Ruthenium-catalysed synthesis of functionalized 4*H*-chromene derivatives from 1,3-dicarbonyl compounds and 2-hydroxy benzyl alcohols

A thesis submitted towards partial fulfilment of requirements of BS-MS dual degree program (2015 – 2020)

By

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CERTIFICATE

This is to certify that this dissertation entitled **"Ruthenium-catalysed synthesis of functionalized 4*H*-chromene derivatives from 1,3-dicarbonyl compounds and 2-hydroxy benzyl alcohols"** towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents the work carried out by **Naveen Kumar Digrawal** at Indian Institute of Science Education and Research under the supervisor of Dr. Boopathy Gnanaprakasam, Assistant Professor, Department of Chemistry during the academic year 2019-2020.

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DECLARATION

I hereby declare that the matter embodied in the report entitled **"Ruthenium-catalysed synthesis of functionalized 4*H*-chromene derivatives from 1,3-dicarbonyl compounds and 2-hydroxy benzyl alcohols"** are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Science Education and Research, Pune under the supervisor of Dr. Boopathy Gnanaprakasam and the same has not been submitted elsewhere for any other degree.

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Dedicated to my Family, Teachers, Friends & Lord Shiva.

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Contents

LIST OF FIGURES

LIST OF TABLES

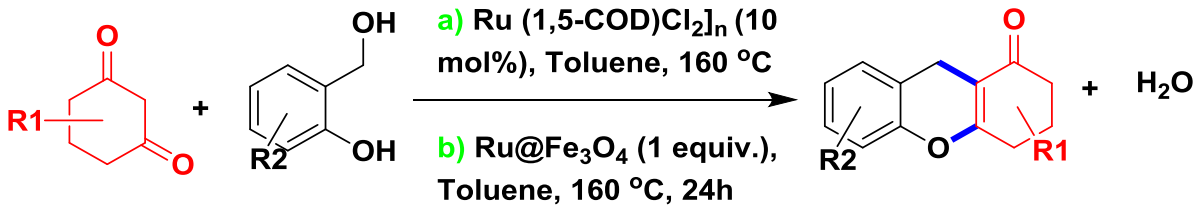
ABBREVIATIONS

DCE	1, 2-Dichloroethane
ACN	Acetonitrile
MeOH	Methanol
EtOAc	Ethyl acetate
KOAc	Potassium acetate
DCM	Dichloromethane
rt	Room temperature
h	Hour
DMF	Dimethylformamide
mL	Millilitre
mmol	Millimole
min	Minute
Hz	Hertz
IR	Infrared
M^+	Metal Ion
NMR	Nuclear magnetic resonance
$CDCl_3$	Deuterated chloroform
IPA	Isopropyl alcohol
ESI	Electron spray ionisation
TMHD	2,2,6,6-Tetramethyl-3,5-heptanedione
TEBA	Triethylbenzylammonium chloride
CAN	Ceric ammonium nitrate
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
TMS	Tetramethylsilane
p-TsOH	Para-toluene sulfonic acid

ABSTRACT

Chromenes (Benzopyrans) is one the most classified medicinal pharmacophore which appears as important structural component (core moiety) in many natural products and generated significant attention because of their important biological properties such as antiallergic, antitumor, antiviral, antioxidant and antiinflammatory etc. The derivatives of benzopyran core moiety are capable of interacting with a variety of cellular targets to achieve their wide ranging biological activities. Furthermore, these compounds show photochromic effects. These compounds are important because many of them naturally occur in plants and exhibit a variety of interesting biological activities. So, It is highly desirable to develop an effective, operationally straightforward, and environmentally friendly practical process over recorded procedures for synthesizing substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones.

In this dissertation, we have studied the borrowing hydrogen concept, which is considered as a green and well-known synthetic approach from economic point of view to form C-C bond. Consequently, we developed an one-pot pathway for the synthesis of substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones in domino manner, consisting of intermolecular (C-C bond) benzylation followed by intramolecular (C-O bond) arylation. The reactions of 2-hydroxybenzyl alcohols and cyclic-1,3-dicarbonyl compounds (easily available and non toxic) were catalysed using $[Ru(1,5\text{-}COD)_2Cl_2]_n$ and $Ru@Fe_3O_4$ MNP to produce 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones and derivatives with moderate to good yields. Besides, demonstrated and characterized an efficient supported heterogeneous $Ru@Fe_3O_4$ MNP catalyst which improved the catalytic system in terms of easy preparation, recovery, and recyclability for the synthesis 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones in moderate yields.



R1 = -Me, -H, Ph
R2 = -H,-OMe, -NO_2, -Br

14 examples for a), upto 94% yield.
5 examples for b), up to 69% yield.

1. INTRODUCTION

1.1 Benzopyrans (Chromenes)

Natural products with wide range of structural diversity have a great impact on research interfaces of organic chemistry and biology which ultimately motivated the synthetic chemical community for their isolation to study structure activity relationships. Nowadays, many specialists from the fields of chemical biology, organic chemistry and drug discovery are working for isolation of new molecular moieties from naturally occurring compounds having pharmacological activity.[1] Among them, it has been found that oxygen containing heterocycles like chromanes, chromenes, coumarins and tetrahydroxanthenones have great importance as these moiety acts as APIs in many pharmaceutical drugs.[2] Especially, 1-Benzopyrans (Chromenes) is one the most classified medicinal pharmacophore which appears as core moiety in many natural products (such as genistein, hesperidin, and warfarin) (Fig. 1) as well as synthetic products [3] and generated significant attention because of their important biological properties including antitumor, anti-HIV, antimicrobials, anti-inflammatory, anticoagulants, antibacterial, antiviral, antioxidant and antiplatelet as well as anti-breast cancer activities.[4-12]The derivatives of benzopyran core are capable of interacting with different cellular targets which directly leads to their wide ranging biological activities. In addition, some of the derivatives of benzopyranes show ability to stop electron transportation through inhibition at NADH.[13]

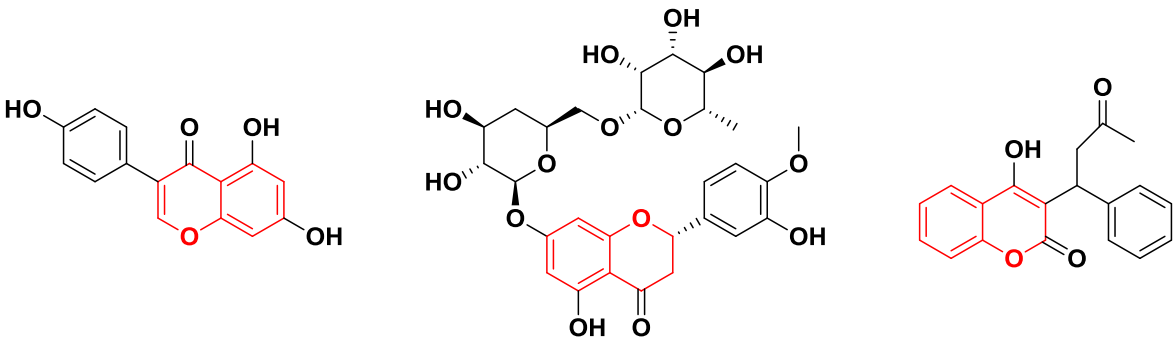


Figure 1. Natural products which contain 1-benzopyran as a core moiety.

The main purpose to synthesize chromenes and homologous compounds is not only to study the structure-activity relationship (SAR) with their extensive biological activities, but also for having the important applications in medicinal and materials science in chemistry due to their important photophysical and photochemical properties. For example, use of these compounds as leuco dye and fluorescence probes to diagnose the cellular behaviour.[14,15] Chemically, it is a heterocyclic ring system which consists of benzene ring fused with a pyran ring. Benzopyrans considered as a basic back bone of various types of polyphenols and usually found in natural alkaloids, flavonoids, anthocyanins and tocopherols. The structural skeletons of 1-benzopyran includes chroman **1**, 4*H*-chromene **2** and 2*H*-chromene **3** as shown in Figure 2 . In this project, we have included only derivatives of tetrahydroxanthene-1-ones as functionalized 4*H*-1-benzopyrans.[16]

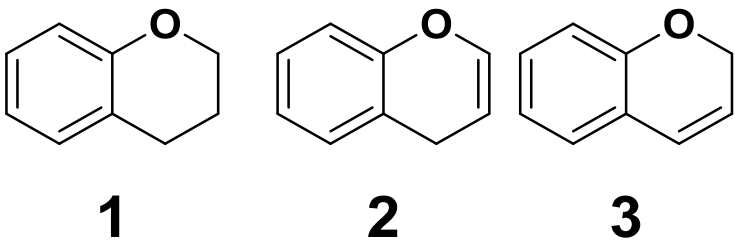
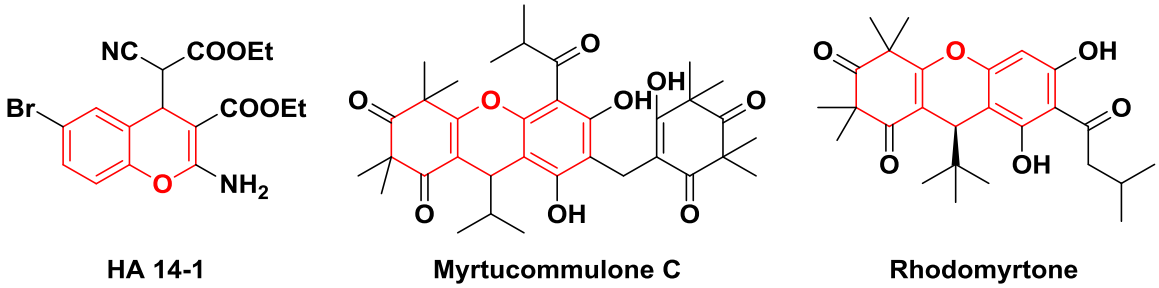


Figure 2. Abundant structural isomers of Benzopyran (chromene)

1.2 4*H*-1-Benzopyrans (Chromenes)

As a class of heterocyclic compounds the 4*H*-chromenes **2** (also known as *4H*-1-benzopyran) are quite unusual and there are only limited examples of natural products which contain this as core moiety have been synthesised. However, some of the well known 4*H*-chromene derivatives have been tested as potent chemo-therapeutic agents for the treatment of various cancer diseases. For example, EPC2407 (MX 116407), HA 14-1, Myrtucommulone C and Rhodomyrtone (Fig. 3) tested active as anti-cancer and anti-viral.[17-20] Therefore, the synthesis of 4*H*-chromenes and

related derivatives has attracted significant attention towards the synthetic chemical community for their Nobel biomedical applications.



HA 14-1 Myrtucommulone C Rhodomyrtone

Figure 3. Examples of biologically active compounds having 4*H*-chromene as a core moiety.

Several synthetic methods for the synthesis of functionalized 4*H*-chromes have been published over the years. Such traditional approaches for the synthesis of tetrahydro-1*H*-xanthen-1-ones often cover the condensation reactions of 1,3-dicarbonyl compounds with salicylaldehydes promoted by Knoevenagel – Michael These conventional approaches to produce tetrahydro-1*H*-xanthen-1-ones mostly covers the Knoevenagel–Michael condensation reactions of 1,3-dicarbonyl compounds with salicylaldehydes promoted by $CeCl_3$,[21] *p*-toluenesulfonic acid (PTSA),[22] triethylbenzylammonium chloride (TEBA),[23] tetra-n-butylammonium fluoride,[24] Zn[L-proline]$_2$,[25] and ZnO nanoparticles[26] as a heterogeneous catalyst as well as copper(I)-catalyzed intramolecular C-O bond formation [27].

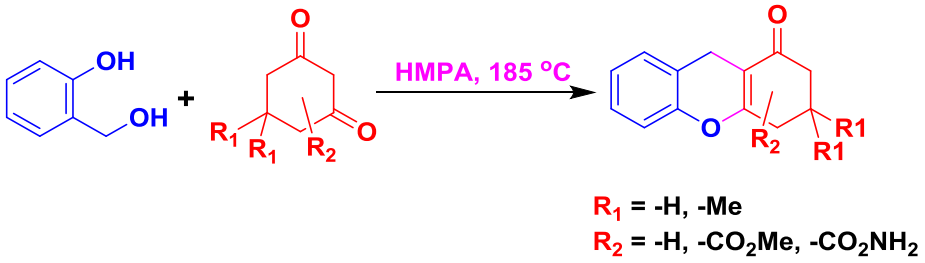
Till now, there are only very few reports are available for the synthesis of "2,3,4,9-tetrahydro-1*H*-xanthen-1-one skeleton" which offers synthetic advantages as an versatile starting material to access lots of natural products and complex compounds. However, the available synthetic strategies includes multi-component condensation reaction of aldehyde, naphthol and dimedone.[28] In 2015, Zuxing Mao and co-workers reported a method for the preparation of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones using 2-bromobenzyl bromide and cyclic-1,3-dicarbonyl compounds which is promoted by "CuO/oxalohydrazide/hexane-2,5-dione" in aqueous KOH media.[29] Recently, Yongjia Shang and co-workers developed an another method to synthesise substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones using propargylic amines or diaryl amines and cyclic-1,3-dicarbonyl compounds catalysed *via* $FeCl_3$.[30] Synthesis of functionalized tetrahydroxanthene-1-ones is important because many of them occur in plants and exhibit a

range of interesting activities. As some of the reported efficient processes over the years described below.

1.3 Synthetic approaches for biologically active 4*H*-benzopyranes derivatives.

- ***3,4-Dihydro- 1(2H)-xanthenones synthesis via condensation.***

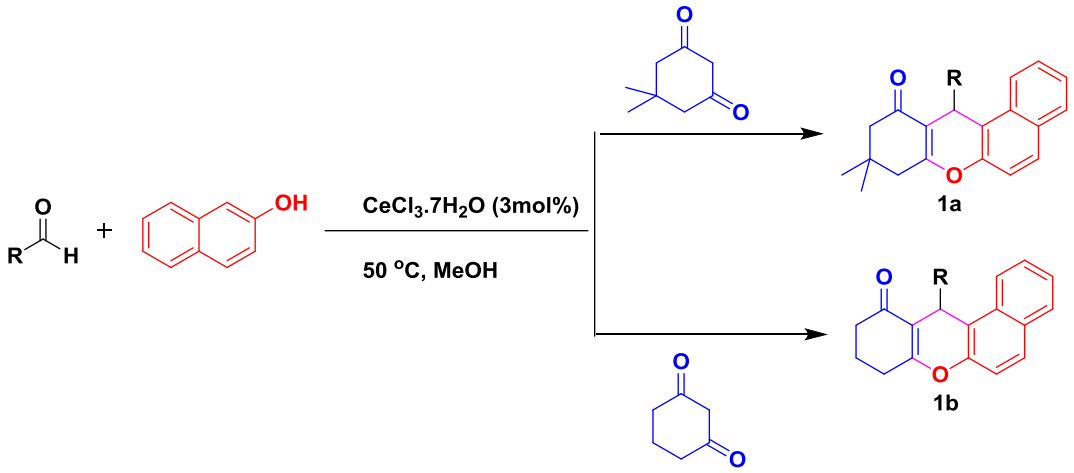
In 1972, Peter Yate and coworkers reported the condensation approach, using cyclic-1,3-dicarbonyl compounds with 2-hydroxybenzyl alcohol to synthesise 3,4-dihydro-1(2*H*)–xanthenones in low to medium yields with HMPA at 185 ^{o}C (Scheme 1).[31]



Scheme 1. Synthesis of 4*H*-chromenes *via* condensation

- ***Synthesis of 4H-chromene derivatives using Ce(III)Cl$_3$ as catalyst.***

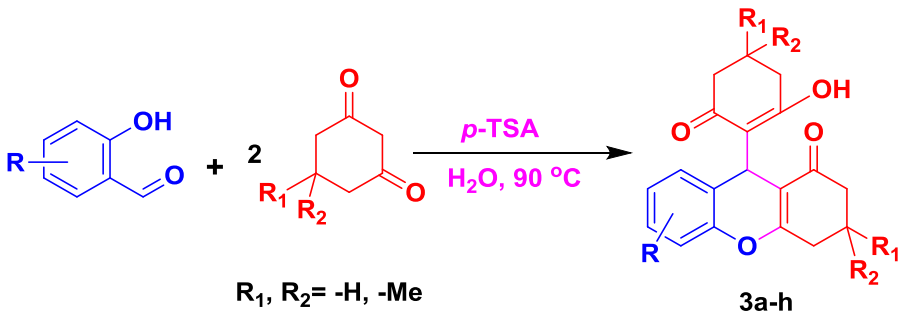
In 2011, Mazaahir Kidwai and co-workers developed a method to synthesise the tetrahydrobenzo[a]-xanthen-11-one and benzo[f]chromen-3-ones skeletons *via* multi-component reaction of aldehydes, beta- naphthol and cyclic-1,3-dicarbonyl compounds as starting materials in presence of lanthanide metal (cerium(III) chloride) and methanol (Scheme 2). This process is basically depends on the catalytic activity of lewis acid Ce(III) metal catalyst.[21]



Scheme 2. $CeCl_3.7H_2O$ catalyzed three component condensation to produce 4*H*-chromene derivatives.

- ***Synthesis of 4H-benzopyran derivatives catalysed by p-TSA.***

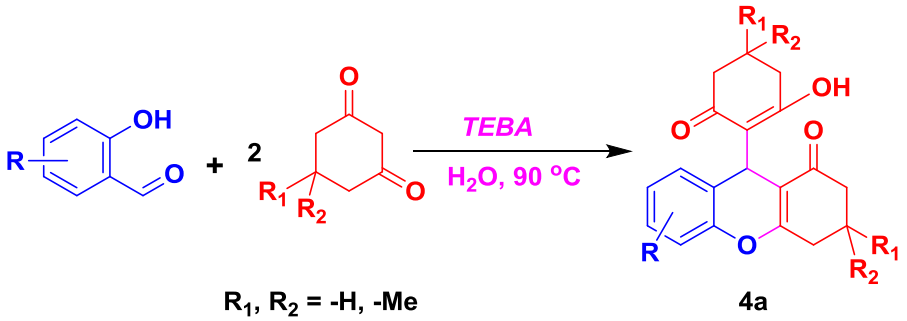
In 2013, Lingaiah Nagarapu have reported a *p*-TSA-catalysed, tandem Knoevenagel condensation, Michael addition, and cyclodehydration of salicylaldehydes and dimedones or 1,3-cyclohexanedione to produce benzopyran derivatives **3a–h** underwater in considerable yields (Scheme 3).[22]



Scheme 3. Synthesis of 4*H*-benzopyranes catalyzed by *p*-TSA.

- ***Synthesis of 4H-benzopyran derivatives catalyzed by TEBA.***

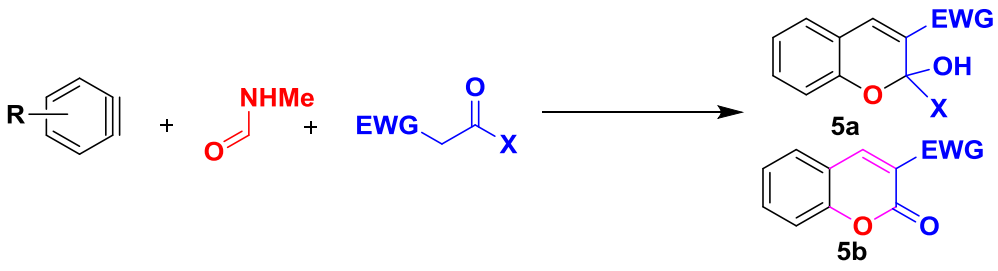
In the same year, Xiang-shan Wang have reported a procedure for the synthesis of 1-oxo-1,2,3,4,9,10-hexahydroxanthene and their derivatives **(4a)** from substituted salicylaldehydes and 1,3-cyclohexanediones catalyzed by TEBA in water at 90 ^{o}C (Scheme 4).[23]



Scheme 4. Synthesis of 4*H*-benzopyranes catalyzed by TEBA.

- ***2H-Chromenes and coumarin derivatives synthesis via multicomponent couping reaction.***

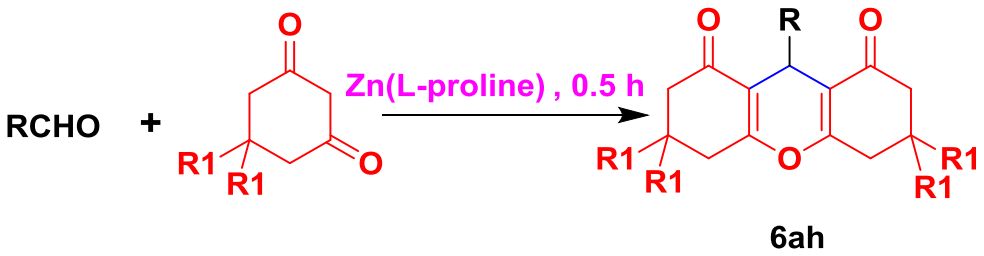
Hideto Miyab and co-workers reported a three-component coupling reaction triggered by the insertion of substituted arynes into the C=O bond of dimethylformamide (DMF) to produce the 2*H*-chromene **(5a)** and coumarin **(5b)** derivatives (Scheme 5).[32]



Scheme 5. Insertion of arynes into the C=O bond of an amide (DMF) compounds. EWG = electron withdrawing group.

