

Subscriber access provided by Kaohsiung Medical University

# Copper-Catalyzed Vinylogous Aerobic Oxidation of Unsaturated Compounds with Air

Hai-Jun Zhang, Alexander W. Schuppe, Shi-Tao Pan, Jin-Xiang Chen, Bo-Ran Wang, Timothy R. Newhouse, and Liang Yin J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.8b01886 • Publication Date (Web): 16 Mar 2018 Downloaded from http://pubs.acs.org on March 16, 2018

# Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7

8 9 10

11

12 13

14

15

16

17

18 19

20

21

22

23

24

25

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

# Copper-Catalyzed Vinylogous Aerobic Oxidation of Unsaturated Compounds with Air

Hai-Jun Zhang,<sup>1</sup> Alexander W. Schuppe,<sup>2</sup> Shi-Tao Pan,<sup>1</sup> Jin-Xiang Chen,<sup>1</sup> Bo-Ran Wang,<sup>1</sup> Timothy R. Newhouse,<sup>2,\*</sup> Liang Yin<sup>1,\*</sup>

<sup>1</sup>CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

<sup>2</sup>Department of Chemistry, Yale University, 225 Prospect, New Haven, Connecticut 06520-8107, United States

Supporting Information Placeholder

**ABSTRACT:** A mild and operationally simple copper-catalyzed vinylogous aerobic oxidation of  $\beta$ , $\gamma$ - and  $\alpha$ , $\beta$ -unsaturated esters is described. This method features good yields, broad substrate scope, excellent chemo- and regioselectivity and good functional group tolerance. This method is additionally capable of oxidizing  $\beta$ , $\gamma$ - and  $\alpha$ , $\beta$ -unsaturated aldehydes, ketones, amides, nitriles and sulfones. Furthermore, the present catalytic system is suitable for bisvinylogous and trisvinylogous oxidation. TMG was found to be crucial in its role as a base, but we also speculate it serves as a ligand to copper(II) triflate to produce the active copper(II) catalyst. Mechanistic experiments conducted suggest a plausible reaction pathway via an allyl copper(II) species. Finally, the breadth of scope and power of this methodology is demonstrated through application to complex natural product substrates.

# INTRODUCTION

Selective oxidation is one of the most critical reaction types utilized in both academic and industrial settings,<sup>1</sup> which allows conversion of petroleum-based feedstocks to useful chemicals of higher oxidation state such as alcohols, carbonyl compounds and epoxides. Among various oxidants, oxygen represents the most easily accessible and abundant oxidant, which can lead to an environmentally benign source for the oxidative functionalization of organic molecules.<sup>2</sup> A catalyst is indispensable to achieve a selective transformation due to the high activation energy of oxygen.<sup>3</sup> Moreover, poor selectivity and limited substrate scope, as well as over-oxidation are found as significant limitations.<sup>4</sup>

Recently, noteworthy advances have been achieved in transition metal-catalyzed selective aerobic oxidation of C-H bonds to C-C, C-N and C-O bonds and oxidation or cleavage of C-C double bonds.<sup>5,6</sup> Furthermore, various heterocycles have been synthesized by metal-catalyzed aerobic oxidation.<sup>7</sup> Considering the issues of relative safety, extremely low cost, sustainable abundance and ease of manipulation, performing aerobic oxidation using air is highly preferred. However, it is often challenging to employ air instead of oxygen in metal catalyzed aerobic oxidations due to reduced reactivity at lower oxygen concentration.<sup>8</sup> Although a significant number of transition-metal-catalyzed aerobic oxidations have been developed, practical and efficient hydroxylations with air as the oxidant are still highly desirable.

Among the various transition metal catalysts used in selective oxidation with oxygen, copper is widely recognized as ideal due to its natural abundance, cost effectiveness and sustainability.<sup>9,10</sup> More importantly, copper shows excellent reactivity: Cu<sup>0</sup>, Cu<sup>1</sup>, Cu<sup>11</sup>, and Cu<sup>111</sup> oxidation states can be easily accessed, which enables radical pathways or two-electron bond formations. In addition to its redox properties, copper has the additional possibility of acting as a Lewis acid either through  $\sigma$ -coordination to basic oxygen functionality or through  $\pi$ -coordination with numerous functional groups. Such reactivity is leveraged by metalloenzymes, possessing copper in the active site, which are utilized by nature as efficient catalysts for aerobic oxidation reactions.<sup>11</sup> In synthetic chemistry, copper-catalyzed or - mediated aerobic hydroxylations have been intensively studied and led to a number of important synthetically useful oxidation reactions, which have been applied in numerous industrial settings.<sup>12,13</sup>

Scheme 1. Copper-Catalyzed Vinylogous Aerobic Oxidation of  $\beta$ , $\gamma$ -Unsaturated Esters and Undesired Oxidation Pathways

A. Copper-Catalyzed Oxidation of Ketones with O2



B. Copper-Catalyzed Vinylogous Oxidation of  $\beta_{s\gamma}$ -Unsaturated Compounds with Air



One particular class of oxidation reaction is the oxidation of enolates, which is a direct and efficient way to obtain  $\alpha$ -hydroxyl carbonyl compounds.<sup>14</sup> In the classic oxidation of steroids,  $\alpha$ -hydroxylation has been possible using molecular oxygen as an oxidant:<sup>15</sup> generation of an enolate in the presence of a strong base (such as LDA), nucleo-

ACS Paragon Plus Environment

60

1

philic attack of oxygen by the enolate and reduction of newly formed peroxide by a trialkyl phosphite.<sup>16</sup> Phase-transfer catalysis has also been applied for aerobic oxidation of ketones and 2-oxindoles.<sup>17</sup> Several other oxidants, such as oxaziridines<sup>18-20</sup> and MoOPH,<sup>21</sup> compliment  $\alpha$ -hydroxylation of enolates with molecular oxygen.

More recently, copper-catalyzed  $\alpha$ -hydroxylation of ketones has emerged as an efficient and sustainable alternative to the use of stoichiometric oxidations in the preparation of  $\alpha$ -hydroxyl carbonyl compounds (Scheme 1A).<sup>22</sup> Although significant advances have been achieved in the aerobic oxidation of enolates via copper catalysis<sup>22</sup> or other transition metal catalysts,<sup>23</sup> there is no report of a transitionmetal-catalyzed vinylogous oxidation of dienolates. Due to competitive  $\alpha$ -hydroxylation and other deleterious side reactions related to the proximal olefin in both the starting material and product, it is challenging to simultaneously control both chemoselectivity and regioselectivity while solving the problem of over-oxidation (Scheme 1B).

 $\gamma$ -Hydroxyl- $\alpha$ , $\beta$ -(*E*)-alkenoic esters are important motifs present in naturally occurring compounds, such as macrolides.<sup>24</sup> These functional groups play an important role as Michael acceptors for thiol containing side chains in enzymatic binding sites.<sup>25</sup> Moreover, they served as versatile intermediates in a wide range of chemical manipulations in organic synthesis.<sup>26</sup> One of the most commonly employed methods for the oxidation of dienolates employs oxygen and P(OEt)<sub>3</sub>, in which the dienolates are generated by deprotonation of  $\beta$ , $\gamma$ unsaturated or  $\alpha,\beta$ -unsaturated ketones or esters in the presence of LDA.<sup>27</sup> However, very strong bases, such as LDA, are significantly limited in their functional group tolerance as a result of poor regioselectivity, low efficiency and over-oxidation. In 2017, two of us (A. W. S. and T. R. N.) utilized a vinylogous hydroxylation reaction with molecular oxygen to afford a  $\gamma$ -hydroxyl- $\alpha$ , $\beta$ -(E)-alkenoic ester molety, which was a key intermediate in the total synthesis of (±)andirolide N.<sup>28</sup> Here, we report a copper-catalyzed vinylogous aerobic oxidation of  $\gamma$ , $\gamma$ -disubstituted  $\beta$ , $\gamma$ - and/or  $\alpha$ , $\beta$ -unsaturated compounds under air, leading to a broad array of  $\gamma$ -hydroxyl- $\alpha$ ,  $\beta$ -(E)-unsaturated compounds (including esters, aldehydes, ketones, amides, nitriles and sulfones) in high yield.

