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HETEROGENEOUS CATALYTIC ALCOHOLS OXIDATION

MOLECULAR O_2 VS HYDROGEN ACCEPTORS AS OXIDANTS

Cu/Al_2O_3 catalyzed transfer hydrogenation reaction allows the set up of a simple, safe, selective and clean protocol for the oxidation of secondary and allylic alcohols under very mild conditions.

The oxidation of alcohols to carbonyl compounds is an essential functional group transformation in organic synthesis. Countless methods have been developed to perform this reaction, the most popular being represented by the Collins [1], Jones [2], pyridinium chlorochromate (PCC) [3], pyridinium dichromate [4] and Swern [5] oxidations. Most of these methods suffer from the use of stoichiometric toxic reagents, cryogenic conditions and/or the production of copious amounts of wastes.

An alternative approach is the use of a catalyst in combination with a stoichiometric oxidant, e.g. tetrapropylammonium perruthenate (TPAP) with stoichiometric N-methylmorpholine (NMO) [6] while the use of supported [7-8] or unsupported[9] stable nitroxyl free radical precursor TEMPO and of hypervalent iodine reagents [10] are alternative to metal based oxidants.

Much more attractive is the use of molecular oxygen or air as terminal oxidant, therefore the development of catalysts for the aerobic oxidation of alcohols has been explored by using a wide variety of metals. Very active copper based homogeneous systems have been set up [11], whereas the heterogeneous ones mainly rely on the use of noble metals [12].

An exhaustive review by Mallat and Baiker covers the literature up to mid-2003 [12c]. The best catalytic systems reported are probably the Pd/hydroxyapatite one by Kaneda *et al*. [13] and Ru/Al_2O_3 set up by Mizuno [14] both active under 1 atm of O_2 and even in the absence of solvent.

The activity of the two catalysts are compared in Table 1.

Pd/apatite system is much more active for benzylic and allylic alcohols than for aliphatic ones. In particular the Pd/hydroxyapatite system allows oxidation of 1-Ph-ethanol into acetophenone in the absence of solvents with a TON based on Pd approaching 236,000, three order of magnitude larger than those previously reported for any catalytic system under an atmospheric O_2 pressure:

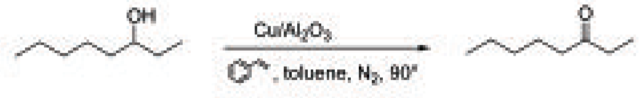
Ru/Al_2O_3 is much more active than the Pd catalyst for the oxidation of non activated alcohols. In particular 2-octanol was oxidized with TON=950, giving 95% of 2-octanone under solvent free conditions, although at a rather high temperature (150 °C). However primary alcohols were selectively oxidized even in the presence of secondary ones.

More recently, several Au based systems have been proposed. In particular Au/CeO_2 was found to be more active than the Pd/hydroxyapatite system in the oxidation of 3-octanol when using a Dean Stark apparatus and more selective in the oxidation of allylic alcohols [15].

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 few cases of alcohols transfer dehydrogenation promoted by heterogeneous catalysts are known. Recently three palladium based systems have been reported by Hayashi [16] and Baiker [17], both active only in the oxidation of aromatic or allylic alcohols and one based on Ru [18].

We recently reported that a low loading supported copper catalyst, 8% Cu/Al_2O_3 is very effective in selective oxidation of non activated aliphatic secondary alcohols under hydrogen transfer dehydrogenation conditions [19].

Thus, by adding styrene in equimolar ratio with respect to the substrate as a hydrogen acceptor, it is possible to completely oxidise alcohol with excellent activity and selectivity:



The by-product ethylbenzene, obtained through an irreversible hydrogenation, can be easily removed from the reaction mixture together with the solvent. This reaction protocol is general for secondary alcohols and particularly efficient for unactivated ones. Selected results obtained with this procedure are reported in Table 2.

Three main features are apparent from the results reported: i) the uncomplete conversion of benzylic alcohols (entry 4), ii) the inactivity towards primary alcohols (entries 2 and 5) and iii) the high activity towards unactivated secondary alcohols (entries 6-17).

