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Letter

Cu(I)-Catalyzed Oxidative Cyclization of Enynamides: Regioselective Access to Cyclopentadiene Frameworks and 2-Aminofurans

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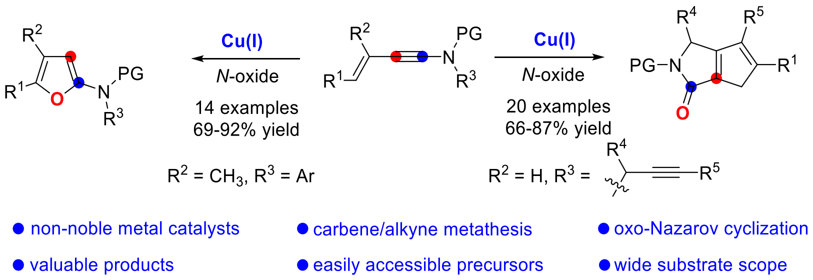
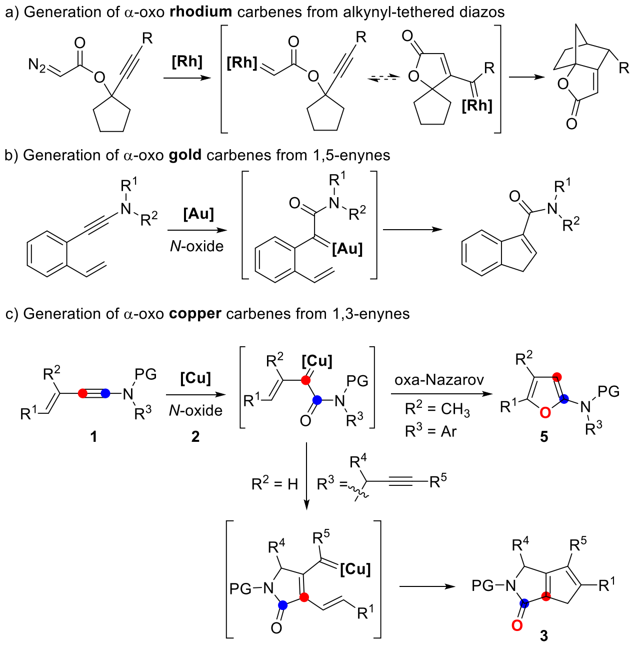


ABSTRACT: An efficient Cu(I)-catalyzed oxidative cyclization of alkynyl-tethered enynamides for the construction of fused bicyclic cyclopentadiene derivatives is disclosed. The cascade proceeds through alkyne oxidation, carbene/alkyne metathesis, and formal (3 + 2) cycloaddition. Employing aryl-tethered enynamides as starting materials, substituted 2-aminofurans can be exclusively formed.

The highly efficient construction of cyclopentadiene skeletons, which have proven to be versatile building blocks since the first reports of the preparation and characterization of 1,3-cyclopentadiene in 1896 by Kraemer and Spilker,[1] is an important subject in organic synthesis. Cyclopentadienes with maleimide derivatives can be smoothly converted into bicyclo[2.2.1]heptene frameworks, which are found in drug candidates as well as in bioactive molecules, via the Diels−Alder reaction.[2] Although numerous imposing methods have been developed for the synthesis of functionalized cyclopentadienes,[3] a practical and efficient approach for the synthesis of this type of skeleton remains an intriguing theme for the synthetic community.

Carbo- or heterocycles can be readily constructed by transition-metal-catalyzed carbene reactions in organic synthesis.[4] Among those, carbene/alkyne metathesis reactions have received particular attention in recent years, as this access would provide great potential in the assembly of structurally complex molecules.[5] Notably, vinyl metal carbene intermediates generated via carbene/alkyne metathesis reactions, as pioneered by Padwa[6] and Hoye,[7] have been widely applied to various catalytic annulations, including cycloadditions,[8] Buchner reactions,[9] and C−H insertions.[10] For example, May et al.[10a] disclosed the rhodium-catalyzed carbene/alkyne metathesis, leading to bridged polycyclic products with alkynyl-tethered diazo substrates (Scheme 1a). In addition, the Xu group developed a dirhodium-catalyzed intramolecular carbene/alkyne metathesis of alkynyl-tethered styryl diazo substrates to give bicyclic cyclopentadiene derivatives.[8a] However, the use of hazardous, not readily accessible diazo

Scheme 1. Generation of α-Oxo Metal Carbenes



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compounds has severely limited further synthetic applications of this strategy. Consequently, the development of alternative and general approaches is still highly desirable.

