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Recent advances in homogeneous transition metal-catalyzed aerobic alcohol oxidations

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1. Introduction

The oxidation of an alcohol to the corresponding carbonyl product is a vital and common transformation in synthetic organic chemistry. Consequently, there are a vast number of diverse methods that accomplish this fundamental functional group manipulation. Unfortunately, many of the most common methods suffer from the use of forcing conditions and/or toxic stoichiometric oxidants. An emerging alternative process, which may address these issues, is the implementation of a catalyst in combination with molecular oxygen as the stoichiometric oxidant. The use of molecular oxygen as the stoichiometric oxidant should be advantageous because it is inexpensive, readily available, and ultimately produces benign byproducts such as H_2O. The attractive nature and potential of developing catalysts for aerobic alcohol oxidations have led to a significant increase in research effort as described in several recent reviews.[1–6] Therefore, this review will discuss the most recent developments and the key initial discoveries in the area of homogeneous,[7] metal-catalyzed aerobic oxidations of alcohols.

2. General challenges

Several challenges exist in the development of transition metal-catalyzed aerobic alcohol oxidations. Because numerous methods are available for the oxidation of alcohols, practicality plays an important role in any new method. This includes mild reaction temperatures, low pressures of O_2 especially in flammable organic solvents, low catalyst loading, and avoidance of costly/toxic additives. Other key challenges common to any new method are functional group tolerance and the ability to chemoselectively oxidize an alcohol in the presence of other groups susceptible to oxidation. Within

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this, an ultimate goal would be to develop catalysts that control the ability to oxidize one class of alcohols (i.e., secondary) in the presence of another (i.e., primary). Lastly, the development of diastereo- and/or enantioselective alcohol oxidations would provide another potentially useful tool for synthetic chemists.

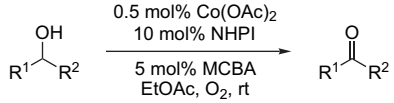
3. Catalyst systems

The subsequent sections describe in detail the different metal catalysts used in aerobic alcohol oxidation. Two key areas will be highlighted: synthetic potential and mechanistic considerations. It should be noted that this is not an exhaustive review of the topic and the examples are presented to illustrate the current state of the art and to describe the current mechanistic proposals.

3.1. Cobalt

In 1981, Tovrog and co-workers published the first Co-catalyzed aerobic oxidation of alcohols using Co–nitro complexes.[8] Following this early disclosure, several systems for Co-catalyzed aerobic alcohol oxidations have emerged. Ishii and co-workers have shown that combining *N*-hydroxyphthalimide (NHPI) with Co(III)-complexes, a variety of alcohols were successfully oxidized under aerobic conditions.[9,10] In their most recent report, addition of small amounts of benzoic acid increased the rate of alcohol oxidation, and the optimized procedure utilized 0.5 mol % $Co(OAc)_2$, 10 mol % NHPI, and 5 mol % *m*-chlorobenzoic acid (MCBA) under an oxygen atmosphere at room temperature (Table 1). This method was successful for the oxidation of secondary aliphatic, allylic, and benzylic alcohols (entries 1–4). Primary alcohols were oxidized to the corresponding carboxylic acids, and internal vicinal diols were converted to the corresponding diketones in modest yields (entries 5 and 6). In contrast, oxidation of terminal vicinal diols resulted in C–C bond cleavage and formation of the corresponding carboxylic acid.

Table 1. $Co(OAc)_2$/NHPI-catalyzed aerobic alcohol oxidation



Entry	Substrate	Time (h)	Yield (%)
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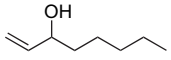
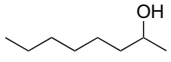
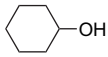
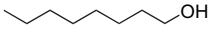
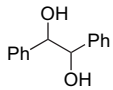
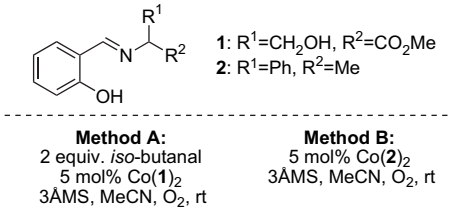
2		20	67
3		20	75
4		20	83
5[a]		20	78[b]
6[c,d]		20	84

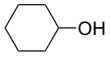
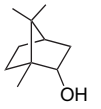
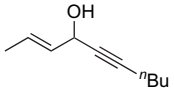
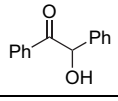
[a] *m*CPBA (1 mol %) substituted for MCBA.
[b] Product was corresponding acid.
[c] $Co(OAc)_2$ (1 mol %), no MCBA.
[d] Product was diketone.

In addition to Ishii's report, both Iqbal and Sain have disclosed similar examples of Co(II)-Schiff base catalyzed aerobic alcohol oxidations (Table 2, Method A and Method B, respectively).[11–14] These systems successfully oxidize both secondary aliphatic and benzylic alcohols (entries 1–6). Furthermore, Sain showed that α-hydroxyketones were oxidized using ligand **2**. The main difference between the two systems was the addition of *iso*-butanal in Method A. Adjusting the amount of added *iso*-butanal resulted in selective oxidation of benzyl alcohol to benzaldehyde as well as the oxidation of substrates containing olefins and/or alkynes without oxidation of the unsaturated bonds (entry 7). Mechanistically, Iqbal proposed the Co-complex with *iso*-butanal bound (**B**) was oxidized by molecular oxygen to form **C** (Scheme 1). **C** then oxidizes the aldehyde to the corresponding acid with concomitant formation of a Co(IV)-oxo species (**D**). **D** is responsible for the oxidation of alcohol to the corresponding carbonyl product with reduction to the Co(II)–Schiff base complex **A**.

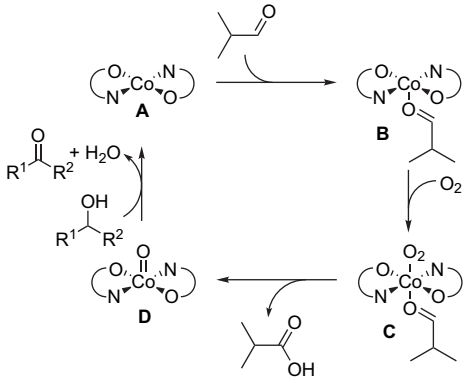
Sain and co-workers have also shown that a Co–phthalocyanine complex catalyzes the aerobic oxidation of alcohols.[15,16] This procedure utilized 5 mol % catalyst and 1 equiv of KOH in xylenes at reflux under an O_2 atmosphere for the oxidation of secondary benzylic, aliphatic, and propargylic alcohols (Table 3). In addition, the Co-catalyst was

Table 2. Co-Schiff base catalyzed aerobic alcohol oxidations



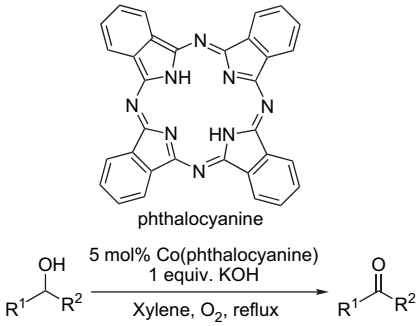
Entry	Substrate	Method	Time (h)	Yield (%)
1		B	5.5	96
2[a]		A	16	78
3		A	16	79
4		B	15	45
5		A	16	70
6		B	20	40
7		A	16	55
8		B	2.5	95

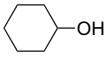
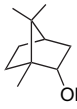
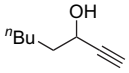
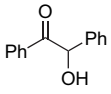
[a] *iso*-Butanal (1 equiv).



