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Convenient palladium-catalyzed aminocarbonylation of anilines to *N*-arylbenzamides

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ABSTRACT

The first one-pot diazotization/aminocarbonylation reaction of anilines to benzamides has been developed. In the presence of commercially available palladium acetate/P(*o*-Tolyl)$_3$ as the catalyst system without base at low temperature (50 °C) a variety of amides were synthesized in moderate to good yields.

Palladium-catalyzed coupling reactions have become a general tool for achieving all kinds of synthetic transformations of aryl and heteroaryl compounds.[1,2] Nowadays, palladium catalysts are regularly applied for the synthesis of pharmaceuticals, agrochemicals, as well as advanced materials both on the laboratory as well as on the industrial scale. Among the different known palladium-catalyzed coupling processes, carbonylation reactions allow for the direct incorporation of CO, the most inexpensive and readily available C1-source, into parent molecules resulting in a variety of carboxylic acid and carbonyl derivatives.[3]

Compared to aryl halides, aryldiazonium salts have been so far much less explored as substrates in palladium-catalyzed cross-coupling reactions.[4] The first carbonylation reactions of the latter substrates were reported by Matsuda and co-workers already in 1981.[5] Here, sodium acetate was used as the nucleophile to provide mixed anhydrides. More recently, improvements of this methodology were realized by Siegrist et al.[6] Nevertheless, until date only few examples of alkoxycarbonylations[7] and reductive carbonylations [8] of diazonium compounds were reported. In addition, carbonylative coupling reactions of aryldiazonium salts with organotin reagents to give ketones were disclosed by Kikukawa's group.[9] Instead of organotin reagents also aryl boronic acids can be used as shown in 2002 by Andrus et al.[10] Later on, the same group described the related coupling of aryl boronic acids, aryldiazonium salts, ammonia, and CO in the presence of palladium catalysts to give aryl amides in high yields.[11] Notably, all these published carbonylation processes make use of pre-formed aryldiazonium tetrafluoroborate salts ArN_2BF_4 as coupling partners.[5–11] With respect to the commercial availability and the hazardous preparation of ArN_2BF_4, it would be interesting to develop processes in which anilines can be in situ activated to give the respective aryldiazonium salts. Based on our continuing interest in palladium-catalyzed carbonylations,[12] and considering the importance of benzamides,[13] here we wish to report for the first time a general palladium-catalyzed one-pot diazotization/aminocarbonylation sequence of anilines to benzamides.[14] Compared with the more common aminocarbonylation of aryl halides,[15] this methodology proceeds under milder conditions and allows for the use of abundant and easily available anilines.

Initially, the carbonylation of aniline was studied as a model reaction. Activation of aniline should proceed via well known diazotization with *tert*-butyl nitrite in the presence of 1.3 equiv of acetic acid. Subsequent formation of the aryl–palladium complex, carbonylation, and amidation would then lead to the product. Indeed, the desired transformation took place toward *N*-phenylbenzamide and in the first set of experiments we tested the influence of different phosphine ligands (2 or 4 mol %) in the presence of 2 mol % of Pd(OAc)$_2$ in DMF at 90 °C (Table 1). In general, monodentate phosphines such as PPh_3, PCy_3, TFP, $BuPAd_2$, and P(*o*-Tolyl)$_3$ gave better yields (Table 1, entries 1–5; 38–81%) compared to bidentate ligands (Table 1 and 6–12; 16–61%).

Best results were obtained in the presence of inexpensive P(*o*-Tolyl)$_3$, which was used as a standard ligand for further optimization experiments.

Next, the influence of different solvents was investigated in more detail (Table 2). Nonpolar solvents, for example, heptane resulted in only 17% of the amide (Table 2, entry 1). Also DME,

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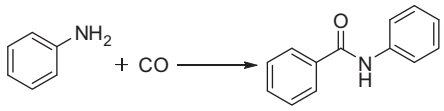
Table 1
Aminocarbonylation of aniline: variation of ligands[a]



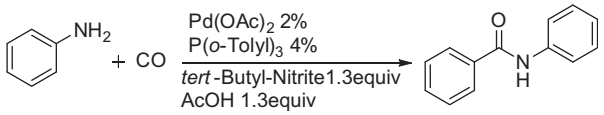
Entry	Ligand (mol %)	Yield[b] (%)
1	PPh_3	62
2	PCy_3	75
3	TFP	57
4	$BuPAd_2$	38
5	P(*o*-Tolyl)$_3$	81
6	DPPE	16
7	DPPP	35
8	DPPF	23
9	Xantphos	39
10	DIOP	43
11	DPPB	40
12	DPEphos	61

