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Synthesis of Amides via Palladium-Catalyzed Amidation of Aryl Halides

Huanfeng Jiang,* Bifu Liu, Yibiao Li, Azhong Wang, and Huawen Huang

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

jianghf@scut.edu.cn

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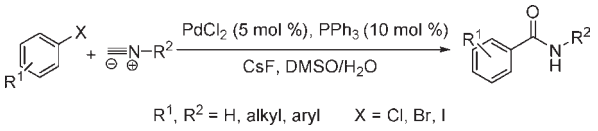
ABSTRACT



A new and efficient method for the synthesis of amides via palladium-catalyzed C−C coupling of aryl halides with isocyanides is reported, by which a series of amides were formed from readily available starting materials under mild conditions. This transformation could extend its use to the synthesis of natural products and significant pharmaceuticals.

Amides are an important class of *N*-containing compounds in organic chemistry and also potential precursors for the synthesis of numerous natural products, potent pharmaceuticals, and bioactive polymers.[1] The most prevalent strategy for preparation of amides relies heavily on activated carboxylic acid derivatives[2] or rearrangement reactions[3] induced by a base or acid, which generally involves tedious procedures or needs anhydrous conditions. Transition-metal-catalyzed reactions have emerged as an effective tool for the formation of carbon−carbon and carbon−heteroatom bonds and, hence, have attracted intensive synthetic attention.[4] Recent significant developments among them are direct amide synthesis from alcohols and amines using Ag-,[5] Ru-,[6] and Rh-based[7] catalytic systems by liberating H_2. Based on our research interest in palladium catalysis, we found a few reported examples concerning palladium-catalyzed aminocarbonylation for the synthesis of amides from aryl halides.[8] However, the use of toxic carbon monoxide limited the scope of this kind of reaction (Scheme 1a).[9] Thus, the palladium-catalyzed

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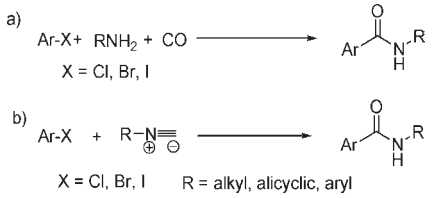
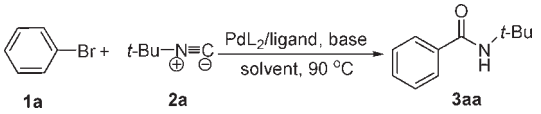
Scheme 1. (a) Reported Methods for the Aminocarbonylation of Aryl Halides and (b) the Method Presented Herein



direct amidation of aryl halides under mild conditions and without toxic chemical waste in tedious procedures remains a challenging goal. Isocyanides, a kind of unsaturated molecule similar to carbon monoxide, would be the most acceptable to substitute carbon monoxide for the synthesis of amides, which will not only represent a new path for palladium-catalyzed synthesis of amides but also simplify the original strategies (Scheme 1b). To the best of our knowledge, no examples of utilizing isocyanides as a source of both a carboxy and amino group have been described.[10,11] Herein, we report this novel and practical synthesis of amides via palladium-catalyzed C−C coupling of aryl halides with isocyanides.

In an initial attempt, bromobenzene (**1a**) was used as a model compound for the reaction with *tert*-butyl-isocyanide (**2a**) to screen the reaction conditions (Table 1). In the presence of the $PdCl_2$ catalyst (5 mol %), no desired product **3aa** was detected without any base (entries 1, 2). The screening of various bases revealed that the identity of the base was proven critical to the success of the aminocarbonylation reaction (entries 3−8). Only trace amounts of **3aa** were detected when *t*-BuOK and NEt_3 were used (entries 5, 6). The best result was obtained when CsF was utilized as the base, affording **3aa** in 90% yield (entry 8). Other bases such as KOH and K_2CO_3 were not very good for this transformation (entries 3, 4), but Cs_2CO_3 was also found to be effective for this reaction system (entry 7). Further optimization revealed that PPh_3 was essential in this reaction as well. Without PPh_3, the yield decreased to 71% (entry 9). And a lower yield of **3aa** was obtained when $PdCl_2$ was replaced by other palladium catalysts so far tested (entries 10−12). We next tested the aminocarbonylation reaction in the presence of different solvents. DMSO/H_2O (10:1) was superior to any other solvents

