Organic LETTERS

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Pd/C Catalyzed Carbonylation of Azides in the Presence of Amines

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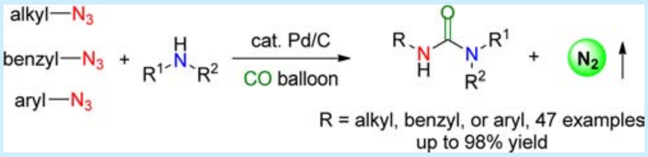
S *Supporting Information*

ABSTRACT: A facile and efficient Pd/C-catalyzed carbonylation of both aliphatic and aromatic azides in the presence of amines is reported. Serving as the widely existed fragments in an array of biological pharmaceuticals, functionalized unsymmetrical ureas were straightforwardly synthesized by using readily available and cheap azides with amines under CO atmosphere, with the extrusion of N_2 as the only byproduct. It was found that not only aryl azides but also benzyl and alkyl azides were suited for this methodology. Another feature of this procedure was the employment of a highly efficient palladium charcoal catalytic system.



Ureas are one of the most important bioactive functional units and synthetic components, specifically alkyl/benzyl unsymmetrical ureas are widely used in an array of pharmaceuticals and agrochemicals, such as CCR1 antagonist,[1a] PSMA targeting probes,[1b] and cumyluron[1c] (Figure 1).

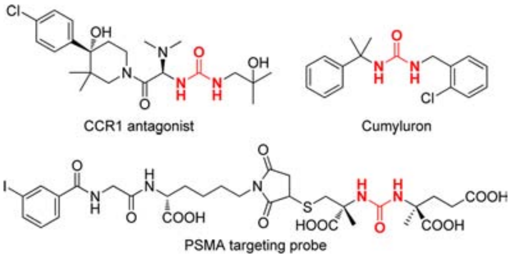
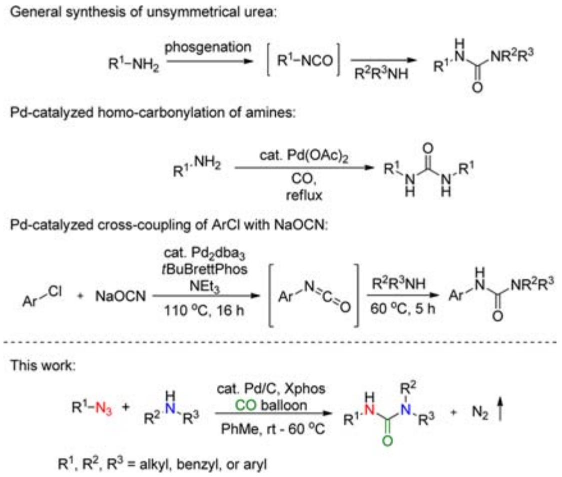


Figure 1. Selected examples of biological alkyl/benzyl unsymmetrical ureas.

Furthermore, by serving as hydrogen-bond donors,[2] ureas can also be used as efficient and air-stable organocatalysts[3] or ligands for transition metals.[4] Due to their great importance in various research areas, synthetic approaches toward functionalized ureas have drawn much attention.

Generally, ureas are synthesized via isocyanate intermediates, which are commonly generated by phosgenation of arylamines,[5] reductive carbonylation of nitroaromatics,[6] or Curtius rearrangement.[7,8] Unfortunately, either the precursors of these methods lack environmental friendliness or atomic economy, or the substrate scope is limited. Recently, studies in urea synthesis have focused on transition-metal-catalyzed reactions. Buchwald et al. reported a Pd-catalyzed cross-coupling of aryl chlorides with sodium cyanate, which represented a practical way to synthesize unsymmetrical ureas.[9] Nonetheless, the application of this method is limited to aromatic ureas. However, Pd-catalyzed carbonylation is well established as one of the most important ways to synthesize compounds bearing carbonyl functionality.[10] Pd-catalyzed coupling of amines in the presence of CO and oxidant provided an alternative strategy to accessing ureas (Scheme 1).[11] However, symmetrical urea was usually the dominate product, which is also the major byproduct in other urea formation strategies via transition-metal-catalyzed carbonylation in the presence of amines.