#### RESULTS AND DISCUSSION

1. Optimization of Reaction Conditions. Based on our previously disclosed asymmetric vinylogous Mannich-type reaction catalyzed by a chiral copper(I) complex,<sup>29</sup> we envisioned that a copper-dienolate, generated upon deprotonation by a base, might be selectively oxidized by oxygen to produce a  $\gamma$ -hydroxyl- $\alpha$ , $\beta$ -(E)-alkenoic ester. In line with the above hypothesis, we commenced the investigation by using  $\gamma,\gamma$ -disubstituted  $\beta,\gamma$ -unsaturated ester **1a** as the substrate and Cu[(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> as the catalyst (Table 1). Addition of a reductant proved to be crucial, as the oxidation without any reductant resulted in 33% yield (entry 1), while the addition of PPh<sub>3</sub> as a reductant led to the product in 82% yield (entry 2). Other reductants were less successful, including the commonly employed reductant P(OEt)<sub>3</sub> (entry 3),<sup>30</sup> PBu<sub>3</sub> and Ph<sub>2</sub>PMe (see SI). Other triaryl phosphines were also investigated and PPh<sub>3</sub> outperformed these reductants.<sup>31</sup> Various other commercially available copper salts and solvents were found to be less successful (see SI). Although all copper salts examined catalyzed the desired aerobic oxidation, the use of Cu(OTf)<sub>2</sub> resulted in an increased yield (entry 4 and see SI).

Table 1. Optimization of the Reaction Conditions with  $\gamma,\gamma$ -Disubstituted  $\beta,\gamma$ -Unsaturated Esters under Oxygen Atmosphere<sup>*a*</sup>

	Ph Y O	Cu s base redu O <sub>2</sub> b	salt (5 mol %) e (1.2 equiv) uctant (1.5 equiv) palloon	но ү		O Ph
	Me T		<sup>c</sup> (0.2 M), rt, 4-48 h	Ph Me <sup>α</sup>		
	1a-5a			6a	-10a	11
entry	substrate	reductant	Cu salt	base	yield (%) <sup>b</sup>	yield of 11 (%) <sup>b</sup>
1	1a, R = Bn	-	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	TMG	33	21
2	1a, R = Bn	PPh <sub>3</sub>	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	TMG	82	8
3	1a, R = Bn	P(OEt) <sub>3</sub>	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	TMG	0	0
4	1a, R = Bn	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	85	8
5	1a, R = Bn	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	<sup>i</sup> Pr <sub>2</sub> NEt	0	0
6	1a, R = Bn	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	Barton's Base	43	22
7	1a, R = Bn	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	hppH	9	30
8	2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	87	8
9	3a, R = Et	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	82	10
10	4a, R = <sup>t</sup> Bu	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	72	13
11	5a, R = Ph	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	53	15
12 <sup>c</sup>	2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	87	8
13 <sup>d</sup>	2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	87	8
14 <sup><i>d</i>,</sup>	<sup>e</sup> 2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	87	8
15 <sup>d,</sup>	<sup>e, f</sup> 2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	90	8
16 <sup><i>d</i>,:</sup>	<sup>f,g</sup> 2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	TMG	87	10
17 <sup>d,</sup>	<sup>e, f</sup> 2a, R = Me	PPh <sub>3</sub>	-	TMG	0	0
18 <sup><i>d,</i></sup>	<sup>e, f</sup> 2a, R = Me	PPh <sub>3</sub>	Cu(OTf) <sub>2</sub>	-	0	0

<sup>a</sup>1a-5a: 0.2 mmol. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis of reaction crude mixture. <sup>c</sup>Air balloon employed. <sup>d</sup>Undried THF (water content ≤ 1000 ppm) and air balloon employed. <sup>e</sup>0.8 equiv TMG employed. <sup>f</sup>1.3 equiv PPh<sub>3</sub> employed. <sup>g</sup>0.3 equiv TMG employed. 60 h. TMG = tetramethyl guanidine. Barton's Base = 2-<sup>f</sup>Bu-1,1,3,3-tetramethylguanidine. hppH = 1,3,4,6,7,8-Hexahydro-2*H*-pyrimidd[1,2-a]pyrimidine.

A stronger amine base was indispensable as weaker bases (such as <sup>i</sup>Pr<sub>2</sub>NEt, Et<sub>3</sub>N, and Cy<sub>2</sub>NMe) were ineffective (entry 5 and see SI). Barton's base and hppH gave inferior results (entries 6-7). Studies on the identity of the ester group determined that a methyl ester was optimal (entry 8). The use of other ester substituents such as ethyl, tert-butyl and phenyl also led to product formation, albeit in lower yield (entries 9–11). It is very encouraging for process chemistry applications that under an atmosphere of air the vinylogous oxidation proceeded with comparable yield (entry 12). Adding water to the catalytic oxidative system did not affect the reaction outcome, which successfully enabled the vinylogous oxidation to proceed using undried THF under air (entry 13). 0.8 Equiv TMG was found to be ideal to promote the reaction to finish in 24 h without impacting the yield (entry 14). Reducing the amount of PPh<sub>3</sub> resulted in a slightly increased yield (entry 15). A catalytic amount of TMG (0.3 equiv) was also effective but prolonged reaction time was required (entry 16). Control experiments indicated that both copper(II) triflate and TMG were crucial in the present vinylogous oxidative system (entries 17 and 18). Furthermore, other metal salts including Lewis acids (such as  $Ni(OTf)_2$ ,  $Sc(OTf)_3$ ,  $Yb(OTf)_3$  and  $InBr_3$ ) and redox-active metal salts (such as FeSO<sub>4</sub>·7H<sub>2</sub>O, FeCl<sub>3</sub>, Mn(OAc)<sub>2</sub>·4H<sub>2</sub>O and Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O) were completely ineffective, highlighting the power of the copper catalyst system (see SI).

Scheme 2. Vinylogous Aerobic Oxidation of 2a under Reported Reaction Conditions (<sup>1</sup>H NMR yield was given)



The reported reaction conditions for the aerobic oxidation of carbonyl compounds<sup>15e,15f,22b</sup> and vinylogous aerobic oxidation of  $\beta$ , $\gamma$ unsaturated compound<sup>28</sup> were also investigated for the  $\gamma$ hydroxylation of **2a** (Scheme 2). Jiao's transition-metal-free condition,<sup>15e</sup> for the  $\alpha$ -hydroxylation of carbonyl compounds, was not efficient for the vinylogous oxidation of dienolates, as only 14% **7a** was obtained. Gnanaprakasam's transition-metal-free system<sup>15f</sup> was unproductive and product **7a** was not detected. Schoenebeck's catalytic system<sup>22b</sup> using Cu<sub>2</sub>O as the catalyst was not effective for this transformation either. At last, the condition reported from the total synthesis of (±)-andirolide N<sup>28</sup> was less effective to produce **7a** (46% vield in addition to 20% acetophenone).

