Green, Catalytic Oxidations of Alcohols

ROGER A. SHELDON,* ISABEL W. C. E. ARENDS, GERD-JAN TEN BRINK, AND ARNÉ DIJKSMAN

Delft University of Technology, Biocatalysis and Organic Chemistry, Julianalaan 136, 2628 BL Delft, The Netherlands

ABSTRACT

Three methods are described, in the context of the guiding principles of green chemistry, for the catalytic oxidation of alcohols. The first employs a recyclable oligomeric TEMPO catalyst (PIPO) and sodium hypochlorite as the oxidant in a bromide-free and chlorinated hydrocarbon solvent-free system. The second involves a ruthenium/TEMPO catalyst and oxygen as the oxidant. The third consists of a recyclable water-soluble palladium–diamine complex in conjunction with air as the oxidant in an aqueous biphasic system. The mechanisms of the ruthenium/TEMPO- and palladium-catalyzed oxidations are discussed, and the mechanism of the former is compared with that of the analogous copper/TEMPO catalyst.

The oxidation of primary and secondary alcohols to aldehydes or carboxylic acids and ketones, respectively, is a pivotal reaction in organic synthesis.[1] Traditionally, such transformations have been performed with stoichiometric inorganic oxidants, notably chromium(VI) reagents.[2] However, from both economic and environmental viewpoints, there is an urgent demand for greener, more atom efficient methods that employ clean oxidants such as O_2 and H_2O_2 and a (preferably recyclable) catalyst. Such methods would conform to 4 of the 12 guiding principles of green chemistry proposed by Anastas and Warner.[3] Hence, our research in this area is aimed at eliminating waste, maximizing the incorporation of raw materials into the final product, avoiding, where possible, the use of auxiliary substances including solvents, and employing (recyclable) catalysts. In this Account we shall describe

Roger A. Sheldon (born 1942) received a Ph.D. in chemistry from the University of Leicester (UK) in 1967. Following a postdoctoral sojourn with Jay Kochi, he was with Shell Research, Amsterdam, from 1969 to 1980. From 1980 to 1990, he was R&D director of DSM-Andeno (Venlo, The Netherlands). In 1991, he was appointed Professor of Organic Chemistry at Delft University of Technology. His research interests are mainly concerned with the application of catalytic methods, in particular catalytic oxidations, using homogeneous and heterogeneous catalysts and biocatalysts, in organic synthesis.

Isabel W. C. E. Arends (born 1966) studied chemistry at the University of Leiden (The Netherlands), where she received her Ph.D. in 1993, under the supervision of R. Louw and P. Mulder. Postdoctoral work followed with K. U. Ingold at the National Research Council in Canada on liquid-phase oxidations catalyzed by biomimetic iron complexes. She joined the group of R. A. Sheldon in 1995, and her research interests include metal-catalyzed selective oxidations, redox molecular sieves, and biomimetic vanadium systems.

Gerd-Jan ten Brink (born 1971) did his undergraduate studies at the VU (Amsterdam) under the supervision of F. Bickelhaupt. He received his Ph.D. in 2001, and is currently working as a post-doc for Avantium Technologies (Delft, The Netherlands).

Arné Dijksman (born 1973) did his undergraduate studies at the University of Utrecht under the supervision of G. van Koten. He received his Ph.D. in 2001. His main interests are in the development of efficient catalysts for the oxidation of alcohols using clean and cheap oxidants.
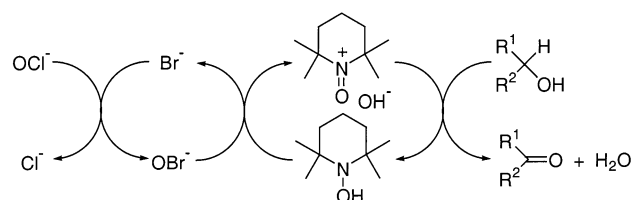
FIGURE 1. TEMPO-catalyzed bleach-oxidation of alcohols using bromide as cocatalyst.

three different systems which meet some or all of the above-mentioned criteria.

Our starting point was a method which is being increasingly applied on both an industrial and a laboratory scale: the 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO)-catalyzed oxidation of alcohols with sodium hypochlorite (household bleach) as depicted in reaction 1.[4] The active
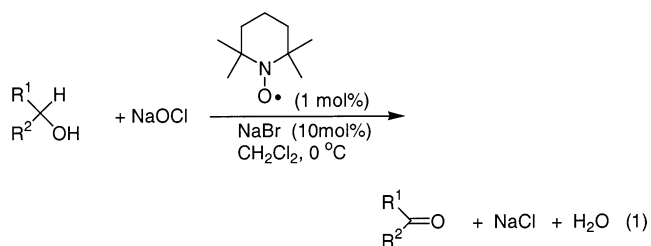
oxidant in this system is the corresponding oxoammonium cation. Oxidation of the alcohol affords the corresponding carbonyl compound and the reduced form of TEMPO, the hydroxylamine, TEMPOH. The latter is then reoxidized by NaOCl to regenerate the oxoammonium cation. In the generally applied procedure,[5] sodium bromide (10 mol %) is used as a cocatalyst, as the reoxidation step is more favorable with hypobromite and the sodium bromide produced is readily reoxidized by hypochlorite (Figure 1).

