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A Palladium-Catalyzed Domino Procedure for the Synthesis of Unsymmetrical Ureas

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Abstract. A palladium-catalyzed carbonylative procedure for the synthesis of unsymmetrical ureas has been developed. This one-pot one-step cascade procedure is consisted by three individual processes: carbonylation, Curtius rearrangement, and nucleophilic addition. A series of unsymmetrical ureas were prepared from easily available aryl iodides and amines in moderate to excellent yields. This procedure provides a convenient and practical approach for unsymmetrical urea synthesis.

Keywords: Cascade reaction ; Unsymmetrical urea ; Carbonylation ; Curtius rearrangement ; Palladium catalyst

Urea is an important structural unit that presents in a wide range of natural products, pharmaceuticals and agrochemicals (Figure 1).[1] For example, Sorafenib is a multi-targeted inhibitor of several tyrosine and Raf family kinases. Cumyluron is a urea herbicide mainly used for the control of creeping grasses. Additionally, due to the high hydrogen-bonding ability of ureas, they are also widely used in molecular recognition[2] and also as organocatalysis.[3]

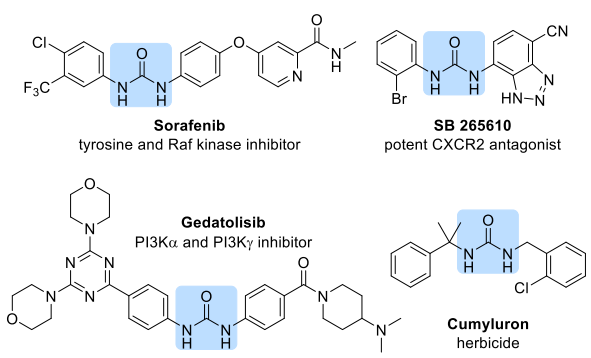
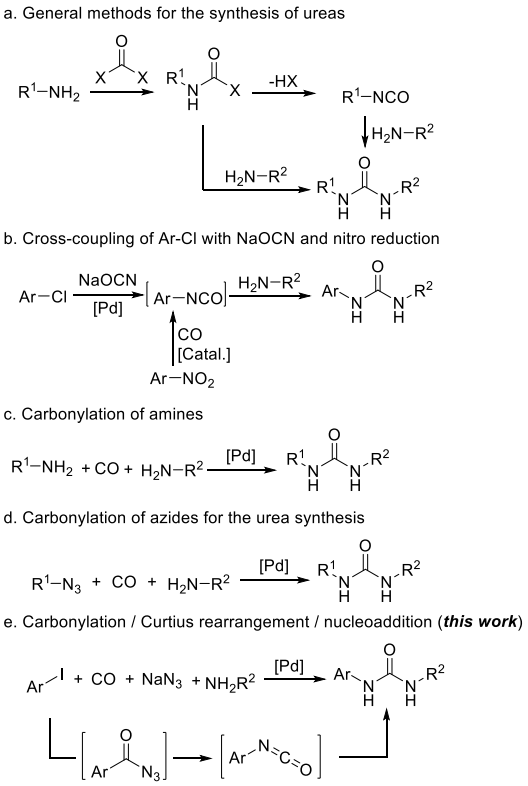


Figure 1. Selected examples of urea derivatives in pharmaceuticals and agrochemicals.

