4. Introduction:

The addition of oxygenated species to an activated or inactivated carbon centre represents a synthetically powerful and straightforward access towards carbon-oxygen bond formation reactions. The stated area of reaction includes varieties of synthetic methodologies including hydroxylation, *o*-arylation, epoxidation etc. which have attracted a great deal of interest in recent decades due to their immense applications in the field of pharmaceuticals, material science etc. However, in the present thesis we only focus on hydroxylation reaction to synthesize phenols and its derivatives.

Phenols and its derivatives are considered as ubiquitous structural scaffold present in many natural products such as amino acids, coal tar, flavonoids and hormones [1]. In addition, they are potential pharmacological agent having antitumour, antiviral, anticardioprotective and antimutagenicity activities [2]. Phenol was first discovered in 1834 by Runge who isolated several components from coal tar [1]. The isolation of phenols from natural product was a very tedious process and the yield was also very low. In 1849, Hunt developed the first synthetic protocol to synthesize phenols from diazonium salt [1]. In 1860, it was Griess who reported another synthetic method to produce the same from aromatic diazo compound [1]. The synthesis of phenolic compounds from benzene sulphonic acid was reported by F. A. Kekule in 1867 [3]. Later, Dow and Bayer developed a synthetic methodology which utilized aryl halide as a precursor [1]. In their method, first chloro benzene was synthesized by chlorinating benzene, then it was hydrolyzed with NaOH followed by acidification with HCl to obtain the desired product. But, the demerits of the method is that only small fraction of halide was transformed to phenol even at 360 ˚C and 300 atm pressure. Aryl halide was also used by Rashig and Hooker as a synthon to produce phenol by oxychlorination method [4], in which the chlorobenzene was hydrolyzed over calcium phosphate catalyst and with steam under a high pressure of 400-450 atm. In 1950, a fascinating protocol was developed which suppressed the other technologies to synthesize phenols and was widely used in both industrial and academic sectors for many years. In this method, benzene was first transformed to cumene by Friedel Crafts alkylation with propene in presence of phosphoric acid, aluminium chloride and sulphuric acid. The resulting product was oxidized in presence of air/oxygen at high temperature to get the corresponding phenol [5]. Benzene sulphonate method [2] was developed in 1978 which involved sulphonation

of benzene followed by neutralization with sodium sulphite resulting sodium salt of benzene sulphonic acid and acidification of the salt yielded the corresponding phenol.

Although the discussed methods are used for the synthesis of phenol from different starting materials, yet most of the methods are found to be incompetent towards their practical application because the methods have some drawbacks like involvement of harsh reaction conditions, low yields of the product, formation of excess byproducts etc. Moreover, the functionalized phenol cannot be easily synthesized by these methods. In 1999, Hartwig and co-worker reported palladium complex catalyzed efficient hydroxylation of aryl halides [6] with KOH. Later, Buchwald and Chan introduced bulky tri-*tert*-butyl phosphine and biphenylphosphine ligands for Pd catalyzed direct hydroxylation of aryl halides [7] using KOH as hydroxyl source. In 2009, a competent imidazole based-Pd complex catalyzed protocol for hydroxylation of aryl halide was demonstrated by Beller and co-worker [8]. An iridium catalyzed hydroxylation method to synthesize phenol was described by Smith and co-workers. The procedure involved one pot, aromatic borylation followed by oxidation [9]. In recent times, copper catalyzed synthetic protocols have also been developed for the synthesis of phenols. On the other hand, it was noticed that high temperature and ligand associated reaction condition are the major requirement when aryl halide was taken as starting material for the transformation. So, considerable attention has been devoted to develop some efficient alternative strategies eliminating the drawbacks of existing methodologies.

During the last decades, arylboronic acids come out to be an excellent alternative synthon for the synthesis of phenols which are associated with numerous advantages such as higher stability, wide availability, safe to handle and large functional group tolerance etc. Moreover, it is considered as less toxic than other organometallic compounds. The first transformation of arylboronic to phenol was reported by Ainley and challenger with alkaline H_2O_2 and later it was modified by Kuvila [10]. Although the reaction pathway was green, yet electron withdrawing group substituted arylboronic acids furnished lower yields and led some unwanted side-products. In 1955, Webb and Levy [11] reported a quick hydroxylation of arylboronic acid using potassium peroxomonosulphate as an oxidizing agent in aqueous acetone (**Fig. 1**), but the protocol was found to be imperfect towards wide substrate scope.

In water, H_2O_2 mediated protocol without using any additive was reported by Surya Prakash [12] and his co-workers in 2001 which encompassed transformation of a variety of arylboronic acids to phenol (**Fig. 1**).

A simple methodology was developed by Kianmeher and his co-worker which utilized cheap and easily available NH_2OH [13] in alkaline medium (**Fig. 1**).

A regioselective synthesis of phenol from arylboronic acid was reported by Surya Prakah and co-worker utiliziling poly-*N*-Vinylpyrrolidone/H_2O_2 and poly-4-vinylpyridine/H_2O_2 as catalyst for the desired transformation [14] (**Fig. 1**).

Fuchigami *et al.* developed an electrochemical cathodic hydroxylation of arylboronic acid under oxygen atmosphere [15] (**Fig. 1**). The superoxide ion formed at cathode was the driving force for the transformation.

A room temperature Cu catalyzed transformation [16] of arylboronic acid to phenol was reported by Wang *et al.* in presence of strong base KOH (**Fig. 1**). The catalytic protocol involved $CuSO_4$ as the catalyst and 1,10-phenanthroline as ligand in water which was applicable towards a wide range of structurally diverse arylboronic acids.

In 2011, a phosphine based palladium complex was utilized [17] in the transformation of arylboronic acid to phenol under oxygen atmosphere (**Fig. 1**).

A visible light mediated synthesis of phenol from arylboronic acid was developed by W. J. Xiao and his co-workers using air as oxidant and $[Ru(bpy)_3Cl_2]^.6H_2O$ as catalyst in presence of *i*Pr$_2$NEt in DMF [18] (**Fig. 1**).

Yokomatsu and co-workers reported [19] a simple and efficient protocol for this transformation using copper (II)-β-cyclodextrin, a dinuclear complex at room temperature in water.

A thiol promoted hydroxylation of arylboronic acid to phenols [20] was developed by Kaewmati *et al.* under metal free conditions (**Fig. 1**) which required high temperature for efficient transformation.

Utilization of surfactant as enhancer in a copper catalyzed *ipso*-hydroxylation of arylboronic acid to phenol was reported by Inamoto *et al.* which needed $CuCl_2$ as catalyst and Brij-s-100 as surfactant under oxygen atmosphere at room temperature [21] (**Fig. 1**). The efficiency of *N*-oxide as oxidant for this transformation at room temperature in DCM was reported by Zhu and co-workers [22] (**Fig. 1**).
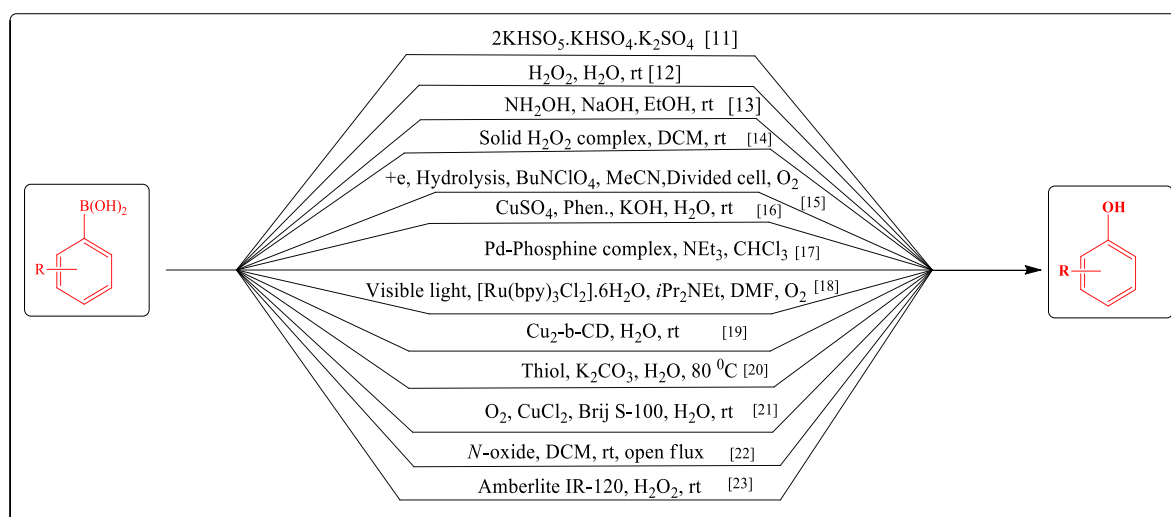
Fig. 1: *Ipso*-hydroxylation of arylboronic acid to phenol

Mulakayala [23] and co-workers reported an efficient method for this transformation using Amberlite IR-120 resin as heterogeneous recyclable catalyst and H_2O_2 as oxidant (**Fig. 1**).

A TBHP [24] mediated synthetic protocol was also developed in alkaline medium which transformed arylboronic acid easily to phenol at room temperature (**Fig. 2**).

