Pergamon

Tetrahedron Letters 41 (2000) 4343–4346

TETRAHEDRON
LETTERS

Copper-catalyzed aerobic oxidation of alcohols under fluorous biphasic conditions

Bodo Betzemeier,[a] Marco Cavazzini,[b] Silvio Quici[b] and Paul Knochel[a,]*

[a]*Institut für Organische Chemie der Ludwig-Maximilians-Universität, Butenandtstraße 5-13,*
D-81377 München, Germany
[b]*Centro CNR Sintesi e Stereochimica di Specali Sistemi Organici e Dipartimento di Chimica Organica e Industriale,*
via Golgi 19, I-20133 Milano, Italy

Received 6 April 2000; accepted 10 April 2000

Abstract

A catalytic amount of perfluoroalkyl substituted bipyridine **1** (2 mol%), CuBr·Me_2S (2 mol%) and TEMPO (3.5 mol%) allow the oxidation of various alcohols to aldehydes and ketones in a fluorous biphasic system of chlorobenzene and perfluorooctane directly with oxygen. The catalyst can be used for several reaction runs without a loss of reactivity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: bipyridine; copper; fluorous phase; oxidation; TEMPO.

The oxidation of primary and secondary alcohols to aldehydes and ketones is one of the most important transformations in organic chemistry both at a laboratory and industrial scale.[1] Therefore, it is surprising that only a few examples of *catalytic* oxidations using cheap oxidation agents such as oxygen or hydrogen peroxide have been reported.[2] Most reactions require stoichiometric amounts of often toxic oxidation reagents. The removal of traces of those reagents from the reaction mixture is often costly and difficult. Recently, we have described the utility of fluorous biphase catalysis[3,4] for oxidation reactions.[5] In such a system, perfluoroalkylated catalysts have been used to achieve a selective solubility in perfluorinated solvents whereas the reagents and starting materials are soluble in the organic phase. This method allows a facile separation of the catalyst from the product by decantation of the fluorous phase. Furthermore, the catalyst can be potentially reused for further reaction runs.[4d]

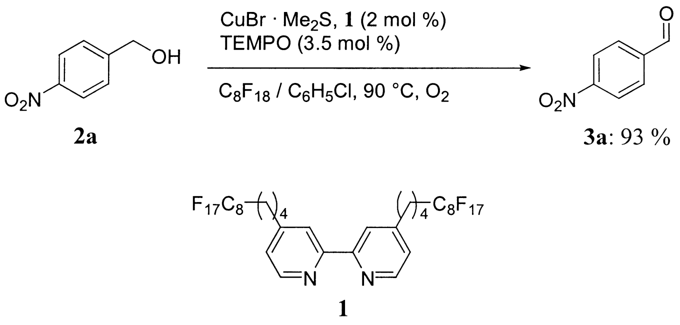
The use of perfluoroalkylated bipyridines of type **1** as ligand for the ruthenium-catalyzed epoxidation of *trans*-stilbene have been reported by one of us recently.[6] Semmelhack et al.[7] have also described the aerobic oxidation of primary and secondary alcohols to the corresponding

---

* Corresponding author. Fax: +49-89-21807679; e-mail: paul.knochel@cup.uni-muenchen.de, quici@mailserver.unimi.it

PII: S0040-4039(00)00620-1

aldehydes and ketones catalyzed by copper(I) chloride and 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO).[8] This work led us to design a similar reaction in a fluorous phase by modifying the copper catalyst with the fluorinated ligand **1**. The catalyst prepared in situ from CuBr·Me_2S and the perfluoroalkylated bipyridine **1** is selectively soluble in perfluorooctane as indicated by its green colour. With 2 mol% of this catalyst and TEMPO (3.5 mol%) the oxidation of 4-nitrobenzylalcohol (**2a**) to 4-nitrobenzaldehyde (**3a**) has been carried out in a biphasic system of perfluorooctane and chlorobenzene at 90°C under a gentle stream of oxygen. After 4 h the conversion was completed and the aldehyde **3a** was isolated in 93% yield (Scheme 1).



2a

3a: 93 %

1

Scheme 1.

To demonstrate the recyclability of the catalyst, the fluorous phase containing the catalyst was reused several times for further reaction runs without a significant decrease in yield and in rate. Even after eight cycles, 86% of analytical pure 4-nitrobenzaldehyde (**3a**) was isolated (Table 1).

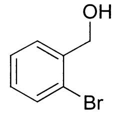
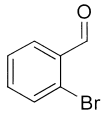
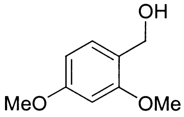
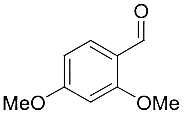
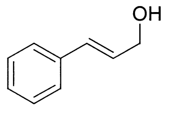
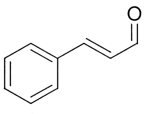
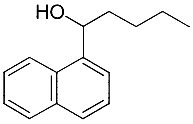
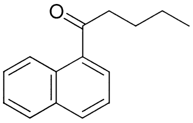
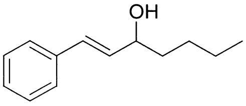
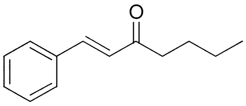
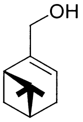
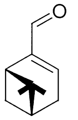
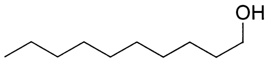
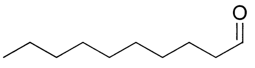
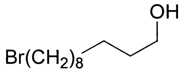
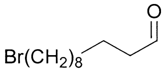
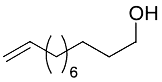
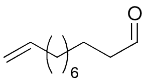
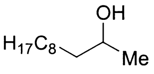
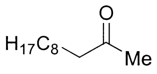
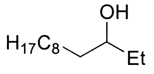
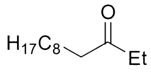
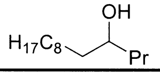
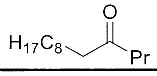
Table 1
Reuse of the catalyst solution for the oxidation of 4-nitrobenzylalcohol

