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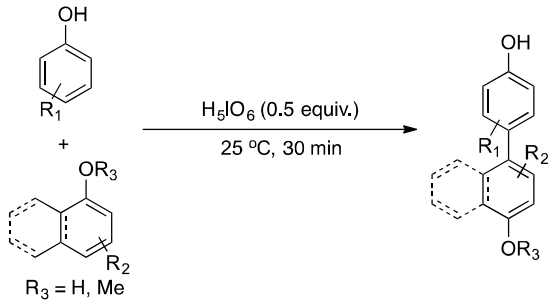

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Oxidative Phenol-Arene and Phenol-Phenol Cross-Coupling Using Periodic Acid

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ABSTRACT

A simple, metal-free protocol for unsymmetrical biaryl coupling using H_5IO_6 is reported. H_5IO_6 was evaluated for a novel application in the oxidative cross-coupling of phenol-arene, phenol-phenol, and phenol-naphthol compounds. In this work, most of the couplings were completed within 30 minutes at ambient temperature. 30 coupling products were conveniently obtained using only 0.5 equivalent of H_5IO_6 in HFIP. A mechanism by which the transformation occurs is proposed.

1. Introduction

The preparation of unsymmetrical biaryl motifs continues to draw significant attention because of the ubiquity of this scaffold in phenolic natural products and a range of other compounds of importance in the food and pharmaceutical industries. Biaryl compounds are widely applied as ligands in organometallics[1] and as synthons of bioactive natural products,[2] and they are heavily utilized in pharmaceuticals and polymeric materials.[3] The most common means of accessing unsymmetrical biaryl constructs are based on classic cross-coupling reactions such as the Suzuki or Stille couplings, which usually require pre-functionalized aryl rings and protection of phenol groups.[2f,4] Although the accomplishment of the transformation *via* oxidative cross-coupling of phenols can potentially overcome the aforementioned hurdles, this approach can lead to the concurrent formation of undesired homo-coupling adducts, polymers, quinones, and Pummerer's ketones.[5] Nevertheless, A series of direct unsymmetrical oxidative arylation strategies have been developed in the last few decades.[6] The use of transition metals such as Cu(II),[7] Ru,[8] and V[9] have been reported to synthesize the unsymmetrical bi-phenols. Recently, Pappo and co-workers demonstrated that an Fe(III) metal complex could provide an excellent alternative for connecting biaryl bonds directly from two unfunctionalized phenolic components.[10] As a case in point, Cr[5] mediated regioselective *para-para*, *para-ortho*, and *ortho-ortho* couplings have been elegantly illustrated by the Kozlowski group. Meanwhile, reports of metal-free oxidative methods have also emerged. Oxidation systems such as hypervalent-iodine (III) and the iodo-methoxybenzene/Oxone[11] developed by the Kita group, as well as DDQ[12], SeO_2[13], and $K_2S_2O_8$[14] have been reported. Except that, metal- and reagent-free electrochemical oxidation protocol was also successfully achieved by Boron-doped diamond (BBD) electrode.[15]

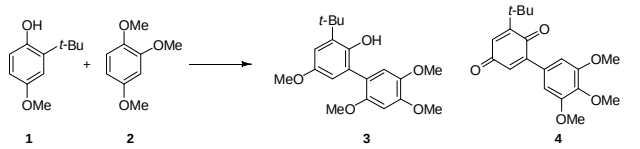
Periodic acid (H_5IO_6) is an inexpensive commercially available reagent in which iodine exists in the oxidation state of VII. It is a commonly used oxidant for cleavage of vicinal diols. In addition, its moderate acidity (pKa = 3.29[16] compared to 0.23 of TFA) and superior water solubility make it compatible with biological systems and selective for specific functional groups.[17] According to some published reports of metal-free oxidants,[11,14] both oxidative potential and acidity are necessary for oxidant-mediated cross-coupling of phenols. We believed that the combination of its strong oxidative potential and acidity make periodic acid a possible candidate for phenol oxidative cross-coupling. Here, we report a new facile and straightforward protocol for the accomplishment of unsymmetrical phenol-arene, phenol-phenol, and phenol-naphthol linkages with H_5IO_6 at ambient temperature.

2. Results/Discussion

We commenced our investigation by surveying the conditions required for unsymmetrical oxidation of 2-(*tert*-butyl)-4-methoxyphenol **1** and 1,2,4-trimethoxybenzene **2** with different oxidants (Table 1). None of the desired product was formed with *p*-Chloranil in DMF at room temperature. Ceric ammonium nitrate (CAN) or Oxone in 1,1,1,3,3,3-hexafluoropropropan-2-ol (HFIP) provided only a trace amount of the targeted hetero-adduct **3** (entries 2 & 3). One general photoredox conditions were also investigated which a catalytic amount of $Ru(bpy)_3Cl_2$ (10 mol%) was used under aerobic condition, but no product was

observed, and both starting materials remained intact. However, we were encouraged to find that a stoichiometric amount of iodine and iodic acid HIO_3 (V) generated 21% and 12% of the desired product **3** respectively in acetonitrile (entry 5, 6). Using higher oxidation state iodine in the form of periodic acid (H_5IO_6) in HFIP led to complete consumption of the materials, no desired product **3** is isolated, and byproduct benzoquinone **4** was obtained in 72% yield due to the over-oxidation.[8, 14c] Reducing the loading of H_5IO_6 to 0.5 equivalent furnished **3** in 73% yield. Further screening led to the optimized reaction conditions shown in entry 9, where 1.5 equivalents of **2** produced **3** in 84% yield within 30 minutes. Finally, the conditions using iodine or HIO_3 in HFIP were evaluated (entries 12, 13). The results were observed to be inferior to those of the aforementioned optimized conditions. It is worth noting that the use of half equivalent of periodic acid is critical for the optimal yield, increase or decrease of oxidant loading will lead to either benzoquinone adduct or incomplete reaction.

