Organic LETTERS

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Palladium-Catalyzed Multicomponent Reaction (MCR) of Propargylic Carbonates with Isocyanides

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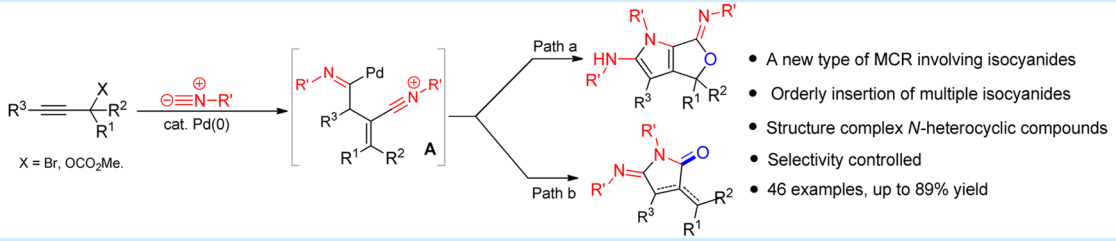
Supporting Information



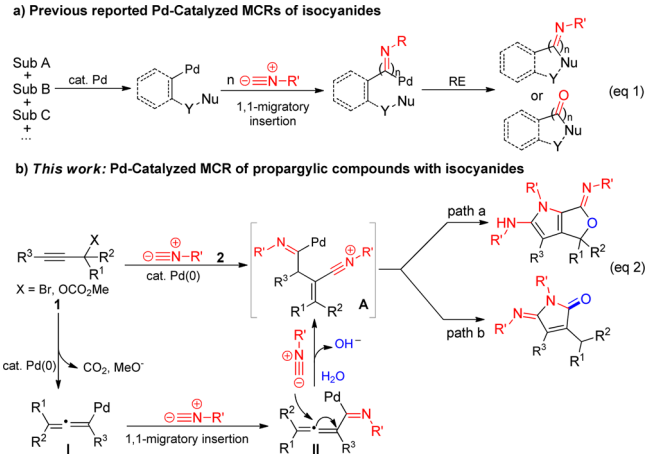
ABSTRACT: A palladium-catalyzed multicomponent reaction (MCR) of propargylic carbonates with isocyanides is reported. Remarkably, the orderly insertion of isocyanides affords two types of valuable *N*-heterocyclic products (*Z*)-6-imino-4,6-dihydro-1*H*-furo[3,4-*b*]pyrrol-2-amines and (*E*)-5-iminopyrrolones in high yields. Systematic analysis of the reaction conditions indicates that the selectivity of these N-heterocyclic products can be controlled by ligands and temperature.

Multicomponent reactions (MCRs) have held a prominent position in modern synthetic chemistry for the facile construction of complex molecules from readily accessible starting materials.[1] Since the elegant pioneering work of Passerini and Ugi with isocyanides as reaction components, isocyanides have been strongly associated with the success of MCRs.[2] Recently, transition-metal-catalyzed MCRs involving isocyanides have been widely explored.[3] Particularly, due to the high efficiency of palladium catalysis in C−N, C−O, and C−C bond formation reactions,[4] the palladium-catalyzed MCRs of isocyanides have become an efficient strategy to synthesize heterocyclic and carbocyclic compounds.[5,6] However, the reported methods mainly focused on a single insertion of isocyanide via the aryl- or alkenyl-palladium intermediates (Scheme 1, eq 1).[7] To date, few successful examples of multiple insertion of isocyanides have been disclosed. But the insertion of isocyanides commonly occurred at one site which limited the diversity of the products.[8] On the other hand, the multicomponent reactions which allowed the tandem multiple insertion of isocyanides in an orderly manner were considerably rare.[9]

This might be attributed to the fact that isocyanides have difficulty in exhibiting different reactivities under the same reaction system, and the uncontrollable multiple insertion of isocyanides is also a serious problem.[10] Therefore, reaction with intermediates bearing diverse potential reactive sites with isocyanides may be an efficient strategy to achieve the orderly insertion of isocyanides.

