Palladium-Catalyzed Arylation of 2,6-Di-*tert*-butylphenol with Aryl Bromides to Produce 1,1'-Biphenyl-4-ol Derivatives

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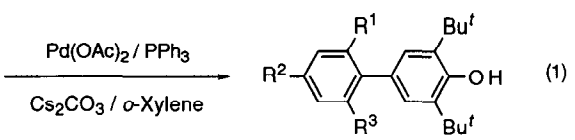
A sterically hindered phenol, 2,6-di-*tert*-butylphenol, efficiently reacts with various bromobenzenes in the presence of a palladium catalyst and a base to selectively afford the corresponding 1,1'-biphenyl-4-ol derivatives.

The palladium-catalyzed substitution reaction of aryl halides is now recognized to be of genuine synthetic utility.[1] For the synthesis of biaryls, whose skeletons are found in a wide range of important compounds including natural products and organic functional materials,[2] the Suzuki and Stille coupling reactions using arylboronic acids and arylstannanes, respectively, are often employed.[1] Meanwhile, we have recently reported that intermolecular mono- and di-arylation reactions of phenolic compounds such as 2-phenylphenols and naphthols with aryl halides using palladium catalysts can regioselectively take place at the spatially neighboring positions of phenolic function, forming one or two aryl-aryl linkages.[3,4] The coordination of phenolic oxygen to palladium is considered to be the key of the reactions. In the context of the study of the arylation of phenols by palladium catalysis, we found that aryl bromides efficiently react with a sterically hindered phenol, 2,6-di-tert-butylphenol whose oxygen is difficult to coordinate to the metal, at its *p*-position to give the corresponding coupled products in good yields (Eq. 1).[5] While some methods for the preparation of 3,5-di-*tert*-butyl-1,1'-biphenyl-4-ols,[6-9] which may form relatively stable radicals by oxidation,[7] have been reported, the present reaction seems to be more widely applicable as well as straightforward, since a variety of aryl bromides can be used. It should also be mentioned that the *tert*-butyl groups in the products may be readily removed in the presence of acids,[7c,8,10] affording 1,1'-biphenyl-4-ols which are useful compounds for the construction of organic non-linear optical materials[11] and liquid crystalline systems.[12]

1a: $R^1 = R^2 = R^3 = H$
1b: $R^1 = R^3 = H$, $R^2 = CO_2Et$
1c: $R^1 = R^3 = H$, $R^2 = CN$
1d: $R^1 = R^3 = H$, $R^2 = Ph$
1e: $R^1 = R^3 = H$, $R^2 = OMe$
1f: $R^1 = OMe$, $R^2 = R^3 = H$
1g: $R^1 = R^3 = Me$, $R^2 = H$

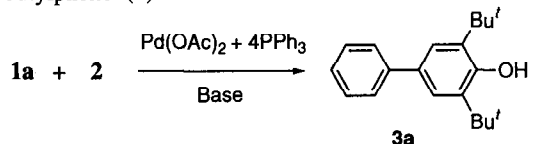


3a-g (1)

When bromobenzene (**1a**) (1.2 mmol) was treated with 2,6-di-*tert*-butylphenol (**2**) (1 mmol) in the presence of $Pd(OAc)_2$ (0.025 mmol, 2.5 mol%), PPh_3 (0.1 mmol), and Cs_2CO_3 (1.2 mmol) in refluxing *o*-xylene (b.p. 143 °C) for 1 h, 3,5-di-*tert*-butyl-1,1'-biphenyl-4-ol (**3a**) was quantitatively produced (Entry 1 in Table 1).[13] The same result was also obtained by using 1 mol% of $Pd(OAc)_2$ (Entry 2). A decrease in the reaction temperature to 120 °C reduced both the reaction rate and the yield of **3a** (Entry 3). While K_2CO_3 could be used in place of Cs_2CO_3, a longer reaction time was required to complete the reaction (Entry 4). The use of Na_2CO_3 gave no expected product (Entry 5), suggesting that the identity of base is one of the most significant factors determining the reaction efficiency. The reaction was sluggish in a polar solvent such as DMF (Entry 6). It was also confirmed that the reaction did not proceed in the absence of the palladium catalyst.

Table 2 summarizes the results for the reaction of substituted bromobenzenes **1b-g** with **2**. In all cases, the corresponding arylated products **3b-g**, bearing electron-withdrawing or -donating groups could be formed in fair to good yields. It is noted that in the case using 4-methoxy-1-bromobenzene (**1e**), the reaction with the catalyst system of $Pd(OAc)_2$ / $P(4\text{-}MeOC_6H_4)_3$ afforded a better result compared with that using $Pd(OAc)_2$ / PPh_3 which caused the contamination of phenyl group from PPh_3 in the product to give a mixture of **3e** and **3a** (2.3:1).[14] In the reaction using a sterically hindered bromobenzene, 2,6-dimethyl-1-bromobenzene (**1g**), in the presence of $Pd(OAc)_2$ /

Table 1. Reaction of bromobenzene (**1a**) with 2,6-di-*tert*-butylphenol (**2**)[a]

