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Regioselective arylation of benzanilides with aryl triflates or bromides under palladium catalysis

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Abstract

Benzanilides efficiently undergo diarylation upon treatment with aryl triflates or bromides in the presence of a palladium-based catalyst system to give the corresponding *N*-(2,6-diarylbenzoyl)anilines in good to excellent yields.

Keywords: anilides; arylation; aryl halides; palladium; palladium compounds.

Palladium-catalyzed arylation reactions using aryl halides and their synthetic equivalents including aryl triflates are now recognized to be of genuine synthetic utility.[1] The reactions with various arylmetal species, especially with arylboronic acids (the Suzuki–Miyaura coupling), are often employed for the preparation of unsymmetrical biaryls. Meanwhile, we recently reported that (a) 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] and (b) benzyl phenyl ketones undergo arylation on the two *ortho*-positions of the carbonyl group as well as the α-position to give diphenymethyl 2,6-diphenylphenyl ketone derivatives.[3] The coordination of phenolate or enolate oxygen of the substrates to intermediary arylpalladium species is considered to be the key for these reactions.[2,3] Thus, for further development of the new catalytic coupling, it seems to be crucial to find effective functional groups other than enolate oxygen. Consequently, we examined the reactions of aryl bromides or triflates with benzoic acid, benzenesulfonanilide and benzamide which have different acidities.[4,5] As a result, we observed that the third compound, which is the least acidic among the substrates, can efficiently undergo diarylation to give *N*-(2,6-diphenylbenzoyl)aniline (Table 1). Note that 2,6-diarylbenzoic acid derivatives are useful building blocks for preparing cyclophanes and related cyclic compounds having a terphenyl moiety with functionality.[6]

When benzanilide (**1a**) (1 mmol) was treated with phenyl triflate (**2a**) (4 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.3 mmol, P/Pd=6) and Cs_2CO_3 (4 mmol) in DMF at 110°C for 24 h, a mixture of *N*-(2-phenylbenzoyl)aniline (**4**) (48%) and *N*-(2,6-diphenylbenzoyl)aniline (**5**) (37%) was

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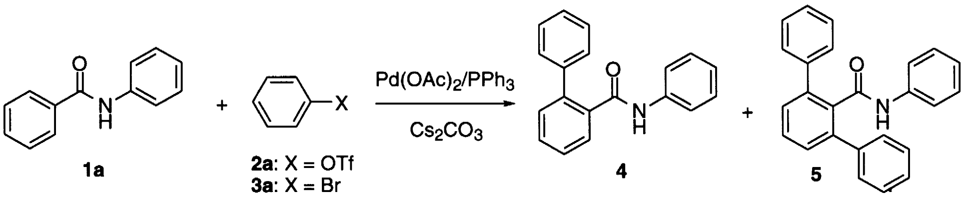
Table 1

Reaction of benzanilide (**1a**) with phenyl triflate (**2a**) or bromobenzene (**3a**)[a]



Entry	Triflate or bromide	P/Pd[b]	Solvent	Time / h	Yield[c] / %		Recovery of **1a**[c] / %
					4	**5**	
1	**2a**	6	DMF	24	48	37	14
2	**2a**	6	Toluene	24	0	(96)	0
3	**2a**	4	Toluene	23	0	(81)	0
4	**2a**	8	Toluene	47	0	(94)	0
5	**3a**	6	DMF	47	57(37)	13	28
6	**3a**	6	Toluene	69	55	32	9
7[d]	**3a**	6	*o*-Xylene	47	0	(80)	0

[a] The reaction was carried out under N_2 at 110 °C (bath temperature). [**1a**]:[**2a** or **3a**]:[Cs_2CO_3]:[Pd] = 1:4:4:0.05 (in mmol).

[b] Ratio of PPh_3/$Pd(OAc)_2$.

[c] Determined by GC analysis based on **1a** used. Value in parenthesis is isolated yield.

