Copper Catalyzed Hydroxylation of *ortho*-Bromobenzylic Alcohols

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Department of Chemistry

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Declaration

I hereby declare that the matter embodied in this report is the result of investigation carried out by me in the Department of Chemistry, Indian Institute of Technology Hyderabad under the supervision of **Dr. G. Satyanarayana**.

In keeping with general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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Approval Sheet

This thesis entitled **"Copper Iodide Catalyzed Hydroxylation of α,α-dialkyl-(2-bromoaryl)methanols to α,α-dialkyl-(2-hydroxyaryl)methanols"** by Jyoti Nandi is approved for the degree of Master of Science from IIT Hyderabad.

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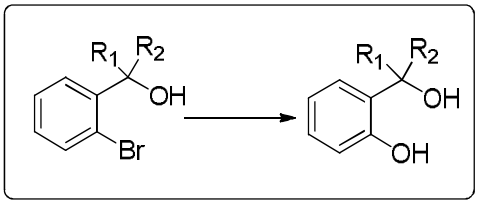
Dedicated

To

My family

Abstract

An efficient CuI/1,10-phenanthrolinecatalysed hydroxylation of α,α-dialkyl-(2-bromoaryl)methanols to α,α-dialkyl-(2-hydroxyaryl)methanols has been achieved. The synthesis of these phenols was performed using various α, α-dialkyl-(2-bromoaryl)methanols with Cs_2CO_3 as base at 120 ℃ in a mixed solvent system (^{t}BuOH-DMF-H_2O).



Contents

Copper Catalyzed Hydroxylation of *ortho*-Bromobenzylic Alcohols

1. Introduction:

Phenols are very important intermediates in chemical, pharmaceutical, and material industries.[1] The development of a mild and highly efficient method for synthesis of phenols over classical protocols has gained considerable attention in synthetic chemistry. Though the manufacturing of phenol is classically industrially achieved by the three-step Hock process,[2] it suffers from the major disadvantage of low conversion rates at every step and overall high energy cost. A further drawback is the formation of inevitable by-product acetone. For most of the substituted and functionalised phenols, non-oxidative methods were developed such as the straight nucleophilic substitution[3] of aryl sulfonic acid and aryl halides and the hydroxylation of diazoarenes.[4] Usually, these methods require harsh conditions and activated substrates. A recent means of synthesizing phenols is by the aromatic C-H activation/ borylation/ oxidation sequence reported by Smith and Maleczka.[5] This method is particularly useful for the preparation of non-ortho-substituted phenols.

Recently, a very efficient catalytic system based on palladium-phosphine complex was developed by the groups of Buchwald, Kwang and Beller,[6] which led to hydroxylation of aryl halides under mild reaction conditions. However, the replacement of palladium as catalyst by less expensive copper (I) salts would allow for economic benefits and also reduce toxicity issues. In recent years, copper-catalysed coupling reactions have been widely used in the synthesis of diaryl ethers and aryl alkyl ethers.[7] However, the direct hydroxylation of aryl halides still remains a challenge.

More recently, a highly efficient copper- catalysed procedure for the direct hydroxylation of aryl halides in the presence of ligands was disclosed by You and Taillefer independently[8] and research showed that a well-defined ratio of water/ organic solvent was the key factor, whereas water alone was inefficient.

2. Pharmacological and Medicinal Importance:

Phenols have high pharmacological and medicinal importance in addition to this they serve as versatile synthetic intermediates.[9] Polyphenols are bioactive substances that are widely distributed in the vegetable kingdom[11] and are present in high concentrations in typical components of the Mediterranean diet, such as fruits, vegetables, red wine and olive oil. A number of epidemiological studies indicate that the dietary factors may influence the development of certain types of cancer and degenerative pathologies, including cardiovascular diseases and cataract. In this respect, it is well documented that the daily consumption of fruits and vegetables enriched with polyphenols are associated with a lowered risk of these diseases.[10] For example, hydroxytyrosol[(3,4-dihydroxyphenyl)ethanol], one of the major natural phenolic compounds, present in olive fruits, virgin olive oil, table olives and waste streams generated during olive processing.[12] This compound has shown antimicrobial, hypoglycemic, hypolipidemic and hypocholesterol properties.

It is well known that oxidation induced by free radicals can result in cell membrane disintegration, membrane protein damage and DNA mutation (Slater, 1984; Halliwell, 1994), which can further initiate or propagate the development of many diseases such as cancers, liver injury and cardiovascular diseases (Yagi, 1987). To prevent these oxidation related diseases, blocking the generation of free radicals is important.

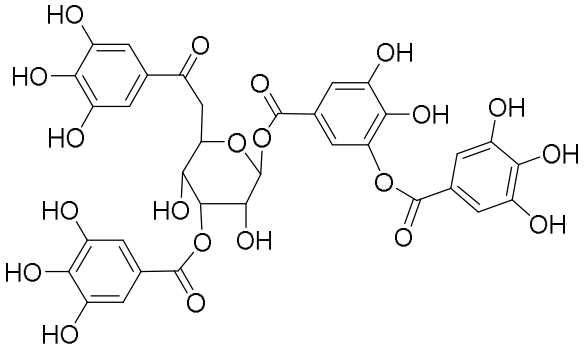
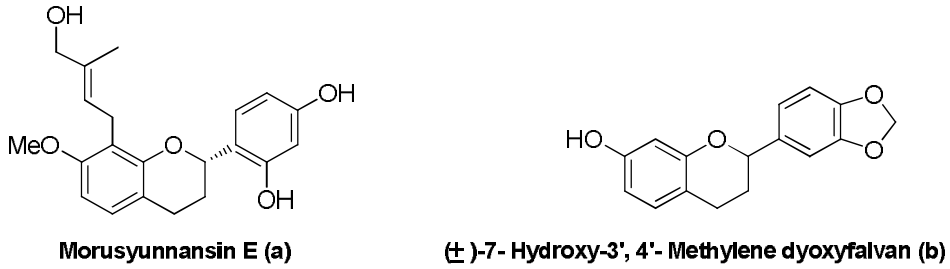


Figure 1. Tannic acid – a type of Tannin

Pomegranate ellagitannins, most abundant tannin (polyphenoliccompound) in pomegranate juice has free-radical scavenging properties[14] and has high potential to cause biological effects in humans.[15] Consumption of the above reduces systolic blood pressure by inhibiting serum angiotensin-converting enzyme[16] and also inhibits viral infections.[17] Pomegranate extracts also have antibacterial affects against dental plaque.[18]

One more example is the flavonoids which reduce the risk of cancer and coronary heart diseases. A few examples with such potential are depicted below in figure 2.



Morusyunnansin E (a) **(±)-7- Hydroxy-3', 4'- Methylene dyoxyfalvan (b)**

Figure 2: Morusyunnasin E (**a**) showed potent inhibitory effects on mushroom tyrosinase, 6 (±)-7-Hydroxy-3', 4'-Methylenedioxyfalvan (**b**) 7 and it's 7-glycoside have been traditionally used for the treatment of diabetes, ear and chest aliments and some viral infection.

3. Phenols in Polymer Industry:

Phenol-formaldehyde (example bakelite) polymers make excellent wood adhesives for plywood and particle board because they form chemical bonds with phenol like lignin component of wood. Lignin, a natural complex polymer of phenols, can be used in thermosetting resins, in thermoplastic blends and in surfactant applications.[19] The predominant industrial utilization of lignosulphonates is as dispersants, plasticisers and water-reducing agents in concrete preparation.

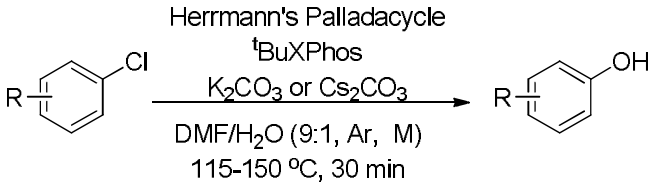
The demand for nondiscoloring antioxidant system has increased in polymer industry in recent years, various phenolic and phosphite materials promises to be a solution to obtain such systems. U.S.Pat. No. 3080338 reveals that certain phosphite type stabilizers may be used in combination with certain phenolic type antioxidants to protect synthetic rubbery polymers against breakdown and discoloration.

4.Background:

Because of their unique structural features and importance in biological activity, phenols have drawn much attention from synthetic chemists. Therefore, reasonably good number of synthetic strategies are reported in the literature for the synthesis of phenols. A few of them are discussed below.

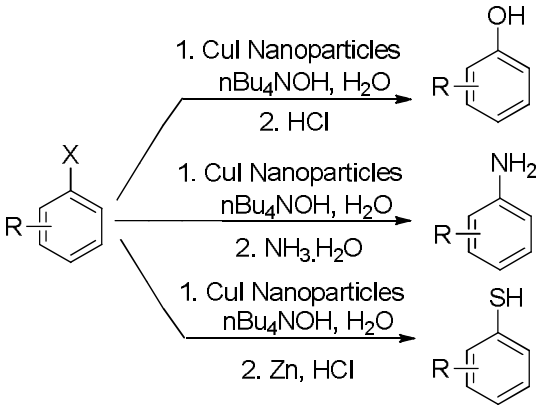
Previously reported methods on hydroxylation:

The palladium catalyzed microwave-assisted hydroxylation of aryl chlorides in the presence of a weak base (carbonate) was developed by Chao, Grace, Chen and Ji-Wang,[20] which converts aryl and heteroaryls chlorides to phenols and can be used when aryl chlorides is functionalized with a ketone, aldehyde, ester, nitrile or amide (Scheme 1).



