# Efforts towards Alkyne insertion reaction via Oxidative Dearomatization

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*Under the supervision of*

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This is to certify that the material presented and performed experiments in this project entitled "**Efforts towards Alkyne insertion Reactions via Oxidative Dearomatization**" is a bonafide record work done by **Mr. Rahul Kumar,** student of NIT Rourkela, for requirements of the degree of Master of Science for his research project.
He has successfully completed his project work under my guidance in the academic year 2014-2015 in this institute. I wish him all the best for his future

Date: 06.05.2014
NIT Rourkela

Dr. Debayan Sarkar
Project Guide

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I owe my heartfelt thanks to my parents and younger sister for their constant love, sacrifice, moral support, encouragement and motivation which led me to attain the fruits of success in pursuing my future career. I would like to thank God for His blessings.

Rahul Kumar.

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# Introduction:

In the realm of organic chemistry, organic synthesis reigns supreme as the most fascinating area of activity. The dearomatization[1] reactions are widely recognized as powerful methods for the synthesis of highly functionalized three dimensional structures from simple planar aromatic compounds. Recently, great efforts have been devoted to the development of oxidative dearomatization processes. Phenols are a readily available chemical feedstock and widely used as starting materials in organic synthesis. Dearomatization reactions of phenols are of wide interest because of their potential for the preparation of cyclohexadienones, which often serve as structural cores prevalent in various biologically active natural products and pharmaceuticals, or as valuable synthetic intermediates.The enantioselective oxidative dearomatization of phenols and their analogues is a key reaction for the synthesis of several natural products. Oxidative Dearomatization has been nucleophilic or, electrophilic in nature as shown in figure-1. The basic step has been expected to go through a simultaneous nucleophilic addition to a cyclohexadienone intermediate. The driving force of the reaction is depends on the activating reagents, structural feasibility and cascade reaction sequence as shown in figure-2.

**Nu = nucleophilic oxygen/carbon** **E = electrophilic carbon**
**A = activating agent** **P = protective group**

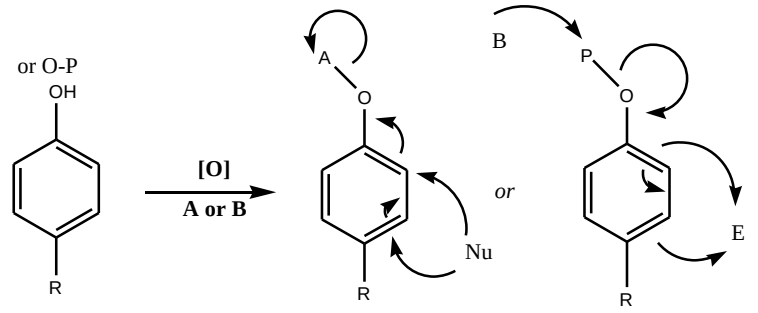



**Figure-1**

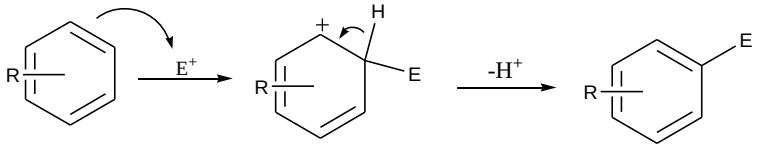



**Figure-2**

Till today, synthetic protocols towards Dearomatization reaction have been carried out using –

1. Enzymatic Catalysis
2. Thermal or photochemical catalysed
3. Transition metal catalysed
4. Hypervalent Iodine catalysed
5. Birch reduction or hydrogenation process as shown in figure 3.

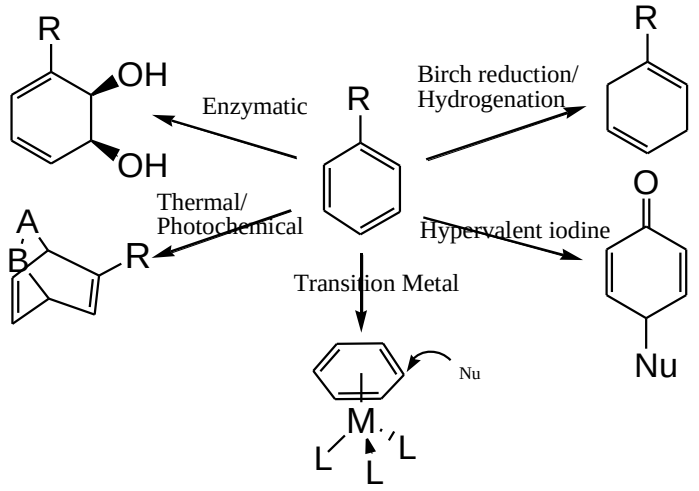



**Figure-3**

Recent years have seen great progress in the development of asymmetric hypervalent iodine reagents and catalysts for use in enantioselective oxidation dearomatization reactions. Highly effective hypervalent organoiodine catalytic method for the highly enantioselective oxidative dearomatization of phenols have been developed which in the presence of an appropriate external or internal nucleophile (Nu) leading to the respective cyclohexadienones. The mechanism of this reaction most likely involves the initial formation of the phenoxyiodine(III) followed by elimination of PhI and the generation of cationic phenoxenium intermediates which finally combine with the nucleophile (figure 4 and 5)[1a-d] .

