Sustainable Approach Towards the Functionalization of Carbonyl Derivatives: Alkylation, Rearrangement and Lactonization

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By
NIRMALA MOHANTA
(ID: 20183579)



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This Thesis is Dedicated* to *My Mother, Father, and All My Family Members for Their Unwavering Love and Support that have Contributed to My Success.

DECLARATION

I declare that this written submission represents my ideas in my own words and where other's ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.



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Date: 04/05/2022

(Supervisor)

Dr. Boopathy Gnanaprakasam
(Associate Professor**)**

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ABBREVIATION

° C	Degrees Celsius	GC	Gas chromatography
M	Micro	h	Hour (s)
t_R	Residence time (in flow)	Hz	Hertz
Ac	Acetyl	HRMS	High-resolution mass spectroscopy
Ar	Aryl	IR	Infra-red
Aq	Aqueous	J	Coupling constant in NMR
APIs	Active pharmaceutical ingredients	L	Ligand
Bn	Benzyl	LA	Lewis-acid
bs	Broad singlet	M	Molar (mol L^{-1})
Bu	Butyl	m/z	mass to charge ratio
bpy	Bipyridyl	m	multiplet (in NMR)
calcd.	Calculated	Me	Methyl
cat.	Catalytic	MS	Mass spectroscopy
conc.	Concentrated	Mp	Melting point
$CDCl_3$	Deuterated chloroform	mg	Milligram
DFT	Density Functional Theory	mmol	Millimole
DCM	Dichloromethane	mL	Mililiter
DCE	Dichloroethane	NMR	Nuclear magnetic resonance
DEPT	Distortionless enhancement by polarization transfer	OAc	Acetate
DMF	*N, N*-Dimethyl formamide	Ph	Phenyl
		PTSA	*Para*-toluenesulfonic acid
DMSO	Dimethyl sulfoxide	*R*-BNDHP	(R)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate
DMSO-d_6	Duterated dimethyl sulfoxide	rt	Room temperature
DMA	*N,N'*-Dimethylacetmide	*S*-BNDHP	(S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate
equiv	Equivalents	Sn	Tin
ESI TOF	Electrospray ionization time-of-flight	*tert*	Tertiary
EI	Electron impact	TBHP	*tert*-butyl hydroperoxide
ESI	Electron spray ionization	TLC	Thin layer chromatography
Et	Ethyl	TMS	Tetramethyl silane
EtOAc	Ethyl acetate	THF	Tetrahydrofuran
FTIR	Fourier-transform infrared spectroscopy	TON	Turnover number
g	gram(s)	TS	Transition state
GC-MS	Gas chromatography-mass spectrometry	TOF	Turnover frequency

PREFACE

Organic chemistry plays pivotal role in the development of drugs, pharmaceuticals and cosmetics for the welfare of humanbeings. In organic synthesis, functionalization of different moieties are crucial steps to accomplish multistep synthesis of natural products and biologically active molecules. Performing organic synthesis sustainably is of utmost importance in minimizing its harmful effects on the environment. By adopting sustainable practices in synthesis, we can effectively reduce the negative impact of organic synthesis on the environment. In recent years, there has been a growing interest in developing synthetic transformations such as C-C and C-X bond formation in sustainable manner that utilizes various green chemistry tools. Now, carbonyl compounds constitute wide range of natural products and drugs. In this regard, functionalization of carbonyl derivatives is a fundamental area of research in organic chemistry. The traditional methods for carbonyl functionalization often rely on harsh reagents and conditions that can generate large amounts of waste and impart negative environmental impacts. In this direction, this thesis presents the results of a study on the sustainable approaches toward the functionalization of carbonyl derivatives, including alkylation, rearrangement, and lactonization.

Chapter 1: Introduction to Sustainable Approach for Organic Transformation, and Functionalization of Carbonyl Group

At the outset, chapter 1 described a brief introduction of sustainable chemistry and organic transformation in sustainable manner by utilization of various green chemistry tools. Subsequently, the overview for the functionalization of the carbonyl group and various organic transformations using carbonyl derivatives via C-C bond formation involving catalytic and non-catalytic approaches were described. The subsequent section outlines the synthetic approaches that involved for the synthesis of various heterocyclic compounds by using carbonyl functionalized compounds. At the end, the requirement for the development of newer approaches for the C-C, C-O and C-N bond construction towards the synthesis of carbonyl derivatives and heterocycles are highlighted.

Chapter 2: Selective C3-Alkoxylation and C2-Alkylation of 1,3-Dicarbonyl Compounds via Continuous Flow: Applications in the Synthesis of Ondansetron, Phenoprocoumon, and Warfarin

This chapter depicts a heterogeneous catalyzed selective functionalization of 1,3-dicarbonyl compounds via C-C and C-O bond formation using alcohols under batch and continuous

flow. Chapter 2 is subdivided into two sections. Section A describes a highly efficient protocol for C3-alkoxylation of cyclic 1,3-dicarbonyl derivatives using alcohols in the presence of environmentally benign amberlyst®-15 catalyst for the synthesis of β-keto-vinylogous esters. In an extension of this work, transetherification and their reverse reaction in the presence of alcohols and water by using amberlyst®-15 in continuous flow. In section B, the C2-alkylation of 1,3-dicarbonyl compounds by using secondary alcohols and amberlyst-15 in continuous flow has been described. Further, this approaches were directed to the synthesis of various bioactive heterocyclic compounds such as ondansetron, phenprocoumon, and warfarin. In both the section, literature background, the objective of the work, optimization studies, substrate scope, and gram-scale synthesis are described in detailed manner.

Chapter 3: Catalytic Selective Methylallylation at Quaternary Carbon-Centre using *tert*-Butyl Acetate

This chapter describes sustainable protocol for the methyallylation at the quaternary carbon center of oxindole derivatives in the presence of homogeneous as well as heterogeneous catalyst under batch/flow condition. Initially, the literature background on importance of quaternary carbon-containing oxindole moieties and previous reports on methylallyaltion and vinylation of C3-hydroxy oxindole derivatives are described. Subsequently, the objective of the work, optimization for the selective methylallyation using Lewis acid and in-situ generated isobutylene gas is described. Further, selective vinylation and methylallylation using In- and Ni-catalyst with the substrates scope were delineated. This chapter also reports the In-catalyzed rearrangement of the peroxyoxindole derivatives for the construction of methylallyl functionalized 1,4-benzooxazinone derivatives with detailed optimization, substrate scope and detailed mechanistic investigation using DFT.

Chapter 4: $FeCl_2$-Catalyzed rearrangement of aryl peroxyoxindole into 1,3-benzooxazin-4-one

In this chapter, we have presented the discovery of $FeCl_2$-catalyzed rearrangement of aryl peroxyoxindole into 1,3-benzooxazin-4-one. Initially, the literature background on the rearrangement of peroxides and peroxyoxindoles are described. Subsequently, this chapter details about the optimization of the reaction using various metal catalysts and demonstrate the generality of the developed method for the synthesis of different 1,3-benzooxazin-4-one derivatives. In addition, this method was applied for the synthesis of elastase inhibitors and

demonstrated in gram-scale. Finally, the mechanism of the catalytic path is well-explained using DFT and experimental support.

Chapter 5: Annulation of Alkene with *α, β*-Unsaturated Keto-Carboxylic Acid to Synthesize *γ*-Lactone

This chapter presents the Fe@zeolite catalyzed lactonization reaction. At the outset a detailed overview and various approaches for the lactonization reaction are provided. Then, optimization of the lactonisation reaction using alkene or in situ generated *iso*-butylene and *α,β*-unsaturated keto-carboxylic acids in the presence of heterogeneous catalyst is depicted. Subsequently, the substrate scope for the annulation of various alkenes with varying substitutions at *α,β*-unsaturated keto-carboxylic acids are reported. Finally, the plausible mechanism of the lactonization reaction is described.

Chapter 1

Introduction to the Sustainable Organic Transformation and Functionalization of Carbonyl Derivatives

1. Introduction to the Sustainable Organic Transformation and Functionalization of Carbonyl Derivatives

1.1. Abstract

Chemistry is important for manufacturing fine chemicals, pharmacophores, minerals, and energy for the sustainable development of society. Organic synthesis is the corepart of chemistry and plays a key role in accomplishing a shift to a circular economy, by providing sustainable strategies for the use of feedstock chemicals (or building blocks) and energy sources. Here, the significance of sustainable chemistry and the approaches toward the development of sustainable organic transformation is summarised. The adaptation of various types of technology and concepts to perform the organic transformation sustainably along with examples are described in this chapter. Subsequently, the general overview of the functionalization of carbonyl compounds and the selective functionalization of carbonyl derivatives is depicted. Moreover, the synthesis of heterocyclic compounds using a carbonyl compound containing molecules and the selected examples of synthetic development to achieve heterocyclic compounds by utilization of carbonyl derivatives are recapitulated. The objectives and rationale of the project of this thesis are delineated at the end of this chapter.

1.2. Introduction to the sustainable chemistry

In the last decades, sustainability is one of the terms that more often plays a vital role in both scientific and non-scientific development.[1] "*Sustainable development should meet the needs of the present without compromising the ability of future generations to meet their own needs*" states the World Commission on Environment and Development in one of their reports entitled "Our Common Future".[2] Moreover, for an action to be sustainable, the fundamental principle of sustainability needs to be addressed and balanced.

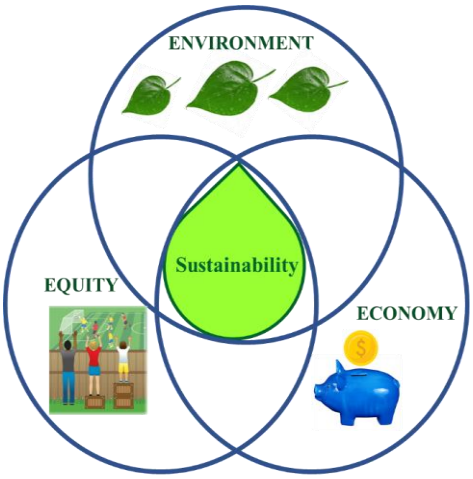


Figure 1: The element of sustainable development

The fundamental principle of sustainability consists of Economic, Environment, and Equity (3E's i.e., See Figure 1).[3] Although, all branches of sciences including physics, biology, human and social science are important for sustainable development, chemistry is the science associated with the word "Sustainable" as well.

Sustainable chemistry development is always a new door to stimulate innovation across all sectors to design and discover new chemicals and production processes having the goals of protecting and enhancing human health and the environment.[4] It includes the following salient aspects:


Refrain from utilizing materials that are persistent, bio-accumulative, and hazardous.


Decreases the utilization of non-renewable resources.


Diminishes the environmental damage caused by chemical processing and manufacturing.


Provides industry-beneficial technologies that are economically advantageous and competitive.

The evaluation of every chemical, reaction, or process must be conducted based on the definition of sustainable chemistry. This is essential since some aspects of green chemistry may not be fully sustainable, and vice versa. Consequently, it is important to prioritize the selection of chemicals, reactions, and processes that align with both sustainability and green principles. In this context, while developing sustainable organic reactions, it is crucial to consider the principles of green chemistry. Therefore, any sustainable strategy for organic transformation should be guided by the 12 principles (Figure 2) of green chemistry.



Figure 2: The 12 principles of green

Organic transformation is not only the core of the pharmaceutical industries but also for many other industries such as fertilizer industries, agricultural product processing industries, chemical processing/supplying industries, etc.[5] These industries mostly rely on organic transformation, in which they utilized many raw materials and solvents to afford the desired products along with a large number of chemical wastes. In this context, it will be more challenging to synthesize the complex

organic molecules such as ciprofloxacin **1** (used to treat bacterial infection)[6], darunavir **2** (treat and prevent HIV/AIDS)[7], remdesivir **3** (broad-spectrum antiviral medication)[8], vitamin B_{12} **4**, etc. in large quantities in a sustainable manner and under human needs (Figure 3). In 1972, Woodward and Eschenmoser took 12 years to achieve the complete synthesis of vitamin B12, using a range of organic reactions for forming carbon-carbon, carbon-oxygen and carbon-nitrogen bonds. Industries face a significant challenge in meeting the needs of a growing global population within a reasonable timeframe while ensuring that future needs are not compromised. Considering above mentioned facts, chemical industries need to make revolutionary changes in their manufacturing product by adopting green and sustainable chemistry.

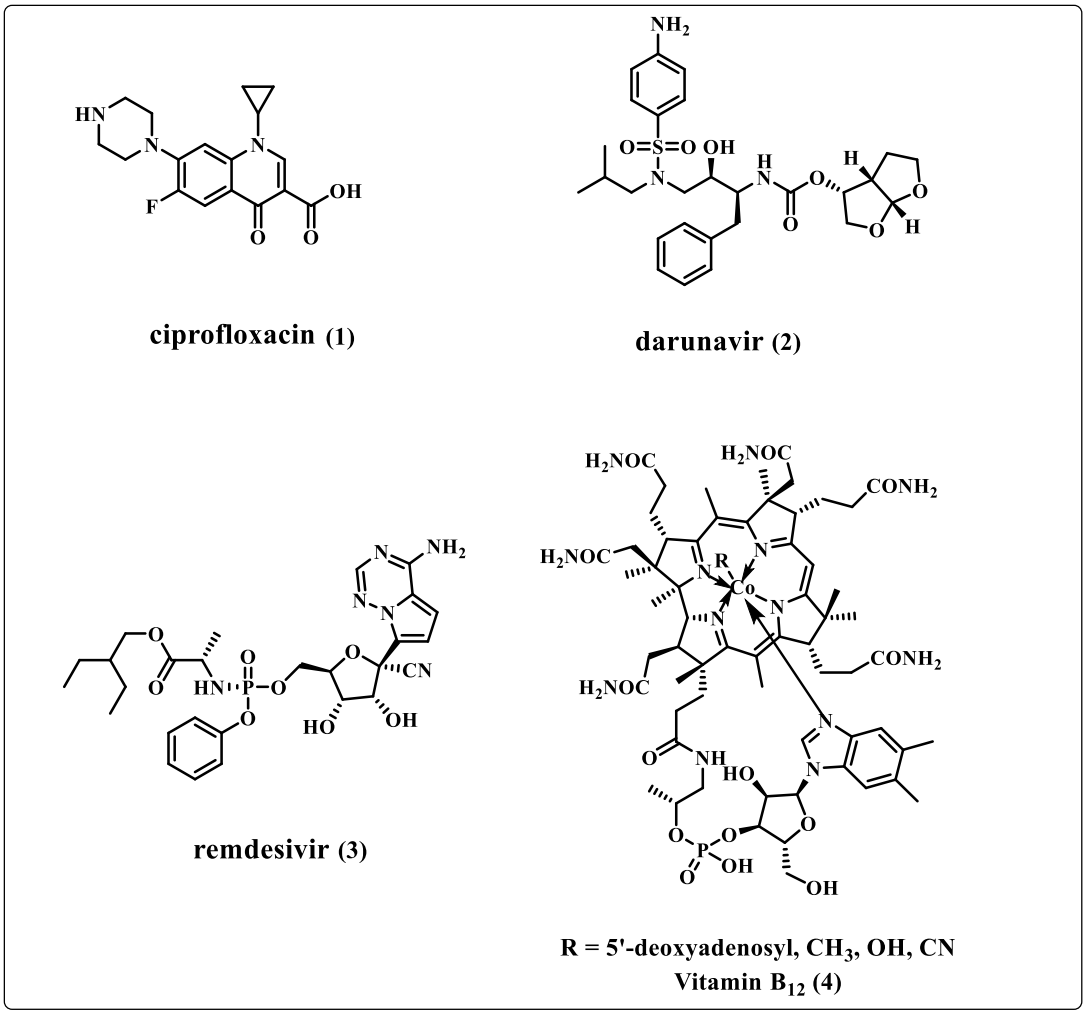


Figure 3: The examples of organic molecules used as drugs

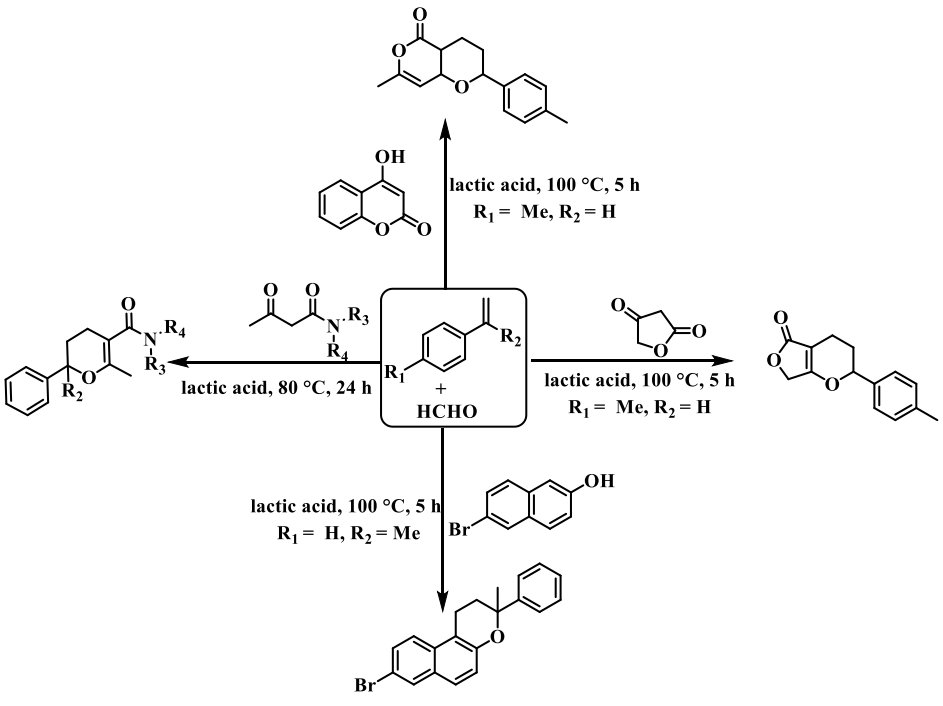
1.3. Sustainable organic transformation

The development of organic transformation for the synthesis of various fine chemicals, natural products, and biologically active molecules always gains the attraction in chemical and pharmaceutical industries.[10] Sustainable chemistry has a goal to shift the perspective of chemists

towards synthesis, focusing on the development of eco-friendly methods, rather than creating new techniques. It emphasizes adapting existing ones to be more sustainable, such as using renewable resources, optimizing reaction conditions, and reducing waste and energy usage. By adopting a comprehensive approach to chemical synthesis, sustainable chemistry aims to mitigate the negative impact of chemistry on the environment and promote a sustainable future. Most importantly different synthetic strategies are used to incorporate environmental considerations as early as possible in the process design stage. Because of the aforementioned facts, synthetic chemistry was used to merge numerous ideas and technologies into the sustainable production of desired molecules. Here are some aspects of green chemistry principles (for 12 principles of green chemistry, see Figure 2) that should be considered when performing organic reactions sustainably.

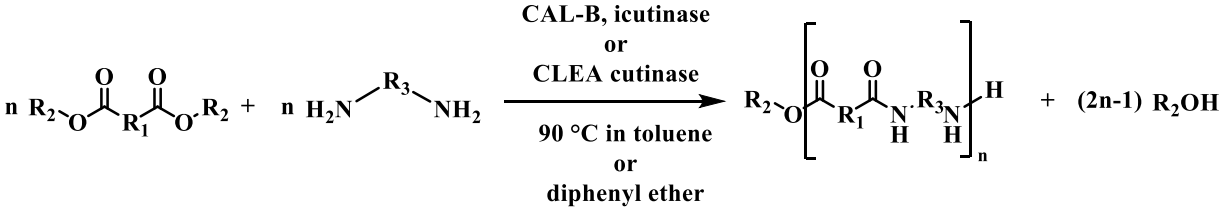
1.3.1. Use of renewable feedstocks

For life on Earth to persist, the resources we use for our daily needs must be renewable. Sustainable chemistry is primarily focused on developing and implementing competitive processes and products while considering the origin of resources as either fossil or renewable. In this context, the development of organic transformation using bio-based materials such as a solvent, and catalyst gained the attention of synthetic chemists.[11] For example, in 2012, Gu and co-workers disclosed that lactic is a promising bio-based solvent for chemical reactions via the illustration of a few examples of organic reactions (Scheme 1).[11b]



Scheme 1: Reactions of styrene and HCHO in lactic acid

Similarly, Loos and co-workers reported the enzyme-catalyzed synthesis of aliphatic/aromatic oligo amides using CAL-B and icutinase (Scheme 2).[12]



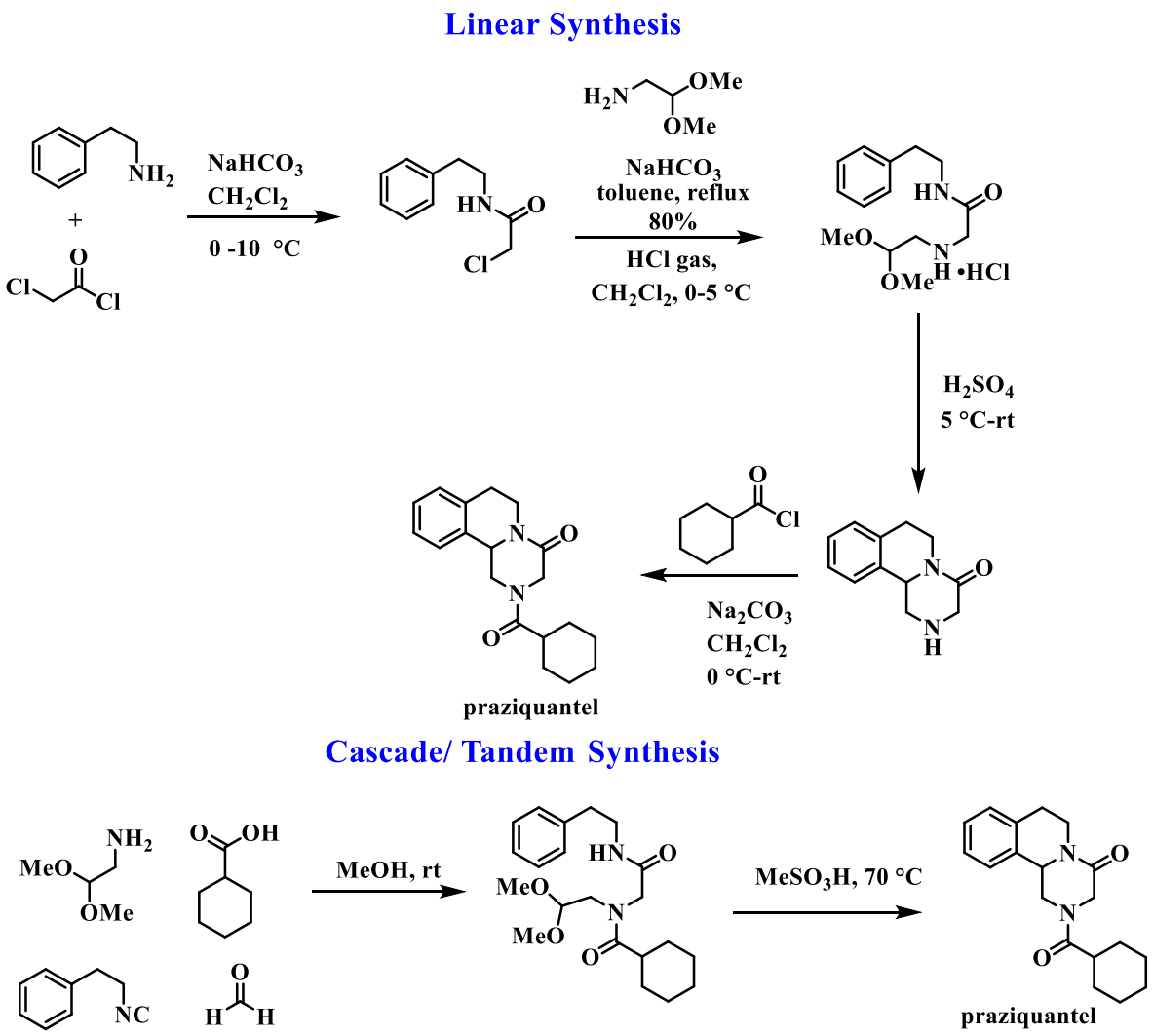
Scheme 2: Enzymatic reaction between aliphatic or aromatic diamines and diesters

1.3.2. Atom economy

In 1990, Barry Trost introduced the atom economy (AE) as a green standard.[13] One effective approach for aiding in reaction selection is the consideration of atom economy. This method involves evaluating the proportion of atoms from the reactants that end up being incorporated into the final product. To achieve a sustainable synthesis, a productive strategy is to employ chemistry that results in a high degree of integration between the starting materials and the final product, thereby minimizing the generation of waste as a by-product. In this context, organic reactions are considered atom-economic reactions and can be broadly categorized into two types: (I) cascade reactions, and (II) rearrangement reactions.

1.3.2.1. Cascade reaction

The cascade reaction is a series of chemical reactions that includes at least two successive reactions, with each succeeding reaction only occurring as a result of the chemical functionality created in the preceding phase.[14] Cascade reaction also known as a domino reaction or tandem reaction. The most significant praziquantel (PZQ) manufacturer produces this medicine in five steps that mostly include the production of amide bonds through the intramolecular *N*-acyliminium Pictet-Spengler cyclization,[15] which is the crucial transformation. This method is very reliable and does not involve any hazardous chemicals. However, a superior strategy exists in the form of a multi-component reaction. By preparing an already acylated intermediate via a Ugi four component reaction (CR) before cyclization, Dömling has reduced the complete synthetic protocol to only two steps based on a comparable cyclization approach (Scheme 3).[16]

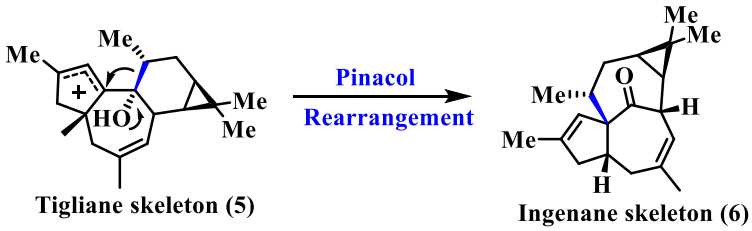


Scheme 3: Linear vs. cascade synthesis of praziquantel

1.3.2.2. Rearrangement reaction

Rearrangement reactions involve the rearrangement of atoms within a molecule to form a new isomer. These reactions can be classified into several types, including carbon-carbon rearrangements, carbon-heteroatom rearrangements, and heteroatom-heteroatom rearrangements, depending on the types of atoms involved in the migration.[17] In many cases, rearrangement reactions are a powerful concept for constructing complex molecular frameworks, as they can often lead to the formation of bonds that are difficult to access using other synthetic approaches. Because many rearrangement reactions involve the migration of a functional group within a molecule, they are often intramolecular reactions.[18] As it appeared in chemistry with the concept of atom economy, which is evaluate the product and waste formation of the reaction. Therefore, the rearrangement reaction has been used in the synthesis of a wide range of natural products and pharmaceuticals.[19] However,

among numerous organic rearrangement reactions,[18] the Pinacol rearrangement is a useful reaction in organic synthesis, as it provides a straightforward method for the conversion of diols to carbonyl compounds.[20] Baran and co-workers reported a method for the synthesis of ingenane skeleton from tigliane skeleton via pinacol rearrangement.[21]



Scheme 4. Synthesis of ingenane skeleton via pinacol rearrangement

1.3.3. Catalysis

A catalyst can significantly increase the rate of a reaction by reducing the required activation energy.[22] The use of a catalyst often results in less waste being generated compared to reactions that used stoichiometric amounts of reagents. Catalysts are classified into two types: homogeneous and heterogeneous. While it may be challenging to determine the superior catalyst for organic transformations, heterogeneous catalysts are more applicable to industries and are considered more sustainable due to their ease of recovery and reuse. Therefore, the heterogeneous catalyst is the main focus of our work for this thesis, and a description of it is given below.

1.3.3.1. Heterogeneous catalysis:

The heterogeneous catalysis mainly works in a two-phase system (Figure 4), which minimizes the contamination of metal in the product. In 1912, Paul Sabatier was awarded the Nobel prize for his excellent work on the hydrogenation of unsaturated organic substances using a metal surface as a catalyst.[23] Later the generality of the hydrogenation reactions was observed in palladium on carbon. Similarly, there are numerous reports available on the heterogeneous-based synthesis of organic molecules. The heterogeneous catalysts are mainly based on solid-supported metal catalysts and organo-catalysts.

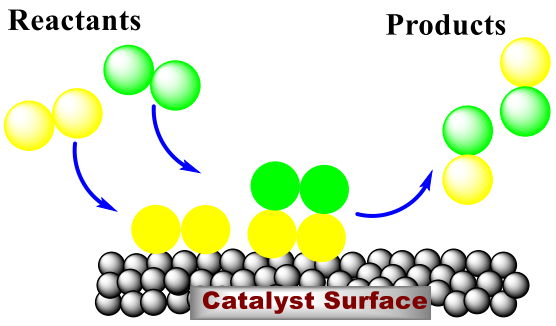
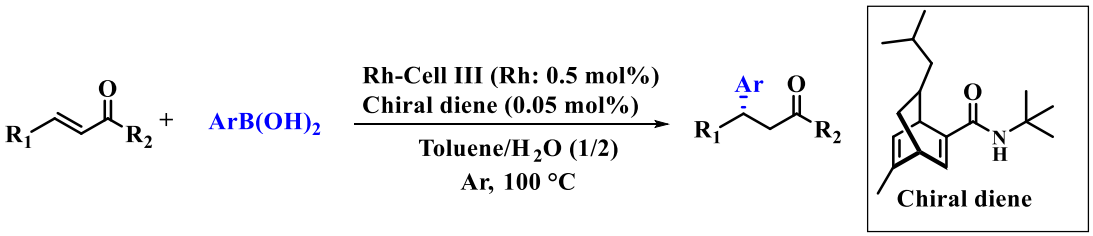


Figure 4: Heterogeneous catalyst system

Here, we described a recent example of an organic reaction using a heterogeneous catalyst. For the last few decades, Shu Kobayashi and his co-workers were working on polymer and nanoparticle-based heterogeneous catalysts.[24] In 2015, they developed cellulose-supported chiral rhodium

nanoparticles as sustainable heterogeneous catalysts for asymmetric carbon-carbon bond formation via Michel addition (Scheme 5).[24f]



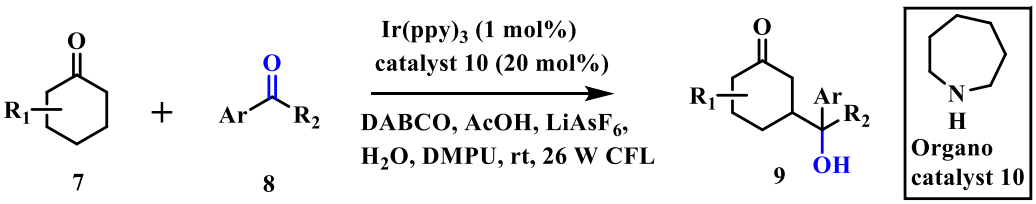
Scheme 5: Asymmetric Michel addition reaction using chiral heterogeneous catalyst

1.3.4. Safe chemicals design and energy efficiency

To promote sustainability, we need to explore different eco-friendly methods for organic transformations. Technology can play a significant role in achieving this goal by enabling us to develop cleaner synthetic processes that are less harmful than traditional chemical synthesis methods.[25] This approach not only ensures a safer working environment but also enhances atom economy, and energy efficiency, and minimizes chemical waste discharge. Several technologies can be used in organic transformations to facilitate a sustainable approach, which we will discuss further in this thesis.

1.3.4.1. Photochemistry

Photosynthesis is a vital process in our life cycle, as it enables plants to utilize light energy to produce oxygen and carbohydrates through chemical reactions. Taking inspiration from nature, organic chemists in particular are interested in the use of light energy to conduct reactions sustainably, which is a renewable energy source, and its ability to use environmentally friendly materials.[26] Additionally, many photochemical reactions can be performed with high efficiency and low waste.[26] The use of light energy chemical reaction can be traced back to Joseph Priestley, who observed the formation of nitrogen oxide from HNO_3 acid upon exposure to sunlight.[27] The discovery of photochemical reactions has led to the development of several organic transformations for synthesizing organic molecules using light.[28] Recently, David Macmillan and co-workers reported the $Ir(ppy)_3$ (photo redox catalyst) and amine **10** (organocatalyst) catalyzed *β*-functionalization of cyclic ketones **7** with aryl ketones **8** which afforded derivatives of **9** (Scheme 6).[28b]



Scheme 6. David Macmillan's photochemical approach for *β*-functionalization of the carbonyl compound

1.3.4.2. Flow chemistry

"Continuous flow chemistry" is the process of performing chemical reactions in a reactor. Flow chemistry involves combining reactive components at a mixing junction and then directing them to a temperature-controlled reactor for continuous chemical reaction and high-volume production in less time (Figure 5). The Haber-Bosch process, which won Haber a Nobel Prize in 1918, is a historical example of this approach used for the continuous industrial scale production of ammonia.[29] Traditionally, the batch processes were prevalent but has several drawbacks, including issues with safety, sustainability, and scalability. Therefore, pharmaceutical companies are attempting to carry out all organic transformations using continuous flow processes. Continuous flow chemistry is an emerging process technology that can fulfill the demand for large quantities of fine chemicals and drugs.

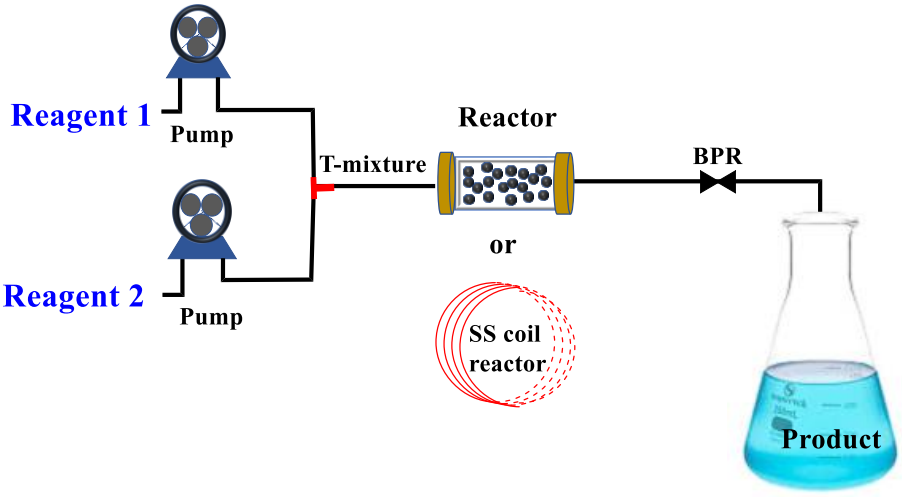


Figure 5: A representation for continuous flow set-up

There are various types of continuous flow systems for organic reactions, which are determined by the key parameters of residence time, mixing, pressure, and temperature. Furthermore, Kobayashi and co-workers[30] have proposed four general categories for continuous flow systems that have been represented in figure 6.

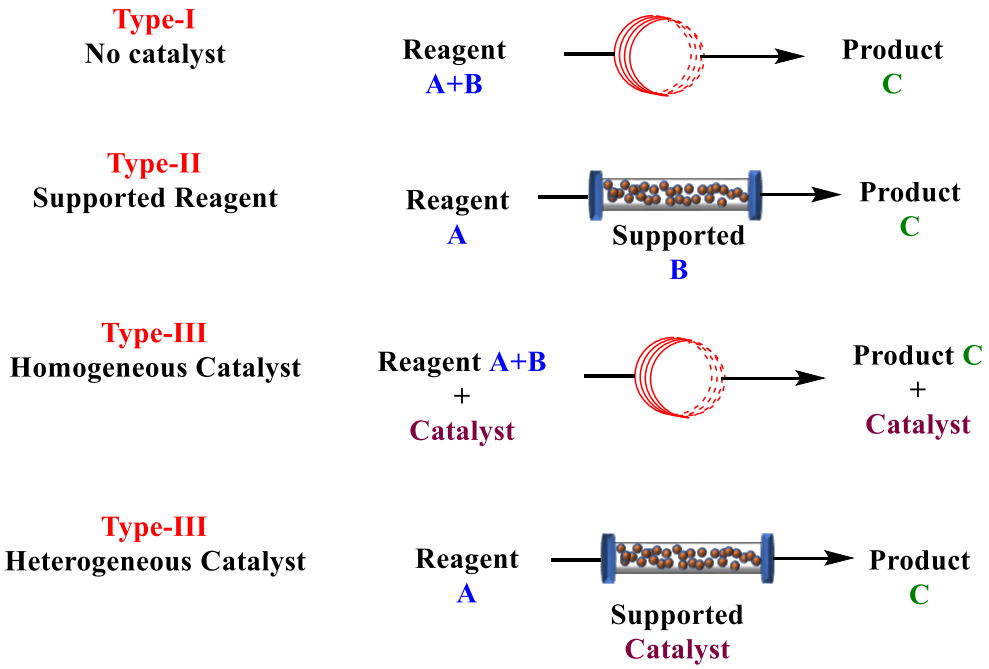
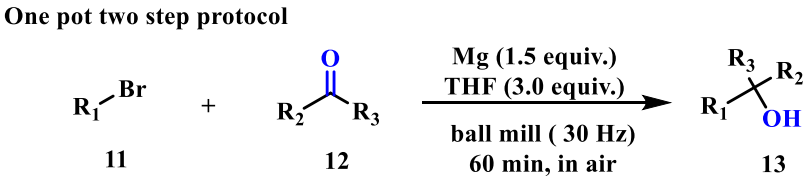


Figure 6: Types of the continuous flow system

The use of continuous flow reactions has been observed in both academia and industries due to it provides numerous advantages, such as waste reduction, improved safety, easy scalability, and higher product yields in shorter times.[31] These advantages are leading the synthetic chemistry community towards sustainable chemistry practices.

1.3.4.3. Mechanochemistry

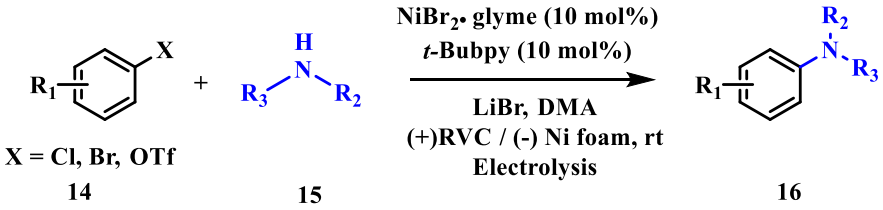
Mechanochemistry is a sustainable and efficient approach to the synthetic organic chemistry that is gaining renewed interest. This technique involves inducing chemical reactions through the direct absorption of mechanical energy, providing an alternative to traditional activation methods. Unlike traditional methods that often require toxic solvents and generate large amounts of waste, mechanochemical reactions are conducted in the solid state or small amounts of solvent, leading to reduced waste generation and lower energy requirements.[32] In this context, several methods have been reported on mechanochemistry by introducing an environmentally benign sustainable approach for the synthesis of organic molecules.[33] Ito research group reported mechanochemistry driven solvent free Grignard reagent added product **13** in one step utilizing halide **11** and ketone/aldehyde **12** in the presence of magnesium using ball milling condition (Scheme 7).[34] The reaction smoothly proceeded in presence of air and eliminated the requirement of an inert atmosphere.



Scheme 7. Ito's approach for the Grignard reaction uses ball milling conditions in presence of air

1.3.4.4. Electro-organic chemistry

For over 170 years, Kolbe's discovery of using electricity as a reagent for organic transformation has gained significant attention as a sustainable approach.[35] This technology has attracted the interest of scientists as electricity can now be sourced from renewable resources such as wind, solar, and hydropower.[36] As a result, many industries have shown interest in this approach. In recent years, various research groups have been actively working on electro-organic synthesis. Recently, Baran and co-workers reported Ni-catalysed electrochemical synthesis of arylamine **16** utilizing aryl halide **14** and amine **15** (Scheme 8). In this method, the scope of the reaction has been described along with detailed mechanistic studies.[37] Furthermore, the developed method is integrated with continuous flow and scaled up to 100 gm scale.



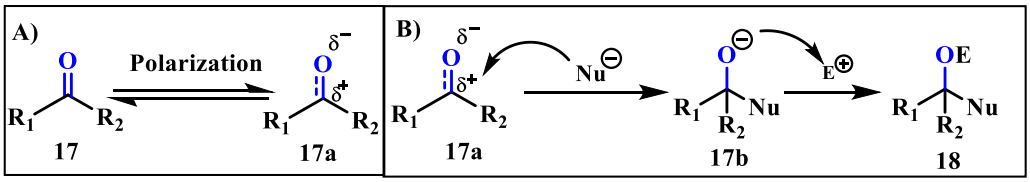
Scheme 8. Electrochemical-driven synthesis of aryl amine

Organic transformations play a vital role in both academia and industry in driving the field of chemistry towards greater sustainability and environmental responsibility. We have already discussed (in the sections 1.2-1.3) about the various green chemistry tools to performed the organic reaction sustainably. Carbonyl compounds are particularly crucial in organic synthesis as they are highly versatile and contribute to the construction of a wide range of natural products and complex organic molecules. This thesis focuses on a sustainable approach to functionalizing carbonyl compounds and synthesizing heterocyclic compounds. The strategy employed involves integrating continuous flow with a heterogeneous catalysis system and rearrangement concepts. The use of continuous flow chemistry allows for precise control of reaction conditions and reduces waste generation compared to traditional batch processes. Heterogeneous catalysis systems, which involve the use of solid catalysts, offer several advantages such as high catalytic activity, selectivity, and

reusability. Additionally, rearrangement concepts can be utilized to form new bonds and create complex molecular structures in an environmentally friendly manner. By adopting this sustainable approach, it is possible to achieve efficient and selective synthesis of carbonyl compounds and heterocyclic compounds while minimizing the environmental impact of chemical processes.

1.4. Overview for the functionalization of carbonyl group (C=O) containing compound

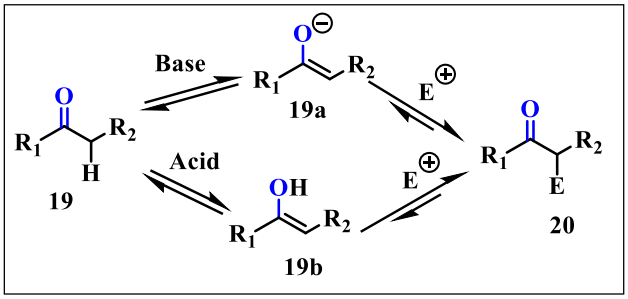
The polarized C=O bond **17a** of carbonyl compound **17** always provides the +ve charge at the carbon center and the -ve charge at the oxygen center (Scheme 9A).[38] The +ve charge of the carbon center attracts the -ve charge and nucleophilic addition (**18**) happens to the carbon center of the carbonyl group (Scheme 9B).[38]



Scheme 9. A) Bond polarization, and B) Nucleophilic addition to the carbonyl group

The keto-enol tautomerism is a type of isomerism that occurs in compounds containing a carbonyl group (C=O). The carbonyl group can exist in two different forms: the keto form **19** and the enol form **19b**. In basic conditions, the carbonyl group can be deprotonated, which can lead to the formation of the enolate anion via removal of a proton from the α-carbon. The resulting structure is called an enolate anion **19a**.[38]

In acidic conditions, the carbonyl group can be protonated, which can lead to the formation of the enol form. This process involves the transfer of a proton from the acidic medium to the carbonyl oxygen, resulting in the formation of a double bond between the carbonyl carbon and the adjacent carbon atom. The resulting structure is called an enol **19b**, which has a hydroxyl (-OH) group attached to the carbonyl carbon. The keto-enol tautomerism is an important concept in organic chemistry, as it can have significant implications for the reactivity and properties of compounds containing a carbonyl group.[38] Due to this the carbonyl group-containing molecules undergo the functionalization at the α-position of the carbonyl group (**20**) (Scheme 10).[38]

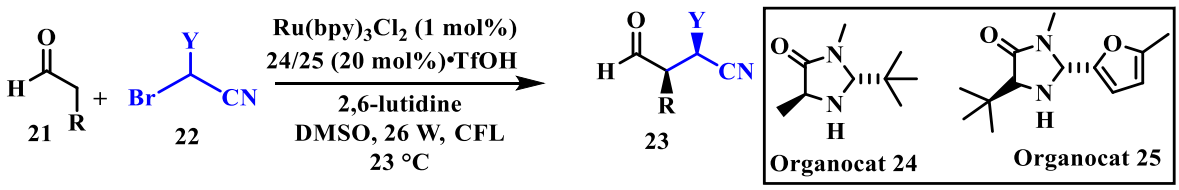


Scheme 10. α-functionalization of the carbonyl group

The 1,3-dicarbonyl compounds are always found in enol form, due to the transfer of a proton from the central -CH_2 group of the keto form to one of the oxygen atoms of the same molecule.[38] In this context, selectively functionalizing this group can be difficult.[39] The main focus of our research is to develop a sustainable method for selectively functionalizing the 1,3-dicarbonyl group in carbonyl derivatives, as well as using those derivatives to synthesize drugs and heterocyclic compounds. Therefore, the representative literature studies on functionalization of C=O containing derivatives is described in this section.

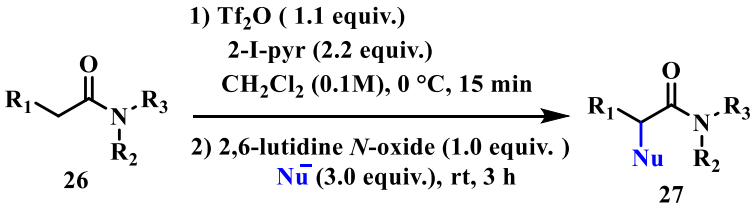
1.4.1. Selective functionalization of carbonyl derivatives

The versatile reactivity of carbonyl compounds towards the nucleophilic addition or α-functionalization renders it difficult to achieve selective α-carbon. However, several research groups have developed various methods for the selective functionalization of carbonyl compounds and successfully synthesized various fine chemical, APIs. There are numerous named[38,18] and unnamed[38,40] reactions are available in the nucleophilic addition to the carbonyl group such as the Grignard reaction, Cannizaro reaction, benzoin condensation, etc. Similarly, the Aldol condensation reaction involves two consecutive reactions, i.e. an α-functionalization reaction to form an enolate ion and a nucleophilic addition reaction of the enolate ion with another carbonyl compound to form an aldol.[41] Moreover, there were numerous reports available on the selective α-functionalization of the carbonyl group.[42] Recently, Macmillan and co-workers[43] disclosed a report on photochemically driven enantioselective α-alkylation of aldehydes **21** using the $Ru(bpy)_3Cl_2$ and organocatalyst **24**/**25** in the presence of 2,6-lutidine and light (Scheme 11). The application of this reaction afforded the pharmacophore fragment from β-cyanoaldehyde derivatives **23**.



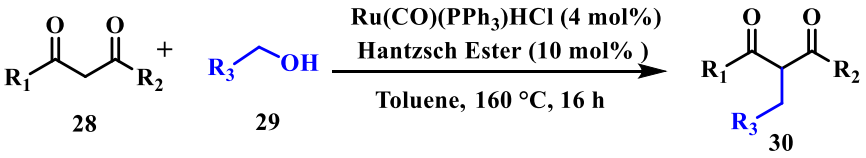
Scheme 11. Macmillan's approach for the *α*-alkylation of carbonyl derivatives

Interestingly, in 2019 Maulide group reported the chemo-selective *α*-functionalization of amides with heteroatom nucleophiles in milder conditions (Scheme 12).[44] In this method, the in situ Umpolung of amides **26** provides a general platform for their *α*-functionalization with readily available nucleophilic reagents that can be used for the synthesis of *α*-halogenation, *α*-amination, *α*-oxygenation, and *α*-thiolation of amides **27**.



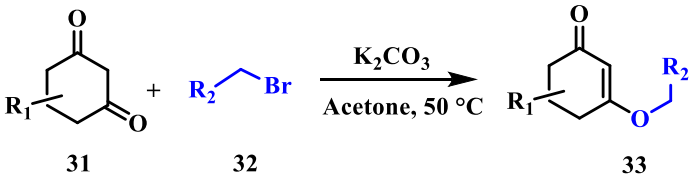
Scheme 12. Maulide's approach for the *α*-functionalization of the carbonyl compounds

In 2016, the selective functionalization of the 1,3-dicarbonyl compound **28** was reported by Cini *et al.* (Scheme `13).[45] In this reaction, the various C-alkylation of 1,3-dicarbonyl derivative **30** was synthesized with primary alcohol **29** in the presence of ruthenium-catalyst.



Scheme 13. Cini's approach for selective alkylation of 1,3-dicarbonyl derivatives

According to McGlacken and co-workers, the selective O-alkylation of 1,3-dicarbonyl derivatives **33** was accomplished, when 1,3-dicarbonyl **31** was treated with alkyl bromide **32** in the presence of K_2CO_3 (Scheme 14). [46]

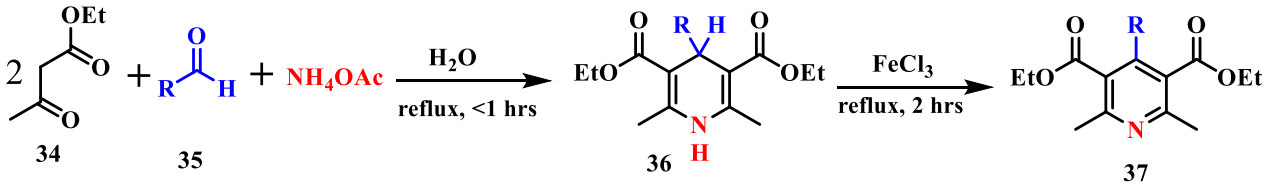


Scheme 14. McGlacken's approach for the selective *O*-alkylation of 1,3-dicarbonyl derivatives

1.4.2. Synthesis of the heterocyclic compound using carbonyl derivative

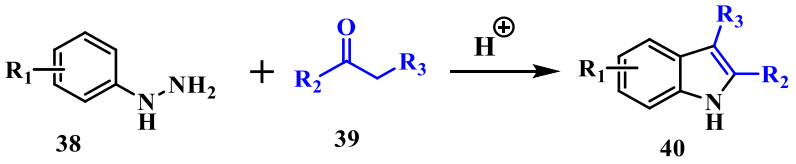
Heterocyclic scaffolds are the most significant class of organic molecules. These compounds contain heteroatoms such as nitrogen, oxygen, and sulfur-containing five/six-membered heterocyclic compounds are frequently found in natural products and are easier to synthesize.[47] The presence of biologically active properties is not the only reason for the use of heterocyclic compounds, they are also utilized to modify the solubility, lipophilicity, polarity, and hydrogen bonding capacity of biologically active agents.[48] This makes heterocyclic compounds a leading factor in enhancing drug properties.

The carbonyl compounds play a key role in the organic reaction as an intermediate to synthesize various heterocyclic derivatives. In this context, the carbonyl group-containing molecules such as amides, ketones, esters, and carboxylic acids are mainly responsible for the synthesis of nitrogen and oxygen containing heterocyclic compounds such as pyridine, pyrrole, benzooxazine, lactam, lactone and furan respectively. The Hantzsch pyridine synthesis, which was developed in 1881, is a pioneering method for synthesizing heterocyclic compounds using carbonyl compounds (Scheme 15).[49] This reaction involves aldehydes **35**, *β*-keto ester **34**, and a nitrogen source such as ammonium acetate to synthesize pyridine **37**.



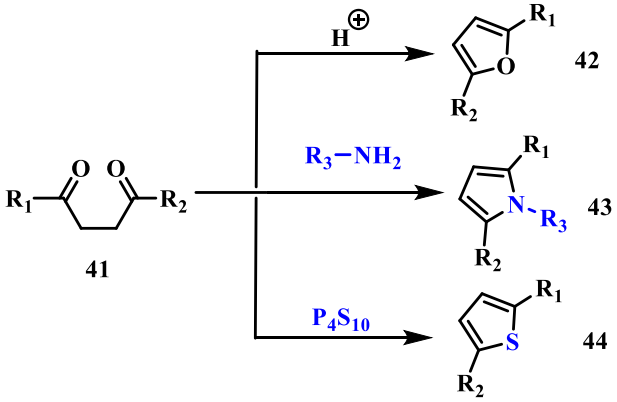
Scheme 15. Hantzsch pyridine synthesis using 1,3-dicarbonyl derivatives

In 1883, Fischer disclosed a method for synthesizing the aromatic heterocycle indoles **40** using aldehyde or ketone derivatives **39** and phenylhydrazine derivatives **38** under acidic conditions (Scheme 16).[50]



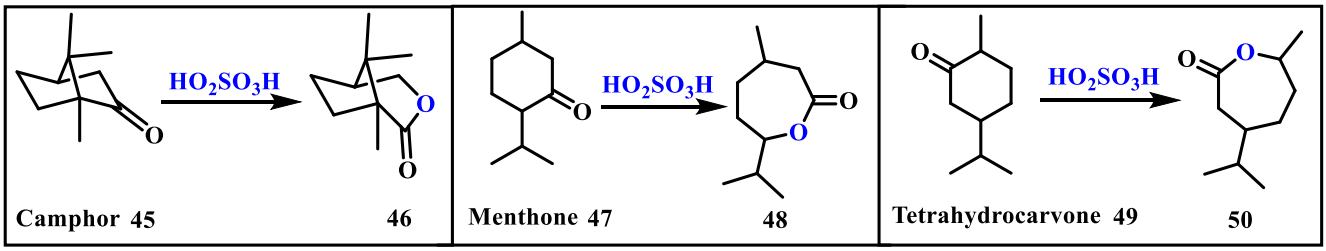
Scheme 16. Fischer indole synthesis using carbonyl compounds

In 1884, Paal and Knorr developed a versatile method for synthesizing heterocyclic compounds such as furans **42**, pyrroles **43**, and thiophenes **44** from 1,4-dicarbonyl derivatives **41** (Scheme 17). [51] This reaction has become widely recognized and utilized in the production of natural products, pharmaceuticals, and materials science due to its ability to generate a diverse array of heterocyclic compounds.



Scheme 17. Paal–Knorr synthesis for heterocyclic compounds using 1,4-dicarbonyl derivatives

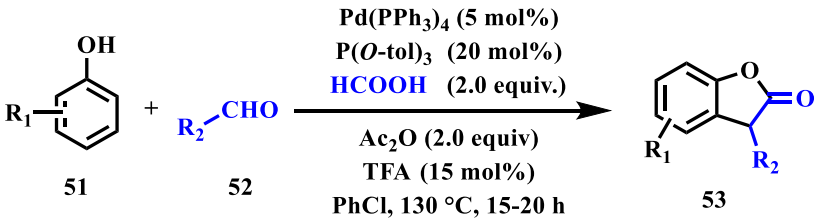
Similarly, In 1899, Baeyer and Villager developed a pioneering method for synthesizing lactones. They successfully utilized peroxymonosulfuric acid to synthesize lactones **46**, **48**, and **50** from camphor **45**, menthone **47**, and tetrahydro carvone **49** respectively (Scheme 18).[52]



Scheme 18. Synthesis of oxygen containing heterocycles using carbonyl derivatives

Recently, Wu and co-workers reported the palladium-catalyzed carbonylative synthesis of benzofuran-2(*3H*)-ones. The variety of benzofuran-2(*3H*)-one derivative **53** was successfully

synthesized from phenols **51** and aldehydes **52**, where formic acid was used as the CO source (Scheme 19).[53]



51 52 53

Scheme 19. Wu's approach for the oxygen-containing heterocycle using carbonyl derivatives

1.5. Aim and objective of thesis work

The functionalization of carbonyl groups has been widely used in the synthesis of various biologically active compounds, natural products, and APIs through the formation of C-C, C-O, and C-N bonds. However, developing sustainable and efficient methods for these transformations is a major challenge in organic chemistry. Heterocyclic compounds are important scaffolds in drug discovery and development, and the carbonyl group is a key intermediate in their synthesis. Despite the importance of substrates like 1,3-dicarbonyl cyclohexane, oxindoles, and coumarin derivatives, the development of sustainable approaches for their functionalization is limited due to the requirement for stoichiometric amounts of bases, expensive catalysts, and high temperatures. Therefore, the objective of this thesis is to develop sustainable methods for the functionalization of carbonyl compounds to achieve biologically active heterocyclic derivatives in modern chemical syntheses.

Objectives of the project:

- **Selective C3-Alkoxylation and C2-Alkylation of 1,3-Dicarbonyl Compounds via Continuous Flow: Applications in the Synthesis of Ondansetron, Phenoprocumon, and Warfarin.**

The objective of this project is to develop a sustainable and scalable method for the selective alkoxylation and alkylation of 1,3-dicarbonyl compounds using alcohol as a reagent and solvent. Traditional methods utilizing strong acids, metal catalysts, and halogenated reagents are not only challenging but also difficult to scale up. Therefore, we aim to establish an environmentally friendly protocol that eliminates the use of strong acids and tedious work-up processes. To achieve this, we will explore the development of metal-free conditions using polymer-based heterogeneous catalysts. Additionally, we envision the selective alkylation of 1,3-dicarbonyl compounds sustainably. To facilitate the scalability of the developed method, we will employ a continuous flow module for rapid

and multigram synthesis. Finally, we aim to integrate this organic transformation in a continuous flow system for the synthesis of commercially available drugs, such as Ondansetron, Phenoprocumon, and Warfarin.

- **Catalytic selective methylalyllation at quaternary carbon-centre using *tert*-butyl acetate**

The synthesis of quaternary carbon centers is a challenging task in organic chemistry, but it is crucial for the development of natural products, drugs, and other value-added products. The synthesis of vinylated/allylated quaternary carbons is a fascinating area of research in modern organic synthesis due to their biological properties and usefulness in the synthesis of natural products. Our objective is to develop a approach to synthesize vinylated/allylated oxindole derivatives, which should overcome the limitations of existing methods, such as the use of expensive pre-functionalized reagents, stoichiometric amounts of the base, and transition metals. Our approach involves the Lewis acid-catalyzed synthesis of selective C3-vinylated/allylated oxindole derivatives using in situ-generated isobutylene from *tert*-butyl acetate. Additionally, this method also provides the quaternary carbon-containing benzooxazine derivatives via the rearrangement of peroxides. Further, we aimed to developed this process using heterogeneous catalysis system to make the method transition metal-free and easier to scale up. Finally, we proposed to integrated this method into continuous flow, allowing for more efficient and sustainable synthesis of these important compounds.

- **$FeCl_2$-Catalyzed rearrangement of aryl peroxyoxindole into 1,3-benzooxazin-4-one**

The quaternary organic peroxide groups can easily undergo organic rearrangement reactions due to the weak strength of O-O bond. Many peroxide rearrangement reactions, including the Baeyer-Villiger, Hock cleavage, and Crigee rearrangement, provide various carbonyl groups containing molecules such as ketones and esters. The heterocyclic compound such as lactone can be synthesized from the rearrangement of peroxide intermediate of carbonyl compounds (ketone derivatives). From the previous report, we hypothesize to synthesize various heterocyclic peroxides and study the rearrangement of C3-peroxides of oxindole derivatives (amide derivatives) for the ring expansion and achieved biological active heterocyclic compound.

- **Annulation of the alkene with *α, β*-unsaturated keto-carboxylic acid towards synthesis of *γ*-lactones**

Lactone derivatives are highly valuable in the field of pharmaceuticals due to their ability to act as biomimetics and active pharmacophores. Numerous synthetic methods have been developed to

synthesize lactones derivatives. Traditionally, lactones are synthesized via intramolecular cyclization of corresponding hydroxy acid/ester derivatives or intermolecular cyclization of an alkene with α-halo esters/acids. Moreover, lactones have been synthesized using metal catalysts, such as nickel or copper, and photocatalysts with the addition of ligands, bases, and additives. Our goal is to develop an easily scalable method for synthesizing lactones using a heterogeneous catalyst. To achieve this, we proposed to develop a method for synthesizing γ-lactone derivatives via annulation of in situ generated isobutylene or commercially available alkene with α, β-unsaturated keto-carboxylic acids using heterogeneous catalysis system. This approach has the potential to be highly valuable in the pharmaceutical industry for the synthesis of a variety of lactone derivatives.

Chapter 2:

Selective C3-Alkoxylation and C2-Alkylation of 1,3-Dicarbonyl Compounds via Continuous Flow: Applications in the Synthesis of Ondansetron, Phenoprocumon, and Warfarin

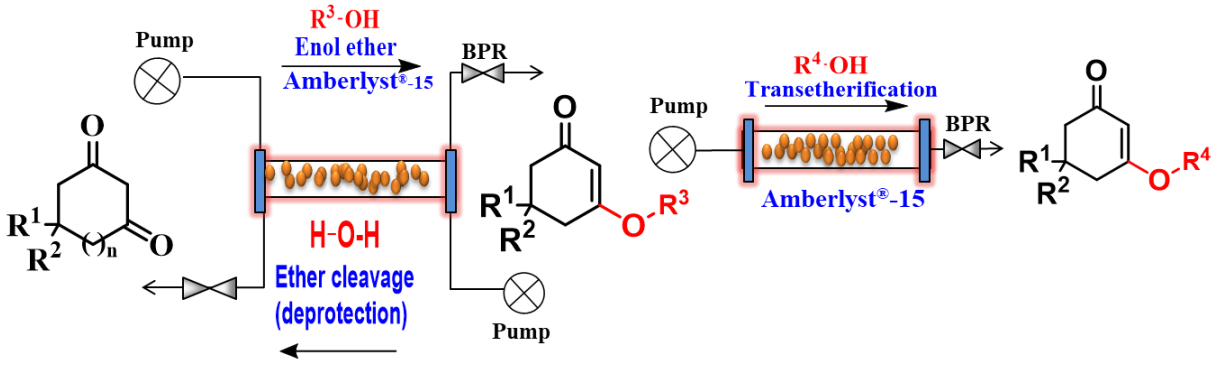
Chapter 2: Section A

C3-Alkoxylation of 1,3-dicarbonyl derivatives and its applications

2A. C3-Alkoxylation of 1,3-dicarbonyl derivatives and its applications

2A.1. Abstract

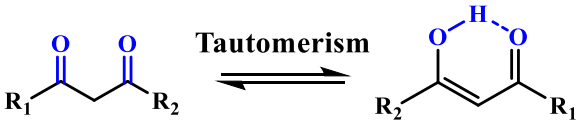
The following section of the chapter delineates an environmentally benign approach for the synthesis of vinylogous ester derivatives of 1,3-diketone under continuous flow using amberlyst®-15 as a heterogeneous catalyst. This methodology is highly efficient for the synthesis of a library of linear alkylated vinylogous esters using various cyclic-1,3-dicarbonyl derivatives and alcohols in excellent yield. Furthermore, the efficiency of the catalyst (amberlyst®-15) was determined by performing the long-time experiment in a continuous-flow up to 40 h provided 8.0 g of the vinylogous ester with TON = 28.6 and TOF = 0.715 h^{-1}. The synthetic application of vinylogous ester such as a continuous flow sequential trans-etherification of vinylogous esters with various alcohols has been achieved in high yield. Reversibly, the deprotection of the alkoxy group or hydrolysis of vinylogous ester into ketone using environmentally benign water as a solvent and amberlyst®-15 as a catalyst under continuous flow was successfully achieved. The integration of eco-friendly heterogeneous catalyst amberlyst®-15 into the continuous flow and the development of a metal-free approach makes the process "sustainable".



2A.2. Introduction

2A.2.1 Reactivity of 1,3-dicarbonyl compounds

The molecules having the carbonyl (C=O) at the 1 and 3 positions are classified as 1,3-dicarbonyl derivatives and are also known as 1,3-dicarbonyl derivatives. In 1976, Drexler and Field reported the existence of keto-enol equilibria of 1,3-dicarbonyls and *β*-keto-esters and this was confirmed by conducting an NMR experiment on the study of solvent and temperature effects on it (Scheme 20).[54]



Scheme 20. Keto-enol form of 1,3-dicarbonyl compounds

The enol form of the 1,3-dicarbonyl compound is more stable as it possesses intramolecular hydrogen bonding.[55] However, the intramolecular hydrogen bonding is stronger in the acyclic 1,3-dicarbonyl compounds than in the cyclic 1,3-dicarbonyl compounds. The 1,3-dicarbonyl possess mainly 3-reactive sites: i) C2-position of 1,3-dicarbonyl group, ii) C3-position of 1,3-dicarbonyl group, iii) Oxygen atom of enol group (See figure 7).

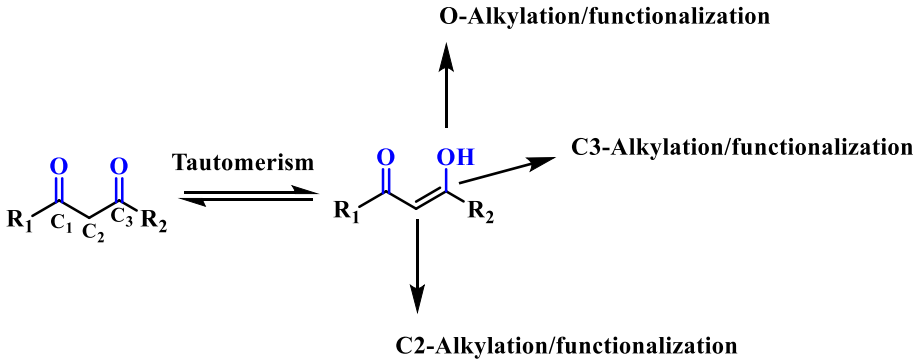


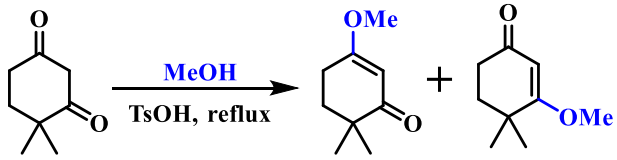
Figure 7. Reactive site of 1,3-dicarbonyl compounds

The C2-position of the 1,3-dicarbonyl compounds easily undergoes alkylation and functionalization as it possesses a highly acidic proton containing carbon. Similarly, the enol oxygen can act as a nucleophile and it is reactive towards the electrophilic center or electron deficiency atom. Moreover, the enol form of the 1,3-dicarbonyl compound resulted in the functionalization of the C3-position via direct substitution of the -OH group. However, it is difficult to functionalize the C3-position of the acyclic 1,3-dicarbonyl group as compared to the C3-position of cyclic1,3-dicarbonyl derivatives,[56] as it possess intramolecular hydrogen bonding. Therefore, the enol form of 1,3-dicarbonyl compounds is more stable. In this context, the selective functionalization of the 1,3-dicarbonyl group is more challenging for the organic chemist. The cyclic1,3-dicarbonyl compounds are not only an indispensable core moiety of natural products and biologically active molecules[57] but C3-functionalization of the cyclic 1,3-dicarbonyl compounds such as C3-alkoxylation, C3-amination are also a key intermediate of organic transformation towards the synthesis of biologically active and organic complex molecules.[58] Furthermore, the C3-alkoxylation of 1,3-dicarbonyl group and C3-amination of 1,3-dicarbonyl called as vinylogous ester and vinylogous amine respectively.

2A.2.2. Literature overview on the synthesis of C3-alkoxy-1,3-dicarbonyl compounds

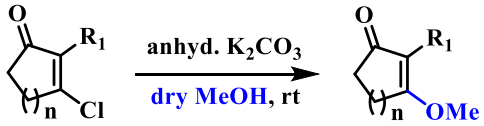
A plethora of methods has been reported for the synthesis of alkoxylation of 1,3-dicarbonyl compounds (vinylogous ester). Traditionally vinylogous esters (*β*-keto-enol ether) have been synthesized by utilizing the 1,3-dicarbonyl and alcohol/alkyl halides.[59] A few selected methods for the synthesis of vinylogous esters have been described in this section.

In 1993, Zimmerman and co-workers reported the synthesis of the vinylogous ester by utilizing 4,4-dimethylcyclohexane-1,3-dione and MeOH in presence of TsOH.[60] This reported method described only one derivative (Scheme 21).



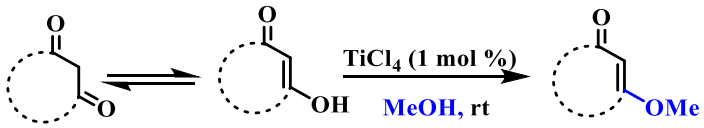
Scheme 21. Zimmerman's approach for C3-methoxy-cyclo-1,3-hexadione

Subsequently, after a year Modro and co-workers developed the base-mediated synthesis of *β*- keto-enol ether utilizing 3-chloro-cycloalkenones and methanol (Scheme 22).[61]



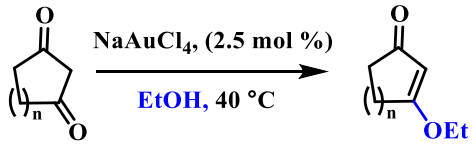
Scheme 22. Modro's approach for C3-alkoxylation of 1,3-diones

Porta and co-workers reported the $TiCl_4$-catalyzed synthesis of vinylogous esters using MeOH. In this report, various cyclic 1,3-diketones has been studied.[62] However, this developed method uses only methanol as an alcohol derivative (Scheme 23).



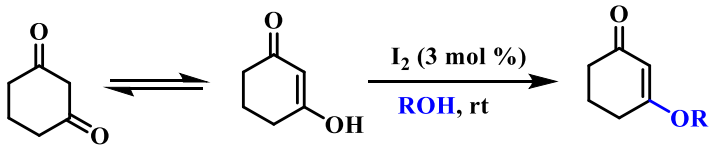
Scheme 23. Porta's approach for C3-alkoxylation of cyclic-1,3-diones

In 2001, Marinelli and co-workers reported the Au-catalyzed functionalization of cyclic-1,3-diketone.[63] In this report the vinylogous ester was synthesized by using EtOH as the source of the ethoxy group. The developed report is not only limited to ethoxy functionalized derivative, it also provides the C3-amine, sulphur, and phosphorus derivatives (Scheme 24).



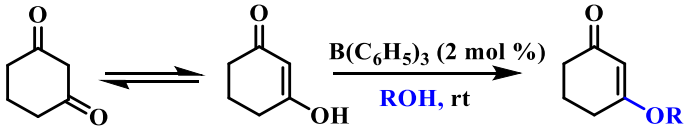
Scheme 24. Marinelli's approach for C3-alkoxylation of 1,3-diones

Interestingly, Zubaidha and co-workers reported the synthesis of a vinyl ester using iodine as the catalyst.[64] Using this method various derivatives of vinylogous ester have been successfully synthesized by varying alcohol in the reaction (Scheme 25).



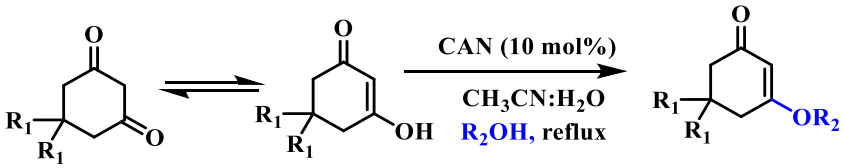
Scheme 25. Zubaidha's approach for C3-alkoxylation of cyclic-1,3-diones

Similarly, after a subsequent year, Chandrasekhar and co-workers reported the $B(C_6F_5)_3$-catalyzed synthesis of *β*- keto-enol ethers from 1,3-dicarbonyls (Scheme 26**)**.[65]



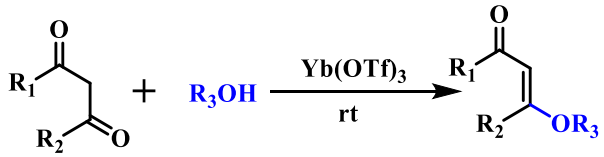
Scheme 26. Chandrasekhar's approach for C3-alkoxylation of cyclic-1,3-diones

In 2006, Roy and co-workers reported the C3-alkoxy functionalization of 1,3-dicarbonyls using ceric ammonium nitrate as the catalyst. Here, the reaction requires a high temperature to achieve the C3-alkoxy derivatives of cyclic cyclic-1,3-diones (Scheme 27**)**. [66]



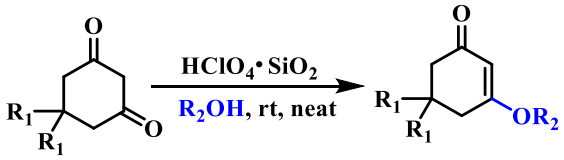
Scheme 27. Roy's approach for C3-alkoxylation of cyclic-1,3-diones

In the same year, a similar report was disclosed by Curini and co-workers for the synthesis of *β*-keto enol ethers using ytterbium triflate as a catalyst (Scheme 28**)**. [67]



Scheme 28. Curini's approach for C3-alkoxylation of 1,3-diones

In 2007, Das and co-workers reported a heterogeneous silica-supported acid catalyzed ($HClO_4 \cdot SiO_2$) mediated synthesis *β*-keto enol ethers utilizing 1,3-dicarbonyl derivative (Scheme 29**)**.[68]



Scheme 29. Das's approach for C3-alkoxylation of cyclic-1,3-diones

2A.3. Objectives of the work

Vinylogous esters are extensively used as intermediate in several organic transformations due to their ability to undergo functional group interconversion (FGI). In particular, they have been employed as synthons of various natural products and biologically active molecules (Figure 8).[69] These molecules can be achieved by converting vinylogous esters into another functional group via C-C bond formation, ene reaction, cycloaddition, oxidation, etc.

As shown in figure 8, the biologically active molecules such as heterumadiennone **54** and puupehedione **55** (both possess anti-tumor, anti-tuberculosis, and anti-cancer properties), DAz-2 **56** (used for in vivo labeling), (-)-xylogranatopyridine B **57** (having phosphatase-inhibitory activity), (+)-elatol **58** (having anti-bacterial activity, anti-fungal activity) and model substrate for azadirachtin **59** (having antifeedant activity growth inhibitory properties against insects) can be synthesized by using vinylogous esters as a promising precursor. All the described biologically active molecules can be achieved after 2-21 steps from the vinylogous ester, which indicate the development of a sustainable approach for the synthesis of vinylogous esters. Moreover, the developed method should be easy to scale up.

Numerous synthetic methods are available for the synthesis of vinylogous esters. However, the traditional approach was efficient for the synthesis of vinylogous esters but it contains some limitations such as the use of the stoichiometric amount of strong acid, metal catalyst, the longer time, and higher temperature. Moreover, during the synthesis of vinylogous ester, H_2O is one of the by-products. The production of water in the reaction medium drives the reaction in a backward direction via the hydrolysis process. Therefore, the continuous removal of water is required to achieve a better yield of

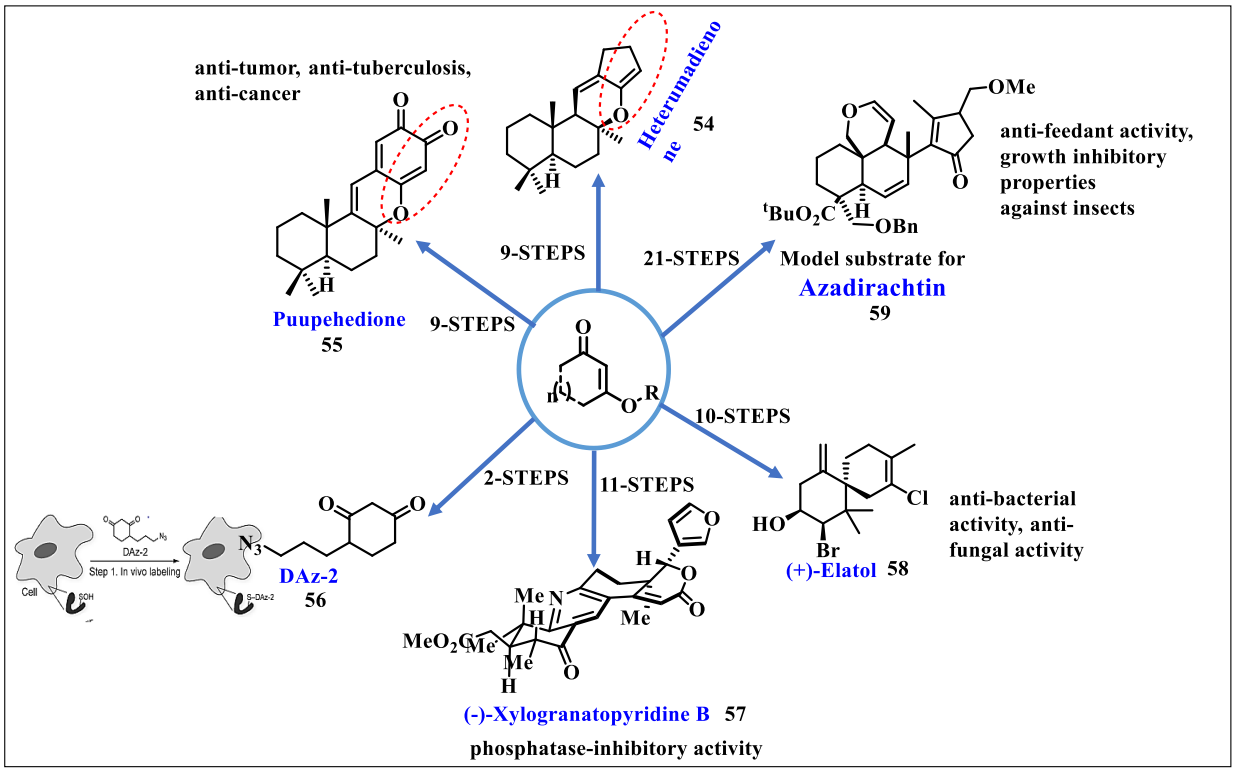


Figure 8. Vinylogous esters for the synthesis of bioactive natural products/drugs

the desired product. Further, this reversible nature of the vinylogous ester provides a direct impact on the yield of the product and difficulties for the gram scale synthesis under batch conditions.

By considering the above challenges/limitations, there is a demand to develop a sustainable approach for the synthesis of vinylogous ester, which is easy to perform, scale up the reaction, maintains the milder reaction conditions to avoid the tedious workup as well as the use of expensive metal catalyst, and eliminate the use of hazardous acids. Therefore, to utilize sustainable techniques, including heterogeneous catalysis and flow chemistry to achieve organic transformation in an environmentally benign manner has been planned. Further, the use an environmentally benign catalyst such as a polystyrene polymer-supported catalyst for the synthesis of vinylogous ester in a sustainable manner has been proposed.

2A.4. Results and discussion

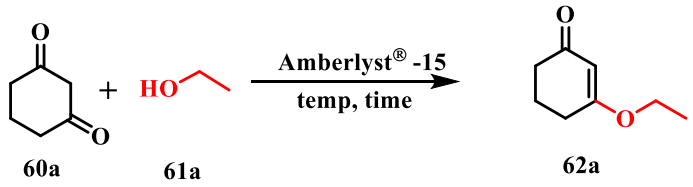
To overcome the mentioned drawbacks, the reactive vinylogous ester synthesis under continuous flow in a shorter duration has been developed, which can shift the equilibrium into vinylogous ester and restrict the reversible nature of vinylogous ester. In an extension was to develop a sustainable and efficient process for vinylogous esters synthesis, the integration of heterogeneous catalysis with continuous flow is the superior choice due to greater selectivity, increased safety, improved yield, and easy to scale up the developed reaction. Herein, the environmentally benign amberlyst®-15 catalyzed the synthesis of vinylogous esters using alcohols and cyclic-1,3-dicarbonyl compounds was

reported. In an extension of this work, transetherification, and their reverse reaction in continuous flow using simple and ample precursors such as alcohols, and water was developed.

2A.4.1. Optimization studies under batch: Alcohol as a solvent and reagent

The investigation was initiated by choosing 1,3-cyclohexanedione (**60a**) and ethanol (**61a**) as a model substrate. Initially, the control experiments was performed, in the absence of any acidic source at room temperature and 80 °C (Table 1, entries 1 and 2), resulting in no product formation. Next, the addition of 25 mg of amberlyst®-15 in 0.5 mmol ketone and 2 mL ethanol at room temperature afforded **62a** in 72% isolated yield (Table 1, entry 3). Moreover, an increase in yield of **62a** was observed while increasing the catalyst loading up to 50 mg. Increasing the temperature of the reaction up to 60 °C resulted in a higher yield (82%) of product **62a** (Table 1, entries 4 and 5). Besides, a slight improvement in yield (88%) was observed, when the reaction mixture was heated at 80 °C (Table 1, entry 6).

Table 1. Optimization of reaction conditions for C3-alkoxylation of cyclic 1,3-dicarbonyl compound



60a 61a 62a

entry	catalyst in (mg)	temp (°C)	Time (h)	yield (%)
1	-	rt	5	no reaction
2	-	80	5	no reaction
3	25	rt	5	72
4	50	rt	5	76
5	50	60	5	82
6	50	80	5	88

Reaction condition: 1,3-cyclohexanedione (**60a**, 0.5 mmol), amberlyst® -15, and ethanol (**61a**, 2 mL) were stirred at the specified temperature.

2A.4.2. Optimization studies under continuous flow

To make the designed strategy successful, the aim was to conduct the reaction using a continuous flow setup. The continuous flow shown in figure 9 is the vapourtec R-series model. It consists of:

i) **Input Tank**: The solvent and reagents are kept to flow into the system.

ii) **Pump**: Pump is responsible for moving the solvent mixture from the input tank to the to the reactor.

iii) **Reactor**: The reactor is a compartment and the reaction occurs in the reactor.

iv) **Back pressure regulator (BPR)**: The purpose of the back pressure regulator is to control the flow rate of the reactants into the reactor and to maintain a constant pressure in the reactor.

Experiment set up for the synthesis of vinylogous ester:

step 1: 0.1M solution of 1,3-cyclohexadione was made in a 30 mL vial and reagent tube was deep into the vial.

Step 2: The 6.6 x 150 mm Omnifit® bed reactor was packed with amberlyst®-15 and kept in the reactor chamber as shown in figure 9.

Step 3: The reagent vial and reactor were connected through a pump.

After the completaion of all the above mention 3-step, the instrument was turn on and performed the reaction in the continuous flow instrument (Figure-9).

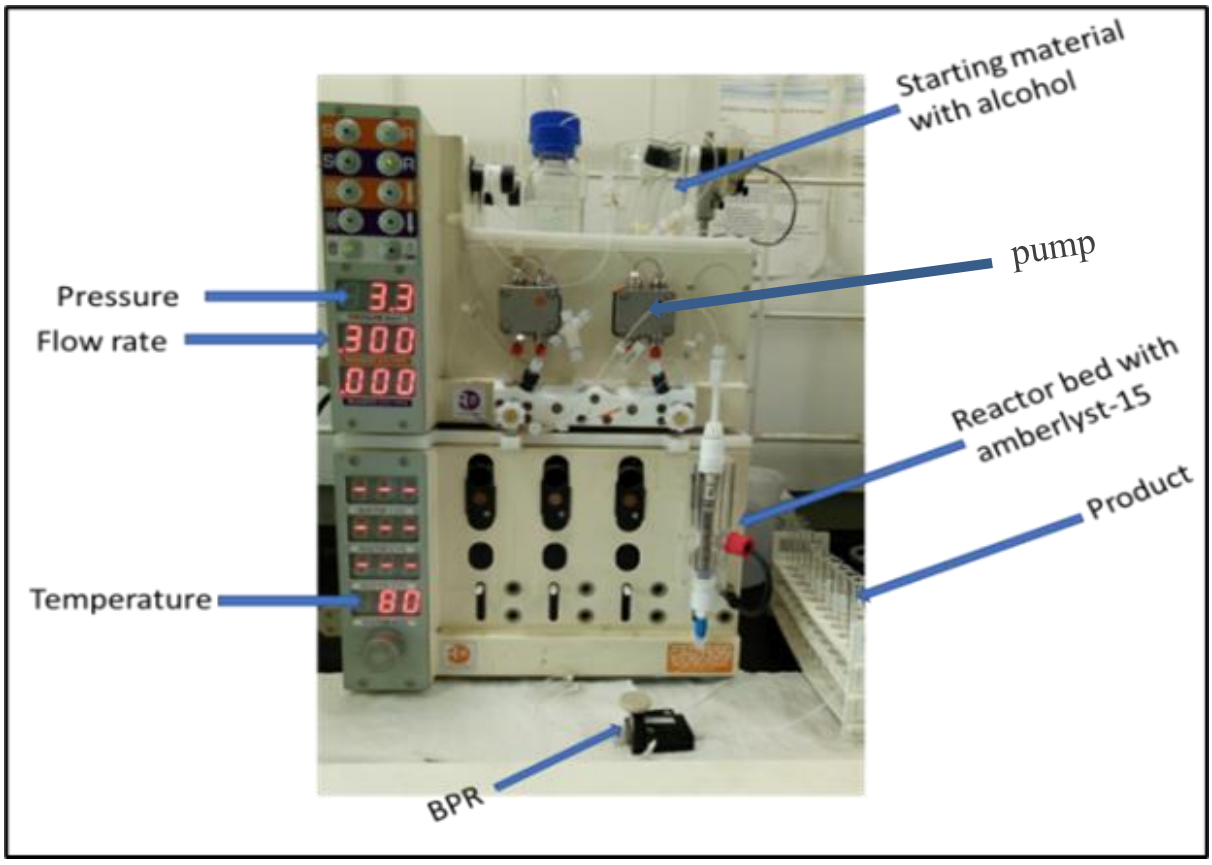
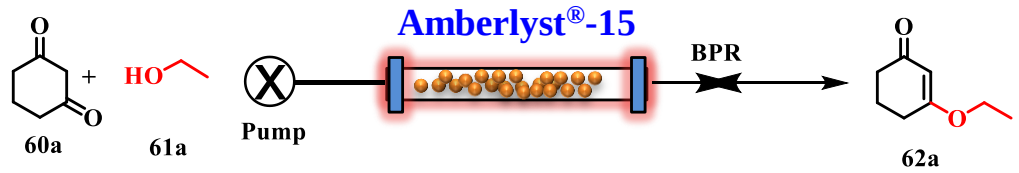


Figure 9. Setup of the continuous flow reactor

Knowing various parts of continuous flow setup and with the result of batch optimization, the initial reaction mixture was pumped through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of amberlyst® -15, 4 cm bed height). Initially, optimization was performed at room temperature for the 1st and 2nd runs with 0.3 mL flow rate and 0.2 M concentration of 1,3-cyclohexadione **60a** in ethanol

61a, which provided 48% and 93% isolated yield of the product **62a** (Table 2, entries 1 and 2). Further, the various experiments were carried out by varying temperatures, flow rates, and concentrations. The results are summarized in Table 2 (entries 3-9). For instance, 0.1 M solution of **60a** in ethanol at 0.3 mL flow rate at 60 °C afforded 95% of product **62a** (Table 2, entry 3). The decrease in yield was observed when the concentration increased to 0.2 M at 80 °C and 100 °C (Table 2, entries 4 and 5). After several experiments, the reaction with 0.3 mL flow rate and 0.1 M solution at 80 °C proved to be the best optimized condition to afford **62a** (99%) in 4.6 minutes of residence time (t_R) (Table 1, entry 9).

Table 2. Optimization of reaction conditions in continuous-flow[a]

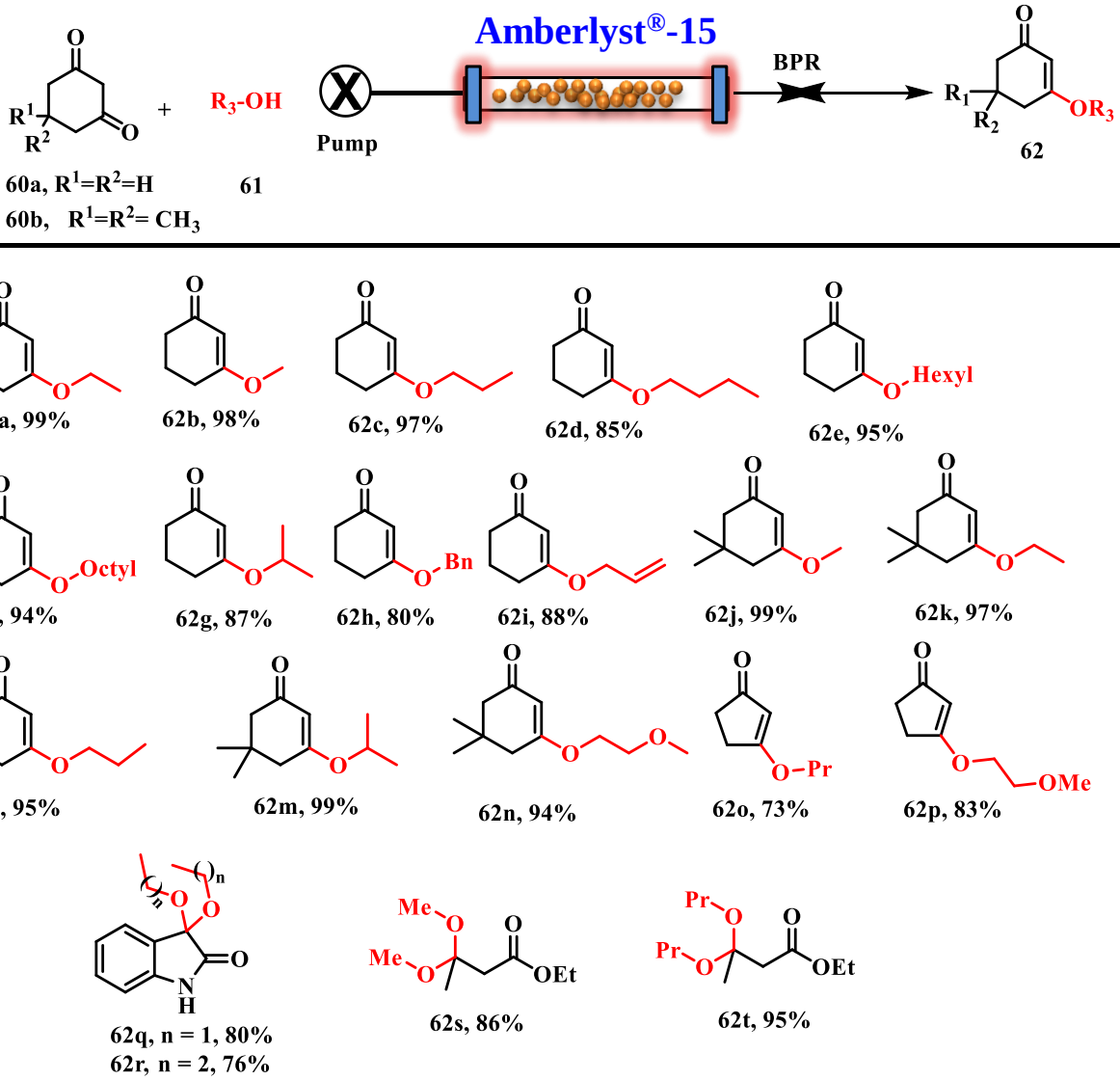


entry	flow rate (in mL/min)	temp (°C)	substrate concentration (M)	t_R (min)/number of runs	yield (%)
1	0.3	rt	0.2 M	4.6/1	48
2	0.3	rt	0.2 M	9.2/2	93
3	0.3	60	0.1 M	4.6/1	95
4	0.3	80	0.2 M	4.6/1	73
5	0.3	100	0.2 M	4.6/1	86
6	0.2	80	0.2 M	6.8/1	93
7	0.2	100	0.2 M	6.8/1	88
8	0.3	80	0.15 M	4.6/1	83
9	0.3	80	0.1 M	4.6/1	99
10	0.5	80	0.1 M	2.7/1	78
11[b]	0.3	80	0.1 M	4.6/1	72

[a]**Reaction condition:** 0.1 molar solution of **60a** in ethanol **61a** was prepared and flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of amberlyst® -15, 4 cm bed height) (Vapourtec R-series) at a specified temperature, [b]Reaction carried out using Amberlite-120. The mentioned yields are isolated yields. Residence time (t_R) = Total volume of the reactor/Total flow rate of reagent coming to the reactor.

2A.4.3. Substrate scope for the C3-alkoxylation of 1,3-dicarbonyl

Having established optimal conditions, the scope and generality of the reaction towards the various alcohols using different 1,3-dicarbonyl derivatives was investigated. The reaction of cyclohexane-1,3-dione **60a** with linear alcohols such as ethanol **61a**, methanol **61b**, propanol **61c**, butanol **61d**, hexanol **61e**, and octanol **61f** afforded an excellent yield of the corresponding desired products **62b-62f** (Scheme 30). Subsequently, the diketone subjected with an optimal set of conditions with a secondary alcohol such as *iso*-propyl alcohol **61g**, afforded **62g** in very good yield (Scheme 30). Pleasingly, the synthesis of C3-alkoxyl -1,3-dicarbonyl derivatives using the developed method is not



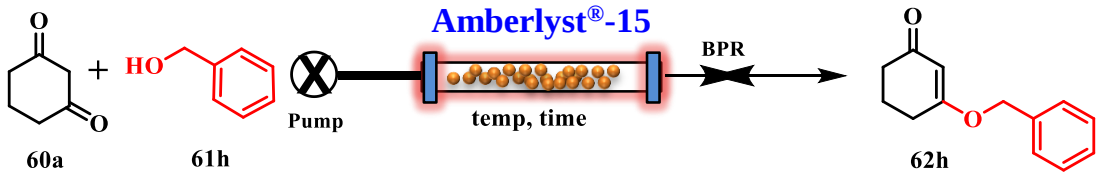
Reaction condition: 0.1 M solution of 1,3-diketone **60** in alcohol **61** were prepared and 0.3 mL/min was flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of amberlyst®-15, 4 cm bed height, residence time t_R = 4.6 min) (Vapourtec R-series) at 80 °C.

Scheme 30. Substrate scope for C3-alkoxylation of 1,3-dicarbonyl using alcohol

only applicable for aliphatic alcohols, the reaction of benzyl alcohol **61h** and allyl alcohol **61i** with cyclohexane-1,3-dione provided **62h** and **62i** in very good yield. Moreover, the scope of the reaction was extended with various 1,3-dione derivatives. The vinylogous ester derivatives of 5,5-dimethylcyclohexa-1,3-dione **60b** and cyclopenta-1,3-dione **60c** such as **62j-62p** have been synthesized smoothly under this reaction using linear or branched alcohols in excellent yield. Moreover, 3,3-diethoxyoxyindolin-2-one derivatives **62q** and **62r** were successfully synthesized from the reaction of isatin **60d** with ethanol **61a**. Further, the acyclic 1,3-dicarbonyl compound **60e** with methanol **61b** and propanol **61c** under similar reaction conditions provided respective ketals **62s** and **62t** in 86% and 95% yield.

In organic transformation, the alcohol considered as green solvent for the reaction.[70] It is very difficult to use all the alcohol as solvent due to the expensive, viscosity nature and excess use of functionalized alcohol undergoes self-coupling. Considering the above challenges, the reaction was reoptimized using a stoichiometric amount of alcohol in the reaction. In the initial investigation, **60a** and **61h** were considered model substrates.

Table 3. Optimization of reaction conditions in continuous flow

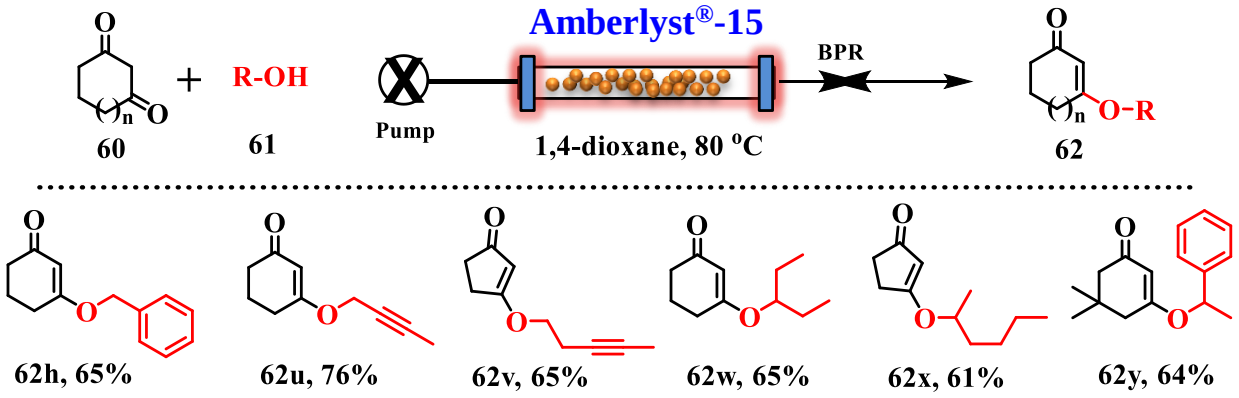


entry	conc. of 1,3-cyclohexadione	conc. of benzyl alcohol	solvent	flow rate (mL/min)	time	yield (%)
Batch conditions (conc. in mmol) [a]						
1	0.5	0.5	1,4-dioxane	-	1.5 h	80
2	0.5	0.5	Toluene	-	1.5 h	90
3	0.5	0.5	THF	-	1.5 h	75
Flow conditions (benzyl alcohol conc in molar)[b]						
4	1 mmol	0.1 M	1,4-dioxane	0.3	4.6 min	trace
5	1 mmol	0.3 M	1,4-dioxane	0.3	4.6 min	50
6	1 mmol	0.5 M	1,4-dioxane	0.3	4.6 min	65

Reaction conditions: 0.5 mmol of **60a** + 0.5 mmol of benzyl alcohol **61h** and 2 mL solvent + amberlyst®-15 (50 mg) were heated at 80 °C in a resealable tube for 2 h. [b]Mentioned concentrations of **60a** in benzyl alcohol were flown through the Omnifit® packed bed reactor (628 mg of amberlyst®-15, 4 cm bed height, for residence time t_R, see table) (Vapourtec R-series) in 80 °C.

with solvent 1,4-dioxane and afforded 80% of the product **62h** under batch conditions (Table 3, entry 1). The 90% and 75 % of the product **62h** were obtained with the use of solvents such as toluene and THF respectively (Table 3, entries 2 and 3). With this optimization, the reaction was transfer to continuous flow. In the batch condition, among all the solvents, toluene was the best medium for the reaction. To perform the reaction under continuous flow, the reagents should be soluble in the solvent. As 1,3-cyclohexadione is not soluble in the toluene, 1,4-dioxane was chosen as the solvent for the reaction. Initially, **60a** was dissolved with 0.1 M of benzyl alcohol with the 1,4-dioxane and afforded a trace amount of product **62h** in 4.6 min (Table 3, entry 4). The increase in the yield was observed by increasing the concentration of benzyl alcohol up to 0.3 M and 0.5 M, providing 50% and 65% of the desired product (Table 3, entries 5 and 6).

After having the optimization condition in hand, the scope of the reaction using alcohol as a solvent was explored (Scheme 31). Under the optimized reaction conditions, alcohol bearing functional group such as alkyne proceeded efficiently and afforded respective vinylogous ester product **62u** in 76% yield. Similarly, when alkyne functionalized alcohol treated with 1,3-cyclopentadione afforded the 3-(pent-3-yn-1-yloxy)cyclopent-2-en-1-one **62v** in 65 % of the yield. Furthermore, the secondary alcohols such as 3-pentanol, 2-hexanol, and 1-phenyl ethanol were also successfully reacted with 1,3-dione derivatives well to afford respective *β*-vinylogous esters **62w-62y** in moderate yield.



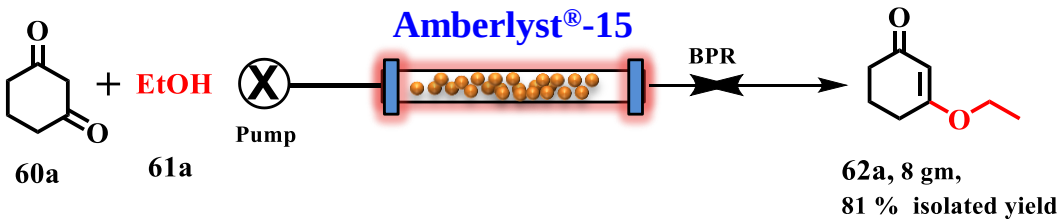
Reaction condition: 1 mmol of **60a** was dissolved in 0.5 M solution of alcohol in 1,4-dioxane (10 mL) and was flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of amberlyst®-15, 4 cm bed height, residence time t_R = 4.6 min) at 80 ˚C.

Scheme 31. Substrate scope for C3-alkoxylation of 1,3-dicarbonyl using alcohol as a reagent in continuous flow

2A.4.4. Gram scale synthesis in a continuous flow

To scale up the reaction and to show the stability of the catalyst amberlyst®-15, **60a** and ethanol (**61a**) was chosen for the long-time experiment (Scheme 32**)**. For instance, 0.1M solution of **60a**

(8 g, 72.12 mmol) in ethanol was continuously pumped into the reactor for 40 h having a flow rate of 0.3 mL/min and afforded 57.22 mmol of **62a** with TON (turnover number)= moles of product/moles of catalyst = 28.61 and TOF (turnover frequency) =TON/time = 0.715 h^{-1}. The formation of product **60a** was periodically monitored by using ^{1}H-NMR (Figure 10). The result of the ^{1}H-NMR indicated that overall >94% of **62a** was produced over 20 h of the continuous flow synthesis. After 20 h of the reaction, a slightly decreasing in the product formation **62a** up to 90% was observed and it remain constant up to 40 h of the reaction (Figure 11). However, after 40 h, the reaction was stopped, but the catalyst was still active to afford 90% of the product, which



Scheme 32. Gram-scale synthesis in a continuous flow

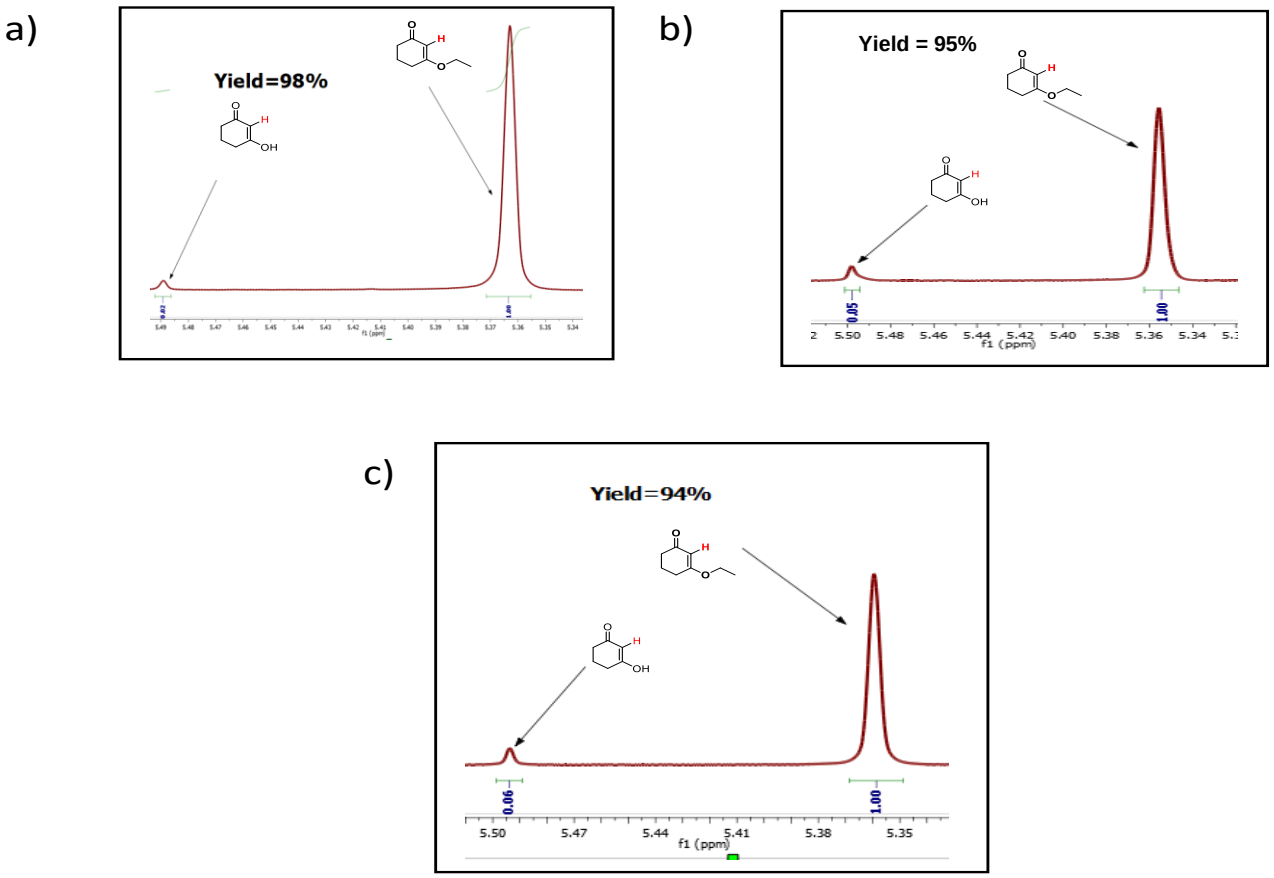


Figure 10. ^{1}H-NMR monitoring of the reaction in long-run experiments; a) after 2 h, b) after 10h, c) after 20 h.

confirmed that the efficiency of the activity of amberlyst®-15 was high for the synthesis of a vinylogous ester using the developed protocol. The loss of activity of amberlyst®-15 for the different organic transformations is known, but very minimal loss of the activity of the catalyst was observed after 20 h of the reaction.

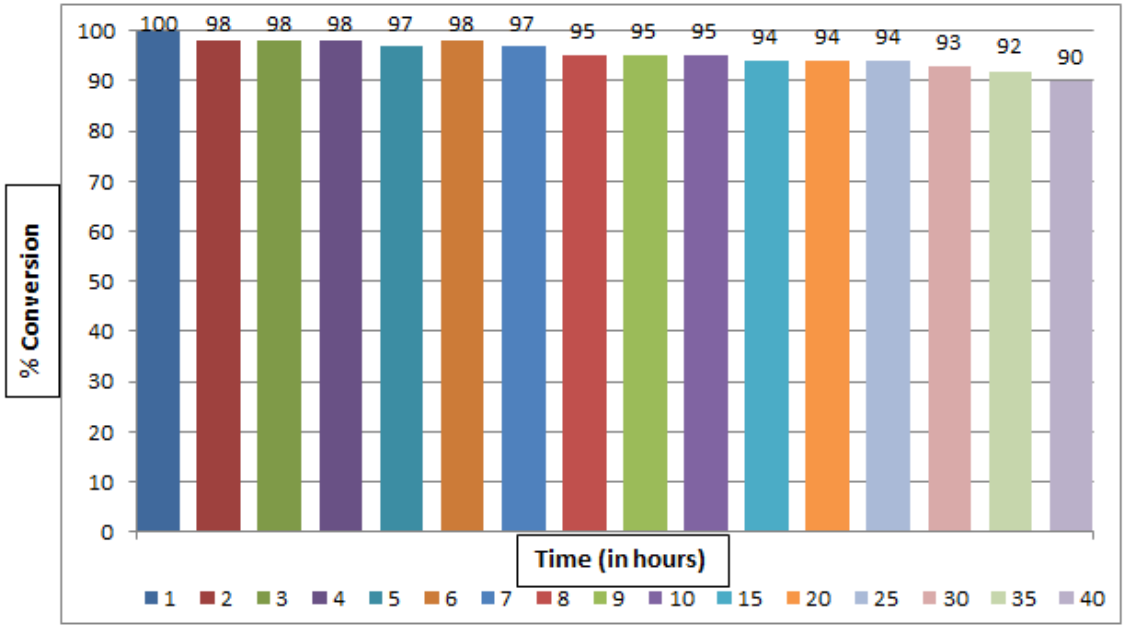
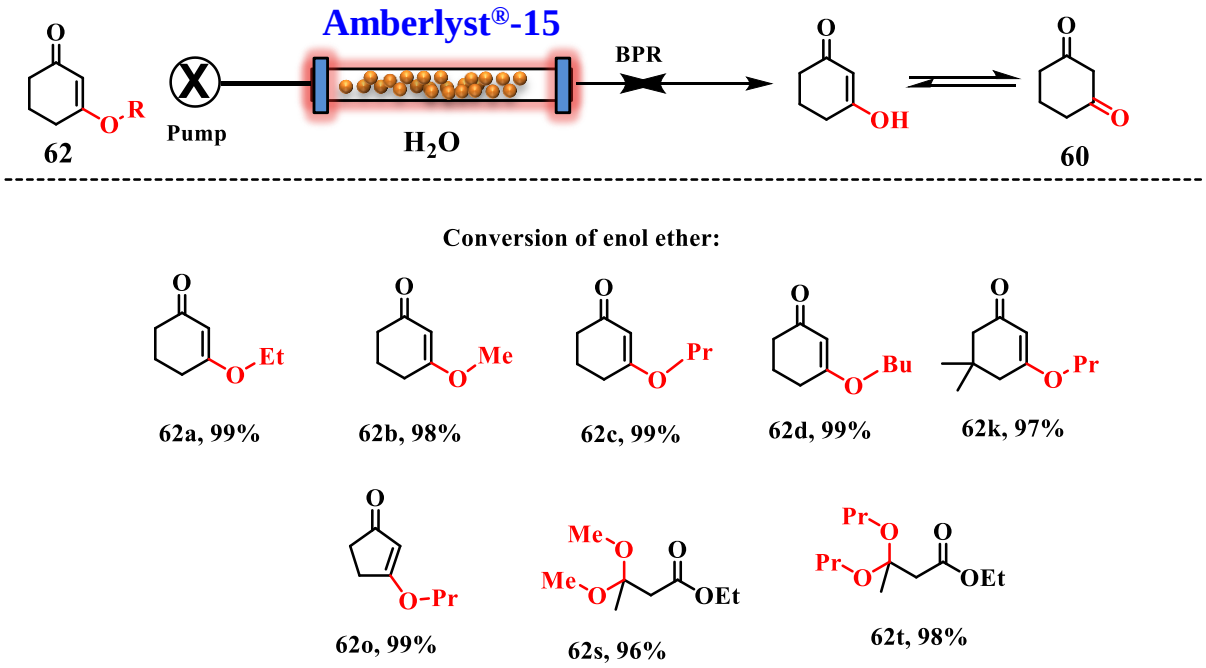


Figure 11. A long-time experiment for the formation of **62a** over 40 h

2A.4.5. Deprotection of alkoxy group from the *β*-vinylogous esters

Deprotection is an important transformation in organic synthesis to achieve the complex organic molecules, biologically active compounds, and natural products. In this aspect, the reversible transformation of vinylogous ester or deprotection of alkoxy group from vinylogous ester using water as reagent and solvent is one of the attractive goals in sustainable chemistry. Hence, the objective was to accomplish the reversible transformation, the selective and milder hydrolysis of a vinylogous ester using environmentally benign amberlyst®-15 as a catalyst under a continuous flow approach. To achieve the best optimization reaction condition for the deprotection of the alkoxy group, a set of reactions was performed. Thus, the investigation began with a control experiment, vinylogous ester **62a** was allowed for the hydrolysis in the presence of water, providing 10% of the deprotected product **60a** after 4 h under the batch condition without a catalyst. Upon addition of a stoichiometric amount of the amberlyst®-15, the complete hydrolysis of the **62a** into **60a** was observed in 3 h. Next, the highly water-soluble vinylogous esters such as **62a** and **62b** were flown (0.1 M, 0.1 mL/min, t_R = 13.6 min) into the Omnifit column reactor prepacked with the amberlyst®-15, results in >98% conversion to 1,3-cyclohexadiones. However,

the C3-alkoxy compounds of 1,3-cyclicdiones **62c**, **62d**, **62k,** and **62o** were not soluble in water. As the vinylogous esters are insoluble in water, these compounds was dissolved in a 1:1 mixture of water and ACN and flown into the reactor affording the lower conversion (48-52%) of the diketone under continuous flow. Interestingly, water suspension of these compounds was flown into the omnifit column reactor prepacked with the amberlyst®-15 by the help of syringe pump, which led rapid hydrolysis to afford the1,3-diketone in >95% yield. Similarly, ketal derivatives **62s** and **62t** were also flown into the column reactor for the deprotection of the alkoxy group and afforded respective diones in >98% yield (Scheme 33).



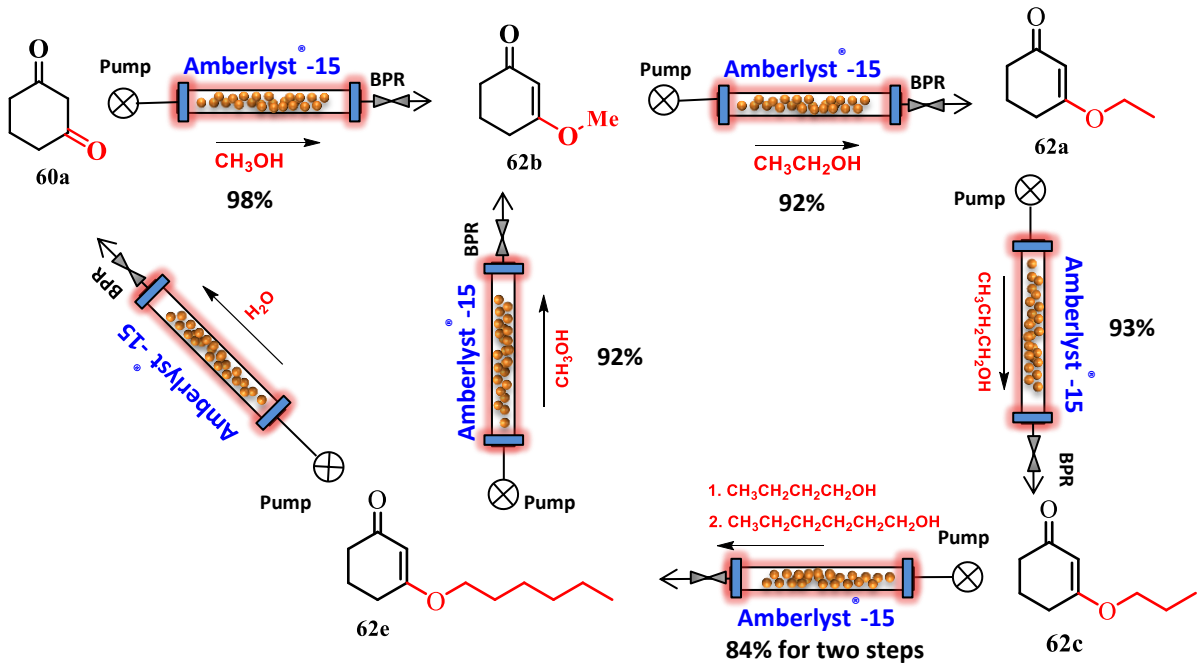
Reaction condition: 0.1 M solution of **62** in water and ACN (1:1) mixture, was flown (0.1 mL/min) through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of amberlyst®-15, 4 cm bed height) at room temperature (Residence time t_R = 13.6 min).

Scheme 33. Continuous flow hydrolysis of a vinylogous ester using water and amberlyst®-15

2A.4.6. Transetherification of vinylogous ester

Transetherification is a key organic transformation in the synthetic community due to its reactivity and easy accessibility. Developing a sustainable approach for transetherification is an important aspect of a chemical process. Therefore, transetherification of vinylogous ester under continuous flow mode was investigated. For this study, vinylogous ester **62b** was chosen as a model substrate and a set of conditions was attempted. The optimized condition for the transetherification was established by flowing 0.3 mL/min of the flow rate of the 0.1 M solution of vinylogous ester in ethanol to the Omnifit column reactor prepacked with the amberlyst® -15 and heated at 80 °C to afford the

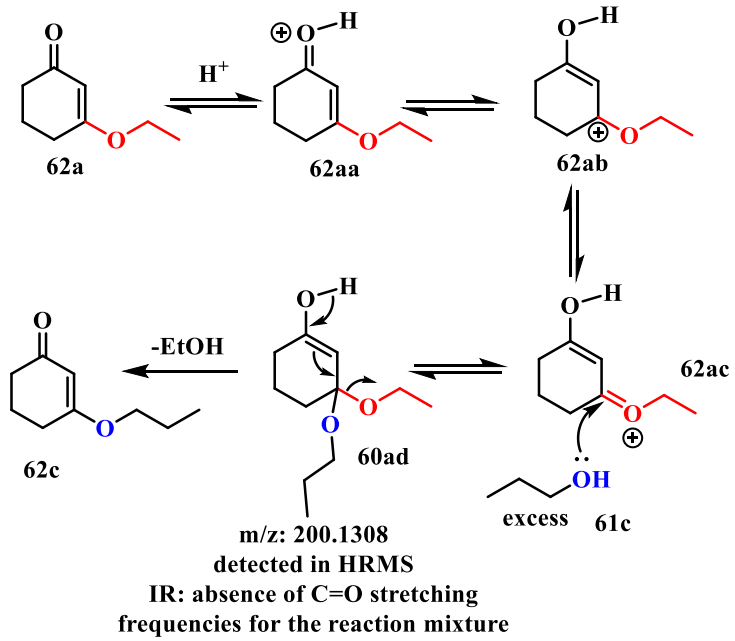
vinylogous ester **62a** in 92% yield (Scheme 34). Under similar experimental conditions and flow rate, vinylogous ester **62b** was transetherified using propanol solvent to give the vinylogous ester **62c** in 93% yield (Scheme 34). Similarly, continuous transetherification was carried to the vinylogous ester **62e** in 84% yield (for two consecutive transetherification steps) in continuous flow mode. Finally, the hexyl group was exchanged with the methyl via transetherification of vinylogous ester **62e** in methanol under a continuous flow process to afford the corresponding vinylogous ester **62b** in 92% yield (Scheme 34). Furthermore, this transetherification of vinylogous ester was performed in grams under continuous flow.



Scheme 34. Transetherification of vinylogous esters using alcohols under continuous flow

2A.4.7. Mechanism for the transetherification

The mechanism of the amberlyst®-15 mediated transetherification of the vinylogous ester is proposed in Scheme 35. Initially protonation of the C=O of the cyclic vinylogous ester **62a** to give the intermediate **62aa**. The absence of the C=O (figure 12 (i)) functional group of the reaction mixture in the IR spectra indicates the formation of the intermediate **62aa** (Figure 12(ii)). The intermediate **62aa** is resonance stabilized to generate the intermediates **62ab** and **62ac**. Further, the oxonium intermediate **62ac** is attacked by the alcohol to afford the ketal intermediate **62ad**. The HRMS spectra of the amberlyst®-15 mediated reaction of **62a** and *n*-propanol show a peak at *m/z* 200.1308 confirming the formation of the intermediate **62ad** (Figure 12(iii)). Finally, the keto-enol tautomerism assisted in the elimination of ethanol from the intermediate **62ad** to form the transetherified product **62c**.



Scheme 35. A plausible mechanism for the transetherification of a vinylogous ester using alcohol

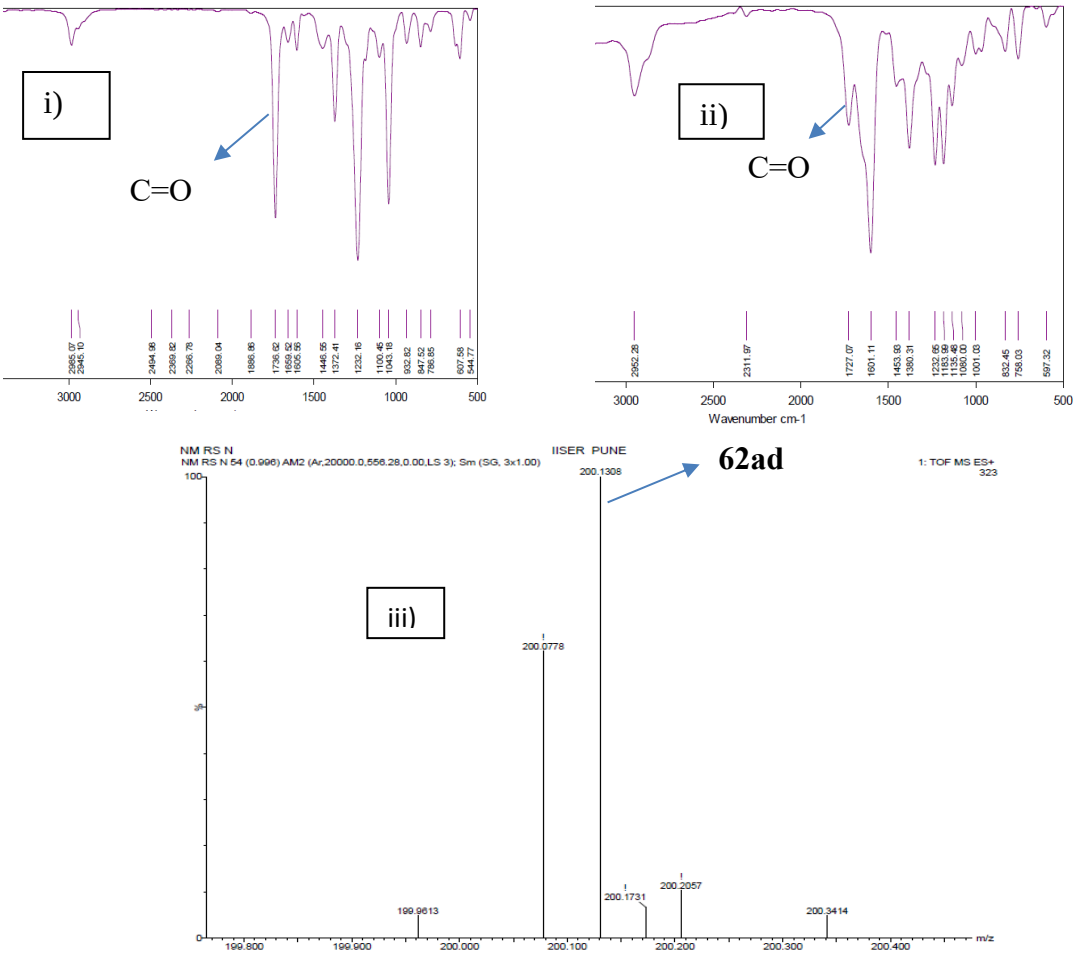


Figure 12. Experiments for the mechanism; i) IR spectra of **62a**; ii) IR spectra of transetherification reaction mixture; iii) HRMS spectra of the reaction mixture.

2A.5. Conclusion

In conclusion, an environmentally benign approach for the synthesis of vinylogous ester from commercially available 1,3-diketone using amberlyst®-15 under continuous flow mode was developed. This process has been generalized with a variety of vinylogous esters tethered by aliphatic, alkene, alkyne, and aromatic substituents with rapid access (t_R = 4.6 min) in excellent yield with high selectivity. The long-time studies in a continuous-flow up to 40 h revealed the efficiency of the amberlyst®-15 catalyst with TON= 28.6 and TOF= 0.715 h^{-1}, which generated 8g of vinylogous ester in 40 h continuous synthesis. This methodology was also extended for continuous transetherification of vinylogous ester to another vinylogous ester in higher yield under continuous flow mode. Interestingly, the possible reverse reaction of vinylogous esters to ketones (hydrolysis of vinylogous ester) was achieved effectively under a continuous flow process. The mechanism for the transetherification was also proposed with experimental evidence.

2A.6. Experimental section and characterization data

2A.6.1. General information and data collection

All the chemicals were purchased from Sigma Aldrich and SD Fine Chemicals and used without further modification. All solvents were purchased from Rankem and Finar Chemicals. Deuterated solvents were used as received. Column chromatographic separations performed over 100-200 Silica-gel. Visualization was accomplished with UV light and/or PMA stain followed by heating. The flow chemistry experiments were carried out on Vapourtec R-series with glass column (Omntifit, 6.6 x 150 mm). ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker 400 MHz or JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up in the experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E Fourier transform infrared spectrometer.

2A.6.2.Experimental procedure

(i) General procedure for preparation of vinylogous esters by using amberlyst®-15 under batch reaction

In a 20 mL resealable reaction vial, 1,3-cyclohexadione **60a** (56 mg, 0.5 mmol) and amberlyst®-15 (50 mg) were added to ethanol **61a** (2 mL), and the reaction vial was sealed using a crimper. The reaction mixture was stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was filtered and washed with DCM. The organic layer was concentrated under reduced pressure, and

the residue was subjected to column chromatography purification (EtOAc: n-hexane = 25:75) affording cyclic vinylogous esters as a pure compound **62a**.

(ii) General procedure for preparation of vinylogous esters by using amberlyst®-15 under continuous flow.

A 0.1 M solution of the 1,3-cyclodiketone **60** (1 mmol in 10 mL of alcohol **61**) was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 °C at 3.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc: *n*-hexane = 25:75) purification afforded corresponding vinylogous esters.

(iii) General procedure for preparation of vinylogous esters using alcohol and 1,3-dicarbonyl in the presence of amberlyst®-15 under continuous flow

A 0.5 M solution of alcohol was made with 1,4-dioxane. A 0.1 M solution of the 1,3-cyclodiketone (**60a,** 1 mmol in 10 mL of 0.5 M alcohol solution) was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 5.5 cm after passing solvent) of bed heated in 80 °C and maintained 3.3 bar pressure. The organic layer was concentrated under reduced pressure followed by column chromatography (EtOAc: *n*-hexane = 10:90) purification afforded corresponding vinylogous esters.

(IV) General procedure for transetherification of vinylogous esters using alcohol in the presence of amberlyst®-15 under continuous flow

The 0.1 M solution of vinylogous ester **62** (4 mmol) was prepared in alcohols (30 mL) and flown (0.3 mL/min) through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated in 80 °C temperature and maintained 3.3 bar pressure. The organic layer was concentrated under reduced pressure to get the vinylogous ester product. Further, the residue made 0.1 M solution in *n*-butanol, and the above procedure was repeated to afford corresponding vinylogous esters. Similarly, sequential transetherification of vinylogous esters has been achieved using solvent *n*-hexanol, methanol, and ethanol. In all the reactions, the starting material of vinylogous ester was completely converted to other vinylogous esters.

(V) General procedure for hydrolysis of vinylogous esters under continuous flow

The 0.1 M solution vinylogous esters or ketal (0.5 mmol) was prepared in water (5 mL) and flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.2 bar pressure having flow rate 0.1 mL/min. The reaction was monitored by TLC, and the reaction fraction was concentrated in a rotary evaporator to afford 1,3- cyclohexadione derivatives.

(VI) Study of the lifetime of catalyst and gram-scale synthesis of vinylogous esters

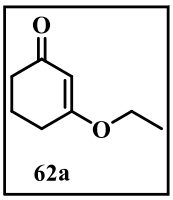
The gram-scale synthesis of vinylogous esters was achieved by using general procedure (ii). The 0.1 M solution of 1,3-cyclohexadione (8.085 g in 720 mL of ethanol) was prepared and flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 °C at 3.3 bar pressure for 40 h. The reaction mixture was monitored periodically by ^{1}H NMR analysis. All the reaction fraction was concentrated in a rotary evaporator to afford 8.112 g of vinylogous esters **62a** as a yellowish oil.

(VII) Experimental procedure for detection of intermediate in transetherification reaction:

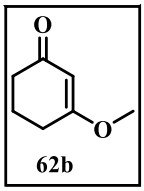
In a 20 mL of the resealable reaction vial, 3-ethoxycyclohex-2-en-1-one (**62a**, 0.5 mmol) was taken in *n*-propanol (2 mL) followed by amberlyst®-15, and the vial was sealed using a crimper. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly taken in a syringe, and the IR and HRMS analysis for the reaction mixture was recorded.

2A.6.3. Analytical data for products

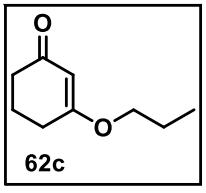
3-Ethoxycyclohex-2- en-1-one 62a[71] was synthesized by following the experimental procedure (ii) using 1,3-cyclohexadione (0.1 M solution in 10 mL of ethanol), afforded 99% (138.5 mg) as a yellowish oil compound **62a**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.28 (s, 1H), 3.84 (q, *J* = 6.8 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.27 (t, *J* = 6.8 Hz, 3H), 1.94−1.88 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 177.9, 102.7, 64.2, 36.8, 29.1, 21.3, 14.1 ppm. **FTIR** (neat): 2954, 1728, 1598, 1412, 1314, 1222, 1125, 1091, 769, 568cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_8H_{13}O_2$ $(M + H)^+$: 141.0916; found: 141.0925.



3-Methoxycyclohex-2-en-1-one 62b[72] was synthesized by following the experimental procedure (ii) using 1,3-cyclohexadione (0.1 M solution in 10 mL of methanol), afforded 99% (124.8 mg) as a yellowish oil compound **62b**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.37 (s, 1H), 3.69 (s, 3H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.01−1.94 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.9, 178.9, 102.5, 55.8, 36.9, 28.9, 21.4 ppm. **FTIR** (neat): 2953, 2315, 1724, 1590, 1458, 1369, 1226, 1179, 1060, 753, 601cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_7H_{11}O_2$ $(M + H)^+$: 127.0759; found: 127.0762.

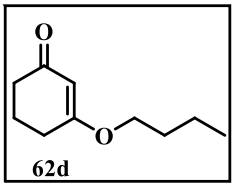


3-Propoxycyclohex-2-en-1-one 62c[73] was synthesized by following the experimental procedure (ii) using 1,3-cyclohexadione (0.1 M solution in 10 mL of propanol), afforded 97% (149.3 mg) as a yellowish oil compound **62c**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.00−1.93 (m, 2H), 1.78−1.70 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 200.0, 178.3, 102.8, 70.1, 36.9, 29.2, 22.0, 21.4, 10.5 ppm.

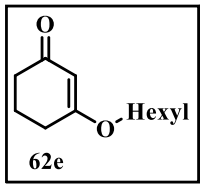


FTIR (neat): 2952, 1727, 1601, 1453, 1380, 1232, 1183, 1001, 758, 597 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_9H_{15}O_2$ $(M + H)^+$: 155.1072; found: 155.1078.

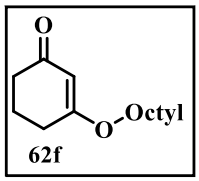
3-Butoxycyclohex-2-en-1-one 62d was synthesized by following the experimental procedure (ii) using 1,3-cyclohexadione (0.1 M solution in 10 mL of *n*-butanol), afforded 85% (142.4 mg) as a yellowish oil compound **62d**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.79 (t, *J* = 6.4 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H), 2.30 (t, *J* = 6 Hz, 2H), 1.97−1.90 (m, 2H), 1.70−1.63 (m, 2H), 1.43−1.34 (m, 2H), 0. 91 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 178.1, 102.7, 68.3, 36.8, 30.6, 29.1, 21.3, 19.2, 13.8 ppm. **FTIR** (neat): 2954, 2879, 2313, 1724, 1593, 1461, 1222, 1181, 1065, 748, 667 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_{17}O_2$ $(M + H)^+$: 169.1229; found: 169.1238.



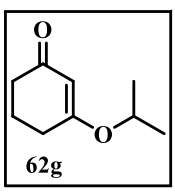
3-(Hexyloxy)cyclohex-2-en-1-one 62e was synthesized by following the experimental procedure (iv) using 3-butoxycyclohex-2-en-1-one **62d** in (0.1 M solution in 25 mL of *n*-hexanol) afforded 95% (462.5 mg) as a yellowish oil compound **62e**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 2.01−1.94 (m, 2H), 1.75−1.68 (m, 2H), 1.42−1.29 (m, 6H), 0.9 (t, *J* = 6.8 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 200.0, 178.3, 102.9, 68.8, 36.9, 31.6, 29.2, 28.6, 25.7, 22.7, 21.9, 14.1 ppm. **FTIR** (neat): 2944, 2834, 2310, 1718, 1589, 1465, 1298, 1110, 1034, 786, 610 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{12}H_{21}O_2$ $(M + H)^+$: 197.1463; found: 197.1469.



3-(Octyloxy)cyclohex-2-en-1-one 62f was synthesized by using a syringe pump. Due to the high viscosity of octanol, the Vapourtec R-series pump was not able to flow the *n*-octanol. 1,3-cyclohexadione (0.1 M solution in 10 mL of octanol) was taken in the syringe pump and flown through the reactor bed at 0.3 mL/min, at 80 °C temperature, afforded 94% (210.3 mg) as a yellowish oil compound **62f**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.33 (s, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6 Hz, 2H), 1.99−1.93 (m, 2H), 1.74−1.64 (m, 2H), 1.37−1.22 (m, 10H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 200.2, 178.2, 102.8, 68.7, 36.9, 31.9, 29.3, 29.1, 28.6, 26.0, 22.7, 21.3, 14.5 ppm. **FTIR** (neat): 2929, 2862, 2314, 1727, 1592, 1461, 1233, 1184, 1090, 756, 607 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{25}O_2$ $(M + H)^+$: 225.1855; found: 225.1861.

