Direct Oxidation of Primary Alcohols to Carboxylic Acids

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Abstract Oxidation of primary alcohols to carboxylic acids is a fundamental transformation in organic chemistry, yet despite its simplicity and extensive use, it remains a subject of active research for synthetic organic chemists. Within the last seven years, a great number of new methods have emerged that utilize transition metal compounds as catalysts for acceptorless dehydrogenation of alcohols to carboxylates. The interest in this reaction is explained by its atom economy, which is in accord with the principles of sustainability and green chemistry. Therefore, the methods for the direct synthesis of carboxylic acids from alcohols is ripe for a modern survey, which we provide in this review.

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Key words alcohol, carboxylic acid, oxidation, transition metal, catalysis, transfer dehydrogenation, acceptorless dehydrogenation

1. Introduction

Oxidation of primary alcohols to carboxylic acids is utilized extensively in total syntheses of many important bioactive compounds, for example, luzopeptins (antitumor and antiretroviral antibiotics), bistramide A,2 verbalactone,3 (-)-lyngbyaloside B,4 and other medicinal scaffolds.5 Common methods for this oxidation use transition metal-based oxidants that generate stoichiometric portions of metallic waste, which is environmentally unfriendly. Although this is not a problem for small scale laboratory syntheses, the issue becomes critical when the reaction is scaled up. One approach is to replace the metal-based oxidants with oxygen, sodium hypochlorite, or sodium chlorite, as they produce only water and sodium chloride as by-products. Another solution is performing alcohol oxidation in an acceptorless dehydrogenation mode, with hydrogen gas evolved as the only waste product. This reaction pathway is enabled both by conditions based on transition metal catalysts and electrolytic reactions.

In this review, we group alcohol oxidation methods into three categories: stoichiometric, acceptorless, and electrolytic, based on the criteria of Gibbs free energy, reaction pH, and by-product (Scheme 1); stoichiometric group, in turn, is subdivided into oxometallate oxidation and transfer dehydrogenation. Stepwise methods for alcohol oxidation are reviewed elsewhere.

Scheme 1 Comparison of alcohol-to-acid oxidation methods

2. Thermodynamics of Primary Alcohol Oxidation

We compiled the available thermodynamic data on alkaneto-carboxylic acid oxidation and represented these as Gibbs free energy and Frost diagrams (Figure 1). The Frost diagrams for carbon can be plotted based on experimental data or derived from the free energy profiles; these are generally consistent in our hands. Comparing the Gibbs and Frost diagrams for methane, it is clear that although the two graphs trend similarly, noteworthy differences arise with different reaction conditions: the Gibbs diagram is considering the reaction participants at their standard states, while the Frost diagram is dealing with 1 M aqueous solutions.
The first step in the oxidation sequence of primary alcohols is dehydrogenation to the corresponding aldehyde (Scheme 2A).

The reaction is endergonic and characterized by the $\Delta_r G^\circ$ values 56.3 (R = H), 45.9 (R = CH$_3$), 29.2 (R = C$_2$H$_5$), and 27.5 kJ/mol (R = C$_6$H$_5$). The corresponding standard redox potential for couple CH$_3$(OH)/CH$_3$OH at pH = 0 is +0.237 V. This reaction is typically performed in neutral non-aqueous solutions (to prevent hydration and overoxidation) or acidic aqueous solutions for the synthesis of volatile aldehydes that can be removed from a boiling reaction mixture by distillation.

Once the aldehyde is formed and hydrated, an excess of oxidant can easily convert an aldehyde hydrate to the corresponding acid. Although this second step proceeds with a slight decrease of the system's free energy (Figure 1A), the overall alcohol to carboxylic acid oxidation (Scheme 2B) remains endergonic and is characterized by the $\Delta_r G^\circ$ values 42.1 (R = H), 22.0 (R = CH$_3$), 24.9 (R = C$_2$H$_5$), and 12.9 kJ/mol (R = C$_6$H$_5$). These numbers, as well as the slopes of graphs in the free energy and Frost diagrams, demonstrate that the possibility for an oxidant to convert alcohol to acid is determined by redox potential of the first oxidation step (ca. +0.25 V), since it is the highest among the two. Also, the material balance requires water to enable this transformation.

The system's pH affects thermodynamics of alcohol oxidation dramatically, since all the redox potentials depend on [H$^+$] according to the Nernst equation (Figure 1B). In the sequence CH$_3$OH $\rightarrow$ CH$_3$(OH) $\rightarrow$ HCOOH $\rightarrow$ H$_2$CO$_3$, the growing acidity of the species makes the conjugate bases increasingly more stable, thus decreasing the corresponding redox potentials in the alkaline solution. Carboxylates behave analogously. Therefore, oxidation of alcohols to carboxylates by water in alkaline solution is extremely exergonic, so an alcohol can be oxidized spontaneously by water to produce two equivalents of H$_2$. This explains why all catalytic acceptorless dehydrogenation methods in section 5 utilize aqueous hydroxide solutions or solid alkali metal hydroxides as selective basic regents for carboxylate generation.

