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Palladium-Catalyzed Oxidative Arylation of Tertiary Benzamides: *Para*-Selectivity of Monosubstituted Arenes

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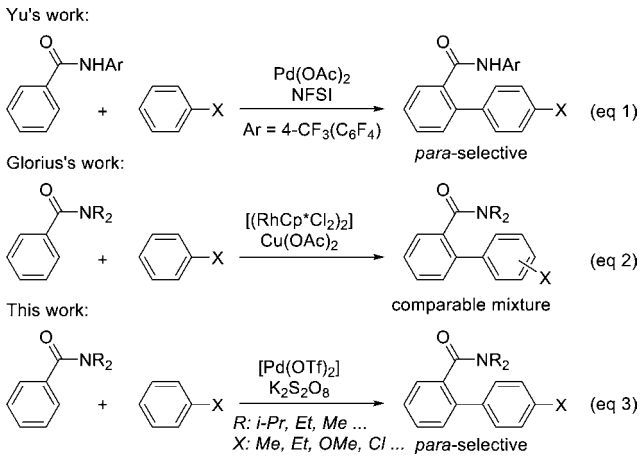
Supporting Information

ABSTRACT: A mild and efficient protocol for the high *para*-selective arylation of monosubstituted arenes with tertiary benzamides has been developed via palladium-catalyzed oxidative coupling reactions. Due to the mild conditions and the easy availability of substrates and oxidant, this method could potentially provide a practical approach for the synthesis of *para*-substituted biaryl compounds.

The ubiquity of biaryl scaffolds in a large number of natural products, medicinal agents, and organic materials ensures a constant demand for their efficient and selective synthesis.[1] The oxidative coupling reaction between 2-fold aryl C−H bonds undoubtedly emerged as the most elegant method because of its obvious advantages such as fewer reaction steps.[2] However, poor chemo- and regioselectivity greatly limited their synthetic utility.[3] With the assistance of directing groups such as pyridines, anilides, amides, imines, and carbamates, chemists could achieve the oxidative coupling reactions selectively at the *ortho*-position of the directing group.[4] For simple arenes without a coordinated moiety, steric hindrance is always responsible for selectivity, which gives a mixture of regioisomers.[5] Buchwald, Dong, and Sanford, respectively, achieved the synthetically useful regioselectivity of anisole recently.[6] Yu and co-workers then reported the first highly *para*-selective arylation of monosubstituted arenes with acidic amides (Scheme 1, eq 1).[7] It is believed that the [ArPd(IV)F] species is partially responsible for the *para*-selectivity, and so the combination of an acidic amide directing group and a bystanding F^+ oxidant is essential. Cheng and You also reported palladium-catalyzed *para*-selective arylation of toluene with aryl aldoxime ethers, *N*-methoxybenzamides, and anilides.[8]

The directed ortho metalation (DoM) of tertiary benzamides with a stoichiometric amount of lithium reagent and further transformations had been well developed.[9] However, their catalytic process has greatly lagged behind.[10,11] Generally, the weak coordination of the amide group and the electron-deficiency of the aryl ring were supposed to account for the low reactivity of tertiary benzamides in transition-metal-catalyzed C−H activation reactions. Therefore, a more electrophonic cationic catalyst could offer a possible solution. Glorius and co-workers recently realized Rh(III)-catalyzed cross-dehydrogenative arylation of tertiary benzamides with simple arenes, and a mixture of *meta*- and *para*-arylation products was obtained when a monosubstituted arene was used (Scheme 1, eq 2).[12] The arylation of tertiary benzamides with aryl iodides or intramolecular arenes was also reported using $Pd(OAc)_2$ as the catalyst in the presence of trifluoroacetic acid.[13] Herein, we report the first *para*-arylation of monosubstituted arenes with various tertiary benzamides via palladium-catalyzed oxidative coupling reactions.

