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Pd(II)-Catalyzed Tandem Heterocyclization of 1-(1-Alkynyl)cyclopropyl Oxime Derivatives for the Synthesis of Functionalized Pyrroles

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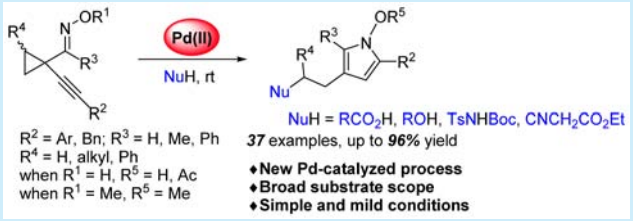
Supporting Information

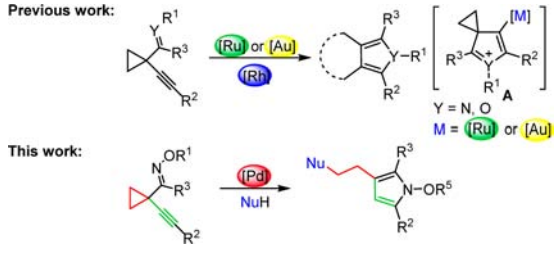
ABSTRACT: An efficient approach for the synthesis of highly functionalized pyrroles has been developed by a $Pd(TFA)_2$-catalyzed tandem heterocyclization of 1-(1-alkynyl)cyclopropyl oxime derivatives under mild conditions. The reaction first proceeded via an intramolecular nucleophilic attack followed by a ring-opening process and then intermolecular nucleophilic attack as well as protonation to afford the desired products in moderate to excellent yields.



Among all of the nitrogen-containing heterocycles, pyrrole is one of the most important motifs in organic chemistry. The synthesis and reactivity of pyrrole and its derivatives have attracted continuing interest over the years in natural product synthesis,[1] medicinal chemistry,[2] materials science,[3] and supramolecular chemistry[4] due in large part to their unique structures.

For this reason, various methods for the synthesis of highly substituted pyrroles and their derivatives have been developed.[5] In addition to traditional approaches, a number of transition-metal-catalyzed methods have also been extensively investigated.[6] However, new and practically useful synthetic methods are still highly desirable. Over the past decades, 1-(1-alkynyl)cyclopropyl compounds have been used to efficiently construct highly substituted furans[7] and pyrroles[8] through Au-, Rh-, or Ru-catalyzed tandem cyclization reactions (Scheme 1). In the cases of Au- or Ru-catalyzed ones, the reactions proceed first through the coordinate with the alkynyl moiety in substrates, leading to heterocyclization and thus giving the intermediate **A**. Different from Au and Ru, the Rh(I)-catalyzed cyclization takes place first with oxidative addition of cyclopropane, generating rhodacyclobutane and then undergoing a rapid intramolecular nucleophilic attack to fused furan- or pyrrole-derived rhodacyclopentane and the subsequent insertion of carbon monoxide and reductive elimination to furnish the products. Palladium salts and complexes have been extensively utilized in various cross-coupling reactions[9] and C−H and/or C−C bond activations.[10] Application in the heterocyclization of 1-(1-alkynyl)cyclopropyl compounds has never been reported before. We envisaged that the Pd complex could be used as a carbophilic π-acid for the activation of 1-(1-alkynyl)cyclopropyl compounds, therefore giving the corresponding heterocyclization products. Herein, we report a novel and efficient Pd(II)-catalyzed tandem heterocyclization of 1-(1-alkynyl)cyclopropyl oxime derivatives for the production of functionalized pyrroles under mild conditions (Scheme 1, this work).

