Alkenylation of Naphthalimide *via* Ruthenium(II)-Catalysed C-H Activation

Thesis Submitted

In the partial fulfilment of requirement of degree

Masters of Science

In

Chemistry

By

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UNDER THE SUPERVISION OF

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Punjab, India

July, 2019

CERTIFICATE

This is to certify that the thesis entitled "**Alkenylation of Naphthalimide *via* Ruthenium(II)-Catalysed C-H Activation**" submitted by **Ms. Diksha Bansal** in the partial fulfillment of the requirement for the degree of **Masters of Science in Chemistry** from **Thapar Institute of Engineering and Technology, Patiala** is a bonafide piece of work carried out under the guidance and supervision **Dr. Kamaldeep Paul,** Associate Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala and no part of project has been submitted for award of any other degree in this or any other university.

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This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

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Candidate's Declaration

I hereby declare that the matter embodied in this project entitled "**Alkenylation of naphthalimide *via* Ruthenium(II)-catalysed C-H Activation**" is an authentic research work done by me in the partial fulfilment of the requirement for the Award of degree of **Masters of Science in Chemistry,** submitted in the **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** under the supervision of **Dr. Kamaldeep Paul,** Associate Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala. All the ideas and references have been duly acknowledged.

In keeping with the general practise in reporting scientific observations, due acknowledgement has been made whenever the work described is based on the findings of other investigators. Any oversight due to error of judgement is regretted.

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Diksha

Date: 15/July/19

DIKSHA BANSAL

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Abstract

We explored Metal-Catalyzed C-H activation, also provides a scaffold to confront the challenge of site-selectivity. One successful approach has been used was of substrate-based control. Using substrates that can co-ordinate to the metal centre *via* the formation of a dative bond. These so called “directing groups”, include nitrogen heterocyclic, amides, oxime ethers/esters, and imines. Upon coordination of the directing group to the metal centre, metal- mediated C-H activation occurs preferentially at a proximal C-H bond resulting in the formation of a metallocycle.

Here we have discussed our results to develop site-selective C-H functionalization reactions. Latent moiety (naphthalimides) also has a weakly directing carbonyl group and strongly directing group N is used which were substituted with various alkenyl moieties using ruthenium catalyst. The introduction of alkene functionality to the compound allows further derivation to form more complex and decorated structures.

Dedicated to my Parents and Brothers

1. Introduction

1.1 What is C-H bond Activation?

Activation of C-H bond is often referred to as one of the "Holy Grails" in chemistry.[1] Carbon-hydrogen bond activation is the breaking of the σ-C-H bond and further reaction without the requirement of overcoming large activation energy. It is reasonable to propose that activation of σ-C-H bond means to enhance its reactivity towards a reagent. This results in splitting of bond and triggering into two "particles" in place of one initial species.

In other words the main conclusion drawn from "activation" of a C-H bond is the replacing a strong bond (thermodynamically stable) with a weak (thermodynamically less stable) bond. This weaker bond permits the further functionalization of molecules much more easily than C-H bonds.

Aliphatic hydrocarbons are ubiquitous in nature, but their lack of chemical reactivity in defined reactions (other than combustion, cracking and the generation of synthesis gas)[2] has prevented their direct conversion into valuable chemical products. Therefore, derivatization of C-H bond assisted in transformation of cheap and abundant alkenes into other worthful compounds.

Ability to carry out direct transformation of an unfunctionalized precursors into complex molecules is a great concern in synthetic organic chemistry. One of the proficient method for forming carbon-carbon (C-C) bonds needs activation and subsequent functionalization of carbon-hydrogen (C-H) bonds.[3] Toxic halogenated by-products resulted from many of the alternative methods for C-C bond formation can be better removed *via* direct C-H functionalisation and it is also atom- economical.

1.2 Difficulties

C-H bonds are particularly strong bonds. These C-H bonds are notoriously inert to both homolytic and heterolytic cleavage. Therefore, any methodology must be highly selective for the C-H bond while leaving all others intact. For example, the selective for the target pharmaceutical Fluoxetine, sold as "Prozac," shown in **Figure 1**, possesses multiple, unique C-H bonds, including differently substituted aromatic sp^2 multiple, as well as primary, secondary, and tertiary sp^3 C-H bonds. Site-selective functionalization of any one of these various sites could be desirable for structure-activity relationship studies in the pursuit of new drug derivatives or to study pharmacokinetics.

An attractive strategy for overcoming these challenges is the use of a transition metal catalyst that "activate" the C-H bond by lowering the activation energy for bond scission. A transition metal catalyst can coordinate to a C-H σ-bond, donating electron density into the σ* orbital. This in turn weakens the C-H bond and can leads to the formation of a metal-carbon bond.

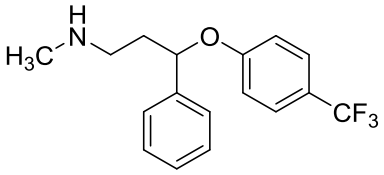
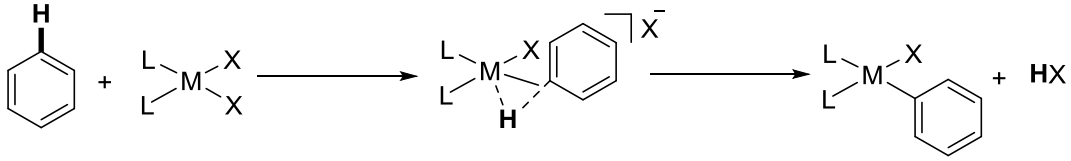


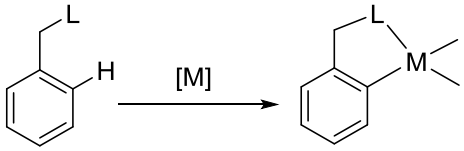
Figure 1. The pharmaceutical "Prozac" contains multiple C-H bonds

The resulting organometallic intermediate can then be further manipulated to release different carbon-X bonds, where X is halogen, oxygen, nitrogen, carbon, etc **(Scheme 1.1)**.



Scheme 1.1. Metal-catalyzed C-H activation.

cMetal-catalyzed C-H activation also provides a framework for addressing the challenge of site-selectivity. One successful approach has been the use of substrate-based control. For example, one method is to use substrates that can co-ordinate to the metal centre through the formation of a dative bond. These so called "directing groups", include nitrogen heterocyclic, amides, oxime ethers/esters, and imines. Upon co-ordination of the directing group to the metal centre, metal-mediated C-H activation occurs preferentially at a proximal C-H bond, resulting in the formation of a metallocycle **(Scheme 1.2)**. Metal-mediated formation of a cyclometallated organometallic intermediate, which can undergo further functionalization. The focus of this project is the catalyst-assisted activation of carbon-hydrogen bonds with imide as the directing group for the substitution of various acrylates to the biological active naphthalimide moiety.



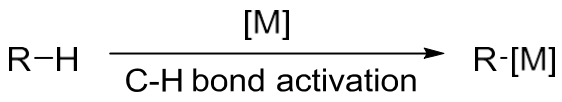
Scheme 1.2. Ligand directed C-H activation

2. Review of Literature

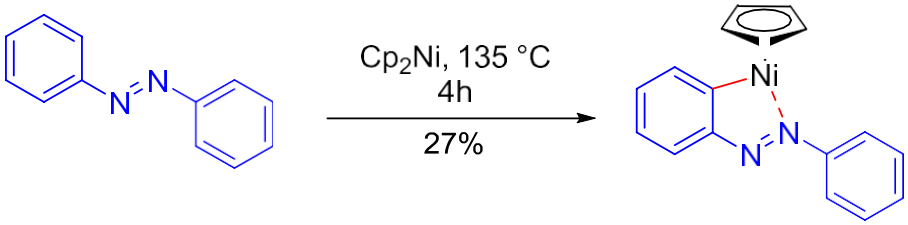
2.1 Transition Metal Mediated Aromatic C-H Bond Activation

In the middle of 1960s, it was demonstrated that transition metal complexes are capable of inserting into aromatic C-H bonds through the participation of the π orbitals. Transition metal complexes have been used to cleave unactivated C-H bonds to furnish more reactive carbon-metal bonds **(Scheme 2.1)**. In 1963, the first example of this concept is reported by Kleiman and Dubeck.[4a] An *ortho*-C-H bond of azobenzene was cleaved with stoichiometric Cp_2Ni, forming a 5-membered nickellacycle after heating at 135 ^oC for 4h **(Scheme 2.2)**. The azo functional group

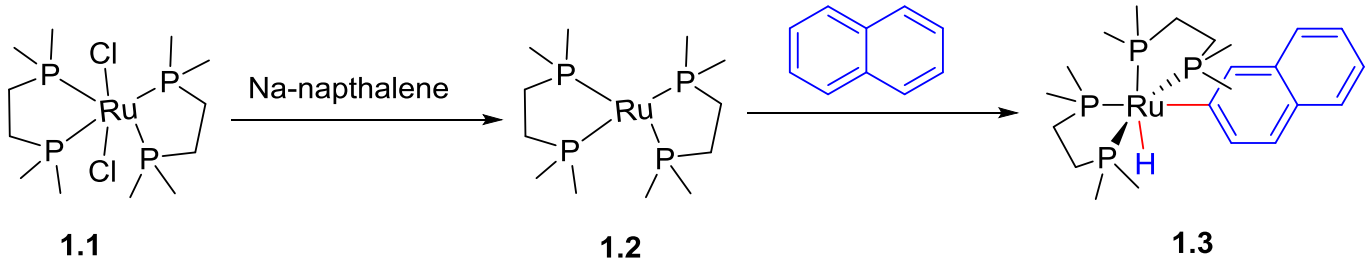
worked as a coordinating directing group to bring the metal in close proximity to the *ortho* C–H bond to be cleaved, resulting in high level of regioselectivity. Later, the first ruthenium mediated C-H bond cleavage was published in 1965 by Chatt and Davidson[4b] and reported that the di-(1,2-bisdimethylphosphinoethane)ruthenium(0) complex [Ru(0)(dmpe)$_2$] **1.2** was generated by reduction of [Ru(II)(dmpe)$_2$Cl$_2$] **1.1**. One C-H bond of naphthalene was activated by the Ru(0)(dmpe)$_2$ complex **1.2** to form **1.3 (Scheme 2.3)**.[4c] This is the first reported example of "C-H bond activation" of an aromatic hydrocarbon by a transition metal complex.



