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Palladium Catalyzed Cascade Azidation/Carbonylation of Aryl Halides with Sodium Azide for the Synthesis of Amides

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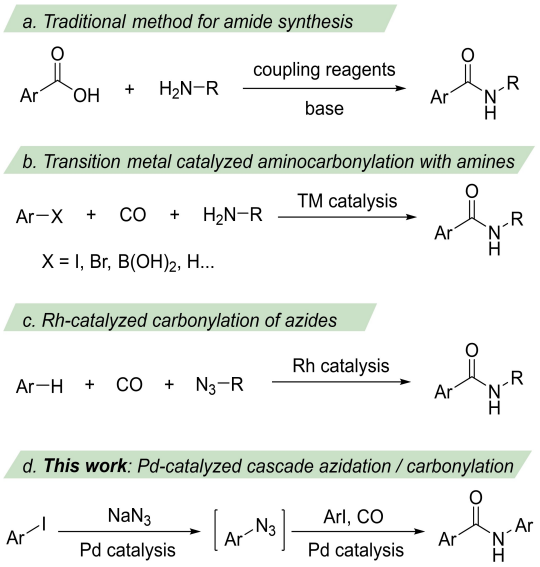
Abstract: Amide synthesis is one of the most important transformations in organic chemistry due to their ubiquitous presence in our daily life. In this communication, a palladium catalyzed cascade azidation/carbonylation of aryl halides for the synthesis of amides was developed. Both iodo- and bromobenzene derivatives were transformed to the corresponding amides using $PdCl_2$/xantphos as the catalyst system and sodium azide as the nitrogen-source. The reaction proceeds via a cascade azidation/carbonylation process. A range of alkyl and halogen substituted amides were prepared in moderate to good yields.

The amide structural motif is truly ubiquitous in our daily life and is widely present in bioactive molecules (e.g., peptides and proteins), natural products and pharmaceutical compounds (e.g., paclitaxel, penicillin).[1] This structure also serves as important intermediates and ligands for transition metal catalysis.[2] Thus, the synthesis of this functional group is paramount in organic chemistry. Traditional method for amide synthesis involves the condensation of carboxylic acids or their derivatives (acyl chloride, acyl imidazole, anhydride, or activated ester) with amines, which usually suffers harsh conditions and is accompanied with a large amount of waste (Scheme 1a).[3] Recently, a series of innovative catalytic amidation reactions have been developed for amide synthesis.[4] Among them, transition-metal-catalyzed aminocarbonylation of aryl halides and related compounds with amines provides a direct and step economic methods.[5] Many excellent aminocarbonylation methods have been developed employing amines as the nucleophiles (Scheme 1b).[6]

On the other hand, organic azides have found tremendous applications in organic transformations, especially for the construction of various heterocycles.[7] In particular, organic azide have been widely used as convenient nitrene precursor, which releases N_2 to produce an electron-deficient nitrene species upon irradiation. This nitrene intermediate is a high-reactive agent that is capable of inserting into a C–H bond.[8] For example, Bao, Gu and Xia developed an effective Rh-



Scheme 1. Approaches for the Synthesis of Amide.

catalyzed intermolecular C–H amidation of (hetero)arenes to synthesize amides via carbonylation of nitrene intermediates (Scheme 1c).[9] Organic azides were employed as the nitrene precursors. The preparation of aryl azides are mainly based on the replacement of diazonium salts with sodium azide[10] or direct coupling of aryl halides with sodium azide[11] under the catalysis of transition metals. We assume that the in-situ generated aryl azide could be directly used for a cascade carbonylation reaction and produce amides (Scheme 1d). With a continuous interest in developing carbonylative methods for amide synthesis,[12] we herein report a palladium catalyzed cascade azidation/carbonylation of aryl halides for the synthesis of amides.