Table 2. Substrate Scope of γ,γ-Disubstituted β,γ-Unsaturated Esters in Copper-Catalyzed Vinylogous Oxidation under Air Atmosphere<sup>a</sup>



<sup>1</sup>Solated yield reported on 0.2 mmol scale. <sup>b</sup>36 h. <sup>o</sup>240 h. <sup>d</sup>(E)-**2**/(E)-**12** = 9/1. <sup>e</sup>(E)-**2**/(E)-**12** = 10.6/1. <sup>f</sup>(E)-**2**/(E)-**12** = 5/1. 48 h. <sup>g</sup>(E)-**2**/(Z)-**2** = 1/2. 144 h. <sup>f</sup>60 h. <sup>f</sup>2/(E)-**12** = 9.8/1.3 equiv TMG and O<sub>2</sub> were used. Reflux, 48 h. <sup>j</sup>(E)-**2**/(E)-**12** = 22/1. 3 equiv TMG and O<sub>2</sub> were used. Reflux, 48 h. <sup>f</sup>2/(E)-**12** = 14.4/1. 20 mol % Cu(OTf)<sub>2</sub>, 3 equiv TMG and O<sub>2</sub> were used. Reflux, 60 h. <sup>f</sup>2/(E)-**12** = 4.3/1. 3 equiv TMG and O<sub>2</sub> were used.

2. Investigation of the Substrate Scope. The substrate scope of  $\gamma,\gamma$ -disubstituted  $\beta,\gamma$ -unsaturated esters was evaluated under the optimized reaction conditions (Table 2). In most cases, pure (E)- $\beta$ , $\gamma$ unsaturated esters were employed. However, due to the difficulty of obtaining a single alkene isomer, in some instances (E)-/(Z)-mixtures were directly subjected to vinylogous oxidation for the exploration of the substrate scope. A series of aromatic substituents were well tolerated at the R<sup>1</sup> position. Both electron-donating groups, such as methyl (7b, 7n), phenyl (7c), methoxy (7d, 7o), dimethylamino (7e); and electron-withdrawing groups, such as fluoride (7f), chloride (7g, 7p), bromide (7h, 7q), trifluoromethyl (7i), trifluoromethoxy (7j), methyl ester (7k), nitro (7l) and cyano (7m), did not have a significant effect on the yield. However, ortho-chlorophenyl led to moderate yield possibly due to the increased steric hindrance (7r). Both 2-naphthyl (7s) and 2-thienyl (7t) were compatible, affording corresponding products in good yield.

The substituent at the  $R^2$  position was extended from methyl to ethyl (7**u**), isopropyl (7**v**) and cyclopropyl (7**w**) successfully. In the cases of substrates with bis-aliphatic substituents, vinylogous oxidation was sluggish at room temperature. Thus an elevated reaction temperature and oxygen balloon were required to obtain oxidized products in moderate yield (7**x**-7**aa**). It is noteworthy that a trisubstituted alkene was tolerated in the present oxidative conditions (7**y**). Furthermore,  $\beta$ , $\gamma$ -unsaturated esters with other oxidation prone functional groups, such as ketone (7**ab**) and unprotected secondary and tertiary alcohols (7**ac**, 7**ad**), were also suitable substrates.

Table 3. Substrate Scope of  $\gamma,\gamma$ -Disubstituted  $\alpha,\beta$ -Unsaturated Esters in Copper-Catalyzed Vinylogous Oxidation under Air Atmosphere<sup>a</sup>



<sup>e</sup>lsolated yield reported on 0.2 mmol scale. <sup>b</sup>40 h. <sup>c</sup>72 h. <sup>d</sup>240 h. <sup>e</sup>(E)-**12**/(E)-**2** = 11/1. <sup>f</sup>(E)-**12**/(E)-**2** = 2.6/1. <sup>g</sup>36 h. <sup>h</sup>108 h. <sup>i</sup>48 h. <sup>j</sup>90 h.

As  $\alpha,\beta$ -unsaturated esters (12) are more commonly encountered in organic synthesis, we wanted to extend the reaction conditions to these substrates. However, the  $pK_a$  of the  $\gamma$ -proton in 12a is significantly higher than the  $pK_a$  of  $\alpha$ -protons in 2a,<sup>32</sup> which results in a more challenging deprotonation step. By increasing the amount of TMG to 1.2 equiv, the current catalytic system was successfully applied to  $\gamma,\gamma$ -disubstituted  $\alpha,\beta$ -unsaturated esters (12) (Table 3). Various  $\alpha,\beta$ -unsaturated esters containing an aryl and a methyl substituent at the  $\gamma$ -position were efficiently oxidized to generate  $\gamma$ -hydroxyl- $\alpha,\beta$ -(*E*)-alkenoic esters in good yield (7a–7q, 7ae–7ag). However, a bulky aryl group, such as *ortho*-methyl phenyl (7af), had a diminishing effect on the yield. It is encouraging that 2-naphthyl (7s) and 2-thienyl (7t) groups were well-tolerated. The aliphatic substituent was not limited to methyl, as substrates with ethyl (7u) and cyclopropyl (7w) were competent substrates. The aliphatic substituent was further expanded to the long alkyl chains containing various functional groups. Product **7ah** was generated in 32% yield presumably due to interference of a primary alcohol unit. The reaction of TBS-protected substrate **12ai** proceeded smoothly to give the product **7ai** in 67% yield. An acetal group was also tolerated under the present condition (**7aj**). The ester **12ak** containing a mono-substituted olefin was also a competent substrate, giving the product **7ak** in 80% yield. The substrates with two aliphatic substituents at the  $\gamma$ -position were completely inert under the current catalytic system, presumably due to the increased  $pK_a$  of the  $\gamma$ -proton in **12**.

Table 4. Preliminary Substrate Scope of  $\gamma,\gamma$ -Disubstituted  $\alpha,\beta$ -Unsaturated Aldehydes and Ketones in Copper-Catalyzed Vinylogous Oxidation under Air Atmosphere<sup>a</sup>



<sup>a</sup>lsolated yield reported on 0.2 mmol scale.  ${}^{b}\beta_{1}$ -Unsaturated **13** was used with O<sub>2</sub>. 20 min.  ${}^{c}\beta_{1}$ -Unsaturated **14** was used.  ${}^{d}0.4$  equiv TMG was used.