Due to their important applications in pharmaceuticals and also synthetic chemistry, several efficient approaches have been developed for the synthesis of functionalized ureas.[4] Traditionally, ureas were prepared by the nucleophilic addition of isocyanates with amines[5] or stepwise addition of amines to phosgene derivatives[6] (Scheme 1, a). Both reactions involve the use of hazardous reagent such as phosgene or isocyanates. Alternatively, transition metal-catalyzed cross-coupling reaction provides an attractive option. Buchwald and co-workers developed an efficient protocol for the synthesis of unsymmetrical ureas by palladium-catalyzed cross coupling of aryl chlorides and triflates with sodium cyanate (Scheme 1, b).[7] The aryl isocyanate can be generated *in-situ* by reduction of nitro compounds in the presence of CO as well. Additionally, transition metal-catalyzed carbonylation reactions,[8] as one of the most powerful methods for the synthesis of carbonyl-containing compounds, have also been applied in the synthesis of ureas. For example, transition metal catalyzed oxidative carbonylation of amines provides a direct route for the synthesis of ureas (Scheme 1, c).[9] Zhang's group reported a carbonylation of azides in the presence of amines for unsymmetrical ureas synthesis (Scheme 1, d).[10] However, besides the usage of CO gas, the needs of already prepared organo azides as the starting material creates new challenges. Hence, developing direct and one pot process for urea synthesis from readily available materials is still highly desirable.

With our continuous interests in developing carbonylation based cascade reactions for the synthesis of various carbonyl-containing compounds,[11] we were recently interested in developing a general procedure for synthesis of unsymmetrical ureas from commercially abundant aryl halides. We assume that the carbonylation reaction of aryl halides with suitable azide would generate the corresponding aroyl azides, which might undergo a Curtius rearrangement to give the corresponding isocyanates, subsequently nucleophilic addition of amines to the in-situ generated isocyanates would provide the desired unsymmetrical

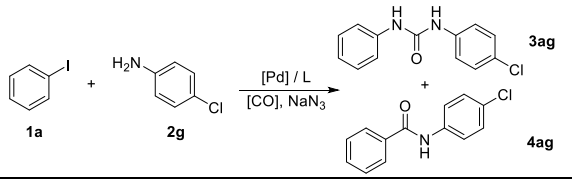
ureas (Scheme 1, e). One of the main challenges of this cascade reaction is the high tendency of palladium-catalyzed aminocarbonylation reaction of aryl halides which will lead to amides production. Here it's important to mention that Grushin and co-workers developed a palladium catalyzed azidocarbonylation reaction of aryl iodides with sodium azide.[12] From the previous achievements, we realized the importance of proper combination of catalysts and ligands on the final success.[13] Herein, we present our recent result on the palladium catalyzed carbonylation/Curtius rearrangement/nucleophilic addition cascade reaction for the synthesis of unsymmetrical ureas with formic acid as the CO source via an in-situ formed formic acetic anhydride in *In-Ex* tube.



Scheme 1. Representative procedures for ureas synthesis.

Initially, iodobenzene **1a** and 4-chloroaniline **2g** were selected as the model substrates for this cascade reaction. It's worth to mention explain that as inorganic salt NaN_3 was used as one of the reagents, phase transfer catalyst (PTC) was added to improve its solubility. To our delight, by using Pd_2dba_3/Xantphos as the catalytic system, the desired urea **3ag** was obtained in 61% yield in the presence of 1.2 equivalents of NaN_3 and 0.2 equivalent of TBAI in THF at 60 ℃ (Table 1, entry 1). Amide **4ag** was detected as the main by-product. A series of palladium catalysts such as $Pd(OAc)_2$, $PdCl_2$ and $Pd(acac)_2$ were explored in this reaction. The reaction yield can be increased to 78% with $PdCl_2$ as the catalyst (Table 1, entry 3). Then, we investigated the ligands effect and found out that ligands influenced the reaction significantly. Only trace amount of the desired urea product **3ag** was detected when DPEphos was used as the ligand (Table 1, entry 5). Amide **4ag** was obtained in high yield. Other phosphine ligands including PCy_3, PPh_3 and DPPF were all failed to promote this reaction and no urea product **3ag** could be obtained (Table 1, entry 6, see details in SI). The screening of solvents revealed the important role of solvents on the outcome of this reaction. When the reaction was conducted in MeCN or DCE, the desire product **3ag** was isolated in 70% and 57% yields, respectively (Table 1, entries 8 and 9). However, when the reaction was carried out in toluene, the yield decreased to 19% (Table 1, entry 7). The reaction yield can be increased to 89% when 1,4-dioxane was used as the solvent (Table 1, entry 10). On the other hand, if we increase the reaction temperature to 90 ℃ or 120 ℃, the yields decreased to 82% and 66%, respectively (Table 1, entries 11 and 12). However, no reaction occurred at 30 ℃. Here, the decreased yield at higher temperature can be explained by the increased yield of the amide **4ag** and also the diarylurea product exchange the ArNH-moiety with external amines. Then, a series of additives were examined. Comparable yields were obtained in the presence of TBAB (tetrabutylammonium bromide) and TBAHS (tetrabutylammonium hydrogen sulfate) (88% and 83% yields, respectively. See SI). Finally, an excellent yield of 97% was obtained when the reaction was performed in the absence of any additives (Table 1, entry 14). In order to see the efficiency of palladium precursors in the absence of additive, the palladium catalysts were tested again and good yields can be obtained in general (Table 1, entries 15-17). Notably, 89% yield can be obtained as well with $Mo(CO)_6$ (2 equiv.) as the CO source under the same conditions (Table 1, entry 18). However, we decided continual with formic acid for the substrate scope due to the produce of metallic waster