Scheme 1. Proposed mechanism for the Co-Schiff base catalyzed aerobic alcohol oxidation.

Table 3. Co-phthalocyanine catalyzed aerobic alcohol oxidation



Entry	Substrate	Time (h)	Yield (%)
1		1	94
2		3	95
3		5.5	75
4		7	92
5		7	70
6		0.2	96

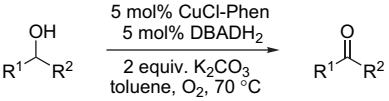
applied to the oxidation of a variety of α-hydroxyketones (entry 6).

While multiple systems have been developed for the Co-catalyzed aerobic alcohol oxidation, several limitations remain. Most secondary alcohols are converted to ketones, but primary alcohols are often oxidized to the carboxylic acid. To date, Ishii's system is the most synthetically useful due to the low catalyst loadings and mild conditions. Unfortunately, few mechanistic studies have been reported to assist in the development of improved catalysts.

3.2. Copper

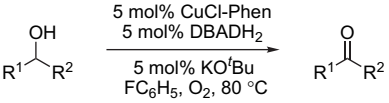
In 1984, Semmelhack reported the first practical Cu-catalyzed aerobic oxidation of alcohols. In this early disclosure, 10 mol % CuCl and 10 mol % TEMPO were used to oxidize primary benzylic, allylic, and aliphatic alcohols in DMF under an O_2 atmosphere at room temperature.[17] Using these standard conditions, secondary alcohols were oxidized but with significantly slower rates compared to primary alcohols. Since Semmelhack's early work, several reports on Cu-catalyzed aerobic alcohol oxidations have appeared and the topic has been thoroughly reviewed.[2,3] Much of the catalyst development has been pioneered by Markó and co-workers.[18–22] In Markó's initial report, an assortment of alcohols were oxidized using 5 mol % CuCl, 5 mol % phenanthroline, 5 mol % di-*tert*-butyl hydrazine-1,2-dicarboxylate ($DBADH_2$), and 2 equiv of K_2CO_3 (Eq. 1).[22] Unfortunately, this initial system required 2 equiv of a strong base and was not effective for the oxidation of primary aliphatic alcohols. More recently, it was shown that a change of the solvent from toluene to fluorobenzene allowed the use of catalytic K_2CO_3 or KO*t*-Bu instead of 2 equiv of K_2CO_3 (Eq. 2). Under catalytic base conditions, alcohols with α-chiral centers were oxidized with no observed racemization of the chiral center. However, the procedure continued to be inconsistent for the oxidation of primary aliphatic alcohols. Further additive evaluation led to the discovery that addition of catalytic *N*-methylimidazole (NMI) provided an efficient catalyst system for the oxidation of primary aliphatic alcohols (Eq. 3).

Generation 1



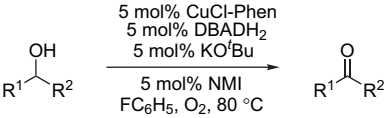
(1)

Generation 2



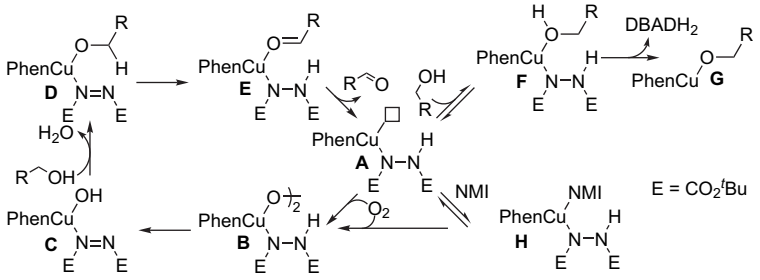
(2)

Generation 3



(3)

A number of mechanistic experiments and possible roles of the additives have led to a proposed mechanism (Scheme 2). First, the active catalyst **A** is oxidized by molecular oxygen to form a Cu(II)-hydrazide derivative **B**. Following homolytic cleavage of **B** and intramolecular hydrogen abstraction, **C** is formed. This is followed by ligand substitution with the alcohol to form the Cu(I)-alkoxide **D**. Intramolecular hydride transfer to DBAD followed by dissociation of the aldehyde reforms the active Cu(I)-catalyst **A**. To support this mechanism, **A** was prepared independently and exposed to alcohol under anaerobic conditions. This resulted in no alcohol oxidation; however, when oxygen was added, rapid conversion to the product was observed, thus implying preliminary oxidation of **A** with O_2 prior to alcohol oxidation.



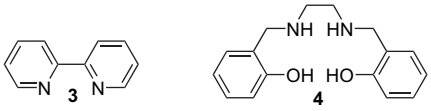
Scheme 2. Mechanism for Cu-DBADH$_2$ catalyzed aerobic oxidation of alcohols.

After discovering additives such as NMI improved the oxidation of primary aliphatic alcohols, an addition to the mechanistic proposal was made. It was shown that Cu(Phen)-alkoxides derived from primary aliphatic alcohols (such as **G**) do not undergo oxidation and thus the addition of NMI was believed to competitively bind to **A** preventing catalyst deactivation through this process.

In addition to Markó's developments, two groups have recently reported chemoselective oxidations of primary alcohols using Cu. After evaluating a variety of Cu-sources and ligands, Sheldon and co-workers demonstrated that the use of 2,2′-bypyridine as a ligand for $CuBr_2$ in combination with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) resulted in oxidation of primary benzylic, allylic, and aliphatic alcohols to the corresponding aldehydes with no overoxidation to the acid observed (Table 4, Method A).[23,24] Secondary alcohols were not oxidized, and when mixtures of primary and secondary alcohols were exposed to the reaction conditions, only the primary alcohol was converted. In a related system, Punniyamurthy and co-workers recently disclosed an oxidation that employed a salen-type ligand on Cu that also chemoselectively oxidized primary alcohols (Table 4, Method B).[25] While this system had a similar scope to Sheldon's, it required a pure O_2 atmosphere as well as elevated temperatures (100 °C). Additionally, the authors showed that the catalyst could be recycled up to three times with no loss in activity by using an aqueous workup.

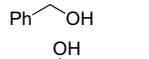
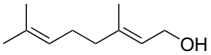
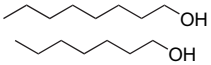
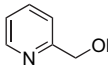
Both groups proposed a mechanism based on galactose oxidase-catalyzed oxidation of alcohols.[26] In these proposals, Cu(II) undergoes ligand exchange to form a Cu-alkoxide **B** that binds with TEMPO (Scheme 3). The Cu-TEMPO intermediate **C** can proceed to the aldehyde via hydrogen atom abstraction by TEMPO with concomitant formation of **D**. Molecular oxygen is proposed to reoxidize TEMPOH to TEMPO followed by reoxidation of Cu(I) by TEMPO. The authors proposed that the key to the chemoselectivity is the formation of intermediate **C** wherein secondary alcohols cannot arrange in a manner to undergo hydrogen transfer due to the steric interactions.

