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Palladium-Catalyzed *Ortho*-Selective C−H Oxidative Carbonylation of *N*-Substituted Anilines with CO and Primary Amines for the Synthesis of *o*-Aminobenzamides

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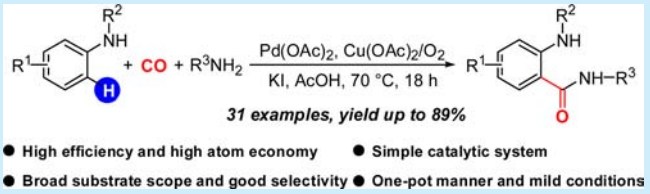
Supporting Information

ABSTRACT: An efficient, one-pot strategy with high selectivity and high atom economy for the synthesis of *o*-aminobenzamides has been developed via palladium-catalyzed *ortho*-selective C−H oxidative carbonylation of *N*-substituted anilines with CO and primary amines. A wide range of *N*-substituted anilines and primary amines can be tolerated in this transformation to afford the corresponding *o*-aminobenzamides in moderate to excellent yields under mild conditions.



Palladium-catalyzed oxidation carbonylation reactions with CO have proven to be one of the most important methods for the synthesis of many carbonyl-containing compounds such as carboxylic acids and their various derivatives.[1] In recent years, considerable attention has been focused on the palladium-catalyzed carbonylation of C−H bonds in the presence of CO, and much progress has been made in this field.[2] Despite these achievements, the direct C−H carbonylation on the aromatic ring of aromatic amines in the presence of amines affording the corresponding amides still remains unexplored because the exploration of efficient directing groups and efficient catalytic systems to suppress the competitive carbonylation of amines to ureas during the intermolecular aminocarbonylation of aryl C(sp^2)−H exhibits outstanding challenges.

O-Aminobenzamides and their derivatives have attracted special research interest due to their remarkable applications as important reactive intermediates in organic synthesis.[3] In addition, they also find utilization in medicinal chemistry due to their biological activities such as antimicrobial activity,[3i] antithrombotic activity,[4] glycogen phosphorylase inhibition,[5] and thyroid-stimulating hormone receptor (TSHR) antagonistic activity.[6] The main methods for the synthesis of these compounds involve the ring opening of isatoic anhydride,[6,7] coupling of anthranilic acid with amines,[6,8] *N*-arylation between 2-bromobenzenamine and benzonitrile,[9] the amidation of alcohols with 2-aminobenzonitrile,[10] or *N*-Fries rearrangement of *N*-carbamoyldiarylamines.[11] However, these methods generally suffer from limitations such synthetic precursors that are not easily accessible, low atom economy, and sometimes substrate generality. Thus, the development of a facile and efficient strategy for the synthesis of *o*-aminobenzamides is highly desirable. In 2012, Guan reported a novel approach to isatoic anhydrides via an anthranilic acid intermediate through palladium-catalyzed *ortho*-selective C−H bond carbonylation of *N*-alkylanilines.[2h] Subsequently, *o*-aminobenzoates were successfully prepared via the palladium-catalyzed C−H bond oxidative carbonylation of *N*-alkylanilines in the presence of an alcohol by Guan and Lei, respectively.[12] To the best of our knowledge, the *ortho*-selective C−H oxidative carbonylation of *N*-substituted anilines with amines leading to *o*-aminobenzamides has not been developed. Inspired by Guan's and Lei's work, we conjectured that *o*-aminobenzamides are also likely to be obtained by the palladium-catalyzed *ortho*-selective C−H bond oxidative carbonylation of *N*-substituted anilines in the presence of an amine. Here, we present an efficient approach with high selectivity and high atom economy to *o*-aminobenzamides via the palladium-catalyzed *ortho*-selective C−H oxidative carbonylation of commercially available *N*-substituted anilines with CO and primary amines (Scheme 1).

