On the stability of the copper-(S)-proline catalyst in the enantioselective allylic acyloxylation of alkenes

Aviva Levina [1], Françoise Hénin, Jacques Muzart *

Unité "Réarrangements Thermiques et Photochimiques" Associée au CNRS, Université de Reims Champagne–Ardenne, B.P. 347,
51062 Reims Cedex, France

Abstract

Visible spectroscopic studies of the enantioselective allylic benzoyloxylation of cyclohexene by t-butyl peroxybenzoate in the presence of catalytic amounts of $Cu\{(S)\text{-proline}\}_2$ indicate that this chelate remains largely unmodified under the experimental conditions.

Keywords: Chirality; Catalysis; Alkene acyloxylation; Copper–proline complex; Oxidation; Peroxide

1. Introduction

The metal-catalysed oxidation of alkenes is a useful method of introducing functionality [1]. The value of such transformations is greatly enhanced if the generation of a stereogenic centre can be achieved in this way [2]. The well-known Kharasch–Sosnovsky methodologies — $Cu/Bu^tOOH/RCO_2H$ or $Cu/Bu^tOOC(O)R$ — [3] have approached this when performed in the presence of optically active species [4–8]. Pathways represented by Eqs. (1, 2, 4, 5) and (3, 4, 5) have been proposed to rationalize allylic acyloxylation under achiral conditions [9] [2]. The steps involved in the latter pathway with formation of a pericyclic transition state A have been the subject of considerable controversy [10]. The simplest way to explain the enantioselective variants of the Kharasch–Sosnovsky reactions is to envisage the intervention of optically active species as

ligands of the copper atom, at least in the intermediate A.

$$Bu^tOOH + Cu(I) \longrightarrow Bu^tO^{\cdot} + Cu(II)OH \qquad (1)$$

$$Cu(II)OH + RCO_2H \longrightarrow Cu(II)OCOR + HOH \qquad (2)$$

$$RCO_3Bu^t + Cu(I) \longrightarrow Bu^tO^{\cdot} + Cu(II)OCOR \qquad (3)$$

$$(4)$$

$$A$$

$$(5)$$

In the course of our studies on the enantioselective allylic oxidation of alkenes under the conditions summarized in Eq. 6, the best results were obtained when

---

* Corresponding author.

[1] On leave from Riga Technical University.

[2] The nature of the initial copper salt (Cu(I) or Cu(II)) usually has no significant effect: some in situ-produced carbon radicals would reduce Cu(II) when the starting salt is in that oxidation state [9,10d].
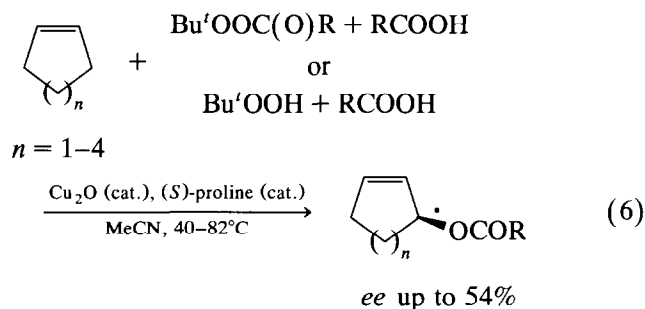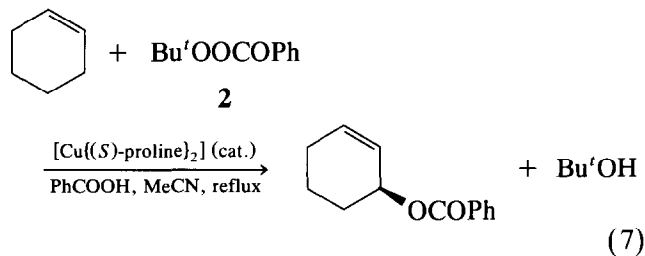
using both (S)-proline as the optically active species inducing the enantioselectivity (ee) and a ratio of [(S)-proline]/[Cu(I)] of 2 [8]. Furthermore, the benzoyloxylation of cyclohexene was achieved with similar yields and ee's when using a $Cu(I)_2O$/(S)-proline mixture of 1 : 4 or the chelate complex [Cu(II){(S)-proline}$_2$] (1) as catalyst [8,11].