Run	Yield / %	Run	Yield / %
1	93	5	88
2	86	6	85
3	87	7	81
4	81	8	86

With this method, various primary and secondary alcohols have been oxidized with high selectivity to their corresponding aldehydes and ketones. Under these reaction conditions, not only benzylic and allylic alcohols (entries 1–6 of Table 2) but also aliphatic alcohols (entries 7–12 of Table 2) were smoothly oxidized. However, benzylic alcohols react faster (2–7 h) compared to aliphatic alcohols (7–13 h).

For secondary aliphatic alcohols, the success of the reaction is strongly dependent on the steric environment of the carbinol moiety. With 4-tridecanol (**2n**) a conversion of only 31% was observed after 17 h, while the reaction of the less hindered alcohols **2l** and **2m** was completed within 8 and 12 h, respectively (entries 10–12 of Table 2).

Table 2
Aldehydes and ketones prepared under fluorous biphasic conditions

Entry	Alcohol of type **2**		Aldehyde/Ketone of type **3**		Yield[a] / %
1		**2b**		**3b**	96
2		**2c**		**3c**	93
3		**2d**		**3d**	79
4		**2e**		**3e**	91
5		**2f**		**3f**	84
6		**2g**		**3g**	76
7		**2h**		**3h**	73
8		**2i**		**3i**	81
9		**2k**		**3k**	78
10		**2l**		**3l**	71
11		**2m**		**3m**	69
12		**2n**		**3n**	31[b]

[a] Isolated yield of analytically pure product; [b] conversion after 17 h

We have shown that the perfluoralkylated bipyridine **1** is an efficient ligand for the performance of the copper-catalyzed oxidation of various primary and secondary alcohols to their corresponding aldehydes and ketones under fluorous biphasic conditions. The facile recovering of the catalyst is a great advantage of this method since it allows its reuse without observing a significant decrease in reactivity.[9]

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm 'Peroxidchemie' and Leibniz program), the European Union (COST-program 'Fluorous medium: a tool for environmentally compatible oxidation processes') and the Fonds der Chemischen Industrie for generous financial support. The companies BASF AG (Ludwigshafen), Bayer AG (Leverkusen), ELF Atochem SA (Pierre-Benite, France) and Chemetall GmbH (Frankfurt) are acknowledged for the generous gift of chemicals.

References

1. (a) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, P. *Synthesis* **1994**, 639; (c) Procter, G. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon: Oxford, 1991; Vol. 7, p. 305.
2. (a) Murahashi, I.; Naota, T.; Oda, Y.; Hirai, N. *Synlett* **1995**, 733; (b) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Regnaut, I. C.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433; (c) Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 1439.
3. Horváth, I.; Rábai, J. *Science* **1994**, *266*, 72.
4. For recently published reviews, see: (a) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057; (b) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641; (c) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37; (d) Betzemeier, B.; Knochel, P. *Top. Curr. Chem.* **1999**, *206*, 61; (e) Fish, R. H. *Chem. Eur. J.* **1999**, *5*, 1677.
5. (a) DiMagno, S. G.; Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5312; (b) Pozzi, G.; Montanari, F.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1997**, 69; (c) Pozzi, G.; Cinato, F.; Montanari, F.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1998**, 877; (d) Klement, I.; Lütjens, H.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1454 (e) Betzemeier, B; Lhermitte, F.; Knochel, P. *Synlett* **1999**, 489.
6. Quici, S.; Cavazzini, M.; Ceragioli, S.; Montanari, F.; Pozzi, G. *Tetrahedron Lett.* **1999**, *40*, 3647.
7. Semmelhack, M. F.; Schmidt, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374.
8. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591.
9. **Typical procedure**: For preparation of 4-nitrobenzaldehyde (**3a**) a 25 mL (Schlenk) flask was charged with the bipyridine **1** (44 mg, 40 μmol, 2 mol%) dissolved in perfluorooctane (2 mL) and CuBr·Me_2S (9.2 mg, 40 μmol, 2 mol%) dissolved in a small amount of dimethyl sulfide leading to a deep green solution. After stirring for 0.5 h, a solution of 4-nitrobenzylalcohol (**2a**: 306 mg, 2.0 mmol) and TEMPO (10.0 mg, 67 μmol, 3.4 mol%) in chlorobenzene (2 mL) was added. The biphasic reaction mixture was stirred at 90°C for 3 h while a gentle stream of oxygen was passing. At the end of the reaction, the mixture was cooled to 0°C, the organic layer was decanted and the fluorous phase was washed with chlorobenzene (3×2 mL). The combined organic phases were diluted with ether (30 mL) and washed with brine. After drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo the crude product was purified by flash chromatography (pentane:ether, 4:1) yielding pure 4-nitrobenzaldehyde (**3a**, 281 mg, 93%) as a pale yellow solid. The fluorous phase was separated and was used directly for further reaction runs.