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Synthesis of 2-isoxazolyl-2,3-dihydrobenzofurans *via* palladium-catalyzed cascade cyclization of alkenyl ethers†

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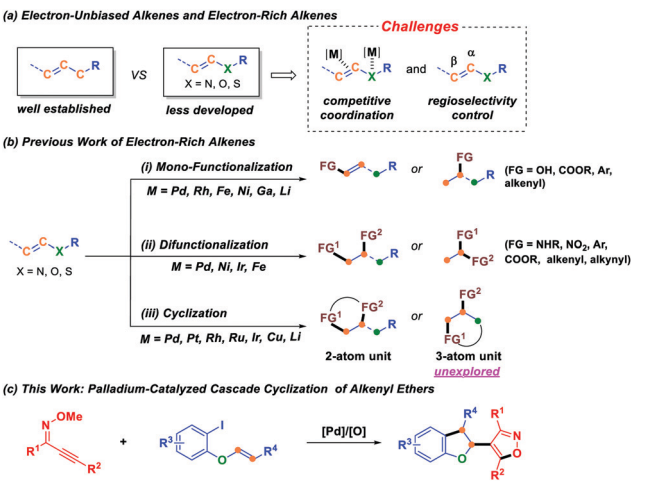
A novel palladium-catalyzed cascade cyclization reaction of alkenyl ethers with alkynyl oxime ethers for the construction of polyheterocyclic scaffolds has been developed, in which the electron-rich alkene moiety functions as a three-atom unit, simultaneously dealing well with the coordination and regioselectivity of electron-rich olefins under metal catalysis. The strategy features excellent regio- and chemoselectivities as well as good functional group tolerance. Moreover, the newly formed 2-isoxazolyl-2,3-dihydrobenzofuran products can be further transformed to diverse complex heterocycles, demonstrating their potential applications in organic synthesis and medicinal chemistry.

Polyheterocyclic compounds, possessing different heterocyclic skeletons as well as rich reactive sites, usually display more excellent biological or pharmaceutical activities than single heterocyclic compounds.[1] Among them, 2-heteroaryl-substituted benzodihydrofurans have attracted much attention due to their extraordinary pharmaceutical activities compared with simple furans.[2] For example, Liliflol A, a molecule containing 2-heteroaromatic-2,3-dihydrobenzofuran, is a selective COX-2 inhibitor.[3] Recent studies also proved that the introduction of the benzofuran moiety can improve the antitumor activity of novel farnesyltransferase inhibitors, which exhibit effective enzyme inhibitory activity.[4] Additionally, isoxazoles are found to be one significant class of structural skeletons in drug molecules with a wide range of biological activities, such as anti-inflammatory,[5] antinociceptive[6] and anticancer activities.[7] RX-37 is explored as a new type of potent bromodomain and extra terminal protein (BET) inhibitor, which selectively inhibits cell growth in human acute leukemia cell lines.[8] Thus, the development of novel and efficient methods for the facile construction of diverse polyheterocycles is highly desirable, especially for those bearing both benzodihydrofuran and isoxazole cores.[9]

On the other hand, alkenes and their derivatives are some of the most frequently used synthetic feedstocks for the building of various functionalized molecules.[10] Compared with a large amount of research on electron-deficient alkenes, electron-rich ones receive less attention. The possible reason is the massive interactions of the transition metal with the lone pairs of electron-rich olefins, which severely limit their insertion reactivity and selectivity owing to the profound electronegativity of nitrogen as well as oxygen or sulfur atoms and the repulsion effect from their electron pairs (Scheme 1a).[11] Until now, three reaction modes have been established for the transformations of electron-rich alkenes (Scheme 1b): (i) mono-functionalization including hydroxylation,[12a] esterification,[12b] alkenylation[12c] and arylation;[12d–g] (ii) difunctionalization including hydroarylation,[13a] hydroamination,[13b] hydroalkenylation,[11,13c] and amine esterification;[13d] and (iii) cyclization reactions leading to different donor-substituted cyclobutanes, pyrrolidines,



Scheme 1 Reaction modes of electron-rich olefins under metal catalysis.

