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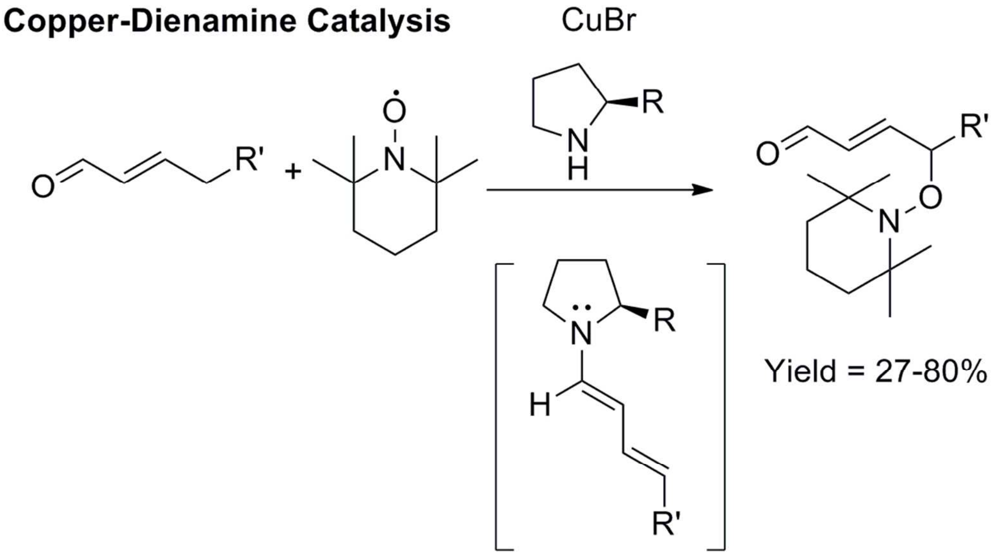

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Copper-Dienamine Catalysis: γ-Oxyamination of α,β-Unsaturated Aldehydes

Cite this: DOI: 10.1039/x0xx00000x

Xuan-Huong Ho,[a] Won-Ji Jung,[a] Pranab K. Shyam,[a] Hye-Young Jang[a,b]*

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A multicatalytic system composed of copper complexes and *sec*-amine compounds is proposed for γ-oxyamination of α,β-unsaturated aldehydes. Using copper complexes in dienamine catalysis expands the scope of the reaction to include TEMPO radicals. Furthermore, copper catalysts oxidize allylic alcohols to form α,β-unsaturated aldehydes, enabling the one-pot oxidation/oxyamination of allylic alcohols.

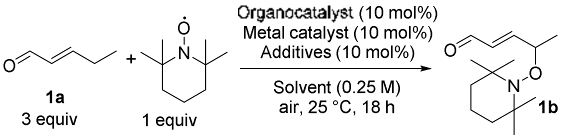
Extensive studies on amino catalysis have resulted in environmentally friendly, efficient, and highly stereoselective synthetic tools to form a wide range of pharmaceutically and synthetically useful organic compounds.[1,2,3] Depending on the catalytically active species, the amino catalysis is categorized as enamine catalysis, iminium catalysis, or multicatalysis involving several sequences of enamine and iminium catalysis. In addition to these categories, dienamine and trienamine catalysis were recently reported by Jørgensen and Chen, in which poly conjugated enals form dienamine and trienamine intermediates to afford complicated organic structures in a one-pot reaction.[4,5]

Metal complexes have also been used to expand the scope of aminocatalysis, leading to a diverse range of new organocatalytic reactions including radical reactions and photoreactions.[6,7] Our research group has reported 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) radical addition to aldehydes under enamine-electrolysis conditions and enamine-metal-catalyzed conditions.[8] Under enamine-metal-catalyzed conditions, TEMPO was added to aldehydes to provide synthetically versatile α-oxyaminated aldehydes. Considering the similar nucleophilic character of enamines and dienamines, it is speculated that the enamine-metal-catalyzed α-oxyamination protocol may be used for the dienamine-catalyzed γ-oxyamination of α,β-unsaturated aldehydes. The γ-oxyaminated α,β-unsaturated aldehydes are related to γ-hydroxy carbonyl compounds, which are commonly found in lipid peroxidation associated with oxidative stress.[9] Common syntheses of γ-hydroxy α,β-unsaturated aldehydes are oxidative cleavage of the double bond in polyenol, triple bond reduction of propargyl alcohol derivatives, and Wittig reaction of α-hydroxy aldehydes. There is no direct method to install an oxygen functional group at the γ-position of α,β-unsaturated aldehydes.[10]

