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Reversal of Polarity in Masked *o*-Benzoquinones: Rapid Access to Unsymmetrical Oxygenated Biaryls

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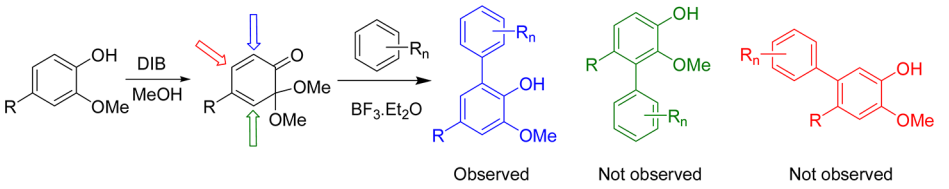
ABSTRACT



An unprecedented diacetoxyiodobenzene induced direct arylation of guaiacol derivatives and electron-rich arenes using a Lewis acid as an activator furnishes unsymmetrical biaryls without prefunctionalization of both coupling partners. The addition of electron-rich arenes on the α-position of electrophilic masked *o*-benzoquinones in an anti-Michael addition fashion affords the highly oxygenated unsymmetrical biaryls in good to excellent yields.

C−C bond forming reactions are the most fundamental transformations in organic synthesis. Among all C−C bond forming reactions, aryl−aryl bond forming reactions[1] have received much attention in recent years because of the frequent occurrence of the biaryl unit in many natural products[2] and pharmaceutically active compounds.[3] This motif is an integral part of organic conductors, light-emitting diodes, electron transport devices, liquid crystals, and catalysts in organic synthesis.[4] The aryl−aryl bond forming reactions also play a key role in asymmetric synthesis,[5] molecular catalysis,[6] and material science.[7] There exist several traditional cross-coupling methods for the synthesis of biaryls. Most commonly, these biaryls can be synthesized by cross-coupling between prefunctionalized substrates such as aryl halide electrophiles and metal derivatives of aryl fragment nucleophiles *via* metal-mediated reactions such as Stille, Suzuki−Miyaura, Negishi, Himaya, or Kumada couplings.[8] Although these methods offer mild conditions, better selectivities, and high yielding reactions, they involve prefunctionalization of both coupling partners that may be expensive or their preparation requires many synthetic steps, during which the formation of undesired homocoupling products and often toxic byproducts may occur.

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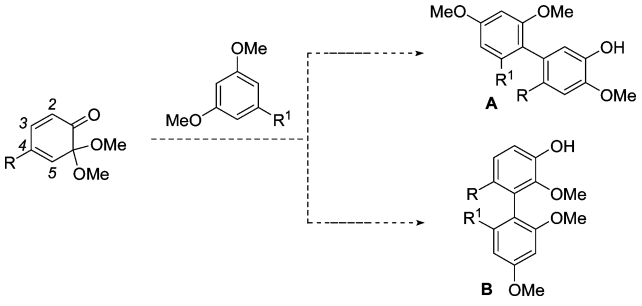
Moreover, due to the presence of the transition-metal impurities, it is difficult to purify the final products. In the past few decades, numerous methods have been reported for the synthesis of biaryls through oxidative cross-coupling using oxidizing agents bearing heavy metals such as Pb^{IV}, Ru^{IV}, Tl^{III}, V^{V}, and Rh^{III}.[9] However, these oxidants are expensive and highly toxic. In this context, oxidative cross-coupling of two nonactivated arenes by using hypervalent iodine reagents is one of the convenient and environmentally benign methods for the synthesis of biaryls.[10]

Recently, Waldvogel et al. reported the first anodic and selective cross-coupling reaction between 2-methoxyphenol and an electron-rich arene by using boron-doped diamond electrodes.[11] Kita et al. developed a method for the synthesis of oxygenated biaryls by the addition of electron-rich arenes to *p*-benzoquinone monoketals in a fluorinated solvent in the presence of montmorillonite.[12] Herein we present a Lewis acid mediated rapid synthesis of oxygenated unsymmetrical biaryls from simple 2-methoxyphenols and electron-rich arenes *via* the *in situ* generated masked *o*-benzoquinones.