Comparing the standard redox potentials for the HCOO$^-$/CH$_3$OH ($-0.876$ V) and H$_2$O/H$_2$ ($-0.828$ V) couples, methanol is expected to be oxidized by 1 M hydroxide solution at room temperature, generating dihydrogen ($\Delta_r G^\circ = -18.5$ kJ/mol). According to our calculations, $\Delta_r G^\circ$ of primary alcohol oxidation to carboxylate (Scheme 2C) has the following values: -36.1 (R = H), -57.6 (R = CH$_3$), and -86.8 kJ/mol (R = C$_6$H$_5$). Although the reaction is highly favored, it is extremely slow at room temperature, and forcing conditions (350 °C) are required to overcome the activation barrier. This is the underlying reason that modern catalyst development has been important in this space, currently enabling methods with dramatically milder conditions (60 °C).

### 3. Oxometallate Oxidation

Metal-based stoichiometric oxidizing agents are typically derived from oxo and hydroxo complexes of high-valent transition metals. Table 1 summarizes all oxometallates that can oxidize alcohols or aldehydes, with oxidation products shown in parentheses. We characterize the thermodynamic oxidative ability of the oxometallates with the standard electrode potentials ($E^\circ$ vs. RHE, V) that correspond to reduction of a highest oxometallate to a water-stable oxide/hydroxide. Reduction of oxo complexes requires protons, so the corresponding electrode potentials will depend on pH, thus the

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**Scheme 2 Alcohol dehydrogenation pathways**

**A.** RCH$_2$OH($\text{aq}$) $\rightarrow$ RCHO($\text{aq}$) + $\text{H}_2$($\text{g}$) ($\Delta_r G^\circ > 0$)

**B.** RCH$_2$OH($\text{aq}$) + H$_2$O($\text{aq}$) $\rightarrow$ RCOOH($\text{aq}$) + 2H$_2$($\text{g}$) (H$_2$O) ($\Delta_r G^\circ > 0$)

**C.** RCH$_2$OH($\text{aq}$) + NaOH($\text{aq}$) $\rightarrow$ RCOONa($\text{aq}$) + 2H$_2$($\text{g}$) (NaOH) ($\Delta_r G^\circ < 0$)
potential of any redox couple in Table 1 varies from the lowest value (pH = 14, blue) to the highest value (pH = 0, red). This explains why oxo anions are generally more oxidizing in acid. We can draw several conclusions from the data: the most powerful oxidants are derived from the first row metals: V, Cr, Mn, and Fe. The highest oxometallates of Nb, Ta, Mo, W, Tc, and Re are extremely stable and do not oxidize alcohols on their own. The highest metalates and oxides of the group 9 and 10 elements are quite rare, and information about their reactivity with alcohols is missing in the literature.

### Table 1: The standard electrode potentials (E° vs. RHE, V) for reduction of high-valent transition element oxo and hydroxo complexes in alkaline (pH = 14, blue) and acidic (pH = 0, red) aqueous solutions and their ability to oxidize alcohols and aldehydes

<table>
<thead>
<tr>
<th>Element</th>
<th>E° (V vs. RHE, V)</th>
<th>Oxidation State</th>
<th>Complex</th>
<th>Oxidation Potential (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb/V</td>
<td>-1.2/0.3</td>
<td>Nb(V)/Nb(IV)</td>
<td>Nb(V)</td>
<td>-1.2/0.3</td>
</tr>
<tr>
<td>Mo/V</td>
<td>-0.94/0.32</td>
<td>Mo(V)/Mo(IV)</td>
<td>Mo(V)</td>
<td>-0.94/0.32</td>
</tr>
<tr>
<td>W/V</td>
<td>-1.2/0.06</td>
<td>W(V)/W(IV)</td>
<td>W(V)</td>
<td>-1.2/0.06</td>
</tr>
<tr>
<td>OsO4</td>
<td>0.108/1.02</td>
<td>Os(VI)/Os(V)</td>
<td>Os(VI)</td>
<td>0.108/1.02</td>
</tr>
<tr>
<td>Au/OH+</td>
<td>0.600/1.50</td>
<td>Au(III)/Au(I)</td>
<td>Au(III)</td>
<td>0.600/1.50</td>
</tr>
</tbody>
</table>

*Since Cu(I) is unstable in acidic aqueous solution without special ligands, the red potential is given for Cu(I)/Cu(0) couple.*

Oxidation with oxometallates has been known for more than a century, as these are among the most studied and reliable of methods for alcohol to carboxylate conversion. While these have high rates and mild conditions, they generate metal-containing waste, which makes them unfit for application at scale. These stoichiometric methods are systematically surveyed here, because understanding the chemistry available to the stoichiometric metal systems has enabled the community to convert many, and hopefully many more going forward, to efficient catalytic systems.

