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Palladium-Catalyzed Multiple Arylation of Phenyl Ketones with Aryl Bromides

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Abstract: Benzyl phenyl ketones undergo triarylation upon treatment with excess aryl bromides in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Cs_2CO_3 as base in *o*-xylene on the α- and two *ortho*-positions of the carbonyl group to give diphenymethyl 2,6-diphenylphenyl ketone derivatives as the predominant products. Acetophenone and diphenylmethyl phenyl ketone similarly undergo tetra- and diarylations, respectively.

Keywords: Aryl Halides; Arylation; Ketones; Palladium and compounds

Palladium-catalyzed arylation reactions using aryl halides and their synthetic equivalents are now recognized to be of genuine synthetic utility.[1] For example, the Heck reaction with alkenes and the Suzuki and Stille coupling reactions with organoboronates and organostannanes, respectively, are often employed for the preparation of substituted aromatic compounds. Recently, it was described that ketones and α,β-unsaturated carbonyl compounds can effectively undergo arylation at their α-[2-5] and γ-positions,[6] respectively, under the conditions similar to those for the Heck reaction. Meanwhile, we also reported that mono- and/or diarylation reactions of phenolic compounds such as 1-naphthols and 2-phenylphenols with aryl halides using a palladium catalyst can regioselectively occur on their unactivated 8- and 2'-positions, respectively.[2] The coordination of phenolic oxygen to intermediary arylpalladium species is considered to be the key for the coupling reactions. Consequently, one may expect that enolate oxygen from an aromatic ketone functions like phenolate oxygen. Indeed, we have found that benzyl phenyl ketones undergo arylation not only on the α-position, but also two *ortho*-positions of the carbonyl group to give diphenymethyl 2,6-diphenylphenyl ketone derivatives as the predominant products.[7,8] Acetophenone and diphenylmethyl phenyl ketone can similarly undergo tetra- and diarylations, respectively. The multiple arylation seems to be useful as a synthetic method of oligo-phenyl compounds.

When the reaction of benzyl phenyl ketone **1a** (1 mmol) with bromobenzene **2a** (4 mmol) was carried out in the presence of $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol) and Cs_2CO_3 (4 mmol) in *o*-xylene at 160 °C (bath temperature) for 5 h, a mixture of mono-, di- and triphenylated products **3**-**5** was formed; the yields were 47, 35 and 9%, respectively (Entry 1

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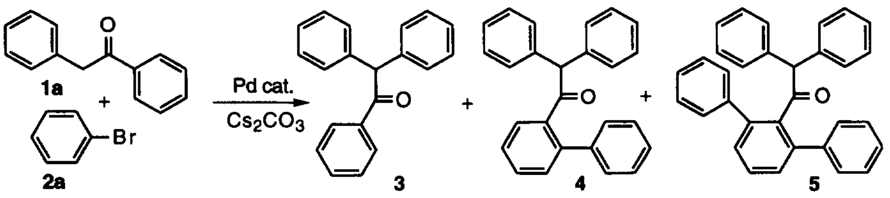
Table 1. Reaction of Benzyl Phenyl Ketone **1a** with Bromobenzene **2a**[a]



Entry	Pd cat.	Solvent	Time / h	Yield / %[b]		
				3	**4**	**5**
1	$Pd(OAc)_2/4PPh_3$	*o*-Xylene	5	47	35	9
2	$Pd(OAc)_2/4PPh_3$	*o*-Xylene	22	1	5	54
3	$Pd(OAc)_2/4PPh_3$	DMF	2	79	5	0
4	$Pd(OAc)_2/4PPh_3$	DMF	22	3	1	0
5[c]	$Pd(PPh_3)_4$	*o*-Xylene	20	6	7	61
6	$Pd(OAc)_2/4P(o\text{-Tolyl})_3$	*o*-Xylene	22	91	7	0
7[d]	$Pd(OAc)_2/4PPh_3$	*o*-Xylene	24	96	3	0