Recently, palladium-catalyzed transformations of propargylic compounds have attracted much attention,[11] providing various valuable allenyl compounds,[12] disubstituted allylic products,[13]

Scheme 1. Palladium-Catalyzed MCRs of Isocyanides



heterocycles, and carbocycles[14] in high yields. Generally, an allenylpalladium intermediate was involved via the oxidative addition of palladium(0) catalysis to propargylic compounds. In this context, we envisaged that the successive insertion of isocyanides may be achieved through the same allenylpalladium intermediate (Scheme 1, eq 2). First, isocyanide might go through the 1,1-migratory insertion with the *in situ* formed allenylpalladium intermediate **I**. Then another isocyanide could react with the allenes moiety via nucleophilic addition.[15] The

Received: October 9, 2016

DOI: 10.1021/acs.orglett.6b02999
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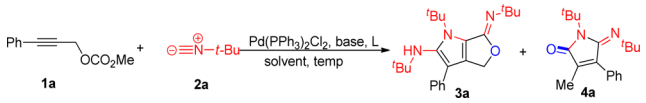
newly formed intermediate **A** might become the active species to construct valuable *N*-heterocyclic compounds. Herein, we present our recent progress in palladium-catalyzed MCRs of propargylic compounds with isocyanides to construct 6-imino-4,6-dihydro-1*H*-furo[3,4-*b*]pyrrol-2-amines and 5-iminopyrrolones, which are useful skeletons in biochemistry.[16]

Initially, propargylic carbonate (**1a**) and *tert*-butyl isocyanide (**2a**) were chosen as model substrates in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), and CsF (0.4 mmol) in DMSO (2 mL) at 80 °C (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



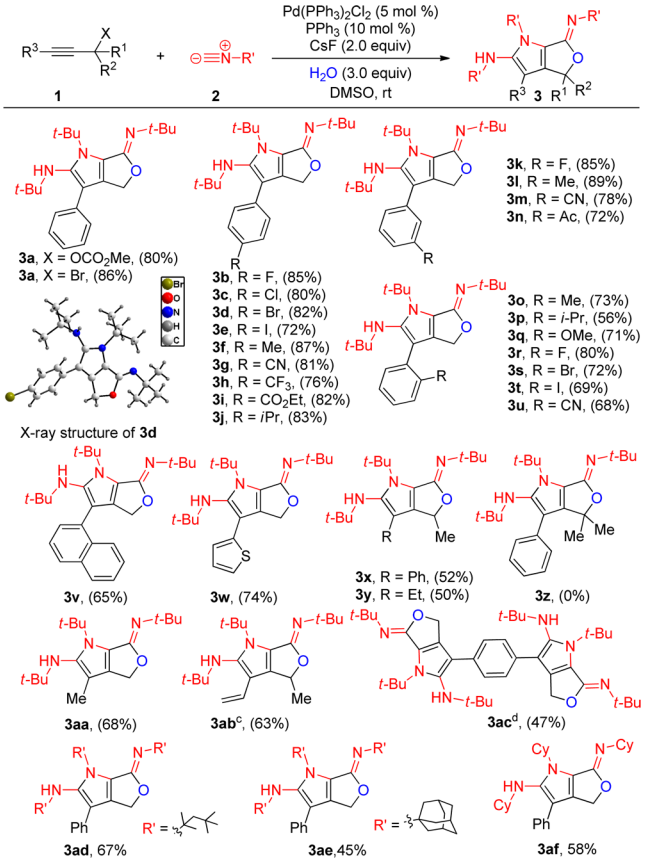
entry	base	ligand	solvent	temp (°C)	yield of **3a** (%)[b]	yield of **4a** (%)[b]
1	CsF	PPh_3	DMSO	80	50	31
2	CsF	PPh_3	CH_3CN	80	42	26
3	CsF	PPh_3	DMF	80	47	27
4	CsF	PPh_3	toluene	80	35	22
5	K_2CO_3	PPh_3	DMSO	80	16	5
6	Et_3N	PPh_3	DMSO	80	20	9
7	–	PPh_3	DMSO	80	n.d.	n.d.
8[c]	**CsF**	**PPh_3**	**DMSO**	**rt**	**85 (80)**	**trace**
9	CsF	PPh_3	DMSO	110	10	68
10	CsF	$P(t\text{-}Bu)_3$	DMSO	110	20	56
11	CsF	DPPE	DMSO	110	12	70
12	CsF	DPPF	DMSO	110	12	73
13[d]	CsF	DPPF	DMSO	110	10	76
14[d,e]	**CsF**	**DPPF**	**DMSO**	**110**	**8**	**82 (75)**

