Synthesis of *Ortho* Quinone Methide Precursors

A Project Report Submitted in Partial Fulfillment
of the Requirement for the award of the Degree of
Master of Science
in
CHEMISTRY
BY
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CSIR-NATIONAL INSTITUTE FOR INTERDISCIPLINARY
SCIENCE AND TECHNOLOGY (CSIR-NIIST) - THIRUVANANTHAPURAM-695019
JUNE 2020

DECLARATION

I hereby declare that the project report entitled ***“Synthesis of ortho-quinone methide precursors*** *”is a bonafide record of the work carried out by me under the supervision of Dr. K. V. Radhakrishnan at Organic chemistry Section of the CSIR - National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram, for the partial fulfillment of the Degree of Master of Science in Chemistry, from School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala. I also declare that no part of this dissertation had been presented for any Degree, Diploma, Fellowship or other similar title of any other university or institution.*

Athulya

Thiruvananthapuram *Athulya Jagathakumar*
June 2020

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CERTIFICATE

This is to certify that ***Ms. Athulya Jagathakumar*** *has worked on* ***"Synthesis of ortho-quinone methide precursors"*** *under my supervision at the Organic Chemistry Section of CSIR - National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram (during January 2020 to June 2020), for the partial fulfillment of the Degree of Master of Science in Chemistry, from School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala.*

Trivandrum
June 2020

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22 July 2020
Kottayam

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Athulya Jagathakumar

CONTENTS

INTRODUCTION

1. QUINONE METHIDES

Quinone methides (QMs) are highly reactive short living intermediates having a cyclohexadiene core along with an exocyclic alkylidene and a carbonyl group mainly at *ortho* or *para* position. The 1,2- and 1,4-quinone methides i.e., *ortho*- and *para*-quinone methides, are formally neutral molecules; and the zwitterionic aromatic resonance structures of those are highly relevant, which make these molecules highly polarized and thus reactive at those sites. QMs are considered as Michael acceptors even though their reactivity is much more pronounced, if compared to standard enones. In fact, the conjugate addition of nucleophiles in to simple enones causes a small decrease in the stability of the system. It is due to the formation of enol intermediates and simultaneous loss of conjugation. But the addition of nucleophiles to QMs shows a large increase in the π-stabilization energy, due to the formation of a fully aromatic ring system; this provides a considerable driving force that enhances the reactivity of QMs in to a great extent[1] .

Quinone methides (QMs) are highly reactive short living intermediates having a cyclohexadiene core along with an exocyclic alkylidene and a carbonyl group mainly at ortho or para position. The 1,2- and 1,4-quinone methides i.e., ortho- and para-quinone methides, are formally neutral molecules; and the zwitterionic aromatic resonance structures of those are highly relevant, which make these molecules highly polarized and thus reactive at those sites. QMs are considered as Michael acceptors even though their reactivity is much more pronounced, if compared to standard enones. In fact, the conjugate addition of nucleophiles in to simple enones causes a small decrease in the stability of the system. It is due to the formation of enol intermediates and simultaneous loss of conjugation. But the addition of nucleophiles to QMs shows a large increase in the π-stabilization energy, due to the formation of a fully aromatic ring system; this provides a considerable driving force that enhances the reactivity of QMs in to a great extent[1]

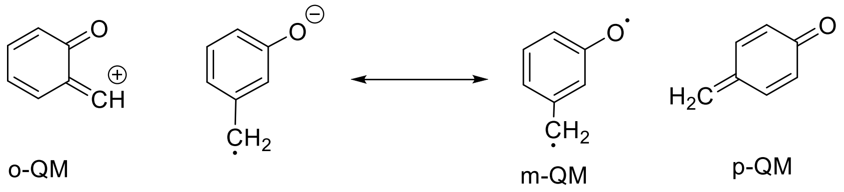


Figure.1.1. Three isomeric forms of quinone methides

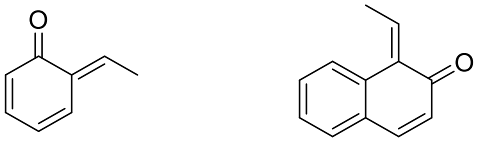


Figure.1.2.

m-QM is a resonance hybrid of two canonical forms, one is zwitterionic form stabilized by aromatic conjugation, increasing polarity, so increase the reactivity. Unlike benzoquinone, *o*- and *p*-Quinone methides are highly polarized compounds. They give aromatized phenol derivatives. But *o*-QM exists in *E/Z* geometric isomers those are fluxional in nature and behave as a combination of a charged Zwitterionic and biradical structures.

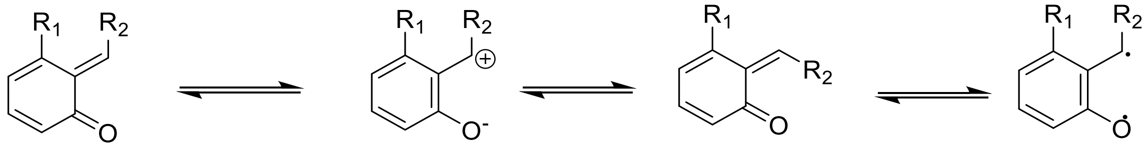


Figure.1.3.

The distribution among these geometrical isomers is due to differences between non bonded interactions.

- If R_1 is smaller than oxygen, then *E*-configuration is preferred and vice versa.
- The *E/Z* ratio gives the important in governing diastereoselective outcome for Diel-Alder cyclo additions. Due to the partial Zwitterionic character, they both are electrophile and nucleophile.
- Their reactivity with nucleophile is important in biological systems.ie; they react with amino acids and proteins and inhibit the action of some enzymes.
- It is important as the ultimate cytotoxines responsible for the function of agents such as antitumor drugs, antibiotics and DNA alkylators.
- They are involved in metabolic formation of formaldehyde.*o*-QM is used to understand the chemistry of anthracycline antitumor antibiotic.
- The important clinical drugs: cisplatin, psoralens, mitomycin c are induce DNA ISC (interstrand cross-links) formation, which can disrupt the cell maintenance and replication.

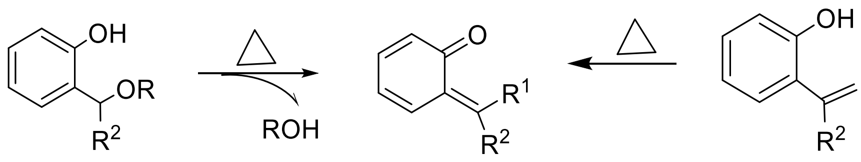
Both reductive and oxidative metabolisms form quinone methides and important in drug design and drug safety.

ortho Quinone methide is a highly reactive versatile intermediate in organic synthesis and have important role as a reactive intermediate in organic synthesis, material chemistry, fine chemicals and pharmaceuticals. These are formed by reaction between phenol and aldehyde in presence of acid or base, and are short lived and highly reactive intermediates in many reactions. It is first suggested by Fries. The first direct evidence is given by Gardner in 1963 by trapping it at -100centigrade.It also used as an intermediate in [4+2] Cycloaddition reactions with variety of dienophile. Chemical behavior of these reactive intermediates are resembles that of *α, β*-Unsaturated ketones due to the presence of 1,3-cyclohexadiene core substituted with a carbonyl and oxymethylene group. It reacts very rapidly with nucleophile and undergo efficient Diels-Alder reactions with electron rich olefins.

A number of methods for the generation of *o*-QMs have been developed till date, enabling the straightforward construction of diverse aromatic molecules with successful applications to a number of complete syntheses of complex natural products. In the past decade, the most popular methods were photochemical initiation of *o*-(a-phenyl) substituted phenols or thermal initiation of various substituents on the benzene ring of *ortho*-methyleneacetoxy phenols. Lewis acids, base and chemical oxidants were also used to generate *o*-QM.

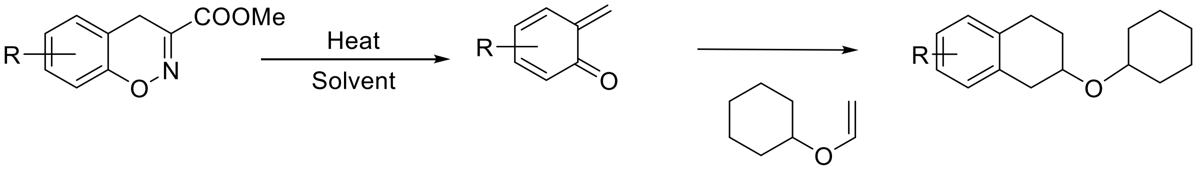
The excellent way to prepare *o*-QM is thermal and base initiation. In which good to excellent stereo selectivity and gives good yield. Only a limited number of accounts have been reported where acid is used to generate the *o*-QMs. i.e.; Acid is rarely used to generate the *o*-QM. This is due to low compatibility of acids with dienophiles and because of greater ionic character of the reaction conditions that result in a product with low sterioselectivity.

All thermal generation techniques preclude the application of nucleophiles that are thermally unstable. With any given precursor, there is a substantial temperature range for initiation that depends upon the substituents. In general, if the process involves significant no bonded interactions, then the temperature requirements are higher, while extended conjugation or other stabilizing factors lower the overall temperature requirements.



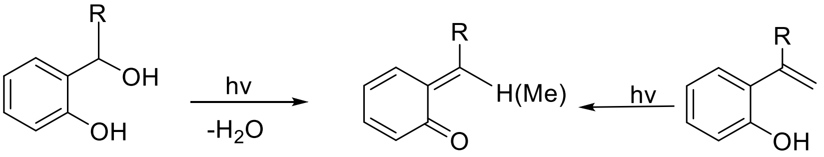
Scheme.1.1. Thermal generation of *o*-QM

In thermal generation, by Retro Diels Alder reaction convert the 4H-1, 2-benzoxazines to *o*-QM under thermal conditions. Which undergo Diels Alder reaction with vinyloxycyclohexane to give chroman derivative.



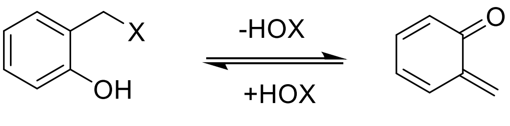
Scheme.1.2. Thermal generation

If *o*-QM intermediate is generated by light induced water elimination from *o*-hydroxy benzyl alcohols and by intramolecular proton transfer (ESIPT) in o-hydroxy styrene.



Scheme.1.3. Photochemical generation of *o*-QMs

o-QM by photolysis of *ortho*-hydroxy benzyl substrates in aqueous solution is another method as given below[2],



Scheme.1.4.

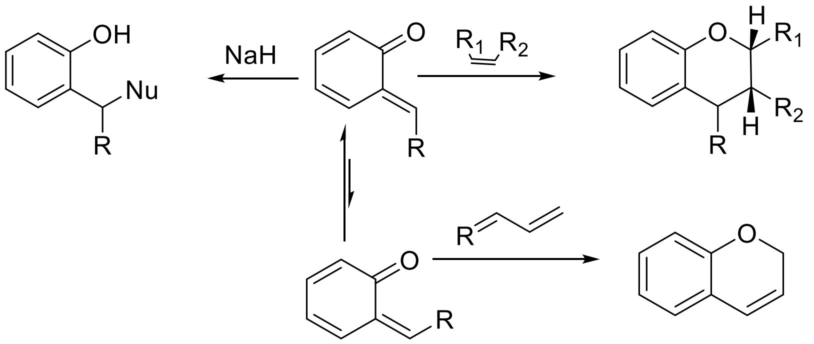
The direct involvement of an *o*-QM intermediate has been confirmed by laser flash photolysis. Use of 266 nm excitation wavelengths in acetonitrile solvent gave a well-defined signal with two maxima around 300 and 400 nm.