Table 1. Initial Investigation of Unsymmetrical Coupling.[a]



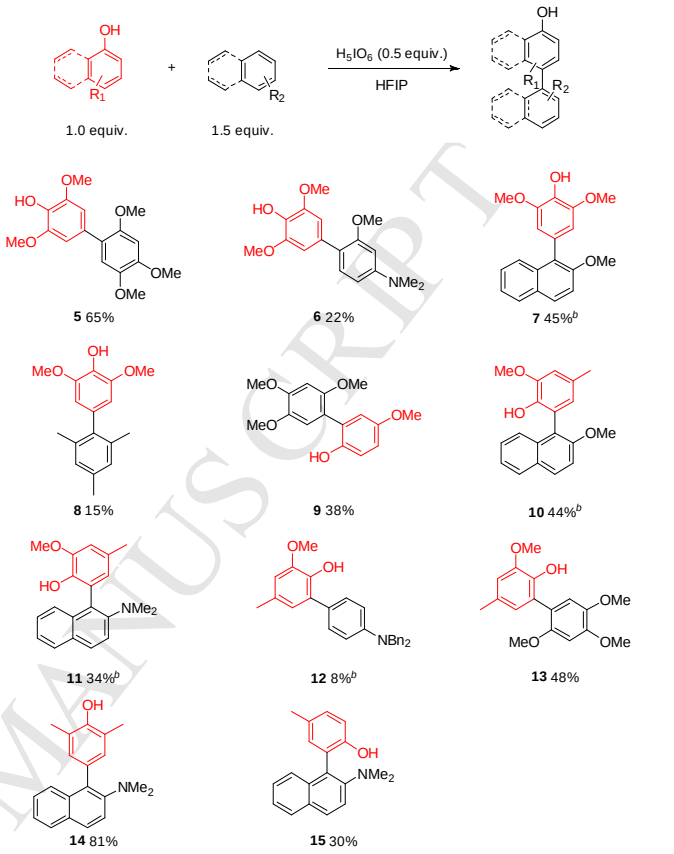
1 **2** **3** **4**

Entry	oxidant	solvent	ratio of **2**/**1**	amount of oxidant	yield of **3**(%)[b]
1	p-chloranil	DMF	1:1	1.0	NR
2	CAN	HFIP	1:1	1.0	trace
3	Oxone	HFIP	1:1	1.0	trace
4	$Ru(bpy)_3Cl_2$/air	CH_3CN	1:1	0.1	NR
5	I_2	CH_3CN	1:1	1.0	21
6[e]	HIO_3	CH_3CN	1:1	1.0	12
7[e]	H_5IO_6	HFIP	1:1	1.0	0[c]
8[e]	H_5IO_6	HFIP	1:1	0.5	73
9[e]	H_5IO_6	HFIP	1.5:1	0.5	84[d]
10[e]	H_5IO_6	HFIP	1.5:1	0.6	73
11[e]	H_5IO_6	HFIP	1.5:1	0.4	58
12[e]	HIO_3	HFIP	1:1	1.0	66
13	I_2	HFIP	1:1	1.0	15

[a] All reactions were carried out in 0.2 M solutions of **1** under air at room temperature. [b] All yields were confirmed by ^1H NMR with DMSO as the internal standard. [c] byproduct benzoquinone **4** was isolated in 72% yield. [d] isolation yield. [e] the oxidant was dissolved in DMF (2.50 M) which was then added to the reaction.

With the optimized protocol in hand, the scope of the cross-coupling of phenols and arenes was probed (Table 2). A small library of phenols and arenes were subjected to the optimized conditions. In the presence of oxidant, the *para* position of 2,6-dimethoxyphenol was coupled with electron-rich arenes, providing products **5** (65%), **6** (22%) and **7** (45%) respectively. The reaction of 2,6-dimethoxyphenol and relatively electron-poorer mesitylene generated the product **8** in low yield (15%). Similarly, the *ortho*-position of 4-methoxyphenol and 2-methoxy-4-methylphenol reacted with different arenes, affording the products **9** (38%), **10** (44%), **11** (34%), **12** (8%), **13** (48%). Specifically, the *para*-position couplings generally led to better yields when compared to the *ortho*-position adducts, presumably due to steric effects. Furthermore, phenols lack of methoxyl substitutes such as 2,6-dimethylphenol and *p*-cresol were also coupled with *N*,*N*-dimethyl-2-naphthylamine and provided the adducts **14** (81%) and **15** (30%) respectively. Mix solvent of HFIP/CH_3NO_2 was used for the formation of compounds **7**, **10** and **11** due to the poor solubility of arenes in HFIP alone.