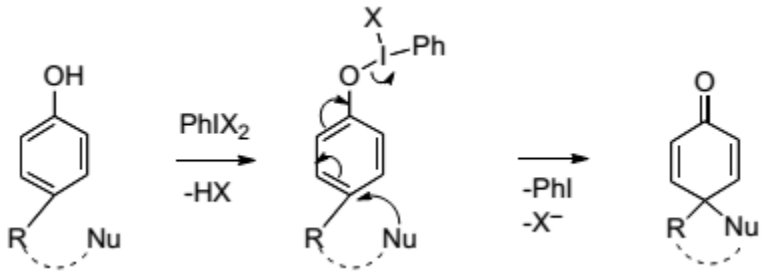



**Figure-4**

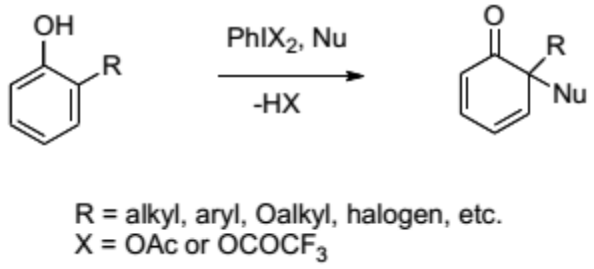
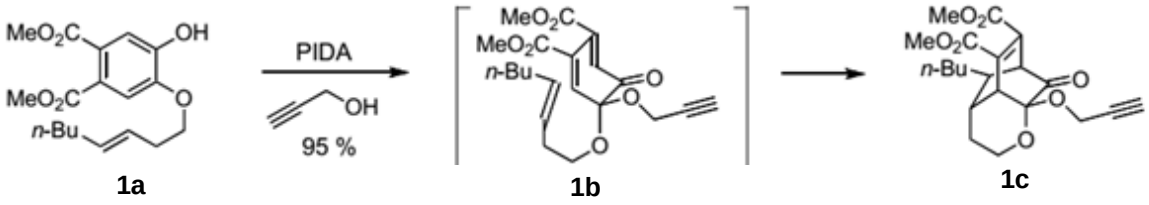



**Figure-5**

Various nucleophiles, such as water, alcohols, fluoride ion, carboxylic acids, amides, oximes, allylsilanes and electron-rich aromatic rings, have been used successfully in this reaction in either an inter- or intra-molecular mode.

Our synthetic strategy involves the idea of Wood's[8] work on intra-molecular cycloaddition prompted by oxidative dearomatization. Phenol(**1c**) upon oxidation with phenyliodo(III)diacetate (PIDA), forms a phenoxonium that is intercepted by propargyl alcohol to form the intermediate diene(**1b**), which undergoes a subsequent intramolecular Diels-Alder reaction to afford (**1c**).

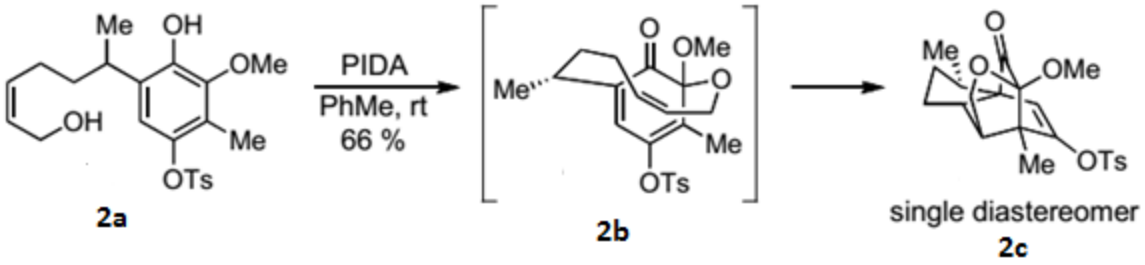



**1a** **1b** **1c**

**Scheme:1** Wood's oxidative dearomatization and intramolecular cycloaddition

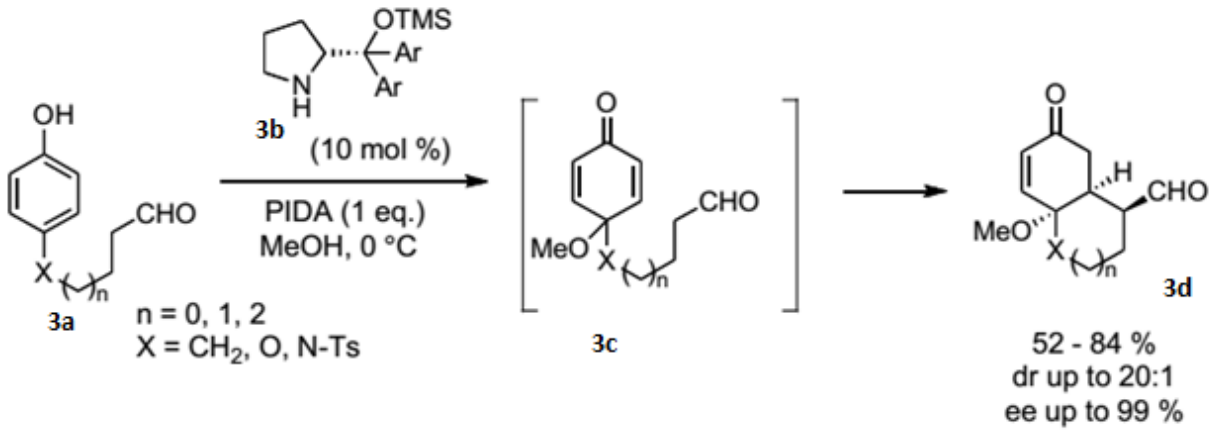
The oxidative dearomatization step may also proceed intramolecularly, as demonstrated by Danishefsky[9] in studies towards the synthesis of the sesquiterpenoid. Treatment of phenol **2a** with PIDA in toluene presumably affords the intermediate o-quinone acetal **2b,** which undergoes a transannular Diels-Alder reaction to give **2c** as a single diastereomer (Scheme ).