1.1 Reactions of *ortho* – quinone methides

ortho quinone methides are the building blocks of many natural products and pharmaceutical compounds[3].Their reactivity is understood by two canonical forms: a biradical species or a polarized zwitter ion[4]. Thier structures shows the susceptibility of *o*QMs to undergo nucleophilic attack at the methide carbon, along with rearomatization as the thermodynamic driving force[5] .They are emerging as very useful intermediates and so they can be used in linchpin reactions for the construction of complex natural products[6].

1.1.1 Electrocyclization and Cycloaddition

The transient nature of *ortho* – quinone methides is due to their propensity to undergo rapid re-aromatisation, either by the Michael addition of nucleophiles or often more usefully by the cycloaddition with 2π partners or via oxa-6π- electro cyclisation[7].

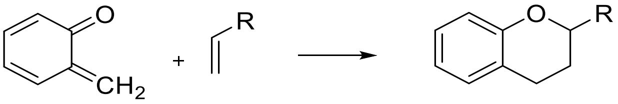


Scheme.1.5.

o-QMs are labile intermediates and are stabilized by metal coordination. In the condensed phase, the parent compound has only been characterized spectroscopically at extremely lower temperatures; because of its high reactivity. The evidence by spectroscopic method, for a zwitter ionic form of *ortho* quinone methide is derived from vitamin E is only possible at -78°C through the stabilization by interaction with N-methyl morpholine N-oxide. These experiments show that how difficult it is to isolate quinone methides.

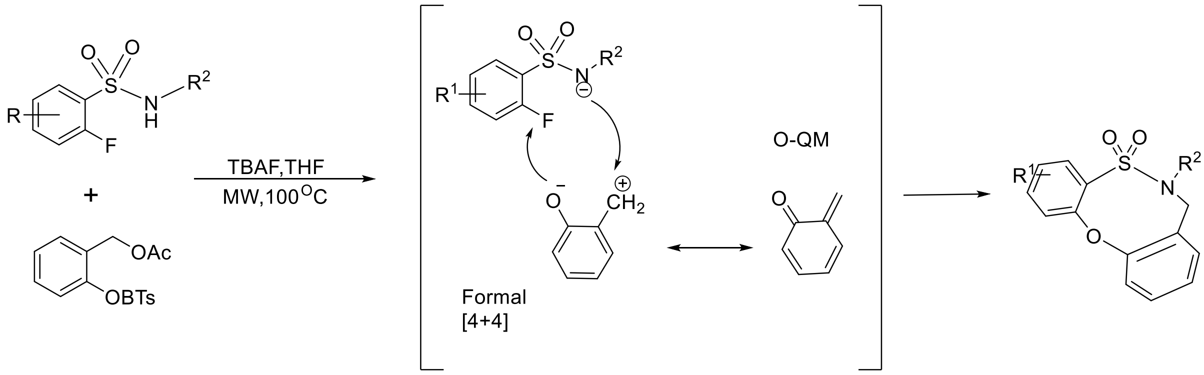
The NMR spectroscopic data for parent *ortho* quinone methide molecule is not available since they are unstable. So, the metalated parent *ortho* quinone methide complexes were examined using 2-D NMR spectroscopic techniques to understand its structure and reactivity. *ortho* quinone methides are also the key intermediates in the action of several anti-tumors and anti-biotic drugs[7].

[4+2] Cycloaddition: *ortho*-Quinone methides are versatile intermediates involving a minimum of seven carbon atoms, which are mainly involved in 1,4- Michael type additions as well as aza-Michael reactions with various nucleophiles. *o*-QMs also give Diels-Alder cycloaddition products. *o*-QM especially derived from 4-hydroxycoumarin undergo [4 + 2] cycloaddition reaction with penta-fulvenes to afford pyranocoumarin and pyranopyrone[9].



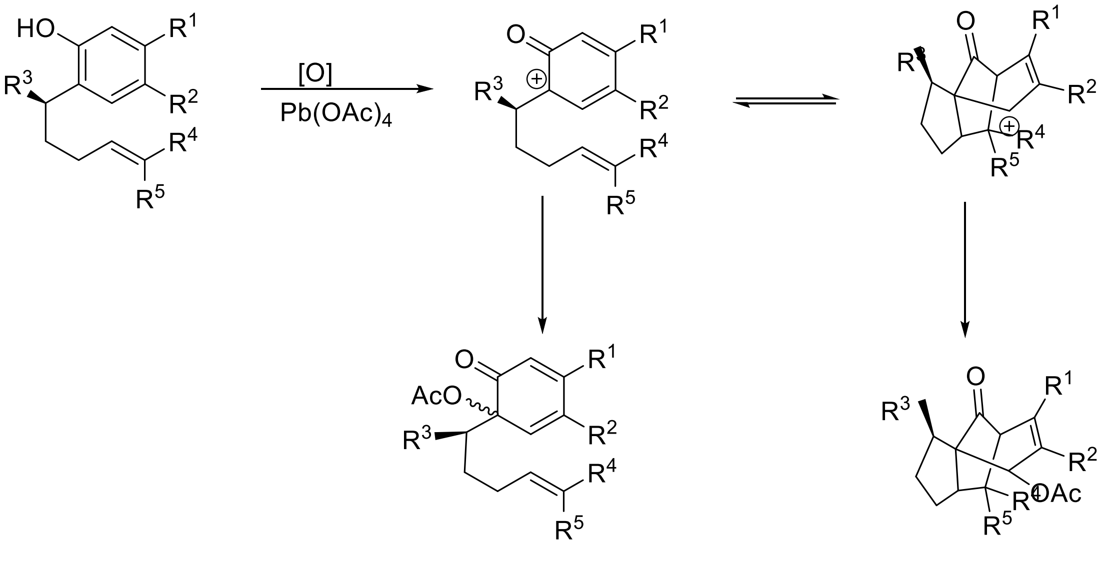
Scheme.1.6. Reactivity of **ortho**-quinone methide with alkenes

[4+4] cycloaddition: A one-pot [4 + 4] cyclization pathway leads to the generation of eight-membered sultams via in situ generated *o*-QM. It was reported by Hanson and co-workers[10]. They examined the pairing of ambiphilic synthons in a complementary fashion, where by *o*-fluorobenzenesulfonamides are merged with in situ generated *o*-QM in a [4 + 4] cyclization pathway to provide dibenzooxathiazocine dioxides under microwave (MW) conditions. This is the first report that represents the use of *o*-QM in a formal hetero [4 + 4] cyclization reaction.



Scheme: 1.7.

[5+2] cycloaddition (phenoxonium analogous to *o*-QM): α-cedrene, a-Pipitzol, and sec-Cedrenols are prepared by the oxidative dearomatizationinduced [5 + 2] cycloadditions. Phenols with differentortho (pent-4-enyl) substitutions were directly prepared from salicylaldehydes by low temperature *o*-QM generation and consumption. It involves the oxidative dearomatization of an *ortho*-(pent-4-enyl)-phenol, along with an intramolecular [5 + 2] cycloaddition of the respective phenoxonium intermediates with the attached olefin, which provides the respective derivatives[7].



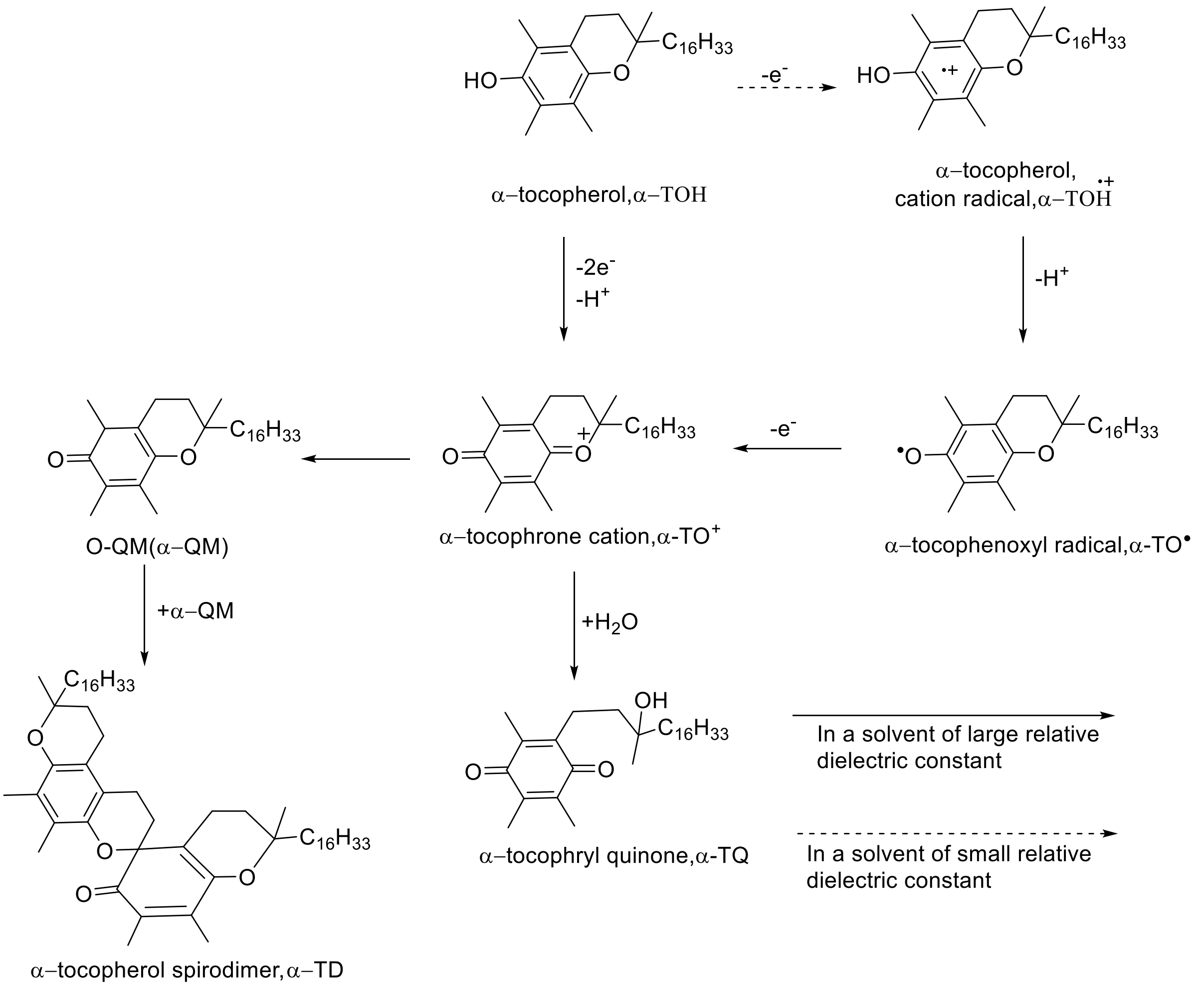
Scheme: 1.8

1.1.2 Alkylation on *o*-QM

DNA Alkylation: The strength of the leaving group attached to the benzylic position of *o*-QM the formation of QMs depends on, in the presence of biological nucleophiles (dN)[11] . The reactions and formation of QMs are also responsive to the presence of electron-withdrawing groups and electron-donating groups. The trends of reactivity of QMs are consistent with the electron deficient nature of the QM intermediate. The Electron-donating groups greatly facilitate initial QM generation and its regeneration from adducts formed by the nucleophiles of deoxynucleosides (dN) that also function as good leaving groups. In contrast to electron donating groups; electron-withdrawing groups suppresses greatly the initial formation of QMs and its regeneration from the reversible deoxynucleoside adducts .The stability of *o*-QM is mainly influenced by the electronic perturbation over it, and the kinetics of the product formed is also altered by the reaction with deoxynucleosides[12]. Electron-rich QMs reacts slowly with nucleophiles than the electron-poor QMs. but this reaction is highly selective. These characteristics provide the explanations for the product profiles observed after DNA has been exposed to various QMs[13]. These characteristics are used to understand the stability and reactivity of QM conjugates for target-promoted and gene-specific alkylation[14].