Scheme 1. General Synthetic Approach Towards Ureas



Transition-metal-catalyzed selective C−N bond formation via a highly reactive metal−nitrene intermediate has attracted great attention recently due to its apparent synthetic value for assembling diverse *N*-containing functional molecules.[12] Compared with those traditional methods responsible for metal−nitrene generation involving oxidation of amides[13] or preactivated nitrene precursors,[14] the employment of azide[15] as the substrate has afforded an environmentally friendly and simple strategy to construct *N*-containing compounds since it does not require an external oxidant and generates N_2 as the only byproduct. Transition-metal-catalyzed coupling reaction be-

Received: February 6, 2016
Published: March 25, 2016

ACS Publications

DOI: 10.1021/acs.orglett.6b00381

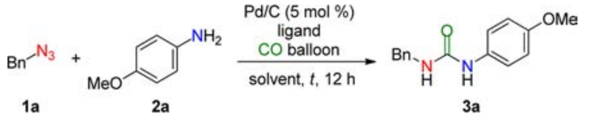
tween nitrene and σ-donor/π-acceptor ligand, including isocyanides[16] and CO,[17] to introduce nitrogen moiety into unsaturated systems, has experienced considerable growth during recent decades. Catalytic carbonylation of nitrene with amines has become a potential efficient way to synthesize unsymmetrical ureas. For example, Collman et al. first reported a palladium mediated carbonylation of arylazide with amines.[17a] However, harsh conditions such as high pressure of CO limited its further development. Jiao et al. reported a $PdCl_2$-catalyzed carbonylation of arylazides with alcohols to generate carbamates under a balloon of CO atmosphere very recently.[17c] Nonetheless, the method was ineffective for the generation of ureas. Additionally, Pd-catalyzed direct carbonylation of alkyl/benzyl azides has scarcely been reported. In view of the importance of ureas and our interest in nitrene chemistry, we have paid much attention to establishing a robust and highly efficient transition-metal catalyzed synthesis of unsymmetrical ureas via nitrene intermediates from not only aryl, but also benzyl and alkyl azides.

Furthermore, compared to general homogeneous catalysts, palladium charcoal has promising opportunities in “green chemistry” because it can be safely handled, removed, and recycled from the reaction mixture by simple filtration.[18] Thus, the development of Pd/C catalyzed reactions is highly desirable.

Herein, we report a Pd/C catalyzed carbonylation of benzyl/alkyl/aryl azides in the presence of amines to generate unsymmetrical ureas under mild conditions.

At the outset of our study, we selected the model reaction conditions using (azidomethyl)benzene **1a** and 4-methoxyaniline **2a** as the substrates to optimize the reaction conditions. Using Pd/C as the catalyst without any ligand, we detected only trace amounts of the desired product **3a** (Table 1, entry 1). After exploring the ligand effect, unexpectedly, the phosphorus ligands influenced the product yields significantly. As a result, the reaction yield increased up to 91% in the presence of XPhos as the ligand (entry 6). In further exploration steps, we examined various solvents. When reactions were carried out in dioxane and DCE, comparable yields were obtained (72% and 73%, respectively, entry 8 and 9); moderate yield was obtained when experiment was carried out in CH_3CN (67%, entry 10). Finally, when we changed the reaction temperature to 40 °C, much of **1a** remained unreacted so that the yield decreased to 35% (entry 11). While increasing to 80 °C, the yield also reduced to 73% because of the expected homocoupling of intermediate isocyanatobenzene (entry 12).