Interestingly, the benzylic stereocentre in **2a** controls the diastereofacial selectivity of the oxidative dearomatization step thereby securingthe stereoselectivityof the cycloaddition.




**Scheme:2** Danishefsky's oxidative dearomatization and transannular cycloaddition

The oxidative dearomatization of symmetrical p-substituted phenols results in the formation of meso-cyclohexadienones. Various two-step methods have been reported to desymmetrize these compounds into enantioenriched products. An impressive one-pot, catalytic protocol was reported by Gaunt[11] that makes use of a pyrrolidine catalysed intramolecular desymmetrizing 1,4-addition to themeso-intermediate . Phenolic substrates of type **3a** are treated with PIDA in the presence of pyrrolidine catalyst **3b** to afford the dearomatized dienone **3c** (Scheme 3 ). Subsequent enamine formationand Michael addition affords annulated products of type **3d**, many of which in high yield and stereoselectivity.

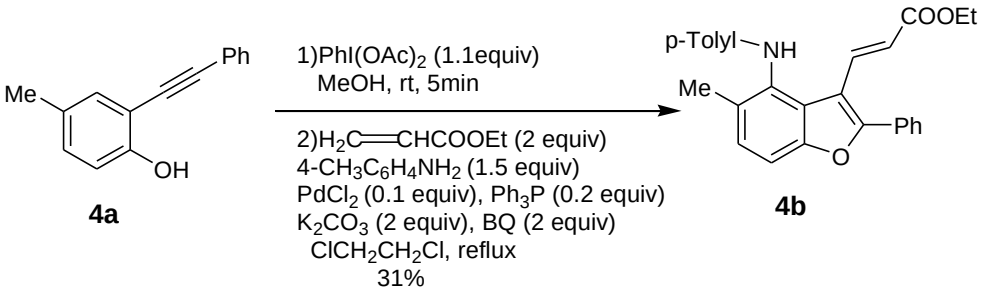



**Scheme:3** Gaunt's oxidative dearomatization and in-situdesymmetrization

Cyclization routes have been particularly attractive because of their inherent potential for achieving a rapid increase in skeletal complexity. A number of cyclization or cascade cyclization/cross-coupling reactions of 2-alkynyl-phenols have been developed. However, these elegant methods of cyclization only enable the synthesis of benzofurans with diverse substitutions on the five-membered ring. A direct conversion of 2-alkynyl-phenols to 3,4-

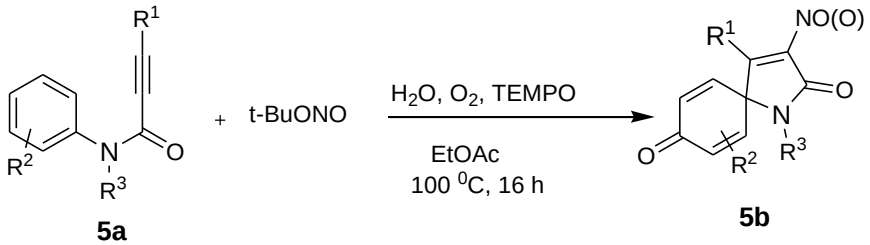
difunctionalized benzofurans (Scheme 4). This protocol involved an oxidative dearomatization to break the aromaticity of 2-alkynylphenols, a palladium-catalyzed domino reaction to simultaneously install two functional groups at C3 and the C4 positions, and an aromatization to restore the aromatization.

(Diacetoxyiodo)benzene facilitated oxidative dearomatization of 4-methyl-2-(2-phenylethynyl)phenol[13] **4a** in methanol. The Deleterious cyclization or oxidation of the sensitive alkynyl group was not observed. The crude dearomatization product was directly used to test the palladium-catalyzed domino reaction with p-toluidine and ethyl acrylate. When 0.1 equivalents of $PdCl_2$ were used together with 0.2 equivalents of $Ph_3P$, 4-amino-substituted 3-alkenylbenzofuran **4b** was obtained with 7% yield. Various oxidants were added to promote the regeneration of catalytic $Pd^{II}$ from $Pd^0$ formed in Heck coupling. Addition of 2 eq. of benzoquinone (BQ) improved the yield to 31%. Various Optimization have been to increase the yield upto 76%.




**Scheme 4**

Very recently, a new method for the nitrative spirocyclization of alkynes via alkyne insertion mechanism[14] has been reported. This method involves the oxidative difunctionalization of alkynes initiated by a radical attack pathway using *t*-BuONO (*tert*-butyl nitrite) combined with water as the nitro source and TEMPO [(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl] as the initiator, and it represents a new example of oxidative alkyne difunctionalization *via* the formation of C—N/C—C bonds for the assembly of nitroalkene unit-containing spirocycles.

