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Propargylic C—H activation using a Cu(II) 2-quinoxalinol salen catalyst and *tert*-butyl hydroperoxide

Clayton C. Black, Anne E.V. Gorden *

Department of Chemistry and Biochemistry, College of Sciences and Mathematics, Auburn University, Auburn, AL 36849-5319, USA

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ABSTRACT

The oxidation of alkynes to α,β-acetylenic carbonyls was achieved using only 1 mol% of a Cu(II) 2-quinoxalinol salen catalyst with *tert*-butyl hydroperoxide. These reactions proceed under mild conditions (70 °C) with excellent selectivity, producing yields up to 78%, and were used on a variety of alkyne substrates to produce the desired corresponding α,β-acetylenic ketones. In addition, these reactions can be run under aqueous conditions using a sulfonated version of the 2-quinoxalinol salen with good yields, reducing the need for volatile organic solvents.

Introduction

The ability to directly install an oxygen onto a C—H bond through C—H activation or oxidation reactions is potentially extremely useful in synthetic organic chemistry; however, being able to do so has proven to be a great challenge. Much of the research towards this has exploited transition metal catalysis to overcome the high activation requirements of these reactions.[1–6] While several examples of C—H oxidation reactions exist, very few examples of propargylic oxidations have been reported. Examples reported previously include the use of expensive transition metals such as rhodium, higher catalyst loading, long reaction times, or they may use multiple additives in addition to the catalyst.[7–12] The synthesis of α,β-acetylenic ketones is of wide interest due to their use as starting materials for the synthesis of heterocycles, nucleosides, aromatic compounds, anticancer agents, and other versatile compounds.[13–19]

Because of increasing concerns about the impacts of chemical industry on the environment, we are interested in making reactions more environmentally friendly. One way to achieve this is by using more earth abundant lower toxicity transition metals, such as copper, for catalysis. Recently, we have reported the use of a Cu(II)-2-quinoxalinol salen (Salqu) catalyst in combination with *tert*-butyl hydroperoxide (TBHP) to facilitate allylic, benzylic, and propargylic alcohol oxidations.[20–24] These reactions were done on a variety of different substrates producing very good yields (up to 99%). As this method was highly successful when applied to allylic C—H bonds and propargylic alcohols, we reasoned that the combination of Salqu and TBHP should also facilitate C—H activation and oxidation of propargylic groups lacking an alcohol.

Herein, we report the use of a Cu(II)-salqu catalyst for the direct oxidation of alkynes to α,β-acetylenic ketones. These reactions are carried out in mild conditions using only 1 mol% of Cu(II) catalyst at 70 °C obtaining good yields (up to 78%) in very good time (4h). The reactions can be performed in either acetonitrile or aqueous media by using a sulfonated water soluble catalyst (complex **2**) (Fig. 1).

Results and discussion

In preliminary studies, 1-phenyl-1-pentyne was chosen as a model substrate for oxidation and optimization of reactions. The oxidation of 1-phenyl-1-pentyne (0.5 mmol) with 1.0 mol% of the catalyst **1** in acetonitrile (10 mL) with dropwise addition of

TBHP (4 equivalents) at 70 °C afforded the α,β-acetylenic ketone **4a** in 78% yield in just 4 h (Table 1 entry 1).

Encouraged by these results, several reactions were performed with varying conditions to optimize the yield. Other examples of oxidation reactions using transition metal catalysts in combination with TBHP as the oxidant have used the addition of base as a way to accelerate the reaction rate.[25–27] However, in our case, the use of base (K_2CO_3) additive leads to a decrease in overall yield (Table 1 entries 2 and 3). In an effort to help increase the oxidative capabil-

* Corresponding author.
E-mail address: gordeae@auburn.edu (A.E.V. Gorden).

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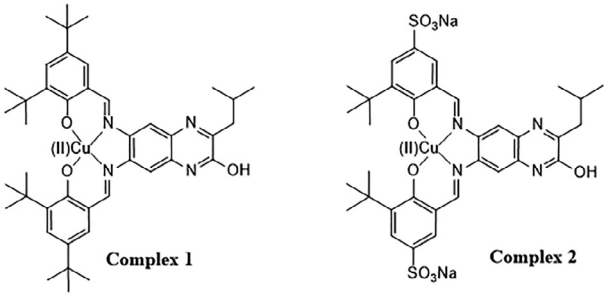


Fig. 1. Complex **1** (left) Cu(II) 2-quinoxalinol salen (Salqu) catalyst. Complex **2** (right) sulfonated 2-quinoxalinol salen (sulfosalqu) catalyst.

ities of TBHP, the use of Tetrabutylammonium iodide (TBAI) as cooxidant has also been employed, but this was also found to result in a significant decrease in overall yield (Table 1 entry 4).[28] Reducing the temperature also gave a lower yield (Table 1 entry 5). When the heat added to the reaction was reduced, only a trace amount of the desired product was produced (Table 1 entry 6).

