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23. G. H. Fredrickson, A. Ajdari, L. Leibler, J. P. Carton, *Macromolecules* **25**, 2882 (1992).
24. H. W. Xi and S. T. Milner, *ibid.* **29**, 4772 (1996).
25. F. J. Solis and G. T. Pickett, *ibid.* **28**, 4307 (1995).
26. D. Long, A. Ajdari, L. Leibler, *Langmuir* **12**, 1675 (1996).
27. By volume conservation ($L = \sigma v/N$, v is the monomer volume), $\langle \phi_c^2 \rangle \propto \sigma^2 \langle L_c^2 \rangle$ where ϕ_c and L_c are, respectively, the concentration and layer height fluctuations.
28. R. Kubo, M. Toda, N. Hashitsume, *Statistical Physics II: Nonequilibrium Statistical Mechanics* (Spring-

er, Berlin, 1985).

29. We thank G. Petekidis for his assistance and constructive comments, A. N. Semenov for critically reading the manuscript, and M. Stamm for stimulating discussions. Part of this research was sponsored by the European Union (International Scientific Cooperation, contract ISC*CT93-0951) and by NATO's Scientific Affairs Division (Science for Stability Programme). B.F. acknowledges the support of an NSF/NATO postdoctoral fellowship.

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Copper-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones: An Efficient, Aerobic Alternative

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An efficient, copper-based catalyst has been discovered that oxidizes a wide range of alcohols into aldehydes and ketones under mild conditions. This catalytic system utilizes oxygen or air as the ultimate, stoichiometric oxidant, producing water as the only by-product.

The oxidation of alcohols into aldehydes and ketones is a ubiquitous transformation in organic chemistry, and numerous oxidizing agents are available to effect this key reaction (1). In most instances, these reagents are required in stoichiometric amounts and are usually toxic, or hazardous, or both. Moreover, purification of the reaction products is often demanding and laborious. Despite the industrial importance of this process and the ever-growing environmental concerns, surprisingly few efficient catalytic oxidations of alcohols have been described (2). The scarcity of alcohol oxidation processes that simply use oxygen or air as the ultimate stoichiometric oxidant is particularly notable (3, 4).

We describe an efficient, aerobic catalytic system for the transformation of alcohols into carbonyl compounds under mild conditions. Our work was inspired by the seminal report of Jallabert and Rivière and co-workers (5) on the aerobic oxidation of benzylic alcohols mediated by copper-amine complexes (6, 7). This method, however expedient, unfortunately requires 2 equivalents (equiv) of copper complex per equivalent of alcohol. Moreover, it is severely limited in scope to some benzylic alcohol substrates.

Initial investigations of the effect of various additives on promoting catalyst turnover led to a remarkable result. Substituted azo compounds, such as diethylazodicarboxylate (DEAD) or its *tert*-butyl (Bu^t) analog (DBAD) strikingly improve not only the turnover and the lifetime of the catalyst but also the rate of the reaction (8). The corresponding hydrazines, DEADH₂ and DBADH₂, are even more competent co-additives.

Further studies showed that the nature of the copper counterion is critical to the success of the reaction, with chloride, acetate, and triflate proving to be the most effective. Among a variety of ligands tested, diamines such as phenanthroline (phen) and its derivatives are particularly efficient. Whereas polar solvents (such as acetonitrile) inhibit the reaction, smooth aerobic oxidation takes place in apolar solvents such as benzene. More significant from a practical viewpoint, toluene and trifluoromethylbenzene are superior solvents to benzene and lead to an important increase in reaction rates (9).

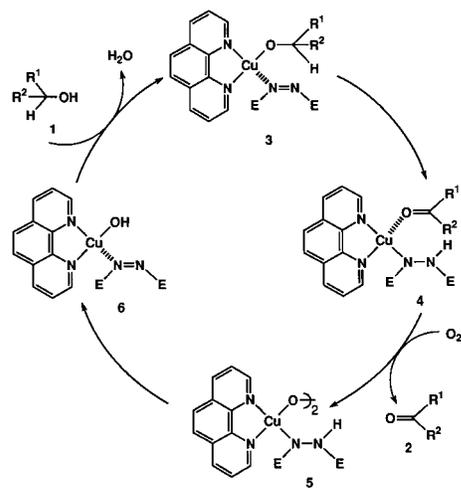
Under the following conditions (5% CuCl, 5% phen, 5% DBADH₂, 2 equiv K₂CO₃, O₂ or air, toluene, 70° to 90°C), a wide range of primary, secondary, allylic, and

