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Rhodium-HMPT-catalyzed direct *ortho* arylation of phenols with aryl bromides

Shuichi Oi,* Shun-ichiro Watanabe, Susumu Fukita and Yoshio Inoue*

Department of Materials Chemistry, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan

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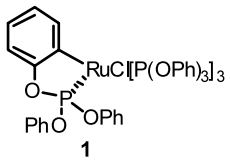
Abstract—Direct *ortho* arylation of phenols with aryl bromides catalyzed by a rhodium complex and hexamethylphosphorous triamide (HMPT) have been developed. A plausible reaction mechanism involving in situ generation of arylphosphites from phenols and HMPT, phosphorus-directed *ortho* metalation, and transesterification of the arylated arylphosphites with the substrate phenols is proposed.

Transition metal-catalyzed cross-coupling reactions of aromatic compounds have recently been recognized to be of greatly useful synthetic utility. Reactions of various arylmetal compounds with aryl halides or their synthetic equivalents catalyzed by nickel or palladium complexes are widely employed for preparations of unsymmetrical biaryls.[1] Recently, transition metal-catalyzed direct C–C bond formation on the aromatic compounds, involving the activation of aromatic C–H bond, has been attracting much attention in terms of synthetic efficiency and minimization of atomic waste.[2] For the direct arylation of aromatic compounds, Miura and co-workers reported that phenolic compounds such as 1-naphthols and 2-phenylphenols,[3] benzyl phenyl ketones,[4] benzanilides,[5] and arylcarbinols[6] were arylated with aryl halides in the presence of palladium catalysts. We reported the arylation of pyridylbenzenes with tetraarylstannanes catalyzed by rhodium(I)–phosphine complexes[7] and the arylation and alkenylation of pyridylbenzenes[8] or aromatic imines[9] with organic halides catalyzed by ruthenium(II)–phosphine complexes. Kakiuchi and co-workers reported the arylation of arylketones with arylboronates catalyzed by ruthenium complexes.[10] In these reactions, coordination of the functional groups, such as hydroxyl, pyridyl, imono, and carbonyl groups, to the transition metals promotes the *ortho* metalation, forming stable five- or six-membered metallacycles. When phenols are converted to phosphites, coordination of the phosphorus atom should also direct the *ortho* metalation forming the stable five-membered metallacycles. Actually, such complex of ruthenium **1** was isolated by the reaction of $RuHCl(PPh_3)_4$ with triphenylphosphite[11] and was applied as a catalyst to the direct *ortho* ethylation of phenol with ethylene.[12] The reaction mechanism of the ethylation of phenol probably involves the transesterification of the reacted triarylphosphite with the substrate phenol, which makes the phosphorus atom recyclable. These studies prompted us to examine the direct arylation of phenols with aryl halides via the phosphorus-directed *ortho* metalation of intermediary arylphosphites. We report here the *ortho* arylation of phenols with aryl bromides catalyzed by rhodium-HMPT system, which would involve the in situ generation of the corresponding arylphosphites, the phosphorus-directed *ortho* metalation, and the transesterification of the arylated arylphosphites with the substrate phenols.[13]



1

The reaction of *meta*-cresol (**2a**) with bromobenzene (**3a**) was initially examined in the presence of various transition metal complexes (5 mol% on metal), triphenylphosphite (20 mol%), and K_2CO_3 (2.0 equiv.) in toluene at 100°C for 20 h. Among the transition metal complexes examined, chloro-bridged dimer complex of Rh, $[RhCl(cod)]_2$, was found to exhibit catalytic activity affording the desired *ortho* phenylated product

Keywords: arylation; phenol; rhodium catalyst; aryl halide.
* Corresponding authors. E-mail: oishu@aporg.che.tohoku.ac.jp