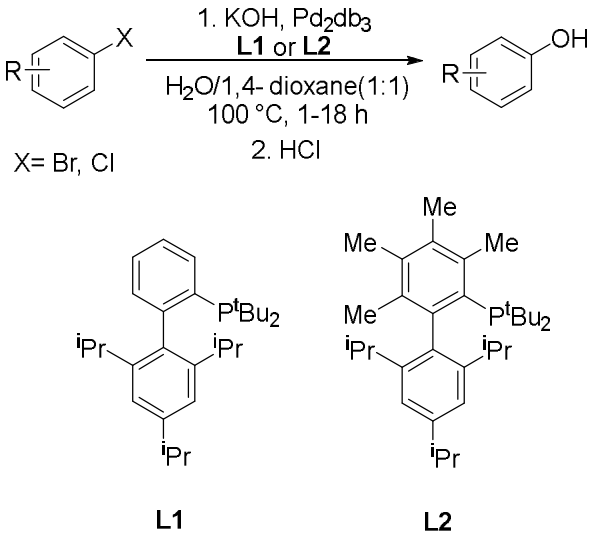
Scheme 1.

CuI-nanoparticles-catalysed selective synthesis of phenols, anilines and thiophenols from aryl halides was developed in the absence of both ligands and organic solvents by Xu, Liang, Cai, Qi, Yang and Feng (Scheme 2).[21]



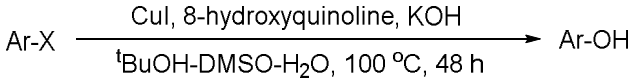
Scheme 2.

Synthesis of phenols from aryl halides with KOH as nucleophile source and catalytic system based on Pd_2dba_3 and ligands **L1** or **L2** in a solvent of aqueous 1,4-dioxane and KOH as base (Scheme 3).[20]



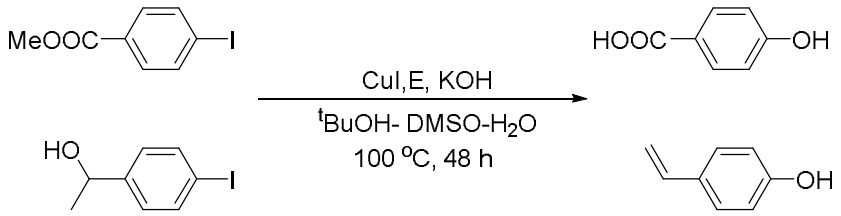
Scheme 3.

The CuI/8-hydroxyquinoline-catalysed direct hydroxylation of aryl iodides with KOH takes place at 100 ℃ in a mixed solvent system (^{t}BuOH-DMSO-H_2O), providing the corresponding phenols in great diversity. Aryl bromides are found to be rather less reactive under these reaction conditions (Scheme 4).[23]



Scheme 4.

When methyl 4-iodobenzoate was used, 4-hydroxybenzoic acid was isolated in 90 % yield, indicating that the ester moiety could not survive under these conditions. While both hydroxylation and dehydration occurred when 1-(4-iodophenyl)ethanol was utilized, as evident from the formation of 4-vinylphenol in 60% (Scheme 5).



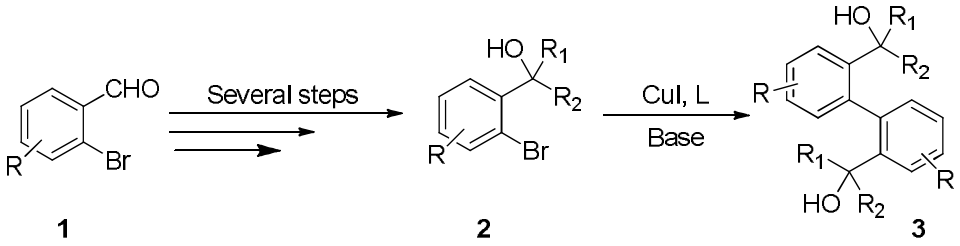
Scheme 5.

In Scheme 1 and 3, the reactions involve palladium catalytic system, which is more expensive compared to copper catalytic system. Also the former has toxicity issues which can be avoided if we switch to the latter. In Scheme 2, copper iodide nanoparticles are used that are also expensive compared to the commercial one. In Scheme 4, the authors have used commercially available copper iodide, but the reaction does not have functional group tolerance.

From the above discussion, it is clear that most of these methods possess several disadvantages such as low yields of products, long reaction time, harsh reaction conditions, tedious work-ups and large amount of toxic metal waste with solvent, requirement of inert atmosphere and use of stoichiometric or relatively expensive reagents. Therefore, the transition metal catalyzed hydroxylation still needs further development.

5. Results and Discussion:

Our initial aim was based on the use of transition metal mediated Ullmann type coupling for the synthesis of biaryls **3** starting from the bromo-benzaldehydes **1** as shown in Scheme 6.



Scheme 6.

The requisite starting materials, 2-bromobenzadehydes, **1** (Figure 2) were prepared using the literature reported bromination reaction conditions.[27]

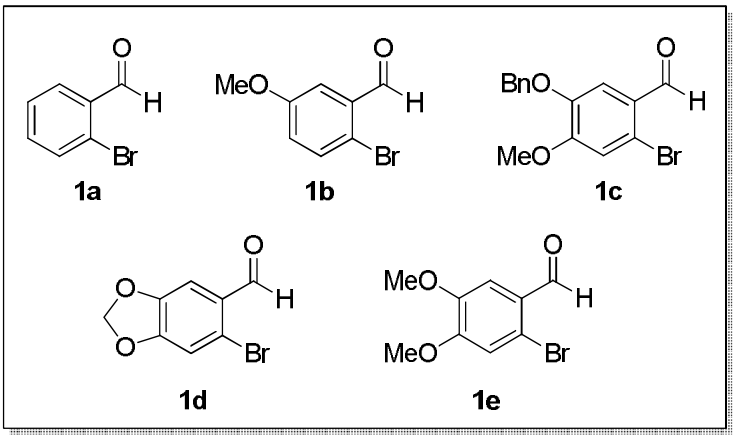
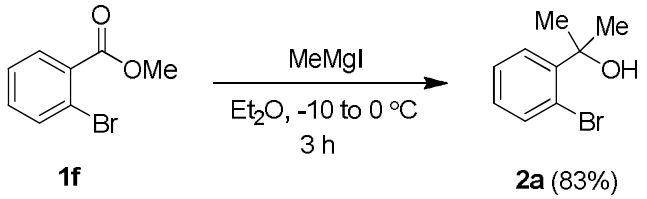


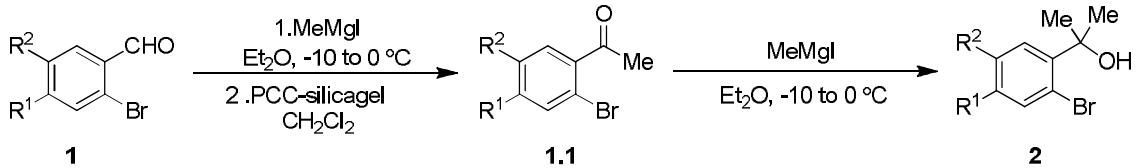
Figure 2. The 2-bromobenzaldehydes **1** were used as the starting materials.

The 2-bromotertiary alcohols **2**, the synthetic precursors for the final step i.e. Ullmann type coupling reaction, were synthesized by performing Grignard reaction on the 2-bromomethyl ester **1f**. Thus, direct addition of methyl Grignard to the commercially available methyl-2-bromomethylbenzoate **1f** furnished the corresponding tertiary alcohol **2a** (Scheme 7).



Scheme 7.

While, the other tertiary alcohols **2b-2e** were prepared from the corresponding 2-bromobenzaldehydes **1b-1e**, by step wise manner, (Scheme 8) using methyl Grignard addition, oxidation and methyl Grignard addition protocol (Figure 3).



Scheme 8.

