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## A novel Pd-catalyzed *N*-dealkylative carbonylation of tertiary amines for the preparation of amides<sup>†</sup>

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A novel and convenient protocol for the formation of amides via palladium-catalyzed N-dealkylative carbonylation of alkyl tertiary amines has been developed. In the presence of  $PdCl_2(PhCN)_2$ , CuO, PhCN and CO, a range of substituents on both aryl iodides and alkyl tertiary amines were compatible with the reaction to afford a series of N,N-disubstituted amides in moderate to excellent yields.

The amides are very important functional groups with a variety of biological activities.<sup>1</sup> Amide moieties are found in many biologically active compounds and natural products and in numerous agrochemicals and pharmaceuticals.<sup>2</sup> Transition metal-catalyzed carbonylation<sup>3</sup> was first reported by Heck *et al.* in 1974 as a powerful synthetic tool for amide formation.<sup>4</sup>

The palladium-catalyzed carbonylation of aryl halides and amines in the presence of carbon monoxide has undergone a great deal of development recently<sup>5</sup> (Scheme 1, eqn (1)). This reaction is generally limited to primary and secondary amines because cleavage of the highly stable C–N bond of a tertiary amine is challenging. Activation of this bond has attracted much attention<sup>6,7</sup> and a few catalytic systems have been developed for the Pd-catalyzed carbonylation of tertiary amines.<sup>8</sup> These methods have some limitations, such as harsh conditions, long reaction times and low yields. Herein, we report a novel and convenient Pd-catalyzed carbonylation of aryl iodides with tertiary amines and carbon monoxide *via* C–N bond cleavage for the formation of *N*,*N*-disubstituted amides (Scheme 1, eqn (2)). Importantly, the protocol can be applied in synthesizing  $\alpha$ -keto amide derivatives.

Treatment of 4-iodoanisole (1a) with tributylamine (2a) in the presence of  $Pd(OAc)_2$  (5 mol%) and CuO (1.3 equiv.) in DMSO at 100 °C for 16 h under a CO atmosphere (1 atm, 25 mL) gave *N*,*N*-dibutyl-4-methoxybenzamide (3a) in 43% yield (Table 1, entry 1). And then,  $Pd(MeCN)_2Cl_2$ ,  $Pd(PhCN)_2Cl_2$  and  $Pd(PPh_3)_4$ were also investigated (Table 1, entries 2–4) and  $Pd(PhCN)_2Cl_2$ 



Scheme 1 Transition metal-catalyzed carbonylation of amines for the synthesis of amides.

gave the highest yield of **3a**. Various solvents were also screened (DMF, DMAc, MeCN, toluene, PhCN and dioxane) with PhCN giving the best results (Table 1, entries 5–10). Notably, when the reaction was carried out in a solvent with a high boiling point, enhanced reaction activity was observed. Various oxidants were also screened (such as ZnO, TBHP, Cu(OAc)<sub>2</sub> and CuCl<sub>2</sub>), however, CuO was found to be the most effective (Table 1, entries 9 and 11–14). Interestingly, TBHP, a non-metal oxidant, furnished **3a** in 69% yield. The optimum conditions were found to be three equivalents of CuO at 100 °C (Table 1, entries 15–19). The use of O<sub>2</sub> and CuO (20 mol%) instead of CuO (3 equiv.) as an oxidant lowered the yield of **3a** (Table 1, entry 20).

The scope of substrates 1 and 2 was then explored (Table 2). Substrates 1b-1e, which contain electron donating or electron withdrawing groups, were well tolerated under the optimal conditions to give moderate to excellent yields of the target products. Treatment of iodobenzene 1b with amine 2a in the presence of Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>, CuO and benzonitrile gave 3b in 62% yield (Table 2, entry 1). The reaction of substrate 1c, bearing a p-CH<sub>3</sub> group, gave an excellent yield of product 3c (Table 2, entry 2). Iodides 1d-1e, which contain electron deficient groups, such as *p*-CN and *p*-Br, provided the corresponding products in moderate yields (Table 2, entries 3 and 4). Bulky substrates 1f and 1g also reacted with tributylamine 2a to give target products 3f and 3g in 62% and 68% yield, respectively (Table 2, entries 5 and 6). A moderate yield was also observed when m-CH<sub>3</sub> iodobenzene 1h reacted with amine 2a under standard conditions (Table 2, entry 7). Gratifyingly, double carbonylation products

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Table 1 Palladium-catalyzed carbonylation of 4-iodoanisole (1a) with tributylamine  $(2a)^a$ 

	+ CC	) + NBu <sub>3</sub>	[Pd] O NBu <sub>2</sub>		
N	1a	2a	MeO	3a	
Entry	[Pd]	Oxidants	Solvents	Т	Yield <sup><math>b</math></sup> (%)
1	$Pd(OAc)_2$	CuO	DMSO	100	43
2	$Pd(MeCN)_2Cl_2$	CuO	DMSO	100	48
3	$Pd(PhCN)_2Cl_2$	CuO	DMSO	100	55
4	$Pd(PPh_3)_4$	CuO	DMSO	100	46
5	$Pd(PhCN)_2Cl_2$	CuO	DMF	100	65
6	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	DMAc	100	50
7	$Pd(PhCN)_2Cl_2$	CuO	MeCN	100	Trace
8	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	Toluene	100	43
9	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	PhCN	100	72
10	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	Dioxane	100	Trace
11	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	ZnO	PhCN	100	35
12	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	TBHP	PhCN	100	69
13	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	$Cu(OAc)_2$	PhCN	100	NR
14	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuCl <sub>2</sub>	PhCN	100	40
$15^c$	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	PhCN	100	78
<b>16</b> <sup>d</sup>	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	PhCN	100	91
17 <sup>e</sup>	$Pd(PhCN)_2Cl_2$	CuO	PhCN	100	68
18	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	PhCN	120	64
19	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	CuO	PhCN	80	68
$20^{f}$	$Pd(PhCN)_2Cl_2$	CuO	PhCN	100	68