This trend is markedly different from that observed over almost all the oxidation catalytic systems reported so far, both based on a metal and on a radical precursor, which always preferentially convert benzylic alcohols with respect to the others, thus suggesting that a different mechanism is operating in the present case.

Nevertheless, dehydrogenation of benzyl alcohols can help to elucidate the reaction mechanism [20]. Competitive oxidation of differently substituted benzyl alcohols allowed to obtain a linear plot of log(kx/kH) versus the Brown-Okamoto $\sigma+$, with a slope corresponding to a Hammet $\rho+$ value of -0.75, diagnostic of a carbocation type intermediate. Therefore benzylic alcohols should exhibit the fastest reaction rates, owing to the higher stability of their corresponding carbocations. It is therefore apparent that the uncomplete conversion observed under our experimental conditions is not due to an intrinsically poor reactivity of the substrates, but to inadequacy of styrene as hydrogen acceptor, unable to prevail over the aromatic aldehyde formed, highly activated towards hydrogenation with Cu/Al_2O_3.

Although a suitable acceptor for the transfer dehydrogenation of benzylic alcohols has not yet been found, under the present conditions the low conversion of benzylic alcohols is just an apparent drawback. Indeed it has a plus side as it allows to finely-tune the system selectivity. This makes the catalytic system unique among all the others known, operating both under aerobic and anaer-

Tab. 1 - Oxidation of different alcohols over Pd/hydroxyapatite and Ru/Al_2O_3

Substrate	Catalyst	Mol % metal	T (°C)	Solvent	TOF
1-Ph-ethanol	1,4% Ru/Al_2O_3	2.5	83	$PhCF_3$	40
	0.3 Pd HAP 0	0.2	90	“	490
	1,4% Ru/Al_2O_3	0.1	150	none	340
	0.3 Pd HAP 0	0.0004	160	“	9800
	“	0.04		H_2O	98
2-octanol	1,4% Ru/Al_2O_3	2.5	83	$PhCF_3$	18
	0.3 Pd HAP 0	0.6	90	“	6
			150	none	300
cyclopentanol	1,4% Ru/Al_2O_3	5	83	$PhCF_3$	6
	0.3 Pd HAP 0	0.6	90	“	4

Tab. 2 - Transfer dehydrogenation of different substrates by using Cu/Al_2O_3[a]

Entry	Substrate	t (h)	Conversion (%)	Selectivity (%)
1	2-octanol	4	100	100
2	1-octanol	24	4	100
3	2,4-dimethyl-pentan3-ol	6	100	100
4	Benzyl alcohol	20	51.5	100
5	2-phenylethanol	24	1	100
6	cyclohexanol	3	99	98
7	2-methylcyclohexanol	3.5	99	100
8	3-methylcyclohexanol	3	100	100
9	4-methylcyclohexanol	1.5	100	100
10	carveol	2.5	100	88
		1.5[b]	100	95
11	Perillyl alcohol	6	95	91
12	cyclooctanol	0.5	100	100
13	cyclododecanol	2	97	100
14	adamantanol	1.5	100	100
15	5α,3β,-androsterone	2.5	100	96
16	(-)-menthol	48	50	100
17	Neo-menthol	6	97	100

styrene/substrate=mol/mol, N_2 (1 atm), 90 °C; b reaction carried out by using 2 equivalent of hydrogen acceptor

obic conditions, that preferentially oxidise benzylic alcohols with respect to non-activated secondary ones.

Moreover it is possible to selectively oxidise secondary alcohols in the presence of primary ones without using any protecting group, as shown in the case of competitive oxidation of cyclooctanol and 1-octanol (Fig. 1).

It is also worth noting that the use of transfer dehydrogenation allows to operate under anaerobic atmosphere, thus avoiding the formation of overoxidation products, often observed when using oxygen, and the possible concerns linked to the use of O_2 in the presence of flammable solvents.