$$Bu'OOC(O)R + RCOOH$$
$$\text{or}$$
$$Bu'OOH + RCOOH$$

$n = 1-4$

$$\xrightarrow[\text{MeCN, 40–82°C}]{\text{Cu}_2\text{O (cat.), (S)-proline (cat.)}} \quad \text{OCOR} \qquad (6)$$

ee up to 54%

These observations led us to question the role of 1 as active catalyst. Consequently we became interested in determining the stability of the coordination of proline to copper. This report describes our main investigations in this area, which examined the oxidation of cyclohexene using 1 as catalyst and Bu'OOC(O)Ph (2) as oxidant (Eq. 7).

$$\text{cyclohexene} + \text{Bu'OOCOPh}$$
$$\mathbf{2}$$

$$\xrightarrow[\text{PhCOOH, MeCN, reflux}]{\text{[Cu{(S)-proline}_2] (cat.)}} \quad \text{OCOPh} + Bu'OH \qquad (7)$$

2. Experimental

2.1. General

The complex [Cu{(S)-proline}$_2$] (1) was synthesized by treatment of copper(II) carbonate with a hot-water solution of (S)-proline according to the classical procedure [12]. Other reagents were commercially available. Cyclohexene was passed through alumina and then distilled over CaH$_2$ under argon. Acetonitrile was distilled successively under argon from P$_2$O$_5$ and CaH$_2$.

2.2. General procedure for the asymmetric benzoyloxylation of cyclohexene

A mixture of 1 (0.4 mmol, 116 mg), PhCOOH (3.0 mmol, 366 mg — added to ensure the solubility and stability of the mixture) and cyclohexene (10 mmol, 1.0 ml) was dissolved with magnetic stirring in MeCN (96 mmol, 5.0 ml). The mixture was then heated at 82 °C

Table 1
Influence of the total amount and semicontinuous addition of the oxidant on the enantioselectivity [a]

Run	Bu'OOC(O)Ph (mmol)	Heating time [b] (h)	2-Cyclohexenylbenzoate		
			Yield [c] (%)	$[\alpha]_D^{20}$ [d]	ee [e] (%)
1	4.0	2	71	−69	38
2	0.4	2	76	−86	47
3	0.4×2	2×2	63	−77	43
4	0.4×3	2×3	48	−79	44
5	0.4×4	2×4	61	−72	40

[a] General conditions: 10 mmol (1 ml) cyclohexene, 0.4 mmol of [Cu{(S)-proline}$_2$], 3 mmol PhCOOH, 96 mmol (5 ml) MeCN. [b] Conversion of the oxidant > 95%. [c] Isolated yield calculated on the total amount of Bu'OOC(O)Ph introduced. [d] The negative optical rotations demonstrate the S configuration of the samples [8]. [e] Data from ^{1}H NMR spectra in the presence of [Eu(hfc)$_3$] and $[\alpha]_D$ values.

and portions of Bu'OOC(O)Ph (1–4 portions — see Table 1 and text in Section 3 for quantities and conditions) were added, the time between two additions was about 2 h. The reaction was followed by thin-layer chromatography and at the end of the reaction the mixture was cooled to room temperature and a sample (0.5 ml) was withdrawn to record the visible spectrum. The rest of the mixture was added to saturated aqueous NaHCO$_3$ (50 ml) and extracted with Et$_2$O (2 × 15 ml). The visible spectrum of the resulting aqueous layer was recorded without further dilution. The organic layer was washed with water and dried over MgSO$_4$. After evaporation of the solvents, 2-cyclohexenyl benzoate was isolated by flash chromatography (petroleum ether/ EtOAc = 95/5). Optical rotations were measured in CHCl$_3$ as solvent.