In preliminary experiments, we treated iodobenzene **1a** with sodium azide in the presence of palladium catalyst under an atmosphere of CO. To our delight, *N*-phenylbenzamide **3a** was successfully obtained in 72% yield using the $PdCl_2$/PPh_3 catalyst system in dioxane (Table 1, entry 1). Subsequently, a range of phosphine ligands were examined for this reaction. The electronic and steric properties of the phosphine ligands played an important role in this reaction. Electron-rich trialkyl phosphine ligands were found to be less efficient in this reaction. When PCy_3 and $BuPAd_2$ were used as the ligand, the yields of **3a** were decreased to 12% and 33%, respectively (Table 1, entries 2 and 3). Aninline was detected as the main by-product, which might be resulted from the higher reaction rate of azidation than carbonylation. Bidentate phosphine ligands

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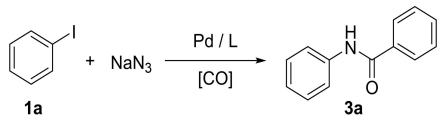
Table 1. Optimization of the Reaction Conditions.[a]

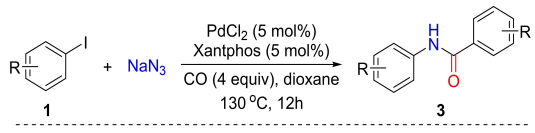


1a 3a

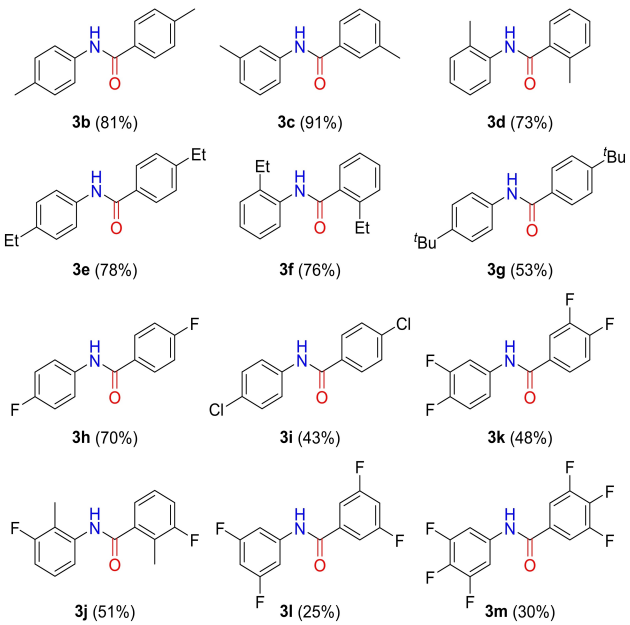
Entry	[Pd]	Ligand	Sol.	Yield [%][b]
1	$PdCl_2$	PPh_3	Dioxane	72
2	$PdCl_2$	PCy_3	Dioxane	12
3	$PdCl_2$	$BuPAd_2$	Dioxane	33
4	$PdCl_2$	DPEphos	Dioxane	44
5	**$PdCl_2$**	**Xantphos**	**Dioxane**	**90**
6	$Pd(OAc)_2$	Xantphos	Dioxane	60
7	$Pd(TFA)_2$	Xantphos	Dioxane	83
8	$PdCl_2$	Xantphos	toluene	84
9	$PdCl_2$	Xantphos	MeCN	53
10	$PdCl_2$	Xantphos	DMF	0
11[c]	$PdCl_2$	Xantphos	Dioxane	67
12[d]	$PdCl_2$	Xantphos	Dioxane	0
13[e]	$PdCl_2$	Xantphos	Dioxane	69
14[f]	$PdCl_2$	Xantphos	Dioxane	49

[a] Reaction conditions: Iodobenzene **1a** (0.5 mmol), NaN_3 (0.75 mmol), [Pd] (5 mol%), ligand (10 mol% for monodentate ligand, 5 mol% for bidentate ligand), [CO] ($HCOOAc + Et_3N$, 4 eq.), solvent (2 mL), 130 °C, 12 h. [b] Isolated yields. [c] 110 °C. [d] 90 °C. [e] [CO] ($HCOOAc + Et_3N$, 3 eq.). [f] [CO] ($HCOOAc + Et_3N$, 2 eq.). $BuPAd_2$: Butyldi-1-adamantylphosphine. DPEphos: Oxydi-2,1-phenylene)bis(diphenylphosphine. Xantphos: Dimethylbisdiphenylphosphinoxanthene.

Table 2. Substrate Scope of Iodobenzenes.[a]



1 3



[a] Reaction conditions: Iodobenzene **1** (0.5 mmol), NaN_3 (0.75 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), [CO] ($HCOOAc + Et_3N$, 4 eq.), dioxane (2 mL), 130 °C, 12 h. Isolated yields.