[a] $Pd(OAc)_2$ (2 mol %), ligand (4 mol % P), AcOH (1.3 mmol), DMF (2 mL), aniline (2.3 mmol), *tert*-BuONO (1.3 mmol), CO (10 bar), 90 °C, 16 h.
[b] Yield was determined by GC using hexadecane as internal standard. TFP = tris-2-furylphosphine; P(*o*-Tolyl)$_3$ = tri(*o*-toyl)phosphine; DPEphos = bis(2-diphenylphosphinophenyl)ether; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DIOP = (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane.

dioxane, and toluene gave low yields of the product (20–29%; Table 2, entries 2–4). In acetonitrile and NMP 44% and 41% of the amide were produced, respectively (Table 2, entries 5 and 6), while DMF gave surprisingly *N*-phenylbenzamide in 81% yield. The yield of the product is further improved to 99% by decreasing the reaction temperature to 50 °C (Table 2, entry 7). Obviously, the in situ generated PhN_2OAc is more stable and gives less side reactions at lower temperature. However, running the model reaction under 1 bar of CO, only 25% yield of the amide was achieved (Table 2, entry 8).

With optimized conditions in our hands (Table 2, entry 7), we studied the scope and limitations of this novel methodology (Table 3). *p*-Toluidine gave 75% of the corresponding *N*-aryl amide (Table 3, entry 1). Electron-rich methoxy- and methylthio-substituted anilines are more sensitive and led to decreased yields of the corresponding *N*-aryl benzamides (Table 3, entries 3–6). On the other hand, anilines with electron-withdrawing substituents gave improved yields (58–96%) of amides (Table 3, entries 7–11). Chloride- and bromide-substituted anilines showed no additional activation

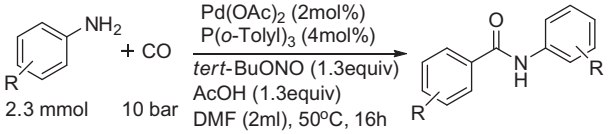
Table 2
Aminocarbonylation of aniline: variation of solvents and reaction parameters[a]

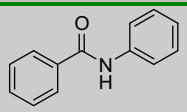
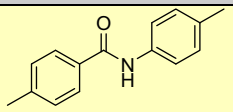
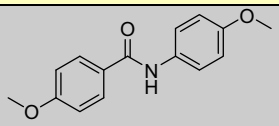
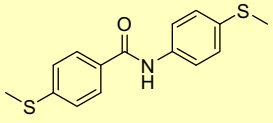
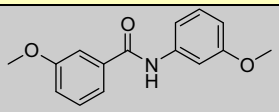
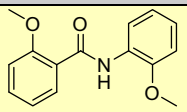
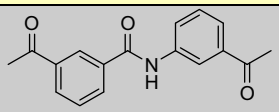
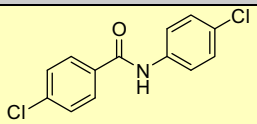
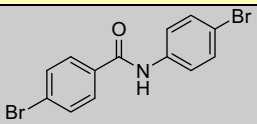
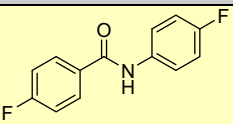
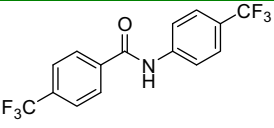


Entry	Solvent	Yield[b] (%)
1	Heptane	17
2	DME	20
3	Dioxane	26
4	Toluene	29
5	CH_3CN	44
6	NMP	41
7	DMF	99[c]
8	DMF	25[d]

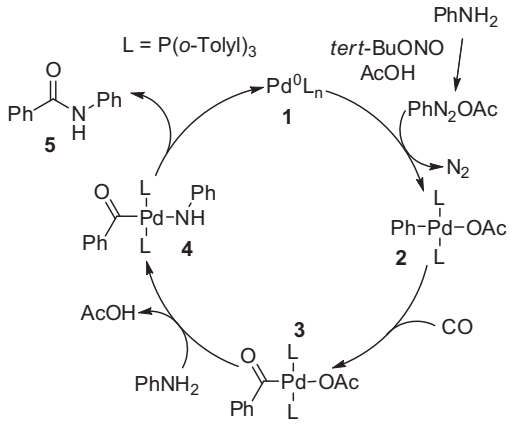
[a] $Pd(OAc)_2$ (2 mol %), P(*o*-Tolyl)$_3$ (4 mol %), AcOH (1.3 mmol), DMF (2 mL), aniline (2.3 mmol), *tert*-BuONO (1.3 mmol), CO (10 bar), 90 °C, 16 h.
[b] Yield was determined by GC using hexadecane as the internal standard.
[c] 50 °C.
[d] 50 °C, CO (1 bar). DME = 1, 2-dimethoxyethane.

