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EFFECT OF ARYL SUBSTITUENTS ON INTRAMOLECULAR CYCLIZATION OF 2,2'-BIPHENOQUINONES

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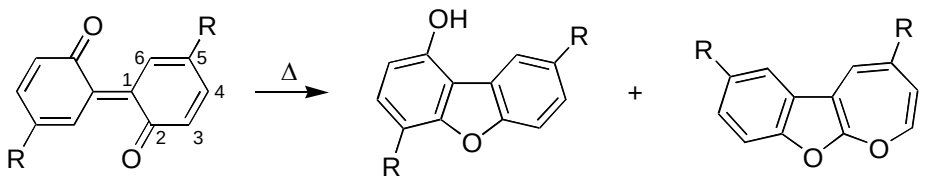
Abstract – Effect of aryl substituents on intramolecular cyclizations of 3,3',5,5'-tetraaryl-2,2'-biphenoquinones (Ar = phenyl (**1a**) and 4-methoxyphenyl (**1b**)) has been studied. In benzene, **1a** gave 2,4,6,8-tetraphenyldibenzofuran-1-ol (**10**) gradually as a main product, indicating the phenyl substituents preferred to stabilize the intermediate by delocalization of the negative charge rather than that of the positive one. In contrast, the reaction of **1b** occurred spontaneously in order to give a complex mixture, which should be due to 4-methoxyphenyl substituent at the 3 position.

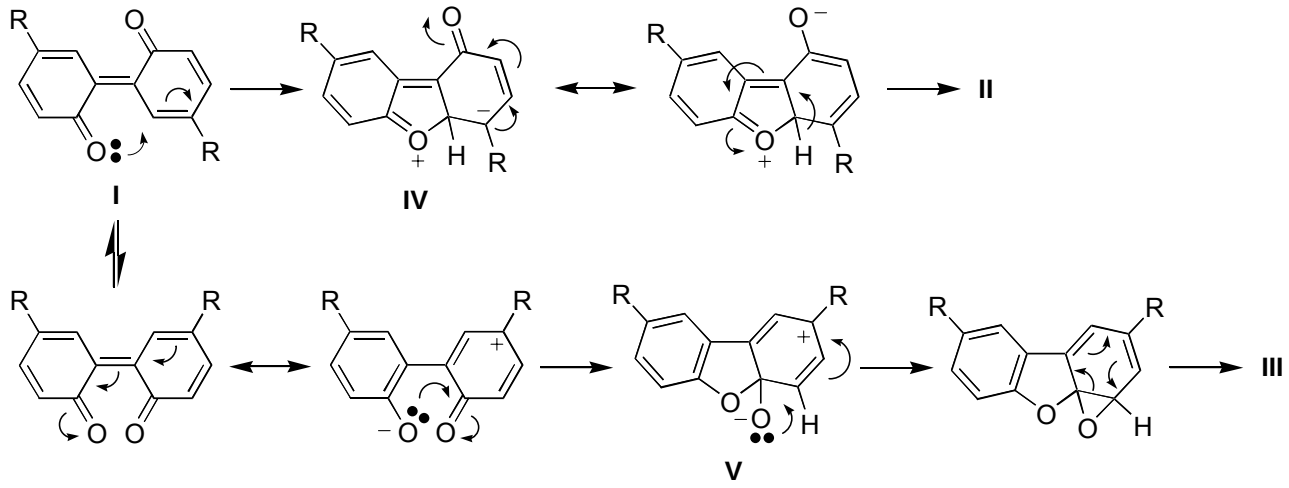
INTRODUCTION

2,2'-Biphenoquinone (**I**) is a more reactive isomer of 4,4'-biphenoquinone so as to undergo thermal cyclization facilely to give either dibenzofuran (**II**) or oxepino[2,3-*b*]benzofuran (**III**).[1-4] According to Wan et al.,[1] the mode of reaction depends upon the substituent (R) at the 5 (and 5') position. When R is an electron-donating substituent, such as methoxy and methyl groups,[1a-b] **III** is yielded preferably. This is explained in terms of the substituent effect of the R, which stabilizes the intermediate **V** by resonance



