olefins, chiral primary amine and Rh(I) catalysts was same as the one-pot procedure. Although imine obtained in the first step, with relatively high yield, the C-H bond activation step in the presence of a metal catalyst, which leads to the final product formation was not effective. Overall neither the cooperative catalytic nor two-step method was successful in performing the *ortho*-alkylation or *β*-functionalization reactions.

In the case of the intramolecular C-H bond activation of inole-3-crboxaldehyde, a three step procedure had been attempted in order to establish that the C-H activation step can proceed. The

imine intermediate can be achieved through correspond alkylation and condensation reactions with relatively high yields. However, early attempts at the C-H bond activation step with commercially available Rh catalysts showed no activity. We were able to successfully develop a stereoselective intramolecular C-H activation method utilizing (*R*)-(−)-1-aminoindane as a chiral amine for inducing enantioselectivity and 1:6 ratio of $[Rh(coe)_2Cl]_2$ catalyst and $P(Cy)_3$ ligand as a metal catalyst. Via this method, we could obtain the annulated product with high enantioselectivity.

3.2. Future Works

In this study, we developed an efficient method for intramolecular C-H bond activation of indole-3-carboxaldehyde derivatives utilizing 1:6 ratio of $[Rh(coe)_2Cl]_2$ and $P(Cy)_3$ ligand as catalytic system and (*R*)-(−)-1-aminoindane as a chiral amine which induced high enantioselectivity to this reaction. In the future, the resulted annulated products should be analyzed by X-ray spectroscopy to determine the absolute configuration of enantiomers. Moreover, optimization of the reaction conditions can increase the yields and efficiency of this method. This will allow for the employment of this method for C-H bond activation in the synthesis of other organic molecules, which are important scaffolds of drug candidates and biomolecules.

This optimization involves improving the ratio of the catalyst and ligand, utilizing another electron-donating ligand with an appropriate coordination to the metal complexes or changing the reaction solvent by using polar solvents or a mixture of two different solvents such as toluene and THF. As mentioned earlier, a wide range of olefins can be used in this intramolecular procedure, therefore, modifying tethered olefins with electron donating or electron withdrawing substituents could be effective in improving this method. These substituents might provide an appropriate electronic control at the step of olefin coordination to the Rh catalyst and carbon-carbon bond formation between olefin and activated carbon-hydrogen bond.

We can also examine a series of chiral primary amines with rigid structure in order to induce an appropriate steric control as well as electron withdrawing substituent which can decrease the electron density of the coordinated Rh and facilitate the reductive elimination step.[34]

Chapter 4

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Chapter 5

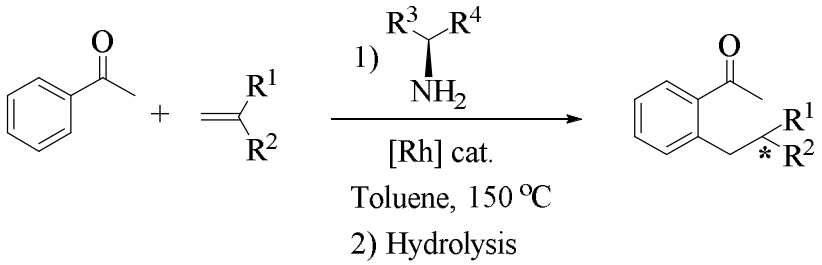
Experimental Procedures & Spectral Data

5.1. General methods

Unless otherwise noted, all starting materials, Rh(I) catalysts and ligands were purchased from Aldrich commercial source and used without any further purification. Toluene was distilled under argon from sodium/benzophenone and acetone was used directly from the supplier (Sigma-Aldrich solvents, reagent grade) without any further purification. Organic extracts were concentrated using Heidolph rotary evaporator at 40 ^{o}C and under high pressure. Thin Layer Chromatography was performed on TLC silica gel 60 F_{245}-µm. Column chromatography was performed over SiliCycle 40-63 µm (230-400 mesh) silica gel using pressurized air. ^{1}HNMR and ^{13}CNMR spectra were obtained in $CDCl_3$ and were recorded on Bruker AV-300 instrument. NMR chemical shifts (δ) are reported in ppm and the number of peaks has been classified as: s (Singlet), d (Doublet), t (Triplet), q (Quartet), quin (Quintet), dd (Doublet of doublet) and m (Multiplet). HPLC analyses were performed on chiral pack IA 150 × 4.6, 5 µm with a flow rate of 1 mL/min and 10 % THF: 90 % Hexane as eluent (Sigma-Aldrich solvents, HPLC grade).

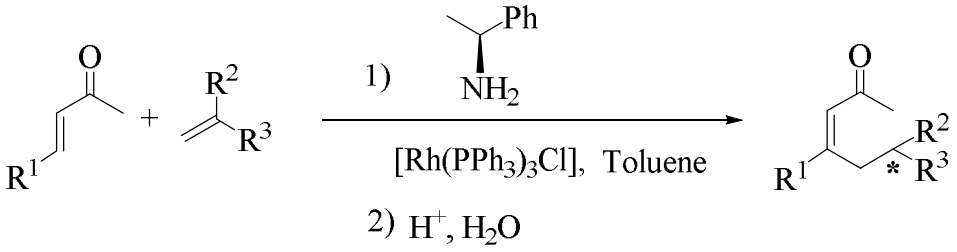
5.2. Intermolecular C-H Bond Activation Experimental Methods

General Procedure for Ortho-Alkylation of Aromatic Ketones:



To a screw capped vial equipped with a stir bar was added acetophenone (1 eq., 1 mmol), alkene (3 eq., 3 mmol), Rh(I) catalyst (5 mol% based upon ketone) and amine (50 mol% based upon ketone) in dry toluene (1 mL per 1 mmol ketone). The vial was closed and the mixture stirred at 150 °C for 24h. The crude mixture was treated with 1 N HCl solution or passed through a silica gel column to hydrolyze the ketimine and afford the *ortho*-alkylated product.

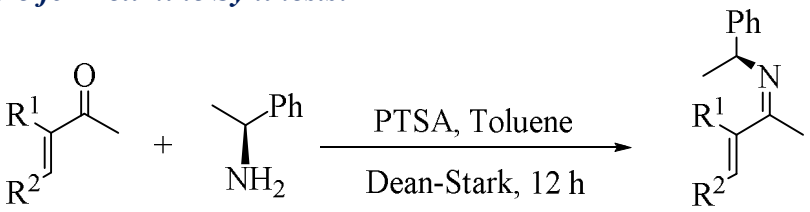
General Procedure for β-Functionalization of α-β Unsaturated Ketones:



A screw capped vial equipped with a stir bar was charged with *α-β* unsaturated ketones (1 eq., 1 mmol), alkene (3 eq., 3 mmol), Rh(I) catalyst (5 mol% based upon ketone) and (*S*)-(−)-*α*-methylbenzylamine (50 mol% based upon ketone) in dry toluene (1 mL per 1 mmol ketone). The vial was closed and the mixture was heated to 150 °C for 24h. After which time the crude mixture

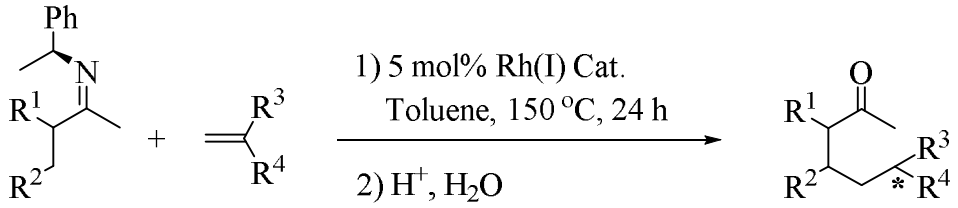
was treated by 1 N HCl solution in order to ketimine hydrolysis and acquiring the *β*-functionalized product.

General Procedure for Ketimine Synthesis:



A solution of ketone (1.1 eq., 1.1 mmol), (*S*)-(−)-*α*-methylbenzylamine (1 eq., 1 mmol) and $TsOH.H_2O$ (20 mol % based upon ketone) in dry toluene (5 mL per 1.1 mmol ketone) was heated to reflux under Dean-Stark conditions over 5Å molecular sieves (1 g per 5 mL toluene). After 12 h, the crude mixture was purified by column chromatography on silica with an eluent of 90:10 petroleum ether-ethyl acetate (Silica was pretreated with 10% trimethylamine in petroleum ether).

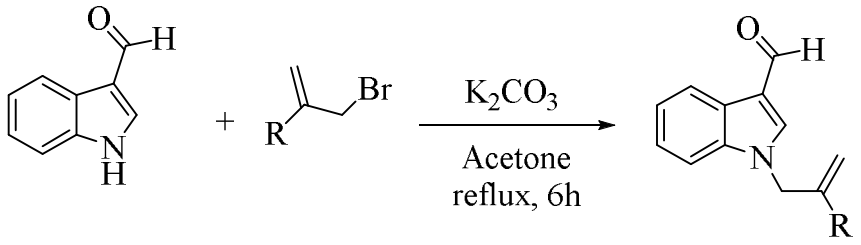
General Procedure for C-H Bond Activation of Ketimine:



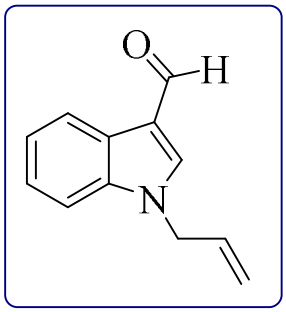
A screw capped vial equipped with a stir bar was charged with ketimine (1 eq., 1 mmol), alkene (1.2 eq., 1.2 mmol) and Rh(I) catalyst (5 mol% based upon ketimine) in dry toluene (1 mL per 1 mmol ketimine). The vial was closed and the reaction mixture was stirred at 150 °C. After 24 h the crude mixture was treated by 1N HCl solution to hydrolyze the ketimine and afford the C-H activated product.