Scheme 2.1. Transition metal assisted C-H bond activation



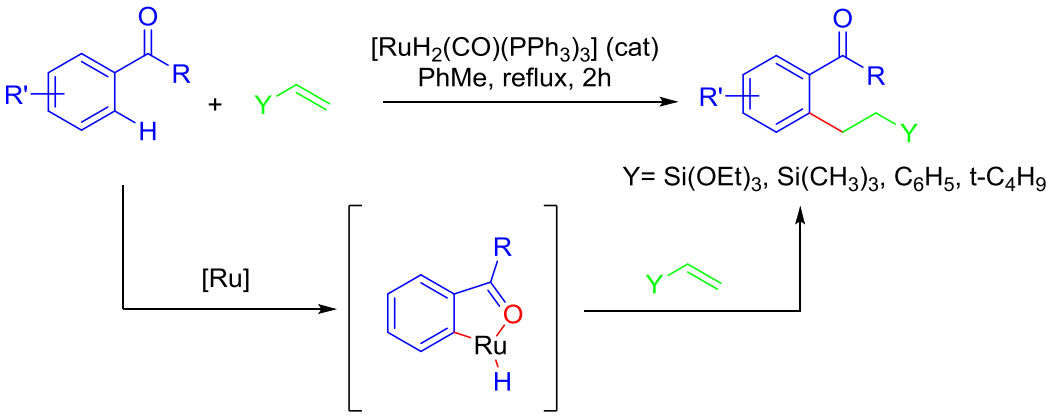
Scheme 2.2. First example of transition metal-mediated C-H bond cleavage



Scheme 2.3. First example of ruthenium mediated C-H bond cleavage

2.2 Chelation Assisted C-H Bond Functionalization and Alkylation Reaction

Since the manipulation of unreactive C-H bond was demonstrated in stoichiometric reactions, many efforts have been devoted into developing catalytic versions of C-H bond activation. The field of C-H bond activation chemistry emerged in the 1970s; however, the early works on catalytic C-H activation/functionalization were reported by Jordan *et al.* (1989)[5a] and Moore *et al.* (1992).[5b] The first synthetically useful catalytic C-H functionalization for carbon-carbon (C-C) bond formation was reported in 1993 by Murai and co-workers.[5c] This work involved a ruthenium-catalyzed coupling of an olefin to the *ortho* position of an aromatic ketone **(Scheme 2.4)**. This report highlighted the importance of a chelating group in order to achieve highly reactive and selective system for C-H activation processes.



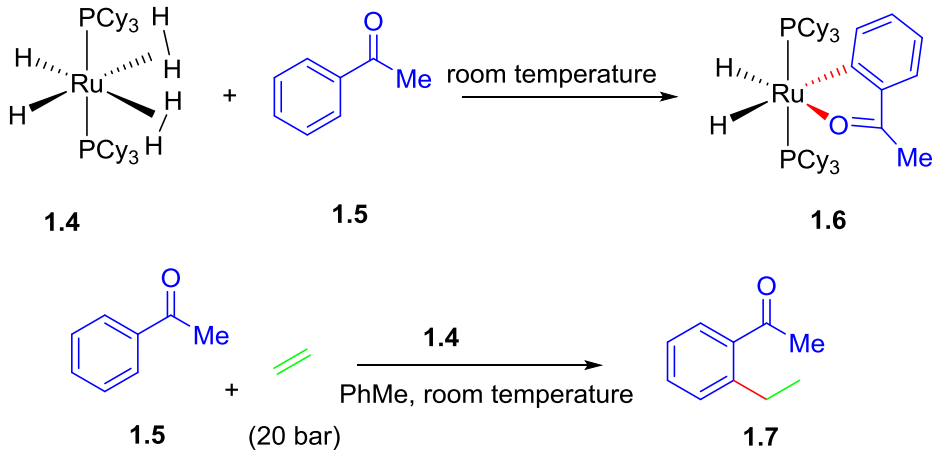
Scheme 2.4. Ru-Catalyzed coupling of an olefin to the *o*-position of an aromatic ketone

Following this breakthrough, a variety of functional groups containing oxygen and nitrogen atoms were identified as suitable directing groups for ruthenium catalyzed C-H bond cleavage/olefin insertion process, such as ester, aldehyde, aldimine, pyridine, oxazoline, and nitrile. This reaction featured high efficiency and regioselectivity without any byproducts, which represented one important direction of organic synthesis to develop atom-, step- and redox-economic reactions.

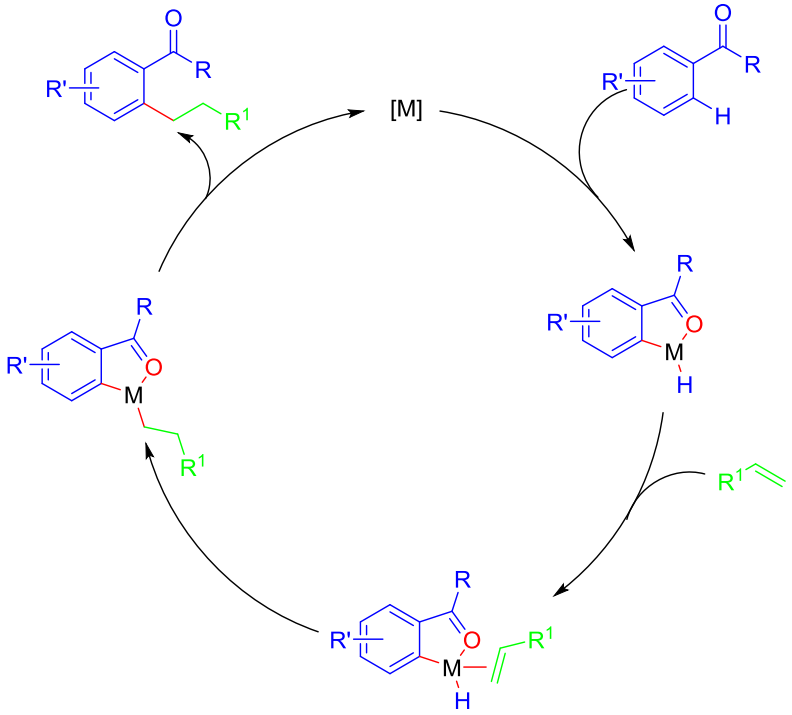
Attempts have been made to develop more reactive catalysts and to understand the reaction mechanism.[5d-5h] Chaudret and coworkers synthesized a ruthenium complex with dihydrogen ligand and prepared a ruthenacycle with η^2-coordinated acetophenone *via* C-H bond cleavage.[5i] The stoichiometric reaction of **1.6** with triethoxyvinylsilane at room temperature gave the mono-insertion product, which was consistent with Murai's hypothesis[6]. Insertion of ethylene was also achieved at room temperature with acetophenone in the presence of catalytic amount of **1.4 (Scheme 2.5)**. These results provided very useful information on C-H bond activation reaction mechanism and demonstrated cyclometalated ruthenium complexes as highly promising catalyst precursor for mild C-H bond activation.

The generally accepted mechanism for *ortho*-alkylation *via* C-H bond activation has been depicted in **(Scheme 2.6)**. First, coordination of transition metal to the chelating oxygen facilitates cleavage of C-H bond in the *ortho* position and generates a matallacycle intermediate.

Next, olefin coordination and subsequent migratory insertion gave a metal alkyl intermediate. Lastly, reductive elimination produced the *ortho* alkylated product and regenerated the initial catalyst, completing the catalytic cycle. The reductive elimination for C-C bond formation was generally proposed as the rate-determining step.



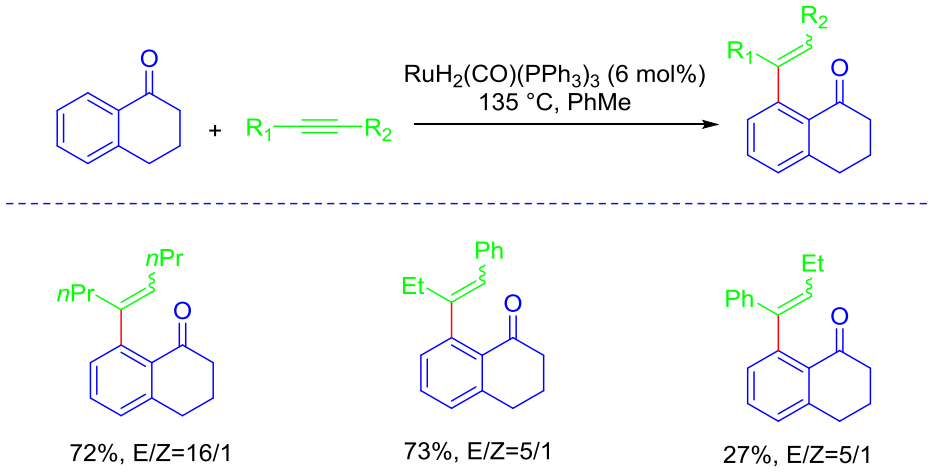
Scheme 2.5. Room temperature aromatic ketone alkylation using Chaudret's catalyst