2.3. Visible spectra

These were recorded on an UVIKON 941-plus spectrophotometer from Kontron Instruments using cells with a 1 cm pathlength. For the spectra shown in Fig. 1, 0.5 ml of the reaction mixture was added to 4.5 ml of MeCN (reference solvent: MeCN). For the spectra of
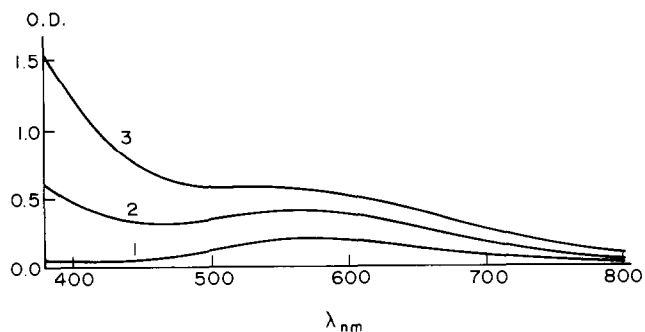

Fig. 1. Visible spectra of the reaction mixtures under conditions of Table 1 and Section 2 Curve 1: run 2 before heating. Curve 2: run 2 after heating. Curve 3: run 3 after the heating periods.
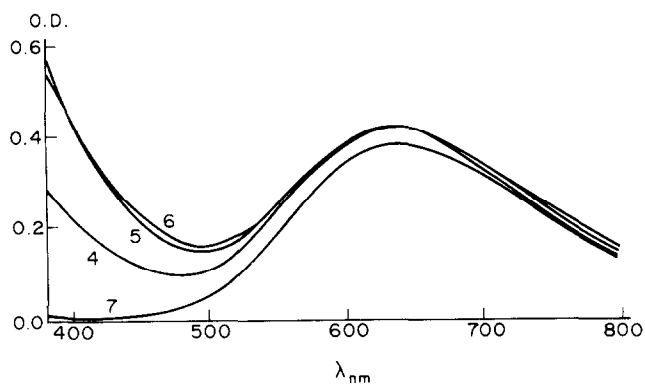
Fig. 2. Visible spectra of the aqueous extraction layers, performed under conditions of Table 1 and Section 2. Curves 4, 5 and 6: according to runs 3, 4 and 5. Curve 7: solution containing 0.4 mmol of 1 in 50 ml of saturated aqueous $NaHCO_3$.

the aqueous layers (Fig. 2), distilled water was used as reference solvent.

3. Results and discussion

During the reaction performed under the conditions of run 1 (Table 1), the reaction mixture changed from deep blue, which is characteristic of the initial copper chelate complex [12a], to green. This suggested the degradation of 1, which could be caused by 2 [9,10d]. We therefore suspected that a lower initial oxidant-to-catalyst ratio might be less destructive towards 1, allowing an increase in the enantioselectivity.

Consequently, we carried out experiments where the maximum amount of 2 available in the mixture was stoichiometrically equivalent to 1 (runs 2–5). After consumption of the oxidant, which was determined by TLC, the reaction was either stopped (run 2), or a new portion of 2 was introduced to the reaction mixture (semicontinuous method — runs 3–5). These experiments showed that the ee diminished slightly when successive batches of 2 were added. Thus, the semicontinuous addition of the oxidant is not a viable way to raise the ee of the benzoylation.

We also observed that the colour of the reaction mixture changed completely even when only one stoichiometric proportion of 2 was consumed (run 2). Nevertheless, subsequent additions of 2 also led to the optically active product (runs 3–5). Thus, the colour change is not associated with the degradation of the species which induces the enantioselectivity. The reasons for the colour changes became more understandable from a study of the visible spectra of the reaction mixtures.

The visible spectrum of the reaction mixture was recorded first before heating (Fig. 1, curve 1): the band at $\lambda_{max} = 572$ nm corresponds to an absorption of 1 providing the initial blue colour of the solution [12a].

During heating, a strong absorption with a $\lambda_{max} < 400$ nm appeared (Fig. 1, curves 2 and 3). The combination of the two above-mentioned absorptions probably causes the green colour of the final reaction mixtures. The organic compounds formed through the oxidation process, 2-cyclohexenylbenzoate and t-butanol (Eq. 7), do not absorb light within the spectral range studied. Indeed, we have verified that their addition to the sample used for recording curve 1 did not modify the visible spectrum. Thus, the appearance of the absorption at $\lambda_{max} < 400$ nm was probably due to the accumulation of by-products. This strong absorption in the UV region probably also caused the slight increase of the absorption at 572 nm. Taking this into account, curves 1, 2 and 3 indicate that 1 remains present during the oxidation process.