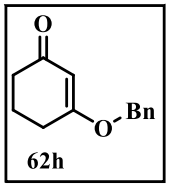


3-Isopropoxycyclohex-2-en-1-one 62g[74] was synthesized by following the experimental procedure (ii) using 1,3-cyclohexadione (0.1 M solution in 10 mL of propan-2-ol), afforded 87% (134.1 mg) as a yellowish oil compound **62g**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 4.45−4.36 (m, 1H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.97−1.91 (m, 2H), 1.27 (d, *J* = 6 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 200.0, 177.1, 103.1, 71.3, 36.8, 29.7, 21.6, 21.3 ppm. **FTIR** (neat): 2978, 2310, 1730, 1641, 1595,

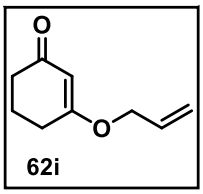


1461, 1230, 1187, 1000, 757, 608 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_9H_{15}O_2$ $(M + H)^+$: 155.1072; found: 155.1078.

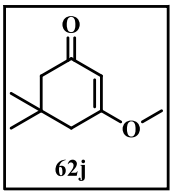
3-(Benzyloxy)cyclohex-2-en-1-one 62h[75] was synthesized by following the experimental procedure (ii) using 1,3- cyclohexadione (0.1 M solution in 10 mL of benzylalcohol), afforded 80% (161.8 mg) as a yellowish oil compound **62h**. **^{1}H NMR** (400 MHz, MeOD-d4): δ 7.39−7.38 (m, 3H), 7.37− 7.32 (m, 2H), 5.51 (s, 1H), 5.00 (s, 2H), 2.52 (t, *J* = 6.4 Hz, 2H), 2.35 (t, *J* = 6 Hz, 2H), 2.04−1.97 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, MeOH-d_4): δ 203.4, 181.2, 136.8, 129.7, 129.4, 128.9, 103.7, 71.9, 37.5, 30.0, 22.3 ppm. **FTIR** (neat): 3029, 2947, 2947, 2881, 2315, 1734, 1648, 1597, 1359, 1221, 1175, 863, 743 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{15}O_2$ $(M + H)^+$: 203.1072; found: 203.1079.



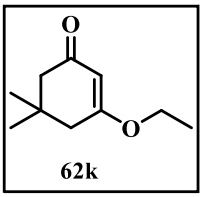
3-(Allyloxy)cyclohex-2-en-1-one 62i[68] was synthesized by following the experimental procedure (ii), using 1,3-cyclopentadione (0.1 M solution in 10 mL of allyl alcohol), afforded 88% (133.6 mg) as a yellowish liquid compound **62i**. **^{1}H NMR** (400 MHz, $CDCl_3$ + CCl_4): δ 6.00−5.90 (m, 1H), 5.39−5.28 (m, 3H), 4.37 (d, *J* = 5.6 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2 Hz), 2.02−1.95 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$ + CCl_4): δ 199.3, 177.1, 131.6, 119.1, 103.4, 62.2, 36.9, 29.2, 21.4 ppm. **FTIR** (neat): 2947, 2896, 2213, 2166, 1589, 1345, 1222, 1179, 1135, 988, 761cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_9H_{12}O_2Na$ $(M + Na)^+$: 175.0735; found: 175.0739.



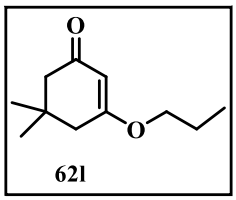
3-Methoxy-5,5-dimethylcyclohex-2-en-1-one 62j[76] was synthesized by following the experimental procedure (ii) using 5,5- dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of methanol), afforded 99% (152.4 mg) as a yellowish oil compound **62j**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.35 (s, 1H), 3.67 (s, 3H), 2.25 (s, 2H), 2.19 (s, 2H), 1.05 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 177.1, 101.2, 55.8, 50.8, 42.8, 32.6, 28.3 ppm. **FTIR** (neat): 2956.40, 2312.12, 1649.43, 1601.68, 1456.82, 1373.03, 1221.59, 1147.82, 1013.68, 754.09, 602 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_9H_{15}O_2$ $(M + H)^+$: 155.1072; found: 155.1080.



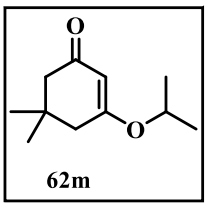
3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one 62k[77] was synthesized by following the experimental procedure (ii) using 5,5- dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of ethanol), afforded 99% (163.1 mg) as a yellowish oil compound **62k**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 2H), 2.17 (s, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 176.3, 101.6, 64.3, 50.8, 43.0, 32.6, 28.6, 14.2 ppm. **FTIR** (neat): 2956, 2884, 2312, 1723, 1649, 1599, 1464, 1368, 1216, 1149, 1031, 752, 628 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_{16}O_2$ $(M + H)^+$: 169.1229; found: 169.1235.



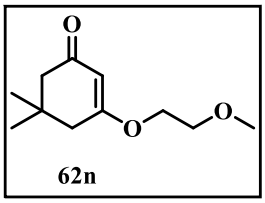
5,5-Dimethyl-3-propoxycyclohex-2-en-1-one 62l[77] was synthesized by following the experimental procedure (ii) using 5,5- dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of propanol), afforded 95% (191.1 mg) as a yellowish oil compound **62l**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.26 (s, 2H), 2.19 (s, 2H), 1.72 (m, 2H), 1.05 (s, 6H), 0.96 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 176.5, 101.6, 70.2, 50.9, 43.0, 32.6, 28.4, 22.0, 10.5 ppm. **FTIR** (neat): 2959, 2881, 2310, 1722, 1598, 1463, 1367, 1218, 1147. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{19}O_2$ $(M + H)^+$: 183.1385; found: 183.1390.



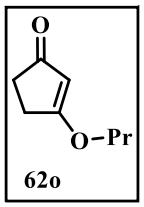
3-Isopropoxy-5,5-dimethylcyclohex-2-en-1-one 62m was synthesized by following the experimental procedure (ii) using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of propan-2-ol), afforded 99% (180.3 mg) as a yellowish oil compound **62m**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 4.41 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.27 (d, *J* = 6 Hz, 6H), 1.04 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 175.3, 101.9, 71.0, 50.8, 43.5, 32.5, 28.3, 21.6 ppm. **FTIR** (neat): 2966, 2881, 2310, 1726, 1650, 1600, 1464, 1380, 1226, 1152, 1054, 758, 639 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{19}O_2$ $(M + H)^+$: 183.1385; found: 183.1389.



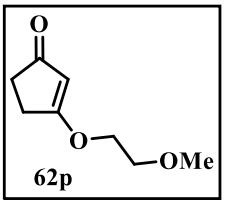
3-(2-Methoxyethoxy)-5,5-dimethylcyclohex-2-en-1-one 62n was synthesized by following the experimental procedure (ii) using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of 2-methoxyethanol), afforded 94% (186.3 mg) as a yellowish oil compound **62n**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 1H), 3.98−3.95 (m, 2H), 3.69−3.67 (m, 2H), 3.41 (s, 3H), 2.32 (s, 2H), 2.20 (s, 2H), 1.05 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 176.2, 101.8, 70.2, 67.8, 59.3, 50.8, 42.8, 32.6, 28.4 ppm. **FTIR** (neat): 2959, 2311, 2170, 1729, 1650, 1607, 1463, 1376, 1228, 1136, 1041, 751, 659cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{20}O_3$ $(M + H)^+$: 199.1334; found: 199.1343.



3-Propoxycyclopent-2-en-1-one 62o was synthesized by following the experimental procedure (ii), using 1,3-cyclopentadione (0.1 M solution in 10 mL of n-propanol), afforded 73% (102.5 mg) as a yellowish oil compound **62o**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.27 (m, 1H), 3.92 (t, *J* = 6.8 Hz, 2H), 2.61− 2.59 (m, 2H), 2.44−2.41 (m, 2H), 1.83−1.74 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 206.3, 190.6, 104.8, 73.6, 34.0, 28.6, 22.1, 10.4 ppm. **FTIR** (neat): 2967, 2934, 2246, 1676, 1584, 1411, 1344, 1289, 1183, 724, 651 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_8H_{12}O_2Na$ $(M + Na)^+$: 163.0735; found: 163.0739.

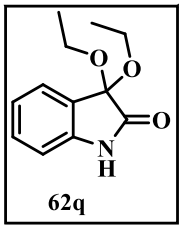


3-(2-Methoxyethoxy)cyclopent-2-en-1-one 62p was synthesized by following the experimental procedure (ii), using 1,3-cyclopentadione (0.1 M solution in 10 mL of 2-methoxy ethanol), afforded 83% (130.2 mg) as a yellowish oil compound **62p**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.31 (m, 1H), 4.13−4.11 (m, 2H), 3.73−3.71 (m, 2H), 3.43 (s, 3H), 2.67− 2.61 (m, 2H), 2.46−2.44 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 206.2, 190.2, 105.2, 71.1, 70.2, 59.4, 34.3, 28.6 ppm. **FTIR** (neat): 2964, 2251, 1738, 1590, 1345, 1189, 1126, 1039, 719, 649 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_8H_{12}O_3$ $(M + Na)^+$: 179.0684; found: 179.0692.



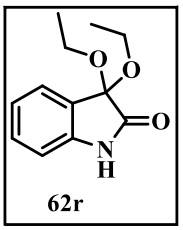
62p

3,3-Diethoxyindolin-2-one 62q was synthesized by following the experimental procedure (ii), using isatin (0.1 M solution in 10 mL of ethanol), afforded 80% (177.2 mg) as a yellowish solid compound **62q. ^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02 (bs, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.06 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 3.98−3.90 (m, 2H), 3.84−3.77 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 173.2, 140.4, 130.6, 126.2, 125.3, 122.9, 110.8, 97.2, 59.0, 15.4 ppm. **FTIR** (neat): 3198, 2978, 2922, 2309, 1727, 1615, 1466, 1259, 1054, 751, 659cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{12}H_{15}NO_3Na$ $(M + Na)^+$: 244.0950; found: 244.0956.



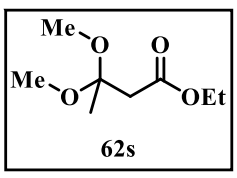
62q

3,3-Dipropoxyindolin-2-one 62r was synthesized by following the experimental procedure (ii) using isatin (0.1 M solution in 10 mL of propanol), afforded 76% (211.9 mg) as a yellowish solid compound **62r**. Melting point: 79−83 °C. **^{1}H NMR** (400 MHz, MeOD-d_4): δ 7.36 (d, J = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 3.77−3.72 (m, 2H), 3.65−3.61 (m, 2H), 1.62−1.53 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, MeOH-d_4): δ 175.0, 142.7, 131.7, 127.3, 126.3, 123.4, 111.7, 90.7, 65.9, 24.1, 10.9 ppm. **FTIR** (neat): 2967, 2882, 2312, 1734, 1617, 1467, 1201, 1059, 757cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{19}NO_3Na$ $(M + Na)^+$: 272.1263; found: 272.1266.



62r

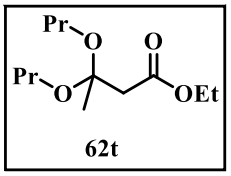
Ethyl 3,3-dimethoxybutanoate 62s was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL of methanol) and was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) at a flow rate of 0.3 mL/min, loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography using n-hexane purification, afforded 86% (151.5 mg) ethyl-3,3-dimethoxybutanoate **62s**. **^{1}H NMR** (400 MHz, $CDCl_3$ + CCl_4): δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.21 (s, 6H), 2.64 (s, 2H), 1.45 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H}** NMR (100 MHz, $CDCl_3$ + CCl_4): δ 169.7, 99.9, 60.6, 48.5, 42.5, 22.0, 14.4 ppm. **FTIR**



62s

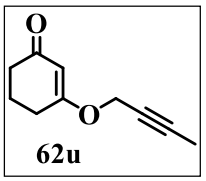
(neat): 2983, 2942, 2832, 1735, 1626, 1462, 1380, 1227, 1139, 1096, 931, 762, 649 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_8H_{16}O_4Na$ $(M + Na)^+$: 199.0946; found: 199.0948

Ethyl-3,3-dipropoxybutanoate 62t was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL of propanol) and was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) at a flow rate of 0.3 mL/min, loaded with amberlyst®-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column c chromatography using n-hexane purification, afforded 95% (220 mg) ethyl 3,3-dipropoxybutanoate **62t**. **^{1}H NMR** (400 MHz, $CDCl_3$ + CCl_4): δ 4.13 (q, *J* = 6.8 Hz, 2H), 3.43−3.34 (m, 4H), 2.66 (s, 2H), 1.59−1.50 (m, 4H), 1.48 (s, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 0.9 (t, *J* = 7.6 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$ + CCl_4): δ 169.9, 99.5, 62.4, 60.5, 43.4, 23.3, 23.1, 14.4, 11.0 ppm. **FTIR** (neat): 2984., 2934., 1737., 1712., 1627., 1391., 1315., 1149., 1065., 915, 754. cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{12}H_{24}O_2Na$ $(M + Na)^+$: 255.1572; found: 255.1579.



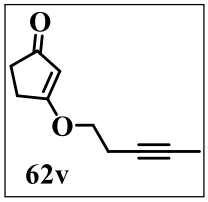
62t

3-(But-2-yn-1-yloxy)cyclohex-2-en-1-one 62u was synthesized by following the experimental procedure (iii), using 1,3- cyclohexadione (1 mmol) in 0.5 M solution of but-2-yn-1-ol in 1,4-dioxane afforded 76% (121.1 mg) as a yellowish solid compound **62u**. Melting point: 57−65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.44 (s, 1H), 4.50 (q, *J* = 2.4 Hz, 2H), 2.43 (t, *J* = 6 Hz, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 2.02−1.96 (m, 2H), 1.86 (dt, J = 2.8 Hz, 0.4 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.9, 176.8, 103.7, 85.4, 72.3, 57.0, 36.9, 28.9, 21.3, 3.9 ppm. **FTIR** (neat): 2954, 2313, 2240, 1731, 1650, 1603, 1358, 1222, 1180, 1069, 907, 762, 600 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_{13}O_2$ $(M + H)^+$: 165.0916; found: 165.0921.



62u

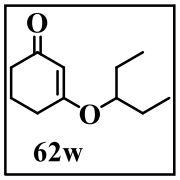
3-(Pent-3-yn-1-yloxy)cyclopent-2-en-1-one 62v was synthesized by following the experimental procedure (iii), using 1,3- cyclopentadione (1 mmol) in 0.5 M solution of pent-3-yn-1-ol in 1,4-dioxane afforded 64% (105.3 mg) as a y ellowish solid compound **62v**. Melting point: 50−51 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (m, 1H), 4.03 (t, *J* = 7.2 Hz, 2H), 2.65−2.62 (m, 2H), 2.46−2.43 (m, 2H), 1.79 (t, *J* = 2.8 Hz, 2H), 1.64 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 176.2, 101.8, 70.2, 67.8, 59.3, 50.8, 42.8, 32.6, 28.4 ppm. **FTIR** (neat): 2927, 2243, 17021, 15911, 1439, 1347, 1184, 1059, 954, 705, 599 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_{12}O_2Na$ $(M + Na)^+$: 187.0735; found: 187.0739.



62v

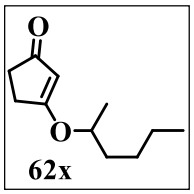
3-(Pentan-3-yloxy)cyclohex-2-en-1-one 62w was synthesized by following the experimental procedure (iii) using 1,3- cyclohexadione (1 mmol) in 0.5 M solution of pentane-3-ol in 1,4-dioxane, afforded 65% (118.5 mg) as a yellowish oil compound **62w**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s,

1H), 4.06−4.00 (m, 1H), 2.3 9 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 2.00−1.94 (m, 2H), 1.66−1.59 (m, 4H), 0.89 (t, *J* = 6 Hz, 6H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 200.7, 177.9, 103.0, 80.9, 36.8, 29.6, 25.7, 21.3, 9.5 ppm. **FTIR** (neat): 2959, 2311, 2170, 1729, 1650, 1607, 1463, 1376, 1228, 1136, 1041, 751, 659 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{18}O_2Na$ $(M + Na)^+$: 205.1204; found: 205.1212.



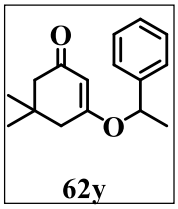
62w

3-(Hexan-2-yloxy)-cyclopent-2-en-1-one 62x was synthesized by following the experimental procedure (iii), using 1,3- cyclopentadione (1 mmol) in 0.5 M solution of hexan-2-ol in 1,4-dioxane, afforded 61% (111.4 mg) as a yellowish liquid compound **62x**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.25 (m, 1H), 4.27−4.19 (m, 1H), 2.60−2.57 (m, 2H), 2.43−2.41 (m, 2H), 1.73−1.52 (m, 4H), 1.31 (d, *J* = 6 Hz, 5H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm. **$^{13}C\{^{1}H\}$** NMR (100 MHz, $CDCl_3$): δ 206.5, 189.7, 104.8, 79.3, 35.7, 33.9, 29.1, 27.6, 22.7, 19.4, 14.1 ppm. **FTIR**: 2934, 2824, 2234, 1712, 1565, 1423, 1355, 1278, 1182, 745, 661 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{18}O_2Na$ $(M + Na)^+$: 205.1204. found: 205.1210.



62x

5,5-Dimethyl-3-(1-phenylethoxy)cyclohex-2-en-1-one 62y was synthesized by following the experimental procedure (iii), using 5,5-dimethyl-1,3-cyclohexadione (1 mmol) in 0.5 M solution of 1-phenylethan-1-ol in 1,4-dioxane, afforded 64% (140 mg) as a yellowish oil compound **62y**. **^{1}H NMR** (400 MHz, MeOD-d_4): δ 7.39−7.34 (m, 3H), 7.32−7.29 (m, 2H), 5.37 (q, *J* = 6.4 Hz,1H), 5.27 (s, 1H), 2.41 (dd, *J* = 27.6 Hz, 17.6 Hz, 2H), 2.16 (dd, *J* = 25.6 Hz, 16.4 Hz, 2H), 1.59 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 3H), 1.01 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, MeOH-d_4): δ 202.7, 178.3, 143.0, 129.8, 120.0, 126.4, 104.2, 78.4, 51.2, 44.0, 33.5, 28.4, 28.1, 24.2 ppm. **FTIR** (neat): 3022, 2964, 2313, 1725, 1601, 1457, 1216, 753, 667 cm^{-1}. **HRMS** (ESI-TOF) m/z: calculated for $C_{16}H_{21}O_2$ $(M + H)^+$: 245.1542; found: 245.1544.



62y

2A.6.4. Appendix I

Copies of ^{1}H and ^{13}C NMR spectra and crystal structure of representative compounds

Entry	Figure No	Data	Page No
62a	13 & 14	^{1}H and ^{13}C	65
62d	15 & 16	^{1}H and ^{13}C	66
62i	17 & 18	^{1}H and ^{13}C	67
62l	19 & 20	^{1}H and ^{13}C	68
62m	21 & 22	^{1}H and ^{13}C	69
62o	23 & 24	^{1}H and ^{13}C	70
62q	25 & 26	^{1}H and ^{13}C	71
62s	27 & 28	^{1}H and ^{13}C	72
62w	29 & 30	^{1}H and ^{13}C	73

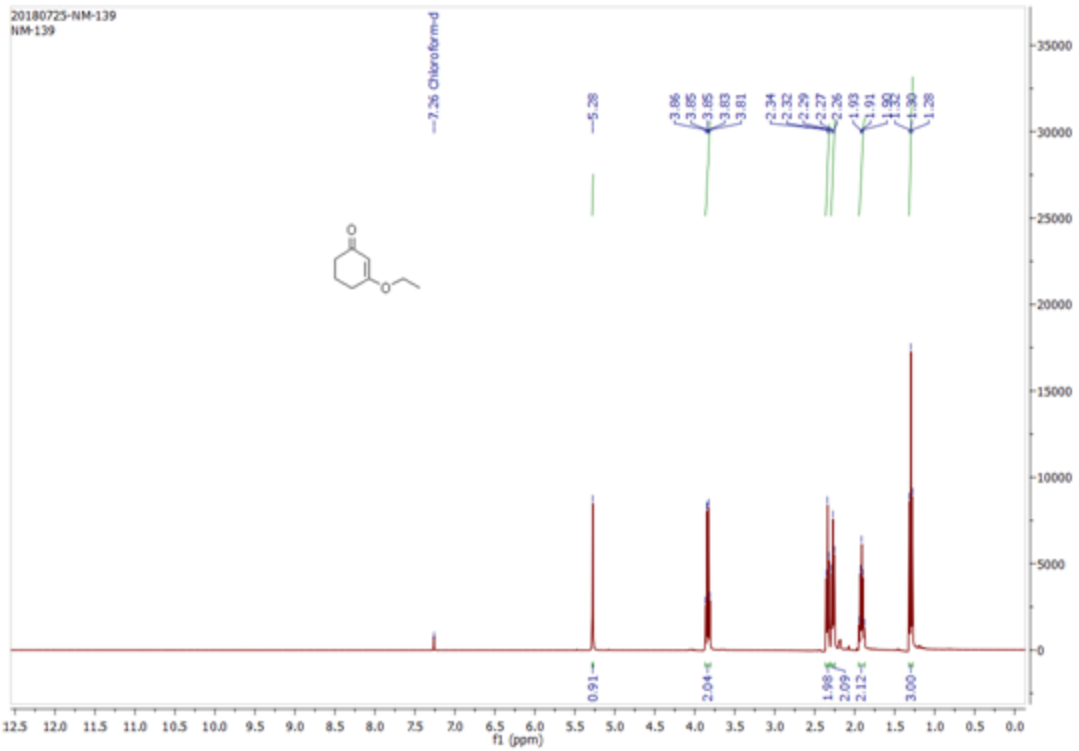


Figure 13. ^{1}H NMR of compound **62a**

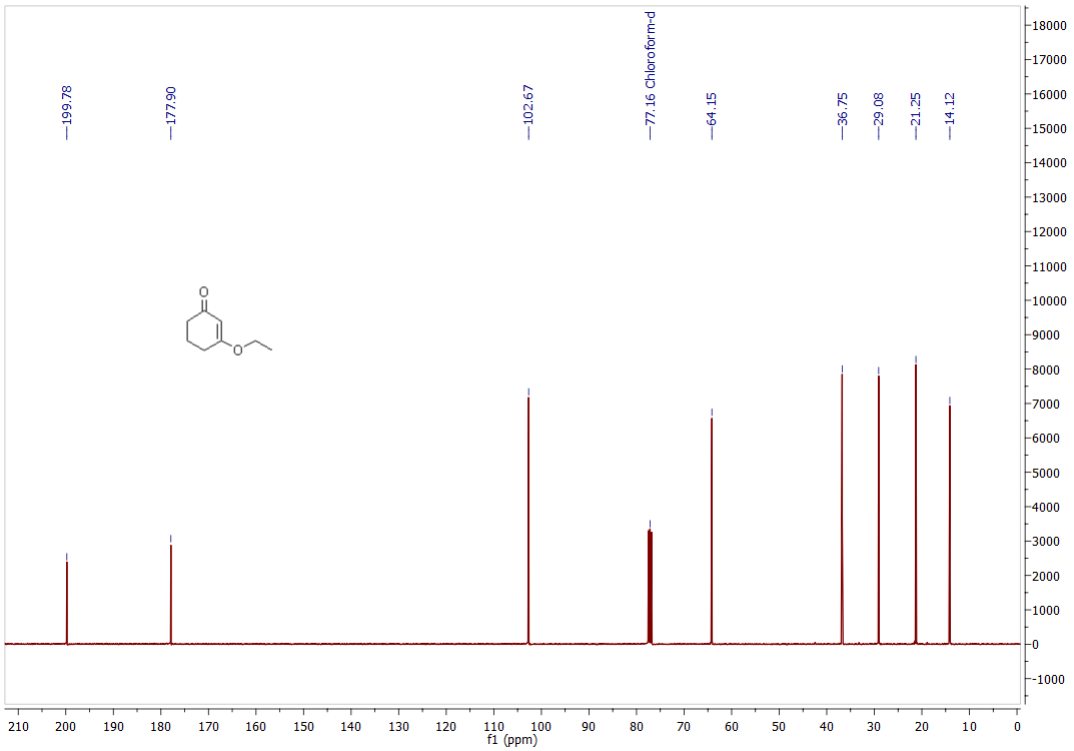


Figure 14. ^{13}C NMR of compound **62a**

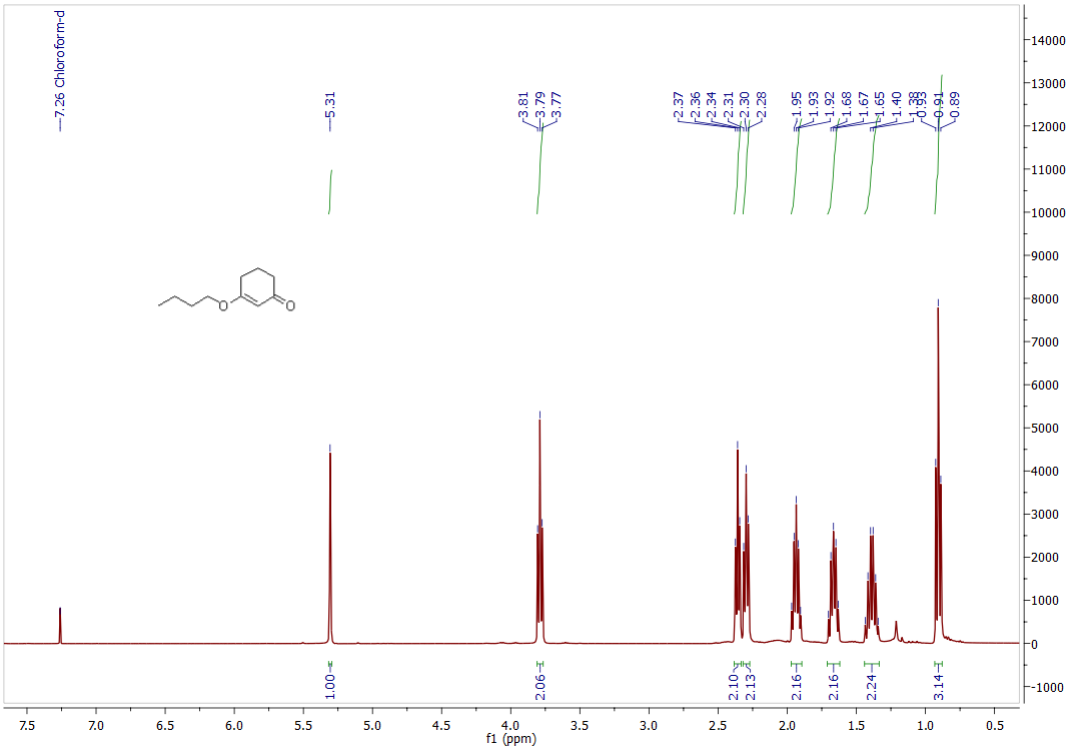


Figure 15. ^{1}H NMR of compound **62d**

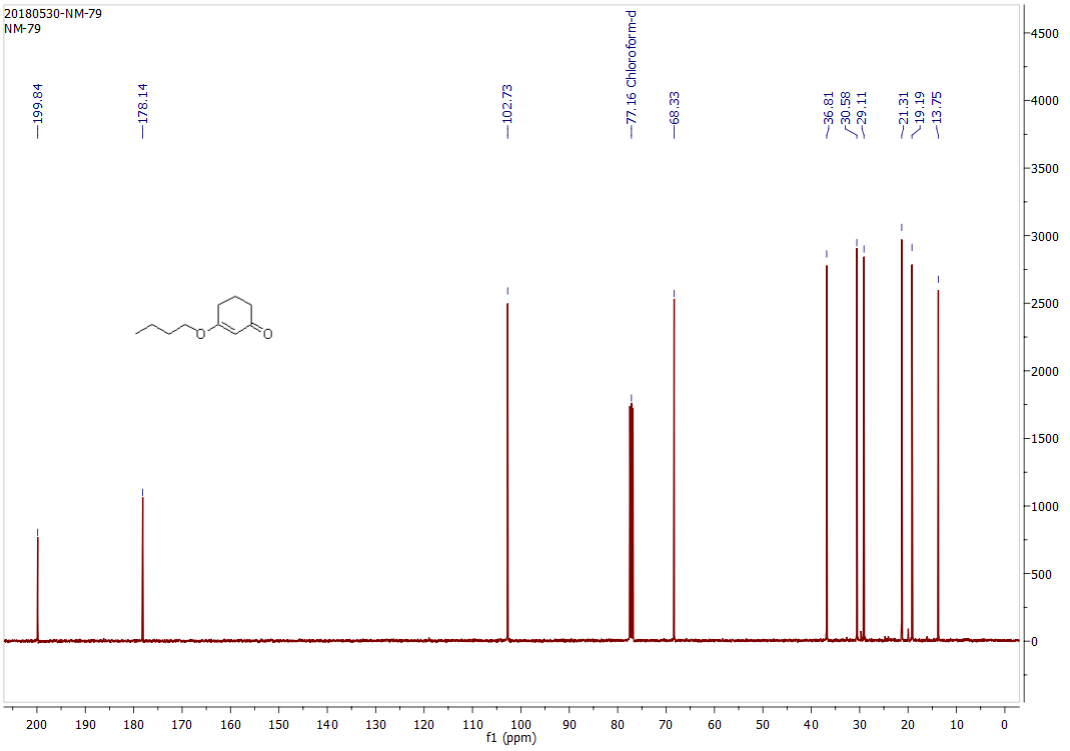


Figure 16. ^{13}C NMR of compound **62d**

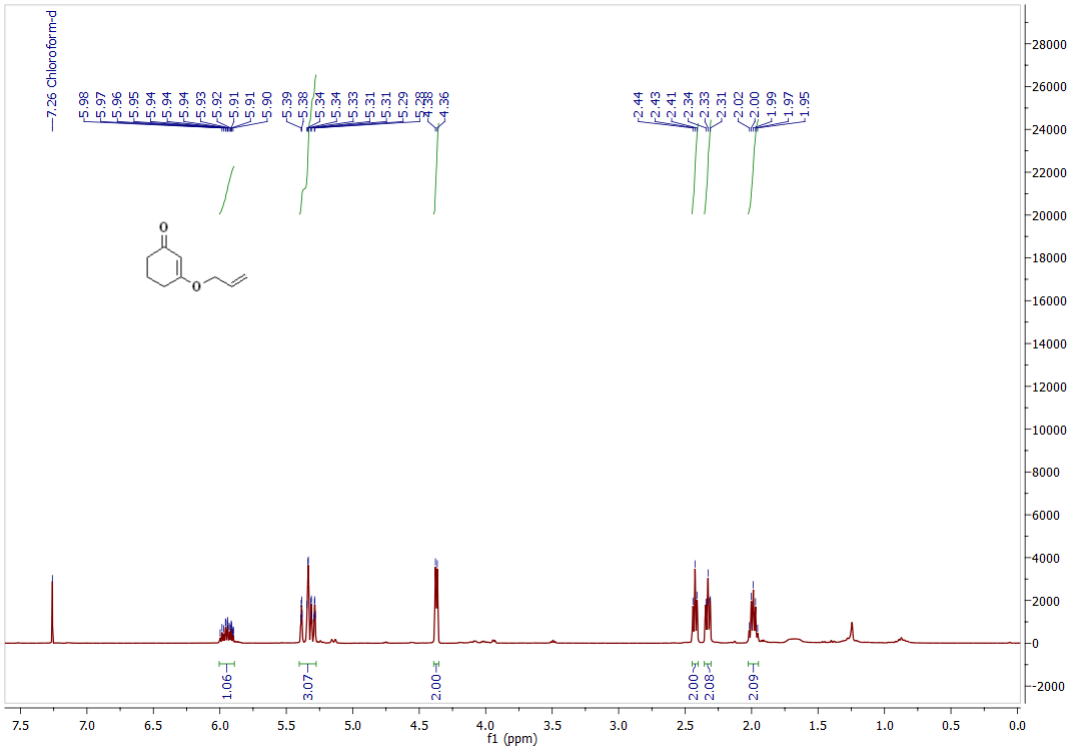


Figure 17. ^{1}H NMR of compound **62i**

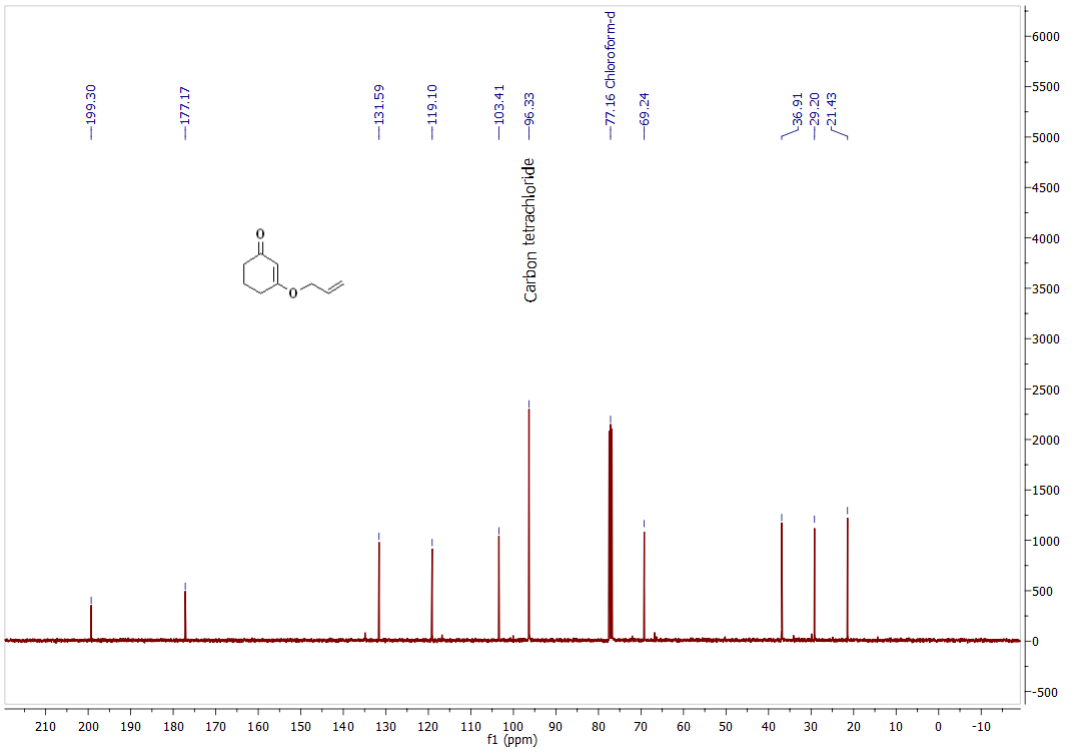


Figure 18. ^{13}C NMR of compound **62i**

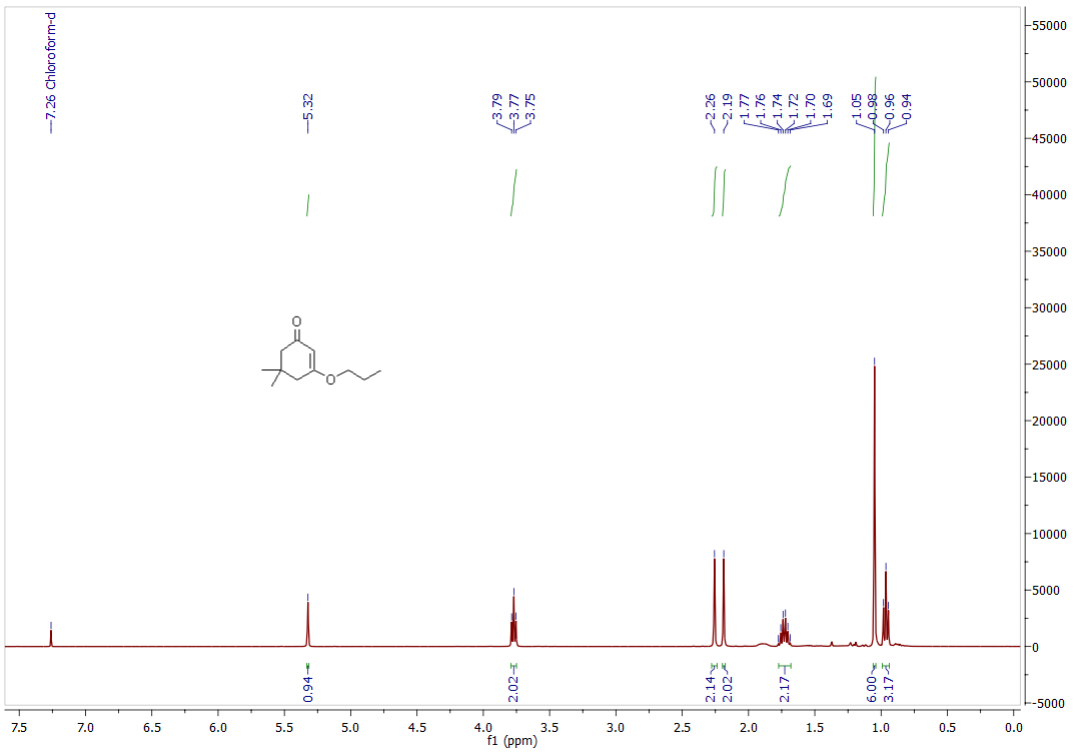


Figure 19. ^{1}H NMR of compound **62l**

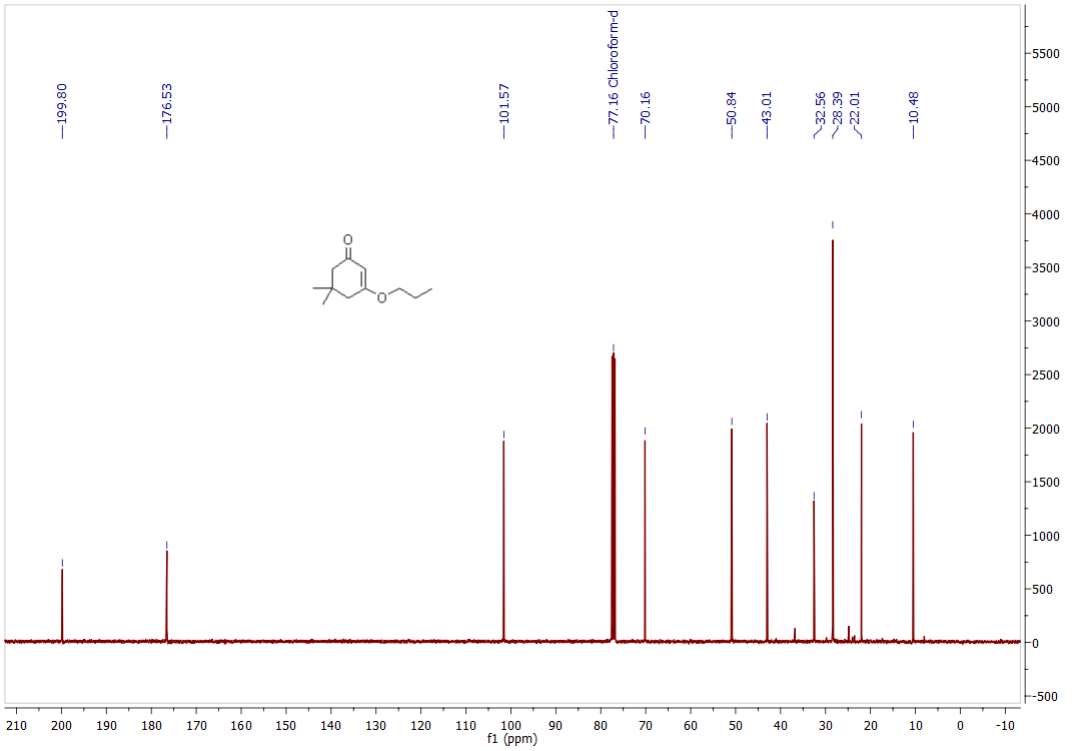


Figure 20. ^{13}C NMR of compound **62l**

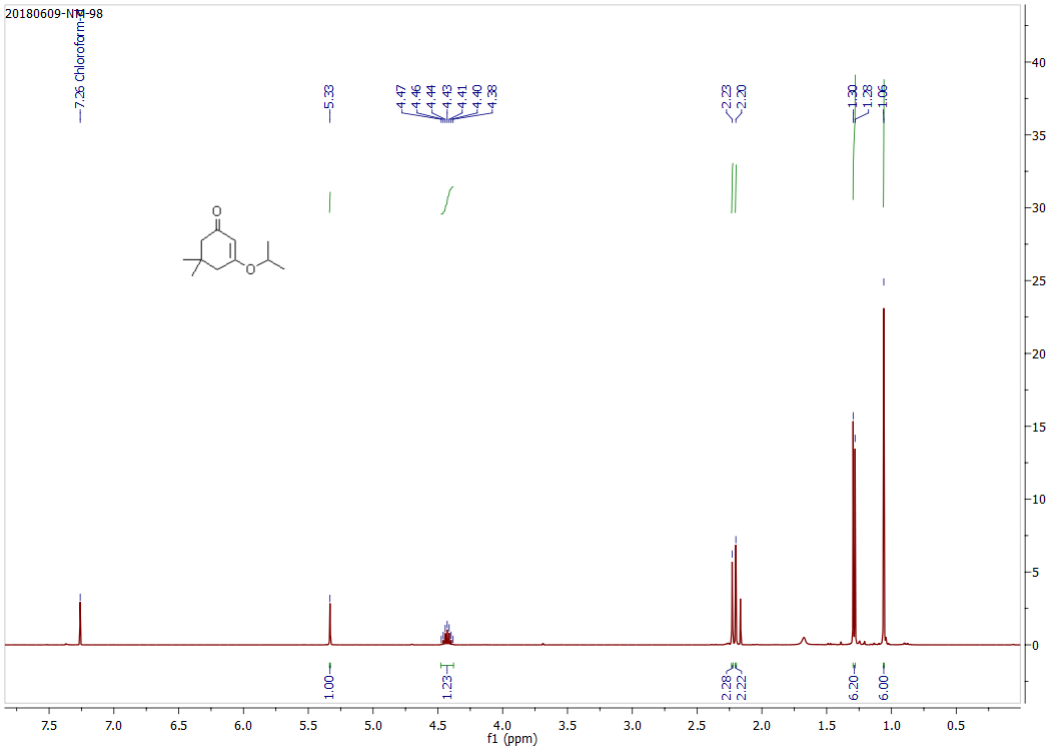


Figure 21. ^{1}H NMR of compound **62m**

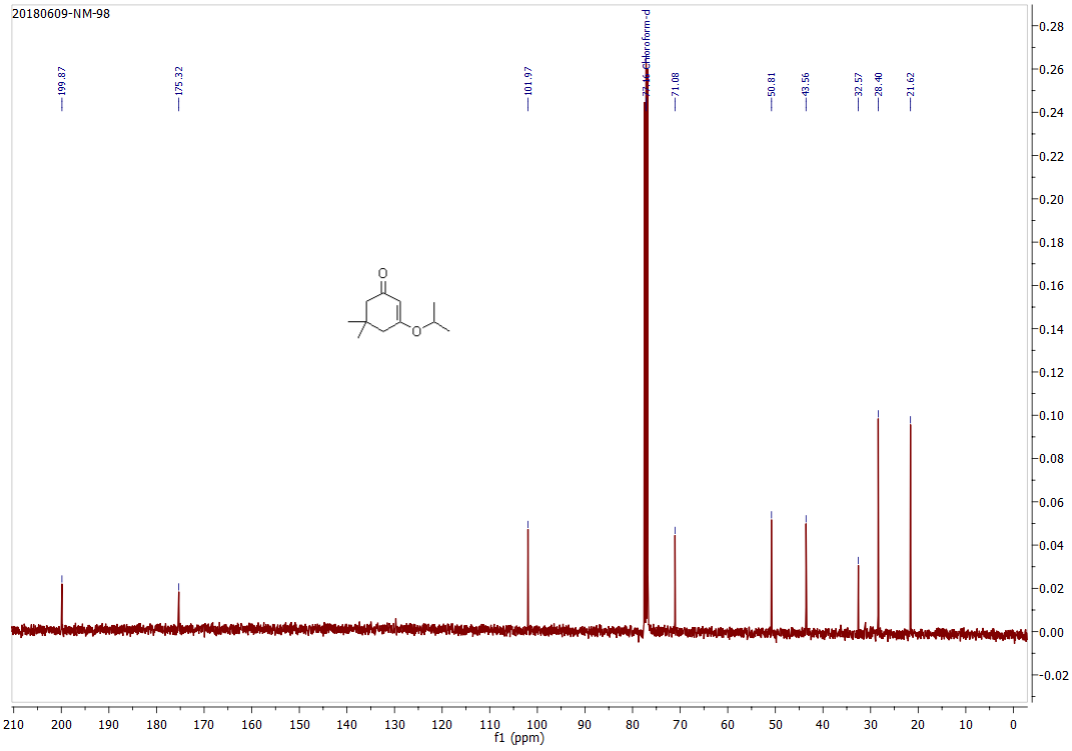


Figure 22. ^{13}C NMR of compound **62m**

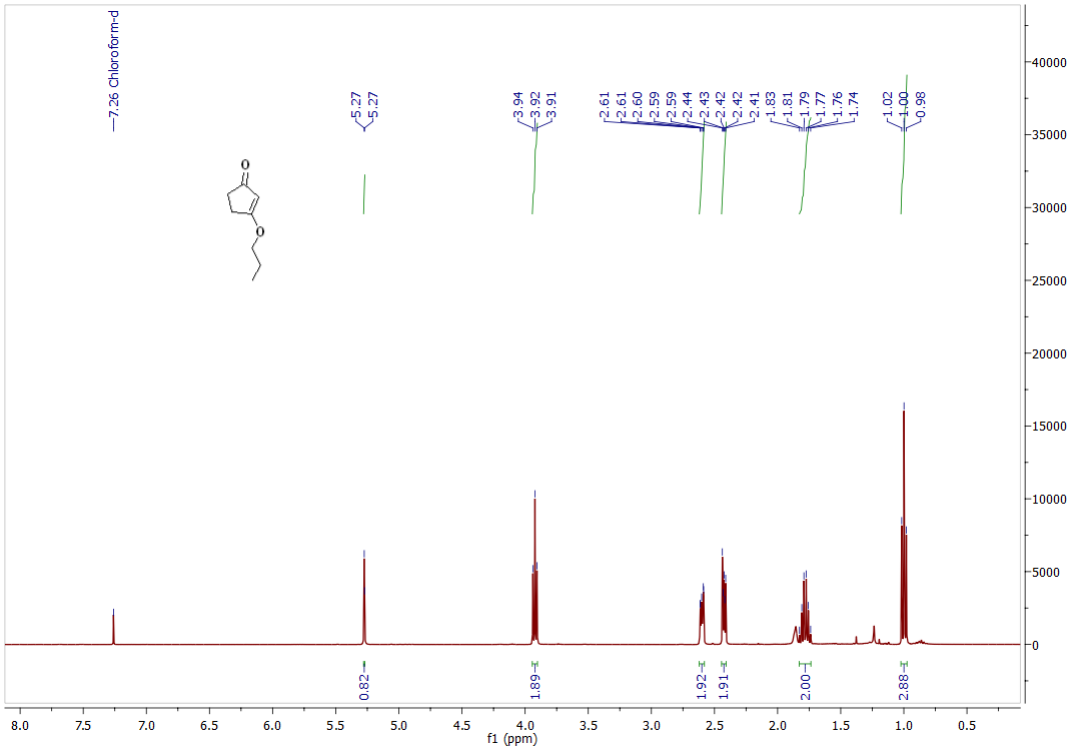


Figure 23. ^{1}H NMR of compound **62o**

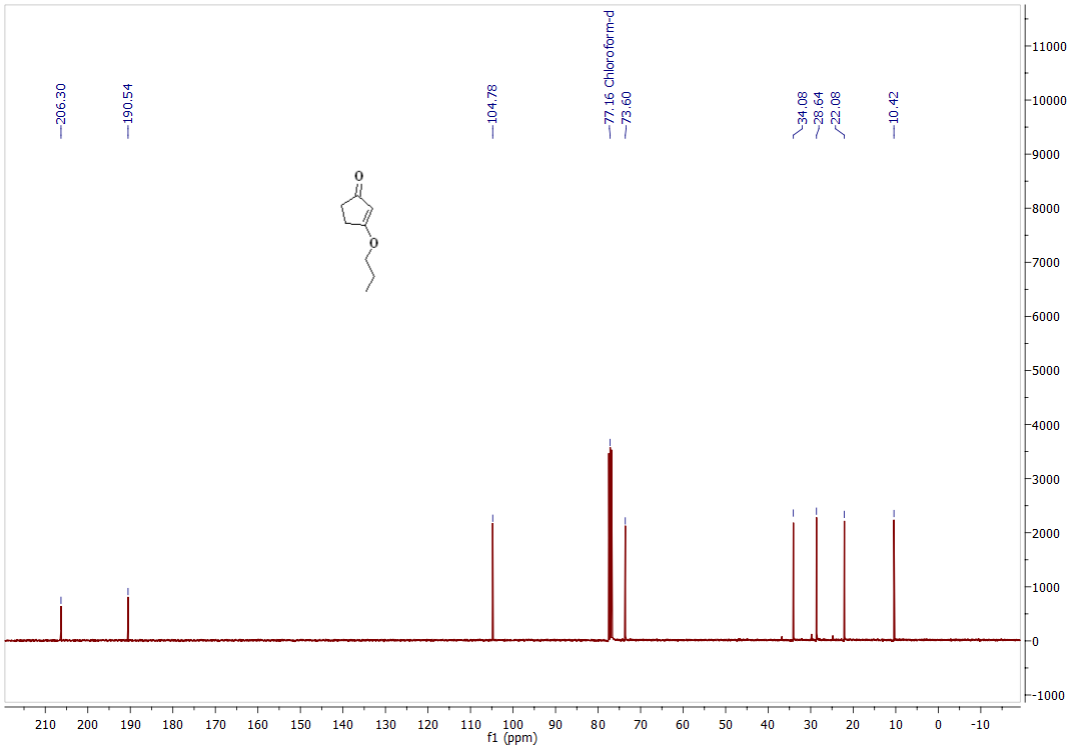


Figure 24. ^{13}C NMR of compound **62o**

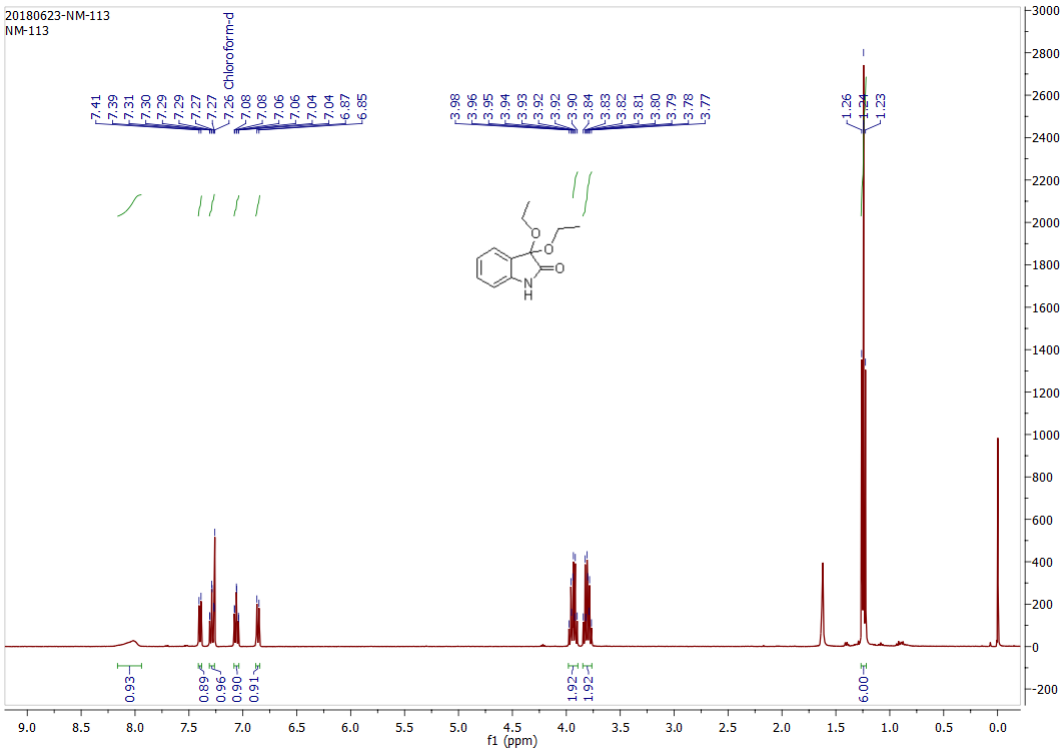


Figure 25. ^{1}H NMR of compound **62q**

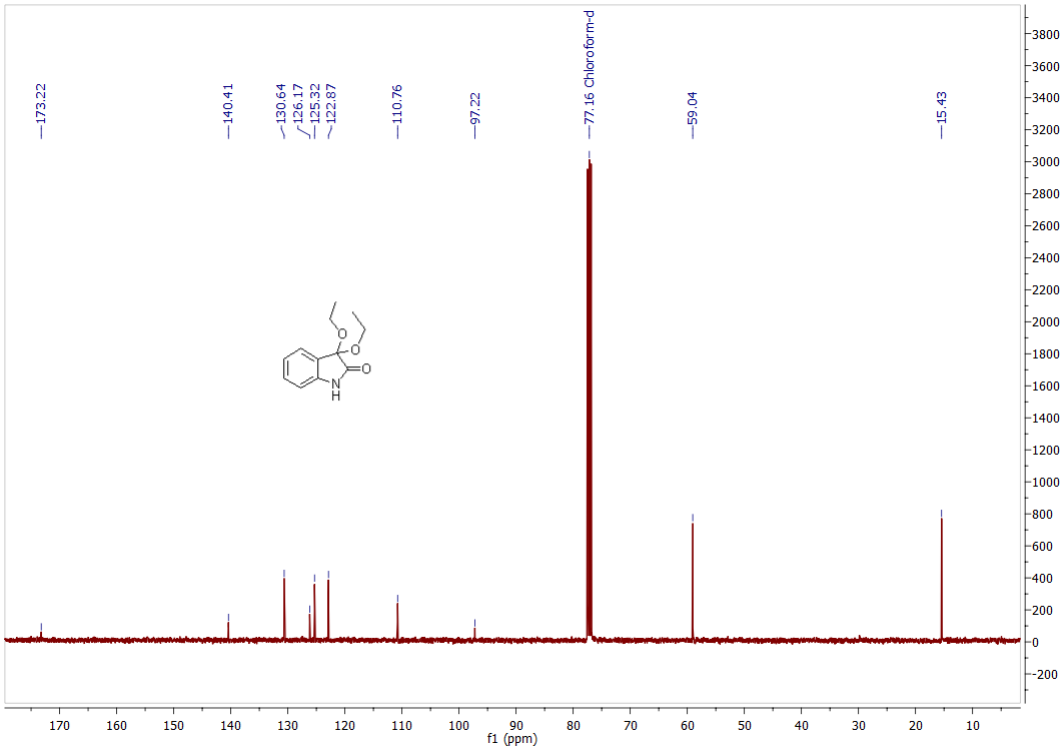


Figure 26. ^{13}C NMR of compound **62q**

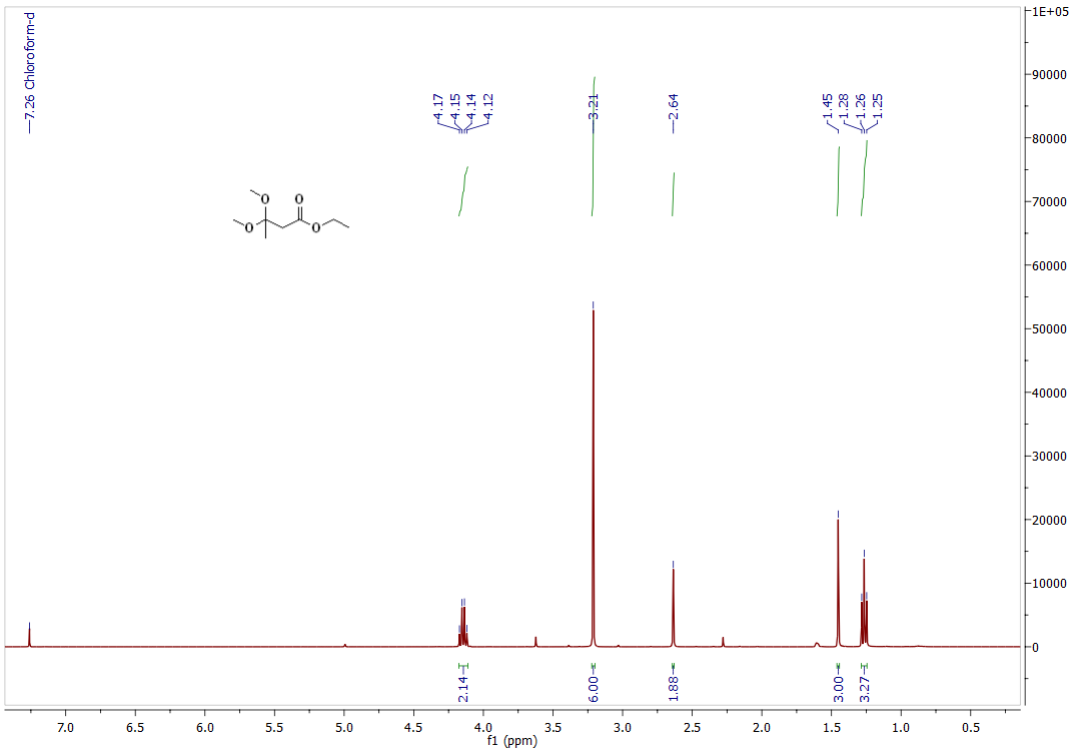


Figure 27. ^{1}H NMR of compound **62s**

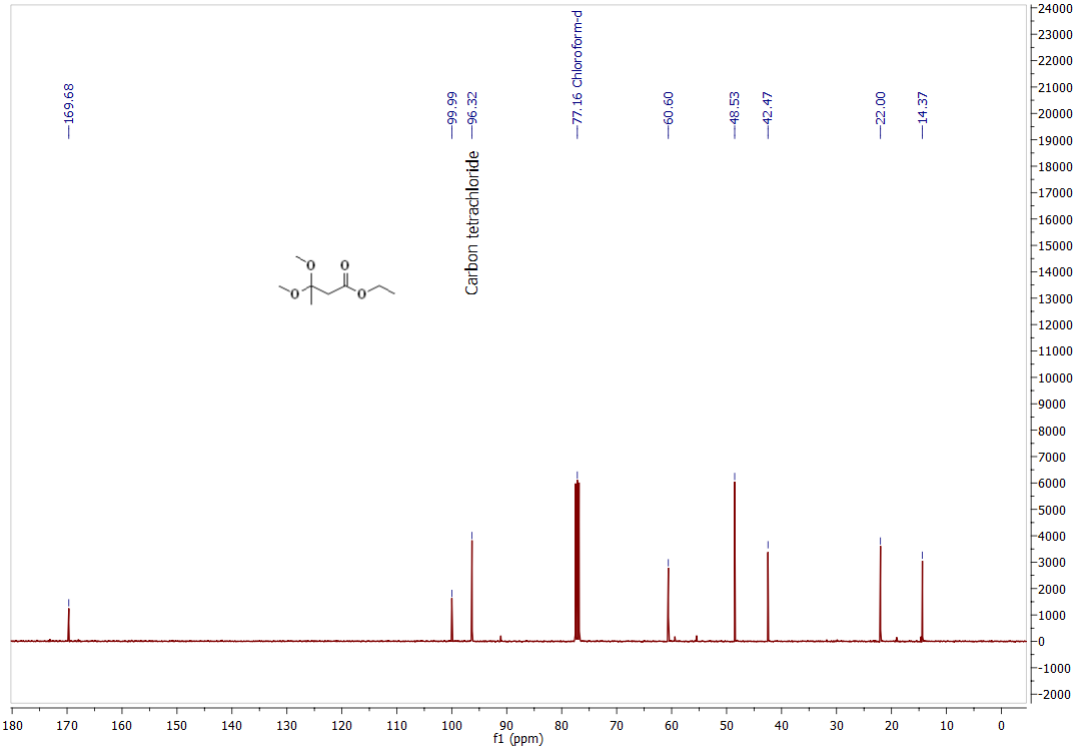


Figure 28. ^{13}C NMR of compound **62s**

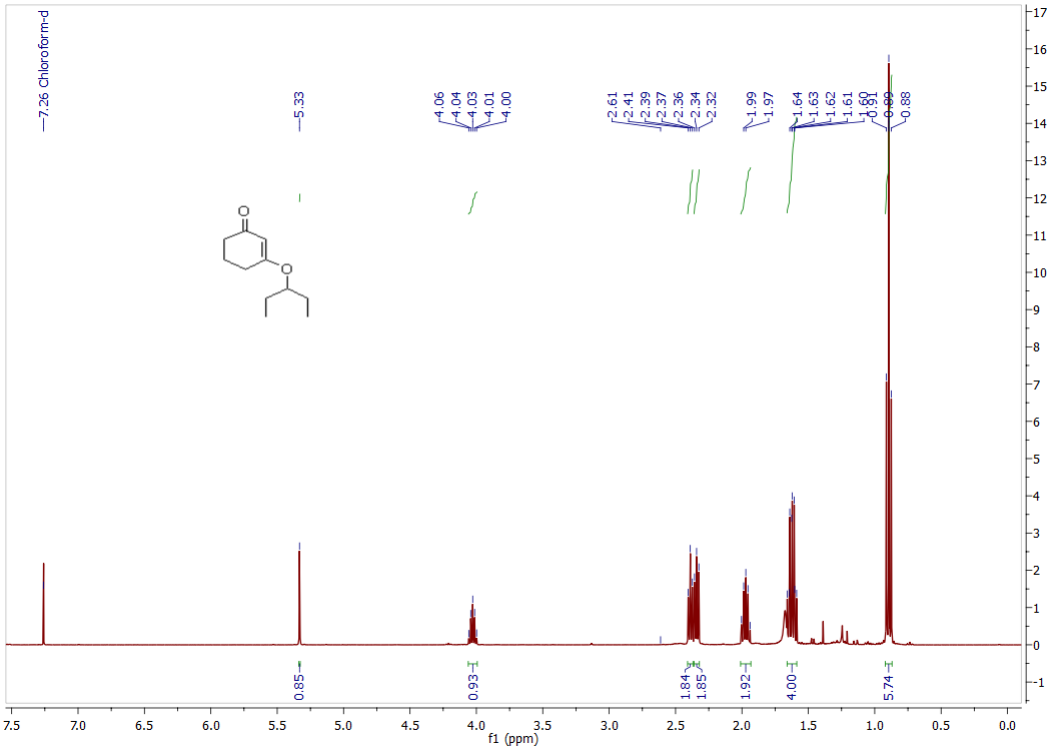


Figure 29. ^{1}H NMR of compound **62w**

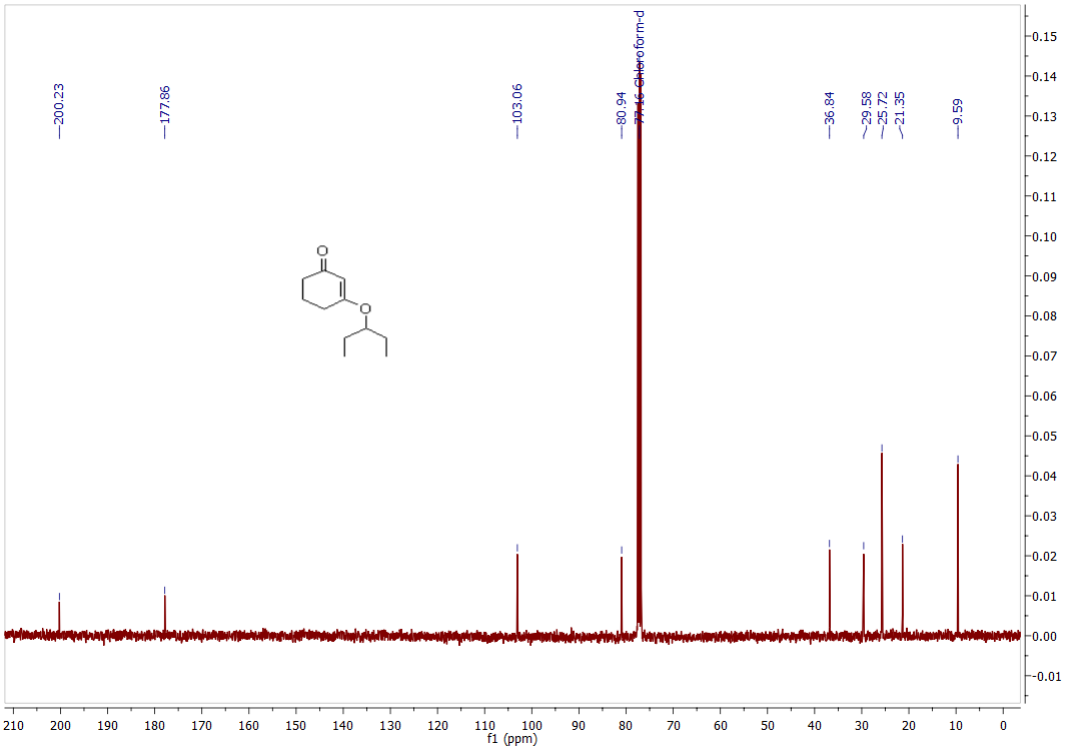


Figure 30. ^{13}C NMR of compound **62w**

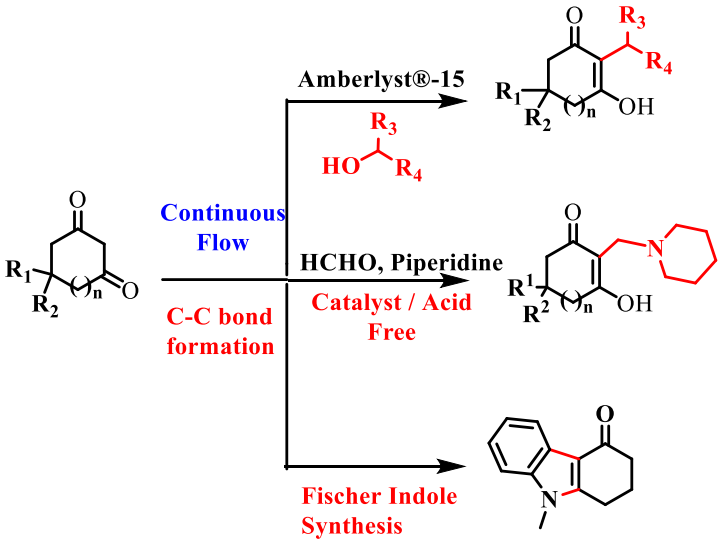
Chapter 2: Section B

C2-Alkylation of 1,3-Dicarbonyl Compounds in Continuous Flow: Applications in the Synthesis of Ondansetron, Phenoprocumon, and Warfarin

2B. C2-Alkylation of 1,3-Dicarbonyl Compounds via Continuous Flow: Applications in the Synthesis of Ondansetron, Phenoprocumon, and Warfarin

2B.1. Abstract

Continuous flow driven synthesis of various valuable fine chemicals, APIs, and drugs using inexpensive catalysts is highly attractive and desirable in the chemical industry and pharmaceutical industry. This chapter described an operationally simple and highly efficient protocol for the alkylation of the 1,3-dicarbonyl compounds using secondary alcohols in presence of amberlyst®-15 under continuous flow. A wide range of C2-alkylation of 1,3-dicarbonyl derivatives was synthesized under sustainable approach. Moreover, the amberlyst®-15 is a highly recyclable and reusable catalyst for the alkylation of 1,3-dicarbonyl compounds. Additionally, a catalyst-free condition for the Mannich reaction was developed under the continuous flow module. A continuous flow integration of Fischer indole and Mannich reaction strategy for the synthesis of ondansetron with an improved yield was demonstrated in the gram scale.



2B.2. Introduction and literature background of alkylation of 1,3-dicarbonyl derivatives

Alkylation is the fundamental organic transformation for the synthesis of different complex organic molecules.[78] The development of a scalable method for the alkylation reaction by eliminating the use of halogenated and hazardous reagents and avoiding toxic waste generation is one of the sustainable and highly demanding process for the chemical industry. In this context, the use of a heterogeneous catalyst for the alkylation of the 1,3-dicarbonyl compounds using alcohols gains the attention of the synthetic community. In particular, alkylation of 1,3-dicarbonyl compounds is a formidable challenge, not merely because of the synthetic application in natural products and the pharmaceutical industry, but also due to the fact of the difficulty in achieving selectivity in mono-alkylation over dialkylation by conventional alkylating reagents.[79] However, the resulting alkylated1,3-dicarbonyl motifs are found in biologically active compounds and commercially available drugs (Figure 31).[80]

For example, phenprocoumon **63** and warfarin **65** are commercially available drugs and both are used to prevent blood clots from forming or growing larger in blood and blood vessels. In addition, dimethyl 2-{*p*-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethoxy]benzyl}malonate **64** has the potential for the treatment of diabetes. The flocoumafen **66** and thioflocoumafe **67** are known for the suppression of LPS-induced NO generation *in vitro* and which is possible to lead compounds for anti-inflammatory agents.[80a]

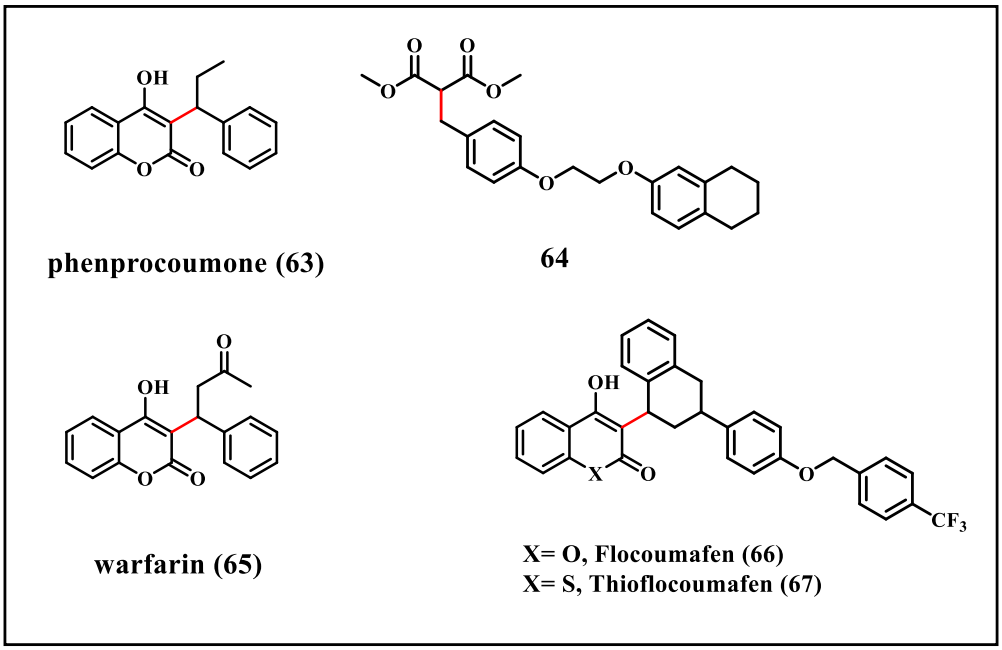
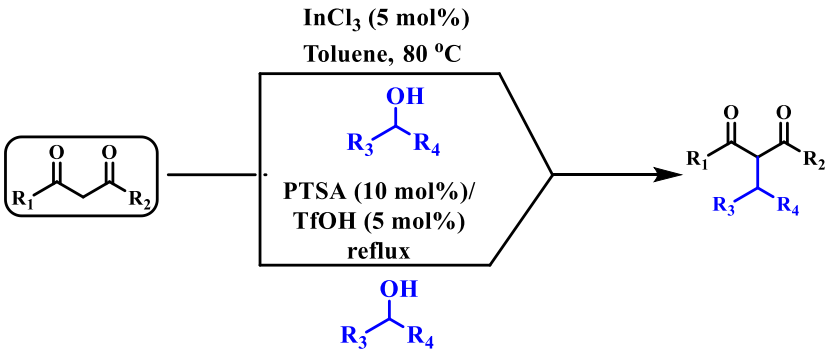


Figure 31. Biologically active compounds having 1,3-dicarbonyl motifs and can be synthesized via alkylation

Most importantly, synthetic methods for the regio- and chemoselective alkylation of the 1,3-dicarbonyl compounds are highly demanding in multi-step chemical synthesis.[81] Another problem associated in alkylation reactions was competing for C vs O-alkylation.[82] Despite this reaction being widely acclaimed in organic synthesis, direct use of alcohol as an alkylating reagent is the most attractive approach which reduces the multistep required for pre-activation and it also generates the non-hazardous environmentally benign water as a byproduct.[83] However, the direct substitution of alcohols by the nucleophile is difficult due to the poor leaving group ability of the hydroxyl group. Early examples for the alkylation of 1,3-dicarbonyl compounds used activated alcohols, for example, alkyl halides and tosylate/mesylate compounds, to make a better-leaving group for the substitution reaction.[84] Notably, transition metal complexes catalyzed propargylation/allylation/benzylation of 1,3-dicarbonyl compounds with propargylic alcohols/allylic alcohols/ secondary benzylic alcohols have been reported. Recently, in 2006 Akio Baba's and Sanz's research group reported a couple of methods for the synthesis of alkylated 1,3-dicarbonyl derivatives using $InCl_3$ and Brønsted acid (*p*-toluene sulphonic or TfOH acid) as catalyst (Scheme 36).[85, 86]



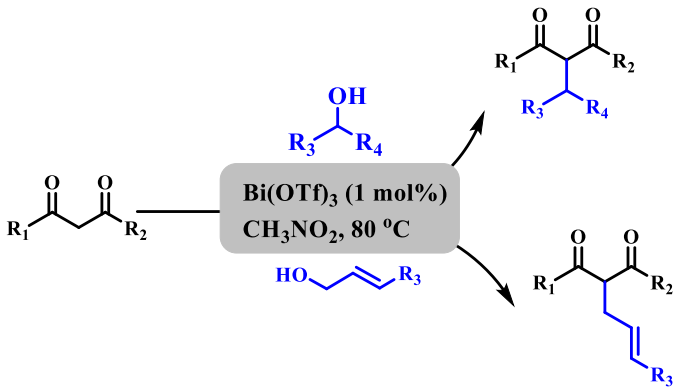
Scheme 36. Baba's and Sanz's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

In 2007, several research groups independently developed various acid catalyzed synthetic routes for the alkylation of 1,3-dicarbonyl derivatives. Kobayashi and co-workers reported surfactant type Brønsted acid catalyzed C2-alkylation of the 1,3-dicarbonyl group via nucleophilic substitution synthetic route (Scheme 37).[87]



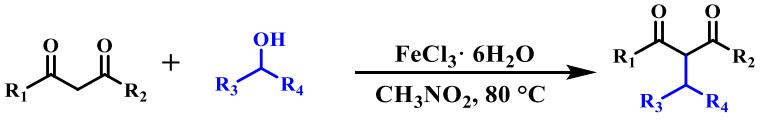
Scheme 37. Kobayashi's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

Similarly, Rueping and co-workers reported the $Bi(OTf)_3$ catalyzed synthesis of various alkylated 1,3-dicarbonyl derivatives using the 1° and 2° alcohol derivatives. This method is well tolerated with different kinds of alcohol derivatives (Scheme 38).[88]



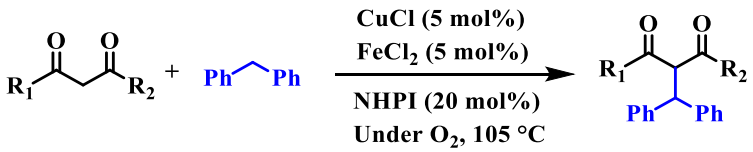
Scheme 38. Rueping's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

In the same year 2007, Beller and co-workers reported a method to achieve various C2-alkylated 1,3-dicarbonyl derivatives using $FeCl_3 \cdot 6H_2O$ catalyzed direct C-C bond construction between benzylic carbon of alcohols and 1,3-dicarbonyls derivatives (Scheme 39).[89]



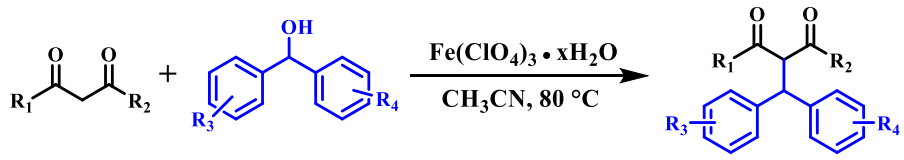
Scheme 39. Beller's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

In 2010, Li and co-workers disclosed a report for the synthesis of C2-alkylated 1,3-dicarbonyl derivatives via catalytic alkylation of benzylic C–H bonds with 1,3-dicarbonyl compounds utilizing oxygen as oxidant (Scheme 40).[90]



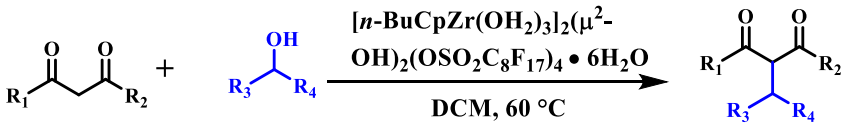
Scheme 40. Li's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

Subsequently, Kim and co-workers reported an efficient $Fe(ClO_4)_3 \cdot xH_2O$ catalyzed direct C-C bond formation between benzylic alcohols to afford C2-alkylated 1,3-dicarbonyl derivatives (Scheme 41). [91]



Scheme 41. Kim's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

In 2018, Xu, Liang, Tang, and co-workers collaboratively developed an air-stable μ^2-hydroxyl bridged cationic binuclear complexes of zirconocene perfluorooctanesulfonates and used as a catalyst for the synthesis of C2-alkylation of 1,3-dicarbonyl compounds (Scheme 42).[92]



Scheme 42: Xu's, Liang's, and Tang's approach for the C2-alkylation of 1,3-dicarbonyl compounds.

2B.3. The objective of the present work

This project aims to address the limitations of current methods for the alkylation of 1,3-dicarbonyl compounds using alcohol as the nucleophile. Existing methods have primarily focused on the use of acid catalysis under batch conditions, with the limited investigation of the reactivity of cyclic 1,3-dicarbonyl compounds by using recyclable catalysts. Furthermore, multi-component reactions involving acid or metal catalysts have been studied for the synthesis of *β*-amino carbonyl derivatives, but an acid/metal-free approach is desirable for improved environmental sustainability. To overcome these limitations, this project is proposed to the develop a continuous flow process for the alkylation of 1,3-dicarbonyl compounds using secondary alcohols. The project will investigate the reactivity of

both acyclic and cyclic 1,3-dicarbonyl compounds and explore the potential of reusable and recyclable catalysts for this transformation. In addition, the goal of this project to develop an acid/metal-free multicomponent reaction (Mannich reaction) of 1,3-dicarbonyls, aldehyde, and secondary amines for the synthesis of *β*-amino carbonyl derivatives. This green approach will improve the environmental sustainability of the synthesis process. Overall, the project aims to develop a practical and efficient continuous flow process for the large-scale production of 1,3-dicarbonyl compounds and their derivatives.

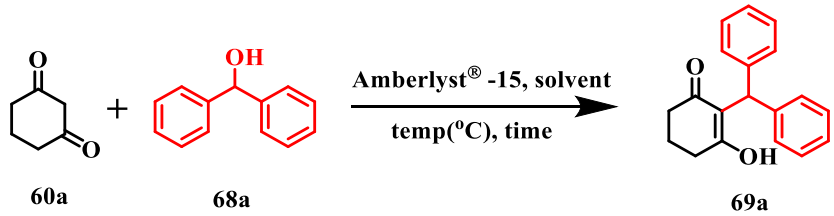
2B.4. Results and discussion

Herein, the alkylation of various 1,3-dicarbonyl compounds using secondary alcohol in the presence of amberlyst®-15 was developed under a continuous flow process. The reactivity of 1,3-dicarbonyls with diphenylmethanol derivatives is mainly associated with the concentration i.e equimolar concentration undergoes nucleophilic substitution to afford C2-alkylated product rather than *O*-alkylation, which might be due to the formation of a more stable benzylic carbocation from diphenyl methanol derivatives under acidic environment. Additionally, this application extended to synthesize various *β*-amino-1,3-dicarbonyl derivatives under continuous-flow mode via a multi-component strategy. A continuous flow synthesis of ondansetron using 1,3-dicarbonyls is also described in a short route with high yield and gram-scale demonstration. The advantages of the present approach involve environmentally benign, scalable to multigram, metal-free, and non-hazardous reactions with water as a by-product.

2B.4.1. Optimization studies for the C2-alkylation of 1,3-dicarbonyls under batch condition

Initial investigation begins with 1,3-cyclohexadione **60a** and diphenylmethanol **68a**, considered as model substrates for the reaction to achieve product **69a**. A control experiment was performed in absence of acid that failed the reaction (Table 4, entry 1). Similarly, the starting material **60a** and **68a** was remain unreacted in the reaction while the reaction performed with a stoichiometric amount of amberlyst®-15 at room temperature (Table 4, entry 2). Increasing the temperature to 80 °C leads to a 10% formation of product **69a** (Table 4, entry 3). Interestingly, 35% of the product **69a** was isolated when the reaction was carried out with equal weight proportion of amberlyst®-15 and **60a**, heated at 100 °C (Table 4, entry 4). A parallel control experiment was performed with the absence of a catalyst at 100 °C resulted in no reaction. An improvement in yield up to 50% was observed with the addition of two-fold excess of amberlyst®-15 with respect to **60a** at 100 °C (Table 4, entry 5). The role of solvent was investigated with various solvents like DMF, 1,4-dioxane, toluene, H_2O and THF mixture, and ACN. Interestingly, product **69a** was afforded in higher yield (77%) using H_2O: THF (3:1) as a solvent (Table 4, entries 6-14).

Table 4. Optimization for the C2-alkylation of 1,3-dicarbonyls under the batch.



60a 68a 69a

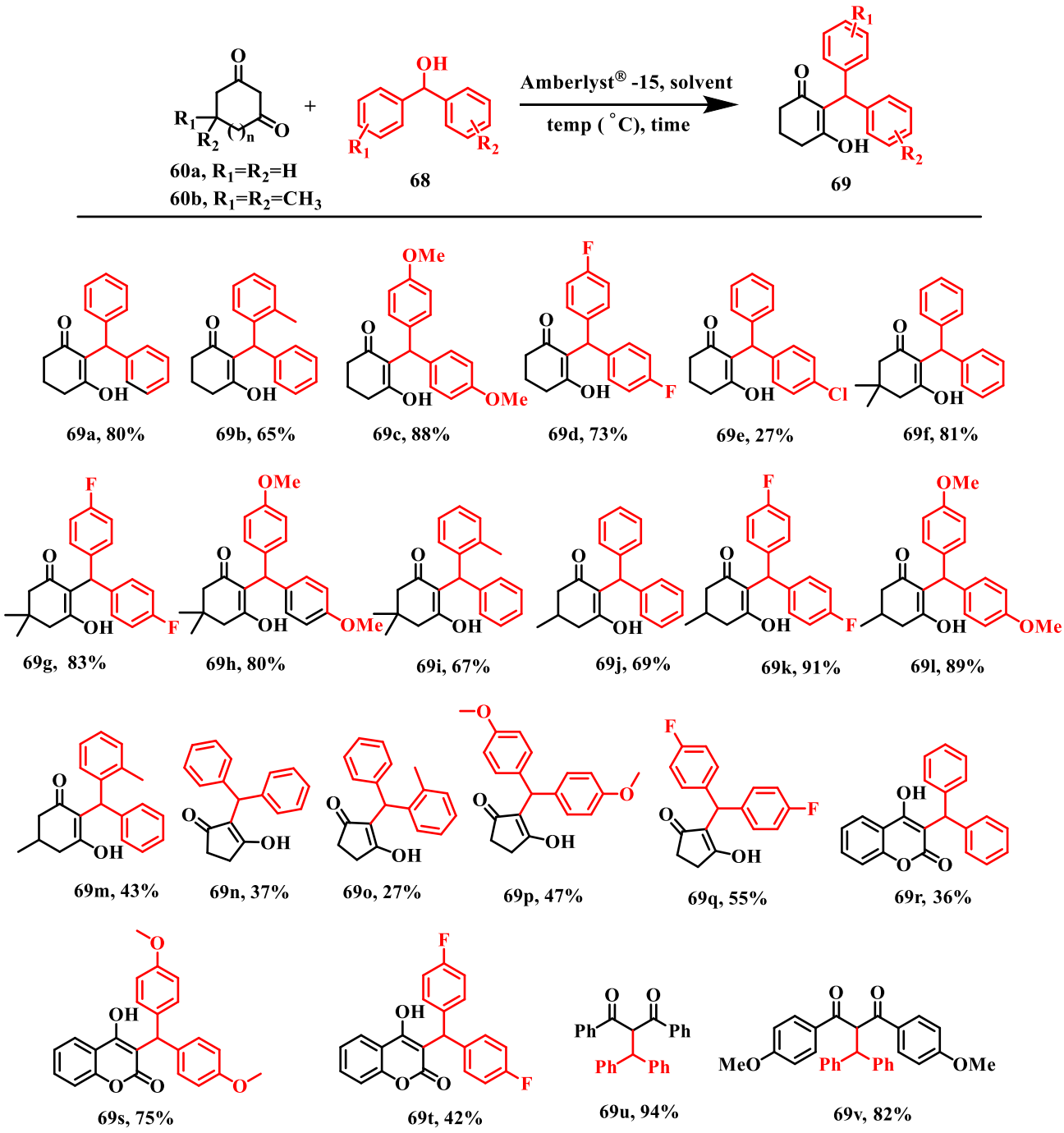
entry[a]	solvent	time (h)	temp (°C)	yield (%)
1[b]	THF	12	rt	no reaction
2[c]	THF	12	rt	no reaction
3[c]	THF	12	80	10
4[c]	THF	12	100	35
5	THF	12	100	50
6	DMF	12	100	no reaction
7	1,4-dioxane	12	100	42
8	Toluene	12	100	73
9	H_2O: THF (1:1)	12	100	32
10[c]	H_2O: THF (1:1)	12	100	20
11	H_2O: THF (3:1)	12	100	80
12	H_2O: THF (3:1)	3	100	50
13[d]	H_2O: THF (3:1)	12	100	77
14[e]	H_2O: THF (1:1)	12	100	30
15	ACN	8	100	75
16	ACN	5	100	71
17	ACN	3	100	65
18	ACN	12	100	82

[a]**Reaction conditions**: **60a** (0.5 mmol), **68a** (0.6 mmol), and amberlyst®-15 (amberlyst®-15 : **60a** (2 : 1 , w/w ratio)) was stirred in a vial. [b]absence of catalyst; [c] amberlyst®-15 : **60a** (1 : 1, w/w ratio). [d]**60a** (0.5 mmol). [e] amberlyst®-15: **60a** (2.5 : 1, w/w ratio).

Finally, ACN solvent turn out to be the best reaction medium for this transformation. Moreover, upon decreasing reaction time up to 3 hours, a significant decrease in yield (65%) was observed (Table 4, entries 15-17). The best yield of **69a** i.e., 82% was obtained by using a 2:1 ratio of amberlyst®-15 and 1,3-cyclohexadione in ACN at 100 °C for 12 hours (Table 4, entry 18).

2B.4.2. The substrate scope for C2-alkylated 1,3-dicarbonyl compounds under batch

Having the optimal condition in hand, the interest went to explore the C–C bond formation using various 1,3-dicarbonyl derivatives and secondary alcohols (Scheme 43). Thus, various substituted benzhydrol with cyclohexane 1,3-dione was subjected to the optimized conditions afforded the C2-substituted cyclohexane-1,3-dione derivatives **69b–e** in moderate to good yield. The reaction of 5,5-dimethylcyclohexane-1,3-dione **60b** or 5-methylcyclohexane-1,3-dione **60f** with secondary alcohols **64** afforded the respective C2-alkylated products **69f–m** in very good yield. Furthermore, C2-alkylation was also successful with cyclopentane-1,3-dione to afford the corresponding products **69n–q** in moderate yield. Next, the substrate scope for the alkylation reaction was extended with coumarin derivatives and acyclic-1,3-dione with various secondary alcohols to afford libraries of C2-alkyl-1,3-carbonyl derivatives **69r–v** (Scheme 43). Although these reactions worked well with the secondary alcohols derived from diphenylmethane, other activated alcohols based on the allylic and propargylic secondary alcohol derivatives were not successful. This might be due to the presence of the acid-sensitive olefin interfering with the reactivity of the alcohol protonation to form the electrophile.



Reaction conditions: 1,3-diketone (0.5 mmol), alcohol (0.6 mmol), amberlyst®-15 (2: 1 w/w with 1,3-diketone) and ACN (3 mL) were heated in a sealed tube at 100 °C for 12 h.

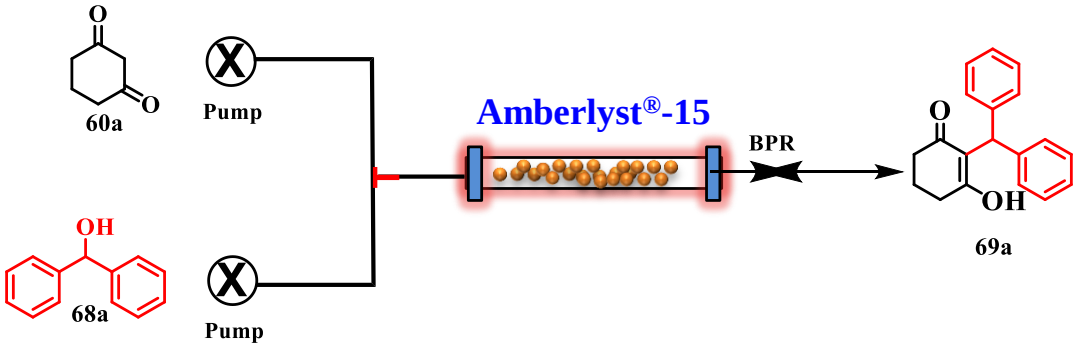
Scheme 43. Substrate scope for C2-alkylation of 1,3-dicarbonyl under the batch condition

2B.4.3. Optimization studies for the C2-alkylation of 1,3-dicarbonyls under the continuous flow

Next, this reaction was integrate under the continuous flow module. Initially, the reaction was performed at room temperature with a flow rate of 0.1 mL min^{-1} and 0.1 M concentrations of each reactant showed no reaction (Table 5, entry 1). The 0.1 M solution of **60a** and 0.12 M solution of **68a** was then flown with flow rates of 0.1 mL min^{-1} of each solution through the pre-packed amberlyst®-

15 bed reactor heated at 80 °C and afforded 50% of product **69a** (Table 5, entry 2). The excellent yield (96%, Table 5, entry 3) was obtained by increasing the reactor temperature to 100 °C with a t_R = 18 min. To get the target product in a shorter reaction time, solutions of **60a** (0.1 M in 5 mL ACN) and **68a** (0.12 M in 5 mL ACN) were flown through a packed bed reactor with flow rates of 0.15 mL min^{-1} and 0.2 mL min^{-1}, respectively, at 100 °C. This reaction produced 78% and 73% of the yield of product **69a** with a retention time of 12 and 9 min respectively (Table 5, entries 4 and 5). Other solvents such as THF and THF/H_2O under this optimized condition resulted in poor yield (Table 5, entries 6 and 7). Comparatively, the flow condition became superior over the batch for the formation of product **69a**, which resulted in increasing the efficiency of the reaction by rapid reactions in t_R = 18 min and increase the yield to 96%.

Table 5. Optimization for the C2-alkylation of 1,3-dicarbonyls under the continuous flow

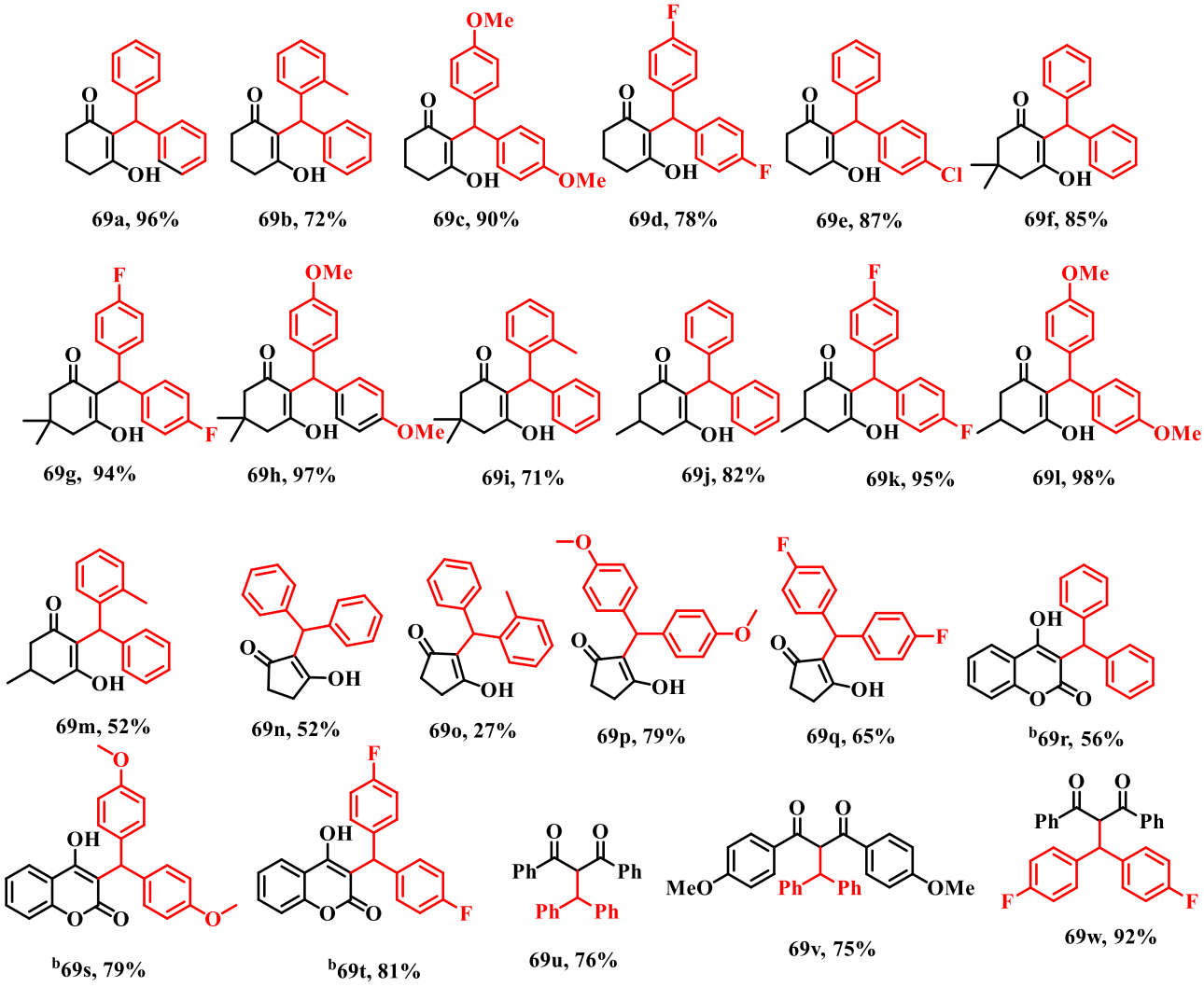


entry[a]	solvent	residence time (t_R min)	temp. (°C)	yield of 69a (%)
1	ACN	18	rt	no reaction
2	ACN	18	80	50
3	ACN	18	100	96
4[b]	ACN	12	100	78
5[c]	ACN	9	100	73
6	THF	18	100	50
7	THF: H_2O (9:1)	18	100	no reaction

[a]**Reaction Conditions**: The solution of **60a** (0.1 M) and **68a** (0.12 M) in ACN were flown through Omnifit® (6.6 × 150 mm) pre-packed bed (amberlyst®-15 filled up to 5 cm, 1000 mg) at 100 °C with a 0.1 mL/min flow rate of each solution under 3.5 bar pressure; [b]flow rate of each solution was 0.15 mL/min; [c]flow rate of each solution was 0.2 mL/min.

2B.4.4. The substrate scope of C2-alkylated 1,3-dicarbonyl compounds under continuous flow

As a result of this improved efficiency under continuous flow, an optimized condition was subjected to the various substrate scope (Scheme 44). The flowing solution of cyclohexane-1,3-dione (**60,** 0.1 M) and various secondary alcohols **68** (0.12 M) into the amberlyst®-15 bed, under optimized condition, resulted in the respective alkylated product **69b–e** in an excellent yield. Similarly, other dicarbonyl compounds such as 5,5-dimethylcyclohexane-1,3-dione **60b** or 5-dimethylcyclohexane-1,3-dione **60f** with secondary alcohols were subjected to continuous flow and afforded the products **69f–m** up to 98% yield. When this flow condition was performed with cyclopentane-1,3-dione **60d**



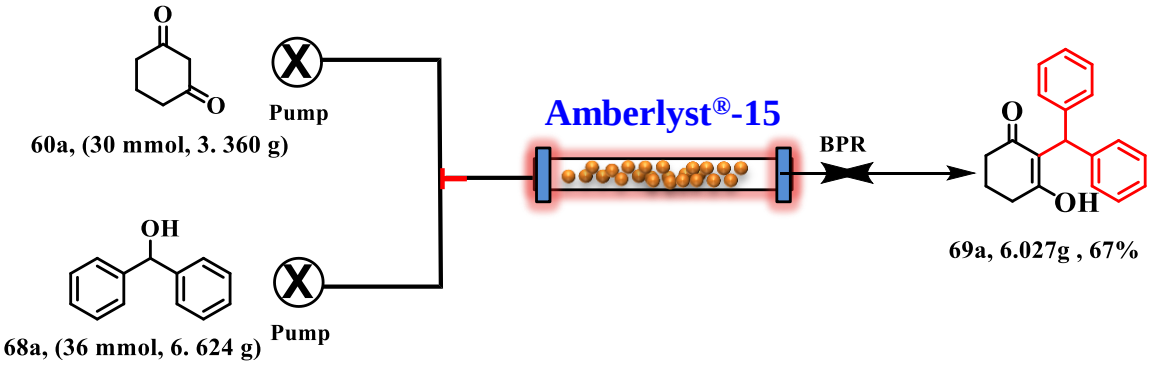
[a]**Reaction conditions**: the solution of **60a** (0.1 M) and **68a** (0.12 M) in ACN were flown through Omnifit® (6.6 × 150 mm) prepacked bed (amberlyst®- 15 filled up to 5 cm, 1.0 g) at 100 °C with a 0.1 mL min^{-1} flow rate of each solution under 3.5 bar pressure; [b]ACN : THF (9: 1) was used as a solvent.

Scheme 44. Substrate scope for C2-alkylation of 1,3-dicarbonyl under continuous flow

with several secondary alcohols, furnished the respective products **69n–q** in t_R = 18 min duration (Scheme 44). Further, the flow reaction of 4-hydroxycoumarin **60g** with secondary alcohols provided therapeutically[93] important products **69r–t** in very good yield. The acyclic 1,3-diones also successfully reacted with secondary alcohols under the continuous flow to afford the respective products **65u–w** in very good yield.

2B.4.5. Long-time experiment and gram-scale synthesis under continuous flow

It is known that there is a significant loss in the activity of amberlyst®-15 for the other chemical transformation.[94] Hence, to know the stability and efficiency of the catalyst for this reaction, a long-time experiment for up to 50 h was performed under continuous flow and 67 % (6.027 g) of **69a** was isolated by utilization of 3.360g of **60a** and 6.624g of **68a** continuously in 50 h (Scheme 45). This study showed that the efficiency of the catalyst decreased drastically after 10 h to give a 50% of conversion (Figure 32). The decrease in the yield was observed due to the formation of water in the reaction, which may be accumulated in the porous amberlyst®-15 and result in lower activity.



Scheme 45. Gram-scale synthesis of C2-alkylation of 1,3-dicarbonyl under continuous flow

Next, the periodically reactivation of the catalyst and continuously use it for a longer period was performed. Consequently, the periodic washing and drying of the amberlyst®-15 packed bed reactor are required for better activity. Interestingly, the reactivity of the catalyst was regained after reactivation of amberlyst®-15 using 0.1 M of HCl solution in methanol and repeatedly washing with pure methanol. Further, the conversion of starting material was periodically monitored by NMR (Figure 33). A multi-gram scale for the synthesis of **69a** was demonstrated under continuous flow and resulted in 85% yield i.e., 5.7 g after 40 h by the periodic activation of amberlyst®-15 (Figure 34).

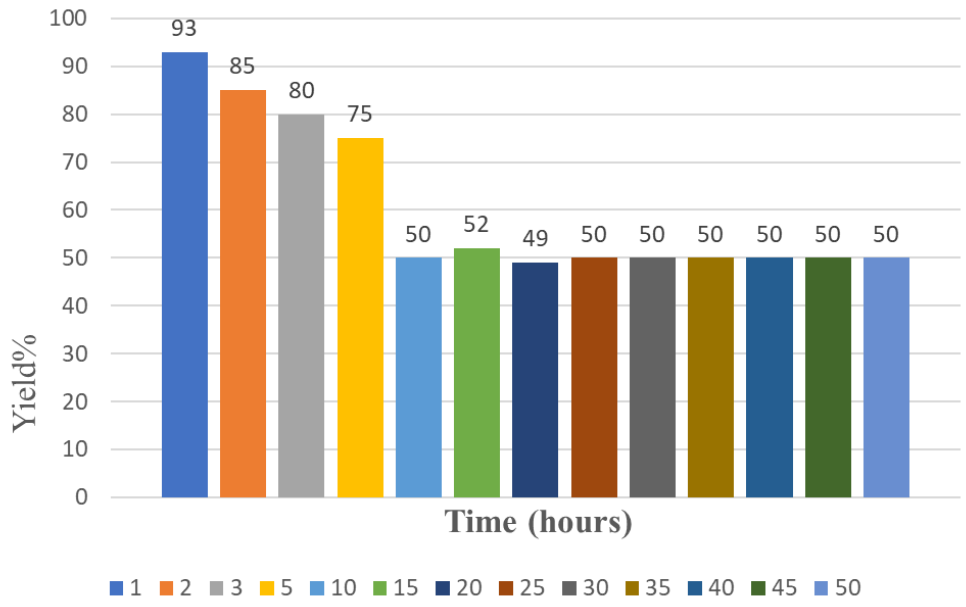


Figure 32. Long time experiment without reactivating the catalyst

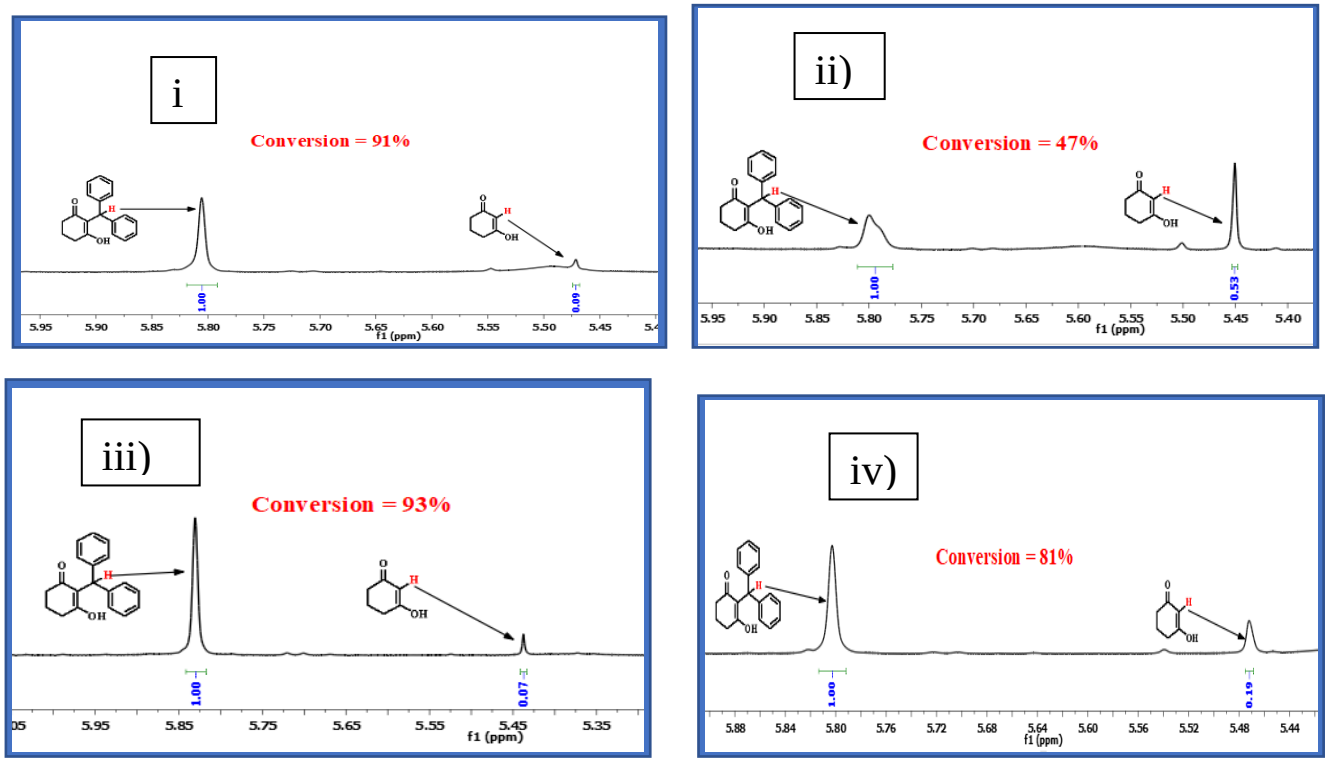


Figure 33. ^{1}H-NMR monitoring reaction mixture over long run experiments: i) After 2 h; ii) After 10 h; iii) After 11 h; iv) After 15 h before washing of amberlyst®-15

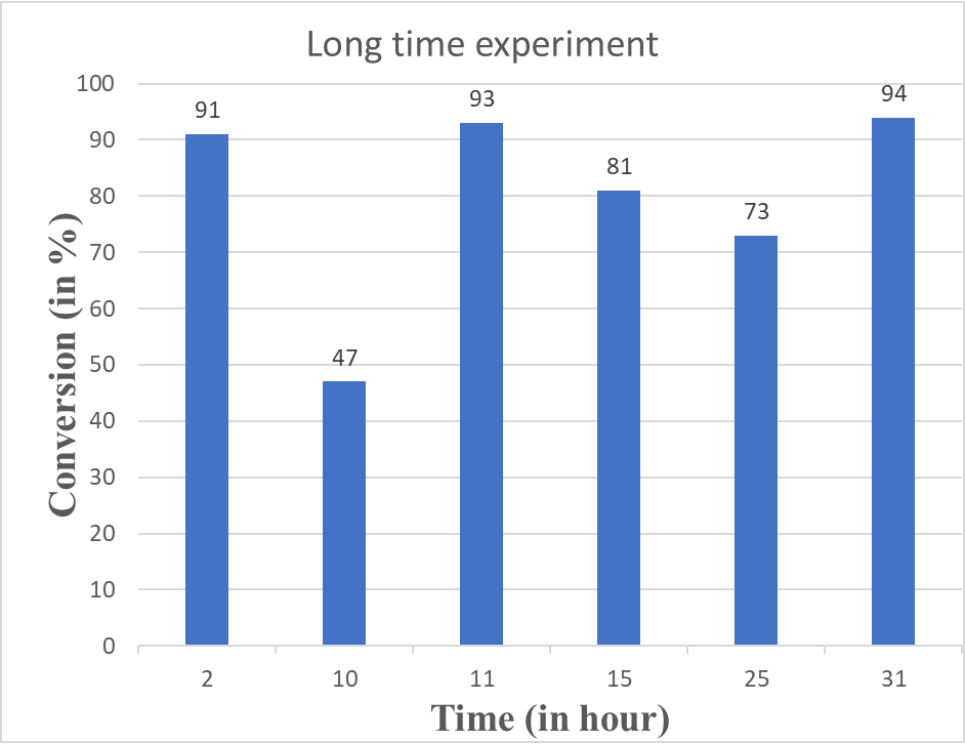
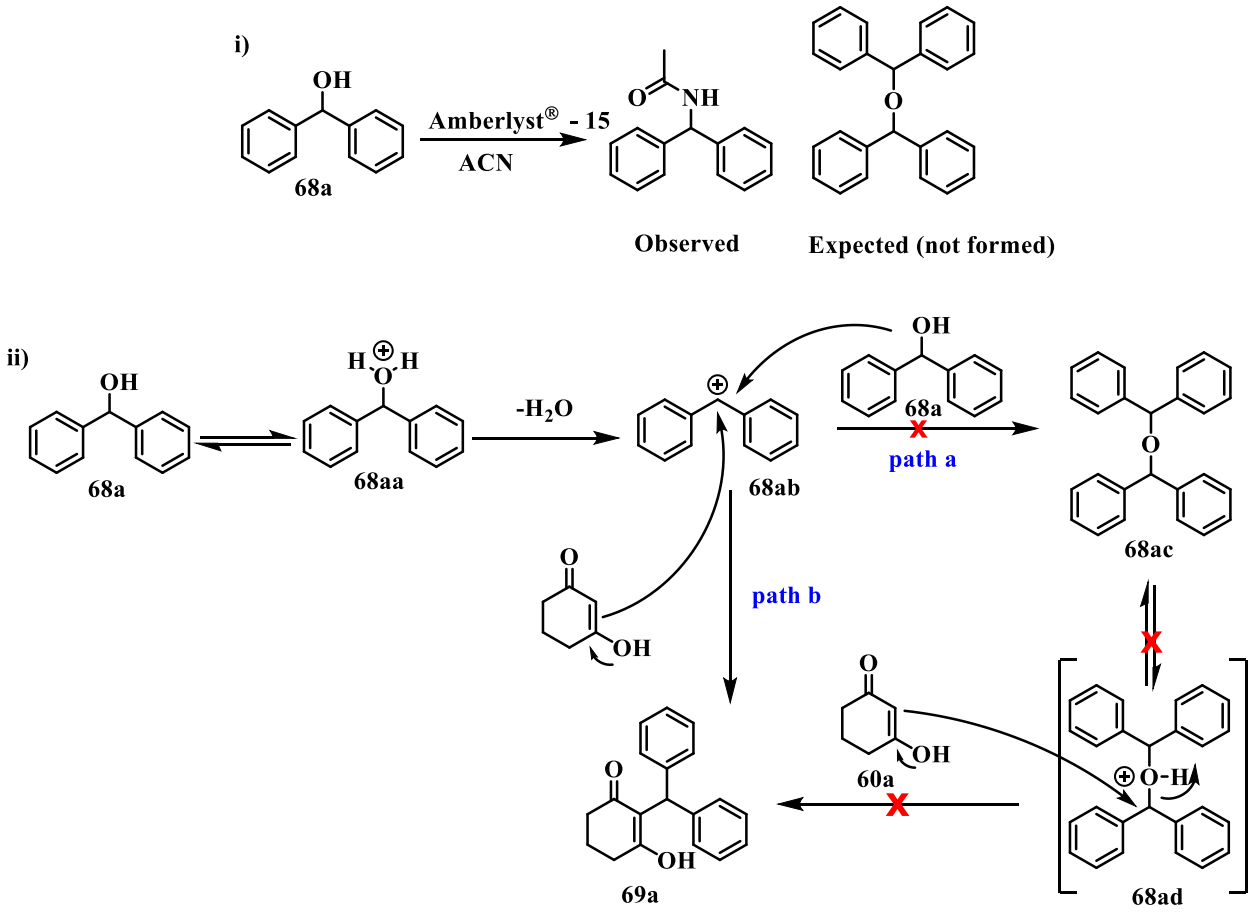


Figure 34. Long-time experiment for the synthesis of **69a** under continuous flow with periodic reactivation of the catalyst

2B.4.6. Mechanistic path of the C2-alkylation of 1,3-dicarbonyls

With the knowledge of the previous report, the possible mechanism of C2-alkylation of 1,3-dicarbonyl was proposed in scheme 46 (ii). Initially, the protonation of **68a** provides **68aa**. The removal of water from intermediate **68aa** resulted in the formation of carbocation intermediate **68ab**. Next, the formation of the **69a** may proceed via path a or path b. In path a the oxygen atom of another molecule of **68a** reacts with the in situ generated carbocation intermediate **68ab** and provides the ether **68ac**. Further, the protonation of intermediate **68ac** gives the intermediate **68ad**. The nucleophilic carbon of **60a,** i.e**.** C2-carbon reacts with the benzylic carbon of intermediate **68ad** and gives the product **69a**. Further to confirm the reaction path a, a control experiment has been performed (Scheme 46 (i)) in absence of **60a** to isolate the intermediate **68ad**. But any trace amount of formation of the intermediate **68ad** was not observed. This result confirms the reaction proceeds via path b, where the nucleophilic C2-carbon of **60a** directly reacts with benzylic carbocation intermediate **68ab** and gives the desired product **69a**.

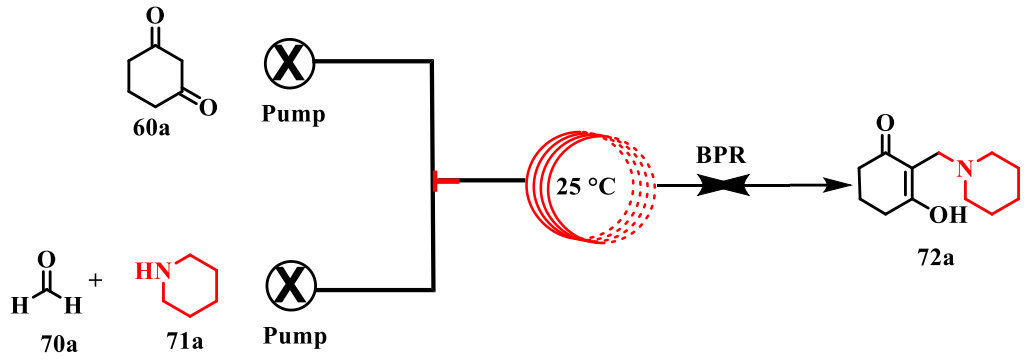


Scheme 46. i) Control experiment for the mechanism; ii) Plausible mechanism of C2-alkylation of 1,3-dicarbonyl compound

2B.4.7. Mannich reaction using 1,3-dicarbonyls, aldehydes, and amines under continuous flow

Next, the focus was on developing the continuous flow addition of enolate, with the iminium ion generated by the reaction of the formaldehyde with secondary amine (Mannich reaction). Thus, 0.1 M cyclohexane-1,3-dione **60a** in ACN (0.1 mL) and 0.12 M of formaldehyde **70a** with piperidine **71a** (0.12 mL) were pumped into the 5 mL SS tubular reactor at room temperature results in 100% conversion with 85% isolated yield of product **72a** in the absence of any acid source (Table 6, entry 1). Increasing the flow rate of the solutions of the reaction mixture to 0.15 mL furnished similar results (Table 6, entry 2). Further, increasing the flow rate to 0.2 mL/min of each solution provides a decrease in the conversion and yield of product **72a** (Table 6, entry 3). Similarly, an increase in the concentration of the reactant under an optimized flow rate (0.15 mL each) provided a lower conversion and significantly retarded the yield of product **72a** (Table 6, entry 4). The continuous flowing of the reaction mixture for 40 h resulted in 10.6 g of the product **72a** in 83% yield.

Table 6. Optimization for the Mannich reaction under flow.

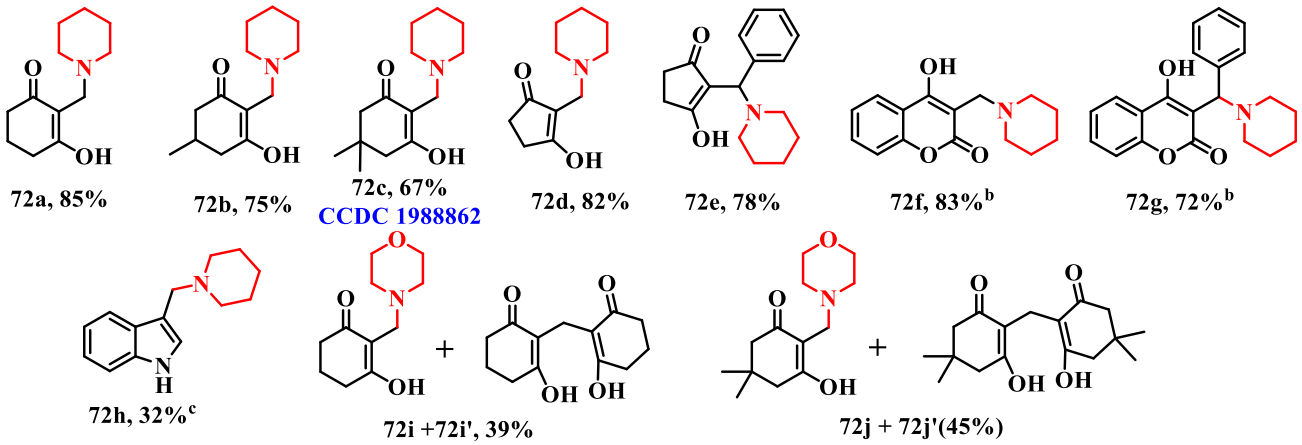


entry[a]	conc. of 60a (M)	conc. of 70a + 71a (M)	flow rate (mL /min each)	time (t_R, min)	yield of 72a (%)
1	0.1	0.12	0.1	25	100
2	0.1	0.12	0.15	16	100
3	0.1	0.12	0.2	12.5	95
4	0.2	0.2	0.15	16	80

[a]**Reaction conditions**: A solution of 1,3-diketone (**60a**, 0.1 M) and formaldehyde (**70a**) + piperidine (**71a**, 0.12 M) in ACN were flown through a 5 mL SS tubular reactor (Vaportec R-series) at 25 °C.

2B.4.8. The substrate scope for Mannich reaction using 1,3-dicarbonyls, aldehydes, and amines under continuous flow

To demonstrate the broad substrate scope, several 1,3- dicarbonyl (**60**) derivatives were reacted with aldehyde and amine under the flow-optimized condition. As a result, several series of *β*-amino-1,3-dicarbonyl derivatives **72b–d** were obtained rapidly under the continuous flow condition in excellent yield (Scheme 47). Further scope of this method was elaborated with the benzaldehyde and piperidine, resulting in the Mannich adduct **72e** in 78% yield with t_R = 16 min (Scheme 47). Application of this process was also extended with a coumarin derivative to afford the respective products **72f**, **72g** in 83% and 72% yield. In the case of indole when this Mannich reaction was performed, a lower yield of product **72h** was observed in 4 h at 80 °C. Other secondary amines (such as morpholine (**71b**) and diethyl amine (**71c**)) were also subjected under the above optimized reaction condition, resulting in the unstable Mannich addition product, which rapidly underwent dimerization under the experimental condition (**72i** + **72i′**, **72j** + **72j′**, Scheme 47).



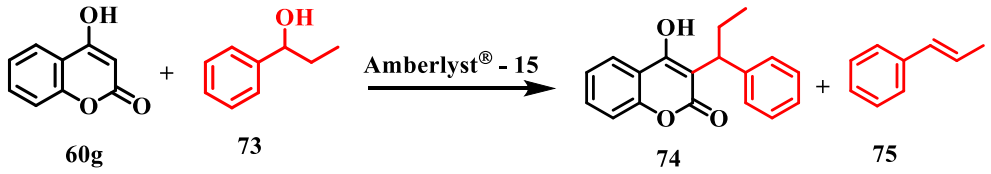
[a]**Reaction conditions**: A solution of 1,3-diketone **60** (0.1 M) and aldehyde **70** + piperidine **71** (0.12 M) in ACN were flown through a 5 mL SS-coil reactor (Vaportec R-series) at 25 °C.

Scheme 47. Substrate scope for Mannich reaction under continuous flow.

2B.4.9. Continuous flow approach for the synthesis of phenprocoumon

Phenprocoumon is a long-acting blood thinner used to treat thromboembolic disorders, thrombophilia, and atrial fibrillation with artery embolisms. It is also used for the long-term treatment of myocardial infarction with an increased risk of thromboembolism.[95] Next, the focus is to synthesize phenprocoumon using the developed method. According to the optimized reaction conditions for the alkylation of 1,3-diones, investigation in batch condition was initiated. Initially, the trace of the amount of product **74** was observed when **60g** and **73** were heated at 100 °C for 12 h (Table 7, entry 1). Moreover, various solvents such as THF, DCE, CH_3NO_2, and DME were screened to achieve a higher yield of the desired product **74**. This resulted DCE as the best medium for the reaction and providing 35% of the desired product (Table 7, entries 2-5). With this optimization, the reaction was integrated with the continuous flow module. Since the **60g** is not soluble in the DCE, the investigation started with a mixture of solvents, and several parameters were screened to achieve the desired product in a higher yield. The results of this reaction under continuous flow were summarized in Table 7 (entries 6-9). However, the synthesis of phenprocoumon under continuous flow was remained unsuccessful.

Table 7. Optimization for the synthesis of phenprocoumon.



entry	substrate 60g (mmol)	substrate 73 (mmol)	Solvent	temp (°C)	Time	Yield%	
						74	75
Batch condition[a]							
1[a]	0.5	0.6	ACN	100	12 h	trace	
2[a]	0.5	0.6	THF	100	12 h	-	45
3[a]	0.5	0.6	DCE	100	12 h	35	21
4[a]	0.5	0.6	CH_3NO_2	100	12 h	20	21
5[a]	0.5	0.6	DME	100	12 h	No reaction	
Continuous flow condition[b]							
6[b]	0.1M	0.12M	DCE: THF (4:1)	100	8.6 min	-	41
7[b]	0.1M	0.12M	DCE: THF (4:1)	100	17.2 min	trace	52
8[b]	0.1M	0.12M	DCE: THF (4:1)	0	8.6 min	-	41
9[b]	0.1M	0.12M	THF:CH_3NO_2 (4:1)	100	17.2 min	No reaction	

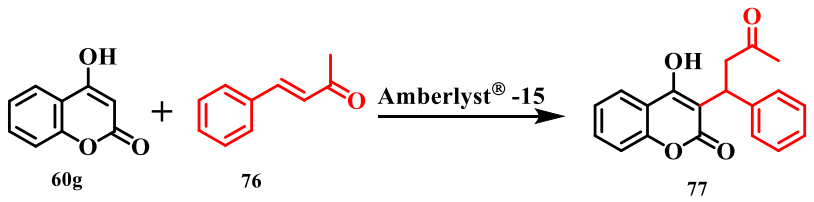
Reaction conditions: [a]batch condition: **60g** (0.5 mmol) and **69** (0.6 mmol) were taken in a resealable vial with mentioned solvent and amberlyst®-15 (2:1, w/w with **60g**) and heated the reaction mixture at 100 °C for 12 h; [b]flow condition: the solution of **60g** (0.1 M) and **73** (0.12 M) with mentioned solvent were flown through pre-packed (amberlyst®- 15 filled up to 5 cm, 1.0 g) Omnifit® (6.6 × 150 mm) bed heated at 100 °C.

2B.4.10. Continuous flow approach for the synthesis of warfarin

The developed method was utilized to synthesize warfarin, a commercially available drug used to prevent blood clots such as deep vein thrombosis and pulmonary embolism and to prevent stroke in people who have atrial fibrillation, valvular heart disease, or artificial heart valves.[96] Initially, the reaction was performed in the batch condition and the results of the reaction for the synthesis of warfarin were described in table 8. Next, 45% of desired product was obtained, when the reaction was performed at 100 °C by treating **60g** with **76** in presence of amberlyst®-15 for 24 h (Table 8, entry3). With this optimization, the reaction was transfer into the continuous flow module. The reaction was performed under continuous flow by varying different parameters, but unable

to synthesize the warfarin under continuous flow (Table 8, entries 4-7).

Table 8. Optimization for the synthesis of warfarin.



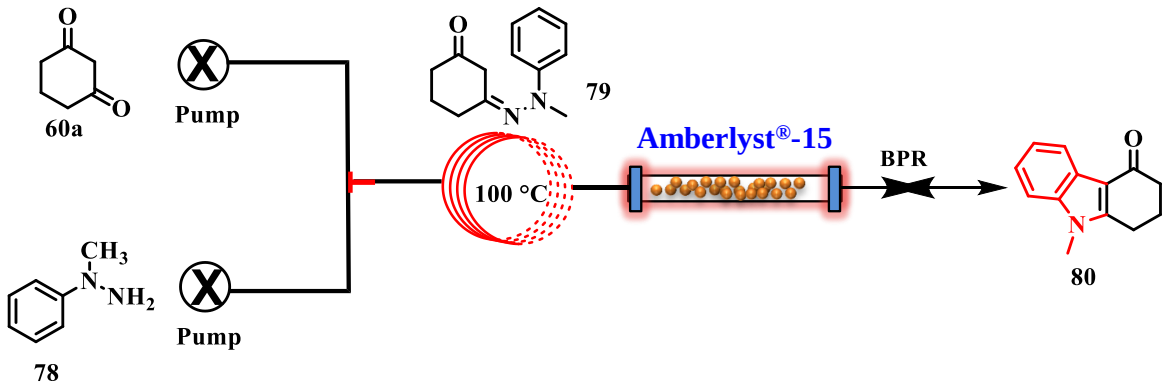
entry	substrate 60g (mmol)	substrate 76 (mmol)	solvent	temp (°C)	time	Yield (%)
Batch condition[a]						
1[a]	0.5	0.6	THF	100	24 h	11
2[a]	0.5	0.6	THF	120	24 h	11
3[a]	0.5	0.6	ACN	100	24 h	45
Continuous flow condition[b]						
4[b]	0.1M	0.12M	ACN: THF (4:1)	100	8.6 min	NR
5[b]	0.1M	0.12M	ACN: THF (4:1)	100	17.2 min	NR
6[b]	0.1M	0.12M	ACN: THF (4:1)	120	17.2 min	NR
7[b]	0.1M	0.12M	DMF	100	17.2 min	NR

Reaction conditions: [a]batch condition: **60g** (0.5 mmol) and **76** (0.6 mmol) was taken in resealable vial with mentioned solvent and amberlyst®-15 (2:1, w/w with **60g**) and heated the reaction mixture at 100 °C for 12 h; [b]flow condition: the solution of **60g** (0.1 M) and **76** (0.1 M) with mentioned solvent were flown through pre-packed (amberlyst®- 15 filled up to 5 cm, 1.0 g) Omnifit® (6.6 × 150 mm) bed heated at mentioned temperature; NR = no reaction.

2B.4.11. Continuous flow synthesis of the ondansetron precursor

Ondansetron is a commercially available drug used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery.[97] Ondansetron consists of two heterocyclic cores i.e., carbazole and 2-methylimadazole. In this context, the carbazole intermediate **76** was synthesized with the gram-scale using the Fischer indole strategy under continuous flow in high yield. Initially, the control experiment was performed by directly pumping 0.1 M of cyclohexadione **60a** and 0.12 M of *N*-methylphenylhydrazine **78** to the bed reactor in the absence of the amberlyst®-15 catalyst, as well as the absence of the ss-coil reactor, and resulted in no reaction (Table 9, entry 1 and 2). Several reactions were performed by varying different reaction parameters to obtain compound **80** in higher

Table 9. Optimization for the synthesis of carbazole.

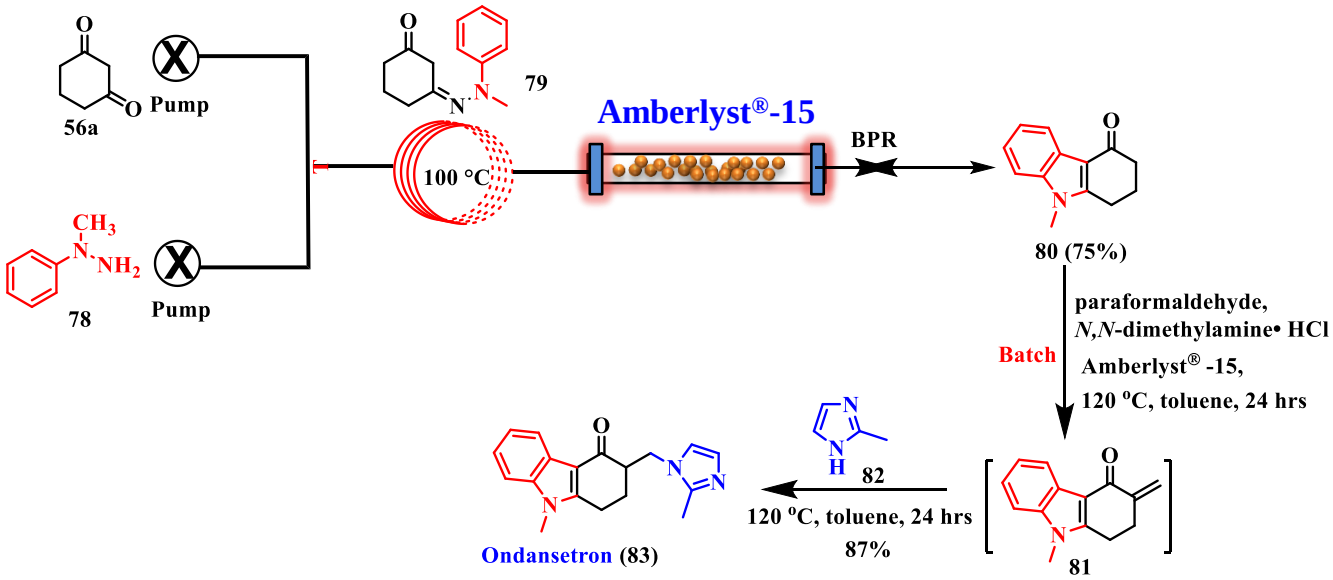


entry[a]	conc.		flow rate (mL/min each)	temp. of coil reactor (°C)	yield of 79 (%)	temp. of bed reactor (°C)	yield of 80 (%)
	60a (M)	78 (M)					
1	0.1	0.12	0.1	-	-	rt	-
2[b,c,d]	0.1	0.12	0.1	-	-	110	-
3	0.1	0.12	0.1	rt	-	-	-
4	0.1	0.12	0.1	60	Trace	-	-
5	0.1	0.12	0.1	80	35	-	-
6	0.1	0.12	0.1	100	82	rt	-
7	0.1	0.12	0.2	100	Trace	-	-
8	0.1	0.15	0.1	100	90	110	75

[a]**Reaction conditions**: The solution of 1,3-cyclohexadione **60a** in water and *N*-methylhydrazine **78** in ethanol were flown through 10 mL SS coil reactor at 100 °C followed by the pre-packed bed (amberlyst®-15 filled up to 7 cm, 1400 mg) at 110 °C with a 0.1 mL/min flow rate of each solution under 3.5 bar pressure; [b]DMF; [c]DMSO; [d]1,4-dioxane.

yield via the intermediate **79** (Table 9, entries 2-7). The best optimized condition was obtained by cyclohexane-1,3-dione **60a** (0.1 M in water) and *N*-methyl phenylhydrazine **78** (0.1 M in ethanol), and flown at a flow rate of 0.1 mL min^{-1} of each solution of the reactant into SS tubular reactor heated at 100 °C. Subsequently, the reaction mixture was passed through an Omnifit® (6.6 × 150 mm^2) pre-packed with amberlyst®-15 at 110 °C. The solvent was evaporated and the crude residue was recrystallized to afford the 9-methyl-1,2,3,9-tetrahydro-4Hcarbazol-4-one **80** in 75% yield (Table 9, entry 8). Next, a multi-component reaction was performed using the carbazole derivative **80**, paraformaldehyde, and *N*, *N*-dimethyl amine·HCl under batch conditions. This reaction mixture was

heated in the presence of amberlyst®-15 at 120 °C for 24 h. Subsequently, 2-methyl imidazole **82** was added to the reaction mixture and heated at 120 °C for 24 h to furnish the commercially available drug ondansetron **83** with 87% yield after recrystallization. The overall yield of this route is 65%, which is higher than the previously available route for the ondansetron drug. A gram-scale synthesis of this reaction was performed and afforded an 82% yield of **83** (Scheme 48).