Table 4. Cu-TEMPO catalyzed aerobic alcohol oxidations

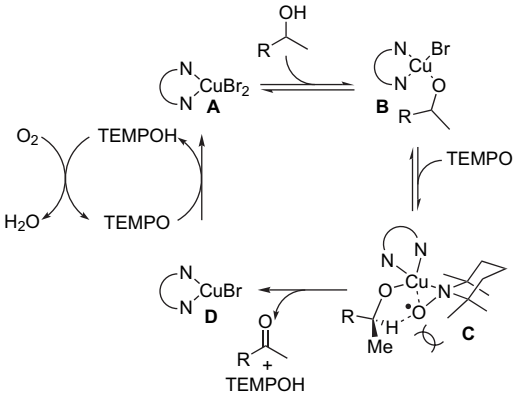


Method A:
5 mol% Cu(**3**)Br_2
5 mol% TEMPO, 5 mol% KO*t*Bu
MeCN:H_2O (2:1), air, rt

Method B:
5 mol% Cu(**4**)
5-7 mol% TEMPO
toluene, O_2, 100 °C

Entry	Substrate	Method	Time (h)	Yield (%)
1		A	2.5	>99
2		B	10	99
3		A	5	N.R.
4		B	12	2
5		A	5	>99
6		B	23	79
7[a]		A	24	95
8		B	21	90
9		B	26	92

[a] Reaction performed at 40 °C.

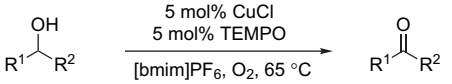


Scheme 3. Cu-TEMPO catalyzed aerobic alcohol oxidation.

The application of nontraditional organic solvents, which can allow simple product purification and catalyst recycling, presents an appealing alternative to the use of traditional organic solvents in this chemistry. In 2002, Ansari and Gree reported a CuCl-TEMPO catalyzed aerobic alcohol oxidation that succeeded in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) (Eq. 4).[27] This method was successful for the oxidation of primary and secondary benzylic and allylic alcohols using 5 mol % CuCl and 5 mol % TEMPO at 65 °C. Aliphatic alcohols were also successfully oxidized under these conditions, but with significantly slower rates and often with incomplete conversion. While the ionic liquid could be recycled up to eight times with little decrease in the efficiency, the authors were not able to recycle the catalyst. More recently, Jiang and Ragauskas used a pyridyl based ionic liquid, 1-butyl-4-methylpyridinium hexafluorophosphate ([bmpy]PF_6),

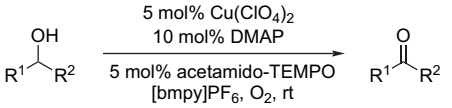
along with acetamido-TEMPO (a TEMPO source that can be recycled in ionic liquids) and DMAP for the Cu-catalyzed aerobic alcohol oxidation (Eq. 5).[28] The reactions were successful at room temperature for the chemoselective oxidation of a broad range of primary benzylic, allylic, and aliphatic alcohols with no oxidation of secondary alcohols observed. In contrast to Ansari and Gree's system, the catalyst/ionic liquid could be recycled up to five times with only a slight lowering of catalyst activity.

Ansari and Gree



(4)

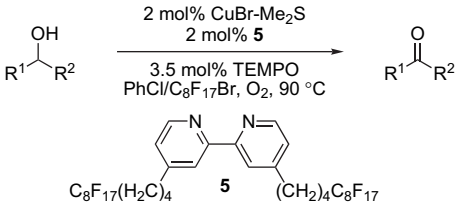
Jiang and Ragauskas



(5)

A biphasic solvent system has also been employed by Knochel and co-workers for Cu-catalyzed aerobic alcohol oxidations to enhance catalyst recyclability.[29] This was accomplished using a bipyridine ligand containing fluorinated 'ponytails' in combination with a chlorobenzene/perfluorooctyl bromide solvent mixture (Eq. 6). The oxidation was successful for a variety of primary and secondary benzylic, allylic, and aliphatic alcohols. As seen previously, primary alcohols generally oxidized more rapidly than secondary alcohols. Additionally, the authors demonstrated that the fluorous layer containing the catalyst could be reused up to eight times with little loss of catalyst activity.

Knochel and Coworkers



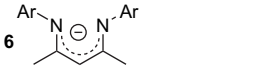
(6)

Overall, several useful systems have been developed for Cu-catalyzed aerobic alcohol oxidations. Markó and co-workers have developed multiple generations of catalysts for the oxidation of a broad scope of alcohols under mild conditions. Several groups have also developed catalyst systems that employ TEMPO in combination with Cu both in traditional and nontraditional solvents. Additionally, use of ligands in these oxidations produces a sterically encumbered environment at the Cu-center, thus resulting in a chemoselective oxidation of primary alcohols.

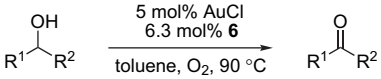
3.3. Gold

While gold salts have emerged as viable catalysts for several synthetic transformations, only one example of a homogeneous Au-catalyzed aerobic oxidation of alcohols has been reported.[30] In early evaluations, Shi and co-workers revealed several stoichiometric oxidants (O_2, H_2O_2, TBHP) in combination with catalytic AuCl and a monoanionic bidentate ligand **6** produced active systems for the oxidation of benzyl alcohol. Optimization of an aerobic oxidation led to the use of 5 mol % AuCl and 6.3 mol % **6** in toluene at 90 °C under an atmosphere of oxygen for the oxidation of primary and secondary benzylic and allylic alcohols (Table 5). Of particular note, the catalyst loading could be lowered to 1 mol % (entry 1) or the oxygen atmosphere was replaced with an air atmosphere with extended reaction times. Cyclic secondary aliphatic alcohols oxidized well under the standard conditions, but no examples of straight chain secondary aliphatic alcohols were reported (entry 6). A limitation of this system was that the primary aliphatic alcohols had slower oxidation rates and formed aldol byproducts (entry 7).

Table 5. Au-catalyzed aerobic alcohol oxidation



Ar = 2,6-di-*iso*-PrPhenyl



Entry	Alcohol	Time (h)	Yield[a] (%)
1[b]	Ph, OH	24	96
2	*p*-MeO-Ph, OH	10	99
3	*p*-F-Ph, OH	24	99
4	*p*-NO_2-Ph, OH	36	92
5	Ph, OH	24	96
6	OH	24	99
7	OH	48	68

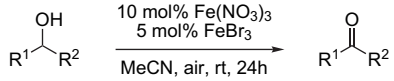
[a] GC-yield.
[b] AuCl (1 mol %), **6** (1.2 mol %).

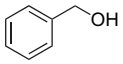
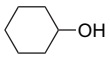
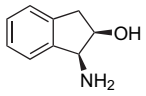
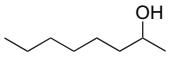
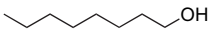
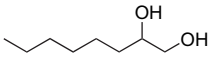
While very little work on the Au-catalyzed aerobic oxidation has been reported, Shi's report is very encouraging for future development. This system does require forcing conditions, but further mechanistic studies, ligand variation, and scope evaluation could result in an excellent system for the aerobic oxidation of alcohols using gold catalysts.