1.1.3 Coupling reactions

The coupling of *o*-QM is mainly done by redox reactions. Especially the redox reactions of vitamin E in 1, 2-dichloroethane with oxidants in water/1,2dichloroethane interface [15]. There is the oxidation reaction of α-tocopherol (TOH) withMnO_4^- inDCEhasbeenexplainedbya series of reactions. After the formation of a-TD in hexane and *o*-QM of a-TOH produced during the oxidation of α-TOH dimerises easily to α-TD [16].

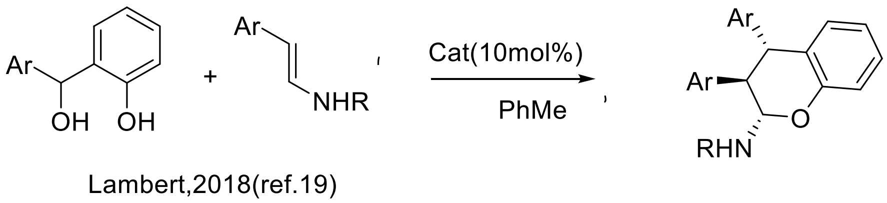


Scheme 1.9

1.1.4 Concerted Cycloaddition Reactions

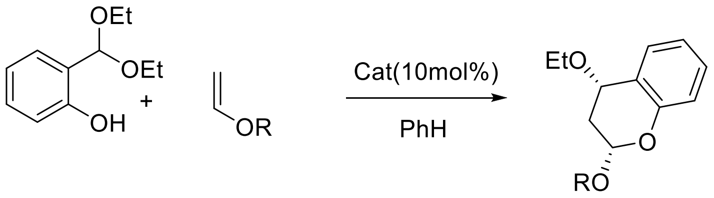
Cycloaddition reactions of *o*-QM and *o*-QM intermediates, acting as dienes in concerted hetero-Diels–Alder (HDA) reactions, are well developed. Good reaction partners include highly polarized cyclic dienophiles such as cyclic enamides[17]. In 2017, the asymmetric cycloaddition of acyclic enamides to *o*-QMs was achieved by Pan and coworkers using a BINOL-derived CPA catalyst [18].

A helically chiral pentacarboxypentadiene (PCCP) has also been shown by Lambert, Vetticatt, and co-workers[19] to be a potent catalyst for the generation and HDA reactions of *o*QMs with vinyl ethers.



Scheme.1.10.

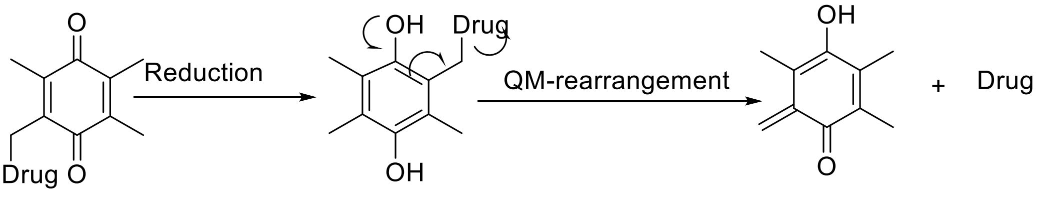
By employing a cyclic enamidedienophile the Schneider group were able to access polycyclic structures[20]. A complementary approach to polycyclic products is to install a tether of appropriate length between the *o*QMdiene and the dienophile. An elegant approach to achieving such tethering is to orchestrate the condensation of an alcohol bearing the dienophile with an aldehyde which becomes the Cterminus of an *o*QM; i.e., a Prins-type reaction.



Scheme: 1.11.

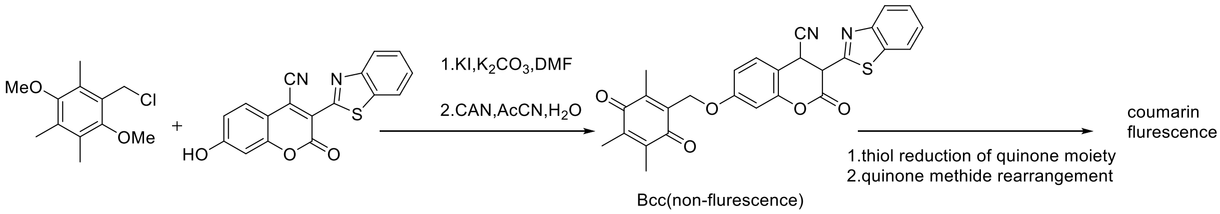
1.1.5 Rearrangement reactions

The chemical transformation of fluorogenic BCC triggered by thiols proceeds through a tandem benzoquinone reduction and QM type rearrangement reactions, which are spontaneous andIrreversible at physiological temperatures in aqueous media[21]. In general, the intracellular reduction of the quinone moiety produces the corresponding hydroquinone thatinstinctively releases the deactivated drug and gives compound via a QM-type rearrangement.



Scheme: 1.12.

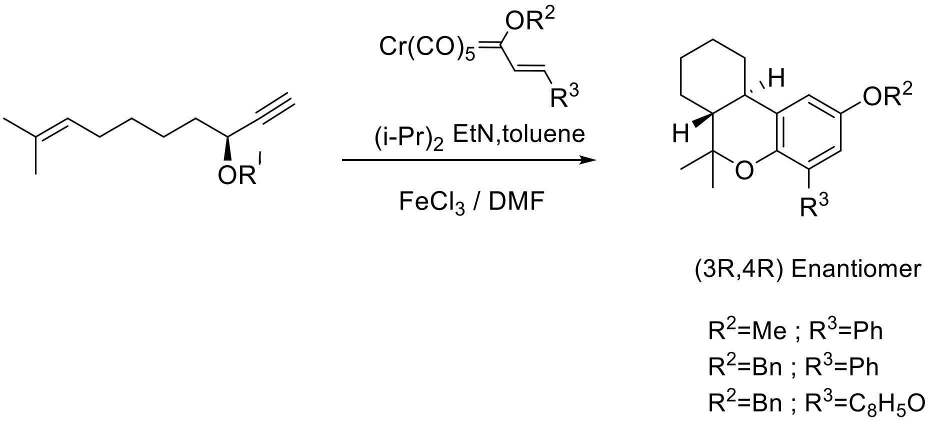
QM-type rearrangement reaction sequence has been employed as part of the fluorescence releasing mechanism for latent fluorophores or the drugs release mechanism of theprodrugs.



Scheme: 1.13: Drugs release mechanism of the prodrugs.

1.1.6 Complex formation with metals

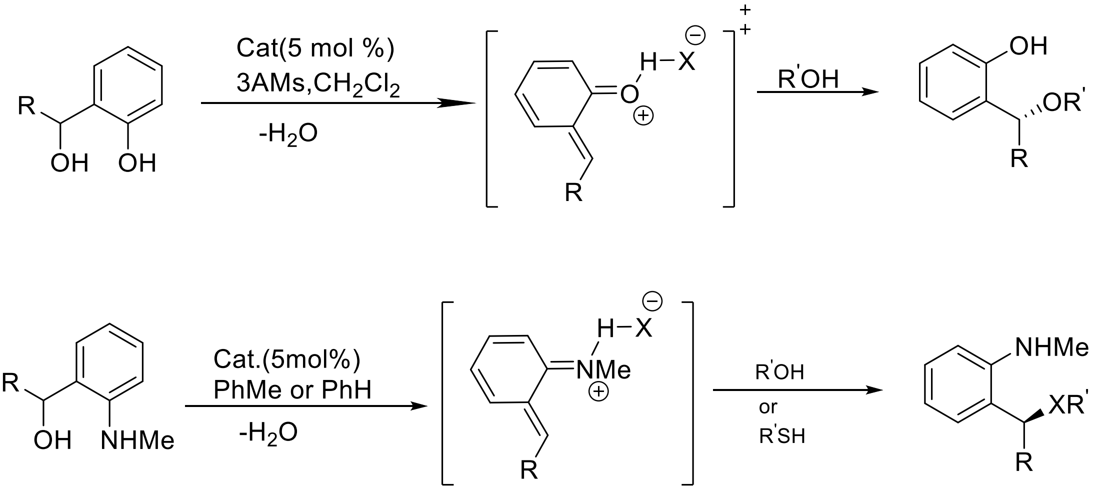
In the presence of a base the reactions of Chromium carbene complexes with enynyl propargyl ethers gives the hexahydrodibenzopyrans after an oxidative workup. It is reported byKorthals and Wulff [22]. The involvement of a [4 + 2] cycloaddition of a Cr complexed *o*-QM intermediate was inferred from the observed high asymmetric induction.



Scheme: 1.14 [4 + 2] Cycloaddition of a Cr complexed *o*-QM with enynyl propargyl ethers.

1.1.7 Conjugate addition reactions

*o*QM and *o*QMI intermediates are generally accessed/unmasked by elimination and once unveiled them can be regarded as α, β-unsaturated carbonyl derivatives. They are strongly activated towards conjugate addition reactions. Historically, potent soft nucleophiles such as 1, 3- dicarbonyl derivatives[23] were most widely employed in this role, but the thermodynamic driving force provided by concomitant rearomatization allows for participation of a wide range of alternative nucleophiles. For example, Sun and coworkers[24] and the Rueping group [25]independently reportedthe addition of alcohols to *o*QMs and alcohols/thioethers to *o*QMIs, respectively.

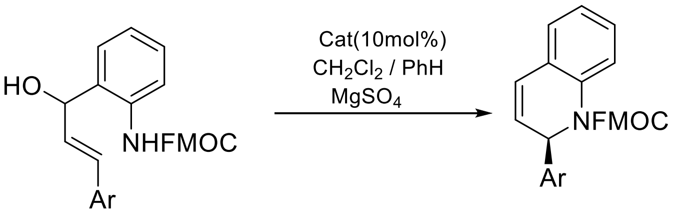


Scheme: 1.15.

1.1.8 Stepwise addition reactions

The most recently described annulation reactions of 1, 2-disubstitutedaromatic substrates capable of forming *o*QM and *o*QMI intermediates proposed to proceeds through the concerted HAD mechanisms. Some of the initial work on the reactive intermediates depicted them in their carbocationic resonance form. For example, the conjugate addition of indols to *o*QMs is described by Bach and Co-workers as involving a benzylic carbocation being trapped by the C3 of the indole[26]. In this case, BINOL- derived CPA is used to unmask the carbocation by ionization.