Scheme 1. Tandem Cyclization Reaction of 1-(1-Alkynyl)cyclopropyl Derivatives



The initial examination on the reaction of 1-(1-alkynyl)-cyclopropyl oxime ether **1a** was carried out in acetic acid (AcOH) at room temperature in the presence of $Pd(OAc)_2$ (5 mol %) under argon atmosphere. We were pleased to find that the desired product **2a** was given in 88% NMR yield within 2 h (Table 1, entry 1), and its structure was determined by 2D spectrum (see the Supporting Information). This result inspired us to explore better conditions for this reaction, and the results are summarized in Table 1. The use of other Pd catalysts such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $Pd(TFA)_2$, and $Pd(OTf)_2$ revealed that $Pd(TFA)_2$ and $Pd(OTf)_2$ were both more efficient catalysts, affording **2a** in 93% and 94% yields, respectively (Table 1, entries 2−5). Because $Pd(OTf)_2$ is very hygroscopic upon exposure to air,[11] we chose $Pd(TFA)_2$ as the catalyst in this reaction. The catalyst loading has also been examined, and we found that increasing the employed amount of $Pd(TFA)_2$ to 10 mol % afforded **2a** in a yield similar to that

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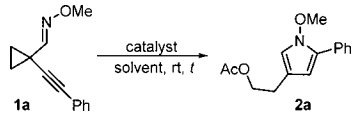
Table 1. Optimization of the Reaction Conditions[a]



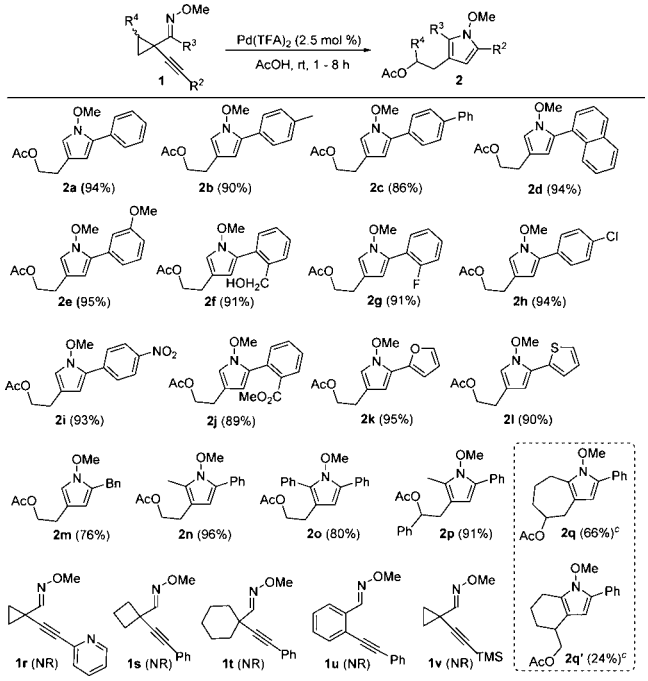
entry	cat. (mol %)	solvent	time (h)	yield[b] (%)
1	$Pd(OAc)_2$ (5)	AcOH	2	88
2	$Pd_2(dba)_3$ (2.5)	AcOH	2	82
3	$Pd(PPh_3)_4$ (5)	AcOH	2	90
4	$Pd(TFA)_2$ (5)	AcOH	2	94
5	$Pd(OTf)_2$ (5)	AcOH	2	93
6	$Pd(TFA)_2$ (10)	AcOH	2	93
7	$Pd(TFA)_2$ (2.5)	AcOH	2	97 (94)[c]
8	$Pd(TFA)_2$ (1.0)	AcOH	2	90
9[d]	$Pd(TFA)_2$ (5)	AcOH	2	21
10	$Pd(TFA)_2(PPh_3)_2$ (5)	AcOH	2	43
11[e]	$Pd(TFA)_2$ (5)	CH_2Cl_2	2	62
12		AcOH	24	0
13	$Sc(OTf)_3$ (5)	AcOH	24	trace
14	$\{Rh(CO)Cl_2\}_2$ (2.5)	AcOH	24	trace
15	$Ru_3(CO)_{12}$ (2.5)	AcOH	24	trace
16	$Pt(COD)Cl_2$ (5)	AcOH	24	74
17	PPh_3AuOTf (5)	AcOH	24	79

[a]The reaction conditions: 0.1 M in solvent unless otherwise specified. [b]The yield was determined by ^1H NMR spectroscopic data using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]The ligand PPh_3 (5 mol %) was added. [e]With 5 equiv of AcOH.