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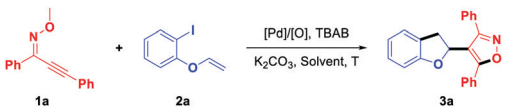
isoxazolidines, isoxazoles, cyclohexenes and cyclohepta[*b*]indoles.[14a–f] However, the above-mentioned methods typically focus on utilizing electron-rich olefins as two-carbon units, while the employment of electron-rich olefins as three-atom units (C=C–X) is relatively unexplored and challenging due to the regio- and chemoselectivity control. Herein, we disclose an efficient palladium-catalyzed cascade cyclization reaction of alkenyl ethers with alkynyl oxime ethers for the selective construction of 2-isoxazolyl-2,3-dihydrobenzofurans (Scheme 1c).

O-Methyl oxime (**1a**) and *o*-iodophenyl alkenyl ether (**2a**) were employed as model substrates for the optimization of reaction conditions, and the results are summarized in Table 1. Gratifyingly, in the presence of 10 mol% of $Pd(OAc)_2$, 2.0 equiv. of $CuCl_2$, 1.0 equiv. of TBAB and 2.0 equiv. of K_2CO_3 in DMF, the desired 4-(2,3-dihydrobenzofuran-2-yl)-3,5-diphenylisoxazole product (**3a**) was detected in 42% NMR yield (Table 1, entry 1). Solvent investigation revealed that THF was the optimal choice, which provided **3a** in 64% yield (Table 1, entries 2–4). The influence of different palladium catalysts was then explored, and 15 mol% of $Pd(OAc)_2$ gave the best result (Table 1, entries 5–8). Next, different oxidants, such as AgOAc, BQ, $CuBr_2$ and $CuCl_2$, were tested (Table 1, entries 9–12). When 2.5 equiv. of $CuCl_2$ was used in this reaction system, the desired heterocycle **3a** was afforded in 74% yield (Table 1, entry 12). Temperature examination showed that 60 °C was the most suitable for this transformation (Table 1, entries 13 and 14). A control experiment further suggested that **3a** could not be obtained without palladium catalyst (Table 1, entry 15). Therefore, the optimal reaction conditions were determined as follows: **1a** (0.2 mmol), **2a** (2.0 equiv.), $Pd(OAc)_2$ (15 mol%), $CuCl_2$ (2.5 equiv.), TBAB (1.0 equiv.) and K_2CO_3 (2.0 equiv.) in THF at 60 °C for 12 h (Table 1, entry 13).

Under the optimized reaction conditions, the generality and limitations of this palladium-catalyzed cascade cyclization were explored. The effects of substituents on the alkynyl oxime ethers (R^1) were first investigated (Table 2). To our delight, aryl substituted alkynyl oxime ethers with an electron-donating or electron-withdrawing group at the *para*-, *meta*- or *ortho*-position of the phenyl ring were well tolerated in this reaction (**3a–3j**). The structure of product **3c** was confirmed unambiguously by X-ray diffraction (CCDC† 2000121). Particularly, aryl oximes with strong electron-withdrawing groups, such as $-CF_3$ and $-SCF_3$ groups, were also compatible with this transformation, and the corresponding products **3f** and **3g** were obtained in 74% and 77% yields, respectively. When the substrate with the naphthyl substituent was applied, the target product **3k** could be isolated in 72% yield. In addition, the reaction of 2-furan-substituted oxime ether proceeded smoothly under the optimal conditions, leading to **3l** in 75% yield. Moreover, the oxime ether bearing cyclohexyl could be converted to the desired product **3m** in moderate yield. Encouraged by these promising results, various alkynyl oxime ethers with different substituents