- ***Xanthenediones synthesis catalysed by [Zn(L-Proline)$_2$].***

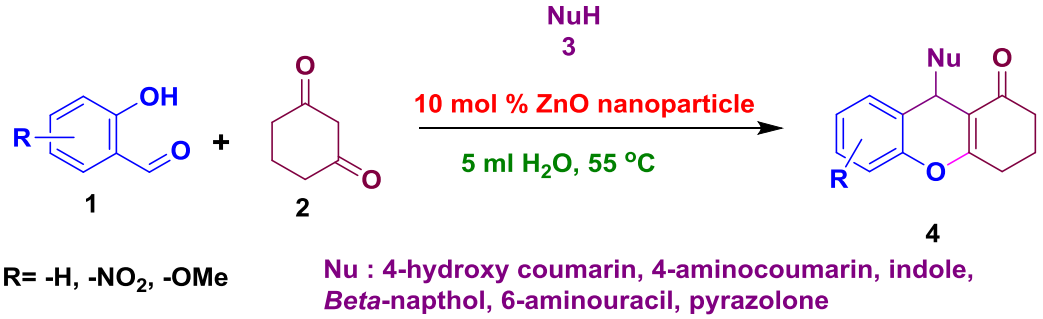
In 2011, Mazaahir Kidwai and co-workers again reported an procedure using Zn[(L-Proline]$_2$ complex as a catalyst for the condensation of aldehydes with dimedones to produce xanthenediones **(6ah)** (Scheme 6). Zn[(L-Proline]$_2$ is heterogeneous lewis acid catalyst which suits for the reaction condition.[25]



Scheme 6. Synthesis of xanthenediones in the presence of Zn[(L)Proline]$_2$ as a catalyst

- ***Isolation of functionalized 4H-chromenes catalysed by Zno nanoparticles.***

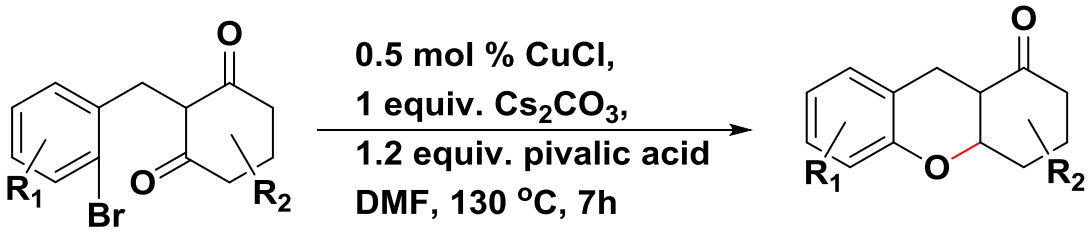
In 2013, Asish R. Das and co-workers developed a protocol using nanoparticle catalyzed organic synthesis enhancement (NOSE) chemistry. The synthesis of functionalized 4*H*-chromene derivatives **(4)**, catalyzed by ZnO nanoparticles using cyclic-1,3-dione and salicylaldehydes is described (Scheme 7).[26]



Scheme 7. Synthesis of 4*H*-chromene derivatives using ZnO nanoparticles as a catalyst.

- ***Copper(I) catalysed 2,3,4,9-Tetrahydro-1H-xanthen-1-ones synthesis.***

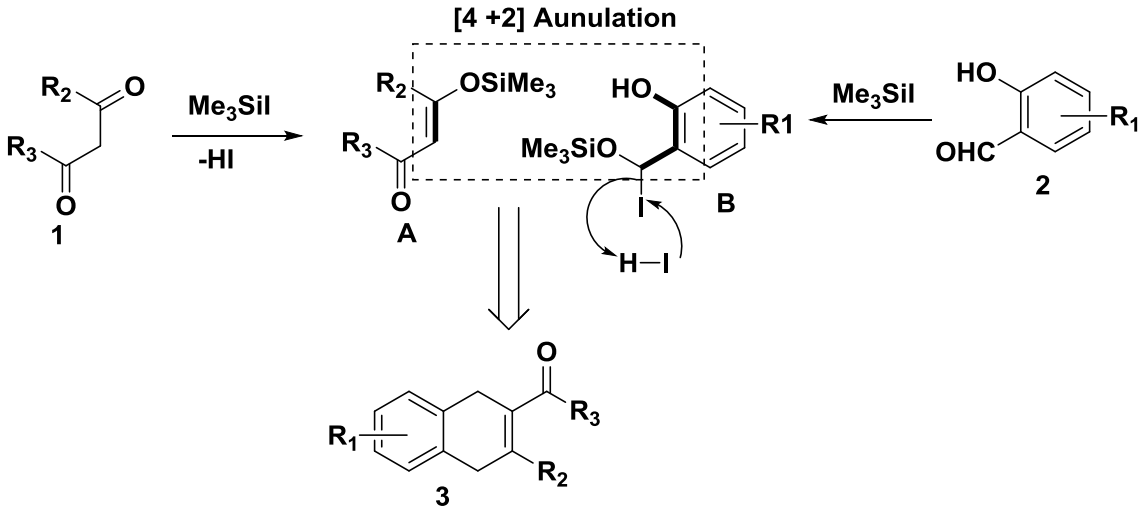
In 2012, Uwe Beifuss and co-workers synthesised 2,3,4,9-tetrahydro1*H*-xanthen-1-ones and derivatives *via* reaction between 2-bromobenzyl bromides and 1,3-cyclohexanediones using CuCl as a catalyst and equvivalent amount Cs_2CO_3 at 130 ^oC and developed a one-pot reaction with "intermolecular C-benzylation followed by intramolecular O-arylation" (Scheme 8).[27]



Scheme 8. Synthesis of 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones derivatives using Cu(I)Cl.

- ***Me_3SiI-promoted synthesis of 4H-benzopyrans.***

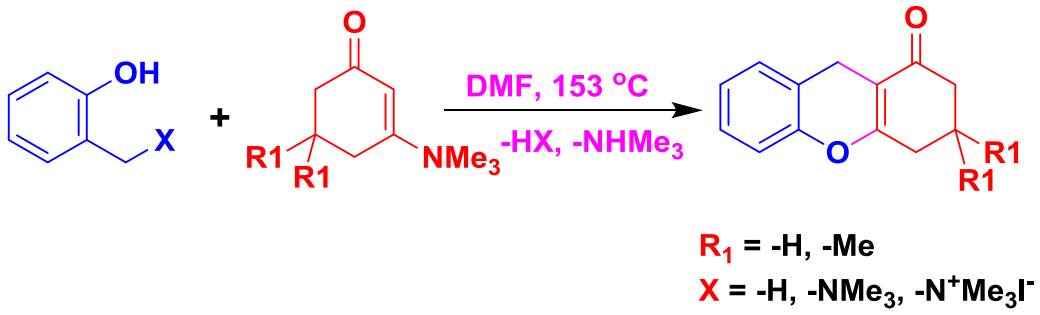
In 2012, Feijun Wang and co-workers have developed a method using Me_3SiI as a promoter for the reaction between salicylic aldehydes with 1,3-dicarbonyl compounds to produce 4*H*-benzopyran derivatives **(3)** in average yields. The method consists of more than one step: [4+2] cyclisation followed by reduction (Scheme 9).[33]



Scheme 9. Me_3SiI promoted reaction synthesis of 4*H*-chromene derivatives.

- ***Synthesis of 4H-chromene derivatives via trapping of o-quinone methides.***

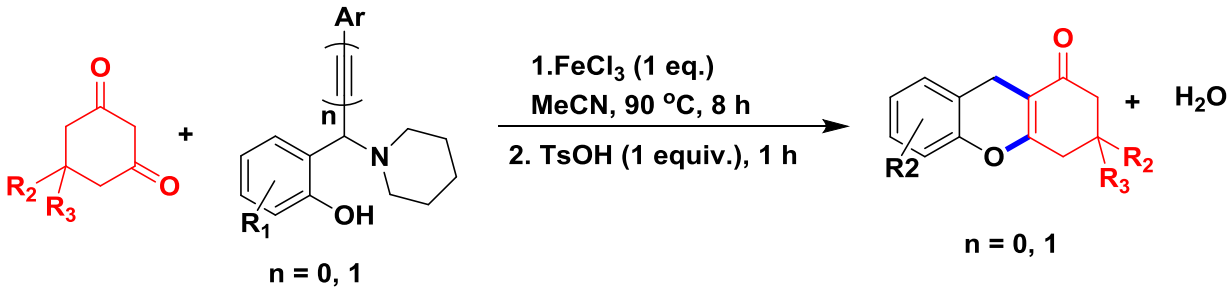
In 2012, Vitaly A. Osyanin reported a method which is used for isolation of 2,3,4,9-tetrahydro-1*H*-xanthene-1-ones and 8,9,10,12-tetrahydro-11*H*-benzo[a]xanthen-11-ones *via* trapping of o-quinone methides. The condensation reaction of dimethylamino-2-cyclohexen-1-ones with hydroxybenzyl alcohols was performed using refluxing with DMF as a solvent (Scheme 10).[34]



Scheme 10. Synthesis of 4*H*-chromene derivatives *via* trapping of o-quinone methides

- ***$FeCl_3$ catalyzed synthesis of 4H-chromenes*.**

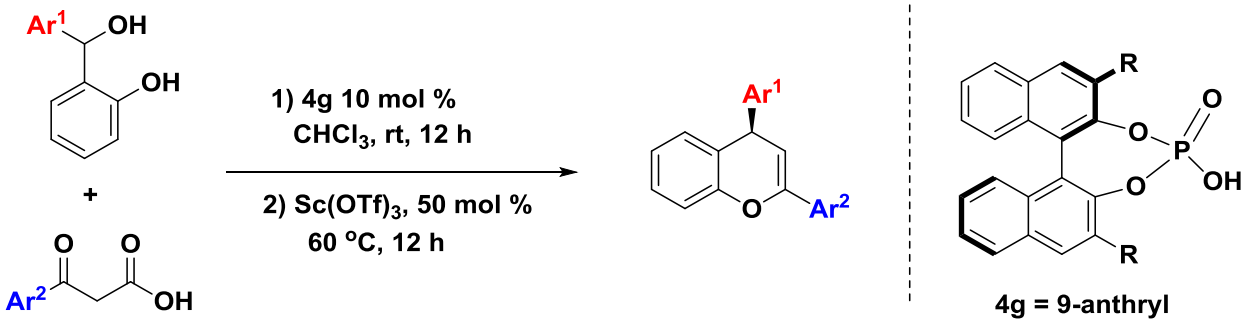
In 2016, Xinwei developed a strategy which used $FeCl_3$ as a catalyst to synthesise 9-aryl/arylethynyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones derivatives by using propargylic amines or diaryl amines and 1,3-cyclohexanediones as starting materials in acetonitrile solvent.(Scheme 11).[30]



Scheme 11. Synthesis of 4*H*-chromenes promoted with $FeCl_3$.

- ***Bronsted and lewis acid catalyzed asymmetric synthesis of 4H-chromenes.***

Recently in 2018, Dae Young Kim and co -workers reported a new procedure using asymmetric catalysis to produce 2,4-diaryl-1-benzopyrans in presence of both bronsted and lewis acids *via* decarboxyaltion of β-keto acids. It follows enantioselective sequential cyclization and dehydration with intermediate formation of o-quinone methides (Scheme 12).[35]



Scheme 12. Enantioselective synthesis of 4*H*-chromenes.

Mostly from the reported conventional methods to construct functionalized tetrahydro-1*H*-xanthen-1-ones involves use of strong acid or base as catalyst to facilitate the condensation of suitable nucleophiles with aldehydes. Each of these above methods has their own merits, while most of them are suffering with major limitations such as less atom economy, longer reaction time, costly reagents, difficult workup processes, usage of strong acids and bases, less yields, lack of availability and non-reusability of the catalysts, required preparation of starting materials, multi-step reactions with use of multicomponents and hazardous reaction condition. Moreover, the strong disadvantage of nearly all reported methods/ procedure is that the catalysts are consumed in the reaction, it means mostly homogeneously catalysed method are available. Therefore, a new catalytic system extended to heterogeneous catalysts for synthetic strategies to construct functionalized tetrahydro-1*H*-xanthen-1-ones in one-pot with highly atom economic process is still highly desirable and remain demanding, specially in terms of inclusive structural diversity of 4*H*-benzopyran containing molecules with Nobel biomedical applications.

1.4 Borrowing Hydrogen Methodology

In recent years, metal-catalyzed borrowing hydrogen (BH) or hydrogen autotransfer technique is emerged an attractive and greener catalytic approach to form C–C bond which is an essential need for synthesis of many natural and synthetic products for modern synthetic sustainable chemistry.[36] It is a well-defined and efficient approach that combines hydrogen transfer (skipping direct use of H_2) with more than one intermediate transformations which take place *via* one step in domino manner to get complex molecules with C-C and C-X bond without any need of difficult work-up processes. Basically, BH methodology associated with the hydrogen abstraction using metal catalyst from alcohols (oxidation) to produce respective carbonyl compounds *in situ*, which further undergoes to a condensation type reaction of carbonyl compound (aldol- or Knoevenegal-) with nucleophilic enolate (N- or C-) to form imine or olefin as an intermediate. In the end, metal catalysed hydrogenation of imine or olefin occurs from "borrowed" hydrogen to get the reduction products in the form of α-branched carbonyl compounds (Fig. 4). In addition, the roll of metal catalyst is intended to facilitate the redox process involved in this whole process in order to yield the desired product by leaving behind eco-friendly H_2O as byproduct. Since, with this fast growing new world of science and technologies we must not leave the nature polluted so, to fulfil the natures need with development, there is always a need of nature friendly synthetic processes. Because of this high demand, the direct alkylation of compounds containing active methylene group using alcohols *via* BH method has gained significant attraction recently. As this is accepted as one of the main synthetic approaches from principles of green chemistry point of view.[37] Also, the use of cheap and renewable starting materials like alcohol as an alkylating agent makes it highly atom economic and efficient. Additionally, provides a salt free environment by eliminating the use of alkyl halides (mutagenic) generating water as only byproduct.

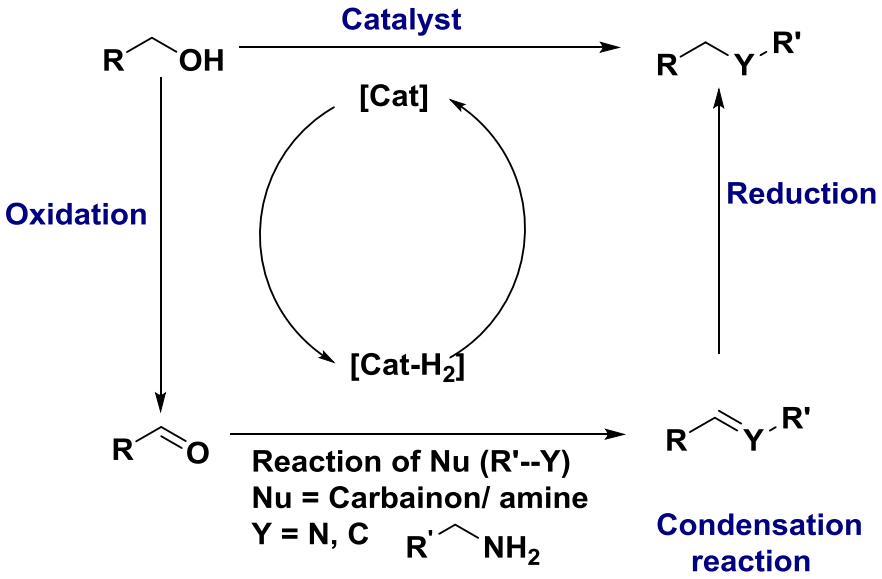


Figure 4. Borrowing hydrogen concept

The metal catalysed α-alkylation of carbonyl compounds having active methylene group using alcohols was extensively studied. According to previous reports, mainly Ru and Ir containing organometallic compounds have been well studied as effective homogeneous catalysts for this process. Over the time with increasing demand, other metals like Rh, Au, Cu, Ni, Fe, Mn, Pd, and Os were also studied extensively. However, use of this transformation includes limited group of compounds (mostly ketones, esters, amides, nitriles, and heteroarenes) having activated methylene group with alkylating agents as alcohols, amine and alkanes etc. Usually, this catalytic method requires a specific manufactured catalyst with external ligand and base to activate the inactivated starting materials like alcohols.[36-37] In this regard, the development of new catalytic system (homogeneous as well as heterogeneous) with no extra ligand and base for the alkylation of carbonyl compounds using BH approach is highly desirable. With the best of our knowledge Ruthenium catalyzed synthesis of 4*H*-chromenes *via* borrowing hydrogen methodology is not reported at yet. Therefore, we proposed to study a catalytic system (Ru-catalysts, the highly efficient one for BH concept) that can be used to synthesize substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones *via* and α-alkylation of cyclic 1,3-diketone using 2-hydroxybenzyl alcohol followed by o-arylation, without the need of an inert atmosphere.

2. Methods

2.1 Experimental section

Material and instrumentations:

All experiments were carried out without the need of an inert atmosphere in an oil bath in vials (size: 20 mL) sealed with a septum. All the chemicals used were purchased from trusted commercial sources like Sigma Aldrich and Alfa-Aesar. Deuterated solvents were used as received. Column chromatography was performed over 100−200 mesh sized silica gel. All the solvents were dried and used as received from vendors. All of the starting materials and reagents were commercially available and used as received without further purification. "Dichloro(1,5-cyclooctadiene)ruthenium(II), polymer" (CAS Number: 50982-12-2) was purchased from Sigma Aldrich. ^{1}H NMR spectra were recorded on, JEOL (400 MHz) and Bruker (400 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectroscopic data were recorded with a 100 MHz. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Chemical shifts have been discribed in ppm units downfield from TMS. All reactions were monitored by Thin Layer Chromatography (TLC). The visualisation of spots was accomplished with UV light and PMA, DNP and I_2 stain followed by heating. High-resolution mass spectra's (HRMS) were recorded with Waters-synapt G2 using electrospray ionisation (ESI-TOF). The quantitative analysis of molecular hydrogen gas was performed by using a gas chromatograph (GC) equipped with a TCD detector (Agilent 7890), a 100-mesh Carbosieve column, a maximum temperature of 225 °C, and a flow rate of 4 mL/min for hydrogen and 14 mL/min for other gases. The temperature gradients of the detector and the oven were 200 and 60 °C, respectively. The temperature of the injector was 150 °C during the experiment.

2.2 Synthetic procedures

2.2.1 General Experimental procedure for the synthesis of heterogeneous Ru@Fe_3O_4 MNP catalyst: In a 250 ml round-bottom flask, 40 mL distilled water along

with a composition of $FeCl_3.6\ H_2O$ (2 g, 7.4 mmol) and $FeCl_2.4\ H_2O$ (1 g, 3.7 mmol) was mixed and stranded to be stirred at 80 ° C for 30 min. Then, to maintain pH of the reaction around 11-12 aqueous ammonia solution (25 % (w/ w)) was added over a period of 5 min. The resulting black dispersion was stirred vigorously at room temperature for 1 h, and then same was refluxed for 1 h. The ferromagnetic Fe_3O_4 nanoparticles were extracted by using magnetic decantation and washed with ethanol and distilled water many times, and then kept in oven for 4 h at 80 ^oC for drying. Further, coating of the ruthenium metal was obtained by ultrasonic dispersion of mixture prepared by using 0.9 g of Fe_3O_4 magnetic nanoparticles (MNPs) and 0.2 g of $RuCl_3.6\ H_2O$ in 10 ml of ethanol. After the completion of dispersion process, the obtained particles were removed manually using a magnet and washed with ethanol and dried for 4 h at 80 ^oC. Then, to get the $Ru@Fe_3O_4$ magnetic nanoparticles, aqueous ammonia (25 % (w/w)) was added to the reaction mixture under intense stirring. Finally, the $Ru@Fe_3O_4$ MNP were obtained using magnet, deionized water and ethanol was used for washing then, dried in an oven for overnight at 100 ^oC.

2.2.2 Borrowing Hydrogen reaction procedure:

2.2.2(a) ***General experimental procedure for the synthesis of 2,3,4,9-tetrahydro-1H-xanthen-1-one derivatives in batch reaction*****:** In a 20 mL seal tube, cyclohexane-1,3-dione **(1a)** (0.5 mmol) was added along with 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and dichloro(1,5-cyclooctadiene)ruthenium(II), polymer(10 mol%) as a catalyst in toluene (2 ml). The tube was sealed, and the reaction mixture was allowed to stir at 160 ^oC and maintained this temperature for 24h. After completion of reaction, the mixture was allowed to cool at room temperature, and without any workup, the filtration was done by using cotton with DCM and methanol, and concentrated using rotary evaporation under vacuum. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 75: 25) on silica gel to afford the desired products in pure form.

2.2.2(b) ***General experimental procedure for the synthesis of 2,3,4,9-tetrahydro-1H-xanthen-1-one derivatives using Ru@Fe_3O_4 MNP catalyst*** **:** In a seal tube (20 mL), cyclohexane-1,3-dione **(1a)** (0.5 mmol), Ru@Fe_3O_4 MNP (100 mg), 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and toluene as solvent (2 mL) were added. Then the tube was sealed, and the reaction mixture was allowed to stir at 160 °C for 24h. After completion of the reaction, the mixture was allowed to cool at room temperature, and the filtration was done by using cotton with DCM and methanol, and concentrated using rotary evaporation under vacuum. The crude product was purified by column chromatography (EtOAc: n-hexane = 25:75) on silica gel to afford the pure product.

For control experiment with only Fe_3O_4 MNP reaction was carried with same procedure and found 27 % yield (3 times lesser than Ru coated nanoparticle).

2.2.3 General experimental Procedure for the Control Experiment in the Absence of Catalyst: In a seal tube (20 mL), cyclohexane-1,3-dione **(1a)** (0.5 mmol), 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and toluene as solvent (2 mL) were added. Then the tube was sealed, and the reaction mixture was allowed to stir at 160 °C for 24h. After completion of the reaction, the mixture was allowed to cool at room temperature and concentrated using rotary evaporation under vacuum. The crude product was purified by column chromatography (EtOAc: n-hexane = 25:75) on silica gel to afford the pure product as 2,3,4,9-tetrahydro-1*H*-xanthen-1-one **(1)** in 52% yield.

2.2.4 Experimental procedure for catalyst recovery for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-one: In a seal tube (20 ml), heterogeneous Ru@Fe_3O_4 MNP catalyst (100 mg), cyclohexane-1,3-dione **(1a)** (0.5 mmol), 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and toluene as solvent (2 mL) were added. Then, the tube was sealed, and the reaction mixture was allowed to stir at 160 °C for 24 h. After completion of the reaction, the mixture was allowed to cool at room temperature and the Ru coated magnetic catalyst was separated from mixture by using magnet and washed 3-4 times with toluene and DCM, then kept it for drying for overnight and directly used for the next run using same procedure.

