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Palladium-Catalyzed Carbonylative Synthesis of 1,5-Dihydro-2*H*-pyrrol-2-ones from Propargyl Amines and Benzyl Chlorides

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Abstract: A palladium-catalyzed double carbonylation of propargyl amines and benzyl chlorides employing benzene-1,3,5-triyl triformate (TFBen) as the CO source has been developed. By using this protocol, various 1,5-dihydro-2*H*-pyrrol-2-ones were produced in good yields.

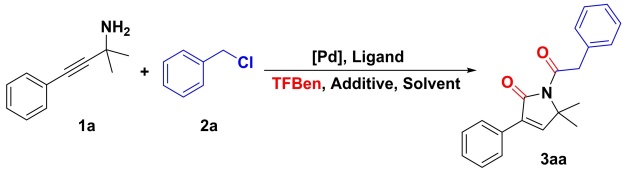
Keywords: double carbonylation; 1,5-dihydro-2*H*-pyrrol-2-ones; palladium catalysis; propargyl amines; benzyl chlorides

1,5-Dihydro-2*H*-pyrrol-2-ones are recognized as a class of important moieties frequently found in numerous natural products and pharmaceuticals with biological activities such as anti-diabetic (Ypaoamide B[1] and Glimepirid[2]), anti-tumor (Isomalyngamide A[3]), anti-biotic (Althiomycin[4a]), and immunosuppressive property (Microcolin A[4b]). In order to establish these useful skeletons, many synthetic methods have been realized.[5] However, alternative procedures are continuing under demand.

In the construction of carbonyl-containing scaffolds in organic synthesis, transition-metal-catalyzed carbonylative reactions have become one of the most efficient and straightforward approaches.[6,7] However, only a few studies have been reported on the carbonylation of propargyl amines to access amides or lactams. In 1996, Alper and coworkers developed a selective carbonylation of propargyl amines for the synthesis of 2,4- or 2,3-dienamides in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and DPPP under 40.8 atm CO pressure.[8] Ma's group reported a facile and efficient method for the synthesis of (*E*)-α-chloroalkylidene-β-lactams *via* a palladium-catalyzed cyclocarbonylation of propargyl amines with $CuCl_2$ and benzoquinone under 20.4 atm of CO.[9] Notably, the transformation features the *trans*-chlorometalation of the triple bond of propargyl amines. Recently, our group realized a palladium-catalyzed cyclocarbonylation of propargyl amines with TFBen (benzene-1,3,5-triyl triformate) to access 2-oxo-2,5-dihydropyrroles.[10] In this reaction, TFBen[11] was employed as the CO source and the key promoter as well. Herein, we now disclose a palladium-catalyzed double carbonylative cyclization of propargyl amines, benzyl chlorides, and TFBen for the expedite construction of 1,5-dihydro-2*H*-pyrrol-2-one scaffolds.

At the outset, the propargyl amine **1a** was reacted with benzyl chloride **2a** and TFBen in the presence of $Pd(OAc)_2$ as the catalyst and phosphine ligand at 110 °C in MeCN for 24 h (Table 1, entries 1–5). Gratifyingly, the reaction with DPPF gave the highest yield (82%) of the desired product **3aa** (Table 1, entry 4), while other phosphine ligands gave much inferior results. Then, a few palladium catalysts were examined and lower yields of **3aa** were obtained (Table 1, entries 6–8). Moreover, employing other solvents such as DMSO, DMF, toluene, and DCM gave reduced yields (Table 1, entries 9–12). It was shown that the reaction yield was decreased to 76%

Table 1. Optimization of Reaction Conditions.[a]