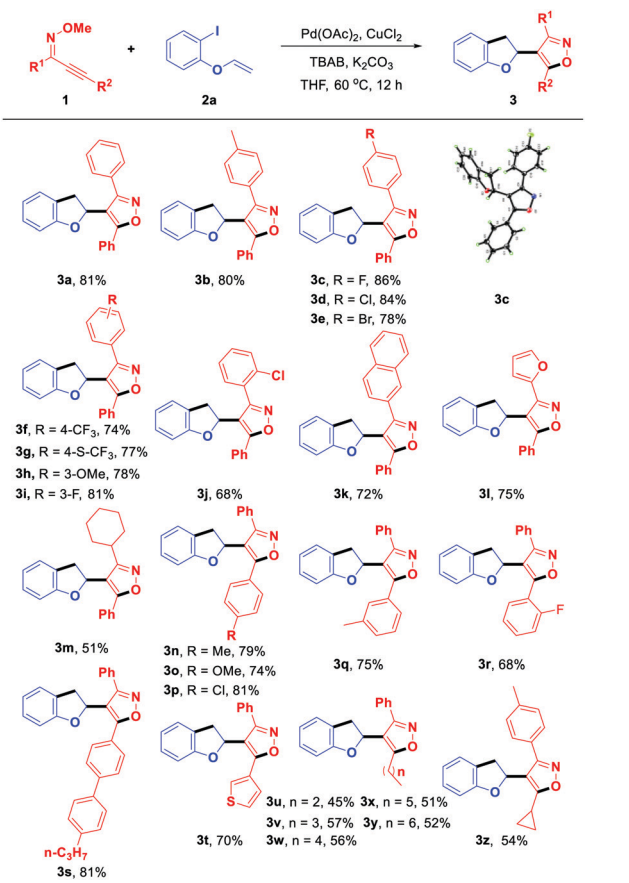
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	*T* (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	$CuCl_2$	DMF	110	42
2	$Pd(OAc)_2$	$CuCl_2$	Toluene	110	27
3	$Pd(OAc)_2$	$CuCl_2$	MeCN	110	36
4	$Pd(OAc)_2$	$CuCl_2$	THF	110	64
5	$Pd(TFA)_2$	$CuCl_2$	THF	110	57
6	$PdCl_2$	$CuCl_2$	THF	110	47
7	$Pd(PPh_3)_2Cl_2$	$CuCl_2$	THF	110	25
8[c]	$Pd(OAc)_2$	$CuCl_2$	THF	110	72
9[c]	$Pd(OAc)_2$	AgOAc	THF	110	n.d.
10[c]	$Pd(OAc)_2$	BQ	THF	110	Trace
11[c]	$Pd(OAc)_2$	$CuBr_2$	THF	110	52
12[cd]	$Pd(OAc)_2$	$CuCl_2$	THF	110	74
13[cde]	**$Pd(OAc)_2$**	**$CuCl_2$**	**THF**	**60**	**87 (81)**
14[cde]	$Pd(OAc)_2$	$CuCl_2$	THF	r.t.	37
15[de]	—	$CuCl_2$	THF	60	n.d.

[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.4 mmol), palladium catalyst (10 mol%), oxidant (2.0 equiv.), TBAB (1.0 equiv.), and K_2CO_3 (2.0 equiv.) in the indicated solvent (2.5 mL) for 4.5 h. [b] NMR yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] With 15 mol% of catalyst. [d] With 2.5 equiv. of oxidant. [e] 2 h. Data in parentheses indicate isolated yields. TBAB = tetrabutyl ammonium bromide; BQ = *p*-benzoquinone; n.d. = not detected; r.t. = room temperature.

Table 2 Scope of alkynyl oxime ethers[a]

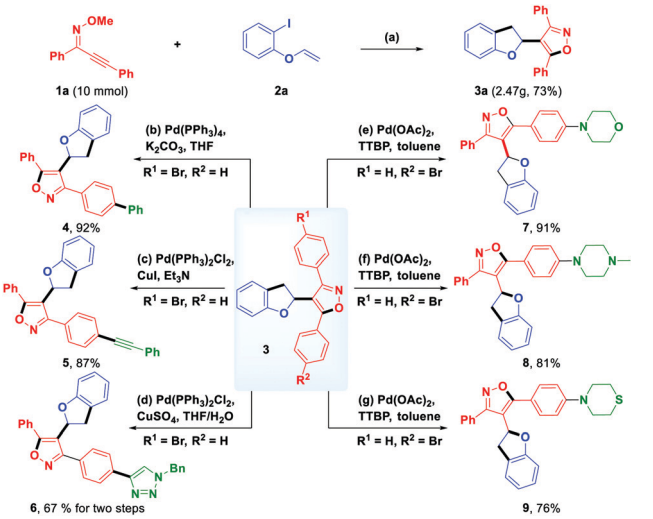


[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (15 mol%), $CuCl_2$ (2.5 equiv.), TBAB (1.0 equiv.), K_2CO_3 (2.0 equiv.), THF (2.5 mL), 60 °C, 12 h.