using 5 mol % of catalyst (Table 1, entry 6). However, reducing the employed $Pd(TFA)_2$ to 2.5 mol % produced **2a** in 97% NMR yield along with 94% isolated yield under otherwise identical conditions (Table 1, entry 7). Further reducing the catalyst loading to 1 mol % did not improve the reaction outcome, giving **2a** in 90% yield (Table 1, entry 8). In addition, we also found that the yield of **2a** would be lower when PPh_3 was added as a ligand or even using $Pd(TFA)_2(PPh_3)_2$ as the catalyst, suggesting that the addition of extra ligand would hamper the coordination of substrate and Pd catalyst (Table 1, entries 9 and 10). Next, we utilized different solvents with 5 equiv of AcOH instead of using AcOH as the solvent and found that the reaction became less effective, giving **2a** in 62% yield (Table 1, entry 11; for more details about the optimization of this reaction, see Table S1 in the Supporting Information). No reaction occurred in the absence of Pd catalyst (Table 1, entry 12). Lewis acid $Sc(OTf)_3$ (5 mol %) and other transition-metal catalysts such as $\{Rh(CO)Cl_2\}_2$ (2.5 mol %) and $Ru_3(CO)_{12}$ (5 mol %) produced **2a** in trace amounts in AcOH at room temperature (Table 1, entries 13−15). $Ph_3PAuOTf$ and $Pt(COD)Cl_2$ could also catalyze the reaction but gave **2a** in lower yields than those catalyzed by $Pd(TFA)_2$ (Table 1, entries 16 and 17).

With the identification of the best reaction conditions, we investigated the generality of the reaction using a variety of oxime ethers **1b−v** (R^4 = H, Scheme 2). Regardless of whether electron-donating or electron-withdrawing groups were introduced on the aromatic R^2 group, the reactions proceeded smoothly, affording the desired products **2b−j** in high yields. The heteroaromatic R^2 group also tolerated the standard conditions, giving the corresponding products **2k** and **2l** in good yields. The substituent on the terminal alkyne could also be an aliphatic group such as Bn, affording the desired product **2m** in 76% yield. Furthermore, the substituent on oxime ether

Scheme 2. Substrate Scope of 1[a,b]



[a]Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol) and $Pd(TFA)_2$ (2.5 mol %) in AcOH (2.0 mL), rt. [b]Isolated yields are provided. [c]The yield was determined by ^1H NMR spectroscopic data, **2q**/**2q′** = 4.2/1.

moiety could be an alkyl or an aryl group, in which the desired products **2n** and **2o** were produced in 96% and 80% yields, respectively. Phenyl-substituted cyclopropane **1p** (R^4 = Ph, *E*-configuration)[8a] could afford the corresponding product **2p** in 91% yield with excellent regioselectivity. However, as for the bicyclic substrate **1q** (*E*-configuration),[8a] the desired product **2q** was obtained in 66% yield along with an isomeric product **2q′** in 24% yield.

In the cases of oxime ethers **1s**, **1t**, and **1u** bearing cyclobutane, cyclohexane, or benzene, no reaction occurred under standard conditions, indicating that the cyclopropane is crucial in the reaction. For substrates **1r** and **1v**, the reactions did not give the desired products under the standard conditions. In the case of substrate **1r**, 2-pyridyl may coordinate with Pd(II) catalyst leading to the deactivation of it. The substrate **1v** may be hard to accept the nucleophilic attack of nitrogen atom because of the steric bulkiness and electronic effect of TMS group.

Besides AcOH, other nucleophiles have been also tested, and the results are shown in Scheme 3. The use of carboxylic acid, ibuprofen, afforded the desired product **3a** in 82% yield. Using alcohols as nucleophiles produced the corresponding products **3b−e** in 43−93% yields. Furthermore, the N-nucleophile and C-nucleophile could be also used in this reaction, affording the corresponding products **3f** and **3g** in 88% and 74% yields. In the cases of EtSH and $^nBuNH_2$, no reaction occurred under the standard conditions presumably because they may coordinate with Pd(II) catalyst, leading to the deactivation of Pd catalyst. The weak nucleophile such as indole did not afford the product, suggesting that a strong nucleophile is required in this reaction.

