Multiple Arylation of Phenols around the Oxygen under Palladium Catalysis

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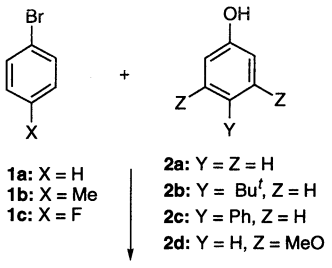
(Received June 21, 1999; CL-990533)

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]

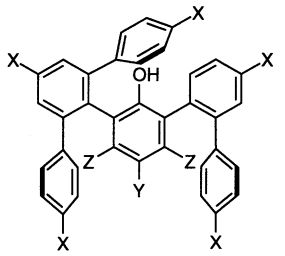
When phenol (**2a**) (1 mmol) was treated with bromobenzene (**1a**) (8 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), and Cs_2CO_3 (8 mmol) in refluxing *o*-xylene under nitrogen for 32 h, the corresponding pentaphenylated compound **3** was produced in an isolated yield of 58% 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.

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),



1a: X = H
1b: X = Me
1c: X = F

2a: Y = Z = H
2b: Y = Bu^t, Z = H
2c: Y = Ph, Z = H
2d: Y = H, Z = MeO



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.

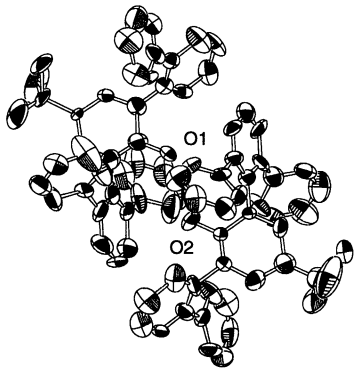
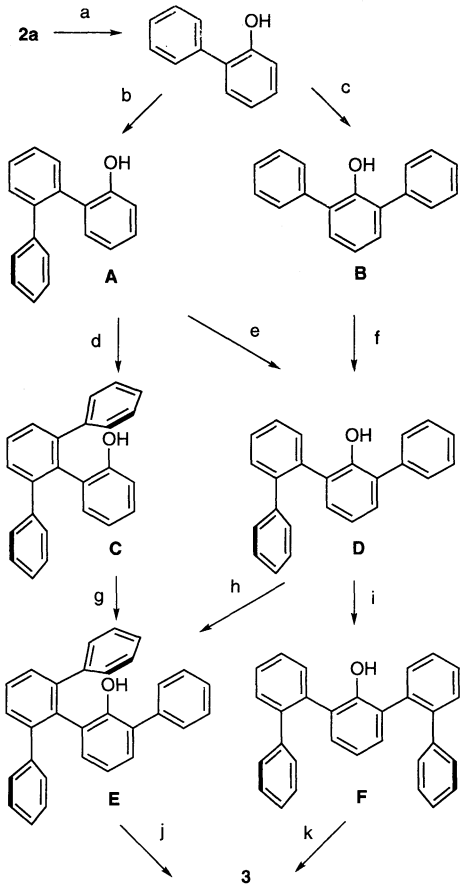


Figure 1. ORTEP drawing of compound **4** composed of two molecules.

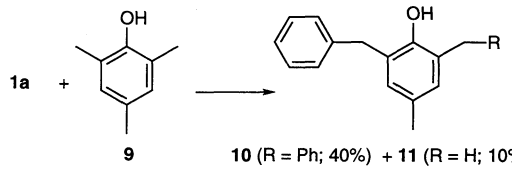
and the ratio of peak areas of **A**-**F** and **3** in the GLC chart was 16:1:20:5:15:19:24. This may imply that **2a** is pentaphenylated to **3** *via* any possible intermediary products, while each step occurs

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.

This work was partly supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. We thank Dr. N. Kanehisa and Ms. E. Mochizuki of Osaka University for helpful assistance in obtaining the X-ray data.

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12 Crystal data for **4**: $C_{40}H_{34}O$, Mw = 530.71, monoclinic, space group $P2_1$ (#4), T = 288 K, a = 10.216(4), b = 15.597(4), c = 19.52(1) Å, β = 102.40(4)°, V = 3037(2) Å, Z = 4, 2689 reflections measured, R = 0.104, Rw = 0.104.
13 By contrast, 2,6-di-*tert*-butylphenol undergoes arylation on its *p*-position.[2c]