2.2.5 Experimental Procedure for H_2 detection Using Gas Chromatography Analysis:

In two 20 mL seal tubes, cyclohexane-1,3-dione **(1a)** (0.5 mmol) was added along with 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and dichloro(1,5-cyclooctadiene)ruthenium(II), polymer(10 mol%) as a catalyst in toluene (2 ml) under a inert atmosphere (N_2 gas) to avoid interference of other gases. Then, the tube was tightly sealed and the reaction mixture was allowed to stir at 160 °C for 16 h. Then, with the help of gastight glass syringe the gaseous phase of reaction mixture was injected into the GC instrument and results were compared with control reaction mixture (before heating) where there was only O_2 was detected at retention time 2.815 min. (intense peak). The liberation of H_2 was detected (after heating) at retention time 0.886 min. (intense peak) by GC analysis.

2.2.6 Experimental Procedure for Detection of metal hydride using NMR analysis.

In an overnight oven dried NMR tube for at least 12 h and was charged with $[Ru(1,5\text{-}COD)Cl_2]_n$ (20 mol %), cyclohexane-1,3-dione **(1a)** (0.15 mmol), and 2-hydroxybenzyl alcohol **(1b)** (0.15 mmol) in benzene-d6 (0.6 ml). Then, the NMR tube was allowed to heat for 30 min. at 80 °C in an oil bath. Afterwards, the study of ^1H NMR was performed using the technique of NMR spectroscopy. Signals of the metal hydride were measured at δ -20.01 and -45.28 ppm. After that, the same sample was again heated for 1 h at 90 ° C and hydride signals were detected at δ −20.00 (decrease in intensity) and – 45.28 (more intense). For the hydride signals there was no chemical shift change observed. The formation of an intermediate ruthenium hydride (Ru−H) during the reaction supported by these verified experimental evidences.

2.2.7 Lifetime study for the heterogeneous $Ru@Fe_3O_4$ MNP catalyst.

In a seal tube (20 mL), heterogeneous $Ru@Fe_3O_4$ MNP catalyst (100 mg), cyclohexane-1,3-dione **(1a)** (0.5 mmol), 2-hydroxybenzyl alcohol **(1b)** (1 mmol) and toluene as solvent (2 mL) were added. Then, the tube was sealed, allowing the resultant reaction mixture to stir for 24 h at

160 °C. Upon completion, the reaction mixture was allowed for cooling to room temperature and the magnet was used to separate the supported catalyst. The catalyst was further washed with toluene and ethyl acetate 3 to 4 times, then dried and used directly for the next cycle. We analyzed 5 runs of the same catalyst.

2.3 Analytical data for the products:

2,3,4,9-tetrahydro-1*H*-xanthen-1-one (1).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst : Prepared according to general procedure 2.2.2(a), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **1** (0.0833 g, 24 h, 83.3%) as a pale yellow crystalline solid.

With $Ru@Fe_3O_4$ MNP catalyst: Prepared according to general procedure 2.2.2(b), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **1** (0.0691 g, 24 h, 69.1%) as a pale yellow crystalline solid.

With Fe_3O_4 MNP catalyst: Prepared according to general procedure 2.2.2(b), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **1** (0.0271 g, 24 h, 27.1%) as a pale yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (m, 2H), 7.05 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 3.50 (s, 2H), 2.56 (t, J = 6.2 .Hz, 2H), 2.46(t, J = 6.6Hz, 2H), 2.05(m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 167.0, 149.8, 129.8, 127.7, 124.7, 120.9, 116.5, 110.1, 36.7, 27.8, 21.2, 20.7.

HRMS (ESI) m/z calculated for $C_{13}H_{12}O_2$ $(M+H)^+$: 201.0915, found: 201.0919

5-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (2).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst : Prepared according to general procedure 2.2.2(a), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydrox-3-methoxybenzyl alcohol (0.154 g, 1

mmol) to afford 4*H*-benzopyane derivative **2** (0.0693 g, 24 h, 69.3%) as orange yellow crystalline solid.

With $Ru@Fe_3O_4$ MNP catalyst: Prepared according to general procedure 2.2.2(b), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.154 g, 1 mmol) to afford 4*H*-benzopyane derivative **2** (0.0318 g, 24 h, 31.8%) as a orange yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 (t, J= 7.96 Hz, 1H), 6.75 (m, 2H), 3.89 (s, 3H), 3.51 (s, 2H), 2.64 (t, J = 6.28 Hz, 2H), 2.47 (t, J = 6.3 Hz, 2H), 2.06 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 167.1, 148.2, 139.6, 124.7, 122.3, 121.7, 110.5, 110.4, 56.5, 37.1, 28.2, 21.6, 21.1.

HRMS (ESI) m/z calculated for $C_{14}H_{14}O_3$ $(M+H)^+$: 231.1021, found: 231.1027.

7-nitro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst : Prepared according to general procedure 2.2.2(a), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydrox-5-nitrobenzyl alcohol (0.1691 g, 1 mmol) to afford 4*H*-benzopyane derivative **3** (0.0734 g, 24 h, 73.4%) as white yellow crystalline solid.

With $Ru@Fe_3O_4$ MNP catalyst: Prepared according to general procedure 2.2.2(b), using cyclohexane-1,3-dione (0.056 g, 0.5 mmol), 2-hydrox-5-nitrobenzyl alcohol (0.169 g, 1 mmol) to afford 4*H*-benzopyane derivative **3** (0.0378 g, 24 h, 37.8%) as a white yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.10 (m, 1H), 3.61 (s, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 2.51 (t, J = 6.3 Hz, 2H), 2.12 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 166.3, 154.7, 144.6, 126.0, 124.1, 122.6, 117.7, 110.2, 37.0, 27.8, 21.7, 20.9.

HRMS (ESI) m/z calculated for $C_{13}H_{11}NO_4$ $(M+H)^+$: 246.0766, found: 246.0767

3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5,5-dimethylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **4** (0.0476 g, 24 h, 47.6%) as white crystalline solid.

With $Ru@Fe_3O_4$ MNP catalyst: Prepared according to general procedure 2.2.2(b), using 5,5-dimethylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **4** (0.0247 g, 24 h, 24.7%) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, J = 6.9Hz, 2H), 7.05 (0t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 3.51 (s, 2H), 2.42 (s, 2H), 2.32 (s, 2H), 1.12 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 164.9, 149.8, 129.5, 127.4, 124.4, 120.6, 116.3, 108.5, 50.4, 45.7, 31.9, 28.2 (2C), 20.8.
HRMS (ESI) m/z calculated for $C_{15}H_{16}O_2$ $(M+H)^+$: 229.1228, found: 229.1230.

3,3-dimethyl-7-nitro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5,5-dimethylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxy-5-nitrobenzyl alcohol (0.154 g, 1 mmol) to afford 4*H*-benzopyane derivative **5** (0.0405 g, 24 h, 40.5%) as white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 6.9Hz, 2H), 7.11 (d, *J* = 9.5 Hz, 1H), 3.57 (s, 2H), 2.53 (m, 2H), 1.93 (m, 2H), 1.34 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 171.7, 154.1, 144.3, 127.5, 123.7, 122.2, 117.6, 108.3, 35.6, 35.0, 33.7, 25.5 (2C), 21.7.
HRMS (ESI) m/z calculated for $C_{16}H_{18}O_3$ $(M+H)^+$: 274.1079, found: 259.1082.

5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5,5-dimethylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxy-3-methoxybenzyl alcohol (0.154 g, 1 mmol) to afford 4*H*-benzopyane derivative **6** (0.0378 g, 24 h, 47.6%) as yellowish white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (t, J = 7.9Hz, 1H), 6.76 (t, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.51 (s, 2H), 2.52 (s, 2H), 2.33 (s, 2H), 1.12 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 165.0, 147.8, 139.5, 124.4, 121.9, 121.3, 110.10, 108.7, 56.1, 50.7, 41.5, 32.3, 28.5 (2C), 21.2.

HRMS (ESI) m/z calculated for $C_{16}H_{18}O_3$ $(M+H)^+$: 259.1334, found: 259.1335.

3-methyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (7).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5-methylcyclohexane-1,3-dione (0.062 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **7** (0.0676 g, 24 h, 67.6%) as pale white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (m, 2H), 7.07 (m, 1H), 6.96 (d, J = 8.4Hz, 1H), 3.51 (m, 2H), 2.54 (m, 2H), 2.31 (s, 2H), 2.19 (m, 1H), 1.13 (d, J = 6.2Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 166.4, 145.0, 129.9, 127.7, 124.7, 120.9, 116.6, 109.7, 45.1, 35.9, 28.5, 21.23, 21.1.
HRMS (ESI) m/z calculated for $C_{14}H_{14}O_2$ $(M+H)^+$: 215.1072, found: 215.1075.

5-methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (8).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5-methylcyclohexane-1,3-dione (0.062 g, 0.5 mmol), 2-hydroxy-3-methoxybenzyl alcohol (0.154 g, 1 mmol) to afford 4*H*-benzopyane derivative **8** (0.0434 g, 24 h, 43.46%) as pale white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (t, J = 8.0 Hz, 1H), 6.74 (dd, J =7.5Hz, 2H), 3.87 (s, 3H), 3.49 (m, 2H), 2.60 (dd, J = 11.3, 8.4 Hz, 2H), 2.34 (d, J = 15.1 Hz, 2H), 2.16 (m, 2H), 1.11 (d, J = 6.2Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 166.1, 147.8, 139.5, 124.4, 121.9, 121.0, 110.3, 109.5, 56.1, 45.0, 35.9, 28.4, 21.3, 21.0.

HRMS (ESI) m/z calculated for $C_{14}H_{14}O_2$ $(M+H)^+$: 245.1177, found: 245.1178.

3-methyl-7-nitro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one(9).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 5-methylcyclohexane-1,3-dione (0.062 g, 0.5 mmol), 2-hydroxy-5-nitrobenzyl alcohol (0.169 g, 1 mmol) to afford 4*H*-benzopyane derivative (0.0483 g, 24 h, 48.3%) as white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (m, 2H), 7.08 (m, 1H), 3.87 (s, 3H), 3.58 (m, 2H), 2.57 (m, 2H), 2.31 (m, 2H), 2.18 (m, 2H), 1.15 (d, J = 6.2Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 166.8, 154.4, 144.3, 125.7, 125.1, 123.8, 117.5, 109.4, 56.1, 44.9, 35.5, 28.3, 21.3, 21.0.

HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4$ $(M+H)^+$: 260.0922, found: 260.0927.

4,4-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one(10).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 4,4-methylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **10** (0.0721 g, 24 h, 72.1%) as white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J = 6.8Hz, 2H), 7.05 (m, 1H), 6.99 (m, 1H), 3.48 (s, 2H), 2.57 (t, J = 6.3Hz, 2H), 1.88 (t, J = 6.3Hz, 2H), 1.16 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 165.0, 149.9, 129.8, 127.6, 124.6, 121.0, 116.4, 108.1, 40.3, 34.4, 24.8, (2C), 21.7.

HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4$ $(M+H)^+$: 229.1228, found: 229.1230.

4,4-dimethyl-7-nitro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (11).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 4,4-methylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxy-5-nitrobenzyl alcohol (0.169 g, 1 mmol) to afford 4*H*-benzopyane derivative **11** (0.0584g, 24 h, 58.4%) as pale white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 12.2Hz, 2H), 7.06 (d, J = 8.8Hz, 1H), 3.56 (s, 2H), 2.60 (t, J = 6.3Hz, 2H), 1.91 (t, J = 6.3Hz, 2H), 1.16 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 163.4, 153.1, 143.7, 125.2, 123.2, 121.8, 116.79, 107.3, 39.9, 33.7, 29.3, 24.1 (2C), 21.3.
HRMS (ESI) m/z calculated for $C_{15}H_{15}NO_4$ $(M+H)^+$: 274.1079 , found: 274.1087.

5-methoxy-4,4-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (12).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 4,4-methylcyclohexane-1,3-dione (0.070 g, 0.5 mmol), 2-hydroxy-3-methoxybenzyl alcohol (0.154 g, 1 mmol) to afford 4*H*-benzopyane derivative **12** (0.0467g, 24 h, 46.7%) as white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (t, J = 7.9Hz, 1H), 6.76 (t, J = 7Hz, 2H), 3.98 (s, 3H), 3.48 (s, 2H), 2.65 (t, J = 6.3Hz, 2H), 1.89 (d, J = 12.7Hz, 2H), 1.15(s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 164.7, 147.8, 139.5, 124.3, 121.4, 113.6, 108.1, 56.2, 40.4, 34.4, 31.9, 29.8, 24.8, 21.8.
HRMS (ESI) m/z calculated for $C_{16}H_{18}O_3$ $(M+H)^+$: 259.1334, found: 259.1338.

9a-methyl-2,3,9,9a-tetrahydro-1*H*-xanthen-1-one (13).

With $[Ru(1,5\text{-}COD)Cl_2]_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 2-methylcyclohexane-1,3-dione (0.062 g, 0.5 mmol), 2-hydroxybenzyl alcohol (0.124 g, 1 mmol) to afford 4*H*-benzopyane derivative **13** (0.102g, 24 h, 95.32%) as white crystalline solid, only soluble in highly polar solvent like MeOH, DMSO etc...

^{1}H NMR (400 MHz, DMSO-D6): complicated probably due to Enanitiomers formation

^{13}C NMR (100 MHz, DMSO-D6): every peak has an adjacent peak, so there are two similar compounds present.

HRMS (ESI) m/z calculated for $C_{14}H_{14}O_2$ $(M+H)^+$: 215.1072, found: 215.1069

9a-methyl-7-nitro-2,3,9,9a-tetrahydro-1*H*-xanthen-1-one (14).

With [Ru(1,5-COD)Cl$_2$]$_n$ catalyst: Prepared according to general procedure 2.2.2(a), using 2-methylcyclohexane-1,3-dione (0.062 g, 0.5 mmol), 2-hydroxy-5-nitrobenzyl alcohol (0.169 g, 1 mmol) to afford 4*H*-benzopyane derivative **14** (0.117g, 24 h, 90.89%) as white crystalline solid, only soluble in highly polar solvent like MeOH, DMSO etc...

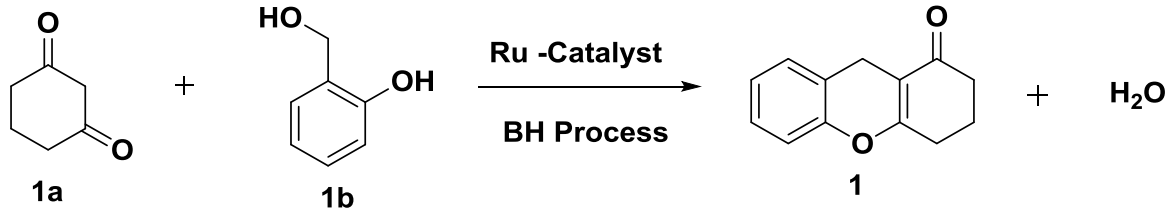
^{1}H NMR (400 MHz, $CDCl_3$): complicated probably due to Enantiomers formation.

^{13}C NMR (100 MHz, DMSO-D6): δ 219.9, 166.4, 150.6, 135.8, 133.1, 132.8, 127.0, 110.6, 58.3, 39.23, 38.5, 29.4, 28.8.

HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4$ $(M+H)^+$: 260.0922, found: 260.0924.

3. RESULTS AND DISCUSSION

On the basis of our previous results[38] and literature survey over Borrowing Hydrogen process to generate C-C bond[39], we decided to develop a BH method to construct "2,3,4,9-tetrahydro-1*H*-xanthen-1-ones derivatives" *via* one-pot pathway in domino manner, consisting of intermolecular (C-C bond) benzylation followed by intramolecular (C-O bond) arylation using 2-hydroxybenzyl alcohols with a cyclic 1,3-diketones. These results of our research are revealed in this dissertation.



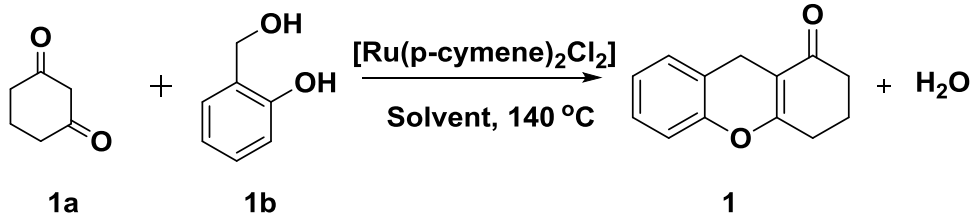
Scheme 13. Initial Experiment for the "Ru(II)-Catalyzed synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones from 2-hydroxybenzyl alcohols and cyclic 1,3-diketones" (model reaction).

3.1 Solvent study at different temperatures

The starting point was the Ru(II)-catalyzed reaction between **(1a)** cyclohexane-1,3-dione (0.5 mmol, 1 equiv.) and **(2a)** 2-hydroxybenzyl alcohol (0.75 mmol, 1.25 equiv.). When **1a** and **2a** were reacted in the presence of 2 mol% $[Ru(p\text{-cymene})_2Cl_2]_2$ as the catalyst in acetonitrile at 120°C for 24h (Scheme 13) afforded 42% of the xanthenone **1** as well as some amount of unreacted 2-hydroxybenzaldehyde observed in the TLC. The structure of the product **1** was unambiguously confirmed with the help of NMR and HRMS analysis. Encouraged by the preliminary results, we have optimized the reaction condition with respect to solvent at different temperatures, at 110°C (Table 1, entry 1) for the same reaction decrease in yield (30%) was observed. Next, the reaction was performed in toluene at 140 ^{o}C resulting in 52% yield (Table 1,

entry 2) of desired product. The optimized results are summarised in table 1. The reason why we choose toluene as a best solvent because it is well studied solvent for the Borrowing Hydrogen Process and have ability to sustain at higher temperature.

Table 1. Solvent study at various temperatures for borrowing hydrogen reaction in batch



1a 1b 1

entry	1b (mmoles)	1a (mmoles)	Catalyst (2.5 mol%)	Solvent	Time (h)	yield (%)
1.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	ACN (110°C)	24	30
2.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Toluene	24	52
3.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Dioxane	24	27
4.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	DMF	24	19
5.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Water	24	-
6.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Dry ACN	24	43

Reaction condition: 1a (1 mmol), catalyst (2.5 mol%), solvent (2 mL) and were stirred at 140 ^{o}C, the mentioned yields are isolated yield.

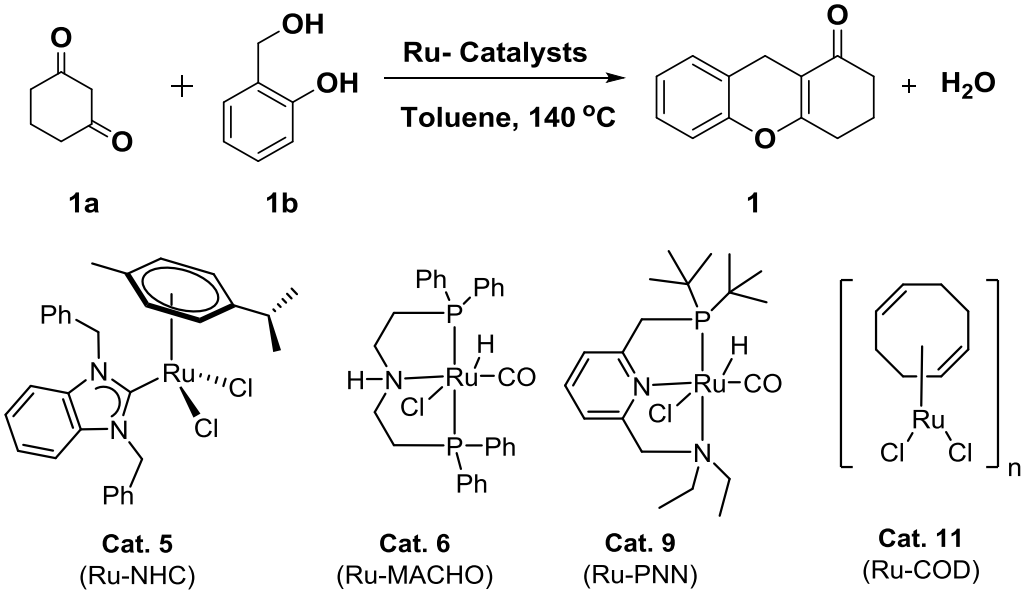
3.2 Catalytic studies and substrate scope

After getting best solvent condition at 140 ^{o}C, we moved towards the catalyst study (Table 2) for the same reaction. Among several Ru-catalyst, 10 mol% $[Ru(II)(1,5\text{-}(COD)Cl_2)]_n$ catalyst provides best yield of 53% (Table 2, entry 11). The increased loading of this catalyst also

checked and no improvement in yield was observed (Table 2, entry 16). Since this catalyst is polymer so some times at higher temperatures it behaves homogeneous catalyst. As it was heterogeneous at 140 ^{o}C and we checked the recyclability of catalyst for second cycle at 140^{o}C resulting 48% yield. And also, if we allow the same reaction for longer time we got improved yield by 10-12% (Total 62 -64%) after 48 h (Table 2, entry 17).

Also screened various heterogeneous supported catalysts [Ru@Fe_3O_4], [Mn@Fe3O4], [Ru@Alumina] and we found [Ru@Fe_3O_4] with 42% (Table 2, entry 13) as the best catalyst for the BH reaction. The reason we choose to synthesise [Ru@Fe_3O_4] MNP as a catalyst because it is cheap to prepare, environmental friendly, less amount of ruthenium with highly ferromagnetic properties that ultimately leads to easy separation process with high thermal stability.