**Vanadium(V).** Alcohol oxidation with vanadium oxidants has not attracted much attention from organic chemists, however, it is known that reduction of vanadium pentoxide V2O5 with ethanol in aqueous sulfuric acid was utilized for the synthesis of [VO(H2O)3]SO4, where the organic by-product was reported as acetaldehyde. A vanadate-TEMPO catalytic system was used for benzy alcohol oxidation to benzaldehyde with hydrogen peroxide. In this case, peroxovanadates, but not oxovanadate, VO3−, could be responsible for the oxidation.

**Chromium(VI).** Many chromium(Ⅵ) reagents have been applied to oxidation of organic compounds. All of the chromium-to-carboxylic acid transformations that take place in an aqueous solution proceed under acidic conditions. In organic synthesis, an aqueous acidic solution of Cr(VI) Jones reagent, is typically prepared with chromium trioxide CrO3 or potassium dichromate K2Cr2O7 and aqueous sulfuric acid. The Jones method requires acetone as a cosolvent to increase solubility of organic substrates and facilitate separation of the carboxylic acid products from inorganic salts. With this method most primary alcohols are oxidized to carboxylic acids, tolerating alkenes and alkyynes.

The oxidation can also be done under neutral non-aqueous conditions, following Corey-Schmidt method, with pyridinium dichromate [Cr2O7(2-PyCOO)]− (M = Mo and W) oxidize secondary alcohols directly in methanol at 50 °C, yielding up to 1.7 mol of ketone per mol of the complex. Catalytic methods for secondary alcohol oxidation were also developed that use ammonium heptamolybdate, (NH4)6Mo7O24·4H2O, or sodium tungstate, Na2WO4·2H2O, as catalysts and aqueous hydrogen peroxide solution as an oxidant. The peroxotungstate system can also oxidize primary alcohols to carboxylic acids under acidic conditions when a phase-transfer catalyst is used, [NCH4(CO2H)3]2H2O, the yield of benzoic and octanoic acids by this method is 87%. Manganese(VII). Potassium permanganate, KMnO4, is widely used in organic synthesis, generally under basic conditions. Oxidation under acidic conditions is less selective and is appropriate only for simple alcohols; for example, 6-methyloctanoic acid (66%) was obtained during oxidation with KMnO4 in H2SO4 solution at room temperature. Under anhydrous and heterogeneous conditions solid sodium...
permanaganate, NaMnO₄·H₂O, can oxidize alcohols and aldehydes in refluxing hexane (69 °C), giving, for example, octanoic and benzoic acids with 67 and 81% yields, respectively. KMnO₄ reacts with many functional groups, such as C=C, C≡C, -NH₂, -SH, -SR, -PR₂. Moreover, permanaganate can unpredictably cleave unactivated C-H and C-C bonds, which limits the scope of its synthetic application. Other issues with KMnO₄ include its low solubility in organic solvents and resistance against further oxidation of some intermediate aldehydes.

Iron(VI). The redox potential values suggest that ferrate(VI) ion, FeO₄²⁻, is more powerful oxidant than MnO₄⁻; however nothing is known about its reactions with alcohols in aqueous media. Still, K₂FeO₄ converts benzyl alcohol to benzaldehyde in pentane at room temperature in quantitative yield. In our view, oxidation of alcohols to carboxylates by ferrate(VI) could have applicated utility, since iron is abundant and non-toxic.

Ruthenium(VIII, VII, and VI). Ruthenium tetroxide, RuO₄, has many recent synthetic applications. It may be unfamiliar to some organic practitioners, because it's typically generated in situ from RuCl₃ or Ru₂O₃ and an oxidant such as Na₂O₂, H₂O₂, NaBrO₃, NaClO, or Ca(ClO)₂ to manage its toxicity. RuO₄ is incompatible with alkenes, alkynes, geminal diols, ethers, and compounds with activated methylene group. Being a very powerful oxidizer it can cleave C-C bonds in aromatic compounds.

Upon reduction, RuO₄ forms lower oxo complexes: per ruthenate (RuO₄⁻), as in the very successful Ley reagent, and ruthenate (RuO₄²⁻), which can oxidize alcohols as well, but is less aggressive than RuO₄. Oxidation of alcohols to aldehydes in organic solvents by (n-ProRN)RuO₄ (TPAP, the Ley reagent) proceeds catalytically (10 mol%) in combination with excess NMO · H₂O in acetonitrile at room temperature to drive the reaction further to carboxylic acids. The yields of aliphatic and benzoic acids are high (70-94%), however, 4-methyl- and 4-methoxybenzyl alcohols give only 26% and 32%, respectively. Under these conditions double and triple bonds are tolerated. TPAP can also be used as an electrocatalyst for converting 1-butanol to butanal (34%), by applying a potential of 1.3 V in acetonitrile.