Table 2. Cross-Coupling between Phenols and Arenes.[a]



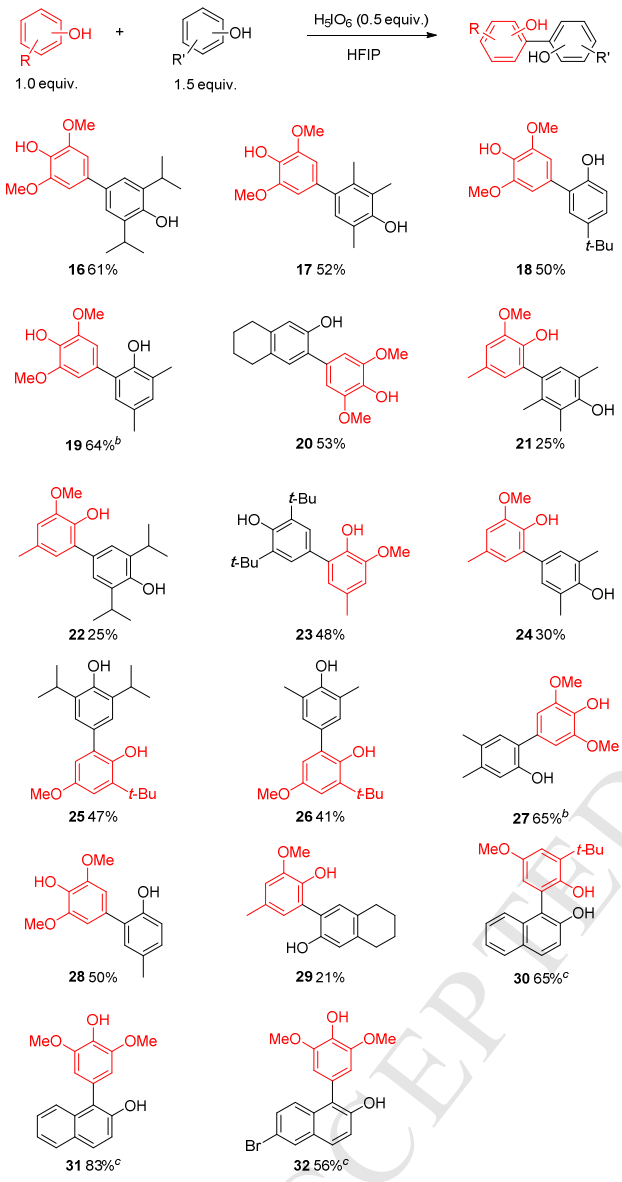
[a] All reactions were carried out by adding 0.5 equivalent of H_5IO_6 (2.50 M in DMF) to a solution of phenol (0.2 mmol) and arene (0.3 mmol) in HFIP at room temperature under air. [b] Products were obtained using 1:1 HFIP/CH_3NO_2 as the solvent.

To expand the reaction scope of our protocol, we extended our investigations to include phenol-phenol oxidative couplings. A total of 17 examples are illustrated in Table 3. Similar to the outcome of the phenol-arene oxidation, the H_5IO_6 mediated selective couplings produced from moderate to good yields in most cases. The reaction can provide *para-para* cross-coupling products **16** (61%), **17** (52%), *para-ortho* cross-coupling products **18** (50%), **19** (64%), **20** (53%), **21** (25%), **22** (25%), **23** (48%), **24** (30%), **25** (47%), **26** (41%), **27** (65%), **28** (50%) and *ortho-ortho* cross-coupling product **29** (21%). Finally, the reactions between phenol and naphthol were also proved to be efficient using H_5IO_6 protocol and be able to tolerate the presence of a halogen, leading to adduct **30** (65%), **31** (83%), **32** (56%).

In order to further understand the reaction mechanism, the effect of the solvents was considered (Scheme 1). In the highly polarized solvents such as 2,2,2-Trifluoroethanol (TFE) or HFIP, oxidation of phenols **33** and **33a** produced adduct **19** in 34% and 64% yields respectively; whereas non-protic solvent dichloroethane furnished the same product with 12% yield. Fluoroalcohols are known to stabilize the radical cation intermediate and boost coupling yield,[18] and the existing strong hydrogen bonding interaction between HFIP and phenol could shift the oxidation potential and nucleophilicity of phenol

substrates under reaction condition.[19] For *ortho*-methoxyl phenol, it was proposed by Pappo group that the intramolecular hydrogen bond could be altered to an intermolecular fashion by HFIP and the liberated free phenol hydroxyl group may be more accessible for chelation and oxidation.[10b] Our experiments appeared to support such theory.

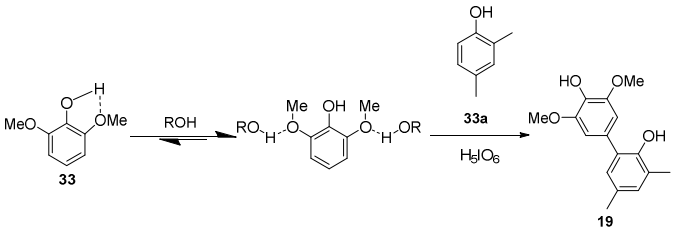
Table 3. Cross-Coupling between Different Phenols.[a]



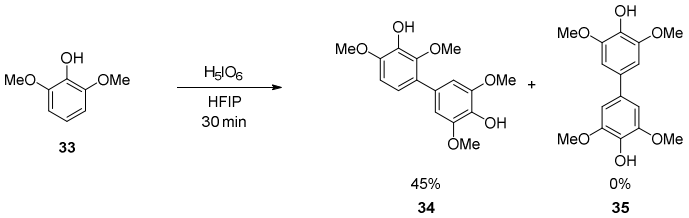
[a] All reactions were carried out by adding 0.5 equivalent of H_5IO_6 (2.50 M in DMF) to a solution of the phenol mixture (0.2 M) in HFIP at room temperature under air. [b] Reactions were complete within 3 h. [c] HFIP/CH_3NO_2 (1:1) were used as the solvent.