Boruah [25] (**Fig. 2**) and co-workers developed an efficient methodology which involved sodium chlorite as an oxidant eliminating H_2O_2, transformed boronic acids and boronate esters easily to corresponding phenols within short reaction time.

Our group also developed a number of convenient protocols for the synthesis of phenols using H_2O_2 and some additives within short reaction time, *viz.* H_2O_2-I_2 [26] (**Fig. 2**), H_2O_2-alumina [27] (**Fig. 2**), H_2O_2-AgNPs@K10 [28] (**Fig. 2**), H_2O_2-boric acid [29] (**Fig. 2**) etc. are the effective catalytic system. At the same time, Gohain [30] (**Fig. 2**) *et al.* reported H_2O_2-PEG catalyzed method for the same transformation within short reaction time.

Very recently, Chetia and co-workers reported two natural base promoted room temperature methodologies for *ipso*-hydroxylation of arylboronic acids in presence of H_2O_2 in water. They have used "water extract of rice straw ash" [31] (**Fig. 2**) and "water extract of banana peel ash" [32] (**Fig. 2**) as the source of base. The ash components contain some active metal ion species like Na, K, Ca etc. which on dilution forms hydroxides of the corresponding ions.

From the above discussions, it can be predicted that lots of new modifications have been achieved for *ipso*-hydroxylation of arylboronic acids. But, most of the protocols are accompanied by the utilization of strong acid or base. Thereby, researchers are paying more interest to develop new methodologies using either acid/base free condition or very mild acidic condition.
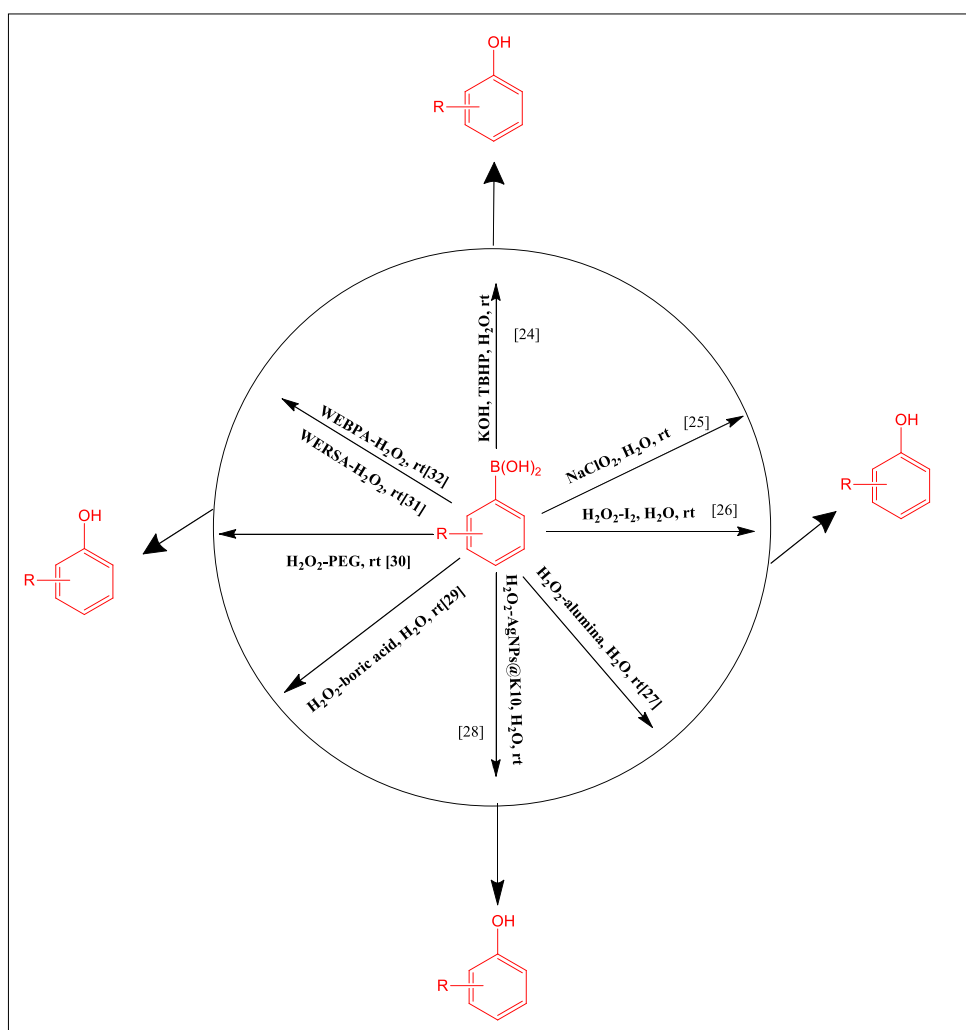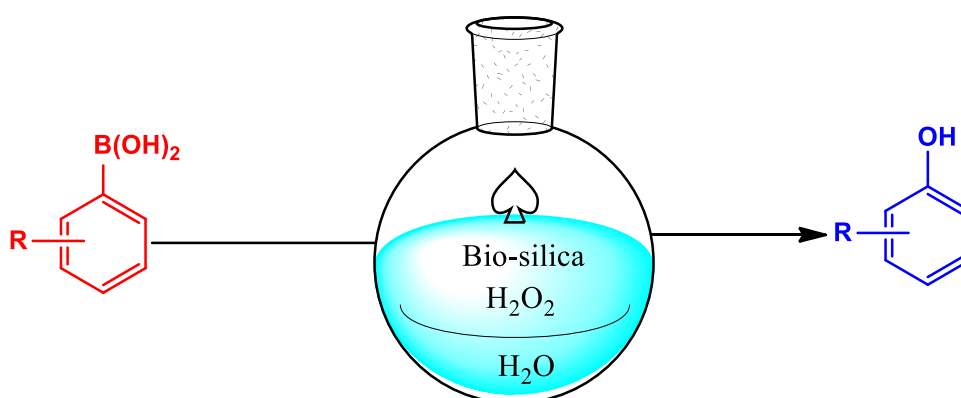

Fig. 2: *Ipso*-hydroxylation of arylboronic acid to phenol

CHAPTER 4
Section 4.1

A mild and efficient *ipso*- hydroxylation of arylboronic acid catalyzed by bio-silica

R= H, 4-Me, 4-OMe, 4-CHO, 2-Me, 3-CN, 4-*t*Bu etc.

Water as solvent
No ligand, no heat
Easily available reusable catalyst
Minimum amount of mild oxidizing agent
No transition metal

The work described in this section has been published in *Tetrahedron Letters*, 2015, *56*, 1780-1783.

4.1. A. Introduction:

During last few decades, 'Green Chemistry' is a primary issue taken into consideration when a new synthetic methodology is designed and developed. Hence, nowadays, chemists are paying more attention towards the development of environment friendly, clean and safe methodologies which involve inexpensive chemical reagents/catalysts and also associated low E-factor [33], high atom economy to reduce the generation of waste product(s). In the challenging era of chemistry, innovation of a new synthetic protocol becomes inefficient without the approach of green chemistry as the same deals with no pollution or environmental risks. Considering all the above factors, development of catalyst which is environment friendly, air and moisture stable, inexpensive and can enhance these reactions under mild reaction condition is a topic of great interest. In this respect, bio-silica (diatomaceous earth (DE) or diatomite) [34] is a natural, inert and stable matrix, considered as a prospective green alternative in organic synthesis. Bio-silica is a porous inorganic material with large surface area having hydroxyl groups on the surface. The main constituents of bio-silica are (87–91%) SiO_2, small quantities of Fe_2O_3 and Al_2O_3 [35]. It is mainly used as catalyst support, filter, adsorbent, insulating material etc. Bio-silica is also the main mineral component of the sponge skeletal element, commercially available in different forms and varies in shape, particle size, and porosity. Bio-silica is considered as non-toxic material which has a great capacity to absorb water owing to its surface property [36].

On the other hand aqueous hydrogen peroxide is a well-known environmentally acceptable, stoichiometric oxidant and shows a high efficiency per weight of the oxidant [26].

In the present study, we wish to report a mild protocol for *ipso*-hydroxylation of arylboronic acid with excellent yield and short reaction time, which utilizes bio-silica as a reusable, heterogeneous catalyst and aqueous H_2O_2 as an oxidant.

4.1. B. Experimental:

General information:

^{1}H and ^{13}C NMR spectra of the products were recorded in a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Chemical shift values are expressed in ppm. Coupling constants are expressed in Hertz. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F$_{254}$ (Merck). UV light and Iodine vapour were used as visualizer. Chemicals are obtained from commercial source. Bio-silica was purchased from Renkem chemicals having components silica, alumina and iron oxide.

General procedure for the hydroxylation of phenol:

In a 50 mL round-bottomed flask, a mixture of arylboronic acid (1 mmol), H$_2$O$_2$ (30% aq, 0.2 mL), bio-silica (5 mg) and 2 mL of water was added and stirred at room temperature in aerobic condition. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was diluted with 20 mL of water and extracted with (3×20) mL of diethyl ether and the combined organic layer was washed with brine and dried over by Na$_2$SO$_4$ and evaporated in a rotary evaporator under reduced pressure. The crude was purified by column chromatography (hexane/ethylacetate, 9:1) on mesh silica (100–200) to get the desired product. The products were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy and mass spectrometry.