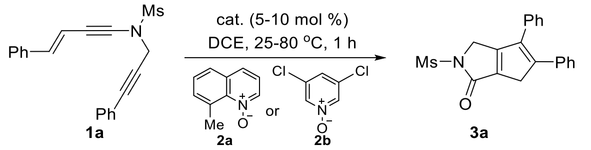
Recently, gold catalysis has been rapidly developed, which has provided a fungible method for the formation of carbenes[11] via alkyne oxidations, as pioneered by L. Zhang.[12] Among these advances, enyne oxidations have attracted increasing attention, and various synthetic methods have been developed.[13] For instance, Liu et al.[13a] disclosed the gold-catalyzed oxidative enyne cyclization, affording 3-carbonyl-1*H*-indene compounds (Scheme 1b). Although a few other variants have been discovered by Tang,[13b] J. Zhang,[13c] L. Zhang,[13d] and Li,[13e] these enyne oxidations have been restricted to noble-metal catalysts, which has severely hampered the practical application of this approach. To our knowledge, non-noble-metal-catalyzed alkynyl-tethered enyne oxidation to generate vinyl metal carbene intermediates has not been reported to date.

Inspired by the previously described results, we envisaged that α-oxo metal carbene might be formed through the non-noble-metal-catalyzed oxidative cyclization of alkynyl-tethered enynamides **1** with *N*-oxides **2** (Scheme 1c). The carbene intermediate, probably highly electrophilic, could be further attacked by the tethered alkynyl group to lead to a carbene/alkyne metathesis reaction, giving bicyclic cyclopentadiene derivatives **3**. However, two possible competitive reactions are confronted: (1) This type of carbene intermediate is easily dioxidized by an *N*-oxide,[13b,14] and (2) the generated alkenyl metal carbene can proceed to an oxa-Nazarov cyclization via a metal-stabilized allylic cation intermediate.[13f,15] Herein we disclose a novel procedure for the highly regioselective synthesis of a range of cyclopenta[*c*]pyrrol-1(2*H*)-ones. Of particular note is that this protocol represents the first generation of α-oxo copper carbenes via the copper-catalyzed intermolecular reaction of alkynyl-tethered enynamides and *N*-oxides.

As shown in Table 1, the reaction of enynamide **1a** and oxidant **2a**, by using copper catalysis, was first investigated. To our delight, the desired cyclopenta[*c*]pyrrol-1(2*H*)-one **3a** was indeed formed in 45% yield (entry 1). Later, additional copper catalysts were further screened, and $Cu(CH_3CN)_4PF_6$ could commendably catalyze this reaction to give **3a** in 62% yield (entries 2−4). Moreover, **3a** can be also obtained when other Lewis acids such as $Zn(OTf)_2$ and $Y(OTf)_3$ are used as the catalyst, but in significantly decreased yields (entries 5 and 6). Subsequently, a temperature screening was carried out, and **3a** could be generated in 84% yield when this cascade reaction worked best at 60 °C (entries 7 and 8). Further screening of oxidants revealed that **3a** was obtained in 21% yield by the use of 3,5-dichloropyridine *N*-oxide **2b** (entry 9), and no formation of **3a** was observed in the absence of an oxidant (entry 10). No **3a** was detected when Brønsted acids such as TsOH and MsOH were used as the catalyst (entries 11 and 12). Notably, cyclopenta[*c*]pyrrol-1(2*H*)-one **3a** was formed in only 23 and 10% yield in the presence of typical noble-metal catalysts $Ph_3PAuCl/AgNTf_2$ and $[Rh(CO)_2Cl]_2$, respectively (entries 13 and 14).