Scheme 48. Amberlyst®-15 mediated synthesis of ondansetron

2B.5. Conclusions

In summary, a metal-free approach for the synthesis of C2- alkylated 1,3-dicarbonyl derivatives was developed using an environmentally benign amberlyst®-15 medium under a batch/continuous flow condition in an excellent yield with functional group tolerance. A gram-scale synthesis was demonstrated up to 6.5 g under the continuous-flow mode. An acid/metal-free condition for the Mannich reaction was established by incorporating 1,3-dicarbonyls, aldehyde, and a secondary amine under continuous flow for the first time. A synthetic application was demonstrated for the synthesis of commercially available drugs phenprocoumon, warfarin, and ondansetron drug. The ondansetron drug was successfully synthesized with a multi gram scale under the semi continuous flow for the first time.

2B.6. Experimental section and characterization data

2B.6.1. General information and data collection

Commercially available reagents and solvents were used for the starting material without further purification. All the alcohols and 1,3-dione were purchased from Sigma-Aldrich, while amberlyst®-15 from SD Fine-Chem. Visualization was accomplished with UV light and/or PMA stain followed by heating. Column chromatographic separations performed over 100-200 Silica-gel. The flow chemistry experiments were carried out on Vapourtec R-series with a glass column (Omntifit, 6.6 x 150 mm) for the heterogeneous system, while homogeneous reactions were performed in SS coiled tubular reactor. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker 400 MHz and JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. High-resolution mass spectra were obtained with waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-II Fourier transform infrared spectrometer

2B.6.2. Experimental procedure

A) General procedure for the synthesis of product 69 by using amberlyst®-15 under batch condition

The 1,3-dione (**60**, 0.5 mmol), amberlyst®-15 (2:1 amberlyst®-15:1,3-dione, w/w ratio) and secondary alcohol (0.6 mmol) were charged to a 20 mL glass tube followed by 3 mL of acetonitrile. The tube was sealed using a crimper and the reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture solution was decanted into a round bottom flask. The amberlyst®-15 was washed 5 times with DCM and added to the same round bottom flask. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography purification (EtOAc: *n*-hexane = 20:80) and afforded desired C2-alkylated-1,3-dicarbonyl product **69**.

B) General procedure for the synthesis of product 69 by using amberlyst®-15 under continuous flow

The 0.1 M solution of the 1,3-dione **60** (1 mmol in 10 mL ACN) in a 30 mL vial and 0.12 M of alcohol (**68**, 1.2mmol in 10 mL ACN) was taken in another 30 mL vial and flown through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 5 cm (1.0 g, void volume = 1.56 mL swollen up to 6 cm after passing solvent) of bed heated at 100 °C temperature and 3.5 bar pressure. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc: *n*-hexane = 25:75) purification and afforded corresponding C2-alkylated-1,3-dicarbonyl product **69**.

C) General procedure for Mannich reaction under continuous-flow

0.1 M solution of 1,3-cyclodiketone **60** was made with ACN in a vial. 1 mmol of the aldehyde **70** and 1 mmol of piperidine **71** was dissolved in another vial with 10 mL of ACN. Then, both reagent solutions were flown through the 5 mL SS coil at room temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure followed by column chromatography (Methanol: DCM = 10:90 or EtOAc: *n*-hexane = 20:80) purification afforded corresponding *β*-amino-C2 substituted 1,3-dicarbonyl derivatives compound **72**.

D) Study of the lifetime of catalyst and gram scale synthesis

The multi-gram of 2-benzhydryl-3- hydroxycyclohex-2-en-1-one **69a** was prepared by using general procedure A. 0.1 M solution of 1,3-cyclohexadione (3.360g in 300 mL ACN) and 0.12 M of diphenylmethanol **68a** (6.624 g in 300 mL ACN) was prepared and flown continuously (without washing the catalyst) through packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 5 cm (1 g, swollen up to 7 cm after passing solvent) heated at 100 °C temperature with 3.5 bar pressure. Evaporation of the solvent and column purification afforded 6.027 g (67%) of compound **69a** as a white powder.

E) The large-scale synthesis of Mannich reaction product 72a

0.1 M solution of cyclohexane-1,3-dione (**60a**, 10 mmol) was made with 100 mL of ACN in a vial. 10 mmol the formaldehyde **70a** and 10 mmol of piperidine **71a** were dissolved in another vial with 100 mL of ACN. Then, both reagent solutions were flown 0.15 mL/min each through the 5 mL SS coil in room temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure followed by column chromatography (methanol: DCM = 10:90 or EtOAc: n-hexane = 20:80) purification afforded 2-(piperidin-1-ylmethyl)cyclohexane-1,3-dione **72a** (10 g, 83%) .

F) General procedure for the synthesis of ondansetron

i) Synthesis of 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one 80 in continuous-flow: 0.1 M of 1,3-cyclohexadione (280 mg in 25 mL of water) and 0.12 M of phenylhydrazine (366 mg in 25 ml of ethanol) was taken in 30 mL of vial separately. The solutions 1,3-cyclohexadione **60a** and phenylhydrazine **78** were flown to the 10 mL of tubular SS coil reactor heated at 100 °C and subsequently, the reaction mixture was passed continuously to packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 7 cm of bed heated at 110 °C temperature with 3.5 bar pressure. After completion of the reaction, the ethanol was evaporated under a high vacuum. 490 mg (75%) of 9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one **80** was afforded as a yellowish solid compound by the recrystallization process.

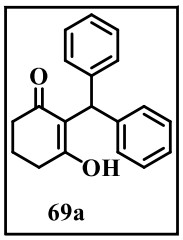
ii) Synthesis of Ondansetron 83: 0.5 mmol of 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one **80** was taken in a 20 ml resealable vial charged with paraformaldehyde (1.5 mmol), *N*, *N*-dimethylamine hydrochloride (1.5 mmol) and amberlyst®-15 (200 mg) in 5 mL of toluene. The reaction mixture was heated at 120 °C for 24 h. After complete consumption of 9-methyl-1,2,3,9-tetrahydro-4Hcarbazol-4-one (monitored by TLC), 2-methylimidazole (**82**) was added to the same reaction mixture and heated at 120 °C for 24 h. After cooling the reaction mixture to room temperature, the toluene was evaporated under a high vacuum. The reaction mass was washed by water and 255 mg of ondansetron **83** was afforded as a white solid compound.

G) Procedure for the recyclability of catalyst

0.1 M solution of 1,3-cyclohexadione **60a** (3.360 g in 300 mL ethanol) and 0.12 M of diphenyl methanol (**68a**, 6.624g in 300 mL) was prepared and flown continuously (without washing the catalyst) through packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst®-15 up to 5 cm (1 g, swollen up to 7 cm after passing solvent) heated at 100 °C temperature at 3.5 bar pressure up to 10 h. Depletion of the rate of product formation was observed. Thus, a 50 mL solution of 0.1 M of HCl in MeOH was passed through the amberlyst®-15 packed bed at a flow rate of 0.25 mL/min to regain the catalytic activity of the catalyst. Then, amberlyst®-15 was washed with pure methanol until the pH of the solution is nearly 7. The amberlyst®-15 was heated in the reactor bed at 110 °C for 1.5 h to dry the catalyst. Similarly, the catalyst was washed periodically with 0.1 M of HCl in MeOH and pure MeOH and reactivated after each 5 h.

2B.6.3. Analytical data for the product

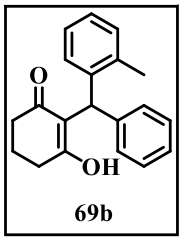
2-Benzhydryl-3-hydroxycyclohex-2-en-1-one 69a was synthesized by following the experimental procedure B by using 1,3-cyclohexadione **60a** (0.1 M solution in 10 mL ACN) and diphenyl methanol **68a** (0.12M solution in 10 mL ACN) afforded 96% (267.4 mg) as a white solid powder. **Melting point**: 144-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 4H), 7.27-7.24 (m, 3H), 7.18-7.16 (m, 3H), 5.94 (s, 1H), 5.87 (s, 1H), 2.48 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.03 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.5, 172.4, 141.7, 129.2, 128.8, 127.2, 118.6, 44.5, 36.8, 29.6 ppm. **FTIR (**neat): 3030, 2925, 1700, 1576, 1372, 1272, 1190, 1083, 700 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{18}O_2$ $(M+H)^+$: 279.1385, found: 279.1385.



69a

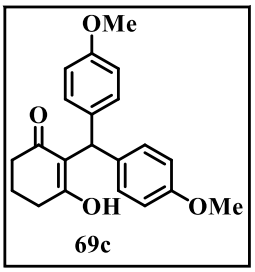
3-Hydroxy-2-(phenyl(*o*-tolyl)methyl)cyclohex-2-en-1-one 69b was synthesized by following the experimental procedure B by using 1,3-cyclohexadione **60a** (0.1 M solution in 10 mL ACN) and 2-methylbenzhydrol **68b** (0.12 M solution in 10 mL ACN) afforded 72% (209.6 mg) as a white solid powder. **Melting point:** 151-152 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 3H), 7.24-7.18

(m, 2H), 7.16- 7.12 (m, 3H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.02 (s, 1H), 5.88 (s, 1H), 2.48 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.25 (s, 1H), 2.04-1.97 (m, 2H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 197.4, 172.7, 141.4, 140.3, 138.0, 131.5, 129.3, 128.8, 127.5, 127.4, 127.3, 126.8, 117.1, 42.5, 36.9, 29.7, 20.8, 19.8 ppm. **FTIR** (neat): 3020, 2920, 2584, 2367, 1731, 1565, 1363, 1191, 737 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{20}O_2$ $(M+H)^+$: 293.1541, found: 293.1548.



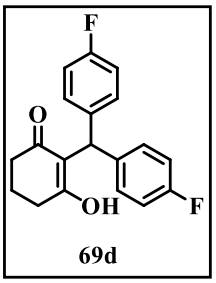
69b

2-(Bis(4-methoxyphenyl)methyl)-3-hydroxycyclohex-2-en-1-one 69c was synthesized by following the experimental procedure B by using 1,3-cyclohexadione **60a** (0.1 M solution in 10 mL ACN) and 4,4'-dimethoxybenzhydrol **68c** (0.12 M solution in 10 mL ACN) afforded 90% (350.2 mg) as a white solid powder. **Melting point:** 177-178 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.09-7.09 (m, 4H), 6.87-6.84 (m, 4H), 6.04 (s, 1H), 5.72 (s, 1H), 3.79 (s, 6H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 1.99 (p, *J* = 6.4 Hz, 2H) ppm. **$^{13}C\{^{1}H\}$** NMR (100 MHz, $CDCl_3$): δ 197.6, 172.3, 158.7, 133.8, 129.8, 118.7, 114.6, 55.4, 42.9, 29.7, 20.8 ppm. **FTIR** (neat): 2950, 2844, 1712, 1590, 1567, 1454, 1374, 1243, 1169, 935, 826 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}O_2$ $(M+H)^+$: 339.1596, found: 339.1606.



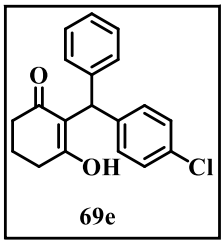
69c

2-(Bis(4-fluorophenyl)methyl)-3-hydroxycyclohex-2-en-1-one 69d was synthesized by following the experimental procedure B by using 1,3-cyclohexadione **60a** (0.1 M solution in 10 mL ACN) and 4,4'-difluorobenzhydrol **68d** (0.12 M solution in 10 mL ACN) afforded 78% (244.5 mg) as a white solid powder. **Melting point:** 169-170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14-7.11 (m, 4H), 7.04-6.97 (m, 4H), 6.01 (s, 1H), 5.78 (s, 1H), 2.49 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 2.00 (p, *J* = 6.4 Hz, 2H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 197.6, 172.4, 161.8 (d, *J* = 244.69 Hz) 137.1 (d, *J* = 3.21 Hz) 130.1 (d, *J* = 7.88 Hz), 118.3, 43.1, 36.9, 29.8, 20.7 ppm. **FTIR** (neat): 2922, 2864, 1730, 1572, 1486, 1372, 1256, 1095, 1017, 818 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{16}F_2O_2$, $(M+H)^+$: 315.1197; found: 315.1204.



69d

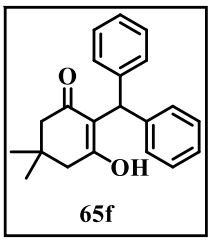
2-((4-Chlorophenyl)(phenyl)methyl)-3-hydroxycyclohex-2-en-1-one 69e was synthesized by following the experimental procedure B by using 1,3-cyclohexadione **60a** (0.1 M solution in 10 mL ACN) and 4-chlorobenzhydrol **68e** (0.12 M solution in 10 mL ACN) afforded 82% (256.2 mg) as a white solid powder. **Melting point:** 119-121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 7H), 7.19-7.11 (m, 7H), 6.28 (s, 1H),6.18 (d, *J* = 7.6 Hz, 1H), 5.80 (s, 1H), 2.45 (t, *J* = 6Hz, 2H), 2.40 (t, *J* = 6Hz, 2H), 2.00-1.96 (m, 2H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 197.6, 172.6,



69e

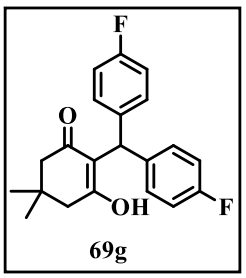
169.4, 141.9,140.2, 130.3,129.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.0,127.6, 127.3, 118.3, 56.7, 36.8, 29.8, 24.0, 20.7 ppm. **FTIR** (neat): 2945, 2854, 1719, 1539, 1485, 1130, 1031, 788, 610 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{17}ClO_2$ $(M+H)^+$: 313.0991, found: 313.0995.

2-Benzhydryl-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one 69f[98] was synthesized by following the experimental procedure B using 5,5-dimethylcyclohexa-1,3-dione **60b** (0.1 M solution in 10 mL ACN) and diphenyl methanol **68a** (0.12 M solution in 10 mL ACN) afforded 85% (261.4 mg) as a white solid powder. **Melting point:** 142-143 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.31 (m, 4H), 7.27-7.25 (m, 2H), 7.18- 7.16 (m, 4H), 5.85 (s, 1H), 2.35 (s, 2H), 2.30 (s, 2H), 1.09 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.4, 170.5, 141.7, 129.7, 129.2, 128.8, 127.2, 117.4, 53.2, 50.6, 44.5, 43.3, 32.0, 20.5 ppm. **FTIR** (neat): 2922, 2864, 1730, 1572, 1486, 1372, 1256, 1095, 1017, 818 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}O_2$ $(M+H)^+$: 307.1698, found: 307.1700.



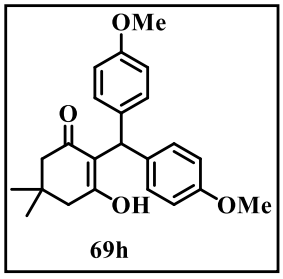
65f

2-(Bis(4-fluorophenyl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one 69g was synthesized by following the experimental procedure B using 5,5-dimethylcyclohexa-1,3dione **60b** (0.1 M solution in 10 mL ACN), 4,4'-difluorobenzhydrol **68d** (0.12 M solution in 10 mL ACN) afforded 94% (320.3 mg) as a white solid powder. **Melting point:** 228-230 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.34 (m, 1H), 7.14 – 7.11 (m, 4H), 7.02-6.94 (m, 3H), 5.76 (s, 1H), 2.36 (s, 2H), 2.29 (s, 2H), 1.08 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6 + $CDCl_3$): δ 196.8, 177.1, 157.9, (d, *J* = 246 Hz), 139.0, 129.8 (d, *J* =7.54 Hz), 116.4, 113.8 (d, *J* =7.54 Hz), 50.4, 43.4, 42.5, 31.4, 27.8 ppm. **FTIR** (neat): 2945, 1715, 1590, 1375, 1256, 1153, 1021, 736 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{20}F_2O_2$ $(M+H)^+$: 343.1510, found: 343.1519.



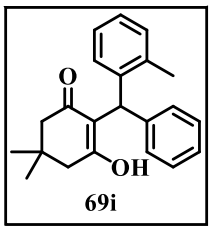
69g

2-(Bis(4-methoxyphenyl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one 69h was synthesized by following the experimental procedure B using 5,5-dimethylcyclohexa-1,3dione **60b** (0.1 M solution in 10 mL ACN) and 4,4'-dimethoxybenzhydrol **68c** (0.12 M solution in 10 mL ACN) afforded 97% (356 mg) as a white solid powder. **Melting point:** 194-195 ˚C, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08-7.06 (m, 4H), 6.88- 6.84 (m, 4H), 5.99 (s, 1H), 5.70 (s, 1H), 3.79 (s, 6H), 2.34 (s, 2H), 2.29 (s, 2H), 1.08 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.3, 170.3, 158.7, 133.7, 129.8, 117.7, 114.6, 55.4, 56.6, 43.6, 42.9, 31.9, 28.4 ppm. **FTIR** (neat): 2944, 1720, 1582, 1507, 1371, 1310, 1245, 1172, 1028, 827 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{26}O_4$ $(M+H)^+$: 367.1907, found: 367.1909.



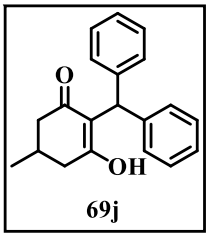
69h

3-Hydroxy-5,5-dimethyl-2-(phenyl(otolyl)methyl)cyclohex-2-en-1-one 69i was synthesized by following the experimental procedure B using 5,5-dimethylcyclohexa-1,3-dione **60b** (0.1 M solution in 10 mL ACN) and 2-methylbenzhydrol **68b** (0.12 M solution in 10 mL ACN) afforded 71% (227 mg) as a white solid powder. **Melting point:** 155-156 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H), 7.27-7.18 (m, 3H), 7.15-7.12 (m, 3H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.05 (s, 1H), 5.86 (s, 1H), 2.35 (s, 2H), 2.30 (s, 2H), 1.09 (d, *J* = 4.4 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.1, 170.8, 141.6, 140.2, 137.9, 131.4, 129.3, 128.8, 127.5, 127.4,127.2, 126.8, 116.1, 50.6, 43.3, 42.5, 31.8, 28.6, 28.5, 19.7 ppm. **FTIR** (neat): 3268.29, 3050.31, 2933.95, 1594, 1370, 1278, 1089, 835, 700 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{24}O2$ $(M+H)^+$: 321.1855, found: 321.1860.



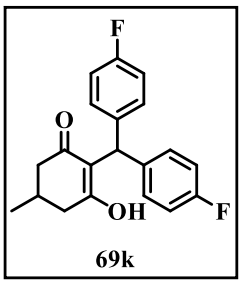
69i

2-Benzhydryl-3-hydroxy-5-methylcyclohex-2-en-1-one 69j was synthesized by following the experimental procedure B using 5-methylcyclohexa-1,3-dione **60f** (0.1 M solution in 10 mL ACN) and diphenyl methanol **68a** (0.12 M solution in 10 mL ACN) afforded 82% (240.7 mg) as a white solid powder. **Melting point:** 142-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 6H), 7.09 -7.06 (m, 4H), 6.00 (s, 1H), 5.74 (s, 1H), 2.53-2.44 (m, 2H), 2.30-2.25 (m, 2H), 2.13-2.07, (m, 1H), 1.07 (d, *J* = 6, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.4, 171.7, 139.1, 133.1, 130.1, 129.3, 129.2, 128.9, 117.6, 44.9, 43.4, 37.9 ppm. **FTIR** (neat): 3041, 2942, 1545, 1378, 1152, 1078, 892, 710 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{20}O_2$ $(M+H)^+$: 293.1542, found: 293.1548.



69j

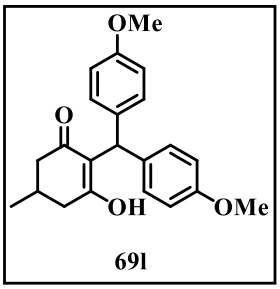
2-(Bis(4-fluorophenyl)methyl)-3-hydroxy-5-methylcyclohex-2-en-1-one 69k was synthesized by following the experimental procedure B using 5-methylcyclohexa-1,3-dione **60f** (0.1 M solution in 10 mL ACN) and 4,4'-difluorobenzhydrol **68d** (0.12M solution in 10 mL ACN) afforded 95% (310.9 mg) as a white solid powder. **Melting point:** 209-210 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14-7.09 (m, 4H), 7.04 - 6.99 (m, 4H), 5.77 (s, 1H), 5.78 (s, 1H), 2.55-2.45 (m, 2H), 2.30-2.26 (m, 2H), 2.15-2.08, (m, 1H), 1.08 (d, *J* = 6, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 197.4, 171.6, 162.0 (d, *J* = 244 Hz), 137.1, 130.3 (d, *J* = 3.89), 130.2 (d, *J* = 3.94), 118.0, 116.2 (d, *J* = 10.24 Hz), 116.0 (d, *J* = 10.35 Hz), 45.0, 43.1, 37.7, 29.9, 28.2, 21.0 ppm. **FTIR** (neat): 2921, 2857, 2362, 1723, 1504, 1375, 1227, 1156, 1015, 753 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{18}F_2O_2$ $(M+H)^+$: 329.1353, found: 329.1358.



69k

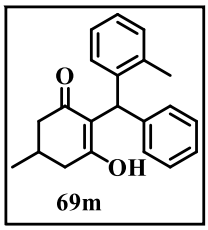
2-(Bis(4-methoxyphenyl)methyl)-3-hydroxy-5-methylcyclohex-2-en-1-one 69l was synthesized by following the experimental procedure B using 5-methylcyclohexa-1,3-dione (**60f**, 0.1 M solution in 10 mL ACN) and 4,4'-dimethoxybenzhydrol **68c** (0.12 M solution in 10 mL ACN) afforded 98%

(344.8 mg) as a white solid powder. **Melting point:** 127-129 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 8.4, 4H), 6.85 (d, *J* = 8.4 Hz, 4H), 6.06 (s, 1H), 5.70 (s, 1H), 3.78 (d, *J* = 1.2 Hz, 6H), 2.53-2.40 (m, 2H), 2.26 – 2.24 (m, 2H), 2.13-2.04 (m, 1H), 1.07 (d, *J* = 6, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ197.6, 171.6, 158.7, 158.7, 133.8, 133.7, 129.8, 129.8, 118.3, 114.7, 129.8, 118.3, 114.6, 114.5, 55.4, 45.1, 43.0, 32.7, 28.2, 21.0 ppm. **FTIR** (neat): 3403, 2923, 2857, 1731, 1606, 1510, 1457, 1375, 1247, 1178, 1031, 833, 638 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{24}O_4$ $(M+H)^+$: 353.1753, found: 353.1754.



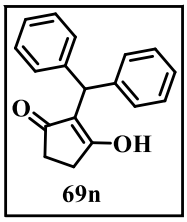
69l

3-Hydroxy-5-methyl-2-(phenyl(o-tolyl)methyl)cyclohex-2-en-1-one 69m was synthesized by following the experimental procedure B using 5-methylcyclohexa-1,3-dione **60f** (0.1 M solution in 10 mL ACN) and 2-methylbenzhydrol **68b** (0.12 M solution in 10 mL ACN) afforded 52% (160.2 mg) as a white solid powder. **Melting point:** 240-242 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.27-7.25 (m, 1H), 7.23- 7.18 (m, 2H), 7.16-7.11 (m, 3H), 6.94-6.89 (m, 1H), 6.08 (s, 1H), 5.86 (d, *J* = 8.8 Hz, 1H), 2.54 – 2.40 (m, 2H), 2.30-2.24 (m, 5H), 2,15-2.06 (m, 1H), 1.08 (d, *J* = 5.6, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$); selected signal for one of the diastereoisomer: δ 197.3, 172.1, 131.5, 129.3, 128.8, 127.5, 127.4, 126.8, 116.7, 45.1, 42.6, 37.8, 28.4, 21.0, 19.8 ppm. **FTIR** (neat): 2925, 2637, 2600, 1580, 1508, 1376, 1247, 1174, 1029, 829 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}O_2$ (M+H) +: 307.1698, found: 307.1702.



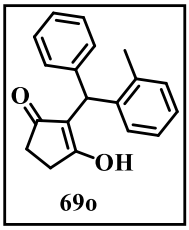
69m

2-Benzhydryl-3-hydroxycyclopent-2-en-1-one 69n was synthesized by following the experimental procedure B using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN) and diphenyl methanol **68a** (0.12 M solution in 10 mL ACN) afforded 52% (137.8 mg) as a white solid powder. **Melting point:** 178-180 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 4H), 7.28-7.24 (m, 2H), 7.16-7.13 (m, 4H), 5.27 (s, 1H), 2.51 (s, 4H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 141.0, 129.1, 128.8, 127.3, 119.6, 50.0, 31.0, 29.9 ppm. **FTIR** (neat): 2948, 2854, 1772, 1542, 1371, 1256, 1205, 733 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{16}O_2$ $(M+H)^+$: 265.1229, found: 265.1233.



69n

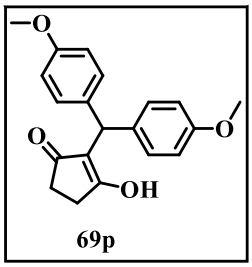
3-Hydroxy-2-(phenyl(o-tolyl)methyl)cyclopent-2-en-1-one 69o was synthesized by following the experimental procedure B using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN) and 2- methylbenzhydrol **68b** (0.12 M solution in 10 mL ACN) afforded 27% (76.5 mg) as a white solid powder. **Melting point:** 191-193 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.29-7.27 (m, 1H), 7.23-7.19 (m, 2H), 7.18-7.12 (m, 3H), 6.92-6.90 (d, *J* = 8, 1H), 5.95 (s, 1H), 5.37 (s, 1H), 2.58 (s, 1H), 2.48 (s, 1H),



69o

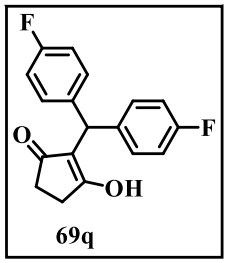
2.24 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 140.7, 139.2, 137.4, 131.5, 129.3, 128.7, 127.5, 127.4, 126.6, 118.6, 42.2, 29.9, 19.9 ppm. **FTIR** (neat): 2918, 2854, 1732, 1562, 1373, 1271, 1206, 1057, 733 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{18}O_2$ $(M+H)^+$: 279.1385, found: 279.1386.

2-(Bis(4-methoxyphenyl)methyl)-3-hydroxycyclopent-2-en-1-one 69p was synthesized by following the experimental procedure B using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN) and 4,4'-dimethoxybenzhydrol **68c** (0.12 M solution in 10 mL ACN) afforded 79% (255.8 mg) as a white solid powder. **Melting point:** 207-208 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.4 Hz, 4H), 6.85 (d, *J* = 8.4, 4H), 5.17 (s, 1H), 3.78 (s, 6H) 2.49 (s, 4H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 158.5, 133.6, 129.8, 120.1, 114.2, 55.4, 43.3, 30.2 ppm. **FTIR** (neat): 3258, 3050, 2921, 2855, 1688, 1647, 1593, 1448, 1285, 1195, 1085, 751, 698 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{20}O_4$ $(M+H)^+$: 325.1440, found: 325.1445.



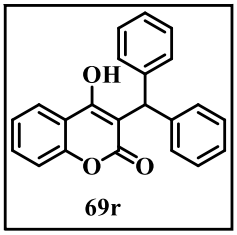
69p

2-(Bis(4-fluorophenyl)methyl)-3-hydroxycyclopent-2-en-1-one 69q was synthesized by following the experimental procedure B using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN) and 4,4'-difluorobenzhydrol **68d** (0.12 M solution in 10 mL ACN) afforded 65% (195.6 mg) as a white solid powder. **Melting point:** 234-235 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.13-7.11 (m, 4H), 7.09-7.00 (m, 4H), 5.23 (s, 1H), 2.54 (s, 4H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 162.0 (d, *J* = 8.34 Hz), 159.6, 138.1, 132.3, 130.5 (d, *J* = 7.83Hz), 124.0, 123.6, 116.3 (d, *J* = 20.27 Hz) 114.8 (d, *J* = 20. 99 Hz) 107.5 ppm. **FTIR** (neat): 2923, 2842, 1574, 1508, 1377, 1248, 823, 734 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{14}O_2F_2(M+H)^+$: 301.1040 found: 301.1042.



69q

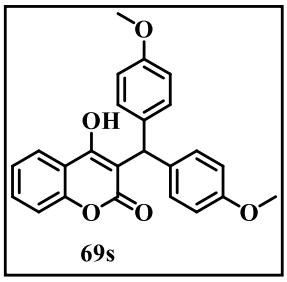
3-Benzhydryl-4-hydroxy-2*H*-chromen-2-one 69r[91] was synthesized by following the experimental procedure B using 4-hydroxy-2*H*-chromen-2-one **60g** (0.1 M solution in 9:1 mL of ACN: THF) and diphenyl methanol **68a** (0.12 M solution in 10 mL ACN) afforded 57% (187.3 mg) as a white solid powder. **Melting point:** 179-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.38-7.34 (m, 4H) 7.32-7.29 (m, 3H), 7.26-7.21 (m, 5H), 5.96 (s, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.4, 160.8, 152.9, 140.1, 132.3, 129.6, 128.9, 128.0, 124.0, 123.3, 116.6, 109.9, 47.5 ppm. **FTIR** (neat): 3252, 3067, 2923, 1611, 1556, 1503, 1385, 1224, 1104, 831, 752 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{16}O_3$ $(M+H)^+$: 329.1177, found: 329.1183.



69r

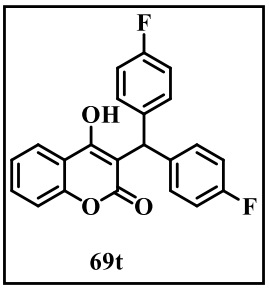
3-(Bis(4-methoxyphenyl)methyl)-4-hydroxy-2*H*-chromen-2-one 69s[91] was synthesized by following the experimental procedure B using 4-hydroxy-2*H*-chromen-2-one **60g** (0.1 M solution in

9:1 mL of ACN:THF) and 4,4'-dimethoxybenzhydrol **68c** (0.12 M solution in 10 mL ACN) afforded 79% (306.7 mg) as a white solid powder. **Melting point:** 146-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 8 Hz, *J* = 1.2 Hz, 1H); 7.57-7.53 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.30-7.28 (m, 1H), 7.21 (d, *J* =8.8 Hz, 4H), 6.93 (d, *J* = 8.8 Hz, 4H), 6.44 (s, 1H), 5.86 (s, 1H), 3.83 (s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 163.3, 160.7, 159.8, 132.1, 129.9, 124.00, 123.2, 116.6, 116.5, 114.9, 108.2, 55.4, 46.0 ppm. **FTIR** (neat): 3097, 2930, 2844, 1693.10, 1614, 1505, 11246, 1177, 1034, 901, 737 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{20}O_5$ $(M+H)^+$: 389.1389, found: 389.1391.



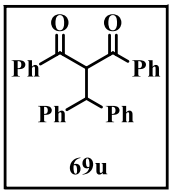
69s

3-(Bis(4-fluorophenyl)methyl)-4-hydroxy-2*H*-chromen-2-one 69t[91] was synthesized by following the experimental procedure B using 4-hydroxy-2*H*-chromen-2-one **60g** (0.1 M solution in 9:1 mL of ACN:THF) and 4,4'-difluorobenzhydrol **68d** (0.12 M solution in 10 mL ACN) afforded 81% (295.2 mg) as a white solid powder . **Melting point:** 199-200 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8 Hz, 1H); 7.56 (t, *J* = 8.4 Hz, 1H), 7.34-7.28 (m, 2H), 7.24-7.22 (m, 4H), 7.08 (t, *J* =8.8 Hz, 4H), 6.14 (s, 1H), 5.92 (s, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.6, 163.2, 161.9 (d, *J* = 243 Hz), 152.9, 135.6 (d, *J* = 3.25), 130.5 (d, *J* = 8.02 Hz), 116.7 (d, *J* = 21.37), 116.7, 115.9, 107.6, 46.0 ppm. **FTIR** (neat): 3282, 2920, 1598, 1375, 1285, 1228, 1094, 829, 750 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{16}O_3F2$ $(M+H)^+$: 365.0989, found: 365.0990.



69t

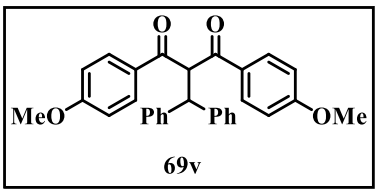
2-Benzhydryl-1,3-diphenylpropane-1,3-dione 69u[91,92] was synthesized by following the experimental procedure B using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN) diphenyl methanol **68a** (0.12 M solution in 10 mL ACN) afforded 76% (296.3 mg) as a white solid powder. **Melting point:** 200-201 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 3H); 7.49-7.45 (m, 2H), 7.35-7.31 (m, 5H), 7.29-7.27 (m, 1H), 7.24-7.22 (m, 4H), 7.16-7.12 (m, 3H), 7.07-7.03 (m, 2H), 6.34 (d, *J* = 11.6 Hz, 1H), 5.34 (d, *J* = 11.6 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 194.2,141.8, 137.1, 133.3, 128.8, 128.8, 128.7, 128.4, 127.7, 127.6, 126.8, 62.5, 57.2, 52.6 ppm. **FTIR** (neat): 2920, 2857, 1732, 1570, 1376, 1224, 943 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{28}H_{22}O_2$ $(M+H)^+$: 413.1517; found: 413.1522.



69u

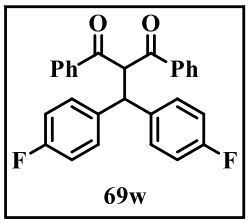
2-Benzhydryl-1,3-bis(4-methoxyphenyl)propane-1,3-dione 69v[90] was synthesized by following the experimental procedure B using 1,3-bis(4-methoxyphenyl)propane-1,3-dione **60j** (0.1M solution in 10 mL ACN) and diphenyl methanol **68a** (0.12M solution in 10 mL ACN) afforded 84% (378.8

mg) as a white solid powder. **Melting point:** 161-163 ˚C; **^{1}H NMR** (400 MHz, MeOH-d_4): δ 7.35-7.29 (m, 2H), 7.25-7.22 (m, 4H), 7.16-7.12 (m, 2H), 7.07-7.03 (m, 2H), 6.82-6.79 (m, 4H), 6.26 (d, *J* = 8 Hz, 1H), 6.19 (d, *J* = 11.6 Hz, 1H), 3.81(s, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, MeOH-d_4): δ 192.7, 163.7, 142.2, 141.6, 131.2, 128.8, 128.6, 128,4, 127.6, 126.6, 113.8, 57.2, 55.5, 52.4 ppm. **FTIR** (neat): 3043, 2923, 2853, 1667, 1595, 1510, 1262, 1025, 839, 700 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{26}O_4$ $(M+H)^+$: 451.1909, found: 451.1908.



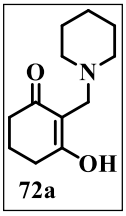
69v

2-(Bis(4-fluorophenyl)methyl)-1,3-diphenylpropane-1,3-dione 69w[92] was synthesized by following the experimental procedure B using 1,3-diphenylpropane-1,3-dione **60i** (0.1M solution in 10 mL ACN) and 4,4'-difluorobenzhydrol **68d** (0.12M solution in 10 mL ACN) afforded 92% (391.4 mg) as a white solid powder. **Melting point:** 216-217 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$ + CCl_4) δ 7.84-7.81 (m, 4H); 7.48 (tt, *J* = 8.5 Hz, *J* = 12 Hz, 2H), 7.37-7.33 (m, 4H), 7.16-7.13 (m, 4H), 6.86-6.81 (m, 4H), 6.12 (d, *J* = 11.6 Hz, 1H), 5.28 (d, *J* = 11.6 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) 193.4, 161.8 (d, *J* = 244.97 Hz), 137.6 (d, *J* = 3.18 Hz), 137.1, 133.5, 129.9 (d, *J* = 7.85 Hz), 128.9 (d, *J* = 3.08 Hz), 115.7 (d, *J* = 21.2), 63.6, 50.6 ppm. **FTIR** (neat): 2918, 1687, 1594, 1504, 1254, 972, 824, 753 cm^{-1}. **HRMS** (ESITOF) m/z calculated for $C^{28}H^{20}O_2F_2$ $(M+H)^+$: 427.1510; found: 427.1517.



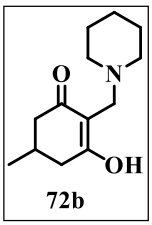
69w

3-Hydroxy-2-(piperidin-1-ylmethyl)cyclohex-2-en-1-one 72a was synthesized by following the experimental procedure C using 1,3-cyclohexadione **60a** (0.1M solution in 10 mL ACN), formaldehyde **70a** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 85% (177.8 mg) as a yellowish semi-solid . **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.90 (s, 2H), 3.35 (d, *J* = 13.2 Hz, 2H), 2.55 (t, *J* = 12 Hz, 2H), 2.32, (t, *J* = 6.4 Hz, 4H), 1.95-1.87 (m, 6H), 1.71-1.67 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 193.4, 101.3, 55.0, 52.3, 35.5, 32.5, 29.8, 24.1, 22.8, 21.7 ppm. **FTIR** (neat): 2937, 1615, 1494, 1037, 729 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{12}H_{19}NO_2$ $(M+H)^+$: 210.1494, found: 210.1496.



72a

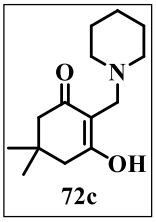
3-Hydroxy-5-methyl-2-(piperidin-1-ylmethyl)cyclohex-2-en-1-one 72b was synthesized by following the experimental procedure C using 5-methylcyclohexa-1,3-dione **60f** (0.1 M solution in 10 mL ACN), formaldehyde **70a** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 75% (167.1 mg) as a white solid powder. **Melting point:** 144-146 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.88 (s, 2H), 3.34 (d, *J* = 11 Hz, 2H), 2.54 (t, *J* = 11.6 Hz, 2H), 2.36-2.32 (m, 2H), 2.08-2.00 (m, 2H), 1.89-1.70 (m, 6H), 1.40 (m, 1H), 1.01 (d,



72b

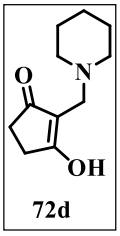
J = 6.4 Hz, 3 Hz) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 193.0, 100.9, 54.8, 52.3, 43.9, 29.8, 29.0, 24.0, 22.8, 21.5 ppm. **FTIR** (neat): 2957, 2881, 1754, 1654, 1423, 1242, 1059, 757 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{21}NO_2$ $(M+H)^+$: 224.1650, found: 224.1655.

3-Hydroxy-5,5-dimethyl-2-(piperidin-1-ylmethyl)cyclohex-2-en-1-one 72c was synthesized by following the experimental procedure C using 5,5-dimethylcyclohexa-1,3-dione **60b** (0.1M solution in 10 mL ACN), formaldehyde **70a** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 67% (158.8 mg) as a white solid powder. **Melting point:** 152-154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.88 (s, 2H), 3.32 (m, 2H), 2.54 (t, *J* = 10 Hz, 2H), 2.19 (bs, 4H), 1.74 (m, 5H), 1.40 (s, 1H), 1.03 (s, 6H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 192.1, 100.0, 54.8, 52.3, 49.2, 46.1, 32.1, 29.8, 28.9, 24.0, 22.8 ppm. **FTIR** (neat): 2937, 1582, 1496, 1420, 1135, 1079, 923 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{23}NO_2$ $(M+H)^+$: 238.1807, found: 238.1808.



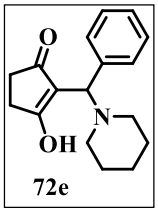
72c

3-Hydroxy-2-(piperidin-1-ylmethyl)cyclopent-2-en-1-one 72d was synthesized by following the experimental procedure C using 1,3-cyclopentadione (0.1M solution in 10 mL ACN), formaldehyde (**0a** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 82% (195.8 mg) as a white solid powder. **Melting point:** 212-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.58 (s, 2H), 2.70 (s, 2H), 2.25 (m, 4H), 1.86 (s, 5H), 1.39 (s, 1H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 203.0, 102.6, 53.9,50.9, 44.6, 32.8, 29.7, 23.2, 22.2 ppm. **FTIR** (neat): 2922, 2816, 2342, 1721, 1618, 1423, 1222, 1054, 751 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{25}NO_3$ $(M+H)^+$: 272.1260, found: 272.1266.



72d

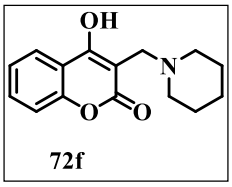
3-Hydroxy-2-(phenyl(piperidin-1-yl)methyl)cyclopent-2-en-1-one 72e was synthesized by following the experimental procedure C using 1,3-cyclopentadione **60d** (0.1 M solution in 10 mL ACN), benzaldehyde **70b** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 78% (271.1 mg) as a white solid powder. **Melting point:** 260-261 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.35 (bs, 1H), 7.28-7.26 (m, 1H), 7.24-7.23 (m, 2H), 7.19-7.14 (m, 1H), 7.11-7.09 (m, 2H), 5.47 (s, 1H), 2.66-2.55 (m, 4H), 2.49-2.34(m, 5H), 2.07-2.00 (m, 4H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 192.0, 190.9, 137.8, 128.2, 126.5, 125.9, 116.4, 33.5, 32.9, 20.1 ppm. **FTIR** (neat): 2936, 1731, 1591, 1373, 1159, 854, 734 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{25}NO_3$ $(M+H)^+$: 272.1260, found: 272.1266.



72e

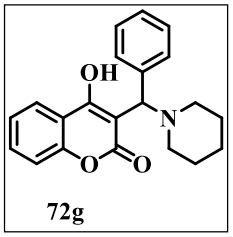
4-Hydroxy-3-(piperidin-1-ylmethyl)-2H-chromen-2-one 72f was synthesized by following the experimental procedure C using 4-hydroxy-2H-chromen-2-one **60g** (0.1M solution in 9:1 mL of ACN: THF), benzaldehyde **70b** and piperidine **71a** (1 mmol of each in 10 ml ACN) afforded 72% (267.4 mg) as a white solid powder. **Melting point:** 180-181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ

7.88-7.86 (m, 1H), 7.39- 7.34 (m, 1H), 7.21-7.06 (m, 2H), 4.16 (s, 2H), 3.59 (d, *J* = 12.4 Hz, 2H), 2.81 (m, 2H), 1.94-1.85 (m, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 179.8, 176.3, 167.4, 166.0, 154.2, 154.9, 132.1, 131.4, 125.3, 124.4, 123.2, 123.2, 121.4, 120.00, 116.6, 116.5, 88.0, 86.5, 55.3, 52.8, 23.5, 22.5, 22.0, 20.1 ppm. **FTIR** (neat): 2940, 2863, 2576, 1650, 1601, 1527, 1420, 1272, 1217, 1045, 920, 752, 684 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{17}NO_3$ (M+H)+ : 260.1286, found: 260.1297.



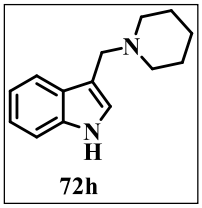
72f

4-Hydroxy-3-(phenyl(piperidin-1-yl)methyl)-2*H*-chromen-2-one 72g[99] was synthesized by following the experimental procedure C using 4-hydroxy-2*H*-chromen-2-one (**60g**, 0.1M solution in 9:1 mL of ACN:THF), benzaldehyde **66b**) and piperidine (**71a**, 1 mmol of each in 10 ml ACN) afforded 79% (264.4 mg) as a white solid powder. **Melting point:** 153-154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 1H), 7.62-7.52 (m, 2H), 7.47-7.43 (m, 1H), 7.35-7.30 (m, 3H), 7.24-7.21 (m, 2H), 5.13 (s, 1H), 3.83 (d, *J* = 12.4 Hz), 2.99 (d, *J* = 12.4, 1H), 2.75 (t, *J* = 12 Hz, 1H), 2.34-2.31 (m, 2H), 1.93-167 (m, 6H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 174.0, 164.4, 154.2, 136.2, 131.5, 129.4, 129.3, 124.3, 123.1, 121.0, 116.7, 95.0, 71.6, 54.0, 51.8, 24.4, 22.6 ppm. **FTIR** (neat): 3049, 2949, 2877, 2373, 1714, 1580, 1373, 1256, 1151, 1021, 735 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{21}NO_3$ $(M+H)^+$: 336.1600, found: 336.1608



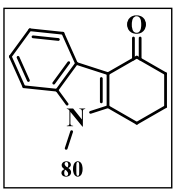
72g

3-(Piperidin-1-ylmethyl)-1*H*-indole 72h[100] was synthesized by following the experimental procedure C using indole (0.1M solution in 10 mL ACN), formaldehyde and piperidine (1 mmol of each in 10 ml ACN) heated at 80 °C, afforded 32% (69.4 mg) as an oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70- 7.68 (m, 1H), 7.45-7.43 (m, 1H), 7.22-7.20 (m, 1H), 7.18-7.13 (m, 2H), 4.81 (s, 1H), 2.53-2.50 (m, 4H), 1.62-1.55 (m, 3H), 1.43-1.26 (m, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 137.4, 128.9, 121.7, 119.5, 119.3, 110.9, 110.3, 68.7, 54.4, 53.9, 51.9, 26.0, 26.0, 24.4, 24.0 ppm. **FTIR** (neat): 3342, 2932, 1579, 1467.37, 1201.92, 1059, 757.02 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{18}N_2$ $(M+H)^+$: 215.1548, found: 215.1552.



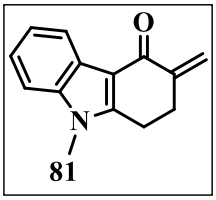
72h

9-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one 80[101] was synthesized by following the experimental procedure F(i). **Melting point:** 193-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.24 (m, 1H), 7.30-7.27 (m, 3H), 3.72 (s, 3H), 2.95 (t, *J* = 6 Hz, 2H), 2.58 (t, *J* = 6 Hz, 2H), 2.30-2.23 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 193.9, 152.0, 137.5, 124.8, 123.9, 123.1, 122.7, 121.8, 112.8, 109.2, 38.0, 30.0, 23.4, 22.3 ppm. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{13}NO$ $(M+H)^+$: 200.1075, found: 200.1078.



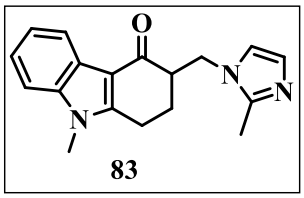
80

9-Methyl-3-methylene-1,2,3,9-tetrahydro-4*H*-carbazol-4-one 81 was synthesized by following the experimental procedure F(ii). **Melting point:** 118-119 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.34-8.31(m, 1H), 7.31-7.30 (m, 3H), 6.15-6.14 (m, 1H), 5.39-5.38 (m, 1H), 3.71 (s, 3H), 3.05-3.04 (m, 2H), 2.99-2.98 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 183.4, 151.8, 143.7, 125.3, 123.4, 122.9, 122.1, 119.0, 109.4, 31.1, 30.0, 22.7 ppm. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{13}NO$ $(M+H)^+$: 212.1075, found: 212.1079.



81

9-Methyl-3-((2-methyl-1*H*-imidazol-1-yl)methyl)-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**83**) was synthesized by following the experimental procedure F(ii). **Melting point:** 221-222 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26-8.24(m, 1H), 7.32-7.29 (m, 3H), 6.93 (d, *J* = 1.2 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H) 4.67 (dd, *J* = 14.8 Hz, *J* = 4 Hz, 1H) 4.08 (dd, *J* = 14.8 Hz, *J* = 2.2 Hz, 1H), 3.70 (s, 3H), 2.99-2.97 (m, 1H), 2.92-2.82 (m, 2H), 2.43 (s, 3H), 2.22-2.17 (m, 1H) 1.95-1.85 (m, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 191.7, 151.4, 145.1, 137.8, 127.5, 124.8, 123.6, 123.1, 121.7, 119.9, 112.4, 109.5, 47.4, 45.8, 30.0, 26.7, 21.6, 13.4 ppm. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{19}N_3O$ $(M+H)^+$: 294.1606, found: 294.1608.



83

2B.6.4. Appendix II

Copies of ^{1}H and ^{13}C NMR spectra of representative compounds

Entry	Figure No	Data	Page No
69c	35 & 36	^{1}H and ^{13}C	109
69i	37 & 38.	^{1}H and ^{13}C	110
69m	39 & 40.	^{1}H and ^{13}C	111
69p	41 & 42.	^{1}H and ^{13}C	112
69r	43 & 44	^{1}H and ^{13}C	113
69u	45 & 46	^{1}H and ^{13}C	114
72b	47 & 48	^{1}H and ^{13}C	115
72g	49 & 50	^{1}H and ^{13}C	116
80	51 & 52	^{1}H and ^{13}C	117
83	53 & 54	^{1}H and ^{13}C	118
68c	55	ORTEP structure	119

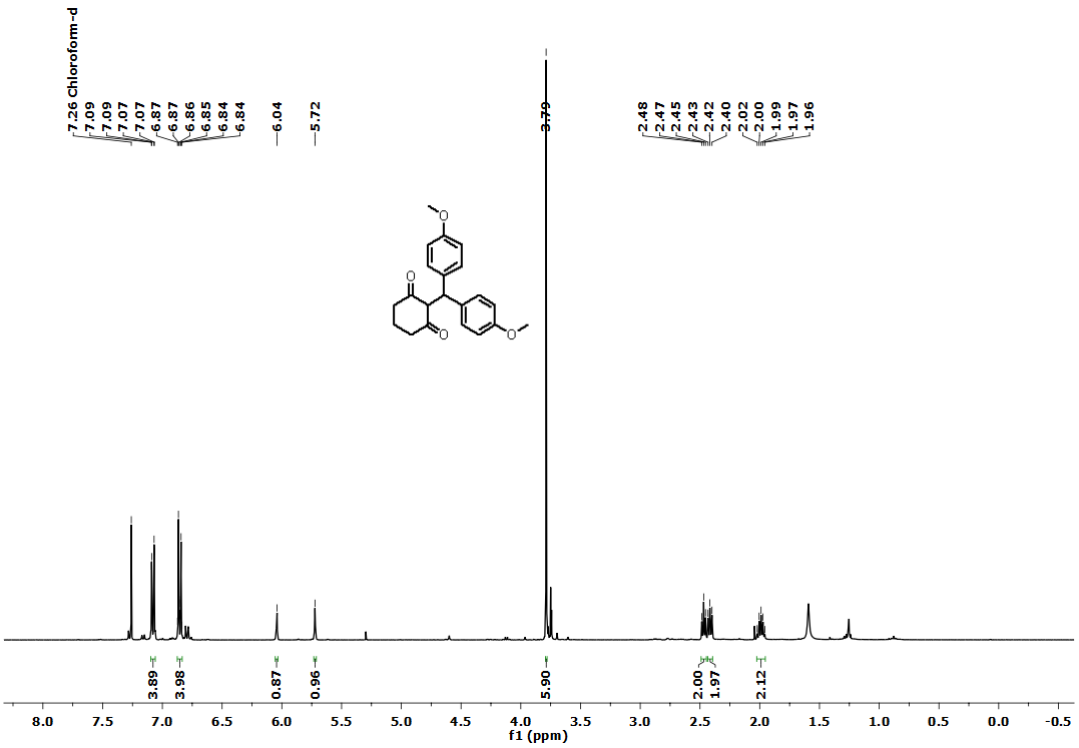


Figure 35: ^{1}H NMR of Compound **69c**

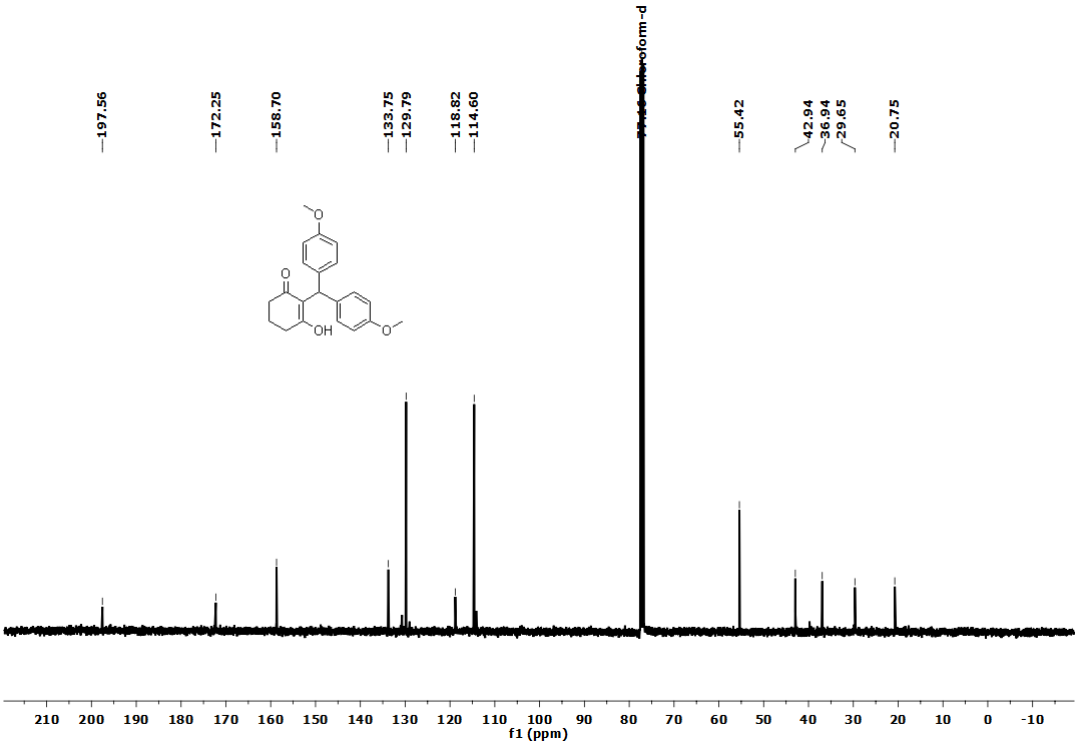


Figure 36: ^{13}C NMR of Compound **69c**

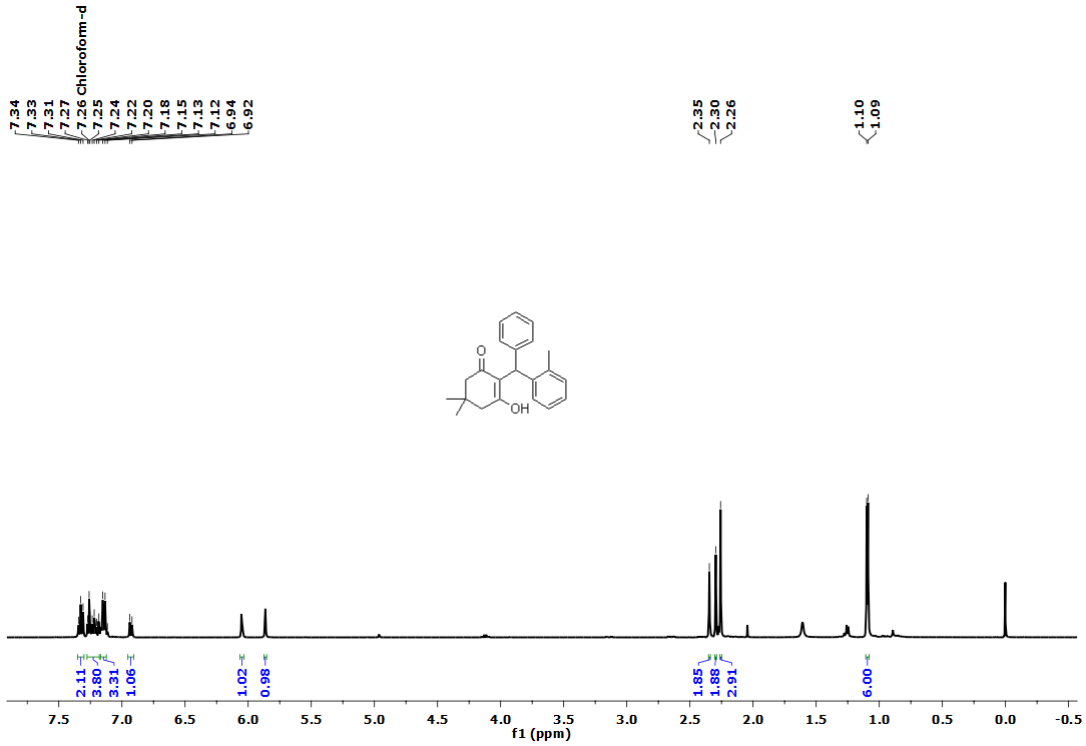


Figure 37:[1]H NMR of Compound **69i**

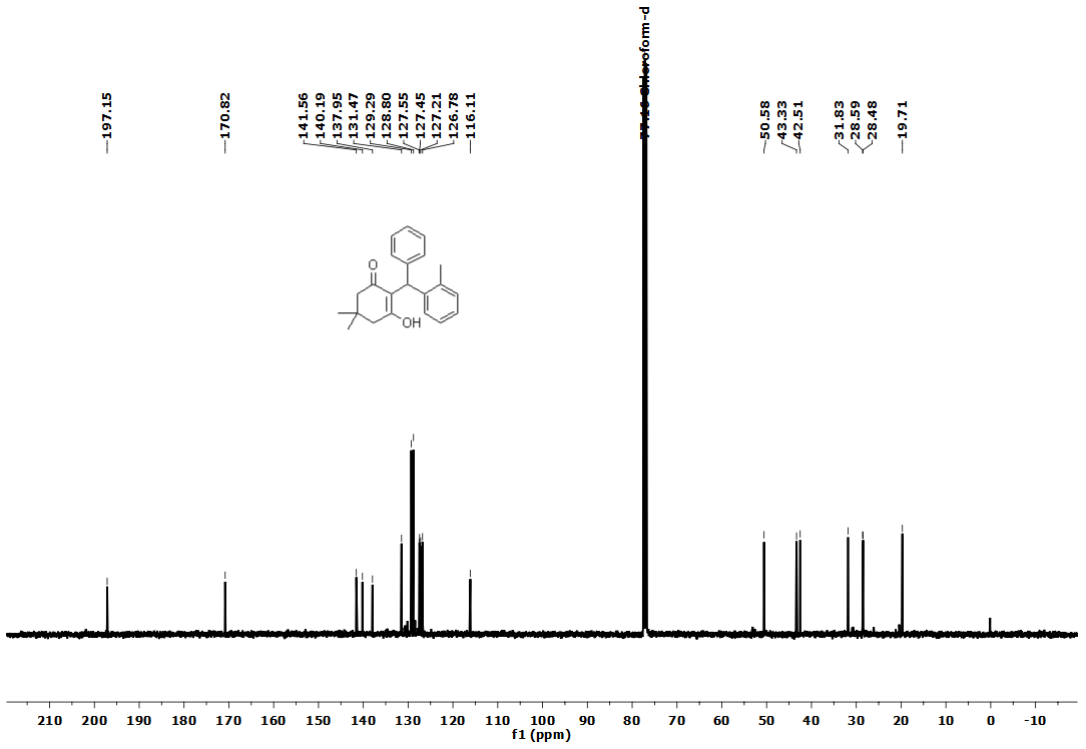


Figure 38: [13]C NMR of Compound **69i**

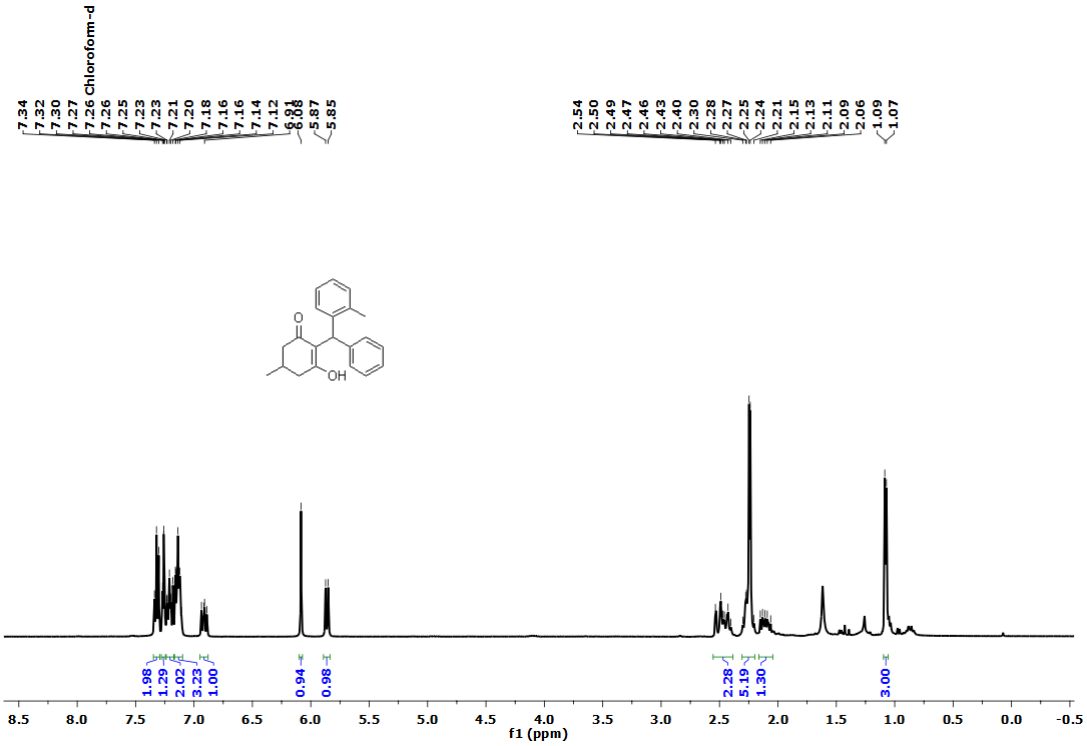


Figure 39: ^{1}H NMR of Compound **69m**

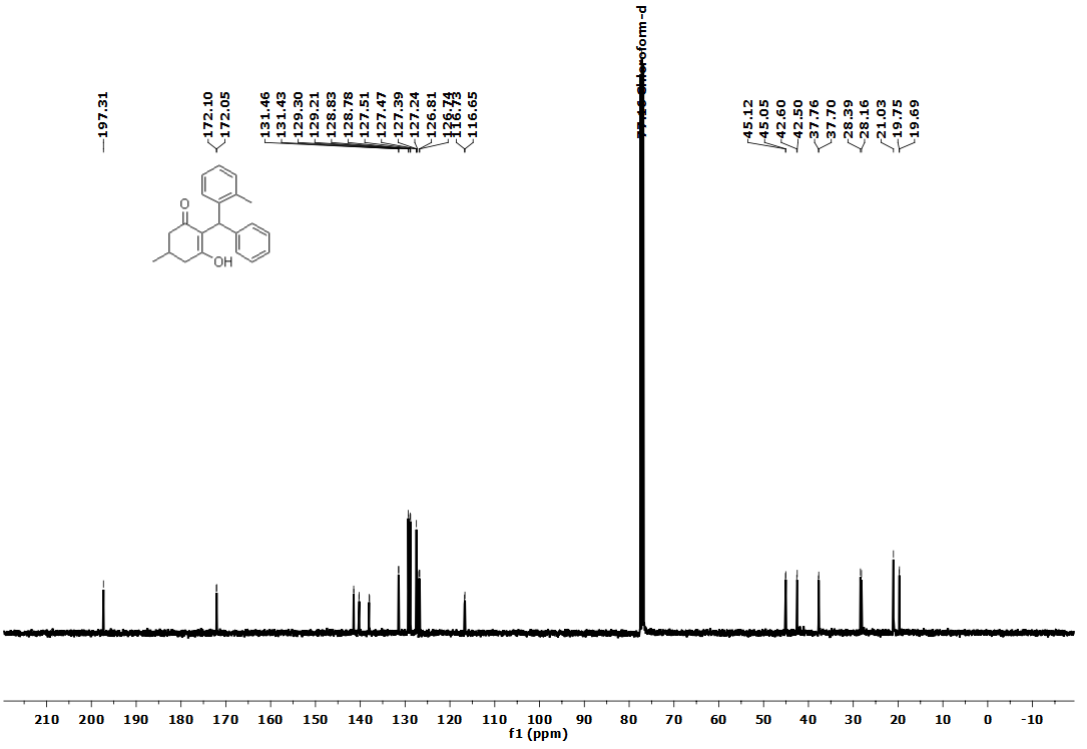


Figure 40: ^{13}C NMR of Compound **69m**

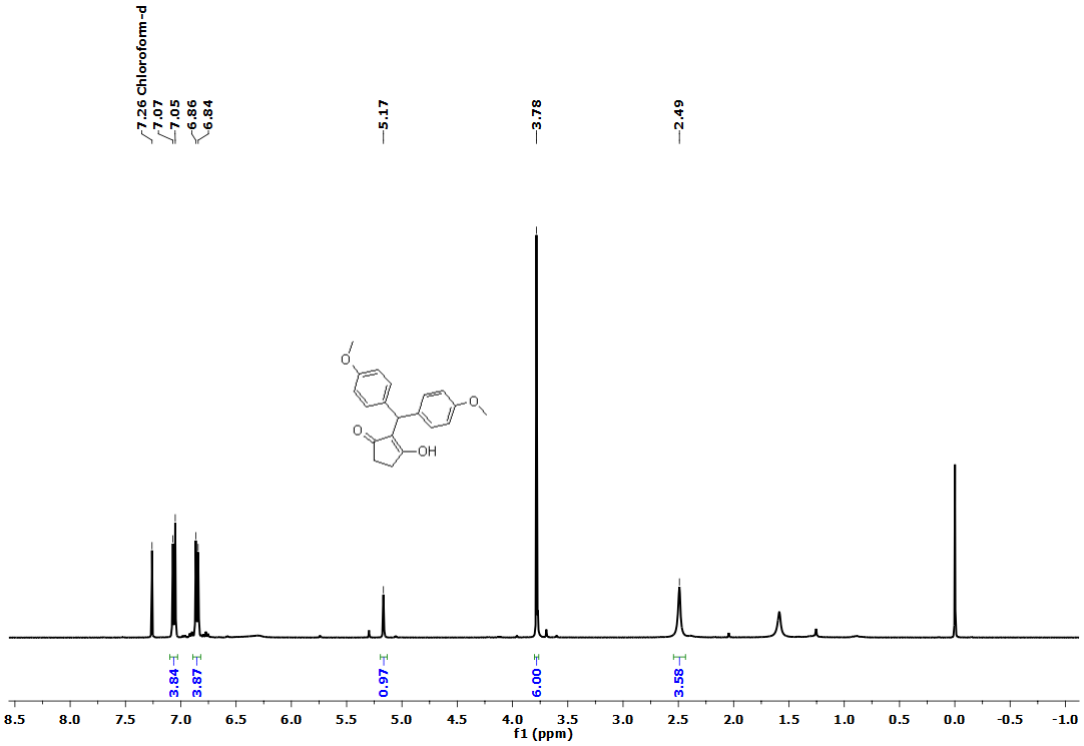


Figure 41: ^{1}H NMR of Compound **69p**

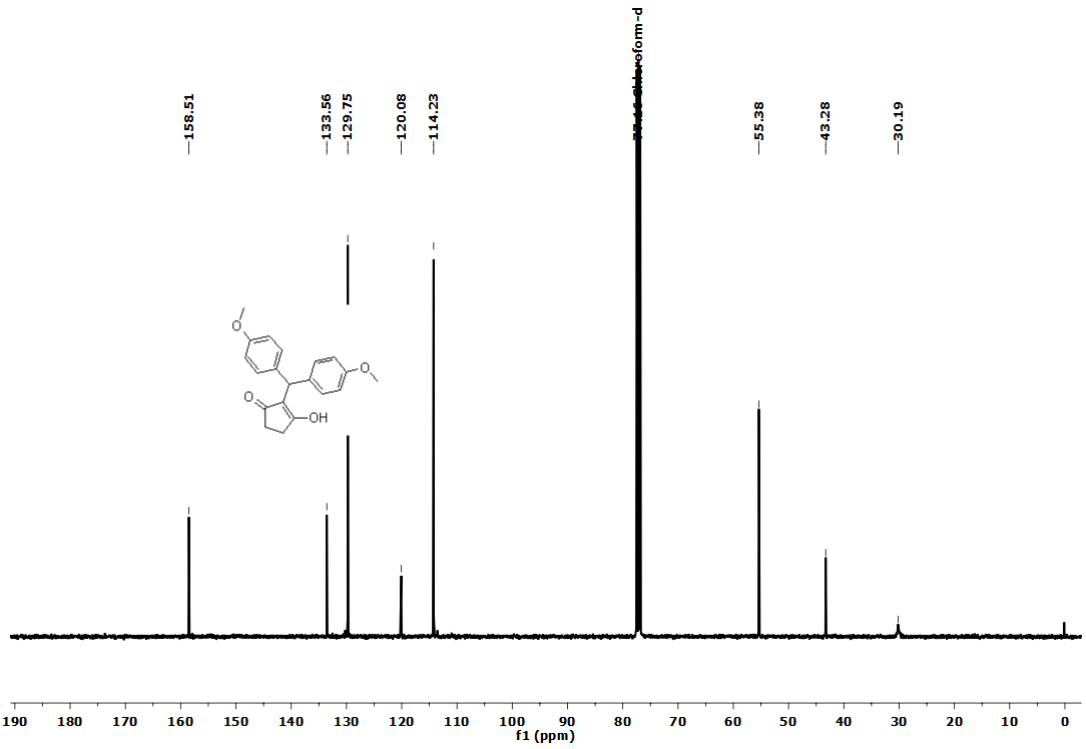


Figure 42: ^{13}C NMR of Compound **69p**

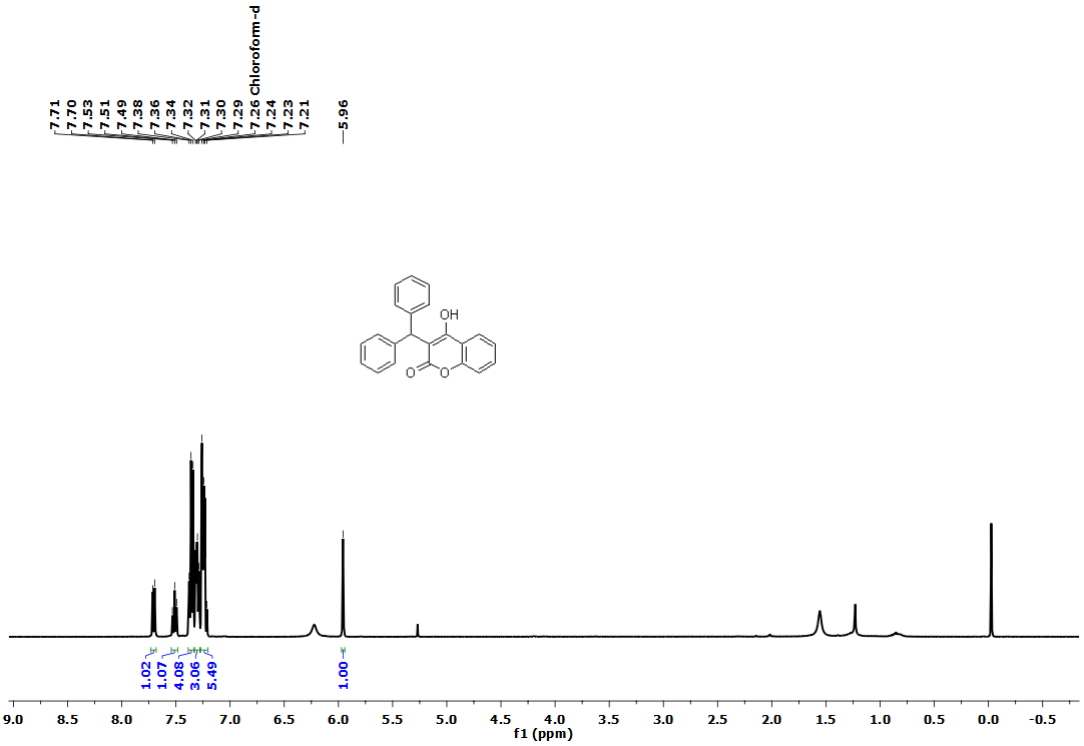


Figure 43:[1]H NMR of Compound **69r**

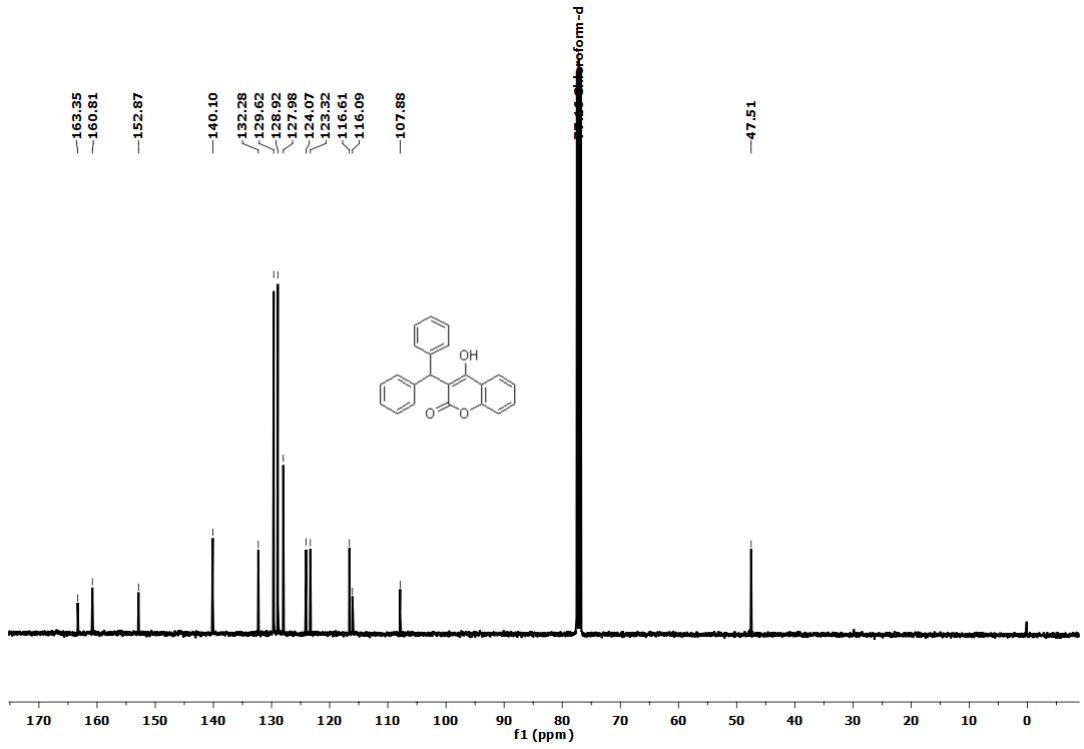


Figure 44: [13]C NMR of Compound **69r**

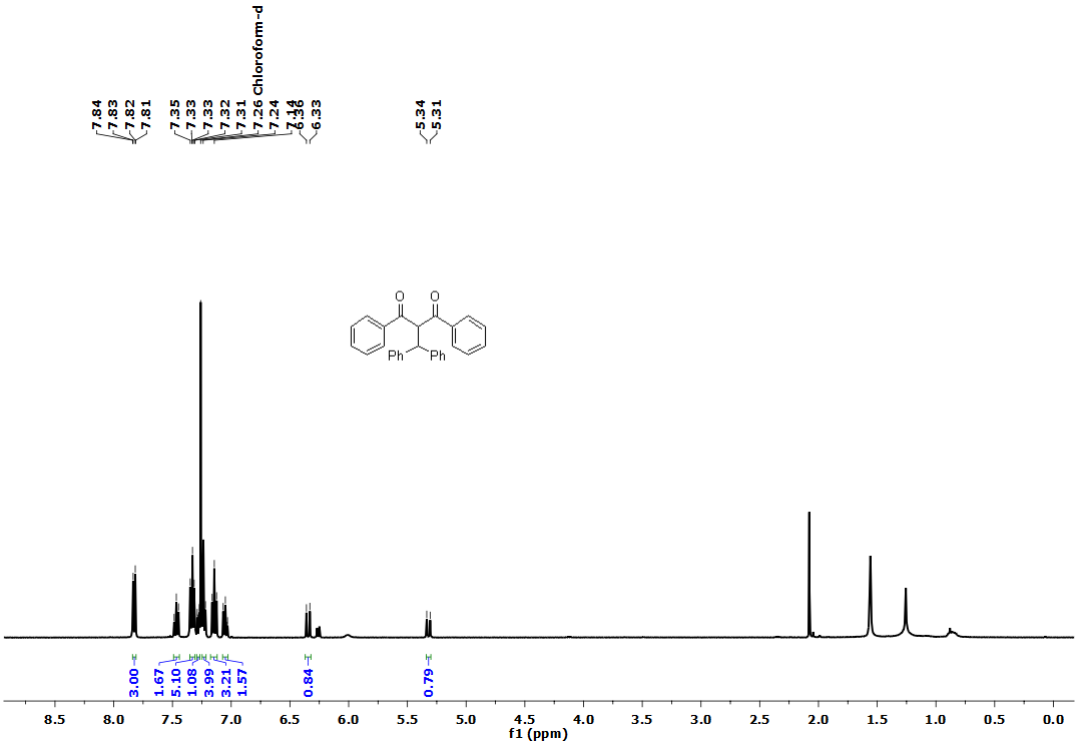


Figure 45: ^{1}H NMR of Compound **69u**

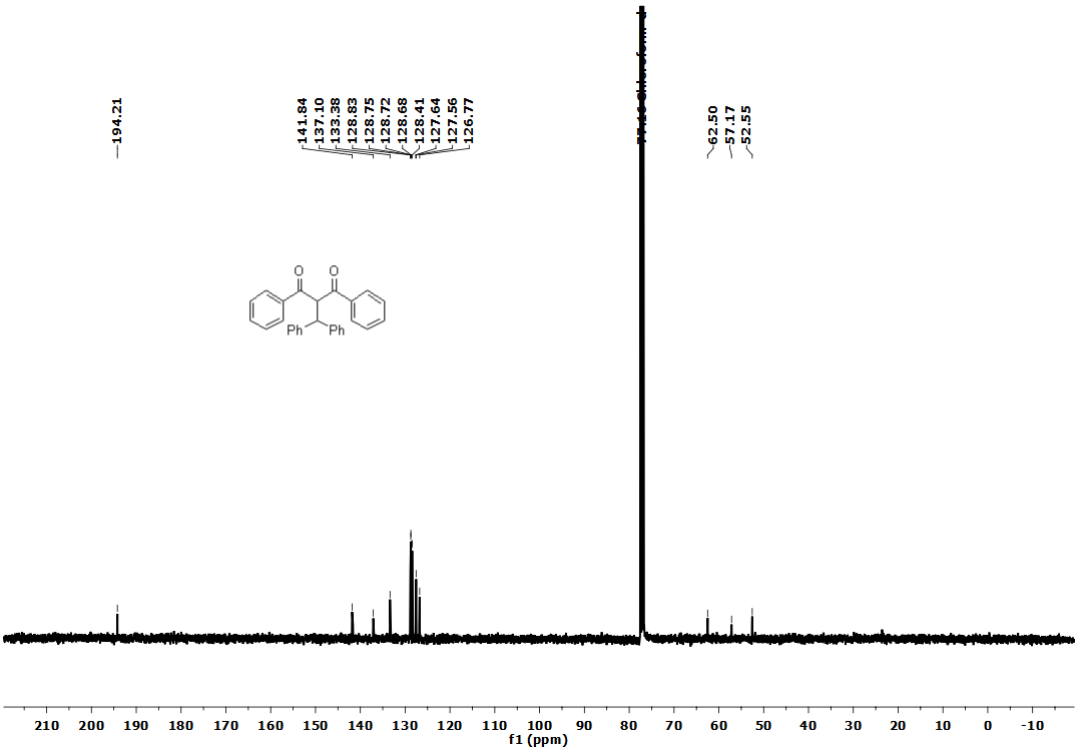


Figure 46: ^{13}C NMR of Compound **69u**

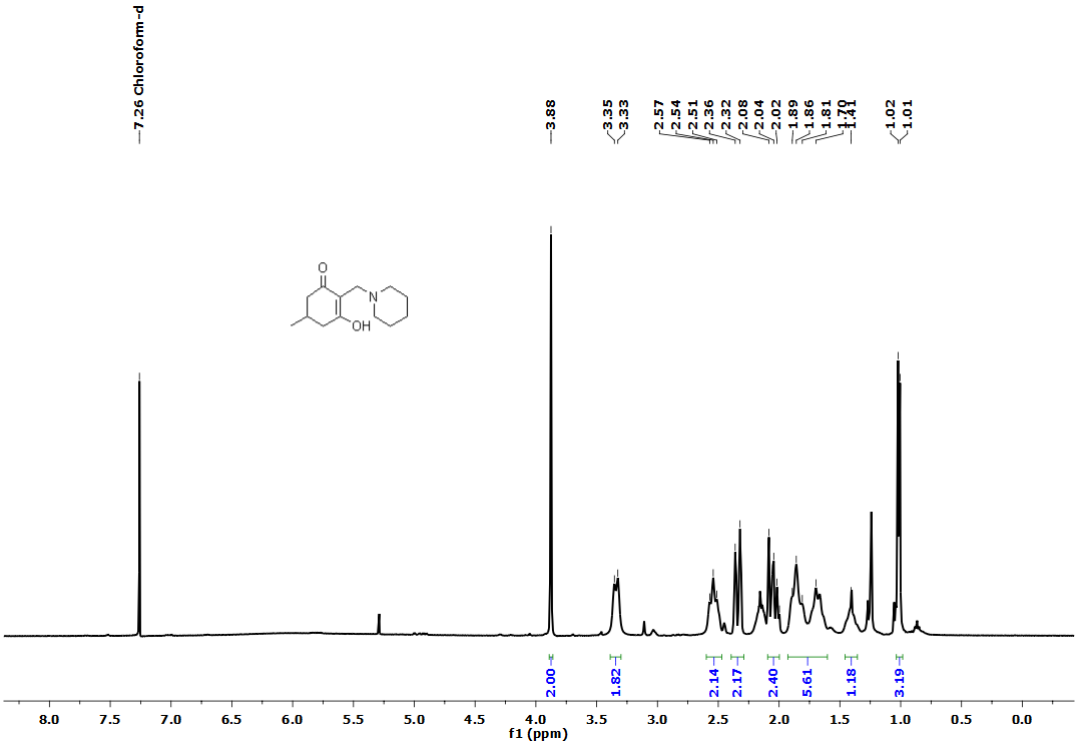


Figure 47:[1]H NMR of Compound **72b**

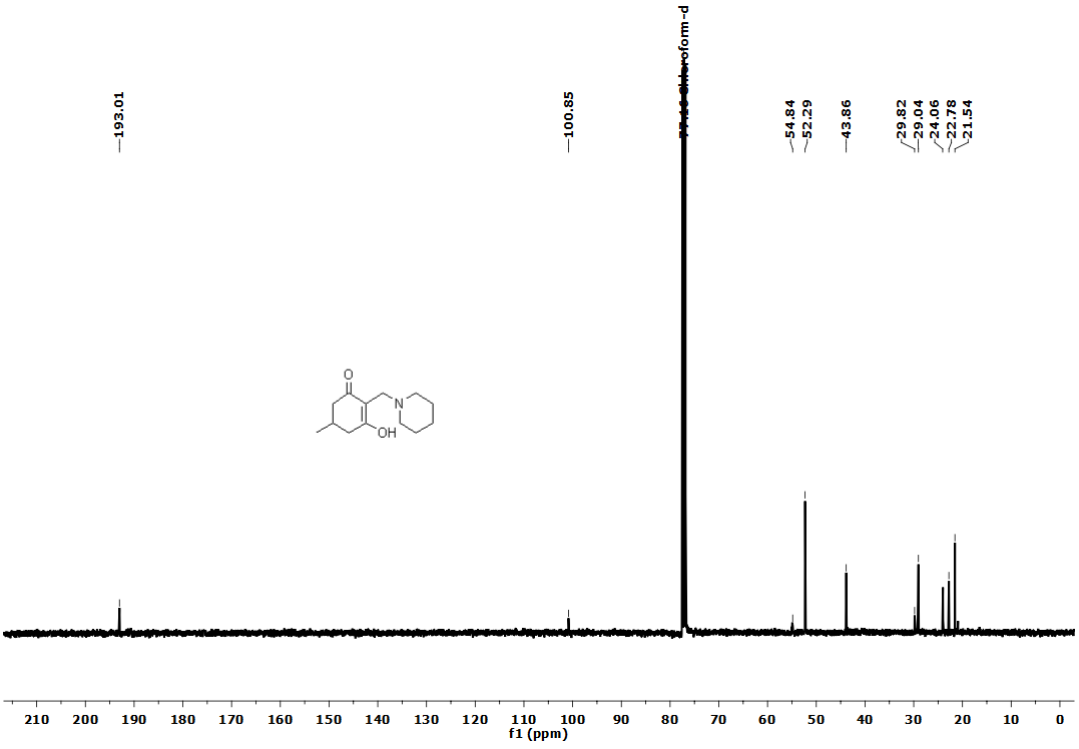


Figure 48:[13]C NMR of Compound **72b**

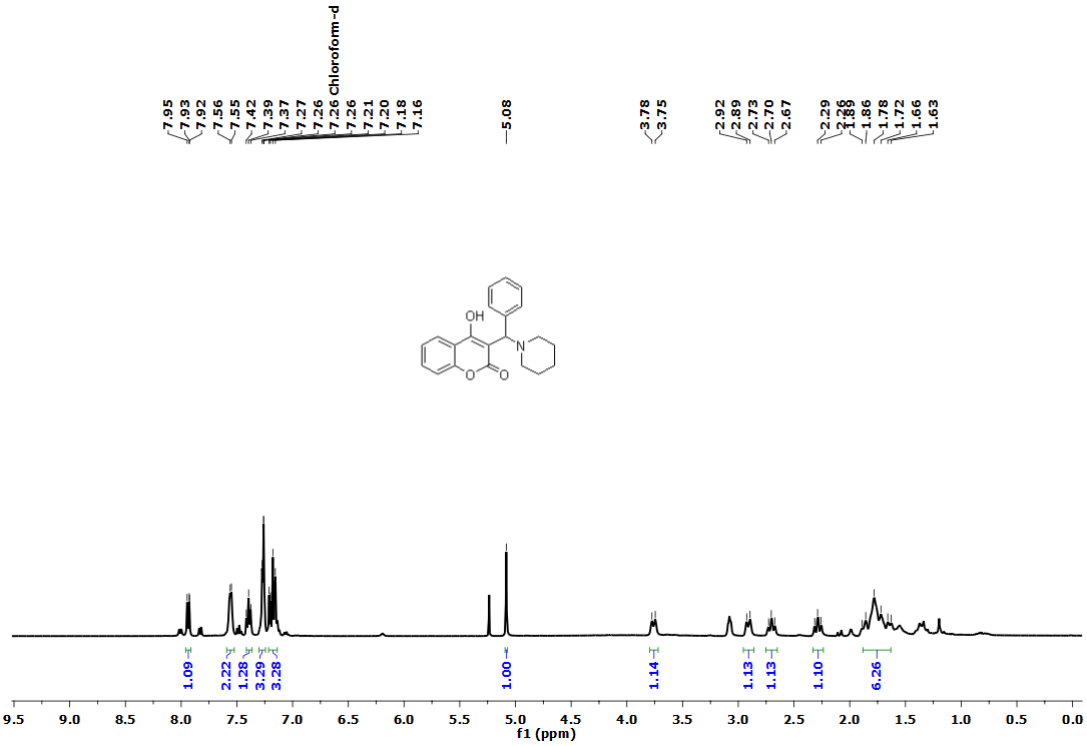


Figure 49:[1]H NMR of Compound **72g**

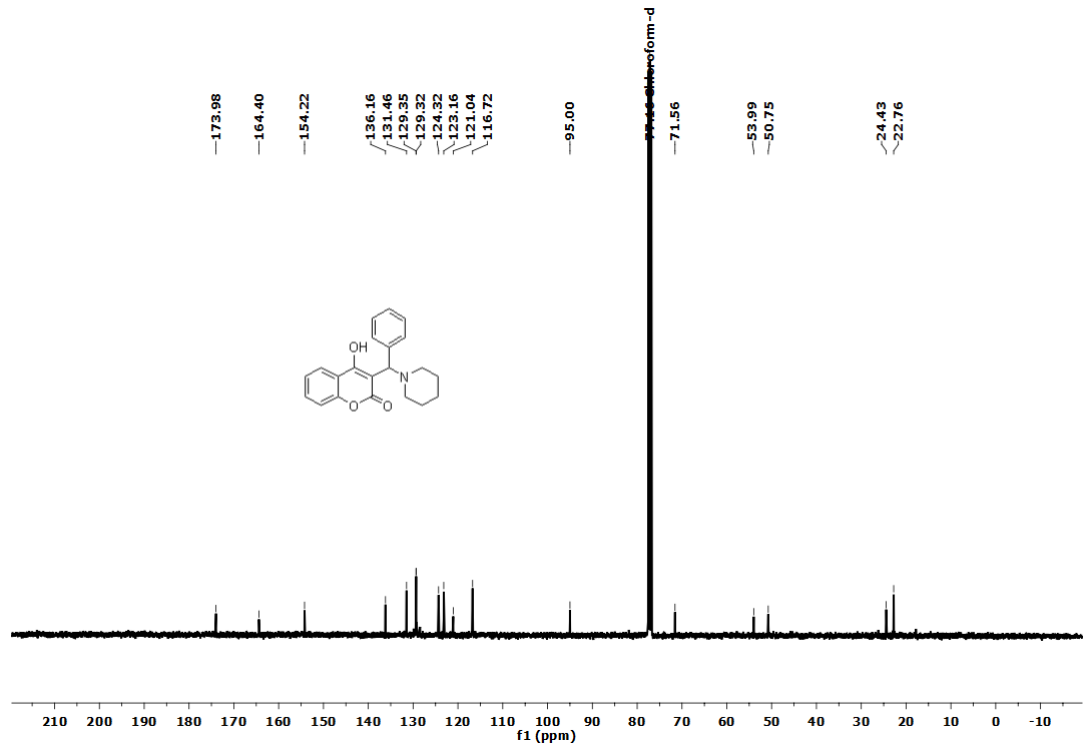


Figure 50:[13]C NMR of Compound **72g**

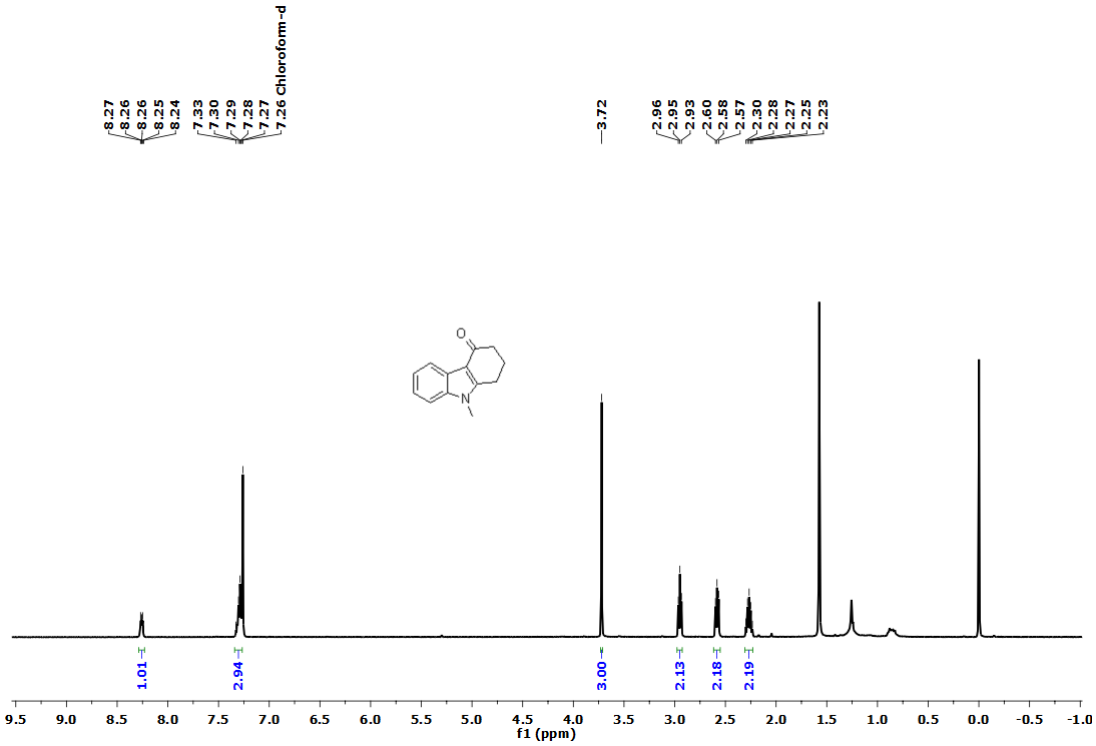


Figure 51: ^{1}H NMR of Compound **80**

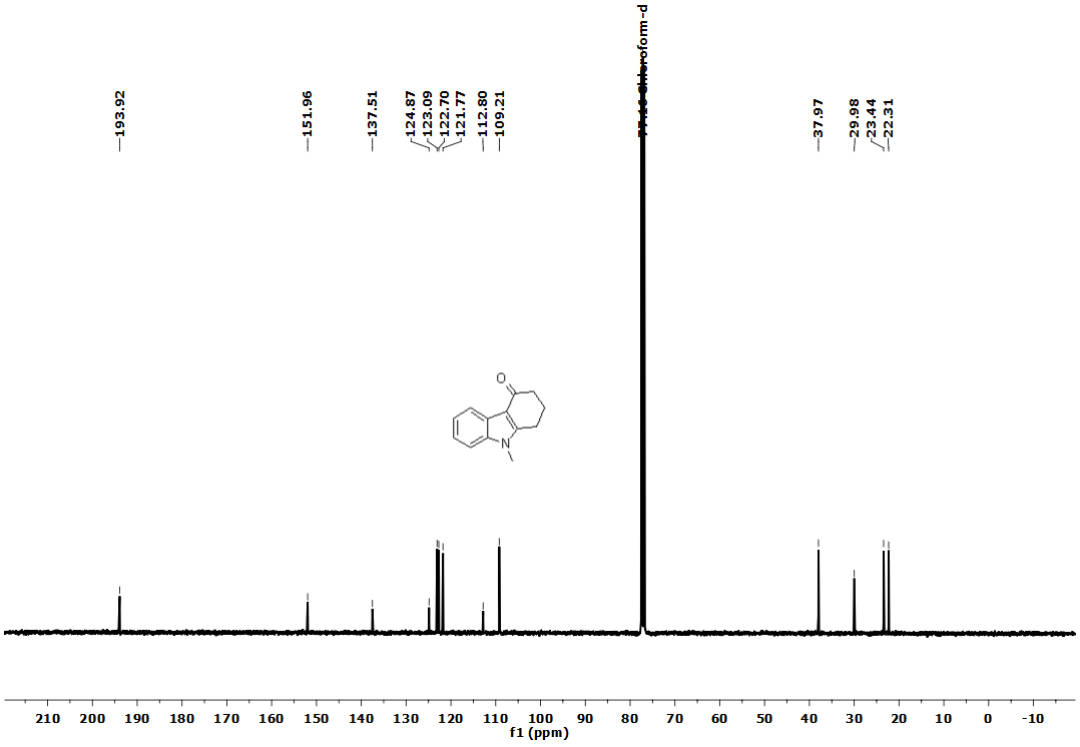


Figure 52: ^{13}C NMR of Compound **80**

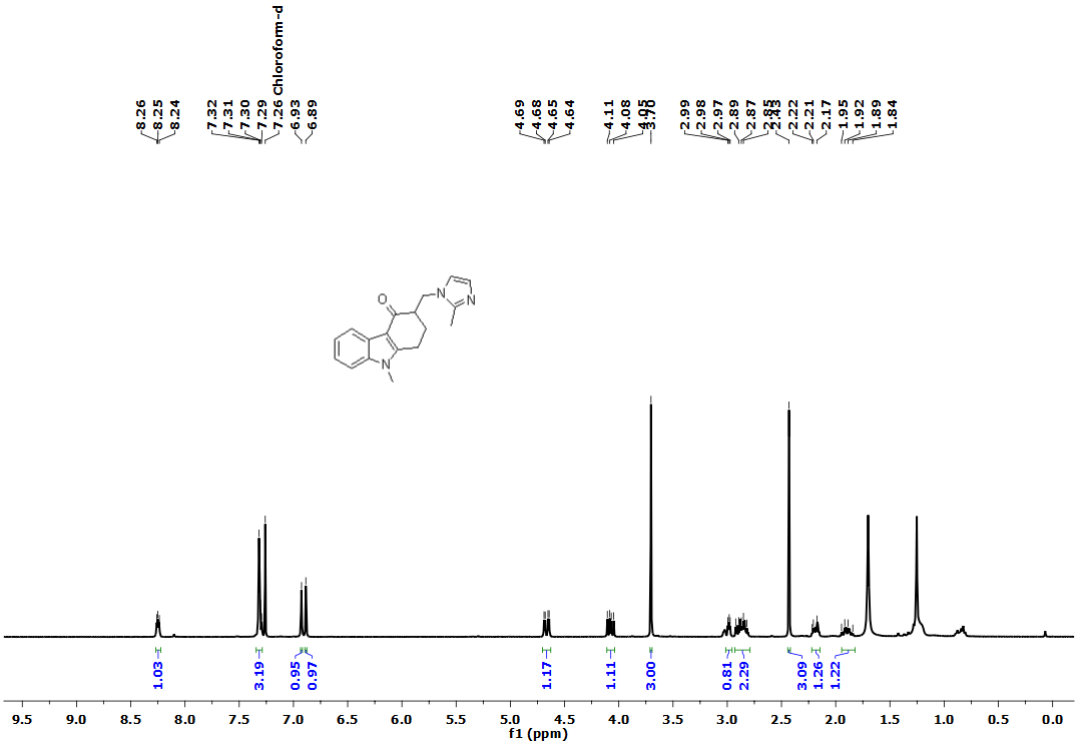


Figure 53:[1]H NMR of Compound **83**

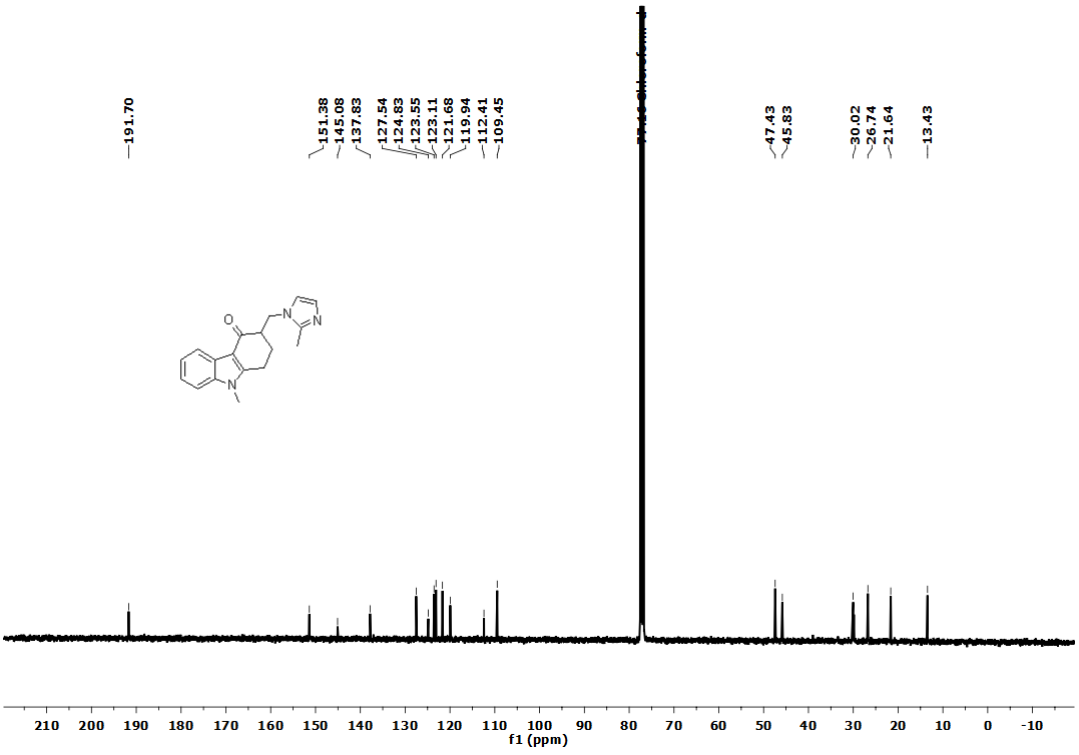


Figure 54:[13]C NMR of Compound **83**

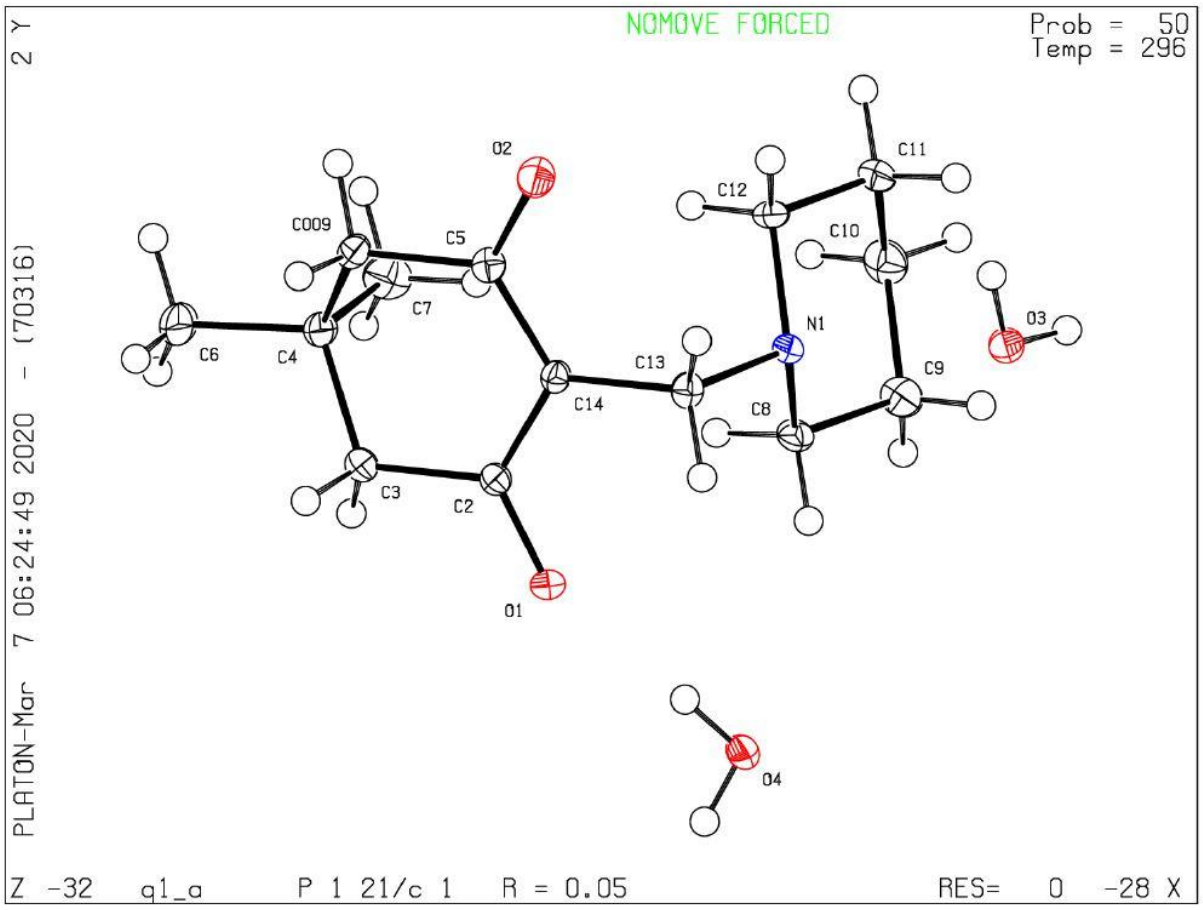


Figure 55: ORTEP diagram of **68c**

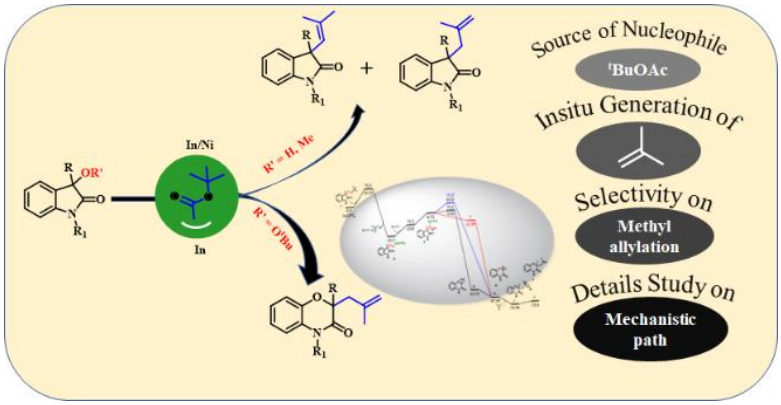
Chapter 3

Catalytic Selective Methylallylation at Quaternary Carbon-Centre using *tert*-Butyl Acetate

3. Catalytic Selective Methylallylation at Quaternary Carbon-Centre using *tert*-Butyl Acetate

3.1. Abstract

In this chapter, for the first time, Indium catalyzed selective methylallylation and vinylation of C3-hydroxy oxindole derivatives was demonstrated using in situ generated *iso*-butylene gas from *tert*-butyl acetate. Using the present protocol, a library of C3-methyallylated and vinylated oxindole derivatives are synthesized in good to excellent yield. This protocol is highly selective to afford the methylallylated product by switching the metal from indium to nickel. Further, the selectivity of the reaction was supported by DFT calculation. Interestingly, methylallyl functionalized 1,4-benzoxazin-3-one derivatives were formed through the sequential rearrangement of peroxyoxindole and the subsequently nucleophilic attack by *iso*-butylene. To maintain the safety and minimize the flammable nature of *iso*-butylene, this reaction was transformed into a continuous flow. Moreover, the current methyallyation reaction is scalable using the heterogeneous catalyst amberlyst®-15 in a continuous flow with increased safety in a sustainable manner. In mechanistic studies, it was observed that the reaction is dependent upon the concentration of peroxide and catalyst, confirmed by kinetic analysis. The detailed mechanism for this reaction and rationalization for the selectivity has been provided in this chapter using kinetics and Density Functional Theory (DFT) studies.



3.2. Introduction for quaternary carbon centre

The chemical and biological behaviours of organic molecules are exclusively suggested by their structure which dictates their ability to bind and orient to a particular target. In many biologically active

organic molecules and natural products structure are attractive or demanding due to the three-dimensional orientation of substituents at carbon stereocentres and enhanced properties of new molecules.[102] Efficaciously constructing a quaternary carbon centre with four substituen most challenging in organic syntheses due to steric hindrance and marginally reactive functional groups. In the 20th century, synthetic chemists were able to successfully develop numerous catalytic approaches for synthesizing quaternary carbon centers.[103] Quaternary stereocentres are found in many biologically active small molecule natural products, for example, abiraterone (**84**), cortisone (**85**), morphine (**86**), and Communesin F (**87**) (Figure 56).[104] To obviate the challenge of steric hindrance, the construction of quaternary carbon centres must involve the use of C-C, C-N, and C-X bond-forming reactions that provide the desired three-dimensional orientation of the four attached substituents.

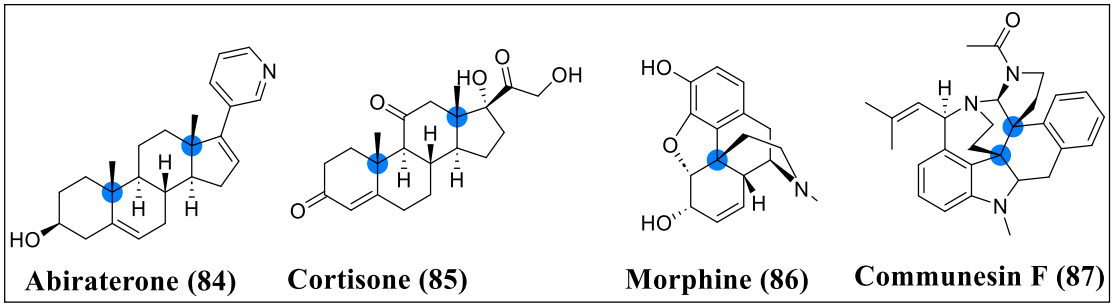


Figure 56. Selected examples of quaternary carbon-containing biologically active compounds

3.3. Introduction to quaternary carbon of oxindole moiety

Nitrogen-containing heterocycle scaffolds with quaternary carbon centres are the most abundant and prevalent classes of building blocks in organic synthesis.[105] In particular, 3,3-disubstituted oxindole derivatives are widely found in numerous biologically active natural products and pharmaceutical compounds.[106] As a result, numerous effort has been made to develop synthetic methods to achieve quaternary carbon-containing oxindole derivatives.[107] There are several methods have been developed for the construction of quaternary carbon in oxindole derivatives via C3-H functionalization of C3-substituted oxindole moiety using a transition metal as a catalyst (Figure 57).[108] Similarly, various methods have been developed for the synthesis of 3,3-disubstituted oxindoles via nucleophilic substitution through C-C bond formation (Figure 57).[109] Among these traditional methods, radical cyclization has emerged as one of the most powerful tools for accessing these structurally diverse functionalized heterocycles, and this strategy is also used for the synthesis of sterically hindered quaternary carbon-containing oxindole derivatives (Figure 57).[110]

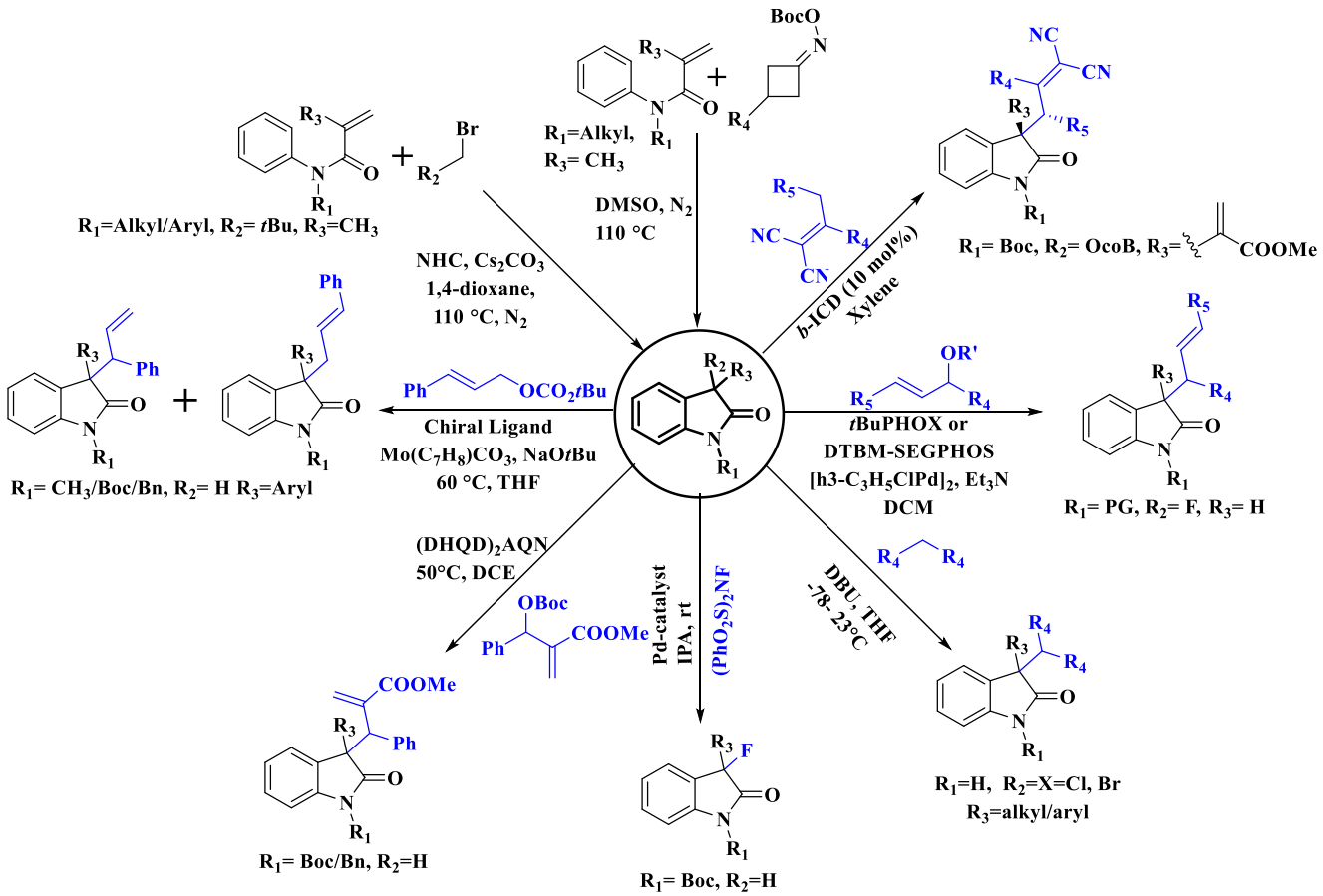
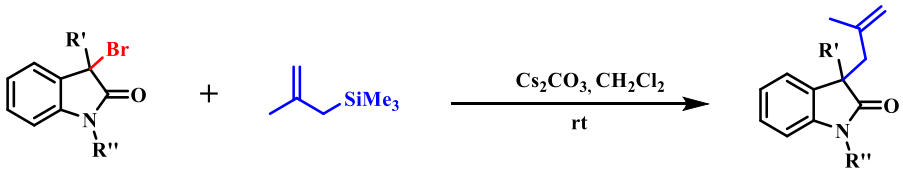


Figure 57. Miscellaneous approach for the construction of quaternary carbon-containing oxindole derivatives

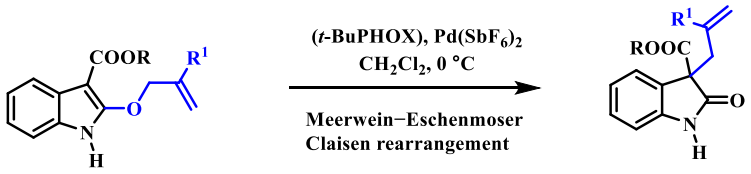
3.4. Literature background on C3-methylallation and vinylation of oxindole derivatives

Despite the fact that there are many reports accessible for quaternary carbon or functionalization at oxindole moiety, there are very few reports available for methylallylation at quaternary carbon. An approach for methylallylating the halogenated quaternary carbon of the oxindole moiety was devised by Funk and co-workers in 2005. They used methylallyl trimethylsilane in the presence of a base. The entire synthesis of (-) Flustramines A and C is also accomplished using this process (scheme 49).[111]



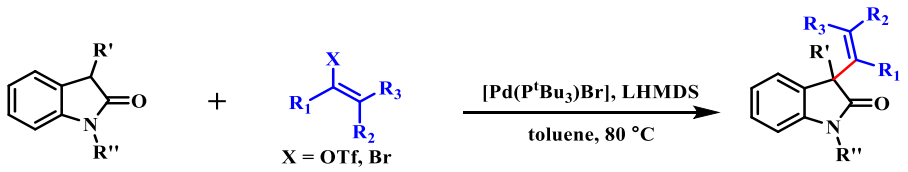
Scheme 49. Funk's approach for the methylallylation at quaternary carbon of oxindole

In 2008, Kozlowski and co-workers reported a palladium catalyst-based Meerwein-Eschenmoser Claisen rearrangement procedure for creating stereoselective methylalylated quaternary carbon centers (scheme 50).[112]



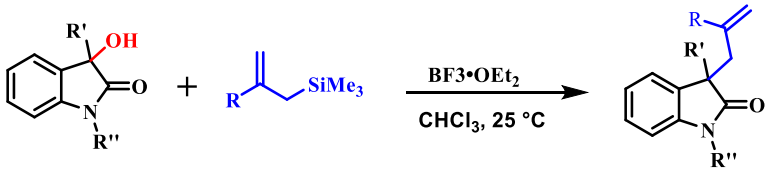
Scheme 50. Kozlowski's approach for the methylallylation at quaternary carbon of oxindole via rearrangement reaction.

In 2007, Faul and co-workers reported the α-vinylation/methylallyaltion of C3-substituted oxindole derivatives using a palladium catalyst. This reaction was also successfully subjected to the α-vinylation/ methylallyaltion of α-hydrogen containing ketones and esters (scheme 51).[113]



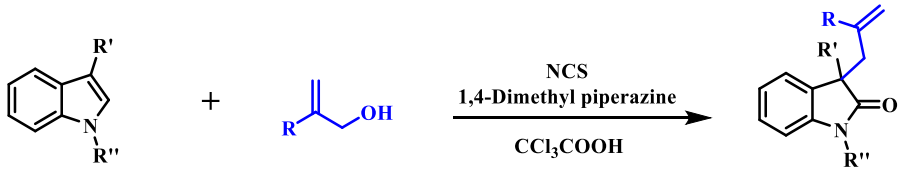
Scheme 51. Faul's approach for the methylallylation at quaternary carbon of oxindoles

Bisai and co-workers developed a method to synthesize quaternary carbon-containing 2-oxindoles using an acid catalyst with C3-hydroxy oxindoles and a silane-functionalized electron-rich substrate in 2014. When a methylallylated silane substrate is subjected to this reaction, it produces methyallylated quaternary carbon derivatives containing 2- oxindoles (scheme 52).[114]



Scheme 52. Bisai's approach for the construction of methylallylated quaternary carbon of oxindole derivatives

Subsequently, Viswanathan and co-workers developed a regioselective Cope rearrangement for the construction quaternary carbon oxindole derivatives in the presence of NCS-catalyst from the treatment of indole compounds and hydroxyl allylated derivatives (scheme 53).[115]



Scheme 53. Viswanathan's approach for the construction of methyallylated quaternary carbon of oxindole derivatives via rearrangement reaction

3.5. The objective of the present work

The objective of this project is to develop a new synthetic route for the formation of quaternary carbon center moieties, specifically vinyl/allyl functionalized quaternary carbon moieties of 2-oxindole core molecules. The importance of this type of functional group interconversion is evidenced by the prevalence of such skeletons in natural products, drugs, and value-added products.[116] Currently, the formation of a vinyl/allyl functionalized quaternary carbon moiety using activated aliphatic alkene is a challenging topic in organic synthesis. While methods for installing methylallyl functionalized quaternary carbon using pre-functionalized alkene as the source for the *α*-vinylation reactions has been developed, they necessitate the use of stoichiometric bases and employ special basic conditions, which can lead to competing reactions such as isomerization.

To address this challenge, the project aims to develop an efficient method for the construction of methylallyl or vinyl quaternary carbon centres using *iso*-butylene derivatives, specifically *tert*-butyl acetate as a source for in situ *iso*-butylene generation. *Iso*-butylene is a commercially and inexpensively available vinylation source, but its propensity for polymerization under experimental conditions limits its reactivity as a nucleophile or electrophile. The proposed method will utilize continuous flow synthesis, with the ultimate goal of scaling up the reaction under flow conditions. The successful development of this method could have significant implications for the synthesis of complex molecules and natural product analogs.

3.6. Results and discussion

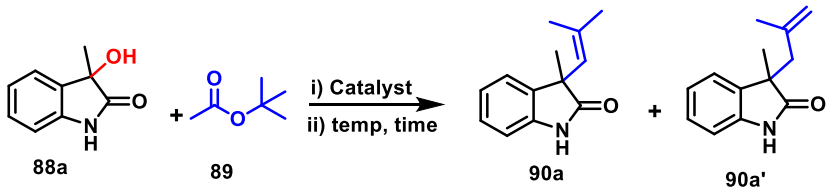
A very simple and sustainable protocol for the methylallylation and vinylation at the quaternary carbon centre of the oxindole was discovered using in situ generated *iso*-butylene from *tert*-butyl acetate as an sustainable approaches for the functionalization of carbonyl derivatives. Here, the Lewis acid catalyzed, highly selective *α*-vinylation and methylallylation of quaternary 3-hydroxy oxindole via direct nucleophilic substitution of the hydroxyl group with *iso*-butylene generated in situ from *tert*-butyl acetate is reported. The Lewis acid regulates the selectivity of methylallylation and vinylation in this

reaction. As a result, $In(OTf)_3$ catalyzes this reaction towards quaternary center selective α-vinylation. This reaction is solely directed by $Ni(OTf)_2$ to produce methylallylation. The sequential rearrangement and nucleophilic addition of *iso*-butylene to peroxyoxindole can be used to produce methylallyl functionalized 1,4-benzoxazin-3-one derivatives. Furthermore, kinetics and DFT studies are used to explain high selectivity and mechanisms in detailed.

3.6.1. Optimization studies

At first, *tert*-butyl acetate was used as the *iso*-butylene source for the synthesis of vinyl 3-methyl-3-hydroxyoxindole **88a**. In the control experiment, *tert*-butyl acetate **89** and **88a** were mixed at ambient temperature and 60 °C without the use of a catalyst, and no reaction was observed (Table 10, entries 1 and 2). Vinylation at the C3 position of **88a** was examined using several Lewis acids. When $In(OTf)_3$ was employed as a catalyst at 60 °C, the highly substituted alkene **90a** (31%, Saytzeff product) was produced as a major product and the less substituted methylallylated molecule **90a'** as a minor product (23%, Hoffmann product) (Table 10, entry 3). The reaction was remain unsuccessful using the catalysts $Cu(OTf)_2$, $Mn(OTf)_2$, $FeCl_3•6H_2O$, $LiClO_4$, and $AlCl_3$ (Table 10, entries 4,5,7,9, and 11). The use of other Lewis acids such as $Sn(OTf)_2$, $Mn(ClO_4)_2•xH_2O$, and $BF_3•O(C_2H_5)_2$ resulted in poor yield of product **90a** (Table 10, entries 6,8 and 10). Further, no product was observed with triflic acid and the starting material was decomposed (Table 10, entry 12). Notably, the vinylation reaction using catalyst $In(OTf)_3$ was highly efficient when used 20 mol% and the reaction yield was 63% (**90a + 90a'**) (Table 10, entry 15). To ensure the optimal reaction conditions, reaction parameters, such as temperature and time, were carefully evaluated (Table 10, entries 15-17). The satisfactory yield of 81% (**90a + 90a'**) was obtained with 20% of $In(OTf)_3$ used and heated at 80 °C for 12 h. The better yield with $In(OTf)_3$ might be due to the higher Lewis acidity than other catalysts. Amazingly, the selectivity on the Hoffman product **90a'** was observed with the $Ni(OTf)_2$ catalyst with 65% of the isolated yield (Table 10, entry 18).

Table 10. Optimization of reaction conditions



entry[a]	catalyst	catalyst loading (mol%)	temp (°C)	yield 90a (%)	yield 90a' (%)
1	-	-	rt	-	-
2	-	-	60	-	-
3	$In(OTf)_3$	10	60	31	23
4	$Cu(OTf)_2$	10	60	no reaction	
5	$Mn(OTf)_2$	10	60	no reaction	
6	$Sn(OTf)_2$	10	60	27	19
7	$FeCl_3•6H_2O$	10	60	no reaction	
8	$Mn(ClO_4)_2•xH_2O$	10	60	15	13
9	$LiClO_4$	10	60	no reaction	
10	$BF_3•O(C_2H_5)_2$	10	60	20	23
11	$AlCl_3$	10	60	no reaction	
12	TfOH	10	60	decomposition	
13	$In(OTf)_3$	10	40	15	10
14	$In(OTf)_3$	10	rt	no reaction	
15	$In(OTf)_3$	20	60	42	21
16	$In(OTf)_3$	20	80	54	27
17	$In(OTf)_3$	20	100	49	29
18	$Ni(OTf)_2$	20	80	-	65

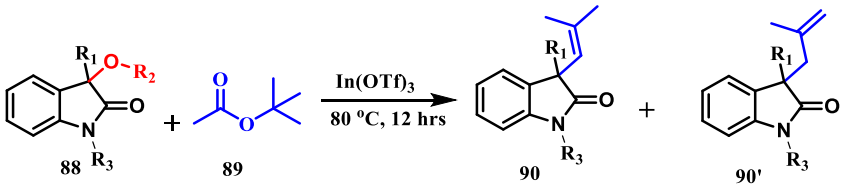
[a]**Reaction condition:** All the reactions were performed using 0.12 mmol of **88a** and the catalyst in *tert*-butyl acetate (**89**, 1.5 mL) was heated at the mentioned temperature in a resealable vial for 12 h.

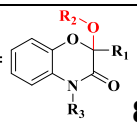
3.6.2. The substrate scope for the methyallyaltion and vinylation

The substrate scope was explored under the optimized reaction conditions (Table 11). The derivatives of 2-oxindole featuring the substituted phenyl group were well tolerated under the developed reaction

condition to acquire a substituted vinyl quaternary compound as the major product. The reaction is proceeded smoothly with the C3-methyl substituted 3-hydroxy oxindole derivative providing a

Table 11. Substrate scope for $In(OTf)_3$ catalyzed *α*-vinylation reaction



entry[a]	substrate			yield %	
	R_1	R_2	R_3	**90a**	**90a'**
1	**88a**: Me	H	H	**90a** (54)	**90a'**(27)
2[b]	**88b**: C_4H_9	H	H	**90b** +**90b'** (59)	
3	**88c**: Me	H	Me	**90c** (58)	**90c'** (25)
4	**88d**: Me	H	C_4H_9	**90d** (41)	**90d'** (32)
5	**88e**: 4-MeC_6H_4	H	Me	**90e** (64)	**90e'** (31)
6	**88f**: 3-FC_6H_4	H	Me	**90f** (52)	**90f'** (32)
7	**88g**: 4-$MeOC_6H_4$	H	Me	**90g** (52)	**90g'** (33)
8	**88h**: 4*t*BuC_6H_4	H	Bn	**90h** (42)	**90h'** (39)
9[b]	**88i**: Naphthyl	H	Bn	**90i** + **90i'** (72)	
10[b]	**88j**: 4-$MeOC_6H_4$	H	Bn	**90j** + **90j'** (**88**)	
11	**88k**: 4-MeC_6H_4	H	BrC_8H_{14}	**90k** (53)	**90k'** (24)
12	**88l**: 4-MeC_6H_4	Me	Me	**90e** (51)	**90e'** (42)
13[b,c]	**1** =  **88m**: Me	Me	Me	**92f + 92f'** (54)	

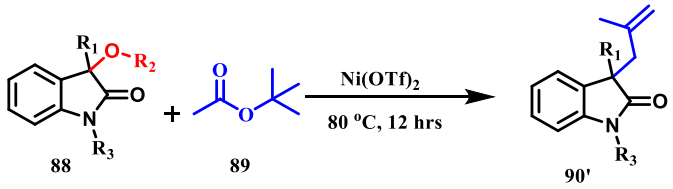
[a]**Reaction condition:** All the reactions were performed using 0.12-0.31 mol of **88** in *tert*-butyl acetate **89** (1.5 mL) with 20 mol% $In(OTf)_3$ at 80 °C in a resealable vial. [b]1:1 ratio by ^{1}H-NMR, [c] **88m** = 2-methoxy-2,4-dimethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one.

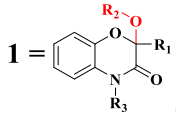
moderate yield as a mixture of vinyl and methylallyl substituted products **90b-d** and **90b'-d'**. The phenyl group with -CH_3, -F, and -OMe attached to the C3-position of 3-hydroxy *N*-methyl oxindole afforded 95% yield of **90e** +**90e',** 84% yield of **90f + 90f'** and 85% yield of **90g + 90g'** respectively. Similarly, other substituted hydroxy oxindole was also well tolerated under the reaction conditions and provided a moderate yield of the desired products, **90h-k,** and **90h'-k'**. Moreover, the reaction with hindered naphthalene substituted 2-oxindole afforded a mixture of **90i** and **90i'** with 83% yield. To determine the generality of quaternary *iso*-butenylation through nucleophilic substitution, C3-methoxy-substituted oxindole was used. Thus, the quaternary vinylation and methylation of C3-methoxy oxindole and 1,4-benzooxazin-3-one derivatives through nucleophilic substitution afforded a satisfactory yield of substituted vinyl and methylallyl products (**90e + 90e'** and **92f + 92f'**) respectively.

3.6.3. The substrate scope for the selective methyallyaltion

Exclusive selectivity on Hoffman product **90a'** i.e methylallylation was isolated when 2-oxindole featuring –OH or –OMe substituted at the C3 position when **88a** treated with *tert*-butyl acetate in the presence of 20 mol% of $Ni(OTf)_2$ as the catalyst (Table 12). Thus, this reaction of alkyl-substituted hydroxy oxindole afforded the moderate yield of the quaternary methylallylated products (**90a'-d'**, Table 12). The exclusive selectivity for **90e'** and **90f'** were observed with aryl-substituted hydroxy oxindoles with a good yield of 61% and 76% respectively (Table 12). *N*-substituted C3-hydroxy oxindole was suitable to produce only the quaternary methylallylated products (**90g'**and **90h'**) in high yields (Table 12). The reaction is also well tolerated with C3-OMe substituted oxindoles (**88l** and **88n**) and 1,4-benzooxazin-3-one **88o** derivative and afforded the selective methylallylated product **90e'**, **90n'**and **90o'** respectively.

Table 12. Substrate scope for $Ni(OTf)_2$-catalyzed α-methylallylation



entry[a]	substrate			yield % (3a')
	R_1	R_2	R_3	
1	**88a**: Me	H	H	**90a'**:65
2	**88b:** C_4H_9	H	H	**90b'**:72
3	**88c:** Me	H	Me	**90c'**:70
4	**88d:** Me	H	C_4H_9	**90d'**:81
5	**88e:** 4-MeC_6H_4	H	Me	**90e'**:61
6	**88f:** 3-FC_6H_4	H	Me	**90f'**:76
7	**88g:** 4-$MeOC_6H_4$	H	Me	**90g'**:79
8	**88h:** 4^{t}BuC_6H_4	H	Bn	**90h'**:66
9	**88l:** 4-MeC_6H_4	Me	Me	**90e'**:65
10	**88n:** 3,5-F,FC_6H_3	Me	Me	**90n'**:72
11	**1** =  **88o:** C_6H_5	Me	Me	**90o'**:77

Reaction Condition: [a]All the reactions were conducted using 0.12-0.31 mmol of **88** in *tert*-butyl acetate (**89**, 1.5 mL) with 20 mol% $Ni(OTf)_2$ at 80 °C in the resealable vial. [b]**88o** =2-methoxy-2-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4H)-one.

3.6.4. DFT studies for the methylallylation and vinylation

Quantum chemical calculations are carried out to understand the feasibility of reaction mechanism. All calculations were performed using Density Functional Theory (DFT) based methodology as implemented in the Gaussian 09 package.4 The structures are optimized using PBE functional[117] with TZVP basis set for C, H, O, S, F, and N atoms and LANL2DZ for Ni, Sn, and In. Vibrational frequency calculations were performed to confirm that each optimized structure corresponds to minima. Solvent effects were included in the calculations as implemented in the SMD model for acetic acid. In cases of

transition states, a preoptimization was carried out prior to the transition state search. The transition state was identified by the presence of a single imaginary frequency. The energies reported in the free energy profile are ΔG values incorporated with zero-point energy corrections for the optimized minima at 298.15 K. Different functionals including dispersion effects (i.e.; B3LYP, PBE, and M06) are benchmarked (see Figure 58 and 60). Finally, the structures were optimized using the PBE functional.