A shortcoming of this method is that it is not waste-free: at least one equivalent of sodium chloride is produced per molecule of alcohol oxidized. However, we contend that this is a considerable improvement compared to stoichiometric oxidation with chromium(VI) reagents. Other shortcomings are the use of sodium bromide as a cocatalyst and dichloromethane as a solvent. Furthermore, although only 1 mol % is used, TEMPO is rather expensive, which means that efficient recycling is an important issue. Hence, several groups have addressed this problem by designing heterogeneous variants of TEMPO, e.g. by anchoring TEMPO to solid supports such as silica[6,7] and the mesoporous silica, MCM-41,[8] or by entrapping TEMPO in sol–gel.[9]

In this context, our attention was attracted by the structure of the commercially available antioxidant, chimassorb 944, an oligomeric, sterically hindered amine (MW ~3000).[10] We surmised that oxidation of chimassorb 944 with H_2O_2 and a catalytic amount of $Na_2WO_4 \cdot 2H_2O$[11] would generate a recyclable oligomeric TEMPO (Figure 2). This new polymer-immobilized TEMPO, which we refer to as polymer-immobilized piperidinyl oxyl (PIPO), proved
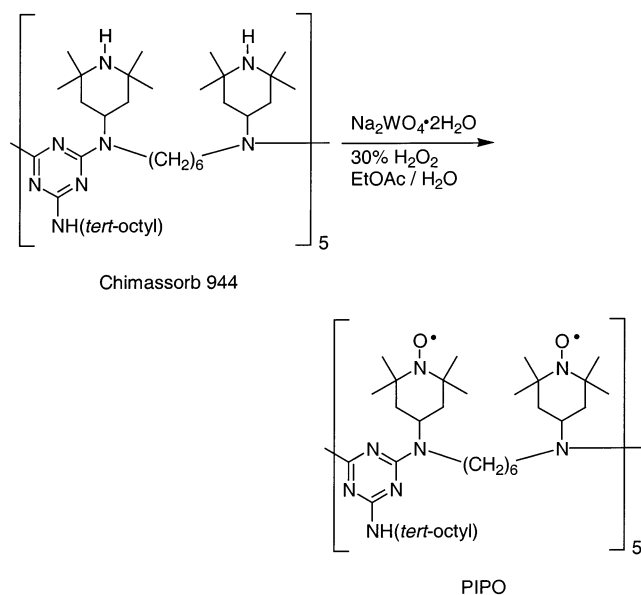
FIGURE 2. Synthesis of PIPO.

Table 1. Chlorinated Solvent- and Bromide-Free PIPO-Catalyzed Oxidation of Alcohols with Hypochlorite[a]

entry	substrate	time (min)	conv (%)	sel (%)
1	octan-1-ol	45	90	50[c]
2[b]		60	95	94
3	octan-2-ol	45	99	>99
4[b]	octan-1-ol/octan-2-ol	45	86/<1	96
5	cyclooctanol	45	100	>99
6	benzyl alcohol	30	100	>99
7	1-phenylethanol	30	100	>99
8	benzyl alcohol/1-phenylethanol	30	95/4	>99
9	butylproxitol	90	89	>99

[a] Reaction conditions: 0.8 mmol of substrate, 2.5 mg of PIPO (1 mol % nitroxyl), 2.86 mL of 0.35 M hypochlorite sol (1.25 equiv), 0.14 g of $KHCO_3$ (for pH 9.1), 0 °C. [b] 2 mL of *n*-hexane as solvent. [c] Octanoic acid and octyl octanoate formed as side products.

to be a very effective catalyst for the oxidation of alcohols with hypochlorite.[12] Under the standard conditions (see above), PIPO dissolved in the dichloromethane layer. In contrast, in the absence of solvent, PIPO was a very effective recyclable heterogeneous catalyst.

Furthermore, the enhanced activity of PIPO compared to that of TEMPO made the use of a bromide cocatalyst redundant. Hence, the use of PIPO in an amount equivalent to 1 mol % of nitroxyl radical provided an effective (heterogeneous) catalytic method for the oxidation of a variety of alcohols with 1.25 equiv of 0.35 M NaOCl (pH 9.1) in a bromide-free and chlorinated hydrocarbon solvent-free medium (Table 1). Under these environmentally benign conditions, PIPO was superior to the already mentioned heterogeneous TEMPO systems and homogeneous TEMPO.[13] In the solvent-free system, primary alcohols, such as octan-1-ol, gave low selectivities to the corresponding aldehyde owing to overoxidation to the carboxylic acid (entry 1). This problem was circumvented by using *n*-hexane as the solvent, in which PIPO is insoluble, affording an increase in aldehyde selectivity from 50 to 94% (entry 2).

In competition experiments, a marked preference for primary compared to secondary alcohols was observed (entries 4 and 8), analogous to results obtained with TEMPO[5] and other heterogenized TEMPO systems.[6]

Notwithstanding the substantial improvement, from a "green" viewpoint, of the PIPO/NaOCl system, compared to traditional stoichiometric methodologies and the currently employed TEMPO/NaOCl system, the use of stoichiometric quantities of NaOCl can still be construed as suboptimal. Hence, we turned our attention to the use of oxygen as the primary oxidant in conjunction with a TEMPO/metal catalyst combination.