With the optimized reaction conditions in hand, we then studied the scope of this transformation. As shown in Scheme 2, the reaction successfully proceeded with various alkynyl-tethered enynamide substrates **1**, and the yields ranged from 66 to 87%. We first examined the different *N*-protecting groups of enynamides, and Ms-protected enynamide **1a** reacted to give the best yields (entries 1−4). We then investigated a range of aryl-substituted enynamides (R^5 = Ar), which delivered the

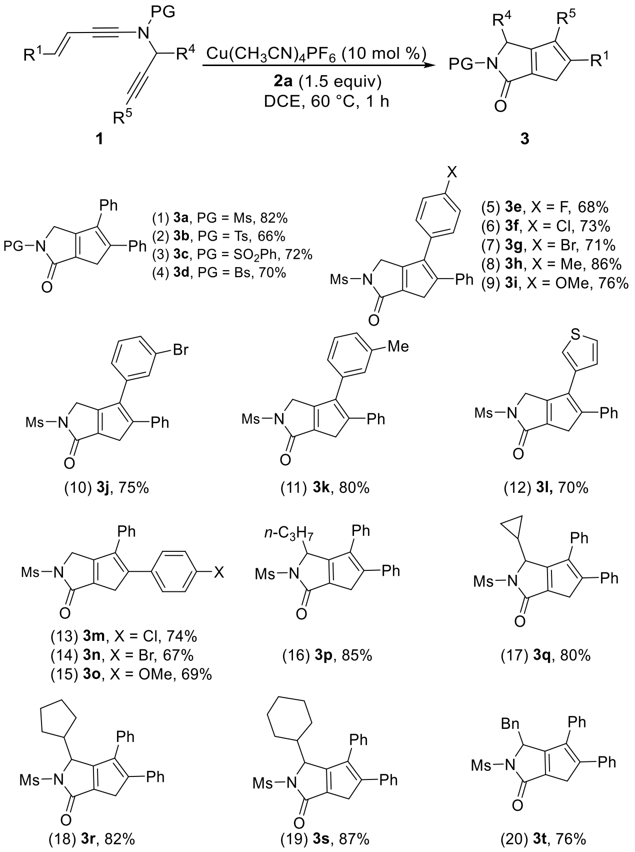
Table 1. Optimization of Reaction Conditions[a]



entry	cat. (*x* mol %)	oxidant	*T* (°C)	yield (%)
1	$Cu(OTf)_2$ (10)	**2a**	80	45
2	CuOTf (10)	**2a**	80	48
3	$Cu(CH_3CN)_4BF_4$ (10)	**2a**	80	42
4	$Cu(CH_3CN)_4PF_6$ (10)	**2a**	80	62
5	$Zn(OTf)_2$ (10)	**2a**	80	11
6	$Y(OTf)_3$ (10)	**2a**	80	16
7	**$Cu(CH_3CN)_4PF_6$ (10)**	**2a**	**60**	**84**
8	$Cu(CH_3CN)_4PF_6$ (10)	**2a**	25	10
9	$Cu(CH_3CN)_4PF_6$ (10)	**2b**	60	21
10	$Cu(CH_3CN)_4PF_6$ (10)		60	<1
11	TsOH (10)	**2a**	60	<1
12	MsOH (10)	**2a**	60	<1
13	$Ph_3PAuCl/AgNTf_2$ (5)	**2a**	60	23
14	$[Rh(CO)_2Cl]_2$ (5)	**2a**	60	10

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), catalyst (5−10 mol %), 0.05 M.

Scheme 2. Reaction Scope Study[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol %), DCE (4.0 mL), 60 °C (60 °C, heating mantle temperature) in vials. Isolated yields are reported. PG = protecting group. Bn = benzyl.

