Selective and Environmentally Benign Aerobic Catalytic Oxidation of Alcohols by a Molybdenum-Copper System

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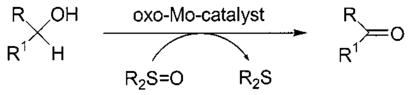
The oxidation of activated primary and secondary alcohols to the corresponding aldehydes and ketones can be carried out with molecular oxygen, in the presence of the bimetallic molybdenum–copper system $MoO_2(acac)_2$–$Cu(NO_3)_2$ as catalyst.

Introduction

The oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, is a fundamental transformation in organic synthesis, that can be now accomplished by several oxidizing reagents. However, in most cases these reagents are very toxic and must be used in stoichiometric amounts.[1] Considering cost and environmental factors, the development of "green" catalytic processes is an important goal.[2]

During the last few years we have been interested in using high oxidation state oxo complexes of transition metals as catalysts for the oxidation and/or isomerisation of alcohols,[3,4] and we recently discovered the catalytic oxidation of primary and secondary alcohols with *cis*-dioxomolybdenum(VI) complexes with sulfoxides or *N*-oxides as cooxidants (Scheme 1).[5]



Scheme 1

Although DMSO is a cheap oxidizing agent, DMS would be an unpleasant side-product in large-scale applications. Here we wish to report the selective catalytic oxidation of alcohols by a new heterobimetallic molybdenum-copper system that uses molecular oxygen as the oxidizing source.

Results and Discussion

In our previous catalytic system, $R_2S{=}O$ was used to reoxidize the molybdenum-dioxo catalyst.[5] Initial investigations showed that substituting $R_2S{=}O$ by dioxygen gave only stoichiometric amount of benzaldehyde for the oxidation of benzylic alcohol. Knowing the capability of copper(I) for the fixation and/or activation of molecular oxygen,[6] we introduced a catalytic amount of copper(I/II) salt in place of the sulfoxide. As we expected, the oxidation of $PhCH_2OH$ was effective with this new heterobimetallic Mo–Cu–O_2 catalytic system in toluene at 100 °C (Scheme 2). Table 1 shows blank experiment results proving that both molybdenum and copper catalysts are essential to oxidize $PhCH_2OH$ to PhCHO under a molecular oxygen atmosphere.

$$RR^1CHOH \xrightarrow[\text{O}_2\text{, PhCH}_3\text{, 100°C}]{\text{Mo-catalyst, Cu-salt}} RR^1C{=}O$$

Scheme 2

Table 1. Comparative blank and catalytic experiment results on $PhCH_2OH$ oxidation

Catalyst[a]	t[b] (h)	PhCHO (%)[c]
Mo^{VI}	5	5
Mo^{VI}/O_2	3	6
Cu^{II}	3	0
Cu^{II}/O_2	3	< 2
Fe^{II}/O_2	5	0
Mo^{VI}/Cu^{II}	3	6
$Mo^{VI}/Cu^{II}/O_2$[d]	3	98
$Mo^{VI}/Fe^{II}/O_2$[d]	5	75

[a] Mo^{VI} = 1 equiv. $MoO_2(acac)_2$, Cu^{II} = 1 equiv. $Cu(NO_3)_2$, Fe^{II} = 1 equiv. $FeBr_2$. – [b] 20 equiv. $PhCH_2OH$, 5 equiv. 4-toluic acid, molecular sieves (4 Å), toluene, 100 °C. – [c] GC determination. – [d] Catalytic run.

Typically, a great variety of Mo complexes can be used (e.g. alkoxides, chlorides, dithiocarbamates...), but further studies showed that the nature of the ligands around the molybdenum center is critical to the success of the reaction, with acetylacetonate ($acac^-$) proving the most effective.[7] On the other hand, varying the nature of the copper(II) counterion had little effect on the rate/yield of the reaction, for example $CuSO_4$, $Cu(OAc)_2$, $CuCl_2$, $Cu(NO_3)_2$, $Cu(acac)_2$ and copper(I) salts such as CuCl can also be used. Other transition metals salts known to activate O_2, such as Co^{II}, Fe^{II} and Mn^{II} have also been tested. With $Co(acac)_2$, $MnBr_2$, or $FeBr_2$ instead of a Cu^{II} salt we observed a slower oxidation of $PhCH_2OH$ with selectivities ranging from 75–94%. The Mo–Fe system, although less active, behaved sim-

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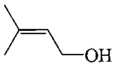
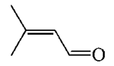
ilarly to the Mo–Cu system, i.e. no oxidation is observed without the Mo catalyst (cf. blank experiments in Table 1); however, we verified that Co^{II} or Mn^{II} alone (i.e. without Mo catalyst) is responsible for some of the alcohol oxidation.[9]