Unsaturated aldehydes and ketones were also submitted to the present catalytic vinylogous aerobic oxidation condition (Table 4).  $\alpha$ , $\beta$ -Unsaturated aldehydes bearing an aryl and a methyl group at the  $\gamma$ position were smoothly converted to the corresponding  $\gamma$ -hydroxyl- $\alpha,\beta$ -(E)-unsaturated aldehydes in reasonably good yield (15a-15d). The substrate derived from melonal (13e) was also suitable, leading to 15e in 52% yield in only 20 min. Moreover, both  $\beta$ ,  $\gamma$ -unsaturated phenyl ketone and  $\alpha,\beta$ -unsaturated phenyl ketone provided the same product in good yield (16a), 67% and 54% yield respectively. The oxidation of  $\alpha,\beta$ -unsaturated methyl ketone afforded **16b** in 76% yield. Subjecting a prenyl phenyl ketone to the current catalytic system led to 16c in 70% yield. Both  $\beta$ ,  $\gamma$ -unsaturated and  $\alpha$ ,  $\beta$ unsaturated cyclic ketones were oxidized to generate y-hydroxyl-yphenyl cyclohexanone (16d) in good yield. Again,  $\gamma,\gamma$ -dialkylsubstituted  $\alpha,\beta$ -unsaturated ketone was completely inert under the present condition.3

Table 5. Preliminary Substrate Scope of  $\gamma,\gamma$ -Disubstituted  $\beta,\gamma$ -Unsaturated Nitriles, Amides and Sulfones in Copper-Catalyzed Vinylogous Oxidation under Air Atmosphere<sup>a</sup>

60

1

2

3

4

2

3

4

5

6

7

8

9

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60



<sup>a</sup>Isolated yield reported on 0.2 mmol scale. <sup>b</sup>α,β-Unsaturated 17, 1.2 equiv TMG and 1.5 equiv PPh<sub>3</sub> were used. 12 h. <sup>c</sup>36 h. <sup>d</sup>3.0 equiv TMG and O<sub>2</sub> were used. Reflux, 48 h.  $e_{\alpha,\beta}$ -Unsaturated 18 and 1.2 equiv TMG were used. 48 h. f1.2 equiv TMG was used. 50 °C, 54 h. g1.2 equiv TMG was used. 79 h. h3.0 equiv TMG was used. 32 h. 0.4 equiv TMG and 1.3 equiv PPh3 were used, 5 h.

The applicability of the reaction conditions was further expanded to unsaturated nitriles, amides and sulfones, which are showcased in Table 5.  $\beta_{\gamma}$ -Unsaturated nitriles bearing one aryl and one methyl substituent were competent substrates and afforded corresponding products in decent yield (20a-20d). An  $\alpha,\beta$ -unsaturated nitrile was also hydroxylated at  $\gamma$ -position successfully (20a). The propensity of substrates containing two aliphatic substituents to undergo vinylogous oxidation was diminished. Therefore, refluxing the reaction mixture under an oxygen atmosphere and prolonged reaction time were required to obtain the product in good yield of these difficult substrates (20e-20f). A nitrile bearing two allylic methyl groups was also a competent substrate under the current catalytic system (20f).

 $\beta,\gamma$ -Unsaturated amides, including Weinreb amide (18a), pyrrolidine amide (18b), dibenzyl amine amide (18c), were also evaluated. The vinylogous oxidation of these amides proceeded smoothly to afford products in reasonably good yield. The functional group compatibility of the current catalytic system was further highlighted when the aniline amide (18d), containing a free N-H, was oxidized in 71% yield (21d). Moreover, a conjugated Weinreb amide substrate was oxidized without difficulty (21a). As for the  $\beta$ , $\gamma$ -unsaturated phenyl sulfones, several examples were studied, which gave  $\gamma$ -hydroxyl- $\alpha$ , $\beta$ -(E)-unsaturated sulfones in good yield (22a-22d). Moreover, vinylogous oxidation of trifluoromethyl sulfone proceeded smoothly to afford product 22e in 55% yield.

Scheme 3. Copper-Catalyzed Bisvinylogous and Trisvinylogous Aerobic Oxidation under Air Atmosphere



Since the vinylogous oxidation of unsaturated esters, aldehydes, ketones, amides, nitriles and sulfones proceeded smoothly, we attempted the more challenging selective bisvinylogous and trisvinylogous oxidation. As shown in Scheme 3, 23 was subjected to copper-catalyzed oxidation system and product 24 was isolated in 80% yield. It was found that two equivalents of TMG was required for complete conversion.  $\alpha, \beta, \gamma, \delta$ -Unsaturated aldehyde 25 was also tested under the current catalytic system. To our delight, product 26 was obtained in 87% yield and the aldehyde functionality was left untouched under the oxidation conditions. As for  $\alpha, \beta, \gamma, \delta$ -unsaturated ketone 27, product 28 was generated in 81% yield. Encouragingly, a more challenging remote oxidation of substrate 29 to product 30 was successfully achieved in 82% yield. Additionally, mono- $\gamma$ -substituted  $\alpha$ , $\beta$ unsaturated or  $\beta$ ,  $\gamma$ -unsaturated esters were also studied and no satisfactory results were obtained.34

As shown in Tables 2-5, many substrates required slightly modified reaction conditions. Generally, the substrates with higher  $pK_a$  of  $\alpha$ protons or y-proton or steric hindrance at y-position need increased reaction time, such as 2d, 2e, 2r, 2u, 2v, 2w, 12b, 12d, 12e, 12u, 12w, **12af-12ak**. While  $\alpha$ , $\beta$ -unsaturated aldehydes and ketones needed less TMG,  $\beta$ ,  $\gamma$ -unsaturated amides and sulfones required more equivalents of TMG than corresponding esters. Moreover, α,β-unsaturated compounds require more TMG than  $\beta_{\gamma}$ -unsaturated compounds, for example, 2 (Table 2) vs 12 (Table 3), 16a and 16d (Table 4B), 20a (Table 5A) and 21a (Table 5B).  $\beta$ , $\gamma$ -Unsaturated compounds with twoalkyl substituents, such as 2x-2aa, 17e and 17f, requires increased amount of TMG and more forcing reaction conditions (refluxing and oxygen instead of air). It is evident now that both the ease of deprotonation and the steric hindrance at the  $\gamma$ -position contributed to the ease of reaction.

3. Insights to the Reaction Mechanism and Proposed Reaction Pathways. Aside from facilitating deprotonation of the substrate, TMG may also act as a ligand to a copper(II) salt to form a Cu(II) complex,<sup>35</sup> which may be the real catalyst. In the case of employing Cu(I) salt, the oxidative atmosphere may transform it to corresponding Cu(II) salt and then Cu(II) catalyst could be accessed. Furthermore, TMG may act as a weak reductant, as hppH has been reported as a reductant in the oxidation of carbonyl compounds.<sup>22b,36</sup> As shown in Table 1 (entry 1), the  $\gamma$ -hydroxylation without PPh<sub>3</sub> led to the formation of the product **7a** in 33% yield. Additionally, when <sup>31</sup>P NMR of the reaction mixture was acquired the signals for PPh<sub>3</sub> and P(O)Ph<sub>3</sub> were observed, but no signal for a copper-PPh<sub>3</sub> complex was detected. It is therefore hypothesized that the role of PPh<sub>3</sub> is to act as a stoichiometric reductant.

The performance of both (*Z*)-2a and (*Z*)-12a in the vinylogous oxidation were also evaluated (Scheme 4). Under the optimal reaction conditions, the same product 7a was obtained in 78% <sup>1</sup>H NMR yield with 5% (*Z*)-2a recovered after the reaction was run for 82 hours, which indicated that (*Z*)-2a was less reactive than (*E*)-2a. (*Z*)-12a was the most inert, which afforded product 7a in 10% yield together with 88% recovered (*Z*)-12a in 90 h. These results suggest that the alkene geometry effected the ease of deprotonation and thus had an important influence on the reaction time. Moreover, the geometry of the generated copper(II)-dienolate complexes may also affect the reaction rate.