Copper and iron complexes are known to form metal-TEMPO species for oxyamination. [8e,8f,8g,11,12] Copper complexes are also known as efficient catalysts for the oxidation of alcohols.[13] In this study, efficient multicatalytic reactions using copper complexes and amine catalysts are used to synthesize γ-oxyaminated α,β-unsaturated aldehydes from allylic alcohols and α,β-unsaturated aldehydes.

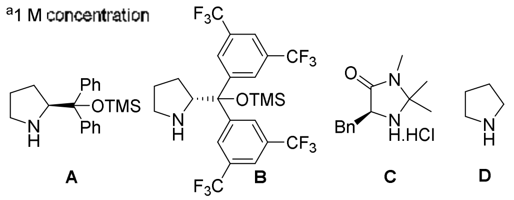
Initially, the reaction conditions for the γ-oxyamination of α,β-unsaturated aldehydes were optimized. The addition of TEMPO to pent-2-enal **1a** was investigated in the presence of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**A**) and metal catalysts. On the basis of previous reports regarding enamine-catalyzed TEMPO addition to saturated aldehydes, copper and iron complexes were thought to be suitable for TEMPO addition to **1a**.[11] As shown in Table 1, CuCl, CuBr, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, and $FeCl_3{\cdot}6H_2O$ were tested, and CuBr afforded **1b** in the highest yield (Table 1, entry 2). To determine the effect of the concentration, the reaction was run at a higher concentration of toluene (1 M), resulting in a lower yield (35%, Table 1, entry 2). The reactivities of the organocatalysts **A**, **B**, **C**, and **D** were compared (Table 1, entries 2 and 8-10). The sterically hindered amine catalyst **B** and imidazolidinone catalyst **C** promoted the reaction, albeit in low yield. Pyrrolidine, an achiral amine, was employed as a catalyst to form **1b** in 50% yield. Other than 2-NO_2-substituted benzoic acid, other carboxylic acids (pivalic acid, adamantane carboxylic acid, and benzoic acid) and *p*-toluene sulfonic acid were tested, but the yield was not improved (Table 1, entries 11-14). Suitable solvents (toluene, $CHCl_3$, THF, CH_3CN, and DMF) for TEMPO addition to **1a** were investigated; the highest yield was obtained with toluene (Table 1, entries 2, 15-18). The γ-oxyamination of **1a** did not occur in the absence of organocatalysts and metal complexes. Although chiral catalysts were used, enantioselectivity was not observed. Presumably, racemization occurs at the γ-position of **1b** during the reaction.

Table 1 Optimization of the γ-oxyamination of α,β-unsaturated aldehyde **1a**



Entry	Metal catalyst	Organo catalyst	Additives	Solvent	Yield
1	CuCl	A	$2\text{-}NO_2PhCO_2H$	Toluene	62%
2	CuBr	A	$2\text{-}NO_2PhCO_2H$	Toluene	68%(35 %)[a]
3	$CuCl_2$	A	$2\text{-}NO_2PhCO_2H$	Toluene	32%
4	$CuBr_2$	A	$2\text{-}NO_2PhCO_2H$	Toluene	60%
5	$Cu(OAc)_2$	A	$2\text{-}NO_2PhCO_2H$	Toluene	57%
6	$Cu(OTf)_2$	A	$2\text{-}NO_2PhCO_2H$	Toluene	32%
7	$FeCl_3.6H_2O$	A	$2\text{-}NO_2PhCO_2H$	Toluene	38%
8	CuBr	B	$2\text{-}NO_2PhCO_2H$	Toluene	22%
9	CuBr	C	$2\text{-}NO_2PhCO_2H$	Toluene	34%
10	CuBr	D	$2\text{-}NO_2PhCO_2H$	Toluene	50%
11	CuBr	A	Pivalic acid	Toluene	39%
12	CuBr	A	$AdamCO_2H$	Toluene	42%
13	CuBr	A	$PhCO_2H$	Toluene	52%
14	CuBr	A	p-TsOH	Toluene	28%
15	CuBr	A	$2\text{-}NO_2PhCO_2H$	$CHCl_3$	31%
16	CuBr	A	$2\text{-}NO_2PhCO_2H$	THF	58%
17	CuBr	A	$2\text{-}NO_2PhCO_2H$	CH_3CN	53%
18	CuBr	A	$2\text{-}NO_2PhCO_2H$	DMF	42%