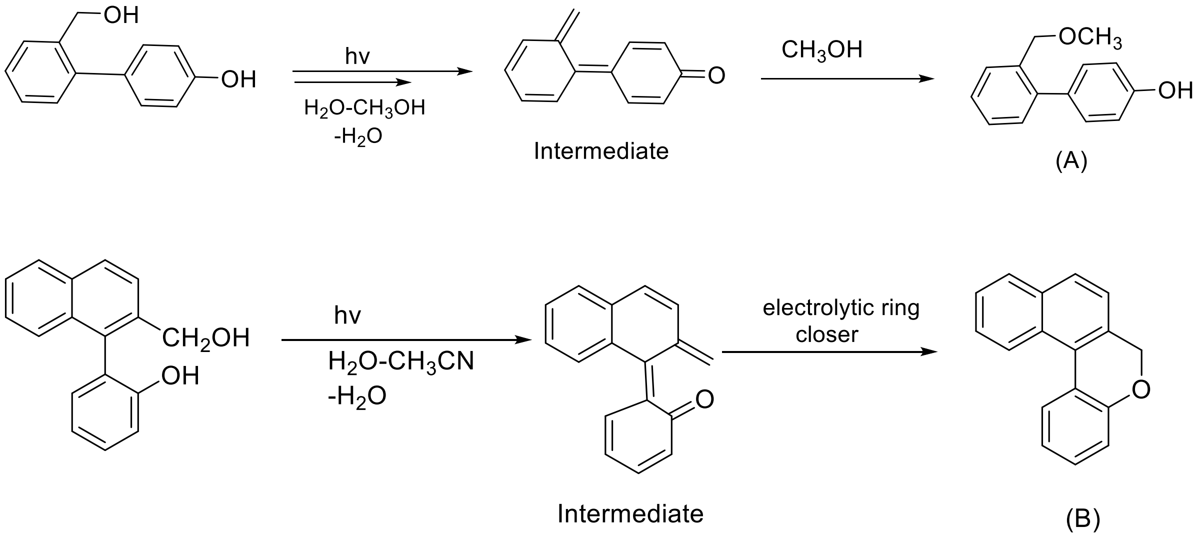
ortho-substituted, Fmoc-protected aniline is developed by Xie and Zhou to engage in an intramolecular allylic substitution reaction, in 2018. While the concerted intramolecular cycloaddition of an *o*QMI intermediate is helps to explain these reactions[27].



Scheme: 1.16.

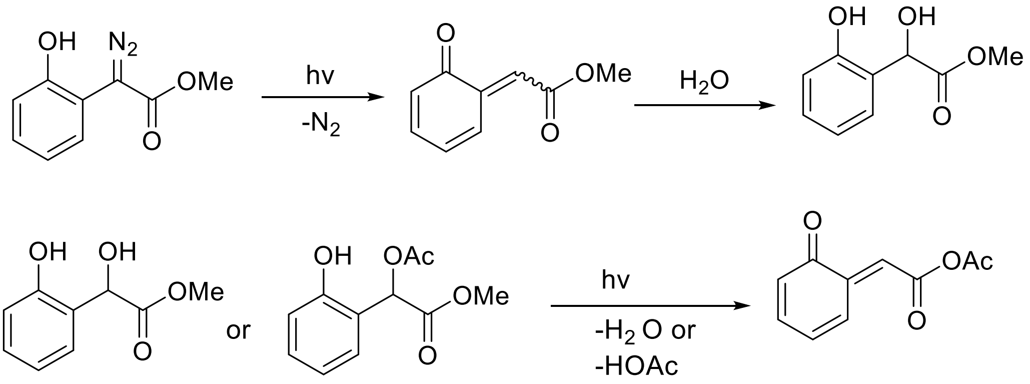
1.1.9 Photochemical reactions

Wan and coworkers studied the photochemistry of a number of *p*-biphenyls and terphenyls substituted with hydroxyl and hydroxymethyl groups in aqueous solutions[28]. They reported that the simple hydroxyl group can strongly and appropriately activate the substituted benzenes or biphenyls towards dehydroxylation. It is due to its strongly electron donating nature, as well as for being carrier of an acidic proton. The corresponding quinone methides (QMs) or biphenyl quinone methides (BQM) are formed as the intermediates.



Scheme: 1.17. Photochemical synthesis of compounds

The flash photolysis of methyl 2-hydroxyphenyldiazoacetate in dilute aqueous perchloric acid solution and acetic acid and biphosphate ion buffers generated a transient species that was identified as *o*-quinone-α-carbomethoxymethide[29].



Scheme: 1.18. Photolysis of methyl 2-hydroxyphenyl diazoacetate.

This structural assignment is based on the solvent isotope effects, the form of buffer catalysis, UV absorption maxima, and the identity of decay rate constants with those determined for the transient, obtained by flash photolysis of other more conventional quinonemethide precursors such as the benzyl alcohol methyl 2-hydroxy mandelate and its acetate, 2-acetoxy-2-hydroxyphenylacetate. New (2-adamantyl) naphthol derivatives, quinonemethide precursors (QMP) were synthesized and their photochemical reactivity was investigated by preparative photolysis, fluorescence spectroscopy, and laser flash photolysis (LFP). All derivatives undergo photosolvolysis via QM intermediates. Presence of adamantly moiety results in different reactivity pattern compared to the non-substituted structure. They also investigated the anti-proliferative activity of the QMPs on three human cancer cell lines: HCT 116 (colon), MCF-7 (breast), and H 460 (lung). Exposure of cells treated with 5 to 300 nm of irradiation led to enhanced anti-proliferative effect on MCF-7 cell line, classifying 5 (or QM5) as a potential lead for further anti-proliferative studies.

1.1.10 Catalytic Asymmetric Reactions with Stabilized *o*-QMs

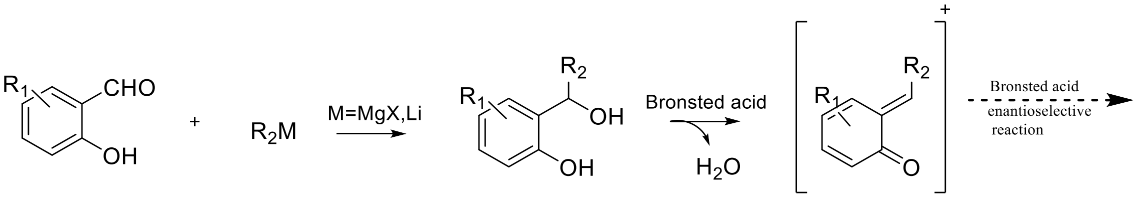
o-QMs have attracted considerable attention because of their intriguing structure and properties. *o*-QMs serve as important intermediates in a variety of biological pathway and enable the straightforward construction of products of broad synthetic utility. Typically, *o*-QMs are generated *in situ* under Lewis acidic, basic, thermal or photochemical conditions. Less usual is the synthesis of stabilized and isolable *o*-QMs whose reactivity is controllable.

Catalytic Asymmetric Reactions with *o*-QMs Generated *in Situ:*

Although the generation of an *o*-QM *in situ* can in principle provides a more general approach, the disclosure of conditions compatible with both a catalytic asymmetric reaction and the formation of a reactive *o*-QM seem to be a very challenging task, unmet until very recently. Furthermore, ease of formation, reactivity and stability of these intermediates are highly dependent on the substitution pattern of their triene portion, with electron donating substituents facilitating their formation and isolation but at the same decreasing reactivity[30] . The elimination of a stable molecule like water from the benzylic position of 2-substitutedphenols is the most common method for the generation of *o*-QMs. In fact, there are several other methods for the generation of *o*-QM is known (oxidations, olefinations, *etc.*), such type of elimination has certainly been the most common platform to form *o*-QMs *in situ* for asymmetric organocatalytic reactions. The type of catalysis that can be used in the asymmetric step is determined by the conditions under which the o-QM is generated. The combinations of both acidic and basic conditions with suitable catalysts have been implemented, thus allowing the productive engagement of a broad range of substrates in organocatalytic enantioselective reactions with *o*-QMs[31].

o-QMs Generated in Situ by Dehydration of ortho-Hydroxybenzylic Alcohols under Brønsted Acid Conditions:

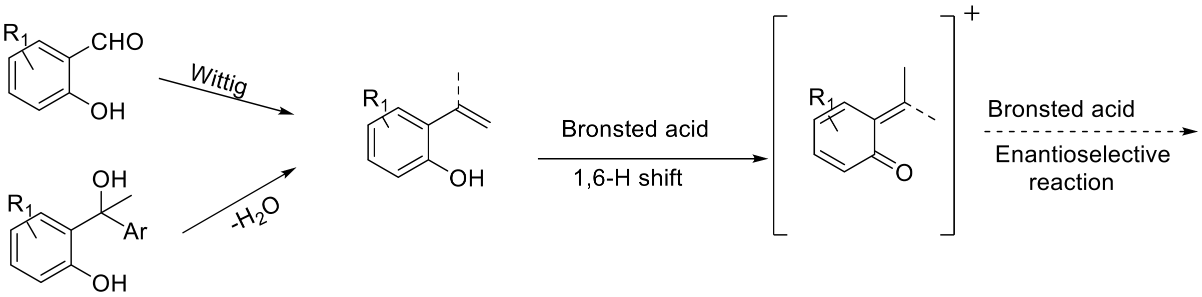
The generation of *o*-QM by dehydration of *ortho*-hydroxybenzyl alcohols maybe the most common methodology exploited for the utilization of *o*-QM in chemical biology, wherein the most investigated form is the QMs having a terminal methylene group. The position of the equilibrium existing between the alcohol and the *o*-QM, as well as the kinetics of *o*-QM formation, is shown to be highly dependent on the conditions (especially pH)[32] and the substituents at the phenolic ring. A general synthetic route to *ortho*-hydroxybenzylic alcohols is the addition of organometallic reagents like Grignard and organolithium in to the salicylaldehydes. Useful protocols can be found in the papers highlighted in this section, which show how these benzylic alcohols can be engaged in Brønsted acid catalyzed transformations, wherein the acid promotes both the formation of the *o*-QM by dehydration and the ensuing enantioselective reaction.



Scheme:1.19. Preparation of ortho-hydroxybenzylic alcohols and reactions under acidic conditions.

o-QMs Generated in Situ by 1, 6-H Shift of ortho-Hydroxystyrenes under Brønsted Acid Conditions:

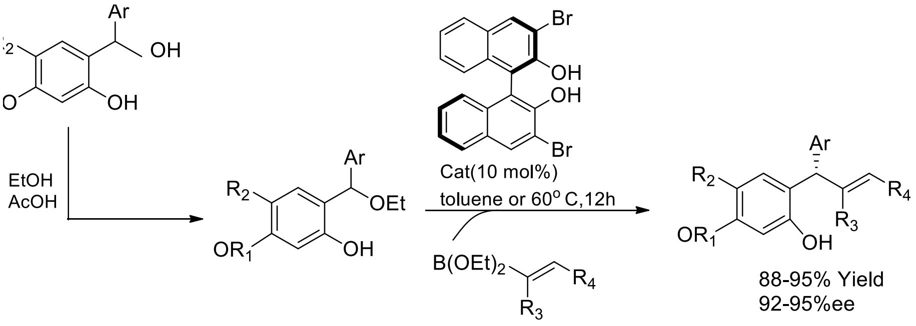
The possibility of using *ortho*-hydroxystyrenes as *o*-QMs precursors in organocatalytic asymmetric reactions with nucleophiles is reported in 2015 by three laboratories almost simultaneously[33]. All three reports deals with chiral phosphoric acid catalysts, providing protocols alternative to the synthetic platform developed by Sigman giving *o*-QM through palladium-hydride initiated H-shifts from these styrenes[34].The Wittig olefination of the corresponding salicylaldehydes, or by dehydration of suitable tertiary alcohols are the two methods for preparing the *ortho*-hydroxystyrenes substrates . The phosphoric acid catalysts are then able to facilitate a 1, 6-H shift by protonating the electron-rich olefin while abstracting the phenolic proton.