Scheme 2.6. Accepted reaction mechanism for Murai reaction

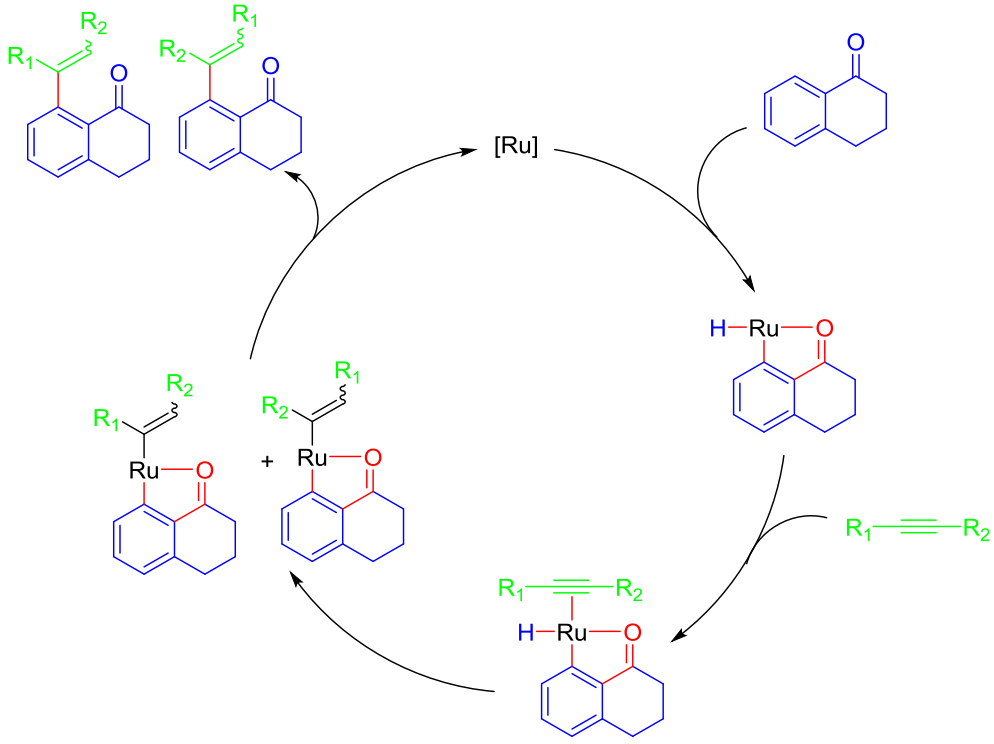
Highly site-selective hydroarylation of alkynes was achieved *ortho* to the directing carbonyl group by a ruthenium catalyst[7a,b] **(Scheme 2.7)**. In the presence of catalytic amount of RuH2(CO)(PPh3)3, α-tetralone reacted with internal alkynes generating the alkenylated arenes. Two possible stereoisomers were obtained in the case of symmetrically substituted internal alkynes while for the unsymmetrically substituted internal alkynes such as 1- phenyl-1-butyne, all of the four regio- and

stereoisomers of the products were observed. There was no strong geometry restriction, allowing both *E* and *Z* isomers to be formed after reductive elimination.



Scheme 2.7. Ruthenium catalyzed alkyne hydroarylation with cyclic α-tetralone

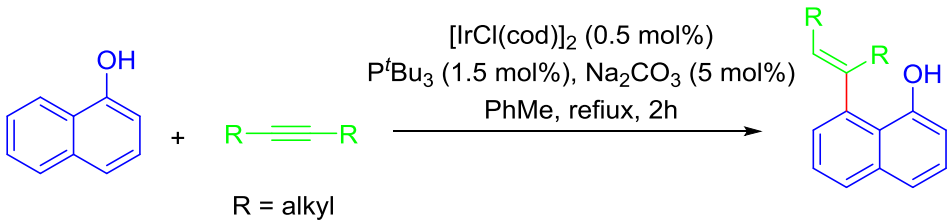
The regio- and stereochemistry results in catalytic alkyne hydroarylation with aromatic ketones were rationalized with a proposed mechanism that is analogous to the hydroarylation of olefines *via* directed C-H bond oxidative addition **(Scheme 2.8)**



Scheme 2.8. Proposed reaction mechanism for alkyne hydroarylation with aromatic ketones initiated by C-H bond oxidative addition

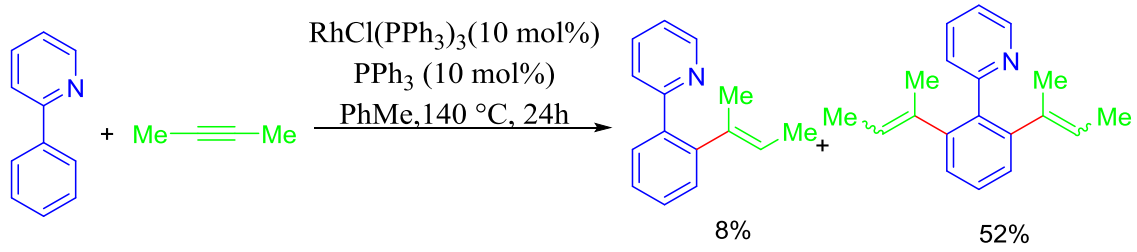
Miura and coworkers disclosed a catalyst system of iridium(I) catalyst precursor and $PtBu_3$ ligand for regioselective hydroarylation of dialkyl alkynes with 1-naphthol in the presence of a catalytic amount of Na_2CO_3 in refluxing toluene [8]**(Scheme 2.9)**.

Alkenylation occurred at the *ortho* position of the hydroxyl group producing only *E*-isomers, probably due to the presence of bulky phosphine ligand on the catalyst. A rhodium(I) catalyst was successfully applied in internal alkyne hydroarylation with 2- phenylpyridines in the presence of a catalytic amount of PPh_3 in refluxing toluene[9] **(Scheme 2.10)**.



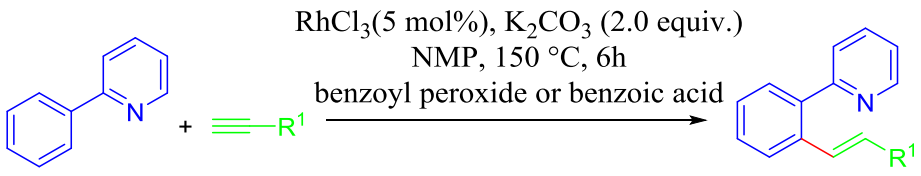
Scheme 2.9. Iridium catalyzed alkyne hydroarylation with 1-naphthol

However, double alkenylated products were formed when the other *ortho* C-H bond was not blocked.



Scheme 2.10. Rhodium catalyzed alkyne hydroarylation with 2-phenylpyridine

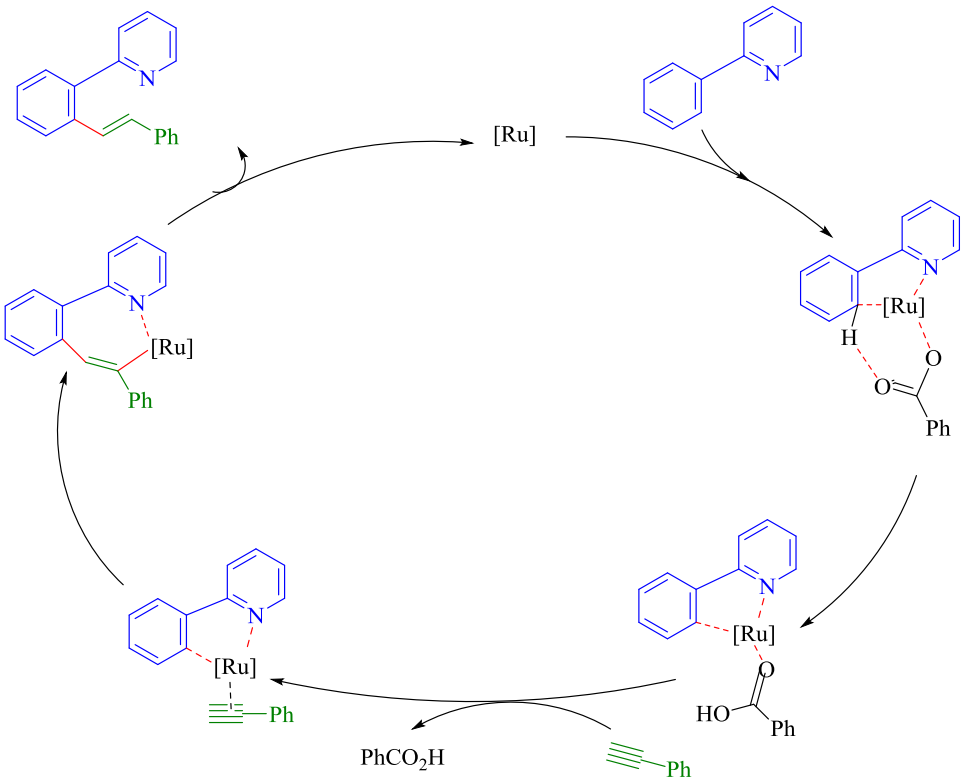
Zhang and coworkers introduced another C-H bond cleavage mechanism for alkyne hydroarylation.[10] In the presence of catalytic amount of $RuCl_3$, alkenylation of 2-arylpyridines at the *ortho* C–H bond proceeded in high regio- and stereo-selectivity with the assistance of stoichiometric benzoyl peroxide or benzoic acid **(Scheme 2.11)**. Besides, arylpyridines, phenylpyrimidine and phenylpyridazine also underwent alkenylation under the same reaction conditions.



