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Pd/C-Catalyzed Aminocarbonylation of Aryl Iodides with Anthranils in Water Using Mo(CO)$_6$ as the CO Source

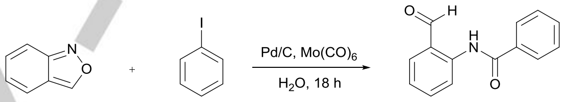
Zechao Wang,[a] Zhiping Yin,[a] and Xiao-Feng Wu*[a]

Abstract: A convenient procedure for the synthesis of *N*-(2-carbonylaryl)benzamides has been developed. Through Pd/C−catalyzed aminocarbonylation of anthranils with various hindered and functionalized aryl iodides, the desired amides were afforded in moderate to good yields. The protocol is advantageous due to the recyclable Pd/C catalyst, safe Mo(CO)$_6$ as the solid CO source, and environmentally benign water as solvent. No inert atmosphere protection is needed.

Transition-metal-catalyzed aminocarbonylation is an interesting and important chemical transformation method for the direct synthesis of aromatic amides via coupling of aryl, heteroaryl, or alkynyl halides with amines, which are important building blocks for various natural products and designed pharmaceutical molecules.[1] Some heterocyclic amides are reported as the potential CNS (central nervous system)-active compounds.[2] Therefore, a large numbers of methods toward amides synthesize have been developed. Since the first report on palladium-catalyzed aminocarbonylation of aryl halides with carbon monoxide from Heck and Schoenberg in 1974,[3] this transformation has been studied by different groups with various homogeneous palladium catalysts,[4-8] such as $PdX_2(PPh_3)_2$,[3] $Pd(dppp)Cl_2$,[5] $Pd(OAc)_2$/DCPP (DCPP = 1,3−bis(dicyclohexylphosphino)propane),[6] $Pd(OAc)_2$/xantphos,[7] and $Pd(OAc)_2/PPh_3$ catalytic system.[8] Concerning the nitrogen partners applied in aminocarbonylation reactions, mostly amines,[9] but also amides,[10] and even organo nitro compounds[11] have all been studied.

Anthranil, a class of benzo fused heterocycle, contains a N-O bond in the ring, has been applied as reagent in nickel-catalysed cross-coupling with organozinc reagents and ring expansion reactions with aryldiazoacetates.[12] More recently, anthranils have used it as nitrogen source by many research groups.[13-16] Hashmi and co-workers studied the C-H annulation of anthranil derivatives with alkynes to produce unprotected 7-acylindoles with gold as the catalyst.[13] Meanwhile, Li's group[14] and Jiao's group[15] studied the applied of anthranils as N source in various C-H activation reactions, respectively. Various of amides were produced in good yields. Tiwari and co-workers developed a novel copper-catalyzed synthesis of functionalized quinolines from the ketones and anthranils with aza-Michael addition as the key step.[16] Inspired by these interesting achievements, and also based on our continual interests in carbonylation chemistry, we become interested in using anthranil as nitrogen source in aminocarbonylation. Herein, we wish to report our new results on aminocarbonylation of aryl iodides with anthranils for the synthesis of *N*-(2-carbonylaryl)benzamides. With Pd/C as a recyclable catalyst, using Mo(CO)$_6$[17] as the solid and safe CO source, and water as the green solvent, the desired amides were formed in good yields. Additionally, the reactions were carried out under air; no inert atmosphere protection is needed.

Table 1 Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Base	Additive	Yield[%][b]
1	Cs_2CO_3	−	16
2	Et_3N	−	42
3	DBU	−	trace
4	DABCO	−	trace
5	DIPEA	−	37
6	Et_3N	TBAB	62
7	Et_3N	TBAC	56
8	Et_3N	TBAHS	49
9	Et_3N	TBAB (5 mol %)	58
10	Et_3N	TBAB (10 mol %)	51
11	Et_3N (1 equiv.)	TBAB	33
12	Et_3N (3 equiv.)	TBAB	73
13[c]	Et_3N (3 equiv.)	TBAB	44
14[d]	**Et_3N (3 equiv.)**	**TBAB**	**83 (81)**
15[e]	Et_3N (3 equiv.)	TBAB	76

[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (0.75 mmol, 2.5 equiv.), Pd/C (3.2 mg, 10 mol %), Mo(CO)$_6$ (0.3 mmol, 1 equiv.), base (0.6 mmol, 2 equiv.), and additive (3 mol %) in distilled H_2O (2 mL) was stirred at 80 °C for 18 h under air. [b] Yields were determined by GC using n−hexadecane as the internal standard. [c] Mo(CO)$_6$ (0.09 mmol, 0.3 equiv.). [d] Mo(CO)$_6$ (0.15 mmol, 0.5 equiv.). [e] Mo(CO)$_6$ (0.24 mmol, 0.8 equiv.).