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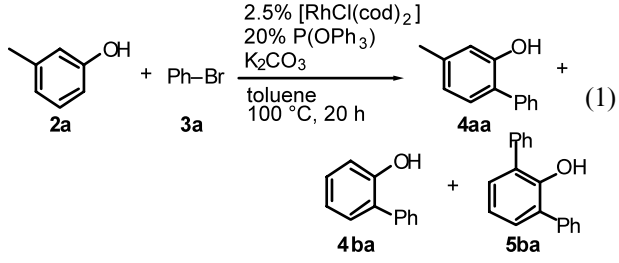
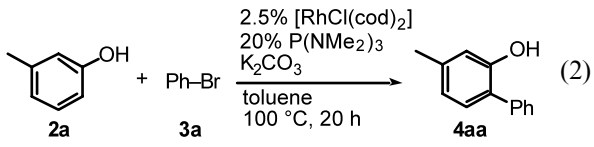
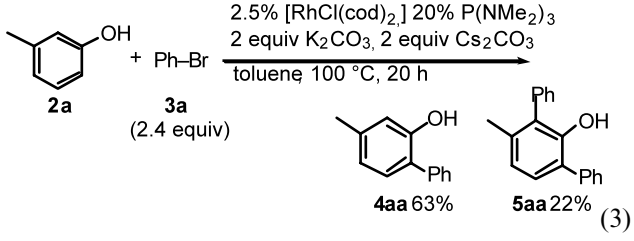
4aa in 12% yield (Eq. (1)). However, a substantial amount of phenylated products of phenol (**4ba** and **5ba**) were formed as byproducts, which would be caused by the transesterification of **2a** with triphenylphosphite. To avoid the formation of these byproducts, the use of hexamethylphosphorous triamide (HMPT) instead of triphenylphosphite was found to be effective. The reaction of HMPT with **2a** would give the corresponding arylphosphite in situ.[14] Indeed, the reaction using 20 mol% of HMPT gave only the desired product **4aa** in 17% yield (Eq. (2)). After optimization of reaction conditions, 63% yield of **4aa** and 22% yield of diphenylated product **5aa** were obtained in the reaction using 2.4 equiv. of bromobenzene in the presence of 2.5 mol% of $[RhCl(cod)]_2$, 20 mol% of HMPT, 2.0 equiv. of K_2CO_3, and 2.0 equiv. of Cs_2CO_3 in toluene at 100°C for 20 h (Eq. (3)).[15,16]



(1)



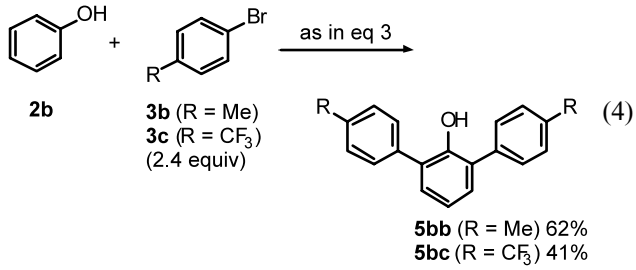
(2)



(3)

The results of the reactions of phenols with bromobenzene under the optimized conditions are shown in Table 1. The reactions of *meta*-substituted phenols, *meta*-cresol (**2a**), *meta*-trifluoromethylphenol (**2e**), and 2-naphthol (**2f**), gave the mono-phenylated products predominantly even when 2.4 equiv. of bromobenzene was used (entries 1, 5, and 6). This is probably due to the steric hindrance of the functional groups on *meta* position. The reactions of phenol (**2b**) and *para*-cresol (**2d**) gave the diphenylated products in good yields (entries 2 and 4). The reaction of *ortho*-cresol (**2c**) also proceeded smoothly to give the phenylated product **4ca** in 76% yield (entry 3). The reaction of 1-naphthol (**2g**) gave not only the monophenylated product at 2-position (**4ga**) in 43% yield but also the diphenylated product at 2- and 8-psitions (**5ga**) in 32% yield (entry 7).

The reactions of phenol (**2b**) with substituted bromobenzenes were then examined. *para*-Bromotoluene (**3b**) and *para*-trifluoromethylbromobenzene (**3c**) afforded the *ortho*-diarylphenols **5bb** and **5bc** in 62 and 41% yield, respectively (Eq. (4)).