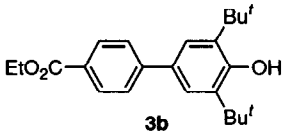
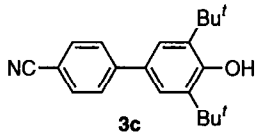
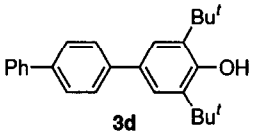
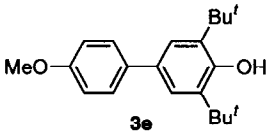
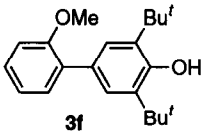
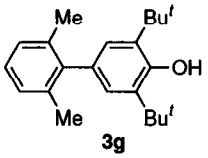


3a

Entry	$Pd(OAc)_2$ / mol%[b]	Base	Time / h	Yield of **3a** / %[c]
1	2.5	Cs_2CO_3	1	~100
2[d]	1	Cs_2CO_3	1	~100
3[e]	5	Cs_2CO_3	30	76
4	2.5	K_2CO_3	2.5	~100
5	2.5	Na_2CO_3	5	0
6[f]	2.5	Cs_2CO_3	1	17

[a]Reaction conditions: **1a** (1.2 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.025-0.05 mmol), PPh_3 (0.1-0.2 mmol), base (1.2 mmol) in refluxing *o*-xylene (5 cm^3) under nitrogen. [b]Based on amount of **2** used. [c]GLC yield based on amount of **2** used. [d]**1a** (3 mmol), **2** (2.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (3 mmol) in *o*-xylene (5 cm^3). [e]Reaction at 120 °C. [f]In DMF (5 cm^3).

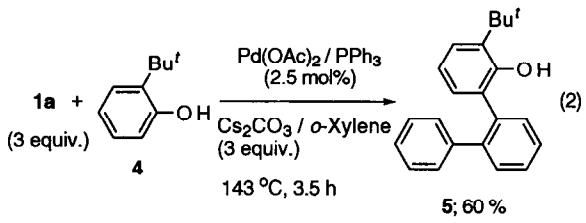
Table 2. Reaction of substituted bromobenzenes **1b-g** with 2,6-di-*tert*-butylphenol (**2**)[a]

1	Time / h	Product[b]	Yield / %[c]
1b	1	 **3b**	97 (78)
1c	1	 **3c**	55 (53)
1d	2	 **3d**	85 (74)
1e[d]	1	 **3e**	74 (51)
1f	18	 **3f**	61 (54)
1g[e]	3	 **3g**	70 (47)

[a]Reaction conditions: **1** (1.2 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (1.2 mmol) in *o*-xylene (5 cm^3) under nitrogen at 143 °C. [b]Satisfactory spectra were obtained in measurements of ^1H NMR and MS. [c]GLC yield based on amount of **2** used. Value in parentheses indicates yield after purification. [d]$P(4\text{-}MeOC_6H_4)_3$ (0.1 mmol) was used in place of PPh_3. [e]PBu^t_3 (0.1 mmol) was used in place of PPh_3.

PPh_3, the contamination of phenyl group was not observed, but the reaction terminated at ca. 50% conversion of **2**. In this case, the use of $Pd(OAc)_2$ / PBu^t_3 was found to improve the reaction efficiency;[15] thus, **3g** was formed in 70% yield.

The present reaction may proceed via the electrophilic reaction of intermediary arylpalladium species with the phenolate from **2** to give diarylpalladium species and the subsequent reductive elimination gives the product.[3b,16] It has been found that only when both the *o*-positions of phenol are masked by *tert*-butyl group, arylation can take place at the *p*-position. Thus, the reaction of 2-*tert*-butylphenol (**4**), whose oxygen seems to be relatively easy to coordinate to the palladium center, using 3 equiv. of **1a** gave 3-*tert*-butyl-1,1':2',1''-terphenyl-2-ol (**5**) in



60% yield as the single major product (Eq. 2), which is similar to the reaction of 2-naphthol;[3b] no *p*-phenylated products were detected by GLC-MS analysis.

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References and Notes

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13 Typical experimental procedure: In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (390 mg, 1.2 mmol) which was then dried at 150 °C *in vacuo* for 2 h. Then, **1a** (188 mg, 1.2 mmol), **2** (206 mg, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), 1-methylnaphthalene (60 mg, internal standard), and *o*-xylene (5 cm^3) were added and the resulting mixture was refluxed with stirring under nitrogen for 1 h. After cooling, the reaction mixture was extracted with diethyl ether, and dried over sodium sulfate. GLC and GLC-MS analyses confirmed formation of **3a** in a quantitative yield. Product **3a** (212 mg, 75%) was also isolated by column chromatography on silica gel using hexane-ethyl acetate as eluent. **3a**: Mp 101-102 °C (lit,[17] 100-101 °C); *Anal.* Found: C, 85.14; H, 9.33%. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28%. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.49 (18H, s), 5.24 (1H, s), 7.28 (1H, t, J = 7.3 Hz), 7.39 (2H, s), 7.40 (2H, t, J = 7.8 Hz), 7.54 (2H, d, J = 7.8 Hz). MS *m/z* 282 (M^+).

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