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.70 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), ligand (10 mol %), base (2.0 equiv), and H_2O (3.0 equiv) in indicated solvent (2 mL) at 80 °C for 2 h. [b]Determined by GC analysis. Dodecane was used as an internal standard. Data in parentheses were isolated yield. [c]For 8 h. [d]CsF (0.5 equiv), DPPF (5 mol %). [e]**2a** (0.50 mmol) adding in three portions.

Interestingly, two products, **3a** and **4a**, were isolated after 2 h. Among various solvents tested, good conversions of the reactants were detected, while the selectivity was still unsatisfactory (entries 2–4). The yields of **3a** and **4a** were decreased without a base or using another base instead of CsF (entries 5–7). We were pleased to find that **3a** could be obtained as major product in 85% yield at room temperature after prolonging the reaction time to 8 h, while the yield of **4a** dropped dramatically (entry 8). Further experiments indicated that the selectivity of **4a** could improve with an increasing in temperature.[17] Next, ligands were tested. DPPF was identified as the best ligand in the formation of **4a** (entries 9–12). Finally, **4a** was isolated in 75% yield by reducing the amount of CsF to 0.5 equiv and adding the *tert*-butyl isocyanide (0.5 mmol) in three portions at 110 °C for 2 h.

Under the optimal reaction conditions, we then examined the scope of this reaction. As shown in Table 2, various functional groups could be tolerated such as methyl, halogen, ester, acyl, trifluoromethyl, and even nitrile groups. The structure of **3d** was further confirmed by X-ray crystallographic analysis.[18] The *Z* configuration of the imine structure was resulted from the steric effect. Pleasingly, a heterocyclic compound such as thiophene was tolerated with a 74% yield. As for a substrate derived from a secondary alkynol, **3x** could

Table 2. Substrate Scope[a,b]



[a]Reaction conditions A: **1** (0.20 mmol), **2** (0.70 mmol), $Pd(PPh_3)_2Cl_2$(5 mol %), PPh_3 (10 mol %), H_2O (3.0 equiv), and CsF (2.0 equiv) in 2 mL of DMSO at room temperature for 8 h. [b]Isolated yields. [c]Hex-3-yne-2,5-diyl dimethyl dicarbonate as substrate. [d]**2a** (1.2 mmol).

also be obtained albeit in moderate yield (52%). However, **3z** was not detected under the optimal reaction conditions. When R^3 was an alkyl group, the reaction proceeded smoothly to afford the desired products **3y** and **3aa** in 50% and 68% yields, respectively. We then evaluated the reactivity of various isocyanides. Alkyl isocyanides such as 1,1,3,3-tetramethylbutyl-isocyanide, adamantyl isocyanide, and cyclohexane isocyanide were compatible in this reaction.