Density Functional Theory (DFT) calculations were carried out using PBE functional to obtain mechanistic insights, understand the reaction pathway, and identify the reaction intermediates. The role of $In(OTf)_3$ and $Ni(OTf)_2$ in catalyzing the product selectivity for nucleophilic substitution (Figure 59 and Figure 61) was discussed. For all the In and Ni species, studies have been performed for the lowest spin state (singlet). The cycle initiates with the coordination of $Ni(OTf)_2$ and $In(OTf)_3$ with incoming substrate **88a** to form intermediate **E3** through the transition state [**TS1**]. This process is thermo-dynamically favorable and the energy barrier is found to be lower for Ni-mediated [**TS1]** (9.57 kcal/mol) as compared to In-mediated [**TS1]** (15.95 kcal/mol). Further, intermediate **88aa** reacts with *iso*-butylene (nucleophile generated in-situ) in presence of HOTf resulting in **88ab** intermediate which is exergonic by 13.09 kcal/mol through [**TS2]**. Finally, the abstraction of hydrogen in presence of (OTf)Ni-OH/$(OTf)_2$In-OH leads to product formation. The selectivity of product formation is dependent particularly on the type of H abstraction. This is indicated in the [**TS3/TS3'**] involved during this process. For $Ni(OTf)_2$, H abstraction via [**TS3'**] (41.4 kcal/mol) results in the formation of a terminal product which is exergonic by 6.14 kcal/mol. When the reaction proceeds via [**TS3]** the transition state barrier is found to be higher resulting in a substituted product that is endergonic by 6.5 kcal/mol. Therefore, it is evident that the pathway followed gives a predominantly terminal substituted product (Hoffman product (**90a'**)). However, in the presence of $In(OTf)_3$, the mixture of products is obtained i.e.; both Hoffmann (-40.9 kcal/mol) and Saytzeff (-39.2 kcal/mol) products are obtained via [**TS3**/**TS3'**]. The energy barrier for [**TS3/TS3'**] in this step corresponds to 39.4 kcal/mol and 40.1 kcal/mol, respectively. These calculations conclude that the formation of a terminal product is feasible over the substituted product when $Ni(OTf)_2$ is involved in the reaction mechanism.

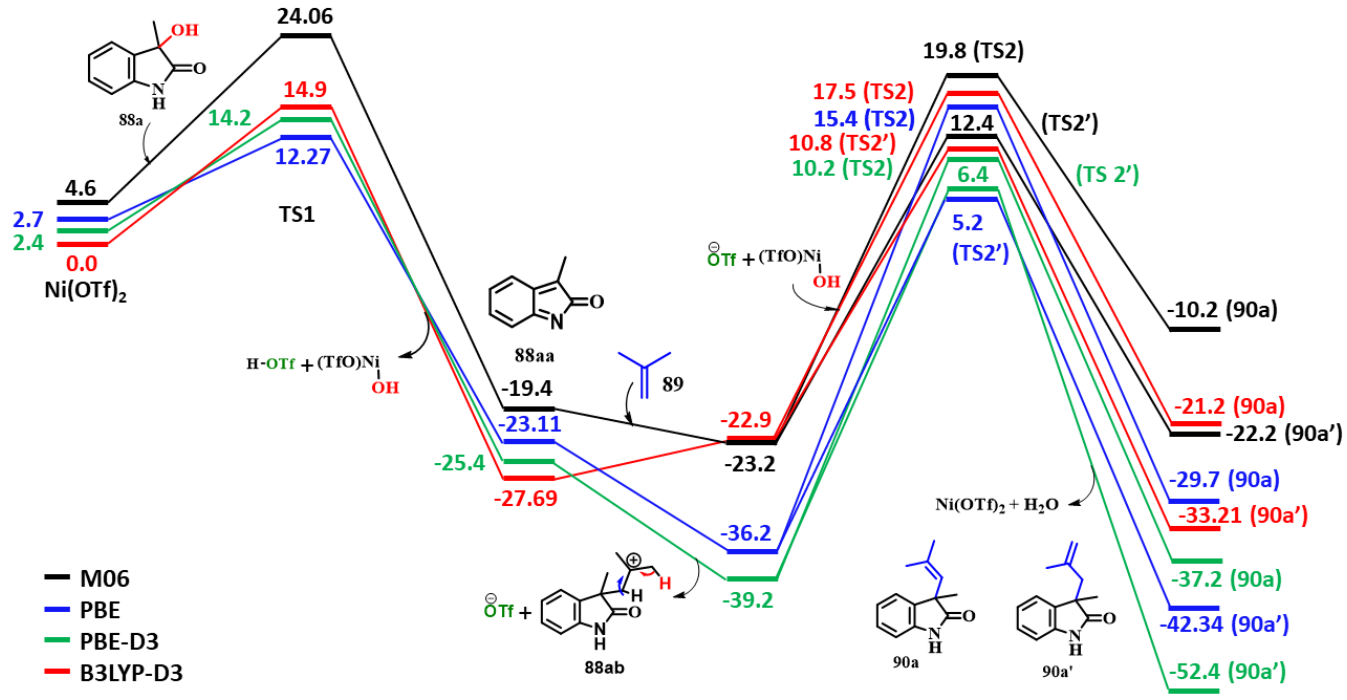


Figure 58: Screening of different functionals with $Ni(OTf)_2$.

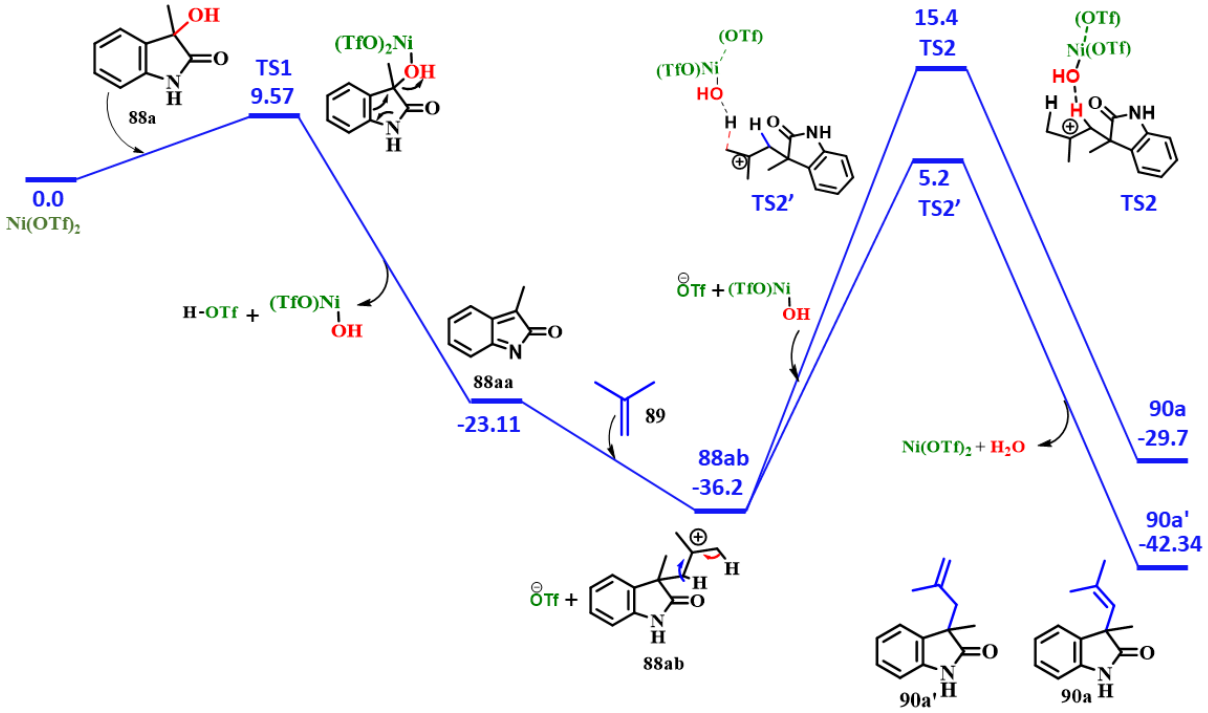


Figure 59: Free energy profile for Ni-catalyzed nucleophilic substitution reaction. The free energy values are given in kcal/mol

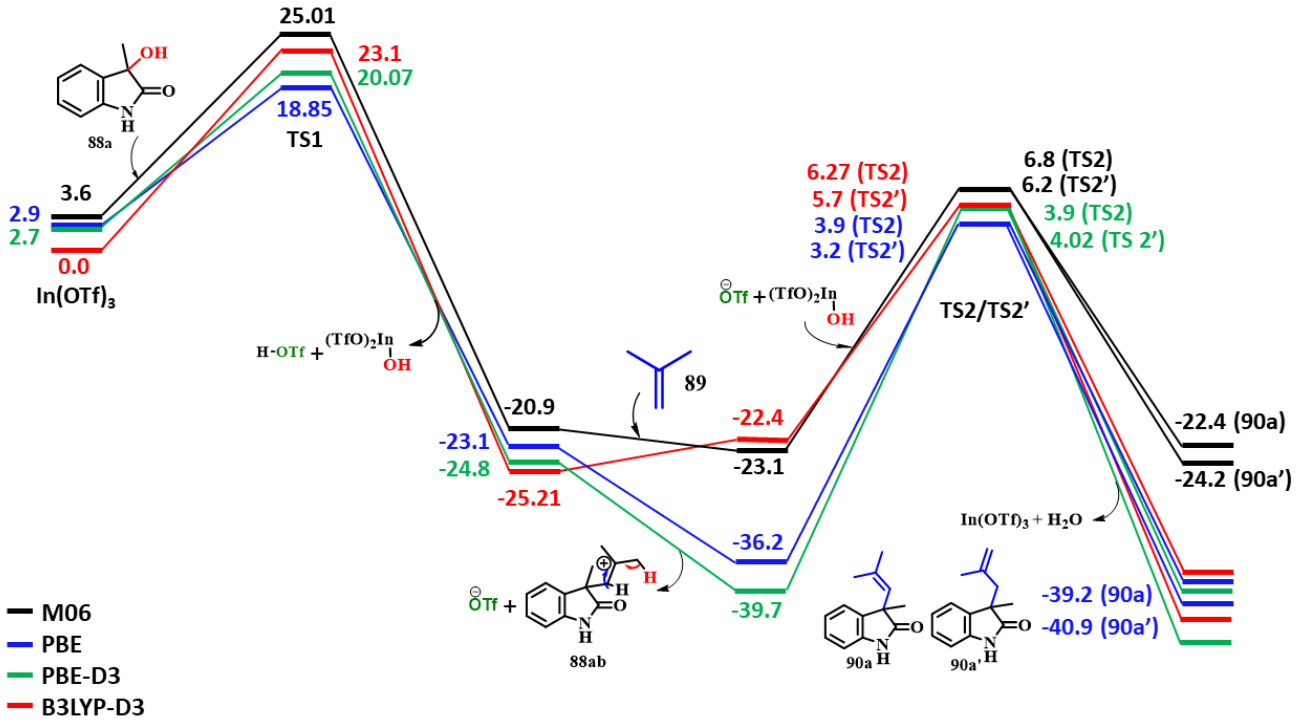


Figure 60: Screening of different functionals with $In(OTf)_3$.

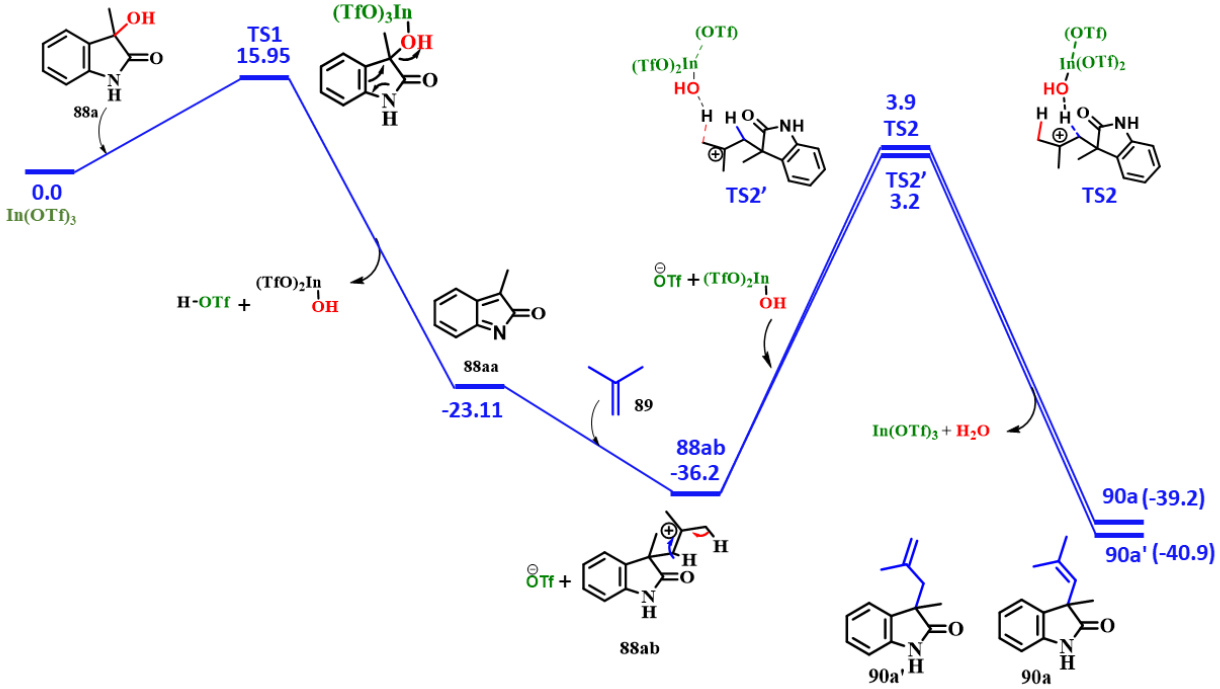


Figure 61: Free energy profile for In-catalyzed nucleophilic substitution reactions. The free energy values are given in kcal/mol.

3.6.5. Plausible Mechanism for the methylallylation of the C3-hydroxy oxindoles

The catalytic cycle (Scheme 54) begins through the coordination of $Ni(OTf)_2$/$In(OTf)_3$ with the oxygen of C3-hydroxy-3-methyl oxindole **88a** to give a transition state [**TS1].** The lone pair on the nitrogen of **TS1** undergoes electronic conjugation to form the intermediate **88aa** with the formation of TfOH acid in the reaction medium. Further, the formation of intermediate **88aa** is confirmed by HRMS analysis (Figure 62). The observed mass of (**88aa**+H) is 146.0602 which is similar to the calculated mass of (**88aa**+H). Next, in situ generated *iso*-butylene undergoes nucleophilic addition at the C3 position of **88aa** to produce the intermediate tertiary carbocation, **88ab** through the **[TS2]**. Finally, $Ni(OTf)_2$-OH abstracts terminal hydrogen via [**TS3'**] to obtain the desired product **90a'**. A similar catalytic cycle occurs in the presence of $In(OTf)_3$ to form the mixture of Hoffmann and Saytzeff products.

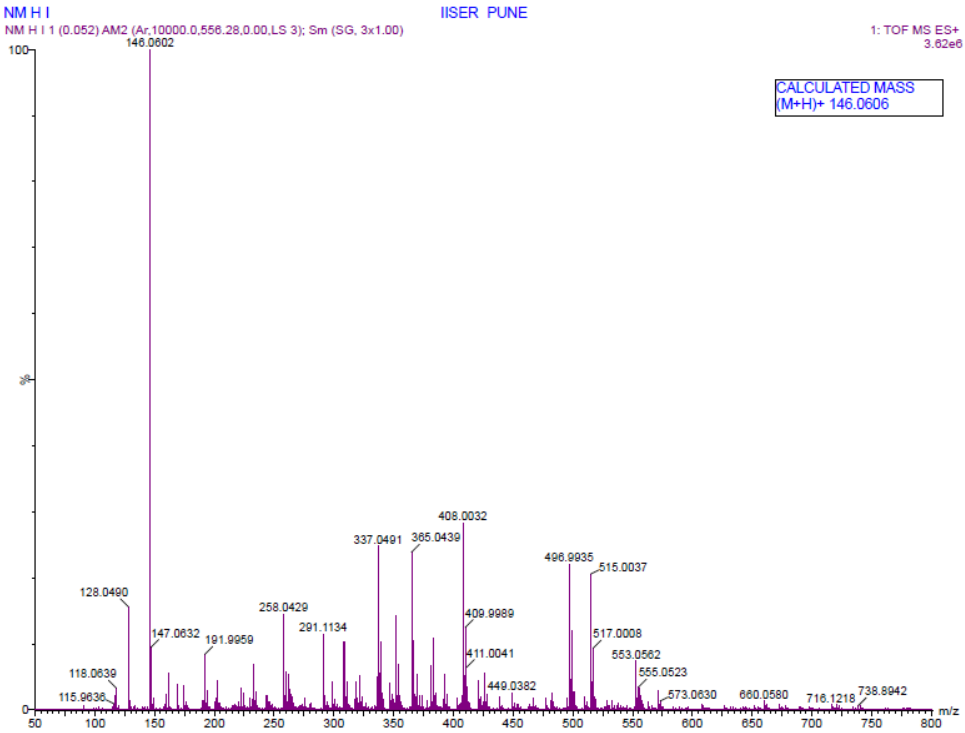
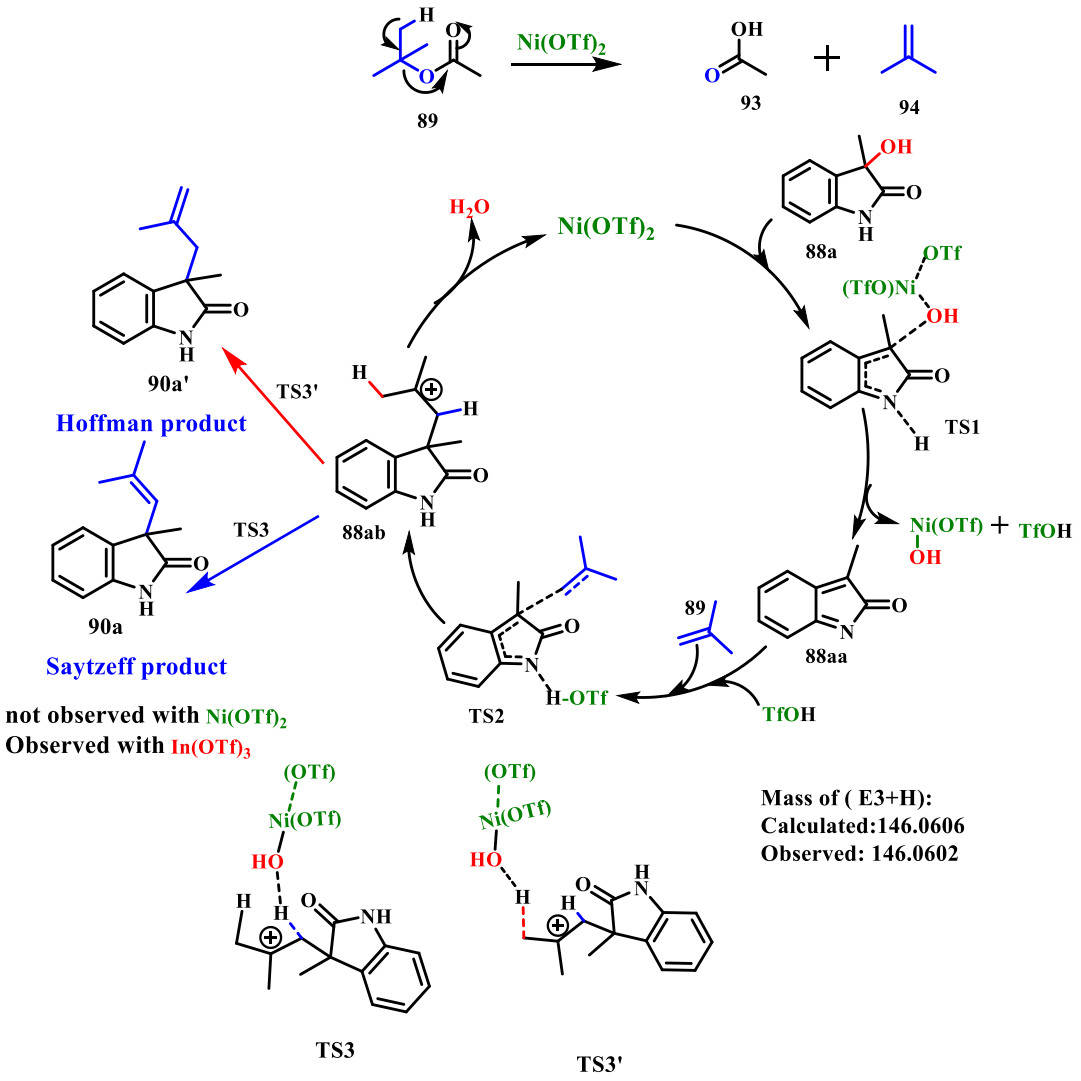


Figure 62: HRMS data of Intermediate **88aa**



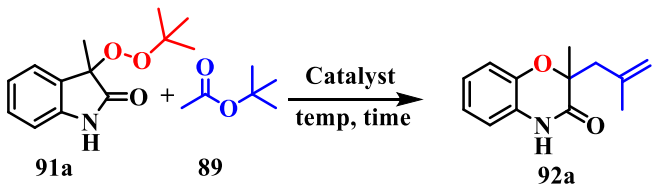
Scheme 54. Plausible catalytic pathway for selective methylallylation

3.6.6. Optimization for the methylallylation via rearrangement of peroxyoxindoles

Subsequently, this reaction with peroxide *N*-functionalized 2-oxindole derivatives was studied to form quaternary methylallyl functionalized 1,4-benzoxazin-3-one. A model reaction was studied for the optimal conditions (Table 13). This reaction did not afford any product in the absence of Lewis acids at room temperature and high temperatures (Table 13, entries 1 and 2). Several Lewis acids, such as $FeCl_3$, $Fe(OTf)_2$, $Mn(OTf)_2$, $Sn(OTf)_2$, $Ni(OTf)_2$, and $Cu(OTf)_2$ (Table 13, entry 1–8) was utilized; however, none of these catalysts achieved satisfactory results. However, sequential rearrangement with exclusive selectivity for methylallylation was observed when 30% of $In(OTf)_3$ was used as a catalyst at 60 °C to afford a 52% yield of **92a** (Table 13, entry 9). This reaction afforded an 85% yield of **92a** after 24 h (Table 13, entry 11). The yield decreased when the temperature increased to 80 °C, and **86a** decomposed when the reaction temperature was 100 °C

(Table 13, entries 12, 13). Moreover, Bronsted acids such as amberlyst®-15 provided 10% of **92a** and TFA failed to provide **92a** (Table 13 entries 14 and 15).

Table 13. Optimization for rearrangement reaction peroxyoxindole.



91a 89 92a

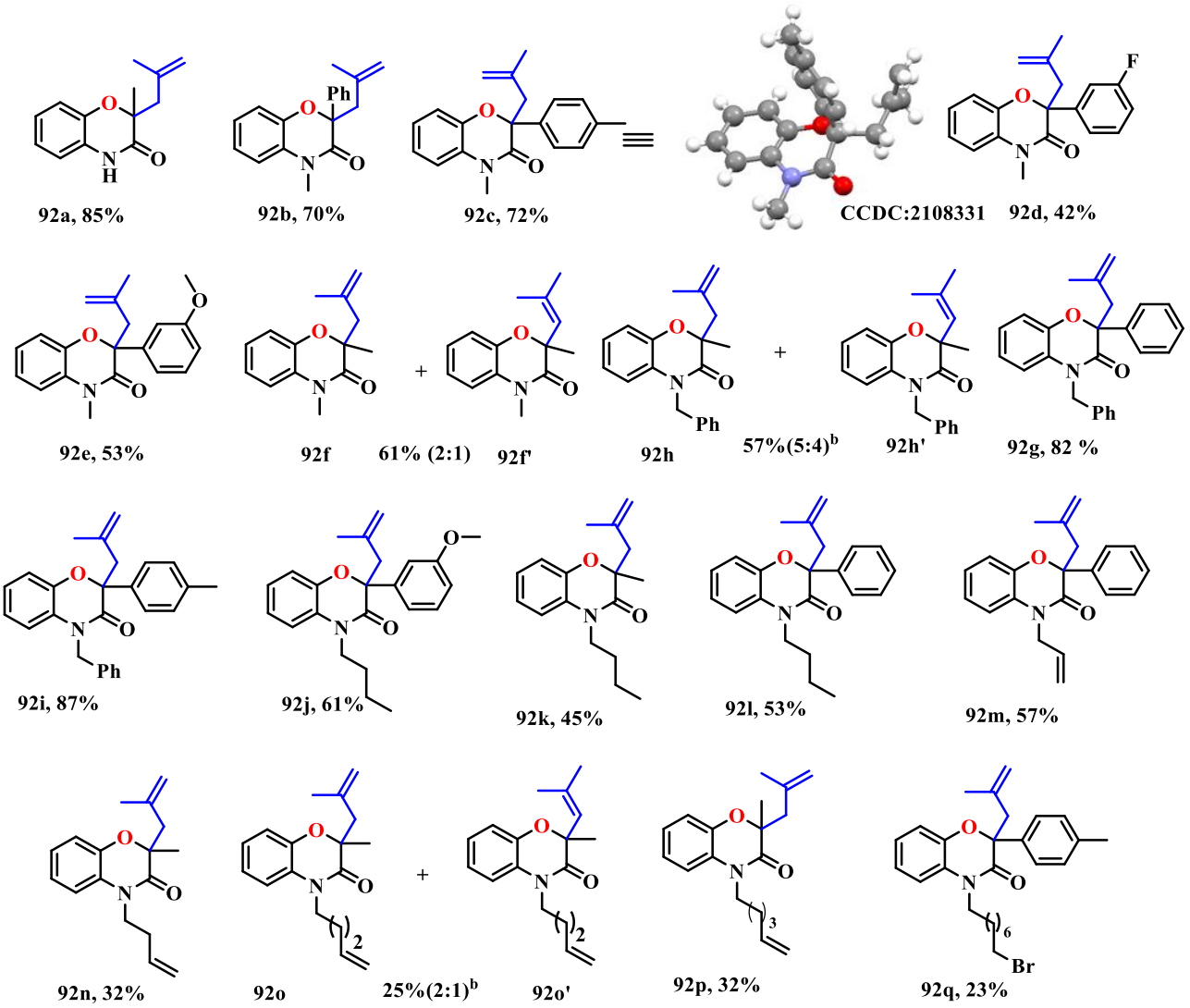
entry[a]	catalyst	temp (°C)	time (hrs)	yield of 92a (%)
1	-	rt	16	no reaction
2	-	60	16	no reaction
3[b]	$FeCl_3$	60	16	0
4	$Mn(OTf)_2$	60	16	no reaction
5	$Sn(OTf)_2$	60	16	45
6	$Fe(OTf)_2$	60	16	0
7	$Ni(OTf)_2$	60	16	no reaction
8	$Cu(OTf)_2$	60	16	no reaction
9	$In(OTf)_3$	60	16	52
10[b]	$In(OTf)_3$	rt	16	0
11[c]	$In(OTf)_3$	60	24	85
12	$In(OTf)_3$	80	24	47
13	$In(OTf)_3$	100	24	decomposition
14[d]	Amberlyst®-15	60	24	10
15	TFA	60	24	decomposition

[a]**Reaction conditions**: All the reactions were performed using 0.21 mmol of **91a** in *tert*-butyl acetate (1.5 mL) with 30 mol% catalysts at a specific temperature in the resealable vial; [b]No expected product was obtained. [c]63% of product **92a** was obtained with 20 mol% $In(OTf)_3$; [d]w/w ratio of 2:1 was used for substrate : Amberlyst®-15.

3.6.7. The substrate scope for the methylallylation via rearrangement of peroxyoxindoles.

Next, the substrate scope for this methylallyl functionalization was explored with various C3-alkylated peroxyoxindole (Scheme 55). Thus, *N*-protected C3-substituted peroxyoxindole, where the

phenyl group had –CH_3, –F, and –OMe, afforded a good yield of the respective methylallyl substituted products **92b–e** in 42-72% yields. Further, the structure of product **92c** is confirmed by



Reaction condition[a]: All reactions were carried out at 0.15-0.21 mmol (50 mg) of **91** in *tert*-butyl acetate (**89**, 1.5mL) using 30 mol % of $In(OTf)_3$ at 60 ^oC in the resealable tube for 24 hrs; [b]NMR conversion.

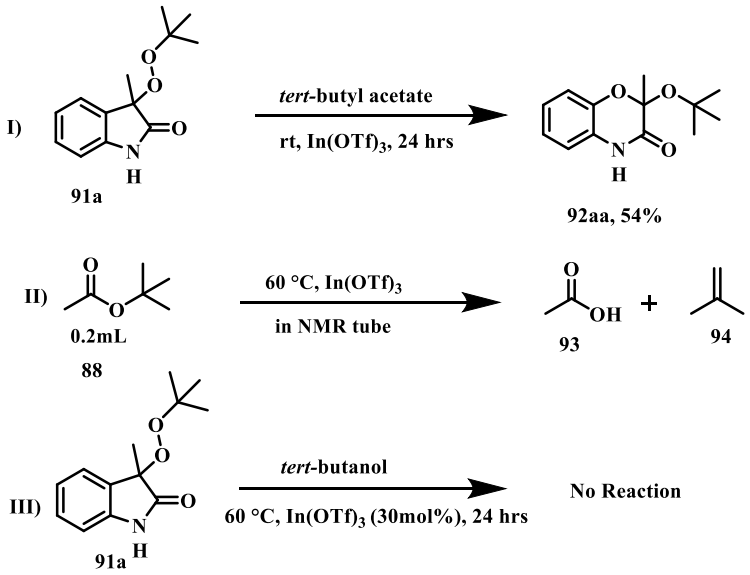
Scheme 55. Substrate scope for the sequential rearrangement and methylallylation reaction[a]

X-ray structure (Figure 94). The *N*-benzyl-protected peroxyoxindole derivatives also underwent a successful methylallylation reaction to provide a good yield of the rearranged products, **92g**–**h**. The decrease in yield was observed for C3-substituted *N*-butyl peroxyoxindole derivatives (**92j-l**). This reaction was tolerant to allyl functionality to afford a 75% yield of a mixture of Hoffmann and Saytzeff products, **92m** and **92m'** (ratio 3:1, Scheme 55). The C3-phenyl *N*-allyl substituted peroxyoxindole afforded selectively **92n** in 57% yield. The yield decreased with increasing the

carbon chain of *N*-substitution of peroxyoxindole, i.e., *N*-allyl, *N*-butene, *N*-pentene, *N*-hexene, *N*-(8-bromooctyl) substituted peroxyoxindole afforded desired **92o**–**r**, respectively.

3.6.8. Experimental studies for the mechanistic investigation of rearrangement reaction

To understand the reaction pathway, a control experiment was performed with *tert*-butyl acetate, **91a** and $In(OTf)_3$ at room temperature (Scheme 56 (I)) resulted attacking of *tert*-butyloxy group at C3-position of 1,4-benzooxazine moiety. This indicates that heating is required for the generation of *iso*-butylene. Further, the reaction was performed in the NMR tube with *tert*-butyl acetate and $In(OTf)_3$ at 60 ^oC (Scheme 56 (II)). Initially, the NMR of the reaction mixture was recorded in the absence of the catalyst (Figure 63 and Figure 64). Later, the catalyst was added into the NMR tube and recorded the NMR, and the characteristic peak of the *iso*-butylene was not observed in the ^1H and ^{13}C spectrum (Figures 65 and 66). Further, the tube was kept in a pre-heated oil bath at 60 ^oC for 12 h. After 12 h, the NMR was recorded. A significant peak at 4.57 ppm (septet) in the ^1H NMR spectrum confirms the *iso*-butylene formation (Figure 67) and which is not observed before heating the reaction mixture.



Scheme 56. Preliminary experiment for the mechanistic study

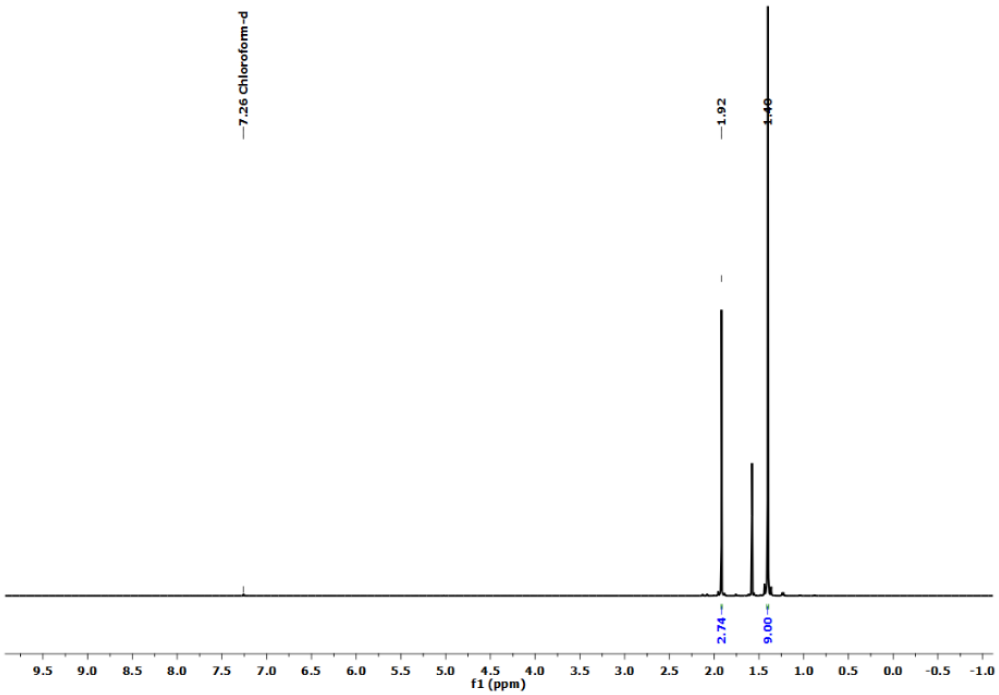


Figure 63: ^{1}H NMR of reaction mixture in absences of $In(OTf)_3$ at room temperature

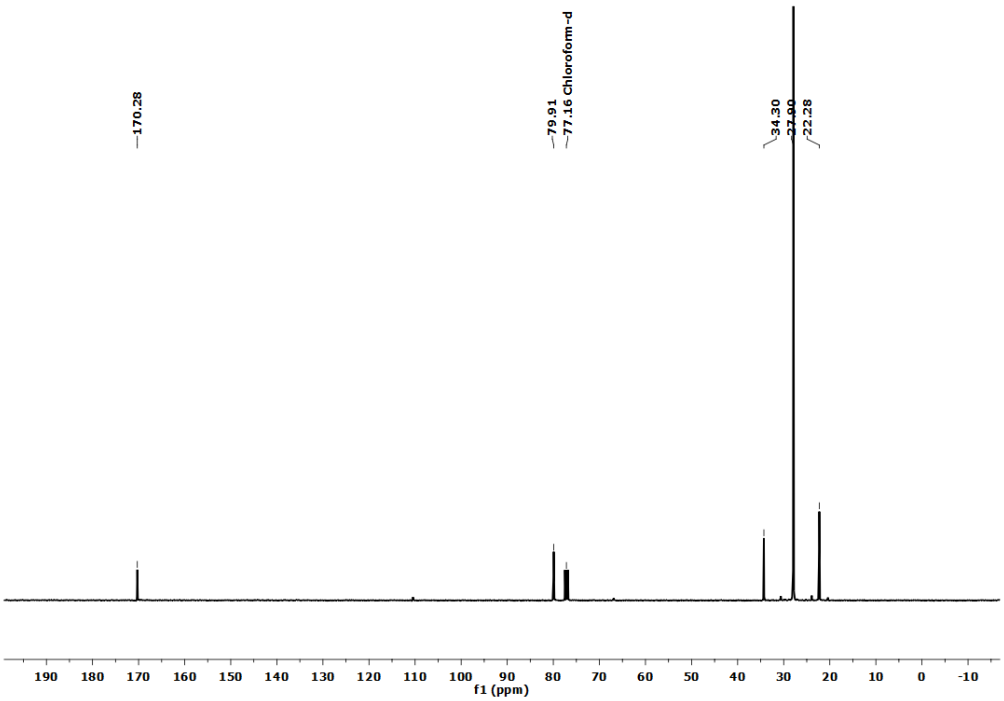


Figure 64: ^{13}C NMR of reaction mixture without $In(OTf)_3$ at room temperature

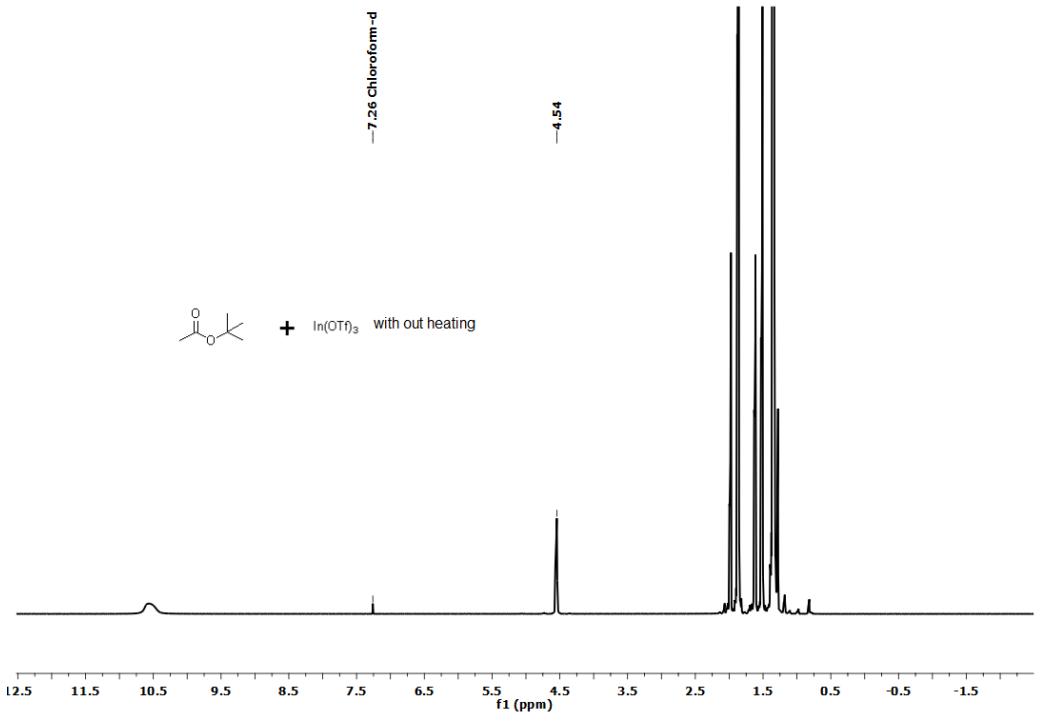


Figure 65: ^{1}H NMR of *tert*-butylacetate with $In(OTf)_3$ before heating the NMR tube

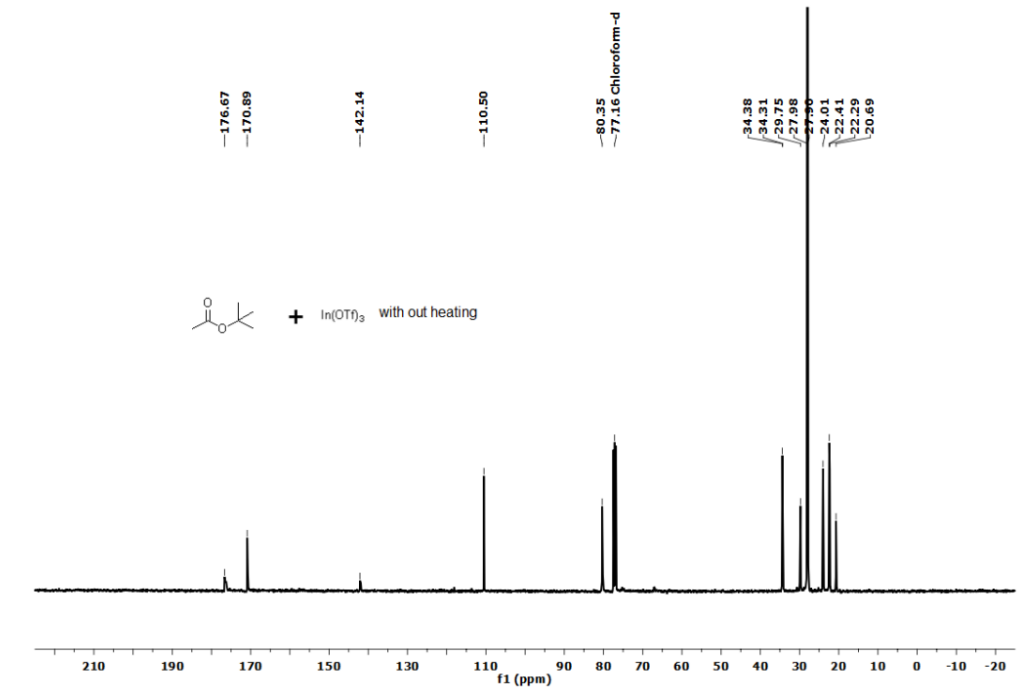


Figure 66: ^{13}C NMR of *tert*-butylacetate with $In(OTf)_3$ before heating the NMR tube

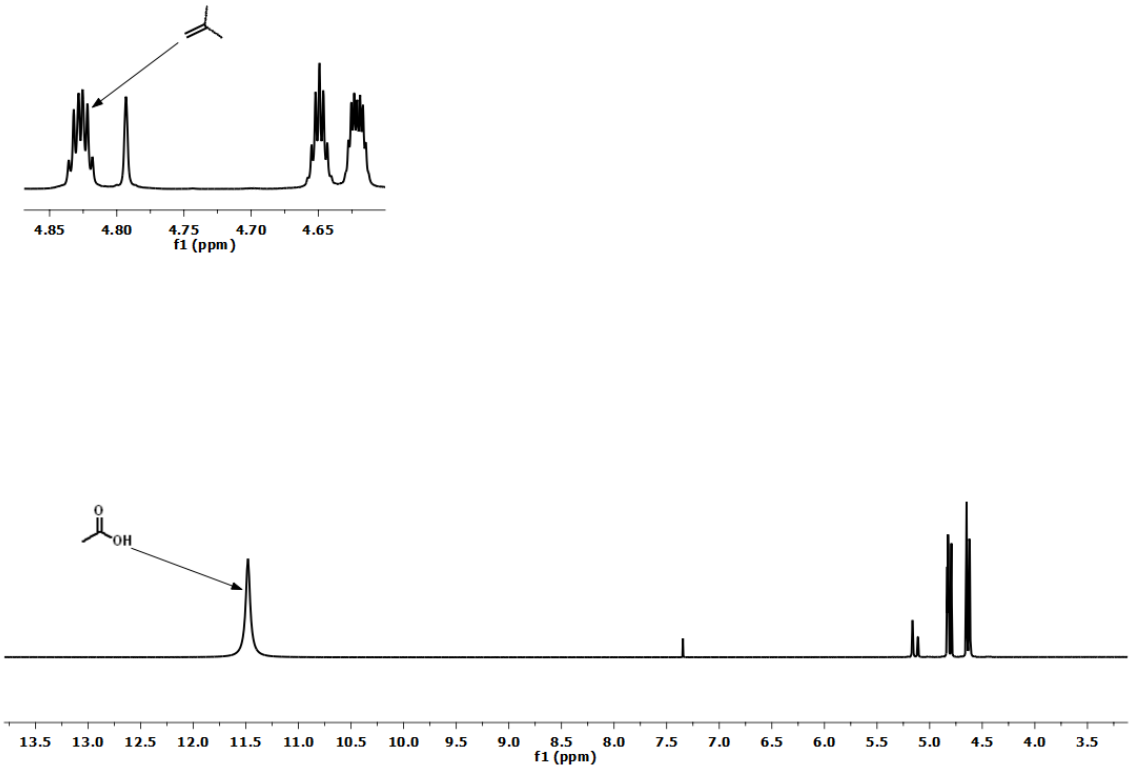


Figure 67: ^{1}H NMR of reaction mixture with $In(OTf)_3$ at 60 ^{o}C

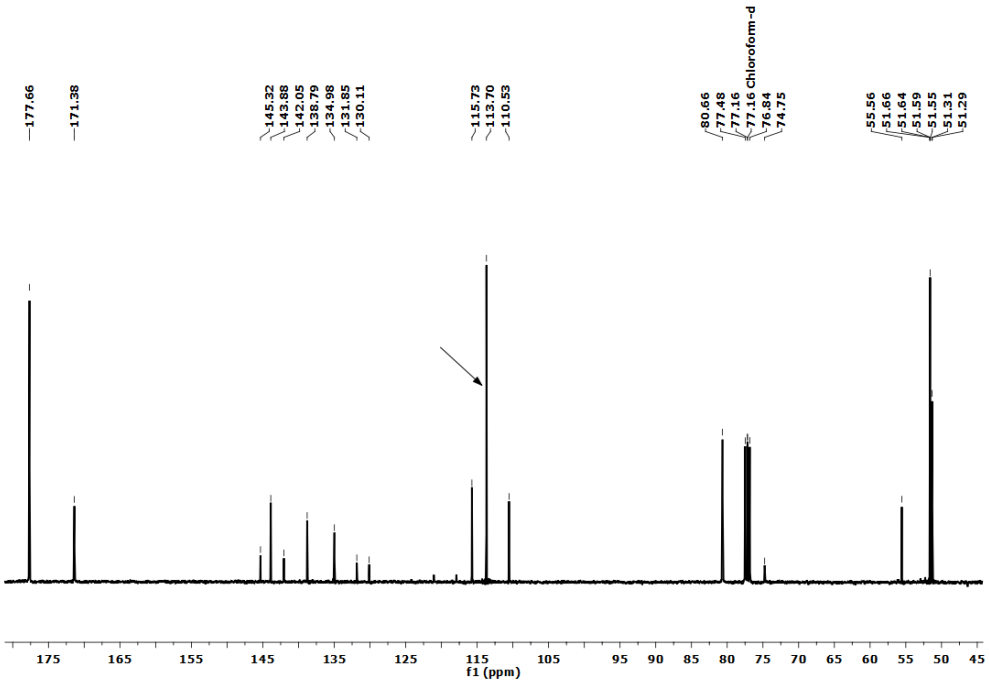


Figure 68: ^{13}**C** NMR of reaction mixture with In(OTf)3 at 60 ^{o}C.

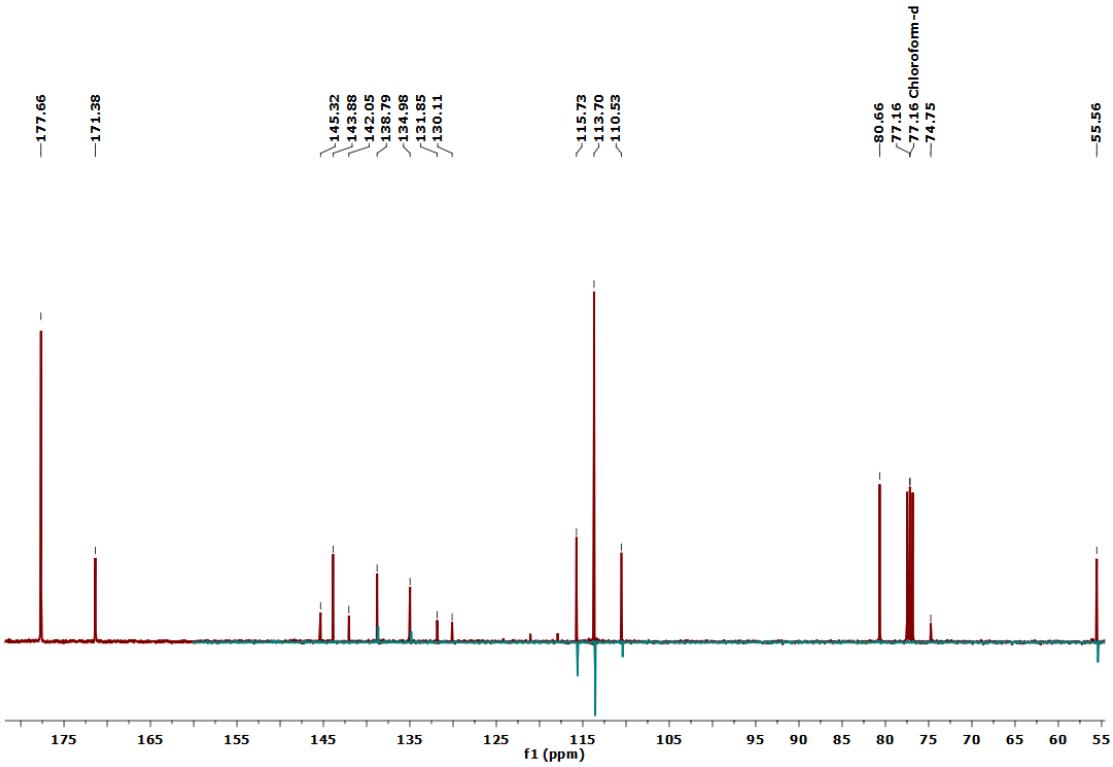


Figure 69: ^{13}C and DEPT-135 stacked NMR of reaction mixture with $In(OTf)_3$ after heating the NMR tube

The peak at 177.66 ppm (-C=O) in $^{13}C\{^1H\}$ NMR spectrum confirms the acetic acid formation and the peak at 138.88 ppm confirms the quaternary carbon of the *iso*-butylene (Figure 68). From the $^{13}C\{^1H\}$ and DEPT-135 NMR spectrum, a peak at 115 ppm ($=CH_2$) confirms the formation of *iso*-butylene gas (Figure 69). The results of these experiments were confirming the in-situ generation of *iso*-butylene in the reaction mixture. Furthermore, the reaction of **91a** with *tert*-butanol resulted in no reaction (Scheme 56 (III)), indicating that *tert*-butanol might coordinate with the Lewis acid, which diminishes the reactivity of Lewis acid.

3.6.9. Kinetic analysis for the rearrangement reaction of peroxyoxindole

The reaction kinetics was studied by varying concentration the catalyst and peroxide **91a**. Moreover, this kinetic study helps to understand the effect of various components on the sequential rearrangement and methylallytion reaction for the formation of **92a** by the initial rate method. Initially, the rate order for the formation of **92a** was determined by measuring the initial rate of the reaction at different concentrations of **91a**. The various concentrations of **91a** (0.05 M, 0.1 M, 0.2 M, 0.3 M, 0.4 M) were reacted with 0.03 M of $In(OTf)_3$ catalyst (Figure 70 (A)). This indicates that the rate of the reaction increases upon increasing the concentration of **91a** and a slope of 0.985 was obtained from the plot of log(rate) versus log(concentration of **91a**) (Figure 70 (B)).

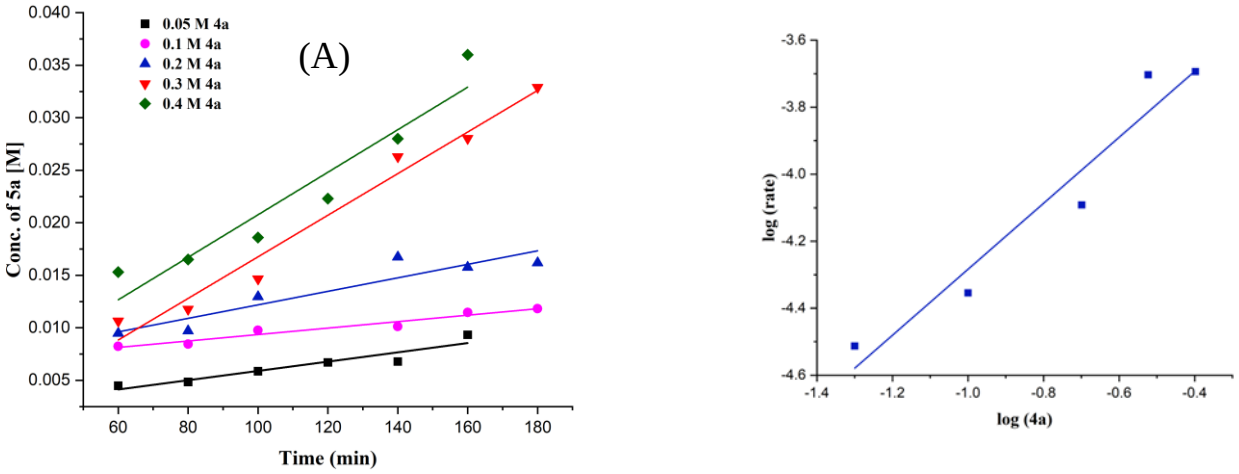


Figure 70. (A)Time-dependent formation of **92a** at different initial concentration of **91a**; (B) Plot of log(rate) vs log (conc. **91a**)

Thus, this sequential rearrangement and substitution reaction to form **92a** majorly depends upon the concentration of compound **91a**. Notably, increasing in the rate was observed upon increasing the loading of $In(OTf)_3$ catalyst (Figure 71 (A)), and a slope 0. 863 was obtained (Figure 71 (B)). This highlights that the reaction is in positive order concerning the catalyst $In(OTf)_3$, and involves multiple steps. From the positive rate order concerning the peroxide **91a** and $In(OTf)_3$, the activation of the peroxide **91a** by the catalyst might be the crucial step in the catalytic cycle.

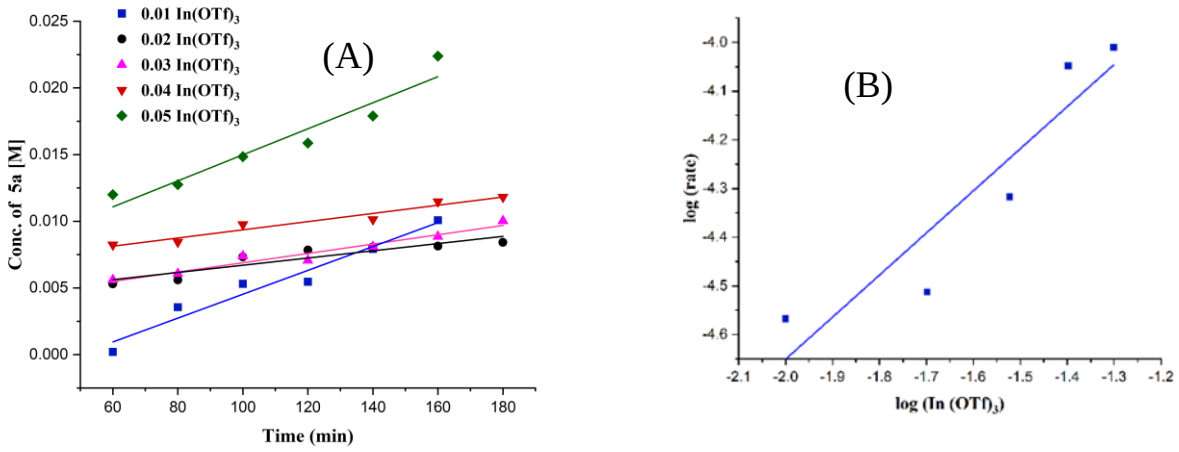


Figure 71. (A)Time-dependent formation of **92a** at different initial concentration of $In(OTf)_3$; (B) Plot of log(rate) *vs* log($In(OTf)_3$)

3.6.10. DFT studies for the rearrangement reaction of peroxyoxindole

To evaluate the energies involved in rearrangement of peroxyoindole derivatives, the energetics were calculated and examined, considering Gnanaprakasam's and coworkers' previous report[117] of $Sn(OTf)_2$-catalyzed rearrangement for peroxyoxindoles. Catalytic cycles of the $Sn(OTf)_2$-catalyzed rearrangement of peroxyoxindoles confirmed that the reaction path proceeds via deprotection of *tert* butyl group from peroxide compound and *in situ* generation of stable 1,4 benzooxazine tertiary carbocation. Next, the feasibility of the $In(OTf)_3$-catalyzed quaternary methylallylation of peroxy-2-oxindole was investigated through skeletal rearrangement and nucleophilic substitution by using *tert*-butyl acetate (Figure 72). The initiation of cycle involves interaction of $In(OTf)_3$ with peroxy substrate **91a** to give coordinated intermediate **91aa** via [**TS1]** with energy barrier of 12.13 kcal/mol. The intermediate **91aa** undergoes protonation at the peroxy oxygen resulting in intermediate **91ab** via [**TS2]** which is endergonic by 14.48 kcal/mol. Here, three possibilities exist, (a) first the intermediate **91ab** can undergo ring expansion via [**TS3']** (6.50 kcal/mol) to intermediate **91ac** indicated in blue color in Figure 74. (b) Secondly, **91ab** can undergo ring expansion, to form hydroxylated intermediate **91ac** through [**TS3]** (with an energy barrier of 1.3 kcal/mol) represented by black color. The removal of hydroxyl anion results in **91ad,** which is exergonic by 6.03 kcal/mol. (c) Lastly, **91ab** can react with the incoming chelated ester to form intermediate **89a'** as shown in red color, which is exergonic by 6.27 kcal/mol which further rearranges to intermediate

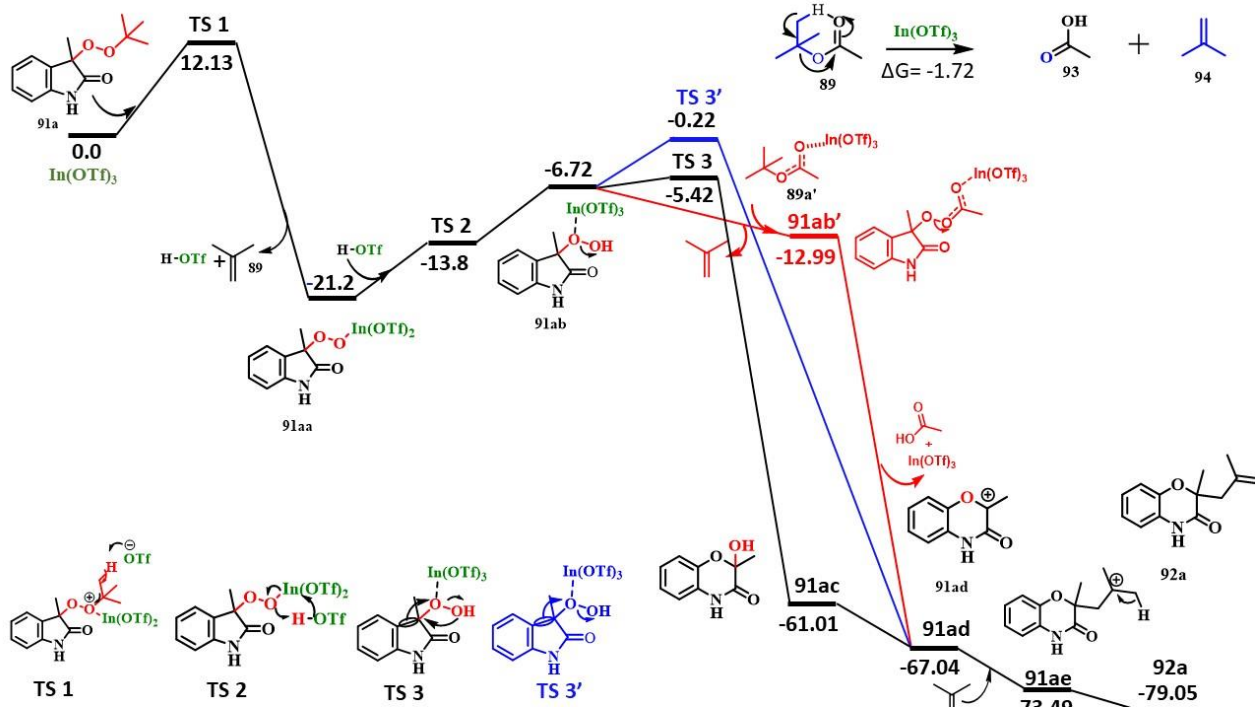
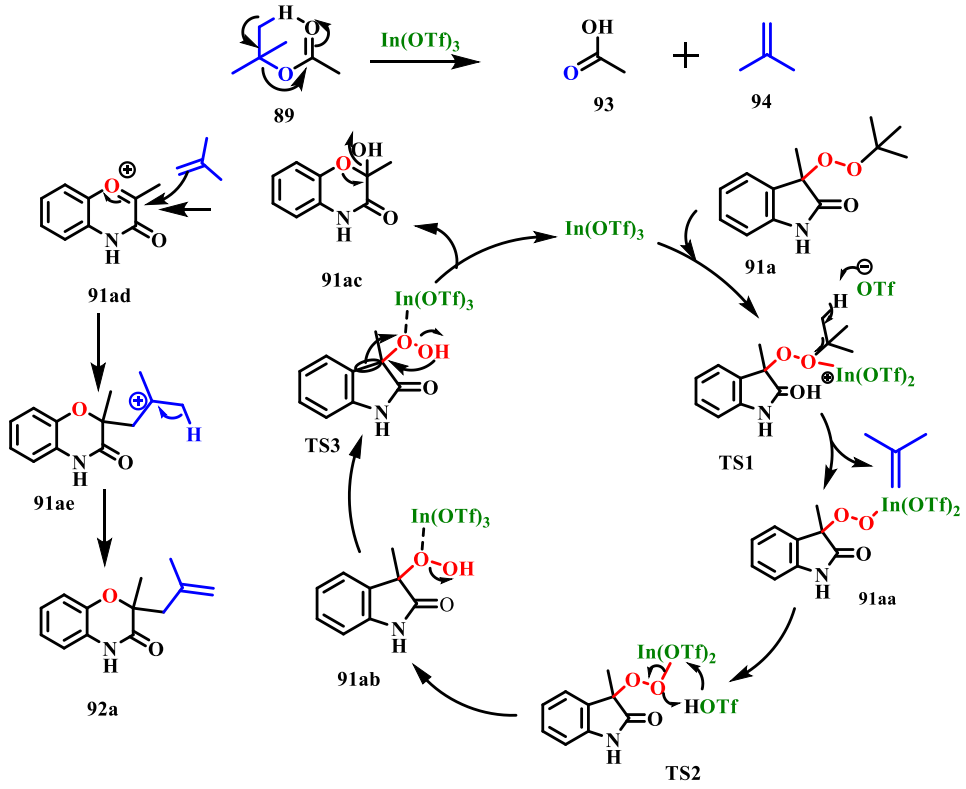


Figure 72. Free energy profile for In-catalyzed rearrangement. The free energy values are given in kcal/mol

91ad. Finally, *iso*-butylene reacts with the protonated intermediate **91ad** resulting in tertiary carbocation **91ae**, which is exergonic by 6.45 kcal/mol. Deprotonation of **91ae** results in the formation of final product **92a**, which is exergonic by 5.56 kcal/mol. DFT studies indicate that all three possibilities are spontaneous. However, the pathway with hydroxy intermediate **91ac** is more favourable. The deprotonation of **91ae** leads to the formation of the final product **92a**, with exergonic energy of 5.56 kcal/mol.

3.6.11. A plausible mechanism for the rearrangement reaction of peroxyoxindole

Based on preliminary experiments, kinetic analysis, computational data, and literature reports[13], a plausible mechanism is proposed (Scheme 57). Initially, *tert*-butyl acetate undergoes ester pyrolysis to produce *iso*-butylene **89**. The catalytic cycle starts with the coordination of $In(OTf)_3$ with peroxyoxindole **91a** to give **TS1**.



Scheme 57. Plausible mechanism for methylallyl functionalization through peroxyoxindole rearrangement

Proton abstraction from transition state **TS1** leads to the formation of intermediate **91aa** with the liberation of *iso*-butylene gas. Intermediate **91ab** formed after the protonation of intermediate **91aa** through transition state **TS2** followed by coordination of regenerated $In(OTf)_3$ from **TS2**. The C3–C4 bond migrates to oxygen attached to the C3 carbon of peroxy group. Simultaneously, the removal of –OH and attack on the C3 position leads to the formation of intermediate **91ac**. Intermediate **91ac** resulted in intermediate **91ad** after –OH removal. The attack of *iso*-butylene on intermediate **91ad** leads to the formation of tertiary carbocation intermediate **91ae**. Finally, deprotonation of **91ae** results in the desired product **92a**.

3.7. Transformation of rearrangement reaction in a continuous flow

While conducting the methylallylation via rearrangement reaction using a resealable reaction vial and observed the development of pressure inside the vial, causing the septum of the aluminium cap to swell during the reaction (Figure 73). As a result, scaling up the reaction in a batch process to gram scale would be challenging. Therefore, the possibility of conducting the reaction was explored using a continuous flow system.

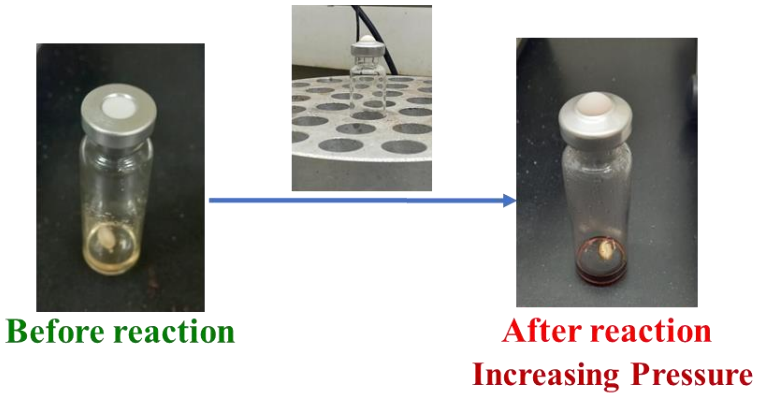


Figure 73. Image of reaction vial during the methylallylation through peroxyoxindole rearrangement reaction in batch

For the large-scale synthesis, the rearrangement of peroxide was integrated into the continuous flow. Initially, the 0.1 M solution of C3-methyl peroxide oxindoles with *tert*-butyl acetate along with $In(OTf)_3$ catalyst was flown to pre-heated SS coil reactor at 80 °C and resulted no product formation. Several parameters such as flow rate, temperature and pressure has been screened to achieve the desired product but the reaction was failed in the homogeneous system. As Gnanaprakasam research group previously reported the rearrangement of peroxyoxindole using amberlyst®-15. Therefore, amberlyst®-15 was selected as catalyst to perform the reaction under continuous flow. At first, 0.1 M solution of **91a** with *tert*-butyl acetate was pumped to the Omnifit reactor bed pre-packed with amberlyst®-15 heated at 80 °C resulted trace amount of desired product.

From the result of previous report on rearrangement disclosed by Gnanaprakasam's research group,[20] the two pre-packed Omnifit reactor bed was integrated with amberlyst®-15 and 0.1 M solution of **91a** with *tert*-butyl acetate was pumped to the integrated reactor bed with 0.1 mL/min flow rate resulted 61% of mixture of product **92a** and **92a'** (Figure 74).

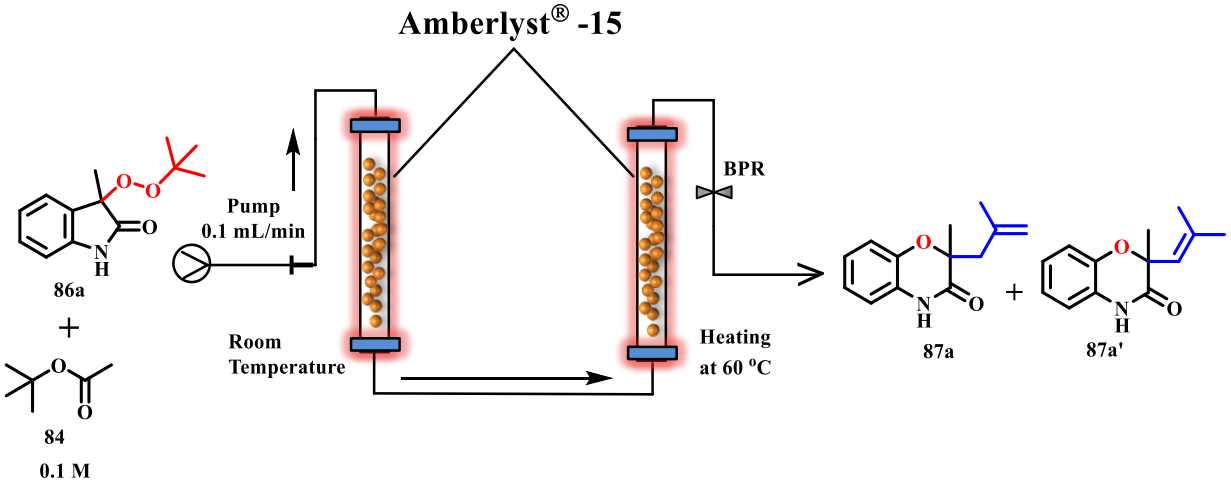


Figure 74. Methylallyl functionalization through peroxyoxindole rearrangement in continuous flow.

3.8. Conclusion

In summary, a new approach was developed for the selective quaternary *α*-vinylation and methylallylation of C3-hydroxy oxindoles and peroxides by using *tert*-butyl acetate in the presence of catalytic $In(OTf)_3$ and $Ni(OTf)_2$. This reaction was demonstrated with a series of vinylated and methylallylated oxindole derivatives. Moreover, $In(OTf)_3$ selectively promoted the quaternary *α*-vinylation of hydroxyl oxindole to afford the Hoffmann product. Interestingly, an exclusive selectivity was obtained for methylallylation of hydroxy oxindole by using catalytic $Ni(OTf)_2$. However, this reaction with peroxyoxindole afforded sequential rearrangement and quaternary methylallylation by using catalytic $In(OTf)_3$. Kinetic studies revealed that both the concentration of reactants and catalysts play a vital role in these reactions. Density Functional Theory (DFT) calculations were performed using PBE functional to obtain the transition state for vinylation and methylallylation reaction. This study was further explained the selectivity for the vinylation and methylallylation reaction when different Lewis acid was used. From the DFT studies, experimental evidences and previous literature report, plausible mechanisms were proposed and justified reaction pathways for the vinylation and methylallylation of hydroxy oxindole and peroxyoxindole.

3.9. Experimental section and characterization data

3.9.1. General information and data collection

Commercially available reagents and solvents were used for the preparation of starting material without further purification. Visualization was accomplished with UV light. Column chromatographic separations were performed over 100-200 Silica-gel. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker 400 MHz and JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha Fourier transform infrared spectrometer. The single-crystal data was collected in Bruker APEX-III. Gas Chromatography analyses were performed using a Shimadzu GC2010 gas chromatograph equipped with a Shimadzu AOC-20i auto injector and a Restek RTX-5 capillary column (30 m x 250 μm). Melting point were recorded on DBK programmable melting point instrument. All melting point were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex IIICCD Duo diffractometer (operated at 1500 W power, 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation. More information on crystal structures (**92c** and **90j'**) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2108331 and 2214336. Although the reaction of a metal salt with organic peroxides leads to an explosive reaction, any issues while using TBHP at 298.15 K was not faced.

3.9.2. Experimental procedure

A) General procedure for methylallylation of C3-hydroxy-3-alkylated oxindole (90)

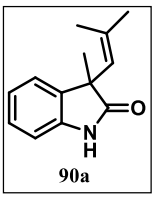
The 1.5 mL of *tert*-butyl acetate was added to the 20 mL resealable vial containing 3-substituted-3-hydroxy oxindole (**88**, 50 mg, 1 equiv.). Then, 20 mol% of $In(OTf)_3$ or $Ni(OTf)_2$ was added to the vial. Finally, the vial was sealed with aluminum cap with septum. Further, the solution was heated at 80 ^{o}C in the preheated oil bath for 12 hrs. After the completion of the reaction, the volatile components were evaporated under vacuo. The residue was purified by silica gel chromatography using EtOAc:*n*-hexane (1:99 to 10:90) to afford desired product **90**.

B) General procedure for methylallylation of C3-peroxide-3-alkylated oxindole (92)

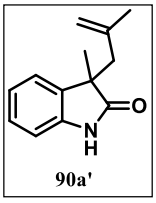
The 1.5 mL of *tert*-butyl acetate was added to the 20 mL resealable vial containing 3-substituted-3-*tert*-butylperoxyoxindole (**91**, 50 mg, 1 equiv.). Then, 30 mol% of $In(OTf)_3$ was added to the vial. Finally, the vial was sealed with an aluminum cap with a septum. Further, the solution was heated in the preheated oil bath at 60 ^{o}C, for 24 hrs. After the completion of the reaction, the volatile

components were evaporated under a vacuum. The residue was purified by silica gel chromatography using EtOAc: *n*-hexane (1:99 to 5:95) to afford desired product **92.**

3.9.3. Analytical data for the product

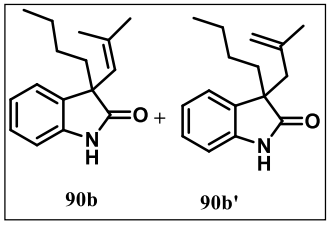


3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90a[117] **and 3-methyl-3-(2-methylallyl)indolin-2-one 90a'** is synthesized by following general experimental procedure A, with mixing of 3-hydroxy-3-methylindolin-2-one (**88a**, 50 mg, 1 equiv.) and $In(OTf)_3$ (20 mol%) in 1.5 mL *tert*-butyl acetate resulted in product **90a** (33.3 mg, 54%) as a white thick liquid and product **90a'** (15 mg, 27%) as a white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (5:95 to 10:90) become white solid after keeping few days. The above reaction resulted 3-methyl-3-(2-methylallyl)indolin-2-one **90a'** with 39.7 mg (65%), when 20 mol% of $Ni(OTf)_2$ use as catalyst after column chromatography purification. **3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90a: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (td, *J*= 7.6, 1.3 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 1H), 7.02 (td, *J* = 7.5, 0.9 Hz, 1H), 6.92 (d, J = 8.1 Hz,1H), 5.44 – 5.40 (m, 1H), 1.72 (d, J = 1.3 Hz, 3H), 1.51 (s, 3H), 1.14 (d, *J* = 0.9 Hz, 3H). ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 183.2, 139.9, 137.9, 136.8, 127.6, 125.3, 123.4, 122.9, 109.9, 49.2, 49.2, 27.7, 26.8, 18.4 ppm. **FTIR** (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for C13H16NO 202.1232; Found 202.1237.



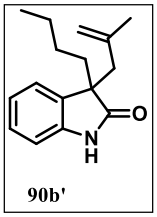
3-methyl-3-(2-methylallyl)indolin-2-one 90a': Melting point: 109−110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 11.9, 4.3 Hz, 2H), 7.03 (dd, *J* = 10.8, 4.2 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.59 (m, 1H), 4.55 (m, 1H), 2.73 (d, *J* = 13.5 Hz, 1H), 2.50 (d, *J* = 13.5 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ δ 183.2, 141.2, 140.4, 134.2, 127.7, 123.5, 122.2, 114.4, 109.8, 49.2, 45.6, 24.9, 23.6.ppm. **FTIR** (neat): 3012, 2801, 1612, 1592, 1355, 1142, 799 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{16}NO$ $(M+H)^+$: 202.1232, found: 202.1235.

3-butyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90b + 3-butyl-3-(2-methylallyl)indolin-2-one 90b' is synthesized by following general experimental procedure A, with mixing of **88b** (50 mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **90b'** + **90b** as inseparable mixture (31 mg, 59%) as thick liquid after column as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (5:95 to 10:90).Data for mixture of product **90b'** + **90b** : **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.20-7.18 (m, 3H), 7.09-7.00 (m, 3H), 6.89-6.8 (m, 2H), 4.55 (m, 1H), 5.35 (s, 1H), 4.57 (m, 1H), 4.54 (s, 1H), 2.70 (d, *J* = 13.2 Hz, 1H,) 2.49 (d, *J* = 13.6 Hz, 1H) 1.62-1.58 (m, 12H), 1.36 (s, 14H), 0.94 (m, 7H) ppm. **^{13}C{^{1}H} NMR**



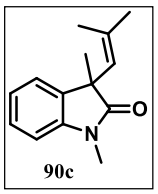
(100 MHz, $CDCl_3$): 141.2, 139.6, 134.2, 128.8, 127.8, 123.8, 122.7, 127.5, 122.3, 114.6, 109.6, 109.5, 54.7, 53.7, 45.6, 41.0, 38.9, 31.9, 31.7, 30.1, 29.8, 26.2, 25.6, 23.9, 23.0, 19.6 ppm. **FTIR** (neat): 3021, 2851, 2341, 1688, 1593, 1451,1322, 1054, 856 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{22}NO$ $(M+H)^+$: 244.1701, found: 244.1706.

3-butyl-3-(2-methylallyl)indolin-2-one 90b' is exclusively synthesized by following general experimental procedure A with mixing of **88b** (50mg, 1 equiv.) and 20 mol% of $Ni(OTf)_2$ in 1.5 ml *tert*-butyl acetate resulted desired product **90b'** (55 mg, 72%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95)become white solid after keeping few days. **3-butyl-3-(2-methylallyl)indolin-2-one (90b'): ^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 (bs, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 4.57 (s, 1H), 4.54 (s, 1H), 2.71 (d, J = 13.4 Hz, 1H), 2.49 (d, J = 13.3 Hz, 1H), 1.95-1.87 (m, 4.5 Hz, 1H), 1.80 – 1.67 (m, 3H), 1.35 (s, 3H), 1.25 – 1.16 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H) ppm. **^{13}C{^{1}H} N MR** (100 MHz, $CDCl_3$): 182.4 141.1, 132.7, 127.8, 123.8, 122.3, 114.6, 109.7, 53.9, 45.6, 38.9, 29.8, 26.2, 23.9, 22.9, 13.9 ppm. **FTIR** (neat): 3021, 2851, 2341, 1688, 1593, 1451,1322, 1054, 856 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{22}NO$ $(M+H)^+$: 244.1701, found: 244.1706.

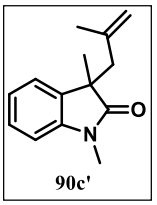


1,3-dimethyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90c[118] **and 1,3-dimethyl-3-(2-methylallyl)indolin-2-one 90c'**[119] is synthesized by following general experimental procedure A with mixing of **88c** (50 mg, 1equiv.) and 20 mol% $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **88c** with yield of 34.98 mg (58%) and **90c'** with yield of 15 mg (25%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95).The above reaction resulted exclusively 1,3-dimethyl-3-(2-methylallyl)indolin-2-one (**90c'**) with 41.78 mg (70 %), when 20 mol% of $Ni(OTf)_2$ used as a catalyst.

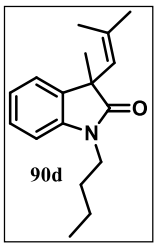
1,3-dimethyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (90c)*:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.14 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.43 – 5.40 (m, 1H), 3.24 (s, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.47 (s, 3H), 1.04 (d, *J* = 1.0 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 180.5, 142.8, 137.3, 136.3, 127.6, 125.7, 123.1, 122.9, 108.1, 48.7, 27.4, 26.8, 26.4, 18.3 ppm. **FTIR** (neat): 3021, 1672, 1590, 1376, 1098, 766 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{18}NO$ $(M+H)^+$: 216.1388, found: 216.1392.



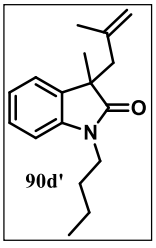
1,3-dimethyl-3-(2-methylallyl)indolin-2-one (90c'): ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.25 (m, 1H),7.19 (d, J = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 4.55 (s, 1H), 4.48 (s, 1H), 3.19 (s, 3H), 2.72 (d, *J* =14 Hz, 1H), 2.47 (d, *J* = 14 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 180.4, 144.4, 143.3, 141.3, 133.8, 129.2, 127.8, 123.2, 122.3, 114.3, 108.1, 54.1, 48.8, 45.8, 30.1, 26.2, 24.8, 23.7, 19.2. **FTIR** (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{18}NO$ $(M+H)^+$: 216.1388, found: 216.1393.



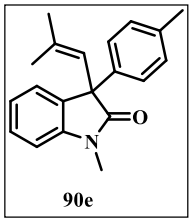
1-butyl-3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90d and **1-butyl-3-methyl-3-(2-methylallyl)indolin-2-on 90d'** is synthesized by following general experimental procedure A, with mixing of **88d** (50mg, 1 equiv.) and 20 mol% $In(OTf)_3$ in 1.5 ml *tert*-butylacetate resulted desired product **90d** with yield of 23.56 mg (41%) and **90d'** with yield of 18.42 mg (32%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95).The above reaction resulted 1-butyl-3-methyl-3-(2-methylallyl)indolin-2-on (**90d'**) with 44.83 mg (81 %), when 20 mol% of $Ni(OTf)_2$ used as a catalyst. **1-butyl-3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90d: ^{1}H NMR** (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, CDCl3) δ 7.22 (td, *J* = 7.7, 1.2 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.02 (td, *J* = 7.5, 0.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.42 – 5.39 (m, 1H), 3.78 – 3.66 (m, 2H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.66 (m, 2H), 1.46 (s, 3H), 1.44 – 1.27 (m, 2H), 1.04 (d, *J* = 0.8 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm.**^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 180.2, 142.3, 137.2, 136.5, 127.4, 125.7, 123.3, 122.6, 108.32, 48.7, 39.9, 29.6, 27.7, 26.8, 20.4, 18.4, 13.9 ppm. **FTIR** (neat): 178.6, 158.9, 144.1, 141.1, 132.6, 131.7, 128.1, 125.8, 122.3, 115.2, 113.9, 113.9, 108.3. 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{24}NO$ $(M+H)^+$: 258.1908, found: 258.1861.



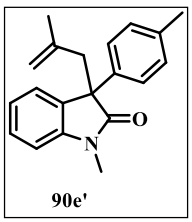
1-butyl-3-methyl-3-(2-methylallyl)indolin-2-on 90d': ^{1}H NMR (400 MHz, $CDCl_3$) : : δ 7.25-7.18 (m, 2H), 7.03 (t, J = 7.6 Hz,1H), 6.83 (d, *J* = 7.6 Hz, 1H), 4.55 (m, 1H), 4.49 (m, 1H), 3.77-3.70 (m, 1H), 3.64-3.57 (m, 1H), 2.72 (d, *J* = 13.6 Hz, 1H,) 2.47 (d, *J* = 13.6 Hz, 1H), 1.62-1.58 (m, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.94 (t, J = 4.8 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 180.2, 142.5, 141.3, 134.0, 129.3, 127.7, 123.4, 122.0, 114.4, 108.3, 54.1, 48.7, 45.7, 39.9, 39.8, 30.2, 29.7, 25.1, 23.9, 20.3, 13.9 ppm. **FTIR** (neat): 3034, 2957, 2921, 2862, 2383, 2312, 1349, 830, cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{24}NO$ $(M+H)^+$: 258.1780, found: 258.1788.



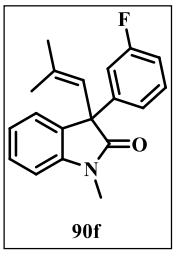
1-methyl-3-(2-methylprop-1-en-1-yl)-3-(*p*-tolyl)indolin-2-one 90e and **1-methyl-3-(2-methylallyl)-3-(*p*-tolyl)indolin-2-one 90e'** synthesized by following general experimental procedure A with mixing of **90e** (50mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **90e** (37.2 mg, 64%) and 1-methyl-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one **90e'** (17.61 mg, 31%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95).The above reaction resulted 1-methyl-3-(2-methylallyl)-3-(*p*-tolyl)indolin-2-one **90e'** with 34.1 mg (61%), when 20 mol% of $Ni(OTf)_2$ used as a catalyst. **1-methyl-3-(2-methylprop-1-en-1-yl)-3-(*p*-tolyl)indolin-2-one 90e** : **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.33-7.28 (m, 1H), 7.24-7.19 (m, 3H), 7.12-7.07 (m, 3H), 6.87 (d, *J* = 7.6 Hz 1H), 5.70 (m, 1H), 3.21 (s, 3H), 2.29 (s, 3H), 1.76 (d, *J* = 1.6 Hz, 3H), 1.26 (d, *J* = 1.6 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 178.5, 143.5, 139.4, 138.2, 136.9, 134.3, 129.3, 128.0, 127.1, 126.3, 125.2, 122.9, 108.1, 57.9, 27.0, 26.7, 21.1, 19.1 ppm. **FTIR** (neat): 3015, 2945, 1634, 1378, 1109, 890 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO$ $(M+H)^+$: 292.1701, found: 292.1705.



1-methyl-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one 90e': **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.34-7.30 (m, 1H), 7.29-7.24 (m, 3H), 7.12-7.08 (m, 3H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.62-4.61 (m, 1H), 4.55 (s, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.18 (s, 3H), 2.90 (d, *J* = 13.6 Hz, 1H), 2.29 (s, 3H), 1.35 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 178.6, 144.1, 141.2, 137.2, 131.8, 129.3, 128.3, 126.9, 125.8, 122.3, 115.1, 108.3, 56.4, 45.6, 26.5, 23.8, 21.1 ppm. **FTIR** (neat): 3012, 2843, 1604, 1356, 1198, 786 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO$ $(M+H)^+$: 292.1701, found: 292.1705

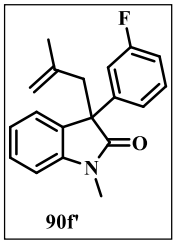


3-(3-fluorophenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90f and **3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one 90f'** synthesized by following general experimental procedure A, with mixing of **88f** (50 mg, 1equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butylacetate resulted desired product **90f** with yield of 29.8 mg (52%) and 3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**90f'**) with yield of 18 mg (32%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95).The above reaction resulted 3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one **90f'** with 43 mg (76%), when 20 mol% of $Ni(OTf)_2$ used as a catalyst. **3-(3-fluorophenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one** (**90f**)**: ^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.28-7.23 (m, 1H), 7.19-7.14 (m, 2H), 7.06-7.04 (m, 2H), 6.98-6.97 (m, 1H), 6.87 (m,1H),), 6.82-6.8 (m, 1H), 5.58-5.57 (m, 1H), 3.15 (s, 3H), 1.70 (d, *J* = 1.2 Hz,

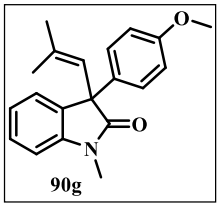


3H), 1.20 (d, *J* = 1.2 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 178.3, 162.2 (d, $J_{C\text{-}f}$ = 163 Hz) 143.4, 138.5, 138.1 (d, $J_{C\text{-}f}$ = 2 Hz) 133.88, 129.0 (d, $J_{C\text{-}f}$ = 6 Hz), 128.3, 126.1, 125.3, 123.1, 115.4 (d, $J_{C\text{-}f}$ = 14 Hz), 108.4, 57.7, 27.0, 26.7, 19.2 ppm. **FTIR** (neat): 2927, 1672, 1522, 1432, 1142, 711 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{19}FNO$ $(M+H)^+$: 296.1451, found: 296.1452.

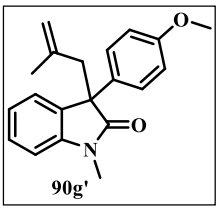
3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one 90f': **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.36-7.32 (m, 1H), 7.25-7.19 (m, 2H), 7.14-7.10 (m, 1H), 6.96-6.91 (m, 2H), 6.90-6.88 (m, 2H), 4.64-4.63 (m, 1H), 4.55 (s, 1H), 3.22 (d, *J* = 13.6 Hz,1H), 3.19 (s, 3H), 2.90 (d, *J* = 13.6 Hz, 1H), 1.34 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, CDCl3): δ 177.8, 162.9 (d, $J_{C\text{-}f}$ = 244 Hz), 155.8, 144.1, 143.2 (d, $J_{C\text{-}f}$ = 7 Hz), 140.7, 130.9, 134.5 (d, $J_{C\text{-}f}$ = 9 Hz), 128.7, 125.9, 122.8, 122.5, 115.6, 114.5 (d, $J_{C\text{-}f}$ = 4 Hz), 114.3, 108.5, 64.6, 56.5, 45.7, 26.6, 23.7 ppm. **FTIR** (neat): 3060, 2925, 1712, 1602, 1477, 1343, 1250, 1126, 1079, 1021, 868 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{19}FNO$ $(M+H)^+$: 296.1451, found:296.1453.



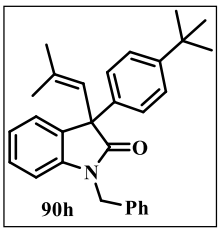
3-(4-methoxyphenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90g and 3-**(3-methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one 90g'** synthesized by following general experimental procedure A, with mixing of 3-hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one **88g** (50 mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **90g** of 59.2 mg (32%) and **90g'** of 19 mg (33%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95).The above reaction resulted 3-(3-methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**90g'**) with 90 mg (79%), when 20 mol% of $Ni(OTf)_2$ used as a catalyst. **3-(4-methoxyphenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one 90g**: **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.31 (td, *J* =1.6Hz, *J* = 8Hz 1H), 7.23 (m, 3H), 7.10 (t, *J* = 0.8Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.81(m, 2H), 5.69-5.67 (m, 1H), 3.76 (s, 3H), 3.21 (s, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.26 (d, *J* = 1.0 Hz, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): 178.7, 158.8, 143.5, 138.1, 134.4, 134.2, 128.4, 128.1, 126.4, 125.3, 123.0, 115.2, 114.0, 108.2, 57.5, 55.4, 27.0, 26.6, 19.2; **FTIR** (neat): 3042, 1698, 1523, 1307, 1103, 786 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_2$ $(M+H)^+$: 308.1650, found: 308.1654.



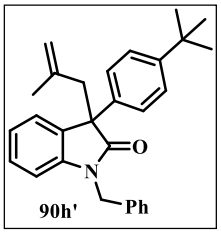
3-(4-methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one 90g': ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.30 – 7.24 (m, 3H), 7.22 – 7.17 (m, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.79 – 6.74 (m, 2H), 4.58 – 4.56 (m, 1H), 4.50 (s, 1H), 3.71 (s, 3H), 3.16 (d, *J* = 3.2 Hz, 1H), 3.13 (s, 3H), 2.84 (d, J = 13.3 Hz, 1H), 1.30 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 178.6, 158.9, 144.1, 141.1, 132.6, 131.7, 128.1, 125.8, 122.3, 115.2, 113.9, 113.9, 108.3, 556.0, 55.4, 45.7, 26.5, 23.8. FTIR (neat): 3012, 1635, 1511, 1460, 1296, 845 cm^{-1}. **FTIR** (neat): 3012, 1635, 1511, 1460, 1296, 845 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_2$ $(M+H)^+$: 308.1650, found: 308.1654.



1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylprop-1-en-1-yl)indolin-2-one 90h and **1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylallyl)indolin-2-one 90h'** were synthesized by following general experimental procedure A, with mixing of **88h** (50mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **90h** with yield of 15.7 mg (42%) and **90h'** with yield of 13. 74 mg (39%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95). The above reaction resulted 1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylallyl)indolin-2-one **90h'** with 23.5 mg (66 %), when 20 mol% of $Ni(OTf)_2$ used as a catalyst. **1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylprop-1-en-1-yl)indolin-2-one 90h: ^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.32-7.31 (m, 3H), 7.25-7.23 (m, 7H), 7.20-7.16 (m, 1H), 7.05 (td, J = 1.2 Hz, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.77-5.76 (m, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.28 (s, 9H), 1.22 (d, J = 1.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 178.6, 150.0, 142.6, 139.5, 138.3, 136.0, 134.4, 128.8, 127.9, 127.6, 126.9, 126.3, 125.6, 125.3, 122.9, 109.2, 57.9, 47.0, 44.2, 41.7, 34.5, 31.4, 28.9, 27.0, 23.6, 19.4, 16.8 ppm. **FTIR** (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{29}H_{32}NO$ $(M+H)^+$: 410.2484, found: 410.2493.

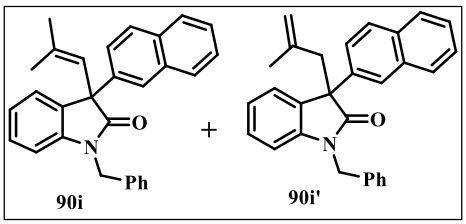


1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylallyl)indolin-2-one 90h': **^{1}H NMR** (400 MHz, $CDCl_3$) : : δ 7.26 (s, 4H), 7.23 – 7.16 (m, 6H), 7.12 (td, J = 7.7, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 4.83 (dd, *J* = 43.3, 15.7 Hz, 2H), 4.59 – 4.57 (m, 1H), 4.56 (s, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3): δ 178.5, 150.2, 143.3, 141.1, 137.8, 136.0, 132.1, 128.7, 128.2, 127.6, 127.5, 126.6, 125.8, 125.6, 122.3, 115.6, 109.4, 56.5, 45.3, 44.1, 34.5, 31.4, 24.0.



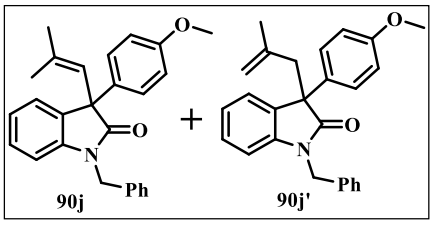
ppm. **FTIR** (neat): 2934, 1667, 1523, 1405, 1123, 845 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{29}H_{32}NO$ $(M+H)^+$: 410.2484, found: 410.2492.

1-benzyl-3-(2-methylprop-1-en-1-yl)-3-(naphthalen-2-yl)indolin-2-one 90i + 1-**benzyl-3-(2-methylallyl)-3-(naphthalen-2-yl)indolin-2-one 90i'** is synthesized by following general experimental procedure A, with mixing of 1-benzyl-3-hydroxy-3-(4-methoxyphenyl)indolin-2-one **88i** (50mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **90i** and **90i'** of 39.51mg (72%) after column purification. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.81 (m, 6H), 7.68 (m, 3H), 7.57 (m, 1H), 7.46-7.44 (m, 4H), 7.44 (m, 14H), 7.25 (m, 2H), 7.09 (m, 2H), 6.8 (m, 2H), 5.82-5.81 (m, 1H), 5.05- 4.84 (m, 4H), 4.94 (m, 1H), 4.70 (s, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 1.83 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): 178.4,178.3, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 126.2, 126.1, 126.0, 125.9, 125.9, 125.7, 125.65, 125.55, 125.3, 125.2, 122.5, 109.5, 58.4, 56.9, 45.2, 44.2, 44.1, 27.1, 24.8, 24.1, 19.7. ppm. **FTIR** (neat): 3014, 2845, 1690, 1523, 1306, 764 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{29}H_{26}NO$ $(M+H)^+$: 404.2014, found: 404.2016.



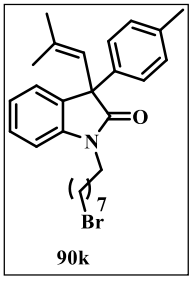
1-benzyl-3-(4-methoxyphenyl)-3-(2-methylprop-1-en-1-yl)indolin-2-one 90j + 1-**benzyl-3-(4-methoxyphenyl)-3-(2-methylallyl)indolin-2-one 90j'** is synthesized by following general experimental procedure A, with mixing of **88j** (50mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butylacetate resulted desired product **90j** with yield of 42.53 mg (83%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95) and become white solid after few days.

Data for 90j +90j': Melting point: 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.35 (d, = 8.8 Hz, 2H), 7.76 (m, 14H), 7.19 (m, 2H), 7.07(td, *J* = 2.8 Hz, *J* = 7.6 Hz, 2H), 6.85 (m, 4H), 6.77 (t, *J* =8.4 Hz, 2H), 5.74 (s, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 2H), 4.83 (d, *J* = 15.7 Hz, 1H), 4.66 (m, 1H), 4.63 (m, 1H), 3.78 (s, 6H), 3.28 (d, *J* = 13.2 Hz, 1H), 2.94 (d, *J* = 13.6 Hz,1H), 1.79 (d, 3H), 1.36 (s, 3H), 1.27 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): 178.7, 178.6, 158.9, 158.8, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 126.2, 125.8, 123.0, 122.3, 115.7, 114.0, 114.0, 109.4. 109.3, 57.6, 56.1, 55.4, 45.5, 44.1, 44.0, 27.0, 24.1, 19.5. ppm. **FTIR (neat)**: 3035,



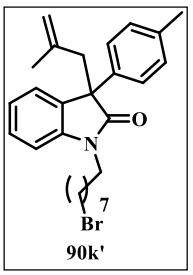
1701, 1608, 1334, 1055, 765 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{26}H_{26}NO_2$ $(M+H)^+$: 384.1963, found: 384.1968.

1-(2-bromooctyl)-3-(2-methylprop-1-en-1-yl)-3-(*p*-tolyl)indolin-2-one 90k *and* ***1*-(2-bromooctyl)-3-(2-methylallyl)-3-(*p*-tolyl)indolin-2-one 90k'** is synthesized by following the general experimental procedure A, with mixing of **88k** (50mg, 1 equiv.) and 20 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **90k** with yield of 27 mg (53%) and **90k'** with yield of 15 mg (29%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.6Hz, 1H), 7.20 (m, 3H), 7.07 (m, 3H), 6.80 (d, *J* = 7.6 Hz, 1H), 5.68 (s,1H), 3.75-3.61 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H) 1.82 (m, 3H), 1.76 (d, *J* = 0.8 Hz,3H), 1.27 (m, 12H). **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): 178.3, 142.9, 139.7, 138.2, 136.8, 134.6, 129.3, 127.9, 127.1, 126.3, 125.4, 122.7, 108.4, 57.9, 40.26, 34.1, 32.9, 29.8, 29.1, 28.7, 28.1, 27.1, 26.9, 21.1, 19.4 ppm. **FTIR** (neat): 3042, 2801, 1678, 1365, 1093, 723 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{27}H_{35}BrNO$ $(M+H)^+$: 468.1902, found: 468.1904.



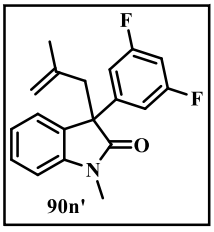
90k

1-(2-bromooctyl)-3-(2-methylallyl)-3-(*p*-tolyl)indolin-2-one 90k': **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.28 (m, 4H), 7.09 (d, *J* = 9.2 Hz, 3H), 6.87 (d, *J* = 8 Hz, 1H), 4.62 (m, 1H), 4.57 (s, 1H), 3.65 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 3.22 (d, *J* = 13.2 Hz, 1H,) 2.89 (d, *J* = 13.2 Hz, 1H), 2.29 (s, 3H,) 1.82(m, 3H), 1.31 (m, 12H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 180.3, 178.3, 153.9, 143.6, 141.0, 137.9, 137.0, 132.1, 129.3, 129.3, 128.1, 126.8, 125.9, 124.3, 122.0, 115.2, 108.5, 77.3, 76.9, 56.2, 45.3, 40.1, 40.1, 34.6, 34.0, 32.8, 29.8, 29.1, 28.7, 28.7, 28.1, 28.1, 27.3, 26.9, 23.9, 21.0 ppm. **FTIR** (neat): 3015, 2876, 1701, 1309, 1099, 764 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{35}BrNO$ $(M+H)^+$: 468.1902, found:468.1909.



90k'

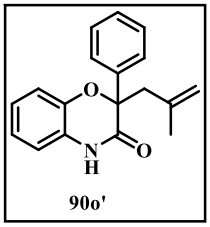
3-(3,5-difluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one 90n' is synthesized by following the general experimental procedure A, with mixing of 3-(3,5-difluorophenyl)-3-hydroxy-1-methylindolin-2-one 88n, 50 mg, 1 equiv.) and 20 mol% of $Ni(OTf)_2$ in 1.5ml *tert*-butyl acetate resulted desired product with 41.7 mg (72%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99 to 5:95). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 (m, 1H), 7.26 (m, 1H), 7.14 (t, *J* = 7.6Hz, 1H), 6.96 (m, 2H), 6.90 (d, J= 8 Hz, 1H), 6.69 (tt, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 4.65 (m,



90n'

1H), 4.56 (s, 1H), 3.20 (s, 3H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 1.34 (s, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$): δ 177.3, 163.0 (d, *J* = 247 Hz), 162.9 (d, *J* = 247 Hz), 144.4 (t, *J* = 9 Hz), 143.9, 140.3, 130.3, 128.9, 125.9, 122.7, 115.8, 110.3 (dd, *J* = 19 Hz, 7 Hz), 108.7, 102.9 (dd, *J* = 19 Hz, 7 Hz), 56.2,45.6, 26.6, 23.6. ppm. **FTIR (neat):** 2901, 1620, 1105, 701 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{18}NO$ $(M+H)^+$: 314.1356, found: 314.1358.

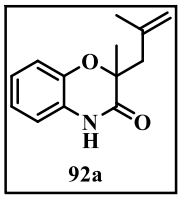
2-(2-methylallyl)-2-phenyl-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 90o' is synthesized by following general experimental procedure A, with mixing of 2-methoxy-2-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one 88o and 20 mol% of $Ni(OTf)_2$ in 1.5 ml *tert*-butyl acetate resulted desired product 90o' of (42 mg) 77% after column purification. **^{1}H NMR** (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, CDCl3): δ 9.20 (s, 1H), 6.73 (m, 9H), 4.60 (s, 2H), 2.92 (d, *J* = 14 Hz, 1H), 2.55 (d, *J* = 14 Hz, 1H), 1.55 (s, 3H) ppm. **$^{13}C\{^{1}H\}$ NMR** (100 MHz, CDCl3):167.9, 142.9, 140.6, 139.1, 128.5, 128.2, 126.2, 125.8, 124.2, 122.5, 117.5, 115.7, 115.6, 84.6, 46.9, 24.7 ppm. **FTIR (neat):** 3220, 3012, 1649, 1306, 1106, 765 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{18}NO_2$ $(M+H)^+$: 280.1338, found: 280.1341**.**



90o'

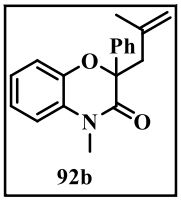
3.9.3.1. Analytical data for the rearrangement products

2-methyl-2-(2-methylallyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92a is synthesized by following general experimental procedure B, with mixing of **91a** (50 mg, 1 equiv.) and 30 mol% $In(OTf)_3$ in 1.5ml *tert*-butyl acetate resulted desired product **92a** with yield of 39.25 mg (85%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (5:95) and become white solid after few days. **Melting point**: 77-78 °C; ^{1}H NMR (400 MHz, CDCl3): δ 8.81 (bs, 1H), 6.99-6.92 (m, 3H), 6.82-6.80 (m, 1H), 4.93 (m, 1H), 4.83 (s, 1H), 2.70 (d, *J* = 14 Hz, 1H), 2.43 (d, *J* = 14 Hz, 1H), 1.83 (s, 3H), 1.55 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) :169.6, 142.3, 140.3, 126.6, 124.3, 122.9, 117.7, 116.0, 115.1, 81.0, 43.4, 24.2, 21.9 ppm. FTIR (neat): 3051, 2879, 1621, 1275, 1186, 812, 689 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{16}NO_2$ $(M+H)^+$ 218.1181; Found 218.1185.



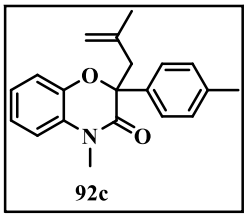
92a

4-methyl-2-(2-methylallyl)-2-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**92b**) is synthesized by following general experimental procedure B, with mixing of **91b** (50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **92b** with yield of 40 mg (70%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.46-7.44 (m, 2H), 7.25-7.14 (m, 3H), 7.12 (dd, *J* = 8 Hz, *J* = 1.6 Hz, 1H), 6.98 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.93 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.80 (dd, *J* = 8 Hz, *J* = 1.6 Hz, 1H), 4.87-4.86 (m, 1H), 4.81 (s, 1H), 3.37 (s, 3H), 3.18 (d, *J* = 14.8 Hz, 1H), 2.81 (d, *J* = 14.4 Hz, 1H), 1.76 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): 166.1, 143.8, 140. 8, 139.3, 129.4, 128.4, 128.0, 125.9, 123.8, 122.5, 117.7, 115.4, 114.57, 84.5, 47.5, 28.9, 24.7 ppm**. FTIR (neat)**: 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{20}NO_2$ $(M+H)^+$ 294.1494; Found 294.1497.



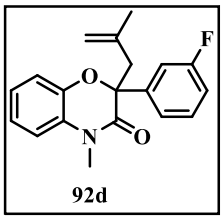
92b

4-methyl-2-(2-methylallyl)-2-(*p*-tolyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one (**92c**) is synthesized by following the general experimental procedure B, with mixing of **91c** (50mg, 1eq.) and 30 mol% of $In(OTf)_3$ in 1mL *tert*-butyl acetate resulted desired product **92c** with yield of 34 mg (72%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99); ^{1}H NMR (400 MHz, CDCl3) : δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8 Hz, 1H), 7.04 (d, *J* = 8 Hz, 2H), 6.95 (dt, *J* = 7.2 Hz, *J* = 22.4 Hz, 2H), 6.80 (d, *J* = 7.6 Hz, *J* = 1H), 4.86 (s, 1H), 4.82 (s, 1H), 3.36 (s, 3H), 3.16 (d, *J* = 14.8 Hz, 1H), 2.79 (d, *J* = 14.8 Hz, 1H), 2.25 (s, 3H), 1.76 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl3) : 166.2, 143.9, 140. 9, 137.7, 136.3, 129. 4, 129.0, 125.7, 123.8, 122.4, 117.7, 115.2, 114.5, 84.5, 47.5, 29.9, 28.9, 24.7, 21.3 ppm. **FTIR** (neat): 3023, 2954, 1701, 1607, 1455, 1321, 1021, 854, 670 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_2$ $(M+H)^+$ 308.1651; Found 308.1654.



92c

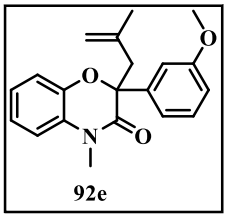
2-(3-fluorophenyl)-4-methyl-2-(2-methylallyl)-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one **92d** is synthesized by following the general experimental procedure-B, with mixing of **91d** (50 mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1ml *tert*-butyl acetate resulted desired product **92d** with yield of 20 mg (42%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99) and become solid after few days. **Melting point**: 46-47 °C; **^{1}H NMR** (400 MHz, CDCl3): δ 7.44-7.40 (m, 2H), 7.11-7.09 (m, 1H), 7.02-6.93 (m, 3H), 6.83-6.81 (m, 1H), 4.88-4.86 (m, 1H), 4.80-4.79 (m, 1H), 3.37 (s, 3H), 3.16 (d, *J* = 14.4 Hz, 1H), 2.80 (d, *J* = 15.6 Hz, 1H), 1.76 (s, 3H).



92d

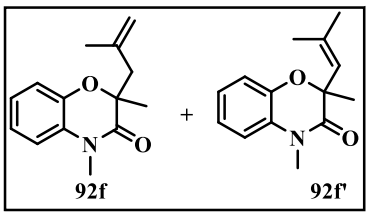
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 162.5 (d, $J_{C\text{-}f}$ = 245 Hz), 143.6, 140.5, 134.9 (d, $J_{C\text{-}f}$ = 3 Hz), 129.3, 127.8 (d, $J_{C\text{-}f}$ = 8 Hz), 123.97, 122.66, 117.70, 115.70, 115.3 (d, $J_{C\text{-}f}$ = 8 Hz), 114.6, 84.2, 47.4, 28.9, 24.6. FTIR (neat): 3052, 2955, 1707, 1606, 1475, 1345, 1086, 1016, 857, 799, 695 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{19}FNO_2$ $(M+H)^+$ 312.1400; Found 312.1403.

2-(3-methoxyphenyl)-4-methyl-2-(2-methylallyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92e is synthesized by following the general experimental procedure B, with mixing of **91e** (50 mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92e** with yield of 24.82 mg (53%) as white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.10 (m, 2H), 7.04-6.91 (m, 4H), 6.82-6.79 (m, 1H), 6.74-6.71 (m, 1H), 4.87 (m, 1H), 4.83 (m, 1H), 3.37 (s, 3H) 3.36 (s, 3H), 3.18 (d, 1H, *J* = 14.8 Hz), 2.80 (d, 1H, *J* = 14.4 Hz), 1.77 (s, 3H). **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$): 165.9, 159.6, 143.8, 140. 9, 140.8, 129.4, 123.9, 122.5, 118.2, 117.7, 115.4, 114.6, 113.4, 111.7, 84.5, 55.3, 47.4, 28.9, 24.7. **FTIR** (neat): 3065, 2951, 1674, 1604, 1535, 1494, 1463, 1128, 958 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.1600; Found 324.1603.



92e

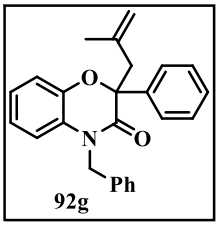
2,4-dimethyl-2-(2-methylallyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one (**92f**) is synthesized by following the general experimental procedure B, with mixing of 3-(*tert*-butylperoxy)-1,3-dimethylindolin-2-one (**91f**, 50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5ml *tert*-butyl acetate resulted desired product **92f** with yield of 28.57 mg (61%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06-6.91(m, 6H), 5.26-5.25 (m, 1H), 4.91- 4.90 (m, 1H), 4.78 (s, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.64 (d, 1H, *J* = 14 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.80 (s, 3H), 1.68(s, 2H), 1.64 (d, 2H), 1.51 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$): 168.5, 168.49, 144.0, 143. 15, 140.45, 139.0, 130.35, 129.8, 123.6, 122.4, 122.35, 117.69, 117.47, 115.89, 114.4, 114.3, 80.6,79.72, 43.45, 29.78, 28.97, 27.1, 24.2, 23.9, 22.2, 19.2 ppm. **FTIR** (neat): 2936, 2856, 1721, 1609, 1496, 897 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{18}NO_2$ $(M+H)^+$ 232.1338; found 232.1342.



92f 92f'

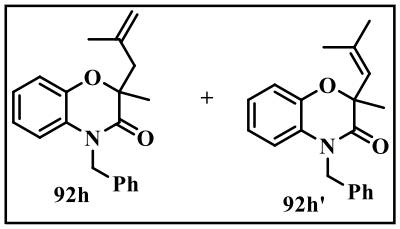
4-benzyl-2-(2-methylallyl)-2-phenyl-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one (**92g**) is synthesized by following the general experimental procedure B, with mixing of **91g** (50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1mL *tert*-butyl acetate resulted desired product **92g** with yield of 37.81 mg (82%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99) and become solid

after few days. **Melting point**: 87-88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.53 – 7.45 (m, 2H), 7.30 – 7.20 (m, 6H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.95 (td, *J* = 7.7, 1.3 Hz, 1H), 6.79 (td, *J* = 8.0, 1.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 16.2 Hz, 1H), 4.96 (d, *J* = 16.2 Hz, 1H), 4.90 (m, 1H), 4.86 (m, 1H), 3.24 (d, *J* = 14.7 Hz, 1H), 2.87 (d, *J* = 14.7 Hz, 1H), 1.80 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 166.1, 143.9, 140.8, 139.1, 136.3, 128.8, 128.7, 128.4, 128.1, 127.4, 126.5, 125.9, 123.9, 122.5, 117.9, 115.6, 115.4, 84.7, 47.5, 45.6, 24.8 ppm. FTIR (neat): 3048, 2923, 2846, 1709, 1088, 830 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{24}NO_2$ $(M+H)^+$ 370.1807; found 370.1807.



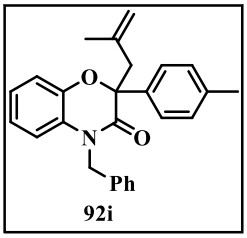
92g

4-benzyl-2-methyl-2-(2-methylallyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92h synthesized by following the general experimental procedure B, with mixing of **91h** (50 mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92h** with yield of 26.54 mg (57%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99); **^{1}HNMR** (400 MHz, $CDCl_3$) : δ 7.34-7.29 (m, 3H), 7.26-7.22 (m, 3H), 7.01-6.95 (m, 3H), 6.93-6.88 (m, 3H),5.32 (m, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 5.05 (d, *J* = 16.4 Hz, 1H), 4.95 (m, 1H), 4.84 (s, 1H), 2.77 (d, *J* = 13.6 Hz, 1H), 2.47 (d, *J* = 13.6 Hz, 1H), 1.85 (s, 1H), 1.83 (d, *J* = 7.4 Hz,1H),1.76 (s, 1H), 1.69 (d, *J* =7.4 Hz, 1H), 1.59 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 168.7, 168.3, 144.1, 143.17, 140.4, 139.3, 136.7, 136.5, 129.1, 128.9, 128.9, 127.5, 127.4, 126.6, 126.5, 124. 1, 123.8, 123.8, 122.5, 122.4, 117. 9, 117.7, 116.9, 115.2, 115.2, 80.6, 79.7, 45.6, 45.6, 43.2, 28.2, 27.1, 24.3, 23.8, 22.1, 19.2. FTIR (neat): 3053, 2939, 2839, 1708, 1600, 1477, 1343, 1254, 1156, 1135, 859 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_2$ $(M+H)^+$ 308.1651; Found 308.1652.



92h 92h'

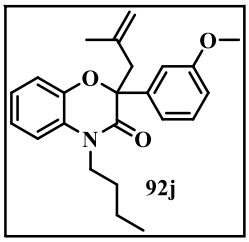
4-benzyl-2-(2-methylallyl)-2-(*p*-tolyl)-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92i is synthesized by following the general experimental procedure B, with mixing of 1-benzyl-3-(*tert*-butylperoxy)-3-(p-tolyl)indolin-2-one (**91i**, 50mg, 1 equiv.) and 30 mol% $In(OTf)_3$ in 1.5 ml *tert*-butyl acetate resulted desired product **92i** with yield of 41.10 mg (87%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, CDCl3) : δ 7.36-7.34 (m, 2H), 7.24-7.22 (m, 3H), 7.13-7.08 (m, 5H), 6.96 (m, 1H), 6.80-6.76 (m, 1H), 6.69-6.67 (m, 1H), 5.36 (d, *J* = 16.4 Hz, 1H), 4.96 (d, *J* = 16.4 Hz, 1H), 4.89 (m, 1H), 4.86 (m, 1H), 3.20 (d, 1H, *J* = 14.8 Hz), 2.82 (d, 1H, *J* = 14.4 Hz), 2.28 (s, 3H), 1.77 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): δ



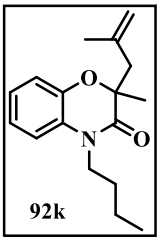
92i

166.1, 143.9, 140.8, 139.1, 136.3, 128.8, 128.7, 128.4, 128.1, 127.4, 126.5, 125.9, 123.9, 122.5, 117.9, 115.5, 115.4, 84.7, 47.5, 45.6, 24.8 ppm. FTIR (neat): 2952, 1722, 1459, 1369, 1238, 1079, 1031, 899, cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{26}NO_2$ $(M+H)^+$ 384.1964; Found 384.1967.

4-butyl-2-(3-methoxyphenyl)-2-(2-methylallyl)-2H-benzo[b][1,4]oxazin-3(4H)-one 92j synthesized by following the general experimental procedure B, with mixing of 1-butyl-3-(*tert*-butylperoxy)-3-(p-tolyl)indolin-2-one (**91j**, 50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92j** (29.54mg, 61%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.15 (t, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.96 (td, *J* = 7.6, 1.6 Hz, 1H), 6.91 (td, *J* = 7.7, 1.6 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.72 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 4.88 – 4.86 (m, 1H), 4.83 (m, 1H), 3.99 – 3.85 (m, 2H), 3.73 (s, 3H), 3.17 (d, *J* = 14.7 Hz, 1H), 2.78 (d, *J* = 14.7 Hz, 1H), 1.77 (s, 3H), 1.67 – 1.61 (m, 1H), 1.57 – 1.48 (m, 1H), 1.38 (dt, *J* = 14.9, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) : 165.6, 159.6, 144.0, 141.1, 140.9, 129.4, 128.5, 123.7, 122.5, 118.2, 118.1, 115.3, 114.6, 113.5, 111.5, 84.3, 55.3, 47.4, 41.8, 29.2, 24.7, 20.2, 13.9 ppm. **FTIR** (neat): 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{27}NO_3$ $(M+H)^+$: 366.2069, found:366.2078.

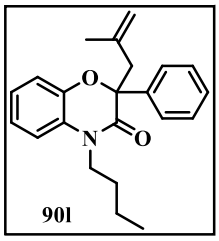


4-butyl-2-methyl-2-(2-methylallyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one 92k synthesized by following the general experimental procedure B, with mixing of 1-butyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one (**91k**, 50mg, 1 equiv.) and 30 mol% $In(OTf)_3$ in 1 mL *tert*-butyl acetate resulted desired product **92k** of 45% (23.14 mg) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26-6.92 (m, 4H), 4.90 (m, 1H), 4.78 (s, 1H), 3.98-3.82 (m, 2H), 2.63 (d, *J* = 14 Hz, 1H), 2.37 (d, *J* = 14 Hz, 1H), 1.80 (s, 3H), 1.64 (m, 2H), 1.51 (s, 3H), 1.41 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 168.1, 143.3, 140.5, 128.8, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 115.9, 114.4, 114.3, 80.3, 43.3, 41.6 ppm. **FTIR** (neat): 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{24}NO_2$ $(M+H)^+$ 274.1807; Found 274.1809.

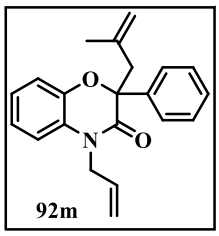


4-butyl-2-(2-methylallyl)-2-phenyl-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92l synthesized by following the general experimental procedure B, with mixing of 1-butyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one **91l** (50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92l** of 53% (29.15 mg) white thick liquid after silica gel chromatography

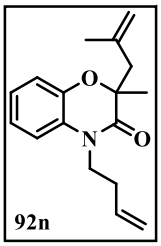
using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.43 (m, 2H), 7.24-7.18 (m, 3H), 7.11 (dd, *J* = 8 Hz, *J* = 1.6 Hz, 1H), 6.93 (m, 2H), 6.80 (dd, *J* = 8 Hz, *J* = 1.6 Hz, 1H), 4.86 (m, 1H), 4.81(s, 1H), 3.92 (m, 2H) 3.17 (d, 1H, *J* = 14.4 Hz), 2.78 (d, 1H, *J* = 14.4 Hz), 1.76 (s, 3H), 1.65 (m, 2H), 1.39 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 165.7, 144.0, 140.9, 139.4, 128.2, 127.9, 125.9, 123.7, 122.4, 118.1, 115.3, 114.5, 84.3, 47.4, 41.77, 29.2, 24.7, 20.2, 13.9 ppm. **FTIR** (neat): 2971, 2310, 1694, 16411593, 1155, 760 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{26}NO_2$ $(M+H)^+$ 336.1964; Found 336.1969.



4-allyl-2-(2-methylallyl)-2-phenyl-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92m synthesized by following the general experimental procedure B, with mixing of **91m** (50mg, 1 equiv.) and 30 mol% $In(OTf)_3$ 20 mol% in 1mL *tert*-butyl acetate resulted desired product **92m** with yield of 27.03 mg (57%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). and become solid after few days. **Melting point**: 82-83 °C ; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.45-7.43 (m, 2H), 7.25 – 7.23 (m, 1H), 7.21 – 7.17 (m, 1H), 7.12 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.97 (td, *J* = 7.8, 1.4 Hz, 1H), 6.88 (td, *J* = 7.9, 1.4 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.87 – 5.78 (m, 1H), 5.11 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.98 (dd, *J* = 17.3, 0.9 Hz, 1H), 4.88 – 4.78 (m, 3H), 4.32 – 4.26 (m, 1H), 3.17 (d, *J* = 14.7 Hz, 1H), 2.81 (d, *J* = 14.7 Hz, 1H), 1.76 (s, 3H) ppm.**^{13}C{^{1}H} NMR** (100 MHz, CDCl3): 165.8, 143.9, 140.77, 139.1, 131.6, 128.6, 128.4, 128.0, 125.9, 123.9, 122.5, 117.9, 116.8, 115.5, 115.1, 84.5, 47.4, 44.3, 24.7 ppm. **FTIR** (neat): 2920, 1713, 1607, 1496, 1476, 1189, 1097, 812 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}NO_2$ 320.1651; Found 320.1654.

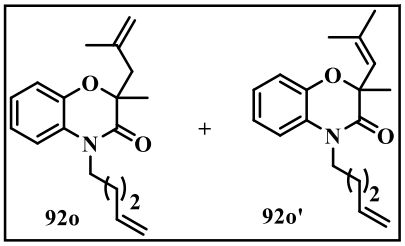


4-(but-3-en-1-yl)-2-methyl-2-(2-methylallyl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92n synthesized by following the general experimental procedure B, with mixing of 1-(but-3-en-1-yl)-3-(*tert*-butylperoxy)-3-methylindolin-2-one (**91n**, 50mg, 1 equiv.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92n** with yield of 15 mg (32%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.03 – 6.93 (m, 7H), 5.89 – 5.76 (m, 2H), 5.25 (dt, *J* = 2.6, 1.3 Hz, 1H), 5.14 – 5.00 (m, 4H), 4.90 (s, 1H), 4.78 (s, 1H), 4.05-3.90 (m, 4H), 2.63 (d, *J* = 14.1 Hz, 1H), 2.44-2.35 (m, 5H), 1.80 (s, 6H), 1.67 (s, 3H), 1.64 (d, *J* = 1.3 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 168.1, 168.0, 144.2, 143.3, 140.4, 139.0, 134.6, 134.5, 129.2, 128.7, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 117.4, 117.3, 115.8, 114.4, 114.2, 80.2, 79.4, 43.3, 41.2, 41.0, 31.7, 31.7, 27.0, 24.1, 23.8, 22.0, 19.1 ppm. **FTIR** (neat): 3071, 2949,

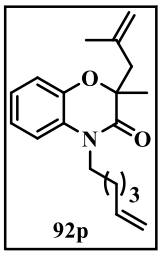


2385, 2306, 934, 751 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{22}NO_2$ 272.1651; Found 272.1654.

2-methyl-2-(2-methylallyl)-4-(pent-4-en-1-yl)-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92o + 2-methyl-2-(2-methylprop-1-en-1-yl)-4-(pent-4-en-1-yl)-2*H*-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92o' synthesized by following the general experimental procedure B , with mixing of 3-(*tert*-butylperoxy)-3-methyl-1-(pent-4-en-2-yl)indolin-2-one (50mg, 1eq.) and 30 mol% of $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product as a mixture of **92o+92o'** with yield of 24.16 mg (25%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). Data for **92o'+ 92o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (m, 8H), 5.84 (m, 2H), 5.24 (s, 1H), 4.90 (s, 1H), 4.78 (s, 1H), 3.92 (m, 4H), 2.63 (d, *J* = 14.4 Hz, 1H), 2.37 (d, *J* = 14.4 Hz, 1H), 2.15 (m, 4H), 1.79 (m, 6H), 1.74 (m, 6H), 1.65 (m, 6H), 1.5 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): 168.1,168.0, 144.2, 143.3, 140.5, 139.3, 137.6, 128.8, 123.8, 123.5, 122.4, 122.4, 118.1, 117.8, 115.9, 115.6, 115.57, 114.4, 114.3, 80.3, 79.5, 43.3, 41.3, 31.1, 27.1, 26.4, 26.3, 24.2, 23.8, 22.0,19.1 ppm. **FTIR** (neat): 3205, 3074, 2979, 2920, 898 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{24}NO_2$ $(M+H)^+$ 286.1807; Found 286.1812.

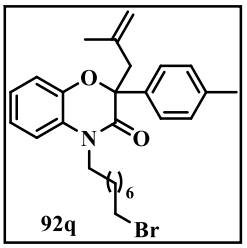


4-(hex-5-en-1-yl)-2-methyl-2-(2-methylallyl)-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92p synthesized by following the general experimental procedure B, with mixing of 3-(*tert*-butylperoxy)-3-methyl-1-(2-methylpent-4-en-2-yl)indolin-2-one (**91p**, 50mg, 1 equiv.) and 30 mol% $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **92p** with yield of 15.78 mg (32%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, CDCl3): δ 7.04 – 6.87 (m, 5H), 5.84-5.74 (m, 4H),5.05 – 4.93 (m, 2H), 4.91 – 4.88 (m, 1H), 4.78 (m, 1H), 3.97-3.84 (m, 2H), 2.63 (d, *J* = 14.1 Hz, 1H), 2.36 (d, *J* = 14.1 Hz, 1H), 2.15 – 2.05 (m, 3H), 1.80 (s, 4H), 1.70 – 1.61 (m, 5H), 1.53 – 1.43 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): δ 168.1, 168.0, 144.2, 143.3, 140.5, 139.0, 138.5, 138.4, 129.3, 128.8, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 115.8, 115.0, 114.9, 114.4, 114.3, 80.3, 79.5, 43.3, 41.8, 41.5, 33.5, 29.8, 27.0, 26.7, 26.7, 26.2 24.2, 23.8, 22.1, 19.1 ppm. **FTIR** (neat): 2948, 2863, 1682, 1603, 1501, 1454, 1266, 1154, 910, 695 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C19H26NO2$ $(M+H)^+$ 300.1964; Found 300.1971.



4-(8-bromooctyl)-2-(2-methylallyl)-2-(p-tolyl)-2H-benzo[*b*][*1,4*]oxazin-3(4*H*)-one 92q synthesized by following the general experimental procedure-B, with mixing of 1-(8-bromooctyl)-3-

(*tert*-butylperoxy)-3-(*p*-tolyl)indolin-2-one **91q**, (50mg, 1 equiv.) and 30 mol% $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate resulted desired product **5q** with yield of 11.23 mg (23%) white thick liquid after silica gel chromatography using EtOAc:*n*-hexane (1:99). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 2H), 7.12 – 7.02 (m, 3H), 6.93 (dtd, *J* = 21.3, 7.6, 1.1 Hz, 2H), 6.80 – 6.78 (m, 1H), 4.86 (s, 1H), 4.82 (s, 1H), 3.93 – 3.89 (m, 2H), 3.40 (t, 2H), 3.15 (d, *J* = 14.7 Hz, 1H), 2.75 (d, *J* = 14.8 Hz, 1H), 2.25 (s, 3H), 1.88 – 1.81 (m, 2H), 1.77 (s, 3H), 1.40-1.23 (m, 10H). **^{13}C{^{1}H} NMR** (100 MHz, CDCl3): 165.9, 159.9, 143.8, 140. 97, 140.8, 129.4, 123.86, 122.5, 122.5, 118.2 117.7, 115.38, 114.6, 113.4, 111.7, 84.5, 55.3, 47.4, 28.9, 24.7. **FTIR** (neat): 2970, 2951, 1674, 1604, 1503, 1494, 1391, 1088, 896, 714 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{35}BrNO_2$ $(M+H)^+$ 484.1851; Found 484.1855.