Air can be conveniently used instead of oxygen without affecting the efficiency of the process. However, the use of air requires slightly longer reaction times. With activated allylic and benzylic alcohols, lower catalyst loading can be used with only a marginal drop in reaction rate (10). In these cases, lower temperatures can also be applied but result in a longer reaction period. Remarkably, catalyst deactivation is not observed during these extended reaction times (11).

The catalyst shows excellent tolerance for a broad range of alcohol substrates and is notably not deactivated by nitrogen- and sulfur-containing compounds. Sensitive aldehydes, such as neral and geranial, are not isomerized under the reaction conditions.

The active catalyst appears to be heterogeneous and adsorbed on the insoluble K₂CO₃ (12). Besides its role as a solid support, the carbonate also acts as a base (13), initiating the addition of the alcohol, or DBADH₂, or both to the copper complex, and as a water scavenger (14). In several instances, K₂CO₃ could be replaced by 4 Å molecular sieves and a catalytic amount of a nonoxidizable base such as KOH or KOBu^t.

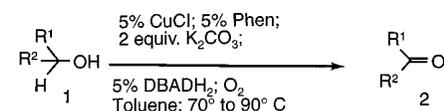
Mechanistic studies suggest that an initial hydrogen-transfer reaction within the copper-alkoxide/azo complex 3 generates the carbonyl-bound hydrazino-copper species 4 (Scheme 1) (15). Upon reaction with oxygen, this copper(I) complex then produces the binuclear copper(II) peroxide 5 (16). Homolytic cleavage followed by hydrogen-atom abstraction from the complexed hydrazine affords the hydroxy Cu(I) species 6. Rapid exchange between the OH ligand and alcohol 1, with concomitant loss of a water molecule, regenerates the loaded catalyst 3 and initiates a second catalytic cycle.



Scheme 1. R¹; R² = alkyl, aryl, heteroaryl, H; E = COOEt, COOBu^t

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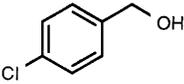
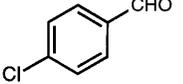
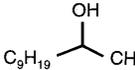
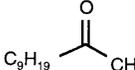
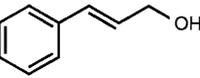
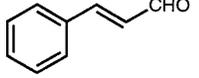
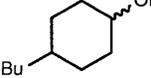
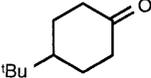
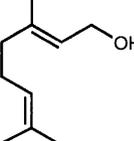
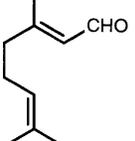
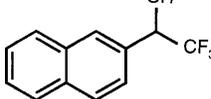
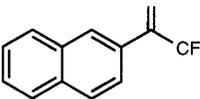
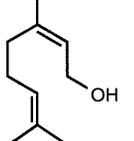
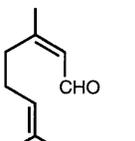
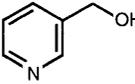
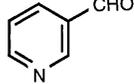
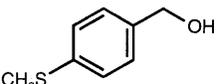
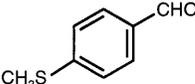
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benzylic alcohols can be smoothly oxidized to the corresponding aldehydes or ketones in good to excellent yields (Table 1).

We have discovered an efficient catalytic system that oxidizes a wide range of alcohols into the corresponding carbonyl compounds under mild conditions and that uses O₂ or

Table 1. All yields are for pure, isolated products and are based on the starting alcohol. No corrections have been made for recovered starting material in case of incomplete conversion. The conversion was measured by gas chromatography and ^1H nuclear magnetic resonance by using the internal standard method (tetradecane) (17).

