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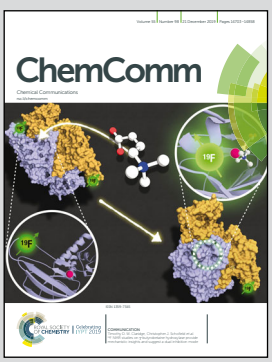

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Palladium-catalyzed enol/enolate directed oxidative annulation: functionalized naphthofuroquinone synthesis and bioactivity evaluation†

Shuaipeng Lv,‡[a] Haitao Liu,‡[a] Jie Kang,[b] Yun Luo,[a] Ting Gong,[b] Zhengqi Dong,[a] Guibo Sun,[a] Chunnian He,[a] Xiaobo Sun*[a] and Lei Wang *[a]

A palladium-promoted oxidative annulation reaction for the synthesis of structurally diverse naphthoquinone-containing heterocycles has been developed, providing switchable access to 1,2-naphthofuroquinones and densely functionalized cyclobutene-fused 1,4-naphthofuroquinones by selective enol/enolate-directed processes. The synthetic application was extended by late-stage functionalization of an anti-HIV drug. The practical value of 1,2-naphthofuroquinone synthesis was highlighted in endothelial protective lead compound development.

The development of efficient approaches to synthesize structurally diverse heterocycles with broad biological activities under readily tuneable catalytic conditions is one of the central goals in modern organic synthesis.[1] Among these heterocycles, naphthofuroquinones are exceptionally prominent due to their existence in numerous biologically active molecules (Fig. 1).[2] However, the reported protocols for naphthofuroquinone construction suffer from disadvantages.[3] Given the broad-spectrum bioactivities of naphthofuroquinones, the development of novel efficient methods for the synthesis of such heterocycles from simple starting materials with high efficiency, including synthetic applications in drug discovery, is highly desirable.

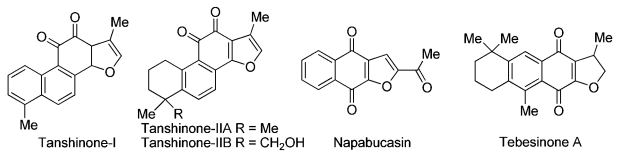

Fig. 1 Representative bioactive natural products and pharmaceuticals.

Within the rapidly growing realm of transition-metal catalysis, oxidative annulation of alkynes with substrates bearing versatile functional groups has emerged as a powerful tactic in heterocycle synthesis and structural diversification.[4] Among the various catalytical strategies, the oxidative annulation of alkynes with carbonyl substrates, especially 1,3-dicarbonyl compounds (or their enol tautomers), to deliver a broad range of heterocycles have been pioneeringly explored by Lam, You and Gogoi's groups.[5] However, these enol/enolate-directed oxidative annulations always achieved product selectivity through transition-metal catalyst control strategies. We hypothesized that it might be possible to realize product versatility by tuning the enol/enolate-directed annulation pathway without catalyst control processes.

Cyclobutenes have attracted considerable attention due to their wide existence as critical scaffolds in biologically relevant molecules and high reactivities for versatile roles originating from ring strain.[6] However, notwithstanding the progress,[7] reported synthetic protocols are incompatible with the extreme value of such four-membered rings. Therefore, the synthesis of cyclobutenes is needed for more flexible routes, especially embedding such densely substituted rings in polycyclic structures.

We envisioned that 2-hydroxy-1,4-naphthoquinone, featuring a keto–enol moiety,[5g,8] could be utilized as a coupling partner with transition-metal catalysis *via* an enol/enolate-directed process to assemble structurally diverse naphthoquinone-containing heterocycles. However, challenges, such as chemoselectivity and transformation efficiency, should be overcome. Herein, we report a successful introduction of enol/enolate-directed palladium-catalyzed oxidative annulation reactions, yielding biologically relevant 1,2-naphthofuroquinones and highly substituted cyclobutene-fused 1,4-naphthofuroquinones together with synthetic applications in late-stage functionalization (LSF) and lead compound development (Scheme 1).

The designed palladium-catalyzed oxidative annulation reaction was evaluated by using 2-hydroxy-1,4-naphthoquinone **1a** (1.0 equiv.) and diphenylacetylene **2a** (5.0 equiv.) in acetonitrile (MeCN) at 100 °C. Interestingly, the reaction proceeded smoothly and afforded the desired product **3a** in moderate yield

[a] *Institute of Medicinal Plant Development, Chinese Academy of Medical Science & Peking Union Medical College, Beijing 100193, P. R. China. E-mail: lwang@implad.ac.cn*
[b] *Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, P. R. China*

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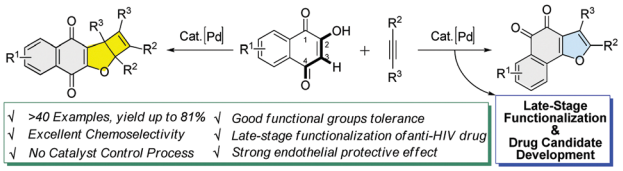
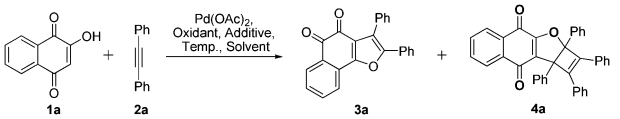
‡ These authors contributed equally.