3.4. Iron

Recently, iron salts have been employed as catalysts for the aerobic oxidation of alcohols. In 2002, Martin and Suárez reported the first Fe-catalyzed aerobic alcohol oxidation that used a combination of $Fe(NO_3)_3$ and $FeBr_3$ to oxidize alcohols to the corresponding aldehydes and ketones under an ambient air atmosphere at room temperature (Table 6).[31] While the scope of this oxidation was not explored in depth, it was shown that secondary aliphatic and primary benzylic alcohols were readily oxidized (entries 1–4). However, primary aliphatic alcohols were not oxidized (entry 5) and no examples of allylic alcohols were reported. Additionally,

Table 6. Fe-catalyzed aerobic alcohol oxidation



Entry	Substrate	Yield (%)
1		80
2		80
3		85
4		75
5		N.R.
6		74[a]

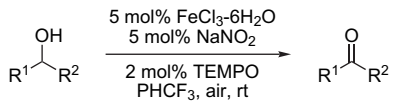
[a] Product corresponds to α-hydroxyketone.

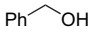
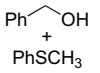
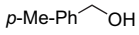
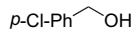
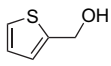
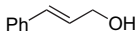
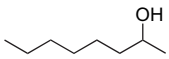
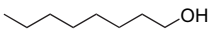
when a terminal 1,2-diol was exposed to the reaction conditions, the corresponding α-hydroxyketone was isolated in 74% yield with no oxidation of the primary alcohol observed. In contrast to the previously described Cu-TEMPO catalyzed oxidation, this represented an effective chemoselective oxidation of secondary aliphatic alcohols (entry 6).

More recently, a Fe-catalyzed aerobic alcohol oxidation was disclosed by Liang and co-workers that utilized $NaNO_2$/TEMPO to oxidize a variety of alcohols.[32] The optimized conditions for this system employed 5 mol % $FeCl_3$, 5 mol % $NaNO_2$, and 2 mol % TEMPO in trifluorotoluene at room temperature under ambient air pressure (Table 7). The scope of this oxidation system included primary and secondary benzylic alcohols along with secondary aliphatic alcohols and cinnamyl alcohol. It is noteworthy that thioethers were not oxidized under the reaction conditions (entry 2). Unfortunately, oxidation of primary aliphatic alcohols resulted in modest selectivity for aldehyde formation with both acid and ester byproducts observed (entry 8). The authors proposed a mechanism analogous to Cu-TEMPO oxidation that included two separate cycles (Scheme 4). Oxidation of the alcohol by a Fe(III)-TEMPO species is proposed to form the desired carbonyl product and a reduced Fe(II)-species. The Fe(III)-catalyst is proposed to be regenerated by the oxidation of Fe(II) with NO_2 wherein NO_2 is formed via rapid oxidation of NO with O_2.

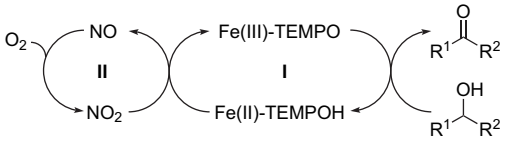
These two catalytic methods are performed under relatively mild conditions for an aerobic alcohol oxidation (room temperature and air atmosphere). However, relatively high catalyst loadings are employed. The Fe-TEMPO system has been explored for a slightly wider scope of alcohols while the $FeBr_3$/$Fe(NO)_3$ system provided a chemoselective oxidation of secondary aliphatic alcohols. These initial studies illustrate the potential of using Fe-based systems for aerobic alcohol oxidation but significant work remains in development of scope and mechanistic elucidation.

Table 7. Fe/TEMPO/$NaNO_2$-catalyzed aerobic alcohol oxidation



Entry	Substrate	Time (h)	Conversion[a] (%)
1		8	>99
2		16	>99[b]
3		8	>99
4		12	>99
5[c]		12	>99
6[c]		12	>99
7[c]		8	>99
8		6	>99[d]

[a] Conversion measured by GC.
[b] No oxidation of the sulfur observed.
[c] $NaNO_2$ (8 mol %) and TEMPO (5 mol %).
[d] Selectivity, 71%.



Scheme 4. Proposed mechanism for Fe/TEMPO/$NaNO_2$-catalyzed aerobic alcohol oxidation.

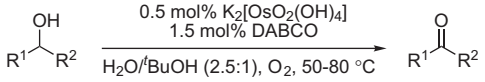
3.5. Osmium

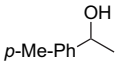
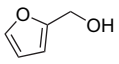
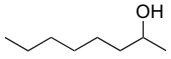
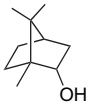
While Os has long been used for the dihydroxylation of olefins,[33] Beller and co-workers recently disclosed the first osmium-catalyzed aerobic alcohol oxidation.[34] This system operates using low catalyst loadings (≤0.5 mol %) along with catalytic DABCO for the oxidation of primary and secondary benzylic alcohols and secondary aliphatic alcohols under an oxygen atmosphere (Table 8). Additionally, by increasing the pressure of air to 40 bar, the catalyst loading could be lowered to 0.005 mol % for the oxidation of *sec*-phenethyl alcohol and benzyl alcohol with turnover numbers (TON) of up to 16,600 (entry 1). Similar to Fe and Au much work remains for the Os-catalyzed aerobic alcohol oxidations. While TON of 16,600 are especially impressive, the reaction requires forcing conditions and the scope and mechanism has not been thoroughly explored to date.

3.6. Palladium

Among the metal complexes explored for the aerobic oxidation of alcohols, palladium has arguably received the most recent attention. In 1977, Schwartz and Blackburn published the first synthetically viable Pd-catalyzed aerobic alcohol oxidation using $Pd(OAc)_2$ in combination with NaOAc.[35]

Table 8. Os-catalyzed aerobic alcohol oxidation



Entry	Substrate	Time (h)	Yield (%)
1		24	83[a]
2		12	93
3		24	85
4		24	59[b]
5		20	98

[a] $K_2[OsO_2(OH)_4]$ (0.005 mol %), DABCO (0.015 mol %), and 40 bar air.
[b] $K_2[OsO_2(OH)_4]$ (1 mol %) and DABCO (3 mol %).

Following this disclosure, 20 years passed with few developments in this field until the late 1990s, when several improved catalyst systems were reported by the Uemura,[36–41] Larock,[42] and Sheldon groups.[43–46] This has led to the development of various catalyst systems and a number of thorough mechanistic studies for Pd-catalyzed aerobic alcohol oxidations including the oxidative kinetic resolution (OKR) of secondary alcohols, which has been extensively reviewed.[1,5,47,48] For the purpose of this review, only the most recent disclosures on Pd-catalyzed aerobic alcohol oxidations will be highlighted.

In 2004, Tsuji and co-workers reported that substituted pyridines prevent formation of Pd-black, and therefore, allowed the Pd-catalyzed aerobic oxidation of alcohols under an air atmosphere using low catalyst loadings with TON up to 1480 (Eq. 7).[49] Use of the sterically encumbered ligand **7** allowed primary and secondary benzylic as well as secondary aliphatic alcohols to be oxidized to the corresponding carbonyl products in fair yields with no Pd-black formation observed.