Ruthenium/TEMPO-Catalyzed Aerobic Oxidation of Alcohols

It was already known from the work of Semmelhack et al.[14] that CuCl/TEMPO is able to catalyze the aerobic oxidation of benzyl alcohol to benzaldehyde. A serious shortcoming of this method, however, is that it is ineffective with less reactive aliphatic and alicyclic alcohols. Hence, we decided to test a range of metal catalysts for the aerobic oxidation of octan-2-ol in the presence of TEMPO as cocatalyst. We found that a combination of $RuCl_2(PPh_3)_3$ (1 mol %) and TEMPO (3 mol %) was particularly effective.[15] Other ruthenium compounds were also tested: $RuCl_3$ gave lower rates, and coordinatively saturated 18-electron complexes, e.g., $RuCl_2(bipy)_2$ and $RuCl_2(DMSO)_4$ were completely unreactive. Other metal chlorides (e.g., $Fe^{II/III}$, Ni^{II}, Pd^{II}, and $Co^{II/III}$) showed negligible activity.[16]

High-valent oxoruthenium complexes, e.g., tetrapropylammonium perruthenate (TPAP), either as such[17,18] or supported on sol−gel[19] or MCM-41,[20] are known to catalyze the aerobic oxidation of nonactivated aliphatic alcohols. Low-valent ruthenium complexes such as $RuCl_2$-$(PPh_3)_3$ are also known to catalyze these reactions, albeit with low rates.[21−23] These reactions involve ruthenium-mediated dehydrogenation of the alcohol as the key step, and rate enhancement is observed in the presence of hydrogen acceptors, such as quinones,[24−26] as cocatalysts. A serious shortcoming of most of these systems is the requirement for relatively large amounts of catalyst (5−10 mol %), additives/cocatalysts (10−20 mol %), and drying agents in order to obtain reasonable activities.[27]

In contrast, relatively small amounts of the $RuCl_2$-$(PPh_3)_3$/TEMPO catalyst were shown to be effective for the aerobic oxidation of a broad range of alcohols (Table 2). The general procedure involved the use of 0.5−2.0 mol % $RuCl_2(PPh_3)_3$ and 1.5−6.0 mol % TEMPO in chlorobenzene at 100 °C, either under an atmosphere of pure O_2 or using a flow of an O_2/N_2 (8/92; v/v) mixture at 10 mL min^{-1} at 10 bar in an autoclave.[15,16] For safety reasons the latter procedure is preferred since the gas-phase mixtures of O_2, N_2, and organic compounds remain outside the explosion limits throughout the reaction. The use of chlorobenzene as solvent would seem to detract from the "green-ness" of the method, but we emphasize that it was used for "analytical reasons"; i.e., it did not interfere with product analysis by GC. We have also shown that these reactions perform equally well in toluene as solvent or, better still, with no solvent at all (entries 2, 3, 6, and 7).

Table 2. Ruthenium-TEMPO-Catalyzed Aerobic Oxidation of Several Alcohols[a]

| entry	substrate	S/C ratio[b]	solvent	time (h)	conv (%)[c]	TON[d]
1	octan-2-ol	100	chlorobenzene	7	98	98
2		100	toluene	7	95	95
3		1225	*e*	1	8.5	104
				5	17	208
4[f]	octan-1-ol	50	chlorobenzene	7	85	43
5[f]	oleyl alcohol[g]	50	chlorobenzene	7	80	40
6[f]		50	toluene	7	75	38
7[f]		380	*e*	1	8.1	31
				5	14	53
8	benzyl alcohol	200	chlorobenzene	2.5	>99	200
9	1-phenylethanol	100	chlorobenzene	4	>99	100
10	cyclooctanol	100	chlorobenzene	7	92	92
11[f]	geraniol	67	chlorobenzene	7	91	61
12[f]	octan-1-ol/octan-2-ol	50	chlorobenzene	7	80/10	40/5
13	benzyl alcohol/1-phenylethanol	200	chlorobenzene	3	90/5	180/10

[a] Reaction conditions: 15 mmol of substrate, $RuCl_2(PPh_3)_3$/TEMPO ratio of 1/3, 30 mL of solvent, 10 mL min^{-1} O_2/N_2 (8/92; v/v), 10 bar, 100 °C. [b] S/C ratio = substrate-to-catalyst ratio in mmol per mmol. [c] Selectivities >99% in all cases. [d] TON = turnover number in mmol of product per of mmol Ru catalyst. [e] "Solvent-free": 30 mL of substrate. [f] O_2 atmosphere. [g] Octadec-9-en-1-ol.

Secondary alcohols generally afforded the corresponding ketone in >99% selectivity at complete conversion. Primary alcohols were converted to the corresponding aldehydes in high selectivity; e.g., octan-1-ol afforded octanal in >99% selectivity at 85% conversion (entry 4). At first sight this would seem surprising, since aldehydes undergo facile autoxidation to the corresponding carboxylic acids under comparable conditions. However, control experiments showed that the TEMPO completely suppressed the autoxidation of aldehydes owing to the well-known propensity of TEMPO for scavenging free radical intermediates, thereby terminating free radical chains.[10] Primary allylic alcohols were selectively converted to the corresponding α,β-unsaturated aldehydes; e.g., geraniol afforded geranial in 99% selectivity at 91% conversion (entry 11). No competing rearrangement of the allylic alcohol to the saturated ketone via ruthenium-catalyzed intramolecular hydrogen transfer[28] was observed.