The most important synthetic applications of ruthenate, RuO₄²⁻, is oxidation of alcohols in alkaline media to carboxylates or ketones. In general, ruthenate does not oxidize alkenes or alkynes at room temperature, for example, oct-7-en-2-ynoic acid was prepared from an alcohol with a good yield (74%) using combination of RuCl₃ (1-2 mol%) and potassium persulfate, K₂S₂O₈ in aqueous KOH solution.

Osmium(VIII and VI). Ethanol can be oxidized to acetate by osmium tetroxide (E=0.03 V, pH = 14) in aqueous KOH solution. In contrast to RuO₄, OsO₄ does not react with alcohols under neutral or acidic aqueous conditions. This makes it a useful and highly selective oxidant for functional groups other than primary alcohols. However, under anhydrous conditions benzyl alcohols are converted to aldehydes using catalytic system OsO₄/CuCl/pyridine and O₂ as a reoxidant.

Copper(II). Silver(I), and Gold(III). Complexes of Cu(II) with carboxylate ligands, such as [Cu(tartrate)₂]²⁻, [Cu(citrate)]⁻, and [Cu(OAc)₄(H₂O)₂]⁻ have been known since the 19th century as analytical reagents in Fehling's, Benedict's, and Barfoed's tests for discovery of reducing sugars and aldehydes. Typically, the reaction is performed in aqueous hydroxide solution at moderate temperature (< 100 °C), Cu(II) oxidizes aldehydes to carboxylates forming a characteristic red precipitate of Cu₂O, which serves as a positive analytical signal. Silver carbonate (Ag₂CO₃) on Celite, known as Fetzon's reagent, oxidizes alcohols to aldehydes and ketones under neutral and anhydrous conditions in refluxing benzene, toluene, or heptane. Silver(I)-ammonia complex, Ag(NH₃)₂⁺, is a primary component in Tollens’ reagent, which selectively oxidizes aldehydes to carboxylates in aqueous hydroxyde solution. Silver oxide, Ag₂O, in a THF/H₂O solution of NaOH was used for oxidation of a primary alcohol to carboxylate (90% yield) in the total synthesis of polyunsaturated endiandric acid E. Gold(III) in the form of Au(OH)₃⁺, generated in situ from AuOCl⁻ and OH⁻, oxidizes ethanol producing solutions of colloid gold and acetate.

Nitrogen and Chlorine Based Oxidants. The use of stable organic aminoxyl radicals for the oxidation of primary and secondary alcohols has been reviewed. Aminoxyl radicals, such as TEMPO and its derivatives 1 and 2 (Figure 2), can catalyze alcohol oxidation when sodium hypochlorite, NaClO, or sodium chlorite, NaClO₂, are used as stoichiometric oxidants. For example, 1 (1 mol%) works in a biphasic system CH₃Cl/H₂O, containing NaClO, NaHCO₃, and KBr. Primary alcohols are quantitatively oxidized to aldehydes in a few minutes at 0 °C. Further oxidation to carboxylic acids is slow, but the reaction is completed in a few minutes by addition of catalytic amounts of phase-transfer catalyst [NCH₃(CH₂)₇]₃Cl. The reaction is highly selective and applicable to aliphatic and benzylic alcohols (few examples of acids, 87-96%).

Alternative method employs TEMPO (2-7 mol%) and NaClO (1-4 mol%) as catalysts, while NaClO₂ serves as an oxidant. It seems that TEMPO together with NaClO oxidize an alcohol to intermediate aldehyde, which is further oxidized to an acid by chlorite, thus regenerating hypochlorite. The reaction is conducted in CH₃CN phosphate buffer (pH 7) at 35 °C. The side-reaction of aromatic chlorination is greatly suppressed because concentration of NaClO remains low throughout the reaction. Yields of aliphatic, benzoic and chiral amino acids are above 85% (Scheme 3).

![Figure 2 Examples of catalysts for stoichiometric oxidation of alcohols to carboxylates](image-url)
Carboxylates and why such reactions have special utility. We think that this is a key reason why there's no path backwards that enables formation of a formation, once the Guerbet alcohol is formed from an aldol, conditions, aldolization become possible. Unlike ester when an intermediate aldehyde is generated under basic conditions, the Tishchenko-like ester formation pathway is a potential reason for this. Another, more pressing issue is the Guerbet pathway: when an intermediate aldehyde is generated under basic conditions, aldolization become possible. Unlike ester formation, once the Guerbet alcohol is formed from an aldol, there's no path backwards that enables formation of a carboxylate. We think that this is a key reason why there have been few examples of catalytic conversion of alcohols to carboxylates and why such reactions have special utility.

**Scheme 3 Oxidation of chiral amino alcohols by TEMPO/NaClO/NaClO2 system**

Comparisons between TEMPO/NaClO and TEMPO/NaClO/NaClO2 catalytic systems suggest that the later gives higher yields of acids. However, this procedure is not applicable to unsaturated alcohols and substrates with exceedingly electron-rich aromatic rings. The reaction can also be performed with polystyrene-immobilized aminoxyl radical 2 (10 mol%).