Scheme: 1.20. Preparation of *ortho*-hydroxystyrenes and reactions under acidic conditions.

o-QMs Generated in Situ by Alcohol Elimination from ortho-Hydroxybenzylic Ethers under Lewis Acid Conditions:

Luan and Schaus extended the reaction to less stable o-QMs through their generation in situ[35]. Because the ortho-hydroxybenzylic alcohol does not give the optimal results as o-QMs precursors, the corresponding more stable ethyl ethers, readily prepared in acidic ethanol, proved to be more suitable. Under conditions essentially identical to the ones employed with pre-formed o-QMs, a range of ethers could be applied to the reaction. Its scope was thus considerably extended, although an electron donating ether substituent at the phenol ring was still required.



Scheme: 1.21. Addition of vinyl boronates to o-QMs generated from ortho-hydroxybenzylic ethers.

o-QMs Generated in Situ by Desilylation—Halide Elimination from ortho-Silyloxy Benzylic Halides under Lewis Basic Conditions:

The substrates like *o*-Silyl protected phenols bearing a leaving group at the benzylic position, such as a halide (especially fluorides) are introduced to overcome the poor stability of the corresponding free phenols, and to guarantee an ionic control over the *o*-QM generation[36]. Their preparation necessarily involves the silyl protection of the phenol followed by either radical halogenations[37] or hydroxide substitution[38]. It depends on the phenolic structure employed. This method of *o*-QM generation is successfully exploited in asymmetric organocatalysis by Scheidt, by flanking the stoichiometric fluoride Lewis base, used to generate the *o*-QM, with chiral Lewis basic catalysts which are able to combine selectively with the nucleophilic component: N-heterocyclic carbenes (NHCs)[39].

o-QMs Generated in Situ by Desilylation—Halide Elimination from ortho-Silyloxy Benzylic Halides under Brønsted Acid Conditions:

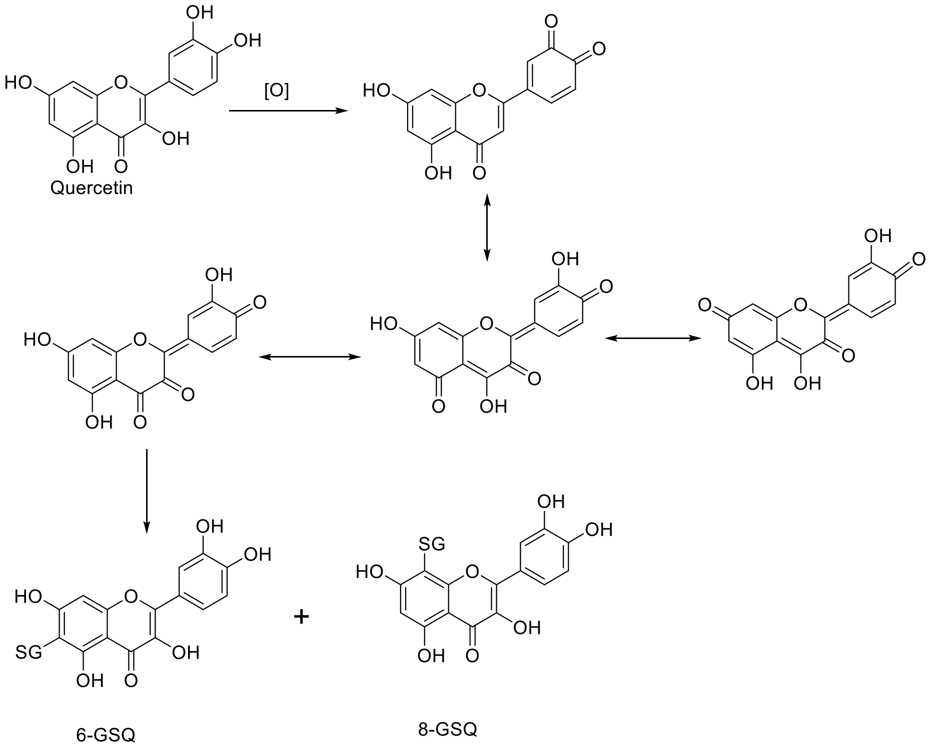
Porco and coworkers reported that acidic conditions are more effective than usual fluoride treatment in generating an *o*-QM-like intermediate from an *o*-TBS pyrone, and that this o-QM species undergoes indole additions[40].In Jacobsen laboratory, this synthetic transformation was put into its catalytic enantioselective version, where the combination of chiral thiourea and achiral Brønsted acid (BzOH) catalysts are used. Which promotes enantioselective additions of 3-substitued indoles to a pyrone-derived *o*-QM[41] .Whereas the reaction was found to beinsensitive to the achiral acid co-catalyst used, the leaving group on the pyrone had a pronounced effect. Also, the presence of the indole N-H was essential for enantioselectivity. So an Achiral Brønsted acid promoted desilylation delivers a pyrone, which suffers elimination of its leaving group forming an *o*-QM-like cationic intermediate. Coordination of the leaving group to the thiourea catalyst favors its elimination and provides a chiral environment around the reactive cationic intermediate.

o-QMs Generated in Situ by Sulfinic Acid Elimination from 2-Sulfonylalkyl Phenols under Brønsted Basic Conditions:

A straightforward approach to *o*-QMs generation is the base induced elimination of a leaving group from the benzylic position of suitably functionalized phenols. But the poor stability of *ortho*-hydroxybenzylic halides prevented this approach from being fully adopted. This stability issue was avoided recently, by adding a leaving group different from a halide namely arylsulfonyl moiety. In 2013, Zhou reported the preparation of 2-arylsulfonylalkyl phenols from the corresponding alcohols and their utilization in a synthesis of 2, 3-benzofurans; o-QMs intermediates were generated from these sulfonyl species under mild Brønsted basic reaction conditions[42].

1.1.11 Tautomerism

On the oxidation of quercetin, it exists in the four tautomeric forms. In these four isomers, one is *o*-quinone isomer and remaining three are quinone methide isomers[43]. A glutathionyl adduct formation occurs at the positions C6 and C8 of the quercetin A ring to give 6-GSQ and 8-GSQ; it is due to relatively high abundance of the quinone methide isomers.



Scheme: 1.22. Glutathionyl adduct formation at the quercetin ring[44].

2. APPLICATIONS OF *o*-QMS

The applications of *ortho*-quinonemethides (*o*-QMs), which have becomepowerful, fascinating, and highly efficient intermediates in organic synthesis. Recent advances toward the generation, reactivity and application of *o*-QMs in organic synthesis offers a bright future for the development of novel methodologies for the synthesis of many natural and man-made compounds. It can be seen that many well-established different methodologies were successfully applied to *o*-QMs by worldwide laboratories to more environmentally benign approaches. This area is clearly expanding in many aspects and will reveal spectacular applications in the near future, ranging from organic synthesis, material chemistry, fine chemicals, and pharmaceuticals to the synthesis of natural products. Definitely, much more remains to be done in this field, and in the next few years, we will see many new, exciting findings in *o*-QMs chemistry. Moreover, it will lead to the serendipitous discovery of many more new reactions, for as much as we may know; chemistry always has new and intriguing surprises in store[45]

o-QMs react with electron-rich dienophiles in inverse-electron demand hetero-Diels-Alder reactions[46] . The optimized reaction conditions were used to explore the scope of the two-component hetero-Diels−Alder reactions. We evaluated diols featuring both electron-rich and -deficient substituents[47] . Catalytic, enantioselective Diels–Alder (DA) reactions belong to the most fundamental and powerful tools in constructing enantioenriched six-membered ring systems[48]. Particularly, catalytic asymmetric inverse-electron-demand (IED) hetero-DA reactions have proven to be efficient and atom-economical methods for the synthesis of six-membered heterocycles with perfect regio- and stereoselectivities[49]. As a result, elegant developments have been achieved in the research area of catalytic asymmetric IED aza-DA reactions[50], which employed 1-azadienes[51] or 2-azadienes[52] as electron-deficient dienes to react with electron-rich dienophiles in the presence of either chiral metal catalysts or organocatalysts. These well-developed approaches afforded nitrogenous heterocycles such as tetrahydropyridines and tetrahydroquinolines in excellent stereoselectivities[53].

Recently, *ortho*-hydroxybenzyl alcohols have emerged as active reaction partners in asymmetric catalysis for their characteristic of being readily converted into *ortho*-quinone methide (*o*-QM) intermediate[54] in the presence of a Bronsted acid and should serve as a suitable diene for catalytic asymmetric IED oxa-DA reactions. However, previous reports on catalytic enantioselective transformations of *ortho*-hydroxybenzyl alcohols only included conjugate additions and stepwise cyclization[55].

3. ORGANOMETALLICS

Organometallic chemistry, a major branch of organic as well as inorganic chemistry constitutes the study of the relationship of the bond between a metal and a carbon atom. It also involves the synthesis of new organometallic compounds, their reactivity and stability. The key feature of an organometallic compound is simply the definition as well; the bond between a carbon and any metal. As any basic chemistry student knows, the electronegativity of a carbon atom is around 2.5, which makes it less electronegative than halogens, oxygen and nitrogen which are the most commonly encountered atoms in organic molecules. This implies that in most of the organic compounds the carbon atom has a partial charge. This enables many of the conventional reactions to happen. However, when one wants to make a bond between carbon atoms this feature becomes a disadvantage. At this point, organometallics lend a helping hand. Usually metal atoms have electropositive character, hence when they form bonds with carbon, the carbon atom develops a partial negative charge and exhibits a carbanionic character. This carbanionic character can not only aid in the formation of bonds between carbon atoms but can also be put to use in a variety of reactions. This important character of an organometallic compound is the reason that organometallic chemistry is such a widely researched field. [56]

There are a variety of organometallic reagents based on the metal used and type of functional group contained in the reagent. Theoretically most of the metals can be made into organometallic compounds, though the need differs according to the application. For a synthetic organic chemist, the ease of synthesis and handling of the reagent is an important factor. In the case of an inorganic chemist, it is the organometallics that can be novel and their electronic characters. There are a lot of organometallic reagents available these days commercially for a variety of uses. A brief description of the most commonly used Grignard reagents has been added below[57].

1) Organolithium compounds

Lithium has an electronegativity at 0.98. The difference in the electronegativity between carbon and lithium is significant making organolithium reagents quite reactive and highly basic in nature. These factors make it a useful nucleophile reagent but also difficult to handle. They are not very stable thermally and hence require stringent conditions for synthesis and handling. They are incompatible with water, oxygen and carbon dioxide and involves a completely inert and dry atmosphere.