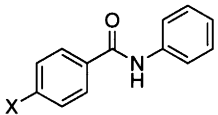
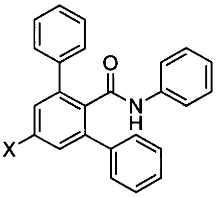
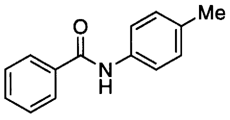
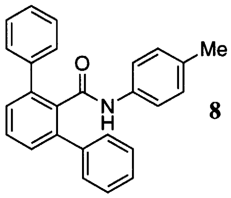
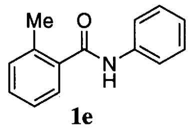
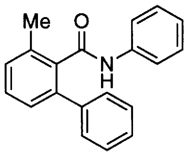
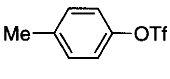
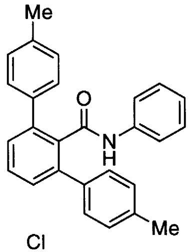
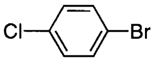
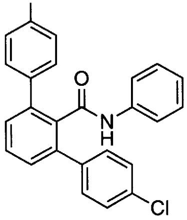
[d] Reaction at 150 °C (bath temperature).

produced, the starting material **1a** (14%) being recovered (entry 1 in Table 1). The reaction in toluene in place of DMF proceeded much more smoothly, giving the diphenylated compound **5** in a yield of 96% (entry 2). The ratio of PPh_3 to $Pd(OAc)_2$ was also found to affect the reaction. The yield of **5** was reduced by decreasing the P/Pd ratio to 4 (entry 3). The reaction became slower at the ratio of 8, while **5** was obtained in 94% yield after 47 h (the ratio of **4**:**5** at 24 h was ca. 1:2) (entry 4). The reaction using bromobenzene (**3a**) was considerably slower than that using **2a**. However, an acceptable yield of **5** (80%) was obtained in the reaction in *o*-xylene at 150°C.

Table 2 summarizes results for the reactions of a number of benzanilides **1a**–**e** with triflates **2a**,**b** and bromide **3b**.[7,8] *N*-(4-Methoxybenzoyl)- and *N*-(4-chlorobenzoyl)anilines (**1b**,**c**) and *N*-benzoyl-4-methylaniline (**1d**) reacted with **2a** to give the corresponding diphenylated products **6**–**8** in excellent yields (entries 1–3). From the reaction of *N*-(2-methylbenzoyl)aniline (**1e**) with **2a** was obtained the expected mono-phenylated compound **9** (entry 4). The reactions of **1a** with 4-methylphenyl triflate (**2b**) and 4-bromochlorobenzene (**3b**) also afforded diarylated compounds **10** and **11** (entries 5 and 6). In these reactions using **2b** and **3b**, $P(4\text{-}MeC_6H_4)_3$ and $P(4\text{-}ClC_6H_4)_3$ were used as ligands in place of PPh_3 in order to avoid the contamination of phenyl group from the phosphine.[9]

It has been reported that (a) acetanilide undergoes palladation at the *ortho*-position of the aniline moiety upon treatment with $Pd(OAc)_2$,[10] and (b) intramolecular cyclization of haloamides forming a C–N bond takes place in the presence of a palladium catalyst.[11] No products arylated at the *N*-phenyl group and amide nitrogen of **1** were, however, detected in the present reaction. While further studies are required to discuss the detailed mechanism of the arylation, it may be reasonable to consider that the coordination of amide anion generated from **1** to intermediary arylpalladium species occurs as the key step, which is similar to the reactions of phenols and phenyl ketones.[2,3] In consistent with this, a

Table 2
Reaction of benzanilides **1a**–**e** with aryl triflates **2a**,**b** or bromide **3b**[a]

Entry	**1**	**2**	Product		Yield[b] / %
1 2	 **1b**: X = OMe **1c**: X = Cl	**2a** **2a**		**6**: X = OMe **7**: X = Cl	95 93
3	 **1d**	**2a**		**8**	96
4[c]	 **1e**	**2a**		**9**	79
5[d]	**1a**	 **2b**		**10**	74
6[e]	**1a**	 **3b**		**11**	78

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[a] Reaction conditions: **1** (1 mmol), **2** or **3** (4 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.3 mmol), Cs_2CO_3 (4 mmol), in toluene (8 cm^3) at 110 °C under N_2 for 22-47 h unless otherwise noted.

[b] Isolated yield.