The 1-(1-alkynyl)cyclopropyl oxime **4** itself could also be used as substrate to synthesize the corresponding functionalized pyrroles upon $Pd(TFA)_2$ catalysis in $AcOH/Ac_2O$ or

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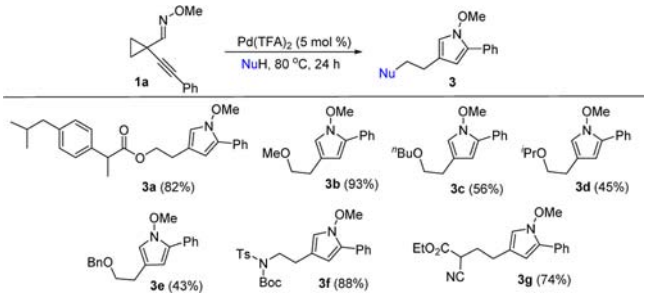
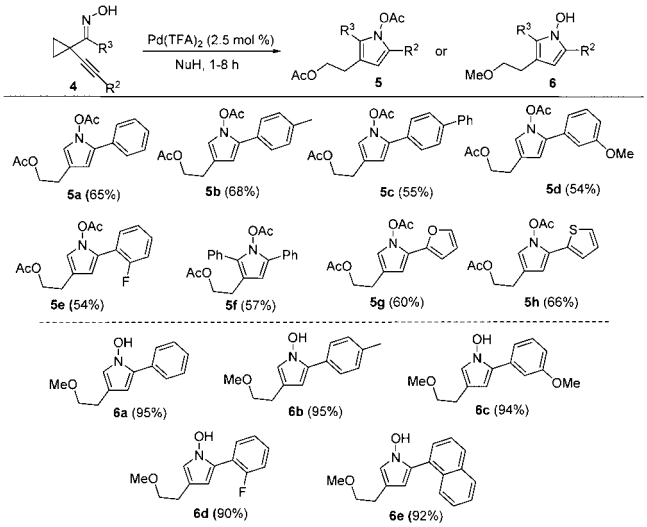
Scheme 3. Scope of the Employed Nucleophiles[a,b]



[a]Unless otherwise specified, all reactions were carried out using **1a** (0.4 mmol), NuH (0.8 mmol) and $Pd(TFA)_2$ (5 mol %) in DCM (0.4 mL), 80 °C, 24 h. [b]Isolated yields are provided.

methanol. The reaction outcomes and substrate scope are summarized in Scheme 4. The substituent on the alkyne

Scheme 4. Substrate Scope of 4[a−c]

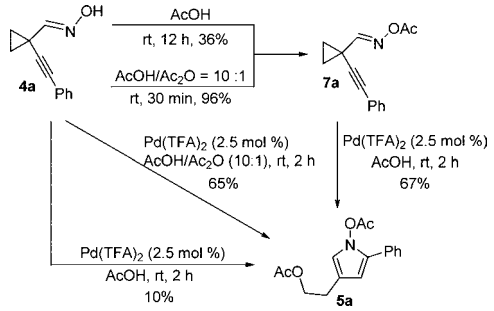


[a]Reaction conditions for **5**: **4** (0.2 mmol) and $Pd(TFA)_2$ (2.5 mol %) in $AcOH/Ac_2O$ (2.0 mL, v/v = 10:1), rt. [b]Reaction conditions for **6**: **4** (0.2 mmol) and $Pd(TFA)_2$ (2.5 mol %) in MeOH (2.0 mL), rt. [c]Isolated yields are provided.

functionality could be a variety of substituted phenyl rings as well as furyl and thienyl moieties, giving the desired products **5a−h** in moderate yields in $AcOH/Ac_2O$. The electronic property of the substituent at the phenyl ring did not have significant impact on the reaction outcome. Different from pyrroles **5**, 1*H*-pyrrol-1-ols **6**, which were difficult to synthesize by other methods,[12] could be easily obtained in excellent yields when MeOH was used as the nucleophile. Substrates **4** bearing either electron-donating or electron-withdrawing substituents at the benzene ring all afforded the corresponding products **6a−e** in good to excellent yields ranging from 90% to 95%.