4.1. C. Results and discussion:

Initially, we started our *ipso*-hydroxylation protocol by examining the effectiveness of H$_2$O$_2$ (30% aqueous) in the oxidative hydroxylation reaction choosing phenylboronic acid as the model substrate. At first, only H$_2$O$_2$ (2 mL) was used to carry out the reaction at room temperature and 57% of phenol was detected as the only product in 24 h (Table 1, Entry 1). However, use of bio-silica as a catalyst for the reaction furnished better yield (76%) of the product (Table 1, Entry 2). During the course of the reaction we came across solubility problem and a sticky reaction mass was observed in the reaction vessel under solvent free conditions. Hence, to overcome this problem we have performed the reaction

using 2 mL of water (as solvent) and observed an excellent conversion to phenol (Table 1, Entry 3). In the next attempt, the effect of different solvents in the reaction system was also observed and results are summarized in Table 1 (Entries 3–10). Smooth progress of the reaction was observed in both protic and aprotic solvents though significant variations in yields were noticed. We observed maximum yield of the reaction when water was used as a solvent. Further, we tried the same reaction in 50% aqueous MeOH, MeCN, THF and it provided good results in the case of 50% aqueous MeOH and aqueous MeCN (Table 1, Entries 8 and 9) compared to aqueous THF (Table 1, Entry 10). From this screening result, we observed the best results in case of water as solvent (Table 1, Entry 3).

Table 1. Optimization of reaction condition for bio-silica catalyzed *ipso*-hydroxylation of Phenylboronic acid[a]

$$\text{C}_6\text{H}_5-\text{B(OH)}_2 \xrightarrow[\text{H}_2\text{O (2 mL), rt}]{\text{H}_2\text{O}_2 \text{ (30\% aq, 2 mL), bio-silica (50 mg)}} \text{C}_6\text{H}_5-\text{OH}$$
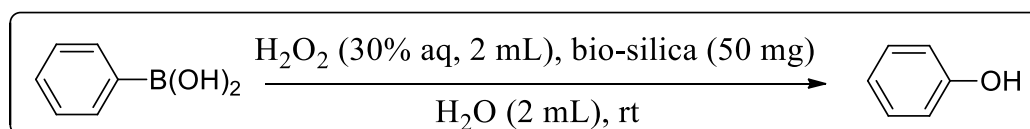
Entry	Catalyst (mg)	Solvent (2 mL)	Time (min)	Yield (%)[b]
1	None	Water	1440	57
2	Bio-silica	None	45	76
3	Bio-silica	Water	0-5	93
4	Bio-silica	Methanol	0-5	90
5	Bio-silica	Acetonitrile	15	87
6	Bio-silica	THF	25	70
7	Bio-silica	DCM	15	89
8	Bio-silica	Methanol:Water (1:1)	10	90
9	Bio-silica	Acetonitrile:Water (1:1)	15	90
10	Bio-silica	THF:Water (1:1)	25	80

[a]Reaction condition: Phenylboronic acid (1 mmol), H_2O_2 (30% aq., 0.2 mL), bio-silica (50 mg) unless otherwise noted. [b]Isolated yield

Triggered by these motivating results, in the next assessment, we planned to optimize the amount of catalyst and oxidant. Initially, the reaction was examined with different amounts of the catalyst; using 2 mL of H_2O_2 and found that 5 mg of the catalyst delivered efficient conversion of 1 mmol of starting material to the desired product (Table 2, Entries 4 *vs* 5). In the next, we tried to optimize the amount of oxidant taking 5 mg of

catalyst which resulted 0.2 mL of the oxidant was adequate to convert 1 mmol of the phenylboronic acid to phenol (Table 2, Entries 8 *vs* 9).Nevertheless, the reaction did not proceed in absence of either bio-silica or the oxidant H_2O_2.

Table 2. Screening of the reaction for the amount of catalyst and oxidant in *ipso*-hydroxylation of phenylboronic acid[a]
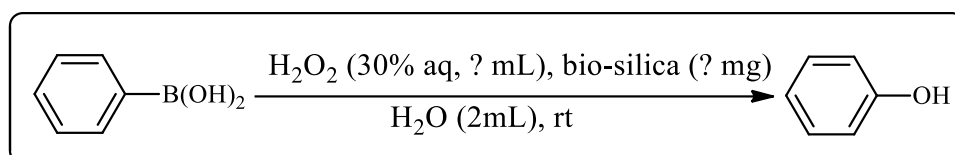
Entry	Amount of catalyst (mg)	Amount of oxidant (mL)	Conversion
1	50	2	Full
2	30	2	Full
3	10	2	Full
4	5	2	Full
5	3	2	Incomplete
6	5	1	Full
7	5	0.5	Full
8	5	0.2	Full
9	5	0.1	Incomplete

[a]Reaction condition: Phenylboronic acid (1 mmol)

After gaining such an excellent result, we extended the optimized reaction conditions to a wide variety of electronically diverse arylboronic acids to explore the scope and limitations the current procedure using bio-silica and hydrogen peroxide (Table 3). It was observed that the position of the substituent and the electronic nature had little effect on the reaction process. Both electron donating and withdrawing group substituted phenylboronic acids like Me, Et, OMe, F, Cl etc. afforded good to excellent yields. Additionally, hetero aryl as well as sterically hindered boronic acids also undergo easy transformation with high percentage yield (Table 3, Entries 10–13). The Results are summarized in the Table 3.

Table 3. Synthesis of phenol catalyzed by bio-silica[a]
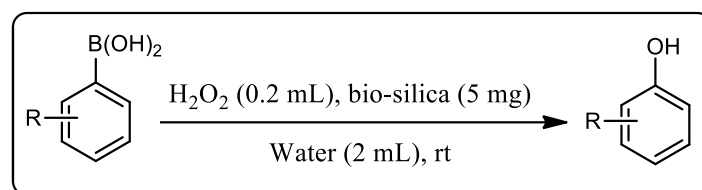
Entry	R	Time (min)	Yield (%)[b,c]
1	H	0-5	93
2	4-OMe	5	92
3	2-Me	5	90
4	3-Me	5	89
5[d]	4-CHO	10	90
6	4-Cl	5	92
7	4-F	5	93
8[e]	3-CN	10	88
9	4-Et	5	87
10[d]	4-*tert*-butyl	20	88
11	2,4-diflouro	10	91
12	3-triflouromethyl	10	92
13	3-methoxy-5-pyridine	20	89

[a]Reaction conditions: Phenylboronic acid (1 mmol), biosilica (5 mg), H_2O_2 (30% aq, 0.2 mL), water (2 mL). [b]Isolated yield. [c]All compounds are characterized by ^1H NMR, ^{13}C NMR. [d]1 mL of ethanol was added. [e]1mL of H_2O_2 was added.

A plausible mechanistic pathway has been proposed for the *ipso*-hydroxylation of arylboronic acid to phenol (**Fig. 1**). It is assumed that, at first, bio-silica reacts with H_2O_2 and forms a silica-peroxide composite [**(i)** in the **Fig. 1**] which then reacts with the starting material phenylboronic acid to form an adduct (A) which then upon rearrangement and consequent water loss, produced the adduct B, which upon hydrolysis produce phenol.

Mechanism of the reaction:
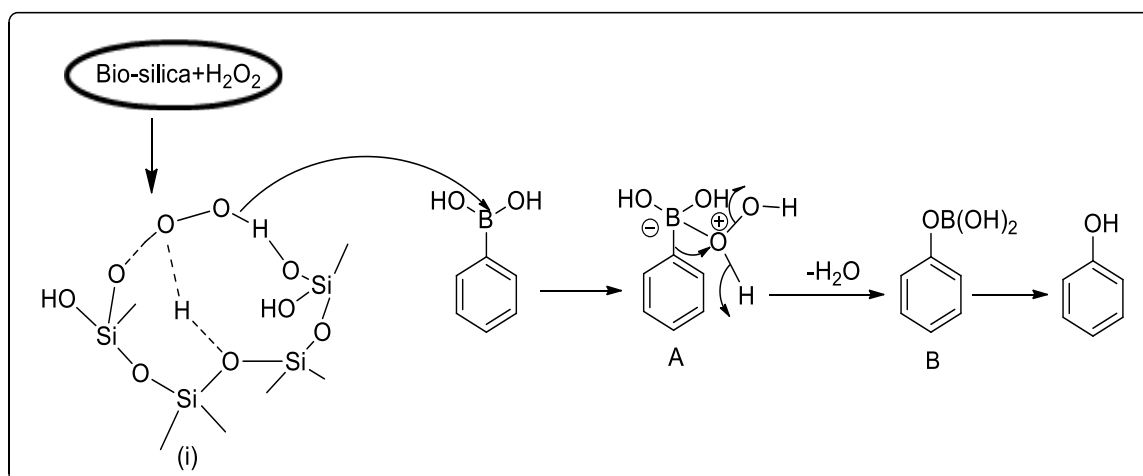
Fig. 1. Proposed mechanistic pathway for the synthesis of phenol

The reusability of a catalyst is a great benefit in the cost reduction of process chemistry. As a result, the reusability of the catalyst was investigated. For that, we carried out the hydroxylation of phenylboronic acid taking 1 mmol of the substrate under the optimized reaction conditions. After completion of the first run, the catalyst, bio-silica was filtered and washed with diethyl ether followed by water. The recovered catalyst then allowed drying in an oven overnight (100 °C) which was used for further reaction. To our delight, the catalyst remained efficient and the reaction provided almost constant yields up to sixth run (Table 4, Entries 1–6).