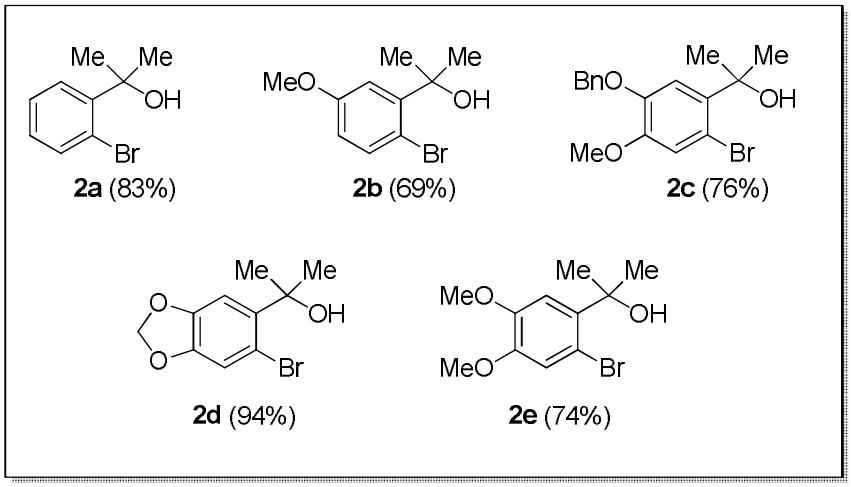
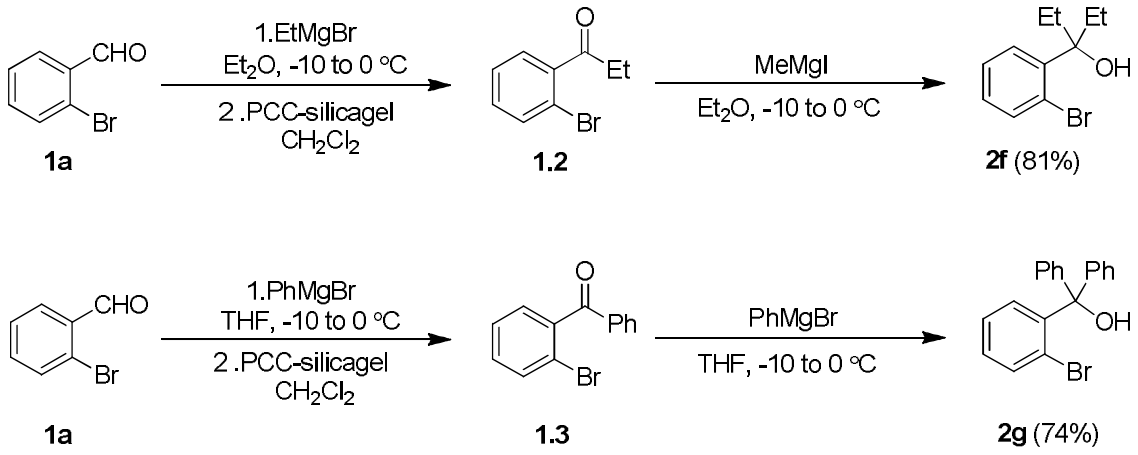


Figure 3.

Similarly, the tertiary alcohols **2f** and **2g** were prepared using ethyl Grignard addition/phenyl Grignard addition, oxidation and ethyl Grignard addition/phenyl Grignard addition protocol (Scheme 9).

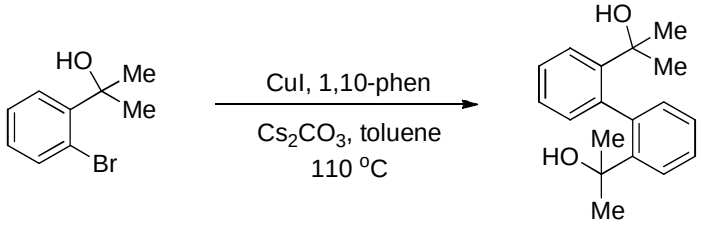


Scheme 9.

The synthesis of all above 2-bromotertiary alcohols **2** is reported in the literature.[28,29] Their structures were confirmed by their NMR and IR data with that of the reported ones.

In our investigation, initially we have chosen 2-(2-bromophenyl)propan-2-ol **2a** as a model study in the presence of copper iodide and 1,10-phenanthroline under different conditions as summarized in Table 1. The best result was obtained by using toluene as solvent and Cs_2CO_3 as base (0.5 equiv) at 110 °C. Under these optimized condition, the reaction selectively gave 2, 2'-([1,1'-biphenyl]-2,2'-diyl)bis(propan-2-ol) **1a**, in 67% yield (Table 1).

Table 1. Screening reaction conditions for the synthesis of biaryl product **3a**.[a]



2a **3a**

Entry	Solvent Used	Base Used	Base Equivalent	Time (hr)	Yield(%)
1	DMF	K_3PO_4	2 equivalent	24	-
2	DMF	K_3PO_4	0.5 equivalent	24	-
3	DMF	Cs_2CO_3	2 equivalent	24	10%
4	DMF	Cs_2CO_3	0.5 equivalent	24	15%
5	DMSO	Cs_2CO_3	2 equivalent	24	-
6	DMSO	Cs_2CO_3	0.5 equivalent	24	-
7	DMSO	K_3PO_4	2 equivalent	24	18%
8	DMSO	K_3PO_4	0.5 equivalent	24	
9	DMA	Cs_2CO_3	0.5 equivalent	24	-
10	toluene	K_3PO_4	0.5 equivalent	24	-
11	**toluene**	**Cs_2CO_3**	**0.5 equivalent**	**24**	**61%**

[a]All reactions were carried out in reflux conditions at 110 °C.

Now, with the optimized conditions in hand, to check the feasibility and generality of the method, other 2-bromotertiary alcohols were explored under these conditions. However, even after several attempts, the reaction was unsuccessful on 2-bromotertiary alcohols **2b**, **2c**, **2d** and **2e** (Figure 4) to yield the biaryl products.

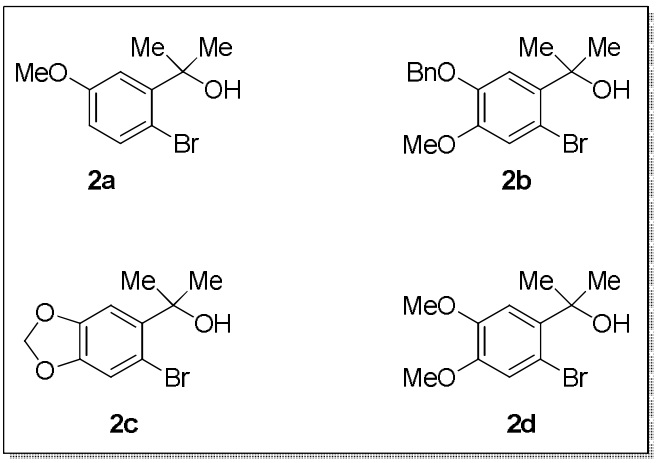
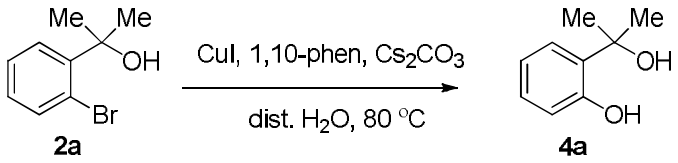


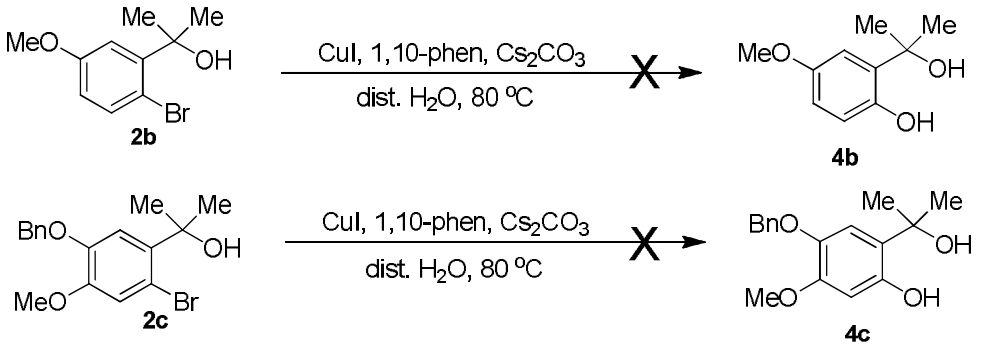
Figure 4.

As the above mentioned substituted tertiary alcohols failed to furnish the coupled biaryl products, we turned our interest towards the copper mediated hydroxylation using the same starting materials **2**. The reaction when performed under the similar conditions but in the presence of distilled water (0.5 ml) as the solvent was found suitable for hydroxylation and gave the product 2-(2-hydroxypropan-2-yl)phenol **4a** (Scheme 10). While, the reaction with the ligands L-prolin/2-2' bipyridyl were observed to be futile. Then, we decided to perform the reaction in water medium.



Scheme 10.

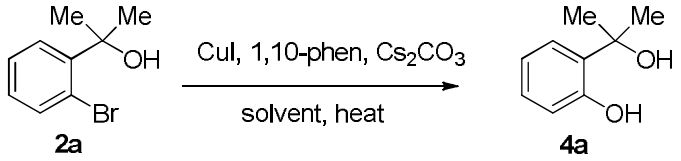
However, as it was noticed in the biaryls case, the attempts to further increase the scope and feasibility of this hydroxylation strategy by implementing the substituted tertiary alcohols **2b & 2c**, were unsuccessful to generate the corresponding hydroxylated products **4b** and **4c** (Scheme 11).



Scheme 11.

In an attempt to make the hydroxylation feasible, the following optimizations were tried. As depicted in Scheme 11, sole use of water resulted in 62% yield (Table 2, entry 1). Upon using a binary solvent system, as in, entries 2 & 3 of table 2**,** the reaction was impeded and resulted in recovering the starting materials. But astonishingly, the ternary solvent system yielded the hydroxylated product **xx** in more improved yields of 67% (Table 2, entry 4).

Table 2. Optimization of the hydroxylation reaction with the copper catalyst.