5.3. Intramolecular C-H Activation Experimental Methods

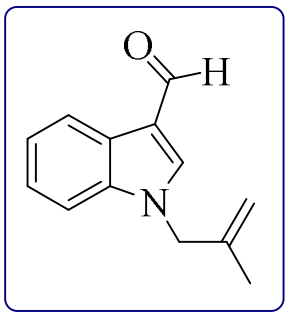
General Procedure for Alkylation of Indole-3-Carboxaldehyde: [25]



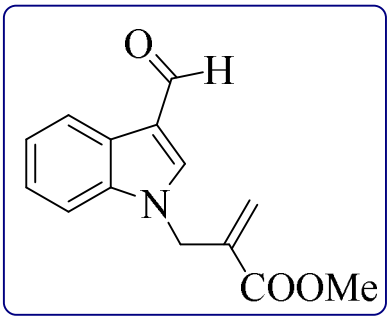
To a solution of indole-3-carboxaldehyde (1 eq., 1 mmol) and potassium carbonate (5 eq., 5 mmol) in acetone (10 mL per 1 mmol indole-3-carboxaldehyde) was added allyl bromide (3 eq., 3 mmol). The reaction mixture was heated to reflux for 6 h. The mixture was cooled to room temperature, filtered and concentrated. The crude was chromatographed on silica gel (5% EtOAc/CH_2Cl_2) to afford the pure indole-3-carboxaldehyde.



Yield: 95% as a light yellow solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10.02 (s, 1H), 8.33 (m, 1H), 7.74 (s, 1H), 7.3 (m, 3H), 6.03 (m, 1H), 5.34 (m, 1H), 5.22 (m. 1H), 4.8 (m, 2H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 184.55, 138.20, 137.36, 131.65, 125.47, 124.05, 123.01, 122.17, 119.07, 118.44, 110.26, 49.53.

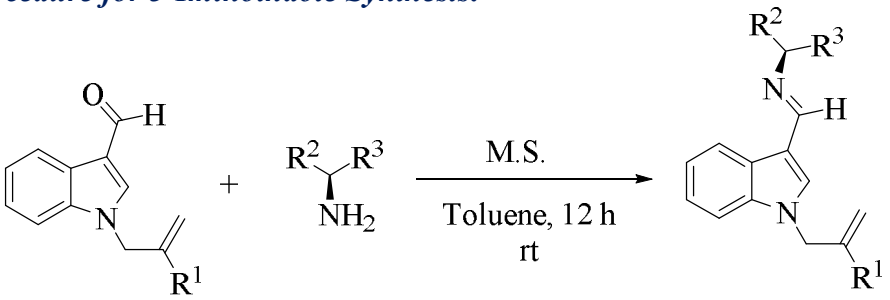


Yield: 92% as a light yellow solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10 (s, 1H), 8.33 (m, 1H), 7.69 (s, 1H), 7.31 (m, 3H), 5.00 (m, 1H), 4.80 (m, 1H), 4.68 (m, 2H), 1.71 (s, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 184.52, 139.31, 138.86, 137.51, 125.27, 123.92, 122.87, 121.96, 118.14, 114.16, 110.40, 53.18, 19.77.

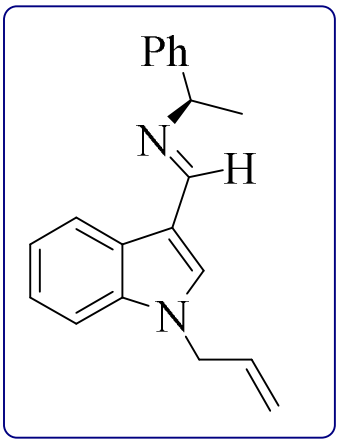


Yield: 87% as an orange oil, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10 (s, 1H), 8.31 (m, 1H), 7.77 (s, 1H), 7.31 (m, 3H), 6.35 (m, 1H), 5.45 (m, 1H), 5.03 (m, 2H), 3.8 (s, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 183.69, 168.40, 142.73, 139.29, 136.80, 128.75, 124.24, 123.63, 122.06, 118.39, 113.85, 112.25, 51.62, 47.14.

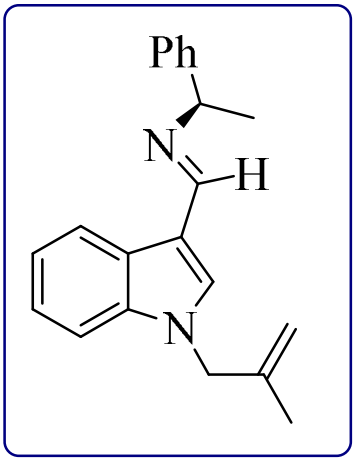
General Procedure for 3-Iminoindole Synthesis:[25]



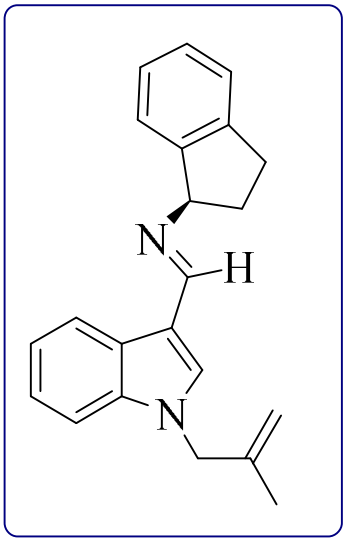
A round bottom flask was charged with a solution of alkylated indole-3-carboxaldehyde (1.1 eq., 1.1 mmol) in dry toluene (3 mL per 1.1 mmol alkylated indole). Amine (1 eq., 1 mmol) was added to the solution and the reaction mixture stirred for 12h at room temperature over 5Å molecular sieves. The mixture was diluted with toluene, filtered through celite and concentrated by rotary evaporator under reduced pressure. This reaction yielded 3-iminoindoles with quantitative conversion and they have been used for the next step without any further purification.



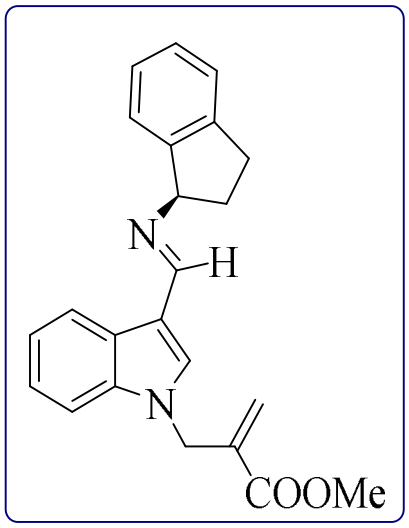
Orange oil, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 8.66 (s, 1H), 8.63 (m, 1H), 7.64 (s, 1H), 7.61 (m, 1H), 7.43 (m, 3H), 7.37 (m, 2H), 7.28 (m, 2H), 6.04 (m, 1H), 5.32 (m, 1H), 5.30 (m, 1H), 4.74 (m, 2H), 4.60 (q, 1H), 1.77 (d, J = 6.70 Hz, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 153.33, 146.35, 137.09, 132.63, 131.62, 128.33, 126.71, 126.55, 123.92, 122.19, 121.06, 118.81, 117.91, 114.83, 110.18, 109.50, 70.30, 49.58, 48.90, 25.77.



Orange oil, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 8.62 (s, 1H), 8.57 (m, 1H), 7.62 (m, 1H), 7.60 (s, 1H), 7.43 (m, 3H), 7.34 (m, 4H), 5.00 (m, 1H), 4.82 (m, 1H), 4.66 (m, 2H), 4.55 (q, J = 6.54 Hz, 1H), 1.9 (d, J = 6.62 Hz, 3H), 1.81 (s, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 153.35, 146.44, 140.44, 137.51, 132.18, 129.10, 128.37, 128.20, 126.62, 125.27, 123.09, 122.42, 121.06, 114.83, 113.25,111.28 ,109.95, 70.30, 52.73, 25.77, 19.77.

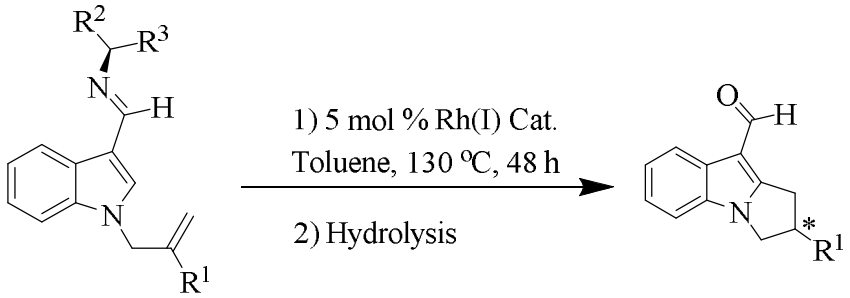


Yellow solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 8.70 (s, 1H), 8.36 (m, 1H), 7.50 (s, 1H), 7.33 (m, 2H), 7.27 (m 2H), 7.22 (m, 3H), 4.99 (m, 1H), 4.90 (t, J = 7.4 Hz, 1H), 4.83 (m, 1H), 4.68 (m, 2H), 3.71 (m, 1H), 3.00 (m, 1H), 2.54 (m, 1H), 2.35 (m, 1H), 1.73 (s, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 154.34, 151.36, 150.70, 143.68, 140.31, 137.19, 127.94, 127.20, 126.15, 124.57, 124.30, 122.90, 121.85, 121.45, 121.06, 113.39, 109.75, 52.79, 41.61, 34.86, 30.95, 19.90.



Yellow solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 8.73 (s, 1H), 8.46 (m, 1H), 7.54 (s, 1H), 7.37 (m, 2H), 7.33 (m, 2H), 7.27 (m, 3H), 6.36 (m, 1H), 5.38 (m, 1H), 5.02 (m, 2H), 4.94 (t, J = 7.34 Hz, 1H), 3.87 (s, 3H), 3.23 (m, 1H), 3.04 (m, 1H), 2.59 (m, 1H), 2.4 (m, 1H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 156.39, 149.14, 143.16, 142.12, 140.51, 139.30, 137.43, 128.14, 125.58, 124.76, 124.54, 124.08, 123.10, 122.92, 122.67, 119.40, 110.24, 109.96, 75.16, 50.32, 45.19, 30.14, 29.68.

