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Effect of oxygen substituents on the regioselectivity of the Pd-assisted biaryl coupling reaction of benzanilides

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Abstract—This study investigated the effect of oxygen substituents in the benzoyl part of *N*-(2-iodophenyl)benzamide on the coupling position in its Pd-assisted biaryl coupling reaction. Benzamide with methylenedioxy and acyloxy groups yielded the *ortho*-product formed predominantly by connection to a more hindered carbon. The mechanism is discussed from the perspectives of both steric and coordinated effects.

Intramolecular aryl–aryl coupling reactions involving a palladium reagent have been used to synthesize many condensed aromatic compounds.[1] Recently, we reported the synthesis of condensed heteroaromatic compounds using biaryl coupling reactions with palladium reagents[2,3] and the syntheses of naphthobenzazepines and pyrrolophenanthridine alkaloids by regioselective C–H bond activation using the intramolecular coordination of the amine to Pd.[4]

Examining the synthesis of trisphaeridine, we found that the coupling reaction of *N*-(2-iodophenyl)benzamide (**1a**) possessing a methylenedioxy group with $Pd(OAc)_2$ and PPh_3 in the presence of Na_2CO_3 in DMF produced the *ortho*-product (**2a**), which was formed by connection to a more hindered carbon and the *para*-product (**3a**) in a 4 to 1 ratio.[2c] By contrast, Cai et al. reported that the biaryl coupling reaction of *N*-(2-bromophenyl)-3,4-methylenedioxybenzamide (**1**, R^1+R^2 = –OCH_2O–, R^3 = H) catalyzed by $Pd(OAc)_2$ in the absence of phosphine ligand in DMA exclusively gave the *para*-product crinasiadine (**3**, R^1+R^2 = –OCH_2O–, R^3 = H) with a 48.5% yield.[5,6] Vila et al. investigated the influence of substituents on the phenyl ring in the palladation of Schiff bases (**A**). They found that the bulkiness of the methoxy group at C_3 and an ethylenedioxy group at C_3 and C_4 hindered direct metallation by Pd^{II} at the C_2 (*ortho*) position to give the cyclopalladation product at the C_6 (*para*) position; they further found that the methylenedioxy group did not impede palladation of the phenyl ring at the C_2 (*ortho*) position to selectively produce the *ortho*-product.[8] Moreover, Dyke et al. reported that the cyclopalladation of benzylamine (**B**) possessing a methoxy or methylenedioxy group occurred at the C_6 (*para*) position,[9] in contrast to the results of Vila et al. mentioned above. Therefore, we investigated the influence of oxygen substituents on coupling position in the Pd-assisted reaction of *N*-(2-iodophenyl)benzamides (**1**).[10]

The results of the coupling reactions using methods A [$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and K_2CO_3 (200 mol %)], B[2d,e] [$Pd(OAc)_2$ (100 mol %), DPPP (100 mol %), *n*-Bu_3P (100 mol %), and Ag_2CO_3 (200 mol %)], and C [$Pd(OAc)_2$ (10 mol %), (*o*-tol)$_3$P (20 mol %), and K_2CO_3 (200 mol %)] in DMF under reflux are summarized in Table 1 (Scheme 1).

First, the reactions of **1** using Method A were examined. The coupling reactions of **1a** and **1b** possessing a methylenedioxy group gave the *ortho*-products **2a**

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Table 1. Results of biaryl coupling reactions of benzanilides (**1**) in DMF under reflux[a]

Run	Substrate	Method	Yield (%)	Ratio[b]
			2+3	**2:3**
1	**1a**	A	69	8.5:1
2		B	Quant	9.2:1
3	**1b**	A	Quant	7.5:1
4		B	84	11.5:1
5		C	96	5.6:1
6	**1c**	A	Quant	2.9:1
7		B	Quant	3.8:1
8		C	Quant	2.0:1
9	**1d**	A	86	0.9:1
10		B	85	1.1:1
11		C	Quant	0.4:1
12	**1e**	A	93	1.0:1
13		B	98	1.3:1
14		C	Quant	0.6:1
15	**1f**	A	96	1.2:1
16		B	Quant	1.3:1
17		C	Quant	0.4:1
18	**1g**	A	79	1.0:1
19		B[c]	83	1.4:1
20		C	Quant	1.2:1
21	**1h**	A	76	7.0:1
22		B	Quant	8.3:1
23		C	96	2.9:1
24	**1i**	A	Quant	16.5:1
25		B	83	14.6:1
26		C	97	4.0:1
27	**1j**	A	70	4.3:1
28		B	68	6.3:1
29	**1k**	A	78	0.3:1
30		B	Quant	0.4:1
31		C	81	0.1:1