Subsequently, the H_5IO_6 mediated homocoupling of 2,6-dimethoxyphenol was further explored as mechanistic probe based on the Pappo's design (Scheme 2).[10b,10c] Under standard reaction conditions, unsymmetrical bi-phenol **34** was obtained as the solo

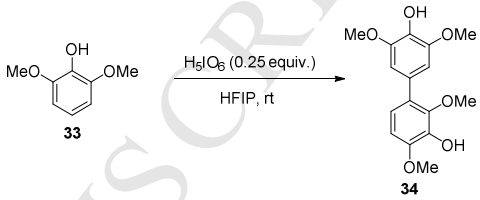
Scheme 1. Possible Solvent Effects.[10b]



Scheme 2. Possible Solvent Effects. [a]



[a] The reaction was carried out by adding 0.25 equivalent of H_5IO_6 (2.50 M in DMF) to a solution of phenol **33** (0.2M in HFIP) at room temperature.



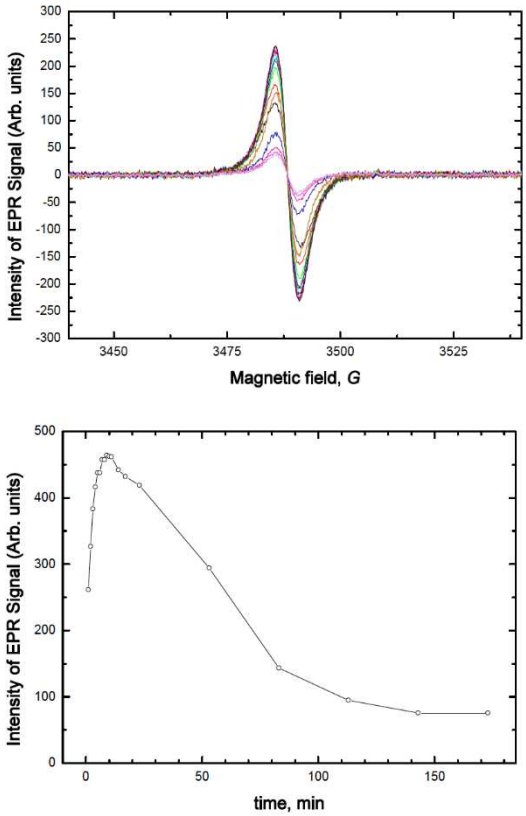
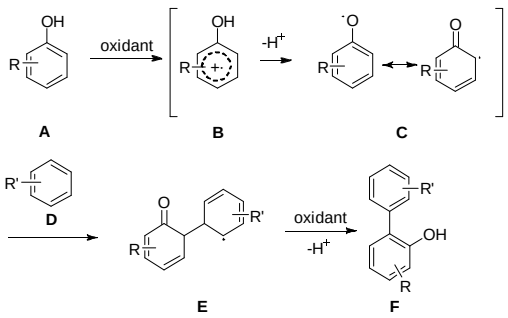


Figure 1. EPR Experiments. EPR spectra: the sample was prepared by adding 0.25 equivalent of H_5IO_6 (0.3 M in DMF) to a solution of phenol **33** (40 mM in HFIP) at room temperature. The measurements were carried out at different time points.

product in 45% yield. Radical-radical and radical-anion coupling mechanism have been proposed by other research groups.[10b,10c,20] The formation of unsymmetrical bi-phenol **34** may be explained by the radical-anion mechanism, while generation of homolytic coupling product **35** is known to undergo outer-shell radical-radical pathway.[10b,10c] Based on the exclusive formation of unsymmetrical product **34**, the H_5IO_6 protocol likely involves in the radical-anion complexes where *para*-phenoxyl radical of

phenol **33** was attached by the most nucleophilic *meta*-position of **33**.

We next carried out Electron Paramagnetic Resonance (EPR) to verify our proposed mechanism.[14b] Mixture of H_5IO_6 (0.25 equiv) and HFIP solution of phenol **33** (40 mM) in 0.7 mm ID capillary was placed into resonator of EPR spectrometer at ambient temperature, and strong absorption signal was observed. A series of EPR spectra (Figure 1a) has been recorded at different time points. Time depending of EPR signal (Figure 1b) shows fast saturation of signal and relatively slow falling curve, which might be attributed to a multi-stage parallel oxidation process. A control experiment using phenol **33** in HFIP alone did not produce any EPR signal. The observation suggested the presence of phenoxyl radical during the oxidation reaction.



Scheme 3. Proposed Reaction Mechanism.

Based on experimental data and literature reports,[10b,14b] we tentatively propose a plausible radical-anion mechanism for the transformation (Scheme 3). We believed that the complexation of phenol **A** with H_5IO_6 resulted in a radical cation **B**, presumably through a SET (single-electron transfer) oxidation process. The phenoxyl radical **C** may be generated from the radical cation **B** after dissociation of H^+. Nucleophilic addition of phenol/arene **D** should produce radical intermediate **E** which lead to the cross-coupling product **F**.

3. Conclusion

In summary, we have demonstrated a facile and straightforward method to prepare unsymmetrical phenol-arene, phenol-phenol and phenol-naphthol adducts using H_5IO_6 as the oxidant. 30 unsymmetrical coupling products can be easily synthesized. This convenient procedure relies on a single reagent without the addition of additives or the need for pre-functionalization, and the reactions are generally accomplished within 30 minutes at the mild condition. Reaction mechanism has been investigated and discussed for further understanding the properties of H_5IO_6. Experimental Section

4. Experimental Section

4.1 General Procedures

To a solution of phenol **A** (0.2 mmol) and phenol or arene **B** (0.3 mmol, 1.5 equiv.) in HFIP (1 mL) at room temperature, was added H_5IO_6 (2.50 M solution in DMF, 0.1 mmol, 0.5 equiv) dropwise in 10 minutes. The resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (eluent: n-hexane/ EtOAc) to afford the product.