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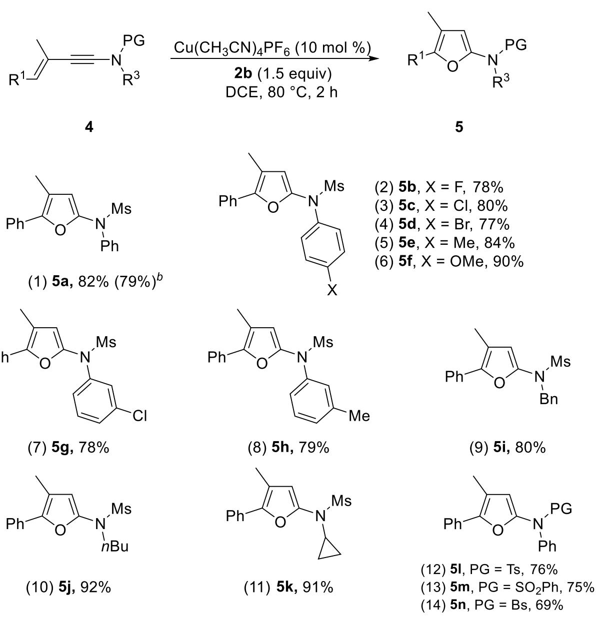
desired cyclopenta[*c*]pyrrol-1(2*H*)-ones **3e**–**k** in 68–86% yields (entries 5–11). Of particular note is the fact that the heterocycle-substituted enynamide **1l** was applicable to this procedure to yield **3l** in 70% yield (entry 12). Moreover, products **3m**–**o** were readily obtained in 67–74% yields (entries 13–15). We tried the reaction using **1u**, where R^1 was an alkyl group, but no desired product was observed. This reaction proceeded smoothly with a range of substituted enynamides, and the resulting products were efficiently afforded. This protocol displayed good functional group compatibility, and enynamides with substituents, such as ^{n}Pr, cyclopropyl, cyclopentyl, cyclohexyl, and Bn, were well tolerated, yielding the desired products **3p**–**t** in 76–87% yield (entries 16–20). Thus this reaction provided a powerful strategy for the construction of bicyclic cyclopentadiene derivatives for organic synthesis.

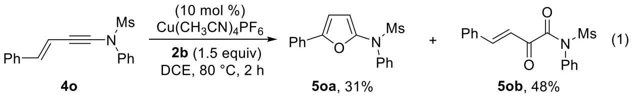
Apart from alkynyl-tethered enynamides, aryl-tethered enynamides reacted under similar conditions to provide substituted 2-aminofurans via an oxa-Nazarov cyclization. This is an unprecedented Cu(I)-catalyzed oxidative cyclization of aryl-tethered enynamides for the construction of substituted furans, which is an alternative approach to the gold-catalyzed oxidative enynamide oxa-Nazarov cyclization, as previously reported by Liu.[13f] Thus the reaction of aryl-tethered enynamides **4** with 3,5-dichloropyridine *N*-oxide **2b** in the presence of Cu(CH$_3$CN)$_4$PF$_6$ (10 mol %) smoothly furnished 2-aminofurans **5a**–**n** in 69–92% yields (Scheme 3). Of note, substituted aromatic rings of different electronic properties were readily tolerated. The molecular structure of **5l** was confirmed by X-ray diffraction. This transformation presumably involved an oxa-Nazarov cyclization of copper-stabilized allylic cations.

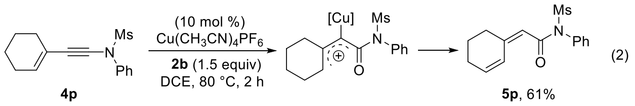
Scheme 3. Reaction Scope for the Formation of 2-Aminofurans 5[a]



[a] Reaction conditions: **4** (0.2 mmol), **2b** (0.3 mmol), Cu(CH$_3$CN)$_4$PF$_6$ (10 mol %), DCE (4.0 mL), 80 °C (80 °C, heating mantle temperature) in vials. Isolated yields are reported. [b] 1.0 mmol scale.

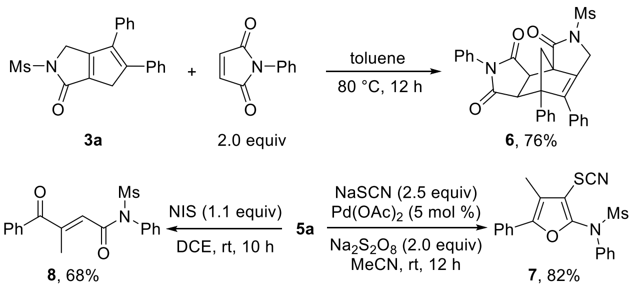
When the scope of this Cu catalysis was extended to aryl-tethered enynamide **4o**, the corresponding 2-aminofuran **5oa** was obtained in 31% yield, and the ketoamide **5ob** was formed in 48% yield (eq 1). These results indicated that the methyl group stabilized the allylic cation toward an oxa-Nazarov cyclization. Moreover, it was found that subjecting 2-cyclohexenyl-1-ethynylamide **4p** to copper catalysis generated dienylamide **5p** in 61% yield (eq 2).





