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Anaerobic oxidation of non-activated secondary alcohols over Cu/Al_2O_3

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A liquid phase, transfer dehydrogenation reaction promoted by an 8% Cu/Al_2O_3 catalyst allows complete conversion of secondary alcohols into ketones under very mild conditions and in short times without any additives.

The development of catalytic methods for alcohol oxidation has been one of the most pursued targets in the last few years, due to the urgency of substituting stoichiometric oxidants used in the fine chemicals industry, often based on toxic metals, with oxygen or air. Very active copper based homogeneous systems have been set up,[1] whereas the heterogeneous ones mainly rely on the use of noble metals.[2] An interesting alternative to aerobic conditions is represented by the use of a readily available organic molecule instead of oxygen as hydrogen acceptor, thus overcoming safety concerns linked with the use of flammable solvents. However, only a few cases of liquid phase alcohols transfer dehydrogenation promoted by heterogeneous catalysts are known.[3] Recently two palladium based systems have been reported by Hayashi[4] and Baiker,[5] both active only in the oxidation of aromatic or allylic alcohols.

Here we wish to report that a low loading supported copper catalyst (namely 8% Cu/Al_2O_3) is very effective in selective oxidation of non-activated aliphatic secondary alcohols under transfer dehydrogenation conditions.

Copper catalysts prepared with a non-conventional chemisorption–hydrolysis technique have been shown to be active and very selective in a wide range of reductions, not only under catalytic hydrogenation conditions but also in hydrogen transfer from secondary alcohols.[6] In particular, a detailed study of the reduction of 4-*tert*-Bu-cyclohexanone exploring especially the effect of the donor alcohol, revealed the existence of a two-step mechanism based on the donor alcohol dehydrogenation followed by the substrate reduction.[7]

These results and the need for heterogeneous and simple systems for the oxidation of hydroxyl groups, prompted us to investigate the activity of copper catalysts, in particular Cu/SiO_2 and Cu/Al_2O_3 in alcohols dehydrogenation reactions. Both catalysts revealed very promising performances (Table 1) although in the absence of an acceptor an equilibrium situation between dehydrogenation and hydrogenation was reached. On the other hand if hydrogen is removed by venting the reactor at regular times (entries 2 and 4) it is apparent that the dehydrogenation reaction can go to completion. It seemed thus more effective to adopt transfer dehydrogenation conditions by exploiting a pivotal feature of these catalytic systems already expressed in other synthetic applications,[6,8] that is their specificity towards hydrogenation of a conjugated system in the presence of an isolated one.

Table 1 Dehydrogenation of 3-octanol under different conditions[a]

Entry	Catalyst	*t* (h)	Conv. %	Selectivity %
1	Cu/SiO_2	48	60	100
2[b]	Cu/SiO_2	20	100	100
3[c]	Cu/SiO_2	3	100	100
4[b]	Cu/Al_2O_3	12	84	100
5[c]	Cu/Al_2O_3	1.5	100	100
6	Al_2O_3	24	0	—

[a] Alcohol (100 mg), catalyst (100 mg), untreated toluene (8 mL), 363 K, N_2. [b] Reaction carried out by venting the reactor. [c] Reaction carried out by using styrene as H_2 acceptor.

Thus, by adding styrene into the reaction mixture as hydrogen acceptor in equimolar ratio with respect to the substrate, complete oxidation of the desired alcohol was obtained in very short reaction times (entries 3 and 5), particularly over Cu/Al_2O_3. The by-product ethylbenzene is easily removed from the reaction mixture together with the solvent.

A remarkable activity is observed for non-activated secondary alcohols, whereas under these conditions 1-octanol and 2-phenylethanol were not oxidized nor did they give any secondary reaction.

Competitive oxidation of cyclooctanol and 1-octanol gave > 97% cyclooctanone, 1-octanol being recovered unchanged, thus showing that this system can selectively oxidize secondary alcohols also in the presence of primary ones.

Selected results obtained in the oxidation of aliphatic alcohols are reported in Table 2.

Table 2 Oxidation of of different aliphatic alcohols over Cu/Al_2O_3[a]

Entry	Substrate	*t* (h)	Conv. %	Selectivity %
1	3-octanol	1.5	100	100
2[b]	3-octanol	2.5	96	100
3	2-octanol	4	100	100
4	1-octanol	24	4	—
5	2,4-dimethylpentan-3-ol	6	100	100
6	Cyclohexanol	3	99	98
7	2-Me-cyclohexanol	3.5	99	100
8	3-Me-cyclohexanol	3	100	100
9	4-Me-cyclohexanol	1.5	100	100
10	4-*tert*-Bu-cyclohexanol	1.5	97	100
11	(−)-menthol	48	80	100[c]
12	Neomenthol	6	97	100[c]
13	Carveol	2.5	100	88
14	Cyclooctanol	0.5	100	100
15	Cyclododecanol	2	97	100
16	Adamantanol	1.5	100	100
17	2-phenylethanol	24	0	—

[a] Alcohol (100 mg), styrene/substrate = mol/mol, catalyst (100 mg), untreated toluene (8 mL), 363 K, N_2. [b] Catalyst pretreated at 453 K. [c] Menthone/isomenthone mixture.