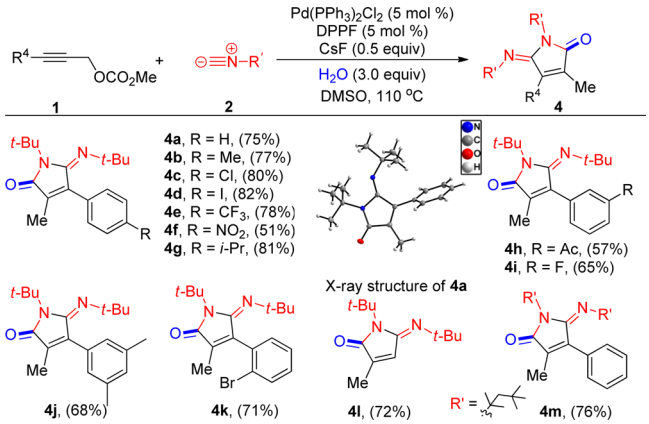
The selective formation of the 5-iminopyrrolone products was also achieved under different reaction conditions. The structure of **4a** was also confirmed by X-ray crystallographic analysis.[18] Next, the substrate scope was examined (Table 3). Various functional groups such as fluorine, chlorine, bromine, iodine, trifluoromethyl, nitro, and acyl were tolerated. In addition, terminal propargylic carbonate also transformed to the desired product smoothly.

For the secondary and third propargylic carbonates, new products **5a** and **5b** bearing an exocyclic double bond were obtained in 80% and 85% yields, respectively (Scheme 2). These results indicated that the multiple substituted alkenes were more stable and higher energy was necessary to promote the double bond isomerization.

Furthermore, this novel transformation and the following hydrolysis reaction gave various maleimide products, which are versatile building blocks and important synthons in organic chemistry[16b] (Scheme 3).

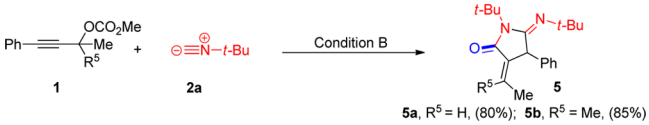
DOI: 10.1021/acs.orglett.6b02999
Org. Lett. XXXX, XXX, XXX–XXX

Table 3. Substrate Scope of 5-Iminopyrrolone[a,b]

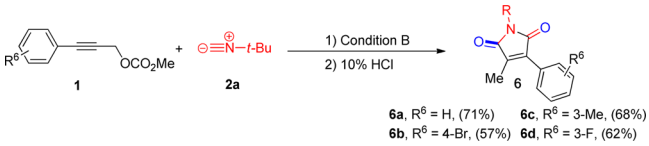


[a]Reaction conditions B: all reactions were performed with **1** (0.20 mmol), **2** (0.50 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), DPPF (5 mol %), H_2O (3.0 equiv), and CsF (0.5 equiv) in 2 mL DMSO at 110 °C for 2 h; Isocyanide was added in three portions. [b]Isolated yields.

Scheme 2. Scope of Secondary and Third Propargylic Carbonates with Double Isocyanide Insertions

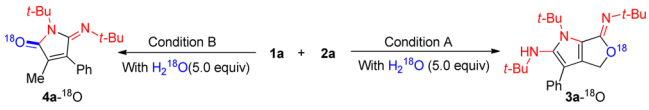


Scheme 3. Synthesis of maleimides



To gain some insights into the mechanism, ^{18}O-isotope labeling experiments were conducted. As depicted in Scheme 4,