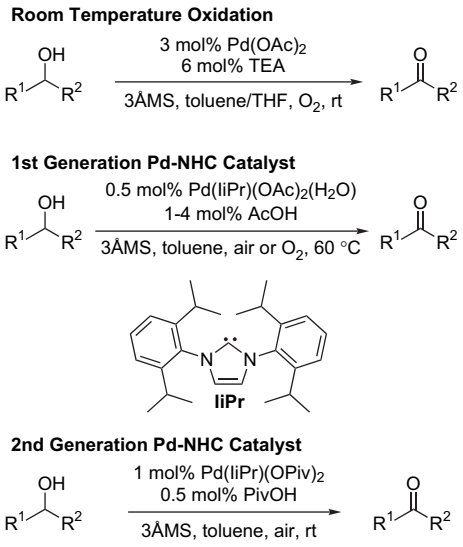
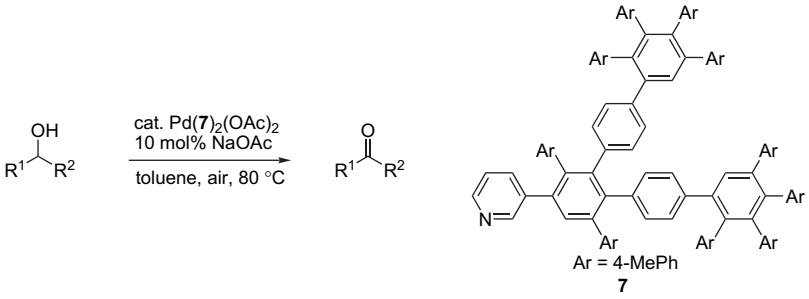


Figure 1. Sigman's Pd-catalyzed aerobic alcohol oxidations.

oxidations reported to date. The scope of this catalyst was compared with the previously reported $Pd(OAc)_2$/TEA[51] and $Pd(IiPr)(OAc)_2$[52] catalyst systems. While the $Pd(IiPr)(OPiv)_2$ system represented a mild oxidation, the scope was limited to the primary aliphatic alcohols and sterically encumbered alcohols were not oxidized well. In addition to reporting a new catalyst, the substrate scope of the three systems was evaluated for more complex substrates including 1,2- and 1,3-mono-protected diols as well as amino alcohols. Overall, the authors demonstrated that both the $Pd(OAc)_2$/TEA and $Pd(IiPr)(OAc)_2$ systems performed well for a broad scope of alcohols, and the $Pd(OAc)_2$/TEA system represented the most convenient of the three catalyst systems developed.

Over the past five years, a considerable number of detailed mechanistic studies have led to a generally accepted mechanism for Pd-catalyzed aerobic alcohol oxidations (Scheme 5).[5,48,53–57] The catalytic cycle begins with binding of the alcohol to the Pd(II)-catalyst to form alcohol bound intermediate **B**. Deprotonation of **B** then occurs to form a Pd-alkoxide (**C**), which undergoes β-hydride elimination to liberate the carbonyl product and form a Pd-hydride species (**D**). The Pd-hydride can reductively eliminate an equivalent

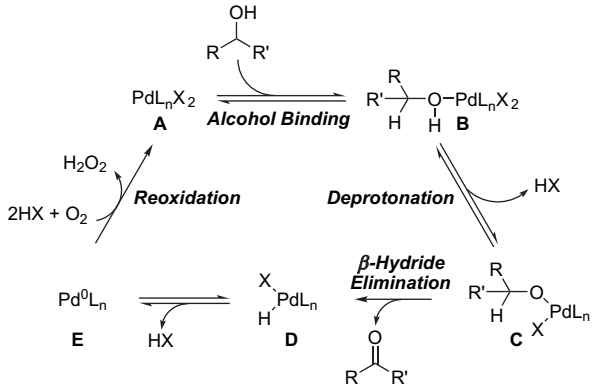


(7)

More recently, Sigman and co-workers have reported a comparison study of three catalyst systems developed within their group (Fig. 1).[50] In this report, a second generation Pd-*N*-heterocyclic carbene catalyst was used to oxidize alcohols at room temperature under an air atmosphere using 1 mol % catalyst. This represented one of the mildest aerobic alcohol

of acid to form Pd(0), which is then reoxidized by molecular oxygen and 2 equiv of acid. For majority of these catalyst systems, β-hydride elimination has been proposed as the rate-limiting step. There are two exceptions to this: the $Pd[(-)\text{-sparteine}]Cl_2$-catalyzed aerobic oxidative kinetic resolution at low [base][58] and $Pd(OAc)_2$/TEA[59] in which

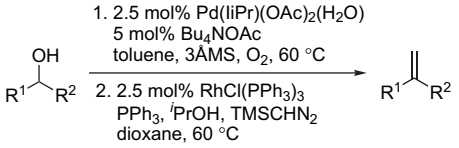
deprotonation is proposed as the rate-limiting step. The mechanistic studies have also led to a better understanding of the role(s) of ligands in the oxidation. Ligands are required to support Pd(0) and prevent metal aggregation and catalyst deactivation; however, excess ligands can also inhibit the oxidation by preventing substrate binding and/or β-hydride elimination.



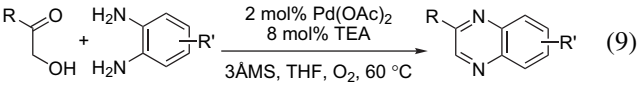
Scheme 5. Generally accepted mechanism for Pd-catalyzed aerobic alcohol oxidation.

More recently, Stahl and co-workers have also studied the role of molecular sieves in the $Pd(OAc)_2$/pyridine and $Pd(OAc)_2$/DMSO system.[60] In Uemura's early work, it was proposed that sieves were responsible for the disproportionation of the hydrogen peroxide formed during reoxidation of Pd(0).[37] Additionally, since water is formed upon disproportionation of the hydrogen peroxide, sieves could also be responsible for sequestering the water.[61] However, Stahl revealed that water did not have an inhibitory effect on the reaction rate, and by monitoring O_2 consumption, it was concluded that addition of 3 Å molecular sieves slowed the disproportionation of hydrogen peroxide. Furthermore, sieves were proposed to accelerate the oxidation by serving as a heterogeneous Brønsted base and to act as a heterogeneous surface to support Pd(0) and prevent aggregation of palladium metal.

Apart from the development of new systems for the Pd-catalyzed aerobic oxidation of alcohols and subsequent mechanistic studies, there are two recent examples of using Pd oxidation catalysts in tandem reactions. Lebel and Paquet have shown that alcohols can be converted directly to the corresponding olefin in a one-pot procedure using $Pd(IiPr)(OAc)_2(H_2O)$ to oxidize the alcohol followed by a Rh-catalyzed olefination reaction (Eq. 8).[62] In all cases, the olefins were isolated in better yields than in the corresponding two-step sequences. More recently, Robinson and Taylor have developed a one-pot procedure for preparing variety of quinoxalines from α-hydroxyketones via a tandem Pd-catalyzed aerobic alcohol oxidation/quinoxaline formation (Eq. 9).[63] Of the catalysts evaluated for the reaction, the $Pd(OAc)_2$/TEA system provided the best yields of the desired products.

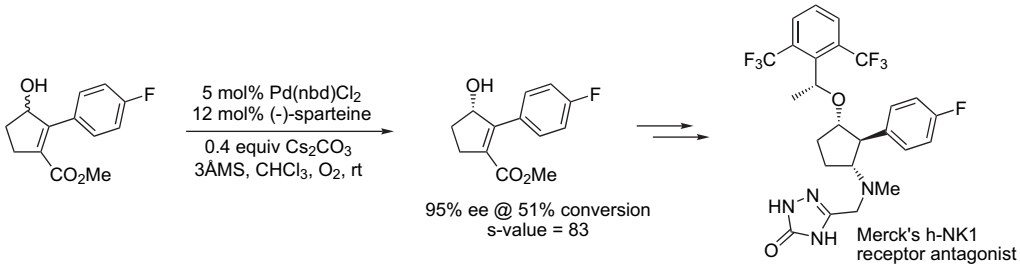


(8)



(9)

In addition to these tandem reactions, Stoltz and co-workers have demonstrated the utility of the recently developed Pd-catalyzed aerobic OKR of alcohols in the synthesis of several pharmaceutical intermediates.[64] In their best result, the 2-arylcyclopentenol precursor to Merck's human neurokinin-1 receptor antagonist[65,66] was resolved with *s*-values up to 83 (Eq. 10).