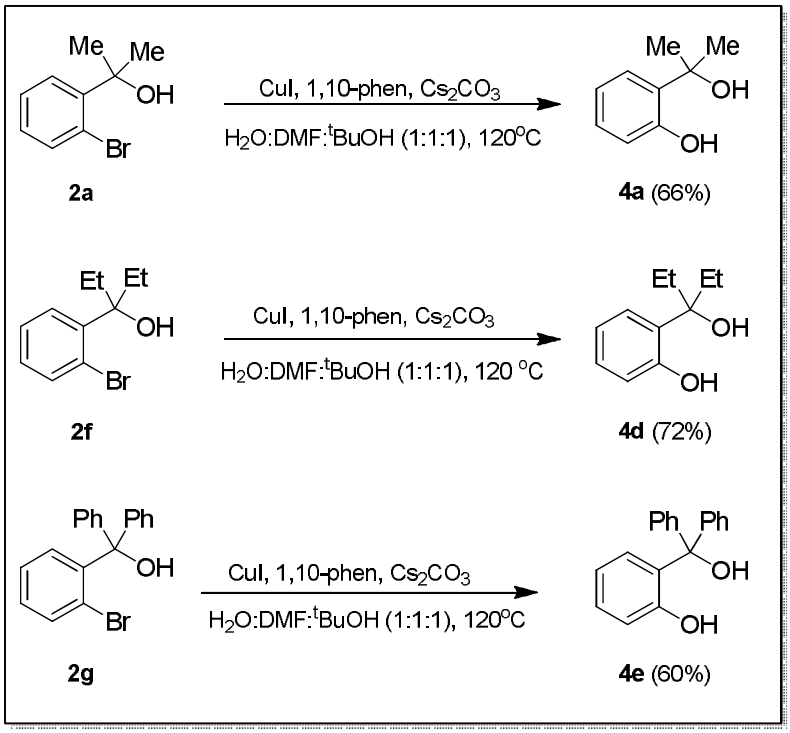


Entry	Solvent Used	Ratio	Temperature(˚C)	Volume(ml)	Yield (%)
1	Water	-	80	0.5	62
2	DMF: Water	9:1	120	0.5	-
3	Toluene:Water	1:4	110	0.5	-
4	**DMF: Water: ^{t}BuOH**	**1:1:1**	**120**	**1.5**	**67**

So, the optimized condition (Table 2, entry 4) was applied to the other unsubstitued tertiary alcohol systems **2f** & **2g.** The method proved to be amenable for the unsubstituted tertiary alcohols and resulted in the corresponding hydroxylated products **4d & 4e** in moderate to good yields.

This method of hydroxylation has its own advantages over the reported methods. [20, 21, 22, 23] Firstly, the selection of the solvent system (DMF: H_2O: ^{t}BuOHsolvent) is unique and it has not been used previously. Secondly, the major applicability of this method can be seen in the usage of tertiary alcohols as the starting materials, as these hydroxylated products **XX** have the potential to be good precursors for a variety of compounds. Thirdly, the usage of 1,10-phenanthroline as ligand is novel and it is noteworthy to mention that it was not executed previously.

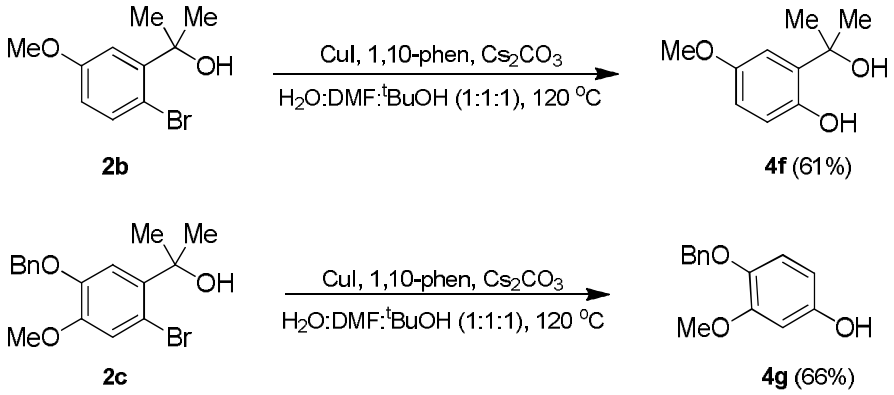
Interestingly, these optimized conditions were amenable to the following systems and furnished the corresponding phenols in good yields, Scheme 12.



Scheme 12.

When the above mentioned conditions were applied to the substituted tertiary alcohols **2b & 2c**, some interesting results were obtained. It was observed that the reactions were highly system specific and resulted in anomalous products. Like as in, when the methoxy substituted alcohol **2b** was used, it resulted in the dihydroxylated product **4f,** which can be explained on the fact that the methoxy group being present in the *meta* position with respect to the alcohol would be slightly deactivating and might have in turn activated its *meta* position to promote the second hydroxylation. Also, when the highly activated system like iso-vaniline system **2c**,

was used under the optimized conditions, it readily gave the nucleophilic substitution-elimination product **4g** by the removal of alcohol moiety as acetone.



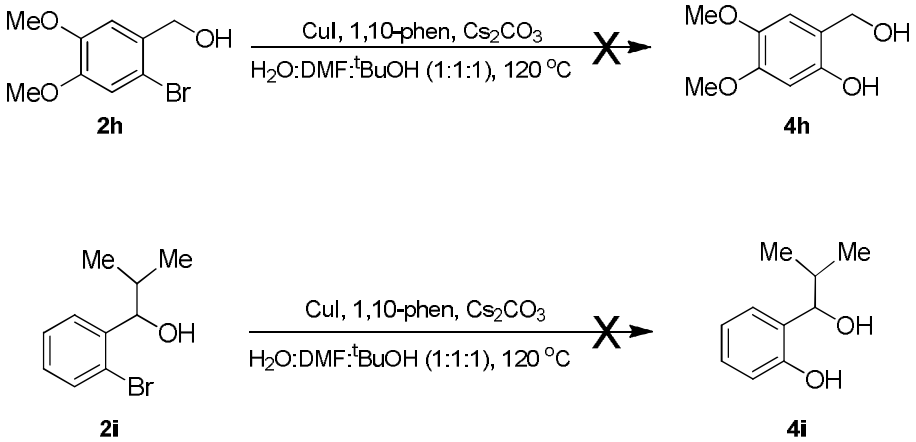
2b **4f** (61%)

2c **4g** (66%)

Scheme 13

Thus the conditions were not suitable to be applied to the aromatic tertiary alcohols with the heavier functionalities. More attempts to optimize the conditions for these systems are in progress.

A few other exceptions are worth mentioning here. For example, reactions on 2-bromo primary alcohol **2h** and secondary alcohol **2i** did not show any progress for the hydroxylation under the above standardized conditions. This may be further tried under different reaction conditions in order to generate the corresponding phenols, **4h** and **4i** as it is unlikely that the reaction does not work at all, Scheme 13.



2h **4h**

2i **4i**

Scheme 13.

The molecular structure of **2-(hydroxydiphenylmethyl)phenol**, **4e** was further confirmed by the single crystal X-ray diffraction analysis of the same as shown in Figure 3 (see Experimental section for X-ray data).

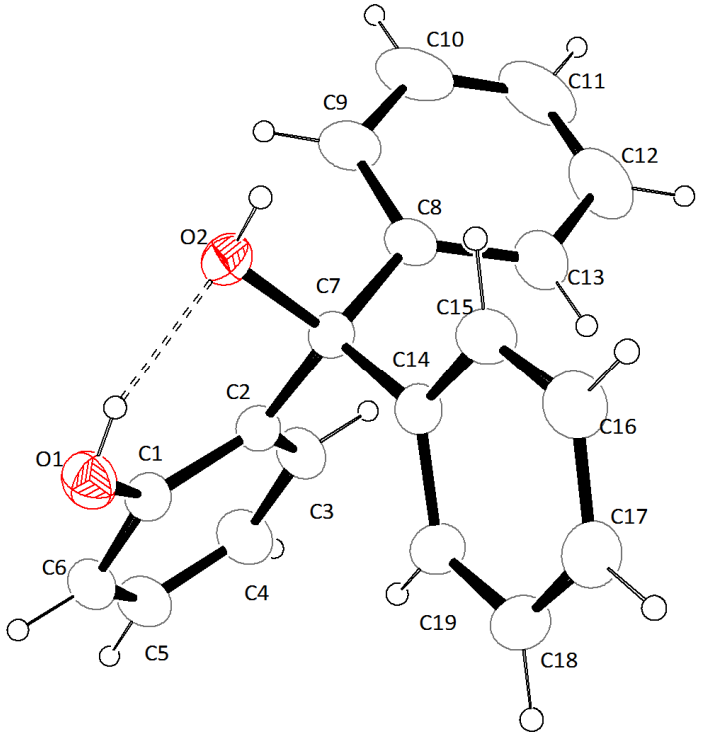


Fig.3.Ortep diagram of **2-(hydroxydiphenylmethyl)phenol, 4e.**

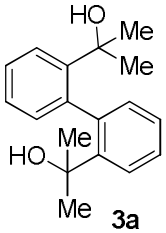
6. Conclusion:

Herein, we were able to find a method for the synthesis of α,α-dialkyl-(2-hydroxyaryl) methanols starting from very simple systems such as 2-bromobenzaldehyde. The method seems to be working well and does not require inert conditions. The development of a unique ternary solvent system, DMF:^{t}BuOH:H_2O(1:1:1) has been devised. Method is quite amenable for the synthesis of phenols from unsubstituted tertiary alcohols. These phenols are highly efficient precursors for the synthesis of many synthetically useful methodologies.

7. Experimental section:

General

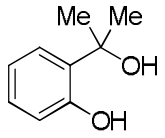
IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on BrukerAvance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ in ppm) and coupling constants (J in Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H =0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on BrukerAvance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ in ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. All small scale dry reactions were carried out using schlenk tube technique. Reactions were monitored by TLC on silica gel using a mixture of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an argon or nitrogen atmosphere. Solvents, petroleum ether, ethyl acetate and dichloromethane were distilled prior use. Petroleum ether with a boiling range of 60 to 80°C was used. Diethyl ether and toluene were dried over benzophenone/sodium. DMF was dried over calcium hydride. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).