Our initial investigation was started with anthranil (**1a**, 1 equiv.), iodobenzene (**2a**, 2.5 equiv.), Pd/C (10 mol %), [Mo(CO)$_6$] (1 equiv.), and Cs_2CO_3 (2 equiv.) in distilled water. To our delight, 16% yield of the desired carbonylation product **3a** was formed after 18 hours at 80 °C (Table 1, entry 1). Subsequently, various bases were tested (Table 1, entries 2-5). Et_3N (triethylamine) was found to be the best in this reaction, whereas DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DABCO (1,4−diazabicyclo[2.2.2]octane), and DiPEA (*N*,*N*-diisopropyl-ethylamine) were all found to be inferior. To further improve the

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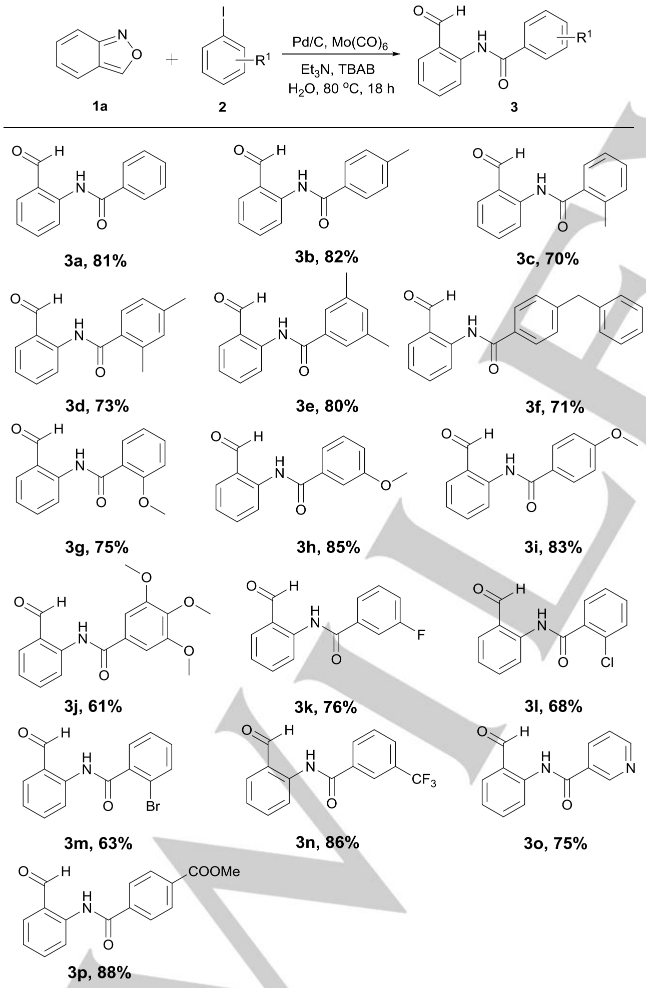
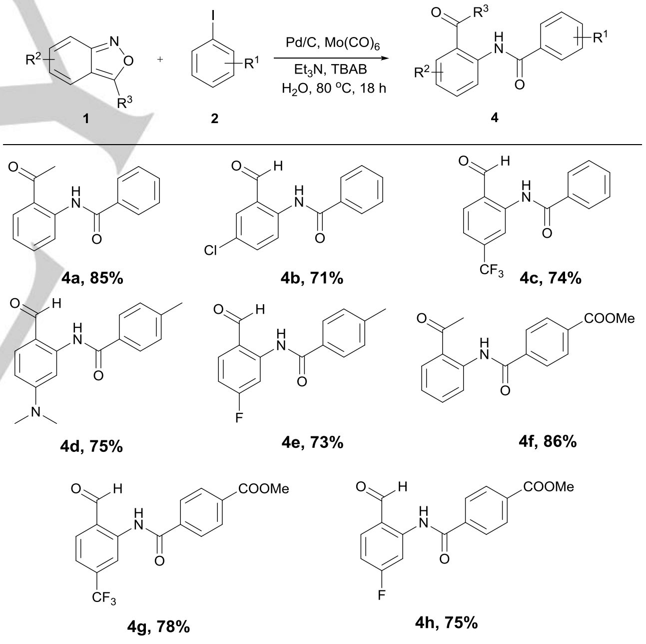
outcome, different additives were used in this reaction (Table 1, entries 6-8). Surprisingly, we found that the desired product **3a** can be formed in 62% yield with TBAB (tetrabutylammonium bromide) as the additive (Table 1, entry 6). Replacement of TBAB with TBAC (tetrabutylammonium chloride) or TBAHS (tetrabutylammonium hydrogen sulfate) proved detrimental to the efficiency of the process, with product **3a** being formed in 56% and 49% yields, respectively (Table 1, entries 7-8). Next we increased the amount of TBAB to 5 mol % and 10 mol % in the reaction conditions (Table 1, entries 9-10). However, the yield of product **3a** decreased. Different loadings of the Et_3N affected the reaction yields, and we obtained 73% yield of product **3a** with 3 equivalents of Et_3N (Table 1, entries 11-12). Notably, the amount of $Mo(CO)_6$ played a crucial role for the outcome of this reaction (Table 1, entries 13-15). The yield of the desired product can be improved to 83% by adding 0.5 equivalent of $Mo(CO)_6$ (Table 1, entry 14). Additionally, the yield decreased with 1.5 equivalent of iodobenzene and only 32% of the desired product could be detected with one equivalent of iodobenzene. The same yield can be obtained if perform the reaction under argon, and proves this system tolerable with aerobic conditions.