For the table 3, the products **15**, **16**, **17**, **18**, **19**, **26**, **27**, **30**, **31** were obtained by using 1.0 equivalent of 2,6-dimethoxyphenol and 1.5 equivalent of another cross-coupling partner. The products of **20**, **21**, **22**, **23**, **28** were obtained by using 1.0 equivalent of 2-methoxy-4-methylphenol and 1.5 equivalent of another cross-coupling partner. The products **24**, **25**, **29** were obtained by using 1.0 equivalent of 2-(*tert*-butyl)-4-methoxyphenol and 1.5 equivalent of another cross-coupling partner.

4.2 Experiment data

*3-(tert-butyl)-2',4',5,5'-tetramethoxy-[1,1'-biphenyl]-2-ol (**3**).*[11b] 57.4 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, s), 6.67 (1H, d, *J* = 2.0 Hz), 6.60 (1H, d, *J* = 2.0 Hz), 6.58 (1H, s), 3.92 (3H, s), 3.84 (3H, s), 3.74 (3H, s), 1.32 (9H, s). HRMS (ESI+) *m/z* calculated for $[(C_{20}H_{26}O_5)H]^+$ 347.1853 found 347.1845.

*3-(tert-butyl)-3',4',5'-trimethoxy-[1,1'-biphenyl]-2,5-dione(**4**).*[8] The compound **4** was obtained using general procedure by adding 1.0 equiv H_5IO_6. 47.5 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* = 4.0 Hz), 6.87 (1H, s), 6.66 (2H, s), 6.07 (1H, s), 3.95 (3H, s), 3.88 (3H, s), 3.83 (3H, s), 3.80 (3H, s), 1.46 (9H, s). HRMS (ESI+) *m/z* calculated for $[(C_{19}H_{22}O_5)H]^+$ 331.1540 found 331.1545.

*2',3,4',5,5'-pentamethoxy-[1,1'-biphenyl]-4-ol (**5**).*[11b] 41.6 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.74 (2H, s), 6.63 (1H, s), 5.52 (1H, s), 3.94 (3H, s), 3.92 (6H, s), 3.88 (3H, s), 3.77 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.6, 148.8, 146.6, 143.2, 133.8, 129.5, 122.5, 114.5, 106.3, 98.5, 56.8, 56.7, 56.4, 56.3, 56.2. HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{20}O_6)H]^+$ 321.1333 found 321.1343.

*4'-(dimethylamino)-2',3,5-trimethoxy-[1,1'-biphenyl]-4-ol (**6**).*[11b] 13.3 mg, 22% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, d, *J* = 8.0 Hz), 6.75 (2H, s), 6.41 (1H, d, *J* = 8.0 Hz), 6.35 (1H, s), 5.45 (1H, s), 3.90 (6H, s), 3.82 (3H, s), 3.00 (6H, s). HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{21}NO_4)H]^+$ 304.1543 found 304.1543.

*2,6-dimethoxy-4-(2-methoxynaphthalen-1-yl) phenol (**7**).*[11b] 27.9 mg, 45% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 6.0 Hz), 7.83 (1H, m), 7.56 (1H, m), 7.39-7.35 (3H, m), 6.60 (2H, s), 5.61 (1H, s), 3.88 (6H, s), 3.87 (3H, s). HRMS (ESI+) *m/z* calculated for $[(C_{19}H_{18}O_4)H]^+$ 311.1278 found 311.1275.

*3,5-dimethoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-4-ol (**8**).*[14b] 8.2 mg, 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (2H, s), 6.37 (2H, s), 5.49 (1H, s), 3.86 (6H, s), 2.33 (3H, s), 2.05 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.0, 139.1, 136.7, 136.4, 133.0, 132.1, 128.0, 105.7, 56.3, 21.0, 20.6. HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{20}O_3)H]^+$ 273.1485 found 273.1472.

*2',4',5,5'-tetramethoxy-[1,1'-biphenyl]-2-ol (**9**).*[11b] 22.1 mg, 38% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 8.0 Hz), 6.86 (2H, m), 6.82 (1H, d, *J* = 3.0 Hz), 6.66 (1H, s), 6.24 (1H, s), 3.95 (3H, s), 3.88 (3H, s), 3.85 (3H, s), 3.81 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 149.7, 149.4, 147.6, 144.4, 126.9, 118.7, 118.4, 116.2, 115.0, 114.0, 98.5, 57.8, 56.5, 56.2, 55.8. HRMS (ESI+) *m/z* calculated for $[(C_{16}H_{18}O_5)H]^+$ 291.1227 found 291.1228.

2-methoxy-6-(2-methoxynaphthalen-1-yl)-4-methylphenol ***(10)***.[11c] 25.9 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 8.8 Hz), 7.84 (1H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 8.8 Hz), 7.36-7.34 (2H, m), 6.80 (1H, s), 6.67 (1H, s), 5.38 (1H, s), 3.96 (3H, s), 3.90 (3H, s), 2.37 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 146.7, 141.4, 133.5, 129.5, 129.2, 128.9, 127.9, 126.4, 125.3, 124.4, 123.6, 122.2, 120.5, 113.9, 111.2, 57.0, 55.9, 21.2. HRMS (ESI+) *m/z* calculated for $[(C_{19}H_{18}O_3)H]^+$ 295.1329 found 295.1338.