(10)

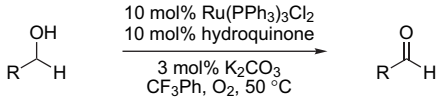
Overall, Pd(II)-catalysis represents one of the most mature fields in the aerobic oxidation of alcohols. The scope of the reaction is the most widely examined and the mechanism is best understood. Future work in this area will focus on identifying/designing new ligands that would allow the oxidation to be performed using low catalyst loadings under mild conditions.

3.7. Ruthenium

There also has been much effort placed on the development of Ru-catalyzed aerobic alcohol oxidations. In 1997, Markó and Ley simultaneously reported TPAP-catalyzed aerobic alcohol oxidations.[67,68] While the two groups used different reaction conditions, both systems worked well for a broad range of alcohols, but primary aliphatic alcohols were not oxidized well in contrast to using NMO as the stoichiometric oxidant.[69] Following these reports, several other Ru-catalysts have been developed for the aerobic oxidation of alcohols. Ishii and co-workers employed a combination of $Ru(PPh_3)_3Cl_2$ and hydroquinone to chemoselectively oxidize primary aliphatic alcohols to the corresponding aldehydes under aerobic conditions (Eq. 11).[70] A year later, Sheldon demonstrated using the same Ru-catalyst in combination with TEMPO that both primary and secondary alcohols were oxidized successfully (Eq. 12).[71,72] Unfortunately, this system requires 10 bar pressure. In 2000, Lee and Chang reported a convenient Ru-catalyzed aerobic alcohol oxidation using $[RuCl_2(p\text{-cymene})]_2$ in combination with Cs_2CO_3 for

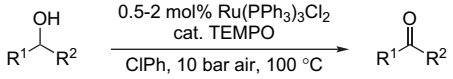
the oxidation of a broad range of alcohols. This system was limited due to the poor oxidation of primary aliphatic alcohols (Eq. 13).[73]

Ishii



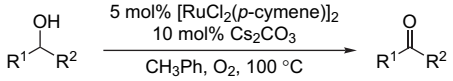
(11)

Sheldon



(12)

Chang



(13)

More recently, Katsuki and co-workers have published several papers on Ru–salen catalysts for aerobic alcohol oxidations. Catalyst **8** was employed to oxidize *o*-hydroxy benzyl alcohol derivatives to the corresponding aldehydes selectively (Eq. 14).[74] This is especially impressive since these substrates have the ability to chelate with the metal and/or undergo other coupling reactions. This catalyst also proved effective for chemoselective oxidation of primary alcohols in the presence of secondary alcohols and upon derivatization of the ligand, catalyst **9** provided better chemoselectivity (Eq. 15).[75,76] Using **9**, it was demonstrated that primary aliphatic alcohols could be selectively oxidized in the presence of secondary aliphatic, benzylic, allylic, and propargylic alcohols.

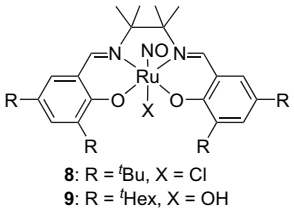
In addition to chemoselective oxidation, chiral salen ligands have been used for the Ru-catalyzed aerobic oxidative kinetic resolution of secondary alcohols and desymmetrization of *meso*-diols (Eq. 16).[77,78] After evaluating several Ru–salen complexes, **10** proved most effective for the oxidative kinetic resolution of secondary alcohols resulting in *s*-values up to 20. In contrast, Katsuki found that catalyst **11** proved most useful for the oxidative desymmetrization of a variety of *meso*-diols. Upon oxidation of the resulting lactol to the corresponding lactone, ees up to 93% were observed (Eq. 17).

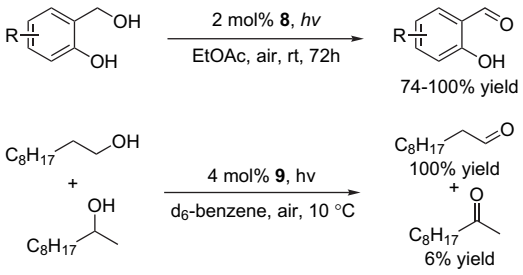
Ruthenium has proven effective for the aerobic oxidation of alcohols. This is especially true for Sheldon's system, which uses low catalyst loadings but requires elevated O_2 pressure. Additionally, Katsuki has developed an efficient chemoselective oxidation of primary aliphatic alcohols. However, much work remains in developing general alcohol oxidation catalysts that employ low catalyst loadings and perform under milder conditions.

3.8. Vanadium

Vanadium has recently been applied to the aerobic oxidation of both α-hydroxycarbonyl compounds and propargylic alcohols. In 1999, Nemoto and co-workers demonstrated that a simple procedure using 1 mol % $VOCl_3$ in acetonitrile at room temperature resulted in the oxidation of α-hydroxycarbonyls in excellent yields (Table 9).[79] This method was successful for the oxidation of a variety of substrates and could be carried out under an air atmosphere, albeit with significantly longer reaction times (entry 2). In addition, aromatic substrates oxidized much more rapidly then aliphatic substrates.

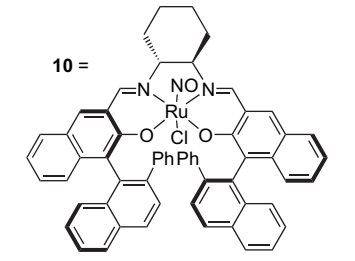
Uemura and co-workers have published a thorough study on the vanadium-catalyzed aerobic oxidation of propargyl alcohols.[80,81] Under optimized conditions (1 mol % $VO(acac)_2$, 3 Å MS, MeCN, O_2, 80 °C), a variety of propargyl alcohols including aryl, vinyl, alkynyl, and aliphatic substrates were successfully oxidized to the corresponding carbonyl products (Table 10). Of the alcohols examined, aryl substrates proved

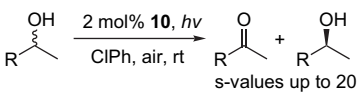




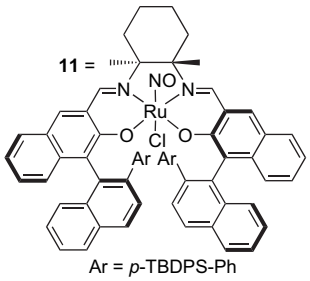
(14)

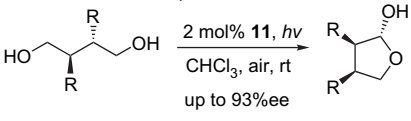
(15)





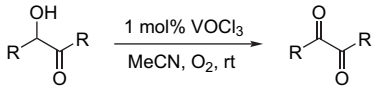
(16)

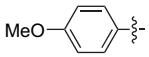
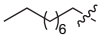




(17)

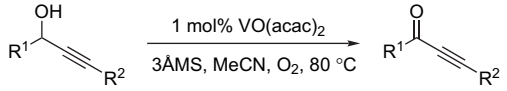
Table 9. V-catalyzed aerobic oxidation of α-hydroxycarbonyls

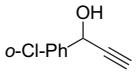
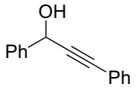
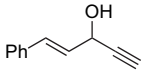
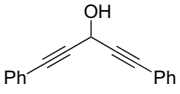
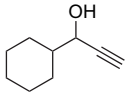
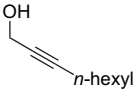


Entry	R	Time (h)	Yield (%)
1		1.5	95
2[a]		11	89
3		1.5	>99
4		5.5	>99
5		12	>99
6		20	95

[a] Reaction carried out under an air atmosphere.