6,6-Dialkoxycyclohexa-2,4-dienones, commonly known as *o*-benzoquinone monoketals or masked *o*-benzoquinones (MOBs),[13] are highly reactive cyclic conjugated dienones. These can be easily generated *in situ* from the corresponding 2-methoxyphenol by using hypervalent iodine reagents such as diacetoxyiodobenzene (DIB) and bis-(trifluoro-acetoxy)iodobenzene (PIFA) in methanol. These linearly conjugated cyclohexadienones are key intermediates in the synthesis of many natural products.[14] These are unique molecules containing diene, α,β- and γ,δ-unsaturated carbonyl and allyl acetal functionality which can readily undergo Diels–Alder, photochemical, and nucleophilic addition reactions.[15] In harnessing the reactivity of MOBs, we were interested in adding electron-rich species to these electron-deficient enones. Our working hypothesis for the design of unsymmetrical biaryls is depicted in Scheme 1. It was envisioned that the electron-rich arenes can add at position 3 or 5 of the *in situ* generated MOB, to provide biaryls of type **A** and/or **B**, respectively.

In a pilot experiment, 4-bromoguaiacol (**1a**) was dearomatized with DIB in MeOH in the presence of 1,3-dimethoxybenzene and the reaction was stirred for 24 h at rt. Only MOB **2a** was observed from the reaction mixture. In another reaction, when 1 equiv of $BF_3 \cdot Et_2O$ was added to the reaction mixture at 0 °C, 4-bromo-2,5-dimethoxyphenol was obtained within 1 min in 36% yield along with 41% of **1a** obtained from the rearomatization of MOB **2a**. To avoid the nucleophilic addition of methanol on the MOBs, we have removed the methanol after oxidation from a methanolic MOB solution by rotary evaporator *in vacuo* and then the residue was diluted with dichloromethane. 1,3-Dimethoxybenzene (**3**) followed by $BF_3 \cdot Et_2O$ were added to this reaction mixture at 0 °C, and to our surprise, biaryl **3a** was obtained in 65% yield in 1 min. This product was obtained from the addition of 1,3-dimethoxybenzene at the C-2 position (α-addition) of the MOB **2a** in an *anti*-Michael type addition followed by rearomatization. In order to obtain the optimal conditions, we carried out the reaction of 4-bromoguaiacol (**1a**) with 1,3-dimethoxybenzene (**3**) in the presence of DIB

Scheme 1. Working Hypothesis for the Synthesis of Oxygenated Biaryls



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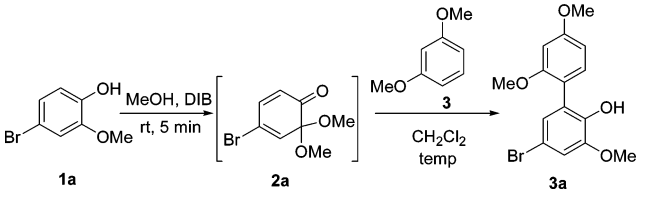
(1 equiv) and various activators under different conditions. The results are shown in Table 1. Our initial studies by using various Brønsted acid activators such as phosphomolybdic acid and 3,5-dinitrobenzoic acid (Table 1, entries 1 and 2) were ineffective toward the synthesis of biaryls, whereas trifluoroacetic acid (Table 1, entry 3) afforded the product **3a** in 53% yield. We continued our studies by using Lewis acid activators such as $FeCl_3$, $ZrCl_4$, and $BF_3 \cdot Et_2O$ which produced the biaryl product **3a** (Table 1, entries 4–10). Among the activators studied, $BF_3 \cdot Et_2O$ produced the biaryl **3a** in higher yield. The reaction in the presence of 1 equiv of $BF_3 \cdot Et_2O$ produced the expected biaryl product in good yield (Table 1, entry 6). In order to increase the yield of product, a detailed screening was adopted by varying the temperature, amount of reagent, and addition sequence of reactant/reagent. It is observed that when the reaction was performed in the presence of 2 equiv of $BF_3 \cdot Et_2O$, the biaryl product was obtained in good yield. It is also noticed that the product was obtained in slightly lower yield (75%) (Table 1, entry 7)

