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Copper(I)-Catalyzed Oxyamination of β,γ-Unsaturated Hydrazones: Synthesis of Dihydropyrazoles

Shanshan Chen,[†,∥] Wenming Chen,[‡,∥] Xu Chen,[†] Guifang Chen,[†] Lutz Ackermann,[§] and Xu Tian*[,†]

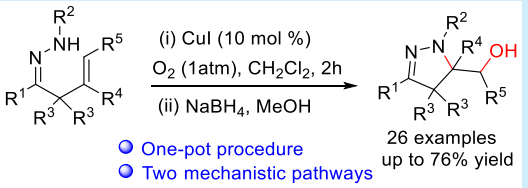
[†]Key Laboratory of Molecular Target & Clinical Pharmacology and the State Key Laboratory of Respiratory Disease, School of Pharmaceutical Sciences & the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 511436, China

[‡]Department of Pharmaceutical Production Center, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha, Hunan 410007, China

[§]Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany

Supporting Information

ABSTRACT: An efficient aerobic copper(I)-catalyzed oxyamination of β,γ-unsaturated hydrazones has been developed. The methodology provides effective access to dihydropyrazole derivatives in a one-pot process utilizing dioxygen as a sustainable sacrificial oxidant. Mechanistic studies have been performed and are suggestive of an aerobic manifold via single electron transfer.



Dihydropyrazoles are widely found in pharmaceutical compounds with a broad spectrum of biological activities (Figure 1).[1] Over the past few decades, an array of methods

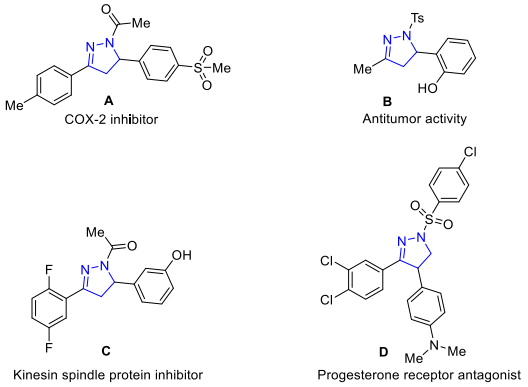
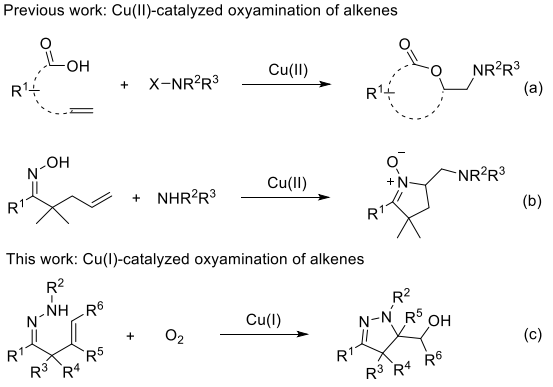


Figure 1. Examples of bioactive dihydropyrazole derivatives.

have been developed for the preparation of dihydropyrazoles. Traditionally, the construction of dihydropyrazoles has mainly been focused on thermal cycloaddition and catalytic cyclization reactions.[2] Recently, hydrazonyl radical-mediated difunctionalizations of β,γ-unsaturated hydrazones have been exploited toward an ideal efficient approach to form the diversely functionalized dihydropyrazoles.[3] In this context, it is reasonable to expect that the cyclization of β,γ-unsaturated hydrazones will provide step-economical access to differently decorated dihydropyrazoles.

The oxyamination of alkenes represents a valuable strategy for the rapid and efficient synthesis of 1,2-amino alcohol derivatives.[4] Thus recent studies have established the transition-metal-catalyzed oxyamination of alkenes, using osmium,[5] rhodium,[6] palladium,[7] copper,[8] gold,[9] and platinum catalysts.[10] Recently, a few examples of radical-mediated oxyamination of alkenes have been reported. For instance, Wang reported a copper(II)-catalyzed oxyamination of alkenes for the synthesis of lactones (Scheme 1a).[11] Subsequently, Yu

Scheme 1. Copper-Catalyzed Oxyamination of Alkenes



developed an iminoxyl radical-promoted oxyamination of alkenes (Scheme 1b).[12] Despite these major achievements, however, most of the approaches rely on the use of stoichiometric amounts of oxidants in the copper catalytic system, such as TEMPO or $PhI(OAc)_2$.[13] Indeed, some of these methodologies required the use of expensive and toxic osmium, rhodium, or gold catalysts. Consequently, environmentally benign and economical methods for the oxyamination of alkenes continue to be in high demand.