Substrate	Product	Yield (Conv.)	Time (min)	Substrate	Product	Yield (Conv.)	Time (min)
		83 (100)	90			88 (90)	120 \ddagger
		89 (100)	60			84 (87)	120 \S
		71 (75)	60*			97 (100)	60 \ddagger
		73 (83)	60 \ddagger			81 (92)	60
						92 (95)	60
				$\text{C}_9\text{H}_{19}\text{CH}_2\text{OH}$	$\text{C}_9\text{H}_{19}\text{CHO}$	73 (87)	45 \parallel

*>95% (E)-geranial. \ddagger >95% (Z)-neral. \S 5 mol % DBAD used instead of DBADH₂. \parallel 10 mol % CuCl. Phen and 10 mol % DBAD were used in this experiment. Under the standard conditions, a 60% yield of ^1Bu cyclohexanone was obtained. \ddagger 10 mol % CuCl. Phen and 10 mol % DBADH₂ used in this experiment. Under the standard conditions, an 80% conversion was observed and a 65% yield of decanal was obtained.

air as the ultimate stoichiometric oxidant. This process is not only economically viable and applicable to large-scale reactions, but it is also environmentally friendly.

Further studies are needed to delineate the intimate mechanistic steps and expand the scope of this oxidation process.

REFERENCES AND NOTES

- For general reviews on oxidation reactions, see R. C. Larock, *Comprehensive Organic Transformations* (VCH Publishers, New York, 1989), pp. 604–615; R. A. Sheldon and J. K. Kochi, *Metal-Catalysed Oxidations of Organic Compounds* (Academic Press, New York, 1981); W. P. Griffith and J. M. Joliffe, *Dioxygen Activation and Homogeneous Catalytic Oxidation*, L. L. Simandi, Ed. (Elsevier, Amsterdam, 1991); G. Procter, *Comprehensive Organic Synthesis*, S. V. Ley, Ed. (Pergamon, Oxford, 1991), vol. 7.
- For catalytic oxidations, see, for example, S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* (1994), p. 639; S. I. Murahashi, T. Naota, Y. Oda, N. Hirai, *Synlett*. (1995), p. 733; K. Krohn, I. Vinke, H. Adam, *J. Org. Chem.* **61**, 1467 (1996), and references therein.
- For other catalytic aerobic oxidations, see, for example, S.-I. Murahashi, T. Naota, J. Hirai, *J. Org. Chem.* **58**, 7318 (1993); T. Inokuchi, K. Nakagawa, S. Torii, *Tetrahedron Lett.* **36**, 3223 (1995); T. Iwahama, S. Sakaguchi, Y. Nishiyama, Y. Ishii, *ibid.*, p. 6923, and references therein.
- Most of these aerobic oxidations use the "Mukaiyama trick," that is, O₂ is used in the presence of at least a stoichiometric amount of a reactive aldehyde such as pivalaldehyde. The active oxidizing species is probably the peracid or the metal-peracyl derivative. Under these conditions, 1 equivalent of acid is always formed as a by-product.
- C. Jallabert and H. Rivière, *Tetrahedron Lett.* (1977), p. 1215; C. Jallabert, C. Lapinte, H. Rivière, *J. Mol. Catal.* **7**, 127 (1980); C. Jallabert and H. Rivière, *Tetrahedron* **36**, 1191 (1980); C. Jallabert, C. Lapinte, H. Rivière, *J. Mol. Catal.* **14**, 75 (1982).
- For other pertinent studies on aerobic oxidation of alcohols with copper complexes, see, for example, P. Capdevielle, D. Sparfel, J. Baranne-Lafont, N. K. Cuong, M. Maumy, *J. Chem. Res. (S)* **1993**, 10 (1993), and references therein; M. Munakata, S. Nishibayashi, H. Sakamoto, *J. Chem. Soc. Chem. Commun.* (1980), p. 219; S. Bhaduri and N. Y. Sapre, *J. Chem. Soc. Dalton Trans.* (1981), p. 2585; M. F. Semmelhack, C. R. Schmid, D. A. Cortes, C. S. Chon, *J. Am. Chem. Soc.* **106**, 3374 (1984).