General Procedure for C-H Bond Activation of 3-Iminoindoles by Rh(I) Catalyst:

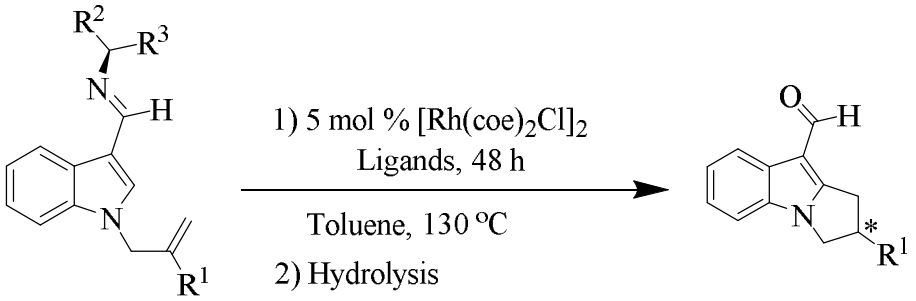


Reaction under air: A screw capped vial equipped with a stir bar was charged with 3-iminoindole (1 eq., 1 mmol) and Rh(I) catalyst (5 mol% based upon 3-iminoindole) in dry toluene (5 mL per 1mmol 3-iminoindole). The vial was closed and the reaction mixture was stirred at 130 °C for 48 hours. After which time the crude mixture was treated with 1 N HCl solution or passed through a silica gel column in order to hydrolyze the imine and afford the crude C-H activated product. The crude was purified by a column chromatography (SiO_2, 30% EtOAc/Hexane) to afford the annulated product.

Reaction under dry conditions: A two neck round bottom flask which has a steady flow of argon was charged with 3-iminoindole (1 eq., 1 mmol) and Rh(I) catalyst (5 mol% based upon 3-iminoindole) in dry toluene (5 mL per 1mmol 3-iminoindole). The reaction mixture was stirred at

130 °C under dry conditions. After 48 h the crude mixture was treated with 1 N HCl solution or passed through a silica gel column in order to hydrolyze the imine and afford the crude C-H activated product. The crude was purified by a column chromatography (SiO_2, 30% EtOAc/Hexane) to afford the annulated product.

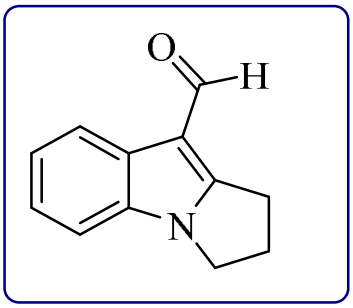
General Procedure for C-H Bond Activation of 3-Iminoindoles by a Mixture of $[Rh(coe)_2Cl]_2$ Catalyst & Ligand:



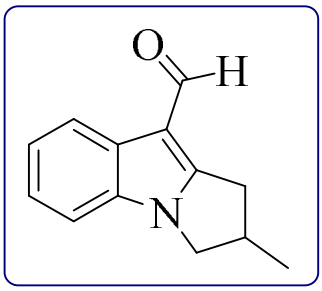
Reaction under air: A screw capped vial equipped with a stir bar was charged with $[Rh(coe)_2Cl]_2$ catalyst (5 mol% based upon 3-iminoindole) and ligand (10 mol% or 30 mol% based upon 3-iminoindole) in dry toluene (5 mL per 1mmol 3-iminoindole). The mixture was stirred at room temperature for 15 minutes in order to perform ligand exchange. After which time, 3-iminoindole (1 eq., 1 mmol) were added to the catalysts mixture and the resulting reaction mixture was stirred for 48 h at 130 °C. The crude mixture was treated with 1 N HCl or passed through a silica gel column to hydrolyze the imine and afford the crude C-H activated product. The crude was purified by a column chromatography (SiO_2, 30% EtOAc/Hexane) to afford the annulated product.

Reaction under dry conditions: A two neck round bottom flask with a steady flow of argon was charged with a mixture of $[Rh(coe)_2Cl]_2$ catalyst (5 mol% based upon 3-iminoindole) and ligand (10 mol% or 30 mol% based upon 3-iminoindole) in dry toluene (5 mL per 1mmol 3-iminoindole). The mixture was stirred under dry conditions and at room temperature for 15 minutes in order to perform ligand exchange. After which time 3-iminoindole (1 eq., 1 mmol) were added to the

catalysts mixture and the resulting reaction mixture was stirred for 48 h at 130 °C under dry conditions. The crude mixture was treated with 1 N HCl or passed through a silica gel column to hydrolyze the imine and afford the crude C-H activated product. The crude was purified by a column chromatography (SiO_2, 30% EtOAc/Hexane) to afford the annulated product.



Yield: 28% as a white solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10.05 (s, 1H), 8.21 (m, 1H), 7.29 (m, 3H), 4.17 (t, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 7.3 Hz, 2H), 2.76 (quin, *J* = 7.6 Hz, 2H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 184.16, 148.25, 133.19, 125.46, 122.56, 120.31, 119.75, 112.19, 108.63, 53.47, 46.65, 25.74.



Yield: 35% as a white solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10.03 (s, 1H), 8.20 (m, 1H), 7.28 (m, 3H), 4.31 (dd, *J* = 7.73, 10.48 Hz, 1H), 3.73 (dd, *J* = 6.37, 10.48 Hz, 1H), 3.52 (dd, *J* = 8.04, 17 Hz, 1H), 3.23 (m, 1H), 2,93 (dd, *J* = 6.51, 17 Hz, 1H), 1.37 (d, *J* = 6.83 Hz, 3H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 183.39, 155.24, 145.54, 128.65, 125.72, 123.00, 122.42, 51.68, 50.34, 49.48, 48.95, 29.72, 25.74, 21.31.

HPLC analysis (IA column, flow rate of 1ml/min, 10% THF: 90% Hexane, 100 min wait time): peak 1 = 80.30 min (major enantiomer) and peak 2 = 88.10 min (major enantiomer).

Peak #	Ret Time [min]	Width [min]	Height [mAU]	Area %
1	80.303	2.7202	551.7	73.044
2	88.103	2.5289	219	26.956

$$\%\ \text{enantiomeric excess (ee)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

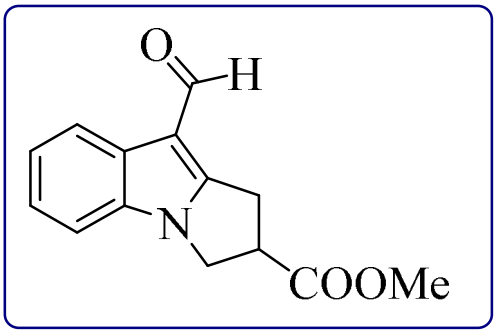
Major isomer= % 73 ee Minor isomer= % 27 ee

HPLC analysis of racemic mixture (IA column, flow rate of 1ml/min, 10% THF: 90% Hexane, 100 min wait time): peak 1 = 83.07 min and peak 2 = 91.55 min.

Peak #	Ret Time [min]	Width [min]	Height [mAU]	Area %
1	83.07	3.0492	335.9	49.96
2	91.55	2.692	390.2	50.64

$$\%\ \text{enantiomeric excess (ee)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

Equal amount of both enantiomer was observed



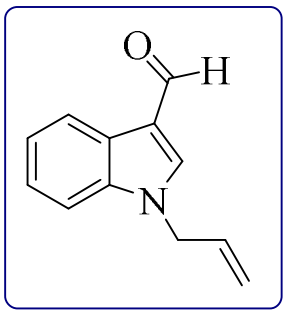
Yield: 26% as a white solid, ^{1}HNMR (300 MHZ, $CDCl_3$): δ 10.04 (s, 1H), 8.34 (m, 1H), 7.28 (m, 3H), 4.56 (dd, *J* = 8.66, 14.22 Hz, 1H), 4.38 (dd, *J* = 5.99, 14.33 Hz, 1H), 3.66 (s, 3H), 3.40 (m, 1H), 2.74 (dd, *J* = 9.11, 14.50 Hz, 1H), 2.35 (dd, *J* = 4.08, 14.16 Hz, 1H). ^{13}CNMR (300 MHZ, $CDCl_3$): δ 186.17, 175.23, 143.20, 131.40, 126.54, 122.78, 121.10, 119.54, 111.00, 108.39, 70.33, 49.28, 48.86, 25.75.

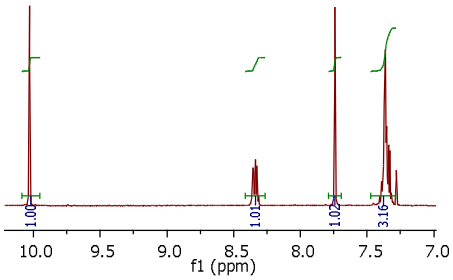
HPLC analysis (IA column, flow rate of 1ml/min, 10% THF: 90% Hexane, 70 min wait time): peak 1 = 45.67 min (minor enantiomer) and peak 2 = 50.03 min (major enantiomer).