Scheme 4. Catalytic Vinylogous Aerobic Oxidation of (E)-/(Z)- $\beta$ , $\gamma$ -Unsaturated Esters and (E)-/(Z)- $\alpha$ , $\beta$ -Unsaturated Esters (<sup>1</sup>H NMR yield was given)



The vinylogous oxidation of **2a** proceeded in equal efficiency with TEMPO or 1,1-diphenylethylene as an additive. These two experimental observations argue against a radical based mechanism and suggest a two-electron process is operative (Table 6, entry 2 and 3). Vinylogous oxidation of **2a** also proceeded nicely in the dark or in the presence of DABCO, indicating that singlet oxygen was not involved in the reaction process (Table 6, entry 4 and 5).<sup>15e, 37</sup>

 Table 6. Catalytic Vinylogous Aerobic Oxidation under Some

 Special Conditions<sup>a</sup>



<sup>a</sup>Isolated yield reported on 0.2 mmol scale. <sup>b</sup>24 h.

# Scheme 5. <sup>18</sup>O Labeling Experiment



Scheme 6. Treating Product 7a with the Reaction Condition



An <sup>18</sup>O labeling experiment was performed with **19a** as the substrate as shown in Scheme 5, which demonstrated that the oxygen atom in the newly formed hydroxyl group originates from  $O_2$  rather than surreptitious water. Experiments using mass spectrometry led to the detection of <sup>18</sup>O-incorporated triphenyl phosphine oxide. These observations demonstrate the fate of molecular oxygen is incorporation into the alcohol product and oxidation of the terminal reductant. In order to probe how the acetophenone (**11**) byproduct in the reaction arises, product **7a** was subjected to the standard reaction conditions (Scheme 6), and 100% **7a** was recovered without any **11**. This control experiment demonstrated that the formation of acetophenone was not generated from decomposition or over-oxidation of **7a**, which suggests that **11** is formed by an alternative pathway from the starting material **2a**.

Scheme 7. Efforts to Capture a Peroxide Species through an Intramolecular Oxo-Michael Addition

2

3

4 5

6

7

8

9

10

11

12

13 14

15

16

17

18

19

20 21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

60

A. Capture of a Peroxide Species



Dienone **31**, containing an additional  $\alpha,\beta$ -unsaturated ketone unit, was designed to capture the suspected peroxide species (Scheme 7A). In accord with literature precedent on the oxidation of enolates with molecular oxygen,<sup>16</sup> it was our expectation that the present vinylogous oxidation proceeds via a peroxide intermediate such as A (Scheme 7C). When compound 31 was subjected to the standard reaction condition, products 32 and 33 were separately formed in 40% and 23% yield, respectively, as mixtures of diastereomers (1:1 dr) (Scheme 7A). The expected product 33 presumably arises via an oxa-Michael reaction after  $\gamma$ -hydroxylation occurs, while product 32 represents an over-oxidation product. Product 32 could be formed as outlined in Scheme 7C, wherein the initially formed  $\gamma$ -peroxy intermediate A undergoes an oxa-Michael reaction before reduction of the peroxide can occur. The resulting intermediate B would then be expected to decompose to the observed product 32 via the alkoxide C. It was therefore hypothesized that in the absence of PPh3 a greater quantity of 32 would be formed. Indeed, in the absence of PPh3 product 32 was isolated in 80% yield and 1:1 dr (Scheme 7A).

The decomposition of the endoperoxide **B** to the product **32** via this pathway would require that both oxygen atoms incorporated are derived from the same molecule of O<sub>2</sub>. To evaluate whether this is the case or if the two oxygen atoms are introduced independently, we conducted an experiment using a 1:1 mixture of O<sub>2</sub> and <sup>18</sup>O<sub>2</sub> (Scheme 7B). If the oxygen atoms are derived from one molecule of O<sub>2</sub>, as in endoperoxide **B**, we would expect a distribution of the doubly labeled <sup>16</sup>O product and the doubly labeled <sup>18</sup>O product. While if the epoxide **32** is formed by an alternative other pathway involving two discrete molecules of O<sub>2</sub>, we would expect a statistical distribution of products. Analysis of the mass spectrum data provided direct evidence that one molecule of O<sub>2</sub> leads to the product **32** consistent with the intermediacy of the endoperoxide **B**.

Scheme 8. Proposed Mechanism for the Copper-Catalyzed Aerobic Vinylogous Oxidation



Although speculative at this juncture,<sup>16</sup> we proposed a plausible reaction pathway for this vinylogous oxidation as shown in Scheme 8. The copper(II) complex V is formed through the coordination of TMG to copper(II) triflate.<sup>35</sup> In the presence of TMG, copper(II) dienolate W is generated, which would have an equilibrium with allyl copper(II) species X. It would be expected that oxidation of W would result in  $\alpha$ -oxidation, while oxidation of **X** would result in  $\gamma$ -oxidation and lead to the formation of a copper(II) peroxide species Y. Peroxide Y would be reduced through attack of PPh<sub>3</sub> at the less hindered distal peroxide oxygen atom to generate an alkoxide, which would be protonated to afford the final product 7a and regenerate the copper(II) complex V. Alternatively, the intermediate Y could afford a fourmembered endo-peroxide Z by an intramolecular oxa-Michael addition, which collapses to give the side product acetophenone (11) and regenerate the copper(II) complex V. An additional possibility that cannot be ruled out at this time is the role of bimetallic copper complexes, including those with bridging oxygen ligands.<sup>38</sup>

Scheme 9. Copper-Catalyzed 10 g-Scale Vinylogous Aerobic Oxidation



**4. Scalability of Vinylogous Oxidation Condition.** The robustness of the present vinylogous hydroxylation was showcased by a 10 g-scale oxidation of **2a**. As shown in Scheme 9, 8.93 grams of product **7a** was isolated in 82% yield, which demonstrated that the 10 g-scale reaction had the same efficiency as the milligram-scale reaction. Moreover, the vinylogous oxidation performed in 10 g-scale in the open air also proceeded in the same efficiency (see SI). An initial clear pale yellow mixture gradually changed to green, finally to dark green.

Scheme 10. Application of the Present Catalytic Vinylogous Aerobic Oxidation to Structure Modification and Total Synthesis of Natural Products



5. Application of the Present Methodology. The utility of this  $\gamma$ hydroxylation methodology was showcased for the modification of natural product derivatives (Scheme 10). For example, estr-5(10)-ene-3,17-dione (34) was selectively oxidized under the standard condition to afford 10\beta-hydroxyestr-4-ene-3,17-dione (35) in 56% yield. Both the allylic and tertiary C-H bonds were left intact under the oxidation condition. Tibolone (36), a synthetic steroid drug used mainly for treatment of endometriosis, was submitted to standard vinylogous oxidation condition and oxidized to 37 in 56% yield, which represents a fast and effective method to access Tibolone derivatives. Moreover, 3β-hydroxyandrosta-5,15-dien-17-one (38) was also a competent substrate for the current vinylogous oxidation reaction, which was selectively oxidized to give 3B,14B-dihydroxyandrosta-5,15-dien-17one (39) in 55% yield. The spectral data for products  $35^{39}$  and  $39^{40}$  are in agreement with the data previously reported; product 37 was characterized by X-ray crystallography. The prevalence of unsaturated carbonyl functionalities in synthetic intermediates and natural products makes the present method very attractive to carry out remote oxidation rapidly and efficiently.

The present vinylogous oxidation system was also employed in the synthesis of a natural product (Scheme 10). Iso-odoratin (40), which has multiple sites of potential oxidation, was subjected to the standard oxidation condition and selectively transformed to the corresponding  $\gamma$ -hydroxylated compound (41), a late-stage intermediate in the synthesis of (±)-andirolide N,<sup>28</sup> in 65% yield. The success of the standard reaction condition with this complex substrate suggests that these conditions may be quite general and see use in numerous other contexts.