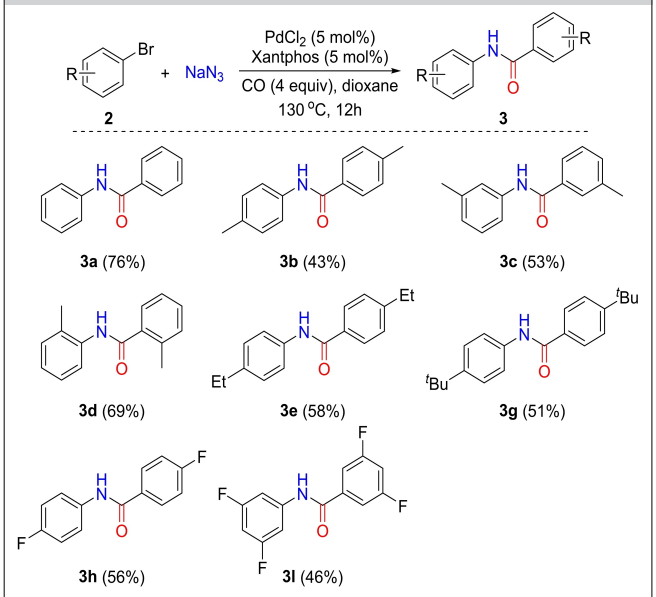
were also effective and the steric effect of the ligands affected the yields of this reaction significantly. Bidentate phosphine with larger bite angle led to a significant increase in the yield of **3a** (Table 1, entries 4 and 5, see details in SI). The yield of **3a** was improved to 90% when Xantphos was used as the ligand (Table 1, entry 5). Then, a series of palladium catalysts such as $Pd(OAc)_2$, $Pd(TFA)_2$, and $Pd(PPh_3)_4$ were tested in this reaction. All the catalysts tested were found to be less active and produced the desired product **3a** in decreased yields (Table 1, entries 6 and 7, see details in SI). Screening of the solvent revealed that dioxane is the optimal solvent. Decreased yields were obtained when the reaction were performed in toluene and CH_3CN (Table 1, entries 8 and 9, see details in SI). No desired product **3a** was obtained when strong polar solvents such as DMF and DMSO were used as the solvent (Table 1, entry 10, see details in SI). Moreover, the reaction temperature also played an important role in the overall efficiency of the reaction. The yield of **3a** was decreased to 67% when the reaction was conducted at 110 °C, while no amide **3a** was obtained when decreasing the reaction temperature to 90 °C (Table 1, entries 11 and 12). Finally, since the coordination and release of CO to the aryl palladium complex is a reversible process, the CO partial pressure also influenced the yield of this reaction significantly. Reducing the amount of CO resulted in decreasing of the yield (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand (Table 1, entry 5), we began to investigate the generality of this aminocarbonylation reaction with a series of substituted aryl iodides. As summarized in Table 2, alkyl substituents at different position of the phenyl ring of iodobenzene were suitable substrates and provided the desired products in good yields (Table 2, **3b**–**3g**). The steric hindrance of the substituents didn't affect the yields significantly (Table 2, **3b** *vs* **3d**, **3f** *vs* **3g**). In addition, halogen substituents such as fluoride and chloride were compatible in this aminocarbonylation reaction and produced the corresponding products without breaking the C–X bonds (Table 2, **3h**–**3m**).

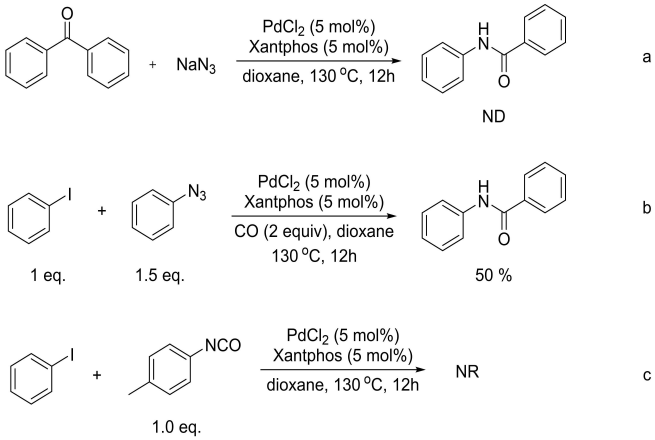
Subsequently, a series of different substituted bromobenzene were tested in this reaction (Table 3). Aryl bromides, compared to iodobenzenes, are more abundant and less expensive materials. Usually, it is more challenging for transition metal catalyzed carbonylation of aryl bromides owing to their higher activation barrier of the C–Br bond activation. To our delight, under the same reaction condition, bromobenzene was conveniently applied in this reaction and afforded phenylbenzamide in 76% yield (Table 3, **3a**). A series of alkyl and fluoro-substituted bromobenzenes were also tolerated and provided the corresponding phenylbenzamide derivatives in moderate yields.

