Multiple Arylation of Phenols around the Oxygen under Palladium Catalysis

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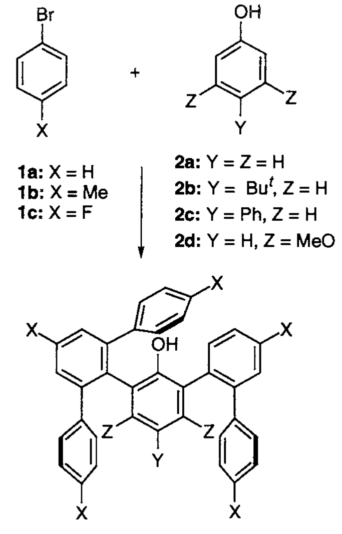
Phenols undergo pentaarylation around the oxygen upon a single treatment with excess aryl bromides in the presence of a palladium catalyst system to produce 2-(1,1'-biphenyl-2-yl)-6-(1,1':3',1''-terphenyl-2'-yl)phenol derivatives.

Palladium-catalyzed arylation reactions using aryl halides and their synthetic equivalents are now recognized to be of genuine synthetic utility.[1] We recently reported that intermolecular mono- and/or di-arylation reactions of phenolic compounds such as 2-phenylphenols and naphthols with aryl halides using palladium catalysts can efficiently occur at the spatially neighboring positions of phenolic function, forming one or two aryl-aryl linkages. The coordination of phenolic oxygen to intermediary arylpalladium species is considered to be the key for the coupling reactions *via* the cleavage of aromatic C-H bond.[2,3] In the context of the study, we have found that phenol itself and 3- or 4-substituted ones can effectively undergo multiple arylation around the oxygen up to five times; treatment of the phenols with excess aryl bromides affords sterically crowded 2-(1,1'-biphenyl-2-yl)-6-(1,1':3',1''-terphenyl-2'-yl)phenols.[4-6] The compounds appear to be interesting materials as bulky O-ligands[7] as well as the precursors of relatively stable radicals[8] and polycondensed aromatics.[9]

When phenol (**2a**) (1 mmol) was treated with bromobenzene (**1a**) (8 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), and Cs_2CO_3 (8 mmol) in refluxing *o*-xylene under nitrogen for 32 h, the corresponding pentaphenylated compound **3** was produced in an isolated yield of 58% as the single major product (Scheme 1).[10] The reaction seems to be rather efficient based on the fact that five C-C bonds were formed. Essentially the same product yield (57%) was achieved with a half amount of the palladium species, though a longer reaction time (110 h) was required. The reaction in a polar solvent, DMF which is an effective solvent for the arylation of 2-phenylphenol and naphthols, however, gave no detectable amount of coupling products. Thus, the use of a less polar solvent appears to be crucial for the multiple arylation of phenol itself to take place. The reactions of 4-*tert*-butylphenol (**2b**) and 1,1'-biphenyl-4-ol (**2c**) with **1a** and those of **2a** with 4-bromotoluene (**1b**) and 4-fluorobromobenzene (**1c**) in *o*-xylene also gave pentaarylated compounds **4**-**7**. In the reactions using **1b** and **1c**, $P(4\text{-}MeC_6H_4)_3$ and $P(4\text{-}FC_6H_4)_3$ were used as ligands in place of PPh_3 to avoid the contamination of phenyl group from the phosphine.[11] The arylation could take place even using 3,5-dimethoxyphenol (**2d**) to afford a highly crowded compound **8**. Note that the structure of **4** was able to be unambiguously confirmed by X-ray analysis (Figure 1).[12] It was found that it exists in a face-to-face packing, in spite of the fact that the oxygen is considerably hindered.



3: X = Y = Z = H; 58% (32h)
4: X = Z = H, Y = Bu^t; 59% (24 h)
5: X = Z = H, Y = Ph; 58% (72 h)
6: X = Me, Y = Z = H; 31% (48 h)$^{a)}$
7: X = F, Y = Z = H; 14% (48 h)$^{b)}$
8: X = Y = H, Z = MeO; 43% (48 h)

Scheme 1. Reaction conditions: **1** (8 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), Cs_2CO_3 (8 mmol), *o*-xylene (5 cm^3), N_2, reflux. a) $P(4\text{-}MeC_6H_4)_3$ was used in place of PPh_3. b) $P(4\text{-}FC_6H_4)_3$ was used in place of PPh_3.