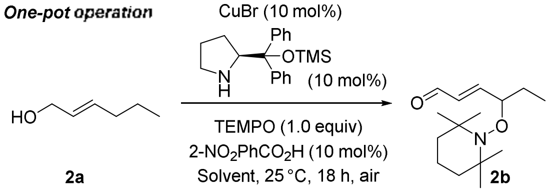
[a] 1 M concentration



The optimized conditions for the γ-oxyamination of α,β-unsaturated aldehydes involved CuBr and TEMPO, which are known as good oxidation catalysts for allylic alcohols. Therefore, a tandem reaction including the oxidation of allylic alcohols and the γ-oxyamination of α,β-unsaturated aldehydes was attempted (Tables 2 and 3). Using allylic alcohol **2a** as a starting material, a one-pot reaction involving allylic alcohol oxidation and γ-oxyamination was conducted to afford the desired tandem oxidation/γ-oxyamination product **2b** in 19-42% yield (Table 2). With a higher concentration (1 M) of the solvent, the yields of **2b** were increased to 43-56% (Table 2).

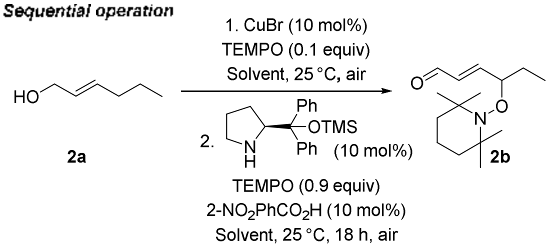
In the one-pot reaction, the incomplete oxidation of **2a** was presumed to cause the low yield of **2b** (34%, 0.25 M toluene). Therefore, a sequential procedure of oxidation followed by γ-oxyamination was attempted; the oxidation of **2a** was conducted in a solution of CuBr (10 mol%) and TEMPO (0.1 equiv) in an air atmosphere, and the subsequent γ-oxyamination was carried out in a solution of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (10 mol%), $2\text{-}NO_2$-substituted benzoic acid (10 mol%), and TEMPO (0.9 equiv) in an air atmosphere (Table 3). With toluene (1 M) as a solvent, both the sequential addition protocol and one-pot operation show similar yields; however, $CHCl_3$ and THF show decreased yields with the sequential operation (36% in $CHCl_3$ and 30% in THF). With CH_3CN and DMF, the sequential method gave higher yields of **2b** (67% and 80% in CH_3CN and DMF, respectively). The oxidation time of **2a** in CH_3CN and DMF is relatively shorter, which results in increased yields with the sequential protocol. In toluene, $CHCl_3$, and THF, the slow oxidation results in similar or lower yields with the sequential operation compared to the one-pot reaction. While **2a** undergoes the slow oxidation in $CHCl_3$ and THF for one day, the catalytic activity of copper complexes decreases, which affects the yield of the copper-catalyzed oxyamination (2nd step). In the tandem reaction, alcohols remained without being converted to either aldehydes or oxyaminated aldehydes in toluene, $CHCl_3$, and THF, resulting in low yield.

Table 2 One-pot reaction of the tandem oxidation/γ-oxyamination of allylic alcohol **2a**



Entry	Solvent	Yield (concentration)
1	Toluene	34% (0.25 M), 56% (1 M)
2	$CHCl_3$	42% (0.25 M), 43% (1 M)
3	THF	28% (0.25 M), 47% (1 M)
4	CH_3CN	32% (0.25 M), 48% (1 M)
5	DMF	19% (0.25 M), 45% (1 M)

Table 3 Sequential operation of the tandem oxidation/γ-oxyamination of allylic alcohol **2a**