- For oxidation of alcohols into acids with copper complexes, see V. P. Tetyakov, G. P. Zimtseva, E. S. Ruddkov, A. V. Bogdanov, *React. Kinet. Catal. Lett.* **19**, 263 (1982); A. M. Sakharov and I. P. Skibida, *J. Mol. Catal.* **48**, 157 (1988); L. Feldberg and Y. Sasson, *J. Chem. Soc. Chem. Commun.* (1994), p. 1807.
- Stoichiometric amounts of substituted azo-compounds have been used to oxidize magnesium alkoxides to the corresponding carbonyl compounds; see K. Narasaka, A. Morikawa, K. Saigo, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **50**, 2773 (1977). The decomposition mechanism of hydrazines in the presence of copper-complexes has been reported; see H. Erlenmeyer, C. Flierl, H. Sigel, *J. Am. Chem. Soc.* **91**, 1065 (1969); Y. Zhong and P. K. Lim, *ibid.* **111**, 8398 (1989).
- Several other substituted aromatic solvents such as *o*-, *m*-, and *p*-xylene or trimethylbenzene were tested. None proved as efficient as toluene. The reason for the enhanced competency of toluene over other solvents is not yet understood.
- In view of the low cost of the copper(I) chloride and Phen ligand used, we typically use 5 mol % of the complex. This amount also ensures rapid oxidation of the alcohol substrates.
- The catalyst lifetime is intimately linked to the amount of azo/hydrazine derivative present. Indeed, the oxidation reaction stops when all of the DEAD/DBAD or the corresponding hydrazines disappear. These co-additives are consumed by a side reaction: The attack of the reactant alcohol on the carboalkoxy group of the copper-azo complex affording the unsymmetrical carbonate. DBAD or DBADH₂, being less sensitive to this competitive reaction, are thus preferred to DEAD or DEADH₂.
- Filtration of the heterogeneous mixture gives a solution devoid of any oxidizing ability. When the remaining solid is resuspended in toluene and an alcohol added in the presence of O₂, smooth transformation into the corresponding carbonyl compound ensues, thus indicating the heterogeneous nature of the active oxidant.
- The stoichiometric oxidation of copper (I) alkoxides into aldehydes and ketones by O₂, though in very low yields, has been reported previously: P. Capdevielle, P. Audebert, M. Maumy, *Tetrahedron Lett.* **25**, 4397 (1984).
- Azeotropic removal of H₂O can also be used. A catalytic amount of base is still required to initiate the reaction.
- This species can be prepared independently by adding CuCl/Phen to the sodium salt of DEADH₂ or DBADH₂. In the presence of oxygen, smooth oxidation of an alcohol takes place.
- For excellent reviews on the formation, isolation, and reactions of dinuclear copper (II) peroxides, see K. D. Karlin and Y. Gultneh, *Prog. Inorg. Chem.* **35**, 219 (1987); A. D. Zuberbühler, in *Copper Coordination Chemistry: Biochemical and Inorganic Perspectives*, K. D. Karlin and J. Zubieta, Eds. (Adenine, Guilderland, NY, 1983), p. 237.
- Typical experimental procedure: In a 2-liter three-necked flask (equipped with mechanical stirrer, oxygen inlet, and reflux condenser) were placed CuCl (1.98 g, 20 mmol) and 1,10-phenanthroline (3.60 g, 20 mmol). Toluene (800 ml) and K₂CO₃ (110 g,