Table 10. $VO(acac)_2$-catalyzed oxidation of propargylic alcohols

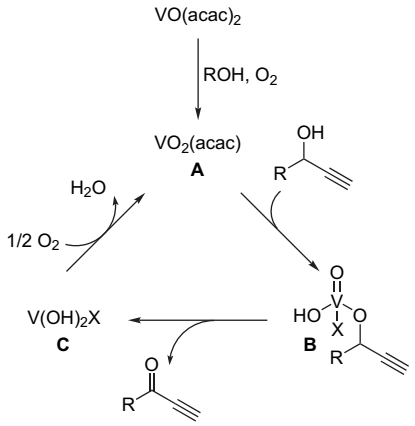


Entry	Substrate	Yield[a] (%)
1		65
2		81
3		65
4		76
5		41
6[b]		62

[a] GC yield.
[b] $VO(acac)_2$ (5 mol %).

to oxidize most effectively. Of note, a primary propargyl alcohol was successfully oxidized, but requires increased catalyst loadings (5 mol %) to obtain good yields (entry 6). On further optimization, the authors showed that the use of hexafluoroacetylacetonate as the ligand on V and as an additive led to slightly better yields for problematic substrates. Besides propargyl alcohols, an assortment of other alcohols was exposed to the reaction conditions. Unfortunately, the conditions only provided poor to moderate yields for the oxidation of simple benzylic, aliphatic, and allylic alcohols.

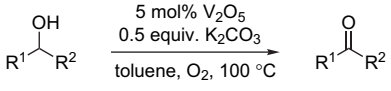
After exploring the scope of the V-catalyzed aerobic alcohol oxidation, several mechanistic experiments were performed. The stoichiometry of alcohol to oxygen was determined to be 2:1 by measuring oxygen uptake. The authors also found that radical inhibitors did not affect the rate of oxidation. Furthermore, use of electron spin resonance spectroscopy provided evidence that $VO(acac)_2$ was not involved and V(V) may be the active species in the oxidation. Combining these experiments, the authors proposed a mechanism involving initial oxidation of V(IV) to V(V) by O_2 followed by the attack of alcohol to form a V-alkoxide species **B** (Scheme 6). Elimination of the alkoxide would result in product formation and V(III) **C**, which could then be reoxidized by O_2 to reform the active V(V) catalyst **A**.

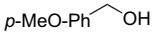
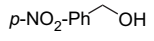
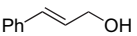
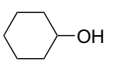
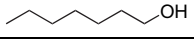


Scheme 6. Proposed mechanism for V-catalyzed aerobic oxidation of propargylic alcohols.

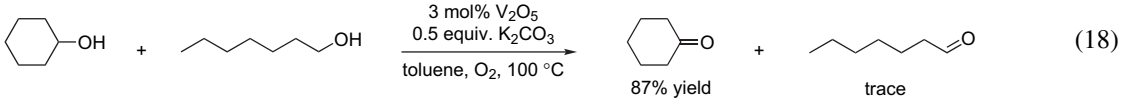
In addition to Uemura's work, Velusamy and Punniyamurthy have used V_2O_5 to broaden the scope of oxidation to benzylic, allylic, and aliphatic alcohols.[82] This oxidation required 5 mol % V_2O_5 and 0.5 equiv of K_2CO_3 in toluene at 100 °C under an oxygen atmosphere (Table 11). This method showed little dependence on the electronics of benzylic alcohols for the oxidation (entries 1–4). While the oxidation of secondary aliphatic alcohols proceeded well, primary aliphatic alcohols provided only moderate

Table 11. V_2O_5-catalyzed aerobic alcohol oxidation



Entry	Substrate	Time (h)	Yield (%)
1		24	82
2		13	95
3		22	92
4		25	79
5		22	87
6		15	89
7		24	43

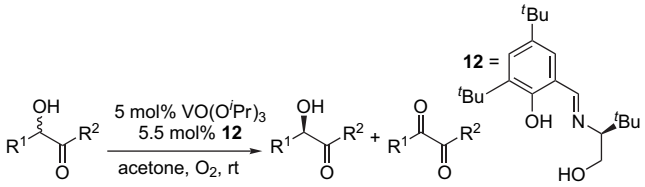
yields of the corresponding aldehydes (38–43%) (entry 7). With this in mind, the authors exposed a mixture of cyclohexanol and 1-heptanol to modified reaction conditions (3 mol % V_2O_5) to test for a chemoselective oxidation. This experiment resulted in an 87% isolated yield of cyclohexanone and only a trace amount of heptanal (Eq. 18). Therefore, this system has the potential to be used for the chemoselective oxidation of secondary aliphatic alcohols.

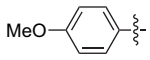
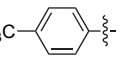
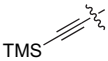


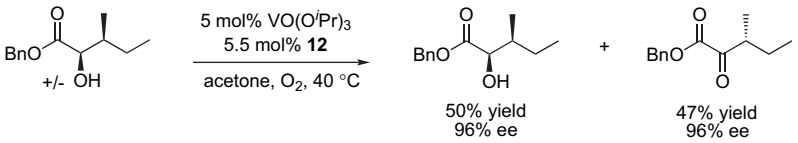
(18)

While several groups have worked on V-catalyzed general alcohol oxidations, Toste and co-workers have recently shown that chiral vanadium complexes catalyze the oxidative kinetic resolution (OKR) of α-hydroxy esters.[83] In this report, a tridentate ligand with an O,N,O-binding motif proved most effective (Table 12). A variety of racemic aryl, vinyl, and alkyl substituted α-hydroxy esters were efficiently resolved with selectivity factors ranging from 12 to >50. Unfortunately, application of this system to the OKR of a propargyl α-hydroxy ester resulted in a poor resolution (entry 6). In addition to the efficient resolution of simple α-hydroxy esters, racemic substrates with α-chiral centers were effectively resolved to yield both the enantioenriched alcohol and ketone in excellent yields and ee's (Eqs. 19 and 20).