Scheme 2.11. Ruthenium catalyzed terminal alkyne hydroarylation with 2-phenylpyridines

The authors proposed that inspite of an oxidative addition pathway mechanism of C-H bond cleavage involved

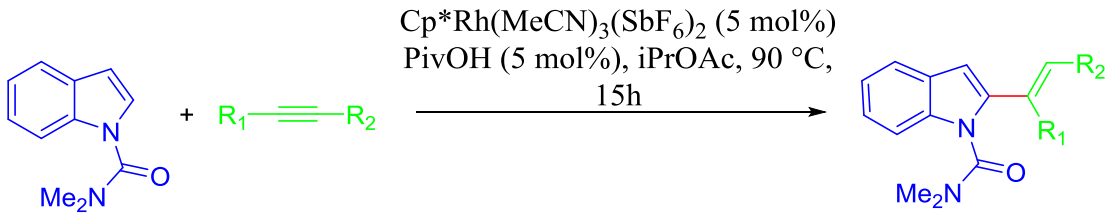
concerted metalation-deprotonation pathway. The catalytic reaction occurs *via* coordination-assisted benzoate-accelerated deprotonation at the *ortho* C-H position of the pyridyl group by ruthenium through the formation of intermediate, generating a ruthenacycle intermediate. Alkyne coordination and migratory insertion into the Ru-C linkage provided a cyclic vinyl-Ru intermediate. Subsequent protonation gave the alkenylated product and the initial active catalyst was regained **(Scheme 2.12).**



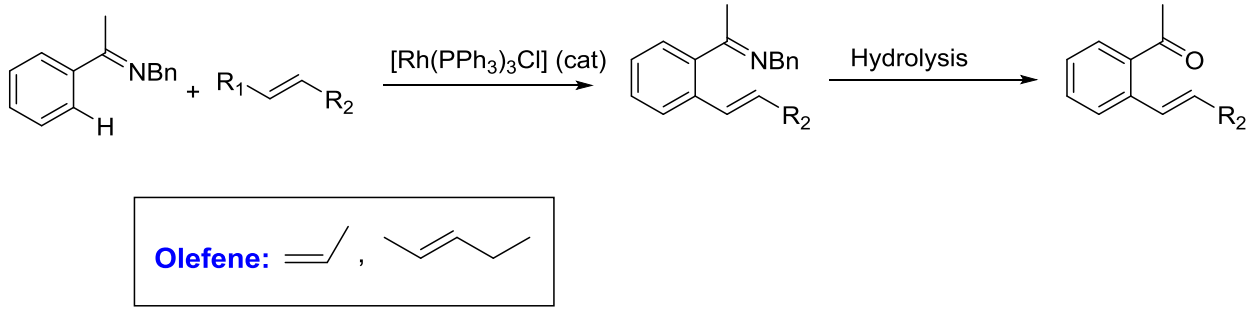
Scheme 2.12. Proposed reaction mechanism for ruthenium catalyzed alkyne hydroarylation

In 2010, Fagnou and coworkers reported a cationic rhodium complex catalyzed alkyne hydroarylation with indole derivatives initiated by C-H bond activation *via* a proposed concerted metallation-deprotonation mechanism for C-H bond activation (**Scheme 2.13**)[11].With the aid of PivOH additive, 2-alkenylindoles were obtained in good yields with high regio- and stereoselectivity in *i*PrOAc under relatively lower reaction temperature. This catalytic system for *ortho*-C-H alkenylation could also be applied to other heterocycles, such as pyrroles, furans, and benzamides.

Inspite of high yields and good selectivity towards mono-alkylation at the *ortho* position this chemistry was only relevant to terminal, non-isomerizable olefin substrates. For this reaction internal and isomerizable alkenes were not effective substrates. Later, Jun and co-workers elaborated the olefin substrate scope of this conversion and include both terminal and internal olefins In all cases internal olefines underwent isomerization to terminal alkenes instead of preliminary alkylation to give linear products.[12]



Scheme 2.13. Rhodium catalyzed alkyne hydroarylation with indoles

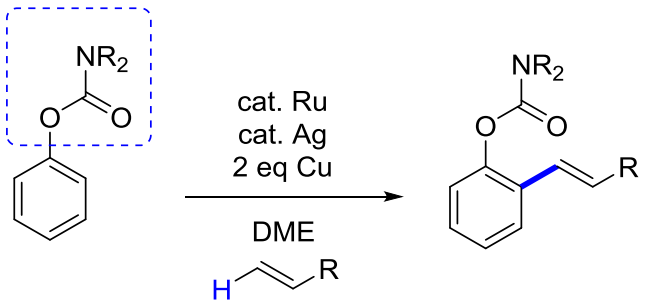


Scheme 2.14. The imine directed C-H functionalisation

By converting aromatic ketones to the corresponding ketimines, chelation of the Lewis-basic imine nitrogen assisted the Rh catalyzed C-H activation at the *ortho* position on the aromatic ring. ketones were isolated in high yields upon hydrolysis of the corresponding alkylated ketimine products, corresponding **(Scheme 2.14)**.

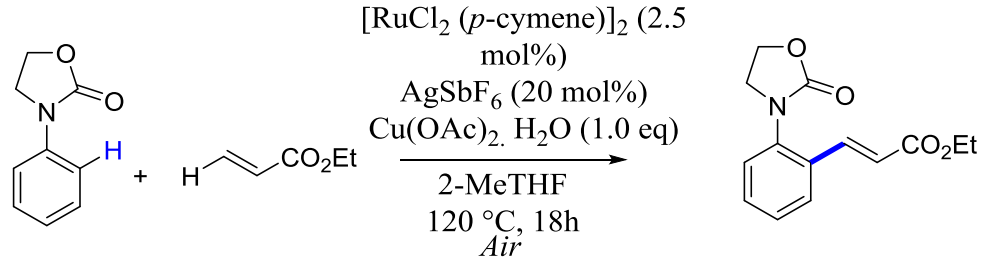
Due to instigate developments from Oi and Inoue, Ackermann, and Bruneau and Dixneuf, ruthenium catalyzed C-H bond derivatisation has seen widespread application into the modern synthetic world[13].

A breakthrough in ruthenium(II) catalysts was brought by Ackermann that evolved a strategy to install different functionalities utilising the influence of weakly coordinating carbonyl directing groups[14] **(Scheme 2.15)**.

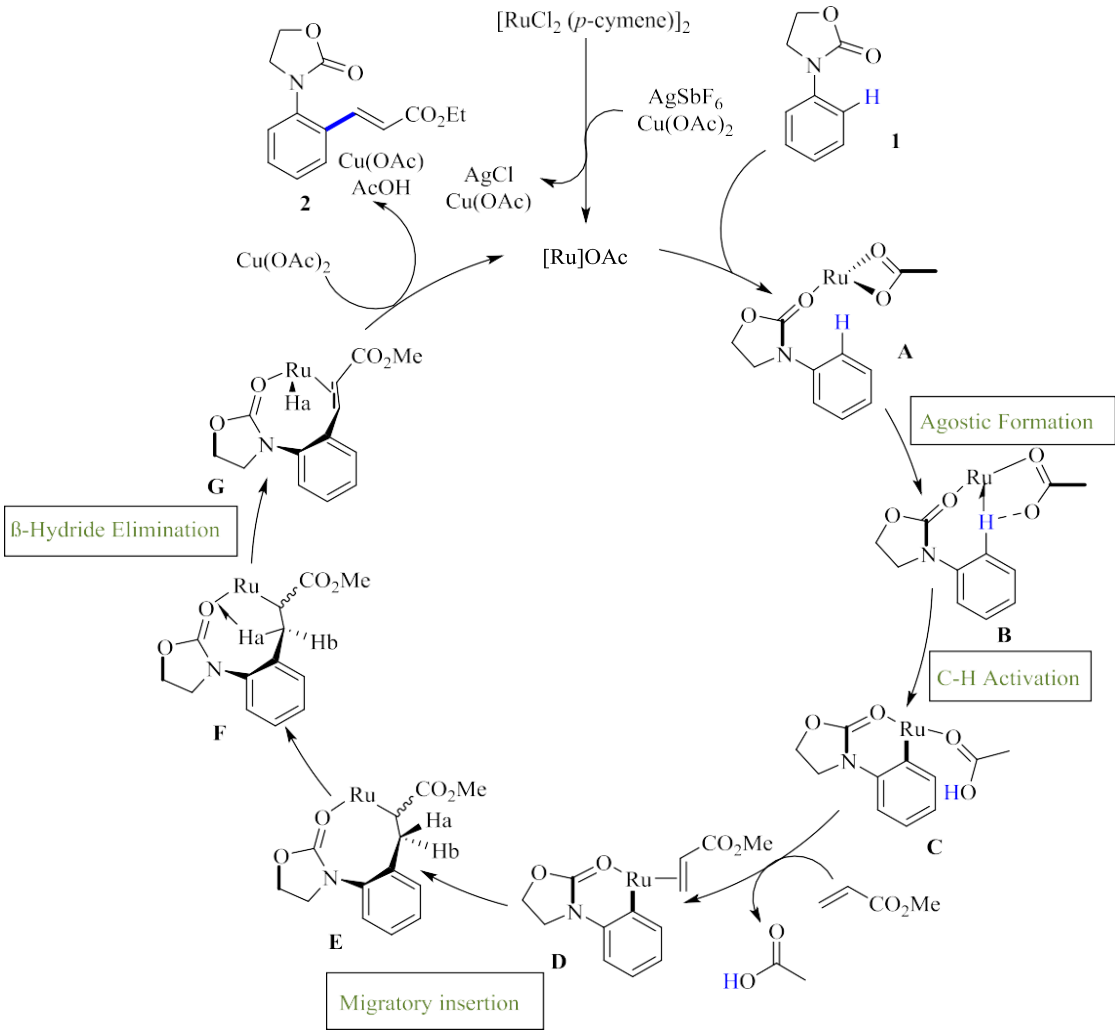


Scheme 2.15. The carbamate directed C-H functionalization reported by Ackermann

C-H functionalization *via* ruthenium catalyst was first reported by Christopher G. Frost on oxazolidinone directing group. Cyclometalation and subsequent functionalization resulted was modeled on an alkenylation reaction, which led to the synthesis of over 25 novel substituted *N*-aryloxazolidinone motifs with up to 94% yields having absolute mono-selectivity **(Scheme 2.16)**. This methodology granted acess to biologically relevant derivatives of oxazolidinone pharmaceuticals and could be applied to late stage drug modification.[15]



Scheme 2.16. The oxazolidinone directed C-H functionalization



Scheme 2.17. Proposed mechanism for synthesis of oxazolidinone

Although the directing group allowed precise region-control of alkenylation at the *ortho* position **(Scheme 2.17)**, it typically remains intact on the product structure after the reaction and leads to several limitations. First, the directing group on the product could cause over-reaction, which leads to a mixture of mono-and dialkenylated products. Second, additional synthetic steps would be required to remove these directing groups or transform into more synthetically useful functionalities. Third, the general inability of common directing groups to access *meta*- and *para*-alkenylated products limits its application. Besides, all of the current catalyst systems of functional group-directed alkyne hydroarylation require harsh reaction conditions, such as high reaction temperatures and requirement of heavy salt additives, which restricts the utility and functional group compatibility. Lastly, the precise control over regio- and stereoselectivity is still an unsolved problem. All these longstanding challenges have incited to develop novel molecules with C-H functionalisation.