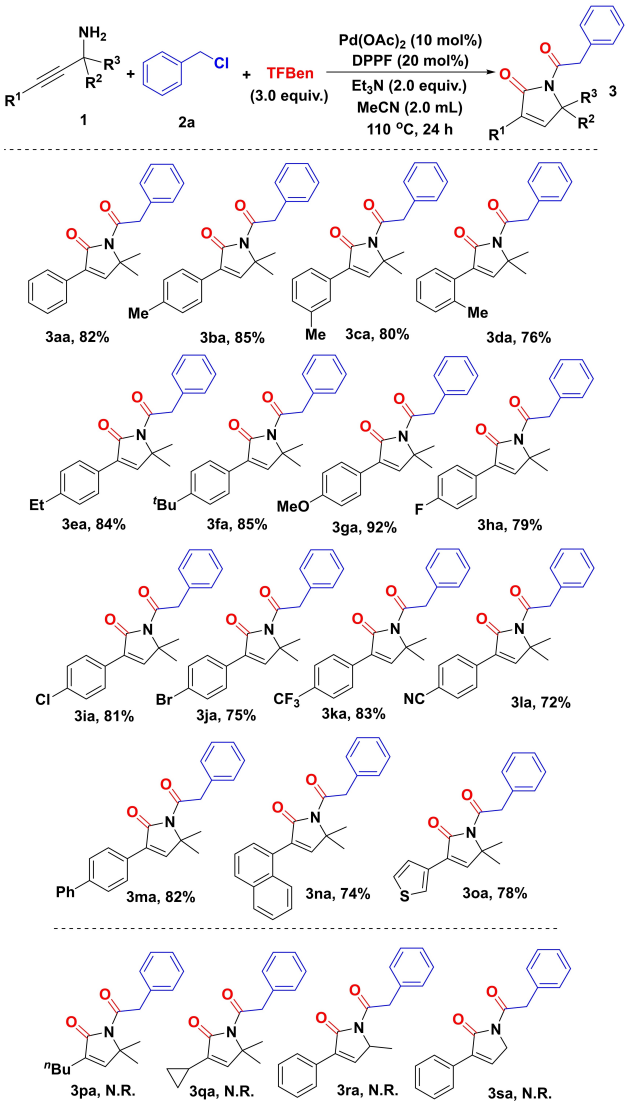


Entry	Catalyst	Ligand	Solvent	Yield (%)
1	$Pd(OAc)_2$	PPh_3	MeCN	10
2	$Pd(OAc)_2$	PCy_3	MeCN	12
3	$Pd(OAc)_2$	DPPP	MeCN	20
4	**$Pd(OAc)_2$**	**DPPF**	**MeCN**	**82**
5	$Pd(OAc)_2$	Xantphos	MeCN	0
6	$Pd(acac)_2$	DPPF	MeCN	70
7	$Pd(TFA)_2$	DPPF	MeCN	67
8	$Pd(PPh_3)_2Cl_2$	DPPF	MeCN	0
9	$Pd(OAc)_2$	DPPF	DMSO	28
10	$Pd(OAc)_2$	DPPF	DMF	27
11	$Pd(OAc)_2$	DPPF	toluene	74
12	$Pd(OAc)_2$	DPPF	DCM	0
13[b]	$Pd(OAc)_2$	DPPF	MeCN	76
14[c]	$Pd(OAc)_2$	DPPF	MeCN	43
15[d]	$Pd(OAc)_2$	DPPF	MeCN	64
16[e]	$Pd(OAc)_2$	DPPF	MeCN	38

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 equiv.), TFBen (3.0 equiv.), catalyst (10 mol%), ligand (20 mol%), Et_3N (2.0 equiv.), solvent (2.0 mL), 110 °C, 24 h, isolated yield.
[b] Catalyst (5 mol%), ligand (10 mol%).
[c] TFBen (2.0 equiv.).
[d] 120 °C.
[e] 100 °C. DPPP: 1,3-bis(diphenylphosphino)propane. DPPF: 1,1′-bis(diphenylphosphino)ferrocene. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

when the catalyst loading was reduced (Table 1, entry 13). The reaction efficiency dropped as well when the loading of phosphine ligand was decreased. Additionally, when the amount of TFBen was decreased, only 43% yield of **3aa** was achieved (Table 1, entry 14). Finally, raising or reducing the temperature hampered the reaction (Table 1, entries 15–16). In the case of shorten the reaction time to 18 hours, large amount of non-cyclized intermediate could be detected and lead to the decreased yield of the final product.