As with the TEMPO/NaOCl system, the Ru/TEMPO displayed a marked preference for primary versus secondary alcohols in competition experiments (entries 12 and 13). A similar preference for primary versus secondary alcohol moieties was also displayed in intramolecular competition (reactions 2 and 3). Unfortunately, a number of

(2)

(42%)   (46%)

(3)

(64%)   (<1%)   (5%)
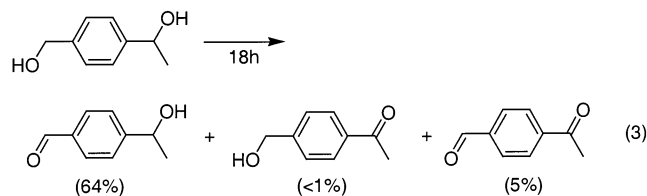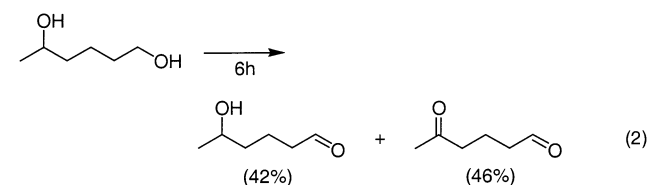
alcohols containing additional heteroatoms (Figure 3) were unreactive,[16] which we attribute to deactivation of the catalyst by coordination of the heteroatom to ruthenium.
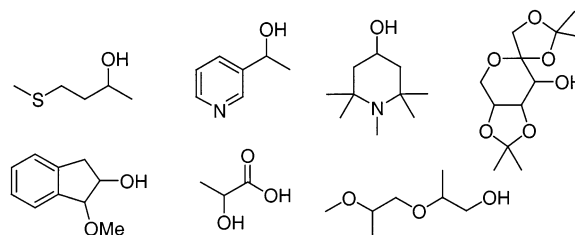
FIGURE 3. Unreactive alcohols, i.e., heteroatom-containing alcohols.

Mechanistic Studies of the Ru/TEMPO System

To clarify the mechanism of the Ru/TEMPO system, we turned our attention to the oxidation of octan-2-ol using a stoichiometric amount of TEMPO and a catalytic amount of $RuCl_2(PPh_3)_3$ in an inert (N_2) atmosphere.[16] Octan-2-ol and TEMPO were found to react in a 3:2 molar ratio to afford octan-2-one and the corresponding piperidine (TEMPH) in the same ratio (reaction 4). We assume that the initially formed TEMPOH rapidly disproportionates to TEMPO and TEMPH, consistent with the observation that all attempts to prepare TEMPOH[29] under an inert atmosphere resulted in the formation of TEMPH.

Similarly, stoichiometric oxidation of benzyl alcohol

(4)
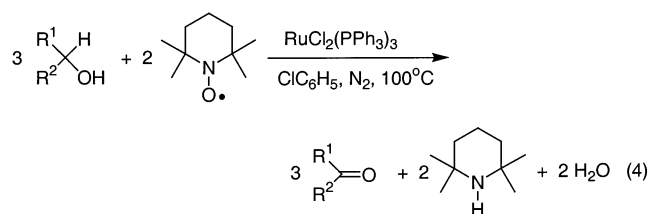
afforded benzaldehyde and TEMPH in a 3:2 ratio.[16] The kinetic isotope effect of the $RuCl_2(PPh_3)$-catalyzed anaerobic oxidation was determined using *p*-methyl-α-deuteriobenzyl alcohol as substrate.[16] A kinetic isotope effect (k_H/k_D) of 5.1 and 3.4 was observed at 25 °C and 100 °C, respectively. These values were similar to those observed (see later) in the catalytic aerobic oxidation at the same temperature, consistent with the notion that hydrogen abstraction from the alcohol involves the same step under both aerobic and anaerobic conditions.

These results could be rationalized by assuming that the alcohol substrate undergoes dehydrogenation by the
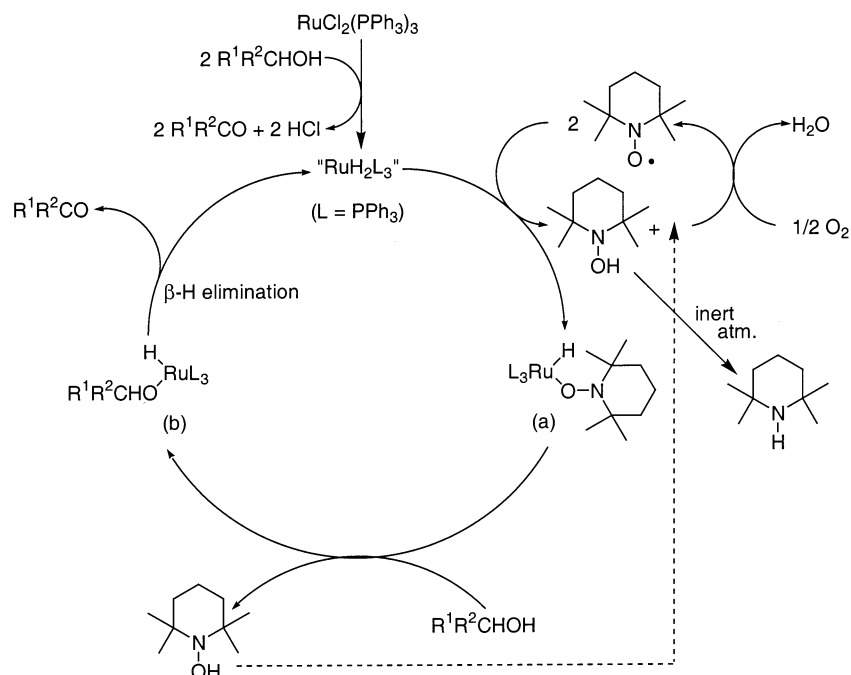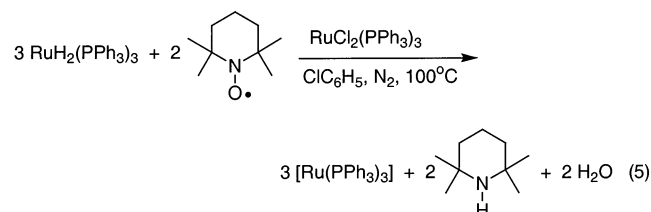
FIGURE 4. Proposed mechanism for the Ru/TEMPO-catalyzed aerobic oxidation of alcohols.