0.80 mol) were added and the mixture was stirred for 30 min at room temperature. DBADH₂ (4.60 g, 20 mmol) and *p*-chlorobenzyl alcohol (57.0 g, 0.40 mol) were added successively, and the mixture was heated for 1.5 hours on an oil-bath between 80° to 90°C while O₂ was gently bubbled through the reaction mixture. After cooling to room temperature, the mixture was diluted by addition of Et₂O (500 ml; Et, ethyl) and filtered through a pad of

Celite. The solution was washed successively with water (200 ml), 1 M HCl (200 ml), and 200 ml of saturated aqueous NaCl solution, dried over MgSO₄, and evaporated in vacuo. The resulting residue was distilled (boiling point between 95° and 98°C, 18 torr) to afford 46.5 g (83%) of *p*-chlorobenzaldehyde. ¹H nuclear magnetic resonance (NMR) (CDCl₃, 300 MHz) δ_H 9.98 (1H, s), 7.82 (2H, d, coupling constant *J* = 8.4 Hz), 7.50 (2H, d, *J* =

8.4 Hz). ¹³C NMR (CDCl₃, 75.5 MHz) δ_C 191.3, 141.5, 135.4, 131.5, and 130.0.

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Formation of Chiral Interdigitated Multilayers at the Air-Liquid Interface Through Acid-Base Interactions

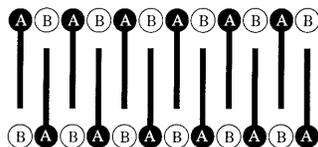
Ivan Kuzmenko, Ronith Buller, Wim G. Bouwman, Kristian Kjær, Jens Als-Nielsen, Meir Lahav, Leslie Leiserowitz*

Thin interdigitated films composed of a long-chain, water-insoluble chiral acid (*p*-pentadecylmandelic acid of absolute configuration *R*) and a water-soluble chiral base (phenylethylamine, *R'*) were constructed at the air-solution interface. The (*R*, *R'*) structure was characterized to near-atomic resolution by grazing-incidence x-ray diffraction (GIXD). The two diastereomeric systems, (*R*, *R'*) and (*R*, *S'*), demonstrate similar surface pressure–molecular area isotherms, but their structures are completely different on the molecular level, as monitored by GIXD. Complementary data on these two architectures were provided by atomic force microscopy.

An important goal of supramolecular chemistry is to find methods to control and stabilize the assembly of molecules into larger structures. One approach is to use the air-solution interface to regulate the assembly process by incorporating strong directional interactions for the generation of ultrathin films. The formation of multilayer films from long-chain molecules with polar head groups by the Langmuir-Blodgett (LB) method is straightforward, but the films must be transferred to a substrate and are not especially stable even after transfer. Such a formation process is governed by relatively weak hydrophobic and hydrophilic interactions.

We have considered the effect of using stronger acid-base interactions to control assembly and have constructed an interdigitated film at the air-solution interface akin to that of a natural membrane (1). We did this by spreading a water-insoluble, long-chain acid on an aqueous solution containing the complementary amine. Compression of the film causes alternating acid-base groups to emerge at either side of the membrane, whereas the central part contains the interdigitated hydrophobic groups of the acid in space-filling contact across a central

plane (Scheme 1). Both the acidic (A) and



Scheme 1.

basic (B) head groups are attached to a chiral carbon center, and the layering and ordering in these films differ greatly between acids and bases of the same handedness (*R*, *R'*) versus opposite handedness (*R*,

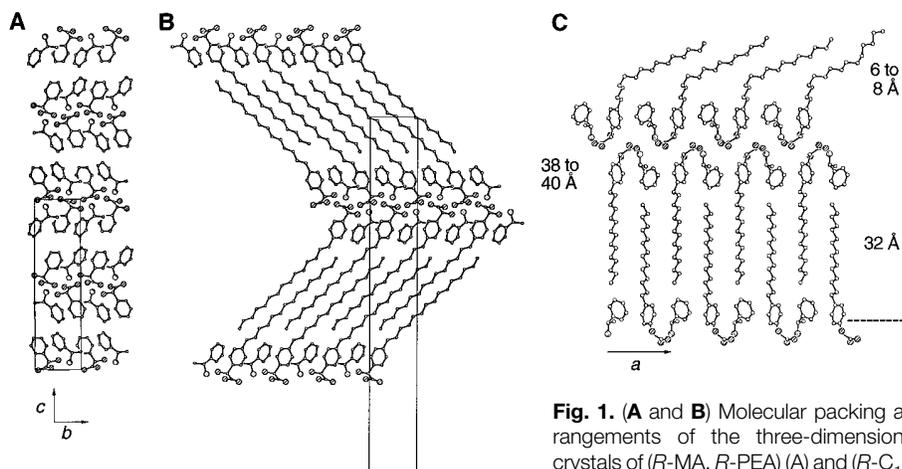


Fig. 1. (A and B) Molecular packing arrangements of the three-dimensional crystals of (*R*-MA, *R*-PEA) (A) and (*R*-C₁₅-MA, *R*-PEA) (B) viewed along the *a* axis.

(C) Packing arrangement of the interdigitated (*R*-C₁₅-MA, *R*-PEA) trilayer viewed along the *b* axis. The amorphous and crystalline parts are indicated by the upper and lower arrows at the right; the dashed line represents the air-water interface.

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