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Palladium-Catalyzed Three-Component Reaction of Propargyl Carbonates, Isocyanides, and Alcohols or Water: Switchable Synthesis of Pyrroles and Its Bicyclic Analogues

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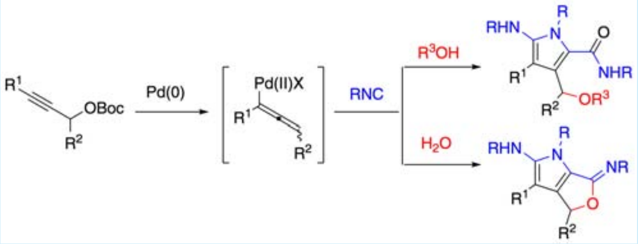
Ⓢ *Supporting Information*

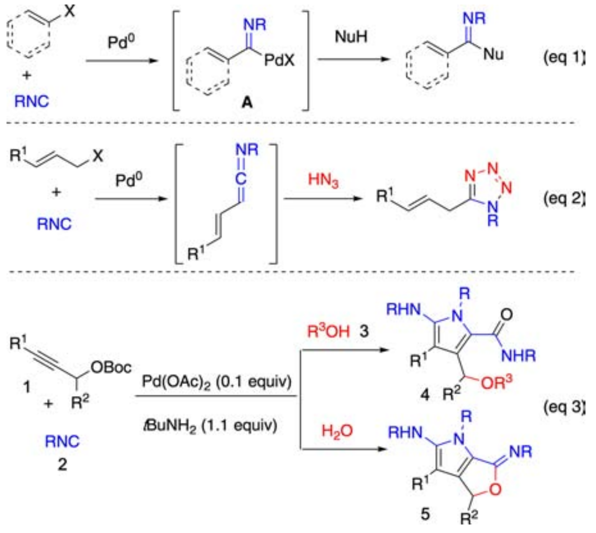
ABSTRACT: In the presence of a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of *tert*-butylamine, the reaction of propargyl carbonates, isocyanides, and alcohols afforded polysubstituted aminopyrroles in good yields. Using water as a nucleophile instead of alcohol, the same reaction provided 1,4-dihydro-6*H*-furo[3,4-*b*]pyrrol-6-imines. A triple isocyanide insertion to the hypothetic (σ-allenyl)palladium(II) intermediate was involved in these ABC_3-type multicomponent reactions. The key role of *tert*-butylamine was accounted for by its reaction with in situ generated carbon dioxide to form the carbamic acid, which in turn served as a nucleophile to trap the nitrilium intermediate.



The successful exploitation of transition-metal-catalyzed isocyanide insertion process has led to the development of many efficient protocols for the synthesis of a variety of acyclic *N*-containing architectures and *N*-heterocycles.[1] Since Whitby's seminal papers on the Pd-catalyzed three-component reaction of isocyanides, arylhalides, and amines,[2] a tin-free version of Kosugi and Migita's synthesis of amidines,[3] many elegant transformations have been reported in the past dozen years.[4,5] All of these reactions involved the generation of aryl or vinyl imidoylpalladium species followed by ligand exchange and reductive elimination to afford products with the formation of a key $C(sp^2)-C(sp^2)$ bond (eq 1, Scheme 1). Transformations leading to the formation of a $C(sp^3)-C(sp^2)$ bond via an alkyl imidoylpalladium intermediate remain scarce.[6]

We have very recently communicated a novel synthesis of ketenimines by a Pd-catalyzed reaction of allyl carbonates with isocyanides (eq 2, Scheme 1).[7−9] As a continuation of this project, we became interested in the Pd-catalyzed reaction of propargyl carbonates with isocyanides. A recent paper by Wu, Jiang and co-workers[10] dealing with the same transformation prompted us to disclose herein our own results. As it is shown (eq 3, Scheme 1), Pd-cataylzed reaction of propargyl carbonates **1**, isocyanides **2**, and alcohols **3** in the presence of a stoichiometric amount of *tert*-butylamine afforded 2-aminopyrroles **4** in good yields. When water was used as a nucleophile under otherwise identical conditions, the reaction provided bicyclic 1,4-dihydro-6*H*-furo[3,4-*b*]pyrrol-6-imines **5**. We note that multicomponent synthesis of 2-aminopyrroles **4**, which is the main focus of the present communication, was not described in Wu and Jiang's paper. 2-Aminopyrrole has been found as a key structure unit in natural products[11] and is present in many bioactive molecules.[12] Although a large number of new pyrrole syntheses have been reported in recent years,[13] relatively few examples are known for the efficient synthesis of 2-aminopyrroles.[14]