**4. Transfer Dehydrogenation**

Transfer dehydrogenation methods are a much more appealing approach to accomplishing alcohol oxidation than conditions that generate a stoichiometric metal waste stream. Although the stoichiometric metal-based oxidation methods were essential to the development of organic synthesis, in the modern era of catalysis, these should "disappear from use".

Particularly regarding the conversion of primary alcohols, it's important to note that there are a large number of catalysts that will convert alcohols to esters, in a Tishchenko-like process. Such reactions proceed through an intermediate aldehyde, which is in equilibrium with its hemiacetal (Scheme 4). The latter is readily converted to an ester under dehydrogenation conditions. While this has been known for a long time, there are relatively few examples of dehydrogenation methods that convert alcohols to carboxylates or carboxylic acids directly. The Tishchenko-like ester formation pathway is a potential reason for this. Another, more pressing issue is the Guerbet pathway: when an intermediate aldehyde is generated under basic conditions, aldolization become possible. Unlike ester formation, once the Guerbet alcohol is formed from an aldol, there's no path backwards that enables formation of a carboxylate. We think that this is a key reason why there have been few examples of catalytic conversion of alcohols to carboxylates and why such reactions have special utility.

**Scheme 4 Pathways of an aldehyde dimerization under the catalytic conditions**

Catalytic transfer dehydrogenation methods employ a catalyst and a hydrogen acceptor with relatively low redox potential: alkenes, ketones, DMSO, or even O2. The catalysts typically involve complexes of platinum group metals. For example, two very clever Rh complexes containing a tridentate diolol amido ligand, 3 and 4 above, catalyze hydrogen transfer in aqueous hydroxide solution from alcohols to acceptors like cyclohexanone, 1-hexene, and O2 with the aid of a co-catalyst, Pd/C. The scope of the method includes benzylic and aliphatic alcohols, diols, and glycerol. These reactions enable the synthesis of cis-aminic acid (50%), 4-bromobenzoic acid (77%), and 3-furan carboxylic acid (84%). Alkenes are partially hydrogenated under these conditions. Aerobic oxidation of alcohols catalyzed by 4 (1 mol%) was performed in an aqueous dimethyl sulfoxide solution of NaOH, where DMSO acts as a hydrogen peroxide scavenger. Citronellol and geraniol were converted to the acids with 64% and 81% yields without alkene hydrogenation (Scheme 5). Remarkably, both catalysts 3 and 4 operate at room temperature but 3 gives higher yields of the acids (up to 99%).

**Scheme 5 Catalytic transfer dehydrogenation of citronellol and geraniol**

Oxidation of alcohols with O2 takes place on the surface of various forms of metallic Pd, Pt, and Ru, including Pd and Pt nanoparticles. These reactions are typically conducted in hot aqueous hydroxide solution under 1 atm of O2, providing high yields of carboxylic acids (90-99%). The most popular version of this method uses Pt/C (5-10 mol%), which is known as Heyns oxidation. The catalyst loading is high, but the system can be reused multiple times without noticeable loss of activity. Typically, the reaction proceeds in a hot aqueous solution of NaHCO3 with the aid of a co-catalyst, NaHCO3. Water can be replaced with ethyl acetate, acetic acid, or heptane, but in this case the products are aldehydes. This fact illustrates the importance of water for enabling alcohol to carboxylic acid oxidation that proceeds via intermediate formation of an aldehyde hydrate.

**5. Acceptorless Dehydrogenation**

For the first time, primary alcohols were dehydrogenated directly to carboxylates without a catalyst under forcing conditions in the 19th century by J. B. Dumas (1840) and later E. Reid et al. converted primary alcohols to carboxylic acid salts and H2 by heating with hydroxide at 350 oC. In the 21st century, it was found that the reaction is catalyzed by compounds of transition metals, the corresponding methods are summarized in Table 2. Under solvent-free conditions aliphatic and benzoic acids were prepared with moderate to good yields (50-90%) at 150–160°C using pincer complexes of nickel and manganese, 5 and 6. Complex 6 tolerates aryl halides, amines, alkenes, derivatives of pyridine and thiophene. Furthermore, some
particularly oxidatively-sensitive pharmaceutical agents were prepared with 6 in moderate yields (Figure 3). Several methods utilize pincer complexes of manganese, iron, and cobalt, 7–9, in high-boiling hydrocarbon solvents, such as toluene (bp 111 °C) and mesitylene (bp 165 °C).65,66

Surprisingly, such simple compounds as silver carbonate67 and zinc oxide68 enable this reaction as well. In the latter case, hydrogenation of alkenes and aryl halides were detected as side reactions.