1,8-Naphthlimides are well-known and extensively researched compounds, not only because of the biological activity of some examples[16], but also having the properties of intercalation with nucleobases. Thus, due to synthetic and biological importance of naphthalimide, researchers have great interest to synthesize the derivatives of this moiety.1,8-Naphthalimides (benz[*de*]isoquinolin-1,3-diones) possess excellent antitumour property towards diverse murine and human cells.[17]

Moreover, 1,8-Naphthalimide dyes have a strong yellow-green fluorescence and good photo-stability due to their conjugated ring structure, with absorbance and emission generally occurring in the 450-330 nm and 560-370 nm regions, respectively.

3. Aims and Objectives

Based on well known literature report, it was envisioned the strategy, which takes advantage of an efficient Ru-catalyzed C-H bond activation reaction. This strategy has been utilized for remote C-H functionalization which uses strongly directing N and weakly coordinating carbonyl group and formation of metallacycle which enables radical functionalization and according to reports from Oi and Inoue, Ackermann, and Bruneau and Dixneuf, weakly coordinating carbonyl directing groups could be used to install diverse functionality. Inspired from these reports, latent moiety (naphthalimides) which also has a weakly directing carbonyl group and strongly directing group N, is used. Acrylates are most appropriate of the other alternatives because of their electron deficient nature.

4. Experimental

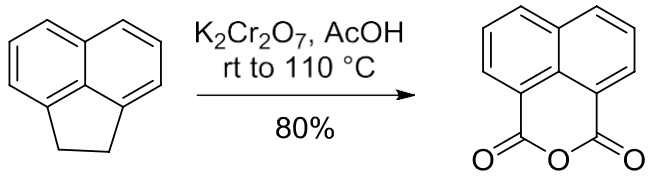
4.1 General Chemistry

All reactions were performed in oven-dried glass wares. Without further purification, commercial grade solvents were used, supplied by Lobachem, Spectrochem and Sigma Aldrich. 500MHz and 125MHz NMR spectrometer were used for recording ^{1}H and ^{13}C NMR spectra, respectively using $CDCl_3$ as solvent. The chemical shifts of derivatives were shown in parts per million taking TMS as reference and all the values of coupling constant (*J*) are

in Hz. Thin layer chromatography has been used to observe the reactions using plates coated with silica gel HF-254. All synthesised compounds were purified by column chromatography using silica gel 60-120 mesh. Ethyl acetate, chloroform and hexane were used as eluents for TLC and column chromatography.

4.2 Synthesis of C-H Alkenylated Products

A) Procedure for Synthesis of 1,8-Naphthalic Anhydride (2):-

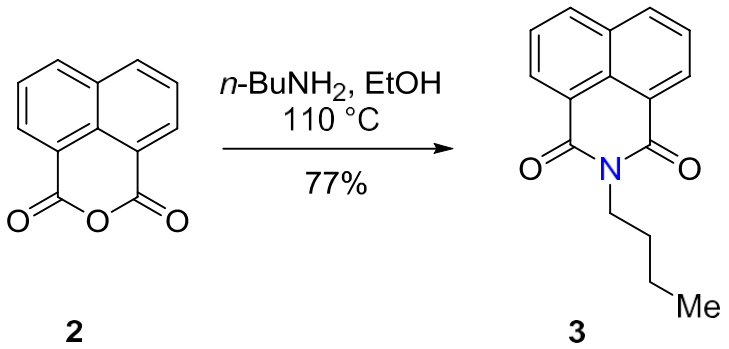


1 **2**

Scheme 4.1. Preparation of **2**

Acenapthene (5g, 0.032 moles) was added into a 250ml round bottomed flask. Acetic acid (150ml) followed by potassium dichromate ($K_2Cr_2O_7$, 25g, 0.063moles) was added taking 5g each time, slowly to avoid bumping because the reaction became exothermic. Now, place a condenser over it and keep it at 110˚C for overnight. Work up was done by adding water into the reaction mixture. Now, let the reaction mixture containing water was stirred for about 10 min so that precipitates could be settled down. Filtered the precipitates with the help of buchner funnel. Creamish coloured precipitates were formed, dried in an oven to get 1,8-naphthalic anhydride **(2)** in 80% yield.

B) Procedure for Synthesis of 2-Butyl-1*H*-benzo[*de*]isoquinolin-1,3(2*H*)-dione (3):-



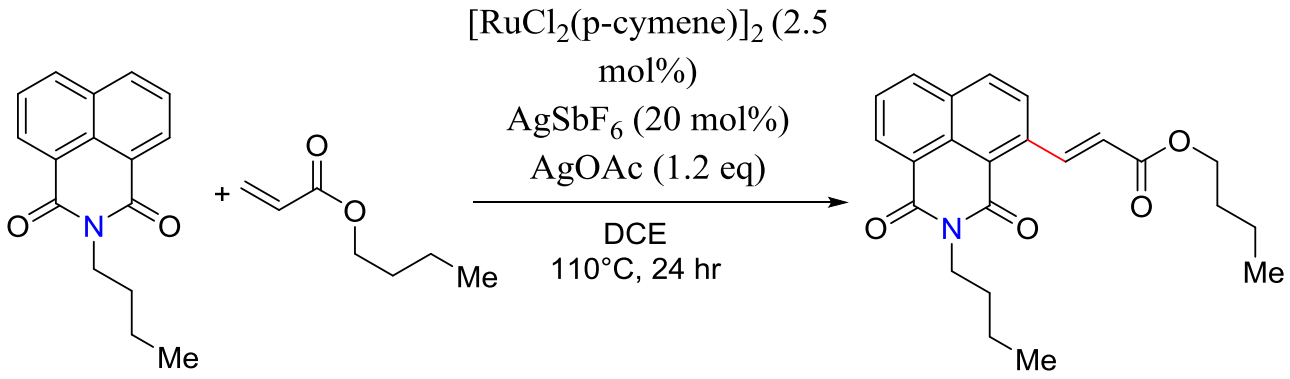
2 **3**

Scheme 4.2. Preparation of **3**

1,8-Naphthalic anhydride **(2)** was taken (500 mg, 2.52 mmol) in ethanol in a round bottomed flask and then slowly adding n-butyl amine (554 mg, 7.57 mmol) at room temperature for 2 hours and then 30-40 minutes on heating at 110˚C. After cooling to rt, the reaction was concentrated under vacuum. The crude product was purified by column chromatography using 60-120 silica gel, to get the desired product. The compound **3** was obtained as light yellow solid (492 mg, 77% yield), R_f = 0.55 (30% $CHCl_3$ in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.59 (d, *J* = 7.3

Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 2H), 4.23 – 4.17 (m, 2H), 1.80 – 1.70 (m, 2H), 1.48 (dt, *J* = 15.0, 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.2, 133.8, 131.6, 131.1, 128.1, 126.9, 122.8, 40.3, 30.2, 20.4, 13.9.

C) Synthesis of Butyl-3-(2-butyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-4- yl)acrylate (4):-



3 **4**

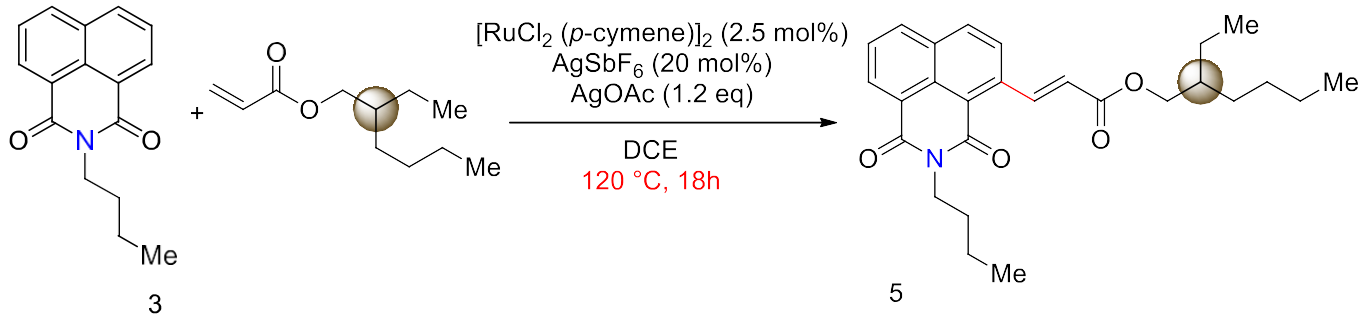
Scheme 4.3. Preparation of **4**

In an oven dried round bottomed flask, to a solution of **3** (100 mg, 0.4 mmol), n-butyl acrylate (154 mg, 1.2 mmol) in $[RuCl_2(p\text{-cymene})]_2$ (6.12 mg, 2.5 mol%), $AgSbF_6$ (13.7 mg, 10 mol%) and AgOAc (80 mg, 0.48 mmol) in DCE (3ml) were added. The reaction mixture was heated (followed by condensation) to 110 °C for 24 h. After complete the reaction, the solvent was removed in vacuo and the crude mixture was purified using column chromatography using (60-120 silica gel, 10% EtOAc in hexane) to give C-H alkenylated product. The compound **(4)** was obtained as a yellow solid (97.6 mg, 65% yield). R_f = 0.35 (10% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.99 (d, *J* = 16.0 Hz, 1H), 8.66 (d, *J* = 7.3 Hz, 1H), 8.20 (dd, *J* = 8.1, 5.6 Hz, 2H), 7.79 (t, *J* = 7.9 Hz, 2H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 4.22 – 4.17 (t, 2H), 1.75 (dd, *J* = 15.0, 6.9 Hz, 4H), 1.47 (dd, *J* = 15.2, 7.7 Hz, 4H), 1.00 (td, *J* = 7.4, 2.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 166.4, 164.1, 163.7, 145.2, 140.7, 133.7, 131.9, 128.6, 127.8, 127.3, 123.5, 123.0, 119.8, 64.8, 40.5, 30.8, 30.2, 20.4, 19.2, 13.8.