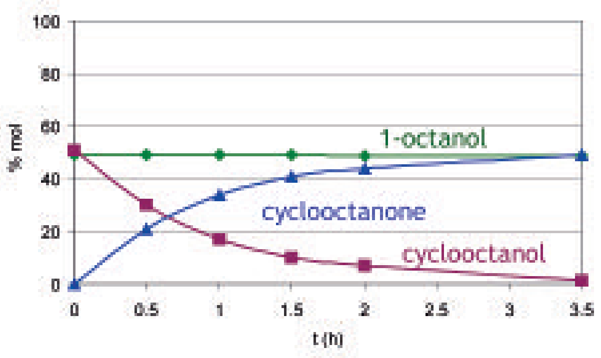


Fig. 1 - Competitive dehydrogenation of cyclooctanol and 1-octanol. Reaction conditions: 1-octanol (0.5 mmol), cyclooctanol (0.5 mmol), styrene (1 mmol), 8% Cu/Al2O3 (100 mg), toluene (8 mL), 363 K, N_2 atmosphere

A remarkable activity is observed for non activated secondary alcohols that are less easily oxidized by other systems. A striking activity was observed in particular for cyclohexanol and a series of substituted cyclohexanols (entries 6-11). In the case of 4-tert-Bu-cyclohexanol, e.g., the activity based on the total metal content (TOF=3.5 h^{-1}) is comparable with that observed under aerobic conditions both over 1% Pd/MgO (TOF=3.5 h^{-1}) [12b] and 1% Ru/Al_2O_3 (TOF=2.1 h^{-1}) [14], 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 $g_{product}/g_{catalyst}$xh, 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 order of magnitude for the dehydrogenation of cyclooctanol.

The catalyst is efficient for at least six catalytic runs without relevant loss in activity nor in selectivity. The Cu content before the 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.

Steric effects also play a significant role, as it is apparent in the monosubstituted cyclohexanols series (entries 7-9) and from comparison between linear and branched substrates (entry 1 vs 3). This effect is so strong that in disubstituted cyclohexanols the reaction takes place at reasonable rates only when the -OH group is in axial conformation, as shown by the comparison of (-)-menthol (entry 16) and neo-menthol (entry 17). This particular behaviour could once more be exploited for synthetic purposes, in order to set up a kinetic resolution process. This has indeed been achieved in the one-pot hydrogenation of pennyroyal oil into menthol [21] (Tab. 3).

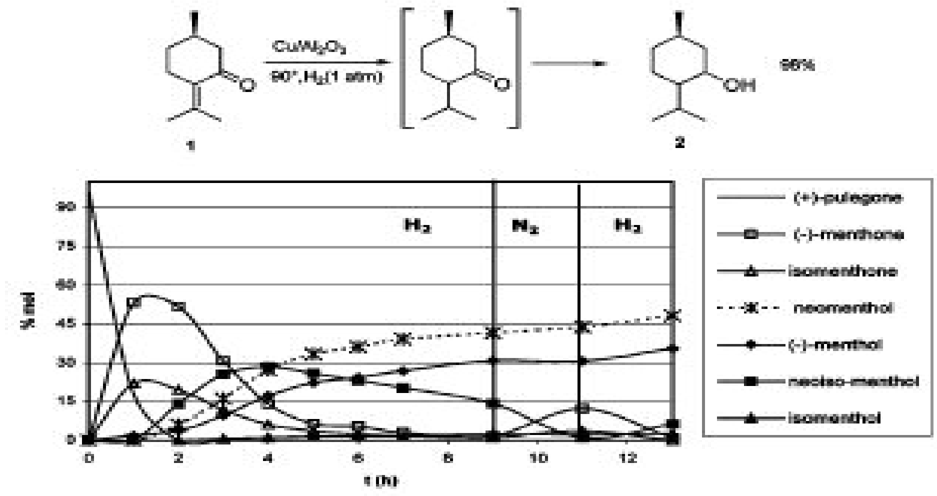


Fig. 2

Pennyroyal oil is a very low value mint oil, mainly constituted by pulegone 1, a toxic component, usually refractory towards hydrogenation. With Cu/alumina it is possible to hydrogenate pulegone directly into menthols 2 under very mild experimental conditions. In the menthols mixture produced the isomer with the worst organoleptic tones, the diaxial neoisomenthol initially formed in quite high content, preferentially dehydrogenates, thus giving menthol and neomenthol Fig. 2. This is an example of multi-functional process obtained combining both hydrogenation and selective dehydrogenation activity in order to set up a dynamic kinetic resolution.