[a] All reactions were carried out in DMF under Ar atmosphere and reflux for 15–30 min. Method A [Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), and K$_2$CO$_3$ (200 mol %)]. Method B [Pd(OAc)$_2$ (100 mol %), DPPP (100 mol %), *n*-Bu$_3$P (100 mol %), and Ag$_2$CO$_3$ (200 mol %)]. Mehtod C [Pd(OAc)$_2$ (10 mol %), (*o*-tol)$_3$P (20 mol %), and K$_2$CO$_3$ (200 mol %)].

[b] Determined by HPLC and NMR analysis.

[c] K$_2$CO$_3$ (200 mol %) as a base in place of Ag$_2$CO$_3$, because **If** was gradually decomposed by using Ag$_2$CO$_3$.

and **2b** as the major products; these products were formed by connection to a more hindered carbon (see runs 1 and 3). By contrast, the reaction of benzamides (**1d** and **e**) possessing methoxy group(s) under the same reaction conditions gave the corresponding coupling products (**2** and **3**) in a ratio of 0.9–1.0 to 1, showing nearly equal selectivity (see runs 9 and 12). The reaction of compounds with an ethylenedioxy group gave **2c** and **3c** in a ratio of 2.9 to 1, which was an intermediate value between **1b** possessing a methylenedioxy group and **1d** and **e** possessing a methoxy group(s) (see run 6). Interestingly, even **1f** possessing a bulky *tert*-butoxy group yielded **2f** and **3f** in a ratio of 1.2 to 1 (see run 15). The reaction of **1g** possessing a phenol group gave **2g** and **3g** in almost equal amounts (see run 18), although Rawal et al. reported that the coupling reaction of iodocarbamate (**4a**) possessing a phenol group using Herrmann's palladacycle catalyst[11] and Cs$_2$CO$_3$ in DMA exclusively gave a 76% yield of the *ortho*-product (**5a**);[12] the reaction of the bromo ether (**4b**) with Pd(PPh$_3$)$_4$ and *t*-BuOK in DMA predominantly provided the *ortho*-product (**5b**) in an 87% yield.[12]

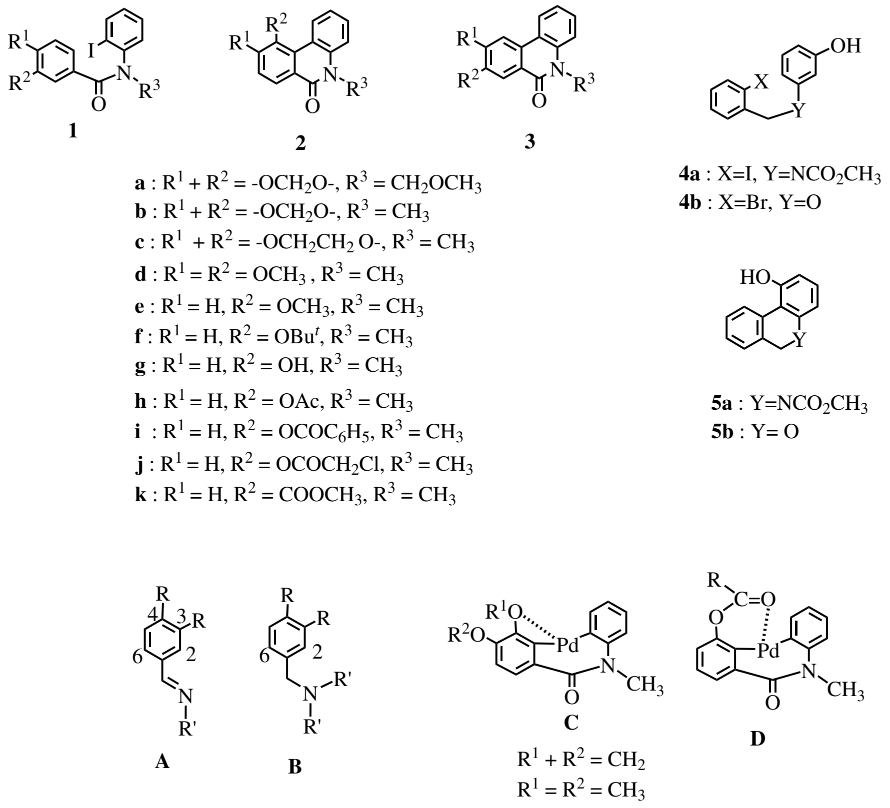
The regioselectivity of the coupling reaction involving two possible positions, C$_2$ (*ortho*) and C$_6$ (*para*), can be discussed based on steric and electronic effects. The difference in the regioselectivity of methoxy and methylenedioxy groups reflects the steric bulkiness of the methoxy group[8] and the fact that the lone pair of electrons in the methylenedioxy oxygen atom is more electronegative than that in the methoxy oxygen atom because of reduced resonance of the π-electron on the benzene ring compared with those of other oxygen groups.[13] Therefore, the lone pair of electrons in the methylenedioxy oxygen atom would coordinate to the Pd^{II} on the square-planer complex more tightly to produce the *ortho*-product predominantly via the intermediate (**C**).