Table 2. Catalyst study for borrowing hydrogen reaction in batch



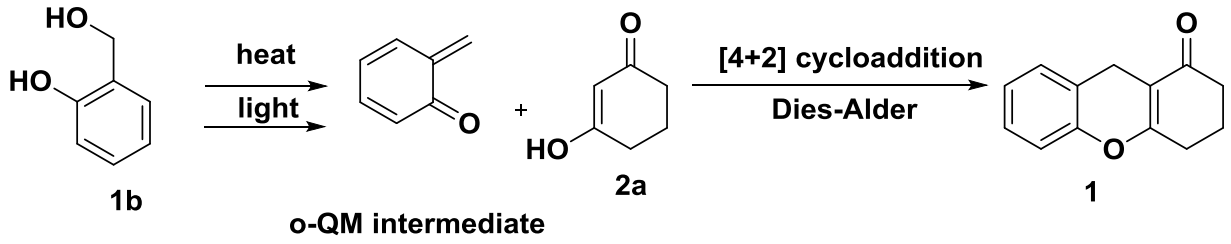
entry	Ru-Catalysts	Ru-Catalyst (Mol%)	Time (h)	yield (%)
1.	[Ru(p-cymene)Cl_2]$_2$	2.5	24	52

2.	$[Ru(p\text{-}cymene)Cl_2]_2$	5	24	50
3.	$Ru(bpy)_3Cl_2.6H_2O$	2.5	24	43
4.	$RuCl_3.\ 6H_2O + PPh_3$	2.5+2.5	24	traces
5.	[Ru-NHC]	2.5	24	38.3
6.	Ru-MACHO	2.5	24	30
7.	$Ru(1,10\text{-}phen)_3Cl_{2.}\ nH_2o$	2.5	24	43.23
8.	$Ru(PPh_3)_3(CO)HCl$	2.5	24	decomposed
9.	Milstiein catalyst precursor (Ru-PNN)	2	24	15.25
10.	$[Ru(C_5Me_5)Cl_2]_n$	15 mg	24	19.5
11.	**$[Ru(1,5\text{-}COD)Cl_2]_n$**	**15 mg (10 mol%)**	24	**53**
12.	$[Ru(PPh_3)_3(Cl)_2]$	2.5	24	Complicated reaction mixture
13.	$[Ru@Fe_3O_4]$	2.5	24	43.1
14.	$[Mn@Fe_3O_4]$	2.5	24	traces
15.	[Ru@Alumina]	2.5	24	traces
16.	$[Ru(1,5\text{-}COD)Cl_2]_n$	30 mg	24	51.5
17.	**$[Ru(1,5\text{-}COD)Cl_2]_n$**	**15mg**	48	**63%**

Reaction condition: 1a (1 mmol), catalyst (2.5 to 10 mol%), toluene (2 mL) and were stirred at 140 ^oC, the mentioned yields are isolated yield.

As maximum yield after optimization was observed 53% with $[Ru(1,5\text{-}COD)Cl_2]_n$ (Table 2, entry 11). In order to improve the yield, additives were added in the reaction such as Lewis acid (Ag(OTf), KI), ligands (PPh_3 with different catalyst) and bases but no improvement in yield was observed. However, with bases (^tBuOK, Cs_2CO_2, K_2CO_3) complicated reaction mixture was observed. Also, higher loading of the catalyst was tried and no change in yieal observed (Table2, entry 16).

To verify role of the catalyst a control experiment was performed, the same reaction has been carried out in absence of catalyst at 140 °C and 160°C in toluene which gave 18 % and 51% yield, respectively. Since, at higher temp. and with white light 2-hydroxybenzyl alcohol can generate o-QM (o-Quinone methide) as reactive and versatile intermediate species. The chemical activity of o-QMs is somewhat similar to that of α, β-unsaturated ketones due to the presence of a carbonyl and exomethylene substituted center of 1,3-cyclohexadienes. They react very quickly with nucleophiles (-C, -N) and undergo effective Diels – Alder reactions with electrone rich-olefins to produce C-C or C-X bonds. Its use as a convertible intermediate in organic synthesis increased extensively, particularly in many tandem [4 + 2] cycloaddition reactions with a variety of dienophiles.



Scheme 14. A possible mechanism was hypothesized in absence of catalyst.

So, we thought of taking polar solvent as more enol form (**2a**) of cyclohexane-1,3-dione will be present as dienophile in solution to carry out [4+2] cycloaddition easily via Dies-Alder mechanism (Scheme 14). But, experimentally in polar solvents such as DMSO and DMF at 160 °C, 24 hr traces and 39% respectively of desired product **1** respectively were observed. In addition to this hypothesis, photochemical reaction study was also done in presence of photoredox catalyst $[Ru(bpy)_3Cl_2].6H_2O$ (2.5 mol%) and desired product **1** was observed with 28% yield. Although, these alternative developed processes were also interestingly efficient and

environment friendly in terms of atom economy and simplicity over reported one pot procedures. But without going deeper into this new aspect of project I continued optimization of borrowing hydrogen reaction procedure.

From the above studies we can see that temperature and activity of catalyst are very much related to each other. As per our hypothesis higher temperature increases the activity of catalyst which have very crucial role for this process. However, the decisive role of $[Ru(1,5\text{-}COD)Cl_2]_n$ was observed when the reaction was performed at 160 °C in toluene for 24 h which afforded 82.3% conversion of compound **(1)** (Table 3, entry 5).

Table 3. Temperature study for the model reaction (Scheme 13).

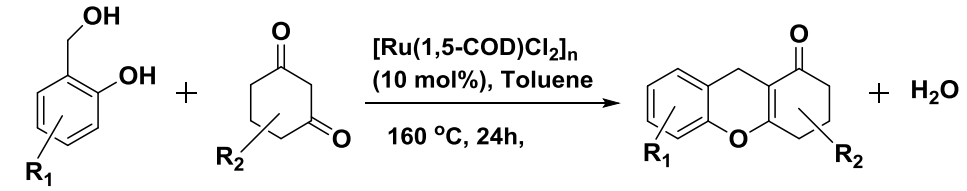
entry	1b (mmoles)	1a (mmoles)	Catalyst	Solvent	Temp.	yield (%)
1.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	ACN	110°C	30
2.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Toluene	120 °C	42
3.	1.5	1	$Ru(p\text{-}cymene)_2Cl_2$	Toluene	140 °C	52
4.	1.5	1	$[Ru(1,5\text{-}COD)Cl_2]_n$	Toluene	140 °C	53
5.	**1.5**	**1**	**$[Ru(1,5\text{-}COD)Cl_2]_n$**	**Toluene**	**160 °C**	**82.6**

Reaction condition: 1a (1 mmol), catalyst (2.5 to 10 mol%), solvent (2 mL) and were stirred for 24 h, the mentioned yields are isolated yield.

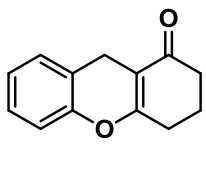
3.2.1 Substrate scope using $Ru(1,5\text{-}COD)Cl_2]_n$ as catalyst

With the established optimised reaction condition in hand (Scheme 15), we performed reactions with a variety of cyclic-1,3-diones with different aromatic 2-hydroxybenzyl alcohols. Substrate scope for this transformation summarised in **Scheme 15**. We have performed the reaction with cyclic-1,3-diones such as cyclohexane-1,3-dione **(1a)** with 2-hydroxybenzyl alcohols (**1b)**, 2-hydrox-3-methoxybenzyl alcohols **(2b)**, 2-hydroxy-5-nitrobenzyl alcohols **(3b)**, and 5-bromo-2-

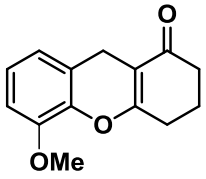
hydroxybenzyl alcohols **(4b)** which afforded desired products **1**, **2**, **3, 16** in moderate to good yield 82.3%, 69.3%, 73.4%, and 94.5% respectively. Furthermore, other substituted cyclic-1,3-diones such as 5,5-dimetylcyclohexane-1,3-dione **(2a)**, 5-methylcyclohexane-1,3-dione **(3a)** and 4,4-dimethylcyclohexane-1,3-dione **(4a)** also reacted well with **1b, 2b,** and **3b** to afford **4, 6, 5, 7, 8, 9 and 10, 12, 11** in 47.6%, 37.8%, 72.4%, 67.63%, 43.66%, 48.36% and 72.4%, 46.7%, 58.4% yield respectively. Interestingly, this reaction is well tolerant to electron donating (methoxy-) and electron withdrawing (nitro-) functional groups. Unfortunately, borrowing hydrogen process was unsuccessful with 5-bromo-2-hydroxybenzyl alcohols **(4b)**. In this case, formation of 5-bromo-2-hydroxybenzaldehyde **(14)** was confirmed with 94.5% yield. Also for cyclopenta-1,3-diones, 4-Hydroxycoumarin as well as aliphatic-1,3-diones the method was not successful. 2-methylcyclohexane-1,3-dione (**5a**) reacted well with 2-hydroxybenzyl alcohols (**1b)** and 2-hydroxy-5-nitrobenzyl alcohols **(3b)** gaves **13** and **14** in 95.32% and 90.89% yield respectively and these two compounds seems to be in enantiomers. The structure **(13, 14)** confirmed from HRMS and ^{13}C NMR.



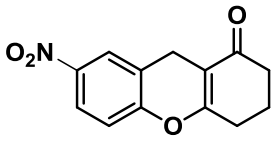
R_1= -H (1b), -Me (2b), -NO_2 (3b), -Br (4b).
R_2= -H (1a), -Me (3a, 5a), - Me_2 (2a, 4a).



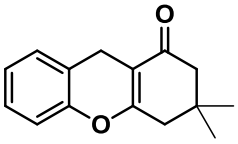
1, 82.3%



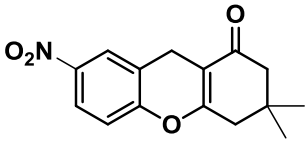
2, 69.3%



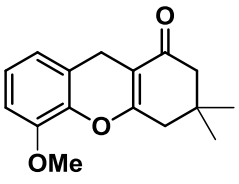
3, 73.4%



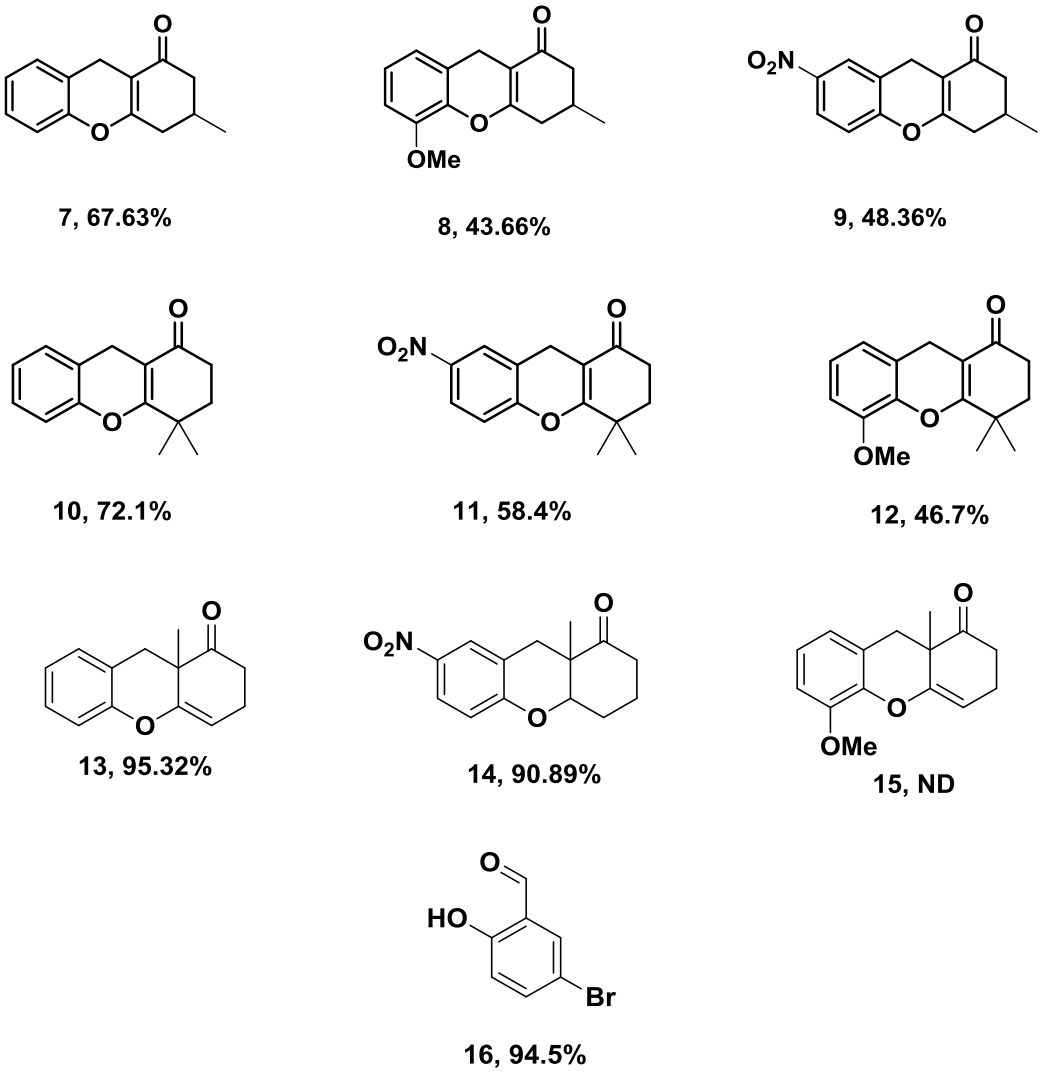
4, 47.6%



5, 72.4%



6, 37.8%%



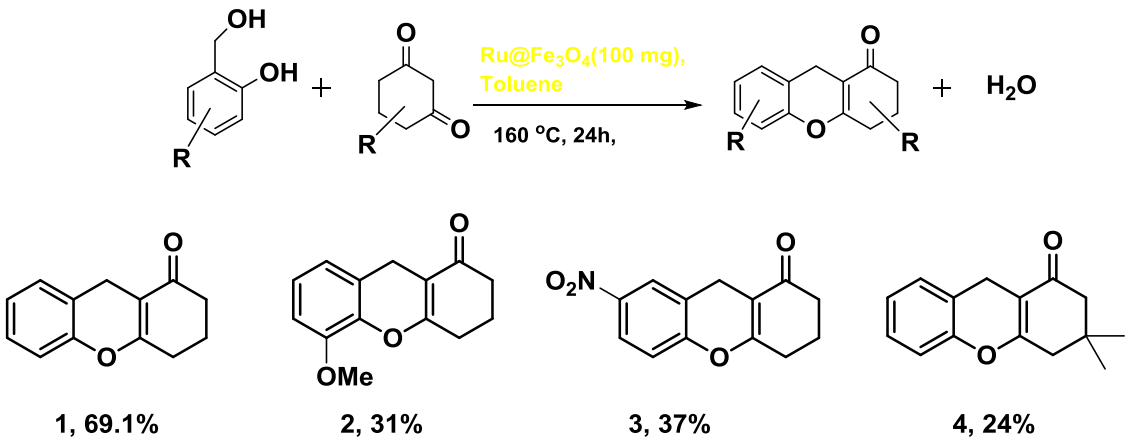
Scheme 15. Substrate scope for 2,3,4,9-tetrahydro-1*H*-xanthen-1-one derivatives using BH process.

3.2.2 Synthesis of heterogeneous Ru@MNP catalyst and characterisation

The synthesis of nano-sized $Ru@Fe_3O_4$ was obtained through the procedure stated for $Fe(OH)_3@Fe_3O_4$.[40] and observed that the prepare catalyst was having ferromagnetic properties confirmed using external magnet which ultimately offers ease of separation and having high thermal stability as well as also confirmed very low leaching of metal from supported catalyst during this high temperature reaction from the observed yields.

3.2.3 Catalytic Studies of $Ru@Fe_3O_4$ MNP for borrowing hydrogen process:

Initially, a control experiment with only Fe_3O_4 MNP as catalyst with model substrates **1a** and **1b** were carried out which gave 27.3% yield of compound **1** which is 3 times lesser than with $Ru@Fe_3O_4$ MNP as catalyst. However, with $Ru@Fe_3O_4$ MNP using standard optimized condition, cyclohexane-1,3-dione **(1a)** with 2-hydroxybenzyl alcohol (**1b)**, 2-hydrox-3-methoxybenzyl alcohol **(2b)**, 2-hydroxy-5-nitrobenzyl alcohol **(3b)** which afforded desired products in 69%, 31%, 37% yields, respectively. Also, 5,5-dimethylcyclohexane-1,3-dione **(2a)** well reacted with 2-hydroxybenzyl alcohol (**1b)** gave 24% yield. The results are summarized in **Scheme 16.** At lower temperatures fewer yields observed (Table 2, entry 13).



Scheme 16. Substrate scope for synthesis of 4*H*-chromene derivatives.

3.2.4 Recyclability of the $Ru@Fe_3O_4$ MNP catalyst

The reusability and recyclability of the $Ru@Fe_3O_4$ MNP catalyst was studied using standard reaction conditions for the borrowing hydrogen procedure to produce compound **1** over the 5 cycles (Fig. 5). Additionally, it is observed that the catalyst has not lost its activity so we can still use it for further transformations. Over the completion of each cycle, the catalyst was separated

using a magnet and subsequently, washed with toluene and ethyl acetate 3 to 4 times, then kept it for drying for overnight at 100 °C before each cycle and then the catalyst was directly used for the next cycles. The average product yield remained the same without any prolongation of reaction time. Such findings clearly demonstrate that over a prolonged reaction, the catalyst's efficiency was not lost.

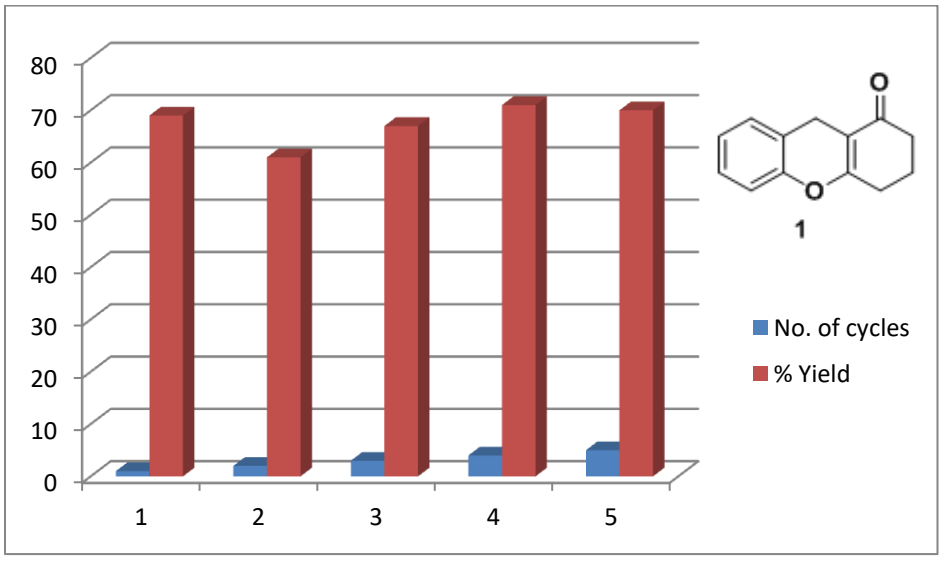
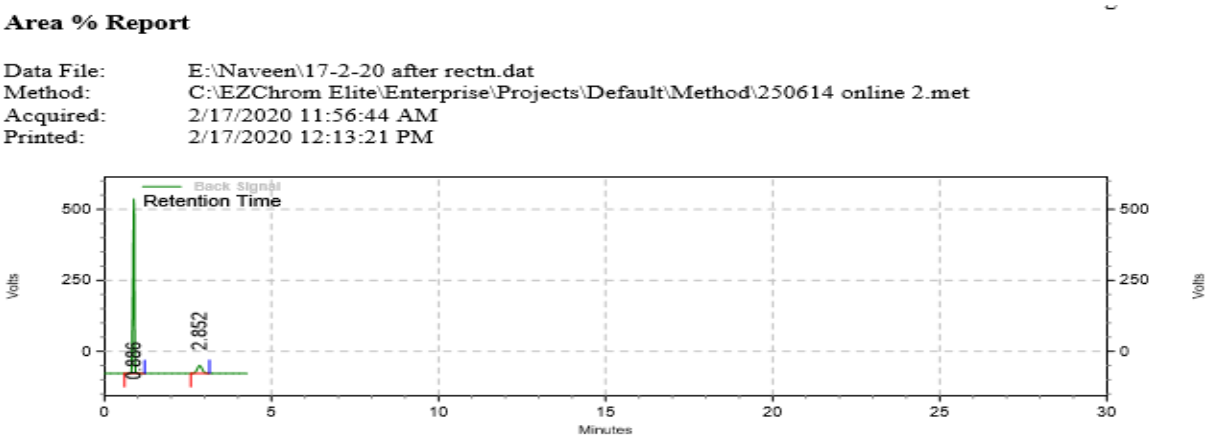


Figure 5. Recyclability of Ru@Fe_3O_4 MNP for the synthesis 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones **(1)**

3.3 Mechanistic studies

We have suggested a mechanistic pathway from the experimental findings and literature studies for "the one-pot synthesis of 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones which based on borrowing hydrogen principle". This reaction proceeds *via* domino manner, consisting of intermolecular (C-C bond) benzylation followed by intramolecular (C-O bond) arylation from the reactions of *2*-hydroxybenzyl alcohols and cyclic-1,3-dicarbonyl compounds in presence of Ru-catalysts. The BH strategy follows three steps: Step-1.) The ruthenium catalysed dehydrogenation (oxidation) of alcohol **1b** to temporarily produce aldehyde **1b′** and Ru−H_2 complex. To verify this step, metal hydride signals and release of H_2 gas was confirmed using ^{1}H NMR experiment and gas chromatography (GC) analysis, respectively (Figure 6). Step-2.)