In exploring the use of different solvents, using dichloromethane (DCM) led to a much lower yield, even when running the reaction for 24 h (entries 7 and 8). Acetonitrile likely gives the highest yield due to having a high oxygen solubility (8.1 mM).[29] Previous studies with catalyst **1** have shown the important role of molecular oxygen in the allylic oxidations. Employing a simple Cu(II) salts (entries 10–12), under comparable conditions even in higher catalyst loading (10%), resulted in only a modest yields (17–31%) after 4–6 h. Also, the absent any metal catalyst resulted in only 8% yield, indicating the important role of copper (Table 1 entry 9). Throughout the optimization experiments, entry 1 – using acetonitrile at 70 °C, 1 mol% catalyst, and 4 equivalents of TBHP – produced the best overall yield within a reaction time of 4 h.

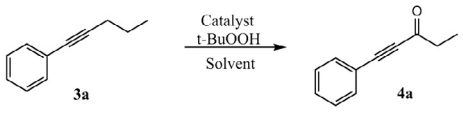
In order to demonstrate the potential utility of these reactions in water, our model substrate (**3a**) was tested using a water soluble sulfonated version of catalyst **1,** catalyst **2**. Complex **2** (1 mol%) was also able to oxidize **3a** in just 4 h resulting in a yield of 64% (Table 1 entry 13). Using this aqueous system, we can reduce or eliminate the use of volatile organic solvents which has the potential to increase the hazards in large scale oxidation reactions.[30,31] Doing these reactions in water provides a much greener and safer approach without sacrificing yields. It also greatly increases the ease of product isolation because the reaction is done in an "on water" fashion..[32] Subsequent to oxidation – once the stirring has stopped, the substrate separates from the water and can easily be removed from the catalyst/aqueous solution by means of a separatory funnel.

A series of differently functionalized substrates were oxidized using the conditions previously optimized with 1-phenyl-1-pentyne. The results of these are given in Table 2 as isolated yields. Shortening the length of the R group suffers a slight decrease in isolated yield (Table 2 entry 2). Substrate **3c** gives an example that this reaction works in the absence of aromatic compounds while also producing a good isolated yield. However, terminal alkynes **3d** and **3f** produced lower yields even when the time was increased to 16 h or 20 h. Previous reports also demonstrated low yields and longer reaction times when oxidizing these types of terminal alkynes.[8–11,33] This could be due to competition from a Glaser coupling reaction in the presence of the copper catalyst.[34]

To overcome the potential competing Glaser coupling reaction, terminal alkynes can be protected with TMS following standard procedures (**3g**).[35] With the protected substrates, we were able to decrease the reaction time from 16 h to 4 h while also significantly increasing the overall yield (**3g**). Allowing the reaction to proceed for 16 h in order to compare to the terminal alkyne, leads to an overall yield more than double the unprotected terminal alkyne (57%).

Entry 5 shows an example possessing a C—H position that is both benzylic and propargylic activated resulting in oxidation with an isolated yield of 77%. Because our catalyst has been shown to oxidize benzylic positions, we would expect a higher yield with the added functional group; however, the added bulk of the aromatic compound can hinder the reactive site of the molecule yielding a smaller yield then desired. For the symmetrical alkyne (entry **3**) we only observed oxidation on one side of the alkyne without

Table 1
Optimization of the reaction conditions.



Entry	Catalyst[a]	Solvent	T °C	Time	Additive[b]	Yield (%)[c]
1	**Complex 1**	**CH_3CN**	**70**	**4 h**		**78**
2	Complex **1**	CH_3CN	50	1 h	K_2CO_3	26
3	Complex **1**	CH_3CN	50	24 h	K_2CO_3	15
4	Complex **1**	CH_3CN	50	4 h	TBAI	4
5	Complex **1**	CH_3CN	50	4 h		47
6	Complex **1**	CH_3CN	RT	24 h		trace
7	Complex **1**	CH_2Cl_2	40	4 h		17
8	Complex **1**	CH_2Cl_2	40	24 h		45
9	None	CH3CN	70	4 h		8
10	$Cu(OAc)_2$ 10 mol%	H_2O	80	6 h		26
11	$Cu(acac)_2$ 10 mol%	H_2O	80	4 h		31
12	$Cu(NO_3)_2$ 10 mol%	H_2O	80	4 h		17
13	Complex **2**	H_2O	80	4 h		64

[a] 1 mol% unless otherwise stated.
[b] 50 mol%.
[c] GC yields using internal standard method.