Scheme 1. Palladium-Catalyzed Arylation of Arenes with Benzamides



With tertiary benzamide **1a** and toluene as substrates, we started our study by searching the Pd catalysts. $Pd(OTf)_2$ could smoothly drive the coupling reaction to afford the desired biaryl product **3a** in 62% yield with a *para*/*meta* ratio of 13:1 (Table 1, entry 1). After further condition screening,

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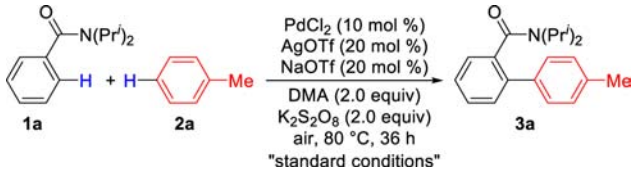
Table 1. Palladium-Catalyzed *Para*-Arylation of Toluene with Benzamide[a]



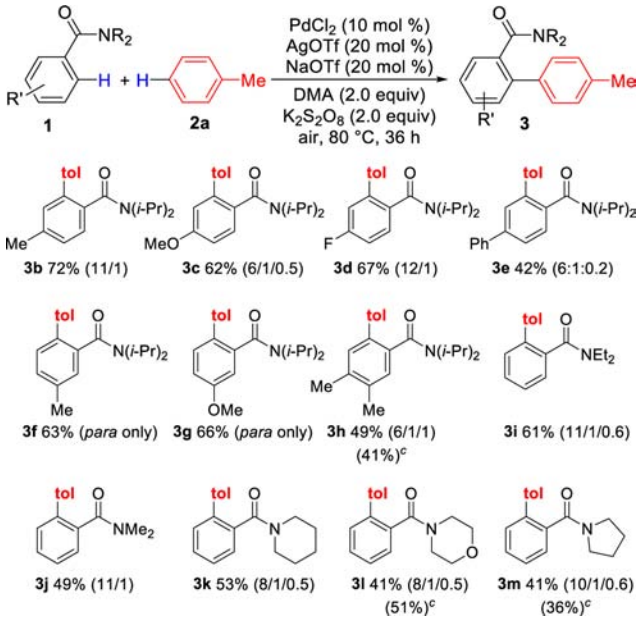
entry	changes from "standard conditions"	yield[b] (%)
1	$Pd(OTf)_2$, no AgOTf or NaOTf	62 (13/1)
2	none	75 (14/1)
3	no AgOTf or NaOTf	13 (11/1)
4[c]	$Pd(OAc)_2$, no AgOTf or NaOTf	<5
5[c]	$Pd(OTFA)_2$, no AgOTf or NaOTf	<5
6	no AgOTf	52 (6/1/0.2)
7	no NaOTf	55 (9/1/0.3)
8	no DMA	35 (3/1/0.1)
9	DMA: 3.0 equiv	72 (12/1)
10	NMP instead of DMA	58 (7/1/0.2)
11	DMF instead of DMA	53 (6/1/0.3)
12[c]	$Cu(OAc)_2$ instead of $K_2S_2O_8$	<5
13[c]	$PhI(OAc)_2$ instead of $K_2S_2O_8$	<5
14[d]	NFSI instead of $K_2S_2O_8$	20 (19/1)
15	$(NH_4)_2S_2O_8$ instead of $K_2S_2O_8$	10 (15/1/0.2)
16	$Na_2S_2O_8$ instead of $K_2S_2O_8$	38 (11/1)
17	under Ar	68 (14/1)
18[c]	under O_2	<5

[a]Standard conditions: benzamide **1a** (0.5 mmol), $PdCl_2$ (10 mol %), AgOTf (20 mol %), NaOTf (20 mol %), DMA (2 equiv), $K_2S_2O_8$ (2 equiv), toluene (3 mL), 80 °C, 36 h. [b]Isolated yields and regioselectivity (*p*/*m* or *p*/*m*/*o*) determined by GC. [c]No desired product detected by GC. [d]NFSI: *N*-fluorobenzenesulfonimide.