Peak #	Ret Time [min]	Width [min]	Height [mAU]	Area %
1	45.671	1.478	16.2	4.514
2	50.038	1.931	262.08	95.48

$$\%\ \text{enantiomeric excess (ee)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

Major isomer= % 95 ee Minor isomer= % 5 ee


O
H
N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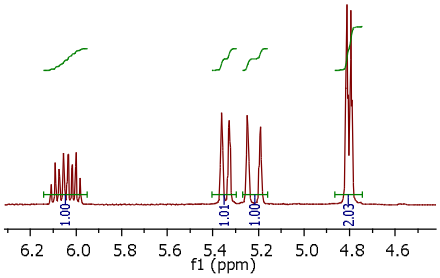
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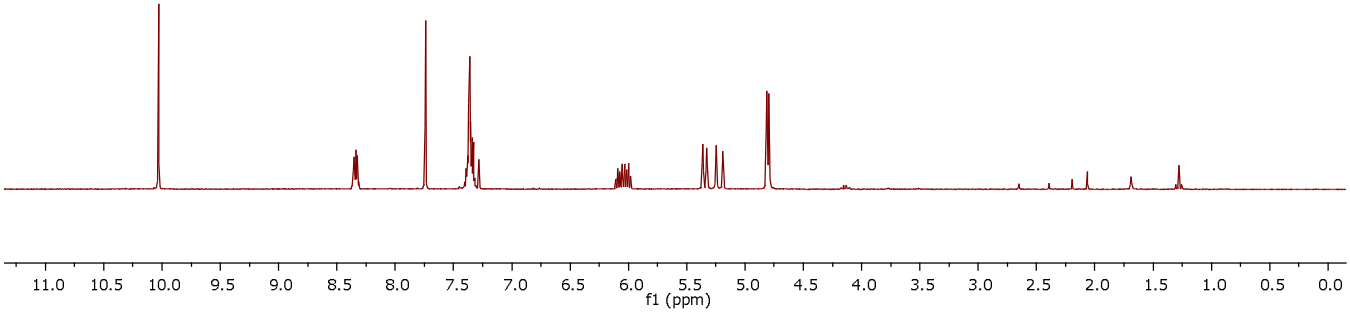
4.6
f1 (ppm)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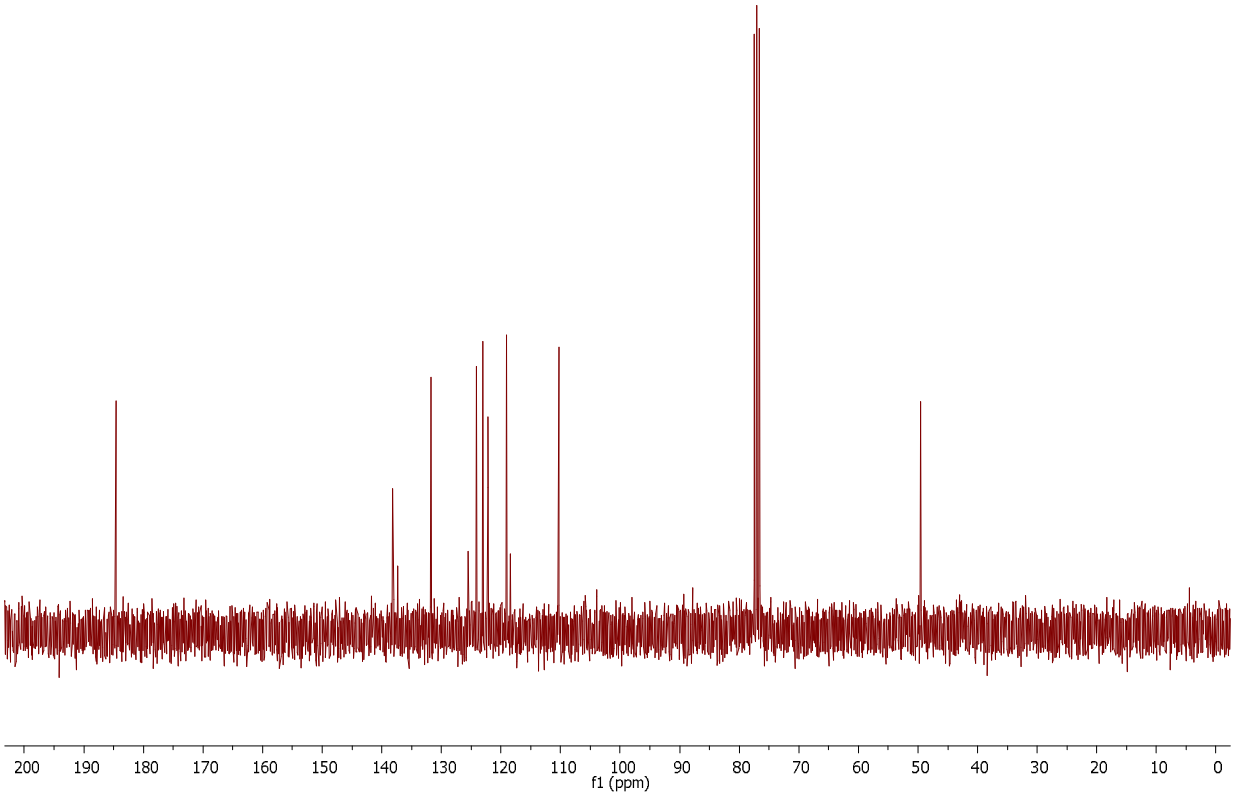
f1 (ppm)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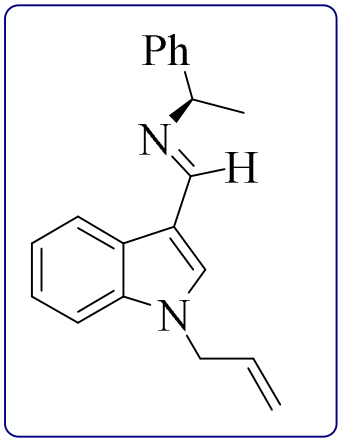
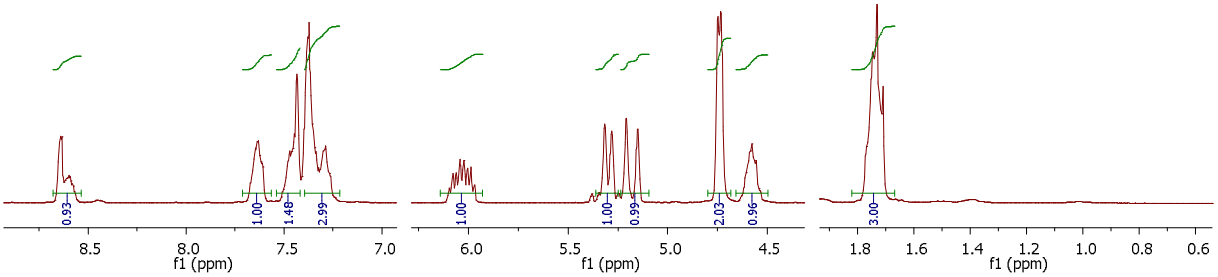
10
0
f1 (ppm)


Ph
N
H
N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1.6
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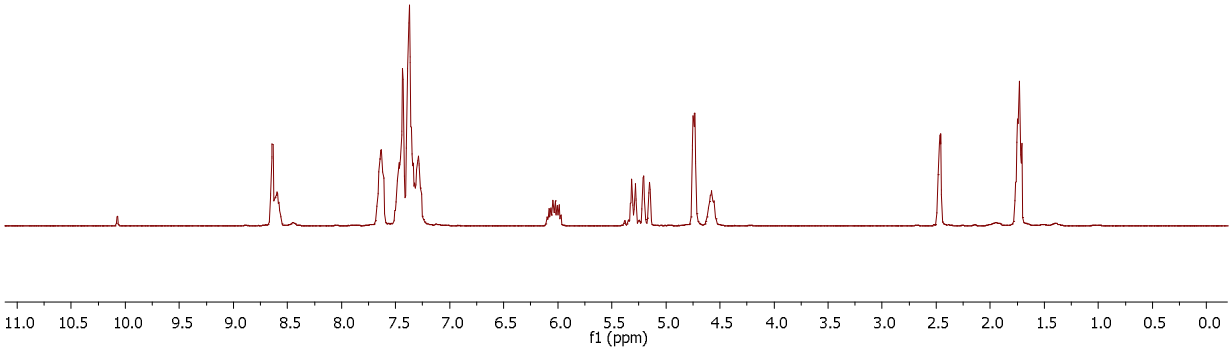
0.6
f1 (ppm)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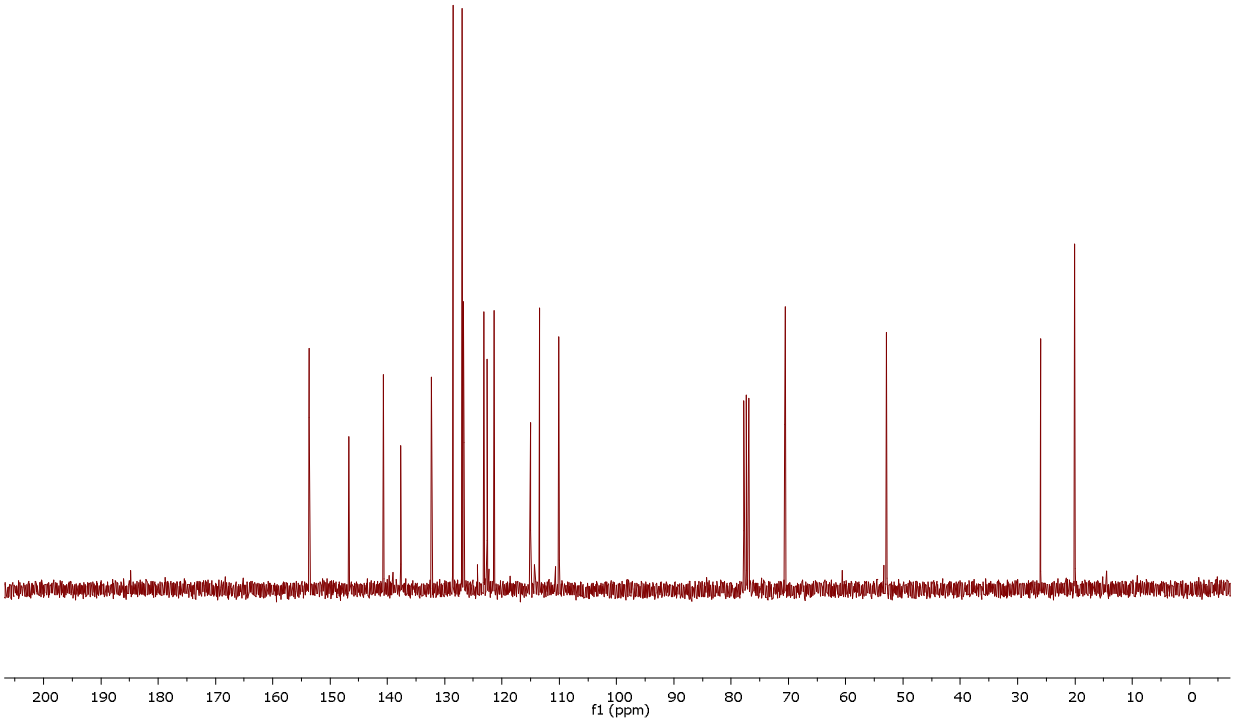
f1 (ppm)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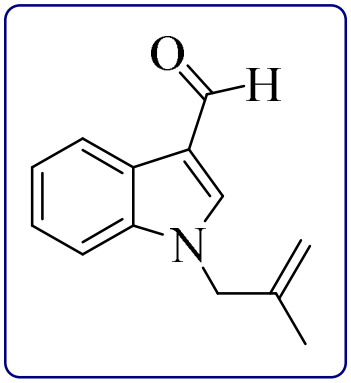
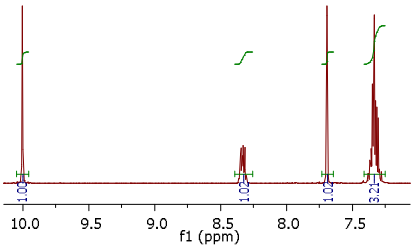