Scheme 1. Pd-Catalyzed Isocyanide Insertion Reactions



Ethyl propargyl carbonate **1a**, *tert*-butyl isocyanide **2a**, and ethanol **3a** were chosen as test substrates. With the knowledge that isocyanides are good ligands for palladium, $Pd(OAc)_2$ was chosen as a precatalyst in the absence of a phosphine ligand. As it is summarized in Table 1, the reaction failed to provide

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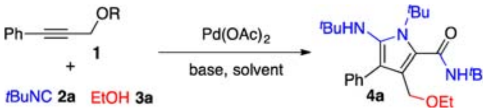
Table 1. Multicomponent Synthesis of Pyrrole 4a: Survey of Reaction Conditions[a]



entry	R	Pd loading	solv	base	yield (%)[b]
1	CO_2Et (**1a**)	5 mol %	DCE	–	–
2	CO_2Et (**1a**)	5 mol %	DCE	K_2CO_3	–
3	CO_2Et (**1a**)	5 mol %	DCE	K_3PO_4	–
4	CO_2Et (**1a**)	5 mol %	DCE	$BnNH_2$	11
5	CO_2Et (**1a**)	5 mol %	DCE	$BuNH_2$	35
6	CO_2Et (**1a**)	5 mol %	DCE	$tBuNH_2$	42
7	CO_2Et (**1a**)	–	DCE	$tBuNH_2$	–
8[c]	CO_2Et (**1a**)	10 mol %	DCE	$tBuNH_2$	56
9[c]	CO_2Et (**1a**)	10 mol %	DCE	$tBuNH_2$	69
10[c,d]	CO_2Et (**1a**)	10 mol %	DCE	$tBuNH_2$	65
11[c]	CO_2Et (**1a**)	10 mol %	THF	$tBuNH_2$	13
12[c]	CO_2Et (**1a**)	10 mol %	MeCN	$tBuNH_2$	29
13[c]	CO_2Et (**1a**)	10 mol %	toluene	$tBuNH_2$	50
14[c,e]	CO_2Et (**1a**)	10 mol %	DCE	$tBuNH_2$	trace
15[c,f]	CO_2Et (**1a**)	10 mol %	DCE	$tBuNH_2$	54
16[c]	$CO_2{}^tBu$ (**1b**)	10 mol %	DCE	$tBuNH_2$	77
17[c]	Ac (**1c**)	10 mol %	DCE	$tBuNH_2$	–

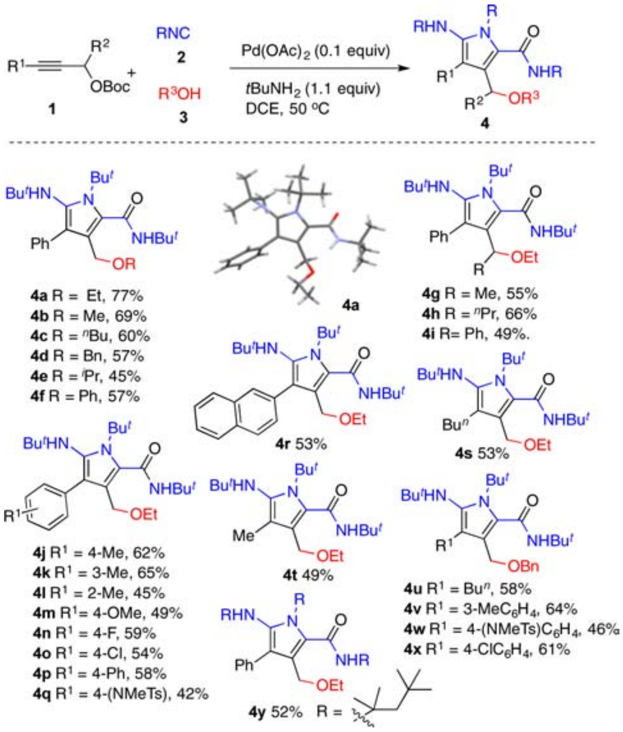
[a] Standard conditions: propargyl carbonate **1** (0.2 mmol), *t*BuNC (**2a**, 0.31 mmol), EtOH (5.0 equiv), base (1.1 equiv), solvent (1.0 mL), 50 °C, Ar, 8 h. [b] Isolated yield. [c] *t*BuNC (0.8 mmol). [d] EtOH (10.0 equiv). [e] The reaction was performed at room temperature. [f] The reaction was carried out at 80 °C.

any insertion product in the absence of base or in the presence of an inorganic base (entries 1–3). However, an *N*,2,3,4,5-pentasubstituted pyrrole **4a** was isolated in 11% isolated yield when benzylamine (1.1 equiv) was added to the reaction mixture (entry 4, Table 1). Using hindered and less nucleophilic *tert*-butylamine as a base under otherwise identical conditions, the yield of pyrrole **4a** was increased to 42% (entry 6, Table 1). The structure of compound **4a** was determined by NMR and HRMS and was fully confirmed by X-ray diffraction analysis.