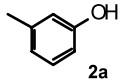
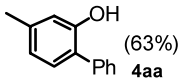
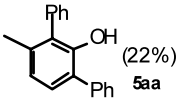
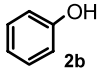
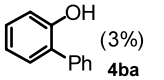
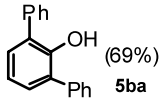
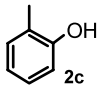
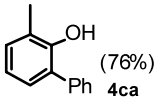
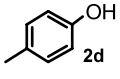
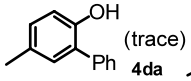
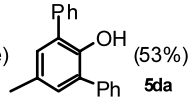
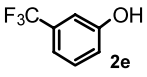
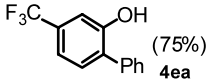
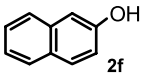
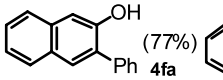
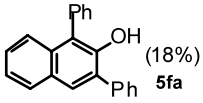
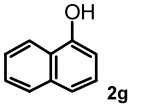
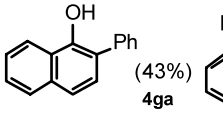
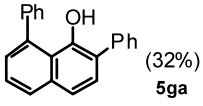


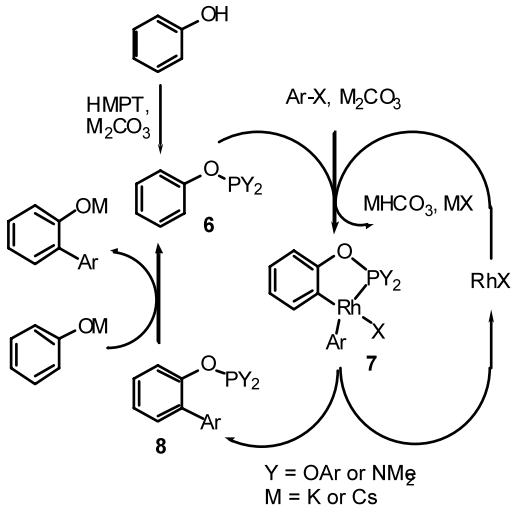
(4)

An outline of a plausible reaction mechanism is shown in Scheme 1. Initially, the reaction of substrate phenol with HMPT would give the phenylphosphite **6**. A control experiment confirmed that the reaction of HMPT with an excess amount of phenol in the presence of K_2CO_3 in toluene at 100°C gave a mixture of mono- and di-phenylphosphite. The phenylphosphite **6** would then react with the aryl halide and RhX in the presence of base to give the five-membered rhodacycle **7**. The reductive elimination of the arylated phenylphosphite **8** from **7** regenerates RhX and the transesterification of **8** with potassium or cesium phenoxide gave the product and phenylphosphite **6** again.

Although details for the formation of rhodacycle **7** from **6** with the aryl halide and RhX are not yet clear,

Table 1. Rhodium-HMPT-catalyzed phenylation of phenols with bromobenzene[16]

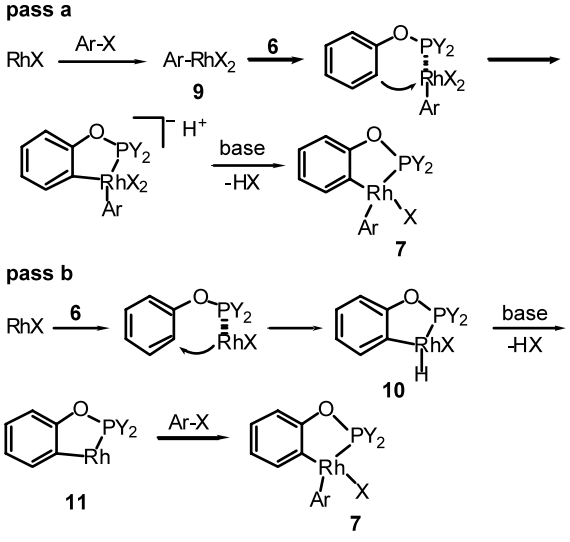
entry	1	product (yield)	
		mono (**4**)	di (**5**)
1	 **2a**	 (63%) **4aa**	 (22%) **5aa**
2	 **2b**	 (3%) **4ba**	 (69%) **5ba**
3	 **2c**	 (76%) **4ca**	
4	 **2d**	 (trace) **4da**	 (53%) **5da**
5	 **2e**	 (75%) **4ea**	
6	 **2f**	 (77%) **4fa**	 (18%) **5fa**
7	 **2g**	 (43%) **4ga**	 (32%) **5ga**