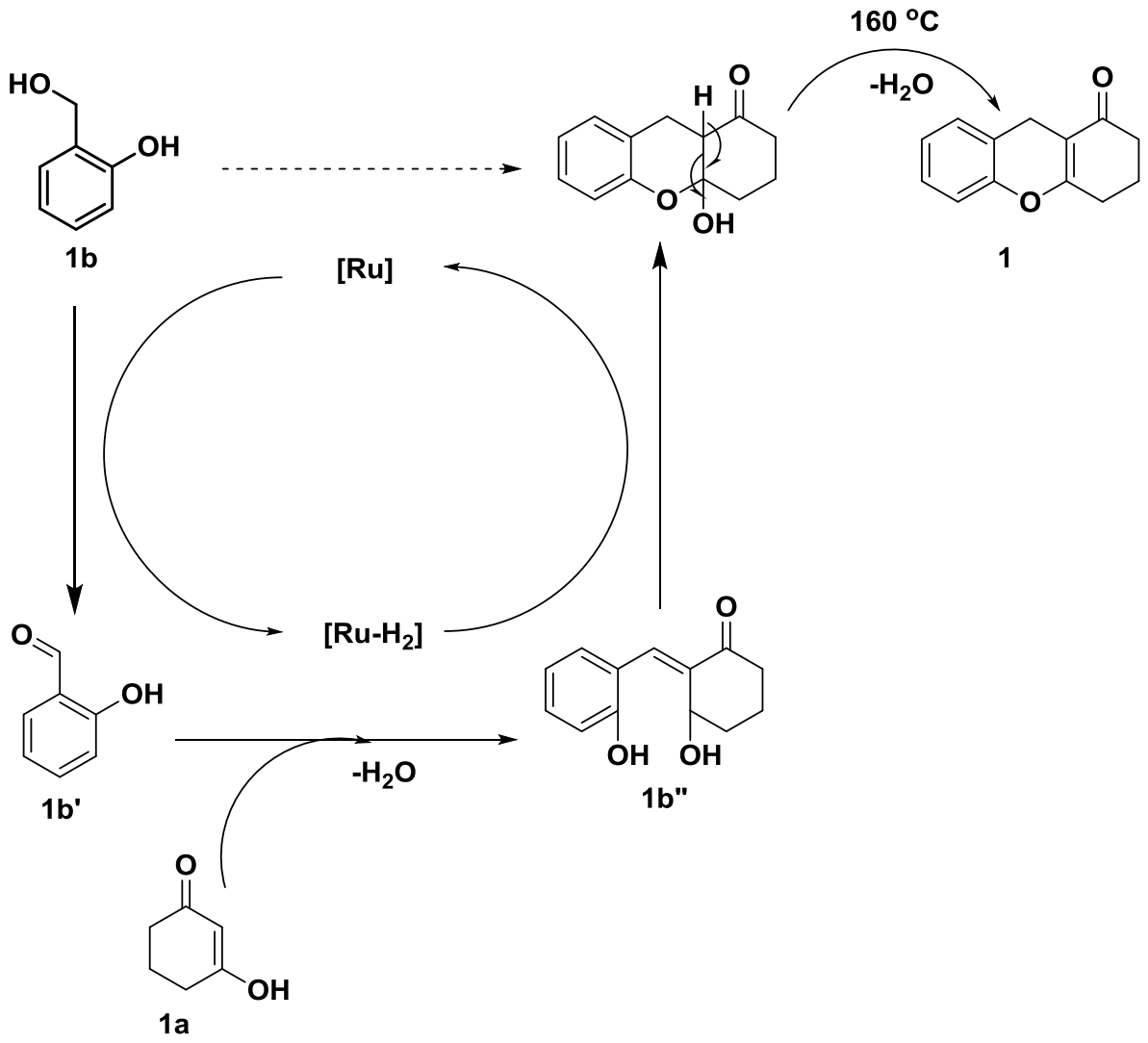
Nucleophilic addition of enol form of cyclohexane-1,3-dione to aldehyde **1b'** in the absence of any base to afford the unsaturared (E)-3-hydroxy-2-(2-hydroxybenzylidene)cyclohexan-1-one **(1b″)** as an intermediate. Step-3.) The unsaturated product converted to reduced product promoted *via* metal hydride during dehydrogenation followed by thermally forced dehydration leads to formation of "2,3,4,9-tetrahydro-1*H*-xanthenones" **1** (Scheme 17).



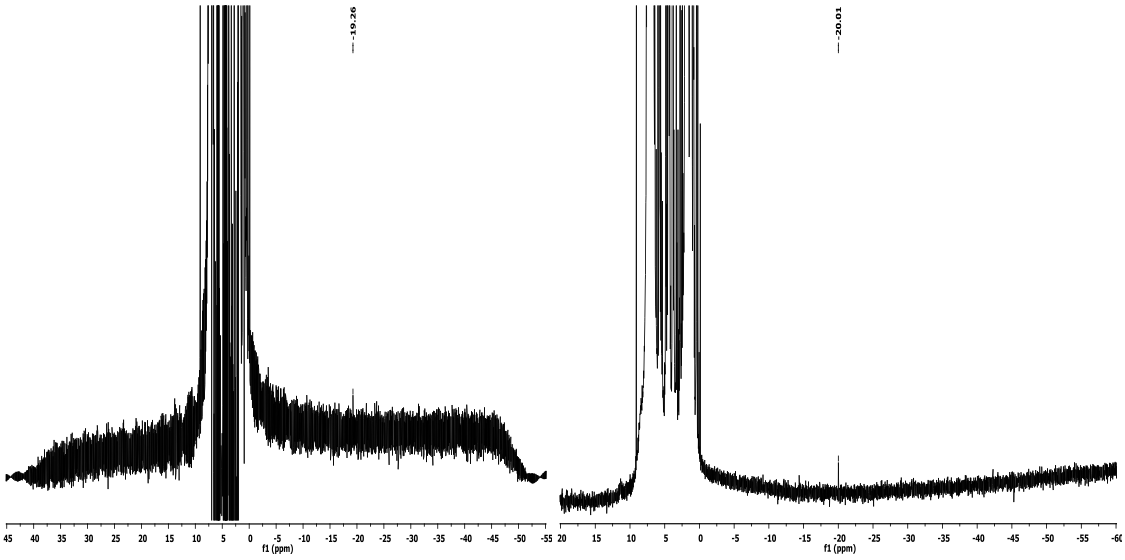
Back Signal
Results

Retention Time	Area	Area %	Height	Height %
0.886	14601573	86.76	4721693	95.72
2.852	2228807	13.24	210969	4.28
Totals	16830380	100.00	4932662	100.00

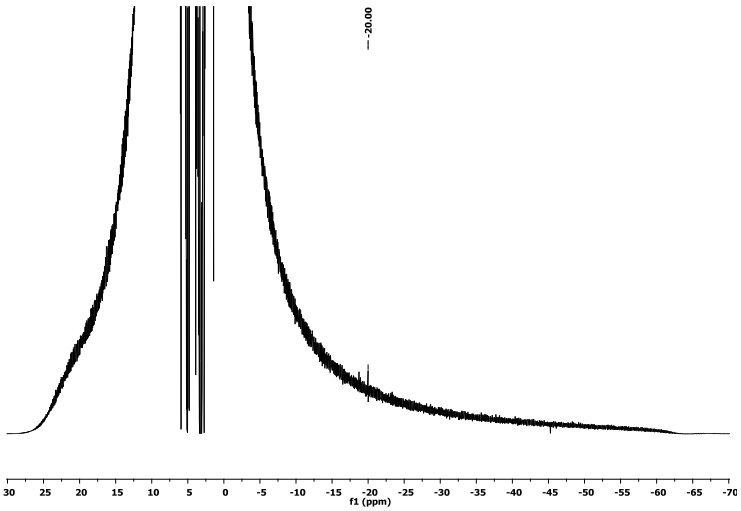
Figure 6. H_2 gas detection using GC analysis.



Scheme 17. Plausible mechanism for the borrowing hydrogen procedure using Ru-catalyst.



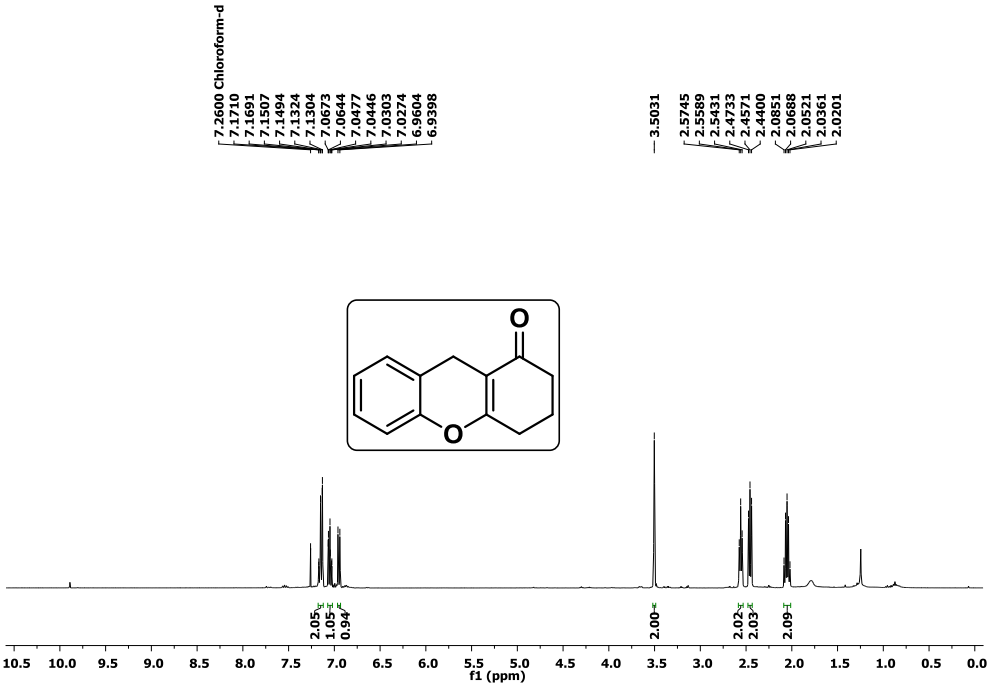
1st and 2nd ^{1}H NMR experiment



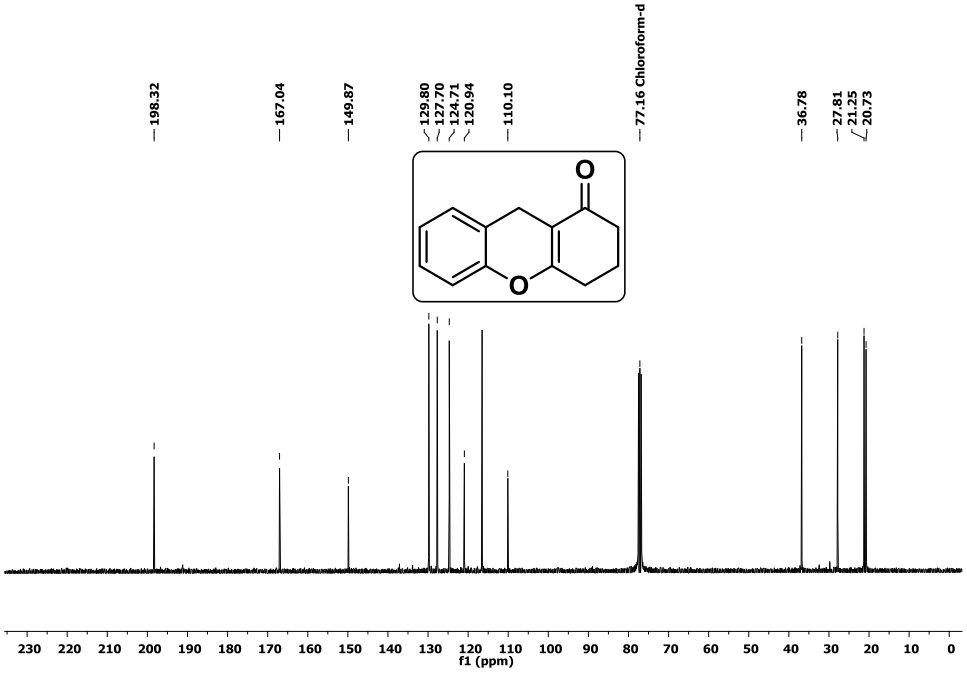
3rd ^{1}H NMR experiment

Figure 7. ^{1}H NMR experiments for [Ru-H] detection.

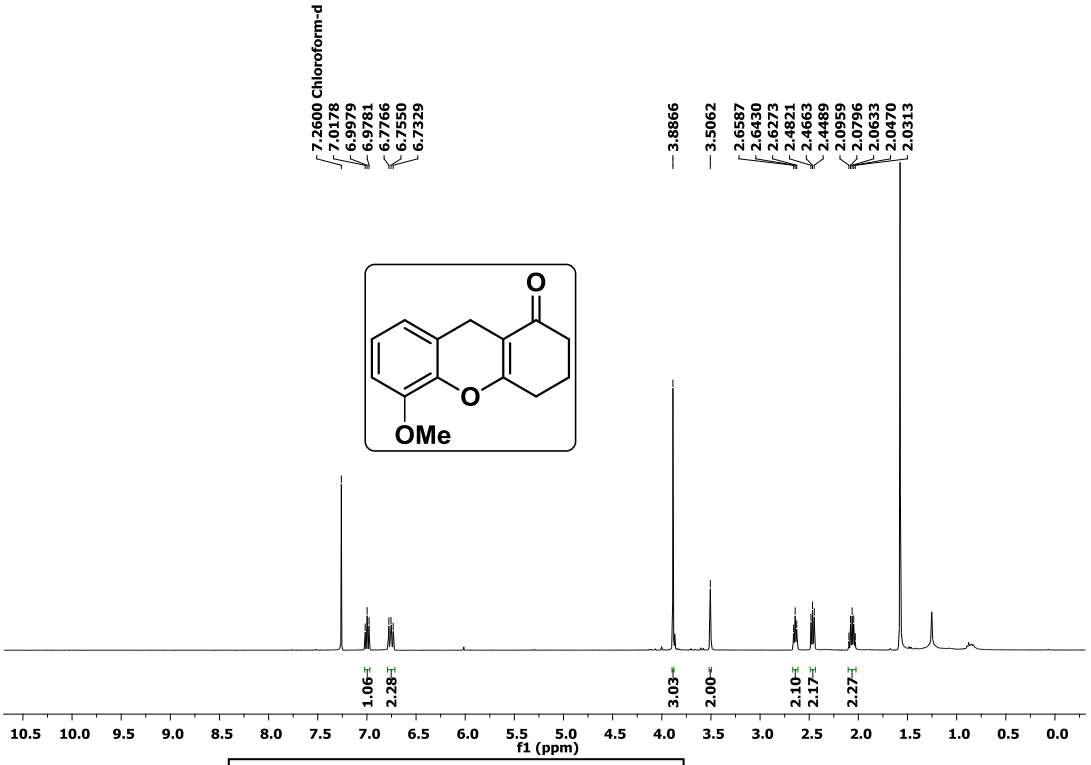
4. a) Copies of NMR Spectra's for products.