O
H
N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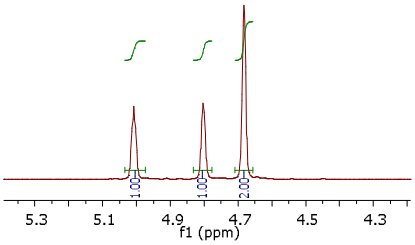
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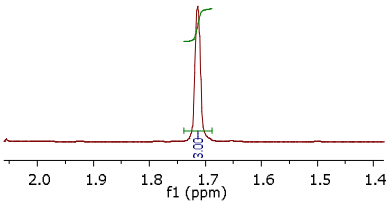
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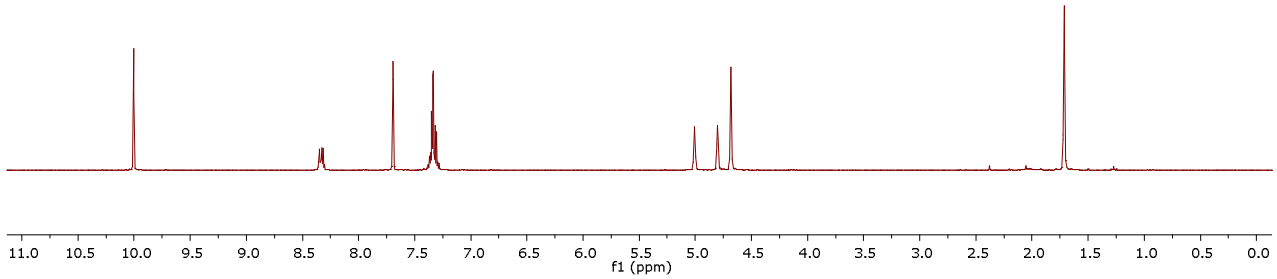
1.4
f1 (ppm)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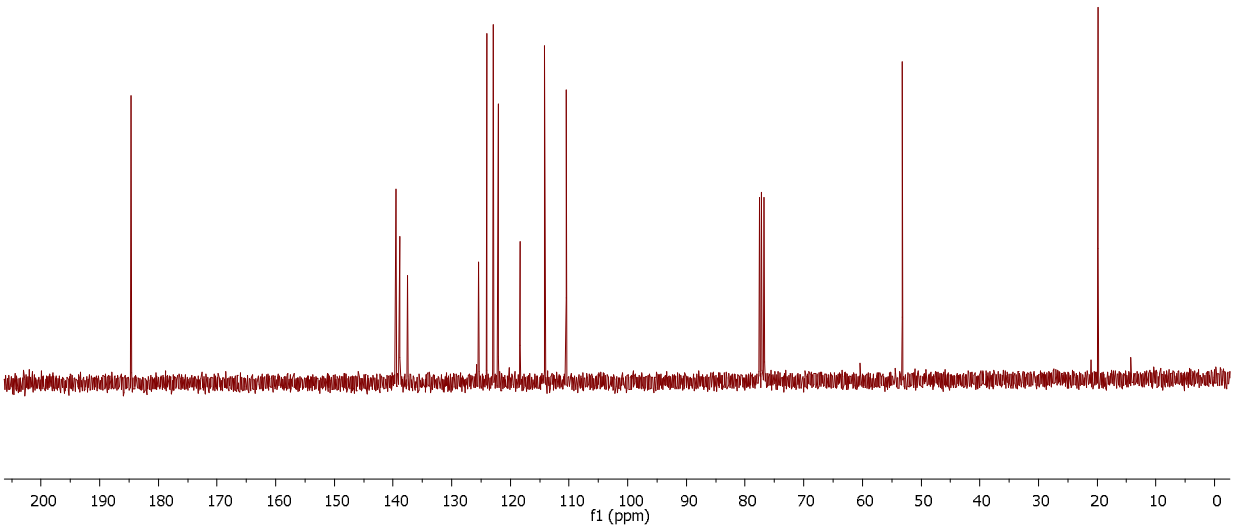
0.0
f1 (ppm)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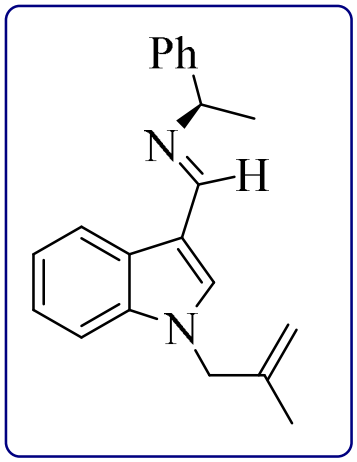
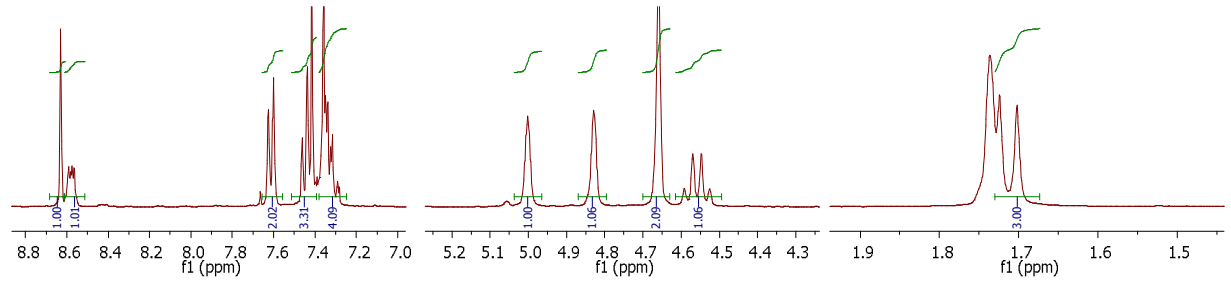