Table 1. Optimization of Reaction Conditions[a]



entry	Pd source/ligand	base	solvent	yield[b] (%)
1	$PdCl_2$	–	DMSO	n.r
2	$PdCl_2/PPh_3$	–	DMSO	n.r
3	$PdCl_2/PPh_3$	KOH	DMSO	36
4	$PdCl_2/PPh_3$	K_2CO_3	DMSO	70
5	$PdCl_2/PPh_3$	*t*-BuOK	DMSO	trace
6	$PdCl_2/PPh_3$	NEt_3	DMSO	trace
7	$PdCl_2/PPh_3$	Cs_2CO_3	DMSO	80
8	$PdCl_2/PPh_3$	CsF	DMSO	94 (90)
9	$PdCl_2$	CsF	DMSO	71
10	$PdBr_2/PPh_3$	CsF	DMSO	64
11	$Pd(OAc)_2/PPh_3$	CsF	DMSO	70
12	Pd/C (10%)	CsF	DMSO	10
13[c]	$PdCl_2/PPh_3$	CsF	DMSO	trace
14[d]	$PdCl_2/PPh_3$	CsF	DMSO	trace
15	$PdCl_2/PPh_3$	CsF	DMF	61
16	$PdCl_2/PPh_3$	CsF	CH_3CN	n.r
17	$PdCl_2/PPh_3$	CsF	1,4-dioxane	40
18[e]	$PdCl_2/PPh_3$	CsF	DMSO	60

[a] Reactions conditions: All reactions were performed with **1a** (1.0 mmol), **2a** (1.2 mmol), PdX_2 (5 mol %), PPh_3 (10 mol %), base (1.0 equiv), and 0.1 mL of H_2O in 1.0 mL of solvent at 90 °C for 12 h unless otherwise noted. n.r. = no reaction. [b] Yields and conversions are based on **1a**, detected by GC-MS. Number in parentheses is isolated yield. [c] 1.0 mL of H_2O was added to the DMSO. [d] The reactions was carried out under a nitrogen atmosphere in extra-dried DMSO. [e] Reaction at 70 °C for 15 h.

(entries 13−17). Notably, the reaction was sluggish when extra-dried DMSO was employed (entry 14). Lower temperature disfavored the reaction, and the reaction gave a 60% yield after 15 h (entry 18).

With the optimized conditions in hand, we next focused on the generality of the reaction with regard to both coupling partners (Scheme 2). Upon repeating the reaction with *tert*-butyl-isocyanide (**2a**), it was found that both electron-poor and -rich phenyl bromides (**1b**−**1p**) can be successfully converted to the corresponding products (**3ba**−**3pa**) in good to excellent yields. Generally, the phenyl bromides with electron-withdrawing groups (**1h**−**1p**) afforded higher yields of the products than that of electron-donating groups (**1b**−**1e**, **1g**), and the former needed much less reaction time. We also found that the reaction of polycyclic aryl bromides as well as heteroaryl bromides (**1s**−**1u**) proceeded very well to afford the corresponding amides in good yields. Various alkyl, cycloalkyl, and aryl isocyanides (**2a**−**2f**) were also employed to probe the scope of the reaction substrates. All the isocyanides were found suitable for this transformation, affording the corresponding amides in good yields. Even if sterically bulky isocyanides such as **2e** and **2f** were used, the reaction gave the corresponding products in acceptable yields, indicating this transformation can tolerate various substrates with steric bulk and a different electronic nature.