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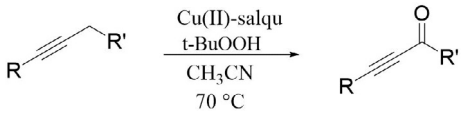
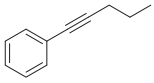
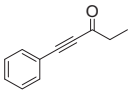
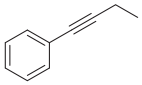
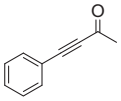
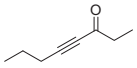
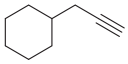
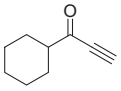
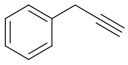
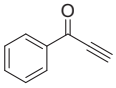
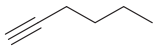
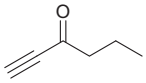
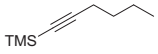
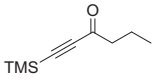
Table 2
Substrate scope of various alkynes.

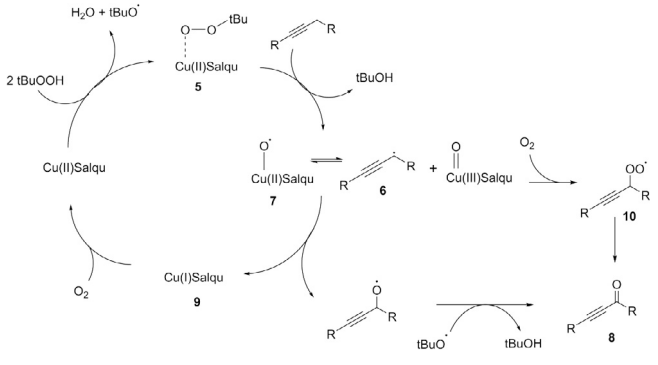


Entry	Substrate		Product		Yield[a,b]
1		3a		4a	78
2		3b		4b	71
3		3c		4c	68
4[c]		3d		4d	13[e]
5		3e		4e	77
6[d]		3f		4f	23[e]
7		3g		4g	36[e] 57[d,e]

[a] Reaction conditions: substrate (0.5 mmol), CH_3CN (10 mL), TBHP (2 mmol), complex 1 (1 mol%), 70 °C, 4 h.
[b] Isolated yields.
[c] 20 h.
[d] 16 h.
[e] GC Yield.

over oxidation. This is likely due to the electron withdrawing effect of the ketone once oxidation occurs, hindering the formation of the propargylic radical species needed for second oxidation cycle.

Based on previous studies with Cu(II)-salqu, we speculate this reaction goes through a radical mechanism (Scheme 1).[21] This reaction is starting with TBHP binding to Cu(II)-salqu (**5**). This complex then likely reacts with the alkyne and undergoes homolytic cleavage of the O—O bond producing *tert*-butyl alcohol, Cu(II)-salqu—O(**7**), and a propargylic radical species (**6**). This cycle can then follow 2 possible pathways that result in the observed products. In one pathway, Cu(II)-salqu—O· can undergo reductive elimination to produce the α,β-acetylenic ketone (**8**) and Cu(I)-salqu (**9**). In the other pathway, **6** will react with O_2 to form **10** and the loss of oxygen produces **8**. Previous studies with ^{18}O confirm both possible pathways. The Cu(I)-salqu species is likely regenerated by molecular oxygen which can then restart the catalytic cycle. Increasing the equivalents of TBHP added to the reaction does not further increase the reaction rate or isolable yields. Although, only 2 equivalents of TBHP is consumed in the proposed mechanism, 4 equivalents is likely required due to decomposition of TBHP at higher temperatures and the importance of free oxygen in the reaction.



Scheme 1. Proposed mechanism.

Conclusion

In summary, we have reported the use of Cu(II) salqu catalyst for C—H activation in the oxidation of propargylic groups to α,β-Acetylenic ketones. Using only 1 mol% of catalyst, we are able to achieve up to 78% isolated yield. A series of alkynes were oxidized including ones containing aromatic groups. However, terminal alkynes posed a challenge with our catalyst which can be combatted with the use of TMS group to regain appreciable yields. Also, we have demonstrated that these reactions can be carried out in water using a slightly modified water soluble catalyst.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.030.

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