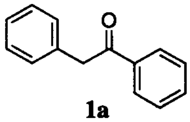
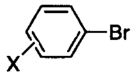
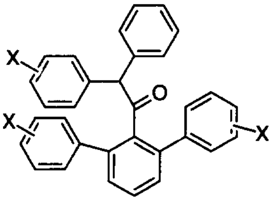
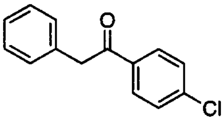
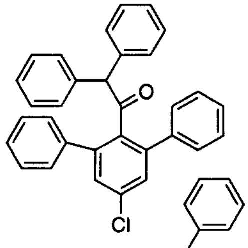
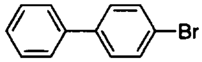
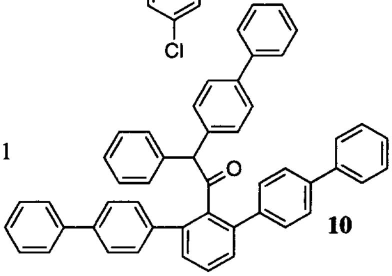
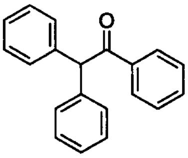
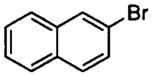
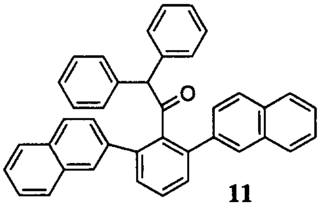
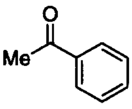
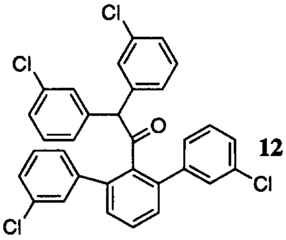
[a] The reaction was carried out under N_2 at 160 °C (bath temperature). [**1a**]:[**2a**]:[Cs_2CO_3]:[Pd] = 1:4:4:0.01 (in mmol). [b] Determined by GLC analysis based on **1a** used. [c] [Pd] = 0.005. [d] K_2CO_3 was used in place of Cs_2CO_3.

in Table 1). By prolonging reaction time to 22 h, the triphenylated compound **5** was selectively obtained in a yield of 54% (Entry 2). While the reaction in DMF for 2 h selectively gave **3** as reported previously,[2b] an intractable mixture was formed after 22 h (Entries 3 and 4). Thus, the use of a less polar solvent seems to be essential for the present triphenylation. Interestingly, the reaction with $Pd(PPh_3)_4$ (0.5 mol%) in place of $Pd(OAc)_2/4PPh_3$ (1 mol%) in *o*-xylene afforded **5** in an enhanced yield of 61% (Entry 5). The use of a bulky phosphine $P(o\text{-Tolyl})_3$ and a less effective base K_2CO_3 in place of PPh_3 and Cs_2CO_3, respectively, appeared to suppress the arylation on the phenyl ring leading to **4** and **5** (Entries 6 and 7).

Table 2 summarizes the results for the reactions of a number of phenyl ketones **1a-d** and aryl bromides **2a-f** using $Pd(PPh_3)_4$. The reaction of **1a** with 3-trifluoromethyl-, 3-chloro-, and 4-chlorobromobenzenes **2b-d** gave the corresponding triarylated products **6-8**, as did the reaction with **2a**. By contrast, the reaction with 4-bromoanisole did not afford the expected triarylated product, giving a mixture of mono- and diarylated products (64 and 26% after 22 h). This indicates that an electron-donating substituent on bromobenzene retards the arylation on the phenyl ring. By introducing an electron-withdrawing group to **1a** was found to be enhanced the reaction. Thus, the reaction of benzyl 4-chlorophenyl ketone **1b** with **2a** proceeded much faster than that of **1a**. From the reactions of **1a** with 4-bromobiphenyl **2e** and of diphenylmethyl phenyl ketone **1c** (= **3**) with 2-bromonaphthalene **2f** were obtained compounds **10** and **11** which have 8 and 7 aromatic rings, respectively. By starting from acetophenone **1d** together with **2c** was successfully obtained tetraarylated product **12**.