Scheme 1.

two possible pathways can be assumed (Scheme 2). In the pass a, oxidative addition of the aryl halide to RhX generates the trivalent arylrhodium species **9**,[17] which then reacts electrophilically with phosphite **6** by the aid of the coordination of the phosphorus atom to give the rhodacycle **7** after the elimination of HX. In the pass b, oxidative addition of the phosphite **6** to RhX generates the rhodium hydride complex **10** and the elimination of HX gives the monovalent rhodacycle **11**. Then, the oxidative addition of the aryl halide to **11** gives the rhodacycle **7**.

In conclusion, the reaction reported herein provides a useful method of direct arylation of the *ortho* positions of phenols with the aryl bromides. In this reaction, the arylphosphite is the key compound, which actually undergoes the arylation reaction. However, there is no need to prepare the arylphosphites correspond to the substrate phenols because the in situ reaction of phenols with HMPT generates the corresponding arylphosphites. Further investigations to extend the scope of the reaction are currently in progress.



Scheme 2.

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15. The effect of the base was examined in the reaction of phenol with bromobenzene (Table 1, entry 2). When 4 equiv. of K_2CO_3, Cs_2CO_3, and K_2CO_3/Cs_2CO_3 (1:1) was used, the yields of **5ba** were 13, 57, and 69%, respectively. In all cases, only a small amount of **4ba** was obtained.
16. **Typical reaction procedure**: To a mixture of $[RhCl(cod)]_2$ (12.5 mg, 0.025 mmol), K_2CO_3 (276.4 mg, 2.0 mmol), and