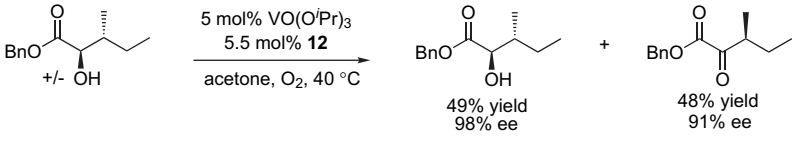
Table 12. V-catalyzed aerobic OKR of α-hydroxy esters



Entry	R^1	R^2	Time (h)	Yield (%)	ee (%)	*s*
1		OEt	10	49	99	>50
2		OMe	5.5	38	95	13
3		OMe	4	35	98	29
4		OBn	16	45	92	18
5		O^{i}Pr	90	37	98	30
6		OEt	16	53	50	6



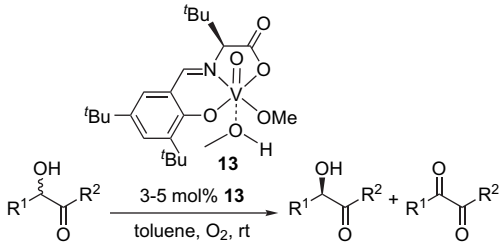
(19)

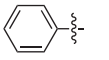
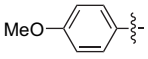
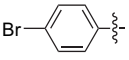


(20)

More recently, Chen and co-workers have published OKR of both α-hydroxy esters and amides using a similar O,N,O-chelating tridentate ligand (Table 13).[84] The procedure utilized 3–5 mol % catalyst **13** in toluene at room temperature under an oxygen atmosphere. The catalyst system was most efficient for the OKR of aryl α-hydroxy esters and amides with *s*-values ranging from 5 to 1057 with slightly higher *s*-values than Toste's method. The system was also successful for a vinyl α-hydroxy ester and amide but aliphatic substrates gave varying results (entries 4–6). Overall, the procedure generally resulted in higher *s*-values for the oxidation of benzyl amides relative to the benzyl esters.

Table 13. V-catalyzed aerobic OKR of α-hydroxy esters and amides



Entry	R^1	R^2	Time (h)	Yield (%)	ee (%)	*s*
1		OBn	12	45	98	458
		NBn	25	47	99	1057
2		OBn	57	49	70	10
		NBn	106	38	77	7
3		OBn	15	43	88	28
		NBn	24	45	99	>80
4		OBn	5.5	40	96	27
		NBn	9	47	>99	>211
5		OBn	63	46	71	14
		NBn	142	46	95	81
6	Me	OBn	83	36	37	2
		NBn	92	47	33	3

While the use of vanadium for the aerobic oxidation of alcohols has only been explored recently, the potential utility has been demonstrated. It has proven to be the most effective metal for the aerobic oxidation of propargylic alcohols and for the oxidative kinetic resolution of α-hydroxy esters. Continued work on the development of more effective

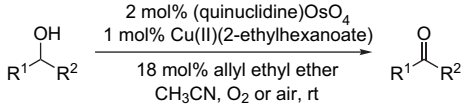
general alcohol oxidations and oxidative kinetic resolutions remains.

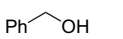
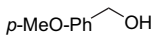
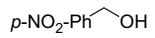
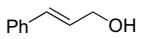
3.9. Other systems

Besides applying individual metals for aerobic alcohol oxidations, there are also a limited number of reports of bimetallic homogeneous alcohol oxidations. The use of bimetallic systems can offer the advantage of one metal activating the alcohol while the other activates molecular oxygen preventing catalyst decomposition and thus more efficient catalysis. In the late 1990's Osborn and co-workers published separate reports of Os–Cu, Ru–Cu, and Mo–Cu bifunctional aerobic alcohol oxidations.[85–87] All three of these systems employed relatively low catalyst loadings (1 mol %) and were most successful for the oxidation of primary benzylic alcohols. While very little mechanistic work was performed the authors proposed that in all the oxidations Cu was most likely responsible for the activation of O_2 and the other metal for the oxidation of alcohol. Shapley and co-workers have also reported similar Os–Cr and Ru–Cr systems for the aerobic oxidation of alcohols.[88] In these reports, primary alcohols were oxidized most effectively with the best chemoselectivity realized for aliphatic alcohols. The authors showed that the oxidation was reversible and a competitive isotope effect of 1.9 for the oxidation of PhCHDOH was observed.

A more recent report by Muldoon and Brown utilized a Os–Cu bifunctional catalyst system for the aerobic oxidation of alcohols at room temperature.[89] This oxidation occurs using 2 mol % (quinuclidine)OsO_4 and 1 mol % Cu(ethylhexanoate) (Table 14). The authors stated that the use of quinuclidine as a ligand for Os resulted in a 10-fold increase in activity. This oxidation was successful for a variety of benzylic and allylic alcohols. As with Osborn's report, aliphatic alcohols were not oxidized well.

Table 14. Os/Cu-catalyzed aerobic oxidation



Entry	Alcohol	Time (h)	Yield (%)
1		6	98
2		6	97
3		10	98
4		8	97
5		15	96

There are also several reports of other metals catalyzing the aerobic oxidation of alcohols. This includes two reports by Kim and co-workers of bifunctional systems where catalytic TEMPO or *N*-hydroxyphthalimide oxidizes a range of alcohols. Catalytic Ce is used to reoxidize the TEMPO/*N*-hydroxyphthalimide and O_2 is proposed as the terminal oxidant to reoxidize Ce.[90,91] In 1998, Ruiz and co-workers reported a unique Mn–oxamato complex that catalyzed the aerobic oxidation of secondary benzylic alcohols. A primary benzylic alcohol was oxidized to the corresponding acid and no further examples of the substrate scope were given.[92] There is also one example of a Rh-catalyzed aerobic alcohol oxidation that utilized $RhCl_3$ or $Rh(ClO_4)_3$ along with either $BiCl_3$ and/or LiCl to oxidize secondary aliphatic alcohols to the corresponding ketones.[93]

4. Conclusion

The last 10 years has seen a considerable increase of interest in the area of metal-catalyzed aerobic alcohol oxidations. Of the work presented in this review, Markó's Cu-(phen) and Sigman's $Pd(OAc)_2$/TEA and $Pd(IiPr)(OAc)_2(H_2O)$ systems are the most mature. All three of these methods have been explored for a broad scope of alcohols and work under relatively mild conditions. In addition, several of the catalyst systems discussed show high potential for synthetic utility. This is especially true for chemoselective oxidations. Unfortunately, even with the significant amount of work applied to the development of a variety of catalyst systems, application in target synthesis has yet to be realized.

Mechanistically, very little work has been performed to elucidate the fine details for many of the metal-catalyzed aerobic alcohol oxidations. Pd-catalyzed aerobic alcohol oxidations are an exception to this and the mechanistic details are well understood. While there has been relatively little mechanistic work for the majority of systems, it is interesting to note the significant differences/similarities in proposed pathways of many of the systems discussed in this review. There seems to be two general mechanistic motifs: (1) the oxidation of the alcohol occurs at the metal center, which can proceed by either one or two electron pathway and involve a β-hydride elimination or β-hydrogen abstraction as a key step and (2) a co-oxidant is responsible for the oxidation of alcohol wherein the metal activates the co-oxidant and alcohol or the metal is responsible for reoxidation of the additive with O_2.

While there has been a tremendous amount of effort applied to the development and improvement of metal-catalyzed aerobic alcohol oxidations, many improvements can be envisioned. Performing aerobic alcohol oxidation under mild conditions (room temperature, air atmosphere) while employing low catalyst loadings should be an important goal of researchers. Additionally, in order for these methods to be used in target synthesis, the scope of the individual systems must be broadened to include more complex alcohols that are synthetically relevant.

References and notes

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Biographical sketch

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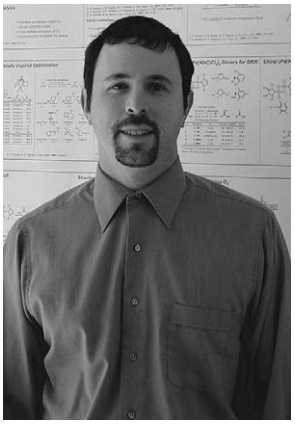

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