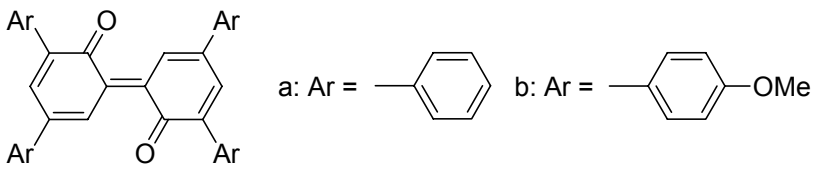
I II III

To the memory of the late Professor Dr. John Daly



Scheme 1

and/or inductive effects. In contrast, 2,2'-biphenoquinones bearing an electron-withdrawing substituent, such as chloro group,[1a-b] give **II** rather than **III**, because the R stabilizes the intermediate **IV** also by resonance and/or inductive effects (Scheme 1). Based on the resonance theory, these explanations should be reasonably applicable to substituents at the 3 and 3' positions. Effect of aryl substituents at the 5 and 3 positions on the cyclization of 2,2'-biphenoquinones appears to be an interesting issue, because they can stabilize both **IV** and **V** by delocalization of the negative and positive charges, respectively; however those compounds have been rarely studied. Thus, in the present study, 3,3',5,5'-tetraaryl-2,2'-biphenoquinones have been synthesized and their cyclization reactions studied. As the stabilization effect on the intermediate was expected to vary depending on the nature of aryl substituent, phenyl (**1a**) and 4-methoxyphenyl (**1b**) substituents were employed. It should be noted that bulkiness of the aryl group at 3 position would not prevent formation of the epoxide ring in a steric manner (Scheme 1), because 3,3',5,5'-tetra-*tert*-butyl-2,2'-biphenoquinone was known to give oxepino[2,3-*b*]benzofuran in a good yield.[3a]



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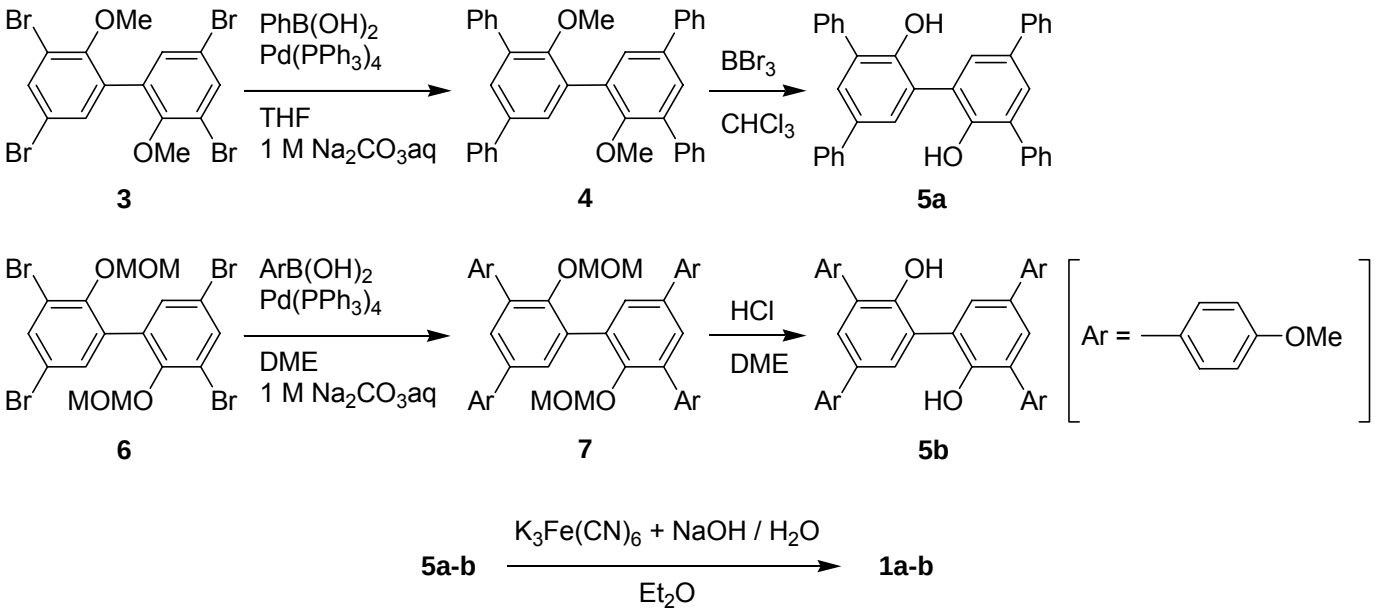
RESULTS AND DISCUSSION

