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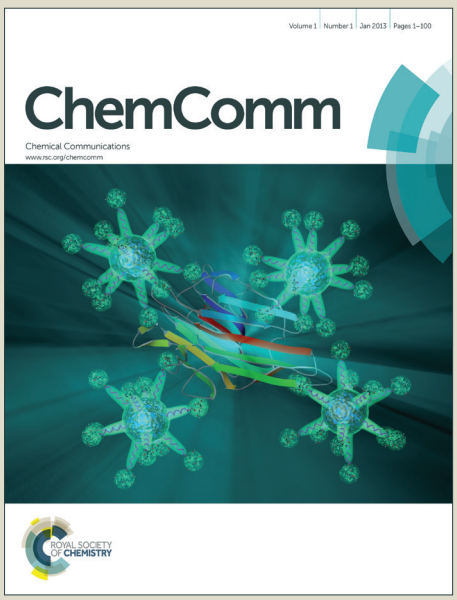

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ARTICLE TYPE

Regioselective Synthesis of Oxazole Derivatives *via* Palladium-Catalyzed and Copper-Mediated Cascade Oxidative Cyclization

Jia Zheng, Min Zhang, Liangbin Huang, Xiaohan Hu, Wanqing Wu, Huawen Huang, Huangfeng Jiang*

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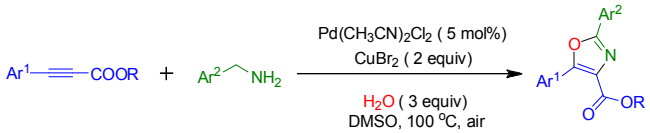
A novel Pd-catalyzed/Cu-mediated oxidative cyclization has been developed for the synthesis of trisubstituted oxazoles, which is thought to proceed through cascade formation of C-N and C-O bonds. In this protocol, four hydrogen atoms were removed and water was used as the oxygen atom source.

Alkynes as available substrates have been used widely in organic synthesis during the past decades.[1] In particular, effective transformations of alkynes catalyzed by transition metals have been reported as powerful strategies to construct C-C, C-O or C-N bonds.[2] For example, Au has been reported to make many efforts to the transformation of C-C triple bond due to its powerful soft Lewis acidic nature.[3] As well, Ag and Cu have also been disclosed to activate alkynes to construct multiple bonds in a single process.[4] In addition, besides playing an important role in C-C cross-coupling reactions, Pd also exhibits significance in the activation of unsaturated C-C bonds, which has drawn much attention in modern organic synthesis.[5] Our group has been focused on nucleopalladation process, such as aminopalladation, halopalladation and oxypalladation, which are practical approaches to transfer alkenes and alkynes efficiently.[6]

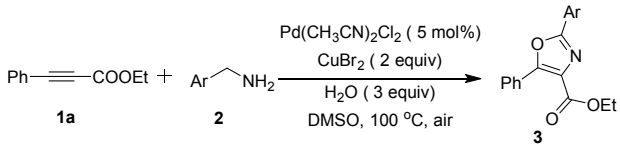
On the other hand, the oxazole moiety, which has attracted increasing attention, is a significant structure in numerous bioactive natural products.[7] Furthermore, a great number of pharmacologically synthetic molecules show biologically activities which are oxazole-containing.[8] Thus, various novel methods have been developed for the synthesis of this aromatic heterocycle (Scheme 1). Generally, they can be directly formed by the oxidation of oxazolines.[9] Another route to these structures is metal-catalyzed bimolecular annulation.[10] The intramolecular oxidative cyclization of precursors also provides a convenient access.[11] Some other methods, such as intramolecular Wittig reaction,[12] iodide-promoted oxidative coupling,[13] cyclization of propargylamides[14] have been developed as well. However, the development of simple and efficient methods for the preparation of trisubstituted oxazoles is still desirable. As our continuous interest in the oxidative functionalization of alkynes and heterocyclic compound synthesis,[6a, 6b, 6c] herein, we report a novel bimetal catalytic oxidative cyclization of propargyl esters and benzylamines to form oxazoles, with an oxygen atom obtained from water. As accessible starting materials, propargyl esters could be obtained from terminal alkynes.[15] This transformation is supposed to go through the cascade formation of C-N and C-O bonds, which affords an efficient and regioselective protocol to oxazoles.



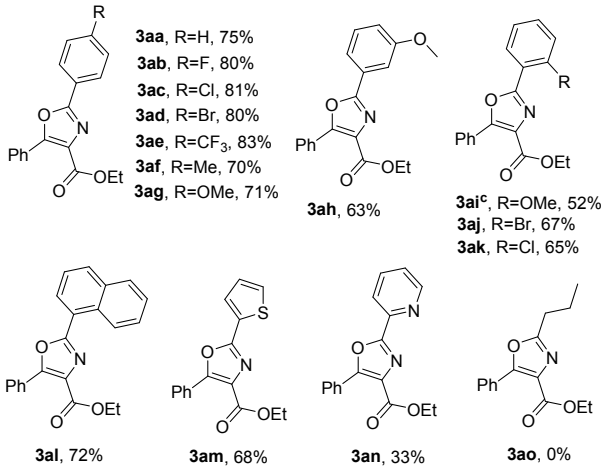
Scheme 1. Bimetal-catalyzed formation of oxazoles.