Molecular oxygen (O_2) is considered to be an ideal and environmentally friendly oxidant.[14] Thus dioxygen activation

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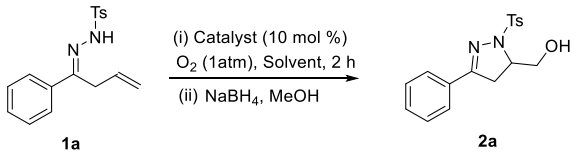
has drawn the great interest of organic chemists because of its enormous importance in chemistry and biochemistry.[15] Copper catalysts are used to combine molecular oxygen in organic synthesis owing to their abundant valence states and the affinity with oxygen.[16] As a result, numerous facile copper-based catalytic systems have been developed for aerobic synthesis.[17] Consequently, we envisioned exploiting copper catalysts for an intermolecular oxyamination of β,γ-unsaturated hydrazones with molecular oxygen to realize the difunctionalization of alkenes (Scheme 1c).

At the outset of our studies, we optimized the reaction conditions for the desired copper-catalyzed oxyamination of β,γ-unsaturated hydrazone **1a**. Initial attempts to form the desired cyclization product **2a** under basic conditions starting from **1a** resulted in an unsatisfactory yield (18%). It is noteworthy that a side reaction formed an undesired product in the screening reactions. Further careful analytical characterization demonstrated that it was an alkylhydroperoxide product. (See later for further discussions.) We were pleased to find that an in situ reduction by $NaBH_4$ resulted in the formation of the highly functionalized dihydropyrazoles. The product **2a** was obtained in a moderate yield using CuCl as the catalyst in dichloromethane at 25 °C (Table 1, entry 1).

Table 1. Optimization Studies for the Copper-Catalyzed Oxyamination of β,γ-Unsaturated Hydrazones[a]



1a **2a**

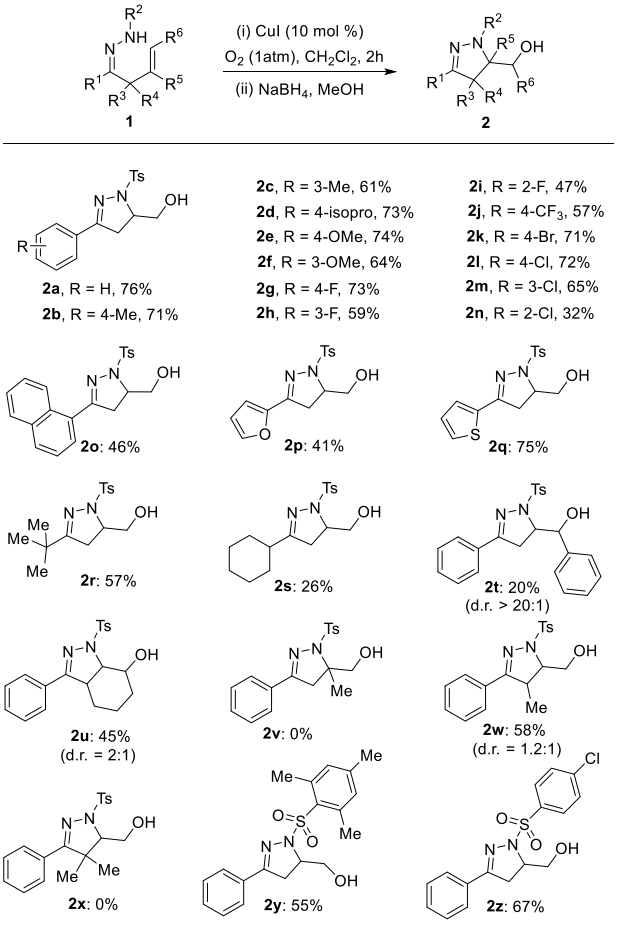
entry	catalyst	solvent	T (°C)	yield (%)[b]
1	CuCl	CH_2Cl_2	25	41
2	CuBr	CH_2Cl_2	25	48
3	**CuI**	**CH_2Cl_2**	**25**	**76**
4	CuI	toluene	25	20
5	CuI	DCE	25	71
6	CuI	THF	25	68
7	CuI	MeCN	25	70
8	CuI	Ph−Cl	25	45
9	CuI	CH_2Cl_2	40	62
10	CuI	CH_2Cl_2	25	60[c]
11	$Cu(OAc)_2$	CH_2Cl_2	25	57