2-(2-(dimethylamino)naphthalen-1-yl)-6-methoxy-4-methylphenol ***(11)***. Brown oil, 20.9 mg, 34% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, br s), 7.88 (1H, d, *J* = 8.8 Hz), 7.81 (1H, d, *J* = 6.4 Hz), 7.80 (1H, d, *J* = 6.4 Hz), 7.45 (1H, d, *J* = 8.8 Hz), 7.40-7.30 (2H, m), 6.79 (1H, s), 6.75 (1H, s), 3.96 (3H, s), 2.72 (6H, s), 2.36 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.7, 146.8, 142.0, 133.6, 130.9, 129.0, 128.8, 128.2, 127.8, 126.3, 126.1, 125.3, 124.4, 117.7, 111.7, 56.0, 43.8, 21.3. IR ν_{mas} (film): 3526, 3424, 3057, 2933, 2843, 2786, 1595 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{20}H_{21}NO_2)H]^+$ 308.1645 found 308.1655.

3',5'-diisopropyl-3-methoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol ***(12)***. Brown oil, 6.5 mg, 8% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.30 (4H, m), 7.27-7.23 (6H, m), 6.82 (2H, d, *J* = 8.0 Hz), 6.77 (2H, d, *J* = 8.0 Hz), 6.68 (1H, s), 6.66 (1H, s), 4.60 (4H, s), 3.85 (3H, s), 2.32 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.5, 148.9, 145.3, 144.6, 138.8, 133.2, 128.6, 126.8, 121.1, 119.1, 119.0, 113.9, 113.5, 56.0, 54.9, 21.2. IR ν_{mas} (film): 2922, 2849, 1503, 1267, 1224, 956 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{28}H_{27}NO_2)H]^+$ 410.2115 found 410.2113.

2',3,4',5'-tetramethoxy-5-methyl-[1,1'-biphenyl]-2-ol ***(13)***.[11b] 29.2 mg, 48% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.85 (1H, s), 6.71 (1H, d, *J* = 1.8 Hz), 6.69 (1H, m), 6.65 (1H, s), 5.99 (1H, s), 3.94 (3H, s), 3.91 (3H, s), 3.86 (3H, s), 3.81 (3H, s), 2.33(3H, s). HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{20}O_5)H]^+$ 305.1384 found 305.1380.

4-(2-(dimethylamino)naphthalen-1-yl)-2,6-dimethylphenol ***(14)***.[6f] 47.2 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, t, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 8.0 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.35-7.27 (2H, m), 6.98 (2H, s), 4.66 (1H, s), 2.62 (6H, s), 2.32 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 148.9, 134.1, 131.2, 130.8, 130.2, 129.7, 128.0, 127.6, 125.7, 125.5, 123.5, 122.6, 119.6, 44.2, 16.1. HRMS (ESI+) *m/z* calculated for $[(C_{20}H_{21}NO)H]^+$ 292.1696 found 292.1721.

2-(2-(dimethylamino)naphthalen-1-yl)-4-methylphenol ***(15)***. Yellow oil, 16.7 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.0 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 7.04 (2H, d, *J* = 8.0 Hz), 6.72 (2H, d, *J* = 8.0 Hz), 2.94 (6H, s), 2.29 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 130.6, 129.9, 129.3, 127.6, 126.4, 125.4, 123.6, 121.3, 119.2, 114.8, 42.8, 20.6. IR ν_{mas} (film): 2917, 2848, 2789, 1598, 1500, 1373, 1228, 1211, 1165, 1074, 987, 809 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{19}H_{19}NO)H]^+$ 278.1539 found 278.1536.

3,5-diisopropyl-3',5'-dimethoxy-[1,1'-biphenyl]-4,4'-diol ***(16)***.[13] 40.3 mg, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (2H, s), 6.73 (2H, s), 5.49 (1H, s), 4.81 (1H, s), 3.96 (6H, s), 3.21 (2H, m), 1.34 (6H, s), 1.32 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 147.1, 134.2, 133.9, 133.8, 122.3, 104.0, 56.38, 56.37, 27.4, 22.8. HRMS (ESI+) *m/z* calculated for $[(C_{20}H_{26}O_4)H]^+$ 331.1904 found 331.1901.

3',5'-dimethoxy-2,3,5-trimethyl-[1,1'-biphenyl-4,4'-diol] ***(17)***. White solid, 183−185 °C, 30.0 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, s), 6.48 (2H, s), 5.50 (1H, s), 4.69 (1H, s), 3.89 (6H, s), 2.27 (3H, s), 2.25 (3H, s), 2.16 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.1, 146.5, 134.8, 133.9, 133.3, 133.0, 129.2, 122.3, 119.7, 106.4, 56.30, 56.28, 17.4, 15.8, 12.3. IR ν_{mas} (film): 3491, 2937, 2843, 1607, 1405, 1206, 1087 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{20}O_4)H]^+$ 289.1434 found 289.1449.

5-(tert-butyl)-3',5'-dimethoxy-[1,1'-biphenyl]-2,4'-diol ***(18)***.[10b] 30.2 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (1H, m), 7.23 (1H, d, *J* = 6.0 Hz), 6.94 (1H, d, *J* = 12.0 Hz), 6.67 (2H, s), 5.60 (1H, s), 5.19 (1H, s), 3.93 (6H, s), 1.34 (9H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1, 147.6, 143.4, 134.4, 128.4, 127.5, 126.8, 126.0, 115.1, 105.7, 56.37, 56.38, 34.2, 31.6. HRMS (ESI+) *m/z* calculated for $[(C_{18}H_{22}O_4)H]^+$ 303.1591 found 303.1589.