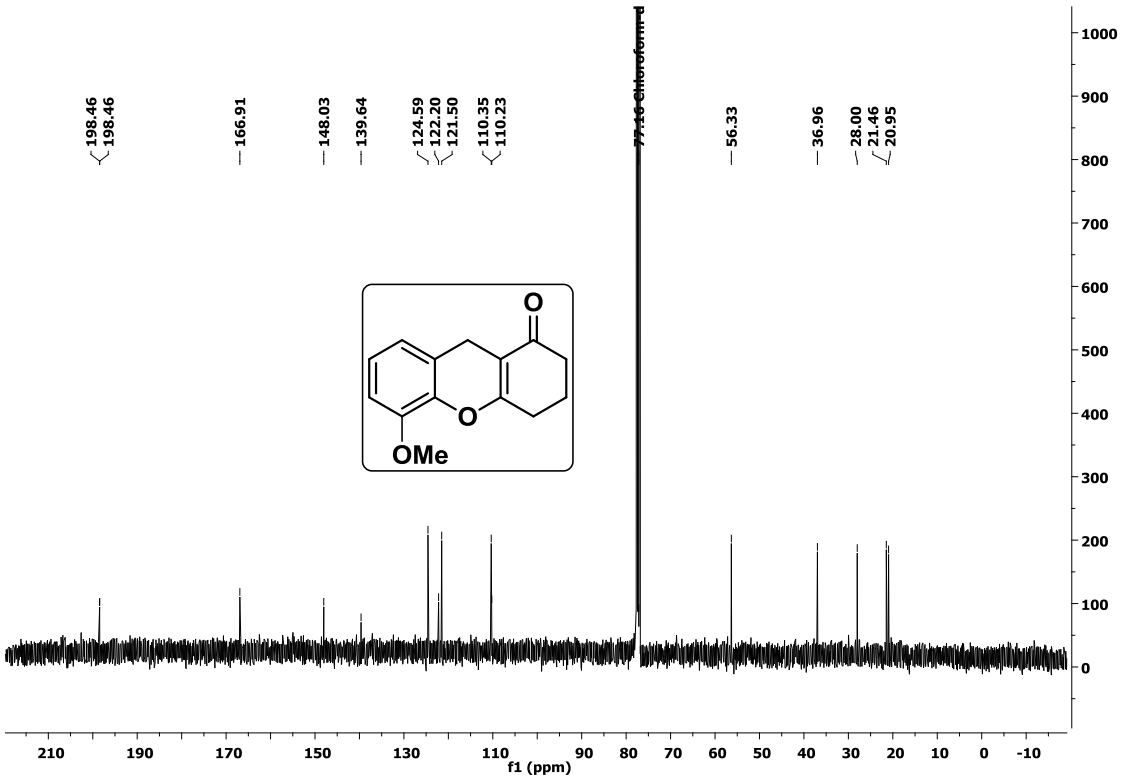
^{1}H NMR of compound 1



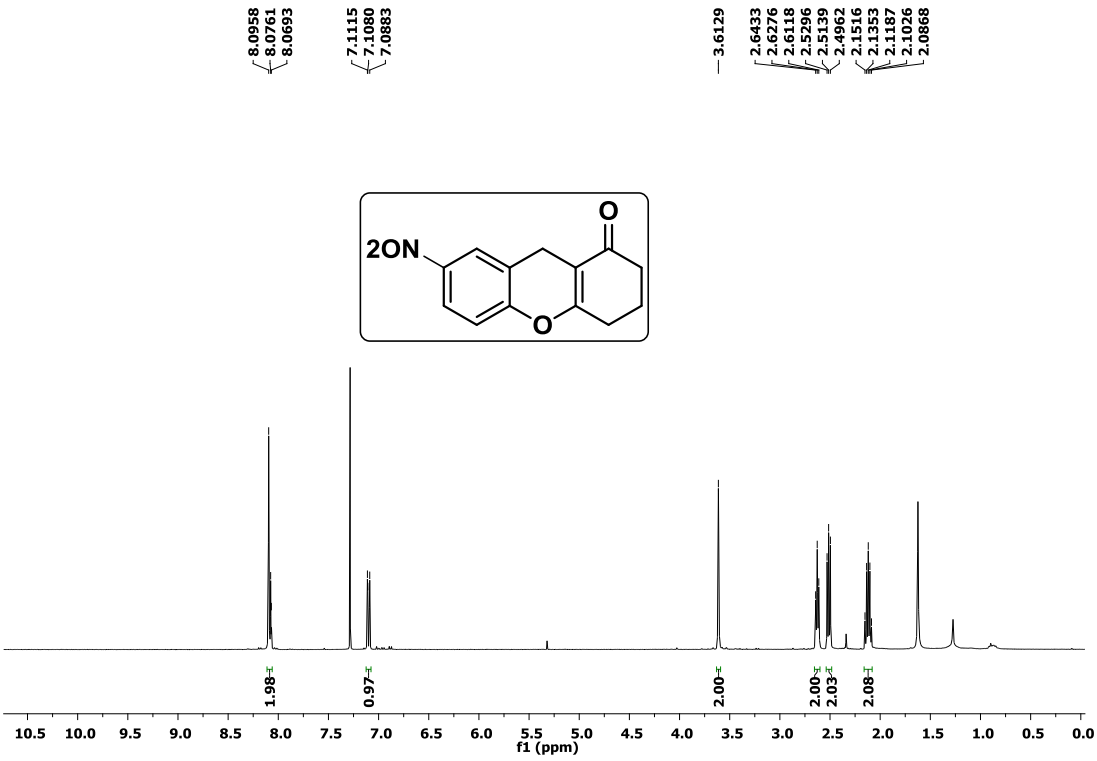
^{13}C NMR of compound 1



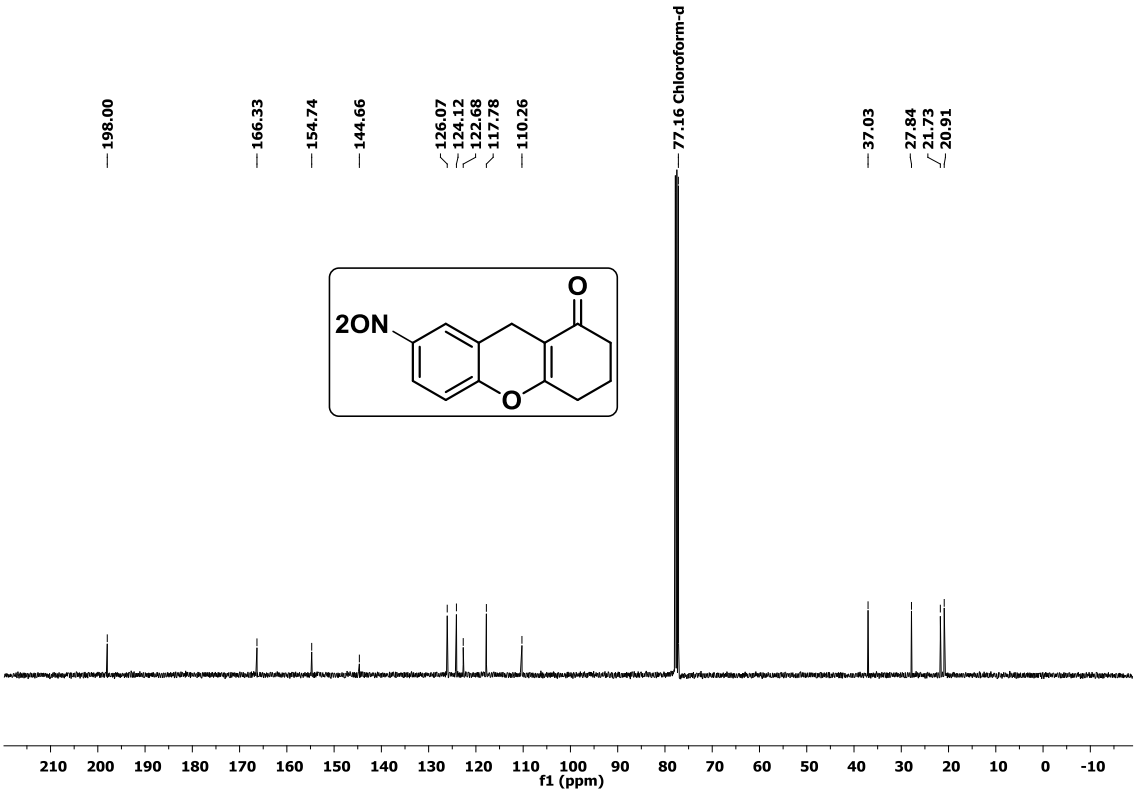
^{1}H NMR of compound 2



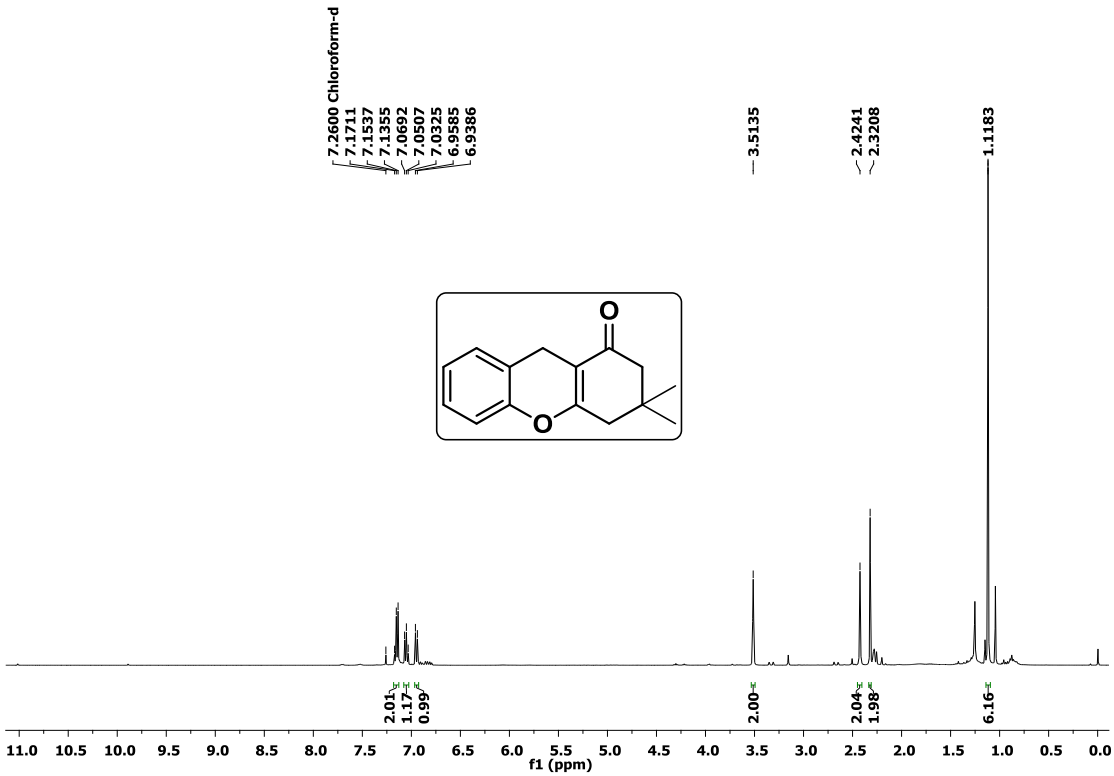
^{13}C NMR of compound 2



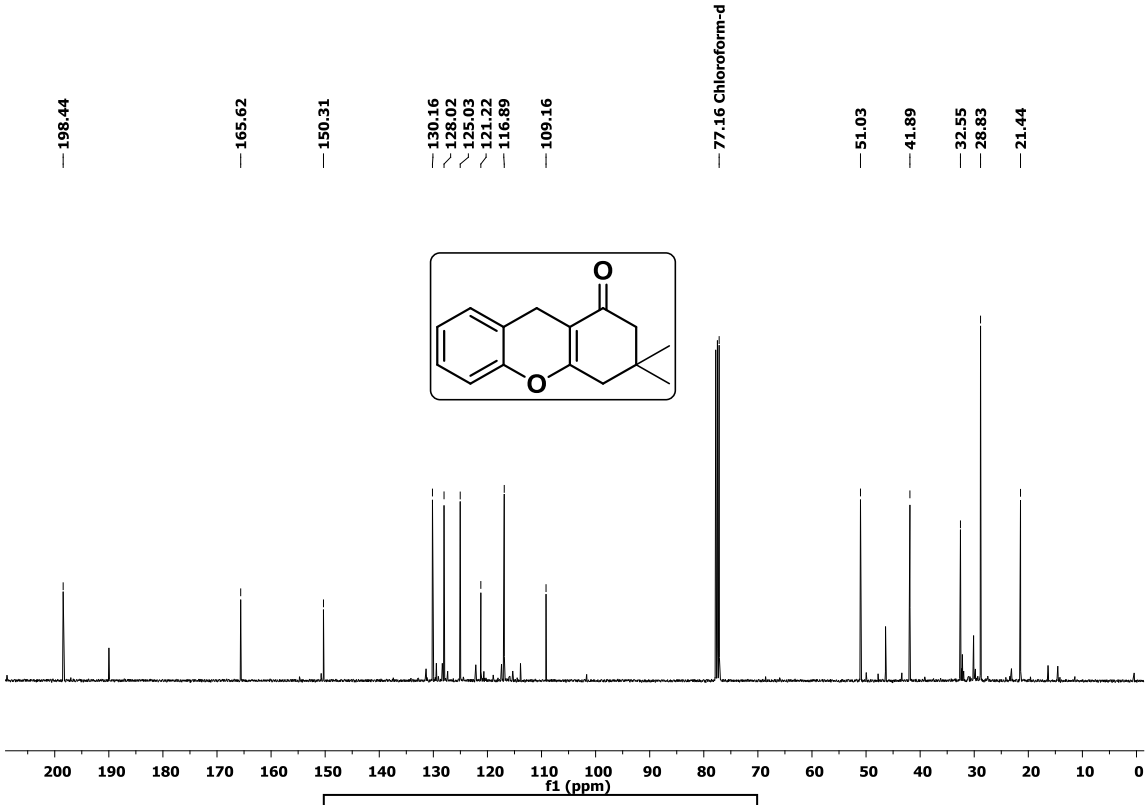
^{1}H NMR of compound 3



^{13}C NMR of compound 3



^{1}H NMR of compound 4



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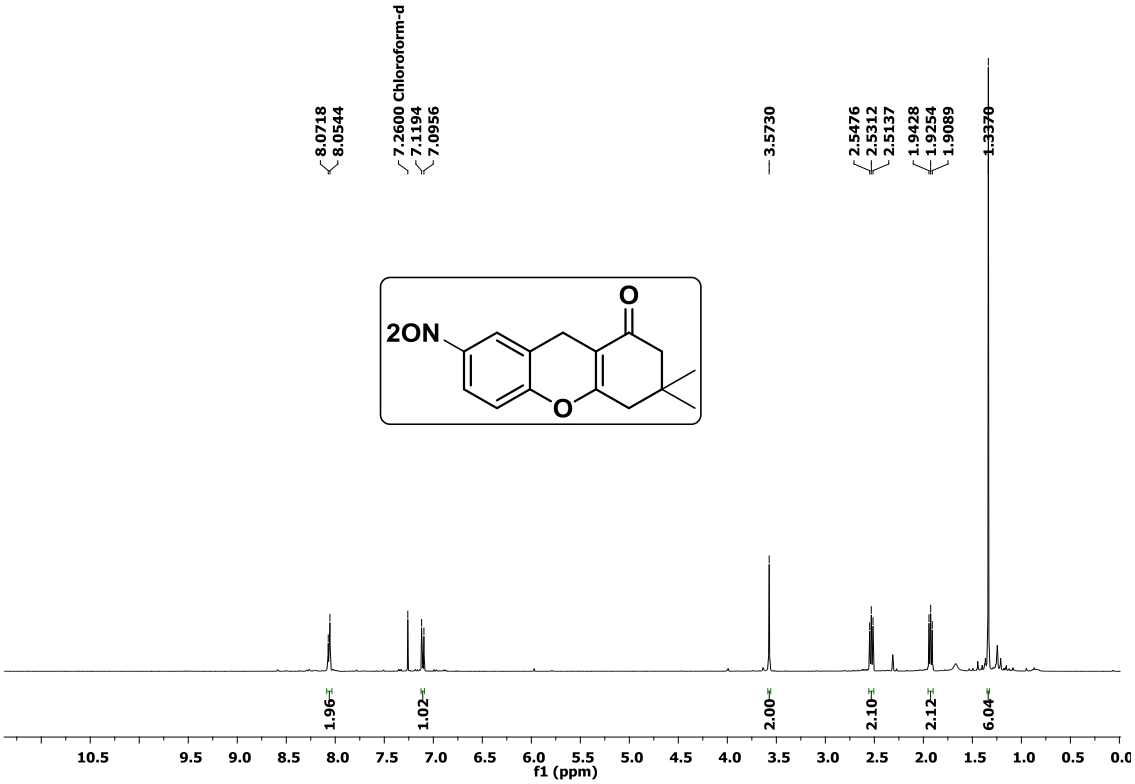
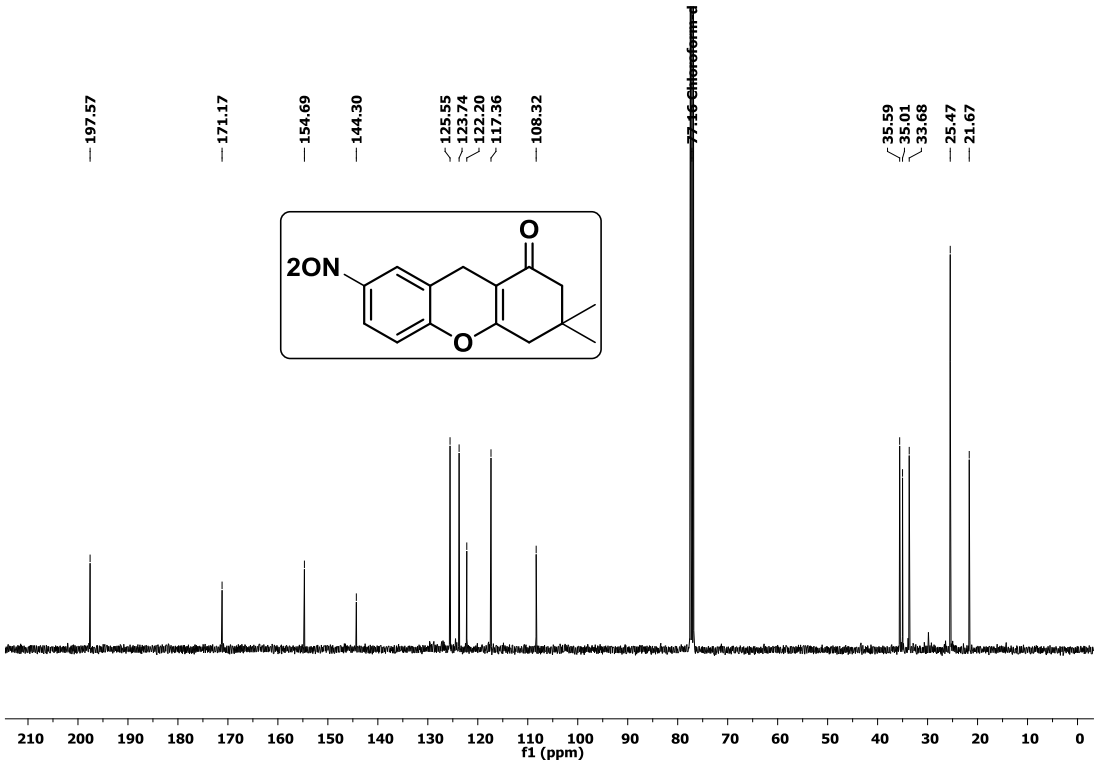
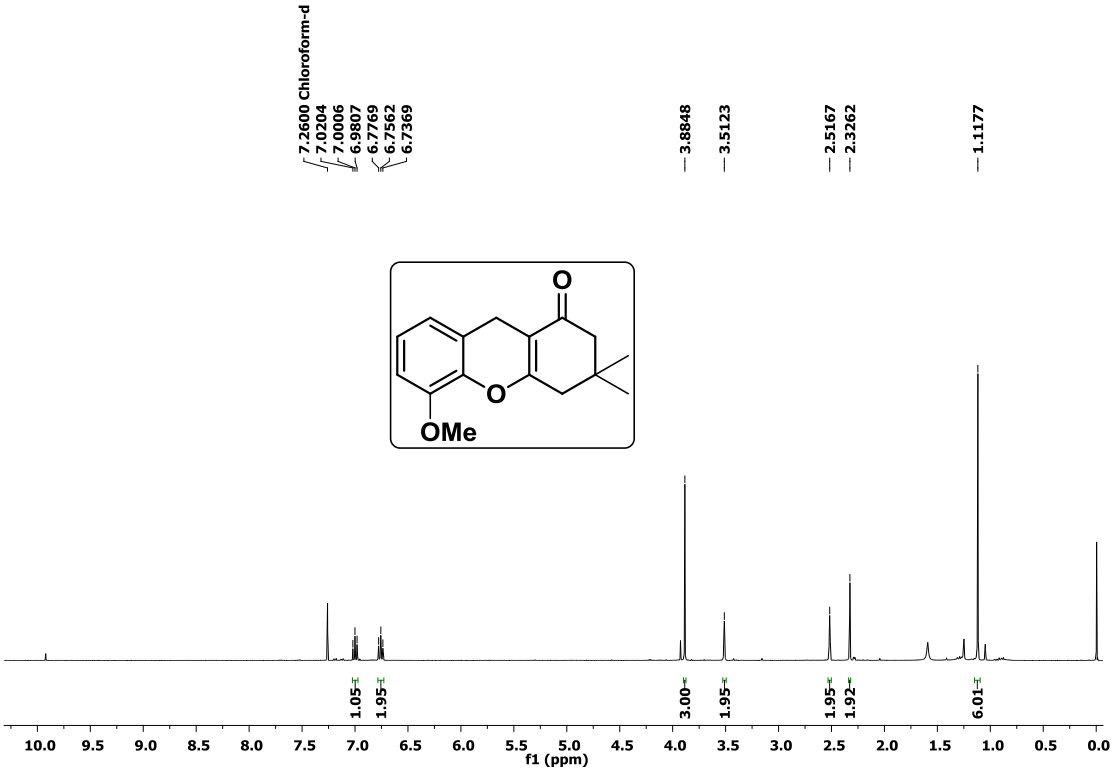


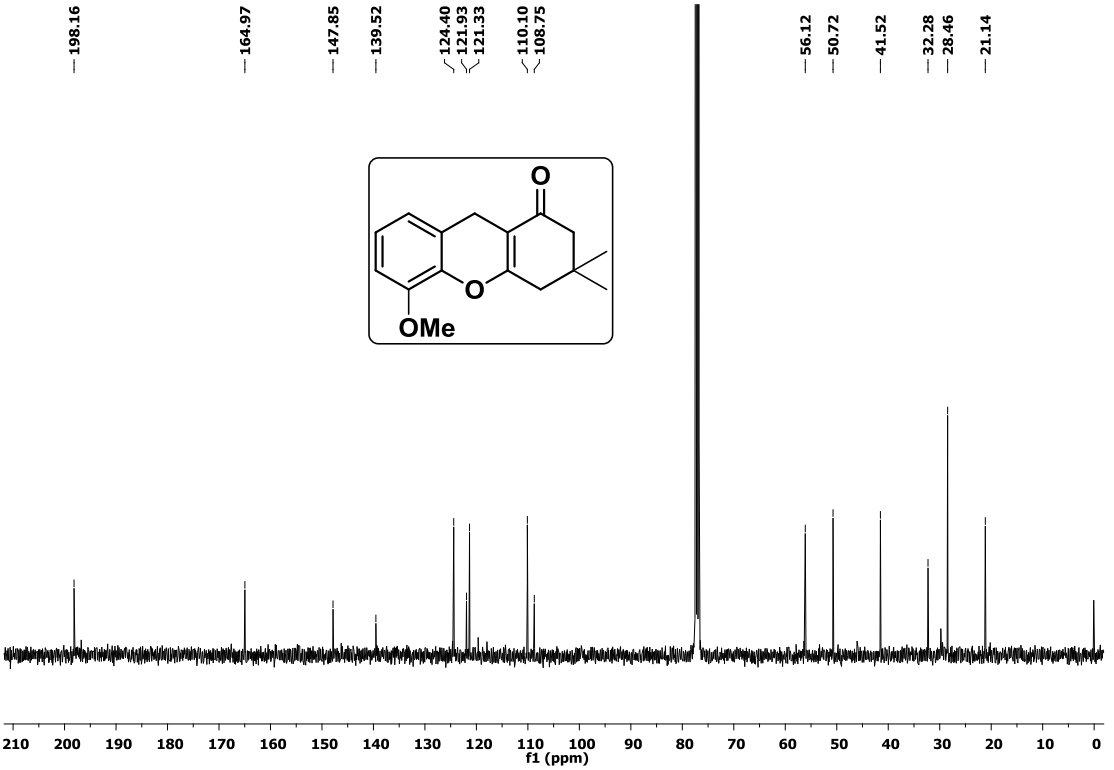
^{1}H NMR of compound 5



^{13}C NMR of compound 5



^{1}H NMR of compound 6



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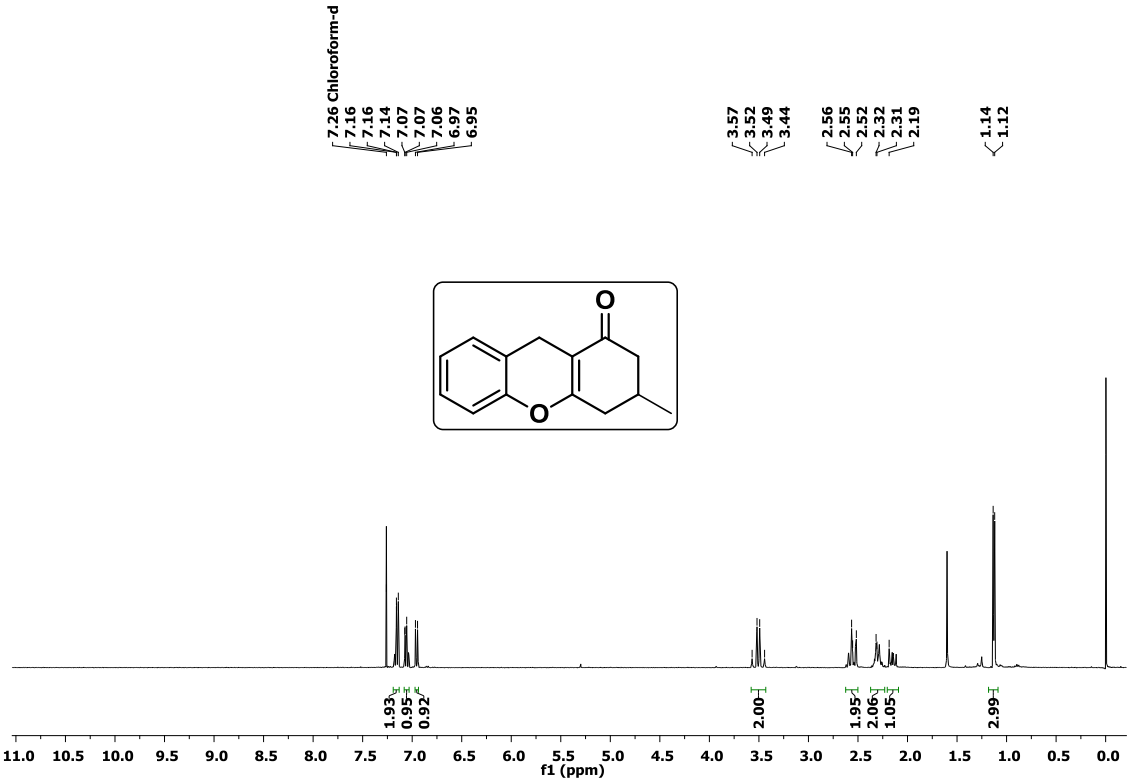
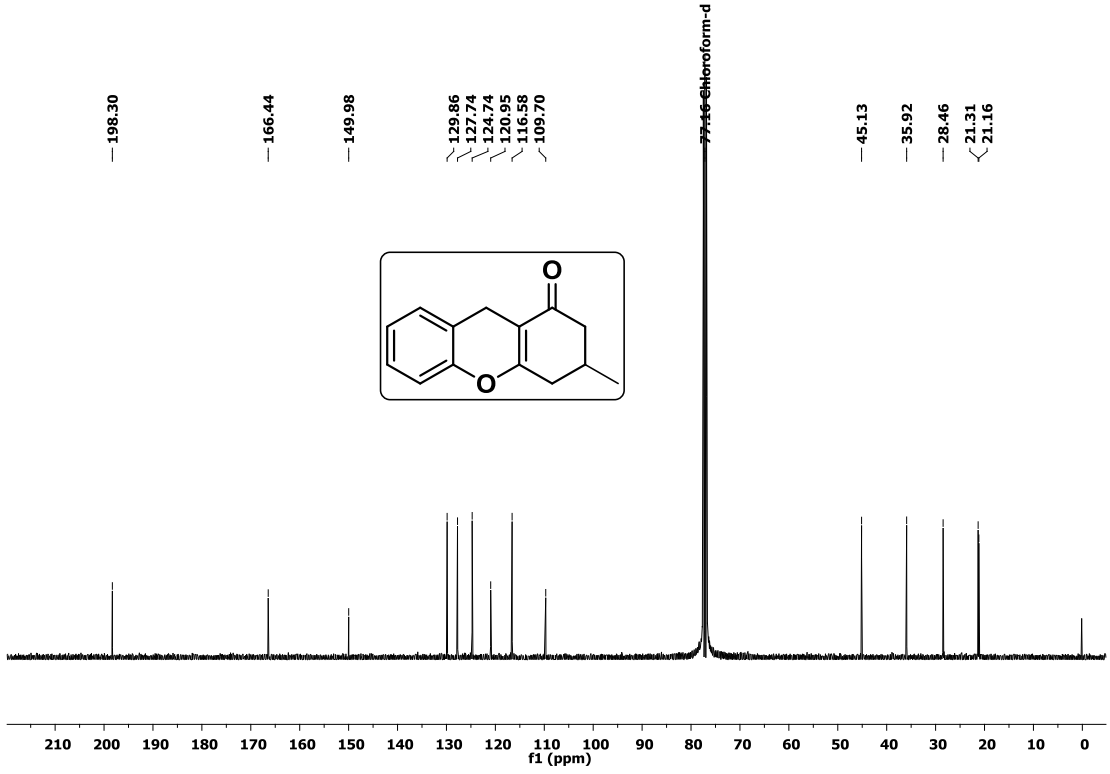
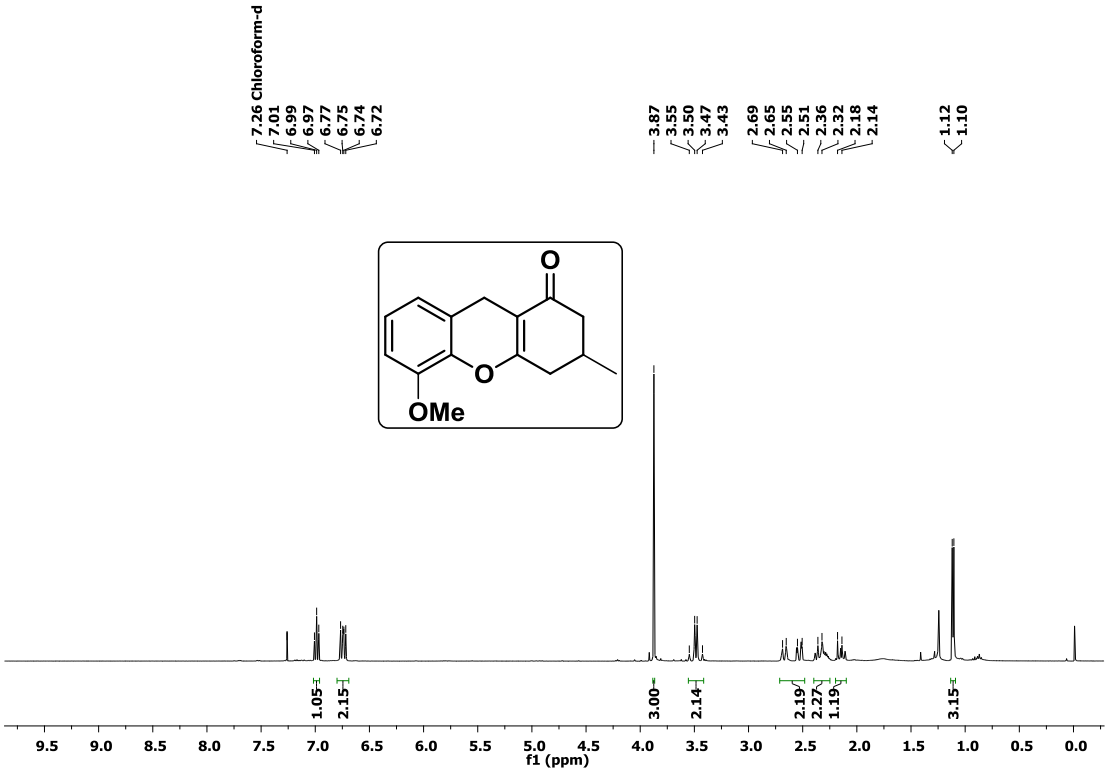