Ph
N
H
N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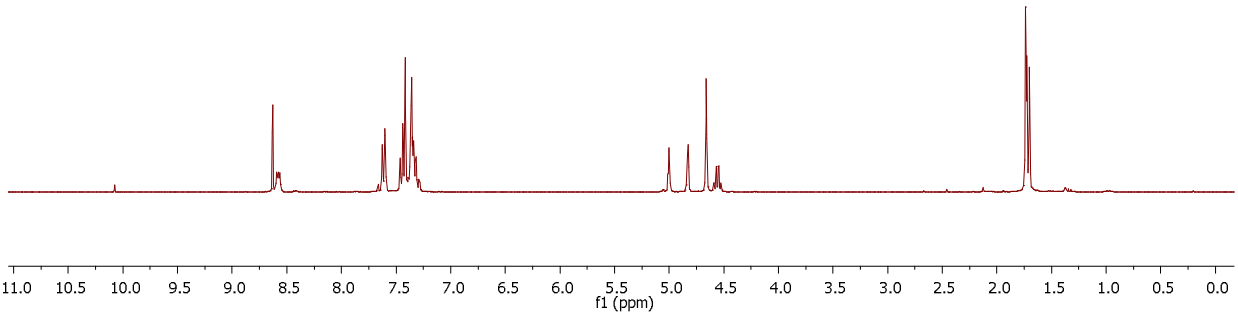
2.09
1.06
f1 (ppm)
3.00
f1 (ppm)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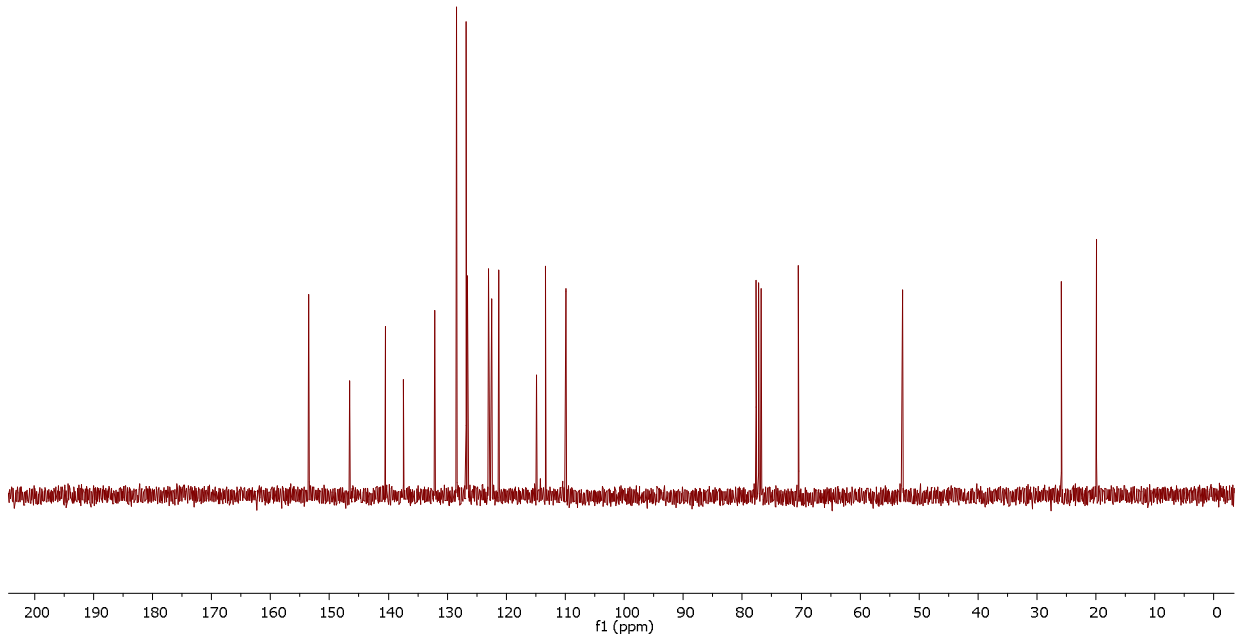
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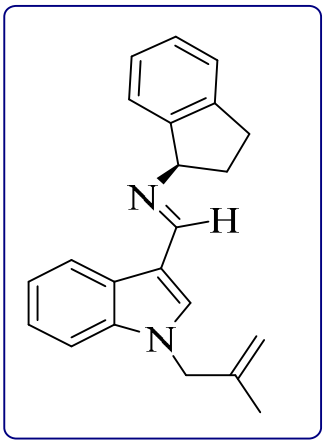
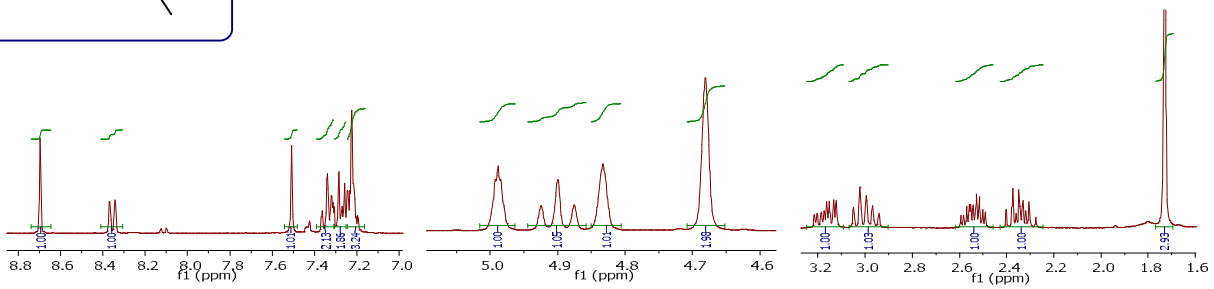

N
H
N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f1 (ppm)
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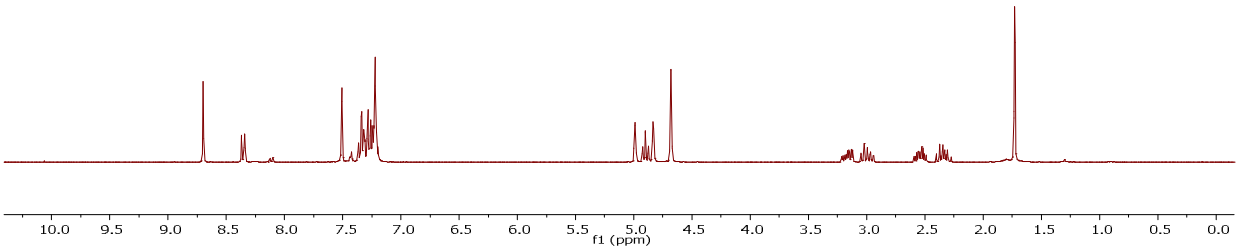
f1 (ppm)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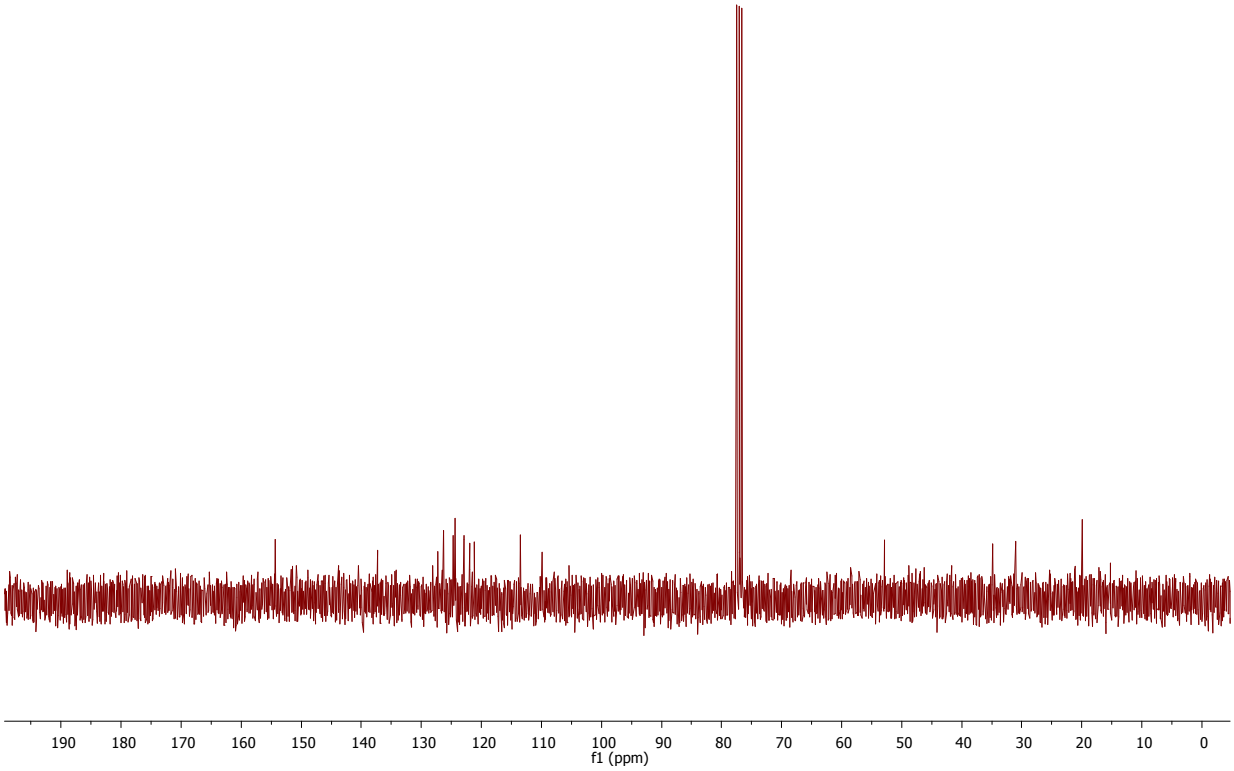
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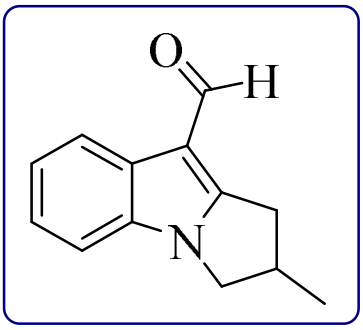
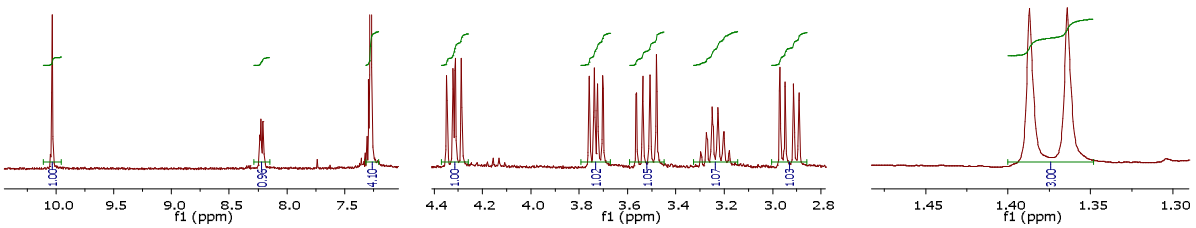