Cs_2CO_3 (651.6 mg, 2.0 mmol) in toluene were added phenols (1.0 mmol), HMPA (32.6 mg, 0.2 mmol), and bromobenzene (376.8 mg, 2.4 mmol) and the mixture was stirred at 100°C for 20 h under N_2. After the reaction mixture was cooled to room temperature, 10 mL of diethyl ether and 10 mL of conc. HCl were added to the reaction mixture and the mixture was stirred vigorously for 1 h. Organic layer was extracted by diethyl ether, washed with sat. NaCl aq., and dried over $MgSO_4$. After the solvent was removed, the residue was purified by silica gel flash chromatography using hexane/AcOEt (10:1). Spectroscopic data for new compounds: **4aa**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48–7.43 (m, 4H), 7.38–7.35 (m, 1H), 7.13 (d, 1H, $J=8.1$ Hz), 6.82–6.80 (m, 2H), 5.14 (s, 1H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.2, 139.4, 137.1, 130.0, 129.2, 129.1, 127.6, 125.2, 121.7, 116.4, 21.2. IR (Neat): 3520, 3028, 2919, 1889, 1625, 1486, 1486, 1288, 1153, 942, 767, 701, 582, 461 cm^{-1}. Anal calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.55; H, 6.70. **5aa**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57–7.55 (m, 2H), 7.51–7.48 (m, 2H), 7.44–7.39 (m, 3H), 7.34–7.31 (m, 3H), 7.22 (d, 1H, $J=7.8$ Hz), 6.93 (d, 1H, $J=7.8$ Hz), 4.98 (s, 1H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.6, 138.0, 136.7, 135.7, 130.2, 129.4, 139.24, 129.22, 128.6, 128.4, 128.0, 127.1, 125.7, 122.0, 20.4. IR (Neat): 3535, 3027, 2921, 1612, 1477, 1406, 1242, 1111, 775, 700 cm^{-1}. Anal calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.81; H, 6.36. **4ea**: mp 56.5–57.5°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57–7.50 (m, 2H), 7.48–7.43 (m, 3H), 7.36–7.32 (m, 1H), 7.27–7.23 (m, 2H), 5.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6, 135.6, 131.521, 131.505, 131.2, 130.6, 129.6, 128.9, 128.7, 125.2, 117.552, 117.519, 117.478, 117.438, 113.078, 113.040, 113.002, 112.963. IR (KBr): 3326, 1417, 1338, 1167, 1116, 1076, 909, 695 cm^{-1}. Anal calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.82; H, 3.90. **4fa**: mp 118.0–118.5°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (d, 4H, $J=8.3$ Hz), 7.734 (s, 1H), 7.726 (d, 1H, $J=7.9$ Hz), 7.75–7.51 (m, 4H), 7.46–7.42 (m, 2H), 7.34 (t, 1H, $J=7.3$ Hz), 7.33 (s, 1H) 5.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.7, 136.8, 134.3, 130.4, 129.5, 129.31, 129.26, 128.9, 128.2, 127.8, 126.5, 126.2, 123.9, 110.2. IR (KBr): 3515, 3054, 1626, 1437, 1173, 757, 707 cm^{-1}. Anal calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.22; H, 5.60. **4ga**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32–8.26 (m, 1H), 7.85–7.79 (m, 1H), 7.58–7.40 (m, 8H), 7.36 (d, 1H, $J=8.4$ Hz), 5.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 147.7, 137.4, 134.2, 129.6, 29.3, 127.9, 127.6, 127.5, 126.5, 125.5, 124.3, 122.4, 121.2, 120.2. IR (KBr): 3276, 1561, 1321, 1050, 814, 758, 695 cm^{-1}. Anal calcd for $C_{18}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.20; H, 5.63. **5ga**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (dd, 1H, $J=8.2$, 1.3 Hz), 7.56 (d, 1H, $J=8.6$ Hz), 7.53–7.49 (m, 4H), 7.48–7.433 (m, 5H), 7.425–7.37 (m, 2H), 7.30 (tt, 1H, $J=7.4$, 1.3 Hz), 7.23 (dd, 1H, $J=7.2$, 1.2 Hz), 5.72 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.3, 142.1, 138.6, 137.1, 135.2, 129.8, 129.5, 129.2, 128.9, 128.6, 128.5, 128.3, 128.1, 127.0, 125.0, 124.1, 121.5, 120.8. IR (KBr): 3483, 1577, 1491, 1362, 1092, 833, 761, 697 cm^{-1}. Anal calcd for $C_{22}H_{16}O$: C, 89.16; H, 5.44. Found: C, 88.86; H, 5.71. **5bb**: mp 89.6–90.6°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, 4H, $J=8.1$ Hz), 7.30–7.23 (m, 6H), 7.03 (d, 1H, $J=7.8$ Hz), 5.40 (s, 1H) 2.41 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.4, 137.4, 134.6, 129.7, 129.5, 129.2, 128.6, 120.6, 21.2. IR (KBr): 3553, 1514, 1444, 1396, 1321, 1222, 828, 784, 749 cm^{-1}. Anal calcd for $C_{16}H_{12}O$: C, 87.56; H, 6.61. Found: C, 87.28; H, 6.77. **5bc**: mp 124.4–126.4°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, 4H, $J=8.4$ Hz), 7.68 (d, 4H, $J=8.4$ Hz), 7.03 (d, 2H, $J=7.3$ Hz), 7.12 (t, 1H, $J=7.6$ Hz), 5.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2, 141.0, 130.6, 130.1, 129.797, 129.731, 127.8, 125.893, 125.587, 125.820, 125.783, 125.460, 122.8, 121.3, 119.6. IR (KBr): 3565, 1617, 1450, 1323, 1152, 1111, 1064, 851, 794, 750 cm^{-1}. Anal calcd for $C_{20}H_{12}F_6O$: C, 62.83; H, 3.16. Found: C, 62.87; H, 3.26.

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