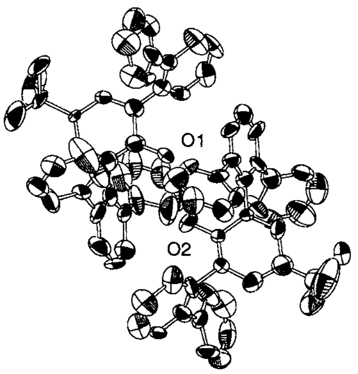
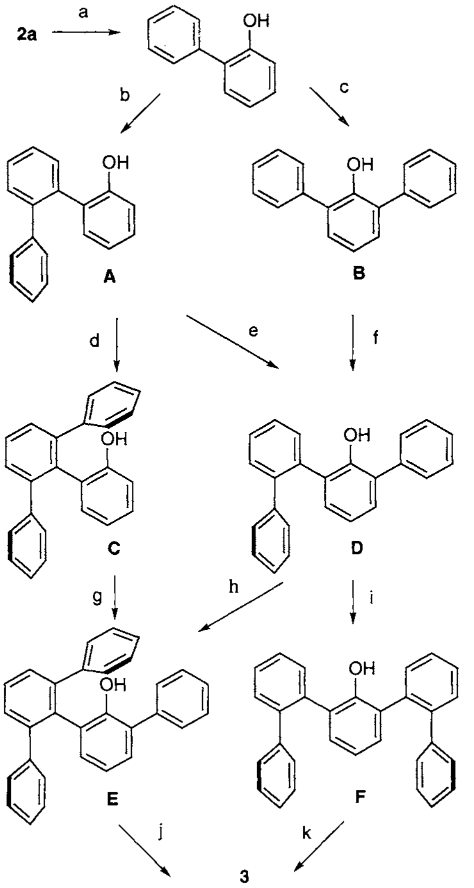


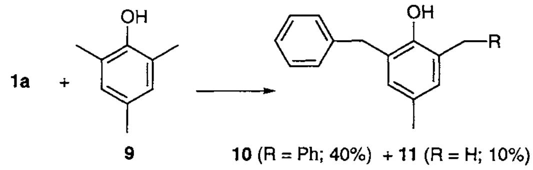
Figure 1. ORTEP drawing of compound **4** composed of two molecules.

Analysis of the reaction mixture using **1a** and **2a** at a reaction time of 5 h by GLC-MS confirmed the formation of two kinds of each of di-, tri-, and tetraphenylated phenols **A**-**F** (identified using authentic samples) together with **3** (Scheme 2), and the ratio of peak areas of **A**-**F** and **3** in the GLC chart was 16:1:20:5:15:19:24. This may imply that **2a** is pentaphenylated to **3** *via* any possible intermediary products, while each step occurs with different ease. The reaction seems to proceed preferably *via* **A** rather than **B**. It may involve two mechanistic patterns: (a) Paths **a**, **c**, **e**, and **g** are considered to involve the reaction of *in situ* generated phenylpalladium species with the corresponding phenolates, and (b) the other paths proceed *via* the activation of an aromatic C-H bond by the intermediary complex.[2] The fact that no detectable amount of hexaphenylated product was formed may be attributed to steric reasons.



Scheme 2. Reaction sequence leading to compound **3**.

It should be noted that compounds **D** (76%) and **F** (66%) could be obtained from the reactions of **B** with limited amounts of **1a** (1.2 and 2.4 equiv., respectively), indicating that such kinds of tri- and tetraarylated phenols can be selectively prepared from 2,6-diarylphenols.[13] On the other hand, treatment of 2,4,6-trimethylphenol (**9**) with **1a** was found to give 2,6-dibenzyl-4-methylphenol (**10**) along with 2-benzyl-4,6-dimethylphenol (**11**) (Scheme 3). This suggests that the present catalytic system is also applicable to the intermolecular arylation of relatively less reactive sp^3 C-H bond.[3a]



Scheme 3. Reaction conditions: **1a** (2.4 mmol), **9** (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (2.4 mmol), *o*-xylene (5 cm^3), N_2, reflux, 6 h.

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13 By contrast, 2,6-di-*tert*-butylphenol undergoes arylation on its *p*-position.[2c]