SELECTIVE OXIDATION OF BENZYL ALCOHOLS TO ALDEHYDES WITH A SALOPHEN COPPER(II) COMPLEX AND \textit{t}er{\textit{t}}-BUTYL HYDROPEROXIDE AT ROOM TEMPERATURE

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GRAPHICAL ABSTRACT

Abstract An efficient and selective oxidation of benzyl alcohols has been developed using a salophen copper(II) complex as the catalyst and \textit{t}er{\textit{t}}-butyl hydroperoxide (TBHP) as the oxidant in the presence of base. Moderate to excellent yields of the corresponding benzaldehydes were obtained at room temperature without the carboxylic acids being formed.

Keywords Benzyl alcohols; salophen copper(II) complex; selective oxidation

INTRODUCTION

As one of the most important raw materials, aldehydes are widely used in organic synthesis for the preparation of fine chemicals both in laboratory and industry.\textsuperscript{[1]} Traditional methods for the synthesis of aldehydes mainly rely on the oxidation of alcohols,\textsuperscript{[2]} organic halides,\textsuperscript{[3]} amines,\textsuperscript{[4]} alkenes,\textsuperscript{[5]} and the methyl group on the aromatic ring.\textsuperscript{[6]} Among these methods, the oxidation of alcohols is convenient and effective because of atom economy, available raw materials, and relative greater yields.\textsuperscript{[7]} Many transition-metal compounds have been used for this purpose, such as vanadium (V),\textsuperscript{[8]} cobalt (Co),\textsuperscript{[9]} copper (Cu),\textsuperscript{[10]} manganese (Mn),\textsuperscript{[11]} ruthenium (Ru),\textsuperscript{[12]} rhodium (Rh),\textsuperscript{[13]} palladium (Pd),\textsuperscript{[14]} iron (Fe),\textsuperscript{[15]} and chromium.

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In contrast to other metals, Cu is an abundant metal with less toxicity. There are several reported methods in which Cu has been used as a cheap and “green” catalyst for the oxidation of alcohols.

Copper catalytic systems employing 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) or dialkylazodicarboxylate as cocatalysts have emerged as some of the most effective methods in the oxidation of alcohols to aldehydes. The first-generation copper-catalyzed aerobic oxidation protocol, which was developed by Riviere and Jallabert, employed equivalents of CuCl and 1,10-phenanthroline (Phen). Subsequently, Marko and coworkers developed a series of catalytic systems for aerobic alcohol oxidation using the catalytic amount of CuCl and Phen as the catalyst in combination with dialkylazodicarboxylates as redox-active cocatalysts, which exhibited the broadest scope of alcohol oxidation. On the other hand, the Cu-TEMPO system was also widely used for the oxidation of alcohols. The related catalytic system, which consists of a copper salt with 2,2'-bipyridine as a ligand and TEMPO as a cocatalyst, could also enable the mild aerobic oxidation of primary alcohols to aldehydes.

Meanwhile, salen-type Schiff bases, including the salen and salophen Schiff bases, can be prepared by condensation between aldehydes and amines in different reaction conditions. They are able to stabilize many different metals in various oxidation states with four coordinating sites and control the performance of metals in a large variety of useful catalytic transformations. Schiff base metal complexes are of great importance for catalysis, such as the asymmetric epoxidation of alkenes and oxidation of alcohols. Transition-metal Schiff base complexes that catalyzed oxidation of alcohols were attractive, especially for their more accessible synthesis conditions and versatile coordination structures. Salen-Cu(II) could be used in the oxidation of primary alcohols to the carboxylic acids in good yields. However, when combined with TEMPO, the salen-Cu(II) complex could selectively oxidized the alcohols to the corresponding aldehydes at reflux temperature. Because the system described requires the toxic TEMPO and high temperature, a mild, “green,” and efficient catalytic system is still desirable.

Herein, we developed an efficient method for the oxidation of benzyl alcohols to the corresponding aldehydes using a salophen copper(II) complex (Scheme 1) as the catalyst and tert-butyl hydroperoxide (TBHP) as the source of oxygen in the presence of base. To our delight, excellent yields and good selectivity were achieved for a variety of benzyl alcohols with no trace of corresponding carboxylic acid.

RESULTS AND DISCUSSION

The oxidation of benzyl alcohol was first investigated as the model reaction and the results are summarized in Table 1. Very poor yields were obtained when
no catalyst or base was used (Table 1, entries 1 and 2), which indicated that both of them are necessary for the oxidation.