3a

2,2'-([1,1'-biphenyl]-2,2'-diyl)bis(propan-2-ol), 3a: In an oven dried Schlenk tube, were added 2-(2-bromophenyl)propan-2-ol, **2a** (107.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7 mol%), 1,10-phenanthroline (19.8 mg, 21.5mol%) and Cs_2CO_3 (81.4 mg, 0.25 mmol) followed by addition of toluene (2 mL) at room temperature for 5 minutes under a nitrogen atmosphere.

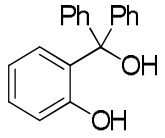
The stirred reaction mixture was then heated in an oil bath at 110 °C for 24 h. Progress of the reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:02 to 95:05) furnished the biaryl product, **3a**(45.2 mg, 67%). [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**2a**)=0.38, R_f(**3a**)=0.18, UV detection] IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3383, 2972, 2930, 1478, 1439, 1212, 752 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ=7.54 (dd, 2H, *J*=7.8 and 1.5 Hz, Ar-H), 7.18 (dd, 2H, *J*=7.8 and 1.5 Hz, Ar-H), 7.09 (ddd, 2H, *J*=8.8, 7.8 and 1.0 Hz, Ar-H), 6.82 (dd, 2H, *J*=8.3 and 1.0 Hz, Ar-H), 3.33 (br. s, 2H, OH), 1.69 [s, 6H, Ar-C$(CH_3)_2$], 1.67 [s, 6H, Ar-C$(CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.4 (s, 2C, 2 ×Ar-C), 138.8 (s, 2C, 2 ×Ar-C), 128.4 (d, 2C, 2 ×Ar-CH), 126.5 (d, 2C, 2 ×Ar-CH), 123.4 (d, 2C, 2 ×Ar-CH), 119.4 (d, 2C, 2 ×Ar-CH), 72.1 [s, 2C, 2 ×Ar-*C*(OH)$(CH_3)_2$], 30.2 [q, 4C, 4 ×Ar-C(OH)(*C*$H_3)_2$] ppm.



4a

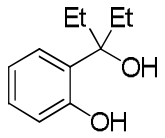
2-(2-hydroxypropan-2-yl)phenol, 4a: In a Schlenk tube, were added 2-(2-bromophenyl)propan-2-ol, **2a** (107.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7mol%), 1,10-phenanthroline (19.8 mg, 21.5 mol%) and Cs_2CO_3(651.6mg, 2.0mmol) followed by addition of DMF:H_2O:^{t}BuOH(1:1:1) for 5 minutes. The stirred reaction mixture was then heated in an oil bath at 120°C for 24 h. Progress of the hydroxylation reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:02 to 95:05) furnished the corresponding phenol 4**a** (53.7mg,66%). [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**2a**)=0.38, R_f(**4a**)=0.30, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}):

ν_{max} =3431, 2922, 2852, 1507, 1194, 697 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ=9.11 (br. s, 1H, Ar-OH), 7.14 (ddd, 1H, *J*=8.8, 6.4 and 1.5 Hz, Ar-H), 7.07 (dd, 1H, *J*=7.8 and 1.5 Hz, Ar-H), 6.84 (d, 1H, *J*=7.3 Hz, Ar-H), 6.84 (dd, 1H, *J*=7.3 and 1.0 Hz, Ar-H) 3.15 (br. s, 1H, OH), 1.64 [s, 6H, Ar-C(CH_3)$_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=155.4 (s, Ar-C), 131.1 (s, Ar-CH), 128.8 (d, Ar-CH), 125.3 (d, Ar-CH), 119.6 (d, Ar-CH), 117.4 (d, Ar-CH), 75.8 [s, Ar-*C*(OH)(CH_3)$_2$], 30.2 [q, 2C, 2 ×Ar-C(OH)(*C*H_3)$_2$] ppm.



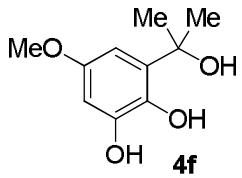
4e

2-(hydroxydiphenylmethyl)phenol, 4e: In a Schlenk tube, were added (2-bromophenyl)diphenylmethanol, **2g** (169.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7mol%), 1,10-phenanthroline (19.8 mg, 21.5 mol%) and Cs_2CO_3(651.6mg, 2.0mmol) followed by addition of DMF:H_2O:^{t}BuOH(1:1:1) for 5 minutes. The stirred reaction mixture was then heated in an oil bath at 120 °C for 24 h. Progress of the hydroxylation reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:02 to 95:05) furnished the corresponding phenol **4e** (83.0mg, 60%). [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**2g**)=0.50, R_f(**4e**)=0.37, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} =2920, 2851, 1261, 721 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz):): δ=8.15 (br. s, 1H, Ar-OH), 7.45–7.27 (m, 5H, Ar-H), 7.26–7.12 (m, 5H, Ar-H), 6.88 (dd, 1H, *J*=8.3 and 1.5 Hz, Ar-H), 6.74 (ddd, 1H, *J*=8.8, 7.3 and 1.5 Hz, Ar-H), 6.52 (dd, 1H, *J*= 7.8 and 2.0 Hz, Ar-H) 3.78 (br. s, 1H, OH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=155.9 (s, Ar-C), 114.8 (s, Ar-C), 130.0 (d, Ar-CH), 129.5 (d, Ar-CH), 128.2 (d, 4C, 4 ×Ar-CH), 127.9 (d, 2C, 2 ×Ar-CH), 127.7 (d, 4C, 4 ×Ar-CH), 119.1 (d, Ar-CH), 117.5 (d, Ar-CH), 84.4 [s, Ar-*C*(OH)(Ph)$_2$] ppm.HR-MS (ESI+) m/z calculated for $[C_{19}H_{15}O]^+$=$[(M+H)–H_2O]^+$: 259.1117; found: 259.1120



4d

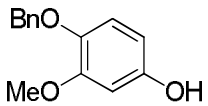
2-(3-hydroxypentan-3-yl)phenol, **4d:** In a Schlenk tube, were added 3-(2-bromophenyl)pentan-3-ol, **2f** (121.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7mol%), 1,10-phenanthroline (19.8 mg, 21.5 mol%) and Cs_2CO_3(651.6mg, 2.0mmol) followed by addition of DMF:H_2O:^{t}BuOH(1:1:1) for 5 minutes. The stirred reaction mixture was then heated in an oil bath at 120 °C for 24 h. Progress of the hydroxylation reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:02 to 95:05) furnished the corresponding phenol **4d** (65mg, 72%). [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**2f**)=0.40, R_f(**4d**)=0.38, UV detection].IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} =3357, 2919, 2850,1234, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=9.48 (br. s, 1H, Ar-OH), 7.13 (ddd, 1H, *J*=8.8, 6.4 and 2.0 Hz, Ar-H), 6.90 (dd, 1H, *J*=7.8 and 2.0 Hz, Ar-H), 6.84 (dd, 1H, *J*=8.3 and 1.0 Hz, Ar-H), 6.80 (ddd, 1H, *J*=8.3, 6.4 and 1.0 Hz, Ar-H) 2.42 (br. s, 1H, OH), 2.05–1.88 [m, 2H, Ar-C(C*H*$_2$CH$_3$)], 1.87–1.70 [m, 2H, Ar-C(C*H*$_2$CH$_3$)] 0.87 [t, 6H, Ar-C(CH$_2$C*H*$_3$)$_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.0 (s, Ar-C), 128.5 (d, Ar-CH), 126.8 (d, Ar-CH), 126.4 (s, Ar-C), 119.1 (d, Ar-CH), 117.6 (d, Ar-CH), 82.4 [s, Ar-*C*(OH)(CH$_2$CH$_3$)$_2$], 34.1 [t, 2C, 2 ×Ar-C(OH)(*C*H$_2$CH$_3$)$_2$], 7.8 [q, 2C, 2 ×Ar-C(OH)(CH$_2$*C*H$_3$)$_2$] ppm.



4f

3-(2-hydroxypropan-2-yl)-5-methoxybenzene-1,2-diol, 4f: In a Schlenk tube, were added 2-(2-bromo-5-methoxyphenyl)propan-2-ol, **2b** (122.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7mol%), 1,10-phenanthroline (19.8 mg, 21.5 mol%) and Cs_2CO_3(651.6mg, 2.0mmol) followed by addition of DMF:H_2O:^{t}BuOH(1:1:1) for 5 minutes. The stirred reaction mixture

was then heated in an oil bath at 120 °C for 24 h. Progress of the hydroxylation reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 60:40 to 50:50) furnished the corresponding phenol **4f** (60mg, 61%). [TLC control (petroleum ether/ethyl acetate 50:50), R_f(**2b**)=0.50, R_f(**4f**)=0.30, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} =3280, 2921, 2850, 1494, 1463, 1210, 1042, 758 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ=9.21 (br. s, 1H, Ar-OH), 6.80–6.73 (m, 2H, Ar-H), 4.75 (br. s, 1H, Ar-H), 3.76 (s, 3H, Ar-OCH_3), 1.63 [s, 6H, Ar-C$(CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=153.1 (s, Ar-C), 145.2 (s, Ar-C), 134.5 (s, Ar-C), 128.0 (s, Ar-C), 114.7 (d, Ar-CH), 112.3 (d, Ar-CH), 74.9 [s, Ar-*C*(OH)$(CH_3)_2$], 55.8 (q, Ar-OCH_3), 30.0 [q, 2C, 2 ×Ar-C(OH)(*C*$H_3)_2$] ppm.