3.9.4. Appendix III

Copies of ^{1}H and ^{13}C NMR spectra of representative compounds

Entry	Figure No	Data	Page No
90a	77 & 78	^{1}H and ^{13}C	164
90a'	79 & 80	^{1}H and ^{13}C	165
90e	81 & 82	^{1}H and ^{13}C	166
90o'	83 & 84	^{1}H and ^{13}C	167
92a	85 & 86	^{1}H and ^{13}C	168
92e	87 & 88	^{1}H and ^{13}C	169
92j	89 & 90	^{1}H and ^{13}C	170
92m	91 & 92	^{1}H and ^{13}C	171
92o &92o'	93 & 94	^{1}H and ^{13}C	172
90j'	95	ORTEP	173
92c	96	ORTEP	173

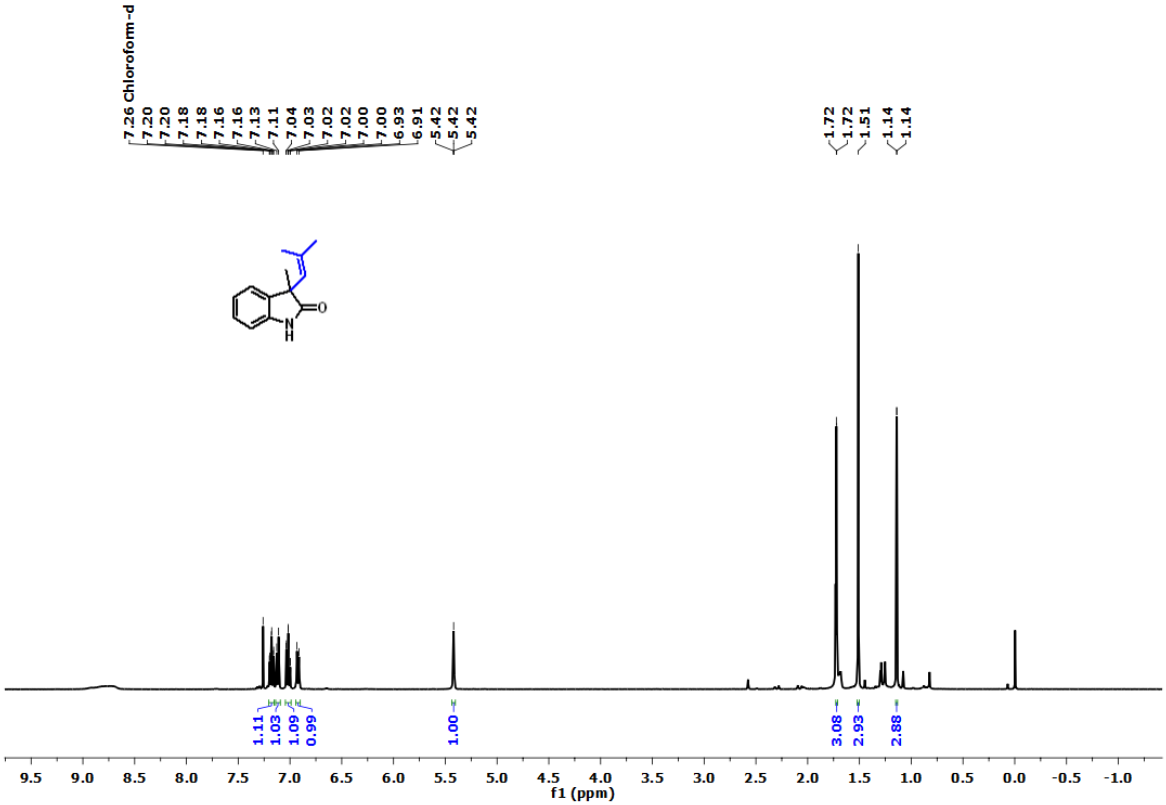


Figure 75: ^{1}H NMR of Compound **90a**

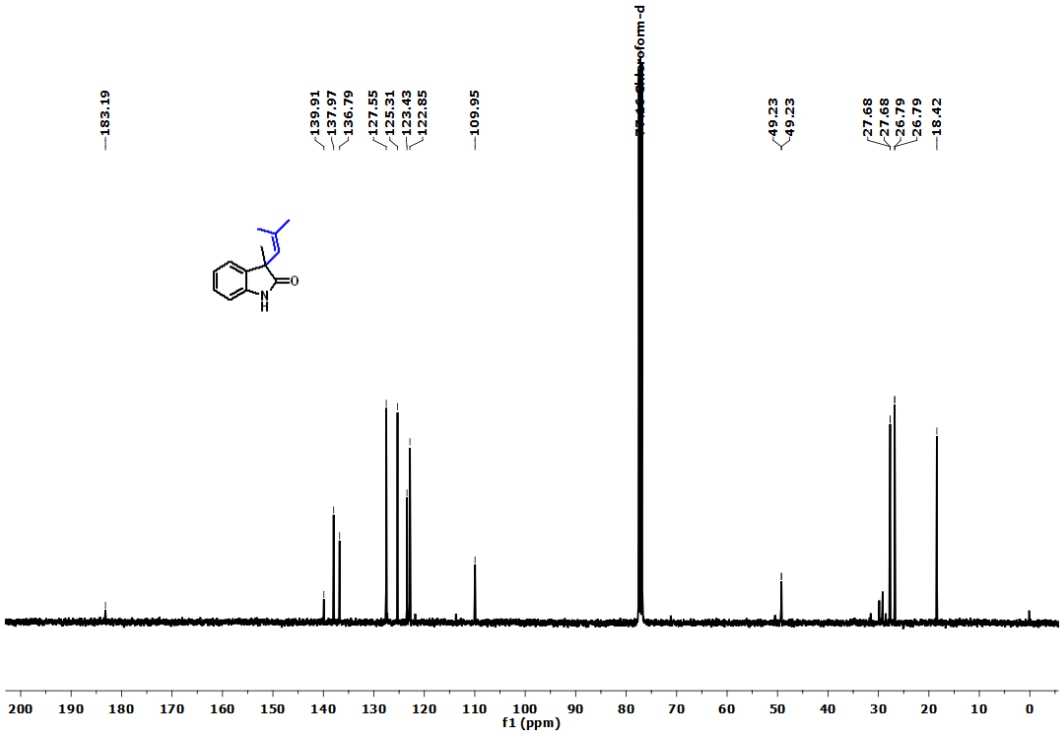


Figure 76: ^{13}C NMR of Compound **90a**

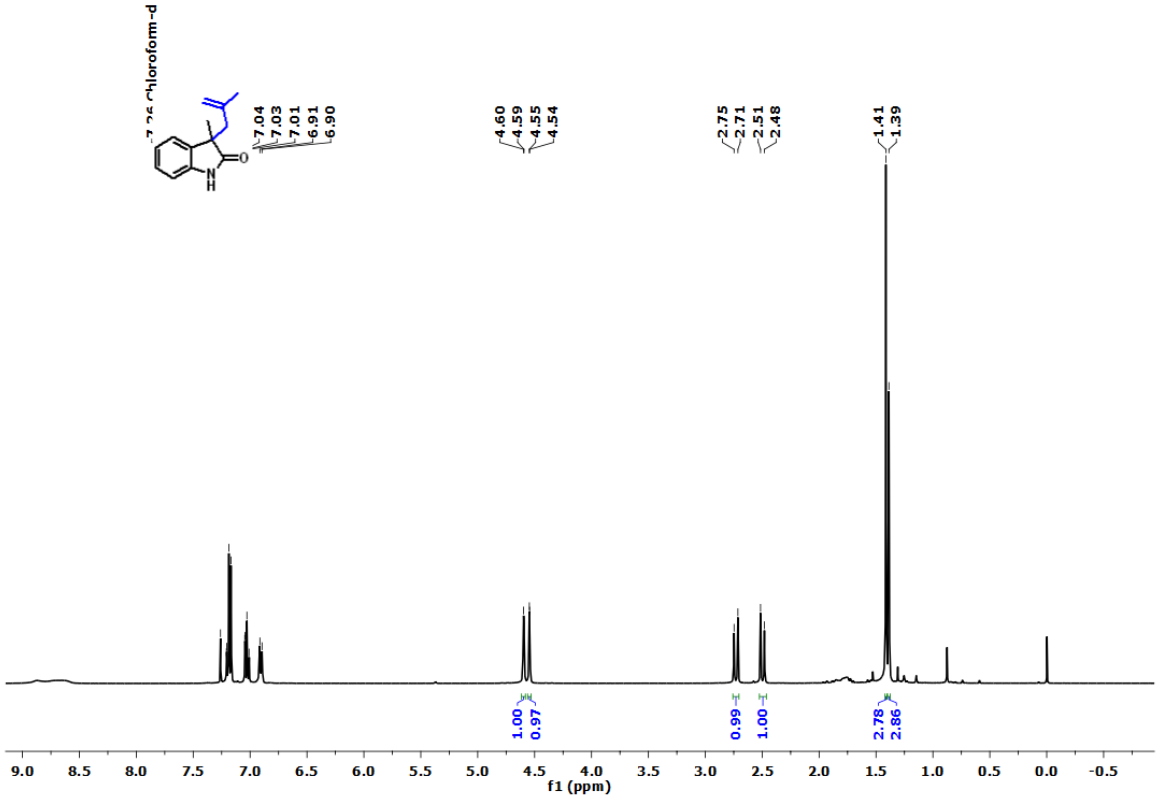


Figure 77: ^{1}H NMR of Compound **90a**'

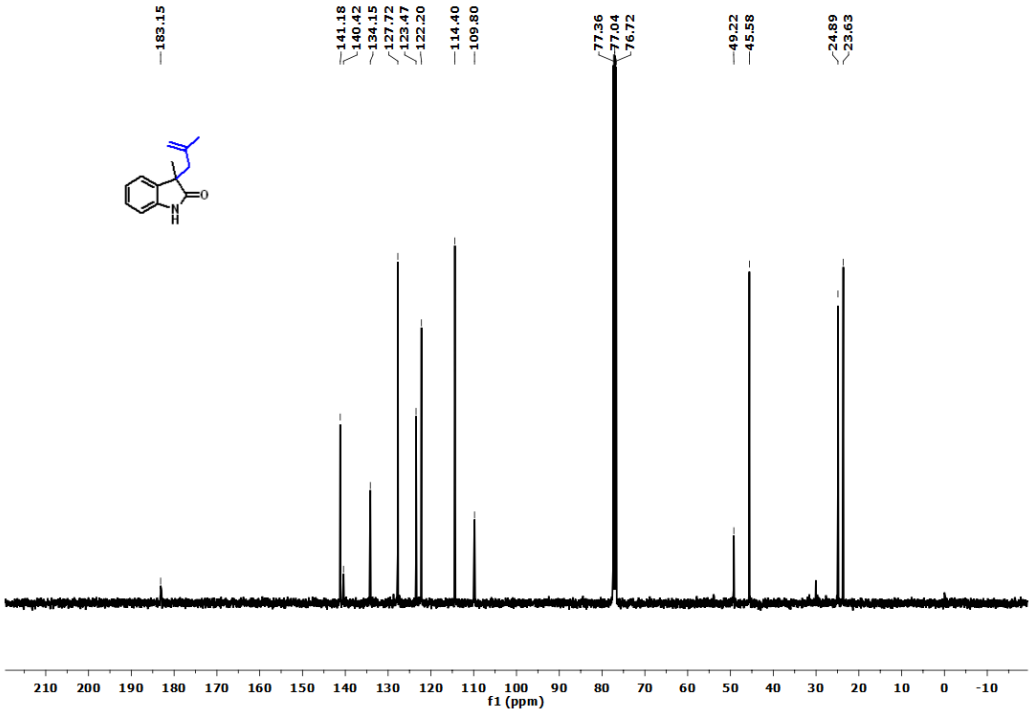


Figure 78: ^{13}C NMR of Compound **90a**'

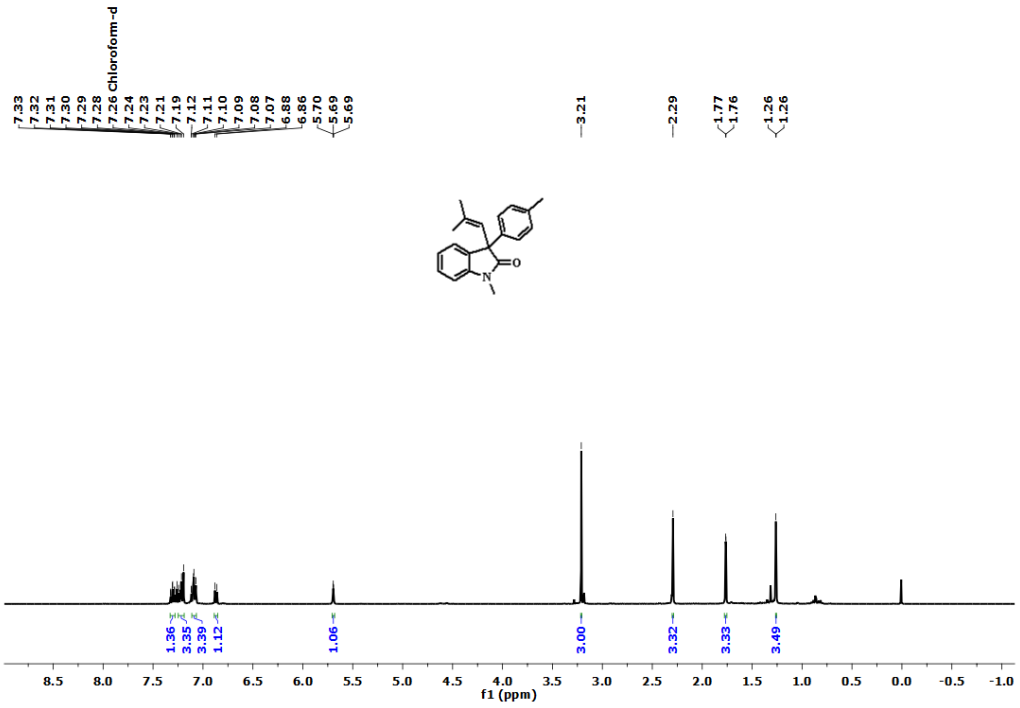


Figure 79:[1]H NMR of Compound **90e**

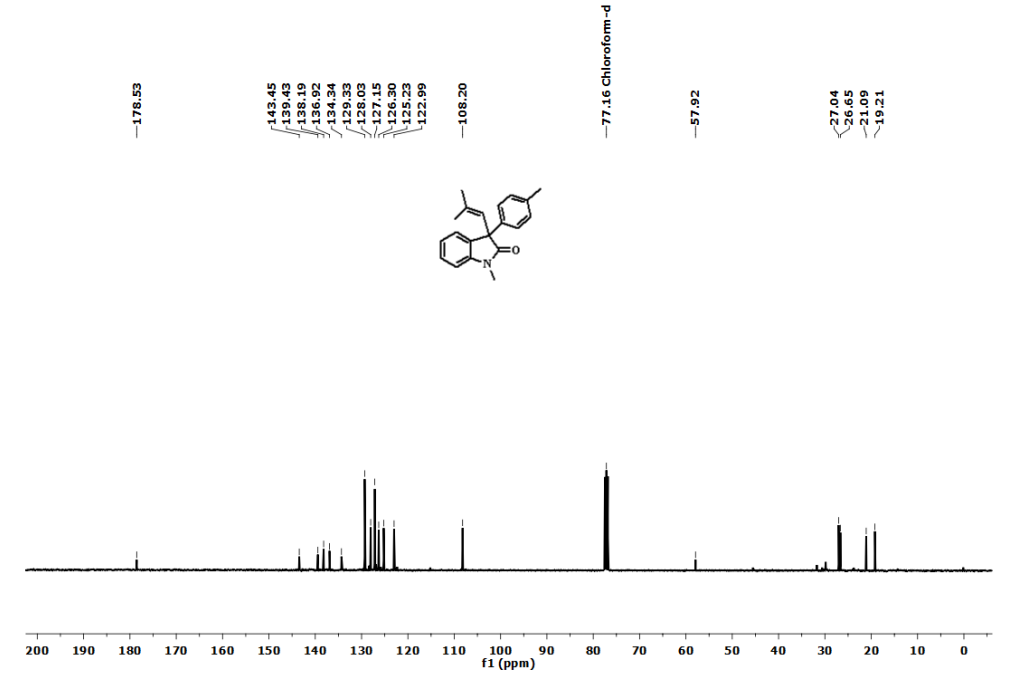


Figure 80: [13]C NMR of Compound **90e**

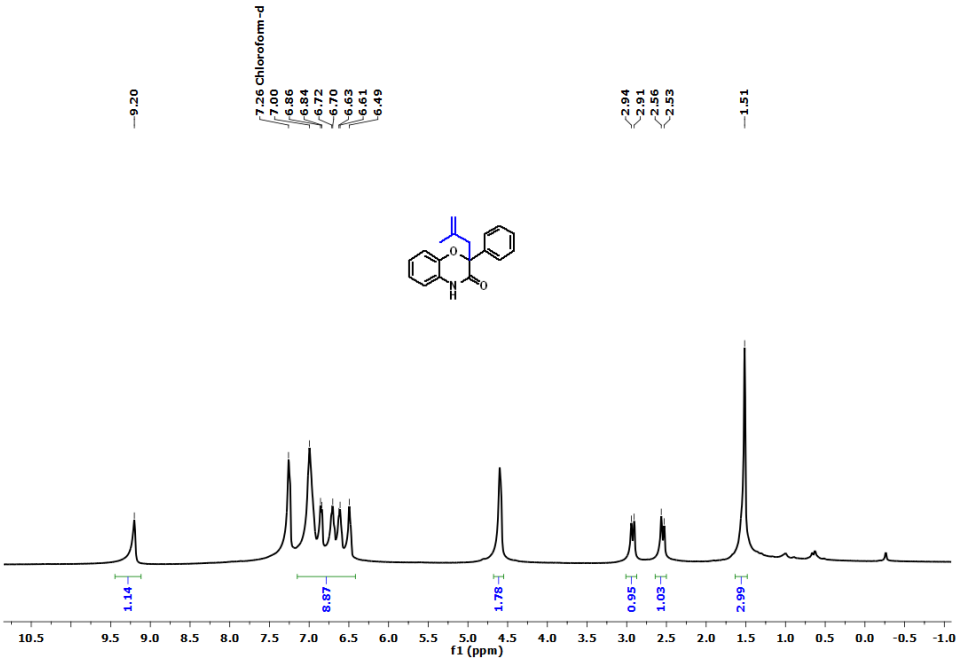


Figure 81: ^{1}H NMR of Compound **90o'**

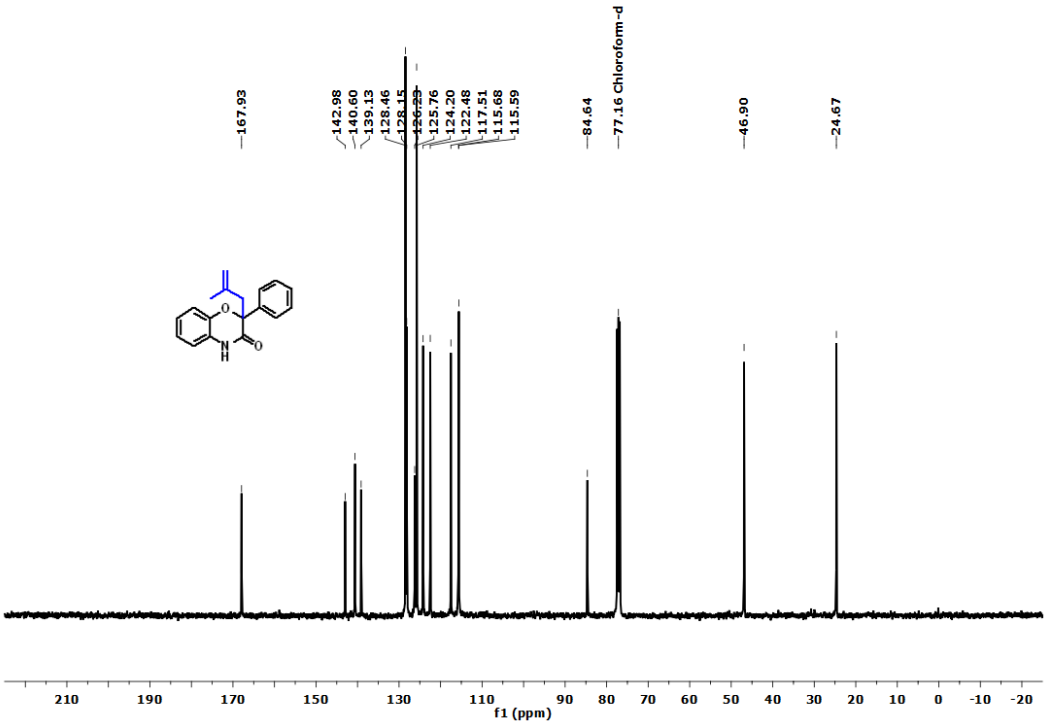


Figure 82: ^{13}C NMR of Compound **90o'**

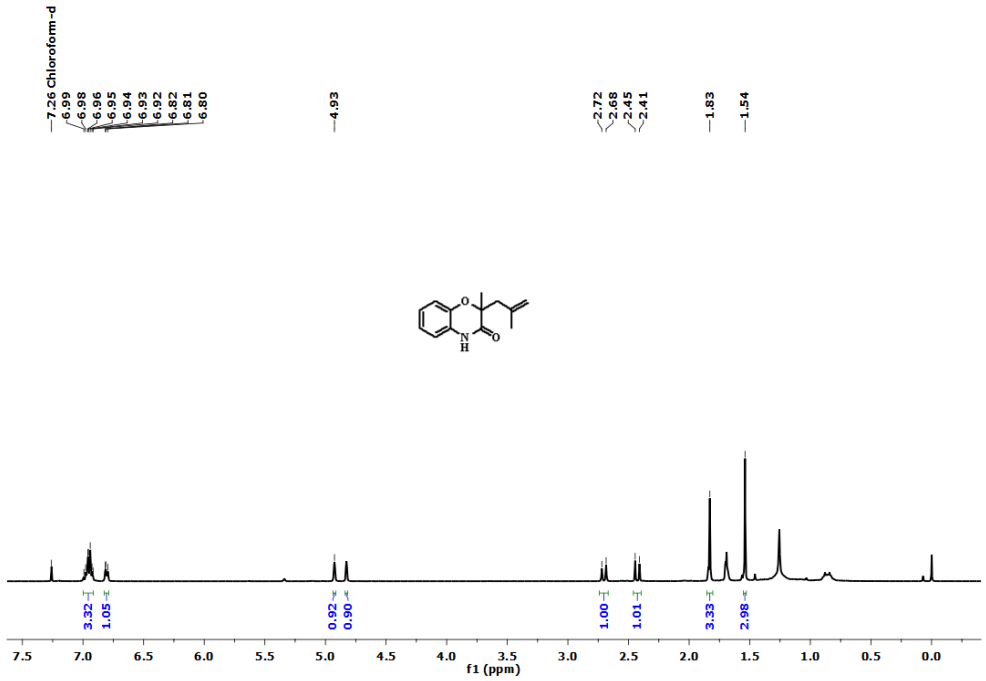


Figure 83: ^{1}H NMR of Compound **92a**

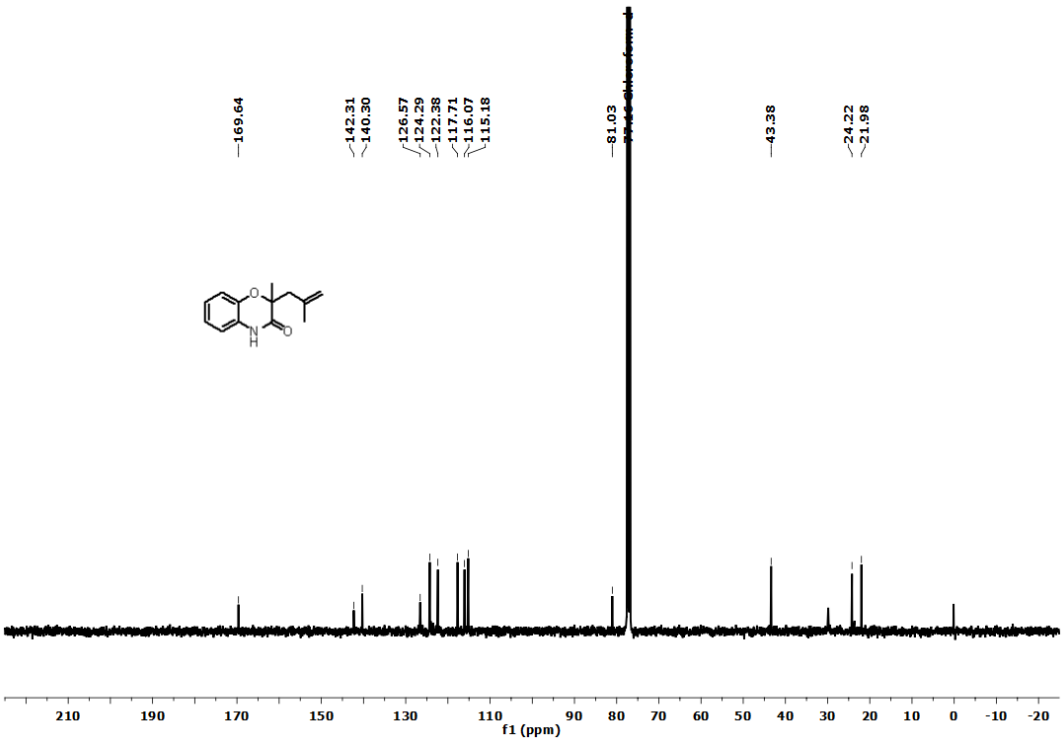


Figure 84: ^{13}C NMR of Compound **92a**

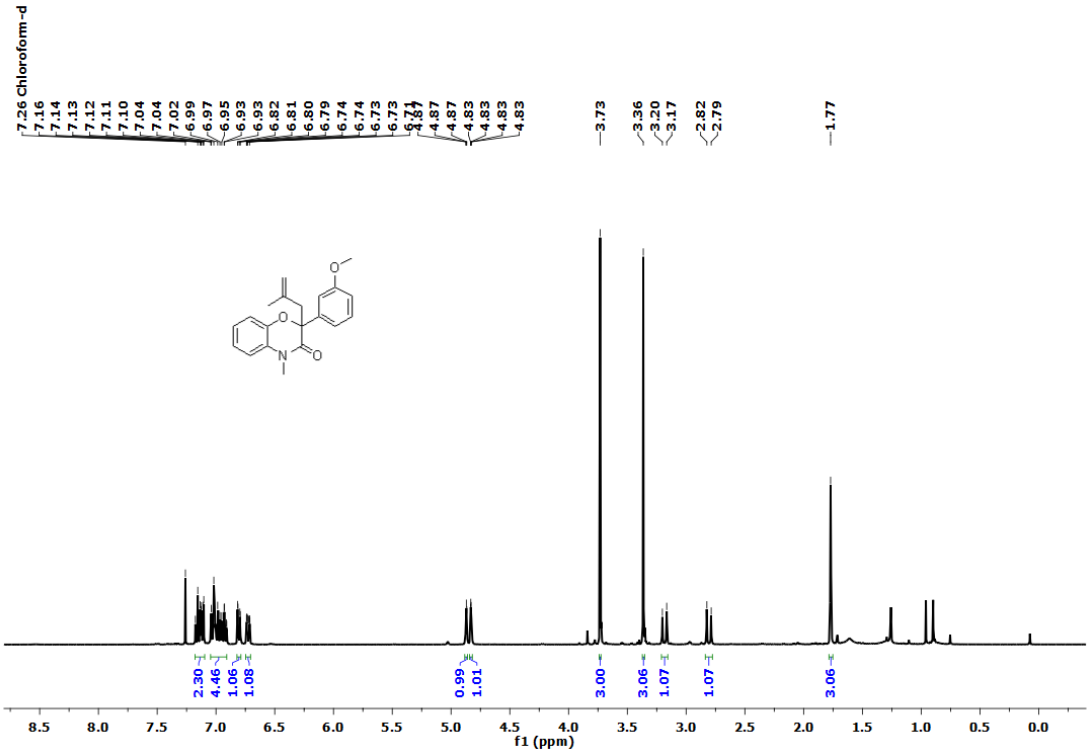


Figure 85: ^{1}H NMR of Compound **92e**

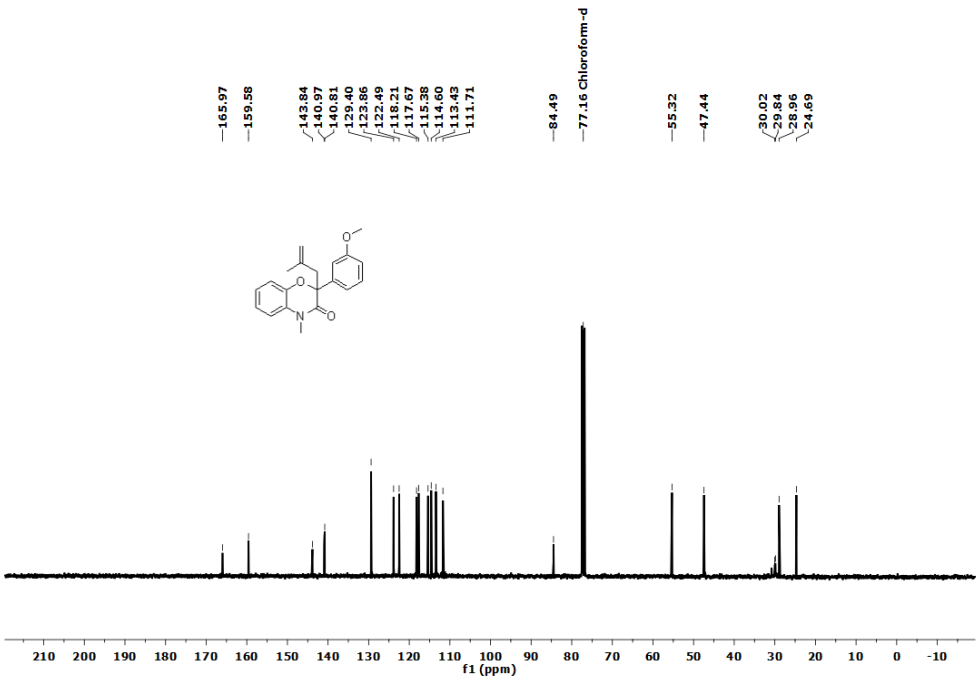


Figure 86: ^{13}C NMR of Compound **92e**

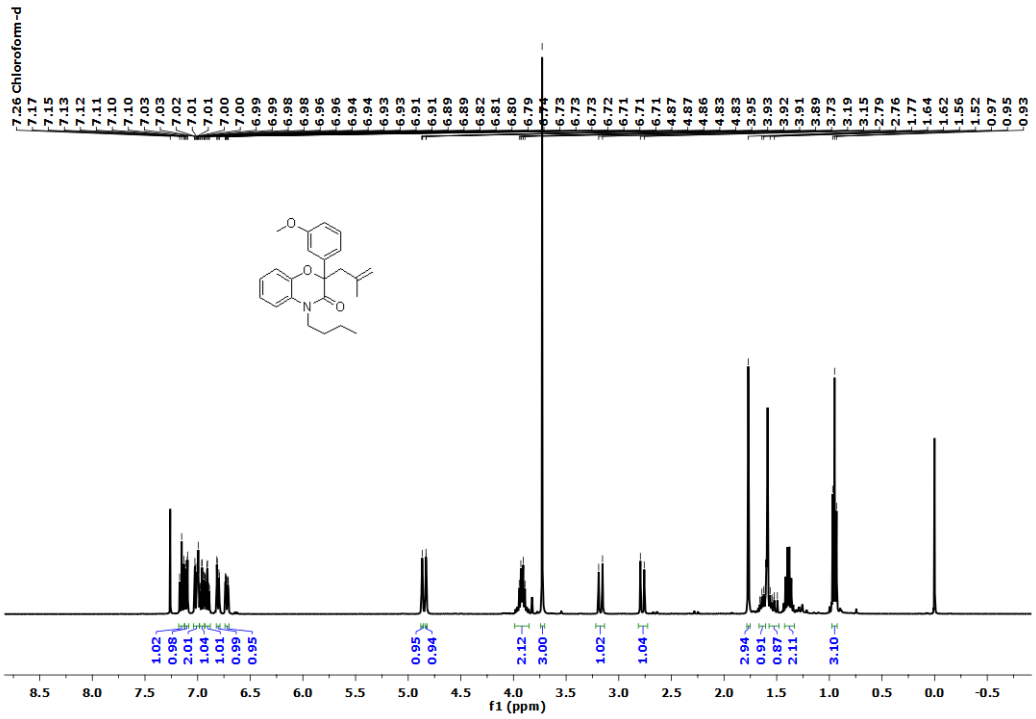


Figure 87: ^{1}H NMR of Compound **92j**

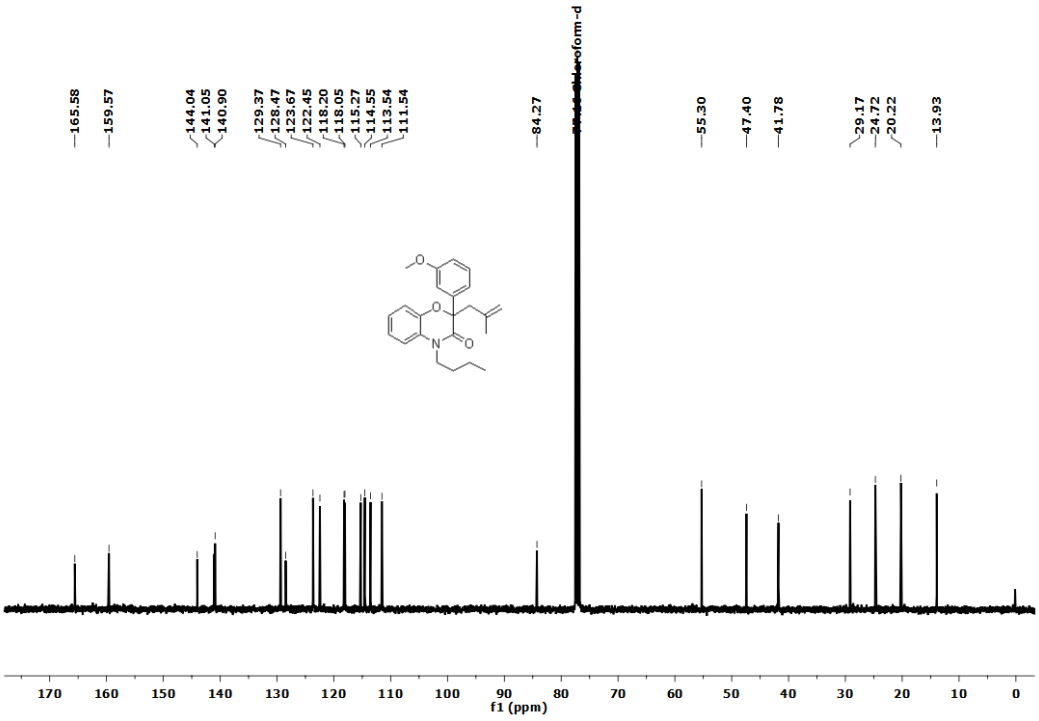


Figure 88: ^{13}C NMR of Compound **92j**

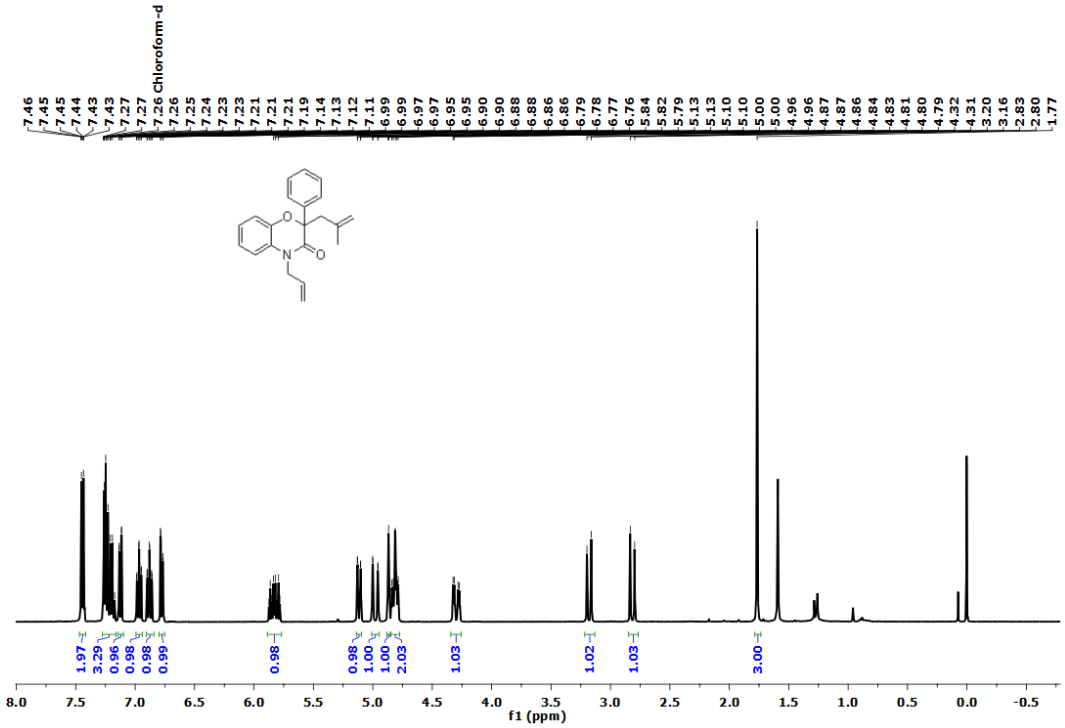


Figure 89: ^{1}H NMR of Compound **92m**

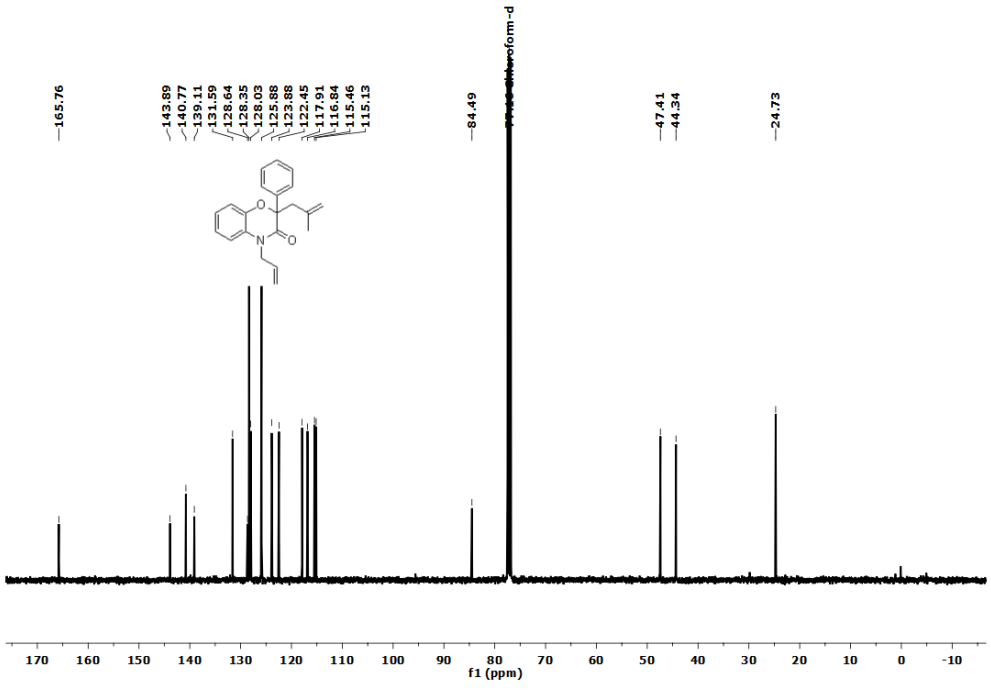


Figure 90: ^{13}C NMR of Compound **92m**

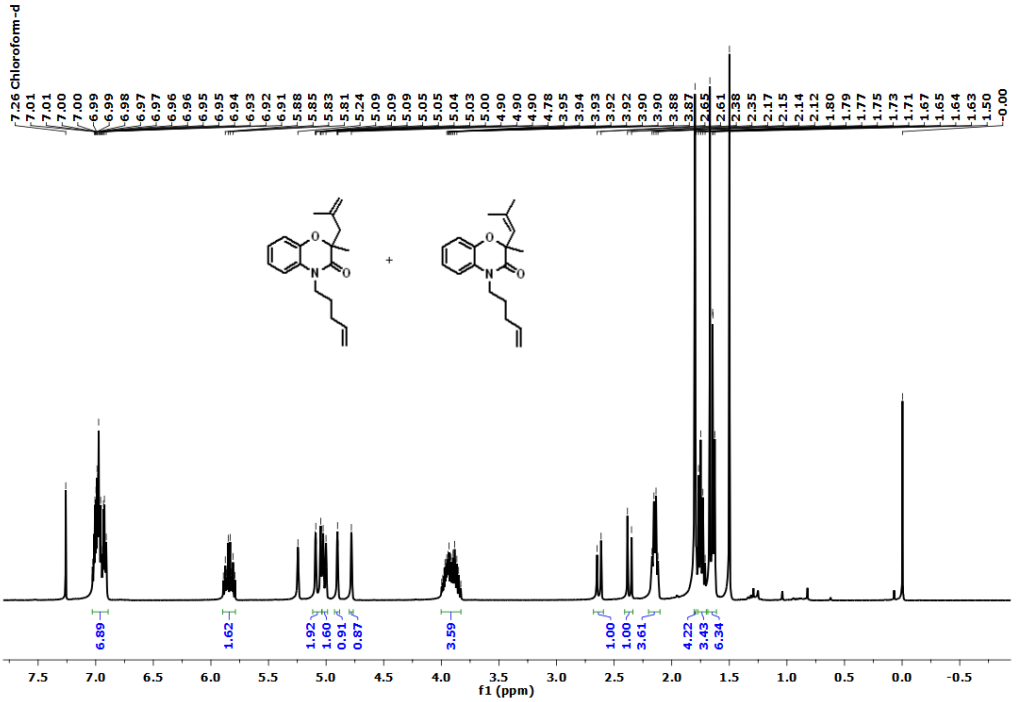


Figure 91: ^{1}H NMR of Compound **92o** and **92o'**

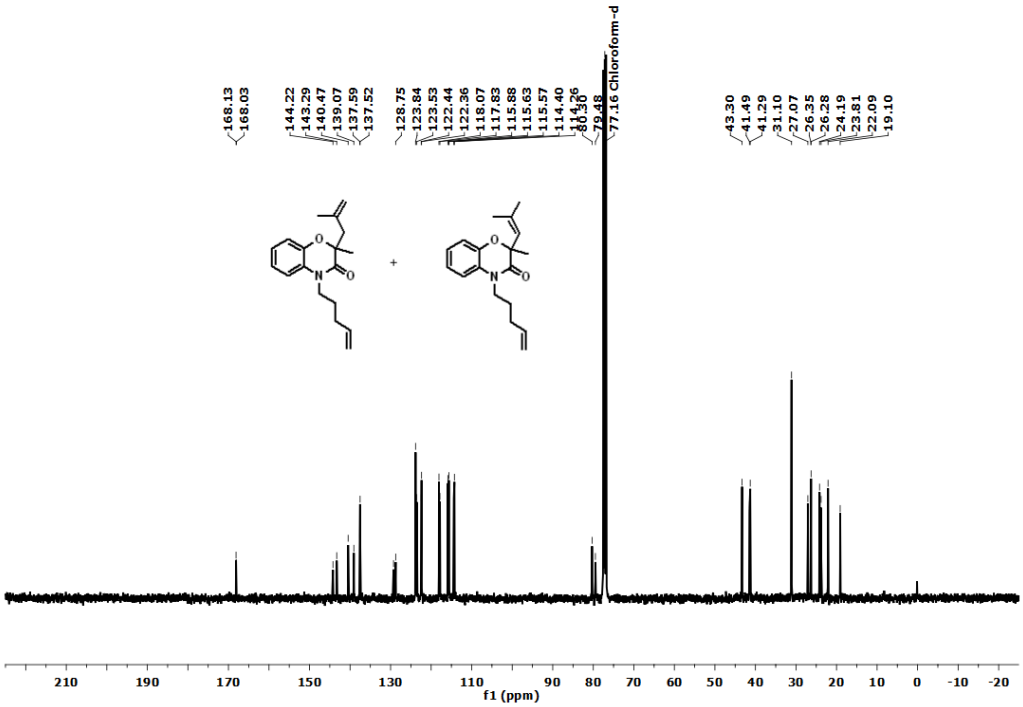


Figure 92: ^{13}C NMR of Compound **92o** and **92o'**

Datablock platon_sq - ellipsoid plot

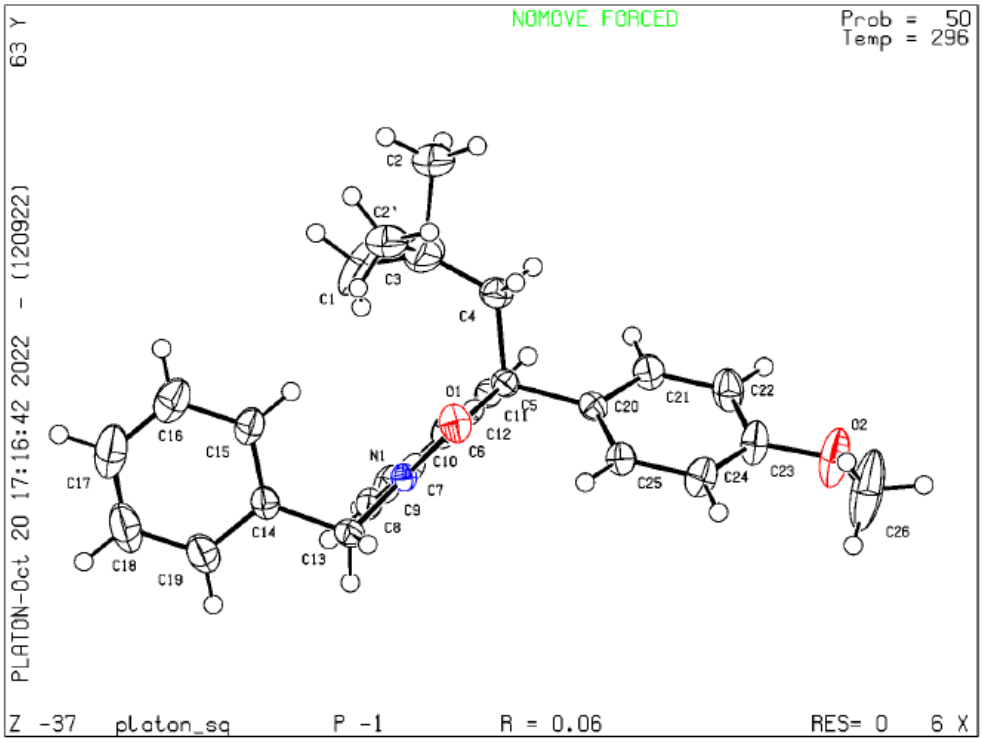


Figure 93: ORTEP – diagram of **90j'**

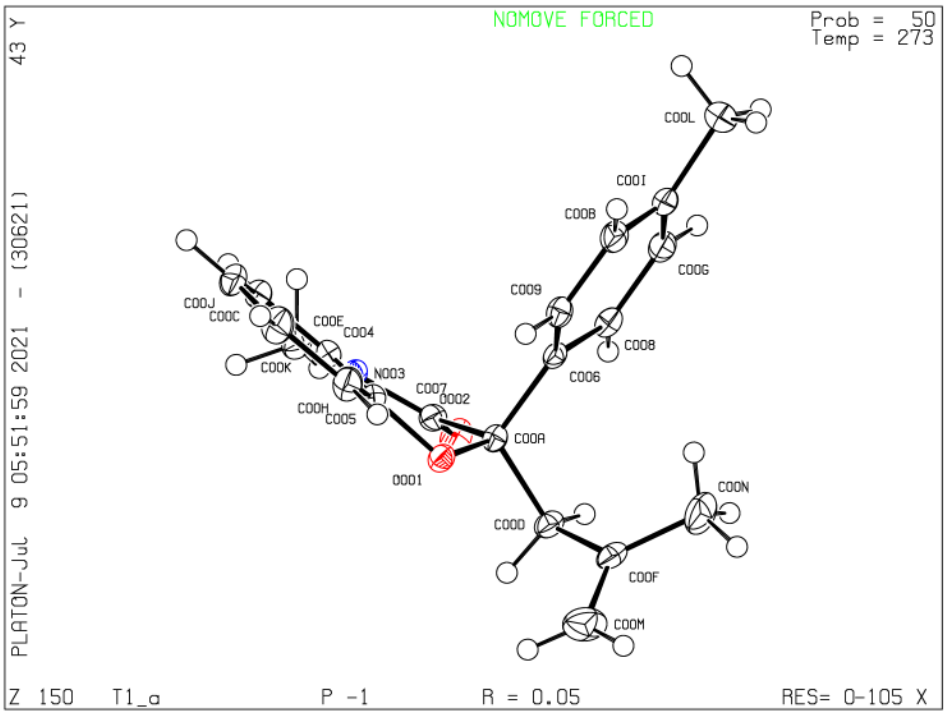


Figure 94: ORTEP – diagram of **92c**

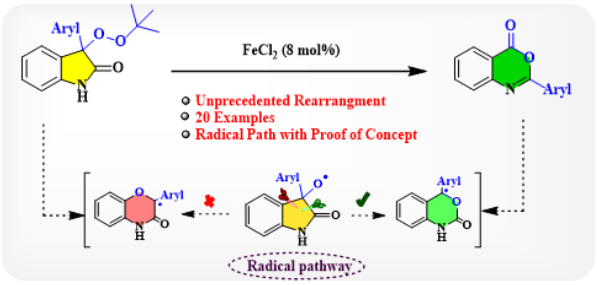
Chapter 4

$FeCl_2$-Catalyzed rearrangement of aryl peroxyoxindole into 1,3-benzooxazin-4-one

4. $FeCl_2$-Catalyzed rearrangement of aryl peroxyoxindole into 1,3-benzooxazin-4-one

4.1. Abstract

In this chapter, $FeCl_2$-catalyzed radical rearrangement of aryl peroxyoxindoles into 1,3-benzoxazin-2-one to obtain biologically active aryl substituted 1,3-benzoxazin-4-one derivatives has been described. Mechanistically, this skeletal rearrangement of peroxides proceeded via radical pathways and was well supported by a series of experimental findings and DFT studies.



4.2. Literature background for the rearrangement of peroxides

The molecular rearrangement represents a diversified strategy for rapidly introducing complexity in organic synthesis.[121] Traditionally, based on the nature of migratory group rearrangement reactions are classified into nucleophilic, electrophilic, radical, and sigmatropic rearrangements. The migratory group can be disconnected from carbon to carbon (such as Pinacol,[122] Wagner-Meerwein,[123] and Favorskii[124] rearrangement), or carbon to a heteroatom (such as Hofmann,[125] Schmidt,[126] Curtius,[127] and Beckmann[128] rearrangement), or from heteroatom to carbon (such as Wittig,[129] Steven,[130] and Sommelet-Houser[131] rearrangements). Unlike these reactions, in 1899, Baeyer and Villiger reported the synthesis of ester and lactone from the ketone, and it took fifty years to the confirmed mechanism of the reaction[132] (Figure 95). It was established that the reaction proceeds via tetrahedral intermediate formed (i.e., Criegee intermediate) addition of peroxy acid to the carbonyl carbon of ketone. This high energy intermediate undergoes the rearrangement via a 1,2-migratory shift through the disconnection of weak peroxy bond (O-O bond) was described by Criegee[133] in 1945 (Figure 95).

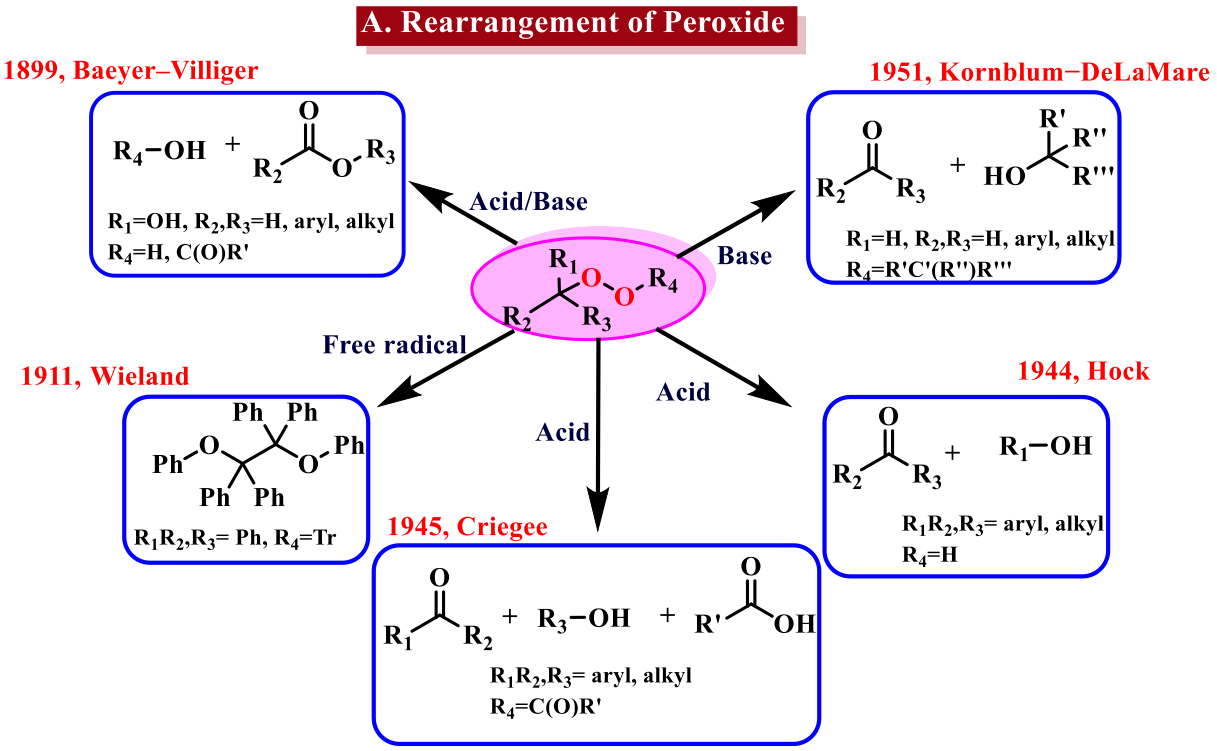
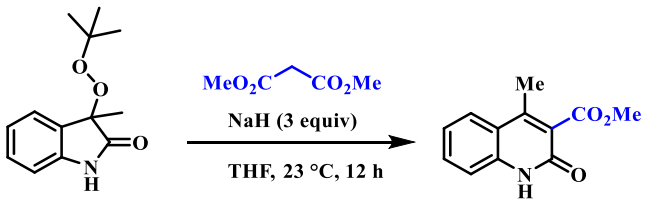


Figure 95. Rearrangement of peroxides

The organic peroxides moiety becomes an intriguing scaffold and undergoes several transformations due to the presence of low bond energy of the peroxide bond. In particular, Hock disclosed protic acid/Lewis acid catalyzed rearrangement of hydroperoxide via radical path[134] (Figure 95), which is the key step of the cumene process for the synthesis of phenol. But, the radical rearrangement of peroxides via homolytic cleavage is reported by Wieland[135] for the first time in 1911 (Figure 95). In 1951, the reaction of organic peroxides afforded ketone and tertiary alcohol peroxide was observed Kornblumand DeLaMare[136] (Figure 95). Later on, there are several named[137] and unnamed[138] rearrangements of peroxides moiety documented. However, the development of new types of rearrangement continues to be a compelling subject for methodology development and mechanism studies.

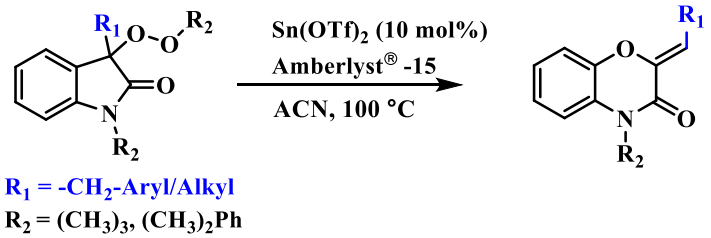
4.3. Literature background on the rearrangement of peroxyoxindoles

Nitrogen-containing heterocyclic compounds are not only indispensable compounds such as thiamin (vitamin B1), riboflavin (vitamin B2), pyridoxine (vitamin B6), or biologically active natural product used in traditional therapeutic or approved prescribed drugs but some of them are synthetic derivatives available in the market as medicines.[139] Due to the omnipresence of *N*-heterocycles in both pharmaceutical and natural products, they have always been an attractive target for synthetic organic and medicinal chemists. In 2016, Stoltz and co-workers reported the base-mediated oxidative fragmentation and rearrangement of peroxyoxindole to achieve quinolone (scheme 58).[140]



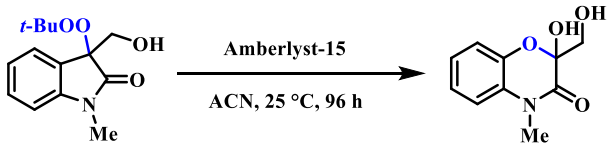
Scheme 58. Rearrangement of peroxyoxindoles for the synthesis of quinolone

Over the last few years, Gnanaprakasam's research group was engaged with functionalization and synthesis of *N*-containing heterocyclic compounds.[141] As a part of their recent ongoing interest in the synthesis of nitrogen-containing heterocycles, through several rearrangement reactions of C3-substituted peroxides was reported.[142] In 2019, the same group for the first time reported the intramolecular rearrangement of C3-substituted peroxides to biologically active C2-alkene substituted 1,4-benzoxazin-3-one derivatives[118a] (Scheme 59). But, the generality of this methodology is limited to the C3-substituted peroxyoxindoles.



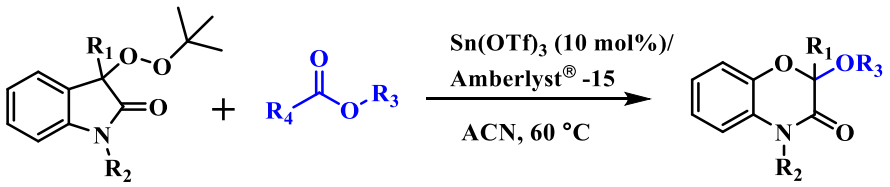
Scheme 59. Rearrangement of peroxyoxindoles for the synthesis of 1,4-benzoxazin-3-ones

Subsequently, in 2019, Hajra and co-workers developed an acid-catalyzed rearrangement of peroxyoxindole to 2-hydroxy-2-hydroxymethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (scheme 60).[143]



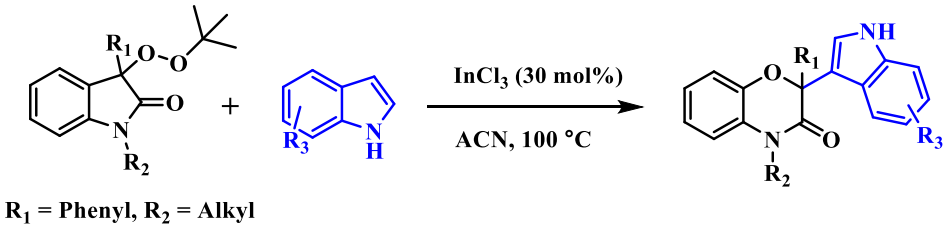
Scheme 60. Hajra's developed rearrangement of peroxyoxindoles for synthesis of 1,4-benzoxazin-3-ones

In 2020, Gnanaprakasam and coworkers reported the Sn(OTf)$_2$/amberlyst®-15 catalyzed Criegee type rearrangement of peroxyoxindole for the synthesis of C2-alkoxy substituted 1,4-benzooxazin-3-one derivatives via catalytic dual activation of esters and peroxyoxindoles (scheme 61). [118b\



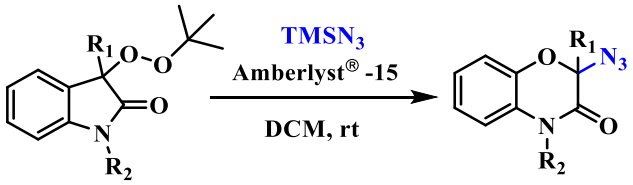
Scheme 61. The rearrangement of peroxyoxindoles for the synthesis of 1,4-benzooxazin-3-one derivatives

In 2021, Gnanaprakasam and co-workers reported the rearrangement reaction of peroxyoxindole and indolylation. In this reaction C2-indole substituted 1,4-benzooxazin-3-one derivatives was synthesized using $InCl_3$ via sequential rearrangement of peroxyoxindoles (scheme 62).[142a]



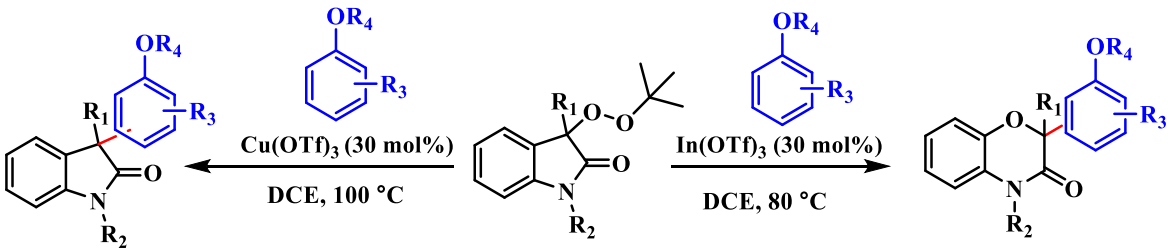
Scheme 62. The sequential rearrangement and indolylation of peroxyoxindoles

Subsequently, Gnanaprakasam and coworkers has reported the continuous flow driven rearrangement of peroxyoxindoles followed by azidation of in situ generated 1,4-benzooxazin-3-one carbocation using amberlyst®-15 as catalyst (scheme 63). [142b]



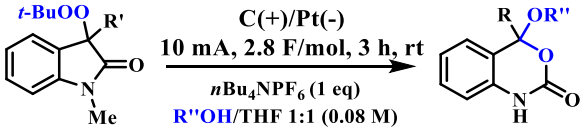
Scheme 63. The continuous flow direct rearrangement and azidation of peroxyoxindoles

In 2022, Lewis acid catalyzed rearrangement reaction of quaternary peroxyoxindoles with phenols was reported by Gnanaprakasam's research group. In this reaction, indium catalyzed regiospecific coupling of phenol with peroxyoxindole for the construction of 2,2-disubstituted 1,4-benzooxazin-3-ones via sequential rearrangement and nucleophilic substitution of phenol was reported (Scheme 64).[142c]



Scheme 64. The rearrangement reaction of peroxyoxindole to synthesize phenol-substituted 1,4-benzooxazin-3-one derivatives

In 2022, Maulide and co-workers discovered a new electrochemical rearrangement reaction that converts 3-hydroxyoxindoles into benzooxazinone derivatives. The reaction proceeds via the formation of peroxyoxindole intermediates, which then undergo a skeletal rearrangement to give the desired benzooxazinones (scheme 65).[144]



Scheme 65. The electrochemical- driven rearrangement of peroxyoxindole

4.4. The objective of the present work

The objective of this project is to develop a sustainable approach toward the synthesis of nitrogen-containing heterocyclic compounds, particularly 1,3-benzooxazin-4-one, which is commonly found in pharmaceuticals and has a wide range of biological applications (Figure 96).[145] Similarly, 4*H*-benzo[*d*][1,3]oxazin-4-one, which is a key pharmacophore, for example, the cetilistat (**96**), is used for treating obesity (Figure 96).[146] Some of these derivatives possess excellent elastase inhibitors (**95**) and C1r protease inhibitors (Figure 96).[146] The traditional method for synthesizing benzoxazin-4-one derivatives involves the reaction of anthranilic acid with an acylchloride in the presence of a stoichiometric amount of base.[147] Further, many transition metal catalyzed protocols, including Pd, Co, Cu, and so on, have been used to assemble 1,3-benzoxazine core.[148] However, the use of peroxyindoles as a precursor for the synthesis of 1,3-benzoxazin-4-one via rearrangement has not been explored. This project aims to investigate rearrangement reactions to develop a new and efficient method for the synthesis of 1,3-benzooxazin-4-one. The atom economy of the proposed rearrangement reaction makes it an attractive strategy for the development of organic transformations toward the synthesis of biologically active organic molecules.

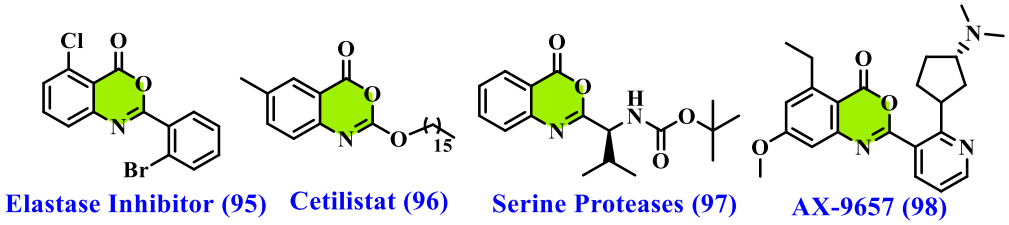


Figure 96. Biological significance of 1,3-benzooxazin-4-one derivatives

4.5. Results and discussion

For the last few years, Gnanaprakasam's research group has been engaged on the development of Lewis acid catalysed rearrangement of peroxyoxindole for the synthesis of various 1,4-benzooxazin-3-one derivatives. Notably, all these rearrangements proceed through a common 1,4-benzooxazine carbocation intermediate in the presence of Lewis acid catalysts such as $Sn(OTf)_2$, $In(OTf)_3$, and $InCl_3$. In this context, the behavior of C3-substituted peroxide toward Fe catalysts was investigated. Herein, Fe(II)-catalyzed rearrangement of C3-aryl substituted peroxyoxindole for syntheses of biologically important 1,3-benzooxazin-4-one derivatives via the radical path (Figure 97) is reported.

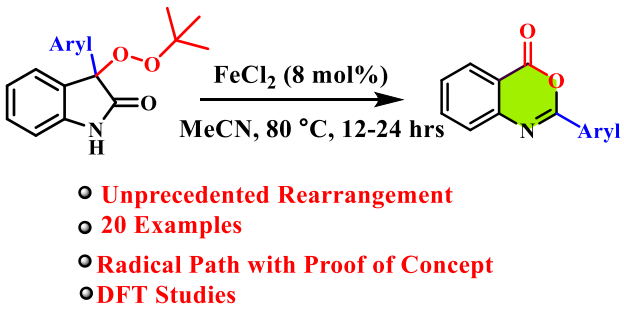
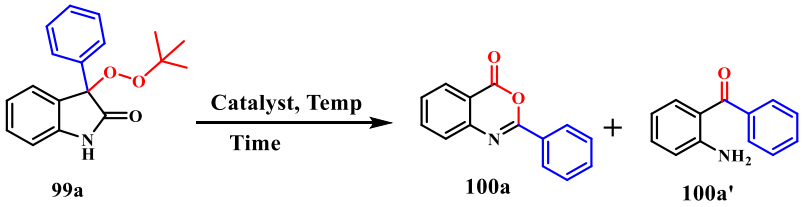


Figure 97. Rearrangement of peroxyoxindoles for the construction of 1,3-benzooxazin-4-ones

4.5.1. Optimization studies

The C3-phenyl peroxide of 2-oxindole **99a** was chosen for the initial optimization of the reaction conditions (Table 14). A couple of control experiments was performed, but the reaction did not proceed either in the absence of the catalyst or 10 mol% of $FeCl_2$ at room temperature (Table 14, entries 1 and 2). Next, peroxide **99a** was heated at 60 °C with 10 mol% of $FeCl_2$ in ACN affording 33% of **100a** and 7% of 2-aminobenzophenone (**100a**') (Table 14, entry 3). To achieve better yield and high selectivity of product **100a** various metal catalyst was screened. The $MnCl_2$ afforded 23% of **100a** (Table 14, entry 4). The **99a** remained unreacted with $Mn(OTf)_2$, and $Zn(OTf)_2$ (Table 14, entries 5 and 6). Notably, 18% of **100a** was formed with $Fe(OTf)_2$ (Table 14, entry 7). The desired product **100a** was not observed with $Ni(OTf)_2$, $In(OTf)_3$, $Sn(OTf)_2$, $Ca(OTf)_2$, Cu(I)Cl, amberlyst®-15, and triflic acid (Table 14, entries 8-14). All the above results signify that Fe(II)-catalyst has a vital role in this transformation. An increase in yield of **100a** was noticed when increasing the

Table 14. Optimization of the rarrangement reaction



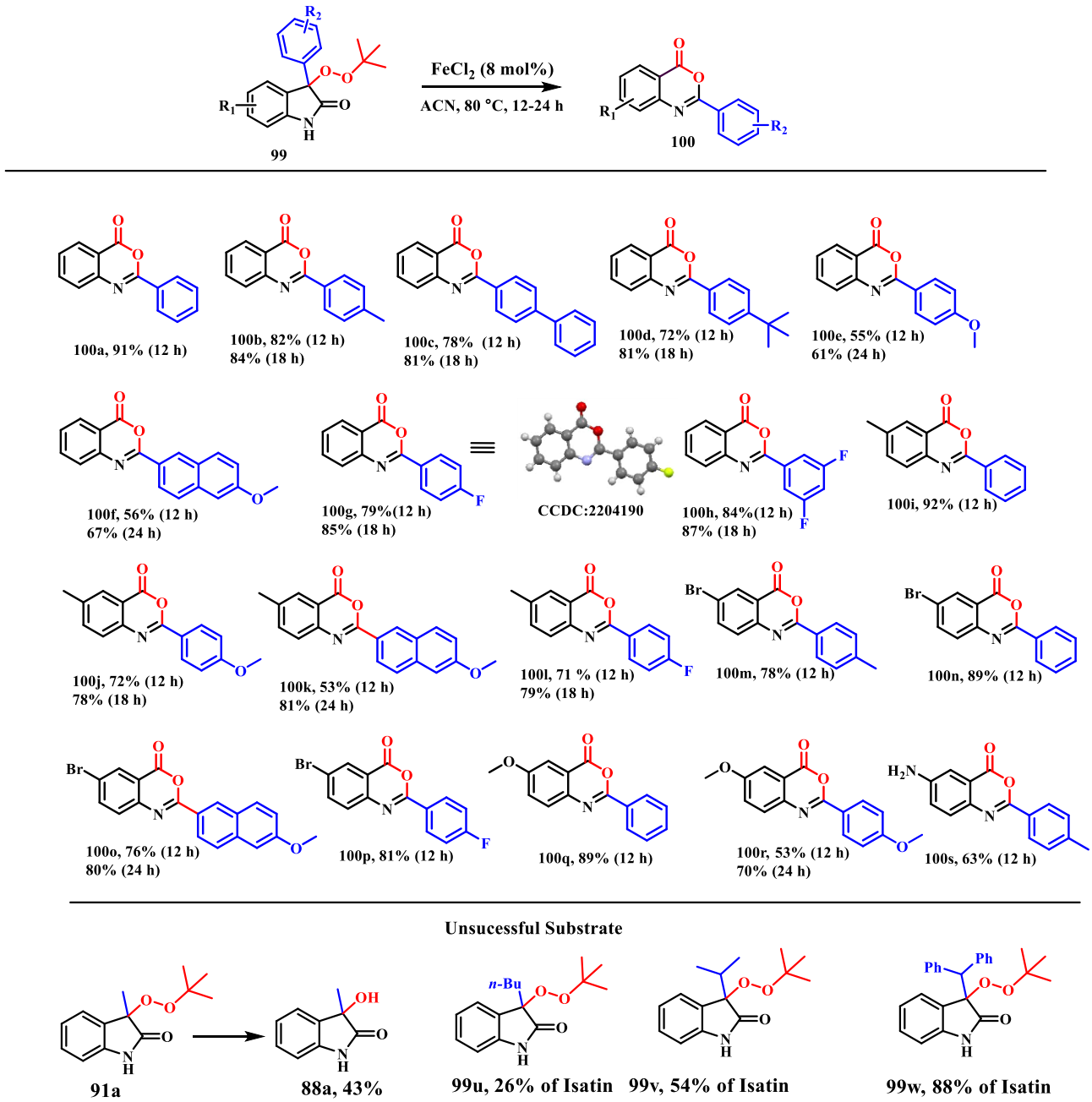
entry[a]	catalyst	solvent	temp (°C)	yield (%)	
				100a	100a'
1	-	ACN	rt	No reaction	
2[b]	$FeCl_2$	ACN	rt	No reaction	
3[b]	$FeCl_2$	ACN	60	33	7
4[b]	$MnCl_2$	ACN	60	23	-
5[b]	$Mn(OTf)_2$	ACN	60	No reaction	
6[b]	$Zn(OTf)_2$	ACN	60	No reaction	
7[b]	$Fe(OTf)_2$	ACN	60	18	12
8[b]	$Ni(OTf)_2$	ACN	60	0	
9[b]	$In(OTf)_3$	ACN	60	0	
10[b]	$Sn(OTf)_2$	ACN	60	0	
11[b]	$Cu(OTf)_2$	ACN	60	0	
12[b]	Cu(I)Cl	ACN	60	0	
13[c]	Amberlyst®-15	ACN	60	0	
14[b]	Triflic acid	ACN	60	0	
15[b]	$FeCl_2$	ACN	80	82	Trace
16	$FeCl_2$	*t*-BuOAc	80	89	-
17	$FeCl_2$	EtOAc	80	27	13
18	$FeCl_2$	THF	80	31	21
19	$FeCl_2$	DCE	80	5	25
20	$FeCl_2$	Dioxane	80	10	15
21	$FeCl_2$	DMF	80	21	19
22	$FeCl_2$	DMSO	80	4	31
23	$FeCl_2$	ACN	80	91	-
24[d]	$FeCl_2$	ACN	80	No Reaction	
25[e]	$FeCl_2$	ACN	80	25	-
26[f]	$FeCl_2$	ACN	80	35	42

[a]**Reaction condition**: 0.25 mmol **99a** was taken in resealable vial, loaded with 8 mol% of catalyst, solvent (2 mL), and heated at mention temperature for 12 h; [b]10 mol% catalyst; [c]amberlyst®-15:**99a**, 1:1(w/w); [d]1 mol% catalyst; [e]5 mol% catalyst; [f]20 mol% catalyst.

reaction temperature to 80 ^{o}C and a trace amount of **100a**' (Table 14, entry 15). Moreover, to eliminate **100a**' completely from the reaction, the reaction was investigated with various solvents (Table 14, entries 16-23). ACN was shown as the best reaction medium and **100a'** was diminished from the reaction by decreasing the catalyst loading to 8 mol% (Table 14, entry 23). Further decrease in the catalyst loading caused poor yield of the desired product (Table 14, entries 24 and 25), and increasing the catalyst loading lead to the formation of **100a'** in higher yield (Table 14, entry 26). Finally, 91% of **100a** was isolated by treating **99a** with 8 mol% of $FeCl_2$ at 80 ^{o}C for 12 h (Table 14, entry 23).

4.5.2. Substrate scope for the rearrangement of peroxyoxindoles

Having optimized reaction condition in hand, the generality of the substrate scope for this rearrangement reaction was explored. An array of diversely functionalized C3-aryl peroxyoxindole underwent this rearrangement protocol in the presence of $FeCl_2$ to afford the corresponding product **100** in good to excellent yields (Scheme 66). For example, the C3-aryl peroxyoxindole derivatives bearing electron-donating groups in benzene ring such as methyl, phenyl, t*ert*-butyl, and -OMe afforded good to excellent yields (**100a-e**). Similarly, electron-rich –OMe substituted naphthalene furnished 56% of **100f**, under the optimized reaction condition. The phenyl group bearing electron-withdrawing groups such as –F and difluoro afforded excellent yields of the desired products (**100g-h**). Moreover, the C3- substituted peroxyoxindole core moiety bearing methyl, Br, -OMe, and -NH_2 substitutions at the aryl part also underwent the rearrangement and provided **100i-s** in good yields. Moreover, C3-methyl substituted peroxyoxindole **91a** resulted cleavage of *tert*-BuO group and give 43% of hydroxy product **88a**. Similarly, **99u**, **99v** and **99w** afforded isatin **101** with the developed method via the Hock cleavage mechanism.[118a]

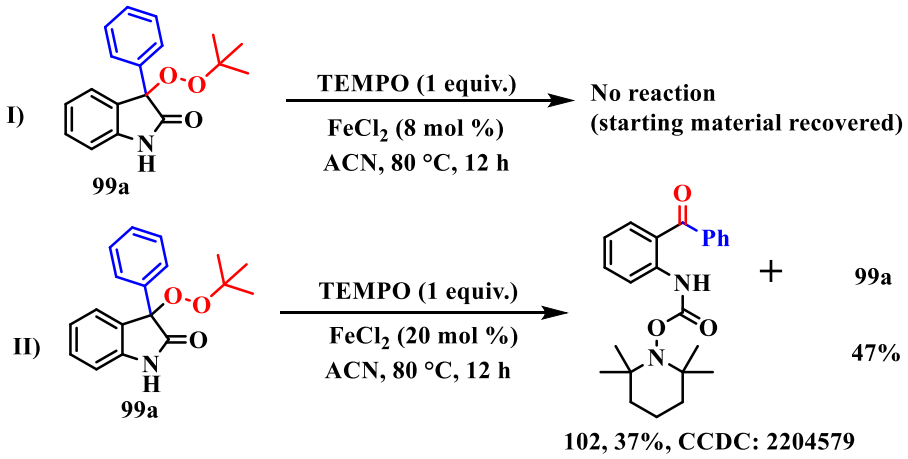


[a]**Reaction conditions**: 0.25 mmol **99** and 8 mol% of $FeCl_2$ was taken in resealable vial with 2 mL of ACN and heated at 80 °C for 12 h; [b]heated for 18 h; [c]heated for 24 h Mentioned yields are isolated yields**.**

Scheme 66. Substrate scope for the rearrangement of peroxyoxindoles

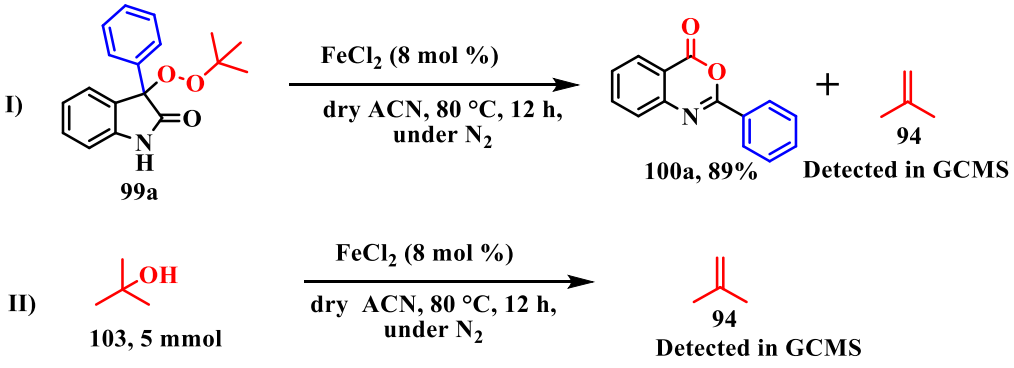
4.5.3. Mechanistic investigations for the rearrangement reaction

To gain insights into the mechanism of the developed $FeCl_2$-catalyzed rearrangement of peroxyoxindole, numerous control experiments were performed. The reaction was completely suppressed when 1 equivalent of radical scavenger TEMPO was added to the optimized condition,



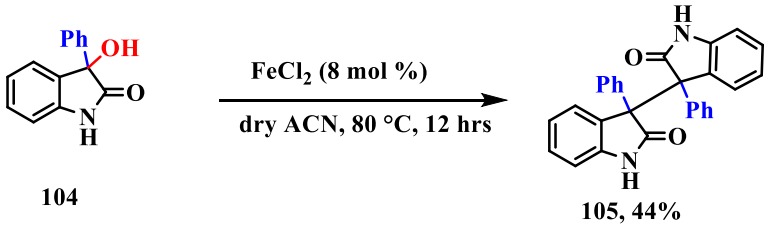
Scheme 67. Radical quenching reaction for the rearrangement reaction

indicating a free radical pathway (Scheme 67(I)). TEMPO-based adduct product **102** was also isolated when 20 mol% of $FeCl_2$ was used, confirming that **100a'** was formed with higher catalyst loading (Scheme 67(II)). To confirm the source of carbonyl oxygen of the ester group of **100a**, the reaction was performed under nitrogen with dry ACN solvent, yielding 89% of **100a** (Scheme, 68(I)). This result confirmed that the ester carbonyl oxygen was attributed by either the peroxyl oxygen attached to the *t*-butyl group or the carbonyl oxygen of the amide group in the absence of H_2O. Further, the hypothesis of homolytic cleavage of peroxide bond was strengthened by the detection of *iso*-butylene in GCMS (See section **4.8.3.2.**, Figure 100 and 101). To confirm whether the *tert*-butoxy group was responsible for the generation of *iso*-butylene, the *tert*-butanol **103** was used in the optimized reaction condition and injected it into the GCMS. The detectation of *iso*-butylene was confirming that *tert*-butoxy was the source of *iso*-butylene (Scheme 68(II)).



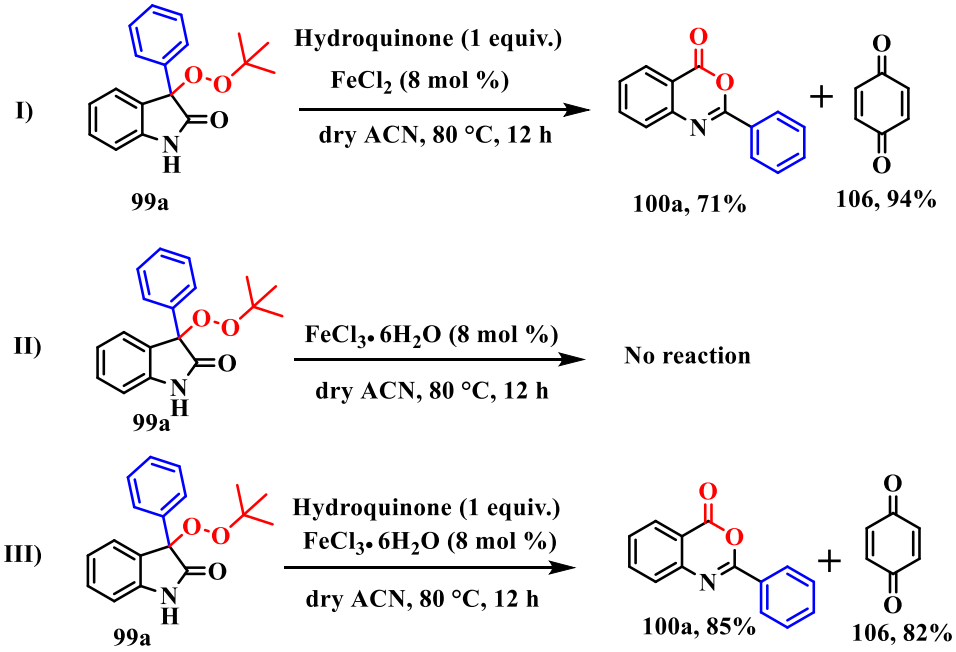
Scheme 68. Experiment for the detection of *iso*-butylene

Further, to confirm whether C3-hydroxy oxindole was one of the intermediates **104**, the optimized reaction condition was performed with **104**, and afforded 44% of **105** (Scheme 69). This result of the reaction confirmed that C3-hydroxy oxindole **104** was not formed in the reaction and was not an intermediate of the reaction.



Scheme 69. Control experiment with 3-hydroxy-3-phenyl oxindole

Further, to confirm the formation of radical and active catalyst of the reaction, a set of reactions was performed in conjunction with the oxidation reaction of hydroquinone to benzoquinone in the presence of $FeCl_3$.[149] Thus, the hydroquinone was added in the optimal reaction condition, afforded benzoquinone **106** and **100a** (Scheme 70(I)). This confirmed the generation of Fe(III) in the reaction medium. Product **100a** was not formed when Fe(III) was used as the catalyst (Scheme 70(II)). However, the same reaction proceeded smoothly when hydroquinone was added as an additive (Scheme 70(II)), implying the crucial role of Fe(II) in the reaction and that the in situ generated Fe(III) plays a vital role in this rearrangement.



Scheme 70. Experiments to confirm the active catalyst

4.5.4. DFT studies

DFT studies were performed using M06-2X functional[150] to obtain additional mechanistic insights about the iron-catalyzed rearrangement of peroxyoxindole derivatives. All calculations were done using Density Functional Theory (DFT) based methodology as implemented in the Gaussian 16 package.[117] The structures were optimized using M06-2X functional in combination with 6-311++G(d,p) basis set. The local minima were confirmed by frequency analysis having no imaginary

frequencies. Solvent effects were incorporated in the calculations as implemented in SMD model for acetonitrile. In cases of transition states, a preoptimization was carried out before the transition state search. Intrinsic reaction coordinate (IRC) calculations were done to confirm that every transition-state structure is corresponding to that of the reactant, intermediate, or products. The transition state was identified by the presence of a single imaginary frequency. The energies reported in the free energy profile are ΔG values incorporated with zero-point energy corrections for the optimized minima at 298.15 K.

Firstly, the electronic state of the active catalyst $FeCl_2$, involved in the catalytic process was studied. The absolute electronic energies obtained for singlet, triplet and quintet were envisioned and are found - 2184.108028 Hartrees, -2184.099873 Hartrees, and 2184.250868 Hartrees, respectively. So, the quintet state is more stable and feasible than the singlet and triplet states. Similarly, for Fe(III) species, there exists doublet, quartet, and sextet out of which sextet is found to be the most feasible state depending on the electronic energies. Hence, further calculations are carried out considering the quintet state of $FeCl_2$ and the sextet state of Fe(III) moieties. The relative Gibbs free energies for all moieties involved are shown in Figure 98. The reaction was first initiated through the interaction of $FeCl_2$ with C3-phenyl peroxyoxindole **99a** to form alkoxy radical **99aa** via [**TS1**] and in situ generation of Fe(*t*-BuO)Cl_2. The energy barrier obtained for this step was 16.3 kcal/mol. The rearrangement within alkoxy radical **99aa** generated two intermediates, namely, tertiary radical **99ab** or carbonyl radical **99ab'**, via [**TS2**]/[**TS2**'] (Figure 99). However, barriers involved in the formation of **99ab** [25.2 kcal/mol] were lower than that of **99b'**. Simultaneously, the Fe-mediated *tert*-butoxy intermediate formed in earlier steps generated *iso*-butylene and Fe(III)(OH)Cl_2 (Figure 99, eq. 1). Here, two possibilities exist; first, Fe(III)(OH)Cl_2 interacts with **99ab** to give hydroxy intermediate **99ac** via [**TS3**], which is exergonic by 28.0 kcal/mol. Then, **99ac** can either undergo decarboxylation, forming **100a'** via [**TS 5**'] or react with decarboxylation, forming **100a'** via [**TS 5**'] or reacts with the $FeCl_2$ catalyst to form radical **99ad** and $HFeCl_2$ via [**TS 5**]. Although the reaction is spontaneous in both ways, the barrier involved for decarboxylation is considerably high (40.5 kcal/mol), indicating that **100a'** may have been a minor product. This was followed by the 1,3-phenyl shift within **99ad**, resulting in the radical intermediate **99ae** via [**TS 6**], corresponding to the energy barrier 5.8 kcal/mol. Then, proton abstraction by **99ae** led to **99af** via [**TS 7**]; this was accompanied by the regeneration of the $FeCl_2$ catalyst.

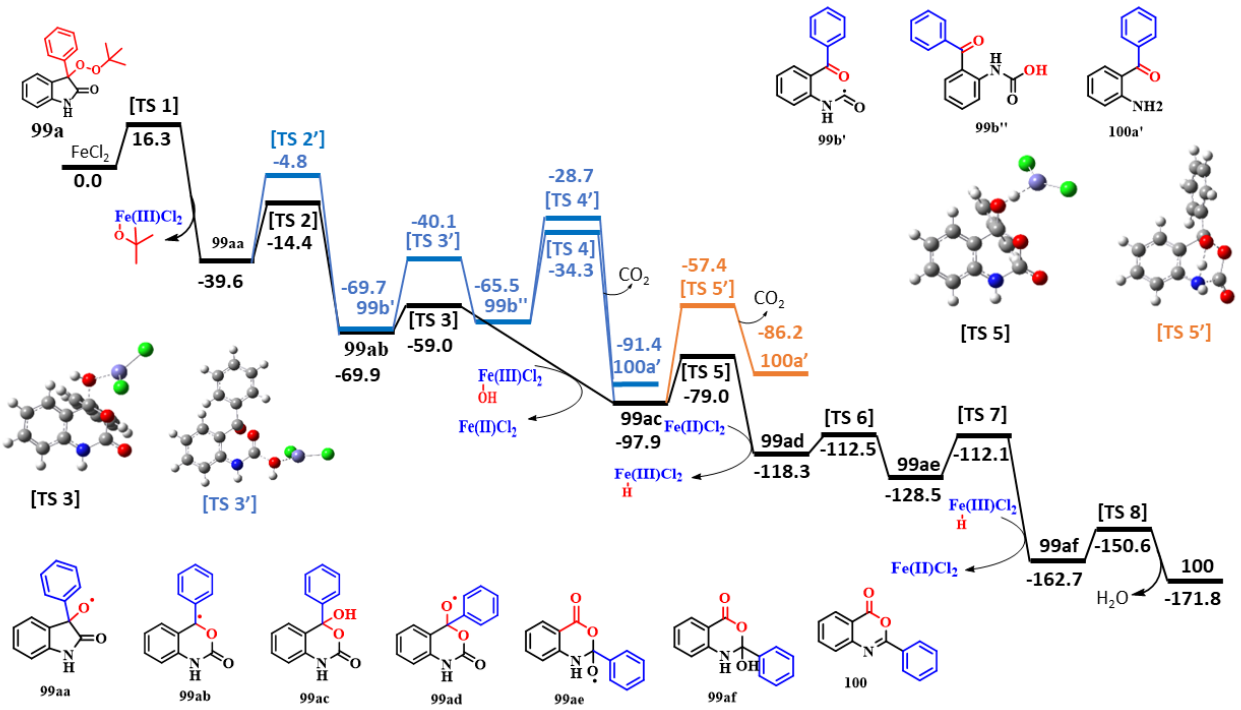
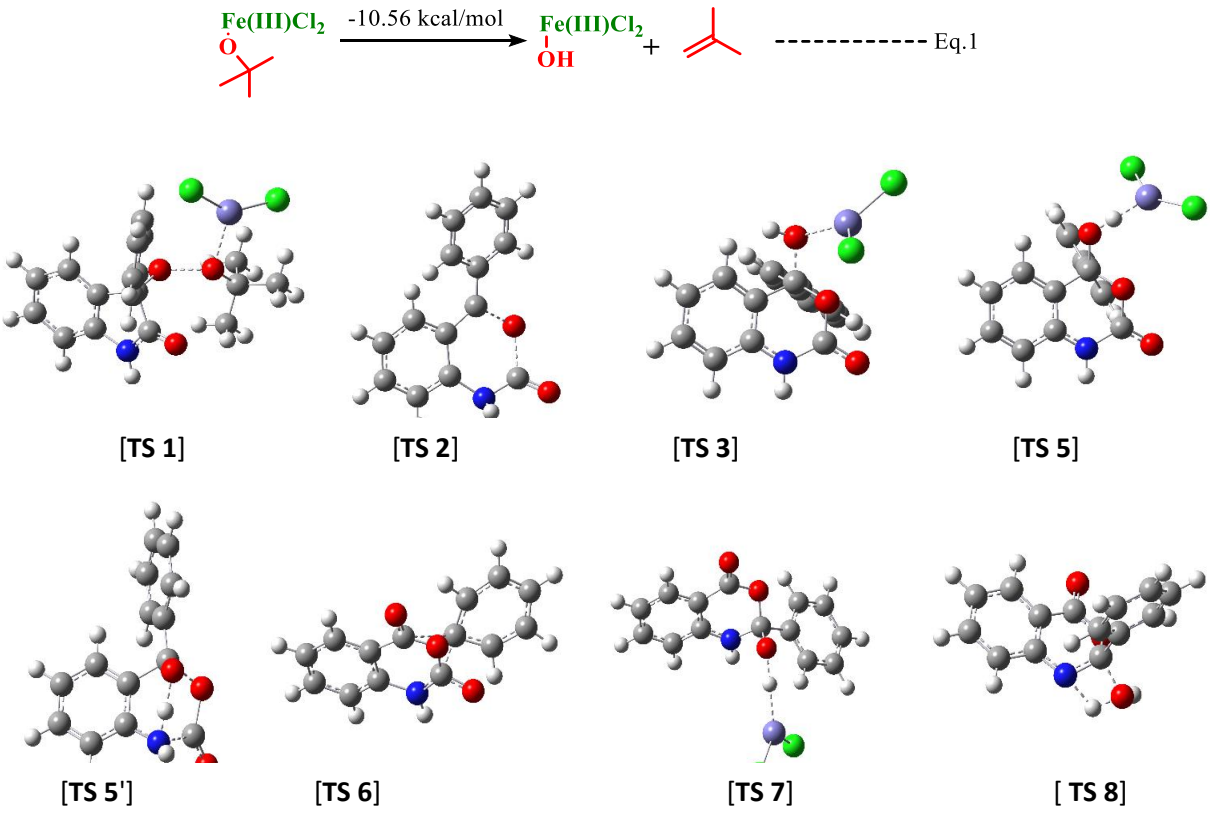


Figure 98: Ball and stick model of optimized transition states involved in the reaction pathway



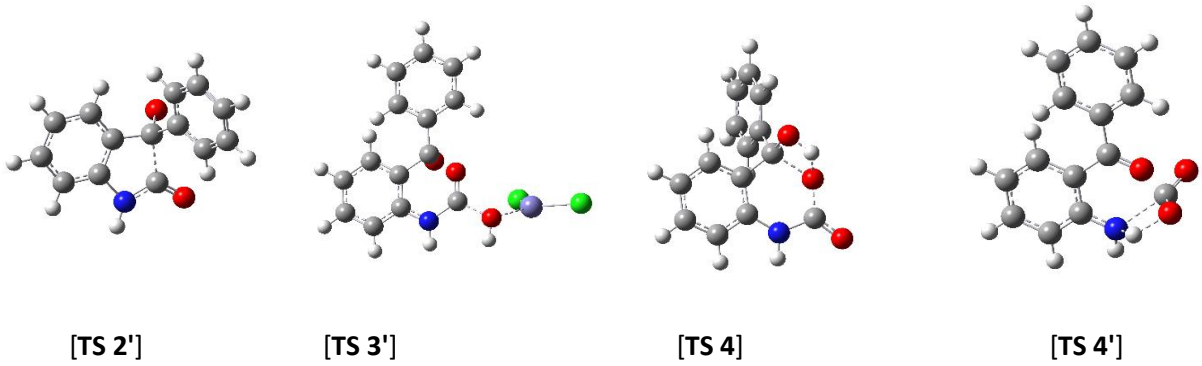
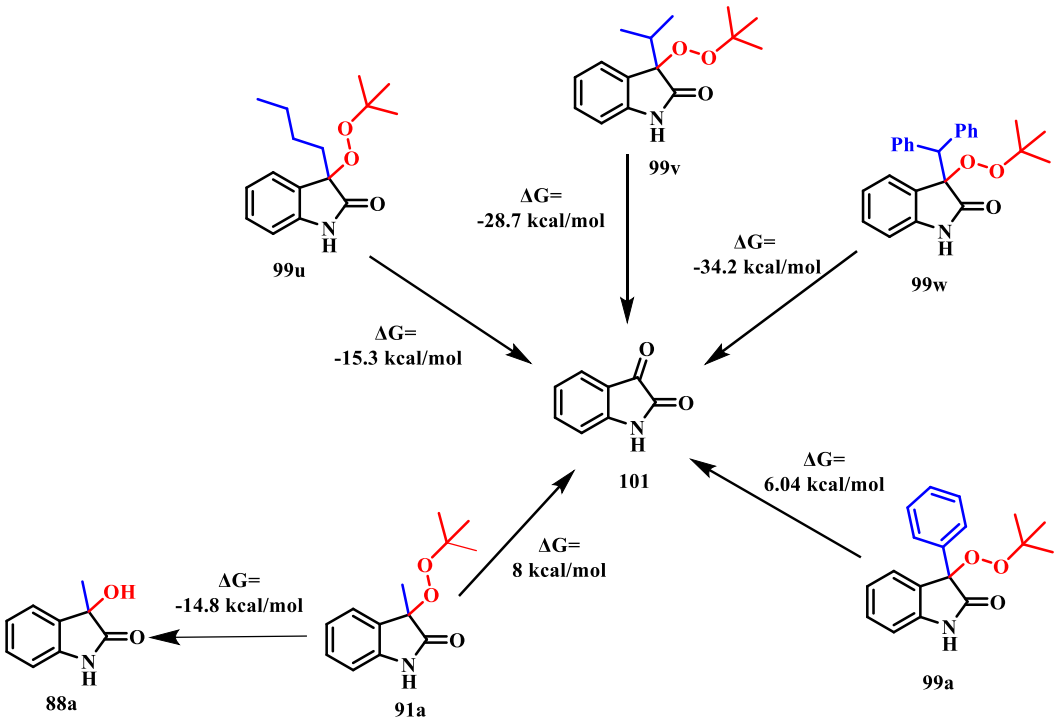


Figure 99: Free energy profile for the $FeCl_2$-catalyzed rearrangement of peroxyoxindoles. The free energy values are given in kcal/mol

The energy barrier for this step was determined to be 16.4 kcal/mol. Lastly, the removal of H_2O from the intermediate **99af** resulted in the formation of **100a** via [**TS 8**], which was exergonic by 9.1 kcal/mol. The alternative path that may have coexisted was the reaction of $Fe(III)(OH)Cl_2$ with **99b'** to give acid intermediate **99b''** via [**TS 3'**], which was endergonic by 4.2 kcal/mol. Next, intermediate **99ab''** formed may have rearranged to form **99ac** via [**TS 4**] or may have undergone decarboxylation to form **100a'** through [**TS 4''**]. However, the energy barrier for forming **99ac** was 31.1 kcal/mol, which was lower than the energy barrier for the formation of **100a'**. Thus, the pathway involving

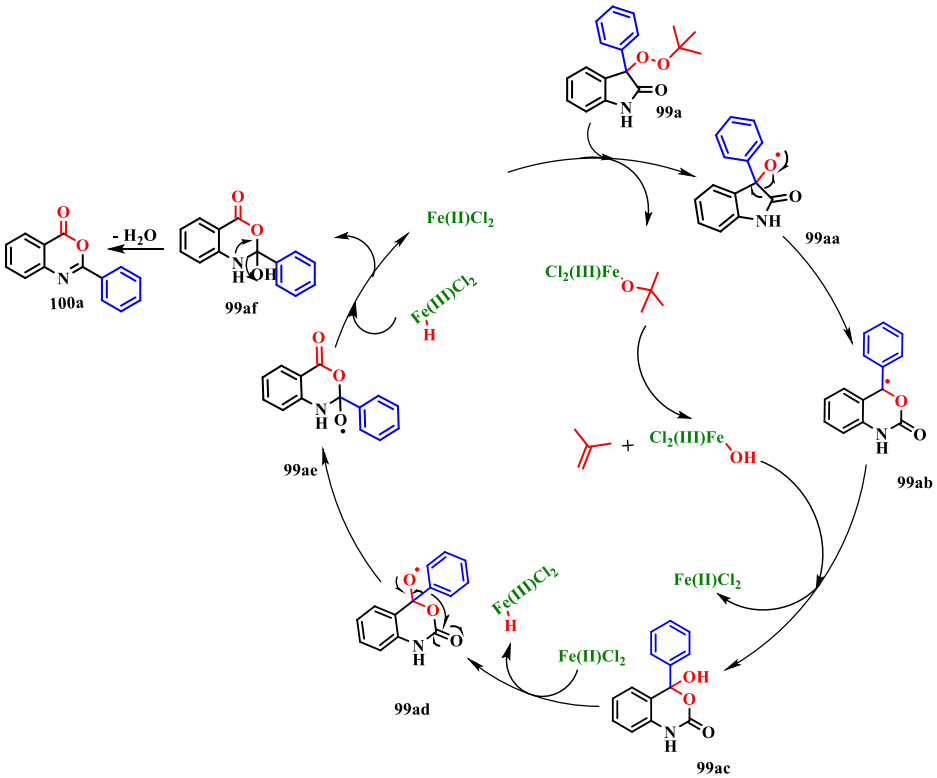


Scheme 71: Gibb's Free energy calculation for the feasibility of formation of isatin

tertiary radical intermediate **99ab** was determined to be more feasible. Further, tried to understand the formation of isatin **101** by taking different substrates and it has been found that this reaction was not feasible with peroxide having alkyl substitution viz **91a**, **99u**, **99v**, and **99w**. The formation of isatin is highly feasible for *iso*-phenyl, *iso*-propyl, and *n*-butyl substitutions as indicated by the Gibbs free energies. This has been explained by Gibb's free energy calculation for the feasibility (Scheme 71). Gibb's free energy for the reactant **99a** to form the isatin **101** is 6.04 kcal/mol which is not feasible for the reaction to occur.

4.5.5. The plausible mechanism

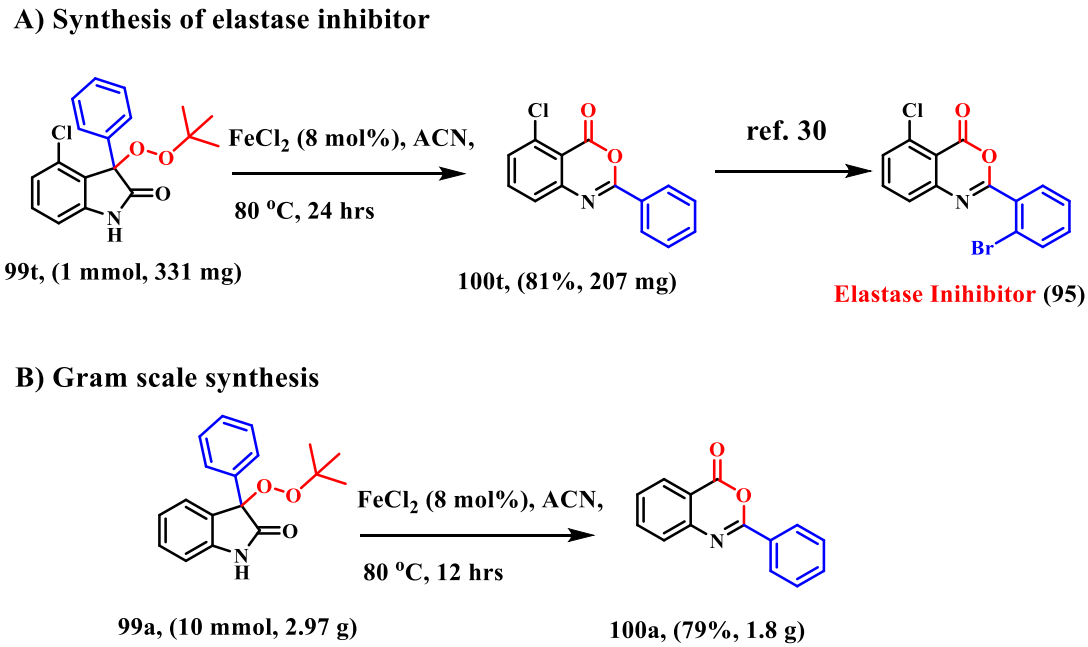
Based on the experimental evidence and DFT studies, the mechanism for this unprecedented rearrangement reaction was rationalized (Scheme 72). Initially, the coordination of $Fe(II)Cl_2$ with the oxygen atom of peroxide led to the cleavage of the peroxide (–O–O–) bond and formed the radical intermediate **99aa**. $Fe(II)Cl_2$ was converted to $Fe(III)(t\text{-}BuO)Cl_2$, which generated *iso*-butylene in the reaction medium (Scheme 68). Subsequently, the homolytic cleavage of the C2–C3 bond of **99aa**, generated the 1,3-benzoxazin-4-one tertiary radical **99ab**. The hydroxy-substituted 1,3-benzoxazin-4-one moiety **99ac** was obtained by the interaction of the radical intermediate **99ab** with $Fe(III)(OH)Cl_2$. The acetal radical intermediate **99ad** was generated when **99ac** interacted with the in situ regenerated $Fe(II)Cl_2$ via single electron transfer (SET). The radical relay occurs at **99ad** lead to



Scheme 72: Proposed mechanism for the catalytic path for the rearrangement reaction

the migration of the phenyl ring to the amide carbonyl and provided the radical intermediate **99ae**. Furthermore, the transfer of hydrogen to the **99ae** from Fe(III)(H)Cl_2 yielded the intermediate **99af.** Finally, the removal of H_2O from **99af** afforded **100a,** accompanied by the regeneration of $FeCl_2$.

4.6. Synthesis of elastase inhibitor and gram-scale synthesis



Scheme 73: Synthetic applications of the rearrangement reaction

For the synthetic utility of the reaction, a biologically active compound **95t** was synthesized using the developed rearrangement method. Further, the bromination of **95t** using the reported method provide elastase inhibitor **90** (Figure 96).[151] The gram scale reaction was performed by taking 10 mmol **99a** under the optimized reaction condition, afforded 79% (625 mg) of **100a** (Scheme 73).

4.7. Conclusion

In conclusion, the $FeCl_2$-catalyzed rearrangement of C3-aryl peroxyoxindole was developed, which is a new synthetic route for the synthesis of biologically active 1,3-benzoxazin-4-one derivatives. Using the developed method, an elastase inhibitor was synthesized, and a gram-scale reaction was demonstrated. This rearrangement reaction was well supported with broad substrate scope having good to excellent yields. Moreover, this reaction proceeded via a radical path through the SET mechanism, which is well supported by experiments and DFT studies.

4.8. Experimental section and characterization data

4.8.1. General information and data collection

Commercially available reagents and solvents were used for the preparation of starting material without further purification. Visualization was accomplished with UV light. Column

chromatographic separations performed over 100-200 Silica-gel. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker 400 MHz and JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha Fourier transform infrared spectrometer. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation and Cu Kα radiation.

4.8.2. Experimental procedure

4.8.2.1. General procedure for rearrangement reaction:

A resealable vial was charged with **99** (0.25 mmol), anhydrous $FeCl_2$ (8 mol%), and 2 mL of ACN. The mixture was stirred for 12 h at 80 ^{o}C. After completion of the reaction, the volatile compound was evaporated under a vacuum. The desired product **100** was purified through column chromatography using EtOAc/ hexane (varies from 5:95 to 15: 85).\

4.8.2.2. General procedure for large scale synthesis of 100a

A round bottom flask was charged with **99a** (10 mmol, 3 g), anhydrous $FeCl_2$ (8 mol%) and 10 mL of ACN. The mixture was refluxed for 12 h at 80 ^{o}C. After completion of reaction, the volatile compound was evaporated under vaccum. The crude residue was purified through column chromatography using EtOAc/ hexane (varies from 1:99 to 5:95) to afford **100a** in 79% yield (1.8 g).

4.8.3. Experiments for the mechanistic studies

4.8.3.1. Experiment with radical quencher TEMPO

The above reaction was performed in a resealable vial, with a mixing of anhydrous $FeCl_2$ (8 mol%), TEMPO as radical quencher followed by 3-(*tert*-butylperoxy)-3-phenylindolin-2-one **99a**, (0.25 mmol, 1equiv.) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^{o}C. The TLC analysis confirmed the starting material **99a** remained unreacted in the reaction. This confirmed that the catalyst is quenched by the TEMPO. When the above mention reaction treated with 20 mol% of $FeCl_2$ resulted in the 37% of 2,2,6,6-tetramethylpiperidin-1-yl (2-benzoylphenyl)carbamate **102** and 47% of **99a** recovered from the reaction. The reaction confirmed that with increasing the catalyst loading formation radical was faster and further the radical is combined with TEMPO and afforded carbamate **102**.

4.8.3.2. Experiment for the detection of *iso*-butylene

The reaction was performed in a resealable vial charged with 3-(*tert*-butylperoxy)-3-phenylindolin-2-one **99a**, (0.25 mmol, 1equiv.), anhydrous $FeCl_2$ (8 mol%) and in dry ACN (2 mL) under nitrogen. The mixture was stirred for 12 h at 80 ^oC. After 12 h, the gaseous part of the reaction vial was injected into the GCMS with the help of a gas-tight syringe. An isobutylene peak at the retention time of 1.010 min (Figure 100) was observed.

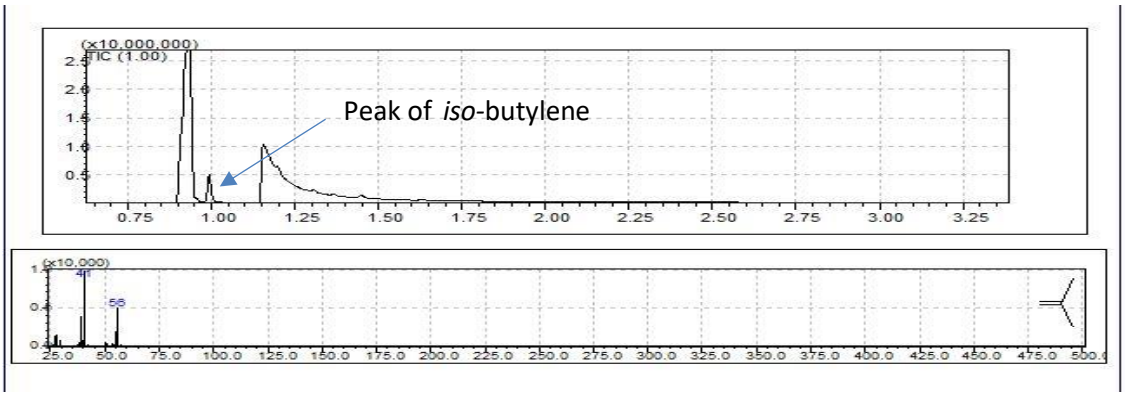


Figure 100: GCMS spectra for *iso*-butylene detection in the reaction mixture

To confirm the source of generation of isobutylene, the reaction was performed in a resealable vial charged with *tert*-butanol **103** (5 mmol), anhydrous $FeCl_2$ (8 mol%), and in dry ACN (1 mL) under nitrogen and the reaction mixture was stirred for 12 h at 80 ^oC. After 12 h, the gaseous part of the reaction mixture from the vial was injected to the GCMS with the help of gas-tight syringe. The isobutylene peak at the retention time of 1.010 min (Figure 101) was observed**.**

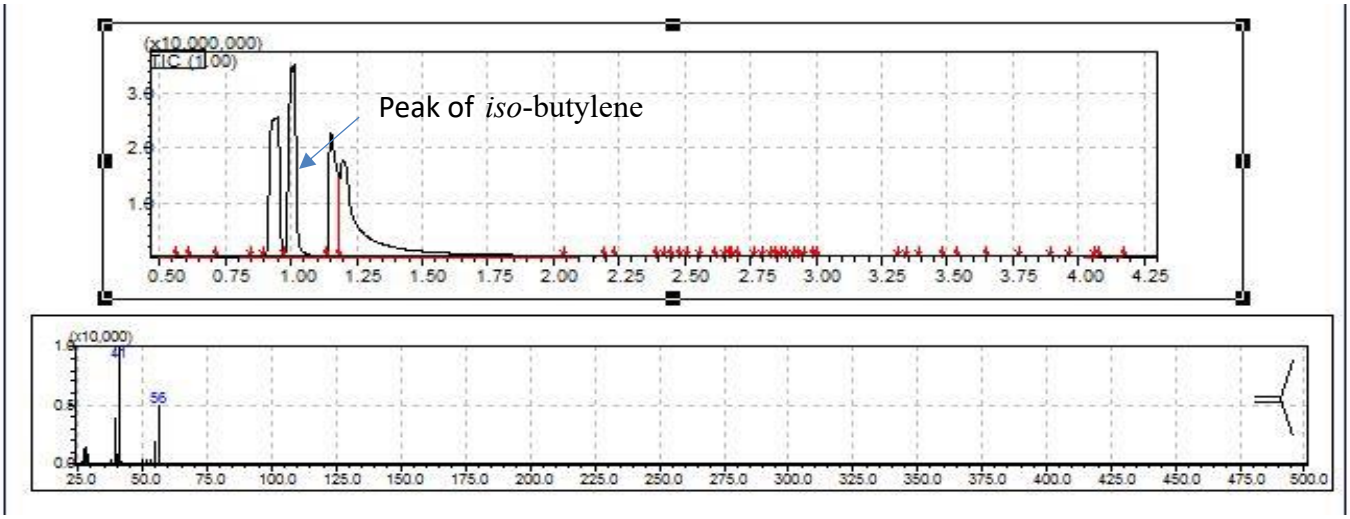


Figure 101: GCMS spectra for *iso*-butylene detection in the reaction of *tert*-butanol

4.8.3.3. Experiment with 3-hydroxy-3-phenyl peroxyoxindole 104

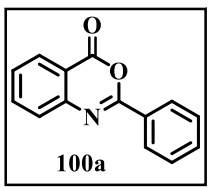
To confirm, whether the catalytic path proceeds via the formation of C3-hydroxy phenyl oxindole **104** or **104** is one of the intermediates of the reaction. Compound **104** was subjected to the optimized reaction condition. The reaction was performed in a resealable vial charged with **104** (0.25 mmol, 1. equiv.), $FeCl_2$ (8 mol%) in dry ACN (2 mL). The reaction mixture was heated at 80 ^oC for 12 h. After the completion of the reaction, volatile compounds were evaporated under a vacuum. The crude reaction mixture is purified through column chromatography and 44% of **105** was isolated. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.41 – 7.35 (m, 2H), 7.32 – 7.16 (m, 12H), 7.06 – 6.99 (m, 2H), 6.95 (d, *J* = 8.5 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$ + Acetone-d_6): δ 164.09, 141.97, 138.67, 134.46, 131.22, 128.94, 128.57, 127.88, 127.28, 126.87, 125.56, 123.47, 122.73, 120.67, 120.21, 117.65, 115.58, 97.34.

4.8.3.4. Experiment with hydroquinone

To confirm the key role of $FeCl_2$ in the catalytic path the reaction was performed in a resealable vial charged with **99a** (0.25 mmol, 1 equiv.), $FeCl_2$ (8 mol%) in dry ACN (2 mL) along with hydroquinone (0.25 mmol, 1 equiv.). The reaction mixture was heated at 80 ^oC for 12 h. After the completion of the reaction, volatile compounds were evaporated under a vacuum. The crude reaction mixture is purified through column chromatography and 94% of 1,4-benzoquinone **106** and 71% of **100a** were isolated. This reaction confirmed the in-situ generation of $FeCl_3$. Similarly, the reaction performed in the presence of $FeCl_3$ (8 mol %) and hydroquinone (0.25 mmol), resulted in the 85% of **100a** and 82% of 1,4-benzoquinone **106**. As desired product with $FeCl_3$ was not not observed in the absence of hydroquinone, so this reaction confirmed the in situ generation of $FeCl_3$ and which play a pivotal role in the catalytic cycle.

4.8.4. Analytical data for the products

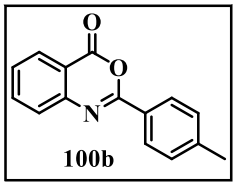
2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100a[152] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-phenylindolin-2-one **99a** (0.25 mmol) and, anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^oC. After complete consumption of starting material, the desired product **100a** was obtained 91% (51 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.34 – 8.30 (m, 2H), 8.25 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.52 (tt, *J* = 3.7, 1.5 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ



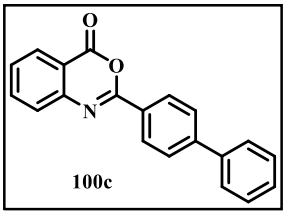
100a

159.7, 157.3, 147.1, 136.7, 132.8, 130.4, 128.9, 128.8, 128.5, 128.4, 127.4, 117.2 ppm. **FTIR** (neat) : 3028, 2928, 2860, 2308, 1722, 1603, 1268 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{10}NO_2$ $(M+H)^+$: 224.0712 found: 224.0715.

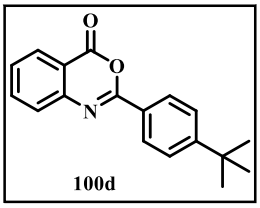
2-(p-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 95b[152] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(p-tolyl)indolin-2-one **99b** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^oC. The desired product **100b** was obtained 82% (49 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 18 h of heating, the starting material was completely consumed and resulted 84% (50 mg) of product **100b**. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.15 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 2H), 7.95 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 159.9, 157.5, 147.3, 143.6, 136.7, 129.7, 128.7, 128.5, 128.16, 127.6, 127.3, 117.1, 21.9 ppm. **FTIR** (neat): 3023, 2918, 2855, 2308, 1808, 1755, 1608, 1258 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{12}NO_2$ $(M+H)^+$: 238.0868, found: 238.0870.



2-([1,1'-biphenyl]-4-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100c[153] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-([1,1'-biphenyl]-4-yl)-3-(*tert*-butylperoxy)indolin-2-one **99c** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^oC. The desired product **100c** was obtained 78% (58 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 18 h of heating, the starting material was completely consumed and resulted 81% (61 mg) of product **100c**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.55 (m, 4H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.08-7.03 (m, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 169.4, 152.1, 143.9, 140.5, 137.0, 130.1, 129.8, 128.9, 127.9, 127.7, 127.3, 127.1, 123.6, 121.1, 77.2 ppm. **FTIR** (neat): 3065, 2927, 2311, 1714, 1621, 1547, 1248 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{14}NO_2$ $(M+H)^+$: 300.1025, found: 300.1029.

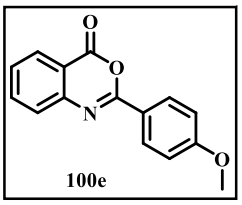


2-(4-(*tert*-butyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100d[153] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(4-(*tert*-butyl)phenyl)-3-(tert-butylperoxy)indolin-2-one **99d** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^oC. The desired product **100d** was obtained 72 % (50 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, The starting material was completely consumed and resulted in 81% (56.5 mg) of product **100d**. **^{1}H**

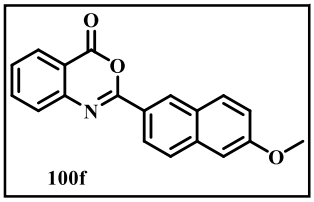


NMR (400 MHz, $CDCl_3$) : δ 8.26 – 8.21 (m, 3H), 7.84 – 7.79 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.55 – 7.47 (m, 3H), 1.37 (s, 9H); **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$): δ 159.9, 157.4, 156.6, 147.3, 136.6, 128.7, 128.3, 128.1, 127.5, 127.3, 125.9, 117.1, 35.3, 31.3 ppm. **FTIR** (neat): 3066, 2963, 2928, 2868, 2309, 1732, 1680, 1591, 1276 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{18}NO_2$ $(M+H)^+$: 280.1337, found: 280.1340.

2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100e[152] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(4-methoxyphenyl)indolin-2-one **100e** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100e** was obtained 55% (35 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted in 61% (38.5 mg) of product **100e**. **^1H NMR** (400 MHz, $CDCl_3$): δ 8.29 – 8.24 (m, 2H), 8.22 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.80 (td, *J* = 8.0, 1.5 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.03 – 6.97 (m, 2H), 3.90 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$): δ 163.4, 159.9, 157.3, 147.5, 136.7, 130.4, 128.7, 127.9, 127.1, 122.7, 116.9, 114.3, 55.7 ppm. **FTIR** (neat): 2921, 2845, 2308, 1753, 1606, 1570, 1256 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{12}NO_3$ $(M+H)^+$: 254.0817, found: 254.0821.

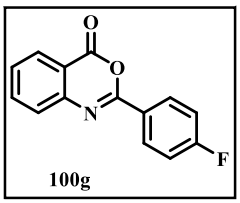


2-(6-methoxynaphthalen-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100f is synthesized by the following general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(6-methoxynaphthalen-2-yl)indolin-2-one **99f** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100f** was obtained 56% (43 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted in 67% (51 mg) of product **100f**. **^1H NMR** (400 MHz, $CDCl_3$) : δ 8.76 (d, *J* = 1.2 Hz, 1H), 8.33 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.91 – 7.81 (m, 3H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.23 – 7.16 (m, 2H), 3.96 (s, 3H) ppm. **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$): δ 159.9, 159.8, 157.6, 147.4, 137.2, 136.7, 131.1, 129.9, 128.8, 128.4, 128.2, 127.5, 127.3, 125.3, 125.0, 119.9, 117.1, 106.0, 55.6 ppm. **FTIR** (neat): 2916, 2840, 2307, 1746, 1597, 1265 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}NO_3$ $(M+H)^+$: 304.0973, found: 304.0975.

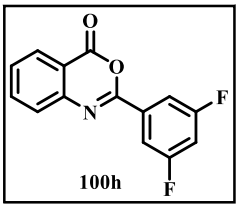


2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100g[153] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(4-fluorophenyl)indolin-2-one **99g** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100g** was obtained 79% (47.5 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 18 h of heating, the starting material

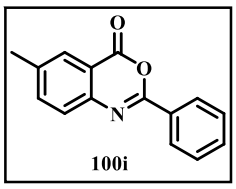
was completely consumed and resulted in 85% (51 mg) of product **100g**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 – 8.30 (m, 2H), 8.24 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.71 – 7.65 (m, 1H), 7.55 – 7.49 (m, 1H), 7.23 – 7.15 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): 165.7 (d, J_{C-F} = 253 Hz), 159.5, 156.4, 147.1, 136.8, 130.9 (d, J_{C-F} = 9 Hz), 128.8, 128.4, 127.3, 126.6 (d, J_{C-F} = 3 Hz), 117.0, 116.1 (d, J_{C-F} = 20 Hz) ppm. **FTIR** (neat): 3069,2917, 2311, 1755, 1597, 1503, 1231 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_9FNO_2$ $(M+H)^+$: 242.0617, found: 242.0620 .



2-(3,5-difluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100h[154] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(3,5-difluorophenyl)indolin-2-one **99h** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^{o}C. The desired product of **100h** was obtained 84% (54.5 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 18 h of heating, the starting material was completely consumed and resulted in 87% (56 mg) of the product **100h**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.89 – 7.81 (m, 3H), 7.71 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.03 (tt, *J* = 8.5, 2.4 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.3(d, J_{C-F} = 248 Hz), 163.1 (d, J_{C-F} = 8 Hz), 158.9, 146.5, 136.9, 133.6 (d, J_{C-F} = 10 Hz), 129.1 (d, J_{C-F} = 22 Hz), 127.6, 117.3, 111.5 (d, J_{C-F} = 20 Hz), 108.1 (d, J_{C-F} = 26 Hz), 107.9 ppm. **FTIR** (neat): 3098, 2923, 1762, 1564, 1501, 1241 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_8F_2NO_2$ $(M+H)^+$: 260.0523, found: 260.0522.

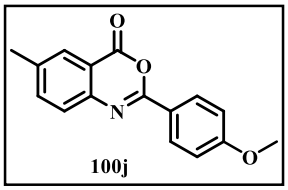


6-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100i[155] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-5-methyl-3-phenylindolin-2-one **99i**, (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^{o}C. The desired product **100i** was obtained 92% (55 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.22 – 8.16 (m, 2H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.78 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.69 – 7.57 (m, 4H), 2.47 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 159.9, 156.6, 144.9, 138.9, 137.9, 132.6, 130.5, 128.9, 128.4, 128.3, 127.2, 116.9, 21.5 ppm. **FTIR** (neat): 3032, 2914, 2857, 2306, 1959, 1747, 1609, 1255 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{12}NO_2$ $(M+H)^+$: 238.0868, found: 238.0868.

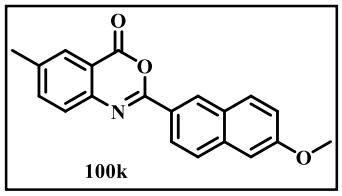


2-(4-methoxyphenyl)-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100j[156] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(4-methoxyphenyl)-5-methylindolin-2-one **99j** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^{o}C. The desired product **100j** was obtained 72% (48 mg)

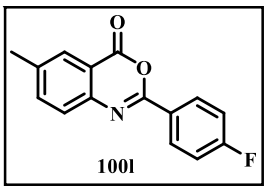
after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 18 h of heating, the starting material was completely consumed and resulted 78% (52 mg) of product **100j**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 – 8.22 (m, 2H), 8.04 – 7.99 (m, 1H), 7.61 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.02 – 6.96 (m, 2H), 3.89 (s, 3H), 2.48 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.3, 160.2, 156.6, 145.3, 138.2, 137.9, 130.3, 128.3, 126.9, 122.9, 116.6, 114.3, 55.7, 21.4 ppm. **FTIR** (neat): 3124, 3060, 2927, 2610, 2308, 1680, 1596, 1234 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{14}NO_3$ $(M+H)^+$: 268.0974, found: 268.0982.



2-(6-methoxynaphthalen-2-yl)-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100k is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(6-methoxynaphthalen-2-yl)-5-methylindolin-2-one **99k** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100k** was obtained 53% (42 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted 81% (64 mg) of product **100k**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.21 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 2.50 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 160.2, 159.7, 156.9, 145.3, 138.6, 137.9, 137.0, 131.0, 129.2, 128.4, 127.4, 127.1, 125.4, 124.9, 119.9, 116.8, 106.0, 55.6, 21.5 ppm. **FTIR** (neat): 2920, 2850, 2387, 1750, 1267 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}NO_3(M+H)^+$: 318.1130, found: 318.1135.

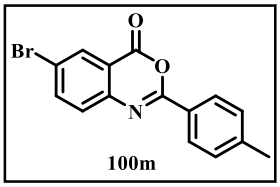


2-(4-fluorophenyl)-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100l is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-3-(4-fluorophenyl)-5-methylindolin-2-one **99l** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100l** was obtained 71% (45 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted 79% (50 mg) of product **100l**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.33 – 8.28 (m, 2H), 8.03 (s, 1H), 7.64 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.13 (m, 2H), 2.49 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 165.6 (d, J_{C-F} = 252 Hz), 159.8, 155.7, 144.9, 138.9, 138.0, 130.7 (d, J_{C-F} = 9 Hz), 128.4, 127.11, 126.7 (d, J_{C-F} = 9 Hz), 116.7, 116.1 (d, J_{C-F} = 22 Hz), 21.5 ppm. **FTIR**

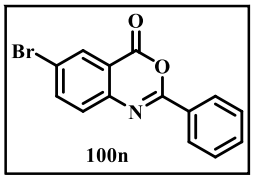


(neat): 2951, 2842, 2391, 1744, 1211 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{11}FNO_2$ $(M+H)^+$: 256.0774, found: 256.0775.

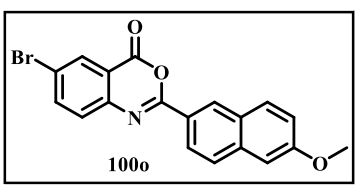
6-bromo-2-(p-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100m[157] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 5-bromo-3-(*tert*-butylperoxy)-3-(p-tolyl)indolin-2-one **99m** (0. 25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100m** was obtained 78 % (61 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.23 (d, *J* = 2.3 Hz, 1H), 8.09 (dd, *J* = 8.6, 2.4 Hz, 3H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 158.6, 146.2, 143.9, 139.8, 131.2, 129.7, 128.9, 128.6, 127.3, 121.3, 118.5, 116.3, 21.9 ppm. **FTIR** (neat): 3075, 2915, 1508, 2848, 2309, 1758, 1596, 1246 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{11}BrNO_2$ $(M+H)^+$: 315.9973, found: 315.9977.



6-bromo-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100n is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 5-bromo-3-(*tert*-butylperoxy)-3-phenylindolin-2-one **99n** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100n** was obtained 89% (67 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 2.3 Hz, 1H), 8.21 (m, 1H), 8.19 (d, *J* = 1.5 Hz, 1H), 8.11 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 2H); δ 158.5, 157.6, 146.0, 139.9, 133.1, 131.3, 130.1, 129.5, 129.1, 128.9, 128.5, 121.6, 118.5 ppm. **FTIR** (neat): 3064, 2920, 2853, 2308, 1810, 1752, 1255 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_9BrNO_2$ $(M+H)^+$: 301.9815, found: 301.9818.

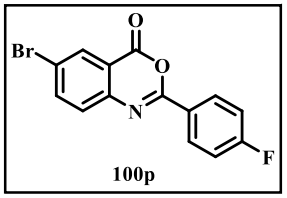


6-bromo-2-(6-methoxynaphthalen-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100o is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 5-bromo-3-(*tert*-butylperoxy)-3-(6-methoxynaphthalen-2-yl)indolin-2-one **99o** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100o** was obtained 76 % (72.5 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted 80% (76 mg) of product **100o**. **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.73 (d, *J* = 1.3 Hz, 1H), 8.36 (d, *J* = 2.2 Hz, 1H), 8.29 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 159.9, 158.7, 157.9, 146.3, 139.8, 137.3, 131.2, 131.1,



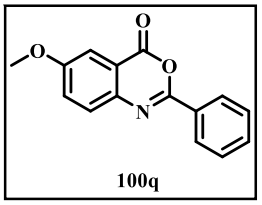
129.7, 128.9, 128.3, 127.5, 124.9, 121.3, 120.0, 55.6. ppm. **FTIR** (neat): 3059,2919, 2850, 2307, 1742, 1593, 1263 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}BrNO_3$ $(M+H)^+$: 382.0079, found: 382.0083.

6-bromo-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100p is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 5-bromo-3-(*tert*-butylperoxy)-3-(4-fluorophenyl)indolin-2-one **99p** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100p** was obtained 81% (64.5 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.28 – 8.22 (m, 3H), 8.10 (dt, *J* = 8.6, 2.3 Hz, 1H), 7.66 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.44 (dd, *J* = 12.3, 5.3 Hz, 2H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 165.9 (d, J_{C-F} = 253 Hz), 158.3, 156.7, 145.9, 139.9, 134.8, 131.3, 131.0 (d, J_{C-F} = 10 Hz), 129.0, 126.3 (d, J_{C-F} = 4 Hz),, 121.6, 118.4, 116.3 (d, J_{C-F} = 22 Hz), ppm. **FTIR** (neat): 2916, 2852, 2308, 1755, 1603, 1253 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_8BrFNO_2$ $(M+H)^+$: 319.9722, found: 319.9729.



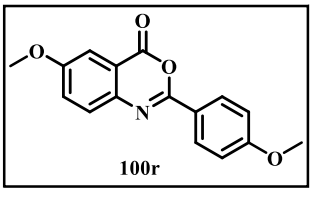
100p

6-methoxy-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100q[156] is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-5-methoxy-3-phenylindolin-2-one **99q** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100q** was obtained 89% (56 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.1 Hz, 2H), 7.59 – 7.41 (m, 5H), 7.34 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 159.9, 159.3, 155.7, 141.2, 132.3, 130.4, 128.8, 128.8, 128.0, 125.9, 117.8, 108.7, 55.9 ppm. **FTIR** (neat): 2923, 2855, 2307, 1714, 1616, 1579, 1266 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{12}NO_3$ $(M+H)^+$: 254.0817, found: 254.0821.



100q

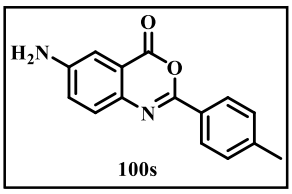
6-methoxy-2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100r is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 3-(*tert*-butylperoxy)-5-methoxy-3-(4-methoxyphenyl)indolin-2-one **99r** (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 °C. The desired product **100r** was obtained 53% (37.8 mg) after purification through column chromatography using EtOAc and hexane (5:95 ratio). After 24 h of heating, the starting material was completely consumed and resulted 70% (50 mg) of product **100r**. **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 8.28 (dd, *J* = 7.7, 5.5 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.63 (dd, *J* = 6.9, 2.3 Hz, 2H), 6.98 (d, *J* = 11.8 Hz, 3H), 3.90 (s, 3H), 3.77 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.9, 154.3, 139.3, 136.7, 136.2, 134.9, 132.8, 130.4, 130.4, 128.7, 127.9, 127.1, 125.7,



100r

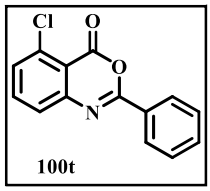
122.1, 114.3, 114.0, 113.9, 55.7, 52.6 ppm. **FTIR** (neat): 2956, 2875, 1712, 1523, 1449, 1106 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{14}NO_4$ $(M+H)^+$: 284.0923, found: 284.0927.

6-amino-2-(p-tolyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 100s is synthesized by following the general experimental procedure 4.8.2.1, with mixing of 5-amino-3-(*tert*-butylperoxy)-3-(*p*-tolyl)indolin-2-one **99s**, (0.25 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 12 h at 80 ^oC. After the complete consumption of starting material, the desired product **100s** was obtained 63% (40 mg) after purification through column chromatography using EtOAc and hexane (15:85 ratio). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.77 (d, *J* = 2.6 Hz, 1H), 8.66 (dd, *J* = 8.9, 2.7 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 160.3, 158.1, 151.8, 146.4, 145.2, 130.8, 129.9, 129.2, 128.7, 126.6, 125.0, 117.4, 22.0 ppm. **FTIR** (neat): 3091, 2922, 2856, 2310, 1760, 1515, 1259 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{13}N_2O_2$ $(M+H)^+$: 253.0977, found:)$^+$: 253.0979.



100s

5-chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 100t is synthesized by following the general experimental procedure 4.8.2.1, with mixing of **99t** (1 mmol) and anhydrous $FeCl_2$ (8 mol%) in ACN (2 mL). The mixture was stirred for 24 h at 80 ^oC. After the complete consumption of starting material, the desired product **100t** was obtained 81% (207 mg) after purification through column chromatography using EtOAc and hexane (15:85 ratio). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 5.4, 3.5 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.60-7.57 (m, 2H), 7.53-7.49 (m, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 157.9, 156.2, 149.5, 136.1, 136.0, 133.1, 130.8, 129.8, 128.9, 128.5, 126.4, 114.8 ppm. **FTIR** (neat): 3074, 2915, 2877, 2358, 1790, 1534, 1155 cm^{-1}. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_9ClNO_2$ $(M+H)^+$: 258.0322, found)$^+$:258.0327.