We set out our studies with the screening of reaction conditions between *N*-methylaniline (**1a**) and *n*-butylamine (**2b**) (Table 1). To our delight, treatment of **1a** with 2.0 equiv of **2b** in CH_3CN under a balloon pressure of CO with $Cu(OAc)_2$ as the oxidant and KI as the additive afforded the desired product **3b** in 51% yield (Table 1, entry 1); in addition,

Scheme 1. Palladium-Catalyzed *Ortho*-Selective C−H Oxidative Carbonylation of *N*-Substituted Anilines

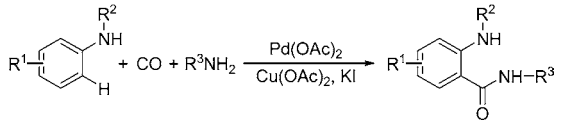


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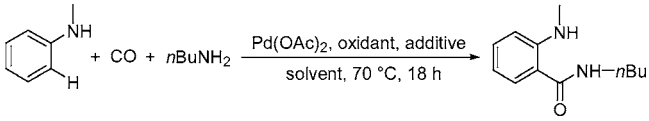
Table 1. Reaction Optimization for the C−H Carbonylation[a]



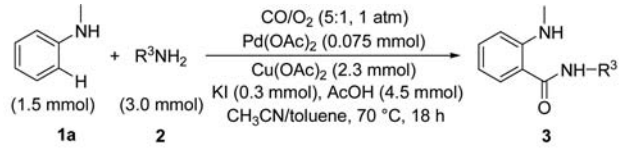
entry	oxidant	solvent	additive	yield[b] (%)
1	$Cu(OAc)_2$	MeCN	KI	51
2	O_2	MeCN	KI	39
3	$CuCl_2$	MeCN	KI	0
4	$CuBr_2$	MeCN	KI	0
5	$K_2S_2O_8$	MeCN	KI	0
6	$Cu(OAc)_2$	tol	KI	49
7	$Cu(OAc)_2$	DMF	KI	45
8	$Cu(OAc)_2$	DMSO	KI	42
9	$Cu(OAc)_2$	1,4-dioxane	KI	50
10[c]	$Cu(OAc)_2$	MeCN/tol	KI	53
11[c,d]	$Cu(OAc)_2$	MeCN/tol	KI/AcOH	69
12[c,d,e]	$Cu(OAc)_2/O_2$	MeCN/tol	KI/AcOH	78
13[c,d,e,f]	$Cu(OAc)_2/O_2$	MeCN/tol	KI/AcOH	78
14[c,d,e,g]	$Cu(OAc)_2/O_2$	MeCN/tol	KI/AcOH	54

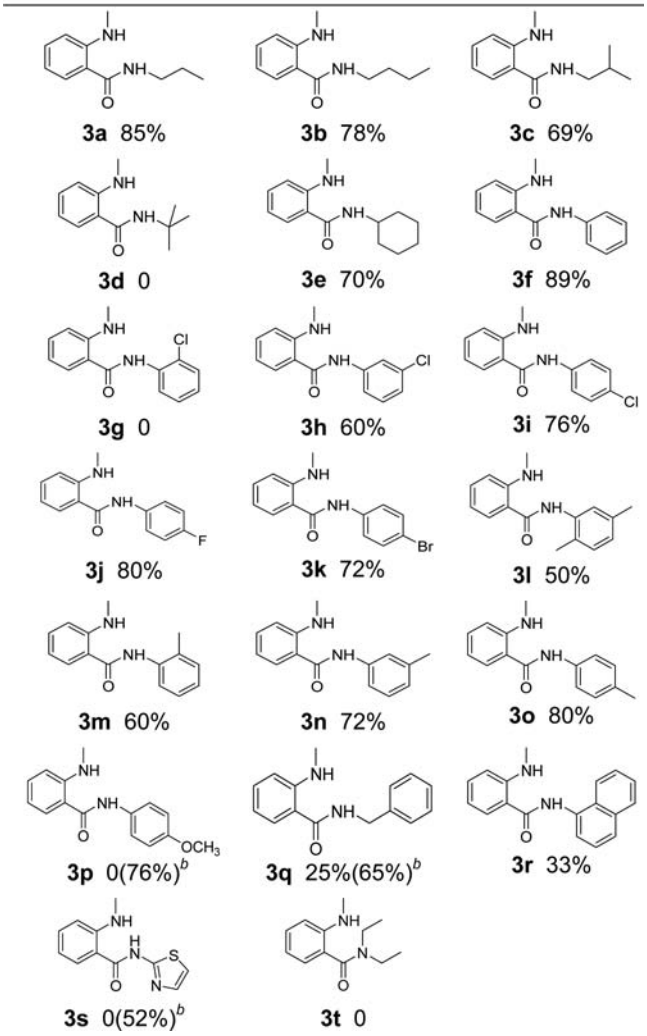
[a]Standard reaction conditions: **1a** (1.5 mmol), **2b** (3.0 mmol), $Pd(OAc)_2$ (0.075 mmol), $Cu(OAc)_2$ (3.0 mmol), KI (0.3 mmol), and solvent (8.0 mL) under 1 atm of CO at 70 °C for 18 h. [b]Isolated yields. [c]CH_3CN/tol (1:1). [d]AcOH (4.5 mmol). [e]CO/O_2 (5:1) 1 atm. [f]$Cu(OAc)_2$ (2.3 mmol). [g]$Cu(OAc)_2$ (1.5 mmol).