Table 1. Unsymmetrical ureas synthesis: Screening of the reaction conditions.[a]



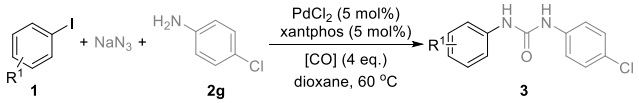
Entry	[Pd]	Ligand	Solvent	PTC	Yield (%)
1	Pd_2dba_3	xantphos	THF	TBAI	61
2	$Pd(OAc)_2$	xantphos	THF	TBAI	67
3	$PdCl_2$	xantphos	THF	TBAI	78
4	$Pd(acac)_2$	xantphos	THF	TBAI	41
5	$PdCl_2$	DPEphos	THF	TBAI	trace
6	$PdCl_2$	PPh_3	THF	TBAI	0
7	$PdCl_2$	xantphos	toluene	TBAI	19
8	$PdCl_2$	xantphos	MeCN	TBAI	70
9	$PdCl_2$	xantphos	DCE	TBAI	57
10	$PdCl_2$	xantphos	dioxane	TBAI	89

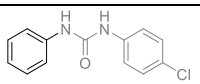
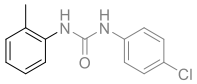
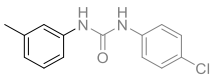
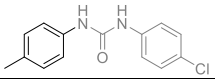
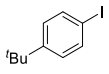
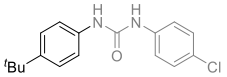
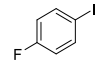
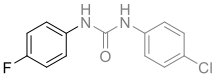
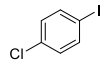
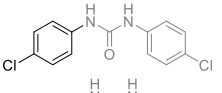
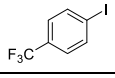
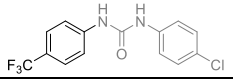
11[b]	$PdCl_2$	xantphos	dioxane	TBAI	82
12[c]	$PdCl_2$	xantphos	dioxane	TBAI	66
13	$PdCl_2$	xantphos	dioxane	TBAB	88
14	**$PdCl_2$**	**xantphos**	**dioxane**	**/**	**97**
15	Pd_2dba_3	xantphos	dioxane	/	81
16	$Pd(OAc)_2$	xantphos	dioxane	/	85
17	$Pd(acac)_2$	xantphos	dioxane	/	73
18	$PdCl_2$	xantphos	dioxane	/	89[d]

[a] Reaction conditions: Iodobenzene (0.75 mmol), 4-chloroaniline (0.5 mmol), palladium (5 mol%), ligand (10 mol% for monodentate ligands and 5 mol% for bidentate ligands), NaN_3 (1.2 eq.), [CO] (2 mmol), additives (0.2 eq.), solvent (2 mL), 60 ℃, 12 h, isolated yields. [b] 90 ℃. [c] 120 ℃. [d] $Mo(CO)_6$ (2 equiv.) instead of [CO]. [CO]: HCO_2H : Ac_2O = 1 : 1. TBAI: tetrabutylammonium iodide. TBAB: tetrabutylammonium bromide.