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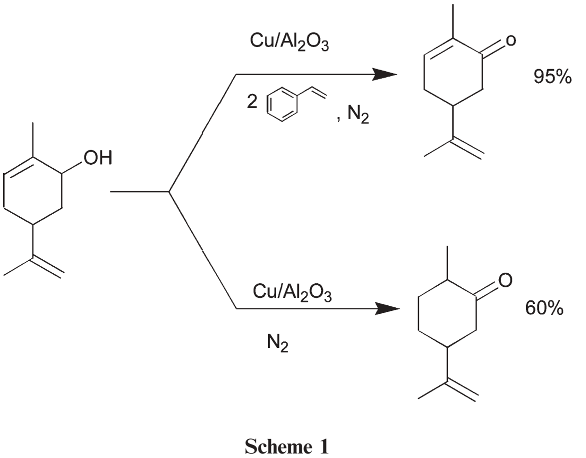
The catalytic activity is quite remarkable, particularly for the substrates that are less easily oxidized by other systems. A striking activity was observed for a series of cyclohexanols (entries 6–13). In the case of 4-*tert*-Bu-cyclohexanol, for example, the activity (TOF = 3.5 h^{-1}) is comparable with that observed under aerobic conditions both over Pd/MgO (TOF = 3.5 h^{-1})[2a] and Ru/Al_2O_3 (TOF = 2.1 h^{-1}),[9] whereas for cyclooctanol the activity (TOF = 12.5 h^{-1}) is higher than that observed for both systems (TOF = 3.2 h^{-1} for Pd/MgO and TOF = 2.7 h^{-1} for Ru/Al_2O_3). However, if we consider productivity expressed as $g_{product}/g_{catalyst}$ h, Cu/Al_2O_3 turns out to be one order of magnitude more active than the other two systems for the dehydrogenation of 4-*tert*-Bu-cyclohexanol and two orders of magnitude for the dehydrogenation of cyclooctanol.

The catalyst was pretreated in H_2 at 543 K before use, but reduction at a much lower temperature resulted in a still very active material (entry 2). It should also be mentioned that these materials are not pyrophoric even in the reduced state, nor do they require anhydrous conditions.

The very high selectivity towards reduction of styrene with respect not only to ketones but also to α,β-unsaturated carbonyls is shown by the reaction of carveol (entry 13) which was oxidized with 88% selectivity under standard conditions and with 95% selectivity only by using 2 equiv. of hydrogen acceptor. On the other hand, in the absence of styrene dihydrocarvone could be obtained in moderate yield directly from carveol, acting as both the hydrogen donor and the acceptor (Scheme 1).

The reaction of (−)-menthol sheds some light on the reaction mechanism. The oxidation of this substrate is rarely reported over heterogeneous catalysts due to its very low reactivity.[10] Its slow oxidation over Cu/Al_2O_3 shows the relevant influence of steric hindrance on this system, apparent also in the substituted cyclohexanols series (entries 6–10) and from the comparison between linear and branched substrates (entry 1 *vs.* 5). This effect is so strong that if the -OH group is in an axial conformation, as in neomenthol, the reaction rate is much faster (entry 12).

In the oxidation of both (−)-menthol and neomenthol a menthone/isomenthone mixture was obtained. Epimerization at C2 strongly suggests that the reaction proceeds through an enolic intermediate, thus also justifying the inactivity of primary alcohols and the differences in reaction rate between 3- and 2-octanol. This trend of reactivity is the opposite to those observed with all the other oxidation heterogeneous systems reported so far.[2]



Scheme 1

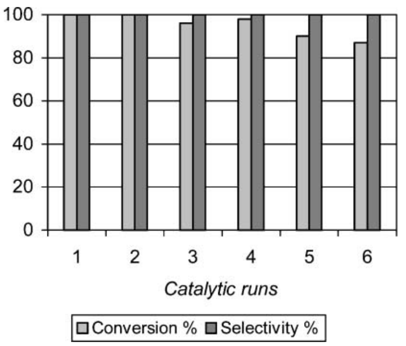


Fig. 1 Conversion and selectivity values obtained in recycling Cu/Al_2O_3 for 3-octanol oxidation at 0.5 h.

To the best of our knowledge this is the first report on a supported copper catalyst used in the liquid phase for selective alcohol dehydrogenation reactions under such mild conditions and of general use. As already shown for hydrogenation reactions,[6a,11] the catalyst is efficient for at least six catalytic runs without relevant loss in activity nor in selectivity (Fig. 1). The Cu content before use and after six runs was found to be unchanged by AAS analysis, while Cu in the filtrates was found to be absent by GF-AAS. Moreover, TPR profiles before and after six runs appeared to be identical, showing the high stability of the metallic phase.

Practical concerns claim for the use of these catalysts for synthetic purposes. In fact, copper catalysts prepared with this technique revealed remarkable performances in different kinds of transformations, varying from hydrogenation to cyclization and acid catalysed reactions,[8] always showing excellent selectivity and good productivity, basic features for the application of heterogeneous catalysts to fine chemicals synthesis.

In all these reactions the use of these materials allows the set up of a simple, safe and clean protocol.

Work is in progress to find the experimental conditions allowing us to oxidize also primary alcohols and to better elucidate the reaction mechanism.†

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Notes and references

† Cu/SiO_2 and Cu/Al_2O_3 catalysts were prepared as already reported[12] by using SiO_2 (BET = 320 $m^2\ g^{-1}$; PV = 1.75 ml g^{-1}) and Al_2O_3 (BET = 280 $m^2\ g^{-1}$; PV = 1.15 ml g^{-1}, Davicat® SMR 24-847) from Grace Davison, Worms, DE and $Cu(NO_3)_2{\cdot}3H_2O$ from Carlo Erba.

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