Scheme 1 Enol/enolate-directed oxidative annulation reactions.

Table 1 Optimization of the reaction conditions[a]



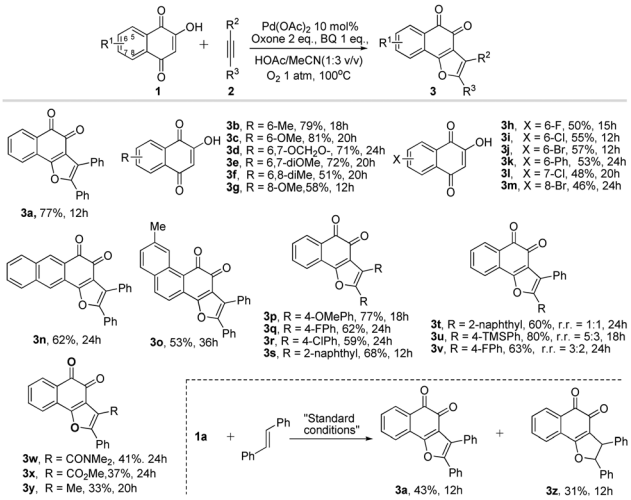
Entry	Solvent	Oxidant/additive	T/°C	Yield[b] (%) 3a	4a
1	MeCN	Oxone	100	42	—
2	MeCN	$CuCl_2$	100	—	49
3[c]	MeCN/AcOH	Oxone	100	61	—
4[c]	MeCN/AcOH	Oxone/BQ/O_2	100	71	—
6[c,e]	MeCN/AcOH	Oxone/BQ/O_2	100	77	—
7[d]	MeCN/AcOH	Oxone/BQ/O_2	100	50	—
8	MeCN	$CuCl_2/N_2$	100	—	22
9	DMA	$CuCl_2/O_2$	100	—	57
10	DMA	$CuCl_2/N_2$	100	—	68

[a] This reaction was run with **1a** (0. 2 mmol, 1 eq.), **2a** (1.0 mmol, 5.0 eq.), $Pd(OAc)_2$ 10 mol%, oxidant (0. 4 mmol, 2 eq.), additive (0. 4 mmol, 2.0 eq.), solvent 2 mL, 100 °C, 24 h. [b] Yield of the isolated product 3a after chromatography. [c] MeCN/AcOH (v/v 3 : 1). [d] MeCN/AcOH (v/v 1 : 1). [e] BQ (0.2 mmol, 1 eq.). O_2 1 atm. N_2 1 atm. BQ = 1,4-benzoquinone.

(Table 1, entry 1). Various solvents were then evaluated, revealing that MeCN was still essential for the high efficiency of this transformation (see ESI†). Further optimizations of reaction conditions indicated that the mixture solvent MeCN/AcOH (v/v 3 : 1), BQ and O_2 could significantly affect the reaction with an increased yield of **3a** (77%) (entry 6). Upon switching from oxone to $CuCl_2$, the selective assembly of **4a** was observed (entry 8). Then, a significant solvent effect on the reactive efficiency was achieved, and DMA was the solvent of choice with the generation of **4a** instead of **3a** with a good yield (68%) under a N_2 atmosphere at 100 °C (entry 10).

With the established optimal reaction conditions in hand, an assessment of the reaction scope to assemble a range of substituted 1,2-naphthofuroquinones was evaluated. As indicated in Table 2, various 2-hydroxy-1,4-naphthoquinones **1** bearing electron-neutral, electron-donating, and electron-withdrawing substituents on the aromatic ring were found to be suitable for this reaction to form the corresponding angular naphthofuroquinones (**3a–m**) with good to excellent yields. However, **1** bearing a strong electron-withdrawing group such as 6-NO_2 exhibited poor reactivity in this kind of reaction (<10% yield). Notably, 2-hydroxy-1,4-anthracenedione and 3-hydroxy-1,4-anthracenedione were also suitable substrates and afforded the desired products with high efficiency (**3n**, **3o**). Also, symmetrical and unsymmetrical diaryl alkynes substituted with electron-rich and electron-deficient groups were all compatible, resulting in the assembly of various