With the optimized reaction conditions in hand (Table 1 entry 14), we turned our attention to investigate the substrates scope of this cascade reaction. Firstly, we tested the generality of aryl iodides for this reaction. As summarized in Table 2, a series of substituted iodobenzenes were successfully applied to this reaction and produced the corresponding products in moderate to excellent yields. Both electron-donating groups (Table 2, entries 2-5) and electron-withdrawing groups (Table 2, entries 6-8) were well tolerated. Generally, substrates with electron-donating groups gave higher yields than those with electron-withdrawing groups. The steric effect of substituent didn't affect the reaction yields (Table 2, entries 2-4). Additionally, halogen such as fluoro-, chloro- and trifluoromethyl-substituted iodobenzenes were also well tolerated in this transformation and delivered the corresponding ureas in 73%, 67% and 76% yields, respectively (Table 2, entries 6, 7 and 8).

Table 2. Unsymmetrical ureas synthesis: Substrates scope of the aryl iodides.[a]

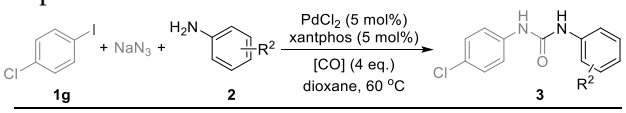


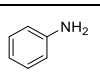
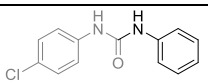
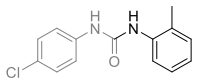
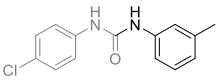
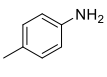
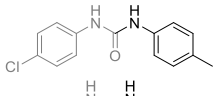
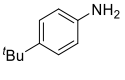
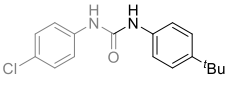
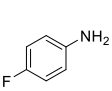
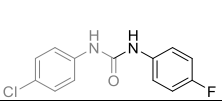
Entry	Aryl iodide	Product	Yield (%)
1			97
2			81
3			79
4			73
5			53
6			73
7			67
8			**76**

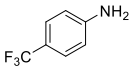
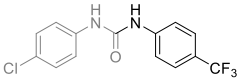
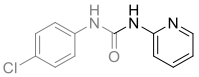
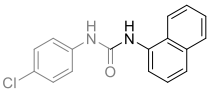
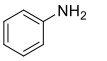
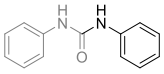
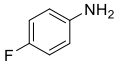
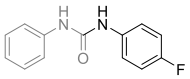
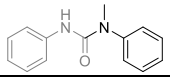
[a] Reaction conditions: aryl iodide (0.75 mmol), 4-chloroaniline (0.5 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), NaN_3 (1.2 eq.), [CO] (2 mmol; HCO_2H (2 mmol), Ac_2O (2 mmol)), 1,4-dioxane (2 mL), 60 ℃, 12 h, isolated yields. [CO]: HCO_2H : Ac_2O = 1 : 1.

Subsequently, we examined the generality of the amine coupling partner for this cascade reaction. As illustrated in Table 3, various substituted anilines were subjected to the optimized conditions. The cascade reaction proceeded smoothly and the corresponding ureas were prepared in moderate to good yields. With amine as the nucleophile, sterically bulky and electron-donating group substituted substrates gave lower yields (Table 3, entry 2 *vs* entry 3, entry 4 *vs* entry 6). Heteroaryl amines such as pyridin-2-amine and naphthalen-1-amine were also tolerated in this transformation and delivered the corresponding products in 71% and 45% yields, respectively (Table 3, entries 8 and 9). In addition, secondary amine can be tolerated as well. For example, when *N*-methylaniline was used in this reaction, the corresponding product was isolated in 58% yield (Table 3, entry 12).