Catalytic carboxylate synthesis by acceptorless dehydrogenation in an aqueous hydroxide solution requires mild reaction conditions (60–100 °C, 1 atm) and can be achieved using heterogeneous palladium and rhodium13 catalysts and homogeneous dirhodium catalyst 10 (Table 2, rows 8, 9, and 5).69 The main side reactions here are aryl halide reduction and decarbonylation of substrate alcohols. For example, Pd/C converts 4-chlorobenzyl alcohol to benzoic acid (55%) within six hours, and Rh/C turns 6-phenylhexanol-1 to 1-phenylpentane (13%). Dehydroxylation of alcohols results from a background catalytic decarbonylation of intermediate aldehydes, which is a typical reaction in chemistry of platinum group metals.

**Ruthenium.** Complexes of ruthenium bearing mono-, di-, and tridentate ligands are the most abundant group of catalysts for acceptorless dehydrogenation of alcohols to carboxylates (Figure 4). The reaction conditions of ruthenium-based catalytic methods are summarized in Table 3. Depending on the ligand structure, the catalysts operate in hydrocarbons, water, or neat. Despite the importance of the ruthenium coordination environment for enabling the catalytic activity, the ligand structure seems to have almost no effect on ruthenium performance among the systems outlined in Table 3.

Complex 11 gives the best yields of benzoic acids (84%) under solvent-free conditions at 150 °C, while the reaction is slow in refluxing aqueous hydroxide solution (37% isolated benzoic acid after 24 h reaction, 82% – after 72 h).70 In the presence of two equivalents of water, 12 gives 2-(dimethylamino)acetic acid with 74% yield. The catalytic system is air tolerant and can be recycled up to five times.71 A group of complexes with a general formula [RuCl2(p-cymene)][NHC], 13-15, demonstrated its efficiency in alcohol dehydrogenation, however, while 13 operates in water by itself,72 complexes 14 and 15 are active in toluene and require tricyclohexylphosphine and the carbene ligand additives, respectively.73-74 Although complex 13 does not tolerate alkenes and amino alcohols, it dehydrogenates diols to diacids with moderate yields (59–63%). Other complexes that operate in refluxing toluene are 16-19.75-78

### Table 2 Characteristics of catalytic acceptorless dehydrogenation methods

<table>
<thead>
<tr>
<th>Complex</th>
<th>Conditions</th>
<th>T, °C</th>
<th>Aliphatic, %</th>
<th>Benzoic, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (1.0)</td>
<td>RDNa, neat</td>
<td>150</td>
<td>40</td>
<td>60-90</td>
</tr>
<tr>
<td>6 (0.2)</td>
<td>NaOH, 2 eq.</td>
<td>160</td>
<td>54-95</td>
<td>61-90</td>
</tr>
<tr>
<td>7 (2.0)</td>
<td>KOH, toluene</td>
<td>120</td>
<td>NMR &gt;99</td>
<td>–</td>
</tr>
<tr>
<td>9 (2.0)</td>
<td>KOH, toluene</td>
<td>140</td>
<td>67-86</td>
<td>67-95</td>
</tr>
<tr>
<td>10 (0.5)</td>
<td>NaOH, H2O, 12 h</td>
<td>100</td>
<td>–</td>
<td>86-95</td>
</tr>
<tr>
<td>Ag2CO3</td>
<td>KOH, mesitylene, 8 h</td>
<td>165</td>
<td>58-91</td>
<td>58-94</td>
</tr>
<tr>
<td>ZnO (20)</td>
<td>KOH, mesitylene, 18 h</td>
<td>164</td>
<td>67-82</td>
<td>60-91</td>
</tr>
<tr>
<td>Pd/C (5.0)</td>
<td>NaOH, H2O, 800 hPa</td>
<td>80</td>
<td>84</td>
<td>66-99</td>
</tr>
<tr>
<td>Rh/C (20)</td>
<td>NaOH, H2O</td>
<td>60-100</td>
<td>81</td>
<td>–</td>
</tr>
</tbody>
</table>

Acceptorless dehydrogenation of primary alcohols is often performed in an aqueous hydroxide solution due to conveniently low boiling point of water and its utility for the product isolation. Complexes with PNN and PNP pincer ligands 20-22 were employed under these conditions. Complex 20 was successfully used for oxidation of diols to give glucaric (61%) and isophthalic acids (99%). Unsaturated alcohols are partially hydrogenated, for example, cinnamyl alcohol gives only 24% of cinnamic acid, and 44% of hydrogenated by-products. Primary amines are not tolerated, as 4-aminobutanol-1 gives 2-pyrrolidone (85%).79 It was shown that catalysis by ruthenium dihydridedihydrogen complex 22 begins with decarbonylation of a primary alcohol that generates the active catalyst 21, which, in general, enables higher yields of carboxylates than precursor 22.80 Complexes 23 demonstrated its utility in a highly valuable transformation of unprotected amino alcohols to amino acids (Scheme 6). The structure of amino alcohol determines the reaction chemoselectivity, in particular, high stability of a five-
membered ring favors the formation of 2-pyrrolidone from 4-aminobutanol-1 rather than 4-aminobutyrate.81