In an oven dried round bottomed flask, to a solution of **3,** (50 mg, 0.2 mmol), ethylhexyl acrylate (119 mg, 0.6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.12 mg, 2.5 mol%), $AgSbF_6$ (6.8 mg, 10 mol%) and AgOAc (80 mg, 0.48 mmol) in DCE (3ml) were added. The reaction mixture was heated to 110 °C for 24 h. After complete the reaction the solvent was removed in vacuo and the crude mixture was purified using column chromatography (60-120 silica gel, 10% EtOAc in hexane) to give C-H alkenylated products.

The compound **(5)** was obtained as a light yellow solid (50.5 mg, 58% yield), R_f = 0.25 (10% EtOAc in Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.01 (d, *J* = 16.0 Hz, 1H), 8.67 (d, *J* = 7.2 Hz, 1H), 8.20 (dd, *J* =

D) Synthesis of 2-Ethylhexyl-3-(2-butyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-4-yl)acrylate (5):-



Scheme 4.4. Preparation of **5**

8.1, 5.7 Hz, 2H), 7.79 (dd, *J* = 8.1, 6.0 Hz, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.20 (t, *J* = 7.1 Hz, 4H), 1.72 (dt, *J* = 8.1, 6.8 Hz, 3H), 1.49 – 1.36 (m, 9H), 1.02 – 0.92 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 166.6, 164.1, 163.7, 145.2, 140.7, 133.8, 133.6, 131.9, 128.6, 127.7, 127.3, 123.4, 122.9, 119.8, 67.4, 40.5, 38.9, 30.5, 30.2, 29.0, 23.9, 23.0, 20.4, 14.1, 13.8, 11.1.

5. Results and Discussion

Using commercially available acenaphthene as an initial substrate, naphthalimide derivatives (4 and 5) were synthesised according to the Schemes 4.1-4.4 respectively.

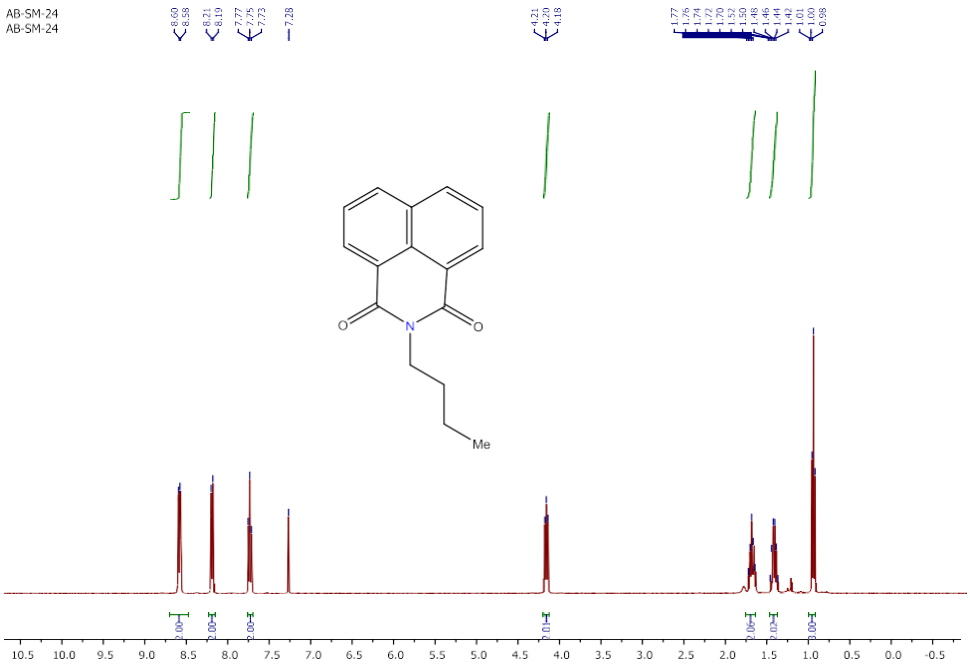


Figure 5.1. ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of compound **3**

Acenaphthene **(1)** was treated with potassium dichromate in acetic acid at 110˚C, for overnight. After work up, the solid compound was filtered and dried, a creamish white solid of 1,8-naphthalic anhydride **(2)** was obtained in 80% yield.

1,8-naphthalic anhydride **(2)** was then treated with n-butyl amine in ethanol as a solvent at room temperature for 2 hours and then transferred to heating for 30-40 minutes, the product was filtered, washed and dried. Crude product was purified by column chromatography, gave light yellow solid **(3)** with 77% yield.

^{1}H NMR spectrum of this compound **(3)** showed 2H doublet at δ (ppm) 8.59 and 8.20 of CH groups in aromatic region, 2H triplet due to CH group at δ 7.75 ppm in aromatic region, 2H multiplet at δ 4.23 – 4.17 ppm due to CH_2, 2H multiplet at δ 1.80 – 1.70 ppm due to CH_2 group, 2H doublet triplet at δ: 1.48 ppm due to CH_2 and 3H triplet at δ 1.00 ppm due to methyl group. ^{13}C NMR spectrum of compound **(3)** showed carbon signals at δ (ppm) 164.2 due to CO groups, δ (ppm) 133.8, 131.6, 131.1, 128.1, 126.9, 122.8 due to aromatic carbons, δ (ppm) 40.3, 30.2, 20.4 due to CH_2 carbons and δ (ppm) 13.9 due to CH_3 group. ^{1}H NMR and ^{13}C spectra confirmed the formation of compound **3**.

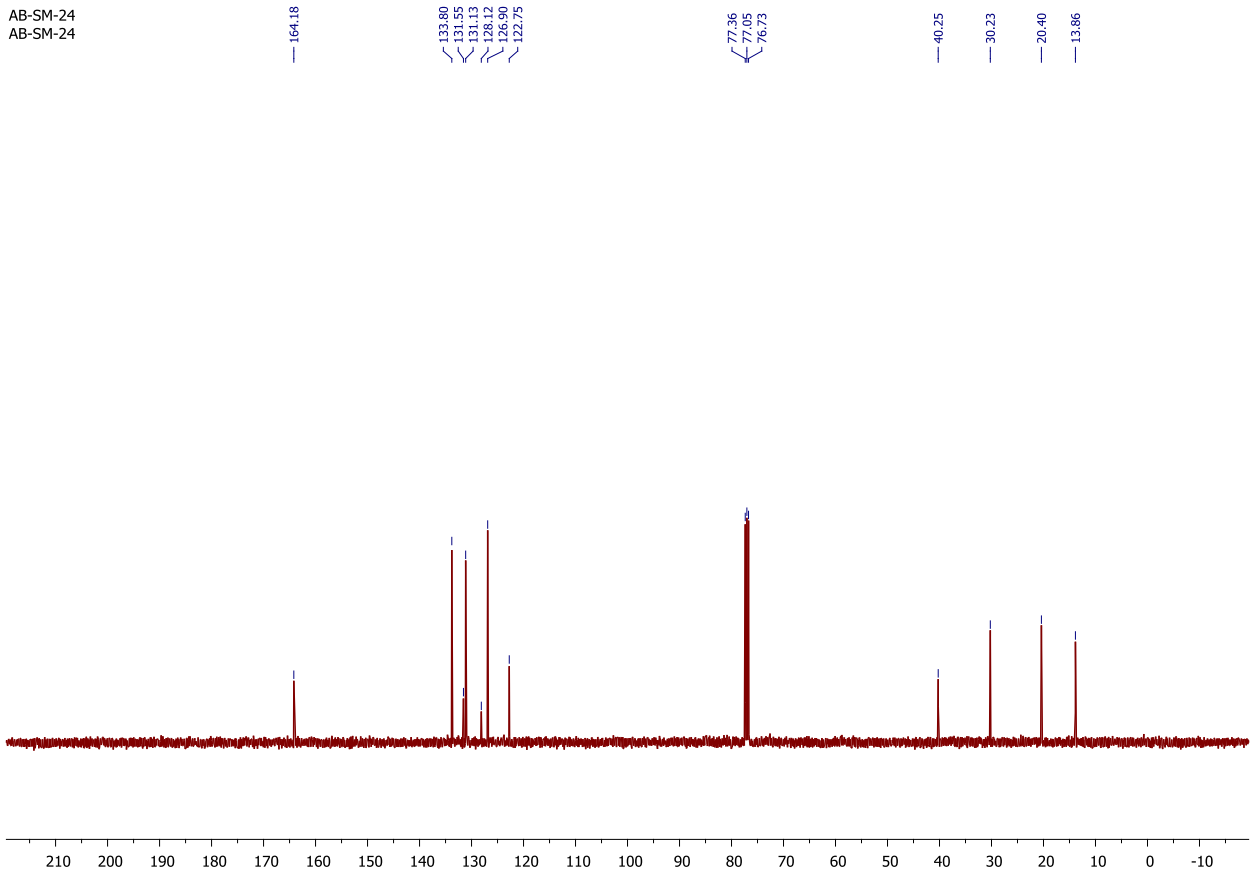


Figure 5.2. ^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of compound **3**