3',5'-dimethoxy-3,5-dimethyl-[1,1'-biphenyl]-2,4'-diol ***(19)***.[11b] 35.1 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, s), 6.87 (1H, s), 6.65 (2H, s), 5.58 (1H, s), 5.22 (1H, s), 3.92 (6H, s), 2.29 (3H, s), 2.28 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.3, 147.6, 134.3, 131.0, 129.2, 128.3, 127.8, 127.4, 124.3, 105.6, 56.4, 20.4, 16.2. HRMS (ESI+) *m/z* calculated for $[(C_{16}H_{18}O_4)H]^+$ 275.1278 found 275.1275.

3-(4-hydroxy-3,5-dimethoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol ***(20)***.[11b] 31.8 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, s), 6.71 (1H, s), 6.65 (2H, s), 5.56 (1H, s), 5.09 (1H, s), 3.91 (6H, s), 2.27 (4H, d, *J* = 16.0 Hz), 1.80 (4H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.0, 147.5, 138.2, 134.2, 130.3, 129.2, 128.0, 125.8, 115.5, 105.6, 56.35, 56.33, 29.3, 28.5, 23.4, 23.1. HRMS (ESI+) *m/z* calculated for $[(C_{18}H_{20}O_4)H]^+$ 301.1434 found 301.1430.

3-methoxy-2',3',5,5'-tetramethyl-[1,1'-biphenyl]-2,4'-diol ***(21)***. White solid, m.p: 165−167 °C. 13.6 mg, 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.70 (1H, s), 6.56 (1H, s), 5.40 (1H, s), 4.67 (1H, s), 3.92 (3H, s), 2.32 (3H, s), 2.24 (6H, s), 2.08 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.5, 146.2, 140.5, 134.2, 129.5, 129.3, 128.7, 128.4, 123.6, 122.1, 119.9, 110.4, 56.0, 21.1, 17.0, 15.8, 12.3. IR ν_{mas} (film): 3401, 2921, 2857, 1463, 1216, 1088 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{17}H_{20}O_3)H]^+$ 273.1485 found 273.1494.

3',5'-diisopropyl-3-methoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol ***(22)***. Yellow amorphous solid, 15.7 mg, 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, s), 6.75 (1H, s), 6.67 (1H, s), 5.62 (1H, s), 4.82 (1H, s), 3.92 (3H, s), 3.22-3.18 (2H, m), 2.34 (3H, s), 1.32 (6H, s), 1.30 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 146.6, 140.3, 133.3, 129.8, 128.9, 128.0, 124.5, 122.8, 110.2, 56.1, 27.3, 22.8, 21.1. IR ν_{mas} (film): 3533, 2960, 2936,

2869, 1463, 1271, 1196 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{20}H_{26}O_3)H]^+$ 315.1955 found 315.1955.

*3',5'-di-tert-butyl-3-methoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol (**23**).*[11b] 32.8 mg, 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, s), 6.75 (1H, s), 6.67 (1H, s), 5.62 (1H, s), 5.23 (1H, s), 3.92 (3H, s), 2.34 (3H, s), 1.48 (18H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.2, 146.6, 140.2, 135.5, 128.9, 128.6, 128.2, 126.0, 122.9, 110.1, 56.1, 34.4, 30.4, 21.2. HRMS (ESI+) *m/z* calculated for $[(C_{22}H_{30}O_3)H]^+$ 343.2268 found 343.2262.

*3-methoxy-3',5,5'-trimethyl-[1,1'-biphenyl]-2,4'-diol (**24**).* Yellow amorphous solid, 15.5 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, s), 6.73 (1H, s), 6.66 (1H, s), 5.62 (1H, s), 4.64 (1H, s), 3.91 (3H, s), 2.33 (3H, s), 2.30 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.5, 146.5, 140.3, 129.7, 129.4, 128.9, 127.3, 122.8, 122.7, 110.2, 56.1, 21.1, 16.0. IR ν_{mas} (film): 3502, 2919, 2853, 1484, 1276, 1122, 809 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{16}H_{18}O_3)H]^+$ 259.1329 found 259.1336.

*3-(tert-butyl)-3',5'-diisopropyl-5-methoxy-[1,1'-biphenyl]-2,4'-diol (**25**).* Brown oil, 33.5 mg, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (2H, s), 6.89 (1H, s), 6.64 (1H, s), 5.22 (1H, s), 4.92 (1H, s), 3.79 (3H, s), 3.22-3.15 (2H, m), 1.44 (9H, s), 1.31 (6H, s), 1.29 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 149.9, 145.3, 137.2, 134.8, 129.4, 129.3, 124.7, 113.2, 111.9, 55.8, 35.1, 29.5, 27.3, 22.7. IR ν_{mas} (film): 3537, 2961, 2872, 1467, 1430, 1198, 1158, 1053, 769 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{23}H_{32}O_3)H]^+$ 357.2424 found 357.2417.