Table 2 1,2-Naphthofuroquinones synthesis[a]

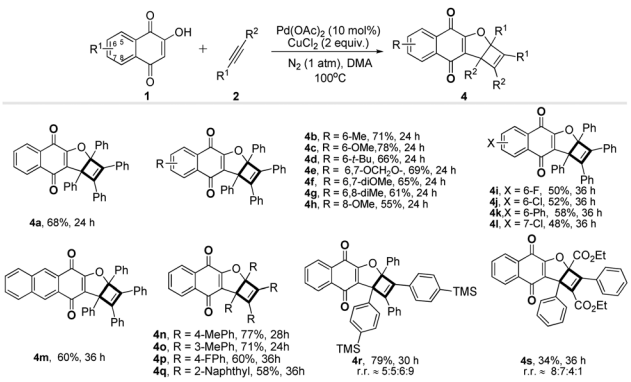


[a] The reaction used **1** (0. 2 mmol, 1 eq.), **2** (1.0 mmol, 5 eq.), $Pd(OAc)_2$ 10 mol%, oxone 2.0 eq., BQ 1.0 eq., O_2 1 atm, solvent 2 mL, 6–36 hours; yields of the isolated product **3** after chromatography.

desired 1,2-naphthofuroquinones with high efficiency (**3p–u**). However, erosive yields were achieved with unsymmetrical alkynes as substrates (**3w–y**). Furthermore, this annulation reaction was also extended by using *E*-stilbene as the starting material and resulting in **3a** and **3z** with moderate yields, respectively. The configurations of compounds **3a**, **3r**, and **3y** were structurally confirmed by X-ray diffraction analysis.[9]

Then, the utility of enol/enolate-directed oxidative annulation procedures was broadened by cyclobutene-embedded 1,4-naphthofuroquinone synthesis. As indicated in Table 3, different naphthoquinone and anthracenedione substrates bearing electron-neutral, -releasing and -withdrawing substituents on the aromatic ring were evaluated, giving the corresponding linear naphthofuroquinone products (**4a–m**) with moderate to very good yields. Also, this annulation protocol in terms of various symmetrical and unsymmetrical diaryl alkynes **2** was explored and achieved the

Table 3 Cyclobutene-fused 1,4-naphthofuroquinones synthesis[a]



[a] The reaction used **1** (0. 2 mmol, 1 eq.), **2** (1.0 mmol, 5.0 eq.), $Pd(OAc)_2$ 10 mol%, $CuCl_2$ 2.0 eq., solvent 2 mL, reaction time 24–36 hours; yields of the isolated product **4** after chromatography.

desired polycyclic heterocycles with high efficiency in most cases (**4n–s**), whereas **4r** and **4s** formed mixtures of regioisomers that were inseparable by column chromatography. The configuration of the products was assigned based on an X-ray crystallographic analysis of compounds **4a**.[10]

The application of the annulation approach in the context of late-stage functionalization (LSF) was also intensively explored.[11] Pharmaceutically relevant molecules such as efavirenz, a commercially available anti-HIV drug, were then investigated (Table 4). However, the targeted functionalized angular naphthofuroquinone derivative was not formed, but yielded exciting 1,4-naphthopyranoquinone products with moderate yields (**5a–c**).[12] Additionally, the extension of the LSF to 4-hydroxycoumarin, a keto–enol moiety embedded heterocycle, was also achieved and formed the corresponding naphthopyranoquinone product **6** with high efficiency. Using the cyclobutene-embedded 1,4-naphthofuroquinone catalytic system, LSF was also performed. However, the functionalized linear naphthofuroquinone derivative was not assembled under the standard conditions.

To further evaluate the pharmaceutical implication of this oxidative annulation strategy, 1,2-naphthofuroquinone synthesis in drug discovery was also explored. The endothelial protective assays of 1,2-naphthofuroquinones *in vitro* were assessed in parallel with sodium tanshinone IIA silate (see ESI†).[13,14] As shown in Fig. 2A and B, we found that **3x** exhibited a strong endothelial protective effect against oxidized low-density lipoprotein (ox-LDL)-induced human umbilical vein endothelial cell (HUVEC) injury. Additionally, **3x** (0.25, 0.5 and 1 μM) has no effects on the normal cells (Fig. 2C). Based on these findings, the endothelial protective mechanism of **3x** was then evaluated. The HUVEC apoptosis was significantly reduced by treating with **3x** (0.25 and 0.5 μM) *via* Annexin V/PI assay compared with the model group, as indicated in Fig. 2D. The expression level of reactive oxygen species, an important factor for cell apoptosis, was remarkably decreased and detected by Carboxy-H2DCFDA staining after **3x** treatment, which implied the anti-oxidative effects of **3x** (Fig. 2E). This result was in accordance with the assay in Fig. 2D. We then examined the expressions of Bcl-2, Bax and cleaved-caspase-3 protein expression levels to further