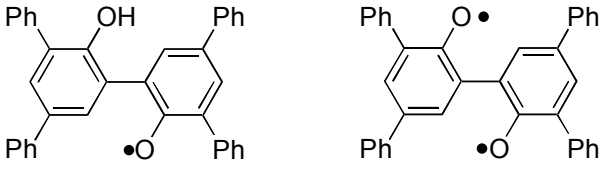
Synthesis of **1a-b** was depicted in Scheme 2. 3,3',5,5'-Tetrabromo-2,2'-dimethoxybiphenyl (**3**) was subjected to Suzuki-Miyaura coupling[5] with phenylboronic acid to give tetraphenylbiphenyl **4**, which was then deprotected in the presence of BBr_3 to yield tetraphenyl-2,2'-biphenol **5a**. On the other hand,



Scheme 2

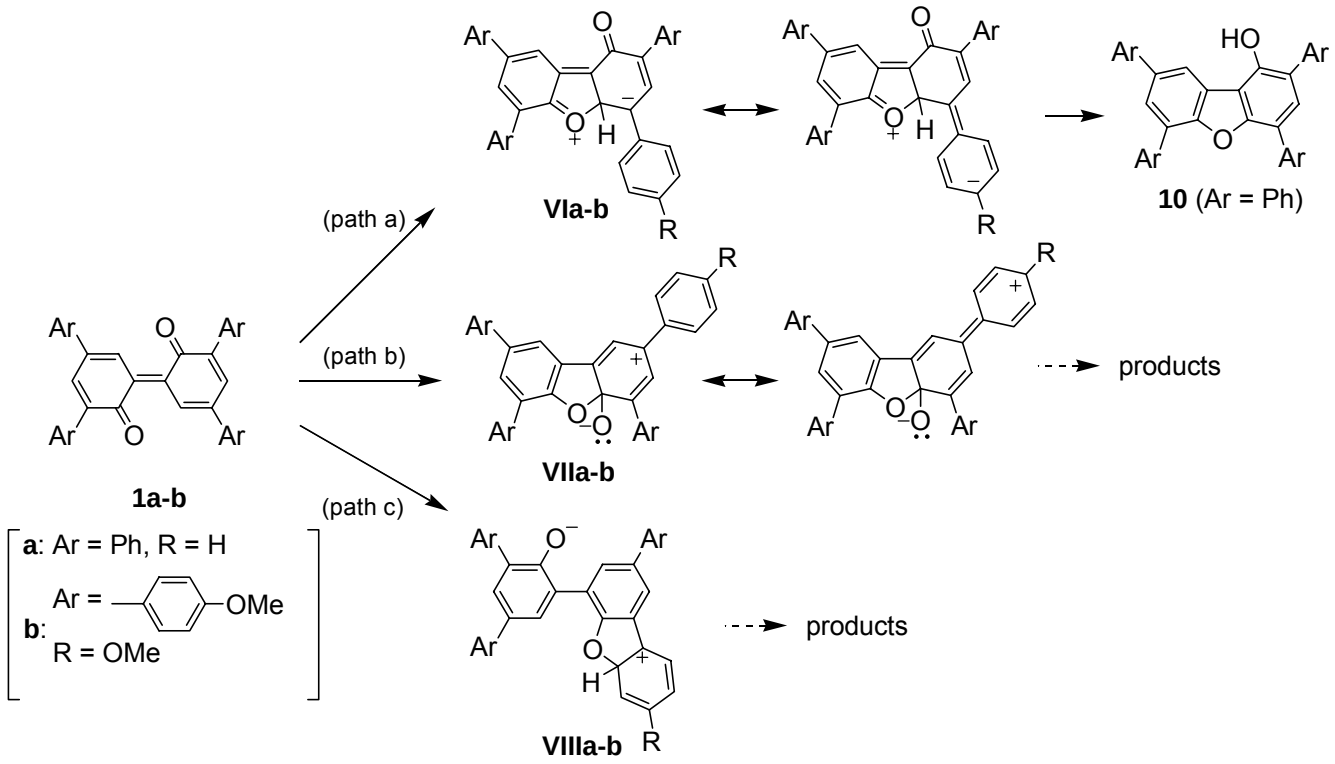
tetrabromo-2,2'-bis(methoxymethoxy)biphenyl (**6**) underwent Suzuki-Miyaura coupling with 4-methoxyphenylboronic acids to yield tetraarylbiphenyl (**7**), which was subjected to acid-catalyzed deprotection to give tetraaryl-2,2'-biphenol **5b**.