over 20% yields of both 1,3-dibutylurea and 3-butyl-1-methyl-1-phenylurea together with a small amount of *N*-methylanthranilic acid and isatoic anhydride could be detected in the reaction system. Further screening of oxidants such as O_2, $CuCl_2$, $CuBr_2$, and $K_2S_2O_8$ revealed that O_2 was less effective than $Cu(OAc)_2$, while $CuCl_2$, $CuBr_2$, and $K_2S_2O_8$ were all totally ineffective (Table 1, entries 2−5). Subsequently, the effects of different solvents were investigated, and the results indicated that the mixed solvent of CH_3CN/toluene gave the best result (Table 1, entriey 10) but other solvents such as toluene, DMF, DMSO, and 1,4-dioxane were also effective (Table 1, entries 6−9). We were pleased to find that the desired product **2b** could be increased significantly when 4.5 mmol of AcOH was added to the reaction system (Table 1, entriey 11). The role of AcOH here is believed to suppress the competitive self- and cross-carbonylation of free amines by tuning their concentration. Subsequently, the combination of $Cu(OAc)_2/O_2$ as oxidant was tested, and it was found that this combination was more beneficial to the present carbonylation reaction (Table 1, entriey 12). On this basis, the load of $Cu(OAc)_2$ was further optimized, and it was found that 2.3 mmol could satisfy this transformation well (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand, we next evaluated the scope and efficiency of the reaction with a series of primary amines. As shown in Scheme 2, the present catalytic system showed good tolerance to a variety of aliphatic and aromatic amines, affording the desired *o*-aminobenzamides in moderate to excellent yields. Generally, the amines with low steric hindrance were more effective than those with high steric hindrance (**3d**, **3t**), suggesting that this method was sensitive to steric factors. The electron effect was also observed in this transformation. Both electron-withdrawing and -donating groups on the benzene ring of substituted anilines were

Scheme 2. Scope of Amines[a]





[a]Reaction coditions: **1a** (1.5 mmol), **2** (3.0 mmol), $Pd(OAc)_2$ (0.075 mmol), $Cu(OAc)_2$ (2.3 mmol), KI (0.3 mmol), CO/O_2 (5:1) 1 atm, AcOH (4.5 mmol) in MeCN/toluene (4.0 mL/4.0 mL) at 70 °C for 18 h. Isolated yields. [b]Amine was added dropwise for 9 h.

tolerated well to produce the corresponding products in good to excellent yields. On the whole, the electron-rich substrates showed better reactivity (**3m**, **3n**, **3o**, **3p**) compared with those electron-deficient ones (**3g**−**k**). Thus, the reaction failed to proceed with 2-chlorobenzenamine most probably due to its negative effects of both steric and electron factors (**3g**). It is noteworthy that the present carbonylation reaction proceeded poorly with 4-methoxybenzenamine and benzylamine. This is because the carbonylation of amines themselves to the corresponding symmetrical ureas was the overwhelming reaction, most probably due to their high reactivity. For this reason, we added these amines dropwise into the reactor to suppress the competitive self-carbonylation side reaction and succeeded in obtaining the desired *o*-aminobenzamides with satisfactory yields (**3p**, **3q**). In addition, thiazol-2-amine was