^{1}H NMR of compound 7



^{13}C NMR of compound 7



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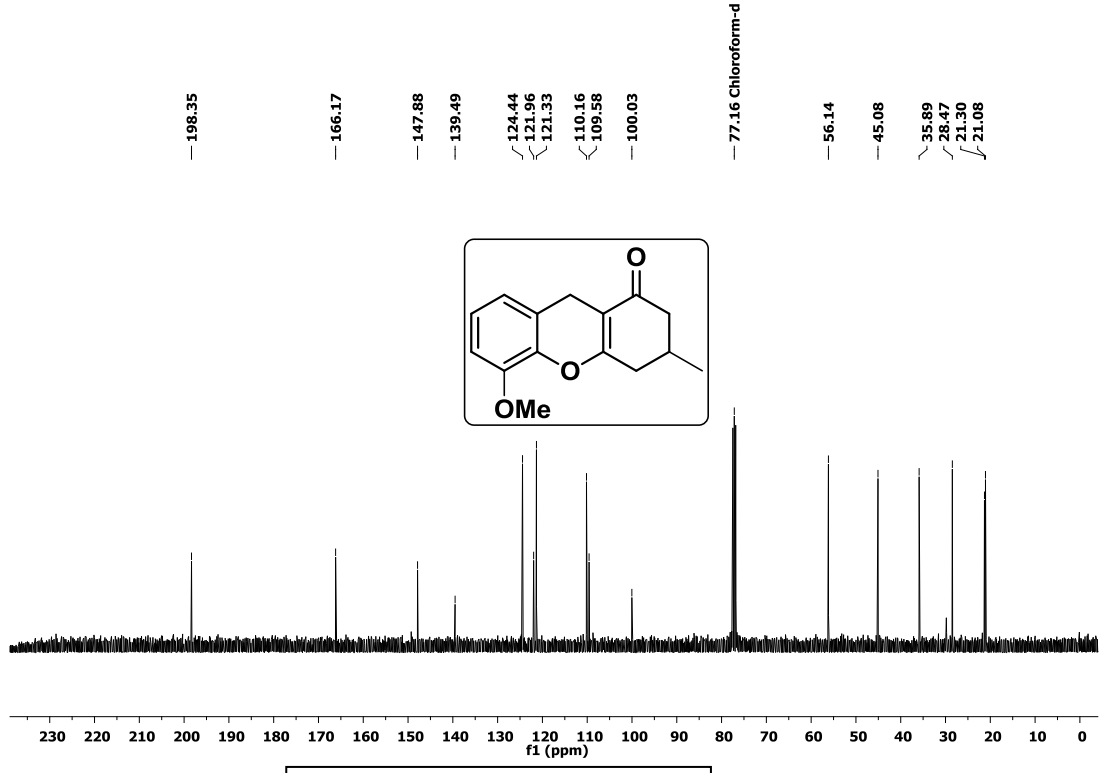

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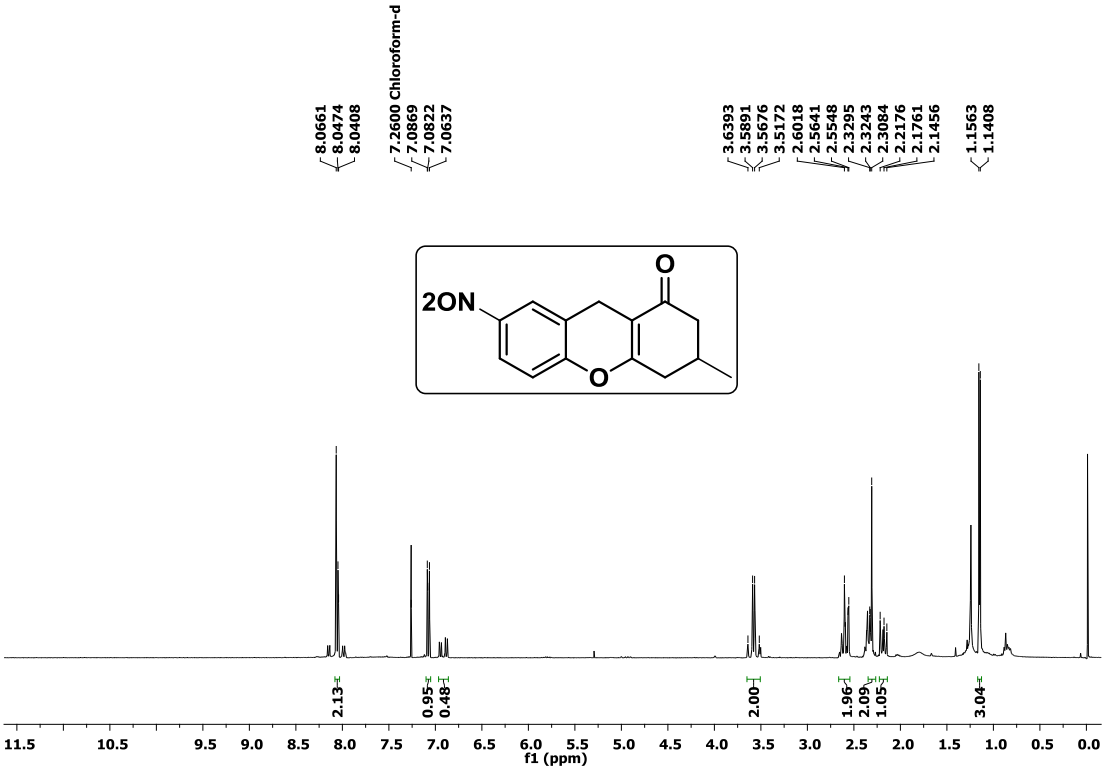

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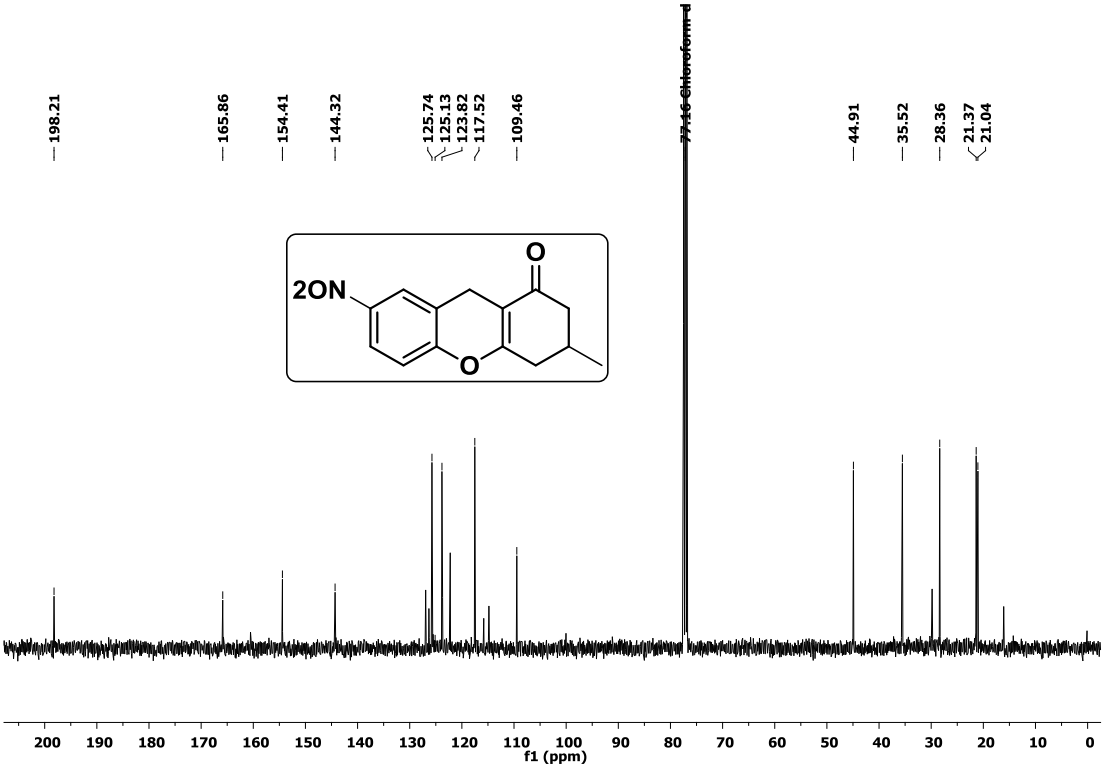

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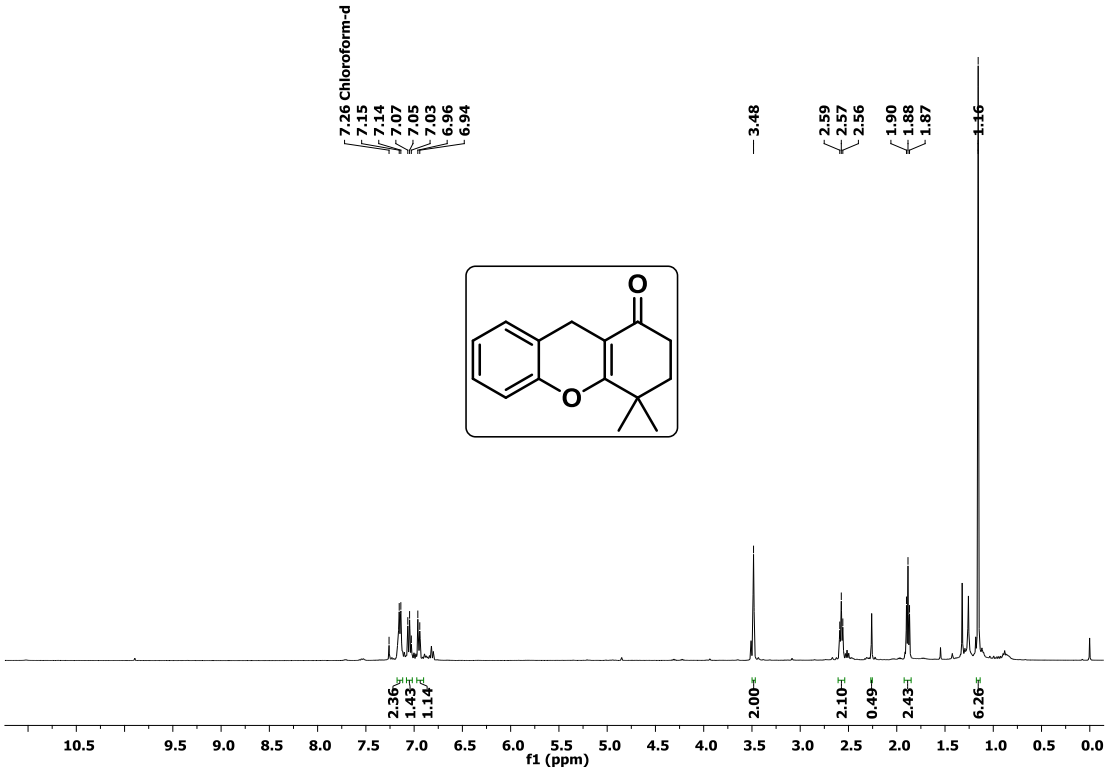
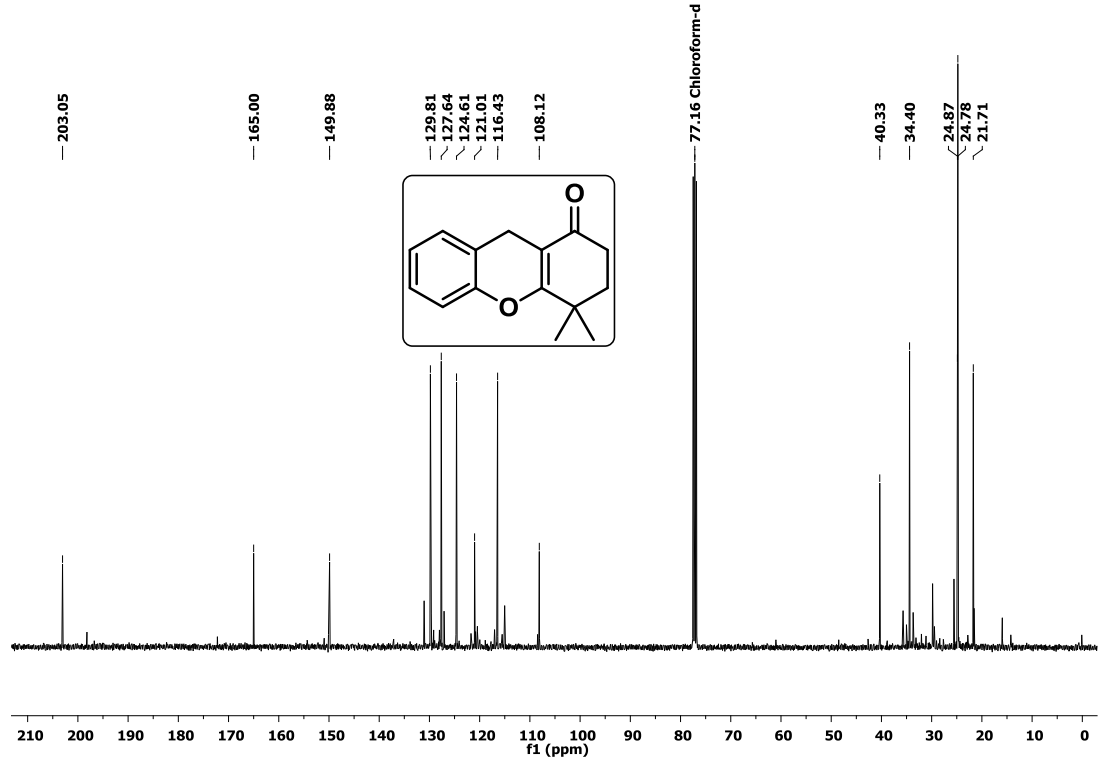


^{1}H NMR of compound 10



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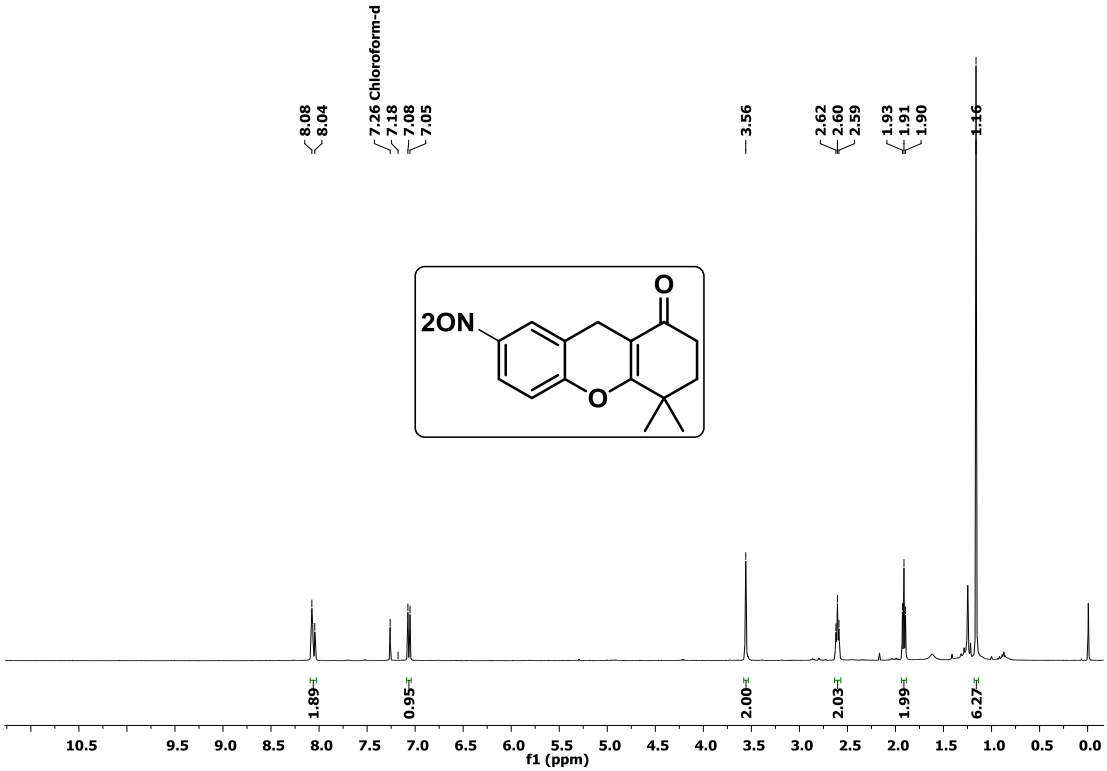

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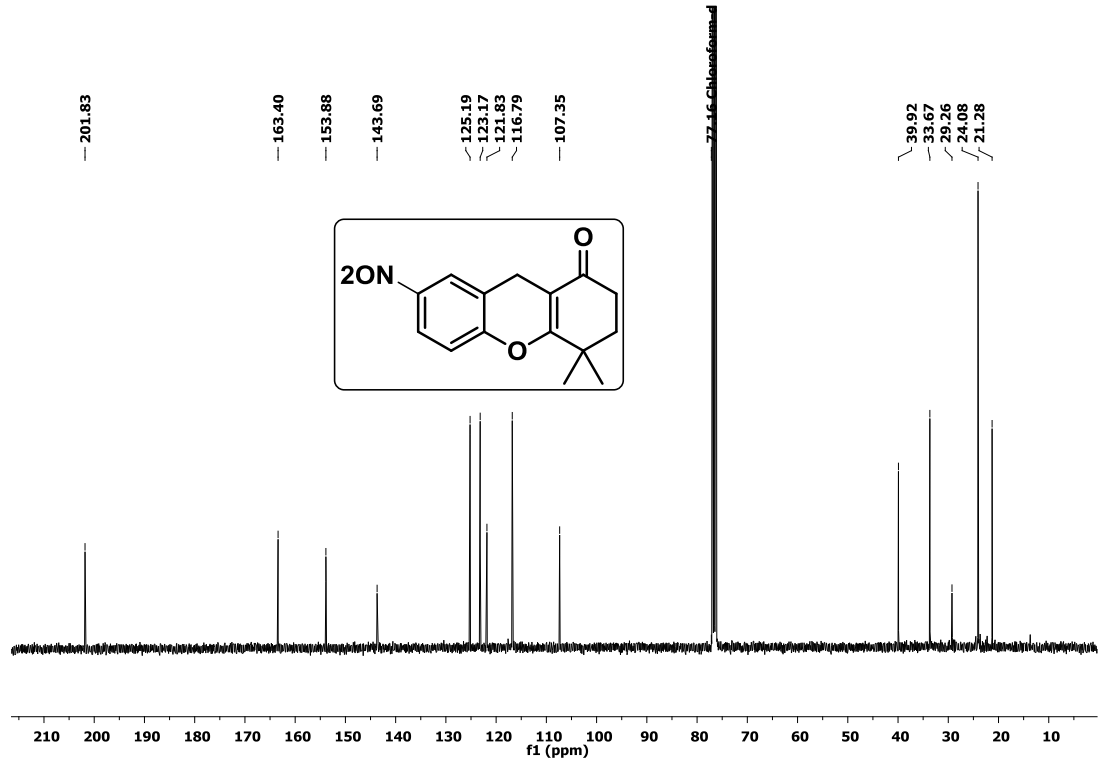