As the optimized conditions established (see ESI for details), we first investigated the scope of different benzylamines. As shown in Table 1, both electron-withdrawing groups (halogen or

Table 2. The reaction of different **2** with **1a**.[a, b]



1a **2** **3**

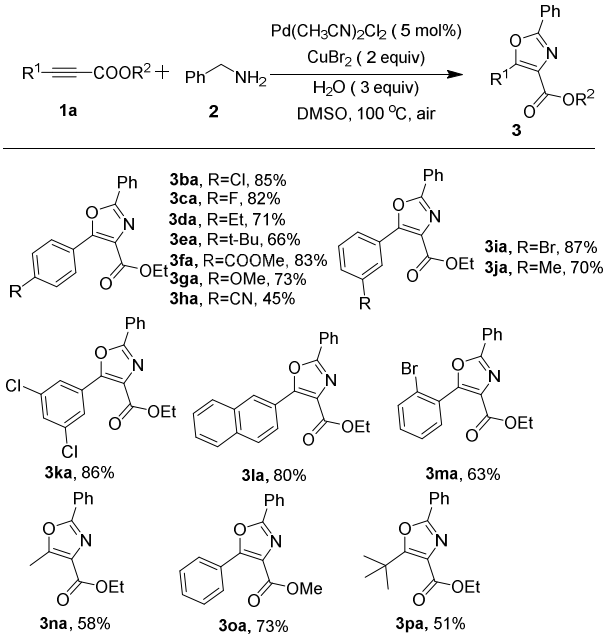


[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), H_2O (1.5 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol%) and $CuBr_2$ (2 equiv) in 1.5 mL DMSO under air at 100 °C for 8 h. [b] Isolated yield. [c] The reaction was stirred for 15 h.

trifluoromethyl, **3ab-3ae**) and electron-donating groups (methyl or methoxy, **3af-3ag**) were well tolerated in the *para*-position which gave good to high yields. However, the presence of *meta*- or *ortho*- substituents on the phenyl ring led to moderate yields (**3ah, 3ai-3ak**). The naphthyl-substituted amine also proceeded well with **1a** to give the desired oxazole **3al** in 72% yield. Besides, heterocyclic amines could be employed as an amine component in the reaction. Thiophene-2-methylamine and 2-pyridinemethanamine afforded the desired products **3am** and **3an** in 68% and 33% yields, respectively. Unfortunately, alkyl-substituted amines gave no desired product **3ao** in this reaction.

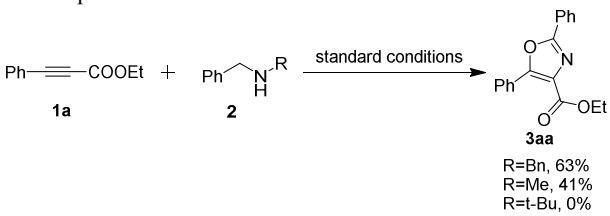
The transformation was further expanded to various substituted ethyl phenylpropiolates (Table 3). Reactions with electron-withdrawing groups, such as halogen or methoxycarbonyl (**3ba**, **3ca** and **3fa**) provided more than 80% yield of the oxazole products. Those electron-donating groups including alkyl and methoxy also proceeded well with benzylamine to form oxazoles in moderate to good yields (**3da**, **3ea** and **3ga**). Only in the case of cyano-substituted ethyl phenylpropiolate, 45% yield of **3ha** was obtained. Associated with the low yield of *N*-heterocyclic amine (Table 2, **3an**), *N*-containing group had a negative effect on the reaction outcome. Besides, *meta* methyl-, bromo- and 3,5-dichloro-substituted component worked well as *para* substituent (**3ia-3ka**). Compared with *meta*-substituted group, *ortho*-substituted one offered relatively lower yield (**3ia** *v.s.* **3ma**). Furthermore, ethyl naphthylpropiolate could be smoothly transformed into the desired products with high yield (**3la**). It is noteworthy that aliphatic substituents were also tolerated in this protocol, which gave the corresponding products **3na** and **3pa** in 58% and 51% yields respectively, suggesting that the transformation is applicable to both aliphatic and aromatic propargyl ester. When ethyl phenylpropiolate was switched to methyl phenylpropiolate, a close yield was obtained (**3oa**). To further confirm the structure, X-ray crystallographic analysis of **3ka** was given (see ESI for details).[16]

Table 3. The reaction of different **1** with **2a**.[a, b]