Table 1. Conditions of Pd-Catalyzed Carbonylation of BnN_3 1a in the Presence of 4-Methoxyaniline 2a[a]

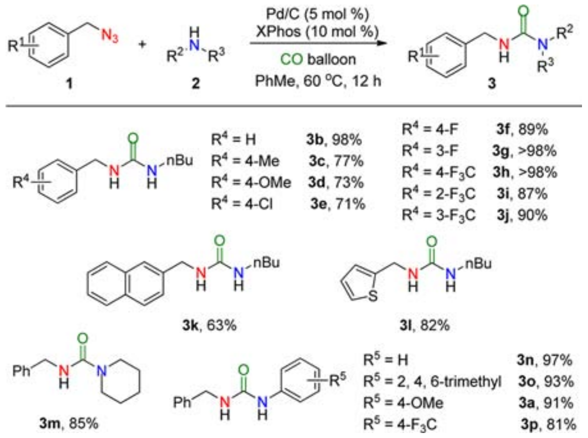


entry	ligand (mol %)	solvent	t (°C)	yield[b] (%)
1	–	PhMe	60	trace
2	PPh_3 (10)	PhMe	60	trace
3	PCy_3HBF_4 (10)	PhMe	60	10
4	DPPP (5)	PhMe	60	6
5	DPPF (5)	PhMe	60	10
6	XPhos (10)	PhMe	60	91
7	XPhos (10)	PhMe	60	trace[c]
8	XPhos (10)	dioxane	60	72
9	XPhos (10)	DCE	60	73
10	XPhos (10)	MeCN	60	67
11	XPhos (10)	PhMe	40	35
12	XPhos (10)	PhMe	80	73

[a]Reaction was carried out with 1.0 equiv of **1a** (0.4 mmol) and 1.2 equiv of **2a** (0.48 mmol). [b]Isolated yield. [c]The reaction was carried out without Pd/C. DPPP = 1,3-Bis(diphenylphos-phino)propane. DPPF = 1,1′-Bis(diphenylphosphino)ferrocene. XPhos = 2-Dicyclohexylphos-phino-2′,4′,6′-triisopropylbiphenyl.

Having optimized conditions for this cross-coupling transformation, we set out to explore the substrate scope with regard to different benzyl azides and amines (Scheme 2). To our delight, not only did benzyl azides bearing an electron-donating group give excellent results (**3c**, **3d**), but those bearing an electron-withdrawing group further afforded better yields (**3e**−**3j**). The reactions with the azides bearing substituents at different positions on the aromatic ring still gave distinguished yields (**3h**−**3j**). Chloride substituent was also well-tolerated on the aromatic ring (**3j**). Other aromatics such as naphthalene and thiophene substituted azides also worked well (**3k**, **3l**). Finally, the scope of amines was examined. Electron-sufficient substituents on the aniline ring gave better yield compared with the electron-deficient ones (91% and 81% for **3a** and **3p**, respectively). Sterically hindered secondary alkyl amines also furnished good yields (**3m**).

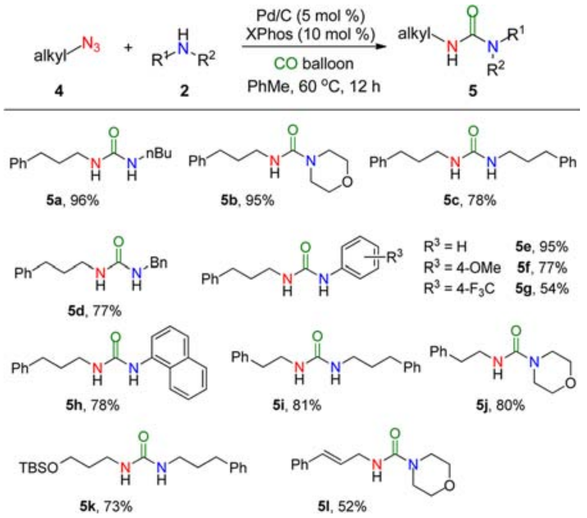
Scheme 2. Pd/C-Catalyzed Carbonylation of Benzyl Azides in the Presence of Amines[a]



[a]Reaction was carried out with 1.0 equiv of **1** (0.4 mmol) and 1.2 equiv of **2** (0.48 mmol). Isolated yield.