100t

4.8.5. Appendix IV

Copies of ^{1}H and ^{13}C NMR spectra of representative compounds

Entry	Figure No	Data	Page No
100a	102 & 103	^{1}H and ^{13}C	202
100c	104 & 105	^{1}H and ^{13}C	203
100e	106 & 107	^{1}H and ^{13}C	204
100g	108 & 109	^{1}H and ^{13}C	205
100i	110 & 111	^{1}H and ^{13}C	206
100k	112 & 113	^{1}H and ^{13}C	207
100m	114 & 115	^{1}H and ^{13}C	208
100t	116 & 117	^{1}H and ^{13}C	209
100h	118	ORTEP	210
97	119	ORTEP	210

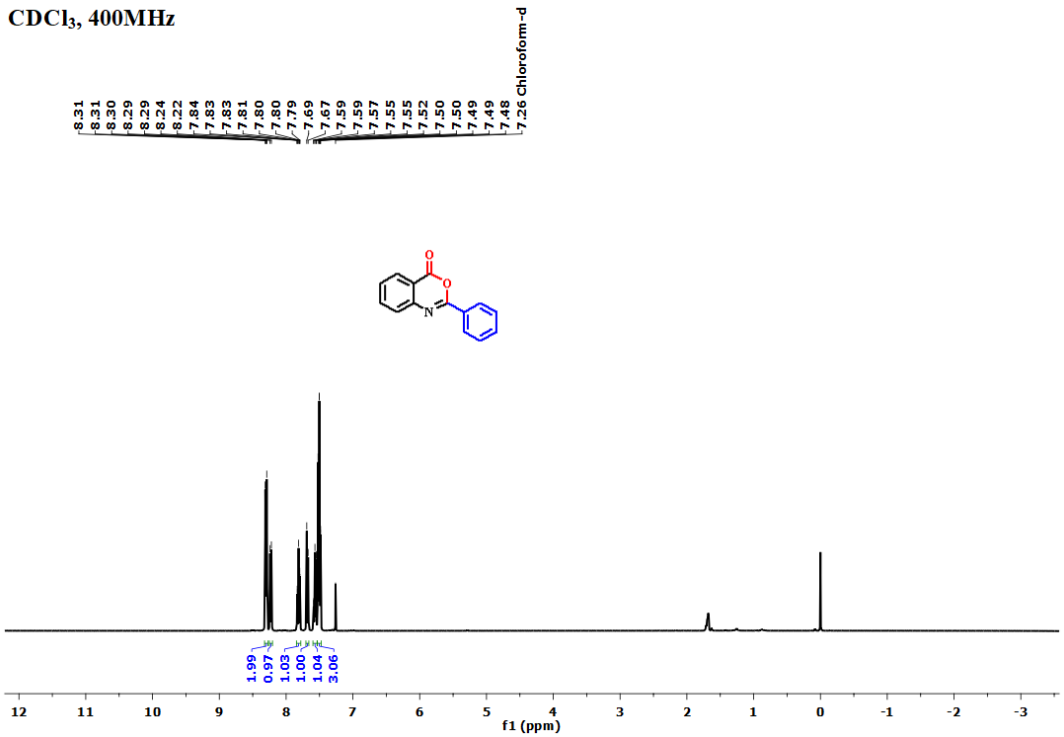


Figure 102: ^{1}H NMR of Compound **100a**

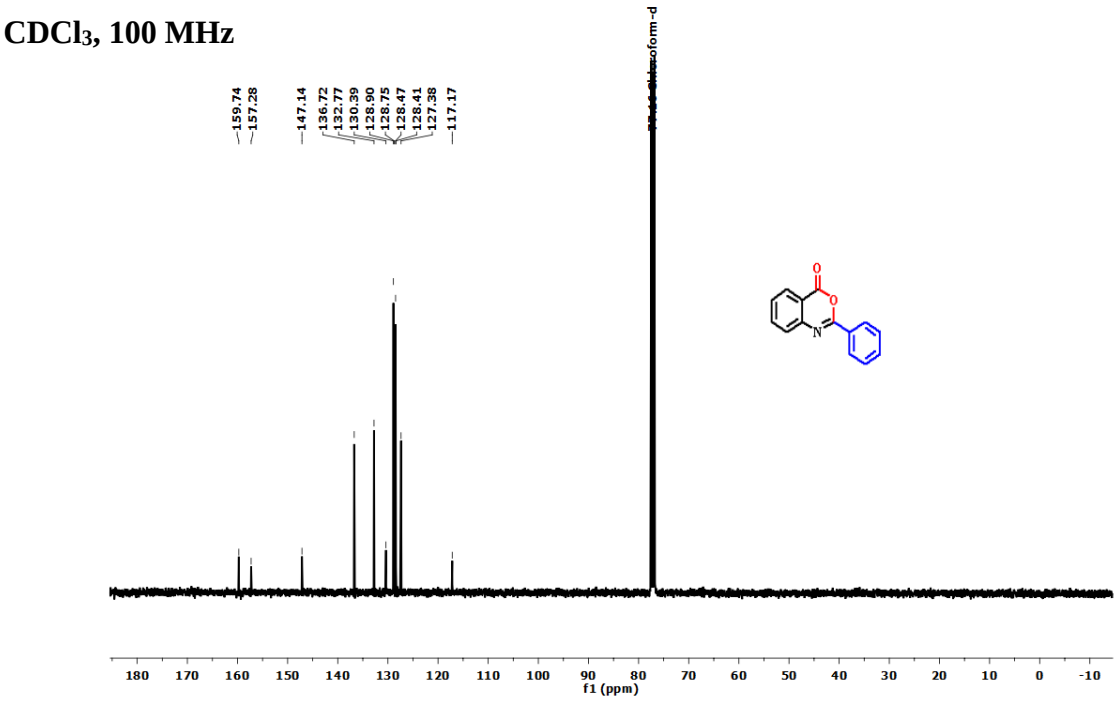


Figure 103: ^{13}C NMR of Compound **100a**

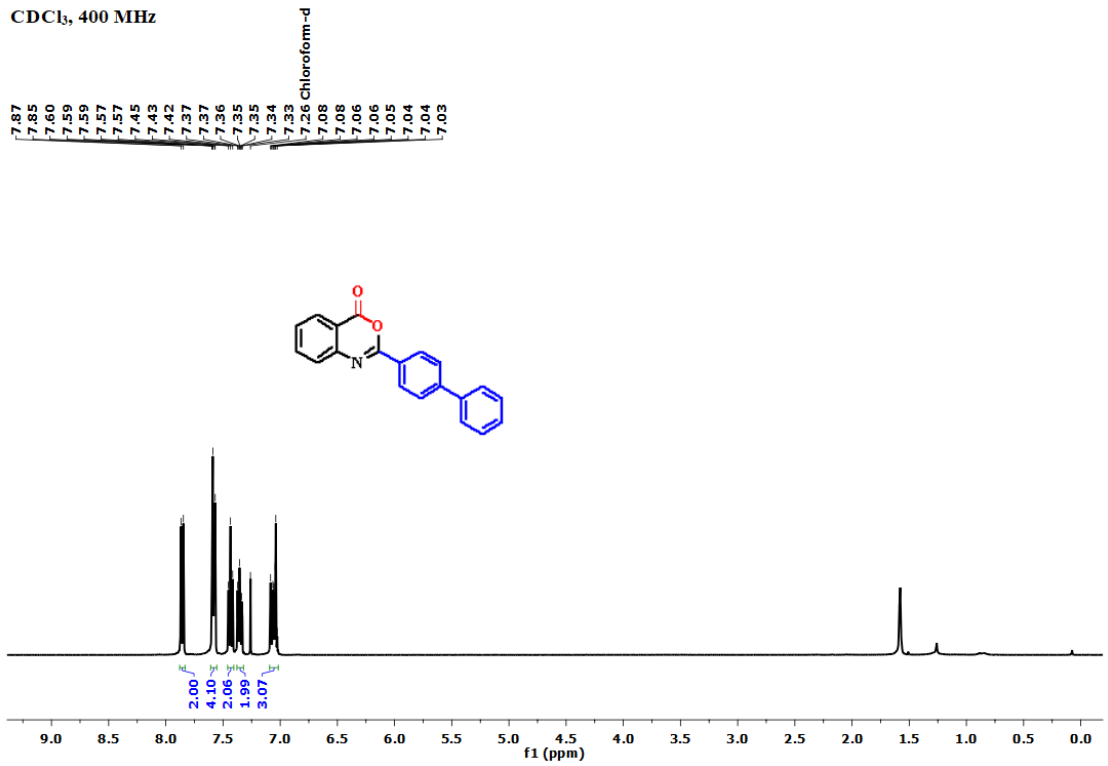


Figure 104: ^{1}H NMR of Compound **95c**

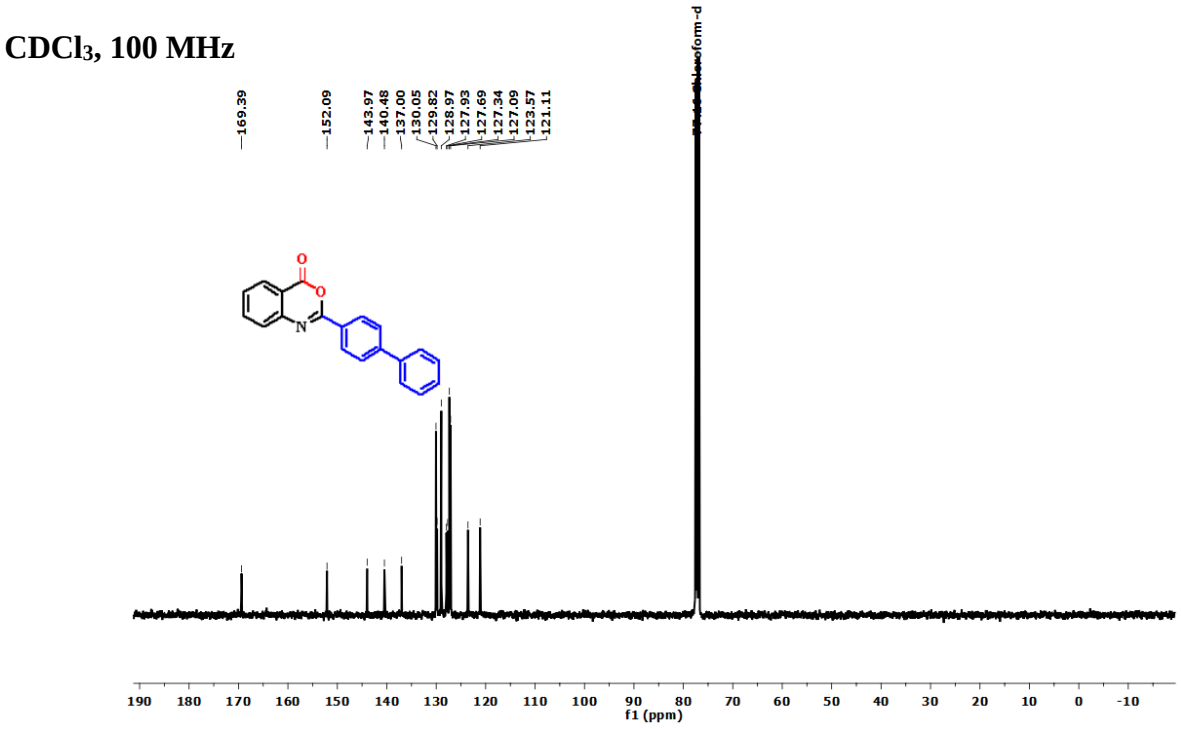


Figure 105: ^{13}C NMR of Compound **95c**

$CDCl_3$, 400 MHz

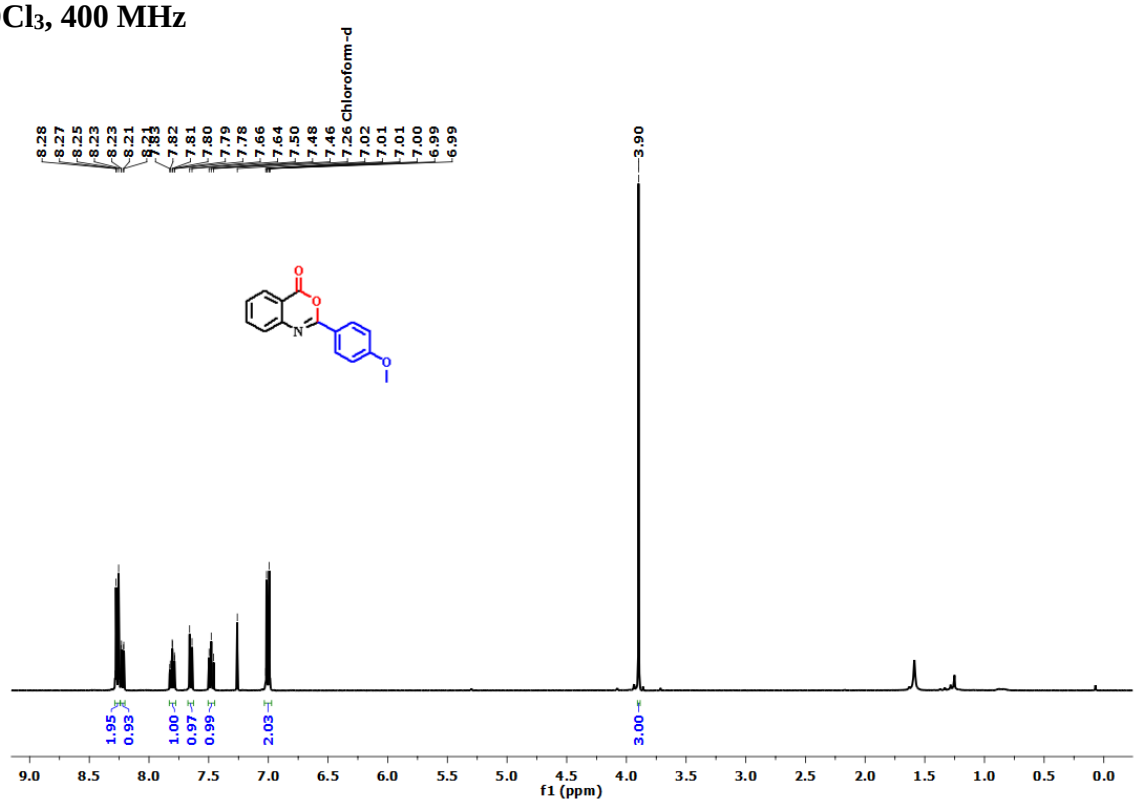


Figure 106: ^{1}H NMR of Compound **95e**

$CDCl_3$, 100 MHz

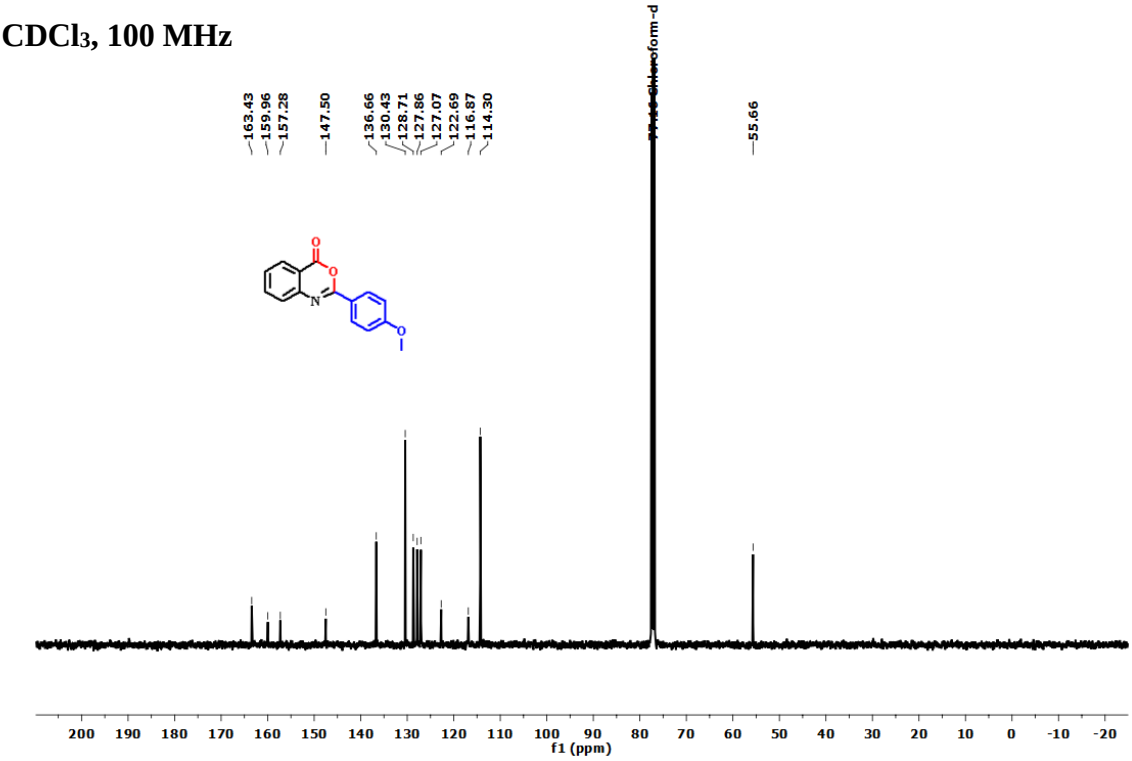


Figure 107: ^{13}C NMR of Compound **95e**

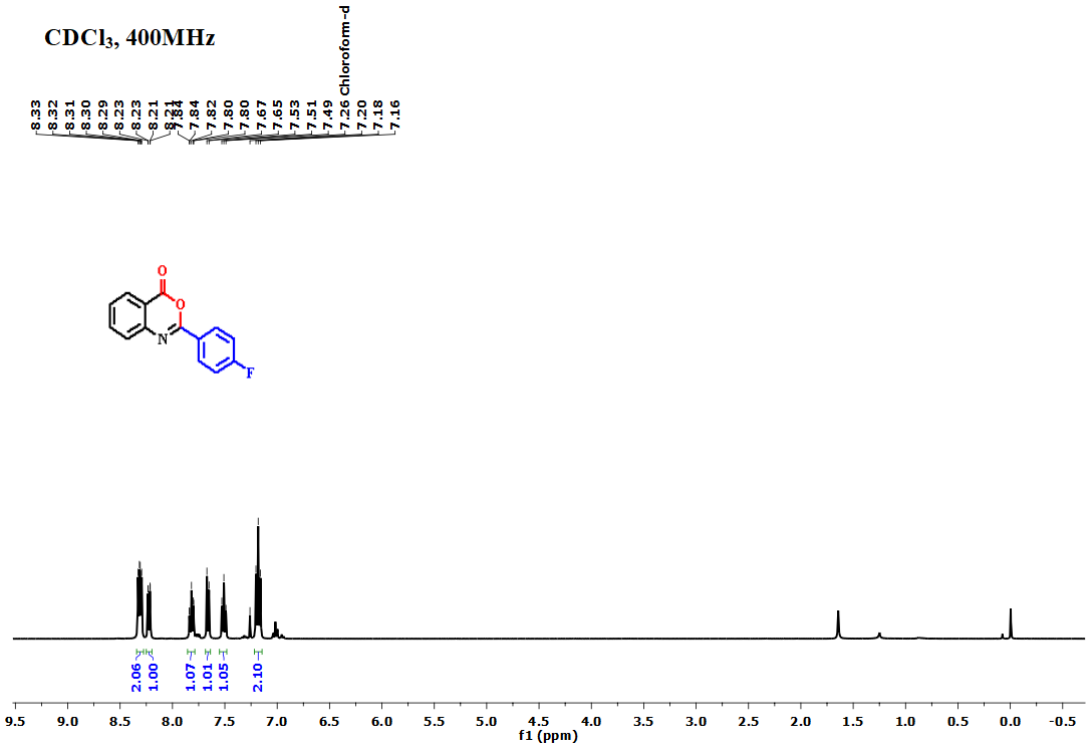


Figure 108: ^{1}H NMR of Compound **95g**

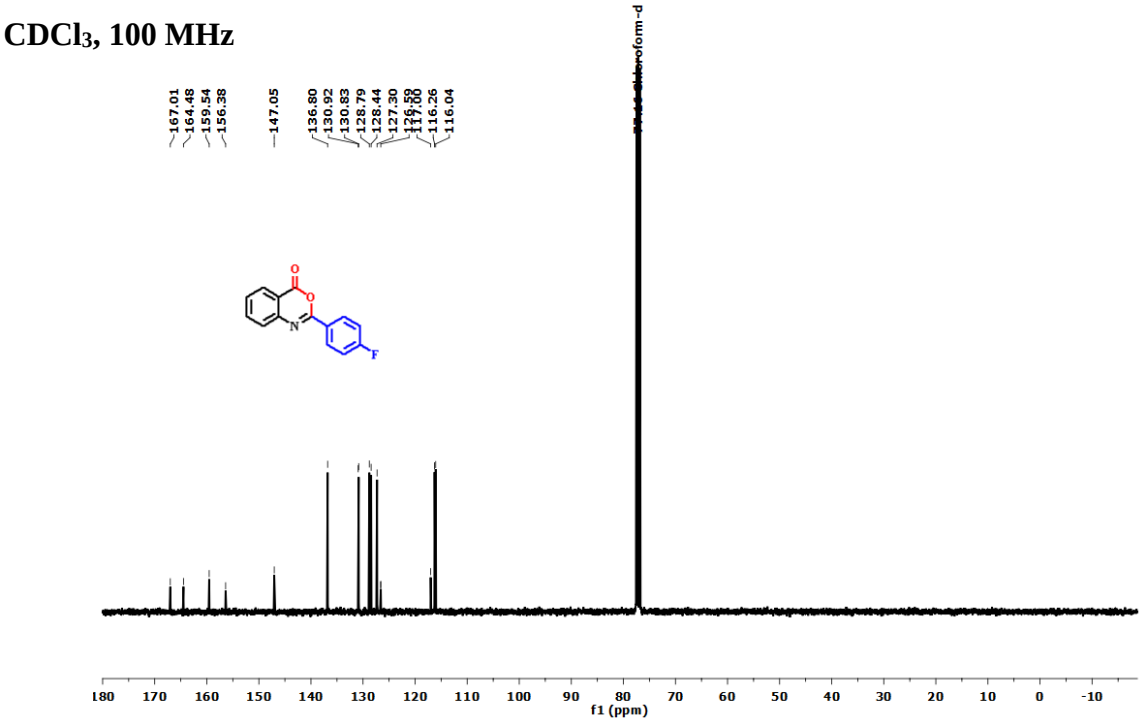


Figure 109: ^{13}C NMR of Compound **95g**

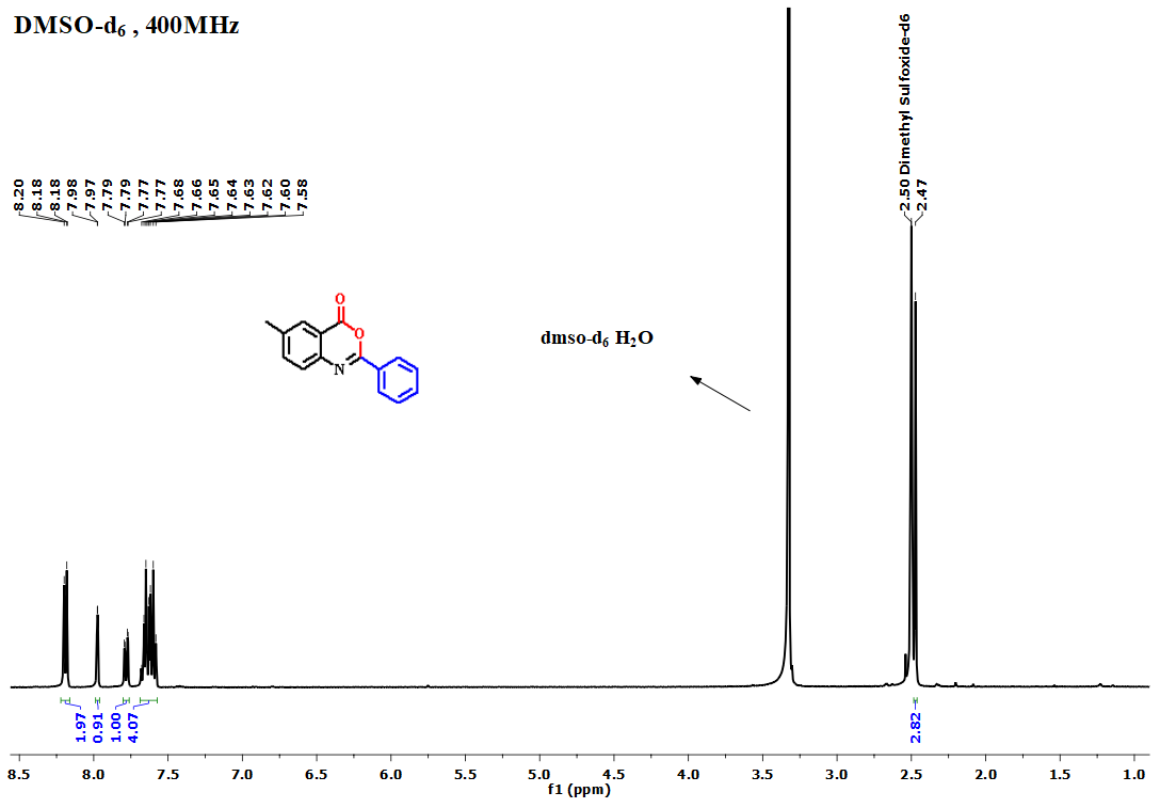


Figure 110: ^{1}H NMR of Compound **95i**

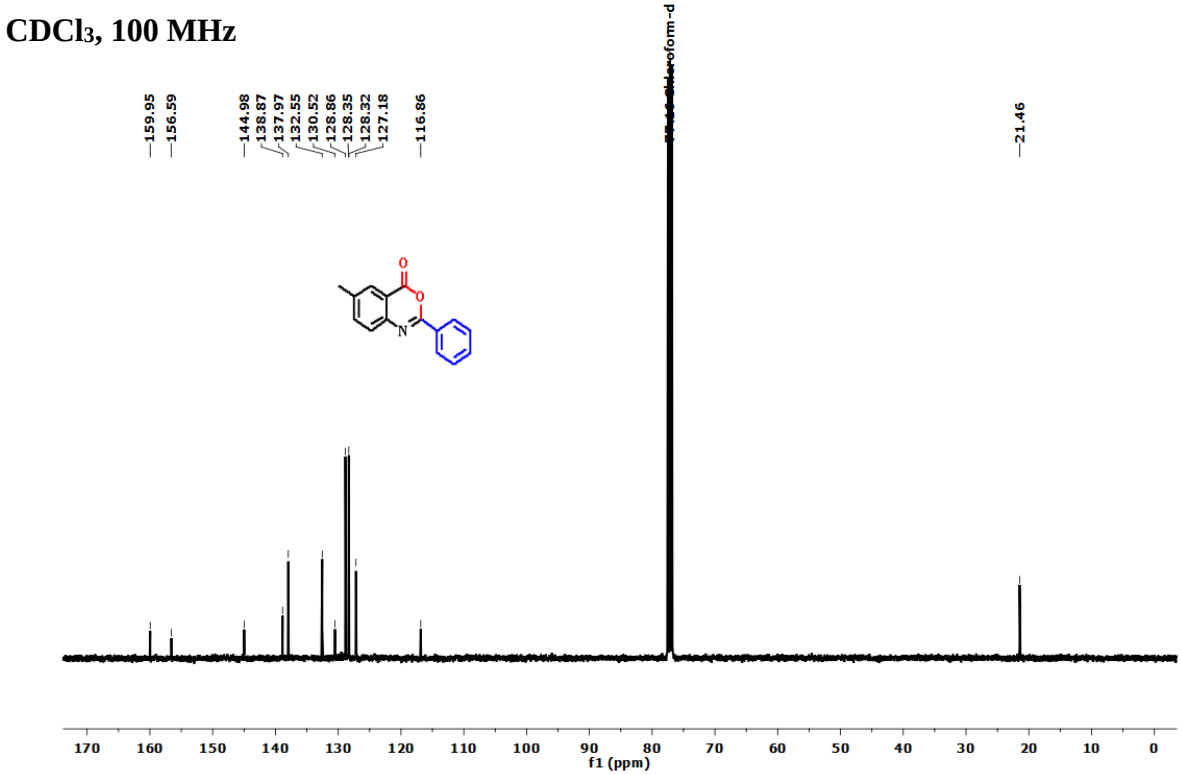


Figure 111: ^{13}C NMR of Compound **95i**

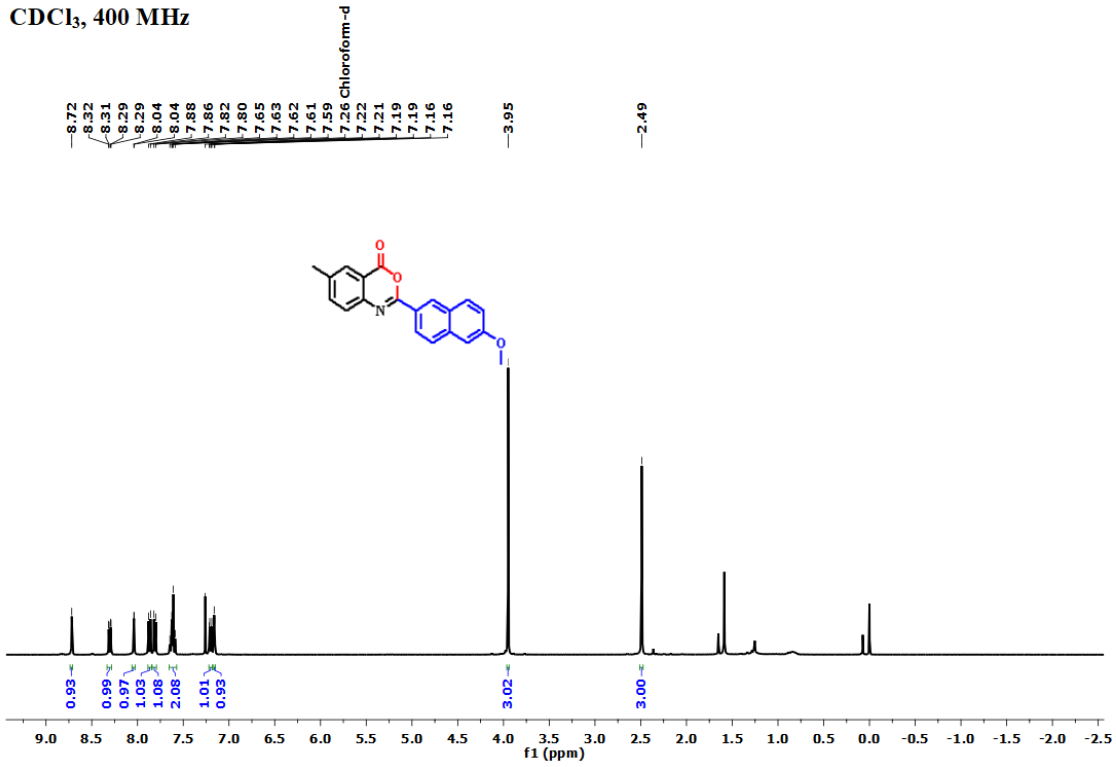


Figure 112: ^{1}H NMR of Compound **95k**

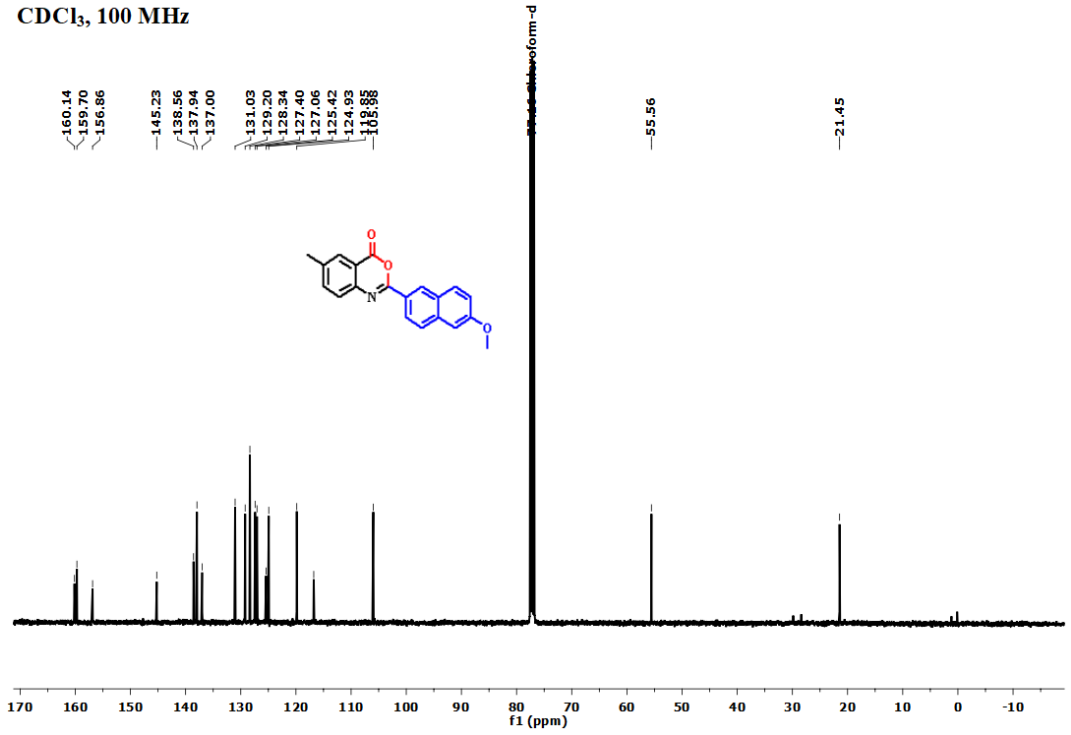


Figure 113: ^{13}C NMR of Compound **95k**

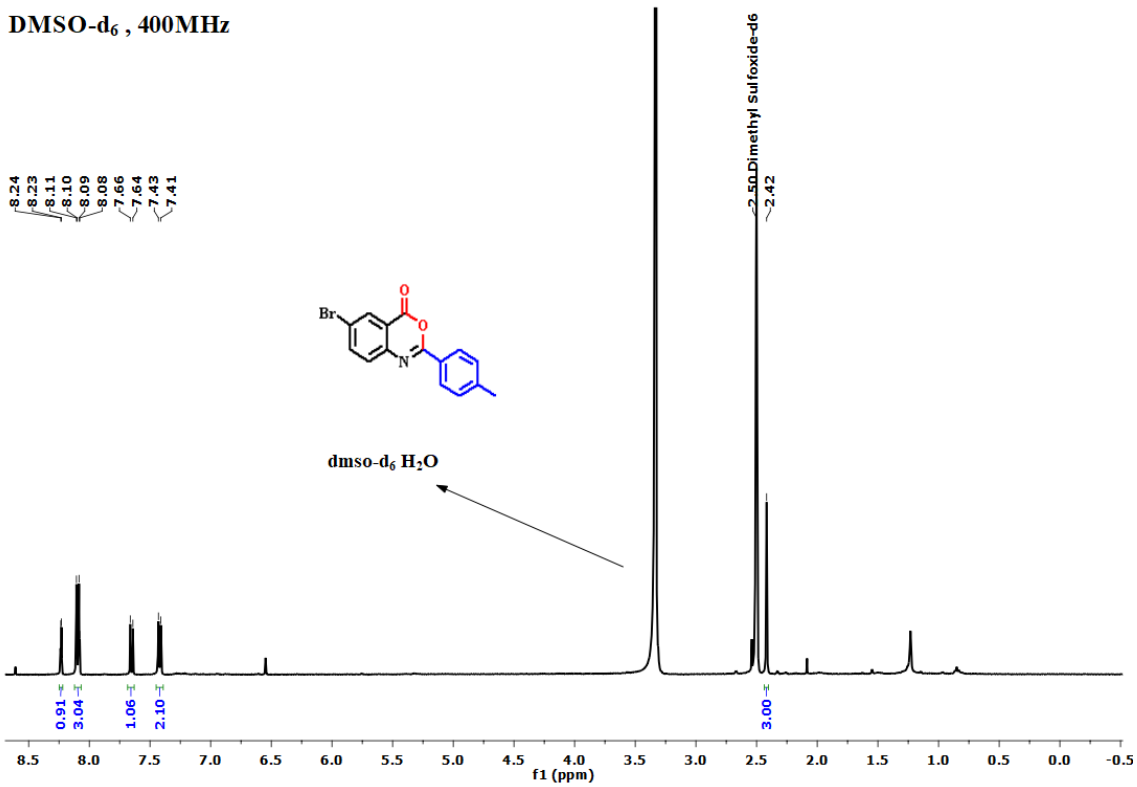


Figure 114: ^{1}H NMR of Compound **95m**

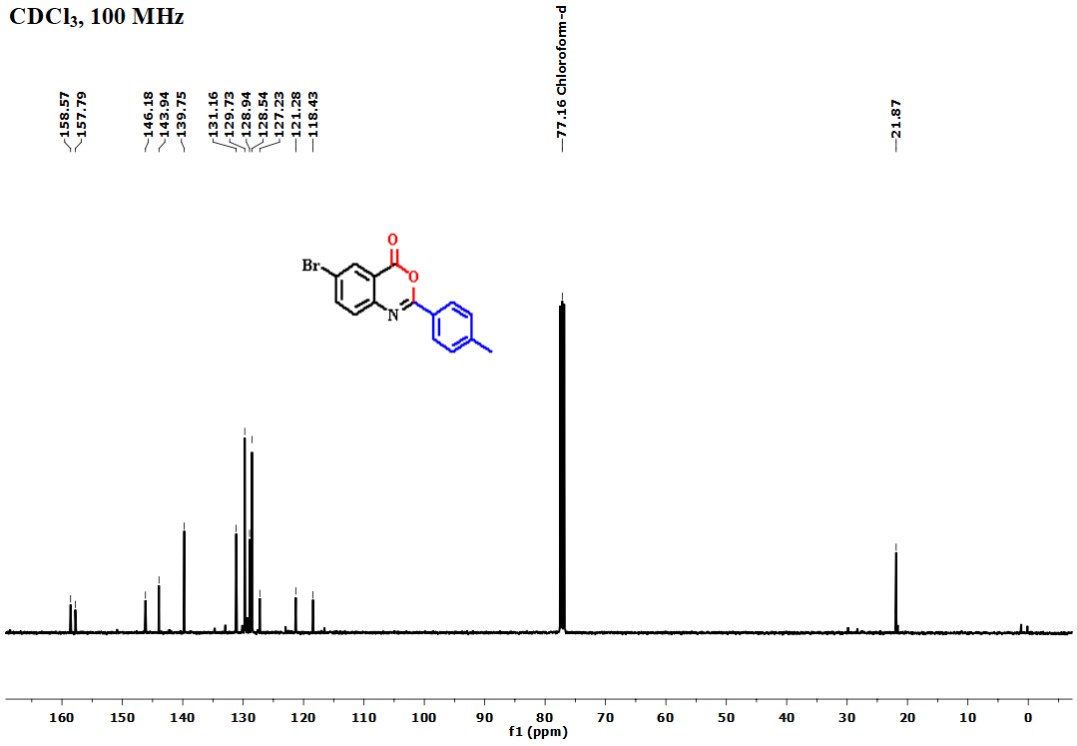


Figure 115: ^{13}C NMR of Compound **95m**

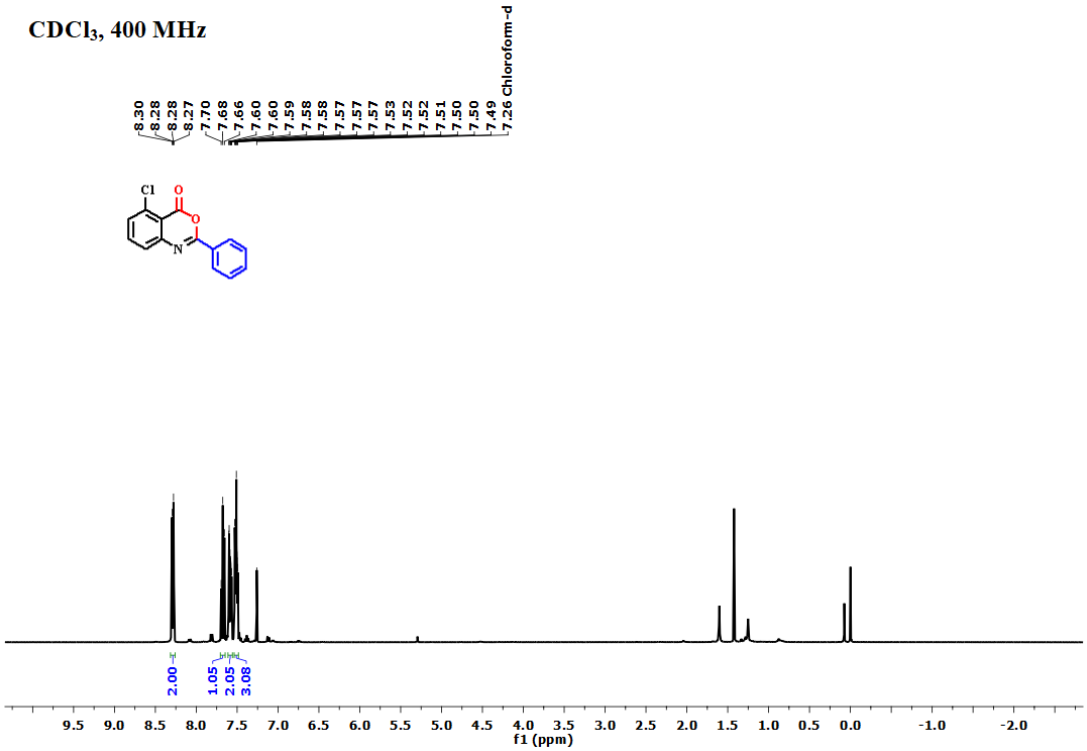


Figure 116: ^{1}H NMR of Compound **95t**

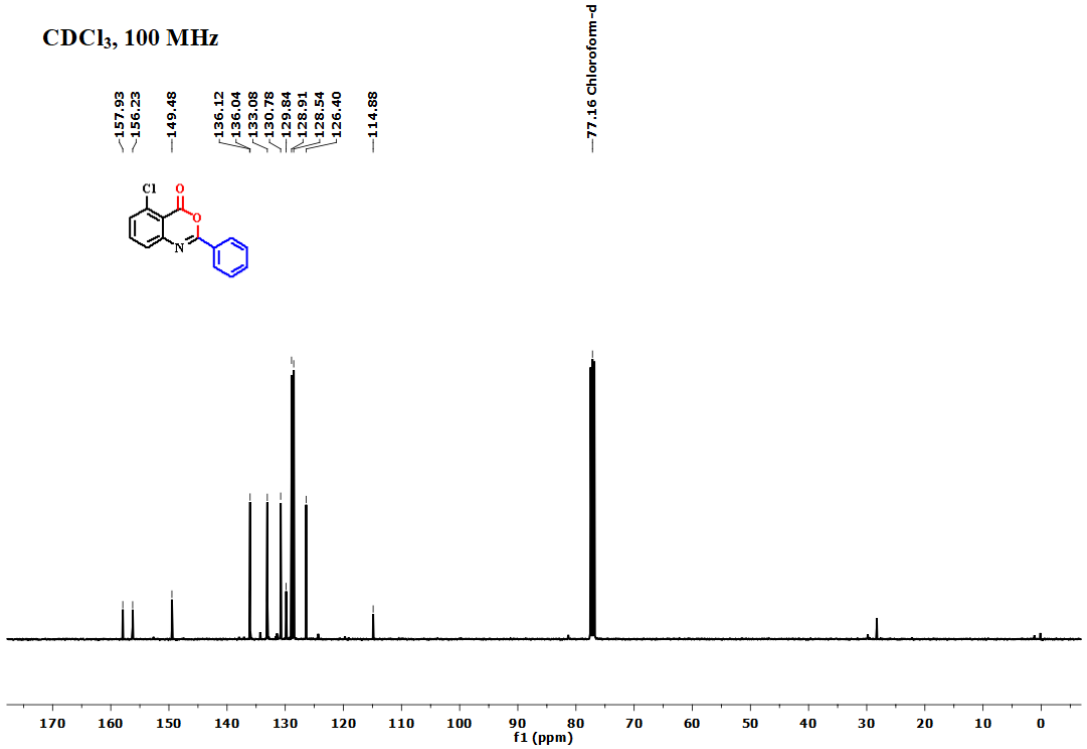


Figure 117: ^{13}C NMR of Compound **95t**

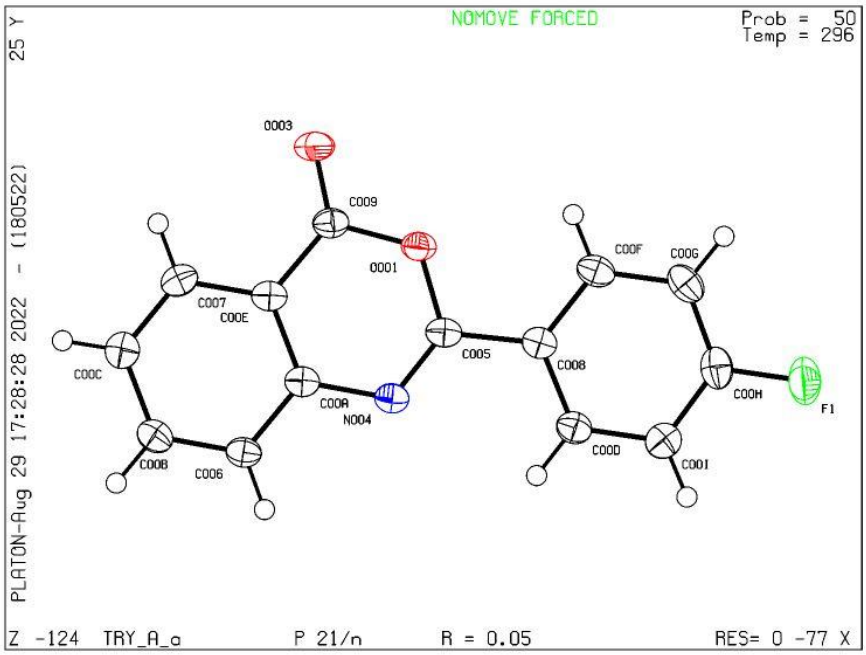


Figure 118: ORTEP Diagram of **95h**

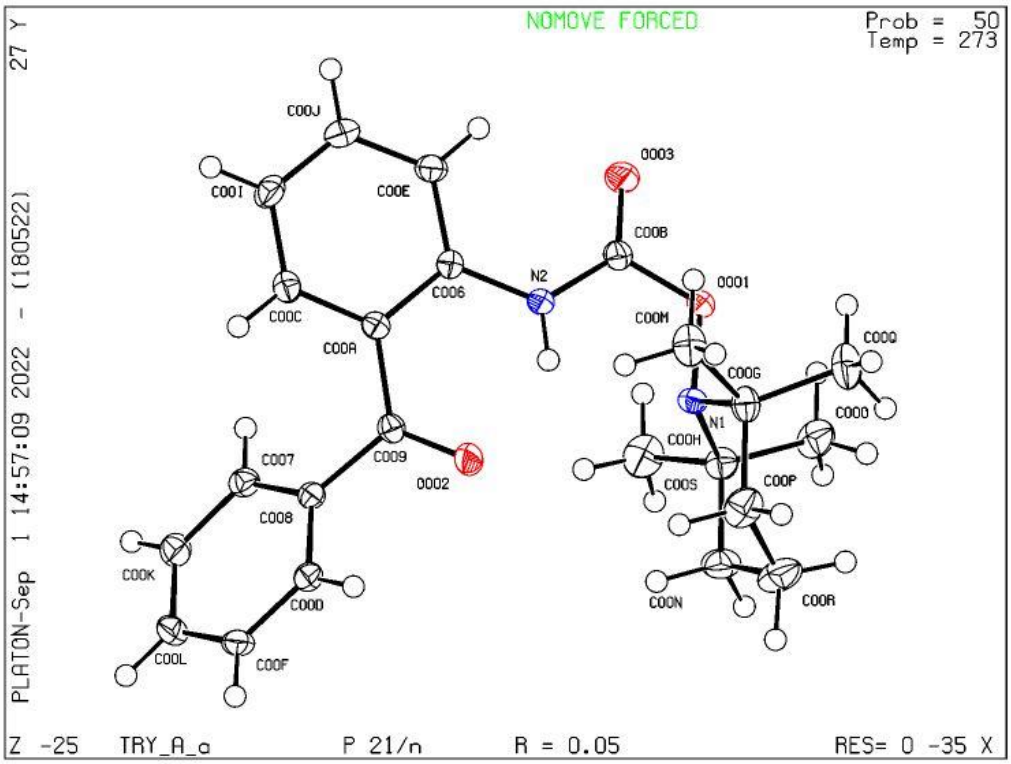


Figure 119: ORTEP Diagram of **97**

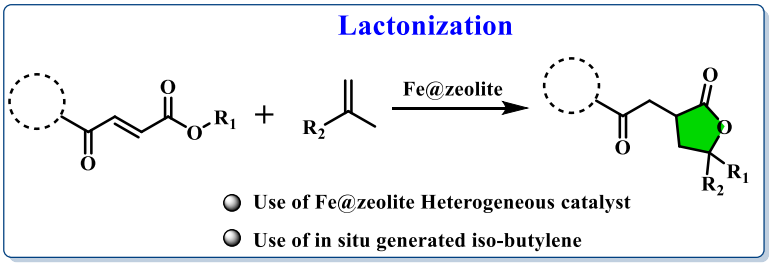
Chapter 5

Annulation of Alkene with α, β-Unsaturated Keto-Carboxylic Acid to Synthesize γ-Lactone

5. Annulation of Alkene with *α, β*-Unsaturated Keto-Carboxylic Acid to Synthesize *γ*-Lactone

5.1. Abstract

In this chapter, the Fe-supported on zeolite (Fe@zeolite) catalyzed lactonization was studied. The present lactonization reaction proceeds via the annulation of an alkene with *α, β*-unsaturated keto-carboxylic acid. Here, the in situ generated iso-butylene and various alkenes with varying substitution was used for substrates in this protocol. This method provides the significance of zeolite-supported Fe-catalyst towards sustainable catalysis and their potential for the synthesis of a wide range of *γ*-lactones.



5.2. Introduction and literature background for the synthesis of γ -lactone

Lactones, specifically *γ*-butyrolactones, are cyclic esters that play a significant role as heterocyclic scaffolds in natural products and pharmaceuticals. [158] They are versatile chemical intermediates used in the synthesis of complex molecules, biologically active compounds, and natural products.[159] Notably, *γ*-butyrolactones have been employed in the production of important substances such as pilocarpine (**102**), enterolactone (**103**), podophyllotoxin (**104**), protolichesterinic acid (**105**) and, cephalosporolide E (**106**) (Figure 120).[159] These compounds exhibit diverse medicinal properties, including anti-glaucoma, anti-estrogenic, anti-carcinogenic, growth regulatory, and anti-inflammatory activities respectively.[159] Additionally, xanthatium strumarium (**107)**, a natural product derived from plants, has been used for various medicinal purposes, such as acting as a diuretic, laxative, and treatment for respiratory and skin conditions, according to traditional medicine practices.[159]

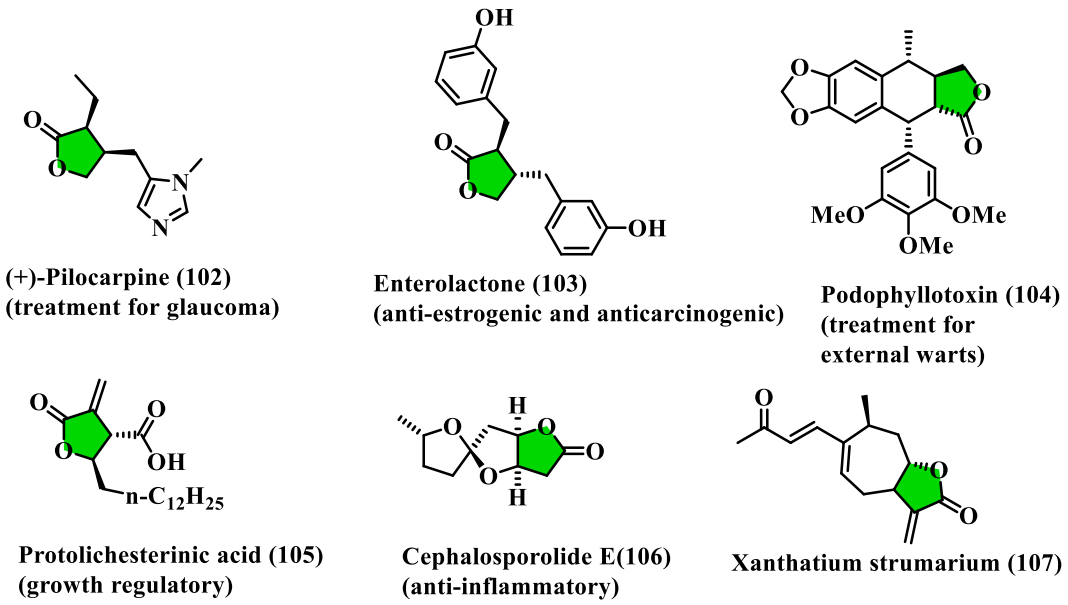
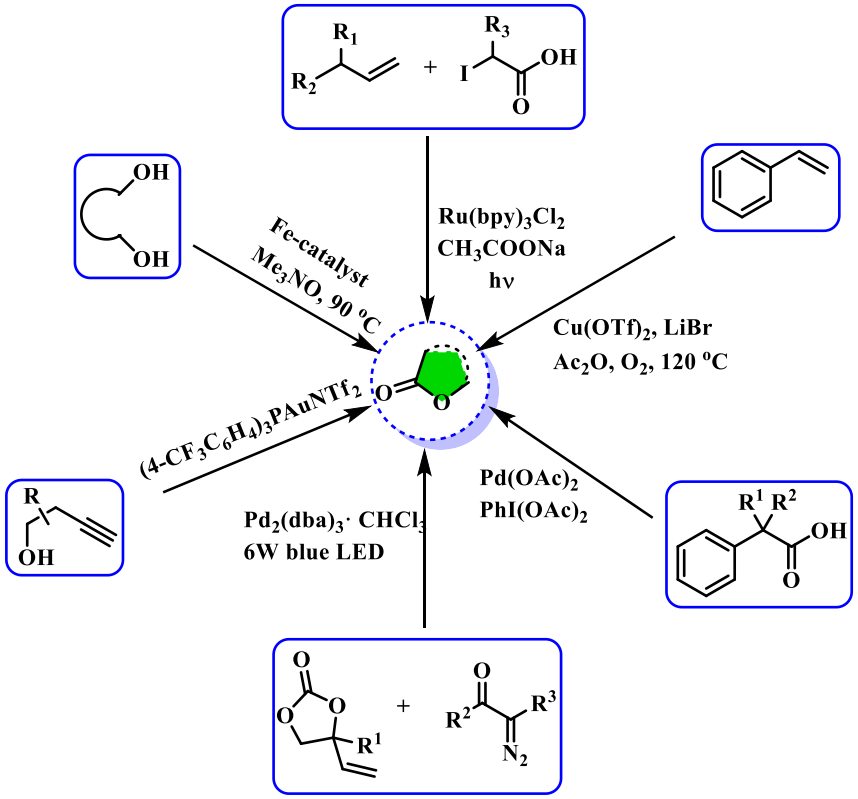


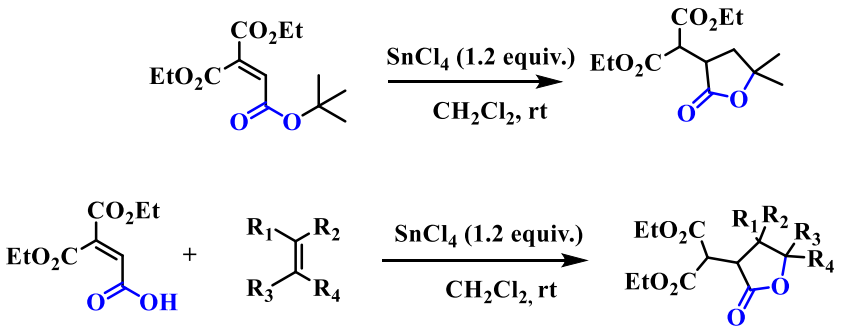
Figure 120: Representative examples of lactone-based biologically active molecules

In the past few decades, there has been significant interest to develop new methods to synthesize the γ-butyrolactone structure due to its widespread prevalence and notable biological activities.[160] In 2010, Jiang and co-workers developed a synthetic approach to γ-lactones through copper-catalyzed intermolecular oxidative [3 + 2] cycloaddition between alkenes and anhydrides (Scheme 74).[161]



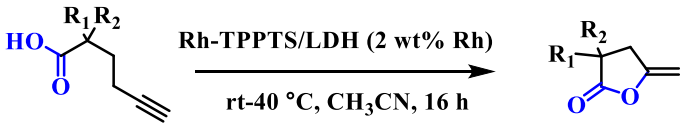
Scheme 74: Various synthetic approaches for the synthesis of lactones

This method provides an efficient way to produce γ-lactones, which plays a key intermediate for the various transformation in the field of organic synthesis. Subsequently, Wang and Ye group reported the synthesis of γ-lactone using Pd and Au catalysts respectively (Scheme 74).[162] Recently, Kokotos and Xiao group independently disclosed the light-mediated synthesis of lactone using Ru and Pd catalysts respectively (Scheme 74).[163] In 2005, Yamazaki and co-workers reported the Lewis acid catalyzed lactonization of ethenetricarboxylate derivatives via inter-molecular trapping of alkenes (Scheme 75).[164]



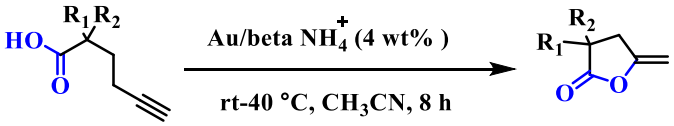
Scheme 75: Yamazaki's approach for the synthesis of γ-lactone

There are many reports on the synthesis of lactones,[165] but only a few of them discuss heterogeneous-mediated synthesis. In 2008, Pârvulescu and co-workers developed a Rh-based heterogeneous catalyst that can be used to synthesize functionalized γ-lactones (Scheme 76).[166]



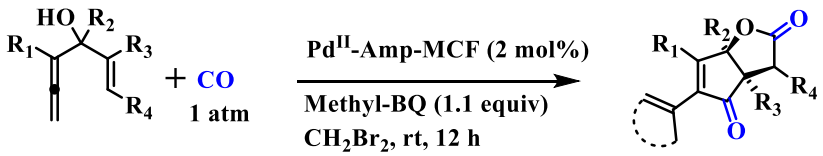
Scheme 76: Pârvulescu's approach for the synthesis of γ-lactone

Similarly, Michelet and co-workers reported a lactonization process using Au-based heterogeneous catalyst (Scheme 77).[167]



Scheme 77: Michelet's approach for the synthesis of γ-lactone

In 2018, Bäckvall and co-workers reported heterogeneous palladium-catalyzed oxidative tandem process for chemo-divergent and diastereoselective synthesis of γ-lactones (Scheme 78).[168]



Scheme 78: Bäckvall's approach for the synthesis of lactone

5.3. The objective of the present work

There are several reports available for the synthesis of *γ*-butyrolactone using various transition metal catalyst. However, the synthesis of *γ*-butyrolactones using heterogeneous catalysts can lead to the development of a more efficient method for producing a wide range of natural products, biologically active compounds and chemical intermediates, which can benefit the environment and the economy. This would involve the use of catalysts that are renewable, abundant, and can be easily recovered and reused, as well as the implementation of green chemistry principles that reduce waste and minimize the use of toxic and hazardous chemicals. The main objective of the project is to develop environmental benign heterogeneous catalysed synthesis of lactone via the combination of *α, β*-unsaturated keto-carboxylic acids with alkene. Moreover, the objective is to use the in situ generated isobutylene for the synthesis of corresponding lactones.

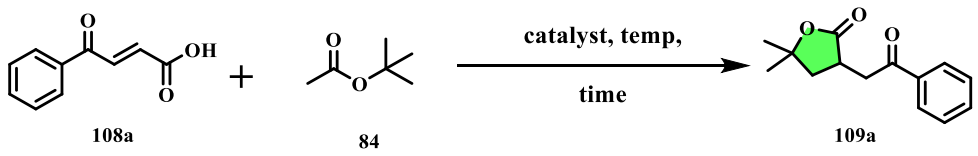
5.4. Results and discussion

The traditional methods for synthesis of lactones involves the intramolecular cyclization of hydroxy acid (seco acid)/ester derivatives. Another established method is the intermolecular cyclization of alkene with *α*-halo esters/acids. In this method lactones were synthesized through annulation of alkene with *α*-halo ester or acid, using different metals such as nickel, copper, or photocatalysts along with ligands, bases, and additives. In the present study, Fe@zeolite was utilized, as a heterogeneous catalyst for the lactonization, because the iron is earth abundant and environmentally friendly. Although iron is commonly used in organic synthesis due to its ability to catalyze various reactions, including cross-coupling, hydrogenation, oxidation, and reduction reactions,[169] but the use of heterogeneous iron catalysts for annulation to synthesize *γ*-lactones is not explored. This study delineate the successful synthesis of *γ*-lactones via iron-catalyzed annulation of alkenes with *α, β*-unsaturated keto-carboxylic acids and their derivatives, without the need for any ligands, bases, or additives. This approach is more efficient than previous methods.

5.4.1. Optimization studies

Based on the previous work (Chapter 3), which involves the use of in situ generated *iso*-butylene for the methylallylation, the *tert*-butylacetate was chosen as source for *iso*-butylene for the synthesis of lactone. In the initial control experiments, the reaction of **108a** and *tert*-butyl acetate (**84**) in the absence of catalyst at room temperature and 100 ^{o}C were tested, the control experiment was unsuccessful to afford any product (Table 15, entries 1). The use of $InCl_3$ at 80 ^{o}C and 100 ^{o}C for

Table 15. Optimization for the lactonization



108a 84 109a

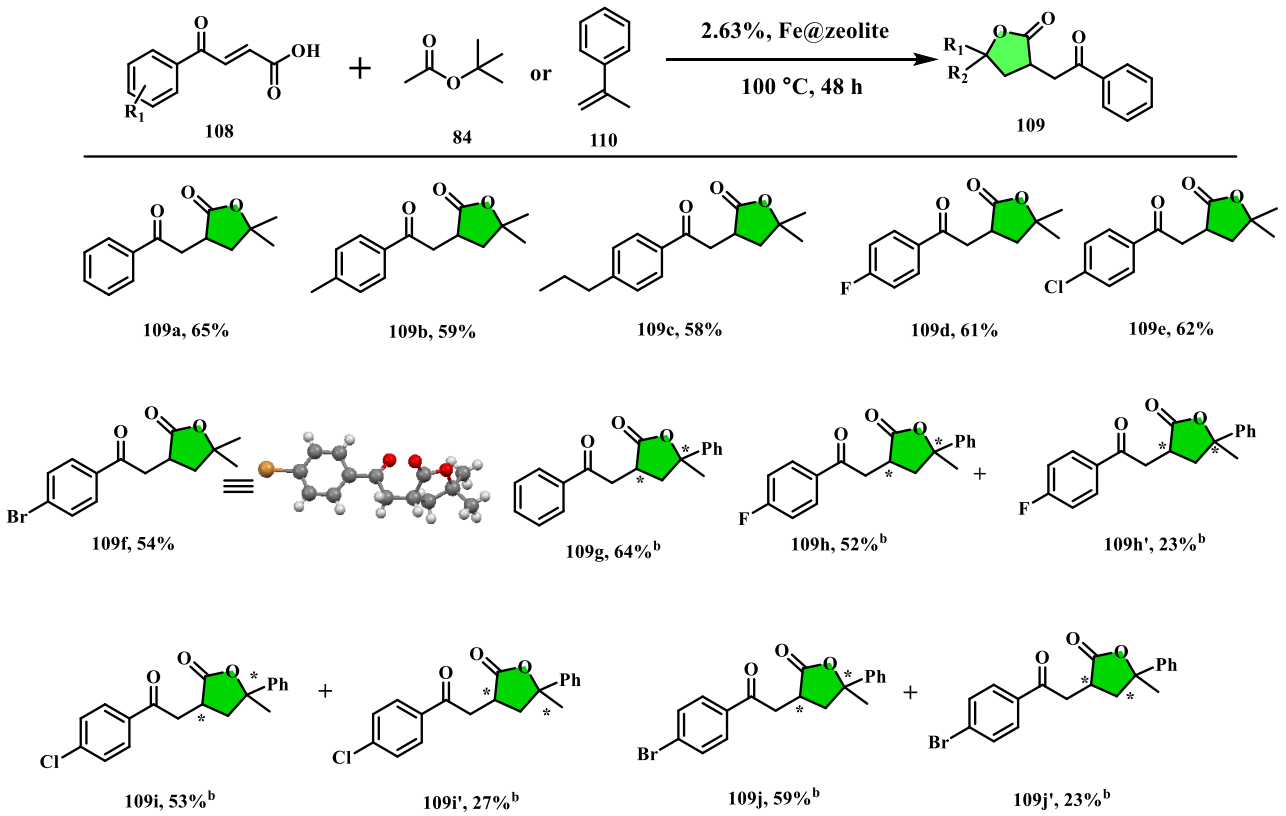
entry[a]	catalyst	catalyst loading (mol%)	temp (^{o}C)	time (h)	yield (%)
1[b]	-	-	100	24	nr
2[c]	$InCl_3$	10	100	24	32
3	$InCl_3$	10	100	48	41
4	$In(OTf)_3$	10	100	48	59
5	$FeCl_2$	10	100	48	31
6	$Sn(OTf)_2$	10	100	48	42
7	*R*-BNDHP	10	100	48	41
8	*S*-BNDHP	10	100	48	59
9	Amberlyst®-15	1:1(w/w)	100	48	32
10	Zeolite beta, Hydrogen	1:1(w/w)	100	48	trace
11	Fe@zeolite	1:1(w/w)	100	48	65
12	Ni@zeolite	1:1(w/w)	100	48	53
13	Fe@MNP	1:1(w/w)	100	48	nr

[a]**Reaction conditions**: All reactions were carried out with **109a** (0.25 mmol), **84** (2 mL), using specified catalyst and were heated in a sealed tube at 100 ^{o}C for mentioned time. [b]rt = room temperature; [c]21% yield at 80 ^{o}C; nr = no reaction.

24 h as well as 4 h provided the lactone **109a** with poor yield (Table 15, entries 2-3). Interestingly, the increase in the yield (41%) of **109a** was observed when increasing the time of the reaction up to 48 h. The other metal catalyst such as $In(OTf)_3$, $FeCl_2$ and $Sn(OTf)_2$ afforded 59%, 31%, and 42% yield of **109a** respectively at 100 ^oC (Table 15, entries 4-6). In an effort to avoid the harsh reaction condition, different types of catalysts were screened. The use of *R*-BNDHP and *S*-BNDHP (1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate) organo-catalysts resulted in 41% and 59% yield of the desired product **109a** respectively (Table 15, entries 7 and 8). Next, to further improve the yield, heterogeneous catalysts were explored. The amberlyst®-15 and zeolite-*H*-beta afforded 32% and trace amount of **109a** respectively (Table 15, entries 9 and 10). On the other hand, heterogeneous supported catalysts Fe@zeolite and Ni@zeolite catalysts produced 65% and 53% of the product **109a** respectively (Table 15, entries 11 and 12). Unfortunately, magnetic nanoparticle-supported Fe@MNP was unable to afford the product **109a** (Table 15, entry 13). Based on the results, Fe@zeolite proved to be the most effective catalyst for the lactonization reaction.

5.4.2. Substrate scope for the lactonization reaction

Next, several substituted carboxylic acids were studied with optimized conditions for the substrate scope. The *α, β*-unsaturated keto-carboxylic acid derivatives reacted smoothly, resulted in the formation of various lactone derivatives (Scheme 79). This reaction involved the annulation of in situ generated *iso*-butylene and phenyl group substituted *α, β*-unsaturated keto-carboxylic acids carboxylic acid derivatives. The presence of electron-donating groups, such as $-CH_3$ and *n*-propyl, on the phenyl group resulted in 59% and 58% yields for the lactone derivatives **109b** and **109c** respectively. The halide substituted carboxylic acid derivatives (**108d-f**) were also subjected to the reaction with *tert*-butyl acetate, resulting in moderate to good yields of the desired products (**109d-f**). The reaction is also efficient with alkenes such as *α*-methyl styrene, and it produced diastereomeric products. When **108a** was treated with *α*-methyl styrene under optimal conditions, a single diastereomeric lactone compound **109g** was obtained with a yield of 64%. However, when halide substituted in the phenyl group of *α, β*-unsaturated keto-carboxylic acid derivatives (-F, -Cl, and -Br) were treated with *α*-methyl styrene, two diastereomeric lactones (**109h-j** and **109h'-j'**) were obtained with moderate yields. For all the substrate scope we have not checked the enantioselective but diastereomeric compounds were isolated from column chromatography.

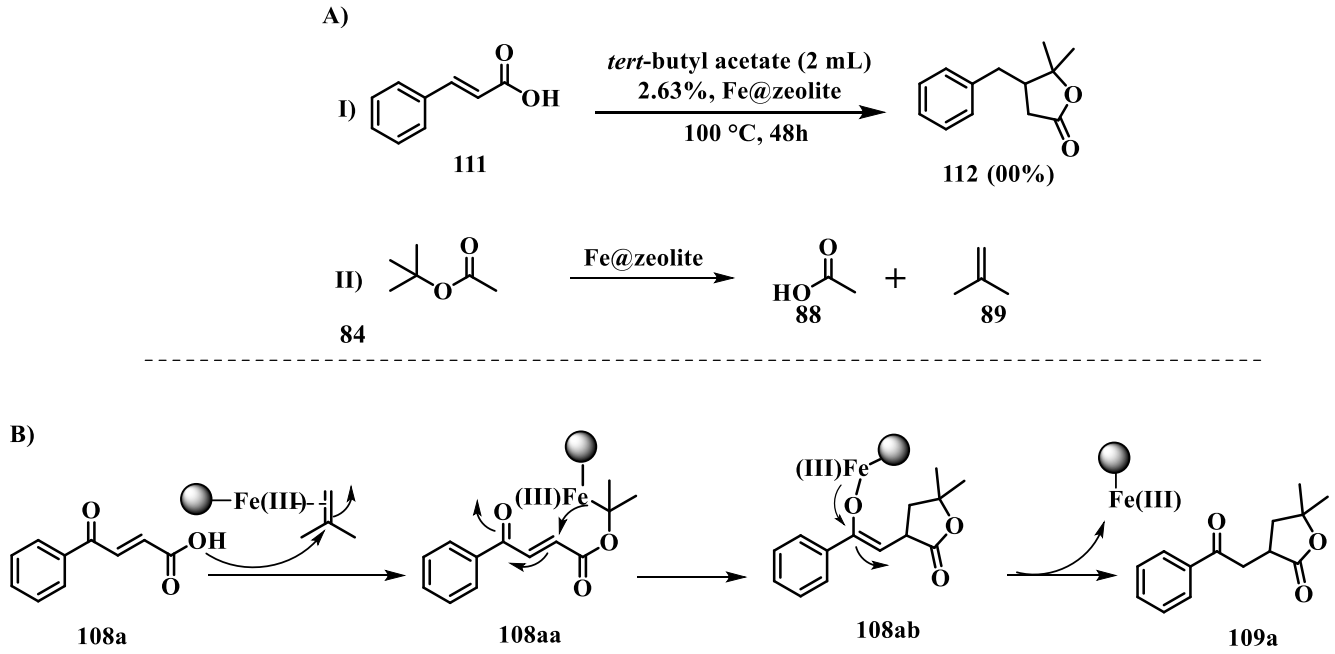


[a]**Reaction Condition:** In a 20 mL re-sealable vial was added with carboxylic acids (**108**, 0.5 mmol), *tert*-butyl acetate (**84**, 2 mL) and Fe@zeolite (1:1 (w/w) with **108**); [b] *α*-methyl styrene (110, 1.2 equiv.) and acetonitrile used as solvent. The mentioned yields are isolated yields.

Scheme 79: Substrate scope for the *γ*-lactones

5.4.3. The possible reaction mechanism

To investigate the reaction mechanism, a control experiment with the carboxylic acid **111**, and *tert*-butyl acetate was performed. This reaction failed to provide the desired product **112** (Scheme 80A)**,** which confirmed the presence of carbonyl group at *γ*-position is driving the reaction towards the forward direction and provide the desired product. Initially, the *tert*-butyl acetate undergoes the ester pyrolysis to produce *iso*-butylene (**89**). The possible reaction mechanism for the lactonization is proposed based on experimental results and literature reports[170,171] (Scheme 80B). The catalytic reaction cycle initiates with attacking of oxygen of carboxylic acid (**109a**) to electrophilic carbon of the Fe@zeolite coordinated *iso*-butylene and resulted the intermediate **108aa**. Next, the intermediate **108aa** undergoes the intra molecular Michel addition resulted the *γ*-lactone via the intermediate **108ab.**



Scheme 80. A) Control experiment for the mechanism; B) The possible reaction mechanism

5.5. Conclusion

In summary, an efficient and environmentally benign process has been developed for the synthesis of *γ*-lactones using a Fe@zeolite heterogeneous catalyst. The use of a Fe@zeolite heterogeneous catalyst has shown promising results in the annulation reaction of an alkene with *α, β*-unsaturated keto-carboxylic acid to synthesize *γ*-lactone. This approach provided a highly environment beingn and efficient method for the preparation of *γ*-lactones, which are valuable intermediates in the synthesis of natural products and pharmaceuticals. The Fe@zeolite catalyst offers several advantages, including its low cost, high stability and reusability, making it an attractive alternative to traditional homogeneous catalysts.

5.6. Experimental section and characterization data

5.6.1. General information and data collection

All the commercially available solvents were used as received without further purification. The chemicals used for the starting material preparation were brought from Sigma Aldrich, BLD pharma and AVRA chemicals. Deuterated solvents were used as received. Column chromatographic separations performed over 100-200 Silica-gel. Visualization was accomplished with UV light and PMA, CAM stain followed by heating. The amberlyst-15 (dry form) and other metal catalysts were purchased from Sigma-Aldrich. The zeolite-*H*-beta was brought from alfa-aesar. ^{1}H and ^{13}C NMR

spectra were recorded on 400 and 100 MHz, respectively, using a Bruker 400 MHz or JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded with Waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-II Fourier transform infrared spectrometer.

5.6.2. Experimental procedure

A) General procedure for the preparation of heterogeneous catalyst Fe@zeolite

The Fe@zeolite was prepared according to the previous report.[171] The experiment involved suspending 5 g of zeolite-*H*-beta (SiO_2:Al_2O_3, Powder, S.A. 620 m2/g, 360:1 mole ratio) in 20 mL of deionized water. The 10% solution of $FeCl_2 \cdot 6H_2O$ was prepared in deionized water, and the stock solution was used to achieve a metal loading over the zeolite samples. The suspension was stirred in a rotary evaporator for 6 h to ensure even dispersion, and water was removed under vacuum. The resulting metal-loaded samples were dried at 120 °C for 12 hours and then calcined at 500 °C for 8 hours. Finally, the metal-loaded Fe@zeolite was utilized for the lactonization process. According to previous report 2.63% Fe loaded on the zeolite.

B) General experimental procedure for the lactonization reaction with *tert*-butyl acatate

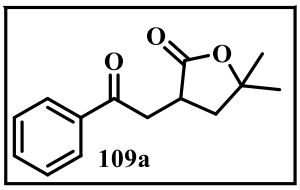
In a 20 mL re-sealable vial (equipped with a stir bar) was added with carboxylic acid **108 (**0.5 mmol), *tert*-butyl acetate **84** (2 mL), and Fe@zeolite (1:1 (w/w) with **108**). The tube was sealed with a cap using a crimper. The reaction mixture was heated at 100 ^oC in a pre-heated oil bath for 48 h. After 48 h, the volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (EtOAc: hexane= 15:85).

C) General experimental procedure for the lactonization reaction with *α*-methyl styrene

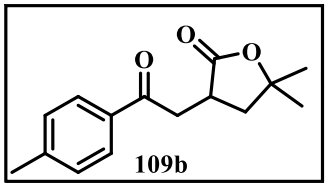
In a 20 mL re-sealable vial (equipped with a stir bar) was added with carboxylic acids **108 (**0.5 mmol), *α*-methyl styrene **110** (1.2 equiv), Fe@zeolite (1:1(w/w) with **108**) and acetonitrile solvent (2 mL) was added and tube was sealed with a cap using a crimper. The reaction mixture was heated at 100 ^oC in a pre-heated oil bath for 48 h. After that, the volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (EtOAc: hexane= 15:85).

5.6.3. Analytical data

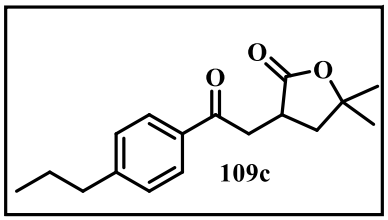
5,5-dimethyl-3-(2-oxo-2-phenylethyl)dihydrofuran-2(3*H*)-one (109a): Prepared according to the general procedure B, using (*E*)-4-oxo-4-phenylbut-2-enoic acid (**108a**, 88 mg, 0.5 mmol) to afford 5,5-dimethyl-3-(2-oxo-2-phenylethyl)dihydrofuran-2(3*H*)-one **109a** (28.5 mg, 65%) as a whitle solid. **Melting point**: 56-57 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.56 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.45 (dd, *J* = 12.3, 4.5 Hz, 2H), 3.66 (dd, *J* = 16.6, 5.8 Hz, 1H), 3.42 – 3.29 (m, 1H), 3.20 – 3.10 (m, 1H), 2.55 – 2.45 (m, 1H), 1.75 (t, *J* = 12.1 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 197.2, 178.3, 136.3, 133.6, 128.8, 128.1, 83.0, 41.8, 39.8, 36.8, 28.9, 27.1 ppm. **FTIR** (neat): 2976, 1760, 1684, 1597, 1450, 1131 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{17}O_3$ $(M+H)^+$: 233.1178, found: 233.1180.



5,5-dimethyl-3-(2-oxo-2-(*p*-tolyl)ethyl)dihydrofuran-2(3*H*)-one (109b): Prepared according to the general procedure B, using (*E*)-4-oxo-4-(*p*-tolyl)but-2-enoic acid (**108b**, 95 mg, 0.5 mmol) to afford 5,5-dimethyl-3-(2-oxo-2-(*p*-tolyl)ethyl)dihydrofuran-2(3*H*)-one **109b** (28 mg, 59%) as a whitle solid. **Melting point**: 105-106 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.24 (m, 2H), 3.66 (dd, *J* = 17.9, 2.6 Hz, 1H), 3.41 – 3.32 (m, 1H), 3.13 (dd, *J* = 18.2, 9.4 Hz, 1H), 2.52 (dd, *J* = 12.6, 9.0 Hz, 1H), 2.41 (s, 3H), 1.74 (t, *J* = 12.1 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.8, 178.5, 144.6, 133.9, 129.5, 128.3, 83.1, 41.9, 39.8, 36.8, 29.0, 27.2, 21.8 ppm. **FTIR** (neat): 2975, 1761, 1680, 1606, 1288, 1181, 1035 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{19}O_3$ $(M+Na)^+$: 247.1334, found: 247.1337.

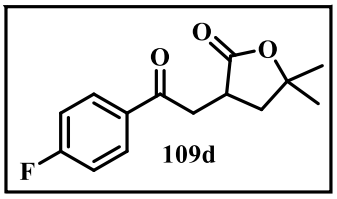


5,5-dimethyl-3-(2-oxo-2-(4-propylphenyl)ethyl)dihydrofuran-2(3*H*)-one (109c): Prepared according to the general procedure (B), using (*E*)-4-oxo-4-(4-propylphenyl)but-2-enoic acid (**108c**, 109 mg, 0.5 mmol) to afford 5,5-dimethyl-3-(2-oxo-2-(4-propylphenyl)ethyl)dihydrofuran-2(3*H*)-one **109c** (28 mg, 58%) as a whitle solid. **Melting point**: 105-107 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.23 (m, 2H), 3.65 (dd, *J* = 18.2, 2.9 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.13 (dd, *J* = 18.2, 9.4 Hz, 1H), 2.66 – 2.61 (m, 2H), 2.51 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.74 (t, *J* = 12.1 Hz, 1H), 1.65 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.8, 178.4, 149.2, 134.1, 128.9, 128.3, 83.0, 41.9, 39.7, 38.1, 36.8, 29.8, 28.9, 27.1, 24.3, 13.8 ppm. **FTIR**



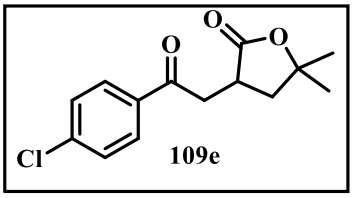
(neat): 2965, 2931, 2871, 2312, 1759, 1680, 1371, 1267, 802 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{17}H_{23}O_3$ $(M+H)^+$: 275.1647, found: 275.1652.

3-(2-(4-fluorophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3H)-one (109d): Prepared according to the general procedure B, using 3(*E*)-4-(4-fluorophenyl)-4-oxobut-2-enoic acid (**108d**, 97 mg, 0.5 mmol) to afford 3-(2-(4-fluorophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3*H*)-one **109d** (30 mg, 61%) as a whitle solid. **Melting point**: 102-103 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02 – 7.97 (m, 2H), 7.14 (ddd, *J* = 9.9, 6.0, 2.5 Hz, 2H), 3.66 (dd, *J* = 18.3, 3.1 Hz, 1H), 3.36 (dtd, *J* = 11.9, 9.1, 3.1 Hz, 1H), 3.13 (dd, *J* = 18.3, 9.2 Hz, 1H), 1.76 (t, *J* = 12.1 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 195.6, 178.2, 166.11 (d, *J* = 254 Hz), 132.8 (d, *J* = 3 Hz), 130.9 (d, *J* = 9 Hz), 116.2 (d, *J* = 22 Hz), 83.1, 41.9, 39.8, 36.8, 29.0, 27.2 ppm. **FTIR** (neat): 2977, 1759, 1684, 1596, 1372, 1034 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{19}FO_3$ $(M+H)^+$: 251.1083, found: 251.1087.



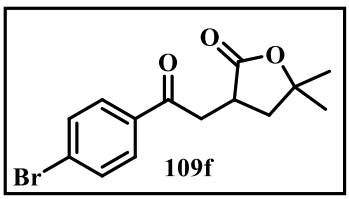
109d

3-(2-(4-chlorophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3*H*)-one (109e): Prepared according to the general procedure B, (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoic acid (**108e**, 105 mg, 0.5 mmol) to afford -(2-(4-chlorophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3*H*)-one **109e** (36.5 mg, 62%) as a whitle solid. **Melting point**: 102-103 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96 – 7.87 (m, 2H), 7.51 – 7.39 (m, 2H), 3.65 (dd, *J* = 18.3, 3.0 Hz, 1H), 3.36 (dtd, *J* = 12.0, 9.1, 3.1 Hz, 1H), 3.12 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.52 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.75 (t, *J* = 12.1 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.0, 178.2, 140.2, 134.7, 129.9, 129.2, 83.2, 41.8, 39.8, 36.8, 29.0, 27.2 ppm. **FTIR** (neat): 2975, 1759, 1685, 1585, 1589, 1189, 1034 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{16}ClO_3$ $(M+H)^+$: 267.0788, found: 267.0792.



109e

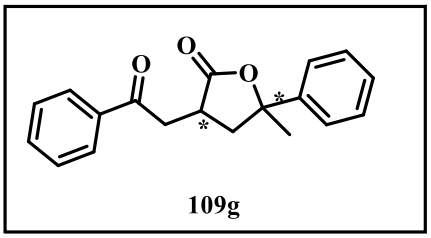
3-(2-(4-bromophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3H)-one (109f): Prepared according to the general procedure B, using 3(*E*)-4-(4-bromophenyl)-4-oxobut-2-enoic acid (**108f**, 126.5 mg, 0.5 mmol) to afford 3-(2-(4-bromophenyl)-2-oxoethyl)-5,5-dimethyldihydrofuran-2(3H)-one **109f** (38 mg, 54%) as a whitle solid. **Melting point**: 88-89 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 – 7.81 (m, 2H), 7.65 – 7.60 (m, 2H), 3.65 (dd, *J* = 18.3, 3.1 Hz, 1H), 3.36 (dtd, *J* = 12.1, 9.1, 3.0 Hz, 1H), 3.11 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.52 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.75 (t, *J* = 12.1 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100



109f

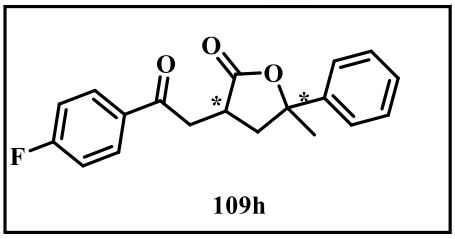
MHz, $CDCl_3$): δ 196.2, 178.2, 135.1, 132.2, 129.7, 128.9, 83.2, 41.9, 39.8, 36.8, 29.0, 27.2 ppm. **FTIR** (neat): 2921, 1758, 1684, 1584, 1394, 1288, 1183 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{19}BrO_3$ $(M+H)^+$: 311.0283, found: 311.0287.

5-methyl-3-(2-oxo-2-phenylethyl)-5-phenyldihydrofuran-2(3*H*)-one (109g): Prepared according to the general procedure C, using (*E*)-4-oxo-4-phenylbut-2-enoic acid (**108a**, 88 mg, 0.5 mmol) afforded 5-methyl-3-(2-oxo-2-phenylethyl)-5-phenyldihydrofuran-2(3*H*)-one **109g** (33 mg, 64%) single diasteromer as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.00 (bs, 1H), 7.75 – 7.68 (m, 2H), 7.47 – 7.39 (m, 3H), 7.16 – 7.12 (m, 1H), 7.08 – 6.99 (m, 2H), 6.87 – 6.84 (m, 1H), 3.61 – 3.47 (m, 2H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 163.7, 141.5, 135.1, 129.4, 128.2, 127.9, 126.6, 124.2, 123.1, 117.5, 115.8, 100.6, 59.8, 15.2 ppm. **FTIR** (neat): 2985, 2314, 1785, 1675, 1132 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{19}O_3$ $(M+H)^+$: 295.1334, found: 295.1336.



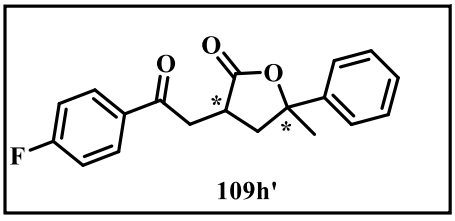
109g

3-(2-(4-fluorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one (109h): Prepared according to the general procedure C, using (*E*)-4-(4-fluorophenyl)-4-oxobut-2-enoic acid (**108c**, 97 mg, 0.5 mmol, afforded two diasteromer of 3-(2-(4-fluorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one **109h** (25 mg, 52%) and **109h'** (11.5 mg, 23%) as a whitle solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 – 7.92 (m, 2H), 7.42 – 7.33 (m, 4H), 7.31 – 7.26 (m, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 3.65 (dd, *J* = 18.3, 3.0 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.08 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.95 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.75 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 195.5, 177.9, 164.6 (d, *J* = 254 Hz), 145.2, 132.7 (d, *J* = 3 Hz), 130.8 (d, *J* = 9 Hz), 128.7, 127.7, 124.3, 116.0 (d, *J* = 29 Hz), 85.5, 42.7, 39.7, 36.6, 28.8 ppm. **FTIR** (neat): 2986, 2312, 1783, 1644, 1541, 1009 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}FO_3$ $(M+H)^+$: 313.1240, found: 313.1247.



109h

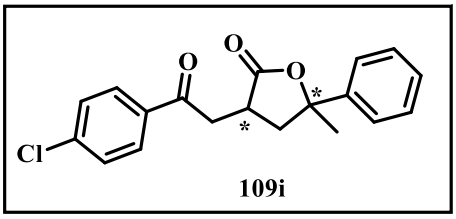
3-(2-(4-fluorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one (109h'): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 8.9, 5.4 Hz, 2H), 7. 43 – 7.35 (m, 4H), 7.34 – 7.28 (m, 1H), 7.14 (t, *J* = 8.6 Hz, 2H), 3.63 (dd, *J* = 18.0, 2.5 Hz, 1H), 3.19 – 3.11 (m, 1H), 3.09 – 2.98 (m, 2H), 2.17 – 2.09 (m, 1H), 1.78 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 195.4, 178.3, 166.1 (d, *J* = 254 Hz), 143.7, 132.8 (d, *J* = 3 Hz), 130. 9, 130.8, 128.8, 127.9, 124.4, 116.0 (d, *J* = 22 Hz), 85.7, 43.3, 39.0, 36.4, 30.6 ppm.



109h'

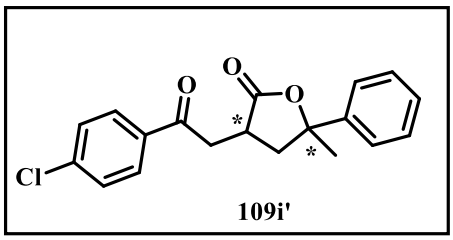
FTIR (neat): 2968, 2326, 1763, 1610, 1558, 1102 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}FO_3$ $(M+H)^+$: 313.1240, found: 313.1250.

3-(2-(4-chlorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one (109i): Prepared according to the general procedure C, using (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoic acid (**108d**, 105 mg, 0.5 mmol) (50 mg, 0.21 mmol) afforded two diasteromer of 3-(2-(4-chlorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one **109i** (29 mg, 53%) and **109i'** (14 mg, 27%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.46 – 7.36 (m, 6H), 7.34 – 7.28 (m, 1H), 3.62 (dd, *J* = 18.1, 2.5 Hz, 1H), 3.20 – 3.11 (m, 1H), 3.09 – 2.98 (m, 2H), 2.18 – 2.08 (m, 1H), 1.78 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 195.8, 178.2, 143.7, 140.2, 134.6, 129.6, 129.2, 128.8, 127.9, 124.4, 85.7, 43.2, 39.1, 36.4, 30.5 ppm. **FTIR** (neat): 2948, 1767, 1698, 1545, 1122, 1061 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}ClO_3$ $(M+H)^+$: 329.0944, found: 329.0946.



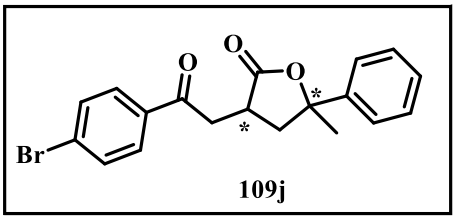
109i

3-(2-(4-chlorophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one (109i'): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.45 – 7.33 (m, 6H), 7.32 – 7.27 (m, 1H), 3.65 (dd, *J* = 18.3, 3.0 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.07 (dd, *J* = 18.4, 9.5 Hz, 1H), 2.95 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.75 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 195.9, 177.8, 145.2, 140.2, 134.6, 129.6, 129.2, 128.7, 127.8, 124.0, 85.5, 42.6, 39.8, 36.5, 28.8 ppm. **FTIR** (neat): 3027, 1766, 1656, 1544, 1225, 1063 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}ClO_3$ $(M+H)^+$: 329.0944, found: 329.0949.



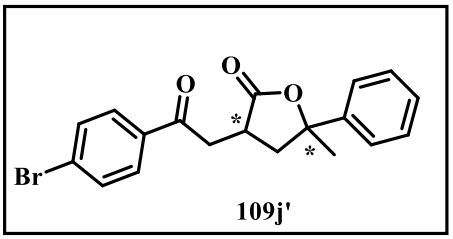
109i'

3-(2-(4-bromophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one (109j): Prepared according to the general procedure C, using 3(E)-4-(4-bromophenyl)-4-oxobut-2-enoic acid **108j** (126.5 mg, 0.5 mmol) afforded two diasteromer of 3-(2-(4-bromophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one **109j** (37.5 mg, 59%) and **109j'** (14 mg, 23%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.7 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.38 (d, *J* = 12.2 Hz, 4H), 7.30 (dt, *J* = 5.1, 2.1 Hz, 1H), 3.65 (dd, *J* = 18.4, 3.1 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.07 (dd, *J* = 18.3, 9.5 Hz, 1H), 2.95 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.75 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.1, 177.8, 145.2, 134.9, 132.2, 129.7, 128.8, 127.8, 124.1, 85.7, 85.6, 42.7, 39.8, 36.5, 28.9 ppm. **FTIR (neat**): 2990, 1768, 1685, 1588, 1224, 1092 cm^{-1}. HRMS (ESI) m/z calculated for C19H18BrO3 $(M+Na)^+$: 373.0439, found: 373.0443.



109j

3-(2-(4-bromophenyl)-2-oxoethyl)-5-methyl-5-phenyldihydrofuran-2(3H)-one (109j'): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.39 (dd, *J* = 9.9, 5.0 Hz, 4H), 7.18 (t, *J* = 4.9 Hz, 1H), 3.62 (dd, *J* = 18.0, 2.5 Hz, 1H), 3.18 – 3.09 (m, 1H), 3.07 – 2.98 (m, 2H), 2.18 – 2.12 (m, 1H), 1.78 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 196.0, 178.2, 143.7, 135.1, 132.2, 129.7, 128.9, 127.9, 124.4, 85.7, 43.2, 39.1, 36.4, 30.6 ppm. **FTIR** (neat): 2998, 2311, 1767, 1709, 1369, 1219, 1091 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}BrO_3$ $(M+Na)^+$: 373.0439, found: 373.0442.



109j'

5.7. Appendix V

Copies of ^{1}H and ^{13}C NMR spectra of representative compounds

Entry	Figure No	Data	Page No
109a	121 & 122	^{1}H and ^{13}C	227
109b	123 & 124	^{1}H and ^{13}C	228
109d	126 & 127	^{1}H and ^{13}C	229
109e	128 & 129	^{1}H and ^{13}C	230
109f	130 & 131	^{1}H and ^{13}C	231
109h	131 & 132	^{1}H and ^{13}C	232
109h'	133 & 134	^{1}H and ^{13}C	233
109i'	135 & 136	^{1}H and ^{13}C	234
109j	137 & 138	^{1}H and ^{13}C	235
109j'	139 & 140	^{1}H and ^{13}C	236
109f	141	ORTEP diagram	237
109j	142	ORTEP diagram	237

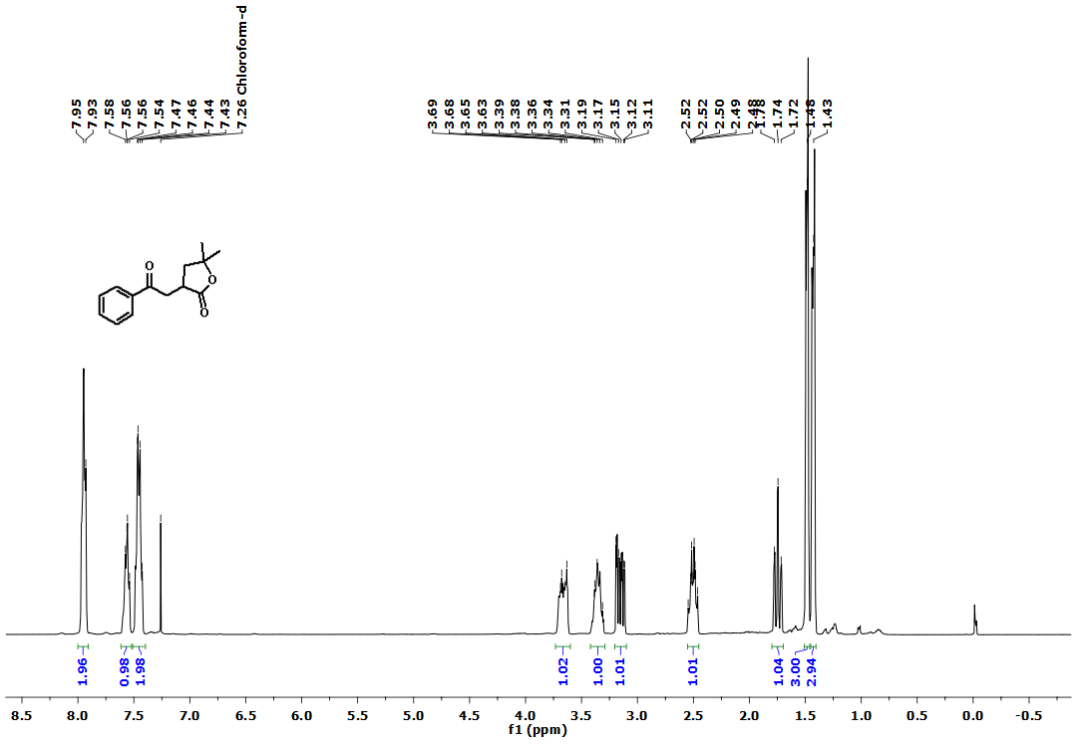


Figure 121: ^{1}H NMR of compound **109a**

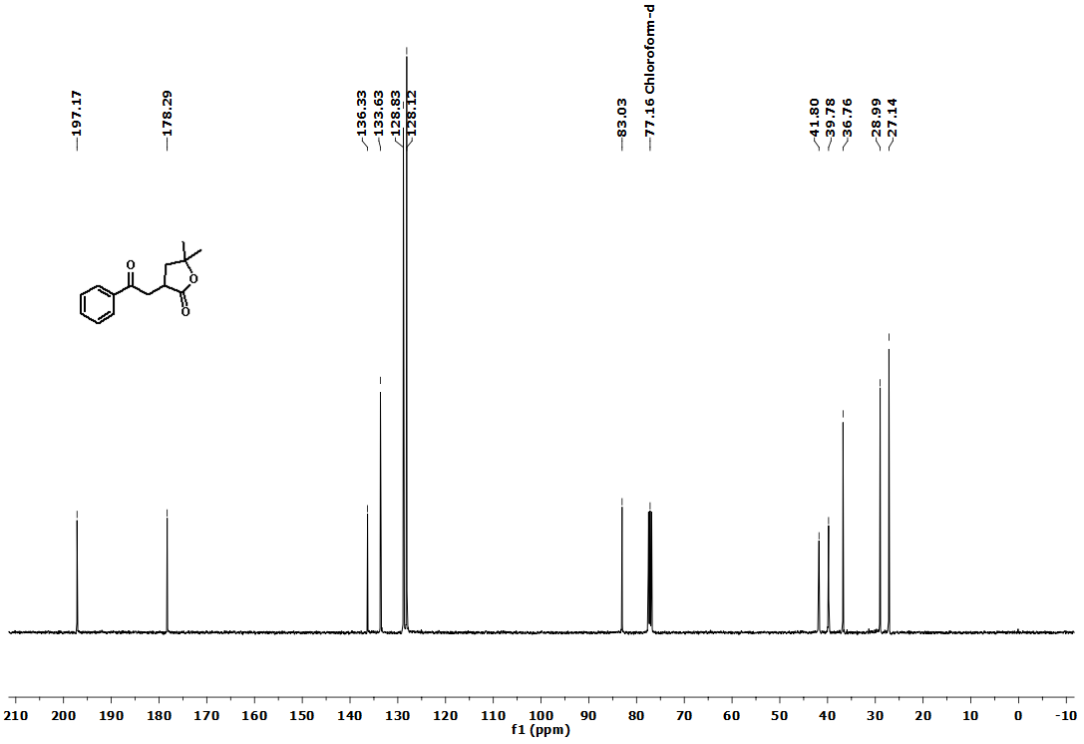


Figure 122: ^{13}C NMR of compound **109a**

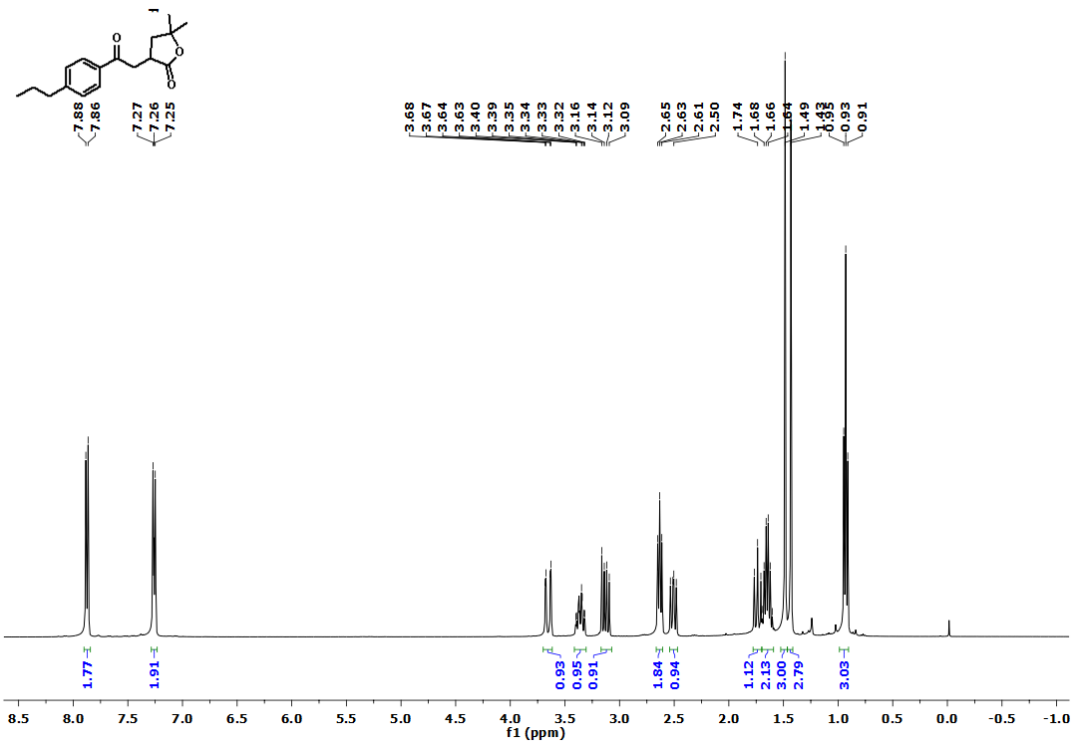


Figure 123: ^{1}H NMR of compound **109b**

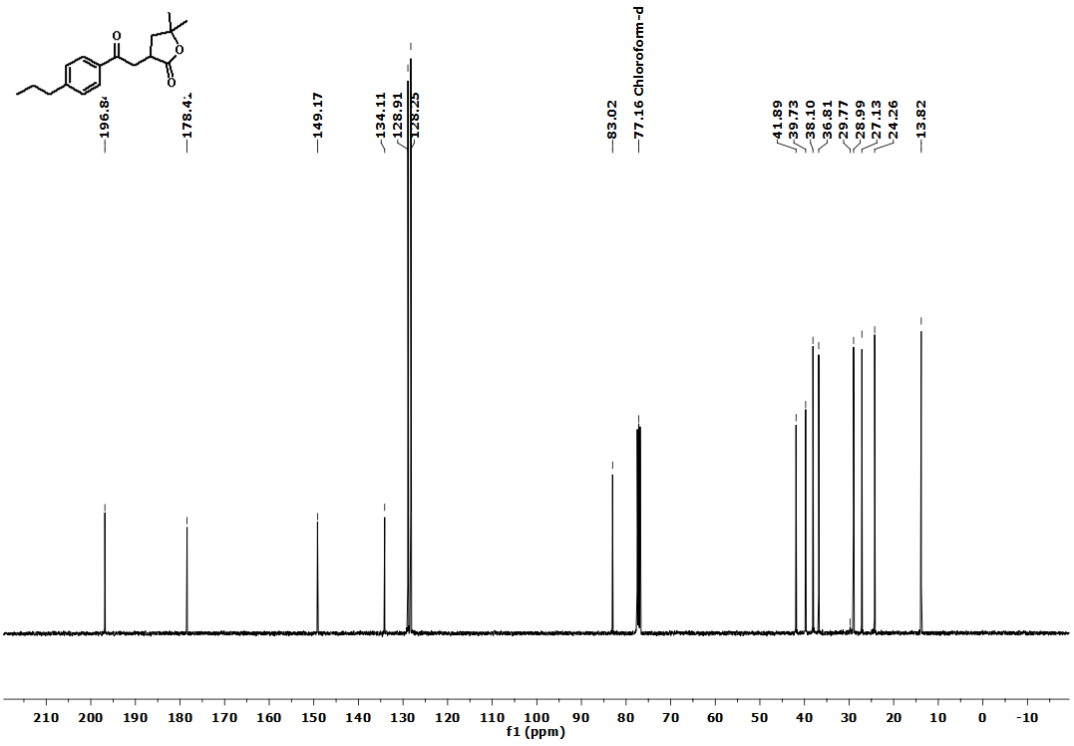


Figure 124: ^{13}C NMR of compound **109b**

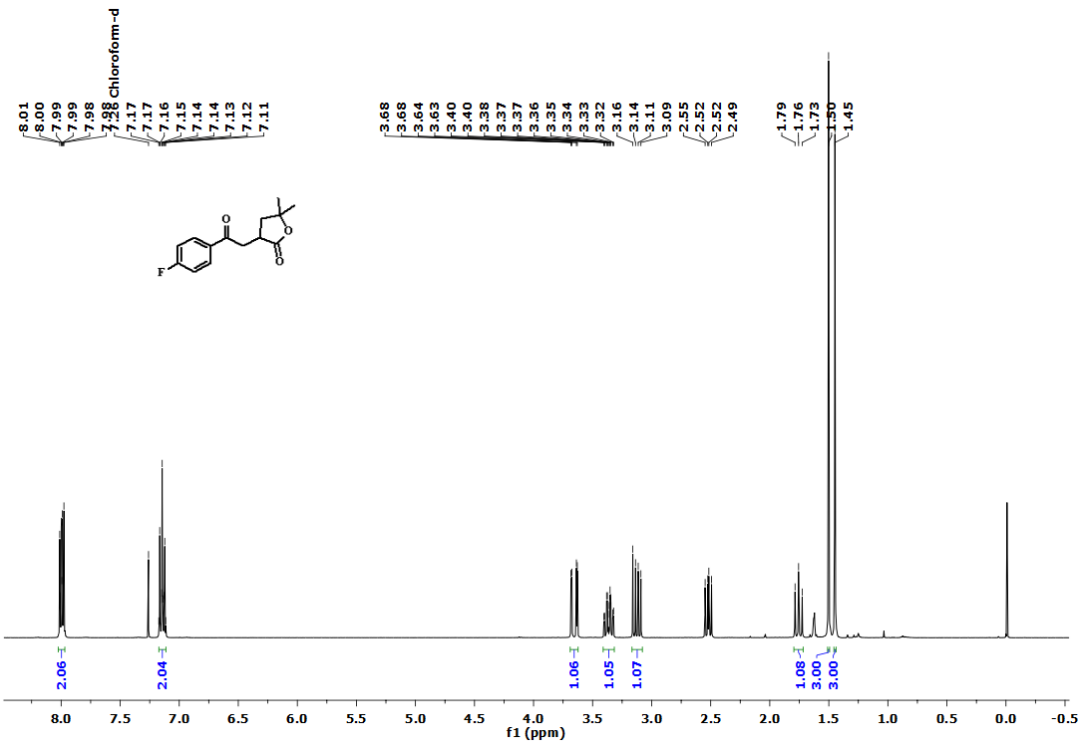


Figure 125: ^{1}H NMR of compound **109d**

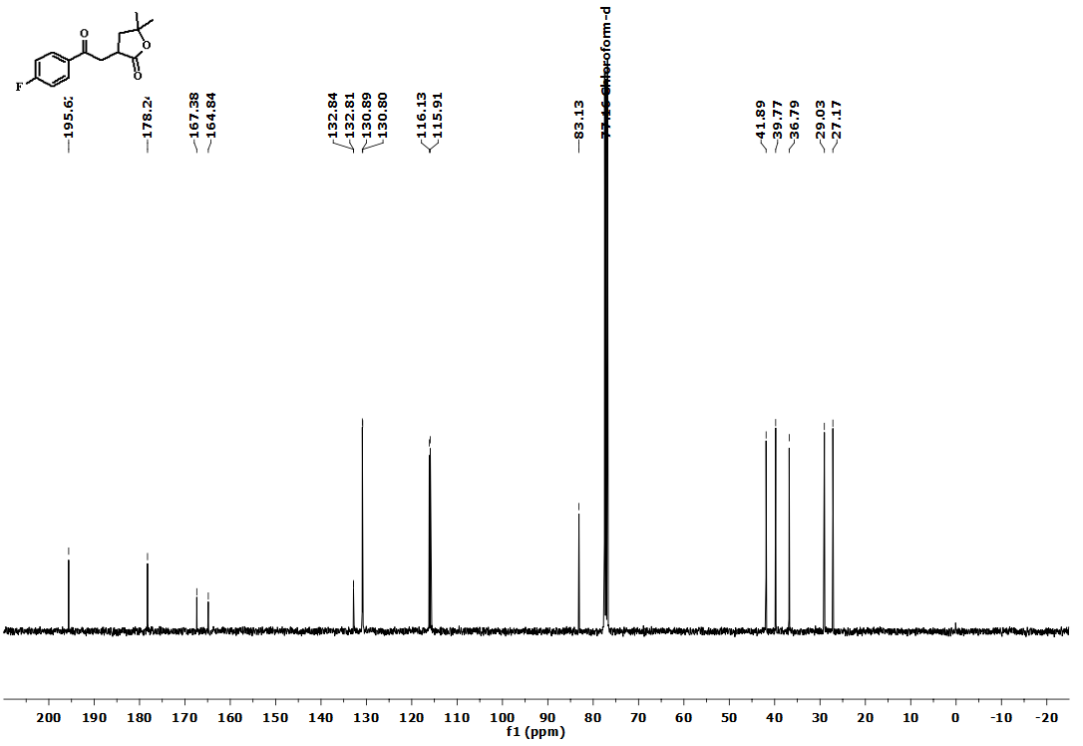


Figure 126: ^{13}C NMR of compound **109d**

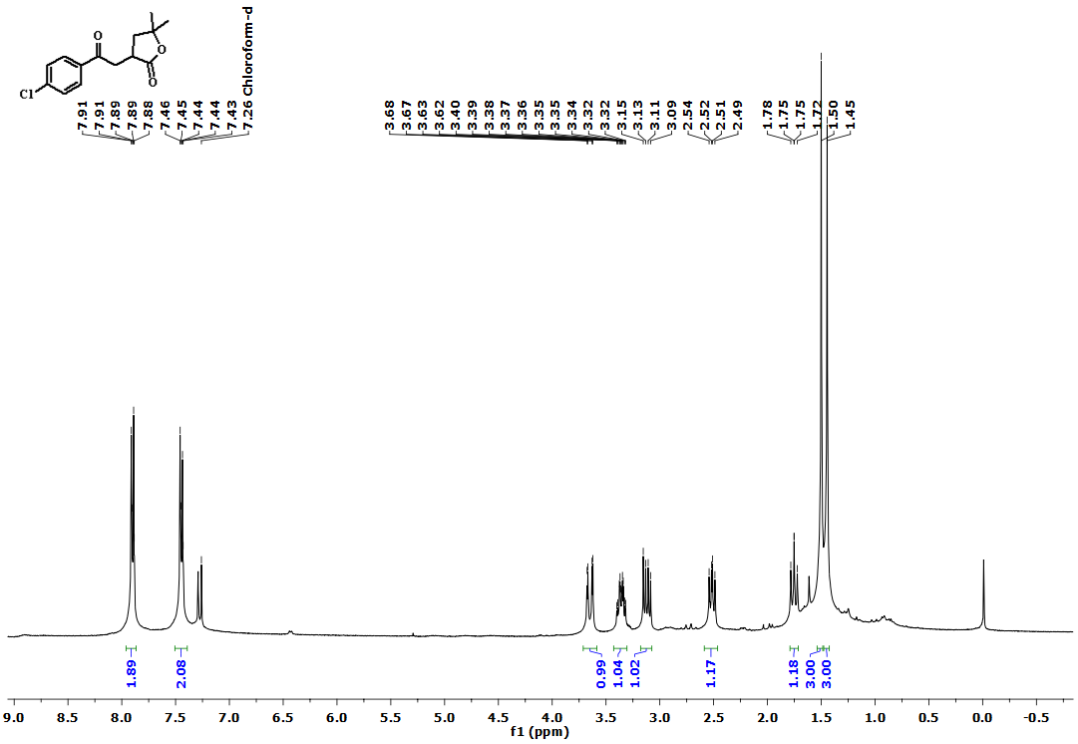


Figure 127: ^{1}H NMR of compound **109e**

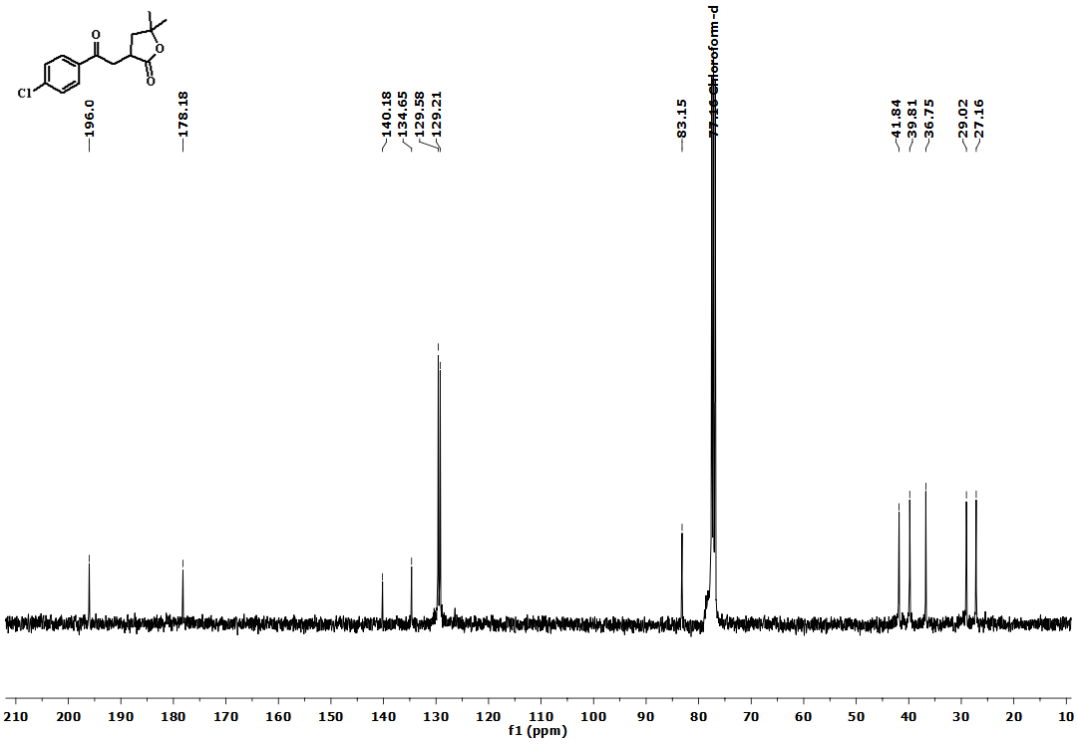


Figure 128: ^{13}C NMR of compound **109e**

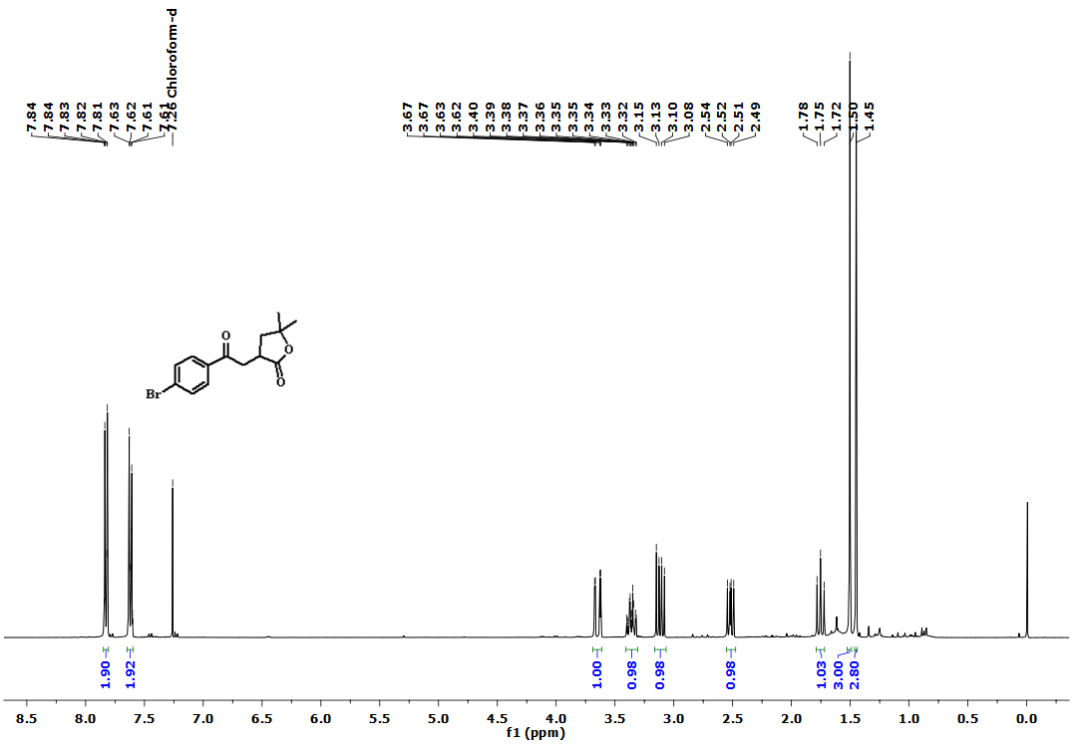


Figure 129: ^{1}H NMR of compound **109f**

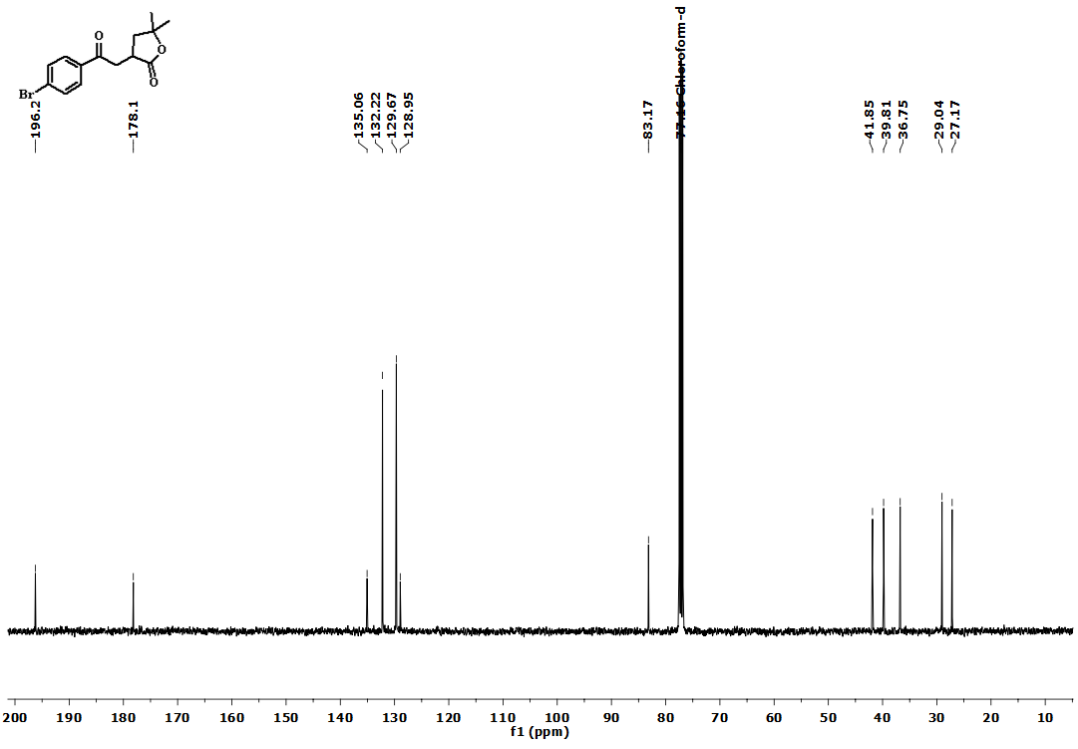


Figure 130: ^{13}C NMR of compound **109f**

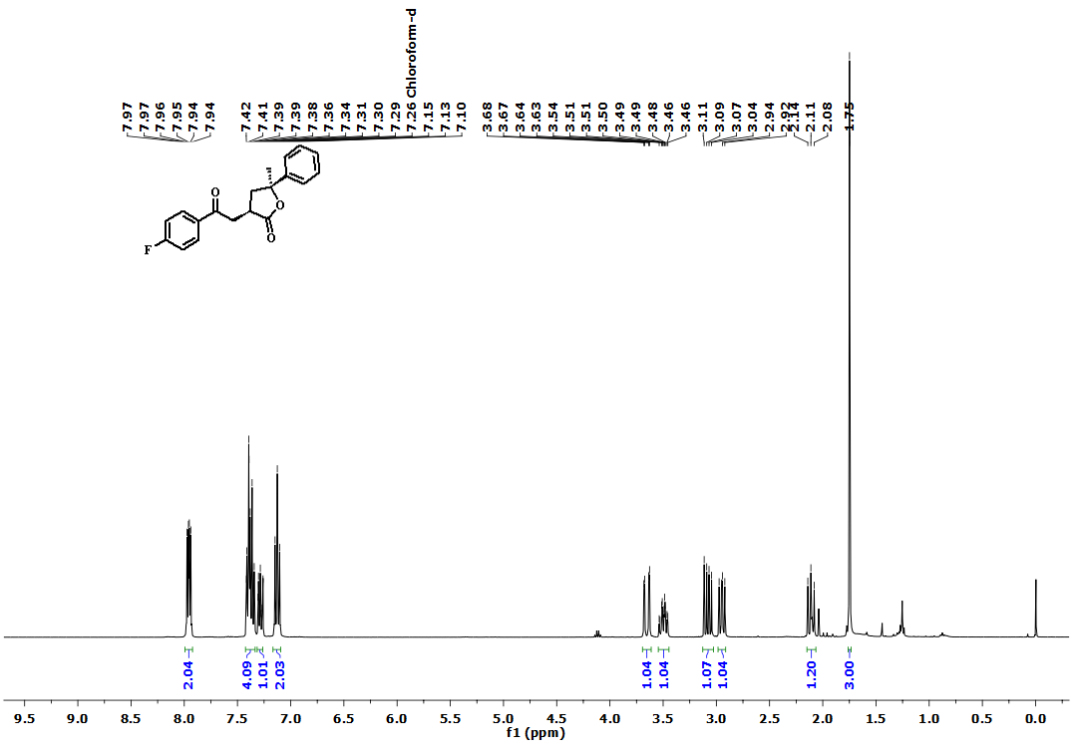


Figure 131: ^{1}H NMR of compound **109h**

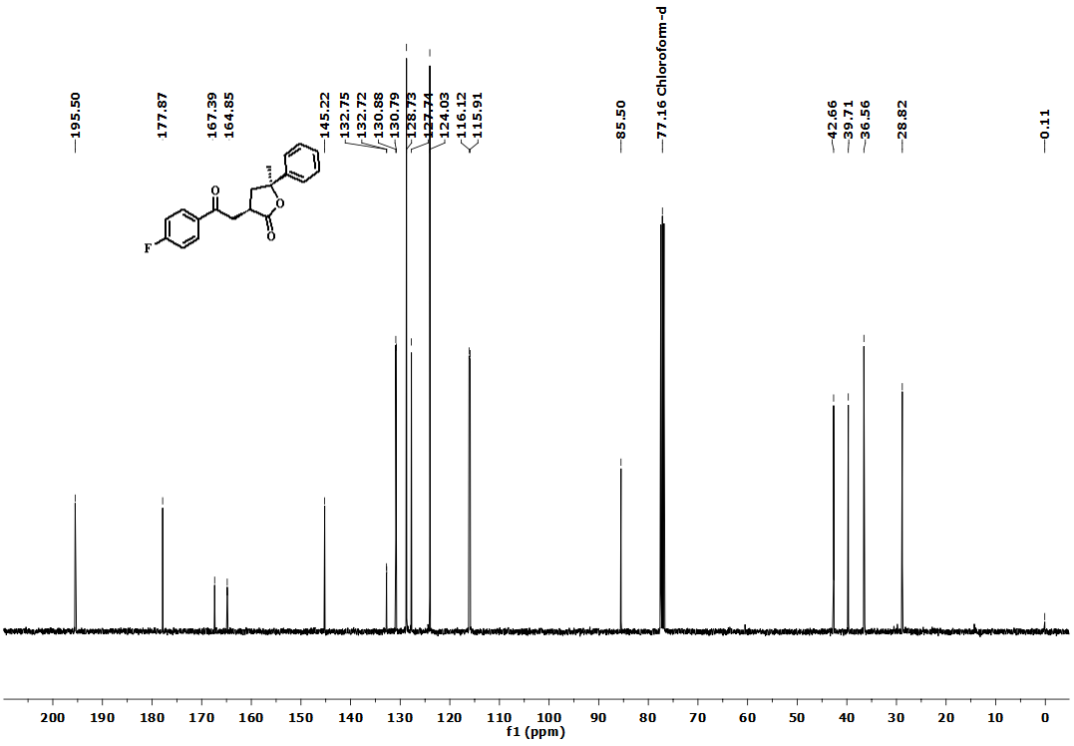


Figure 132: ^{13}C NMR of compound **109h**

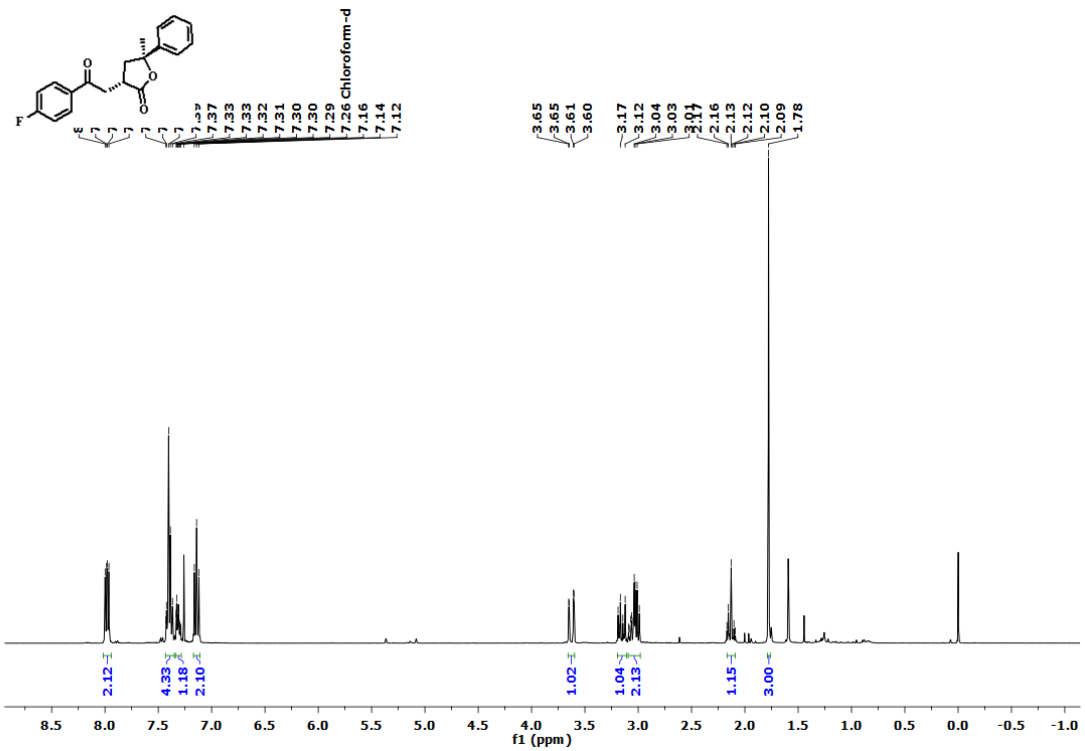


Figure 133: ^{1}H NMR of compound **109h'**

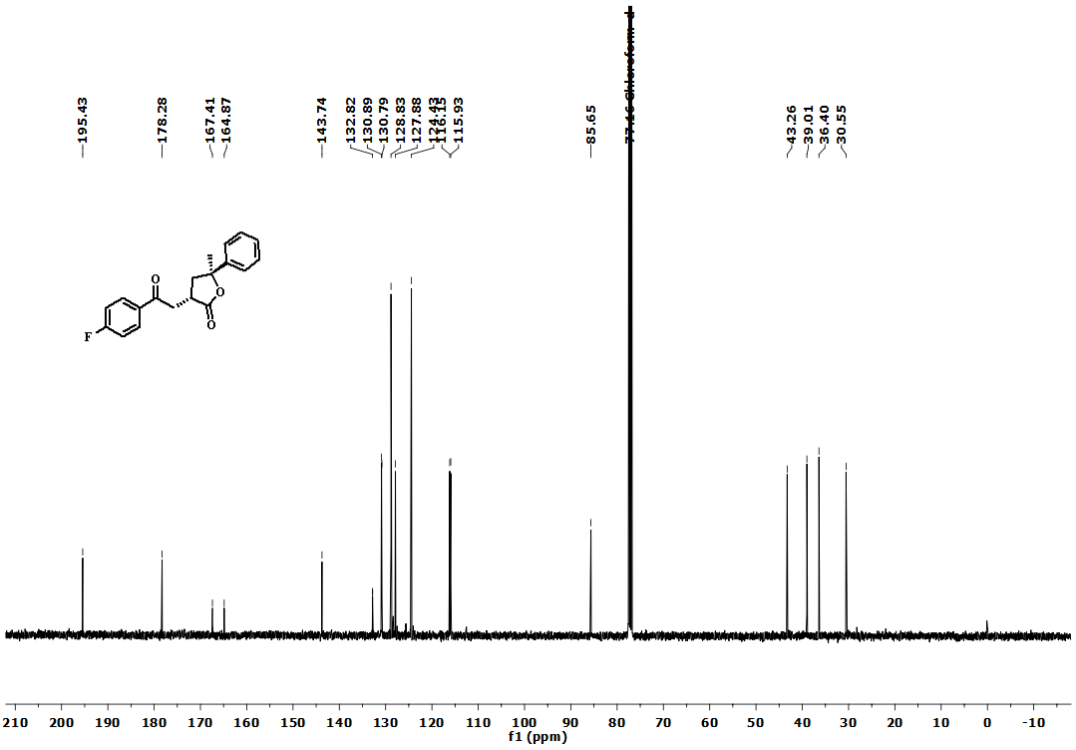


Figure 134: ^{13}C NMR of compound **109h'**

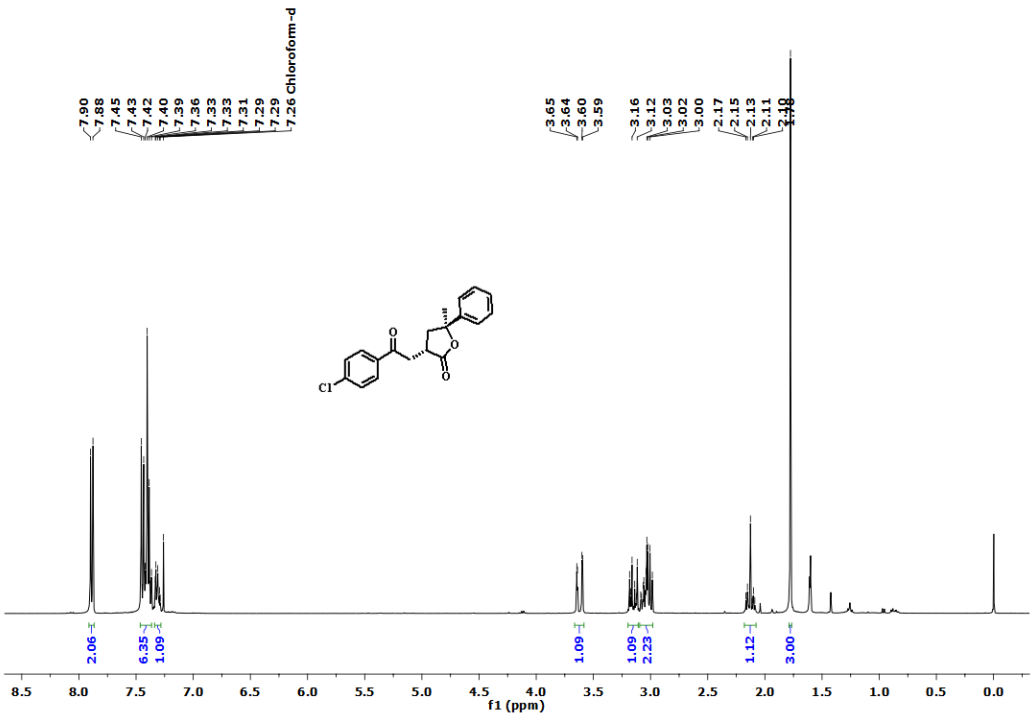


Figure 135: ^{1}H NMR of compound **109i'**

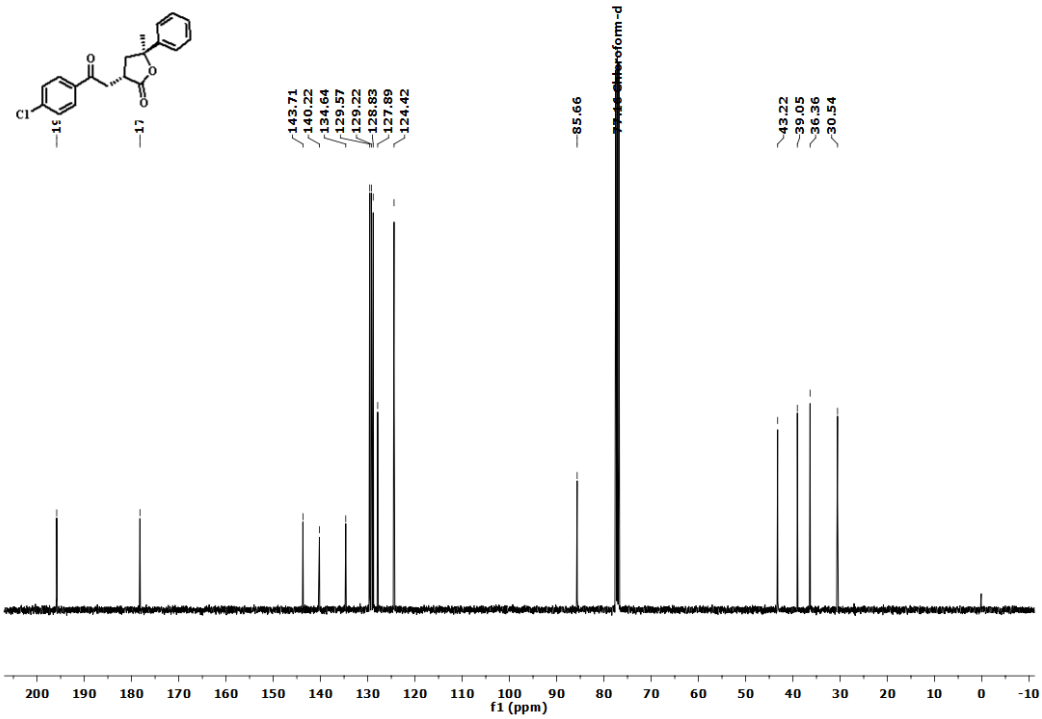


Figure 136: ^{13}C NMR of compound **109i'**

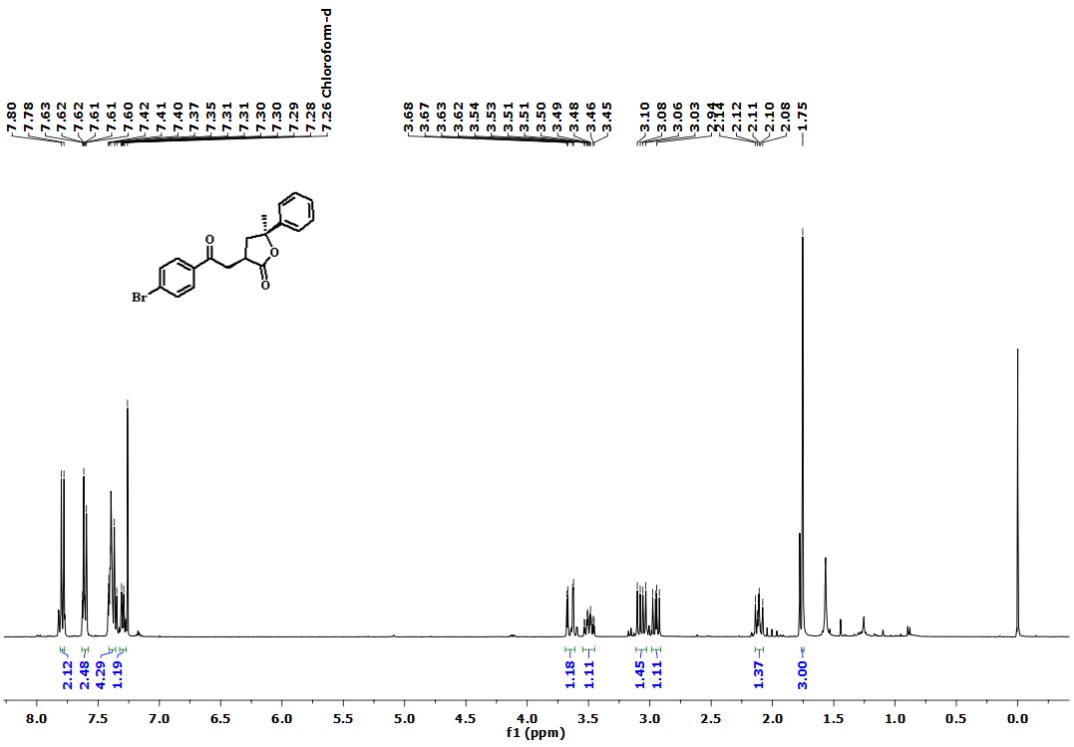


Figure 137: ^{1}H NMR of compound **109j**

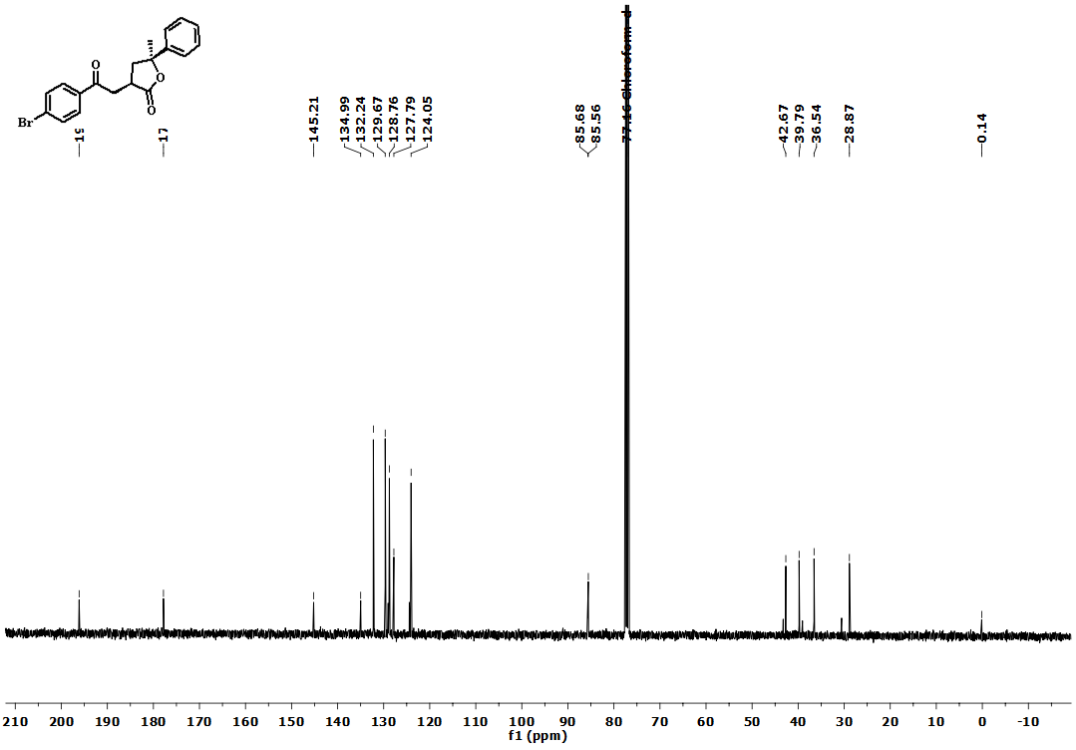


Figure 138: ^{13}C NMR of compound **109j'**

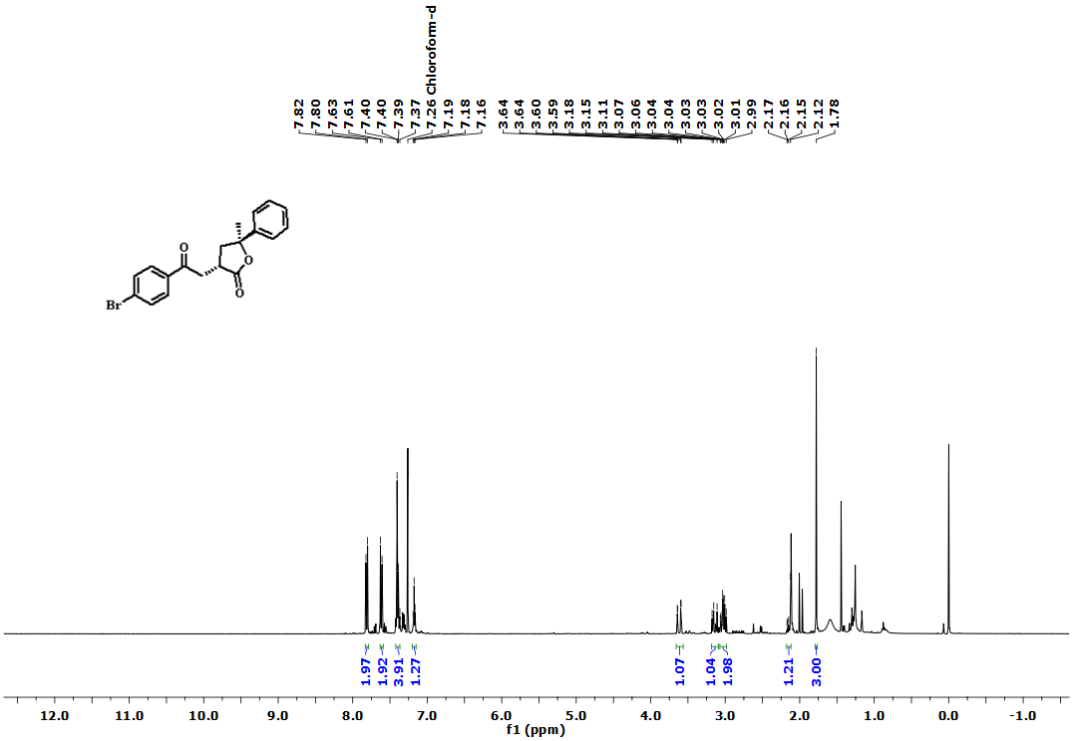


Figure 139: ^{1}H NMR of compound **109j'**

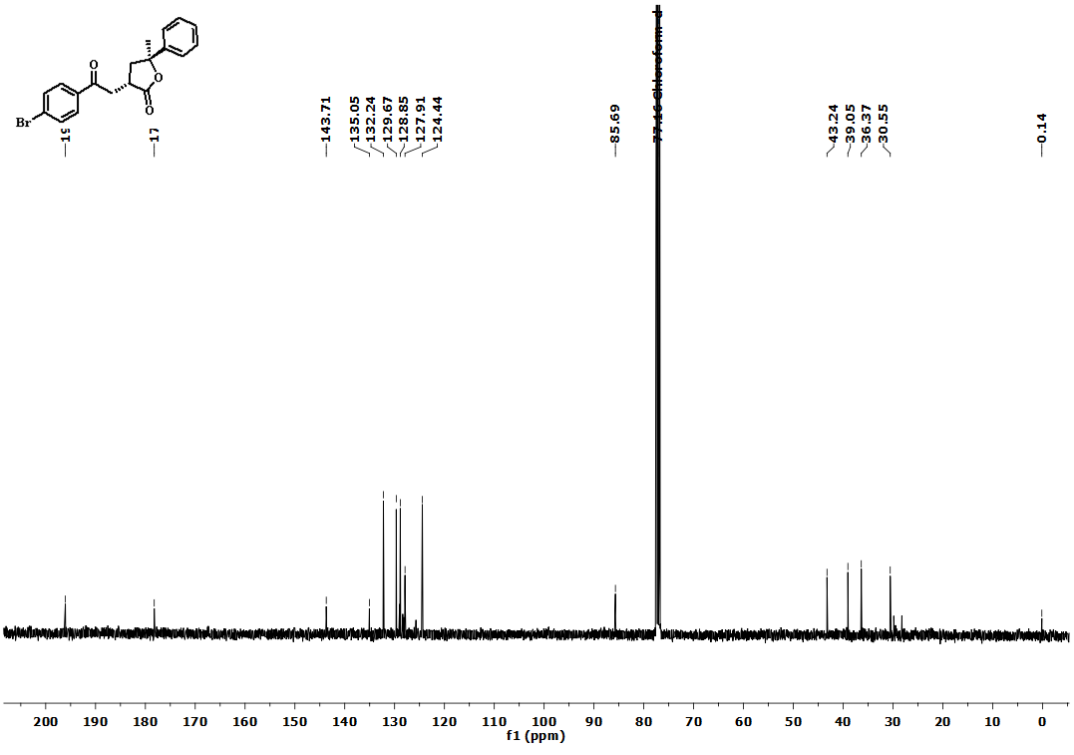


Figure 140: ^{13}C NMR of compound **109j'**

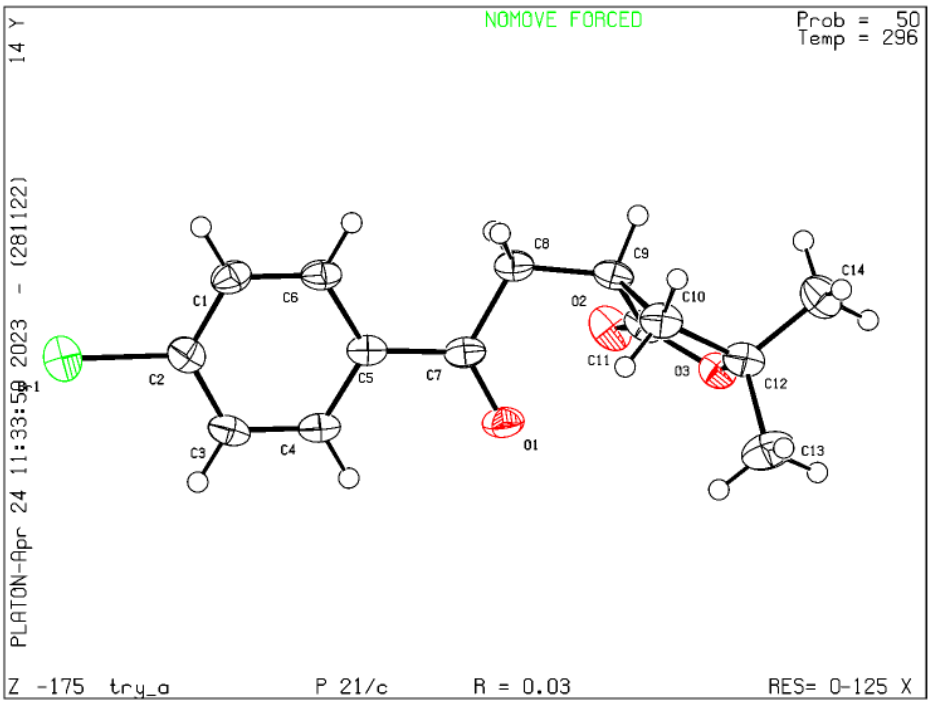


Figure 141: ORTEP diagram of **109f**

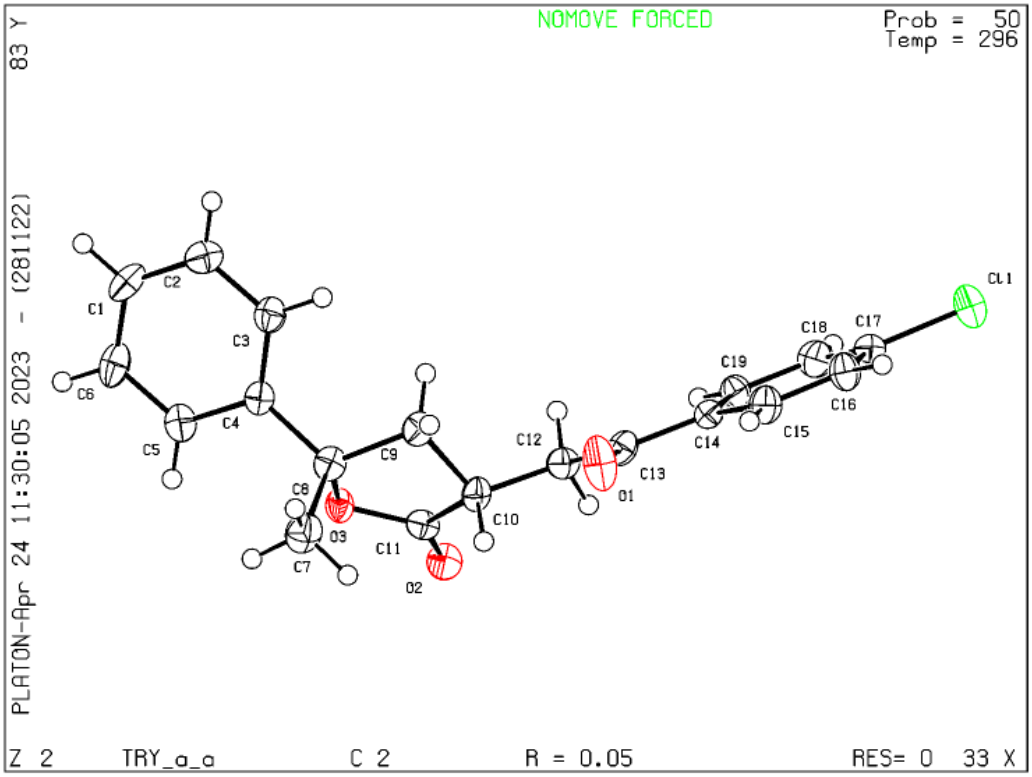


Figure 142: ORTEP diagram of **109j**

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LIST OF PUBLICATION

1. **Mohanta, N**.; Samal, P. P.; Krishnamurty, Sailaja, and Gnanaprakasam, B. $FeCl_2$-Catalyzed Rearrangement of Aryl Peroxyoxindole into 1,3-Benzooxazin-4-one. *Adv. Synth.Catal*. **2023**, *365*, 515–521.
2. **Mohanta, N**.; Pandey, A. M.; Mondal, S. and Gnanaprakasam, B. Catalyst Assisted Selective Vinylation and Methylallylation of Quaternary Carbon Centre by using *tert*-Butyl Acetate. (Accepted in *J. Org. Chem., doi.org/10.1021/acs.joc.2c03072).*
3. **Mohanta, N.;** Nair, K.; Sutar, D. V. and Gnanaprakasam, B. A continuous-flow approach for the multi-gram scale synthesis of C2-alkyl- or β-amino functionalized 1,3-dicarbonyl derivatives and ondansetron drug using 1,3-dicarbonyls**.** *React. Chem. Eng.* **2020**, *5,* 1501.
4. **Mohanta, N.;** Chaudhari, M. B.; Digrawal, N. K. and Gnanaprakasam, B. Rapid and Multigram Synthesis of Vinylogous Esters under Continuous Flow: An Access to Transetherification and Reverse Reaction of Vinylogous Esters. *Org. Process Res. Dev.* **2019**, *23*, 1034.
5. Pandey, A. M.; Digrawal, N. K.; **Mohanta, N.;** Jamdade, A.; Chaudhari, M. B.; Bisht G. S. and Gnanaprakasam, B. Catalytic Acceptorless Dehydrogenation of Amino Alcohols and 2-Hydroxybenzyl Alcohols for Annulation Reaction under Neutral Conditions. *J. Org. Chem*. **2021**, *86,* 13, 8805–8828.
6. Anand, S.; Mardhekar, S.; Raigawali, R.; **Mohanta, N.;** Jain, P.; Shanthamurthy, C. D.; Gnanaprakasam, B. and Kikkeri, R. Continuous-Flow Accelerated Sulfation of Heparan Sulfate Intermediates. *Org. Lett.* **2020,** *22,* 3402–3406.
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8. Parvathalu, N.; Agalave, S. G.; **Mohanta, N.** and Gnanaprakasam, B. Reversible chemoselective transetherification of vinylogous esters using Fe-catalyst under additive free conditions**.** *Org. Biomol. Chem*. **2019**, *17,* 3258**.**
9. Bandyopadhyay, D.; Thirupathi, A.; Dhage, N. M.; **Mohanta, N.** and Peruncheralathan, S.; Nickel catalyzed site selective C–H functionalization of α-aryl-thioamides**.** *Org. Biomol. Chem*. **2018**, *16,* 6405.