When an ethereal solution of **5a** was shaken with an aqueous solution of excess amount of potassium hexacyanoferrate(III) and sodium hydroxide for ten minutes, deep green solids were precipitated.[6] Deep purple solids were obtained from **5b** in a similar manner. Although NMR spectra of these solids could not be recorded due to instability, IR analysis revealed that the obtained solids were composed exclusively of **1a** and **1b**, respectively: for example, most peaks of IR spectra of the green solid were found to be very close to those of **5a** in position and intensity except for broad peak at 3600-3200 cm^{-1} (*i.e.*, stretching vibrations of O-H bond), which was absent in the former. The IR spectra also indicated that the obtained solid was not contaminated by monoradical **8**. Absence of **8** was further confirmed by EPR spectra, where no peak was assigned to **8**. EPR spectra also indicated that **1a** should be represented by a quinonoid canonical form essentially, and contribution of the biradical one (**9**) be negligible. This is similar to the behavior of binaphthoquinone, which was also ESR inactive in solution[7] unlike Bourdon and Calvin's hindered 4,4'-biphenoquinones.[8]



8 **9**

Although **1a** was stable at ambient temperature in solid, it underwent reactions gradually in solution. The decay of **1a** in benzene was followed by monitoring relative intensity of the electronic absorption peak at 708 nm (Figure 1), which became to be zero in one hour. A similar rate of decay was observed in toluene,



Scheme 3

indicating that **1a** did not behave as biradical species again. The main product was 2,4,6,8-tetraphenyldibenzofuran-1-ol **10** (42%), and no oxepino[2,3-*b*]benzofuran was obtained. This indicates that the reaction of **1a** proceeded mainly along path a in Scheme 3, in which the phenyl substituents stabilized the intermediate **VIa** by means of delocalization of the negative charge. Unlike 3,3', 5,5'-tetraphenyl-4,4'-biphenoquinones,[9] a structural isomer of **1a**, no reaction product via intramolecular attack of oxygen atom to the phenyl substituent at the 3 position (path c in Scheme 3) was obtained.

In contrast to **1a**, **1b** was expected to give oxepino[2,3-*b*]benzofuran preferably because electron-donating character of 4-methoxyphenyl substituents in **1b** should stabilize **VIb** to less extent and **VIIb** to more extent. Moreover, 3,3'-di-*tert*-butyl-5,5'-bis(4-*tert*-butylphenyl)-2,2'-biphenoquinones (**11**), which was generated from 2-*tert*-butyl-4-(4-*tert*-butylphenyl)phenol, was reported[3a] to give oxepino[2,3-*b*]benzofuran (**12**) in moderate yield (Scheme 4). Nevertheless, in various organic solvents such as benzene, DMSO, DMF, ethanol, CH_3CN, acetone, THF, CH_2Cl_2, $CHCl_3$, and *n*-hexane, **1b** decayed rapidly to give a complex mixture, from which neither oxepino[2,3-*b*]benzofuran nor dibenzofuran product was detected. Although no mechanistic studies could be performed due to difficulty of the product analysis, comparison of molecular structure of **1b** with that of **11** indicates that 4-methoxyphenyl substituent at the 3 position (not 5) should be responsible for this behavior.