$RuCl_2(PPh_3)_3$, affording the corresponding carbonyl compound and a ruthenium hydride. The function of the TEMPO is to regenerate the ruthenium catalyst by abstracting a hydrogen atom, affording TEMPOH. A likely candidate for the ruthenium hydride species is RuH_2-$(PPh_3)_3$, as observed in $RuCl_2(PPh_3)_3$-catalyzed hydrogen-transfer reactions.[30] Consistent with this notion, RuH_2-$(PPh_3)_4$ was shown to have the same activity as $RuCl_2(PPh_3)_3$ in the Ru/TEMPO-catalyzed aerobic oxidation of octan-2-ol.[16] Additional support for the intermediacy of a ruthenium hydride species was provided by following the stoichiometric reaction of $RuH_2(PPh_3)_3$, generated in situ from $RuH_2(PPh_3)_4$, with an excess of TEMPO in chlorobenzene under an inert atmosphere at 25 °C.[16] The intensity of the Ru−H vibration of $RuH_2(PPh_3)_3$ (2150 cm^{-1}) was monitored using in situ IR. The ruthenium dihydride slowly disappeared with concomitant formation of TEMPH according to the stoichiometry shown in reaction 5, presumably via disproportionation of the TEMPOH intermediate (see above).

On the basis of the results of these stoichiometric reactions, we propose the mechanism shown in Figure 4 for the Ru/TEMPO-catalyzed aerobic oxidation of alcohols. Initial dehydrogenation of the alcohol affords a ruthenium dihydride, which reacts with 2 equiv of TEMPO to form TEMPOH and complex **a** containing a hydride and a piperidinyloxy ligand. In the presence of a large excess of

alcohol, the piperidinyloxy ligand is displaced to form a second equivalent of TEMPOH and an alkoxyruthenium hydride (**b**). The latter undergoes β-hydride elimination, affording the carbonyl compound and regenerating the ruthenium dihydride. In the presence of oxygen, TEMPOH is rapidly oxidized to TEMPO and water. Under anaerobic conditions, TEMPOH is converted to TEMPH.

To provide support for the postulated monohydride complex **a**, we performed the anaerobic oxidation of benzyl alcohol mediated by 5 mol % of both $RuCl_2(PPh_3)_3$ and TEMPO in chlorobenzene at 25 °C.[16] The formation of both TEMPH and a ruthenium monohydride species (ν RuH 2038 cm^{-1}) was observed by in situ IR.

At low TEMPO/Ru ratios, abstraction of hydrogen from the ruthenium hydride by TEMPO is rate limiting, while at ratios higher than 4 the alcohol dehydrogenation becomes rate limiting.[16] Further support for the proposed mechanism was obtained from studies of kinetic isotope effects (k_H/k_D) and Hammett correlations, which were inconsistent with either an oxoruthenium species or an oxoammonium cation as the active oxidant.[16]

In summary, we conclude that our Ru/TEMPO is an effective catalytic system for the aerobic oxidation of a variety of primary and secondary alcohols to the corresponding aldehydes and ketones, respectively.

Copper/TEMPO-Catalyzed Aerobic Oxidation of Alcohols Revisited

In their original report of the CuCl/TEMPO-catalyzed oxidation of benzyl and allylic alcohols Semmelhack et al.[14,31,32] proposed that the copper catalyzes the reoxidation of TEMPO to the oxoammonium cation. On the basis of our results with the Ru/TEMPO system, we doubted the validity of this mechanism. Hence, we subjected the Cu/
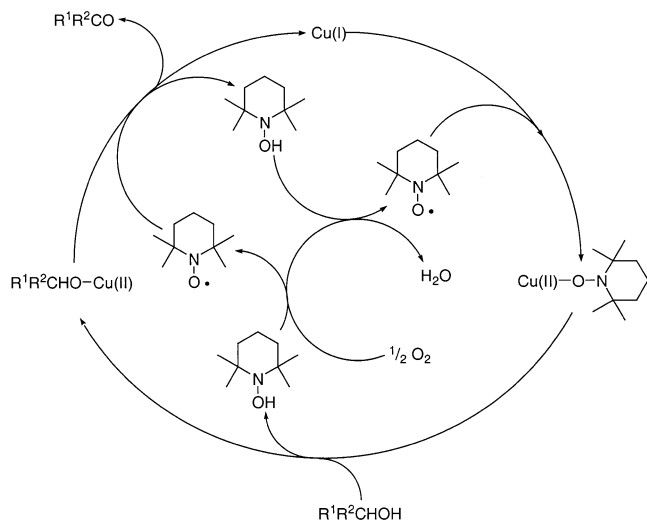
FIGURE 5. Postulated mechanism for the CuCl/TEMPO-catalyzed aerobic oxidation of (activated) alcohols.