Table 3
Palladium-catalyzed aminocarbonylation of anilines[a]



Entry	Product	Isolated Yield [%][b]
1		95
2		75
3		50
4		30
5		58
6		50
7		58
8		96
9		78
10		89
11		69

[a] $Pd(OAc)_2$ (2 mol %), P(*o*-Tolyl)$_3$ (4 mol %), AcOH (1.3 mmol), DMF (2 mL), Aniline (2.3 mmol), *tert*-BuONO (1.3 mmol), CO (10 bar), 50 °C, 16 h.
[b] Yield was calculated based on 1 mmol of starting material.



Scheme 1. Proposed reaction mechanism.

of the C–X bond and isolated yields of 78–96% of halo-substituted *N*-aryl benzamides were achieved (Table 3, entries 8 and 9). Unfortunately, applying heterocyclic anilines no amides were obtained. Instead, only the corresponding reduced product is detected. For example, 5-amino-benzothiazole resulted in the formation of benzothiazole.

With respect to the mechanism (Scheme 1) we assume that the in situ generated PhN_2OAc undergoes oxidative addition to Pd^0 **1**, which is easily formed from $Pd(OAc)_2$ and the phosphine ligand, to form aryl palladium(II) species **2**. Subsequent coordination and insertion of carbon monoxide forms the acyl palladium complex **3**. Exchange of acetate by aniline should give complex **4** and final reductive elimination leads to the terminal product **5** and regenerates the catalyst Pd^0 **1**.

In conclusion, we have developed the first aminocarbonylation of anilines to *N*-aryl benzamides. The procedure proceeds via in situ formation of aryldiazonium salts, from abundantly available anilines and subsequent palladium-catalyzed carbonylation under base-free conditions at low temperature. 11 different *N*-aryl benzamides have been isolated in 30–96% yield.

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13. See for examples: *N*-aryl amides; *The Merck Index*, 11th ed., Merck, Rahway, USA, **1989**.
14. Typical reaction procedure for carbonylation reaction of aniline: $Pd(OAc)_2$ (2 mol %) and P(*o*-Tolyl)$_3$ (4 mol %) were transferred into a vial (4 mL reaction volume) equipped with a septum, a small cannula and a stirring bar. After the vial was purged with argon, DMF (distilled from sodium ketyl, 2 mL), aniline (2.3 mmol), *tert*-butyl nitrite (1.3 mmol), and AcOH (1.3 mmol) were injected into the vial by syringe. Then, the vial was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar was adjusted and the reaction was performed for 16 h at 50 °C. After the reaction, the autoclave was cooled down to room temperature and the pressure was released carefully. To the reaction mixture 6 mL water were added and the solution was extracted 3–5 times with 2–3 mL of ethyl acetate. The extracts were evaporated with adsorption on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (4:1) as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.93–7.99 (m, 2H), 7.76–7.83 (m, 2H), 7.49–7.63 (m, 3H), 7.32–7.39 (m, 2H), 7.11 (t, 1H, J = 7.44 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 139.1, 134.9, 131.5, 128.6, 128.3, 127.6, 123.6, 120.3. GC–MS (EI, 70eV): m/z (%) = 197 (M^+, 60), 105 (100), 77 (40).
15. For selected examples on palladium-catalyzed aminocarbonylation of aryl halides see: (a) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460–8463; (b) Tambade, P. J.; Patil, Y. P.; Bhanage, B. M. *Appl. Organomet. Chem.* **2009**, *23*, 235–240; (c) Szilágyi, A.; Farkas, R.; Petz, A.; Kollár, L. *Tetrahedron* **2009**, *65*, 4484–4489; (d) Salvadori, J.; Balducci, E.; Zaza, S.; Petricci, E.; Taddei, M. *J. Org. Chem.* **2010**, *75*, 1841–1847; (e) Martinelli, J. P.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107.