We investigated the green-ness of our protocol by using the parameters of green chemistry such as atom-efficiency, E-factors etc. and compared these parameters with some reported methods and interestingly got better result than the others (**Table 5**).

Formulae for the calculation of the green matrices

Mass-intensity= Total weight of reactants and byproducts /weight of main product.

E-factor=Total weight of reactants-total weight of products and byproducts /weight of the main product.

Atom economy=Mass of atoms in the desired product $\times$ 100% /Mass of atoms in reactants.

Atom efficiency=Atom economy × percentage yield of the reaction.

Table 4. Reusability of the catalyst in the synthesis of phenol[a]
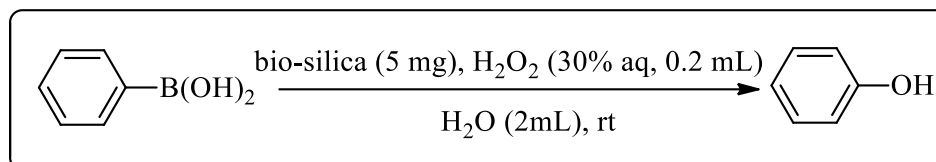
Entry	Run	Catalyst (mg)	Time (min)	Yield (%)[b]
1	1st	50	5	93
2	2nd	30	5	92
3	3rd	20	5	90
4	4th	15	5	90
5	5th	10	7	89
6	6th	5	10	88

[a]Reaction condition: Phenylboronic acid (1 mmol), H_2O_2 (30% aq., 0.2 mL), water (2 mL). [b]Isolated yield.

Table 5. A comparison study between "green-ness" among catalyst/reagents in the hydroxylation of phenylboronic acid to phenol

Entry	Catalyst/Reagent	Mass-intensity	E-factor	Atom economy	Atom-efficiency
1	Al_2O_3/H_2O_2 [31]	35.3	39	60.25	54.43
2	H_3BO_3/H_2O_2 [33]	108	109	60.25	54
3	$NaClO_2$ [29]	54.4	55.4	44.5	43
4	$NH_2OH:HCl:NaOH$[17]	79.15	78.19	26.86	25
5	Our method	27.72	26.68	60.2	55.98

4.1. D. Conclusions:

In conclusion, we have established a mild, reusable catalytic protocol for *ipso*-hydroxylation of arylboronic acid which utilizes bio-silica as a catalyst and aqueous hydrogen peroxide as an oxidant. Bio-silica acts as a novel reusable heterogeneous catalyst in the *ipso*-hydroxylation process which enhances the oxidative catalytic action.

This method has several advantages such as mild reaction condition, excellent yield, safe handling, short reaction time and also applicable to wide variety of functional groups. Moreover, it avoids ligand, base and metal assisted reaction condition. The green-ness of the reaction condition also makes it superior to the existing methodology.

Characterisation data of the products:
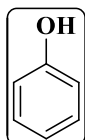
Phenol (Entry 1, Table 3): Brown liquid (Yield=93%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.20- 7.18(m, 2H), 6.84-6.82(m, 3H), 5.21(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.6, 129.9, 120.7, 115.4 ppm.
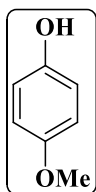
4-methoxyphenol (Entry 2, Table 3): White gum (Yield=92%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.78-6.75(m, 4H), 4.5(s, br, 1H), 3.76(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.8, 149.5, 116.1, 114.9, 55.9 ppm.
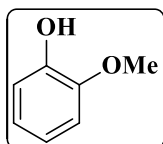
2-methylphenol (Entry 3, Table 3): Brown liquid (Yield=90%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.12-7.05(m, 2H), 6.85-6.81(m, 1H), 6.75(d, *J*=8Hz, 1H), 5.19(s, br, 1H), 3.03(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.7, 130.9, 126.9, 123.7, 120.5, 114.7, 15.6 ppm.
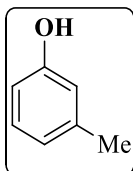
3-methylphenol (Entry 4, Table 3): Colorless gum (Yield=89%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.12-7.09(m, 1H), 6.74-6.72(m, 1H), 6.66-6.65(m, 2H), 4.56(s, br, 1H), 2.29(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.5, 139.9, 129.5, 121.6, 116.1, 112.4, 21.4 ppm.
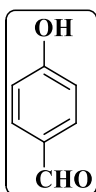
4-formylphenol (Entry 5, Table 3): White gum (Yield=90%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.86(s, 1H), 7.81(d, J=8.4Hz, 2H), 6.98(d, J=8.4Hz, 2H), 6.97(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 191.4, 161.7, 132.6, 129.8, 116.1 ppm.
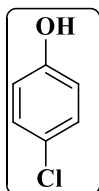
4-chlorophenol (Entry 6, Table 3): Brown liquid (Yield=92%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.17(d, J=7.6Hz, 2H), 6.76(d, J=7.6Hz, 2H), 5.11(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 154.2, 129.5, 125.6, 116.7 ppm.
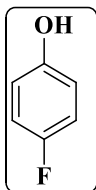
4-flourophenol (Entry 7, Table 3): Yellow liquid (Yield=93%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.90-6.88(m, 2H), 6.79-6.78(m, 2H), 5.5(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.3, 156, 116.3, 116.1 ppm.
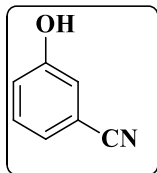

3-cyanophenol (Entry 8, Table 3): White gum (Yield=88%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.32(m, 2H), 7.26-7.25(m, 1H), 7.12(m, 1H), 5.4(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.8, 130.6, 24.1, 120.4, 118.7, 29.7 ppm.
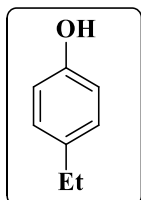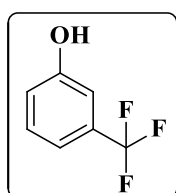

4-ethylphenol (Entry 9, Table 3): Brown liquid (Yield=87%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.07-7.04(m, 2H), 6.77-6.74(m, 2H), 4.10(s, br, 1H), 2.57(q, *J*=8Hz, 2H), 1.19(t, *J*=8Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.4, 136.6, 128.9, 115.2, 28, 15.9 ppm.
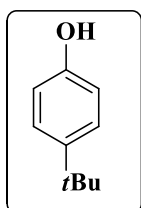

4-*tert*-butylphenol (Entry 10, Table 3): White solid (Yield=88%), mp= 120-125 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25(d, *J*=7.2Hz, 2H), 6.75(d, *J*= 7.2Hz, 2H), 4.5(s, br, 1H), 1.29(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.2, 143.6, 126.4, 114.8, 34.1, 31.5 ppm.
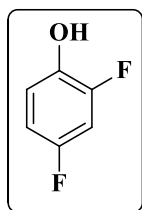
2,4-diflourophenol (Entry 11, Table 3): Yellow liquid (Yield=91%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.99-6.96(m, 1H), 6.69-6.68(m, 1H), 6.55-6.52(m, 1H), 2.99(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.1, 143.7, 117.4, 110.8, 105, 104.8 ppm.


3-triflouromethylphenol (Entry 12, Table 3): Yellow liquid (Yield=92%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30(t, J = 8.1 Hz, 1H), 7.22(d, J =8Hz, 1H), 7.13(s, 1H), 6.96(dd, J_1 =2.5Hz, J_2 =8.1Hz, 1H), 6.30(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.7, 131.5, 130, 124.8, 118.7, 117.2, 112.2 ppm.
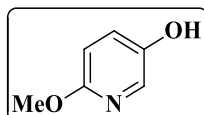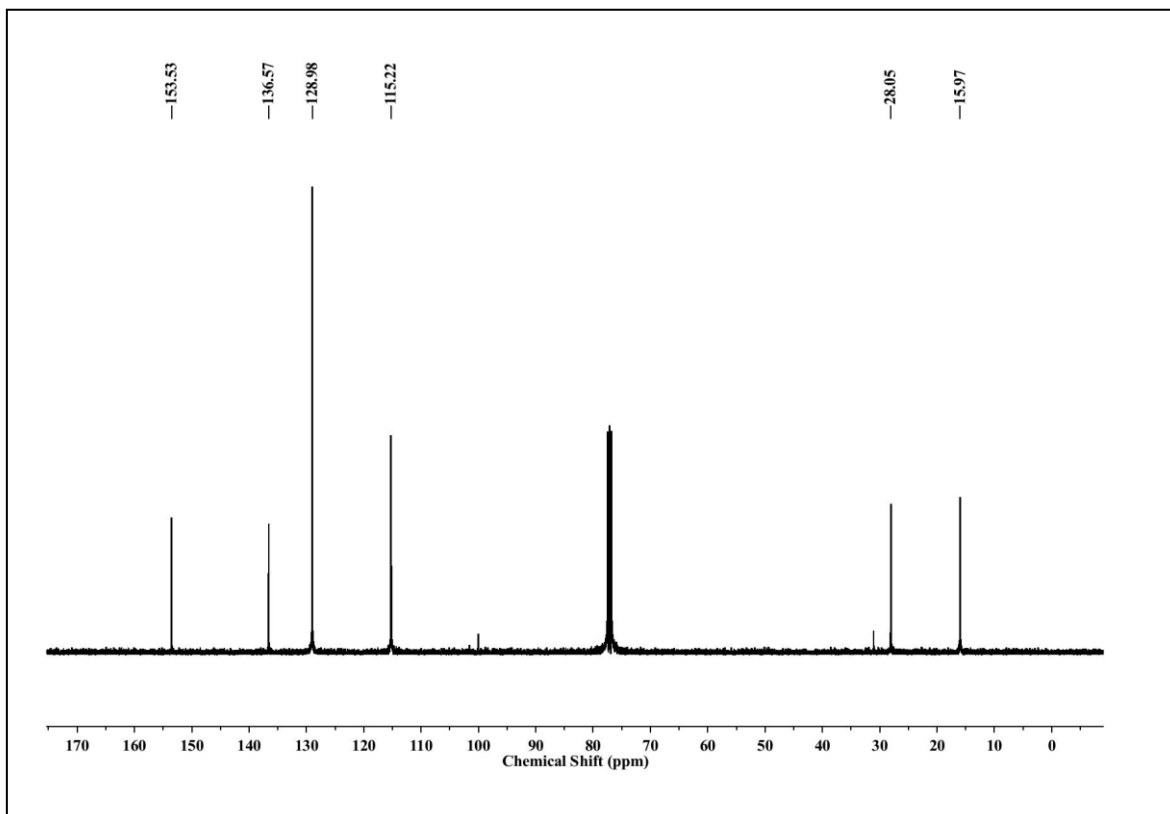