Finally, we have recorded the visible spectra (i) of the aqueous layers obtained from work up of the reaction mixtures (Fig. 2, curves 4, 5 and 6) and ii) of the copper chelate complex in sodium bicarbonate-saturated aqueous solution (Fig. 2, curve 7) [13]. From the comparison of curves 4–7, it follows that at worst a large portion of 1 was recovered at the end of the oxidation process.

4. Conclusions

We have previously considered that the chelate complex 1 has to be present in the reaction mixture in order to obtain reasonable ee's in the formation of the unsaturated esters from copper-catalysed allylic oxidations of alkenes [8]. The present study seems to show that this chelate complex is stable throughout the oxidation process. It is rather difficult to rationalise the results reported here with the mechanism commonly accepted for achiral allylic acyloxylation of alkenes outlined at the beginning of this article. Thus, these results suggest caution when describing the mechanism of this enantioselective catalytic system [14].

References and notes

[1] (a) R.A. Sheldon and J.K. Kochi *Metal-catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981; (b) J.

Muzart, *Bull. Soc. Chim. Fr.*, (1986) 65; c) J. Muzart, *Chem. Rev.*, *92* (1992) 113.

[2] (a) R. Spogliarich, S. Vidotto, E. Farnetti, M. Graziani and N. Verma Gulati, *Tetrahedron: Asymmetry*, *3* (1992) 1001; (b) T. Fukazawa, T. Hashimoto, *Tetrahedron: Asymmetry*, *4* (1993) 2323; (c) A.K. Gupta and R.J. Kazlauskas, *Tetrahedron: Asymmetry*, *4* (1993) 879.

[3] (a) D.J. Rawlinson and G. Sosnovsky, *Synthesis*, (1972) 1; (b) see [1a,b].

[4] D.B. Denney, R. Napier and A. Cammarata, *J. Org. Chem.*, *30* (1965) 3151.

[5] M. Araki and T. Nagase *Ger. Offen.*, (1976) 26 25 030; *Chem. Abstr.*, *86* (1977) 120886r.

[6] U. Leutenegger, *Thesis*, Zürich, 1990, No. 9091.

[7] J. Muzart, *J. Mol. Catal.*, *64* (1991) 381.

[8] A. Levina and J. Muzart, *Tetrahedron: Asymmetry*, *6* (1995) 147.

[9] A.L.J. Beckwith and A.A. Zavitsas *J. Am. Chem. Soc.*, *108* (1986) 8230.

[10] (a) M.S. Kharasch and G. Sosnovsky and N.C. Yang, *J. Am. Chem. Soc.*, *81* (1959) 5819; (b) A.L.J. Beckwith and G.W. Evans *Proc. Chem. Soc.*, (1962) 63; (c) J.K. Kochi, *J. Am. Chem. Soc.*, *84* (1962) 3271; (d) J.K. Kochi and A. Bemis, Tetrahedron, *18* (1962) 483; (e) J.K. Kochi, *J. Am. Chem. Soc.*, *85* (1963) 1958; (f) C. Walling and A.A. Zavitsas, *J. Am. Chem. Soc.*, *85* (1963) 2084; (g) J.K. Kochi and H.E. Mains, *J. Org. Chem.*, *30* (1965) 1862; (h) J.K. Kochi and A. Bemis Tetrahedron, *24* (1968) 5099; (i) A.L.J. Beckwith, G.E. Gream, D.L. Struble *Aust. J. Chem.*, *25* (1972) 1081; (j) A.L.J. Beckwith and G. Phillipou *Aust. J. Chem.*, *29* (1976) 1277.

[11] A similar observation has also been made for the oxidation of cyclopentene (A. Levina, unpublished results).

[12] (a) J.P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, Wiley, New York, 1961, Vol. 2 p. 1312; (b) K. Harada, *Nature*, *205* (1965) Vol. 2, p. 1312; 590; (c) K. Harada and W.W. Tso, *Bull. Chem. Soc. Jpn.*, *45* (1972) 2859.

[13] The absorption band at $\lambda_{max} = 630$ nm is characteristic of **1** in slightly basic media [12a].

[14] G. Consiglio and R.M. Waymouth, *Chem. Rev.*, *89* (1989) 257.