Table 1. Optimization of Reaction Conditions



entry	activator	equiv	temp	time[a]	yield [%][b]
1	phosphomolybdic acid	0.2	0 °C–rt	24 h	nr
2	3,5-dinitrobenzoic acid	2.0	0 °C–rt	24 h	nr
3	TFA	2.0	0 °C	40 min	53
4	$FeCl_3$	2.0	0 °C	20 min	58
5	$ZrCl_4$	2.0	0 °C	10 min	54
6	$BF_3 \cdot Et_2O$	1.0	0 °C	<1 min	65
7	$BF_3 \cdot Et_2O$	2.0	0 °C	<1 min	75
8	$BF_3 \cdot Et_2O$	2.0	−30 °C	<1 min	82
9	$BF_3 \cdot Et_2O$	2.0	−40 °C	<1 min	79
10	$BF_3 \cdot Et_2O$	4.0	−30 °C	<1 min	80

[a] Time after addition of activator. [b] Yield of pure and isolated product. nr: No reaction.

when the reaction was performed at 0 °C in comparison to the reaction that was performed at −30 °C (82%) (Table 1, entry 8). There was no significant difference in the yield of biaryl product **3a**, when the reactions were performed at −40 °C (Table 1, entry 9) or with 4.0 equiv of $BF_3 \cdot Et_2O$ (Table 1, entry 10).

To study the scope of the reaction, we have chosen various guaiacol derivatives and different electron-rich arenes and performed the reactions under optimized conditions. All reactions proceeded cleanly within 1 min (after the addition of $BF_3 \cdot Et_2O$) to afford the corresponding unsymmetrical biaryls in good to excellent yields (Figure 1). Interestingly, in the reactions of 4-halo MOBs with arene **3**, 10–12% of bis-aryl ethers **3a′**–**3c′** were also isolated along with biphenyls **3a**–**3c** (Figure 2).

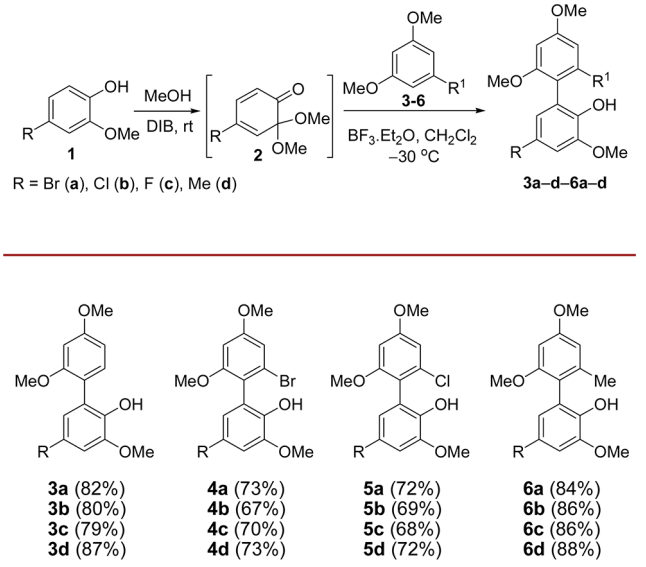


Figure 1. Synthesis of biaryls from guaiacol derivatives and electron-rich arenes.

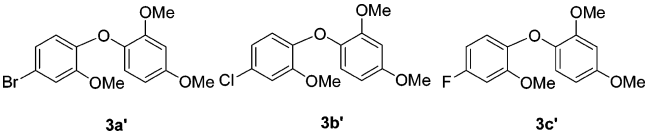


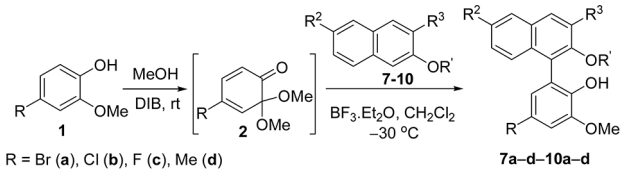
Figure 2. Structures of bis-aryl ethers.

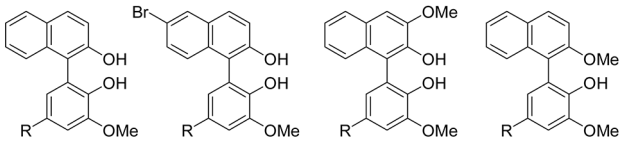
We have further extended this strategy for the reactions of different 4-substituted guaiacols **1a**–**d** and various β-naphthol derivatives **7**–**10**. The reactions proceeded smoothly under similar conditions to furnish the corresponding biaryls in excellent yields (Figure 3).