4g

2-(hydroxydiphenylmethyl)phenol, 4g: In a Schlenk tube, were added (2-bromophenyl)diphenylmethanol, **2c** (175.5 mg, 0.5 mmol), CuI (9.5 mg, 10.7mol%), 1,10-phenanthroline (19.8 mg, 21.5 mol%) and Cs_2CO_3(651.6mg, 2.0mmol) followed by addition of DMF:H_2O:^{t}BuOH(1:1:1) for 5 minutes. The stirred reaction mixture was then heated in an oil bath at 120 °C for 24 h. Progress of the Hydroxylation reaction was monitored by TLC till the reaction is completed. The stirred reaction mixture was then allowed to come to room temperature and monitored by TLC. Then, the mixture was treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:02 to 95:05) furnished the corresponding phenol **4g** (55mg, 66%). [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**2c**)=0.40, R_f(**4g**)=0.29, UV detection].IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} =3259, 2977, 2929, 1235, 1261, 749 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ=7.41 (d, 2H, *J*=7.3 Hz Ar-H), 7.34 (dd, 2H, *J*=7.3 and 6.8 Hz Ar-H), 7.29 (d, 1H, *J*=7.3 Hz Ar-H), 6.71 (d, 1H,

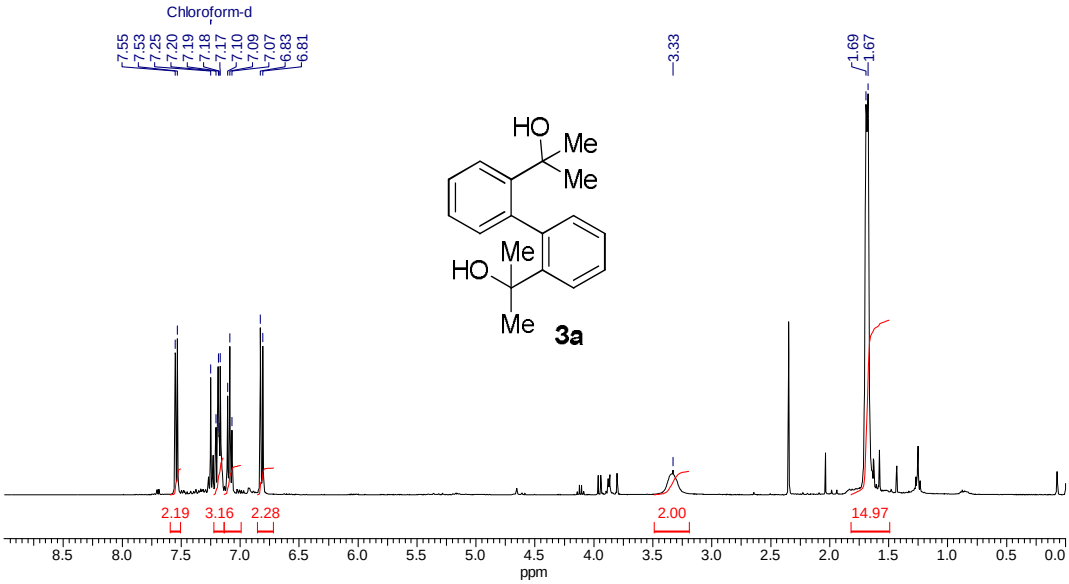
J=8.3 Hz Ar-H), 6.44 (d, 1H, *J*=2.9 Hz Ar-H), 6.24 (dd, 1H, *J*=8.8 and 2.9 Hz Ar-H), 5.32 (br. s, 1H, Ar-OH), 5.05 (s, 3H, Ar-OCH_3), 3.79 [s, 6H, Ar-$C(CH_3)_2$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=150.8 (s, 2C, 2 ×Ar-C), 141.9 (s, Ar-C), 137.3 (s, Ar-C), 128.4 (d, 2C,2 ×Ar-CH), 127.7 (d, Ar-CH), 127.5 (d, 2C, 2 ×Ar-CH), 116.2 (d, Ar-CH), 105.9 (d, Ar-CH), 100.8 (d, Ar-CH), 72.3 (t, Ar-OCH_2), 55.8 (q, Ar-OCH_3) ppm.HR-MS (ESI+) m/z calculated for $[C_{14}H_{13}O_2]^+$=$[(M+H)–H_2O]^+$: 213.0910; found: 213.0874

X-ray crystal structure data for2-(hydroxydiphenylmethyl)phenol, 4e:

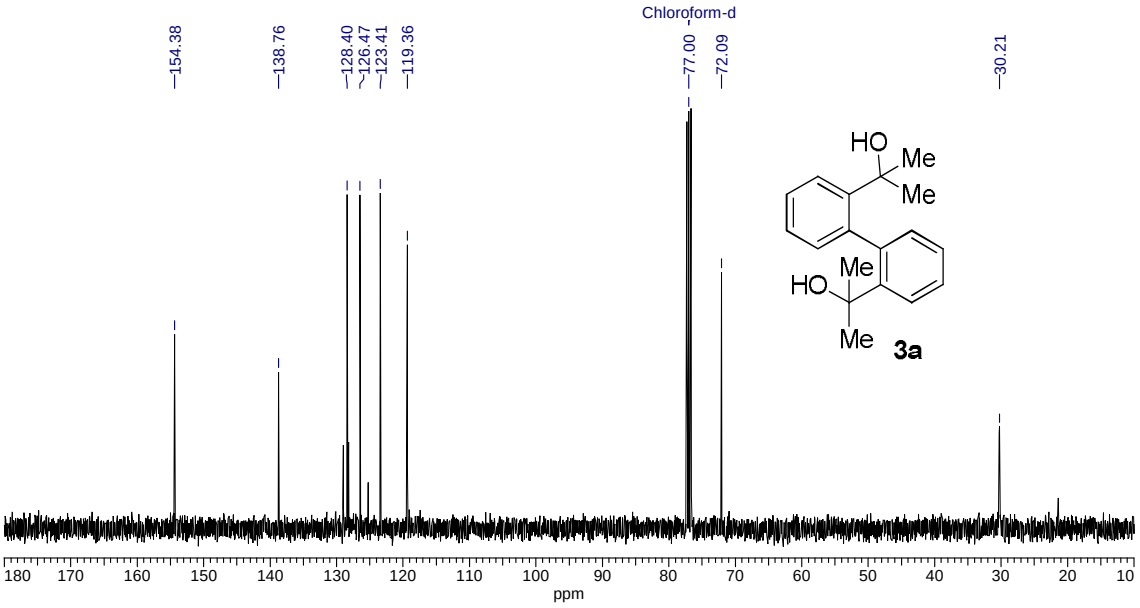
Operator	K. Ravikumar
Instrument	Oxford Super Nova
Empirical formula	$C_{19}H_{16}O_2$
Formula weight	276.32
Crystal system	monoclinic
Space group	C 2/c
a/Å	22.3977(5)
b/Å	8.6292(2)
c/Å	16.0016(4)
α/°	90.00
β/°	107.841(2)
γ/°	90.00
Volume/Å^3	2943.97(12)
Z	8
ρcalcmg/mm^3	1.247
S	1.027
m/mm^{-1}	0.632
F(000)	1168.0

Crystal size/mm^3	0.18 × 0.16 × 0.12
2Θ range for data collection	5.531 to 70.870°
Index ranges	$-27 \leq h \leq 25$, $-9 \leq k \leq 10$, $-12 \leq l \leq 19$
Reflections collected	2796
Data/restraints/parameters	2796/0/192
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	$R_1 = 0.0436$, $wR_2 = 0.1238$
Final R indexes [all data]	$R_1 = 0.0488$, $wR_2 = 0.1318$
Largest diff. peak/hole / e $Å^{-3}$	0.21/-0.18

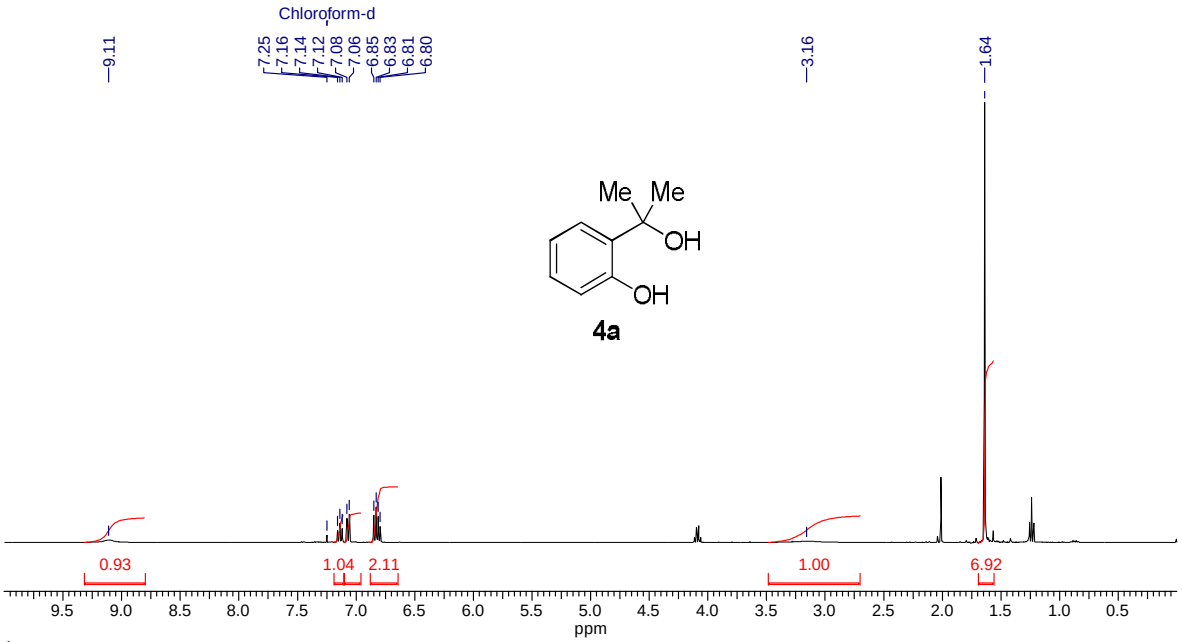
Spectra of all the synthesized compounds, confirmed by NMR:



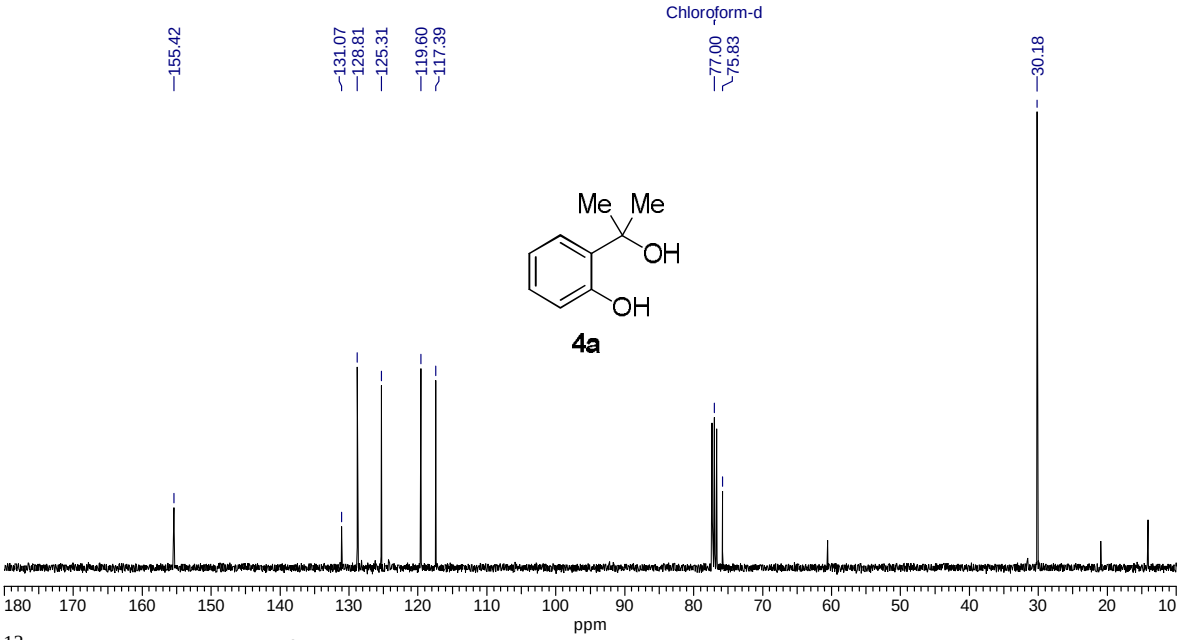
^{1}H NMR (400 MHz) of compound **3a** in $CDCl_3$



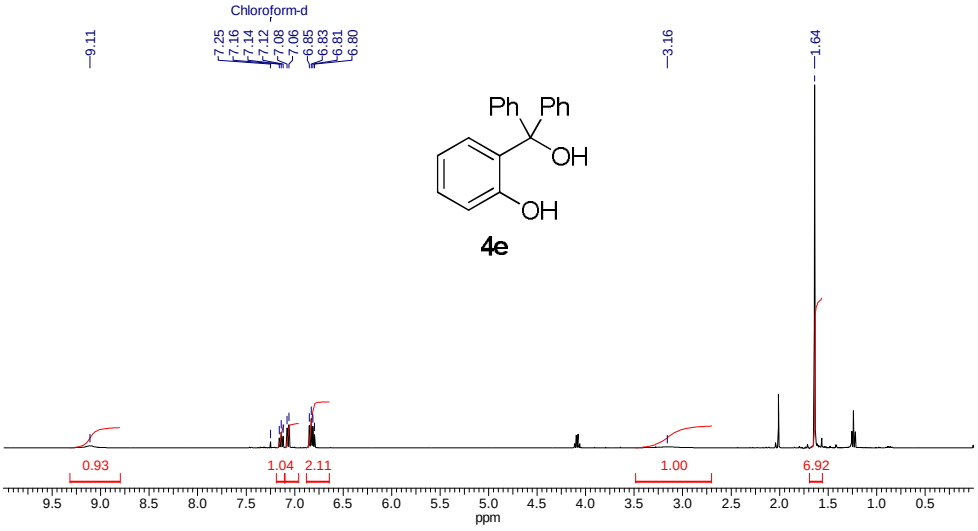
^{13}C NMR (100 MHz) of compound **3a** in $CDCl_3$



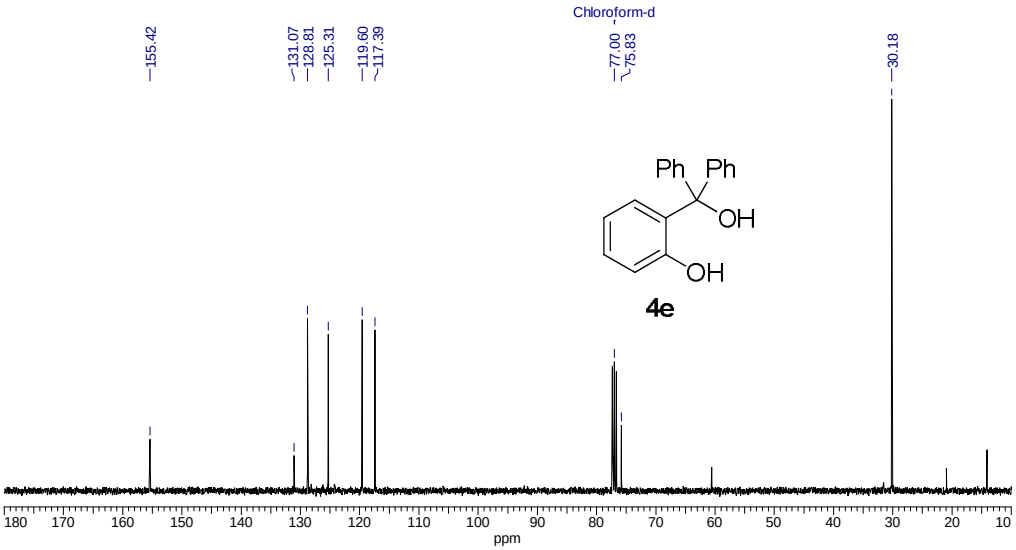
^{1}H NMR (400 MHz) of compound **4a** in $CDCl_3$



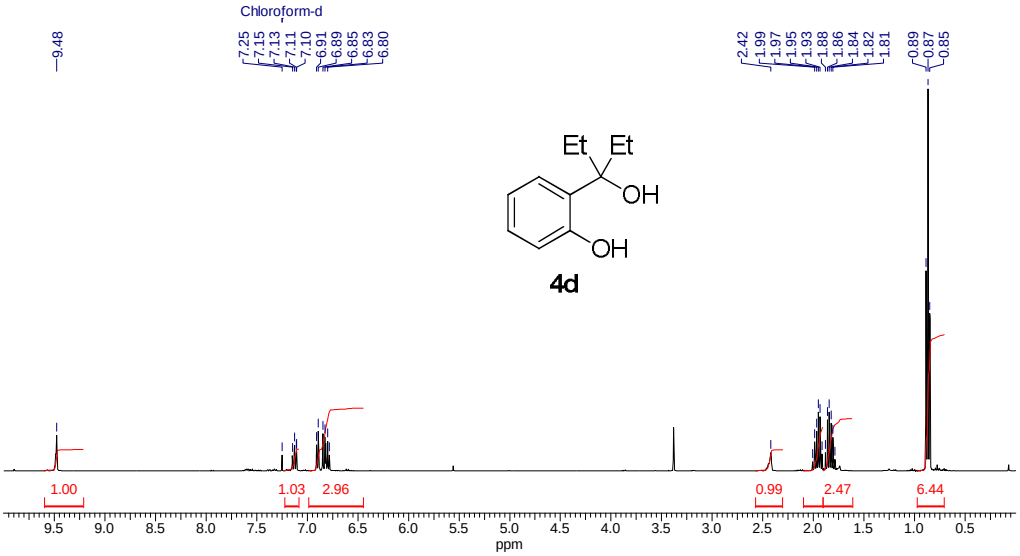
^{13}C NMR (100 MHz) of compound **4a** in $CDCl_3$