To optimize the reaction conditions, the oxidant amount was varied from 0.6 to 2 equiv with other conditions remaining constant (Table 1, entries 6 and 10–18). A trend of increasing yield with oxidant amount was observed up to 1.1 equiv TBHP. There was still no carboxylic acid formed even when the oxidant amount was up to

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**Table 1. Optimizing the conditions for the oxidation of benzyl alcohol**

| Entry | Solvent | TBHP (equiv.) | Catalyst (mol%) | Base (equiv) | Yield (%) |
|-------|---------|---------------|----------------|-------------|-----------|
| 1     | PhMe    | 2.0           | —              | Cs$_2$CO$_3$ (2.0) | 36        |
| 2     | PhMe    | 2.0           | 4.0            | —           | 34        |
| 3     | PhMe    | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 68        |
| 4     | DMF     | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 80        |
| 5     | DMSO    | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 88        |
| 6     | MeCN    | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 93        |
| 7     | Acetone | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 39        |
| 8     | MeOH    | 2.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 62        |
| 9     | CH$_2$Cl$_2$ | 2.0        | 4.0            | Cs$_2$CO$_3$ (2.0) | 92        |
| 10    | MeCN    | 0.6           | 4.0            | Cs$_2$CO$_3$ (2.0) | 91        |
| 11$^c$ | MeCN    | 0.6           | 4.0            | Cs$_2$CO$_3$ (2.0) | 58        |
| 12$^d$ | MeCN    | —             | 4.0            | Cs$_2$CO$_3$ (2.0) | 27        |
| 13$^e$ | MeCN    | —             | 4.0            | Cs$_2$CO$_3$ (2.0) | 36        |
| 14    | MeCN    | 0.8           | 4.0            | Cs$_2$CO$_3$ (2.0) | 92        |
| 15    | MeCN    | 1.0           | 4.0            | Cs$_2$CO$_3$ (2.0) | 94        |
| 16    | MeCN    | 1.1           | 4.0            | Cs$_2$CO$_3$ (2.0) | 95        |
| 17    | MeCN    | 1.4           | 4.0            | Cs$_2$CO$_3$ (2.0) | 95        |
| 18    | MeCN    | 1.7           | 4.0            | Cs$_2$CO$_3$ (2.0) | 92        |
| 19    | MeCN    | 1.1           | 0.5            | Cs$_2$CO$_3$ (2.0) | 93        |
| 20    | MeCN    | 1.1           | 0.75           | Cs$_2$CO$_3$ (2.0) | 95        |
| 21    | MeCN    | 1.1           | 1.0            | Cs$_2$CO$_3$ (2.0) | 95        |
| 22    | MeCN    | 1.1           | 2.0            | Cs$_2$CO$_3$ (2.0) | 96        |
| 23    | MeCN    | 1.1           | 3.0            | Cs$_2$CO$_3$ (2.0) | 95        |
| 24    | MeCN    | 1.1           | 2.0            | Cs$_2$CO$_3$ (1.0) | 93        |
| 25    | MeCN    | 1.1           | 2.0            | Cs$_2$CO$_3$ (0.6) | 90        |
| 26    | MeCN    | 1.1           | 2.0            | NaOH (2.0)     | 66        |
| 27    | MeCN    | 1.1           | 2.0            | NaOH (1.0)     | 90        |
| 28    | MeCN    | 1.1           | 2.0            | NaOH (0.6)     | 99        |
| 29    | MeCN    | 1.1           | 2.0            | NaOH (0.4)     | 97        |
| 30$^f$ | MeCN    | 1.1           | 2.0            | NaOH (0.6)     | 85        |
| 31$^g$ | MeCN    | 1.1           | 2.0            | NaOH (0.6)     | 83        |

$^a$Reaction conditions: benzyl alcohol (0.5 mmol), TBHP, salophen copper(II) complex, and base were stirred under room temperature in air overnight.

$^b$Isolated yields.

$^c$The reaction was performed under argon.

$^d$The reaction was performed in air without the oxidant TBHP.

$^e$O$_2$ was used as the oxidant.

$^f$Cu(OAc)$_2$ was used as the catalyst.

$^g$CuCl was used as the catalyst.
2.0 equiv (Table 1, entry 6). It was worth noting that even when 0.6 equiv of TBHP was used for the oxidation (Table 1, entry 10), the reaction provided the product in 91% yield. It is possible that oxygen may participate in the reaction as the reaction was conducted in the open air. The assumption was proved by the results from the controlled experiments (Table 1, entries 11 and 12). Under the same reaction conditions, O₂ was used as the oxidant but only 36% yield was obtained (Table 1, entry 13). The loading amount of catalyst was also examined (Table 1, entries 6 and 19–23). The best yield was achieved when the amount of the catalyst was 2 mol%. The type and amount of the bases also played important influences on the reaction and 0.6 equiv NaOH resulted in the best yield (Table 1, entries 21 and 24–29). Meanwhile, other Cu sources such as Cu(OAc)₂ and CuCl exhibited less catalytic activity than the salophen Cu(II) complex (Table 1, entries 30 and 31).