[a]Reactions performed on a 0.2 mmol scale using catalyst (10 mol %), $[\mathbf{1a}]_0$ = 0.2 M and $NaBH_4$ (1.5 equiv). [b]Isolated yield. [c]5 mol % of CuI was used.

Different copper(I) salts were explored (entries 2 and 3), and copper iodide provided the best result. Subsequently, other solvents were also investigated, but no better results were obtained (entries 4−8). A lower conversion was observed when the temperature was increased to 40 °C (entry 9). Lowering the catalyst loading to 5 mol % decreased the reactivity (entry 10). In addition, $Cu(OAc)_2$ was also explored, but no better catalytic effect was observed (entry 11). Finally, the best reaction conditions were eventually finalized with 10 mol % of CuI as the catalyst and dichloromethane as the solvent.

With the optimized conditions in hand, we set out to investigate the scope of the transformation. As shown in Scheme 2, the presence of a range of substituents is compatible with the benign copper catalyst. Different substitution patterns

Scheme 2. Scope of the Copper-Catalyzed Oxyamination of β,γ-Unsaturated Hydrazones



at the aromatic moiety of **1** were well tolerated, leading to the corresponding products in moderate to good yield regardless of their electronic properties and position on the phenyl ring (**2a−n**). Substitution with 1-naphthyl at the two-position also gave the moderate yield (**2o**). In addition, the reaction proved to be compatible with heteroaryl frameworks, as shown in the synthesis of the furyl- and thiophenyl-substituted dihydropyrazoles (**2p,q**). Remarkably, the scope of the reaction was successfully extended to include a substrate containing an aliphatic substituent in **1** (**2r**), whereas the use of a cyclohexane-based **1** resulted in a low yield (**2s**). Subsequently, to access the potential for diastereocontrol of the reaction, the scope of the reaction with respect to the alkene moieties was also explored. Aryl- or alkyl-substituted alkenes were tolerated, although the formation of the corresponding products **2t,u** was sluggish in this reaction. A methyl group at the two-position of the alkene was not suitable, probably due to the steric effects (**2v**). It is notable that this protocol was also successfully extended to diversely substituted β,γ-unsaturated hydrazones with a methyl group at α position (**2w**), whereas with the germinal methyl group the reaction was not successful (**2x**). Moreover, various substituents on *N*-arylsulfonyl moieties, including 2,4,6-trimethyl or *para*-chloro groups on the aromatic ring, can also be used in the reaction (**2y,z**).

To demonstrate the synthetic utility of the current procedure, a transformation was performed. As depicted in Scheme 3, cyclization product **2a** could be transformed directly to the pyrazole **3** in good yield.[3c,f,18]

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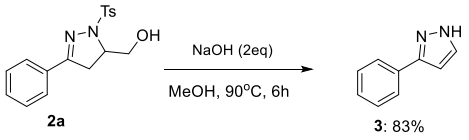
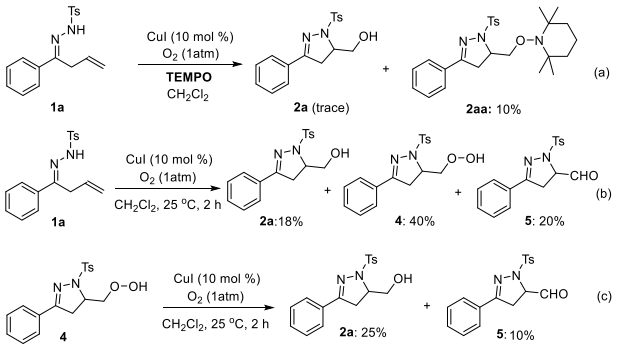
Scheme 3. Transformation of the Cyclization Product 2a