we achieved a better yield and selectivity (75% and 14:1 ratio) with the catalyst generated in situ from $PdCl_2$ and triflate salts (Table 1, entry 2). The combination of $PdCl_2$, AgOTf, and NaOTf was proven to be an efficient catalyst system. In the absence of AgOTf and NaOTf, palladium catalysts such as $PdCl_2$, $Pd(OAc)_2$, and $Pd(OTFA)_2$ could not individually drive the reaction efficiently, which hinted that the OTf might be the anion of choice (Table 1, entries 3–5). The extra amount of OTf anion seemed to be important for a better yield and selectivity. Without either AgOTf or NaOTf, both the catalytic efficiency and selectivity decreased (Table 1, entries 6 and 7). DMA is a key additive for the catalytic oxidative coupling reaction. In the absence of DMA, the yield and ratio of *para*-substituted toluene greatly decreased (Table 1, entry 8). DMF or NMP could also improve the efficiency and selectivity to some extent, but not as efficiently as DMA (Table 1, entries 10 and 11). Several other oxidants were used and failed to drive this transformation efficiently (Table 1, entries 12–16).[14] The reactions were conveniently set up and handled in air on the benchtop. The reaction under argon gave a comparable yield and selectivity (Table 1, entry 17), while the O_2 atmosphere completely shut down the catalytic cycle (Table 1, entry 18).

Under these "standard conditions", we further achieved the oxidative coupling reactions between benzamides and toluene with good efficiency and regioselectivity (Scheme 2). *p*-Methyl- and fluorobenzamide smoothly underwent the directed *ortho*-arylation reactions with toluene to give good yields and *para*/*meta* ratios (**3b**,**d**). However, *p*-methoxy- and

Scheme 2. Scope of Benzamides[a,b]



[a]Benzamide (0.5 mmol), $PdCl_2$ (10 mol %), AgOTf (20 mol %), NaOTf (20 mol %), DMA (2 equiv), $K_2S_2O_8$ (2 equiv), toluene (3 mL), 80 °C, 36 h. [b]Isolated yields and regioselectivity (*p*/*m* or *p*/*m*/*o*) determined by GC. [c]Reactant recovery.

phenylbenzamide gave lower efficiency and selectivity (**3b**,**e**). It is interesting to note that the benzamides with the same substituent at the *meta*-position give much better selectivity: only *para*-substituted products were obtained (**3f**,**g** vs **3b**,**c**). Another methyl group at the *para*-position on 3-methylbenzamide led to lower efficiency and selectivity (**3h**). Benzamides with a methyl group at the *ortho*-position or an acyl group at the *para*-position did not undergo the arylation reactions. That might suggest that steric hindrance, and an electron-withdrawing group on the benzamide would inhibit the reaction. Several *N*-alkyl-substituted benzamides were also carried out in this reaction (**3i**–**m**). These benzamides smoothly underwent the arylation with toluene and similarly gave nice regioselectivity. However, the yield tends to drop over the gradual decline of steric hindrance of the amide groups.

To examine the scope of simple arene substrates further, *N*,*N*-diisopropylbenzamide **1a** was reacted with various arenes (Scheme 3). Benzene smoothly reacted with the benzamide **1a** to give a good yield of 2-phenylbenzamide **3n**. Aryl halides underwent the *para*-arylation reactions with nice yields and selectivity (**3o**–**q**). Chloro- and bromobenzene achieved much better selectivity and gave exclusively *para*-arylation products. The compatibility of halides offers further transformation possibilities to synthesize useful functionalized molecules. Iodobenzene reacted with benzamide **1a** to give 15% yield of phenylation product, which illustrated the instability of aryl C–I bond under present conditions. Several alkylbenzenes were also allowed to react with benzamide **1a**, and biaryl products were obtained (**3s**–**u**). However, both the yield and selectivity tend to decline with increasing steric hindrance of alkyl groups. The electron-rich anisole could react with benzamide **1a** and gave exclusively *para*-arylation product with a moderate yield (**3r**), while the electron-deficient benzotrifluoride gave much lower yield (**3v**). *o*-