Acetate (**1h**) gave the *ortho*-product (**2g**) selectively via connection to a more hindered carbon and subsequent alkaline hydrolysis[14] (see run 21), whereas the ester (**1k**) provided the *para*-product (**3k**) selectively for steric reasons (see run 29).

Benzoate (**1i**) produced the *ortho*-product (**2i**) with better selectivity, while monochloroacetate (**1j**) produced **2j** with less selectivity than **1h** (see runs 24 and 27). These results are attributable to the coordinating ability of carbonyl oxygen to Pd^{II}, such that the *ortho*-product (**2**) was produced selectively via the coordinated intermediate (**D**).

All of the reactions using our new method (Method B),[2d] except run 25, yielded the *ortho*-product (**2**) as the major product; this product was more sterically hindered than the *para*-product (**3**), in comparison with Method A. This indicates that a bidentate ligand (DPPP) is sterically smaller than two monodentate ligands (PPh$_3$) on a square-planar intermediate[2d,f] and suggests that the bulkiness of the ligand affects the regioselectivity. Therefore, reactions were carried out using Method C with (*o*-tol)$_3$P, which has a larger cone angle and is bulkier than PPh$_3$,[15] as the ligand. Table 1 summarizes the results using Method C. The general decrease in *ortho*-products (**2**) from the coupling reaction at the sterically hindered position indicates that ligand bulkiness influences regioselectivity.[16,17]

In conclusion, the ratio of **2** to **3** was influenced by the coordinating ability of substituent(s) to the Pd^{II} complex and by the steric relationship between the substituent(s) and the phosphine ligand.



a : $R^1 + R^2$ = $-OCH_2O-$, $R^3 = CH_2OCH_3$
b : $R^1 + R^2$ = $-OCH_2O-$, $R^3 = CH_3$
c : $R^1 + R^2$ = $-OCH_2CH_2O-$, $R^3 = CH_3$
d : $R^1 = R^2 = OCH_3$, $R^3 = CH_3$
e : $R^1 = H$, $R^2 = OCH_3$, $R^3 = CH_3$
f : $R^1 = H$, $R^2 = OBu^t$, $R^3 = CH_3$
g : $R^1 = H$, $R^2 = OH$, $R^3 = CH_3$
h : $R^1 = H$, $R^2 = OAc$, $R^3 = CH_3$
i : $R^1 = H$, $R^2 = OCOC_6H_5$, $R^3 = CH_3$
j : $R^1 = H$, $R^2 = OCOCH_2Cl$, $R^3 = CH_3$
k : $R^1 = H$, $R^2 = COOCH_3$, $R^3 = CH_3$

4a : X=I, Y=NCO_2CH_3
4b : X=Br, Y=O

5a : Y=NCO_2CH_3
5b : Y= O

$R^1 + R^2 = CH_2$
$R^1 = R^2 = CH_3$

Scheme 1.

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