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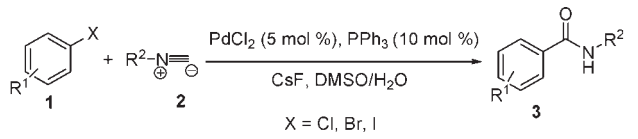
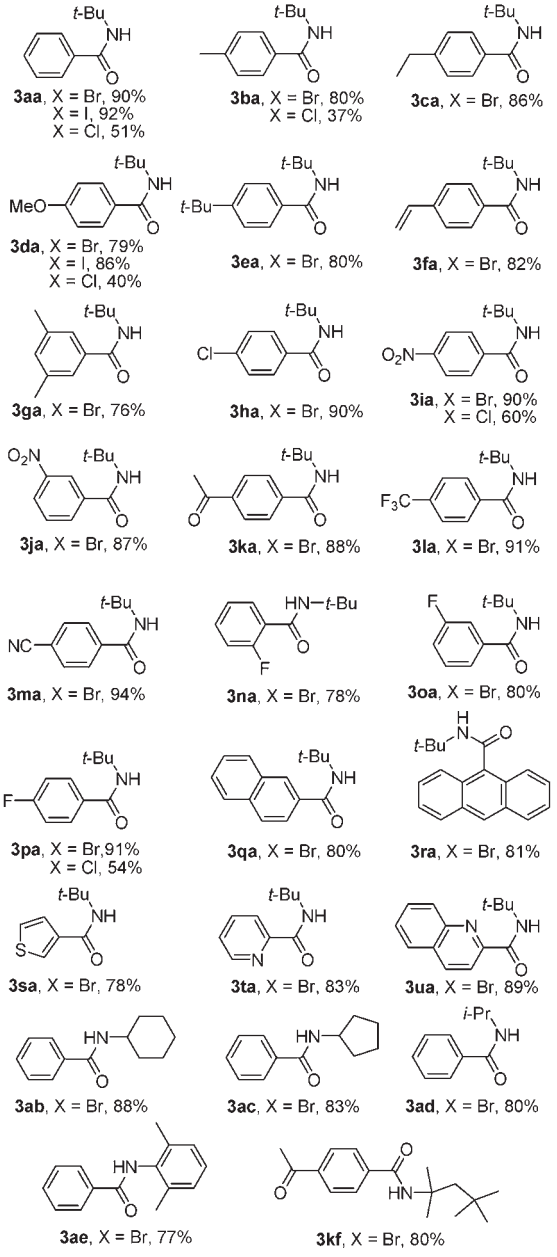
Scheme 2. Palladium-Catalyzed Synthesis of Aryl Amides from Aryl Halide and Isocyanides[a]

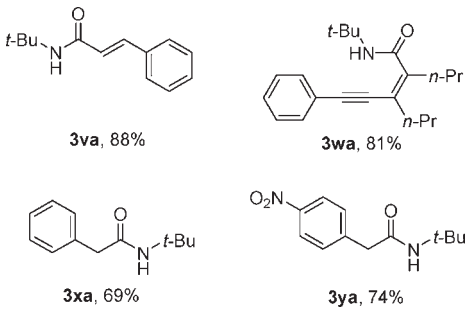




[a] All reactions were carried out using aryl bromides (1.0 mmol), isocyanides (1.2 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), CsF (1.0 equiv), and 0.1 mL of H_2O in 1.0 mL DMSO at 90 °C for 8−12 h unless otherwise noted. All the aryl chlorides were carried out at 110 °C for 15 h. Isolated yield was given.

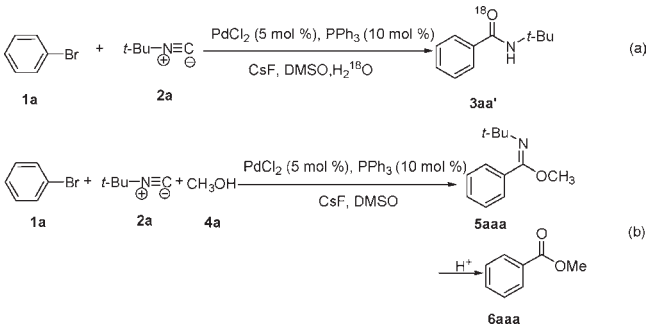
Additionally, the reaction can also be conducted with aryl chlorides and iodides. As expected, the reaction time of aryl iodides (**1a**, **1d**) was shortened and the desired products were furnished in satisfactory yields. Making a strong contrast with high reactivity of aryl iodides, the reaction of aryl chlorides (**1a**, **1b**, **1d**, **1i**, **1p**) could not occur under the same conditions unless the reaction temperature was elevated from 90 to 110 °C. The aminocarbonylation products were obtained only in moderate yields at 110 °C. Unfortunately, when 2-chlorotoluene and 2-chloroanisole were used in the reaction, no corresponding products were detected.