In conclusion the Cu/Al$_2$O$_3$ catalyzed transfer hydrogenation reaction allows the set up of a simple, safe, selective and clean protocol for the oxidation of secondary and allylic alcohols under very mild conditions. Electronic effects and the choice of the acceptor make this catalytic system unique as it allows selective oxidation of a secondary alcohol in the presence of an unprotected primary one and also of a benzylic one. Therefore this method is complimentar to aerobic oxidations over Pd and Ru based catalysts that are selective for primary and benzylic alcohols.

Tab. 3 - Comparison of different catalytic systems in the oxidation of cyclic alcohols

Catalyst	Substrate	Product (gprod/gcat h)	TOF (h^{-1})
1% Pd/MgO	4-tert-Bu-cyclohexanol	0.05	3.5
1,4% Ru/Al$_2$O$_3$		0.05	2.1
8% Cu/Al$_2$O$_3$		0.60	3.5
1% Pd/MgO	Cyclooctanol	0.04	3.2
1,4% Ru/Al$_2$O$_3$		0.05	2.7
8% Cu/Al$_2$O$_3$		2.00	12.5

References

[1] J.C. Collins *et al., Tetrahedron Lett.*, 1968, 3363.
[2] K.E. Harding *et al., J. Org. Chem.*, 1975, **40,** 1664.
[3] E.J. Corey, J.W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
[4] E.J. Corey, G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
[5] A.J. Mancuso, D. Swern, *Synthesis*, 1981, 165.
[6] S.V. Ley et al., *Synthesis*, 1994, 639.
[7] M. Gilhespy *et al., Chem. Commun.*, 2005, 1085.
[8] G. Pozzi *et al., Org. Lett.*, 2004, **6,** 441.
[9] R.A. Sheldon, I.W.C.E. Arends, *Adv. Synth. Catal.*, 2004, **346,** 1051.
[10] H. Tohma, Y. Kita, *Adv. Synth. Catal.*, 2004, **346,** 111.
[11] I.E. Markò *et al., Angew. Chem., Int. Ed.*, 2004, **43,** 1588 and references therein; b) P. Gamez *et al., Adv. Synth. Catal.*, 2004, **346,** 805.
[12] a) A. Abad *et al., Angew. Chem. Int. Ed.*, 2005, **44,** 4066; b) U.R. Pillai, E. Sahle-Demessie, *Green Chem.*, 2004, **6,** 161; c) for a review see T. Mallat, A. Baiker, *Chem. Rev.*, 2004, **104,** 3037.
[13] K. Mori *et al., J. Am. Chem. Soc.*, 2004, **126,** 10657.
[14] a) K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.*, 2002, **41,** 4538; b) K. Yamaguchi, N. Mizuno, *Chem. Eur. J.*, 2003, **9,** 4353.
[15] a) A. Abad *et al., Angew, Chem.*, 2005, **117,** 4134; b) A. Abad *et al., Tetrahedron*, 2006, **62,** 6666; c) A. Abad *et al., Chem. Commun*., 2006, 3178.
[16] a) M. Hayashi *et al., Green Chem.*, 2000, **2,** 257; b) T. Tanaka *et al., Tetrahedron Lett.*, 2005, **46,** 4989.
[17] C. Keresszegi *et al., New J. Chem.*, 2001, **25,** 1163.
[18] R. Karvembu *et al., React. Kinet. Catal. Lett.*, 2005, **86,** 211.
[19] F. Zaccheria *et al., Chem. Commun.*, 2005, 253.
[20] F. Zaccheria *et al., Chem. Eur. Journal*, 2006, **24,** 6426.
[21] N. Ravasio *et al., Applied Catalysis A: General*, 2006, **315,** 114.