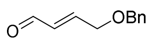
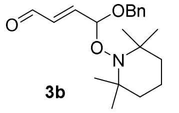
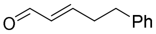
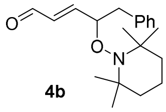
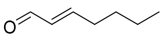
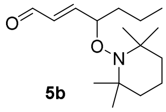
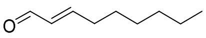
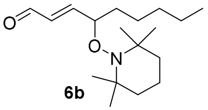
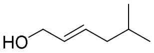
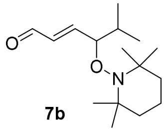
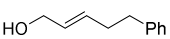
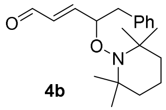
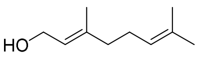
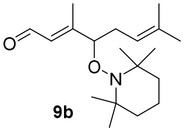
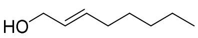
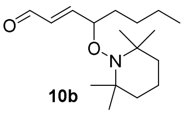


Entry	Solvent	Yield (conc.)	Time (1st step)
1	Toluene	57% (1 M)	1d
2	$CHCl_3$	36% (1 M)	1d
3	THF	30% (1 M)	1d
4	CH_3CN	67% (1 M)	6h
5	DMF	80% (1 M)	4h

Next, diverse α,β-unsaturated aldehydes were subjected to γ-oxyamination using (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**A**), CuBr, and 2-nitro-benzoic acid ($2\text{-}NO_2\text{-}PhCO_2H$) in toluene (Table 4, entries 1-4). 4-Benzyloxy-but-2-enal **3a** was transformed to γ-oxyaminated α,β-unsaturated aldehyde **3b** in 31% yield (Table 4, entry 1). The α,β-unsaturated aldehydes containing an alkyl chain (**4a**, **5a**, and **6a**) participated in the reaction to afford to γ-oxyaminated product **4b** (56% yield), **5b** (51% yield), and **6b** (54% yield), respectively (Table 4, entries 2-4).

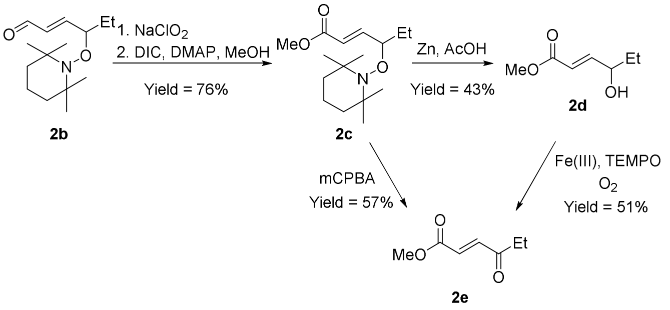
The tandem oxidation/γ-oxyamination of allylic alcohols was conducted in either one-pot in toluene or in two steps in DMF (Table 4, entries 5-8). The tandem protocol has the advantage in converting volatile α,β-unsaturated aldehydes. For example, the isolation of α,β-unsaturated aldehydes derived from the oxidation of 5-methylhex-2-en-1-ol **7a** is not trivial due to the volatility. By using the tandem reaction, **7a** was converted to **7b** in 46% yield without purifying the aldehyde intermediates (Table 4, entry 5). In the case of **8a**, the γ-oxyamination of the oxidized compound of **8a** is shown in entry 2 of Table 4. The yield of the γ-oxyamination of **4a** was 56%, and the two step sequential reaction of **8a** afforded the γ-oxyaminated aldehyde **4b** in 45% yield (Table 4, entry 6). Allylic alcohols possessing a long alkyl chain (**9a** and **10a**) were converted to **9b** and **10b** in 36% and 27% yields, respectively. In the case of **9a**, although *trans*-**9a** was used, isomerization occurred under the conditions to form *trans* and *cis* isomer mixtures of **9b**.