#### CONCLUSION

In conclusion, an operationally simple and highly efficient catalytic system, using copper(II) triflate, TMG, PPh<sub>3</sub> and air, was developed. The present catalytic system for vinylogous aerobic oxidation was suitable for both  $\gamma,\gamma$ -disubstituted- $\beta,\gamma$ -unsaturated esters and  $\gamma,\gamma$ disubstituted-a, \beta-unsaturated esters. A series of functional groups (such as tertiary amine, nitro, ester, nitrile, ketone, primary, secondary and tertiary alcohol, TBS-ether, acetal and olefin) were well tolerated. Unsaturated aldehydes, ketones, amides, nitriles and sulfones were also viable substrates. Furthermore, a mechanism for the vinylogous aerobic oxidation has been proposed based on the experimental ob-

servations. It was postulated that TMG is not only a base for the deprotonation but also a ligand for copper(II) salt to form the real copper (II) catalyst. Finally, the utility of this hydroxylation methodology was showcased with the selective modification of natural product derivatives and the preparation of an advanced synthetic intermediate for the total synthesis of  $(\pm)$ -andirolide N. Application of the vinylogous oxidation to other problems in multistep synthesis, as well as development of a catalytic asymmetric version is currently under investigation in our laboratories.

### ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at:

Experimental procedures, X-ray diffraction, spectroscopic data for all new compounds including <sup>1</sup>H, <sup>19</sup>F and <sup>13</sup>C NMR spectra (PDF)

Crystallographic data (CIF)

### AUTHOR INFORMATION

#### **Corresponding Author**

\*liangyin@sioc.ac.cn \*timothy.newhouse@yale.edu ORCID

Liang Yin: 0000-0001-9604-5198 Timothy R. Newhouse: 0000-0001-8741-7236

Notes

The authors declare no competing financial interests.

#### ACKNOWLEDGMENT

We gratefully acknowledge the financial support from the "Thousand Youth Talents Plan", the National Natural Sciences Foundation of China (No. 21672235), the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB20000000), the "Shanghai Rising-Star Plan" (No. 15QA1404600), CAS Key Laboratory of Synthetic Chemistry of Natural Substances, the National Institutes of Health (1R01-GM118614-01A1), the National Science Foundation (GRFP to A.W.S.), Bristol Myers Squibb (fellowship to A.W.S.), Nalas Engineering, the Sloan Foundation, Yale University, and Shanghai Institute of Organic Chemistry. Additionally, Professor Dr. Jin-han Gui and Dr. Kai Ding at Shanghai Institute of Organic Chemistry are acknowledged for their generous offer of some commercially available steroids.

#### REFERENCES

- (a) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. (1)H. B. Chem. Rev. 2006, 106, 2943-2989. (b) Piera, J.; Bäckvall, J.-E. Angew. Chem., Int. Ed. 2008, 47, 3506-3523. (c) Cavani, F.; Teles, J. H. ChemSusChem 2009, 2, 508-534. (d) Bäckvall, J.-E., Modern Oxidation Methods, 2nd ed., Wiley-VCH: Weinheim, 2011. (e) Gunasekaran, N. Adv. Synth. Catal. 2015, 357, 1990-2010.
- (2)Stahl, S. S. Science 2005, 309, 1824-1826.
- For some recent papers on  $O_2$  activation by transition metals, see: (a) (3)Garcia-Bosch, I.; Company, A.; Frisch, J. R.; Torrent-Sucarrat, M.; Cardellach, M.; Gamba, I.; Güell, M.; Casella, L.; Que, L.; Ribas, X.; Luis, J. M.; Costas, M. Angew. Chem., Int. Ed. 2010, 49, 2406-2409. (b) Long, R.; Mao, K.; Ye, X.; Yan, W.; Huang, Y.; Wang, J.; Fu, Y.; Wang, X.; Wu, X.; Xie, Y.; Xiong, Y. J. Am. Chem. Soc. 2013, 135, 3200-3207. (c) Long, R.; Mao, K.;Gong, M.; Zhou, S.; Hu, J.; Zhi, M.; You, Y.; Bai, S.; Jiang, J.; Zhang, Q.; Wu, X.; Xiong, Y. Angew. Chem., Int. Ed. 2014, 53, 3205-3209. (d) Liang, Y.-F.; Jiao, N. Acc. Chem. Res. 2017, 50, 1640-1653.
- Foote, C. S.; Valentine, J. S.; Greenberg, A.; Liebman, J. F. Eds., (4) Active Oxygen in Chemistry, Blackie Academic & Professional: London, 1995.
- (5)For some recent reviews on transition metal-catalyzed aerobic oxidation: (a) Stahl, S. S. Angew. Chem., Int. Ed. 2004, 43, 3400-3420. (b)

60

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58 59

60

Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Chem. Rev. 2005, 105, 2329–2363. (c) Sigman, M. S.; Jensen, D. R. Acc. Chem. Res. 2006, 39, 221–229. (d) Boisvert, L.; Goldberg, K. I. Acc. Chem. Res. 2012, 45, 899–910. (e) Wu, W.; Jiang, H. Acc. Chem. Res. 2012, 45, 1736–1748. (f) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Chem. Soc. Rev. 2012, 41, 3381–3430. (g) Roduner, E.; Kaim, W.; Sarkar, B.; Urlacher, V. B.; Pleiss, J.; Gläer, R.; Einicke, W.-D.; Sprenger, G. A.; Beifuß, U.; Klemm, E.; Liebner, C.; Hieronymus, H.; Hsu, S.-F.; Plietker, B.; Laschat, S. ChemCatChem 2013, 5, 82–112. (h) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Chem. Rev. 2018, 118, 2636–2679.