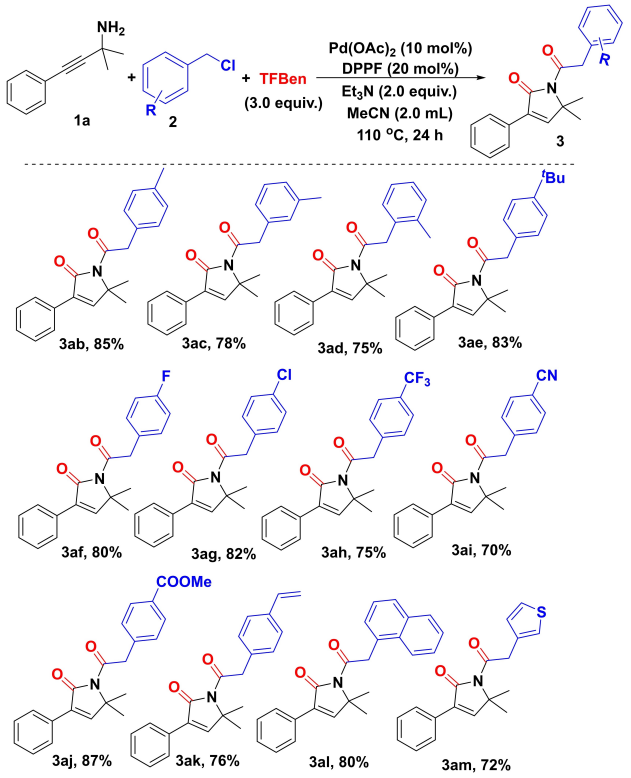
Then, the scope of propargyl amines **1** was investigated under the optimal reaction conditions (Scheme 1). For compounds bearing electron-donating or withdrawing groups, the reaction afforded the corresponding products **3ba–la** in good to excellent yields (72–92%). It was found that substrates with an *o*-Me or *m*-Me group gave lower yields than one with a *p*-Me group, which could be due to the steric hindrance in the cyclocarbonylation step. Furthermore, compounds containing biphenyl and naphthyl units were successfully transformed to the expected products **3ma** and **3na** in 82% and 74% yield, respectively. It



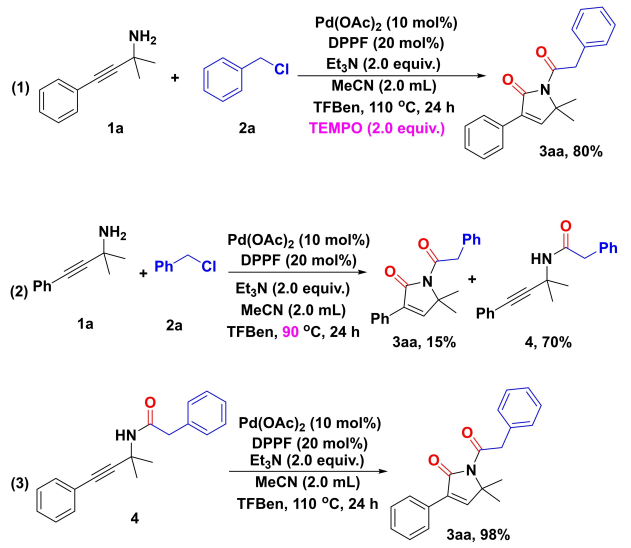
Scheme 1. Scope of propargyl amines. Reaction conditions: **1** (0.5 mmol), **2a** (1.2 equiv.), TFBen (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), DPPF (20 mol%), Et_3N (2.0 equiv.), MeCN (2.0 mL), 110 °C, 24 h, isolated yield.

was noteworthy that the propargyl amine **1o** with a thiophene ring was smoothly converted to the target product **3oa** in 78% yield. Unfortunately, alkyl-substituted compounds failed to give the desired products **3pa-qa**. It is also important to mention that no reaction occurred when mono-substituted (**1r**) and non-substituted propargyl amine (**1s**) were tested. These results suggest that the need of R^2 and R^3 is mainly due to steric effect to promote the cyclization step. The need of aromatic group for R^1 is to maintain the activity of the triple bond and ready for the following addition reaction. A substrate with R^2 and R^3 as ethyl group was tested, but very low yield (< 5%) of the corresponding product was obtained.

Next, a variety of benzyl chlorides **2** were studied in the reaction with the propargyl amine **1a** as shown in Scheme 2. The reaction of compounds with electron-donating or withdrawing substituents furnished the corresponding products **3ab**–**aj** in good yields (70–87%). It was shown that compounds with an *o*-Me or *m*-Me substituent gave lower yields than one with a *p*-Me substituent, suggesting that the steric hindrance might have an effect on the first carbonylation step. Moreover, 1-(chloromethyl)-4-vinylbenzene **2k** and 1-(chloromethyl)naphthalene **2l** worked well to give the desired products **3ak** and **3al** in high yields. Notably, 72% yield of the product **3am** was obtained when 3-(chloromethyl)thiophene **2m** was subjected to the reaction system.