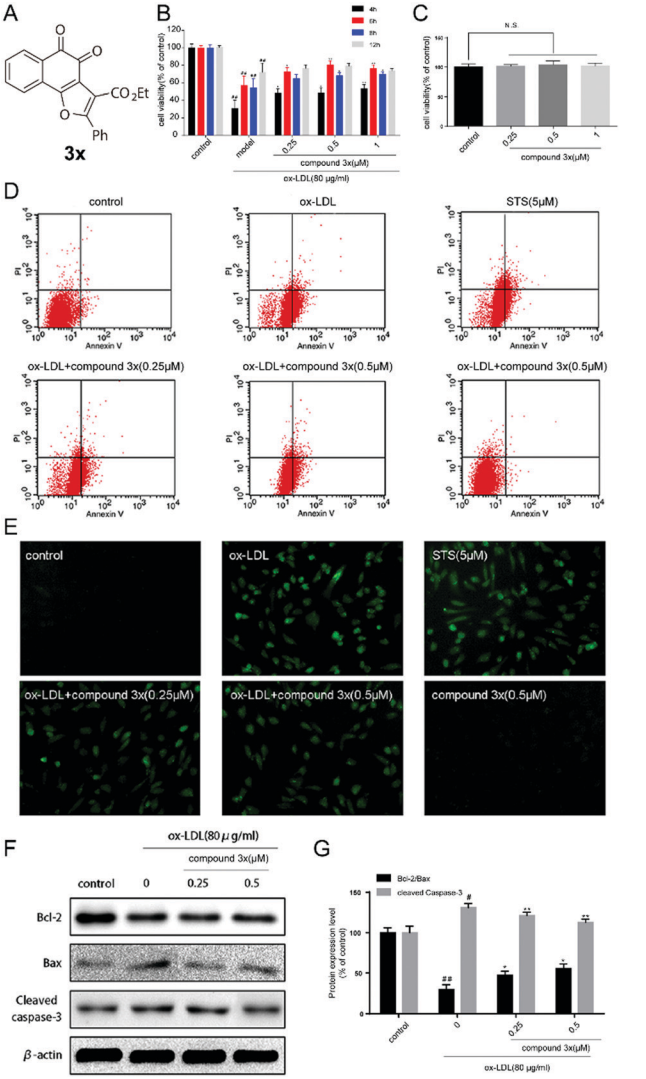
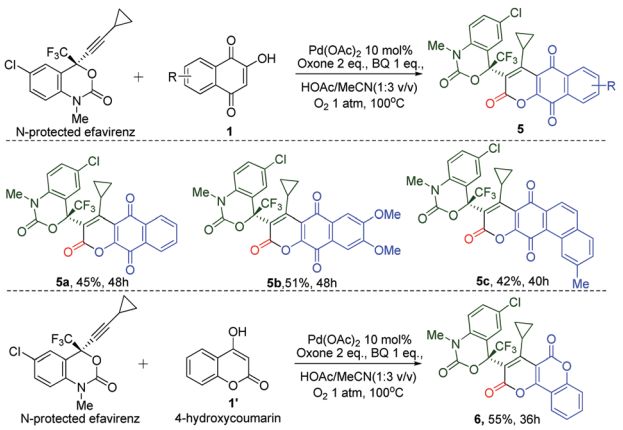


Fig. 2 Protective effects of **3x** on HUVECs injury. All values are expressed as the mean ± SD, $n = 3$. #$p < 0.05$, ##$p < 0.01$ ox-LDL group *vs.* control group; *$p < 0.05$, **$p < 0.01$ *vs.* ox-LDL group. STS = sodium tanshinone IIA silate. See the ESI† for details.

Table 4 Late-stage functionalization of *N*-protected efavirenz



understand the mechanism (Fig. 2F and G). The expressions of Bcl-2/Bax increased in a dose-dependent manner after **3x** treatment, whereas the cleaved-caspase-3 expression was obviously decreased. All the results indicated the promise of **3x** for future applications in the treatment of coronary artery disease based on dramatically strong endothelial protective effects.

In summary, we have developed the first palladium-catalyzed oxidative switchable annulation of naphthalquinones with alkynes to assemble a series of biologically relevant functionalized 1,2-naphthofuroquinones and densely functionalized cyclobutene embedded 1,4-naphthofuroquinones in good yields. Notably, the palladium catalyzed oxidative annulation strategy described here allows the synthesis of the 1,2-naphthofuroquinones with dramatically strong endothelial protective effects and represents an efficient approach to diversify marketed drugs by late-stage functionalization. Further applications of palladium-catalysis for the construction of related heterocycles will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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