6-methoxypyridine-3-ol (Entry 13, Table 3): Yellow gum (Yield=89%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.58(s, br, 1H), 7.76-7.75(m, 1H), 7.27-7.25(m, 1H), 6.69-6.67(m, 1H), 3.81(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.3, 148.5, 132.1, 128.9, 110.9, 54.3 ppm.
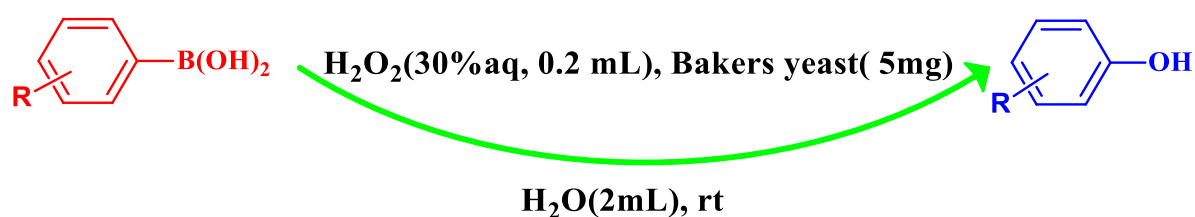
¹H NMR spectrum of 4-ethyl phenol:
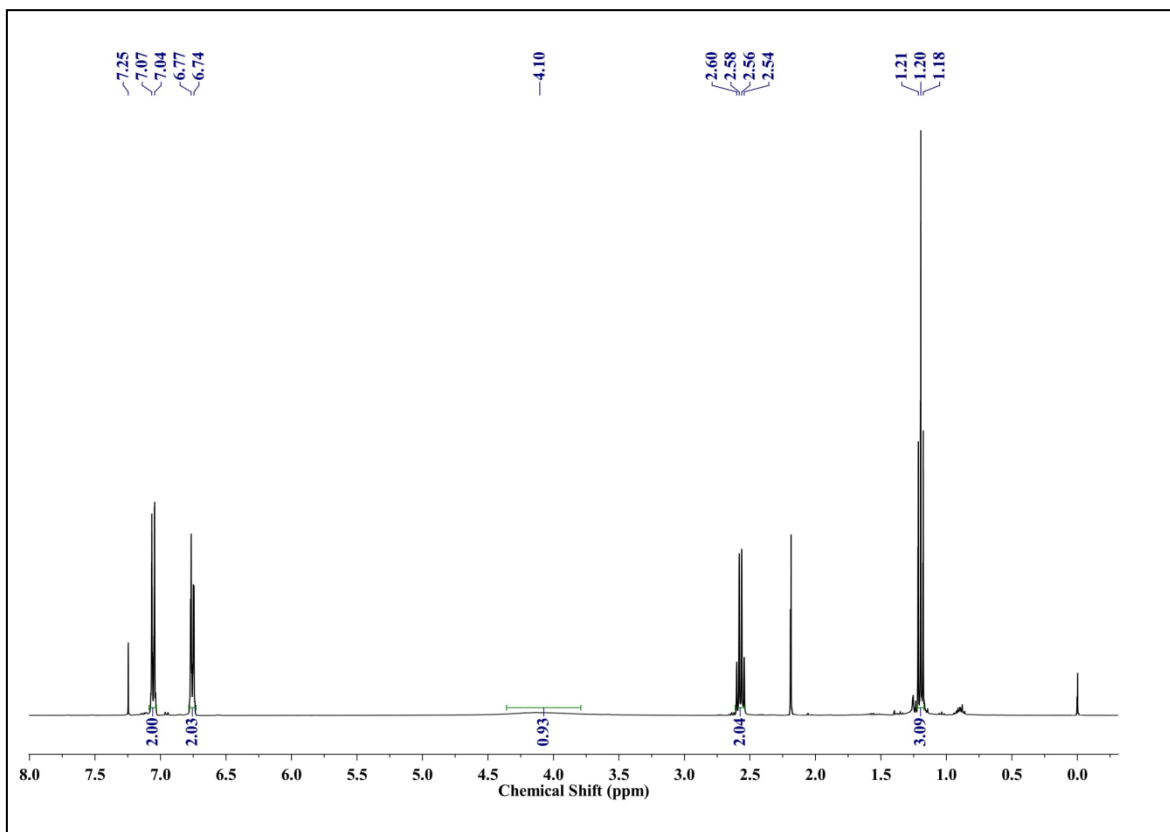
¹³C NMR spectrum of 4-ethyl phenol:

CHAPTER 4

Section 4.2.

Baker's yeast as an efficient reusable bio catalyst for oxidative hydroxylation of aryl/heteroarylboronic acid

$B(OH)_2$ → H_2O_2(30%aq, 0.2 mL), Bakers yeast(5mg) → OH

H_2O(2mL), rt

R= -H, 4-Me, 4-OMe, 2-Me, 3-Me etc.

- Application of reusable bio-catalyst for organic transformation
- Avoids ligand, transition metals and heat
- Short reaction time
- No organic solvent
- Minimum amount of oxidant

4.2. A. Introduction:

In recent decades, the quest for the development of green and sustainable routes for a chemical reaction has gained much popularity in research community. Thus, naturally abundant and environmentally acceptable bio-chemicals hold a superior position in green synthesis. Hence, in current hour of interest, implication of bio-catalysts in organic transformations comes out to be an increasing global demand, because they are environment friendly and possess broad substrate specificities. Additionally, they also demonstrate high stereo selectivity and work under mild reaction conditions. Most of them are commercially available, cheap and do not require the use of cofactors [37]. Baker's yeast (*Saccharomyces cerevisiae*) is a well-known bio-catalyst which is cost effective; simple in handling and does not require the assistance of microbiology for growth [37]. It is widely used to catalyze functional group conversions [38] and plays a vital role in the synthesis of bioactive compounds. Baker's yeast has been a significant constituent of the bakery industry and is non-toxic in nature. Literature is enumerated with reports regarding Baker's yeast catalyzed reduction of ketones to optically active alcohols and synthesis of di hydropyridyl compounds via Hantzsch reaction [39]. So, we turned our attention towards employment of Baker's yeast as an effective bio-catalyst for the oxidative hydroxylation of arylboronic acid. We have already discussed in the introduction portion about the importance of phenolic compounds in field of medicinal chemistry, material science etc. The conventional method for the synthesis of phenol possesses harsh reaction condition, low yield, poor functional group tolerance etc. As a result, simple, mild and easily available precursor for the synthesis of phenol is still demanding and remains an active area of research. Although a majority of the protocols have been established for the synthesis of phenols from arylboronic acids via *ipso*-hydroxylation, yet, most of the protocols require metal catalyst or base/ strong oxidising agents. To the best of our knowledge, there is no report on *ipso*-hydroxylation of arylboronic acid through a bio-catalyst. In continuation to our effort to develop a mild and efficient protocol for the stated purpose, we wish to report a sustainable route for *ipso*-hydroxylation of arylboronic acid which utilizes Baker's yeast as bio-catalyst in presence of hydrogen peroxide as oxidant and water as solvent at room temperature.

4.1. B. Experimental:

General information:

^{1}H and ^{13}C NMR spectra of the products were recorded in a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Chemical shift values are expressed in ppm. Coupling constants are expressed in Hertz. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F$_{254}$ (Merck). UV light and Iodine vapours were used as visualizers. Chemicals were obtained from commercial source.