O
H
N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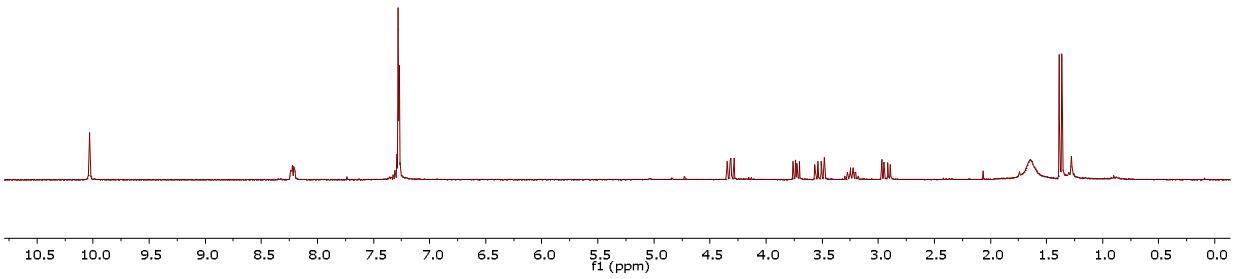
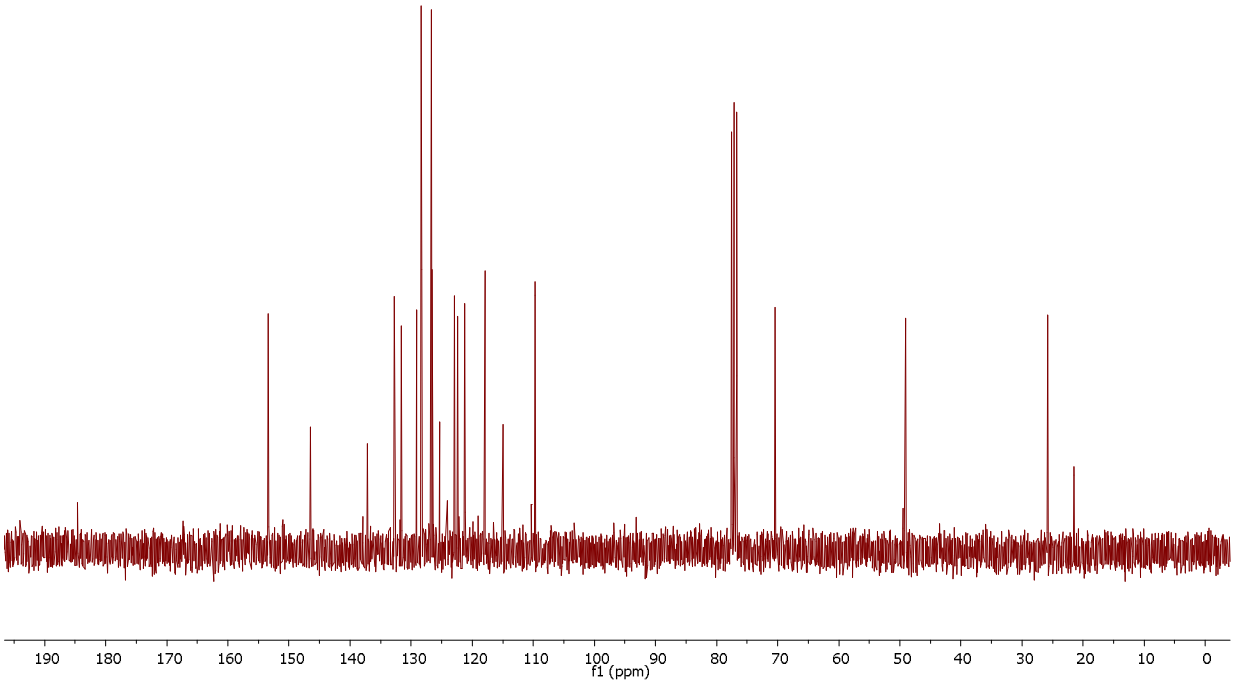
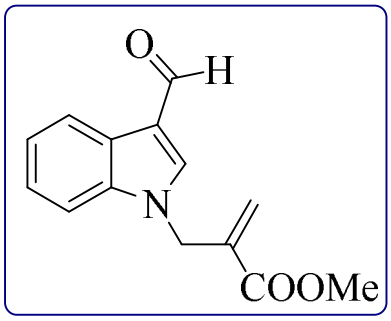
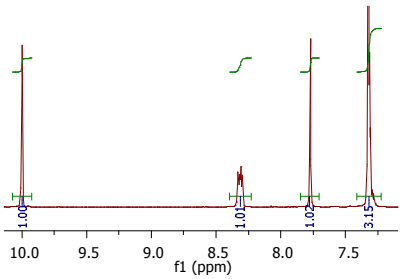
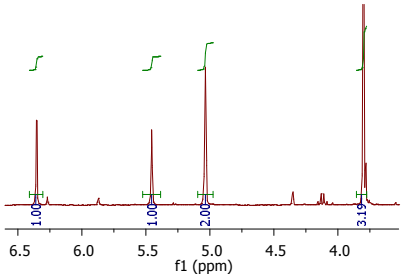
1.07
1.03
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
f1 (ppm)
3.00
1.45 1.40 1.35 1.30
f1 (ppm)

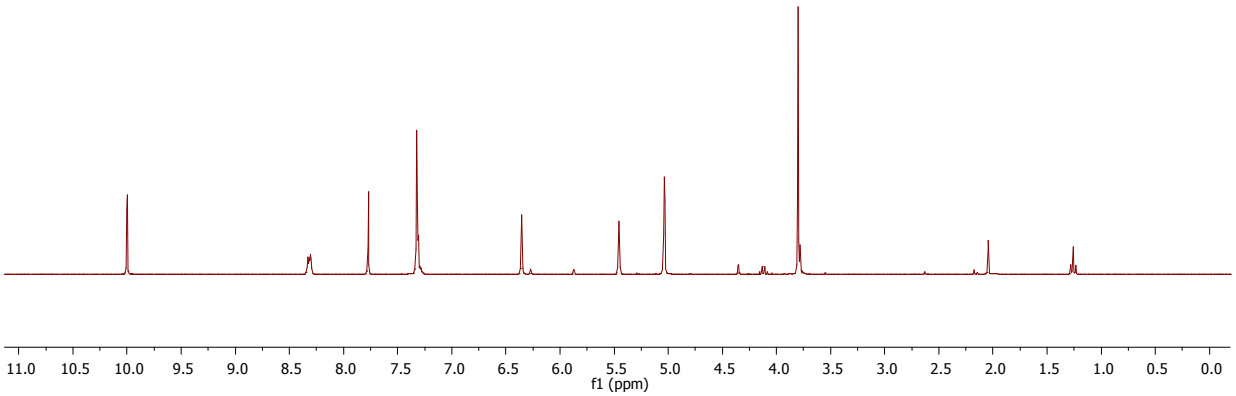

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

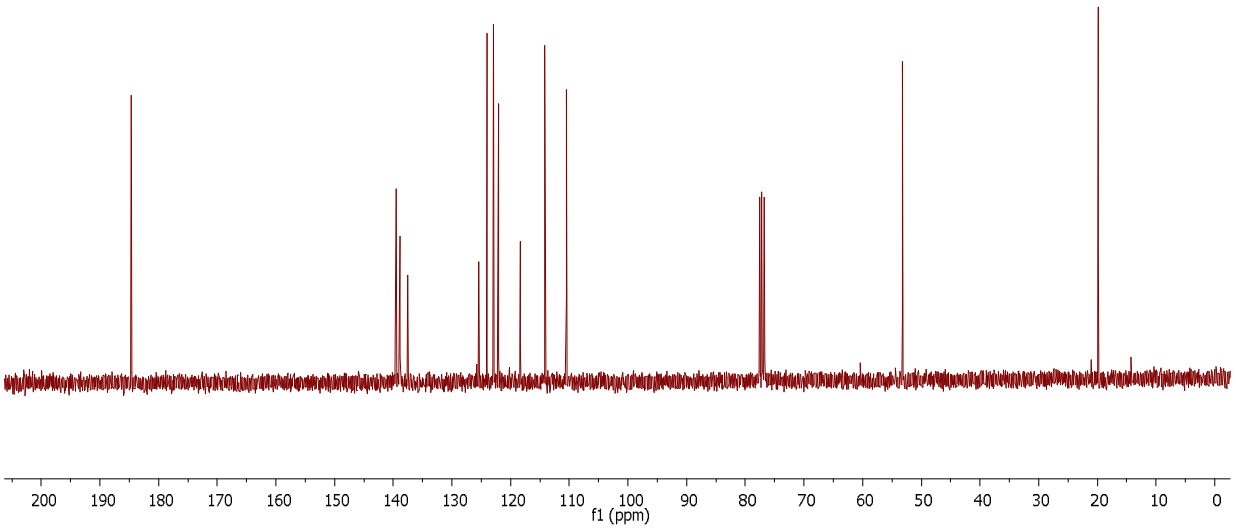

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

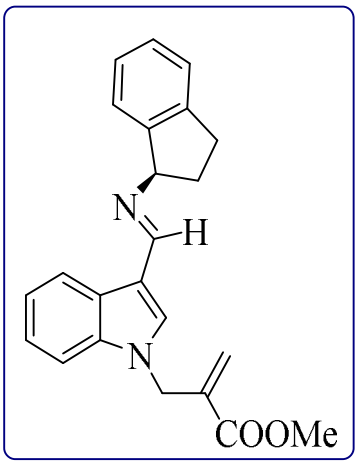

O
H
N
COOMe

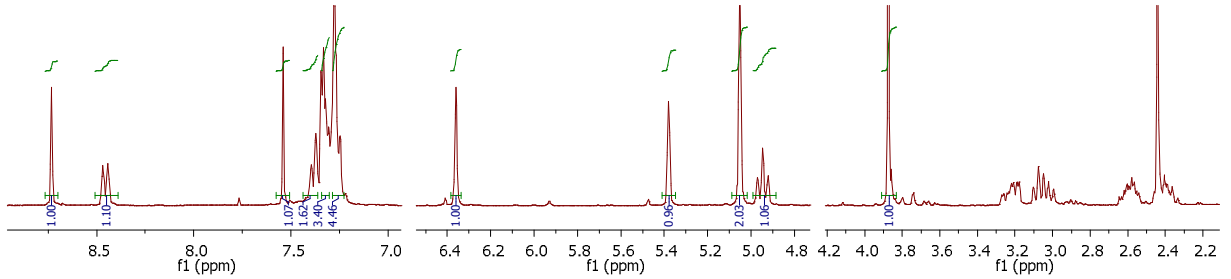

1.00
1.01
1.02
3.15
10.0
9.5
9.0
8.5
8.0
7.5
f1 (ppm)