TEMPO to the same mechanistic studies described above for the Ru/TEMPO system.[33] The results of stoichiometric experiments under anaerobic conditions, Hammett correlations, and kinetic isotope effect studies showed a pattern similar to those found with the Ru/TEMPO system; i.e., they are inconsistent with a mechanism involving an oxoammonium species as the active oxidant. Hence, we propose the mechanism shown in Figure 5 for Cu/TEMPO-catalyzed aerobic oxidation of alcohols.

We have shown, in stoichiometric experiments, that reaction of copper(I) with TEMPO affords a piperidinyloxy copper(II) complex. Reaction of the latter with a molecule of alcohol afforded the alkoxycopper(II) complex and TEMPOH. Reaction of the alkoxycopper(II) complex with a second molecule of TEMPO gave the carbonyl compound, copper(I) and TEMPOH. This mechanism resembles that proposed for the aerobic oxidation of alcohols catalyzed by the copper-dependent enzyme, galactose oxidase, and mimics thereof.[34] Finally, TEMPOH is reoxidized to TEMPO by oxygen. We have also shown that copper in combination with PIPO affords an active and recyclable catalyst for alcohol oxidation.[13]

Aqueous Biphasic Aerobic Oxidation of Alcohols Catalyzed by Palladium(II) Complexes

A general problem in palladium catalysis is its propensity to form palladium metal, which is then difficult to reoxidize to palladium(II). Our approach to circumventing this problem was to stabilize palladium(0) by coordination to oxidatively stable bidentate amine ligands. Using the water-soluble bathophenanthroline disulfonate (PhenS) ligand, we were able to develop a copper- and chloride-free Wacker oxidation of terminal olefins to the corresponding ketones in an aqueous biphasic system at 100 °C.[35,36]

These promising results stimulated us to test the same catalyst in the aerobic oxidation of alcohols. Palladium-(II) salts and complexes,[37–39] Pd-supported hydrotalcite,[40] and Pd/C[41,42] have been widely investigated as catalysts

Table 3. Pd/PhenS-Catalyzed Aerobic Oxidation of Primary and Secondary Alcohols

entry	substrate	time (h)	conv (%)	sel (%)	isolated yield (%)
1	hexan-2-ol	10	100	100	90
2	cyclopentanol	5	100	100	90
3	1-phenylethanol	10	90	100	85
4	butylproxitol	10	100	100	92
5[b]	pentan-1-ol	15	98	97[c]	90
6	hexan-1-ol	12	95	90[d]	80
7	3-methyl-2-buten-1-ol	10	100	96[c]	88
8	benzyl alcohol	10	100	99.8[c]	93

[a] Reaction conditions: primary alcohol and 1-phenylethanol (10 mmol), secondary alcohol (20 mmol), PhenS·Pd(OAc)$_2$ (0.05 mmol), water (50 g), NaOAc (1 mmol), pH ~6.5−11.5, 100 °C, 30 bar air. [b] TEMPO (4 equiv to Pd) was added. [c] Selectivity to aldehyde, acid was formed as the major byproduct. [d] Selectivity to acid; hexanal (7%) and hexyl hexanoate (2%) were also formed.

for the aerobic oxidation of alcohols. A shortcoming of the former is the low activity (TOF < 10 h^{-1}) that is generally observed, and the latter is mostly used with water-soluble substrates, e.g., carbohydrates.[41]

Our concept for the green catalytic oxidation of alcohols consists of using the (PhenS)Pd^{II} complex in an aqueous biphasic system with no additional solvent and air as the oxidant (reaction 6). The product can be separated by decantation and the catalyst recycled in the aqueous phase.
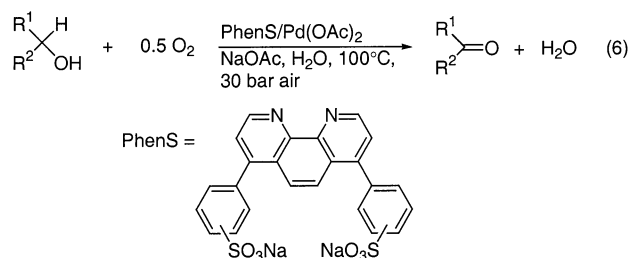
Indeed, this proved to be an extremely effective system for the aerobic oxidation of a variety of alcohols.[43] Using 0.25−0.5 mol % of catalyst with 30 bar air at 100 °C, selectivities of >95% were generally observed at complete conversion in 5−15 h (Table 3). Sodium acetate (5−10 mol %) was generally added for its stabilizing effect on the catalyst. The relatively high pressure (30 bar) is required owing to the low solubility of oxygen in water.