- For some very recent examples on transition metal-catalyzed aerobic (6) oxidation, see: (a) Neu, H. M.; Jung, J.; Baglia, R. A.; Siegler, M. A.; Ohkubo, K.; Fukuzumi, S.; Goldberg, D. P. J. Am. Chem. Soc. 2015, 137, 4614-4617. (b) Gonzalez-de-Castro, A.; Xiao, J. J. Am. Chem. Soc. 2015, 137, 8206-8218. (c) McCann, S. D.; Stahl, S. S. J. Am. Chem. Soc. 2016, 138, 199-206. (d) Das, P.; Saha, D.; Saha, D.; Guin, J. ACS Catal. 2016, 6, 6050-6054. (e) Pattillo, C. C.; Strambeanu, I. I.; Calleja, P.; Vermeulen, N. A.; Mizuno, T.; White, M. C. J. Am. Chem. Soc. 2016, 138, 1265-1272. (f) Anson, C. W.; Ghosh, S.; Hammes-Schiffer, S.; Stahl, S. S. J. Am. Chem. Soc. 2016, 138, 4186-4193. (g) White, P. B.; Jaworski, J. N.; Fry, C. G.; Dolinar, B. S.; Guzei, I. A.; Stahl, S. S. J. Am. Chem. Soc. 2016, 138, 4869-4880. (h) Jiang, X.; Zhang, J.; Ma, S. J. Am. Chem. Soc. 2016, 138, 8344-9347. (i) Ingram, A. J.; Walker, K. L.; Zare, R. N.; Waymouth, R. M. J. Am. Chem. Soc. 2015, 137, 13632-13646. (j) Sheet, D.; Paine, T. K. Chem. Sci. 2016, 7, 5322-5331. (k) Ding, W.; Lu, L.-Q.; Zhou, Q.-Q.; Wei, Y.; Chen, J.-R.; Xiao, W.-J. J. Am. Chem. Soc. 2017, 139, 63-66. (1) Su, H.; Zhang, K.-X.; Zhang, B.; Wang, H.-H.; Yu, Q.-Y.; Li, X.-H.; Antonietti, M.; Chen, J.-S. J. Am. Chem. Soc. 2017, 139, 811-818. (m) Wenzel, M. N.; Owens, P. K.; Bray, J. T. W.; Lynam, J. M.; Aguiar, P. M.; Reed, C.; Lee, J. D.; Hamilton, J. F.; Whitwood, A. C.; Fairlamb, I. J. S. J. Am. Chem. Soc. 2017, 139, 1177-1190. (n) Yu, H.; Ru, S.; Dai, G.; Zhai, Y.; Lin, H.; Han, S.; Wei, Y. Angew. Chem., Int. Ed. 2017, 56, 3867-3871. (o) Gaser, E.; Kozuch, S.; Pappo, D. Angew. Chem., Int. Ed. 2017, 56, 5912-5915.
  - (7) For some recent examples on construction of heterocycles through transition metal-catalyzed aerobic oxidation, see: (a) Chiba, S.; Zhang, L.; Lee, J.-Y. J. Am. Chem. Soc. 2010, 132, 7266–7267. (b) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. Angew. Chem., Int. Ed. 2011, 50, 5678–5681. (c) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. J. Am. Chem. Soc. 2011, 133, 13942–13945. (d) Xu, Z.; Zhang, C.; Jiao, N. Angew. Chem., Int. Ed. 2012, 51, 11367–11370. (e) Wendlandt, A. E.; Stahl, S. S. J. Am. Chem. Soc. 2014, 136, 506–512. (f) Cheng, H.-G.; Miguélez, J.; Miyamura, H.; Yoo, W.-J.; Kobayashi, S. Chem. Sci. 2017, 8, 1356–1359.
    - (8) For some recent examples on catalytic oxidation under air, see: (a) Tian, J.-S.; Loh, T.-P. Angew. Chem., Int. Ed. 2010, 49, 8417–8420.
      (b) Li, S.; Wu, J. Org. Lett. 2011, 13, 712–715. (c) Hanson, S. K.; Wu, R.; Silks, L. A. Org. Lett. 2011, 13, 1908–1911. (d) Su, Y.; Zhang, L.; Jiao, N. Org. Lett. 2011, 13, 2168–2171. (e) Huang, D.; Wang, H.; Xue, F.; Shi, Y. J. Org. Chem. 2011, 76, 7269–7274. (f) Liu, Q.; Wu, P.; Yang, Y.; Zeng, Z.; Liu, J.; Yi, H.; Lei, A. Angew. Chem., Int. Ed. 2012, 51, 4666–4670. (g) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. J. Am. Chem. Soc. 2014, 136, 14858–14865.
  - (9) Zweig, J. E.; Kim, D. E.; Newhouse, T. R. Chem. Rev. 2017, 117, 11680-11752.
  - (10) (a) The Chemistry of Organocopper Compounds; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd.: Chichester, West Sussex, 2009. (b) Copper-Catalyzed Asymmetric Synthesis; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014. (c) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Wang, M.-M.; Dai, H.-X. Synthesis 2016, 48, 4381–4399.
    - (11) (a) Rosenzweig, A. C.; Sazinksy, M. H. Curr. Opin. Struct. Biol.
      2006, 16, 729–735. (b) Chufán, E. E.; Puiu, S. C.; Karlin, K. D. Acc. Chem. Res. 2007, 40, 563–572. (c) Que, L., Jr; Tolman, W. B. Nature 2008, 455, 333–340. (d) Himes, R. A.; Karlin, K. D. Curr. Opin. Chem. Biol. 2009, 13, 119–131.
    - (12) For some recent reviews on copper-mediated or catalyzed aerobic oxidation, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Angew. Chem., Int. Ed. 2011, 50, 11062–11087. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Chem. Rev. 2013, 113, 6234–6458. (c) Ryland, B. L.; Stahl, S. S. Angew. Chem., Int. Ed. 2014, 53, 8824–8838. (d) McCann, S. D.; Stahl, S. S. Acc. Chem.

*Res.* **2015**, *48*, 1756–1766. (e) Zhang, M.; Sun, S.-Z.; Wang, H.-L.; Wang, M.-M.; Dai, H.-X. *Synthesis* **2016**, *48*, 4381–4399.