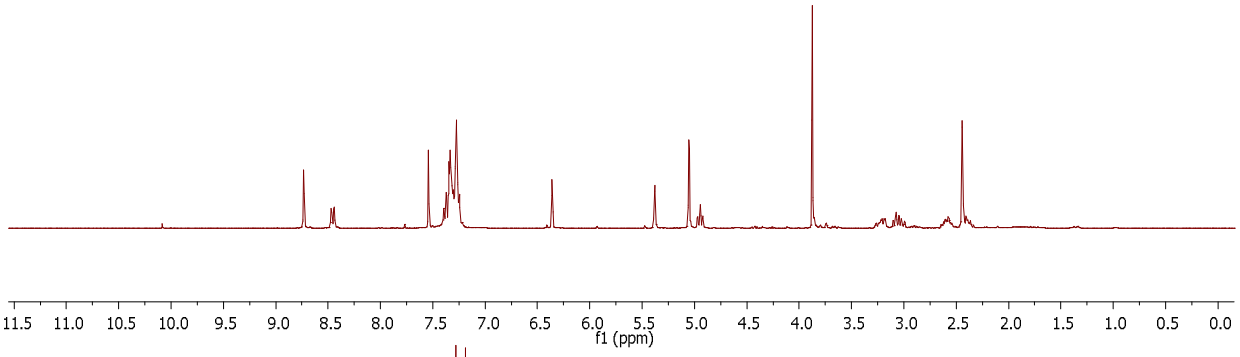

1.00
1.00
2.00
3.19
6.5
6.0
5.5
5.0
4.5
4.0
f1 (ppm)

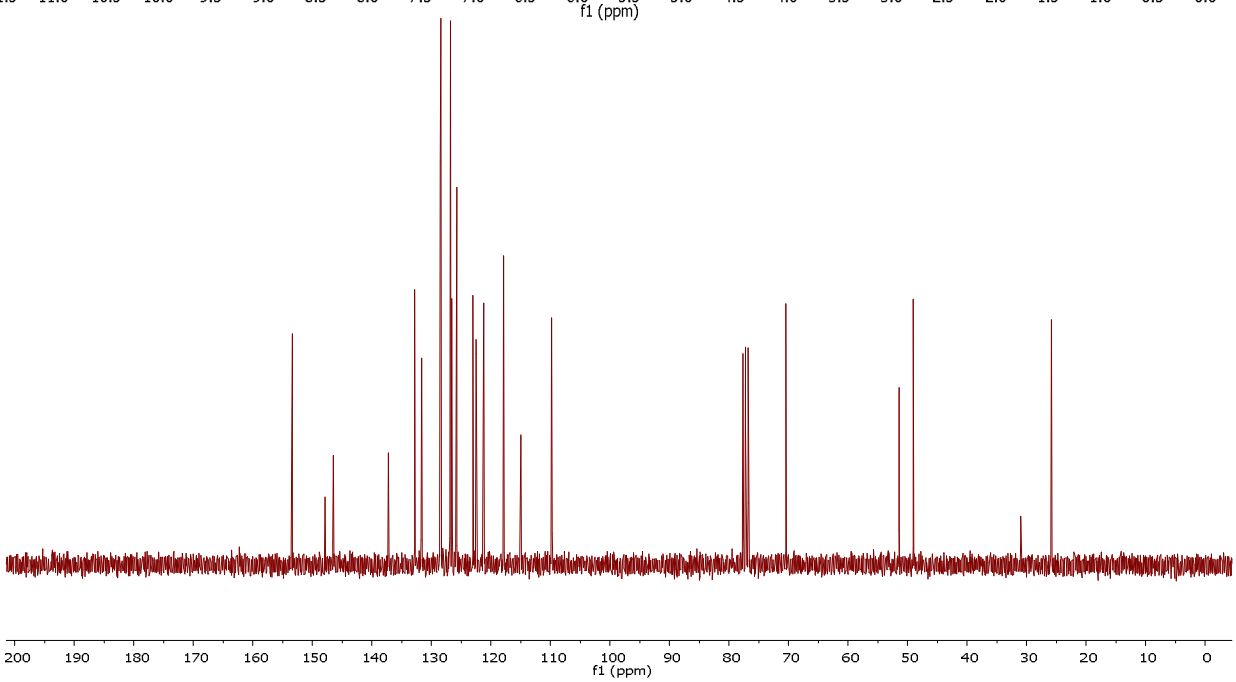

11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

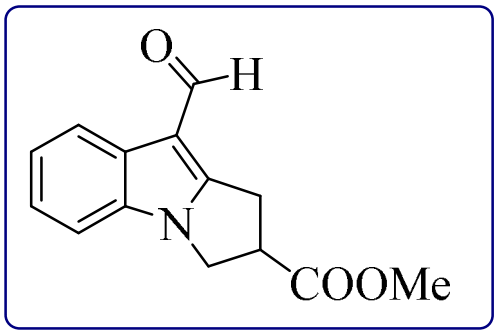

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

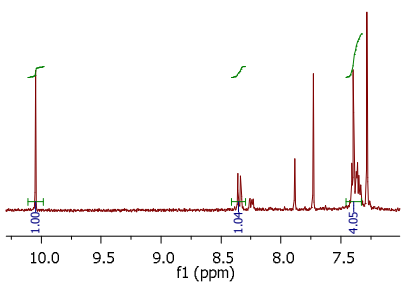

N
H
N
COOMe

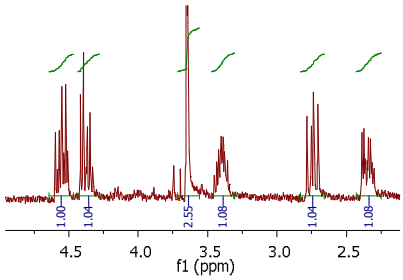

1.00
1.10
1.07
1.62
3.40
4.46
8.5
8.0
7.5
7.0
f1 (ppm)
1.00
0.96
2.03
1.06
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
f1 (ppm)
1.00
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
f1 (ppm)

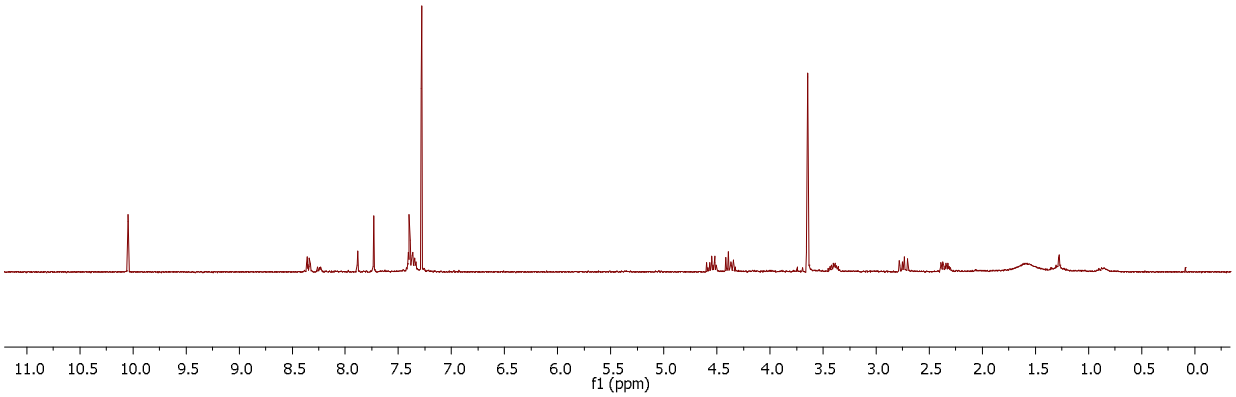

11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

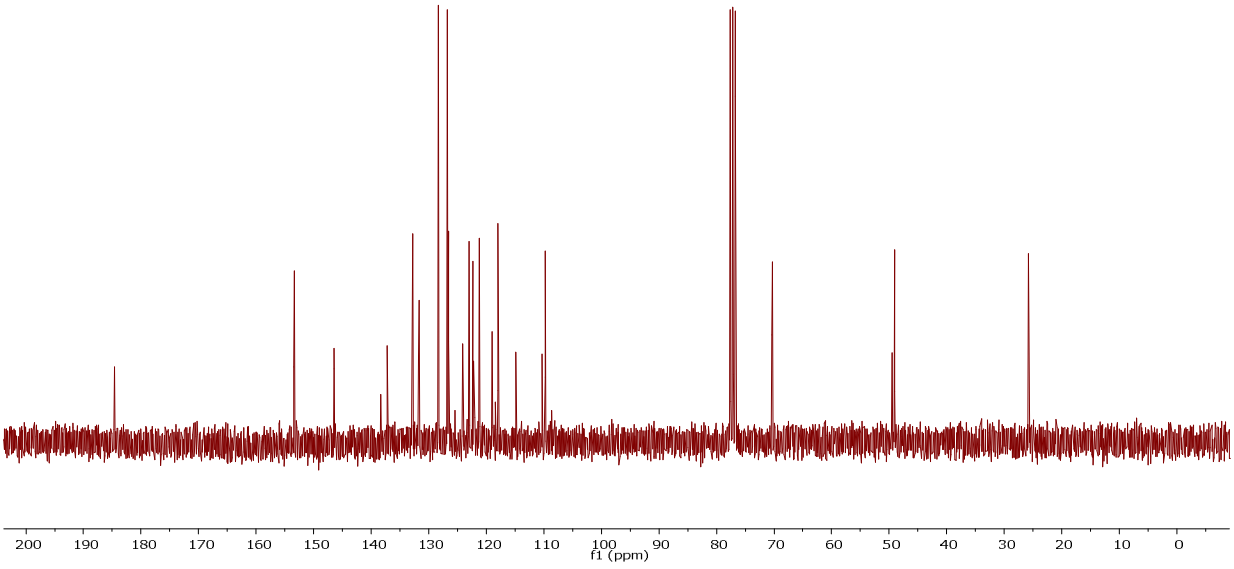

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
H
N
COOMe


1.00
1.04
4.05
10.0
9.5
9.0
8.5
8.0
7.5
f1 (ppm)


1.00
1.04
2.55
1.08
1.04
1.08
4.5
4.0
3.5
3.0
2.5
f1 (ppm)


11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)