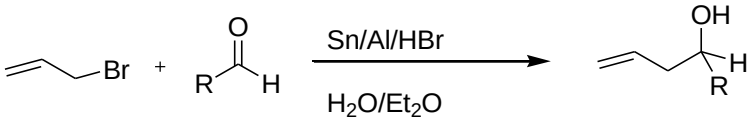



**Scheme 5**

Thus, we have put effort to cyclize 3-alkynylphenol system to form C-C bond formation via intra-molecular oxidative dearomatization in the presence of coupling partner (a nucleophile). The substrate having terminal alkyne was obtained by following Metal mediated Barbier Grignard reaction. The following Barbier Grignard processes are:

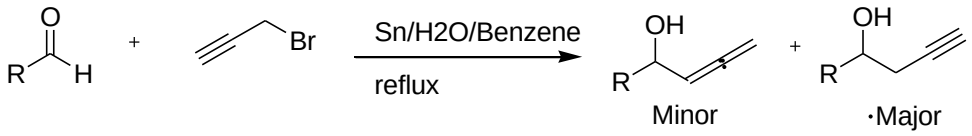
I) Mediated by Tin:

In 1983, Nokami et al. observed an acceleration of reaction rate during the allylation of carbonyl compounds with diallyltin dibromide in ether through the addition of water to the reaction mixture. In one case, by use of a 1:1 mixture of ether/water as solvent, benzaldehyde was alkylated in 75% yield in 1.5 h, while the same reaction only gives less than 50% yield in a variety of organic solvents, such as ether, benzene, or ethyl acetate, even after a reaction time of 10 h. The reaction was equally successful with a combination of allyl bromide, tin metal, and a catalytic amount of hydrobromic acid (Scheme 6). In the latter case, the addition of metallic aluminum powder or foil to the reaction mixture dramatically improved the yield of the product. The use of allyl chloride for such a reaction, however, was not successful.




**Scheme 6**

The reaction of propargyl bromide with aldehydes mediated by tin in water generated a mixture of propargylation and allenylation products (Scheme 7). The selectivity in product formation is rather low.

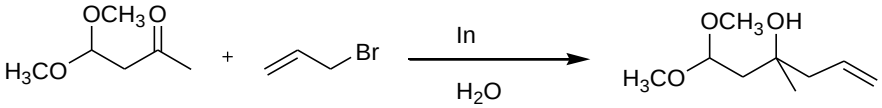



**Scheme 7**

II) Mediated by Indium:

When the allylation was mediated by indium in water, the reaction went smoothly at room temperature without any promoter, whereas the use of zinc and tin usually requires acid catalysis, heat, or sonication. An organic co-solvent is not necessary either. The mildness of the reaction conditions make it possible to use the indium method to allylate a methyl ketone 3 6 in the

presence of an acid sensitive acetal functional group (Scheme 8). Attempts to achieve such transformations with zinc and tin have not been successful.