Table 3. Unsymmetrical ureas synthesis: Substrates scope of the amines.[a]

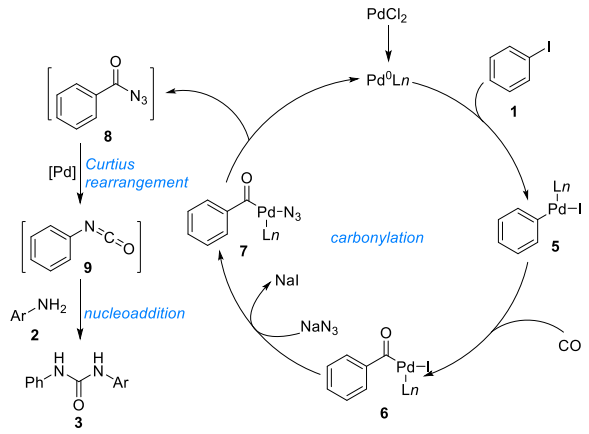


Entry	Anilines	Product	Yield (%)
1			90
2			61
3			81
4			67
5			58
6			94

7			59
8			71
9			45
10			60
11			63
12			58

[a] Reaction conditions: aryl iodide (0.75 mmol), amine (0.5 mmol), $PdCl_2$ (5 mol%), xantphos (5 mol%), NaN_3 (1.2 eq.), [CO] (2 mmol; HCO_2H (2 mmol), Ac_2O (2 mmol)), dioxane (2 mL), 60 ℃, 12 h, isolated yields. [CO]: HCO_2H : Ac_2O = 1 : 1.

Based on our results and also previous literatures,[10,12] a possible reaction mechanism is proposed in Scheme 2. The catalytic cycle starts with the oxidative addition of Pd^0 with iodobenzene **1** to give the corresponding phenyl-palladium complex **5**. Then, carbon monoxide coordinates and insert to intermediate **5** to give an acyl-palladium complex **6**. Then, nucleophilic attack of NaN_3 to the **6** generated the aroyl azide intermediate **8** after reductive elimination. Catalytic active Pd^0 was regenerated and ready for the next catalyst cycle at the same time. Subsequently, catalyzed by palladium, aroyl azide **8** underwent Curtius rearrangement to give the corresponding isocyanate **9**. Finally, nucleophilic addition of amine **2** to isocyanate provides the final urea product **3**.



Scheme 2. Plausible reaction mechanism.

In conclusion, we have developed a versatile palladium-catalyzed carbonylative procedure for unsymmetrical ureas synthesis. This one-pot one-step cascade procedure is consisted by three individual processes: carbonylation, Curtius rearrangement, and nucleophilic addition. A series of unsymmetrical ureas were prepared from easily available aryl iodides and amines in moderate to excellent yields.

Experimental Section

General procedure: $PdCl_2$ (4.5 mg, 5 mol%), Xantphos (14.5 mg, 5 mol%), iodobenzene (0.75 mmol), aniline (0.5 mmol) and sodium azide (0.6 mmol) were transferred into an oven-dried tube and a small test tube was placed in the reaction tube. HCOOH (2 mmol) and Ac_2O (2 mmol) were added to the small test tube (In-ex Tube).[14] 1,4-Dioxane (2 mL) was added to the reaction tube. Then the mixture was stirred at 60 °C for 12 h. After the reaction finished, the crude product was filtered and concentrated under vacuum and was purified by column chromatography on silica gel column EtOAc/petroleum ether (1:5, v/v) to give the desired product.

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A Versatile Palladium-Catalyzed Carbonylative Procedure for the Synthesis of Unsymmetrical Ureas

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