Scheme 3. Synthesis of Amides from Alkenyl Bromides and Benzyl Bromides[a]



[a] All reactions were carried out using alkenyl or benzyl bromides (1.0 mmol), isocyanides (1.2 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), CsF (1.0 equiv), and 0.1 mL of H_2O in 1.0 mL of DMSO at 90 °C for 8−12 h unless otherwise noted. Isolated yield was given.

Scheme 4. Investigation of the Reaction Mechanism[a]



[a] Both (a) and (b) were carried using bromobenzene (1.0 mmol), isocyanides (1.2 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), and CsF (1.0 equiv) in 1.0 mL of extra-dried DMSO at 90 °C for 8 h.

Importantly, alkenyl and benzyl bromides were well tolerated for this transformation (Scheme 3). When 1-((*E*)-2-bromovinyl) benzene (**1v**) and 1-((*Z*)-4-bromo-3-propyl-hept-3-en-1-ynyl) benzene[12] (**1w**) were employed, the reaction carried out effectively, affording the corresponding products **3va** and **3wa** in 88% and 81% isolated yields, respectively. Similarly, benzyl bromides (**1x**, **1y**) can also couple with isocyanides under our conditions.

To obtain a better understanding of the mechanism of the present catalytic process, several reactions were performed as shown in Scheme 4. When bromobenzene (**1a**) was treated in extra-dried DMSO in the presence of $H_2{}^{18}O$,

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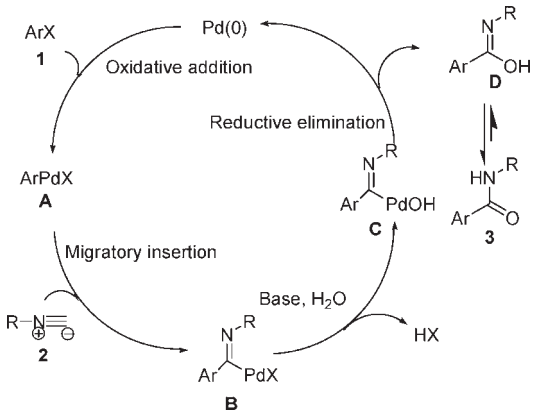
Scheme 5. Proposed Mechanistic Possibility



^{18}O-labeled *N*-*tert*-butylbenzamide (**3aa′**) was observed (Scheme 4a). It was rather interesting that once upon replacing H_2O by CH_3OH (**4a**) as the nucleophile under our reaction system, a ketimine intermediate (**5aaa**) was detected by GC-MS. The methyl benzoate (**6aaa**) was obtained after hydrolysis of ketimine (**5aaa**) with 2 M aqueous hydrochloric acid at room temperature (Scheme 4b).

According to these results, we were tempted to assume the mechanism of the reaction as follows (Scheme 5). Initial oxidative addition of aryl halide (**1**) to a zerovalent Pd species afforded aryl palladium intermediate **A**. Then the intermediate **B** was formed by the migratory insertion of isocyanide (**2**) into **A**.[13] With the aid of the base, −X was replaced by −OH and the intermediate **C** formed. A subsequent reductive elimination of intermediate **C** formed an unstable product (**D**), and the active catalyst species Pd(0) regenerated. Immediately, the unstable product (**D**) isomerized to give the final product (**3**).

In summary, we have demonstrated an efficient method for the synthesis of amides via palladium-catalyzed C−C coupling of aryl halides with isocyanides for the first time, which is clearly different from the conventional procedures. The reactions are operationally simple and avoid using toxic carbon monoxide and acid chloride, which must be used in an anhydrous system. Most importantly, this transformation may be used to discover new nature products and significant pharmaceuticals. Studies aimed at developing related transformations are underway.

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Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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