The mechanism of palladium-catalyzed α-arylation of ketones has been previously

Table 2. Reaction of Phenyl Ketones **1a-d** with Aryl Bromides **2a-f**[a]

1	2 (mmol)	Time / h	Product[b]	Yield / %[c]
 **1a**	 **2b**: X = 3-CF$_3$ (4) **2c**: X = 3-Cl (4) **2d**: X = 4-Cl (4)	44 23 24	 **6**: X = 3-CF$_3$ **7**: X = 3-Cl **8**: X = 4-Cl	68 (41) (54) 39 (25)
 **1b**	**2a** (4)	6	 **9**	65 (59)
1a	 **2e** (4)	21	 **10**	(30)
 **1c**	 **2f** (3)	23	 **11**	(43)
 **1d**	**2c** (5)	23	 **12**	61 (34)

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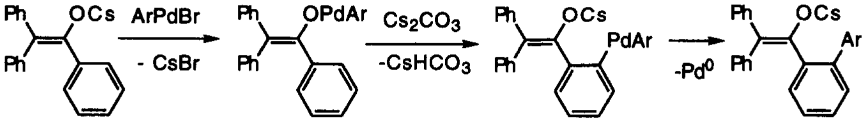
[a] Reaction conditions: **1** (1 mmol), Pd(PPh$_3$)$_4$ (0.005 mmol), Cs$_2$CO$_3$ (3-5 mmol), in *o*-xylene (5 cm^3) under N$_2$.
[b] Satisfactory spectra were obtained in measurements of ^{1}H and ^{13}C NMR and MS. Melting points of **7-11** were 36-37, 161-162, 108-110, 196-198 and 188-190 °C, respectively. Compounds **6** and **12** were obtained as viscous oils. [c] Determined by GLC analysis. Value in parentheses indicates yield after isolation.

discussed.[2-4] The arylation on the aromatic ring of phenyl ketones may proceed *via* the coordination of enolate from diarylmethyl aryl ketones to intermediary arylpalladium species followed by *ortho*-palladation and successive reductive elimination, which is similar to the



reaction of 1-naphthols and 2-phenylphenols.[2] Murai *et al.* reported that the ruthenium-catalyzed *ortho*-alkylation of aromatic ketones including acetophenone and benzophenone with alkenes *via* C-H activation proceeds under neutral conditions.[7] Consequently, benzophenone which can not yield enolate was treated with **2a** under the present conditions, but no reaction occurred. This may partly support the above enolate route.

Acknowledgement

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8. Rhodium-catalyzed arylation of 2-phenylpyridine with arylstannanes: S. Oi, S. Fukita, Y. Inoue, *Chem. Commun.*, **1998**, 2439.
9. Typical procedure: In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (1.30 g, 4 mmol) which was dried at 150 °C *in vacuo* for 2 h. Then, **1a** (196 mg, 1 mmol), **2a** (628 mg, 4 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol), 1-methylnaphthalene (ca. 70 mg as internal standard for GLC analysis) and *o*-xylene (5 cm^3) were added and the resulting mixture was stirred under nitrogen at 160 °C for 20 h. After cooling, the reaction mixture was poured into dilute HCl, extracted with diethyl ether and dried over sodium sulfate. Product **5** (170 mg, 40%) was isolated by column chromatography on silica gel using hexane-toluene (80:20, v/v): M.p. 138-138.5 °C; ^1H NMR (600 MHz, $CDCl_3$) $\delta = 4.69$ (s, 1H), 6.66 (d, $J = 7.9$ Hz, 4H), 6.96 (t, $J = 7.7$ Hz, 4H), 7.02 (t, $J = 7.0$ Hz, 2H), 7.18 (d, $J = 7.9$ Hz, 4H), 7.23 (t, $J = 7.4$ Hz, 4H), 7.26-7.28 (m, 4H), 7.43 (t, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 65.6$, 126.3, 127.3, 127.8, 127.9, 128.6, 128.6, 129.3, 129.7, 137.6, 139.4, 140.0, 140.1, 202.9; MS *m/z* 424 (M^+). Anal. Calcd for $C_{32}H_{24}O$: C, 90.53; H, 5.70. Found: C, 90.38; H, 5.79.