![Scheme 6 Catalytic dehydrogenation of amino alcohols by complex 23](image)

**Table 3** Characteristics of ruthenium-catalyzed acceptorless dehydrogenation methods

<table>
<thead>
<tr>
<th>Catalyst (mol%)</th>
<th>Conditions</th>
<th>T, °C</th>
<th>Aliphatic Acids, %</th>
<th>Benzoic Acids, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (0.2)</td>
<td>CsOH, neat, 24 h</td>
<td>150</td>
<td>70</td>
<td>57-84</td>
</tr>
<tr>
<td>12 (0.1)</td>
<td>NaOH, 2.0 eq. H₂O, 3 h</td>
<td>130</td>
<td>25-96</td>
<td>10-90</td>
</tr>
<tr>
<td>13 (1.0)</td>
<td>NaOH, H₂O, 24 h</td>
<td>100</td>
<td>52-92</td>
<td>45-91</td>
</tr>
<tr>
<td>14 (1.0)</td>
<td>PCy₃, NaOH, toluene, 6 h</td>
<td>120</td>
<td>51-88</td>
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</tr>
<tr>
<td>15 (0.0125)</td>
<td>NHC, KOH, toluene, 12 h</td>
<td>120</td>
<td>56-95</td>
<td>52-92</td>
</tr>
<tr>
<td>16 (2.0)</td>
<td>KOH, toluene, 6 h</td>
<td>110</td>
<td>20-80</td>
<td>39-86</td>
</tr>
<tr>
<td>17 (0.5)</td>
<td>KOH, toluene, 6 h</td>
<td>120</td>
<td>50-68</td>
<td>45-89</td>
</tr>
<tr>
<td>18 (1.0)</td>
<td>NHC, KOH, toluene, 24 h</td>
<td>120</td>
<td>55-98</td>
<td>68-95</td>
</tr>
<tr>
<td>19 (0.2)</td>
<td>KOH, toluene, 18 h</td>
<td>120</td>
<td>65</td>
<td>79-89</td>
</tr>
<tr>
<td>20 (0.2)</td>
<td>NaOH, H₂O, 18 h</td>
<td>100</td>
<td>61-88</td>
<td>83-99</td>
</tr>
<tr>
<td>21, 22 (1.0)</td>
<td>NaOH, H₂O, 20 h</td>
<td>100</td>
<td>32-92</td>
<td>85</td>
</tr>
<tr>
<td>23 (5.0)</td>
<td>NaOH, H₂O, 6-24 h</td>
<td>100</td>
<td>59-99</td>
<td>62-99</td>
</tr>
<tr>
<td>24 (0.5)</td>
<td>KOH, H₂O, toluene, 48 h</td>
<td>120</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>25 (1.0)</td>
<td>NaOH, H₂O, 2-propanol, 12 h</td>
<td>98</td>
<td>19-34</td>
<td>25-71</td>
</tr>
</tbody>
</table>

While the majority of ruthenium catalysts are derivatives of Ru⁰, a complex of zero-valent ruthenium 24 and a mixed-valent triruthenium cluster 25 are the two exceptions. Satisfactory performance of 24 was demonstrated on a few substrate alcohols, including propylene glycol that gives lactic acid with 55% yield.82 Complex 25 exhibits poor catalytic activity as suggested by the low yields of acids.83

Complex 26 (Ru-MACHO) dehydrogenates polyols such as ethylene glycol, glycerol, and sorbitol with KOH in diglyme at 125 °C. Based on NMR data, 2.5 ppm of 26 convert glycerol to lactate with 67% yield within 24 h (Scheme 7). Sometimes propylene glycol forms as a major side-product.84

![Scheme 7 Dehydrogenation of glycerol to lactate by ruthenium and iridium catalysts](image)
Iridium. A series of iridium compounds were studied as catalysts for glycerol dehydrogenation to potassium lactate, among them commercial heterogeneous (Ir/C, IrO3, IrCl3) and homogenous catalysts ([Cp*IrCl2]3, [IrCl(COD)]3, [IrCl(CO)2]3), as well as complexes with 1,3-dimethylimidazol-2-ylidene ligand, for example, mono- and bis-carbene derivatives: [IrCl(COD)(NHC)], [IrCl(CO)2(NHC)], and 27-29 (Scheme 7). It was established that bis-carbene complexes 27-29 possess superior catalytic activity among the series and is characterized by the following turnover numbers: 30100 (27), 2400 (28), and 4760 (29). The highest conversion of glycerol is 94% and it was reached with 0.036 mol% of the catalytic system was not well studied.84