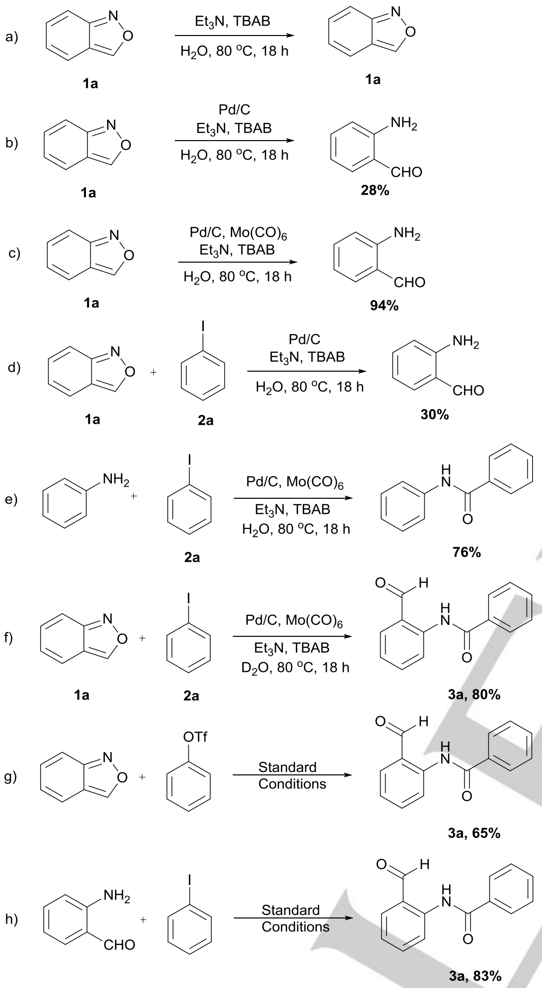
Scheme 1. Amides synthesis; variation of aryl iodides. Reaction conditions: Anthranil **1a** (0.3 mmol, 1 equiv.), aryl iodides **2** (0.75 mmol, 2.5 equiv.), Pd/C (3.2 mg, 10 mol %), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv.), Et_3N (0.9 mmol, 3 equiv.), TBAB (0.009 mmol, 3 mol %), H_2O (2 mL), 80 °C, 18 h, air, isolated yield.

With the optimized conditions in hand (Table 1, entry 14), a series of aryl iodides were tested subsequently. As shown in Scheme 1, various aryl iodides with either electron-donating or electron-withdrawing groups worked well under our reaction conditions and gave the corresponding amides in moderate to good yields. Substrates can tolerate various functional groups such as CH_3, Bn, OCH_3, CF_3, Br, Cl, F, and COOMe. However, aryl iodides substituted with OH, NH_2 or NO_2 could not give the desired carbonylation products. The system permitted the reaction of sterically hindered aryl iodides such as 2−iodotoluene 2−iodoanisole, 1-chloro-2-iodobenzene and 2-bromoiodobenzene with anthranils providing 70%, 75%, 68%, and 63% yield, respectively (**3c**, **3g**, **3l**, **3m**). The reaction of the heterocyclic iodide 3-iodopyridine with anthranil proceeded smoothly under these reaction conditions and providing 75% yield of the desired product **3o**. Interestingly, methyl 4-iodobenzoate reacted with anthranil and provided the highest yield of the corresponding product **3p** in 88%.