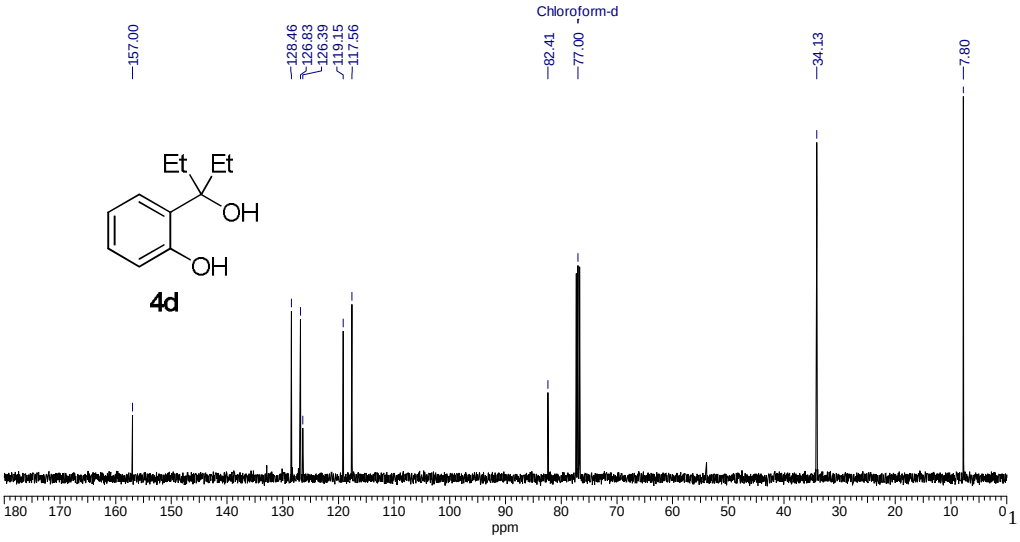
^{1}H NMR (400 MHz) of compound **4e** in $CDCl_3$



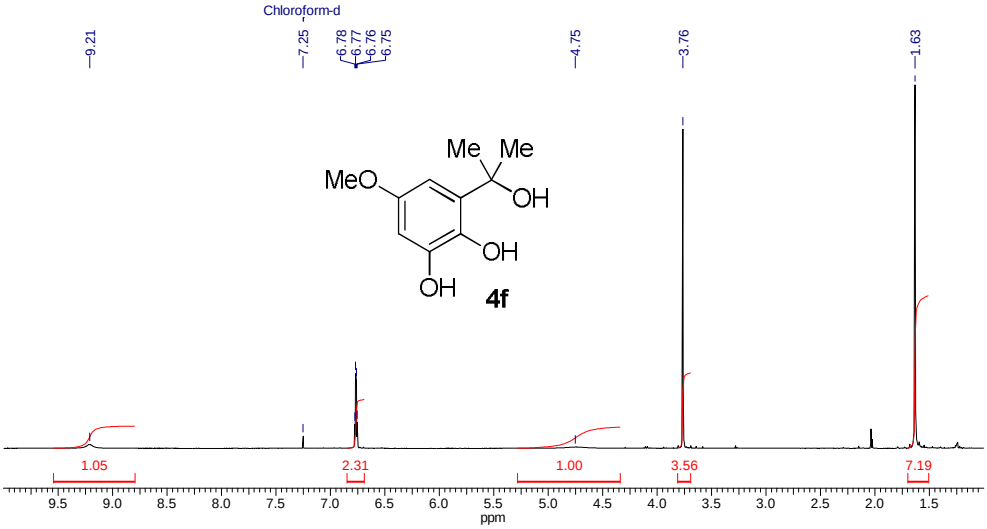
^{13}C NMR (100 MHz) of compound **4e** in $CDCl_3$



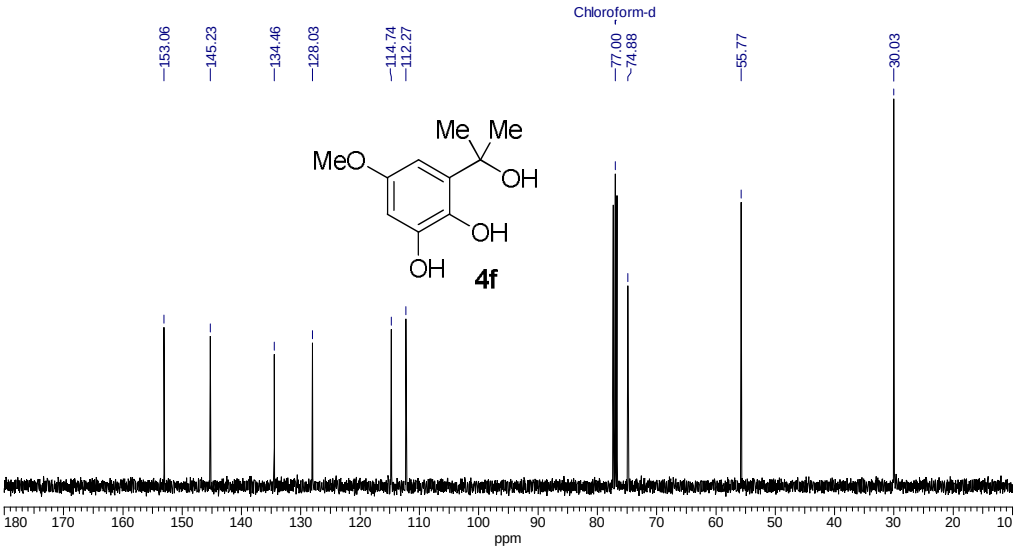
^{1}H NMR (400 MHz) of compound **4d** in $CDCl_3$



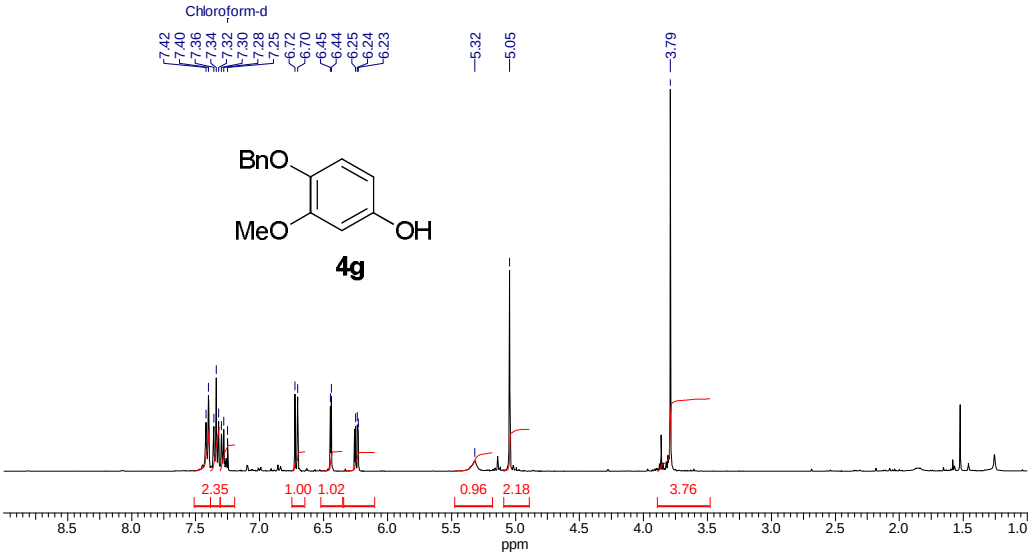
^{13}C NMR (100 MHz) of compound **4d** in $CDCl_3$



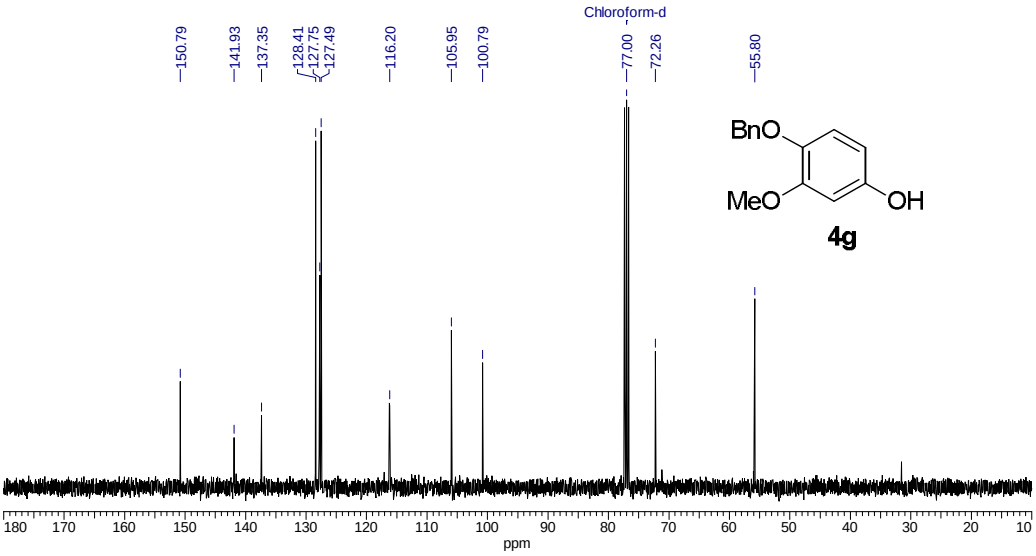
^{1}H NMR (400 MHz) of compound **4f** in $CDCl_3$



^{13}C NMR (100 MHz) of compound **4f** in $CDCl_3$



^{1}H NMR (400 MHz) of compound **4g** in $CDCl_3$



^{13}C NMR (100 MHz) of compound **4g** in $CDCl_3$

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