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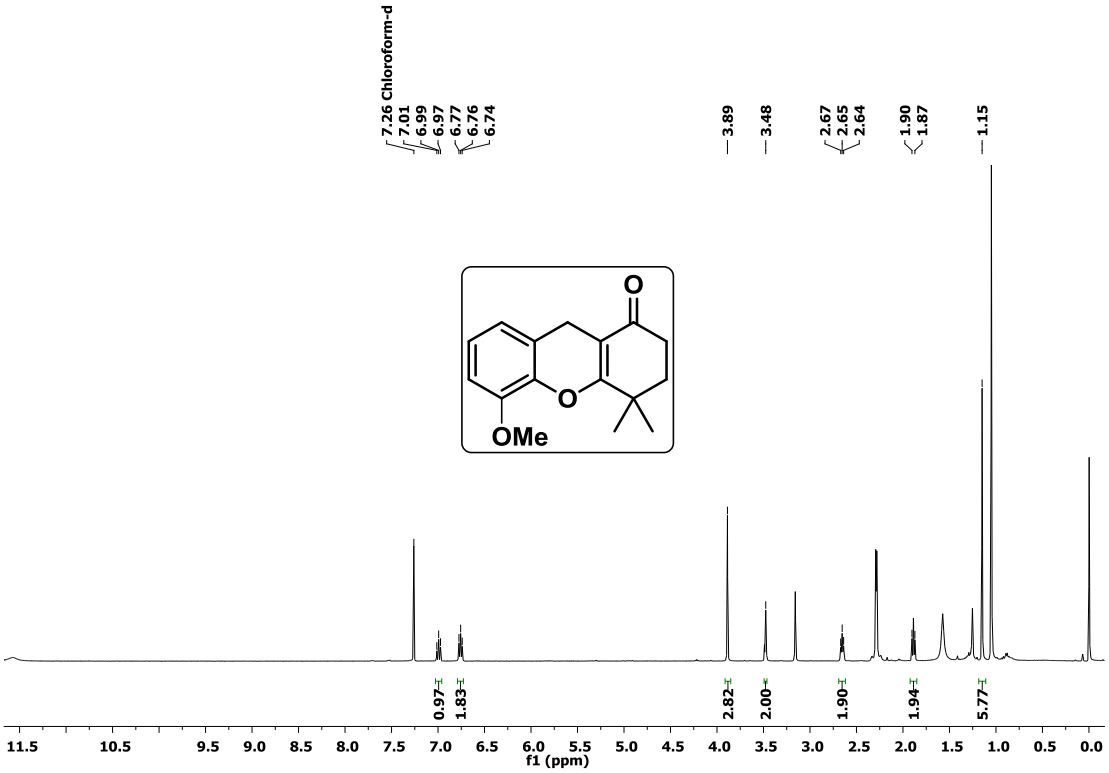
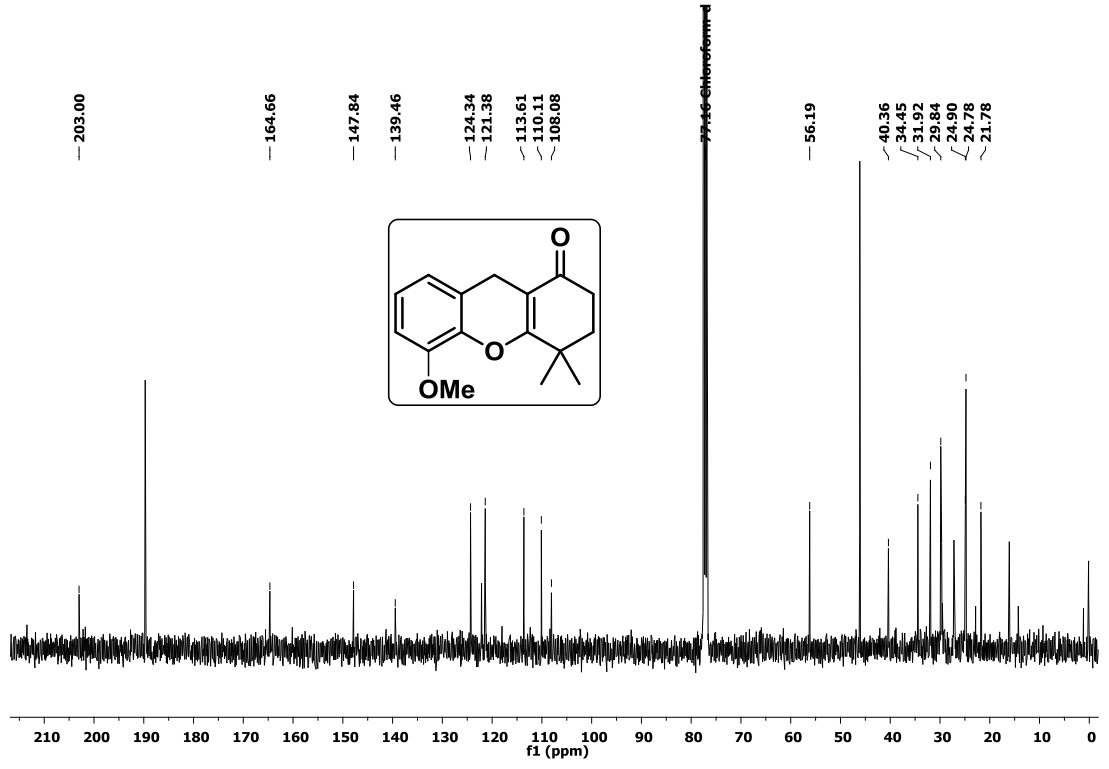


^{1}H NMR of compound 12



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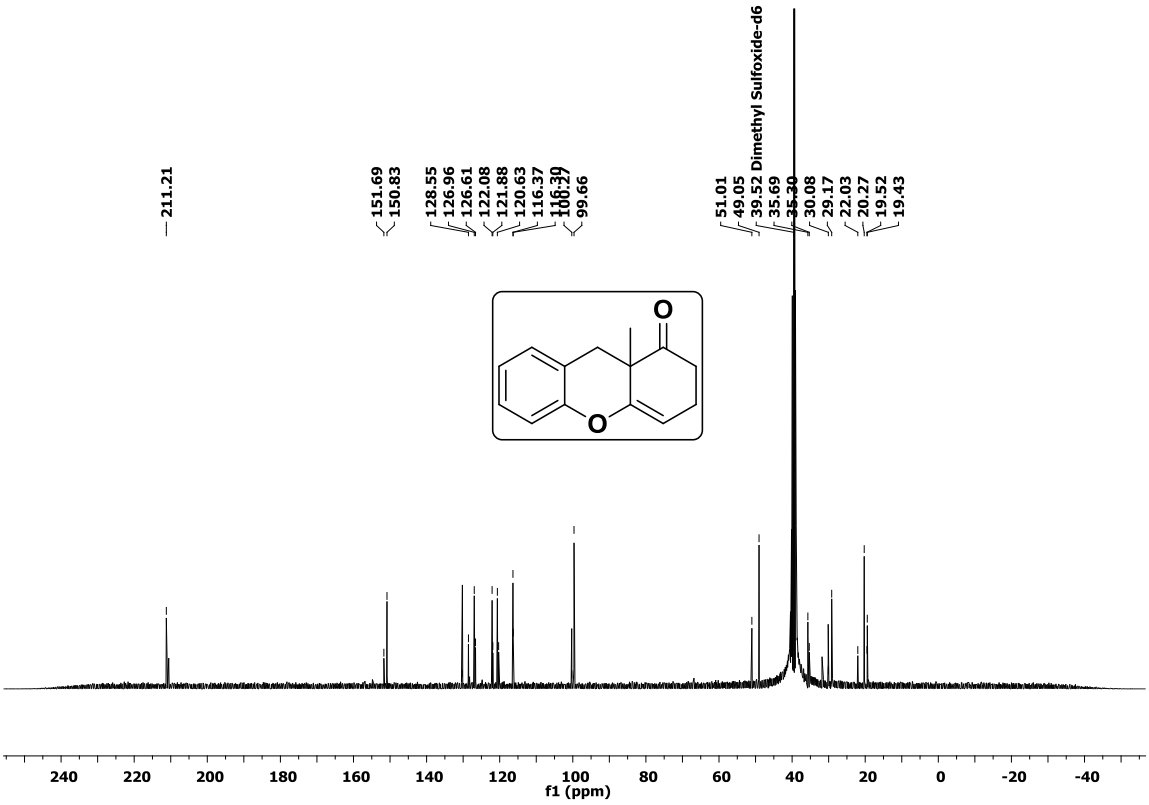

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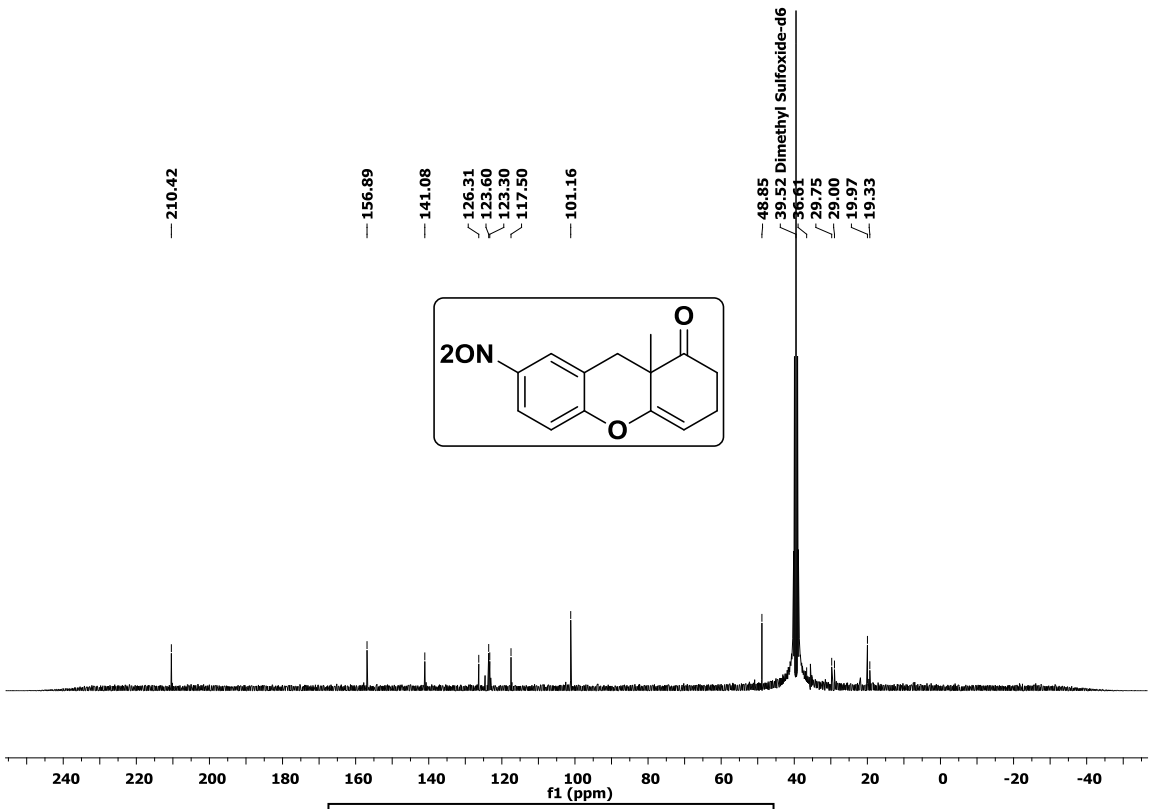
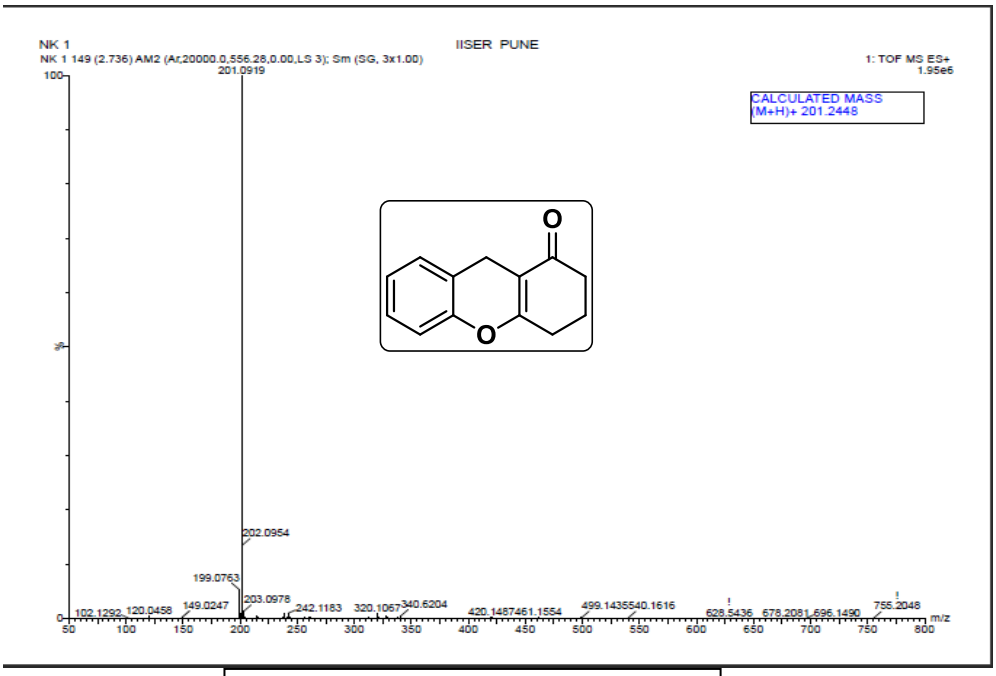
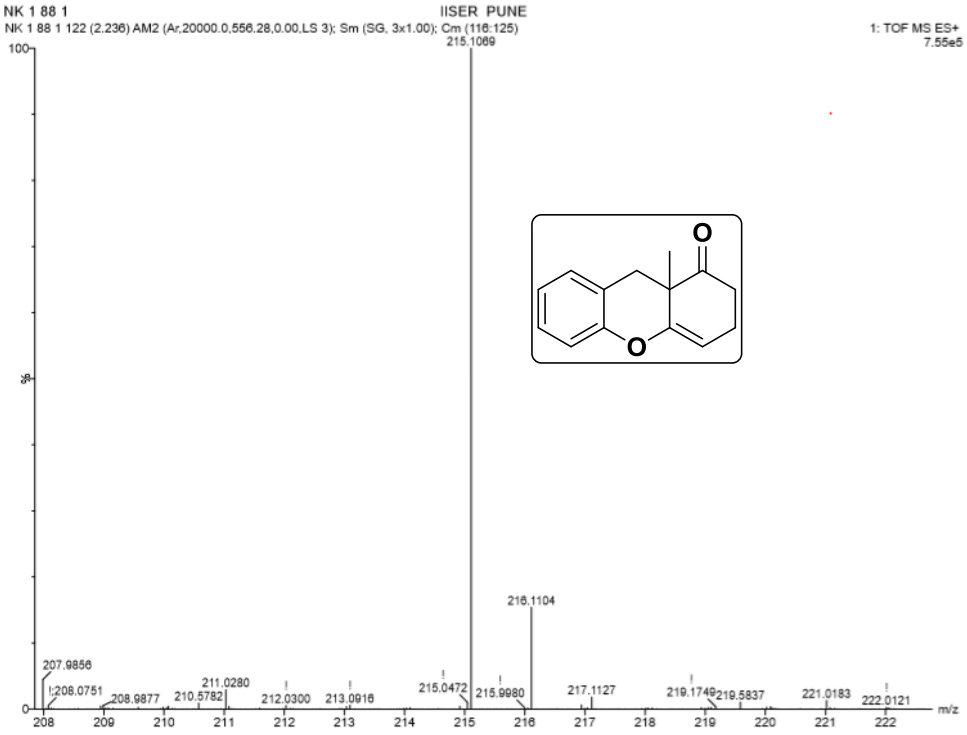


^{13}C NMR of compound 14

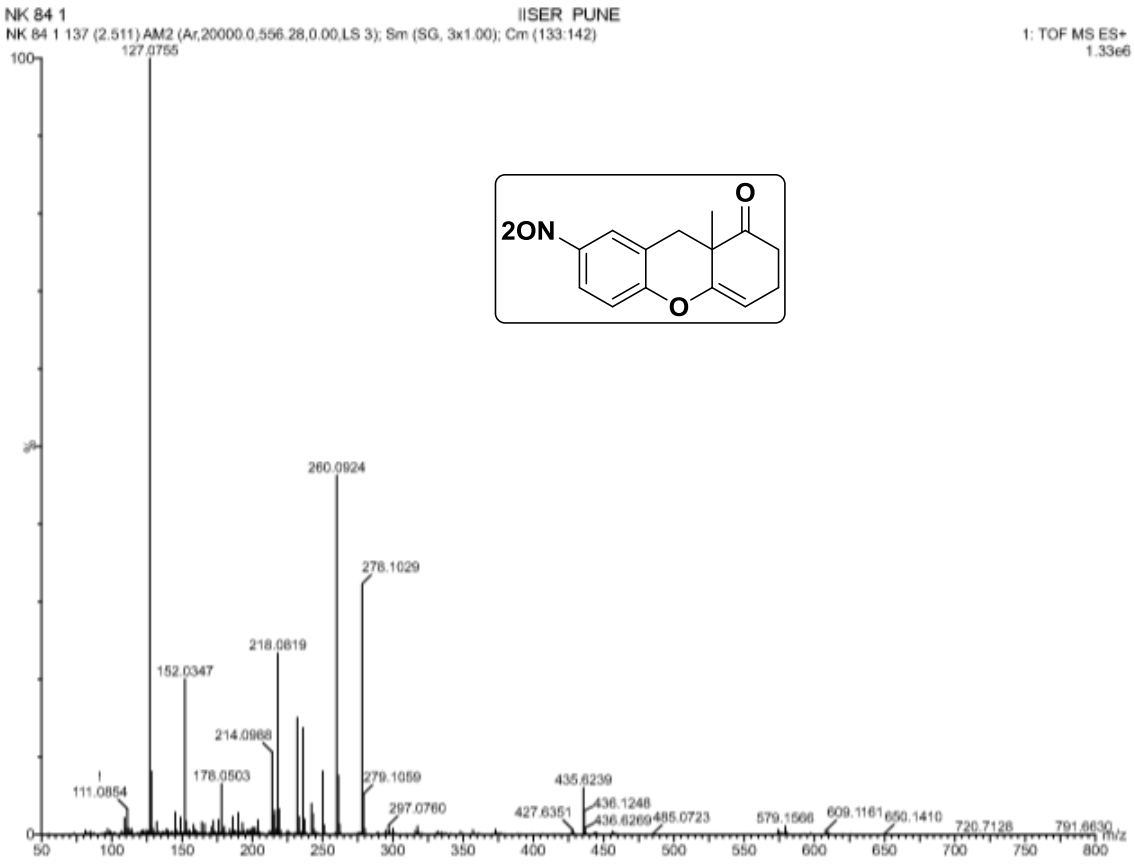
b) Copies of HRMS spectra's



HRMS spectra for compound 1



HRMS spectra for compound 13



HRMS spectra for compound 14

The structure and mass of all the isolated compounds were confirmed by spectroscopic analysis like NMR and HRMS and the corresponding data are described in section 2.3.

5. CONCLUSION

Herein, we report an operationally straightforward, efficient and green approach, borrowing hydrogen methodology for construction of functionalized 4*H*-chromene derivatives. Developed a new catalytic system of Ru-catalysts ($[Ru(1,5\text{-}COD)Cl_2]_n$ and $Ru@Fe_3O_4$ MNP) that can be used to synthesize substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones *via* and α-alkylation of cyclic 1,3-diketone using 2-hydroxybenzyl alcohol followed by o-arylation, without the need of an inert atmosphere. The developed process is highly atom efficient and follows one-pot pathway for the synthesis of "2,3,4,9-tetrahydro-1*H*-xanthen-1-ones and related derivatives" in a domino manner, consisting of intermolecular (C-C bond) benzylation followed by intramolecular (C-O bond) arylation for their Nobel biomedical applications. Also, developed nature friendly reaction conditions for the synthesis of 4*H*-chromenes by using greener, inexpensive and nonhazardous reagents like alcohols with the formation of water as only byproduct. As in our knowledge, "ruthenium catalyzed synthesis of 2,3,4,9-tetrahydro-1*H* xanthen-1-ones *via* borrowing hydrogen methodology" is not reported at yet. The striking advantage of this process is easy and fast isolation of products. Hence, we also demonstrated and found that $Ru@Fe_3O_4$ MNP is an efficient and highly robust heterogeneous catalyst for the preparation of 4*H*-chromene derivatives. Also, found that the catalyst is easily recyclable with 100% efficiency which means no activity loss. In addition, we have developed photochemical reactions as an alternate pathway for the synthesis of target product and a possible mechanism was hypothesized. Also, with the help of experimental foundations like hydride detection and hydrogen liberation experiments we have proposed a plausible pathway. All the products were well characterised by NMR, high-resolution mass spectroscopy.

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