(R^2) were then tested. Regardless of the electronic nature of the *para*-substituents, **3n–3p** could all be obtained in good yields. Delightfully, both *meta*- and *ortho*-substituted aryl oximes were well adapted in this protocol and transformed to the corresponding products **3q** and **3r** in 75% and 68% yields, respectively. Notably, the bulky aromatic-substituted alkynyl oxime ether was found to be a suitable substrate for this transformation, and the target heterocycle **3s** was formed in 81% yield. It should be noted that the polyheterocyclic product **3t** (R^2 = 3-thienyl) was also obtained in 70% yield, suggesting that the heterocyclic substrates exhibited good compatibility with this system. More importantly, diverse aliphatic alkynes worked well under the standard reaction conditions. Both acyclic alkyl chain- (n = 2–6) and cyclopropyl-substituted alkynyl oxime ethers were tolerable in this reaction, converting to the desired products **3u–3z** in 45%–57% yields.

Next, the scope of alkenyl ethers **2** was examined under the optimal conditions. As shown in Table 3, diverse alkenyl ethers bearing various functional groups, such as electron-donating groups (CH_3, *t*-Bu) and electron-withdrawing groups (Br, CF_3, Cl) at the *para*- and *meta*-positions of the aryl ring, transformed smoothly to the corresponding isoxazolyl-substituted dihydrobenzofurans **3aa–3ae** in 47–56% yields. Unfortunately, when 2-fluorine substituted alkenyl ether was applied in this cascade cyclization, only trace product **3af** could be detected. It is worth noting that the internal alkene ether was compatible with this process, affording the desired product **3ag** in 62% yield. The *anti*-relationship of the methyl group and the isoxazole moiety of **3ag** was characterized by analyzing the X-ray crystallography data (CCDC† 2053026, see the ESI† for details). However, the corresponding products **3ah** and **3ai** from trisubstituted alkene ethers could not be obtained, which might be due to the steric hindrance of internal alkene ethers.

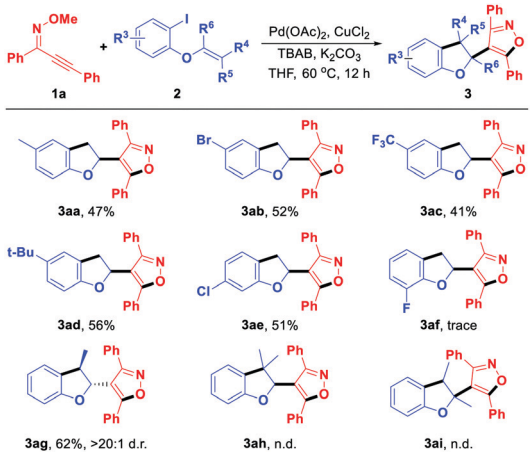
To evaluate the utility of this method, a gram-scale experiment was performed (Scheme 2). Under the standard conditions, the reaction was successfully scaled up to 10 mmol, and the desired product **3a** was obtained in 73% yield (Scheme 2a). The synthetic value was further demonstrated by various efficient transformations. For instance, the Pd-catalyzed Suzuki coupling of **3e** and phenylboronic acid gave biphenyl compound **4** in 92% yield (Scheme 2b) and the Sonogashira coupling of **3e** with phenylacetylene afforded the desired functionalized alkyne **5** in 87% yield (Scheme 2c). Furthermore, a conjugated triazole skeleton **6** was synthesized in 87% yield *via* click reaction (Scheme 2d). Notably, the products could be transformed into diverse N-heterocycles, such as morpholine **7**, piperazine **8**, and thiomorpholine **9**, which showed their potential applications in materials science and medicinal chemistry (Scheme 2e–g).