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Rapid and Multigram Synthesis of Vinylogous Esters under Continuous Flow: An Access to Transetherification and Reverse Reaction of Vinylogous Esters

Nirmala Mohanta, Moreshwar B. Chaudhari, Naveen Kumar Digrawal, and Boopathy Gnanaprakasam*

Department of Chemistry, Indian Institute of Science Education and Research, Pune 411008, India

Supporting Information

ABSTRACT: An environmentally benign approach for the synthesis of vinylogous esters from 1,3-diketone and its reverse reaction under continuous-flow has been developed with alcohols in the presence of inexpensive Amberlyst-15 as a catalyst. This methodology is highly selective and general for a range of cyclic 1,3-dicarbonyl compounds which gives a library of linear alkylated and arylated vinylogous esters in good to excellent yield under solvent and metal free condition. Furthermore, the long-time experiment in a continuous-flow up to 40 h afforded 8.0 g of the vinylogous ester with turnover number (TON) = 28.6 and turnover frequency (TOF) = 0.715 h^{-1} using Amberlyst-15 as a catalyst. Furthermore, a continuous-flow sequential transetherification of vinylogous esters with various alcohols has been achieved in high yield. Reversibly, this vinylogous ester was deprotected or hydrolyzed into ketone using environmentally benign water as a solvent and Amberlyst-15 as a catalyst under continuous-flow process.

KEYWORDS: *vinylogous esters, transetherification, vinylogous ethers hydrolysis, reverse reaction, continuous-flow reaction, Amberlyst-15*

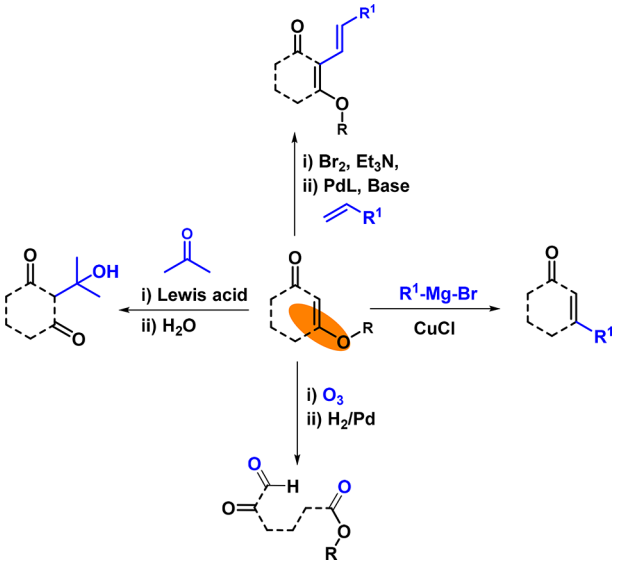
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1. INTRODUCTION

Functional group interconversions (FGIs) are the imperative reactions in organic synthesis and among the most common synthetic methods. The development of a new strategy for the protection/deprotection of functional groups in chemical synthesis remains an attractive research area, and a wide array of synthetic methodologies continue to be reported.[1] The vinylogous esters are considered as a versatile and reactive key intermediate in many chemical transformations due to their ability to undergo FGI.[2] Numerous studies have been performed to convert β-keto-vinylogous esters into other functional groups, such as C−C bond formation[3] (coupling reactions), ene reaction,[4] cycloaddition,[5] oxidation,[6] homologation,[7] acid catalyzed reactions with acetals or ketals to give aldol-type adducts, and other reactions[7] (Scheme 1). The widespread applications in the synthesis of natural products,[8] bioactive molecules,[9] and materials[10] make β-keto-vinylogous esters promising precursor in synthetic organic chemistry. A plethora of synthetic methods are available for the synthesis of β-keto-vinylogous esters starting from diketo compounds and alcohols using a stoichiometric or catalytic pathway.[11] The use of stoichiometric strong organic acids, higher temperature, and longer reaction time precludes their use with the substrate bearing sensitive functionalities.

The vinylogous esters are reactive functional groups toward the acids (Brönsted and Lewis), which has been prepared in the presence of stoichiometric/catalytic acid with great care; i.e., continuous removal of water being produced in this transformation is required. This is due to the equilibrium between ketone and vinylogous ester under prolonged acidic reaction condition in the presence of water. Further, this reversible nature of the vinylogous esters renders a direct impact on the yield and stability of the vinylogous esters in the course of the reaction.

Scheme 1. Versatility of Cyclic Vinylogous Ester



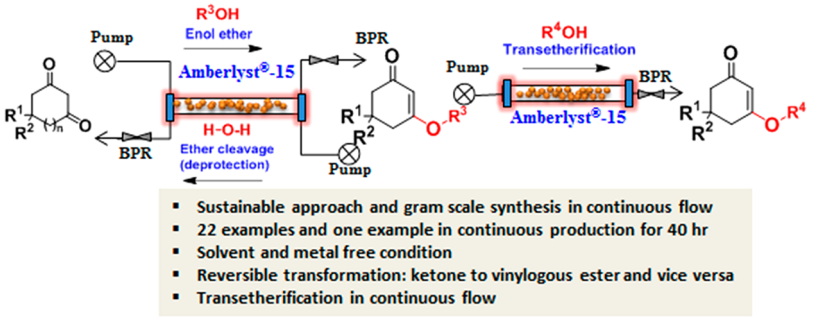
Continuous-flow chemistry has emerged as a powerful process intensification technology for various synthetic transformations[12] which comprises several advantages includes precise control of reaction time, temperature, concentration, and stoichiometry. As a result, it obeys the many green chemistry principles such as reduced energy requirements and

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Scheme 2. Present Studies on the Synthesis of Enol Ether, Reverse Reaction, and Transetherification in Continuous-Flow



time and minimizes exposure to hazardous chemicals or reactive intermediates and avoids the generation of unwanted byproducts and waste. Consequently, manufacturing of bulk chemicals, pharmaceuticals, and petrochemicals has been carried out in a continuous passion. This machine-assisted approach is very useful to avoid labor-intensive practices and gives access to work on a 24/7 regime. Furthermore, it permits access of a safer and greener route along with on-demand synthesis as a choice.

Thus, we envision the development of the reactive vinylogous ester synthesis under continuous-flow in shorter duration, which can shift the equilibrium into vinylogous ester avoiding the prolonged exposure to hydrated acidic condition. To overcome the drawbacks mentioned above, catalysis integrated with continuous-flow often is the superior choice due to greater selectivity, increased safety, improved yield, and expeditious nature. In an extension of our efforts to develop a greener and efficient process for the valuable chemical synthesis, we have anticipated the synthesis of chemically important intermediate vinylogous esters in a continuous-flow.

Herein, we report Amberlyst-15, as the H^+ source, catalyzed the synthesis of β-keto-vinylogous esters, transetherification, and their reverse reaction in continuous-flow using simple and ample precursors such as diketo compounds, alcohols, and water (Scheme 2). To the best of our knowledge, this is the first report on the selective synthesis of β-vinylogous esters in a continuous-flow process using Amberlyst-15 as a supported catalyst.

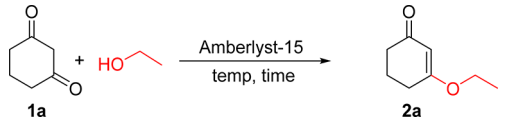
2. RESULTS AND DISCUSSION

In the course of our investigation, we have chosen cyclohexane-1,3-dione and ethanol as a model substrate. Initially, we do not observe any product in control experiments which were performed in the absence of any acidic source at room temperature and 80 °C (Table 1, entries 1 and 2). The addition of 25 mg of Amberlyst-15 in 0.5 mmol of ketone and 2 mL of ethanol at room temperature afforded **2a**, in 72% isolated yield (Table 1, entry 3). Higher yield for the formation of **2a** was observed when increasing the catalyst concentration to 50 mg at room temperature and heating at 60 °C (Table 1, entries 4 and 5).

However, a slight improvement in yield (88%) was observed when the reaction mixture was heated at 80 °C (Table 1, entry 6). With these optimized conditions in the batch, we sought to transform them in a continuous-flow (see Figure 1).

Initial optimization was performed at room temperature with one and two runs with 0.3 mL flow rate and 0.2 M concentration, which provided 48% and 93% isolated yield of the product **2a** (Table 2, entries 1 and 2). To check the effect

Table 1. Optimization of Reaction Conditions in Batch[a]



1a 2a

entry	catalyst (mg)	temp (°C)	time	yield (%)
1		rt[b]	5 h	no reaction
2		80	5 h	no reaction
3	25	rt	5 h	72
4	50	rt	5 h	76
5	50	60	5 h	82
6	50	80	5 h	88

[a]Reaction condition: 1,3-cyclohexanedione (0.5 mmol), Amberlyst-15, and ethanol (2 mL) were stirred at the specified temperature. [b]rt: room temperature.

of temperature, flow rate, and concentration various experiments were performed, and results are summarized in Table 2 (entries 3–9). For instance, 0.1 M solution of **1a** in ethanol at 0.3 mL flow rate at 60 °C afforded 95% of product **2a** (Table 2, entry 3). Later, a decrease in yield was observed when the concentration increased to 0.2 M at 80 and 100 °C (Table 2, entries 4 and 5). Finally reaction with 0.3 mL flow rate and 0.1 M solution at 80 °C proved to be the best-optimized condition which afforded **2a** (99%) in 4.6 min of residence time (t_R) (Table 2, entry 8). The use of other resin viz Amberlite-120 afforded **2a** in 72% yield (Table 2, entry 10).

With these investigations, the generality of the reaction was explored with a variety of alcohols using different diketo compounds. The reaction of cyclohexane-1,3-dione with linear alcohols such as ethanol, methanol, propanol, butanol, hexanol, and octanol afforded an excellent yield of the products (Scheme 3, **2a**–**2f**). Furthermore, the reaction of secondary alcohol isopropyl alcohol with the diketone afforded **2g** in excellent yield (Scheme 3). To our delight, not only is this reaction restricted to aliphatic alcohols, but also the reaction of benzyl alcohol and allyl alcohol with cyclohexane-1,3-dione provided 3-(benzyloxy)cyclohex-2-en-1-one **2h** and 3-(allyloxy)cyclohex-2-en-1-one **2i** in very good yield. Additionally, we have extended the reaction scope with 5,5-dimethylcyclohexane-1,3-dione and cyclopentane-1,3-dione using linear or branched alcohols to yield **2j**–**2p** in excellent yield. However, the reaction of isatin with ethanol and propanol provided 3,3-dialkoxyindolin-2-one **2q** and **2r** in very good yield (Scheme 3). Interestingly, reaction of acyclic 1,3-dicarbonyl compounds with methanol and propanol under similar reaction condition afforded the respective ketal **2s** and **2t** in 86% and 96% yield, respectively (Scheme 3).

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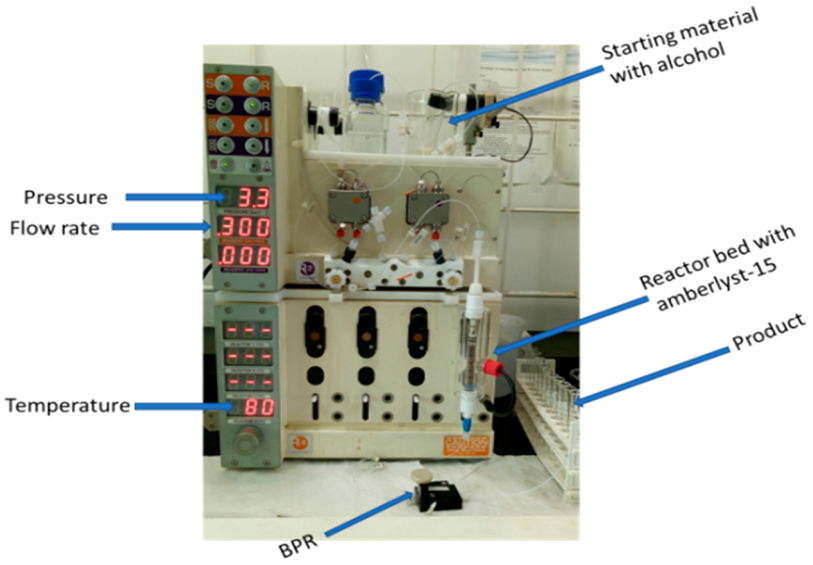
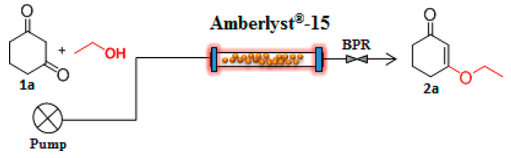


Figure 1. Full setup for continuous-flow reactor.

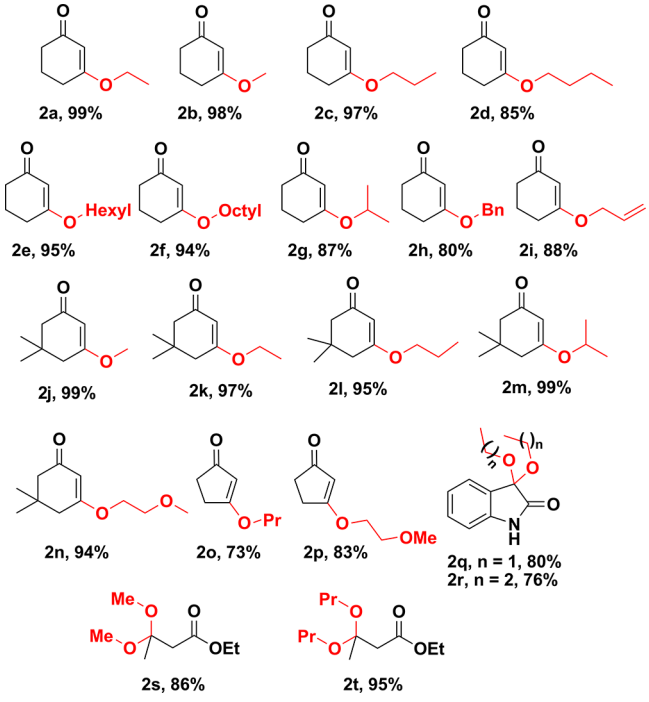
Table 2. Optimization of Reaction Conditions in Continuous-Flow[a]



entry	flow rate (mL)	temp (°C)	substrate concentration (M)	t_R/number of runs	yield (%)
1	0.3	rt	0.2	4.6/1	48
2	0.3	rt	0.2	4.6/2	93
3	0.3	60	0.1	4.6/1	95
4	0.3	80	0.2	4.6/1	73
5	0.3	100	0.2	4.6/1	86
5	0.2	80	0.2	6.8/1	93
6	0.2	100	0.2	6.8/1	88
7	0.3	80	0.15	4.6/1	83
8	0.3	80	0.1	4.6/1	99
9	0.5	80	0.1	2.7/1	78
10[b]	0.3	80	0.1	4.6/1	72

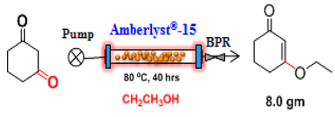
[a]Reaction condition: 0.1 molar solution of **1a** in ethanol was prepared and was flown through the 6.6 × 150 mm Omnifit packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height) (Vapourtec R-series) at a specified temperature; t_R= residence time in minutes. [b]Reaction carried out using Amberlite-120. The mentioned yields are isolated yields.

Scheme 3. Substrate Scope for β-Keto Enol Ether in Continuous-Flow[a]



[a]Reaction condition: 0.1 molar solution of 1,3-diketone **1** in alcohol was prepared, and 0.3 mL/min was flown through the 6.6 × 150 mm Omnifit packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, residence time t_R = 4.6 min) (Vapourtec R-series) at 80 °C.

Scheme 4. Gram-Scale Synthesis in Continuous-Flow



To show the stability and efficiency of the Amberlyst-15, we have performed a long-time experiment in continuous-flow. The substrate **1a** and ethanol were chosen as a model substrate for this purpose. For instance, 72.12 mmol of reactant was pumped continuously for 40 h with a flow rate of 0.3 mL/min to afford 57.22 mmol of product with TON (turnover number) = 28.61 and TOF (turnover frequency) = 0.715 h^{-1} (Scheme 4). The conversion of the product **2a** was determined by using ^{1}H NMR, clearly indicating that up to 20 h of continuous-flow synthesis led to compound **2a** in >94% yield (Figure 2). Continuing the synthesis after 20 h, the yield is slightly decreased to 90% after 40 h. Periodically, the yield of the continuous-flow synthesis of **2a** was monitored by ^{1}H NMR and is accounted in Figure 3. Although we have stopped our reaction after 40 h, the catalyst still affords 90% of the product **2a**. This clearly shows that the Amberlyst-15 is still

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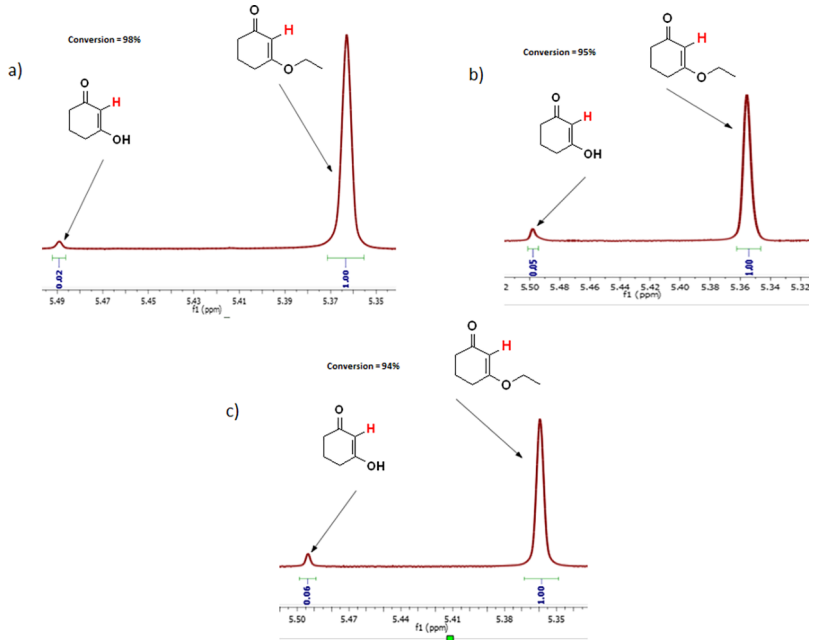


Figure 2. ^{1}H NMR monitoring of the reaction in long-run experiments: (a) after 2 h, (b) after 10 h, and (c) after 20 h.

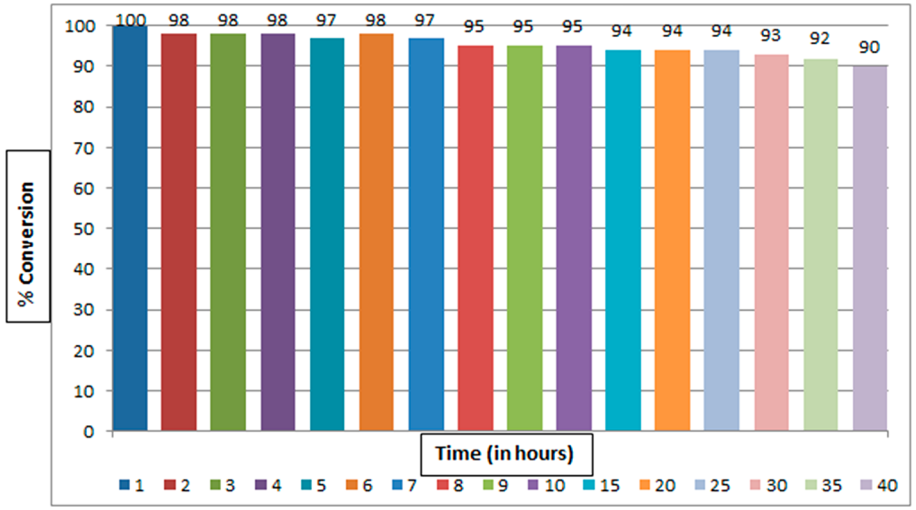


Figure 3. Continuous-flow synthesis of **2a** over 40 h.

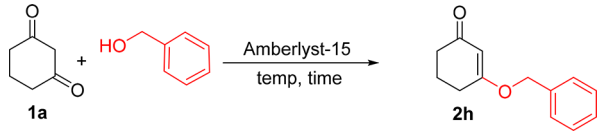
active for this transformation. Although it is known that there is significant loss in activity of Amberlyst-15 for the other chemical transformation,[15,16] we found that very nominal loss in activity over a longer period of the reaction.

To avoid excess usage of special alcohols, further optimizations of the reaction especially for the highly viscous alcohols were performed using cosolvent, and the optimized results are shown in Table 3. Under these optimized conditions, alcohol bearing sensitive alkyne functionality was worked efficiently to afford 3-(but-2-yn-1-yloxy)cyclohex-2-en-1-one **2u** in 76% yield (Scheme 5). A similar reaction with cyclopentane-1,3-dione afforded the respective vinylogous ester **2v** in 65% yield. Secondary alcohols such as 3-pentanol, 2-hexanol, and 1-phenylethanol were also successfully reacted well to afford *β*-vinylogous esters **2w**−**2y** in moderate yield (Scheme 5).

Use of water as a reagent as well as solvent for the chemical transformation is one of the attractive goals in green chemistry. In this aspect, the reversible transformation of vinylogous ester to the dicarbonyl compounds is one of the important transformations catalyzed by acid.[13] Therefore, we sought to achieve the reversible transformation, i.e., selective and milder hydrolysis of vinylogous ester under an environmentally benign continuous-flow approach. To achieve hydrolysis of vinylogous ester under continuous-flow, a set of reactions was attempted (Scheme 6). Thus, vinylogous ester **2a** was allowed to hydrolyze in the presence of water, leading to 10% yield after 4 h under batch condition. Upon addition of stoichiometric Amberlyst-15 in the same reaction, a complete conversion of **2a** was observed to ketone **1a** after 3 h. Interestingly, vinylogous esters **2a** and **2b** are highly soluble in water, which were flown (0.1 M, 0.1 mL/min, t_R = 13.6 min) in to the Omnifit column reactor prepacked with the Amberlyst-15, resulting in >98% conversion to ketone (Scheme 6). However, compounds **2c**, **2d**, **2l**, and **2o** were not soluble in water. As a result of vinylogous ester being

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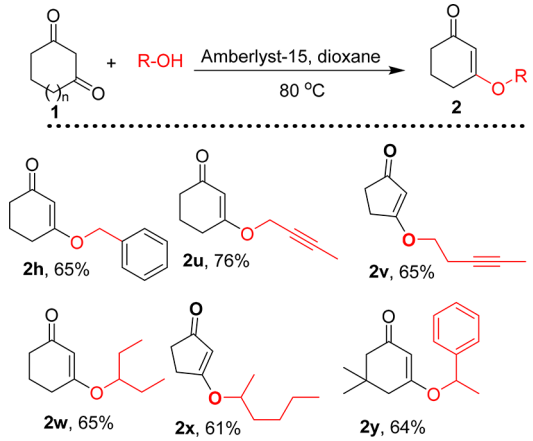
Table 3. Optimization of Reaction Conditions in Continuous-Flow



entry	concn of 1a	concn of benzyl alcohol	solvent	flow rate in mL	time	yield (%)
Batch Conditions (Concentration in mmol)[a]						
1	0.5	0.5	1,4-dioxane		1.5 h	80
2	0.5	0.5	toluene		1.5 h	90
3	0.5	0.5	THF		1.5 h	75
Flow Conditions (Benzyl Alcohol Concentration in M)[b]						
4	1 mmol	0.1 M	1,4-dioxane	0.3	4.6 min	trace
5	1 mmol	0.3 M	1,4-dioxane	0.3	4.6 min	50
6	1 mmol	0.5 M	1,4-dioxane	0.3	4.6 min	65

[a]Reaction conditions: 0.5 mmol of **1a** + 0.5 mmol of benzyl alcohol and 2 mL of solvent + Amberlyst-15 (50 mg) were heated at 80 °C in a resealable tube for 2 h. [b]Reaction conditions: 1 mmol of **1a** was dissolved in 0.1 M, or 0.3, or 0.5 M solution of benzyl alcohol and was flown through the Omnifit packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, for residence time t_R, see table) (Vapourtec R-series) at 80 °C.

Scheme 5. Substrate Scope for β-Keto Enol Ether in Continuous-Flow[a]

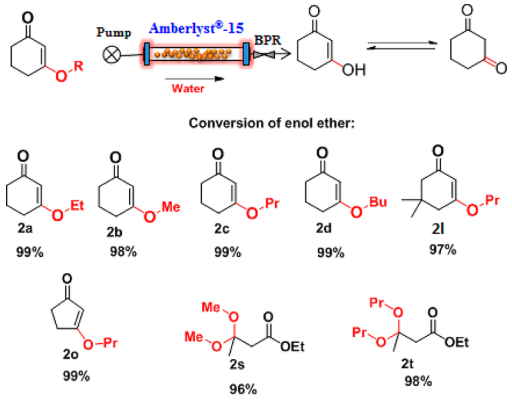


[a]Reaction condition: 1 mmol of **1a** was dissolved in 0.1 M solution of alcohol in 1,4-dioxane (10 mL) and was flown through the 6.6 × 150 mm Omnifit packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, residence time t_R = 4.6 min) at 80 °C.

insoluble in water, these compounds were dissolved in a 1:1 mixture of water and ACN and flown into the reactor affording the 48−52% conversion of the ketone under continuous-flow (Scheme 6). Interestingly, a water suspension of these compounds was flown into the Omnifit column reactor prepacked with the Amberlyst-15, which led to rapid hydrolysis to afford the 1,3-diketone in >95% yield. Similarly, ketal derivatives **2s** and **2t** were also flown into the column reactor for the hydrolysis to give the respective dicarbonyl compounds in >96% and 98% yield.

Transetherification[14] is an important transformation in organic synthesis due to its reactivity and easy accessibility. Developing an environmentally benign approach for the transetherification is an important aspect in the chemical

Scheme 6. Continuous-Flow Hydrolysis of Vinylogous Ester Using Water and Amberlyst-15[a]



[a]Reaction condition: 0.1 M solution of **2** in water was flown (0.1 mL/min) through the 6.6 × 150 mm Omnifit packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height) at room temperature (residence time t_R = 13.6 min).

process. Thus, transetherification using vinylogous ester under continuous-flow mode was investigated (Scheme 7). For this study, vinylogous ester **2b** was chosen as a model substrate, and a set of conditions were attempted. The optimized condition for the transetherification was established by flowing 0.3 mL/min of the 0.1 M solution of vinylogous ester in ethanol to the Omnifit column reactor prepacked with the Amberlyst-15 and heated at 80 °C to afford the vinylogous ester **2a** in 92% yield (Scheme 7). Under similar experimental condition and flow rate, vinylogous ester **2a** was transetherified using propanol solvent to give the vinylogous ester **2c** in 93% yield (Scheme 7). Similarly, continuous transetherification was carried out on the vinylogous ester **2e** in 84% yield (for two consecutive transetherification steps) in continuous-flow mode. Finally, the hexyl group exchanged with the methyl via transetherification of vinylogous ester **2e** in methanol under a continuous-flow process to afford the corresponding vinylogous ester **2b** in 92% yield (Scheme 7). Furthermore, this transetherification of vinylogous ester was performed in gram under continuous-flow.

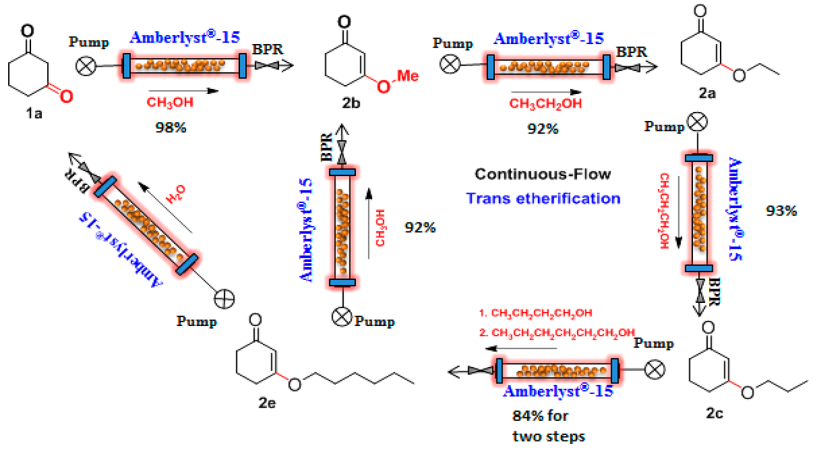
The mechanism of the Amberlyst-15 mediated transetherification of vinylogous ester is proposed in Scheme 8. Initially, there is protonation of the C═O of the cyclic vinylogous ester **A** to give the intermediate **B**. The absence of the C═O functional group of the reaction mixture in the IR spectra clearly indicates the formation of the intermediate **B** (Figure 4ii). The intermediate **B** is resonance stabilized to generate the intermediates **C** and **D**. Further, the oxonium intermediate **D** is attacked by the alcohol to afford the ketal intermediate **E**. The HRMS spectra of the Amberlyst-15 mediated reaction of **A** and *n*-propanol show a peak at *m*/*z* 200.1308 confirming the formation of the intermediate **E** (Figure 4iii). Finally, the keto−enol tautomerism assisted elimination of ethanol from the intermediate **E** to form the transetherified product **F**.

3. CONCLUSIONS

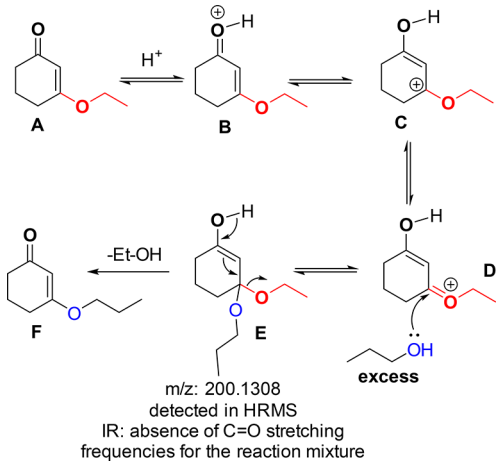
In conclusion, we have developed an environmentally benign approach for the synthesis of vinylogous ester from commercially available 1,3-diketone using Amberlyst-15 under continuous-flow mode. This process has been

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Scheme 7. Transetherification of Vinylogous Ester Using Alcohols under Continuous-Flow



Scheme 8. Plausible Mechanism for the Transetherification of Vinylogous Ester Using Alcohol



generalized with a variety of vinylogous esters tethered by aliphatic, alkene, alkyne, and aromatic substituents with rapid access (t_R = 4.6 min) in excellent yield with high selectivity. The long-time studies in a continuous-flow up to 40 h revealed the efficiency of the Amberlyst-15 catalyst with TON= 28.6 and TOF= 0.715 h^{-1}, which generated 8 g of vinylogous ester in 40 h continuous synthesis. This methodology was also extended for continuous transetherification of vinylogous ester to another vinylogous ester in higher yield under continuous-flow mode. Interestingly, the possible reverse reaction of vinylogous esters to ketones (hydrolysis of vinylogous ester) was achieved effectively under a continuous-flow process. The mechanism for the transetherification was also proposed with the experimental evidence.

4. EXPERIMENTAL SECTION

4.1. General Information and Data Collection. All the chemicals were purchased from Sigma-Aldrich and SD Fine Chemicals and used without further modification. All solvents were purchased from Rankem and Finar Chemicals. Deuterated solvents were used as received. Column chromatographic separations were performed over 100−200 silica-gel. Visualization was accomplished with UV light and/or PMA stain followed by heating. The flow chemistry experiments were carried on Vapourtec R-series with glass column (Omntifit, 6.6 × 150 mm). ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz, respectively, using a Bruker 400 MHz or JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments are as follows: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were obtained with a Waters-synapt G2 instrument using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E Fourier-transform infrared spectrometer.

4.1.A. General Procedure for Preparation of Vinylogous Esters Compounds by Using Amberlyst-15 under Batch Reaction. In a 20 mL glass tube, 1,3-cyclohexadione (56 mg, 0.5 mmol) and Amberlyst-15 (50 mg) were added to alcohol (2 mL), and the tube was sealed using a crimper. The reaction mixture was stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was filtered and washed with DCM. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography purification (EtOAc: *n*-hexane = 25:75) affording cyclic vinylogous esters ether as a pure compound **2**. A similar reaction protocol was followed for the synthesis of other cyclic vinylogous ester derivatives by taking 1,3-cyclic diketone (0.5 mmol) and 50 mg of Amberlyst-15 (50 mg).

4.1.B. General Procedure for Preparation of Vinylogous Esters by Using Amberlyst-15 under Continuous-Flow. A 0.1 M solution of the 1,3-cyclodiketone (1 mmol in 10 mL of alcohol) was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 °C temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc: *n*-hexane = 25:75) purification affording corresponding vinylogous esters compounds.

4.1.C. General Procedure for Preparation of Vinylogous Esters Using Alcohol and 1,3-Diketone in the Presence of Amberlyst-15 under Continuous-Flow. A 0.5 M solution of alcohol was made with 1,4-dioxane. A 0.1 M solution of the 1,3-cyclodiketone (1 mmol in 10 mL of 0.5 M alcohol solution) was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 5.5 cm after passing solvent) of bed heated at 80 °C temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure

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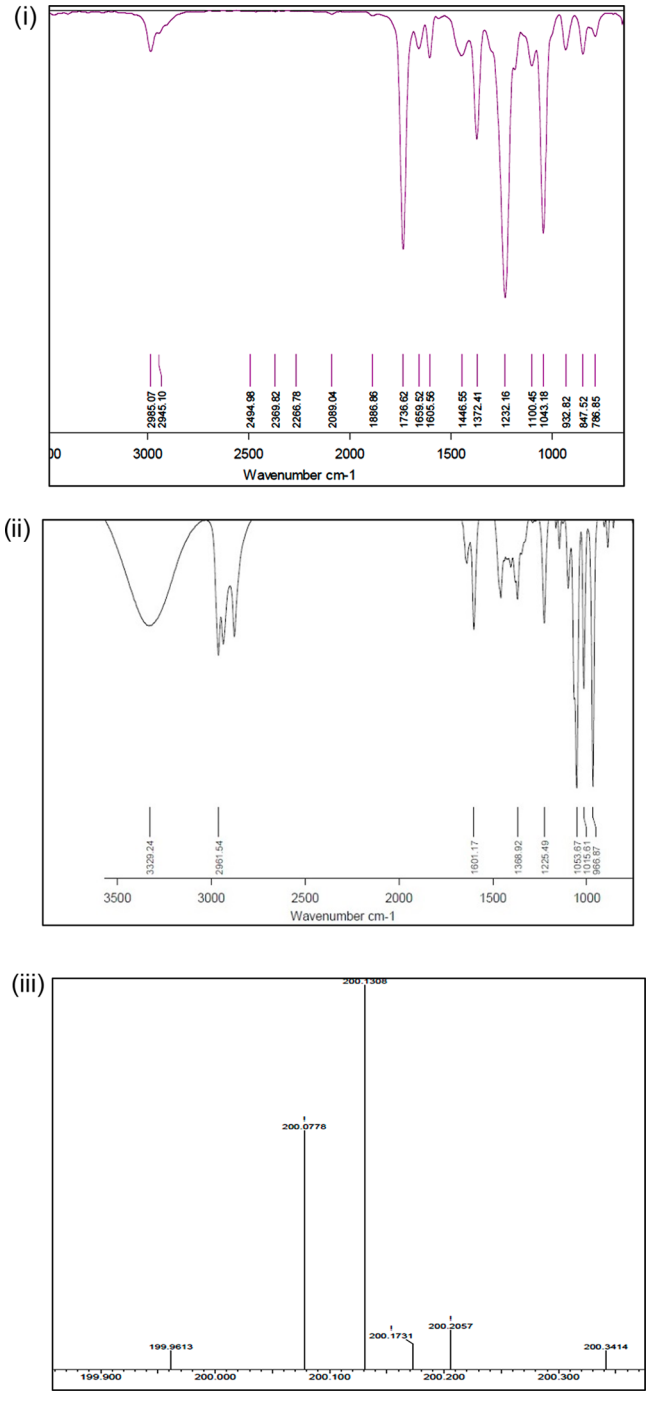


Figure 4. Mechanistic evidence: (i) IR spectra of **2a**; (ii) IR spectra of transetherification reaction mixture; and (iii) HRMS spectra of reaction mixture.

followed by column chromatography (EtOAc: *n*-hexane = 10:90) purification affording corresponding vinylogous esters.

4.1.D. General Procedure for Transetherification of Vinylogous Esters Using Alcohol in the Presence of Amberlyst-15 under Continuous-Flow. A 0.1 M solution of 3-ethoxycyclohex-2-en-1-one (**2a**, 4 mmol) was prepared in *n*-propanol (30 mL) and flown (0.3 mL/min) through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 °C temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure to get the vinylogous ester product. Further, the residue made a 0.1 M solution in *n*-butanol, and the above procedure was repeated to afford corresponding vinylogous esters. In a similar manner, sequential transetherification of vinylogous esters has been achieved using solvent *n*-hexanol, methanol, and ethanol. In all the reactions, the starting material of vinylogous ester was completely converted to other vinylogous esters.

4.1.E. General Procedure for Hydrolysis of Vinylogous Esters under Continuous-Flow. A 0.1 M solution vinylogous esters or ketal (0.5 mmol) was prepared in water (5 mL) and flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.2 bar pressure having flow rate 0.1 mL/min. The reaction was monitored by TLC, and the reaction fraction was concentrated in a rotary evaporator to afford 1,3-cyclohexadione.

4.1.F. Study of Lifetime of Catalyst and Gram-Scale Synthesis of Vinylogous Esters. The gram-scale synthesis of vinylogous esters was achieved by using general procedure B (section 4.1.B). A 0.1 M solution of 1,3-cyclohexadione (8.085 g in 720 mL of ethanol) was prepared and flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 °C temperature at 3.3 bar pressure for 40 h. The reaction mixture was monitored periodically by ^{1}H NMR analysis. All the reaction fraction was concentrated in a rotary evaporator to afford 8.112 g of vinylogous esters **2a** as a yellowish oil.

4.1.G. Experimental Procedure for Detection of Intermediate in Transetherification Reaction. In a 20 mL of glass tube, 3-ethoxycyclohex-2-en-1-one (**2a**, 0.5 mmol) was taken in n-propanol (2 mL) followed by Amberlyst-15, and the tube was sealed using a crimper. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly taken in syringe, and the IR and HRMS analysis for the reaction mixture was recorded.

4.1.H. Analytical Data for Products. 3-Ethoxycyclohex-2-en-1-one (**2a**)[16] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL of ethanol) affording 99% (138.5 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.28 (s, 1H), 3.84 (q, J = 6.8 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 2.27 (t, J = 6.8 Hz, 2H), 1.94−1.88 (m, 2H), 1.30 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.78, 177.90, 102.67, 64.15, 36.75, 29.08, 21.25, 14.12. FT-IR: 2954.24, 1728.68, 1598.77, 1412.65, 1314, 1222.42, 1125.60, 1091.52, 769.23, 568.24 cm^{-1}. HRMS (ESI) m/z: calcd for $C_8H_{12}O_2$ $(M + H)^+$, 141.0916; found, 141.0925.

3-Methoxycyclohex-2-en-1-one (**2b**)[17] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL of methanol) affording 99% (124.8 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (s, 1H), 3.69 (s, 3H), 2.40 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 2.01−1.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.99, 178.90, 102.48, 55.75, 36.86, 28.96, 21.36. FT-IR (neat): 2953.87, 2315.29, 1724.89, 1590.46, 1458.78, 1369.83, 1226.41, 1179.69, 1060.78, 753.04, 601.90 cm^{-1}. HRMS (ESI) m/z: calcd for $C_7H_{10}O_2$ $(M + H)^+$, 127.0759; found, 127.0762.

3-Propoxycyclohex-2-en-1-one (**2c**)[18] was synthesized by following the experimental procedure B using 1,3-cyclo-

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hexadione (0.1 M solution in 10 mL of propanol) affording 97% (149.3 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.78 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.33 (t, J = 6.4 Hz, 2H), 2.00−1.93 (m, 2H), 1.78−1.70 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.04, 178.27, 102.81, 70.13, 36.87, 29.16, 22.02, 21.37, 10.52. FT-IR: 2952.28, 1727.07, 1601.11, 1453.93, 1380, 1232.65, 1183.99, 1001.03, 758.03, 597.32 cm^{-1}. HRMS (ESI) m/z: calcd for $C_9H_{14}O_2$ $(M + H)^+$, 155.1072; found, 155.1078.

3-Butoxycyclohex-2-en-1-one (**2d**) was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL of *n*-butanol) affording 85% (142.4 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.79 (t, J = 6.4 Hz, 2H), 2.36 (t, J = 6.4 Hz, 2H), 2.30 (t, J = 6 Hz, 2H), 1.97−1.90 (m, 2H), 1.70−1.63 (m, 2H), 1.43−1.34 (m, 2H), 0.91 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.84, 178.14, 102.73, 68.33, 36.81, 30.58, 29.11, 21.31, 19.19, 13.75. FT-IR (neat): 2954.40, 2879.20, 2313.28, 1724.37, 1593.24, 1461.02, 1222.62, 1181.79, 1065.22, 748.22, 667.12 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{10}H_{16}O_2$ $(M + H)^+$, 169.1229; found, 169.1238.

3-(Hexyloxy)cyclohex-2-en-1-one (**2e**) was synthesized by following the experimental procedure of transetherification using 3-butoxycyclohex-2-en-1-one (**2d**) in (0.1 M solution in 25 mL of *n*-hexanol) affording 95% (462.5 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.82 (t, J = 6.4 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6 Hz, 2H), 2.01−1.94 (m, 2H), 1.75−1.68 (m, 2H), 1.42−1.29 (m, 6H), 0.9 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.03, 178.27, 102.84, 68.75, 36.90, 31.57, 29.20, 28.63, 25.74, 22.67, 21.39, 14.13. FT-IR: 2944.26, 2834.76, 2310.19, 1718.52, 1589.98, 1465.80, 1298.50, 1110.66, 1034.34, 786.44, 610.97 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{12}H_{20}O_2$ $(M + H)^+$, 197.1463; found, 197.1469.

3-(Octyloxy)cyclohex-2-en-1-one (**2f**) was synthesized by using a syringe pump. Due to the high viscosity of octanol, the Vapourtec R-series pump was not able to flow the *n*-octanol. 1,3-Cyclohexadione (0.1 M solution in 10 mL of octanol) was taken in syringe and flown through reactor bed at 0.3 mL/min, at 80 °C temperature affording 94% (210.3 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 1H), 3.80 (t, J = 6.8 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.33 (t, J = 6 Hz, 2H), 1.99−1.93 (m, 2H), 1.74−1.64 (m, 2H), 1.37−1.22 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.23, 178.21, 102.78, 68.69, 36.84, 31.83, 29.29, 29.23, 29.14, 28.59, 26.00, 22.71, 21.33, 14.16. FT-IR (neat): 2929.90, 2862.30, 2314.45, 1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{14}H_{24}O_2$ $(M + H)^+$, 225.1855; found, 225.1861.

3-Isopropoxycyclohex-2-en-1-one (**2g**)[19] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL of propan-2-ol) affording 87% (134.1 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 4.45−4.36 (m, 1H), 2.34 (t, J = 6.4 Hz, 2H), 2.31 (t, J = 6.8 Hz, 2H), 1.97−1.91 (m, 2H), 1.27 (d, J = 6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.02, 177.10, 103.09, 71.26, 36.79, 29.66, 21.57, 21.31. FT-IR (neat): 2978.67, 2310.65, 1730.60, 1641.95, 1595.51, 1461.11, 1230.90, 1187.26, 1000.27, 757.95, 608.98 cm^{-1}. HRMS (ESI) m/z: calcd for $C_9H_{14}O_2$ $(M + H)^+$, 155.1072; found, 155.1078.

3-(Benzyloxy)cyclohex-2-en-1-one (**2h**)[20] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL of benzylalcohol) affording 80% (161.8 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, MeOD-d_4): δ 7.39−7.38 (m, 3H), 7.37−7.32 (m, 2H), 5.51 (s, 1H), 5.00 (s, 2H), 2.52 (t, J = 6.4 Hz, 2H), 2.35 (t, J = 6 Hz, 2H), 2.04−1.97 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 203.14, 181.17, 136.81, 129.65, 129.44, 128.95, 103.72, 71.85, 37.46, 30.02, 22.34. FT-IR: 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1734.79, 1648.08, 1597.17, 1359.34, 1221.55, 1175.66, 863.08, 743.15 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{13}H_{14}O_2$ $(M + H)^+$, 203.1072; found, 203.1079.

3-(Allyloxy)cyclohex-2-en-1-one (**2i**)[11g] was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL of allyl alcohol) affording 88% (133.6 mg) as a yellowish liquid compound. ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 6.00−5.90 (m, 1H), 5.39−5.28 (m, 3H), 4.37 (d, J = 5.6 Hz, 2H), 2.43 (t, J = 6.4 Hz, 2H), 2.33 (t, J = 6.4 Hz, 2 Hz), 2.02−1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 199.30, 177.17, 131.59, 119.10, 103.41, 62.24, 36.91, 29.20, 21.43. FT-IR: 2947.30, 2896.91, 2213.25, 2166.25, 1589.46, 1345.83, 1222.23, 1179.43, 1135.53, 988.73, 761.04 cm^{-1}. HRMS (ESI) m/z: calcd for $C_9H_{12}O_2$ $(M + Na)^+$, 175.0735; found, 175.0739.

3-Methoxy-5,5-dimethylcyclohex-2-en-1-one (**2j**)[21] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of methanol) affording 99% (152.4 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (s, 1H), 3.67 (s, 3H), 2.25 (s, 2H), 2.19 (s, 2H), 1.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.77, 177.14, 101.20, 55.77, 50.80, 42.75, 32.61, 28.34. FT-IR (neat): 2956.40, 2312.12, 1649.43, 1601.68, 1456.82, 1373.03, 1221.59, 1147.82, 1013.68, 754.09, 602.35 cm^{-1}. HRMS (ESI) m/z: calcd for $C_9H_{14}O_2$ $(M + H)^+$, 155.1072; found, 155.1080.

3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one (**2k**)[22] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of ethanol) affording 99% (163.1 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.87 (q, J = 7.2 Hz, 2H), 2.24 (s, 2H), 2.17 (s, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.77, 176.32, 101.55, 64.30, 50.79, 43.01, 32.54, 28.54, 14.18. FT-IR (neat): 2956.43, 2884.89, 2312.03, 1723.53, 1649.47, 1599.53, 1464.58, 1368.81, 1216.68, 1149.36, 1031.43, 752.88, 628.50 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{10}H_{16}O_2$ $(M + H)^+$, 169.1229; found, 169.1235.

5,5-Dimethyl-3-propoxycyclohex-2-en-1-one (**2l**)[22] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of propanol) affording 95% (191.1 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (S, 1H), 3.77 (t, J = 6.4 Hz, 2H), 2.26 (s, 2H), 2.19 (s, 2H), 1.72 (m, 2H), 1.05 (s, 6H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.80, 176.53, 101.57, 70.16, 50.84, 43.01, 32.56, 28.39, 22.01, 10.48. FT-IR: 2959.17, 2881.44, 2310.50, 1722.54, 1598.80, 1463.91, 1367.11, 1218.58, 1147.97. HRMS (ESI) m/z: calcd for $C_{11}H_{18}O_2$ $(M + H)^+$, 183.1385; found, 183.1390.

3-Isopropoxy-5,5-dimethylcyclohex-2-en-1-one (**2m**) was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of

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propan-2-ol) affording 99% (180.3 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 4.41 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.27 (d, J = 6 Hz, 6H), 1.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.80, 175.25, 101.90, 71.02, 50.78, 43.49, 32.50, 28.33, 21.55. FT-IR: 2966.01, 2881.94, 2310.43, 1726.02, 1650.87, 1600.63, 1464.21, 1380.26, 1226.90, 1152.05, 1054.82, 758.78, 639.20 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{11}H_{18}O_2$ $(M + H)^+$, 183.1385; found, 183.1389.

3-(2-Methoxyethoxy)-5,5-dimethylcyclohex-2-en-1-one (**2n**) was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL of 2-methoxyethanol) affording 94% (186.3 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 1H), 3.98−3.95 (m, 2H), 3.69−3.67 (m, 2H), 3.41 (s, 3H), 2.32 (s, 2H), 2.20 (s, 2H), 1.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.77, 176.23, 101.81, 70.22, 67.82, 59.30, 50.79, 42.79, 32.57, 28.36. FT-IR (neat): 2959.92, 2311.92, 2170.72, 1729.73, 1650.26, 1607.76, 1463.70, 1376.35, 1228.08, 1136.64, 1041.23, 751.46, 659.57 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{11}H_{18}O_3$ $(M + H)^+$, 199.1334; found, 199.1343.

3-Propoxycyclopent-2-en-1-one (**2o**) was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL of n-propanol) affording 73% (102.5 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27 (m, 1H), 3.92 (t, J = 6.8 Hz, 2H), 2.61−2.59 (m, 2H), 2.44−2.41 (m, 2H), 1.83−1.74 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.30, 190.59, 104.78, 73.60, 34.08, 28.64, 22.06, 10.42. FT-IR: 2967.17, 2934.64, 2246.12, 1676.46, 1584.73, 1411.72, 1344.25, 1289.43, 1183.57, 724.32, 651.14 cm^{-1}. HRMS (ESI) m/z: calcd for $C_8H_{12}O_2$ $(M + Na)^+$, 163.0735; found, 163.0739.

3-(2-Methoxyethoxy)cyclopent-2-en-1-one (**2p**) was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL of 2-methoxyethanol) affording 83% (130.2 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (m, 1H), 4.13−4.11 (m, 2H), 3.73−3.71 (m, 2H), 3.43 (s, 3H), 2.67−2.61 (m, 2H), 2.46−2.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.15, 190.24, 105.17, 71.12, 70.21, 59.37, 34.24, 28.63. FT-IR: 2964.77, 2251.33, 1738.96, 1590.97, 1345.35, 1189.58, 1126.01, 1039.62, 719.60, 649.78 cm^{-1}. HRMS (ESI) m/z: calcd for $C_8H_{12}O_3$ $(M + Na)^+$, 179.0684; found, 179.0692.

3,3-Diethoxyindolin-2-one (**2q**) was synthesized by following the experimental procedure B, using isatin (0.1 M solution in 10 mL of ethanol) affording 80% (177.2 mg) as a yellowish solid compound. Melting point: 69−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (bs, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.06 (td, J = 7.6 Hz, 0.8 Hz, 1H), 3.98−3.90 (m, 2H), 3.84−3.77 (m, 2H), 1.24 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.22, 140.41, 130.64, 126.17, 125.32, 122.87, 110.76, 97.22, 59.04, 15.43. FT-IR (neat): 3198.45, 2978.91, 2922.69, 2309.47, 1727.33, 1615.39, 1466.95, 1259.02, 1054.35, 751.51, 659.57 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{12}H_{15}NO_3$ $(M + Na)^+$, 244.0950; found, 244.0956.

3,3-Dipropoxyindolin-2-one (**2r**) was synthesized by following the experimental procedure B using isatin (0.1 M solution in 10 mL of propanol) affording 76% (211.9 mg) as a yellowish solid compound. Melting point: 79−83 °C. ^{1}H NMR (400 MHz, MeOD-d_4): δ 7.36 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 3.77−3.72 (m, 2H), 3.65−3.61 (m, 2H), 1.62−1.53 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 175.02, 142.69, 131.67, 127.26, 126.29, 123.39, 111.66, 90.74, 65.88, 65.88, 24.09, 10.95. FT-IR: 2967.60, 2882.16, 2312.22, 1734.96, 1617.66, 1467.37, 1201.92, 1059.91, 757.02 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{14}H_{19}NO_3$ $(M + Na)^+$, 272.1263; found, 272.1266.

Ethyl 3,3-dimethoxybutanoate (**2s**) was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL of methanol) and was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) at a flow rate of 0.3 mL/min, loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography using n-hexane purification affording 86% (151.5 mg) ethyl 3,3-dimethoxybutanoate compounds. ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 4.15 (q, J = 7.2 Hz, 2H), 3.21 (s, 6H), 2.64 (s, 2H), 1.45 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 169.68, 99.99, 60.60, 48.53, 42.47, 22.00, 14.37. FT-IR: 2983.81, 2942.16, 2832.30, 1735.06, 1626.09, 1462.19, 1380.78, 1227.42, 1139.80, 1096.74, 931.19, 762.90, 649.42 cm^{-1} . HRMS (ESI) m/z: calcd for $C_8H_{16}O_4$ $(M + Na)^+$, 199.0946; found, 199.0948.

Ethyl 3,3-dipropoxybutanoate (**2t**) was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL of propanol) and was flown through the packed bed reactor (Omnifit, 6.6 mm i.d. × 150.0 mm length) at a flow rate of 0.3 mL/min, loaded with Amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography using n-hexane purification affording 95% (220 mg) ethyl 3,3-dipropoxybutanoate compounds. ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 4.13 (q, J = 6.8 Hz, 2H), 3.43−3.34 (m, 4H), 2.66 (s, 2H), 1.59−1.50 (m, 4H), 1.48 (s, 3H), 1.25 (t, J = 6.8 Hz, 3H), 0.9 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 169.92, 99.54, 62.39, 60.46, 43.36, 23.28, 23.12, 14.41, 11.00. FT-IR: 2984.61, 2934.43, 1737.43, 1712.73, 1627.17, 1391.98, 1315.37, 1149.57, 1065.52, 915.12, 754.28 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{12}H_{24}O_2$ $(M + Na)^+$, 255.1572; found, 255.1579.

3-(But-2-yn-1-yloxy)cyclohex-2-en-1-one (**2u**) was synthesized by following the experimental procedure C, using 1,3-cyclohexadione (1 mmol) in 0.5 M solution of but-2-yn-1-ol in 1,4-dioxane affording 76% (121.1 mg) as a yellowish solid compound. Melting point: 57−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (s, 1H), 4.50 (q, J = 2.4 Hz, 2H), 2.43 (t, J = 6 Hz, 2H), 2.35 (t, J = 6.4 Hz, 2H), 2.02−1.96 (m, 2H), 1.86 (dt, J = 2.8 Hz, 0.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.88, 176.79, 103.71, 85.36, 72.27, 57.03, 36.83, 28.97, 21.29, 3.86. FT-IR: 2954.22, 2313.21, 2240.62, 1731.10, 1650.10, 1603.87, 1358.40, 1222.68, 1180.52, 1069.84, 907.60, 762.26, 600.72 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{10}H_{12}O_2$ $(M + H)^+$, 165.0916; found, 165.0921.

3-(Pent-3-yn-1-yloxy)cyclopent-2-en-1-one (**2v**) was synthesized by following the experimental procedure C, using 1,3-cyclopentadione (1 mmol) in 0.5 M solution of pent-3-yn-1-ol in 1,4-dioxane affording 64% (105.3 mg) as a yellowish solid compound. Melting point: 50−51 °C. ^{1}H NMR (400 MHz,

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$CDCl_3$): δ 5.31 (m, 1H), 4.03 (t, J = 7.2 Hz, 2H), 2.65−2.62 (m, 2H), 2.46−2.43 (m, 2H), 1.79 (t, J = 2.8 Hz, 2H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.77, 176.23, 101.81, 70.22, 67.82, 59.30, 50.79, 42.79, 32.57, 28.36. FT-IR: 2927.29, 2243.55, 1702.41, 1591.31, 1439.77, 1347.61, 1184.29, 1059.36, 954.63, 705.52, 599.66 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{10}H_{12}O_2$ $(M + Na)^+$, 187.0735; found, 187.0739.

3-(Pentan-3-yloxy)cyclohex-2-en-1-one (**2w**) was synthesized by following the experimental procedure C using 1,3-cyclohexadione (1 mmol) in 0.5 M solution of pentane-3-ol in 1,4-dioxane affording 65% (118.5 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 1H), 4.06−4.00 (m, 1H), 2.39 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6 Hz, 2H), 2.00−1.94 (m, 2H), 1.66−1.59 (m, 4H), 0.89 (t, J = 6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.73, 177.86, 103.06, 80.94, 36.84, 29.58, 25.72, 21.35, 9.59. FT-IR (neat): 2959.92, 2311.92, 2170.72, 1729.73, 1650.26, 1607.76, 1463.70, 1376.35, 1228.08, 1136.64, 1041.23, 751.46, 659.57 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{11}H_{18}O_2$ $(M + Na)^+$, 205.1204; found, 205.1212.

3-(Hexan-2-yloxy)-cyclopent-2-en-1-one (**2x**) was synthesized by following the experimental procedure C, using 1,3-cyclopentadione (1 mmol) in 0.5 M solution of hexan-2-ol in 1,4-dioxane affording 61% (111.4 mg) as a yellowish liquid compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (m, 1H), 4.27−4.19 (m, 1H), 2.60−2.57 (m, 2H), 2.43−2.41 (m, 2H), 1.73−1.52 (m, 4H), 1.31 (d, J = 6 Hz, 5H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.47, 189.69, 104.72, 79.27, 35.66, 33.84, 29.13, 27.60, 22.65, 19.35, 14.12. FT-IR: 2934.77, 2824.34, 2234.22, 1712.66, 1565.73, 1423.82, 1355.55, 1278.64, 1182.57, 745.23, 661.14 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{11}H_{18}O_2$ $(M + Na)^+$, 205.1204. found, 205.1210.

5,5-Dimethyl-3-(1-phenylethoxy)cyclohex-2-en-1-one (**2y**) was synthesized by following the experimental procedure C, using 5,5-dimethyl-1,3-cyclohexadione (1 mmol) in 0.5 M solution of 1-phenylethan-1-ol in 1,4-dioxane affording 64% (140 mg) as a yellowish oil compound. ^{1}H NMR (400 MHz, MeOD-d_4): δ 7.39−7.34 (m, 3H), 7.32−7.29 (m, 2H), 5.37 (q, J = 6.4 Hz,1H), 5.27 (s, 1H), 2.41 (dd, J = 27.6 Hz, 17.6 Hz, 2H), 2.16 (dd, J = 25.6 Hz, 16.4 Hz, 2H), 1.59 (d, J = 6.4 Hz, 3H), 1.08 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 202.65, 178.32, 143.01, 129.84, 120.02, 126.40, 104.16, 78.37, 51.19, 44.01, 33.53, 28.41, 28.10, 24.19. FT-IR: 3022.63, 2964.80, 2313.47, 1725.35, 1601.88, 1457.35, 1216.51, 753.31, 667.96 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{14}H_{16}O_2$ $(M + H)^+$, 245.1542; found, 245.1544.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00067.

Additional NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gnanaprakasam@iiserpune.ac.in.

ORCID

Boopathy Gnanaprakasam: 0000-0002-3047-9636

Notes

The authors declare no competing financial interest.

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A continuous-flow approach for the multi-gram scale synthesis of C2-alkyl- or β-amino functionalized 1,3-dicarbonyl derivatives and ondansetron drug using 1,3-dicarbonyls†

Nirmala Mohanta, Krishna Nair, Dasharath Vishambar Sutar and Boopathy Gnanaprakasam *

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Continuous-flow chemistry is a modern technology that encompasses the green chemistry principles for the multi-gram synthesis of various API and drugs. Herein, we have developed a highly efficient and environmentally benign metal-free alkylation of 1,3-dicarbonyl compounds using secondary alcohols in the presence of inexpensive Amberlyst®-15 under continuous-flow. This method has a broad substrate scope with a variety of secondary alcohols and water as a byproduct. The Amberlyst®-15 is recyclable and reusable for the alkylation reaction under batch/continuous-flow technology. Furthermore, a continuous-flow technology driven Mannich reaction was demonstrated under an acid-free condition. In addition, a continuous-flow Fischer indole strategy for the ondansetron with an improved yield was demonstrated. Additionally, all these reactions were demonstrated with multi-gram scale synthesis without lowering the yield under batch/continuous-flow technology.

Introduction

Alkylation is a prevalent and fundamentally applied organic reaction in chemical synthesis.[1–3] The development of a sustainable alkylation reaction using non-halogenated/non-hazardous reagents that can be scaled up and avoids copious waste, is one of the attractive processes in modern chemical industry. In particular, the alkylation of β-dicarbonyl compounds is a formidable challenge, not merely because of the synthetic application in natural products and the pharmaceutical industry, but also due to the fact of the difficulty in achieving selectivity in monoalkylation over dialkylation by conventional alkylating reagents. Most importantly, the synthetic methods for the regio- and chemoselective alkylation of the 1,3-dicarbonyl compounds are highly demanding in the multi-step chemical synthesis.[4,5] Early examples for the alkylation of β-dicarbonyl compounds use activated alcohols, including alkyl halides and tosylated/mesylated compounds, in order to make a better leaving group for the substitution reaction.[6–8] Another problem associated with the alkylation reactions were the competing *C vs. O*-alkylations.[9] In spite of this reaction being widely acclaimed in organic synthesis, a direct use of alcohol as an alkylating reagent is the most attractive approach and reduces the multiple steps required for pre-activation. It also generates the non-hazardous environmentally benign water as a byproduct.[10,11] However, a direct substitution of alcohols by the nucleophile is difficult due to the poor leaving group ability of the hydroxyl group. Notably, transition metal complexes that have catalyzed the propargylation/allylation/benzylation of β-dicarbonyl compounds with propargylic alcohols/allylic alcohols/secondary benzylic alcohols have been reported. Interestingly, Baba and co-workers reported the Lewis acid ($InCl_3$) catalyzed direct nucleophilic substitution of allylic and benzylic alcohols.[12,13] The alkylation of active methylene using alcohols in the presence of other Lewis acids such as $Bi(OTf)_3$ (ref. 14) and $BF_3{\cdot}OEt_2$ (ref. 15 and 16) were also studied. In addition, a triple-fold excess of β-dicarbonyl compounds is required when the reaction is performed using Fe or Zr-catalyzed benzylation with a substituted benzyl alcohol.[17–21] A metal-free condition using the triflic acid/dodecylbenzenesulfonic acid/toluenesulfonic acid monohydrate (PTS)/immobilized Amberlyst-15 catalyzed nucleophilic substitution of alcohols with β-dicarbonyl compounds was reported by the Sanz, Kobayashi and Bhanage groups independently.[22–26] Although limited reports are available for the acid-catalyzed direct nucleophilic attack of alcohols by the enolate of 1,3-dicarbonyl compounds under the batch process,[12] the

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Pune, Dr. Homi Bhabha Road, Pune 411008, Maharashtra, India. E-mail: gnanaprakasam@iiserpune.ac.in

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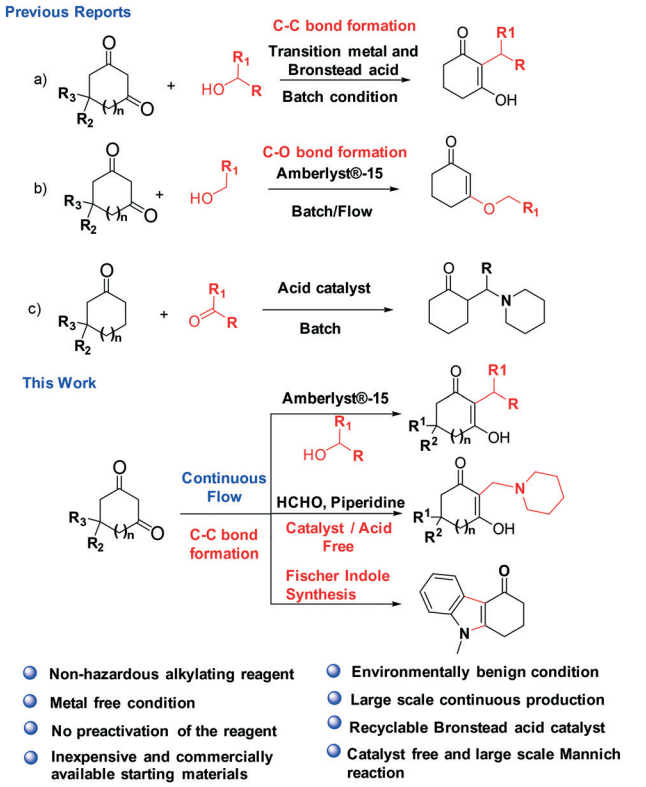
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reusable acid catalyzed method was not studied. Furthermore, no reports have shown the reusable/recyclable environmentally benign catalytic conditions with continuous production in a large-scale alkylation of β-dicarbonyl compounds using secondary alcohols.

In a previous report, we described the multi-gram approach for the vinylogous ester from β-dicarbonyl compounds and alcohol in the presence of the recyclable Amberlyst®-15 as a catalyst under the continuous flow approach. This reaction has been promoted by an excess amount of alcohols or neat condition.[27] This reaction is facilitated by the protonation of the C═O of the 1,3-dicarbonyl, and which furthermore, has been surrogated by an excess alcohol as a nucleophile. Moreover, the multi-component reactions involving the addition of an enolate of 1,3-dicarbonyls with an iminium ion generated from aldehyde and secondary amines using various metals or acid catalysts to afford the β-amino carbonyl compounds were studied in the literature.[28–31] Acid or metal catalysts are very crucial for this transformation. However, an acid/metal-free multicomponent reaction (Mannich reaction) of 1,3-dicarbonyls, aldehyde and secondary amines is the most attractive green approach for the synthesis of β-amino carbonyl derivatives.

Continuous flow chemistry is an emerging and alternative technology for the industrial batch process in which many reaction parameters can be easily optimized, including the extreme high temperature and high-pressure reactions with increased safety maneuvers. Thus, we envision developing a scalable and environmentally benign continuous flow process for the alkylation of β-dicarbonyl compounds using alcohol.

Herein, we report the alkylation of various 1,3-dicarbonyl compounds using alcohol in the presence of Amberlyst®-15 under the continuous-flow process (Scheme 1). The different reactivities of 1,3-dicarbonyls with diphenylmethanol derivatives are mainly associated with the concentration, *i.e.*, an equimolar concentration undergoes nucleophilic substitution to afford the C2-alkylated product rather than that for *O*-alkylation, which might be due to the formation of a more stable benzylic carbocation from the benzhydrol derivatives under an acidic environment. Additionally, this application was extended to synthesize various β-amino-1,3-dicarbonyl derivatives under continuous-flow mode *via* multi-component strategy. A continuous-flow synthesis of ondansetron using 1,3-dicarbonyls is also described in a short synthesis route with high yield and gram-scale demonstration (Scheme 1). The advantages of the present approach involve it being environmentally benign, scalable to multigram, metal-free and a non-hazardous reaction with water as the byproduct.



Scheme 1 State of the art for the alkylation of cyclic 1,3-dicarbonyls.

Results and discussion

C–C bond formation using alcohols and dicarbonyls under batch condition

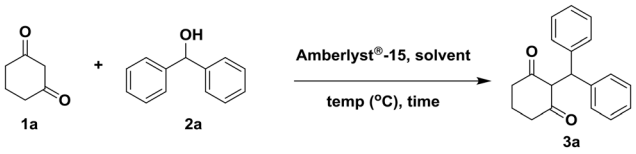
The initial optimization for batch condition begins with 1,3-cyclohexadione **1a** and diphenylmethanol **2a** in THF as the model reaction to generate product **3a**. A control experiment was performed in the absence of acid, and resulted in no reaction (entry 1, Table 1). No reaction was observed after performing the reaction with a stoichiometric amount of Amberlyst®-15 at room temperature (entry 2, Table 1). Increasing the temperature to 80 °C led to 10% of the product **3a** (entry 3, Table 1).

To our delight, 35% of the product **3a** was isolated when the reaction was carried out with an equal weight proportion of Amberlyst®-15 and **1a** heated at 100 °C (entry 4). A parallel control experiment in the absence of the catalyst at 100 °C resulted in no reaction. An improvement in the yield of up to 50% was observed on the addition of a two-fold excess of Amberlyst®-15 with respect to **1a** at 100 °C. The role of the solvent for this reaction was investigated with various solvents like DMF, 1,4-dioxane, toluene, H_2O and THF mixture, and ACN. Interestingly, the product **3a** was afforded in higher yield (77%) using the H_2O : THF (3 : 1) mixture as a solvent (entry 13). The ACN turn out to be an ideal solvent for this transformation. Moreover, upon decreasing the reaction time by up to 3 hours, a significant decrease in the yield (65%) was observed. The best yield (82%) of **3a** was obtained by using a 2 : 1 ratio of Amberlyst®-15 and 1,3-cyclohexadione in ACN at 100 °C in 12 hours (entry 15). Having the optimal condition in hand, our interest went to exploring the C–C bond formation using various 1,3-dicarbonyl derivatives and secondary alcohols (Scheme 2). Thus, the subjection of the optimized conditions for the

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Table 1 Optimization[a] of the C–C bond formation under the batch method

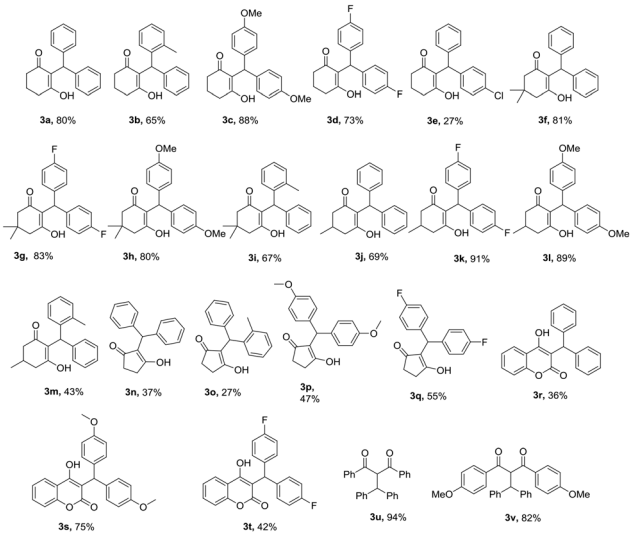


Entry	Solvent	Time (h)	Temp. (°C)	Yield (%)
1[b]	THF	12	rt	No reaction
2[c]	THF	12	rt	No reaction
3[c]	THF	12	80	10
4[c]	THF	12	100	35
5	THF	12	100	50
6	DMF	12	100	No reaction
7	1,4-Dioxane	12	100	42
8	Toluene	12	100	73
9	$1H_2O$: 1THF	12	100	32
10[c]	$1H_2O$: 1THF	12	100	20
11	$3H_2O$: 1THF	12	100	80
12	$3H_2O$: 1THF	3	100	50
13[d]	$3H_2O$: 1THF	12	100	77
14[e]	$1H_2O$: 1THF	12	100	30
15	ACN	12	100	82
16	ACN	8	100	75
17	ACN	5	100	71
18	ACN	3	100	65

[a] Reaction condition: **1a** (0.5 mmol), **2a** (0.6 mmol) and Amberlyst®-15 (2 : 1 Amberlyst®-15 : **1a**, w/w ratio) was stirred in a vial. [b] Absence of catalyst. [c] Amberlyst®-15 : **1a** (1 : 1 Amberlyst®-15 : **1a**, w/w ratio). [d] **2a** (0.5 mmol). [e] Amberlyst®-15 (2.5 : 1 Amberlyst®-15 : **1a**, w/w ratio).

reaction of cyclohexane-1,3-dione with various substituted benzhydrols afforded the C2-substituted cyclohexane-1,3-dione derivatives (**3b–e**) in moderate to good yield.

The reaction of 5,5-dimethylcyclohexane-1,3-dione or 5-methylcyclohexane-1,3-dione with secondary alcohols afforded the respective C2-alkylated products **3f–m** in very good yield. Furthermore, C2 alkylation was also successful with cyclopentane-1,3-dione to afford the corresponding products **3n–q** in moderate yield. Next, we extended the substrate scope for the alkylation reaction with coumarin derivatives and acyclic-1,3-dione with various secondary alcohols to afford libraries of 1,3-carbonyl derivatives **3r–v** (Scheme 2). Although these reactions worked well with the secondary alcohols derived from diphenylmethane, other activated alcohols based on the allylic and propargylic secondary alcohol derivative were not successful. This might be due to the presence of the acid-sensitive olefin interfering with the reactivity of the alcohol protonation to form the electrophile.



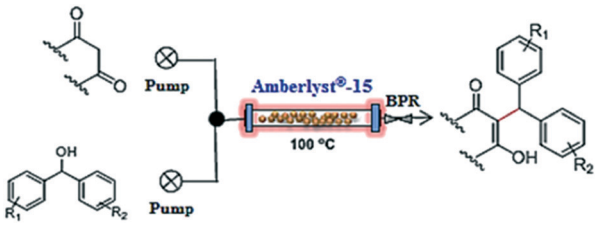
Scheme 2 Substrate scope for the alkylation reaction. Reaction condition for batch: 1,3-diketone (0.5 mmol), alcohol (0.6 mmol), Amberlyst®-15 (2 : 1 w/w with 1,3-diketone) and ACN (3 mL) were heated in a sealed tube at 100 °C for 12 h.

C–C bond formation using alcohols and dicarbonyls under the flow condition

Next, we turned our attention to integrate this reaction under the continuous flow module. Initially, the reaction was performed[40] at room temperature with a flow rate of 0.1 mL min^{-1}. 0.1 M concentrations of each reactant showed no reaction (Table 2, entry 1). 0.1 M solution of **1a** and 0.12 M solution of **2a** were then flowed through the Amberlyst®-15 packed bed reactor with flow rates of 0.1 mL min^{-1} of each solution at 80 °C to afford 50% of product **3a** (Table 2, entry 2). The excellent yield (96%, Table 2, entry 3) was obtained by increasing the reactor temperature to 100 °C with a t_R = 18 min. To get the target product in a shorter reaction time, solutions of **1a** (0.1 M in 5 mL ACN) and **2a** (0.12 M in 5 mL ACN) were flowed through a packed bed reactor with flow rates of 0.15 and 0.2 mL min^{-1}, respectively, at 100 °C. This reaction produced 78 and 73% of the yield of product **3a** with

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Table 2 Optimization under continuous-flow condition

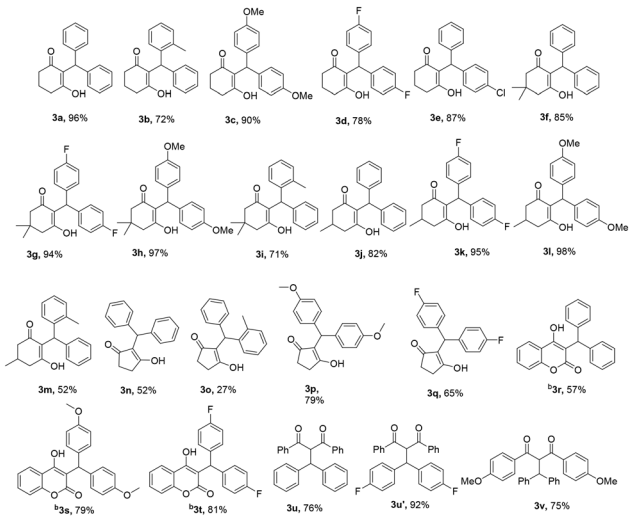


Entry	Solvent	Residence time (t_R min)	Temp. (°C)	Isolated yield of **3a** (%)
1[a]	ACN	18	rt	No reaction
2[a]	ACN	18	80	50
3[a]	ACN	18	100	96
4[b]	ACN	12	100	78
5[c]	ACN	9	100	73
6[a]	THF	18	100	50
7[a]	THF : H_2O (9 : 1)	18	100	No reaction

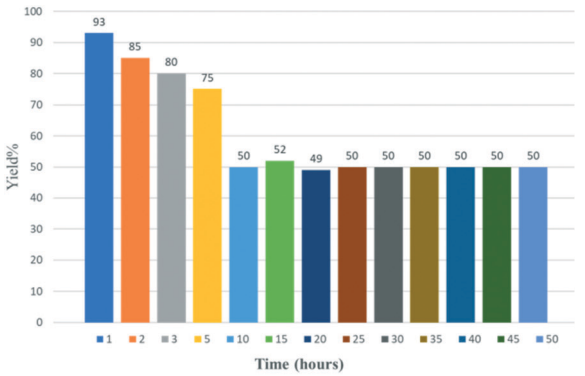
[a] Reaction condition: the solution of **1a** (0.1 M) and **2a** (0.12 M) in ACN were flown through Omnifit® (6.6 × 150 mm) pre-packed bed (Amberlyst®-15 filled up to 5 cm, 1.0 g) at 100 °C with a 0.1 mL min^{-1} flow rate of each solution under 3.5 bar pressure. [b] Flow rate of each solution was 0.15 mL min^{-1}. [c] Flow rate of each solution was 0.2 mL min^{-1}.

a retention time of 12 and 9 min respectively (Table 2, entry 4 and 5).

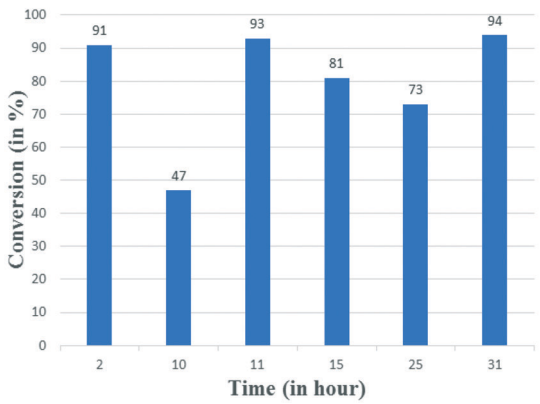
Other solvents under this optimized condition, such as THF and THF/H_2O, results in poor yield. Comparatively, the flow condition became superior over the batch for the formation of product **3a**, which resulted in increasing the efficiency of the reaction by rapid reactions in t_R = 18 min and increasing the yield to 96%. Furthermore, we have tested the other green or less hazardous solvents for C–H peroxidation, and the results are summarized in Table 1, entries 10–12. The low yield of the product was observed in the presence of solvents like 1,4-dioxane, DME and DMF (Table 1, entries 4–6). As a result of this improved efficiency under continuous flow, an optimised condition was subjected to the various substrate scopes. Thus, flowing the solution of



Scheme 3 Substrate scope under continuous-flow. [a]Reaction conditions: the solution of **1a** (0.1 M) and **2a** (0.12 M) in ACN were flown through Omnifit® (6.6 × 150 mm) prepacked bed (Amberlyst®-15 filled up to 5 cm, 1.0 g) at 100 °C with a 0.1 mL min^{-1} flow rate of each solution under 3.5 bar pressure; [b]ACN : THF (9 : 1) was used as solvent.



(a)



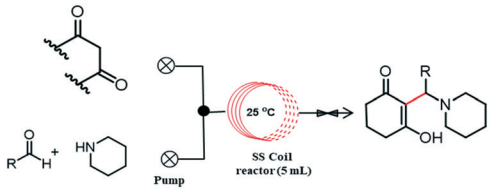
(b)

Fig. 1 a) Long time experiment without activation for the stability of the catalyst. b) Long term experiment for the synthesis of **3a** under continuous-flow with periodic reactivation of the catalyst.

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Table 3 Optimization[a] for the continuous-flow Mannich reaction

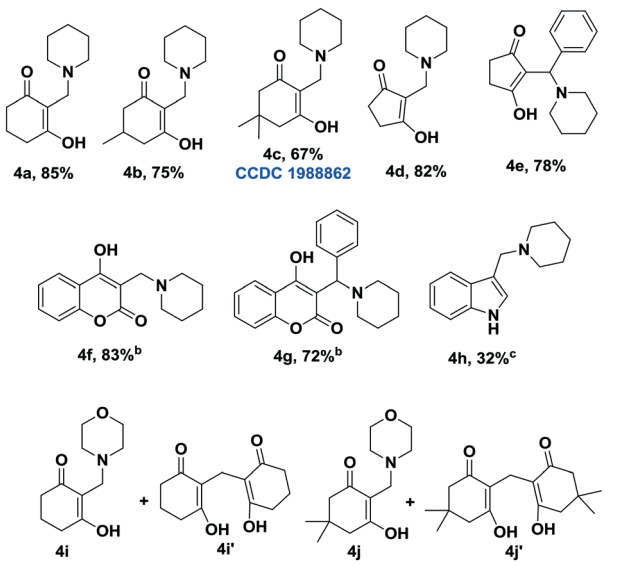


Entry	1,3-Diketone (M)	Formaldehyde 2 + piperidine 3 (M)	Flow rate (mL min^{-1})	Time (t_R, min)	Conversion (%)
1	0.1	0.12	0.1	25	100
2	0.1	0.12	0.15 mL each	16	100
3	0.1	0.12	0.2 mL each	12.5	95
4	0.2	0.2	0.15 mL each	16	80

[a] Reaction conditions: the solution of 1,3-diketone (0.1 M) and formaldehyde + piperidine (0.12 M) in ACN were flowed through a 5 mL SS tubular reactor (Vaportec R-series) at 25 °C.

cyclohexane-1,3-dione (0.1 M) and various secondary alcohols (0.12 M) into the Amberlyst®-15 bed under optimized conditions resulted in the respective alkylated product **3b–e** in an excellent yield (Scheme 3). Similarly, other dicarbonyl compounds (5-dimethylcyclohexane-1,3-dione or 5,5-dimethylcyclohexane-1,3-dione with secondary alcohols) were subjected under flow condition to afford the products **3f–m** at up to 98% yield (Scheme 3).

When this flow condition was performed with cyclopentane-1,3-dione with several secondary alcohols, furnished the respective products **3n–q** in t_R = 18 min duration (Scheme 3). Further, flow reaction of 4-hydroxy coumarin with secondary alcohols provided the therapeutically[32,33] important products **3r–t** in very good yield (Scheme 3). Acyclic 1,3-dione was also successfully reacted with secondary alcohols under the continuous flow condition to afford the respective products **3u–v** in very good yield (Scheme 3).



Scheme 4 Substrate scope under continuous-flow. [a]The solution of 1,3-dione (0.1 M) and aldehyde + amine (0.12 M) in ACN were flowed at 0.15 ml min^{-1} each through 5 mL of the SS tubular reactor (Vapourtec R-series) at 25 °C under 3.5 bar pressure. [b]ACN : THF (9 : 1) was used as the solvent; [c]heated at 80 °C.

Long-term experiment and gram-scale synthesis under flow

Although it is known that there is a significant loss in the activity of Amberlyst®-15 for the other chemical transformation,[34,35] we can periodically reactivate it and continuously use it for the longer period. Water has been produced in the reaction, which may be accumulated in the porous Amberlyst®-15 and results in lower activity. Hence, to know the stability of the catalyst, a long-time experiment for up to 50 h was performed under continuous flow (Fig. 1a). This study showed that the efficiency of the catalyst decreased drastically after 10 h to give 50% of conversion (see Fig. 1(a)). Consequently, the periodic washing and drying of the Amberlyst®-15 bed is required for better activity. Interestingly, the reactivity of the catalyst was regained after reactivation of Amberlyst®-15 using 0.1 M of HCl in methanol and pure methanol (see procedure 3, ESI†). A multi-gram scale for the synthesis of **3a** was demonstrated under continuous flow results of 5.7 g with 85% yield after 40 h by the periodic activation of Amberlyst®-15 (see Fig. 1(b)).

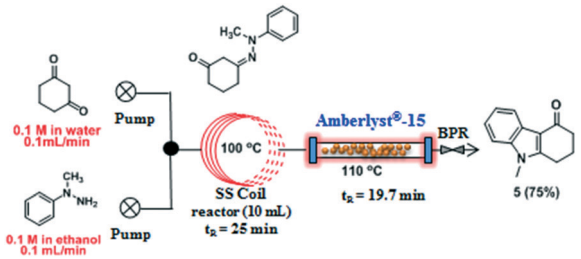
Mannich reaction using dicarbonyls, aldehyde and amines under continuous flow

Next, we intended to develop the continuous flow addition of enolate, with the iminium ion generated by the reaction of the formaldehyde with secondary amine (Mannich reaction). Thus, flowing 0.1 M cyclohexane-1,3-dione in ACN (0.1 mL) and 0.12 M of formaldehyde + piperidine (0.12 mL) into the 5 mL SS tubular reactor at room temperature or 80 °C results in 100% conversion with 85% isolated yield of product **4a** in the absence of any acid source (Table 3, entry 1).

Increasing the flow rate of this solution to 0.15 mL furnished similar results (Table 3, entry 2). Further increasing the flow rate to 0.2 mL each produced a decrease in the conversion and yield of product **4a** (Table 3, entry 3). Similarly, an increase in the concentration of the reactant

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Table 4 Optimization[a] for the continuous-flow Fischer indole reaction

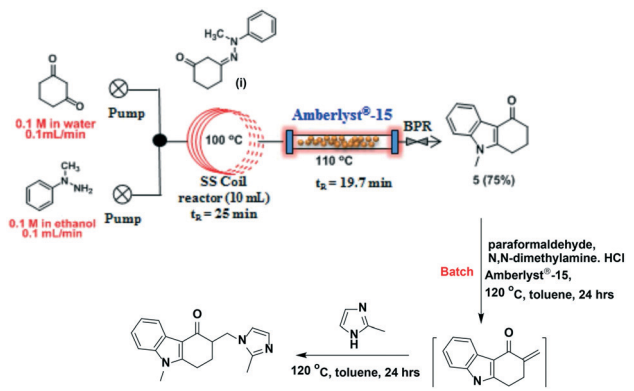


Entry	Conc. (M) R_1	Conc. (M) R_2	Flow rate (mL min^{-1})	Temp of tubular reactor (°C)	Yield (%) (i)	Temp of bed reactor (°C)	Yield (%)
1	0.1	0.12	0.1 each	—	—	rt	—
2[b,c,d]	0.1	0.12	0.1 each	—	—	110	—
3	0.1	0.12	0.1 each	rt	—	—	—
4	0.1	0.12	0.1 each	60	Trace	—	—
5	0.1	0.12	0.1 each	80	35	—	—
6	0.1	0.12	0.1 each	100	82	rt	—
7	0.1	0.12	0.2 each	100	Trace	—	—
8	0.1	0.15	0.1 each	100	90	110	75

[a] The solution of 1,3-cyclohexadione in water and *N*-methylhydrazine in ethanol were flowed through 10 mL of an SS coil reactor at 100 °C followed prepacked bed (Amberlyst®-15 filled up to 7 cm, 1.4 g) at 110 °C with a 0.1 mL min^{-1} flow rate of each solution under 3.5 bar pressure. [b] DMF. [c] DMSO. [d] 1,4-Dioxane.

under an optimized flow rate (0.15 mL each) provided a lower conversion, and significantly retarded the yield of product **4a** (Table 3, entry 4). The continuous flowing of the reaction mixture for 40 h resulted in 10.6 g of the product **4a** in 83% yield.

To demonstrate the broad substrate scope, several 1,3-dicarbonyl derivatives were reacted with aldehyde and amine under the flow optimized condition. As a result, several series of β-amino-1,3-dicarbonyl derivatives (**4b–d**) were obtained rapidly under the continuous flow condition in excellent yield (Scheme 4). Further scope of this method was elaborated with the benzaldehyde and piperidine, resulting in the Mannich adduct **4e** in 78% yield with t_R = 16 min (Scheme 4). Application of this process was also extended with a coumarin derivative to afford the respective products **4f**, **4g**[36] in 83% and 72% yield. A lower yield of product **4h**[37] was observed for 4 h in the case of indole when this Mannich reaction was performed at 80 °C. Other secondary amines (such as diethyl amine and morpholine) were also reacted under the above optimized reaction condition, resulting in the unstable Mannich addition product, which rapidly underwent dimerization under the experimental condition (**4i** + **4i′**, **4j** + **4j′**, Scheme 4).



Scheme 5 Amberlyst®-15 mediated synthesis of ondansetron.

Continuous flow synthesis of the ondansetron precursor

The carbazole intermediate **5** (ref. 38) was prepared on the gram-scale using the Fischer indole strategy[39] under continuous-flow in high yield. Initially, the control experiment was performed by flowing 0.1 M of cyclohexadione and 0.12 M of *N*-methylphenylhydrazine to the bed reactor in the absence of the Amberlyst®-15 catalyst, as well as the absence of the tubular reactor (batch condition), and it produced no reaction. Several reactions were performed by varying different reaction parameters to obtain compound **5** in higher yield *via* the intermediate i (Table 4). The best optimised condition was obtained by cyclohexane-1,3-dione (0.1 M in water) and *N*-methyl phenylhydrazine (0.1 M in ethanol), and was flowed at 0.1 mL min^{-1} each into SS tubular reactor heated at 100 °C. Subsequently, the reaction mixture was passed through an Omnifit® (6.6 × 150 mm^2) prepacked with Amberlyst®-15 at 110 °C. The solvent was evaporated and the crude residue was recrystallized to afford the 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one **5** in 75% yield.

Next, a multi-component reaction was performed using the carbazole derivative **5**, *para* formaldehyde and *N*,*N*-dimethyl amine·HCl under batch conditions. This reaction

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mixture was heated in the presence of Amberlyst-15 at 120 °C for 24 h. Subsequently, 2-methyl imidazole was added to the reaction mixture and heated at 120 °C for 24 h to furnish the commercially available drug ondansetron **7** in 87% yield after recrystallization.

The overall yield of our route is 65%, which is better than the commercially available route for the ondansetron drug. A gram-scale synthesis of this reaction was performed to afford an 82% yield of **7** (Scheme 5).

Conclusions

In summary, a metal-free approach for the synthesis of C2-alkylated 1,3-dicarbonyl derivatives was developed using the environmentally benign Amberlyst®-15 medium under a batch/continuous-flow condition in an excellent yield with functional group tolerant. A gram-scale synthesis was demonstrated for up to 6.5 g under the continuous-flow mode. An acid/metal-free condition for the Mannich reaction was established by incorporating 1,3-dicarbonyls, aldehyde and a secondary amine under continuous flow for the first time. A synthetic application was demonstrated by synthesizing the commercially available ondansetron drug on the multi-gram scale for the first time.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the Council of Scientific and Industrial Research [02(0296/17/EMR-II)] and SERB (CRG/2018/003935), India. N. M. thanks IISER-Pune for a research fellowship. D. V. S. thanks UGC for the research fellowship. B. G. thanks, IISER-Pune, CSIR and SERB for the research support.

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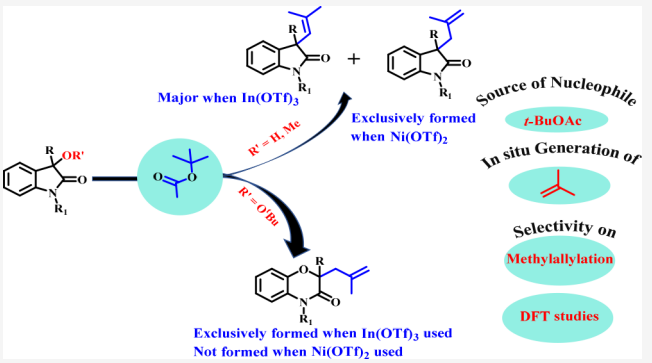
Catalyst-Assisted Selective Vinylation and Methylallylation of a Quaternary Carbon Center Using *tert*-Butyl Acetate

Nirmala Mohanta, Pragnya Paramita Samal, Akanksha M. Pandey, Shankhajit Mondal, Sailaja Krishnamurty, and Boopathy Gnanaprakasam*

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ABSTRACT: The $In(OTf)_3$-catalyzed α-vinylation of various hydroxy-functionalized quaternary carbon centers using in situ generated isobutylene from *tert*-butyl acetate is presented as a novel synthetic methodology. Moreover, *tert*-butyl acetate is a nonflammable feed stock and is a readily available source for the in situ production of vinyl substituents, as demonstrated by the vinylation reaction with quaternary hydroxy/methoxy compounds. Moreover, an excellent selectivity for methylallylation over vinylation was obtained with $Ni(OTf)_2$ as a catalyst. In the case of peroxyoxindole, methylallyl-functionalized 1,4-benzoxazin-3-one derivatives were formed through the sequential rearrangement of peroxyoxindole followed by the nucleophilic attack by isobutylene. The detailed mechanism for this reaction and rationalization for the selectivity are provided using kinetics and density functional theory studies.



INTRODUCTION

From the perspective of synthesis, the interconversion of functional groups at quaternary carbon centers is imperative because many natural products, drugs, and value-added products features such skeletons.[1] Efficaciously constructing a quaternary carbon center with four substituents is very challenging in organic syntheses due to steric hindrance and marginally reactive functional groups. Thus, various approaches have been reported for the formation of different quaternary carbon centers in the past few decades.[2] In modern chemical syntheses, direct nucleophilic substitution for olefination (vinyl/allyl), which has been used in many total syntheses, at quaternary centers is a fascinating research topic because of its benefits such as atom economy and sustainability.[2a,3] Few methods for vinylation and allylation at the oxindole core using prefunctionalized aliphatic alkenes were reported.[4] Funk et al. reported the C3-allylation of 3-alkyl-3-bromoindolin-2-one with allyl stannenes or allyl trimethylsilane derivatives to produce C3-allyl-substituted 2-indolinones using a stoichiometric amount of base (Figure 1A-I).[5] Subsequently, Huang et al. reported the Pd-catalyzed α-vinylation of carbonyl compounds using bromo alkenes in the presence of LiHMDS (Figure 1A-II).[6] Kozlowski et al. proposed catalytic Meerwein−Eschenmoser Claisen rearrangement for the synthesis of allyl oxindoles with a quaternary stereocenter using Pd catalysts (Figure 1A-III).[7] Bisai et al. reported the quaternary allyl functionalization of 3-hydroxy-3-aryl-2-oxindoles with various allyl trimethylsilane derivatives in the presence of catalytic Lewis acids.[8] Additionally, α-vinylation of cyclic amides with arylacetylenes in a metal-free environment was reported.[9] The Helquist research group reported the Ni-catalyzed α-vinylation of carbonyl compounds using ketone enolates with alkenyl halides (Figure 1A-IV).[10] The Ni-catalyzed α-vinylation of β-keto amides/esters using hypervalent iodine salts was described.[11]

All the aforementioned procedures used prefunctionalized alkenes as a source for α-vinylation/methylallylation and required stoichiometric bases. Furthermore, these reactions involve specific basic conditions that cause isomerization to be a competing reaction. However, the catalytic selective vinylation/methylallylation of a quaternary carbon center using isobutylene has not been reported. Although isobutylene is an inexpensive and commercially available source, its polymerization propensity under experimental conditions and highly flammable property limit its reactivity as a nucleophile, which remains an unresolved problem.[12] Therefore, developing an efficient method to construct vinyl or methylallyl quaternary carbon centers using isobutylene derivatives is highly appealing. While various approaches have been reported for

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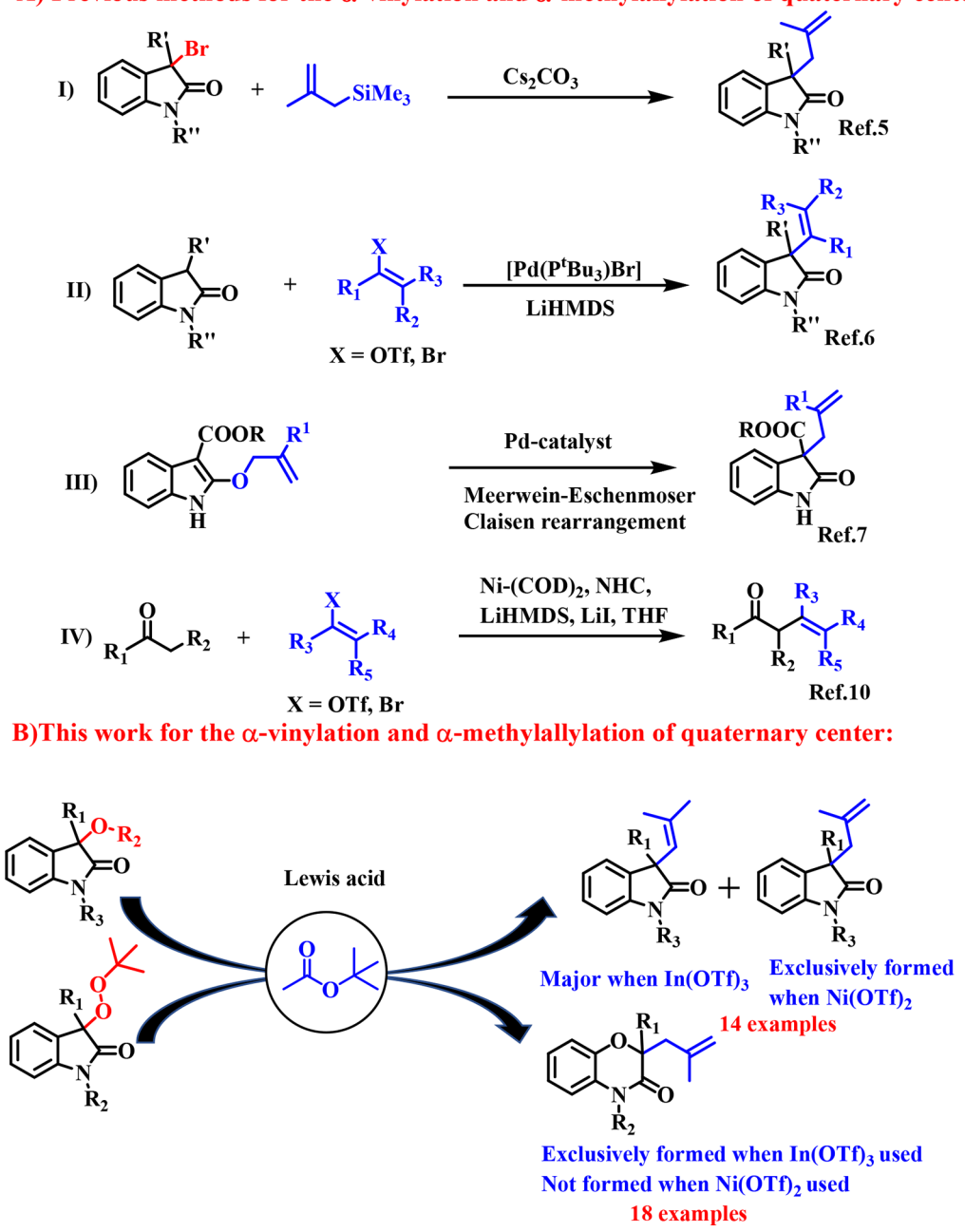


Figure 1. State of the art for the vinylation and methylallylation of a quaternary center.

the in situ generation of isobutylene,[12] no study has been reported on selective catalytic vinylation or methylallylation at the quaternary hydroxy or peroxy-functionalized carbon center using isobutylene.

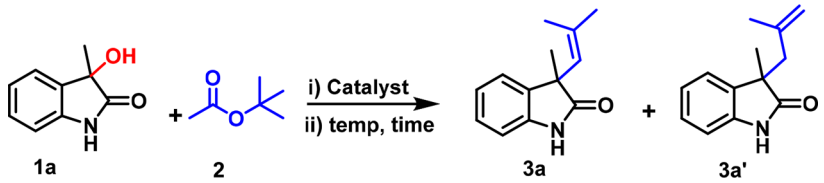
In this study, we report the Lewis acid-catalyzed highly selective *α*-vinylation and methylallylation of quaternary 3-hydroxyoxindole or peroxyoxindole through the direct nucleophilic substitution of the hydroxyl/peroxy group with isobutylene generated in situ from *tert*-butyl acetate (Figure 1B). In this reaction, the Lewis acid controls the selectivity of methylallylation and vinylation. Thus, $In(OTf)_3$ catalyzes this reaction toward selective *α*-vinylation at the quaternary center. $Ni(OTf)_2$ directs this reaction exclusively for the formation of methylallylation, whereas peroxyoxindole undergoes the sequential reaction that involves skeletal rearrangement and nucleophilic addition of isobutylene to synthesize various methylallyl-functionalized 1,4-benzooxazin-3-one derivatives. Furthermore, the high selectivity for the In- and Ni-catalyzed vinylation and methylallylation reactions and plausible mechanism were supported by kinetics and DFT studies.

RESULTS AND DISCUSSION

Initially, we performed the vinylation of 3-methyl-3-hydroxyoxindole **1a** using *tert*-butyl acetate as the isobutylene source. In the control experiment, **1a** was stirred with *tert*-butyl acetate without a catalyst at room temperature and 60 °C, and no reaction was observed (Table 1, entry 1 and 2). Several Lewis acids were tested for vinylation at the C3 position of **1a**. The highly substituted alkene **3a** (31%, Saytzeff product) as a major product and the less substituted methylallylated compound **3a′**

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Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (30 mol %)	catalyst loading (mol %)	temperature (°C)	yield **3a** (%)	yield **3a′** (%)
1			rt		
2			60		
3	$In(OTf)_3$	10	60	31	23
4	$Cu(OTf)_2$	10	60	no reaction	no reaction
5	$Mn(OTf)_2$	10	60	no reaction	no reaction
6	$Sn(OTf)_2$	10	60	27	19
7	$FeCl_3•6H_2O$	10	60	no reaction	no reaction
8	$Mn(ClO_4)_2·xH_2O$	10	60	15	13
9	$LiClO_4$	10	60	no reaction	no reaction
10	$BF_3·O(C_2H_5)_2$	10	60	20	23
11	$AlCl_3$	10	60	no reaction	no reaction
12	TfOH	10	60	decomposition	decomposition
13	$In(OTf)_3$	10	40	15	10
14	$In(OTf)_3$	10	rt	no reaction	no reaction
15	$In(OTf)_3$	20	60	42	21
16	$In(OTf)_3$	20	80	54	27
17	$In(OTf)_3$	20	100	49	29
18	$Ni(OTf)_2$	20	80		65

[a]Reaction conditions are as follows: All the reactions were performed using 0.12 mmol **1a** and catalyst in *tert*-butyl acetate (1.5 mL). The mixture was heated at the mentioned temperature in a resealable vial for 12 h.

as a minor product (23%, Hoffmann product) were obtained when $In(OTf)_3$ was used as a catalyst at 60 °C (Table 1, entry 3). This reaction was unsuccessful when $Cu(OTf)_2$, $Mn(OTf)_2$, $FeCl_3·6H_2O$, $LiClO_4$, and $AlCl_3$ were used as catalysts (Table 1, entries 4, 5, 7, 9, and 11, respectively). The use of other Lewis acids such as $Sn(OTf)_2$, $Mn(ClO_4)_2·xH_2O$, and $BF_3·O(C_2H_5)_2$ resulted in poor yields of the desired product (Table 1, entries 6, 8, and 10, respectively). Further, no desired product was observed with triflic acid, and the starting material was decomposed (Table 1, entry 12). Notably, the vinylation reaction using catalyst $In(OTf)_3$ was highly efficient when 20 mol % catalyst was used, and the reaction yield was 63% (**3a** + **3a′**) (Table 1, entry 15). To ensure the optimal reaction conditions, reaction parameters, such as temperature and time, were carefully evaluated (Table 1, entries 15−17). The best yield of 81% (**3a** + **3a′**) was obtained when 20 mol % $In(OTf)_3$ was used and the reaction mixture was heated at 80 °C for 12 h. The better yield with $In(OTf)_3$ might be due to its higher Lewis acidity than other catalysts.

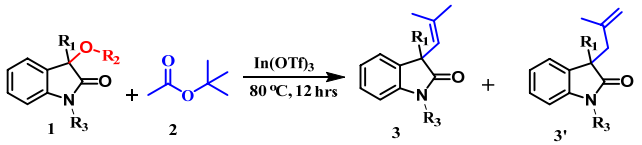
The substrate scope was explored under the optimized reaction conditions (Table 2). The derivatives of 2-oxindole featuring the substituted phenyl group were well tolerated under the developed reaction conditions to acquire a substituted vinyl quaternary compound as the major product. The reaction proceeds smoothly with the C3-methyl substituted 3-hydroxyoxindole derivatives, providing moderate yields of vinyl- and methylallyl-substituted products (**3b−3d** and **3b′−3d′**). The phenyl group with $-CH_3$, −F and −OMe attached to the C3 position of 3-hydroxy *N*-methyl oxindole afforded the products in 95% (**3e** + **3e′**), 84% (**3f** + **3f′**), and 85% (**3g** + **3g′**) yields, respectively. Similarly, other substituted hydroxyoxindoles were also well tolerated under the reaction conditions and provided moderate yields of the desired products, **3h−k** and **3h′−k′**. Moreover, the reaction with hindered naphthalene-substituted 2-oxindole afforded a mixture of **3i** and **3i′** with an 83% yield. To determine the generality of quaternary *iso*-butenylation through nucleophilic substitution, we used C3-methoxy-substituted oxindole. Thus, the quaternary methylallylation of C3-methoxy oxindole and 1,4-benzooxazin-3-one derivatives through nucleophilic substitution afforded satisfactory yields of substituted vinyl and methylallyl products (**3e** + **3e′** and **5f** + **5f′**), respectively.

The Hoffman product (**3a′**), i.e methylallylation, was isolated with exclusive selectivity when a 2-oxindole featuring a −OH or −OMe substitution at the C3 position was treated with *tert*-butyl acetate in the presence of 20 mol % $Ni(OTf)_2$ as the catalyst (Table 3). Thus, this reaction of alkyl-substituted hydroxyoxindole afforded moderate yields of the quaternary methylallylated products (**3a′−3d′**, Table 3). A high yield and exclusive selectivity for **3e′** and **3f′** were observed with aryl-substituted hydroxyoxindole (Table 3). *N*-Substituted C3-hydroxyoxindole was suitable to produce only the quaternary methylallylated products (**3g′−3o′**) in high yields (Table 3).

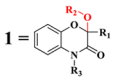
Quantum chemical calculations are carried out to understand the feasibility of the reaction mechanism. Computational details for the same are given in the Supporting Information, section 5, DFT calculation. Different functionals including dispersion effects (*i.e.*, B3LYP, PBE, and M06) were benchmarked (see the SI, Figures S13 and S14). Finally, the structures were optimized using PBE functional. Density Functional Theory (DFT) calculations were carried out using PBE functional to obtain mechanistic insights, to understand the reaction pathway, and to identify the reaction intermediates. We have discussed the role of $In(OTf)_3$ and $Ni(OTf)_2$ in catalyzing the product selectivity for nucleophilic substitution (see Figure 2). For all the In and Ni species,

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Table 2. Substrate Scope of the $In(OTf)_3$-Catalyzed α-Vinylation Reaction[a]

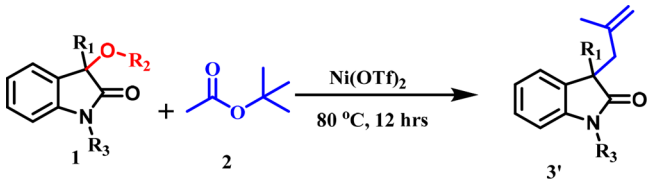


1 2 3 3'

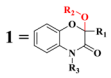
Entry	Substrate			Yield %	
	R_1	R_2	R_3	**3a**	**3a'**
1	**1a**: Me	H	H	**3a** (54)	**3a'**(27)
2[b]	**1b**: C_4H_9	H	H	**3b** +**3b'** (59)	
3	**1c**: Me	H	Me	**3c** (58)	**3c'** (25)
4	**1d**: Me	H	C_4H_9	**3d** (41)	**3d'** (32)
5	**1e**: 4-MeC_6H_4	H	Me	**3e** (64)	**3e'** (31)
6	**1f**: 3-FC_6H_4	H	Me	**3f** (52)	**3f'** (32)
7	**1g**: 4-$MeOC_6H_4$	H	Me	**3g** (52)	**3g'** (33)
8	**1h**: 4-*t*BuC_6H_4	H	Bn	**3h** (42)	**3h'** (39)
9[b]	**1i**: Naphthyl	H	Bn	**3i** + **3i'** (72)	
10[b]	**1j**: 4-$MeOC_6H_4$	H	Bn	**3j** + **3j'** (83)	
11	**1k**: 4-MeC_6H_4	H	BrC_8H_{14}	**3k** (53)	**3k'** (29)
12	**1l**: 4-MeC_6H_4	Me	Me	**3e** (51)	**3e'** (42)
13[b,c]	**1** =  **1m**: Me	Me	Me	**5f** + **5f'** (54)	

[a]Reaction conditions are as follows: All the reactions were performed using 0.12−0.31 mol **1** in *tert*-butyl acetate (1.5 mL) with 20 mol % $In(OTf)_3$ at 80 °C in a resealable vial. [b]1:1 ratio by ^1H NMR. [c]**1m** = 2-methoxy-2,4-dimethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one.

Table 3. Substrate Scope of the $Ni(OTf)_2$-Catalyzed α-Methylallylation[a]



1 2 3'

Entry	Substrate			Yield % (**3'**)
	R_1	R_2	R_3	
1	**1a**: Me	H	H	**3a'**:65
2	**1b:** C_4H_9	H	H	**3b'**:72
3	**1c:** Me	H	Me	**3c'**:70
4	**1d:** Me	H	C_4H_9	**3d'**:81
5	**1e:** 4-MeC_6H_4	H	Me	**3e'**:61
6	**1f:** 3-FC_6H_4	H	Me	**3f'**:76
7	**1g:** 4-$MeOC_6H_4$	H	Me	**3g'**:79
8	**1h:** 4-^{t}BuC_6H_4	H	Bn	**3h'**:66
9	**1l:** 4-MeC_6H_4	Me	Me	**3e'**:65
10	**1n:** 3,5-$F_2C_6H_3$	Me	Me	**3n'**:72
11	**1** =  **1o:** C_6H_5	Me	H	**3o'**:54

[a]Reaction conditions are as follows: All the reactions were conducted using 0.12−0.31 mmol **1** in *tert*-butyl acetate (1.5 mL) with 20 mol % $Ni(OTf)_2$ at 80 °C in the resealable vial. [b]**1o** = 2-methoxy-2-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one.

studies have been performed for the lowest spin state (singlet). The cycle initiates with the coordination of $Ni(OTf)_2$ and $In(OTf)_3$ with incoming substrate **1a** to form intermediate **E3** through transition state [**TS1**]. This process is thermodynamically favorable, and the energy barrier is found to lower for Ni-mediated [**TS1**] (9.57 kcal/mol) as compared to In-mediated [**TS1**] (15.95 kcal/mol). Further, the reaction of intermediate **E3** with isobutylene (nucleophile generated in situ) in the presence of HOTf results in the **G3** intermediate, which is exergonic by 13.09 kcal/mol through [**TS2**]. Finally, abstraction of H in the presence of (OTf)Ni−OH/$(OTf)_2$In−OH leads to product formation. The selectivity of product formation is dependent particularly on the type of H abstraction. This is indicated in the involvement of [**TS3**/**TS3′**] during this process.

For $Ni(OTf)_2$, H abstraction via [**TS3′**] (41.4 kcal/mol) results in the formation of the terminal product, which is exergonic by 6.14 kcal/mol. Meanwhile, when the reaction proceeds via [**TS3**], the transition state barrier is found to be higher, resulting in the substituted product that is endergonic by 6.5 kcal/mol. Therefore, it is evident that the pathway followed gives predominantly the terminally substituted product (Hoffman product (**3a′**)). However, in the presence of $In(OTf)_3$, mixtures of products are obtained, *i.e.*, both Hoffmann (−40.9 kcal/mol) and Saytzeff (−39.2 kcal/mol) products are obtained via [**TS3**/**TS3′**]. The energy barriers for [**TS3**/**TS3′**] in this step correspond to 39.4 and 40.1 kcal/mol, respectively. These calculations conclude that formation of terminal product is feasible over the substituted product when $Ni(OTf)_2$ is involved in the reaction mechanism.

The catalytic cycle (Scheme 1) begins through the coordination of $Ni(OTf)_2$/$In(OTf)_3$ with the oxygen of C3-hydroxy-3-methyloxindole (**C3**) to give transition state [**TS1**]. The lone pair on the nitrogen of **TS1** undergoes electronic conjugation to form the intermediate **E3** with the formation of triflic acid in the reaction medium. Further, the formation of intermediate **E3** is confirmed by HRMS (see the SI, Figure S130). The mass of (**E3** + H) was found to be 146.0602 which is similar with the calculated mass of (**E3** + H). Next, *in situ* generated isobutylene undergoes nucleophilic addition at the C3 position of **E3** to produce the intermediate tertiary carbocation **G3** through [**TS2**]. Finally, $Ni(OTf)_2$−OH abstracts a terminal hydrogen via [**TS3′**] to obtain the desired product, **3a′**. A similar catalytic cycle occurs in the presence of $In(OTf)_3$ to form the mixture of Hoffmann and Saytzeff products.