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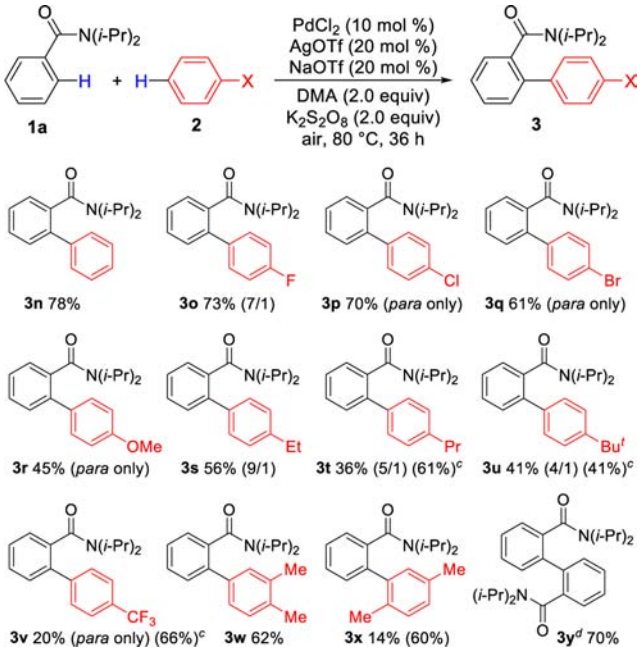
Scheme 3. Scope of Simple Arenes[a,b]



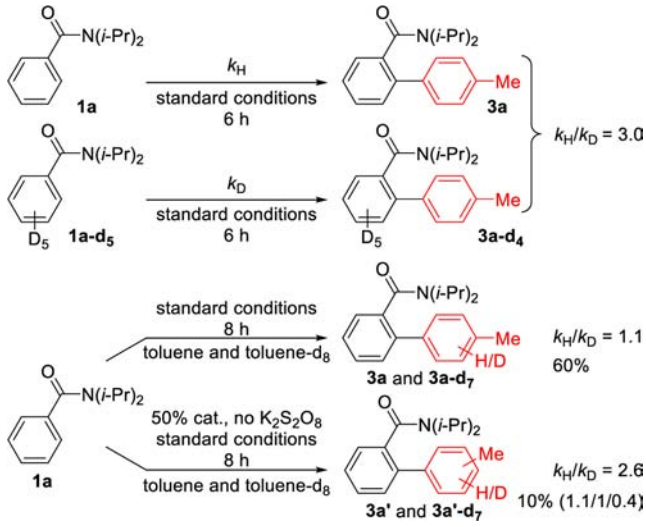
[a]Benzamide **1a** (0.5 mmol), $PdCl_2$ (10 mol %), AgOTf (20 mol %), NaOTf (20 mol %), DMA (2 equiv), $K_2S_2O_8$ (2 equiv), arene (3 mL), 80 °C, 36 h. [b]Isolated yields and regioselectivity (p/m or $p/m/o$) determined by GC. [c]Reactant recovery. [d]Reaction in dioxane without DMA addition.

Xylene reacted smoothly with benzamide **1a** to afford 1,2,4-substituted product **3w**. However, the reaction of *p*-xylene took place sluggishly and gave product **3x** in 14% yield. The reactivity disparity revealed the great effect of the steric hindrance of simple arenes. In the absence of another simple arene, the homocoupling reaction of benzamide **1a** took place (**3y**). A mixture of two monosubstituted arenes was allowed to react with the benzamide **1a**, and the electron-rich one reacted faster, which was consistent with an electrophilic palladation process in the C−H activation of simple arenes (see the Supporting Information).[15]