They are both put to use as a base for deprotonation and as a synthetic reagent for preparing organic compounds. Aside from these applications, organolithium reagents can also be used as a starting material for synthesis of other organometallic compounds[58]

2) Organozinc reagents

The first organozinc compound, a pyrophoric - diethylzinc, was discovered accidently by Edward Frankland in 1849, when he was heating a mixture of zinc and ethyl iodide. They are also one of the first organometallics used in organic synthesis. They are less reactive than organolithium reagents, making it easier to handle. Though they get oxidized easily, they are compatible with a variety of functional groups enabling them to selectively react in a multi-functional group organic system. They are mostly available commercially as a THF stabilized solution[59]

3) Organocopper Reagents

Organocopper reagents also known as Gilman's reagents were discovered in 1936 are used in a multitude of ways in synthetic organic chemistry. They are weakly basic and act as a nucleophilic source in addition and substitution reactions. The unique feature of the organocopper compounds are that they have a range of reactivity profile and subsequently they have a wide range of applications. They can be used for conjugate addition, enolate trapping, alkylation, arylation and acylation to name a few[59]
Reactions involving organocopper reagents must also be carried out in an inert atmosphere and most of them are synthesised from organolithium compounds

3.1 GRIGNARD REAGENTS

Among all the organometallic reagents, there is a very important and famous reagent -organomagnesium reagents also popularly known as the Grignard Reagents. The reaction involving a Grignard reagent is named as a Grignard reaction. It is one of the basic reactions which has been taught to students even in the high-school level, and as a laboratory experiment during the graduate studies in chemistry. Every student involved in the chemistry world would have at least performed the Grignard reaction once during their course of study or work. It is such an important part of the education and research since it is still the widely used method for creating the bond between carbons.

The Grignard reagent was first discovered by Victor Grignard in the year 1900. Victor August Grignard was born in 1871 dedicated most of his life to the field of organic chemistry. He was born in a poor family and had a humble attitude. His first attempt to major in mathematics failed forcing him to join in the army. However, after a year of service he returned and obtained his degree in mathematics. In the same year he transferred to chemistry to work under Barbier and Bouveault to work on stereochemistry. Grignard soon lost his interest in the same and was asked to work on organometallic chemistry. Barbier pointed out to him that how a Saytzeff reaction which failed in the presence of zinc gave low yields in the presence of magnesium. On repeating Barbier's experiments, Grignard encountered similar difficulties, until he hit upon the idea of performing the reaction in separate stages. He began by gradually adding an ethereal solution of an alkyl halide to an equivalent amount of magnesium metal, submerged in anhydrous ether. The two substances combined to form an alkyl magnesium halide, later to become known as a 'Grignard reagent'. It was protected from the atmosphere by a blanket of ether vapour, and to prevent the solvent evaporating away Grignard installed a reflux condenser above the reaction vessel.

With these precautions Grignard was able to prepare a wide variety of alkyl and aryl magnesium halides which remained stable in ethereal solution, while still retaining their potency. By gradually introducing them to organic compounds with suitable functional groups, and then treating the resulting complexes with water or a dilute acid, he could accomplish many useful synthetic reactions. One example was the breaking of a carbonyl bond in an aldehyde or ketone molecule to form a secondary or tertiary alcohol. When he demonstrated a test –tube preparation to Barbier, he was congratulated for this original idea.

Some of these reactions released so much heat that the containing vessel needed to be surrounded with ice. Others, however, had to be encouraged with gentle warming, or a suitable catalyst. Grignard realised that the solvent played a key role in the success of his process, and he proposed that the organomagnesium halide molecule formed a stable relationship with one or more molecules of ether. Later researches proved him correct, and the complex – in which the oxygen atoms of two ether molecules each donate an electron pair to the magnesium atom – was shown to have a tetrahedral structure. Grignard was awarded the Nobel Prize in 1912 for his immense contribution with the aid of the organomagnesium reagents.

During the decade following his initial discovery Grignard continued to explore the potentialities of organomagnesium reagents, combining them with a wide range of compounds – including glycols, epoxides and cyanides – to generate many new products. He also took a keen interest in the terpene family of compounds, and synthesised a number of new ones (sometimes in collaboration with Barbier).

More than a century has passed since Grignard's reaction earned him the Nobel prize, and throughout that period his process has remained a valuable aid to organic synthesis. Over the years, its area of utility has been significantly enlarged by the use of other solvents, such as tetrahydrofuran. This heterocyclic ether, formula $(CH_2)_4O$, is frequently employed for Grignard reactions which require temperatures above the boiling point of diethyl ether – for example, the synthesis of the breast cancer drug tamoxifen.

Tamoxifen was synthesised by the British chemical company ICI in the 1960s, in the context of a research programme aimed primarily at producing oral contraceptives. Its therapeutic potential was not fully realised until the 1980s. By 2003 it was estimated that more than 400,000 women are alive today as a result of tamoxifen therapy, and millions more have benefited from palliation and extended disease-free survival. Today, when university research must be justified in terms of its potential impact on society, it is vital to remember that scientific discoveries which appear at first to be of purely academic interest may eventually have massive consequences.

Another instance of the Grignard reaction's continuing fertility is the research project which earned Ei-ichi Negishi of Purdue University in the US a share of the 2010 Nobel prize for chemistry. His development of novel ways to form carbon–carbon bonds, using a variety of organometallic intermediaries, started with attempts to create a new type of Grignard reagent. Grignard would surely have been delighted to know that his discovery was still helping to extend the frontiers of chemical knowledge 100 years after his own Nobel prize.

Students at Bucknell University even wrote the following song to help them understand and remember the Grignard reaction.[60]

Oh Grignard, the Beautiful
(sung to the tune of "America the Beautiful")
The carbonyl is polarized
The carbon end is plus
A nucleophile will thus attack

The carbon nucleus
A Grignard yields an alcohol
Of types there are but three
It forms a bond to correspond
From C to shining C.
A secondary's synthesis
Requires an aldehyde
For tertiary, a carbanion
And ketone may collide
And Grignards add formaldehyde
The product's primary
They stick like glue to CO2
Join C to lonely C.

Magnesium has an electronegativity of 1.31 and the difference in electronegativity between the carbon and magnesium atom is approximately 1.2 lending the carbon atom a significant anionic character. As with all the organometallic compounds, the carbon obtains a partial negative charge and acts as a nucleophile. Most of the Grignard reagents are formulated as RMgX, though in reality it a mixture of species. A Grignard reagent is capable of acting as both a base and a nucleophile as with other organometallic reagents.

The nucleophilic character of the Grignard reagent allows it to react with the electrophilic counterpart in the reaction thereby making the much-coveted C – C single bond. Because of its basic character, it has the intrinsic tendency to react with acidic compounds like carboxylic acid, phenols, thiols, and even alcohols and water. This means that the reaction conditions involving a Grignard reagent must be strictly anhydrous and free from acidic components as much as possible. Grignard reagents are also susceptible to oxygen forming hydroperoxides, and are highly unstable when they are exposed to the atmosphere. Hence, Grignard reagents are generally not isolated and when needed are prepared in situ of the reaction. Usually these reactions are carried out in dry diethyl ether or tetrahydrofuran. Aside from the hypothesis that the Grignard reagent is being stabilized and coordinated by the solvent, the volatile vapours of such solvents prevent the interaction of oxygen and the Grignard reagent. The metal magnesium also must be completely removed of any oxide layers present on its surface before the start of the reaction. This can be done in a variety of ways, the simplest of which involves gentle scratching. The formation of the Grignard reagent is highly exothermic and once the reaction has started, it will continue to reflux in the absence of an external heat source. All these factors encompassing the reaction conditions make the Grignard reaction a tedious process albeit the simplicity of the chemistry [61].

3.2 SYNTHESIS OF GRIGNARD REAGENTS

The Grignard reagents are typically prepared from the reaction between an organic halide and the metallic magnesium in the form of turnings. Although Grignard reagents have been extensively used in the industry, since Grignard reaction is one of the few practical routes for the construction of carbon – carbon bonds as well as other bonds between various elements and carbon. Even so there is still no commercial scale production process for Grignard reagents because of some drawbacks. Safety is a major issue when carrying out such an exothermic reaction in large scale and the cost of using a Grignard reagent in a larger scale is also a main factor. Five components contribute to the cost of using a Grignard reagent

a) Magnesium metal
b) The halide
c) The solvent
d) The substrate
e) Disposal of the unwanted by-products

The preparation of Grignard involves the initial addition of magnesium turnings devoid of the oxide layer followed by the slow addition of the organic halide, RX into the reaction flask, along with the addition of excess of solvent. The initiation of the reaction mostly happens within the addition of 10 wt% of the organic halide. This can be understood with the heat evolved because of the exothermic reaction. Turbidity may also develop in many cases but this can be misleading as it could be just the magnesium breaking down. Often a milky appearance can be observed but this is due to the presence of moisture. The slow addition of the halide is very important in regard to safety since the complete addition may result in a sudden exothermic impact. This may cause breaking of the reaction flask and release of the contents to the atmosphere. Many factors affect the feasibility of the Grignard reaction like

a) Quality of the magnesium
b) Amount and dryness of the solvent

c) Organic halide

3.2.1 The solvent

The most important criteria to be met by the solvent is that it must be as anhydrous as possible. Even the presence of a moisture content by .02 % will deter the formation of the Grignard reagent. In the presence of water, hydrolysis of the Grignard reagent results in the formation of the species ROH, complicating the purification process of the desired product. The absence of oxygen is very important as well even though it doesn't prevent the formation of the reagent, it could react with the formed reagent and form a peroxo species. The last factor is the solubility of the reagents in the selected solvent. Almost all Grignard reactions are carried out in thoroughly dried THF. Most of the commercially available Grignard reagents are supplied as solutions in ether or THF.

3.2.2 The Metal

The magnesium turnings are usually protected by an oxide layer which prevent them from reacting with the halide. The activation of the metal can be done in a variety of ways. They include addition of iodine, ultrasonication or washing the magnesium turnings with acid. Another way to circumvent this problem is by using freshly chipped magnesium turning with a small quantity of the required Grignard reagent.

3.2.3 The halide

The halide used in the reaction must also be free of moisture and oxygen because of the reasons explained above. Any residual impurity of HX in the reagent RX can be removed by passing it through molecular sieves.

The reactivity of the different halogen atoms in the formation of the Grignard reaction is as follows:

I > Br > Cl >> F

And the reactivity of the organic part is as follows:

Allyl, benzyl > 1° alkyl > 2° alkyl, cycloalkyl = 3° alkyl, aromatic > vinyl

There is an intrinsic problem while using the organohalide – formation of the homocoupled product. Usually the more reactive the substrate more is the formation of the homocoupled product. Another important factor to be taken into account is that the substrate must not contain functional groups that could react with the Grignard reagent. This will result in the formation of undesired side products thereby reducing the yield and hindering in the purification. Despite all the care taken, there is always some amount of homocoupled product formed. This is a major drawback while conducting the Grignard reaction.

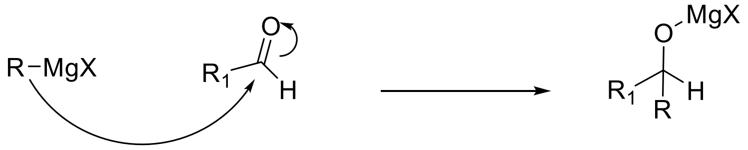
Though there are many challenges in each of the component involved in the preparation of the Grignard reagent, this process is the most widely followed. This is so because, with the proper care and stringent measures, all the conditions can be met for the formation of the Grignard reagent. They can be quite easily made in the research laboratory, industry or even in the graduate level chemistry lab.