Further synthetic transformations of the synthesized cyclopentadiene frameworks were also explored, as shown in Scheme 4. The treatment of cyclopenta[*c*]pyrrol-1(2*H*)-one **3a** with *N*-aryl-substituted maleimide led to the corresponding adduct **6** in 76% yield through the Diels–Alder reaction. Furthermore, 2-aminofuran **5a** could be converted into the 2-amino-3-thiocyanatofuran **7** in 82% yield via a palladium-catalyzed sp^2 C–H bond thiocyanation.[16] The treatment of **5a** with *N*-iodosuccinimide (NIS) delivered product **8** in 68% yield.

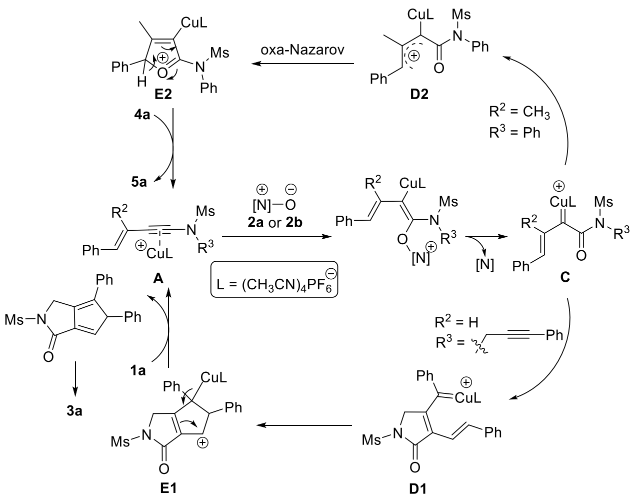
Scheme 4. Transformation of the Products



A possible mechanism for the formation of **3a** and **5a** is presented (Scheme 5). First, **A** is formed through the coordination of the catalytic [Cu^{I}] species to the aminated triple bond, which is site-selectively trapped by the 8-methylquinoline *N*-oxide **2a** or 3,5-dichloropyridine *N*-oxide **2b** to give α-oxo alkenylcopper carbene intermediate **C**.[17] Subsequently, this species is attacked by the internal alkynyl group and converted to intermediate **D1** through carbene/alkyne metathesis. **D1** then undergoes cyclization to yield bicyclic intermediate **E1** rather than the previously observed second oxidation to form the diketone compound.[13b,14] Finally, proto-demetalation/proton transfer proceeds smoothly to provide the final product **3a**. When R^3 = Ph, carbene intermediate **C**, with its resonance contributor **E2**, undergoes an oxa-Nazarov cyclization. Proton transfer and ligand exchange furnish product **5a**.

In summary, prior to this study, intermolecular oxidation reactions of enynes with pyridine *N*-oxides or quinoline *N*-oxides were limited to noble-metal catalysts. Herein we report a copper-catalyzed oxidative cyclization of alkynyl-tethered enynamides, leading to various bicyclic cyclopentadiene

Scheme 5. Plausible Reaction Mechanism for the Formation of 3a and 5a



derivatives in good to excellent yields. This reaction sequence involved the initial formation of α-oxo copper carbene species followed by carbene/alkyne metathesis and formal (3 + 2) cycloaddition, providing easy access to the cyclopenta[*c*]pyrrol-1(2*H*)-ones. Moreover, the resulting fused cyclopentadienes can smoothly react with maleimides in a Diels–Alder reaction to provide bicyclo[2.2.1]heptene frameworks. Furthermore, this Cu catalysis is also applicable to the regioselective synthesis of substituted 2-aminofurans through the copper-catalyzed oxa-Nazarov cyclization of aryl-substituted enynamides with 3,5-dichloropyridine *N*-oxide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02317.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2007966 and 2007969 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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