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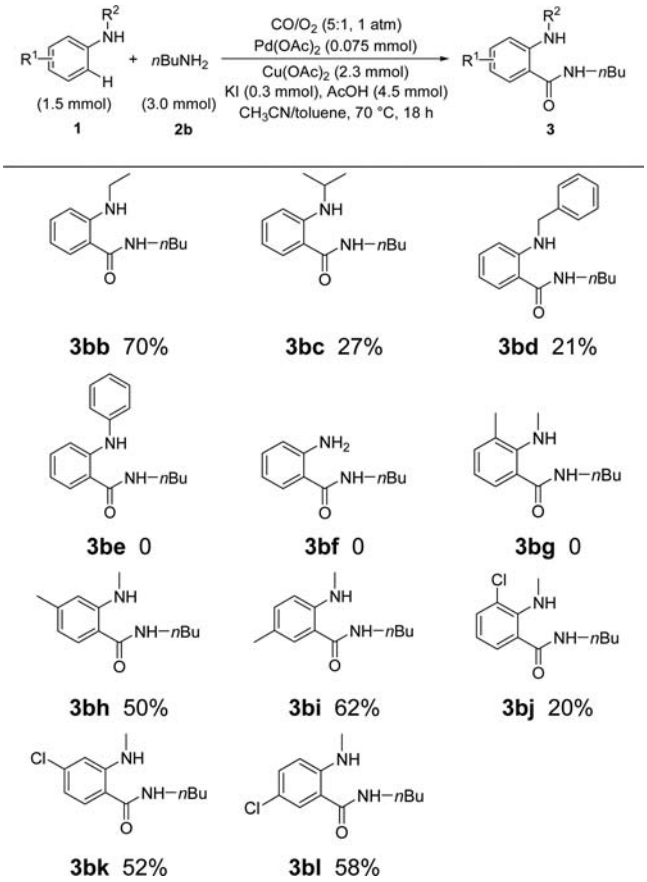
chosen as a representative of heterocyclic amines to test its applicability and found it worked smoothly with the above titration method (**3s**). Finally, we also used diethylamine as a representative aliphatic secondary amine; unfortunately, the reaction failed to proceed, probably due to its high steric hindrance and weak reactivity (**3t**).

Subsequently, to further expand the scope of this methodology, we applied the present catalytic system to a variety of *N*-substituted anilines (Scheme 3). The results indicated that

Scheme 3. Scope of *N*-Substituted Anilines[a]



[a]Reaction coditions: **1** (1.5 mmol), **2b** (3.0 mmol), $Pd(OAc)_2$ (0.075 mmol), $Cu(OAc)_2$ (2.3 mmol), KI (0.3 mmol), CO/O_2 (5:1) 1 atm, AcOH (4.5 mmol) in MeCN/toluene (4.0 mL/4.0 mL) at 70 °C for 18 h. Isolated yields.

steric factors of *N*-substituted anilines play an important role in the carbonylation reaction. Generally, the *N*-substituted anilines with low hindrance (**3bb,bh,bi,bk,bl**) were proved to possess higher activity than those with high steric hindrance (**3bc–be,bg,bj**), affording the desired *o*-aminobenzamides in higher yields (50%–70%) than the latter (0–27%). Both *N*-substituted anilines with electron-donating groups and those with electron-withdrawing groups on their benzene rings were effective substrates for this transformation, affording the desired products in 50–62% yields (**3bh,bi**, **3bk,bl**), which indicated that electronic effects had little effect on this transformation. We also used *N*-unsubstituted aniline and found significant amounts of symmetrical diphenylurea and dibutylurea rather than the desired *o*-aminobenzamide were formed (**3bf**).

In summary, the first palladium-catalyzed reaction protocol for *ortho*-selective C–H oxidative carbonylation of *N*-substituted anilines toward valuable *o*-aminobenzamides has been developed. This methodology demonstrated good functional-group tolerance, high selectivity, and high atom economy. The carbonylation reaction of *N*-substituted anilines could proceed efficiently with CO and commercially available primary amines at 1 atm pressure in a one-pot manner, affording the corresponding *o*-aminobenzamides in moderate to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02255.

General experimental procedures, spectral data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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