In conclusion, this paper describes synthesis and reactivity of 3,3',5,5'-tetraaryl-2,2'-biphenoquinones **1a** and **1b**. EPR and UV/Vis study revealed that **1a** should be represented by a quinonoid canonical form essentially, being similar to binaphthoquinones and unlike Bourdon and Calvin's hindered

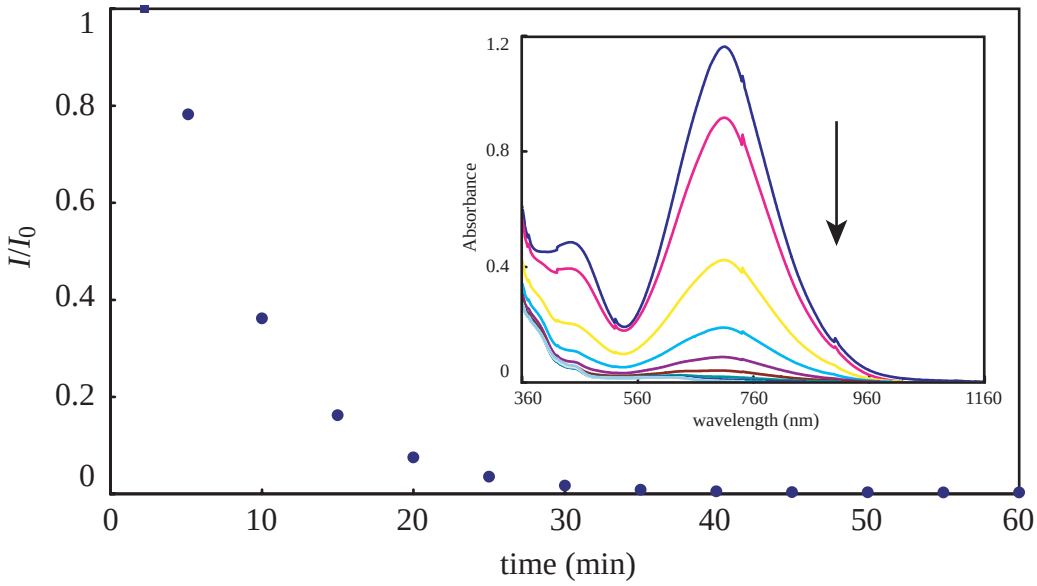


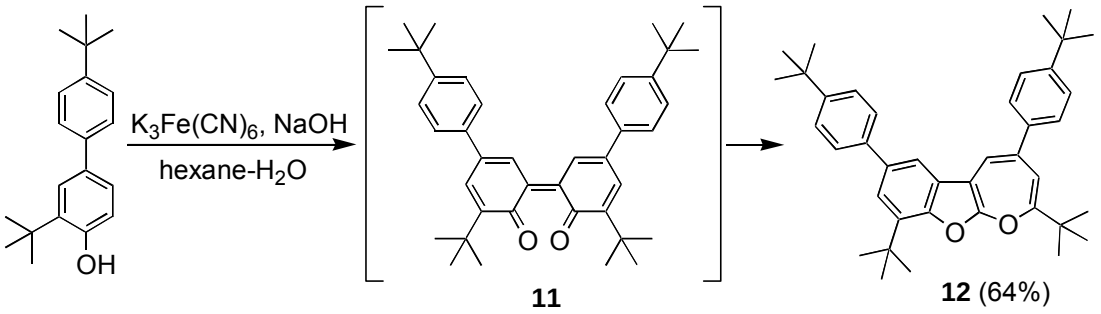
Figure 1. Time dependent relative intensity (I/I_0) of absorption peak at 708 nm of **1a** in benzene. (inset) Time course of the thermal decay of **1a**.

4,4'-biphenoquinones. The phenyl substituents in **1a** were found to stabilize the intermediate by delocalization of the negative charge to give dibenzofuran as a main product in a moderate yield. In contrast, the reactions of **1b** afforded a complex mixture probably because of the 4-methoxyphenyl substituent at the 3 (not 5) position.

EXPERIMENTAL

General. All commercially available chemicals were used without further purification. Melting points were determined on microscopic thermometer without correction. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) with tetramethylsilane as internal reference. Mass spectra were conducted on a JEOL MStation JMS-700 (EI) and a JEOL JMS-SX102A (HRMS/EI). Infrared spectra were measured on a JASCO FT/IR-6100. EPR spectra were recorded on a Brucker EMX EPR Spectrometer.