*3-(tert-butyl)-3',5'-diisopropyl-5-methoxy-[1,1'-biphenyl]-2,4'-diol (**26**).* [13] 24.6 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, s), 6.87 (1H, d, *J* = 3.6 Hz), 6.59 (1H, d, *J* = 3.6 Hz), 5.18 (1H, s), 4.73 (1H, s), 3.77 (3H, s),), 2.31 (6H, s), 1.43 (9H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 152.1, 145.2, 137.3, 129.6, 129.0, 128.7, 124.1, 113.4, 111.5, 55.7, 35.1, 29.5, 16.0. HRMS (ESI+) *m/z* calculated for $[(C_{19}H_{24}O_3)H]^+$ 301.1798 found 301.1807.

*3',5'-dimethoxy-4,5-dimethyl-[1,1'-biphenyl]-2,4'-diol (**27**).*[11b] 35.6 mg, 65% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (1H, s), 6.80 (1H, s), 6.64 (2H, s), 5.58 (1H, s), 5.13 (1H, s), 3.91 (6H, s), 2.26 (3H, s), 2.23 (3H, s). HRMS (ESI+) *m/z* calculated for $[(C_{16}H_{18}O_4)H]^+$ 275.1278 found 275.1274.

*3',5'-dimethoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol (**28**).*[11b] 26.0 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, dd, *J* = 7.8, 1.8 Hz), 7.03 (1H, d, *J* = 1.8 Hz), 6.89 (1H, d, *J* = 6.0 Hz), 6.65 (2H, s), 5.60 (1H, s), 5.19 (1H, s), 3.91 (6H, s), 2.32 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2, 147.6, 134.4, 130.4, 129.9, 129.5, 128.0, 127.9, 115.4, 105.6, 56.38, 56.37, 20.5. HRMS (ESI+) *m/z* calculated for $[(C_{15}H_{16}O_4)H]^+$ 261.1121 found 261.1124.

*1-(2-hydroxy-3-methoxy-5-methylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**29**).* Colorless oil, 11.9 mg, 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, s), 6.77 (1H, s), 6.75 (1H, s), 6.72 (1H, s), 6.10 (2H, s), 3.94 (3H, s), 2.77 (4H, d, *J* = 1.2 Hz), 2.34 (3H, s), 1.80 (4H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.1, 146.3, 139.3, 138.5, 131.1, 130.4, 129.7, 124.0, 123.9, 122.9, 117.6, 110.8, 56.1, 29.2, 28.6, 23.5, 23.2, 21.2. IR ν_{mas} (film): 3353, 2923, 2854, 1490, 1413, 1296, 1094 cm^{-1}. HRMS (ESI+) *m/z* calculated for $[(C_{18}H_{20}O_3)H]^+$ 285.1485 found 285.1496.

*1-(3-(tert-Butyl)-2-hydroxy-5-methoxyphenyl)naphthalen-2-ol (**30**).*[15b] 41.9 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 8.8 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.45-7.37 (3H, m), 7.33 (1H, d, *J* = 8.8 Hz), 7.08 (1H, s), 6.64 (1H, s), 5.35 (1H, s), 4.71 (1H, s), 3.77 (3H, s), 1.46 (9H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.4, 152.0, 146.9, 139.1, 133.0, 131.0, 129.2, 128.3, 127.4, 124.2, 123.9, 119.2, 117.6, 115.9, 114.2, 112.0, 55.7, 35.2, 29.4. HRMS (ESI+) *m/z* calculated for $[(C_{21}H_{22}O_3)H]^+$ 323.1642 found 323.1635.

*1-(4-hydroxy-3,5-dimethoxyphenyl)naphthalen-2-ol (**31**).*[14a] 49.1 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz), 7.49 (1H, d, *J* = 8.0 Hz), 7.38-7.34 (2H, m), 7.28 (1H, d, *J* = 8.0 Hz), 6.64 (2H, s), 5.69 (1H, s), 5.33 (1H, s), 3.90 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.3, 147.9, 134.6, 133.5, 129.5, 128.8, 128.0, 126.5, 124.63, 124.60, 123.3, 121.0, 117.2, 107.4, 56.39, 56.37, 53.5. HRMS (ESI+) *m/z* calculated for $[(C_{18}H_{16}O_4)H]^+$ 297.1121 found 297.1120.

*6-Bromo-1-(4-hydroxy-3,5-dimethoxyphenyl) naphthalen-2-ol (**32**).*[11b] 42.0 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, s), 7.72 (1H, d, *J* = 12.0 Hz), 7.43 (1H, d, *J* = 8.0 Hz), 7.35 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 12.0 Hz), 6.60 (2H, s), 5.70 (1H, s), 5.33 (1H, s), 3.90 (6H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.6, 148.0, 134.9, 132.0, 129.92, 129.87, 129.7, 128.5, 126.6, 123.9, 121.2, 118.3, 117.1, 107.2, 56.42, 56.41. HRMS (ESI+) *m/z* calculated for $[(C_{18}H_{15}BrO_4)H]^+$ 375.0226 found 375.0211.

*2,3',4,5'-tetramethoxy-[1,1'-biphenyl]-3,4'-diol (**34**).*[10c] 27.5 mg, 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, d, *J* = 8.0 Hz), 6.80 (2H, s), 6.73 (1H, d, *J* = 8.0 Hz), 5.72 (1H, s), 5.53 (1H, s), 3.94 (3H, s), 3.92 (6H, s), 3.58 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.84, 146.82, 144.5, 138.7, 133.8, 129.2, 127.9120.2, 106.9, 105.6, 60.5, 56.32, 56.27. HRMS (ESI+) *m/z* calculated for $[(C_{16}H_{18}O_6)H]^+$ 307.1176 found 307.1164.

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Supplementary Material

Supplementary data to this article can be found online at https:

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