Finally, to obtain some insight into the reaction pathway of this aminocarbonylation reaction, the following control experiments were carried out (Scheme 2). Firstly, benzophenone was treated with NaN_3 under the standard condition in the absence of CO. However, no *N*-phenylbenzamide **3a** was detected and benzophenone was recovered in high yield (Scheme 2a). This result indicates that benzophenone was not an intermediate in this transformation. Thus, excluded the homocarbonylative

Table 3. Substrate Scope of Bromobenzenes.[a]



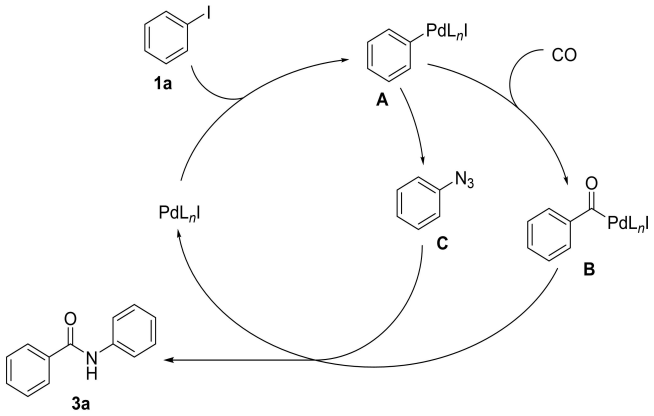
[a] Reaction conditions: Bromobenzene **2** (0.5 mmol), NaN_3 (0.75 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), [CO] ($HCOOAc + Et_3N$, 4 eq.), dioxane (2 mL), 130 °C, 12 h. Isolated yields.



Scheme 2. Control Experiments.

coupling/Schmidt reaction[13] pathway, which usually involves strongly acidic conditions. Then, iodobenzene was treated with azidobenzene under the standard condition without NaN_3, the corresponding product *N*-phenylbenzamide **3 a** was obtained in 50% yield (Scheme 2b). This observation reveals that azidobenzene intermediate might be involved in this aminocarbonylation reaction. In addition, when iodobenzene was treated with 4-tolyl isocyanate under the standard condition without CO and NaN_3, no reaction occurred (Scheme 2c).

Based on our preliminary observation and previous literatures, a plausible mechanism for this aminocarbonylation reaction was proposed in Scheme 3. Initially, the oxidative addition of C–I bond of iodobenzene **1 a** to the in-situ generated Pd(0) forms an phenyl-palladium complex **A**. Complex **A** could be converted into acyl palladium intermediate **B**,



Scheme 3. A Plausible Mechanism.

after coordination and insertion of CO. At the same time, nucleophilic attack of azide to phenyl-palladium complex **A** provides azidobenzene **C**. Then, nucleophilic attack of azidobenzene **C** to aryl-palladium complex **B** generated the desired product **3 a** and regenerated the active Pd(0) catalyst. However, the reaction pathway of benzoyl azide (formed by the reaction of intermediate **B** with NaN_3) and phenyl amine (generated from the hydrolysis of azidobenzene) to be possible reaction intermediates cannot be excluded at this stage.

In summary, we have developed a palladium catalyzed cascade azidation/carbonylation of aryl halides for the synthesis of amides. Using $PdCl_2$/xantphos as the catalyst system and sodium azide as the nitrogen-source, both iodobenzene and bromobenzene derivatives were converted to the corresponding amides via a cascade azidation/carbonylation process. A range of alkyl and halogen substituted amides were prepared in moderate to good yields.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: carbonylation · amide synthesis · azidation · cascade · Pd-catalyzed

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