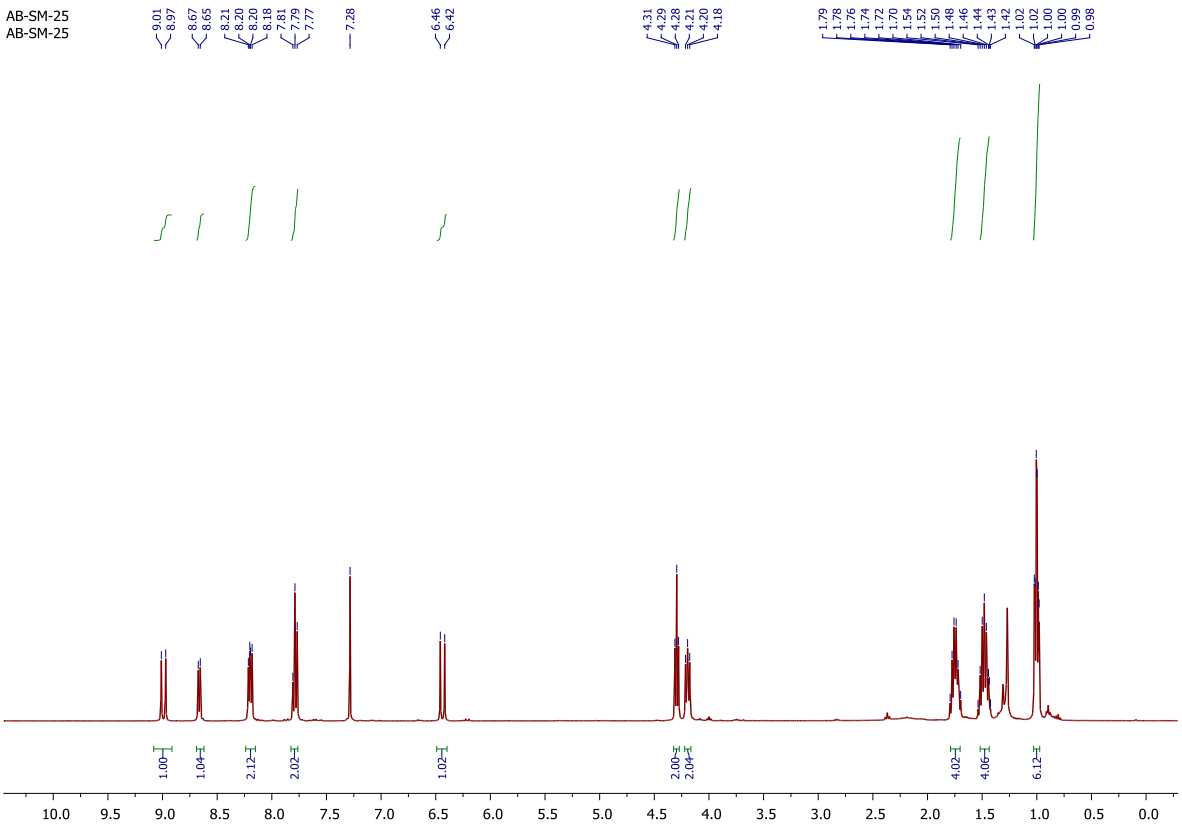


Figure 5.3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **4**

The desired alkenylation proceeded only in presence of the catalyst $RuCl_2(p\text{-cymene})_2$ which could not be possible with other catalysts and among a set of representative solvents, DCE was found to be the best solvent and olefination failed to proceed in the absence of $AgSbF_6$ as the co-catalyst. Hence, **3** was treated with n-butyl acrylate (3 equiv.) in the presence of Ru catalyst (2.5 mol%), activator ($AgSbF_6$) and AgOAc, taking DCE as a solvent at 110˚C, for overnight, as a result of which a yellow solid **(4)** was obtained which was purified by column chromatography to get the yield of 65%.

This compound was confirmed by ^{1}H NMR spectroscopy which showed 1H doublet at δ 8.99 ppm of trans CH proton, 1H doublet at δ 8.66 ppm due to aromatic CH, 2H double doublet at δ 8.20 ppm due to aromatic protons, 2H triplet at δ 7.79 ppm, 1H doublet at δ 6.44 ppm due to trans CH protons , 2H triplet at δ 4.29 ppm due to CH_2 attached with O, 2H triplet at δ 4.22-4.17 ppm due to CH_2 attached with N, 4H double doublet at δ 1.75 ppm, 4H double doublet at δ 1.47 ppm due to four methylene groups, 6H triple doublet at 1.00 ppm due to two CH_3 groups. ^{13}C NMR spectrum showed peaks at δ 166.4, 164.1, 163.7 due to CO groups, δ 145.2, 140.7, 133.7, 131.9, 128.6, 127.8, 127.3, 123.5, 123.0, 119.8 due to aromatic carbon atoms, δ 64.8, 40.5, 30.8, 30.2, 20.4 due to butyl CH_2 groups and δ 19.2, 13.8 due to butyl CH_3 groups.