The addition of 5 equivalents of a carboxylic acid (e.g. 4-toluic acid) to the molybdenum-copper system improved the rate and yields of the reaction; stronger acids such as *p*-TsOH have the opposite effect.[10] For similar reasons, we used powdered molecular sieves (4 Å) to trap the water formed during the alcohol oxidation, which improved the catalyst lifetime.[2a,2c,5] Therefore, our typical catalytic system consists of $MoO_2(acac)_2$ (1 equiv.), $Cu(NO_3)_2$ (1 equiv.), 4-toluic acid (5 equiv.), substrate (alcohol, 20 equiv.), powdered activated molecular sieves (4 Å), 1 atm of O_2 in toluene[11] at 100 °C.

The catalytic oxidation of various alcohols takes place under these conditions, and a few results are presented in Table 2. Primary benzylic alcohols are oxidized with nearly total selectivity to aldehydes with no further oxidation to the corresponding acid (Entries 1–5). Secondary benzylic alcohols are oxidized to ketones with good selectivity but at lower rates (Entry 6). Allylic alcohols are oxidized by this method with poor selectivity (Entries 7–8), a common side-reaction being isomerisation[5] to an allylic alcohol or dehydration leading to formation of an ether. Longer periods of reaction are needed for the oxidation of aliphatic alcohols, with only moderate selectivity (Entries 9–12), and in the case of *t*$BuCH_2OH$ further oxidation into *t*$BuCO_2H$ was observed at 120 °C (Entry 11). Attempts to oxidize more than 20 equivalents of substrate lead to lower rates due to deactivation of the catalyst by the water formed. Therefore, the activity of the Mo–Cu system appears to be lower than that of Ru–Cu systems,[2b,2c,4] and is limited to the oxidation of benzylic alcohols.

Table 2. Oxidation of various alcohols with the Mo–Cu–O_2 catalytic system

Entry	Substrate[a]	t (h)	Product	Yield %[b]	Conversion %[b]	Selectivity %[b]
1	$PhCH_2OH$	3	PHCHO	98	100	98
2	4-Me-$C_6H_4CH_2OH$	2.5	4-Me-C_6H_4CHO	92	100	92
3	4-Cl-$C_6H_4CH_2OH$	3	4-Cl-C_6H_4CHO	98	100	98
4	4-NO_2-$C_6H_4CH_2OH$	2	4-NO_2-C_6H_4CHO	97	100	97
5	4-CF_3-$C_6H_4CH_2OH$	5	4-CF_3-C_6H_4CHO	97	100	97
6	PhCH(OH)Et	5	PhC(O)Et	54	60	90
7		1		43[c]	90	48
8	cyclohexen-2-ol	1.5	cyclohexen-2-one	10	83	12[d]
9	cyclohexanol	6	cyclohexanone	37	58	64
10	1-hexanol	10	1-hexanone	16	67	24
11	*t*$BuCH_2OH$	1	*t*BuCHO	43[e]	60	72
12	*t*$BuCH_2OH$	3	*t*BuCHO / *t*$BuCO_2H$	13 / 30[e]	66	20[f]

[a] 20 equiv. alcohol, 1 equiv. $MoO_2(acac)_2$, 1 equiv. $Cu(NO_3)_2$, 5 equiv. 4-toluic acid, MS 4 Å, toluene, 100 °C, 1 atm O_2. – [b] GC determination. – [c] Solvent: 1,2-dichlorobenzene, side-reaction: isomerisation into 2-methyl-3-buten-2-ol (32%). – [d] Side-reaction: etherification into ROR (R = cyclohexene) (30%). – [e] At 120 °C. – [f] Selectivity in aldehyde + acid: 66%.

Studies on the oxidation of a series of *para*-substituted benzylic alcohols (R = Me, H, Cl, CF_3, NO_2) show no correlation with Hammett σ parameters and little variation in rate on the *para* substituent. Hence, benzyl radicals would appear not to be involved in the rate determining step of the oxidation process,[12,13] a conclusion which is further supported by the observation that radical traps such as 2,4,6-tri-*tert*-butylphenol or galvinoxyl have no effect on the rate of the oxidation. The catalytic oxidation of PhCH(D)OH with the Mo–Cu system at 100 °C gives a product ratio of PhCDO/PhCHO = 3.0. In parallel experiments, the overall rate of the catalytic oxidation of $PhCH_2OH$ and $PhCD_2OH$ at 100 °C gives a value of $k_H/k_D = 1.8$. Overall, these results support the direct involvement of the benzylic C–H bond in the rate-determining step.