3.3 REACTIONS OF GRIGNARD REAGENTS

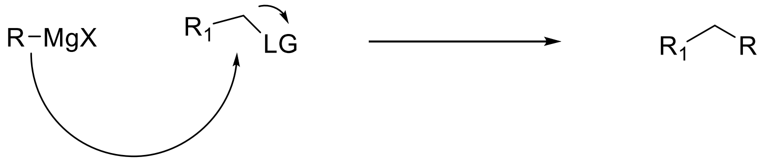
As already described the C – Mg bond is polarized in the Grignard reagent giving the carbon a partial negative charge. This polarization is less as compared to organolithium reagents making the Grignard reagents more selective than the former. It is more reactive than the zinc and copper organometallics and react more vigorously with electrophiles. Basically, the Grignard reagent is just a source for a nucleophilic carbanion. As a result, over the years there are numerous reports of reactions between the Grignard reagent and a broad spectrum of electrophilic substrates. Aside from the traditional uses of Grignard reagents there have many publications which explore the reactivity of the Grignard reagents with transition metal salts[62]. . From all the reports, the reactions of a Grignard reagent can be summarized and classified into any one of the three categories:

a) Nucleophilic Addition or substitution

The most utilized reaction of the Grignard reagent is the nucleophilic attack of its carbon atom on various electrophiles. The basic scheme is shown below for both addition and substitution.

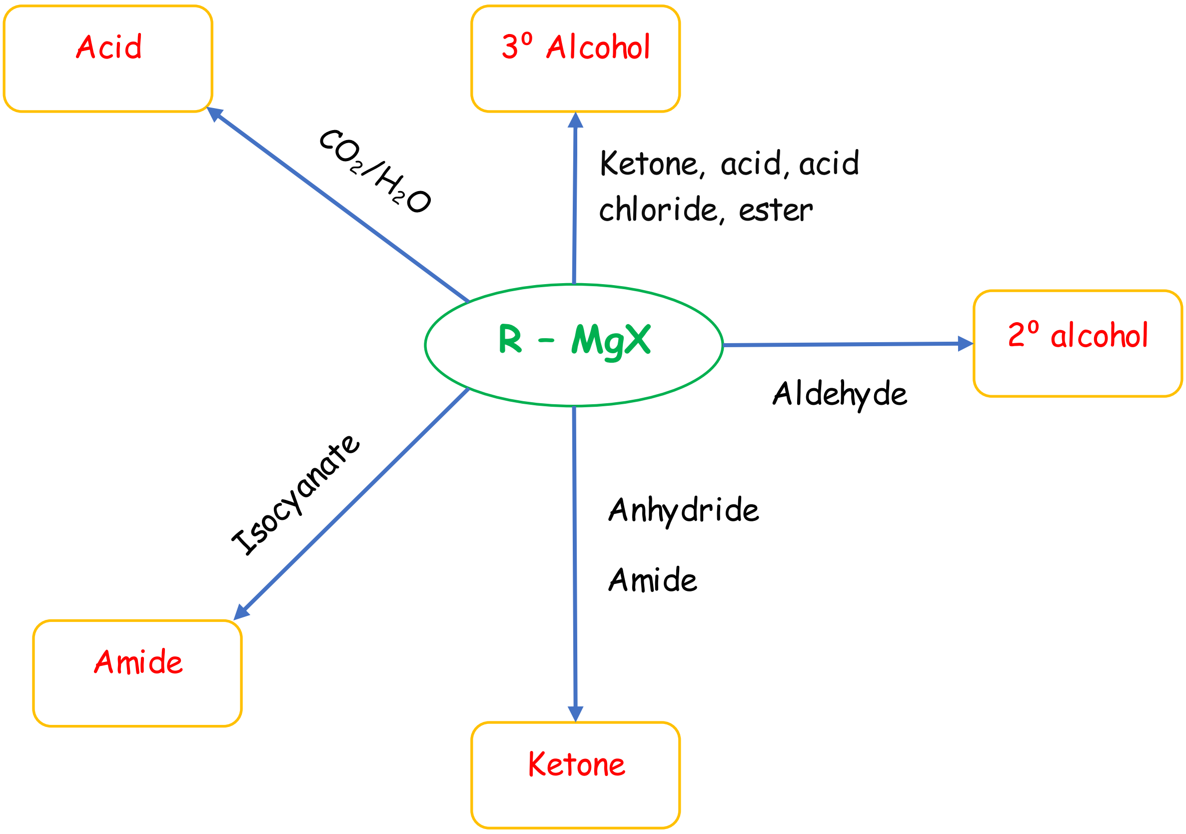


Example of Nucleophilic Addition of Grignard Reagent



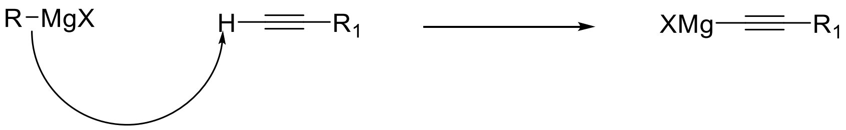
Example of Nucleophilic Substitution of Grignard Reagent

The above two reactions have the potential to produce a variety of building blocks in synthetic chemistry enforcing the importance of the Grignard reagent. Grignard reagents react with most substrates that contain polar multiple bonds like ketones, nitriles, sulfones, imines and highly strained ring systems like epoxide. The figure drawn below shows some of the important functional groups that can be produced using the Grignard reagent.



b) Acts as a base for proton abstraction

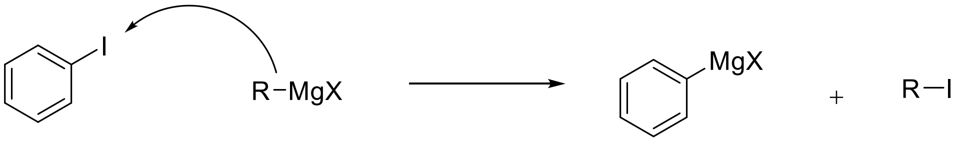
In the presence of an acidic hydrogen, the basic character of the Grignard reagent prompts it to abstract the hydrogen. An example of this reaction can be illustrated with an alkyne.



Grignard Reagent acting as a base

c) Exchange of the halogen from magnesium metal

This reaction is a basic halogen exchange reaction between a Grignard reagent and another organic halide. An interesting application of this reaction is the synthesis of highly functionalized Grignard reagent using the magnesium-iodine exchange.



Magnesium - Halogen Exchange

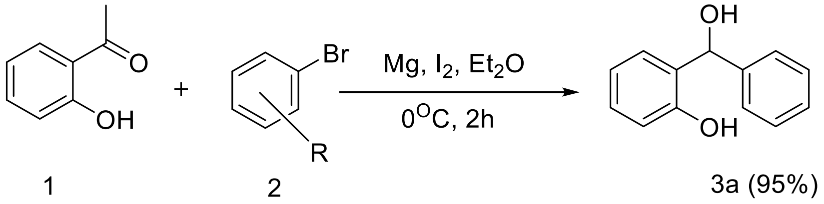
CONCLUSION

The Grignard reaction can be used to make *tert*–benzyl alcohols from 2-hydroxy benzaldehydes and corresponding variety of organic halides. This Grignard adduct can be used as a precursor for the formation of *o* – quinone methides in situ. In this work, different Grignard adducts have been synthesized, isolated and characterized. These have been further used in reaction with 1,3 – diketones to give a product where the Grignard adduct acts as quinone methide.

RESULTS AND DISCUSSION

In our lab we prepared a Brønsted acid catalyst based on pentacarboxycyclopentadienes (PCCPs), which are strongly acidic and simple to prepare from chiral alcohol precursors inspired from Gheewalaetal. Here we utilize the prepared Brønsted acid for the synthesis of biologically relevant aryl chromenes from *in-situ* generated *ortho*-quinine methides via inverse-electron demand Diels-Alder reaction.

We started our investigation with the synthesis of *ortho*-hydroxybenzyl alcohols. We opted the Grignard reaction for the preparation of diols, reaction between salycylaldehyde and aryl magnesium halides in presence of ether at 0°-rt afford the expected diol derivatives in excellent yield.



The scope of the reaction was checked with various aryl halides. Aryl halides bearing different substituents reacted smoothly with **1** affording the corresponding diols in good yield and the results are summarized in Table 1.

Table 1. Substrate scope of the reaction

Entry	R	Product	Yield (%)
1	H	**3a**	95
2	4-OCH3	**3b**	90
3	1,3-CH3	**3c**	93
4	3-OCH3	**3d**	91