Synthesis of 3,3',5,5'-tetraphenyl-2,2'-dimethoxybiphenyl (4). A bi-layer solution of 3,3',5,5'-tetrabromo-2,2'-dimethoxybiphenyl (**3**)[10] (1.53 g, 2.87 mmol) and phenylboronic acid (1.57 g, 12.9 mmol) in THF (30 mL) and 1 mol L^{-1} aqueous Na_2CO_3 (20 mL) was degassed with argon. After tetrakis(triphenylphosphine)palladium (0.664 g, 0.575 mmol) was added, the reaction mixture was refluxed for overnight. After cooling, organic layer was separated, and aqueous layer was extracted with Et_2O. Combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness. From the crude product, **4** (1.38 g, 93%) was isolated by preparative column chromatography (SiO_2, *n*-hexane/EtOAc 10:3) as a white powder.



Scheme 4

Mp 81-86 ºC. ^{1}H NMR ($CDCl_3$): δ = 7.70-7.63 (12H, m, Ar), 7.46-7.40 (8H, m, Ar), 7.36 (2H, t, *J* = 7.3 Hz, Ar), 7.31 (2H, t, *J* = 7.3 Hz, Ar), 3.35 (6H, s, OMe). ^{13}C NMR ($CDCl_3$): δ = 154.94, 140.37, 138.81, 136.52, 135.35, 133.15, 129.44, 129.35, 129.24, 128.73, 128.27, 127.21, 127.11, 126.99, 60.74. MS: m/z = 518 (M^+). HRMS (m/z): 518.2247 (M^+, calcd. 518.2246 for $C_{38}H_{30}O_2$).

Synthesis of 3,3',5,5'-tetraphenyl-2,2'-biphenol (5a). To a solution of **4** (1.38 g, 2.66 mmol) in $CHCl_3$ (20 mL) was dropwised boron tribromide (0.57 mL, 6.1 mmol) at 0 ºC. After stirring for 3 h, the reaction mixture was quenched with MeOH (5 mL) then water (5 mL), and organic substances were extracted into $CHCl_3$. The organic solution was washed with water and brine, dried over Na_2SO_4, and the solvent was removed under vacuum leaving **5a** (1.24 g, 95%) as a white solid. Since the obtained **5a** was practically pure, it was used in the next reaction without further purification.

Mp 189-192 ºC (lit.,[2a] 189-192 ºC). ^{1}H NMR ($CDCl_3$): δ = 7.65 (2H, d, *J* = 2.4 Hz, Ar), 7.64-7.62 (10H, m, Ar), 7.50 (4H, t, *J* = 7.2 Hz, Ar), 7.44-7.40 (6H, m, Ar), 7.34-7.31 (2H, m, Ar), 5.94 (2H, s, OH).

Synthesis of 3,3',5,5'-tetrakis(4-methoxyphenyl)-2,2'-dimethoxymethoxybiphenyl (7). A bi-layer solution of 3,3',5,5'-tetrabromo-2,2'-bis(methoxymethoxy)biphenyl (**6**)[11] (1.96 g, 3.33 mmol) and 4-methoxyphenylboronic acid (2.28 g, 15.0 mmol) in DME (120 mL) and 1 mol L^{-1} aqueous Na_2CO_3 (80 mL) was degassed with argon. After tetrakis(triphenylphosphine)palladium (0.77 g, 6.7 mmol) was added, the reaction mixture was refluxed for overnight. After cooling, organic layer was separated, and aqueous layer was extracted with EtOAc. Combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness. From the crude product, **7** (2.06 g, 88%) was isolated by preparative column chromatography (SiO_2, *n*-hexane/EtOAc 2:1) as a white powder.

Mp 76-84 ºC. ^{1}H NMR ($CDCl_3$): δ = 7.66 (2H, d, *J* = 2.6 Hz, Ar), 7.62 (4H, d, *J* = 8.8 Hz, Ar), 7.58 (4H, d, *J* = 8.8 Hz, Ar), 7.53 (2H, d, *J* = 2.4 Hz, Ar), 6.99 (4H, d, *J* = 8.8 Hz, Ar), 6.97 (4H, d, *J* = 8.8 Hz, Ar), 4.53 (4H, s, -OC<u>H</u>$_2$OMe), 3.85 (6H, s, ArO<u>Me</u>), 3.83 (6H, s, ArO<u>Me</u>), 2.76 (6H, s, -OCH$_2$O<u>Me</u>). ^{13}C NMR ($CDCl_3$): δ = 159.06, 158.86, 151.44, 136.57, 135.53, 133.96, 132.95, 131.41, 130.65, 129.11,

128.51, 127.97, 114.19, 113.69, 98.79, 56.33, 55.30, 55.25. MS: m/z = 698 (M^+). HRMS (m/z): 698.2883 (M^+, calcd. 698.2880 for $C_{44}H_{42}O_8$).