Secondary alcohols generally afforded the corresponding ketone in essentially quantitative yield. Primary aliphatic alcohols, e.g., hexan-1-ol, afforded the corresponding carboxylic acid. This constitutes an improvement on existing methods for performing this transformation which require the addition of 1 equiv of base to neutralize the acid product (see earlier). However, the desired product of a primary alcohol oxidation is often the corresponding aldehyde, and we surmised, on the basis of our Ru/TEMPO studies (see above), that the addition of a catalytic amount of TEMPO would suppress the overoxidation to the carboxylic acid. This proved to be the case: the addition of 2 mol % of TEMPO (4 equiv based on Pd) resulted in the selective formation of the aldehyde (entry 5). Interestingly, primary allylic and benzylic alcohols

afforded the corresponding aldehyde in high selectivity (entries 7 and 8) without the need for addition of TEMPO.

Since the reaction takes place in the aqueous phase, where the catalyst resides, the alcohol substrate should be at least sparingly soluble in water. Most alcohols are only partially soluble in water, which means that the alcohol concentration and, hence, the rate remain constant throughout most of the reaction. For the smaller (more soluble) alcohols, such as pentan-2-ol, cyclopentanol, cyclohexanol, etc., rates were an order of magnitude higher (TOF ≈ 100 h^{-1}) than those of other aerobic alcohol oxidations reported to date. In a homologous series of alkanols, the rate decreases with increasing chain length, consistent with the decreasing solubility in water. Nonetheless, even higher alcohols were oxidized at reasonable rates; e.g., octan-2-ol and nonan-2-ol gave TOFs of 20 and 14 h^{-1}, respectively. Higher rates may be achieved with these less soluble alcohols through the addition of cosolvents or additives, such as alkanesulfonates or anthraquinone-2-sulfonate, which increase the concentration of the alcohol in the water phase.[44]

The presence of a single ether functionality (e.g., entry 4) did not affect the catalyst performance. Alcohols containing N and S functionalities and substrates containing multiple O functionalities (see Figure 3) were unreactive, which we attribute to competing coordination to the palladium catalyst.

Allylic alcohols are oxidized selectively without competing (Wacker) oxidation of the double bond. In contrast, when the alcohol functionality is far removed from the olefinic double bond, the substrate undergoes selective oxidation at the double bond, as shown in reactions 7 and 8. This was surprising since alcohols are oxidized with

$$(7)$$

conv. 60%
sel. 90%

$$(8)$$

conv. 75%
sel. 80%
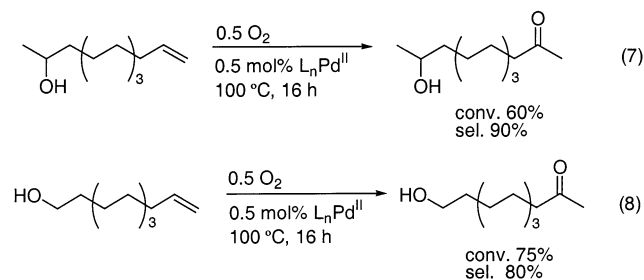
rates an order of magnitude higher than the oxidation rates of olefins. A possible explanation is that the olefinic double bond selectively coordinates to the palladium(II) catalyst.

Finally, we showed that, in the oxidation of hexan-2-ol, the catalyst could be recycled four times with negligible (<5%) loss of activity, which was attributable to inevitable mechanical losses on the small scale used.

Mechanistic Studies of the Pd/PhenS Catalyst

We investigated the effect of the PhenS/Pd ratio on the reaction rate.[44] When less than a 1:1 ratio was used, the rate decreased and palladium black formation was observed. When higher ratios were used, the rate similarly decreased and the color of the solution changed from
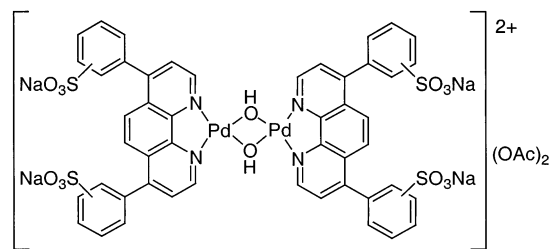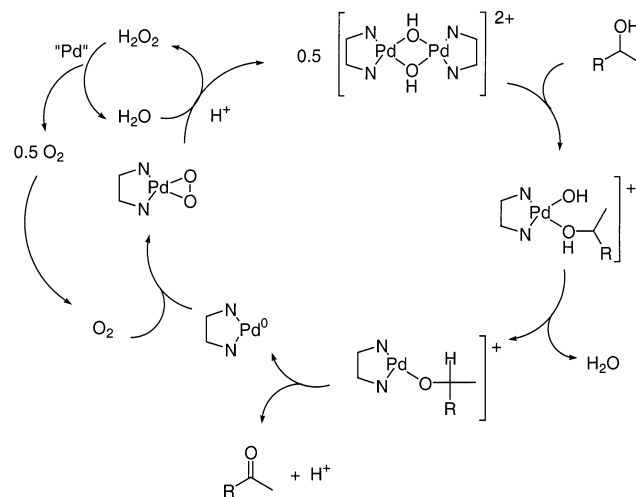
FIGURE 6. Dihydroxyl bridged palladium dimer.