- (13) For some very recent examples on copper-catalyzed aerobic oxidation, see: (a) Lee, Y. E.; Cao, T.; Torruellas, C.; Kozlowski, M. C. J. Am. Chem. Soc. 2014, 136, 6782–6785. (b) Esguerra, K. V. N.; Fall, Y.; Petitjean, L. P.; Lumb, J.-P. J. Am. Chem. Soc. 2014, 136, 7662–7668. (c) Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. Angew. Chem., Int. Ed. 2014, 53, 3236–3240. (d) Xu, C.; Zhang, L.; Luo, S. Angew. Chem., Int. Ed. 2014, 53, 4149–415. (e) Xu, B.; Lumb, J.-P.; Arndtsen, B. A. Angew. Chem., Int. Ed. 2015, 54, 4208–4211. (f) McCann, S. D.; Stahl, S. S. J. Am. Chem. Soc. 2016, 138, 199–206. (g) Liu, M.; Li, C.-J. Angew. Chem., Int. Ed. 2016, 55, 10806–10810. (h) Xu, B.; Hartigan, E. M.; Feula, G.; Huang, Z.; Lumb, J.-P.; Arndtsen, B. A. Angew. Chem., Int. Ed. 2016, 55, 15802–15806. (i) Iron, M. A.; Szpilman, A. M. Chem. Eur. J. 2017, 23, 1368–1378.
- (14) (a) Jones, A. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I.; Ley, S. V., Ed.; Pergamon Press Ltd.: Oxford, 1991; Vol. 7, pp 151–191. (b) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In *Organic Reactions*; Overman L. E., Ed.; John Wiley & Sons Inc.: New York, 2003; Vol. 62, pp 1–356.
- (15) (a) Adam, W.; Metz, M.; Prechtl, F.; Renz, M. Synthesis, 1994, 563–566. (b) El-Qisairi, A. K.; Qaseer, H. A. J. Organomet. Chem. 2002, 659, 50–55. (c) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. Angew. Chem., Int. Ed. 2007, 46, 5951–5954. (d) Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. Org. Lett. 2010, 12, 1496–1499. (e) Liang, Y.-F.; Jiao, N. Angew. Chem., Int. Ed. 2014, 53, 548–552. (f) Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. Org. Lett. 2017, 19, 3628–3631.
- (16) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. J. Org. Chem. 1968, 33, 3294–3297. (b) Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. J. Org. Chem. 1981, 46, 5383–5389. (c) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. J. Am. Chem. Soc. 1985, 107, 3253–3266. (d) Hartwig, W.; Born, L. J. Org. Chem. 1987, 52, 4352–4358. (e) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. J. Org. Chem. 1989, 54, 4576–4581.
- (17) (a) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* 1988, 29, 2835–2838. (b) Dehmlow, E. V.; Wagner, S.; Müller, M. *Tetrahedron* 1999, 55, 6335–6346. (c) Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Eur. J. Org. Chem.* 2002, 2087–2093. (d) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* 2008, 10, 1593–1595. (e) Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* 2012, 14, 4762–4765. (f) Sim, S.-B. D.; Wang, M.; Zhao, Y. *ACS Catal.* 2015, 5, 3609–3612.
- (18) Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. Chem. Rev. 2014, 114, 8016–8036.
- (19) For some selected examples on diastereoselective oxidation of oxazolidinone-based chiral amide enolates by oxaziridines, see: (a) Monma, S.; Sunazuka, T.; Nagai, K.; Arai, T.; Shiomi, K.; Matsui, R.; Ōmura, S. Org. Lett. 2006, 8, 5601–5604. (b) Pichlmair, S.; de Lera Ruiz, M.; Vilotijevic I.; Paquette, L. A. Tetrahedron 2006, 62, 5791–5802. (c) Zhang, L.; Zhu, L.; Yang, J.; Luo, J.; Hong, R. J. Org. Chem. 2016, 81, 3890–3900.
- (20) For some selected examples on catalytic asymmetric oxidation by oxaziridines, see: (a) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. P. Natl. Acad. Sci. U. S. A. 2004, 101, 5810-5814. (b) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. J. Am. Chem. Soc. 2006, 128, 16488-16489. (c) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T. Angew. Chem., Int. Ed. 2009, 48, 803-806. (d) Smith, A. M. R.; Rzepa, H. S.; White, A. J. P.; Billen, D.; Hii, K. K. J. Org. Chem. 2010, 75, 3085-3096. (e) Jiang, J.-J.; Huang, J.; Wang, D.; Zhao, M.-X.; Wang, F.-J.; Shi, M. Tetrahedron: Asymmetry 2010, 21, 794-799. (f) Li, J.; Chen, G.; Wang, Z.; Zhang, R.; Zhang, X.; Ding, K. Chem. Sci. 2011, 2, 1141-1144. (g) Takechi, S.; Kumagai, N.; Shibasaki, M. Tetrahedron Lett. 2011, 52, 2140-2143. (h) Zou, L.; Wang, B.; Mu, H.; Zhang, H.; Song, Y.; Qu, J. Org. Lett. 2013, 15, 3106-3109. (i) Naganawa, Y.; Aoyama, T.; Nishiyama, N. Org. Biomol. Chem. 2015, 13, 11499-11506.
- (21) (a) Vedejs, E. J. Am. Chem. Soc. 1974, 96, 5944–5946. (b) Vedejs, E.; Engler, D. A.; Telschow, J. E. J. Org. Chem. 1978, 43, 188–196.
  (c) Hara, O.; Takizawa, J.; Yamatake, T.; Makino, K.; Hamada, Y. Tetrahedron Lett. 1999, 40, 7787–7790. (d) Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. Tetrahedron 2002, 58, 9737–9740.

м

(22) (a) Arai, T.; Sato, T.; Noguchi, H.; Kanoh, H.; kaneko, K.; Yanagisawa, A. *Chem. Lett.* **2006**, *35*, 1094–1095. (b)Tsang, A. S.-K.; Kapat, A.; Schoenebeck, F. J. Am. Chem. Soc. **2016**, *138*, 518–526.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

60

- (23) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. J. Am. Chem. Soc. 2011, 133, 1760–1762.
- (24) For some selected examples, see: (a) Dubost, C.; Markó, I. E.; Ryckmans, T. Org. Lett. 2006, 8, 5137–5140. (b) Shiina, I.; Takasuna, Y.; Suzuki, R.; Oshiumi, H.; Komiyama, Y.; Hitomi, S.; Fukui, H. Org. Lett. 2006, 8, 5279–5282. (c) Fukui, H.; Shiina, I. Org. Lett. 2008, 10, 3153–3156.
- (25) Du, Z.; Kawatani, T.; Kataoka, K.; Omatsu, R.; Nokami, J. *Tetrahedron* 2012, 68, 2471–2480.
- (26) (a) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* 2001, 627–628. (b) Rao, K. S.; Mukkanti, K.; Reddy, D. S.; Pal, M.; Iqbal, J. *Tetrahedron Lett.* 2005, *46*, 2287–2290. (c) Keeri, A. R.; Gualandi, A.; Mazzanti, A.; Lewinski, J.; Cozzi, P. G. *Chem. –Eur. J.* 2015, *21*, 18949–18952.
- (27) (a) Masamune, S.; Brooks, D. W.; Morio, K.; Sobczak, R. L. J. Am. Chem. Soc. 1976, 98, 8277–8279. (b) Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. Tetrahedron 1992, 48, 7013–7032. (c) Jackson, R. W.; Higby, R. G.; Shea, K. J. Tetrahedron Lett. 1992, 33, 4685–4698.
- (28) Schuppe, A. W.; Newhouse, T. R. J. Am. Chem. Soc. 2017, 139, 631–634.
- (29) Zhang, H.-J.; Shi, C.-Y.; Zhong, F.; Yin, L. J. Am. Chem. Soc. 2017, 139, 2196–2199.
- (30) The γ-hydroxylation of 2a with P(OEt)<sub>3</sub> failed at room temperature. However, 40% 7a was obtained when the reaction was heated at 55 °C for 24 h.



(31) Several triaryl phosphines were examined in the  $\gamma$ -hydroxylation of **2a**. Except for the electron-rich P(4-MeO-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, other phosphines led to **7a** in good yield. Particularly, both (*R*)-BINAP and (*R*)-Tol-BINAP (0.65 equiv) worked with equal efficiency as PPh<sub>3</sub>. The product **7a** was obtained in good yield but without any asymmetric induction. Therefore, it is less likely that the complex of phosphine and copper(II) or copper(I) was involved as a catalyst in the present vinylogous hydroxylation.



<sup>a1</sup>H NMR yield reported on 0.2 mmol scale. <sup>b</sup>**2a** remained and unchanged. <sup>c</sup>0.65 equiv bisphosphine employed.

- (32) Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. Org. Lett. 2007, 9, 3387–3390.
- (33) γ,γ-Dialkyl-substituted α,β-unsaturated ketone, such as 42, was subjected to the optimized reaction condition. However, no reaction occurred judging from the TLC and crude NMR analysis.

(34) Mono- $\gamma$ -substituted  $\alpha$ , $\beta$ -unsaturated or  $\beta$ , $\gamma$ -unsaturated esters were also studied and no satisfactory results were obtained.



- (35) The complex of TMG and Cu(II) was reported, see : Longhi, R.; Drago, R. S. *Inorg. Chem.* **1965**, *4*, 11-14.
- (36) Both TMG and hppH belong to guanidine, whose structures were depicted below.



hppH

(37) Quannes, C.; Wilson, T. J. Am. Chem. Soc. 1968, 90, 6527-6528.

TMG

- (38) Elwell, C. E.; Gagnon, N. L.; Neisen, B. D.; Dhar, D.; Spaeth, A. D.; Yee, G. M.; Tolman, W. B. *Chem. Rev.* 2017, *117*, 2059–2107.
- (39) Buděšínský, M.; Fajkoš, J.; Günter, J.; Kasal, A. Collect. Czech. Chem. Commun. 2005, 70, 507-518.
- (40) Reich, I. L.; Reich, H. J.; Kneer, N.; Lardy, H. Steroids 2002, 67, 221-233.

# Journal of the American Chemical Society