[c] Triflate **2a** (2 mmol) and Cs_2CO_3 (2 mmol) were used.

[d] $P(4\text{-}MeC_6H_4)_3$ was used in place of PPh_3.

[e] Reaction using $P(4\text{-}ClC_6H_4)_3$ in place of PPh_3 in *o*-xylene at 150 °C.

preliminary investigation into the mechanism using *N*-propylbenzamide and *N*,*N*-dimethylbenzamide suggested that an amide hydrogen is required for the reaction to take place: the former compound could react with **2a** in toluene to give a mixture of mono- and diphenylated products (35% and 14%, respectively, by GC), whereas the latter gave no coupling products.

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7. Typical procedure: a mixture of **1a** (197 mg, 1 mmol), **2a** (904 mg, 4 mmol), Pd(OAc)$_2$ (11.2 mg, 0.05 mmol), PPh$_3$ (78 mg, 0.3 mmol), Cs_2CO_3 (1.30 g, 4 mmol) and toluene (8 cm^3) was stirred under nitrogen at 110°C for 24 h. After cooling, the reaction mixture was poured into dilute HCl, extracted with ethyl acetate and dried over sodium sulfate. Evaporation of the solvent and washing the residual solid well with hexane gave product **5** (335 mg, 96%). Mp 279–280°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ=6.95 (t, J=7.3 Hz, 1H), 7.15 (t, J=7.3 Hz, 2H), 7.20 (d, J=7.3 Hz, 2H), 7.29 (d, J=7.3 Hz, 2H), 7.36 (t, J=7.3 Hz, 4H), 7.43 (d, J=7.8 Hz, 2H), 7.50 (d, J=7.3 Hz, 4H), 7.60 (t, J=7.8 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ=120.01, 123.66, 127.46, 128.25, 128.53, 128.63, 129.06, 129.11, 136.49, 138.62, 139.53, 140.38, 166.76; MS m/z 349 (M$^+$). Anal. calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.83; H, 5.49; N, 4.00.
8. Selected data for **6**: mp 240–242°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=55.53, 114.72, 120.43, 124.42, 127.75, 128.43, 128.48, 128.65, 128.67, 137.33, 140.32, 142.25, 159.68, 166.96. Anal. calcd for $C_{26}H_{21}NO_2$: C, 82.30; H, 5.58; N, 3.69. Found: C, 82.16; H, 5.64; N, 3.59. For **7**: mp 258–259°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=120.64, 124.80, 128.17, 128.43, 128.62, 128.75, 129.10, 134.03, 135.06, 136.89, 138.95, 142.13, 166.19. Anal. calcd for $C_{25}H_{18}ClNO$: C, 78.20; H, 4.70; Cl, 9.24; N, 3.60. Found: C, 78.13; H, 4.74; Cl, 9.21; N, 3.64. For **8**: mp 282–283°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.83, 120.74, 127.62, 128.44, 128.59, 129.22, 129.31, 129.36, 134.30, 134.52, 135.64, 140.26, 140.33, 166.96. Anal. calcd for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85. Found: C, 85.73; H, 5.90; N, 3.79. For **9**: mp 137–138°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.68, 120.45, 124.66, 127.40, 127.62, 128.46, 128.57, 128.80, 129.35, 129.56, 136.14, 136.17, 137.31, 139.22, 140.18, 167.93. Anal. calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.46; H, 6.03; N, 4.88. For **10**: mp 269–270°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.14, 120.55, 124.48, 128.43, 128.68, 129.17, 129.19, 129.37, 135.44, 137.30, 137.31, 137.34, 140.30, 167.31. Anal. calcd for $C_{27}H_{23}NO$: C, 85.91; H, 6.14; N, 3.71. Found: C, 85.56; H, 6.24; N, 3.69. For **11**: mp >290°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ=120.57, 124.99, 128.72, 128.92, 129.51, 129.61, 130.05, 134.15, 135.74, 137.05, 138.52, 139.34, 166.61. Anal. calcd for $C_{25}H_{17}Cl_2NO$: C, 71.78; H, 4.10; Cl, 16.95; N, 3.35. Found: C, 71.59; H, 4.18; Cl, 16.76; N, 3.31.
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