General procedure for the hydroxylation of phenol:

In a 50 mL round-bottomed flask, to a mixture of arylboronic acid (1 mmol), 30% aq. H$_2$O$_2$ (0.2 mL), and Baker's yeast (commercially available as active dry yeast 5 mg), 2 mL of water was added and stirred at room temperature in aerobic condition. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with 20 mL of water and extracted with (3 x 20) mL of diethyl ether and the combined organic layer was washed with brine and dried over Na$_2$SO$_4$ and evaporated to dryness in a rotary evaporator under reduced pressure. The crude was purified by column chromatography (hexane/ethylacetate, 9:1) over silica (mesh 100–200) to get the desired product. The products were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

4. 2. C. Results and discussion:

We started our *ipso*-hydroxylation protocol by choosing phenylboronic acid (1 mmol) as a model substrate, Baker's yeast (15 mg) as catalyst and H$_2$O$_2$ (2 mL) as an oxidant. The reaction mixture was allowed to progress under stirring and within 0-5 minutes, the reaction was found to be completed with 96% of the isolated yield (Table 1, Entry 1). Being inspired by the result, we examined the effectiveness of the catalyst and performed the same reaction in absence of Baker's yeast which afforded only 60% of the isolated yield in 12 hour (Table 1, Entry 2). An experiment was also done in absence of H$_2$O$_2$ adding yeast as a catalyst and 45% of the yield was realized (Table 1, Entry 3). So, from

the above three experiments, it was clear that both H_2O_2 and yeast were needed for effective conversion of phenylboronic acid to phenol. So, in the next assessment, we planned to optimize the reaction condition for the amount of oxidant, H_2O_2 and Baker's yeast, needed for the best conversion. At first, keeping the amount of yeast constant at 15 mg, amount of H_2O_2 was varied from 2 mL to 1 mL, 0.5 mL and 0.2 mL respectively (Table 1, Entries 4-6). However, when the amount of H_2O_2 was reduced, 2 ml of water was required to solubilize the starting material (Table 1, Entry 4,). To note, we found 0.2 mL of the oxidant H_2O_2 was enough to get the best conversion in presence of 15 mg of the biocatalyst Baker's yeast. We also performed a series of experiments by minimizing the amount of the catalyst, keeping fix 0.2 mL of the oxidant. These experiments established that 5 mg of the catalyst could give same amount of yield as given by 15 mg of the Baker's yeast (Table 1, Entry 8). Therefore, after screening, we found that 0.2 mL of H_2O_2 and 5 mg of the catalyst were enough for efficient conversion of 1 mmol of phenylboronic acid to phenol in 2 mL of water (Table 1, Entry 8).

Table 1. Optimization of reaction condition for catalyst and oxidant[a]
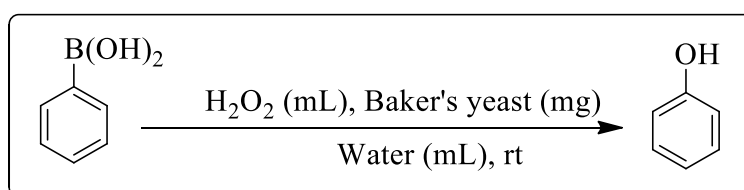

Entry	Yeast(mg)	H_2O_2(mL)	Water (mL)	Time	Yield(%)[b]
1	15	2	-	0-5 min	96
2	-	2	-	12 h	60
3	15	-	-	12 h	45
4	15	1	2	0-5 min	94
5	15	0.5	2	0-5 min	96
6	15	0.20	2	0-5 min	96
7	10	0.20	2	0-5 min	96
8	5	0.20	2	0-5 min	96

[a]Reaction condition: 1 mmol of phenylboronic acid. [b]Isolated yield

With these encouraging results of preliminary investigations, we were inspired to explore the generality of the newly developed procedure under optimised condition with

broad array of sterically hindered, electron withdrawing and electron donating groups substituted at *ortho-*, *meta-* and *para-* positions of arylboronic acids as discussed in Table 2. To our delight, most of the substrates including heteroarylboronic acids provided excellent yields within short reaction time.

**Table 2.** Baker's yeast mediated synthesis of phenol from arylboronic acid[a]
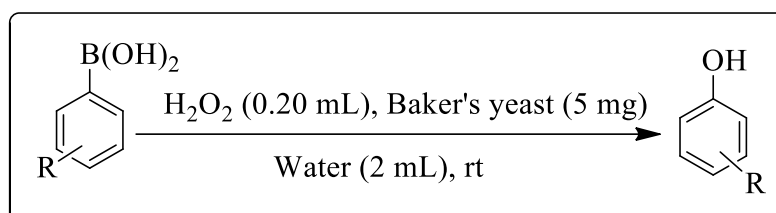
Entry	R	Time (min)	Yield (%)[b,c]
1	H	0-5	96
2	4-NO$_2$	30	92
3	4-NH$_2$	10	92
4	4-OMe	35	93
5	2-Me	25	85
6	2,6-dimethyl	35	91
7	3-Me	0-5	95
8	3-CN	45	94
9	4-Cl	0-5	92
10	4-CHO	45	97
11	4-Et	0-5	93
12	4-*tert*-butyl	10	90
13	2,4-difluoro	35	91
14	Thiophene-2-yl	20	85
15	6-methoxy, 3-pyridyl	20	93
16	6-methoxy-pyridine-3-yl	20	93
17	3-chloro	30	89

[a]Reaction condition: Arylboronic acid (1 mmol), Baker's yeast (5 mg), H$_2$O$_2$ (0.20 mL), [b]Isolated yield, [c]All the compounds were characterised by ^{1}H and ^{13}C NMR spectroscopy

We have tested the efficacy of our catalytic system for phenylboronic acid pinacolester and 3-hydroxy methyl phenylboronic acid pinacol ester. Interestingly, both of them afforded good yield within short reaction time as shown in **Scheme 1**.
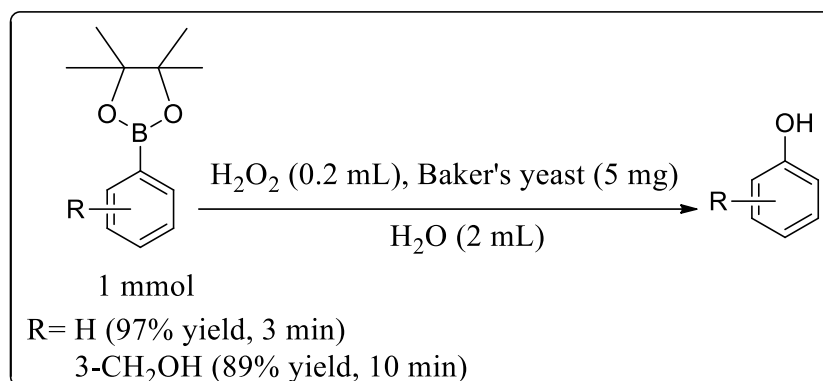
Scheme 1: *Ipso*-hydroxylation of phenylboronic acid pinacolester

During substrate study, it was noticed that reaction of sensitive group functionalized arylboronic acids (Table 2, Entries 10, 14, 15 and 16) and pinacol boronate esters (Scheme 1) were transformed easily to corresponding phenols with high chemoselectivity. In general, aromatic alcohols and aromatic aldehydes are prone to oxidation in presence of oxidizing agent. But, in our case these functionalities are found to be tolerant during hydroxylation and provided *ipso*-hydroxylated product with excellent yields. Similarly, heterocycles such as sulphides and pyridyls easily undergo oxidation to sulphoxides and *N*-oxides in the presence of oxidizing agents such as H_2O_2/ catalyst, mCPBA, oxone etc. However, with our experimental conditions, *ipso*-hydroxylation product was obtained selectively without any by product formation.

We have chosen Baker's yeast as catalyst for this conversion due to the following reasons: (i) yeast decomposes hydrogen peroxide to generate molecular oxygen which can enhance the reaction and (ii) Baker's Yeast generates a variety of enzymes, including lipases. These classes of enzymes happen to be functional proteins and are known to have many amino acid residues, including aspartate and glutamate [37]. On the basis of the explanation of the cited manuscript [37], we propose a plausible mechanism for the reaction.