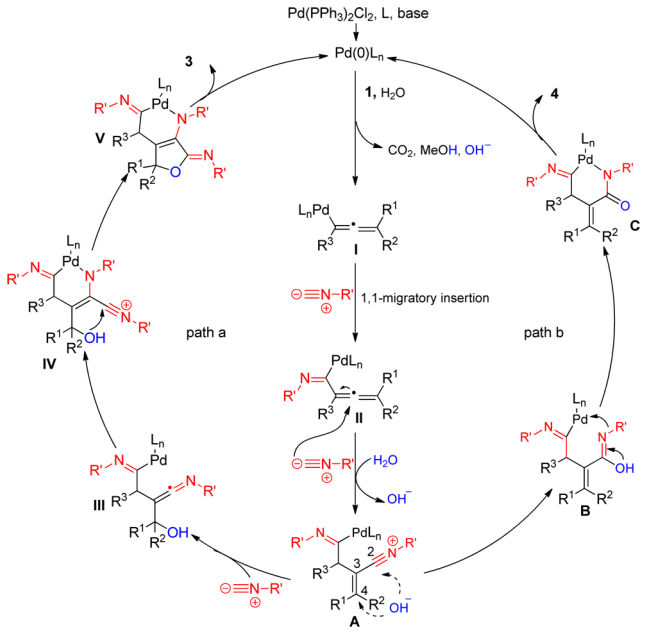
Scheme 4. Mechanistic Studies



the ^{18}O-containing products of **3a**-^{18}O and **4a**-^{18}O were obtained in 73% and 61% yields, respectively. This result indicated that the oxygen atoms of the products originated from water. In addition, **3a** and **4a** cannot be transformed to each other under the optimal reaction conditions, which indicated two different pathways might be involved.

On the basis of the above-mentioned results, a tentative mechanism for this palladium-catalyzed MCR is proposed (Scheme 5).[17] It was initiated by the oxidative addition of **1** to the palladium(0) catalysis, delivering the allenylpalladium species **I**[5] which then transformed to the key intermediate **A** via 1,1-migratiory insertion and the subsequent nucleophilic attack of isocyanides.[19] Next, H_2O as a nucleophilic reagent attacked the intermediate **A** (C2 or C4), determining the selectivity in the formation of products **3** and **4**. In path a, H_2O attacked at the C4 position to give the keteniminium intermediate **III**[17,20] which was then attacked by isocyanide to form the intermediate **IV**. Finally, products **3** were obtained

Scheme 5. A Tentative Mechanism



via the reductive elimination of **V** and subsequent aromatization. Alternatively, in path b, H_2O attacked at the C2 position to produce the intermediate **B** which underwent reductive elimination and isomerization to produce the 5-iminopyrrolones (**4**). This mechanism was consistent with the fact that compounds **3** were the kinetically favored products, which were obtained at room temperature. The steric effect favored the C4 attack when $R^1 = R^2 = H$. With the increase of steric hindrance at the C4 position, the yields of products **3** dropped dramatically (see Supporting Information for details). In contrast, path b was the thermodynamically favored process for the amide intermidate **B**, which was more stable than the keteniminium intermediate **III**.

In conclusion, an intriguing palladium-catalyzed multicomponent reaction (MCR) of propargylic carbonates with isocyanides has been developed. Compared with the extensively studied migratory insertion of isocyanides to aryl- or alkenylpalladium species, the *in situ* formed allenylpalladium species bearing multiple reaction sites allowed the successive insertion of multiple isocyanides in an orderly manner. A broad range of (*Z*)-6-imino-4,6-dihydro-1*H*-furo[3,4-*b*]pyrrol-2-amines and (*E*)-5-iminopyrrolones were synthesized efficiently. The selectivity of the products can be controlled by the reaction conditions. The detailed reaction mechanism and further synthetic applications of this transformation are forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02999.

Typical experimental procedure and characterization for all products (PDF)

Crystallographic data for **3d** (CIF)

Crystallographic data for **4a** (CIF)

DOI: 10.1021/acs.orglett.6b02999
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21490572, 2147205, and 21420102003), and Pearl River S&T Nova Program of Guangzhou (201610010160) for financial support.

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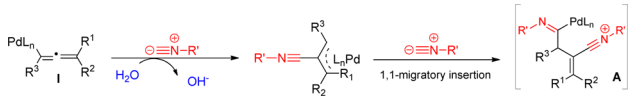
(18) CCDC 1457794 (**3d**) and CCDC 1457793 (**4a**) contain the supplementary crystallographic data. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(19) Nucleophilic and then 1,1-migratory insertion of isocyanides may also potentially form the intermediate **A**.



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DOI: 10.1021/acs.orglett.6b02999
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