The regiochemistry of the biaryls was confirmed by ^{1}H NMR. From the ^{1}H NMR spectra of all compounds the coupling constants for the protons of guaiacol moiety are found to be in the range 1.5–3.0 Hz (meta-coupling) which indicates that there is no ortho-coupling in the guaiacol moiety of the biaryl products. This supported the conclusion that the electron-rich arene attacks at position 2 of MOB leading to the formation of a 6-substituted biaryl product. The structures of **5a** (Figure 4) and **8b** were further confirmed by single crystal X-ray analyses.[16]

To increase the scope of the present work, we have performed the reactions of creosol (**1d**) with various electron-rich arenes such as resorcinol (**11**), *p*-cresol (**12**), and *N*-methylpyrrole (**13**) under the optimized conditions.

(16) **5a**: CCDC 903587; **8b**: CCDC 897065.





7a (90%) **8a** (86%) **9a** (90%) **10a** (81%)
7b (95%) **8b** (88%) **9b** (92%) **10b** (78%)
7c (94%) **8c** (86%) **9c** (91%) **10c** (82%)
7d (96%) **8d** (88%) **9d** (92%) **10d** (84%)

Figure 3. Biaryls derived from guaiacol derivatives and various β-naphthols.

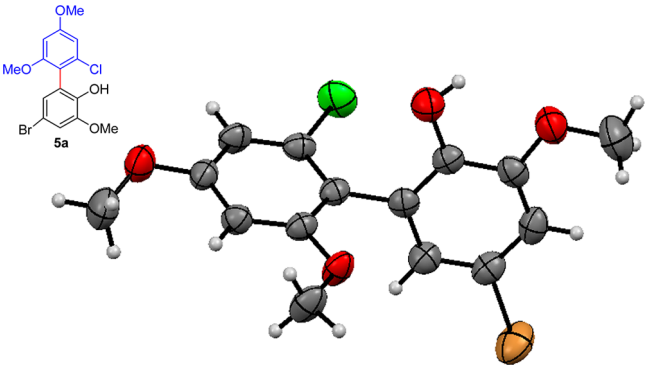
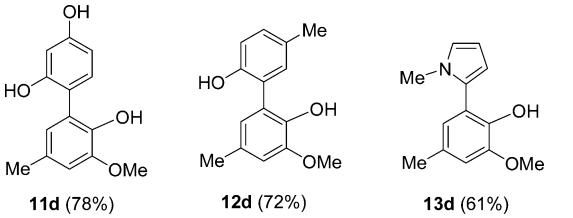


Figure 4. ORTEP plot of **5a**.

The corresponding biaryls **11d**–**13d** were obtained in good yields (Figure 5).

To find out whether there will be a reaction at position 4 of 4-unsubstituted guaiacol derivatives, we have examined the reaction of 5-methylguaiacol (**1e**) and arene **3** under the same conditions. As anticipated the biaryl **3e** derived from the addition of arene at position 4 of MOB was isolated (Scheme 2).

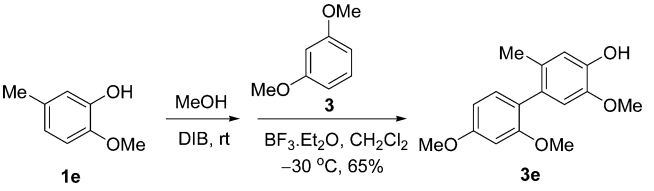
One would expect the addition of a nucleophile on position 3 or 5 of an MOB, which is a conjugated dienone.[15a]



11d (78%) **12d** (72%) **13d** (61%)

Figure 5. Scope of electron-rich arenes.

Scheme 2. Reaction of a 4-Unsubstituted Guaiacol Derivative



However, in the presence of a Lewis acid, the nucleophile attacks position 2 or 4 of the MOB in an umpolung fashion, which is an unprecedented event in MOB chemistry.

In conclusion, we have reported for the first time a rapid and straightforward chemical method for the efficient synthesis of unsymmetrical biaryls from the reaction between simple guaiacol derivatives and electron-rich arenes in the absence of supplemental transition metals by using a Lewis acid activator. Mild and aerobic conditions, enhanced regioselectivities, and the absence of self-coupling are the other merits of this protocol. The current methodology illustrates the efficacy of masked *o*-benzoquinones in combining two electron-rich arenes to offer highly oxygenated biaryls.

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Supporting Information Available. Experimental procedure, characterization data, and copies of NMR spectra of unsymmetrical biaryls. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.