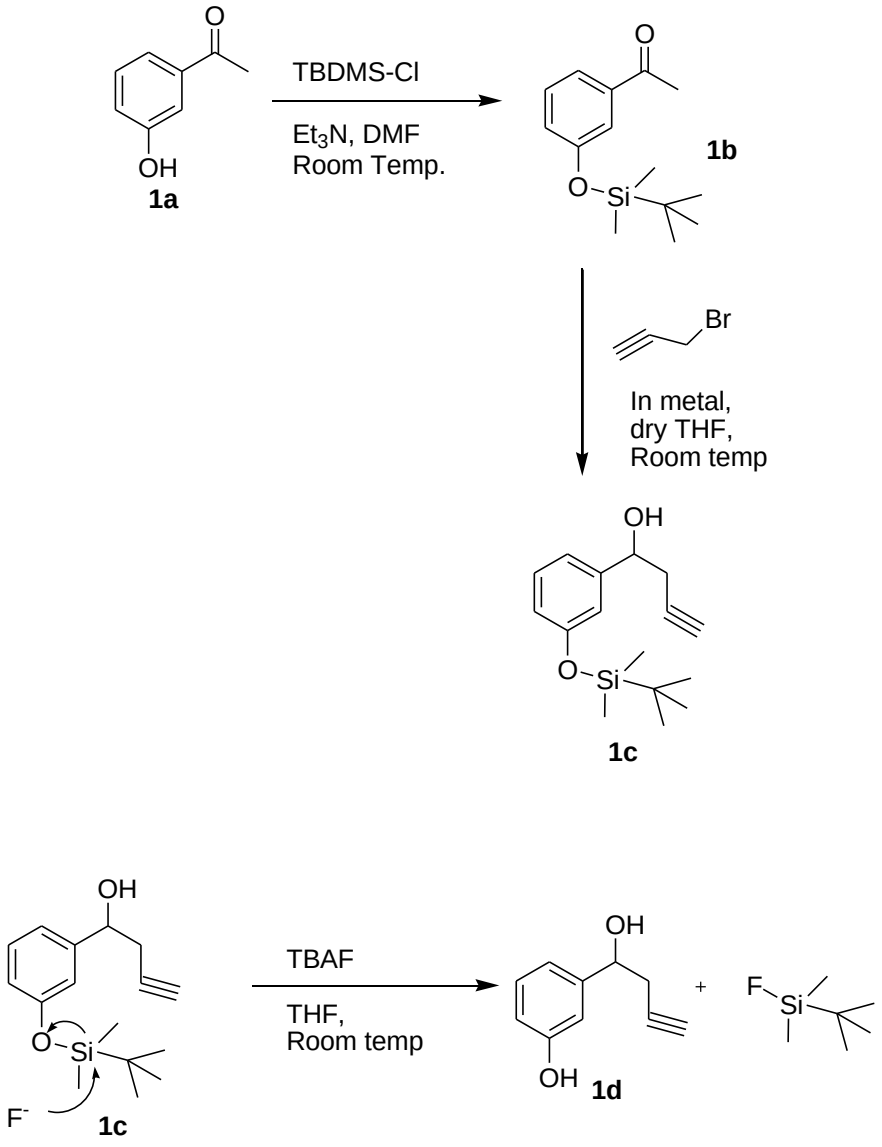

**Scheme 8**

| **M(Metal)** | **Yield, %** |
|---|---|
| Zn | 0 and destruction of starting materials |
| Sn | 10 (under sonication) |
| In | 70 |

Using indium-copper or indium-silver as radical initiator, Barbier-Grignard-type alkylation reaction of aldehydes with unactivated alkyl halides proceeded efficiently in water to give the desired products in moderate to good yields. Among the several metals tested, indium proved to be the best metal for this transformation than zinc, aluminum, tin etc. Without CuI or AgI, the reactions proceeded sluggishly to give the desired products in poor yields.

## Results and Discussion:

In the present work, we have synthesized the substrate 3-(1-hydroxybut-3-ynyl)phenol(**1d**) as a precursor compound. The following procedure is followed for the synthesis of 3-(1-hydroxybut-3-ynyl)phenol(**1d**).




**Scheme 1**

In the above reaction scheme, m- Hydroxy Benzaldehyde (1 eq.) **1a** was dissolved in DMF followed by the addition of triethyl amine(1.5 eq) in an inert atmosphere . The reaction mixture was allowed to stir for some time at room temperature, then *tert*-Butyldimethylsilyl chloride(TBDMS-Cl)(1.5 eq.) was added to the reaction mixture for protecting the phenolic –OH group to obtain **1b** with the yield of 80%. The protection process was completed in around 18 hours.

Then the silyl protected system **1b** was reacted with propargylic bromide via Indium-mediated Barbier Grignard mechanism. In this reaction, Indium metal(1.2eq) was taken in dry THF followed by the addition of propargylic bromide(1.2 eq.) in an inert atmosphere. The reaction mixture was then left to stir for 1-2 hours at room temperature, grey colour precipitate indicates the formation of grignard. Then compound **1b** was added to the reaction mixture. Here catalytic amount of KI was added to increase the reactivity of In-metal**.** The completion of reaction was confirmed by TLC (thin layer chromatography) that took approximately 18 Hrs.. The yield of the product obtained was 65% (**1c**).

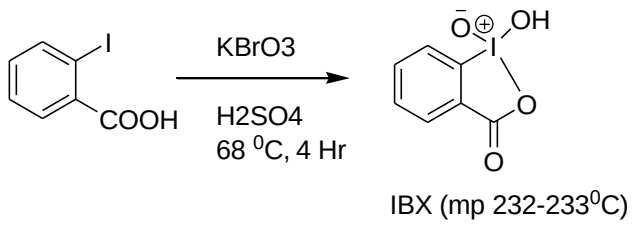
Then deprotection of **1c** was done using TBAF (tert-butylammonium fluoride). For this substrate **1c** was dissolved in THF and allowed to stir for some time, then TBAF was added to the solution. The reaction mixture then was left to stir for 10-12 hours at room temperature. The product **1d** obtained was confirmed by TLC and the yield was 70%.

The product **1d** acted as a precursor compound which in the presence of heptavalent iodine catalyst ($I^{3+}$ or $I^{5+}$) were thought to go for cyclization process. The cyclization process involved alkyne insertion for C-C bond formation in the presence of a nucleophile (MeOH). For Cyclization process, hypervalent iodine complexes were prepared.

## HYPERVALENT IODINE COMPLEXES:

## IBX Preparation:

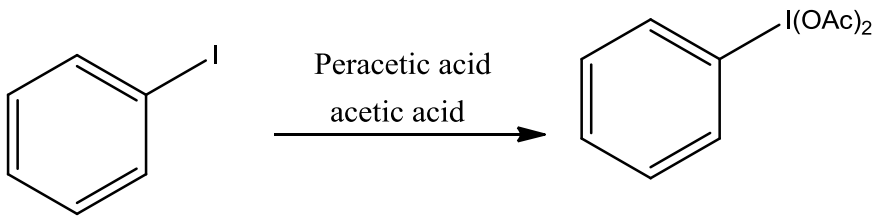
0.89gm of $KBrO_3$ was added over 0.5 hour to a vigorously stired mix of 2-iodobenzoic (1 gm) and17 ml of 0.73 M $H_2SO_4$ in 55 °C bath. The mix was stirred for 4 hours at 68 °C and then coled with an ice bath. The solid obtained was filtered and washed with 16.44 ml of $H_20$ and 5 ml of ethanol and yield was 93%.