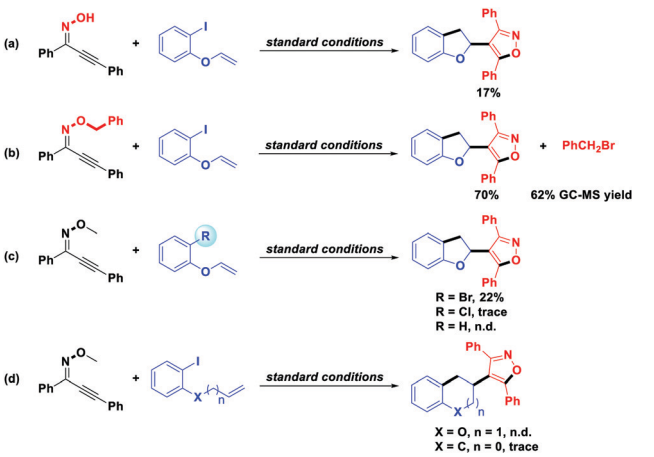
Scheme 2 Gram-scale reaction and synthetic applications (conditions: see the ESI† for details).

Several control experiments were conducted to clarify the reaction mechanism (Scheme 3). Firstly, when using oxime as the substrate, the desired product **3a** was detected in only 17% yield under the standard conditions (Scheme 3a), while the *O*-benzyl oxime transformed to **3a** in 70% yield, with benzyl

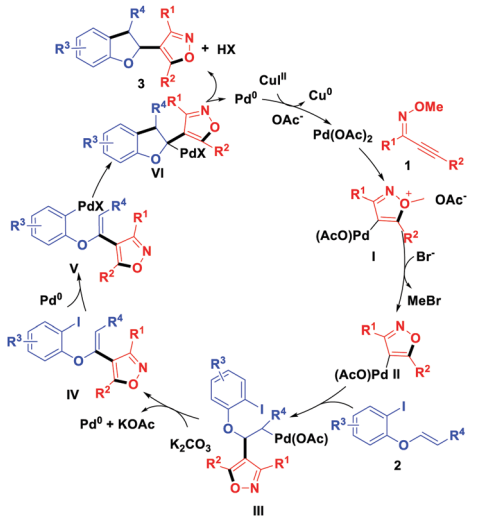
Table 3 Scope of alkenyl ethers[a]



[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (15 mol%), $CuCl_2$ (2.5 equiv.), TBAB (1.0 equiv.), K_2CO_3 (2.0 equiv.), THF (2.5 mL), 60 °C, 12 h.



Scheme 3 Mechanistic studies.



Scheme 4 Proposed mechanism.

bromide detected by GC analysis (Scheme 3b), which suggested the initiation process of this cascade cyclization reaction. Additionally, when the *iodo*-substituent in **2a** was changed to –bromo, –chloro or –H, the yield of **3a** decreased dramatically or even could not be obtained, indicating that the oxidative addition might be involved in this process and the C–I bond exhibited the highest reactivity (Scheme 3c). Moreover, when the reaction was conducted with 1-(allyloxy)-2-iodobenzene instead of **2a**, the corresponding chroman product could not be detected, illustrating the key role of the alkenyl ether moiety in the success of this transformation (Scheme 3d).

Based on the above experimental results and previous reports,[15] a plausible reaction mechanism is proposed (Scheme 4). The reaction is initiated by *trans*-oxypalladation of alkynyl oxime ethers **1**, generating the oxonium intermediate **I**, which would transform to the alkenylpalladium intermediate **II** *via* the elimination of methyl bromide. Subsequently, migratory insertion of *o*-iodophenyl alkenyl ether **2** into the C–Pd bond affords the key alkylpalladium species **III**. Next, β-hydrogen elimination of **III** gives the key intermediate **IV**, which undergoes oxidative addition to afford the arylpalladium intermediate **V**. Then an intramolecular Heck coupling occurs and generates the alkylpalladium intermediate **VI**. Finally, the protonolysis of **VI** yields the desired product **3** and a palladium(II) species, which continues to the catalytic cycle with the aid of $CuCl_2$.

In summary, we developed a palladium-catalyzed cascade cyclization reaction of alkenyl ethers with alkynyl oxime ethers, providing an efficient and convenient strategy for the construction of various 2-isoxazolyl-2,3-dihydrobenzofurans. Noteworthily, the electron-rich alkene moiety served as a three-atom unit, realizing the selective synthesis of a structurally novel polyheterocyclic skeleton. With merits such as a facile operation process, high regio- and chemoselectivities, and good tolerance of functional groups, the protocol shows potential applications in organic synthesis and medicinal chemistry. Further studies on the substrate scope and biological activities of the polyheterocyclic products are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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