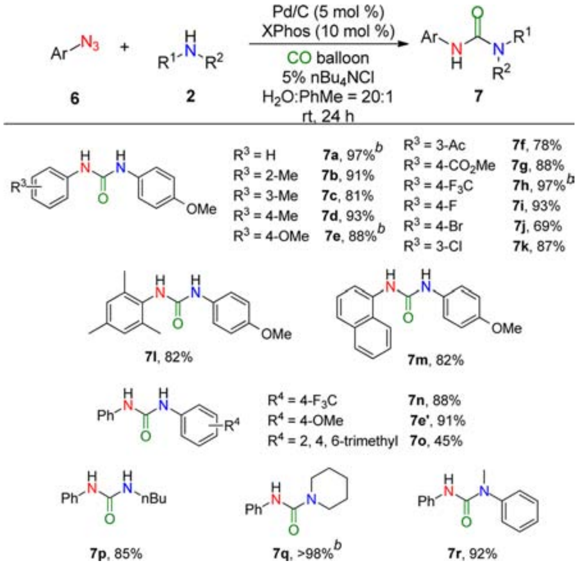
Although we have presented broad substrate generality of benzyl azides with high level of functional group tolerance, further application of this Pd-catalyzed reaction still remains challenging. The installation of aliphatic ureas was also envisioned to be highly desirable. Because alkyl azides are much less active than benzyl azides,[19] the standard conditions in Table 1 did not go well in this transformation. However, the reaction could furnish the desired unsymmetrical alkyl ureas in acceptable to high yields by properly changing the order of addition of substrates (for more details, see Supporting Information). Encouraged by this result, the scope of alkyl azides was subsequently investigated (Scheme 3). To our delight, the anticipated products were all obtained in high yields when secondary alkyl or benzyl amines were used as the nucleophile (**5a**−**5d**). Reactions of aromatic amines bearing either electron-donating or electron-withdrawing substituents afforded the desired products in good yields (**5e**−**5h**). More importantly,

Scheme 3. Pd/C-Catalyzed Carbonylation of Alkyl Azides in the Presence of Amines[a]



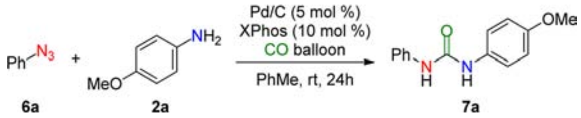
[a]Reaction conditions: **4** (0.4 mmol), PhMe (4 mL) was added and reacted for 4 h under CO (1 atm), then **2** (0.48 mmol) was added and reacted for another 8 h. Isolated yield.

Scheme 4. Pd/C-Catalyzed Carbonylation of Aromatic Azides in the Presence of Amines[a]



[a]Reaction was carried out with 1.0 equiv of **6** (0.4 mmol) and 1.2 equiv of **2** (0.48 mmol). Isolated yield. [b]When only PhMe was used as solvent and no *n*Bu$_4$NCl was added, the isolated yield of **7a** was 90%, **7e** was 81%, **7h** was >98%, and **7q** was >98%.

Table 2. Recycling Test[a]



run[b]	yield[c] (%)	run[b]	yield[c] (%)
1	94	2	88
3	88	4	86
5	82		

[a]Reaction conditions: **6a** (0.4 mmol), **2a** (0.48 mmol), XPhos (0.04 mmol), and PhMe (4 mL) were added and reacted for 12 h under CO (1 atm). [b]Reaction products carried out with the same batch of Pd/C. [c]Yield was determined by HPLC analysis.

various functionalized alkyl azides also gave good reaction yields (**5i**–**5l**).