To gain some insight into the possible reaction mechanism, a series of control experiments was then carried out (Scheme 4). First, to verify the oxygen atom in the final product, we

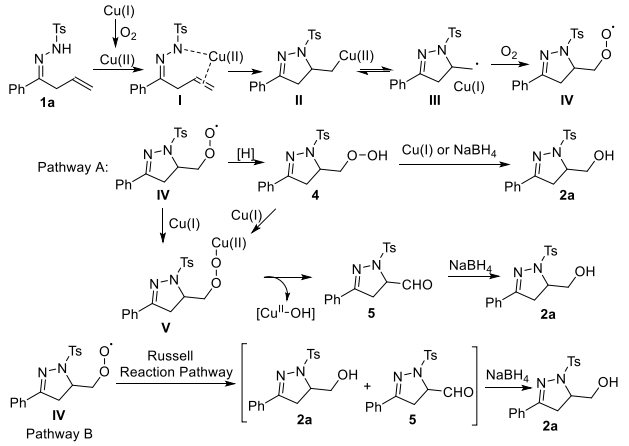
Scheme 4. Control Experiments



performed the ^{18}O isotopic labeling experiments. This indicated that the oxygen atom in the catalytic system was not derived from water. Subsequently, performing the reaction under a nitrogen atmosphere was sufficient to prevent **2a** formation (Supporting Information). The above results suggested that the molecular oxygen participated in the reaction and was incorporated into the final products. In addition, when the radical scavenger TEMPO was added to the reaction under otherwise identical conditions, a trace amount of the desired product **2a** was obtained, and the pyrazoline **2aa**, which was generated from the trapping of the C-centered radical intermediate **III** by TEMPO, was formed in 10% yield. (Scheme 4a). This finding indicated that the reaction process probably proceeded through a radical mechanism. It is notable that the alkylhydroperoxide **4** was formed in the catalytic system (Scheme 4b). Interestingly, when alkylhydroperoxide **4** was tested, only a low conversion of **2a** as well as **5** was obtained (Scheme 4c). Moreover, kinetics studies showed that the intermediate **4** was not the main source in the formation of **2a** (Figure S1), which means the desired product **2a** was probably generated from two different pathways.

Two plausible activation pathways based on the literature precedence[19] and our control experiments are proposed in Scheme 5. Initially, the intramolecular aminocupration of **1a** occurs upon alkene activation by the Cu(II) species, generated from the Cu(I) salt with molecular oxygen, which would provide the alkyl−copper complex **II**. Intermediate **II** may undergo homocleavage to form the radical intermediate **III**. This mechanistic rationale is in good agreement with the formation of carbon-centered radical intermediates **III**.[8c,20] Subsequently, intermediates **III** could be easily immediately trapped by dioxygen to generate the key alkylhydroperoxy radical **IV**. Following pathway A, alkylhydroperoxide **4** is formed via a hydrogen abstraction, and compound **5** is generated through intermediate **V**, followed by the elimination of [Cu(II)-OH] species. Subsequently, product **2a** is obtained after the reduction by $NaBH_4$ from compounds **4** and **5**. In

Scheme 5. Proposed Mechanism



addition, following Pathway B, the alkylhydroperoxy radical **IV** could transform to product **2a** and compound **5** via well-known alkylperoxo radical chemistry (e.g., the Russell mechanism),[21] whereas species **5** could be directly reduced to final product **2a**.

In summary, we have discovered a copper(I)-catalyzed oxyamination of β,γ-unsaturated hydrazones to access dihydropyrazoles derivatives in a one-pot process utilizing dioxygen as a sustainable sacrificial oxidant. Mechanistic studies suggest that two pathways are likely involved in the catalytic process. We believe that our findings will inspire more detailed mechanistic understanding and induce the development of further straightforward methods to access dihydropyrazole. Thus they will provide new opportunities and conceptual perspectives for the discovery and development of biologically active compounds. Further studies on the mechanism and synthetic applications of these reactions are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02733.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xtian@gzhmu.edu.cn.

ORCID

Lutz Ackermann: 0000-0001-7034-8772

Xu Tian: 0000-0002-4508-8347

Author Contributions

‖S.C. and W.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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