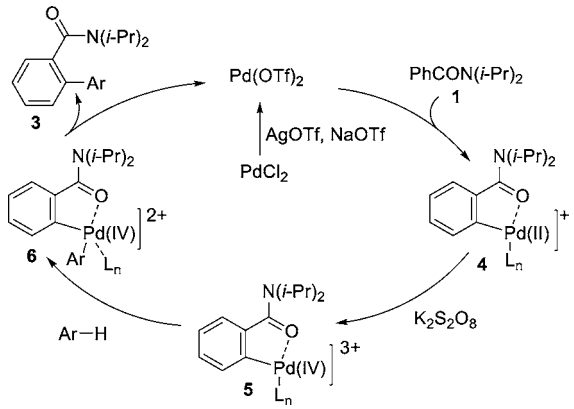
To obtain further insight of the reaction process, the initial reaction rates were measured separately with benzamide **1a** and benzamide **1a**-d_5 (Scheme 4). A kinetic isotope effect of 3.0 was observed, suggesting that the C−H bond cleavage of benzamide could be the rate-determining step in the present catalytic reaction. The benzamide **1a** was then allowed to react with a 1:1 mixture of toluene and toluene-d_8, and a small isotope effect was observed (k_H/k_D = 1.1).[16] A similar reaction was carried out with 50% catalyst in the absence of $K_2S_2O_8$, and only a 10% yield of product was obtained, which confirmed that the reaction could not be achieved catalytically without addition of oxidant $K_2S_2O_8$. Moreover, it is interesting to note that the reaction gave a primary isotope effect (k_H/k_D = 2.6) and poor selectivity ($p/m/o$ = 1.1/1/0.4) simultaneously (see the Supporting Information). The contrasting results in the presence or absence of oxidant $K_2S_2O_8$ illustrated that the Pd(IV) intermediate could be an original reason for the small isotope effect and *para*-selectivity.

On the basis of the observations described above and reported previously, a possible mechanism for the present catalytic oxidative coupling reaction was proposed as shown in Scheme 5. The cationic $Pd(OTf)_2$ generated in situ from

Scheme 4. Kinetic Isotope Effects



Scheme 5. Possible Reaction Pathway



$PdCl_2$ and triflate salts could serve as the true active catalyst, which is electrophilic enough to coordinate with the amide carbonyl group with subsequent C−H bond activation to afford intermediate **4**.[17] Pd(II) intermediate **4** was then oxidized by $K_2S_2O_8$ to cationic Pd(IV) intermediated **5**, which would undergo a fast C−H activation with a monosubstituted arene with high *para*-selectivity to afford intermediate **6**. The following reductive elimination then resulted in product formation and Pd catalyst regeneration. During the whole process, DMA could possibly serve as a ligand for the Pd species.

In summary, we have developed an oxidative coupling reaction to achieve high *para*-selective arylation of mono-substituted arene with tertiary benzamides. Because of the mild conditions, the readily available tertiary benzamides, and the convenient $K_2S_2O_8$ oxidant, this process could potentially offer a practical approach to *para*-substituted biaryl compounds. Various benzamides and arenes were studied, and the substituted groups on both substrates proved to be important for the efficiency and *para*-selectivity. However, a clear understanding of the substitution effect is still obscure. Further detailed mechanism studies and applications of this transformation are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Intriguingly, NFSI, reported as an efficient oxidant in Yu's work, did not work well in our reaction, while $K_2S_2O_8$, which gave poor selectivity (*p*/*m*, 1.7/1) in Yu's work, was efficient and selective.

(15) Michael and co-workers reported a palladium-catalyzed carboamination of alkenes with high *para*-selective C−H activation of monosubstituted arenes. Mechanism studies indicated that the C−H activation of simple arenes takes place in two separate steps: intermolecular selectivity-determining binding and subsequent rapid C−H activation. (a) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488−9489. (b) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945−15951.

(16) A similar small isotopic effect was found by Michael and Yu in the *para*-selective functionalization of monosubstituted arenes with Pd(IV) as a crucial intermediate. See refs 7 and 15.

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