The anions facilitates the abstraction of a proton from H_2O_2 to generate a nucleophile $^{(-)}$OOH. This nucleophile drives the process to give the corresponding phenol

(**Fig. 1**). A series of control reactions have been performed to establish the mechanism. It is reported [37] that yeast contains some amino acid residues like aspartate, glutamate etc. Therefore, we performed a reaction using aspartic acid and H_2O_2 which resulted almost a comparable yield with our optimized reaction condition (Table 3, Entry 2). Experiments were also done by using only aspartic acid as catalyst without any oxidant and also in the presence of base along with aspartic acid (Table 3, Entries 3 and 4). But, both of the reactions failed to show a positive result. Again, from literature it is found that yeast decomposes H_2O_2 and produces O_2 [40]. Therefore, a reaction was performed in O_2 atmosphere for clarification of the mechanistic route. Nevertheless, the generation of molecular oxygen does not find a place in the reaction route and this fact has been established based on our findings, as discussed in Entry 5 of table 2, that the oxidative hydroxylation does not take place in oxygen atmosphere alone. The reaction failed in N_2 atmosphere with our optimized reaction condition that confirms the necessity of aerial oxygen (Table 3, Entry 6). At last, the reaction was performed by taking sodium aspartate and H_2O_2 which afforded excellent yield and supports our plausible mechanism.
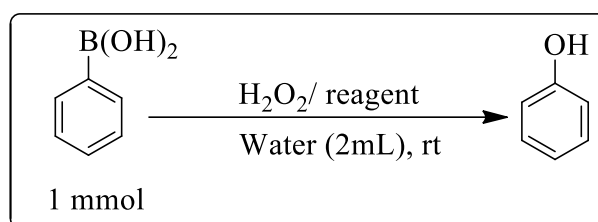
Plausible mechanism of the reaction:
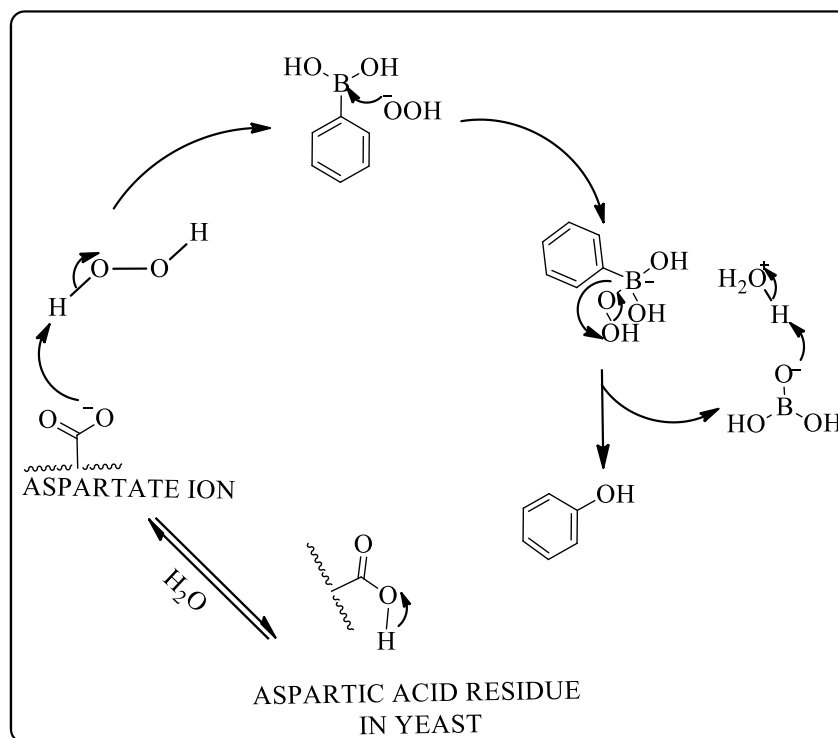

Fig. 1: Plausible Mechanism of the reaction

Table 3. Controlled reaction in favour of the proposed mechanism

$$B(OH)_2 \xrightarrow[\text{Water (2mL), rt}]{H_2O_2/ \text{ reagent}} OH$$

1 mmol

Entry	Reagent	Time (min)	Yield (%)[a]
1[b]	Yeast (5 mg) + H$_2$O$_2$ (0.2 mL)	2	95
2[b]	Aspartic acid (5 mg) + H$_2$O$_2$ (0.2 mL)	2	90
3[b]	Aspartic acid (5 mg)	180	Nil
4[b]	Aspartic acid (5 mg) + Base (1 M NaOH)	180	Nil
5[c]	None	180	Nil
6[d]	Yeast (5 mg) + H$_2$O$_2$ (0.2 mL)	180	5
7	Sodium aspartate (5 mg) + H$_2$O$_2$ (0.2 mL)	2	90

[a]Isolated Yield. [b]Reaction under air. [c]Reaction in the O$_2$ atmosphere. [d]Under N$_2$ atmosphere

Again, from the green chemistry point of view reusability is considered as one of the most attractive properties of a catalyst. We examined the reusability of the bio-catalyst by choosing the model reaction with 3 mmol of phenylboronic acid, 15 mg of the bio-catalyst (Baker's yeast), 0.6 mL of the oxidant H$_2$O$_2$ in 5 mL of water. After completion of the reaction, the mixture was extracted with ethyl acetate and the aqueous layer was filtered. The catalyst was recovered from the residue and dried which was used for further reactions. We are glad to mention that the catalyst showed efficiency up to sixth run and afforded almost constant yield of product formation.

Table 4: Reusability of the catalyst

B(OH)$_2$ Baker's yeast (15 mg), H$_2$O$_2$ (0.6 mL)   OH

Water(5 mL), rt

3 mmol
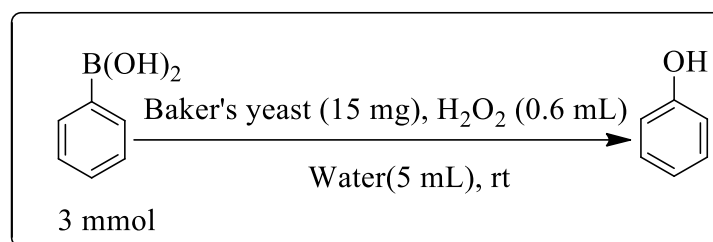
Entry	Run	Time	Yield (%)
1	1st	1 min	96
2	2nd	2 min	96
3	3rd	2 min	96
4	4th	5 min	93
5	5th	5 min	93
6	6th	6 min	90

To note, the shelf life of the used catalyst Baker's yeast goes down after about half an hour, as we are not using any additive such as glucose, for the Baker's yeast to feed on. However, this is not much relevant to our reaction protocol because the oxidative hydroxylation occurs within a matter of few minutes.

4.2. D. Conclusions:

We have developed a mild and efficient bio-catalyst Baker's yeast catalyzed room temperature oxidative hydroxylation of arylboronic acid to phenol in the presence of a minimal amount of green oxidant H$_2$O$_2$ which requires very short time to completion with an excellent yield of product formation. Alternatively, the reaction protocol is compatible with various *o-*, *m-* and *p*-substituted phenylboronic acids. The central attraction of this protocol is that it avoids metal, organic solvent and ligand for the transformation. From this point of view, this protocol can be accepted as a green and sustainable alternative for *ipso*-hydroxylation of arylboronic acid.
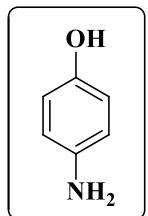
Characterisation data of the products:
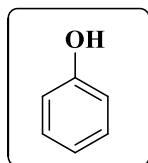
Phenol (Entry 1, Table 2): Brown liquid (Yield=96%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23(d, *J*=8Hz, 2H), 6.83(d, *J*=8Hz, 3H), 4.21(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.5, 129.7, 120.8, 115.4 ppm.
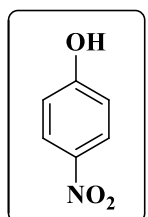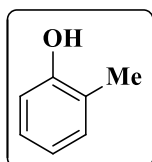

4-nitrophenol (Entry 2, Table 2): Brown solid (Yield=92%), mp= 110-112 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.17(d, *J*=8Hz, 2H), 6.94(d, *J*=8Hz, 2H), 5.96(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 161.8, 141.4, 126.4, 115.8 ppm.

4-aminophenol (Entry 3, Table 2): Black amorphous solid (Yield=92%), mp= 185-190 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.34(s, br, 1H), 6.46(d, *J*=8Hz, 2H), 6.43(d, *J*=8Hz, 2H), 4.4 (s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 148.7, 141.0, 116.0, 115.8 ppm.
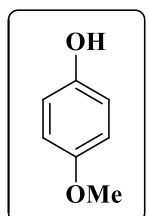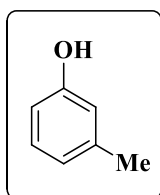

4-methoxyphenol (Entry 4, Table 2): White gum (Yield=93%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.78-6.75(m, 4H), 4.40(s, br, 1H), 3.76(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.8, 149.5, 116.1, 114.9, 55.9 ppm.
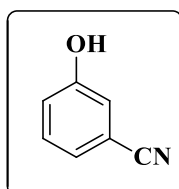
2-methylphenol (Entry 5, Table 2): Brown liquid (Yield=85%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11-7.09(m, 2H), 6.85-6.81(m, 1H), 6.75(d, J=8Hz, 1H), 5.19(s, br, 1H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.5, 139.9, 129.5, 121.6, 116.1, 102.5, 29.8, 21.4 15.6 ppm.
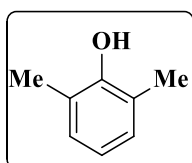
2,6-dimethylphenol (Entry 6, Table 2): White solid (Yield=91%), mp= 115-120 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.98-6.96(m, 2H), 6.77-6.75(d, J=8Hz, 1H), 4.7(s, br, 1H), 2.24 (m, 6H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.2, 128.6, 123.0, 120.2, 15.9 ppm.
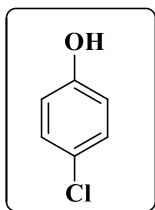

3-methylphenol (Entry 7, Table 2): Colourless gum (Yield=95%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11-7.09(m, 1H), 6.75-6.73(m, 1H), 6.66-6.65(m, 2H), 4.31(s, br, 1H), 2.29(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.5, 139.9, 129.5, 121.6, 116.1, 112.4, 21.4 ppm.
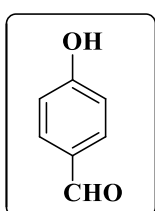

3-cyanophenol (Entry 8, Table 2): White gum (Yield=94%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.32(m, 2H), 7.26-7.24(m, 1H), 7.12(m, 1H), 5.75(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.0, 130.7, 124.7, 120.6, 118.7, 113.1 ppm.