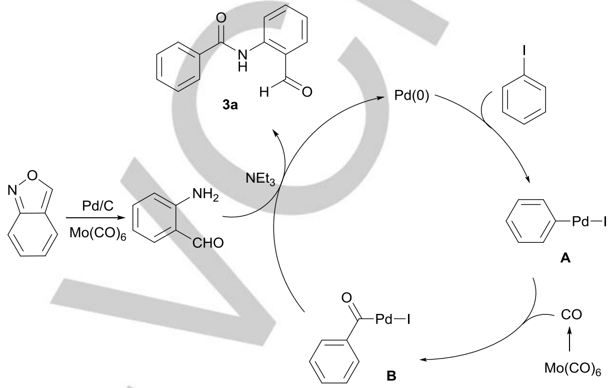
Scheme 2. Amides synthesis; variation of anthranils. Reaction conditions: Anthranils **1** (0.3 mmol, 1 equiv.), aryl iodides **2** (0.75 mmol, 2.5 equiv.), Pd/C (3.2 mg, 10 mol %), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv.), Et_3N (0.9 mmol, 3 equiv.), TBAB (0.009 mmol, 3 mol %), H_2O (2 mL), 80 °C, 18 h, air, isolated yield.

Then, various anthranils were investigated for further extending the substrates scope (Scheme 2). Several substituted anthranils performed well and delivered the corresponding amides in moderate to good yields. Owing to the mild reaction conditions, different functional groups, such as F, Cl, CF_3, and NMe_2, can be contained in the substrates. In addition, introduction of a substituted methyl group into the 3−position of the anthranil ring was fully tolerated, giving the desired amides in 85% and 86% yields (**4a** and **4f**). Additionally, as one advantages of heterogeneous catalyst, catalyst recycle experiments were performed as well. In our model system, the catalyst can be reused for several times (see SI), and 54 % yield can still be achieved at the third run. 4-Bromoisoxazole was tested with iodobenzene as well, but no desired product could be detected.



Scheme 3. Control experiments, isolated yield.

To understand the mechanism, some control experiments were performed. From the Scheme 3a and 3b, we found that the cleavage of N−O bond would take place in the presence of Pd/C and the presence of $Mo(CO)_6$ improves the yield (Scheme 3, c). In the absence of $Mo(CO)_6$, no direct crosscoupling product 2-(phenylamino)benzaldehyde could be detected but only 2−aminobenzaldehyde was formed in 30% yield (Scheme 3, d). These results shown the importance of Pd/C and the dual roles of $Mo(CO)_6$ (promote the generation of 2−aminobenzaldehyde and CO source). We can get *N*−phenylbenzamide in 76% yield when aniline instead of anthranil under our standard conditions (Scheme 3, e). Then D_2O was used as the solvent in Scheme 3f. We could only get **3a** in 80% yield, and no deuterated product was detected which might due to the instability of N-D bond. Notably, PhOTf can be applied as the substrate as will and provide the desired product in 65% yield without any further optimization (Scheme 3, g). And 2-aminobenzaldehyde was tested as well and gives 83% of the corresponding product under our standard conditions (Scheme 3, h).



Scheme 4. Proposed mechanism.

According to the control experiments, we postulated a possible reaction mechanism for this palladium-catalysed aminocarbonylation (Scheme 4). Firstly, the iodobenzene reacted with palladium to give the aryl palladium complex **A**. Then carbon monoxide, which was produced from $Mo(CO)_6$, coordinated and inserted into palladium complex **A** to generate the acyl palladium complex **B**. This acyl palladium complex **B** reacted with 2−aminobenzaldehyde to give the final product and regenerated the palladium catalyst for the next catalytic cycle.

In conclusion, we have developed a convenient procedure for the synthesis of *N*-(2-carbonylaryl)benzamides. Moderate to good yields of the desired amides can be prepared with good functional group tolerance. Additionally, this procedure also have advantages such as recyclable Pd/C catalyst, safe $Mo(CO)_6$ as the solid CO source, water as environmentally benign solvent, and no inert gas protection.

Experimental Section

General procedure: In a 25 mL sealed tube, a mixture of anthranils 1 (0.3 mmol, 1 equiv.), aryl iodides 2 (0.75 mmol, 2.5 equiv.), Pd/C (3.2 mg, 10 mol %), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv.), Et_3N (0.9 mmol, 3 equiv.), and TBAB (0.009 mmol, 3 mol %) in distilled water (2 mL) was stirred at 80 °C under air. After 18 h, the mixture was cooled to room temperature. The residue was diluted with H_2O solution (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under vacuum. The crude products were purified by using column chromatography on silica gel (pentane/ethyl acetate) to give the pure products.

Acknowledgements

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Keywords: Palladium • anthranils • green chemistry • carbonylation • Domino reaction

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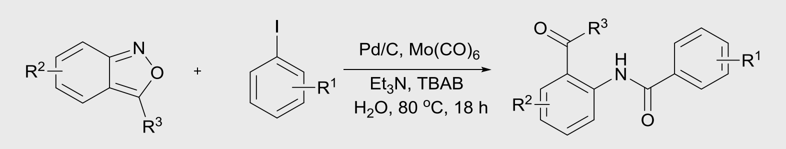

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