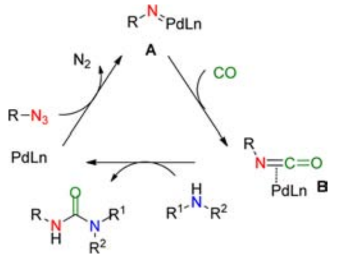
Having successfully surveyed benzyl and aliphatic azides, we considered expanding the methodology to aryl azides. Owing to the greater reactivity of aryl azides than others, a better result was achieved when the reaction was implemented at room temperature. To our surprise, this cross-coupling reaction proceeded even in aqueous media. After screening some additives to "put" this reaction in water, we found the best conditions eventually: water containing with 5% PhMe and 5% ^{n}Bu$_4$NCl. Generally, the transformation of azides with either electron-donating groups (Me, OMe) or electron-withdrawing groups (CF$_3$, F, Ac, CO$_2$Me) resulted in good yields (**7a**–**7k**) (Scheme 4). Sterically hindered azides worked just as fine (**7l**–**7m**). In addition, halogen substituents were well-tolerated on the aromatic ring (**7i**–**7k**), thus offering a handle for further functionalization and cross-coupling chemistry. To explore the generality of this reaction further, the scope of amines was then examined. The transformation of different amines with phenyl azide worked equally well (**7n**–**7r**). Both electron-donating and electron-withdrawing substituents on the aniline aryl ring afforded the desired products in good yields. Besides, sterically hindered secondary amines gave good yield (**7q**, **7r**).

Since Pd/C could be easily separated from the reaction mixture by simple filtration, we examined the carbonylation of phenyl azide **6a** in the presence of aniline **2a** using recycled Pd/C catalyst (Table 2). We were pleased that the same batch of 5 mol % Pd/C was capable of catalyzing at least 5 runs with >80% yield (the addition of fresh XPhos was necessary).

Whether Pd/C in the catalytic cycle works as a heterogeneous catalyst or undergoes a Pd leaching process is highly contentious.[20] Pd/C-catalyzed Heck/Suzuki–Miyaura reactions accompanied by a Pd leaching process has been reported, in which Pd leached into the solution, catalyzed the reaction, and redeposited on the charcoal at the end of the reaction.[21] In this Pd/C catalytic carbonylation of azides, recycling test in Table 2 gave a much better result compared to the references of a Pd leaching process. In addition, the filtrate of a preincubated mixture of Pd/C and XPhos was found to be catalytically inactive.[22,23]

On the basis of Pd-nitrene intermediate as stated earlier,[17,23,24] a plausible mechanism is proposed in Scheme 5. First, from organic azide as the substrate, the probable palladium nitrene species **A** is formed simultaneously with the release of N$_2$. Subsequently, the insertion of CO into palladium nitrene species **A** occurred to give Pd-coordinated isocyanate **B**. Finally, nucleophilic attack of amine at isocyanate **C**, which is promoted

Scheme 5. Proposed Mechanism



by palladium/phosphine complexes, affords desired unsymmetrical ureas as the eventual product along with the regeneration of Pd catalyst.

In summary, we have described a Pd/C-catalyzed carbonylation of azides in the presence of amines. This methodology provides a facile and efficient approach from simple and cheap organoazides with amines under atmospheric CO conditions, obtaining unsymmetrical ureas with good functional group tolerance. A series of unsymmetrical disubstituted benzyl, alkyl, and aryl ureas were effectively synthesized using this method. Further, the palladium charcoal catalyst is advantageous for industrial applications of this reaction. Further studies of the mechanistic detail are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00381.

Experimental procedures along with characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is supported by the National Natural Science Foundation of China (No. 21302219), Chinese Universities Scientific Fund (2016QC040), the National S&T Pillar Program of China (2015BAK45B01), and the Beijing National Laboratory of Molecular Sciences (BNLMS).

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(22) The mixture of Pd/C (21 mg, 0.02 mmol) and XPhos (19 mg, 0.04 mmol) was vigorously stirred in PhMe for 4 h at rt. Then the mixture was filtered though a 0.45 μm filter, and the colorless filtrate was used for a reaction of phenyl azide **6a** (53 mg, 0.4 mmol) with aniline **2a** (59 mg, 0.48 mmol) under CO atmosphere. After 24 h, HPLC analysis showed that the yield of urea **7a** was < 10%.

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