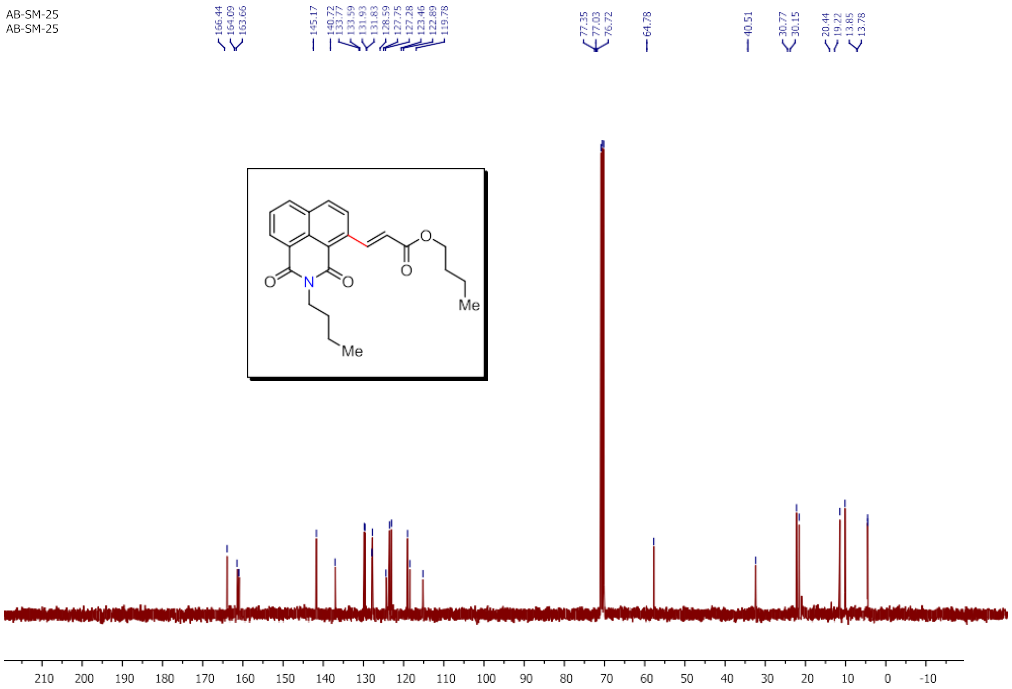


Figure 5.4. ^{13}C NMR spectrum of (125 MHz, $CDCl_3$) of compound **4**

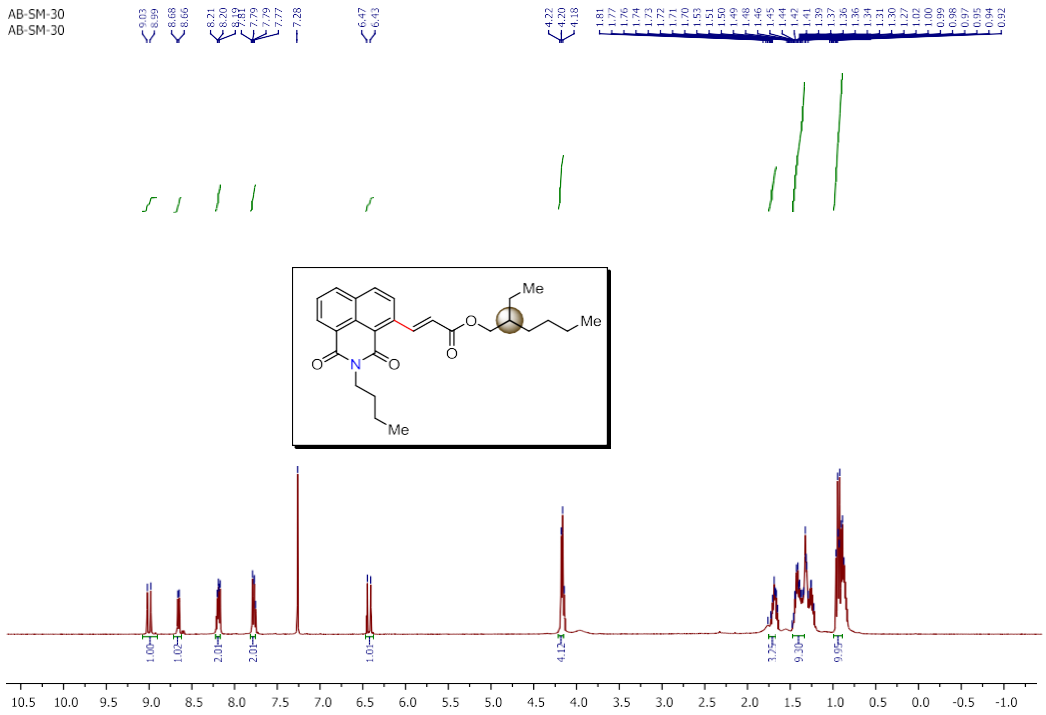


Figure 5.5. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **5**

Similarly compound **3** was treated with 2-ethylhexyl acrylate in the presence of Ru catalyst (2.5 mol%), $AgSbF_6$ and AgOAc, taking DCE as a solvent at 110˚C, for overnight to get 58% yield of light yellow solid **(5)** which is purified by column chromatography. ^{1}H NMR spectrum of compound **5** showed 1H doublet at δ 9.01 ppm due to CH proton, 1H doublet at δ 8.67 ppm due to two CH group of aromatic region, 2H double doublet at δ 8.20 ppm which showed aromatic protons, 2H double doublet at δ 7.79 ppm of aromatic protons, one doublet at δ 6.45, triplet of 4H at δ 4.20, double doublet at δ 1.72 of 3H, two multiplets at δ 1.49-1.36 and δ 1.02- 0.92 ppm of nine and ten protons, respectively. ^{13}C NMR spectrum showed signals at δ 166.6, 164.1, 163.7 due to three CO groups, δ 145.2, 140.7, 133.8, 133.6, 131.9, 128.6, 127.7, 127.3, 123.4, 122.9, 119.8 due to aromatic carbons, δ 67.4, 40.5, 38.9, 30.5, 30.2, 29.0, 23.9, 23.0, 20.4, 14.1, 13.8, 11.1 due to saturated methylene and methyl groups of butyl and 2-ethylhexyl acrylate . ^{1}H NMR and ^{13}C NMR spectra confirmed the synthesis of compound **5.**

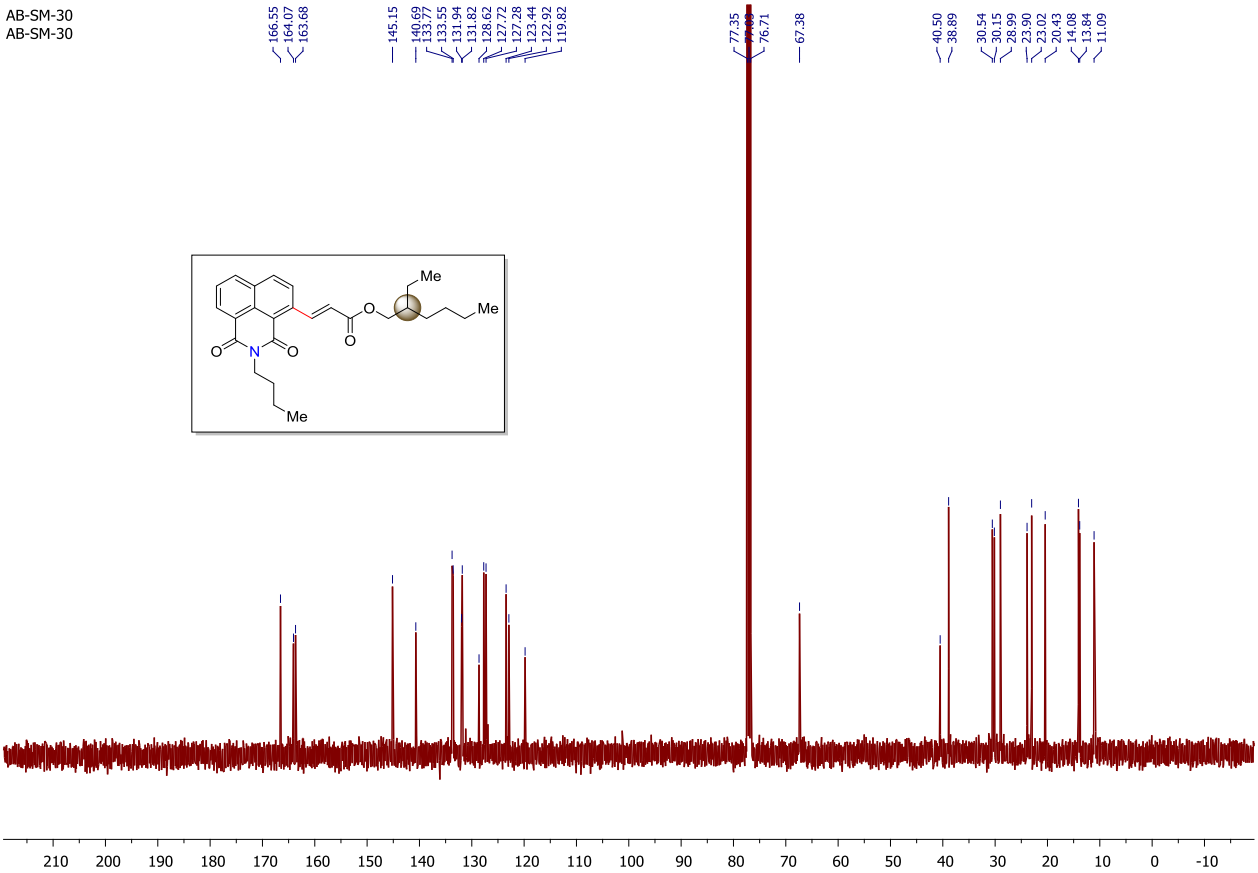
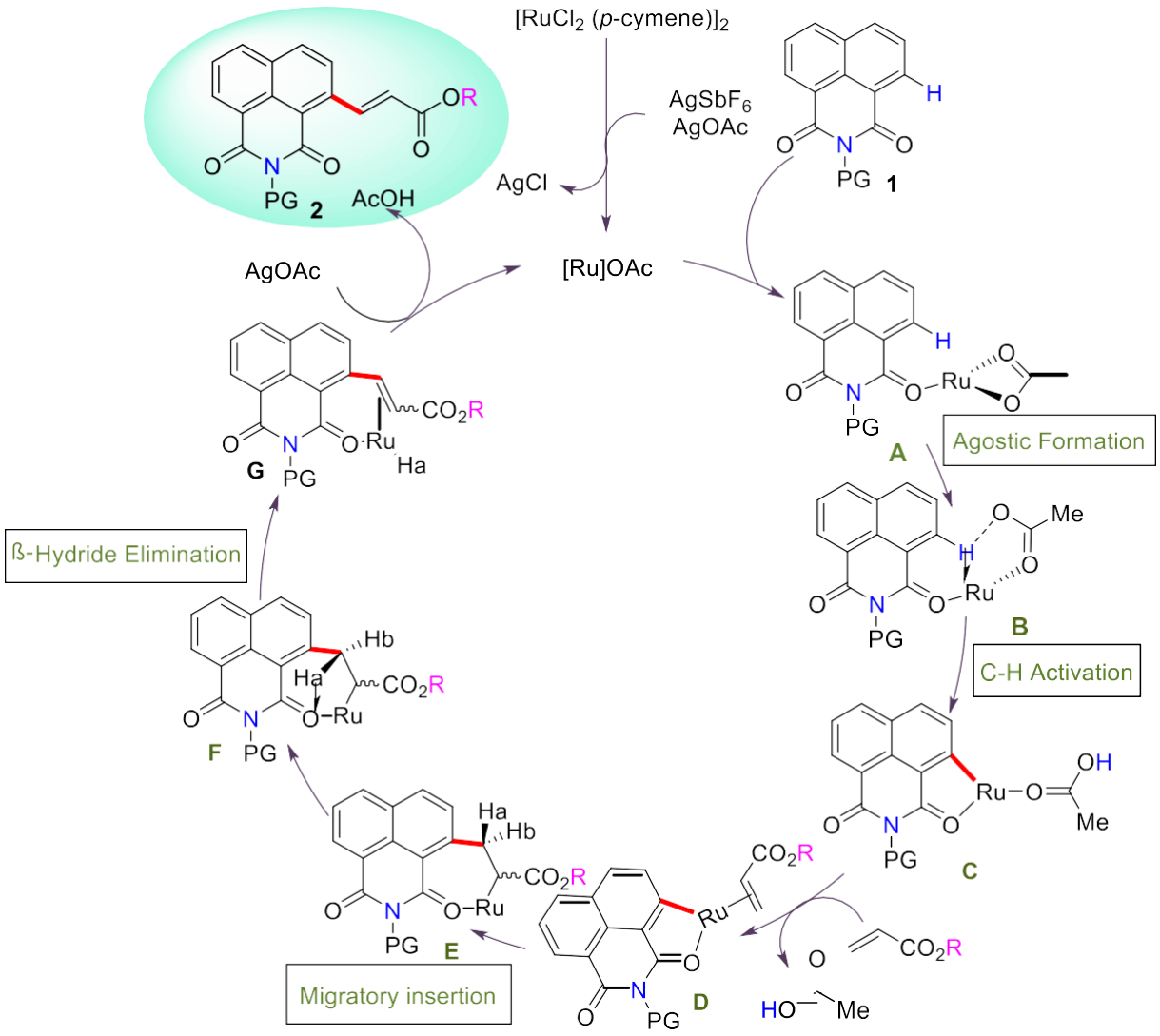


Figure5.6.^{13}C NMR spectrum of (125 MHz, $CDCl_3$) of compound **5**

6. Proposed Mechanism:-



7. Conclusion

Metal-Catalysed C-H site-selective derivatization becomes an efficient technique to explore anticancer drugs due to formation of a metallacycle, formed by directing groups with metal catalyst, where we have shown effective functionalization of naphthalimides with acrylates using Ru catalyst, which highlights the importance of chelating groups using imide as the directing group. Thus, target compounds **4** and **5** were successfully synthesised in good yields and characterised with ^{1}H and ^{13}C NMR spectroscopy.

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