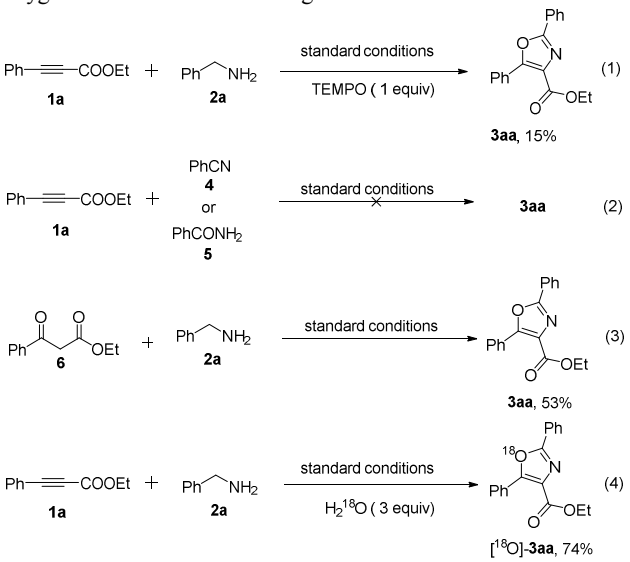
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), H_2O (1.5 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol%) and $CuBr_2$ (2 equiv) in 1.5 mL DMSO under air at 100 °C for 8 h. [b] Isolated yield.

Finally, some *N*-substituted benzylamines were subjected to this transformation (Scheme 2). Desired product **3aa** was obtained in 63% and 41% yields, respectively when using *N*-methylbenzylamine and *N*,*N*-dibenzylamine as the substrates. However, when substituted group was changed to *t*-Bu, no desired product was detected.



Scheme 2. The scope of *N*-substituted benzylamines.

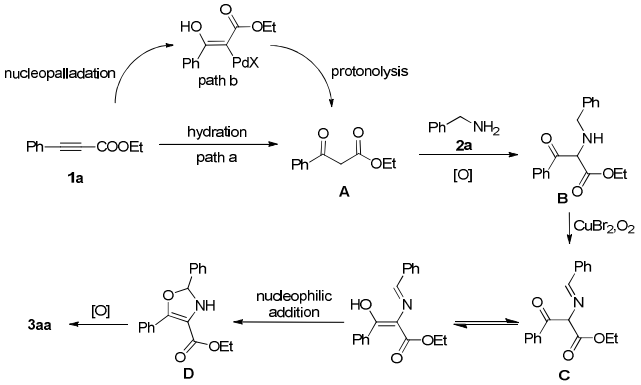
To gain a deeper insight into the mechanism of this cascade oxidative cyclization, several control experiments were conducted. The desired product was only obtained in very low yield when TEMPO was added [Scheme 3, Eq. (1)]. No desired product **3aa** was generated when benzonitrile **4** or benzamide **5** reacted with benzylamine **2a** under the standard conditions, which might exclude that **4** or **5** was the intermediate in this reaction [Scheme 3, Eq. (2)]. Moreover, when changing ethyl phenylpropiolate (**1a**) to ethyl benzoylacetate, 53% yield of **3aa** was obtained [Scheme 3, Eq. (3)]. Subsequently, we performed ^{18}O-labled experiments to confirm the oxygen atom source. The reaction of **1a** and **2a** generated ^{18}O-labeled product [^{18}O]-**3aa** in 74% yield when $H_2{}^{18}O$ was employed under the standard conditions [Scheme 3, Eq. (4)], which demonstrated that the oxygen atom of the oxazole ring came from water.



Scheme 3. Control experiments.

On the basis of experimental results above, a plausible mechanism for this cascade oxidative cyclization is proposed in Scheme 4. This reaction might be initiated by hydration of **1a** (path a), or oxypalladation of **1a** followed by protonolysis (path b), to generate intermediate **A.** Next, intermediate **B** was formed by the reaction of intermediate **A** and benzylamine **2a** *via*

oxidative amination.[17] Afterward, intermediate **B** could be oxidized by O_2 and Cu^{II} to give intermediate **C**. Then intermediate **D** was obtained by nucleophilic addition. Finally, the oxidation of intermediate **D** afforded the desired product **3aa**.



Scheme 4. Possible mechanism for this cascade oxidative cyclization.

In summary, we have developed a novel and efficient approach to forge C-N and C-O bonds in one process for the synthesis of trisubstituted oxazole derivatives. Products with great regioselectivity could be obtained in this bimetal catalytic transformation. Moreover, in this protocol four hydrogen atoms were removed and one oxygen atom was obtained from water, which exhibited high atom economy. The mechanism and synthetic applications of this reaction are under further studies in our laboratory and the results will be reported in due course.

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Notes and references

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. Fax: +86 20-87112906; Tel: +86 20-87112906; E-mail: jianghf@scut.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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