An Update from a Pioneer of Greener Methods for Industrially Relevant Oxidations

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Introduction

Aldehydes and ketones are common functional groups in pharmaceutical, agrochemical, and fine chemical products and intermediates, and they are often prepared by oxidation of the corresponding alcohols. Classical oxidation routes generally suffer from large amounts of toxic waste and poor functional group compatibility. Due to the importance of these functional groups, significant effort has been made to develop synthetically more appealing oxidation routes, and aerobic oxidation methods have received considerable attention in recent years. TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) is a stable organic nitroxy1 that has found widespread application in alcohol oxidation reactions. This topic is the focus of a recent comprehensive review by Bobbitt, Brückner, and Merkoh. The use of inexpensive stoichiometric oxidants, such as sodium hypochlorite (NaOCl), bromine, or PhIOAc2, often enables TEMPO to be used in catalytic quantities, and one of the most common protocols features stoichiometric NaOCl in combination with catalytic TEMPO and bromide in a buffered organic–aqueous biphasic solvent mixture (the “Anelli oxidation”). An important recent development in this area is the recognition that less sterically hindered bicyclic nitroxyls, such as ABNO (9-azabicyclo[3.3.1]nonane-N-oxyl), AZADO (2-azadamanatane- N-oxyl), and related derivatives, often significantly improve the efficiency and scope of the alcohol oxidation reactions (Figure 1).

The development of nitroxy-catalyzed alcohol oxidations that employ O2 as the terminal oxidant has been achieved by using a variety of co-catalysts, including transition-metal salts, polyoxometalates, or metalloenzymes (laccase). Cu/nitroxy catalyst systems have emerged as the most versatile and effective among this group. The mechanism of these reactions is believed to involve cooperative one-electron redox chemistry at Cu and the nitroxy (Scheme 1, Part (a)). Alternative transition-metal-free protocols have been identified that employ nitrous oxide (NO2) co-catalysts to achieve alcohol oxidation with O2 as the terminal oxidant. The mechanism of the latter reactions is believed to involve a NO/NO2 redox cycle coupled to a hydroxylamine/oxygenammonium cycle, which resembles the mechanism of the NaOCl/nitroxy-catalyzed alcohol oxidation methods mentioned above (Scheme 1, Part (b)).

Whereas aerobic alcohol oxidation reactions have historically been the focus of attention, they are rarely used in organic chemical synthesis. Widespread adoption of aerobic alcohol oxidations will require a number of specific issues to be addressed. For example, the methods must exhibit high functional-group tolerance and chemoselectivity, feature simple reaction setup, have short reaction times, and employ low-cost reagents and/or catalysts. The present article describes the development and synthetic applications of a series of Cu(nitroxy)- and nitroxy/NO2-based aerobic alcohol oxidation methods that meet all or most of these criteria.

Cu/Nitroxy-Catalyzed Aerobic Oxidation of Alcohols

Semmelhack was the first to explore the synthetic scope of Cu/TEMPO-catalyzed aerobic alcohol oxidation. CuCl and TEMPO were identified as effective cocatalysts for the aerobic oxidation of activated alcohols. Stoichiometric quantities of copper and TEMPO were required to oxidize less reactive aliphatic alcohols. This Cu/TEMPO oxidation method has been employed in a number of synthetic routes to prepare complex molecules, especially for the oxidation of allylic alcohols. Knochel and co-workers reported in 2000 the first Cu/TEMPO-based catalyst system that is effective for the aerobic oxidation of aliphatic alcohols. However, the use of fluorobiphasic reaction conditions and a perfluorooalkyl-substituted bipyrindine ligand for the Cu catalyst probably limited the widespread adoption of this method. Subsequently, Sheldon and co-workers demonstrated that a simple catalyst system (5 mol % of each of CuBr2/bpy/TEPOMeO-Bu; bpy = 2,2’-bipyridine) enabled the efficient oxidation of activated (allylic and benzylic) alcohols in acetonitrile–water, and it could also oxidize aliphatic alcohols at somewhat higher temperatures and for longer reaction times. A Cu/salen catalyst system reported by Punniamurthy and co-workers successfully oxidized aliphatic alcohols, but required more forcing reaction conditions (100 °C). In 2009, Kumpulainen and Koskinen reported a catalyst composed of Cu2+/bpy/TEPOMeO-DVB (1,8-diazabicyclo[5.4.0]-undec-7-ene) and/or NMI (N-methylimidazole) that exhibited excellent reactivity towards unactivated aliphatic alcohols at room temperature.