FIGURE 7. Mechanism of the (PhenS)Pd-catalyzed oxidation of alcohols.

yellow (1:1) via orange (1.5:1) to red (>2:1), suggesting the formation of less reactive, higher ligated complexes of palladium. Hence, we conclude that the active catalyst is a 1:1 complex of PhenS with Pd(II).

Further mechanistic information was obtained from kinetic studies. The reaction was shown to be first order in alcohol concentration by using a water-soluble alcohol, propan-2-ol. The reaction rate exhibited a square root dependence on the palladium concentration. This suggests a pre-equilibrium between a dimeric complex and a catalytically active monomer. Palladium complexes of diamines[36] and diphosphines[45] are known to form hydroxyl-bridged dimers in aqueous solution, and, in the pH range 4−9, the Pd/PhenS complex exists mainly as the yellow dihydroxyl-bridged dimer shown in Figure 6. As noted above, the catalytic oxidations of alcohols were performed in the presence of 5−10 mol % NaOAc, which corresponded to a pH of 6.5.

Increasing the pH up to 11, by addition of NaOH, had no effect on the rate, consistent with the notion that the function of the NaOAc is to stabilize the catalyst toward palladium black formation and not to act as a base. On the basis of the results of kinetic studies and investigations of the nature of the catalyst, we propose the catalytic cycle depicted in Figure 7 for the PhenS/Pd(II)-catalyzed aerobic oxidation of alcohols. In the first step, the hydroxyl-bridged dimer dissociates, via reaction with the alcohol substrate, to form a monomeric complex containing a hydroxide ligand and a coordinated alcohol molecule. Loss of water from this complex, which would not be base-dependent, would afford a labile alkoxypalladium(II)

complex, which would undergo facile β-hydride elimination to afford the carbonyl product and either a palladium hydride species or palladium(0) and a proton. We favor the latter since we consider it unlikely that a [PhenPd-H]$^+$ species will be formed in water at neutral or basic pH. Subsequent reaction of the palladium(0) complex with dioxygen will afford an η-peroxypalladium(II) complex.[46] Reaction of the latter with water affords hydrogen peroxide,[46] via an intermediate hydroperoxopalladium(II) complex, and regenerates the hydroxyl-bridged dimer. Since the catalyst is present in the water phase, it will cause rapid decomposition of the hydrogen peroxide. In contrast, when the palladium catalyst resides in the organic phase (chlorobenzene solvent), H_2O_2 forms a separate, aqueous phase, thus circumventing its decomposition by the catalyst.[47]

Without tightly coordinating ligands, or under low oxygen pressure, cluster formation from palladium salts may take place. We believe that, under our reaction conditions, active clusters are not formed. Such species would show different reactivity, such as strongly preferred oxidation of primary allylic alcohols[48] or isomerization of allylic alcohols to saturated carbonyl functionalities.[49] Furthermore, the reaction always started without any induction period, and the reaction mixtures always remained bright yellow and no change in color could be detected by UV spectroscopy that could be linked to the formation of (giant) palladium clusters.

According to our proposed mechanism, the introduction of substituents at the 2 and 9 positions in the PhenS ligand would, as a result of steric hindrance (see Figure 6), promote dissociation of the dimer and enhance the reactivity of the catalyst. This proved to be the case: introduction of methyl groups at the 2 and 9 positions (the ligand is commercially available and is known as bathocuproin) tripled the activity in 2-hexanol oxidation.[44] Investigations are currently underway aimed at optimizing the steric and electronic effects of substituents in the diamine ligand for the catalytic oxidation of alcohols.

Green Context and Future Directions

As we noted earlier, our goal is to eliminate waste, maximize the incorporation of raw materials into the final product, avoid where possible the use of auxiliary substances and organic solvents, and replace stoichiometric reagents with (preferably recyclable) catalysts.

In the first method described, we took a system, NaOCl with a TEMPO catalyst, which is known to be effective for the oxidation of a broad range of primary and secondary alcohols, and developed a new catalyst (PIPO) which is not only recyclable but also more active than TEMPO. This enabled us to avoid the use of sodium bromide as an additive and dichloromethane as solvent. However, this method still employs a stoichiometric oxidant, NaOCl, which generates about 1 equiv of NaCl as waste.

Hence, our goal with the second system (Ru/TEMPO) was to replace NaOCl with O_2, which generates 1 equiv of

water as the sole coproduct. This system proved to be effective for the aerobic oxidation of a variety of primary and secondary alcohols, in *optima forma* in a solvent-free system. Shortcomings of this system are the lack of reactivity of alcohols bearing N and S substituents and problematical recycling of the catalyst in active form. Attempts to use the heterogeneous PIPO in combination with Ru have, as yet, been unsuccessful. In contrast, the PIPO/Cu combination is active but only with relatively reactive alcohols.

In the third system, PhenS/Pd, we have incorporated all four of the "green features" mentioned above. The system employs O_2 as the oxidant, in a solvent-free (apart from water) medium, with facile recycling (via decantation) of the catalyst. The shortcoming is, here again, the lack of activity with some alcohols bearing N and S substituents.

With regard to future directions, there is still much room for improvement of these systems. We are currently focusing our effort on improving catalyst activities, which, although generally higher than previously observed, are still relatively low (e.g., TOF $\approx$ 100 h^{-1}). Further broadening of the scope, perhaps as a result of increased activity, would similarly enhance practical utility.

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