IBX (mp 232-233$^0$C)

**Scheme 2**

# PIDA Preparation:

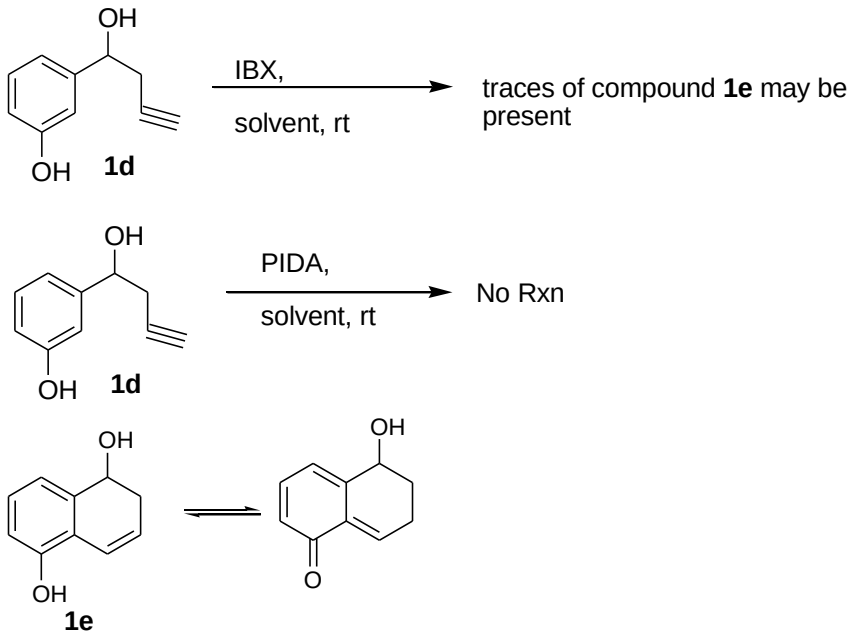



**Scheme 3**

The apparatus consists of a 200-ml. beaker equipped with a magnetic stirrer or any other type suitable for stirring a small volume of liquid. The flask is charged with 0.10 mole of iodobenzene and is immersed in a water bath maintained at 30°C. 0.24 mole of commercial 40% peracetic acid is added dropwise to the well-stirred iodobenzene over a period of 30–40 minutes. Stirring is continued for another 20 minutes at a bath temperature of 30°C, during which time a homogeneous yellow solution is formed. Crystallization of iodosobenzene diacetate may begin during this period.

The beaker is chilled in an ice bath for 1 hour. The crystalline diacetate that separates is collected on a Büchner funnel and washed with three 20-ml. portions of cold water. After drying for 30 minutes on the funnel with suction, the diacetate is dried overnight in a vacuum desiccator containing calcium chloride. The dried diacetate weighs (83–91%) and melts at 158–159° with decomposition.

Here, in the last step alkyne insertion for cyclization process was tried in different conditions. Reacting **1d** with PIDA(phenyl iododiacetate ) in THF and DCM, we did not get any result, but when **1d** was tried with IBX complex in THF, crude NMR roughly indicates **1e** as we could not isolate it and get the satisfactory results. The compound seems quite unstable in nature.