Subsequently, we studied this reaction with peroxide *N*-functionalized 2-oxindole derivatives to form quaternary methylallyl-functionalized 1,4-benzoxazin-3-one. A model reaction was studied for the optimum conditions (Table 4). This reaction did not afford any product in the absence of Lewis acids at room and high temperatures (Table 4, entries 1 and 2). We utilized several Lewis acids, such as $FeCl_3$, $Fe(OTf)_2$, $Mn(OTf)_2$, $Sn(OTf)_2$, $Ni(OTf)_2$, and $Cu(OTf)_2$ (Table 4, entries 1−8); however, none of these catalysts achieved satisfactory results. In the sequential rearrangement, exclusive selectivity for methylallylation was observed when 30 mol % $In(OTf)_3$ used as a catalyst at 60 °C, affording a 52% yield of **5a** (Table 4, entry 9). This reaction afforded an 85%

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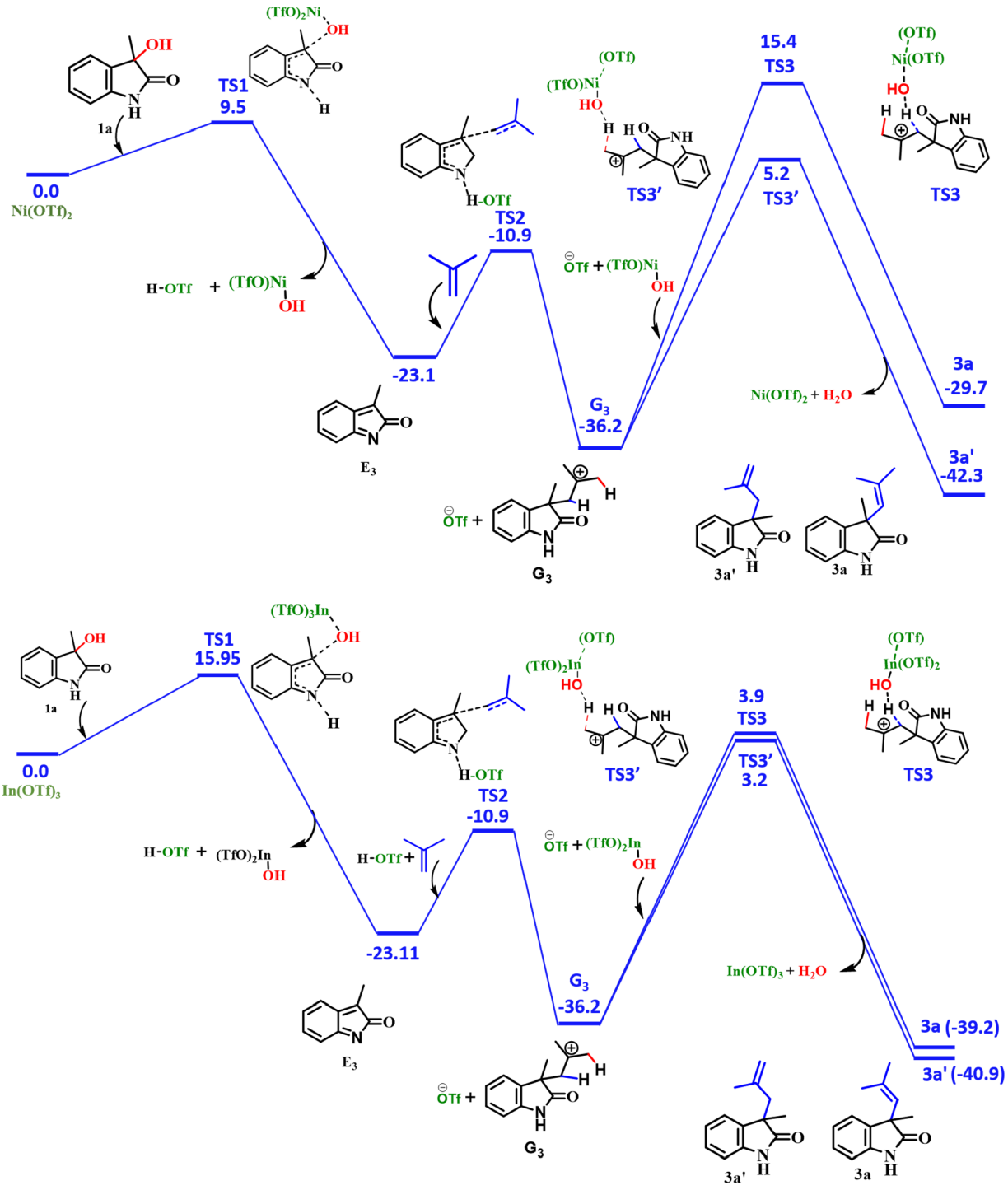


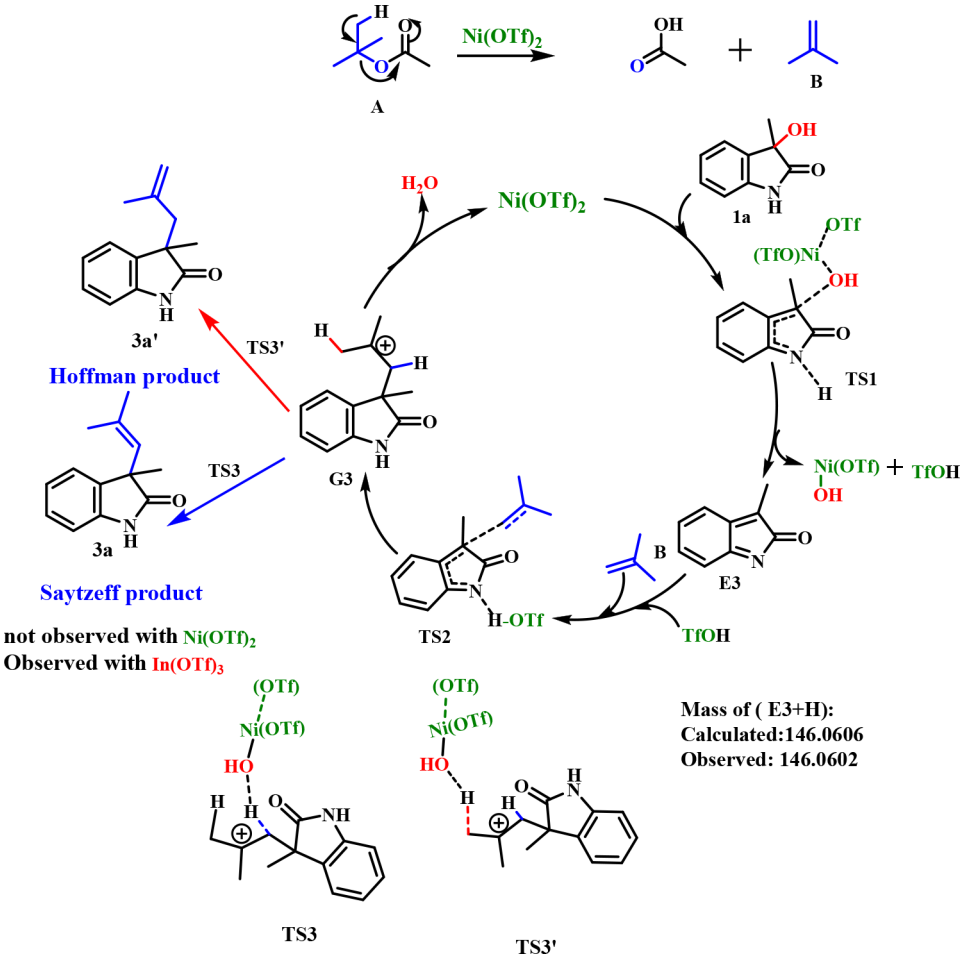
Figure 2. (Top) Free energy profile for Ni-catalyzed nucleophilic substitution reactions. The free energy values are given in kcal/mol. (Bottom) Free energy profile for In-catalyzed nucleophilic substitution reactions. The free energy values are given in kcal/mol.

yield of **5a** after 24 h (Table 3, entry 11). The yield decreased when the temperature increased to 80 °C, and **4a** decomposed when reaction temperature was 100 °C (Table 4, entries 12 and 13, respectively). Moreover, Brønsted acids failed to provide **5a** (Table 4, entries 14 and 15).

Subsequently, we explored the substrate scope for this methylallyl functionalization with various C3-alkylated peroxyoxindoles (Scheme 2). Thus, *N*-protected C3-substituted peroxyoxindole, where the phenyl group had $-CH_3$, −F, and −OMe, afforded good yields of the respective methylallyl substituted products **5b**−**5e** (42−72% yields). Further, the structure of product **5c** is confirmed by X-ray structure analysis (Figure 3). The *N*-benzyl-protected peroxy-oxindoles also underwent successful methylallylation reactions to provide a good yield of the rearranged products **5g**−**5h**. The decrease in yield was observed for C3-substituted *N*-butyl peroxyoxindole derivatives (**5j**−**5l**). The C3-phenyl *N*-allyl substituted peroxyoxindole afforded selectively **5m** in a 57% yield. The yield decreased with as the carbon chain of the *N*-substitution of peroxyoxindole increased, *i.e.*, *N*-butene-, *N*-pentene-, *N*-

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Scheme 1. Plausible Catalytic Pathway



hexene-, *N*-(8-bromooctyl)-substituted peroxyoxindoles afforded desired **5n**−**5q**, respectively.

To understand the reaction pathway, a control experiment was performed with *tert*-butyl acetate, **4a**, and $In(OTf)_3$ at room temperature (Scheme 3I), which resulted in the attack of the *tert*-butyloxy group at the C3-position of the 1,4-benzooxazine moiety. This indicates that heating is required for the generation of isobutylene. Further, the reaction was performed in the NMR tube with *tert*-butyl acetate and $In(OTf)_3$ at 60 °C (Scheme 3II). This experiment confirmed the in situ generation of isobutylene by NMR analysis (SI, Figures S4−S8). Furthermore, the reaction of **4a** with *tert*-butanol resulted in no reaction (Scheme 3III), indicating that *tert*-butanol might coordinate with the Lewis acid, which diminishes reactivity of the Lewis acid.

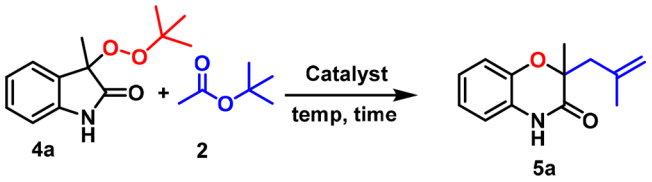
The reaction kinetics was studied by varying the catalyst and peroxide **4a** concentration. Moreover, this kinetic study helps to determine the effect of various component on the sequential rearrangement and methylallylation reaction for the formation of **5a** by the initial rate method. Initially, the rate order for the formation of **5a** was determined by measuring the initial rate of the reaction at different concentrations of **4a**. The various concentrations of **4a** (0.05, 0.1, 0.2, 0.3, and 0.4 M) were reacted with 0.03 M $In(OTf)_3$ catalyst (see the SI, Table S1 and Figure S2). This indicates that the rate of the reaction increases upon increasing the concentration of **4a**, and a slope 0.970 was obtained from the plot of log(rate) versus log([**4a**]) (Figure 4a). Thus, this sequential rearrangement and substitution reaction to form **5a** mainly depends upon the concentration of compound **4a**. Notably, an increase in the rate was observed upon increasing the loading of $In(OTf)_3$ catalyst (see the SI, Table S2 and Figure S3), and a slope of 0.863 was obtained (Figure 4b). This highlights that the reaction is positive order with respect to the catalyst $In(OTf)_3$ and involves multiple steps. From the positive rate order with respect to the peroxide **4a** and $In(OTf)_3$, the activation of the peroxide **4a** by the catalyst might be the crucial step in the catalytic cycle.

To evaluate the energies involved in the rearrangement of peroxyoindole derivatives, we have also calculated and examined the energetics by taking into account our previous report[13] of $Sn(OTf)_2$-catalyzed rearrangement for peroxyoxindoles, as presented in the SI (see the SI, Figures S9 and S10, respectively). Catalytic cycles (see the SI, Schemes S4 and S5) of the $Sn(OTf)_2$-catalyzed rearrangement of peroxyoxindoles confirmed that the reaction path way proceeds via deprotection of the *tert*-butyl group from the peroxide compound and *in situ* generation of a stable 1,4-benzooxazine tertiary carbocation. With the knowledge of the reaction path of the $Sn(OTf)_2$-catalyzed rearrangement of peroxyoxindoles, we investigated the feasibility of the $In(OTf)_3$-catalyzed quaternary methylallylation of peroxy-2-oxindole through skeletal rearrangement and nucleophilic substitution using *tert*-butyl acetate (Figure 5).

The initiation of the cycle involves the interaction of $In(OTf)_3$ with peroxy substrate **4a** to give coordinated

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Table 4. Optimization of Reaction Conditions on Peroxyoxindole[a]



entry	catalyst	temperature (°C)	time (h)	yield of **5a** (%)
1		rt	16	no reaction
2		60	16	no reaction
3[b]	$FeCl_3$	60	16	0
4	$Mn(OTf)_2$	60	16	no reaction
5	$Sn(OTf)_2$	60	16	45
6	$Fe(OTf)_2$	60	16	0
7	$Ni(OTf)_2$	60	16	no reaction
8	$Cu(OTf)_2$	60	16	no reaction
9	$In(OTf)_3$	60	16	52
10[b]	$In(OTf)_3$	rt	16	0
11[c]	$In(OTf)_3$	60	24	85
12	$In(OTf)_3$	80	24	47
13	$In(OTf)_3$	100	24	decomposition
14[d]	Amberlyst-15	60	24	10
15	TFA	60	24	decomposition

[a]Reaction conditions are as follows: All the reactions were performed using 0.21 mmol **4a** in *tert*-butyl acetate (1.5 mL) with 30 mol % catalyst at a specific temperature in the resealable vial. [b]No expected product was obtained. [c]63% of product **5a** was obtained with 20 mol % $In(OTf)_3$. [d]A w/w ratio of 2:1 was used for substrate Amberlyst-15.

intermediate **D** via [**TS1**] with an energy barrier of 12.13 kcal/mol. The intermediate **D** undergoes protonation at the peroxy oxygen to form intermediate **E** via [**TS2**], which is endergonic by 17.48 kcal/mol. Here, three possibilities exist: (a) First, the intermediate **E** can undergo ring expansion via [**TS3′**] (6.50 kcal/mol) to intermediate **H**, as indicated in blue in Figure 4. (b) Second, **E** can undergo ring expansion to form hydroxylated intermediate **G** through [**TS3**] (with an energy barrier of 1.3 kcal/mol), as represented by black. In this path, the removal of the hydroxyl anion results in **H**, which is exergonic by 6.03 kcal/mol. (c) Lastly, **E** can react with the incoming chelated ester to form intermediate **F**, as shown in red, which is exergonic by 6.27 kcal/mol. **F** further rearranges to intermediate **H**. Finally, isobutylene reacts with the protonated intermediate **H** to form tertiary carbocation **I**, which is exergonic by 6.45 kcal/mol. Deprotonation of **I** results in the formation of final product **5a**, which is exergonic by 5.56 kcal/mol. DFT studies indicate that all three possibilities are spontaneous. However, the pathway with hydroxy intermediate **G** is more favorable. The deprotonation of **I** leads to the formation of final product **5a**, with an exergonic energy of 5.56 kcal/mol.

On the basis of preliminary experiments, kinetic analysis, computational data, and literature reports,[13] a plausible mechanism is proposed (Scheme 4). Initially, *tert*-butyl acetate undergoes ester pyrolysis to produce isobutylene (**B**). The catalytic cycle starts with the coordination of $In(OTf)_3$ with peroxyoxindole **4a** to give [**TS1**]. Proton abstraction from transition state [**TS1**] leads to the formation of intermediate **D** with the liberation of isobutylene gas. Intermediate **E** forms after the protonation of intermediate **D** through transition state [**TS2**], followed by the coordination of regenerated $In(OTf)_3$ from [**TS2**]. The C3−C4 bond migrates to the oxygen attached to the C3 carbon of the peroxy group. Simultaneously, the removal of −OH and attack on the C3 position lead to the formation of intermediate **G**. Intermediate **G** results in intermediate **H** after −OH removal. The attack of isobutylene on intermediate **H** leads to the formation of tertiary carbocation intermediate **I**. Finally, proton abstraction from **I** results in the desired product **5a**.

CONCLUSION

In summary, we have developed a new approach for the selective quaternary α-vinylation and methylallylation of hydroxy groups and peroxides using *tert*-butyl acetate in the presence of catalytic $In(OTf)_3$ and $Ni(OTf)_2$. This reaction was demonstrated with a series of vinylated and methylallylated oxindole derivatives. Moreover, $In(OTf)_3$ selectively promoted the quaternary α-vinylation of hydroxyl oxindole to afford the Hoffmann product. Interestingly, an exclusive selectivity was obtained for the methylallylation of hydroxyoxindole using catalytic $Ni(OTf)_2$. However, this reaction with peroxyoxindole afforded sequential rearrangement and quaternary methylallylation when catalytic $In(OTf)_3$ was used. Kinetic studies revealed that both the concentration of reactants and catalysts play a vital role in these reactions. Density functional theory (DFT) calculations were performed using PBE functional to obtain the transition states for the vinylation and methylallylation reaction. This study further explained the selectivity for the vinylation and methylallylation reaction when different Lewis acid was used. From the DFT studies, experimental evidence and previous literature report, plausible mechanisms were proposed and justified the reaction pathway for the vinylation and methylallylation of hydroxyoxindole and peroxyoxindole.

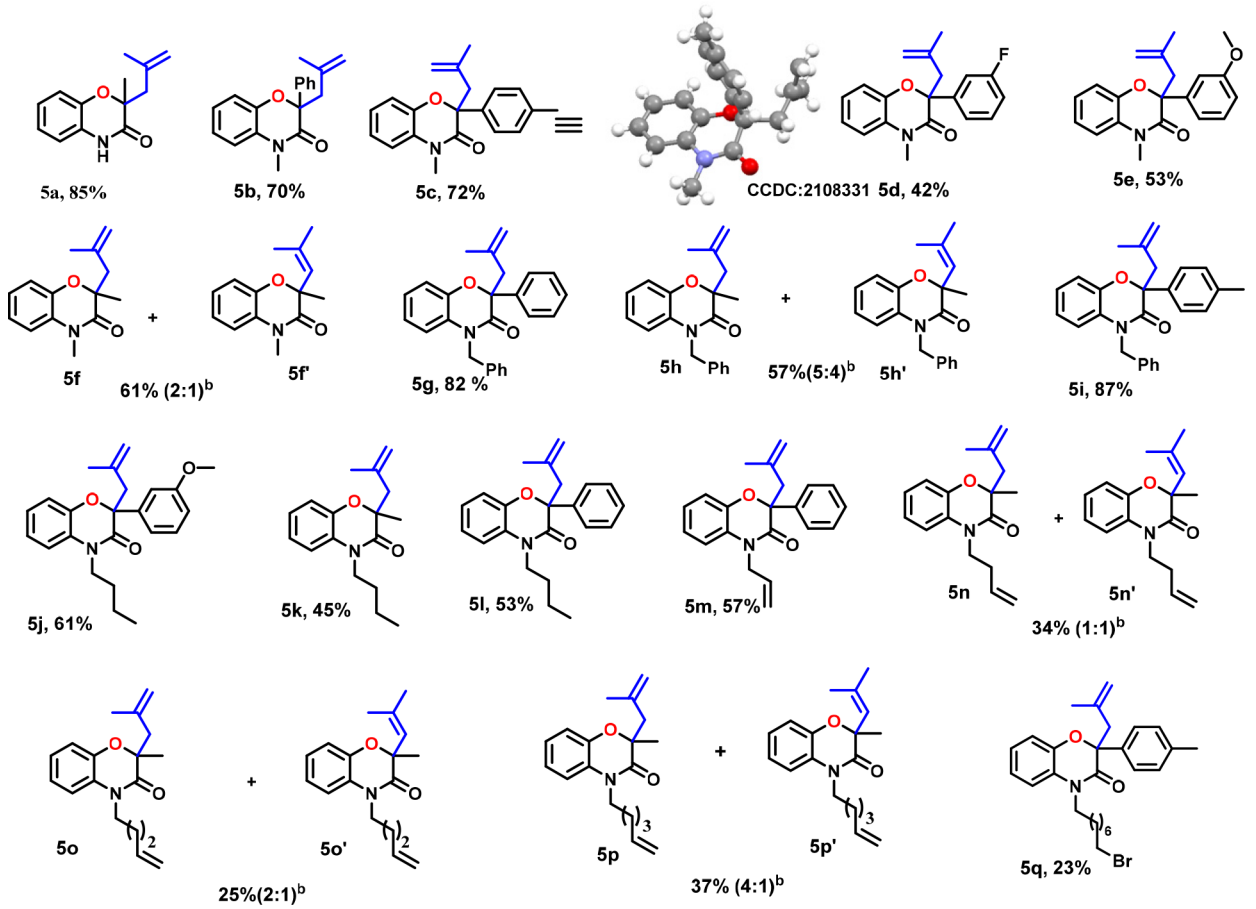
EXPERIMENTAL SECTION

General Information and Data Collection. Commercially available reagents and solvents were used for the preparation of starting material without further purification. Visualization was accomplished with UV light. Column chromatographic separations were performed over 100−200 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively, using Bruker 400 MHz and JEOL 400 MHz spectrometers. Abbreviations used in the NMR experiments are as follows: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. High-resolution mass spectra were obtained with a Waters-synapt G2 instrument using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha Fourier transform infrared spectrometer. The single-crystal data were collected on a Bruker APEX-III instrument. Gas Chromatography analyses were performed using a Shimadzu GC2010 gas chromatograph equipped with a Shimadzu AOC-20i auto injector and a Restek RTX-5 capillary column (30 m × 250 μm). Melting points were recorded on DBK programmable melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex IIICCD Duo diffractometer (operated at 1500 W power; 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation. More information on crystal structures (**5c** and **3j′**) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition numbers 2108331 and 2214336. Although the reaction of a metal salt with organic peroxides leads to an explosive reaction, we have not faced any issues while using TBHP.

Computational Details. All calculations were performed using a density functional theory (DFT) based methodology as implemented in the Gaussian 09 package.[14] Different functionals including dispersion effects (*i.e.*, B3LYP, PBE, and M06) are benchmarked

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Scheme 2. Substrate Scope of the Sequential Rearrangement and Methylallylation Reaction[a]



[a]Reaction conditions are as follows: All reactions were carried out with 0.15−0.21 mmol (50 mg) **4** in *tert*-butyl acetate (1.5 mL) using 30 mol % $In(OTf)_3$ at 60 °C in the resealable tube for 24 h. [b]NMR conversion.

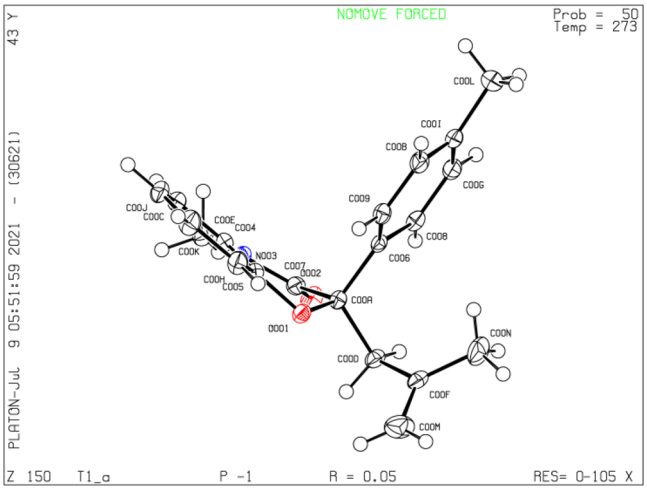
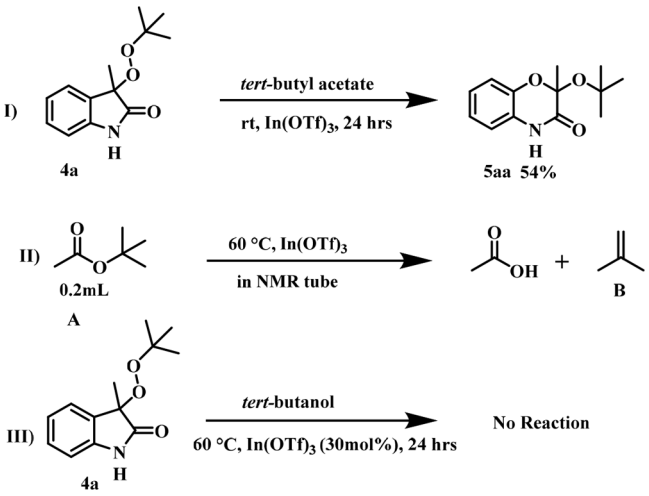


Figure 3. ORTEP diagram of **5c**

Scheme 3. Preliminary Experiment for the Mechanistic Study



(see the SI, Figures S13 and S14). Finally, the structures are optimized using the PBE functional[15] with the TZVP basis set for C, H, O, S, F, and N atoms and LANL2DZ for Ni, Sn, and In. Vibrational frequency calculations were performed to confirm that each optimized structure corresponds to a minimum. Solvent effects were included in the calculations as implemented in SMD model for acetic acid. In cases of transition states, a preoptimization was carried out prior to the transition state search. The transition state was identified by the presence of a single imaginary frequency. The energies reported in the free energy profile are ΔG values incorporated with zero-point energy corrections for the optimized minima at 298.15 K.

General Procedure A for the Methylallylation of C3-Hydroxy-3-alkylated Oxindole (3). 1.5 mL of *tert*-butyl acetate was added to the 20 mL resealable vial containing 3-substituted-3-

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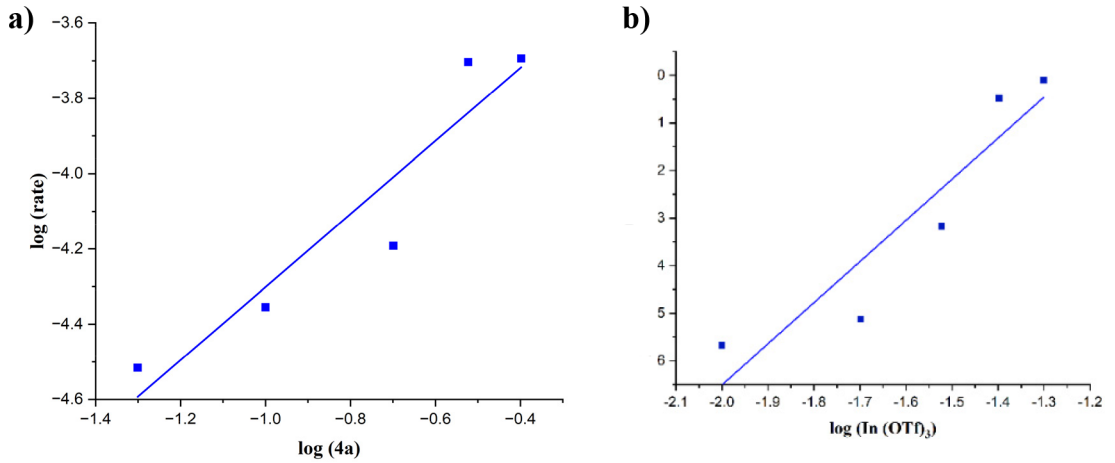


Figure 4. (a) Plot of log(rate) versus log([**4a**]). (b) Plot of log(rate) versus log($In(OTf)_3$).

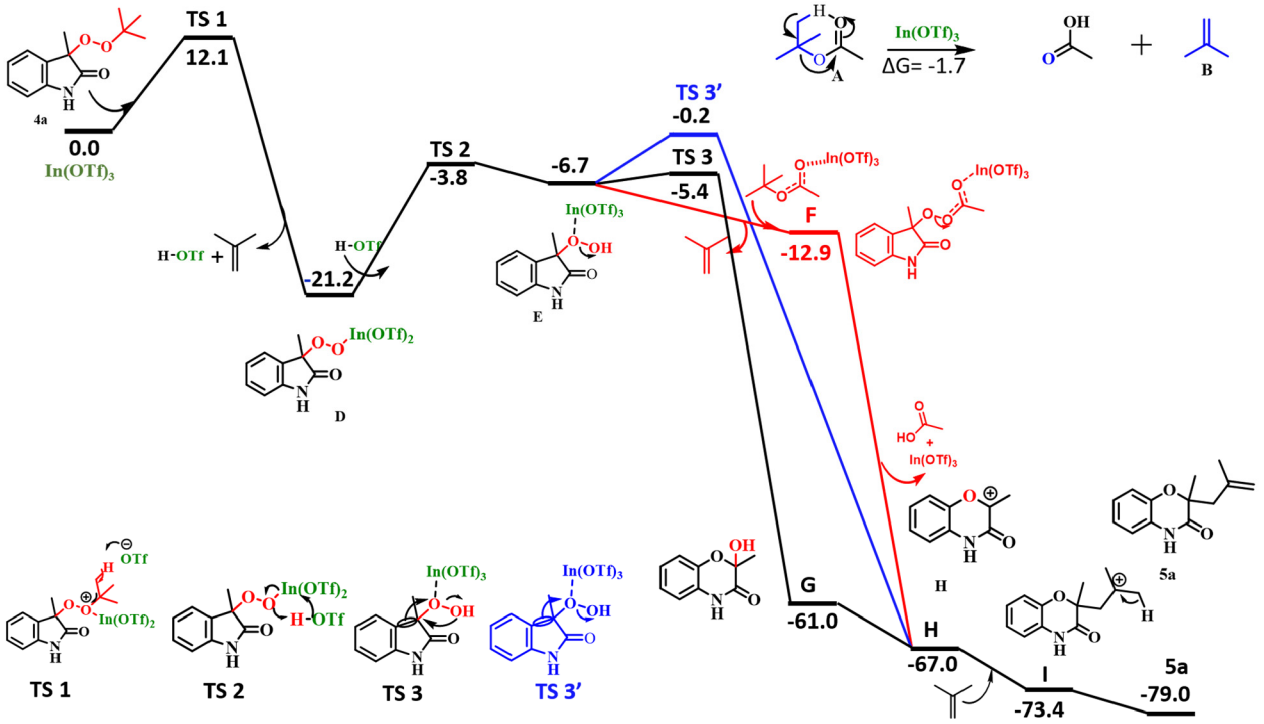


Figure 5. Free energy profile for In-catalyzed rearrangement. The free energy values are given in kcal/mol.

hydroxyoxindole (50 mg, 1 equiv). Then, 20 mol % $In(OTf)_3$ or $Ni(OTf)_2$ was added to the vial. Finally, the vial was sealed with an aluminum cap with a septum. Further, the solution was heated at 80 °C in the preheated oil bath for 12 h. After the completion of the reaction, the volatile components were evaporated under vacuum. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (1:99 to 10:90) to afford desired product **3**.

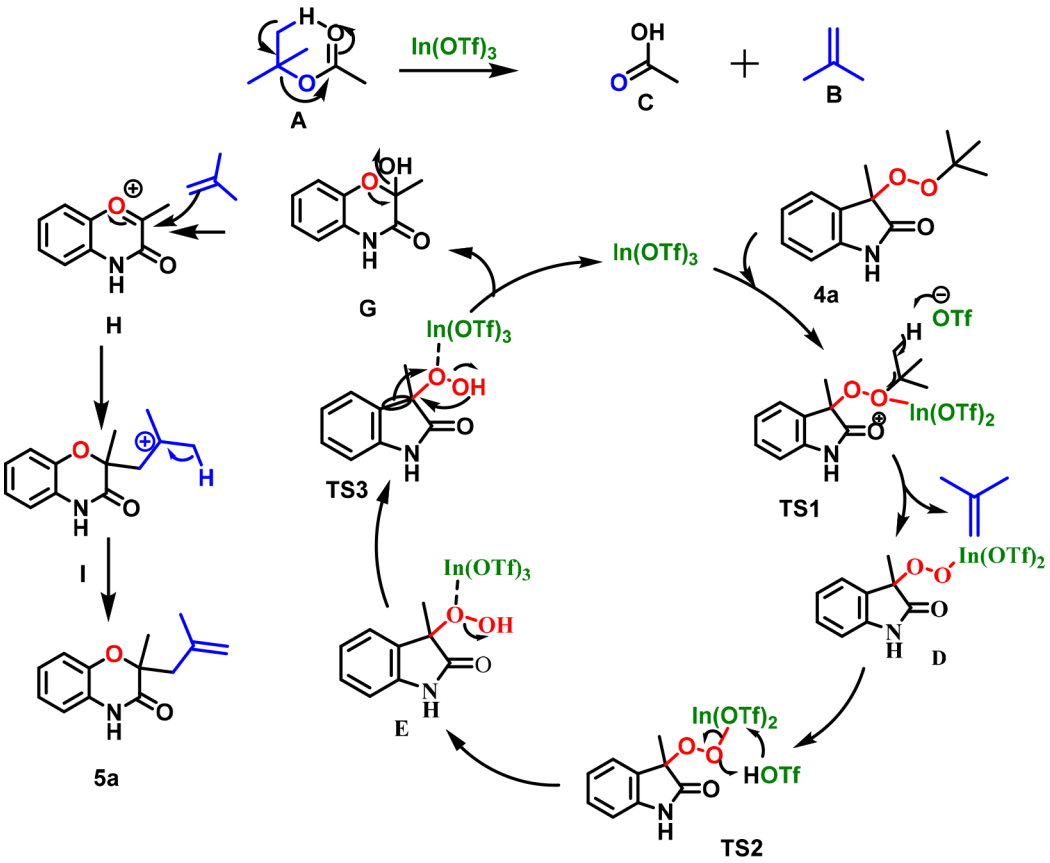
General Procedure B for the Methylallylation of C3-Peroxide-3-alkylated Oxindole (5). 1.5 mL of *tert*-butyl acetate was added to the 20 mL resealable vial containing 3-substituted-3-*tert*-butylperoxyoxindole (50 mg, 1 equiv). Then, 30 mol % $In(OTf)_3$ was added to the vial. Finally, the vial was sealed with an aluminum cap with a septum. Further, the solution was heated in the preheated oil bath for at 60 °C for 24 h. After the completion of the reaction, the volatile components were evaporated under vacuum. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95) to afford desired product **5**.

General Procedure C for the Synthesis of 3-Hydroxy Oxindole Derivatives. *General Procedure C(i) for the 3-Alkyl-3-hydroxyoxindole Derivatives (**1a**–**1d**).*[16] The 3-alkyl oxindole (1 mmol), KO*t*Bu (1 mmol), and toluene (4 mL) were added to a round-bottom flask. Then, the mixture was stirred at room temperature (25 °C) in open air for 24 h. After completion of the reaction, the volatile solvent was removed under vacuum and the crude reaction mixture was directly purified by silica gel column chromatography using EtOAc/*n*-hexane (30:70) to afford the products **1a**–**1d**.

*General Procedure C(ii) for the 3-Aryl-3-hydroxy-Substituted Oxindole Derivatives (**1e**–**1n**).*[17] In a two-neck round-bottom flask, bromobenzene derivative (1 equiv) was dissolved in anhydrous THF. To the reaction mixture were added Mg turnings (1.2 equiv). The reaction flask was warmed using hot air gun to initiate the reaction. The reaction mixture was then stirred under N_2 until most of the Mg turnings had disappeared. The resulting Grignard solution was cooled to 0 °C and added dropwise to a solution of isatin derivatives (1 equiv) in THF. The resulting solution was stirred at 0 °C for complete consumption of the reactant, and the TLC analysis indicated complete consumption of the starting material. The reaction

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Scheme 4. Plausible Mechanism for Methylallyl Functionalization through Peroxyoxindole Rearrangement



mixture was then quenched by the addition of saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude 3-aryl-3-hydroxy-substituted oxindole derivatives. The residue was directly purified by silica gel column chromatography using EtOAc/*n*-hexane (30:70 to 50:50) to afford the products **1e−1m**.

*General Procedure C(iii) for **1m** and **1o**.*[13b] To a 20 mL resealable vial were added $Sn(OTf)_2$ (0.1 equiv, 10 mol %), dimethyl carbonate (1 mL), and there peroxyoxindole compound (150 mg, 1 equiv). The tube was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 60 °C in an oil bath for 14 h. After 14 h, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel chromatography using EtOAc/*n*-hexane (20:80) to afford the products **1n** and **1o**.

General Experimental Procedure D for the Synthesis of Peroxyoxindole (4).[18] To a round-bottom flask were added $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %) and 2,2-bipyridine (5 mol %) in acetonitrile. The solution was stirred at room temperature for 20−30 min until it obtained a deep-brown color, and then 3-substituted oxindole compound (1 equiv) was added. Finally, 5.0−6.0 M TBHP in a decane solution (4 equiv) was added to the above solution. The reaction mixture was kept at room temperature under stirring for 4 h. After completion of the reaction, the volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography using EtOAc/*n*-hexane (10:90 to 20:80) to afford the product **4**.

Analytical Data for 3-Hydroxy Oxindole Derivatives (1). *3-Hydroxy-1,3-dimethylindolin-2-one (**1c**).*[19] **1c** was synthesized according to general procedure C(i), using 1,3-dimethylindolin-2-one (500 mg, 3.1 mmol), to afford 3-hydroxy-1,3-dimethylindolin-2-one (473 mg, 89%).^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (d, J = 7.6 Hz, 1H), 7.35−7.31 (m, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 3.20 (s, 3H), 3.05 (s, 1H), 1.61 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 178.7, 164.2, 142.9, 131.4, 129.8, 123.6, 123.4, 108.7, 73.8, 26.4, 24.9.

*3-(3-Fluorophenyl)-3-hydroxy-1-methylindolin-2-one (**1f**).*[20] **1f** was synthesized according to general procedure C(ii), using 1-methylindoline-2,3-dione (500 mg, 3.11 mmol), to afford 3-hydroxy-3-(3-fluorophenyl)-3-hydroxy-1-methylindolin-2-one (663 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (td, J = 0.4 Hz, J = 7.6 Hz, 1H), 7.29 (m, 2H), 7.12 (m, 3H), 6.99 (m, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.26 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 177.1, 164.2, 161.9, 143.6, 142.8, 142.8, 131.3, 130.4, 130.3, 130.3, 125.0,123.9, 121.1, 121.1, 115.5, 115.3, 113.0, 112.8, 109.0, 26.8.

*3-Hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (**1g**).*[21] **1g** was synthesized according to general procedure C(ii), using 1-methylindoline-2,3-dione (500 mg, 3.11 mmol), to afford 3-hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (685 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 4H), 7.09 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.84 (m, 2H), 3.77 (s, 3H), 3.23 (d, J = 4.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 159.7, 132.2, 131.7, 129.9, 126.9, 125.0, 123.6, 114.1, 108.8, 55.4, 26.6.

*1-Benzyl-3-(4-(tert-butyl)phenyl)-3-hydroxyindolin-2-one (**1h**).*[22] **1h** was synthesized according to general procedure C(ii), using 1-benzylindoline-2,3-dione (500 mg, 2.11 mmol), to afford 1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-hydroxyindolin-2-one (618 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 1.2 Hz, 3H), 7.33−7.31 (m, 2H), 7.24−7.20 (m, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 5.04 (d, J = 16 Hz, 1H), 4.84 (d, J = 16 Hz, 1H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 177.8, 151.4, 142.7, 137.2, 135.6, 129.8, 129.0, 127.4, 125.8, 125.1, 123.7, 109.9, 44.1. 34.7, 31.4.

*1-Benzyl-3-hydroxy-3-(naphthalen-2-yl)indolin-2-one (**1i**).*[23] **1i** was synthesized according to general procedure C(ii), using 1-benzylindoline-2,3-dione (500 mg, 2.11 mmol), to afford 1-benzyl-3-hydroxy-3-(naphthalen-2-yl)indolin-2-one (547 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.82−7.78 (m, 3H), 7.49−7.47 (m, 2H), 7.42−7.40 (m, 1H), 7.36−7.35 (m, 1H), 7.32−7.30 (m,

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1H), 7.27−7.23 (m, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 5.10 (d, J = 16 Hz, 1H), 4.87 (d, J = 16 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 142.8, 137.6, 135.6, 133.3, 130.1, 129.1, 128.8, 128.4,128.0, 127.8, 127.5, 126.5, 125.2, 124.5, 123.8, 123.1, 110.0, 78.3, 44.3.

Analytical Data for Products 3a−3o and 3a′−3o′. *3-Methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3a**)*[24] *and 3-Methyl-3-(2-methylallyl)indolin-2-one (**3a′**).* **3a** and **3a′** were synthesized following general experimental procedure A by mixing 3-hydroxy-3-methylindolin-2-one (50 mg, 1 equiv) and $In(OTf)_3$ (20 mol %) in 1.5 mL of *tert*-butyl acetate to form product **3a** (33.3 mg, 54%) as a thick white liquid and product **3a′** (15 mg, 27%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (5:95 to 10:90), which became white solids after being kept for a few days.

The above reaction formed 3-methyl-3-(2-methylallyl)indolin-2-one (**3a′**) with a yield of 39.7 mg (65%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst after column chromatography purification.

*3-Methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (td, J = 7.6, 1.3 Hz, 1H), 7.12 (d, J = 7.1 Hz, 1H), 7.02 (td, J = 7.5, 0.9 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 5.44−5.40 (m, 1H), 1.72 (d, J = 1.3 Hz, 3H), 1.51 (s, 3H), 1.14 (d, J = 0.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.2, 139.9, 137.9, 136.8, 127.6, 125.3, 123.4, 122.9, 109.9, 49.2, 27.7, 26.8, 18.4. FTIR (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1237.

*3-Methyl-3-(2-methylallyl)indolin-2-one (**3a′**).* Melting point: 109−110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 11.9, 4.3 Hz, 2H), 7.03 (dd, J = 10.8, 4.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 4.59 (m, 1H), 4.55 (m, 1H), 2.73 (d, J = 13.5 Hz, 1H), 2.50 (d, J = 13.5 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.2, 141.2, 140.4, 134.2, 127.7, 123.5, 122.2, 114.4, 109.8, 49.2, 45.6, 24.9, 23.6. FTIR (neat): 3012, 2801, 1612, 1592, 1355, 1142, 799 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1235.

*Large-Scale Synthesis of Compounds **3a** and **3a′**.* *tert*-Butyl acetate (4 mL) was added to the 20 mL resealable vial containing 3-substituted-3-hydroxyoxindole (163 mg, 1 mmol). Then, 20 mol % $In(OTf)_3$ was added to the vial. Finally, the vial was sealed with an aluminum cap with a septum. Further, the solution was heated at 80 °C in the preheated oil bath for 12 h. After the completion of the reaction, the volatile components were evaporated under vacuum. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (1:99 to 10:90) to afford the desired product **3a** in a 44% yield (88 mg) and **3a′** in a 26% yield (52 mg).

*3-Butyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3b**) + 3-Butyl-3-(2-methylallyl)indolin-2-one (**3b′**).* **3b** + **3b′** was synthesized following general experimental procedure A by mixing **1b** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **3b′** + **3b** as an inseparable mixture (31 mg, 59%) as a thick white liquid after column after purification in silica gel chromatography using EtOAc/*n*-hexane (5:95 to 10:90).

^1H NMR (400 MHz, $CDCl_3$): δ 7.20−7.18 (m, 3H), 7.09−7.00 (m, 3H), 6.89−6.8 (m, 2H), 4.55 (m, 1H), 5.35 (s, 1H), 4.57 (m, 1H), 4.54 (s, 1H), 2.70 (d, J = 13.2 Hz, 1H,) 2.49 (d, J = 13.6 Hz, 1H) 1.62−1.58 (m, 12H), 1.36 (s, 14H), 0.94 (m, 7H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.2, 139.6, 134.2, 128.8, 127.8, 127.5, 123.8, 122.7, 122.3, 114.6, 109.6, 109.5, 54.7, 53.7, 45.6, 41.0, 38.9, 31.9, 31.7, 30.1, 29.8, 26.2, 25.6, 23.9, 23.0, 19.6. FTIR (neat): 3021, 2851, 2341, 1688, 1593, 1451, 1322, 1054, 856 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO$ 244.1701, found 244.1706.

*3-Butyl-3-(2-methylallyl)indolin-2-one (**3b′**).* **3b′** was exclusively synthesized following general experimental procedure A by mixing **1b** (50 mg, 1 equiv) and 20 mol % $Ni(OTf)_2$ in 1.5 mL of *tert*-butyl acetate to form desired product **3b′** (55 mg, 72%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95), which became a white solid after being kept for a few days

^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (bs, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 4.57 (s, 1H), 4.54 (s, 1H), 2.71 (d, J = 13.4 Hz, 1H), 2.49 (d, J = 13.3 Hz, 1H), 1.95−1.87 (m, 4.5 Hz, 1H), 1.80−1.67 (m, 3H), 1.35 (s, 3H), 1.25−1.16 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 182.4 141.1, 132.7, 127.8, 123.8, 122.3, 114.6, 109.7, 53.9, 45.6, 38.9, 29.8, 26.2, 23.9, 22.9, 13.9. FTIR (neat): 3021, 2851, 2341, 1688, 1593, 1451, 1322, 1054, 856 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO$ 244.1701, found 244.1706.

*1,3-Dimethyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3c**)*[25] *and 1,3-Dimethyl-3-(2-methylallyl)indolin-2-one (**3c′**).*[26] **3c** and **3c′** was synthesized following general experimental procedure A by mixing **1c** (50 mg, 1equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **3c** with a yield of 34.98 mg (58%) and **3c′** with a yield of 15 mg (25%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction resulted in exclusively in 1,3-dimethyl-3-(2-methylallyl)indolin-2-one (**3c′**) with a yield of 41.78 mg (70%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*1,3-Dimethyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3c**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.14 (dd, J = 7.3, 0.8 Hz, 1H), 7.04 (td, J = 7.5, 0.9 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.43−5.40 (m, 1H), 3.24 (s, 3H), 1.70 (d, J = 1.3 Hz, 3H), 1.47 (s, 3H), 1.04 (d, J = 1.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.5, 142.8, 137.3, 136.3, 127.6, 125.7, 123.1, 122.9, 108.1, 48.7, 27.4, 26.8, 26.4, 18.3. FTIR (neat): 3021, 1672, 1590, 1376, 1098, 766 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1392.

*1,3-Dimethyl-3-(2-methylallyl)indolin-2-one (**3c′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 4.55 (s, 1H), 4.48 (s, 1H), 3.19 (s, 3H), 2.72 (d, J = 14 Hz, 1H), 2.47 (d, J = 14 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.4, 143.3, 141.3, 133.8, 129.2, 127.8, 123.2, 122.3, 114.3, 108.1, 54.1, 48.8, 45.8, 30.1, 26.2. 24.8, 23.7, 19.2. FTIR (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1393.

*1-Butyl-3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3d**) and 1-Butyl-3-methyl-3-(2-methylallyl)indolin-2-on (**3d′**).* **3d** and **3d′** were synthesized following general experimental procedure A by mixing **1d** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butylacetate to form desired product **3d** with a yield of 23.56 mg (41%) and **3d′** with a yield of 18.42 mg (32%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction resulted in 1-butyl-3-methyl-3-(2-methylallyl)-indolin-2-on (**3d′**) with a yield of 44.83 mg (81%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*1-Butyl-3-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one(**3d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, J = 7.7, 1.2 Hz, 1H), 7.15−7.12 (m, 1H), 7.02 (td, J = 7.5, 0.7 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.42−5.39 (m, 1H), 3.78−3.66 (m, 2H), 1.70 (d, J = 1.2 Hz, 3H), 1.66 (m, 2H), 1.46 (s, 3H), 1.44−1.27 (m, 2H), 1.04 (d, J = 0.8 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.2, 142.3, 137.2, 136.5, 127.4, 125.7, 123.3, 122.6, 108.32, 48.7, 39.9, 29.6, 27.7, 26.8, 20.4, 18.4, 13.9. FTIR (neat): 178.6, 158.9, 144.1, 141.1, 132.6, 131.7, 128.1, 125.8, 122.3, 115.2, 113.9, 113.9, 108.3. 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}NO$ 258.1858, found 258.1861.

*1-Butyl-3-methyl-3-(2-methylallyl)indolin-2-on (**3d′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.25−7.18 (m, 2H), 7.03 (t, J = 7.6 Hz,1H), 6.83 (d, J = 7.6 Hz, 1H), 4.55 (m, 1H), 4.49 (m, 1H), 3.77−3.70 (m, 1H), 3.64−3.57 (m, 1H), 2.72 (d, J= 13.6 Hz, 1H,) 2.47 (d, J= 13.6 Hz, 1H), 1.62−1.58 (m, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.94 (t, J= 4.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.2, 142.5, 141.3, 134.0, 129.3, 127.7, 123.4, 122.0, 114.4, 108.3, 54.1, 48.7, 45.7, 39.9, 39.8, 30.2, 29.7, 25.1, 23.9, 20.3, 13.9. FTIR (neat): 3034, 2957,

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2921, 2862, 2383, 2312, 1349, 830, cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}NO$ 258.1780, found 258.1788.

*1-Methyl-3-(2-methylprop-1-en-1-yl)-3-(p-tolyl)indolin-2-one (**3e**) and 1-Methyl-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one (**3e′**).* **3e** and **3e′** were synthesized following general experimental procedure A by mixing **1e** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate to form desired product **3e** (37.2 mg, 64%) and 1-methyl-3-(2-methylallyl)-3-(*p*-tolyl)indolin-2-one **3e′** (17.61 mg, 31%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction proced 1-methyl-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one **3e′** with a yield of 34.1 mg (61%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*1-Methyl-3-(2-methylprop-1-en-1-yl)-3-(p-tolyl)indolin-2-one (**3e**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.28 (m, 1H), 7.24−7.19 (m, 3H), 7.12−7.07 (m, 3H), 6.87 (d, *J* = 7.6 Hz 1H), 5.70 (m, 1H), 3.21 (s, 3H), 2.29 (s, 3H), 1.76 (d, *J* = 1.6 Hz, 3H), 1.26 (d, *J* = 1.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.5, 143.5, 139.4, 138.2, 136.9, 134.3, 129.3, 128.0, 127.1, 126.3, 125.2, 122.9, 108.1, 57.9, 27.0, 26.7, 21.1, 19.1. FTIR (neat): 3015, 2945, 1634, 1378, 1109, 890 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO$ 292.1701, Found 292.1705.

*1-Methyl-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one (**3e′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.30 (m, 1H), 7.29−7.24 (m, 3H), 7.12−7.08 (m, 3H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.62−4.61 (m, 1H), 4.55 (s, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.18 (s, 3H), 2.90 (d, *J* = 13.6 Hz, 1H), 2.29 (s, 3H), 1.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.6, 144.1, 141.2, 137.2, 131.8, 129.3, 128.3, 126.9, 125.8, 122.3, 115.1, 108.3, 56.4, 45.6, 26.5, 23.8, 21.1. FTIR (neat): 3012, 2843, 1604, 1356, 1198, 786 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO$ 292.1701, found 292.1705

*3-(3-Fluorophenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3f**) and 3-(3-Fluorophenyl)-1-methyl-3-(2-methylallyl)-indolin-2-one (**3f′**).* **3f** and **3f′** were synthesized following general experimental procedure A by mixing **1f** (50 mg, 1equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butylacetate to form desired product **3f** with a yield of 29.8 mg (52%) and 3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3f′**) with a yield of 18 mg (32%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction resulted in 3-(3-fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one **3f′** with a yield of 43 mg (76%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*3-(3-Fluorophenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)indolin-2-one (**3f**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.23 (m, 1H), 7.19−7.14 (m, 2H), 7.06−7.04 (m, 2H), 6.98−6.97 (m, 1H), 6.87 (m, 1H),), 6.82−6.8 (m, 1H), 5.58−5.57 (m, 1H), 3.15 (s, 3H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.20 (d, *J* = 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.3, 162.2 (d, J_{C-F} = 163 Hz) 143.4, 138.5, 138.1 (d, J_{C-F} = 2 Hz) 133.88, 129.0 (d, J_{C-F} = 6 Hz), 128.3, 126.1, 125.3, 123.1, 115.4 (d, J_{C-F} = 14 Hz), 108.4, 57.7, 27.0, 26.7, 19.2. FTIR (neat): 2927, 1672, 1522, 1432, 1142, 711 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}FNO$ 296.1451, found 296.1452.

*3-(3-Fluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3f′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.32 (m, 1H), 7.25−7.19 (m, 2H), 7.14−7.10 (m, 1H), 6.96−6.91 (m, 2H), 6.90−6.88 (m, 2H), 4.64−4.63 (m, 1H), 4.55 (s, 1H), 3.22 (d, *J*= 13.6 Hz,1H), 3.19 (s, 3H), 2.90 (d, *J*= 13.6 Hz, 1H), 1.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.8, 162.9 (d, J_{C-F} = 244 Hz), 155.8, 144.1, 143.2 (d, J_{C-F} = 7 Hz), 140.7, 130.9, 134.5 (d, J_{C-F} = 9 Hz), 128.7, 125.9, 122.8, 122.5, 115.6, 114.5 (d, J_{C-F} = 4 Hz), 114.3, 108.5, 64.6, 56.5, 45.7, 26.6, 23.7. FTIR (neat): 3060, 2925, 1712, 1602, 1477, 1343, 1250, 1126, 1079, 1021, 868 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}FNO$ 296.1451, found 296.1453.

*3-(4-Methoxyphenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)-indolin-2-one (**3g**) and 3-(3-Methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3g′**).* **3g** and **3g′** were synthesized following general experimental procedure A by mixing 3-hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **3g** in a yield of 29.5 mg (52%) and **3g′** in a yield of 19 mg (33%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction resulted in 3-(3-methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3g′**) with a yield of 45 mg (79%), when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*3-(4-Methoxyphenyl)-1-methyl-3-(2-methylprop-1-en-1-yl)-indolin-2-one (**3g**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (td, *J* = 1.6 Hz, *J*= 8 Hz 1H), 7.23 (m, 3H), 7.10 (t, *J*= 0.8 Hz, 1H), 6.87 (d, *J*= 7.2 Hz, 1H), 6.81(m, 2H), 5.69−5.67 (m, 1H), 3.76 (s, 3H), 3.21 (s, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.26 (d, *J* = 1.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.7, 158.8, 143.5, 138.1, 134.4, 134.2, 128.4, 128.1, 126.4, 125.3, 123.0, 115.2, 114.0, 108.2, 57.5, 55.4, 27.0, 26.6, 19.2. FTIR (neat): 3042, 1698, 1523, 1307, 1103, 786 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1654.

*3-(4-Methoxyphenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3g′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.30−7.24 (m, 3H), 7.22−7.17 (m, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.79−6.74 (m, 2H), 4.58−4.56 (m, 1H), 4.50 (s, 1H), 3.71 (s, 3H), 3.16 (d, *J* = 3.2 Hz, 1H), 3.13 (s, 3H), 2.84 (d, *J* = 13.3 Hz, 1H), 1.30 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.6, 158.9, 144.1, 141.1, 132.6, 131.7, 128.1, 125.8, 122.3, 115.2, 113.9, 113.9, 108.3, 556.0, 55.4, 45.7, 26.5, 23.8. FTIR (neat): 3012, 1635, 1511, 1460, 1296, 845 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1654.

*1-Benzyl-3-(4-(tert-butyl)phenyl)-3-(2-methylprop-1-en-1-yl)-indolin-2-one (**3h**) and 1-Benzyl-3-(4-(tert-butyl)phenyl)-3-(2-methylallyl)indolin-2-one (**3h′**).* **3h** and **3h′** were synthesized following general experimental procedure A by mixing **1h** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **3h** with a yield of 15.7 mg (42%) and **3h′** with a yield of 13.74 mg (39%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

The above reaction resulted in 1-benzyl-3-(4-(*tert*-butyl)phenyl)-3-(2-methylallyl)indolin-2-one (**3h′**) with a yield of 23.5 mg (66%) when 20 mol % $Ni(OTf)_2$ was used as a catalyst.

*1-Benzyl-3-(4-(tert-butyl)phenyl)-3-(2-methylprop-1-en-1-yl)-indolin-2-one (**3h**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.31 (m, 3H), 7.25−7.23 (m, 7H), 7.20−7.16 (m, 1H), 7.05 (td, *J*= 1.2 Hz, *J*= 7.2 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.77−5.76 (m, 1H), 4.94 (d, *J*= 15.6 Hz, 1H), 4.85 (d, *J*= 15.6 Hz, 1H), 1.77 (d, *J*= 1.2 Hz, 3H), 1.28 (s, 9H), 1.22 (d, *J*= 1.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.6, 150.0, 142.6, 139.5, 138.3, 136.0, 134.4, 128.8, 127.9, 127.6, 126.9, 126.3, 125.6, 125.3, 122.9, 109.2, 57.9, 47.0, 44.2, 41.7, 34.5, 31.4, 28.9, 27.0, 23.6, 19.4, 16.8. FTIR (neat): 2924, 1677, 1508, 1449, 1106, 811 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{32}NO$ 410.2484, found 410.2493.

*1-Benzyl-3-(4-(tert-butyl)phenyl)-3-(2-methylallyl)indolin-2-one (**3h′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 4H), 7.23−7.16 (m, 6H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 4.83 (dd, *J* = 43.3, 15.7 Hz, 2H), 4.59−4.57 (m, 1H), 4.56 (s, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.5, 150.2, 143.3, 141.1, 137.8, 136.0, 132.1, 128.7, 128.2, 127.6, 127.5, 126.6, 125.8, 125.6, 122.3, 115.6, 109.4, 56.5, 45.3, 44.1, 34.5, 31.4, 24.0. FTIR (neat): 2934, 1667, 1523, 1405, 1123, 845 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{32}NO$ 410.2484, found 410.2492.

*1-Benzyl-3-(2-methylprop-1-en-1-yl)-3-(naphthalen-2-yl)indolin-2-one (**3i**) + 1-Benzyl-3-(2-methylallyl)-3-(naphthalen-2-yl)indolin-2-one (**3i′**).* **3i** + **3i′** were synthesized following general experimental procedure A by mixing 1-benzyl-3-hydroxy-3-(4-methoxyphenyl)-indolin-2-one (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL *tert*-butyl acetate to form desired product **3i** and **3i′** of 39.51 mg (72%) after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

^1H NMR (400 MHz, $CDCl_3$): 7.81 (m, 6H), 7.68 (m, 3H), 7.57 (m, 1H), 7.46−7.44 (m, 4H), 7.44 (m, 14H), 7.25 (m, 2H), 7.09 (m, 2H), 6.8 (m, 2H), 5.82−5.81 (m, 1H), 5.05- 4.84 (m, 4H), 4.94 (m, 1H), 4.70 (s, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 3.09 (d, *J*= 13.2 Hz, 1H), 1.83 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100

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MHz, $CDCl_3$): δ 178.4, 178.3, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 126.2, 126.1, 126.0, 125.9, 125.9, 125.7, 125.65, 125.55, 125.3, 125.2, 122.5, 109.5, 58.4, 56.9, 45.2, 44.2, 44.1, 27.1, 24.8, 24.1, 19.7. FTIR (neat): 3014, 2845, 1690, 1523, 1306, 764 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{29}H_{26}NO$: 404.2014, found 404.2016.

*1-Benzyl-3-(4-methoxyphenyl)-3-(2-methylprop-1-en-1-yl)-indolin-2-one (**3j**) + 1-Benzyl-3-(4-methoxyphenyl)-3-(2-methylallyl)indolin-2-one (**3j′**).* **3j** + **3j′** were synthesized following general experimental procedure A by mixing **1j** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butylacetate to form desired product **3j** with a yield of 42.53 mg (83%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95), which become a white solid after a few days.

Melting point: 89−90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J*= 8.8 Hz, 2H), 7.76 (m, 14H), 7.19 (m, 2H), 7.07(td, *J*= 2.8 Hz, *J*= 7.6 Hz, 2H), 6.85 (m, 4H), 6.77 (t, *J*= 8.4 Hz, 2H), 5.74 (s, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 2H), 4.83 (d, *J* = 15.7 Hz, 1H), 4.66 (m, 1H), 4.63 (m, 1H), 3.78 (s, 6H), 3.28 (d, *J*= 13.2 Hz, 1H), 2.94 (d, *J*= 13.6 Hz, 1H), 1.79 (d, 3H), 1.36 (s, 3H), 1.27 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.7, 178.6, 158.9, 158.8, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 126.2, 125.8, 123.0, 122.3, 115.7, 114.0, 114.0, 109.4. 109.3, 57.6, 56.1, 55.4, 45.5, 44.1, 44.0, 27.0, 24.1, 19.5. FTIR (neat): 3035, 1701, 1608, 1334, 1055, 765 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{26}H_{26}NO_2$ 384.1964, found 384.1968.

*1-(2-Bromooctyl)-3-(2-methylprop-1-en-1-yl)-3-(p-tolyl)indolin-2-one (**3k**) and 1-(2-Bromooctyl)-3-(2-methylallyl)-3-(p-tolyl)-indolin-2-one (**3k′**).* **3k** and **3k′** were synthesized following general experimental procedure A by mixing **1k** (50 mg, 1 equiv) and 20 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **3k** with a yield of 28.5 mg (53%) pure and **3k′** + **3k** (as an inseparable mixture) with a yield of 15 mg (29%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

*1-(2-Bromooctyl)-3-(2-methylprop-1-en-1-yl)-3-(p-tolyl)indolin-2-one (**3k**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J*= 7.6 Hz, 1H), 7.20 (m, 3H), 7.07 (m, 3H), 6.80 (d, *J*= 7.6 Hz, 1H), 5.68 (s,1H), 3.75−3.61 (m, 2H), 3.38 (t, *J*= 6.8 Hz, 2H), 2.29 (s, 3H) 1.82 (m, 3H), 1.76 (d, *J*= 0.8 Hz, 3H), 1.27 (m, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.3, 142.9, 139.7, 138.2, 136.8, 134.6, 129.3, 127.9, 127.1, 126.3, 125.4, 122.7, 108.4, 57.9, 40.26, 34.1, 32.9, 32.1, 29.8, 29.1, 28.7, 28.1, 27.1, 26.9, 21.1, 19.4. FTIR (neat): 3042, 2801, 1678, 1365, 1093, 723 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{27}H_{35}BrNO$ 468.1902, found 468.1904.

*1-(2-Bromooctyl)-3-(2-methylallyl)-3-(p-tolyl)indolin-2-one (**3k′**).* Selected signals. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 4H), 7.09 (d, *J*= 9.2 Hz, 3H), 6.87 (d, *J*= 8 Hz, 1H), 4.62 (m, 1H), 4.57 (s, 1H), 3.65 (m, 2H), 3.38 (t, *J*= 6.8 Hz, 2H), 3.22 (d, *J*= 13.2 Hz, 1H,) 2.89 (d, *J*= 13.2 Hz, 1H), 2.29 (s, 3H,) 1.82(m, 3H), 1.31 (m, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.3, 178.3, 153.9, 143.6, 141.0, 137.9, 137.0, 132.1, 129.3, 129.3, 128.1, 126.8, 125.9, 124.3, 122.0, 115.2, 108.5, 77.3, 76.9, 56.2, 45.3, 40.1, 40.1, 34.6, 34.0, 32.8, 29.8, 29.1, 28.7, 28.7, 28.1, 28.1, 27.3, 26.9, 23.9, 21.0. FTIR (neat): 3015, 2876, 1701, 1309, 1099, 764 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{27}H_{35}BrNO$ 468.1902, found 468.1909.

*3-(3,5-Difluorophenyl)-1-methyl-3-(2-methylallyl)indolin-2-one (**3n′**).* **3n′** was synthesized following general experimental procedure A by mixing 3-(3,5-difluorophenyl)-3-hydroxy-1-methylindolin-2-one (50 mg,1 equiv) and 20 mol % $Ni(OTf)_2$ in 1.5 mL of *tert*-butyl acetate to form desired product with a yield of 41.7 mg (72%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95).

^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.26 (m, 1H), 7.14 (t, *J*= 7.6 Hz, 1H), 6.96 (m, 2H), 6.90 (d, J= 8 Hz, 1H), 6.69 (tt, *J*= 2.4 Hz, *J*= 8.8 Hz, 1H), 4.65 (m, 1H), 4.56 (s, 1H), 3.20 (s, 3H), 3.13 (d, *J*= 13.2 Hz, 1H), 2.86 (d, *J*= 13.2 Hz, 1H), 1.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.3, 163.0 (d, $J_{C\text{-}F}$ = 247 Hz), 162.9 (d, $J_{C\text{-}F}$ = 247 Hz), 144.4 (t, $J_{C\text{-}F}$ = 9 Hz), 143.9, 140.3, 130.3, 128.9, 125.9, 122.7, 115.8, 110.3 (dd, $J_{C\text{-}F}$ = 19 Hz, 7 Hz), 108.7, 102.9 (dd, $J_{C\text{-}F}$ = 19 Hz, 7 Hz), 56.2, 45.6, 26.6, 23.6. FTIR (neat): 2901, 1620, 1105, 701 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{18}F_2NO$ 314.1356, found 314.1358.

*2-(2-Methylallyl)-2-phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**3o′**).* **3o′** was synthesized following general experimental procedure A by mixing 2-methoxy-2-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one and 20 mol % $Ni(OTf)_2$ in 1.5 mL of *tert*-butyl acetate to form desired product **3o′** in a yield of 31 mg (54%) after column purification.

^1H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 6.73 (m, 9H), 4.60 (s, 2H), 2.92 (d, *J* = 14 Hz, 1H), 2.55 (d, *J* = 14 Hz, 1H), 1.55 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.9, 142.9, 140.6, 139.1, 128.5, 128.2, 126.2, 125.8, 124.2, 122.5, 117.5, 115.7, 115.6, 84.6, 46.9, 24.7. FTIR (neat): 3220, 3012, 1649, 1306, 1106, 765 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1338, found 280.1341.

Analytical Data for the Peroxyoxindole Products. *3-(tert-Butylperoxy)-1-methyl-3-phenylindolin-2-one (**4b**).*[26] **4b** was synthesized following general experimental procedure D using 1-methyl-3-phenylindolin-2-one (250 mg, 1.1 mmol) to afford 3-(*tert*-butylperoxy)-1-methyl-3-phenylindolin-2-one (256 mg, 82%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.44 −7.43 (m, 2H), 7.39 −7.35 (m, 2H), 7.33 −7.31 (m, 3H), 7.13 (t, *J* = 8 Hz, 1H), 6.87 (d, *J*= 7.6 Hz, 1H), 3.20 (s, 1H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 174.2, 144.7, 136.2, 129.9, 129.0, 128.5, 127.3, 126.3, 122.7, 108.2, 86.3, 80.9, 26.7, 26.5.

*3-(tert-Butylperoxy)-1-methyl-3-(p-tolyl)indolin-2-one (**4c**).*[27] **4c** was synthesized following general experimental procedure D using 1-methyl-3-(*p*-tolyl)indolin-2-one (250 mg, 1.1 mmol) to afford 3-(*tert*-butylperoxy)-1-methyl-3-(*p*-tolyl)indolin-2-one (257 mg, 75%).

^1H NMR (400 MHz, $CDCl_3$): 7.40 −7.35 (m, 4H), 7.14−7.11 (m, 3H), 6.86 (d, *J*= 7.6 Hz, 1H), 3.19 (s, 1H), 2.32 (s, 3H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 144.7, 139.0, 133.2, 129.2, 128.6, 127.3, 126.2, 122.6, 108.2, 86.1, 80.8, 26.7, 26.5, 21.3.

*3-(tert-Butylperoxy)-3-(3-fluorophenyl)-1-methylindolin-2-one (**4d**).* **4d** was synthesized following general experimental procedure D using 3-(3-fluorophenyl)-1-methylindolin-2-one (250 mg, 1 mmol) to afford 3-(*tert*-butylperoxy)-3-(3-fluorophenyl)-1-methylindolin-2-one (270 mg, 79%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.42 −7.38 (m, 1H), 7.35 −7.33 (m, 1H), 7.31 −7.25 (m, 1H), 7.31 −7.25 (m, 1H), 7.02 (td, *J*= 1.6 Hz, *J*= 8.4 Hz, 1H), 6.88 (d, *J*= 8 Hz, 1H), 3.21 (s, 3H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.5, 162.6 (d, $J_{C\text{-}F}$ = 253 Hz), 144.6, 138.7, 138.6 (d, $J_{C\text{-}F}$ = 7 Hz), 130.2, 130.0 (d, $J_{C\text{-}F}$ = 8 Hz), 128.10, 126.29, 122.90, 116.0 (d, $J_{C\text{-}F}$ = 81 Hz), 114.6 (d, $J_{C\text{-}F}$ = 23 Hz), 108.4, 85.8, 81.1, 26.6, 26.5.

*3-(tert-Butylperoxy)-1,3-dimethylindolin-2-one (**4f**).*[26] **4f** was synthesized following general experimental procedure D using 1,3-dimethylindolin-2-one (200 mg, 1.2 mmol) to afford 3-(*tert*-butylperoxy)-1,3-dimethylindolin-2-one (236 mg, 61%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.33 −7.26 (m, 2H), 7.06 (t, 1H), 6.80 (d, *J*= 7.6 Hz, 1H), 3.19 (s, 3H), 1.51 (s, 3H), 1.09 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.3, 143.6, 129.7, 129.4, 123.9, 122.4, 122.4, 107.9, 81.9, 80.2, 26.4, 26.14, 20.4.

*1-Benzyl-3-(tert-butylperoxy)-3-phenylindolin-2-one (**4g**).* **4g** was synthesized following general experimental procedure D using 1-benzyl-3-(*tert*-butylperoxy)-3-phenylindolin-2-one (250 mg, 0.8 mmol) to afford 1-benzyl-3-(*tert*-butylperoxy)-3-phenylindolin-2-one (230 mg, 71%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.49 −7.47 (m, 2H), 7.37 −7.34 (m, 4H), 7.31 −7.22 (m, 6H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J*= 7.6 Hz, 1H), 5.24 (d, *J* = 16 Hz, 1H), 4.62 (d, *J* = 16 Hz, 1H), 1.23 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 143.7, 136.1, 135.6 129.9, 129.1, 128.7, 128.6, 128.5, 127.5, 127.4, 127.1, 126.3, 122.75, 109.5, 86.3, 81.1, 43.8, 26.7.

*1-Benzyl-3-(tert-butylperoxy)-3-methylindolin-2-one (**4h**).* **4h** was synthesized following general experimental procedure D using 1-benzyl-3-methylindolin-2-one (250 mg, 1.1 mmol) to afford 1-benzyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one (275 mg, 80%).

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^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.33 (m, 1H), 7.28−7.24 (m, 5H), 7.16 (td, J = 1H), 7.05−7.01 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.27 (d, J = 16 Hz, 1H), 4.60 (d, J = 16 Hz, 1H), 1.57 (s, 3H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.5, 142.7, 135.7, 129.8, 129. 4, 128.7, 127.1, 124.0, 122.6, 109.3, 82.0, 80.6, 43.6, 26.6, 20.3.

1-Benzyl-3-(tert-butylperoxy)-3-(p-tolyl)indolin-2-one (4i). **4i** was synthesized following general experimental procedure D using 1-benzyl-3-(*p*-tolyl)indolin-2-one (250 mg, 0.8mmol) to afford 1-benzyl-3-(*p*-tolyl)indolin-2-one (229 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 −7.35 (m, 3H), 7.31 −7.21 (m, 7H), 7.16 (d, J= 8 Hz, 2H), 7.08 (t, J= 7.6 Hz, 1H), 6.65 (d, J= 7.6 Hz, 1H), 5.23 (d, J= 16 Hz, 1H), 4.62 (d, J= 16 Hz, 1H), 2.34 (s, 3H), 1.21 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 143.7, 139.2, 135.7, 133.1, 129.8, 129.3, 128.7, 128.6, 127.5, 127.1, 126.3, 122.7, 109.4, 86.2, 81.1, 43.8, 26.7, 21.4.

1-Butyl-3-(tert-butylperoxy)-3-(3-methoxyphenyl)indolin-2-one (4j).[26] **4j** was synthesized following general experimental procedure D using 1-butyl-3-(3-methoxyphenyl)indolin-2-one (220 mg, 1.3 mmol) to afford 1-butyl-3-(*tert*-butylperoxy)-3-(3-methoxyphenyl)indolin-2-one (215 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 −7.33 (m, 2H), 7.21 (t, J= 8 Hz, 1H), 7.10 (dd, J= 7.6 Hz, J= 0.8 Hz, 1H), 7.07 −7.06 (m, 1H), 6.94 −6.91 (m, 1H), 6.88 −6.84 (m, 2H), 3.85−3.80 (m, 1H), 3.78 (s, 3H), 3.81−3.54 (m, 1H), 1.72−1.61 (m, 2H);1.40−1.32 (m, 2H), 1.17 (s, 9H); 0.92 (t, J= 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.9, 159.7, 144.2, 137.8, 129.9, 129.4, 126.4, 126.4, 122.4, 119.5, 114.4, 113.2, 108.6, 86.1, 80.9, 55.4, 39.9, 29.4, 26.6, 20.1, 13.9.

1-Butyl-3-(tert-butylperoxy)-3-methylindolin-2-one (4k).[26] **4k** was synthesized following general experimental procedure D using 1-butyl-3-methylindolin-2-one (200 mg, 1.25 mmol) to afford 1-butyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one (230 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 −7.26 (m, 2H), 7.04 (t, J= 8 Hz, 1H), 6.81 (d, J= 7.6 Hz, 1H), 3.85−3.88−3.80 (m, 1H), 3.60−3.53 (m, 1H), 1.69−1.61 (m, 2H), 1.49 (s, 3H), 1.42−1.33 (m, 2H), 1.08 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.2, 143.2, 130.0, 129.4, 124.1, 122.2, 108.4, 81.8, 80.3, 39.6, 29.4, 26.5, 20.3, 20.1, 13.9.

1-Butyl-3-(tert-butylperoxy)-3-phenylindolin-2-one (4l). **4l** was synthesized following general experimental procedure D using 1-butyl-3-phenylindolin-2-one (250 mg, 0.95 mmol) to afford 1-butyl-3-(*tert*-butylperoxy)-3-phenylindolin-2-one (304 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 −7.42 (m, 2H), 7.38 −7.31 (m, 5H), 7.10 (td, J= 0.8 Hz, J= 8 Hz, 1H), 6.88 (d, J= 7.6 Hz, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 1.71−1.59 (m, 2H), 1.42−1.33 (m, 2H), 1.18 (s, 9H), 0.92 (t, J= 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 144.2, 136.3, 129.8, 128.9, 128.8, 128.5, 127.3, 126.4, 122.4, 108.6, 86.1, 80.9, 39.9, 29.4, 26.7, 20.1, 13.9.

1-Allyl-3-(tert-butylperoxy)-3-phenylindolin-2-one (4m). **4m** was synthesized following general experimental procedure D using 1-allyl-3-phenylindolin-2-one (250 mg, 1 mmol) to afford 1-allyl-3-(*tert*-butylperoxy)-3-phenylindolin-2-one (234 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 −7.44 (m, 1H), 7.37 −7.32 (m, 5H), 7.28 −7.27 (m, 1H), 7.14−7.10 (m, 1H), 6.83 (d, J= 7.6 Hz, 1H), 5.86−5.77 (m, 1H), 5.23−5.14 (m, 2H), 4.52 - 4.42 (m, 1H), 4.20−4.15 (m, 1H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.0, 143.9, 136.2, 130.9, 129.9, 129.1, 128.6,128.6,127.3, 126.3, 122.7, 117.7, 109.3, 86.2, 81.0, 42.2, 26.7.

1-(But-3-en-1-yl)-3-(tert-butylperoxy)-3-methylindolin-2-one (4n). **4n** was synthesized following general experimental procedure D using 1-(but-3-en-1-yl)-3-methylindolin-2-one (250 mg, 1.25 mmol) to afford 1-(but-3-en-1-yl)-3-(*tert*-butylperoxy)-3-methylindolin-2-one (249 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 −7.43 (m, 2H), 7.39 −7.35 (m, 2H), 7.33 −7.31 (m, 3H), 7.13 (t, J= 8 Hz, 1H), 6.87 (d, J= 7.6 Hz, 1H), 3.20 (s, 1H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.2, 144.7, 136.2, 129.9, 129.0, 128.5, 127.3, 126.27, 122.7, 108.2, 86.26, 80.87, 26.68, 26.5

3-(tert-Butylperoxy)-3-methyl-1-(pent-4-en-1-yl)indolin-2-one (4o). **4o** was synthesized following general experimental procedure D using 3-methyl-1-(pent-4-en-1-yl)indolin-2-one (250 mg, 1.2 mmol) to afford 3-(*tert*-butylperoxy)-3-methyl-1-(pent-4-en-1-yl)indolin-2-one (284 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.85−5.78 (m, 1H), 5.09−4.93 (m, 2H), 3.88−3.82 (m, 1H), 3.63−3.51 (m, 1H), 2.14−2.08 (m, 2H), 1.79−1.75 (m, 2H), 1.50 (s, 3H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.2, 144.7, 136.2, 129.9, 129.0, 128.5, 127.3, 126.3, 122.7, 108.2, 86.3, 80.9, 26.7, 26.5.

3-(tert-Butylperoxy)-1-(hex-5-en-1-yl)-3-methylindolin-2-one (4p). **4p** was synthesized following general experimental procedure D using 1-(hex-5-en-1-yl)-3-methylindolin-2-one (250 mg, 1.1 mmol) to afford 3-(*tert*-butylperoxy)-1-(hex-5-en-1-yl)-3-methylindolin-2-one (261 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.26 (m, 2H), 7.07−7.03 (m, 1H), 6.80 (d, J= 7.6 Hz, 1H) 5.84 −5.78 (m, 1H), 5.06- 5.05 (m, 1H), 5.02−4.96 (m, 1H), 3.89−3.82 (m, 1H), 3.61−3.54 (m, 1H), 2.14−2.08 (m, 2H), 1.79- 1.74 (m, 2H), 1.49 (s, 3H), 1.28−1.23 (m, 2H), 1.49 (s, 3H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.2, 143.1, 137.6, 130.0, 129.4, 124.1, 122.3, 115.4, 108.3, 81.8, 80.3, 39.7, 30.9, 26.5, 26.5, 20.3.

Analytical Data for Products 5. *2-Methyl-2-(2-methylallyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5a).*[5] **5a** was synthesized following general experimental procedure B by mixing **4a** (50 mg, 1 equiv) and 30 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5a** with a yield of 39.25 mg (85%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (5:95), which became a white solid after a few days.

Melting point 77−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (bs, 1H), 6.99−6.92 (m, 3H), 6.82−6.80 (m, 1H), 4.93 (m, 1H), 4.83 (s, 1H), 2.70 (d, J= 14 Hz, 1H), 2.43 (d, J= 14 Hz, 1H), 1.83 (s, 3H), 1.55 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.6, 142.3, 140.3, 126.6, 124.3, 122.9, 117.7, 116.0, 115.1, 81.0, 43.4, 24.2, 21.9. FTIR (neat): 3051, 2879, 1621, 1275, 1186, 812, 689 $^{-1}$. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1185.

Large-Scale Synthesis of Compound 5a. *tert*-Butyl acetate (4 mL) was added to the 20 mL resealable vial containing 3-substituted-3-*tert*-butylperoxyoxindole (235 mg, 1mmol). Then, 30 mol % $In(OTf)_3$ was added to the vial. Finally, the vial was sealed with an aluminum cap with a septum. Further, the solution was heated in the preheated oil bath for at 60 °C for 24 h. After the completion of the reaction, the volatile components were evaporated under vacuum. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (1:99 to 5:95) and afforded desired product **5a** in a 71% (155 mg) yield.

4-Methyl-2-(2-methylallyl)-2-phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (5b). **5b** was synthesized following general experimental procedure B by mixing **4b** (50 mg, 1 equiv) and 30 mol % $In(OTf)_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5b** with a yield of 40 mg (70%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.44 (m, 2H), 7.25−7.14 (m, 3H), 7.12 (dd, J= 8 Hz, J= 1.6 Hz, 1H), 6.98 (td, J= 7.6 Hz, J= 1.6 Hz, 1H), 6.93 (td, J= 7.6 Hz, J= 1.6 Hz, 1H), 6.80 (dd, J= 8 Hz, J = 1.6 Hz, 1H), 4.87−4.86 (m, 1H), 4.81 (s, 1H), 3.37 (s, 3H), 3.18 (d, J = 14.8 Hz, 1H), 2.81 (d, J= 14.4 Hz, 1H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 143.8, 140. 8, 139.3, 129.4, 128.4, 128.0, 125.9, 123.8, 122.5, 117.7, 115.4, 114.57, 84.5, 47.5, 28.9, 24.7. FTIR (neat): 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1494, found 294.1497.

4-Methyl-2-(2-methylallyl)-2-(p-tolyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5c). **5c** was synthesized following general experimental procedure B by mixing **4c** (50 mg, 1 equiv) and 30 mol % $In(OTf)_3$ in 1 mL of *tert*-butyl acetate to form desired product **5c** with a yield of 34 mg (72%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

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^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J= 8.4 Hz, 2H), 7.10 (d, J= 8 Hz, 1H), 7.04 (d, J= 8 Hz, 2H), 6.95 (dt, J= 7.2 Hz, J= 22.4 Hz, 2H), 6.80 (d, J= 7.6 Hz, J= 1H), 4.86 (s, 1H), 4.82 (s, 1H), 3.36 (s, 3H), 3.16 (d, J= 14.8 Hz, 1H), 2.79 (d, J= 14.8 Hz, 1H), 2.25 (s, 3H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.2, 143.9, 140. 9, 137.7, 136.3, 129. 4, 129.0, 125.7, 123.8, 122.4, 117.7, 115.2, 114.5, 84.5, 47.5, 29.9, 28.9, 24.7, 21.3. FTIR (neat): 3023, 2954, 1701, 1607, 1455, 1321, 1021, 854, 670 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1654.

*2-(3-Fluorophenyl)-4-methyl-2-(2-methylallyl)-2H-benzo[b][1,4]-oxazin-3(4H)-one (**5d**).* **5d** was synthesized following general experimental procedure B by mixing **4d** (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1 mL of *tert*-butyl acetate to form desired product **5d** with a yield of 20.10 mg (42%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99), which became a solid after a few days.

Melting point: 46−47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.40 (m, 2H), 7.11−7.09 (m, 1H), 7.02−6.93 (m, 3H), 6.83−6.81 (m, 1H), 4.88−4.86 (m, 1H), 4.80−4.79 (m, 1H), 3.37 (s, 3H), 3.16 (d, J= 14.4 Hz, 1H), 2.80 (d, J= 15.6 Hz, 1H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 162.5 (d, J_{C-F} = 245 Hz), 143.6, 140.5, 134.9 (d, J_{C-F} = 3 Hz), 129.3, 127.8 (d, J_{C-F} = 8 Hz), 123.97, 122.66, 117.70, 115.70, 115.3 (d, J_{C-F} = 8 Hz), 114.6, 84.2, 47.4, 28.9, 24.6. FTIR (neat): 3052, 2955, 1707, 1606, 1475, 1345, 1086, 1016, 857, 799, 695 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{19}H_{19}FNO_2$ 312.1400, found 312.1403.

*2-(3-Methoxyphenyl)-4-methyl-2-(2-methylallyl)-2H-benzo[b]-[1,4]oxazin-3(4H)-one (**5e**).* **5e** was synthesized following general experimental procedure B by mixing **4e** (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5e** with a yield of 24.82 mg (53%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.10 (m, 2H), 7.04−6.91 (m, 4H), 6.82−6.79 (m, 1H), 6.74−6.71 (m, 1H), 4.87 (m, 1H), 4.83 (m, 1H), 3.37 (s, 3H) 3.36 (s, 3H), 3.18 (d, 1H, J= 14.8 Hz), 2.80 (d, 1H, J= 14.4 Hz), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.9, 159.6, 143.8, 140. 9, 140.8, 129.4, 123.9, 122.5, 118.2, 117.7, 115.4, 114.6, 113.4, 111.7, 84.5, 55.3, 47.4, 28.9, 24.7. FTIR (neat): 3065, 2951, 1674, 1604, 1535, 1494, 1463, 1128, 958 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{20}H_{22}NO_3$ 324.1600, found 324.1603.

*2,4-Dimethyl-2-(2-methylallyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5f**) + 2,4-Dimethyl-2-(2-methylprop-1-en-1-yl)-2H-benzo[b]-[1,4]oxazin-3(4H)-one (**5f′**).* **5f** + **5f′** was synthesized following general experimental procedure B by mixing 3-(*tert*-butylperoxy)-1,3-dimethylindolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5f** + **5f′** with a yield of 28.57 mg (61%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06−6.91 (m, 6H), 5.26−5.25 (m, 1H), 4.91- 4.90 (m, 1H), 4.78 (s, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.64 (d, 1H, J= 14 Hz, 1H), 2.40 (d, J= 14.4 Hz, 1H), 1.80 (s, 3H), 1.68(s, 2H), 1.64 (d, 2H), 1.51 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168. 5, 168.49, 144.0, 143. 15, 140.45, 139.0, 130.35, 129.8, 123.6, 122.4, 122.35, 117.69, 117.47, 115.89, 114.4, 114.3, 80.6,79.72, 43.45, 29.78, 28.97, 27.1, 24.2, 23.9, 22.2, 19.2. FTIR (neat): 2936, 2856, 1721, 1609, 1496, 897 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1342.

*4-Benzyl-2-(2-methylallyl)-2-phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**5g**).* **5g** was synthesized following general experimental procedure B by mixing **4g** (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1 mL of *tert*-butyl acetate to form desired product **5g** with a yield of 37.81 mg (82%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99), which became a solid after a few days.

Melting point: 87−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.45 (m, 2H), 7.30−7.20 (m, 6H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.2 Hz, 2H), 6.95 (td, J = 7.7, 1.3 Hz, 1H), 6.79 (td, J = 8.0, 1.3 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.39 (d, J = 16.2 Hz, 1H), 4.96 (d, J = 16.2 Hz, 1H), 4.90 (m, 1H), 4.86 (m, 1H), 3.24 (d, J= 14.7 Hz, 1H), 2.87 (d, J = 14.7 Hz, 1H), 1.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 143.9, 140.8, 139.1, 136.3, 128.8, 128.7, 128.4, 128.1, 127.4, 126.5, 125.9, 123.9, 122.5, 117.9, 115.6, 115.4, 84.7, 47.5, 45.6, 24.8. FTIR (neat): 3048, 2923, 2846, 1709, 1088, 830 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{25}H_{24}NO_2$ 370.1807, found 370.1808.

*4-Benzyl-2-methyl-2-(2-methylallyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5h**) + 4-Benzyl-2-methyl-2-(2-methylprop-1-en-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5h′**).* **5h** + **5h′** was synthesized following general experimental procedure B by mixing **4h** (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5h** + **5h′** with a yield of 26.54 mg (57%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.29 (m, 3H), 7.26−7.22 (m, 3H), 7.01−6.95 (m, 3H), 6.93−6.88 (m, 3H),5.32 (m, 1H), 5.22 (d, J= 16.4 Hz, 1H), 5.05 (d, J= 16.4 Hz, 1H), 4.95 (m, 1H), 4.84 (s, 1H), 2.77 (d, J= 13.6 Hz, 1H), 2.47 (d, J= 13.6 Hz, 1H), 1.85 (s, 1H), 1.83 (d, J= 7.4 Hz,1H), 1.76 (s, 1H), 1.69 (d, J = 7.4 Hz, 1H), 1.59 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.7, 168.3, 144.1, 143.17, 140.4, 139.3, 136.7, 136.5, 129.1, 128.9, 128.9, 127.5, 127.4, 126.6, 126.5, 124. 1, 123.8, 123.8, 122.5, 122.4, 117. 9, 117.7, 116.9, 115.2, 115.2, 80.6, 79.7, 45.6, 45.6, 43.2, 28.2, 27.1, 24.3, 23.8, 22.1, 19.2. FTIR (neat): 3053, 2939, 2839, 1708, 1600, 1477, 1343, 1254, 1156, 1135, 859 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1652.

*4-Benzyl-2-(2-methylallyl)-2-(p-tolyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5i**).* **5i** was synthesized following general experimental procedure B by mixing 1-benzyl-3-(*tert*-butylperoxy)-3-(p-tolyl)-indolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5i** with a yield of 41.10 mg (87%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 2H), 7.24−7.22 (m, 3H), 7.13−7.08 (m, 5H), 6.96 (m, 1H), 6.80−6.76 (m, 1H), 6.69−6.67 (m, 1H), 5.36 (d, J= 16.4 Hz, 1H), 4.96 (d, J= 16.4 Hz, 1H), 4.89 (m, 1H), 4.86 (m, 1H), 3.20 (d, 1H, J= 14.8 Hz), 2.82 (d, 1H, J= 14.4 Hz), 2.28 (s, 3H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.1, 143.9, 140.8, 139.1, 136.3, 128.8, 128.7, 128.4, 128.1, 127.4, 126.5, 125.9, 123.9, 122.5, 117.9, 115.5, 115.4, 84.7, 47.5, 45.6, 24.8. FTIR (neat): 2952, 1722, 1459, 1369, 1238, 1079, 1031, 899, cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{26}H_{26}NO_2$ 384.1964, found 384.1967.

*4-Butyl-2-(3-methoxyphenyl)-2-(2-methylallyl)-2H-benzo[b]-[1,4]oxazin-3(4H)-one (**5j**).* **5j** was synthesized following general experimental procedure B by mixing 1-butyl-3-(*tert*-butylperoxy)-3-(p-tolyl)indolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5j** (29.54 mg, 61%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 7.8, 1.6 Hz, 1H), 7.04−6.98 (m, 2H), 6.96 (td, J = 7.6, 1.6 Hz, 1H), 6.91 (td, J = 7.7, 1.6 Hz, 1H), 6.81 (dd, J = 7.9, 1.5 Hz, 1H), 6.72 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 4.88−4.86 (m, 1H), 4.83 (m, 1H), 3.99−3.85 (m, 2H), 3.73 (s, 3H), 3.17 (d, J = 14.7 Hz, 1H), 2.78 (d, J = 14.7 Hz, 1H), 1.77 (s, 3H), 1.67−1.61 (m, 1H), 1.57−1.48 (m, 1H), 1.38 (dt, J = 14.9, 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 159.6, 144.0, 141.1, 140.9, 129.4, 128.5, 123.7, 122.5, 118.2, 118.1, 115.3, 114.6, 113.5, 111.5, 84.3, 55.3, 47.4, 41.8, 29.2, 24.7, 20.2, 13.9. FTIR (neat): 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{23}H_{28}NO_3$ 366.2069, found 366.2078.

*4-Butyl-2-methyl-2-(2-methylallyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5k**).* **5k** was synthesized following general experimental procedure B by mixing 1-butyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1 mL of *tert*-butyl acetate to form desired product **5k** in a yield of of 45% (23.14 mg) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

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^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−6.92 (m, 4H), 4.90 (m, 1H), 4.78 (s, 1H), 3.98−3.82 (m, 2H), 2.63 (d, J= 14 Hz, 1H), 2.37 (d, J= 14 Hz, 1H), 1.80 (s, 3H), 1.64 (m, 2H), 1.51 (s, 3H), 1.41 (m, 2H), 0.96 (t, J= 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 143.3, 140.5, 128.8, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 115.9, 114.4, 114.3, 80.3, 43.3, 41.6. FTIR (neat): 2950, 2312, 2175, 1734, 1678, 1593, 1151, 896 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1807, found 274.1809.

*4-Butyl-2-(2-methylallyl)-2-phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**5l**).* **5l** was synthesized following general experimental procedure B by mixing 1-butyl-3-(*tert*-butylperoxy)-3-methylindolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5l** in a yield of 53% (29.15 mg) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.24−7.18 (m, 3H), 7.11 (dd, J= 8 Hz, J= 1.6 Hz, 1H), 6.93 (m, 2H), 6.80 (dd, J= 8 Hz, J= 1.6 Hz, 1H), 4.86 (m, 1H), 4.81(s, 1H), 3.92 (m, 2H) 3.17 (d, 1H, J= 14.4 Hz), 2.78 (d, 1H, J= 14.4 Hz), 1.76 (s, 3H), 1.65 (m, 2H), 1.39 (m, 2H), 0.95 (t, J= 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 144.0, 140.9, 139.4, 128.2, 127.9, 125.9, 123.7, 122.4, 118.1, 115.3, 114.5, 84.3, 47.4, 41.77, 29.2, 24.7, 20.2, 13.9. FTIR (neat): 2971, 2310, 1694, 16411593, 1155, 760 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{26}NO_2$ 336.1964, found 336.1969.

*4-Allyl-2-(2-methylallyl)-2-phenyl-2H-benzo[b][1,4]oxazin-3(4H)-one (**5m**).* **5m** was synthesized following general experimental procedure B by mixing **4m** (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ 20 mol % in 1 mL of *tert*-butyl acetate to form desired product **5m** with a yield of 27.03 mg (57%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99), which became a solid after a few days.

Melting point: 82−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.43 (m, 2H), 7.25−7.23 (m, 1H), 7.21−7.17 (m, 1H), 7.12 (dd, J = 8.0, 1.3 Hz, 1H), 6.97 (td, J = 7.8, 1.4 Hz, 1H), 6.88 (td, J = 7.9, 1.4 Hz, 1H), 6.77 (dd, J = 8.0, 1.3 Hz, 1H), 5.87−5.78 (m, 1H), 5.11 (dd, J = 10.5, 0.9 Hz, 1H), 4.98 (dd, J = 17.3, 0.9 Hz, 1H), 4.88−4.78 (m, 3H), 4.32−4.26 (m, 1H), 3.17 (d, J = 14.7 Hz, 1H), 2.81 (d, J = 14.7 Hz, 1H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.8, 143.9, 140.77, 139.1, 131.6, 128.6, 128.4, 128.0, 125.9, 123.9, 122.5, 117.9, 116.8, 115.5, 115.1, 84.5, 47.4, 44.3, 24.7. FTIR (neat): 2920, 1713, 1607, 1496, 1476, 1189, 1097, 812 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{21}H_{22}NO_2$ 320.1651, found 320.1654.

*4-(But-3-en-1-yl)-2-methyl-2-(2-methylallyl)-2H-benzo[b][1,4]-oxazin-3(4H)-one (**5n**) + 4-(But-3-en-1-yl)-2-methyl-2-(2-methyl-prop-1-en-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5n′**).* **5n** + **5n′** were synthesized following general experimental procedure B by mixing 1-(but-3-en-1-yl)-3-(*tert*-butylperoxy)-3-methylindolin-2-one (100 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5n** + **5n′** with a yield of 31 mg (34%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03−6.93 (m, 7H), 5.89−5.76 (m, 2H), 5.25 (dt, J = 2.6, *1.3* Hz, 1H), 5.14−5.00 (m, 4H), 4.90 (s, 1H), 4.78 (s, 1H), 4.05−3.90 (m, 4H), 2.63 (d, J = 14.1 Hz, 1H), 2.44−2.35 (m, 5H), 1.80 (s, 6H), 1.67 (s, 3H), 1.64 (d, J = 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 168.0, 144.2, 143.3, 140.4, 139.0, 134.6, 134.5, 129.2, 128.7, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 117.4, 117.3, 115.8, 114.4, 114.2, 80.2, 79.4, 43.3, 41.2, 41.0, 31.7, 31.7, 27.0, 24.1, 23.8, 22.0, 19.1. FTIR (neat): 3071, 2949, 2385, 2306, 934, 751 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{17}H_{22}NO_2$ 272.1651, found 272.1654.

*2-Methyl-2-(2-methylallyl)-4-(pent-4-en-1-yl)-2H-benzo[b][1,4]-oxazin-3(4H)-one (**5o**) + 2-Methyl-2-(2-methylprop-1-en-1-yl)-4-(pent-4-en-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5o′**).* **5o** + **5o′** were synthesized following general experimental procedure B by mixing 3-(*tert*-butylperoxy)-3-methyl-1-(pent-4-en-2-yl)indolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product as a mixture of **5o′** + **5o** with a yield of 24.16 mg (25%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (m, 8H), 5.84 (m, 2H), 5.24 (s, 1H), 4.90 (s, 1H), 4.78 (s, 1H), 3.92 (m, 4H), 2.63 (d, J= 14.4 Hz, 1H), 2.37 (d, J= 14.4 Hz, 1H), 2.15 (m, 4H), 1.79 (m, 6H), 1.74 (m, 6H), 1.65 (m, 6H), 1.5 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 168.0, 144.2, 143.3, 140.5, 139.3, 137.6, 128.8, 123.8, 123.5, 122.4, 122.4, 118.1, 117.8, 115.9, 115.6, 115.57, 114.4, 114.3, 80.3, 79.5, 43.3, 41.3, 31.1, 27.1, 26.4, 26.3, 24.2, 23.8, 22.0, 19.1. FTIR (neat): 3205, 3074, 2979, 2920, 898 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{24}NO_2$ 286.1807, found 286.1812.

*4-(Hex-5-en-1-yl)-2-methyl-2-(2-methylallyl)-2H-benzo[b][1,4]-oxazin-3(4H)-one (**5p**) + 4-(Hex-5-en-1-yl)-2-methyl-2-(2-methyl-prop-1-en-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**5p′**).* **5p** + **5p′** were synthesized following general experimental procedure B by mixing 3-(*tert*-butylperoxy)-3-methyl-1-(2-methylpent-4-en-2-yl)-indolin-2-one (100 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL *tert*-butyl acetate to form desired product **5p** + **5p′** with a yield of 33.5 mg (37%) as a thick white liquid after purification in silica gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): 1H NMR (400 MHz, CDCl3) δ 7.04−6.87 (m, 5H), 5.84−5.74 (m, 4H), 5.05−4.93 (m, 2H), 4.91−4.88 (m, 1H), 4.78 (m, 1H), 3.97−3.84 (m, 2H), 2.63 (d, J = 14.1 Hz, 1H), 2.36 (d, J = 14.1 Hz, 1H), 2.15−2.05 (m, 3H), 1.80 (s, 4H), 1.70−1.61 (m, 5H), 1.53−1.43 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 168.0, 144.2, 143.3, 140.5, 139.0, 138.5, 138.4, 129.3, 128.8, 123.9, 123.8, 123.5, 122.4, 122.3, 118.0, 117.8, 115.8, 115.0, 114.9, 114.4, 114.3, 80.3, 79.5, 43.3, 41.8, 41.5, 33.5, 29.8, 27.0, 26.7, 26.7, 26.2 24.2, 23.8, 22.1, 19.1. FTIR (neat): 2948, 2863, 1682, 1603, 1501, 1454, 1266, 1154, 910, 695 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{19}H_{26}NO_2$ 300.1964, found 300.1971.

*4-(8-Bromooctyl)-2-(2-methylallyl)-2-(p-tolyl)-2H-benzo[b][1,4]-oxazin-3(4H)-one (**5q**).* **5q** was synthesized following general experimental procedure-B by mixing 1-(8-bromooctyl)-3-(*tert*-butyl-peroxy)-3-(p-tolyl)indolin-2-one (50 mg, 1 equiv) and 30 mol % In(OTf)$_3$ in 1.5 mL of *tert*-butyl acetate to form desired product **5q** with a yield of 11.23 mg (23%) as a thick white liquid after silica purification in gel chromatography using EtOAc/*n*-hexane (1:99).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.30 (m, 2H), 7.12−7.02 (m, 3H), 6.93 (dtd, J = 21.3, 7.6, 1.1 Hz, 2H), 6.80−6.78 (m, 1H), 4.86 (s, 1H), 4.82 (s, 1H), 3.93−3.89 (m, 2H), 3.40 (t, 2H), 3.15 (d, J = 14.7 Hz, 1H), 2.75 (d, J = 14.8 Hz, 1H), 2.25 (s, 3H), 1.88−1.81 (m, 2H), 1.77 (s, 3H), 1.40−1.23 (m, 10H). 13C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.9, 159.9, 143.8, 140. 97, 140.8, 129.4, 123.86, 122.5, 122.5, 118.2 117.7, 115.38, 114.6, 113.4, 111.7, 84.5, 55.3, 47.4, 28.9, 24.7. FTIR (neat): 2970, 2951, 1674, 1604, 1503, 1494, 1391, 1088, 896, 714 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{27}H_{35}BrNO_2$ 484.1851, found 484.1855.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c03072.

Copies of ^{1}H and ^{13}C NMR spectra and crystallographic data (PDF)

Cartesian coordinates for select compounds (TXT)

FAIR data, including the primary NMR FID files, for compounds **1c**, **1f**−**1i**, **3a**−**3k**, **3k** + **3k′**, **3a′**−**3h′**, **3n′**, **3o′**, **4b**−**4d**, **4f**−**4p**, **5a**−**5e**, **5f** + **5f′**, **5g**, **5h** + **5h′**, **5i**−**5m**, **5n** + **5n′**, **5o** + **5o′**, **5p** + **5p′**, and **5q** (ZIP)

Accession Codes

CCDC 2108331 and 2214336 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The

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Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Boopathy Gnanaprakasam − *Department of Chemistry, Indian Institute of Science Education and Research, Pune, Maharashtra 411008, India;* orcid.org/0000-0002-3047-9636; Email: gnanaprakasam@iiserpune.ac.in

Authors

Nirmala Mohanta − *Department of Chemistry, Indian Institute of Science Education and Research, Pune, Maharashtra 411008, India*

Pragnya Paramita Samal − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory (CSIR-NCL), Pune, Maharashtra 411008, India*

Akanksha M. Pandey − *Department of Chemistry, Indian Institute of Science Education and Research, Pune, Maharashtra 411008, India*

Shankhajit Mondal − *Department of Chemistry, Indian Institute of Science Education and Research, Pune, Maharashtra 411008, India*

Sailaja Krishnamurty − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory (CSIR-NCL), Pune, Maharashtra 411008, India;* orcid.org/0000-0001-5090-1892

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c03072

Notes

The authors declare no competing financial interest.

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$FeCl_2$-Catalyzed Rearrangement of Aryl Peroxyoxindole into 1,3-Benzooxazin-4-One

Nirmala Mohanta,[a] Pragnya Paramita Samal,[b] Sailaja Krishnamurty,[b] and Boopathy Gnanaprakasam[a,*]

[a] Department of Chemistry, Indian Institute of Science Education and Research, 411008 Pune, India
E-mail: gnanaprakasam@iiserpune.ac.in
[b] Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory (CSIR-NCL), 411008 Pune, India

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Abstract: We report an $FeCl_2$-catalyzed radical rearrangement of aryl peroxyoxindoles into 1,3-benzooxazin-2-ones to obtain a variety of aryl substituted 1,3-benzooxazin-4-ones in moderate to good yields. Mechanistically, this skeletal rearrangement of peroxyoxindoles proceeded via radical pathway and was well supported with a series of experimental findings and DFT studies.

Keywords: Peroxyoxindole; $FeCl_2$; Rearrangement; 1,3-Benzooxazin-4-one; Ring expansion

Nitrogen-containing heterocyclic compounds are prevalent structures in many drugs and natural products.[1] Among the several heterocyclic compounds, benzooxazines and benzooxazin-4-one motifs comprise important scaffolds that are widely found in a wide range of natural products and biologically active compounds.[2] These compounds are found in pharmaceuticals such as 4*H*-benzo[*d*][1,3]oxazin-4-one, which is a key pharmacophore in cetilistat and is used for treating obesity. Some of these derivatives possess excellent elastase inhibitors and C1r protease inhibitors (Figure 1(A)).[3]

As 1,3-benzooxazin-4-one is prevalent in both pharmaceutical and diverse biological applications, they have always been an attractive target for synthetic organic and medicinal chemists. Traditionally, the reaction of anthranilic acid with acyl chloride in the presence of a stoichiometric amount of base is typically used for synthesizing benzooxazin-4-one derivatives (Figure 1(B)).[4] Further, many transition metal catalyzed protocols, including Pd, Co, Cu, and so on, have been used to assemble 1,3-benzooxazine core.[5] A series of methods have revealed the use of

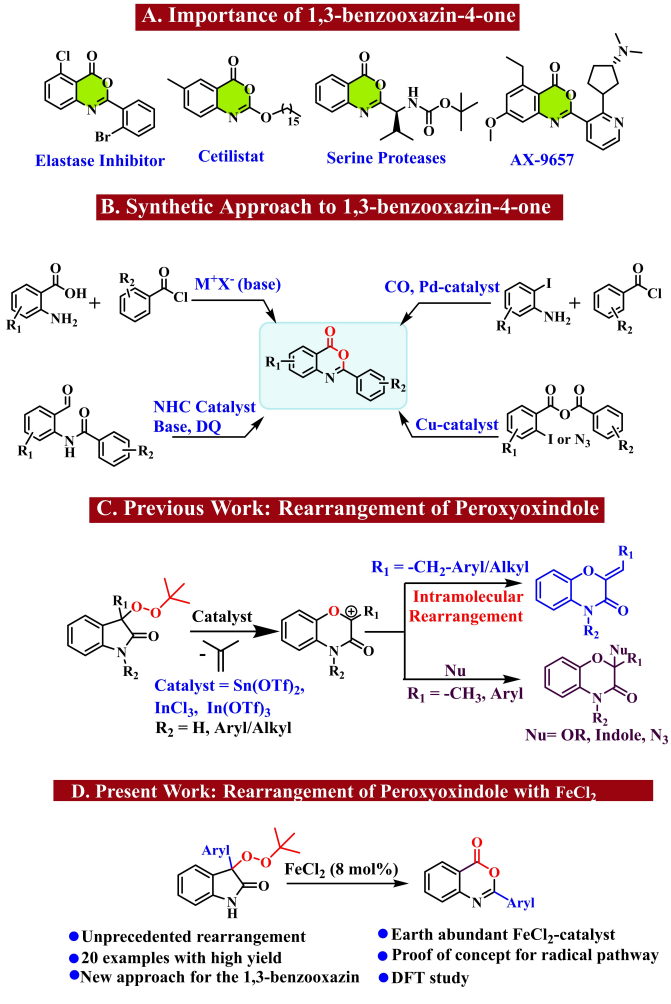


Figure 1. State of the art for the 1,3-benzooxazin-4-ones and the rearrangement of peroxyoxindoles.

Pd-catalyzed carbonylative cyclization of haloarenes to construct benzoxazinone skeletons (Figure 1(B)).[5a–c]

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The Cu-catalyzed tandem C–N coupling/rearrangement method used for the synthesis of 1,3-benzooxazin-4-ones was reported by Ge et al. (Figure 1(B)).[5e] In 2016, Wang et al. reported the catalytic aza-Wittig reaction of acid anhydrides for synthesizing 1,3-benzooxazin-4-ones (Figure 1(B)).[5f] Wang and co-workers also developed *N*-heterocyclic carbene catalyzed tandem cyclization strategy for synthesizing benzooxazinones (Figure 1(B)).[6] However, no studies have reported for tandem rearrangement of peroxyoxindole for synthesizing 1,3-benzooxazin-4-one.

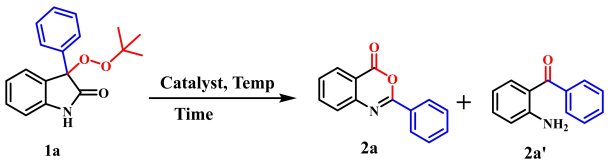
The organic peroxide moiety is an intriguing scaffold, and it undergoes several transformations due to the presence of the weak peroxide bond. Several named[7] and unnamed[8] rearrangements have been reported using peroxides. Organic peroxides undergo rearrangement to provide oxygen-containing heterocycles such as lactones;[9] however, this has been limited to the synthesis of *N*-heterocyclic compounds. Thus, there is considerable research interest for identifying new rearrangements for developing new methodologies and studying mechanisms.

As a part of our recent ongoing interest in the synthesis of *N*-containing heterocycles, we have focused on the rearrangement of C3-substituted peroxides.[10] In 2020, for the first time, the intramolecular rearrangement of C3-substituted peroxides to biological active C3-alkene substituted 1,4-benzooxazin-3-one derivatives was reported (Figure 1(C)).[10a] However, the generality of this methodology is limited up to the C3-substituted peroxides bearing only –CH_2–alkyl/–CH_2–phenyl groups at the C3 position. Subsequently, we presented a few more rearrangement reactions in the presence of nucleophiles such as –OMe, Indole, and N_3 for the synthesis of C3-substituted 1,4-benzooxazin-3-one derivatives (Figure 1(C)).[10c–d]

Notably, all these rearrangements proceeded through a common 1,4-benzooxazine carbocation intermediate in the presence of Lewis acid catalysts such as $Sn(OTf)_2$, $In(OTf)_3$, and $InCl_3$. In this context, we investigated the behavior of C3-substituted peroxide toward Fe catalyst. Herein, to the best of our knowledge, for the first time, we report $FeCl_2$ catalyzed rearrangement of C3-aryl substituted peroxyoxindoles for synthesizing biologically important 1,3-benzooxazin-4-one derivatives via the radical path through the SET mechanism (Figure 1(D)). The reaction mechanism is well supported by experimental studies and DFT calculation.

The C3-phenyl peroxide of 2-oxindole **1a** was selected for the initial optimization of the reaction conditions (Table 1). In a control experiment, the reaction did not proceed either in the absence of the catalyst or 10 mol% of $FeCl_2$ at room temperature (Table 1, entry 1 and 2). Next, peroxide **1a** was heated at 60 °C with 10 mol% of $FeCl_2$ in MeCN affording

Table 1. Optimization of the reaction.[a]



entry	catalyst	solvent	temp (°C)	yield (%) 2a	2a'
1	–	MeCN	rt	No reaction	
2[b]	$FeCl_2$	MeCN	rt	No reaction	
3[b]	$FeCl_2$	MeCN	60	33	7
4[b]	$MnCl_2$	MeCN	60	23	–
5[b]	$Mn(OTf)_2$	MeCN	60	No reaction	
6[b]	$Zn(OTf)_2$	MeCN	60	No reaction	
7[b]	$Fe(OTf)_2$	MeCN	60	18	12
8[b]	$Ni(OTf)_2$	MeCN	60	0	
9[b]	$In(OTf)_3$	MeCN	60	0	
10[b]	$Sn(OTf)_2$	MeCN	60	0	
11[b]	$Cu(OTf)_2$	MeCN	60	0	
12[b]	Cu(I)Cl	MeCN	60	0	
13[c]	Amberlyst®-15	MeCN	60	0	
14[b]	Triflic acid	MeCN	60	0	
15[b]	$FeCl_2$	MeCN	80	82	Trace
16	$FeCl_2$	*t*-BuOAc	80	89	–
17	$FeCl_2$	EtOAc	80	27	13
18	$FeCl_2$	THF	80	31	21
19	$FeCl_2$	DCE	80	5	25
20	$FeCl_2$	Dioxane	80	10	15
21	$FeCl_2$	DMF	80	21	19
22	$FeCl_2$	DMSO	80	4	31
23	$FeCl_2$	MeCN	80	91	–
24[d]	$FeCl_2$	MeCN	80	No reaction	
25[e]	$FeCl_2$	MeCN	80	25	–
26[f]	$FeCl_2$	MeCN	80	35	42

[a] **Reaction condition**: 0.25 mmol **1a** was taken in resealable vial, charged with 8 mol% of catalyst, solvent (2 mL), and heated at mention temperature for 12 hrs.
[b] 10 mol% catalyst.
[c] amberlyst®-15:**1a**, 1:1 (w/w).
[d] 1 mol% catalyst.
[e] 5 mol% catalyst
[f] 20 mol% catalyst.

33% of **2a** and 7% of 2-aminobenzophenone (**2a'**) (Table 1, entry 3). To achieve better yield and high selectivity of product **2a** various metal catalyst was screened. The $MnCl_2$ afforded 23% of **2a** (Table 1, entry 4). The **1a** remained unreacted with $Mn(OTf)_2$, and $Zn(OTf)_2$ (Table 1, entry 5–6). Notably, 18% of **2a** was formed with $Fe(OTf)_2$ (Table 1, entry 7). The desired product **2a** was not observed with $Ni(OTf)_2$, $In(OTf)_3$, $Sn(OTf)_2$, $Ca(OTf)_2$, Cu(I)Cl, amberlyst®-15, and triflic acid (Table 1, entry 8–14). All the above results signify that Fe(II)-catalyst has a vital role in this transformation. Increase in yield of **2a** was noticed with increasing reaction temperature to 80 °C (Table 1,

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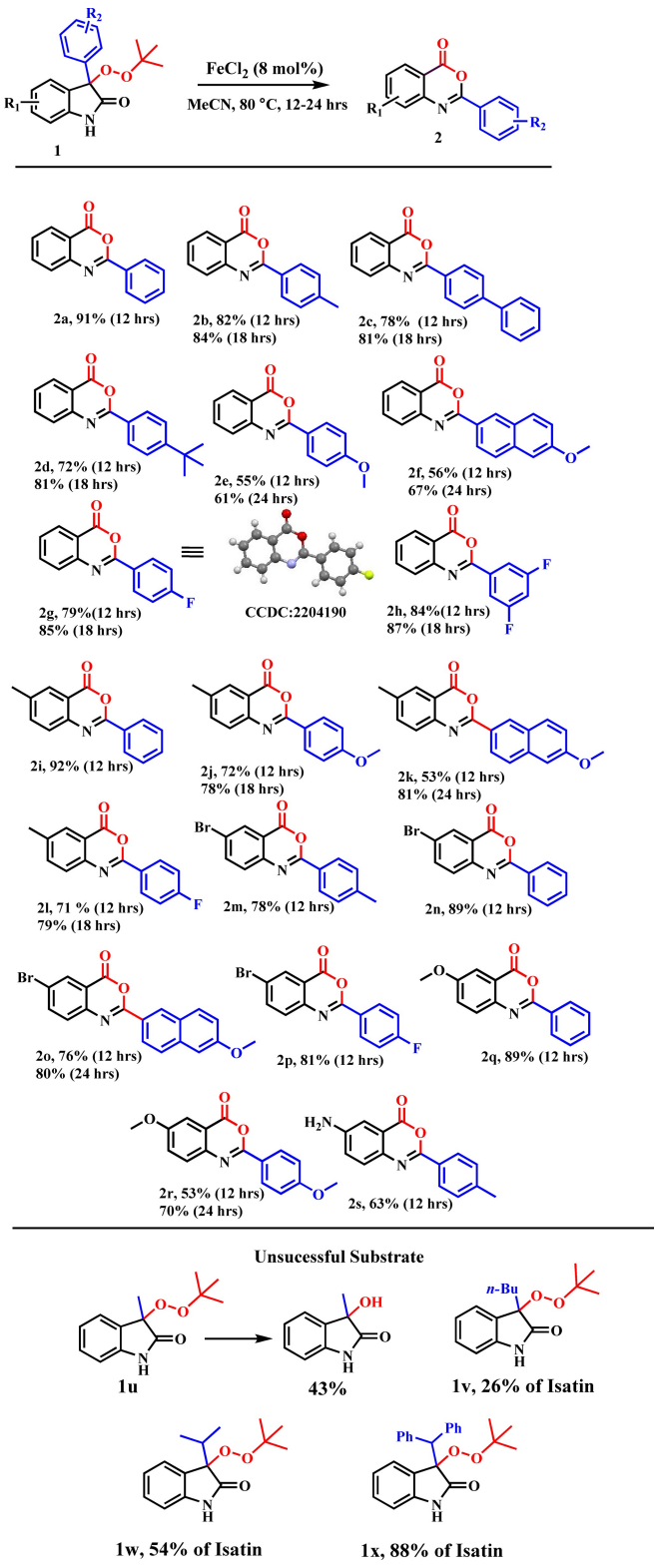
entry 15) with trace amount of **2a'**. Moreover, to eliminate **2a'** completely from the reaction, the reaction was investigated with various solvents (Table 1, entries 16–23). MeCN appeared as the best reaction medium and **2a'** was diminished from the reaction by decreasing the catalyst loading upto 8 mol% (Table 1, entry 23). Further decrease in the catalyst loading caused poor yield of desired product (Table 1, entry 24 and 25) and with increasing the catalyst loading lead the formation of **2a'** in higher yield (Table 1, entry 26). Finally, entry 23 (Table 1) was turn out as best optimized condition and 91% of **2a** was isolated by treating **1a** with 8 mol% of $FeCl_2$ at 80 °C for 12 hrs .

Under the optimized reaction condition, we explored the generality of the substrate scope for this rearrangement reaction. An array of diversely functionalized C3-aryl peroxyoxindole underwent this rearrangement protocol in the presence of $FeCl_2$ to afford the corresponding product **2** in good to excellent yields (Scheme 1). For example, the C3-aryl peroxyoxindole derivatives bearing electron donating groups in aryl such as methyl, phenyl, *tert*-butyl, and –OMe afforded good to excellent yields (**2b**–**2e**). Similarly, electron rich –OMe substituted naphthalene 56% of **2f**, under the optimized reaction condition.

The phenyl group bearing electron-withdrawing groups such as –F and difluoro afforded excellent yields of the desired products (**2g**–**2h**). Moreover, the C3-substituted peroxyoxindole core moiety bearing methyl, Br, –OMe, and $–NH_2$ substitutions at the aryl part also underwent the rearrangement and provided **2i**–**2s** in good yields. Furthermore, the complete consumption of starting material was observed after heating the reaction mixture for longer time (see, Scheme 1), which resulted increase in yield of **2b**–**2l**, **2o** and **2r**. Moreover C3-methyl substituted peroxyoxindole **1u** resulted only deprotection of *tert*-BuO group to furnish C3-hydroxyoxindole. However, the peroxides **1v**, **1w** and **1x** afforded isatin with the developed method via Hock cleavage mechanism.[10a]

Furthermore, to show the synthetic application of this method, we have synthesized scaffold **2t** in 81% yield after 24 hrs (Scheme 2A). This intermediate (**2t**) is subsequently brominated according to the literature method to afford elastage inhibitor.[11] Moreover, a gram scale reaction was performed with 10 mmol of **1a** using the optimized reaction condition, affording 79% (1.8 g) of **2a** (Scheme 2B).

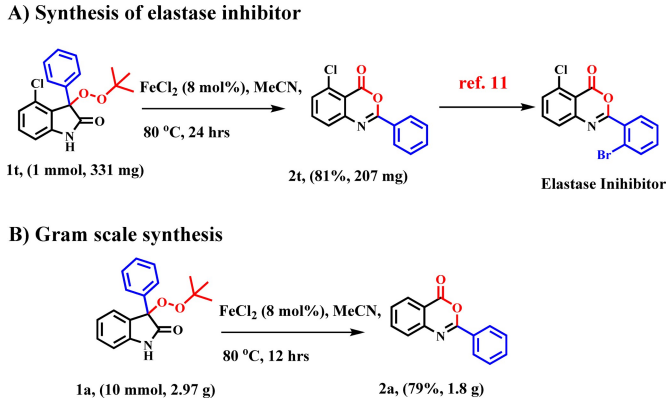
To gain insights into the mechanism of the developed $FeCl_2$-catalyzed rearrangement of peroxyoxindole, numerous control experiments were performed. The reaction was completely suppressed when 1 equivalent of radical scavenger TEMPO was added to the optimized condition, indicating a free radical pathway (Scheme 3(I)). We also isolated the TEMPO-based adduct **3a** using 20 mol% $FeCl_2$, confirming that **2a'** has formed with higher catalyst loading (Scheme 3(II)). To confirm the source of carbonyl oxygen of the ester group of **2a**, the reaction was performed



Scheme 1. Substrate scope for the rearrangement.

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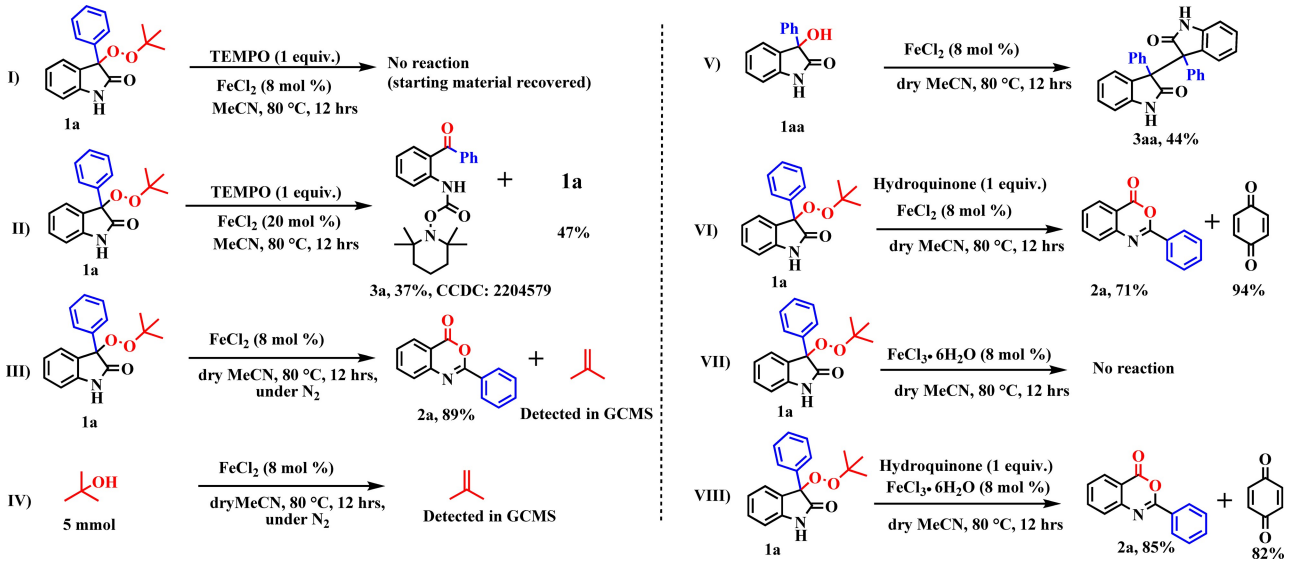
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Scheme 2. Synthetic application of the rearrangement reaction.

under nitrogen with dry MeCN solvent, yielding 89% of **2 a** (Scheme 3(III)). This result confirmed that the ester carbonyl oxygen was attributed by either the peroxy oxygen attached to the *t*-butyl group or the carbonyl oxygen of the amide group in the absence of H_2O. Further, our hypothesis of homolytic cleavage of peroxide bond was strengthened by the detection of isobutylene in GCMS (See SI, Scheme 2(III), Section 3.2). To confirm whether the *tert*-butoxy group was responsible for the generation of isobutylene, we treated *tert*-butanol with the optimized reaction condition and injected it into the GCMS. Isobutylene was detected, confirming that *tert*-butoxy was the source of isobutylene (Scheme 3(IV)). For further confirmation using C3-hydroxy oxindole, which was one of the intermediates (**1 aa**), the optimized reaction condition was performed with **1 aa**, affording 44% of **3 aa** (Scheme 3(V)). This result confirms that there was no formation of C3-hydroxy oxindole as a intermediate in the reaction. Further, to confirm the formation of radical, we performed a set of reactions in conjunction with the oxidation reaction of hydroquinone to benzoquinone in the presence of $FeCl_3$.[12] Thus, we added hydroquinone in the optimal reaction condition, which led to form benzoquinone and **2 a** (Scheme 3(VI)). This result confirmed the generation of Fe(III) in the reaction medium. Moreover, **2 a** was not formed when Fe(III) was used as a catalyst (Scheme 3(VII)). However, the same reaction proceeded smoothly when we added hydroquinone as an additive (Scheme 3(VIII)), implying the crucial role of Fe(II) in the reaction. Thus, in situ generated Fe(II) by reduction of Fe(III) in the presence of hydroquinone plays a vital role in this rearrangement.

DFT studies were performed using M06-2X functional[13] to obtain additional mechanistic insights about the iron-catalyzed rearrangement of peroxyoxindole derivatives. The details for the same are presented in supplementary section 4. Firstly, we have tried to understand the electronic state of the active catalyst i. e. $FeCl_2$ involved in the catalytic process. We envisaged that the absolute electronic energies obtained for singlet, triplet and quintet are – 2184.108028 Hartrees, – 2184.099873 Hartrees and 2184.250868 Hartrees, respectively. So, quintet state is more stable and feasible than singlet and triplet states. Similarly, for Fe(III) species, there exists doublet, quartet and sextet out of which sextet is found to be the most feasible state depending on the electronic energies. Hence, further calculations are carried out considering quintet state of $FeCl_2$ and sextet state of Fe(III) moieties. The relative Gibbs free energies for all moieties involved are shown in Figure 2. The reaction



Scheme 3. Experimental studies for the mechanism.[a]

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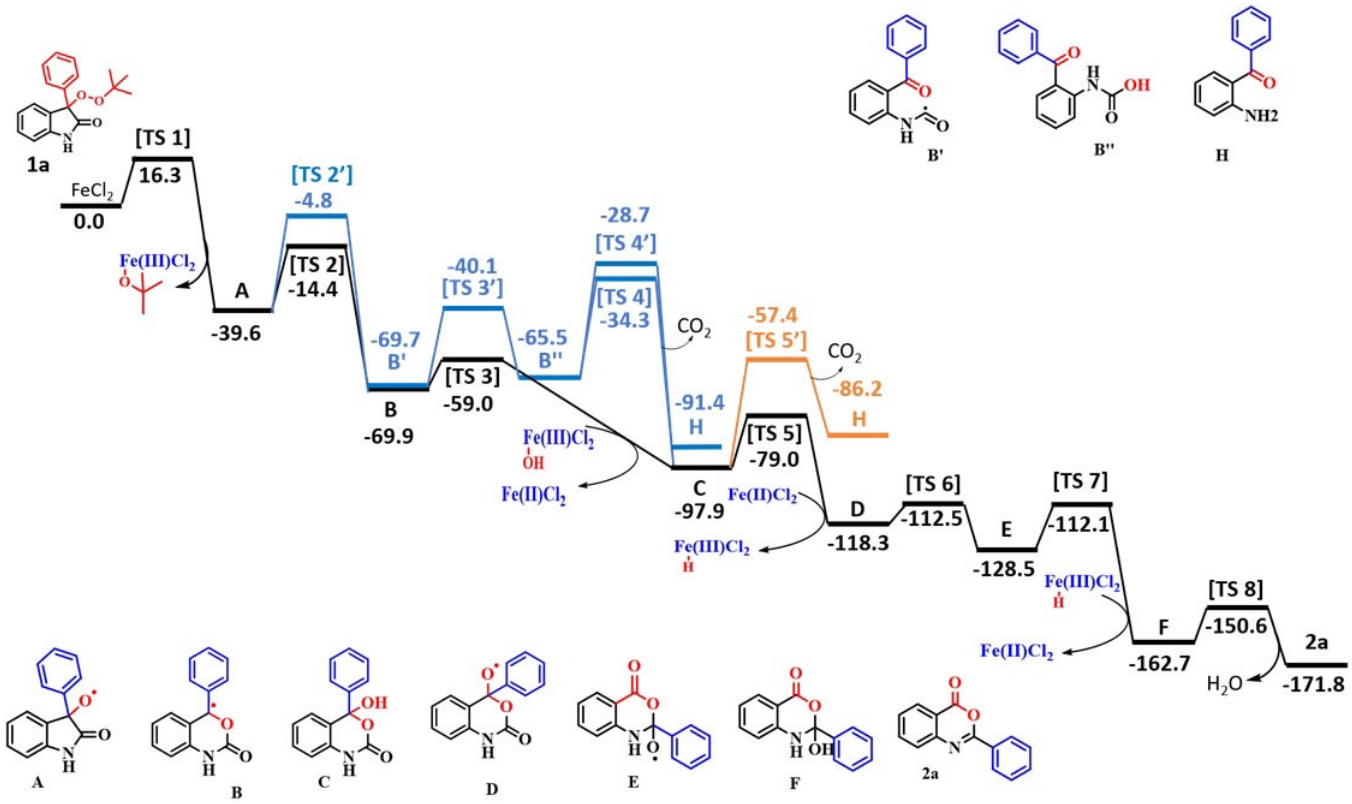


Figure 2. Free energy profile for the $FeCl_2$-catalyzed rearrangement of peroxyoxindoles. The free energy values are given in kcal/mol.

was first initiated through the interaction of $FeCl_2$ with C3-phenyl peroxyoxindole (**1a**) to form alkoxy radical **A** via [**TS1**] and in situ generation of Fe(*t*-BuO)Cl_2. The energy barrier obtained for this step was 16.3 kcal/mol. The rearrangement within alkoxy radical **A** generated two intermediates, namely, tertiary radical **B** or carbonyl radical **B′**, via [**TS2**]/[**TS2′**] (Figure S3). However, barriers involved in the formation of **B** [25.2 kcal/mol] were lower than that of **B′**. Simultaneously, the Fe-mediated *tert*-butoxy intermediate formed in earlier steps generated isobutylene and Fe(III)(OH)Cl_2 (Figure S3, eq. 1). Here, two possibilities exist; first, Fe(III)(OH)Cl_2 interacts with **B** to give hydroxy intermediate **C** via [**TS3**], which is exergonic by 28.0 kcal/mol. Then, **C** can either undergo decarboxylation, forming **H** via [**TS5′**] or reacts with decarboxylation, forming **H** via [**TS5′**] or reacts with the $FeCl_2$ catalyst to form radical **D** and $HFeCl_2$ via [**TS5**]. Although the reaction is spontaneous in both ways, the barrier involved for decarboxylation is considerably high (40.5 kcal/mol), indicating that **H** may have been a minor product. This was followed by the 1,3-phenyl shift within **D**, resulting in the radical intermediate **E** via [**TS6**], corresponding to the energy barrier 5.8 kcal/mol as the reaction from **D** to **E** proceeds through a distinctively mechanism in the quartet state. Calculation shows explicitly value of 4.2 kcal/mol for formation of **P** (see supplementary section 4, Scheme S6) which reveals that 1,3-phenyl migration proceeds through a stepwise radical dissociation recombination process which is regarded to be fast in nature. Performed calculations suggest that **P** structure is unstable however very close to **E** in their single point energies.

Subsequently, a proton abstraction by **E** led to **F** via [**TS7**] and this was accompanied by the regeneration of the $FeCl_2$ catalyst. The energy barrier for this step was determined to be 16.4 kcal/mol. Lastly, enolization at intermediate **F** resulted in the formation of **2a** via [**TS8**], which was exergonic by 9.1 kcal/mol. The alternative path that may have coexisted was the reaction of Fe(III)(OH)Cl_2 with **B′** to give acid intermediate **B″** via [**TS3′**], which was endergonic by 4.2 kcal/mol. Next, intermediate **B″** formed may have rearranged to form **C** via [**TS4**] or may have undergone decarboxylation to form **H** through [**TS4″**]. However, the energy barrier for forming **C** was 31.1 kcal/mol, which was lower than the energy barrier for the formation of **H**. Thus, the pathway involving tertiary radical intermediate **B** was determined to be more feasible. This reaction was not feasible with peroxide having alkyl substitution viz **1u**, **1v**, **1w**, and

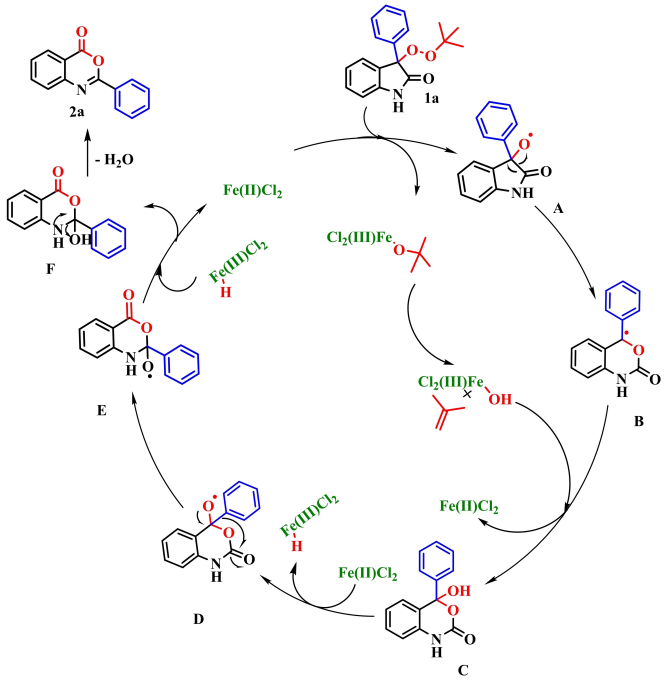
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1 x. This has been explained by the Gibb's free energy calculation for the feasibility of formation of isatin (See SI, Section 4, Scheme S5). The Gibb's free energy for the reactant **1 a** to form the isatin is 6.04 kcal/mol which is not feasible for the reaction to occur.

Based on the experimental evidence and DFT studies, we rationalized the mechanism for this unprecedented rearrangement reaction (Scheme 4). Initially, the coordination of $Fe(II)Cl_2$ with the oxygen atom of peroxide led to the cleavage of the peroxide (–O–O–) bond and formed the alkoxy radical intermediate **A**. $Fe(II)Cl_2$ was converted to $Fe(III)(tBuO)Cl_2$, which generated isobutylene in the reaction medium (Scheme 3(III)). Subsequently, the addition of alkoxy radical **A** to the amide carbonyl carbon via the cleavage of the C2–C3 bond of **A** generated the 1,3-benzoxazin-4-one tertiary radical **B**. The hydroxy-substituted 1,3-benzoxazin-4-one moiety **C** was obtained by the interaction of the radical intermediate **B** with $Fe(III)(OH)Cl_2$. The acetal radical intermediate **D** was generated when **C** interacted with the in situ regenerated $Fe(II)Cl_2$ via single electron transfer (SET). The relay of radical in **D** led to aryl migration to the amide carbonyl and provided the radical intermediate **E**. Furthermore, the transfer of hydrogen to the **E** from $Fe(III)(H)Cl_2$ yielded the intermediate **F**. Finally, the removal of H_2O from **F** afforded **2 a**, accompanied by the regeneration of $FeCl_2$.

In conclusion, we developed the $FeCl_2$-catalyzed rearrangement of C3-aryl peroxyoxindole for the synthesis of biologically active 1,3-benzooxazin-4-one derivatives. This rearrangement reaction was well supported with broad substrate scope having good to excellent yields. Moreover, this reaction proceeded via a radical path through the SET mechanism, which is well supported by experiments and DFT studies.



Scheme 4. Proposed mechanism for the catalytic path.

Experimental Section

General procedure for the rearrangement reaction: A resealable vial was charged with **1** (0.25 mmol), anhydrous $FeCl_2$ (8 mol%) and 2 mL of MeCN. The reaction mixture was stirred for 12 hrs at 80 °C. After completion of reaction, the volatile compound was evaporated under vaccum. The crude residue was purified through silica-gel column chromatography using EtOAc/hexane (varies from 5:95 to 15:85) to afford the product **2**.

General procedure for large scale synthesis of 2 a: A round bottom flask was charged with **1 a** (10 mmol, 3 g), anhydrous $FeCl_2$ (8 mol%) and 10 mL of MeCN. The mixture was refluxed for 12 hrs at 80 °C. After completion of the reaction, the volatile compound was evaporated under vaccum. The crude residue was purified through column chromatography using EtOAc/hexane (varies from 1:99 to 5:95) to afford **2 a** in 79% yield (1.8 g).

The X-ray crystal structure: Crystallographic data are deposited with the Cambridge Crystallographic Data Centre (CCDC) under the following accession numbers: **2 h** (2204190), **2 m** (2204567) and **3 a** (2204579). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif.

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