Although the complete mechanism of oxidation with this new catalytic system is not yet fully understood, we propose the catalytic cycle depicted in Figure 1 based on the above observations for the oxidation of $PhCH_2OH$. An initiation would first result in the formation of an alkoxide complex (**a**) by displacement of the acac ligand, as already seen in the oxidation of alcohols with other molybdenum catalysts[5] and by previous experiments carried out in our laboratory, which show that such exchange processes occur

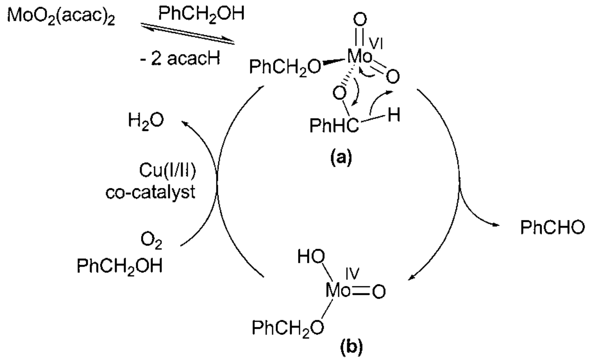


Figure 1. Proposed mechanism for the Mo–Cu–O_2-catalysed oxidation of $PhCH_2OH$; apparently low coordinate species **b** represented in this figure will have additional neutral ligands, such as alcohol, which have been omitted for simplicity

readily at electrophilic Mo^{VI} centers.[3,14] This point is further consistent with the higher rate of oxidation of $PhCH_2OH$ vs. PhCH(Et)OH which may result from the fact that prior coordination of the alcohols to the metal would be disfavored for the latter. A concerted process involving the transfer as a hydride of a β-hydrogen atom of the alkoxo ligand to one of the molybdenum-oxo entities via a five-membered cyclic transition state follows in a rate-determining step, with formation of PhCHO and a Mo^{IV} species (**b**). This transfer would result in the observed moderate primary kinetic isotope effect and is similar to the hydride transfer in other Mo-catalysed systems for the oxidation of alcohols.[5] The reoxidation of (**b**) into (**a**) by the copper salt in the presence of molecular oxygen is unclear. We can exclude a mechanism in which a copper(II) species may serve as the sole oxidant for the molybdenum by a pure redox Wacker-type process,[15] because the oxidation of $PhCH_2OH$ in the absence of molecular oxygen but with a twofold excess of Cu^{II} salt relative to the substrate (i.e. Mo/Cu/substrate = 1:40:20) proceeds with different characteristics (slow rate and very low selectivity in benzaldehyde) than the normal catalytic system under dioxygen atmosphere (Mo/Cu/substrate = 1:1:20).[16] In consequence, the regeneration of the Mo^{VI} active species (**a**) most certainly involves the activation of dioxygen by the copper co-catalyst.[17]

Further studies are needed to clarify the molybdenum reoxidation pathway and the exact function of the copper and carboxylic acid co-catalysts.

Conclusion

In conclusion, we describe a new, ecologically benign, Mo–Cu catalytic system for the aerobic oxidation of alcohols. Although so far limited to the oxidation of benzylic alcohols and with only moderate activities, this catalytic system remains very interesting from a mechanistic point of view and has been extended to the oxidation of alcohols by other oxo-metal complexes with higher activities.[4,21]

Experimental Section

General: All the substrates were purchased from Aldrich or Lancaster and were carefully dried over a suitable drying agent before use, distilled and stored under nitrogen (over molecular sieves 4 Å for liquids) in a glove box. 4-Toluic acid (Aldrich) was dried over P_2O_5 under vacuum. Molecular sieves (4 Å) were activated at 150 °C under vacuum, powdered and stored in a glove box. Toluene was dried over sodium, distilled and stored over molecular sieves in a glove box. $MoO_2(acac)_2$ was purchased from Aldrich or prepared following a literature procedure.[22] $Cu(NO_3)_2$ was obtained by drying $Cu(NO_3)_2{\cdot}2.5H_2O$ under vacuum at 100 °C for 48 hours and stored under nitrogen. $PhCD_2OH$ was prepared by treating ethyl benzoate with $LiAlD_4$ in diethyl ether, followed by hydrolysis with sodium hydroxide (10%), and distillation from CaH_2. PhCH(D)OH was prepared by treating PhCHO with $LiAlD_4$ in THF, followed by hydrolysis with $Na_2SO_4{\cdot}10H_2O$, dried with anhydrous $MgSO_4$, and distilled from CaH_2. The analyses of the catalytic reactions were carried out with a Hewlett–Packard 5890 Series II Gas Chromatograph equipped with a flame ionisation detector (FID) and a Hewlett–Packard HP-1 methyl silicon gum column of length 10 m, diameter 0.53 mm and 2.65 µm film thickness.