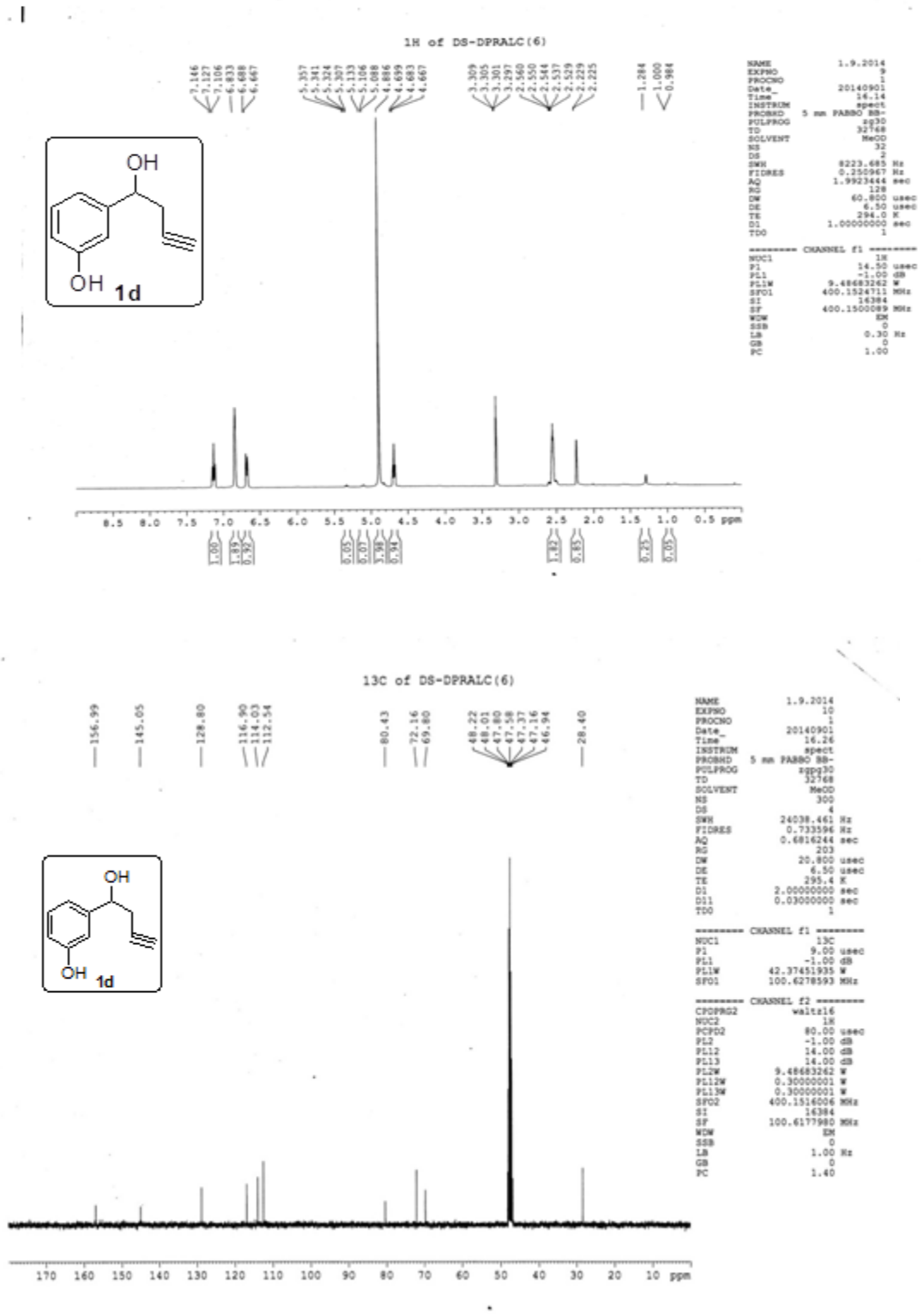


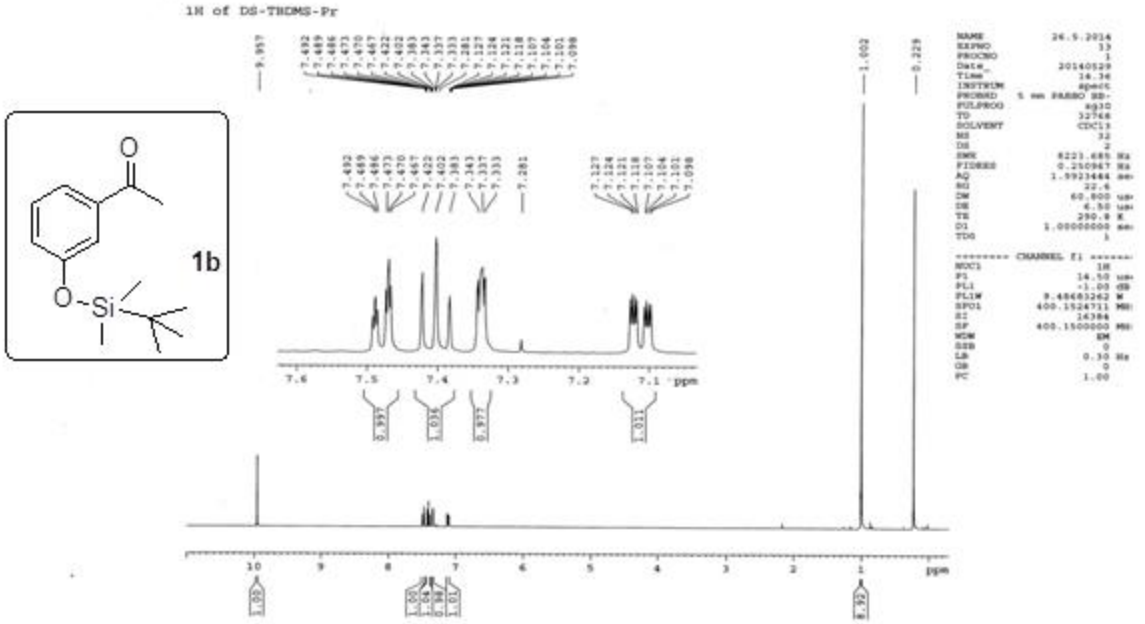

1,2-dihydronaphthalene-1,5-diol

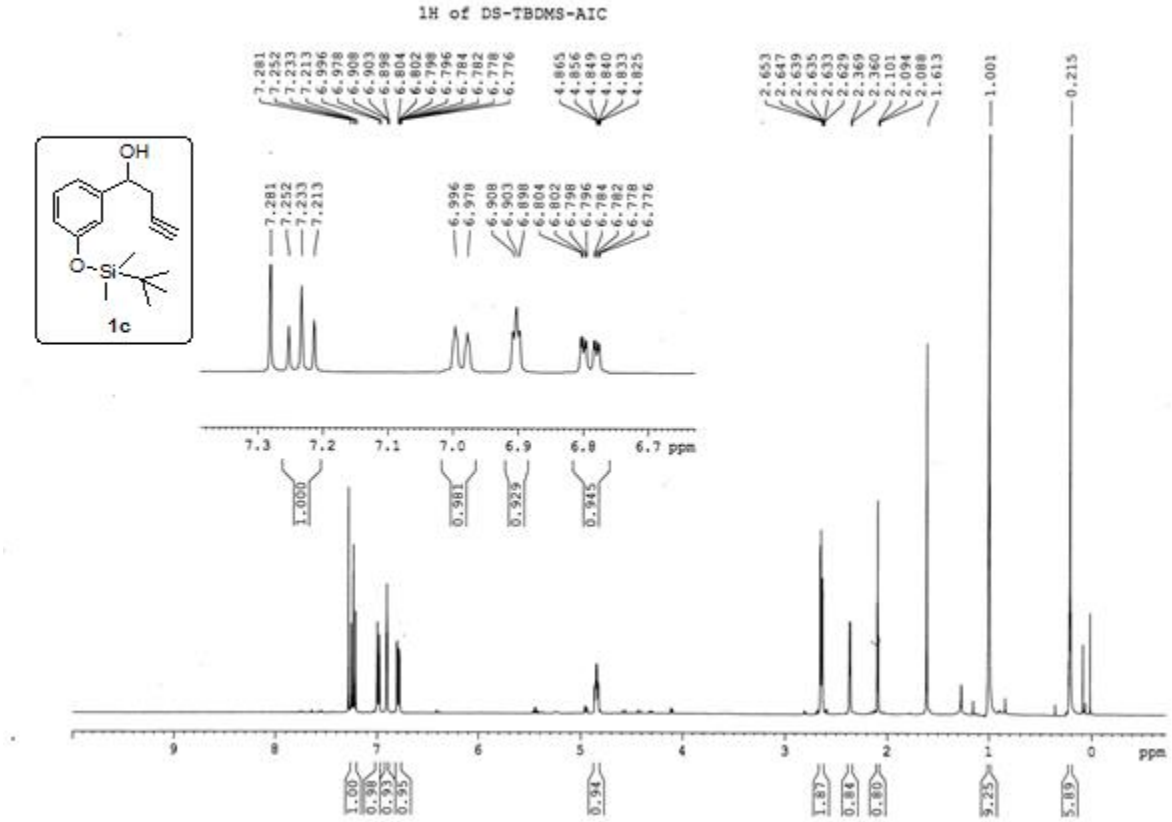
## Experimental section:

Analytical thin layer chromatography (TLC) was carried out using silica gel 60 $F_{254}$ pre-coated plates. Visualization was accomplished with UV lamp or $I_2$ stain. Silica gel 230-400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all reagents were purified prior to use following the guidelines of Perrin and Armerego.[14] All commercial reagents were used as received. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, $\delta$) relative to tetramethyl silane ($\delta$ 0.00). $^1$H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded at 125 MHz. Mass spectra (MS) were obtained using ESI mass spectrometers. IR spectra were recorded as neat for liquid and in KBr for solids. Melting points were determined using a hot stage apparatus and are uncorrected.

# Selected NMR Spectra:




1H of DS-TBDMS-Pr
1b


1H of DS-TBDMS-AIC
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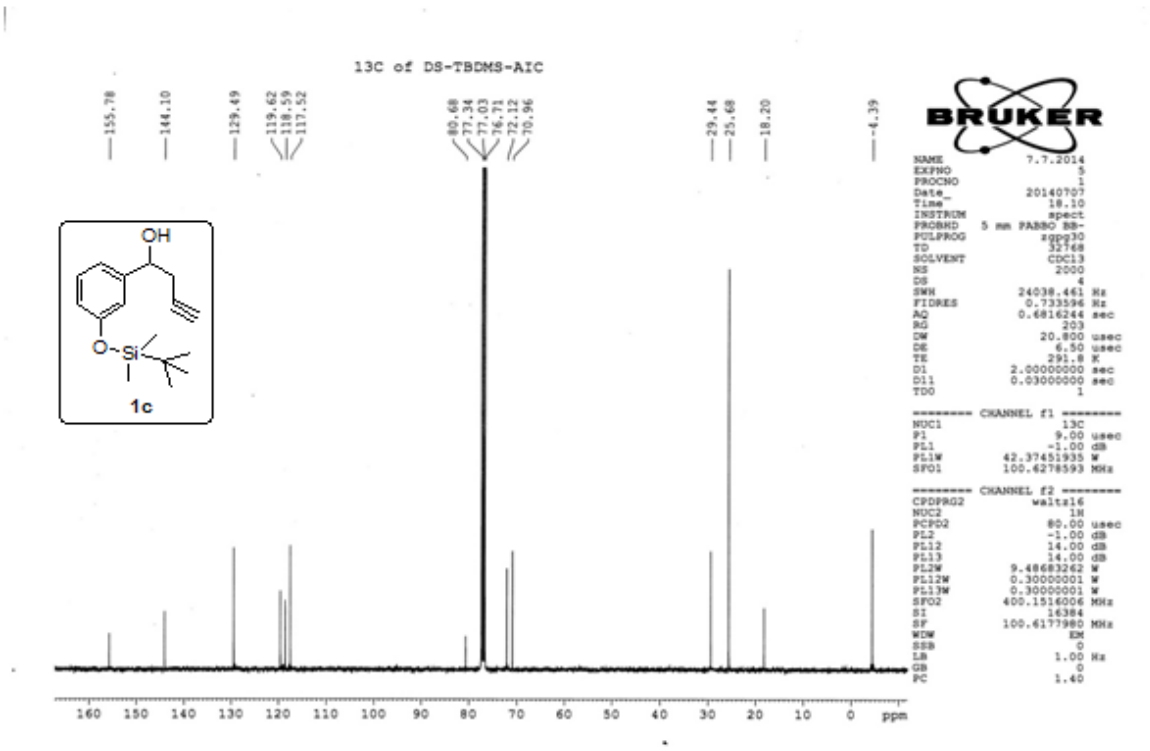


# Conclusion:

Synthesis of 1,2-dihydronaphthalene-1,5-diol have been tried using $I^{3+}$ and $I^{5+}$ complexes taking 3-(1-hydroxybut-3-ynyl)phenol as a precursor compound employing intramolecular oxidative dearomatization via alkyne insertion. All the synthesized products are monitored using TLC and Column Chromatography and confirmed by NMR data.

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