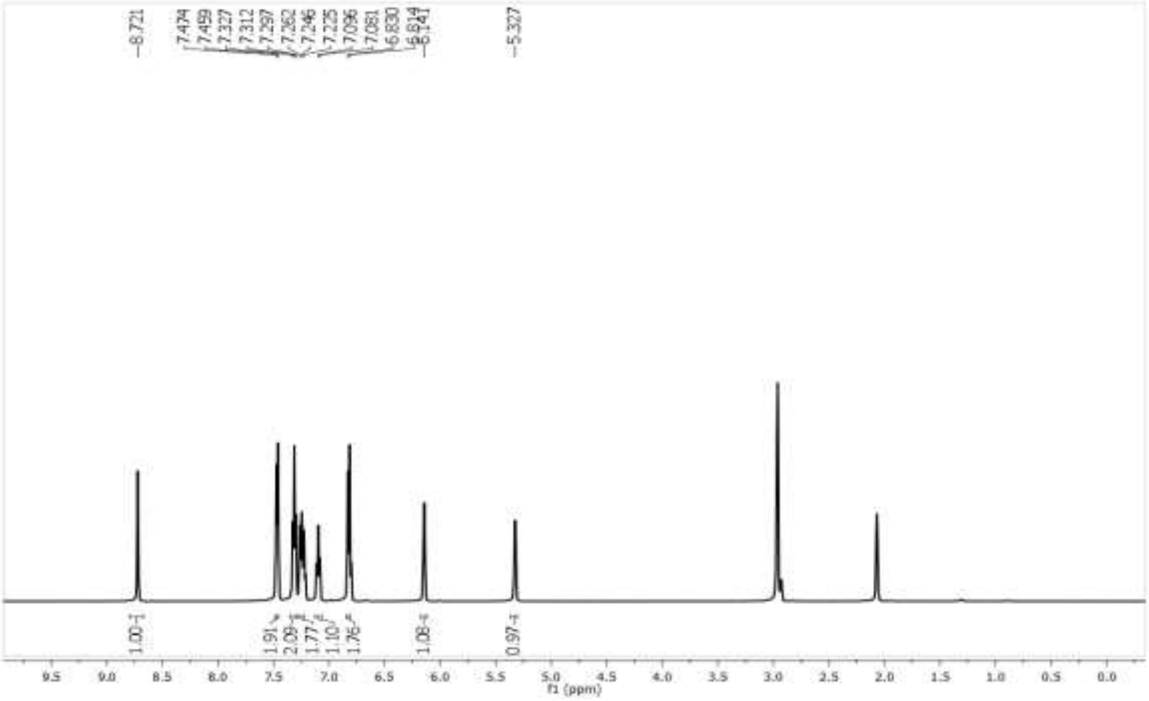


Figure.2.6. ^{1}H NMR of compound spectrum of Compound **3a**

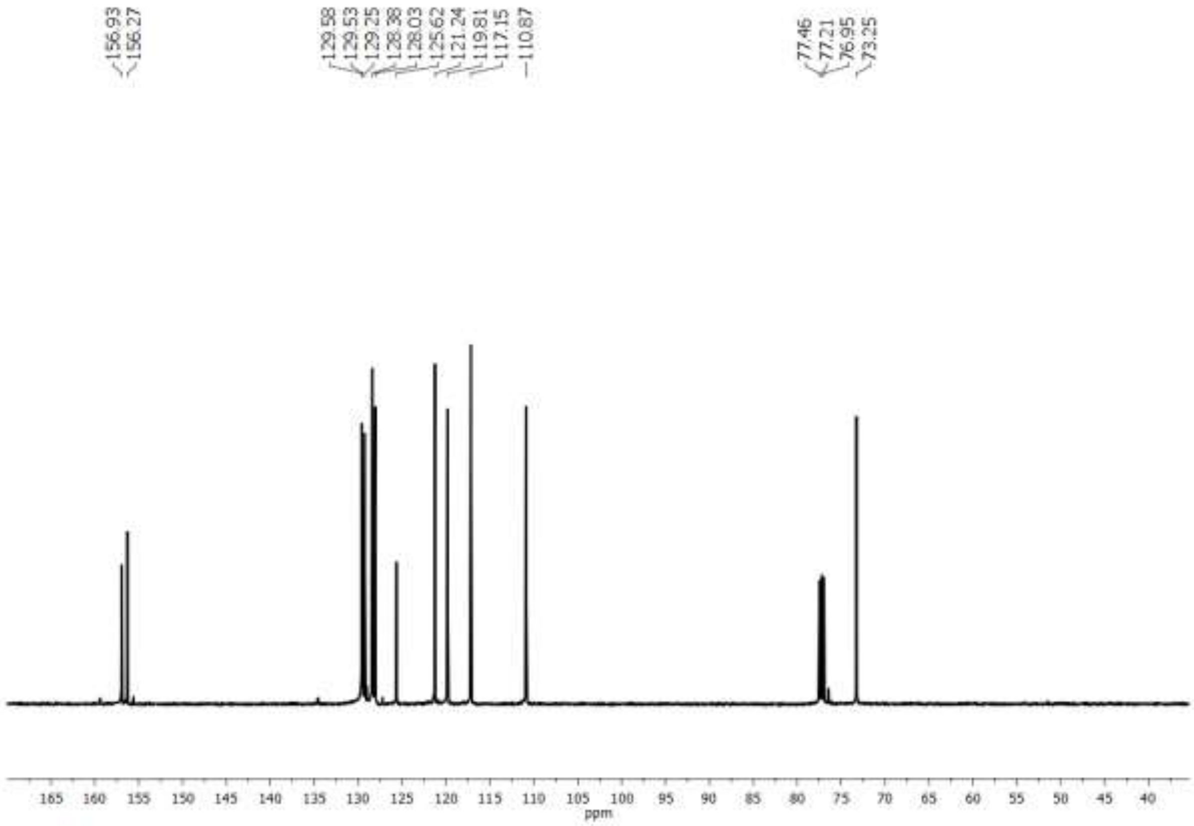
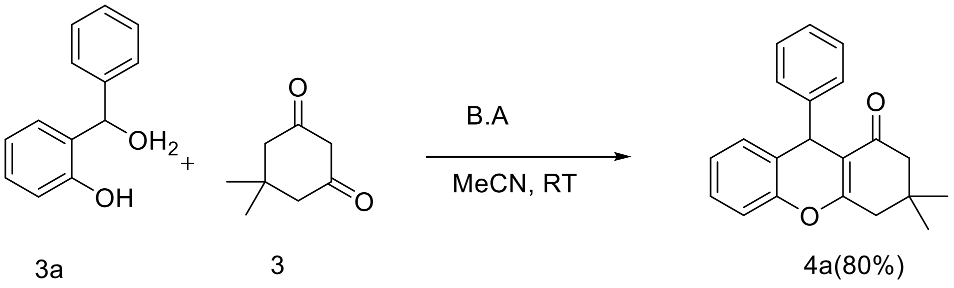


Figure.2.7. ^{13}C NMR of compound spectrum of Compound **3a**

Then we initiated our studies by investigating the reaction of prepared orthohydroxy benzyl alcohol (1 equiv) and 1,3-cyclohexadione (2 equiv) in the presence of pentacarboxycyclopentadienes based bronsted acid (20 mol%) in CH_2Cl_2 at 0oC- RT. The desired cyclized 4H-chromene product **4a** was obtained in good yields within 24 h.The structre of the product was confirmed by various spectroscopic techniques.



Scheme: 2.6.

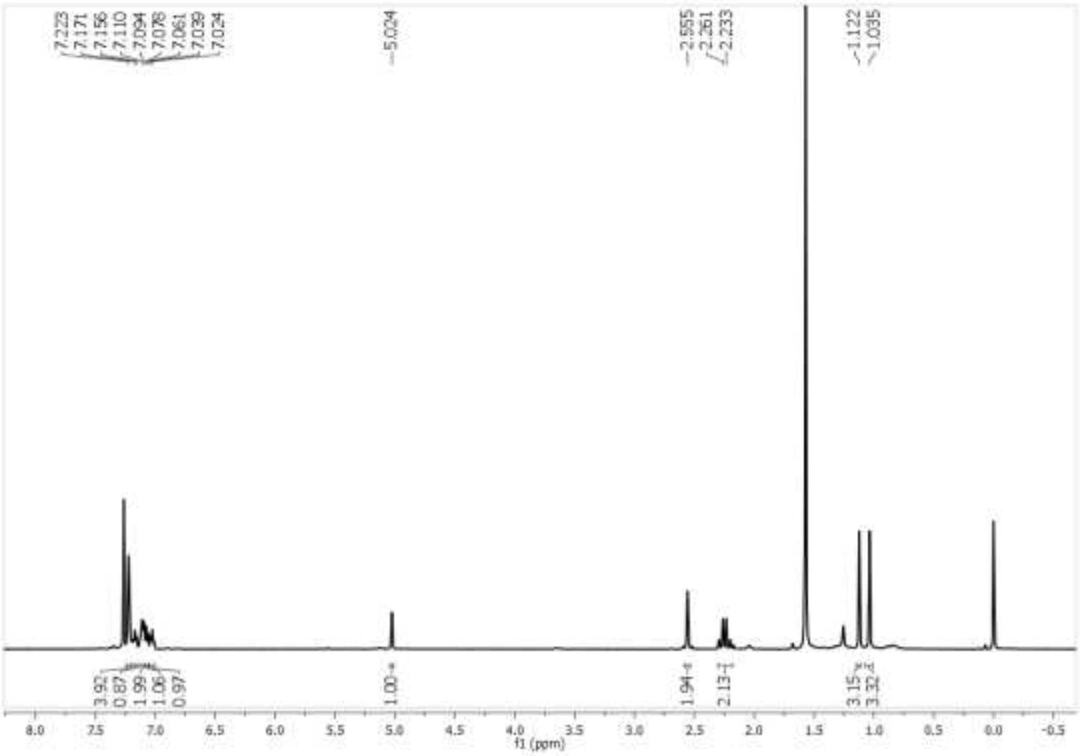


Figure.2.8. ^{1}H NMR of compound spectrum of Compound **4a**

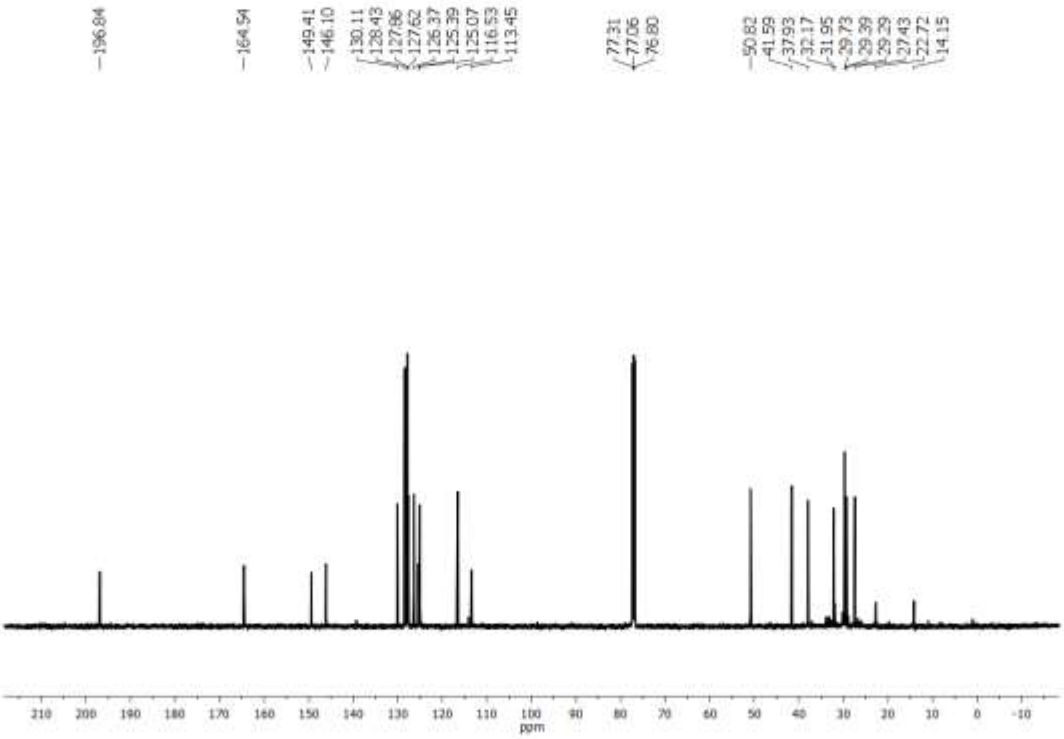


Figure.2.9. ^{13}C NMR of compound spectrum of Compound **4a**

CONCLUSION

In this work we use the Bronsted acid as the catalyst to enhance the reaction. The Bronsted Lowry concept was proposed by Johannes Nicolaus Bronsted and Thomas Martin Lowry. According to Bronsted Lowry concept, acids are species which can donate a proton while bases are species that can accept proton which requires a lone pair of electrons to form an H+ bond. The Bronsted definition of acid and base is a special case of Lewis definition. According to them, any Bronsted acid is a Lewis base and vice-versa. In each case, the base which contains a lone pair according to Lewis concept and which is proton acceptor by Bronsted theory, they both will react with acid and form covalent bond. When a Bronsted acid dissociates, it increases the concentration of H+ in solution or the Bronsted acid dissociates by taking a proton from the solution (H_2O) to generate OH- ions in the reaction medium. There are Amphoteric compounds which can act as both Bronsted Lowry acid and base together.

Bronsted acid is used for the formation of esters and acetals and the cleavage of C-O bonds, such as hydrolysis. Bronsted acid can activate the alkene, alkyne, carbonyl, imine, and hydroxyl groups to form carbocation, vinylic carbocation, oxonium salt, iminium salt etc. which can promote nucleophilic addition reaction.

The concept of conjugate acid-base pairs is also introduced by Bronsted Lowry concept. A conjugate acid-base pairs are species which differ by an (H+) ion. The common Bronsted acids are HCl, H_2SO_4 and inadition to this triflouromethane sulphonic acid (TfOH) is also developed as super strong Bronsted acid, which is about 100 times stronger than sulphuric acid. And Similarily a nitrogen acid (Tf_2NH) was also developed to study the catalytic activity.

The specialty of this work is that the bronsted acid used in the reaction is prepared in the lab.As we discussed in the introduction our products are derivatives of chromene also known as benzopyrans, one of the privileged scaffold which appears as an important structural component in various natural products and also possess useful photochemical properties. The derivatives of benzopyran moiety can be capable of interacting with a variety of cellular targets which leads to their wide ranging biological activities such as antitumor, antihepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, antispasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermal, vasodilatory, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic activity. The potency of these clinically useful pharmacophore in treatment of cancer and inflammation and other activities encouraged the development of some more potent and significant compounds.The SAR studies reported that the substitution in the chromene nucleus with the specific groups increases the ability of the molecule to prevent diseases[63].Also they are important intermediates in the synthesis of many natural products.

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