Toluene in the presence of stoichiometric amount of KOH. 89 The probably consequence of the similarity between isoelectronic iridium- and ruthenium-based catalytic systems, which is with the catalyst because of uncontrolled hydrogenation. This substrate scope limitation demonstrates a close analogy between iridium- and ruthenium-based catalytic systems, which is probably a consequence of the similarity between isoelectronic RuII and IrIII, which appear to be common oxidation states for driving the dehydrogenation catalytic cycles. Mechanistic studies show that precatalyst 34 undergoes a highly complex series of transformations before it turns to the active catalyst 36 (Figure 5). The key steps involve β-hydride elimination and isomerisation of COD ligand, to give 35, followed by aldehyde decarboxylation and ortho-metallaition of the pyridine ring. This example demonstrates that rationalizing catalytic activity based on precatalyst structure without knowing the structure of catalytic species can be misleading. Although the mechanisms of ruthenium and iridium catalyst activation in acceptorless alcohol dehydrogenation are generally poorly understood, it is evident that a combination of phosphate, carbene, and carbonyl ligands in the coordination environment of the metals raises the chance of manifesting the catalytic activity.

6. Electrochemical Methods

Anodic oxidation of aliphatic alcohols to aldehydes, ketones, acids, and esters has been well-reviewed.80-83 The material balances of alcohol electrooxidation and acceptorless dehydrogenation are identical, since none of them needs a stoichiometric oxidant. However, during electrolysis generation of dihydrogen and carboxylate/acid is separated in space; and since the reaction is driven by the external voltage, the limitations of acceptorless dehydrogenation, associated with positive ΔrGo in neutral and acidic solutions, do not apply for electrochemical methods. For example, anodic oxidation of 1-hexanol in 5% aqueous H2SO4 at 12 °C gives hexanoic acid (17%) and n-hexyl hexanoate (17%). Electrolysis was conducted at current density of 11 mA/cm² and current efficiency of 60% (with respect to acid) using lead cathode and lead dioxide coated anode.92

Still, majority of the reported electrochemical methods utilize basic aqueous solutions. Electrolysis of acetate, propionate, and butyrate from the corresponding alcohols was accomplished on a nickel oxide anode (1M KOH, 50 °C, 10 mA/cm²).93 Electrolysis with nickel hydroxide anode and steel cathode enables efficient synthesis of carboxylates in the presence of alkenes, aldehydes, and heterocycles (1M NaOH, 25 °C, 16 mA/cm², 2.0 V).94 For example, benzoic (86%), propiolic (51%), butyric (92%), and 2-furan carboxylic acids (79%) were obtained this way. Oxidation of ethanol to acetaldehyde, and then to acetate was reported using a redox couple [RuO4(bipy):Py]2+/[Ru(bipy)(H2O)(bipy):Py] as electrocatalytic system in hydrophosphate buffer (pH = 7, 50 °C, 0.8-1.0 V).95 Recently, another electrocatalytic method was developed that uses aminoxy radical 37 as a catalyst, thus enabling highly efficient synthesis (83-99% yields) of aliphatic and benzoic acids, pyridine and quinoline carboxylic acids, and chiral derivatives of amino acids (Scheme 8). The reaction is conducted in carbonate buffer (pH = 10, 0.9 V) and it is the best electrooxidation method known up to date.96
7. Outlook

There are numerous methods for oxidation of primary alcohols to carboxylic acids, yet many practitioners prefer to use stoichiometric methods, due to their reliability, short reaction times, and low cost. The historically recent discovery of catalytic acceptorless dehydrogenation methods has demonstrated the utility and a potential of this approach. However, certain acceptorless dehydrogenation conditions can suffer incompatibility with certain functional groups, such as alkenes, alkynes, aryl halides, and esters in cases, probably, because of the high reduction potential of transient metal hydrides and strongly alkaline reaction conditions that are present in the cycle. Resolving the issue would make these methods more commonly practiced in synthetic organic chemistry. Electrochemical oxidation of primary alcohols is not yet studied extensively, but anodic oxidation is more versatile than chemical oxidation since it gives options to control the process by tuning the voltage, current density, pH, and anode material. The available data suggest that the substrate scope of the electrolytic methods is broader than that of acceptorless dehydrogenation, since these typically tolerate alkenes, alkynes, heterocycles, and amino alcohols. Electrolysis is easily neglected by synthetic chemists, though, because of the requisite infrastructure of apparatus, buffers, etc.

Stoichiometric methods for alcohol oxidation probably should disappear from use in the 21st century in order to facilitate more sustainable production of bulk and fine chemicals. Enabling this transition will require continued work from the catalysis and electrochemical communities to enable more ideal syntheses. We should focus on simple, mild operating conditions, tolerance of highly functionalized alcohol targets, and careful studies of selectivity in challenging molecular contexts.

Conflict of Interest

T.J.W. is a founder V.C. is a stakeholder in a startup company, Catapower Inc, which is working to commercialize complex 30 for lactate synthesis.

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References