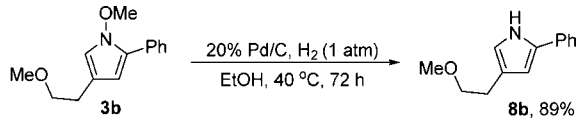
The control experiments were conducted using **4a** as substrate (Scheme 5). Stirring **4a** in AcOH afforded **7a** in 36% after 12 h, but stirring **4a** in $AcOH/Ac_2O$ (10:1) gave **7a** in 96% yield within 30 min, suggesting that adding Ac_2O accelerated the formation of **7a**. The further examination revealed that **5a** is derived from **7a** upon Pd(II) catalysis. Carrying out the reaction of **4a** directly in AcOH only afforded **5a** in 10% yield. The yields of pyrroles **5** produced in $AcOH/Ac_2O$ are lower than those of pyrroles **2** because the formed N-OAc can easily undergo the oxidative addition with Pd catalyst, causing the formation of some byproducts.[13] Carrying out the reaction in methanol gave pyrrol-1-ols **6** in high yields perhaps because the oxidative addition of N−OH bond to Pd catalyst is difficult to take place, thus suppressing the side reaction.

Scheme 5. Control Experiments



To show the synthetic utility of the product, hydrogenation of **3b** by H_2 in EtOH at 40 °C gave the corresponding pyrrole **8b** in 89% yield in the presence of Pd/C (20%) catalyst (Scheme 6).

Scheme 6. Transformation of the Product



To gain more insight into the reaction mechanism, the deuterium-labeling experiment of **1a** was performed in CD_3OD under the standard conditions, giving [D]-**3b** in 52% yield along with 99% D^1 and 14% D^2 incorporation (Scheme 7). The existence of 14% D^2 might be a consequence of electrophilic palladation and subsequent protonation of **3b** (for more details, see the Supporting Information).[14]

Scheme 7. Deuterium-Labeling Experiment

On the basis of above control and deuterium-labeling experiments, a plausible reaction mechanism has been outlined in Scheme 8. The coordination of Pd(II) to the alkyne moiety of **1a** generates intermediate **A**, which undergoes intramolecular nucleophilic attack by the nitrogen atom in oxime ether to give azocarbenium intermediate **B** via heterocyclization. The cyclopropane moiety in this intermediate undergoes intermolecular nucleophilic attack to afford the corresponding Pd−pyrrole species **C**. Subsequent protonation of **C** leads to the final product **2a** and regenerates the catalytic species.

In summary, we have disclosed a novel protocol for the synthesis of highly functionalized pyrroles by a Pd(II)-catalyzed tandem heterocyclization from 1-(1-alkynyl)cyclopropyl oxime derivatives under mild conditions. The reaction proceeds via a heterocyclization followed by a ring-opening process under nucleophilic attack and a sequential protonation to give the desired products in moderate to excellent yields. Further efforts

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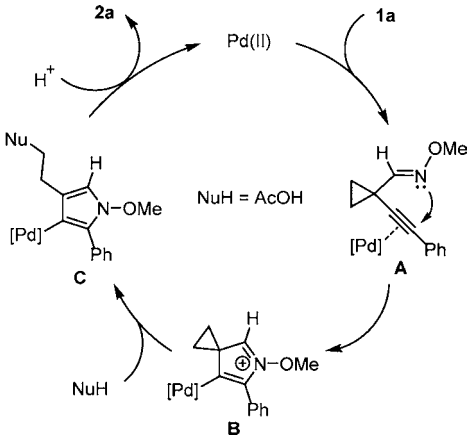
Scheme 8. Proposed Reaction Mechanism



are in progress to develop the application of this method in the synthesis of biologically active molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02068.

General experimental procedure and characterization data of the products; copies of NMR spectra(PDF)

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Notes

The authors declare no competing financial interest.

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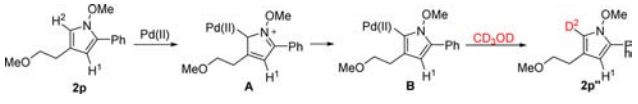

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