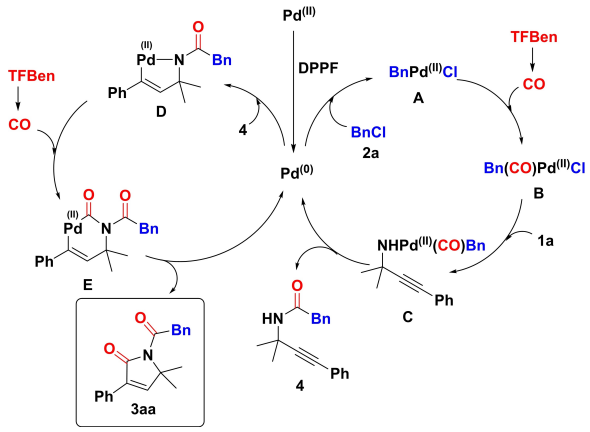
Scheme 2. Scope of benzyl chlorides. Reaction conditions: **1a** (0.5 mmol), **2** (1.2 equiv.), TFBen (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), DPPF (20 mol%), Et_3N (2.0 equiv.), MeCN (2.0 mL), 110 °C, 24 h, isolated yield.



Scheme 3. Control experiments.

In order to better understanding of the reaction pathway, a set of control experiments were conducted (Scheme 3). When TEMPO (2.0 equiv.) was added to the reaction system under standard conditions, the target product **3aa** was achieved in 80% yield, indicating that a radical process could be ruled out here (Scheme 3, eq 1). Reducing the reaction temperature to 90 °C led to 15% of the final product **3aa** and 70% of the mono-carbonylated product **4** (Scheme 3, eq 2). Subsequently, **4** could be converted to the desired product **3aa** in 98% yield under standard conditions (Scheme 3, eq 3). These findings suggested that the mono-carbonylated product **4** was a key intermediate in the double carbonylation of propargyl amines and benzyl chlorides. Notably, under our standard conditions, when TFBen was replaced with $Mo(CO)_6$ (3 equiv.) or acetic formic anhydride (3 equiv.), only non-cyclized intermediate **4** could be detected.

On the basis of previous reports[10–12] and above control experiments, a plausible mechanism for the palladium-catalyzed double carbonylation of propargyl amines and benzyl chlorides has been proposed (Scheme 4). Initially, the active Pd(0) catalyst, formed from Pd(II) and DPPF, can react with benzyl chloride **2a** to give the Pd(II) intermediate **A** *via* oxidative addition. Subsequently, CO is released from TFBen and is inserted to **A**, providing the acyl Pd(II) complex



Scheme 4. Plausible mechanism.

B. The nucleophilic addition of the propargyl amine **1a** to **B** leads to the Pd(II) species **C**, which can undergo reductive elimination to form the mono-carbonylated product **4**. Then, the reaction of **4** and Pd(0) generates the Pd(II) complex **D**. In this step, a $Pd^{II}H$ complex should be generated in advance and then followed by insertion into the triple bond to give complex **D**. The key Pd(II) intermediate **E** can be formed *via* the second CO insertion of **D**. Finally, reductive elimination of **E** affords the target product **3aa** and regenerates the active Pd(0) catalyst for the next catalytic cycle.

In conclusion, we have developed a new approach to access 1,5-dihydro-2*H*-pyrrol-2-one skeletons *via* a palladium-catalyzed double carbonylation of propargyl amines and benzyl chlorides. Using TFBen as the CO source, the reaction affords various 1,5-dihydro-2*H*-pyrrol-2-ones in good yields.

Experimental Section

General Procedure

Propargyl amines **1** (0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (11.2 mg, 10 mol%), DPPF (55.4 mg, 20 mol%), and a 2.5 mL vial containing TFBen (315 mg, 1.5 mmol, 3.0 equiv.) were added to an oven-dried *In-Ex* tube[13] (15 mL) which was then placed under vacuum and refilled with nitrogen three times. Et_3N (140 μL, 1.0 mmol, 2.0 equiv.), benzyl chlorides **2** (0.6 mmol, 1.2 equiv.) and MeCN (2.0 mL) were added into the tube *via* syringe. The tube was sealed and stirred at 110 °C for 24 h. Upon the reaction was completed, the resulting mixture was filtered through a pad of tripolite and washed with EtOAc. The filtrate was concentrated under vacuum and purified by silica gel column using chromatography (PE/EA) to obtain the corresponding products **3**.

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