Synthesis of 3,3',5,5'-tetrakis(4-methoxyphenyl)-2,2'-biphenol (5b). To a solution of **7** (0.086 g, 0.12 mmol) in DME (40 mL) was added 3 mol L^{-1} hydrochloric acid (6.0 mL, 18 mmol) at ambient temperature. After refluxing for 3 h, the reaction mixture was cooled, and organic substances were extracted into Et_2O. The solution was washed with water and brine, dried, and the solvent was removed under vacuum leaving **5b** (0.068 g, 90%) as a white solid. Since the obtained **5b** was practically pure, it was used in the next reaction without further purification.

Mp 99-101 ºC. ^{1}H NMR ($CDCl_3$): δ = 7.56-7.53 (12H, m, Ar), 7.02 (4H, d, *J* = 8.8 Hz, Ar), 6.96 (4H, d, *J* = 8.8 Hz, Ar), 5.88 (2H, s, OH), 3.86 (6H, s, OMe), 3.83 (6H, s, OMe). ^{13}C NMR ($CDCl_3$): δ = 159.28, 158.93, 148.87, 134.18, 132.97, 130.55, 129.66, 129.57, 128.90, 128.84, 127.84, 125.44, 114.31, 114.23, 55.35, 55.34. MS: m/z = 610(M^+). HRMS (m/z): 610.2353 (M^+, calcd. 610.2355 for $C_{40}H_{34}O_6$).

General prodecedure of preparation of 3,3',5,5'-tetraaryl-2,2'-biphenoquinones. In a separatory funnel was placed a solution of 0.10 g of 3,3',5,5'-tetraaryl-2,2'-biphenol in 10 mL of Et_2O or EtOAc. To this solution was added a solution of 0.85g (2.6 mmol) of potassium hexacyanoferrate(III) and 0.20 g (5.0 mmol) sodium hydroxide in water (12 mL), and the resulting mixture was vigorously shaken for about 10 min. The precipitate was isolated by suction filtration, washed with several portion of water, and dried in a vacuum desiccator. Yield **1a**, 80%; **1b**, 32%.

Synthesis of 2,4,6,8-tetraphenyldibenzofuran-1-ol (10). A solution of 100 mg (0.20 mmol) of **1a** in 100 mL of benzene was stirred at ambient temperature. When the starting material disappeared on TLC, the solvent was removed under vacuum leaving a reaction mixture, which was subject to preparative column chromatography (SiO_2, *n*-hexane/$CHCl_3$ 1:1) to isolate **10** (42 mg, 42%) as a white powder.

Mp 235-239 ºC. ^{1}H NMR ($CDCl_3$): δ = 8.41 (1H, d, *J* = 1.8 Hz, Ar), 8.03 (2H, dd, *J* = 8.4, 1.1 Hz, Ar), 7.96 (2H, dd, *J* = 8.4, 1.1 Hz, Ar), 7.88 (1H, d, *J* = 1.8 Hz, Ar), 7.77 (2H, dd, *J* = 8.2, 1.3 Hz, Ar), 7.60-7.58 (5H, m, Ar), 7.55-7.53 (2H, m, Ar), 7.51-7.47 (5H, m, Ar), 7.45-7.42 (1H, m, Ar), 7.40-7.36 (2H, m, Ar), 5.99 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ = 154.45, 152.66, 147.79, 141.51, 137.31, 136.45, 136.28, 136.05, 129.78, 129.46, 128.83, 128.73, 128.67, 128.62, 128.47, 128.24, 128.15, 127.86, 127.57, 127.22, 127.09, 125.58, 125.18, 124.88, 122.81, 120.65, 118.49, 113.27. MS: m/z = 488(M^+). HRMS (m/z): 488.1776 (M^+, calcd. 488.1776 for $C_{36}H_{24}O_2$).

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