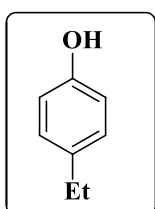**4-chlorophenol (Entry 9, Table 2):** Brown liquid (Yield=92%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18(d, *J*=8Hz, 2H), 6.76(d, *J*=8Hz, 2H), 5.0(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 154.2, 129.5, 125.6, 116.7 ppm.



4-formylphenol (Entry 10, Table 2): White gum (Yield=97%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.86(s, 1H), 7.81(d, *J*=8.4Hz, 2H), 6.98(d, *J*=8.4Hz, 2H), 6.59(s, br, 1H) 2.20(acetone from impurity) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 191.4, 161.7, 132.6, 129.8, 116.1 ppm.


4-ethylphenol (Entry 11, Table 2): Brown liquid. (Yield=93%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.05(d, *J*=8Hz, 2H), 6.75(d, *J*=8Hz, 2H), 4.11(s, br, 1H), 2.55(q, *J*=8Hz, 2H), 1.19(t, *J*=8Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.5, 136.5, 128.9, 115.2,31.0, 28.0, 15.9 ppm.
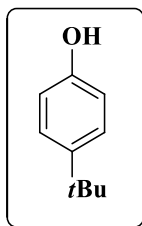
4-*tert*-butylphenol (Entry 12, Table 2): White solid. (Yield=90%), mp= 120-127 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.26(d, *J*=7.2Hz, 2H), 6.75(d, *J*=7.2Hz, 2H), 1.29(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.1, 143.6, 126.2, 114.8, 34.1, 31.6 ppm.
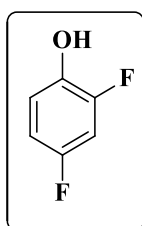
2,4-difluorophenol (Entry 13, Table 2): Yellow liquid (Yield=91%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.99-6.96(m, 1H), 6.69-6.68(m, 1H), 6.55-6.52(m, 1H), 2.92(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.1, 143.7, 117.4, 110.8, 105, 104.8 ppm.
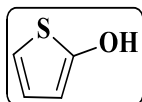
2-hydroxythiophene (Entry 14, Table 2): Yellow liquid (Yield=85%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.85(s, 1H), 6.69-6.68(m, 1H), 6.55-6.52(m, 1H), 2.92(s, br, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.1, 143.7, 117.4, 110.8, 105, 104.8 ppm.
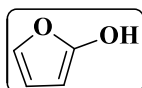
2-hydroxyfuran (Entry 15, Table 2): White liquid (Yield=85%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.92(s, 1H), 7.57-7.55(m, 1H), 6.41-6.39(m, 1H), 4.13-4.12(m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 154.18, 133.61, 100.42, 87.2 ppm.
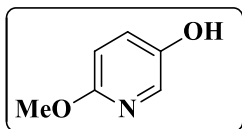
6-methoxypyridine-3-ol (Entry 16, Table 2): Yellow gum (Yield=93%), ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.76-7.75(m, 1H), 7.36(s, br, 1H), 7.27-7.24(m, 1H), 6.71-6.69(m, 1H), 3.86(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.4, 148.3, 132.2, 128.8, 111.0, 54.2 ppm.

^{1}H NMR spectrum of thiophene-2-ol
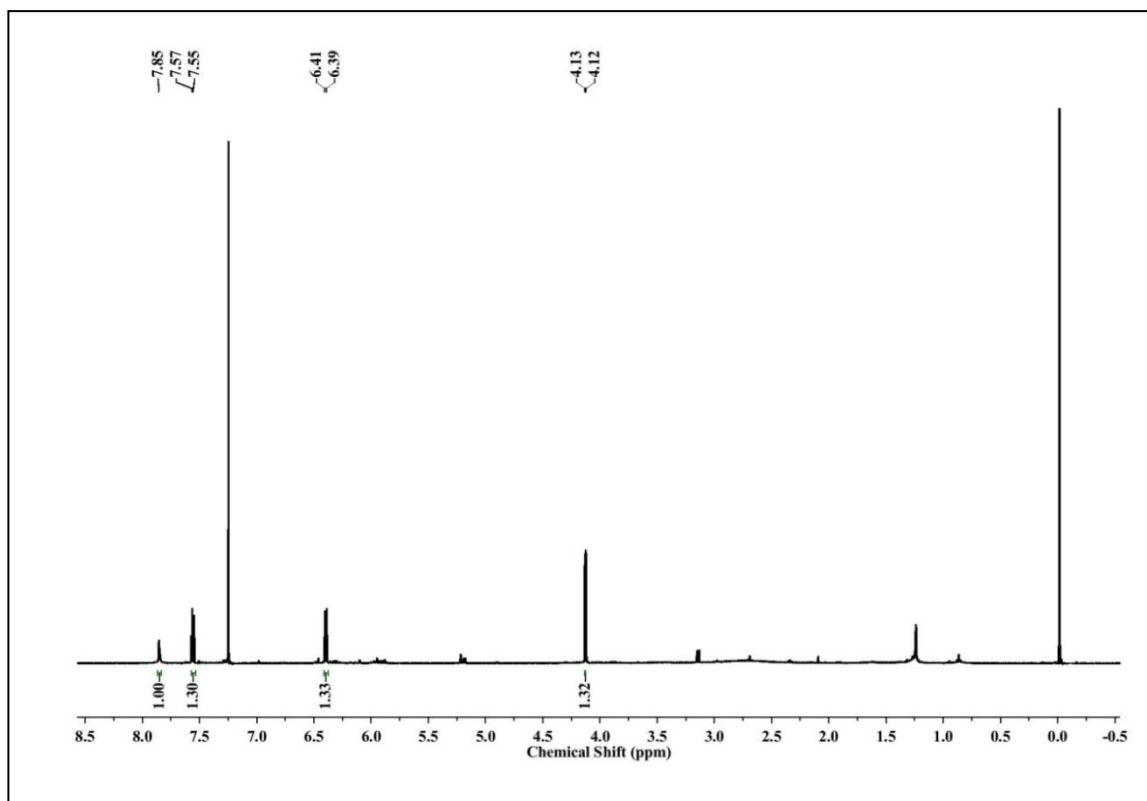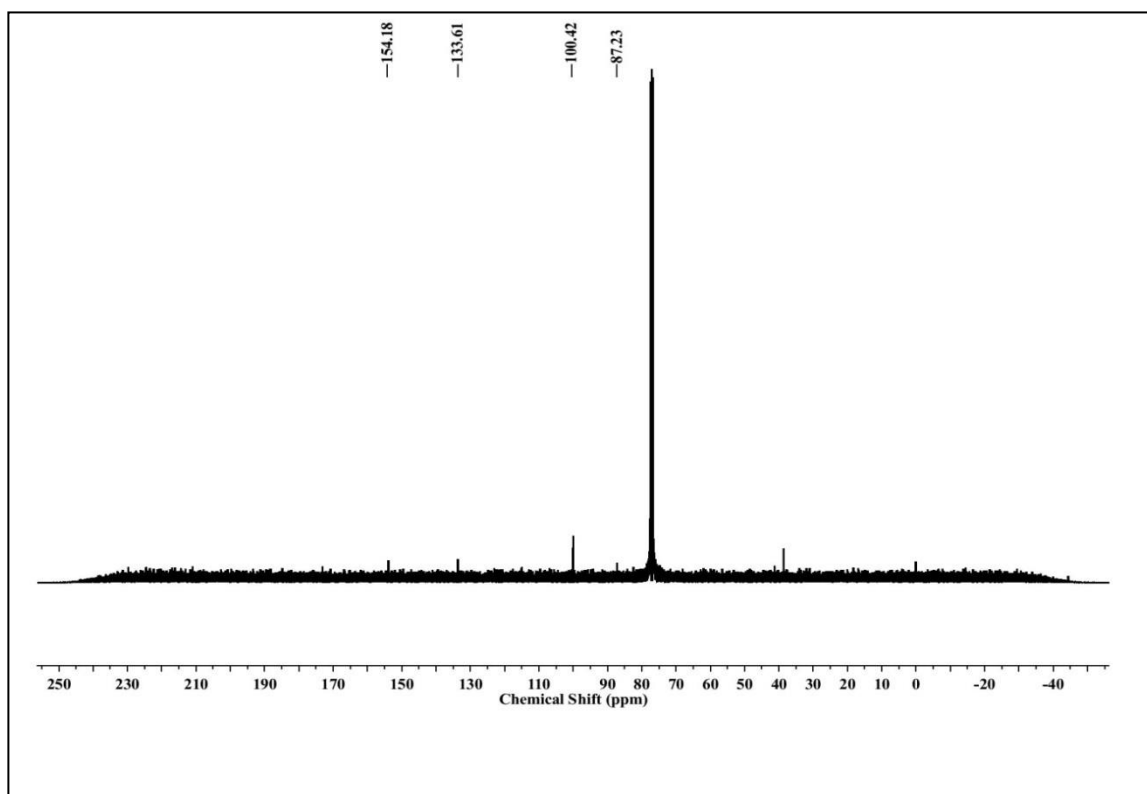

^{13}C NMR spectrum of thiophene-2-ol

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