Table 4 Examples of the γ-oxyamination of α,β-unsaturated aldehydes and the oxidation/γ-oxyamination of allylic alcohols

Entry	Reactant	Product	Yield
1	 **3a**	 **3b**	31%
2	 **4a**	 **4b**	56%
3	 **5a**	 **5b**	51%
4	 **6a**	 **6b**	54%
5	 **7a**	 **7b**	46%[a]
6	 **8a**	 **4b**	45%[a]
7	 **9a**	 **9b**	36%[b]
8	 **10a**	 **10b**	27%[a]

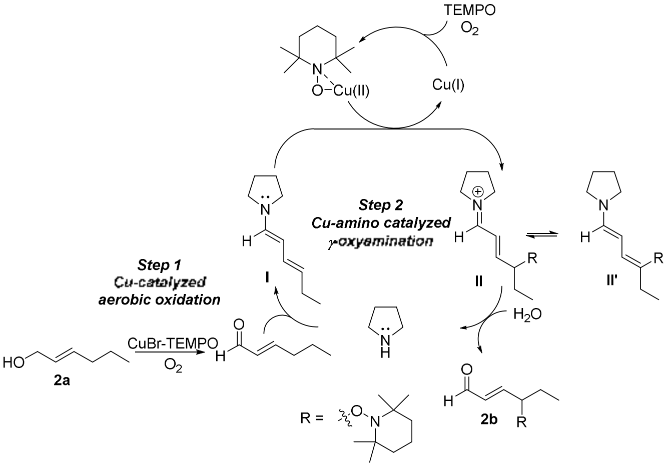
[a] Sequential addition in DMF, [b] One-pot reaction in toluene

The synthetic utility of our method was shown by the synthesis of γ-hydroxy ester **2d** and 1,4-dicarbonyl compound **2e** (Scheme 1). The γ-hydroxy- and γ-oxo-α,β-unsaturated carbonyl compounds have been utilized in a diverse range of organic reactions e.g., cycloadditions and Michael reactions.[14,15] The oxidation followed by esterification of γ-hydroxy unsaturated aldehyde **2b** afforded the corresponding ester **2c** in 78% yield. The addition of zinc metal (Zn) to the reaction mixture of **2c** in acetic acid gave **2d** in 43% yield. The subsequent aerobic oxidation of **2d** provided **2e** in 51% yield. Compound **2e** was directly formed by the reaction of **2c** with mCPBA with the yield of 57%.



Scheme 1 Modification of **2b** to form γ-hydroxy ester **2d** and 1,4-dicarbonyl compound **2e**

A plausible reaction mechanism for the tandem copper-catalyzed oxidation and copper-aminocatalyzed oxyamination of α,β-unsaturated aldehydes is shown in Scheme 2. In step 1, copper-TEMPO complexes are used to oxidize **2a**. The oxidized compound goes into the dienamine cycle, forming dienamine intermediate **I**. Upon the addition of the copper-TEMPO complex to **I**, iminium intermediate **II** was formed. Due to the acidity of the γ-carbon, **II** was converted to dienamine intermediate **II′**, which prevented the further addition of nucleophiles at the β-position of **II**. Various nucleophiles were tested, but the formation of β,γ-substituted aldehydes was not observed. After the hydrolysis of **II** or **II′**, the desired product **2b** was obtained.



Scheme 2 A plausible reaction mechanism for tandem oxidation/γ-oxyamination

Conclusions

We have presented a multicatalytic reaction where a copper catalyst and an amine catalyst were used to promote both the γ-oxyamination of α,β-unsaturated aldehydes and the tandem aerobic oxidation of allylic alcohols/γ-oxyamination of α,β-unsaturated aldehydes. Diverse allylic alcohols and α,β-unsaturated aldehydes were converted to γ-oxyaminated α,β-unsaturated aldehydes. The copper-catalyzed oxyamination at the γ-position of α,β-unsaturated aldehydes occurs via a dienamine species, which is reported for the first time in this work.

Acknowledgements

This study was supported by the Korea Research Foundation (No. 2009-0094046 and 2013008819) and the Korea CCS R&D Center (KCRC) grant funded by the Korea Government (Ministry of Education, Science and Technology) (No.2012-0008935).

Notes and references

[a]Division of Energy Systems Research, Ajou University, Suwon 443-749, Korea, E-mail:hyjang2@ajou.ac.kr; Fax: +82312191615; Tel: +82 31 219 2555
[b]Korea Carbon Capture & Sequestration R&D Center, Deajeon 305-343, Korea.

Electronic Supplementary Information (ESI) available: detailed experimental and spectral analysis for new compounds. See DOI: 10.1039/c000000x/

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