Since 3 mol of isocyanide was incorporated into the product **4a**, an excess of *t*BuNC (mol ratio **2a**/**1a** = 4/1) was used for the subsequent survey of reaction conditions. After having screened the catalyst loading, the solvent, the reaction temperature, and the nature of the carbonate, the optimum conditions consisted of performing the reaction of **1b** (*tert*-butoxycarbonate) with **2a** and EtOH (**3a**, 5.0 equiv) in 1,2-dichloroethane (DCE) in the presence of $Pd(OAc)_2$ (0.1 equiv) and $tBuNH_2$ (1.1 equiv) at 50 °C (entry 16). Under these conditions, pyrrole **4a** was isolated in 77% yield. Of note, the above reaction did not take place in the absence of $Pd(OAc)_2$ (entry 7, Table 1) and the reaction of propargyl acetate **1c** with **2a** failed to produce **4a** under optimized conditions (entry 17).

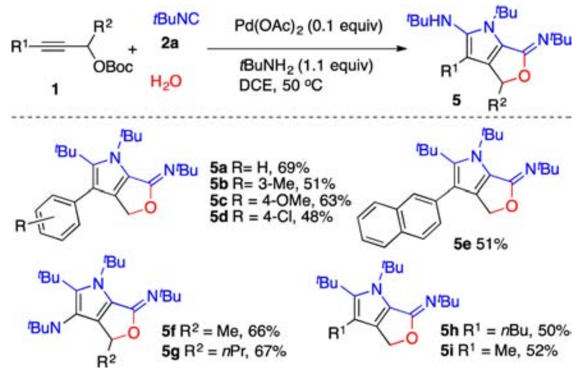
The scope of the reaction was next examined under the standard conditions [$Pd(OAc)_2$ (0.1 equiv), $tBuNH_2$ (1.1 equiv), DCE (*c* 0.2 M), 50 °C]. As illustrated in Scheme 2, primary alcohols (MeOH, EtOH, *n*BuOH, BnOH), a secondary alcohol (*i*PrOH), and phenol (PhOH) participated in this reaction to furnish the corresponding pyrroles (**4a**–**4f**) in moderate to good yields. The presence of a substituent α to the carbonate function was tolerated leading to pyrroles **4g**–**4i** in reasonable yields. The aryl group with different electronic and steric properties (**4j**–**4r**, **4v**–**4x**) as well as alkyl substituents (**4s**, **4t**, **4u**) at the alkyne terminal position were compatible to the reaction conditions. 1,1,3,3-Tetramethylbutyl isocyanide took part in the reaction to afford **4y** in 52% yield. However, due to the strong coordinating properties of the isocyano group, primary and secondary isocyanides failed to participate in this reaction.[15]

Scheme 2. Catalytic Multicomponent Synthesis of 2-Aminopyrroles 4



Water was next used as a nucleophile due to the hypothesis that an intermediate with multiple electrophilic centers might be produced in the above domino process.[16] To our delight, the reaction of **1a**, **2a**, and H_2O (5.0 equiv) under our standard conditions furnished indeed bicycle **5a** in 69% isolated yield. As presented in Scheme 3, the reaction was quite general with respect to the structure of propargyl carbonates. Alkyl and aryl substituents with different electronic properties (R^1 and R^2) are tolerated to afford 1,4-dihydro-6*H*-furo[3,4-*b*]pyrrol-6-imines **5a**–**5i** in good yields. The synthesis of this bicycle has been reported recently by Wu, Jiang and co-workers.[10]

Scheme 3. Pd-Catalyzed Multicomponent Synthesis of 1,4-Dihydro-6*H*-furo[3,4-*b*]pyrrol-6-imines 5