<sup>*a*</sup> Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), [Pd] (5 mol%), oxidant (1.3 equiv.), and solvent (2 mL) at 100  $^{\circ}$ C under a CO atmosphere (1 atm, 25 mL) for 16 h. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> CuO (2 equiv.). <sup>*d*</sup> CuO (3 equiv.). <sup>*e*</sup> CuO (4 equiv.). <sup>*f*</sup> CuO (20 mol%) and O<sub>2</sub> instead of CuO (3 equiv.).

 $\alpha$ -keto amide **3i** and amide **3j** were formed from 1,2-diiodobenzene **1i** and 1,4-diiodobenzene **1j** in 40% and 55% yield, respectively (Table 2, entries 8 and 9).

The scope of tertiary amines was also examined and the standard conditions were compatible with tertiary amines 2b-2j (Table 2, entries 10-18). Alkyl tertiary amines 2b-2f performed well with 1a, furnishing the corresponding amides 3k-3o in 68-91% yield (Table 2, entries 10-14). Surprisingly, N-ethyl-Nisopropylpropan-2-amine 2g was compatible with the optimal conditions forming target product 3p in 37% yield together with another carbonylation product 3q in 7% yield (Table 2, entry 15). The reaction of substrate 1a with 2h gave desired product 3r in 61% yield (Table 2, entry 16). Target products 3s and 3t were isolated from the reaction between bioactive 2i and 2j with iodide 1a in 76% and 25% yield, respectively (Table 2, entries 17 and 18). Interestingly, primary amine 2k and secondary amine 21 are confirmed suitable substrates for the reaction, to produce carbonylation product 3u and 3a in 62% and 95% yield respectively (Table 2, entries 19 and 20).

Based on previous reports,  ${}^{5h,6c,7d,9}$  as well as our results, a possible mechanism was proposed as outlined in Scheme 2. Initially, the PdL<sub>n</sub> species inserts into ArI and combines with aryl iodide and CO to form intermediate **A**, which then reacts with secondary amines to give Pd complex **C** (iminium-type intermediate **B** generated with the aid of CuO, which can be hydrolyzed to produce secondary amines and by-products). Finally, **C** then undergoes reductive elimination to afford the target molecule and the PdL<sub>n</sub> catalyst is regenerated with CuO.

**Table 2** Palladium-catalyzed carbonylation reactions of aryl iodides (1) with tertiary amines  $(2)^a$ 

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1		R <sup>3</sup> CO, P	hCN, 100 °C, 16 h	R <sup>3</sup> 3	
Entry	Ar–I	Amines	Products	Yield <sup>b</sup> (%)	
1	الک ا ۱b	2a	NBu <sub>2</sub>	62, <b>3b</b>	
2	lc	2a	NBu <sub>2</sub>	92, <b>3c</b>	
3 <sup>c</sup>	NC Id	2a	NC NBu <sub>2</sub>	50, <b>3d</b>	
4	Br	2a	Br NBu <sub>2</sub>	50, <b>3e</b>	
5		2a	NBu <sub>2</sub>	62, <b>3f</b>	
6 <sup><i>d</i></sup>	OCH <sub>3</sub> lg	2a	Meo OMe	68, 3g	
7	l lh	2a	NBu <sub>2</sub>	67, <b>3h</b>	
8		2a	NBu <sub>2</sub> NBu <sub>2</sub>	40, <b>3i</b>	
9 <sup><i>d</i></sup>	I	2a	O NBu <sub>2</sub>	55, <b>3j</b>	
10	1a	Net <sub>3</sub> 2b	MeO NEt2	70, <b>3k</b>	
11	1a	NPr <sub>3</sub> 2c	MeO NPr2	70, 3 <b>l</b>	
12	1a	Nhex <sub>3</sub> 2d	MeO Nhex <sub>2</sub>	90, <b>3m</b>	
13	1a	Noct <sub>3</sub> 2e	MeO Noct <sub>2</sub>	91, <b>3n</b>	
14	1a	NBn <sub>3</sub> 2f	MeO NBn2	68, <b>30</b>	
15 <sup><i>d</i>,<i>e</i></sup>	1a	$\sim N^{N}$	MeO	37, <b>3p</b>	



<sup>*a*</sup> Reaction conditions: Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (5 mol%), CuO (3 equiv.), and PhCN (2 mL) at 100 °C under a CO atmosphere (1 atm, 25 mL) for 16 h. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> 30 h. <sup>*d*</sup> 24 h. <sup>*e*</sup> Another carbonylation product *N*,*N*-diisopropyl-4-methoxybenzamide (**3q**) was isolated in 7% yield.



Scheme 2 Proposed mechanism for the reaction.

In summary, a protocol for the preparation of amides *via* the palladium-catalyzed carbonylation of aryl iodides and tertiary amines has been described. Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>, CuO, CO and benzonitrile were found to be the optimum conditions for this reaction and a number of aryl iodides and tertiary amines are tolerated to furnish amides in moderate to excellent yields. Importantly, the protocol uses commercially available tertiary amines as the coupling partner. Work to extend the scope and application of this reaction is currently underway.

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