General Procedure for the Oxidation of $PhCH_2OH$: In a typical oxidation experiment, under nitrogen (glove box), $PhCH_2OH$ (257 mg, 20 equiv.), $MoO_2(acac)_2$ (39 mg, 1 equiv.), $Cu(NO_3)_2$ (23 mg, 1 equiv.), 4-toluic acid (81 mg, 5 equiv.), powdered molecular sieves (4 Å) (400 mg), and 2 g of toluene were placed in a 5- or 10-mL flask equipped with a stir bar and a reflux condenser. The reaction flask was connected to a molecular oxygen vacuum Schlenk line and heated at 100 °C for 3 h under 1 atm of O_2. Yield of PhCHO: 98% (determined by GC).

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[7] Compare, for example, the oxidation of $PhCH_2OH$ into PhCHO at 100 °C: $MoO_2(acac)_2$ 3 h/98% PhCHO, $MoCl_5$ 5 h/55% PhCHO, $[PPh_4][MoO_2(NCS)_4]$ 6 h/63% PhCHO, $MoO_2(Et_2dtc)_2$ 12 h/82% PhCHO. We have also used with success immobilized Mo catalyst such as PBI·Mo (PBI = polybenz-

imidazol)[8] which is less sensitive to degradation by water (yield of PhCHO after 10 h: 98%).

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[10] Strong acids like *p*-TsOH have a detrimental effect on the catalysis, therefore the beneficial effect observed with a carboxylic acid may not come from its acidic proton character (as previously seen with other alcohols oxidation catalysts[5]) but from the coordinating properties of its carboxylate anion.

[11] 1,2-Dichlorobenzene can also be used, but we observed in some cases unwanted side-products. With donor solvents such as DMF and MeCN, rates are strongly decreasing, probably by inhibition of the copper function.

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[13] Non linear plots can also be due to other causes such as complications arising from side-reactions, steric effects from large *para* substituents, or cyclic transition states: [13a] H. Maskill, in *The Physical Basis of Organic Chemistry*, Oxford University Press, **1985**, chapter 10, pp. 405–473. – [13b] J. March, in *Advanced Organic Chemistry*, 3rd ed., Wiley Interscience, **1985**, chapter 9, pp. 237–250.

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[16] In a Wacker-type process, to convert one equivalent of $PhCH_2OH$ to PhCHO, the catalytic system would need two equivalents of Cu catalyst in order to reoxidize the Mo center. To check the possibility of a pure redox Wacker-type process we performed the oxidation of $PhCH_2OH$ (20 equiv.) in the absence of O_2 with 1 equivalent of $MoO_2(acac)_2$ and 40 equiv. of copper(II) salt [$Cu(NO_3)_2$ or $Cu(OAc)_2$], at 100 °C for 3 hours. The reaction was carried out both in the absence of 4-toluic acid and with 5 equivalents of 4-toluic acid. In the reaction performed in the absence of carboxylic acid, we observed only the formation of 2% of PhCHO (instead of 29% with the "normal" Mo–Cu–O_2 system). In the presence of carboxylic acid, we observed the formation of 30% of PhCHO, but with a low selectivity (selectivity was only 60%, instead of 98% for the Mo–Cu–O_2 system). We believe that most of the PhCHO formed in anaerobic conditions in presence of 4-toluic acid results from a Cu-catalysed oxidation of $PhCH_2OH$ because in a blank experiment (40 equivalents Cu^{II}, 5 equivalents 4-toluic acid, but no Mo catalyst) we formed ca. 18% of PhCHO. We also noticed the same behavior with our Mo–Fe system when performing the same kind of experiments with an excess of Fe^{III} salt under argon [$MoO_2(acac)_2$ 1 equivalent, $FeCl_3$ 40 equivalents, 4-toluic acid 5 equivalents, $PhCH_2OH$ 20 equivalents 100 °C, 5 hours] with formation of only 3% PhCHO (with a selectivity in PhCHO of only 4%) which is in contrast to 75% PhCHO (selectivity in PhCHO: 75%) with the Mo–Fe system under O_2 (Mo/Fe 1:1).

[17] Copper(I) and iron(II) complexes are well known to coordinate, activate and transfer molecular oxygen.[6,18–20] We believe the Mo^{IV} complex is first oxidized to Mo^{V} by a redox process induced by the Cu^{II} salt which would generate a Cu^{I} species. The Cu^{I} species is essential for the next step which would involve the activation of O_2 and would result in the oxidation of the Mo^{V} complex with regeneration of the Mo^{VI} catalytic species **a**, possibly through a heterobimetallic μ-peroxo- or μ-oxo-Mo^{VI}–Cu^{II} complex.

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