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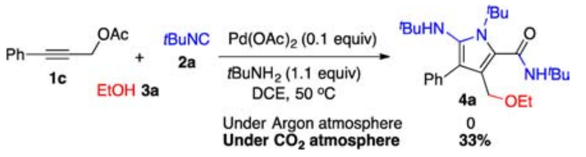
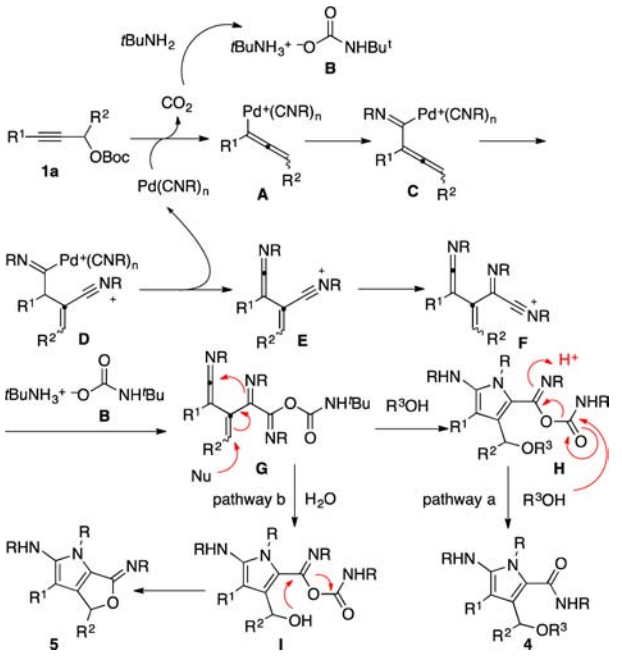
The critical role of *t*BuNH$_2$ played in our reactions is intriguing. Together with the fact that the propargyl acetate **1c** failed to react with *t*BuNC (**2a**) and EtOH (**3a**) under our reaction conditions prompted us to assume that carbon dioxide generated in the case of propargyl carbonate **1a** might play a role. Indeed, performing the reaction of acetate **1c** with **2a** and **3a** under a CO$_2$ atmosphere under otherwise identical conditions afforded pyrrole **4a** in 33% yield (Scheme 4).

Scheme 4. Role of Carbon Dioxide: A Control Experiment



Scheme 5. Possible Reaction Pathway



On the basis of the aforementioned experimental results, a possible catalytic cycle was proposed to account for the formation of both compounds **4** and **5** (Scheme 5). Addition of isocyanide coordinated Pd(0) species, generated in situ from Pd(OAc)$_2$, to **1a** would produce (σ-allenyl)palladium(II) species **A** with concurrent generation of CO$_2$.[17] The latter would be trapped by *t*BuNH$_2$ to afford carbamate anion **B**.[18] Migratory insertion of isocyanide would produce **C**[19] which, upon nucleophilic addition of isocyanide, would furnish nitrilium intermediate **D**.[20] β-Hydride elimination from the latter would generate ketenimine **E**. After addition of another equivalent of isocyanide, interception of the resulting nitrilium by carbamate anion **B** would afford **G**.[21] 1,4-Addition of alcohol onto the conjugated imine **G** followed by cyclization of the resulting enamine onto the ketenimine would furnish aminopyrrole **H**, which, upon the second nucleophilic attack of alcohol, would produce the observed product **4** (pathway a). On the other hand, 1,4-addition of H$_2$O onto the conjugated imine **G** would produce **I** which then underwent intramolecular acylation of the resulting alcohol to afford the bicycle **5** (pathway b). Overall, 3 equiv of isocyanide reacted with a (σ-allenyl)palladium(II) intermediate in an orchestrated manner to afford highly functionalized 2-aminopyrroles and its bicyclic derivatives. In spite of the great progress achieved on the Pd-catalyzed imidoylative process, multicomponent reactions involving controlled double or triple insertion of isocyanides remained uncommon.[22]

In conclusion, two Pd-catalyzed multicomponent reactions were developed. In the presence of a catalytic amount of Pd(OAc)$_2$ and a stoichiometric amount of *tert*-butylamine, the reaction of propargyl carbonates, isocyanides, and alcohols afforded pentasubstituted pyrroles in good yields. Using water as a nucleophile, the reaction was diverted to produce 1,4-dihydro-6*H*-furo[3,4-*b*]pyrrol-6-imines. A triple isocyanide insertion to the hypothetic (σ-allenyl)palladium(II) intermediate was involved in these ABC$_3$-type multicomponent reactions.[23] The key role of *tert*-butylamine to the occurrence of the process was accounted for by its reaction with in situ generated carbon dioxide to form the carbamic acid, which in turn served as a nucleophile to trap the nitrilium intermediate.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03592.

Experimental procedures, product characterization data, ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

X-ray crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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