Hoover and Stahl developed a CuOTf/bpy/TEPOMeO/NMI catalyst system that was effective in the oxidation of benzylic, allylic, propargylic, and aliphatic alcohols under ambient air (Scheme 2). A significant improvement in catalytic activity was associated with the use of a copper(I), rather than a copper(II), source. Cu salts with non-coordinating anions (e.g., CuOTf) were especially effective. The mild reaction conditions were compatible with numerous functional groups, including aryl halides, anilines, nitrogen and sulfur heterocycles, and sulfides. This method is compatible with base-sensitive substrates owing to the lack of stoichiometric or strongly basic additives. For example, (Z)-allylic alcohols were successfully oxidized to (Z)-enals without alkene isomerization, and N-Boc-prolinol was oxidized to the aldehyde without epimerization. As observed with other Cu/TEMPO catalyst systems, secondary alcohols did not undergo effective oxidation.

The chemoselectivity for primary over secondary alcohols was exploited in the oxidation of diols that contained both primary and secondary alcohols. Reactions of 1,5-diols led to efficient lactonization in high yields (Scheme 2). A subsequent study by Root and Stahl demonstrated the feasibility of implementing these reactions on a large scale by employing continuous-flow reaction conditions. Short reactor residence times (<5 min) were demonstrated for activated alcohols, with somewhat longer times (30–45 min) required for aliphatic alcohols.

Figure 1. Nitroxy Derivatives Employed in Aerobic Alcohol Oxidations. (Ref. 5)

Scheme 1. (a) Mechanism of Cu/Nitroxy-Catalyzed Alcohol Oxidation via a Cooperative Pathway. (b) NO2-Coupled Hydroxylamine–Oxammonium Mechanism for Aerobic Alcohol Oxidation. (Ref. 6)
**Effective Primary and Secondary Alcohol Oxidation with Cu/Bicyclic Nitroxyl**

<table>
<thead>
<tr>
<th>Method</th>
<th>Cu(MeCN)OTf (5 mol %)</th>
<th>bpy (5 mol %)</th>
<th>TEMPO (1 mol %)</th>
<th>NMI (10 mol %)</th>
<th>MeOH, rt, air, 1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Noteworthy 1st Alcohol</td>
<td>88% (A)</td>
<td>&gt;95% ee</td>
<td>95%</td>
<td>&gt;98% (50 °C)</td>
</tr>
<tr>
<td>B</td>
<td>Noteworthy 2nd Alcohol</td>
<td>97% (A)</td>
<td>&gt;95% ee</td>
<td>96%</td>
<td>&gt;98% (50 °C)</td>
</tr>
</tbody>
</table>

* Using CuBn instead of CuOTf and DBU instead of NMI.

* From unprotected 1,5-diol.

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Br</td>
<td>88%</td>
<td>Cu(MeCN)OTf, bpy, TEMPO, MeOH, air, rt, 1 h</td>
</tr>
<tr>
<td>R = Br</td>
<td>&gt;95%</td>
<td>Cu(MeCN)OTf, bpy, TEMPO, MeOH, air, rt, 1 h</td>
</tr>
</tbody>
</table>

* 5-Me-AZADO was utilized instead of AZADO.

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**Notes:**
- 90% of the alcohol product was isolated as the ethyl ether after treatment with a Wittig reagent. 60 °C, 70 °C, O₂ balloon.
Practical Aerobic Alcohol Oxidation with Cu/Nitroxyl and Nitroxyl/NO. Catalyst Systems
Kelley C. Miles and Shannon S. Stahl*

Method A

Method B

Method C

Noteworthy Examples:

<table>
<thead>
<tr>
<th>Method</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cu/Nitroxyl</td>
<td>10 mol % HAc, rt, 1.5 h</td>
<td>98% (B)</td>
</tr>
<tr>
<td>B</td>
<td>NaNO₂</td>
<td>10 mol % H₂O₂, rt, 2-6 h</td>
<td>93% (B)</td>
</tr>
<tr>
<td>C</td>
<td>iodosABINO (5 mol %), NaCN</td>
<td></td>
<td>97% (B)</td>
</tr>
</tbody>
</table>

* NaNO₂ (1.2 equiv) was used.
* F-AZADO (3 mol %) was employed.
* NaNO₂ (20 mol %) HAc (10 equiv), and NaCN (0.5 M) were utilized.
Alcohol oxidation is one of the most frequently performed oxidation reactions in organic chemistry. In collaboration with Professor Shannon Stahl, Aldrich offers the Stahl Aerobic Oxidation Solutions: 796549, and coming soon, 796557.

Both solutions contain 1-methylimidazole (NMI), 2,2’-bipyridyl (bpy), and either TEMPO or ABNO; all you have to do is add the copper catalyst and your substrate!

**Features**
- Easy reaction setup and workup procedures
- Most reactions proceed at room temperature open to the air
- TEMPO offers chemoselective oxidation of primary alcohols
- ABNO offers rapid oxidation of both primary and secondary alcohols
- Broad substrate scope and high functional group tolerance

For more information on these solutions, visit Aldrich.com/aerobic-oxidation