To determine the application scope of this catalytic system, a wide range of benzyl alcohols were oxidized under the optimized conditions (Table 2). All the benzyl alcohols employed were converted into the corresponding aldehydes with excellent yields and selectivity, and no carboxylic acids were detected with

Table 2. Oxidation of primary alcohols under optimized conditions

| Entry | R          | Yield (%) |
|-------|------------|-----------|
| 1     | 4-Cl       | 97        |
| 2     | 4-Br       | 97        |
| 3     | 4-NO₂      | 85        |
| 4     | 4-CN       | 83        |
| 5     | 4-CF₃      | 87        |
| 6     | 4-Me       | 95        |
| 7     | 4-OMe      | 96        |
| 8     | 2-Cl       | 96        |
| 9     | 2-Br       | 98        |
| 10    | 2-I        | 69        |
| 11    | 2-NH₂      | 41        |
| 12    | 2-Br-4,5-(OMe)₂ | 69    |
| 13    | 3-NO₂      | 84        |
| 14    | 3-CF₃      | 85        |
| 15    | 3-Cl       | 96        |
| 16    | 3-Br       | 97        |
| 17    | 3-Me       | 93        |
| 18    | 2,4-Cl₂    | 92        |
| 19    | 1-Phenylethanol | 95   |
| 20    | 2-Phenylethanol | 6⁹      |
| 21    | n-Octanol  | 4⁹        |

⁹Reaction conditions: alcohols (0.5 mmol), salophen copper(II) complex (2 mol%), TBHP (1.1 equiv), and NaOH (0.6 equiv) in acetonitrile were stirred under room temperature in air overnight.

³Isolated yield.

³GC yield.
high-performance liquid chromatography (HPLC) after the reaction completed. No obvious influence of the electronic effects was found in the reaction, and both benzyl alcohols containing the electron-withdrawing and electron-donating groups could produce the reaction with satisfactory yields (Table 2, entries 1–7). 2-Iodobenzyl alcohol provided a poor yield, which may be explained by the steric effects of the iodo substituent (Table 2, entry 10). In the case of 2-aminobenzyl alcohol (Table 2, entry 11), an undesired by-product of imine was afforded, leading to a poor yield. The aliphatic primary alcohol exhibited low conversion and poor reactivity (Table 2, entries 20 and 21), but there was still no trace of carboxylic acid.

Finally, a probable mechanism for this reaction has been proposed (Fig. 1). The role of the base is to deprotonate the alcohol and accelerate the formation of the benzyloxy-Cu(II) complex 1 by favoring the coordination of the resulting alcoholate to the salophen copper(II) complex. The aldehydes were then obtained by the reaction of the benzyloxy-Cu(II) complex with the oxidant TBHP with release of the by-product H$_2$O and the tert-butoxy-Cu(II) complex 2. Finally, the tert-butoxy-Cu(II) complex exchanged with the starting alcohol to release the tert-butyl alcohol and completed the catalytic cycle.

CONCLUSION

In summary, a mild and selective oxidation method of benzyl alcohols to the corresponding aldehydes has been established when using the TBHP as the oxidant and a salophen copper(II) complex as the catalyst in the presence of NaOH at room temperature. In this protocol, a variety of benzyl alcohols are oxidized to the corresponding aldehydes in moderate to excellent yields and no overoxidation takes place.
EXPERIMENTAL

All reagents were purchased from commercial sources and used without treatment; 70% TBHP in water was used. The products were purified by column chromatography over silica gel. $^1$H NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer and tetramethylsilane (TMS) was used as a reference. A Nicolet IS-10 spectrometer was recorded for IR spectroscopy.

Preparation of Salophen H$_2$

$O$-Phenylene diamine (108 mg, 1 mmol) in 5 mL MeOH was added to a stirred mixture of salicylaldehyde (244 mg, 2 mmol) in 10 mL MeOH. The resulting orange mixture was stirred overnight at room temperature. The solid product was collected by filtration, washed with cool alcohol, and dried in vacuo (256 mg, yield: 81%); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 13.05 (s, 2 H), 8.63 (s, 2 H), 7.46–7.31 (m, 6 H), 7.27–7.20 (m, 2 H), 7.05 (d, $J = 8.2$ Hz, 2 H), 6.92 (t, $J = 7.4$ Hz, 2 H).

Preparation of Salophen Copper(II) Complex

Solution of salophen H$_2$ ligand (189 mg, 0.5 mmol) in EtOH (10 mL) and Cu (OAc)$_2$.H$_2$O (99 mg, 0.5 mmol) in water (1 mL) were mixed and refluxed with vigorous stirring for 2 h. The resulting solution was then cooled to room temperature and filtered. After filtration, the solid product was washed with H$_2$O, MeOH, and Et$_2$O subsequently, then dried in vacuo to afford the desired copper complex (139 mg, yield 71%). IR: $\nu$ (cm$^{-1}$) =1602, 1519, 1334.

Typical Procedure for the Oxidation of Alcohols

Alcohol (0.5 mmol), salophen copper(II) complex (2 mol%), NaOH (0.6 equiv), and 70% TBHP in water (1.1 equiv) were dissolved in acetonitrile (5 mL), and the homogeneous solution was stirred at room temperature in air overnight. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue was purified over silica gel by column chromatography (10–25% EtOAc in hexane). All the products were known compounds and were identified by comparison of their physical and spectra data with those of authentic samples.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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